SYNTHETIC AND SPECTROSCOPIC STUDIES OF 1,4-BENZODIAZEPINE ANALOGUES

THESIS

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CONTENTS

ABBREVIATIONS

THF	=	tetrahydrofuran
Ether	=	diethyl ether
DCC	=	dicyclohexylcarbodiimide
DMF	=	dimethyl formamide
DMAP	=	4-methylaminopyridine
DDQ	=	dichlorodicyanobenzoquinone
DBU	=	1,8-diazabicyclo-[5.4.0]undecene-7
LDA	=	lithium diisopropylamide
NMR	=	nuclear magnetic resonance
IR	=	infra red
DEPT	=	distortionless enhancement by polarisation transfer
COSY	=	$^{1}H—^{1}H$ correlation spectroscopy
HETCOR	=	$^{1}H—^{13}C$ heteronuclear correlation spectroscopy
s	=	singlet
br s	=	broad singlet
d	=	doublet
dd	=	doublet of doublets
ddd	=	double doublet of doublets
dddd	=	double double doublet of doublets
tt	=	triplet of triplets
m	=	multiplets
Ac	=	acetyl group
Et	=	ethyl
1°	=	primary

ACKNOWLEDGEMENTS

I wish to express my deep appreciation to Professor P.T. Kaye for his interest, help and expert guidance in the cours of supervising this research project. I am also happy to acknowledge the assistance of Professors M. Brown and S. Daya in the analyses of the kinetic data and receptor binding studies, respectively. A word of thanks to R. Grue for typing this thesis and I. Ramaite for proof-reading part of this work. My sincere gratitude is extended to my sister (M.M.) for her financial and moral support throughout my studies. Financial assistance from the Foundation for Research Development, Snyckers Family Trust and Deutscher Akademischer Austauschdienst is also acknowledged with appreciation.

To Evelyne and Phatudi, and my mother, sister (Mmabore) and niece (Khomotšo), for their support throughout my studies.

ABSTRACT

In this project, an extensive range of benzodiazepine analogues have been synthesised *via* Schmidt reaction of specially prepared flavanone, 4-quinolone and 1-thioflavanone precursors; nitrogen insertion being effected by use of trimethylsilyl azide in trifluoroacetic acid. In some cases, several of the benzodiazepine analogues have also been prepared by alternative cyclisation routes. A detailed kinetic-mechanistic study of the Schmidt reaction of flavanones has been carried out using ^{1}H NMR spectroscopy to explain the observed regiochemistry of nitrogen insertion. The reaction rates, for the formation of both amide and tetrazolo derivatives have been found to be influenced by the electronic effects of the A- and B-ring substituents. A series of benzodiazepine analogues have been shown to undergo regioselective A-ring chlorination with *t*-butylhypochlorite; the products being characterised by ^{1}H NMR, IR and mass spectroscopy. The mass spectrometric fragmentation patterns of series of 2-aryl-4-quinolones, and 2-aryl-1,4-benzodiazepinones and their tetrazolo[1,5-*d*] analogues have been elucidated using a combination of low-resolution, high-resolution and metastable-peak analyses.

The binding affinities of various benzodiazepine analogues for rat brain benzodiazepine receptors have been evaluated using a radioreceptor assay technique. Structure-activity relationships were investigated to establish the effects of various A-, B- and C-ring substituents on binding affinity. The conformational preferences of selected systems have been studied using a combination of multi-pulse ^{1}H NMR spectroscopy, X-ray crystallography and computer modelling techniques with a view to establishing the influence of conformation on binding affinity.

1. INTRODUCTION

1.1 LITERATURE SURVEY ON THE CHEMISTRY AND PHARMACOLOGY OF BENZODIAZEPINES AND THEIR ANALOGUES

1.1.1 HISTORY OF THE DISCOVERY OF BENZODIAZEPINES

The discovery of benzodiazepines is an example of serendipity in the development of new drugs. In the 1930's, Sternbach synthesised several compounds thought to belong to the class 3,1,4-benzodiazepines.[1,2] Twenty years later, however, it was discovered that these compounds did not contain the 7-membered oxadiazepine ring, but were, in fact, quinazolin-3-oxides.[1]

By the mid 1950's there was a need for drugs with greater selectivity in the treatment of anxiety but fewer side effects than phenothiazine.[1] In 1955, Sternbach and co-workers at Hoffman La Roche, New Jersey, in their research in this direction prepared a number of quinazolin-3-oxide derivatives, by treatment of chloromethylquinazolin-*N*-oxide **1** with various amines.[1] Thirty nine of these compounds, prepared using secondary amines, showed no biological activity. The last compound to be prepared was obtained using the primary amine, methylamine, and was submitted for clinical evaluation in 1957 as the quinazolin-3-oxide derivative **2** (Scheme 1). Preliminary results showed that this product exhibited sedative and hypnotic properties.[1,2] It also showed similar efficacy to chlorpamazine as a muscle relaxant and, unlike phenobarbital, showed no direct hypnotic activity below toxic dosage.[2] These results stimulated further studies on this product, and it became apparent that the initial structural assignment and classification as a quinazolin-3-oxide derivative was incorrect. It was clear that by using methylamine, the reaction followed a different route from that undergone when secondary amines were used. The product was, in fact, found to contain a 7-membered oxadiazepine ring instead of the 6-membered ring as in **2** and was characterised as 7-chloro-2-

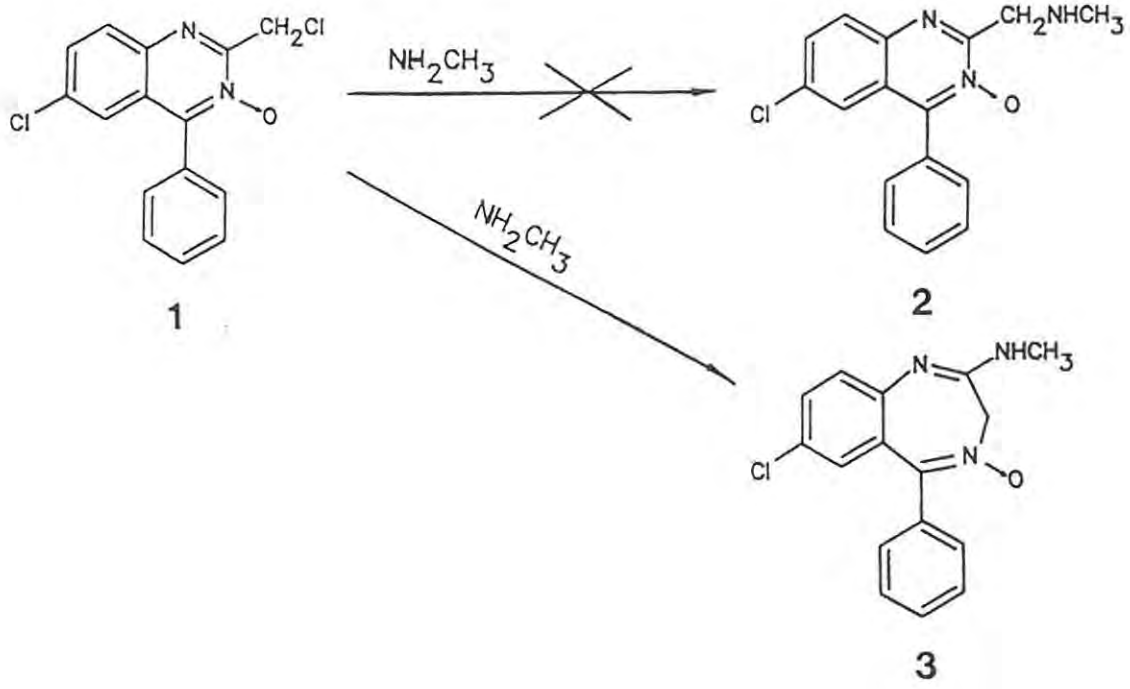
(*N*-methylamino)-5-phenyl-1,4-benzodiazepin-4-oxide **3**. Compound **3** was given the name chlordiazepoxide and was marketed as Librium in 1960.[1-4]

Since the introduction of Librium as a minor tranquilliser a large number of 7-membered heterocyclic compounds with the benzodiazepine moiety have been synthesised and tested for psychotropic properties.[1,2,3,5] These compounds exhibit a variety of biological activities. They serve as anxiolytics, muscle relaxants, hypnotics and anticonvulsants for people suffering from epilepsy.[1,2,3,6,7]

In 1959, diazepam **4** was synthesised and was found to be five to ten times more potent than chlordiazepoxide.[1] Diazepam was marketed as Valium in 1963 and was the first 1,4-benzodiazepine derivative that did not contain the basic alkylamino group found in the chlordiazepoxide-type framework. The increased biological activity of diazepam showed that both the methylamino and N^4-oxide functions present in chlordiazepoxide could be removed with retention of activity. This observation stimulated the development of derivatives that are free from the N^4-oxide and methylamino grouping. It was also discovered that diazepam **4** and diphenylhydantoin **5** (which have different chemical structures, but similar spatial properties) are both effective anticonvulsant agents.[1,8] This indicated that the stereochemical characteristics could be of paramount importance.

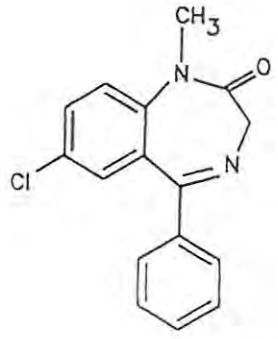
There are several established methods for the synthesis of benzodiazepine derivatives. Many patents and scientific papers continue to appear describing new methods for preparing known and new benzodiazepines. Emphasis has been placed on the alteration and replacement of heteroatoms with the aim of modifying the pharmacological activity. This led to compounds containing various substituents at the 3-position of the chlordiazepoxide or diazepam-type framework, nitrogen atoms at positions other than 1 and 4, and those with no phenyl group at the 5-position. Compounds in which nitrogen atoms have been replaced by other heteroatoms have also been reported. Recent developments include compounds with an additional ring

fused to the 7-membered ring and those in which the fused benzo ring has been replaced by a heterocyclic ring. A brief discussion of the synthesis and pharmacological activities of some representative examples will be included in this section.



1 2 3

Scheme 1



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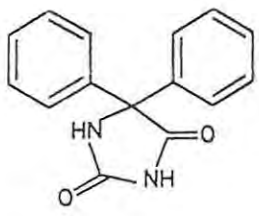

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1.1.2 CHEMISTRY AND PHARMACOLOGY OF BENZODIAZEPINE ANALOGUES

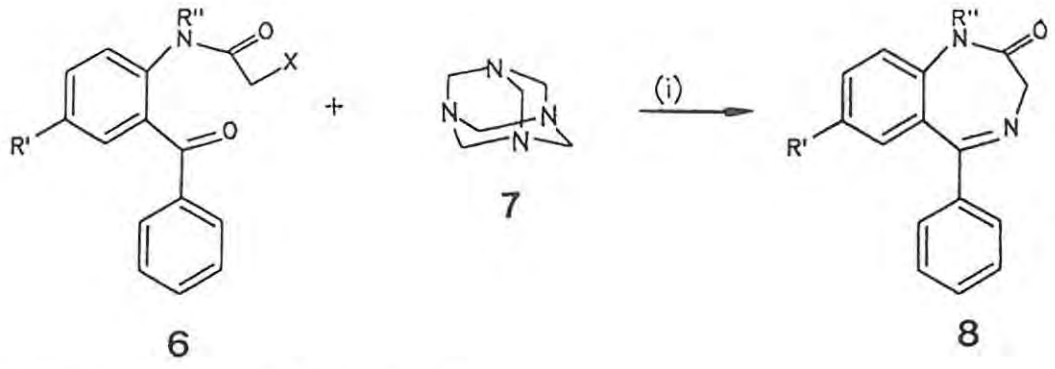
(a) 1,4-BENZODIAZEPINE DERIVATIVES

Most of the 1,4-benzodiazepines are generally prepared by ring enlargement of appropriate 2-(*α*-chloroalkyl)quinazolin-3-oxides with amines[1] (or hydroxide ions[9]) as shown in Scheme 1. Recently, hexamine **7** was used in the synthesis of 1,4-benzodiazepine derivatives (Scheme 2).[10] Use of hexamine has advantages over that of ammonia in cyclising 2-haloacetamido-5-chlorobenzophenone **6** into 1,4-benzodiazepin-2-one **8**, in that side reactions are minimised and yields are improved. Hexamine can also be used to oxidise a preformed tetrahydro 7-membered ring as in the synthesis of 2,3-dihydro-1,4-benzodiazepine **10** from 1,2,3,4-tetrahydro derivative **9** (Scheme 3).

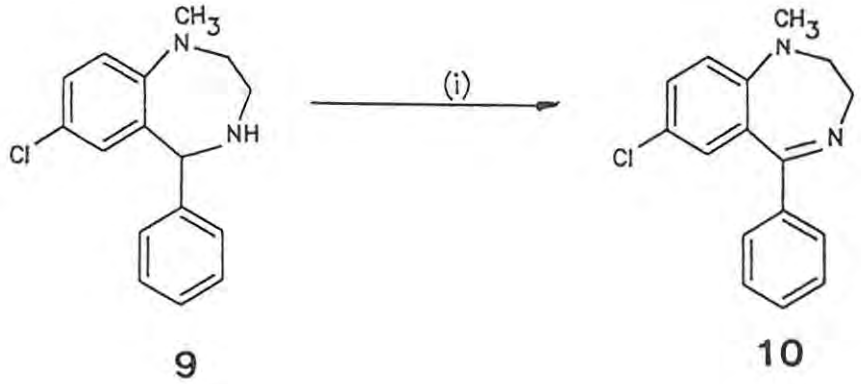
Introduction of various substituents (halogeno, amino, hydroxyl, ether and ester functions) at the 3-position of 1,4-benzodiazepine derivatives led to compounds with increased sedative, anticonvulsant and muscle relaxant activities.[11] For example, the N^4-oxide derivative **11** was first acylated to afford the 3-ester derivative **12** which was hydrolysed to give the 3-hydroxy derivative **13** (Scheme 4), which can be halogenated or etherified by conventional methods. The 3-amino derivative **15** was prepared from the 3-halogeno precursor, or directly, by heating 2-acetamido-2-amino-2'-benzoyl-4'-chloroacetanilide **14** (Scheme 5).[13]

Bromazepam **16** and tetrazepam **17** are examples of 1,4-benzodiazepines that do not contain a phenyl substituent at the 5-position, and they exhibit anxiolytic and muscle relaxant activities, respectively.[2] The 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-ones **20** (a), (b) and (c) have been prepared from isatoic anhydride derivatives **18** and appropriate *α*-aminoacetophenone hydrochlorides **19** (Scheme 6).[15(a),16] *o*-Chlorophenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one **20** (c), exhibits anticonvulsant and central nervous system activities.[15(a)] Recently, 4-alkoxy-1,4-benzodiazepin-5-ones **24** have been prepared utilising tandem Staudinger and aza-Wittig reactions of [*N*-(*o*-azidobenzoyl)]-*α*-amino esters **23** (Scheme 7).[17] 1,4-Benzodiazepine-2,5-

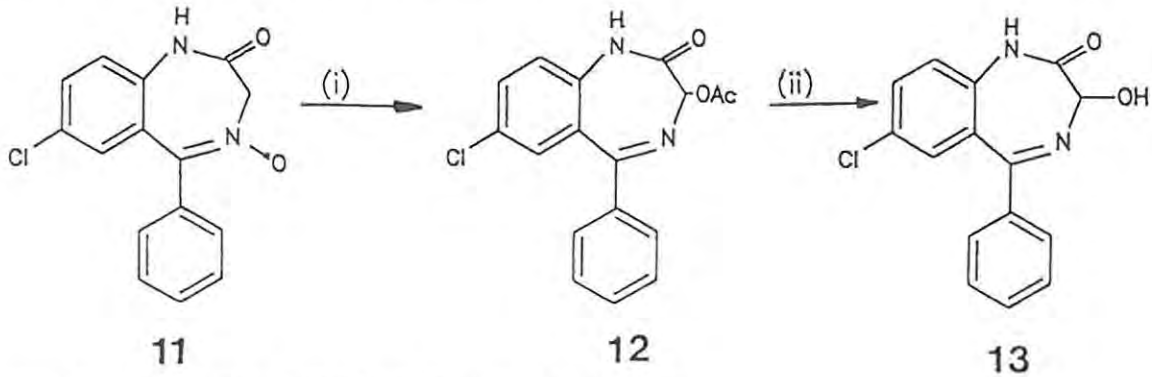
dione derivatives **27** can be prepared by coupling amino acid *N*-carboxyanhydrides **25** with Boc-anthranilic acid **26**, followed by deprotection of the Boc group and ring expansion (Scheme 8).[21] 1,2,3,4-Tetrahydro-9-hydroxy-2-methoxy-5*H*-1,4-benzodiazepin-5-one **29**, prepared by ring closure of compound 28 (Scheme 9),[18] showed similar anti-tumour activities to that exhibited by anthramycin **30**, a pyrrolo[2,1-*c*]-1,4-benzodiazepine derivative.[18-20]



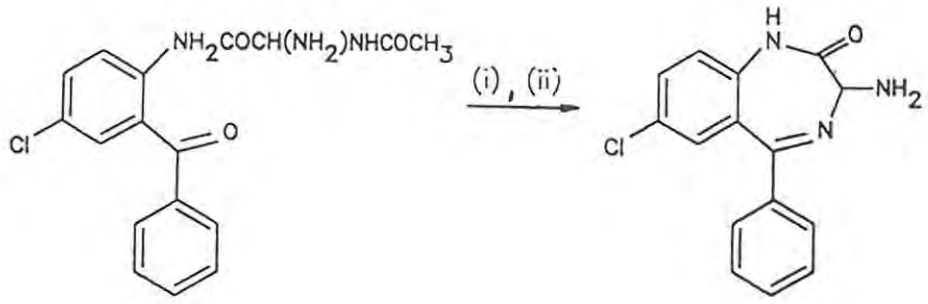
Scheme 2 Reagents: (i) EtOH, heat



Scheme 3 Reagents: (i) **7**, AcOH, heat

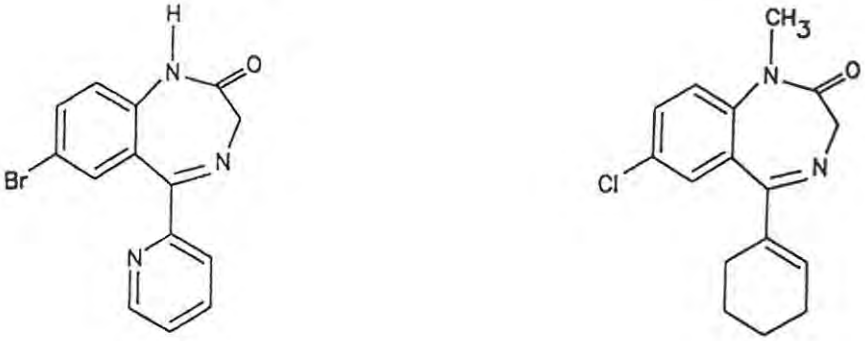


Scheme 4 Reagents: (i) Ac_2O or AcCl; (ii) NaOH (aq)

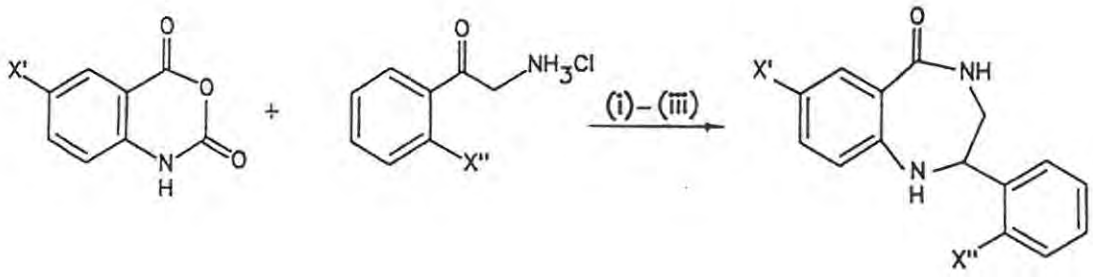


14 **15**

Scheme 5 Reagents: (i) heat; (ii) HCl

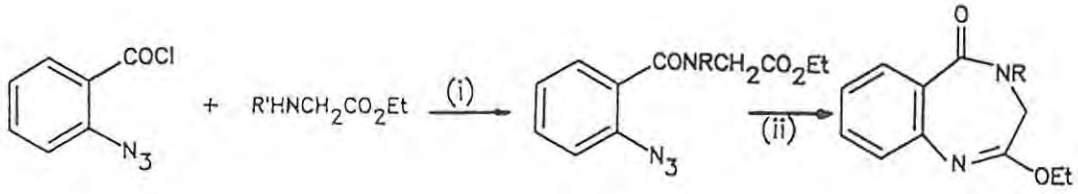


16 **17**



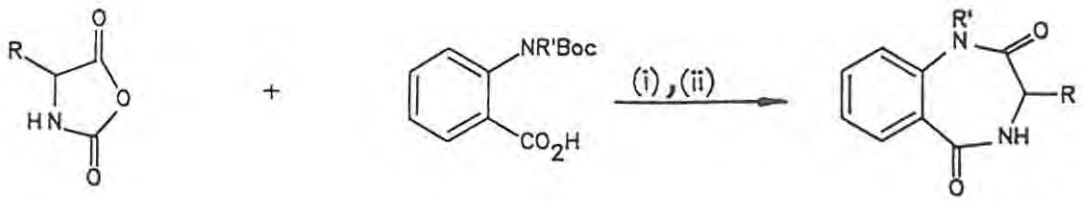
18 **19** **20**

Scheme 6 Reagents: (i) Na_2CO_3, H_2O; (ii) xylene, heat; (iii) $LiAlH_4$, THF
20 (a) X = CH_3, X′ = H; (b) X = H, X′ = Cl; (c) X = Cl, X′ = H



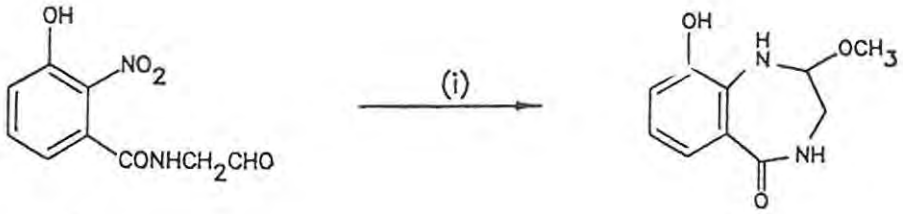
21 **22** **23** **24**

Scheme 7 Reagents: (i) NEt_3, THF, r.t.; (ii) PBu_3, xylene, heat



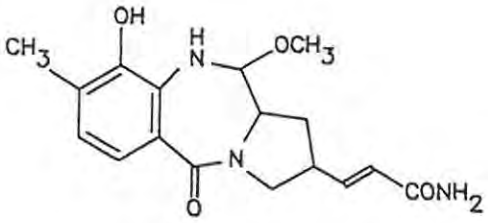
25 26 27

Scheme 8 Reagents: (i) DCC, DMAP; (ii) DMF, HCl



28 29

Scheme 9 Reagents: (i) H_2, Pd-C, MeOH or Fe/AcOH/MeOH



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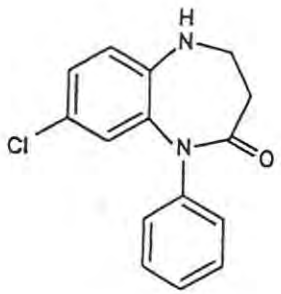
(b) **1,5-BENZODIAZEPINES**

The 1,5-benzodiazepines have also attracted considerable interest. Clobazam **31**, for example, has been marketed as an anxiolytic agent.[2] This 1,5-benzodiazepine has been found to have anti-anxiety properties between those of chlordiazepoxide and diazepam.[22] A number of simple 1,5-benzodiazepines involving modifications of the clobazam-type framework have been prepared and tested for psychotropic properties. Some of these compounds, for example, the

1,5-benzodiazepine **32**, showed sedative, muscle relaxant and anticonvulsant activities.[2] Among the 1,5-benzodiazepin-2-one, some 2,3-dihydro-4-methyl-1*H*-1,5-benzodiazepin-2-one derivatives **33** (a), exhibit sedative, tranquillising and analgesic properties.[23,24] The 4-aryl derivative **33** (b) was also found to possess tranquillising properties.[24]

Several methods have been reported in the literature for the synthesis of 1,5-benzodiazepines. The general approach to these compounds involves the condensation of aromatic 1,2-diamines with various compounds including *α*,ß-unsaturated acids,[25] ß-ketoesters,[24,25] conjugated acetylenic imidate salts,[26] dimethyl allene-1,3-dicarboxylates,[27] isoxazoles[28] and isoxazolones.[29] The 1,5-benzodiazepine-2-thiones **36** have been prepared by condensing aromatic 1,2-diamines **34** with 3,3-dimercapto-1-aryl-2-propen-1-ones **35** (Scheme 10).[30,31] These products can also be prepared by thionating the oxygen analogues with phosphorus pentasulphide in pyridine. 3*H*-1,5-Benzodiazepines **38** were obtained by reacting benzoyl substituted ketene dithioacetals **37** with various aromatic 1,2-diamines **34** (Scheme 11).[32] Compounds **38** can also be obtained by S-methylation of 1,5-benzodiazepine-2-thiones **36** with methyl iodide.[30,31,33] Compounds related to products **36** and **38** serve as important synthetic intermediates for various heterocyclic compounds including C-2 substituted benzodiazepines **39** (Scheme 12).[33] *N*-Alkylated derivatives **40** when condensed with aromatic aldehydes in refluxing ethanol in the presence of piperidine catalyst afforded the 3-substituted 1,5-benzodiazepin-2-one derivatives **41** (Scheme 13).[23]

When simpler transformations of 1,4- and 1,5-benzodiazepines became exploited to the level of unrewarding significance, chemists directed their efforts to synthetic analogues in which the heterocyclic ring is varied. Some of these products act like benzodiazepines, while others show opposite effects. Thus, for example, they may induce anxiety, antagonise, block or promote some actions of classical benzodiazepines.



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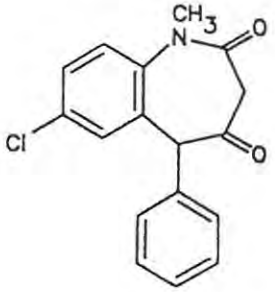

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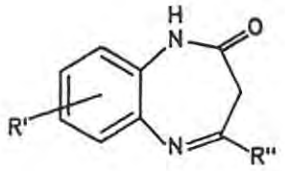
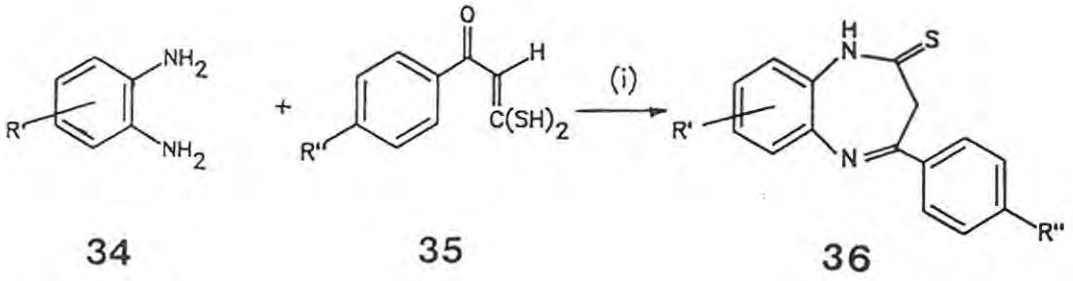
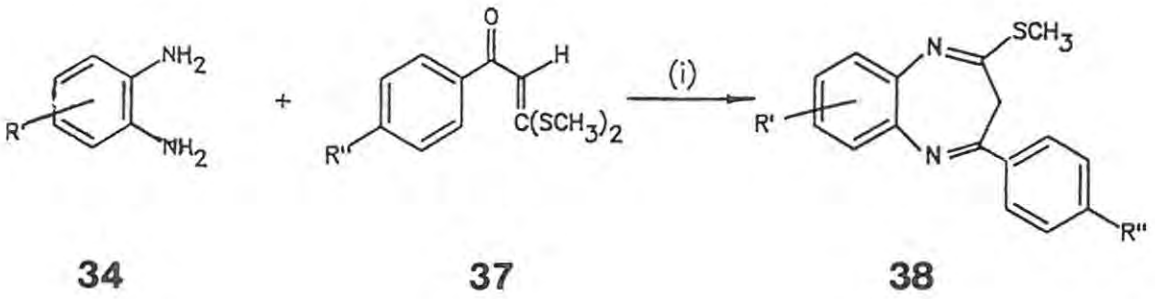


33 (a) R" = CH_3;
(b) R' = H, R" = Ph



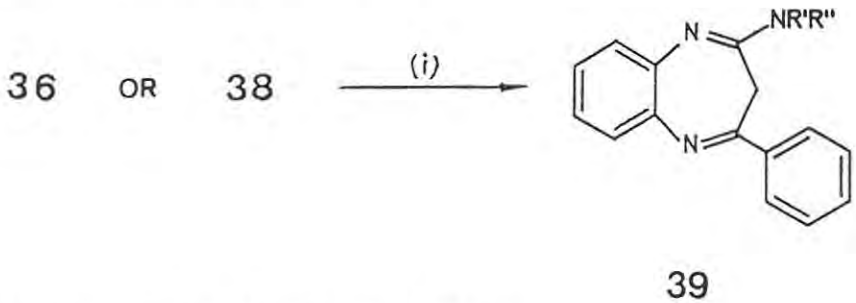
34 35 36

Scheme 10 Reagents: (i) xylene, heat



34 37 38

Scheme 11 Reagents: (i) xylene, heat;



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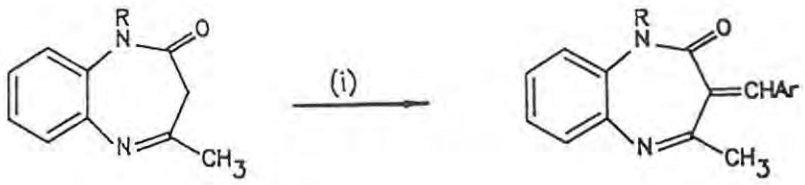
Scheme 12 Reagents (i) NHR'R", MeOH, heat



40 41

Scheme 13 Reagents (i) ArCHO, piperidine acetate, ethanol

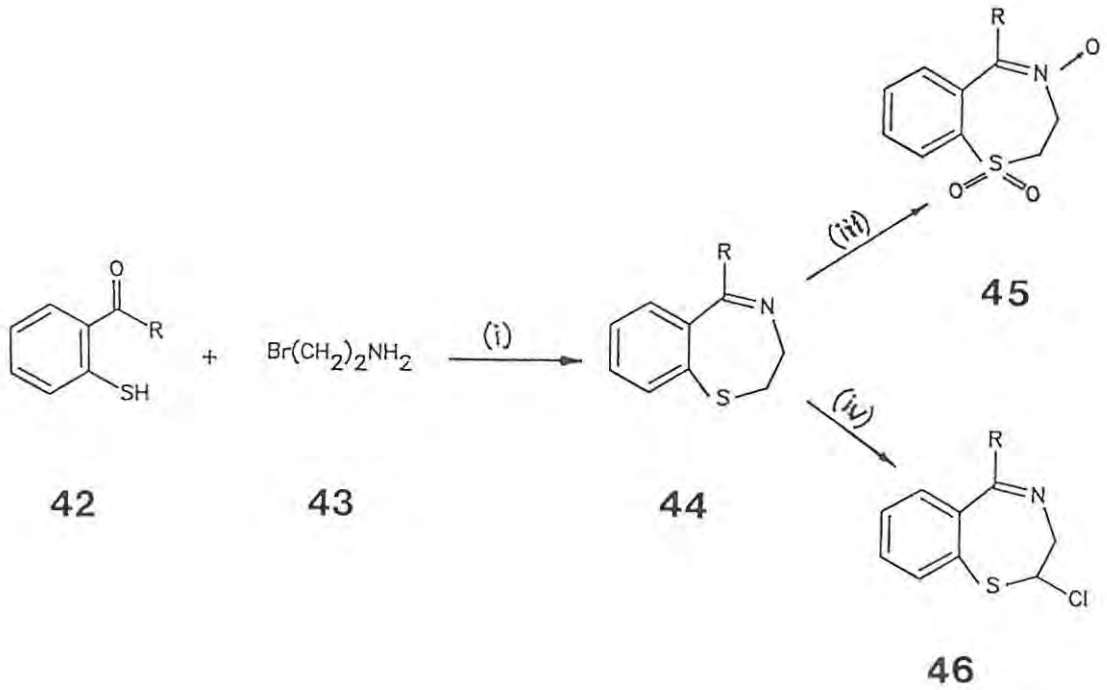
(c) **1,4- AND 1,5-BENZOTHIAZEPINES**

In these compounds one of the two nitrogens has been replaced by sulphur atom at position 1 to give the thioether linkage. 2,3-Dihydro-1,4-benzothiazepines **44** bearing alkyl, aryl or pyridyl substituents at positions 5 were prepared by condensation of mercaptoketones **42** with 2-bromoethylamine **43** (Scheme 14).[34] These compounds (**44**) can undergo various reactions including oxidation of nitrogen and sulphur atoms with hydrogen peroxide, and C-2—chlorination with inorganic chlorides (SO_2Cl_2) to afford products **45** and **46**, respectively. 1,4-Benzothiazepinones **49** have been prepared by reacting 2-thiosalicylic acid **47** with appropriate *α*-nitrostyrene derivatives **48** (Scheme 15).[35,36] Compound **49** has been found to have minor tranquillising effects.[38]

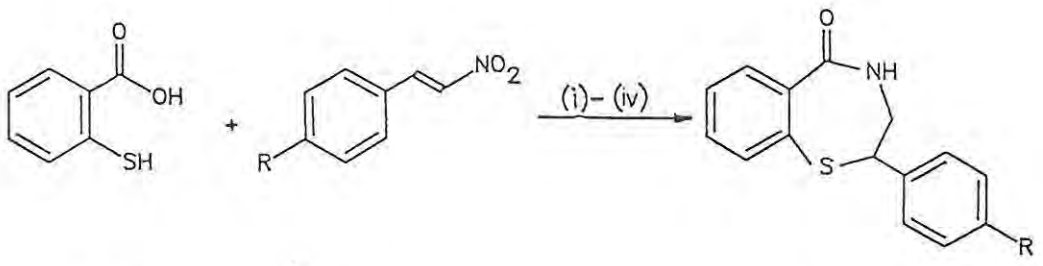
Most preparations of 1,5-benzothiazepinones are based on the condensation of 2-aminothiophenol **50** with *α*,ß-unsaturated acids, esters or ketones.[37]
1,5-Benzothiazepinone **52** (a) (R = H) was obtained by condensing 2-aminothiophenol **50** with either 3-bromo-3-phenylpropionic acid or cinnamic acid **51** (Scheme 16).[37-40] The adamantyl derivatives **52** (b)[41] and (c)[42] exhibit antidepressant activities. Compounds **52** (d), (e) and (f) were found to calm rats with lesions in the septal area of the brain and to show no ataxia at their effective dosage.[37,43,44] The latter property made them superior to chlordiazepoxide, use of which is accompanied by ataxia at effective dosage. Lancelot *et al.*[38] prepared a series of 1,5-benzothiazepinones substituted at position 2 with thienyl, *n*-butyl, furyl and pyridyl groups

using a similar approach. The 1,5-benzothiazepinone **55** was prepared by condensing 2-aminothiophenol **50** with dimethyl allene-1,5-dicarboxyester **52**, followed by cyclisation of the resulting intermediate **54** (Scheme 17).[27]

The most important 1,5-benzothiazepinone used in clinical applications is diltiazem, which exhibits coronary vessel dilating activity.[46-47] Its hydrochloride derivative **59** has been used in cardiovascular medicine as an effective anti-anginal agent with calcium channel blocking activity. Diltiazem was prepared by condensation of 2-nitrothiophenol **56** and 3-(4-methoxyphenyl)glycidate **57** according to Scheme 18.[45,46] The thiolactam derivatives **60**, obtained by thionating its amide analogue with phosphorous pentasulphide in pyridine,[48] was converted to the 4-methylthiolactam ether **61** with methyl iodide.[48,49(a)] Conversion of the thioamide to the thiolactam ether facilitates nucleophilic attack by hydrazine derivatives to form compounds **62** which, in turn, serve as intermediates for the formation of tricyclic 1,5-benzothiazepine derivatives (see page 20). The 4,1-benzothiazepine **64** was prepared by cyclising (2-aminobenzylmercapto)acetic acid **63** in refluxing pyridine (Scheme 20).[50]

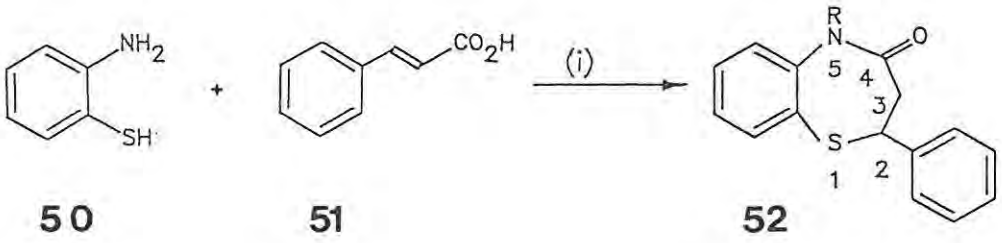


Scheme 14 Reagents: (i) NaOH; (ii) pyridine, heat; (iii) H_2O_2, AcOH; (iv) SO_2Cl_2



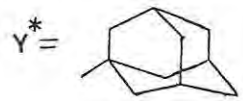
47 48 49

Scheme 15 Reagents: (i) EtOH, heat; (ii) $SOCl_2$, $CHCl_3$, heat; (iii) $SnCl_2.2H_2O$, MeOH, heat; (iv) xylene, heat

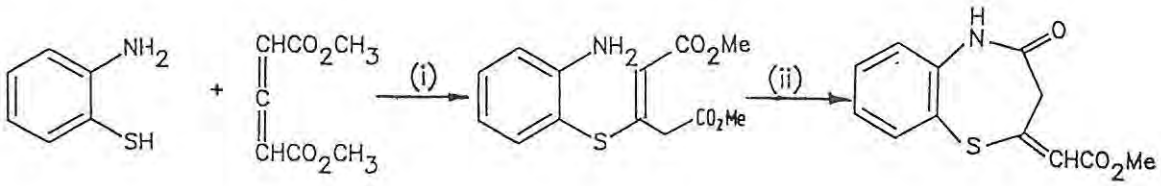


50 51 52

(a) R = H
* (b) R = $(CH_2)_nR'N(CH_2)_n$-Y
* (c) R = $(CH_2)_2N(CH_3)$-Y
(d) R = $(CH_2)_2N(CH_3)_2$
(e) R = $(CH_2)N(Et)_2$
(f) R = $(CH_2)_3N(CH_3)_2$

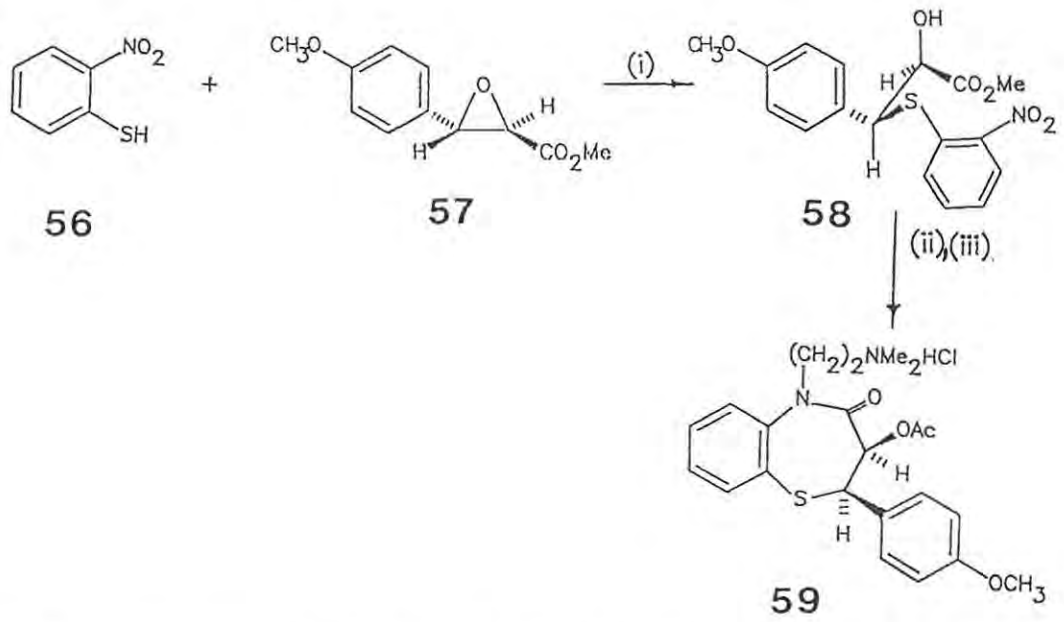


Scheme 16 Reagents: (i) heat

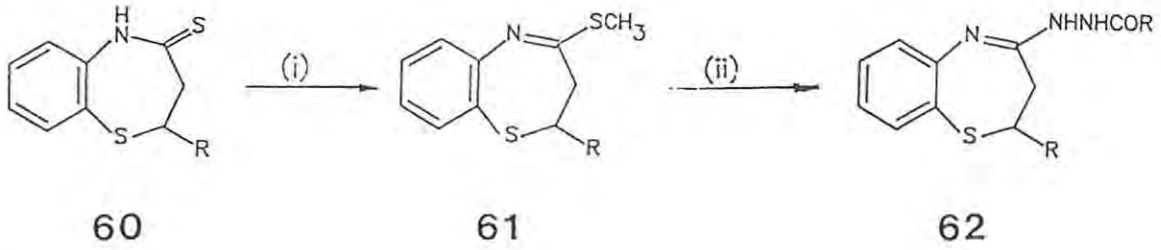


50 53 54 55

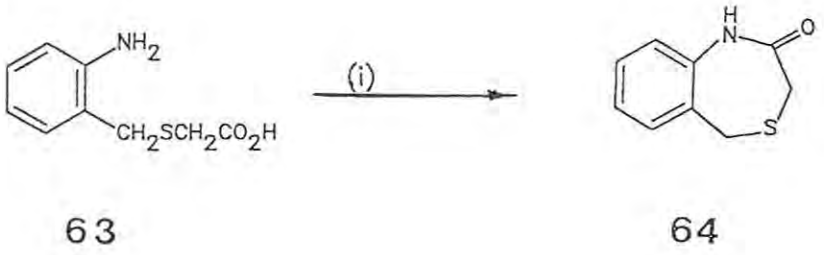
Scheme 17 Reagents: (i) MeOH, 20°C; (ii) heat



Scheme 18 Reagents: (i) CH_3CN, heat; (ii) 10% Pd/C, NaOH (aq); (iii) xylene, heat



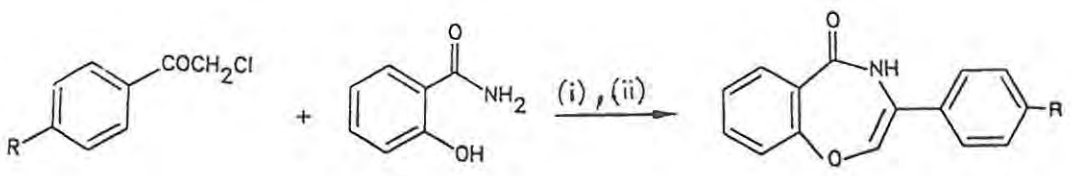
Scheme 19 Reagents: (i) CH_3I, NaH, THF; (ii) NH_2NHCOR



Scheme 20 Reagents: (i) pyridine, heat

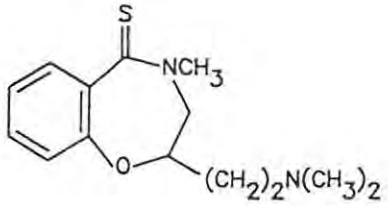
(d) 1,4 AND 1,5-BENZOXAZEPINONES

These compounds differ from benzodiazepines in that one nitrogen has been replaced with oxygen at position 1 to give the ether linkage. Benzoxazepinones have been prepared and tested for properties similar to those of benzodiazepines. Among benzoxazepinone analogues there are compounds possessing analgesic, sedative and anticonvulsant activities. 3-Phenyl-1,4-benzoxazepin-5(4*H*)-one **67** (R = H), which exhibits analgesic and anti-inflammatory properties, has been prepared by the Schenker method from salicylamide **65** and phenacyl chloride **66** (Scheme 21).[51-53] The 1,4-benzoxazepine-5-thione derivative **68** was found to offer protection against histamine-induced lethality in the guinea pig and showed no sedative effects in cats.[54] *N*-Substituted derivatives of the 1,5-benzoxazepinone **69** were found to possess psychotropic activity.[55(a)] 1,5-Benzoxazepin-4-one **73**, which was found to exhibit psychotropic activity, was obtained by condensation of 2-aminophenol **70** with 3-chloro-propionyl chloride **71**, followed by cyclisation of intermediate **70**, under basic conditions (Scheme 22),[55(b)] The 1,5-benzoxazepinone derivative **74**, which is a 1-oxa analogue of diltiazem **59**, was prepared from 2-nitrophenol and 3-(4-methoxyphenyl)glycidate as illustrated for diltiazem in Scheme 18.[45] The *cis*-isomer (**74**) showed vasodilating activity while the *trans*-isomer did not. It has been observed, however, that the presence of oxygen at position 1 in **74** resulted in decreased vasodilating activity and increased toxicity compared to diltiazem. An efficient synthetic route to 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **79** involves cyclisation of 3-(2-aminophenoxy)butyric acid **78** (Scheme 23).[56] Compounds **78** were obtained by condensation of 2-nitrothiophenols **75** with ß-butyrolactone **76** followed by reduction of the nitro intermediates **77**. In another development in the chemistry of benzoxazepines, attempted distillation of *o*-[2-hydroxyethylmethylamino]benzamide **80** afforded 1-methyl-2,3-dihydro-4,1-benzoxazepin-5(1*H*)-one **81** (Scheme 24).[57] 1,2,4,5-Tetrahydro-4,1-benzoxazepine **82**(a) and 3,5-dihydro-4,1-benzoxazepin-2-one **80**(b) possess sedative, tranquillising and hypnotic activities.[58]



65 66 67

Scheme 21 Reagents: (i) K_2CO_3, KI, acetone, heat; (ii) *p*-TsOH, toluene, heat



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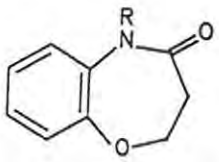

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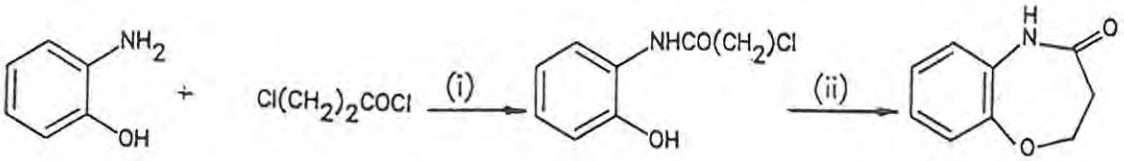
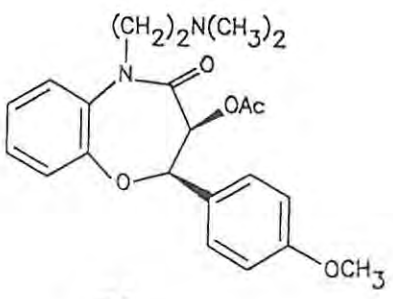


70 71 72 73

Scheme 22 Reagents: (i) K_2CO_3, PhH, heat; (ii) KOH, EtOH, heat



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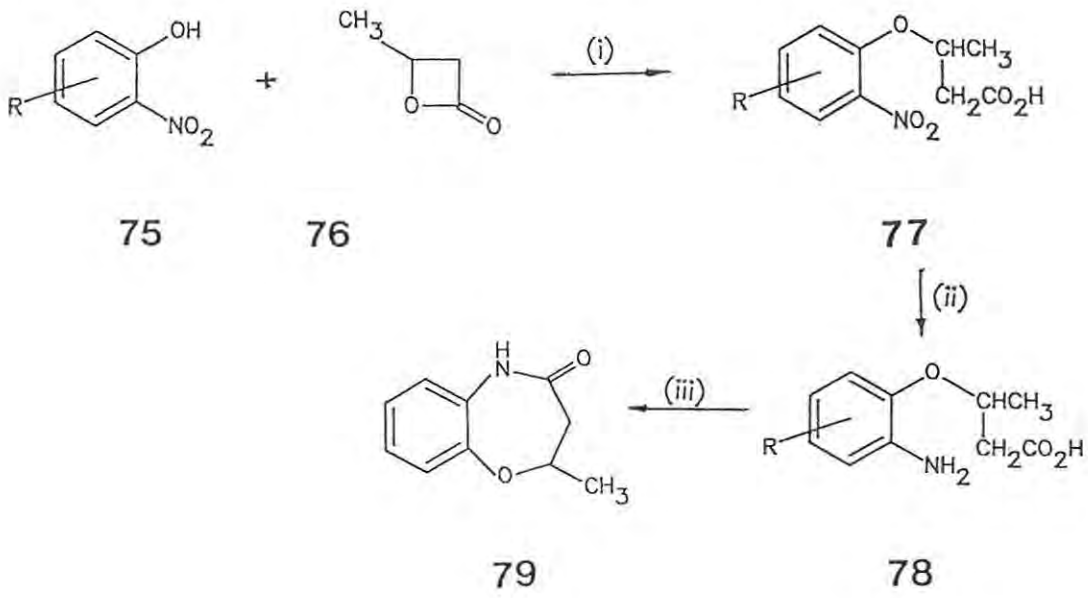
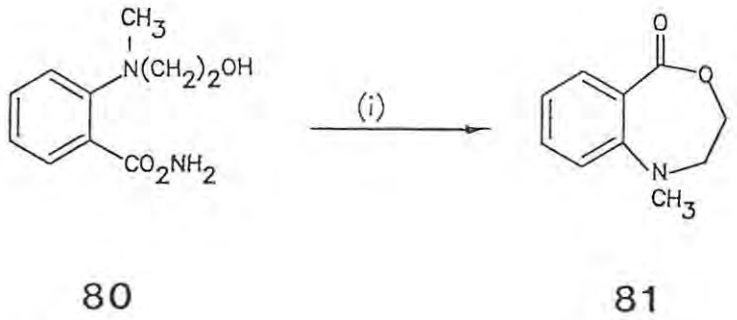
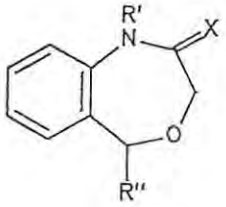


Scheme 23 Reagents: (i) DMF, KOH (aq); (ii) 10% Pd/C, EtOH; (iii) DCC, CH_2Cl_2, r.t.



Scheme 24 Reagents: (i) heat



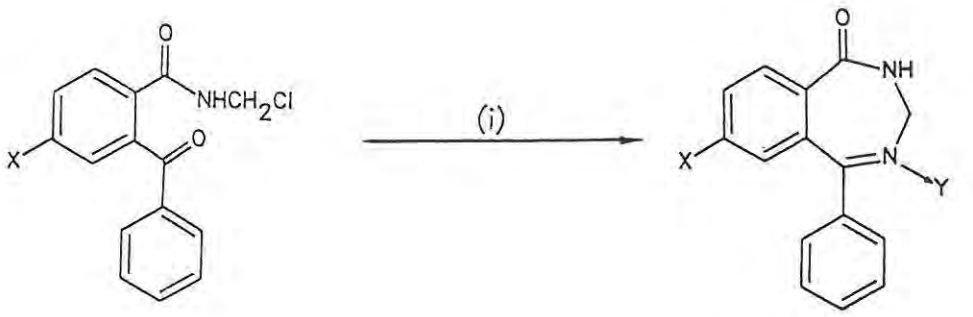
82 (a) R = R′ = H; R″ = Ph, X = H_2; (b) R = R′ = Cl, R″ = H, X = O

(e) 2,4 AND 1,3-BENZODIAZEPINE AND 1-BENZAZEPINE DERIVATIVES

A brief review of the chemistry and pharmacology of these compounds merits consideration. 5-Phenyl-2,3-dihydro-1*H*-2,3-benzodiazepine **84**(a) was isolated from the reaction of *N*-chloromethyl-(2-benzoyl)benzamide **83** with aqueous ammonia in dioxane (Scheme 25).[59] Oxidation of **84**(a) with *m*-chloroperbenzoic acid (MCPBA) afforded N^2-oxide **84**(b) and the oxirane derivative **84**(d) as a by-product. Pharmacological tests showed that the 2,4-benzodiazepinones **84**(a), (b) and (c) exhibit central nervous system activity. Compound **84**(c) possesses anticonvulsant activity comparable with that of diazepam.[59]

Tofisapam **85**, a 2,3-benzodiazepine, has anxiolytic activity, but unlike typical benzodiazepines does not bind to the benzodiazepine receptor.[2] 1,3,4,5-Tetrahydro-2*H*-1,3-benzodiazepin-2-ones **86**(a) and (b) have central nervous system activity.[60] Benzazepinone calcium channel blocking agents **88**(a), (b) and (c) are structural analogues of diltiazem **59** prepared by catalytic reduction of the intermediate **87**, followed by cyclisation with sodium methoxide (Scheme 26).[46,61] The pyrrolidinylmethyl derivatives **88**(b) have increased hypertensive activity and a duration of action similar to the trifluoromethyl substituted derivative **88**(c).[61]

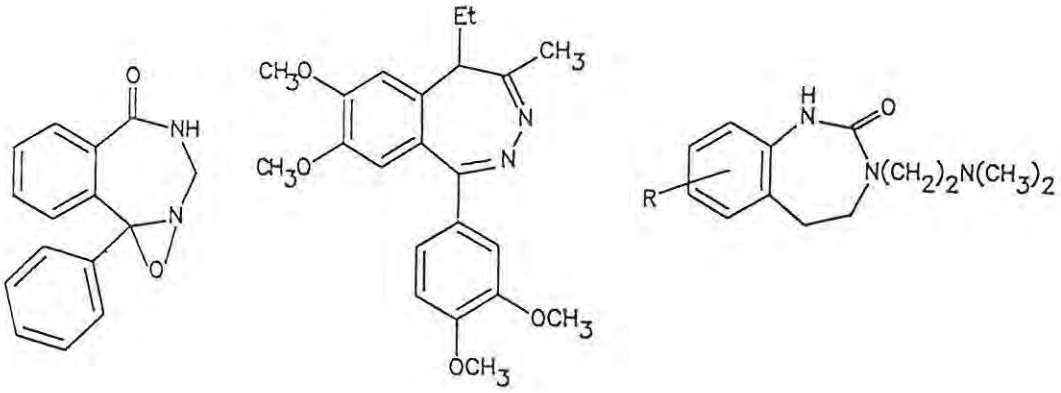
Although structural modifications gave rise to a large number of benzodiazepine derivatives, the need for ligands with high activity and selectivity is still a matter of great concern. Intensive research has continued to date with the aim of producing drugs which have a narrower spectrum of biological activity, *i.e.*, which act more specifically as either anxiolytics, muscle relaxants or hypnotics.[2]



83

84 (a) X = H, Y = void;
(b) X = H, Y = O;
(c) X = Cl, Y = void

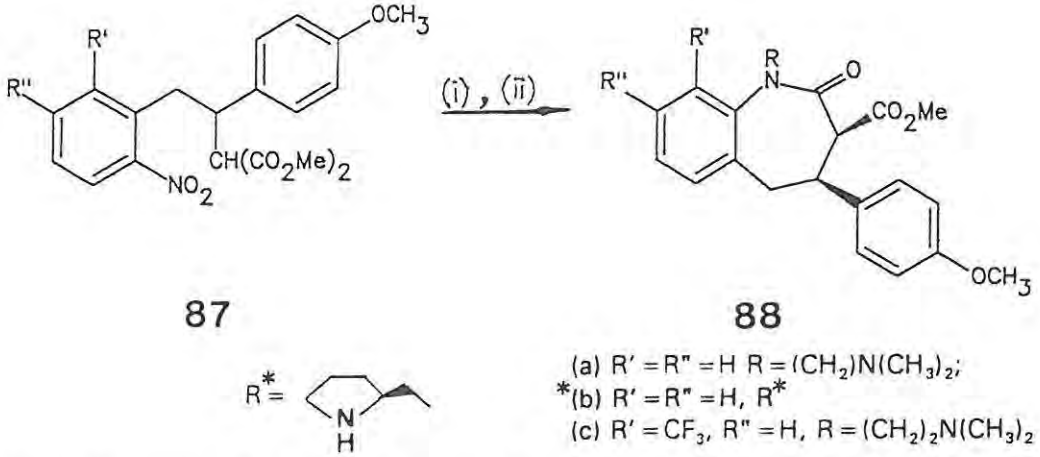
Scheme 25 Reagents: (i) NH_3 (aq), dioxane



84(d)

85

86



87

88

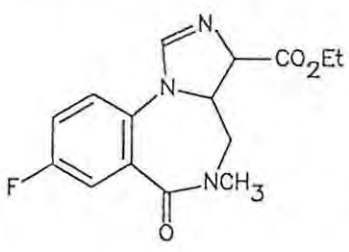
(a) R′ = R″ = H R = $(CH_2)N(CH_3)_2$;
(b) R′ = R″ = H, R
(c) R′ = CF_3, R″ = H, R = $(CH_2)_2N(CH_3)_2$

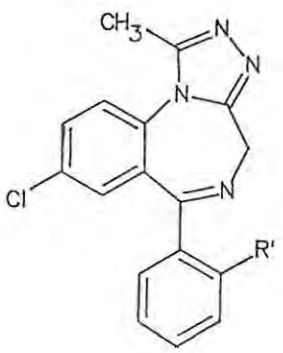
Scheme 26 Reagents: (i) H_2, Pd/C; (ii) NaOMe

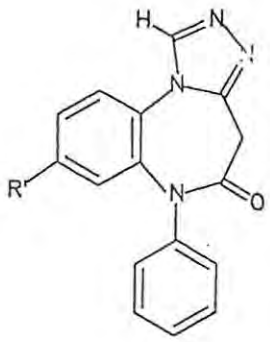
(f) TRICYCLIC BENZODIAZEPINE DERIVATIVES

One of the novel developments in the field of benzodiazepine chemistry is the synthesis of derivatives containing an additional ring fused to the diazepine nucleus. Some of these compounds and their derivatives have been found to have enhanced potency and novel biological activity when compared to the parent benzodiazepines. Specific benzodiazepines have been prepared and are able to block rapidly and completely the action of benzodiazepines by interacting with the benzodiazepine receptor. Flumazenil (Ro15-1788) **89** was found to be a specific benzodiazepine antagonist and may be used for therapeutic application as an antidote in cases of intoxication due to overdoses of benzodiazepines.[2,62] This compound has also been used to counteract the side-effects of 3-methylclonazepam, a benzodiazepine which is effective for treating schistosomiasis and to antagonise the anticonvulsant effect of diazepam, but not of phenobarbitone, thus confirming its selectivity.[62,63] Flumazenil was discovered serendipitously by chemists searching for novel benzodiazepine receptor ligands with a more selective activity profile than the classical benzodiazepines.[62]

Derivatives of 1,4-benzodiazepines such as alprozalam **90**(a) and triazolam **90**(b) have anxiolytic and hypnotic activity, respectively.[2,49(a),64,65] 1,5-Benzodiazepine derivatives containing an additional ring, such as s-triazolo[4,3-*a*]-1,5-benzodiazepine **91**(a) and (b), have anticonvulsant activity.[2]



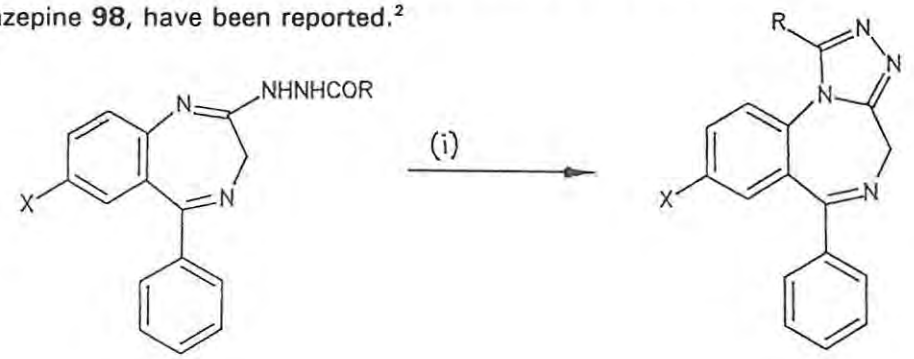




89 **90** (a) R′ = H; (b) R′ = Cl **91** (a) R′ = Cl; (b) R′ = CF_3

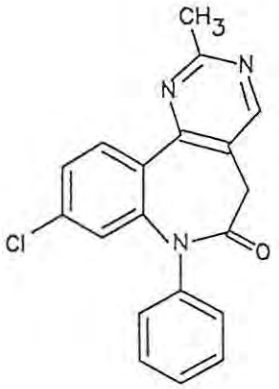
Several methods have been reported for the introduction of the third ring on the benzodiazepine nucleus.[6,49(a),54-77] One of the most commonly used methods involves cyclisation of the hydrazido derivatives **92** to afford tricyclic benzodiazepines **93** as shown in Scheme 27.[49(a),66,67,69,72] Modifications of these systems produce compounds with different pharmacological activities. The amino alkyl derivatives [**93**; X = Cl, R = $CH_2N(CH_3)_2$], for example, exhibit anti-anxiety and antidepressant activity.[64] The 8-bromo derivative [**93**; X = Br, R = $CH_2N(CH_3)_2$] has increased anxiolytic activity, but reduced antidepressant activity. Replacement of chlorine with hydrogen [**93**; X = H, R = $CH_2N(CH_3)_2$] led to a reduced anti-anxiety effect with retention of antidepressant activity.

The 9-chloro-5,7-dihydro-2-methyl-7-phenylpyrimido[5,4-*d*]-1-benzazepin-6(6*H*)-one **94**, prepared through a series of steps from *α*-tetralone, showed pharmacological activity indicative of a potential central nervous system anxiolytic.[75] Cloxazolam **95**, a 1,4-benzodiazepine with an additional ring at positions 4 and 5 of the diazepine nucleus, was found to have greater sedative activity than diazepam.[2,22] The 1,5-benzothiazepine derivatives **96** which have the additional ring at positions 1 and 2 of the heterocyclic ring have been prepared from the hydrazino derivative **62** by a similar method to that outlined in Scheme 27.[49(a)] The pyrano[2,3-*c*]-1,5-benzodiazepines **97**(a) and (b) were prepared by reacting arylidene azalones **41** with malononitrile and ethylcyanoacetate, respectively[23] (Scheme 28). 2,4-Benzodiazepine derivatives with an additional ring at positions 1 and 2, for example, the imidazolo[2,1-*a*]-2,4-benzodiazepine **98**, have been reported.[2]



92 **93**

Scheme 27 Reagents: (i) heat



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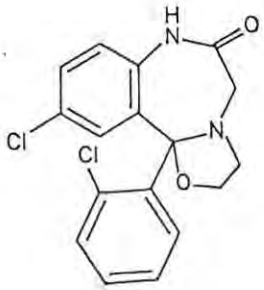

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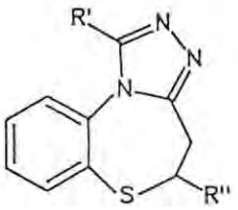

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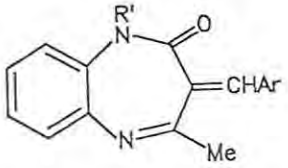
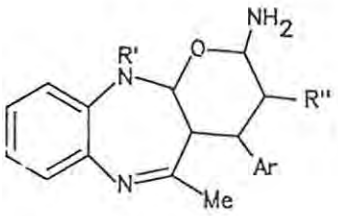


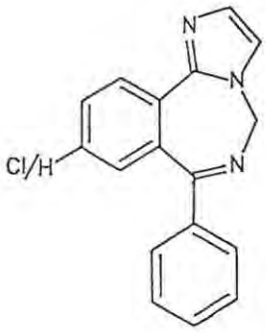
41

(i)



97 (a) R" = CN (b) R" = CO_2H

Scheme 28 Reagents: (i) $NCCH_2R"$

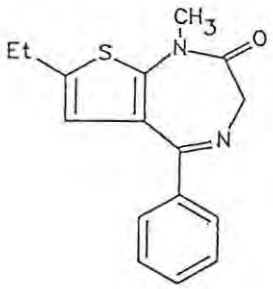


98

(g) "HETERODIAZEPINES"

In these compounds the fused benzo ring has been replaced by a heterocyclic ring, and these compounds resemble benzodiazepines in the overall shape, chemical properties and pharmacological activities. The 1,4-benzodiazepines **99** and **100** have anxiolytic and hypnotic properties, and the latter compound has anxiolytic activity in test animals.[2] The pyridothiazepinone skeleton is accessible by treating 2-mercapto-3-aminopyridine with 3-bromopropionic acid.[78] A novel, general and effective synthetic approach to *N*-substituted and unsubstituted 2-arylpyrido[2,3-*b*]-1,5-thiazepin-4-(5*H*)-ones **103** involves reacting aromatic thiocarboxylates with anions of the 2-chloro-3-acetamidopyridines **102** (Scheme 29).[78]

The synthesis of a wide range of benzodiazepine derivatives has led to a better understanding of structural effects on activity. The structure of the drug and its mode of action, *i.e.* where and how it acts, are major factors in the development of new, more effective drugs with fewer side effects.



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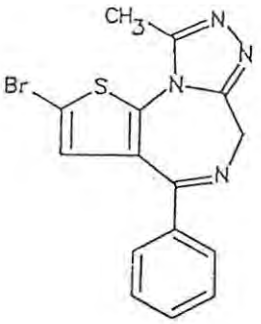
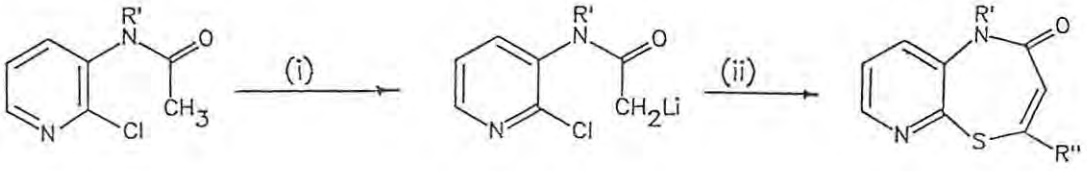


100



101 **102** **103**

Scheme 29 Reagents: (i) LDA, THF; (ii) R"C(S)OEt, dioxane

1.1.3 LIMITATIONS OF THE BENZODIAZEPINES

The high therapeutic indices associated with benzodiazepines gave them advantages over the barbiturates which they have almost replaced. Until recently, benzodiazepines have been considered remarkably safe, with no side effects. It has been discovered, however, that simultaneous intake of benzodiazepines with other drugs or alcohol can be dangerous in some patients.[4,79,80] Drowsiness and fatigue are also problems associated with the use of benzodiazepines.[79,80] The development of tolerance and the risk of drug dependence constitute the main disadvantages of the use of benzodiazepines.[80]

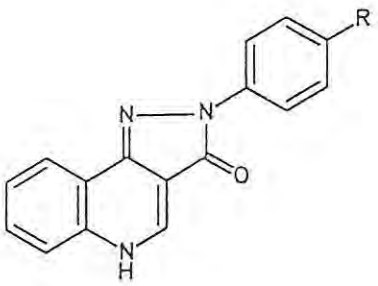
1.2 DISCOVERY OF BENZODIAZEPINE RECEPTORS AND THE MODE OF ACTION OF BENZODIAZEPINE LIGANDS

1.2.1 DISCOVERY OF BENZODIAZEPINE RECEPTORS

The discovery that certain membrane receptors may be blocked by compounds which stimulate or inhibit a biological event led to intense research on the nature of the receptors. In the past, neurotransmitter receptors were studied by indirect methods, some of which involved observing electrical, behavioral and biochemical changes associated with systemic applications of drugs.[81] In some cases, organs believed to contain receptors were excised and the drug under investigation was applied to solutions bathing the tissue and the biological response was then measured. In such cases, the tissue preparations have to be stable, a condition very difficult to achieve. These indirect methods could not reveal the direct interaction between the ligand in question and the receptor. These difficulties were obviated by radioactive assay which monitors the direct interaction of a radioactive ligand with a receptor.

The use of equilibrium-binding techniques led to the discovery of specific high-affinity binding sites for the benzodiazepines in the mammalian central nervous system (CNS).[82,83] These sites were discovered independently in 1977 by H. Möhler and T. Okada, and R. Squires and C. Braestrup.[3] The high-affinity binding of tritium-labelled diazepam (^{3}H-diazepam) to membranes in brain homogenates containing benzodiazepine receptors was a decisive advance in the characterisation of benzodiazepine receptors. It was observed that ^{3}H-diazepam bound to the membranes in brain homogenates in a saturable manner may be specifically displaced by other benzodiazepine ligands.[2,82,83] Other psychoactive drugs such as barbiturates and meprobamate which have similar pharmacological profiles to the benzodiazepines did not influence diazepam binding.[7,83,82]

Although the benzodiazepine receptor has been found to be highly selective for benzodiazepine analogues, some chemically unrelated compounds also bind to the receptor with moderate affinity. 2-Arylpyrazolo[4,3-*c*]-quinolin-3-ones 104, show high affinity for benzodiazepine receptors.[84] The high binding affinity of non-benzodiazepine compounds makes it difficult to generalise the molecular requirements of the recognition site of the receptor itself. Nevertheless, the ability of most benzodiazepines to displace bound ^{3}H-diazepam indicates that the binding sites are the pharmacological receptors through which these drugs produce their effects. Displacement potencies which have been found to correlate with pharmacological activity are considered to be predictive of anxiolytic activity.[2,63,82]



104

The presence of specific benzodiazepine receptors in rat[82] and human[83] brain has now been established. Initial studies on the distribution of brain benzodiazepine receptors indicated that they occur predominantly in the glial cells.[4,85] Current evidence from autoradiographic studies support the view that these receptors occur on neuronal cells.[4] These receptors exhibit differential topographical distribution in the CNS of mammals including man.[2,7,63,85] Benzodiazepine receptor heterogeneity has been demonstrated by benzodiazepine ligands that show moderate affinity to receptors in the rat cerebral cortex but higher affinity to receptors in the cerebellum.[63] High-affinity binding sites for some benzodiazepines have also been located in the kidney, liver, heart, lung and small intestine.[4,7,83] These binding sites possess different pharmacological specificity compared to analogous brain sites. For example, a specific ^{3}H-diazepam binding site in homogenates of rat kidney and liver has low affinity for ^{3}H-diazepam and very high affinity for the test compound (Ro5-4864).[83]

1.2.2 MODE OF ACTION OF BENZODIAZEPINES

Ligands occupying benzodiazepine receptors have been found to have a continuum of intrinsic efficacy, ranging from positive efficacy (anxiolytic, sedative and anti-convulsant agents), through zero efficacy (antagonists) to negative intrinsic efficacy (anxiogenic and pro-convulsant agents).[6] Results from electrophysiological studies relate the mechanism of benzodiazepines to the inhibition of the action of neural transmission by γ-butyric acid (GABA).[3,4,6,7,62,85,86] The benzodiazepine receptor is considered to be an integral part of a GABA-receptor complex.[63,86] GABA is thought to influence membrane conductance by affecting chloride channels in the neuronal membrane. Benzodiazepines have been found to increase the frequency with which chloride channels are opened by GABA.

The GABA-receptor is thought to exist in "high affinity" and "low affinity" states.[3] The state of this receptor is believed to be under the control of GABA-modulin,[3,86] a protein in the nerve cell membrane. Interaction between benzodiazepines and the receptor inactivates GABA-modulin, allowing the GABA-receptor to assume the "high affinity" state and making binding of GABA possible (Figure 1). The benzodiazepine-receptor interaction therefore modulates the efficacy of the GABA-effector system. The GABA-receptor itself does not appear to be a diazepam-specific binding site. This is supported by the fact that GABA agonists and antagonists fail to influence diazepam binding.[4,7,81,82,86] Benzodiazepines on the other hand, fail to bind to GABA-receptors. Despite these very significant findings, the relationship between ligand-receptor interaction and the mechanism of pharmacological response are not fully understood.

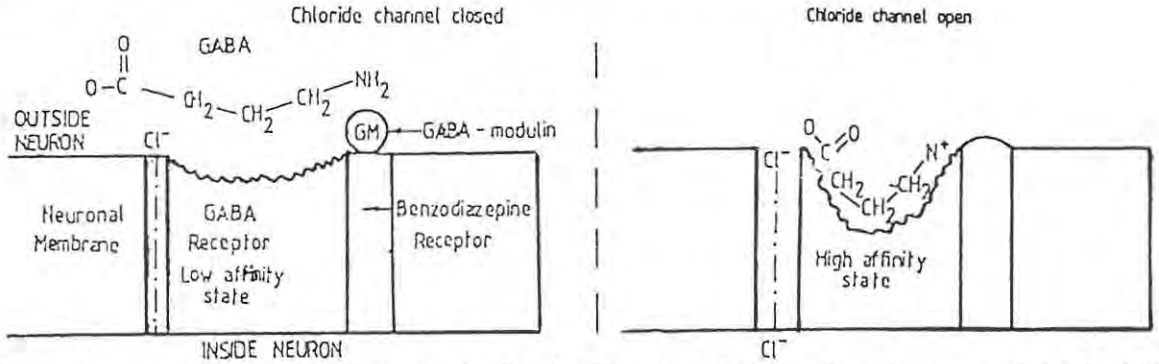


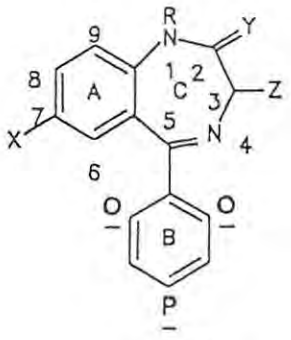
Figure 1: Diagram to represent the "high affinity" and "low affinity" states of the GABA receptor.[3]

1.3 STRUCTURE-ACTIVITY RELATIONSHIPS (SAR)

The biological activity of 1,4 and 1,5-benzodiazepine derivatives has been found to be sensitive to substituent (steric and electronic) effects[1,2,11,22,49(a),64,87,90] and the conformation of the 7-membered ring.[45,46,51]

1.3.1 SUBSTITUENT EFFECTS

The effects of substituents on the biological activity of benzodiazepine derivatives is well documented. It has been observed that selective manipulation of substituents in either rings A, B or C produces various effects on the CNS. For 1,4-benzodiazepines of the general type **105**, electron-withdrawing A-ring substituents (X = halogen, CF_3, NO_2 or CN) at position 7 increase biological activity.[1,2,22,87] Electron-donating groups at this position result in compounds with reduced or no activity. Any substituent at positions 6, 8 or 9 decreases the activity of the benzodiazepine. A C-ring methyl substituent at position 1 enhances activity while groups larger than methyl were found to reduce activity.[1,2,22] Compounds with a substituted amino-ethyl side chain in position 1 [**105**, R = $(CH_2)_2N(CH_3)_2$] show increased activity.[87] Decreased activity is also observed when the 2-oxo group is replaced with a methylene group as in medazepam (**105**, R = CH_3, Y = CH_2, Z = H, X = Cl).[2] Replacement of the carbonyl oxygen with sulphur also leads to compounds with reduced activity. The presence of halogeno, amino or alkoxy groups at position 3 results in compounds with increased CNS activity.[11] On the other hand, the presence of 3-hydroxyl group reduces activity but is accompanied by a more favourable ratio of activity to side effects.[11,22] Sulphur-containing substituents (**106**, Y = SH) lead to reduced activity compared to their hydroxy analogues.[11] A phenyl group at position 5 enhances activity while heterocyclic substituents at this position reduce activity.[2] Activity is also increased when the 5-phenyl ring bears *o*-chloro or *o*-fluoro substituents (mono- or disubstituted) but diminished by *para*-substituents.[1,2,22,87-9]



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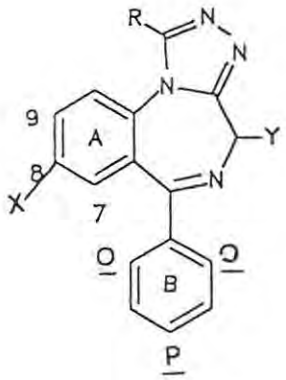

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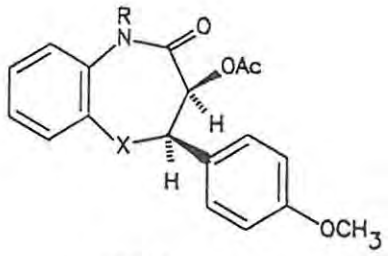
A trend in substituent effects similar to that found in compounds **105** is also observed for the tricyclic derivatives **106**.[49(a),63] The presence of *o*-chlorophenyl ring at position 5 and of chlorine or bromine at position 8 shows increased activity. The presence of these substituents together with the substituted alkylamino group [**106**; $R = CH_2N(CH_3)_2$] at carbon 1 leads to compounds exhibiting various biological effects. The 8-bromo derivative [**106**; $X = Br$, $R = CH_2N(CH_3)_2$] shows increased anxiolytic activity, but reduced antidepressant activity when compared to the 8-chloro derivative. Diminished anti-anxiety but increased antidepressant activity is observed for the 8-unsubstituted derivative [**106**; $X = H$].

Compounds in which the benzo-ring in compounds **105** has been replaced with a pyrazalo or thieno ring show similar general SAR patterns to those observed with classical benzodiazepines.[90] The N^4-oxide and 3-hydroxyl analogues retain activity when the 1-substituent (R) is a small alkyl group. Activity is also enhanced by *o*-fluoro or *o*-chloro substituents on the 5-phenyl ring but diminished by *para*-substituents.

1.3.2 CONFORMATIONAL EFFECTS

In addition to the known effects of the substituents on activity, the conformational properties of the diazepine nucleus are also believed to influence the biological activity of the benzodiazepines. In diltiazem compounds **107** of the benzoxazepine (X = O), benzothiazepine (X = S) and benzazepine ($X = CH_2$) series, it has been found that compounds in which the 2- and 3-substituents are cis to each other have increased activity; in these compounds, the trans-isomers were found to be less active or devoid of activity.[45,46,61] The significance of conformation will be explored in further detail in the discussion (See section 2.8 page 136).



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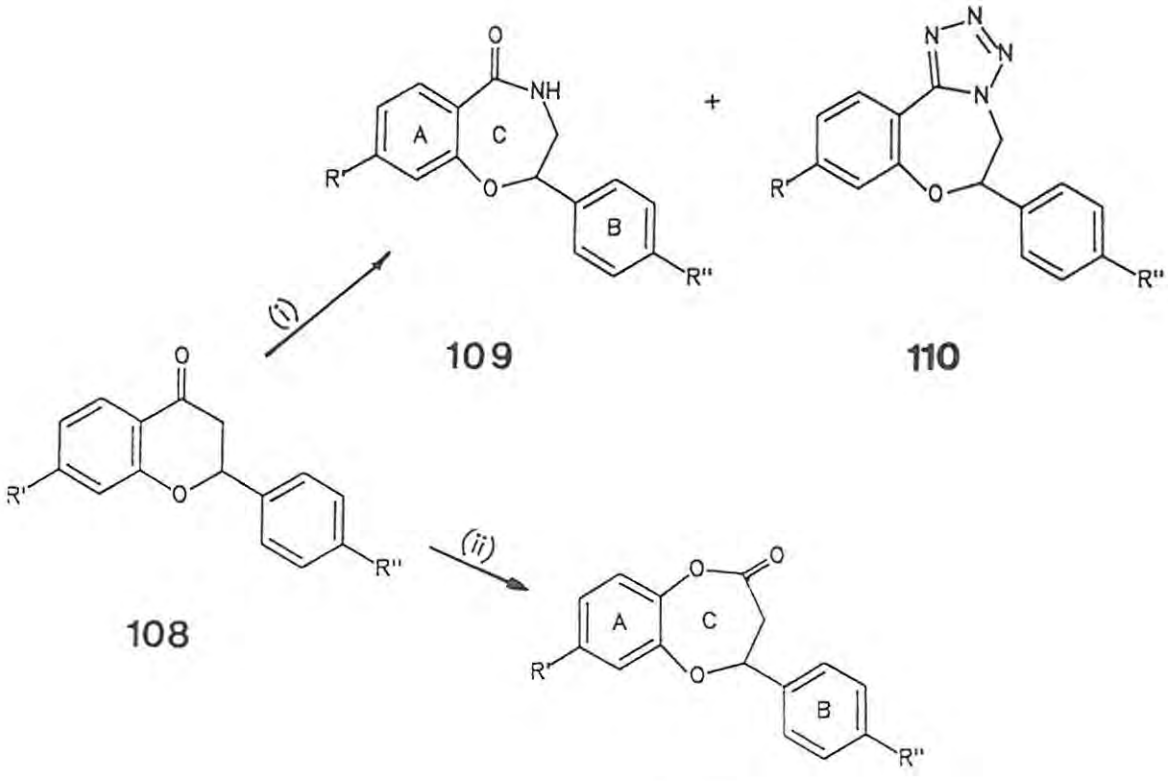
1.4 PREVIOUS WORK RELATED TO THIS PROJECT

Research is in progress, in our laboratory, on the synthesis and biological screening of compounds that have structural resemblance to potent benzodiazepine receptor ligands. Previous studies in the group have involved Schmidt rearrangement[91] and Baeyer-Villiger oxidation[92] of flavanone precursors **108** (Scheme 30). The Schmidt reaction afforded the 1,4-benzoxazepinones **109** and their tetrazolo derivatives **110**, while the Baeyer-Villiger oxidation afforded the 1,5-benzodioxepinone derivatives **111**. The tetrazolo derivatives **110** have structural resemblance to the potent benzodiazepine receptor ligand flumazenil **89** (see page 19). It is expected that by varying heteroatoms in the diazepine moiety and substituents on rings A and B the biological activity can be modified. In this project, attention has been concentrated on the Schmidt reaction to access a range of benzodiazepine analogues. A brief review of this reaction is considered below.



Scheme 30 Reagents: (i) $(CH_3)_3SiN_3$, CF_3CO_2H; (ii) MCPBA, CH_2Cl_2

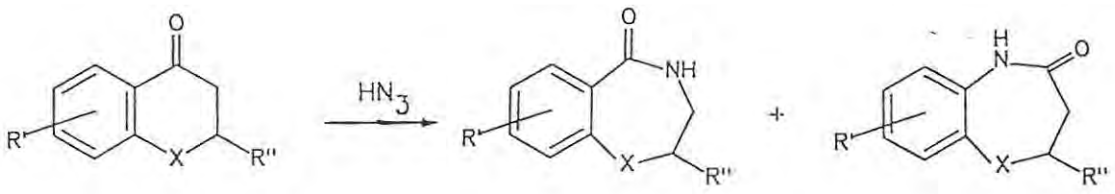
1.4.1 REVIEW OF THE SCHMIDT REACTION

The Schmidt reaction involving nitrogen insertion in carbonyl compounds was first reported in 1923.[93] The actual application of this procedure to cyclic carbonyl compounds, however, only gained interest in the 1960's.[94-8] In this method, ketones are converted to amides under the influence of hydrazoic acid. Huckle *et al.*[94] prepared the 1,4-benzoxazepinone derivatives **113** from chroman-4-ones (**112**; X = O, R* = H) using sodium azide in acidic medium (Scheme 31). In principle, for unsymmetrical compounds, such as chromanone, two regio-isomers, *viz.* 1,4- (**113**) and 1,5-benzoxazepinones (**114**) could be expected as products. However, the authors only isolated the 1,4-isomer from the reaction mixture. Evans and Lockhart[95] extended this reaction to substituted tetralones (**112**, X = CH_2) and also isolated the 1,4-isomer (**113**, X = CH_2, R* = H) as the only product.

Lansbury and Mancuso[96] studied the Schmidt and Beckmann rearrangement of substituted tetralones and their oximes and, in each case, only the 1,4-isomer was isolated. The effect of substituents on the outcome of the Schmidt reaction of substituted chroman-4-ones was studied extensively by Bhalerao and Thyagarajan.[97,98] The presence of alkyl, alkyloxy or halogeno substituents in the 6,7 or 8 positions led to the isolation of the 1,4-isomer. However, a bulky substituent at the 5-position led to the isolation of the 1,5-isomer as the major product. The Schmidt reaction of 1,2,3,4-tetrahydroquinolin-4-ones (**112**; X = NR; R* = H)[99] and thiochromanones (**112**; X = S, R* = H)[100] led to the formation of both 1,4 and 1,5-isomers in different ratios. The same reaction with thiochromanon-1-oxide gave the 1,5-isomer as the sole product.[101]

Krapcho and Turk[102] prepared a compound they believed to be 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5*H*)-one (**114**; X = O, R* = Ph) by reacting flavanone (**112**; X = O, R* = Ph) with sodium azide in acidic medium. However, this reaction was reinvestigated by Msiti and Rimatori,[103] who on the basis of structural analyses and molecular transformations characterised

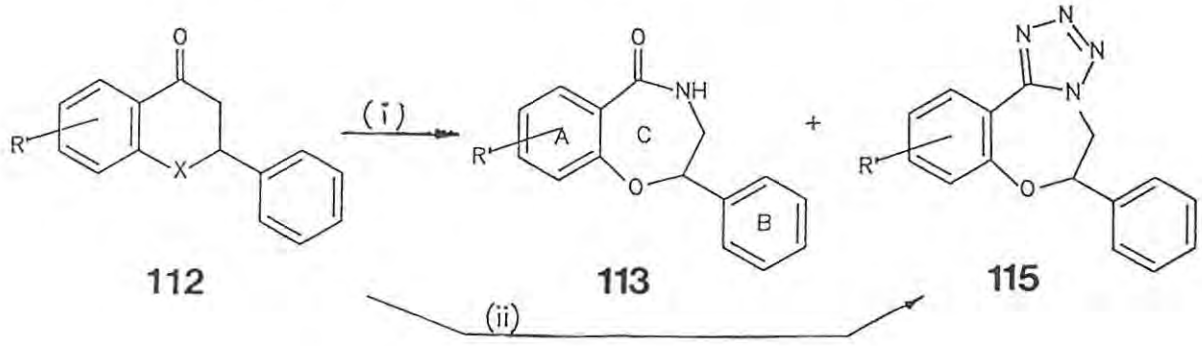
the product as 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**113**; X = O, R' = Ph). In the reaction mixture they also detected the presence of the 1,5-isomer (3%) and the tetrazolo[1,5-*d*] derivative of 2,3-dihydro-2-phenyl-1,4-benzoxazepinone (5%), as by-products. 2,3-Dihydro-2-phenyl-1,4-benzoxazepinone was also isolated by Misiti[104] *via* the Schmidt reaction of 2-hydroxychalcone. The Schmidt reaction of substituted flavanones was further investigated by Misiti and Rimatori[103(b)] and Levai and Bognár.[105] In all cases, the authors isolated the 1,4-isomers.



112 **113** **114**

Scheme 31

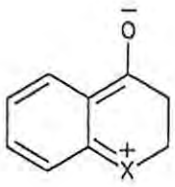
Litkei and Potany[106] isolated 1,4-benzoxazepinone **113** and its tetrazolo derivative **115** by reacting trimethylsilyl azide with flavanones in trifluoroacetic acid (Scheme 32). This reagent system was found to be milder than sodium azide in acidic medium and gave higher yields. The use of trimethylsilyl azide in dichloromethane in the presence of stannic chloride was shown to afford the tetrazolo derivative as the sole product.[106] The Schmidt reaction of 1-thioflavanone has led to the isolation of both 1,4- and 1,5-isomers in a 1:1 ratio.[107(a)] The same reaction with 1-thioflavanone-1,1-dioxide, however, afforded the 1,5-isomer as the sole product.[107(b)]

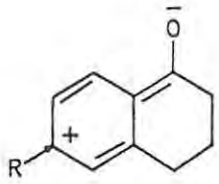


112 **113** **115**

Scheme 32 Reagents: (i) $(CH_3)_3SiN_3$, CF_3CO_2H; (ii) $(CH_3)_3SiN_3$, $SnCl_4$, CH_2Cl_2

The Schmidt reaction, which involves nitrogen insertion, often has advantages over the previously described cyclisation methods for preparing benzodiazepine analogues. The reaction conditions are milder, yields are often higher and, in some cases, both the 1,4- and 1,5-isomers can be isolated in a single reaction. The formation of either one or both regio-isomers can be ascribed to electronic and steric factors. The 1,4-isomer is the result of alkyl migration while the 1,5-isomer arises from aryl migration. The formation of the 1,4-isomer is attributed to conjugation between the phenyl ring and the carbonyl group of the precursor **116**. The resulting partial double bond character of the Ar-CO bond would inhibit aryl migration and thus favour alkyl migration to give the 1,4-isomer. The presence of an electron-donating group at positions 6, 7 or 8 may be expected to stabilise the partial double bond.





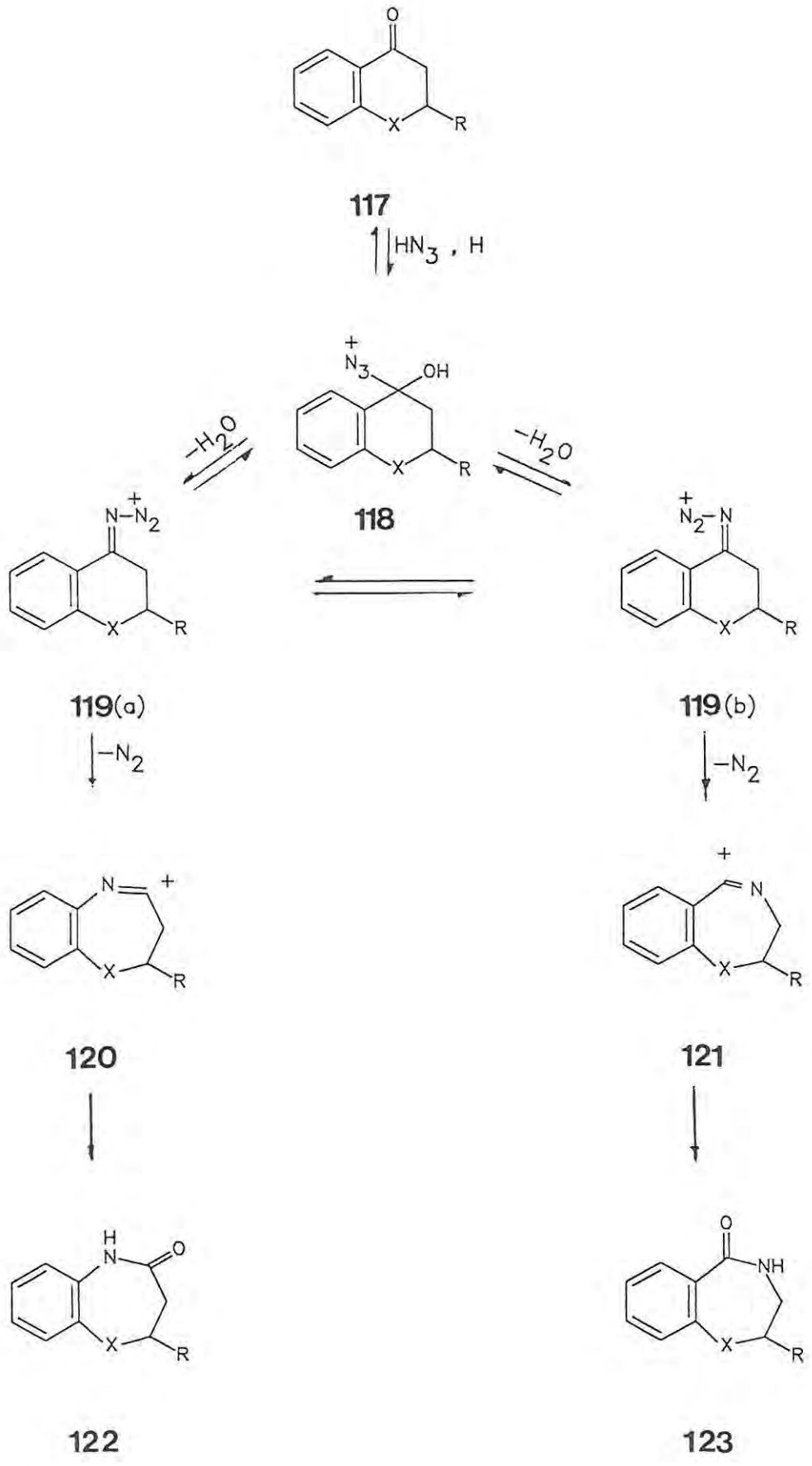
116

X = O, S or NHR

R = electron-releasing group (by inductive effect or resonance effect)

Much work has been carried out in elucidating the mechanism of the Schmidt reaction in order to explain the formation of either one or both isomers.[98,103(b),105,107(a),108] The generally accepted mechanism suggests that the carbonyl group is attacked by hydrazoic acid to form the azidohydrin **118** which dehydrates to the iminodiazonium ion **119** (Scheme 33).[98,105,107(a),108] The latter is believed to exist in *anti* (*E*) **119(a)** and *syn* (*Z*) **119(b)** configurations (relative to the benzo ring), and the ratio of the final products is determined by the ratio of these configurations. Migration is believed to occur when the migrating group is *anti* to the diazonium nitrogens. In the case of tetralones and 2,2-dimethyl-4-chromanones with bulky substituents at the 5-position the *anti*-form will be less favoured and thus aryl migration occurs to form the 1,5-isomer. In the case of chromanones, tetralones and flavanones the iminodiazonium ion leading to the final product exists predominantly in the *anti*-form to afford the 1,4-isomer.

In contrast with the Baeyer-Villiger oxidation of flavanones which affords 1,5-benzodioxepinone derivatives *via* aryl migration, the Schmidt reaction gives the 1,4-benzoxazepinone derivatives from the same precursors *via* alkyl migration (see Scheme 30, page 30). These results motivated us to study the kinetics of both the Schmidt and Baeyer-Villiger reactions of flavanones in order to explain the observed reversal of regioselectivity.



Scheme 33

1.5 AIMS OF THE CURRENT INVESTIGATION

In the preceding sections, the structure, preparation and pharmacology of benzodiazepine analogues have been reviewed. The anxiolytic, anticonvulsant, muscle relaxant, sedative and hypnotic properties of these compounds have made them the most widely prescribed minor tranquillisers in current use. It was also realised that their biological activity is influenced both by substituent and conformational effects.

Specific aims of this project have included:

(i) The synthesis, using the Schmidt reaction and other methods, of a range of benzodiazepine analogues in which the substituents and ring heteroatoms are varied.

(ii) An investigation of selected reactions of the benzodiazepine analogues.

(iii) Detailed mass spectrometric and NMR (^{1}H and ^{13}C) spectroscopic studies of the prepared products.

(iv) The kinetic-mechanistic study of the Schmidt reaction of flavanone precursors, using ^{1}H NMR spectroscopy.

(v) An evaluation of the ability of the synthetic analogues to compete with diazepam for specific binding to the receptors, using radioreceptor assay technique.

(vi) The conformational analysis of the benzodiazepine analogues using ^{1}H DNMR spectroscopy, X-ray crystallography and computer modelling techniques, to explore the effect of conformation on binding affinity.

2. DISCUSSION

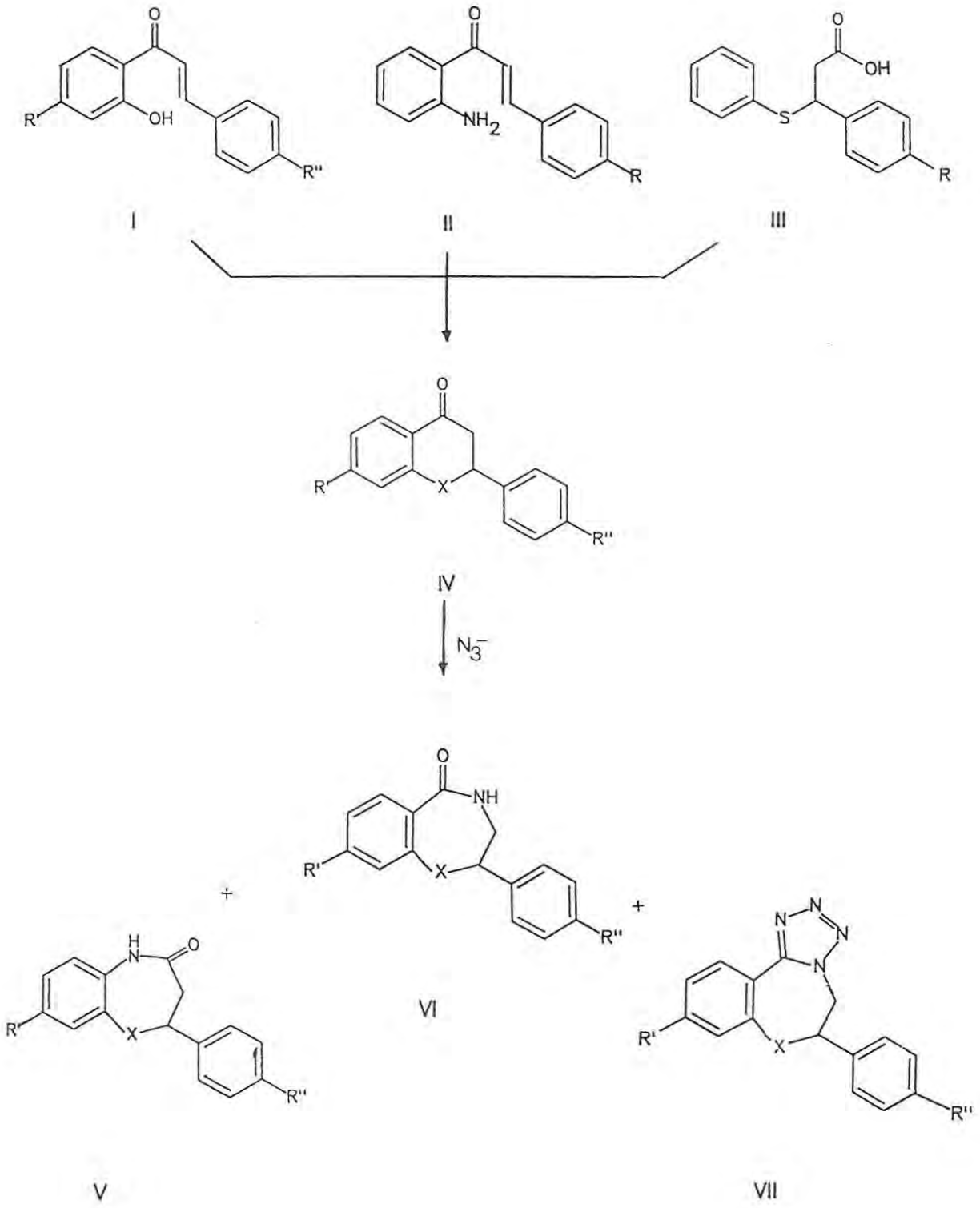
2.1 SYNTHESIS OF BENZODIAZEPINE ANALOGUES

In general, access to the required benzodiazepine analogues **V-VII** was achieved through the Schmidt reaction of specially prepared flavanone (**IV**, X = O), 4-quinolone (**IV**, X = NH) and 1-thioflavanone (**IV**, X = S) precursors (Scheme 34). These precursors were prepared, in turn, from various substrates including 2-hydroxychalcones (**I**), 2-aminochalcones (**II**) and ß-phenylmercaptodihydrocinnamic acids (**III**). The reactivity of the flavanoid ketones **IV** towards the azido ions as well as patterns of the nitrogen insertion make them useful precursors for the synthesis of benzodiazepine analogues *via* the Schmidt reaction. However, these precursors exhibit valuable pharmaceutical properties in their own right. For example they are used in the treatment of respiratory tract and liver diseases.[109] In some cases, the benzodiazepine analogues were also obtained by other methods involving cyclisation reactions. The benzodiazepine analogues were also subjected to ring-chlorination, thionation, alkylation and attempted dehydrogenation.

2.1.1 PREPARATION OF PRECURSORS

(a) FLAVANONES

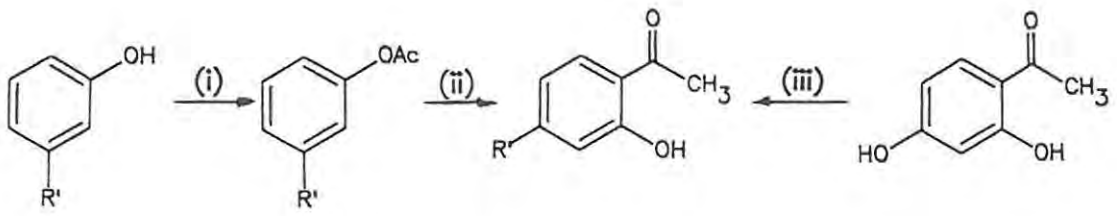
These compounds constitute one of the most important classes of the flavanoids and are found almost exclusively in higher plants.[110] The typical laboratory precursors for the synthesis of flavanones are 2-hydroxychalcones prepared, in turn, by the condensation of 2-hydroxyacetophenones with benzaldehydes.


O
R'
OH
R''
I
O
NH2
R
II
O
OH
S
R
III
O
R'
X
R''
IV
N3−
O
NH
R'
X
R''
VI
+
H
N
O
R'
X
R''
V
+
N
N
N
N
R'
X
R''
VII

Scheme 34

(b) **4-SUBSTITUTED-2-HYDROXYACETOPHENONES**

The 4-halogenoacetophenones **130-132** were prepared *via* Fries rearrangement[111] of the corresponding acetates **127-129**, which were obtained, in turn, by acetylation of the respective 3-halogenophenols **124-126** (Scheme 35).[112] The 3-halogenophenyl acetates **127-129** were prepared in high yield (*ca.* > 86%) by treating the sodium salts of 3-halogenophenols **124-126** with acetic anhydride and were distinguished from their precursors by the appearance of the ^{1}H NMR acetate signal at *ca.* δ 2.2 ppm. The acetates were heated at high temperature (*ca.* 175°C) with anhydrous aluminium chloride to direct the course of the reaction to the *o*-hydroxyacetophenones rather than the *p*-analogues.[111] Reappearance of the ^{1}H NMR hydroxyl signal at *ca.* 12.0-12.8 ppm distinguished the required products from their parent 3-halogenophenyl acetates. The 2-hydroxy-4-methoxyphenyl acetate **134** was obtained by methylation of resacetophenone **133** with dimethyl sulphate as described by Zaman *et al.* (Scheme 35).[113]



133

R'			
F	124	127	130
Cl	125	128	131
Br	126	129	132
OCH_3	-	-	134

Scheme 35 Reagents: (i) NaOH(aq), Ac_2O, 0-5°C, 1h; (ii) $AlCl_3$, 170-180°C, 2h; (iii) $(CH_3)_2SO_4$, Na_2CO_3, acetone, heat, 6h

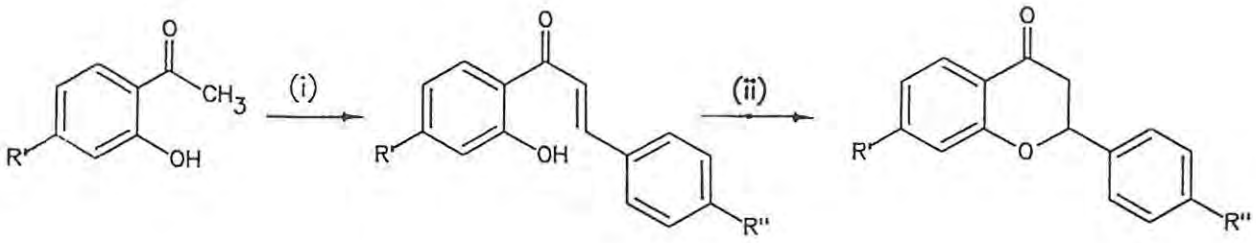
(c) 2-HYDROXYCHALCONES

One of the previously reported methods for the preparation of 2-hydroxychalcones involves the acetylation of phenols with cinnamoyl chloride.[114] However, this procedure requires both the *para*-position and the phenolic hydroxyl group to be protected in order to prevent formation of unwanted products. In this project, the substituted 2-hydroxychalcones **135-143** were prepared by the condensation of the 4-substituted-2-hydroxyacetophenones **130-134** under basic conditions (Scheme 36).[111] 1-(2-Hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one **144**, however, was prepared at room temperature under acidic conditions, since attempted condensation of 2-hydroxyacetophenone **135** with 4-nitrobenzaldehyde, under basic conditions, gave a complicated mixture containing 4'-nitroflavanone **153** (20%); isolated by flash chromatography. 4'-Nitroflavanone **153** has been isolated previously in 70% yield by condensation of 4-nitrobenzaldehyde and 2-hydroxyacetophenone in basic medium, but under somewhat different conditions; the authors also did not detect the expected chalcone.[115] The chalcones were easily distinguished from their precursors by their bright yellow colour and the absence of acetyl signal in their ^{1}H NMR spectra (Fig. 2). They also showed the aromatic and vinyl proton signals in the region *ca.* δ 7.0-8.0 ppm and the phenolic proton signal at *ca.* δ 12.7-13.3 ppm.

(d) CYCLISATION TO FLAVANONES

The most widely used method for the construction of the 2-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one skeleton involves the cyclisation of 2-hydroxychalcones by bases,[115] acids,[116] silica,[117] light,[118,119] a $NiCl_2$-Zn-KI reagent system,[120] and Co(II) Schiff-base complexes.[121] A recently reported method involves the cyclisation of 3-bromo-1-phenylprop-2-ynylaryl ethers using mercury(II) trifluoroacetate.[110] The mechanisms of cyclisation of chalcones to flavanones using both acid and base catalysts have been studied previously.[115,122-126] Flavanones are readily isomerised to chalcones by traces of base, making it difficult to obtain them in appreciable yield in basic medium. In this project, acid catalysis was used and chalcones were typically cyclised to flavanones using orthophosphoric acid in boiling ethanol (Scheme 36).[110] Cyclisation of 2-hydroxy-4'-nitrochalcone **144**, however, was achieved in refluxing glacial acetic acid in the presence of orthophosphoric acid. Although ring closure of the 2-hydroxychalcones under acidic conditions was incomplete after 5 days further heating failed to improve the yield and reactions were normally allowed to run for this period.

Several methods have been used for separating flavanones from chalcones. Gas chromatography, for example, has been used to purify flavanones,[127] but is inappropriate for producing the quantities necessary for a multi-step synthesis. A method by Chen and Chang[111] makes use of the different solubilities of flavanones and chalcones. In this method the reaction mixture is concentrated and the flavanone is allowed to crystallise slowly from the reaction mixture. Since some chalcone also crystallises along, the flavanone must be purified by repeated crystallisations leading to low yields. In our approach, the ethanol was evaporated, water was added and the product was then extracted into chloroform. The crude product was purified by flash chromatography[128] (using toluene or benzene as eluent) to afford the colourless flavanone and the unreacted chalcone precursor. Advantages of this purification method include reduced purification time and reasonable yields (*ca.* > 43%).



R'		R'	R"		
F	**130**	F	H	**136**	**145**
Cl	**131**	Cl	H	**137**	**146**
Br	**132**	Br	H	**138**	**147**
OCH_3	**134**	OCH_3	H	**139***	**148**
H	**135**	H	F	**140**	**149**
H	**135**	H	Cl	**141**	**150**
H	**135**	H	Br	**142**	**151**
H	**135**	H	OCH_3	**143**	**152**
H	**135**	H	NO_2	**144****	**153*****

***139** prepared using, 4-R"-ArCHO, NaOH(aq), 0-5°C, 5d.
****144** prepared using acetic acid, H_2SO_4, 24-27°C, 24h
*****153** prepared using H_3PO_4, acetic acid, heat, 2d.

Scheme 36 Reagents: (i) 4-R"ArCHO, KOH(aq), ethanol, 0-5°C, 5d; (ii) H_3PO_4, ethanol, heat, 5d.

Flavanones are distinguished from their precursors by the absence of phenolic hydroxyl signal in the region *ca.* δ 12.7-13.3 ppm and the appearance of three double doublets at *ca.* δ 2.9, 3.0 and 5.0 ppm; the first two multiplets corresponding to the methylene protons and the third to the methine proton (Fig. 2). ^{13}C NMR Spectroscopy of 7-substituted flavanones has been studied before.[128] In this work we report the extension of this study to flavanones with halogeno, nitro and methoxy substituents at either position 7 or 4' of the A- or B-ring, respectively. Spectra were recorded in deuterated chloroform ($CDCl_3$) and the chemical shifts were assigned by comparison with those of flavanone[128] and consideration of known substituent effects for halogeno, methoxy, and nitro groups.[130] From the chemical shift data detailed in Table 1, several trends are observed. A- and C-Ring chemical shifts of the 4'-substituted derivatives **145-148**, and those of the B- and C-rings of the 7'-substituted

derivatives **149-153** are insensitive to variations of the R' and R"-substituents, respectively. Significant changes in chemical shifts which are substituent influenced are observed for the substituted A- or B-ring. The carbon atom to which fluorine or a methoxy group is attached is deshielded, whereas the carbon atoms *ortho* and *para* to these substituents are shielded. The shielding effect of the *ortho* and *para* carbon atoms in these cases is associated with the electron-donating effect (by resonance) of the methoxy group and fluorine. The coupling constants (J_{CF}) of the 7'- and 4'-fluoro substituted derivatives **145** and **149** were found to be comparable with the calculated values[131] and were significant in the assignment of the peaks. The carbonyl carbon resonates in the narrow range *ca.* δ 190-192 ppm, while the aliphatic C-3 and C-2 nuclei resonate at *ca.* δ 44.3-44.5 and δ 78.5-80.1 ppm, respectively.

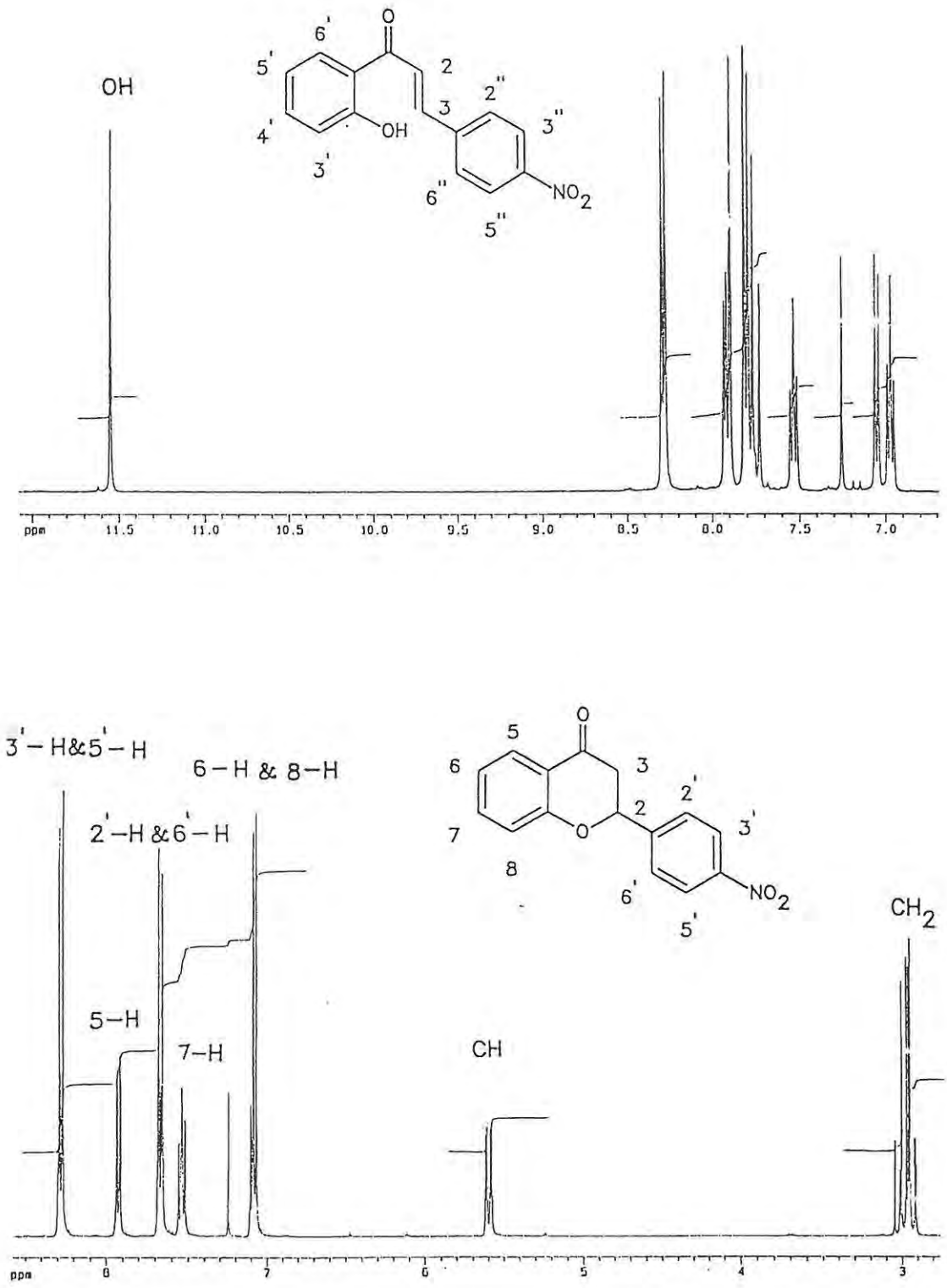
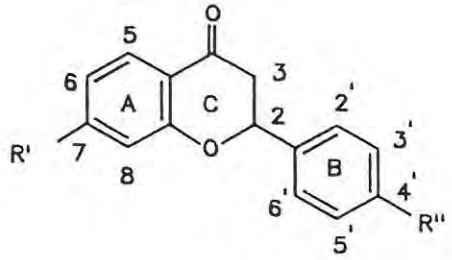


Figure 2: The ^{1}H NMR spectra of 2-hydroxy-4'-nitrochalcone 144 and 4-'nitroflavanone 153

Table 1: **^{13}C NMR chemical shift data (ppm) of the flavanone derivatives in $CDCl_3$ (δ 77.0 ppm)**



No	R′	R"	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1′	C-2′/ C-6′	C-3′/ C-5′	C-4′	OMe
189`	H	H	79.4	44.5	191.6	120.8	126.9	121.4	136.0	118.0	161.4	138.6	126.0	128.7	128.6	
145	F	H	80.1	44.2	190.3	117.9[a]	129.5[b]	110.0[c]	167.5[d]	104.9[e]	163.1[f]	138.3	126.1	128.8	128.9	
146	Cl	H	79.9	44.4	119.5	128.2	128.2	122.4	142.0	118.3	151.8	138.2	126.1	128.9	128.9	
147	Br	H	80.0	44.4	119.9	128.3	128.3	125.3	130.5	121.4	151.7	138.2	126.1	128.9	128.9	
148	OMe	H	79.9	44.3	114.8	128.7	128.7	110.2	155.2	100.9	163.5	138.8	125.1	128.7	128.7	55.0
149	H	F	78.9	44.6	117.9	129.5	129.5	110.0	167.5	104.9	163.1	138.1[g]	128.0[h]	115.7[i]	162.8[j]	
150	H	Cl	78.7	44.4	120.8	127.0	127.0	121.7	136.1	118.0	161.2	137.2	127.4	128.9	134.4	
151	H	Br	78.7	44.4	120.8	127.0	127.0	121.1	136.2	118.0	161.2	137.8	127.7	131.9	122.6	
152	H	OMe	79.3	44.4	120.9	127.0	127.0	121.4	136.0	118.1	161.6	130.7	127.7	114.1	159.9	53.3
153	H	NO_2	78.3	44.6	120.9	127.2	127.2	122.2	136.5	118.0	160.9	145.8	126.8	124.1	148.0	

`**189** 98% purchased from Aldrich Chemical Company

145 (a) $^4J_{CF}$ 2.01Hz; (b) $^3J_{CF}$ 11.07Hz; (c) $^2J_{CF}$ 22.14Hz; (d) $^1J_{CF}$ 256.6Hz; (e) $^3J_{CF}$ 14.09Hz and
149 (f) $^4J_{CF}$ 3.02Hz; (g) $^3J_{CF}$ 8.05Hz; (h) $^2J_{CF}$ 22.1Hz; and (i) $^1J_{CF}$ 247.5Hz

2.1.2 4-QUINOLONES

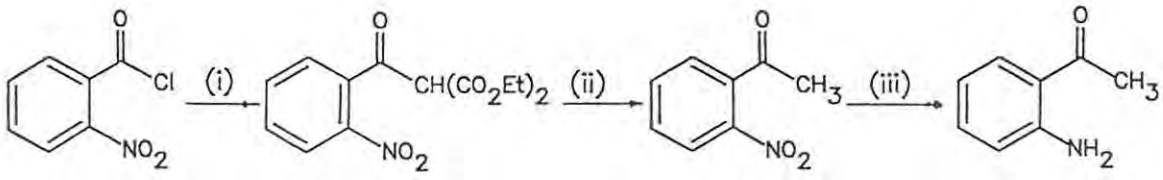
These compounds differ from the flavanones in that the oxygen atom at position 1 has been replaced by an amino group. 2-Phenyl-1,2,3,4-tetrahydro-4-quinolone, and its *N*-tosyl and *N*-acetyl derivatives were first prepared from 2-aminochalcone and its *N*-tosyl and *N*-acetyl derivatives by Mannich,[132] Deisbach[133] and Janzśo,[134] respectively. This cyclisation method was found to be more efficient and more general than an alternative approach involving cyclisation of acrylates, obtained from aryl amines with ß-ketoesters.[136] In this project, the 4-quinolone skeleton was constructed *via* the cyclisation of 2-aminochalcones which were obtained by the aldol condensation of 4-substituted benzaldehydes with 2-aminoacetophenone.

(a) 2-AMINOCHALCONES

2-Aminoacetophenone **157**, a precursor of 2-aminochalcones **158-163** was prepared from 2-nitrobenzoyl chloride **154**[136] *via* a series of steps including the reduction of 2-nitroacetophenone **156** (Scheme 37).[137] A convenient method for the preparation of 2-nitroacetophenone **156** consists of acylation of the magnesiumethoxy derivative of diethyl malonate with 2-nitrobenzoyl chloride **154**, followed by hydrolysis and decarboxylation of the two ester groups of the resulting diethyl acylmalonate intermediate **155** in the presence of aqueous acetic and sulphuric acids.[138,139] Alternative methods involving Friedel-Crafts, Grignard and nitration reactions have been reported to be inappropriate for the synthesis of 2-nitro-acetophenone.[138]

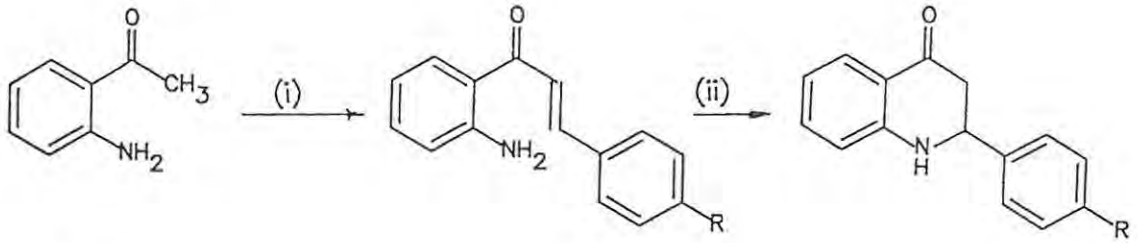
2-Aminoacetophenone **157**, which was distinguished from the nitroacetophenone precursor by the appearance of the amino protons signal in the ^{1}H NMR spectrum of the former, was condensed with 4-substituted benzaldehydes in ethanol in the presence of a catalytic amount of sodium hydroxide (Scheme 38).[140] This reaction proceeds in shorter times than those required for the preparation of the corresponding 2-hydroxychalcones and the yields are also high. The

^{1}H NMR spectra of the 2-aminochalcones (in $CDCl_3$) show the amino, vinyl and aromatic proton signals in the region *ca.* δ 6.0-8.0 ppm (Fig. 3).



154 **155** **156** **157**

Scheme 37 Reagents: (i) $CH_3CH_2OMgCH(CO_2Et)_2$, Et_2O, heat; (ii) AcOH(aq), H_2SO_4, heat; (iii) Sn/HCl, 80°C



157

R		
H	**158**	**164**
F	**159**	**165**
Cl	**160**	**166**
Br	**161**	**167**
OCH_3	**162**	**168**
NO_2	**163**	**169**

Scheme 38 Reagents: (i) 4-R-ArCHO, NaOH, ethanol, 24-27°C, 24h; (ii) H_3PO_4, AcOH, heat, 2-3h

(b) CYCLISATION TO 4'-QUINOLONES

Cyclisation of the 2-aminochalcone derivatives can be achieved under acid or base-catalysed conditions.[140-142] In contrast to the 2-hydroxychalcone isomerisation, the quinolone ring is not opened by either acid or base. Ring closure of 2-aminochalcones **158-163** in orthophosphoric acid-acetic acid medium was employed and was complete within 2-3 hours (Scheme 38). The product in each case was isolated by pouring the cooled reaction mixture into ice-cold water; filtration of the precipitated material afforded the crude orange product which was purified by flash chromatography using toluene as eluent. The ^{1}H NMR spectra of the 4'-quinolone derivatives **164-169** show a pair of double doublets at *ca.* δ 2.7 and 2.8 ppm for the methylene protons; a doublet of doublets at *ca.* δ 4.7 ppm for the methine proton; a singlet at *ca.* δ 4.5 ppm for the amino proton; and aromatic proton signals in the region *ca.* δ 6.6-8.0 ppm (Fig. 3). The splitting patterns of these signals were analysed and the observed coupling constants were consistent with literature values.[140-3]

Although ^{1}H NMR spectroscopy has been widely used for elucidating the structure of 4-quinolones,[144] to our knowledge, no systematic ^{13}C NMR spectroscopic study of these compounds appears to have been reported. In the present study, we report the ^{13}C NMR spectral data for the 4-quinolone derivatives substituted at the 4'-position of the B-ring. Examination of the ^{13}C NMR spectra of the 4-substituted quinolones **164-169** parallel those observed for the flavanone (Table 1). The insensitivity of the A- and C-rings' chemical shifts to variations of R'-substituent is apparent in the ^{13}C NMR spectra of the 4-quinolones (Table 2). However, the C-2 and C-8a nuclei of the 4-quinolones resonate at lower field than those of flavanone analogues, because of the relatively less electronegative nitrogen atom. The infrared spectra of the 4-quinolones show the carbonyl and amino groups at *ca.* ν 1645-1675 and 3300-3370 cm^{-1}, respectively (Table 3). The electron-impact induced mass fragmentation of the prepared quinolones was also studied and will be discussed in detail in Section 2.4(a) (page 94).

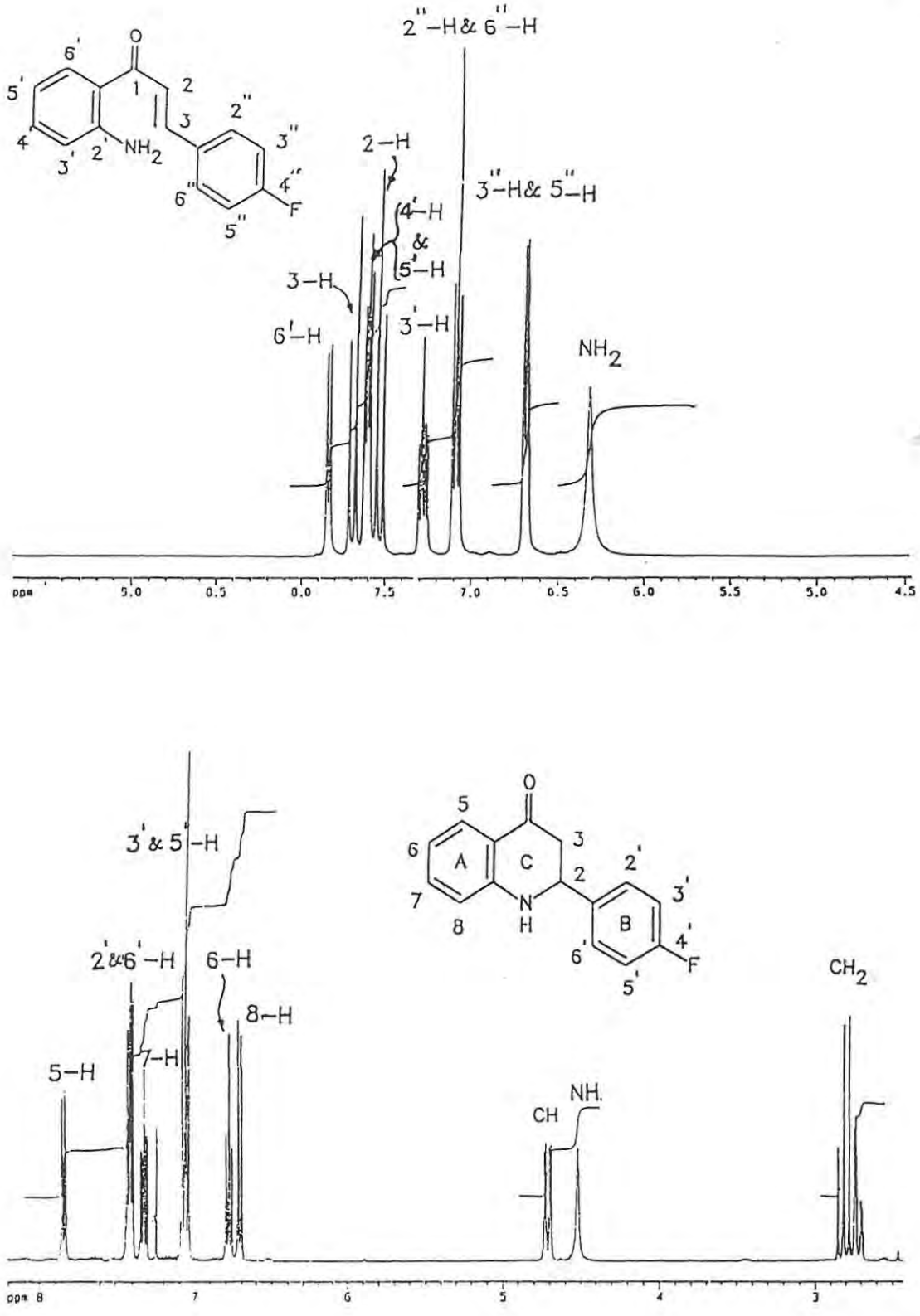
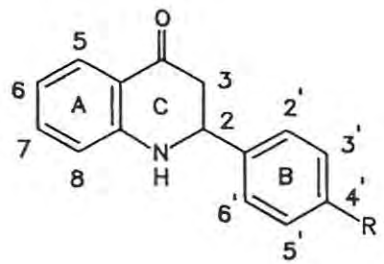


Figure 3: The ^{1}H NMR spectra of 2-amino-4'-fluorochalcone 158 and 4'-fluoro-4-quinolone 164

Table 2: **^{13}C NMR Chemical shift data (ppm) of the 4-quinolone derivatives in $CDCl_3$ (δ 77.0ppm)**



No	R	C-3	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1′	C-2′/ C-6′	C-3′/ C-5′	C-4′	OMe
164	H	46.4	58.5	193.1	119.1	127.6	118.4	135.4	115.9	151.5	141.0	126.6	129.0	128.5	
165	F	46.4	57.8	193.1	119.0	127.5	118.5	135.5	115.9	151.5	136.8[a]	128.3[b]	115.8[c]	162.6[d]	
166	Cl	46.4	57.9	192.8	119.1	127.6	118.7	135.5	115.9	151.3	139.5	129.2	128.0	134.2	
167	Br	46.3	57.9	192.8	119.0	127.6	118.7	135.5	116.0	151.3	140.1	128.3	132.1	122.2	
168	OMe	46.5	57.2	193.5	119.0	127.6	118.3	135.3	115.9	151.6	119.0	127.8	114.3	159.7	55.3
169	NO_2	46.1	57.2	191.8	119.3	127.7	119.2	135.7	116.1	150.9	148.0	127	124.3	148.3	

165 (a) $^4J_{CF}$ 3.0 Hz; (b) $^3J_{CF}$ 8.1 Hz; (c) $^2J_{CF}$ 22.1 Hz; and (d) $^1J_{CF}$ 246.5 Hz

Table 3: Infrared spectral data of 4-quinolones 164-169

No	R"	ν_{max} (KBr)	ν_{max} (KBr)/cm^{-1}
164	H	3345 (NH)	1660 (C=O)
165	F	3320 (NH)	1660 (C=O)
166	Cl	3320 (NH)	1650 (C=O)
167	Br	3310 (NH)	1645 (C=O)
168	OMe	3300 (NH)	1645 (C=O)
169	NO_2	3370 (NH)	1675 (C=O)

2.1.3 1-THIOFLAVANONES

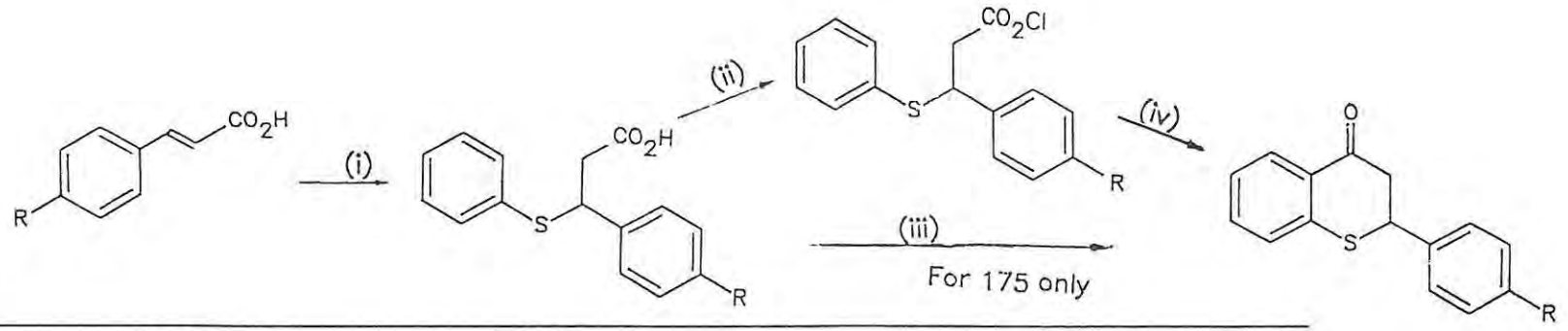
These compounds differ from the flavanones and 4-quinolones in that the oxygen or nitrogen atom at position 1 has been replaced with sulphur to give the thioether linkage.

1-Thioflavanone **185** is one of the simplest representatives of sulphur-containing flavanoids, and was first prepared by Arndt[144] by ring closure of ß-phenylmercaptodihydrocinnamic acid **175** (Scheme 39). Reagents often used to effect the ring closure include phosphoryl chloride,[144] phosphorus pentoxide[145] and concentrated sulphuric acid.[146] However, the use of phosphorus pentoxide has been found to give, in most cases, the thiochromone rather than the 1-thioflavanone.[144]

The ß-phenylmercaptodihydrocinnamic acid derivatives **175-179** were prepared in high yield (*ca.* > 90%) by a literature procedure,[144] involving the condensation of thiophenol with the 4'-substituted cinnamic acids **170-174** (Scheme 39). The products were distinguished from their cinnamic acid precursors by the appearance of three double doublets at *ca.* δ 2.9, 3.1 and 4.6 ppm in their ^{1}H NMR spectra (Fig. 4). The first two multiplets correspond to the methylene protons and the last to the methine proton. Their ^{13}C NMR spectra also confirmed the presence of an increased number of carbon atoms (15).

ß-Phenylmercaptodihydrocinnamic acid **175** was cyclised with phosphoryl chloride to 1-thioflavanone **185** (Scheme 39).[144] However, the extension of this procedure to derivatives substituted at the 4'-position failed to yield the expected 1-thioflavanone derivatives. The use of polyphosphoric acid[145] and concentrated sulphuric acid[146] also failed to yield the expected products. The remaining option was to chlorinate the mercaptocinnamic acids with thionyl chloride to afford cinnamoyl chlorides **180-184** which are suitable precursors for Friedel-Crafts acylation (Scheme 39). No attempt was made to purify the cinnamoyl chloride derivatives and these intermediates were cyclised in reasonable yields (*ca.* > 40%) using, as catalyst, an equimolar amount of anhydrous aluminium chloride. The 4'-methoxycinnamoyl chloride derivative **184**, however, failed to cyclise even under these conditions, affording a complicated mixture of products. The failure of the 4'-methoxycinnamoyl chloride derivative from cyclisation may be the result of co-ordination of the methoxy group with aluminium chloride.[147] The products **185-188** were purified by flash chromatography using toluene or benzene as eluent. Further work is in progress in our group to optimise the yields and the generality of this procedure.

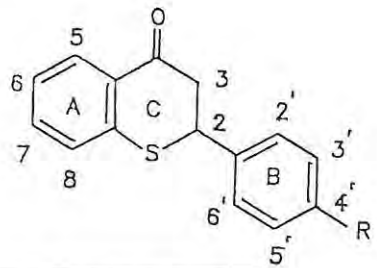
The ^{1}H NMR spectra of the 1-thioflavanones, show the expected double doublets at *ca.* δ 3.2 and 3.3 ppm for the methylene protons, a doublet of doublets at *ca.* δ 4.7 ppm for the methine proton and the aromatic proton signals in the region *ca.* δ 7.0-8.3 ppm (Fig. 4). The ^{13}C NMR spectral data of 1-thioflavanones **185-188** (Table 4) also parallel those of the flavanone and 4-quinolone analogues. The C-2 and C-8a nuclei resonate further upfield than those of the flavanones and 4-quinolones, due to decreased electronegativity of sulphur. Thus ^{13}C NMR spectroscopy can be used to distinguish the flavanoid derivatives. Infrared spectroscopy confirmed the presence of the carbonyl group at *ca.* ν 1675 cm^{-1}. For all products **175-179** and **185-188**, the MS were consistent with the postulated structures and are discussed in Section 2.4(b) (page 98).



R				
H	170	175	180	185
F	171	176	181	186
Cl	172	177	182	187
Br	173	178	183	188
OCH_3	174	179	184	-

Scheme 39: Reagents: (i) PhSH, HBr, CH_3CO_2H, heat, 9h, (ii) $SOCl_2$, $CHCl_3$, heat 30min, (iii) $POCl_3$, heat, 20 min, and (iv) $AlCl_3$, heat, 20min

Table 4: ^{13}C NMR Chemical shift data (ppm) of the 1-thioflavanone derivatives in $CDCl_3$ (δ 77.0ppm)



No	R'	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'
185	H	46.7	45.5	194.3	130.4	133.6	127.2	129.2	125.2	142.1	134.5	138.4	129.0	128.4
186	F	46.8	44.7	194.1	130.4	133.7	127.2	129.2	125.3	141.8	134.4	134.3	115.9	162.5
187	Cl	46.6	44.8	193.9	130.4	133.8	127.2	129.3	125.4	141.9	137.0	128.8	129.2	134.3
188	Br	46.5	44.8	193.9	130.4	133.8	127.2	129.3	125.9	141.9	137.5	129.1	130.4	122.4

186 (a) $^4J_{CF}$ 3.02Hz; (b) $^3J_{CF}$ 8.05Hz; (c) $^2J_{CF}$ 22.1Hz; and (d) $^1J_{CF}$ 247.5Hz

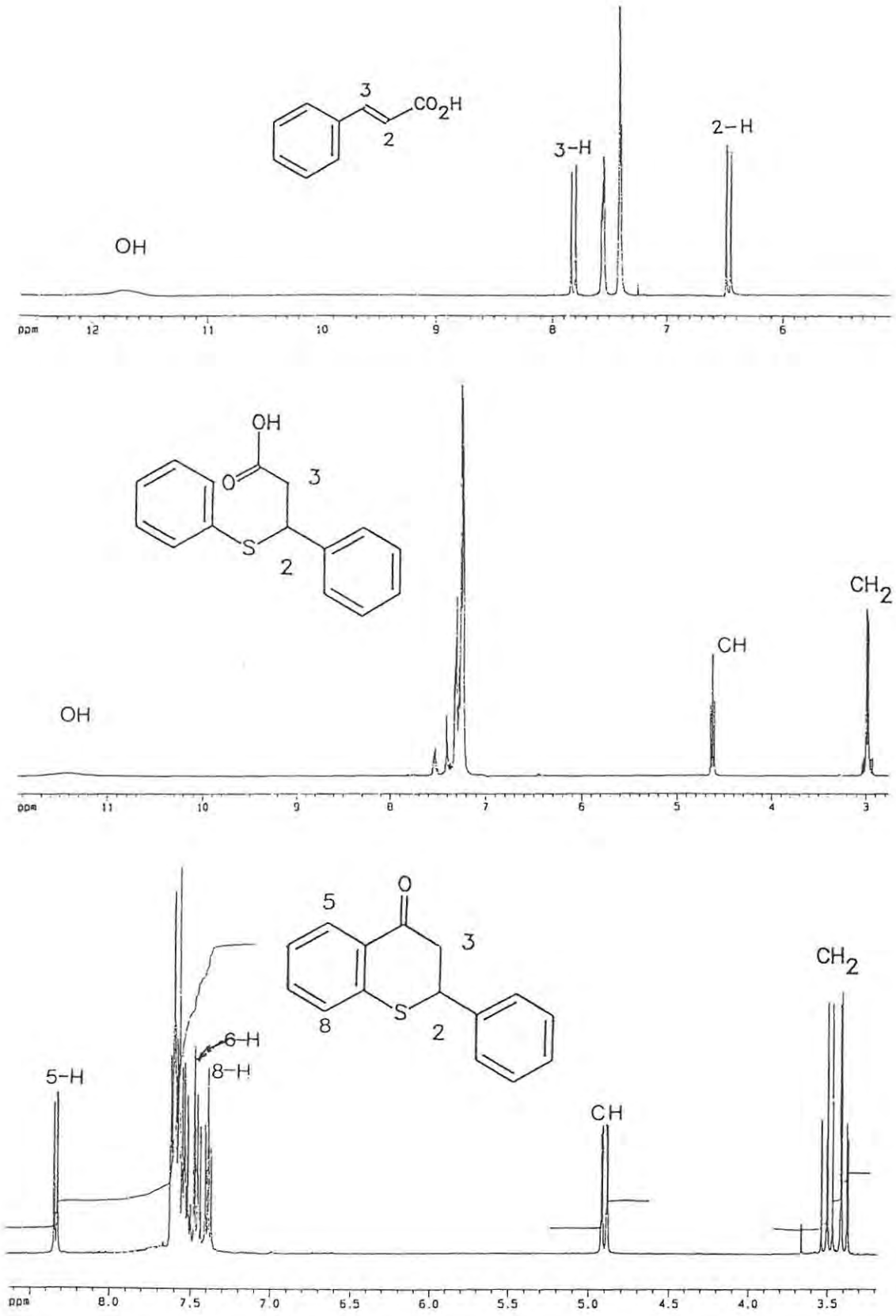


Figure 4: The ^{1}H NMR spectra of cinnamic acid 170, 2-phenylmercaptodihydrocinnamic acid 175 and 1-thioflavanone 185

2.2 SCHMIDT REACTION OF THE FLAVANOID KETONES (FLAVANONES, 4-QUINOLONES AND 1-THIOFLAVANONES): SYNTHESIS OF BENZODIAZEPINE ANALOGUES

(a) PREPARATION OF BENZOXAZEPINONE DERIVATIVES

The flavanones **189** and **145-153** were subjected to the Schmidt reaction using trimethylsilyl azide (TMS-N_3) in trifluoroacetic acid according to a literature procedure[106] (Scheme 40). After 3 days at room temperature, the 1,4-benzoxazepinones (**190** and its substituted analogues) were isolated as the major products together with their 1,4-tetrazolo derivatives (**191** and its substituted analogues), separation being readily achieved by flash chromatography. The tetrazolo derivatives (**191** and its substituted analogues) were also prepared in high yield as sole products by treatment of flavanones (**189** and **145-153**) with TMS-N_3 in dichloromethane in the presence of stannic chloride ($SnCl_4$)[106] (Scheme 40). When flavanone **189** was treated with sodium azide in trifluoroacetic acid at room temperature, the trifluoroacetate derivative **210** was isolated (94%) together with the 1,4-tetrazolo derivative **191** (5%). The trifluoroacetate derivative **210** was easily hydrolysed, in high yield, to the 1,4-benzoxazepinone **190** under acidic conditions. Under these sets of reaction conditions, no products resulting from aryl migration (*i.e.* the 1,5-isomers) were detected. The 1,5-benzoxazepinone derivative **211**, however, was isolated in very low yield (2.5%) along with the 1,4-isomer **190** (40%) and its 1,4-tetrazolo derivative **191** (4%), by treating flavanone **189** with sodium azide in a refluxing acetic-sulphuric acid medium[103,105] (Scheme 41).

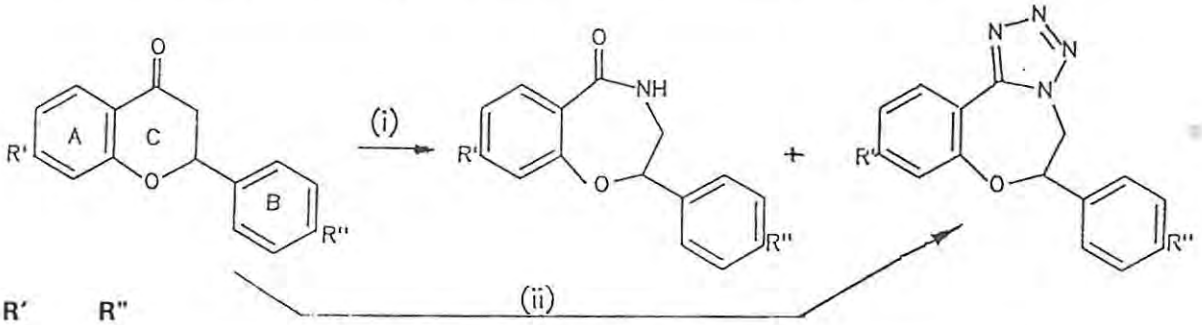
The products detailed in Schemes 40 and 41 were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry. The ^{1}H and ^{13}C NMR spectra of the 1,4-benzoxazepinone **190**, the 1,5-regioisomer **211** and the 1,4-tetrazolo derivative **191** exhibit distinct differences from one another and also from those of the flavanone precursor **189**. The 1,5-isomer **211** is distinguished from its precursor by the appearance of an amide proton signal at *ca.* δ 9.00ppm

in the ^{1}H NMR spectrum (Fig. 5). In the flavanone precursor, the 5-H signal appears downfield (at *ca.* δ 7.80ppm) because of the magnetic anisotropy of the carbonyl group which deshields appropriately orientated adjacent protons.[148] In the ^{1}H NMR spectrum of the 1,5-benzoxazepinone **211**, the corresponding proton (now 6-H) is shifted upfield to *ca.* δ 7.00ppm. The chemical shifts of methine and methylene proton signals of the 1,5-isomer are relatively unaffected by nitrogen insertion and are comparable to those of flavanone.

In the 1,4-isomers (**190** and its substitued analogues), the amide and aromatic proton signals appear in the region *ca.* δ 6.80-8.00ppm; the methylene protons resonate as a pair of double doublets at *ca.* δ 3.50 and δ 3.60ppm, and the methine proton as a double doublet at *ca.* δ 5.50ppm (*eg.* **190**, Fig. 5). The downfield shift of the methylene resonance in the ^{1}H NMR spectra of the 1,4-isomers (relative to the flavanone precursors and the 1,5-regioisomer **211**) is due to the electron-withdrawing inductive effect of the adjacent amide nitrogen. The ^{1}H NMR spectra of the 1,4-tetrazolo derivatives (**191** and its substituted analogues) show an even further downfield shift of the methylene multiplets at *ca.* δ 4.80 and 5.10ppm due to the increased electron-withdrawing effect of the tetrazolo ring (*eg.* **191**, Fig. 5). The magnetic anisotropy of the tetrazolo ring also shifts the 5-H signal further downfield (to *ca.* δ 8.50ppm) than in the corresponding 1,4- and 1,5-benzoxazepinones and their flavanone precursors. The chemical shifts and splitting patterns of the aromatic protons (Tables 5 and 6) can be used to establish substitution patterns in rings A and B. Vicinal couplings between the aliphatic protons were used to probe conformational preferences (see section 2.8).

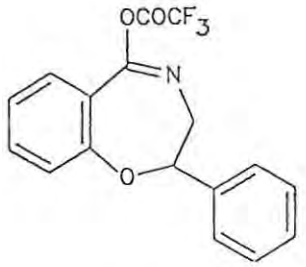
^{13}C NMR Spectroscopy was also used to differentiate benzoxazepinones and their tetrazolo derivatives from their precursors. The shielding or deshielding effects of 8- and 4'-substituents on the A- and B-ring nuclei of the 1,4-benzoxazepinones (Table 7) and their tetrazolo derivatives (Table 8) are similar to those observed for flavanones. The C-ring nuclei, however, while consistent within a series, show marked differences between series. For example, the C-2, C-5 and C-5a nuclei of the 1,4-benzoxazepinones resonate at higher field than the corresponding

nuclei in flavanones (Table 1, pg. 45) and the tetrazoles (Table 8). However, the C-3 nucleus in the tetrazolo derivatives resonates at higher frequency than in the case of flavanones or 1,4-benzoxazepinones, because of the increased electron-withdrawing effect of the tetrazolo ring. The 1,5-isomer may also be distinguished from its 1,4-counterpart by the downfield shift (to *ca.* δ 140.0ppm) of the C-5a signal (due to the adjacent amide nitrogen). The appearance of the amide N-H bond in the IR spectra of the 1,4- and 1,5-benzoxazepinones also differentiates these compounds from their flavanone precursors and the tetrazolo derivatives.

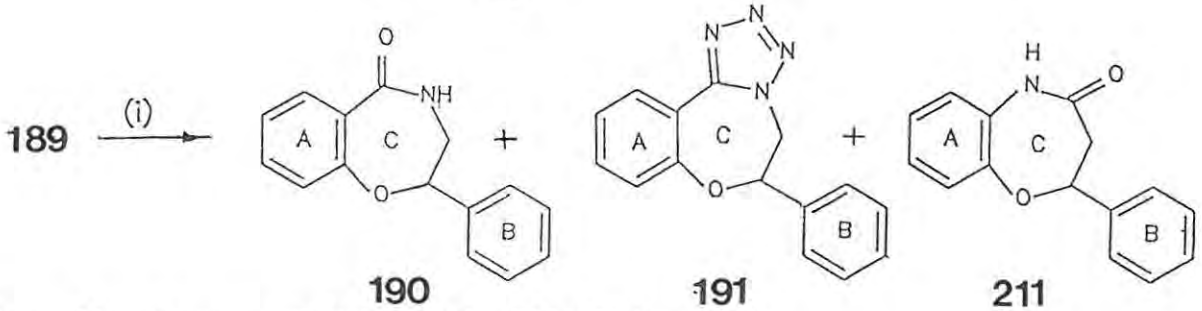


R'	R''			
H	H	**189**	**190**	**191**
F	H	**145**	**192**	**193**
Cl	H	**146**	**194**	**195**
Br	H	**147**	**196**	**197**
OCH_3	H	**148**	**198**	**199**
H	F	**149**	**200**	**201**
H	Cl	**150**	**202**	**203**
H	Br	**151**	**204**	**205**
H	OCH_3	**152**	**206**	**207**
H	NO_2	**153**	**208**	**209**

Scheme 40 Reagents (i) TMS-N_3, CF_3CO_2H, 24-27°C, 3d, (ii) TMS-N_3, $SnCl_4$, 24-27°C, 5d



210



190 **191** **211**

Scheme 41 Reagents (i) NaN_3, H_2SO_4, CH_3CO_2H, heat, 2.5h

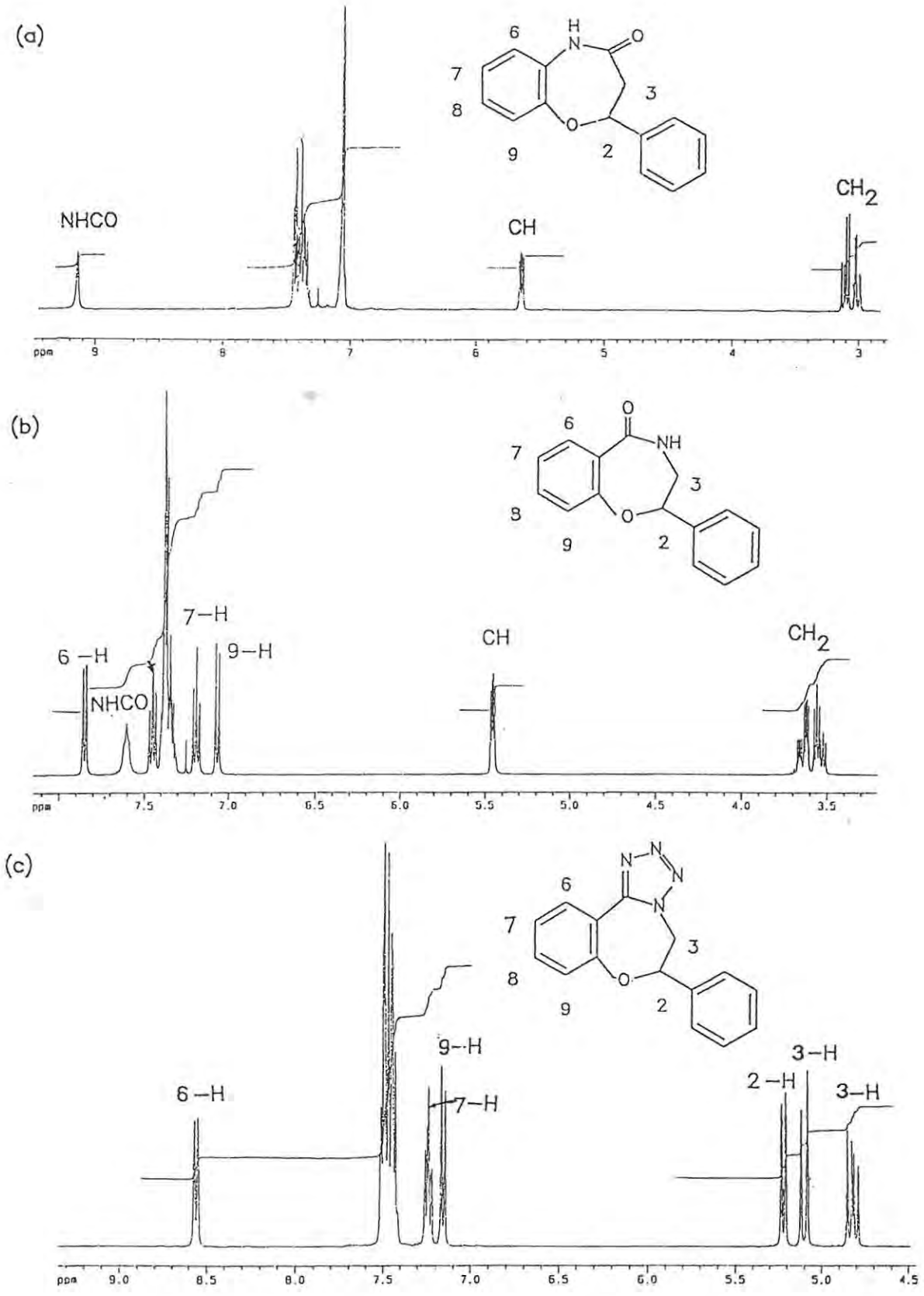
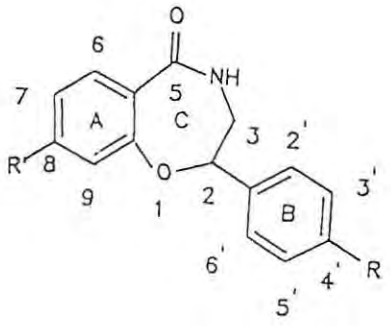


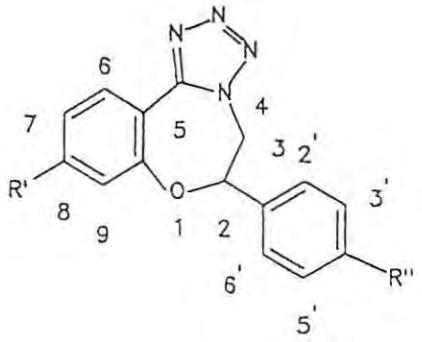
Figure 5: ^{1}H NMR spectra of (a) 1,5-benzoxazepinone 211, (b) 1,4-benzoxazepinone 190 and (c) 1,4-tetrazolo derivative 191

Table 5: **^{1}H NMR Chemical Shifts (δ ppm) and splitting patterns of the A- and B-rings of selected 2-aryl-1,4-benzoxazepinones in $CDCl_3$**



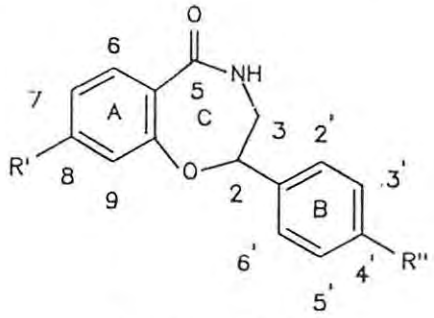
No	R'	R"	A-Ring Protons				B-Ring Protons
			5-H	7-H	8-H	9-H	
190	H	H	7.85 (dd)	7.19 (tt)	7.46 (m)	7.07 (dd)	7.30-7.41 (m, C_6H_5)
196	Br	H	7.75 (d)	7.31 (dd)	---	7.26 (d)	7.33-7.41 (m, C_6H_5)
204	H	Br	7.84 (dd)	7.20 (tt)	7.46 (m)	7.05 (dd)	7.27 (dd, 2'-H and 6'-H) and 7.50 (dd, 3'-H and 5'-H)

Table 6: **^{1}H NMR Chemical shifts (δ ppm) and splitting patterns of the A- and B-rings of selected tetrazolo-1,4-benzoxazepine derivatives in $CDCl_3$**

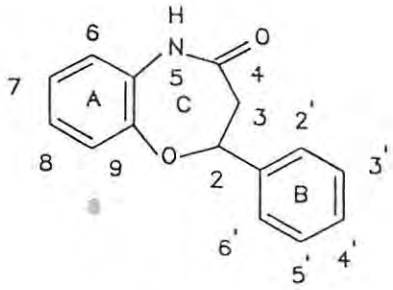


No	R'	R"	A-Ring Protons				B-Ring Protons
			6-H	7-H	8-H	9-H	
193	F	H	8.57 (dd)	6.98 (dq)	---	6.87 (dd)	7.41-7.50 (m, C_5H_5)
201	H	F	8.57 (dd)	7.25 (m)	7.70 (m)	7.16 (d)	7.50 (tt, 2'-H and 6'-H) and 7.17 (tt, 3'-H and 5'-H)

Table 7: ^{13}C NMR Chemical shifts (δ ppm) data of the 1,4- and 1,5-benzoxazepinone derivatives in $CDCl_3$ (δ 77.0ppm)



190—208

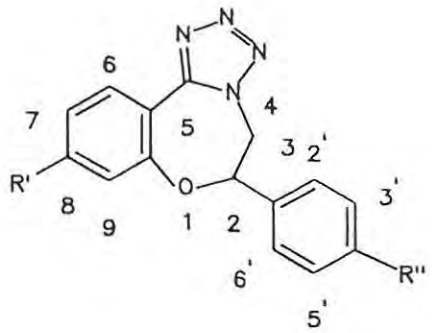


211

No	R'	R''	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/ C-6'	C-3'/ C-5'	C-4'	OMe
190	H	H	85.9	46.3	171.1	125.8	130.9	123.6	133.3	122.4	154.6	139.0	123.6	128.6	128.5	
192	F	H	85.7	46.8	170.0	120.2	128.8[a]	109.0[b]	165.8[c]	109.0[d]	156.8[e]	138.5	126.1	128.8	128.7	
194	Cl	H	85.8	46.6	169.6	123.5	132.5	123.9	139.0	122.4	154.3	138.5	126.2	128.8	128.7	
196	Br	H	85.1	46.1	171.0	122.5	131.0	124.0	133.5	122.3	155.3	138.0	128.0	131.8	131.8	
198	OMe	H	84.8	47.6	170.7	114.6	138.7	109.9	164.3	105.6	161.5	133.9	126.1	128.7	128.5	55.5
200	H	F	85.1	46.3	171.1	128.1	131.0	125.8	133.5	122.4	154.4	134.9[f]	128.1[g]	115.6[h]	162.7[i]	
202	H	Cl	85.1	48.0	171.2	125.6	130.9	123.8	133.4	122.3	154.3	134.9	127.6	128.7	134.2	
204	H	Br	85.9	46.5	169.9	123.9	132.6	126.8	127.1	125.3	155.3	138.5	126.1	128.8	128.7	
206	H	OMe	77.8	45.3	169.8	130.4	125.3	118.6	134.3	118.6	161.5	114.2	128.2	114.5	160.0	55.3
208	H	NO_2	84.6	46.0	170.9	146.0	133.7	124.4	131.0	122.2	154.0	126.0	123.9	127.3	147.9	
211	H	H	82.9	42.2	171.8 (C-4)	140.1	128.5	123.3	124.2	122.2	148.2	130.1	126.0	128.7	128.5	

192 (a) $^3J_{CF}$ 11.01Hz, (b) $^2J_{CF}$ 24.0Hz, (c) $^1J_{CF}$ 252.3Hz, (d) $^2J_{CF}$ 24.0Hz and (e) $^3J_{CF}$ 12.0Hz; and **200** (f) $^4J_{CF}$ 3.0Hz, (g) ^3JHz, (h) $^2J_{CF}$ 21.1Hz and (i) $^1J_{CF}$ 247.6Hz

Table 8: ^{13}C NMR Chemical Shifts (δ ppm) of the tetrazolo-1,4-benzoxazepine derivatives in $CDCl_3$ (δ 77.0 ppm)



No	R'	R''	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'	OMe
191	H	H	79.0	56.2	156.8	113.0	130.4	124.0	133.2	121.5	151.9	136.3	126.0	129.1	129.3	
193	F	H	79.3	55.9	151.4	109.4	132.2[b]	119.9[c]	165.1[d]	108.6[e]	158.2[f]	135.9	126.0	129.1	129.4	
195	Cl	H	79.3	56.0	157.1	111.6	131.3	124.5	138.8	121.8	151.3	135.8	126.0	129.2	129.4	
197	Br	H	79.3	56.0	157.1	112.0	131.4	127.4	126.9	124.8	151.4	135.8	126.0	129.2	129.5	
199	OMe	H	79.1	56.0	163.6	105.4	131.6	111.5	151.9	105.5	158.4	136.4	126.1	129.1	129.3	55.6
201	H	F	78.3	56.1	156.1	112.9	132.2	119.9	165.1	108.6	158.2	132.2[g]	127.0[h]	116.1[i]	129.4[j]	
203	H	Cl	78.3	56.0	156.6	112.9	130.4	124.1	133.3	121.5	151.7	135.2	127.5	129.3	134.8	
205	H	Br	78.3	55.9	156.5	112.9	130.4	124.1	133.3	121.4	151.8	123.3	127.7	132.4	135.3	
207	H	OMe	78.7	56.1	156.9	113.0	130.4	123.9	133.2	121.5	151.9	128.4	127.4	114.5	160.3	55.1
209[a]	H	NO_2	78.0	55.9	156.7	112.9	130.7	124.6	133.6	121.4	142.9	133.6	127.1	124.4	148.4	

209[a] Using DMSO d_6 as solvent; **193** (b) $^4J_{C,F}$ 10.0Hz, (c) $^2J_{C,F}$ 22.03Hz, (d) $^1J_{C,F}$ 254.4Hz, (e) $^2J_{C,F}$ 24.0Hz and (f) $^3J_{C,F}$ 12.02Hz; and **201** (g) $^4J_{C,F}$ 3.02Hz, (h) $^3J_{C,F}$ 8.1Hz, (i) $^2J_{C,F}$ 21.1Hz and (j) $^1J_{C,F}$ 248.5Hz

(b) PREPARATION OF BENZODIAZEPINE DERIVATIVES

The Schmidt reaction of 1,2,3,4-tetrahydro-4-quinolones has been reported to afford the 1,4- and 1,5-benzodiazepine derivatives.[98] However, we have found that Schmidt reaction of 2-aryl-1,2,3,4-tetrahydro-4-quinolones (**164-169**) affords the 1,4-benzodiazepines (**212** and its substituted analogues) and their tetrazolo derivatives (**213** and its substituted analogues) (Scheme 42). Similar regioselectivity was observed for the Schmidt reaction of flavanone derivatives (see Scheme 40, pg. 57). In this case, however, the amide and tetrazolo products were formed in comparable yields by treatment of the 2-aryl-1,2,3,4-tetrahydro-4-quinolones (**164-169**) with TMS-N_3 in trifluoroacetic acid (Scheme 42). The tetrazolo derivative (**219**, R = Br) was also prepared in high yield, and as the sole product, using $SnCl_4$—TMS-N_3 reagent system. Under both sets of reaction conditions, we failed to detect any presence of the 1,5-isomers. The structures of the products detailed in Scheme 42 were established by spectroscopic techniques. During preparation of a manuscript detailing the results of our work in this area, a paper by Tökés and Litkei,[149] describing the preparation of the 1,4-benzodiazepines (**212**, **218** and **220**) and their tetrazolo derivatives (**213**, **219** and **221**) by a similar procedure, appeared in literature. These authors also did not detect the presence of the 1,5-isomers, even when using the NaN_3—H_2SO_4 reagent system.

R			
H	**164**	**212**	**213**
F	**165**	**214**	**215**
Cl	**166**	**216**	**217**
Br	**167**	**218**	**219**[a]
OCH_3	**168**	**220**	**221**
NO_2	**169**	**222**	**223**

Scheme 42: Reagents: (i) TMS-N_3, CF_3CO_2H, 24-27°C, 3d
219 (a) Also prepared using TMS-N_3, $SnCl_4$, CH_2Cl_2, 24-27°C, 5d.

Analysis of the ^{1}H NMR spectra of the 1,4-benzodiazepines (*eg*. Fig. 5) shows: a pair of multiplets for the methylene protons (at *ca.* δ 3.45 and 3.55 ppm); a singlet for the amino proton (at *ca.* δ 4.10-4.30 ppm); a quintet due to the methine proton (at *ca.* δ 4.80 ppm); and signals corresponding to the aromatic protons and amide protons (at *ca.* δ 6.50-8.30 ppm). Patterns in the aromatic, methine and methylene proton chemical shifts similar to those of the oxygen analogues (see Fig. 5, pg. 58) are also observed for the tetrazolo-1,4-benzodiazepine derivatives (*eg*. Fig. 6). However, in the case of the latter, the methine proton signal resonates upfield because of the relatively weak electronegativity of nitrogen. Assignment of these signals was achieved by the use of coupling constants and this will be discussed in Section 2.8.1. The double doublet at *ca.* δ 4.70 ppm due to the first methylene proton overlaps with the amino proton signal.

^{13}C NMR Chemical shift patterns similar to those of the 1,4-benzoxazepinones (see Table 7, page 60) were observed for the analogous 1,4-benzodiazepinones (Table 10). However, in the case of the 1,4-benzodiazepinones, the weaker electron-withdrawing inductive effect of the *N'* atom cause the adjacent carbon nuclei (C-2 and C-9a) to resonate upfield of the corresponding signals in the oxygen analogues. A similar pattern is observed in the tetrazolo systems (Table 10). Infrared spectroscopy was also used to distinguish the amides from their tetrazolo derivatives; the amides being characterized by the carbonyl and N^4-H bands in the regions *ca.* ν 1640-1675 and 3300-3400 cm^{-1} respectively, the latter partially overlapping with the N^1-H band. Mass spectrometry was also used to characterise products prepared in Scheme 42 and will be discussed in detail in Section 2.4(c).

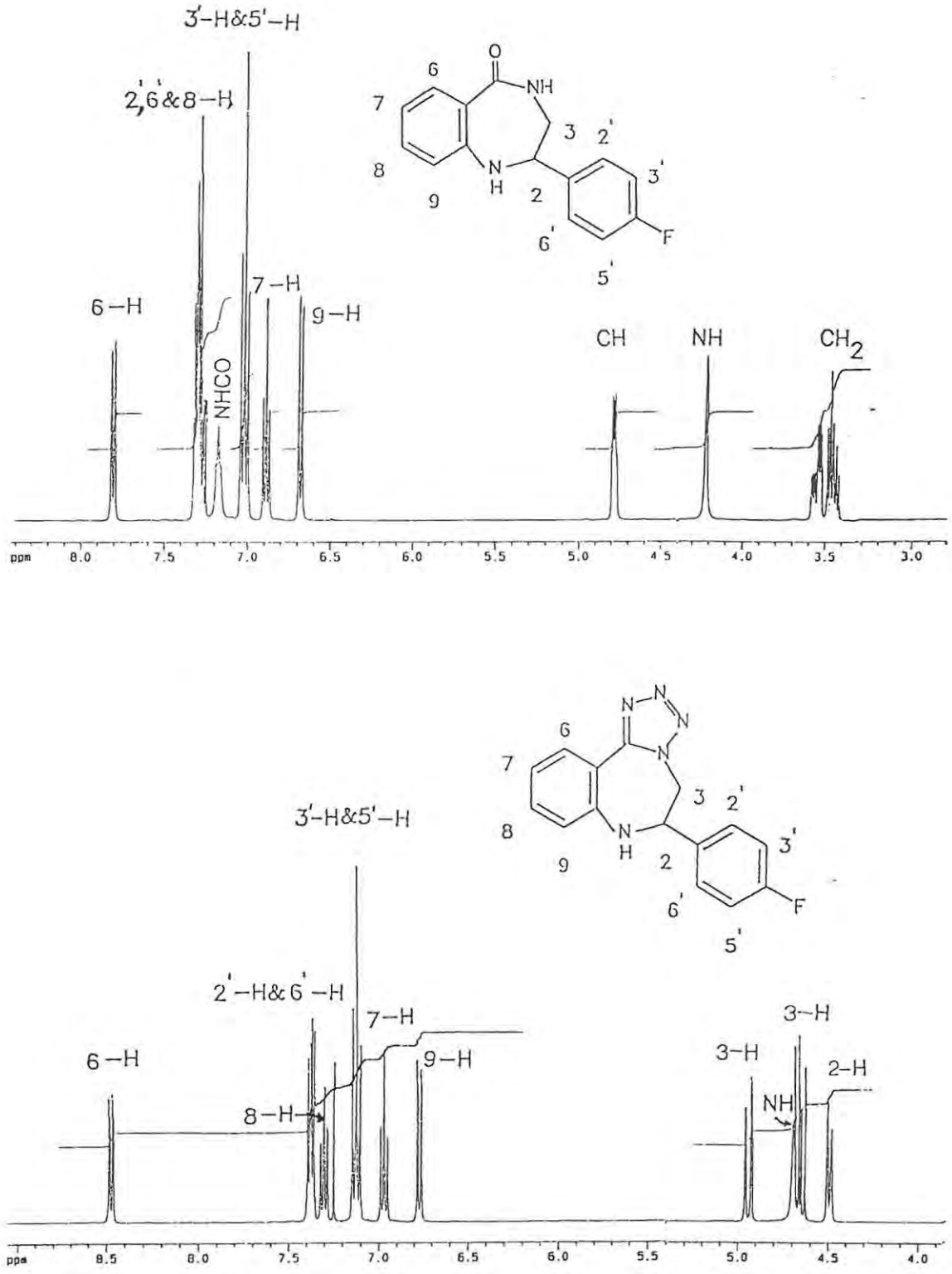


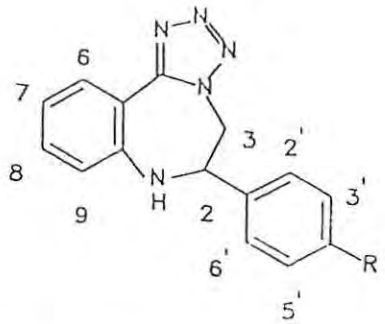
Figure 6: ^{1}H NMR Spectra of the 1,4-benzodiazepin-5-one 214 and its tetrazolo-1,4-benzodiazepine derivative 215 in $CDCl_3$

Table 9: ^{13}C NMR Chemical Shift (δ ppm) data of the 1,4-benzodiazepinones in $CDCl_3$ (δ 77.0 ppm)

No	R	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'	OMe
212	H	64.8	46.8	172.1	120.5	132.2	119.4	132.9	119.2	145.2	142.3	126.7	128.9	128.1	
214	F	64.0	46.7	172.3	120.7	132.1	120.0	132.9	119.3	145.0	138.2[b]	128.3[c]	115.7[d]	162.0[e]	
216	Cl	64.1	46.5	172.1	120.9	132.9	119.8	132.1	119.3	144.9	140.8	128.1	129.0	133.9	
218	Br	64.1	46.5	171.8	122.0	132.1	119.9	133.0	119.4	144.9	141.3	128.5	132.0	128.2	
220	OMe	64.1	47.0	172.5	119.8	132.1	119.2	132.9	119.0	145.3	134.8	127.7	114.2	159.4	55.3
222[a]	NO_2	61.4	44.4	170.1	118.6	128.1	119.0	131.9	116.7	146.5	151.2	131.7	123.3	145.9	

222[a] Using DMSO-d_6 as solvent; and **214** (b) $^4J_{CF}$ 3.0Hz, (c) $^3J_{CF}$ 3.05Hz, (d) $^2J_{CF}$ 22.1Hz and (e) $^1J_{CF}$ 246.5Hz

Table 10: ^{13}C NMR Chemical Shift (δ ppm) data of the tetrazolo-1,4-benzodiazepine derivatives in $CDCl_3$ (δ 77.0 ppm)



No	R	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'	OMe
213	H	57.7	56.5	153.2	107.7	131.1	120.1	132.5	118.8	145.8	138.5	126.7	129.7	129.4	
215	F	56.9	56.3	153.2	107.6	131.1	120.1	132.6	118.8	145.5	154.3[b]	128.5[c]	116.6[d]	163.0[e]	
217	Cl	57.0	56.2	153.2	107.7	131.1	120.3	131.1	118.8	145.4	135.4	128.1	129.9	136.8	
219	Br	57.1	56.1	153.3	107.7	131.1	120.3	132.6	118.8	145.4	137.3	128.4	132.8	123.4	
221	OMe	57.0	56.6	153.2	107.6	131.0	119.9	132.5	118.7	145.8	130.5	127.9	114.9	160.2	55.4
223[a]	NO_2	54.7	53.5	153.3	104.9	130.0	118.7	132.2	117.5	146.1	146.8	129.9	123.5	145.8	

223[a] Using DMSO-d_6 as solvent; and 215 (b) $^4J_{CF}$ 3.02Hz, (c) $^3J_{CF}$ 8.05Hz, (d) $^2J_{CF}$ 22.1Hz and (e) $^1J_{CF}$ 249.5Hz

(c) PREPARATION OF BENZOTHIAZEPINE DERIVATIVES

Schmidt reaction of 1-thioflavanone with sodium azide in acetic acid to afford the 2-phenyl-1,4- and 2-phenyl-1,5-benzothiazepinones in a 1:1 ratio was first reported by Lévai.[107(a)] In another development, this author also prepared the 1,5-regioisomer *via* Beckmann rearrangement of the 1-thioflavanone oxime.[107(b)] Our interest in the Schmidt reaction of flavanoid compounds prompted us to investigate application of the Schmidt reaction to 1-thioflavanones using TMS-N_3 in trifluoroacetic acid. Under these reaction conditions, the 1-thioflavanone **185** afforded the 1,4- **224** and 1,5--benzothiazepinone **225**, as well as the 1,4-tetrazolo derivative **226** (Scheme 43). Extension of this procedure to the previously unknown 4'-halogeno-1-thioflavanones **186-188** afforded the corresponding 1,4- and 1,5-regioisomers in comparable yields. Traces of the tetrazolo-1,4-benzothiazepines were also detected in the reaction mixture, but could not be isolated by careful flash or preparative layer chromatographic techniques. The 1,4-benzothiazepinone **224** was also prepared *via* a literature procedure,[35,37,43] involving several steps starting with the condensation of *o*-nitrostyrene **233** and *o*-thiosalicylic acid **234** (Scheme 44). An alternative approach[38,40] to the 1,5-benzothiazepinones **225**, **228**, **230** and **232**, involving the condensation of 2-aminothiophenol **235** and 4-substituted cinnamic acids **236-239** was also followed (Scheme 45). The structures of the products, prepared either by the Schmidt reaction or by the cyclisation methods, were confirmed to be the same by spectroscopic techniques.

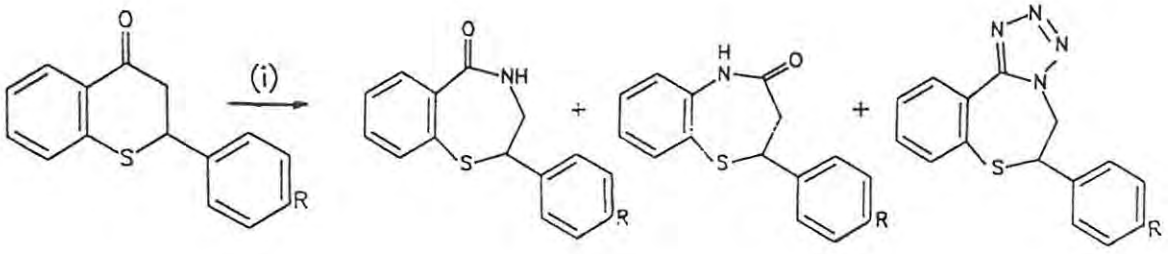
When 1-thiochromanone **240** was treated under the TMS-N_3—trifluoroacetic acid conditions, three products were isolated by flash chromatography and were characterised as 1,4-benzothiazepin-5-one **241**, and the isomeric 1,4-tetrazolo **242** and 1,5-tetrazolo **243** derivatives (Scheme 46). 4,5-Dihydrotetrazolo[5,1-*d*]-1,5-benzothiazepine **243** has been prepared previously,[48(b)] by the reaction of 2,3-dihydro-1,5-benzothiazepin-4-ylhydrazine with sodium nitrite in acidic medium. The 1,4-benzothiazepin-5-one **241** is distinguishable from the 1,4- **242** and 1,5-tetrazolo **243** derivatives by the presence of the amide proton signal (at *ca.* δ

8.71 ppm) in the ^{1}H NMR spectra. The two sets of methylene protons of the 1,4-benzothiazepin-5-one resonate as a pair of triplets at δ 2.62 ppm (2-CH_2) and 3.44 ppm (3-CH_2). In the ^{1}H NMR spectrum of the 1,5-tetrazolo derivative **243**, the two sets of methylene protons resonate as a pair of triplets of triplets at δ 3.38 (3-CH_2) and δ 3.46 (4-CH_2), while those of the 1,4-regioisomer **242** absorb at δ 2.68 (now 2-CH_2) and 4.44 ppm (3-CH_2). In the ^{1}H NMR spectrum of the 1,5-tetrazolo derivative, the 6-H signal resonates significantly upfield (at *ca.* δ 7.80 ppm) from the corresponding signal (now 6-H at *ca.* δ 8.52 ppm) in the 1,4-isomer, possibly reflecting differences in the magnetic anisotropic deshielding effects of the tetrazolo ring in the isomeric compounds.

The carbonyl carbon (^{13}C=O) of the 1,4-benzothiazepin-5-one derivative **241** resonates significantly downfield (δ 173.9 ppm) of the C=N carbon nuclei of the isomeric 1,4- **242** and 1,5-tetrazolo **243** derivatives, both of which resonate at *ca.* δ 153.7 ppm. The C-3 nucleus of the 1,5-tetrazolo isomer **243** resonates at δ 23.5 ppm, while for the isomeric 1,4-derivative **242** the corresponding signal appears at δ 50.8 ppm; for the 1,4-amide derivative **241** the C-3 nucleus resonates at δ 35.5 ppm. The relative downfield shift of the C-3 signal in the spectra of the 1,4-benzothiazepinone **241** and its 1,4-tetrazolo **242** derivative, confirms that the C-3 nucleus is adjacent to nitrogen in both compounds. The ^{13}C NMR spectra of the 1,4-benzothiazepinone **241** and its isomeric 1,4- **242** and 1,5-tetrazolo **243** derivatives are reproduced in Figure 7. Infrared spectroscopy was also used to distinguish the 1,4-amide derivative from its tetrazolo derivatives; the amide being characterised by the carbonyl and N^4-H bands in the regions *ca.* ν 1625 and 3180 cm^{-1}, respectively. The 1,4-benzothiazepinone, and the isomeric 1,4- and 1,5-tetrazolo derivatives were also distinguished from one another by mass spectrometry and this will be discussed in detail in Section 2.4(c).

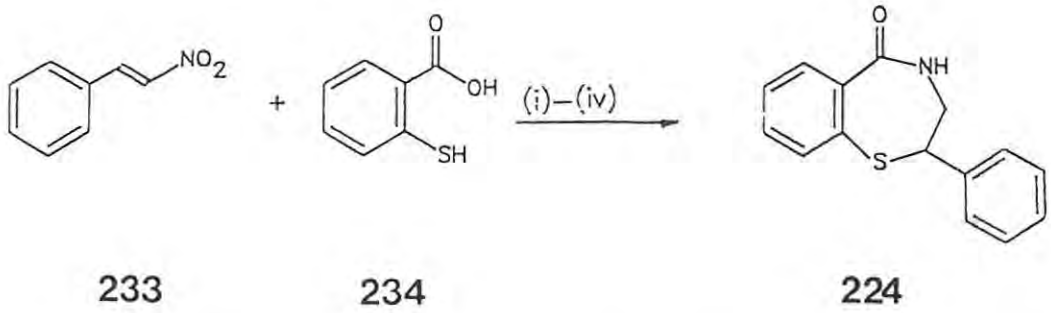
Analysis of the ^{1}H NMR spectra of the 2-aryl-1,4-benzothiazepinones (**224** and its substituted analogues) reveals a pair of double doublets at *ca.* δ 3.30 and 3.50 ppm, for the methylene protons; a double doublet at *ca.* δ 4.60 ppm for the methine proton and a set of multiplets at

ca. δ 7.00-8.00 ppm for the aromatic protons. The amide proton signal is also found in the aromatic region. The ^{1}H NMR spectra of the 1,5-regioisomers (*eg.* **224**, Fig. 8) differ from those of their 1,4-counterparts (*eg.* **225**, Fig. 8) in the aliphatic region, and reveal a multiplet at *ca.* δ 3.00 ppm for the methylene protons and a double doublet at *ca.* δ 5.00 ppm for the methine proton. The proton spectrum of the tetrazolo-1,4-benzothiazepine (**226**, Fig. 8) resembles those of the oxygen (Fig. 5, pg. 58) and nitrogen (Fig. 6, pg. 64) analogues. ^{13}C NMR chemical shift data of the 2-aryl-1,4- (**224** and its substitued analogues) and 2-aryl-1,5-benzothiazepinones (**225** and its substituted analogues) detailed in Tables 11 and 12 show interesting differences in the aliphatic region. The C-3 nucleus of the 1,4-isomers (*eg.* **224**) resonates slightly downfield (at *ca.* 46.5 ppm) of the corresponding nucleus in the 1,5-isomers (*eg.* **225**, at *ca.* δ 41.5 ppm). The C-3 nucleus of the 1,4-tetrazolo analogue **226** resonates at δ 54.7 ppm, while that of the ^{13}C=N nucleus appears upfield (*ca.* δ 154.1 ppm) (Table 11) relative to the carbonyl carbon signal of the 1,4- and 1,5- amides **224** and **225** (at *ca.* δ 172.5 ppm).



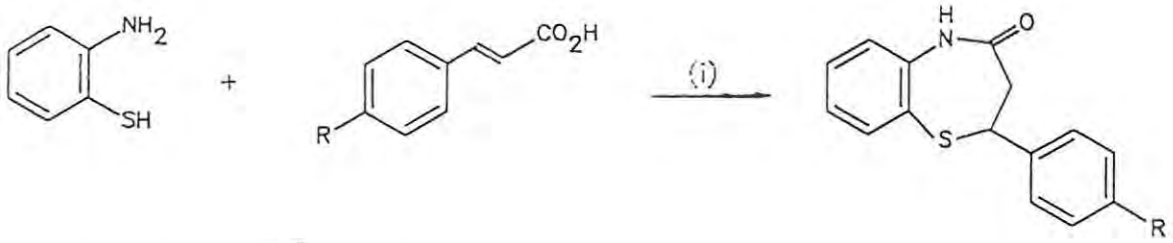
R				
H	185	224	225	226
F	186	227	228	-[a]
Cl	187	229	230	-[a]
Br	188	231	232	-[a]

Scheme 43 Reagents: (i) TMS-N_3, CF_3CO_2H, 24-27°C, 3d.
[a]Compound could not be isolated



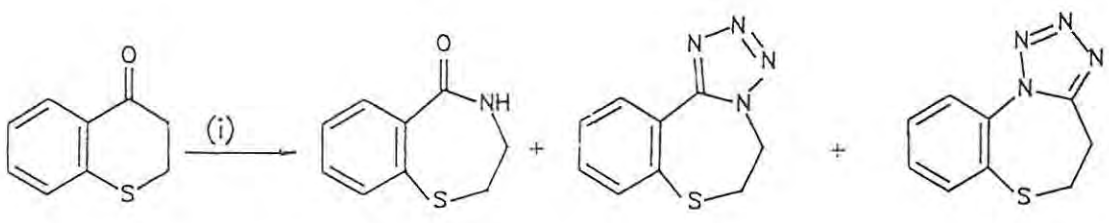
233 234 224

Scheme 44 Reagents: (i) EtOH, heat; (ii) $SOCl_2$, $CHCl_3$, heat; (iii) $SnCl_2.2H_2O$, MeOH, heat and (iv) xylene.



	R		
235	H	236	225
	F	237	228
	Cl	238	230
	Br	239	232

Scheme 45 Reagents (i) heat.



240 241 242 243

Scheme 46 Reagents (i) TMS-N_3, CF_3CO_2H, 24-27°C, 3d.

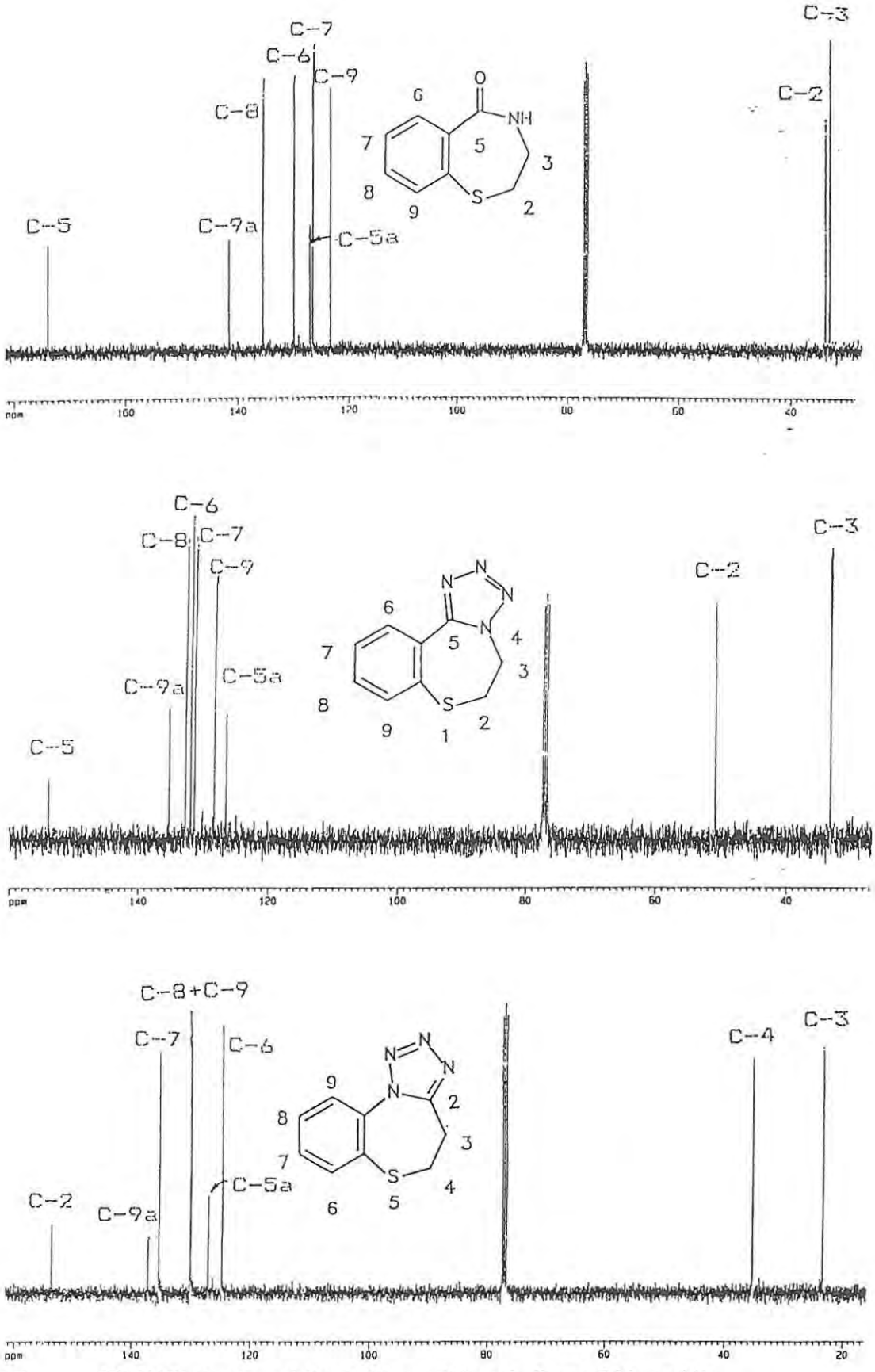


Figure 7: **^{13}C NMR Spectra of the 1,4-benzothiazepin-5-one 241, and its 1,4-tetrazolo[1,5-*d*] 242 and 1,5-tetrazolo[5,1-*d*] 243 derivatives in $CDCl_3$**

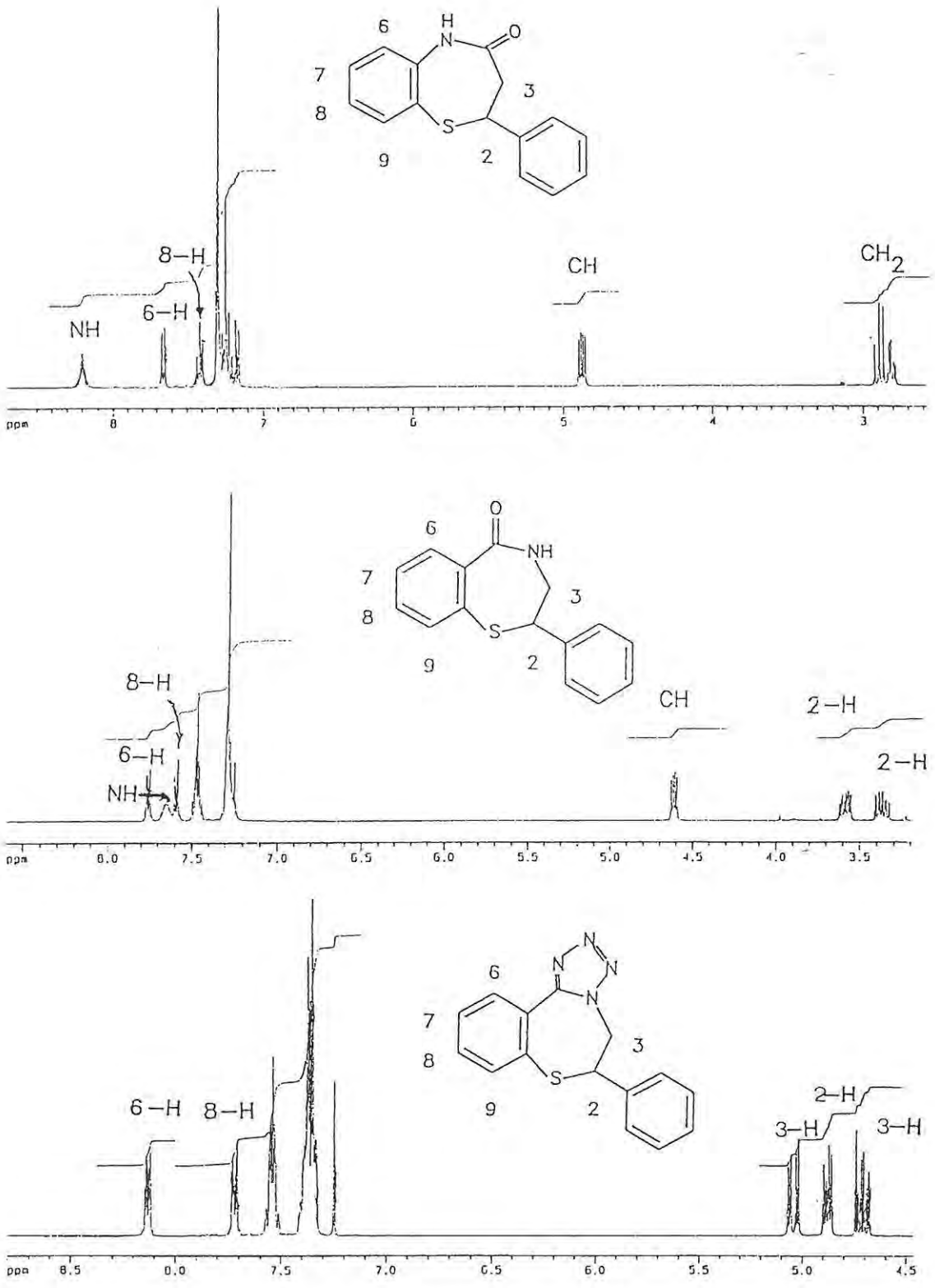
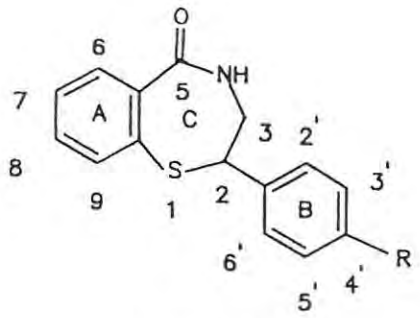
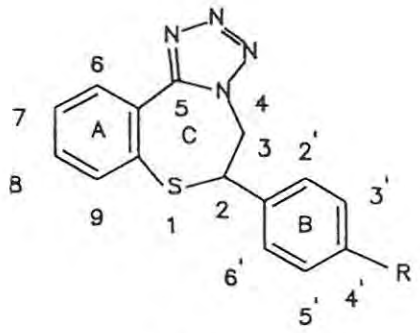


Figure 8: ^{1}H NMR Spectra of the 2-aryl-1,5- 225 and 2-aryl-1,4-benzothiazepinone 224, as well as the tetrazolo-1,4-benzothiazepine derivative 226 in $CDCl_3$

Table 11: **^{13}C NMR Chemical Shifts (δ ppm) data of the 2-aryl-1,4-benzothiazepinone and the 1,4-tetrazolo derivative in $CDCl_3$ (δ 77.0 ppm)**



224–231

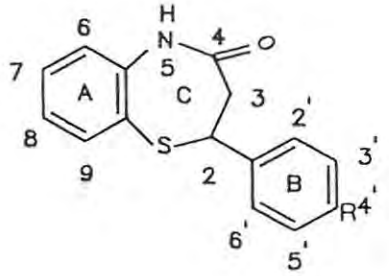


226

No	R	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1′	C-2′/C-6′	C-3′/C-5′	C-4′
224	H	56.2	47.5	172.5	130.2	131.7	129.9	134.3	128.0	141.1	139.9	127.3	128.8	129.2
227	F	55.4	47.6	172.4	130.0	131.7	130.0	134.3	129.4	139.8	136.9[a]	129.0[b]	115.8[c]	162.3[d]
229	Cl	55.4	47.4	172.1	129.8	131.8	130.1	134.3	129.7	139.7	139.5	128.6	129.0	133.9
231	Br	55.5	47.3	172.2	129.8	131.8	130.1	134.3	129.5	140.0	139.7	129.0	132.0	122.0
226	H	54.7	53.5	154.2	128.0	132.1	131.2	134.2	128.8	138.6	133.4	127.1	129.3	129.3

227 (a) $^4J_{CF}$ 3.02Hz, (b) $^3J_{CF}$ 8.05Hz, (c) $^2J_{CF}$ 21.13Hz and (d) $^1J_{CF}$ 247.5Hz

Table 12: ^{13}C NMR Chemical Shift (δ ppm) data of the 2-aryl-1,5-benzothiazepin-4-ones in $CDCl_3$ (δ 77.0 ppm)



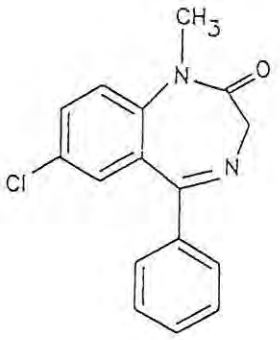
No	R	C-2	C-3	C-4	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'
225	H	53.2	41.5	172.1	126.7	130.2	126.7	135.9	123.2	143.4	141.3	126.4	128.8	127.8
228[A]	F	51.4	41.1	170.5	125.6	130.1	124.9	135.0	123.0	142.4	139.7[a]	128.3[b]	115.2[c]	161.3[d]
230	Cl	52.4	41.3	171.9	126.3	130.4	126.8	135.8	123.3	141.7	141.3	127.9	129.0	133.6
232[B]	Br	52.3	41.2	171.2	125.5	129.9	125.9	135.3	123.1	142.2	141.7	127.9	131.5	121.2

228[A] and 232[B], Using DMSO-d_6 and $CDCl_3$-DMSO-d_6 as solvents, respectively.
228 (a) $^4J_{CF}$ 3.02Hz, (b) $^3J_{CF}$ 8.05Hz, (c) $^2J_{CF}$ 21.13Hz and (d) $^1J_{CF}$ 243.5Hz

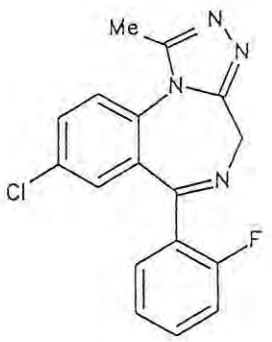
2.3 REACTIONS OF BENZODIAZEPINE ANALOGUES

(a) PREPARATION OF CONJUGATED BENZOXAZEPINONES

The diazepine nucleus of potent benzodiazepine receptor ligands such as diazepam **4** and midazolam **90** contains a high density of π- and lone-pair electrons which enhance the binding efficiency and rigidity (in the preferred conformational arrangement) of the molecule.[2] With the aim of investigating the effect of conjugation on conformation and biological activity we explored the introduction of conjugation into the heterocyclic ring of the 2-phenyl-1,4-benzoxazepinones and their tetrazolo[1,5-*d*] analogues. To our knowledge, no conjugated derivatives of 2-phenyl-1,4-benzoxazepinones (*eg.* **190**) or their tetrazolo[1,5-*d*] analogues (*eg.* **191**) have been reported in the literature.



4

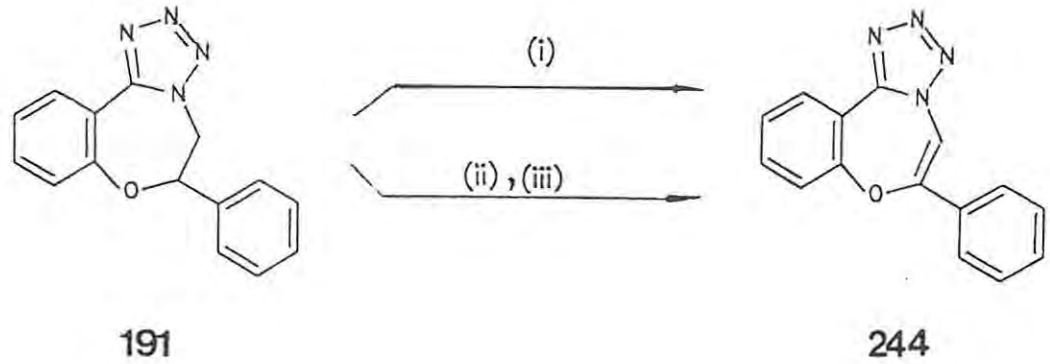


90

(i) Attempted dehydrogenation of benzoxazepinone derivatives

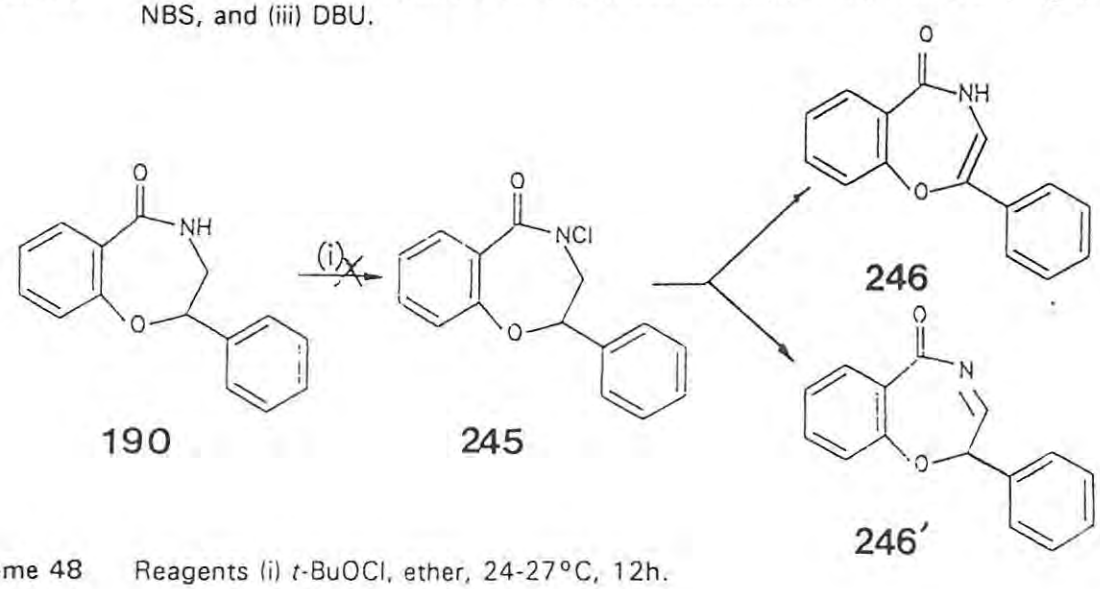
During the course of this project, attempts were also made to introduce a double bond between C-2 and C-3 of the 1,4-benzoxazepine derivatives, but without success. Thus, use of dehydrogenation agents[150] (5% Pd/C and DDQ) failed to introduce unsaturation in the 7-membered ring of the tetrazolo-1,4-benzoxazepine derivative **191** (Scheme 47). The starting material was recovered even after prolonged heating of the reaction mixture. The possibility of introducing the double bond by dehydrobrominating a suitable bromo derivative was then

explored. However, attempted introduction of bromine to compound **191** *via* a deprotonation-bromination sequence using the strong base, lithium diisopropylamide (LDA), followed by bromine or *N*-bromosuccinamide (NBS) led to the recovery of the starting material (Scheme 47). Previous attempts in our laboratory,[91] to deprotonate either C-2 or C-3 of the *N*-benzoyl derivative of the 1,4-benzoxazepinone **190** also failed. These observations led to the conclusion that the aliphatic protons of the 1,4-benzoxazepinone derivatives prepared in this work are not sufficiently acidic to be abstracted, even by a base as strong as LDA. A method to introduce a halogen on the 1,4-benzoxazepinone nitrogen, using *t*-butylhypochlorite (a reagent known to perform such a transformation on amides under mild conditions[151,152]) was then followed (Scheme 48). Flash chromatography of the crude material after work-up afforded the starting material and a nuclear-chlorinated product, but no *N*-chlorinated product was detected. This reaction will be discussed in detail in Section 2.3(b).



191 **244**

Scheme 47 Reagents: (i) DDQ, xylene or 5% Pd/C, decalin, heat, 4d (ii) THF, LDA, Br_2 or NBS, and (iii) DBU.



190 **245**

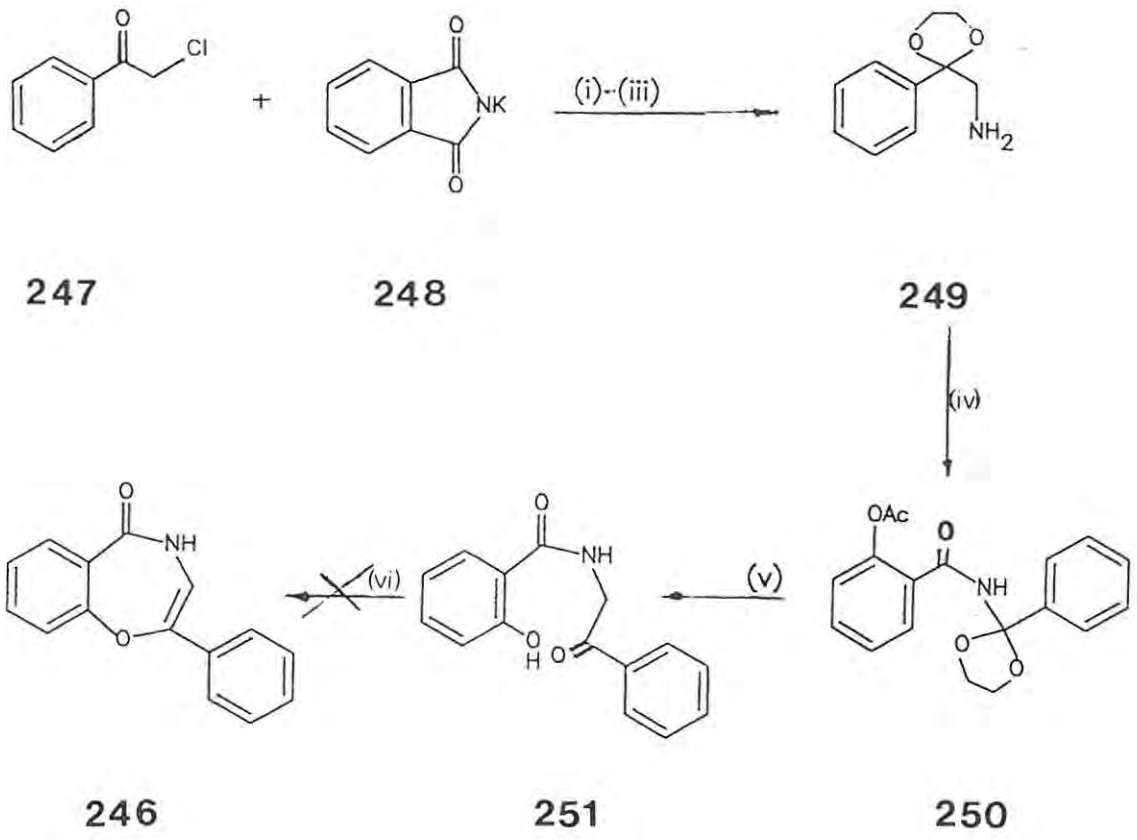
Scheme 48 Reagents (i) *t*-BuOCl, ether, 24-27°C, 12h.

(ii) Cyclisation of salicylamide derivatives

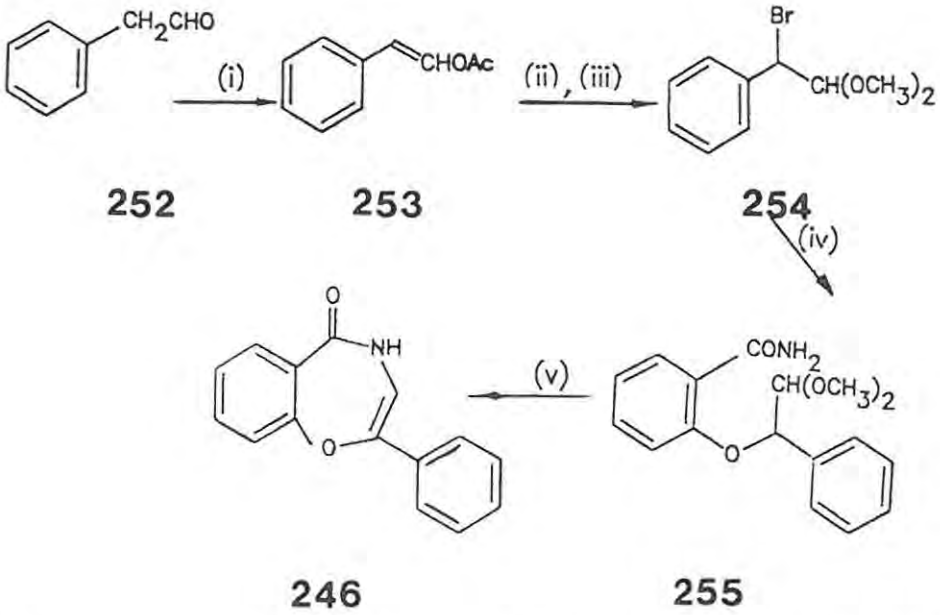
Unsuccessful attempts to dehydrogenate the 1,4-benzoxazepine derivatives led to the investigation of cyclisation as an alternative method for preparing conjugated 2-phenyl-1,4-benzoxazepin-5(4*H*)-ones. The cyclisation methods explored required the preparation of various starting materials as shown in Schemes 49 and 50. In Scheme 49, for example, the first step required the preparation of the aminoacetal **249**; protection as the ketal is essential since the free amino ketone readily self-condenses. The *α*-aminoacetal was prepared according to Scheme 49[153] and was condensed with *o*-acetylsalicyloyl chloride to afford the intermediate **250**. Several attempts to cyclise the deprotected intermediate **251** under neutral and acid-catalysed conditions led to the recovery of the starting material even after prolonged heating.

A successful preparation of the conjugated 2-phenyl-1,4-benzoxazepin-5(4*H*)-one **246** was finally achieved by the Schenker method[61,63] using salicylamide and the bromoacetal **254** under basic conditions, followed by cyclisation-dehydration of the intermediate acetal **255** using *p*-toluenesulphonic acid and a trace of water in toluene (Scheme 50). The bromoacetal **254** was itself prepared *via* a series of steps from phenylacetaldehyde[154] (Scheme 50). The structure of the conjugated 2-phenyl-1,4-benzoxazepin-5(4*H*)-one **246** was confirmed by spectroscopy and, to our knowledge, 2-phenyl derivatives of this type have not been prepared before. However, the analogous 3-phenyl-1,4-benzoxazepin-5(4*H*)-one **258** has been prepared before,[61,63] by a similar method involving the condensation of salicylamide and *α*-chloro-acetophenone. In this project we prepared the 3-phenyl-1,4-benzoxazepin-5(4*H*)-one **258** by condensing salicylamide with *α*-bromoacetophenone **256** under basic conditions, followed by cyclisation of the resulting *o*-phenacylsalicylamide **257** using *p*-toluenesulphonic acid as catalyst (Scheme 51). The ^{1}H NMR spectra of products **246** and **258** outlined in Schemes 50 and 51 are characterised by their vinylic proton signals at δ 5.99 and 6.59 ppm, respectively. The ^{13}C NMR spectra of both products also confirm the presence of fifteen different carbon atoms per molecule and these resonate in the aromatic region *ca.* δ 110-166.5 ppm. The presence, in

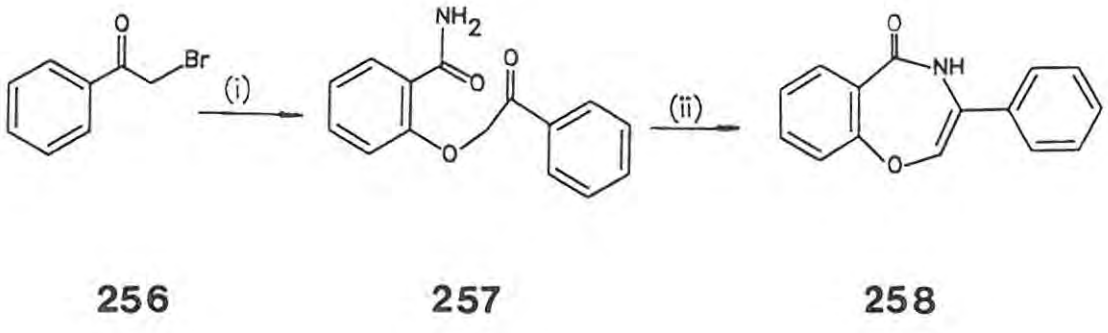
each case, of a carbonyl ^{13}C NMR resonance at *ca.* δ 166.5 ppm (Table 13), and IR carbonyl band at *ca.* ν 1650 cm^{-1} and an IR band at *ca.* ν 3200 cm^{-1} confirm the presence of the amide group in both compounds. The structures of products **246** and **258** were also confirmed by mass spectrometry, and this will be discussed in Section 2.4(c).



Scheme 49 Reagents: (i) DMF, heat, 41h; (ii) $HO(CH_2)_2OH$, *p*-TsOH, toluene, heat; (iii) 30% NaOH, heat; (iv) *o*-acetylsalicyloyl chloride, THF, pyridine; (v) KOH (aq) and (vi) *p*-TsOH, toluene, heat

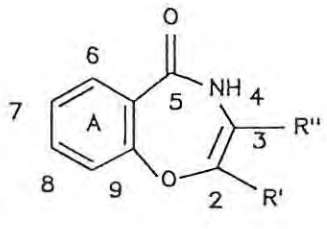


Scheme 50 Reagents: (i) KOAc, Ac_2O, heat; (ii) Br_2, CCl_4; (iii) CH_3OH, 24-25°C, 72h; (iv) salicylamide, K_2CO_3, KI, DMSO, heat and (v) *p*-TsOH, H_2O (2 drops), toluene, heat, 12h

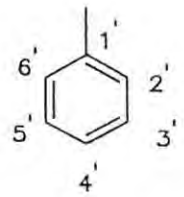


Scheme 51 Reagents: (i) salicylamide, K_2CO_3, KI, DMSO, heat and (ii) *p*-TsOH, toluene, heat

Table 13: ^{13}C NMR Chemical Shift (δ ppm) data of the 2-aryl- 246 and 3-aryl-1,4-benzoxazepinon-5(4*H*)-one 258 derivatives in DMSO-d_6



C_6H_5 =



No	R'	R''	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'
246	H	C_6H_5	158.0	110.4	166.5	126.9	130.7	123.8	133.0	119.6	144.6	132.5	122.7	127.6	126.9
258	C_6H_5	H	134.4	160.2	166.7	126.2	131.5	124.8	133.9	119.9	132.5	129.8	126.3	128.4	128.7

(b) REGIOSELECTIVE A-RING CHLORINATION OF 1,4-BENZODIAZEPINE ANALOGUES

The use of *t*-butylhypochlorite (*t*-BuOCl) for the *N*-chlorination of benzamides was first reported by Clark.[151] This method was extended to anilides by Chasly and Israelstam,[152] who isolated *N*-chloroanilides and nuclear chloroanilides, the former being favoured products in the presence of borax. In view of these observations we attempted to introduce chlorine on the amide nitrogen atom of the 1,4-benzoxazepinone (**190**, X=O, R'=R"=H) using *t*-BuOCl, with the final aim of dehydrohalogenating the *N*-chloroamide derivative **245** to give either the imine **246** or enamine **246'** (See Scheme 48, pg. 76). Flash chromatography of the reaction mixture afforded two fractions, the second corresponding to the starting material. Spectroscopic analysis of the first fraction showed that the chlorine atom had, in fact, been introduced at position 7 of ring A.

Since the nuclear chlorination of benzodiazepine analogues has not been reported before, the reaction using *t*-BuOCl was extended to the substituted-1,4-benzoxazepinones **190-206** and the 1,4-benzodiazepinone **212** with the aim of investigating substituent effects. In principle the strongly electron-donating heteroatoms (O,N) at position 1 (structure A, Scheme 52) are expected to encourage ring chlorination and direct substitution to position 7 or 9. Treatment of the 4'-substituted-1,4-benzoxazepinone derivatives **200-204** (X=O, R'=H, R"=halogen) with *t*-BuOCl, in fact, afforded the corresponding A-ring chlorinated products **259-262**, substitution occurring only at C-7 (Scheme 50).

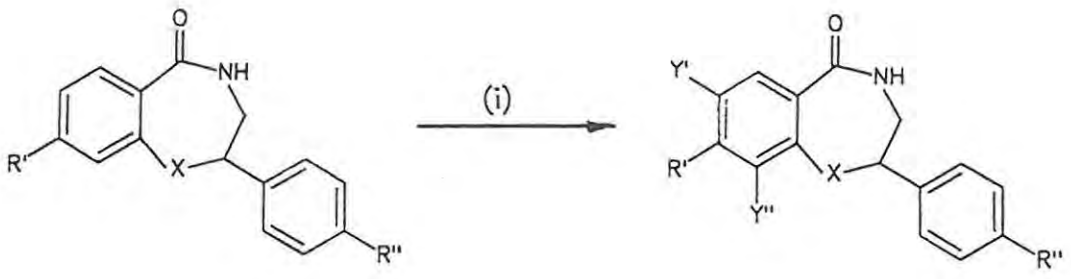
The 8-halogeno derivatives **192-196** (X=O, R'=halogen, R"=H), however, gave no ring-chlorinated products. This is attributed to the electron-withdrawing inductive effect of the halogens, which deactivates the ring. The presence of a methoxy group at position 8 of the benzoxazepinone derivative (**206**, X=O, R'=OCH_3, R"=H), on the other hand, led to the introduction of two chlorine atoms at position 7 and 9. The substitution pattern, in this case,

was established by the spectroscopic techniques discussed below. The double incorporation of chlorine is undoubtedly due to the enhancement of the electron density on the A-ring by the methoxy group. Extension of this procedure to the 1,4-benzodiazepinone derivative (**212**, X=NH, R′=R″=H) also led to a double incorporation of chlorine at position 7 and 9. This introduction of two chlorine atoms in product **264** indicates the increased electron-donating effect of the nitrogen (N^1) as compared to the oxygen (O^1). In all cases, no *N*-chlorinated products were detected and these observations show that *t*-BuOCl is an effective reagent for controlled nuclear chlorination under very mild conditions.

The ^{1}H NMR chemical shifts and splitting patterns of the aromatic protons of the A-ring chlorinated products **190-212** (Table 14) show significant differences from those of their precursors. The ^{1}H NMR spectra of products **259** and **264** and their precursors are illustrated in Figure 9. The 7-H triplet of triplets (at *ca.* δ 7.20 ppm) common in the spectra of the precursors **190-204**, are absent in the spectra of the chloro products **259-262**, confirming substitution at position 7. Double incorporation of chlorine in the A-ring of the 7-methoxy derivative **263** is confirmed by the absence of both the 7-H and 9-H signals at *ca.* δ 6.45 and 6.65 ppm, respectively. This double incorporation is also confirmed by a singlet at δ 8.94 ppm due to the 6-H nucleus, which appears as a doublet in the spectrum of the precursor. Similarly, for the dichlorinated 1,4-benzodiazepinone **264**, the 7-H and 9-H signals are absent, confirming double chlorination of the A-ring in this case. The presence of the amide proton signal in the aromatic region of ^{1}H NMR spectra of the chlorinated products rules out any possibility of the *N*-chlorinated products. The possibility of *N*-chlorination is also ruled out by the presence of the amide N-H band (at *ca.* ν 3300 cm^{-1}) in the IR spectra of chlorinated benzoxazepinones.

Analysis of the ^{13}C NMR data of the chlorinated products and their precursors (Table 15) shows significant changes in A-ring chemical shifts following chlorination. Thus, on monochlorination, an increase in chemical shift from *ca.* δ 124.0 to *ca.* δ 129.0 ppm, is observed for the C-7 nucleus. The other A,B and C-ring carbon nuclei are less sensitive to the incorporated chlorine

atom. In the case of the dichlorinated products **263** and **264**, the C-7 and C-9 nuclei are deshielded relative to those of their precursors, and all the A-ring carbon nuclei are affected by the introduction of chlorine atoms. A DEPT (Distortionless enhancement by polarisation transfer) experiment was also used to establish the number of substituted carbon atoms in the molecule. Mass spectrometry of the chlorinated products also provided confirmation of the extent of chlorination (See Section 2.4(d) for further discussion).

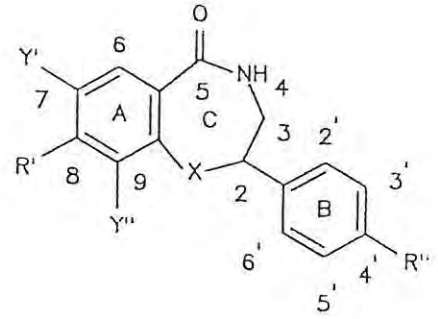


A B

X	R'	R''	No	Y'	Y''	No
O	H	H	**190**	Cl	H	**259**
O	H	F	**200**	Cl	H	**260**
O	H	Cl	**202**	Cl	H	**261**
O	H	Br	**204**	Cl	H	**262**
O	F	H	**192**	-	-	-*
O	Cl	H	**194**	-	-	-*
O	Br	H	**196**	-	-	-*
O	OCH_3	H	**206**	Cl	Cl	**263**
NH	H	H	212	Cl	Cl	**264**

Scheme 52 Reagents (i) *t*-BuOCl, Et_2O, 24-27°C, 24h
*No chlorination observed

Table 14: ^{1}H NMR Chemical Shifts (δ ppm) and splitting patterns of the A- and B-rings of the chlorinated 1,4-benzoxazepinones and 1,4-benzodiazepinone derivatives



No	X	R'	R"	Y'	Y"	A-Ring Protons			B-Ring Protons
						6-H	8-H	9-H	
259	O	H	H	Cl	H	7.84 (d)	8.01 (dd)	7.01 (d)	7.32-7.38 (m, C_6H_5)
260	O	H	F	Cl	H	7.84 (dd)	7.41 (dd)	6.99 (d)	7.35 (m,2'-H & 6'-H) and 7.08 (m, 3'-H & 5'H)
261	O	H	Cl	Cl	H	7.83 (dd)	7.44 (dd)	6.99(d)	7.31 (m, 2'-H & 6'-H) and 7.51 (m, 3'-H & 5'-H)
262	O	H	Br	Cl	H	7.82 (d)	7.41 (dd)	6.99(d)	7.25 (m, 2'-H & 6'-H and 7.51 (m, 3'-H & 5'-H)
263	O	OMe	H	Cl	Cl	7.81 (s)	-	-	7.33-7.44 (m, C_6H_5)
264	NH	H	H	Cl	Cl	7.75 (d)	7.45 (d)	-	7.30-7.40 (m, C_6H_5)

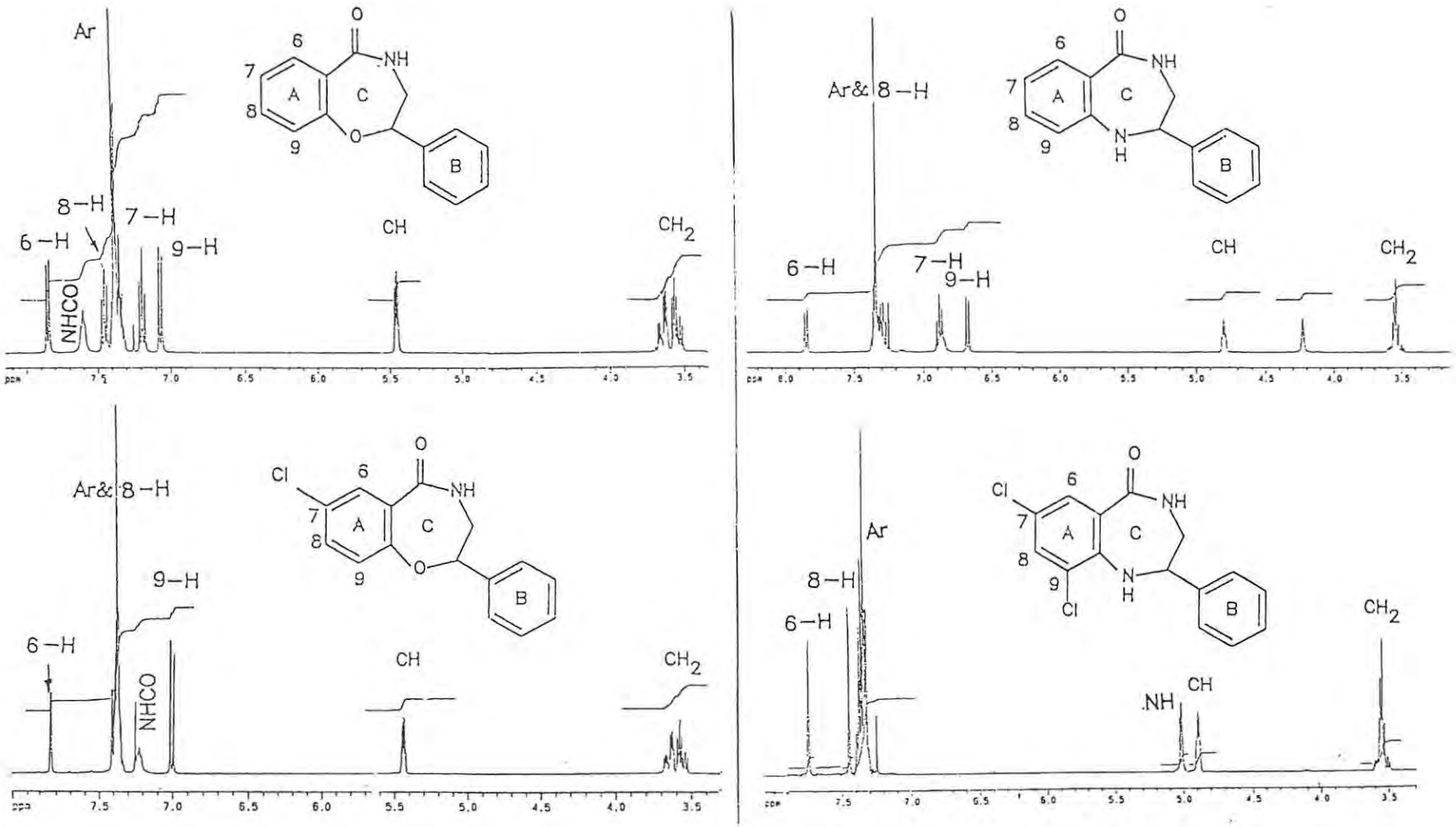
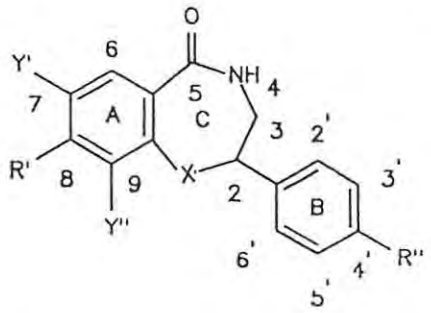


Figure 9: ^{1}H NMR Spectra of the mono- 259 and dichlorinated benzodiazepine 264 derivatives and their precursors.

Table 15: ^{13}C NMR Chemical Shift (δ ppm) data of the A-ring chlorinated benzodiazepine analogues and their precursors in $CDCl_3$ (δ 77.0 ppm).



No	X	R'	R''	Y'	Y''	C-3	C-2	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/ C-6'	C-3'/ C-5'	C-4'
190	O	H	H	H	H	46.3	85.9	171.1	125.8	130.9	123.6	133.3	122.4	154.6	139.0	126.3	128.6	128.5
259	O	H	H	Cl	H	46.4	85.8	169.4	126.8	130.7	129.0	133.4	123.9	153.3	138.3	126.2	128.8	128.7
200	O	H	F	H	H	46.3	85.1	171.1	125.8	130.9	123.9	133.5	122.4	154.4	134.9[a]	128.1[b]	115.6[c]	162.7[d]
260	O	H	F	Cl	H	46.3	85.0	169.3	126.9	130.7	129.3	133.4	123.9	152.9	134.4[a]	128.1[b]	115.8[c]	162.8[d]
202	O	H	Cl	H	H	46.0	85.1	171.2	125.6	130.9	123.8	133.4	122.3	154.3	127.4	127.6	128.7	134.2
261	O	H	Cl	Cl	H	46.2	85.0	169.3	126.9	130.8	129.4	133.4	123.9	152.9	129.4	127.6	129.0	134.6
204	O	H	Br	H	H	46.1	85.1	171.0	125.8	131.0	124.0	133.5	122.3	154.3	138.0	131.8	128.0	122.3
262	O	H	Br	Cl	H	46.1	85.0	169.4	126.7	131.9	129.3	133.5	123.9	152.9	137.5	131.9	127.9	122.7
198*	O	OMe	H	H	H	47.6	84.8	170.7	114.56	138.7	109.9	164.3	105.6	157.5	133.9	126.1	128.7	128.5
263'	O	OMe	H	Cl	Cl	46.4	85.9	168.4	123.2	129.7	124.0	156.1	123.3	50.5	137.9	126.3	128.7	128.8
212	NH	H	H	H	H	46.8	64.8	172.1	120.5	132.2	119.4	132.9	119.2	145.2	142.3	126.7	128.9	128.1
264	NH	H	H	Cl	Cl	46.7	64.4	170.1	122.0	130.8	123.1	132.2	123.0	141.2	139.9	126.5	129.0	128.5

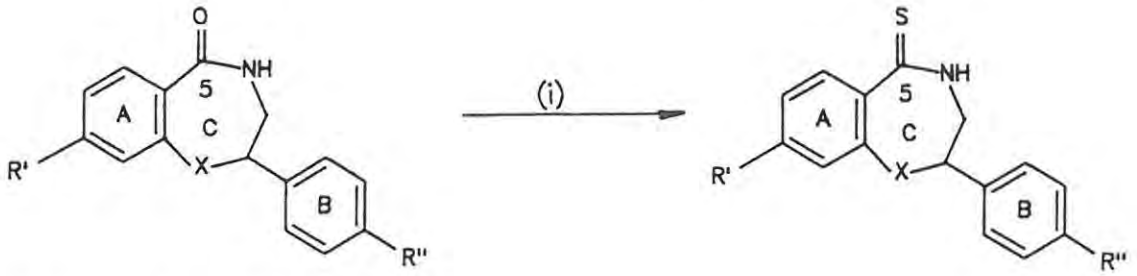
200 and **260** (a) $^4J_{CF}$ 3.02Hz, (b) $^3J_{CF}$ 8.05Hz, (c) $^2J_{CF}$ 22.14Hz and (d) $^1J_{CF}$ 247.5Hz;
198* OCH_3 ^{13}C shift value δ 55.5; and **263'** OCH_3 shift value ^{13}C shift value δ 50.8

(c) THIONATION OF THE BENZODIAZEPINE ANALOGUES

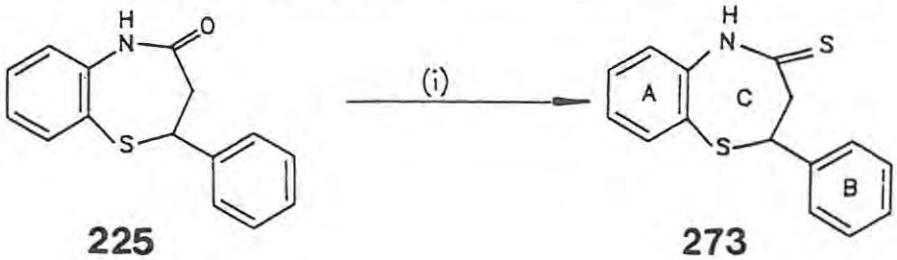
In the light of the SAR studies discussed in the introductory chapter and the fact that carbonyl oxygen is believed to influence benzodiazepine ligand to the receptor, we thionated the carbonyl group of the title compounds to investigate the effect of substituting sulphur for oxygen. Organophosphorus and inorganic phosphorus compounds have found extensive application in synthesis for such transformations.[154,155] In this project, phosphorus pentasulphide (P_2S_5) was used as the reagent of choice to convert the benzodiazepine analogues to their thiolactam derivatives. The thiolactams **265-274** detailed in Scheme 53 were prepared in appreciable yields by treating the benzodiazepine analogues **190-258** with P_2S_5 in refluxing pyridine.[48] The regioisomeric system 4-aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione **276** was prepared by the literature procedure,[30,31,33] involving condensation of 3,3-dimercapto-1-aryl-2-propen-1-one **275** with *o*-phenylenediamine **34** (Scheme 54).

Previous investigations[157] of the ^{1}H NMR spectra of thiocamphor have led to the conclusion that the magnetic anisotropy of the C=S function is qualitatively similar but quantitatively different to the C=O function. In the proton spectra of 1,4-thiaza derivatives **265-272** and **274**, the 6-H nucleus, which is close to the C=S function, is more deshielded and it resonates further downfield than the corresponding nucleus in the analogous carbonyl compounds (Fig. 10). In the ^{1}H NMR spectra of the 1,5-thiaza derivatives **273** and **276**, the methylene protons are slightly more deshielded than the corresponding nuclei in the carbonyl analogues. The observed downfield shift of nuclei near the thiocarbonyl group is attributed to the increased magnetic anisotropy of the C=S function, resulting from the higher polarisability of this bond.[157] Recent progress in thiolactam synthesis has made it possible to obtain important information on the position of the C=S carbon signal in the ^{13}C NMR spectra. The ^{13}C NMR spectral assignment of some 1,4-benzothiazepine-5-thiones have been published previouly,[167] but without detailed discussion. From the ^{13}C NMR chemical shift data in Tables 16 and 17 it can be seen that the thiocarbonyl carbon nucleus in the thiolactams resonates at lower field (at *ca.* δ 200 ppm) than

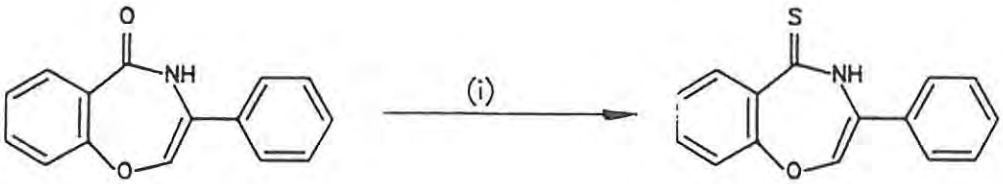
the corresponding carbonyl carbon nucleus in normal lactams (*ca.* δ 170 ppm).



Compd	X	R'	R''	
190	O	H	H	**265**
194	O	Cl	H	**266**
198	O	OCH_3	H	**267**
202	O	H	Cl	**268**
214	NH	H	F	**269**
216	NH	H	Cl	**270**
218	NH	H	Br	**271**
224	S	H	H	**272**

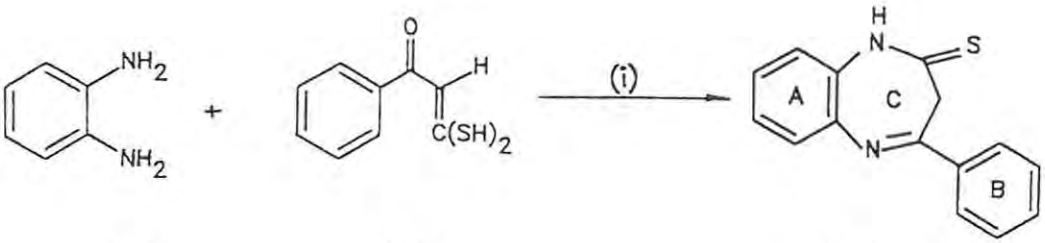


225 **273**



258 **274**

Scheme 53 Reagents: (i) P_2S_5, pyridine, heat



34 **275** **276**

Scheme 54 Reagents: (i) toluene, heat

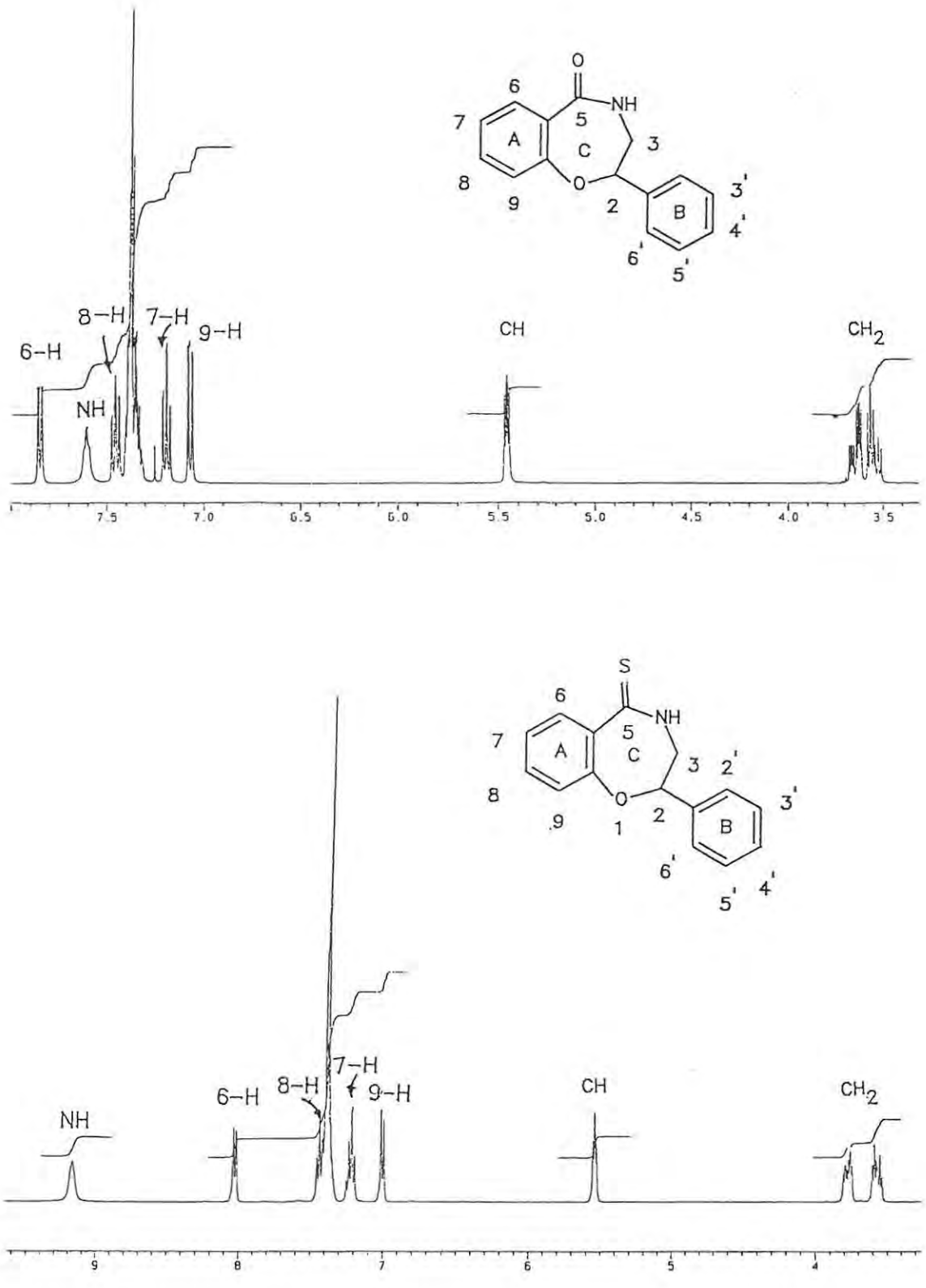
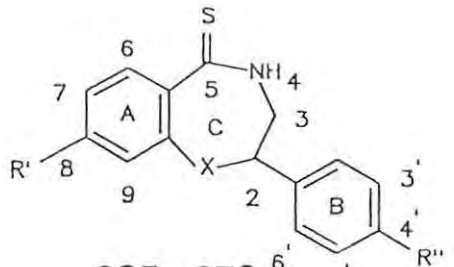
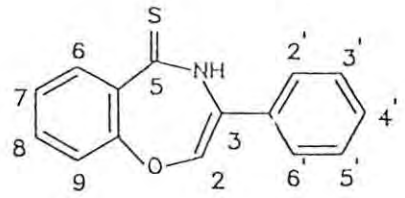


Figure 10: ^{1}H NMR Spectra of 1,4-benzoxazepinon-5-one 190 and its 1,4-benzoxazepine-5-thione 265 derivative

Table 16: ^{13}C NMR Chemical shift data (δ ppm) of the 1,4-thiaza derivatives in $CDCl_3$ (δ 77.0 ppm).



265–272

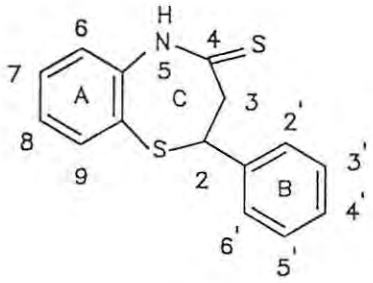


274

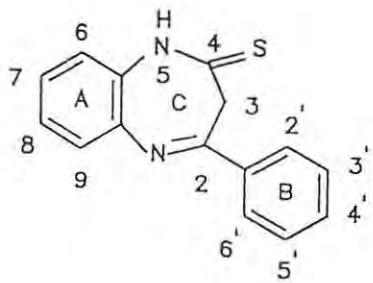
No	X	R'	R''	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1'	C-2'/ C-6'	C-3'/ C-5'	C-4'	OMe
265	O	H	H	87.3	49.6	201.1	132.8	132.8	124.6	133.3	122.7	151.6	138.5	126.3	128.8	128.8	
266	O	Cl	H	87.5	49.6	199.8	131.0	134.0	124.9	138.0	122.9	152.2	138.9	126.2	128.9	129.0	
267	O	OMe	H	87.5	49.7	200.1	124.8	134.8	110.8	164.0	107.2	153.5	138.5	126.2	128.6	128.7	55.6
268	O	H	Cl	86.6	49.4	200.9	132.7	132.8	124.9	133.5	122.6	151.4	134.7	127.7	129.0	132.7	
269	NH	H	F	66.4	49.6	202.3	128.4	133.2	121.1	134.3	120.3	142.5	138.0[a]	128.4[b]	115.8[c]	162.6[d]	
270	NH	H	Cl	65.9	50.2	202.4	128.5	133.2	121.2	134.4	120.3	142.3	140.7	128.1	129.9	134.2	
271	NH	H	Br	65.9	49.6	201.5	128.0	132.4	120.0	133.8	119.8	142.6	141.6	128.4	131.4	121.4	
272	S	H	H	56.8	51.1	202.6	127.5	131.7	131.5	134.4	129.4	144.4	140.6	127.1	128.9	128.2	
274	-	-	-	137.7	131.3	198.1	131.1	133.4	124.2	134.2	119.3	157.8	131.5	125.8	128.0	128.6	

269 (a) $^4J_{CF}$ 3.02Hz, (b) $^3J_{CF}$ 8.05Hz, (c) $^2J_{CF}$ 22.1Hz and (d) $^1J_{CF}$ 247.5Hz

Table 17: ^{13}C NMR Chemical shift data (δ ppm) of the 1,5-thiaza derivatives in $CDCl_3$ (77.0 ppm).



273



275

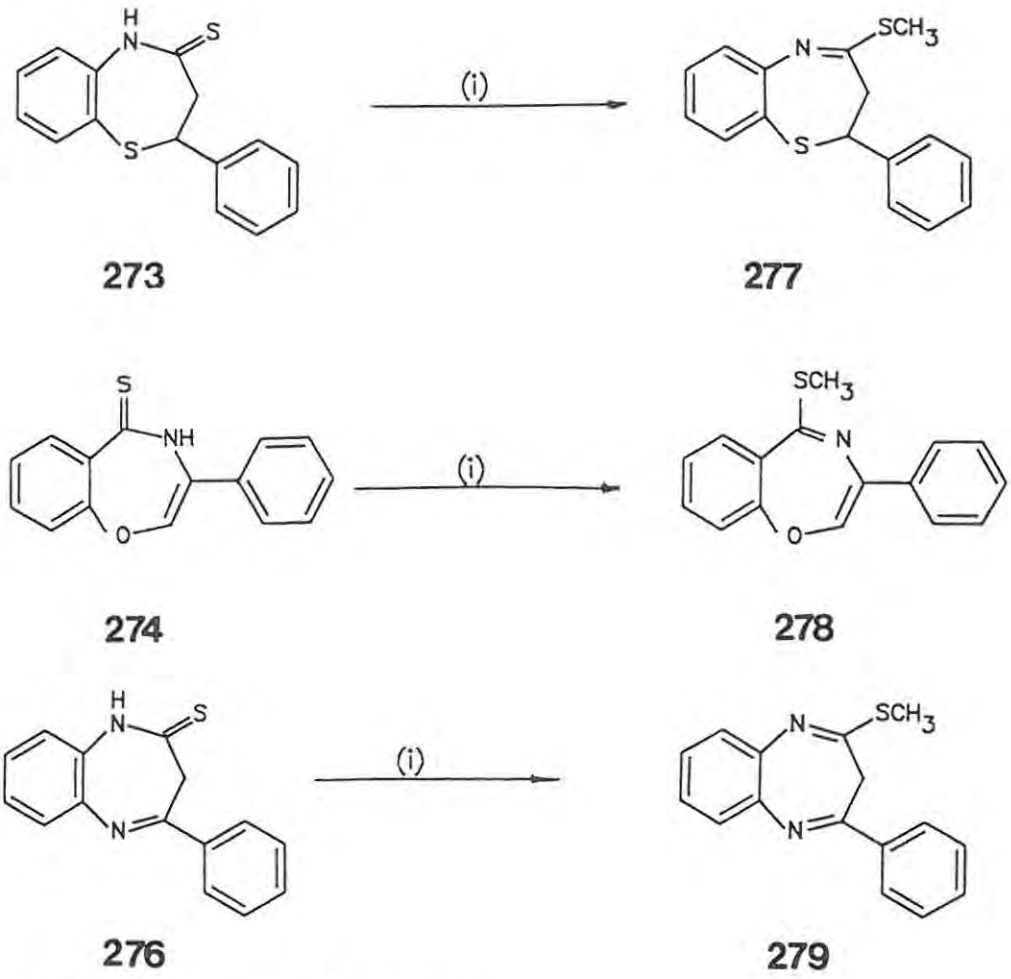
No	C-2	C-3	C-4	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1′	C-2′/C-6′	C-3′/C-5′	C-4′
273	55.0	49.6	203.9	127.4	130.1	127.9	136.0	122.8	143.6	141.5	126.3	128.8	128.0
276[a]	158.8	47.7	192.6	125.9	128.0	125.7	131.1	122.1	140.6	136.4	125.9	131.2	127.7

276[a] using DMSO-d_6 as solvent

(d) ALKYLATION OF THE THIAZA DERIVATIVES

In principle, thiocarbonyl compounds are expected to behave like the corresponding carbonyl compounds in their chemical reactions. However, in practice, thiocarbonyl compounds have been found to be more reactive than their carbonyl counterparts and also to react differently.[157] The high polarizability of the C=S linkage (involving an overlap of a carbon 2p-orbital and a sulphur 3p-orbital, which is less efficient than the 2p-2p overlap of the C=O bond) accounts for their high reactivity.[157] The difference in reactivity has been illustrated by electrophilic attack at sulphur in thioamides,[30,31,33,48,49] rather than at nitrogen as observed in normal amides.[37,105,106]

Methylation was performed on a few of the thiolactam derivatives prepared in this study. The methylthioimino ethers **277-279** were prepared in high yield by the literature procedure,[48] using methyl iodide (Scheme 55) and were easily distinguished from their precursors by spectroscopic techniques. An alternative literature route,[32,33] to compound **279** involves the condensation of 1,2-phenylenediamine with ketenedithioacetals. The conversion of thiolactams to methyl-thiomino ethers has been observed[48,49] to facilitate nucleophilic attack on the thiocarbonyl compounds[49a,b] (*eg.* 4,5-dihydrotetrazolo[5,1-*d*]-1,5-benzothiazepine **243**,[49(a)] page 70 has been synthesised from these intermediates). The appearance of the methyl signals in the ^{1}H NMR (at *ca.* δ 2.50 ppm) and ^{13}C NMR (at *ca.* δ 14.0 ppm) spectra of these compounds, confirms incorporation of the methyl group; while the absence of the IR NH band in these compounds also distinguishes them from their precursors.



Scheme 55 Reagents: (i) MeI, NaH, THF

2.4 MASS SPECTROMETRIC STUDIES OF 2-PHENYL-1,2,3,4-TETRAHYDRO-4-QUINOLONES, 1-THIOFLAVANONES AND THEIR ß-PHENYLMERCAPTO-DIHYDROCINNAMIC ACID PRECURSORS, AND BENZODIAZEPINE ANALOGUES

The major MS fragmentation patterns for several series of compounds prepared in this research have been elucidated by a combination of low-resolution MS, high-resolution MS and metastable peak analysis. The low-resolution mass spectra of representative examples are reproduced in appendix 1.

(a) 2-PHENYL-1,2,3,4-TETRAHYDRO-4-QUINOLONES

The low-resolution mass spectrum of the parent compound **164** is reproduced in Figure 11 and the relative intensities of significant peaks of several compounds on page 97 (Table 18). Previous studies on the fragmentation patterns of flavanones were explained by implicating their 2-hydroxychalcone isomers.[159] However, in the case of the 2-aryl-4-quinolones and the 2-aminochalcones, the mass spectra of the cyclic and open-chain isomers only differ in the relative intensities of the peaks, making it possible to explain the fragmentation pattern of 4-quinolones without implicating their open-chain isomers. The fragmentation patterns of the 2-aryl-1,2,3,4-tetrahydro-4-quinolones detailed in Scheme 56 parallel those of the flavanone analogues. A loss of $H^{\bullet}$ from the molecular ion I affords the resonance stabilised even-electron species II (path 1); for flavanones this (M-1) ion is formulated as 4-hydroxyflavylium tautomer.[159] Ring contraction and loss of the methyl radical from the molecular ion in path 2 affords the cationic species III.

Loss of neutral aryl cyanide from the cationic species III leads to the acylium cation IV. Elimination of an aryl radical from the molecular ion (path 2), in all six of the compounds examined, affords the intense peak (relative intensity ≥ 93% Table 18) corresponding, in fact, to the base peak in the spectra of compounds **166** - **169**. The structure of this fragment can

be formulated as the cationic species IV or its hydroxyquinolium tautomer. Subsequent loss of $H^{\bullet}$ from this ion affords the radical-cation V.

The ions VI (path 4) and VIII (path 5) result from retro-Diels-Alder [RDA] collapse of the molecular ion. The $[RDA]^{+\bullet}$ ion VI (*m/z* 119) is observed in 45-95% relative abundance in the spectra of the 2-aryl-1,2,3,4-tetrahydro-4-quinolones; an analogous $[RDA]^{+\bullet}$ ion (*m/z* 120) in the spectrum of flavanone accounts for the base peak in that compound.[166] The ring contracted ions IX and X are the result of loss of hydrogen cyanide and carbon monoxide from the $[RDA]^{+\bullet}$ ion VI, respectively. In the case of the 4-fluoro derivative **165**, the radical-cation IX is responsible for the base peak. Fragment $C_{12}H_{12}NO$ (II; path 6) in the spectrum of the methoxy analogue **168**, ($R = OCH_3$) while identical to M-1 fragment II ($R = H$) arises, in fact, *via* concerted loss of formaldehyde from the molecular ion ($R = OCH_3$), and is supported by metastable peak data [*m/z* 253-222 (194.8)].

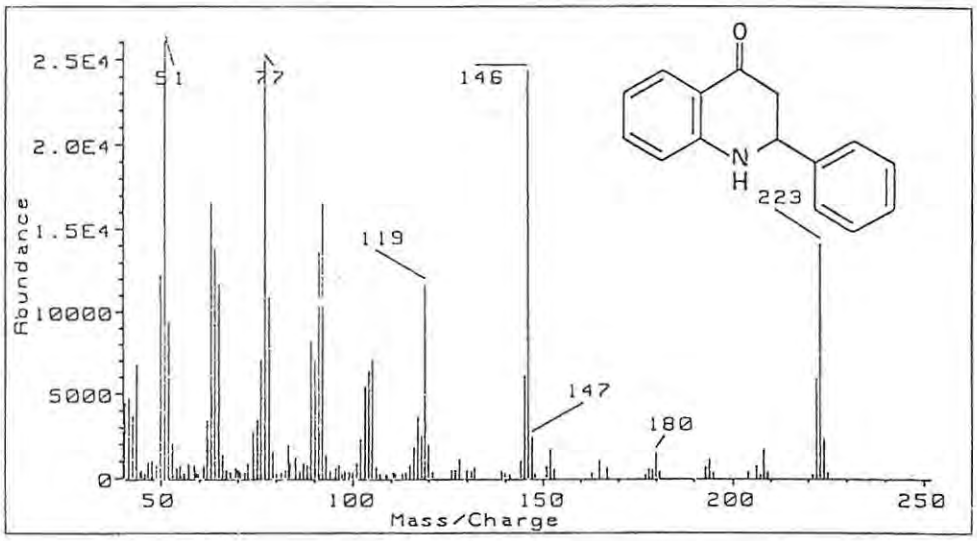
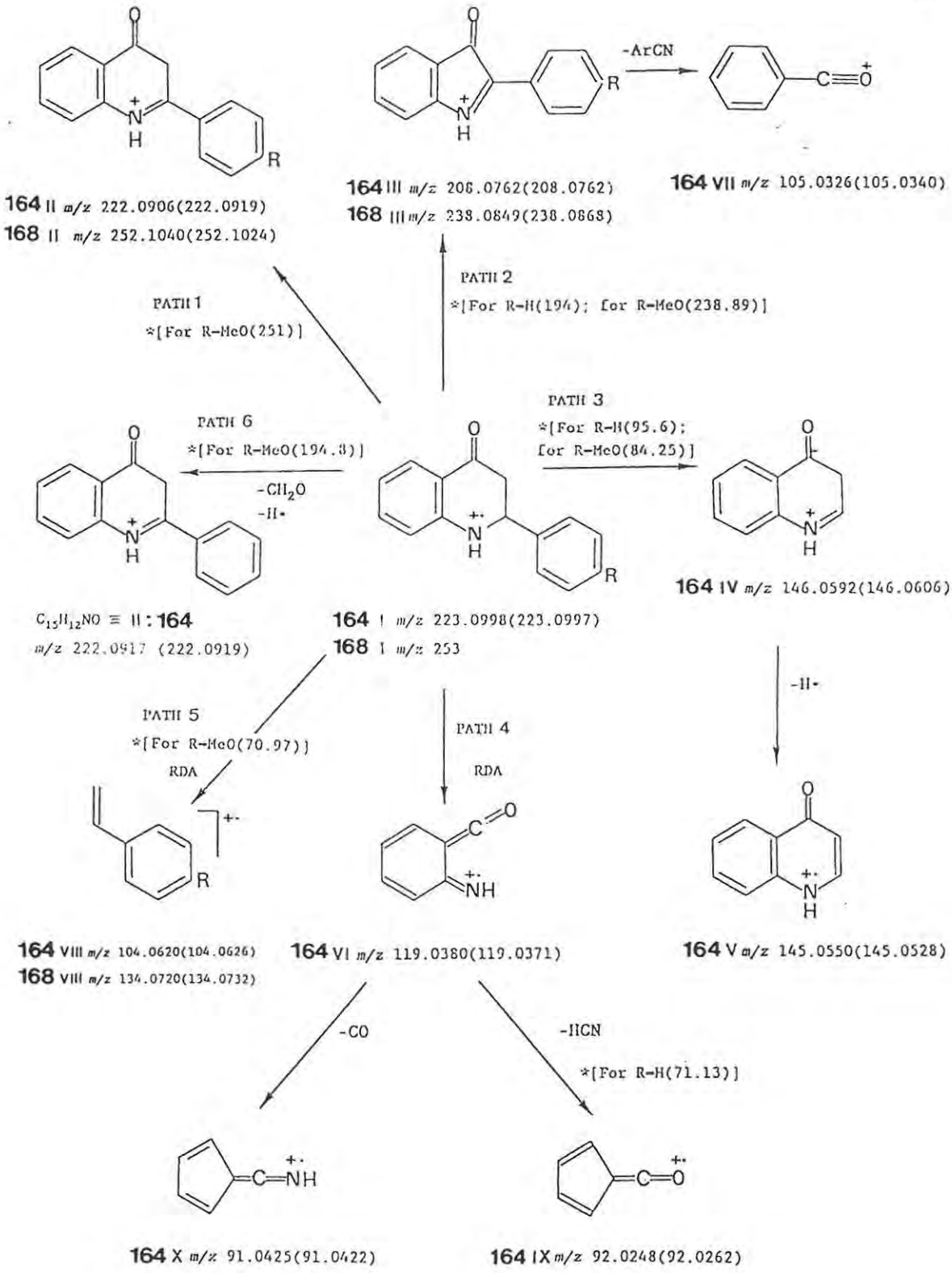
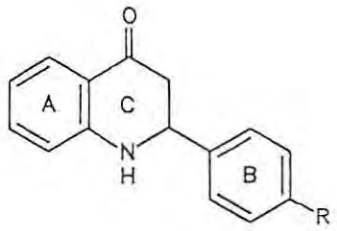


Figure 11: Low-resolution mass spectrum of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone



Scheme 56 MS Fragmentation patterns for 2-phenyl-1,2,3,4-tetrahydro-4-quinolone 164 (R = H) and its 4'-methoxy analogue 168 (R = MeO). Accurate masses (*m/z*) determined for individual ions are followed in parethenses by calculated formula masses; an asterisk indicates a pathway supported by the metastable peak given in parentheses.

Table 18: Selected peaks (*m/z*; followed by % relative abundance) observed for 2-phenyl-1,2,3,4-tetrahydro-4-quinolones 164-169



No	R	Ion Fragment Types									
		I	II	III	IV	V	VI	VII	VIII	IX	X
164	H	223	222	208	146	145	119	105	104	92	91
		54.1	22.4	6.3	93.4	23.2	44.8	27.1	24.5	63.5	52.1
165	F	241	240	226	146	145	119	105	122	92	91
		57.3	22.2	7.5	93.0	19.4	71.5	40.8	20.4	100	40.5
166	Cl	257[a]	256[a]	242[a]	146	145	119	105	138[a]	92	91
		38.2	16.1	4.3	100	27.6	59.6	28.4	10.2	74.6	38.7
167	Br	301[b]	300[b]	286[b]	146	145	119	105	182[b]	92	91
		19.9	7.6	2.9	100	28.9	62.9	27.9	4.2	68.0	40.5
168	OMe	253	252	238	146	145	119	105	134	92	91
		49.5	39.2	6.2	100	16.2	62.4	20.8	35.6	78.0	72.5
169	NO_2	268	267	253	146	145	119	105	149	92	91
		31.7	5.2	2.6	100	12.4	34.8	23.5	1.1	53.8	38.0

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

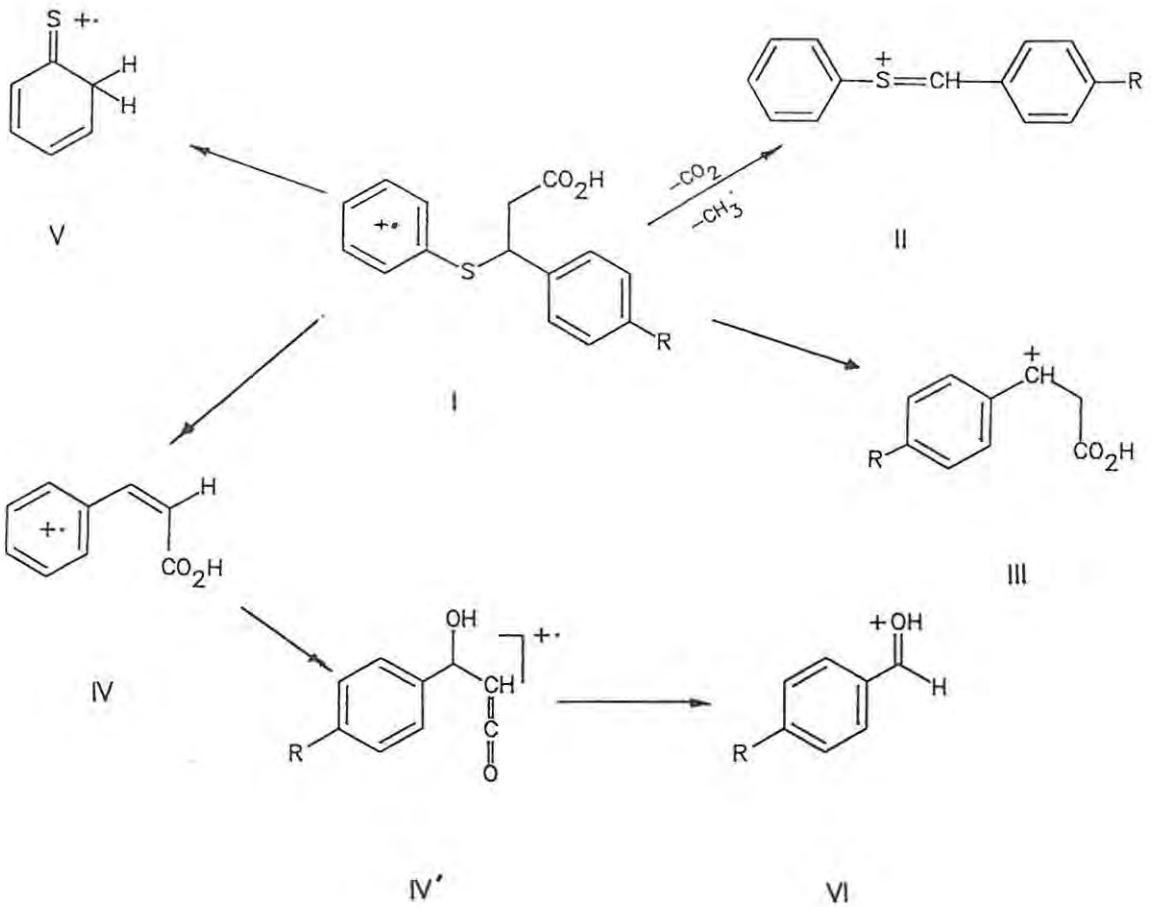
(b) 1-THIOFLAVANONES AND THEIR ß-PHENYLMERCAPTODIHYDROCINNAMIC ACID PRECURSORS

Low resolution mass spectra were obtained for the 1-thioflavanones **185-188** and their ß-phenylmercaptodihydrocinnamic acid precursors **180-184**. A preliminary study of fragmentation patterns of these compounds has been investigated. The proposed fragmentations, outlined in Schemes 57 and 58 have yet to be confirmed by detailed high resolution and metastable peak analysis. The molecular ions I of the ß-phenylmercapto-dihydrocinnamic acids are proposed to undergo cleavage to form the low intensity ion II (relative abundance < 22.0%), while loss of the thiophenyl radical affords the cationic species III (Scheme 57). The cinnamic acid radical-cation IV is the result of loss of thiophenol from the molecular ion, while the complementary ion (*m/z* 110) may be formulated as structure V (or a thiophenol radical cation). Similar fragments have been formulated for higher alkyl ethers of thiophenol and are considered to arise *via* either a McLafferty rearrangement or hydrogen transfer to the heteroatom.[160] A 1,3-hydroxyl shift and subsequent bond cleavage of the cinnamic acid fragment V results in the protonated benzaldehyde VI.[160]

The mass spectral data of the 1-thioflavanones parallels those of flavanone[159] and 2-phenyl-1,2,3,4-tetrahydro-4-quinolones,[161] and the resulting fragments indicate the possibility of an equilibrium between the 1-thioflavanone and the 4-hydroxythioflavylium tautomer (Scheme 58). Loss of $H^{\bullet}$ from the molecular ion (path 1) to form the M-1 ion II is also observed in the spectra of all the 1-thioflavanones detailed in Table 20. The existence of the 4-hydroxythioflavylium tautomer is indicated by the cationic species III which is presumed to result from the loss of the hydroxyl radical from the molecular ion I (path 2). Ring contraction and elimination of a methyl radical from the molecular ion (path 3) to form the cationic species IV is also observed. The cationic species V is the result of loss of the aryl radical (path 4) from the molecular ion; subsequent loss of $H^{\bullet}$ from this *m/z* 163 ion affords the even-electron species VI (*m/z* 162). The structure of the resonance stabilised *m/z* 163 ion can also be formulated as the 4-hydroxy-

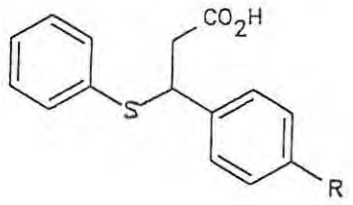
flavylium ion. Precedents for the formation of fragments of the type II, IV and V are provided by the mass spectra of flavanones and 2-aryl-4-quinolones.

The cationic species VII (*m/z* 137; path 5) is probably the result of loss of a styryl radical from the 2-thiochalcone isomer in equilibrium with the 1-thioflavanone. As in the case of flavanones and 2-aryl-1,2,3,4-tetrahydro-4-quinolones, retro-Diels-Alder collapse of the molecular ion of the 1-thioflavanones affords complementary ions VIII and IX (path 6). The $[RDA]^{+\bullet}$ ion VII (*m/z* 136) accounts for the base peak in the spectra of all of these compounds (Table 20). Subsequent loss of carbon monosulphide (CS) and carbon monoxide (CO) from this $[RDA]^{+\bullet}$ ion leads to the conjugated, ring-contracted species XI and X, respectively.



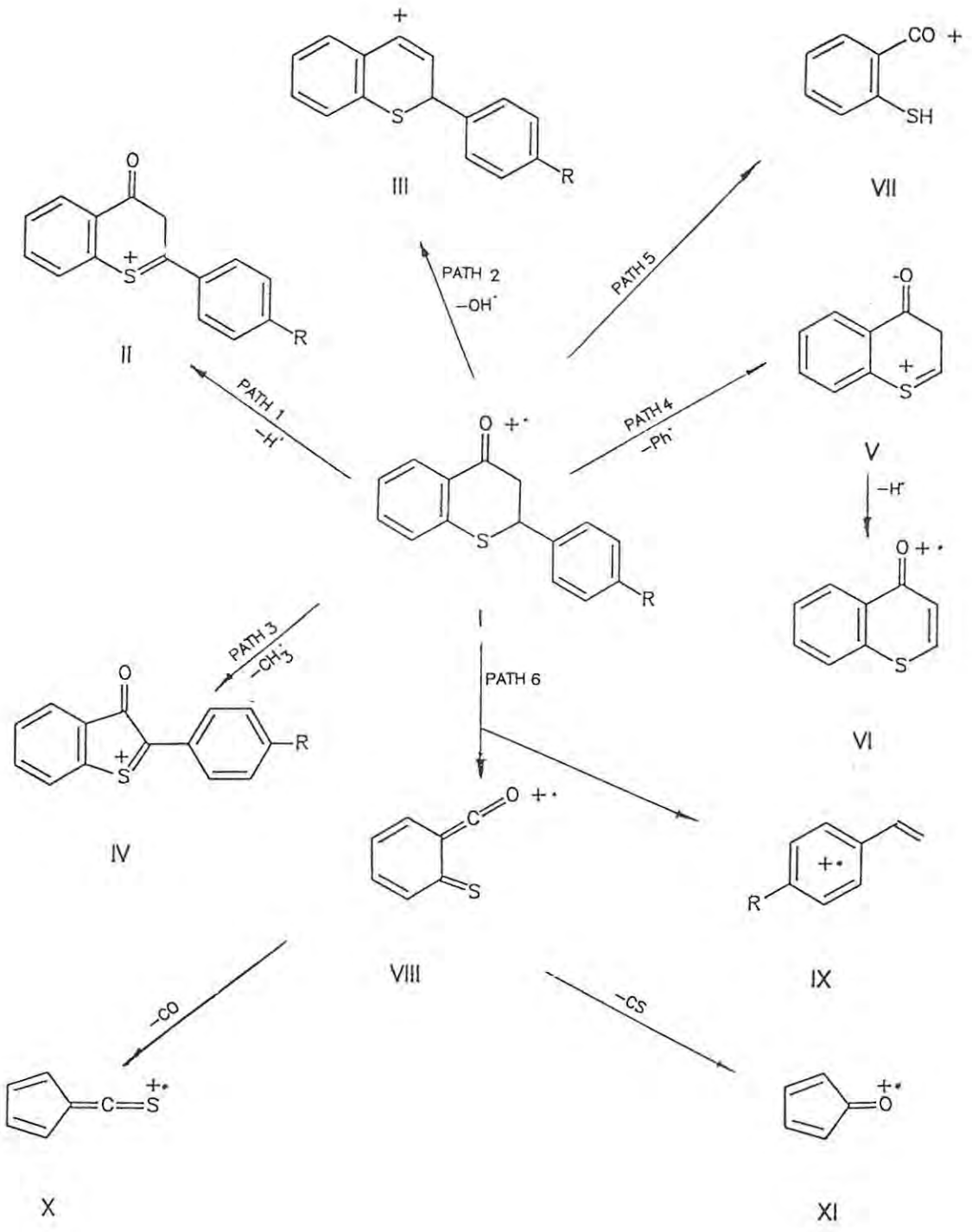
Scheme 57 MS Fragmentation patterns for ß-mercaptodihydrocinnamic acids detailed in Table 19

Table 19: Selected peaks (*m/z*; followed below by % relative abundance) observed for ß-phenylmercaptodihydrocinnamic acids.



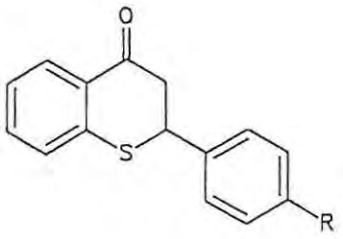
No	R	Ion Fragment Types					
		I	II	III	IV	V	VI
175	H	258	199	149	148	110	107
		42.8	5.0	83.3	18.5	77.6	100
176	F	276	217	167	165	110	125
		17.1	21.2	47.7	4.0	5.9	100
177	Cl	292[a]	233[a]	183[a]	182[a]	110	141[a]
		17.9	0.8	61.8	19.3	52.5	100
178	Br	336[b]	277[b]	227[b]	226[b]	110	185[b]
		11.8	1.2	59.0	5.3	54.7	100
179	OCH_3	288	229	179	178	110	137
		6.1	4.0	95.8	8.5	24.4	100

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br



Scheme 58 MS Fragmentation patterns for 2-phenyl-2,3-dihydro-4*H*-1-benzothiopyran-4-ones detailed in Table 20

Table 20: Selected peaks (*m/z*; followed by % relative abundance) observed for the 2-phenyl-2,3-dihydro-4*H*-benzothiopyran-4-ones



No	R	Ion Fragment Types										
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI
185	H	240	239	225	223	163	162	137	136	104	108	92
		31.6	4.2	0.2	4.6	15.1	8.8	12.0	100	12.9	52.0	5.9
186	F	258	257	243	241	163	162	137	136	122	108	92
		32.1	3.2	0.6	3.5	13.0	12.1	13.6	100	14.2	84.1	8.6
187	Cl	274[a]	273[a]	259[a]	257[a]	163	162	137	136	138	108	92
		27.0	2.7	1.1	2.8	8.8	7.7	12.1	100	9.3	29.4	3.1
188	Br	318[b]	317[b]	303[b]	301[b]	163	162	137	136	182	108	92
		56.2	4.8	4.2	4.6	31.4	24.5	30.5	100	10.8	89.7	11.1

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

(c) MASS SPECTROMETRY OF BENZODIOAZEPINE ANALOGUES PREPARED IN THIS STUDY

Previously in our laboratory, the mass spectrometric behaviour of the 4-phenyl-3,4-dihydro-1,5-benzodioxepin-2-ones,[162] and 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones[163] and their tetrazolo[1,5-*d*] derivatives was studied.[164] In this work we report the extension of these studies to include the following.

(i) **1,4-Benzodiazepin-5-one systems**, *viz.*, 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones, 2-phenyl-2,3-dihydro-1,4-benzothiazepin-5-ones, and conjugated 3-phenyl- and 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5-ones.

(ii) **1,5-Benzoxazepinones and their 1-thia analogues**, *viz.*, 2-phenyl-2,3-dihydro-1,5-benzoxazepine-4(5*H*)-one and 2-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones.

(iii) **Tetrazolo derivatives**, *viz.*, tetrazolo[5,1-*d*]-1,5-benzothiazepine, tetrazolo[1,5-*d*]-1,4-benzothiazepines and tetrazolo[1,5-*d*]-1,4-benzodiazepines.

The fragmentation patterns of the 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones and their tetrazolo-[1,5-*d*] derivatives have been elucidated by means of:

(i) high resolution analysis of significant fragments;

(ii) a comparative study of the low-resolution spectra; and

(iii) metastable peak analyses.

The results of mass spectrometric analysis of the 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones and their tetrazolo[1,5-*d*] derivatives have now been published[165] and a few additional peaks are repeated in this section. Although each class of compounds exhibits individual fragmentation patterns, some general trends have also been observed in the series of analogous systems investigated.

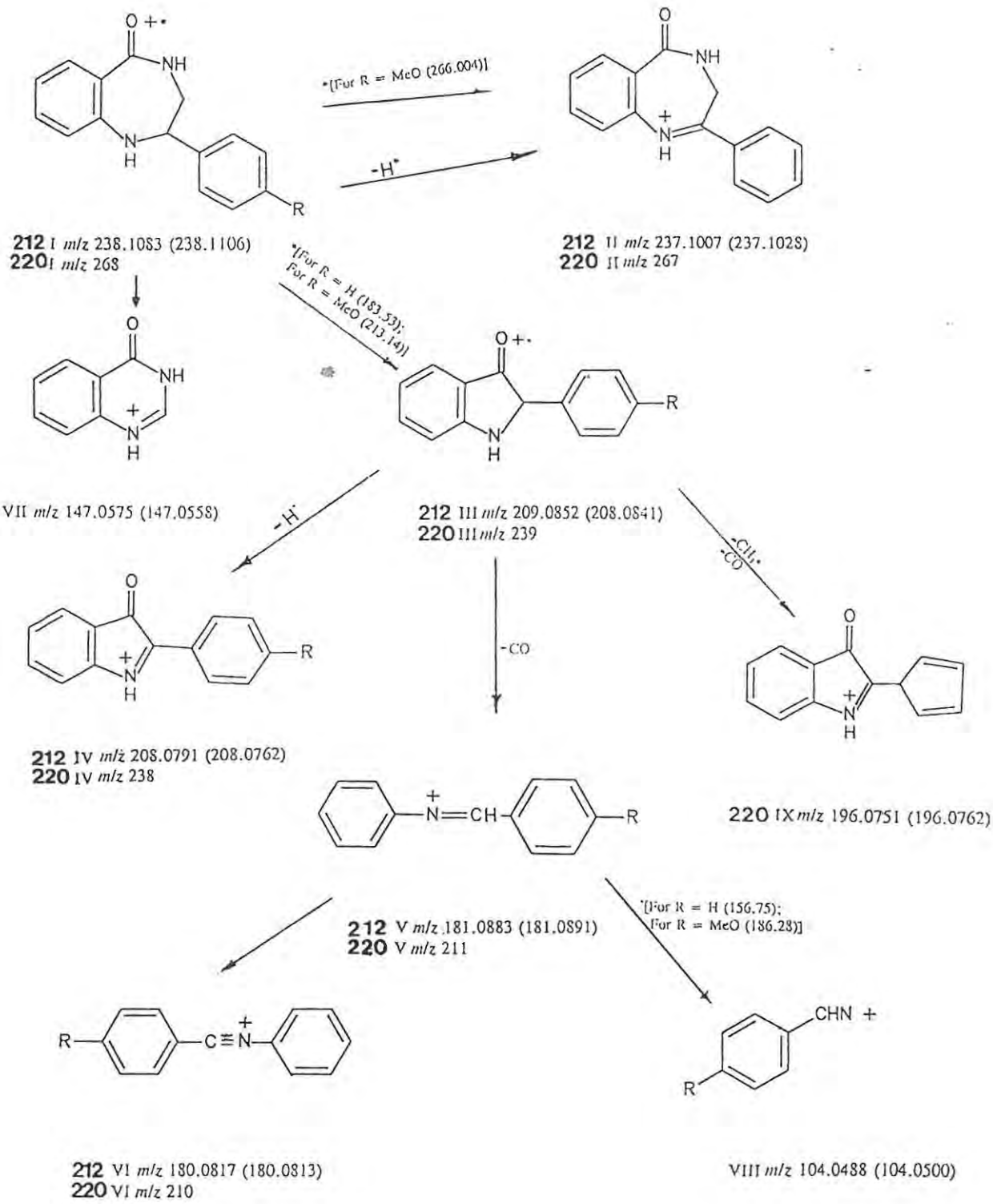
(i) 1,4-Benzodiazepin-5-one derivatives

The major fragmentation characteristic of the 2-phenyl derivatives of the 1,4-benzodiazepin-5-ones detailed in Tables 21 and 22 are summarised in Schemes 59 and 60, respectively. Loss of H$^{\bullet}$ from the molecular ion I of the 1,4-benzodiazepin-5-ones (Scheme 59) affords the resonance-stabilised cation II in a fragmentation similar to that observed for 2-phenyl-1,2,3,4-tetrahydro-4-quinolones.[161] Contraction of the C-ring (the ring assignment following the flavanoid convention) and elimination of $CH_2=NH$ from the molecular ion I to afford the odd-electron species III (Scheme 59) distinguishes the 1,4-derivatives from the 1,5-regioisomers. Formation of fragment III, *via* loss of $CH_2=NH$, is supported by metastable peak data and parallels a fragmentation observed for the analogous 1,4-benzoxazepin-5-ones.[163] This fragmentation (I-III) also provides confirmation of alkyl migration during the Schmidt reaction of the flavanoid precursors. Loss of H$^{\bullet}$ or CO from fragment III affords the even-electron species IV or the radical-cation V, respectively; the latter fragmentation (III-IV) being confirmed by a metastable peak (*m/z* 156.75; for R=H). The odd-electron species V, in turn, eliminates H$^{\bullet}$ or phenyl radical to afford the cationic species VI or VIII, respectively. Contraction of the C-ring and loss of a benzylic radical from the molecular ion I accounts for the even-electron species VII. The base peak for the methoxy analogue (**220**, $R=OCH_3$) at *m/z* 180, while identical to fragment II (R=H) arises, in fact, *via* concerted loss of CH_2O and H$^{\bullet}$ from the molecular ion I (Scheme 59). The C-ring contracted even-electron species IX is the result of loss of $CH_3^{\bullet}$ and CO from fragment III of the methoxy analogue **220**.

The proposed fragmentation patterns for the 2-phenyl-1,4-benzothiazepin-5-one derivatives detailed in Table 22 are outlined in Scheme 60, and have yet to be confirmed by high-resolution and metastable peak analyses. Thus, C-ring contraction and loss of $CH_2=NH$ from the molecular ion I affords the radical-cation II. Loss of CO and H$^{\bullet}$ from the radical-cation II (a process analogous to that observed for 2-phenyl-1,4-benzoxazepin-5-ones[163]) is postulated to provide the cationic species III. Elimination of the benzylic radical from the molecular ion gives

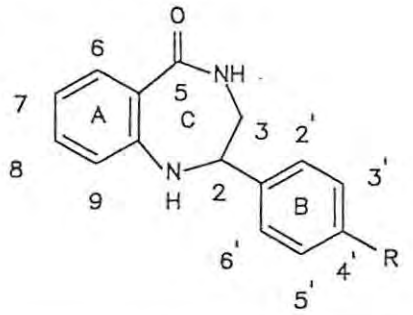
the cationic species, tentatively formulated as IV. The two complementary ions V and VII distinguish the 1,4-benzothiazepin-5-ones from their 1,5-isomers. In the case of the fluoro analogue **227** contribution to the peak at *m/z* 137 is probably due to the cationic species V and/or the radical-cation VII (R = F). The radical-cation VI probably results from the loss of H$^{\bullet}$ from V or HCN and H$^{\bullet}$ from the cationic species IV. Loss of CO from fragment V accounts for the cationic species VIII. Elimination of CO from the radical-cation VI affords the ring-contracted odd-electron species IX.

The low-resolution mass spectral-data were also obtained for the conjugated 2-phenyl- **246** and 3-phenyl-1,4-benzoxazepin-5(4*H*)-one **258**, and show fragmentation patterns (Scheme 61) similar to those of their non-conjugated analogues (Scheme 59). Loss of PhCN or HCN from the molecular ion I (presumably in the imine tautomeric form) affords the radical-cation II (**246**; R' = Ph, R" = H and **258**; R' = H, R" = Ph, respectively). The radical-cation II, in turn, eliminates H$^{\bullet}$ to form the even-electron species III, which then loses CO to afford the resonance-stabilised cationic fragment IV. The latter (R' = H) probably constitutes the base peak in the spectrum of the 3-phenyl derivative **258**. In the case of the 2-aryl derivative **246** (R' = Ph, R" = H) the base peak at *m/z* 105 corresponds to the loss of benzyne from the cationic fragment IV and is tentatively formulated as V. Fragmentation patterns similar to those of the 1,4-benzoxazepin-5-one,[163] 1,4-benzodiazepin-5-one[165] and 1,4-benzothiazepin-5-one derivatives were also observed for their thiaza analogues.



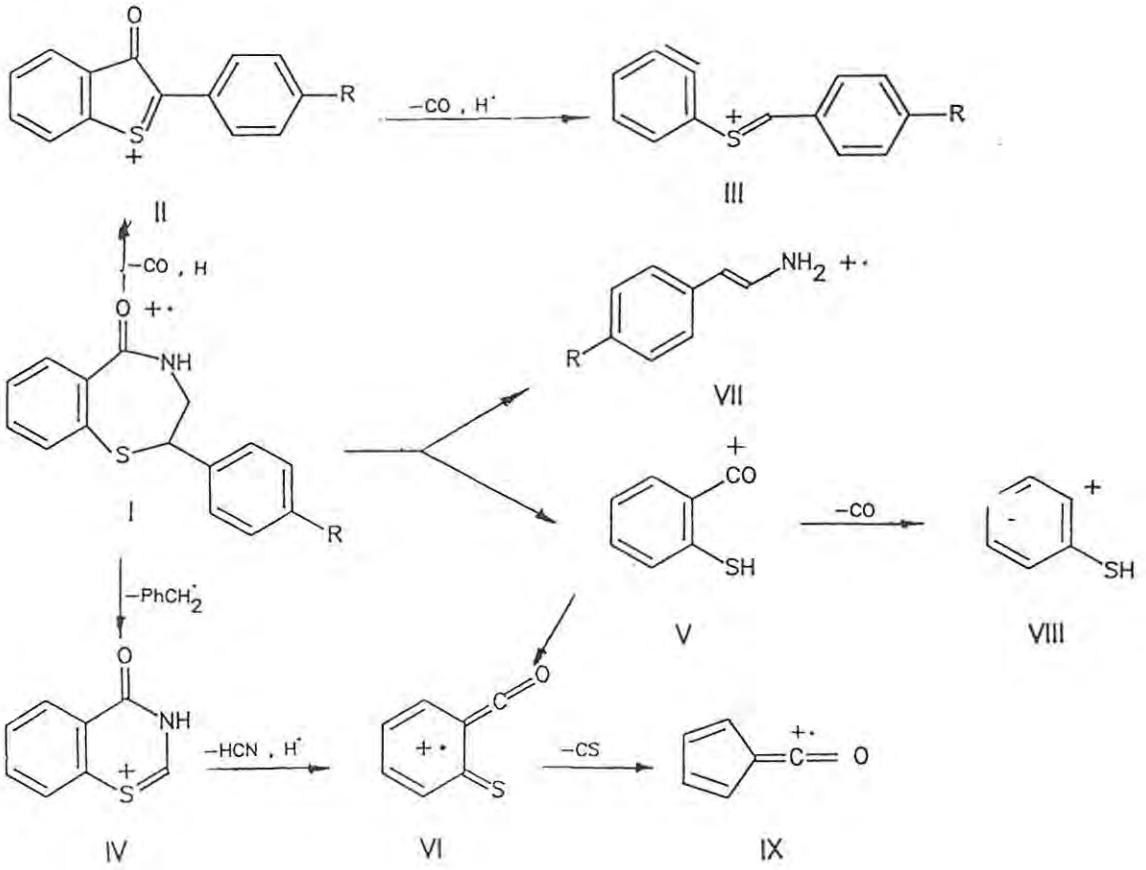
Scheme 59 MS Fragmentation patterns for 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one 212 (R=H) and its 4'-methoxy analogue 220. Accurate masses (*m/z*) determined for individual ions are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable peak given in parentheses.

Table 21: Selected peaks (*m/z*; followed below by % relative abundance) observed for 2-phenyl-1,4-benzodiazepin-5-ones.

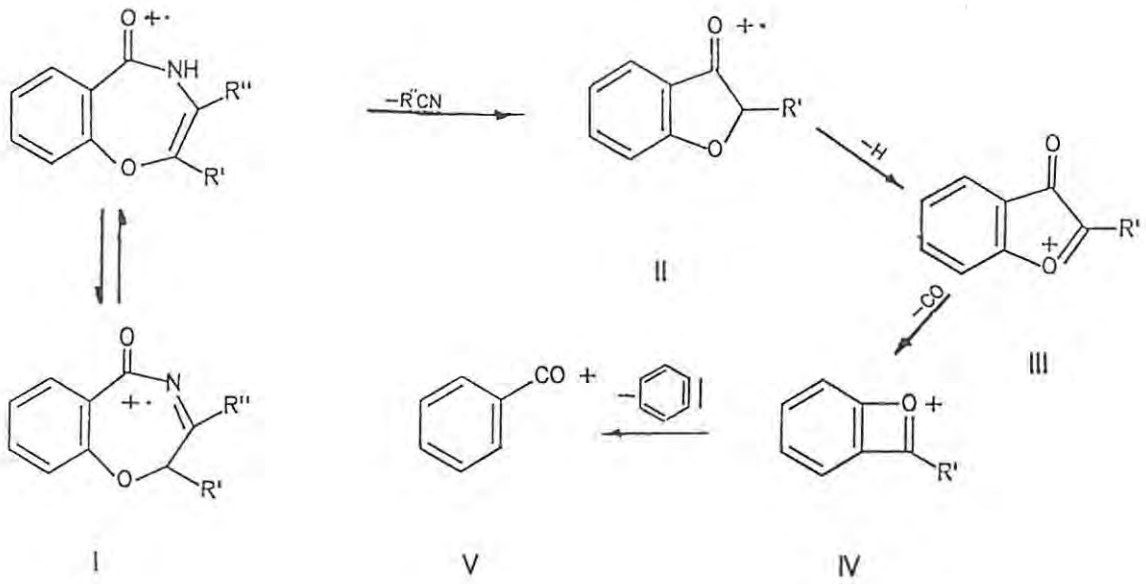


No	R	Ion Fragment Types							
		I	II	III	IV	V	VI	VII	VIII
212	H	238	237	209	208	181	180	147	104
		19.0	7.1	8.0	4.3	33.7	100	5.6	20.6
214	F	256	255	227	226	199	198	147	122
		18.3	6.9	8.4	5.3	30.4	100	4.1	29.1
216	Cl	272[a]	271[a]	243[a]	242[a]	215[a]	214[a]	147	138
		35.4	12.1	18.2	8.3	51.3	100	12.1	35.1
218	Br	316[b]	315[b]	287[b]	286[b]	259[b]	258[b]	147	182
		17.7	5.1	14.3	4.6	23.0	33.7	13.8	15.3
220	OMe	268	267	239	238	211	210	147	134
		72.2	44.4	11.7	10.7	45.0	100	3.7	26.6
222	NO_2	283	282	254	253	226	225	147	149
		40.7	6.3	53.3	5.0	33.8	30.9	4.0	18.6

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

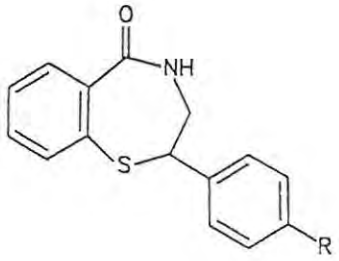


Scheme 60 MS fragmentation patterns for 2-phenyl-1,4-benzothiazepin-5(4*H*)-one derivatives detailed in Table 22.



Scheme 61 MS Fragmentation patterns for conjugated 2-phenyl- 246 and 3-phenyl-1,4-benzoxazepin-5-one 258 derivatives

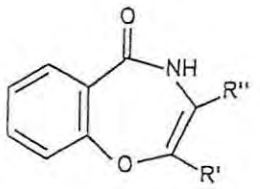
Table 22: Selected peaks (*m/z*; followed below by % relative abundance) observed for 2-phenyl-1,4-benzothiazepin-5-ones.



No	R	Ion type Fragments								
		I	II	III	IV	V	VI	VII	VIII	IX
224	H	255	226	197	164	137	136	119	109	108
		52.1	100	76.0	10.9	17.7	21.8	30.5	22.0	48.9
227	F	273	244	215	182	137	136	137	109	108
		73.2	100	74	1.73	78.3	33.5	78.3	55.0	55.0
229	Cl	289[a]	260[a]	231[a]	198	137	136	153[a]	109	108
		91.2	100	28.7	13.1	41.7	36.0	42.2	36.9	74.7
231	Br	333[b]	304[b]	275	242	137	136	197[b]	109	108
		40.3	56.3	8.9	5.8	62.6	47.1	100	42.1	75.1

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

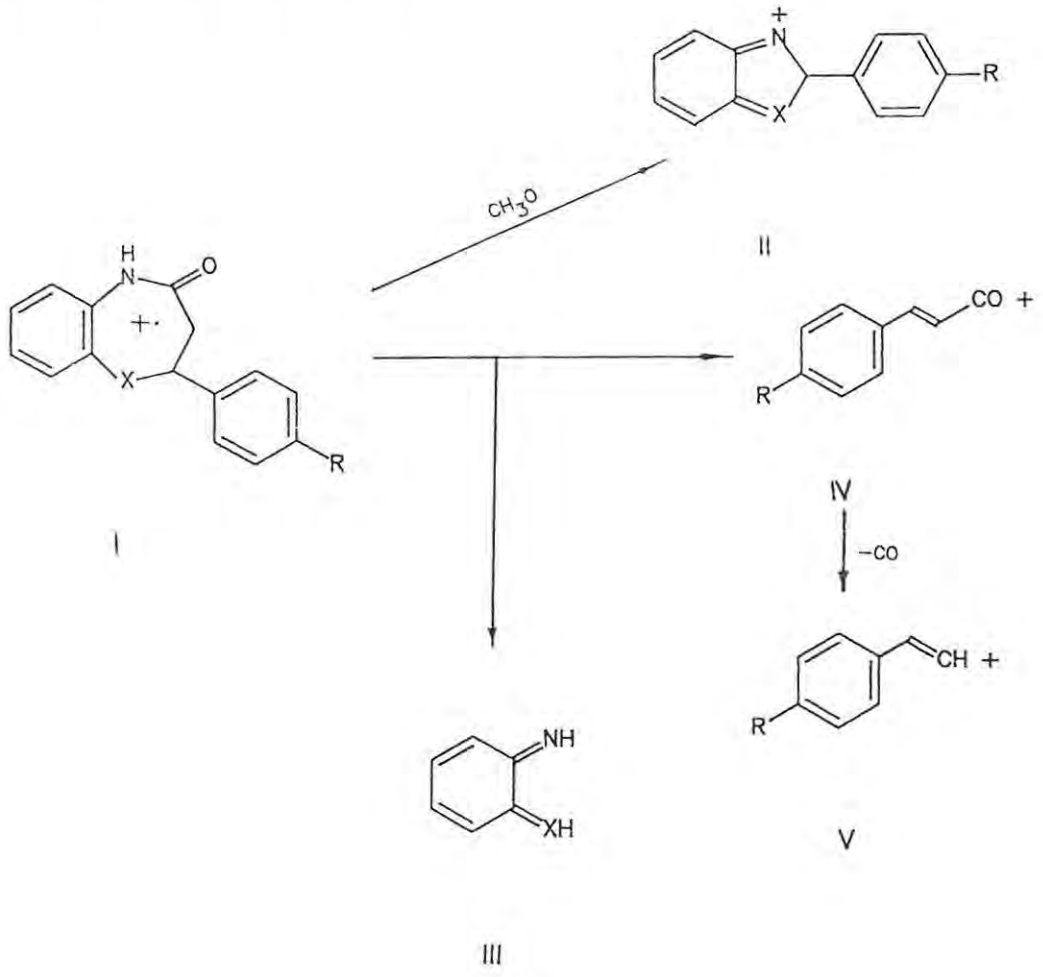
Table 23: Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) observed for 2-phenyl **246** and 3-phenyl-1,4-benzoxazepin-5-one **258**



No	R'	R''	Ion Fragment Type				
			I	II	III	IV	V
246	Ph	H	237 (92.2)	210 (80.7)	209 (13.5)	181 (84.1)	105 (100)
258	H	Ph	237 (56.6)	134 (84.8)	133 (4.3)	105 (100)	

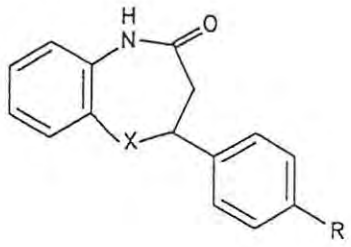
(ii) 1,5-Benzoxazepinone and its 1-thia analogues

2-Phenyl-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-one **211** and the 2-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones detailed in Table 23 appear to exhibit similar fragmentations to those reported for the analogous 4-phenyl-3,4-dihydro-1,5-benzodioxepin-2-ones.[162] Thus C-ring contraction and elimination of an acyl radical from the molecular ion I affords the resonance stabilised fragment II (Scheme 62). The two complementary ions, tentatively formulated as III and IV confirm the molecular ion to be the result of nitrogen-insertion *via* aryl migration during the Schmidt reaction of the precursors. Loss of CO from the even-electron species IV affords the styryl cation V. The fragmentation patterns of the 1,5-thiaza derivatives were found to be similar to those of their amide precursors.



Scheme 62 MS Fragmentation patterns of the 1,5-benzoxazepinone 211 and its 1-thia analogues detailed in Table 22.

Table 24: Selected peaks (*m/z*; followed below by % relative abundance) observed for 1,5-benzoxazepinone 211 and its 1-thia analogues.



No	X	R	Ion Fragment Types				
			I	II	III	IV	V
211	O	H	239	196	131	104	103
			1.2	0.4	100	73.7	68.8
225	S	H	255	212	131	104	103
			43.0	11.5	100	73.7	67.9
228	S	F	273	230	149	122	121
			54.8	14.8	100	81.6	67.9
230	S	Cl	289[a]	246[a]	165[a]	138[a]	137[a]
			43.2	8.8	100	73.6	24.6
232	S	Br	333[b]	290[b]	209[b]	182[b]	181[b]
			37.4	7.7	100	46.5	10.5

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

(iii) **Tetrazolo derivatives**

Mass spectrometry was useful for characterising the tetrazolo[5,1-*d*]-1,5-benzothiazepine (**243**), the tetrazolo[1,5-*d*]-1,4-benzothiazepines (**226** and **242**) and the tetrazolo[1,5-*d*]-1,4-benzodiazepines detailed in Table 23, and also for distinguishing them from their amide analogues. The generalised fragmentation of the 2-phenyltetrazolo[1,5-*d*]-1,4-benzothiazepine **226** and the 2-phenyltetrazolo[1,5-*d*]-1,4-benzodiazepine derivatives are outlined in Scheme 63. Loss of H$^{\bullet}$ from the molecular ion I to afford the M-1 ion II is observed in all the 2-phenyl-tetrazolo[1,5-*d*]-1,4-benzodiazepine analogues examined. Fragmentations that are characteristic of tetrazoles[164,166] include the loss of:-

(i) N_2 to afford the amidine fragment III,

(ii) N_2 and H$^{\bullet}$ to afford the even-electron species IV,

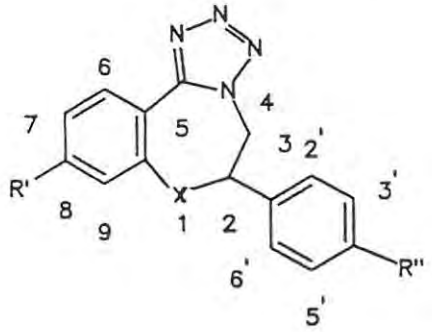
(iii) N_2 and HCN to give the radical-cation species V, and

(iv) N_2, HCN and H$^{\bullet}$ to afford the cationic fragment VI, which constitutes the base peak in the spectra of all six 2-phenyltetrazolo[1,5-*d*]-1,4-benzodiazepines detailed in Table 23.

Elimination of the phenyl radical from VI (X = NH) affords the even-electron species VII, which is tentatively formulated as the 1,3-benzodiazine ($C_8H_6N_2$); further loss of HCN accounts for the peak at *m/z* 102, which is attributed to the cationic species IX. In the case of 1-thia derivative **226**, loss of a phenyl radical from the radical-cation V (X = S) affords the cationic species VII which is tentatively formulated as the 1,3-benzothiazine (C_8H_6SN). The cationic species IX (*m/z* 102) in compound **226** is probably due to the loss of CH_2S from fragment VIII. The methoxy derivative (**221**; X = NH, R = OCH_3) exhibits additional fragmentations that are characteristic of alkyl aryl ethers. Loss of a methyl radical from the even-electron species V, for example, leads to the conjugated cationic fragment X (supported by metastable peak data), which decomposes further with the expulsion of CO to give the radical-cation XI. Loss of H$^{\bullet}$ from the decarbonylated radical-cation XI affords the even-electron species, tentatively formulated as the 1,3-benzodiazine cation XII, while loss of HCN from the former ion accounts for the *m/z* 167 ($C_{12}H_9N$) ion XIII.

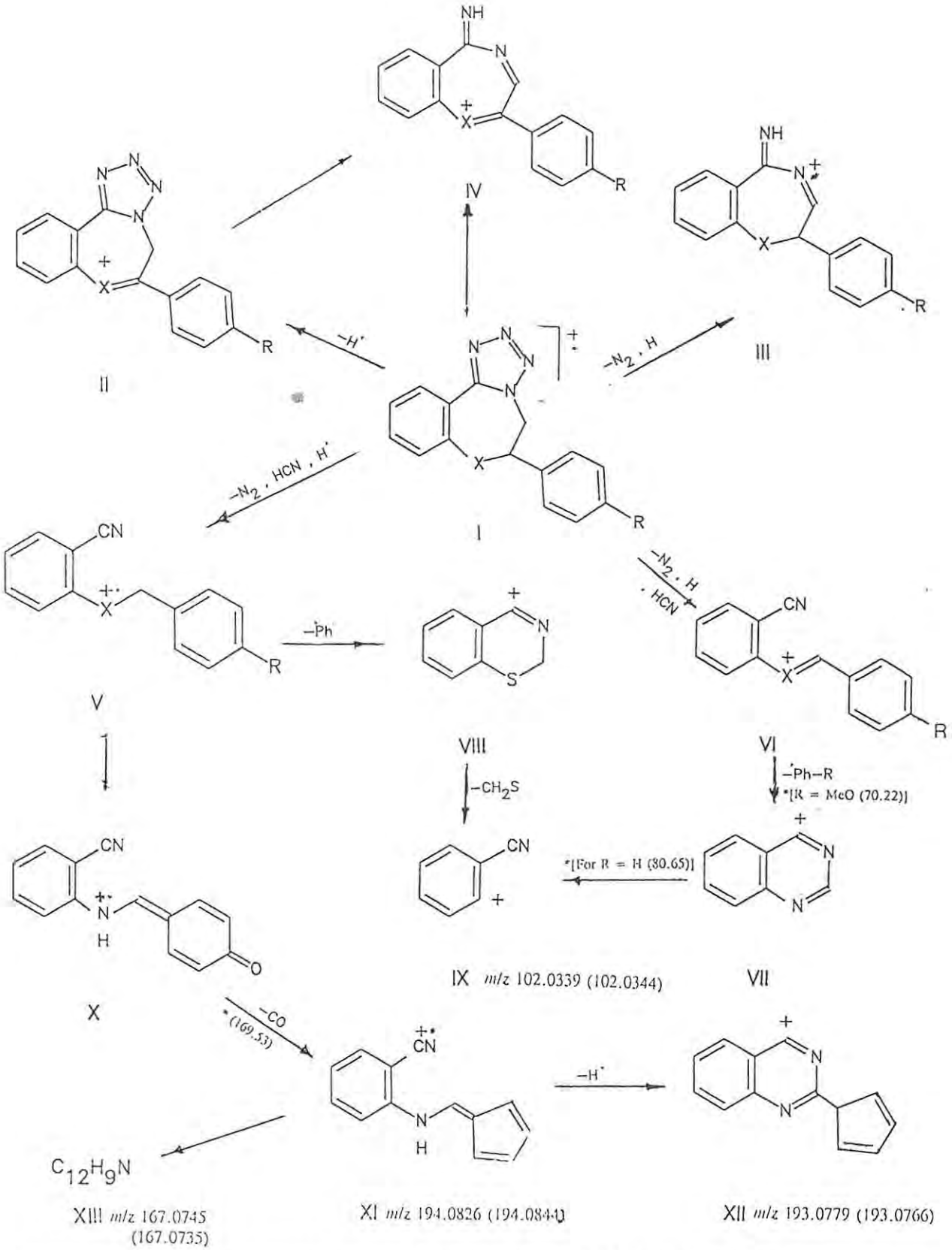
Although the structures of the isomeric tetrazolo[1,5-*d*]-1,4- **242** and tetrazolo[5,1-*d*]-1,5-benzothiazepine **243** have been confirmed to differ by ^{1}H- and ^{13}C NMR spectroscopy (see Section 2.2c), they exhibit a series of fragments with the same masses. The proposed fragmentations outlined in Schemes 64 and 65 have yet to be confirmed by detailed high-resolution MS and metastable peak analysis. However, precedents for the fragmentation of the tetrazolo[1,5-*d*] derivative **242** are provided by the mass spectral analyses of the analogous 2-phenyltetrazolo[1,5-*d*]-1,4-benzoxazepine[164] and -1,4-benzodiazepine[165] derivatives.

Table 25: **Selected peaks (*m/z*; followed below by % relative abundance observed for 2-phenyltetrazolo[1,5-*d*]-1,4-benzodiazepines (X = NH) and 1,4-benzothiazepine (X = S).**

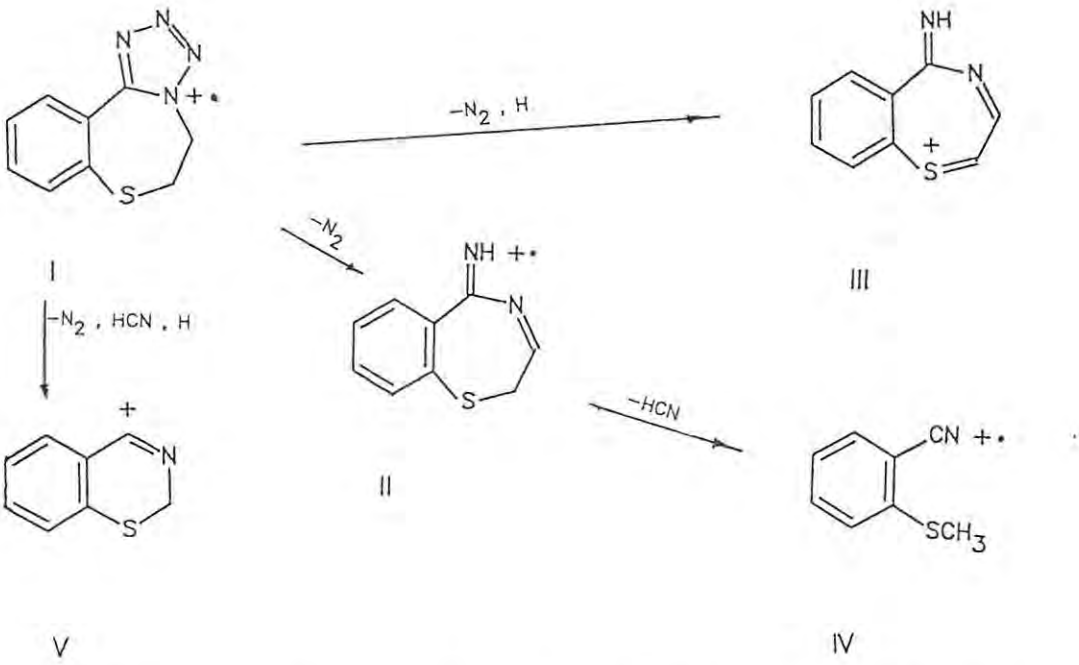


No	X	R	Ion Fragment Types								
			I	II	III	IV	V	VI	VII	VIII	IX
213	NH	H	263	262	235	234	208	207	129	-	102
			18.6	0.1	4.3	22.5	16.0	100	46.4	-	29.0
215	NH	F	281	280	253	252	226	225	129	-	102
			4.5	25.0	6.2	32.3	14.6	100	20.1	-	10.5
217	NH	Cl	297[a]	296[a]	269[a]	268[a]	242[a]	241[a]	129[a]	-	102[a]
			3.7	18.2	11.3	6.3	17.6	100	26.1	-	17.3
219	NH	Br	341[b]	340[b]	313[b]	312[b]	286[b]	285[b]	129[b]	-	102[b]
			17.2	0.1	6.1	32.2	17.3	100	70.7	-	63.2
221	NH	OMe	293	292	265	264	238	237	129	-	102
			3.9	20.1	3.6	17.6	16.0	100	20.5	-	7.0
223	NH	NO_2	308	307	280	279	253	252	129	-	102
			30.8	0.1	10.8	60.1	18.5	100	22.7	-	38.6
226	S	H	280	-	252	251	225	224	-	148	102
			97.4		28.3	92.4	22.1	86.8		100	19.2

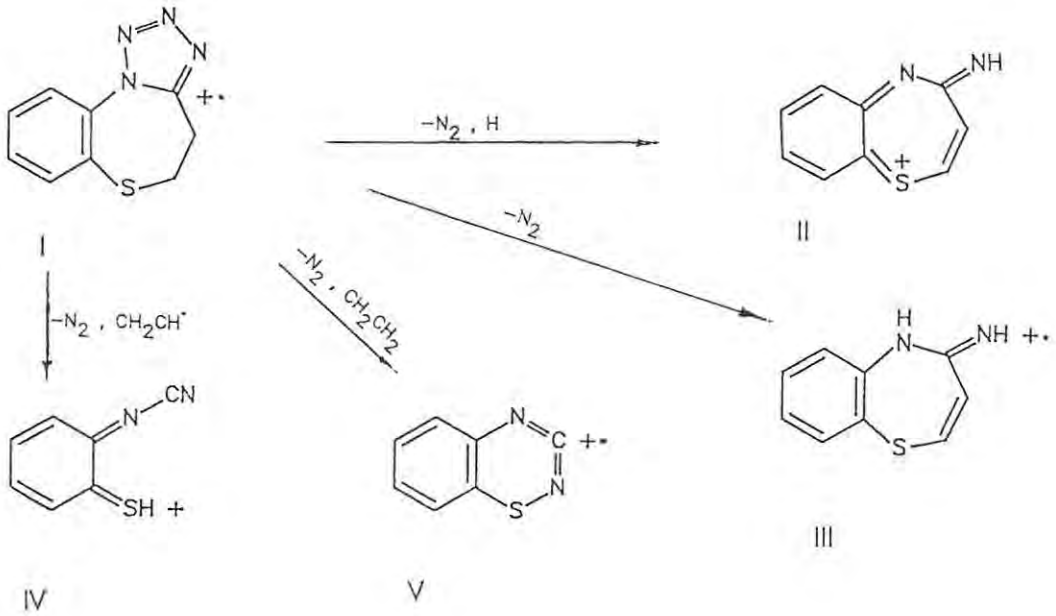
[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br



Scheme 63 MS Fragmentation patterns for 2-phenyltetrazolo[1,5-*d*] derivatives detailed in Table 23; an asterisk indicates a pathway supported by the metastable peak given in parentheses.



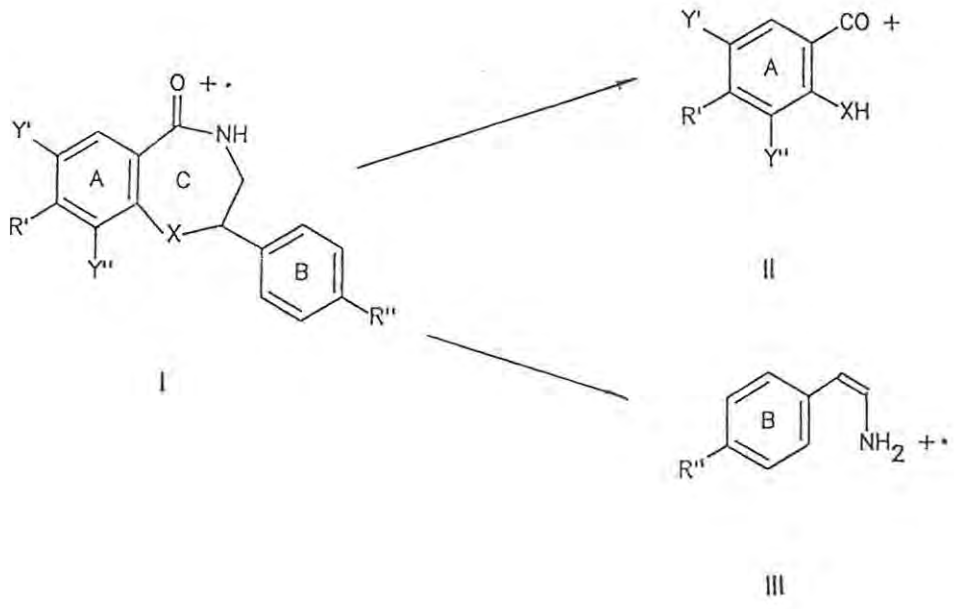
Scheme 64 MS Fragmentation patterns for tetrazolo[1,5-*d*]-1,4-benzothiazepine 242 (*m/z*; followed, in parentheses, by % relative abundance).



Scheme 65 MS Fragmentation patterns for tetrazolo-[5,1-*d*]-1,5-benzothiazepine 243 (*m/z*; followed, in parentheses, by % relative abundance).

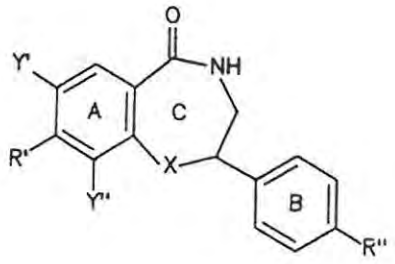
(d) A-RING CHLORINATED 1,4- BENZODIAZEPINE ANALOGUES

Mass spectrometry proved to be a useful technique for structural analysis of the chlorinated products detailed in Table 65. For example, the number of chlorine atoms incorporated and the ring involved were fully confirmed by mass spectrometry. The increase in mass of the molecular ions by 35 or 70 atomic mass units confirms the presence and number of chlorine atoms incorporated. Since the fragmentation patterns of these compounds resemble those of their precursors,[163,165] attention in Scheme 66 is restricted to a consideration of the molecular ion and specific A- and B-ring fragments. Examination of the molecular ion I indicates the incorporation of a single chlorine in compounds **209-262**, but the incorporation of two chlorine atoms in compounds **263** and **264**. From fragment II, observed in all cases, it is apparent that no chlorine was incorporated on the B-ring. In all cases the A-ring fragments III were shown to contain the maximum number of chlorine atoms incorporated in the molecule. These observations obviously preclude incorporation of chlorine on the C-ring.



Scheme 66 Selected MS Fragmentation patterns of the A-ring chlorinated 1,4-benzodiazepine analogues.

Table 26: Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from electron impact mass spectra of the A-ring chlorinated 1,4-benzodiazepine analogues.



No	X	R'	R''	Y'	Y''	Ion Fragment Types		
						I	II	III
259	O	H	H	Cl	H	273[a] (5.5)	155[a] (15.2)	119 (100)
260	O	H	F	Cl	H	291[a] (17.1)	155[a] (66.8)	137 (100)
261	O	H	Cl	Cl	H	307[a] (25.0)	155[a] (92.3)	153[a] (100)
262	O	H	Br	Cl	H	351[a,b] (3.3)	155[a] (34.7)	197[b] (32.6)
263	O	OMe	H	Cl	H	337[a] (3.8)	219[a] (14.2)	119 (100)
264	NH	H	H	Cl	H	306[a] (72.8)	187[a] (2.7)	119 (1.9)

[a] *m/z* value corresponds to ^{35}Cl
[b] *m/z* value corresponds to ^{79}Br

2.5 KINETIC-MECHANISTIC STUDY OF THE SCHMIDT REACTION ON FLAVANONES

The Schmidt reaction of carbonyl compounds is a well studied reaction with several unusual features and a number of workers have investigated the kinetics and mechanism.[93,167,168] The generally accepted mechanism (Scheme 33, p.35) involves formation of an intermediate iminodiazonium ion **119** having either *anti-* (**119a**) or *syn-* configurations (**119b**) (relative to the fused benzene ring), thus accounting for the formation of two isomeric amides from non-symmetrical ketones. The relative proportion of these configurations of the iminodiazonium ion in the reaction mixture determines the ratio of the isomeric products formed. Migration of the substituent *anti* to the diazo group of the iminodiazonium ion **119** accompanied by elimination of N_2 results in formation of the iminocarbonium ions **120** and **121**. Interaction of these ions with nucleophilic reagents (*eg*. H_2O, excess HN_3), present in the reaction mixture, determines the nature of the final products. For example, interaction with water affords amide derivatives, while tetrazoles result from the interaction of the iminocarbonium ions **120** and **121** with excess HN_3. In some cases, only one regioisomeric product is formed.

It has been observed[93] that steric factors have a greater influence on the outcome of the Schmidt reaction on alkylphenyl ketones than electronic factors. These authors found aryl migration to predominate with the formation of the benzanilide product except when the alkyl group is bulky [*eg*. $CH(CH_3)_2$], in which case alkyl migration is favoured. These observations imply that a bulky substituent shifts the equilibrium between the iminodiazonium intermediates (**120** and **121**) in favour of the one in which the bulky group is *anti* to N_2. In their study of the Schmidt reaction of chroman-4-one and 6-methoxytetralone, Lockhart and coworkers[95] isolated, in both cases, the 1,4-amide isomer as the sole product. These observations were attributed to electron-donation by the oxygen either at the *ortho* position (for chromanone) or the *para* position (for 6-methoxytetralone), which increases the double bond character of the bond between the aromatic ring and the carbonyl group, thus inhibiting aryl migration.

Previous investigations of the Schmidt reaction of carbonyl compounds have been carried out using hydrazoic acid[93,98,167,168] or sodium azide[94,95,99] in acidic medium. In the present study, flavanones (which are, in fact, non-symmetrical ketones) were reacted with trimethylsilyl azide (TMS-N_3) in trifluoroacetic acid (TFA) to afford, in each case, two products, characterised as the corresponding 1,4-benzoxazepinone and its tetrazolo[1,5-*d*]-1,4-benzoxazepine derivative; in none of the cases studied was any 1,5-regioisomer detected. This means that the insertion of nitrogen is completely regiospecific and requires migration of the primary alkyl group rather than the aryl group. Surprisingly, in a parallel study,[92] the Baeyer-Villiger oxidation of the same flavanones (using MCPBA in CH_2Cl_2) has afforded the 1,5-benzodioxepinones as the sole products and the alternative 1,4-isomers were not detected. This unexpected reversal of regiochemistry encouraged us to investigate the kinetics of both reactions using ^{1}H NMR spectroscopy and, in this work, particular emphasis has been placed on the Schmidt reaction when effected by TMS-N_3 in trifluoroacetic acid. To our knowledge no prior kinetic-mechanistic studies have been carried out using the TMS-N_3—TFA reagent system.

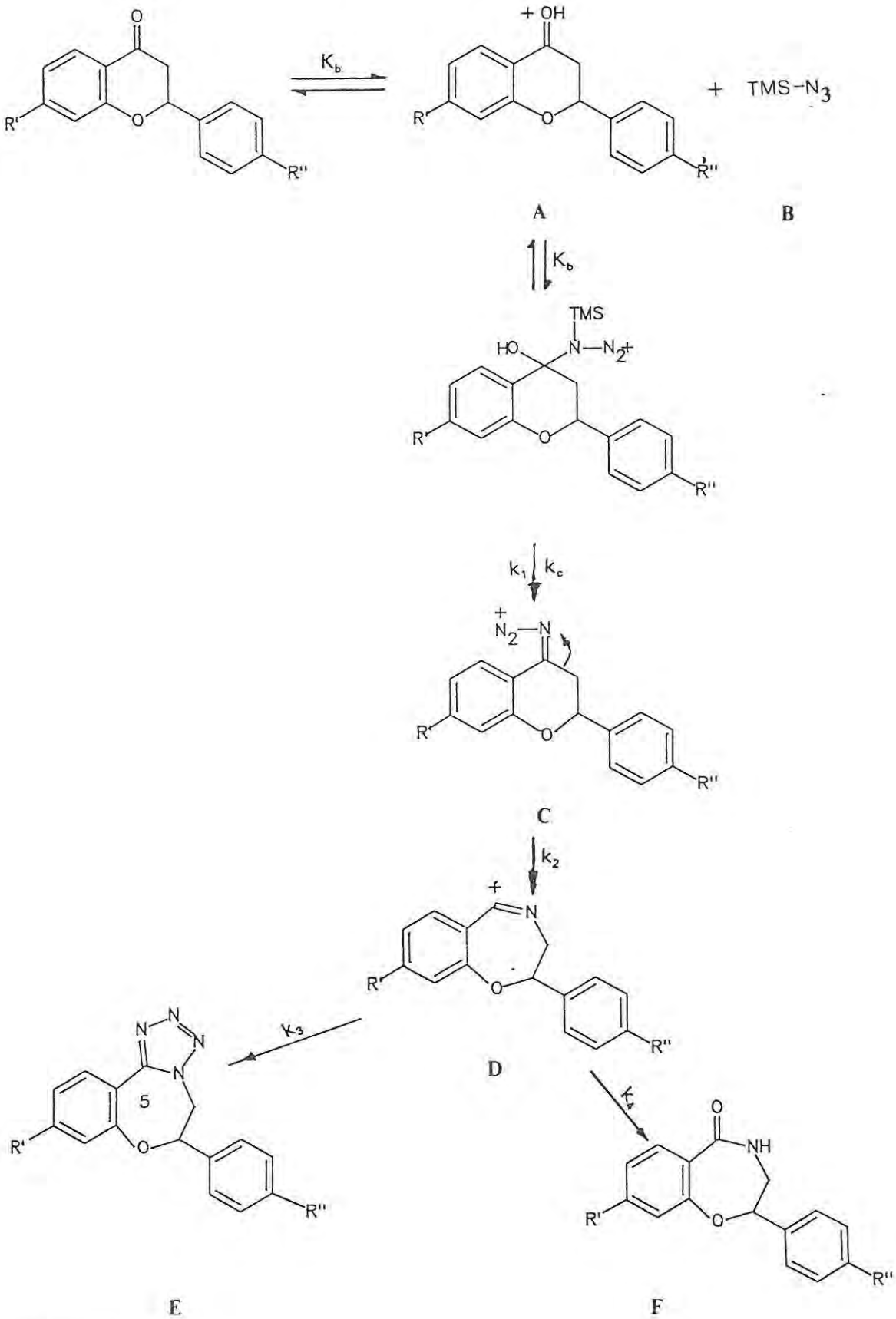
In this investigation, the rate of transformation of selected flavanones (Table 27) was monitored by ^{1}H NMR spectroscopy over 12 h, during which time the consumption of the substrate was found to be more than 50%. The ^{1}H NMR spectra (see Fig. 12) indicate the presence of substrate and products but no build-up of intermediates is apparent. Kinetic analysis of the data is complicated by:—

(i) "simultaneous" formation of two different products;

(ii) the involvement of several, possibly reversible, steps; and

(iii) the fact that two molecules of TMS-N_3 are consumed in the formation of one molecule of the tetrazolo derivative.

These complications precluded standard second-order analysis and required the application of a more complex approach, the results of which are consistent with the mechanism detailed Scheme 67. For analysis of the kinetic data this mechanism may be represented by the simplified, consolidated sequence detailed below (Scheme 68) and the rate equations 1-6.



Scheme 67

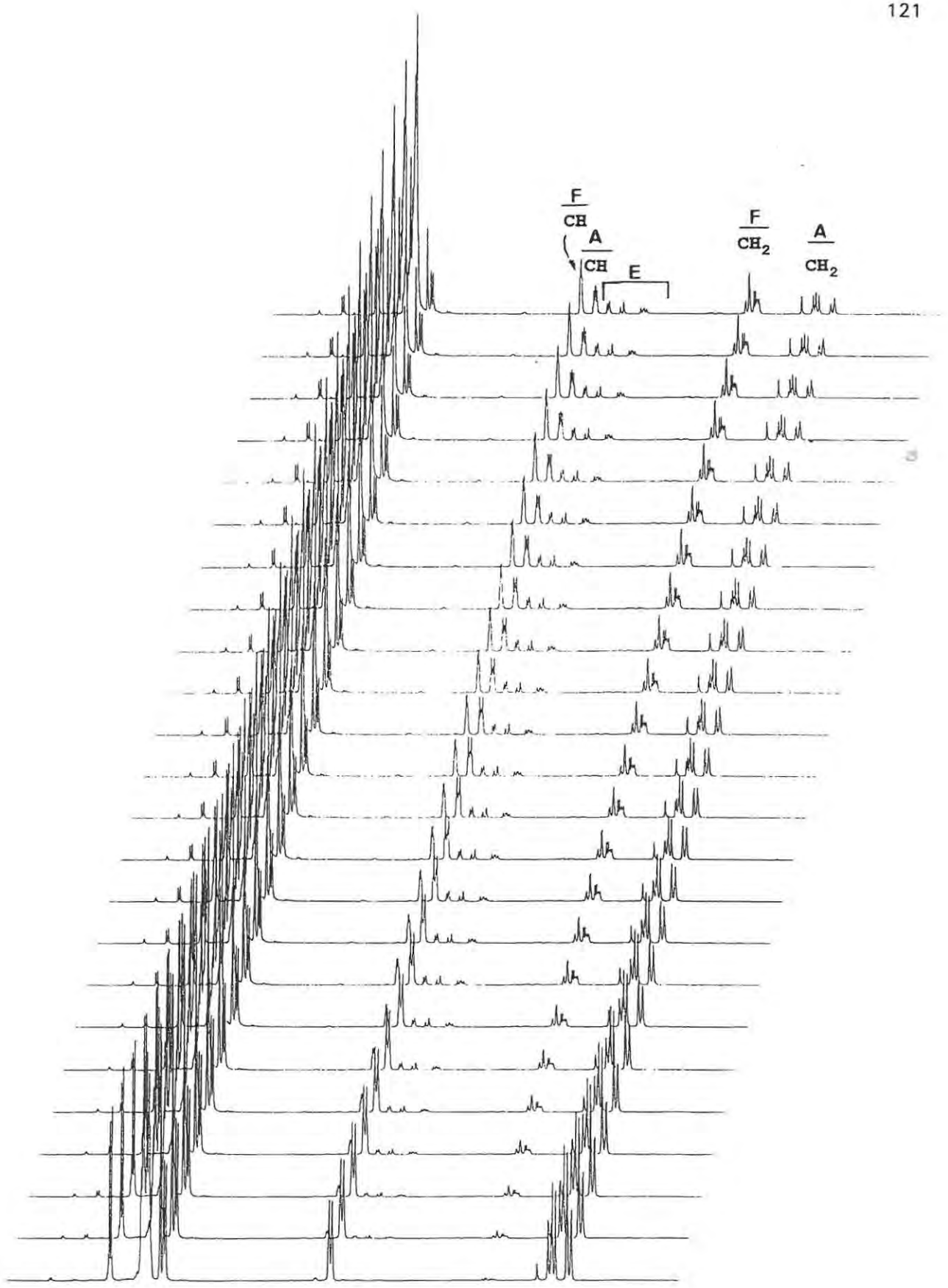
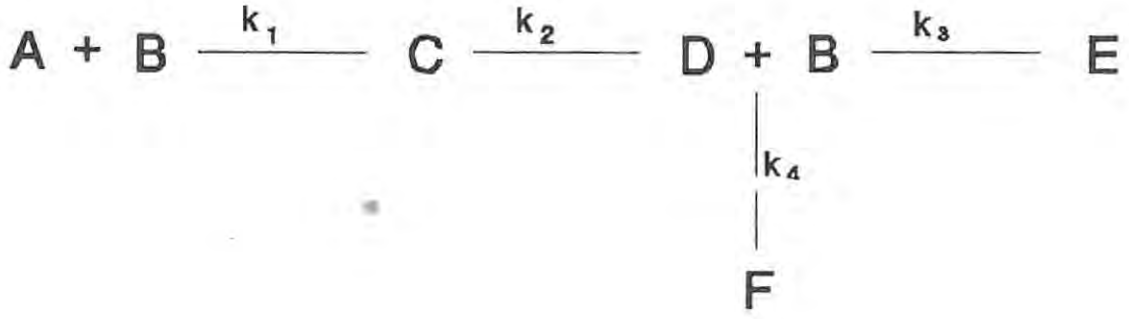


Figure 12: ^{1}H NMR Spectra obtained at 30 minute intervals for the Schmidt reaction of the 4'-bromoflavanone 151 in CF_3CO_2D at 303 K



Scheme 68

Rate equations:

$$\frac{-d[A]}{dt} = k_1[A][B] \quad (1)$$

$$\frac{d[B]}{dt} = -k_1[A][B] - k_3[D][B] \quad (2)$$

$$\frac{d[C]}{dt} = k_1[A][B] - k_2[C] \quad (3)$$

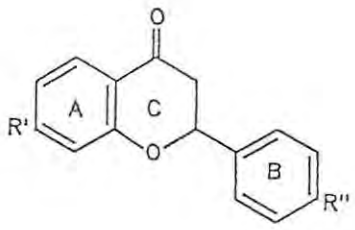
$$\frac{d[D]}{dt} = k_2[C] - k_4[D] - k_3[D][B] \quad (4)$$

$$\frac{d[E]}{dt} = k_3[D][B] \quad (5)$$

$$\frac{d[F]}{dt} = k_4[D] \quad (6)$$

Holding the k_1 value constant and using equations 1-6, trial values for k_2, k_3 and k_4 were varied until computer calculated graphs matched the experimentally determined plots for the rate of consumption of the substrate (**A**) and the rates of formation of the products (**E** and **F**) (see Figs. 13 and 14). The estimated values for k_1, k_2, k_3 and k_4 for each of the compounds examined are detailed in Table 27. The formation of the iminodiazonium ion **C** is the slowest step and thus is rate determining. Since the formation of the iminodiazonium ion **C** from **A** is expected to involve several reversible steps, the rate coefficient k_1 may be viewed as a composite of K_c, K_a and K_b (i.e. $k_1 = k_c K_a K_b$). Loss of N_2 and ring enlargement leading to the formation of the iminocarbonium ion **D** is rapid and relatively insensitive to variation of the 4'- and 7-substituents. The rates of formation of the amide (**F**) and tetrazolo (**E**) products are relatively slow compared to the formation of the intermediate **D**. The rate of formation of product F (k_4) is faster than that of product E (k_3) and both also reflect the effects of the 4'- and 7-substituents as discussed below.

Table 27: **Estimated values of the rate coefficients defined in the reaction scheme 68 (at 303 ± 0.1 K)**



No	R'	R"	k_1	k_2	k_3	k_4
189	H	H	0.00568	0.20	0.03	0.07
145	F	H	0.0035	0.28	0.04	0.08
147	Br	H	0.0033	0.28	0.06	0.13
148	OCH_3	H	0.0046	0.25	0.02	0.05
149	H	F	0.0054	0.26	0.06	0.14
151	H	Br	0.0048	0.28	0.05	0.13
153	H	NO_2	0.0038	0.25	0.06	0.16

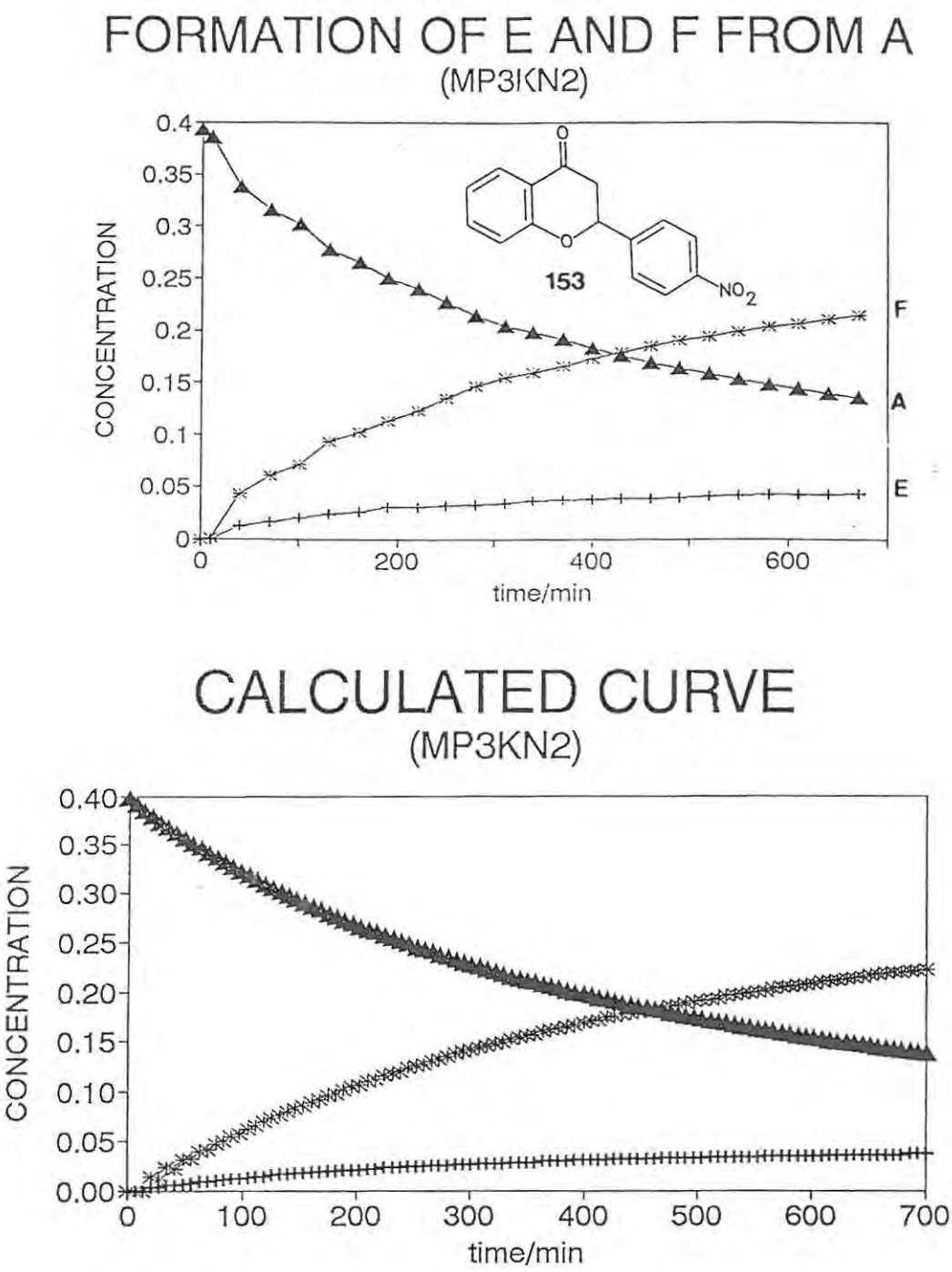


Figure 13: Experimental and calculated curves for the consumption of substrate A and the formation of products E and F as functions of time.

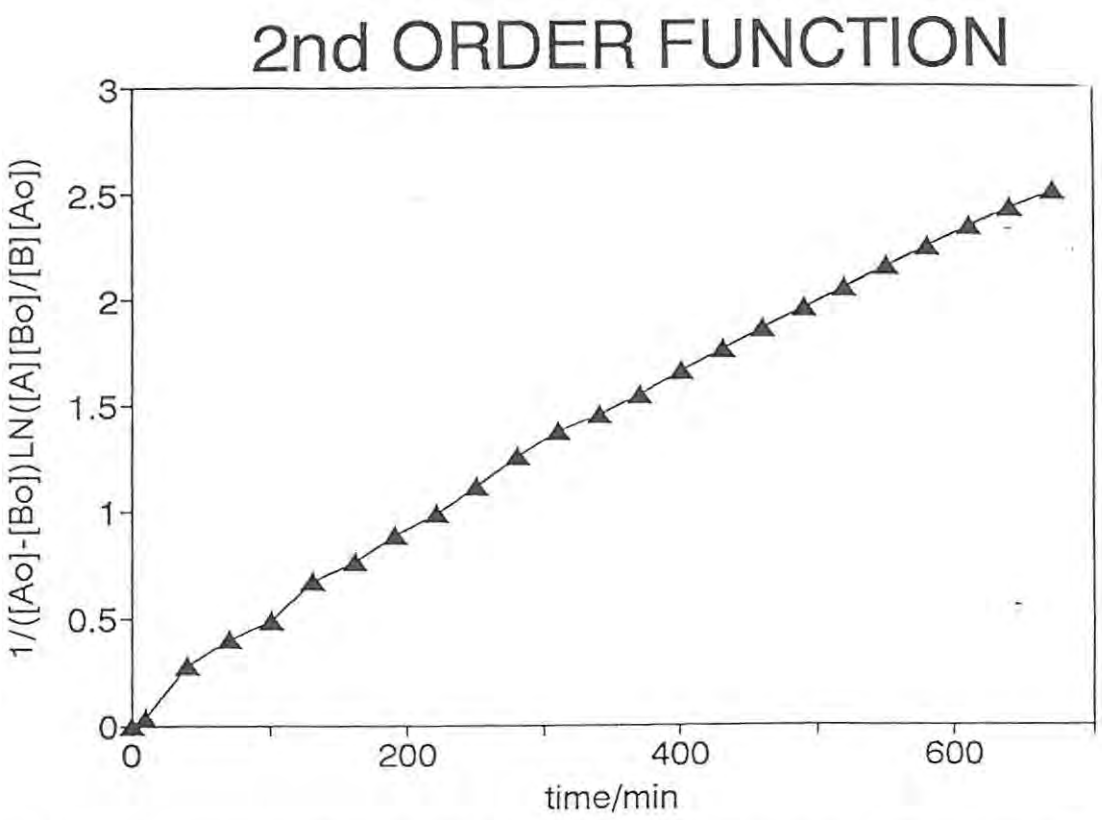
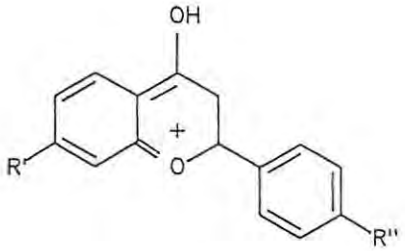


Figure 14: **Second-order linear plot of $\frac{1}{[A]_o[B]_o} \ln\frac{[A][B]_o}{[B][A]_o}$ versus time for the formation of intermediate C**

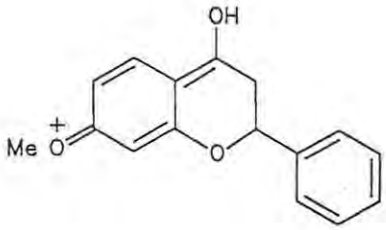
2.5.1 EFFECT OF SUBSTITUENTS ON THE REACTION RATES

In this investigation, we observe 1° alkyl migration instead of the more typical preferential aryl migration.[93] The absence of regioisomers from aryl migration is attributed to conjugative interaction of the ether oxygen with the benzo ring which results in a partial double bond between the aryl group and the carbonyl group. This interaction will inhibit aryl migration. An electron-donating substituent at the 7-position of the A-ring is also expected to encourage such conjugation (**280** I). The magnitude of the rate coefficient k_1 is sensitive to variation of the substituent R′ and exhibits the following trend: k_{obs} (R′): R′ = H > MeO > F > Br. An electron-donating substituent R′ will increase the electron density at the migration origin (C=O), thus stabilising the incipient carbocation and enhancing the reaction rate. While this effect would explain the reactivity sequence (R′ = MeO > Br > F), the fact that k_1 for the parent compound (R′ =H) is greater than k_1 for the methoxy analogue appears to be anomalous.

However, this apparent anomaly may reflect the relative influence of the substituents (R' = H, MeO) on the equilibrium constant K_b. The electron donating MeO group may be expected to discourage the initial nucleophilic addition of the azide species by increasing the electron density at the carbonyl carbon (see **280** II) and thus reducing K_b.



I



II

280

(Assumed to be protonated[176] in CF_3CO_2D)

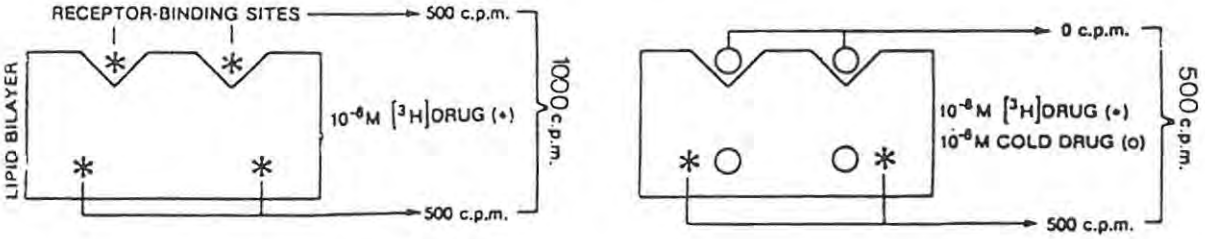
Similar trends in the effect of substituents on the rate coefficients k_1, k_3 and k_4 are observed for the R" substituents [k(R"): R" = H > F > Br > NO_2]. The substituents R", although remote from the reaction centre, have greater influence on the rate coefficient k_1 than R'. An electron-donating substituent (R") at the *para*-position of the B-ring is expected to increase electron density at the methine carbon, thus opposing the electron-withdrawing inductive effect of the ring oxygen and increasing the nucleophilicity of the migrating 1° alkyl group. As a result, the rate of reaction is expected to be enhanced by electron-donating R" groups. Although the results obtained for the rate coefficients k_1, k_2, k_3 and k_4 do not necessarily constitute a unique analysis of the kinetic data, they are, nevertheless, consistent with the proposed mechanism (Scheme 69).

2.6 DETERMINATION OF THE BINDING AFFINITIES OF BENZODIAZEPINE ANALOGUES FOR THE BENZODIAZEPINE RECEPTORS

A range of the benzodiazepine analogues prepared in this work were tested for their ability to compete with ^{3}H-diazepam for specific binding to benzodiazepine receptors, using a radioreceptor binding assay. In this technique, tissues containing the receptors are incubated with a radioactive ligand (D*) of suitable radioactivity (≥ 20 Ci/mmol).[81] The ligand interacts with the receptor (R) to form a receptor-ligand complex (RD*) according to the law of mass action:

$$D^{*} + R \underset{k_{-1}}{\overset{k_{1}}{\rightleftharpoons}} D^{*}R$$

Once the complex is formed, the unbound (free) radiolabelled ligand is removed by filtration (or centrifugation) to permit the determination of bound radiolabelled drug.[81,169] Free radiolabelled material, *i.e.* that not associated with the receptors, is removed by washing the filters or reaction tubes with an ice-cold buffer of known pH. In tissues, the specific binding sites (receptors) occur in relatively small finite numbers and can be saturated with drug molecules (Figure 15). On the other hand, the number of non-specific sites (*eg*. proteins and lipids) in tissues is very large (compared to that of specific binding sites) and are not saturable (Figure 15).[81] Thus, in addition to binding selectively to the receptors, the radiolabelled drug can also bind to non-specific binding sites and be adsorbed onto inert surfaces, *eg*. test tubes and filters. This non-specific binding is determined by a parallel assay using tubes containing excess (100 fold) of an unlabelled ligand, specific for a given receptor. Measurement of binding of the radioactive and non-radioactive ligand provides data on total ligand binding and non-specific binding, respectively.[7,81,169] The difference between the two constitutes the specific binding of the radioactive ligand to the receptors.



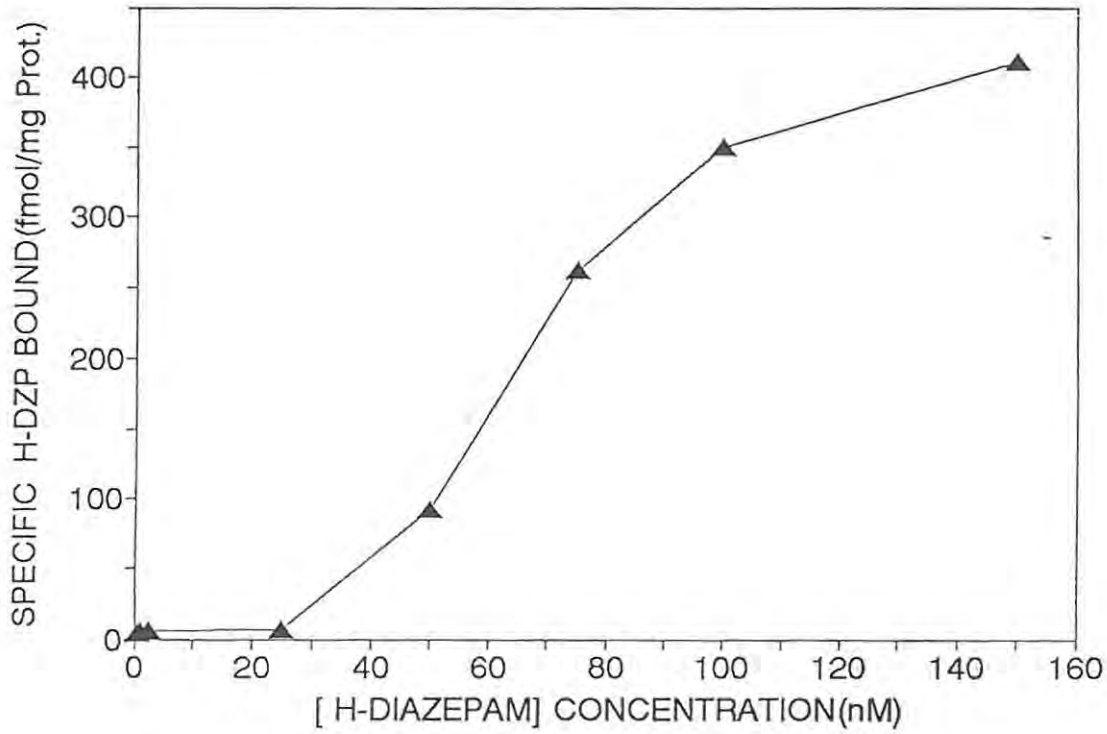
D*: Radioactive drug, D: Non-radioactive drug

Figure 15: Diagrammatic representation of non-specific and specific binding determination.[81]

Because of the high pharmacological activity of diazepam, *in vivo*,[7] this ligand is expected to have a high binding affinity. The receptors, therefore, are expected to be readily saturated by ^{3}H-diazepam. In one set of assays the membranes were incubated with increasing concentrations of ^{3}H-diazepam (0.5-150nM) alone and, in another set, constant concentration of non-radioactive diazepam was added as described in the experimental section. Addition of non-radioactive diazepam displaced 60-70% of the total ^{3}H-diazepam from the receptors, confirming that the binding sites were saturable. A plot of specific ^{3}H-diazepam bound (fmol/mg protein) versus the concentration of ^{3}H-diazepam gave a saturation curve (Figure 16). This saturation curve illustrates the high affinity of diazepam for the receptors. We established the affinity constant, K_D value (the concentration of ^{3}H-diazepam giving half-maximal binding) to be 61 ± 5 nM and the total number of specific binding sites, B_{max}, to be 476 ± 4 fmol/mg protein. These values were subsequently used in the competition studies outlined below.

Benzodiazepine analogues were tested for their ability to displace bound ^{3}H-diazepam from rat brain membranes at various concentrations ranging from 10^{-11} to 10^{-4} M. In principle, at low concentrations of the test drug, little or no competition is expected, while at high

concentrations binding to the receptors is indicated by the decreasing levels of radioactive drug. The test compound is considered to be bound specifically if it displaces up to 50% or more of the radioactive drug.



^{3}H-diazepam (nM)	Specific ^{3}H-DZP binding (fmol/mg protein)
150.0	411.0
100.0	350.0
75.0	263.0
50.0	92.0
25.0	6.4
2.5	5.5
1.0	5.2
0.5	3.7

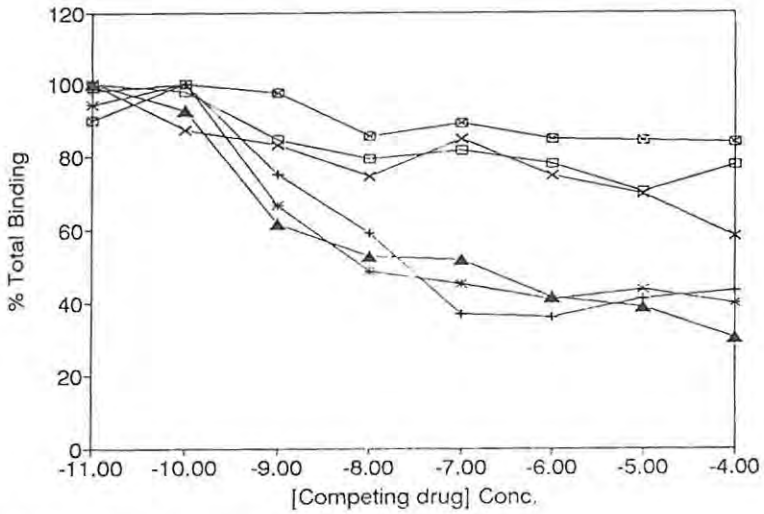
Figure 16: Saturation curve of ^{3}H-diazepam in rat brain membranes

2.7 COMPETITION STUDIES AND THE EFFECT OF SUBSTITUENT OR HETEROATOM VARIATIONS ON BINDING

The binding affinity (expressed as % total binding) of each of the test compounds for the benzodiazepine receptors in rat brain membranes was measured by its ability to displace the specifically bound ^{3}H-diazepam. Plots of % total binding versus concentration of the competing drugs were obtained and are detailed below (Figures 17-23). Analysis of the results (*eg*. Figure 17) shows interesting trends in the effect of substituents on the competitive displacement of ^{3}H-diazepam. We observed that the presence of electron-withdrawing groups (*eg*. F, Cl, Br) at position 8 of the A-ring in compounds **192**, **194** and **196** leads to significant displacement of bound ^{3}H-diazepam. On the other hand, the presence of bromine at position 4' of the B-ring in compound **204** has little if any effect on bound ^{3}H-diazepam. Replacement of the oxygen of the amide group with sulphur leads to diminished binding, even in the presence of an electron-withdrawing group at position 8 of the A-ring, *eg*. compound **266**. Diminished or no competition is observed when the oxygen of the ether linkage at position 1 of the C-ring is replaced with NH (Figure 18) or S (Figure 19). In the case of the 2-phenyl-1,4-benzodiazepinone derivatives, only the 4'-bromo substituted analogue **218** displaced bound ^{3}H-diazepam from the receptors (Figure 18). The thiaza derivatives (Figure 17; **269** and **270**) also failed to displace ^{3}H-diazepam. The above substituent effects parallel those described for potent benzodiazepine receptor ligands (see Section 1.3.1; pg. 27).

The A-ring chlorinated derivatives were also tested for binding. In this series the 7-chloro-4'-fluoro- **260** or 7,4'-dichloro- **261** compounds lead to the displacement of ^{3}H-diazepam (Figure 20), a situation not observed for their precursors. No competition was observed for all the tetrazolo[1,5-*d*] derivatives evaluated (Figure 21-23). Introduction of a tetrazolo group inhibits binding which is observed in the 8-halogeno amide analogues. Lack of binding has also been reported for some analagous tetrazolo[1,5-*d*]-1,4-benzodiazepines not bearing the 2-phenyl substituent **281**.[2] It has also been observed that s-triazolo[4,3-*d*]-1,4-benzodiazepines **282**,[2]

which have a similar arrangement of the D-ring to that of our tetrazolo[1,5-*d*] derivatives exhibit no biological activity. The tetrazolo[5,1-*d*] derivative **243**, which has a similar D-ring arrangement to that of alprozalam **90** (a) (an anxiolytic agent[2]), displaced bound ^{3}H-diazepam from the receptors (Figure 23). These observations presumably show that the arrangement of the D-ring may be critical for binding activity.



No	Y	R'	R"	Symbol
192	O	F	H	▲
194	O	Cl	H	+
196	O	Br	H	✳
204	O	H	H	□
265	S	H	H	×
266	S	Cl	H	⊠

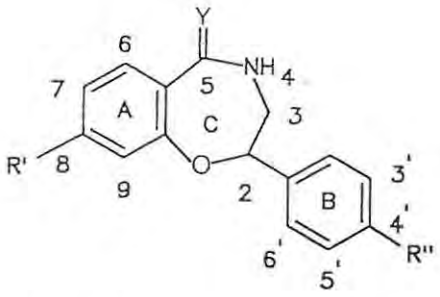
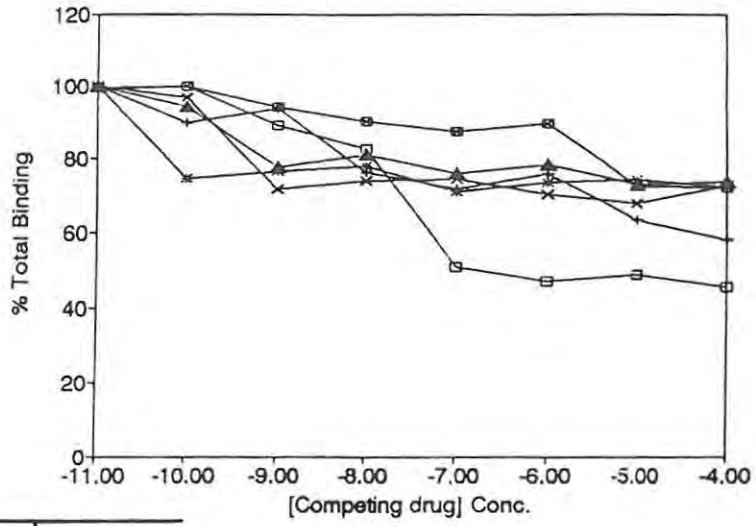


Figure 17: **Competition curves of the 2-phenyl-1,4-benzoxazepinones and their thia derivatives**



No	R'	Symbol
212	H	▲
214	F	+
216	Cl	✳
218	Br	□
269	F	×
270	Cl	⊠

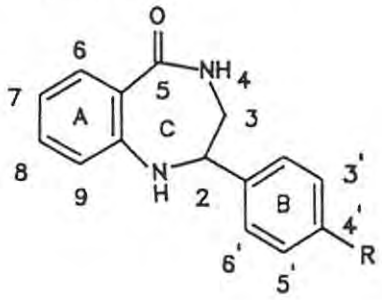
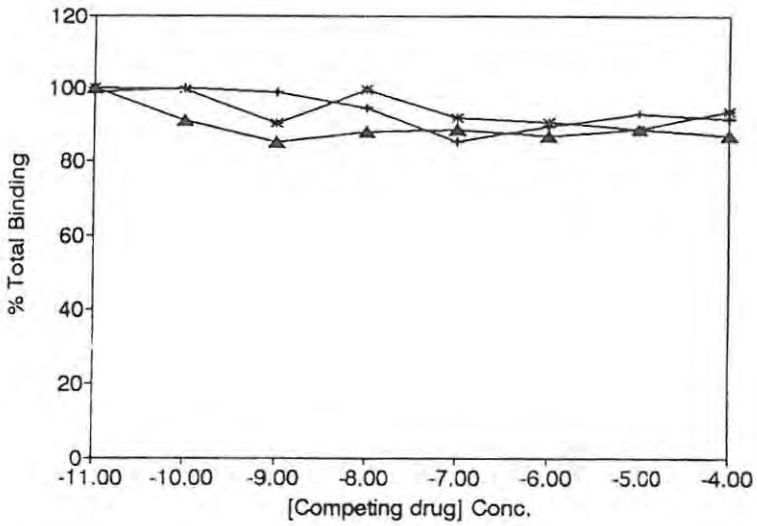
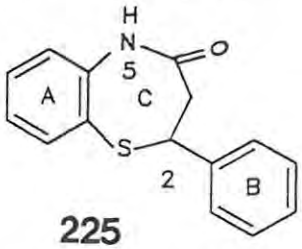


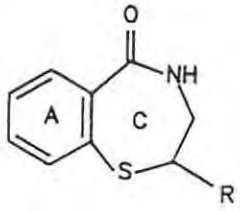
Figure 18: **Competition curves of the 2-phenyl-1,4-benzodiazepinones**



No	R	Symbol
225	-	+
230	PhCl	✳
241	H	▲

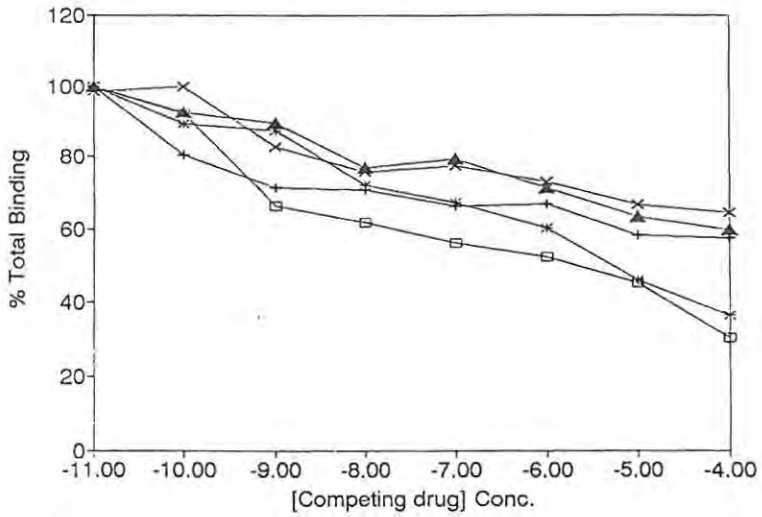


225



230, 241

Figure 19: Competition curves of the 2-phenyl-1,4- and -1,5-benzothiazepinones



No	X	R′	R"	Y′	Y"	Symbol
259	O	H	H	Cl	H	+
260	O	H	F	Cl	H	✳
261	O	H	Cl	Cl	H	□
264	NH	H	H	Cl	Cl	×

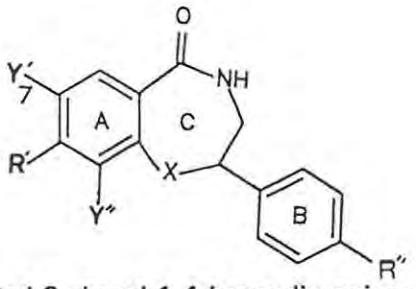
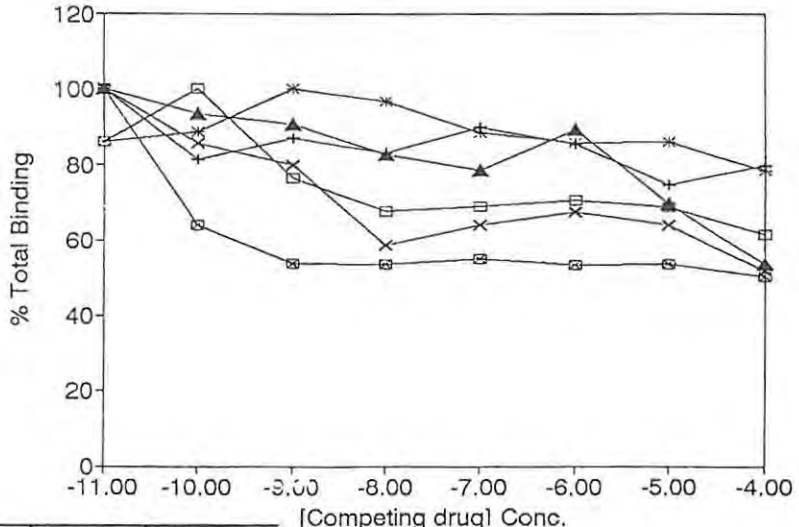


Figure 20: **Competition curves of the A-ring chlorinated 2-phenyl-1,4-benzodiazepines**



No	R′	R"	Symbol
191	H	H	▲
193	F	H	+
199	OCH_3	H	✳
201	H	F	□
205	H	Br	×
207	H	OCH_3	⊠

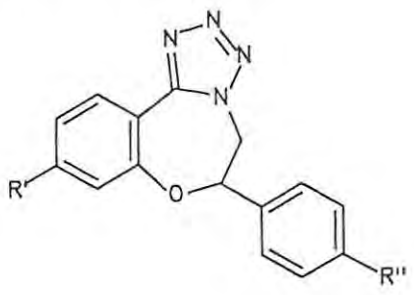
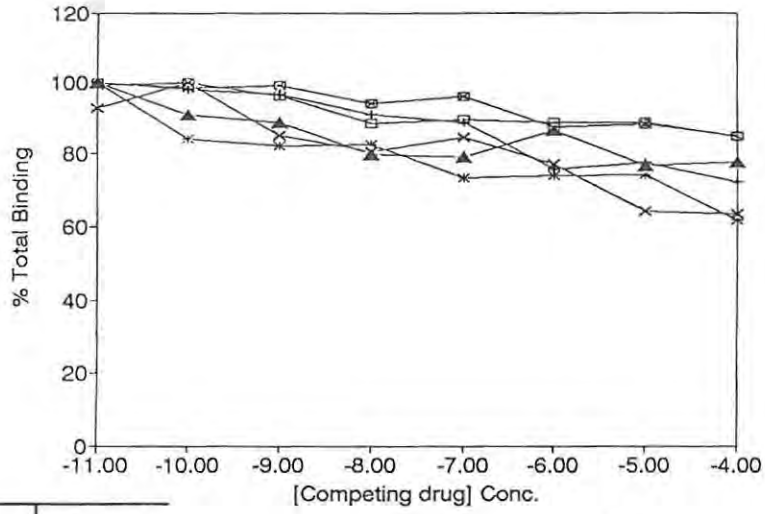


Figure 21: **Competition curves of the 2-phenyltetrazolo-[1,5-*d*]-benzoxazepines**



No	R	Symbol
213	H	▲
215	F	+
217	Cl	✳
219	Br	□
221	OCH_3	×
223	NO_2	⊠

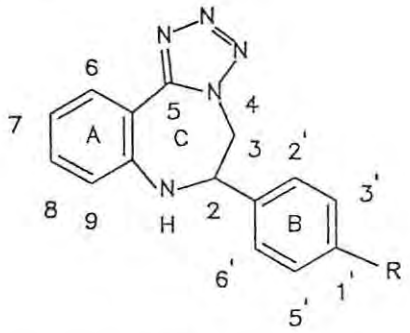
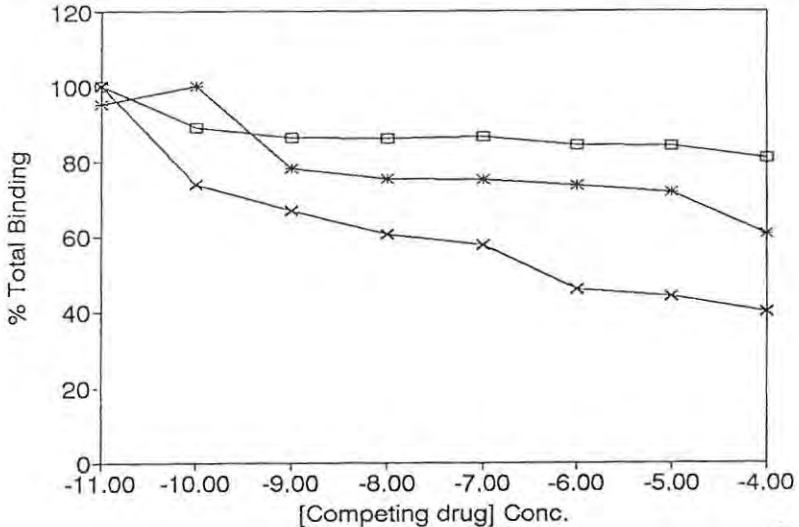
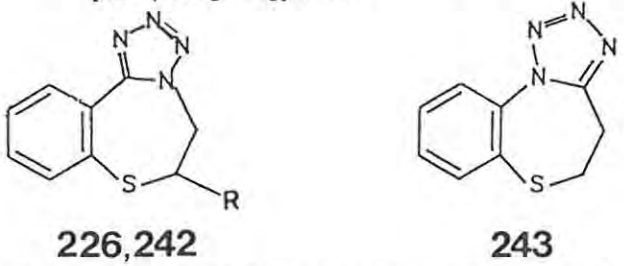


Figure 22: Competition curves of the 2-phenyltetrazolo[1,5-*d*]-1,4-benzodiazepines

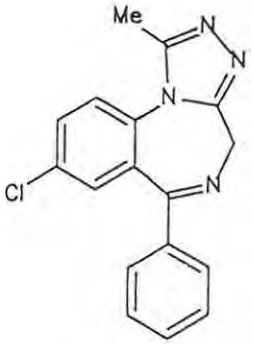


No	R	Symbol
226	Ph	✳
242	H	□
243	-	×

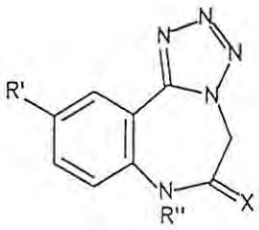


226,242 243

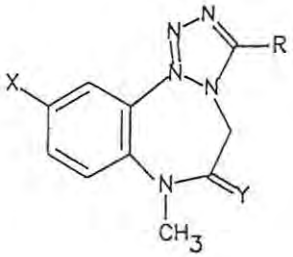
Figure 23: Competition curves of the tetrazolo[1,5-*d*]-1,4-benzothiazepines and tetrazolo[5,1-*d*]-1,5-benzothiazepines



90(a)



281 (a) R' = CF_3, R" = H, X = O
(b) R' = H, R" = Me, X = H_2



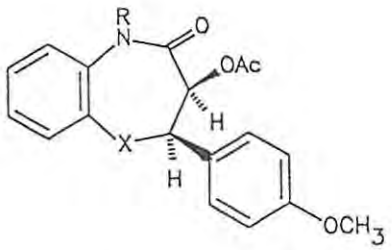
282 (a) R = Me, X = H, Y = H_2
(b) R = H, X = Cl, Y = O

The *in vitro* affinity of a drug, as determined by the radioreceptor method, has been found to predict the potency in biological systems.[163] The simplicity of tissue preparation, storage and assay procedures make this method a powerful primary screening technique for assaying new compounds as fast as they are synthesised. This study lays a foundation in our research group for investigating the effect of structural modification on the binding affinity of benzodiazepine analogues.

2.8 CONFORMATIONAL ANALYSIS OF THE BENZODIAZEPINE ANALOGUES

In addition to the effects of substituents on the biological activity of the benzodiazepines, the conformational properties of the diazepine nucleus have also been found to influence binding of these drugs to the receptors. For example, in the diltiazem-type systems **280**, it has been found that compounds in which the 2- and 3-substituents are *cis* to each other have greater activity than the *trans* isomers.[45,46,61] In our preliminary studies on the binding activities of selected benzodiazepine analogues we have explored the effects of varying the substituents, in rings A, B and C on binding to the receptors. We have also examined the conformational preferences of representative examples in an attempt to link conformational effects with binding affinity.

X-Ray crystallography and ^{1}H NMR spectroscopy have been used extensively to explore the solid state and solution conformations of the molecules.[2,170] Results from ^{1}H NMR spectroscopy are less definitive because of the possible existence, in solution, of more than one conformation. However, results from ^{1}H NMR spectroscopy are likely to approach more closely the true conditions under which the drug exhibits its biological activity when interacting with the receptor. It is generally believed that the preferred conformation in aqueous solution usually approximates to the one which exists in the aqueous environment of tissues.[82-84] Electronic and steric effects have been found to play a role in determining the stereochemistry of the benzodiazepines.[2,171,172] In the present study, ^{1}H NMR spectroscopy, X-ray crystallography and computer modelling techniques were used to probe conformational preferences of the benzodiazepine analogues. A representative example from each series of compounds has been selected for each conformational analysis and it is assumed that the proposed conformations are adopted by all members of a given series.



280: X = CH_2,O,S

2.8.1 ^{1}H NMR SPECTROSCOPY

The splitting patterns and vicinal coupling constants were used to investigate the conformational preferences of benzodiazepine analogues in $CDCl_3$ solution. The 2-phenyl substituted benzodiazepine analogues described in this work possess a chiral centre at C-2 and an adjacent methylene group (C-3). The methylene protons are diastereotopic in any conformation of the benzodiazepine system and couple with each other (J_{gem}) and each couples differently to the *vicinal* 2-H (methine) proton ($J_{trans} \neq J_{cis}$). These diastereotopic methylene protons are, of course, chemically non-equivalent and, consequently, typically give rise to a pair of double doublets. Our first challenge in this investigation was to assign each set of aliphatic proton signals to their respective nuclei in both the amide and tetrazolo series.

In the amide derivatives the methine and methylene signals are well separated in chemical shift (Figures 24 and 25). However, in the tetrazolo derivatives these signals appear in the same region, due to the downfield shift of the methylene proton signals by the increased electron-withdrawing effect of the tetrazolo ring. Although these aliphatic protons exhibit similar splitting patterns for analogous tetrazolo derivatives (oxa, aza or thia) the methine proton signals resonate at different fields reflecting the influence of varying the heteroatom at position 1. The high electronegativity of oxygen shifts the 2-H signal to resonate downfield (*ca.* δ 5.23 ppm) of the corresponding signals in the thia (*ca.* δ 4.88 ppm) and aza (*ca.* δ 4.47 ppm) analogues (Figure 26). The signal assignments are based on comparisons with previous data (where possible), and by use of coupling constants and multi-pulse NMR techniques such as DEPT, COSY and HETCOR (See Figures 27 and 28 for illustrative spectra).

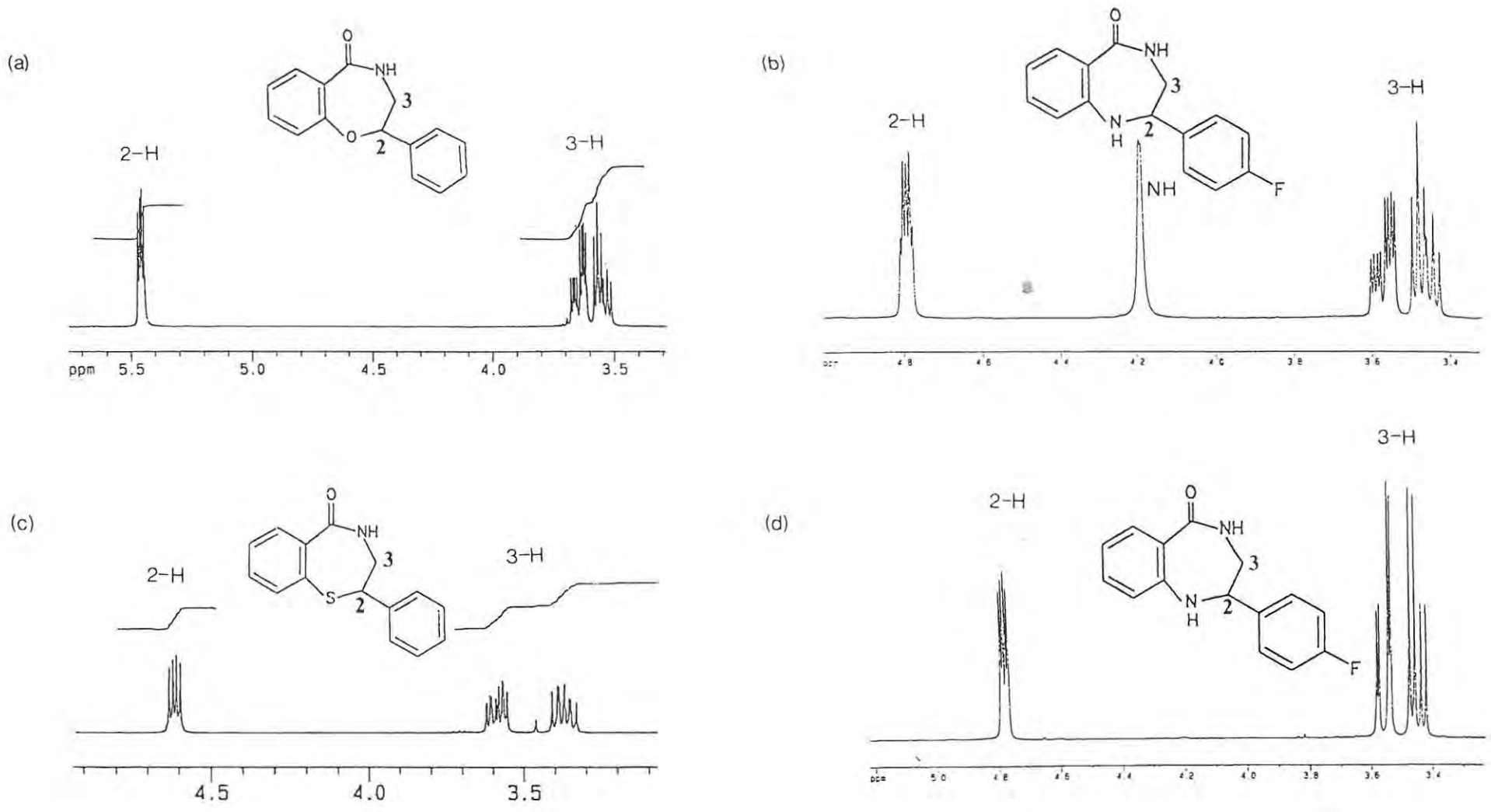


Figure 24: Partial ^{1}H NMR spectra of the (a) 2-phenyl-1,4-benzoxazepinone 190; (b) -1,4-benzodiazepinone 214* and (c) -1,4-benzothiazepinone 224 in $CDCl_3$ illustrating the splitting patterns of the methine and methylene protons.
*Figure (d) for 214 obtained in $CDCl_3$—D_2O medium.

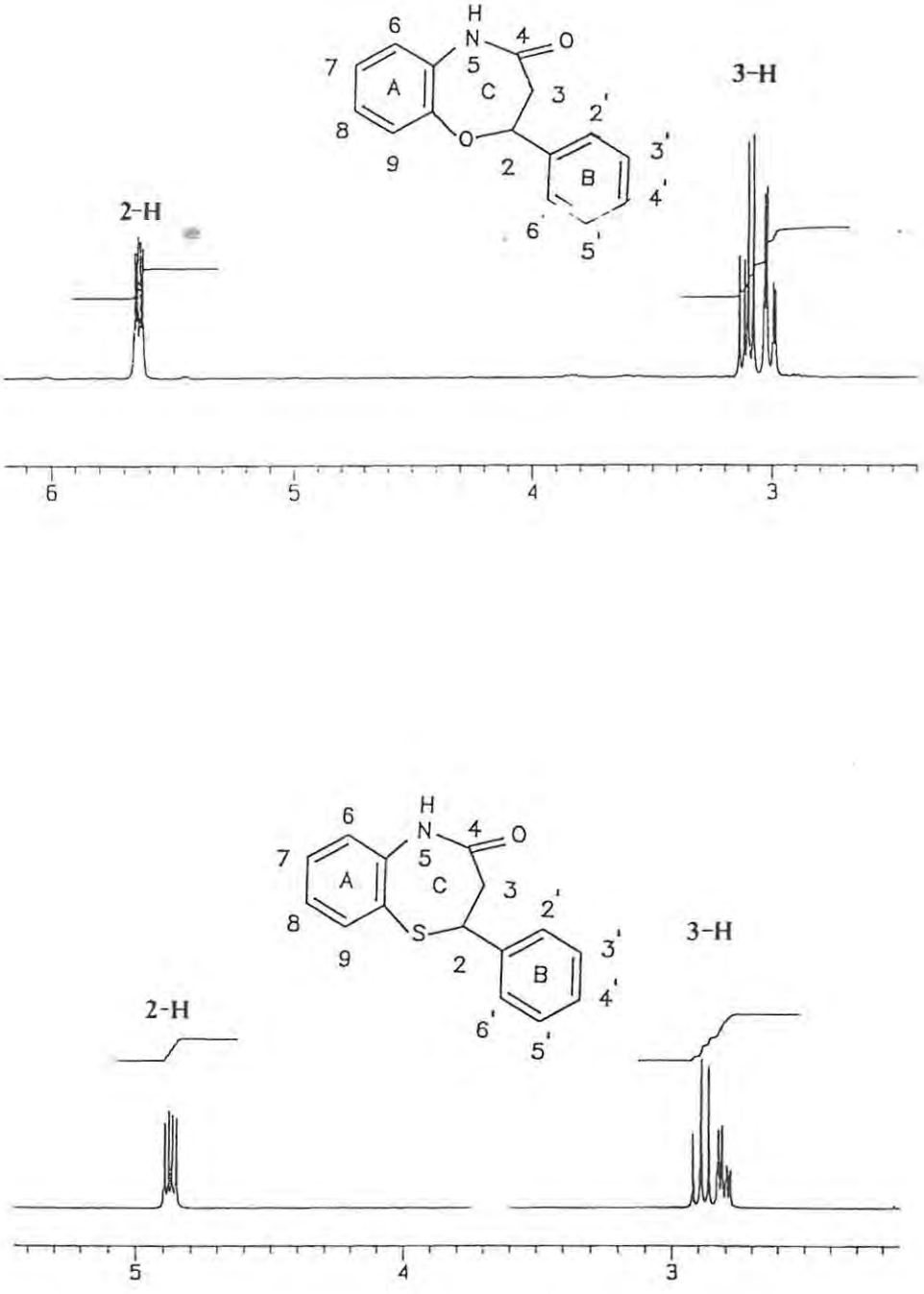


Figure 25: Partial ^1H NMR spectra of the 2-phenyl-1,5-benzoxazepinone 211 and 2-phenyl-1,5-benzothiazepinone 225 in $CDCl_3$ illustrating the splitting patterns of the methine and methylene protons.

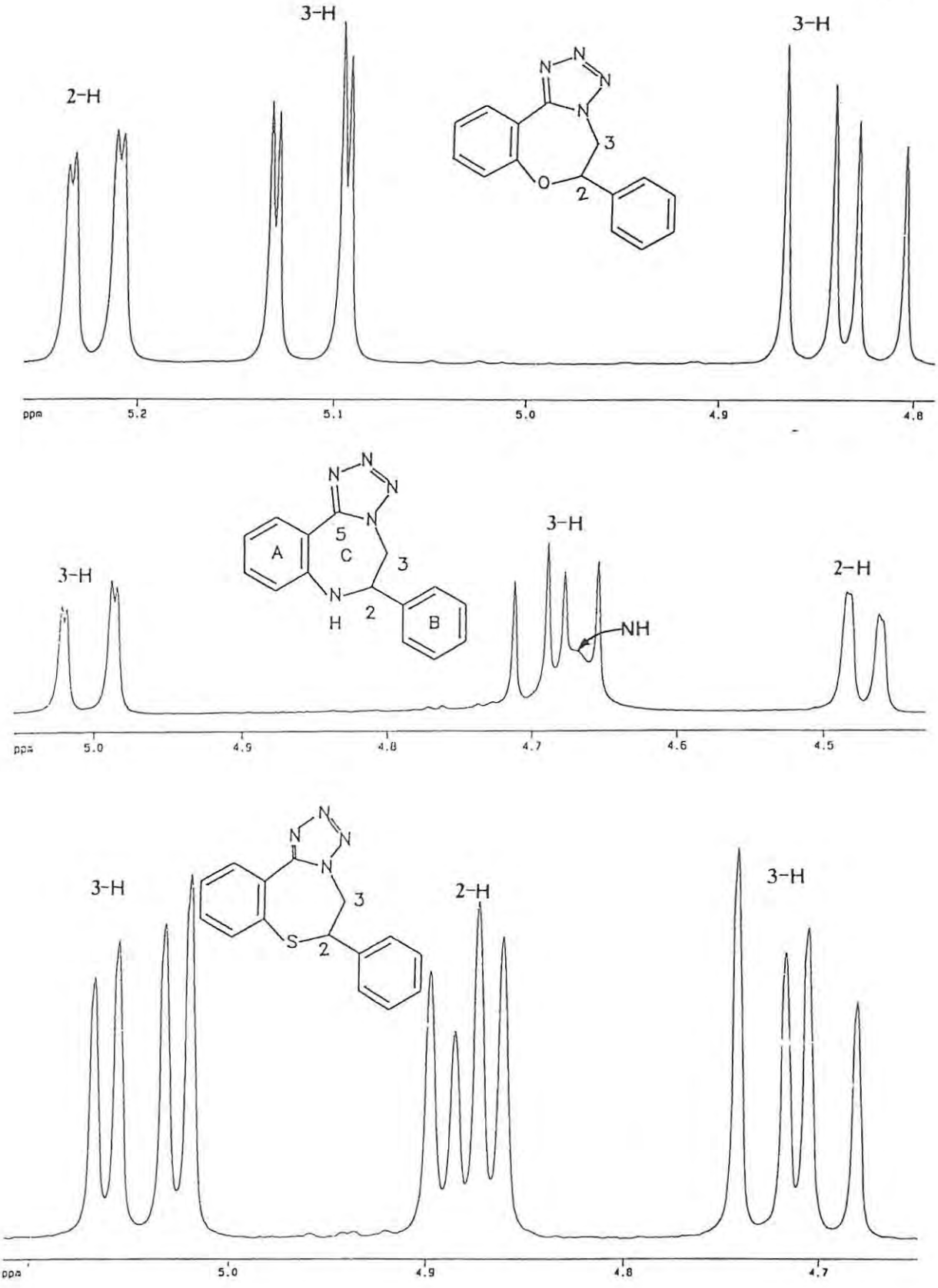


Figure 26: Partial ^{1}H NMR spectra of the 2-phenyltetrazolo[1,5-*d*]-1,4-benzoxazepine 191, -1,4-benzodiazepine 213 and -1,4-benzothiazepine 226 in $CDCl_3$ illustrating the splitting patterns of the methine and methylene protons.

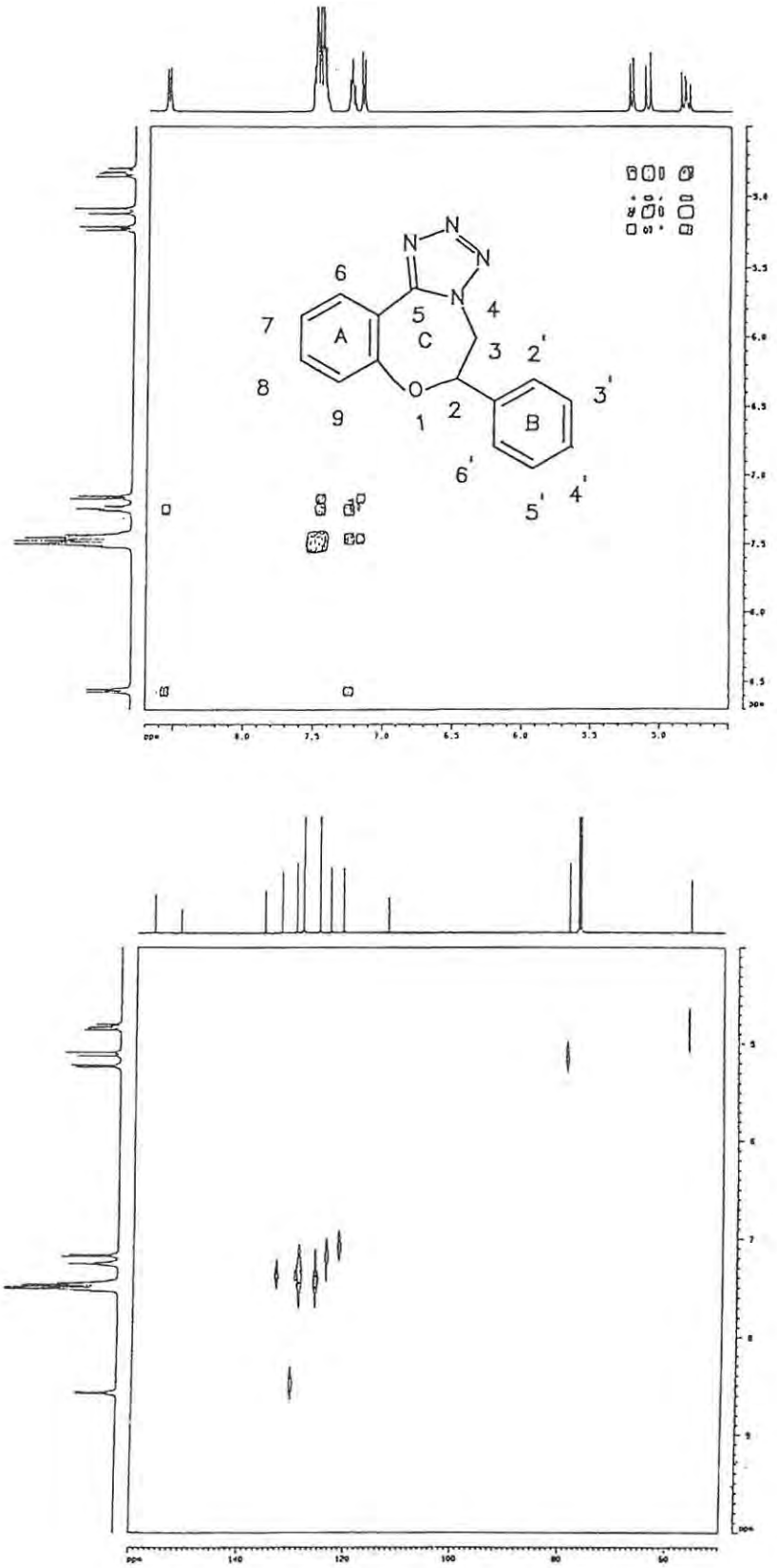


Figure 27: 400 MHz COSY (a) and HETCOR (b) spectra of 2-phenyltetrazolo[1,5-*d*]-benzoxazepine 191 in $CDCl_3$

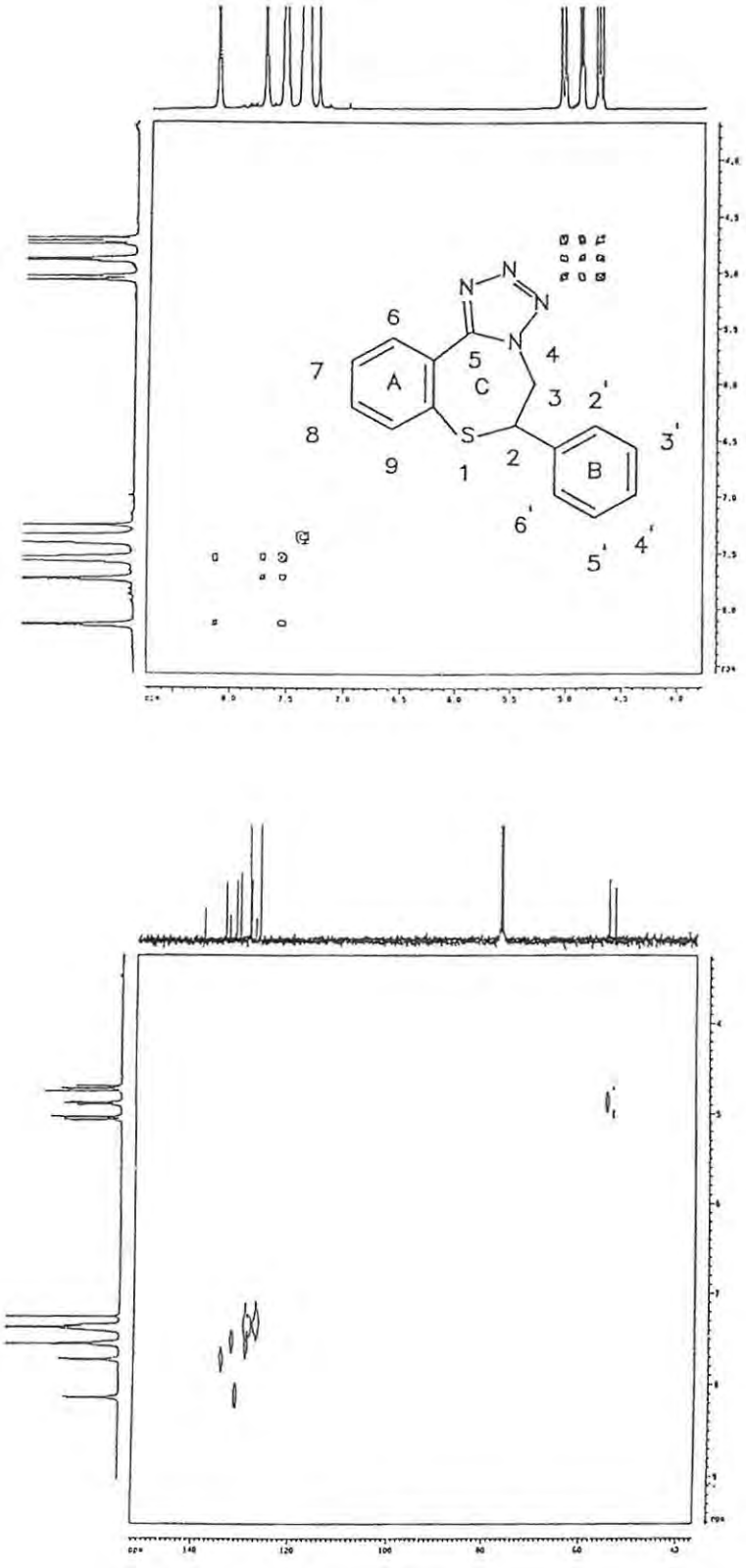
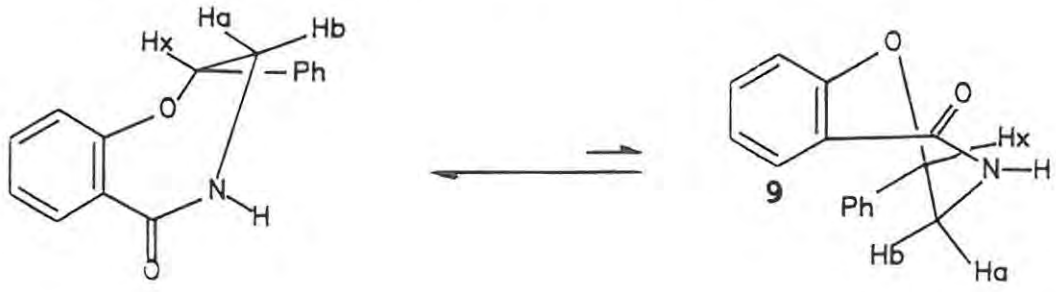


Figure 28: 400 MHz COSY (a) and HETCOR (b) of 2-phenyltetrazolo[1,5-*d*]-1,4-benzothiazepine 226 in $CDCl_3$

2.8.1.1 1,4- AND 1,5-BENZODIAZEPINE ANALOGUES

Several research groups have presented conflicting proposals concerning the stereochemistry of the 7-membered ring of 1,4-benzodiazepines[170] and 1,5-benzodiazepines,[171-174] based on results using ^{1}H NMR spectroscopy, lanthanide shift reagents and Dreiding models. More evidence continues to appear disputing the previously proposed conformational preferences.[170,173] In this section of the discussion, attention is focused on the 2-phenyl derivatives of the 1,4-benzoxazepinones, 1,4-benzodiazepinones and 1,4-benzothiazepinones. Duddeck and Lévai,[168] using Dreiding models and *vicinal* coupling constants (obtained at 200 MHz in $CDCl_3$) considered the conformation of the 2-phenyl-1,4-benzoxazepinones to be flexible and the 2-phenyl ring to be capable of adopting quasi-equatorial I and quasi-axial II orientations (Scheme 69). The *vicinal* H-H coupling constants (J_{ax} = 2.4 and J_{bx} = 0.6 Hz) were reported to correspond to estimated dihedral angles of *ca.* 55-65° and 70-80°, respectively. These authors believe that the quasi-axial form is less stable because of steric interaction between 9-H of the fused benzo ring and the *ortho*-hydrogen of the 2-phenyl substituent, which is orientated perpendicularly to the plane of the benzo ring in conformation II.

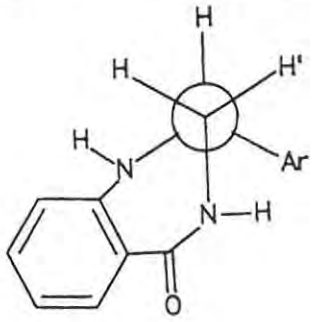


I II

Scheme 69

In another development, in the ^{1}H NMR spectroscopic analysis of 2-phenyl-1,4-benzodiazepinones, Tökes and Litkei[149] reported equal *vicinal* coupling constants for the methylene protons [$J_{ax} = J_{bx}$ = 4.0 Hz (200 MHz; $CDCl_3$)]. These authors also observed a triplet at δ 4.30ppm, corresponding to the methine proton. Based on these observations, they

proposed these compounds to exist in an equilibrium between boat and chair conformations similar to that found in cycloheptene. The boat conformation III [which is similar to conformation I of the 1,4-benzoxazepinone analogues (Scheme 69)] with the 2-phenyl substituent in an equatorial position is considered to be the most favoured form.



III

In our 400 MHz NMR studies of the 1,4-benzoxazepinones and 1,4-benzodiazepinones, however, results which differ significantly from those of Duddeck and Lévai,[168] and Tökés and Litkei[149] were observed. These observations throw a completely different light on the preferred conformations of these compounds. At the lower field (200 MHz) used by these authors, higher order coupling effects may obscure the true coupling pattern which, however, is clearly apparent at 400 MHz and 500 MHz. In our analysis of the 400 MHz ^{1}H NMR spectra of the 2-phenyl-1,4-benzodiazepine analogues (X = O,NH,S) in $CDCl_3$ two sets of high field multiplets, corresponding to the methylene protons, are observed (see Fig. 24). Analysis of these multiplets indicates three sets of coupling constants, *viz.* J_{vic}, $J_{H,NHCO}$ and J_{gem}. In the case of the oxa (X = O) and thia (X = S) derivatives, the methine proton signal resonates as a double doublet with significantly different J_{vic} values. However, the corresponding signal in the spectra of the aza (X = NH) analogues appears as a multiplet due to additional coupling with the N^1-H proton ($J_{H,NH}$); as a result of the overlap of signals the expected ddd is observed as an apparent "quintet" in $CDCl_3$ [Fig. 24 (c)]. Addition of deuterium oxide (D_2O) to the $CDCl_3$ solution of the aza derivative **214** eliminated coupling due to the NH protons and resulted in three sets of double doublets for the methine and methylene protons [Fig. 24 (d)].

The oxa, aza and thia analogues detailed in Table 28 show similar trends in *geminal* and *vicinal* coupling constants. The larger J_{vic} values (6.2-8.8 Hz) clearly indicate anti-coupling, while the smaller J_{vic} values (3.2-5.0 Hz) indicate gauche coupling. In each of the compounds listed in Table 28 the significant difference in *vicinal* coupling constants requires the methine proton (2-Hx) to be gauche to one of the methylene protons (3-Ha) and anti to the other (3-Hb). This arrangement can be achieved if the 2-phenyl ring occupies the quasi-equatorial orientation, illustrated in conformation IV. This conformation, in fact, paralles the energy minimised conformations from computer modelling of the parent compound in each series. Computer modelling and energy minimisation were accomplished using the molecular modelling package HYPERCHEM. Models in which the 2-phenyl group is quasi-axial and the methine and methylene protons are all gauche as proposed by Duddeck and Lévai,[158] and Tökés and Litkei[149] proved to have higher conformational energy when examined by HYPERCHEM (Scheme 70 and experimental section).

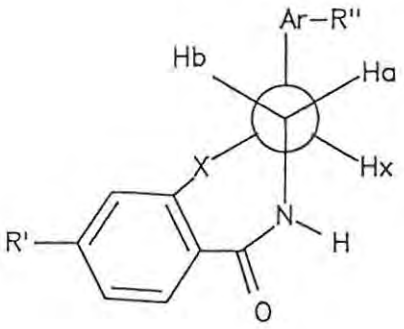
X-Ray crystallographic data was also obtained for the solid-state conformation of the 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one **224** (Fig. 29; the X-ray data from this analysis is tabulated in Appendix 2). In the crystal lattice, compound **224** clearly adopts a conformation which is very similar to that obtained from molecular mechanics analysis and in which:-

(i) the 2-phenyl group occupies a quasi-equatorial orientation and

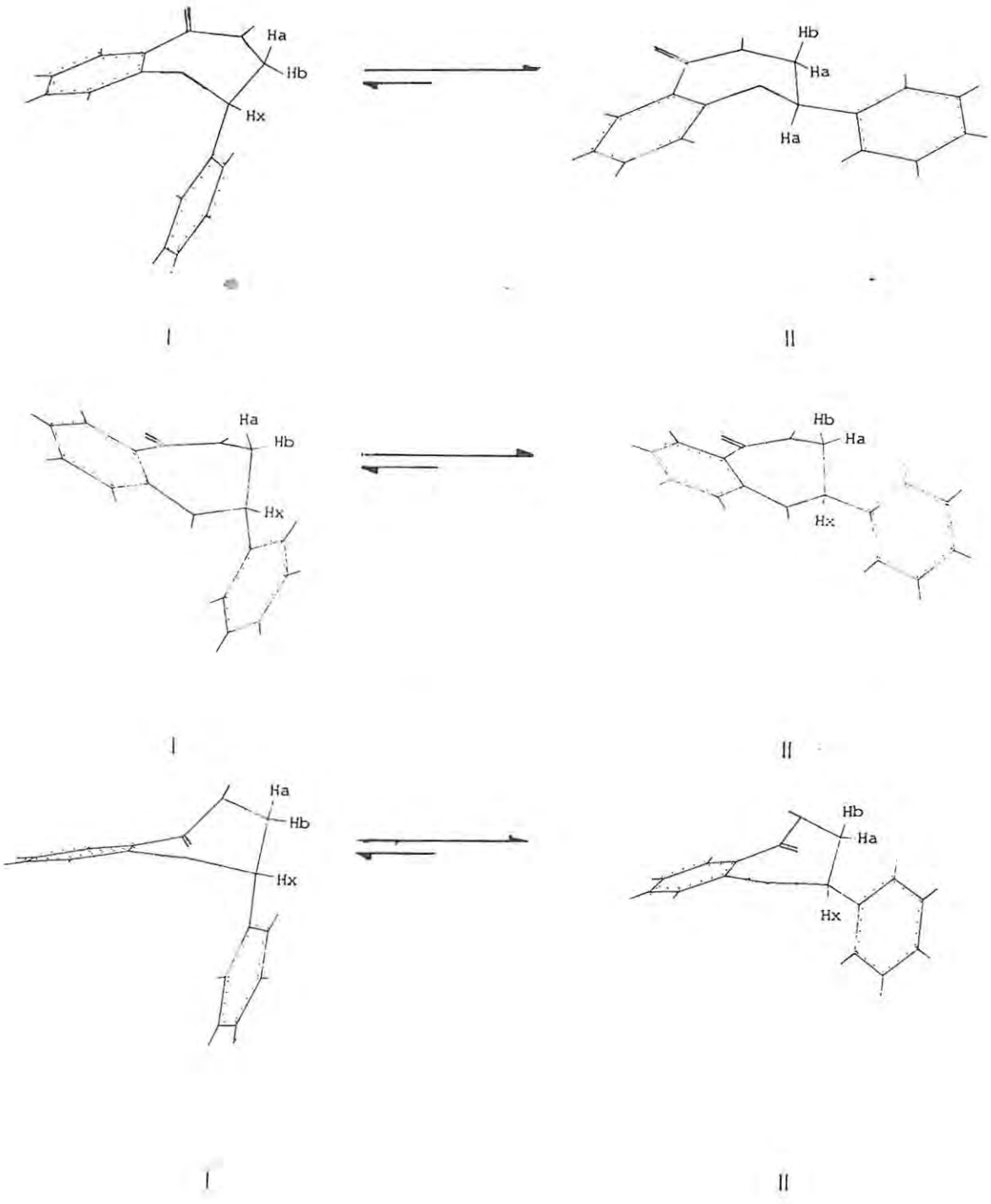
(ii) the methine hydrogen is anti to one of the methylene hydrogen and gauche to the other.

Although the crystal conformation is not necessarily the favoured conformation in solution, nevertheless in the crystal lattice compound **224** clearly adopts the conformation similar to that obtained in solution. Thus the ^{1}H NMR J_{vic} data, the results from molecular mechanics data and the crystal lattice data from X-ray analysis all point to the conformation detailed in Figure 29 rather than the one proposed by Duddeck and Lévai[158] I and Tökés and Litkei[149] (see conformation III).

Table 28: ^{1}H NMR Chemical Shifts [in $CDCl_3$ (followed, in parentheses, by splitting patterns and coupling constants, *J* in Hz)] of the methylene and methine protons of the 2-phenyl-1,4-benzodiazepine analogues.



No	X	R'	R''	3-Hb [ddd (J_{anti}; J_{NH}; J_{gem})]	3-Ha [dddd (J_{gauche}; $J_{H,NH}$; J_{gem})]	2-Hx [dd (J_{gauche}; J_{anti})]
190	O	H	H	3.54 (*J* 6.4; 6.4; 15.4)	3.64 (*J* 3.5, 6.3 & 15.4)	5.46 (*J* 3.4; 6.4)
194	O	Cl	H	3.58 (*J* 6.2, 6.2; 15.4)	3.65 (*J* 3.2, 6.4 & 15.5)	5.45 (*J* 3.2; 6.2)
196	O	Br	H	3.57 (*J* 6.3, 6.3; 15.4)	3.64 (*J* 3.2, 6.4 & 15.4)	5.45 (*J* 3.5; 6.3)
200	O	H	F	3.50 (*J* 6.2, 6.2; 15.4)	3.65 (*J* 3.5, 6.2 & 15.4)	5.43 (*J* 3.5; 6.2)
202	O	H	Cl	3.46 (*J* 6.3, 6.3; 15.4)	3.59 (*J* 3.4, 6.3 & 15.4)	5.38 (*J* 3.5; 6.4)
204	O	H	Br	3.47 (*J* 6.4, 6.4; 15.4)	3.63 (*J* 3.4, 6.2 & 15.4)	5.39 (*J* 3.4; 6.4)
208	O	H	NO_2	3.47 (*J* 6.3, 6.3; 15.4)	3.75 (*J* 3.4, 6.2 & 15.4)	5.53 (*J* 3.4; 6.3)
				ddd (J_{anti}; $J_{H,NHCO}$; J_{gem})	dddd (J_{gauche}; $J_{H,NHCO}$; & J_{gem})	"quintet" (J_{gauche}; $J_{H,NH}$; J_{anti})
212	NH	H	H	3.51 (*J* 6.4; 6.4; 15.0)	3.57 (*J* 3.1; 6.4; 15.0)	4.80 (*J* 3.1; 3.1; 6.4)
214	NH	H	F	3.58 (*J* 6.3; 6.3; 14.8)	3.58 (*J* 3.0; 6.2; 14.8)	4.80 (*J* 3.1; 3.1; 6.3)
216	NH	H	Cl	3.45 (*J* 6.2; 6.2; 14.8)	3.58 (*J* 3.0; 6.5; 14.8)	4.78 (*J* 3.1; 3.1; 6.3)
218	NH	H	Br	3.45 (*J* 6.2; 6.2; 14.8)	3.61 (*J* 3.0; 6.5; 14.9)	4.78 (*J* 3.1; 3.1; 6.2)
222	NH	H	NO_2	3.47 (*J* 6.3; 6.3; 15.0)	3.75 (*J* 3.0; 6.1; 15.0)	4.96 (*J* 3.1; 3.1; 6.4)
				dddd (J_{anti}; $J_{H,NHCO}$; J_{gem})	dddd (J_{gauche}; $J_{H,NHCO}$; J_{gem})	dd (J_{gauche}; J_{anti})
224	S	H	H	3.37 (*J* 8.8; 1.9; 15.1)	3.59 (*J* 5.1; 1.7; 15.1)	4.61 (*J* 5.0; 9.0)
227	S	H	F	3.33 (*J* 8.8; 1.2; 15.2)	3.57 (*J* 5.0; 6.8; 15.1)	4.61 (*J* 4.9; 8.8)
229	S	H	Cl	3.33 (*J* 8.7; 7.2; 15.2)	3.57 (*J* 4.9; 6.7; 15.2)	4.57 (*J* 4.9; 8.7)
231	S	H	Br	3.33 (*J* 8.7; 7.3; 15.2)	3.56 (*J* 5.0; 6.8; 15.2)	4.56 (*J* 5.0; 8.7)



Scheme 70: Conformational equilibria of 2-phenyl-1,4-benzoxazepinone 190, 2-phenyl-1,4-benzodiazepinone 214 and 2-phenyl-1,4-benzothiazepinone 224, respectively.

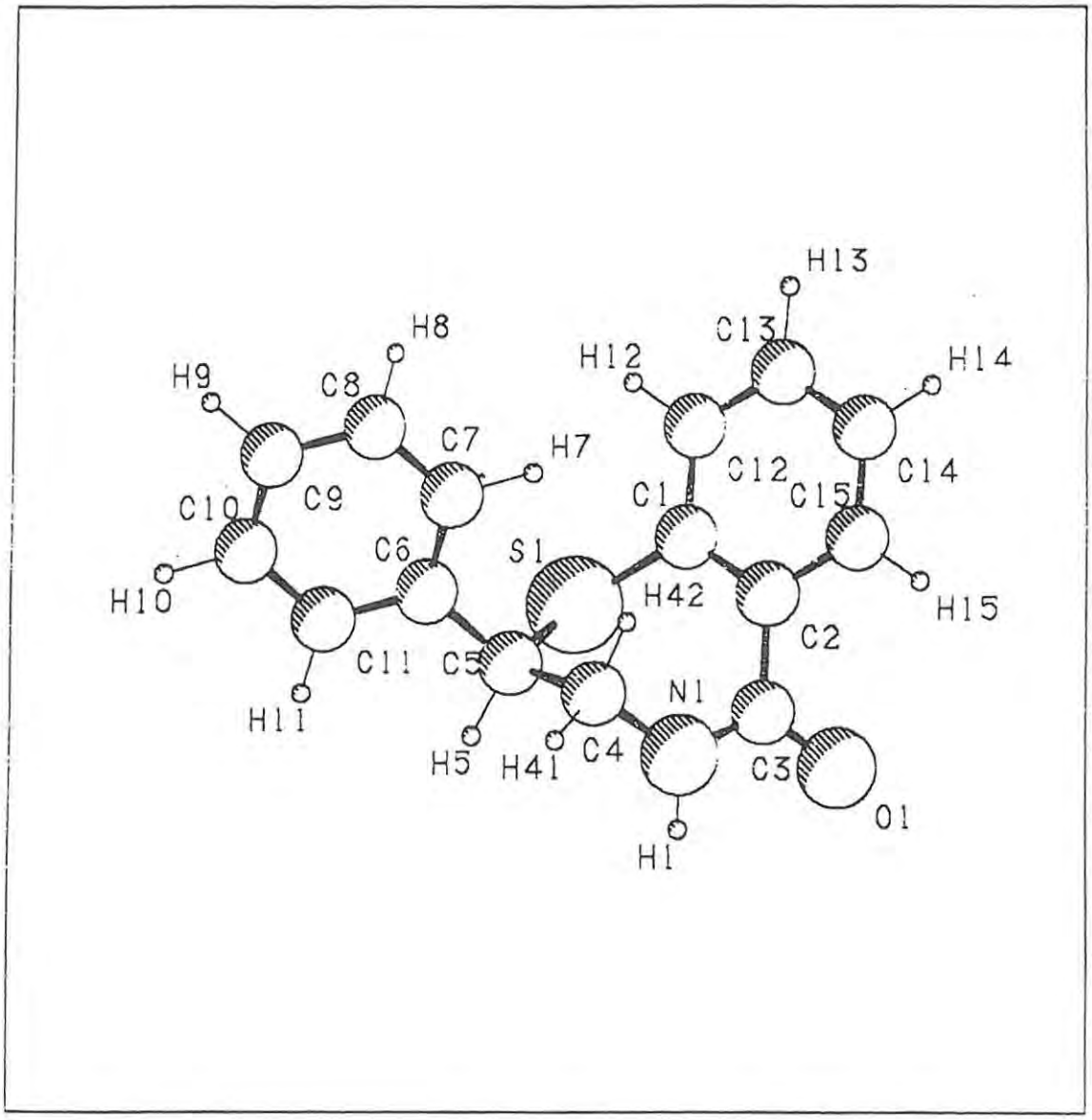
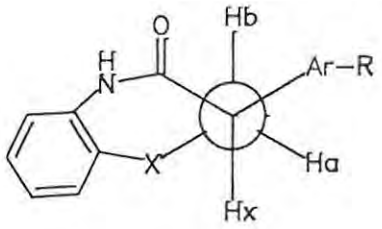


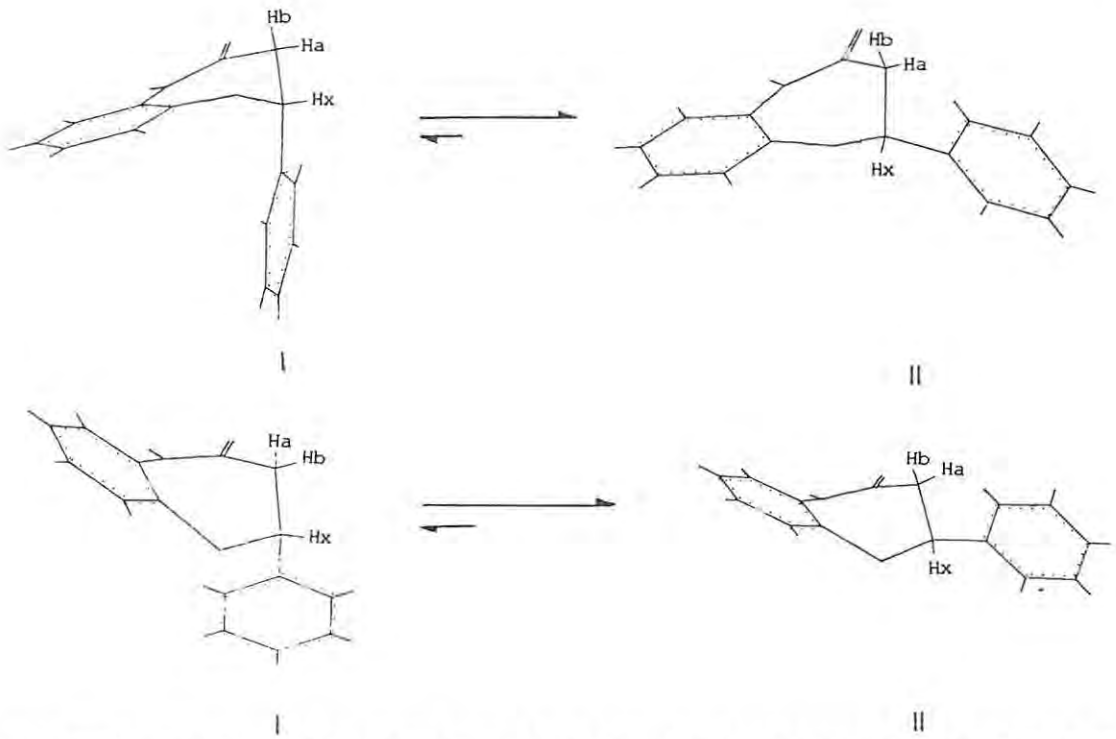
Figure 29: X-Ray crystal structure for the 2-phenyl-3,4-benzothiazepinone 224, showing crystallographic labelling.

In the case of the 1,5-benzoxazepinone (X = O) and the 1,5-benzothiazepinone analogues (X = S) *vicinal* coupling constants of 4.0 and 8.6 Hz (X = O), and 5.7 and 11.1 Hz (X = S) were observed, respectively (Fig. 25 and Table 29). In both series the two different J_{vic} values require the methine proton (2-Hx) to be gauche to one of the methylene protons (3-Ha) and anti to the other (3-Hb). In this arrangement, the 2-phenyl ring is expected to be orientated in quasi-axial or quasi-equatorial position. These observations indicate that the 2-phenyl-1,5-benzoxazepinone **211** and 2-phenyl-1,5-benzothiazepinones **225-232** exhibit similar conformation to those of the 1,4-benzodiazepine analogues. Results from molecular mechanics also confirm the quasi-equatorial orientation of the 2-phenyl ring (conformation II and IV ; Scheme 71).

Table 29: ^{1}H NMR Chemical Shifts (followed, in parentheses, by the splitting patterns and coupling constants, *J* in Hz) of the methylene and methine protons of the 2-phenyl-1,5-benzodiazepine analogues.



No	X	R	3-Ha [dd (J_{gauche}; J_{gem})]	3-Hb [dd (J_{anti}; J_{gem})]	2-Hx [dd (J_{gauche}; J_{anti})]
211	O	H	3.01 (*J* 4.0; 14.9)	3.11 (dd, *J* 8.7; 14.9)	5.65 (*J* 4.0; 8.6)
225	S	H	2.83 (*J* 5.7; 12.6)	2.89 (*J* 11.2; 12.5)	(5.7; 11.2)
228	S	F	2.60 (*J* 5.7; 12.4)	2.71 (*J* 10.3; 12.4)	4.88 (*J* 5.7; 11.1)
230	S	Cl	2.79 (*J* 6.1; 12.5)	2.84 (*J* 10.3; 12.5)	4.85 (*J* 6.1; 10.3)
232	S	Br	2.41 (*J* 1.0; 5.8; 12.5)	2.50 (*J* 10.7; 12.5)	4.53 (*J* 5.8; 10.6)



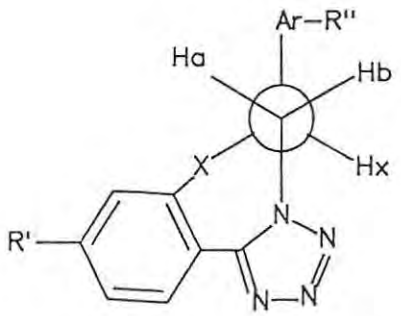
Scheme 71: **Conformational equilibrium of 2-phenyl-1,5-benzodiazepinone 211 and 2-phenyl-1,5-benzothiazepinone 225, respectively.**

2.8.1.2 TETRAZOLO ANALOGUES

The splitting patterns of the methylene and methine protons in the ^{1}H NMR spectra of the oxa (X = O) and thia (X = S) derivatives are characterised by three sets of double doublets (see Fig. 26 and Table 30). On the other hand, in the aza (X = NH) analogues, the methine proton resonates as a broad doublet at *ca* δ 4.5 ppm instead of the expected ddd. This broadening of signals can be attributed to the additional, but unresolved, coupling of the methine proton to the NH proton.[176] Nevertheless, in all three series of analogues (X = O,S,NH), the methine proton exhibits two significantly different *vicinal* H-H coupling constants indicating significantly different torsion angles between the methine proton and each of the methylene protons. The presence of the tetrazolo ring in these compounds is expected to offer some degree of conformational rigidity to the 7-membered heterocyclic ring. Thus, from Table 30 the two different constants J_{vic} 1.5-5.0 Hz and J_{vic} 9.1-9.8 Hz require the methine proton (2-Hx) to be gauche to one of the methylene protons (3-Ha) and anti to the other (3-Hb). Conformations with a quasi-equatorial orientation of the phenyl ring would satisfy these geometric

requirements (Scheme 72) and are similar to that proposed by Tökés and Litkei[148] (for X=NH), using ^{1}H NMR *vicinal* coupling constant data. The proposed conformations, in fact, correspond to the energy minimised conformations obtained from computer modelling of the parent compound in each series (Scheme 72). Furthermore, the aza (X=NH) derivative **213** exhibits a similar conformational preference in the solid state as evidenced by X-ray crystallography (see Fig. 30 and Appendix 2).

Table 30: Chemical shifts [followed, in parentheses, by splitting patterns and coupling constants *J*, (Hz)] of the tetrazolo[1,5-*d*]-1,4-benzodiazepine analogues in $CDCl_3$.



No	X	R'	R''	3-Ha (J_{anti}; J_{gem})	3-Hb (J_{gauche}; J_{gem})	2-Hx (J_{gauche}; J_{anti})
191	O	H	H	4.83 (dd, *J* 9.8; 14.5)	5.13 (dd, *J* 1.5; 14.6)	5.28 (dd, *J* 1.3; 9.8)
193	O	F	H	4.83 (dd, *J* 9.7; 14.7)	5.11 (dd, *J* 1.5; 14.7)	5.25 (dd, *J* 1.4; 9.7)
195	O	Cl	H	4.85 (dd, *J* 9.7; 14.7)	5.12 (dd, *J* 1.4; 14.7)	5.23 (dd, *J* 1.4; 9.7)
197	O	Br	H	4.79 (dd, *J* 9.7; 14.7)	5.12 (dd, *J* 1.4; 14.7)	5.22 (dd, *J* 1.3; 9.7)
199	O	OCH_3	H	4.79 (dd, *J* 9.7; 14.7)	5.08 (dd, *J* 1.4; 14.7)	5.22 (dd, *J* 1.4; 9.7)
201	O	H	F	4.81 (dd, *J* 9.7; 14.7)	5.09 (dd, *J* 1.5; 14.7)	5.23 (dd, *J* 1.5; 9.7)
203	O	H	Cl	4.79 (dd, *J* 9.7; 14.7)	5.08 (dd, *J* 1.5; 14.7)	5.21 (dd, *J* 1.5; 9.7)
205	O	H	Br	4.79 (dd, *J* 9.7; 14.6)	5.08 (dd, *J* 1.5; 14.6)	5.21 (dd, *J* 1.5; 9.7)
207	O	H	OCH_3	4.83 (dd, *J* 9.8; 14.6)	5.07 (dd, *J* 1.4; 14.6)	5.17 (dd, *J* 1.4; 9.7)
209	O	H	NO_2	4.83 (dd, *J* 9.7; 14.7)	5.16 (dd, *J* 1.5; 14.7)	5.37 (dd, *J* 1.5; 9.7)
226	S	H	H	4.71 (dd, *J* 9.8; 14.3)	5.04 (dd; *J* 5.0; 14.3)	4.88 (dd; *J* 5.0; 9.8)
213	NH	H	H	4.67 (dd, *J* 9.1; 13.7)	4.98 (dd, *J* 1.4; 13.7)	4.46 (d*, *J* 9.1)
215	NH	H	F	4.68 (dd, *J* 9.0; 13.7)	4.95 (dd; *J* 1.5; 13.7)	4.50 (d*, *J* 9.1)
217	NH	H	Cl	4.68 (dd, *J* 8.8; 13.7)	4.96 (dd, *J* 1.5; 13.7)	4.51 (d*, *J* 8.8)
219	NH	H	Br	4.67 (dd, *J* 8.8; 13.7)	4.94 (d, *J* 13.7)	4.49 (d*, *J* 8.8)
221	NH	H	OCH_3	4.66 (dd, *J* 9.0; 13.7)	4.98 (d, *J* 13.7)	4.43 (d*, *J* 9.0)
223	NH	H	NO_2	4.69 (dd, *J* 8.8; 13.7)	4.99 (d, *J* 13.7)	4.45 (d*, *J* 8.8)

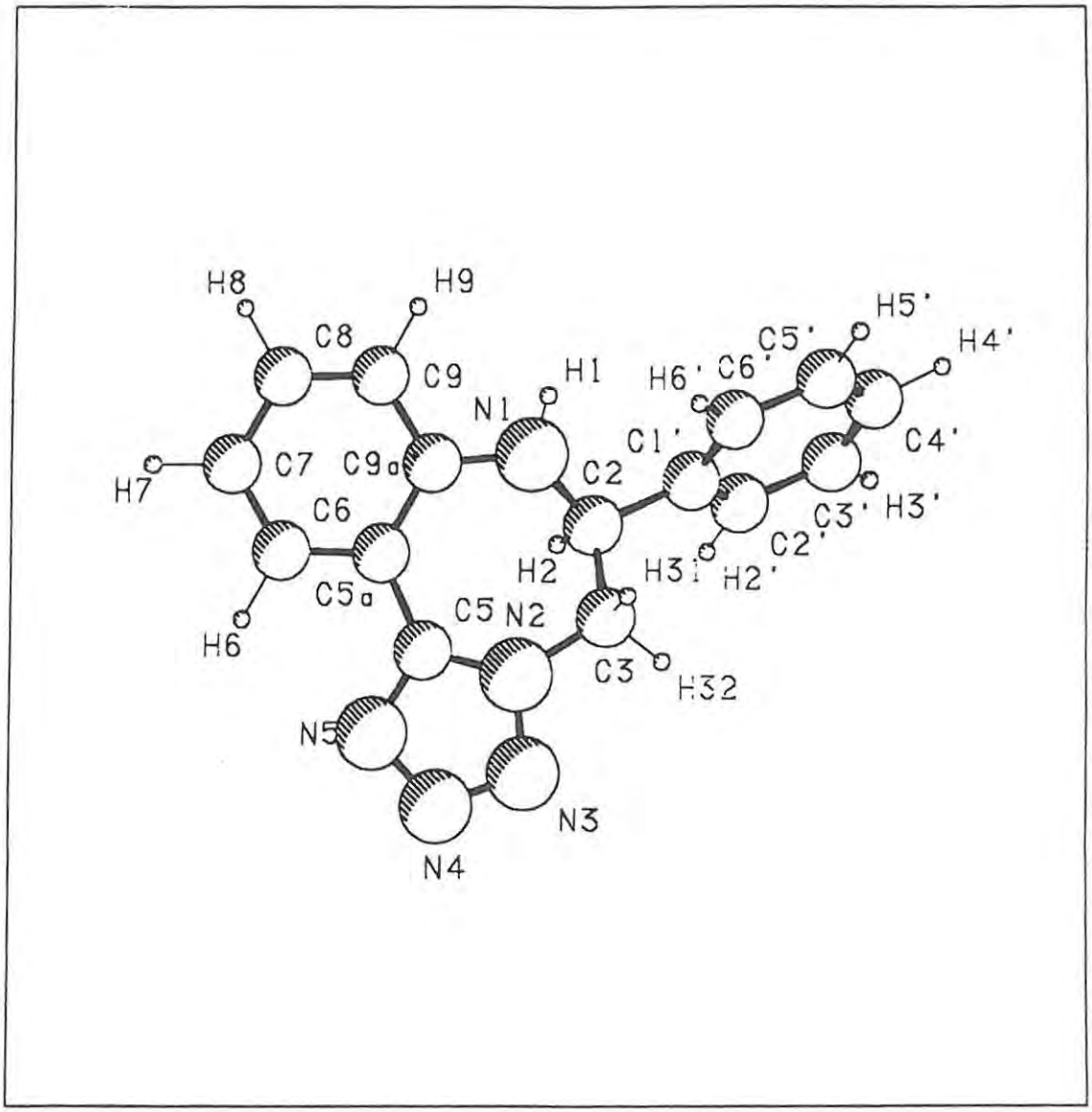
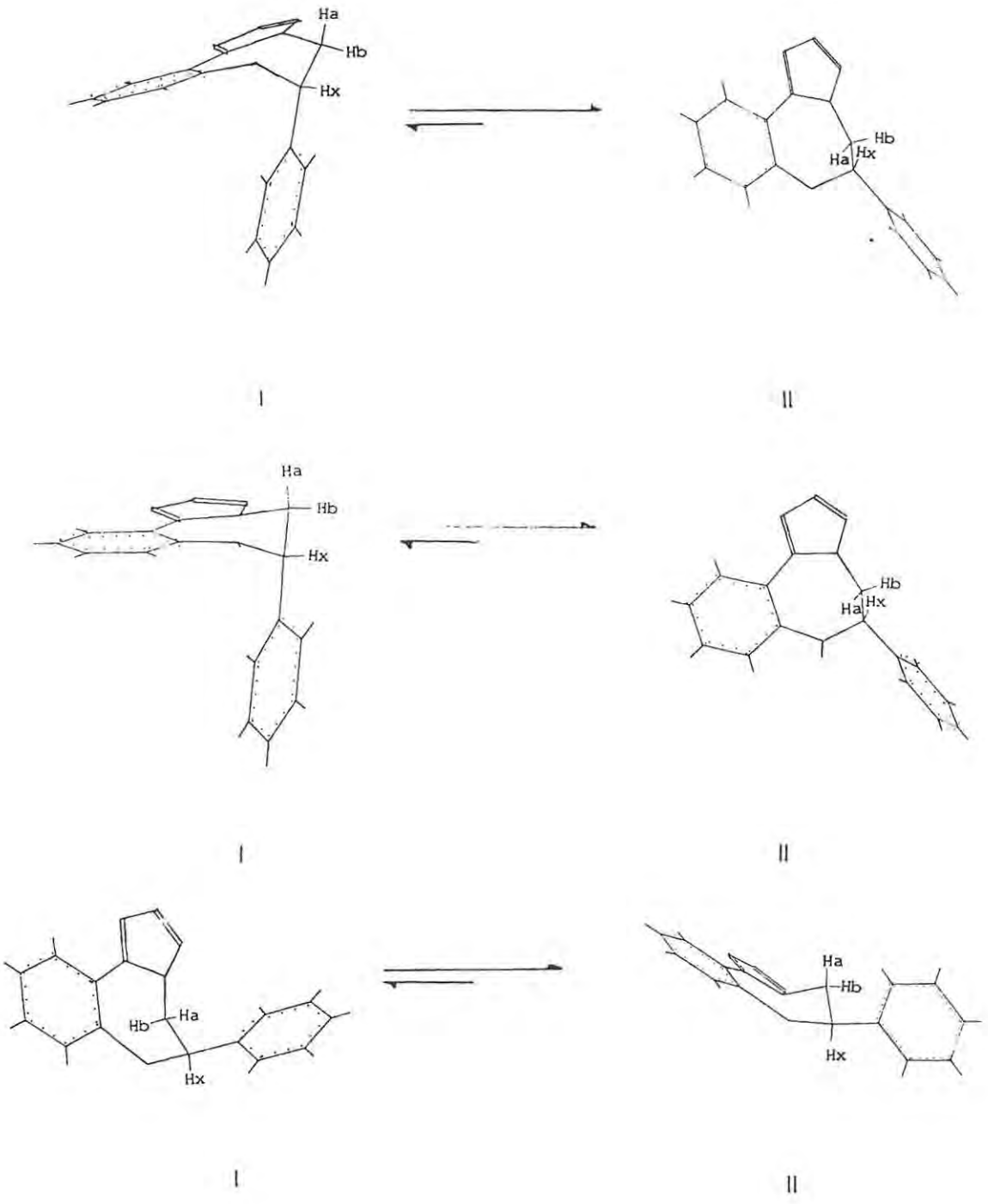


Figure 30: **X-Ray crystal structure of the 2-phenyltetrazolo-1,4-benzodiazepine 213 showing crystallographic labelling.**



Scheme 72: Conformational equilibria for the 2-phenyltetrazolo-1,4-benzodiazepine analogues 191, 213 and 226

Loew *et al.*[177] in empirical and semi-empirical MO studies of 1,4-benzodiazepines, with various substituents on the A-, B- and C-rings, showed that both biologically active and inactive ligands have low energy conformations. These observations argue against conformation as a modulator of recognition at the receptor. On the other hand, results from calculated molecular electrostatic potentials and explicit molecular receptor interactions, led these authors to deduce that high affinity analogues interact with 3 cationic sites on the receptor. These sites were postulated to interact with electron-withdrawing groups at (C-7), the carbonyl group and the imine nitrogen. In our work, both binding and non-binding analogues also appear to exhibit similar conformations within a series. From these observations, it can be concluded that conformational effects have little or no effect on the binding affinities of these compounds to the receptors.

2.9 CONCLUSIONS

During the course of this research several series of benzodiazepine analogues have been successfully prepared (many of the compounds for the first time) and subjected to spectroscopic, conformational and receptor-binding analyses. Schmidt reaction of flavanones, 4-quinolones and 1-thioflavanone precursors has provided convenient access to the benzodiazepine analogues although several cyclisation procedures were also explored to prepare some of the 7-membered heterocyclic compounds. With the aim of investigating the effect of conjugation on the binding affinity and conformation of the benzodiazepine analogues, several approaches for increasing conjugation in the ring expanded systems were explored, but without success. One of these approaches, attempted *N*-chlorination using *t*-BuOCl, resulted in regioselective A-ring chlorination of the 1,4-benzodiazepine analogues. Access to the conjugated 1,4-benzoxazepinone was finally achieved by a cyclisation method involving the condensation of salicylamide and *α*-bromophenylacetaldehyde. Other reactions of the benzodiazepine analogues which were investigated include thionation of several amides (using P_2S_5) and methylation of the resulting thioamides. The structures of the products prepared in this investigation were established using ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic techniques. Detailed mass spectrometric studies were also undertaken for the 4-quinolones and their ring enlarged products, using a combination of low-resolution, high-resolution and metastable-peak analyses. Certain general trends were observed for most of the series analysed.

The kinetic-mechanistic study of the Schmidt reaction of flavanones has shown that nitrogen insertion in the flavanoid compounds is controlled by electronic factors rather than steric ones and occurs *via* alkyl migration. Preliminary results from the binding affinity studies indicate that binding is influenced more by substituent effects than by conformation. The conformational preferences of the various benzodiazepine analogues were investigated using a combination of ^{1}H NMR spectroscopic, X-ray crystallographic and molecular modelling techniques.

While the initial aims of this project have been substantially met, future research is expected to address the following:-

(i) Extension of the cyclisation route for the preparation of a series of conjugated 1,4-benzodiazepine analogues with various substituents and heteroatoms in the A-, B- and C-rings.

(ii) The synthesis of *N*-substituted amide derivatives to enhance binding affinity and, hence, the biological activity of the ligand.

(iii) The introduction of various heterocyclic rings (other than tetrazolo) on the *d*-face of the benzodiazepine frame-work *via* thioamides or their methylthioimino derivatives.

3. EXPERIMENTAL

3.1 GENERAL

All solvents and commercially available reagents were purified when necessary by conventional methods[178] before use. Solvents were evaporated using a rotary evaporator. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Precoated Kieselgel 60F254 plates were used for thin layer chromatography and Merck Kieselgel 60 (0.040-0.063mm) was used as stationary phase for flash chromatography. 60 MHz NMR spectra were recorded on a Perkin Elmer R12a instrument. High field NMR Spectra (^1H and ^{13}C) were recorded on a Bruker AMX400 spectrometer. Chemical shifts are given relative to tetramethylsilane (δ_H = 0 ppm) or $CHCl_3$ (δ_H = 7.25 ppm) and $CDCl_3$ (δ_C 77.0 ppm). Values for coupling constants (J) are given in hertz (Hz).

Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectrometry was performed on a Krators M580RF double focusing magnetic sector instrument by the Cape Technikon Mass Spectrometry Unit. Infrared spectra were recorded on a Perkin-Elmer 180 or Beckmann 4260 spectrophotometer using KBr discs. Combustion analyses were performed at the University of Natal, Pietermaritzburg.

3-Fluorophenyl acetate 127.[112] Acetic anhydride (12.85 g, 126 mmol) was added dropwise to a stirred solution of 3-fluorophenol **124** (4.92 g, 43.9 mmol) and sodium hydroxide (5.04 g, 126 mmol) in water (25 ml) at 0°C. The resulting mixture was stirred at 0-5°C for 1 h and the product was extracted with ether (3 x 30 ml). The combined organic extracts were washed, sequentially, with 10% aq. $NaHCO_3$ (2 x 20 ml) and water (2 x 20 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated and the residue was distilled *in vacuo* to afford 3-fluorophenyl acetate **127** (11.5 g, 94%), b.p. 46-48°C/1 mm Hg (lit.,[112] 77°C/16 mm Hg); δ_H (60 MHz, $CDCl_3$) 2.20 (3H, s, CH_3) and 6.40-7.60 (4H, m, ArH).

3-Chlorophenyl acetate 128.[112] The experimental procedure employed for the synthesis of 3-fluorophenyl acetate **127** was followed, using 3-chlorophenol **125** (10.0 g, 77.8 mmol), sodium hydroxide (4.98 g, 124.5 mmol) and acetic anhydride (12.89 g, 124.5 mmol) in water (200 ml). Work-up afforded an oil which was distilled to give 3-chlorophenyl acetate **128** (11.3 g, 85%), b.p. 53-56°C/0.1 mm Hg (lit.,[112] 105-107°C/13 mm Hg); δ_H (60 MHz, $CDCl_3$) 2.30 (3H, s, CH_3) and 6.80-7.70 (4H, m, ArH).

3-Bromophenyl acetate 129.[112] The experimental procedure employed for the synthesis of 3-fluorophenyl acetate **127** was followed, using 3-bromophenol **126** (10.0 g, 57.8 mmol), sodium hydroxide (3.70 g, 91.7 mmol) and acetic anhydride (9.35 g, 91.7 mmol) in water (100 ml). Work-up afforded an oil which was distilled to give 3-bromophenyl acetate **129** (11.63 g, 94%), b.p. 68-70°C/0.3 mm Hg (lit.,[112] 149°C/40 mm Hg); δ_H (60 MHz, $CDCl_3$) 2.30 (3H, s, CH_3) and 6.90-7.60 (4H, m, ArH).

4-Fluoro-2-hydroxyacetophenone 130.[111] A mixture of 3-fluorophenyl acetate **127** (7.0 g, 45 mmol) and anhydrous aluminium chloride (17.9 g, 135 mmol) was heated at 170-180°C for 1.5 h. The cooled mixture was treated with 10% hydrochloric acid (150 ml) and then steam distilled. The distillate was extracted with chloroform (3 x 60 ml) and the combined organic exracts were washed with 0.5M aq. potassium hydroxide (3 x 30 ml). The combined alkaline

phases were acidified with 10% HCl, and extracted with chloroform (2 x 60 ml). The chloroform solutions were then combined and washed with water (3 x 30 ml). The organic phase was dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford an oil which crystallised to give crude 4-fluoro-2-hydroxyacetophenone **130** (5.57 g, 80%), m.p. 30-33°C (from hexane) (lit.,[91,92] 24°C); δ_H (60 MHz, $CDCl_3$) 2.60 (3H, s, $COCH_3$), 6.50-8.20 (3H, m, ArH) and 12.70 (1H, br s, OH).

4-Chloro-2-hydroxyacetophenone 131.[111] The experimental procedure employed for the synthesis of 4-fluoro-2-hydroxyacetophenone **130** was followed, using 3-chlorophenyl acetate **128** (25.6 g, 0.15 mol) and $AlCl_3$ (48.7 g, 0.36 mol). Work-up afforded an oil which was distilled to give 4-chloro-2-hydroxyacetophenone **131** (25.6 g, 82%), b.p. 78-80°C/0.4 mm Hg (lit.,[111] 121-124°C/15 mm Hg); δ_H (60 MHz, $CDCl_3$) 2.60 (3H, s, $COCH_3$), 6.70-6.90 (2H, m, 3-H and 5-H), 7.60 (1H, d, J 8.0 Hz, 6-H) and 12.40 (1H, s, OH).

4-Bromo-2-hydroxyacetophenone 132.[111] The experimental procedure employed for the synthesis of 4-fluoro-2-hydroxyacetophenone **130** was followed, using 3-bromophenyl acetate **129** (11.63 g, 54.1 mmol) and $AlCl_3$ (21.6 g, 162.3 mmol). Work-up afforded an oil which crystallised to give 4-bromo-2-hydroxyacetophenone **132** (9.75 g, 84%), m.p. 42°C (lit.,[111] 42-43°C); δ_H (60 MHz, $CDCl_3$) 2.60 (3H, s, $COCH_3$), 6.90-7.20 (2H, m, 3-H and 5-H), 7.60 (1H, d, J 8.0 Hz, 6-H) and 12.40 (1H, s, OH).

2-Hydroxy-4-methoxyacetophenone 134.[113] A stirred mixture of resacetophenone **133** (9.8 g, 65 mmol), Me_2SO_4 (8.32 g, 66 mmol) and anhydrous K_2CO_3 (10.0 g, 72 mmol) in dry acetone (100 ml) was boiled under reflux for 6 h. The cooled mixture was filtered with suction and the solid was washed with acetone to ensure complete extraction. The solvent was evaporated under reduced pressure and the excess Me_2SO_4 was destroyed with a 25% ammonia-ice mixture. The product was extracted with chloroform (5 x 30 ml) and the combined organic extracts were washed with water (3 x 30 ml) and then dried (anhyd. $MgSO_4$). The solvent was

evaporated and the residue was distilled to afford 2-hydroxy-4-methoxyacetophenone **134** (7.3 g, 67%), b.p. 293°C/760 mm Hg, m.p. 46-48°C (lit.,[113] m.p. 48°C); δ_H (60 MHz, $CDCl_3$) 2.55 (3H, s, $COCH_3$), 3.85 (3H, s, OCH_3), 6.35-6.60 (2H, m, 3-H and 5-H), 7.70 (1H, d, *J* 9.0 Hz, 6-H) and 12.90 (1H, s, OH).

1-(4-Fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one 136.[111] A mixture of 4-fluoro-2-hydroxyacetophenone **130** (5.0 g, 32.2 mmol) and benzaldehyde (3.43 g, 32.2 mmol) in ethanol (115 ml) was treated with a cold solution of potassium hydroxide (5.4 g, 97.2 mmol) in water (30 ml). The mixture was kept at 0-5°C with occasional shaking for 4 days and was the diluted with water (50 ml). The aqueous mixture was acidified with 20% hydrochloric acid solution and the resulting precipitate was filtered to afford 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** (5.6 g, 72%), m.p. 107-109°C (from ethanol) (lit.,[91,92] 110-111°C); δ_H (60 MHz, $CDCl_3$) 6.70-8.30 (10H, m, CH=CH and ArH) and 12.90 (1H, s, OH).

1-(4-Chloro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one 137.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 4-chloro-2-hydroxyacetophenone **131** (5.4 g, 31.7 mmol) and benzaldehyde (3.1 g, 31.7 mmol) in ethanol (100 ml) and a solution of potassium hydroxide (5.33 g, 95,1 mmol) in water (30 ml). Work-up afforded 1-(4-chloro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **137** (4.48 g, 55%), m.p. 125°C (from ethanol) (lit.,[111] 124-125°C); δ_H (60 MHz, $CDCl_3$) 6.50-8.00 (10H, m, CH=CH and ArH) and 12.70 (1H, s, OH).

1-(4-Bromo-2-hydroxyphenyl)-3-phenyl-2-propen-1-one 138.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 4-bromo-2-hydroxyacetophenone **132** (8.45 g, 39.5 mmol) and benzaldehyde (4.25 g, 39.5 mmol) in ethanol (125 ml) and a solution of potassium hydroxide (7.0 g, 125 mmol) in water (40 ml). Work-up afforded 1-(4-bromo-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **138** (10.6 g, 88%), m.p. 110-113°C (from ethanol) (lit.,[111] 115-116°C); δ_H (60

MHz, $CDCl_3$) 7.00-8.00 (10H, m, CH=CH and ArH) and 12.90 (1H, s, OH).

1-(2-Hydroxy-4-methoxyphenyl)-3-phenyl-2-propen-1-one 139.[113] A stirred solution of 2-hydroxy-4-methoxyacetophenone **134** (9.19 g, 55 mmol) in ethanol (100 ml) was treated with benzaldehyde (11.83 g, 121 mmol) and 50% aq. sodium hydroxide (10 ml). The mixture was stirred at room temperature for 24 h and was diluted with water (50 ml). The aqueous mixture was acidified with 10% hydrochloric acid solution and the product was extracted with ether (3 x 50 ml). The combined organic extracts were washed, sequentially, with 10% aq. $NaHCO_3$ (2 x 30 ml) and water (2 x 30 ml) and then dried (anhyd. $MgSO_4$). The solvent was evaporated under reduced pressure to afford 1-(2-hydroxy-4-methoxyphenyl)-3-phenyl-2-propen-1-one **139** (8.3 g, 60%), m.p. 102-104°C (from ethanol) (lit.,[113] 100-101°C); δ_H (60 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.40-6.70 (2H, m, CH=CH), 7.30-8.10 (8H, m, ArH) and 11.50 (1H, s, OH).

3-(4-Fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one 140.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 2-hydroxyacetophenone **135** (10.97 g, 80.6 mmol) and 4-fluorobenzaldehyde (10.0g, 80.6 mmol) in ethanol (180 ml) and a solution of potassium hydroxide (6.0 g, 107 mmol) in water (50 ml). Work-up afforded 3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **140** (13.0 g, 67%), m.p. 118°C (from ethanol) (lit.,[91,92] 118-119°C); δ_H (60 MHz, $CDCl_3$) 6.80-7.90 (10H, m, CH=CH and ArH) and 12.80 (1H, s, OH).

3-(4-Chlorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one 141.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 2-hydroxyacetophenone **135** (14.52 g, 106.7 mmol) and 4-chlorobenzaldehyde (15.0 g, 106.7 mmol) in ethanol (200 ml) and a solution of potassium hydroxide (8.96 g, 160 mmol) in water (50 ml). Work-up afforded 3-(4-chlorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **141** (15.75 g, 57%), m.p. 148-150°C (from ethanol) (lit.,[91,92] 150°C);

δ_H (60 MHz, $CDCl_3$) 6.90-8.00 (10H, m, CH=CH and ArH) and 12.70 (1H, s, OH).

3-(4-Bromophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one 142.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 2-hydroxyacetophenone **135** (3.7 g, 27 mmol) and 4-bromobenzaldehyde (5.0 g, 27 mmol) in ethanol (100 ml) and a solution of potassium hydroxide (4.5 g, 81 mmol) in water (20 ml). Work-up afforded 3-(4-bromophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **142** (4.5 g, 61%), m.p. 148-149°C (lit.,[91,92] 150°C); δ_H (60 MHz, $CDCl_3$) 6.90-7.90 (10H, m, CH=CH, ArH) and 12.70 (1H, s, OH).

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one 143.[111] The experimental procedure employed for the synthesis of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** was followed, using a mixture of 2-hydroxyacetophenone **135** (14.98 g, 0.11 mol) and 4-anisaldehyde (15.0 g, 0.11 mol) in ethanol (200 ml) and a solution of potassium hydroxide (12.8 g, 1.23 mol) in water (50 ml). Work-up afforded 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one **143** (17.0 g, 61%), m.p. 101-103°C (from ethanol) (lit.,[92] 105-106°C); δ_H (60 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.85-8.20 (10H, m, CH=CH and ArH) and 12.20 (1H, s, OH).

1-(2-Hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one 144.

Method 1. A stirred mixture of 2-nitrobenzaldehyde (7.55 g, 0.05 mol) and 2-hydroxyacetophenone **135** (6.85 g, 0.05 mol) in glacial acetic acid (100 ml) was treated with concentrated sulphuric acid (14.7 g, 0.15 mol) at room temperature. After stirring at room temperature for 48 h the mixture was diluted with water (100 ml). The resulting precipitate was filtered and washed thoroughly with water to afford 1-(2-hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one **144** (7.15 g, 56%), m.p. 208°C (from ethanol-ethyl acetate) (lit.,[115] 207-209°C); δ_H (60 MHz, $CDCl_3$) 6.97-8.30 (10H, m, CH=CH and ArH) and 11.55 (1H, s, OH).

Attempted preparation of 144. Treatment of equimolar amounts (65 mmol) of 2-nitrobenzaldehyde and 2-hydroxyacetophenone **135** with sodium hydroxide (3 pellets) in ethanol (60 ml) at room temperature afforded a complicated mixture of products and no chalcone was detected. However, from this mixture the flavanone **153** (20%) was isolated by flash chromatography using toluene as eluent.

7-Fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one 145.[111] A stirred mixture of 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **136** (2.3 g, 9.7 mmol) and orthophosphoric acid (d. 1.69, 11 ml) in ethanol (150 ml) was boiled under reflux for 4 days. The solvent was evaporated under reduced pressure and water (50 ml) was added to the residue. The product was extracted with chloroform (60 ml) and the organic phase was dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (elution with toluene) to afford the starting material and 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** (1.56 g, 68%), m.p. 60°C (from ethanol) (lit.,[91] b.p. 140°C/0.35 mm Hg); δ_H (400 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 2.9 and 16.9 Hz, 3-H), 3.07 (1H, dd, *J* 13.2 and 16.9 Hz, 3-H), 5.50 (1H, dd, *J* 2.9 and 13.1 Hz, 2-H) and 6.72-7.97 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.2 (C-3), 80.1 (C-2), 104.9 ($^2J_{CF}$ 25.2 Hz, C-6), 110.0 ($^2J_{CF}$ 22.1 Hz, C-8), 117.9 ($^2J_{CF}$ 2.0 Hz, C-4a), 126.1 (C-2' and C-6'), 128.8 (C-3' and C-5'), 128.9 (C-4'), 129.5 ($^3J_{CF}$ 11.1 Hz, C-5), 138.4 (C-1'), 163.1 ($^3J_{CF}$ 14.1 Hz, C-8a), 167.5 ($^1J_{CF}$ 256.6 Hz, C-7) and 190.3 (C-4).

7-Chloro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one 146.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 1-(4-chloro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **137** (4.0 g, 15.5. mmol) and orthophosphoric acid (d. 1.69, 20 ml) in ethanol (150 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 7-chloro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **146** (1.8 g, 45%), m.p. 52-54°C (from ethanol) (lit.,[111] 54-55°C); δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 3.0 and 16.9 Hz, 3-H), 3.07 (1H, dd, *J* 13.0 and 16.9 Hz, 3-H), 5.49 (1H, dd, *J* 3.0 and 13.0 Hz, 2-H) and 7.02-7.87 (8H, m, ArH); δ_C (100

MHz, $CDCl_3$) 44.3 (C-2), 79.9 (C-3), 118.3 (C-8), 119.5 (C-4a), 122.4 (C-6), 126.1 (C-2' and C-6'), 128.2 (C-5), 128.9 (C-3' and C-5'), 128.9 (C-4'), 138.2 (C-1'), 143.0 (C-7), 161.8 (C-8a) and 190.7 (C-4).

7-Bromo-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one 147.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 1-(4-bromo-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **138** (10.0 g, 33 mmol) and orthophosphoric acid (d. 1.69, 70 ml) in ethanol (250 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 7-bromo-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **147** (7.5 g, 75%), m.p. 78-80°C (from ethanol) (lit.,[111] 79-80°C), δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 3.1 and 16.9 Hz, 3-H), 3.10 (1H, dd, *J* 13.1 and 16.9 Hz, 3-H), 5.50 (1H, dd, *J* 3.1 and 12.9 Hz, 2-H) and 7.16-7.78 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.4 (C-3), 80.0 (C-2), 119.9 (C-4a), 121.4 (C-8), 125.3 (C-6), 126.1 (C-2' and C-6'), 128.3 (C-5), 128.9 (C-3' and C-5'), 128.9 (C-4'), 130.6 (C-7), 138.2 (C-1'), 161.7 (C-8a) and 191.0 (C-4).

2,3-Dihydro-7-methoxy-2-phenyl-4*H*-1-benzopyran-4-one 148.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 1-(2-hydroxy-4-methoxyphenyl)-3-phenyl-2-propen-1-one **139** (1.40 g, 5.7 mmol) and orthophosphoric acid (d. 1.69, 10 ml) in ethanol (100 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 2,3-dihydro-7-methoxy-2-phenyl-4*H*-1-benzopyran-4-one **148** (0.66 g, 46%), m.p. 80-82°C (from ethanol) (lit.,[92] 79-81°C), δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 3.0 and 16.9 Hz, 3-H), 3.03 (1H, dd, *J* 13.2 and 16.9 Hz, 3-H), 3.83 (3H, s, OCH_3), 5.47 (1H, dd, *J* 3.0 and 13.2 Hz, 2-H) and 6.50-7.88 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.3 (C-3), 55.6 (OCH_3), 79.9 (C-2), 100.9 (C-8), 110.2 (C-6), 114.8 (C-4a), 126.1 (C-2' and C-6'), 128.7 (C-4'), 128.7 (C-5), 128.8 (C-3' and C-5'), 138.8 (C-1'), 163.5 (C-8a), 166.2 (C-7) and 190.5 (C-4).

2-(4-Fluorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one 149.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **140** (2.0 g, 8.3 mmol) and orthophosphoric acid (d. 1.69, 13.3 ml) in ethanol (150 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 2-(4-fluorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **149** (1.26 g, 63%), m.p. 76°C (from ethanol) (lit.,[91] 79°C), δ_H (400 MHz, $CDCl_3$) 2.87 (1H, dd, *J* 2.8 and 16.8 Hz, 3-H), 3.05 (1H, dd, *J* 13.2 and 16.8 Hz, 3-H), 5.46 (1H, dd, *J* 2.8 and 13.2 Hz, 2-H) and 7.03-7.94 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.6 (C-3), 78.9 (C-2), 115.7 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 118.0 (C-8), 120.9 (C-4a), 127.1 (C-5), 128.0 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 134.6 ($^4J_{CF}$ 3.0 Hz, C-1'), 136.2 (C-7), 161.4 (C-8a), 162.8 ($^1J_{CF}$ 247.5 Hz, C-4') and 191.6 (C-4).

2-(4-Chlorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one 150.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 3-(4-chlorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **141** (15.0 g, 58 mmol) and orthophosphoric acid (d. 1.69, 74 ml) in ethanol (350 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 2-(4-chlorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **150** (6.75 g, 45%), m.p. 88-90°C (from ethanol) (lit.,[91] 87°C), δ_H (400 MHz, $CDCl_3$) 2.87 (1H, dd, *J* 3.0 and 16.8 Hz, 3-H), 3.02 (1H, dd, *J* 13.1 and 16.8 Hz, 3-H), 5.46 (1H, dd, *J* 3.0 and 13.1 Hz, 2-H) and 7.03-7.93 (m, ArH); δ_C (100 MHz, $CDCl_3$) 44.2 (C-3), 78.7 (C-2), 118.0 (C-8), 120.8 (C-4a), 121.7 (C-6), 127.0 (C-5), 127.4 (C-2' and C-6'), 128.9 (C-3' and C-5'), 134.4 (C-4'), 136.1 (C-7), 137.2 (C-1'), 161.2 (C-8a) and 191.2 (C-4).

2-(4-Bromophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one 151.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 3-(4-bromophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one **142** (3.3 g, 10.9 mmol) and orthophosphoric acid (d. 1.69, 10 ml) in ethanol (150 ml). Work-up and flash

chromatography (elution with toluene) afforded the starting material and 2-(4-bromophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **151** (2.3 g, 70%), m.p. 116-118°C (from ethanol) (lit.,[91] 117°C), δ_H (400 MHz, $CDCl_3$) 2.88 (1H, dd, *J* 3.0 and 16.8 Hz, 3-H), 3.03 (1H, dd, *J* 13.0 and 16.8 Hz, 3-H), 5.45 (1H, dd, *J* 3.0 and 13.0 Hz, 3-H) and 7.01-7.94 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.4 (C-3), 78.7 (C-2), 118.0 (C-8), 120.8 (C-4a), 121.7 (C-6), 122.6 (C-4'), 127.0 (C-5), 127.7 (C-2' and C-6'), 131.9 (C-3' and C-5'), 136.2 (C-7), 137.8 (C-1'), 161.19 (C-8a) and 191.3 (C-4).

2,3-Dihydro-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one 152.[111] The experimental procedure employed for the synthesis of 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** was followed using a mixture of 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one **143** (8.5 g, 33.5 mmol) and orthophosphoric acid (d. 1.69, 45 ml) in ethanol (150 ml). Work-up and flash chromatography (elution with toluene) afforded the starting material and 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one **152** (4.95 g, 58%), m.p. 80-82°C (from ethanol); (lit.,[92] 83°C); δ_H (400 MHz, $CDCl_3$) 2.86 (1H, dd, *J* 2.8 and 16.9 Hz, 3-H), 3.10 (1H, dd, *J* 13.3 and 16.9 Hz, 3-H), 3.83 (3H, s, OCH_3), 5.43 (1H, dd, *J* 2.8 and 13.3 Hz, 2-H) and 6.94-7.94 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.4 (C-3), 55.3 (OCH_3), 79.3 (C-2), 114.1 (C-2' and C-6'), 118.1 (C-8), 120.9 (C-4a), 121.4 (C-6), 127.0 (C-5), 127.7 (C-3' and C-5'), 130.7 (C-1'), 136.0 (C-7), 159.9 (C-4'), 161.6 (C-8a) and 192.1 (C-4).

2,3-Dihydro-2-(4-nitrophenyl)-4*H*-1-benzopyran-4-one 153. A stirred mixture of 1-(2-hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one **144** (6.7g, 25 mmol) and orthophosphoric acid (d. 1.69, 35 ml) in glacial acetic acid (150 ml) was boiled under reflux for 2 days. The cooled mixture was diluted with water (150 ml) and the resulting precipitate was filtered. The product was purified by flash chromatography (elution with toluene) to afford the starting material and 2,3-dihydro-2-(4-nitrophenyl)-4*H*-1-benzopyran-4-one **153** (3.5 g, 52%), m.p. 160-162°C (from ethanol) (lit.,[115] 158.5-159.5°C); δ_H (400 MHz, $CDCl_3$) 2.94 (1H, dd, *J* 3.8 and 16.8 Hz, 3-H), 3.02 (1H, dd, *J* 12.3 and 16.8 Hz, 3-H), 5.60 (1H, dd, *J* 3.8 and 12.3 Hz, 2-H) and 7.06-8.30

(8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.6 (C-3), 78.3 (C-2), 118.0 (C-8), 120.9 (C-4a), 122.2 (C-6), 124.1 (C-3' and C-5'), 126.8 (C-2' and C-6'), 127.2 (C-5), 136.5 (C-7), 145.8 (C-1'), 148.0 (C-4'), 160.9 (C-8a) and 190.6 (C-4).

2-Nitrobenzoyl chloride 154.[136] A stirred mixture of 2-nitrobenzoic acid (33.4 g, 0.2 mol) and thionyl chloride (79.0 g, 0.67 mol) was boiled under reflux for 3 h. Excess thionyl chloride was removed by evaporation under reduced pressure and the crude 2-nitrobenzoyl chloride **154** was used in the next step without purification.

2-Nitroacetophenone 156.[138,139] Magnesium turnings (5.4 g, 0.22 mol), absolute ethanol (3.91 g, 0.05 mol) and dry carbon tetrachloride (0.5 ml) were placed in a three-necked flask equipped with a stirrer, dropping funnel and a condenser. The reaction was allowed to commence and after 10 minutes dry ether (150 ml) was added slowly with stirring. A solution of freshly distilled diethyl malonate (35.2 g, 0.22 mol) in absolute ethanol (15.64 g, 0.34 mol) and dry ether (25 ml) was added dropwise to the reaction mixture. The mixture was then boiled under reflux for 3 h, cooled and a solution of 2-nitrobenzoyl chloride **154** (37.0g, 0.2 mol) in dry ether (50 ml) was added dropwise. The resulting mixture was refluxed for an additional 1.5 h and the cooled mixture was treated with 25% H_2SO_4 (250 ml). Stirring was continued at room temperature for 30 minutes and the organic phase was separated. The aqueous phase was extracted with ether (3 x 50 ml) and the combined organic phases were washed with water (3 x 30 ml) and the solvent was removed by evaporation under reduced pressure.

The residue was treated with glacial acetic acid (60 ml), conc. H_2SO_4 (7.6 ml) and water (40 ml) and the resulting mixture was boiled under reflux for 4 h. The cooled mixture was made alkalinic with 20% aq. sodium hydroxide solution and the product was extracted with ether (5 x 60 ml). The combined organic extracts were washed with water (3 x 30 ml), dried (anhyd. $MgSO_4$) and the solvent was removed by evaporation under reduced pressure. The residue was distilled *in vacuo* to afford 3-nitroacetophenone **156** (25.0 g, 76%), b.p. 120-122°C/0.5 mm

Hg (lit.,[138,139] 158-159°C/16 mm Hg); δ_H (60 MHz, $CDCl_3$) 2.50 (3H, s, $COCH_3$) and 7.45-8.30 (4H, m, ArH).

2-Aminoacetophenone 157.[137] A stirred mixture of 2-nitroacetophenone **156** (45.0 g, 0.27 mol) and tin granules (54.0 g, 0.45 mol) in conc. HCl (245 ml) was allowed to warm up steadily to 80°C without heating, and with occasional cooling in an ice-bath. The mixture was then refluxed at 70-80°C for 1 h, cooled and made alkalinic with 20% aq. sodium hydroxide solution. The product was extracted with ether (6 x 50 ml) and the combined organic extracts were washed with water (3 x 30 ml) and then dried (anhyd. $MgSO_4$). Solvent evaporation and distillation *in vacuo* afforded 2-aminoacetophenone **157** (28.8 h, 79%), b.p. 85-87°C/0.5 mm Hg (lit.,[137] 130-131°C/14 mm Hg); δ_H (60 MHz, $CDCl_3$) 3.71 (3H, s, $COCH_3$), 6.40 (2H, br s, NH_2) and 6.50-7.90 (4H, m, ArH).

1-(2-Aminophenyl)-3-phenyl-2-propen-1-one 158.[135] A mixture of 2-aminoacetophenone **157** (4.0 g, 29.6 mmol), benzaldehyde (3.14 g, 29.6 mmol) and sodium hydroxide (3 pellets) in ethanol (20 ml) was stirred at room temperature for 16 h. The precipitate was filtered to afford 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** (3.9 g, 59%), m.p. 70-72°C (from ethanol) (lit.,[135] 71-72°C); δ_H (400 MHz, $CDCl_3$) 6.34 (2H, s, NH_2), 6.65-6.73 (2H, m, CH=CH) and 7.25-7.95 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 115.8 (C-3'), 117.2 (C-5'), 119.0 (C-1'), 123.1 (C-2), 128.2 (C-2" and C-6"), 128.8 (C-3" and C-5"), 130.0 (C-4"), 131.0 (C-6'), 134.2 (C-4'), 135.2 (C-1"), 142.8 (C-3), 151.0 (C-2') and 191.6 (C-1); ν_{max} (KBr) 3450-3300 (NH_2) and 1645 (C=O) cm^{-1}.

1-(2-Aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one 159.[135] The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** was followed, using 2-aminoacetophenone **157** (1.4 g, 10.5 mmol), 4-fluorobenzaldehyde (1.3 g, 10.5 mmol) and sodium hydroxide (3 pellets) in ethanol (20 ml). Work-up afforded *1-(2-aminophenyl)-3-(4-fluorophenyl-2-propen-1-one* **159** (1.5 g, 59%), m.p. 119-121°C (from ethanol) (found: M^+,

241.0887. $C_{15}H_{12}NOF$ requires *M*, 241.0903); δ_H (400 MHz, $CDCl_3$) 6.20 (2H, s, NH_2) and 6.69-7.83 (10H, m, CH=CH and ArH); δ_C (100 MHz, $CDCl_3$) 115.9 (C-2), 116.0 (d, $^2J_{CF}$ 22.1 Hz, C-3" and C-5"), 117.3 (C-6'), 119.0 (C-2'), 122.9 (d, $^5J_{CF}$ 2.0 Hz, C-3), 130.0 (d, $^3J_{CF}$ 8.1 Hz, C-2" and C-6"), 130.9 (C-4') 131.5 (d, $^4J_{CF}$ 3.0 Hz, C-1"), 134.3 (C-3'), 141.6 (C-5'), 151.0 (C-1'), 163.8 (d, $^1J_{CF}$ 251.54 Hz, C-4") and 191.4 (C-1), ν_{max} (KBr) 3500-3300 (NH_2) and 1645 (C=O) cm^{-1}

1-(2-Aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one 160.[135] The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** was followed, using 2-aminoacetophenone **157** (5.0 g, 37.4 mmol), 4-chlorobenzaldehyde (5.21 g, 37.4 mmol) and sodium hydroxide (3 pellets) in ethanol (25 ml). Work-up afforded *1-(2-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one* **160** (5.0 g, 52%), m.p. 82-84°C (from ethanol) (found: M^+, 257.0614. $C_{15}H_{12}NOCl$ requires *M*, 257.0607); δ_H (400 MHz, $CDCl_3$) 6.34 (2H, s, NH_2), 6.61-8.03 (10H, m, CH=CH and ArH); δ_C (100 MHz, $CDCl_3$) 115.9 (C-3'), 117.3 (C-5'), 118.9 (C-1'), 123.6 (C-3), 129.1 (C-3" and C-5"), 129,4 (C-2" and C-6"), 130.9 (C-6'), 133.8 (C-4"), 134.4 (C-4'), 135.9 (C-1"), 141.4 C-3), 151.1 (C-2') and 191.3 (C-1). ν_{max} (KBr) 3480-3300 (NH_2) and 1640 (C=O) cm^{-1}.

1-(2-Aminophenyl)-3-(4-bromophenyl)-2-propen-1-one 161.[135] The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** was followed, using 2-aminoacetophenone **157** (3.0 g, 22.2 mmol), 4-bromobenzaldehyde (4.11 g, 22.2 mmol) and sodium hydroxide (3 pellets) in ethanol (20 ml). Work-up afforded 1-(2-amino-phenyl)-3-(4-bromophenyl)-2-propen-1-one **161** (5.56 g, 83%), m.p. 94°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 6.33 (2H, s, NH_2), 6.70 (2H, m, CH=CH) and 7.20-8.00 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 115.8 (C-3'), 117.3 (C-5'), 119.1 (C-1'), 123.2 (C-2), 128.2 (C-2" and C-6"), 128.9 (C-3" and C-5"), 130.1 (C-4"), 131.0 (C-6'), 134.3 (C-4'), 135.3 (C-1"), 142.9 (C-3), 151.0 (C-2') and 191.7 (C-1'); ν_{max} (KBr) 3460-3310 (NH_2) and 1650 (C=O) cm^{-1}.

1-(2-Aminophenyl)-3-(4-methoxyphenyl)-2-propen-1-one 162.[135] The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** was followed, using 2-aminoacetophenone **157** (5.0 g, 37 mmol), 4-anisaldehyde (4.21 g, 37 mmol) and sodium hydroxide (3 pellets) in ethanol (25 ml). Work-up afforded 1-(2-aminophenyl)-3-(4-nitrophenyl)-2-propen-1-one **163** (6.2 g, 83%), m.p. 140-142°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 6.46 (2H, s, NH_2), 6.70 (2H, m, CH=CH) and 7.26-8.25 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 115.9 (C-3'),117.4 (C-5'), 118.5 (C-1'), 124.1 (C-3" and C-5"), 127.1 (C-2), 128.7 (C-2" and C-6"), 130.9 (C-6'), 134.8 (C-4'), 139.6 (C-3), 141.5 (C-1"), 148.3 (C-4"), 151.3 (C-2') and 190.6 (C-1); ν_{max} (KBr) 3450-3335 (NH_2) and 1645 (C=O) cm^{-1}.

1-(2-Aminophenyl)-3-(4-nitrophenyl)-2-propen-1-one 163.[136] The experimental procedure employed for the synthesis of 1-(2-aminophenyl-3-phenyl-2-propen-1-one **158** was followed, using 2-aminoacetophenone **157** (3.76 g, 27.9 mmol), 4-nitrobenzaldehyde (4.21 g, 27.9 mmol) and sodium hydroxide (3 pellets) in ethanol (25 ml). Work-up afforded 1-(2-amino-phenyl)-3-(4-nitrophenyl)-2-propen-1-one **163** (6.2 g, 83%), m.p. 140-142°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 6.46 (2H, s, NH_2), 6.70 (2H, m, CH=CH) and 7.26-8.25 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 115.9 (C-3'), 117.4 (C-5'), 118.5 (C-1'), 124.1 (C-3" and C-5"), 127.1 (C-2), 128,7 (C-2" and C-6"), 130.9 (C-6'), 134.8 (C-4'), 139.6 (C-3), 141.5 (C-1"), 148.3 (C-4"), 151.3 (C-2') and 190.6 (C-1); ν_{max} (KBr) 3460-3350 (NH_2) and 1650 (C=O) cm^{-1}.

2-Phenyl-1,2,3,4,-tetrahydro-4-quinolone 164.[135] A stirred mixture of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one **158** (2.0 g, 9 mmol) and orthophosphoric acid (d. 1.69, 10 ml) in glacial acetic acid (20 ml) was boiled under reflux for 2.5 hours. The cooled mixture was poured into iced water and the precipitate was filtered, and then purified by flash chromatography (elution with toluene) to afford 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** (1.0 g, 50%), m.p. 148°C (from ethanol) (lit.,[135] 149-150°C); δ_H (400 MHz, $CDCl_3$) 2.76 (1H, dd, *J* 3.8 and 16.2 Hz, 3-H), 2.89 (1H, dd, *J* 13.6 and 16.2 Hz, 3-H), 4.53 (1H, s, NH), 4.74 (1H, dd, *J* 3.8 and 13.6 Hz, 2-H) and 6.64-7.88 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.6 (C-3), 58.5 (C-2), 115.9

(C-8), 118.4 (C-6), 119.1 (C-4a), 126.6 (C-2' and C-6'), 127.6 (C-5), 128.5 (C-4'), 129.0 (C-3' and C-5'), 135.6 (C-7), 141.0 (C-1'), 151.5 (C-8a) and 193.2 (C-4); ν_{max} (KBr) 3345 (NH) and 1660 (C=O) cm^{-1}; *m/z* 223 (M^+, 54.1%)and 146 (93.4%).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone 165.[136] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** was followed using 1-(2-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one **159** (1.0 g, 4.1. mmol) and ortho-phosphoric acid (d. 1.69, 4 ml) in glacial acetic acid (10 ml). Work-up and flash chromatography (elution with toluene) afforded *2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone* **165** (0.9 g, 90%), m.p. 116-118°C (from ethanol); (Found: M^+, 241.0903. $C_{15}H_{12}NOF$ requires *M*, 241.0878); δ_H (400 MHz, $CDCl_3$) 2.70 (1H, dd, *J* 4.0 and 16.2 Hz, 3-H), 2.80 (1H, dd, *J* 13.4 and 16.2 Hz, 3-H), 4.50 (1H, s, NH), 4.70 (1H, dd, *J* 4.0 and 13.4 Hz, 2-H) and 6.70-8.20 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.4 (C-3), 57.8 (C-2), 115.8 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 115.9 (C-8), 118.5 (C-6), 119.0 (C-4a), 127.5 (C-5), 128.3 ($^3J_{CF}$ 8.1 Hz, C-3' and C-5'), 135.5 (C-7), 151.5 (C-8a), 136.8 ($^4J_{CF}$ 3.0 Hz, C-1'), 151.5 (C-8a), 162.6 ($^1J_{CF}$ 246.5 Hz, C-4') and 193.1 (C-4); ν_{max} (KBr) 3320 (NH) and 1660 (C=O) cm^{-1}; *m/z* 241 (M^+, 57.3%) and 92 (100%).

2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone 166.[136] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** was followed using 1-(2-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one **160** (4.0 g, 15.5 mmol) and ortho-phosphoric acid (d. 1.69, 20 ml) in glacial acetic acid (50 ml). Work-up and flash chromatography (elution with toluene) afforded 2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone **166** (2.76 g, 69%), m.p. 146°C (from ethanol) (Found: M^+, 257.068. $C_{15}H_{12}NO^{35}Cl$ requires *M*, 257.0627); δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dddd, *J* 4.2 and 16.2 Hz, 3-H), 2.82 (1H, dd, *J* 13.1 and 16.2 Hz, 3-H), 4.50 (1H, s, NH), 4.72 (1H, dd, *J* 4.2 and 13.1 Hz, 2-H) and 6.64-7.85 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.4 (C-3), 57.9 (C-2), 115.9 (C-8), 118.8 (C-6), 119.1 (C-4a), 127.6 (C-5), 128.0 (C-2' and C-6'), 129.2 (C-3' and C-5'), 134.2 (C-4'),

135.5 (C-7), 139.5 (C-1'), 151.3 (C-8a) and 192.8 (C-4); ν_{max} (KBr) 3320 (NH) and 1650 (C=O) cm^{-1}; *m/z* 257 (M^+, 38.2%) and 146 (100%).

2-(4-Bromophenyl)-1,2,3,4-tetrahydro-4-quinolone 167.[135] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** was followed using 1-(2-aminophenyl)-3-(4-bromophenyl)-2-propen-1-one **161** (3.0 g, 9.9 mmol) and ortho-phosphoric acid (d. 1.69, 12 ml) in glacial acetic acid (35 ml). Work-up and flash chromatography (elution with toluene) afforded 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4-quinolone **167** (2.42 g, 81%), m.p. 168-170°C (from ethanol), (lit.,[140] 171°C); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 4.3 and 16.2 Hz, 3-H), 2.80 (1H, dd, *J* 13.0 and 16.2 Hz, 3-H), 4.35 (1H, s, NH), 4.69 (1H, dd, *J* 4.3 and 13.0 Hz, 2-H) and 6.70-7.86 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.3 (C-3), 57.9 (C-2), 115.0 (C-8), 118.7 (C-6), 119.0 (C-4a), 122.2 (C-4'), 127.6 (C-5), 128.3 (C-2' and C-6'), 132.1 (C-3' and C-5'), 135.3 (C-7), 140.1 (C-1'), 151.3 (C-8a) and 192.8 (C-4); ν_{max} (KBr) 3310 (NH) and 1645 (C=O) cm^{-1}; *m/z* 301 (M^+, 19.9%) and 146 (100%).

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-4-quinolone 168.[135] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** was followed using 1-(2-aminophenyl)-3-(4-methoxyphenyl)-2-propen-1-one **162** (5.5 g, 21.6 mmol) and ortho-phosphoric acid (d. 1.69, 25 ml) in glacial acetic acid (45 ml). Work-up and flash chromatography (elution with toluene) afforded 2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-quinolone **168** (3.4 g, 62%), m.p. 112-114°C (from ethanol) (Found: M^+, 253.1096. $C_{16}H_{15}NO_2$ calculated *M*, 253.1103); δ_H (400 MHz, $CDCl_3$) 2.71 (1H, dd, *J* 3.6 and 16.1 Hz, 3-H), 2.84 (1H, dd, *J* 14.0 and 16.1 Hz, 3-H), 3.81 (3H, s, OCH_3), 4.52 (1H, s, NH), 4.65 (1H, dd, *J* 3.6 and 14.0 Hz) and 6.61-7.86 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.5 (C-3), 55.3 (OCH_3), 57.9 (C-2), 114.3 (C-3' and C-5'), 115.9 (C-8), 118.3 (C-6), 119.0 (C-4a), 127.6 (C-5), 127.8 (C-2' and C-6'), 133.1 (C-4'), 135.5 (C-7), 151.6 (C-1'), 159.7 (C-8a) and 193.5 (C-4); ν_{max} (KBr) 3300 (NH) and 1645 (C=O) cm^{-1}; 253 (M^+, 49.5%) and 146 (100%).

2-(4-Nitrophenyl)-1,2,3,4-tetrahydro-4-quinolone 169.[135] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** was followed using 1-(2-aminophenyl)-3-(4-nitrophenyl)-2-propen-1-one **163** (2.6 g, 9.7 mmol) and orthophosphoric acid (d. 1.69, 10 ml) in glacial acetic acid (20 ml). Work-up and flash chromatography (elution with toluene) afforded 2-(4-nitrophenyl)-1,2,3,4-tetrahydro-4-quinolone **169** (1.16 g, 45%), m.p. 192-194°C (from ethanol), (lit.,[140] 194°C); δ_H (400 MHz, $CDCl_3$) 2.83 (2H, m, 3-H), 4.53 (1H, s, NH), 4.90 (1H, td, *J* 8.2 and 10.1 Hz, 2-H), and 6.71-8.30 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.1 (C-3), 57.9 (C-2), 116.1 (C-8), 119.2 (C-6), 119.3 (C-4a), 124.3 (C-3' and C-5'), 127.5 (C-2' and C-6'), 127.7 (C-5), 135.7 (C-7), 148.0 (C-1'), 148.3 (C-4'), 150.9 (C-8a) and 191.8 (C-4); ν_{max} (KBr) 3370 (NH) and 1675 (C=O) cm^{-1}; 268 (M^+, 31.7%) and 146 (100%).

ß-Phenylmercaptodihydrocinnamic acid 175.[144] A stirred mixture of cinnamic acid **170** (10.0 g, 67.6 mmol) and thiophenol (8.0 g, 72.7 mmol) in HBr-acetic acid (47%, 10 g) was boiled under reflux for 9 hours. The cooled reaction mixture was treated with water (300 ml) and was then steam-distilled to remove the unchanged thiophenol. The hot aqueous layer was decanted and the oily residue was washed twice with hot water. The residue was taken up in chloroform (50 ml) and dried (anhyd. $MgSO_4$). The solvent was evaporated to afford ß-phenylmercaptodihydrocinnamic acid **175** (10.1 g, 76%), m.p. 84-86°C (from hexane) (lit.,[144] 85-86°C); δ_H (400 MHz, $CDCl_3$) 2.96 (1H, dd, *J* 8.1 and 13.9 Hz, 2-H), 3.01 (1H, dd, *J* 7.6 and 13.9 Hz, 2-H), 4.63 (1H, t, *J* 7.7 Hz, 3-H), 7.20-7.60 (10H, m, ArH) and 11.39 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 40.0 (C-2), 48.7 (C-3), 127.6 (C-2' and C-6'), 127.6 (C-4'), 127.9 (C-4"), 128.4 (C-2" and C-6"), 128.5 (C-3' and C-5'), 133.4 (C-1'), 133.5 (C-3" and C-5"), 140.2 (C-1") and 177.0 (C-1); ν_{max} (KBr) 3000 (OH) and 1705 (C=O) cm^{-1}; *m/z* 258 (M^+, 42.8%) and 107 (100%).

ß-Phenylmercaptodihydro-4'-fluorocinnamic acid 176.[144] The experimental procedure employed for the synthesis of ß-phenylmercaptodihydrocinnamic acid **175** was followed using 4-fluorocinnamic acid (5.0 g, 30.0 mmol) and thiophenol (3.52 g, 32.0 mmol) in HBr-acetic acid (47%, 20 g). Work-up afforded *ß-phenylmercaptodihydro-4'-fluorocinnamic acid* **176** (7.4 g, 88.5%),

m.p. 94-96°C (from hexane) (Found: M^+, 276.0641. $C_{15}H_{13}SO_2F$ requires *M*, 276.0324); δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 8.5 and 16.2 Hz, 2-H), 2.98 (1H, dd, *J* 6.8 and 16.2 Hz, 2-H), 4.58 (1H, dd, *J* 6.9 and 8.5 Hz, 3-H), 6.92-7.30 (9H, m, ArH) and 11.0 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 40.6 (C-2), 48.0 (C-3), 115.4 ($^2J_{CF}$ 21.1 Hz, C-3' and C-5'), 128.1 (C-4"), 129.0 (C-2" and C-6"), 129.2 ($^3J_{CF}$ 8.0 Hz, C-2' and C-6'), 133.0 (C-1"), 133.7 (C-3" and C-5"), 135.9 ($^4J_{CF}$ 3.0 Hz, (C-1'), 162.1 ($^4J_{CF}$ 246.5 Hz, C-4') and 176.6 (C-1); ν_{max} (KBr) 3000 (OH) and 1700 (C=O) cm^{-1}; *m/z* 276 (M^+, 17.1%) and 125 (100%).

ß-Phenylmercaptodihydro-4'-chlorocinnamic acid 177.[144] The experimental procedure employed for the synthesis of *ß-phenylmercaptodihydrocinnamic acid* **175** was followed using 4-chlorocinnamic acid **172** (4.0 g, 21.9 mmol) and thiophenol (4.0 g, 36.4 mmol) and HBr-acetic acid (47%, 10 g). Work-up afforded *ß-phenylmercaptodihydro-4'-chlorocinnamic acid* **177** (5.55 g, 87%), mp. 102-104°C (from hexane) (Found: M^+, 292.0324. $C_{15}H_{13}SO_2Cl$ requires *M*, 292.0302); δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 8.5 and 16.3 Hz, 2-H), 2.95 (1H, dd, *J* 6.9 and 16.3 Hz, 2-H), 4.55 (1H, dd, *J* 6.9 and 8.5 Hz, 3-H), 7.10-7.38 (9H, m, ArH) and 10.9 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 40.4 (C-2), 48.1 (C-3), 128.2 (C-4"), 128.7 (C-2' and C-6'), 129.0 (C-3' and C-5'), 129.0 (C-2" and C-6"), 132.8 (C-1'), 133.4 (C-4'), 133.7 (C-3" and C-5"), 138.8 (C-1") and 176.3 (C-1); ν_{max} (KBr) 3000 (OH) and 1700 (C=O) cm^{-1}; *m/z* 292 (M^+, 17.9%) and 141 (100%).

ß-Phenylmercaptodihydro-4'-bromocinnamic acid 178.[144] The experimental procedure employed for the synthesis of ß-phenylmercaptodihydrocinnamic acid **175** was followed using 4-bromocinnamic acid **173** (3.07 g, 13.2 mmol) and thiophenol (2.47 g, 22.5 mmol) in HBr-acetic acid (47%, 20 g). Work-up afforded *ß-phenylmercaptodihydro-4'-bromocinnamic acid* **178** (4.0 g, 90%), m.p. 108°C (from hexane) (Found M^+, 336.9820. $C_{15}H_{13}SO_2Br$ requires *M*, 336.981); δ_H (400 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 8.5 and 16.3 Hz, 2-H), 2.97 (1H, dd, *J* 6.9 and 16.3 Hz, 2-H), 4.53 (1H, dd, *J* 6.9 and 8.4 Hz, 3-H), 7.04-7.41 (9H, m, ArH) and 10.7 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 40.3 (C-2), 48.1 (C-3), 121.5 (C-4'), 128.2 (C-4"), 129.0 (C-2' and C-6'),

129.3 (C-2" and C-6"), 131.6 (C-3' and C-5'), 132.8 (C-1'), 133.7 (C-3" and C-5"), 139.3 (C-1") and 176.3 (C-1); ν_{max} (KBr) 3000 (OH) and 1705 (C=O) cm^{-1}; *m/z* 336 ($M^{\cdot}$, 11.8%) and 185 (100%).

ß-Phenylmercaptodihydro-4'-methoxycinnamic acid 179.[144] The experimental procedure employed for the synthesis of ß-phenylmercaptodihydroxycinnamic acid **175** was followed using 4-methoxycinnamic acid **174** (10.0 g, 56.2 mmol) and thiophenol (6.65 g, 60.4 mmol) in HBr-acetic acid (47%, 20 g). Work-up afforded *ß-phenylmercaptodihydro-4'-methoxycinnamic acid* **179** (13.2 g, 88%), m.p. 88-90°C (from hexane); (Found: M^+, 288.0819. $C_{16}H_{16}SO_3$ requires *M*, 288.0804); δ_H (400 MHz, $CDCl_3$) 2.93 (1H, dd, *J* 8.3 and 15.0 Hz, 2-H), 2.98 (1H, dd, *J* 6.9 and 15.0 Hz, 2-H), 3.76 (3H, s, OCH_3), 4.60 (1H, dd, *J* 6.9 and 8.3 Hz, 3-H), 6.79-7.34 (9H, m, ArH) and 10.45 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 40.8 (C-2), 48.0 (C-3), 55.2 (OCH_3), 113.9 (C-3' and C-5'), 127.8 (C-4"), 128.7 (C-2' and C-6'), 128.8 (C-2" and C-6"), 132.1 (C-1'), 133.3 (C-3" and C-5"), 133.6 (C-1"), 158.9 (C-4') and 176.9 (C-1); ν_{max} (KBr) 3000 (OH) and 1700 (C=O) cm^{-1}; *m/z* 288 (M^+, 6.1%) and 137 (100%).

2,3-Dihydro-2-phenyl-4*H*-benzothiopyran-4-one 185.

Method 1.[144] A stirred solution of ß-phenylmercaptodihydrocinnamic acid **175** (13.0 g, 50.4 mmol) in $POCl_3$ (60.0 g, 390.1 mmol) was boiled under reflux for 20 minutes. The cooled reaction mixture was added slowly to an ice-cold water bath (150 ml) and the oily layer was separated. The oily layer was taken up in chloroform (60 ml) and was washed, sequentially, with 10% aq. NaOH (2 x 30 ml) and water (2 x 30 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* and the product was purified by flash chromatography (elution with benzene) to afford 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** (6.53 g, 54%), m.p. 54-56°C (from CS_2-hexane) (lit.,[144] 55-56°C) (Found: M^+, 240.061. $C_{15}H_{12}SO$ calculated *M*, 240.0587); δ_H (400 MHz, $CDCl_3$) 3.20 (1H, dd, *J* 3.1 and 16.4 Hz, 3-H), 3.31 (1H, dd, *J* 13.0 and 16.4 Hz, 3-H), 4.72 (1H, dd, *J* 3.1 and 13.0 Hz, 2-H), 7.18-7.43 (8H, m, ArH) and 8.15 (1H, dd, *J* 1.0 and 8.0 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 45.5 (C-3), 47.7 (C-2), 125.2

(C-8), 127.2 (C-6), 127.4 (C-2' and C-6'), 128.4 (C-4'), 129.0 (C-3' and C-5'), 129.2 (C-5), 130.4 (C-4a), 133.6 (C-7), 138.4 (C-1'), 142.1 (C-8a) and 194.3 (C-4); ν_{max} (KBr) 1673 (C=O) cm^{-1}; *m/z* 240 (M^+, 31.6%) and 136 (100%).

Method 2. A stirred mixture of ß-phenylmercaptodihydrocinnamic acid **170** (10.0 g, 38.8 mmol) and $SOCl_2$ (5.49 g, 46.5 mmol) in chloroform (30 ml) was refluxed for 30 minutes. The mixture was evaporated *in vacuo* and the crude ß-phenylmercaptodihydrocinnamoyl chloride **180** was used in the next step without purification. ß-phenylmercaptodihydrocinnamoyl chloride was taken up in CS_2 (10 ml) and was added dropwise to a stirred suspension of $AlCl_3$ (5.21 g, 46.6 mmol) in CS_2 (25 ml) at 0-5°C. The mixture was then refluxed for 30 minutes, cooled and poured slowly with shaking onto a mixture of crushed ice (40 g) and HCl (20 ml). The product was extracted with chloroform (3 x 30 ml) and the combined organic extracts were washed, sequentially, with 10% aq. NaOH (2 x 20 ml) and water (2 x 20 ml), and then dried (anhyd. $MgSO_4$). The solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography (elution with benzene) to afford 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** (4.46 g, 48%), m.p. 54-56°C (from CS_2-hexane).

2-(4-Fluorophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one 186. The experimental procedure (Method 2) employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** was followed using ß-phenylmercaptodihydro-4'-fluorocinnamic acid (5.0 g, 18.1 mmol) and $SOCl_2$ (3.21 g, 27.2 mmol) in chloroform (30 ml). Solvent evaporation afforded crude ß-phenylmercaptodihydro-4'-fluorocinnamoyl chloride **181** which was taken up in CS_2 (5 ml) and added dropwise to a stirred suspension of $AlCl_3$ (2.90 g, 21.7 mmol) in CS_2 (15 ml). Work-up and flash chromatography (elution with benzene) afforded *2-(4-fluorophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one* **186** (1.96 g, 42%), m.p. 94-96°C (from CS_2-hexane) (Found: M^+, 258.0488. $C_{15}H_{11}SOF$ requires *M*, 258.0515); δ_H (400 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 3.3 and 16.3 Hz, 3-H), 3.27 (1H, dd, *J* 12.6 and 16.3 Hz, 3-H), 4.71 (1H, dd, *J* 3.3 and 12.6 Hz, 2-H), 7.03-7.43 (7H, m, ArH) and 8.14 (1H, dd, *J* 1.3 and 8.0 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 44.7

(C-3), 46.8 (C-2), 115.9 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 125.3 (C-8), 127.2 (C-6), 129.1 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 129.2 (C-5), 130.4 (C-4a), 133.7 (C-7), 134.3 ($^4J_{CF}$ 3.0 Hz, C-1'), 141.8 (C-8a), 162.5 ($^1J_{CF}$ 247.5 Hz, C-4') and 194.1 (C-4); ν_{max} (KBr) 1675 (C=O) cm^{-1}; *m/z* 258 (M^+, 32.1%) and 136 (100%).

2-(4-Chlorophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one 187. The experimental procedure (Method 2) employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** was followed using ß-phenylmercaptodihydro-4'-chlorocinnamic acid **177** (5.5 g, 18.8 mmol) and $SOCl_2$ (6.66 g, 56.4 mmol) in chloroform (30 ml). Solvent evaporation afforded crude ß-phenylmercaptodihydro-4'-chlorocinnamoyl chloride **182** which was taken up in CS_2 (5 ml) and added dropwise to a stirred suspension of $AlCl_3$ (3.0 g, 22.6 mmol) in CS_2 (25 ml). Work-up and flash chromatography (elution with benzene) afforded *2-(4-chlorophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one* **187** (2.2 g, 48%), m.p. 111-113°C (from CS_2-hexane) (Found: M^+, 274.0220. $C_{15}H_{11}SOCl$ requires *M*, 274.0212); δ_H (400 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 3.3 and 16.4 Hz, 2-H), 3.27 (1H, dd, *J* 12.4 and 16.4 Hz, 3-H), 4.68 (1H, dd, *J* 3.3 and 12.4 Hz, 2-H), 7.02-7.43 (7H, m, ArH) and 8.13 (1H, dd, *J* 1.3 and 8.0 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 44.7 (C-3), 46.5 (C-2), 125.4 (C-8), 127.2 (C-6), 128.8 (C-2' and C-6'), 129.2 (C-3' and C-5'), 129.2 (C-5), 130.4 (C-4a), 133.7 (C-7), 134.3 (C-4'), 137.0 (C-1'), 141.6 (C-8a) and 193.9 (C-4); ν_{max} (KBr) 1670 (C=O) cm^{-1}; *m/z* 274 (M^+, 27.0%) and 136 (100%).

2-(4-Bromophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one 188. The experimental procedure (Method 2) employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** was followed using ß-phenylmercaptodihydro-4'-bromocinnamic acid **178** (4.17 g, 12.4 mmol) and $SOCl_2$ (4.38 g, 37.1 mmol) in chloroform (35 ml). Solvent evaporation afforded crude ß-phenylmercaptodihydro-4'-bromocinnamoyl chloride **183** which was taken up in CS_2 (5 ml) and added dropwise to a stirred suspension of $AlCl_3$ (3.0 g, 22.6 mmol) in CS_2 (25 ml). Work-up and flash chromatography (elution with benzene) afforded *2-(4-bromophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one* **188** (1.74 g, 44%), m.p. 152-154°C (from CS_2-hexane) (Found:

M^+, 317.9698. $C_{15}H_{11}SOBr$ requires *M*, 317.9715); δ_H (400 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 3.3 and 16.4 Hz, 3-H), 3.27(1H, dd, *J* 12.4 and 16.4 Hz, 3-H), 4.67 (1H, dd, *J* 3.3 and 12.4 Hz, 2-H), 7.12-7.51 (7H, m, ArH) and 8.14 (1H, dd, *J*1.4 and 8.0 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 44.8 (C-3), 46.5 (C-2), 122.4 (C-4'), 125.4 (C-8), 127.2 (C-6), 129.1 (C-2' and C-6'), 129.2 (C-5), 130.4 (C-4a), 132.1 (C-3' and C-5'), 133.7 (C-7), 137.5 (C-1'), 141.5 (C-8a) and 193.9 (C-4); ν_{max} (KBr) 1675 (C=O) cm^{-1}; *m/z* 318 (M^+, 56.2%) and 136 (100%).

Attempted synthesis of 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-1-benzothiopyran-4-one. The experimental procedure (Method 2) employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** was followed using ß-phenylmercaptodihydro-4'-methoxycinnamic acid **174** (6.04 g, 21.0 mmol) and $SOCl_2$ (3.0 g, 25.0 mmol) in chloroform (30 ml). Solvent evaporation afforded crude ß-phenylmercaptodihydro-4'-methoxycinnamoyl chloride **184** which was taken up in CS_2 (10 ml) and added dropwise to a stirred suspension of $AlCl_3$ (1.85 g, 13.5 mmol) in CS_2 (10 ml). Work-up afforded a complicated mixture of products and no 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-1-benzothiopyran-4-one was detected.

Note: Attempted cyclisation of the ß-phenylmercaptodihydro-4-substituted cinnamic acid **176-179** using $POCl_3$ (Method 1) led to a complicated mixture of products and no 4'-substituted-1-thioflavanones were detected. Use of polyphosphoric acid[145] and concentrated sulphuric acid also failed to yield the expected products.

2,3-Dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 191.[106] To a stirred solution of 2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **189** (5.0 g, 22.3 mmol) in dry CH_2Cl_2 (150 ml) under N_2 at room temperature, was added $SnCl_4$ (6.97 g, 26.8 mmol) and then TMS-N_3 (5.63 g, 49.1 mmol). After stirring at room temperature for 5 d, the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAc-hexane (6:4)] to afford two fractions:-

(i) starting material, and

(ii) 2,3-Dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (3.94 g, 67%), m.p. 133-135°C (from ethanol) (lit.,[106] 137°C), δ_H (400 MHz, $CDCl_3$) 4.83 (1H, dd, *J* 9.8 and 14.6 Hz, 3-H), 5.13 (1H, dd, *J* 1.5 and 14.6 Hz, 3-H), 5.23 (1H, dd, *J* 1.5 and 9.8 Hz, 2-H), 7.17 (1H, dd, *J* 1.0 and 8.0 Hz, 9-H), 7.25 (1H, ddd, *J* 1.2 and 7.8 Hz, 7-H), 7.43-7.52 (5H, m, C_6H_4 and 8-H) and 8.57 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.2 (C-3), 79.0 (C-2), 113.0 (C-5a), 121.5 (C-9), 124.0 (C-7), 126.0 (C-2' and C-4'), 129.1 (C-3' and C-5'), 129.3 (C-4'), 130.4 (C-6), 133.2 (C-8), 136.3 (C-1'), 151.9 (C-9a) and 156.8 (C-5); ν_{max} (KBr) 1605 (C=N) cm^{-1}.

8-Fluoro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 193.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **145** (1.0 g, 4.1 mmol), $SnCl_4$ (1.17 g, 4.5 mmol) and TMS-N_3 (1.05 g, 9.1 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:2)] afforded two fractions:-

(i) starting material, and

(ii) 8-fluoro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **193** (0.75 g, 65%), m.p. 152-154°C (from ethanol) (lit,.[81] 157°C); δ_H (400 MHz, $CDCl_3$) 4.83 (1H, dd, *J* 9,7 and 14.8 Hz, 3-H), 5.11 (1H, dd, *J* 1.4 and 14.8 Hz, 3-H), 5.25 (1H, dd, *J* 1.4 and 9.7 Hz, 2-H), 6.89 (1H, dd, *J* 2.6 and 9.5 Hz, 9-H), 6.98 (1H, dddd, *J* 2.5 and 8.0 Hz, 7-H), 7.41-7.50 (5H, m, C_6H_5) and 8.57 (1H, dd, *J* 6.4 and 8.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.9 (C-3), 79.3 (C-2), 108.6 ($^2J_{CF}$ 24.0 Hz, C-9), 109.4 ($^4J_{CF}$ 3.0 Hz, C-5a), 119.9 ($^2J_{CF}$ 22.0 Hz, C-7), 126.0 (C-2' and C-6'), 129.1 (C-3' and C-5'), 129.4 (C-4'), 123.2 ($^3J_{CF}$ 10.0 Hz, C-6), 135.9 (C-1'), 151.2 (C-5), 158.2 ($^3J_{CF}$ 12.0 Hz, C-9a) and 165.1 ($^1J_{CF}$ 254.4 Hz, C-8); ν_{max} (KBr) 1610 (C=N) cm^{-1}.

8-Chloro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 195.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 7-chloro-2,3-dihvro-2-phenyl-4*H*-1-benzopyran-4-one

146 (1.0 g, 3.9 mmol), $SnCl_4$ (1.13 g, 4.3 mmol) and TMS-N_3 (0.88 g, 7.7 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:2)] afforded two fractions:-

(i) starting material, and

(ii) 8-chloro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **195** (0.64 g, 55%), m.p. 138-140°C (from ethanol) (lit.,[91] 144°C); δ_H (400 MHz, $CDCl_3$) 4.85 (1H, dd, *J* 9.7 and 14.7 Hz, 3-H), 5.12 (1H, dd, *J* 1.4 and 14.7 Hz, 3-H), 5.23 (1H, dd, *J* 1.4 and 9.65 Hz, 2-H), 7.22 (1H, dd, *J* 2.0 Hz, 9-H), 7.25 (1H, dd, *J* 2.0 and 8.6 Hz, 7-H), 7.41-7.51 (5H, m, C_6H_5) and 8.52 (1H, d, *J* 8.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.0 (C-3), 79.3 (C-2), 111.6 (C-5a), 121.8 (C-9), 124.5 (C-7), 126.0 (C-2' and C-6'), 129.2 (C-3' and C-5'), 129.4 (C-4'), 131.3 (C-6), 135.8 (C-1'), 138.8 (C-8), 151.3 (C-9a) and 157.1 (C-5); ν_{max} (KBr) 1605 (C=N) cm^{-1}.

8-Bromo-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 197.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 7-bromo-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **147** (1.0 g, 3.3 mmol), $SnCl_4$ (1.9 g, 3.63 mmol) and TMS-N_3 (0.84 g, 7.3 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) 8-bromo-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **197** (0.64 g, 57%), m.p. 142-144°C (from ethanol) (lit.,[91] 149°C); δ_H (400 MHz, $CDCl_3$) 4.85 (1H, dd, *J* 9.7 and 14.7 Hz, 3-H), 5.12 (1H, dd, *J* 1.4 and 14.8 Hz, 3-H), 5.22 (1H, dd, *J* 1.3 and 9.7 Hz, 2-H), 7.39-7.68 (7H, m, 9-H, 7-H and C_6H_5) and 8.45 (1H, d, *J* 8.2 Hz, 6-H); δ_H (100 MHz, $CDCl_3$) 56.0 (C-3), 79.3 (C-2), 112.0 (C-5a), 124.8 (C-9), 126.0 (C-2' and C-6'), 126.9 (C-8), 127.4 (C-7), 129.2 (C-3' and C-5'), 129.5 (C-4'), 135.8 (C-9a) and 157.0 (C-5); ν_{max} (KBr) 1605 (C=N) cm^{-1}.

8-Methoxy-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 199.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed, using 7-methoxy-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **148** (1.25 g, 4.9 mmol), $SnCl_4$ (1.41 g, 5.4 mmol) and TMS-N_3 (1.24 g, 10.8 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) *8-methoxy-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **199** (0.22 g, 15%), m.p. 130-132°C (from ethanol) (Found: C, 65.29; H, 4.87; N, 19.01% $C_{16}H_{14}N_4O_2$ requires C, 65.29; H, 4.79, N, 19.04%); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 4.80 (1H, dd, *J* 9.7 and 14.6 Hz, 3-H), 5.08 (1H, dd, *J* 1.3 and 14.7 Hz, 3-H), 5.22 (1H, dd, *J* 1.2 and 9.7 Hz, 2-H), 6.64 (1H, d, *J* 3.2 Hz, 9-H), 6.81 (1H, dd, *J* 3.3 and 8.9 Hz, 7-H), 7.41-7.51 (5H, m, C_6H_5) and 8.46 (1H, d, *J* 8.9 Hz, 6-H); ν_{max} (KBr) 1615 (C=N) cm^{-1}.

2-(4-Fluorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 201.[108] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-fluorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **149** (0.76 g, 3.1 mmol), $SnCl_4$ (0.9 g, 3.5 mmol) and TMS-N_3 (0.88 g, 7.6 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) 2-(4-fluorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **201** (0.467 g, 54%), m.p. 178-180°C (from ethanol) (lit.,[91] 182°C); δ_H (400 MHz, $CDCl_3$) 4.81 (1H, dd, *J* 9.7 and 14.6 Hz, 3-H), 5.09 (1H, dd, *J* 1.6 and 14.6 Hz, 3-H), 5.23 (1H, dd, *J* 1.6 ad 9.7 Hz, 2-H), 7.17 (3H, m, 9-H, 3'-H, and 5'-H), 7.26 (1H, dd, *J* 1.2 and 7.2 Hz, 2'-H and 6'-H) and 8.57 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.1 (C-3), 78.3 (C-2), 112.9 (C-5a), 116.1 ($^3J_{CF}$ 21.1 Hz, C-3' and C-5'), 121.4 (C-9), 124.1 (C-7), 127.9 ($^3J_{CF}$ 8.05 Hz, C-2' and C-6'), 130.4 (C-6), 132.2 ($^4J_{CF}$ 3.0 Hz, C-1'), 133.3 (C-8), 151.9 (C-9a), 156.6 (C-5) and

163.1 ($^1J_{CF}$ 248.5 Hz, C-4'); ν_{max} (KBr) 1610 (C=N) cm^{-1}.

2-(4-Chlorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 203.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-chlorophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **150** (1.0 g, 3.9 mmol), $SnCl_4$ (1.13 g, 4.3 mmol) and TMS-N_3 (0.88 g, 7.7 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) 2-(4-Chlorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **203** (0.542 g, 52%), m.p. 162-164°C (from ethanol) (lit.,[91] 168°C); δ_H (400 MHz, $CDCl_3$) 4.79 (1H, dd, *J* 9.8 and 14.6 Hz, 3-H), 5.08 (1H, dd, *J* 1.5 and 14.6 Hz, 3-H), 5.23 (1H, dd, *J* 1.5 and 9.8 Hz, 2-H), 7.15 (1H, dd, *J* 1.1 and 8.3 Hz, 9-H), 7.25 (1H, m, *J* 1.1 and 7.6 Hz, 7-H), 7.43-7.48 (5H, m, 2'-H, 3'-H, 5'-H, 6'-H and 8-H) and 8.54 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.0 (C-3), 78.3 (C-2), 112.9 (C-5a), 121.5 (C-9), 124.1 (C-7), 127.5 (C-2' and C-6'), 129.3 (C-3' and C-5'), 130.4 (C-6), 133.3 (C-8), 134.8 (C-4'), 135.2 (C-4'), 135.2 (C-1'), 151.9 (C-9a) and 156.6 (C-5); ν_{max} (KBr) 1615 (C=N) cm^{-1}.

2-(4-Bromophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 205.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-bromophenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one **151** (1.0 g, 3.3 mmol), $SnCl_4$ (1.9 g, 3.63 mmol) and TMS-N_3 (0.83 g, 7.26 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) 2-(4-bromophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **205** (0.71 g, 60%), m.p. 178-180°C (from ethanol) (lit.,[91] 182°C); δ_H (400 MHz, $CDCl_3$) 4.79 (1H, dd, *J* 9.7 and 14.6 Hz, 3-H), 5.08 (1H, dd, *J* 1.5 and 14.6 Hz, 3-H), 5.21 (1H, dd, *J* 1.5 and 9.7 Hz, 2-H),

7.15 (1H, dd, *J* 1.1 and 8.3 Hz, 9-H), 7.26 (1H, dd, *J* 1.2 and 7.6 Hz, 7-H), 7.40 (1H, ddd, *J* 2.0 and 8.7 Hz, 2'-H and 6'-H), 7.46 (1H, m, *J* 1.0, 2.0 and 7.8 Hz, 8-H), 7.61 (1H, ddd, *J* 2.0 and 8.7 Hz, 3'-H and 5'-H) and 8.56 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.9 (C-3), 78.3 (C-2), 112.9 (C-5a), 121.4 (C-9), 123.3 (C-1'), 124.1 (C-7), 127.7 (C-2' and C-6'), 130.4 (C-6), 132.2 (C-3' and C-5'), 133.3 (C-8), 135.4 (C-4'), 151.8 (C-9a) and 156.6 (C-5); ν_{max} (KBr) 1615 (C=N) cm^{-1}.

2,3-Dihydro-2-(4-methoxyphenyl)-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 207.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one **152** (1.25 g, 4.9 mmol), $SnCl_4$ (1.41 g, 5.4 mmol) and TMS-N_3 (1.24 g, 10.8 mmol) in CH_2Cl_2 (100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) *2,3-dihydro-2-(4-methoxyphenyl)-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **207** (0.4 g, 28%), m.p. 116-118°C (from ethanol); (Found: C, 65.29; H, 4.88; N, 19.01% $C_{16}H_{14}N_4O_2$ requires C, 65.29; H, 4.79; N, 19.04%); δ_H (400 MHz, $CDCl_3$) 4.83 (1H, dd, *J* 9.8 and 14.6 Hz, 3-H), 5.07 (1H, dd, *J* 1.4 and 14.6 Hz, 3-H), 5.17 (1H, dd, *J* 1.4 and 9.8 Hz, 2-H), 6.98 (2H, m, *J* 2.4 and 9.2 Hz, 3'-H and 5'-H), 7.14 (1H, dd, *J* 1.0 and 8.3 Hz, 9-H), 7.23 (1H, dd, *J* 1.0 and 7.5 Hz, 7-H), 7.39 (2H, m, 2'-H and 6'-H), 7.44 (1H, ddd, *J* 1.5 and 7.8 Hz, 8-H) and 8.55 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.4 (OCH_3), 56.1 (C-3), 78.7 (C-2), 113.0 (C-5a), 114.5 (C-3' and C-5'), 121.5 (C-9), 127.4 (C-2' and C-6'), 128.4 (C-1'), 130.4 (C-6), 133.2 (C-8), 151.9 (C-9a), 156.9 (C-5) and 160.3 (C-4'); ν_{max} (KBr) 1610 (C=N) cm^{-1}.

2,3-Dihydro-2-(4-nitrophenyl)-4*H*-tetrazolo[1,5-*d*-1,4-benzoxazepine 209.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-2-(4-nitro-phenyl)-4*H*-1-benzopyran-4-one **153** (1.2 g, 4.5 mmol), $SnCl_4$ (0.67 g, 4.9 mmol) and TMS-N_3 (1.13 g, 9.8 mmol) in CH_2Cl_2

(100 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions:-

(i) starting material, and

(ii) *2,3-dihydro-2-(4-nitrophenyl)-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **209** (0.51 g, 37%), m.p. 198°C (from ethanol); (Found: M^+, 309.0829. $C_{15}H_{11}N_5O_3$ requires *M*, 309.0862); δ_H (400 MHz, $CDCl_3$) 4.83 (1H, dd, *J* 9.8 and 14.7 Hz, 3-H), 5.16 (1H, dd, *J* 1.5 and 14.7 Hz, 3-H), 5.37 (1H, dd, *J* 1.5 and 9.8 Hz, 2-H), 7.20 (1H, dd, *J* 1.0 and 8.3 Hz, 9-H), 7.31 (1H, ddd, *J* 1.2 and 7.7 Hz, 7-H), 7.50 (1H, dddd, *J* 1.0, 1,7 and 7.8 Hz, 8-H), 7.75 (2H, d, *J* 8.5 Hz, 2'-H and 6'-H), 8.35 (1H, d, *J* 8.8 Hz, 3'-H and 5'-H) and 8.60 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H); δ_C (100 MHz, DMSO-d_6) 55.9 (C-3), 78.0 (C-2), 112.9 (C-5a), 121.4 (C-9), 124.4 (C-2' and C-6'), 142.9 (C-7), 127.1 (C-3' and C-5'), 130.7 (C-6), 133.6 (C-1' and C-8), 142.9 (C-9a), 147.9 (C-4') and 156.7 (C-5); ν_{max} (KBr) 1615 (C=N) cm^{-1}.

2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 190 and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 191.[106] A stirred solution of 2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **189** (3.0 g, 13.4 mmol) in trifluoroacetic acid (35 ml) was treated dropwise with TMS-N_3 (2.31 g, 20.1 mmol) at room temperature under N_2. After stirring the mixture for 3 d., the solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography [elution with EtOAc-hexane (3:2)] to afford three fractions:-

(i) starting material,

(ii) 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.07 g, 2%), m.p. 136-137°C (from ethanol) (lit.,[106] 137°C), and

(iii) 2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** (0.6 g, 20%), m.p. 126-128°C (from ethanol) (lit.,[106] 127°C); δ_H (400 MHz, $CDCl_3$) 3.56 (1H, ddd, *J* 6.0 and 15.3 Hz, 3-H), 3.64 (1H, dddd, *J* 3.5, 6.4 and 15.4 Hz, 3-H), 5.46 (1H, dd, *J* 3.5 and 6.4 Hz, 2-H), 7.07 (1H, dd, *J* 1.0 and 8.2 Hz, 9-H), 7.19 (1H, t, *J* 7.6 Hz, 7-H), 7.30-7.41 (5H, m, C_6H_5), 7.46 (1H, dd, 1.7 and 7.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.3 (C-3), 85.9 (C-2), 122.4 (C-9), 123.6 (C-7), 125.8 (C-5a), 126.3 (C-2' and C-6'), 128.5 (C-4'), 128.6 (C-3' and C-5'), 130.9 (C-6),

133.3 (C-8), 139.0 (C-1'), 154.6 (C-9a) and 171.1 (C-5); ν_{max} (KBr) 3400 (NH) and 1660 (C=O) cm^{-1}.

8-Fluoro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 192 and 8-Fluoro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 193.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** and 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** was followed using 7-fluoro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one (1.0 g, 4.1 mmol) and TMS-N_3 (0.71 g, 6.2 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 8-Fluoro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **193** (0.3 g, 26%), m.p. 154°C (lit,.[91] 157°C); and

(iii) 8-Fluoro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **192** (0.46 g, 44%), m.p. 128-130°C (from ethanol) (lit.,[91] 129°C); δ_H (400 MHz, $CDCl_3$) 3.45-3.60 (2H, m, 3-H), 5.40 (1H, m, 2-H), 6.75 (1H, dd, *J* 2.4 and 9.7 Hz, 9-H), 6.84 (1H, m, *J* 2.5 and 8.8 Hz, 7-H), 7.30-7.40 (5H, m, ArH), 7.70 (1H, br s, NHCO) and 7.95 (1H, dd, *J* 6.8 and 8.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.8 (C-3), 85.7 (C-2), 109.0 ($^2J_{CF}$ 24.0 Hz, C-9), 110.9 ($^2J_{CF}$ 21.0 Hz, C-7), 120.2 (C-5a), 126.1 (C-2' and C-6'), 128.7 (C-4'), 128.8 (C-3' and C-5'), 133.8 ($^3J_{CF}$ 11.0 Hz, C-6), 138.4 (C-1'), 156.8 (C-9a), 165.8 ($^1J_{CF}$ 252.3 Hz, C-8) and 170 (C-5); ν_{max} (KBr) 3400 (NH) and 1665 (C=O) cm^{-1}.

8-Chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 194 and 8-chloro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*-1,4-benzoxazepine 195.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 7-chloro-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **146** (4.0 g, 15.5 mmol) and TMS-N_3 (2.77 g, 24 mmol) in trifluoroacetic acid (35 ml). Work-up and flash chromatography [elution with EtOAc-hexane

(1:1)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 8-chloro-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **195** (0.27 g, 6%), m.p. 138-140°C (from ethanol) (lit.,[91] 144°C), and

(iii) 8-Chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **194** (1.70 g, 40%), m.p. 144-146°C (from ethanol) (lit.,[91] 146°C); δ_H (400 MHz, $CDCl_3$) 3.58 (1H, ddd, *J* 6.0 and 15.5 Hz, 3-H), 3.65 (1H, dddd, *J* 3.2, 6.0 and 15.5 Hz, 3-H), 5.45 (1H, dd, *J* 3.2 and 6.0 Hz, 2-H), 6.88 (1H, br s, NHCO), 7.09 (1H, d, *J* 2.0 Hz, 9-H), 7.15 (1H, dd, *J* 2.0 and 18.5 Hz, 7-H), 7.30-7.42 (5H, m, C_6H_5) and 7.83 (1H, d, *J* 8.5 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.5 (C-3), 85.9 (C-2), 122.4 (C-9), 123.4 (C-5a), 123.8 (C-8), 126.1 (C-2' and C-6'), 128.7 (C-4'), 128.8 C-3' and C-5'), 132.5 (C-6), 138.5 (C-8), 138.9 (C-1'), 155.4 (C-9a) and 169.8 (C-5); ν_{max} (KBr) 3450 (NH) and 1665 (C=O) cm^{-1}.

8-Bromo-2,3-dihydro-2,3-phenyl-1,4-benzoxazepin-5(4*H*)-one 196 and 8-bromo-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 197.[108] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 7-bromo-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **147** (1.0 g, 3.3 mmol) and TMS-N_3 (0.58 g, 5.0 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (1:1)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 8-bromo-2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **197** (0.08 g, 7%), m.p. 142-144°C (from ethanol) (lit.,[91] 149°C), and

(iii) 8-Bromo-2,3-dihydro-2,3-phenyl-1,4-benzoxazepin-5(4*H*)-one **196** (0.44 g, 42%), m.p. 148-150°C (from ethanol) (lit.,[91] 156°C); δ_H (400 MHz, $CDCl_3$) 3.57 (1H, ddd, *J* 6.0 and 12.6 Hz, 3-H), 3.64 (1H, dddd, *J* 3.2, 6.3 and 12.6 Hz, 3-H), 5.45 (1H, dd, *J* 3.2 and 6.3 Hz, 2-H), 7.26 (1H, d, *J* 1.8 Hz, 9-H), 7.31 (1H, dd, *J* 1.8 and 8.4 Hz, 7-H), 7.33-7.41 (5H, m, C_6H_5) and 7.75 (1H, d, *J* 8.4 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.5 (C-3), 85.9 (C-2), 123.9 (C-5a),

125.3 (C-9), 126.1 (C-2' and C-6'), 126.8 (C-7), 127.1 (C-8), 128,7 (C-4'), 128.8 (C-3' and C-5'), 132.6 (C-6), 128.5 (C-1'), 155.3 (C-9a) and 169.9 (C-5); ν_{max} (KBr) 3350 (NH) and 1670 (C=O) cm^{-1}.

2,3-Dihydro-8-methoxy-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 198 and 2,3-dihydro-8-methoxy-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 199.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-8-methoxy-2-phenyl-4*H*-1-benzopyran-4-one **148** (1.2 g, 4.7 mmol) and TMS-N_3 (0.82 g, 7.1 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (4:1)] afforded three fractions, *viz.*,

(i) starting material,

(ii) *2,3-dihydro-8-methoxy-2-phenyl-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **199** (0.04 g, 3%), m.p. 130-132°C (from ethanol), and

(iii) *2,3-dihydro-8-methoxy-2-phenyl-1,4-benzoxazepin-5(4*H*)-one* **198** (0.8 g, 63%), m.p. 164-166°C (from ethanol) (Found: M^+, 269.1053. $C_{16}H_{15}NO_3$ requires *M*, 269.1052); δ_H (400 MHz, $CDCl_3$) 3.42-3.56 (2H, m, 3-H), 3.74 (3H, s, OCH_3), 5.24 (1H, dd, *J* 2.0 and 8.2 Hz, 2-H), 6.47 (1H, d, *J* 2.5 Hz, 9-H), 6.57 (1H, dd, *J* 2.4 and 8.9 Hz, 7-H), 7.33 (5H, m, C_6H_5) and 7.93 (1H, d, *J* 9.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 47.7 (C-3), 55.5 (OCH_3), 84.8 (C-2), 105.6 (C-5a), 109.9 (C-9), 126.1 (C-2' and C-6'), 128.6 (C-4'), 128.7 (C-3' and C-5'), 134.0 (C-1'), 138.7 (C-6), 157.5 (C-9a), 164.5 (C-8) and 170.7 (C-5); ν_{max} (KBr) 3300 (NH) and 1670 (C=O) cm^{-1}.

2-(4-Fluorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 200 and 2-(4-fluorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 201.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-fluorophenyl)-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **149** (2.0 g, 8.3 mmol) and TMS-N_3 (1.43 g, 12.4 mmol) in trifluoroacetic acid (35 ml). Work-up and flash chromatography [elution with EtOAc-

hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 2-(4-fluorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **201** (0.24 g, 10%), m.p. 179-181°C (from ethanol) (lit.,[91] 182°C); and

(iii) 2-(4-fluorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **200** (0.53 g, 25%), m.p. 184°C (from ethanol) (lit.,[91] 183°C); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, ddd, *J* 6.0 and 15.4 Hz, 3-H), 3.65 (1H, dddd, *J* 3.5, 6.0 and 15.4 Hz, 3-H), 5.43 (1H, dd, *J* 3.5 and 6.0 Hz, 2-H), 7.02 (3H, m, 9-H, 3'-H, and 5-'H), 7.20 (1H, ddd, *J* 1.0 and 7.6 Hz, 7-H), 7.37 (2H, m, *J* 2.0, 3.0 and 7.2 Hz, 2'-H and 6'-H), 7.46 (1H, dddd, *J* 1.0, 1.8 and 7.7 Hz, 8-H), 7.50 (1H, br s, NHCO) and 7.83 (1H, dd, *J* 1.8 and 7.7 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.3 (C-3), 85.1 (C-2), 115.6 ($^2J_{CF}$ 21.2 Hz, C-3' and C-5'), 122.4 (C-9), 123.9 (C-7), 125.8 (C-5a), 128.1 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 131.0 (C-6), 133.5 (C-8), 134.9 ($^4J_{CF}$ 3.0 Hz, C-1'), 154.4 (C-9a), 162.7 ($^1J_{CF}$ 247.5 Hz, C-4') and 171.1 (C-5); ν_{max} (KBr) 3320 (NH) and 1665 (C=O) cm^{-1}.

2-(4-Chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 202 and 2-(4-chlorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 203.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-chlorophenyl)-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **150** (2.0 g, 7.7 mmol) and TMS-N_3 (1.34 g, 11.6 mmol) in trifluoroacetic acid (50 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 2-(4-chlorophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **203** (0.29 g, 12%), m.p. 162-164°C (from ethanol) (lit.,[91] 168°C); and

(iii) 2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **202** (0.48 g, 23%), m.p. 134-136°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 3.46 (1H, ddd, *J* 6.0 and 15.4 Hz, 3-H), 3.59 (1H, dddd, *J* 3.5, 6.3 and 15.4 Hz, 3-H), 5.38 (1H, dd, *J* 3.4 and 6.3 Hz, 2-H), 7.03 (1H, dd, *J* 0.7 and 8.1 Hz, 9-H), 7.16 (1H, ddd, *J* 0.9 and 7.5 Hz, 7-H), 7.30 (4H, ddd, *J* 3.1 and 7.5 Hz,

2'-H, 3'-H, 5'-H and 6'-H), 7.80 (1H, dd, *J* 1.8 and 7.8 Hz, 6-H) and 8.08 (1H, t, *J* 5.7 Hz, NHCO); δ_C (100 MHz, $CDCl_3$) 46.0 (C-3), 85.1 (C-2), 122.3 (C-9), 123.8 (C-7), 125.6 (C-5a), 127.6 (C-2' and C-6'), 128.7 (C-3' and C-5'), 130.9 (C-6), 133.4 (C-8), 134.2 (C-4'), 137.4 (C-1'), 154.3 (C-9a) and 171.2 (C-5); ν_{max} (KBr) 3300 (NH) and 1670 (C=O) cm^{-1}.

2-(4-Bromophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 204 and 2-(4-bromophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 205.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-bromophenyl)-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **151** (2.7 g, 8.9 mmol) and TMS-N_3 (1.56 g, 13.5 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (1:1)] afforded three fractions, *viz.*,

(i) starting material,

(ii) 2-(4-bromophenyl)-2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **205** (0.3 g, 10%), m.p. 178-180°C (from ethanol) (lit.,[91] 182° C); and

(iii) 2-(4-bromophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **204** (1.18 g, 42%), m.p. 138-140°C (from ethanol) (lit.,[91] 142°C); δ_H (400 MHz, $CDCl_3$) 3.47 (1H, ddd, *J* 5.8 and 15.4 Hz, 3-H), 3.63 (1H, dddd, *J* 3.4, 6.2 and 15.4 Hz, 3-H), 5.39 (1H, dd, *J* 3.4 and 6.5 Hz, 2-H), 7.05 (1H, dd, *J* 1.0 and 8.2 Hz, 9-H), 7.20 (1H, ddd, *J* 1.0 and 7.6 Hz, 7-H), 7.27 (2H, dd, *J* 1.7 and 7.7 Hz, 8-H), 7.50 (2H, dd, *J* 1.9 and 7.7 Hz, 3'-H and 5'-H) and 7.84 (1H, dd, *J* 1.7 and 7.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.1 (C-3), 85.1 (C-2), 122.3 (C-9), 122.5 (C-4'), 124.0 (C-7), 125.8 (C-5a), 128.0 (C-3' and C-5'), 131.0 (C-6), 131.8 (C-2' and C-6'), 133.5 (C-8), 138.0 (C-1'), 154.3 (C-9a) and 171.0 (C-5); ν_{max} (KBr) 3370 (NH) and 1670 (C=O) cm^{-1}.

2,3-Dihydro-2-(4-methoxyphenyl)-1,4-benzoxazepin-5(4H)-one 206 and 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 207.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-2-

(4-methoxyphenyl)-4*H*-1-benzopyran-4-one **152** (2.0 g, 7.9 mmol) and TMS-N_3 (1.36 g, 11.8 mmol) in trifluoroacetic acid (50 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) *2,3-dihydro-(4-methoxyphenyl)-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **207** (0.27 g, 11%), m.p. 116-118°C (from ethanol), and

(iii) *2,3-dihydro-(4-methoxyphenyl)-1,4-benzoxazepin-5(4*H*)-one* **206** (0.43 g, 20%), m.p. 194°C (from ethanol) (Found: M^+, 269.1045. $C_{16}H_{15}NO_3$ requires *M*, 269.1052); δ_H (400 MHz, $CDCl_3$) 3.49 (1H, ddd, *J* 5.0 and 9.3 Hz, 3-H), 3.71 (1H, dddd, *J* 3.5, 7.0 and 13.9 Hz, 3-H), 3.76 (3H, s, OCH_3), 4.33 (1H, dd, *J* 3.5 and 9.4 Hz, 2-H), 6.53 (1H, s, NHCO), 6.79 (2H, d, *J* 8.6 Hz, 3'-H and 5'-H), 6.83 (1H, quintet, *J* 1.1 and 7.7 Hz, 9-H), 6.97 (1H, dd, *J* 1.0 and 8.4 Hz, 7-H), 7.13 (1H, dd, *J* 1.4 and 8.0 Hz, 8-H), 7.22 (2H, d, *J* 8.6 Hz, 2'-H and 6'-H) and 7.40 (1H, m, *J* 1.5 and 7.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 45.3 (C-3), 55.3 (OCH_3), 77.8 (C-2), 114.2 (C-5a), 114.5 (C-3' and C-5'), 118.6 (C-9), 118.6 (C-7), 125.3 (C-6), 128.2 (C-2' and C-6'), 130.4 (C-5a), 134.3 (C-8), 160.0 (C-4'), 161.5 (C-9a) and 169.8 (C-5); ν_{max} (KBr) 3300 (NH) and 1650 (C=O) cm^{-1}.

2,3-Dihydro-2-(4-nitrophenyl)-1,4-benzoxazepin-5(4*H*)-one 208 and 2,3-dihydro-2-(4-nitrophenyl)-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 209.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-2-(4-nitrophenyl)-4*H*-1-benzopyran-4-one **153** (1.0 g, 3.7 mmol) and TMS N_3 (0.66 g, 5.7 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (1:1)] afforded three fractions, *viz.*,

(i) starting material,

(ii) *2,3-dihydro-(4-nitrophenyl)-4*H*-tetrazolo[1,5-d]-1,4-benzoxazepine* **209** (0.11 g, 10%), m.p. 198°C (from ethanol), and

(iii) *2,3-dihydro-(4-nitrophenyl)-1,4-benzoxazepin-5(4*H*)-one* **208** (0.57 g, 54%), m.p. 172-

174°C (from ethanol) (Found: M^+, 284.0797. $C_{15}H_{12}N_2O_4$ requires *M*, 284.0800); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, ddd, *J* 5.7 and 15.4 Hz, 3-H), 3.75 (1H, dddd, *J* 3.7, 6.0 and 15.4 Hz, 3-H), 5.53 (1H, t, *J* 4.2 Hz, 2-H), 7.10 (1H, dd, *J* 0.7 and 8.2 Hz, 9-H), 7.19 (1H, s, NHCO), 7.24 (1H, ddd, *J* 1.0 and 7.6 Hz, 7-H), 7.50 (1H, ddd, *J* 1.8 and 7.3 Hz, 8-H), 7.60 (2H, d, *J* 8.6 Hz, 2'-H and 6'-H), 7.81 (1H, d, *J* 1.7 and 7.8 Hz, 6-H) and 8.23 (2H, dd, *J* 2.0 and 9.0 Hz, 3'-H and 5'-H); δ_C (100 MHz, $CDCl_3$) 46.0 (C-3), 84.6 (C-2), 122.2 (C-9), 123.9 (C-2' and C-6'), 124.4 (C-7), 126.0 (C-1'), 127.3 (C-3' and C-5'), 131.0 (C-6), 133.7 (C-8), 146.0 (C-5a), 147.9 (C-4'), 154.0 (C-9a) and 170.9 (C-5); ν_{max} (KBr) 3500 (NH) and 1660 (C=O) cm^{-1}.

2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 190, 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*-1,4-benzoxazepine 191 and 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5*H*)-one 211.[103] A stirred mixture of 2,3-dihydro-2-phenyl-4*H*-benzopyran-4-one **189** (5.0 g, 22.3 mmol) and sodium azide (3.0 g, 46.2 mmol) in glacial acetic acid (25 ml) at 0-5°C was treated dropwise with concentrated sulphuric acid (5 ml). The mixture was then stirred for 2 hours at 45-50°C, cooled and poured into iced water (50 ml). The precipitated material was filtered and purified by flash chromatography [elution with EtOAc-hexane (6:4)] to afford four fractions:-

(i) starting material,

(ii) 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** (2.13 g, 40%), m.p. 126-128°C (from ethanol),

(iii) 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.248 g, 4%), m.p. 133-135°C, and

(iv) 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5*H*)-one **211** (0.133 g, 2.5%), m.p. 142-143°C (from ethanol) (lit.,[103] 141-142°C); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 4.0 and 14.9 Hz, 3-H), 3.11 (1H, dd, *J* 8.7 and 14.9 Hz, 3-H), 5.65 (1H, dd, *J* 4.0 and 8.6 Hz, 2-H), 7.06-7.45 (9H, m, ArH) and 9.14 (1H, s, NHCO); δ_C (100 MHz, $CDCl_3$) 42.2 (C-3), 82.9 (C-2), 122.0 (C-9), 123.3 (C-7), 124.4 (C-8), 125.8 (C-6), 126.0 (C-2' and C-6'), 128.5 (C-4'), 128.7 (C-3' and C-5'), 130.1 (C-1'), 140.1 (C-5a), 148.2 (C-9a) and 171.8 (C-4); ν_{max} (KBr) 3300 (NH) and

1665 (C=O) cm^{-1}; *m/z* 239 (M^+, 1.2%) and 131 (100%).

2,3-Dihydro-2-phenyl-5-trifluoroacetoxy-1,4-benzoxazepine 210 and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 191.[106] To a stirred solution of 2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one **189** (5.0 g, 22.3 mmol) in trifluoroacetic acid (25 ml) was added sodium azide (2.18 g, 33.5 mmol) in small portions under N_2. After 3 days, ether (150 ml) was added and the solid product was filtered to afford 2,3-dihydro-2-phenyl-5-trifluoroacetoxy-1,4-benzoxazepine **210** (7.33 g, 98%), m.p. 191°C (from absolute ethanol-hexane) (lit.,[106] 190-192°C); ν_{max} (KBr) 1670 (C=O), 1639 (C=N) cm^{-1}.

The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAc-hexane (4:2)] to afford 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.18 g, 2%), m.p. 133-145°C (from ethanol).

Hydrolysis of 2,3-dihydro-2-phenyl-5-trifluoroacetoxy-1,4-benzoxazepine 210:[106] **Preparation of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-one 190.** A stirred suspension of 2,3-dihydro-2-phenyl-5-trifluoroacetoxy-1,4-benzoxazepine **210** (4.0 g, 11.9 mmol) in water (30 ml) was refluxed for 0.5 h and then allowed to stand at room temperature for 16 h. The crystalline product was filtered to afford 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** (2.4 g, 84%); m.p. 125-126°C (from ethanol) (lit.,[106] 127°C).

2-Phenyl-1,2,3,4-tetrahydro-5*H*-benzodiazepin-5-one 212 and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*-1*H*-1,4-benzodiazepine 213.[103] A stirred solution of 2-phenyl-1,2,3,4-tetrahydro-4-quinolone **164** (1.5 g, 6.7 mmol) in trifluoracetic acid (20 ml) was treated dropwise with TMS-N_3 (1.16 g, 10.1 mmol) at r.t. under N_2. After stirring the mixture for 3d., the solvent was evaporated *in vacuo*, and the residue was taken up in chloroform (50 ml). The resulting solution was washed, sequentially, with 5% aq. NaOH (3 x 10 ml) and water (2 x 10 ml) and then dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAC-hexane (6:4)] to afford three fractions,

viz.,

(i) starting material,

(ii) 2-Phenyl-1,2,3,4-tetrahydro-5*H*-benzodiazepin-5-one **212** (0.8 g, 50%), m.p. 170-172°C (from ethanol) (lit.,[148] 182°C) (Found: M^+, 238.1080. $C_{15}H_{14}N_2O$ calculated *M*, 238.1106); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, dd, *J* 6.4 and 14.9 Hz, 3-H), 3.56 (1H, dddd, *J* 3.6, 6.4 and 14.9 Hz, 3-H), 4.23 (1H, s, NH), 4.79 (1H, dd, *J* 3.6 and 6.4 Hz, 2-H), 6.68 (1H, dd, *J* 0.8 and 8.1 Hz, 9-H), 6.89 (1H, dd, *J* 1.0 and 7.5 Hz, 7-H), 7.26-7.38 (6H, m, C_6H_4 and 8-H) and 7.85 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.8 (C-3), 64.8 (C-2), 119.2 (C-9), 119.4 (C-7), 120.5 (C-5a), 126.7 (C-2' and C-6'), 128.1 (C-4'), 128.9 (C-3' and C-5'), 132.2 (C-6), 132.9 (C-8), 142.3 (C-1'), 145.2 (C-9a) and 172.1 (C-5); ν_{max} (KBr) 3300 (NH) and 1630 (C=O) cm^{-1}; *m/z* 238 (M^+, 19.0%) and 180 (100%).

(iii) 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine **213** (0.65 g, 37%), m.p. 182°C (from ethanol) (lit.,[148] 184°C) (Found: C, 68.51; H, 4.81; N, 26.58%; M^+, 263.1171. $C_{15}H_{13}N_5$ calculated C, 68.47; H, 4.98; N, 26.62; *M*, 263.1157); δ_H (400 MHz, $CDCl_3$) 4.47 (1H, d, *J* 9.0 Hz, 2-H), 4.68 (1H, dd, *J* 9.0 and 13.7 Hz, 3-H), 4.69 (1H, s, NH), 4.99 (1H, dd, *J* 1.2 and 13.7 Hz, 3-H), 6.76 (1H, dd, *J* 0.8 and 8.2 Hz, 9-H), 6.98 (1H, ddd, *J* 1.4 and 7.6 Hz, 7-H), 7.28-7.48 (6H, m, C_6H_4 and 8-H) and 8.52 (1H, dd, *J* 1.4 and 8.2 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.5 (C-3), 57.7 (C-2), 107.7 (C-5a), 118.8 (C-9), 120.1 (C-7), 128.7 (C-2' and C-6'), 129.4 (C-4'), 129.7 C-3' and C-5'), 131.1 (C-8), 132.5 (C-6), 138.5 (C-1'), 145.8 (C-9a) and 153.2 (C-5); ν_{max} (KBr) 3310 (NH) and 1610 (C=N) cm^{-1}; *m/z* 263 (M^+, 18.6%) and 207 (100%).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 214 and 2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine 215.[106] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **212** and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine **213** was followed using 2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone **165** (2.0 g, 8.3 mmol) and TMS-N_3 (1.43 g, 12.4 mmol) in trifluoroacetic acid (30 ml). Work-up and flash chromatography

[elution with EtOAc-hexane (6:4)] afforded three fractions:-

(i) starting material,

(ii) *2-(4-Fluorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one* **214** (0.55 g, 51%), m.p. 176°C (from ethanol) (Found: M^+, 256.1227. $C_{15}H_{13}N_2OF$ requires *M*, 256.1012); δ_H (400 MHz, $CDCl_3$) 3.45 (1H, ddd, *J* 6.4 and 14.8 Hz, 3-H), 3.57 (1H, dddd, *J* 3.7, 6.6 and 14.8 Hz, 3-H), 4.22 (1H, s, NH), 4.71 (1H, dd, *J* 3.1 and 6.5 Hz, 2-H), 6.68 (1H, dd, *J* 0.8 and 8.1 Hz, 9-H), 6.89 (1H, dd, *J* 1.0 and 7.5 Hz, 7-H), 7.00-7.50 (2H, m, 3'-H and 5'-H), 7.26-7.44 (3H, m, 8-H, 2'-H and 6'-H) and 7,82 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.7 (C-3), 64.0 (C-2), 115.7 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 119.3 (C-8), 119.6 (C-7), 120.7 (C-5a), 128.3 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 132.1 (C-6), 132.9 (C-8), 138.2 ($^4J_{CF}$ 3.01, C-1'), 145.0 (C-9a), 162.4 ($^1J_{CF}$ 246.5, C-4') and 172.3 (C-5); ν_{max} (KBr) 3440 (NH) and 1635 (C=N) cm^{-1}; *m/z* 256 (M^+, 18.3%) and 198 (100%); and

(iii) *2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-d]-1*H*-1,4-benzodiazepine* **215** (0.3 g, 25%), m.p. 158-160°C (from ethanol) (Found: M^+, 281.1040. $C_{15}H_{12}N_6F$ requires *M*, 281.1033); δ_H (400 MHz, $CDCl_3$) 4.50 (1H, dd, *J* 1.4 and 13.7 Hz, 2-H), 4.68 (1H, dd, *J* 9.0 and 13.7 Hz, 3-H), 4.69 (1H, s, NH), 4.95 (1H, dd, *J* 1.4 and 13.7 Hz, 3-H), 6.77 (1H, dd, *J* 0.8 and 8.3 Hz, 9-H), 6.97 (1H, ddd, *J* 1.0, 2.0 and 7.5 Hz, 7-H), 7.13 (2H, "quintet", *J* 2.0 and 7.5 Hz, 3'-H and 5'-H), 7.30 (1H, m, *J* 1.4, 1.5 and 7.7 Hz, 8-H), 7.38 (2H, m, *J* 2.0 and 5.9 Hz, 2'-H and 6'-H) and 8.48 (1H, dd, *J* 1.5 and 8.1 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.3 (C-3), 56.9 (C-2), 107.7 (C-5a), 116.6 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 118.8 (C-9), 120.1 (C-7), 128.5 ($^3J_{CF}$ 8.05 Hz, C-3' and C-5'), 131.1 (C-6), 132.6 (C-6), 134.3 ($^4J_{CF}$ 3.0 Hz, C-1'), 145.5 (C-9a), 153.2 (C-5) and 163.0 ($^1J_{CF}$ 249.5 Hz, C-4'); ν_{max} (KBr) 3440 (NH) and 1610 (C=N) cm^{-1}; *m/z* 281 (M^+, 4.1%) and 225 (100%).

2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 216 and 2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine 217.[106] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **212** and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine **213** was

followed using 2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone **166** (1.0 g, 3.9 mmol) and TMS-N_3 (0.67 g, 5.9 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:2)] afforded three fractions:-

(i) starting material,

(ii) 2-(4-chlorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **216** (0.53 g, 50%), m.p. 168-170°C (from ethanol) (Found: C, 65.5; H, 4.8; N, 10%; M^+, 272.0695. $C_{15}H_{13}N_2OCl$ requires C, 66.2; H, 4.8; N, 10.3% *M*, 272.0717); δ_H (400 MHz, $CDCl_3$) 3.45 (1H, ddd, *J* 6.3 and 14.8 Hz, 3-H), 3.58 (1H, dddd, *J* 3.0, 6.5 and 14.8 Hz, 3-H), 4.20 (1H, s, NH), 4.78 (1H, quintet, *J* 3.0 and 6.3 Hz, 2-H), 6.68 (1H, dd, *J* 0.8 and 8.1 Hz, 9-H), 6.90 (1H, ddd, *J* 1.0 and 7.5 Hz, 7-H), 6.90 (1H, s, NHCO), 7.26-7.32 (5H, m, C_6H_4 and 8-H) and 7.81 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.5 (C-3), 64.1 (C-2), 119.3 (C-9), 119.8 (C-7), 120.9 (C-5a), 128.1 (C-2' and C-6'), 129.0 (C-3' and C-5'), 132.1 (C-6), 132.9 (C-8), 128.9 (C-4'), 140.8 (C-1'), 144.9 (C-9a) and 172.0 (C-5); ν_{max} (KBr) 3300 (NH) and 1650 (C=O) cm^{-1}; *m/z* 272 (M^+, 35.4%) and 214 (100%); and

(iii) *2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-d]-1*H*-1,4-benzodiazepine* **217** (0.3 g, 26%), m.p. 170-172°C (from ethanol) (Found: M^+, 297.0818; $C_{15}H_{12}N_5Cl$ requires *M*, 297.1782); δ_H (400 MHz, $CDCl_3$) 4.50 (1H, d, *J* 8.8 Hz, 2-H), 4.68 (1H, dd, *J* 8.8 and 13.7 Hz, 3-H), 4.69 (1H, s, NH), 4.96 (1H, dd, *J* 1.4 and 13.7 Hz, 3-H), 6.77 (1H, d, *J* 8.2 Hz, 9-H), 6.99 (1H, t, *J* 7.6 Hz, 7-H), 7.30-7.38 (3H, m, 8-H, 2'-H and 6'-H), 7.42 (2H, d, *J* 8.5 Hz, 3'-H and 5'-H) and 8.49 (1H, d, *J* 8.1 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.2 (C-3), 57.0 (C-2), 107.7 (C-5a), 118.8 (C-9), 120.3 (C-7), 128.1 (C-2' and C-6'), 129.9 (C-3' and C-5'), 131.1 (C-6), 132.6 (C-8), 135.4 (C-1'), 136.8 (C-4'), 145.4 (C-9a) and 153.2 (C-5); ν_{max} 3290 (NH) and 1605 (C=N) cm^{-1}; *m/z* 297 (M^+, 3.7%) and 241 (100%).

2-(4-Bromophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 218 and 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-*d*]-1*H*-1,4-benzodiazepine 219.[106] The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **212** and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine **213** was

followed using 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4-quinolone **167** (1.0 g, 3.3 mmol) and TMS-N_3 (0.56 g, 4.9 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:1)] afforded three fractions:-

(i) starting material,

(ii) 2-(4-bromophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **218** (0.54 g, 52%), m.p. 154°C (from ethanol) (lit.,[149] 153°C) (Found: M^+, 316.0180; $C_{15}H_{13}N_2OBr$ requires *M*, 316.1212); δ_H (400 MHz, $CDCl_3$) 3.45 (1H, ddd, *J* 6.2 and 14.8 Hz, 3-H), 3.61 (1H, dddd, *J* 3.0, 6.5 and 14.9 Hz, 3-H), 4.16 (1H, s, NH), 4.78 (1H, t, *J* 3.1 Hz, 2-H), 6.48 (1H, s, NHCO), 6.69 (1H, dd, *J* 0.8 and 8,1 Hz,9-H), 6.92 (1H, quintet, *J* 1.0 and 7.5 Hz, 7-H), 7.23 (2H, d, *J* 8.3 Hz, 2'-H and 6'-H), 7.30 (1H, m, *J* 0.8, 1.7 and 7.5 Hz, 8-H) and 7,83 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.5 (C-3), 64.1 (C-3), 119.4 (C-9), 119.9 (C-7), 122.0 (C-5a), 128.2 (C-4'), 128.5 (C-2' and C-6'), 132.0 (C-3' and C-5'), 132.1 (C-6), 133.0 (C-8), 141.3 (C-1'), 144.9 (C-9a) and 172.0 (C-5); ν_{max} (KBr) 3300 (NH) and 1650 (C=O) cm^{-1}; *m/z* 316 (M^+, 17.2%) and 285 (100%); and

(iii) 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-*d*]-1*H*-1,4-benzodiazepine **219** (0.36 g, 32%), m.p. 204°C (from ethanol) (lit.,[149] 208°C) Found: M^+, 341.0277. $C_{16}H_{12}N_6Br$ calculated *M*, 341.0301); δ_H (400 MHz, $CDCl_3$) 4.49 (1H, d, *J* 8.8 Hz, 2-H), 4.67 (1H, dd, *J* 8.8 and 13.8 Hz, 3-H), 4.72 (1H, s, NH), 4.94 (1H, d, *J* 13.6 Hz, 3-H), 6.77 (1H, dd, *J* 0.8 and 8.3 Hz, 9-H), 6.99 (1H, quintet, *J* 0.8 and 7.6 Hz, 7-H), 7.26 (2H, m, *J* 1.7, 2.1 and 8.7 Hz, 2'-H and 6'-H), 7.31 (1H, m, *J* 1.3, 1.7 and 7.7 Hz, 8-H), 7.57. (2H, ddd, *J* 2.1 and 8.7 Hz, 3'-H and 5'-H) and 8.49 (1H, dd, *J* 1.5 and 8.1 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.1 (C-3), 57.1 (C-2), 107.7 (C-5a), 118.8 (C-9), 120.3 (C-7), 123.4 (C-4'), 128.4 (C-2' and C-6'), 128.37 (C-6), 132.6 (C-8), 132.8 (C-3' and C-5'), 137.3 (C-1'), 145.4 (C-9a) and 153.2 (C-5); ν_{max} (KBr) 3320 (NH) and 1605 (C=N) cm^{-1}; *m/z* 341 (M^+, 17.2%) and 285 (100%).

The 2-(4-bromophenyl)tetrazolo derivative **219** was also prepared as the sole product using the following procedure:

To a stirred solution of 2-(4-bromophenyl)-1,2,3,4-tetrahydroquinolone **167** (1.0 g, 3.3 mmol) in

dry CH_2Cl_2 (25 ml) under N_2 at r.t. was added $SnCl_4$ (0.94 g, 3.6 mmol) and then TMS-N_3 (0.83 g, 7.3 mmol). After stirring at r.t. for 5d., the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAc-hexane (6:4)] to afford 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,5-benzodiazepine **219** (0.5 g, 53%), m.p. 205°C (from ethanol) (lit.,[148] 208°C).

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 220 and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,5-benzodiazepine 221. The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **212** and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5*d*]-1*H*-1,4-benzodiazepine **213** was followed using 2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-quinolone **168** (1.0 g, 4.0 mmol) and TMS-N_3 (0.68 g, 5.9 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded three fractions:-

(i) starting material,

(ii) 2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **220** (0.48 g, 45%), m.p. 182-184°C (from ethanol) (lit.,[148] 183°C) (Found: M^+, 268.1194. $C_{16}H_{16}N_2O_2$ calculated *M*, 286.1212); δ_H (400 MHz, $CDCl_3$) 3.47 (2H, t, *J* 5.0 Hz, 3-H), 3.77 (3H, s, OCH_3), 4.09 (1H, s, NH), 5.72 (1H, t, *J* 5.0 Hz, 2-H), 6.65 (1H, dd, *J* 0.7 and 8.1 Hz, 9-H), 6.86 (1H, d, *J* 8.6 Hz, 7-H), 8.22 (2H, dd, *J* 1.8 and 8.0 Hz, 2'-H and 6'-H), 7.27 (1H, dddd, *J* 1.0, 2.5 and 7,5 Hz, 8-H), 7.32 (1H, t, *J* 5.8 Hz, NHCO) and 7.82 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 47.0 (C-3), 55.3 (OCH_3), 64.1 (C-2), 114.2 (C-2' and C-6'), 119.0 (C-9), 119.2 (C-7), 119.8 (C-5a), 127.7 (C-3' and C-5'), 132.1 (C-6), 132.9 (C-8), 134.3 (C-1'), 145.3 (C-9a), 159.4 (C-4') and 172.5 (C-5); ν_{max} (KBr) 3300 (NH) and 1620 (C=O) cm^{-1}; *m/z* 268 (M^+, 72.2%) and 210 (100%); and

(iii) 2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-*d*]-1*H*-1,5-benzodiazepine **221** (0.29 g, 24%), m.p. 143°C (from ethanol) (lit.,[148] 142°C) (Found: M^+, 293.127. $C_{16}H_{15}N_6O$ calculated *M*, 293.1287); δ_H (400 MHz, $CDCl_3$) 4.42 (1H, d, *J* 9.0 Hz, 2-H), 4.64 (1H, dd, *J* 9.0 and 13.6 Hz, 3-H), 4.64 (1H, s, NH), 4.96 (1H, dd, *J* 1.2 and 13.6 Hz, 3-H), 6.74 (1H, dd,

J 0.9 and 8.2 Hz, 9-H), 6.94-6.98 (3H, m, 3'-H, 5'-H and 8-H), 7.27-7.32 (3H, m, 6-H, 2'-H and 6'-H) and 8.50 (1H, dd, *J* 1.5 and 8.1 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.4 (OCH_3), 56.6 (C-3), 57.0 (C-2), 107.6 (C-5a), 114.9 (C-3' and C-5'), 118.7 (C-9), 119.9 (C-7), 127.9 (C-2' and C-6'), 130.5 (C-1'), 131.0 (C-6), 132.5 (C-8), 145.8 (C-9a), 153.2 (C-5) and 160.2 (C-4'); ν_{max} (KBr) 3310 (NH) and 1605 (C=N) cm^{-1}; *m/z* 293 (M^+, 3.9%) and 237 (100%).

2-(4-Nitrophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 222 and 2-(4-nitrophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,5-benzodiazepine 223. The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **212** and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine **213** was followed using 2-(4-nitrophenyl)-1,2,3,4-tetrahydro-4-quinolone **169** (0.2 g, 0.74 mol) and TMS-N_3 (0.13 g, 1.1 mmol) in trifluoroacetic acid (10 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded three fractions:-

(i) starting material,

(ii) *2-(4-nitrophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one* **222** (0.063 g, 30%), m.p. 192°C (from ethanol) (Found: C, 63.1; H, 4.6; N, 14.9% $C_{16}H_{13}N_3O_3$ requires C, 63.6; H, 4.6; N, 14.8%); δ_H (400 MHz, $CDCl_3$) 3.47 (1H, ddd, *J* 6.0 and 15.0 Hz, 2-H), 3.75 (1H, dddd, *J* 3.0, 6.0 and 15.0 Hz, 3-H), 4.20 (1H, d, *J* 2.6 Hz, NH), 4.96 (1H, dd, *J* 4.0 and 8.0 Hz, 3-H), 6.29 (1H, s, NHCO), 6.74 (1H, d, *J* 8.7 Hz, 2'-H and 6'-H), 6.97 (1H, t, *J* 7.6 Hz, 7-H),7.34 (1H, ddd, *J* 1.1 and 7.6 Hz, 8-H), 7.57 (1H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.83 (1H, d, *J* 7.8 Hz, 6-H) and 8.22 (1H, d, *J* 7.8 Hz,6-H); δ_C (100 MHz, DMSO-d_6) 44.4 (C-3), 61.4 (C-2), 116.9 (C-9), 118.6 (C-5a), 119.0 (C-7), 123.3 (C-4' and C-6'), 128.1 (c-6), 131.7 (C-3' and C-5'), 131.9 (C-8), 145.9 (C-4'), 146.5 (C-9a), 151.2 (C-1') and 170.1 (C-5); ν_{max} (KBr) 3370 (NH) and 1660 (C=O) cm^{-1}; *m/z* 283 (M^+, 40.2%) and 225 (100%); and

(iii) 2-(4-nitrophenyl)-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-*d*]-1*H*-1,5-benzodiazepine **223** (0.057 g, 25%), m.p. 230°C (from EtOH-acetone) (Found: M^+, 308.1031. $C_{15}H_{12}N_6O_2$ requires *M*, 308.1022); δ_H (400 MHz, DMSO-d_6) 4.80 (1H, d, *J* 14.2, 2-H), 5.22 (1H, t, *J* 4.9 Hz, 3-H), 5.41 (1H, dd, *J* 6.0 and 14.2 Hz, 3-H), 6.84 (1H, t, *J* 7.6 Hz, 9-H), 7.10 (1H, d, *J* 8.4 Hz,

7-H), 7.36 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 8.09 (1H, d, *J* 8.0 Hz, 6-H) and 8.16 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H); δ_C (100 MHz, DMSO-d_6) 55.5 (C-3), 54.7 (C-2), 104.9 (C-5a), 117.5 (C-9), 118.7 (C-7), 123.6 (C-3' and C-5'), 128.0 (C-6), 129.9 (C-2' and C-6'), 132.2 (C-8), 145.8 (C-4'), 145.1 (C-9a), 146.8 (C-1') and 153.3 (C-5); ν_{max} (KBr) 3350 (NH) and 1600 (C=N) cm^{-1}; *m/z* 308 (M^+, 30.8%) and 25.2 (100%).

2,3-Dihydro-2-phenyl-1,2-benzothiazepin-5(4*H*)-one 224, 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(*5*H)-one 225 and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzothiazepine 226.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one **185** (2.0 g, 8.3 mmol) and TMS-N_3 (1.44 g, 12.5 mmol) in trifluoroacetic acid (25 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one **224** (0.85 g, 40%), m.p. 186°C (from ethanol) (lit.,[35] 180-183°C); δ_H (400 MHz, $CDCl_3$) 3.37 (1H, dddd, *J* 1.9, 8.1 and 15.1 Hz, 3-H), 3.57 (1H, dddd, *J* 1.7, 5.8 and 15.1 Hz, 3-H), 4.61 (1H, dd, *J* 5.0 and 9.1 Hz, 2-H) and 7.20-7.80 (10H, m, NHCO and ArH); δ_C (100 MHz, $CDCl_3$) 47.5 (C-3), 56.2 (C-2), 127.3 (C-2' and C-6'), 128.0 (C-9), 128.8 (C-3' and C-5'), 129.2 (C-4'), 129.9 (C-7), 130.2 (C-5a), 131.7 (C-6), 134.3 (C-8), 139.9 (C-1'), 141.2 (C-9a) and 172.5 (C-5); ν_{max} (KBr) 3310 (NH) and 1750 (C=O) cm^{-1}; *m/z* 255 (M^+, 52.1%) and 226 (100%);

(ii) 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** (0.63 g, 20%), m.p. 176°C (from ethanol) (lit.,[35] 180-181°C); δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dddd, *J* 1.3, 5.7 and 12.6 Hz, 3-H), 2.89 (1H, dd, *J* 11.1 and 12,5 Hz, 3-H), 7.17 (1H, dd, *J* 1.3 and 7.8 Hz, 9-H), 7.22 (1H, ddd, *J* 1.4 and 7.6 Hz, 7-H), 7.26-7.31 (5H, m, C_6H_5), 7.4 (1H, ddd, *J* 1.5 and 7.7 Hz, 8-H), 7.65 (1H, dd, *J* 1.4 and 7.7 Hz, 6-H) and 8.20 (1H, br s, NHCO); δ_C (100 MHz, $CDCl_3$) 41.5 (C-3), 53.2 (C-2), 123.2 (C-9), 126.4 (C-2' and C-6'), 126.7 (C-7), 127.8 (C-4'), 128.8 (C-3' and C-5'), 130.2 (C-6), 135.9 (C-8), 141.3 (C-1'), 143.3 (C-9a) and 172.1 (C-4); ν_{max} (KBr) 3220 (NH) and 1650 (C=O) cm^{-1}; and

(iii) *2,3-dihydro-2-phenyl-4H-tetrazolo[1,5-d]-1,4-benzothiazepine* **226** (0.51 g, 22%), m.p. 124°C (from ethanol) (Found: M^+, 280.0780. $C_{15}H_{12}N_4S$ requires *M*, 280.0783); δ_H (400 MHz, $CDCl_3$) 4.71 (1H, dd, *J* 9.8 and 14.3 Hz, 3-H), 4.88 (1H, dd, *J* 5.0 and 9.8 Hz, 2-H), 5.04 (1H, dd, *J* 5.0 and 14.3 Hz, 3-H), 7.30-7.60 (7H, C_6H_6, H-7 and H-9), 7.72 (1H, m, 8-H) and 8.14 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 53.5 (C-3), 54.7 (C-2), 127.1 (C-2' and C-6'), 128.0 (C-5a), 128.8 (C-9), 129.3 (C-3', C-4' and C-5'), 131.2 (C-7), 132.1 (C-8), 134.2 (C-1'), 134.2 (C-6), 138.6 (C-9a) and 154.2 (C-5); ν_{max} (KBr) 1600 (C=N) cm^{-1}; *m/z* 280 (M^+, 97.4%) and 148 (100%).

2-(4-Fluorophenyl)-2,3-dihydro-1,4-benzothiazepin-5(4*H*)-one 227 and 2-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepin-5(4*H*)-one 228.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-fluorophenyl),2-3-dihydro-4*H*-1-benzothiopyran-4-one **186** (1.0 g, 3.6 mmol) and TMS-N_3 (0.63 g, 5.5 mmol) in trifluoroacetic acid (30 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) *2-(4-fluorophenyl)-2,3-dihydro-1,4-benzothiazepin-5(4H)-one* **227** (0.34 g, 35%), m.p. 188°C (from ethanol) (Found: M^+, 273.0627. $C_{15}H_{12}NOSF$ requires *M*, 273.0623); δ_H (400 MHz, $CDCl_3$) 3.34 (1H, dddd, *J* 7.2, 8.7 and 15.2 Hz, 3-H), 3.57 (1H, dddd, *J* 5.0, 6.8 and 15.1 Hz, 3-H), 4.61 (1H, dd, *J* 4.9 and 8.8 Hz, 2-H) and 6.96-7.74 (9H, m, ArH and NHCO); δ_C (100 MHz, $CDCl_3$) 47.6 (C-3), 55.4 (C-2), 115.7 ($^2J_{CF}$ 21.1 Hz, C-3' and C-5'), 129.0 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 129.4 (C-9), 128.0 (C-5a), 128.0 (C-7), 131.7 (C-6), 134.3 (C-8), 136.9 ($^4J_{CF}$ 3.0 Hz, C-1'), 129.8 (C-9a), 162.3 ($^1J_{CF}$ 247.5 Hz, C-4') and 172.4 (C-5); ν_{max} (KBr) 3305 (NH) and 1745 (C=O) cm^{-1}; *m/z* 273 (M^+, 73.2%) and 244 (100%); and

(iii) 2-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepin-5(4*H*)-one **228** (0.20 g, 20%), m.p. 184°C (from CH_3CN) (lit.,[40] 179°C); δ_H (400 MHz, DMSO-d_6) 2.6 (1H, dd, *J* 5.4 and 12.4 Hz, 3-H), 2.71 (1H, dd, *J* 10.2 and 12.4 Hz, 3-H), 5.02 (1H, dd, *J* 5.6 and 10.2 Hz, 2-H), 7.11-

7.56 (8H, m, ArH) and 9.99 (1H, br s, NHCO); δ_C (100 MHz, DMSO-d_6) 41.1 (C-3), 51.3 (C-2'), 115.2 ($^2J_{CF}$ 115.2 Hz, C-3' and C-5'), 123.0 (C-9), 124.9 (C-7), 125.6 (C-5a), 128.3 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 130.1 (C-6), 135.0 (C-8), 139.7 ($^4J_{CF}$ 3.0 Hz, C-1'), 142.4 (C-9), 161.3 ($^1J_{CF}$ 243.5 Hz, C-4') and 170.5 (C-4); ν_{max} (KBr) 3305 (NH) and 1655 (C=O) cm^{-1}; *m/z* 273 (M^+, 54%) and 149 (100%).

2-(4-Chlorophenyl)-2,3-dihydro-1,4-benzothiazepin-5(4*H*)-one 229 and 2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one 230.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-chlorophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one **187** (1.50 g, 5.5 mmol) and TMS-N_3 (0.94 g, 8.2 mmol) in trifluoroacetic acid (30 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material,

(ii) *2-(4-chlorophenyl)-2,3-dihydro-1,4-benzothiazepin-5(4H)*-one **229** (0.53 g, 33%), m.p. 122°C (from ethanol) (Found: M^+, 289.0340. $C_{15}H_{12}NOSCl$ requires *M*, 289.0327); δ_H (400 MHz, $CDCl_3$) 3.3 (1H, dddd, *J* 7.2, 8.6 and 15.2 Hz, 3-H), 3.55 (1H, dddd, *J* 5.0, 6.7 and 15.2 Hz, 3-H), 4.57 (1H, dd, *J* 5.0 and 8.7 Hz, 2-H), 7.20 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.24 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.42-7.50 (2H, m, 7-H and 9-H), 7.56 (1H, ddd, *J* 1.5, 2.1 and 6.3 Hz, 8-H), 7.73 (1H, ddd, *J* 1.5, 2.2 and 6.4 Hz, 6-H) and 8.21 (1H, t, *J* 6.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 47.4 (C-3), 55.4 (C-2), 128.6 (C-2' and C-6'), 129.0 (C-3' and C-5'), 129.7 (C-9), 129.8 (C-5a), 130.1 (C-7), 131.8 (C-6), 133.9 (C-4'), 134,3 (C-8), 139.5 (C-1'), 139.7 (C-9a) and 172.2 (C-5); ν_{max} (KBr) 3300 (NH) and 1750 (C=O) cm^{-1}; *m/z* 289 (M^+, 91.2%) and 260 (100%); and

(iii) 2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **230** (0.40 g, 25%), m.p. 206°C (from ethanol) (lit.,[37] 204-205°C); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 6.2 and 12.5 Hz, 3-H), 2.84 (1H, dd, *J* 10.2 and 12.5 Hz, 3-H), 4.85 (1H, dd, *J* 6.1 and 10.2 Hz, 2-H), 7.18 (1H, d, *J* 7.8 Hz, 9-H), 7.21-7.28 (5H, m, 7-H and C_6H_4Cl), 7.42 (1H, tt, *J* 1.5 and 7.7 Hz, 8-

H), 7.63 (1H, dd, *J* 1.3 and 7.5 Hz, 6-H) and 8.27 (1H, s, NH); ν_{max} (KBr) 3160 (NH), 1660 (C=O) cm^{-1}; *m/z* 289 (M^+, 43.2%) and 165 (100%).

2-(4-Bromophenyl)-2,3-dihydro-1,4-benzothiazepin-5(4*H*)-one 231 and 2-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one 232.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using 2-(4-bromophenyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one **188** (1.2 g, 3.8 mmol) and TMS-N_3 (0.65 g, 5.6 mmol) in trifluoroacetic acid (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded three fractions, *viz.*,

(i) starting material;

(ii) *2-(4-bromophenyl-2,3-dihydro-1,4-benzothiazepin-5(4*H*)-one* **231** (0.36 g, 28%), m.p. 144°C (from ethanol) (Found: M^+, 332.9818. $C_{15}H_{12}NOSBr$ requires *M*, 332.9823); δ_H (400 MHz, $CDCl_3$) 3.33 (1H, dddd, *J* 7.3, 8.7 and 15.2 Hz, 3-H), 3.56 (1H, dddd, *J* 5.0, 6.8 and 15.2 Hz, 3-H), 4.56 (1H, dd, *J* 5.0 and 8.7 Hz, 2-H), 6.91 (1H, br s, NH), 7.18 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 7.44 (2-H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.46-7.52 (2H, m, 7-H and 9-H), 7.57 (1H, ddd, *J* 1.2, 2.1 and 6.6 Hz, 8-H) and 7.76 (1H, ddd, *J* 1.2, 2.1 and 6.5 Hz, 6-H); δC (100 MHz, $CDCl_3$) 47.3 (C-3), 55.5 (C-2), 122.0 (C-4'), 129.0 (C02' and C-6'), 129.5 (C-9), 129.8 (C-5a), 130.1 (C-7), 131.8 (C-6), 132.0 (C-3' and C-5'), 134.3 (C-8), 139.7 (C-1'), 140.0 (C-9a) and 172.2 (C-5); ν_{max} (KBr) 3350 (NH) and 1745 (C=O) cm^{-1}; *m/z* 304 (M^+, 56.3%) and 197 (100%); and

(iii) *2-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepin-4(*5H*)-one* **232** (0.32 g, 25%), m.p. 217°C (from ethanol) (Found: M^+, 332.9809. $C_{15}H_{12}NOSBr$ requires *M*, 332.9823); δ_H (400 MHz, $CDCl_3$) 2.61 (1H, dd, *J* 5.7 and 12.5 Hz, 3-H), 2.68 (1H, dd, *J* 10.6 and 12.5 Hz, 3-H), 4.67 (1H, dd, *J* 5.8 and 10.6 Hz, 2-H), 7.14 (1H, d, *J* 8.0 Hz, 9-H), 7.18 (1H, d, *J* 8.8 Hz, 2'-H and 6'-H), 7.23 (1H, tt, *J* 1.2 and 7.6 Hz, 7-H), 7.41 (1H, tt, *J* 1.5 and 3.1 Hz, 8-H), 7.43 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 7.53 (1H, br s, NH) and 7.63 (1H, dd, *J* 1.2 and 7.7 Hz, 6-H), 9.66 (1H, d, $J_{H,NH}$ 5.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 110.4 (C-3), 119.6 (C-9), 122.7 (C-2' and

C-6'), 123.8 (C-7), 125.7 (C-5a), 126.9 (C-4'), 127.6 (C-3' and C-5'), 130.7 (C-6), 132.5 (C-1'), 133.0 (C-8), 144.6 (C-9a), 158.0 (C-2) and 166.5 (C-5); ν_{max} (KBr) 3160 (NH) and 1665 (C=O) cm^{-1}; *m/z* 335 (M^+, 34.2 %) and 211 (100%).

2,3-Dihydro-1,4-benzothiazepin-5(4*H*)-one 241, 2,3-dihydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzothiazepine 242 and 4,5-dihydro-5*H*-tetrazolo[5,1-*d*]-1,5-benzothiazepine 243.[108] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** and 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** was followed using thiochroman-4-one **240** (5.0 g, 30.5 mmol) and TMS-N_3 (5.27 g, 45.7 mmol) in trifluoroacetic acid (75 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded four fractions, *viz.*,

(i) starting material,

(ii) 2,3-Dihydro-1,4-benzothiazepin-5(4*H*)-one **241** (1.91 g, 35%), m.p. 216°C (from ethanol) (lit.,[100] 215-216°C); δ_H (400 MHz, $CDCl_3$) 2.62 (2H, t, *J* 7.0 Hz, 2-H), 3.44 (2H, *J* 7.0 Hz, 3-H), 7.12 (1H, dd, *J* 1.1 and 7.9 Hz, 9-H), 7.14 (1H, ddd, *J* 1.3 and 7.7 Hz, 7-H), 7.33 (1H, ddd, *J* 1.5 and 7.7 Hz, 8-H) and 7.58 (1H, dd, *J* 1.4 and 7.7 Hz, 6-H) and 8.71 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 33.6 (C-3), 34.4 (C-2), 123.8 (C-9), 126.4 (C-7), 126.9 (C-5a), 129.8 (C-6), 135.4 (C-8), 141.5 (C-9a) and 173.9 (C-5); ν_{max} (KBr) 3200 (NH) and 1650 (C=O) cm^{-1}; *m/z* 179 (M^+, 100%); and

(iii) *2,3-dihydro-4*H*-tetrazolo[1,5-d]-1,4-benzothiazepine* **242** (1.87 g, 30%), m.p. 108°C (from ethanol) (Found: M^+, 204.1470. $C_9H_8N_4S$ requires *M*, 204.0471); δ_H (400 MHz, $CDCl_3$) 2.68 (2H, quintet, *J* 2.0 and 7.3 Hz, 2-H), 4.44 (2H, dd, *J* 2.0 and 7.3 Hz, 3-H), 7.44-7.52 (2H, m, 7-H and 9-H), 7.66 (1H, ddd, *J* 1.1 amd 7.2 Hz, 8-H) and 8.52 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 33.1 (C-3), 50.8 (C-2), 125.6 (C-5a), 128.4 (C-9), 131.5 (C-7), 132.0 (C-6), 132.8 (C-8), 135.4 (C-9a) and 154.0 (C-5); ν_{max} (KBr) 1610 (C=N) cm^{-1}; *m/z* 204 (M^+, 92.3%) and 148 (100%); and

(iv) 4,5-dihydro-5*H*-tetrazolo[5,1-*d*]-1,5-benzothiazepine **243** (1.56 g, 35%), m.p. 130-132°C (from ethanol) (lit.,[49] 140°C) (Found: M^+, 204.2454. $C_9H_8N_4S$, calculated *M*, 204.0470); δ_H

(400 MHz, $CDCl_3$) 3.38 (2H, ddd, *J* 1.8 and 6.8 Hz, 3-H), 3.46 (2H, ddd, *J* 1.8 and 6.8 Hz, 4-H), 7.45 (1H, ddd, *J* 1.3 and 7.6 Hz, 8-H), 7.56 (1H, ddd, *J* 1.4 and 7.8 Hz, 7-H), 7.74 (1H, dd, *J* 1.3 and 7.7 Hz, 6-H) and 7.80 (1H, dd, *J* 1.2 and 7.9 Hz, 9-H); δ_C (100 MHz, $CDCl_3$) 23.5 (C-3), 35.3 (C-2), 125.0 (C-6), 127.3 (C-5a), 130.2 (C-8), 120.2 (C-9), 125.5 (C-7), 137.3 (C-9a) and 153.7 (C-2); ν_{max} (KBr) 1620 (C=N) cm^{-1}; *m/z* 204 (M^+, 7.6%) and 45 (100%).

2,3-Dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224.[35] A stirred mixture of ß-nitrostyrene **233** (5.0 g, 33.0 mmol) and thiosalicylic acid **234** (5.0 g, 33 mmol) in ethanol (15 ml) was refluxed for 3h. The hot solution was then diluted with water (10 ml), cooled and the crystalline product was filtered. The crystalline product was washed with cold 95% ethanol to afford 2-{[*α*-(nitromethyl)benzyl]thio}benzoic acid (8.31 g, 83%), m.p. 151°C (lit.,[35] 150-152°C).

A suspension of 2-{[*α*-(nitromethyl)benzyl]thio}benzoic acid (7.0 g, 23.1 mmol) and thionyl chloride (15 ml) in chloroform (15 ml) was refluxed for 3 h and volatile material was evaporated under reduced pressure. To the residue was added methanol (25 ml) and the mixture was refluxed for 6h. The mixture was cooled to afford methyl-2-{[*α*-(nitromethyl)-benzyl]thio}benzoate (6.61 g, 90%), m.p. 99-102°C (lit.,[35] 100-102°C).

A mixtire of methyl-2-{[*α*-(nitromethyl)benzyl]thio}benzoate (6.3 g, 19.9 mmol), $SnCl_2.2H_2O$ (18.31 g, 78.5 mmol), methanol (55 ml) and glacial acetic acid (20 ml) was refluxed for 3 h and concentrated under reduced pressure. The mixture was cooled and was made alkaline with a cold solution of 10% aq. K_2CO_3. The product was extracted with a chloroform-ether (3:2) mixture (4 x 40 ml) and the combined organic extracts were, sequentially, washed with water (3 x 20 ml) and dried (anhyd. $MgSO_4$). The solvents were evaporated under reduced pressure and the residue was taken up in ether (35 ml). Small quantity of insoluble oil was discarded and the organic solution was treated with ether-HCl (1:1) mixture (20 ml) to give an oil. The solvent was evaporated under reduced pressure, and the residue was taken up in ether (50 ml).

The organic solution was treated with 10% aq. K_2CO_3 (30 ml) and the product was extracted with chloroform (3 x 20 ml). Chloroform was evaporated under reduced presure to give crude methyl-2-{[*α*-(aminomethyl)benzyl]thio}benzoate (3.89 g, 63%) which was used in the next step without further purification. This product was heated at 150-180°C for 1h, methanol being distilled off during this period. The crude material was purified by flash chromatography [elution with EtOAc-hexane (3:2)] to afford 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one **224** (1.38 g, 40%), m.p. 186°C (from ethanol) (lit.,[35] 180-183°C).

2,3-Dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 225.[37] A mixture of 2-aminothiophenol **235** (0.84 g, 6.8 mmol) and cinnamic acid **236** (1.0 g, 6.8 mmol) was heated at 160-180°C for 1h, water being released during this time. The mixture was then cooled to 90°C and this was poured onto warm acetonitrile (20 ml) to afford 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** (0.52 g, 30%), m.p. 176°C (from CH_3CN) (lit.,[107] 180-181).

2-(4-Fluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one 228.[37] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** was followed, using 2-aminothiophenol **235** (1.13 g, 9.0 mmol) and 4-fluorocinnamic acid **237** (1.5 g, 9.0 mmol). Work-up afforded 2-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **228** (0.93 g, 38%), m.p. 184°C (from CH_3CN) (lit.,[40] 179°C).

2-(4-Chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one 230.[37] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** was followed, using 2-aminothiophenol **235** (1.37 g, 11.0 mmol) and 4-chlorocinnamic acid **238** (2.0 g, 11.0 mmol). Work-up afforded 2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **230** (0.63 g, 20%), m.p. 206°C (from CH_3CN) (lit.,[47] 204-205°C).

2-(4-Bromophenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one 232.[37] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** was followed, using 2-aminothiophenol **235** (0.83 g, 6.6 mmol) and 4-bromocinnamic acid **239** (1.5 g, 6.6 mmol). Work-up afforded *2-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one* **232** (0.71 g, 32%), m.p. 217°C (from CH_3CN).

Attempted dehydrogenation of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine 191

Method 1:[152]

A stirred mixture of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.5 g, 1.89 mmol) and DDQ (0.65 g, 2.84 mmol) in dry toluene (20 ml) was boiled under reflux for 72 hours. The mixture was filtered hot through a sintered glass funnel and the solid material was washed with hot toluene to ensure complete extraction of the product. The solvent was evaporated under reduced pressure and the crude material (0.3 g) was found by ^{1}H NMR spectroscopy to be the starting material.

Method 2:[180]

A stirred mixture of 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.3 g, 1.1 mmol) and 5% Pd/C (0.52 g, 1.8 mmol) in decalin (25 ml) was refluxed for 24 h. The mixture was filtered hot through a sintered glass funnel and the catalyst was washed with hot decalin to ensure complete extraction of the product. The product was allowed to crystallise from the solution and filtered. The crystalline material (0.21 g) was found by ^{1}H NMR spectroscopy to be the starting material.

Method 3:[91]

Lithium diisopropylamide (LDA) was prepared *in situ* by the addition of *n*-butyllithium (1.4 ml, 2.1 mmol) to a stirred solution of diisopropylamine (0.3 ml, 2.1 mmol) in dry THF (12 ml) at -30°C under N_2. The mixture was stirred at this temperature for 1h., cooled to -78°C, and then 2,3-dihydro-2-phenyl-4*H*-tetrazolo[1,5-*d*]-1,4-benzoxazepine **191** (0.5 g, 1.9 mmol) in dry THF (3 ml) was added. After stirring the reaction mixture for 1 h. at -78°C, a solution of *N*-bromosuccinamide (0.34 g, 1.9 mmol) in dry THF (5 ml) was added, whereafter it was

allowed to warm to room temperature over 4h. The mixture was stirred overnight at room temperature and then quenched with 5% aq. $NaHCO_3$ (25 ml). The product was extracted with ether (3 x 10 ml) and dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* and the crude material was found by ^1H NMR spectroscopy to be the starting material.

Comment: Attempted *N*-bromination of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** using LDA followed by *N*-bromosuccinamide or bromine in THF (following method 3) led to the recovery of the starting material.

***N*-[2,2-(Ethylenedioxy)-2-phenyl]phthalimide.**[162] Potassium phthalimide **248** (5.0 g, 27 mmol) was added in small portions to a stirred solution of *α*-chloroacetophenone **247** (3.86 g, 25 mmol) in DMF (20 ml). The mixture was refluxed for 4 h, cooled and then water (100 ml) was added. The product was extracted with chloroform (3 x 40 ml) and the combined organic extracts were washed, sequentially, with 5% aq. NaOH (3 x 20 ml) and water (2 x 20 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated under reduced pressure to afford crude 2-(*N*)-phthalimido)acetophenone (5.83 g, 88%), m.p. 166 °C (lit.,[162] 165-167°C). A stirred solution of the latter (4.5 g, 22 mmol) and ethylene glycol (1.64 g, 26.4 mmol) in *p*-toluenesulphonic acid (0.25 g, 1.3 mmol) was refluxed for 95 h under Dean-Stark conditions. The reaction mixture was cooled, the benzene layer was separated, and the ethylene glycol layer was extracted with ether (2 x 20 ml). Work-up (as above) and solvent evaporation afforded *N*-[2,2-ethylenedioxy)-2-phenylethyl]phthalimide (6.25 g, 92%), m.p. 143-144°C (from ethanol) (lit.,[62] 145°C); δ_H (60 MHz, $CDCl_3$) 3.98 (4 H, m, OCH_2CH_2O), 4.2 (2H, s, CH_2) and 7.40-8.00 (9H, m, ArH).

2,2-(Ethylenedioxy)-2-phenylethanamine 249.[162] A stirred solution of *N*-[2,2-ethylenedioxy)-2-phenylethyl)pthalimide (18.0 g, 58.3 mmol) and 30% aq. NaOH (100 ml) was refluxed for 90 h, cooled and then diluted with water (150 ml). The resulting solution was extracted with ether (3 x 100 ml) and the combined ether extracts were dried over NaOH pellets. Filtration and solvent

evaporation afforded 2,2-(ethylenedioxy)-2-phenylethanamine **249** (8.96 g, 86%), b.p. 86-88°C/5 mm Hg (lit.,[62] 156°C/30 mm Hg); δ_H (60 MHz, $CDCl_3$) 1.51 (2H, br s, NH_2), 3.90 (2H, s, CH_2), 4.00 (4H, m, OCH_2CH_2O) and 7.50 (5H, s, ArH).

O-Acetyl-*N*-[2,2-(ethylenedioxy)-2-phenylethyl]salicylamide 250. A stirred solution of the aminoketal **249** (5.0 g, 27.9 mmol) and triethylamine (2.82 g, 27.9 mmol) in THF (25 ml) was treated dropwise with a solution of 2-acetylsalicyloyl chloride [(5.54 g, 27.9 mmol) prepared by literature procedure[181] from acetylsalicylic acid] in THF (20 ml) at room temperature. The mixture was stirred for 1.5 h at r.t. and filtered. Ethyl acetate (50 ml) was added to the filtrate and the organic solution was washed with water (3 x 30 ml) and dried (anhyd. Na_2SO_4). The solvent was evaporated to afford the intermediate *O-acetyl-N-[2,2-(ethylenedioxy)-2-phenylethyl]salicylamide* **250** (9.1 g, 96%), m.p. 140-142°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 3.77 (4H, m, OCH_2CH_2O), 3.98 (2H, m, CH_2), 6,62, (1H, br s, NH) and 7.02-7.73 (9H, m, ArH); ν_{max} (KBr) 3440 (NH), 1760 (CH_3CO_2) and 1650 (N-C=O) cm^{-1}.

***N*-(Benzoylmethyl)salicylamide 251.** A stirred solution of O-acetyl-*N*-[2,2-(ethylenedioxy)-2-phenylethyl]salicylamide **250** (9.0 g, 26.4 mmol) and 10% aq. NaOH (30 ml) in THF (30 ml) was stirred at r.t. for 18 h and was made acidic with 10% HCl solution. The product was extracted with ethyl acetate (3 x 30 ml), and the combined organic extracts were washed with water (2 x 30 ml) and dried (anhyd. Na_2SO_4). The solvent was evaporated and the residue was taken up in glacial acetic acid (75 ml), and then treated with conc. H_2SO_4 (1.5 ml). The solution was stirred at r.t. for 6 h and the resulting precipitate was filtered to afford *N-(benzoylmethyl)salicylamide* **251** (5.72 g, 85%); m.p. 176-178°C (from ethanol) (Found: M^+, 255.0901. $C_{15}H_{13}NO_3$ requires *M*, 255.0895); δ_H (400 MHz, $CDCl_3$), 4.93 (2H, d, $J_{H,NH}$ 4.1 Hz, CH_2), 6.91-8.05 (10H, m, NH and ArH) and 12.13 (1H, s, OH); ν_{max} (KBr) 3700 (NH), 3400 (OH), 1700 (ArC=O) and 1635 [ArC(O)N] cm^{-1}.

Attempted cyclisation of *N*-(benzoylmethyl)salicylamide 251.[178] A stirred mixture of **251** (5.0 g, 19.6 mmol) and *p*-toluenesulphonic acid (0.18 g, 0.9 mmol) in anhydrous toluene (100 ml) was refluxed under Dean-Stark conditions for 4 d. The solvent was evaporated under reduced pressure and the crude material was found by ^{1}H NMR spectroscopy to be the substrate **251**.

2-Phenyl-1,4-benzoxazepin-5(4*H*)-one 246

(i) **Phenylacetaldehyde enol acetate 253.**[154] A stirred mixture of freshly distilled phenylacetaldehyde **252** (50 g, 0.42 mol) and potassium acetate (7.72 g, 0.74 g) in acetic anhydride (75.6 g, 0.74 mol) was refluxed at 160°C for 2 h. The cooled reaction mixture was washed, sequentially, with water (3 x 20 ml) and 5% aq. Na_2CO_3 (3 x 20 ml). The resultant oil was taken up in chloroform (50 ml), dried (anhyd. $MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was distilled *in vacuo* to afford phenylacetaldehyde enol acetate 253 (40 g, 60%), b.p. 97-99°C/0.5 mm Hg (lit.,[154] 113-115°C/ mm Hg); δ_H (60 MHz, $CDCl_3$) 2.21 (3H, s, -$COCH_3$), 6.53 (1H, d, *J* 7.2 Hz, 2-H), 7.37 (5H, s, ArH) and 8.01 (1H, d, *J* 18.0 Hz, 1-H).

(ii) **α-Bromophenylacetaldehyde dimethyl acetal 254.**[154] A stirred solution of phenylacetaldehyde enol acetate **253** (20.0 g, 0.12 mol) in carbon tetrachloride (50 ml) was cooled in an ice-bath and was treated dropwise with a solution of bromine (19.98 g, 0.12 mol) in carbon tetrachloride (50 ml). The mixture was stirred below 10°C for 1 h and then treated dropwise with 99% methanol (50 ml). After stirring for two days at room temperature, the reaction mixture was diluted with water (250 ml) and the oil was separated and dried (anhyd. Na_2SO_4). Fractional distillation of the crude material (containing small amount of Na_2SO_4) under reduced pressure afforded α-bromophenylacetaldehyde dimethyl acetal **254** (17.6 g, 60%), b.p. 112-114°C/5 mm Hg (lit.,[154] 133-135°C/10 mm Hg); δ_H (60 MHz, $CDCl_3$), 3.30 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 4.80 (2H, m, 1-H and 2-H) and 7,49 (5H, m, ArH).

(iii) **O-(2,2-dimethoxy-1-phenylethyl)salicylamide 254'**. A stirred mixture of salicylamide (3.0 g, 22.0 mmol), *α*-bromophenylacetaldehyde dimethyl acetal **254** (5.4 g, 22.0 mmol), K_2CO_3 (6.28 g, 45.5 mmol) and KI (0.06 g, 0.4 mmol) in dry acetone (55 ml) was refluxed for 12 h. The mixture was filtered and the solvent was evaporated *in vacuo*. The residue was taken up in chloroform (50 ml) and was, sequentially, washed with water (2 x 20 ml) and dried (anhyd. $MgSO_4$). The solvent was evaporated to afford *O-(2,2-dimethoxy-1-phenylethyl)salicylamide* **254'** (2.57 g, 54%), m.p. 84-86°C (Found: M^+, 301.1300. $C_{17}H_{19}NO_4$ requires *M*, 301.1314); δ_H (400 MHz, $CDCl_3$) 3.30 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 4.61 (1H, d, *J* 5.7 Hz, 1-H), 5.20 (1H, d, *J* 5.7 Hz, 2-H), 6.66 (1H, d, *J* 8.3 Hz, 3-H), 6.99 (1H, t, *J* 7.6 Hz, 5-H), 7.22 (1H, ddd, *J* 1.9 and 7.8 Hz, 4-H), 7.30-7.45 (5H, m, C_6H_5), 8.16 (1H, dd, *J* 1.8 and 7.8 Hz, 6-H) and 8.40 (2H, br s, NH_2); *m/z* 301 (M^+, 2.5%) and 75 (100%).

(iv) **2-Phenyl-1,4-benzoxazepin-5(4*H*)-one 246**.[51,53] A stirred mixture of O-(2,2-dimethoxy)-1-phenylethyl)salicylamide **254'** (2.0 g, 6.6 mmol) and *p*-toluenesulphonic acid (0.06 g, 0.3 mmol; containg 2 drops of water) in toluene (100 ml) was refluxed under Dean-Stark conditions for 12 h. The mixture was allowed to cool to afford *2-phenyl-1,4-benzoxazepin-5(4H)-one* **246** (0.88 g, 56%), m.p. 208°C (from toluene) (Found: M^+, 237.0782. $C_{15}H_{11}NO_2$ requires *M*, 237.0790); δ_H (400 MHz, DMSO-d_6) 6.67 (1H, d, $J_{H,NH}$ 5.2 Hz, 3-H), 7.13-7.79 (9H, m, ArH), 8.83 (1H, s, NH); δ_C (100 MHz, DMSO-d_6) 110.4 (C-3), 119.6 (C-9), 122,7 (C-2' and C-6'), 123.8 (C-7), 125.7 (C-5a), 126.9 (C-4'), 127.6 (C-3' and C-5'), 130.7 (C-6), 132.5 (C-1'), 133.0 (C-8), 144.6 (C-9a), 158.0 (C-2) and 166.5 (C-5); ν_{max} (KBr) 3200 (NH) and 1650 (C=O) cm^{-1}; *m/z* 237 (M^+, 92.2%) and 105 (100%).

2-(Phenacyloxy)benzamide 257.[51,53] A stirred mixture of salicylamide (15.07 g, 0.11 mol), K_2CO_3 (31.4 g, 0.23 mol), *α*-bromoacetophenone **256** (23.68 g, 0.12 mol) and KI (0.31 g, 1.87 x 10^{-1} mol) in acetone (280 ml) was refluxed for 12 h. The mixture was filtered hot and the salt was washed with acetone to ensure complete extraction of the product. The solvent was evaporated to afford 2-(phenacyloxy)benzamide **257** (24.4 g, 87%), m.p. 153-155°C (from

ethanol) (lit.,[51,53]; δ_H (60 MHz, $CDCl_3$) 5.40 (2H, s, 2-H) and 7.3-7.8 (11H, m, NH_2 and ArH).

3-Phenyl-1,4-benzoxazepin-5(4*H*)-one 258.[51,53] A stirred mixture of 2-(phenacyloxy)benzamide **257** (5.0 g, 19.6 mmol) and *p*-toluenesulphonic acid (0.17 g, 0.9 mmol) in toluene (150 ml) was refluxed under Dean-Stark conditions for 12 h. The cooled mixture was filtered to afford 3-phenyl-1,4-benzoxazepin-5(4*H*)-one **258** (3.75 g, 75%), m.p. 143°C (from ethanol) (lit.,[51,53] 142-143°C); δ_H (400 MHz, $CDCl_3$) 6.59 (1H, s, 2-H), 7.07 (1H, d, *J* 8.1 Hz, 9-H), 7.13 (1H, br s, NH), 7.23 (1H, t, *J* 8,3, 7-H), 7.36-7.45 (5H, m, C_6H_5), 7.49 (1H, ddd, *J* 1.7 and 7.7 Hz, 8-H) and 7.94 (1H, dd, *J* 1.7 and 7.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 119.9 (C-9), 124.8 (C-7), 126.2 (C-5a), 126.3 (C-2' and C-6'), 128.4 (C-3' and C-5'), 128.7 (C-4'), 129.7 (C-1'), 131.5 (C-6), 132.5 (C-9a), 133.9 (C-8), 134.4 (C-2), 160.2 (C-3) and 166.7 (C-5); ν_{max} (KBr) 3200 (NH) and 1650 (C=O) cm^{-1}; *m/z* 237 (M^+, 56.6%) and 105 (100%).

A-Ring chlorination of 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5-one and 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one derivatives.

***t*-Butylhypochlorite.**[182] A 10-14% sodium hypochlorite solution (256 ml) was placed in a round-bottomed flask equipped with a stirrer. The flask was placed in an ice-bath in the dark and the temperature was allowed to drop to 10°C. A solution of *t*-butanol (19 ml, 0.22 mol) in glacial acetic acid (12.6 ml, 0.22 mol) was added in one portion. The mixture was stirred at 10°C for 5 minutes and the aqueous layer was separated in the dark. The organic layer was washed with 10% aq. Na_2CO_3 (50 ml) and then with water (50 ml). The product was dried over $CaCl_2$, filtered to afford *t*-butylhypochlorite (17.9 g, 75%) which was stored in a cold room over $CaCl_2$ in an amber glass bottle.

7-Chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 259. A stirred solution of 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **190** (1.0 g, 4.2 mmol) in ether (15 ml) was treated dropwise with a solution of *t*-butylhypochlorite (0.68 g, 6.3 mmol) in ether (5 ml) at room

temperature in the dark. The mixture was stirred in the dark for 24 h. and the residue was purified by flash chromatography (elution with EtOAc) to afford two fractions:-

(i) starting material, and

(ii) *7-Chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-one* **259** (0.6 g, 52%), m.p. 146-148°C (from ethanol) (Found M^+, 273.0534. $C_{15}H_{12}NO_2Cl$ requires *M*, 273.0557); δ_H (400 MHz, $CDCl_3$) 3.57 (1H, ddd, *J* 5.9 and 15.5 Hz, 3-H), 3.65 (1H, dddd, *J* 3.4, 6.3 and 15.5 Hz, 3-H), 5.45 (1H, dd, *J* 3.4 and 4.7 Hz, 2-H), 7.01 (1H, d, *J* 8.7 Hz, 9-H), 7.22 (1H, br s, NHCO), 7.32-7.38 (5H, m, C_6H_5), 7.40 (1H, dd, *J* 2.8 and 8.7 Hz, 8-H) and 7.84 (1H, d, *J* 2.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.4 (C-3), 85.8 (C-2), 123.9 (C-9), 126.2 (C-2' and C-6'), 126.5 (C-5a), 128.7 (C-4'), 128.8 (C-3' and C-5'), 129.0 (C-7), 130.7 (C-6), 133.4 (C-8), 138.5 (C-1'), 153.3 (C-9a) and 169.7 (C-5); ν_{max} (KBr) 3410 (NH) and 1660 (C=O) cm^{-1}; *m/z* 273 (M^+, 5.5%) and 119 (100%).

7-Chloro-2-(4-fluorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 260. The experimental procedure employed for the synthesis of 7-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **259** was followed using 2-(4-fluorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **200** (0.35 g, 1.4 mmol) and *t*-BuOCl (0.22 g, 2.0 mmol) in ether (20 ml). Work-up and flash chromatography (elution with EtOAc) afforded two fractions:-

(i) starting material, and

(ii) *7-Chloro-2-(4-fluorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4H)-one* **260** (0.20 g, 49%), m.p. 146°C (from ethanol) (Found: M^+, 291.0447. $C_{15}H_{11}NO_2Cl_2F$ requires *M*, 291.0462); δ_H (400 MHz, $CDCl_3$) 3.51 (1H, ddd, *J* 5.8 and 15.5 Hz, 3-H), 3.64 (1H, dddd, *J* 3.4, 6.3 and 15.5 Hz, 3-H), 5.41 (1H, dd, *J* 3.4 and 6.0 Hz, 2-H), 6.94 (1H, br s, NHCO), 6.99 (1H, d, *J* 8.6 Hz, 9-H), 7.08 (2H, m, *J* 2.0 and 8.9 Hz, 3'-H and 5'-H), 7.35 (2H, m, *J* 2.0 and 5.9 Hz, 2'-H and 6'-H), 7.41 (1H, dd, *J* 2.8 and 8.7 Hz, 8-H) and 7.84 (1H, dd, *J* 1.3 and 2.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.3 (C-3), 85.0 (C-2), 115.8 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 123.9 (C-7), 126.9 (C-5a), 128.1 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 129.3 (C-7), 130.7 (C-6), 133.4 (C-8), 134.4 ($^4J_{CF}$ 3.0 Hz, C-1'), 152.9 (C-9a), 162.8 ($^1J_{CF}$ 247.5 Hz, C-4') and 169.3 (C-5); ν_{max} (KBr) 3200

(NH) and 1660 (C=O) cm^{-1}; *m/z* 291 (M^+, 0.3%) and 137 (100%).

7-Chloro-2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 261. The experimental procedure employed for the synthesis of 7-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **259** was followed using 2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **202** (0.3 g, 1.1 mmol) and *t*-BuOCl (0.18 g, 1.7 mmol) in ether (20 ml). Work-up and flash chromatography (elution with EtOAc) afforded two fractions:-

(i) starting material, and

(ii) *7-chloro-2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4H)-one* **261** (0.158 g, 47%), m.p. 168-170°C (from ethanol) (Found: M^+, 307.0177. $C_{15}H_{11}NO_2Cl_2$ requires *M*, 307.0166); δ_H (400 MHz, $CDCl_3$) 3.51 (1H, ddd, *J* 5.8 and 15.6 Hz, 3-H), 3.65 (1H, dddd, *J* 3.4, 6.3 and 15.5 Hz, 3-H), 5.41 (1H, dd, *J* 3.4 and 5.9 Hz, 2-H), 6.92 (1H, br s, NHCO), 6.99 (1H, dd, *J* 8.6 Hz, 9-H), 7.31 (2H, ddd, *J* 2.0 and 8.5 Hz, 2'-H and 6'-H), 7.37 (2H, ddd, *J* 2.1 and 8.6 Hz, 3'-H and 5'-H), 7.44 (1H, dd, *J* 2.0 and 12.8 Hz, 8-H) and 7.83 (1H, dd, *J* 1.5 and 2.5 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.2 (C-3), 85.0 (C-2), 123.9 (C-9), 126.9 (C-5a), 127.6 (C-2' and C-6'), 129.0 (C-3' and C-5'), 129.4 (C-7), 130.8 (C-6), 133.4 (C-8), 134.6 (C-4'), 137.0 (C-1'), 152.9 (C-9a) and 169.3 (C-5); ν_{max} (KBr) 3200 (NH) and 1640 (C=O) cm^{-1}; *m/z* 307 (M^+, 25%) and 153 (100%).

2-(4-Bromophenyl)-7-chloro-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one 262. The experimental procedure employed for the synthesis of 7-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **259** was followed using 2-(4-bromophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **204** (0.4 g, 1.3 mmol) and *t*-BuOCl (0.24 g, 2.5 mmol) in ether (20 ml). Work-up and flash chromatography (elution with EtOAc) afforded two fractions:-

(i) starting material, and

(ii) *2-(4-Bromophenyl)-7-chloro-2,3-dihydro-1,4-benzoxazepin-5(4H)-one* **262** (0.21 g, 48%), m.p. 192-194°C (from ethanol) (Found: M^+, 350.9625. $C_{15}H_{11}NO_2BrCl$ requires *M*, 350.9663); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, ddd, *J* 5.8 and 15.5 Hz, 3-H), 3.65 (1H, dddd, *J* 3.4, 6.3 and

15.5 Hz, 3-H), 5.39 (1H, *J* 3.3 and 5.9 Hz, 2-H), 6.99 (1H, d, *J* 8.7 Hz, 9-H), 7.19 (1H, br s, NHCO), 7.25 (2H, m, *J* 2.0 and 8.7 Hz, 2'-H and 6'-H), 7.41 (1H, dd, *J* 2.7 and 8.6 Hz, 8-H), 7.51 (2H, m, *J* 2.0 and 8.7 Hz, 3'-H and 5'-H) and 7.82 (1H, d, *J* 2.7 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.1 (C-3), 85.0 (C-2), 122.7 (C-5a), 123.9 (C-9), 126.9 (C-7), 127.9 (C-2' and C-6'), 129.4 (C-4'), 139.7 (C-6), 131.9 (C-3' and C-5'), 133.4 (C-8), 137.5 (C-1'), 152.9 (C-9a) and 169.4 (C-5); ν_{max} (KBr) 3450 (NH) and 1640 (C=O) cm^{-1}; *m/z* 351 (M^+, 3.3%) and 63 (100%).

7,9-Dichloro-8-methoxy-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one 263. The experimental procedure employed for the synthesis of 7-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **259** was followed using 8-methoxy-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **206** (0.4 g, 1.5 mmol) and *t*-BuOCl (0.27 g, 2.5 mmol) in ether (20 ml). Work-up and flash chromatography (elution with EtOAc) afforded two fractions:-

(i) starting material, and

(ii) *7,9-dichloro-8-methoxy-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-one* **263** (0.38 g, 59%), m.p. 206°C (from ethanol) (Found: M^+, 306.0317. $C_{16}H_{12}N_2OCl_2$ requires *M*, 306.0326); δ_H (400 MHz, $CDCl_3$) 3.55 (2H, m, 3-H), 4.90 (1H, m, 2-H), 5.12 (1H, s, NH), 7.30-7.40 (5H, m, C_6H_5), 7.45 (1H, d, *J* 2.6 Hz, 8-H) and 7.75 (1H, d, *J* 2.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 46.7 (C-3), 64.4 (C-2), 123.0 (C-9), 123.1 (C-7), 126.5 (C-2' and C-6'), 128.5 (C-4'), 129.0 (C-3' and C-5'), 130.8 (C-6), 132.2 (C-8), 140.0 (C-1'), 141.2 (C-9a) and 170.1 (C-5); ν_{max} (KBr) 3400 (N^1-H), 3300 (N^4-H) and 1620 (C=O) cm^{-1}; *m/z* 337 (M^+, 4.5%) and 119 (100%).

7,9-Dichloro-2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one 264. The experimental procedure employed for the synthesis of 7-chloro-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **259** was followed using 2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one **264** (0.5 g, 2.1 mmol) and *t*-BuOCl (0.342 g, 3.2 mmol) in ether (25 ml). Work-up and flash chromatography [elution with EtOAc-hexane (6:4)] afforded two fractions, *viz.*,

(i) starting material, and

(ii) *7,9-dichloro-2-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one* **264** (0.38 g, 59%), m.p. 206°C (from ethanol) (Found: M^+, 306.0317. $C_{16}H_{12}N_2OCl_2$ requires *M*, 306.0326); δ_H (400 MHz, $CDCl_3$) 3.55 (2H, m, 3-H), 4.90 (1H, m, 2-H), 5.12 (1H, s, NH), 7.30-7.40 (5H, m, C_6H_5), 7.45 (1H, d, *J* 2.6 Hz, 8-H) and 7.75 (1H, d, *J* 2.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 4.67 (C-3), 6.44 (C-2), 123.0 (C-9), 123.1 (C-7), 126.5 (C-2' and C-6'), 128.5 (C-4'), 129.0 (C-3' and C-5'), 130.8 (C-6), 132.2 (C-8), 140.0 (C-1'), 141.2 (C-9a) and 170.1 (C-5); ν_{max} (KBr) 3400 (N^1-H), 3200 (N^4-H) and 1620 (C=O) cm^{-1}; *m/z* 72.7%) and 248 (100%).

Note:

Treatment of the 8-halogeno-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ones (halogen = F, Cl, Br) with *t*-BuOCl in ether led to the recovery of the starting material after 72 hours.

2,3-Dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione 265.[105] A stirred mixture of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **190** (2.0 g, 8.4 mmol) and P_2S_5 (3.71 g, 16.7 mmol) in dry pyridine (20 ml) was refluxed for 1.5h. The cooled mixture was poured into water (20 ml) and was acidified with 10% hydrochloric acid. The residue was filtered and was purified by flash chromatography [elution with EtOAc-hexane (3:2)] to afford 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** (1.38 g, 64%), m.p. 170°C (from ethanol) (lit.,[105] 174-175°C); δ_H (400 MHz, $CDCl_3$) 3.57 (1H, ddd, *J* 6.0 and 14.8 Hz, 3-H), 3.76 (1H, dddd, *J* 4.2, 6.3 and 14.8 Hz, 3-H), 5.54 (1H, dd, *J* 4.2 and 6.0 Hz, 2-H), 7.0 (1H, dd, *J* 1.0 and 8.05 Hz, 9-H), 7.21 (1H, ddd, *J* 1.1 and 7.6 Hz, 7-H), 7.32-7.39 (5H, m, C_6H_5), 7.43 (1H, dddd, *J* 0.5, 1.7 and 7.7 Hz, 8-H), 8.02 (1H, dd, *J* 1.7 and 7.8 Hz, 6-H) and 9.39 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 49.6 (C-3), 87.3 (C-2), 122.7 (C-9), 124.6 (C-7), 126.3 (C-2' and C-6'), 128.8 C-4'), 128.8 (C-3' and C-5'), 132.8 (C-5a and C-6), 133.3 (C-8), 138.5 (C-1'), 151.6 (C-9a) and 201 (C-5); ν_{max} (KBr) 3200 (NH) cm^{-1}.

8-Chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione 266.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thione

265 was followed, using a mixture of 8-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **194** (0.50 g, 1.83 mmol) and P_2S_6 (0.81 g, 3.66 mmol) in pyridine (10 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *8-chloro-2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4H)-thione* **266** (0.53 g, 50%), m.p. 260°C (from ethanol) (Found: M^+, 289.0329. $C_{15}H_{12}NOSCl$ requires *M*, 289.0309); δ_H (400 MHz, $CDCl_3$) 3.59 (1H, ddd, *J* 6.0 and 14.9 Hz, 3-H), 3.79 (1H, dddd, *J* 4.1, 6.4 and 14.9 Hz, 3-H), 5.55 (1H, dd, *J* 4.1 and 6.0 Hz, 2-H), 7.02 (1H, d, *J* 2.0 Hz, 9-H), 7.19 (1H, dd, *J* 2.0 and 8.5 Hz, 7-H), 7.34-7.43 (5H, m, C_6H_5), 7.99 (1H, d, *J* 8.5 Hz, 6-H) and 9.07 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 49.6 (C-3), 87.5 (C-2), 122.9 (C-9), 124.9 (C-7), 126.2 (C-2' and C-6'), 128.8 (C-3' and C-5'), 129.0 (C-4'), 131.0 (C-5a), 134.0 (C-6), 138.0 (C-8), 138.9 (C-1'), 152.2 (C-9a) and 199.8 (C-5); ν_{max} (KBr) 3205 (NH) cm^{-1}.

2,3-Dihydro-8-methoxy-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione 267.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thione **265** was followed, using a mixture of 2,3-dihydro-8-methoxy-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **198** (2.0 g, 7.4 mmol) and P_2S_6 (3.30 g, 14.8 mmol) in pyridine (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded 2,3-dihydro-8-methoxy-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **267** (1.48 g, 70%), m.p. 154°C from (ethanol) (lit.,[105] 158-159°C); δ_H (400 MHz, $CDCl_3$) 3.59 (1H, ddd, *J* 6.1 and 14.8 Hz, 3-H), 3.76 (1H, dddd, *J* 4.0, 6.3 and 14.9 Hz, 3-H), 3.79 (3H, s, OCH_3), 5.54 (1H, dd, *J* 4.0 and 6.1 Hz, 2-H), 6.51 (1H, d, *J* 2.5 Hz, 9-H), 6.74 (1H, dd, *J* 2.5 and 8.8 Hz, 7-H), 7.31-7.38 (5H, m, C_6H_5), 8.03 (1H, d, *J* 8.8 Hz, 6-H) and 9.25 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 49.8 (C-3), 55.6 (OCH_3), 87.5 (C-2), 107.2 (C-9), 110.8 (C-7), 124.8 (C-5a), 126.2 (C-2' and C-6'), 128,7 (C-3' and C-5'), 128.7 (C-4'), 134.8 (C-6), 138.5 (C-1'), 153.5 (C-9a), 164.0 (C-8) and 200.1 (C-5); ν_{max} (KBr) 3210 (NH) cm^{-1}.

2-(4-Chlorophenyl)-2,3-dihydro-1,4-benzoxazepine-5(4*H*)-thione 268.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thione

265 was followed, using a mixture of 2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **202** (1.0 g, 3.7 mmol) and P_2S_5 (1.62 g, 7.3 mmol) in pyridine (20 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *2-(4-chlorophenyl)-2,3-dihydro-1,4-benzoxazepine-5(4H)-thione* **268** (1.21 g, 57%), m.p. 197-199°C (from ethanol) (Found: M^+, 289.0320. $C_{16}H_{12}NOSCl$ requires *M*, 289.0309); δ_H (400 MHz, $CDCl_3$) 3.52 (1H, ddd, *J* 5.8 and 14.8 Hz, 3-H), 3.78 (1H, dddd, *J* 4.3, 6.3 and 14.8 Hz, 3-H), 5.50 (1H, t, *J* 4.8 Hz, 2-H), 6.99 (1H, dd, *J* 1.0 and 8.1 Hz, 9-H), 7.24 (1H, ddd, *J* 1.2 and 7.6 Hz, 7-H), 7.31-7.37 (4H, m, C_6H_4Cl), 7.44 (1H, ddd, *J* 1.8 and 7.8Hz, 8-H), 8.00 (1H, dd, *J* 1.8 and 7.8 Hz, 6-H) and 9.25 (1H, br s, NHCO); δ_C (100 MHz, $CDCl_3$) 49.4 (C-3), 86.6 (C-2),122.6 (C-9), 124.9 (C-7), 127.7 (C-2' and C-6'), 129.0 (C-3' and C-5'), 132.7 (C-5a), 132.8 (C-6), 133.5 (C-8), 134.7 (C-4'), 136.9 (C-1'), 151.4 (C-9a) and 200.9 (C-5); ν_{max} (KBr) 3200 (NH) cm^{-1}.

2-(4-Fluorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione 269.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 2-(4-fluoro-phenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **214** (0.32 g, 1.3 mmol) and P_2S_5 (0.56 g, 2.5 mmol) in pyridine (10 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *2-(4-fluorophenyl)-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine-5-thione* **269** (0.19 g, 53%), m.p. 188°C (from ethanol) (Found: M^+, 272.0762. $C_{16}H_{13}N_2SF$ requires *M*, 272.0784); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, ddd, *J* 6.6 and 14.3 Hz, 3-H), 3.70 (1H, dddd, *J* 3.6, 6.6 and 14.3 Hz, 3-H), 4.02 (1H, br s. NH), 4.93 (1H, *J* 3.6 and 6.0 Hz, 2-H), 6.68 (1H, d, *J* 6.7 Hz, 9-H), 6.96 (1H, t, *J* 7.6 Hz, 8-H), 7.05 (2H, t, *J* 8.6 Hz, 3'-H and 5'-H), 7.30 (2H, ddd, *J* 1.5 and 7.7 Hz, 2'-H and 6'-H), 8.10(1H, dd, *J* 1.4 and 7.9 Hz, 6-H) and 9.02 (1H, br s, NHCO); δ_C (100 MHz, $CDCl_3$) 50.4 (C-3), 66.4 (C-2), 115.9 ($^2J_{CF}$ 22.1 Hz, C-3' and C-5'), 120.3 (C-9), 121.1 (C-7), 128.4 ($^3J_{CF}$ 8.1 Hz, C-2' and C-6'), 128.4 (C-5a), 133.2 (C-6), 134.3 (C-8), 138.0 ($^4J_{CF}$ 3.0 Hz, C-1'), 142.5 (C-9a), 162.6 (C-4') and 202.3 (C-5); ν_{max} (KBr) 3300 (N^1-H) and 3200 (N^4-H) cm^{-1}.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione 270.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 2-(4-chloro-phenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **216** (0.41 g, 1.5 mmol) and P_2S_5 (0.67 g, 3.0 mmol) in pyridine (10 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *2-(4-chlorophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione* **270** (0.30 g, 69%), m.p. 196-198°C (from ethanol) (Found: M^+, 288.0488. $C_{15}H_{13}N_2SCl$ requires *M*, 288.0488); δ_H (400 MHz, $CDCl_3$) 3.49 (1H, ddd, *J* 6.4 and 14.4 Hz, 3-H), 3.71 (1H, dddd, *J* 3.7, 6.4 and 14.4 Hz, 3-H), 4.01 (1H, br s, NH), 4.92 (1H, dd, *J* 3.6 and 6.1 Hz, 2-H), 6.68 (1H, dd, *J* 0.8 and 8.0 Hz, 9-H), 6.97 (1H, quintet, *J* 1.1 and 7.6 Hz, 7-H), 7.27-7.40 (5H, m, 8-H and C_6H_4Cl), 8.10 (1H, dd, *J* 1.6 and 7.9 Hz, 6-H) and 8.80 (1H, br s, NHCS); 50.2 (C-3), 66.5 (C-2), 120.3 (C-9), 121.3 (C-7), 128.1 (C-3' and C-5'), 128.5 (C-5a), 129.1 (C-2' and C-6'), 133.2 (C-6), 134.2 (C-4'), 134.3 (C-8), 140.7 (C-1'), 142.4 (C-9a) and 202.4 (C-5); ν_{max} (KBr) 3350 (N^1-H) and 3195 (N^4-H) cm^{-1}.

2-(4-Bromophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione 271.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 2-(4-bromophenyl)-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **218** (0.56 g, 1.77 mmol) and P_2S_5 (0.78 g, 3.53 mmol) in pyridine (10 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *2-(4-bromophenyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-5-thione* **271** (0.35 g, 62%), m.p. 212°C (from ethanol) (Found: M^+, 331.9977. $C_{15}H_{13}N_2SBr$ requires *M*, 331.9984); δ_H (400 MHz, $CDCl_3$) 3.33 (1H, ddd, *J* 6.2 and 14.2 Hz, 3-H), 3.56 (1H, dddd, *J* 3.5, 6.4 and 14.2 Hz, 3-H), 4.52 (1H, br s, NH), 4.77 (1H, dd, *J* 3.5 and 6.1 Hz, 2-H), 6.60 (1H, dd, *J* 0.7 and 8.1 Hz, 9-H), 6.76 (1H, quintet, *J* 1.1 and 7.6 Hz, 7-H), 7.10-7.18 (3H, m, 2'-H, 5'-H and 8-H), 7.34 (2H, d, *J* 7.6 Hz, 3'-H and 5'-H), 7.94 (dd, *J* 1.5 and 7.9 Hz, 6-H) and 9.55 (1H, br s, NHCO); δ_C (100 MHz, $CDCl_3$) 4.96 (C-3), 65.9 C(-2), 119.8 (C-9), 120.0 (C-7), 121.4 (C-4'), 128.0 (C-5a), 128.4 (C-2' and C-6'), 131.4 (C-3' and C-5'), 132.4 (C-6), 133.8 (C-8), 141.6

(C-1'), 142.6 (C-9a) and 201.5 (C-5); ν_{max} (KBr) 3400 (N^1-H) and 3200 (N^4-H) cm^{-1}.

2,3-Dihydro-2-phenyl-1,4-benzothiazepine-5(4*H*)-thione 272.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one **224** (1.50 g, 5.9 mmol) and P_2S_5 (2.61 g, 11.68 mmol) in pyridine (25 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *2,3-dihydro-2-phenyl-1,4-benzothiazepine-5(4*H*)-thione* **272** (1.02 g, 64%), m.p. 166-168°C (from ethanol) (Found: M^+, 278.0480. $C_{15}H_{13}NS_2$ requires *M*, 271.0489); δ_H (400 MHz, $CDCl_3$) 3.49 (1H, dddd, *J* 7.5, 9.4 and 14.5 Hz, 3-H), 3.67 (1H, dddd, *J* 5.1, 6.6 and 14.5 Hz, 3-H), 4.73 (1H, dd, *J* 5.1 and 9.4 Hz, 2-H), 7.26-7.34 (5H, m, C_6H_5), 7.41-7.50 (2H, m, 7-H and 9-H), 7.56 (1H, dd, *J* 3.7 and 7.2 Hz, 8-H), 7.98 (1H, dd, *J* 1.8 and 7.3 Hz, 6-H) and 9.37 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 51.1 (C-3), 56.8 (C-2), 127.1 (C-2' and C-6'), 127.5 (C-5a), 128.3 (C-4'), 128.9 (C-3' and C-5'), 129.3 (C-9), 131.5 (C-7), 131.7 (C-8), 134.4 (C-6), 140.6 (C-1'), 144.4 (C-9a) and 202.6 (C-5); ν_{max} (KBr) 3230 (NH) cm^{-1}.

2,3-Dihydro-2-phenyl-1,5-benzothiazepine-4(5*H*)-thione 273.[105] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **225** (2.50 g, 9.8 mmol) and P_2S_5 (4.35 g, 19.6 mmol) in pyridine (25 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded 2,3-dihydro-2-phenyl-1,5-benzothiazepine-4(5*H*)-thione **273** (3.2 g, 62%), m.p. 211°C (from ethanol) (lit.,[48] 203-205°C); δ_H (400 MHz, $CDCl_3$) 3.20 (1H, t, *J* 12.1 Hz, 3-H), 3.37 (1H, dddd, *J* 1.1, 5.1 and 12.1 Hz, 3-H), 4.97 (1H, dd, *J* 5.1 and 12.0 Hz, 2-H), 7.21 (1H, dd, *J* 1.2 and 7.9 Hz, 9-H), 7.25-7.32 (5H, m, 7-H and C_6H_4), 7.45 (1H, ddd, *J* 1.5 and 7.7 Hz, 8-H), 7.58 (1H, dd, *J* 1.3 and 7.7 Hz, 6-H) and 9.94 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 49.6 (C-3), 56.0 (C-2), 122.8 (C-9), 126.3 (C-2' and C-6'), 127.4 (C-5a), 127.9 (C-7), 128.0 (C-4'), 128.8 (C-3' and C-5'), 130.1 (C-6), 136.0 (C-8), 141.5 (C-1'), 143.6 (C-9a) and 203.9 (C-4); ν_{max} (KBr) 3200 (NH) cm^{-1}.

3-Phenyl-1,4-benzoxazepine-5(4*H*)-thione 274.[106] The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzoxazepine-5(4*H*)-thione **265** was followed, using a mixture of 3-phenyl-1,4-benzoxazepin-5(4*H*)-thione **258** (2.0 g, 8.4 mmol) and P_2S_5 (3.73 g, 16.8 mmol) in dry pyridine (35 ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:2)] afforded *3-phenyl-1,4-benzothiazepine-5(4H)-thione* **274** (1.60 g, 75%), m.p. 200°C (from ethanol) (Found: M^+, 253.0578. $C_{15}H_{11}NOS$ requires *M*, 253.0562); δ_H (400 MHz, $CDCl_3$) 6.77 (1H, s, 3-H), 7.00 (1H, dd, *J* 1.0 and 8.1 Hz, 9-H), 7.20 (1H, ddd, *J* 1.1 and 7.6 Hz, 7-H), 7.36-7.43 (5H, m, C_6H_5), 7.47 (1H, dddd, *J* 0.7, 1.7 and 7.7 Hz, 8-H), 8.22 (1H, dd, *J* 1.7 and 8.0 Hz, 6-H) and 9.11 (1H, br s, NHCS); δ_C (100 MHz, $CDCl_3$) 119.3 (C-9), 124.2 (C-7), 125.8 (C-2' and C-6'), 128.0 (C-3' and (C-5'), 128.6 (C-4'), 131.1 (C-5a), 131.3 (C-3), 131.5 (C-1'), 133.4 (C-6), 134.2 (C-8), 137.7 (C-2), 157.8 (C-9a) and 198.1 (C-5); ν_{max} (KBr) 3210 (NH) cm^{-1}.

1,3-Dihydro-4-phenyl-2*H*-1,5-benzodiazepine-2-thione 276.[30,33] *tert*-Amyl alcohol (37.0 g, 0.42 mol) was added dropwise to a stirred suspension of sodium hydride (17.61 g, 0.42 mol) in dry benzene (255 ml) and the mixture was refluxed until the evolution of hydrogen ceased. The cooled mixture was filtered into a clean round-bottomed flask and after cooling in an ice bath a solution of acetophenone (25.0 g, 0.21 mol) and carbon disulphide (31.84 g, 0.42 mol) was added dropwise with stirring. The mixture was then stirred at room temperature for 12 h; then water (100 ml) was added and the benzene layer was separated and extracted with water (5 x 50 ml). The combined aqueous layers were washed with ether (250 ml) and were acidified with 10% aq. H_2SO_4. The solid material was extracted into ether (3 x 50 ml), washed with water and dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* and the solid material was washed with hexane to afford 3,3-dimercapto-1-phenyl-2-propen-1-one **275** (21.4 g, 52%), m.p. 60-61°C (lit.,[33] 63°C), which was used in the next step without further purification.

A stirred mixture of *o*-phenylenediamine **34** (2.75 g, 25.5 mmol) and 3,3-dimercapto-1-phenyl-

2-propen-1-one **275** (5.0 g, 25.5 mmol) in xylene (130 ml) was refluxed for 2.5 h and then allowed to cool. The crystalline material was washed with hexane, dried and washed with water to afford 1,3-dihydro-4-phenyl-2*H*-1,5-benzodiazepine-2-thione **276** (3.87 g, 60%), m.p. 218-220°C (EtOAc) (lit.,[30] 222°C); δ_H (400 MHz, DMSO-d_6) 3.29 (2H, s, 3-H), 7.28-7.60 (8H, m, ArH), 8.21 (1H, dd, *J* 2.1 and 7.9 Hz, 6-H) and 12.54 (1H, s, NHCS); δ_C (100 MHz, $CDCl_3$) 47.7 (C-3), 122.1 (C-9), 125.7 (C-7), 125.9 (C-5a), 125.9 (C-2' and C-6'), 127.7 (C-4'), 131.2 (C-3' and C-5'), 136.4 (C-1') and 140.6 (C-9a).

2,3-Dihydro-4-methylthio-2-phenyl-1,5-benzothiazepine 277.[49] To a stirred suspension of NaH (0.93 g, 3.86 mmol) in dry THF (30 ml) at room temperature was added dropwise a solution of 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one **273** (1.0 g, 3.86 mmol) in THF (5 ml). After stirring at room temperature for 10 minutes, methyl iodide (1.1 g, 7.72 mmol) was added dropwise. The mixture was then stirred at room temperature for 1.5 h and the solvent was evaporated under reduced pressure. The residue was taken up in chloroform (30 ml) and the organic solution was washed with water (2 x 10 ml) and dried (anhyd. $MgSO_4$). The solvent was evaporated to afford 2,3-dihydro-4-methylthio-2-phenyl-1,5-benzothiazepine **277** (0.98 g, 93%), m.p. 104°C (from ethanol) (lit.,[49] 103-105°C); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, SCH_3), 2.68 (1H, dd, *J* 5.3 and 13.2 Hz, 3-H), 2.99 (1H, dd, *J* 12.0 and 13.2 Hz, 3-H), 4.96 (1H, dd, *J* 5.2 and 12.0 Hz, 2-H) and 7.08-7.99 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.4 (SCH_3), 42.7 (C-3), 59.6 (C-2), 122.9 (C-5a), 124.7 (C-9), 124.9 (C-7), 126.2 (C-2' and C-6'), 127.8 (C-4'), 128.9 (C-3' and C-5'), 129.8 (C-6), 135.1 (C-8), 143.8 (C-1'), 152.0 (C-9a) and 171.0 (C-4).

5-Methylthio-3-phenyl-1,4-benzoxazepine 278.[49] The experimental procedure employed for the synthesis of 2,3-dihydro-4-methylthio-2-phenyl-1,4-benzothiazepine **277** was followed, using 3-phenyl-1,4-benzoxazepine-5(4*H*)-thione **274** (2.0 g, 7.9 mmol), NaH (0.19 g, 7.9 mmol) and CH_3I (2.24 g, 15.8 mmol) in dry THF (30 ml). Work-up afforded *5-methylthio-3-phenyl-1,4-benzoxazepine* **278** (1.33 g, 63%), m.p. 78-80°C (ethanol) (Found: M^+, 267.0705. $C_{16}H_{13}NOS$ requires *M*, 267.0718); δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, SCH_3), 6.57 (1H, s, 2-H) and 7.15-

7.65 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (SCH_3), 120.4 (C-9-), 124.9 (C-7), 125.5 (C-2' and C-6'), 133.4 (C-8), 133.7 (C-2), 135.8 (C-1'), 139.1 (C-9a), 161.0 (C-3) and 167.6 (C-5).

2-Methylthio-4-phenyl-3*H*-1,5-benzodiazepine 279.[49] The experimental procedure employed for the synthesis of 2,3-dihydro-4-methylthio-2-phenyl-1,4-benzothiazepine **277** was followed, using 2,3-dihydro-4-phenyl-1*H*-1,5-benzothiazepine **273** (3.0 g, 11.9 mmol), NaH (0.28 g, 11.9 mmol) and CH_3I (3.38 g, 23.8 mmol) in dry THF (30 ml). Work-up afforded 2-methylthio-4-phenyl-3*H*-1,5-benzodiazepine **279** (2.38 g, 75%), m.p. 86-87°C (petroleum ether) (lit.,[31] 87-88°C); δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, SCH_3), 3.39 (2H, s, 2-H), 7.20-8.20 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.8 (SCH_3), 39.5 (C-3), 124.6 (C-6), 125.4 (C-8), 127.7 (C-4'), 128.0 (C-2' and C-6'), 128.6 (C-3' and C-5'), 128.7 (C-7), 130.6 (C-9), 137.2 (C-5a), 140.0 (C-1'), 140.6 (C-9a), 154.0 (C-4) and 156.5 (C-2).

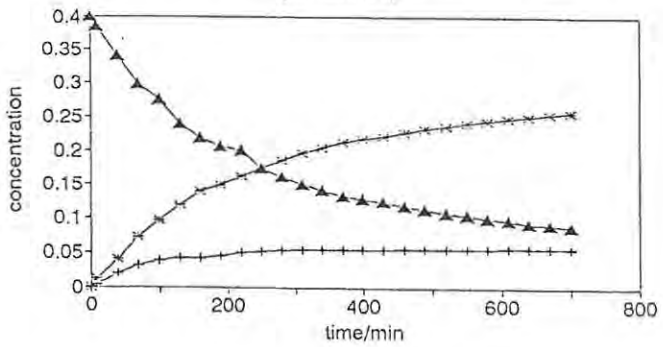
Kinetic Study of the Schmidt reaction of selected flavanones

General Procedure

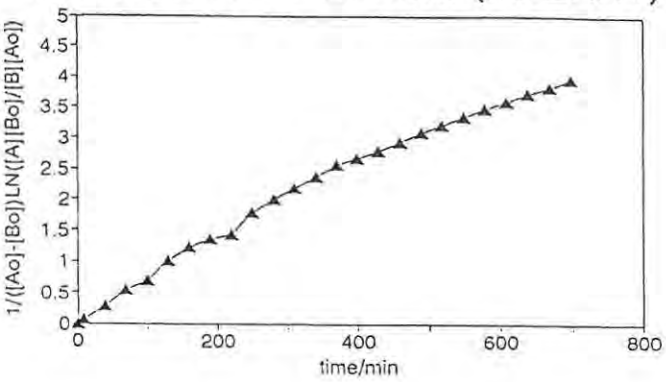
The kinetic measurements were carried out as follows. The flavanone (0.2 mmol) was weighed into an NMR tube and sufficient CF_3CO_2D (to provide the required concentrations of substrate (A); see A_0 in each of the figures below) was weighed into the NMR tube, which was then immediately sealed with a septum. The 400 MHz ^1H NMR spectrum of the substrate was obtained at 303 ± 0.1 K. Thereafter, TMS-N_3 (0.042 ml, 0.3 mmol) was added by means of a syringe, the mixture was shaken (time, $t = t_0$) and the first spectrum of the reaction mixture was obtained as quickly as possible. Subsequent spectra were acquired at 30 minute intervals over *ca.* 12 hours. The total acquisition time for each 32 scan spectrum was 2m 6s. The concentration changes were obtained from the integrals for the methylene proton signals of the corresponding species (i.e. flavanone substrate, and the amide and tetrazole products). All runs were carried out in duplicate and the signals were calibrated relative to the TFA signal at δ 11.3 ppm. The experimental data and corresponding plots for the various kinetic runs are summarised below.

FORMATION OF E AND F FROM A

(MP2KN1)



2nd ORDER FUNCTION (MP2KN1)



KINETIC DATA FOR COMPOUND 189 (MP2KN

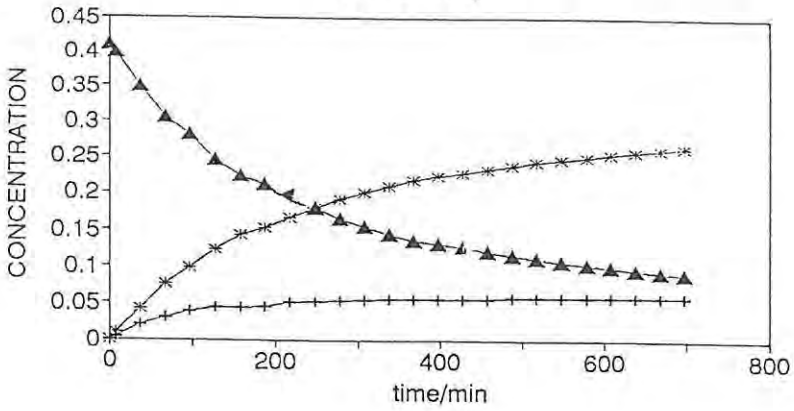
Time	[Ao]= %A	0.4 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.6 Func n=2
0.0	100.00	0.400	0.00	0.000	0.00	0.000	0.600	-0.001
9.4	96.00	0.384	0.80	0.003	3.20	0.013	0.584	0.068
39.4	85.01	0.340	5.09	0.020	9.90	0.040	0.540	0.285
69.4	74.39	0.298	7.67	0.031	17.94	0.072	0.497	0.542
99.4	68.75	0.275	9.42	0.038	23.83	0.095	0.475	0.704
129.4	59.68	0.239	10.57	0.042	29.75	0.119	0.439	1.014
159.4	54.56	0.218	10.60	0.042	34.84	0.139	0.418	1.224
189.4	51.52	0.206	11.05	0.044	37.43	0.150	0.406	1.363
219.4	50.22	0.201	12.48	0.050	40.53	0.162	0.401	1.426
249.4	43.61	0.174	12.76	0.051	43.63	0.175	0.374	1.791
279.4	40.25	0.161	13.14	0.053	46.61	0.186	0.361	2.009
309.4	37.66	0.151	13.43	0.054	48.91	0.196	0.351	2.196
339.4	35.36	0.141	13.55	0.054	51.09	0.204	0.341	2.378
369.4	33.15	0.133	13.58	0.054	53.27	0.213	0.333	2.569
399.4	32.03	0.128	13.62	0.054	54.35	0.217	0.328	2.673
429.4	30.91	0.124	13.65	0.055	55.44	0.222	0.324	2.782
459.4	29.50	0.118	13.73	0.055	56.77	0.227	0.318	2.928
489.4	28.15	0.113	13.82	0.055	58.03	0.232	0.313	3.076
519.4	27.04	0.108	13.84	0.055	59.12	0.236	0.308	3.206
549.4	25.96	0.104	13.89	0.056	60.15	0.241	0.304	3.339
579.4	24.94	0.100	13.92	0.056	61.14	0.245	0.300	3.472
609.4	24.05	0.096	13.94	0.056	62.01	0.248	0.296	3.594
639.4	23.20	0.093	13.96	0.056	62.84	0.251	0.293	3.716
669.4	22.46	0.090	13.97	0.056	63.57	0.254	0.290	3.827
699.4	21.69	0.087	13.98	0.056	64.33	0.257	0.287	3.948

Regression Output:

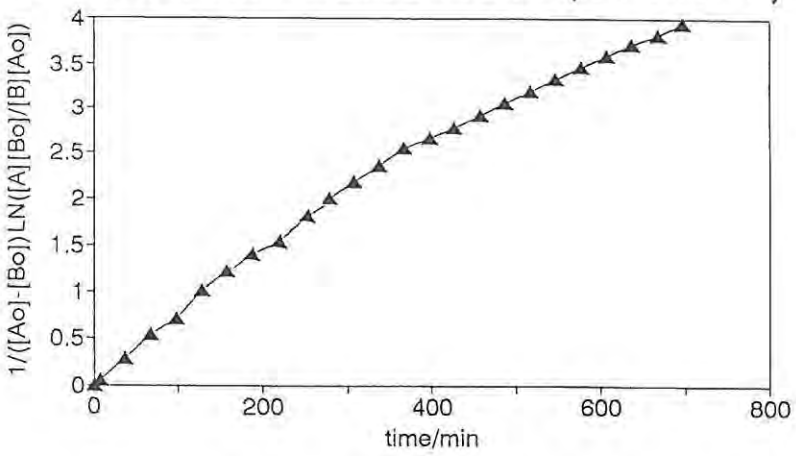
Constant	0.23543
Std Err of Y Est	0.156439
R Squared	0.985111
No. of Observations	25
Degrees of Freedom	23
X Coefficient(s)	0.00568
Std Err of Coef.	0.000146

FORMATION OF E AND F FROM A

(MP2KN2)



2ndORDER FUNCTION (MP2KN2)

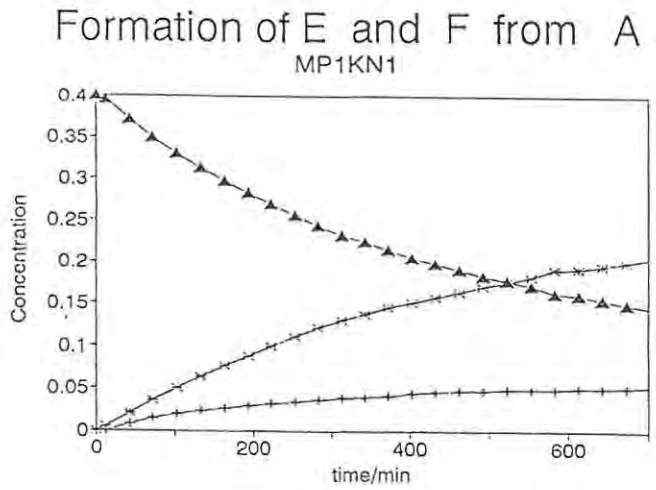


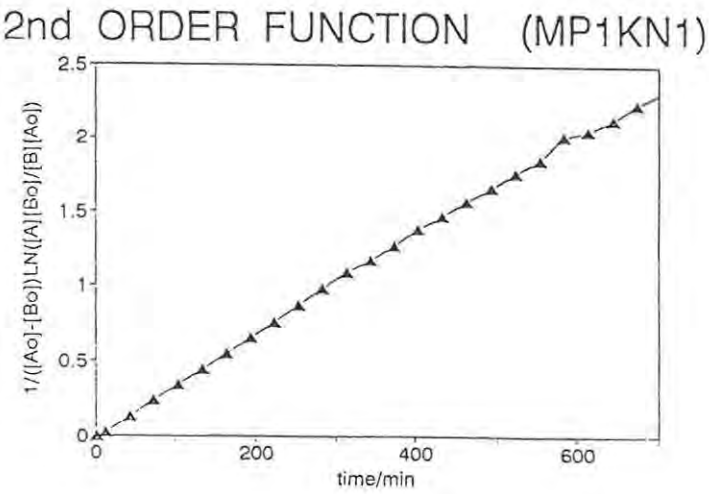
KINETIC DATA FOR COMPOUNL 189 (MP2KN2)

Time	[Ao]= %A	0.41 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.606 Func n=2
0.00	100.00	0.410	0.00	0.000	0.00	0.000	0.606	0.000
7.60	97.00	0.398	0.69	0.003	2.31	0.009	0.594	0.051
37.60	85.01	0.349	5.09	0.021	9.90	0.041	0.545	0.283
67.60	74.40	0.305	7.30	0.030	18.30	0.075	0.501	0.538
97.60	68.75	0.282	9.42	0.039	23.83	0.098	0.478	0.700
127.60	59.68	0.245	10.57	0.043	29.75	0.122	0.441	1.008
157.60	54.56	0.224	10.60	0.043	34.84	0.143	0.420	1.217
187.60	51.52	0.211	11.05	0.045	37.43	0.153	0.407	1.356
217.60	50.22	0.206	12.48	0.051	40.53	0.166	0.402	1.419
247.60	43.61	0.179	12.76	0.052	43.63	0.179	0.375	1.783
277.60	40.25	0.165	13.14	0.054	46.61	0.191	0.361	2.001
307.60	37.66	0.154	13.43	0.055	48.91	0.201	0.350	2.188
337.60	35.36	0.145	13.55	0.056	51.09	0.209	0.341	2.370
367.60	33.15	0.136	13.58	0.056	53.27	0.218	0.332	2.562
397.60	32.03	0.131	13.62	0.056	54.35	0.223	0.327	2.666
427.60	30.91	0.127	13.65	0.056	55.44	0.227	0.323	2.776
457.60	29.50	0.121	13.73	0.056	56.77	0.233	0.317	2.922
487.60	28.15	0.115	13.82	0.057	58.03	0.238	0.311	3.071
517.60	27.04	0.111	13.84	0.057	59.12	0.242	0.307	3.201
547.60	25.96	0.106	13.89	0.057	60.15	0.247	0.302	3.335
577.60	24.94	0.102	13.92	0.057	61.14	0.251	0.298	3.468
607.60	24.05	0.099	13.94	0.057	62.01	0.254	0.295	3.591
637.60	23.20	0.095	13.96	0.057	62.84	0.258	0.291	3.714
667.60	22.46	0.092	13.97	0.057	63.57	0.261	0.288	3.826
697.60	21.69	0.089	13.98	0.057	64.33	0.264	0.285	3.947

Regression Output:

Constant	0.236006
Std Err of Y Est	0.155575
R Squared	0.985287
No. of Observations	25
Degrees of Freedom	23
X Coefficient(s)	0.00567
Std Err of Coef.	0.000145





KINETIC DATA FOR COMPOUND 145 (Run1)

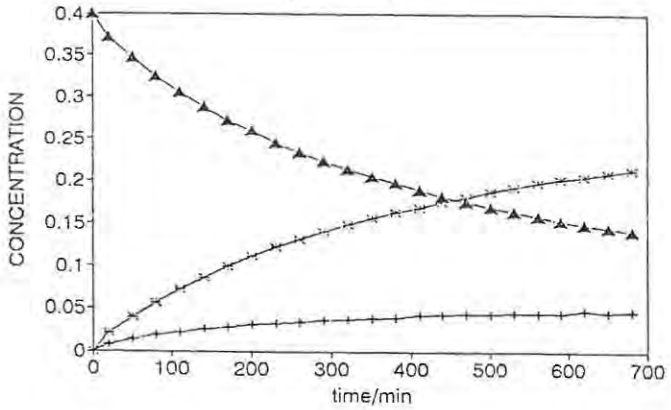
Time	[Ao]= %A	0.4 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.6 Func n=2
0.00	100.00	0.400	0.00	0.000	0.00	0.000	0.600	0.000
12.82	98.75	0.395	0.00	0.000	1.25	0.005	0.595	0.021
42.82	92.97	0.372	1.79	0.007	5.24	0.021	0.572	0.124
72.82	87.43	0.350	3.71	0.015	8.86	0.035	0.550	0.234
102.82	82.65	0.331	4.84	0.019	12.51	0.050	0.531	0.338
132.82	78.33	0.313	5.84	0.023	15.83	0.063	0.513	0.441
162.82	74.29	0.297	6.69	0.027	19.02	0.076	0.497	0.546
192.82	70.60	0.282	7.41	0.030	21.99	0.088	0.482	0.650
222.82	67.26	0.269	8.06	0.032	24.68	0.099	0.469	0.752
252.82	63.83	0.255	8.57	0.034	27.60	0.110	0.455	0.865
282.82	60.85	0.243	9.01	0.036	30.14	0.121	0.443	0.972
312.82	57.88	0.232	9.77	0.039	32.35	0.129	0.432	1.086
342.82	55.92	0.224	9.99	0.040	34.09	0.136	0.424	1.166
372.82	53.70	0.215	10.26	0.041	36.04	0.144	0.415	1.263
402.82	51.21	0.205	11.05	0.044	37.74	0.151	0.405	1.379
432.82	49.37	0.197	11.36	0.045	39.27	0.157	0.397	1.470
462.82	47.50	0.190	11.68	0.047	40.82	0.163	0.390	1.568
492.82	45.82	0.183	11.74	0.047	42.44	0.170	0.383	1.661
522.82	44.14	0.177	12.07	0.048	43.79	0.175	0.377	1.760
552.82	42.71	0.171	12.09	0.048	45.20	0.181	0.371	1.848
582.82	40.30	0.161	12.16	0.049	47.54	0.190	0.361	2.007
612.82	39.75	0.159	12.49	0.050	47.76	0.191	0.359	2.045
642.82	38.63	0.155	12.51	0.050	48.86	0.195	0.355	2.125
672.82	37.20	0.149	12.84	0.051	49.96	0.200	0.349	2.232
702.82	36.17	0.145	12.90	0.052	50.93	0.204	0.345	2.313
732.82	35.27	0.141	12.95	0.052	51.78	0.207	0.341	2.387

Regression Output:

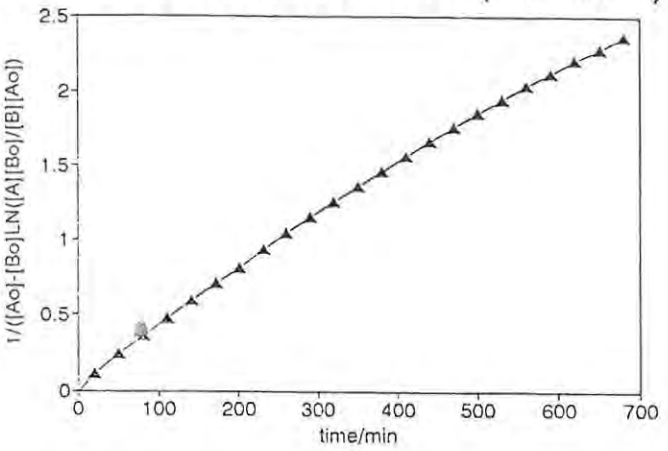
Constant	9.35E-05
Std Err of Y Est	0.020096
R Squared	0.999235
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0034
Std Err of Coef.	1.99E-05

Formation of E AND F FROM A

(MP1KN3)



2nd ORDER FUNCTION (MP1KN3)



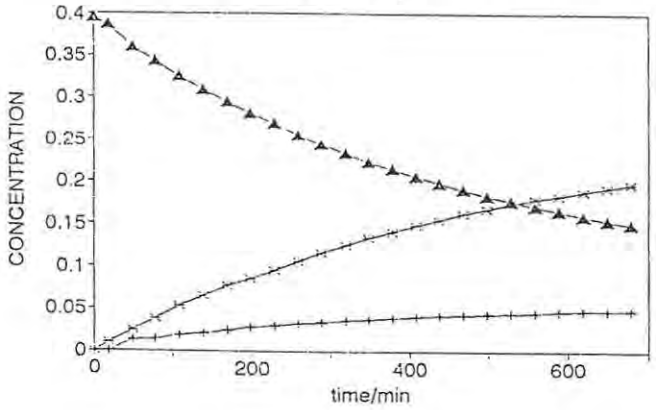
KINETIC DATA FOR COMPOUND 145 (Run 2)

Time	[Ao]= %A	0.3998 [A]	%E	[E]	%F	[F]	[BO]= [B]	0.5997 Func n=2
0.00	100.00	0.400	0.00	0.000	0.00	0.000	0.598	-0.014
20.62	92.84	0.371	1.76	0.007	5.40	0.022	0.569	0.112
50.62	86.61	0.346	3.35	0.013	9.86	0.039	0.544	0.236
80.62	81.16	0.324	4.71	0.019	14.13	0.056	0.523	0.357
110.62	76.34	0.305	5.65	0.023	18.01	0.072	0.503	0.475
140.62	71.98	0.288	6.46	0.026	21.56	0.086	0.486	0.593
170.62	68.02	0.272	7.14	0.029	24.84	0.099	0.470	0.710
200.62	65.01	0.260	7.71	0.031	27.85	0.111	0.458	0.807
230.62	61.38	0.245	8.19	0.033	30.43	0.122	0.444	0.933
260.62	58.53	0.234	8.67	0.035	32.80	0.131	0.432	1.041
290.62	55.89	0.223	9.08	0.036	35.03	0.140	0.422	1.148
320.62	53.45	0.214	9.37	0.037	37.18	0.149	0.412	1.254
350.62	51.32	0.205	9.66	0.039	39.02	0.156	0.403	1.353
380.62	49.22	0.197	9.98	0.040	40.80	0.163	0.395	1.457
410.62	47.2	0.189	10.66	0.043	42.14	0.168	0.387	1.563
440.62	45.33	0.181	10.81	0.043	43.86	0.175	0.379	1.668
470.62	43.77	0.175	11.09	0.044	45.14	0.180	0.373	1.760
500.62	42.23	0.169	11.13	0.044	46.64	0.186	0.367	1.856
530.62	40.87	0.163	11.15	0.045	47.95	0.192	0.362	1.945
560.62	39.55	0.158	11.29	0.045	49.16	0.197	0.356	2.036
590.62	38.41	0.154	11.32	0.045	50.27	0.201	0.352	2.118
620.62	37.23	0.149	11.38	0.048	51.31	0.205	0.347	2.207
650.62	36.26	0.145	11.48	0.046	52.26	0.209	0.343	2.282
680.62	35.24	0.141	11.64	0.047	53.12	0.212	0.339	2.365

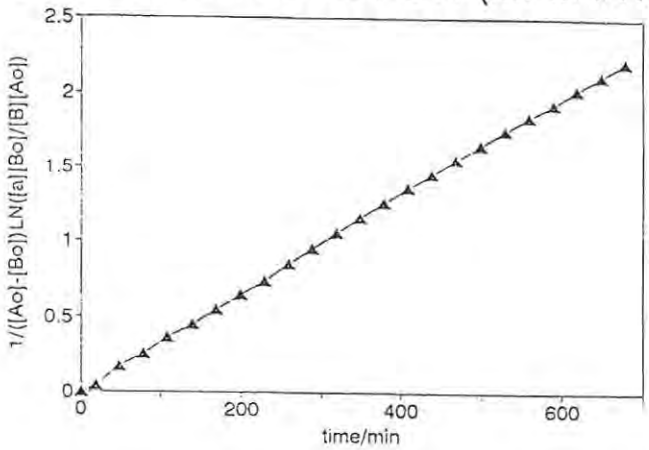
Regression Output:

Constant	0.095501
Std Err of Y Est	0.04744
R Squared	0.996015
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0035
Std Err of Coef.	4.68E-05

FORMATION OF E AND F FROM A
(MP9KN1)



2nd ORDER FUNCTION (MP9KN1)



KINETIC DATA FOR COMPOUND 147 (MP9KN1)

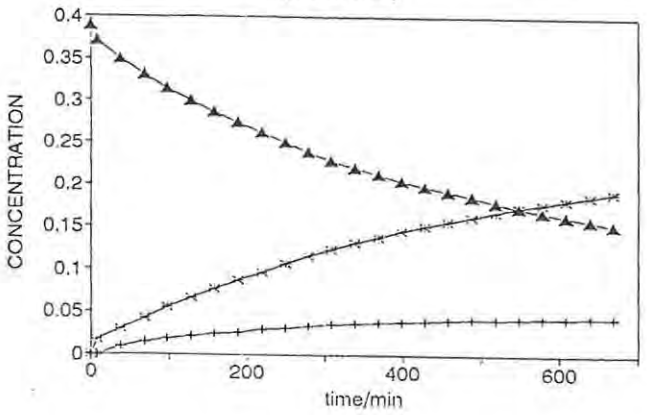
Time	[A]= %A	0.395 [A]	%E	[E]	%F	F	[Bo]= [B]	0.592 Func n=2
0.00	100.00	0.395	0.00	0.000	0.00	0.000	0.592	0.000
18.50	97.77	0.386	0.00	0.000	2.23	0.009	0.583	0.038
48.50	90.89	0.359	3.01	0.012	6.10	0.024	0.556	0.167
78.50	86.87	0.343	3.41	0.013	9.72	0.038	0.540	0.249
108.50	82.20	0.325	4.46	0.018	13.34	0.053	0.522	0.353
138.50	78.25	0.309	5.29	0.021	16.46	0.065	0.506	0.449
168.50	74.51	0.294	6.00	0.024	19.49	0.077	0.491	0.547
198.50	71.09	0.281	7.21	0.028	21.70	0.086	0.478	0.644
228.50	68.18	0.269	7.52	0.030	24.30	0.096	0.466	0.733
258.50	64.73	0.256	8.35	0.033	26.92	0.106	0.453	0.846
288.50	61.82	0.244	8.81	0.035	29.37	0.116	0.441	0.949
318.50	59.05	0.233	9.27	0.037	31.68	0.125	0.430	1.054
348.50	56.51	0.223	9.62	0.038	33.87	0.134	0.420	1.157
378.50	54.22	0.214	10.02	0.040	35.76	0.141	0.411	1.257
408.50	52.00	0.205	10.39	0.041	37.61	0.149	0.402	1.360
438.50	50.07	0.198	10.64	0.042	39.29	0.155	0.395	1.455
468.50	48.10	0.190	10.88	0.043	41.02	0.162	0.387	1.557
498.50	46.42	0.183	11.14	0.044	42.44	0.168	0.380	1.650
528.50	44.75	0.177	11.35	0.045	43.90	0.173	0.374	1.747
558.50	43.26	0.171	11.60	0.046	45.14	0.178	0.368	1.838
588.50	41.86	0.165	11.73	0.046	46.41	0.183	0.362	1.929
618.50	40.44	0.160	11.99	0.047	47.57	0.188	0.357	2.025
648.50	39.11	0.154	12.08	0.048	48.81	0.193	0.351	2.119
678.50	37.82	0.149	12.27	0.048	49.91	0.197	0.346	2.215

Regression Output:

Constant	-0.00385
Std Err of Y Est	0.011436
R Squared	0.999742
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0033
Std Err of Coef.	1.13E-05

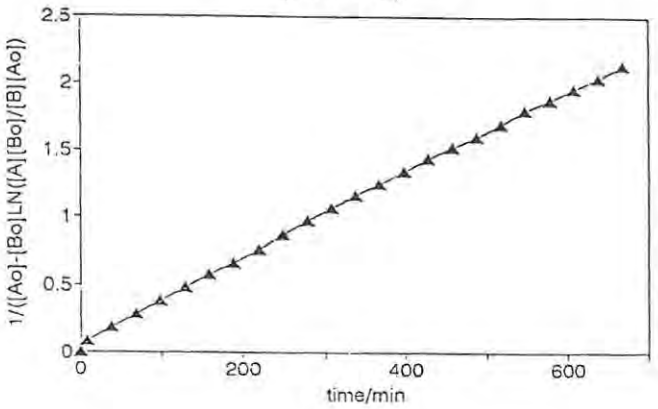
FORMATION OF E AND F FROM A

(MP9KN2)



2nd ORDER FUNCTION (MP9KN2)

(MP9KN2)



KINETIC DATA FOR COMPOUND 147 (MP9KN2)

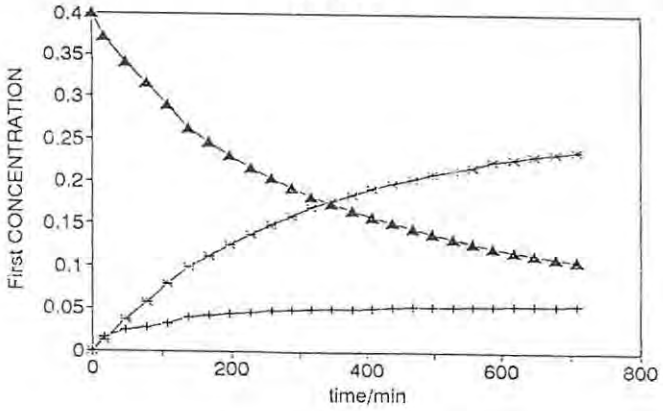
time	[Ao]= %F	0.388 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.582 Func n=2
0.00	100.00	0.388	0.00	0.000	0.00	0.000	0.582	0.000
8.60	95.60	0.371	0.00	0.000	4.40	0.017	0.565	0.078
38.60	90.23	0.350	2.29	0.009	7.48	0.029	0.544	0.183
68.60	85.38	0.331	3.68	0.014	10.94	0.042	0.525	0.286
98.60	81.09	0.315	4.70	0.018	14.21	0.055	0.509	0.386
128.60	77.30	0.300	5.56	0.022	17.14	0.067	0.494	0.481
158.60	73.89	0.287	6.17	0.024	19.94	0.077	0.481	0.574
188.60	70.83	0.275	6.69	0.026	22.48	0.087	0.469	0.663
218.60	67.60	0.262	7.48	0.029	24.92	0.097	0.456	0.764
248.60	64.42	0.250	8.09	0.031	27.49	0.107	0.444	0.871
278.60	61.51	0.239	8.75	0.034	29.74	0.115	0.433	0.977
308.60	59.08	0.229	9.03	0.035	31.89	0.124	0.423	1.071
338.60	56.75	0.220	9.41	0.037	33.84	0.131	0.414	1.167
368.60	54.74	0.212	9.75	0.038	35.51	0.138	0.406	1.255
398.60	52.76	0.205	10.03	0.039	37.21	0.144	0.399	1.346
428.60	50.88	0.197	10.34	0.040	38.78	0.150	0.391	1.438
458.60	49.32	0.191	10.51	0.041	40.17	0.156	0.385	1.518
488.60	47.81	0.186	10.69	0.041	41.50	0.161	0.380	1.600
518.60	46.12	0.179	10.80	0.042	43.08	0.167	0.373	1.695
548.60	44.43	0.172	10.95	0.042	44.62	0.173	0.366	1.796
578.60	43.19	0.168	11.11	0.043	45.70	0.177	0.362	1.874
608.60	41.81	0.162	11.18	0.043	47.01	0.182	0.356	1.965
638.60	40.62	0.158	11.35	0.044	48.03	0.186	0.352	2.046
668.60	39.33	0.153	11.42	0.044	49.25	0.191	0.347	2.139

Regression Output:

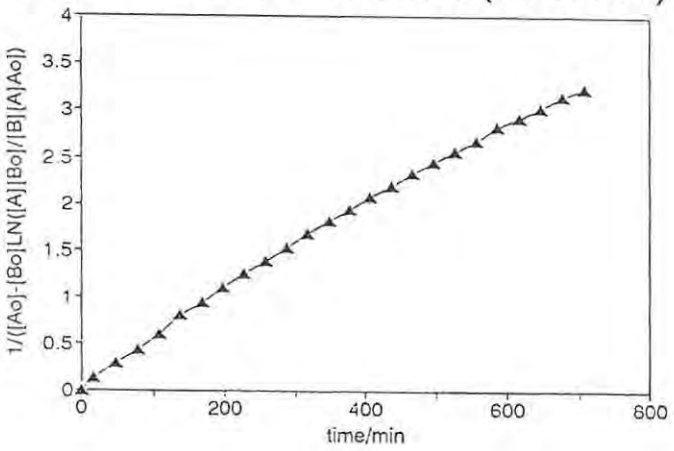
Constant	0.071242
Std Err of Y Est	0.024497
R Squared	0.998691
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0031
Std Err of Coef.	2.42E-05

FORMATION OF E AND F FROM A

MP5KN1



2nd ORDER FUNCTION (MP5KN1)



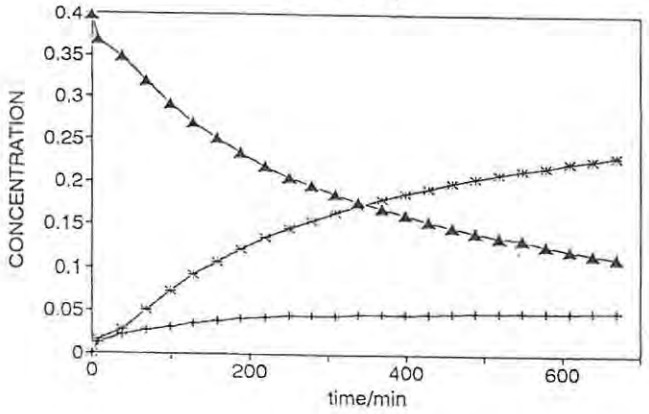
KINETIC DATA FOR COMPOUND 148 (MP5KN1)

Time	[Ao]= %A	0.40 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.599 Func n=2
0.00	100.00	0.400	0.00	0.000	0.00	0.000	0.599	0.000
17.87	92.83	0.371	4.12	0.016	3.05	0.012	0.570	0.127
47.87	85.04	0.340	5.99	0.024	8.97	0.036	0.539	0.285
77.87	78.86	0.315	6.79	0.027	14.35	0.057	0.514	0.429
107.87	72.37	0.289	7.94	0.032	19.69	0.079	0.488	0.600
137.87	65.57	0.262	9.83	0.039	24.60	0.098	0.461	0.808
167.87	61.66	0.247	10.41	0.042	27.93	0.112	0.446	0.944
197.87	57.60	0.230	11.07	0.044	31.33	0.125	0.429	1.099
227.87	54.06	0.216	11.54	0.046	34.40	0.138	0.415	1.250
257.87	50.92	0.204	11.85	0.047	37.23	0.149	0.403	1.396
287.87	48.19	0.193	12.13	0.049	39.68	0.159	0.392	1.535
317.87	45.52	0.182	12.31	0.049	42.17	0.169	0.381	1.682
347.87	43.31	0.173	12.48	0.050	44.21	0.177	0.372	1.814
377.87	41.39	0.166	12.58	0.050	46.03	0.184	0.365	1.937
407.87	39.37	0.157	12.74	0.051	47.89	0.192	0.356	2.076
437.87	37.78	0.151	13.03	0.052	49.35	0.197	0.350	2.193
467.87	36.12	0.144	13.18	0.053	50.85	0.203	0.343	2.323
497.87	34.54	0.138	13.18	0.053	52.24	0.209	0.337	2.454
527.87	33.27	0.133	13.30	0.053	53.43	0.214	0.332	2.566
557.87	32.07	0.128	13.38	0.054	54.55	0.218	0.327	2.677
587.87	30.58	0.122	13.44	0.054	55.98	0.224	0.321	2.824
617.87	29.63	0.119	13.56	0.054	56.81	0.227	0.318	2.923
647.87	28.67	0.115	13.65	0.055	57.68	0.231	0.314	3.027
677.87	27.60	0.110	13.72	0.055	58.68	0.235	0.309	3.149
707.87	26.87	0.107	13.81	0.055	59.32	0.237	0.306	3.236

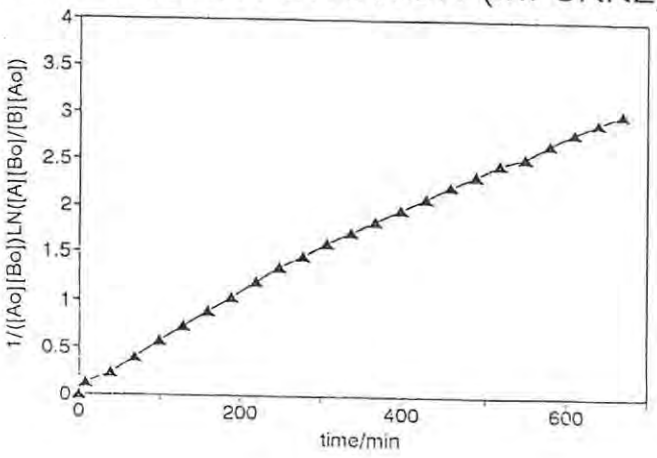
Regression Output:

Constant	0.144692
Std Err of Y Est	0.074602
R Squared	0.994734
No. of Observations	25
Degrees of Freedom	23
X Coefficient(s)	0.0046
Std Err of Coef.	6.92E-05

FORMATION OF E AND F FROM A
(MP5KN2)



2nd ORDER FUNCTION (MP5KN2)

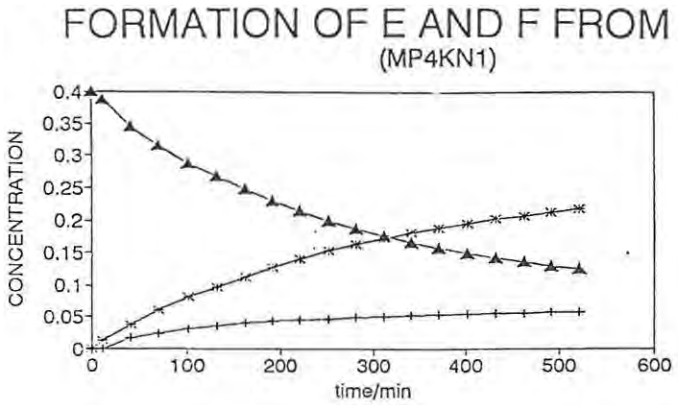


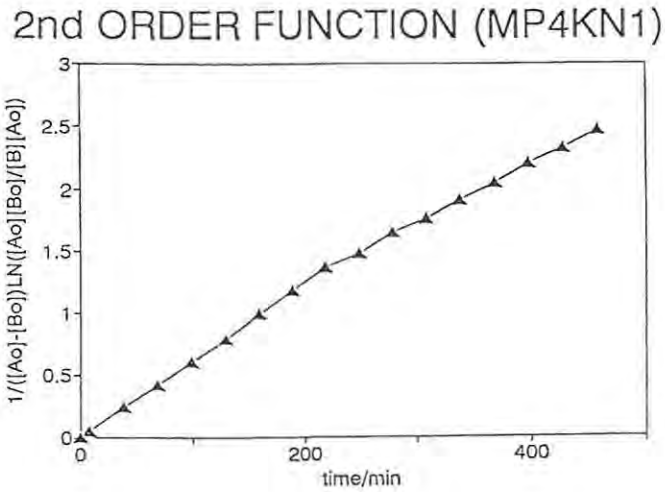
KINETIC DATA FOR COMPOUND 148 (MP5KN2)

Time	[Ao]= %A	0.397 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.596 Func n=2
0.00	100.00	0.397	0.00	0.000	0.00	0.000	0.596	-0.004
8.86	92.83	0.369	3.07	0.012	4.10	0.016	0.567	0.124
38.86	87.58	0.348	5.71	0.023	7.12	0.028	0.546	0.228
68.86	80.13	0.318	6.91	0.027	12.96	0.051	0.517	0.395
98.86	73.42	0.291	7.90	0.031	18.69	0.074	0.490	0.568
128.86	67.96	0.270	8.94	0.035	23.10	0.092	0.468	0.729
158.86	63.15	0.251	9.85	0.039	27.00	0.107	0.449	0.889
188.86	59.03	0.234	10.51	0.042	30.46	0.121	0.433	1.042
218.86	55.14	0.219	10.98	0.044	33.88	0.135	0.417	1.202
248.86	51.89	0.206	11.46	0.045	36.65	0.146	0.405	1.349
278.86	49.38	0.196	11.52	0.046	39.10	0.155	0.395	1.473
308.86	46.87	0.186	11.59	0.046	41.54	0.165	0.385	1.606
338.86	44.86	0.178	11.66	0.046	43.48	0.173	0.377	1.721
368.86	42.85	0.170	11.72	0.047	45.43	0.180	0.369	1.844
398.86	40.91	0.162	11.86	0.047	47.23	0.188	0.361	1.971
428.86	39.11	0.155	12.06	0.048	48.83	0.194	0.354	2.096
458.86	37.35	0.148	12.19	0.048	50.46	0.200	0.347	2.228
488.86	35.80	0.142	12.36	0.049	51.84	0.206	0.341	2.351
518.86	34.36	0.136	12.48	0.050	53.16	0.211	0.335	2.472
548.86	33.66	0.134	12.56	0.050	54.38	0.216	0.332	2.533
578.86	32.04	0.127	12.65	0.050	55.31	0.220	0.326	2.683
608.86	30.68	0.122	12.72	0.050	56.60	0.225	0.320	2.817
638.86	29.63	0.118	12.83	0.051	57.54	0.228	0.316	2.926
668.86	28.63	0.114	12.86	0.051	58.51	0.232	0.312	3.035

Regression Output:

Constant	0.143922
Std Err of Y Est	0.069075
R Squared	0.994876
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0045
Std Err of Coef.	6.84E-05





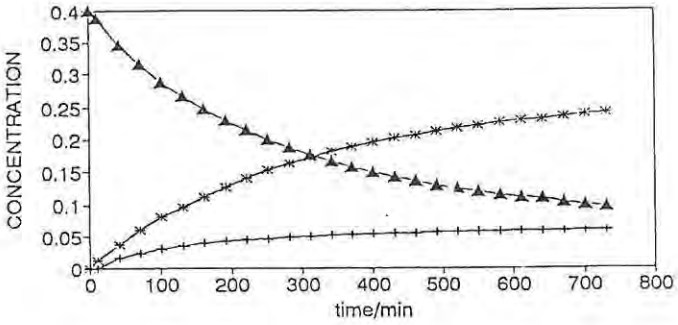
KINETIC DATA FOR COMPOUND 149 (MP4KN1)

	[Ao]=	0.395					[BO]=	0.593
Time	%A	[A]	%E	[E]	%F	[F]	[B]	Func n=2
0.00	100.00	0.395	0.00	0.000	0.00	0.000	0.593	0.000
8.54	97.42	0.385	0.00	0.000	2.58	0.010	0.583	0.044
38.54	87.40	0.345	3.81	0.015	8.79	0.035	0.543	0.237
68.54	79.55	0.314	5.79	0.023	14.66	0.058	0.512	0.416
98.54	72.62	0.287	8.05	0.032	19.33	0.076	0.485	0.599
128.54	66.66	0.263	9.40	0.037	23.94	0.095	0.461	0.780
158.54	60.70	0.240	10.70	0.042	28.60	0.113	0.438	0.988
188.54	56.03	0.221	11.68	0.046	32.29	0.128	0.419	1.175
218.54	51.95	0.205	12.45	0.049	35.60	0.141	0.403	1.359
248.54	49.68	0.196	12.55	0.050	37.77	0.149	0.394	1.471
278.54	46.41	0.183	13.05	0.052	40.54	0.160	0.381	1.647
308.54	44.68	0.176	13.09	0.052	42.23	0.167	0.374	1.747
338.54	42.28	0.167	13.46	0.053	44.26	0.175	0.365	1.897
368.54	40.18	0.159	13.69	0.054	46.13	0.182	0.357	2.038
398.54	38.02	0.150	13.90	0.055	48.08	0.190	0.348	2.195
428.54	36.47	0.144	14.15	0.056	49.38	0.195	0.342	2.315
458.54	34.80	0.137	14.38	0.057	50.82	0.201	0.335	2.454

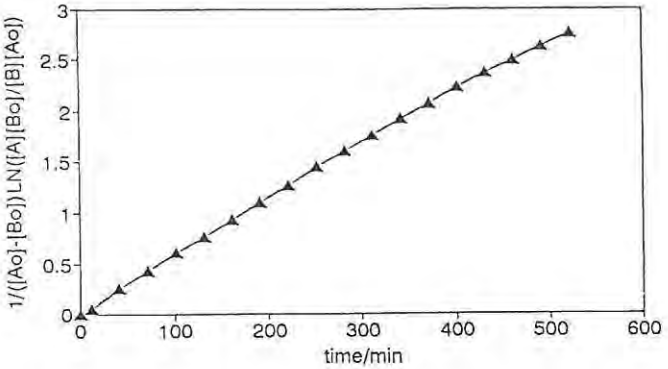
Regression Output:

Constant	0.072175
Std Err of Y Est	0.062878
R Squared	0.994318
No. of Observations	17
Degrees of Freedom	15
X Coefficient(s)	0.00539
Std Err of Coef.	0.000105

FORMATION OF E AND F FROM A
(MP4KN2)



2nd ORDER FUNCTION (MP4KN2)



KINETIC DATA FOR COMPOUND 149 (MP4KN2)

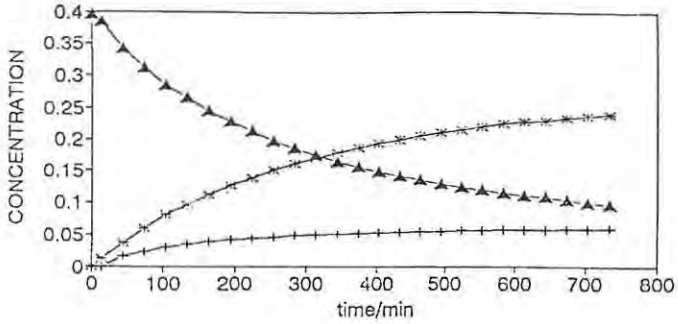
Time	[Ao]= %A	0.4 A	%E	[E]	%F	[F]	[Bo]= [A]	0.599 Func n=2
0.00	100.00	0.400	0.00	0.000	0.00	0.000	0.599	0.000
11.86	97.08	0.388	0.00	0.000	2.92	0.012	0.587	0.050
41.86	86.37	0.345	4.24	0.017	9.39	0.038	0.544	0.257
71.86	78.84	0.315	5.92	0.024	15.24	0.061	0.514	0.429
101.86	71.80	0.287	7.78	0.031	20.42	0.082	0.486	0.616
131.86	67.00	0.268	8.90	0.036	24.10	0.096	0.467	0.762
161.86	61.79	0.247	10.09	0.040	28.13	0.113	0.446	0.939
191.86	57.53	0.230	10.67	0.043	31.80	0.127	0.429	1.102
221.86	53.61	0.214	11.26	0.045	35.13	0.141	0.413	1.270
251.86	49.88	0.200	11.79	0.047	38.33	0.153	0.399	1.447
281.86	46.94	0.188	12.29	0.049	40.77	0.163	0.387	1.602
311.86	44.31	0.177	12.67	0.051	43.04	0.172	0.376	1.753
341.86	41.53	0.166	13.06	0.052	45.41	0.182	0.365	1.928
371.86	39.43	0.158	13.37	0.053	47.20	0.189	0.357	2.072
401.86	37.41	0.150	13.66	0.055	48.93	0.196	0.349	2.221
431.86	35.61	0.142	13.86	0.055	50.53	0.202	0.341	2.364
461.86	34.08	0.136	14.07	0.056	51.85	0.207	0.335	2.494
491.86	32.56	0.130	14.18	0.057	53.26	0.213	0.329	2.631
521.86	31.24	0.125	14.33	0.057	54.43	0.218	0.324	2.758

Regression Output:

Constant	0.05302
Std Err of Y Est	0.041617
R Squared	0.99796
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	0.00535
Std Err of Coef.	5.86E-05

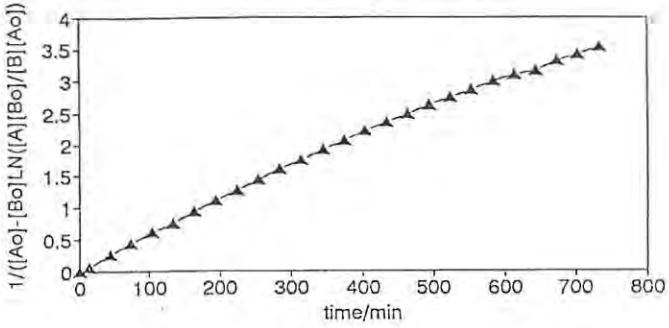
FORMATION OF E AND F FROM A

(MP8KN1)



2nd ORDER FUNCTION

(MP8KN1)



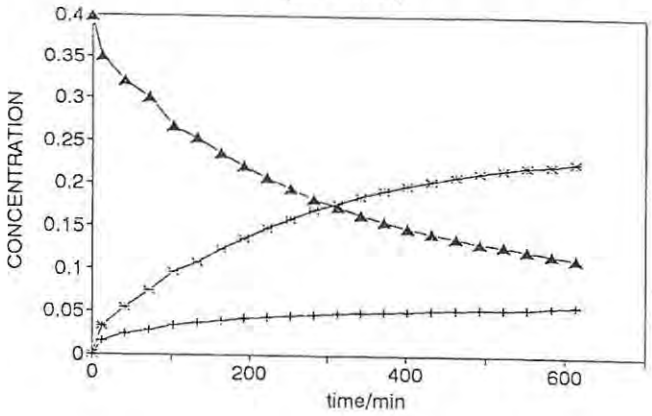
KINETIC DATA FOR COMPOUND 151 (MP8KN1)

	[Ao]=	0.396					[Bo]=	0.6
Time	%A	[A]	%E	[E]	%F	[F]	[B]	Func n=2
0.00	100.00	0.396	0.00	0.000	0.00	0.000	0.600	0.0000
13.99	97.08	0.384	0.00	0.000	2.92	0.012	0.588	0.0499
43.99	86.37	0.342	4.24	0.017	9.39	0.037	0.546	0.2562
73.99	78.84	0.312	5.92	0.023	15.24	0.060	0.516	0.4281
103.99	71.80	0.284	7.78	0.031	20.42	0.081	0.488	0.6144
133.99	67.00	0.265	8.90	0.035	24.10	0.095	0.469	0.7590
163.99	61.79	0.245	10.09	0.040	28.13	0.111	0.449	0.9354
193.99	57.53	0.228	10.67	0.042	31.80	0.126	0.432	1.0977
223.99	53.61	0.212	11.26	0.045	35.13	0.139	0.416	1.2642
253.99	49.88	0.198	11.79	0.047	38.33	0.152	0.402	1.4406
283.99	46.94	0.186	12.29	0.049	40.77	0.161	0.390	1.5942
313.99	44.31	0.175	12.67	0.050	43.04	0.170	0.379	1.7441
343.99	41.53	0.164	13.06	0.052	45.41	0.180	0.368	1.9174
373.99	39.43	0.156	13.37	0.053	47.20	0.187	0.360	2.0599
403.99	37.41	0.148	13.66	0.054	48.93	0.194	0.352	2.2076
433.99	35.61	0.141	13.86	0.055	50.53	0.200	0.345	2.3490
493.99	32.56	0.129	14.18	0.056	53.26	0.211	0.333	2.4775
523.99	31.24	0.124	14.33	0.057	54.43	0.216	0.328	2.6133
553.99	30.05	0.119	14.45	0.057	55.50	0.220	0.323	2.7386
583.99	28.82	0.114	14.62	0.058	56.56	0.224	0.318	2.8580
613.99	27.83	0.110	14.78	0.059	57.39	0.227	0.314	2.9883
643.99	27.38	0.108	14.80	0.059	57.82	0.229	0.312	3.0989
673.99	26.06	0.103	14.96	0.059	58.98	0.234	0.307	3.1509
703.99	25.19	0.100	15.10	0.060	59.71	0.236	0.304	3.3104
733.99	24.36	0.096	15.15	0.060	60.49	0.240	0.300	3.4216
								3.5325

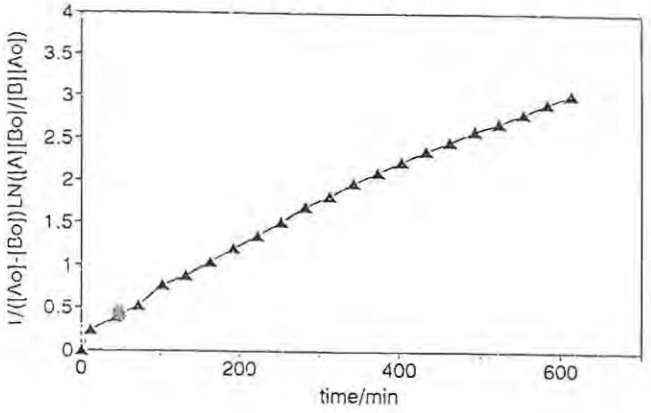
Regression Output:

Constant	0.131324
Std Err of Y Est	0.09384
R Squared	0.993203
No. of Observations	26
Degrees of Freedom	24
X Coefficient(s)	0.0047
Std Err of Coef.	8.22E-05

FORMATION OF E AND F FROM A
(MP8KN2)



2nd ORDER FUNCTION (MP8KN2)
(MP8KN2)



KINETIC DATA FOR COMPOUND 151 (MP8KN2)

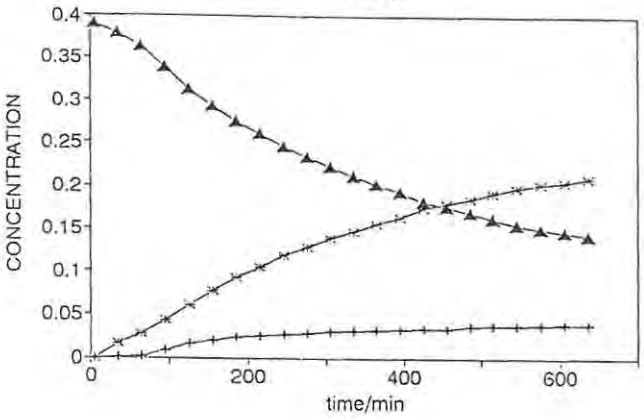
Time	[Ao]= %A	0.398 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.597 Func n=2
0.00	100.00	0.398	0.00	0.000	0.00	0.000	0.597	0.000
12.69	87.78	0.349	3.87	0.015	8.33	0.033	0.548	0.228
42.69	80.47	0.320	5.73	0.023	13.80	0.055	0.519	0.391
72.69	75.40	0.300	7.21	0.029	18.87	0.075	0.499	0.519
102.69	67.06	0.267	8.71	0.035	24.23	0.096	0.466	0.762
132.69	63.60	0.253	9.25	0.037	27.15	0.108	0.452	0.877
162.69	59.24	0.236	9.97	0.040	30.79	0.123	0.435	1.038
192.69	55.24	0.220	10.55	0.042	34.21	0.136	0.419	1.201
222.69	51.89	0.207	11.00	0.044	37.11	0.148	0.406	1.353
252.69	48.81	0.194	11.47	0.046	39.72	0.158	0.393	1.507
282.69	45.69	0.182	11.83	0.047	42.48	0.169	0.381	1.677
312.69	43.37	0.173	12.16	0.048	44.47	0.177	0.372	1.816
342.69	41.15	0.164	12.35	0.049	46.50	0.185	0.363	1.959
372.69	39.19	0.156	12.72	0.051	48.09	0.191	0.355	2.095
402.69	37.48	0.149	12.86	0.051	49.66	0.198	0.348	2.222
432.69	35.86	0.143	13.10	0.052	51.04	0.203	0.342	2.350
462.69	34.47	0.137	13.25	0.053	52.28	0.208	0.336	2.467
492.69	33.12	0.132	13.47	0.054	53.41	0.213	0.331	2.586
522.69	32.05	0.128	13.54	0.054	54.54	0.217	0.327	2.686
552.69	30.87	0.123	13.68	0.054	55.45	0.221	0.322	2.802
582.69	29.68	0.118	14.37	0.057	55.95	0.223	0.317	2.925
612.69	28.73	0.114	14.58	0.058	56.69	0.226	0.313	3.028

Regression Output:

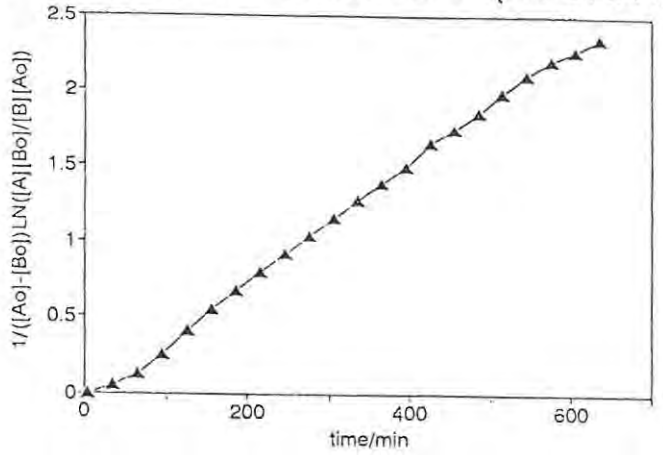
Constant	0.225028
Std Err of Y Est	0.085859
R Squared	0.991937
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	0.0048
Std Err of Coef.	9.68E-05

FORMATION OF E AND F FROM A

(MP3KN1)



2nd ORDER FUNCTION (MP3KN1)

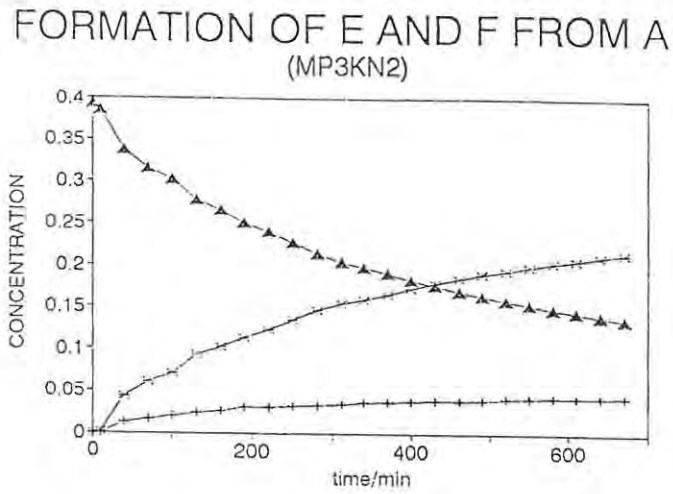


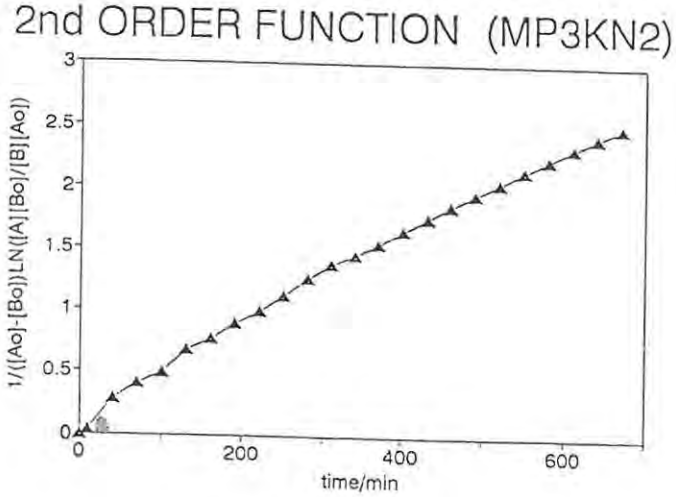
KINETIC DATA FOR COMPOUND 153 (Run1)

Time	[Ao]= %A	0.39 [A]	%E	[E]	%F	[F]	[Bo]= [B]	0.585 Func n=2
5.53	100.00	0.390	0.00	0.000	0.00	0.000	0.585	0.000
35.53	97.04	0.378	0.10	0.000	4.10	0.016	0.573	0.052
65.53	93.05	0.363	0.23	0.001	6.95	0.027	0.558	0.126
95.53	86.84	0.339	2.09	0.008	11.07	0.043	0.534	0.253
125.53	80.20	0.313	4.17	0.016	15.63	0.061	0.508	0.406
155.53	75.04	0.293	5.14	0.020	19.82	0.077	0.488	0.539
185.53	70.61	0.275	5.87	0.023	23.52	0.092	0.470	0.666
215.53	66.82	0.261	6.31	0.025	26.87	0.105	0.456	0.785
245.53	63.10	0.246	6.83	0.027	30.37	0.118	0.441	0.913
275.53	59.98	0.234	7.24	0.028	32.78	0.128	0.429	1.030
305.53	56.90	0.222	7.62	0.030	35.48	0.138	0.417	1.155
335.53	54.25	0.212	7.95	0.031	37.80	0.147	0.407	1.270
365.53	51.81	0.202	8.25	0.032	39.94	0.156	0.397	1.385
395.53	49.63	0.194	8.47	0.033	41.90	0.163	0.389	1.494
425.53	46.69	0.182	8.54	0.033	44.77	0.175	0.377	1.654
455.53	45.19	0.176	8.68	0.034	46.13	0.180	0.371	1.741
485.53	43.33	0.169	9.25	0.036	47.42	0.185	0.364	1.856
515.53	41.44	0.162	9.41	0.037	49.15	0.192	0.357	1.979
545.53	39.71	0.155	9.50	0.037	50.79	0.198	0.350	2.100
575.53	38.35	0.150	9.74	0.038	51.91	0.202	0.345	2.200
605.53	37.53	0.146	9.89	0.039	52.58	0.205	0.341	2.263
635.53	36.44	0.142	9.97	0.039	53.59	0.209	0.337	2.350

Regression Output:

Constant	-0.0699
Std Err of Y Est	0.034952
R Squared	0.998025
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	0.0039
Std Err of Coef.	3.92E-05





KINETIC DATA FOR COMPOUND 153 (Run2)

	Ao=	0.393					[Bo]=	0.589
Time	%A	[A]	%E	[E]	%F	[F]	[B]	Func n=2
0.00	100.00	0.393	0.00	0.000	0.00	0.000	0.589	0.000
10.7	98.00	0.385	0.00	0.000	0.20	0.001	0.581	0.035
40.7	85.84	0.337	3.11	0.012	11.05	0.043	0.533	0.273
70.7	80.32	0.315	4.13	0.016	15.55	0.061	0.512	0.400
100.7	76.86	0.302	5.01	0.020	18.13	0.071	0.498	0.487
130.7	70.45	0.277	5.96	0.023	23.59	0.093	0.473	0.667
160.7	67.35	0.265	6.58	0.026	26.07	0.102	0.461	0.763
190.7	63.68	0.250	7.58	0.030	28.74	0.113	0.446	0.887
220.7	60.95	0.240	7.72	0.030	31.33	0.123	0.436	0.986
250.7	57.61	0.226	8.01	0.031	34.38	0.135	0.422	1.117
280.7	54.33	0.214	8.43	0.033	37.24	0.146	0.410	1.258
310.7	51.81	0.204	8.73	0.034	39.46	0.155	0.400	1.376
340.7	50.28	0.198	9.13	0.036	40.59	0.160	0.394	1.451
370.7	48.54	0.191	9.34	0.037	42.12	0.166	0.387	1.542
400.7	46.46	0.183	9.56	0.038	43.98	0.173	0.379	1.656
430.7	44.74	0.176	9.78	0.038	45.48	0.179	0.372	1.757
460.7	43.10	0.169	9.97	0.039	46.93	0.184	0.365	1.858
490.7	41.67	0.164	10.10	0.040	48.23	0.190	0.360	1.951
520.7	40.31	0.158	10.30	0.040	49.39	0.194	0.354	2.044
550.7	38.94	0.153	10.48	0.041	50.58	0.199	0.349	2.142
580.7	37.68	0.148	10.67	0.042	51.65	0.203	0.344	2.237
610.7	36.49	0.143	10.86	0.043	52.65	0.207	0.339	2.331
640.7	35.40	0.139	10.84	0.043	53.76	0.211	0.335	2.421
670.7	34.46	0.135	10.96	0.043	54.58	0.214	0.331	2.502

Regression Output:

Constant	0.14198
Std Err of Y Est	0.066361
R Squared	0.992999
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.0037
Std Err of Coef.	6.56E-05

Competition Experiments

Materials and methods for radioreceptor binding assay.[183]

Forebrains of Wister rats (supplied by S. Daya of the Biochemistry group) were homogenised gently in a 0.05 M Tris-HCl buffer (pH 7.4) using a glass mortar and teflon pestle, followed by centrifugation at 20 000 rpm for 1 h at 4°C. The supernatant was decanted and the pellet was rehomogenised in Tris-HCl buffer (pH 7.4). Aliquots of the homogeneous sample were used for protein assay using the Folin-Lowry method.[183] The final suspension was found to contain approximately 28.5 mg/ml protein.

Binding assays were carried out in duplicate in a total volume of 250 μl. In one set of tubes, various concentrations of ^{3}H-diazepam* (0.5-150 nM) were incubated with the membranes (Table 31A) and, in another set, non-radioactive diazepam (100 fold excess) was added to the incubation medium containing the membranes and ^{3}H-diazepam (Table 31B) to determine the saturation effect. For competition studies, ^{3}-H-diazepam was incubated with various concentrations of the last drug (10^{-11}-10^{-4} M) in every set of runs, two tubes were included for total binding (^{3}H-diazepam alone) and non-specific binding (^{3}H- and non-radioactive diazepam) (Table 32). In all cases, the mixtures were incubated for 45 minutes at *ca.* 0°C in an ice bath. At the end of the incubation period, ice-cold Tris-HCl (pH 7.4; 3.0 ml) was added to each tube and the mixtures were filtered through Whatman GF/C glass fibre filters. The test tubes were rinsed with ice-cold Tris-HCl buffer (pH 7.4; 3.0 ml), filtered and the filters were washed with an additional portion of buffer (3 ml) to remove unbound (free) ^{3}H-diazepam. The filters were shaken mechanically for 15 minutes in labelled scintillation tubes containing Scintillator 299™ (3 ml). Bound ^{3}H-diazepam was estimated by conventional scintillation counting using a Beckman LS2800 instrument. The experimental data and corresponding plots for various compounds are detailed below.**

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*^{3}H-Diazepam (*N*-methyl-^{3}H; specific activity 96.0 Ci/mmol) was obtained from New England Nuclear Research Products

**Numbers for Figures 12-23 are the same as in the Discussion (see Section 2.7, pg. 130).

Table 31: Binding Assay using ^{3}H-diazepam (^{3}H-DZP) on rat brain membranes

A: Total Binding (B_T)

^{3}H-DZP (nM)	Protein (µl)	Tris-HCl (µl)	^{3}H-DZP (µl)	50% EtOH (µl)	Vehicle (µl)
0.50	200.00	30.00	0.04	9.96	10.00
1.00	200.00	30.00	0.07	9.93	10.00
2.50	200.00	30.00	0.17	9.83	10.00
5.00	200.00	30.00	0.33	9.67	10.00
10.00	200.00	30.00	0.66	9.34	10.00
35.00	200.00	30.00	1.65	8.35	10.00
50.00	200.00	30.00	3.30	6.70	10.00
75.00	200.00	30.00	5.00	5.00	10.00
100.00	200.00	30.00	6.60	3.40	10.00
150.00	200.00	30.00	10.00	10.00	10.00

B: Non-specific binding (B_{ns})

^{3}H-DZP (nM)	Protein (µl)	Tris-HCl (µl)	^{3}H-DZP (µl)	50% EtOH (µl)	DZP (µl)
0.50	200.00	30.00	0.03	9.97	10.00
1.00	200.00	30.00	0.07	9.93	10.00
2.50	200.00	30.00	0.16	9.84	10.00
5.00	200.00	30.00	0.37	9.67	10.00
10.00	200.00	30.00	0.66	9.34	10.00
25.00	200.00	30.00	1.65	8.35	10.00
50.00	200.00	30.00	3.30	6.70	10.00
75.00	200.00	30.00	5.00	5.00	10.00
100.00	200.00	30.00	3.40	3.40	10.00
150.00	200.00	30.00	10.00	0.00	10.00

Table 32: Competition studies using ^{3}H-DZP, non-radioactive DZP and test drug of various concentration (10^{-11}-10^{-4} nM) in a total volume of 250 µl.

Compd	B_T	B_{ns}	10^{-11} nM	10^{-10} nM	10^{-9} nM	10^{-8} nM	10^{-7} nM	10^{-6} nM	10^{-5} nM	10^{-4}nM
Protein	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00
50 % EtOH (µl)	20.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Tris-HCl (µl)	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
^{3}H-DZP (µl)	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
DZP	-	10.00	-	-	-	-	-	-	-	-
Test Drug (µl)	-	-	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00

	% Total Binding					
Conc (M)	192 ▲	194 +	196 ✳	204 □	265 ×	266 □
10^{-11}	100.0	98.0	94.2	100.0	100.0	90.1
10^{-10}	92.6	100.0	100.0	97.9	87.6	100.0
10^{-9}	61.7	75.2	66.8	84.8	83.3	97.4
10^{-8}	52.8	59.0	48.5	79.5	74.6	85.7
10^{-7}	51.9	37.0	45.0	81.9	85.0	89.1
10^{-6}	41.7	36.0	40.8	78.1	75.0	84.9
10^{-5}	38.9	41.1	43.6	70.5	69.9	84.4
10^{-4}	30.1	43.3	39.8	77.8	58.2	84.1

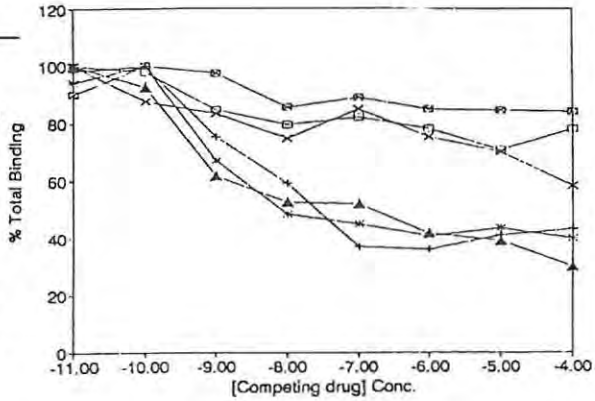


Figure 17: **Competition curves of the 2-phenyl-1,4-benzoxazepinones and thia derivatives 265-266**

	% Total Binding					
Conc (M)	212 ▲	214 +	216 ✳	218 □	269 ×	270 □
10^{-11}	100.0	100.0	100.0	99.3	100.0	99.7
10^{-10}	94.6	90.0	74.6	100.0	97.0	100.0
10^{-9}	77.7	93.9	76.5	89.2	71.6	94.3
10^{-8}	81.2	76.2	78.1	82.9	73.9	90.4
10^{-7}	76.0	71.7	70.9	50.8	74.5	87.6
10^{-6}	78.4	75.9	73.5	47.2	70.2	89.7
10^{-5}	72.9	63.2	74.3	48.9	67.8	72.4
10^{-4}	73.7	57.8	72.1	45.6	72.5	72.1

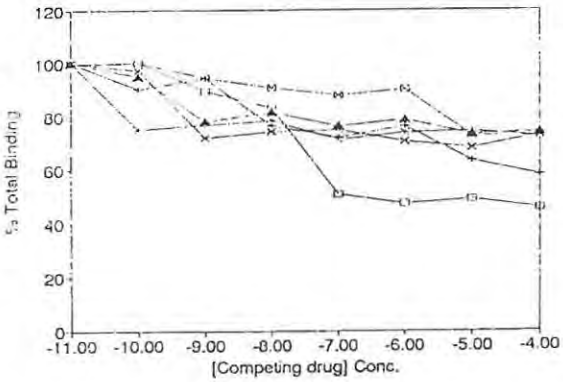


Figure 18: **Competition curves of the 2-phenyl-1,4-benzodiazepinones**

	% Total Binding		
Conc (M)	241 ▲	225 +	230 ✳
10^{-11}	100.0	98.8	100.0
10^{-10}	91.3	100.0	99.7
10^{-9}	85.1	98.8	90.3
10^{-8}	87.9	94.8	99.7
10^{-7}	88.7	85.4	92.0
10^{-6}	86.7	89.7	90.7
10^{-5}	88.9	93.0	89.0
10^{-4}	87.1	91.6	93.8

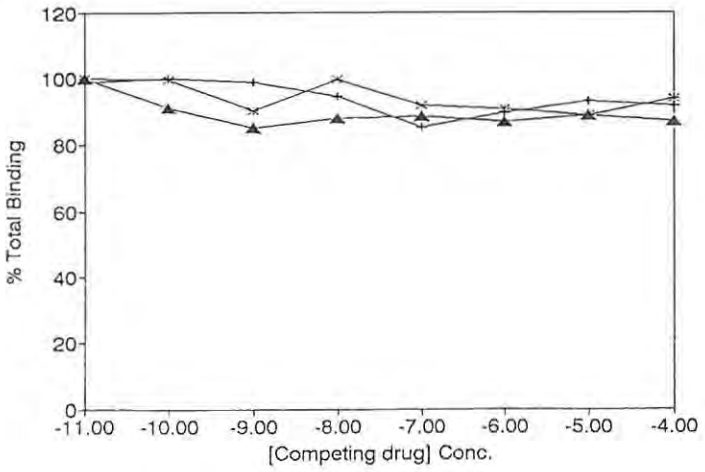


Figure 19: **Competition curves of the 2-phenyl-1,4- and 1,5-benzothiazepinones**

	% Total Binding			
Conc (M)	259 +	260 ✳	261 □	264 ×
10^{-11}	100.0	100.0	100.0	98.7
10^{-10}	80.6	89.4	92.3	100.0
10^{-9}	71.5	87.4	66.3	82.9
10^{-8}	70.8	72.2	61.8	75.9
10^{-7}	66.2	67.2	56.3	77.5
10^{-6}	66.9	60.2	52.2	73.1
10^{-5}	58.3	46.0	45.2	66.8
10^{-4}	57.6	36.5	30.3	64.7

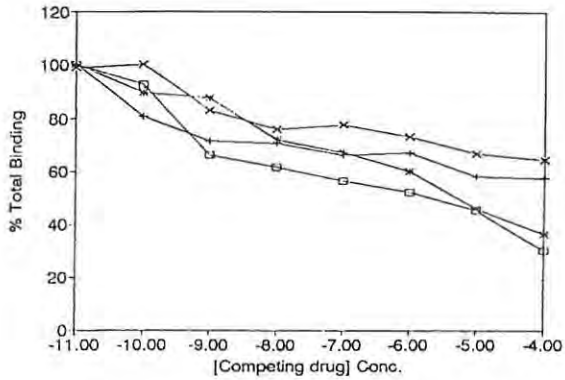


Figure 20: Competition curves of the A-ring chlorinated 2-phenyl-1,4-benzodiazepines

	% Total Binding					
Conc (M)	191 ▲	193 +	199 ✳	201 □	205 ×	207 ⊠
10^{-11}	100.0	100.0	86.1	85.9	100.0	100.0
10^{-10}	93.4	81.4	88.7	100.0	85.6	64.0
10^{-9}	90.8	86.9	100.0	76.4	79.9	53.7
10^{-8}	82.7	83.2	96.7	67.6	58.6	53.5
10^{-7}	78.5	89.8	88.3	68.9	64.0	54.9
10^{-6}	89.4	85.3	85.7	70.5	67.3	53.3
10^{-5}	69.5	74.4	86.0	68.5	64.0	53.5
10^{-4}	53.5	79.6	78.2	61.5	51.6	50.2

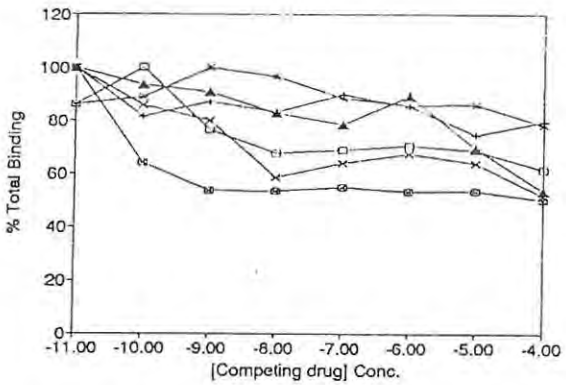


Figure 21: Competition curves of the 2-phenyltetrazolo-[1,5-*d*]-1,4-benzoxazepines

	% Total Binding					
Conc (M)	213 ▲	215 +	217 ✳	219 □	221 ×	223 ⊠
10^{-11}	100.0	100.0	100.0	99.3	92.8	100.0
10^{-10}	90.9	98.1	84.2	100.0	100.0	98.4
10^{-9}	89.0	96.9	82.1	96.4	85.1	99.3
10^{-8}	79.8	91.3	82.7	88.7	80.7	94.2
10^{-7}	79.0	88.9	73.6	89.6	84.4	96.1
10^{-6}	86.6	75.9	73.9	89.0	77.3	87.5
10^{-5}	76.7	77.4	74.3	88.8	64.3	88.3
10^{-4}	77.7	72.4	61.6	84.8	63.4	85.0

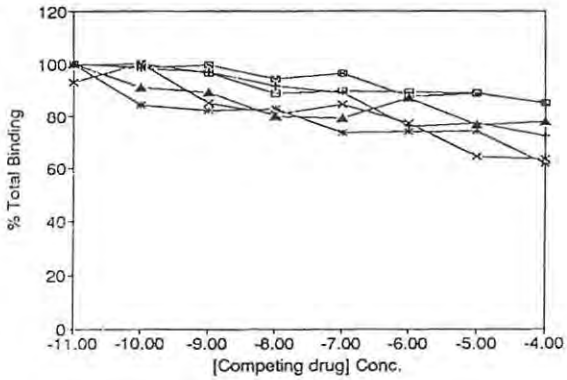


Figure 22: **Competition curves of the 2-phenyltetrazolo[1,5-*d*]-1,4-benzodiazepines**

	% Total Binding		
Conc (M)	226 ✳	242 □	243 ×
10^{-11}	95.0	100.0	100.0
10^{-10}	100.0	88.8	73.8
10^{-9}	77.4	86.0	66.6
10^{-8}	75.1	86.4	60.4
10^{-7}	74.9	86.4	57.6
10^{-6}	73.2	84.1	45.7
10^{-5}	71.5	83.9	43.9
10^{-4}	60.3	80.5	40.0

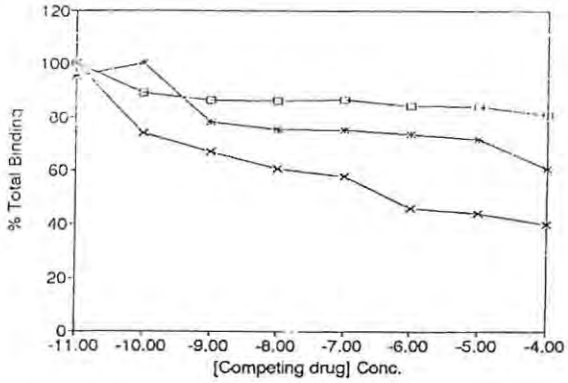
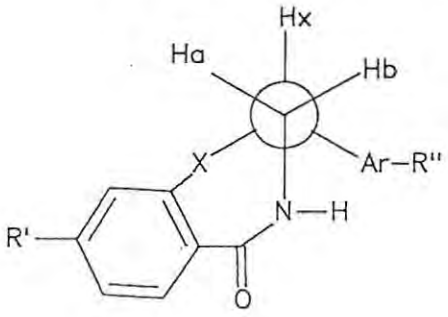


Figure 23: **Competition curves of the 2-phenyltetrazolo[1,5-*d*]-1,4- 226 and tetrazolo[1,5-*d*]-1,4-benzothiazepine 242, as well as their tetrazolo[5,1-*d*]-1,5-benzothiazepine 243**

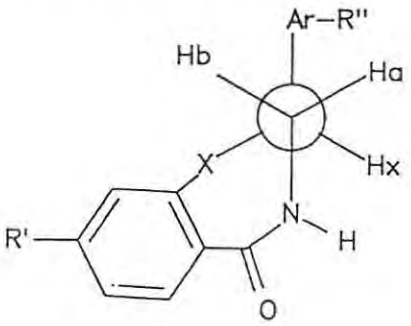
Computer Modelling Analysis

Computer modelling was performed using the HYPERCHEM™ package produced by Autodesk, Inc. Representative compounds from each series were constructed with the 2-phenyl substituent in either an axial or equatorial orientation. Energy minimisations were carried out using Steepest-Descent, Polak-Ribiere and Fletcher-Reeves methods (Tables 33, 34 and 35).

Table 33: **Minimum energies (kcal/mol, followed in parentheses by the total-root-mean-square gradient) for the 2-phenyl-1,4-benzodiazepine analogues.**



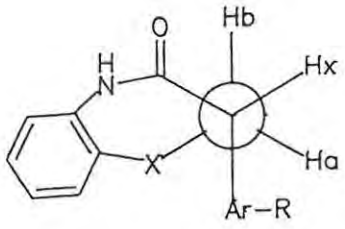
I



II

			Lowest energies		
No	X	Conf	Steepest Descent	Polak-Ribiere	Fletcher-Reeves
190	O	I	12.796 (0.99680)	12.796 (0.99680)	12.796 (0.99675)
		II	11.950 (0.091574)	11.950 (0.091574)	11.950 (0.091574)
212	NH	I	11.564 (0.08737)	11.564 (0.08737)	11.564 (0.087626)
		II	11.548 (0.099871)	11.548 (0.099871)	11.548 (0.099871)
224	S	I	18.550 (0.096224)	18.550 (0.09224)	18.550 (0.096208)
		II	18.106 (0.084987)	18.106 (0.084987)	18.106 (0.084990)

Table 34: **Minimum energies (kcal/mol, followed in parentheses by total-root-mean-square gradient) for the 2-phenyl-1,5-benzodiazepine analogues.**



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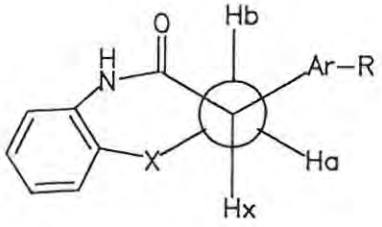
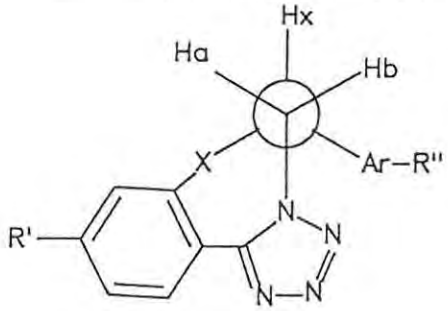


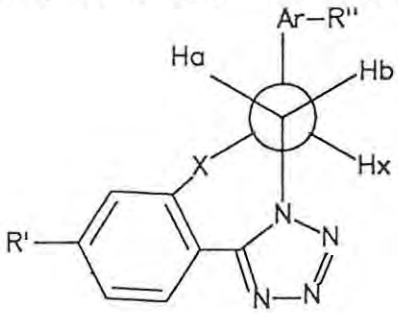
II

			Lowest energies		
No	X	Conf	Steepest-Descent	Polak-Ribiere	Fletcher-Reeves
211	O	I	7.385 (0.096593)	7.385 (0.096593)	7.385 (0.096568)
		II	6.925 (0.092056)	6.925 (0.092055)	6.925 (0.092056)
225	S	I	7.964 (0.095003)	7.964 (0.095003)	7.964 (0.094994)
		II	7.871 (0.083183)	7.871 (0.083183)	7.871 (0.083184)

Table 35: **Minimum energies (kcal/mol, followed in parentheses by total-root-mean-square gradient) for the 2-phenyltetrazolo-1,4-benzodiazepine derivatives.**



I



II

			Lowest energies		
No	X	Conf	Steepest Descent	Polak-Ribiere	Fletcher-Reeves
191	O	I	16.623 (0.0998)	16.623 (0.0998)	16.623 (0.0998)
		II	15.386 (0.082495)	15.386 (0.082493)	15.386 (0.082495)
213	NH	I	16.051 (0.099133)	16.051 (0.099133)	16.051 (0.099133)
		II	15.414 (0.088580)	15.414 (0.08857)	15.414 (0.088579)
226	S	I	16.642 (0.098356)	16.642 (0.098356)	16.642 (0.098356)
		II	15.859 (0.095926)	15.859 (0.95951)	15.859 (0.095926)

X-Ray analysis

X-ray diffraction data were collected at the University of Natal, Pietermaritzburg. The structures were solved by direct methods using SHELXS 86,[185] and refined using SHELX-76.[185] Crystal and collection data are summarised below. The fractional coordinates, anisotropic temperature factors, bond lengths, mean plane data and selected torsion angles are detailed in Appendix 2.

Crystallographic Data

Table 36: Crystal data for 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzodiazepine **218**.*

Formula	$C_{16}H_{13}N_6$
Molar mass	263.12
Crystal system	monoclinic
Space group	$P2_1/n$, no. 14 (non-standard setting of $P2_1/c$)
a (Å)	12.1375 (0.0027)
b (Å)	8.1740 (0.0014)
c (Å)	12.9788 (0.0028)
α	90.0
ß	98.165 (0.0175)
γ	90.0
V (Å^3)	1274.6 (0.45)
Z	4
Dc (g.cm^{-3})	1.37
F (000)	552
μ (mm^{-1})	0.50
Number of reflections ($2 < \theta < 30°$)	4106
Observed reflections [$I > \sigma(I)$]	3108
R, R_w	0.0681, 0.0736
N parameters	189
Weighting Scheme	$w = 0.52[(\sigma^2(F) + 0.0033F^2)]^{-1}$

*Estimated standard deviations in parenthesis

Table 37: Crystal data for 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224.[a]

Formula	$C_{15}H_{13}NOS$
Molar mass	255.0235
Crystal system	needle-shaped
Space group	$P2_1$
a (Å)	5.2794 (0.0016)
b (Å)	8.4094 (0.0009)
c (Å)	14.3929 (0.0014)
α	90
ß	91.352 (0.0206)
γ	90
V (Å^3)	638.8 (0.2)
Z	2
Dc (g.cm^{-3})	1.33
F (000)	268
μ (mm^{-1})	1.95
Number of reflections ($2 < \theta < 30°$)	2040
Observed reflections [$I > \sigma(I)$]	1907
R_1, R_w	0.037, 0.0425
N parameters	170
Weighting Scheme	$w = 0.865[(\sigma^2(F) + 0.001F^2)]^{-1}$

[a]Estimated standard deviations in parentheses.

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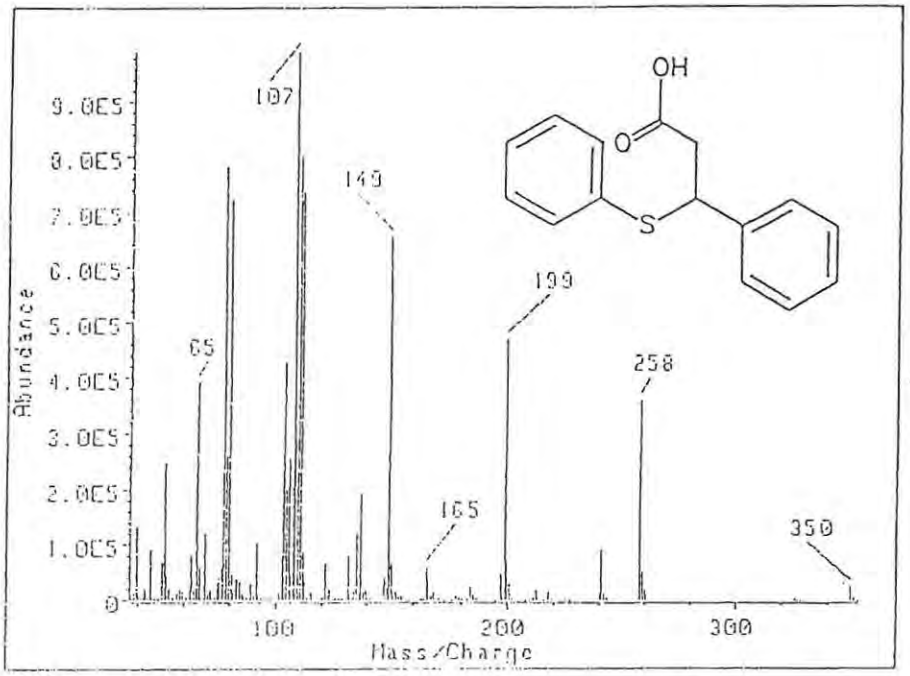
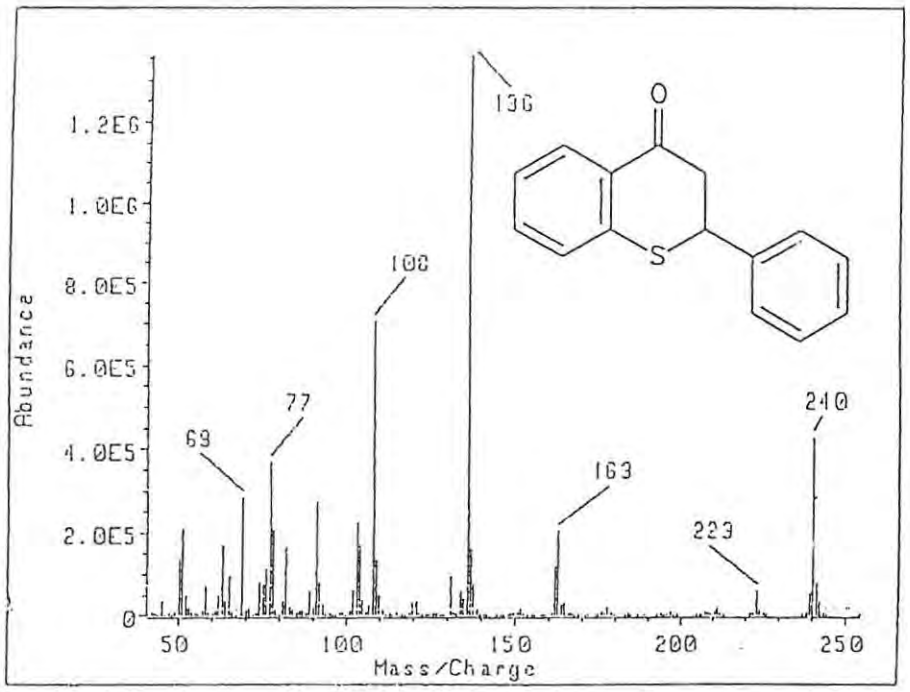
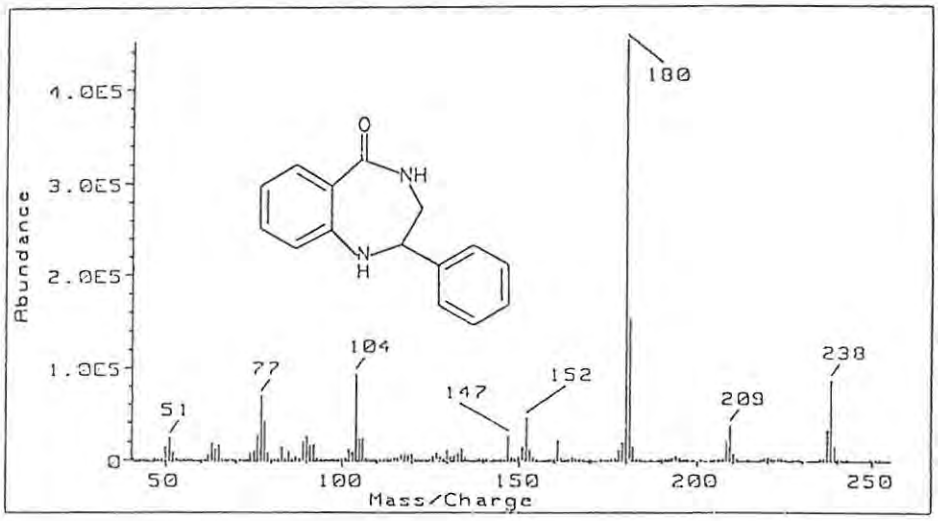
APPENDICES

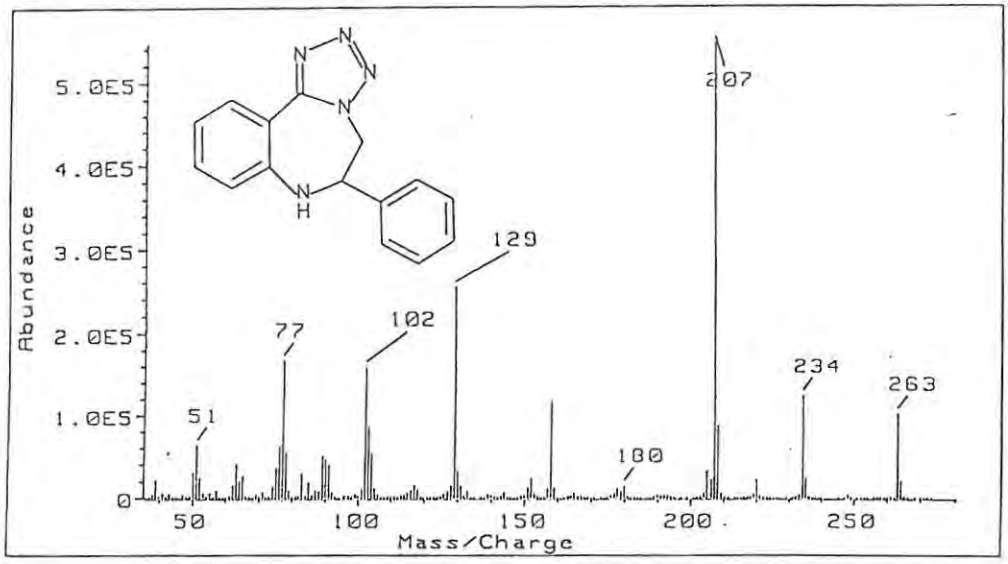
APPENDIX I: MASS SPECTRA OF SELECTED EXAMPLES OF COMPOUNDS PREPARED IN THIS WORK



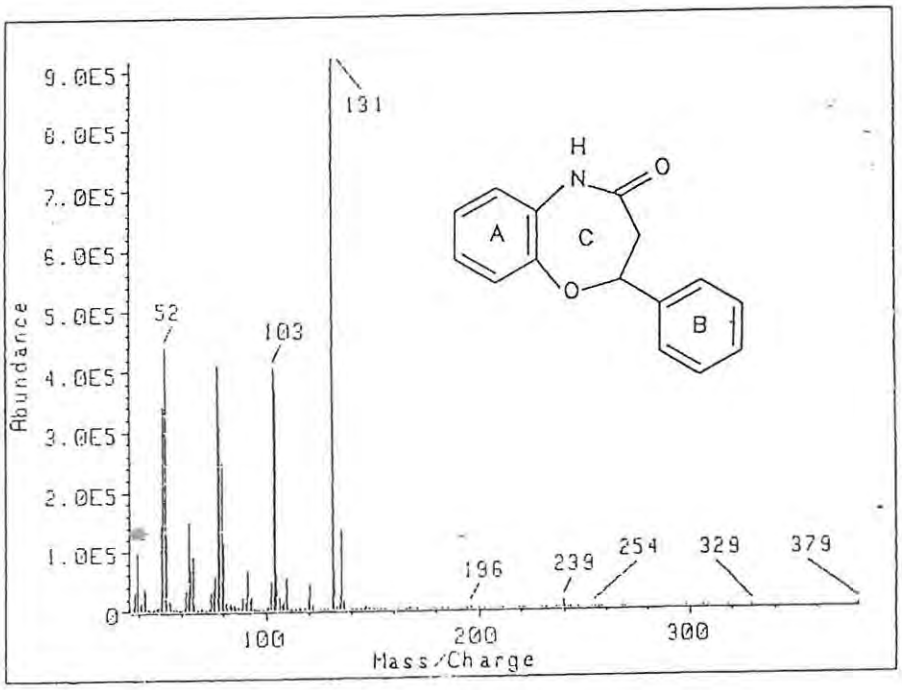


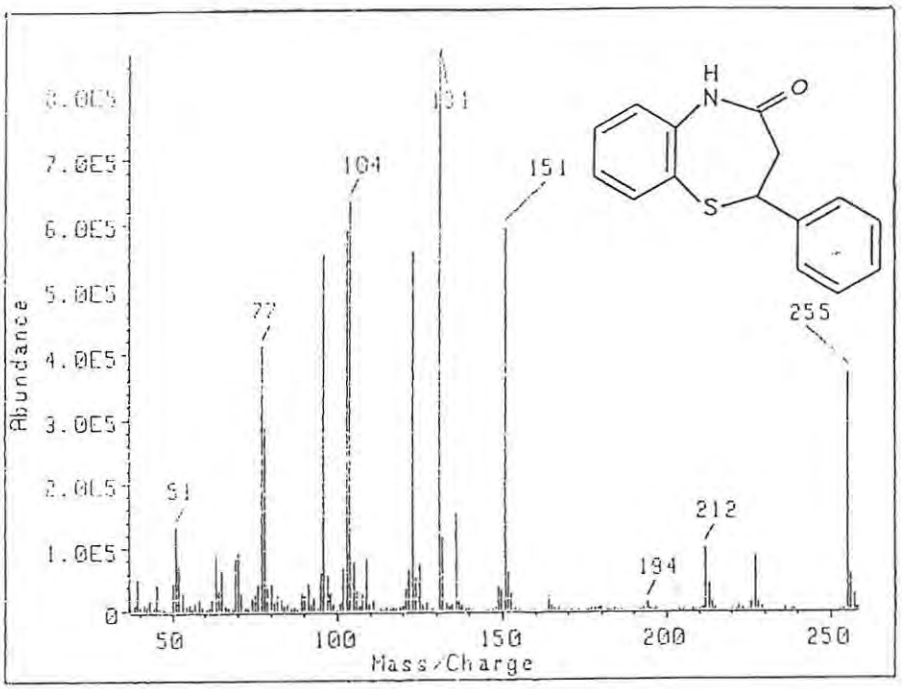
A: Electron-impact mass spectra of ß-phenylmercaptodihydrocinnamic acid 175 and 2,3-dihydro-2-phenyl-4*H*-1-benzothiopyran-4-one 185.



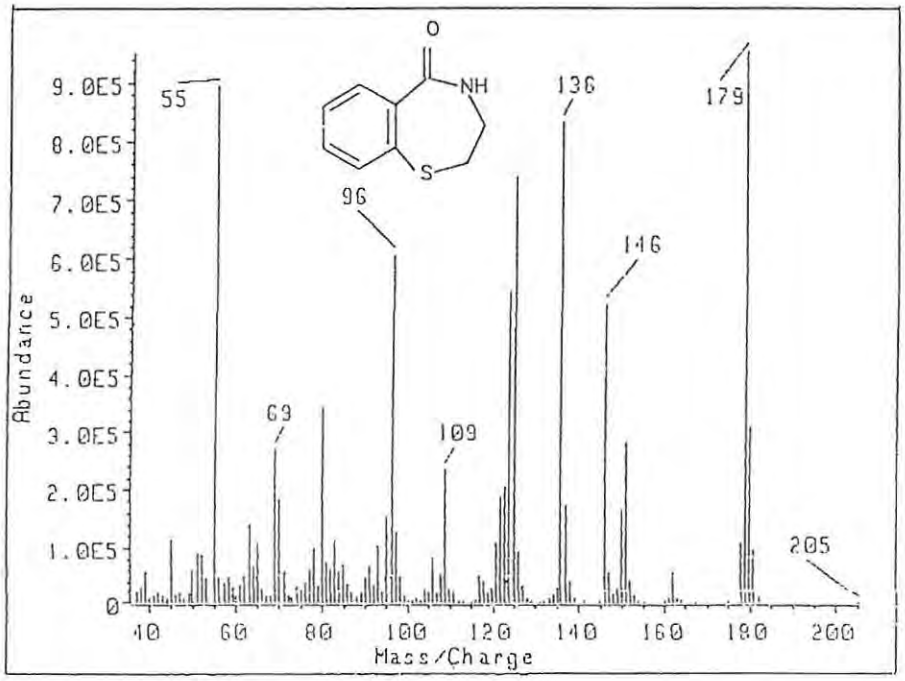


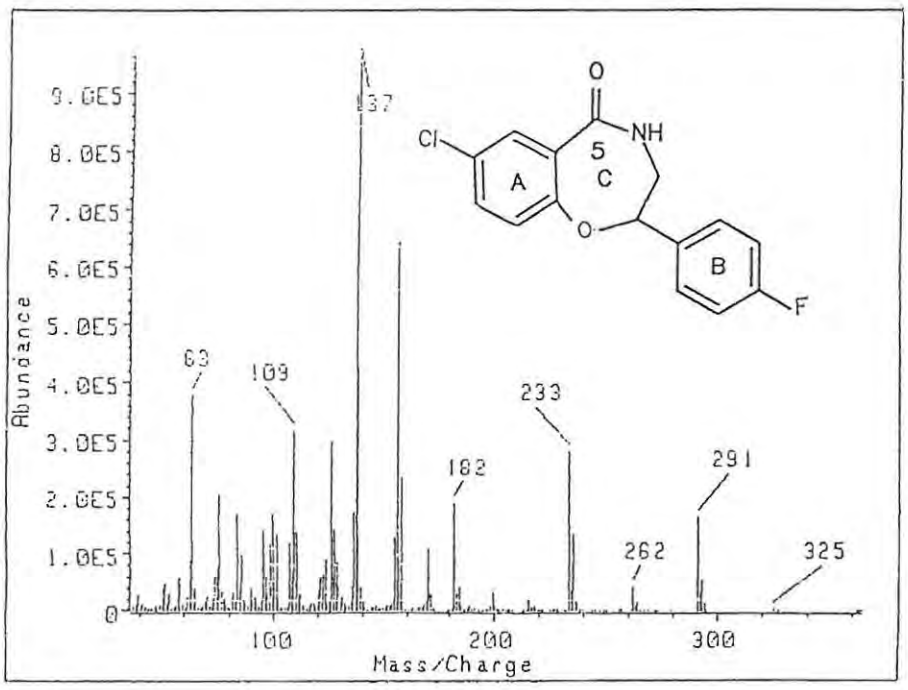
B: Electron-impact mass spectra of 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one 212 and 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1,4-benzodiazepine 213.



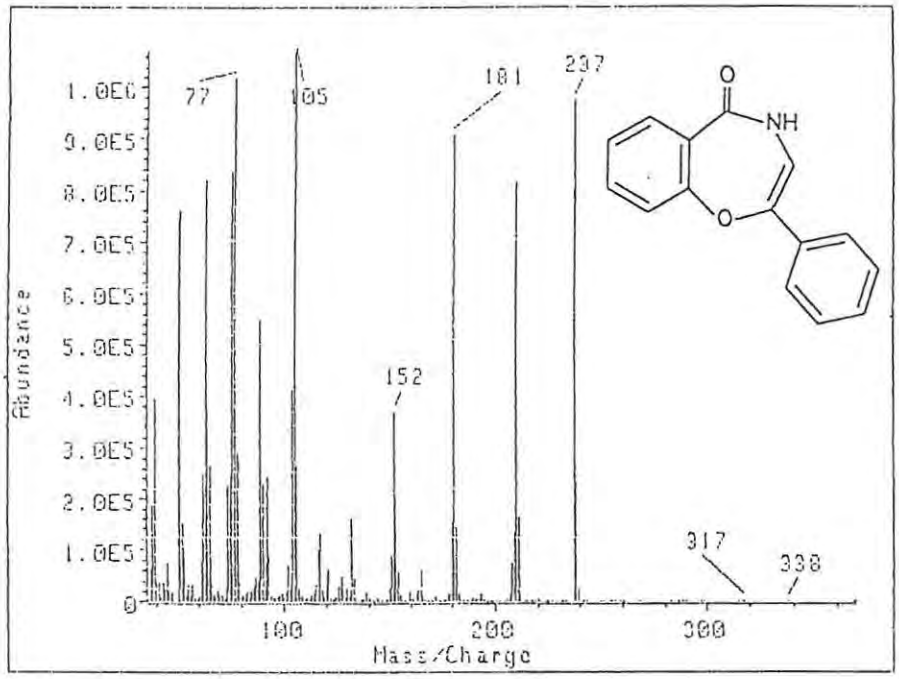


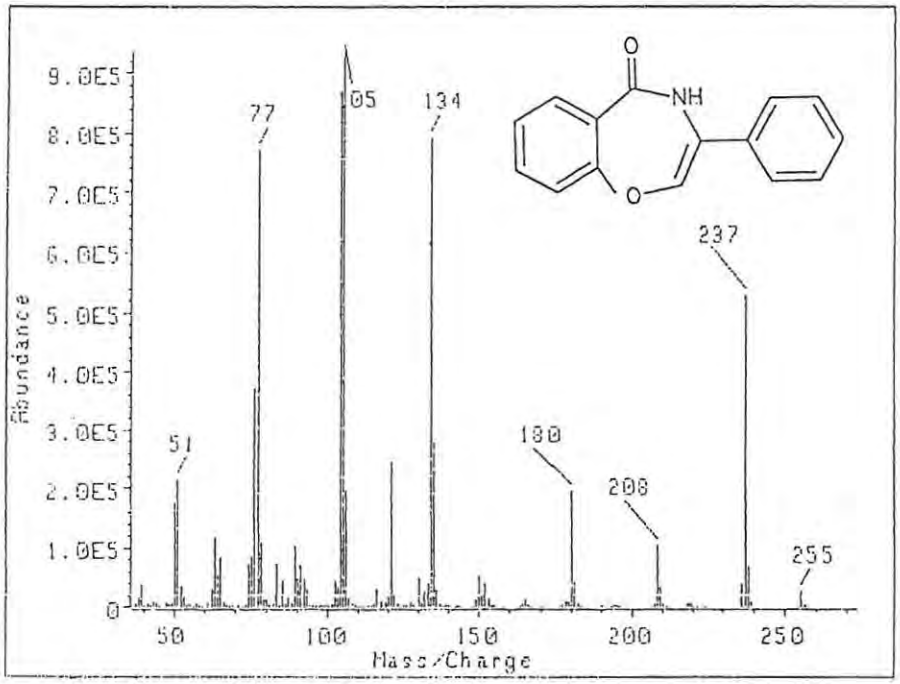
C: Electron-impact mass spectra of 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5*H*)-one 211 and 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 224.



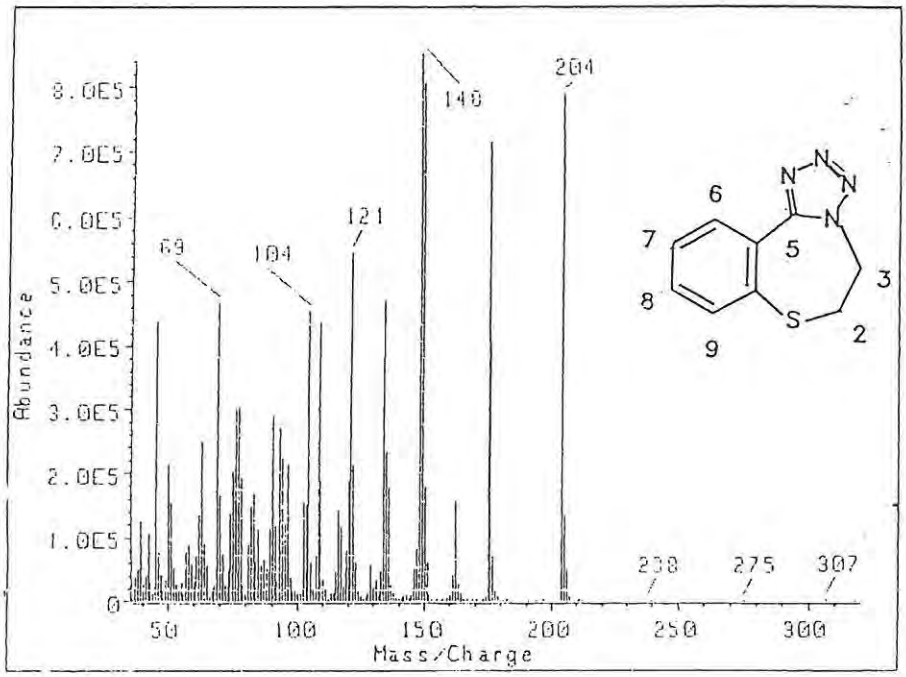


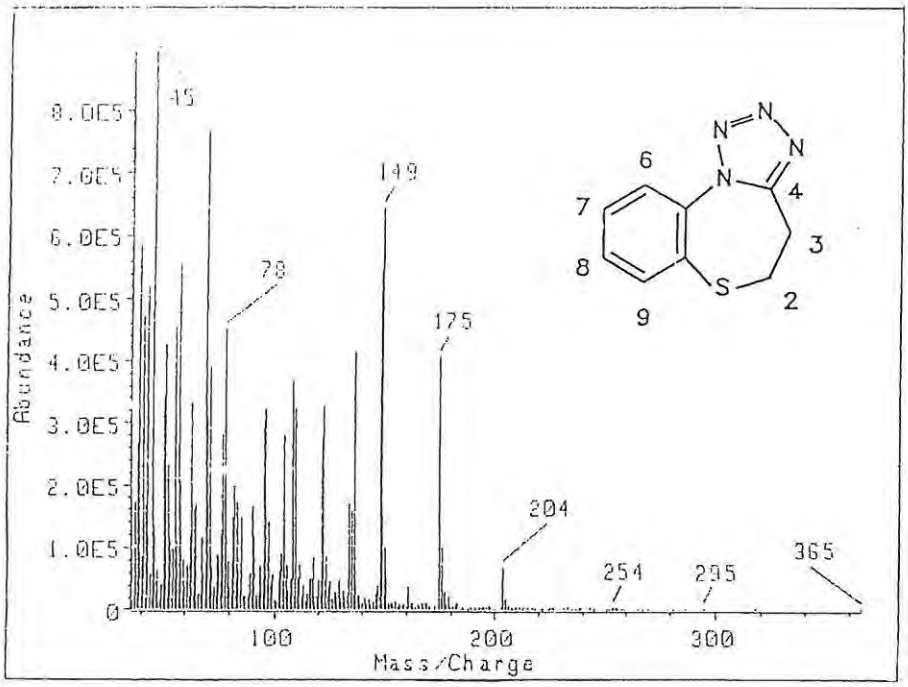
D: Electron-impact mass spectra of 2,3-dihydro-1,4-benzothiazepin-5(4*H*)-one 241 and 7-chloro-2-(4'-fluorophenyl)-1,4-benzoxazepin-5(4*H*)-one 260.





E: Electron-impact mass spectra of 2-phenyl-1,4-benzoxazepin-5(4*H*)-one 246 and 3-phenyl-1,4-benzoxazepin-5(4*H*)-one 258.





F: **Electron-impact mass spectra of 2,3-dihydro-4(*H*)-tetrazolo[1,5-*d*]-1,4-benzothiazepine 242 and 4,5-dihydro-5*H*-tetrazolo[5,1-*d*]-1,5-benzothiazepine 243.**

APPENDIX II: X-RAY CRYSTALLOGRAPHIC DATA

Table 38: Fractional co-ordinates (x 10^4) for 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224 with e.s.d's in parentheses.

Atom	x/a	y/b	z/c
S(1)	125 (01)	711 (0)	257 (0)
O(1)	- 72 (05)	763 (03)	526 (01)
N(1)	-133 (04)	564 (03)	424 (01)
C(1)	-128 (03)	838 (02)	287 (01)
C(2)	-230 (04)	834 (03)	376 (01)
C(3)	-137 (04)	718 (03)	447 (01)
C(4)	-220 (04)	503 (03)	335 (01)
C(5)	- 19 (04)	512 (03)	260 (01)
C(6)	-116 (04)	460 (03)	166 (01)
C(7)	-330 (04)	530 (03)	125 (01)
C(8)	-414 (05)	485 (04)	36 (02)
C(9)	-285 (05)	370 (04)	- 13 (02)
C(10)	- 77 (06)	299 (04)	28 (02)
C(11)	8 (04)	343 (03)	117 (02)
C(12)	-210 (05)	953 (03)	223 (02)
C(13)	-395 (05)	1061 (04)	248 (02)
C(14)	-499 (05)	1056 (04)	334 (02)
C(15)	-416 (05)	944 (03)	399 (02)

Table 39: Anisotropic temperature factors (Å² x 10^3) for the non-hydrogen atoms of 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224

Atom	U11	U22	U33	U23	U13	U12
S(1)	34 (02)	40 (02)	59 (03)	3 (02)	6 (02)	- 3 (02)
O(1)	105 (16)	58 (11)	44 (08)	- 7 (08)	- 13 (09)	-12 (11)
N(1)	68 (12)	42 (09)	40 (08)	2 (07)	- 6 (08)	- 5 (09)
C(1)	37 (08)	32 (09)	44 (09)	-0.1 (07)	1 (06)	-15 (07)
C(2)	45 (09)	37 (09)	43 (09)	- 5 (08)	1 (07)	- 4 (08)
C(3)	59 (11)	44 (10)	40 (08)	- 1 (10)	0.3 (07)	- 6 (11)
C(4)	52 (11)	36 (09)	40 (09)	-0.4 (07)	0 (07)	- 7 (08)
C(5)	38 (09)	32 (08)	49 (09)	- 1 (07)	- 4 (07)	4 (07)
C(6)	37 (08)	34 (08)	46 (09)	- 4 (07)	6 (07)	0 (07)
C(7)	44 (10)	47 (11)	47 (09)	- 8 (09)	1 (08)	6 (09)
C(8)	50 (11)	62 (15)	52 (11)	- 8 (11)	- 3 (09)	3 (11)
C(9)	62 (14)	65 (16)	53 (11)	- 17 (12)	6 (10)	-12 (13)
C(10)	71 (16)	66 (18)	69 (15)	- 31 (14)	19 (12)	2 (13)
C(11)	47 (11)	50 (12)	70 (13)	- 15 (11)	8 (09)	9 (10)
C(12)	58 (58)	40 (10)	56 (11)	7 (09)	- 2 (10)	- 1 (10)
C(13)	57 (14)	43 (12)	82 (17)	52 (12)	- 10 (13)	9 (11)
C(14)	82 (58)	46 (13)	93 (19)	- 11 (13)	- 1 (07)	13 (11)
C(15)	59 (13)	47 (12)	65 (13)	- 13 (11)	9 (11)	2 (10)

Table 40: Bond lengths (Å) and Bond angles (°), with e.s.d's in parentheses for 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224

C(1)—S(1)	1.768 (02)	N(1)—C(3)—O(1)	122.1 (0.2)
C(5)—S(1)	1.842 (03)	C(2)—C(1)—S(1)	121.4 (0.2)
C(3)—N(1)	1.335 (04)	C(2)—C(3)—O(1)	120.4 (0.2)
C(3)—O(1)	1.231 (03)	C(2)—C(3)—N(1)	117.5 (0.2)
C(4)—N(1)	1.446 (02)	C(3)—C(2)—C(1)	121.2 (0.2)
C(1)—C(2)	1.399 (03)	C(4)—N(1)—C(3)	124.5 (0.2)
C(2)—C(3)	1.499 (03)	C(4)—C(5)—S(1)	111.0 (0.1)
C(2)—C(15)	1.391 (03)	C(5)—S(1)—C(1)	103.2 (0.1)
N(1)—C(4)	1.446 (02)	C(5)—C(4)—N(1)	113.1 (0.2)
S(1)—C(5)	1.842 (02)	C(6)—C(5)—S(1)	111.7 (0.1)
C(4)—C(5)	1.528 (03)	C(6)—C(5)—C(4)	112.9 (0.2)
C(6)—C(5)	1.505 (03)	C(7)—C(6)—C(5)	121.2 (0.2)
C(6)—C(7)	1.390 (03)	C(8)—C(7)—C(6)	120.8 (0.2)
C(6)—C(11)	1.390 (03)	C(9)—C(8)—C(7)	120.3 (0.2)
C(7)—C(8)	1.397 (04)	C(10)—C(9)—C(8)	119.3 (0.2)
C(8)—C(9)	1.376 (04)	C(10)—C(11)—C(6)	120.5 (0.2)
C(9)—C(10)	1.371 (05)	C(11)—C(6)—C(5)	120.6 (0.2)
C(10)—C(11)	1.391 (04)	C(11)—C(6)—C(7)	118.1 (0.2)
C(1)—C(12)	1.395 (03)	C(11)—C(10)—C(9)	120.9 (0.2)
C(13)—C(12)	1.382 (04)	C(12)—C(1)—S(1)	118.8 (0.2)
C(14)—C(13)	1.378 (05)	C(12)—C(1)—C(2)	119.5 (0.2)
C(14)—C(15)	1.383 (04)	C(13)—C(12)—C(1)	120.1 (0.2)
		C(14)—C(13)—C(12)	120.4 (0.3)
		C(15)—C(2)—C(1)	119.5 (0.2)
		C(15)—C(2)—C(3)	119.2 (0.2)
		C(15—C(4)—C(13)	120.1 (0.2)

Table 41: Fractional co-ordinates (x 10^3) for 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,5-benzodiazepine 224 with e.s.d.'s in parentheses

Atom	X/A	Y/B	Z/C
N(3)	628 (02)	522 (02)	27 (01)
N(4)	615 (01)	610 (02)	106 (01)
N(5)	608 (01)	517 (02)	191 (01)
N(1)	640 (01)	3 (02)	103 (01)
C(2)	708 (01)	91 (02)	39 (01)
C(3)	646 (02)	237 (02)	15 (01)
N(2)	629 (01)	365 (01)	59 (01)
C(5)	618 (01)	362 (02)	161 (01)
C(5a)	614 (01)	222 (02)	230 (01)
C(6)	599 (02)	257 (02)	333 (01)
C(7)	587 (02)	138 (03)	404 (01)
C(8)	588 (02)	- 25 (02)	373 (01)
C(9)	605 (01)	- 65 (02)	274 (01)
C(9a)	622 (01)	56 (02)	200 (01)
C(1')	743 (01)	- 19 (02)	- 45 (01)
C(2')	848 (01)	- 4 (02)	- 74 (01)
C(3')	880 (02)	-105 (02)	-151 (02)
C(4')	808 (02)	-222 (03)	-198 (01)
C(5')	703 (02)	-235 (03)	-171 (02)
C(6')	670 (02)	-134 (02)	- 95 (01)

Table 42: Anisotropic temperature (Å² x 10^{-3}) for the non-hydrogen atoms of 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,5-benzodiazepine 213

Atom	U11	U22	U33	U23	U13	U12
N(3)	65 (10)	22 (06)	56 (09)	3 (06)	128 (07)	5 (06)
N(4)	63 (09)	23 (06)	63 (10)	- 4 (06)	12 (08)	3 (06)
N(5)	54 (08)	24 (06)	54 (09)	- 8 (06)	12 (07)	2 (06)
N(1)	54 (08)	22 (06)	36 (07)	- 5 (05)	17 (06)	- 2 (05)
C(2)	41 (08)	23 (06)	36 (07)	- 4 (05)	10 (06)	1 (05)
C(3)	61 (10)	27 (07)	37 (08)	- 3 (06)	11 (07)	7 (07)
N(2)	51 (08)	21 (06)	42 (07)	- 1 (05)	9 (06)	4 (05)
C(5)	35 (07)	24 (07)	41 (08)	- 6 (06)	6 (06)	1 (05)
C(5a)	35 (07)	27 (07)	36 (07)	- 6 (06)	7 (06)	2 (05)
C(6)	56 (07)	37 (08)	39 (08)	- 10 (07)	12 (07)	2 (07)
C(7)	72 (12)	49 (11)	38 (09)	- 7 (07)	19 (08)	13 (09)
C(8)	65 (11)	43 (09)	41 (09)	2 (07)	19 (08)	1 (08)
C(9)	52 (09)	29 (07)	41 (08)	1 (06)	16 (07)	- 1 (06)
C(9a')	34 (07)	26 (07)	35 (07)	- 4 (05)	8 (06)	1 (05)
C(1')	41 (08)	26 (06)	32 (07)	- 1 (05)	9 (06)	4 (05)
C(2')	48 (09)	34 (08)	47 (09)	1 (07)	19 (07)	1 (07)
C(3')	59 (11)	49 (10)	50 (10)	2 (09)	28 (08)	9 (09)
C(4')	80 (14)	47 (10)	37 (08)	- 5 (08)	23 (09)	12 (09)
C(5')	76 (14)	52 (11)	46 (10)	- 21 (09)	13 (09)	- 8 (10)
C(6')	49 (09)	45 (10)	42 (09)	- 13 (07)	13 (07)	- 5 (07)

Table 43: Bond Lengths (Å) and Bond Angles (°), with e.s.d.'s in parentheses for 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine 213

N(3)—N(4)	1.288 (02)	N(2)—C(5)—N(5)	107.4 (0.1)
N(2)—N(3)	1.352 (02)	N(2)—N(3)—N(4)	106.1 (0.1)
N(4)—N(5)	1.351 (02)	N(2)—C(3)—C(2)	111.6 (0.1)
C(5)—N(5)	1.337 (02)	N(5)—N(4)—N(3)	111.7 (0.1)
C(2)—N(1)	1.453 (02)	C(1')—C(2)—N(1)	110.5 (0.1)
C(9a)—N(1)	1.384 (02)	C(1')—C(2)—C(3)	107.9 (0.1)
C(2)—C(3)	1.522 (02)	C(3)—C(2)—N(1)	110.0 (0.1)
C(1')—C(2)	1.516 (02)	C(3)—N(2)—N(3)	118.5 (0.1)
C(3)—N(2)	1.455 (02)	C(5)—N(5)—N(4)	105.9 (0.1)
C(5)—N(2)	1.346 (02)	C(5)—N(2)—N(3)	108.9 (0.1)
N(5)—C(5)	1.337 (02)	C(5)—N(2)—C(3)	132.5 (0.1)
C(5a)—C(5)	1.459 (02)	C(5a)—C(5)—N(2)	129.1 (0.1)
C(6)—C(5a)	1.407 (02)	C(5a)—C(5)—N(5)	123.5 (0.1)
C(9a')—C(5a)	1.414 (02)	C(2')—C(1')—C(2)	120.1 (0.1)
C(6)—C(7)	1.368 (02)	C(3')—C(2')—C(1')	120.5 (0.2)
C(7)—C(8)	1.387 (03)	C(4')—C(3')—C(2')	120.1 (0.2)
C(8)—C(9)	1.375 (02)	C(5')—C(4')—C(3')	119.8 (0.2)
C(9a')—C(9)	1.406 (02)	C(5')—C(6')—C(1')	120.5 (0.2)
C(2)—C(1')	1.516 (02)	C(6)—C(5')—C(4')	120.2 (0.2)
C(1')—C(2')	1.388 (02)	C(6')—C(1')—C(2')	118.8 (0.1)
C(1')—C(6')	1.390 (02)	C(6')—C(1')—C(2)	121.1 (0.1)
C(2')—C(3')	1.388 (02)	C(6)—C(5a)—C(5)	116.0 (0.1)
C(3')—C(4')	1.385 (03)	C(7)—C(6)—C(5a)	122.4 (0.2)
C(4')—C(5')	1.374 (03)	C(8)—C(7)—C(6)	119.0 (0.2)
C(5')—C(6')	1.389 (02)	C(9)—C(8)—C(7)	120.4 (0.2)
		C(9)—C(9a')—N(1)	117.3 (0.1)
		C(9)—C(9a')—C(5a)	118.0 (0.1)
		C(9a')—C(9)—C(8)	121.6 (0.2)
		C(9a')—C(5a)—C(5)	125.6 (0.1)
		C(9a')—C(5a)—C(6)	118.4 (0.1)
		C(9a')—N(1)—C(2)	123.1 (0.1)

Table 44: Selected torsion angles (°) of 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224

H5	C5	C6	C7	171.47
H5	C5	C6	C11	-9.91
H1	N1	C4	H41	23.83
H1	N1	C4	H42	142.75
H41	C4	C5	H5	-51.94
H42	C4	C5	H5	-170.88

Table 45: Deviation from mean planes 1-5 of 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4*H*)-one 224

PLANE	1	2	3	4	5
S1	1.7023	0.1196	0.0711	0.0378	0.6364
O1	-0.2026	0.9083	0.4322	0.8588	1.2334
N1	-0.9624	-0.8417	-1.2352	-0.9174	0.3234
H1	-1.4551	-0.7843	-1.2877	-0.8743	0.8577
C1	1.4786	-0.0071	-0.0428	-0.0478	-0.3802
C2	0.6099	0.0039	-0.1816	-0.0259	-0.3665
C3	-0.2129	0.0638	-0.2995	0.0111	0.4671
C4	-1.0679	-1.8992	-2.1680	-1.9787	-0.6117
H41	-2.0113	-2.7091	-3.0477	-2.8013	-0.8442
H42	-1.0384	-2.2480	-2.4426	-2.3042	-1.5123
C5	0.0568	-1.4497	-1.5928	-1.5476	-0.0686
H5	-0.0997	-1.2635	-1.4821	-1.3856	0.7290
C6	0.0065	-2.5200	-2.5247	-2.6195	-1.0831
C7	-0.0032	-3.1286	-3.0265	-3.2007	-2.3269
H7	-0.0125	-2.8572	-2.7745	-2.9063	-2.5870
C8	-0.0041	-4.0881	-3.8541	-4.1618	-3.2436
H8	-0.0176	-4.5559	-4.2404	-4.6081	-4.2083
C9	0.0081	-4.4430	-4.1827	-4.5458	-2.9250
H9	0.0317	-5.1671	-4.8030	-5.2712	-3.6228
C10	-0.0047	-3.8636	-3.7100	-3.9936	-1.7085
H10	-0.0143	-4.1539	-3.9816	-4.3068	-1.4629
C11	-0.0027	-2.9059	-2.8840	-3.0345	-0.7864
H11	-0.0090	-2.4596	-2.5200	-2.6100	0.1674
C12	2.2760	0.0029	0.1297	-0.0159	-1.1170
H12	2.9585	0.0068	0.2499	-0.0202	-1.1237
C13	2.1917	0.0046	0.1441	0.0181	-1.8425
H13	2.8139	0.0166	0.2822	0.0469	-2.4083
C14	1.3193	-0.0078	-0.0157	0.0164	-1.8480
H14	1.2489	-0.0228	-0.0193	0.0267	-2.4310
C15	0.5388	0.0035	-0.1665	0.0062	-1.1051
H15	-0.1284	0.0133	-0.2717	0.0246	-1.0989

Table 46: Selected torsion angles (°) of 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo-[1,5-*d*]-1*H*-1,4-benzodiazepine 213

H2	C2	C1′	C2′	-24.49
H2	C2	C3	H31	-168.49
H2	C2	C3	H32	72.02
H1	N1	C2	H2	-99.81

Table 47: Deviation from mean planes 1-5 of 2-phenyl-1,2,3,4-tetrahydro-4*H*-tetrazolo[1,5-*d*]-1*H*-1,4-benzodiazepine 213

PLANE	1	2	3	4	5
N3	-0.1047	0.0026	-0.3057	-0.0023	-2.6840
N4	0.0038	0.0006	-0.3084	0.1795	-2.5221
N5	0.0662	-0.0036	-0.2113	0.2380	-1.3041
N1	-0.1367	0.0316	0.0509	-0.2298	0.8477
H1	-0.1464	0.0518	0.1278	-0.2861	1.4356
C2	0.5511	0.7837	0.7081	0.4564	0.0177
H2	1.5288	1.7190	1.6391	1.4592	0.4301
C3	-0.1982	0.0332	-0.1446	-0.2397	-1.4228
H31	-1.2347	-0.9773	-1.1440	-1.2931	-1.7651
H32	0.2385	0.5313	0.2873	0.1852	-2.0386
N2	-0.1197	-0.0049	-0.2083	-0.0719	-1.5420
C5	-0.0011	0.0053	-0.1369	0.0893	-0.6940
C5a	0.0332	0.0032	-0.0215	0.0921	0.6560
C6	0.1343	-0.0174	-0.0003	0.2538	1.2961
H6	0.2521	0.0417	0.0032	0.4363	0.7991
C7	0.0930	-0.1054	0.0196	0.1928	2.5225
H7	0.1949	-0.0975	0.0570	0.3426	2.9957
C8	-0.0897	-0.2130	-0.0166	-0.0727	3.1482
H8	-0.1674	-0.3265	-0.0446	-0.1666	4.0987
C9	-0.1612	-0.1649	-0.0056	-0.2059	2.5744
H9	-0.3008	-0.2475	-0.0314	-0.4096	3.0792
C9a	-0.0704	-0.0238	0.0244	-0.0965	1.3311
C1′	0.6655	1.0257	0.9581	0.4816	0.0103
C2′	1.8077	2.2271	2.1206	1.5966	-0.0034
H2′	2.6098	2.9844	2.8415	2.4415	-0.0170
C3′	1.9180	2.4537	2.3544	1.6255	-0.0074
H3′	2.8083	3.3896	3.2599	2.4951	-0.0207
C4′	0.8954	1.4890	1.4364	0.5479	0.0113
H4′	0.9988	1.6822	1.6372	0.5875	0.0377
C5′	-0.2496	0.2867	0.2705	-0.5701	-0.0042
H5′	-1.0548	-0.4723	-0.4538	-1.4181	-0.0122
C6′	-0.3708	0.0493	0.0256	-0.6098	-0.0066
H6′	-1.2812	-0.9049	-0.9008	-1.4992	-0.0345