SYNTHETIC AND SPECTROMETRIC STUDIES

OF BENZODIOXEPINONE DERIVATIVES

THESIS

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CONTENTS

ACKNOWLEDGEMENTS

ABBREVIATIONS

MCPBA   *meta*-chloroperbenzoic acid

DDQ   dichlorodicyanobenzoquinone

DMF   dimethylformamide

LDA   lithium diisopropylamide

THF   tetrahydrofuran

Et_2O diethyl ether

NMR   nuclear magnetic resonance

IR   infra red

DEPT   distortionless enhancement by polarisation transfer

HETCOR ^1H-^{13}C heteronuclear correlation spectroscopy

COSY ^1H-^1H correlation spectroscopy

s   singlet

br s   broad singlet

d   doublet

dd   doublet of doublets

ddd   double doublet of doublets

t   triplet

m   multiplet

Ac   acetyl group

TFA   trifluoroacetic acid

$TMS-N_3$ trimethylsilyl azide

TLC   thin layer chromatography

ABSTRACT

An extensive range of oxygen and sulphur substituted benzodiazepine analogues has been synthesised *via* Baeyer-Villiger and Schmidt reactions of specially prepared flavanone and N-acetyl-4-quinolone precursors. Alternative, cyclisation routes have also been used to prepare some of these compounds. Ring-opening reactions of 1,5-benzodioxepinones have been investigated and a detailed kinetic-mechanistic study of the Baeyer-Villiger reaction of flavanones has been carried out using ^{1}H NMR spectroscopy to explain the observed regiochemistry of oxygen insertion. The electron-impact mass spectrometric fragmentation patterns of series of 4-aryl-1,5-benzoxathiepinones, 3-aryl-4,1-benzoxathiepinones and 3-aryl-4,1-benzoxathiepines have been studied using a combination of low-resolution, high-resolution and metastable-peak analyses. The ^{17}O NMR spectroscopic properties of various oxygenated analogues have also been studied.

The binding affinities of selected benzodiazepine analogues for rat brain benzodiazepine receptors have been evaluated using a radioreceptor assay technique; at certain concentrations, some of test compounds exhibited remarkable potentiation of diazepam binding, others the ability to displace diazepam from benzodiazepine receptors. A conformational analysis of the 7-membered ring systems has been undertaken, using ^{1}H NMR spectroscopic, computer modelling and x-ray crystallographic techniques, and certain conformational preferences have been identified.

To Vhusani and Ndivhuho.

This one is for both of you.

1. INTRODUCTION

A number of seven-membered ring compounds containing one or more hetero atoms have assumed importance due to their important pharmacological properties. For example, the benzodiazepines, librium® and valium® have been widely used as minor tranquilizers (see section 1.3, p. 27). The synthesis, reactivity and biological activity of such compounds have been extensively researched. The following literature review will cover selected systems such as benzodioxepines, benzoxazepines, benzoxathiepines and, very briefly, benzodiazepines.

Many seven-membered ring compounds are prepared by the union of two bifunctional reagents through reactions such as alkylation or acylation of amino, hydroxy or thiol groups. Ring enlargement of the six-membered rings through N or O insertion also provides access to these systems. Benzo- and dibenzo- derivatives prepared as analogues of compounds with valuable pharmacological properties, are the most widely studied classes.

1.1 DIOXEPINES AND THEIR BENZO-DERIVATIVES

Dioxepines are seven-membered ring compounds containing two oxygen atoms. Apart from the 1,3-systems, which have attracted most attention, this group of compounds has not been studied extensively. Dioxepines may be divided into four basic classes, *i.e.* the 1,2- **1**; 1,3- **2**; 1,4- **3** dioxepines and their benzo analogues and the 1,5-benzodioxepines **4**.

1   2   3   4
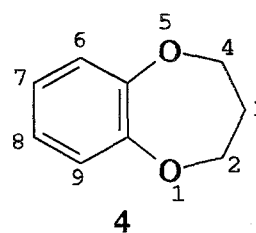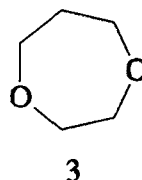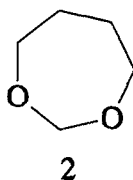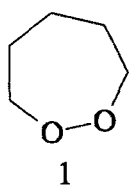
1.1.1 1,3-Dioxepines

The 4,7-dihydro-1,3-dioxepines (*e.g.* compound **7**; Scheme 1) may be prepared by the reaction of *cis*-2-butene-1,4-diols **5** with aldehydes,[1] ketones,[1,2] acetals,[3] trialkyl orthoformates, acetylenes and vinyl ethers.[4] For the reactions with aldehydes and ketones a catalyst such as *p*-toluenesulfonic acid or concentrated sulfuric acid is necessary, and the resulting water may be removed azeotropically. Aldehydes give good yields of 2-substituted 1,3-dioxepines **7**, but the reaction with ketones is less satisfactory and the 2,2-disubstituted derivatives **10** are best obtained by a double exchange reaction between the diol with an acetal and a ketone[4,5] (Scheme 2).

The reaction of *cis*-2-butene-1,4-diol **5** with acetylenes is a poor method for preparing 1,3-dioxepines because of the very low yields obtained, the main product being 2,5-divinyl-1,4-dioxane and a ketone.[4] The dioxane is formed by the condensation of two diol molecules and the water formed from this reaction then reacts with acetylene to give ketones. Low temperatures are necessary in order to get high yields from the reaction of *cis*-2-butene with trialkyl orthoformates[4] **11** (Scheme 3) since high temperatures produce decomposition products. Similar procedures can be used to prepare 2,4-benzodioxepines **14** from 1,2-benzenedimethanol **13**.
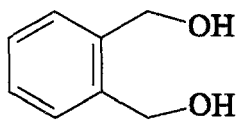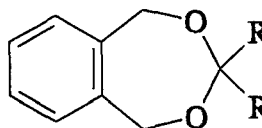
13   14

2,4-Benzodioxepines have been reported[6] to provide a novel means of protecting carbonyl compounds **8** as illustrated in Scheme 4; the protecting group can easily be cleaved under

non-acidic conditions by catalytic hydrogenolysis (Scheme 4). Direct condensation of 1,2-

benzenedimethanol with carbonyl compounds also affords compounds **16**, but in very low

yields (15-20%); the yields are improved by first converting 1,2-benzenedimethanol into an

orthoformate **15** using trimethyl orthoformate.   Recently, Patney[7] reported that

benzodioxepines **16** can be prepared in excellent yields (83-98%) by direct condensation of

1,2-benzenedimethanol with aldehydes or ketones under heterogeneous conditions by

employing a sulfonated charcoal catalyst.

Like other unsaturated hydrocarbons, the double bond in 1,3-dioxepines undergoes halogen

addition and hydrogenation. Brannock and Lappin[1] prepared 5,6-dibromo-4,7-dihydro-1,3-

dioxepine **18** in good yield by addition of bromine to 4,7-dihydro-1,3-dioxepine (Scheme 5)

in carbon tetrachloride at sub-zero temperatures. The dichloro analogue **19** was similarly

obtained by the addition of chlorine to the double bond. Hydrogenation of 4,7-dihydro-1,3-

dioxepine **17** using Raney nickel gave 4,5,6,7-tetrahydro-1,3-dioxepane **20** in excellent yield

(Scheme 6).[1] This is a general reaction for 1,3-dioxepines. Compound **17** also undergoes

a Diels-Alder reaction[8,9] with hexachlorocyclopentadiene to give a product which, if

chlorinated further, is a very active insecticide for caterpillars, brown tail moths, gypsy

moths and ants. Many substituted 1,3-dioxepines copolymerize with dienes such as butadiene

to form latexes and vinyl rubber products with desirable tensile, lubricant and elastic

properties.[4] 4,7-Dihydro-1,3-dioxepines are fairly stable to heat under alkaline conditions.

Treatment with acids, however, results in the formation of 2,5-dihydrofuran and a carbonyl

compound.[4]
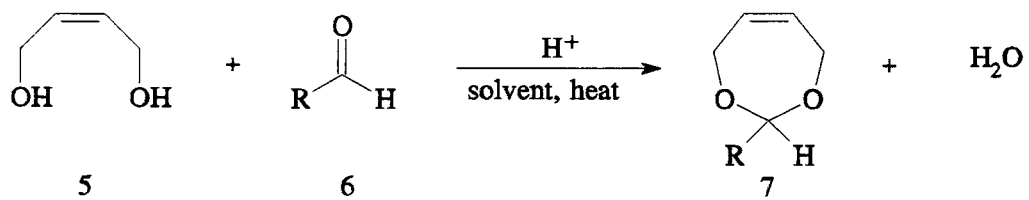
SCHEME 1
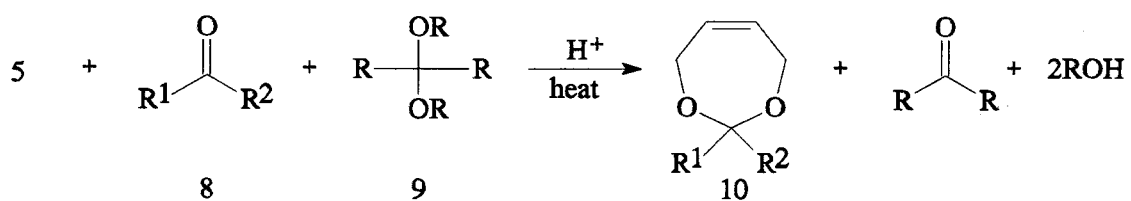
SCHEME 2

SCHEME 3

SCHEME 4

18 ; X=Br
19 ; X=Cl
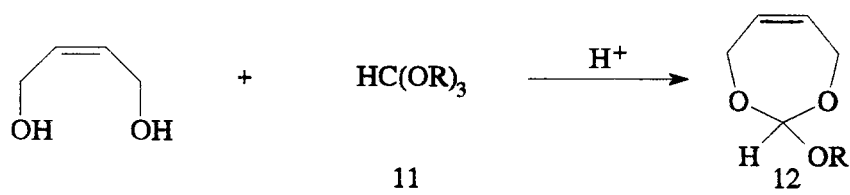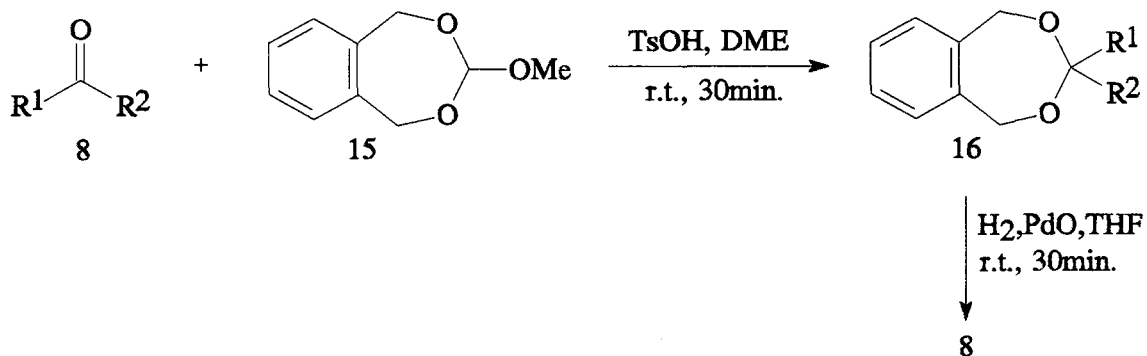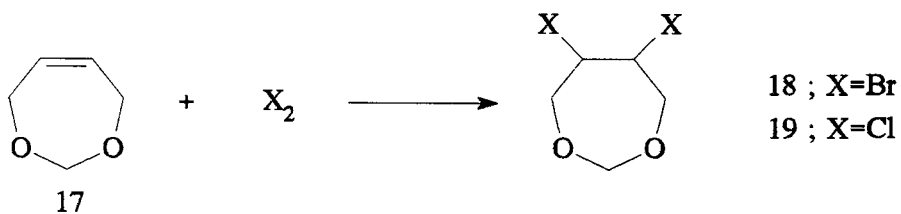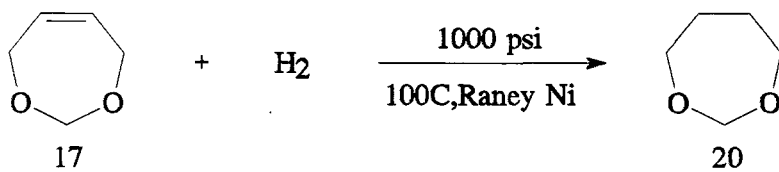
SCHEME 5

SCHEME 6

1.1.2 1,4-Dioxepines

1,4-Dioxepanes of type **21** have been prepared by the treatment of cyclic acetals of ethane-1,2-diol with vinyl ethers in the presence of boron trifluoride, while 1,4-dioxepan-5-one **22** has been prepared by the reaction of bromoform and silver nitrate with aqueous dioxane.[10]

21   **22**

A number of 1,4-benzodioxepines, 1,4-benzodioxepinones and -diones have been reported.[4] The 1,4-benzodioxepine **24** can be prepared by reacting 2-hydroxymethylphenol **23** with 1,2-dibromoethane under basic conditions (Scheme 7). Dawkins and Mulholland[11] showed that treatment of the methyl ester of 2-acetyl-6-chloro-3,5-dimethoxyphenoxyacetic acid **25** with 3M- hydrochloric acid gave the 4-benzodioxepin-3-one **26**, and treatment of this compound with diazomethane gave 9-chloro-2,3-dihydro-5,6,8-trimethoxy-5-methyl-5*H*-1,4-benzodioxepin-3-one **27** (Scheme 8). The reaction of the sodium salt of salicylic acid or its substituted analogues with 2-chloroethanol gave compound **28**[10,12] while 2,3-dihydro-8,9-dimethoxy-1,4-benzodioxepin-3,5-dione **29**, a cyclic anhydride, was prepared[13] by heating 2-carboxy-5,6-dimethoxyphenoxyacetic acid in acetic anhydride. The dilactone **30**, prepared[14] by treating chloroacetylsalicylic acid sequentially with sodium iodide and trimethylamine, reacts with water or primary and secondary amines to form salicyloylglycolic acid **31** and *N*-acylpyrrolidine, (*e.g.* compound **32**; Scheme 9) respectively.[4]

23   **24**

SCHEME 7

6
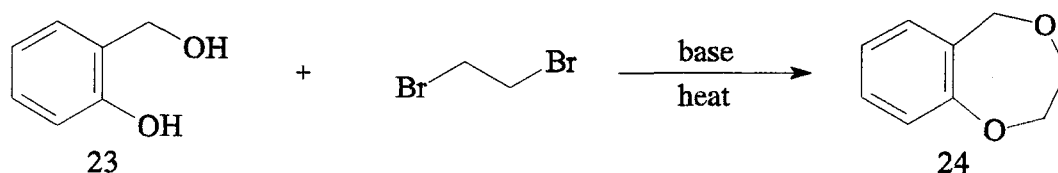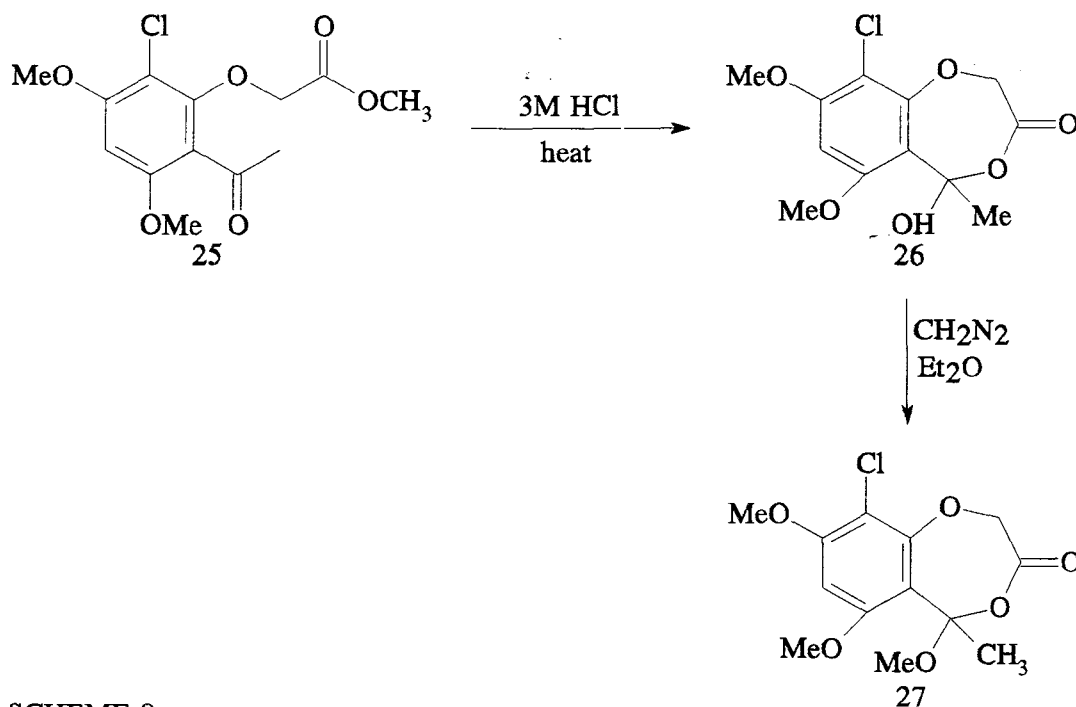
SCHEME 8

Both compounds **31** and **32** exhibit keratolytic and antiviral activity. Some 1,4-benzodioxepines, (*e.g.* compound **33**) show antiinflammatory activity while others (*e.g.* compound **34**) produce local anaesthesia.[15] 3-Aminomethyl-5-phenyl-2,3-dihydro-1,4-benzodioxepines **36**, prepared by cyclisation of the precursors **35**, are useful as sedatives, antiepileptics or antidepressants.[16]
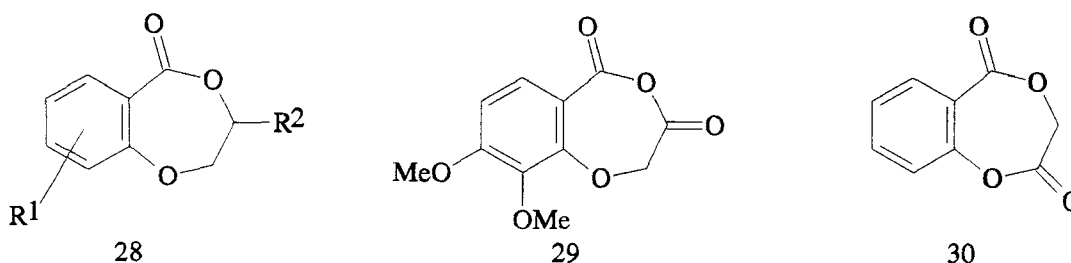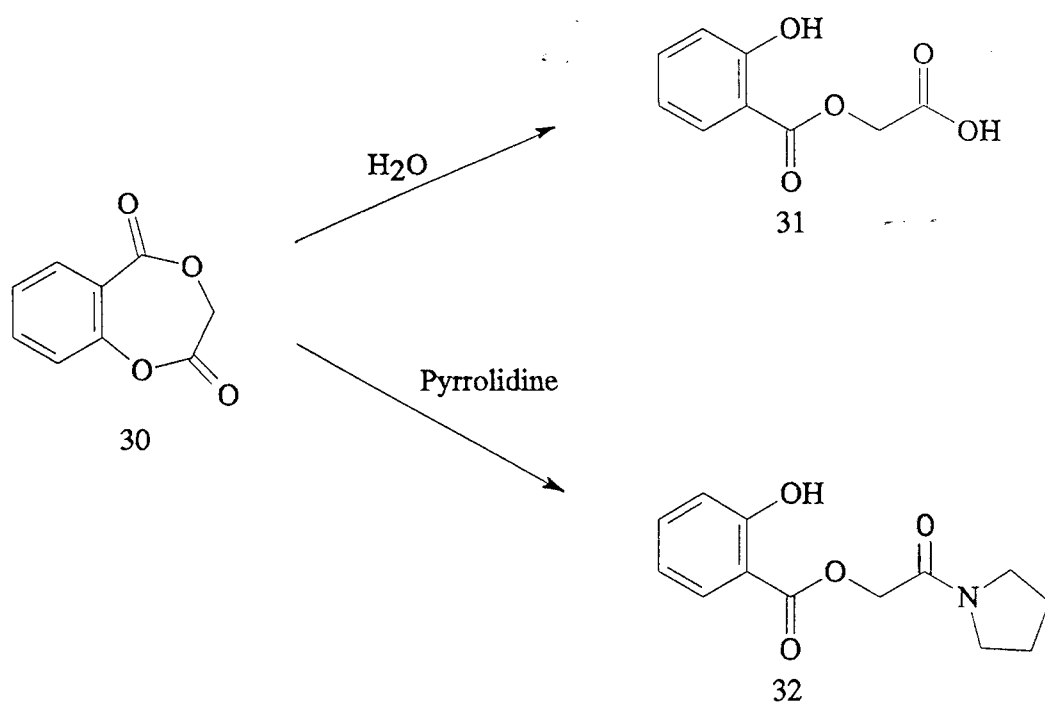
SCHEME 9
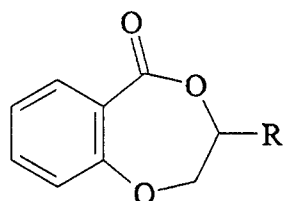
33 R = CH$_2$NHC$_6$H$_4$CF$_3$
34 R = CH$_2$N[CH(CH$_3$)$_2$]$_2$
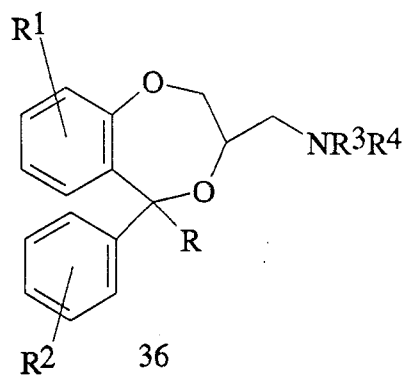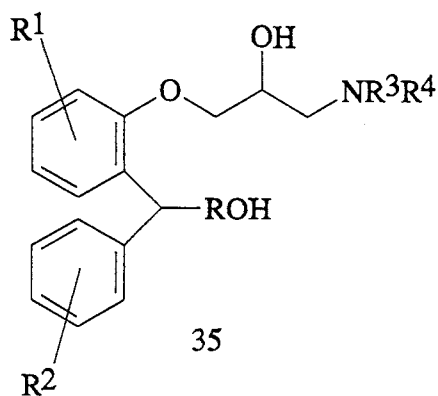
1.1.3   1,5-Benzodioxepines

There are two major routes to the parent 3,4-dihydro-2H-1,5-benzodioxepine **40**, viz., (i) the

base catalysed cyclisation of 1-bromo-3-(2-hydroxyphenoxy)propane **37**[17] and (ii) the

condensation of 1,3-dibromopropane **39** with catechol (1,2-dihydroxybenzene) **38** in the

presence of sodium methoxide[4] (Scheme 10).   3,4-Dihydro-1,5-benzodioxepines with

substituents on the aromatic or aliphatic rings can be prepared from substituted catechols or

substituted 1,3-dihalopropanes.[4] 3-Methyl-3,4-dihydro-2H-1,5-benzodioxepine **43** is obtained

from the reaction of catechol and 1,3-dichloro-2-methylenepropane **41** followed by catalytic

hydrogenation (Scheme 11).   Leonard and Koo[18] prepared a number of secondary amine

derivatives from the reaction of 3,4-dihydro-2H-1,5-benzodioxepine-2-carbonyl chloride **44**

with primary amines and subsequent reduction of the resultant carboxamide derivatives with

lithium aluminium hydride (Scheme 12).   A range of pharmacologically active methylamine,

isopropylamine, butylamine, hydroxyalkylamine, piperazine and piperidine derivatives **46**

were prepared by this route.[18]   Amides of type **45** are also useful as tranquilizers and

sedatives.

3,4-Dihydro-2H-1,5-benzodioxepin-3-one **49**, useful as odorant for foods and perfumes,[19,20]

is a key intermediate in the synthesis of 3-substituted 3,4-dihydro-2H-1,5-benzoxazepine

derivatives which possess pharmacological properties. This intermediate can be prepared via

the reaction of 1,2-dihydroxybenzene with chloroacetonitrile[10] or via a Dieckman

condensation of o-phenylenedioxydiacetate.[20] Rooney et al.[21] also prepared compound **49** by

the Thorpe cyclisation of 1,2-di(cyanomethoxy)benzene **47** to the enamino nitrile **48** which

was then hydrolysed to the required product (Scheme 13).
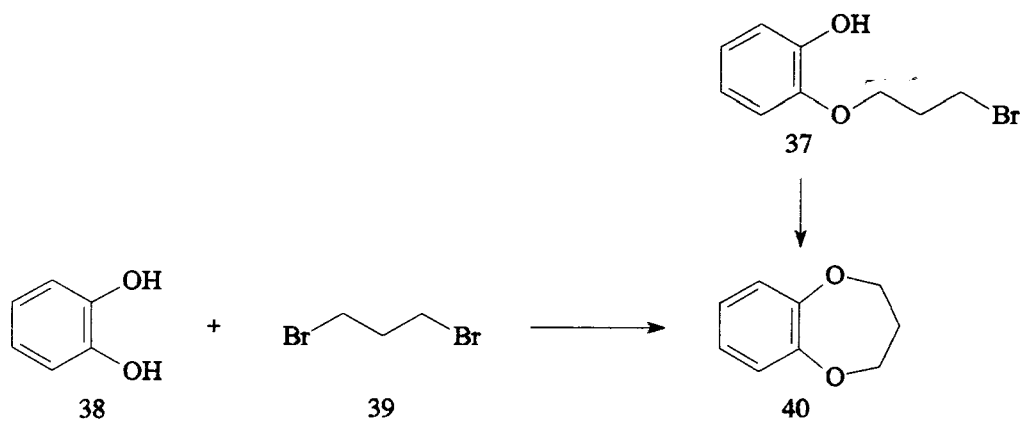
SCHEME 10
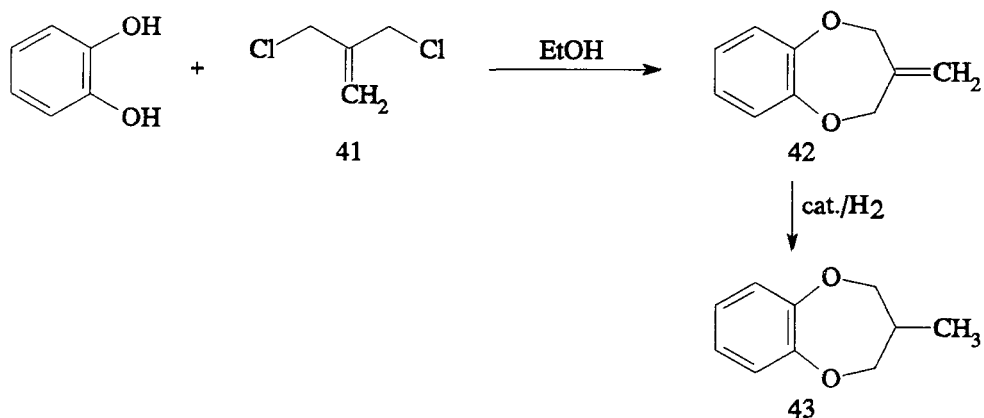
SCHEME 11

SCHEME 12

47   **48**   **49**
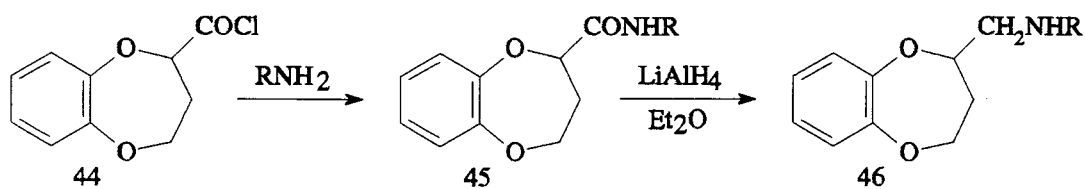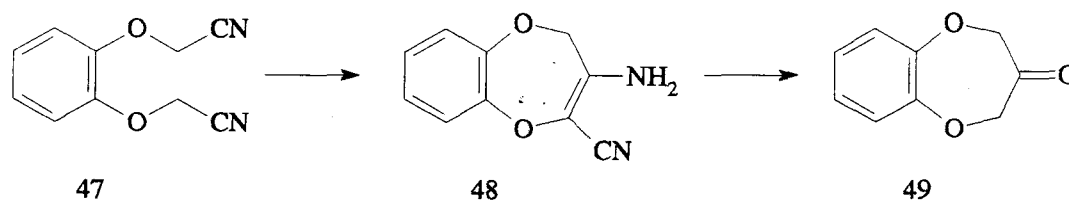
SCHEME 13

They then prepared a number of 2- and 3-substituted 3,4-dihydro-2*H*-1,5-benzodioxepines

(Schemes 14 and 15). Some of these compounds display ß-adrenergic stimulant activity,

especially the secondary amines **53** in which R is an alkyl or arylalkyl group; primary or

tertiary amines, on the other hand, are generally inactive. Compounds of the form **59** have

found use as analgesics, antiarrhythmics and sedatives,[22] while compounds of type **60**

exhibited bronchodilator[23] activity.

The first preparation of 3,4-dihydro-1,5-benzodioxepin-2-one **63** was reported by Eiden and

Schmiz in 1979.[24] They oxidised chromanone **61** with hydrogen peroxide/perchloric acid to

give 2-(*o*-hydroxyphenoxy)propionic acid **62** which was then cyclised with acetic anhydride

to the required product (Scheme 16). Ten years later, Reddy *et al.*[25] reported a facile one-

step synthesis of compound **63** and other derivatives in yields of *ca.* 60% by the Baeyer-

Villiger oxidation of chromanones using *m*-chloroperbenzoic acid (MCPBA) (Scheme 17).

They also synthesised compound **63** in low yield (20%) by condensing catechol with ß-

chloropropionyl chloride. 3,4-Dihydro-4-phenyl-1,5-benzodioxepin-2-ones **65** were first

synthesised very recently,[26] in our laboratory, *via* Baeyer-Villiger oxidation of substituted

flavanones using MCPBA (Scheme 18). It is interesting to note that the regioselective

migration of the aryl substituent (ring A) is opposite to that observed for Schmidt

11

of flavanones[27] (see section 2.4, p. 108).
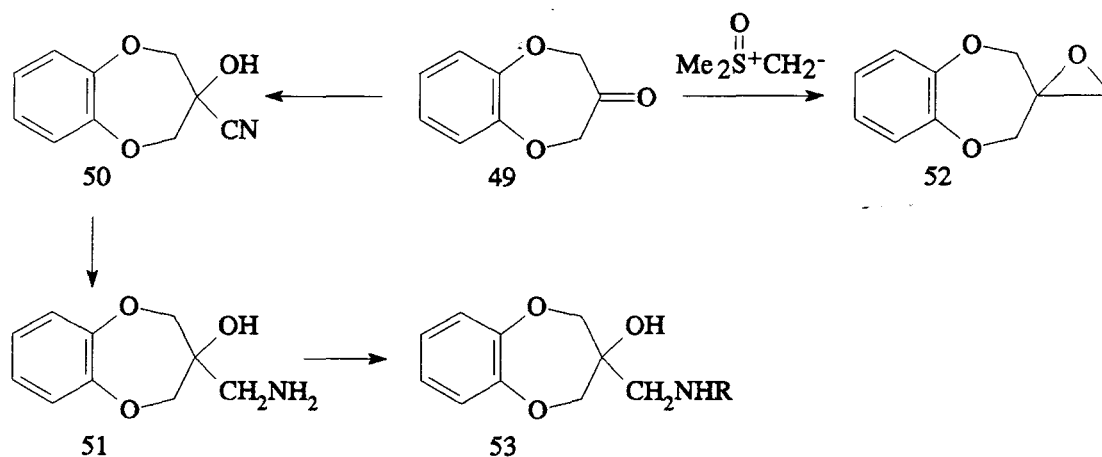
SCHEME 14
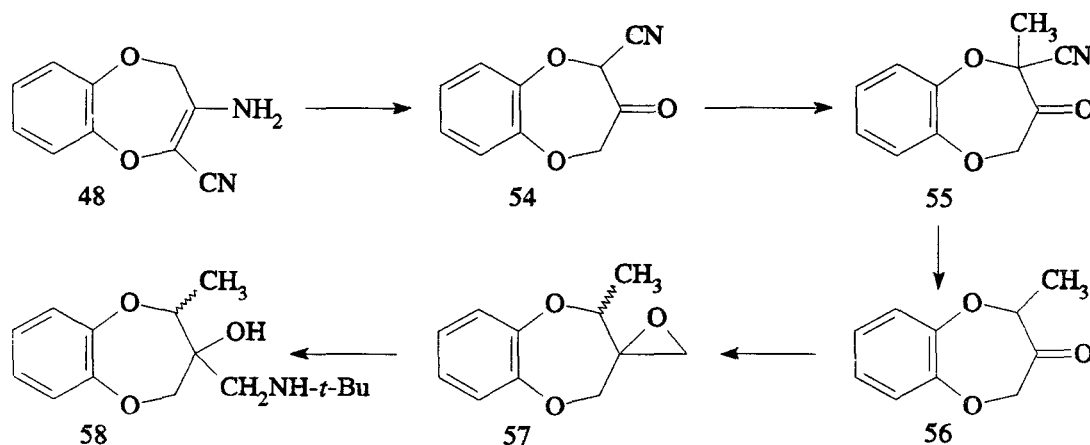
SCHEME 15
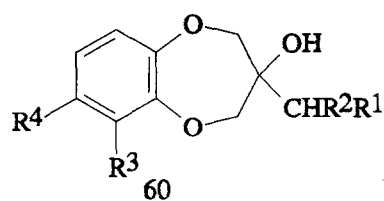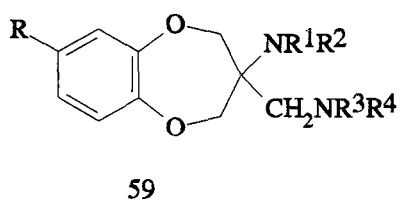
The benzodioxepinones **65** have also been shown to easily undergo solvolytic

transesterification to afford the corresponding methyl esters (see section 2.2, p. 98 for further

discussion), and the fragmentation patterns in the mass spectra of these compounds have also

been studied.[28]

SCHEME 16

(R; R^1 = H,CH$_3$; R=Br,Cl)

SCHEME 17

(R^1=R^2=H, R^1=OMe,Br,F; R^2=OMe,Br,Cl,F)

SCHEME 18

(R^1=C$_2$H$_5$, R^2=R^3=CH$_3$, etc.)

13
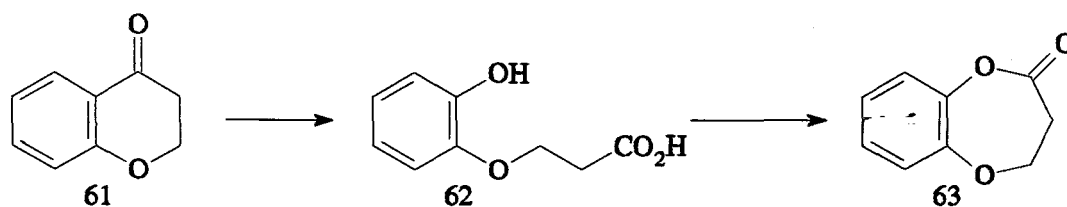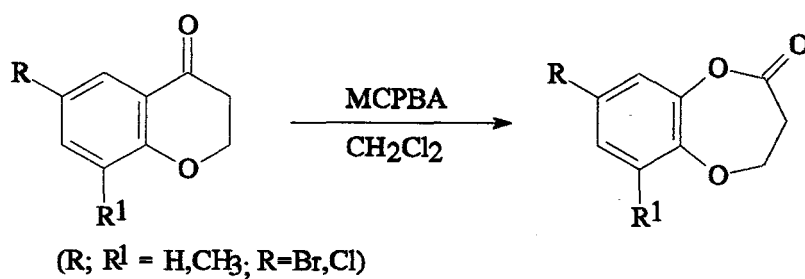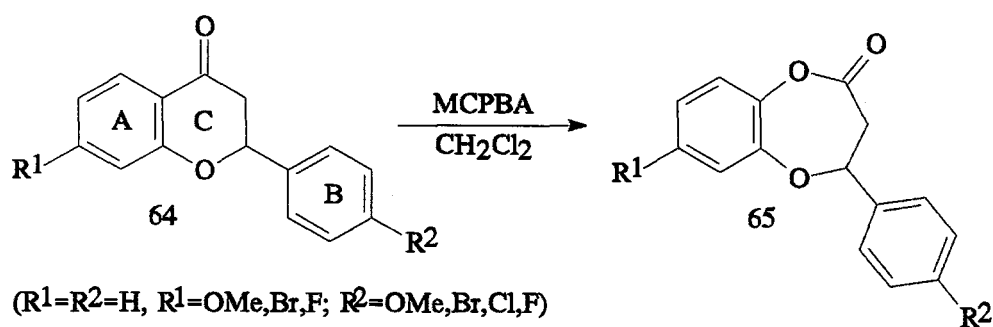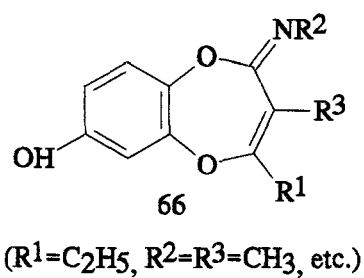
Compounds of type **66**, which may be prepared from *p*-quinone and selected enamines,[29]

have served as useful precursors for pharmacologically active 2*H*-1,5-benzodioxepines, the

α,β-unsaturated imine moiety being susceptible to conjugate addition by various nucleophiles.

Ziegler *et al.*[30] prepared the dilactone **68** by the reaction of catechol with bis(2,4-

dichlorophenyl)benzylmalonate **67** (Scheme 19).
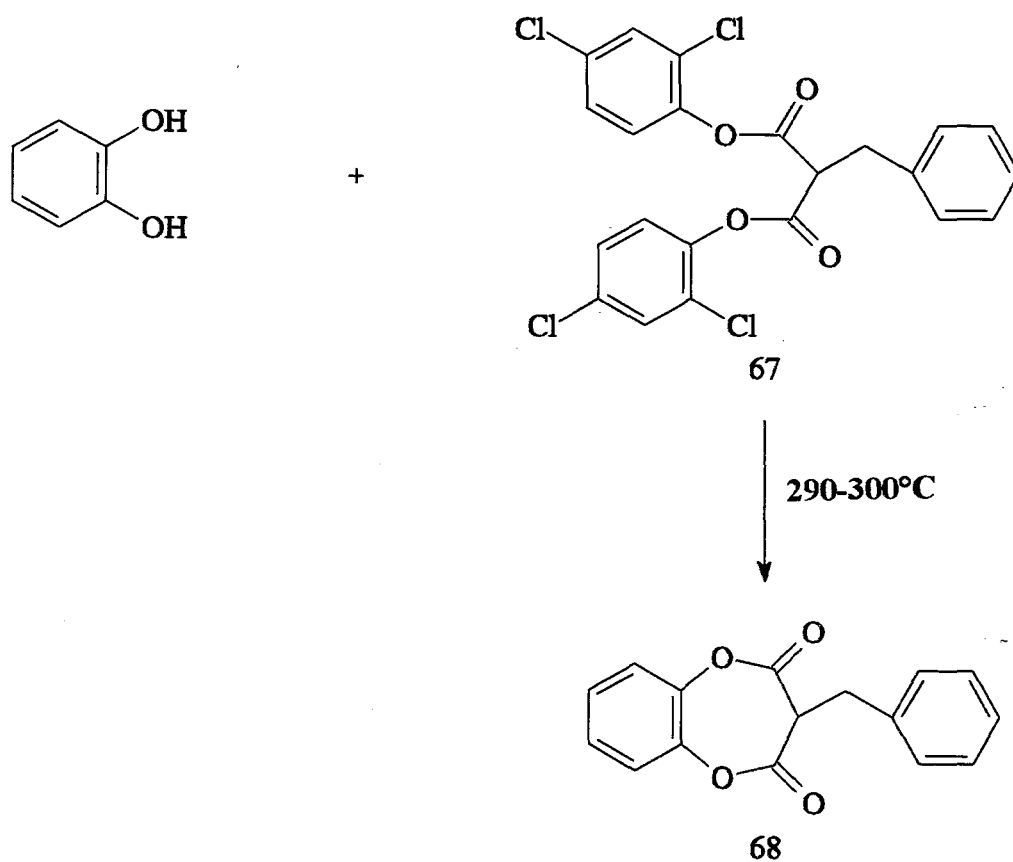
SCHEME 19

The same method was used[31] to prepare the 3-substituted 1,5-benzodioxepin-2,4-diones **69**

in moderate yields by condensation of the corresponding malonyl dichloride with catechol.

These compounds, especially the 3,3-diallyl derivatives, possess central depressant activity,

and their mass spectral fragmentation pathways have been explored.[32]

69
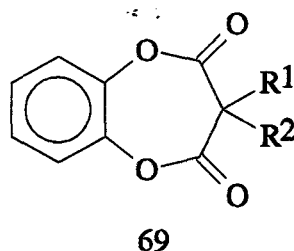
1.1.4   Dibenzodioxepines

There are two known types of dibenzodioxepines, and these are illustrated by 11*H*-dibenzo[*b,e*][1,4]dioxepine **70** and dibenzo[*d,f*][1,3]dioxepine **71**.

70   71
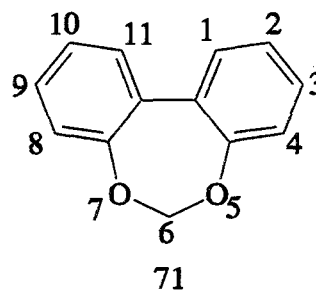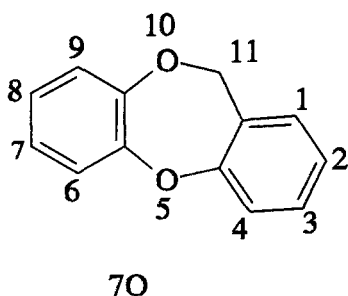
A number of dibenzodioxepine derivatives occur in nature as lactones, usually in lichens and moulds. For example, extraction of the lichen *Lecanora gangaleoides* yielded gangaleoidin **72**,[33] while nidulin **73** was obtained from the mould *Aspergillus nidulans*.[29] In addition to naturally occuring examples, several dibenzodioxepines have been synthesised and the review by Pawloski[4] provides a comprehensive survey of the work done before 1972.

With the aim of studying their photochemical behaviour, Kulkani *et al.*[34] prepared the 11*H*-dibenzo[*b,e*][1,4]dioxepin-11-ones (depsidones) **78-80** by cyclisation of 2-(2-hydroxy-phenoxy)benzoic acid derivatives **77** with acetic anhydride (Scheme 20). An additional mode

15

of cyclisation was observed when polyphosphate ester (PPE) was used, the same acids **77**

yielding fourteen membered dilactones **81** along with the depsidones. Noyce and Weldon[36]

also prepared depsidones by the same general method, but using ß-naphthalenesulfonic acid,

thionyl chloride or pyridine as cyclisation agents.

As is the case for benzodioxepinones, ring opening is a typical reaction of

dibenzodioxepinones such as compound **78**. Acid or base catalysed transesterification have

been shown[35,36] to take place (Scheme 21). Photo-induced α-cleavage (breaking of the bond

between the ester carbonyl and the oxygen) for the phenyl benzoate system, in solvents like

benzene and cyclohexane, leads to "photo-Fries rearrangement" or to solvolysis products

when solvents like methanol are used[36] (Scheme 22).

72

73

74 + 75 → (CuO,K₂CO₃) → 76

(i) hydrolysis
(ii)demethylation

	R¹	R²
78	H	H
79	H	Me
80	Me	H

Ac₂O

77

SCHEME 20

81
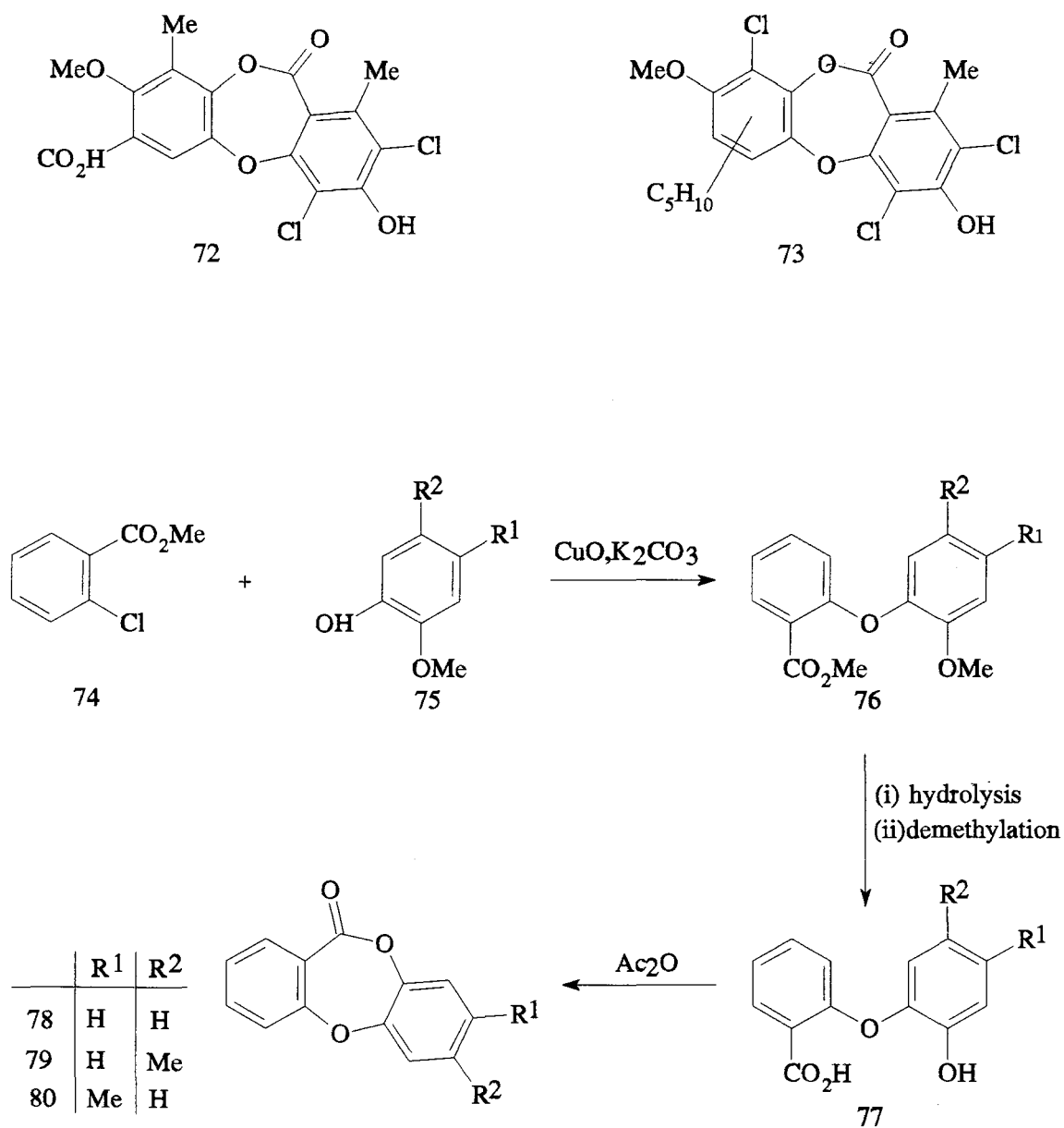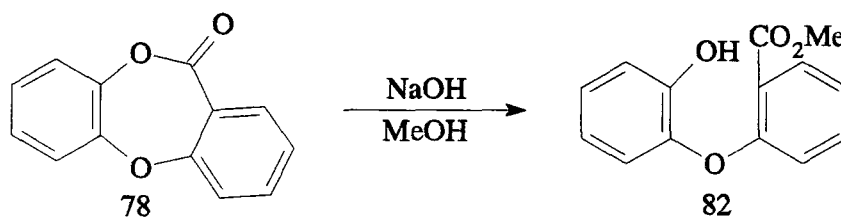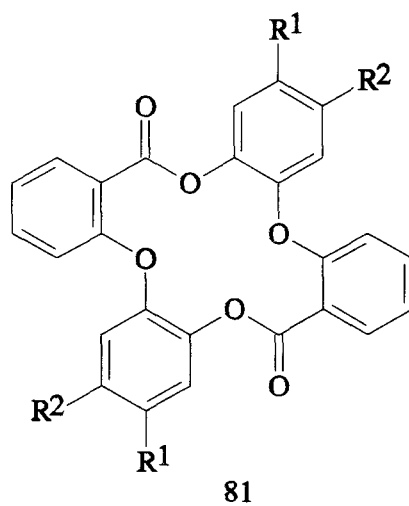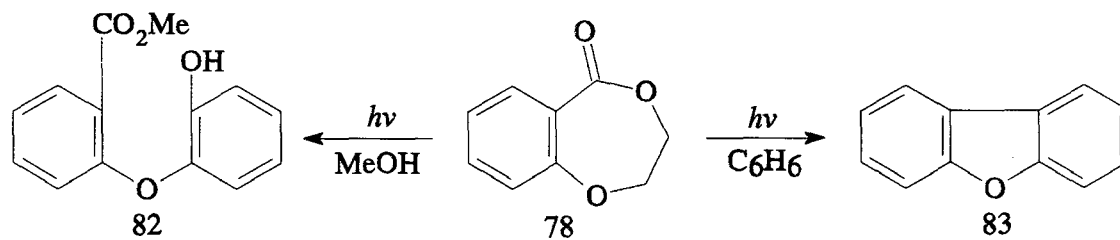
SCHEME 21

SCHEME 22

1.2 BENZOXATHIEPINES

Despite the probable pharmacological activity of 1,5-benzoxathiepine derivatives, their synthesis has not been extensively studied. In fact, relatively few reports on these compounds have appeared in the literature.[37-42] 3,4-Dihydro-2H-1,5-benzoxathiepine **85** was first synthesised[43] from a mixture of 2-hydroxythiophenol and 1,3-dibromopropane irradiated with UV light. Kuyazev et $al.$[44] modified this procedure by simply boiling the mixture of the two substrates in a solution of sodium glycolate in ethylene glycol. They went a step further by also preparing the sulphone **86** and its nitro-substituted derivative **87** (Scheme 23).
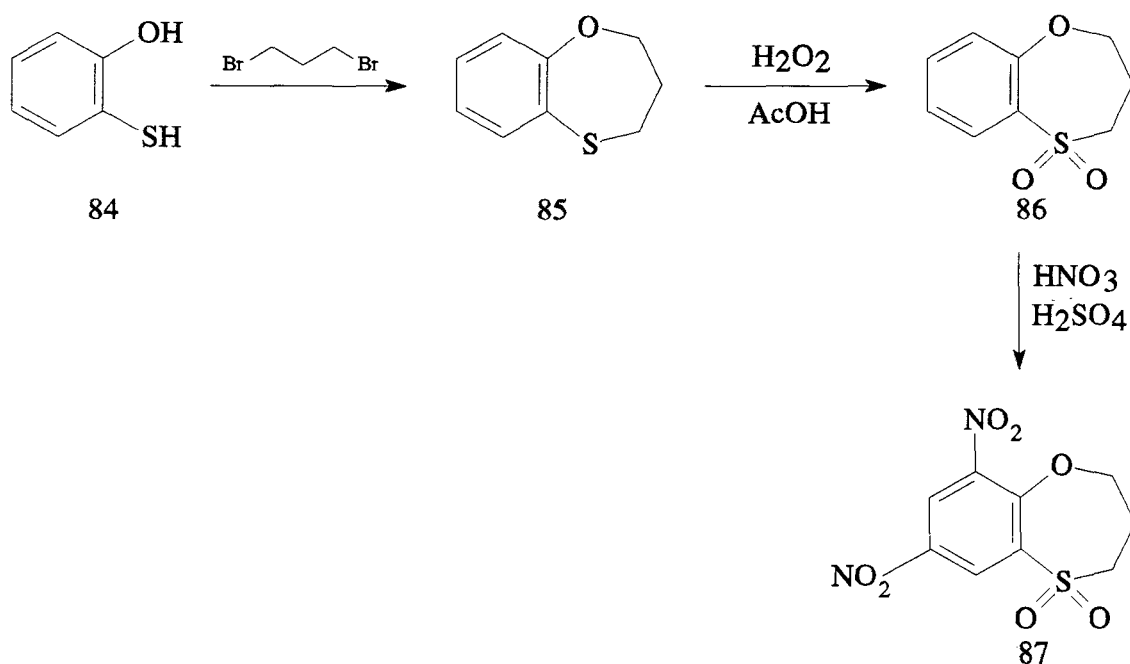
SCHEME 23

Cabiddu *et al.*[38] were the first to introduce a functional group into the 3-position of the 1,5-benzoxathiepine ring by reacting 2-hydroxythiophenols with epichlorohydrins in aqueous alkaline solution (Scheme 24). These results are in contrast to those obtained[44] in the reactions of catechols with epichlorohydrins, in which both 1,4-benzodioxanes and 1,5-benzodioxepines are produced, with the former predominating. It can be concluded that the larger sulfur atom preferentially attacks the exocyclic carbon of the epoxidic moiety, followed by phenoxide attack at the "outer" ring carbon to give compound **90** rather than compound **91**. 1,5-Benzoxathiepines with functional groups at the 2-, 3-, and 4-positions were prepared[45] *via* Dieckman cyclisation of the oxygen -, sulfur - diacetic acid esters **92** which, in turn, were synthesised from 2-hydroxythiophenols (Schemes 25 and 26). Compound **101** was obtained by Thorpe-Ziegler reaction of dinitrile **98** followed by hydrolysis of the resulting 3-amino-2*H*-1,5-benzoxathiepin-4-carbonitrile **99**. This ketonitrile (compound **101**) was also prepared by the reaction of methyl 2-cyanomethylthio-4-methoxyphenoxyacetate **100** (Scheme 27).
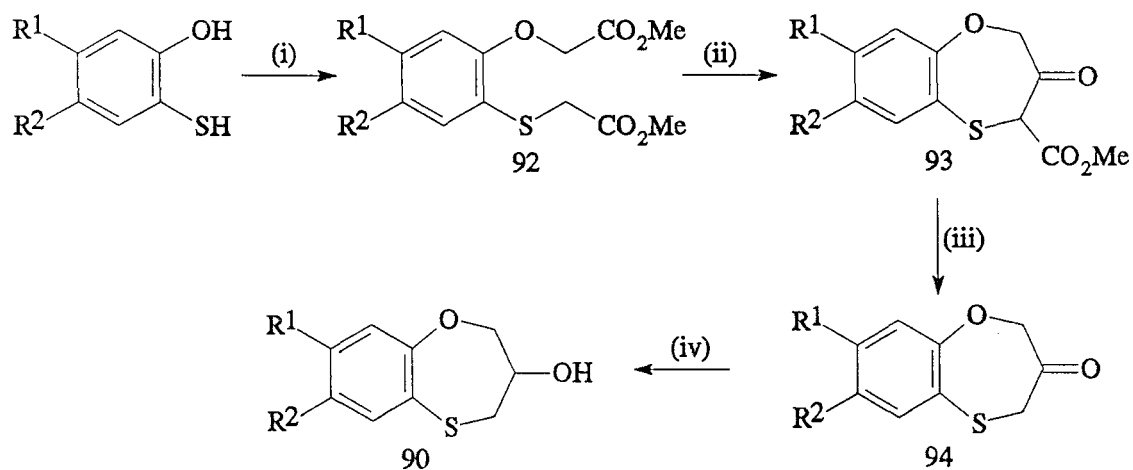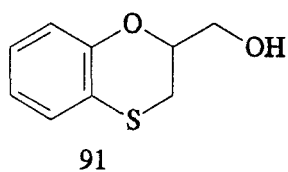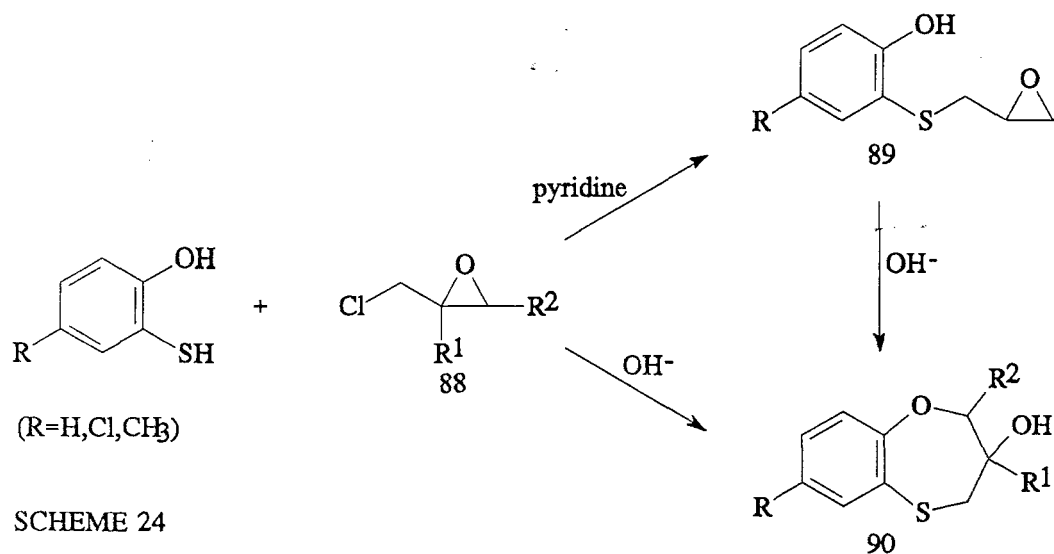
SCHEME 24

SCHEME 25 Reagents: (i)BrCH2CO2Me, (ii)NaOMe, DMF, (iii)H3O+, (iv)NaBH4.

21

Diltiazem **102** has been reported[41] to be a serotonin S_2-receptor-blocking agent and, hence,

Sugihara *et al.*[40] synthesised a number of 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols with an

aminoalkyl group at the 2-, 3- or 4-position with the aim of finding a novel S_2-receptor-

blocker. The piperazinyl derivative **106** proved to be the most potent and the most selective

S_2-receptor-blocker, and the synthesis of this compound is outlined in Scheme 28. Structure-

activity relationships as well as configurational and conformational aspects of compound **106**

and related systems have been studied.[41] Compound **112**, which lacks the 3-hydroxy and 4-

ester groups, is less active than compound **106**, and was prepared as shown in Scheme 29.

The last step of the sequence involves hydrolysis of the acetal group of compound **111**

followed by reductive amination. Being the most suitable substrate from which to synthesise

1,5-benzoxathiepine derivatives, 2-hydroxythiophenol has also been used together with carbon

suboxide to prepare[32,36,42] 3*H*-1,5-benzoxathiepine-2,4-dione **113** (Scheme 30). This

compound has been reported[40] to be antimicrobially active against blastomycetes and Gram-

positive microorganisms. The electron impact mass spectrometry of these compounds has

also been studied.[32] Very little work has been done on 1,4-benzoxathiepine derivatives and,

to our knowledge, the report by Ishibashi *et al.*[39] is the only one to have appeared in the

literature to date. Benzo-fused benzoxathiepine derivatives such as compound **114** have also

been synthesised.[34,36]
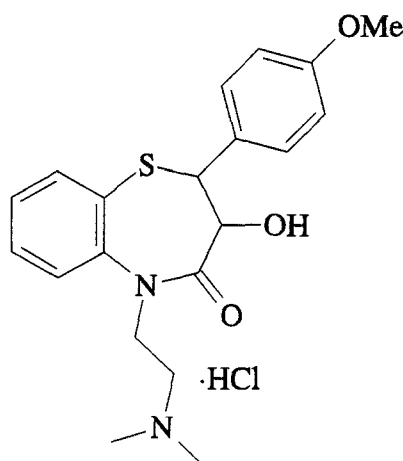
102
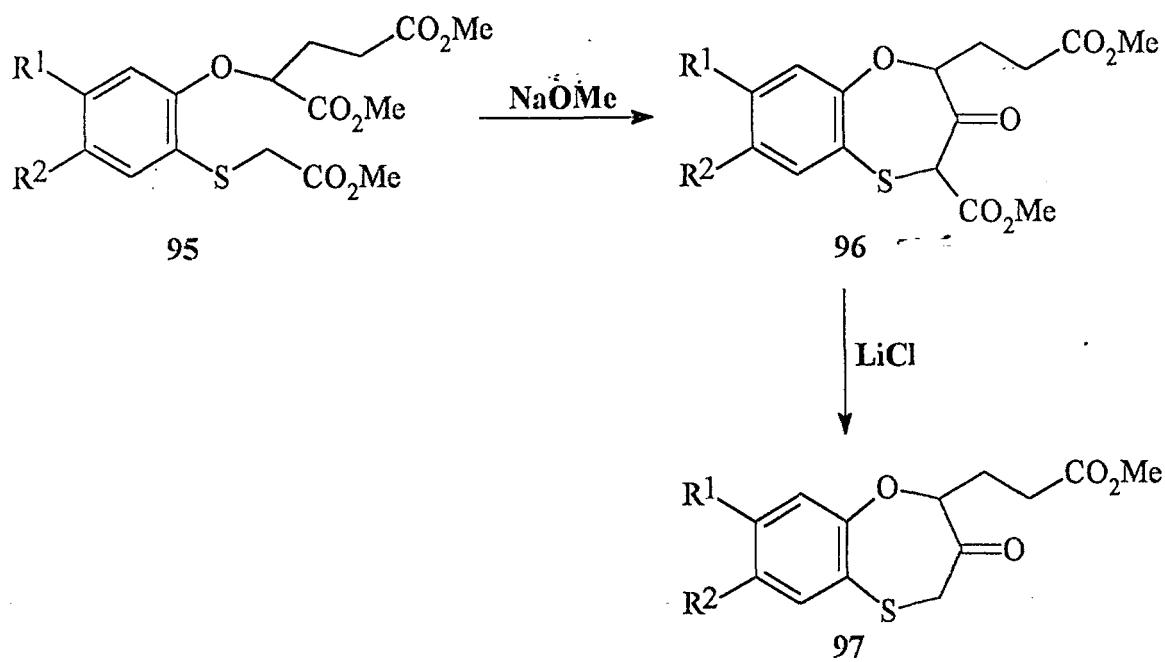
SCHEME 26
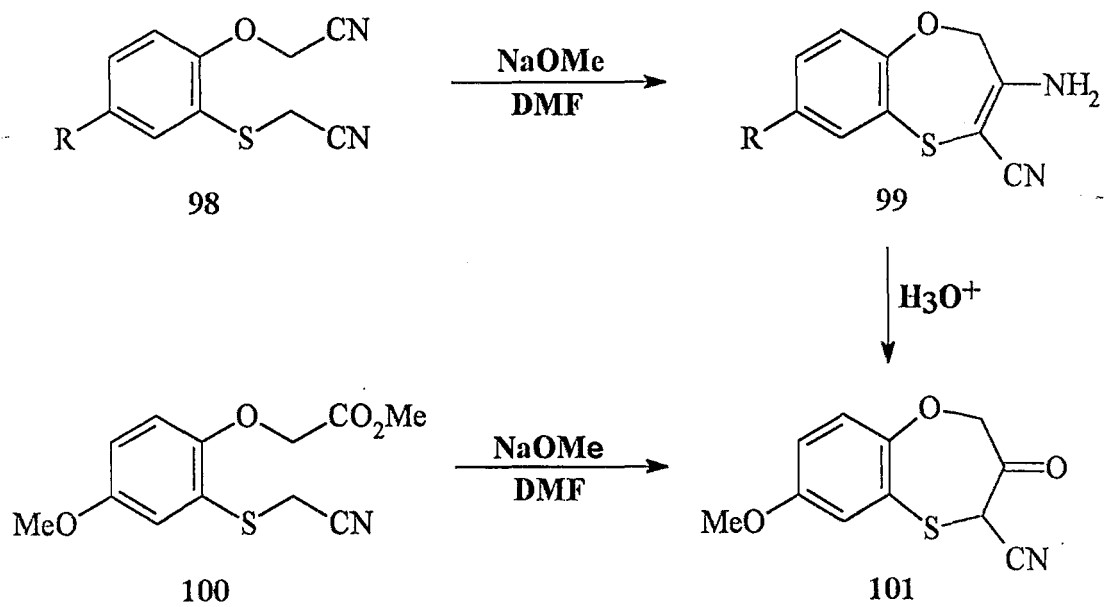
SCHEME 27
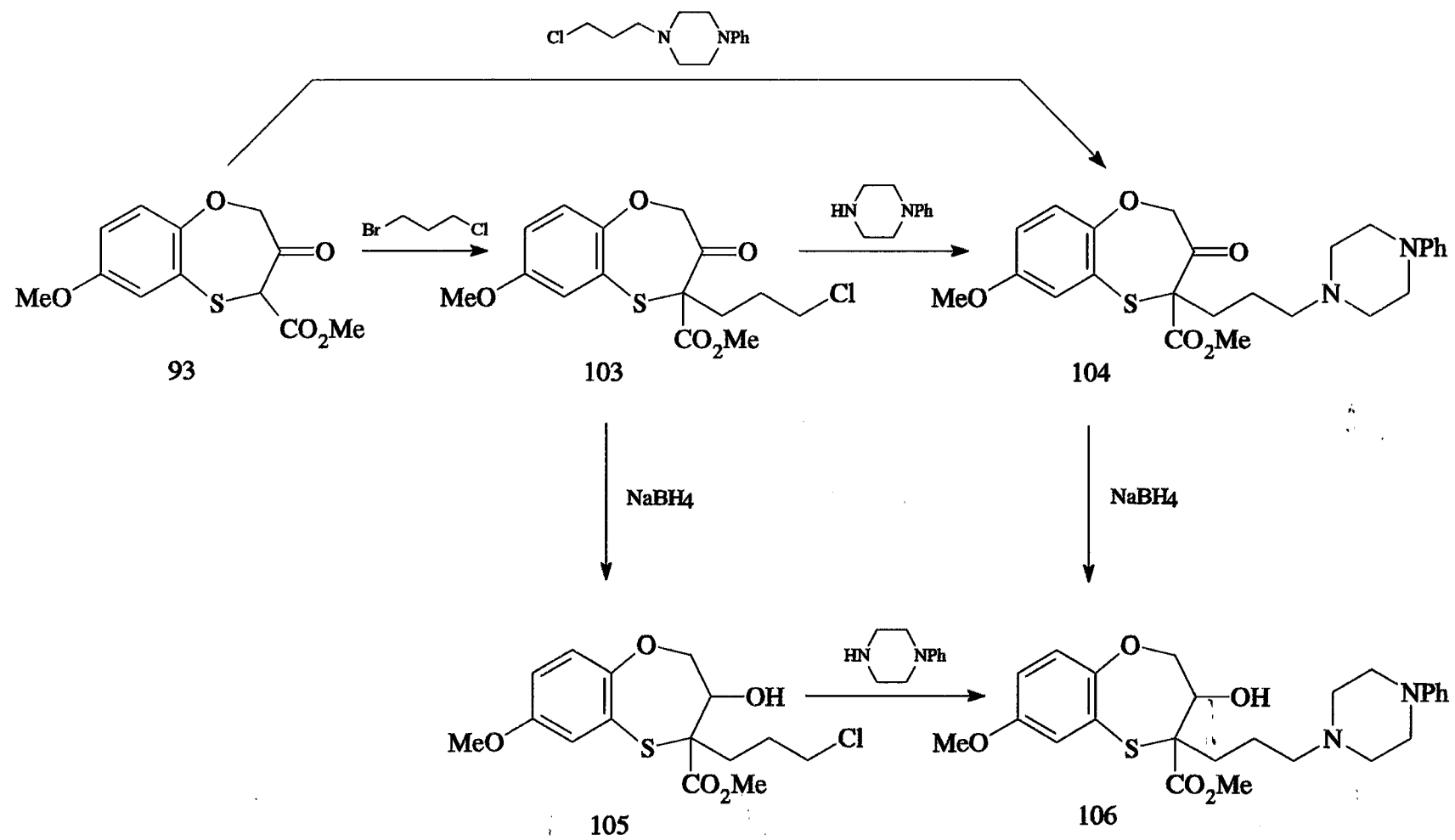
SCHEME 28
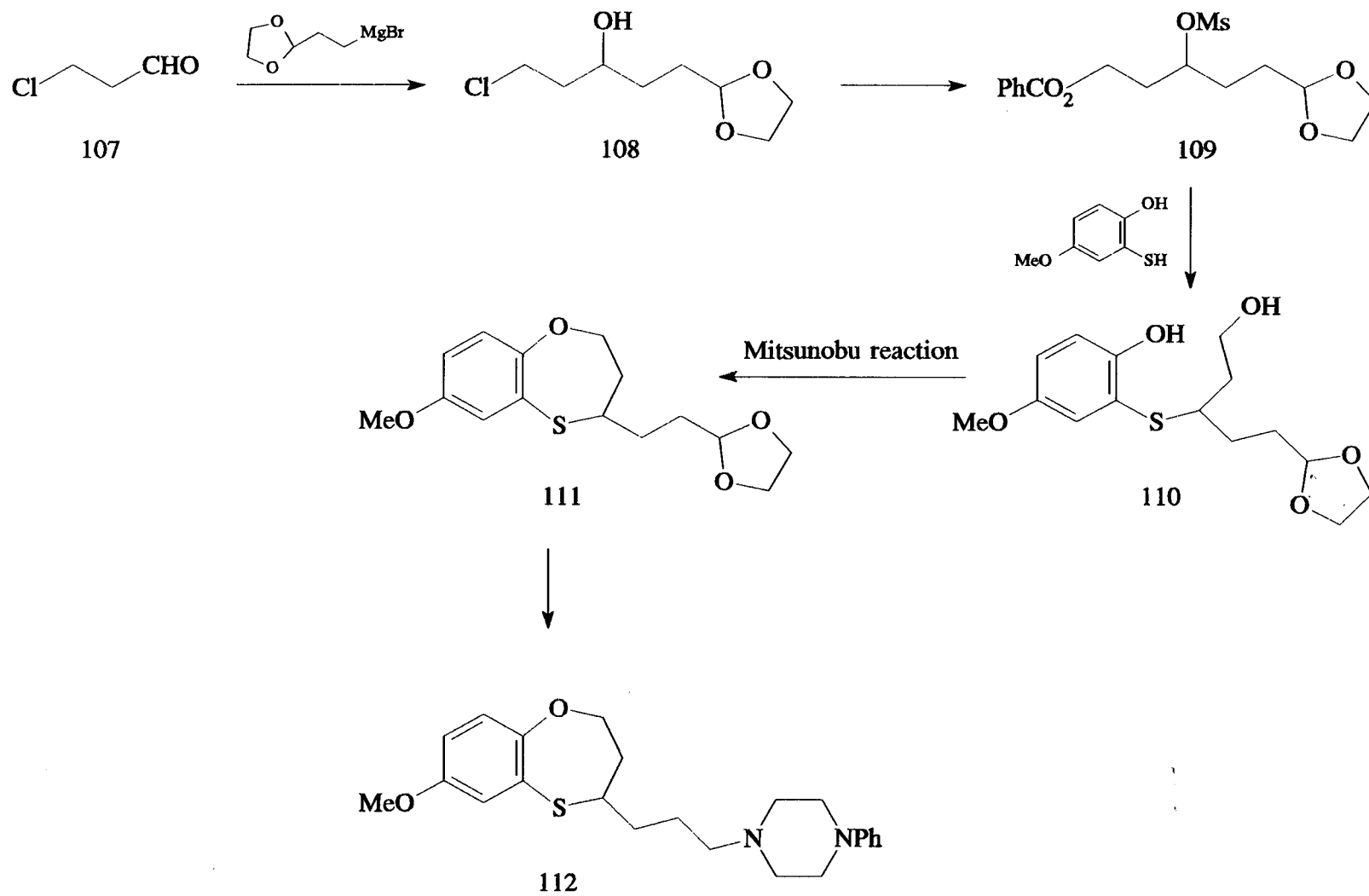
SCHEME 29

SCHEME 30

114
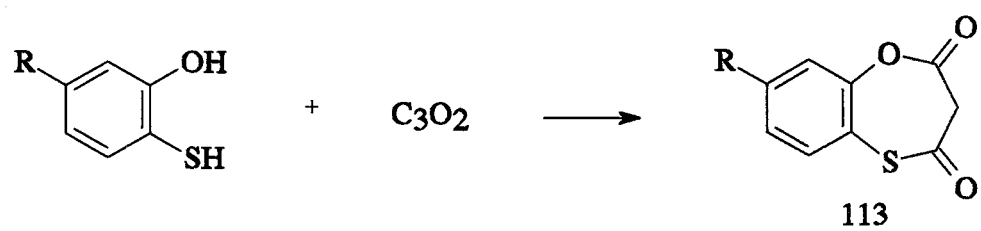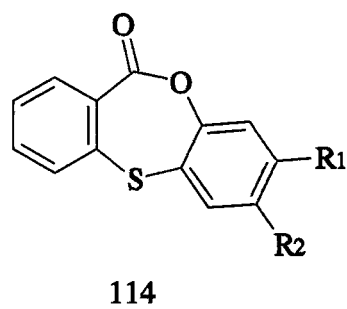
1.3   BENZODIAZEPINES

Benzodiazepines are the most commonly prescribed drugs in the world today. They possess

a broad range of biological activities and are widely used as antianxiety agents,[48] daytime

sedatives,[48,49] tranquilizers,[48] anticonvulsants, hypnotics, muscle relaxants,[49] spasmolytics,[50]

analgesics[51,52] and sleep inducers.[48] 1,4-Benzodiazepine derivatives also interact with various

biological receptors, which are unrelated to the diazepine receptor responsible for the

tranquilizing and antianxiety effects of Valium® (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-

1,4-benzodiazepin-2-one 115), the best known benzodiazepine. Valium® was first synthesised

and characterised in the late 1950's.
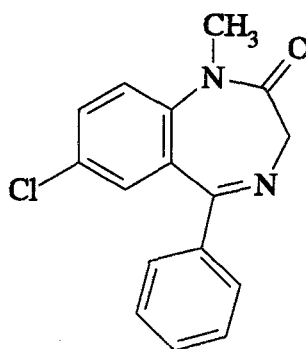
115

Two unexpected transformations led to the discovery and exploitation of the benzodiazepines.

Firstly, in the thirties, Sternbach found that the oximes 116 underwent dehydration to

quinazoline-3-oxides (Scheme 31).[53]   Secondly, reaction of 6-chloro-2-chloromethyl-4-

phenylquinazoline-3-oxide 118 with methylamine gave the ring-expanded product 120 rather

than the expected substitution product 119 (Scheme 32).[54]
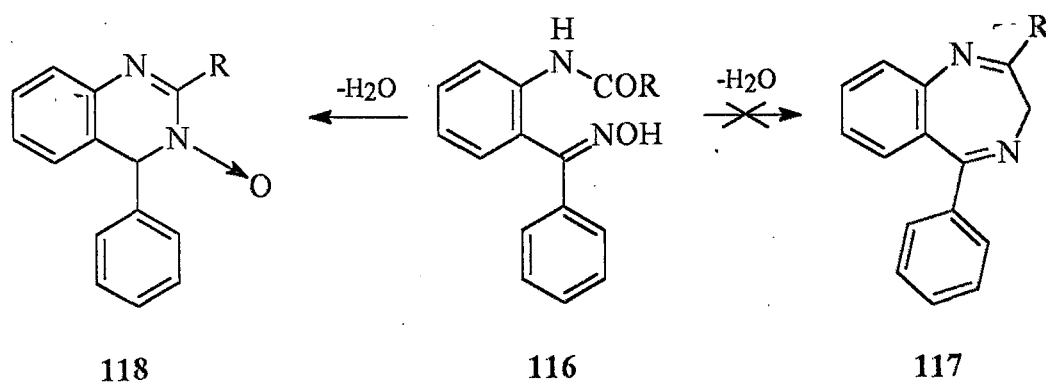
SCHEME 31
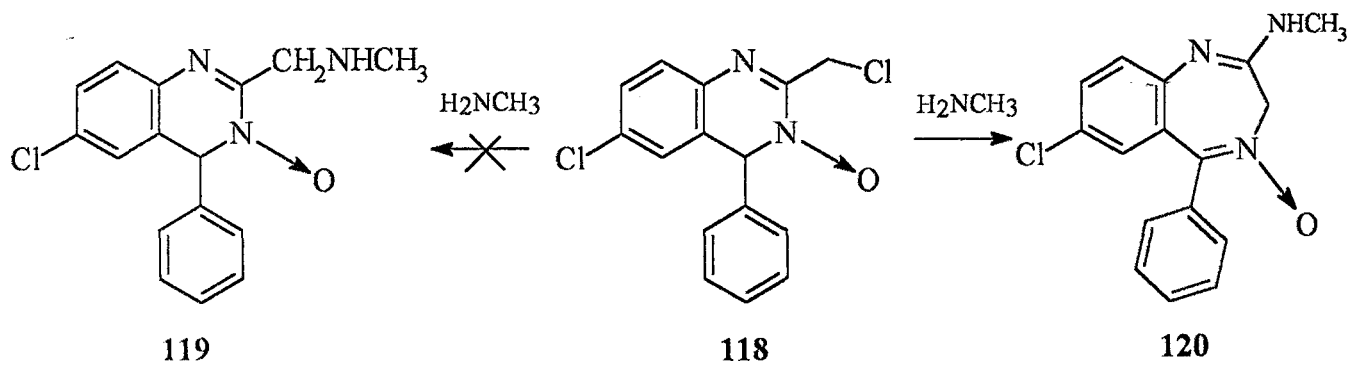
SCHEME 32

Compound **120** (chlordiazepoxide) was found to have hypnotic, sedative, and antistrychnine

effects and was marketed as Librium$^{\circledast}$ in 1960.[53,55,56] Since this first synthesis of a

biologically active benzodiazepine, a large number of 7-membered heterocyclic analogues

have been synthesised and tested for a variety of biological effects.[54-56] There are several

established methods for the synthesis of benzodiazepine derivatives. New methods for

preparing known and new benzodiazepines continue to appear in scientific papers, and much

effort has been expended in modifying pharmacological activity by altering or relocating the

heteroatoms.

1.3.1 1,4-Benzodiazepines

1,4-Benzodiazepines have received intensive study because of their importance in

psychotherapy, and many synthetic routes to these compounds have been described. These

include cyclisation of a variety of substrates such as amino esters (Scheme 33), cyano esters

and many more.[57-60] Reactions between 1,5-bisnitrogen nucleophiles and 1,2-dihalides and

α-halogeno esters have also been reported.[61,62]
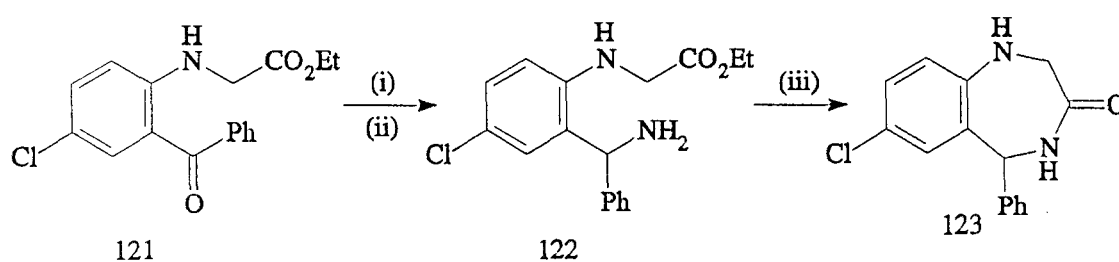
SCHEME 33 Reagents:(i)NH$_2$OH, (ii)H$_2$(Pd), (iii)Pyridine,heat.

1,4-Benzodiazepines are generally prepared, however, by ring-enlargement methods. As indicated above, chlordiazepoxide **120** was obtained[62] by ring-enlargement of quinazoline-3-oxide **118**, which was prepared in turn by the sequence of reactions shown in Scheme 34. It should be noted that increasing the size of the substituent at C-2 and replacing the phenyl group at C-5 by other substituents decreases potency relative to chlordiazepoxide **120**. 1,4-Benzodiazepines can also be synthesised through ring-expansion *via* Schmidt[63] and Beckmann[64] rearrangements of 1,2,3,4-tetrahydroquinolin-4-ones and their oximes respectively. The Schmidt reaction often has advantages over cyclisation methods for preparing benzodiazepine analogues. The reaction conditions are milder and yields are often higher. In some cases, both the 1,4- and 1,5-isomers can be isolated in a single reaction (Scheme 35). Another ring-expansion method involves preparing[10] 1,4-benzodiazepin-2-ones **133** in high yield by oxidation of 2-aminomethylindoles **132** (Scheme 36). This route has been used for the commercial production of several CNS-active compounds.
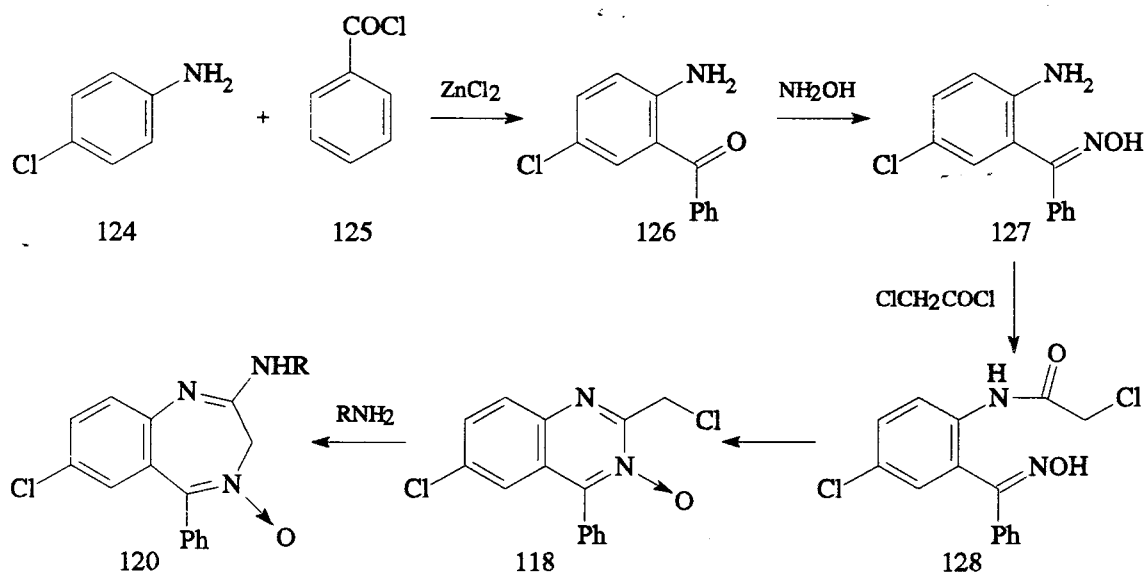
SCHEME 34
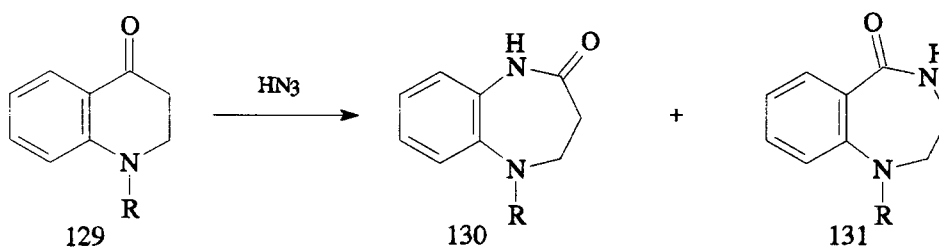
SCHEME 35
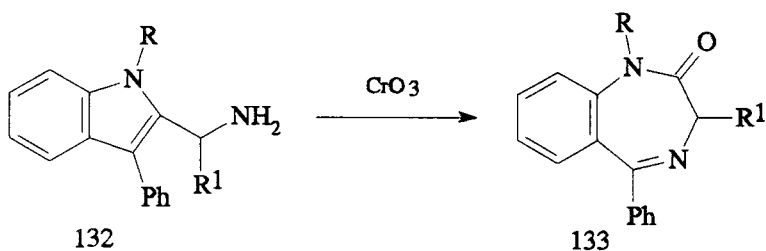
SCHEME 36

Recently,[65] Bunin and Ellman developed a general and expedient method for the synthesis of 1,4-benzodiazepine derivatives on a solid support (Scheme 37) using three separate components: 2-aminobenzophenones, amino acids and alkylating agents. The products, the fully derivatised 1,4-benzodiazepines **137**, can be easily cleaved from the solid support. A range of benzodiazepines with different side chains has been synthesised in high yields using this novel approach.

Many other substituted 1,4-benzodiazepine derivatives, *e.g.* compounds **138** and **139**, are obtained[66-68,70-73] by reasoned modification of the known benzodiazepines. Compound **139** is a selective, orally effective antagonist for peripheral receptors.[73] Methods for effecting transformations of the carbonyl group, *N*-alkylation and *S*-alkylation in the heterocyclic ring have been reported.[68,73] Thiation of compound **140** has been achieved[69] using phosphorous pentasulfide in pyridine to give the thiolactam **141**, which was then alkylated with dimethyl sulfate to afford compound **142**. Recently, Pinto and Fryer[75] reported a novel method for *N*-methylation of the lactam nitrogen in compound **140** using an *N,N*-dimethylformamide - dimethyl acetal mixture, which acts as both reagent and solvent for the reaction (Scheme 38). This method does not require a base and hence has advantages over traditional methods[76] in which the benzodiazepinone anion is treated with an alkyl halide. It has been shown[76] that treatment of compound **143** with excess base may result in ring contraction and rearrangement of the seven-membered ring.

134
2-Aminobenzophenone derivative
linked to solid support.

135

137
1,4-Benzodiazepine derivative
linked to solid support

136
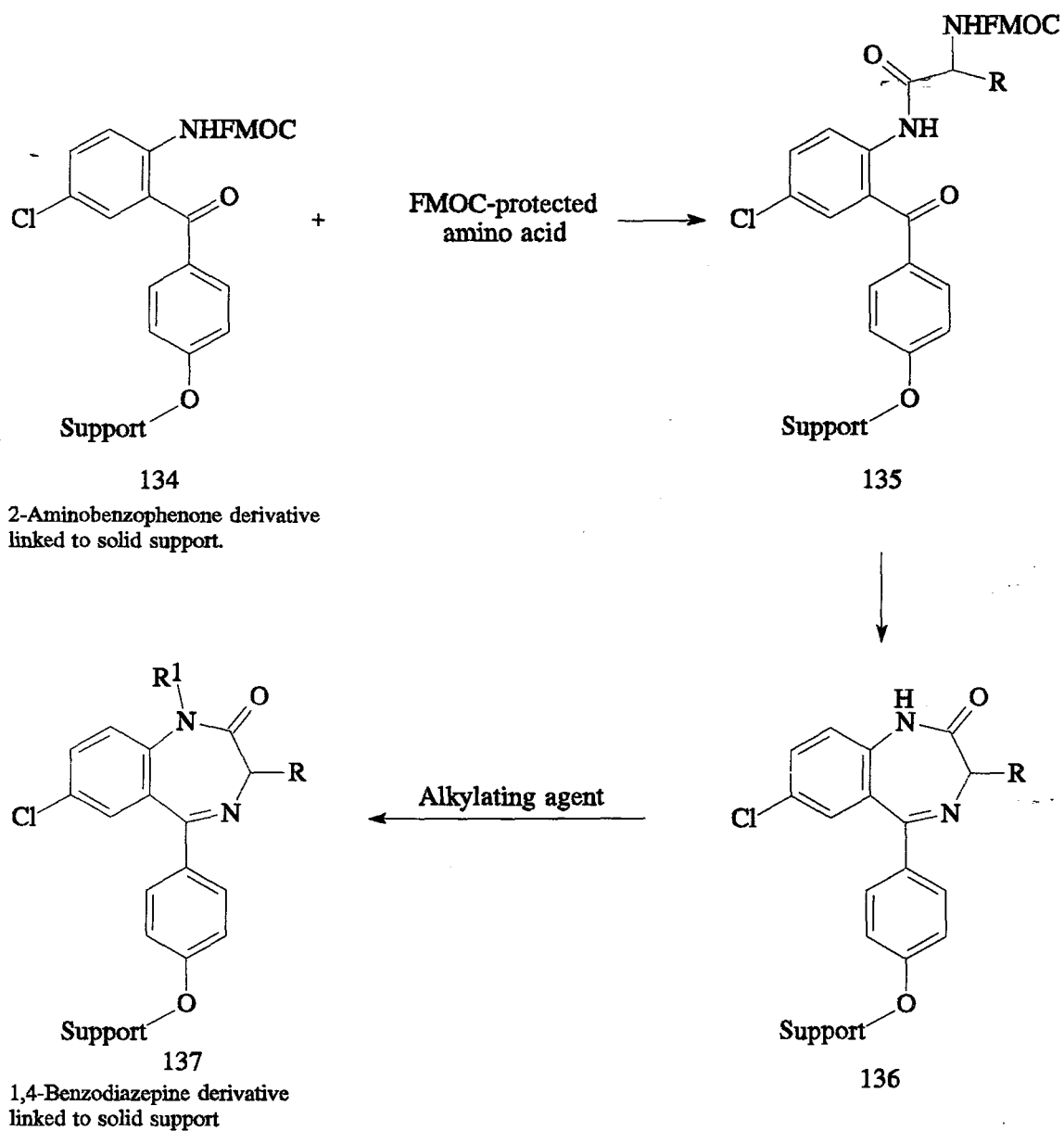
SCHEME 37   FMOC = fluorenylmethoxycarbonyl.

138

139

140

141

142

143
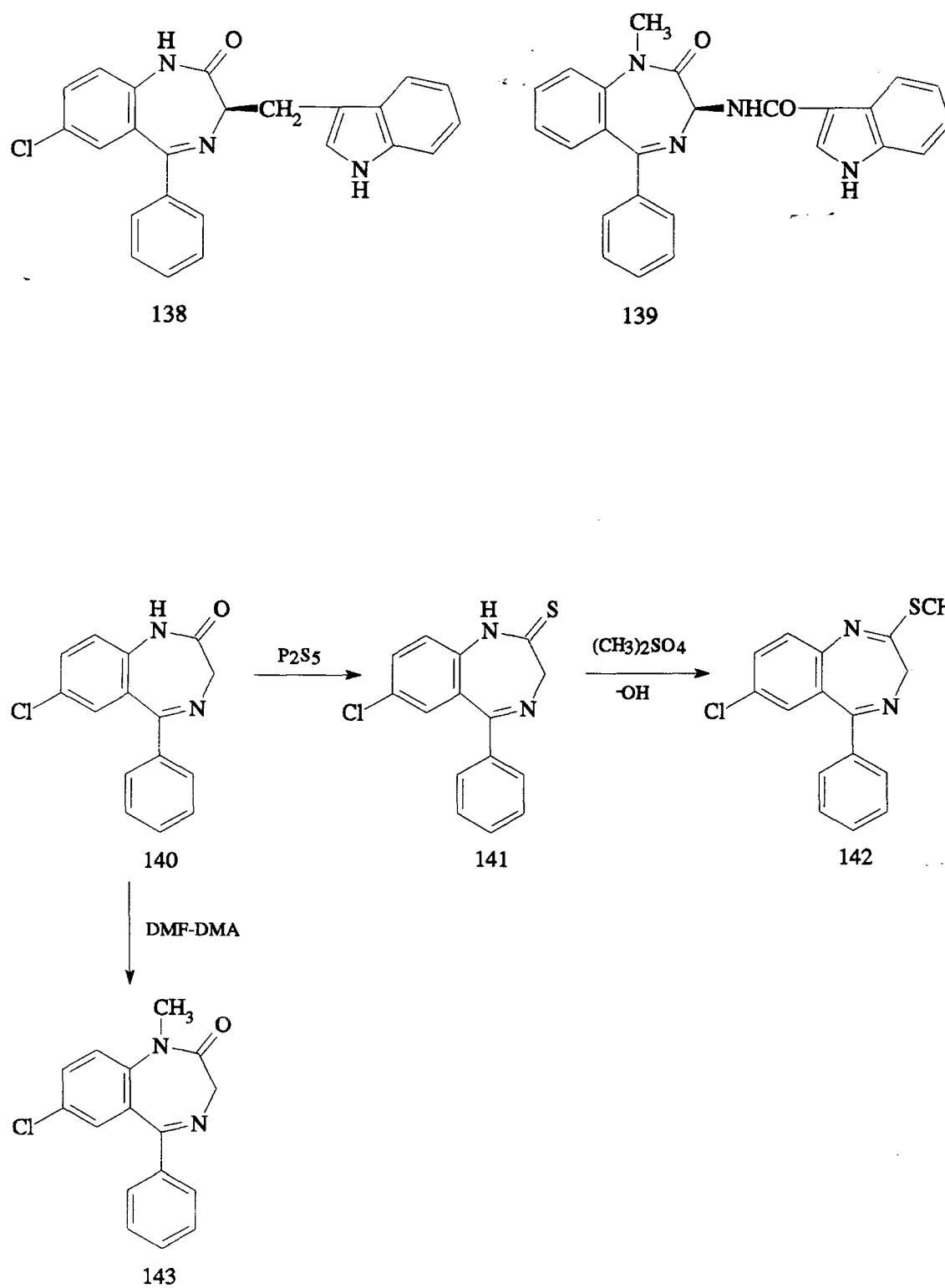
SCHEME 38

1.3.2 1,5-Benzodiazepines

1,5-Benzodiazepines are also important due to their biological activity. It has been reported

that 7-substituted benzodiazepines **144** are psychosedative and tranquilizing agents,[77] while

compounds of the form **145** are anticonvulsive and sedative drugs.[78] 2-[2,3-Dihydro-4-(3-

iodo-4-chlorophenyl)-2-oxo-1*H*-1,5-benzodiazepin-1-yl]acetic acid on the other hand is useful

for treatment of diabetic complications.
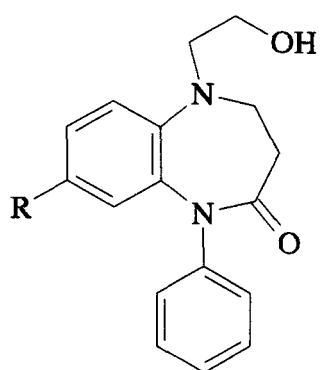
144   **145**
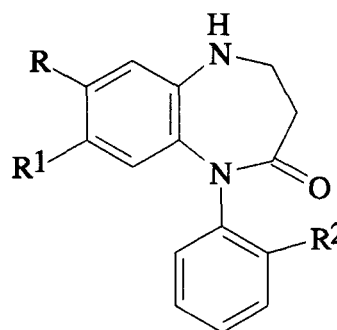
(R = Br,Cl, or N⊖)

In contrast to the synthesis of 1,4-benzodiazepines, there are relatively few methods for the

preparation of 1,5-benzodiazepine derivatives. These are largely limited to condensations

of 1,2-benzenediamine with various substrates, *e.g.* β-keto esters,[79,81] α,β-unsaturated acids,[81]

1-aryl-3,3-dimercapto-2-propen-1-ones,[82-85] conjugated imidate salts,[86] 1-aryl-3,3-

bis(methylthio)-2-propen-1-ones,[87] dimethyl allene-1,3-dicarboxylates,[88] dioxinones and

isoxazolones.[89] Thus, 4-aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones **149** have been synthesised

by the condensation of isoxazolones **147** and 1,2-diamines **146** under acidic conditions

(Scheme 39), while 3*H*-1,5-benzodiazepines **151** were obtained[89] from the reaction of benzoyl

substituted ketone dithioacetals **150** with various 1,2-diamines (Scheme 40). Bonsignore *et*

al.[32] reported the preparation of benzo derivatives of seven-membered heterocyclics including

3*H*-1,5-benzodiazepine-2,4-dione **153**, by reacting 1,2-benzenediamine with carbon suboxide

(propadiene-1,3-dione) **152** in diethyl ether (Scheme 41). These compounds (**153**) show

antimicrobial activity against some Gram-positive microorganisms and blastomycetes.[32]

Other 1,5-benzodiazepine derivatives, *e.g.* compounds **156**, possess CNS-depressant activity.

Their synthesis involves treatment of substituted diphenylamine **154** with malonyl chloride,

followed by reduction with Raney nickel to give the intermediate **155** (Scheme 42); base

catalysed cyclisation and alkylation then affords the 1,5-benzodiazepin-2,4-diones **156**.[90]
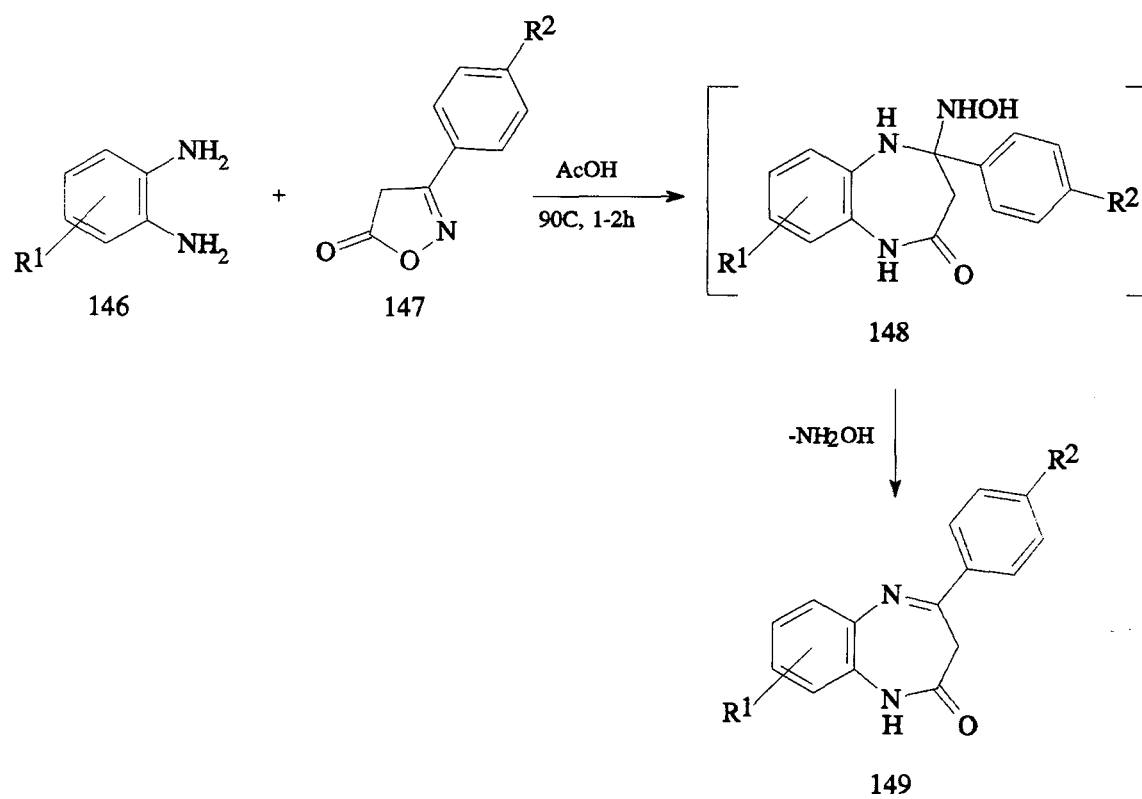
SCHEME 39
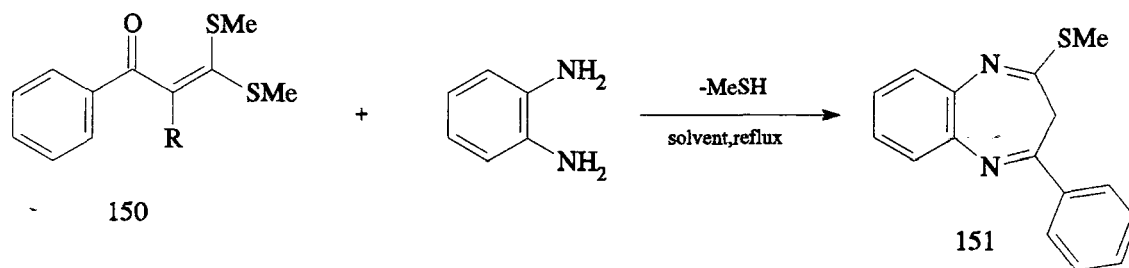
SCHEME 40
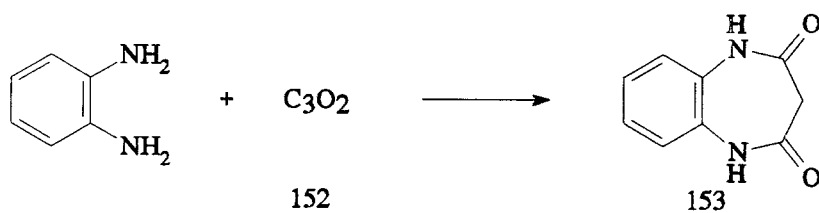
SCHEME 41
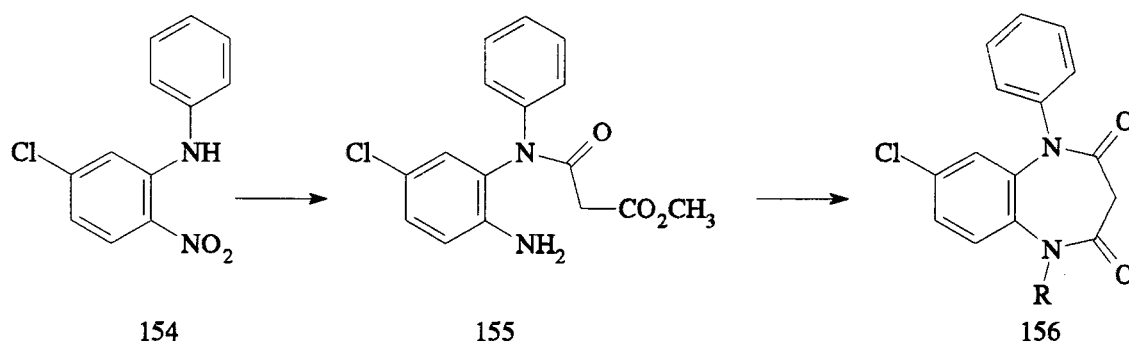
SCHEME 42

1.4. PREVIOUS WORK RELATED TO THE PRESENT STUDY

Previous work related to the present study has involved Schmidt rearrangement[27] and Baeyer-Villiger oxidation[28] of flavanone precursors (Scheme 43). The regioselectivity of heteroatom insertion in the two reactions was found to be opposite, as shown by the formation of compounds **65** and **157** (X=O and Y=O). In a parallel study,[91] attention has been concentrated on the use of the Schmidt reaction to access a variety of benzodiazepine analogues (*e.g.* compounds **157-159**). The NMR spectroscopic properties as well as the mass fragmentation patterns of these compounds have also been studied.
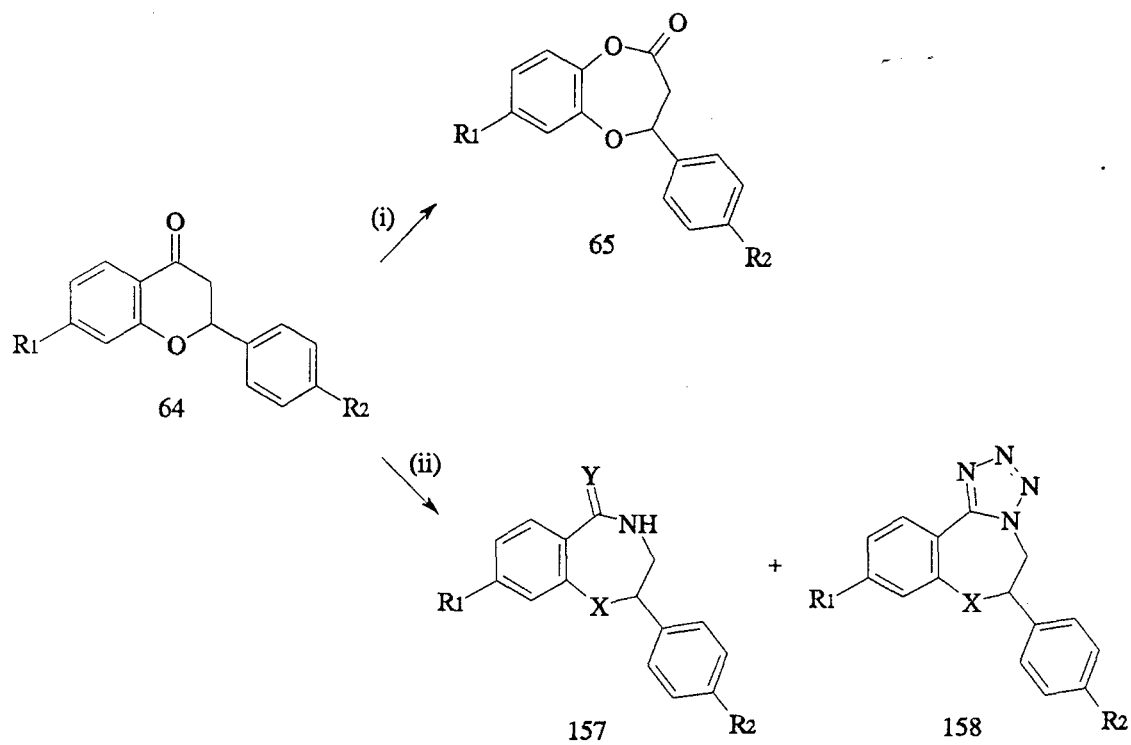
SCHEME 43. Reagents: (i) MCPBA, CH_2Cl_2; (ii) $(CH_3)_3SiN_3$, CF_3CO_2H.
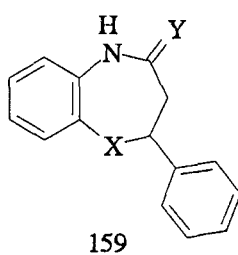
X = O, S, N
Y = O, S

1.5. AIMS OF THE PRESENT INVESTIGATION

This research has been concerned with the extensive development of lines of investigation initiated in an MSc program.[92]   More specifically, the aims of the present study have included the following:-

(i)   The synthesis of a range of benzodioxepine derivatives as benzodiazepine analogues in which the substituents and ring heteroatoms are varied.

(ii)   Detailed mass spectrometric and NMR (^{1}H, ^{13}C and ^{17}O) spectroscopic studies of the benzodioxepine derivatives.

(iii)   An investigation of the kinetics and mechanism of the Baeyer-Villiger oxidation of flavanone precursors, using ^{1}H NMR spectroscopy to elucidate the observed regioselectivity.

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

(v)   The conformational analysis of the benzodiazepine analogues using ^{1}H NMR spectroscopy, X-ray crystallography and computer modelling techniques.

41

2.   DISCUSSION

2.1 SYNTHESIS OF BENZODIAZEPINE ANALOGUES

The required benzodiazepine derivatives were prepared using various synthetic strategies (see Figure 1). These include ring expansion methods [*viz.*, Baeyer-Villiger oxidation of specially prepared flavanones (for benzodioxepines) and Schmidt rearrangement of N-acetylated quinolones (for benzodiazepines)] and cyclisation methods (for benzoxathiepines). In the discussion which follows attention will initially focus on the preparation of the various precursors and their elaboration to benzodiazepine analogues.
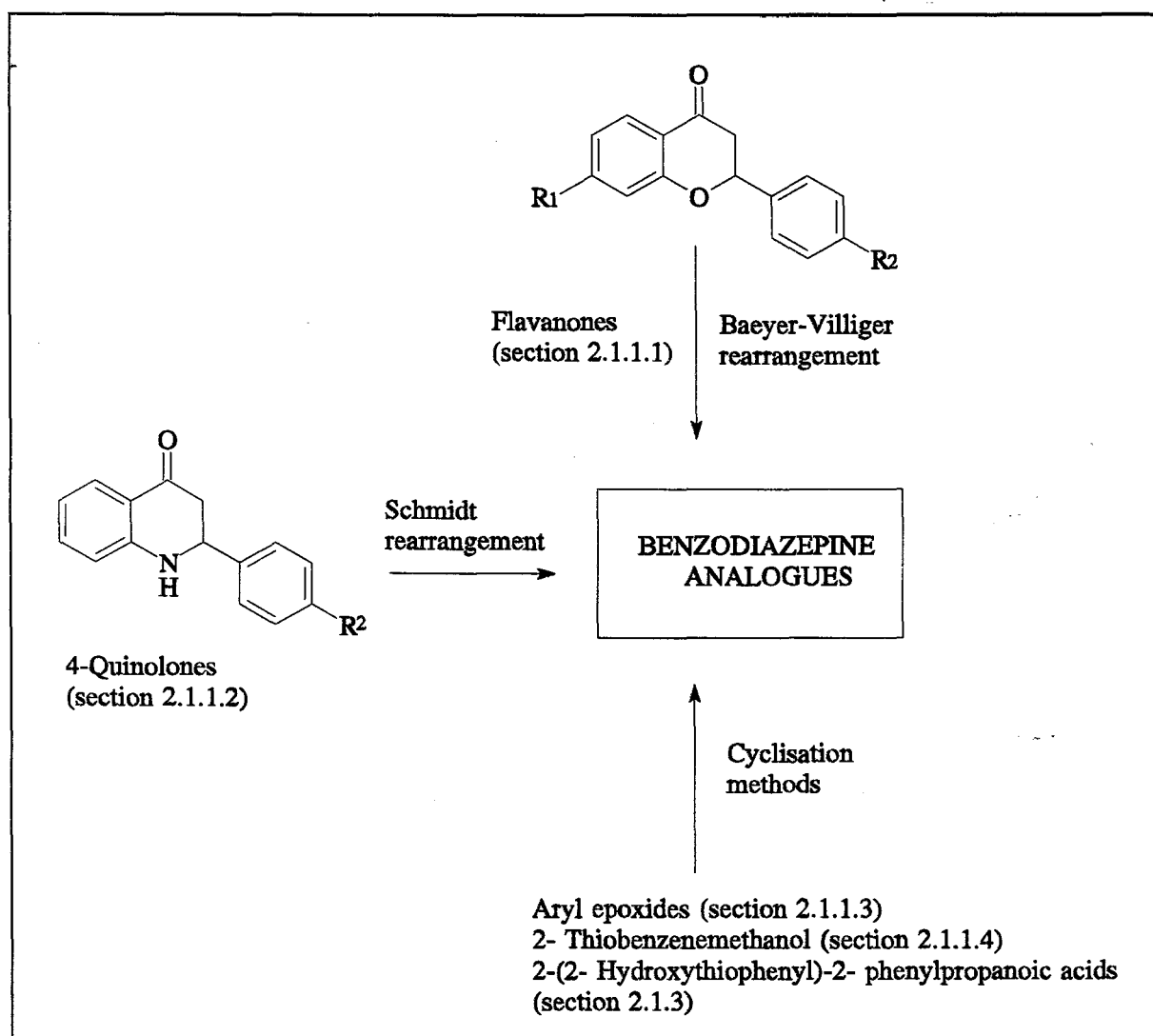
Figure 1: General approaches followed for the preparation of benzodiazepine analogues

2.1.1 PREPARATION OF PRECURSORS

2.1.1.1 Flavanones

Flavanones, which are important intermediates for the synthesis of flavanoids and biflavanoids, are generally prepared by acid- or base-catalysed cyclisation of chalcones, which are typically obtained by base-catalysed condensation of 2-hydroxyacetophenones with benzaldehydes.

(a) 4-Substituted-2-hydroxyacetophenones

The 4-halogeno-2-hydroxyacetophenones **167-169** were readily prepared in high yields as outlined in Scheme 44. The halogenophenols **160-162** were acetylated with acetic anhydride to give the phenyl acetates **163-165**, which were subjected to Fries rearrangement using anhydrous aluminium chloride as a catalyst as described by Bryan et al.[93] The required 2-hydroxyacetophenones were formed by heating the phenyl acetates at high temperature (ca. 175°C)[94,95] and were isolated by steam distillation of the reaction mixture. A different method[96,97] was followed to prepare 2-hydroxy-4-methoxyacetophenone **170**. In this case, the 4-hydroxyl group in 2,4-dihydroxyacetophenone **166** was methylated with dimethyl sulphate-potassium carbonate in acetone.

^{1}H NMR spectoscopy can be used readily to distinguish phenyl acetates from hydroxyacetophenones. The acetate methyl signal resonates at ca. 2.25ppm while the corresponding methyl signal in acetophenones appears upfield at ca. 2.61ppm. Even more noticeable is the absence of an OH signal in the spectra of the phenyl acetates.

166

(iii) ↓

R			
Br	160	163	167
Cl	161	164	168
F	162	165	169
OMe	-	-	170
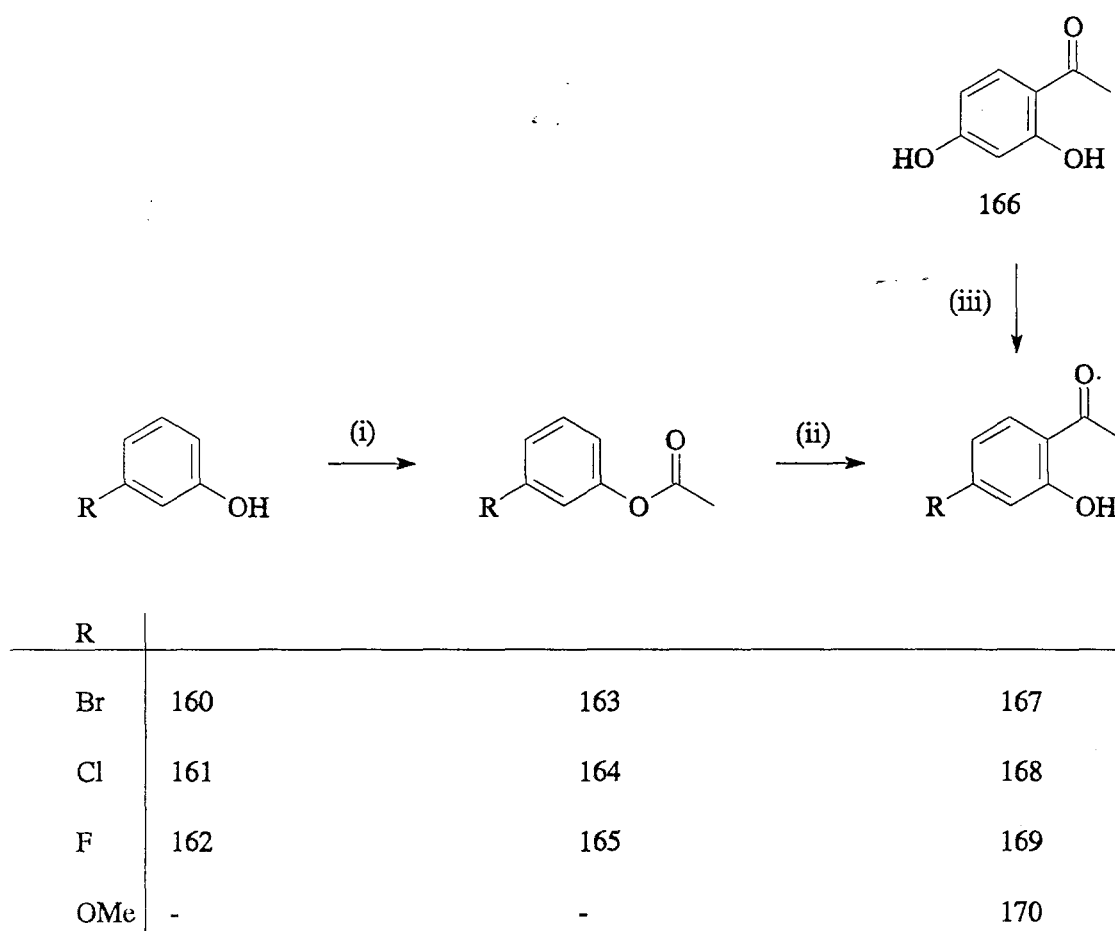
SCHEME 44. Reagents: (i) NaOH-Ac$_2$O, 0-5°C, 1h; (ii) AlCl$_3$, 175-180°C, 3h; (iii) Me$_2$SO$_4$, K$_2$CO$_3$, acetone, heat, 6h.

(b) 2-Hydroxychalcones

2-Hydroxychalcones are versatile intermediates in the synthesis of naturally occurring oxygen heterocycles such as flavanols,[98,99] flavanones,[100-102] and aurones.[103,104] The best synthetic routes to these intermediates involve either Claisen-Schmidt condensation of 2-hydroxy-acetophenones with aryl aldehydes[94,105,106] or the rearrangement of phenyl cinnamates.[107] However, the latter procedure fails to offer much as far as yields are concerned (20-50%). Several condensing agents such as aqueous alkali,[94,108-110] sodium methoxide,[111] piperidine,[109]

mineral acids[109] and solid sodium hydroxide[106] have been used in the condensation of

2-hydroxyacetophenones with aldehydes.   Work has been reported on the kinetics and

mechanism[112-115] of the condensation of benzaldehydes with acetophenone as well as on the

effect of substituents.[116]

2-hydroxyacetophenone (R1) + benzaldehyde (R2) → (i) → chalcone product
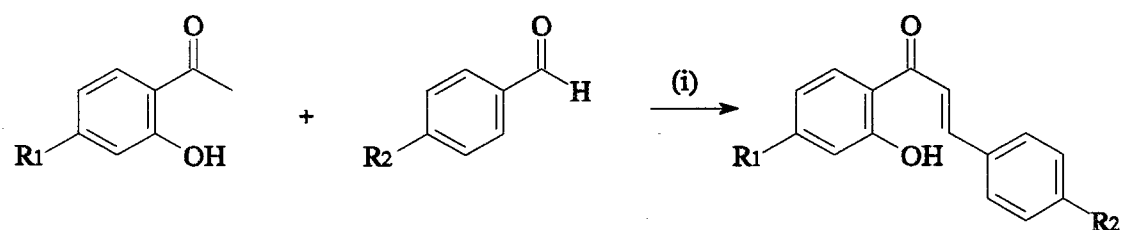
R1		R2		
Br	167	H	-	177
Cl	168	H	-	178
F	169	H	-	179
OMe	170	H	-	180
H	171	H	172	181
H	-	Br	173	182
H	-	Cl	174	183
H	-	F	175	184
H	-	OMe	176	185

SCHEME 45. Reagents: (i) EtOH, base, $0\,^{c}$C

46

In the present study, all of the required 2-hydroxychalcones **177-185** were prepared by condensing a variety of 2-hydroxyacetophenones **167-171** with aromatic aldehydes **172-176** in ethanol using either aqueous sodium hydroxide (for compound **180**) or aqueous potassium hydroxide (for compounds **177-179**, **181-185**) as condensing agents. While the reactions were typically performed at *ca* 4°C, preparation of compound **182** was effected at room temperature (*ca* 25°C).

All of the chalcones were precipitated from the reaction mixtures (by dilution with water, followed by acidification of the reaction mixture) and were then recrystallised from ethanol. Unlike their precursors, the chalcones are bright yellow solids; they are also readily identified by their ^{1}H NMR spectra.

(c) Cyclisation of chalcones to flavanones

The most common way of preparing flavanones is *via* cyclisation of the corresponding chalcones. Both acids and bases have been employed as cyclisation catalysts. Bases which have been used include butylamine,[117] potassium carbonate,[118] pyridine,[119] and dilute sodium hydroxide;[120] while acid catalysts include acetic acid containing a small amount of mineral acid,[121] hydrogen fluoride,[122] and orthophosphoric acid,[123,124] which is the most common reagent used for effecting cyclisation. The base-catalysed cyclisation, however, is complicated by the fact that flavanones are readily isomerised to chalcones by traces of base, hence it is difficult to obtain them in high yield by this method. The kinetics and mechanism of this cyclisation have been investigated previously.[125-129]

Flavanones **186-193**, variously substituted in either aromatic ring, were prepared in moderate

yields by acid-catalysed cyclisation of the corresponding chalcones (Scheme 46). The

chalcones were heated under reflux in ethanol with orthophosphoric acid for four days, after

which the reaction mixtures were concentrated and the required flavanones allowed to

precipitate. The crude flavanones, which were yellow because of chalcone impurities, were

recrystallised repeatedly from ethanol to obtain the pure colourless flavanones. This repeated

recrystallisation accounts for the lower yields obtained.

	R^1	R^2	
177	Br	H	186
178	Cl	H	187
179	F	H	188
180	OMe	H	189
181	H	H	64
182	H	Br	190
183	H	Cl	191
184	H	F	192
185	H	OMe	193
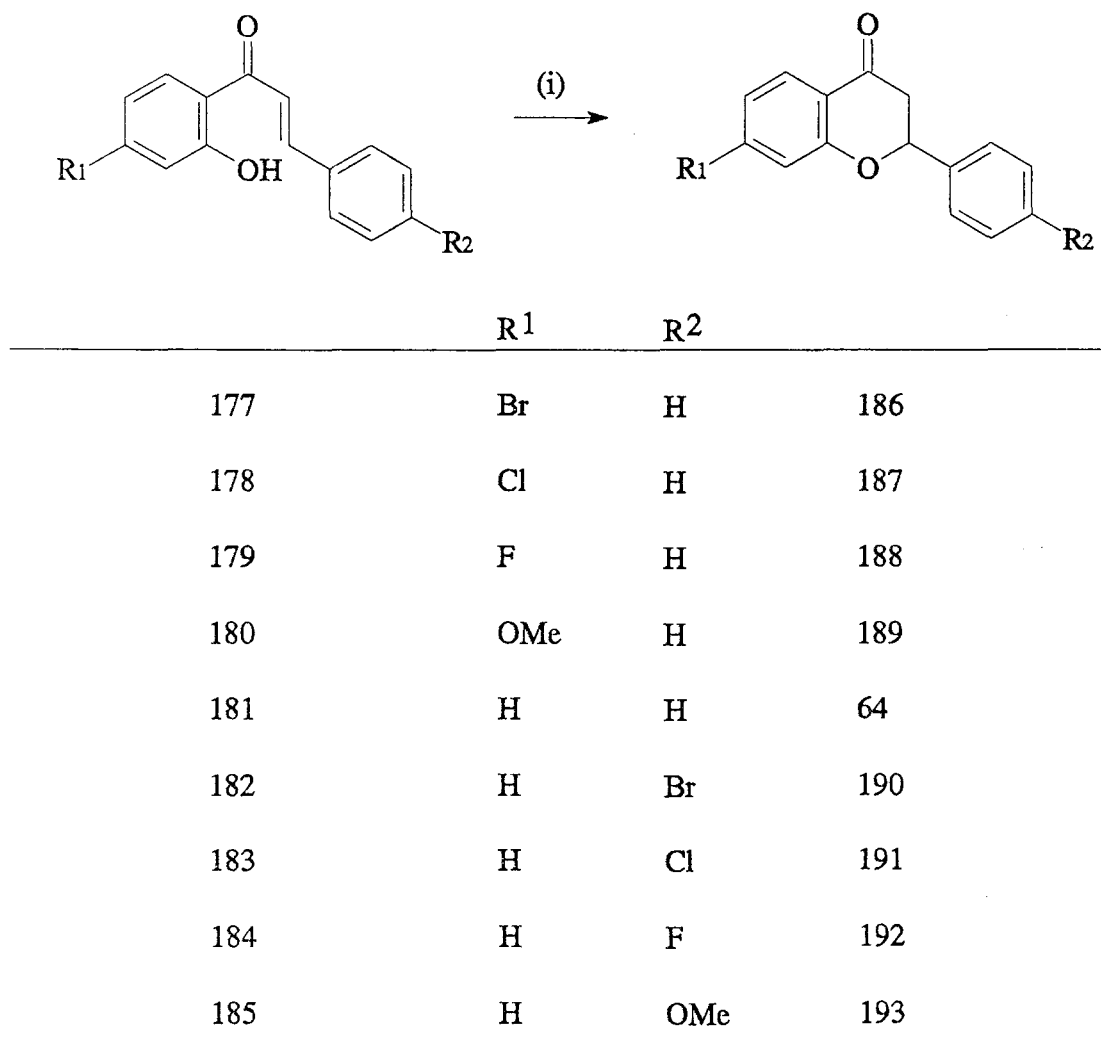
SCHEME 46. Reagents: (i) EtOH, H$_3$PO$_4$, heat.

Figure 2: ¹H NMR spectra of (a) 4′-fluoro-2-hydroxychalcone and (b) 4′-fluoroflavanone

Flavanones are easily distinguished from their isomeric precursors, the chalcones. Flavanones are colourless while chalcones are bright yellow; ^{1}H NMR spectra for flavanones show peaks at *ca.* 3.0ppm and *ca.* 5.6ppm for the 3-methylene and 2-methine protons respectively. These signals are absent in the ^{1}H NMR spectra of chalcones which exhibit vinyl hydrogen signals between 6.9 and 8.5ppm in addition to a hydroxyl signal further downfield (see figure 2).

2.1.1.2 4-Quinolones

2-Aryl-1,2,3,4-tetrahydro-4-quinolones are structurally similar to flavanones, the only difference being the presence of an amino group at position 1 instead of an oxygen atom. These 2-aryl-substituted quinolones are difficult to synthesise by the usual procedure,[130-132] which involves cyclisation of acrylates obtained from the reaction of arylamines with β-keto esters. In the present study, the required 4-quinolones were prepared by the cyclisation of 2-aminochalcones which were obtained, in turn, by the aldol condensation of 4-substituted benzaldehydes with 2-aminoacetophenone.

(a) 2-Aminochalcones

2-Aminoacetophenone **194** was condensed with each of the 4-substituted benzaldehydes **172-176** and **195** in ethanolic solution containing solid sodium hydroxide (Scheme 47). Like the 2-hydroxychalcones, 2-aminochalcones are easily distinguishable from their precursors by their bright yellow colour. NMR spectroscopy, of course, permits unambiguous confirmation of chalcone formation.

	R	
172	H	196
173	Br	197
174	Cl	198
175	F	199
176	OMe	200
195	NO_2	201
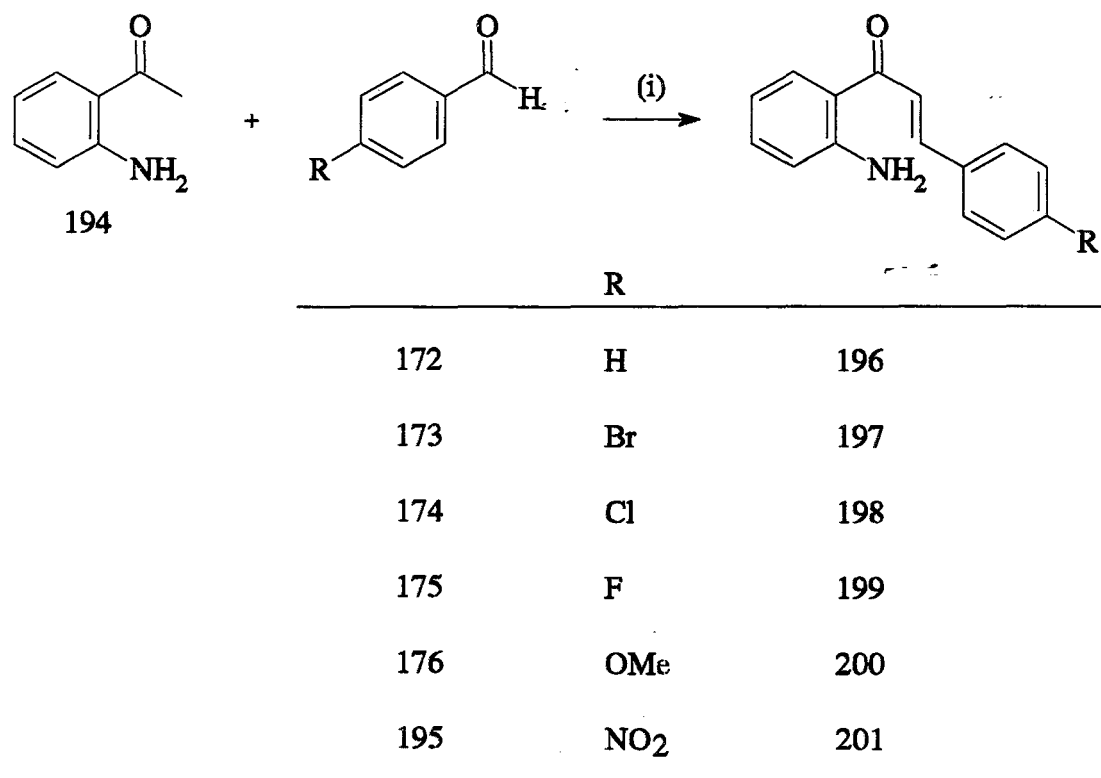
SCHEME 47. Reagents: (i) NaOH, EtOH, r.t., 24h

(b) Cyclisation of Aminochalcones to Quinolones

2-Aminochalcones undergo acid- or base-catalysed cyclisation[133,134] to 1,2,3,4-tetrahydro-4-

quinolones. The 4-quinolones **202-207** were obtained by acid-catalysed cyclisation of the 2-

aminochalcones **196-201**, using orthophosphoric acid in acetic acid (Scheme 48). In contrast

to the cyclisation of 2-hydroxychalcones to flavanones, which required several days, only 2-3

hours were needed for complete reaction. In addition, the quinolones, unlike flavanones, are

stable in acidic or basic medium and opening of the heterocyclic ring is not observed under

these conditions. All of the quinolones prepared were solids and were precipitated, in each

case, by pouring the cooled reaction mixture into an ice-water mixture. The crude product

was filtered off and purified by recrystallisation from ethanol; in a parallel study[91] of the

same compounds, purification was achieved by flash chromatography. The spectroscopic (^{1}H

NMR, ^{13}C NMR and IR) data obtained for the 4-quinolones were found to be consistent with

the reported data.[91]

R	
H	202
Br	203
Cl	204
F	205
OMe	206
NO$_2$	207
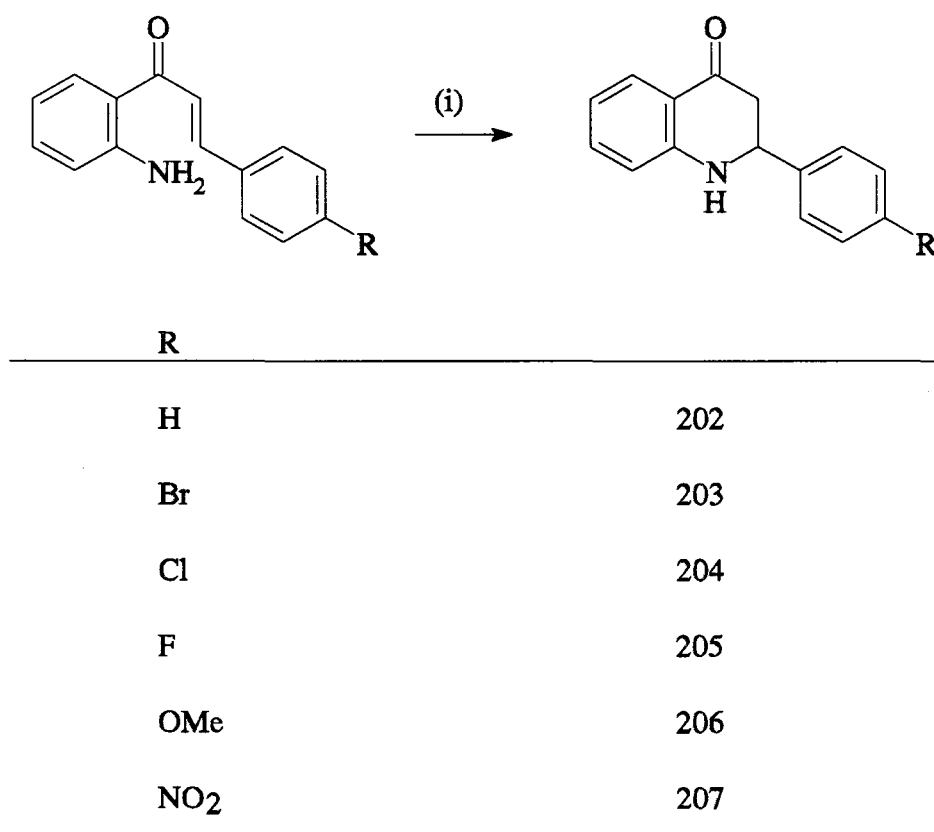
SCHEME 48. Reagents: (i) H$_3$PO$_4$, AcOH, heat, 2-3h

2.1.1.3 Aryl Epoxides

Epoxides exhibit interesting biological properties in their own right and epoxide metabolites of arenes and olefins have been reported[135-137] to be cytotoxic, carcinogenic, and mutagenic. There are several methods[138-141] for preparing epoxides, the conditions depending on whether the desired product is acid-sensitive or not. The epoxidation of acid-sensitive olefins or olefins yielding acid-sensitive epoxides is typically effected by a peroxy acid [usually *m*-chloroperbenzoic acid (MCPBA)] in the presence of a buffer such as solid sodium carbonate, sodium bicarbonate, or disodium hydrogen phosphate.[142]

Since the aryl epoxides **211-213** (Scheme 49) required in this project are very sensitive to acids, and therefore unstable under the normal epoxidizing conditions,[141] a two-phase procedure,[138] which involves the use of MCPBA in dichloromethane in the presence of a buffer, was used to prepare these epoxides from the 4-substituted styrenes **208-210**. The crude products were separated from their starting materials by flash chromatography, eluting with a mixture of ethyl acetate and hexane. 4-Methoxystyrene oxide **214**, however, could not be prepared by this procedure. Epoxidation of 4-methoxystyrene gave an oily product, which was found to be 4-methoxybenzaldehyde (anisaldehyde) **176**. This compound was identified by means of ^{1}H NMR, ^{13}C NMR and IR spectroscopy, its ^{1}H NMR spectrum matching that of an authentic sample. The formation of anisaldehyde may be attributed to oxidative cleavage of the electron-rich alkene and, it should be noted that Hanzlik and Hilbert[139] obtained acetophenones instead of epoxides from the epoxidation of α-substituted styrenes. Compound **214** and other epoxides have been prepared by the reaction of the

corresponding benzaldehydes with Corey's dimethylsulfonium methylide reagent.[143]

R		
Br	208	211
Cl	209	212
F	210	213
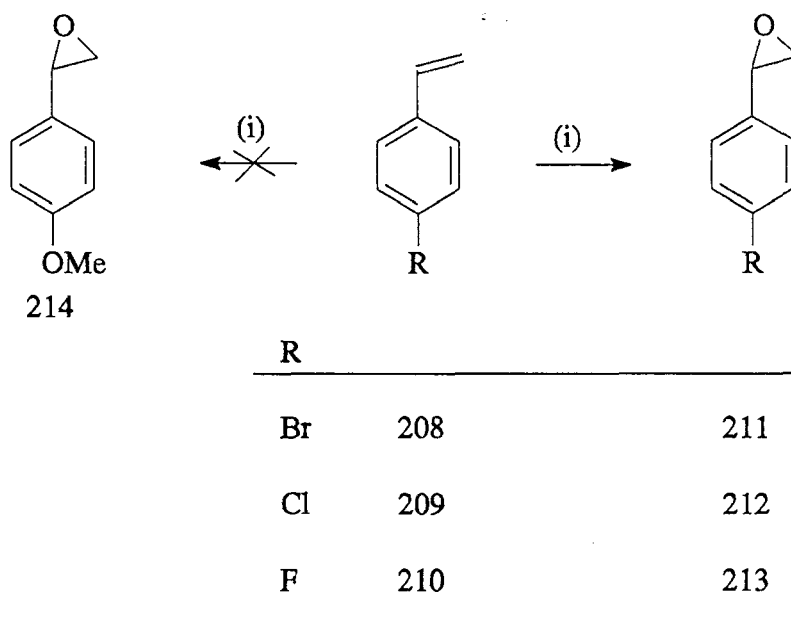
SCHEME 49. Reagents: (i) MCPBA, CH_2Cl_2-phosphate buffer, $0°C$, 12 h

Although the three epoxides **211-213** were oils, like their precursors, they were easily identified by means of ^1H NMR spectroscopy. The epoxides, of course, show three sets of double doublets between 2 and 4ppm, corresponding to the epoxide ring protons instead of the vinyl protons of their styrene precursors which appear between 5 and 6ppm.

2.1.1.4 2-Mercaptobenzenemethanol

2-Mercaptobenzenemethanol **216** was prepared according to the procedure of Arnoldi and Carughi.[144] This involved the reduction of 2-thiobenzoic acid **215** with lithium aluminium hydride in tetrahydrofuran (Scheme 50) to give an oily product which crystallised on standing

to a low melting solid (*ca.* 33°C). Although the reported yield using this procedure is 90%,

we were able to obtain only 65% after performing the experiment twice. The crude alcohol

216 was sufficiently pure to be used without further purification.
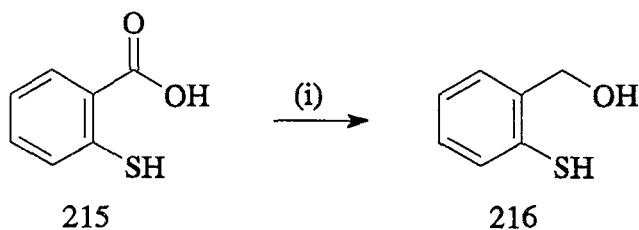
SCHEME 50. Reagents: (i) LiAlH$_4$, THF, r.t., 24h

2.1.1.5 1-Thioflavanone

Thioflavanone 220, one of the simplest sulphur-containing flavanoids, was first prepared by

Arndt[145] by cyclisation of 3-thiophenyl-3-phenylpropionic acid 219 (Scheme 51). Several

reagents may be used for effecting the ring closure of compound 219, and these include

polyphosphoric acid, methanesulphonic acid,[146] phosphoryl chloride,[145] phosphorus pentoxide

and concentrated sulphuric acid.[147] In the present study, cyclisation was achieved using

phosphoryl chloride, and the reaction was complete within twenty minutes. Compound 219

was prepared, in turn, by condensation of thiophenol 217 with cinnamic acid 218 using 45%

hydrogen bromide in acetic acid.

1-Thioflavanone **220** was distinguished from its precursor **219** by the absence of a hydroxyl

signal in its ^{1}H NMR spectrum (figure 3b) and by the presence of three double doublets at

ca. 3.3 and 4.7ppm, due to the methylene and methine protons respectively; the

corresponding protons in compound **219** appear as a multiplet and triplet at *ca.* δ 3 and

4.6ppm respectively (figure 3a).
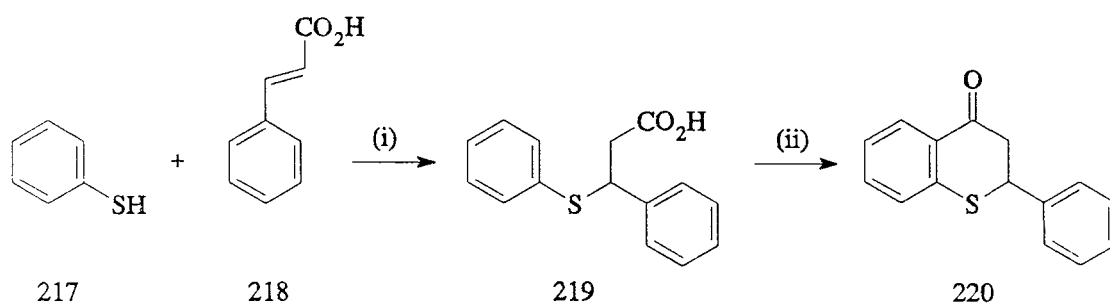
SCHEME 51. Reagents: (i) HBr-AcOH, heat; (ii) POCl$_3$, heat, 20 min.
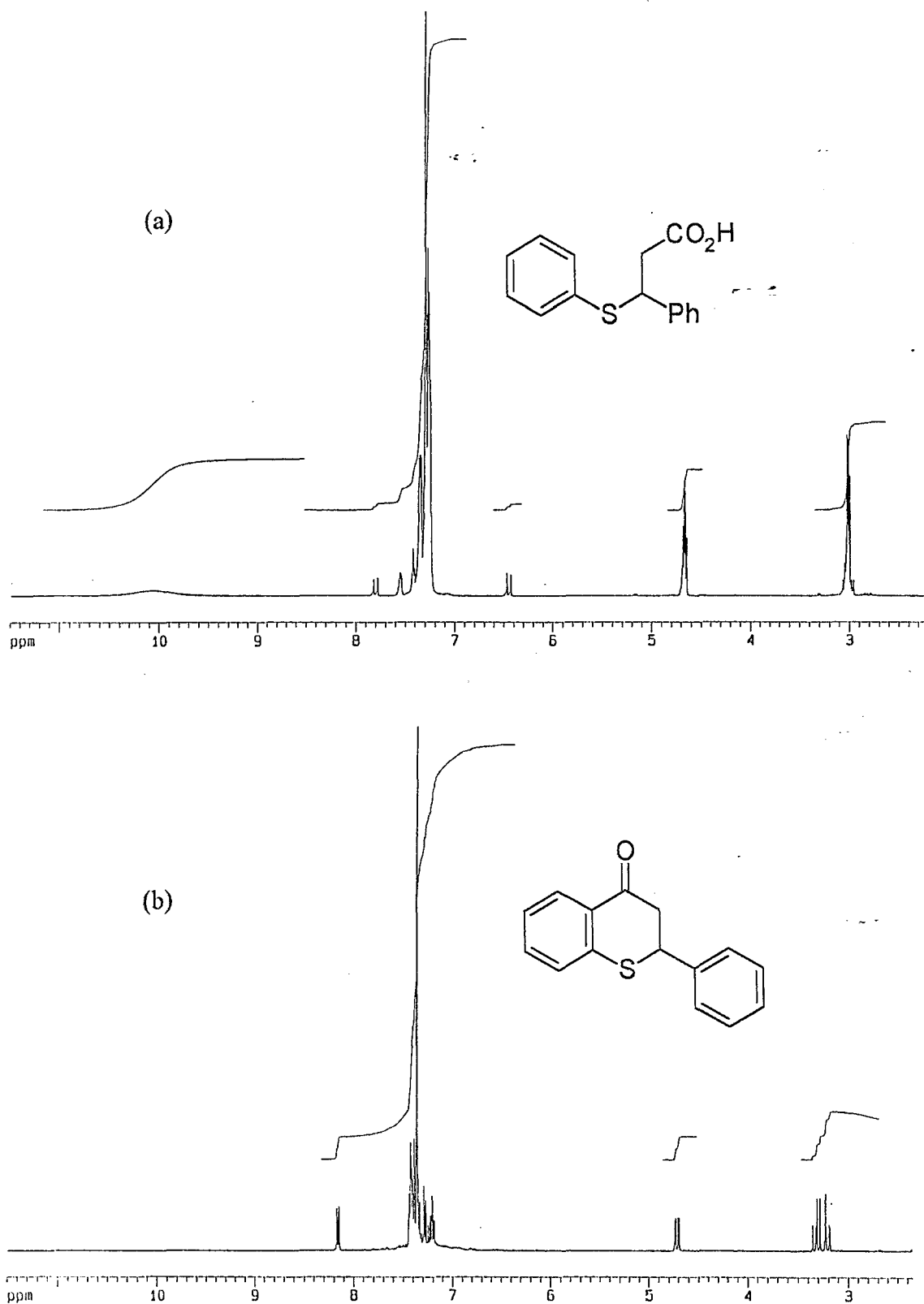
Figure 3: ^{1}H NMR spectra of (a) 3-phenyl-3-thiophenylpropanoic acid and (b) 1-thioflavanone

2.1.2 BAEYER-VILLIGER OXIDATION OF FLAVANONES: SYNTHESIS OF BENZODIOXEPINONES

The Baeyer-Villiger oxidation is one of the most reliable reactions to convert ketones into esters or lactones. It is a classic transformation in synthetic organic chemistry, with varied and extensive applications.[148,149] This type of oxidation was first reported by Baeyer and Villiger in 1899[150] and scientific papers on the reaction still continue to appear in the literature.[151-164] A number of reagents, including hydrogen peroxide[165-167] and organic peracids such as MCPBA,[168] have been used to effect the oxidation. However, the above-mentioned reagents are shock-sensitive and potentially explosive and, hence, further research to find safer and simpler oxidants continues. Several peroxy reagents having reasonable thermal stabilities, such as magnesium monoperoxyphthalate (MMPP)[169] and bis(trimethylsilyl)-peroxide[170] have been used effectively in the Baeyer-Villiger oxidation. Oxidation of ketones by the combined use of molecular oxygen and aldehydes with Fe_2O_3 as a catalyst[171] and by other reagents[156,157,160,162] has also been reported. The regioselectivity of oxygen insertion depends on the migrating group and can be predicted by assuming that the carbon atom best able to support a positive charge migrates most readily. While the classic rearrangement involves migration of a carbon atom, the first example of a Baeyer-Villiger rearrangement involving a migrating phosphoryl moiety has been reported very recently.[161]

The required 1,5-benzodioxepin-2-ones **65** and **221-228** were prepared by Baeyer-Villiger oxidation of the corresponding flavanones **64** and **186-193** following the reported procedure.[26] The crude products, which were all solids, were purified by flash chromatography, eluting

with an ethyl acetate-hexane mixture. The ring-expanded products were shown by ^{1}H and

^{13}C NMR spectroscopy to be the corresponding 1,5-benzodioxepin-2-ones rather than the 1,4-

benzodioxepin-5-ones, and were readily distinguished from their precursor flavanones by

analysis of the methylene and adjacent methine protons. In flavanones, the methylene and

methine protons are observed at *ca.* δ 3.0 and 5.5ppm respectively, whereas in

benzodioxepinones the corresponding proton signals are shifted slightly downfield to δ 3.1

and 5.7ppm respectively. Moreover, in the products, the methine signal appears as a triplet

while in the flavanones, a double doublet is observed (figure 4). The ^{1}H and ^{13}C NMR

spectra of the 1,5-benzodioxepin-2-one derivatives have been discussed in more detail

elsewhere.[26,92] Substituents on either of the aromatic rings of the title compounds do not

seem to have a significant effect on the chemical shift of the methylene and methine protons

(see table 1).

The regioselective migration of the aryl group (ring A) is contrary to that observed for

Schmidt rearrangement of the same flavanones.[27,91] These results prompted us to study the

kinetics of both the Baeyer-Villiger and Schmidt reactions of flavanones in order to explain

the contrasting regioselectivity. (The kinetics of Baeyer-Villiger oxidation of flavanones will

be discussed in section 2.6, page 127).

Alternative routes leading to 1,5-benzodioxepin-2-ones or 1,4-benzodioxepin-5-ones were also

explored. Cyclisation of 2-hydroxyphenyl cinnamate **229**, using acid catalysts such as acetic

acid or trifluoroacetic acid, proved to be difficult. Compound **229** was readily prepared from

catechol and cinnamic acid, following a reported[172] procedure (Scheme 53).
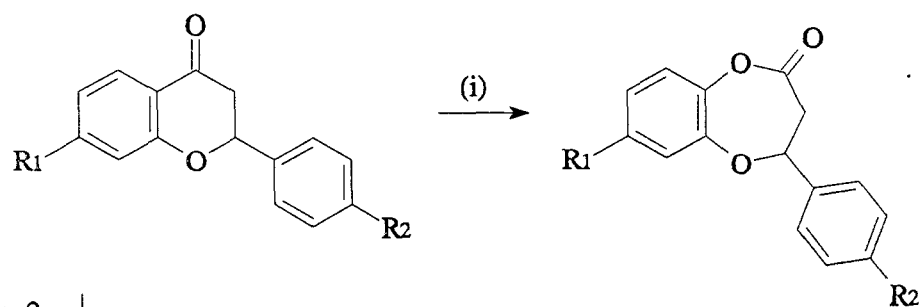
R^1	R^2		
H	H	64	65
Br	H	186	221
Cl	H	187	222
F	H	188	223
OMe	H	189	224
H	Br	190	225
H	Cl	191	226
H	F	192	227
H	OMe	193	228

SCHEME 52. Reagents: (i) MCPBA, CH$_2$Cl$_2$, reflux.
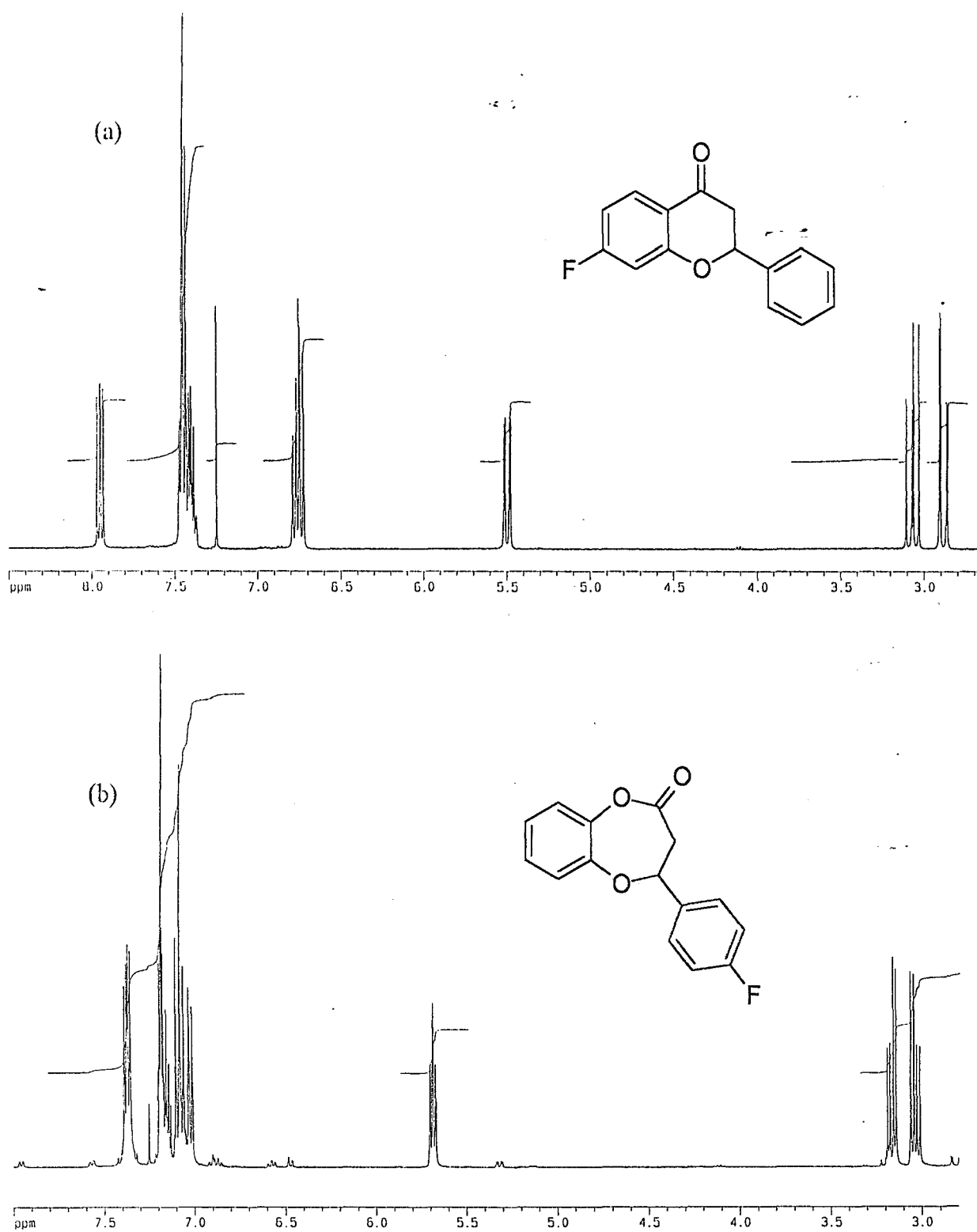
Figure 4:   ¹H NMR spectra of (a) 7-fluoroflavanone and
             (b) 4-fluorophenyl-1,5-benzodioxepin-2-one

Table 1.   ¹H NMR chemical shifts (δ ppm) of the 3- and 4-H protons of 1,5-benzodioxepin-2-one derivatives.
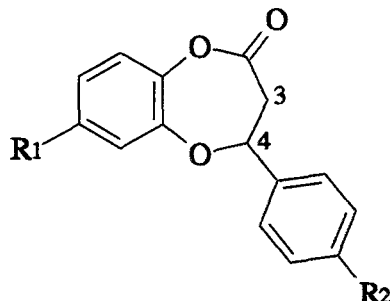
Compd.	R¹	R²	3-H	4-H
65	H	H	3.10	5.72
221	Br	H	3.13	5.72
222	Cl	H	3.12	5.71
223	F	H	3.10	5.71
224	OMe	H	3.13	5.69
225	H	Br	3.10	5.65
226	H	Cl	3.10	5.67
227	H	F	3.10	5.69
228	H	OMe	3.09	5.68

However, attempted hydrobromination of this ester 229, using hydrogen bromide in acetic acid, failed due to acid-catalysed cleavage of compound 229 back to its precursors, catechol and cinnamic acid. Another approach involved the attempted reaction of catechol with the hydrobrominated cinnamic acid 231, but this was also unsuccessful (Scheme 54).
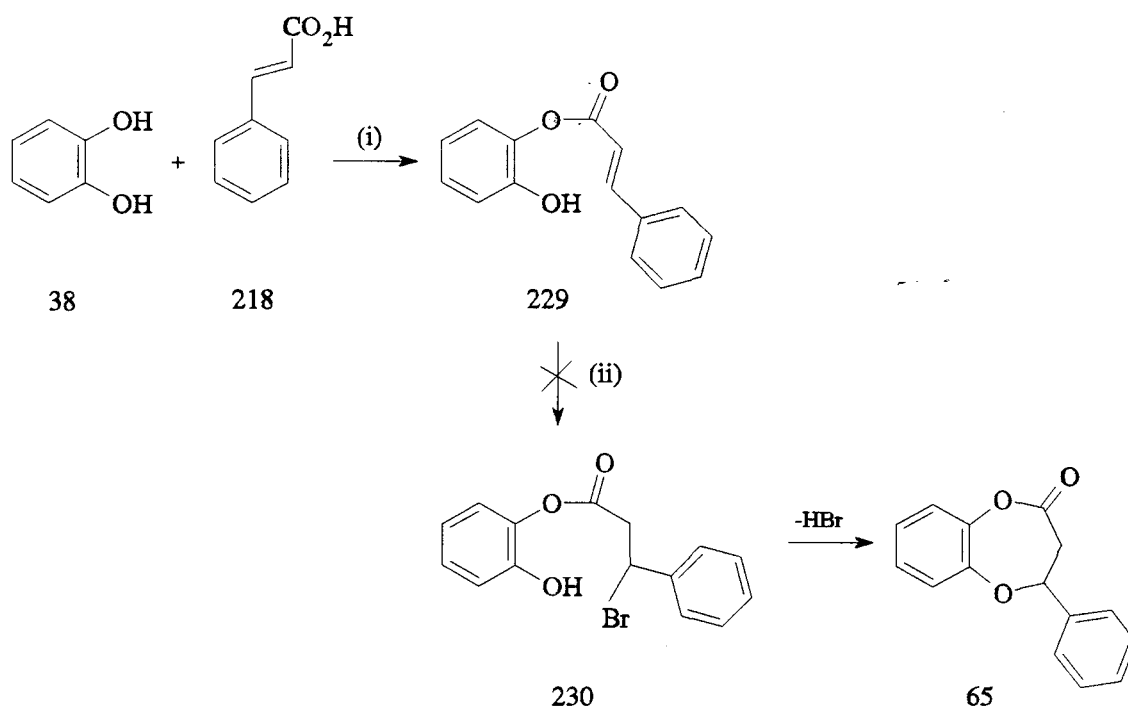
SCHEME 53. Reagents: (i) Py, SOCl$_2$; (ii) HBr-AcOH.

In an attempt to synthesize 1,4-benzodioxepin-5-one **234**, a mixture of 2-hydroxybenzoic acid

232 and styrene oxide **233** was boiled under reflux using a Dean-Stark trap (Scheme 55).

After work-up, TLC of the crude material showed a complex mixture of compounds, which

could not be separated. Furthermore, the required product could not be detected in the ^{1}H

NMR spectrum of the crude mixture. Use of methyl salicylate similarly afforded a complex

mixture of products.

Several attempts were made to introduce a double bond between C-3 and C-4 of the 1,5-

benzodioxepin-2-one derivatives. The first obvious approach was to attempt Baeyer-Villiger

oxidation of flavone **235**, the conjugated derivative of flavanone. After the usual work-up,

only the starting material was recovered as confirmed by TLC and ^{1}H NMR spectroscopy

instead of the expected product(s) **236** or **237**. However, it proved possible to obtain the

conjugated system **239** in very low yield (*ca.* 4%), together with the epoxide **240** as the

major compound, by oxidation of chromone **238**. This substrate, of course, lacks a phenyl

substituent at position 2 (Scheme 56) and this general approach was not pursued further. A

bromination-dehydrobromination approach was then examined (Scheme 57).

1,5-Benzodioxepin-2-ones, however, are susceptible to nucleophilic ring-opening and a

deprotonation-bromination sequence afforded the cinnamate ester **229**. (Ring-opening

reactions of these compounds will be discussed in more detail in section 2.2, p. 98).

The use of oxidative dehydrogenation agents such as palladium or DDQ[173,174] also failed to

produce the required $\Delta^{3,4}$ unsaturation.
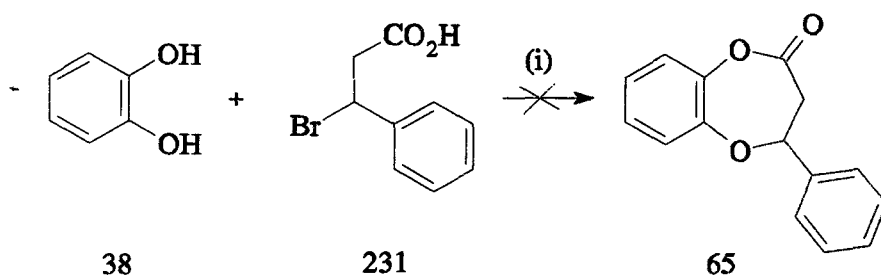
SCHEME 54. Reagents: (i) TsOH, benzene, heat or 1eq. NaH, THF, then TsOH, heat.
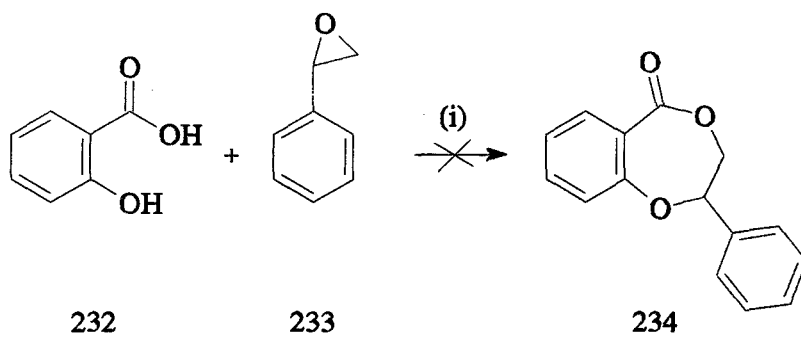
SCHEME 55. Reagents: (i) TsOH, benzene, reflux.
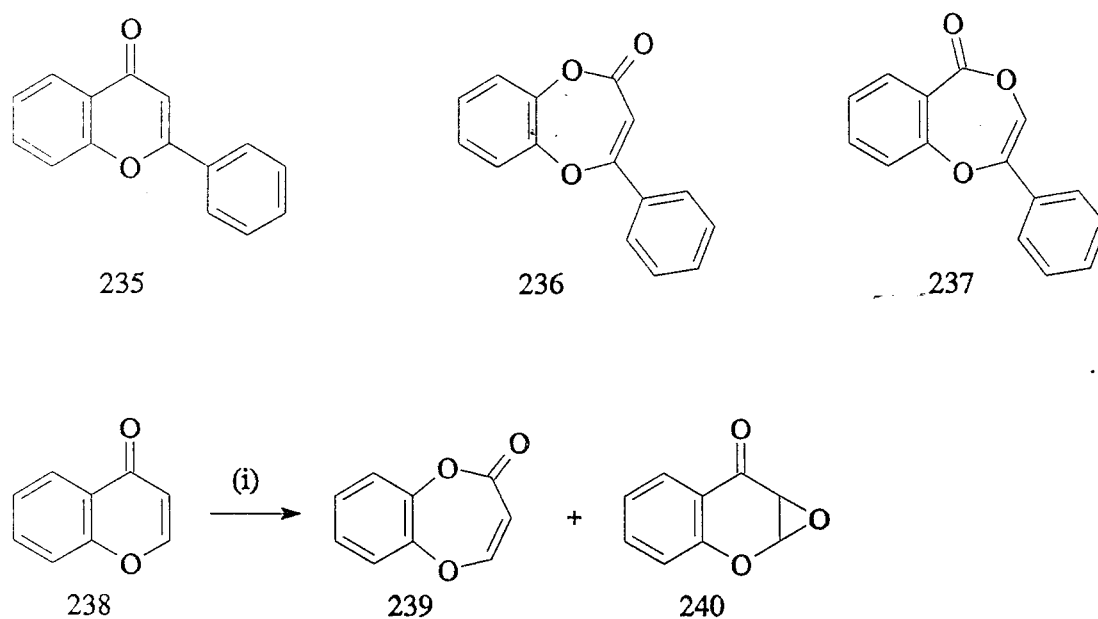
SCHEME 56. Reagents: (i) MCPBA, CH_2Cl_2, heat, 4d.
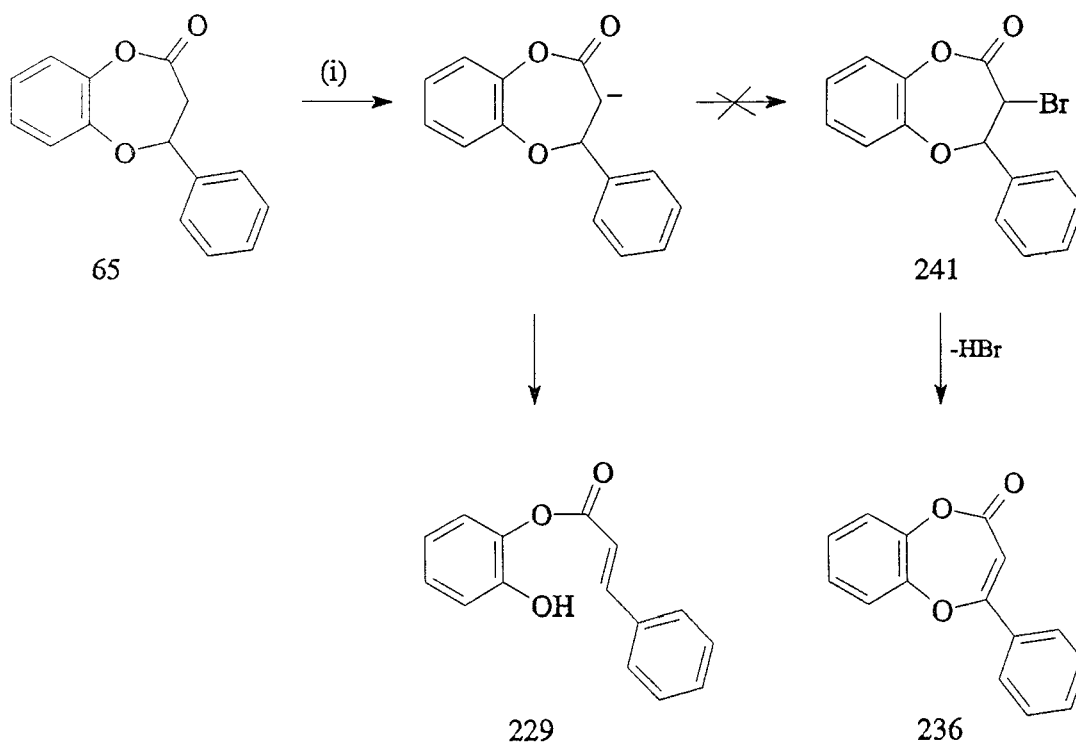
SCHEME 57. Reagents: (i) LDA, -78°C; NBS or Br_2

2.1.3 PREPARATION OF BENZOXATHIEPINE DERIVATIVES

A detailed review of the relatively unexplored chemistry of the benzoxathiepines was given in section 1.2. In the following section the synthesis and NMR spectrometric studies of three series of benzoxathiepine derivatives will be discussed. Their mass spectrometric properties will be discussed in section 2.4, p. 108.

(a) Preparation of 1,5-Benzoxathiepin-2-ones

1,5-Benzoxathiepin-2-ones 250-254 were prepared by reacting 2-hydroxythiophenol 84 with the corresponding cinnamic acids 218 and 242-245 (Scheme 58). Several reaction conditions were employed. The two substrates (compound 84 and the cinnamic acid) were heated at temperatures above 100°C to afford the intermediate carboxylic acid (e.g. compound 219) via conjugate addition. However, this proved to be unsuitable as a general method because of the very high melting points (ca. 300°C) for some of the cinnamic acids. A 48% solution of hydrobromic acid in acetic acid was then used to facilitate the reaction. The HBr-AcOH not only serves as solvent but the HBr also reacts with the cinnamic acid to yield the corresponding 3-bromo-3-phenylpropanoic acid (Scheme 59). Because of the good leaving character of bromine, the chiral carbon of the propionic acid is then very susceptible to attack by the nucleophilic sulphur of the 2-hydroxythiophenol to give the intermediate propionic acids 219 and 246-249. These acids were not isolated but the reaction mixtures, after work-up, were heated under reflux in toluene with a catalytic amount of p-toluenesulphonic acid (p-TsOH) for 12-15 hours.
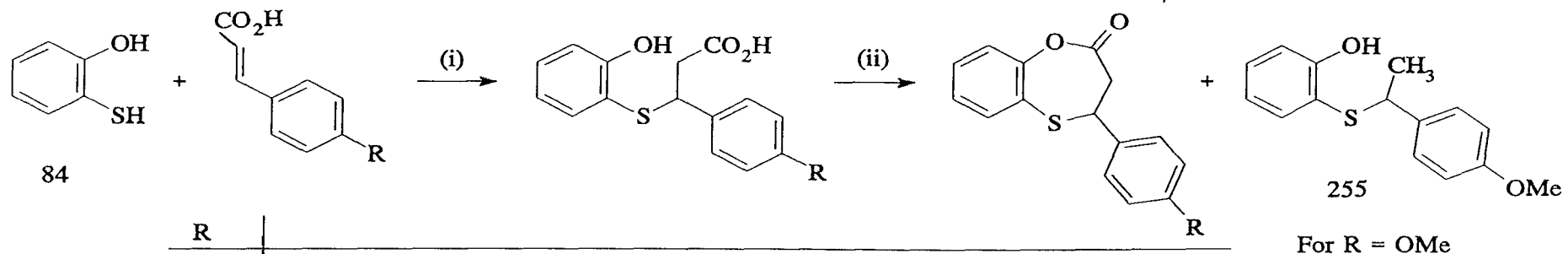
R			
H	218	219	250
Br	242	246	251
Cl	243	247	252
F	244	248	253
OMe	245	249	254

SCHEME 58. Reagents: (i) 45% HBr in AcOH and (ii) TsOH, toluene.
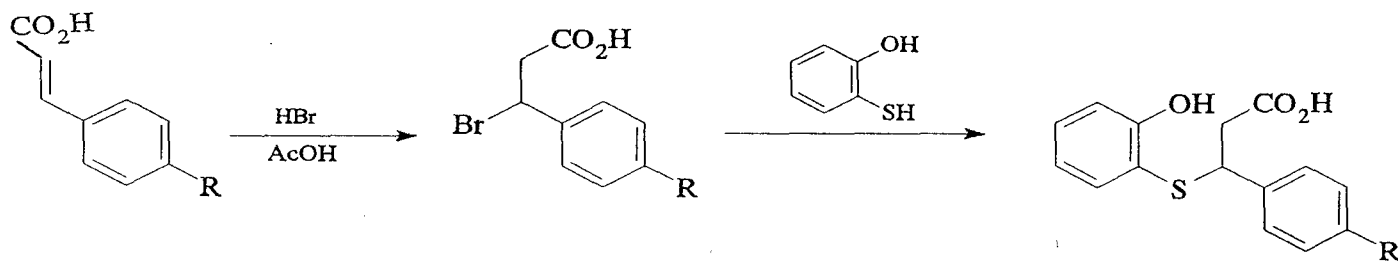
SCHEME 59

Final work-up, followed by flash chromatography, gave the required 1,5-benzoxathiepin-2-ones **250-254** in low yields (4-13%). (No reaction occurred when benzene was used as a solvent instead of toluene). Heating the above mixtures using a Dean-Stark trap, without first isolating the bromo-acid intermediates, did not significantly improve the yields of compounds **250-254**. The yield of 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzoxathiepin-2-one **254**, however, was improved (from 9% to 24%) by heating a mixture of 2-hydroxy-thiophenol with cinnamic acid under N_2 in the absence of HBr-AcOH, followed by heating the resulting reaction mixture in toluene with p-TsOH. The reaction of 2-hydroxythiophenol with 4-methoxycinnamic acid in the presence of HBr-AcOH afforded two products. Thus in addition to the expected product (compound **254**), 1-(2-hydroxyphenylthio)-1-(4-methoxyphenyl)ethane **255** was also isolated. The ^{1}H NMR spectrum (figure 5) of this compound shows a doublet at δ 1.61ppm due to the methyl protons, a singlet at δ 3.79ppm for the methoxy protons and a quartet at δ 4.09ppm for the methine proton. An attempt to prepare 3,4-dihydro-1,5-benzoxathiepin-2-one **257** by Baeyer-Villiger oxidation of thiochromanone, using MCPBA, gave the sulphone **258** and the sulphoxide **259** instead (Scheme 60). Further treatment of compound **259** with MCPBA failed to afford the ring-expanded product **260**.

The benzoxathiepinones **250-254** can be easily distinguished from their propanoic acid precursors (compounds **219** and **246-249**). In the ^{1}H NMR spectrum of the 1,5-benzoxathiepin-2-one **254**, for example, the signal for the methine proton (4-H) appears as a triplet at δ 4.74ppm (Figure 6b), while that of the methine proton (3-H) in compound **249** also appears as a triplet, but is shifted upfield to δ 4.33ppm (Figure 6a).
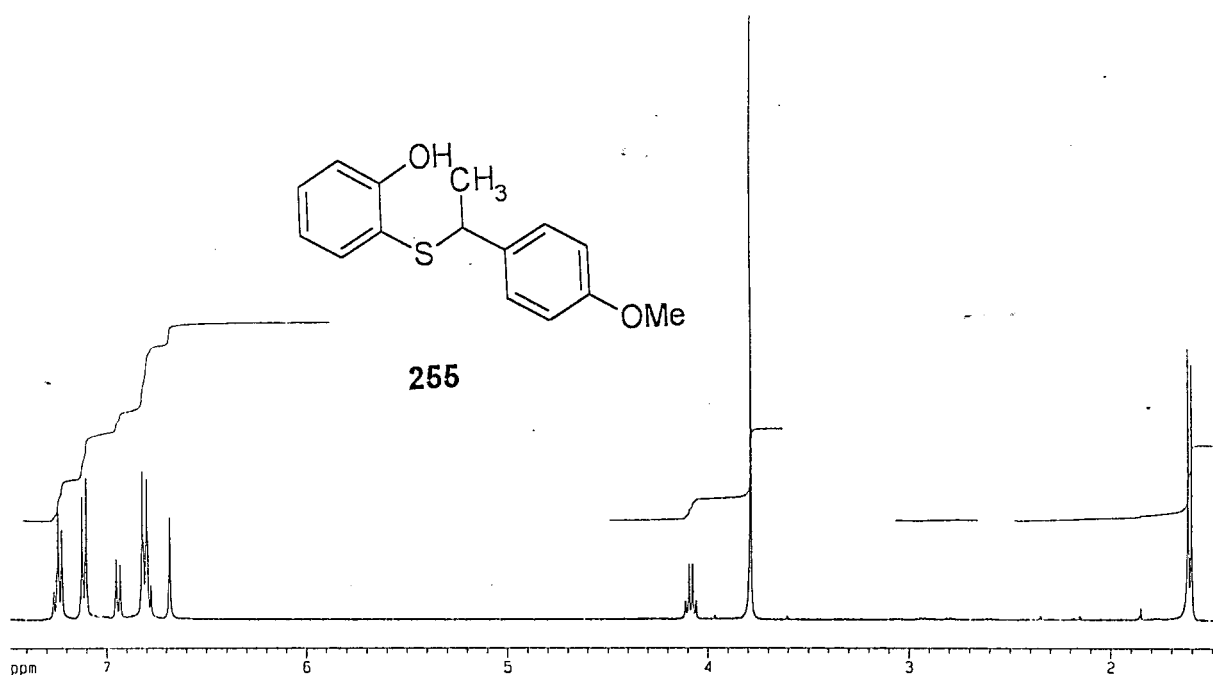
Figure 5:   400   MHz ^{1}H   NMR   spectrum   of   255
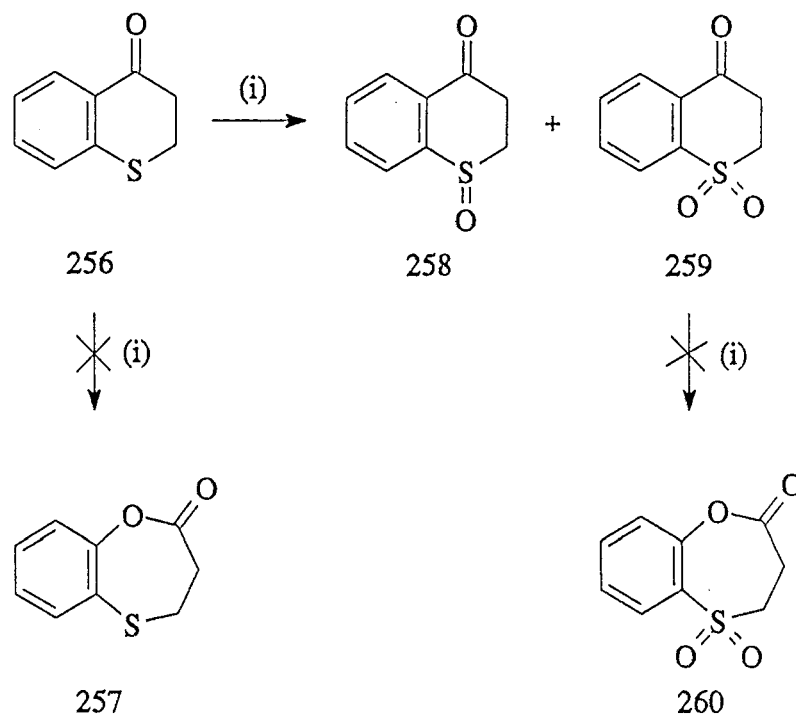
SCHEME 60. Reagents: (i) MCPBA, CH_2Cl_2.
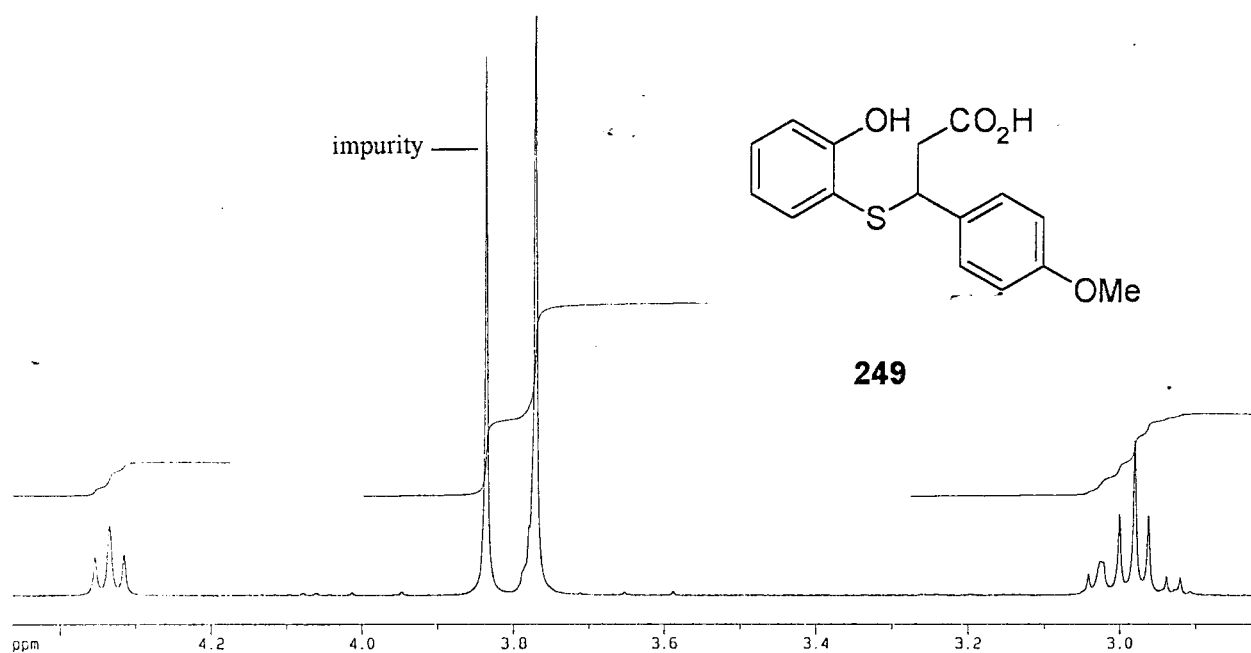
Figure 6(a): Partial 400 MHz ^{1}H NMR spectrum of 3-(2-hydroxyphenyl)-2-(4-methoxy)propionic acid 249 in CDCl$_3$
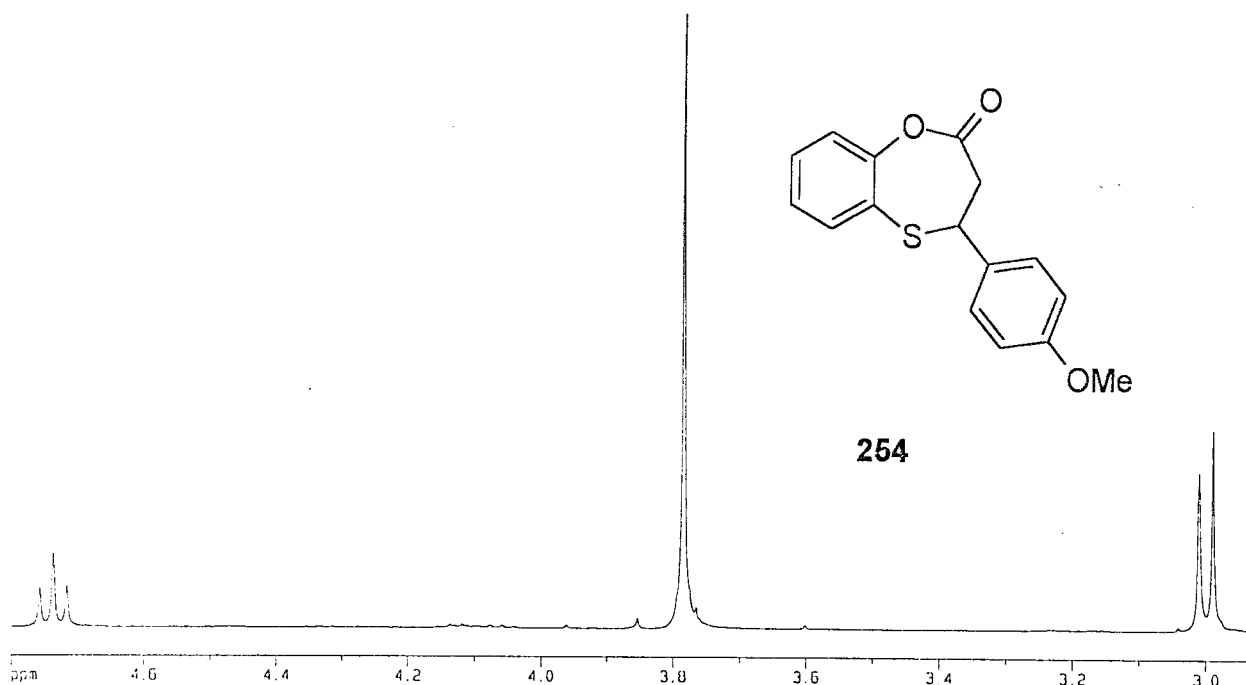
Figure 6(b): Partial 400 MHz ^{1}H NMR spectrum of 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzoxathiepin-2-one 254 in CDCl$_3$

In most of the 1,5-benzoxathiepinones examined, the diastereotopic methylene protons appear as a pair of double doublets at *ca.* δ 3.0ppm. Because these methylene protons are magnetically non-equivalent, they couple with each other and, in turn, with the adjacent 4-methine proton resonating at *ca.* δ 4.7ppm as a double doublet. Replacing the sulphur atom at position 5 with oxygen changes both the chemical shifts and the splitting patterns of the 3-H and 4-H nuclei. In the benzodioxepinone derivatives, the two double doublets due to the 3-methylene protons are further apart and appear at *ca.* δ 3.10ppm, while the methine signal appears as a coalesced double doublet between δ 5.5 and 6.0ppm (compare figure 7a and 7b).

None of the substituents at the *para* position of the 4-phenyl group in 1,5-benzoxathiepinones appears to have any significant effect on the chemical shifts of the methine and methylene protons (see Table 2). The aromatic region also shows the same chemical shift and similar splitting patterns for all the compounds examined. The ^{13}C NMR spectra of these compounds, however, exhibit some differences in the chemical shifts of the aromatic carbons. Table 3 shows that the 4'-substituents, Br, Cl, F and OMe have a significant effect on the chemical shifts of the 4-aryl ring carbons C-1' - C-6', the assignment of which was facilitated by comparison with the C-F coupling constants in compound **253**. In addition, the chemical shift for C-4 in compound **254** appears at δ 55.2ppm, while those of the other compounds in the series appear upfield at *ca.* δ 50ppm. To our knowledge, all the synthesised 1,5-benzoxathiepin-2-one derivatives are new compounds.
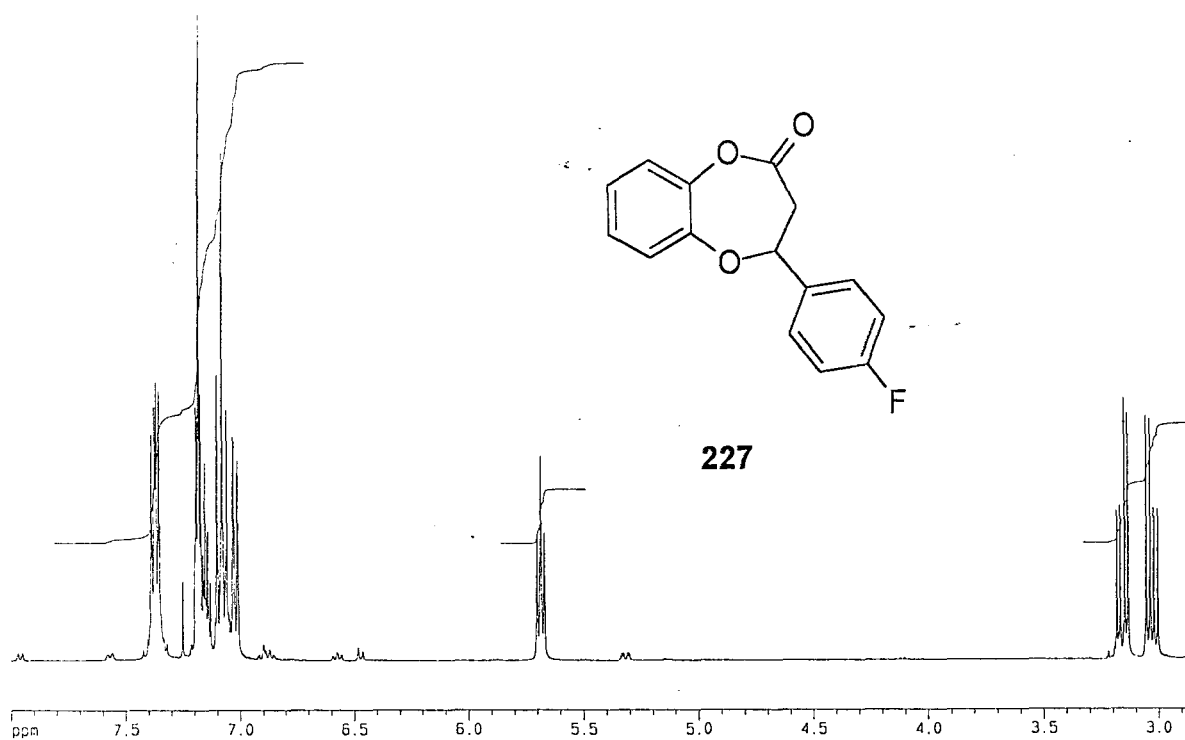
Figure 7(a):   400   MHz ^{1}H   NMR   spectrum   of   3,4-dihydro-4-(4-fluorophenyl)-1,5-benzodioxepin-2-one 227 in CDCl$_3$
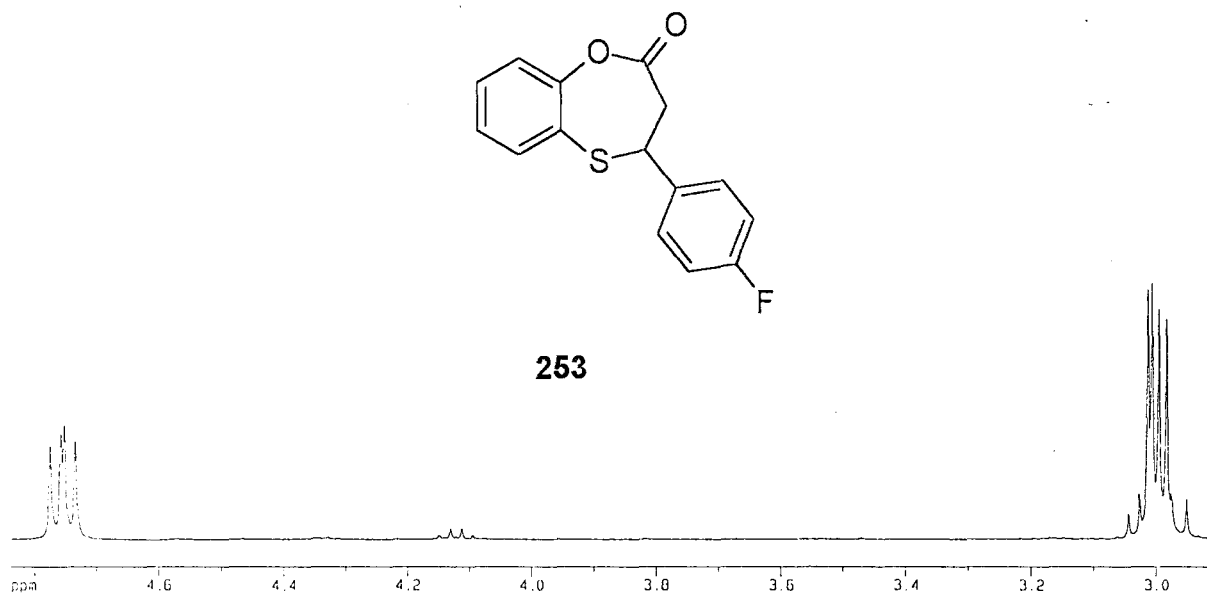
Figure 7(b):   Partial 400 MHz ^{1}H NMR spectrum of 3,4-dihydro-4-(4-fluorophenyl)-1,5-benzoxathiepin-2-one 253

Table 2. ^{1}H NMR chemical shifts (δ ppm) data for 1,5-benzoxathiepin-2-one derivatives in CDCl$_3$
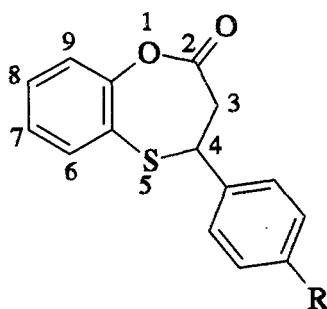
Compd	R	3-H	4-H	6-H	8-H
250	H	2.96	4.70	7.54(dd)	7.43(ddd)
257	Br	2.98	4.72	7.57(dd)	7.49(ddd)
252	Cl	3.00	4.74	7.57(dd)	7.49(ddd)
253	F	3.00	4.75	7.58(dd)	7.49(ddd)
254	OMe	3.00	4.74	7.58(dd)	7.47(ddd)

Table 3. ^{13}C NMR chemical shift (δ ppm) data for 1,5-benzoxathiepinone derivatives in CDCl$_3$ (δ 77.0ppm).
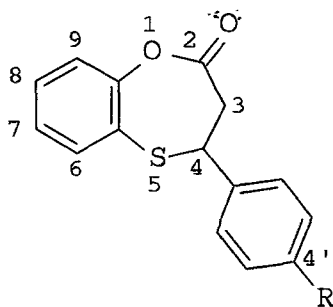
	250	251	252	253	254[a]
R	H	Br	Cl	F	OMe
C-2	167.5	167.1	167.2	167.3	167.5
C-3	40.0	39.8	39.8	40.1	40.1
C-4	50.3	49.6	49.5	49.5	55.2
C-6	136.4	136.4	136.3	136.3	136.3
C-7	128.2	126.7	126.7	126.6	126.5
C-8	131.4	131.6	131.5	131.5	131.2
C-9	120.3	120.4	120.4	120.4	120.2
C-5a	121.6	122.1	121.3	121.4	121.7
C-9a	154.1	154.1	154.0	154.1	154.0
C-1'	141.8	140.6	140.1	137.5[b]	133.8
C-2'/6'	126.3	132.1	129.1	128.1[c]	127.5
C-3'/5'	128.9	128.1	127.7	115.8[d]	114.2
C-4'	126.6	121.3	134.0	162.4[e]	159.3

[a] OCH$_3$ ^{13}C shift value at δ 49.8ppm, [b] ^{4}J$_{CF}$ 3.0Hz, [c] ^{3}J$_{CF}$ 8.1Hz, [d] ^{2}J$_{CF}$ 22.1Hz, [e] ^{1}J$_{CF}$ 247.5Hz.

(b) Preparation of 4,1-Benzoxathiepin-5-ones

4,1-Benzoxathiepin-5-ones **261-263** were prepared as shown in Scheme 61. Mixtures of the specially prepared arylepoxides (**211, 212,** and **233**), thiosalicylic acid **215** and a catalytic amount of p-toluenesulphonic acid (TsOH) in benzene were refluxed for 12 hours. Work-up of the reactions involved dissolving the residues of the reaction mixtures in ethyl acetate, followed by washing the resultant solutions with aqueous sodium bicarbonate (NaHCO$_3$) to remove unreacted thiosalicylic acid and TsOH. The 3-aryl-2,3-dihydro-4,1-benzoxathiepin-5-ones **261-263** were obtained in very low yields (8-26%) together with the 2-aryl-2,3-dihydro-4,1-benzoxathiepin-5-ones **264-266**, which were also isolated in very low yields (2-7%). It was difficult to purify these compounds and hence, some of them (**264-266**) were characterised using only ^{1}H and ^{13}C NMR spectroscopy.

The ^{1}H NMR spectra of the 3-aryl-4,1-benzoxathiepin-5-ones **261-263** follow the same pattern as those of the benzodioxepinones and the 1,5-benzoxathiepinones which were discussed earlier. As expected, the diastereotopic 2-methylene protons resonate at *ca.* δ 3.30ppm as a pair of double doublets, while the 3-methine proton resonates further downfield at *ca.* δ 5.70ppm. The latter signal is an overlapping double doublet; the two coupling constants are equal and, as a result, a triplet is observed. Selected ^{1}H NMR chemical shift data for the compounds in this series are listed in Table 4. Not surprisingly, changing the position of the phenyl substituent from C-3 to C-2 has a significant effect on the chemical shifts of the 2-H and 3-H nuclei. In compounds **264-266**, the methine proton resonates at *ca.* δ 6.0ppm while the 3-H proton signals appear at *ca.* δ 4.0ppm (Table 5).
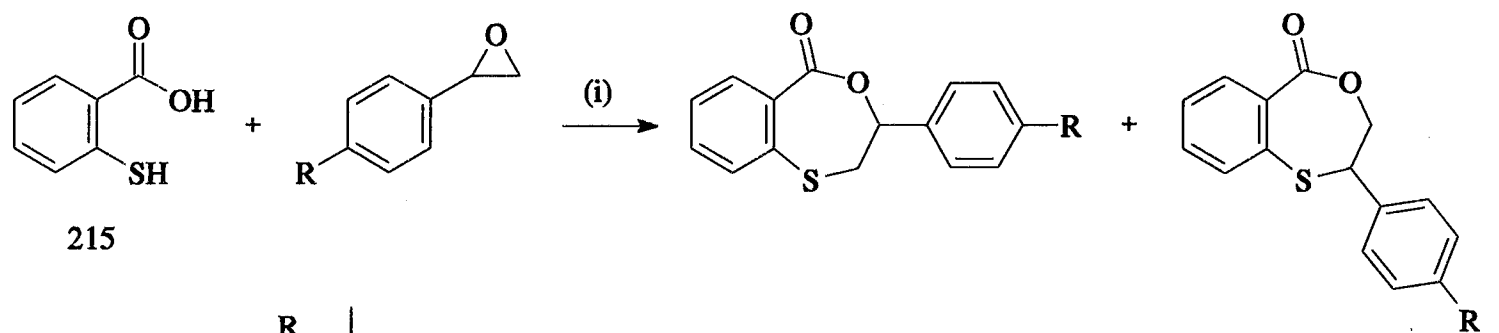
R			
Br	211	261	264
Cl	212	262	265
H	233	263	266

SCHEME 61. Reagents: (i) TsOH, C₆H₆, reflux.

Table 4.   Selected ^{1}H NMR chemical shift data (δ ppm) for 2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-ones 261-263, with the splitting patterns indicated in parentheses.
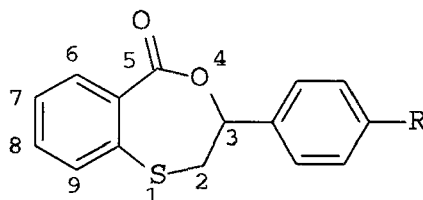
Compd.	R	2-H(2 x dd)	3-H(t)[a]	6-H(dd)	8-H(ddd)
261	Br	3.27	5.66	8.08	7.40
262	Cl	3.32	5.70	8.12	7.43
263	H	3.37	5.74	8.14	7.42

[a] Overlapping dd

Table 5. ^{1}H NMR chemical shift data for the C-ring of the 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-ones 264-266.
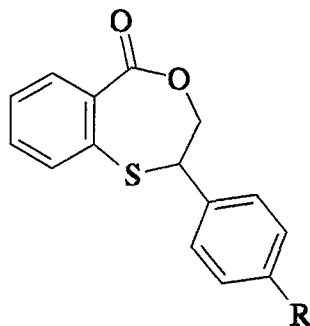
Compd.	R	2-H	3-H
264	Br	6.03	3.97
265	Cl	5.97	3.89
266	H	6.10	3.98

The ^{13}C NMR chemical shifts of the methine and methylene carbons in the two series of compounds (compounds **261-263** and **264-266**) are also affected by the position of the phenyl substituent (Tables 6 and 7). In both series the methine carbon signals appear downfield (due to the adjacent phenyl substituent) compared to the methylene signals. The chemical shifts of the methine carbon in compounds **261-263** are even further downfield compared to those of compounds **264-266** because, in addition to the influence of the adjacent phenyl substituent, the methine carbon is further deshielded by the more electronegative oxygen atom.

Table 6.   ¹³C NMR chemical shift data (δ ppm) for the 2,3-dihydro-3-phenyl-4,1-
benzoxathiepin-5-ones 261-263.
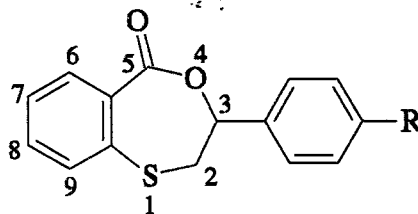
	261	262	263
R	Br	Cl	H
C-2	40.0	39.7	40.6
C-3	82.9	82.8	83.3
C-5	163.7	163.6	163.8
C-6	127.7	127.5	127.6
C-7	133.6	133.5	133.5
C-8	126.7	126.5	126.5
C-9	132.6	132.4	132.4
C-5a*	121.6	123.9	127.4
C-9a*	124.1	133.3	134.5
C-1'	133.5	137.8	138.1
C-2'/C-6'	131.8	130.8	129.5
C-3'/C-5'	131.3	128.7	128.6
C-4'	137.9	132.9	124.1

* These assignments could interchange.

Table 7. ^{13}C NMR shift data for the 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-ones 265 and 266.
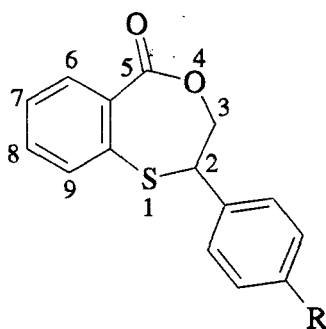
	265	266
R	Cl	H
C-2	77.1	77.9
C-3	65.7	66.0
C-5	165.8	166.0
C-6	131.1	131.0
C-7	132.8	132.7
C-8	124.8	128.5
C-9	131.8	131.9
C-5a*	125.7	125.9
C-9a*	135.4	136.8
C-1'	138.3	138.2
C-2'/C-6'	128.9	128.7
C-3'/C-5'	128.1	126.7
C-4'	134.4	124.7

* These assignments could interchange.

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(c) Preparation of 4,1-Benzoxathiepines

The 4,1-benzoxathiepines **267-270** were prepared as shown in Scheme 62.

2-(Hydroxymethyl)thiophenol **216** (prepared by reduction of thiosalicylic acid; see section 2.1.1.4) and the corresponding epoxystyrenes (**211-213** and **233**) were heated under reflux, using a Dean Stark apparatus, for 72 hours. The reaction mixtures were purified by flash chromatography to give the required products in reasonable yields (43-53%; the conditions were not optimised). In contrast to the reaction of thiosalicylic acid with epoxystyrene, which gave two regioisomeric products [see section 2.1.3(b)], the reaction of 2-(hydroxymethyl)thiophenol with epoxystyrenes yielded only one product in each case. Sulphur, being more nucleophilic than oxygen, attacks the methylene carbon of the epoxystyrene to give an alcohol intermediate which undergoes cyclisation, with the loss of water, to the required benzoxathiepine. Attack at the methine carbon by sulphur does not appear to take place since no trace of other regioisomers was observed.

The ^{1}H NMR chemical shifts and coupling patterns for the 2-methylene and 3-methylene protons are similar to those observed for the 3-phenyl-4,1-benzoxathiepin-5-ones **261-263**, discussed in the preceding section (see Tables 4 and 8). Thus, the 2-methylene protons resonate as a well-resolved pair of double doublets at $ca.$ δ 3.1 and 3.4ppm; while the 3-methine proton signal appears as a triplet at $ca.$ δ 5.4ppm. The 5-methylene protons, being diastereotopic, couple with each other to afford a distorted double doublet at $ca.$ δ 4.9ppm. These 5-H nuclei can be viewed as an AB system, in which the distortion of the doublets depends on the frequency separation ($\Delta\nu$) of the signals. Geminal coupling constants (J_{ab})

of 15Hz were observed. The ^{13}C chemical shift assignments for these compounds are given

in Table 9. Assignment was effected with the help of DEPT and HETCOR experiments and

calculations from correlation tables for ^{13}C-chemical shifts. Table 6 [section 2.1.3(b)] and

Table 9 show that substituting the carbonyl group at position 5 by a methylene group has a

significant effect on some of the chemical shifts, particularly C-7 and C-9; the C-4' signal

-for the bromo derivative also shows a marked shift.

R		
Br	211	267
Cl	212	268
F	213	269
H	233	270
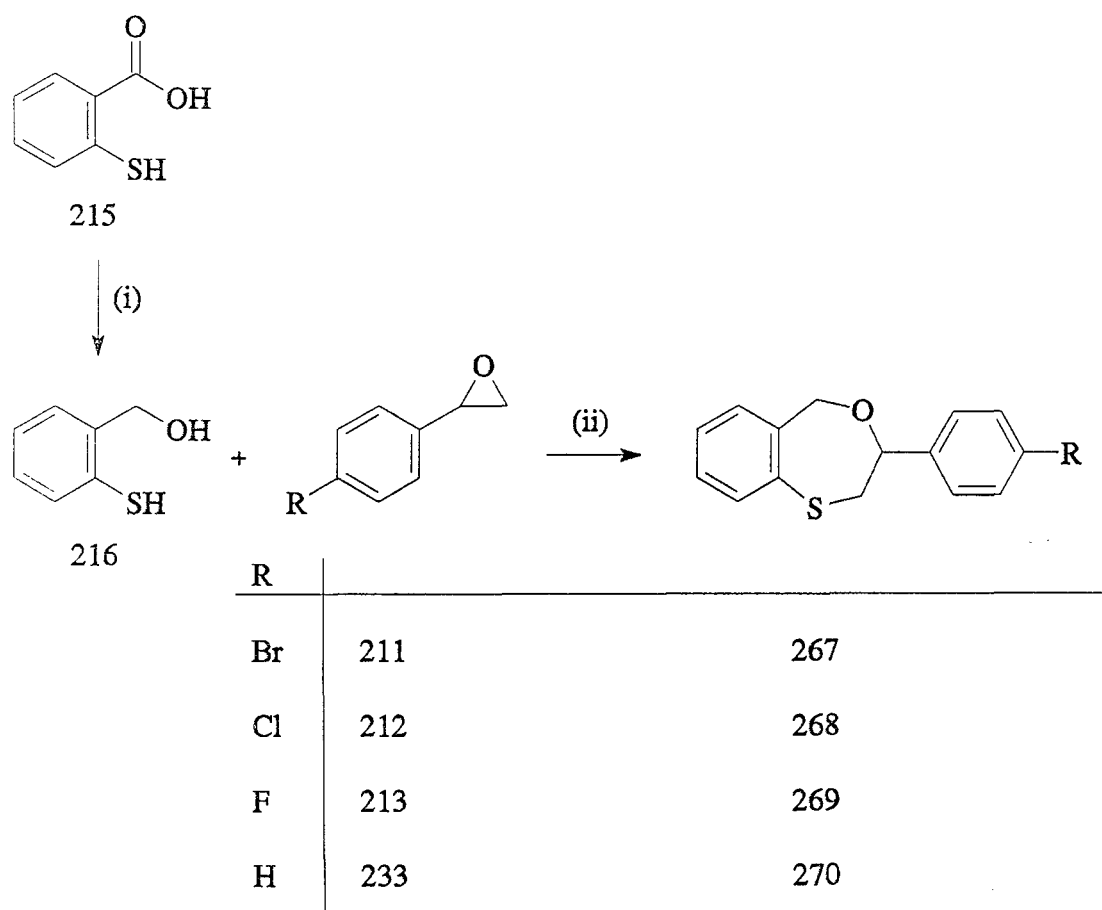
SCHEME 62. Reagents: (i) LiAlH$_4$, THF; (ii) TsOH, C$_6$H$_6$, reflux.

Table 8.   Selected ^{1}H NMR chemical shift data (δ ppm) for the 3-phenyl-4,1-benzoxathiepines 267-270.
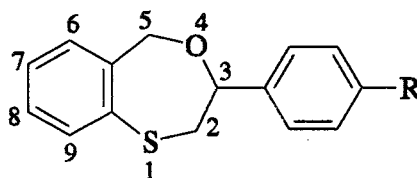
Compd.	R	2-H (2xdd)	3-H (dd)	5-H (dd)	7-H (ddd)	8-H (dd)
267	Br	3.16	5.33	4.88	7.06	6.96
268	Cl	3.18	5.33	4.89	7.06	6.96
269	F	3.17	5.31	4.89	-	-
270	H	3.27	5.41	4.93	7.09	6.98

Table 9. ^{13}C NMR chemical shift data (δ ppm) for the 3-phenyl-4,1-benzoxathiepines 267, 268 and 270.
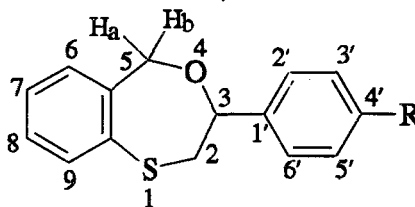
R	267	268	270
	Br	Cl	H
C-2	41.4	41.5	42.3
C-3	81.7	81.9	82.3
C-5	69.7	69.8	69.9
C-5a	135.1	134.6	136.2
C-6	127.2	127.3	127.3
C-7	124.5	124.6	124.4
C-8	125.6	127.2	125.6
C-9	127.1	125.6	127.1
C-9a*	129.4	129.5	129.6
C-1'	131.5	132.7	131.9
C-2'/C-6'	131.3	130.8	129.4
C-3'/C-5'	131.1	128.4	128.3
C-4'	120.8	131.6	126.9
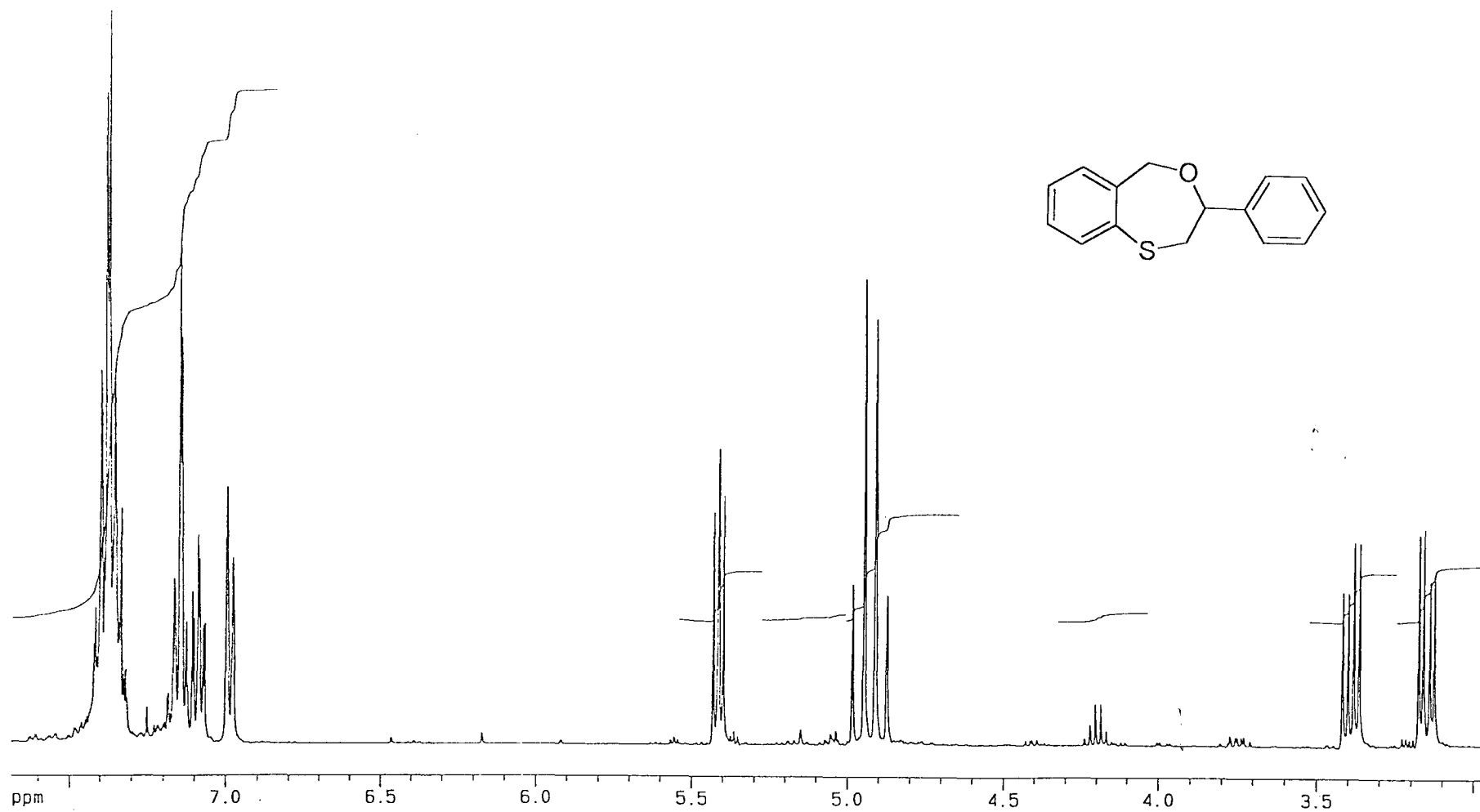
Figure 8:   400 MHz ^{1}H NMR spectrum of 3-phenyl-4,1-benzoxathiepine 270 in CDCl$_3$

2.1.4 PREPARATION OF BENZODIAZEPINE DERIVATIVES

A short review of the well explored chemistry of the benzodiazepines was given in the introduction (section 1.3). The following section will cover the synthesis of a range of such compounds *via* the Schmidt reaction of 4-quinolone precursors.

(a) Preparation of *N*-acetyl-4-quinolones

The *N*-acetyl-4-quinolones **271-274** were obtained in low yields (5-39%) by the reaction of 1,2,3,4-tetrahydro-2-phenyl-4-quinolones **202-205** with acetic anhydride according to the reported procedure[133] (Scheme 63). In addition to the *N*-acetyl-4-quinolones, 4-acetoxy-*N*-acetyl-1,2-dihydro-2-phenylquinolines **275-278** were isolated as the major products (36-63% yields). In contrast to these results, Donnelly and Farrell[133] reported the *N*-acetyl-4-quinolone **271** as the major product with the 4-acetoxy-*N*-acetyl-1,2-dihydro-2-phenylquinoline **275** being the major product only in the presence of sodium acetate.

R			
H	202	271	275
Br	203	272	276
Cl	204	273	277
F	205	274	278
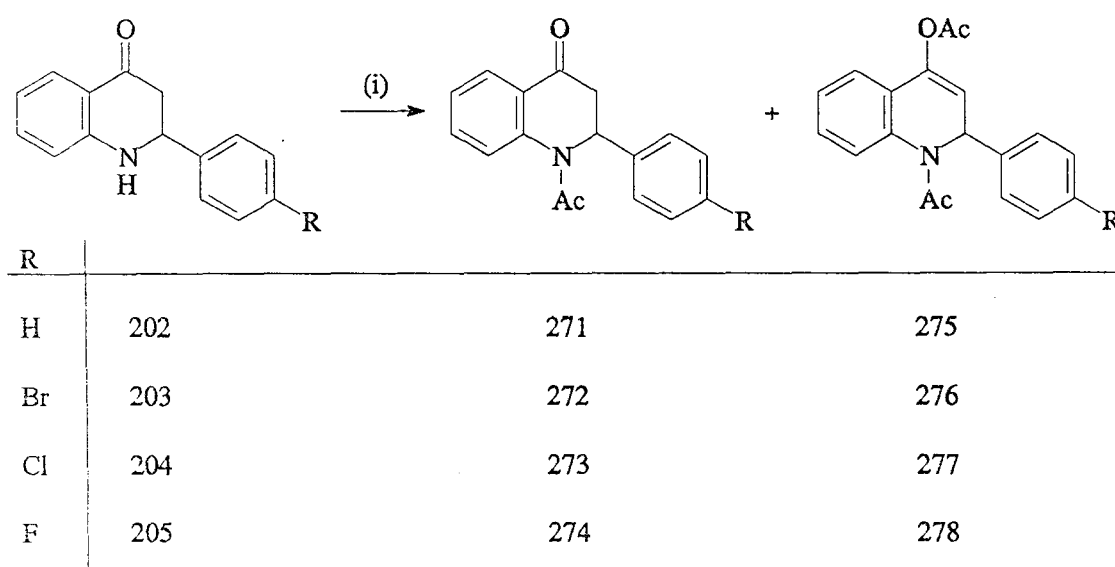
SCHEME 63. Reagents: (i) Ac$_2$O, reflux.

The 4-quinolone derivatives **271-274** can easily be distinguished from the 4-acetoxyquinolines **275-278** by ^{1}H NMR spectroscopy. In compounds **271-274**, a singlet due to the N-acetyl group appears at *ca.* δ 2.4ppm while in compounds **275-278** two singlets due to the acetyl and acetoxy groups are observed at δ 2.27 and 2.35ppm respectively. The quinolones also exhibit two double doublets at *ca.* δ 3.30ppm due to the diastereotopic protons at position 3 as illustrated for N-acetyl-2-(4-bromophenyl)-4-quinolone **272** in figure 9. This signal is, of course, absent in the spectra of the 4-acetoxyquinolines; the signal for the vinyl proton of these quinolines appears as a doublet at *ca.* δ 6.0ppm (figure 10).

The ^{1}H NMR spectra for both the N-acetylquinolones and their 4-acetoxyquinoline derivatives (figures 9 and 10) show line broadening of the 2-H and 8-H signals. This is undoubtedly due to internal rotation of the N-acetyl group. Hindered rotation in amides is well known and often results in the splitting of associated NMR signals. The broad signals observed in figures 9 and 10 presumably represent a post-coalescence condition. Future research will involve a dynamic NMR (DNMR) analysis of these systems to establish substituent effects on *coalescence* temperature and the free energy of activation for internal rotation. ^{13}C NMR data for the N-acetyl-4-quinolones are given in Table 10. The assignment of the chemical shifts was based on data obtained from COSY, DEPT and HETCOR experiments as well as CF coupling constants in the ^{13}C NMR spectrum of the 4'-fluoro derivative **274**.

Table 10. ^{13}C NMR chemical shift (δ ppm) data for the *N*-acetyl-4-quinolone derivatives in CDCl$_3$.
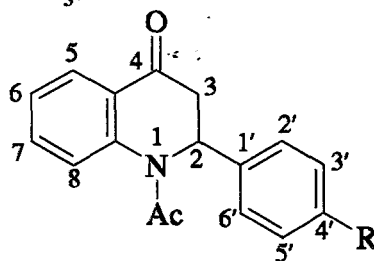
	271	272	273	274
R	H	Br	Cl	F
CH$_3$	23.3	23.3	23.3	23.2
NCO	192.9	192.7	192.8	192.8
C-2	54.7	54.1	54.1	54.0
C-3	42.6	42.4	42.5	42.5
C-4	170.1	170.1	170.1	170.0
C-4a	126.1	121.7	126.0	125.8
C-5	127.5	127.4	127.4	127.2
C-6	125.5	125.7	125.7	125.5
C-7	134.4	134.5	134.5	134.4
C-8	125.1	125.0	125.0	124.9
C-8a	141.8	141.6	141.6	141.5
C-1'	137.9	137.1	136.6	133.7[a]
C-2'/C-6'	128.6	131.7	128.8	128.4[b]
C-3'/C-5'	126.8	128.6	128.2	115.4[c]
C-4'	127.3	125.9	133.6	161.8[d]

[a] $^{*}J_{CF}$ 3.0Hz. [b] $^{3}J_{CF}$ 9.1Hz. [c] $^{2}J_{CF}$ 21.1Hz. [d] $^{1}J_{CF}$ 246.5Hz
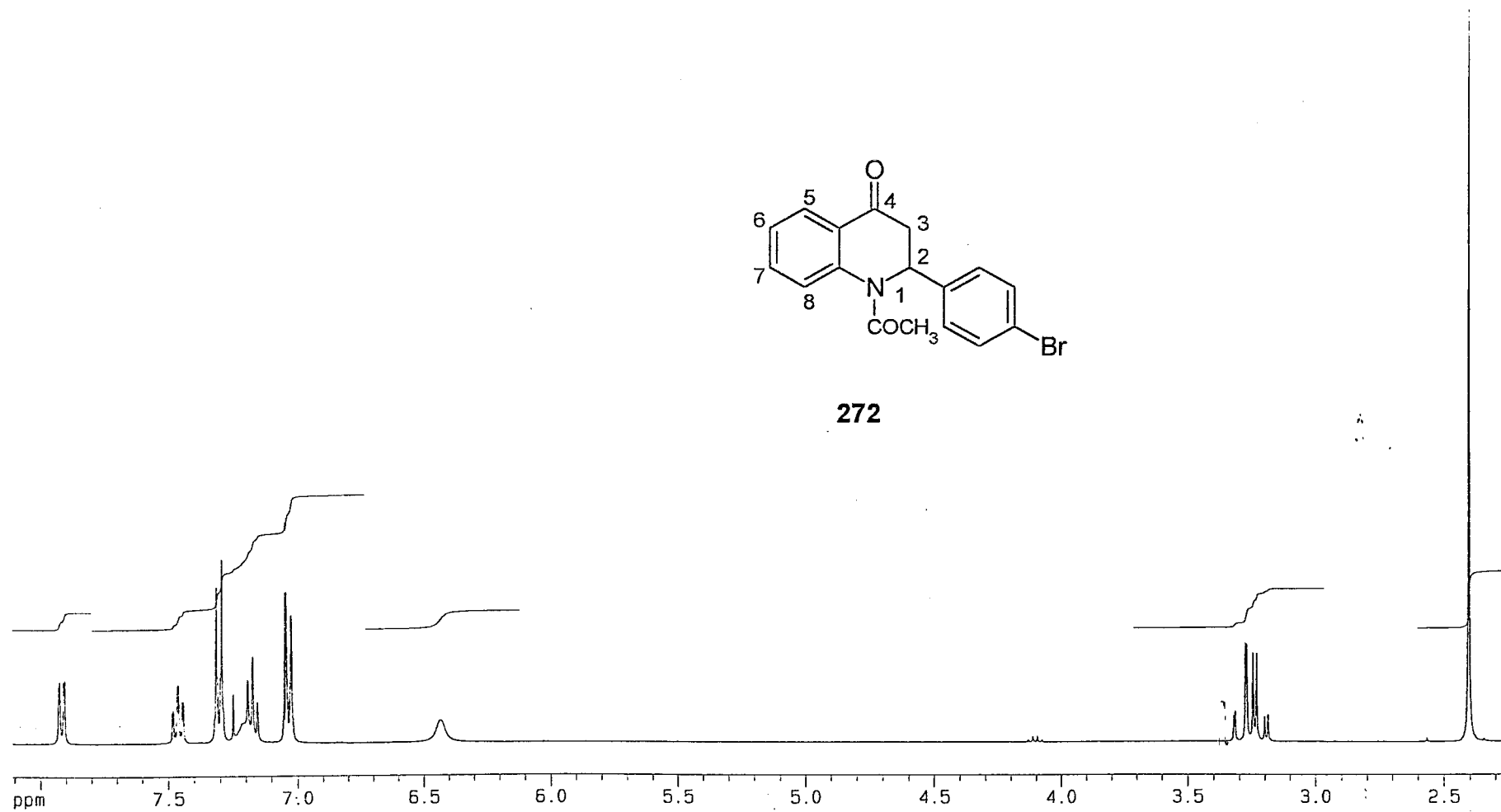
Figure 9:   400 MHz ^{1}H NMR spectrum for N-acetyl-2-(4-bromophenyl)-4-quinolone 272 in CDCl$_3$
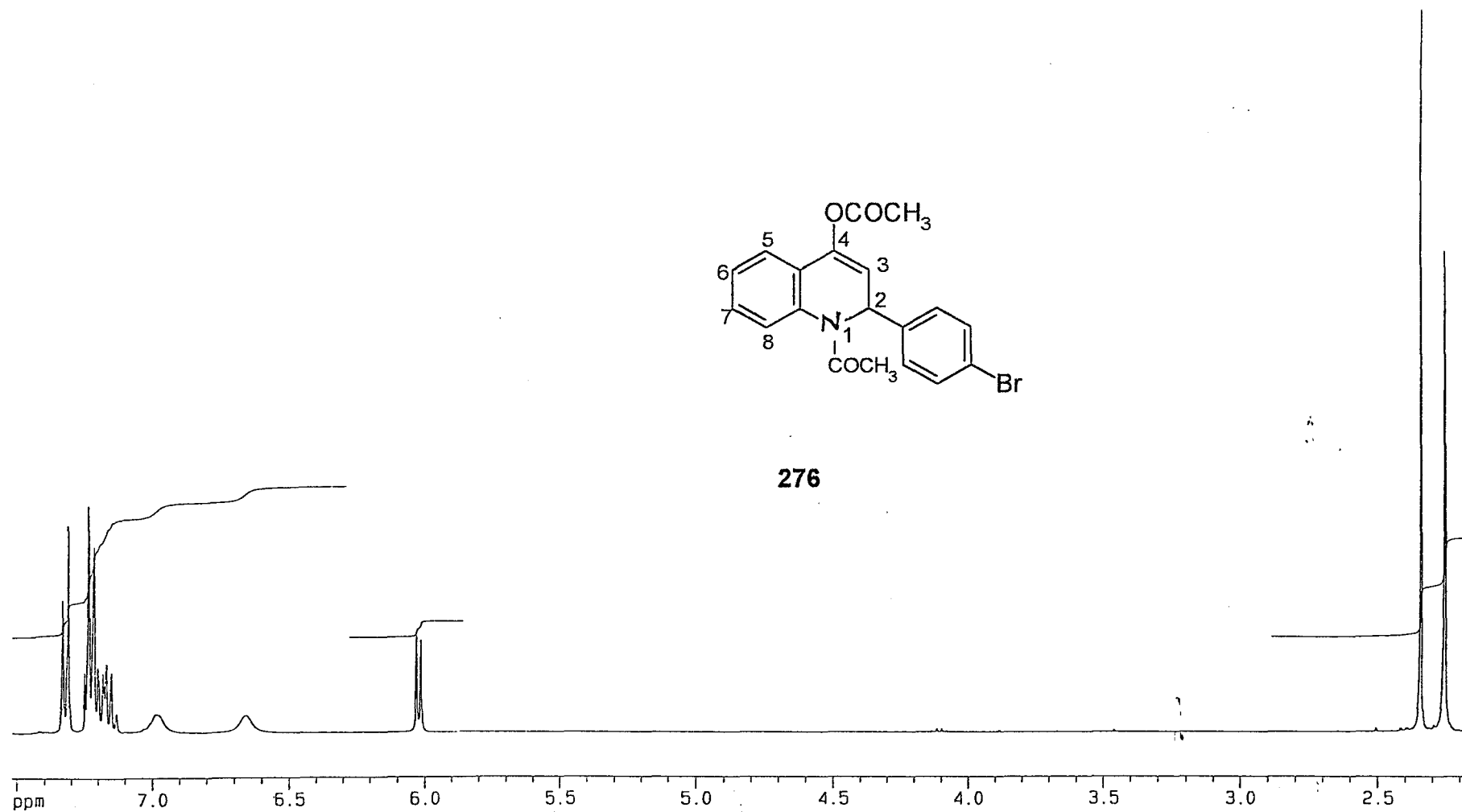
Figure 10: 400 MHz ^{1}H NMR spectrum for 4-acetoxy-N-acetyl-2-(4-bromophenyl)-quinoline 276 in CDCl$_3$

(b) Preparation of 1,4- and 1,5-benzodiazepinones

The Schmidt reaction of 1,2,3,4-tetrahydro-4-quinolone, using sodium azide and sulphuric acid, has been reported to afford the 1,4- and 1,5-benzodiazepine derivatives.[175] However, in our laboratory, it has been found that the azidotrimethylsilane-mediated Schmidt reaction of 2-aryl-1,2,3,4-tetrahydro-4-quinolones affords the 1,4-benzodiazepinones and their tetrazolo derivatives, with no trace of the 1,5-benzodiazepinone derivatives.[91] In contrast to this observation, we have found that Schmidt reaction of N-acetyl-1,2,3,4-tetrahydro-4-quinolones 271-273, using azidotrimethylsilane (TMS-N_3) in trifluoroacetic acid (TFA), affords both the 1,4- and 1,5-benzodiazepinone derivatives (Scheme 64), with the 1,5-isomer being the major product in each case. The products were isolated by flash chromatography and characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The ^{1}H NMR spectra of the 1,4- and 1,5-benzodiazepinones 279-281 and 282-284 show distinct differences from those of the 4-quinolone precursors 271-274. For example, the 1,4-isomer 283 is distinguished from its precursor, compound 272, by the appearance of an amide proton signal at ca. δ 7.6ppm and an upfield shift of the 2-H signal to ca. δ 6ppm, (figure 11).

The 1,4- and 1,5-isomers are distinguished from each other by the different chemical shifts of the 3-H protons. In the 1,5-isomer, the 3-H protons resonate upfield at ca. δ 2.75ppm (figure 12), while the inductive effect of the 4-nitrogen atom causes the 3-methylene proton signals in the 1,4-isomer to shift downfield to ca. δ 3.40ppm (figure 11). In addition, the 3-H signal in the 1,4-isomers is split further due to coupling to the adjacent amide hydrogen.

[13]C chemical shift data for the 1,4-benzodiazepinone derivatives 272, 283 and 284 are summarised in Table 12.

R			
H	271	279	282
Br	272	280	283
Cl	273	281	284
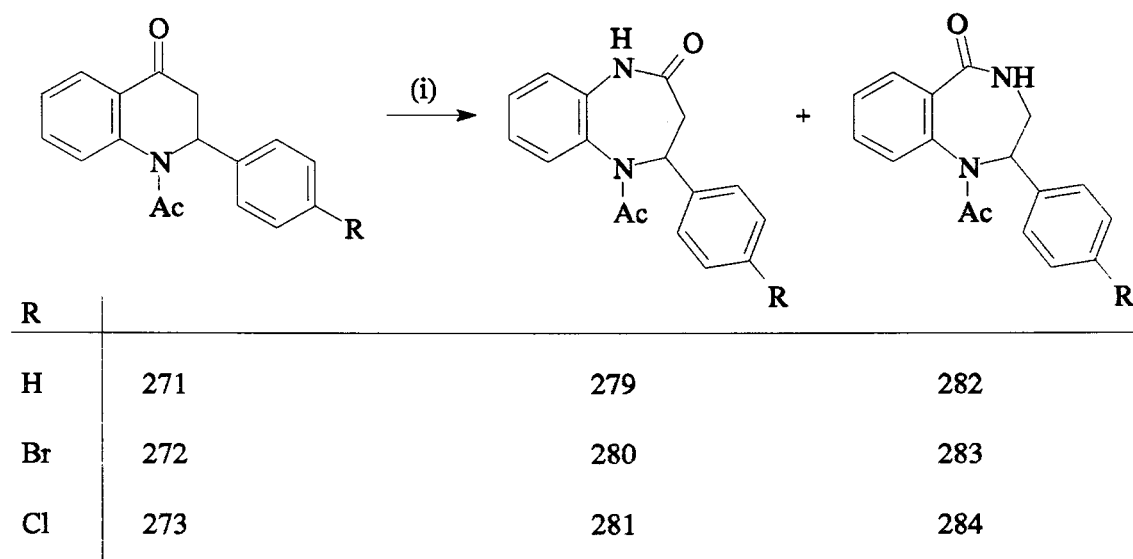
SCHEME 64. Reagents: (i) TMS-N₃, TFA, r.t.

Table 11. ^{1}H NMR chemical shifts (δ ppm) and splitting patterns for the N-acetyl-2,3-dihydro-2-phenyl-1,4-benzodiazepin-5-one derivatives in $CDCl_3$.
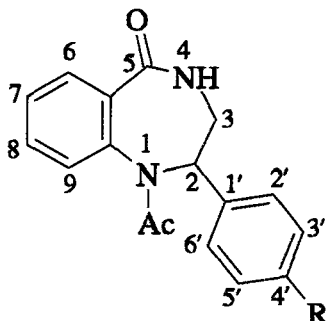
	282	283	284
R	H	Br	Cl
CH₃	1.73 (s)	1.80 (s)	1.80 (s)
2-H	6.34 (dd)	5.95 (dd)	5.97 (dd)
3-H	2.79 (m)	3.41 (m)	3.41 (m)
6-H	7.26 (m)	7.56 (m)	7.56 (m)
7-H	7.26 (m)	7.86 (m)	7.87 (m)
8-H	7.43 (ddd)	7.56 (m)	7.56 (m)
9-H	7.08 (d)	7.06 (m)	7.05 (m)
NH	8.96 (br s)	7.64 (t)	7.16 (t)
2'-H/6'-H	7.28	7.42 (d)	7.27 (d)
3'-H/5'-H	7.28	7.11 (d)	7.17 (d)

Table 12. ^{13}C NMR chemical shift (δ ppm) data for the *N*-acetyl-2,3-dihydro-1,4-benzodiazepin-5-one derivatives 282-284 in CDCl$_3$.
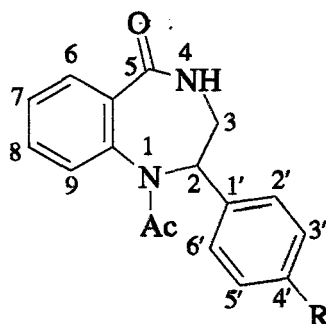
	282	283	284
R	H	Br	Cl
NCO	170.8	170.9	170.9
CH$_3$	22.8	23.0	23.1
C-2	61.1	62.3	62.2
C-3	39.0	44.4	44.5
C-5	173.2	171.2	170.9
C-5a	123.3	122.2	133.1
C-6	128.0	129.3	129.3
C-7	129.7	130.2	130.2
C-8	132.8	132.4	132.4
C-9	131.4	130.3	130.3
C-9a	139.7	137.1	137.1
C-1'	136.2	137.0	136.5
C-2'/C-6'	128.6	131.8	128.9
C-3'/C-5'	126.7	129.0	128.9
C-4'	126.6	133.0	134.1
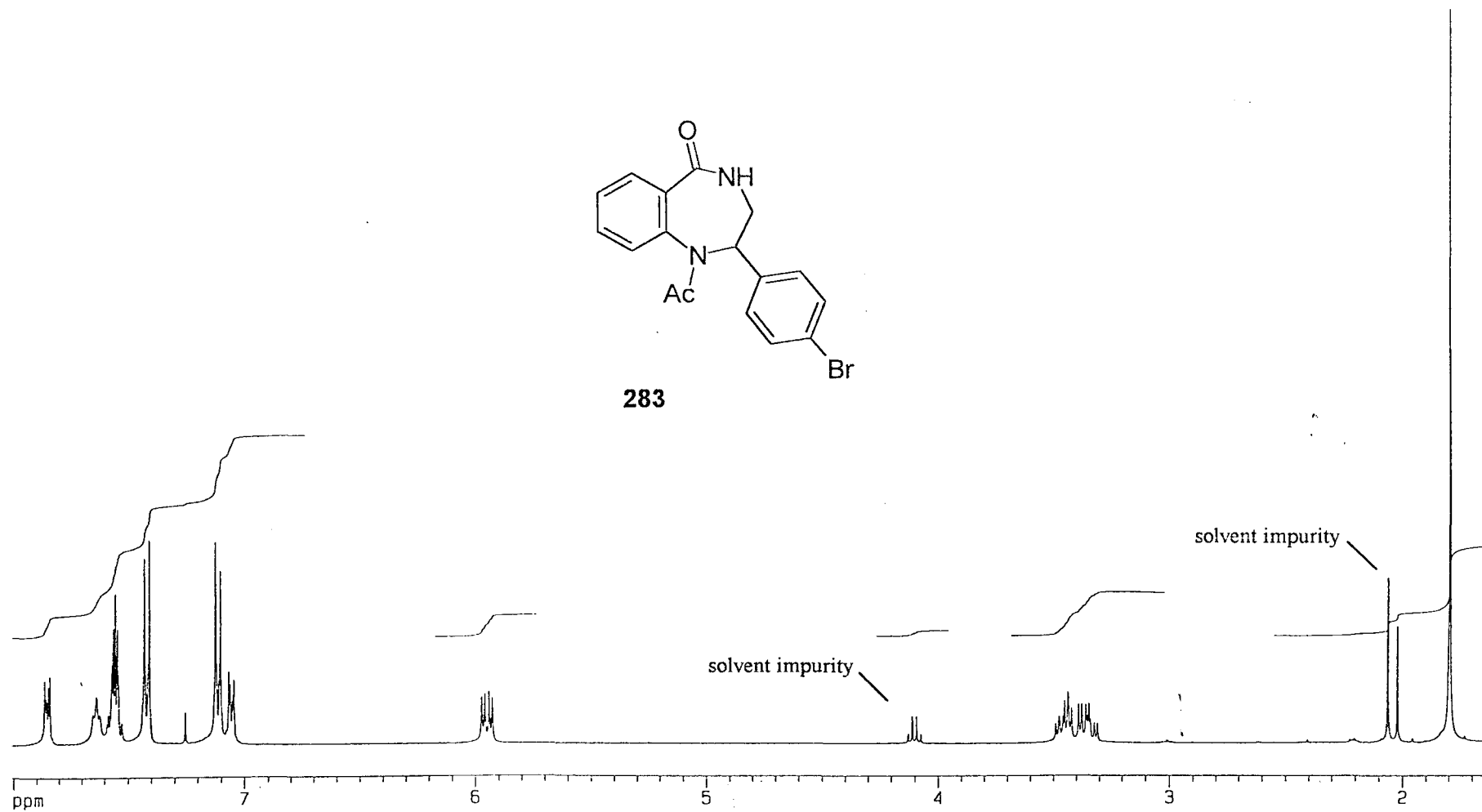
Figure 11:   400 MHz ¹H NMR spectrum for N-acetyl-2,3-dihydro-2-(4-bromophenyl)-1,4-benzodiazepin-5-one **283** in CDCl₃
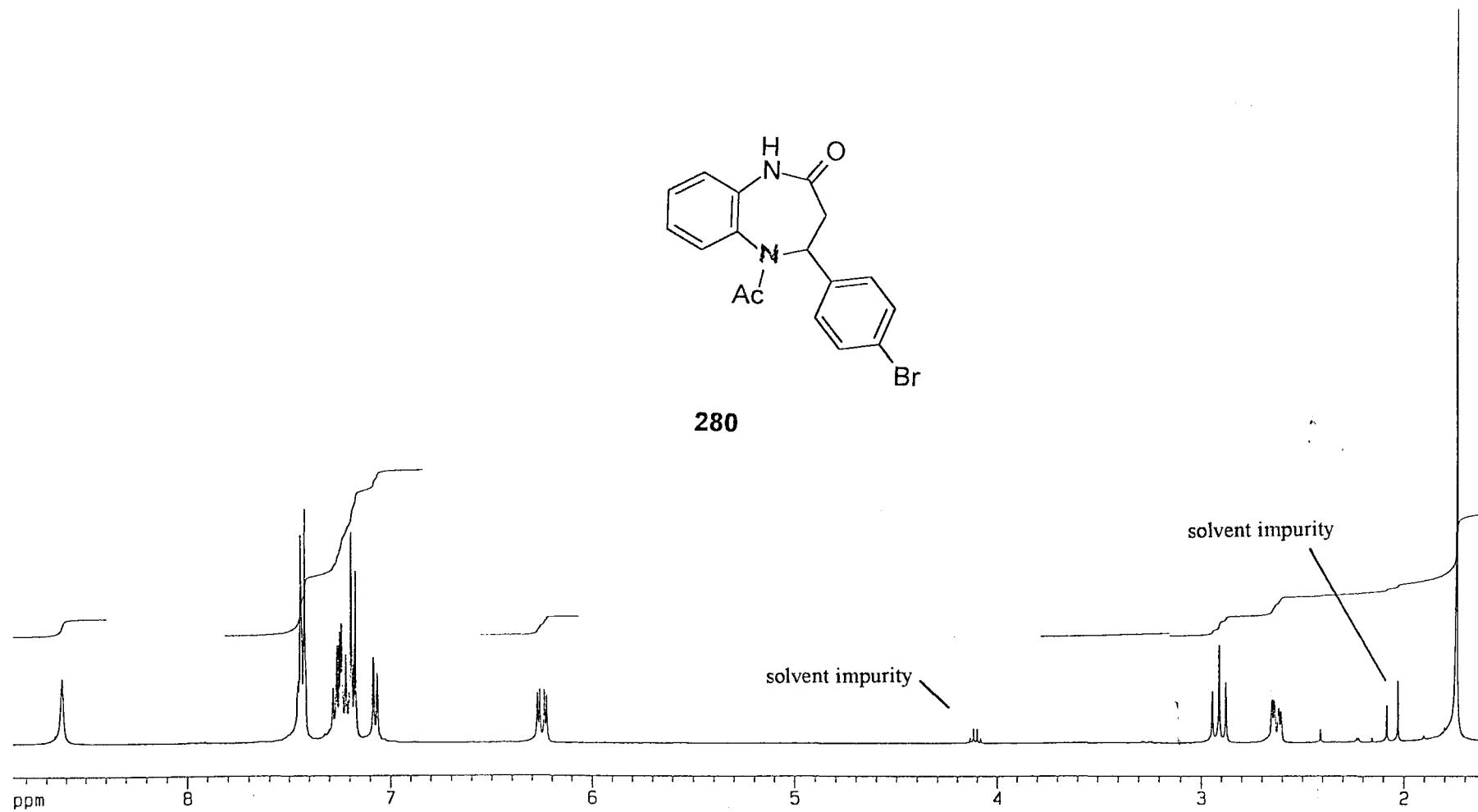
Figure 12: 400 MHz ^{1}H NMR spectrum for N-acetyl-2,3-dihydro-2-(4-bromophenyl)-1,5-benzodiazepin-4-one **280** in CDCl$_3$

2.2 RING-OPENING REACTIONS OF 4-ARYL-3,4-DIHYDRO-1,5-BENZODIOXEPIN-2-ONES

We have previously noted[26] nucleophilic cleavage of the seven-membered ring of 4-aryl-3,4-dihydro-1,5-benzodioxepin-2-ones. Depending on the conditions, these benzodioxepinones may undergo fission of the heterocyclic ring *via* two independent modes (Scheme 65). Phenoxy ethers **285** and **286** were obtained[26] by solvolytic transesterification, which involves fission of the O(1)-C(2) bond of the lactone group (mode I). It was also observed that the lithium enolate of benzodioxepinones **65**, generated with lithium diisopropylamide (LDA) at *ca.* -78°C, undergoes rapid β-elimination to afford the cinnamate ester **229** in a sequence involving fission of the C(4)-O(5) bond. [This kind of ring cleavage (mode II) is discussed later in this section]. The ease with which the seven-membered ring opens, suggested the potential of such benzodioxepinones as effective acylating agents in biological systems. In order to explore further the susceptibility of these compounds to O(1)-C(2) fission, a series of benzodioxepinones were reacted with one equivalent of butylamine (as a model for biogenetic nucleophiles). The corresponding ring-opened, carboxamide products (**287-289**) were, in fact, obtained in reasonably good yields (55-70%) under relatively mild conditions.

One of the aims of this research has been to increase conjugation in the 7-membered ring to afford compounds which resemble the clinically useful benzodiazepines more closely. It was therefore necessary to introduce a double bond between C3 and C4 in the benzodioxepinones. One obvious way to do this, it seemed, would be to effect hydroxyalkylation at position 3, to be followed by dehydration and migration of the exocyclic double bond in the initial

condensation product **291** (Scheme 66). The potential for β-elimination in the enolate

systems **65a** was recognised but it was hoped that rapid attack by a suitable electrophile

would lead to the desired intermediates **290**. Moreover, an analogous pathway for the

piperidine-catalysed transformation of flavanones to their 3-benzyl derivatives has been

reported recently.[176] In the event, however, the benzodioxepine enolate, generated by

addition of LDA to the substrates either in the presence or absence of non-enolizable

aldehydes, underwent ring-opening to catechol monocinnamate **229**, which reacted further

with the added aldehydes (RCHO) to produce the cinnamate esters **293-296**. The ^{1}H NMR

spectra of the esters **293-296** indicated the absence of the aliphatic ABX (CH_2CH) system and

the presence of a methylene singlet (figure 13) - observations which initially led us to assume

the formation of the conjugated derivatives **292**. This conclusion, however, was discarded

after careful examination of the ^{1}H and ^{13}C NMR, MS, and elemental analysis. The

formation of the cinnamate esters **293-296** was also confirmed by spectroscopic comparison

with independently synthesised benzyl cinnamate **293**.

Isolation of the cinnamate esters (**293-296**) under these conditions requires *in situ* reduction

of the added aldehyde RCHO in each case and suggests involvement of a Cannizzaro-type

disproportionation. The Cannizzaro aldehyde disproportionation may be mediated by

nucleophilic bases like sodamide,[177] but participation of the "non-nucleophilic" base, LDA,

in this reaction is surprising and, to our knowledge, unprecedented. A possible mechanistic

sequence which would account for the formation of the observed products is outlined in

Scheme 67. In order to confirm this possibility, benzaldehyde was treated with LDA; the

isolation of *N*,*N*-diisopropylbenzamide and benzyl benzoate, although in low yields, clearly

supports:

(i)   the implication of LDA in a Cannizzaro-type transformation, and

(ii) the participation of the intermediate benzyl alkoxide with benzaldehyde in a

      Tishchenko transformation to afford benzyl benzoate.[178]
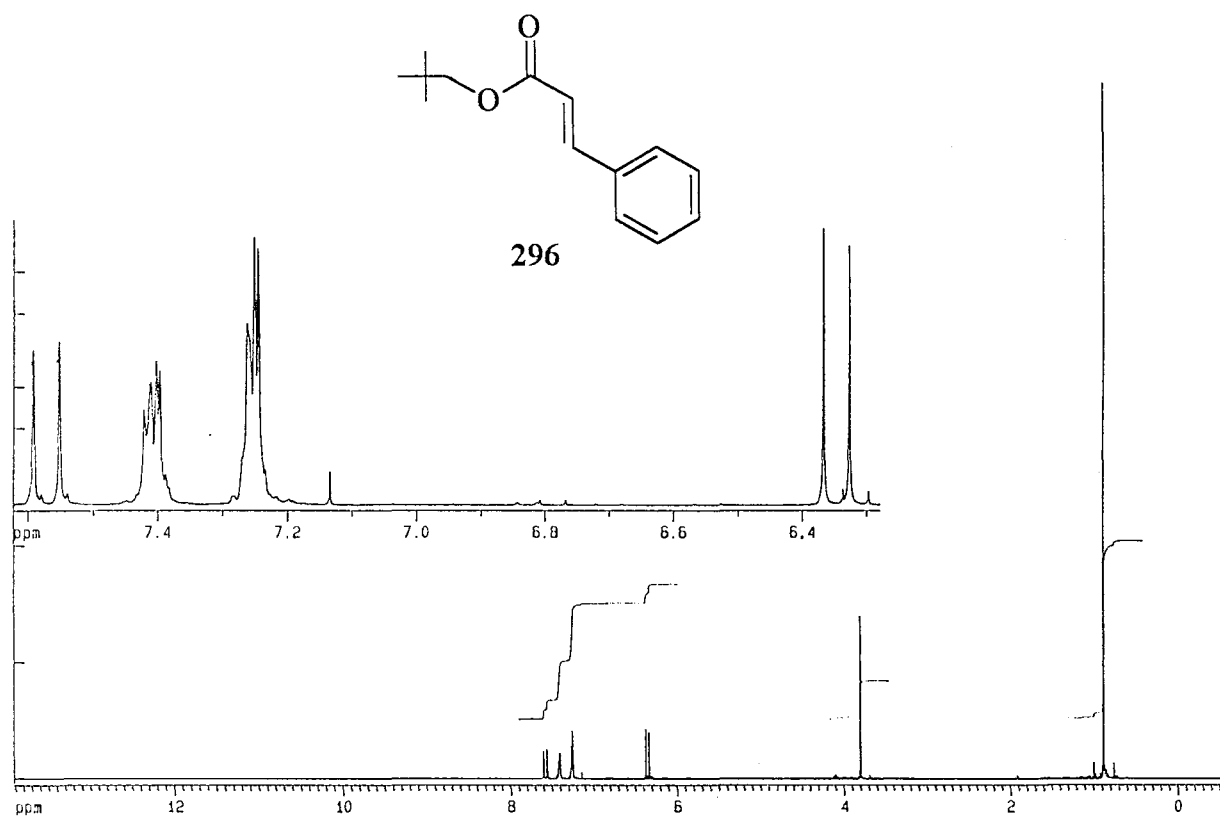
Figure 13:   400 MHz ^{1}H NMR spectrum of 2,2-dimethylpropyl cinnamate 296 in
             CDCl$_3$

R^1	R^2	
Br	H	285
F	H	286
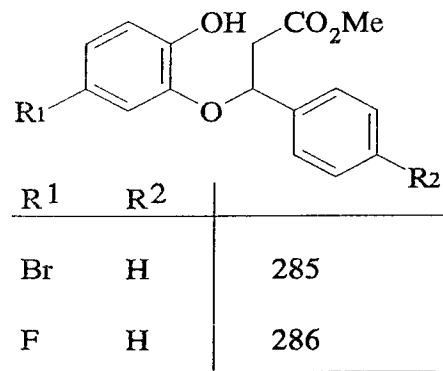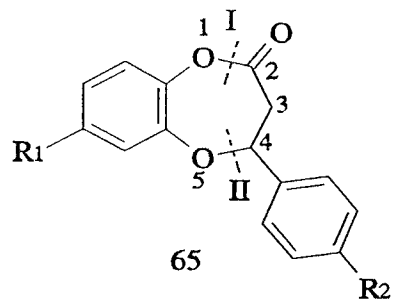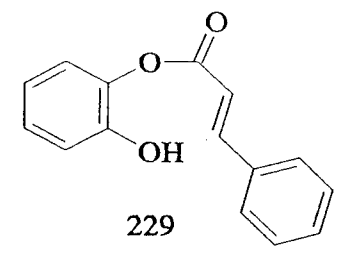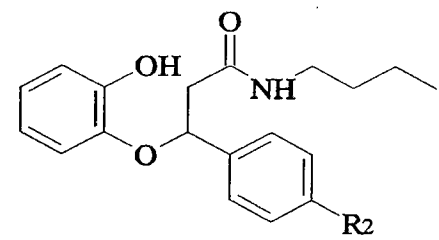
R^2	
H	287
Cl	288
Br	289

SCHEME 65. Reagents: (i) MeOH; (ii) LDA, THF, *ca.* -78°C; (iii) CH$_3$(CH$_3$)$_3$NH$_2$, 70°C.
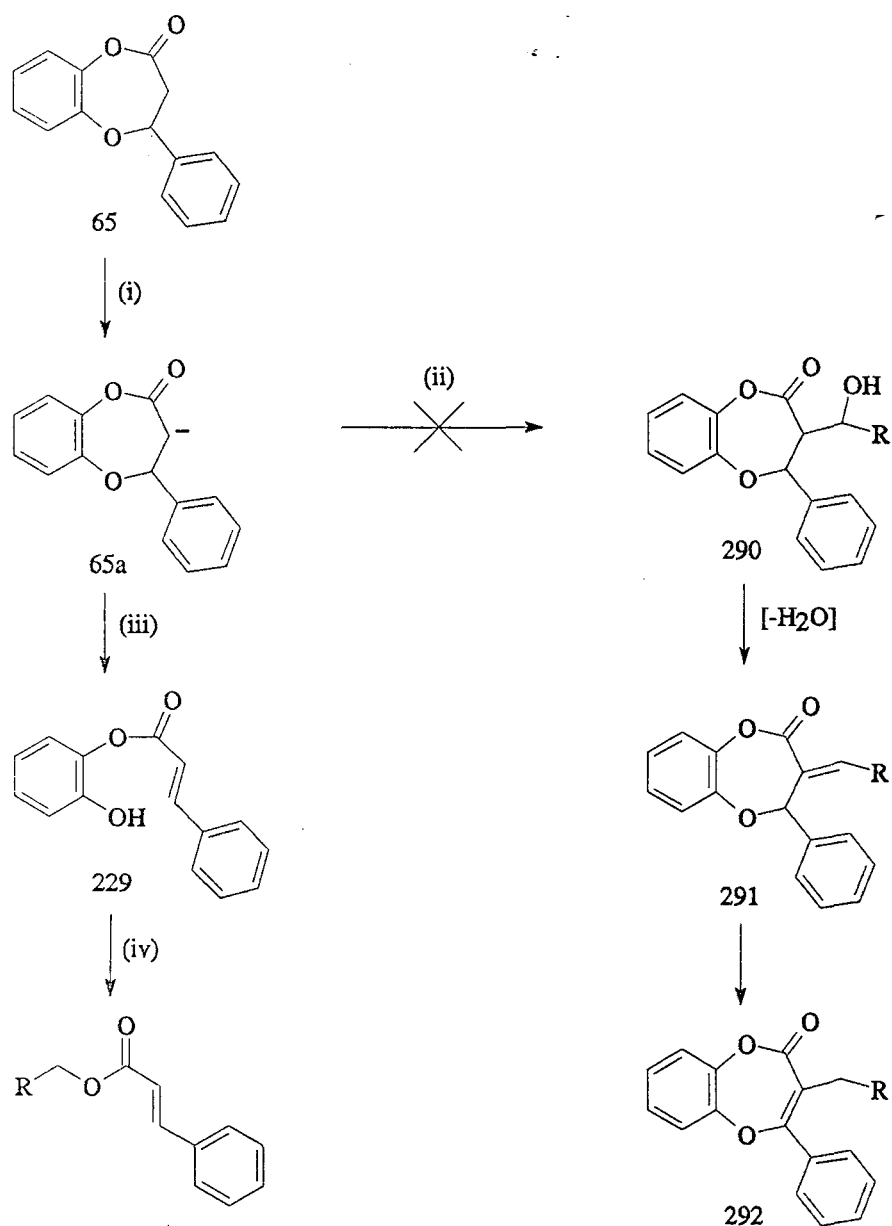
R	
C6H5	293
p-ClC6H4	294
p-NO2H4	295
Bu^t	296

SCHEME 66. Reagents: (i) LDA, THF, *ca.* -78°C;
(ii) RCHO;
(iii) RCHO (present during generation of lithium enolate)
(iv) RCH2OLi (generated *in situ*).
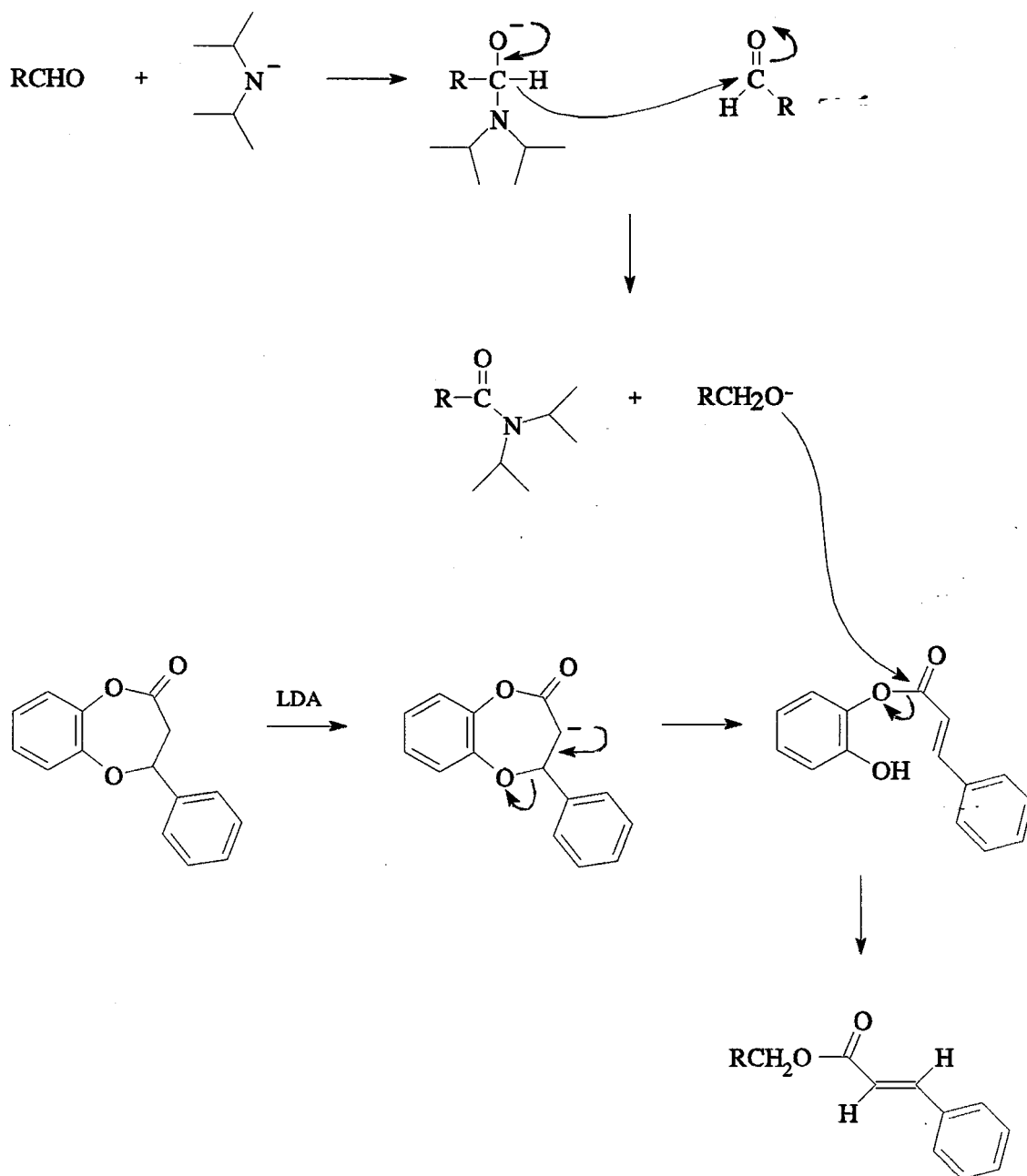
SCHEME 67

2.3 PREPARATION OF SULPHOXIDES AND SULPHONES

While recognising the susceptibility of sulphides to oxidation to sulphoxides and sulphones,

it was hoped that treatment of thiochromanone and thioflavanone precursors under Baeyer-

Villiger conditions might afford some ring-expanded products. In the event, no Baeyer-

Villiger products could be isolated. The various sulphoxides and sulphones which were

obtained (Scheme 68), together with others which were specially prepared (Scheme 69) were,

however, used as model compounds for an ^{17}O NMR study (see section 2.5). All the

sulphoxides and sulphones were obtained by the reaction of the corresponding sulphides with

MCPBA in dichloromethane (Schemes 68 and 69). Compound **259** was also prepared by

reacting the sulphide **256** with 30% hydrogen peroxide in glacial acetic acid.[179]

A combination of ^{13}C NMR, ^{17}O NMR, IR and mass spectrometry were used to differentiate

the sulphoxides and sulphones from their precursors and from each other. The 2- and 3-

methylene nuclei of compounds **256**, **258** and **259** exhibit distinct differences in their ^{1}H

NMR signals (Table 13). The increased multiplicities of both the 2- and 3-methylene signals

in compound **258** presumably reflects the diastereotopicity of the protons in each pair, arising

from the inherent chirality of the unsymmetrical sulphoxide moiety. Of course, the 2- and

3-methylene protons in compounds **256** and **259** could have been expected to exhibit magnetic

non-equivalence being, in principle, AA'XX' systems; in the 400MHz spectra, however,

A_2X_2 patterns (*i.e.* 2 x t) are observed. In the IR spectrum of the sulphoxide **258**, the SO

group absorbs at *ca.* 1055cm^{-1} while the SO_2 group of the sulphone **259** absorbs at *ca.*

1155cm^{-1} (both in the expected ranges). Perhaps the most obvious method to distinguish

between compounds **258** and **259** is mass spectrometry, the sulphoxide affording a molecular

ion peak at m/z 180.023 and the sulphone a corresponding peak at m/z 196.018. ^{17}O NMR

spectroscopy provides another convenient way to differentiate the two compounds (the ^{17}O

NMR spectra will be discussed in detail in section 2.5). Similar analyses permitted

unambiguous characterisation of the other sulphoxides and sulphones prepared (Scheme 69).

^1H NMR chemical shift data for some of these compounds are detailed in Tables 13 and 14.
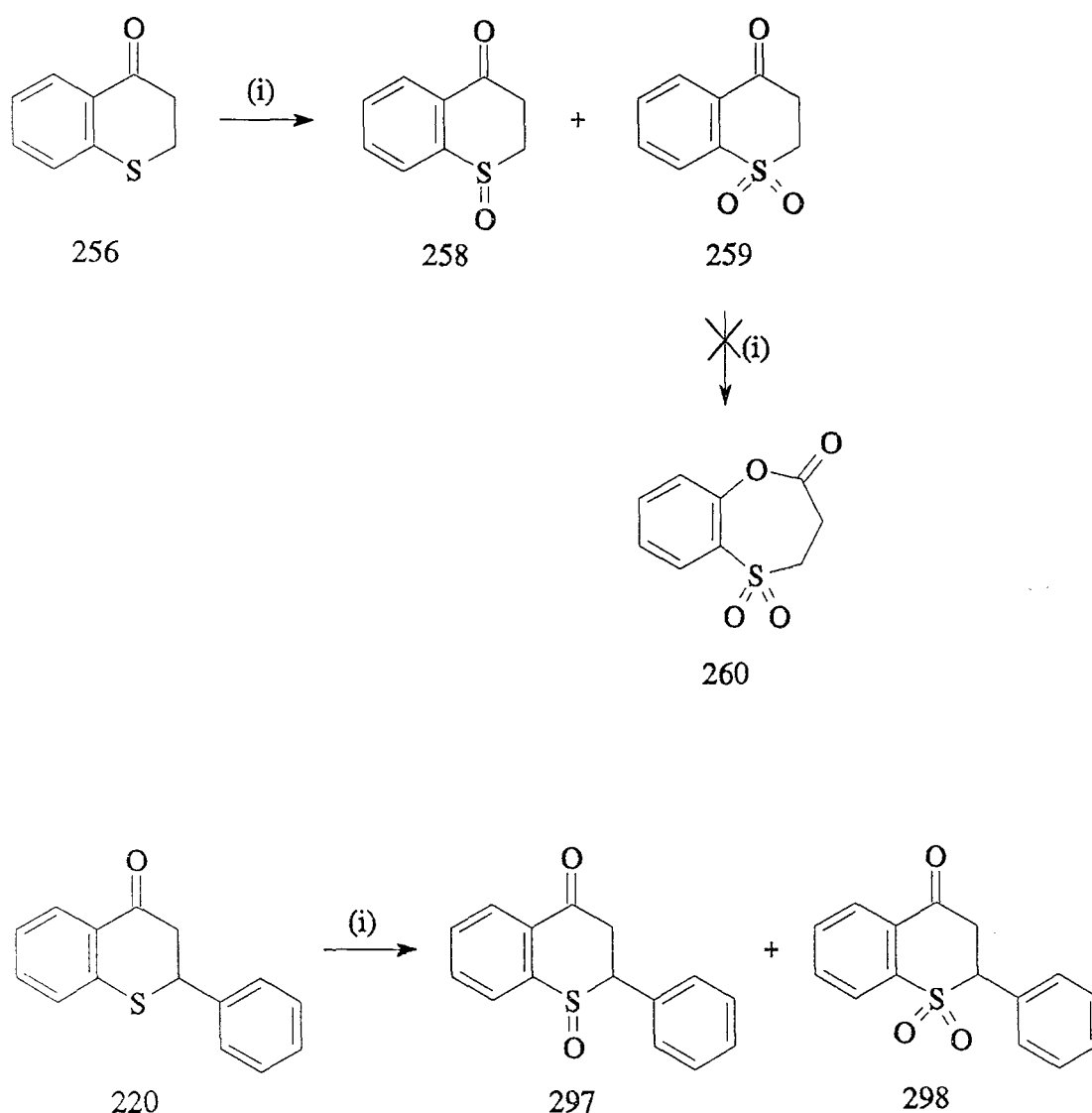
SCHEME 68. Reagents: (i) MCPBA, CH_2Cl_2, reflux.
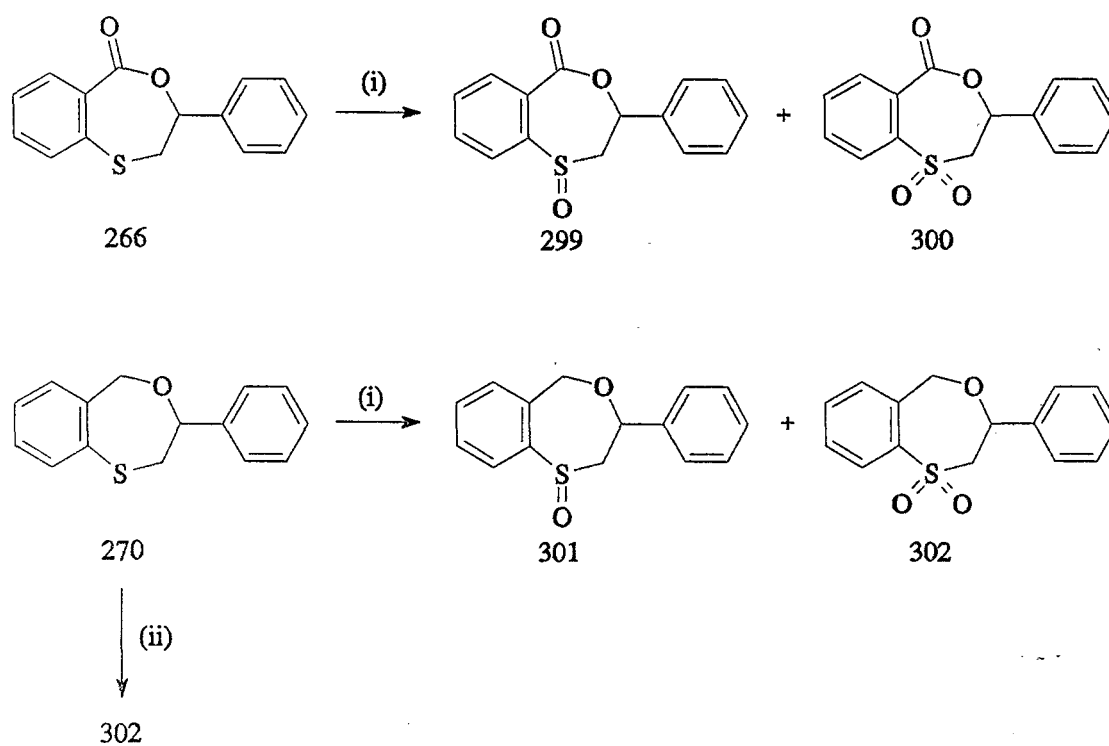
SCHEME 69. Reagents: (i) MCPBA (1eq.), CH_2Cl_2; (ii) MCPBA (2eq.), CH_2Cl_2.

Table 13. ^{1}H NMR chemical shifts (δ ppm) and splitting patterns for compounds 256, 258 and 259 in $CDCl_3$.
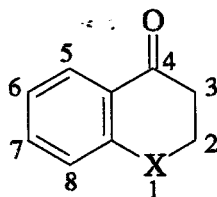
Compd	X	2-H	3-H	5-H(d)	6-H(t)	7-H(t)	8-H(d)
256	S	3.16(t)	2.89(t)	8.03	7.09	7.29	7.19
258	SO	3.42(m)	2.85(m)	8.10	7.61	7.72	7.82
259	SO_2	3.68(t)	3.39(t)	8.09	7.72	7.80	7.98

Table 14. ^{1}H NMR chemical shifts (δ ppm) and splitting patterns for compounds 266, 299 and 300 in $CDCl_3$.
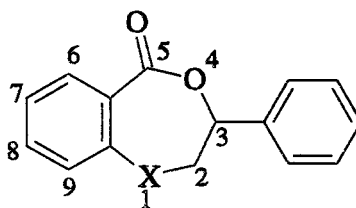
	266	299	300
X	S	SO	SO_2
2-H	3.29, 3.46 (2 x dd)	3.49 (m)	3.50 (2 x dd)
3-H (dd)	5.74	5.22	5.30
6-H	7.24-7.36 (m)	8.24 (dd)	8.08 (dd)
7-H	7.42 (ddd)	7.76 (m)	7.64 (ddd)
8-H	7.24-7.36 (m)[a]	7.76 (m)	7.82 (ddd)
9-H	8.14 (dd)	7.76 (m)	7.89 (dd)
ArH[b] (m)	7.24-7.36	7.26-7.34	7.27-7.40

[a] Overlaps 2-phenyl proton signals.   [b] 2-Phenyl substituent.

2.4   MASS SPECTROMETRIC STUDIES OF BENZODIAZEPINE ANALOGUES

In previous work in our laboratory, the mass spectrometric properties of flavanone-derived

2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-ones[180] and their tetrazolo[1,5-d] analogues,[181]

3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-ones,[28]   and   2-phenyl-1,2,3,4-tetrahydro-1,4-

benzodiazepin-5-ones and their tetrazolo[1,5-d] derivatives[182] have been studied.   In this

project, the mass fragmentations of related series of:- (i) 4-phenyl-1,5-benzoxathiepin-2-ones,

(ii) 3-phenyl-4,1-benzoxathiepin-5-ones and (iii) 3-phenyl-4,1-benzoxathiepines were

investigated.

The fragmentation patterns were explored by high resolution and metastable peak analysis

of significant peaks in the mass spectra of the parent systems, together with comparative

analysis of the low-resolution spectra of the other substituted analogues in each series.

2.4.1   4-Phenyl-1,5-benzoxathiepin-2-ones

The three major pathways proposed for the mass fragmentation of 4-phenyl-1,5-

benzoxathiepin-2-ones are shown in Scheme 70.   In path 1, the radical cation **b**, which is an

isomer of the molecular ion **a**, is obtained through opening of the seven-membered ring.   The

involvement of intermediates analogous to ion **b** has also been reported for the electron-

impact fragmentation of flavanones,[616] benzoxazepinones[613] and their tetrazolo derivatives.[614]

α-Fission of the ester group in **b** leads to the resonance stabilized conjugated acylium ion **c**,

which accounts for the base peak in the mass spectra of all the compounds (**250-254**) in the

series (see Table 15). The even-electron species **d** is then obtained from decarbonylation of the cation **c**. Metastable peak analysis provides independent confirmation of fragmentations **a/b** (*m/z* 256) → **c** (*m/z* 131) → **d** (*m/z* 103).

The remaining pathways (2 and 3) involve two distinct intra-annular rearrangements. In the first, O(1) migrates to C(4) with accompanying elimination of ketene (figure 14a) to produce the thioacetal radical cation **e**. Subsequent loss of H· or a phenyl radical affords the resonance stabilized cations **f** and **g** respectively. Path 3 on the other hand involves migration of S(5) to C(2) and elimination of thiocatechol carbonate (figure 14b) to afford the styryl radical cation **h**. These intra-annular rearrangements parallel those proposed in our earlier study of the mass spectra of 1,5-benzodioxepin-2-one analogues,[555] and in fact, there is a close correspondence between the overall fragmentations exhibited by both series of compounds.

(a)   (b)
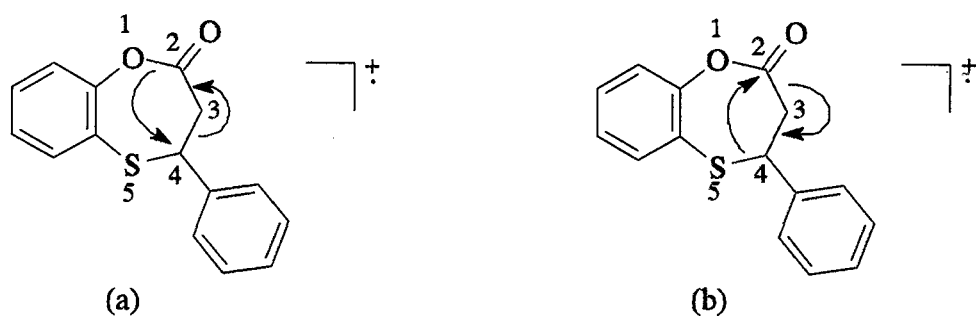
From the mass contributions of the 4'-substituents (Table 15), it can be deduced that:- ion-types **g** are ring A fragments; ion-types **c**, **d**, and **h** are ring B fragments; while ion-types **e** and **f** involve both rings A and B.

c m/z 131.0496
C9H7O (131.0497)

*(m/z 67.035)

b
C15H12SO2

-CO
*(m/z 80.98)

C8H7+

d m/z 103.0552
C8H7+ (103.0548)

PATH 1

a m/z 256.0570
C15H12SO2 (256.0558)

PATH 3

-CH2=C=O
PATH 2

e m/z 214.0453
C13H10SO (214.0453)

f m/z 213.0365
C13H9SO (213.0365)

-H·

-C6H5·

g m/z 137.0061
C7H5SO (137.0061)

h m/z 104.0623
C8H8 (104.0626)
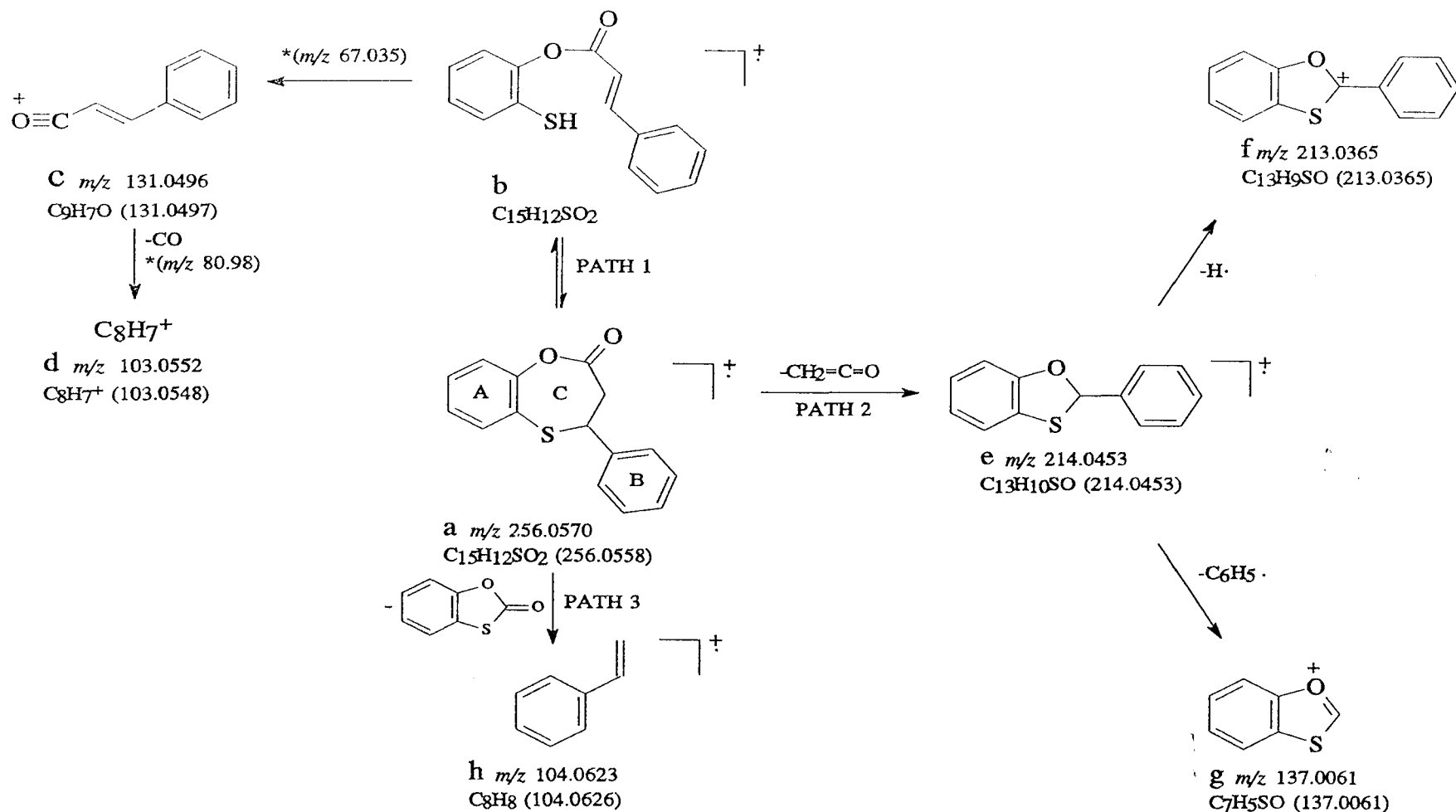
SCHEME 70: MS fragmentation patterns for 4-phenyl-1,5-benzoxathiepin-2-one **250**. The high-resolution masses (m/z) determined for individual ions are followed, in parentheses, by calculated formula masses. Metastable peaks are indicated by means of an asterisk.

110

Table 15.   Mass fragmentation data for selected peaks in the electron-impact mass spectra of 4-phenyl-1,5-benzoxathiepin-2-ones. Nominal masses (m/z) are followed in parentheses by %-relative abundance.
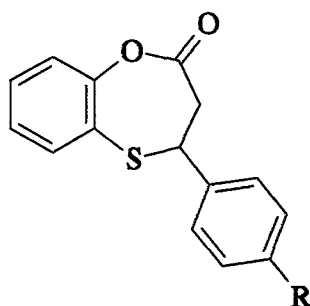
Compd	R	Ion fragment types						
		a/b	c	d	e	f	g	h
250	H	256 (10.1)	131 (100.0)	103 (46.2)	214 (2.4)	213 (9.6)	137 (9.1)	104 (20.1)
251	Br	334 (6.2)	209 (100.0)	181 (8.7)	292 (0.8)	291 (3.0)	137 (6.8)	182 (9.9)
252	Cl	290 (7.7)	165 (100.0)	137 (22.9)	248 (1.1)	247 (4.3)	137 (22.9)	138 (12.5)
253	F	274 (12.5)	149 (100.0)	121 (38.8)	232 (2.2)	231 (10.9)	137 (8.3)	122 (24.6)
254	OMe	286 (11.2)	161 (100.0)	133 (19.4)	244 (1.4)	243 (5.0)	137 (3.6)	134 (24.0)

2.4.2 3-Phenyl-4,1-Benzoxathiepin-5-ones

Two major pathways are observed in the mass fragmentation patterns of 3-phenyl-4,1-benzoxathiepin-5-ones (Scheme 71). In path 1, loss of carbon monoxide from the molecular ion **a** affords the radical cation **b**. This fragmentation is also supported by a metastable peak at m/z 203.06. Path 2 leads via elimination and ring contraction to an even electron species **c** (m/z 165) which is responsible for the base peak in the mass spectra of all three compounds in the series examined (Table 16). Elimination of CO from the base peak fragment affords the cation **d**, while further loss of H· results in the radical cation **e**. Loss of CO again generates yet another radical cation **f**. These fragmentations are independently supported by metastable peak analysis, i.e. **a** (m/z 256) → **c** (m/z 165) → **d** (m/z 137) and **e** (m/z 136) → **f** (m/z 108).

Table 16.   Mass fragmentation data for selected peaks in the electron-impact mass spectra of 3-phenyl-4,1-benzoxathiepin-5-ones. Nominal masses (m/z) are followed in parentheses by % relative abundance.
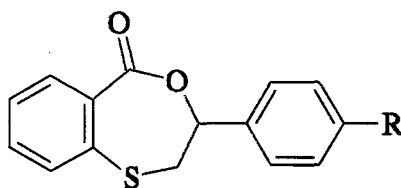
Compd	R	Ion fragment types					
		a	b	c	d	e	f
261	Br	334 (5.5)	306 (0.1)	165 (100.0)	137 (63.7)	136 (77.8)	108 (23.2)
262	Cl	290 (11.3)	263 (0.2)	165 (100.0)	137 (62.7)	136 (73.9)	108 (27.4)
263	H	256 (22.5)	228 (1.4)	165 (100.0)	137 (74.2)	136 (100.0)	108 (38.4)

b m/z 228.0619
$C_{14}H_{12}SO$ (228.0609)

PATH 1 $*(m/z\ 203.06)$
-CO

a m/z 256.0555
$C_{15}H_{12}SO_2$ (256.0558)

-C7H7·
$*(m/z\ 106.35)$
PATH 2

C m/z 165.0007
$C_8H_5SO_2$ (165.0010)

-CO
$*(m/z\ 113.75)$

d m/z 137.0060
C_7H_5SO (137.0061)

-H

e m/z 135.9964
C_7H_4SO (135.9983)

-CO
$*(m/z\ 85.76)$

f m/z 108.0041

C_6H_4S (108.0034)
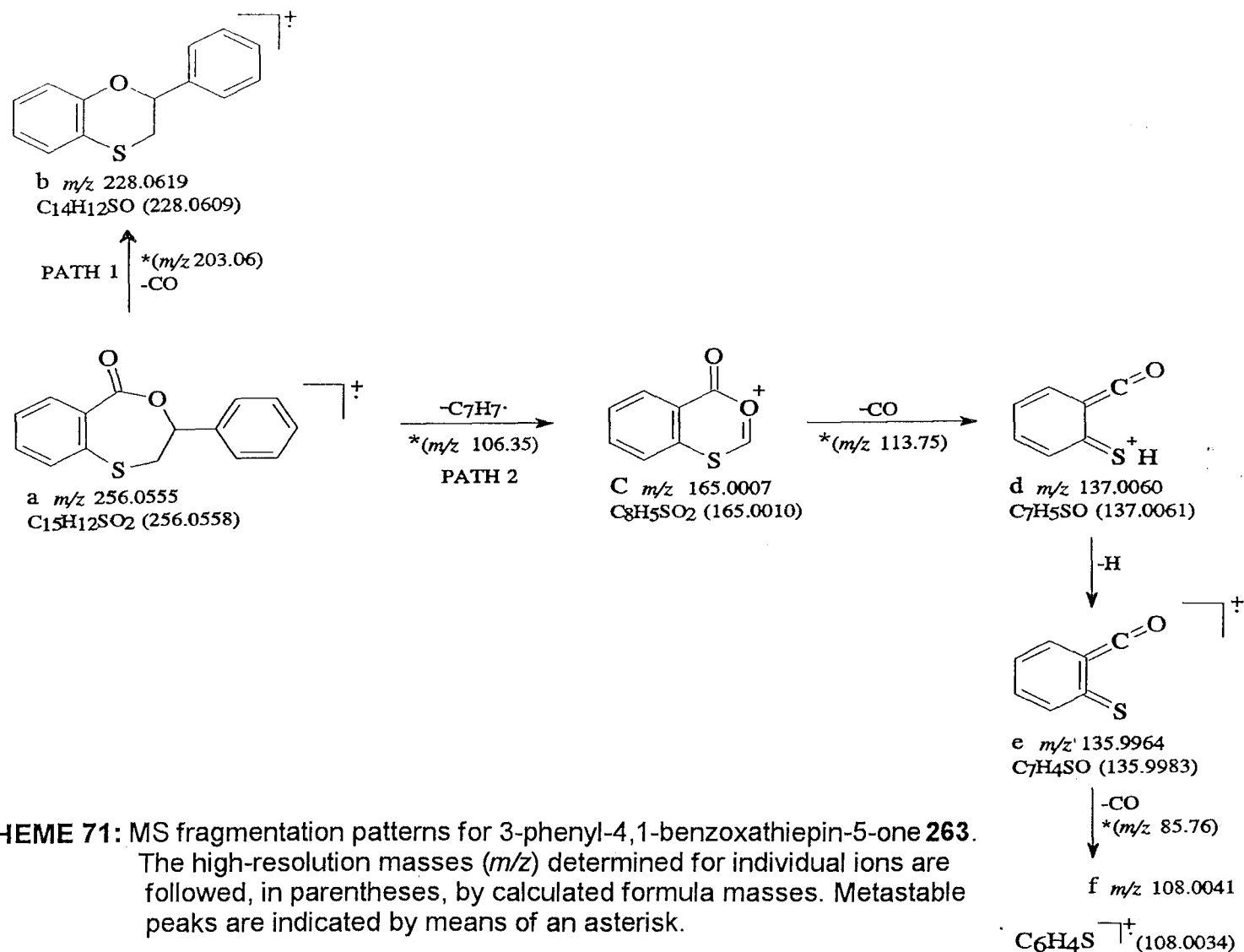
SCHEME 71: MS fragmentation patterns for 3-phenyl-4,1-benzoxathiepin-5-one **263**. The high-resolution masses (m/z) determined for individual ions are followed, in parentheses, by calculated formula masses. Metastable peaks are indicated by means of an asterisk.

2.4.3 3-Phenyl-4,1-Benzoxathiepines

The mass spectra of 3-phenyl-4,1-benzoxathiepines exhibit two major fragmentation pathways (Scheme 72). Path 1 involves loss of C_7H_6SO from the molecular ion **a** to afford the styryl radical cation **b**, followed by elimination of H· which results in the even electron species **c**. In path 2, loss of C_7H_7· affords another even electron species **d**, this fragmentation being supported by a metastable peak at m/z 94.22. This cation is responsible for the base peak in all four compounds examined (Table 17), and its formation and subsequent fission parallel the patterns observed in the mass spectra of the 3-phenyl-4,1-benzoxathiepin-5-ones discussed above. Subsequent fission of the base peak fragment through loss of CO, or H· and CO, affords the cation **e** and the radical cation **f** respectively. Further loss of H· from the latter fragment then accounts for the cation **g** ($C_7H_5S^+$; m/z 121). Both of the foregoing fragmentations are supported by metastable peak analysis, *i.e.* **d** (m/z 151) → **e** (m/z 123) and **d** (m/z 151) → **f** (m/z 122).

c *m/z* 103.0547
C8H7+ (103.0548)

-H•

b *m/z* 104.0614
C8H8 (104.0626)

e *m/z* 123.0264
C7H7S (123.0269)

PATH 1 -C7H6SO

-CO

*(*m/z* 100.192)

a *m/z* 242.0759
C15H14OS (242.0759)

-C7H7•
*(*m/z* 94.22)
PATH 2

d *m/z* 151.0211
C8H7SO (151.0242)

-CO
-H•

*(*m/z* 98.57)

-H•

g *m/z* 121.0126
C7H5S+ (121.0112)

f *m/z* 122.0193
C7H6S (122.0190)
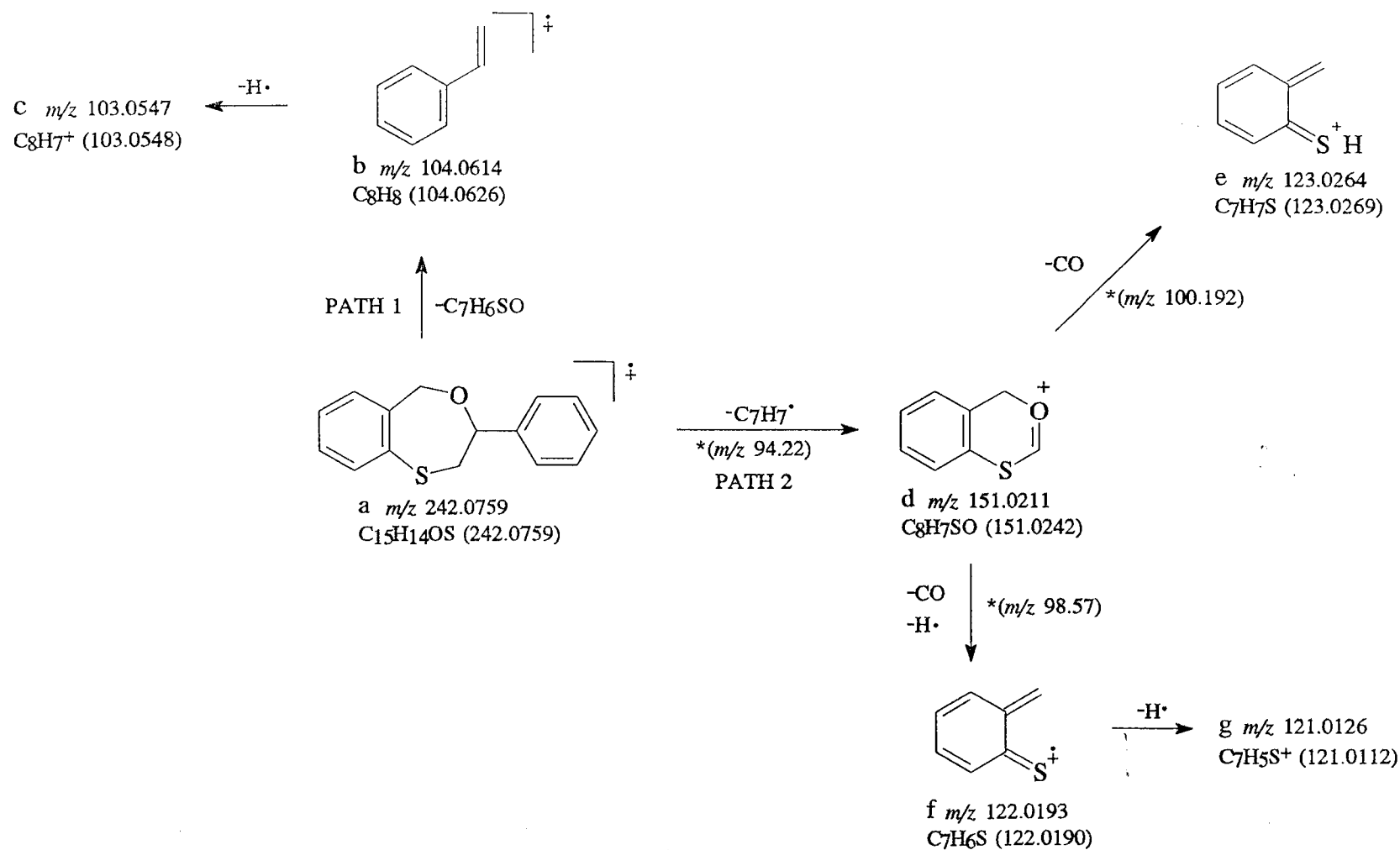
SCHEME 72: MS fragmentation patterns for 3-phenyl-4,1-benzoxathiepin-5-one133. The high-resolution masses (*m/z*) determined for individual ions are followed, in parentheses, by calculated formula masses. Metastable peaks are indicated by means of an asterisk.

115

Table 17.   Mass fragmentation data for selected peaks in the electron-impact mass spectra of 3-phenyl-4,1-benzoxathiepines. Nominal masses (m/z) are followed in parentheses by % relative abundance.
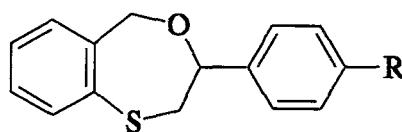
		Ion fragment types						
Compd	R	a	b	c	d	e	f	g
267	Br	320 (5.1)	104 (0.5)	103 (0.7)	151 (100.0)	123 (51.1)	122 (82.4)	121 (75.7)
268	Cl	276 (8.4)	104 (0.4)	103 (1.5)	151 (100.0)	123 (50.0)	122 (73.4)	121 (66.7)
269	F	260 (14.6)	104 (1.7)	103 (0.8)	151 (100.0)	123 (72.7)	122 (100.0)	121 (97.8)
270	H	242 (18.5)	104 (10.4)	103 (4.9)	151 (100.0)	123 (60.1)	122 (96.4)	121 (92.9)

2.5 ^{17}O NMR STUDIES

In spite of various practical difficulties, ^{17}O NMR spectroscopy is rapidly becoming a useful and potentially powerful tool for structure and conformation elucidation as well as a probe for assessing electronic distribution in oxygen-containing organic molecules. The ^{17}O nucleus exhibits low natural abundance (0.037%) and low NMR sensitivity (2.91 x 10^{-2} times that for ^{1}H at constant field), as well as having a quadrupole moment.[183,184] However, the difficulties associated with broad lines and low signal to noise ratios have been greatly reduced by use of high field Fourier Transform (FT) NMR spectrometers. Since the eighties, scientific papers on ^{17}O NMR spectroscopy have appeared in the literature,[185-218] and ^{17}O NMR spectra of compounds such as coumarins,[219] sulphinylimines and isocyanates,[220] chromanones, chromones, flavanones and flavones[221] and their thio derivatives,[222] furan-2,3-diones,[207,217] benzoic and cinnamic acids,[216] oximes,[202] acetophenones and aldehydes,[201,203,210] cyclohexanones,[206] esters,[192] sulphones and sulphoxides,[185,208,223] quinones[188] and many others have been studied. The reviews by Boykin and Baumstark,[218] and by Kintzinger[199] provide comprehensive discussions on this subject.

Various trends have emerged in the chemical shift data that have thus far been collected.[185,208,216,219,220,221,224] ^{17}O NMR chemical shifts appear to be more sensitive to structural variation than those of ^{13}C and ^{15}N nuclei,[225] the downfield shift of the carbonyl oxygen signal, with increasing ring size, being particularly marked in compounds **303-305**.[218,223]

506 ppm

303

528 ppm

304

562 ppm

305
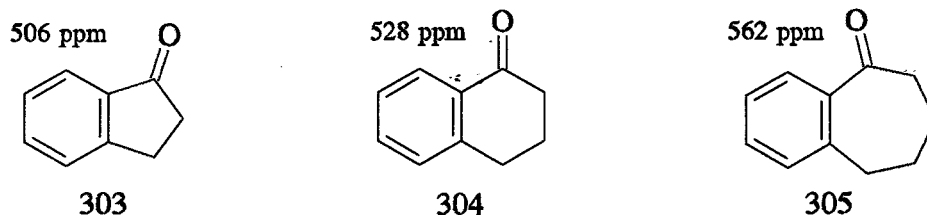
In esters of general formula R'COOR,[192] formates,[226] alcohols and ethers,[227,228] the ^{17}O chemical shift of the alkyl oxygen is shifted downfield ($\Delta\delta$ = 56ppm) as the alkyl substituent (R) changes from methyl to *tert*-butyl. There is also a shielding effect of approximately 50ppm per additional fused benzene ring for quinones (compounds **306-308**) and related carbocyclic ketones, which could be explained by a combination of the effects of increasing conjugation with the carbonyl group and gamma-interactions with the *peri* hydrogens.[188]

635.1 ppm

306

580.7 ppm

307

531.4 ppm

308
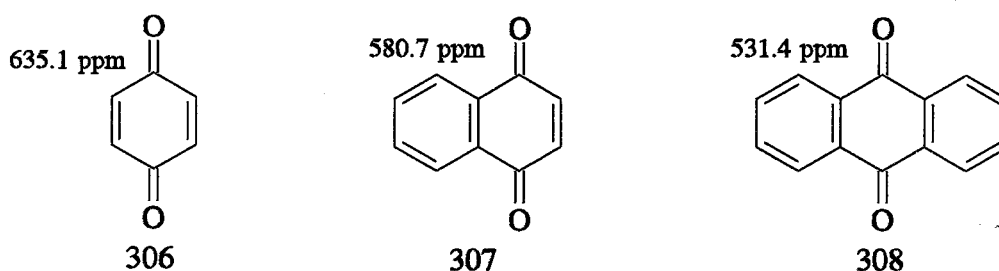
In 1981 Kobayashi *et al.*[229] reported, for the first time, the diastereotopic nature of the two oxygen atoms of a sulphone moiety in chiral molecules, and they attributed this to the tetrahedral geometry of the sulphur atom. This phenomenon was confirmed by Duddeck and Levai[222] who obtained well-separated signals for the two diastereotopic sulphone oxygens in compound **298**.

O
‖   149 & 138 ppm

298
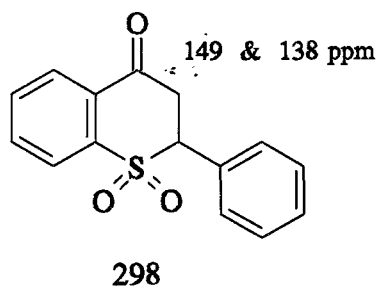
^{17}O NMR spectroscopy shows immense potential as a spectroscopic technique for examining a wide variety of structural problems. Some of the applications of this technique include assessment of hydrogen bonding interactions,[186,190,191,197,200,201,210,212] characterizing the electronic state (including the electrophilicity) of carbonyl compounds,[189,193,230] determination of equilibrium constants[205] and characterization of ozonides.[198] Because of the large chemical shift range and the sensitivity of the carbonyl oxygen's chemical shift to hydrogen bonding, ^{17}O NMR spectroscopy appears to be a promising technique for studying anthracycline-DNA interactions.[188] Although it is apparent that ^{17}O NMR spectroscopy has received considerable attention, this area of spectroscopy is still developing and further research is more than justified.

In the present investigation, ^{17}O NMR studies were prompted by the availability of an extensive range of oxygenated compounds whose ^{17}O NMR spectral properties have not yet been examined. These compounds were subjected to ^{17}O NMR analysis to establish structural and substituent effects on the ^{17}O chemical shifts. Spectroscopic analysis required concentrated samples (200-300mg in 1.5ml CDCl$_3$) and lengthy acquisition times ($\geq$ 18 hours). The ^{17}O NMR data obtained for benzodioxepinones, benzoxathiepinones, benzoxathiepines and various sulphone derivatives are discussed below.

2.5.1 1,5-Benzodioxepinones

The ^{17}O NMR spectra for the 1,5-benzodioxepinones (**65, 222** and **225-228**) were recorded

as described in the experimental section, and the resulting data are summarised in Table 18.

The extremely wide spectral window and the typically broad peaks observed are illustrated

in figure 15. Quantitative measurements of band-widths at half-height were problematic

owing to experimental difficulties such as baseline instability (due to acoustic ringing) and

the different relaxation times of the different oxygen nuclei.

From the data listed in Table 18, it can be concluded that the R^1 and R^2 substituents have

relatively little effect on the chemical shifts for either of the oxygen atoms. As discussed

earlier, ^{17}O NMR shifts are sensitive to ring size. Duddeck *et al.*[221] reported chemical shifts

of 93 and 95ppm for the ether oxygens in the flavanones **64** and **193** respectively, while we

have found that the signals of the corresponding oxygens in the ring-expanded derivatives **65**,

222 and **225-228** are shifted upfield to 79 and 63ppm respectively. The spectrum of the

parent benzodioxepinone **65** exhibits a distinct, broad signal (560-1240Hz) for each oxygen

atom and substitution at either position 7 or 4' leads to even more pronounced broadening

of the bands (see Table 18). This broadening could be due to some loss of isotropic

tumbling and reduced mobility of the molecules.[199,219]
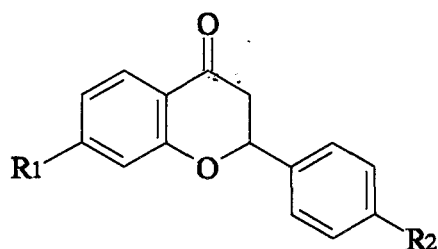
65 ; R^1, R^2 = H

193 ; R^1 = H; R^2 = OMe

Table 18. ^{17}O NMR chemical shifts followed, in parentheses, by estimated band-widths (Hz) at half-height for compounds 65, 222 and 225-228 in CDCl$_3$.
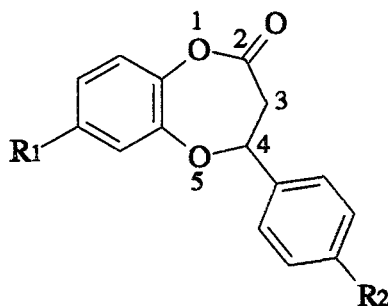
Compd.	R^1	R^2	Chemical Shifts/ppm		
			O^5	O^1	C=O
65	H	H	79 (1240)	212 (600)	397 (560)
222	Cl	H	64 (2209)	213 (885)	396 (966)
225	H	Br	74 (1333)	214 (997)	392 (670)
226	H	Cl	60	211 (640)	394 (925)
227	H	F	74 (1363)	212 (793)	396 (722)
228	H	OMe	63 (2330)	212 (770)	388 (935)
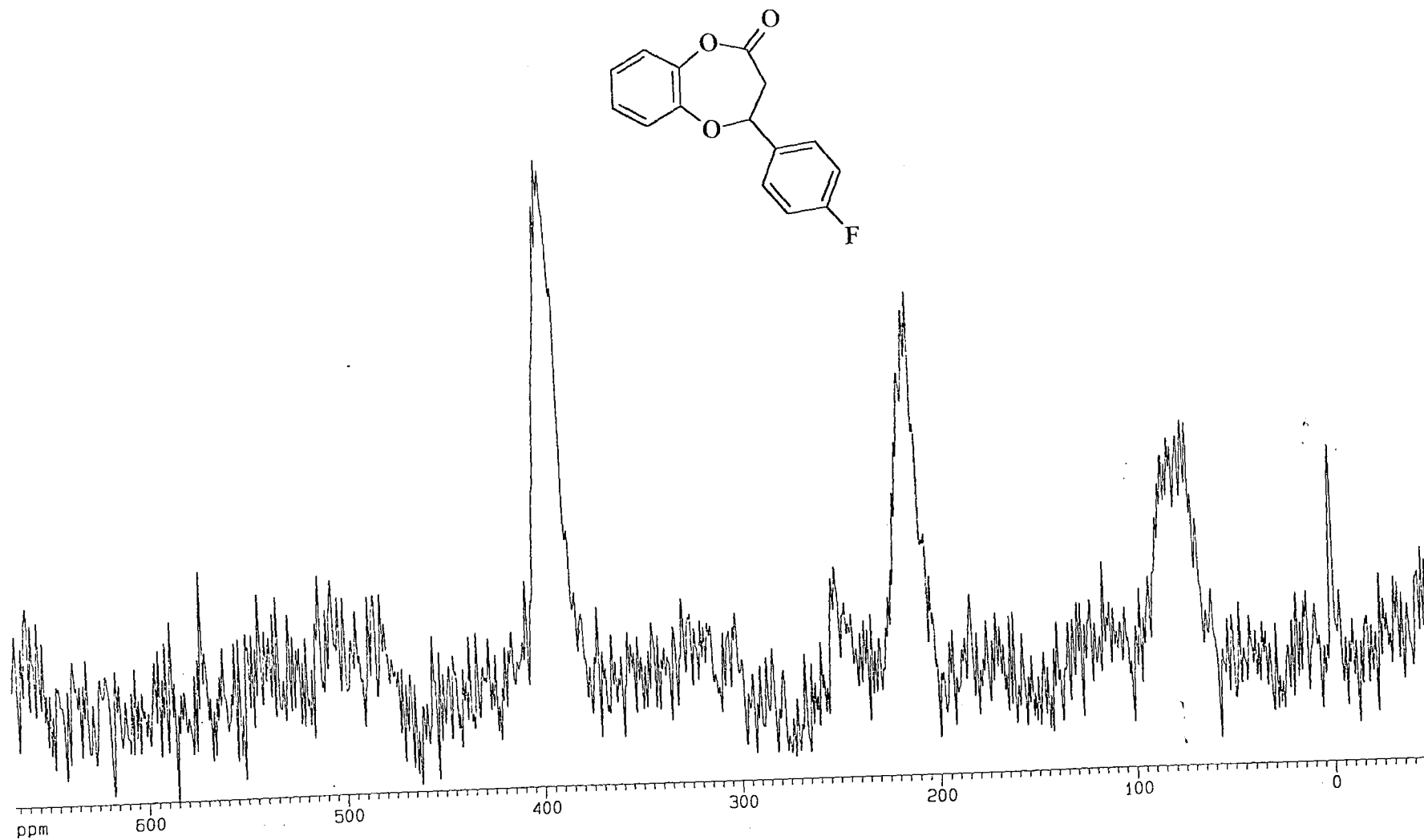
Figure 15: ^{17}O NMR spectrum of 4-(4-fluorophenyl)-1,5-benzodioxepin-2-one **227** in $CDCl_3$

2.5.2   Benzoxathiepines and their sulphoxide and sulphone derivatives

The ^{17}O NMR data obtained for the 1,5-benzoxathiepin-2-ones (**250-253**), 4,1-benzoxathiepin-5-ones (**261-263** and **299-300**) and 4,1-benzoxathiepines (**267**, **269-270** and **301-302**) are summarised in Tables 19-21 respectively. From Table 19 it is clear that varying the 4'-substituent (R = H, Br, Cl, F) does not have any real effect on the chemical shift of either of the oxygen atoms. Comparison of Tables 18 and 19 reveals that the chemical shift of the ester oxygen is shifted downfield ($\Delta\delta$ = $ca.$ 10ppm) when the ether oxygen of compounds **65**, **222** and **225-228** (Table 18) is replaced by sulphur (Table 19); the corresponding downfield shifts of the carbonyl oxygen are, however, less marked.

The following general observations can be made from an analysis of the data in Tables 20 and 21.

(i)   In the benzoxathiepinones (Table 20), the O-4 nucleus experiences shielding ($\Delta\delta$ = 10ppm) on introduction of the 4'-substituents (R = Br, Cl).

(ii)   In the benzoxathiepine series (Table 21), the O-4 nucleus is shielded ($\Delta\delta$ = 6ppm) on introduction of bromine at position 4' but deshielded ($\Delta\delta$ = 3ppm) in the case of the 4'-fluoro analogue.

(iii)   On one hand, there is a pronounced shielding ($\Delta\delta$ = $ca.$ 34ppm) of the ester oxygen (O-4; Table 20) but, on the other hand, deshielding ($\Delta\delta$ = $ca.$ 123ppm) of the ether oxygen (Table 21) when sulphur is replaced by a sulphoxide or sulphone group.

(iv)   The observed chemical shifts for SO_2 (10ppm; Table 20) and SO (146ppm; Table 21) are contrary to reported[208] chemical shifts.

Table 19.   ¹⁷O NMR chemical shifts followed, in parentheses, by estimated band-widths (Hz) at half-height for compounds 250-253 in $CDCl_3$.
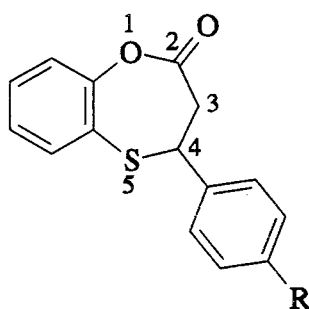
Compd.	R	Chemical Shift/ppm	
		O^1	$C=O$
250	H	220 (1068)	388 (1180)
251	Br	222 (895)	386 (865)
252	Cl	221 (1271)	387 (1414)
253	F	224 (1007)	391 (1180)

Table 20. ^{17}O NMR chemical shifts followed, in parentheses, by estimated band-widths (Hz) at half-height for compounds 261-263 and 299-300 in $CDCl_3$.
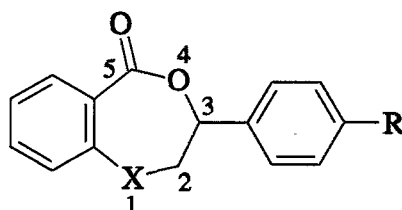
Compd.	R	X	Chemical Shift/ppm			
			O^4	C=O	SO	SO_2
261	Br	S	183[a]	367[a]	-	-
262	Cl	S	183 (1587)	361 (1658)	-	-
263	H	S	193 (1322)	363 (1556)	-	-
299	H	SO	159 (1404)	363 (1149)	3 (905)	-
300	H	SO_2	158 (1546)	385 (1070)	-	10[a]

[a] Band-widths cannot be estimated properly owing to noise distortion of the signal.

Table 21. ^{17}O NMR chemical shifts followed, in parentheses, by estimated band-widths (Hz) at half-height for compounds 267, 269-270 and 301-302 in $CDCl_3$.
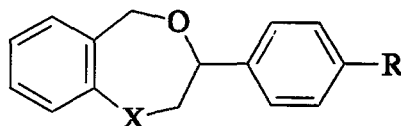
Compd.	R	X	Chemical Shift/ppm		
			O	SO	SO_2
267	Br	S	43 (1057)	-	-
269	F	S	34 (1770)	-	-
270	H	S	37 (1831)	-	-
301	H	SO	159[a,b]	146[a,b]	-
302	H	SO_2	160[a,b]	-	147[a,b]

[a] Band-widths could not be estimated due to noise distortion of the signal.
[b] Values may be interchanged.

2.6 KINETIC-MECHANISTIC STUDY OF THE BAEYER-VILLIGER REACTION ON FLAVANONES

The Baeyer-Villiger oxidation of ketones is a useful and well-established reaction and a brief review was given in section 2.1.2 (page 58). Kinetic and mechanistic studies of the reaction have been reported by several authors;[231-241] and it was found that the reaction follows a second order rate law.

In principle, the Baeyer-Villiger oxidation of flavanones can give either the 1,4- or 1,5-benzodioxepinone regioisomers, if not both. In our present study, flavanones were oxidised by MCPBA in dichloromethane to afford, in each case, only one product, characterised as the 1,5-benzodioxepinone. We could therefore conclude that the insertion of oxygen is completely regiospecific and requires migration of the aryl group rather than the primary alkyl group. Nitrogen insertion *via* Schmidt reaction (using TMS-N$_3$ in TFA) of the same substrates, however, proceeds with the opposite regioselectivity[91] (Scheme 73). To explain these observations, cognate mechanistic studies of both Schmidt[91] and Baeyer-Villiger reactions of flavanones have been undertaken, and in this study, particular emphasis has been placed on the latter. To our knowledge, no previous kinetic studies of the Baeyer-Villiger reaction have been undertaken using ^{1}H NMR spectroscopy - the method used in our investigation; earlier workers have followed the reactions by iodometric titration of residual peroxy acid.

The rate of transformation of selected flavanones to their corresponding benzodioxepinones was monitored by ^1H NMR spectroscopy over 12-14 hours, during which time the formation of the product was found to exceed 50%. The disappearance of the 2-H signal of the flavanone and the appearance of the corresponding 2-H signal of the benzodioxepinone were readily followed (figure 16). Figure 17a shows the concentration of benzodioxepinone formed as a function of time. Plots of such kinetic data, using the equation:-

$$\frac{1}{(a-b)} \ln \frac{b(a-x)}{a(b-x)} = kt$$

where

a = initial conc. of flavanone

b = initial conc. of MCPBA

a-x = conc. of flavanone at time t

b-x = conc. of MCPBA at time t

gave excellent linear correlations (figure 17b), indicating second order kinetics overall (first order in perbenzoic acid and flavanone). The second order rate constants (k_{obs}) are detailed in Table 22, while the proposed mechanism of the reaction is shown in Scheme 74. If step 2 of the proposed mechanism (Scheme 74) is assumed to be rate-determining, the reaction rate may be expressed in terms of the following equation:-

Rate = k_{obs} [flavanone][MCPBA]

where k_{obs} = $K_1 k_2$
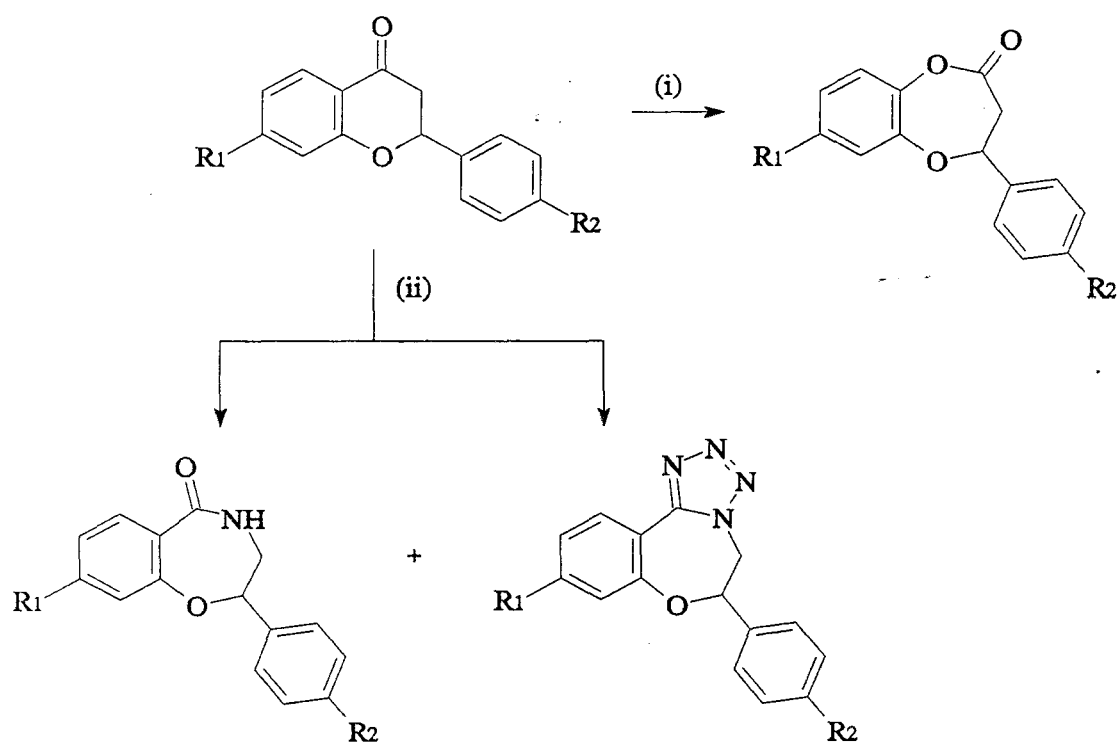
SCHEME 73. Reagents: (i) MCPBA, CH_2Cl_2; (ii) TMS-N$_3$, CF_3CO_2H
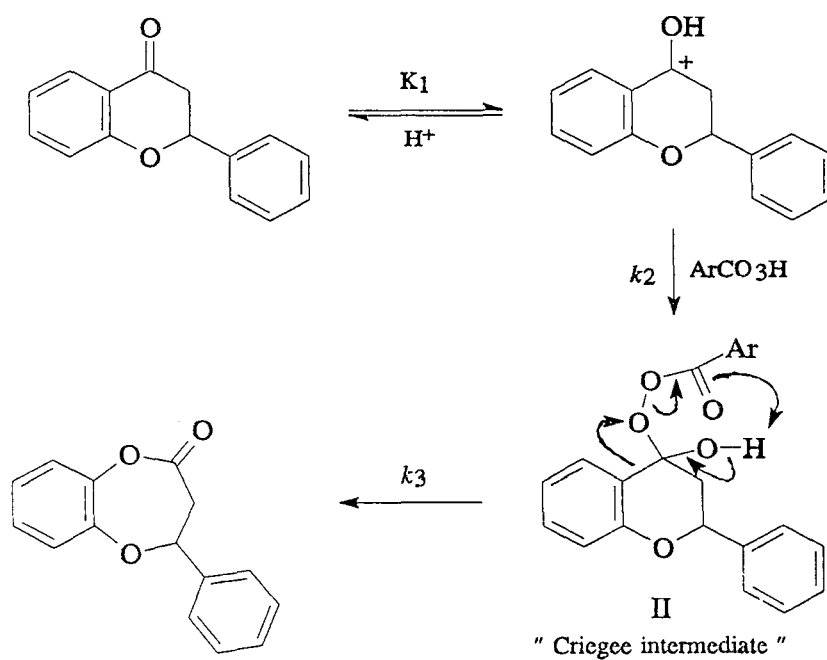
SCHEME 74

Table 22.   Kinetic data for Baeyer-Villiger reactions of flavanones[a] (64, 186, 189-191 and 193) with MCPBA[b] in CD_2Cl_2 at 303K.
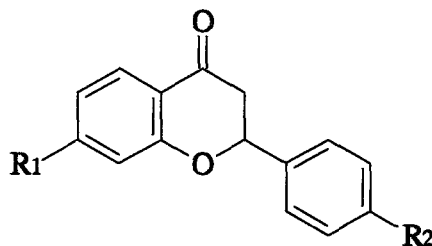
ENTRY	SUBSTRATE			k_{obs}[c]$/l.mol^{-1}.s^{-1}$
	Compd.	R^1	R^2	
1	64	H	H	0.0047
2	64	H	H	0.0053[d]
3	64	H	H	0.0039[e]
4	186	Br	H	0.0034
5	189	OMe	H	0.0055
6	190	H	Br	0.0042
7	191	H	Cl	0.0043
8	193	H	OMe	0.0040

[a] $0.340mol.l^{-1}$.   [b] $0.500mol.l^{-1}$.   [c] Mean of duplicate results; estimated error $\pm$ 0.001373.   [d] [flavanone] = $0.163mol.l^{-1}$.
[e] [MCPBA] = $0.212mol.l^{-1}$.
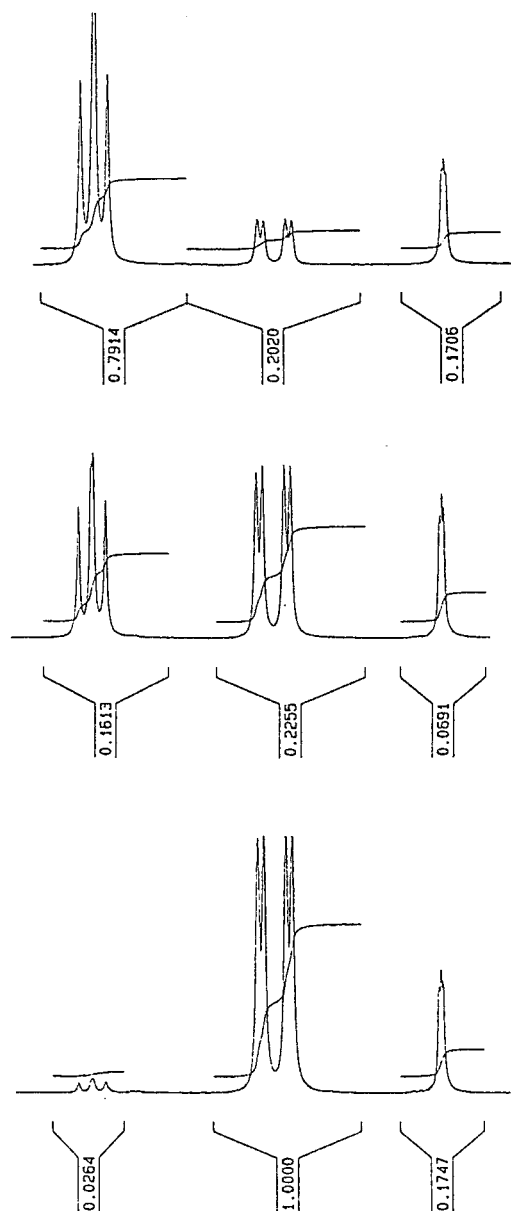
Figure 16: Partial ^{1}H NMR spectra showing the disappearance of the 2-H signal of the flavanone and the appearance of the corresponding 2-H signal of the benzodioxepinone
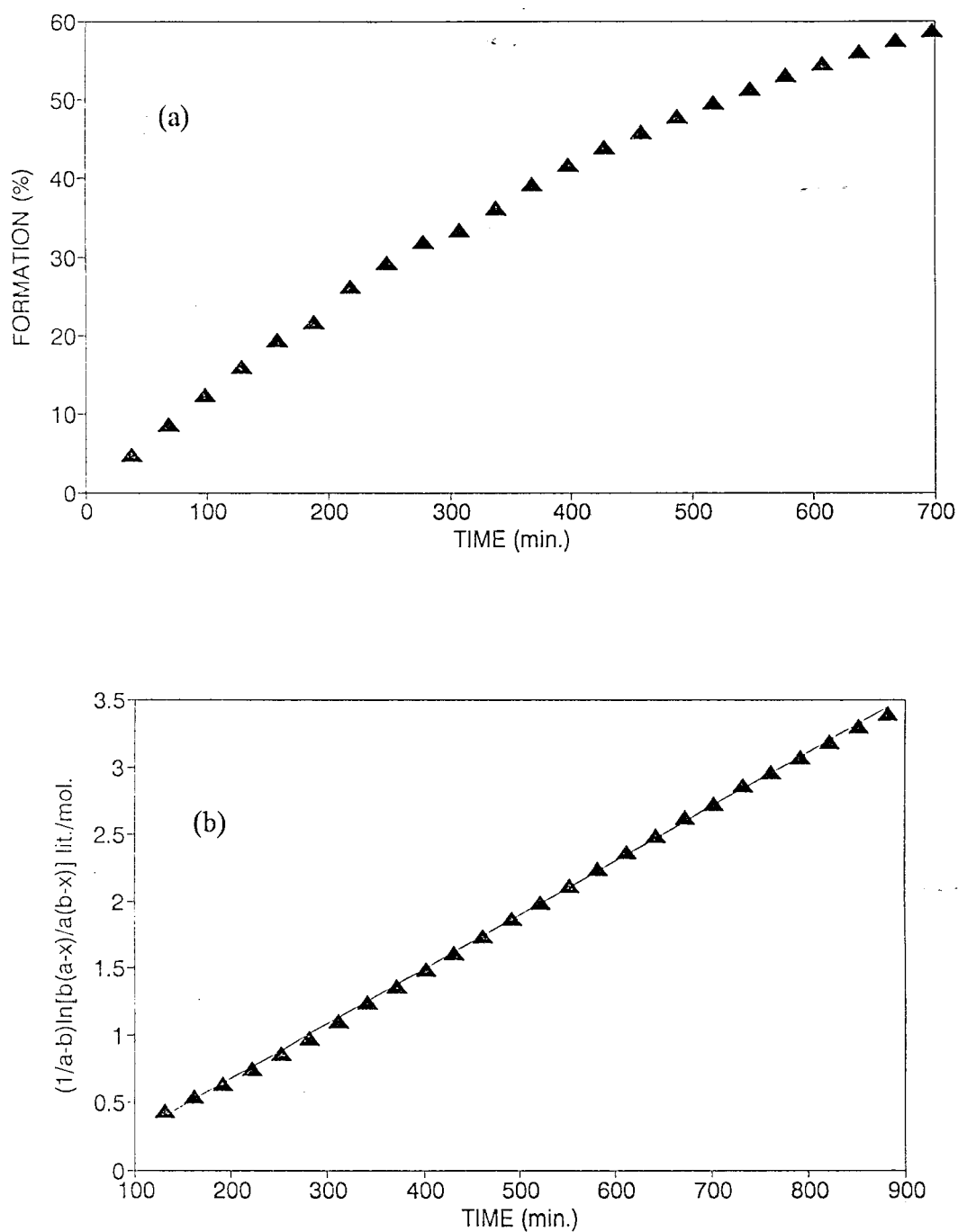
Figure 17:   (a) The concentration of benzodioxepinone formed as a function of time,

(b) Second-order linear plot of $\dfrac{1}{(a-b)} \ln \dfrac{b(a-x)}{a(b-x)}$ versus time for the

formation of benzodioxepinone

The preference for aryl migration is attributed to:

(i)   greater nucleophilicity of the aryl group as compared to the alkyl group; and

(ii)   transition state complex (TSC) stabilisation by incipient delocalisation between the

         migrating aryl group and the migration terminus (O^2).

In the analogous Schmidt reactions, the migration origin is sp^2 (not sp^3) hybridised and

delocalisation towards this centre inhibits aryl migration, thus accounting for the opposite

regioselectivity in heteroatom insertion.

Changing the concentration of either the flavanone or MCPBA should not, in principle, have

any effect on the value of k_{obs}.   However, when the flavanone or MCPBA concentrations

were halved, the value of k_{obs}, in each case, was found to increase or decrease respectively

(see entries 1-3 of Table 22).   This discrepancy may be explained in terms of influence of

the concentration of "free" MCPBA on the polarity of the medium and hence on the initial

equilibrium.

Thus,

(i)   if the flavanone concentration is reduced, the overall polarity increases, and hence the

         equilibrium concentration of the protonated intermediate I and k_{obs} also increase; and

(ii)   reducing the MCPBA concentration should lower the overall polarity, thus resulting

         in a lower k_{obs} value.

2.6.1 The effect of substitution on the reaction rates

The rate of the reaction is affected by both *para* substituents R^1 and R^2, the nature of the effect depending on whether the substituent is electron-donating or -withdrawing. Electron-donating R^1 substituents (*e.g.* OMe) will increase the nucleophilicity of the migrating aryl group *via* lone pair delocalisation (figure 18), whereas electron-withdrawing substituents (*e.g.* Br), will reduce the reaction rate because they decrease the nucleophilicity of the aryl group. The reactivity sequence for R^1 substituents therefore is OMe > H > Br $\approx$ Cl. The R^2 substituents, being remote from the reaction centre, have little influence on the reaction rate (Table 22, entries 6-8).
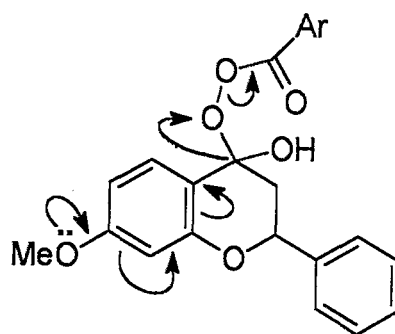
Figure 18

2.7   DETERMINATION OF THE BINDING AFFINITIES OF BENZODIAZEPINE ANALOGUES FOR THE BENZODIAZEPINE RECEPTOR

The observation that many cells respond in a highly selective way to minute concentrations of a particular chemical or drug, led to the hypothesis of cell receptors or specific sites on cells which are the sites of drug action.[242] This observation, coupled with the discovery that certain membrane receptors may be blocked by compounds which stimulate or inhibit a biological event, led to intensive research on the nature of the receptors. The synthesis of structurally related analogues of drugs led to research on the detailed structure-activity relationship between drugs and their receptors.

A group of such drugs that has received much attention is the benzodiazepines. The use of radioactively labelled compounds of high specific activity in studies of brain receptor binding has rapidly advanced the knowledge of biochemical mechanisms of action of benzodiazepines.[243-247] These compounds exert their therapeutic effects by interacting with a high-affinity binding site (receptor) in the brain. The neuropharmacological properties of benzodiazepines in mammals have been attributed to their ability to facilitate γ (gamma)-aminobutyric acid (GABA)-mediated neurotransmission by increasing the frequency of chloride ion channel openings in response to a given GABA stimulus.[248,249]

Radioligand binding methodology facilitates the direct measurement of the ligand-receptor interaction in the absence of cellular influences and functionality-coupled biological responses. Furthermore, the binding of ligand molecules to a receptor population is a second

order reaction which can be quantified by applying kinetic analyses similar to those originally

devised for the study of enzyme catalysed reactions. Thus, the affinity of the ligand for the

receptor and the total number of binding sites present can be readily assessed. The binding

of the radioligand to receptor and non-receptor sites can be distinguished through the

examination of the saturability and pharmacological specificity of the radioligand binding

sites. If binding to these sites *in vitro* is rapid, reversible, stereospecific, and saturable, it

can be concluded that the radioligand has specifically labelled the recognition site of the

receptor.[242,248-251]

The ability of the radioreceptor binding assay to quantitate directly the affinity of a substance

for the receptor provides a powerful screening method for drug selection as well as an ideal

tool for examining structure activity relationships. It has generally been found that a drug's

in vitro affinity, as determined by radioreceptor assay, predicts the potency of the drug in

biological systems, thus providing a primary screening method to assay new compounds as

rapidly as chemists can synthesise them. The assay usually cannot distinguish between

agonists and antagonists for the receptor in question, and it will not predict the indirect

actions of drugs on receptor systems.[124]

A radioreceptor binding assay was used in this study to test a range of synthetic

benzodiazepine analogues for their ability to compete with ^{3}H-diazepam for specific binding

to benzodiazepine receptors. In this technique, receptor-ligand complexes are formed by the

incubation of neuronal membranes rich in the benzodiazepine receptors under study, together

with ^{3}H-diazepam. The ^{3}H-diazepam used for this study had a specific activity of 83.0

Ci/mmol. The interaction of the radioactive ligand (D*) with the receptor (R), which results

in a receptor-ligand complex (D*R), follows the law of mass action.

$$D^* + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} D^*R$$

$$\frac{k_2}{k_1} = K_{D^*} = \frac{[D^*][R]}{[D^*R]}$$
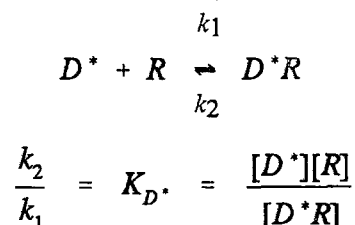
where K_{D^*} = equilibrium dissociation constant of D* for R.

Once the D*R complex is formed, the unbound radioactivity is removed by filtration to allow

determination of the bound radioactivity.[250] Rapid washing of the filters with buffer of

known pH (pH 7.4 for this study) removes radioactivity that is not associated with the

receptors (free radioactivity). In addition to binding selectively to sites pharmacologically

consistent with the presence of a receptor, binding can also occur to sites that are not related

to the receptor under study, due to the association of the radioligand with protein

sequestration sites. The ligand can also bind to the filters used for the isolation of tissue, or

to the test tube in which the reaction is performed. This non-specific binding can be

determined by a parallel assay using tubes with an excess of "cold" (unlabelled) ligand,

specific for a given receptor. (The excess "cold" drug reduces the specific radioactivity of

the radioactive drug to 1% of the original drug, and increases the total drug concentration

100-fold). Measurement of binding of the radioactive and non-radioactive ligand provides

data on total ligand binding and non-specific binding respectively; the difference is the

specific binding of the ligand to the receptors.[244,250] The specific sites can only bind a limited

amount of drug since they become saturated at concentrations equivalent to $10 \times K_D$ where K_D, the affinity constant, is the concentration of drug giving 50% binding. The ligand diazepam, is expected to have a high binding affinity because of its high pharmacological activity at low dosages,[244] and hence the receptors 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, a constant concentration of non-radioactive diazepam was added as described in the experimental section. This 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 saturation curve (figure 19), obtained by plotting specific ^{3}H-diazepam bound (fmol/mg protein) against the concentration of ^{3}H-diazepam, illustrates the high affinity of diazepam for the receptors. The affinity constant, K_D for ^{3}H-diazepam was found to be 61 $\pm$ 5nM and the total number of specific binding sites, B_{max}, to be 476 $\pm$ 4fmol/mg protein. These values were subsequently used in the competition studies described below.
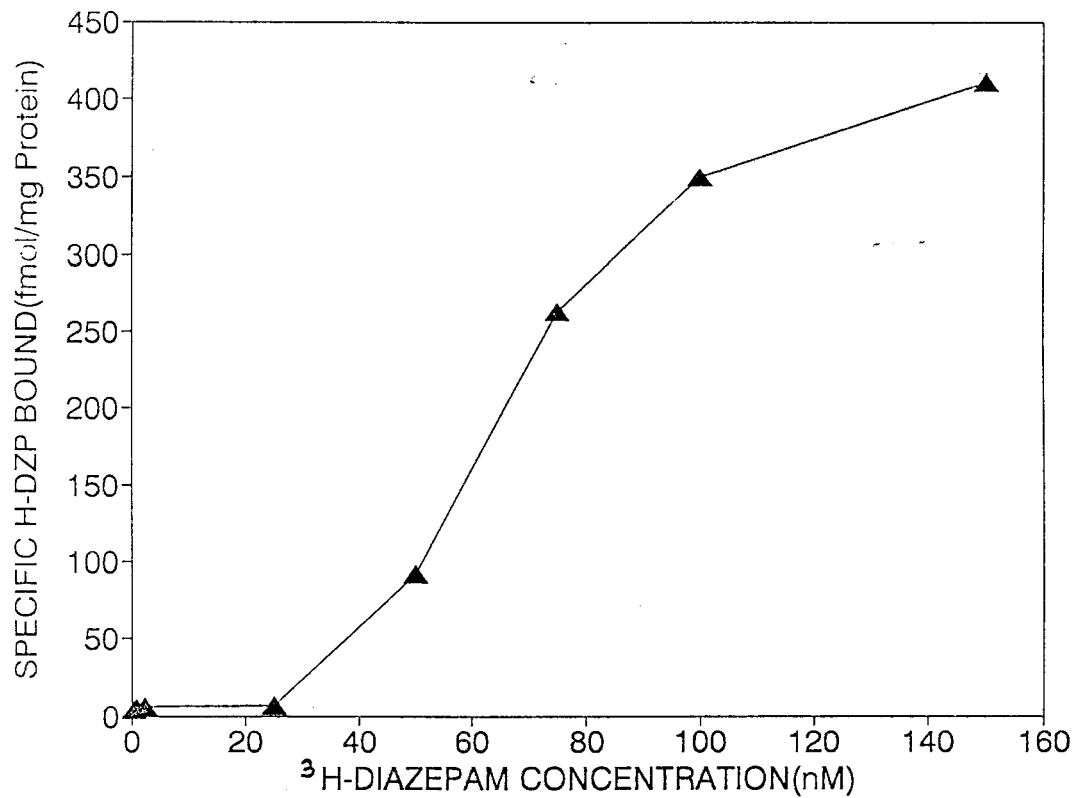
^{3}H-Diazepam conc. (nM)	Specific ^{3}H-Diazepam bound (fmol/mg protein)
150.0	411.0
100.0	350.0
75.0	263.0
50.0	92.0
25.0	6.4
2.5	5.5
1.0	5.2
0.5	3.7

Figure 19:   Saturation curve for ^{3}H-diazepam in rat brain membrane

2.7.1 Binding Competition and Structure Activity Relationship (SAR) Studies

The prepared benzodiazepine analogues were tested for their ability to displace bound ^{3}H-diazepam from rat brain membranes at concentrations ranging from 10^{-11} to 10^{-4}M. In principle, at low concentrations of a test drug little or no competition is expected, while at high concentrations, binding, if there is any, is indicated by the decreasing levels of radioactive drug. The test drug is said to bind specifically if it displaces 50% or more of the radioactive drug. Plots of percentage total binding against concentration of the competing drugs (figures 20-23) were obtained.

At concentrations of 10^{-11}M, compound **228** causes a 100% increase in diazepam binding (figure 20). It thus appears that this agent stimulates or enhances binding of diazepam to its receptor, possibly by acting on another receptor. As the concentration of this compound is increased, there is a steady reduction in this enhanced binding and at 10^{-4}M the diazepam binding is almost back to 100% of total binding. This can be interpreted as meaning that compound **228** does not interfere in any way with the benzodiazepine receptor for its ligand diazepam. Compound **65** has the same effect except that it enhances binding by up to *ca.* 50%. The effects of the other compounds (**222**, **225** and **226**) in the series fluctuate around 120% and these compounds are not considered to enhance binding significantly.

The benzoxathiepinones **250-254**, can be grouped together according to their effects (figure 21). They slightly enhance the binding of diazepam to the benzodiazepine receptor to the extent of 120-160%. It is interesting to note that increasing concentrations of these

compounds does not cause a reduction in diazepam binding as was the case with the benzodioxepinones (figure 20). The p-chloro analogue 252, however, behaves differently from the other compounds in the series. Even at concentrations of 10^{-11}M, compound 252 reduces specific diazepam binding to $ca.$ 30% and this steadily decreases as the concentration is increased. It can therefore be concluded that this compound reduces specific binding of diazepam to its receptor and, hence, itself binds specifically to the benzodiazepine receptor. These studies cannot determine whether this compound is an antagonist or agonist of the receptor site as this has to be shown using behavioural studies.

Figure 22 shows that all of the 4,1-benzoxathiepinones examined are able to interfere with the binding of diazepam to benzodiazepine receptors at concentrations as low as 10^{-11}M. It is evident from the graphs that, as the concentrations of these compounds are increased, there is less and less interference with the receptor, and at $ca.$ 10^{-4}M, specific diazepam binding is almost restored to its normal level. This is a rather unusual phenomenon because, at low concentrations, these compounds interfere directly with the benzodiazepine receptor but, as the concentration is increased, they appear to act on another receptor which, in fact, enhances diazepam binding, thus reversing the inhibitory effect on the receptor.

Figure 23 shows the benzoxathiepine 268 to be capable of inhibiting specific binding of diazepam to its receptor, maintaining diazepam binding at $ca.$ 20% or less over the concentration range examined. The observed reduction in specific diazepam binding implies that this compound (268) binds specifically to the benzodiazepine receptor. This compound, like compound 252, has a p-chloro substituent and has potential benzodiazepine activity. As

is the case with **252**, it cannot be determined whether it is an agonist or antagonist. The activity of compound **267** is very similar to that exhibited by the 4,1-benzoxathiepinone series (compounds **261-263**). The two remaining compounds in the series (**269** and **270**) enhance specific diazepam binding at low concentrations. However, as the concentration is increased, there is a sharp reduction in specific binding of the ^{3}H-diazepam for its benzodiazepine receptor. These two compounds therefore only act on the benzodiazepine receptor at concentrations above *ca.* 10^{-9} and 10^{-7}M respectively. Compound **270**, however, is more potent than compound **269**.

It is apparent that some of the compounds examined exhibit significant binding to benzodiazepine receptors, while others appear to potentiate diazepam binding. These observations certainly warrant further investigation.

Figure 20.   Competing curves for the 4-aryl-1,5-benzodioxepinones.
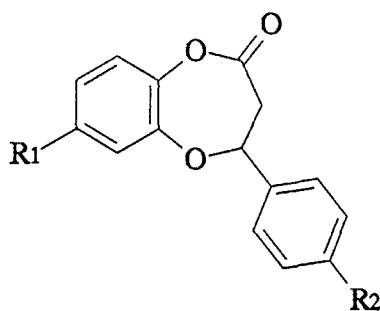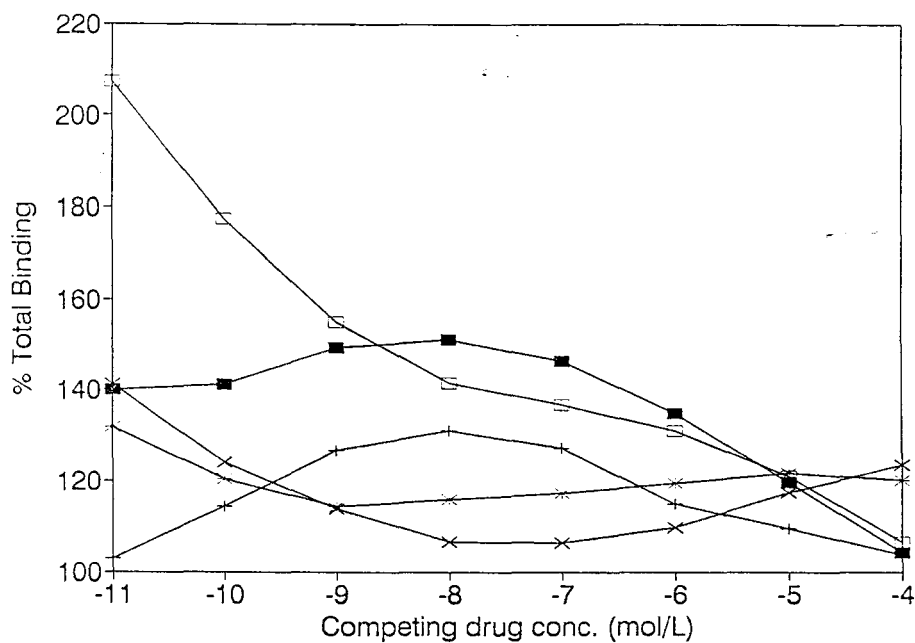
R¹	R²	Compd.	Key
H	H	65	■
Cl	H	222	x
H	Br	225	+
H	Cl	226	*
H	OMe	228	□
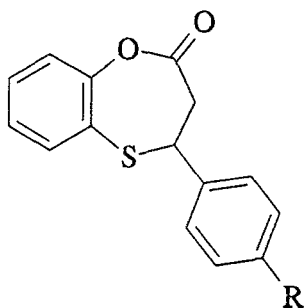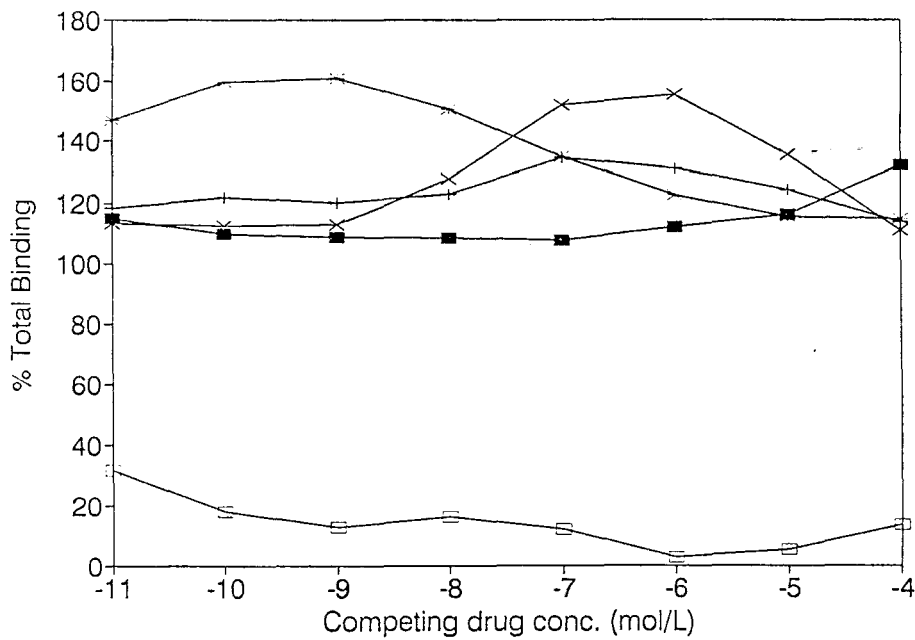
R	Compd.	Key
H	250	■
Br	251	+
Cl	252	□
F	253	*
OMe	254	x

Figure 21.   Competing curves for the 4-aryl-1,5-benzoxathiepinones.
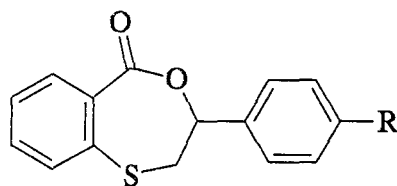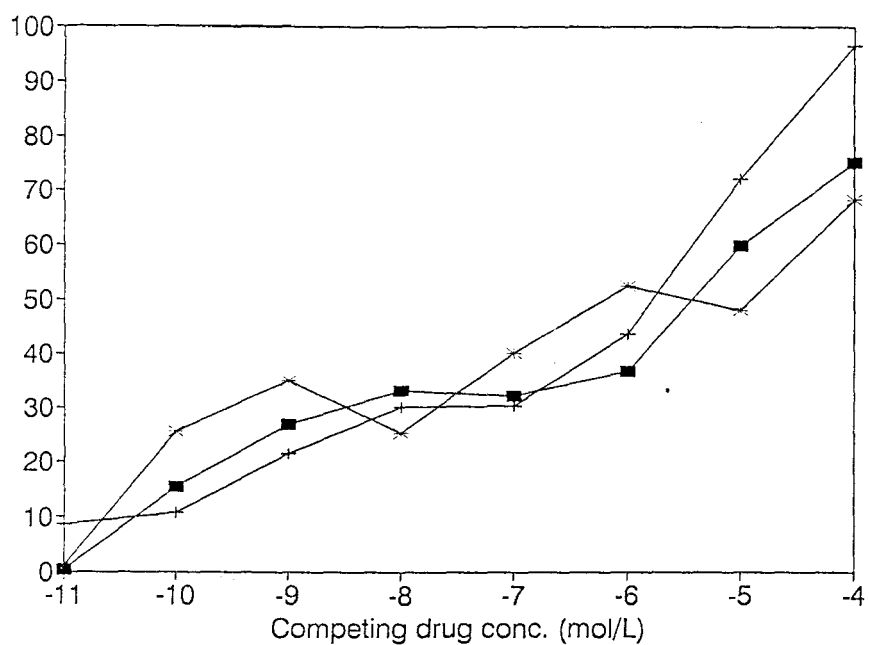
R	Compd.	Key
Br	261	*
Cl	262	+
H	263	■

Figure 22. Competing curves for the 3-aryl-4,1-benzoxathiepinones.

Figure 23.   Competing curves for the 3-aryl-4,1-benzoxathiepines.
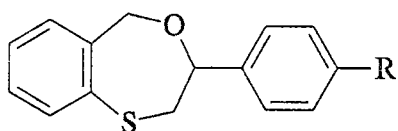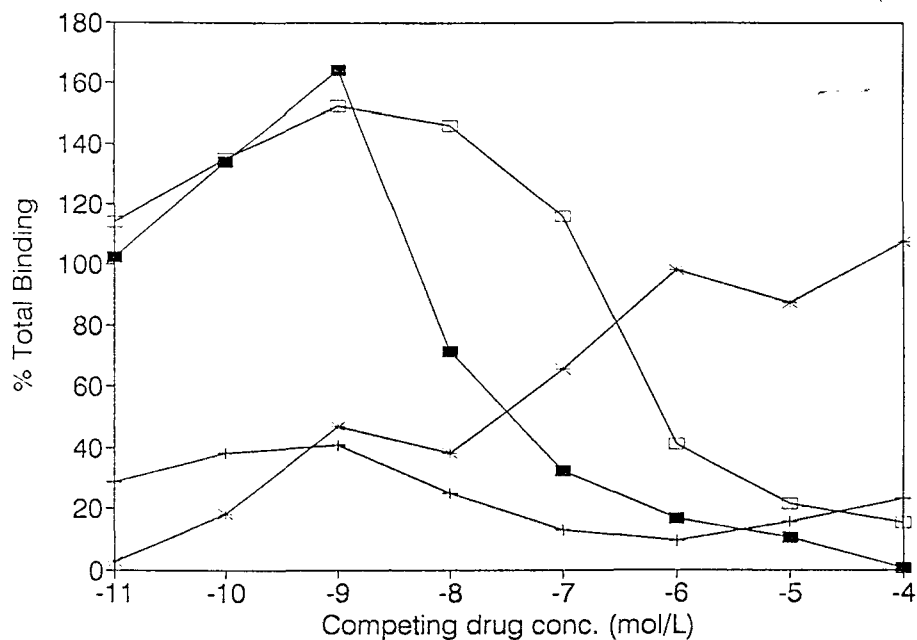
R	Compd.	Key
Br	267	*
Cl	268	+
F	269	□
H	270	■

2.8   CONFORMATIONAL ANALYSIS OF BENZODIAZEPINE ANALOGUES

It was mentioned in section 2.7 that substituents have a profound effect on the biological activity of benzodiazepines. In addition to this, the sterochemistry of these drugs have also been found to influence their binding to benzodiazepine receptors. In the benzoxathiepine 106, for example, it has been found that the hydroxy and N-phenylpiperazinylpropyl groups must be cis to each other and the ester group must be in a quasi-axial position for enhanced biological activity;[40] in diltiazem-type systems 309, a cis arrangement of the substituents is desirable for activity.[252-254]

The conformations of seven-membered compounds have been investigated theoretically and experimentally from the viewpoint of interconversion and pseudo-rotation.[255-257] In an attempt to link conformational effects with binding affinity, we have explored the conformational preferences of compounds prepared in the course of this research. ^{1}H NMR spectroscopy, X-ray crystallography and computer modelling techniques were used to elucidate the preferred conformations.

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309 ; X = CH$_2$, O, S
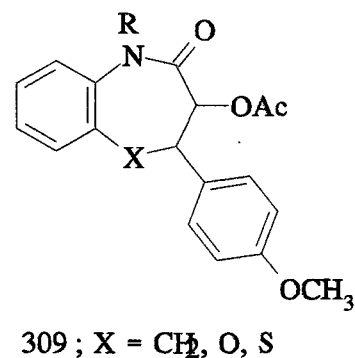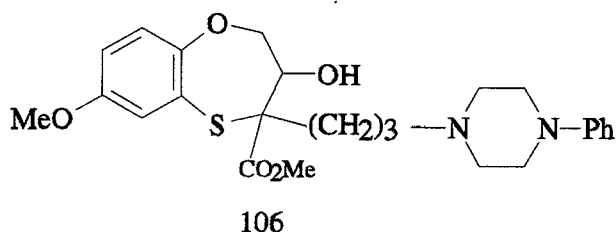
2.8.1 ¹H NMR Spectroscopy and Computer modelling

All the compounds considered in this section possess a chiral centre either at C-3 or C-4, depending on the location of the phenyl substituent. Consequently, the methylene protons, H_a and H_b (see figures 24 and 25) are diastereotopic and therefore chemically non-equivalent. They couple with each other, and in turn, with the adjacent methine proton (H_x). Thus, the methylene protons (H_a and H_b) may be expected to resonate as a pair of double doublets and the methine proton (H_x) as a double doublet further downfield, with $J_{gem} > J_{vic}$ and $J_{ax} \neq J_{bx}$. In some cases, however, the overlap of signals leads to a reduction in the observed multiplicity.

The splitting patterns and vicinal coupling constants were used to determine the preferred conformations of the benzodiazepine analogues in $CDCl_3$ solution. The assignment of each set of aliphatic proton signals to their respective nuclei in all compounds was achieved with the aid of coupling constant data (figures 24 and 25) and multi-pulse NMR techniques, such as DEPT, HETCOR and COSY (see figures 26 and 27 for illustrative spectra) on representative compounds. The aliphatic protons exhibit similar splitting patterns for both the 3- and 4-phenyl substituted systems. However, the low electronegativity of sulphur at position 5 (in the benzoxathiepines) shifts the 4-methine signal upfield (to ca. δ 4.72ppm) compared to the corresponding signal (at ca. δ 5.63ppm) in the benzodioxepinones (figure 24). The diastereotopic 3-methylene protons in the 4-phenyl substituted compounds (figure 24) resonate upfield (at ca. δ 3.00ppm) compared to the corresponding 2-methylene protons (ca. δ 3.3ppm) in the 3-phenyl substituted compounds (figure 25).
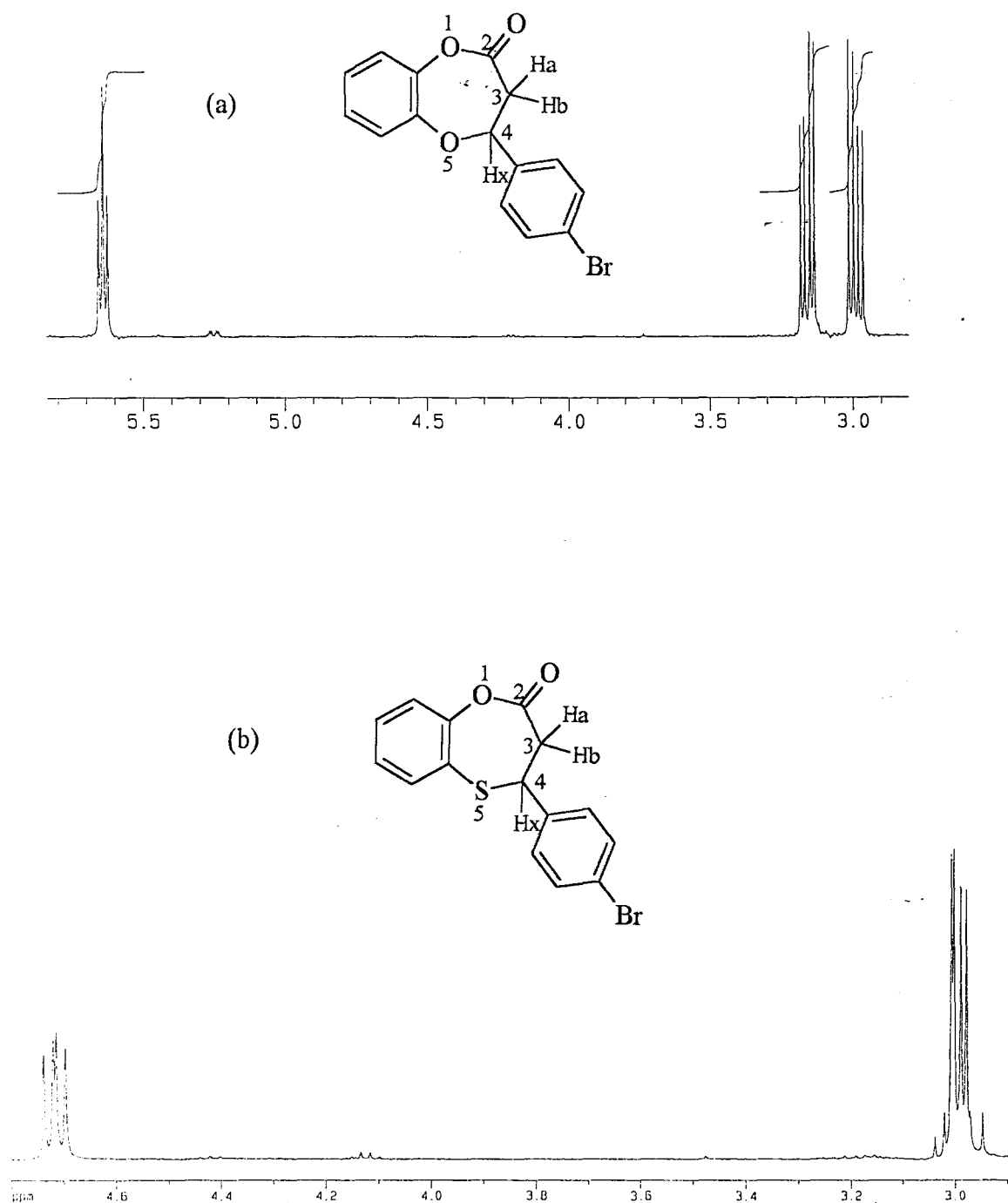
Figure 24: Partial ^{1}H NMR spectra of the (a) 4-(4-bromophenyl)-1,5-benzodioxepinone; (b) 4-(4-bromophenyl)-1,5-benzoxathiepinone in CDCl$_3$ illustrating the splitting patterns of the methine and methylene protons.
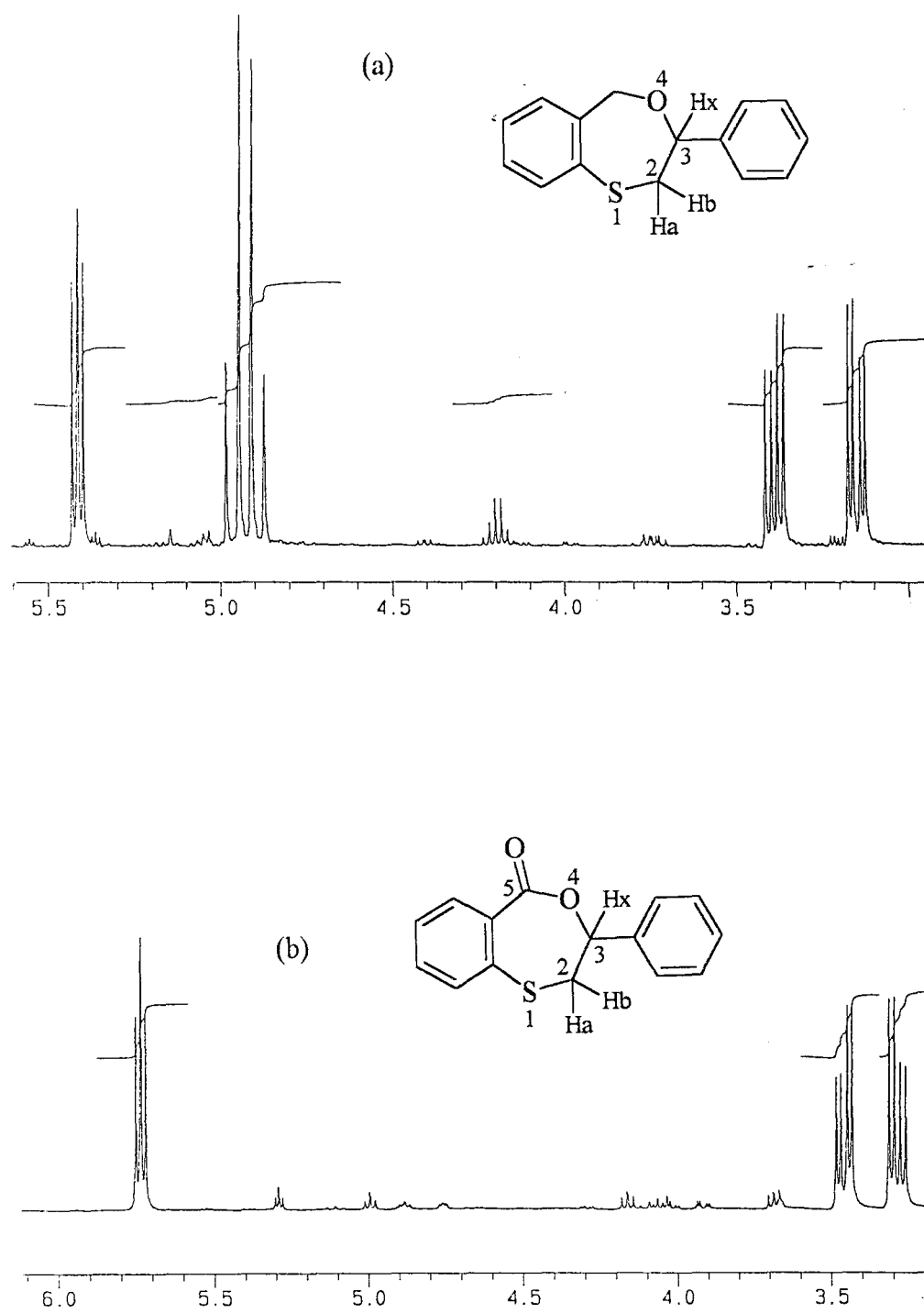
Figure 25:   Partial ¹H NMR spectra of the (a) 3-phenyl-4,1-benzoxathiepine and (b) 3-[henyl-4,1-benzoxathiepinone in $CDCl_3$ illustrating the splitting patterns of the methine and methylene protons.
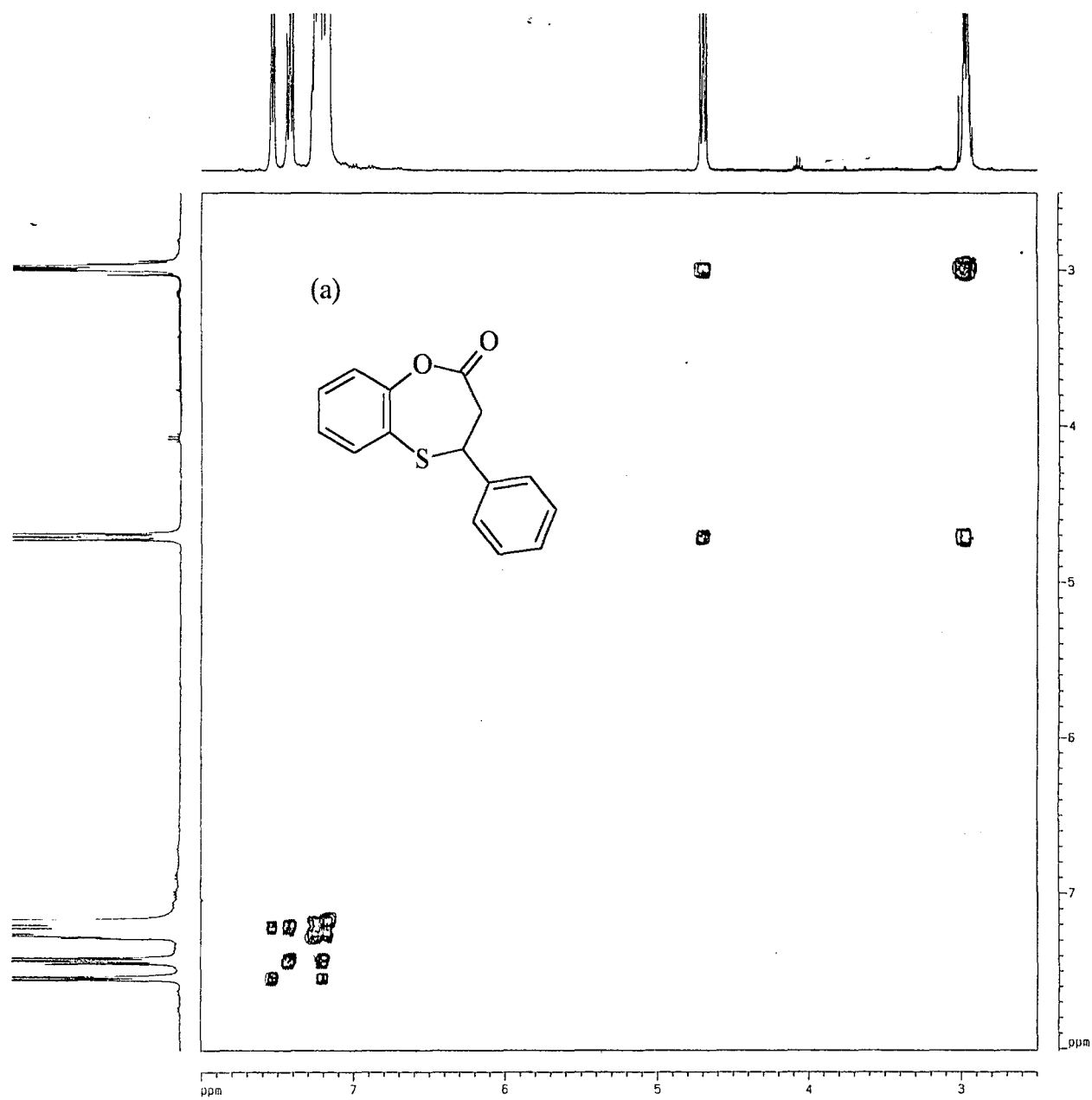
Figure 26(a): 400 MHz COSY spectrum of 4-phenyl-1,5-benzoxathiepin-2-one in CDCl$_3$
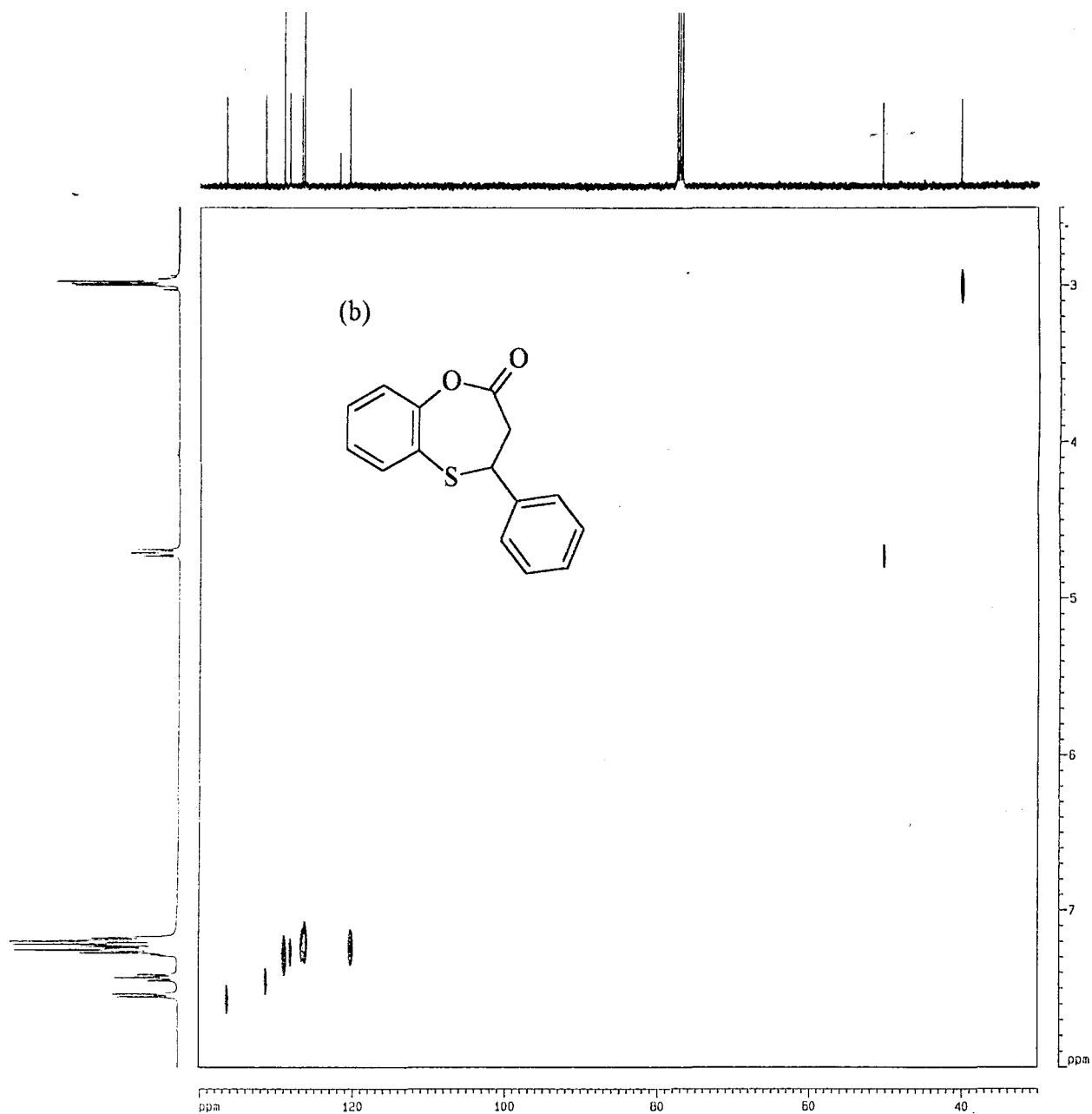
Figure 26(b):   400 MHz HETCOR spectrum of 4-phenyl-1,5-benzoxathiepin-2-one in
                 CDCl₃
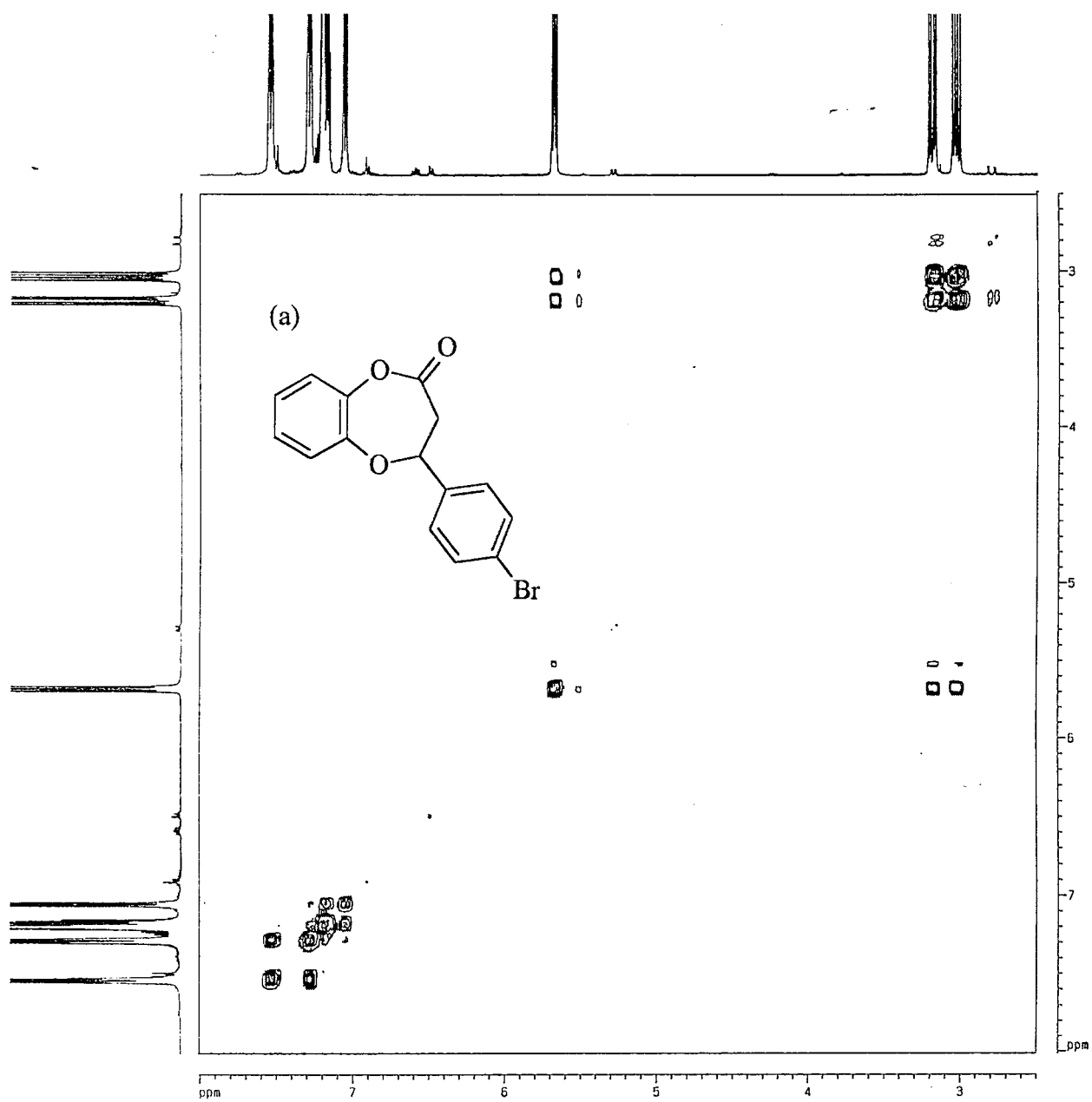
Figure 27(a): 400 MHz COSY spectrum of 4-(4-bromophenyl(-1,5-benzodioxepin-2-one in CDCl₃
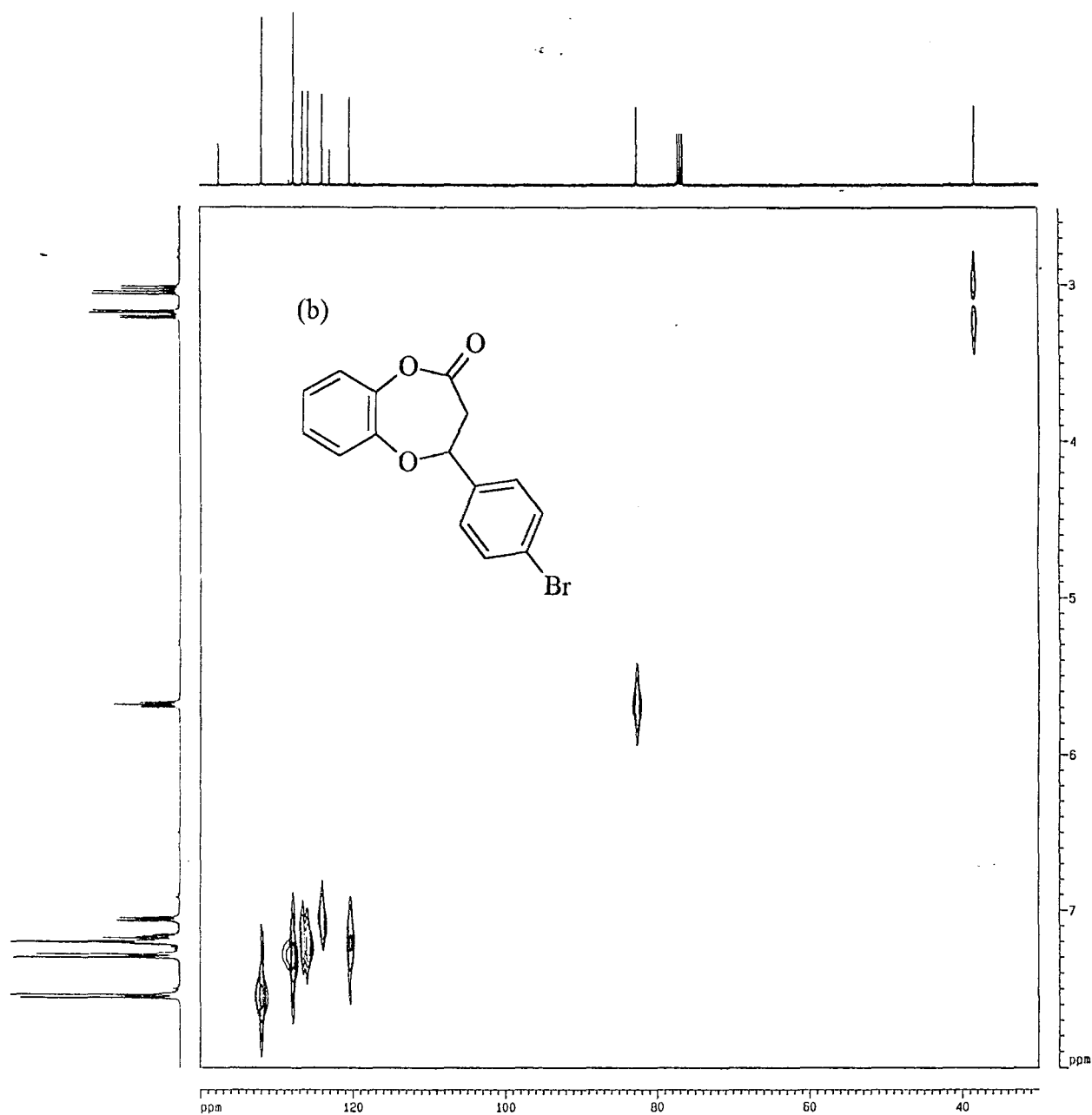
Figure 27(b):   400 MHz HETCOR spectrum of 4-(4-bromophenyl)-1,5-benzodioxepin-2-one in CDCl₃

152a

2.8.1.1 1,5-Benzodioxepinones

The comparable magnitudes of the *vicinal* coupling constants (J_{bx} 5.9-6.6Hz, J_{ax} 6.3-7.2Hz; Table 23) of the benzodioxepinones suggest that the methine proton (4-H_x) is gauche to both methylene protons (3-H_a and 3-H_b). This condition is satisfied by the preferred energy minimised conformation obtained from computer modelling of the parent compound (structure II; figure 28). Of course, the possibility of a dynamic equilibrium, in which the less stable "axial" conformer I makes some contribution, cannot be excluded; the observed *vicinal* coupling constants could then be viewed as weighted averages of the values for each of the contributing conformers.

While solid state and solution conformations may differ, being stabilised by different factors, it is interesting to note that the X-ray crystal structure of 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one **228** (figure 29) is very similar to the computer modelled conformation II (figure 28). In the solid state conformation (figure 29) it is apparent that:-

(i)   the methine hydrogen is, in fact, gauche to each of the methylene protons; and

(ii)   the 4-phenyl group is "equatorially" disposed.

On the basis of the available evidence, we propose that the solid state conformation is largely maintained in solution in $CDCl_3$.

Table 23. ^{1}H NMR chemical shifts followed, in parentheses, by coupling constants (J/Hz) of the methylene and methine protons of 1,5-benzodioxepine analogues.
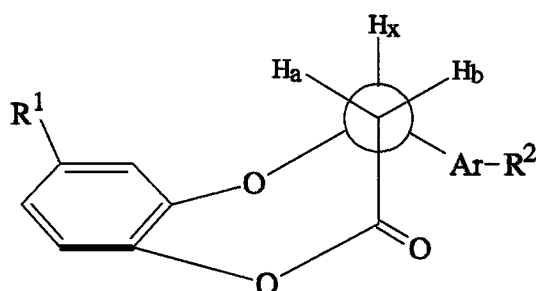
Compd.	R^1	R^2	3-H$_a$ dd(J_{ax};J_{gem})	3-H$_b$ dd(J_{bx};J_{gem})	4-H$_x$ dd(J_{bx};J_{ax})
65	H	H	3.10 (7.3;13.3)	3.15 (5.8;13.3)	5.72 (6.0;7.2)
221	Br	H	3.11 (7.3;13.5)	3.16 (5.8;13.5)	5.72 (5.9;7.1)
222	Cl	H	3.09 (7.5;13.5)	3.15 (5.7;13.6)	5.71 (6.6;6.6)
225	H	Br	2.98 (6.7;13.4)	3.15 (5.9;13.4)	5.64 (6.3;6.3)
226	H	Cl	3.02 (6.9;13.4)	3.17 (5.8;13.4)	5.67 (6.3;6.3)
227	H	F	3.03 (6.9;13.3)	3.16 (5.8;13.3)	5.68 (6.4;6.4)

I   II
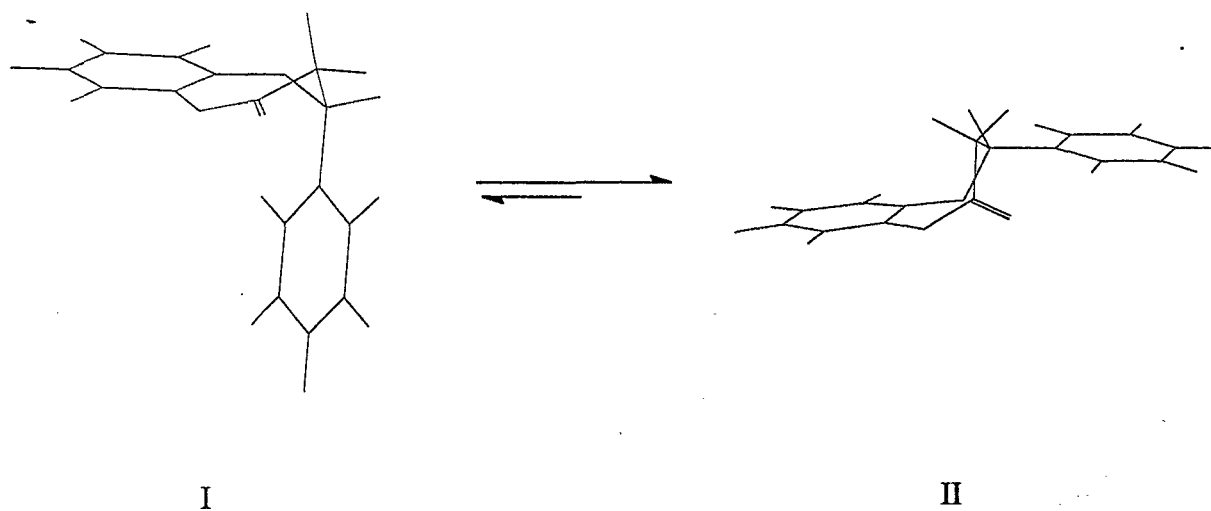
Figure 28:   Conformational equilibria of 4-phenyl-1,5-benzodioxepinone
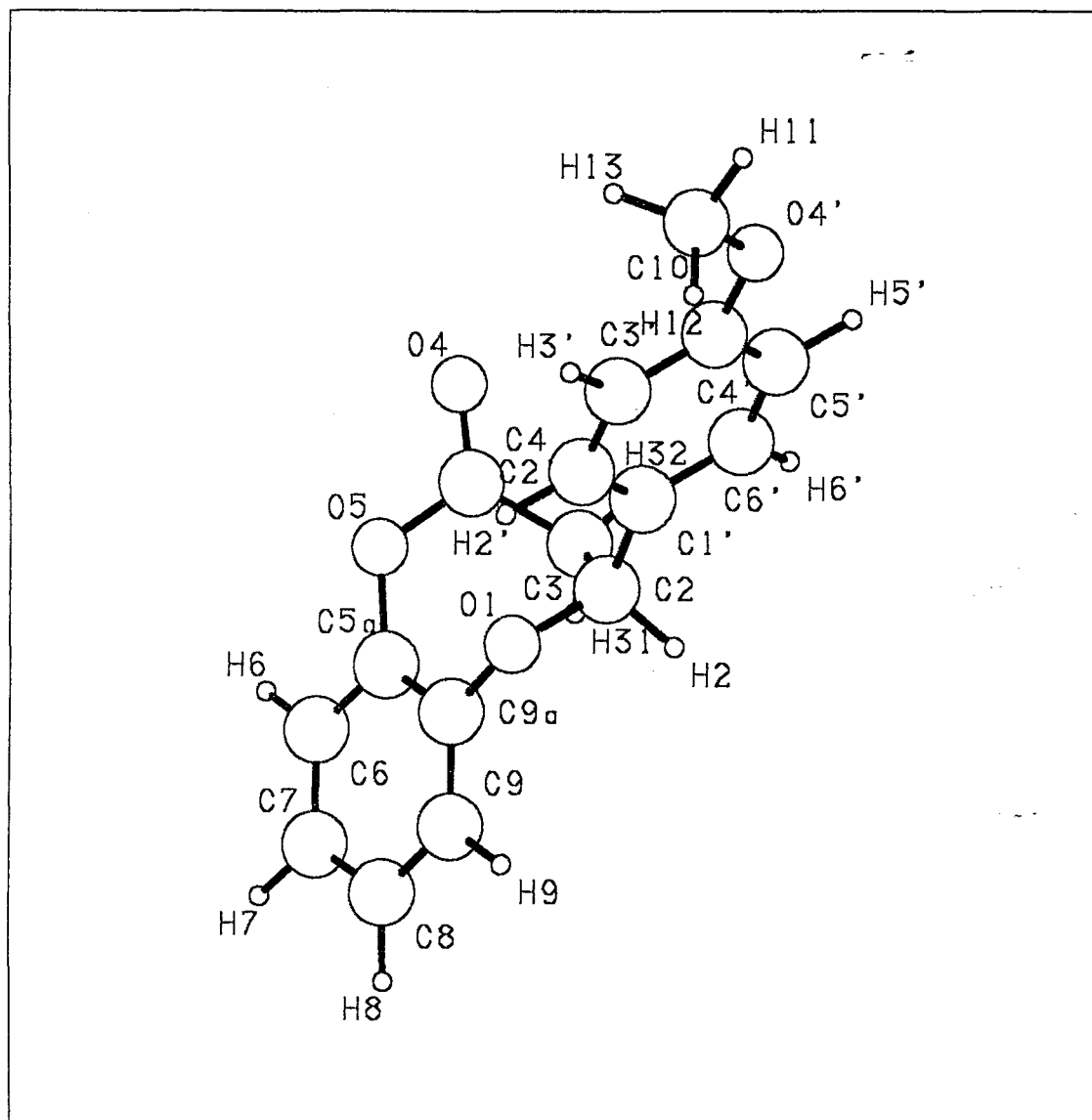
Figure 29: X-ray crystal structure for 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one 228, showing the crystallographic numbering.

2.8.1.2 1,5-Benzoxathiepinones

The relatively large values of the *vicinal* coupling constants (J_{bx} *ca.* 9.5Hz; Table 24) in the 1,5-benzoxathiepinone analogues suggest a dihedral angle of *ca.* 180°, *i.e.* an antiperiplanar arrangement of H_x and H_b. The other methylene hydrogen (3-H_a) exhibits a *vicinal* coupling constant of *ca.* 7.0Hz which indicates an orientation gauche to the methine hydrogen (H_x). This data is consistent with the preferred conformation IV (figure 30), obtained by computer modelling and in which the 4-phenyl substituent is in an equatorial position. In addition, the X-ray crystal structure of 4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one **252** (figure 31) closely resembles the "equatorial" computer modelled conformation IV of the parent compound.

III   IV
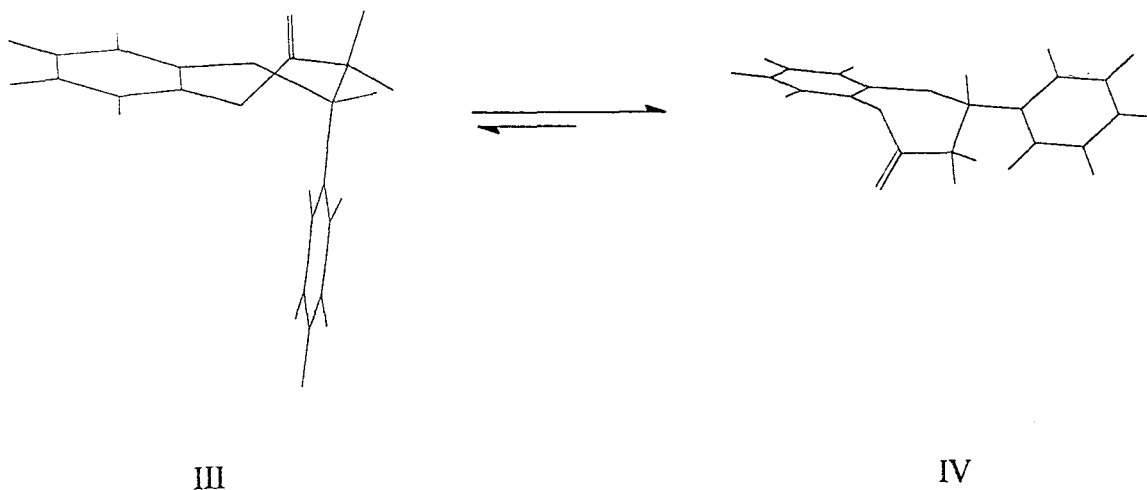
Figure 30:   Conformational equilibria of 4-phenyl-1,5-benzoxathiepin-2-one **250**.

Table 24. ^{1}H NMR chemical shifts followed, in parentheses, by coupling constants (J/Hz) of 1,5-benzoxathiepin-2-one analogues in $CDCl_3$.
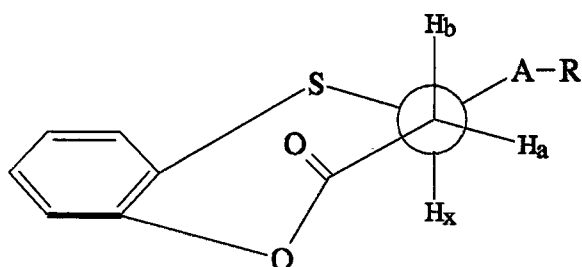
Compd.	R	3-H_a $dd(J_{ax};J_{gem})$	3-H_b $dd(J_{bx};J_{gem})$	4-H_x $dd(J_{ax};J_{bx})$
250	H	2.99 (7.2;12.4)	2.96 (9.7;12.4)	4.70 (7.2;9.5)
251	Br	3.01 (7.1;12.5)	2.97 (9.5;12.5)	4.72 (7.1;9.4)
252	Cl	3.02 (7.1;12.5)	2.98 (9.4;12.5)	4.74 (7.1;9.4)
253	F	3.00 (7.0;12.5)	2.98 (9.5;12.5)	4.75 (7.0;9.4)
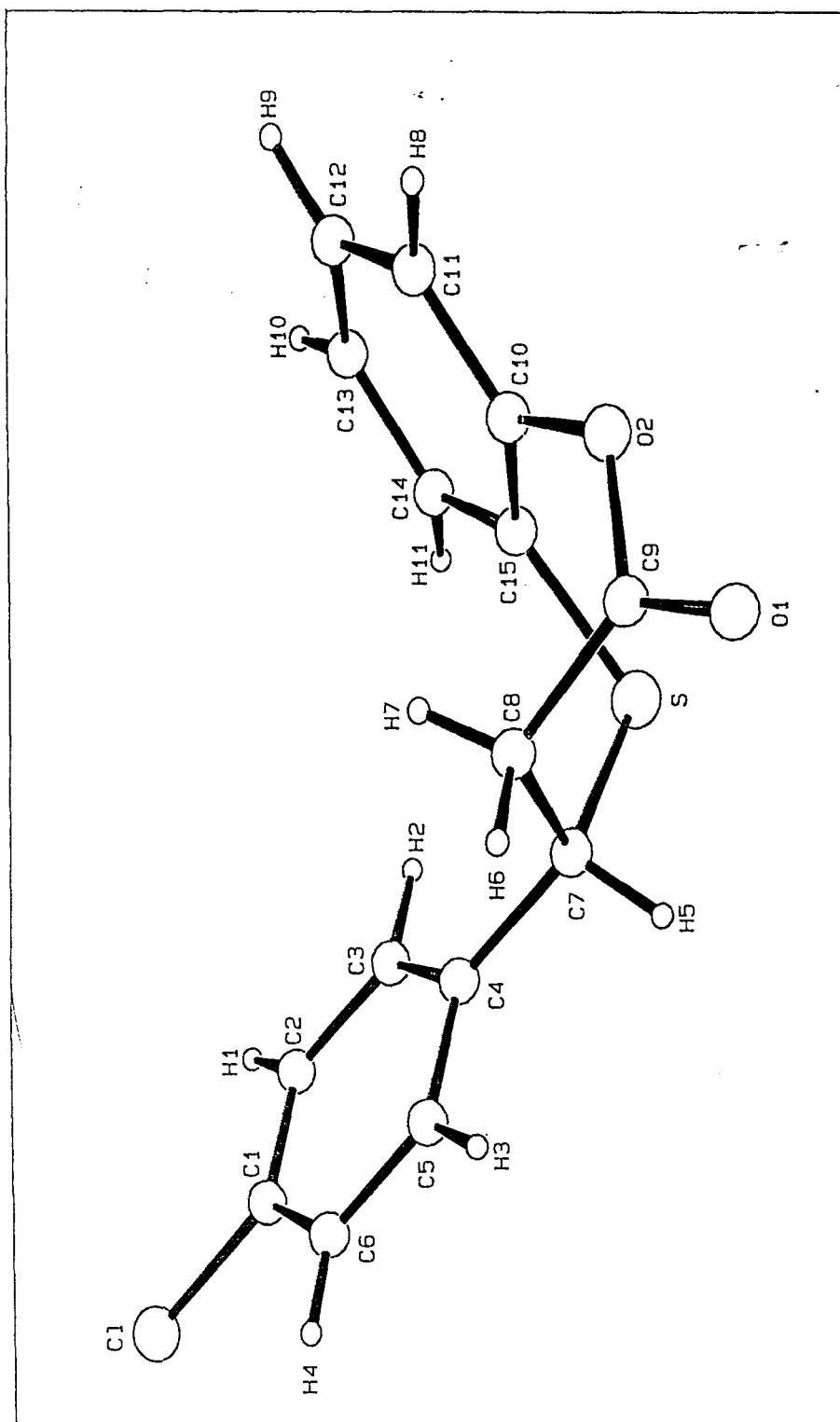
Figure 31:   X-ray   crystal   structure   for   3,4-dihydro-4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one **252**, showing crystallographic numbering.

2.8.1.3 4,1-Benzoxathiepinones

The similarity of all the *vicinal* coupling constants ($J_{ax} \approx J_{bx}$ 6.1-6.8Hz; Table 25) suggest a conformation for the 3-phenyl substituted 4,1-benzoxathiepin-5-ones, in which the methine hydrogen (3-H_x) is gauche to each of the methylene protons (2-H_a and 2-H_b). Computer modelling affords, as the preferred arrangement (figure 32), conformation VI in which the 3-phenyl group is equatorial and the *vicinal* hydrogens are, in fact, all gauche to each other. In the 2-phenyl substituted analogues, however, the *vicinal* coupling constants differ significantly (*i.e.* J_{ax} 4.0Hz $< J_{bx}$ *ca.* 7.4Hz), suggesting substantially different torsion angles between the 2-methine hydrogen (H_x) and each of the 3-methylene hydrogens (H_a and H_b). Predominance of a conformation in which H_x is approximately anti to H_b but gauche to H_a would seem to satisfy these observations. In fact, both energy minimised computer generated conformations (VII and VIII; figure 33) exhibit such stereochemistry, in the more stable conformer VIII, however, the 2-phenyl substituent occupies a quasi-equatorial position.

Table 25. ^{1}H NMR chemical shifts followed, in parentheses, by coupling constants (J/Hz) of 3-phenyl-4,1-benzoxathiepin-5-one analogues in $CDCl_3$.
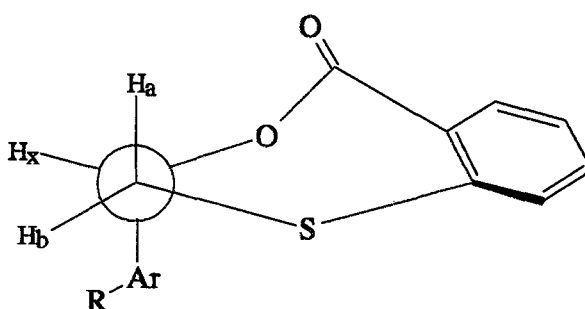
Compd.	R	2-H_a dd(J_{ax};J_{gem})	2-H_b dd(J_{bx};J_{gem})	3-H_x dd(J_{bx};J_{ax})
261	Br	3.20 (6.4;14.4)	3.33 (6.1;14.4)	5.66 (6.2;6.2)
262	Cl	3.25 (6.4;14.4)	3.39 (6.1;14.4)	5.70 (6.3;6.3)
263	H	3.29 (6.8;14.3)	3.46 (6.0;14.3)	5.74 (6.0;6.8)

Table 26. ^{1}H NMR chemical shifts followed, in parentheses, by coupling constants (J/Hz) of 2-phenyl-4,1-benzoxathiepin-5-one analogues in CDCl$_3$.
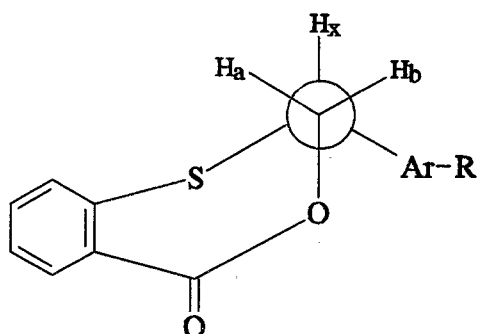
Compd.	R	2-H$_x$ dd(J_{ax};J_{bx})	3-H$_a$ dd(J_{ax};J_{gem})	3-H$_b$ dd(J_{bx};J_{gem})
264	Br	6.03 (4.0;7.3)	3.92 (4.0;12.2)	4.02 (7.3;12.2)
265	Cl	5.97 (4.0;7.3)	3.84 (4.0;12.2)	3.94 (7.4;12.2)
266	H	6.10 (4.0;7.6)	3.93 (4.0;12.2)	4.04 (7.6;12.2)

V   VI
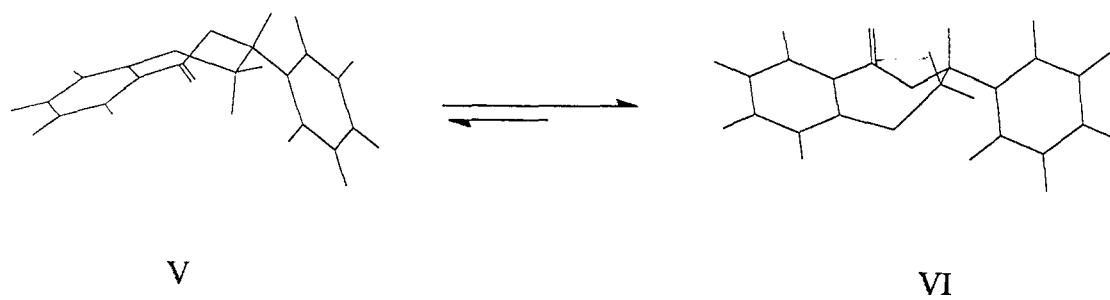
Figure 32:   Conformational equilibria of 3-phenyl-4,1-benzoxathiepin-5-one 263.

VII   VIII
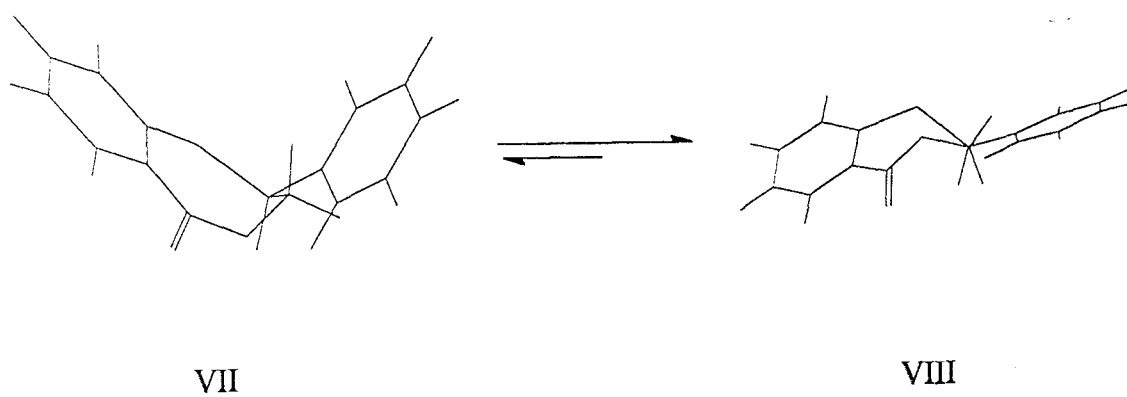
Figure 33:   Conformational equilibria of 2-phenyl-4,1-benzoxathiepin-5-one 266.

2.8.1.4 4,1-Benzoxathiepines

As was the case for the 2-phenyl-4,1-benzoxathiepin-5-ones, the *vicinal* coupling constants

differ (J_{ax} 5.4-5.8 and J_{bx} 6.9-7.1Hz; Table 27), suggesting that the methine hydrogen (3-H_x)

is gauche to one methylene proton (H_a) and anti to the other (H_b). The differences between

J_{ax} and J_{bx}, however, are smaller than in the case of the 2-phenyl-4,1-benzoxathiepinones

discussed earlier. From the computer modelled structures (figure 34) it is apparent that in

the more stable "equatorial" conformer X, the 3-methine hydrogen (H_x) is, in fact, anti to

H_b and gauche to H_a; in the less stable conformer IX, however, H_x is gauche to both H_a and

H_b. Some contribution by the latter conformer IX to the equilibrium population could

account for the observed diminution in the difference between the *vicinal* coupling constants.

From the results of the conformational studies, it appears that the compounds considered

favour a puckered arrangement of the seven-membered ring with an "equatorial" disposition

of the phenyl substituent. Structural variations clearly influence the magnitude of the *vicinal*

couplings between the adjacent methylene and methine hydrogens but, in most cases, gauche-

anti rather than gauche-gauche arrangements to these atoms appear to be favoured.

It should be noted that although the "preferred" computer modelled structures do not

necessarily represent global minima (confirmation would require a detailed molecular

mechanics investigation beyond the scope of the present study), they are chemically

reasonable and, most importantly, consistent with the ^{1}H NMR and X-ray crystallographic

data.

Table 27. ^{1}H NMR chemical shifts followed, in parentheses, by coupling constants (J/Hz) of 3-phenyl-4,1-benzoxathiepine analogues in $CDCl_3$.
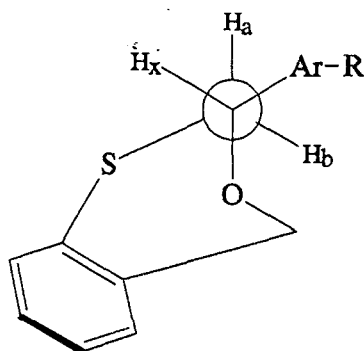
Compd.	R	2-H$_a$ dd(J_{ax};J_{gem})	2-H$_b$ dd(J_{bx};J_{gem})	3-H$_x$ dd(J_{ax};J_{bx})
267	Br	3.06 (5.4;14.2)	3.27 (7.1;14.2)	5.33 (5.5;7.0)
268	Cl	3.08 (5.5;14.2)	3.28 (7.0;14.2)	5.33 (5.5;7.0)
269	F	3.06 (5.6;14.2)	3.27 (6.9;14.2)	5.31 (5.7;7.0)
270	H	3.15 (5.8;14.1)	3.39 (7.0;14.1)	5.41 (5.8;7.0)

IX   X
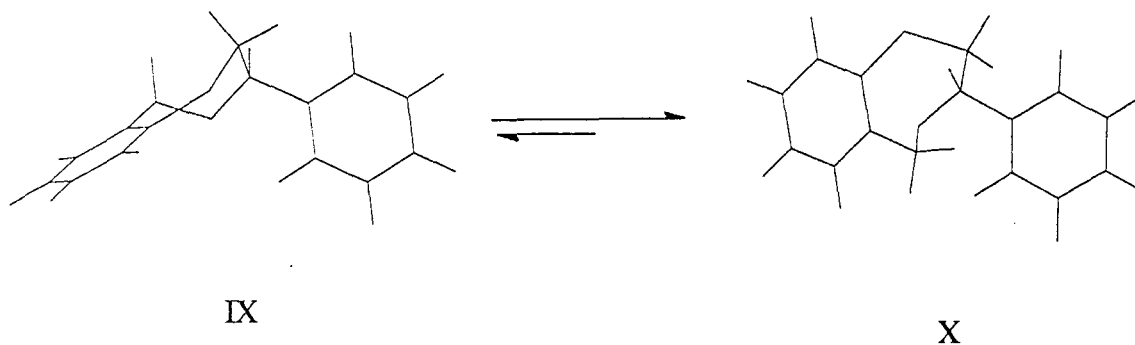
Figure 34:   Conformational equilibria of 3-phenyl-4,1-benzoxathiepine 270.

2.9 CONCLUSION

During the course of this research several series of benzodiazepine analogues have been prepared through ring expansion and cyclisation methods. Many of these compounds were synthesised for the first time and, together with the other compounds, were subjected to spectroscopic, conformational and receptor-binding analysis. A kinetic-mechanistic study of the Baeyer-Villiger reaction of flavanones has also been successfully undertaken to elucidate the regioselectivity of oxygen insertion vis-a-vis nitrogen insertion in parallel Schmidt reactions.[91] These studies have provided useful insights into the chemistry of various benzodiazepine analogues and precursors, and have already led to several publications.[26,28,182]

Future research related to the present study is expected to involve the following:

(i)   Expansion of the heterocyclic ring of the benzo-fused flavanones, thioflavanones and quinolones followed by DNA-intercalation studies of the resulting products.

(ii)   Regioselectivity studies of nitrogen-insertion in the Schmidt reaction of N-acetyl-4-quinolones.

(iii)   DNMR studies of N-acetyl-4-quinolones to explore substituent effects on the internal rotation of the N-acetyl group.

(iv)   Developing methods for increasing unsaturation in the 7-membered ring to obtain conjugated benzodiazepine analogues for further receptor-binding studies.

3.   EXPERIMENTAL

3.1   GENERAL

^{1}H NMR spectra were recorded on a Perkin-Elmer R12a (60MHz) or Bruker AMX 400

(400MHz) instruments. ^{13}C NMR spectra were recorded on a Bruker AMX 400 (100MHz)

spectrometer with proton decoupling. Chemical shifts are quoted on the δ scale and are

referenced using solvent peaks [δ_H = 7.25ppm (CHCl$_3$) and δ_C = 77.0ppm (CDCl$_3$)].

Coupling constants (J) are given in hertz (Hz). IR spectra were recorded on a Perkin-Elmer

180 spectrophotometer using KBr discs unless otherwise stated. Low resolution mass spectra

were recorded on a Hewlett Packard 5988A instrument; high resolution mass spectra were

obtained using a Kratos M580RF double focusing magnetic sector instrument by the Cape

Technikon Mass Spectrometry Unit. Combustion analyses were performed at the University

of Natal, Pietermaritzburg. Melting points were determined on a Köfler hot-stage apparatus

and are uncorrected.

All solvents and commercially available reagents were purified, when necessary, by standard

techniques.[258] Thin layer chromatography (TLC) was performed on MERCK Kieselgel

60F254 precoated plates. Flash chromatography[259] was carried out using MERCK Kieselgel

60 (230-400 mesh).

All ^{17}O NMR spectra were recorded on a Bruker AMX 400 spectrometer equipped with a 5mm broad-band probe operated at 54.26MHz and 303K, using saturated solutions (*ca.* 200-300mg in 1.5ml $CDCl_3$). Acquisition time for all spectra was *ca.* 18 hours. All chemical shifts are relative to D_2O (δ = 0ppm) as external standard. The spectra were recorded without sample spinning.

3.2   PREPARATION PROCEDURES

2,3-Dihydro-2-phenyl-4H-1-benzopyran-4-one (**64**).[94] -

A stirred mixture of 1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one (**181**) (20g, 0.089mol) and orthophosphoric acid (d. 1.69, 86ml) in EtOH (500ml) was boiled under reflux for 3 days. The resulting solution was concentrated and the precipitated product filtered and recrystallised from EtOH to give 2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**64**) (9g, 45%), m.p. 72-73°C (lit.,[260] 75-76°C); ν_{max} (KBr)/cm^{-1} 1690 (C=O); δ_H(400MHz;CDCl$_3$) 2.88 (1H, dd, J 3.0 and 16.8, 3-H), 3.09 (1H, dd, J 13.2 and 16.9, 3-H), 5.50 (1H, dd, J 3.0 and 13.2, 2-H), 7.04-7.08 (2H, m, ArH), 7.37-7.55 (6H, m, ArH) and 7.90 (1H, d, J 1.8, ArH). .

3,4-Dihydro-4-phenyl-1,5-benzodioxepin-2-one (**65**).[26] -

A mixture of 2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**64**) (3g, 13.4mmol) and meta-chloroperbenzoic acid (MCPBA) (50-60%; 5.19g, 15   mmol) in dry dichloromethane (50ml) was boiled under reflux for 24 hours. After evaporating the solvent, the residue was dissolved in ethyl acetate (50ml), washed sequentially with aqueous NaHCO$_3$ and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent resulted in a brown residue which was purified by flash chromatography [elution with EtOAc-hexane (1:4)] to afford 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (**65**) (2g, 62%), m.p. 85-86°C (lit.,[26] 85-86°C); ν_{max} (KBr)/cm^{-1} 1754 (C=O); δ_H(400MHz;CDCl$_3$) 3.07-3.17 (2H, m, 3-H), 5.72 (1H, t, 3-H), 7.03 (1H, d, J 6.8, 8-H), 7.12-7.19 (3H, m, 9-H, 7-H and 6-H) and 7.39 (5H, s, PhH); δ_C(100MHz;CDCl$_3$)

38.5 (C-3), 83.4 (C-4), 120.4 (C-6), 124.2 (C-8), 125.7 (C-9), 126.1 (C-2' and C-6'),

126.5 (C-7), 128.8 (C-3' and C-5'), 129.0 (C-4'), 138.6 (C-9a), 145.2 (C-1'), 145.6 (C-

5a) and 167.4 (C-4).

3-Bromophenyl acetate (**163**).[93] -

Acetic anhydride (19.1ml, 0.213mol) was added dropwise to a stirred solution of 3-

bromophenol (23.4g, 0.135mol) and NaOH (8.5g, 0.213mol) in water (*ca.* 163ml) at

0°C. The resulting mixture was stirred for 1 hour at the same temperature and then

extracted with ethyl acetate (3 x 50ml). The combined extracts were washed with aq.

$NaHCO_3$ (2 x 50ml) and water (2 x 50ml), and then dried (anhyd. $MgSO_4$). The solvent

was evaporated to afford an oil which was distilled to give 3-bromophenyl acetate (**163**)

(26g, 90%), b.p. 124-127°C/13-15mmHg (lit.,[261] 149°C/40mmHg); ν_{max} (thin film)/cm^{-1}

1775 (C=O); δ_H(60MHz;CDCl$_3$) 2.21 (3H, s, CH$_3$) and 6.9-7.45 (4H, m, ArH).

3-Chlorophenyl acetate (**164**).[93] -

The experimental procedure employed for the synthesis of 3-bromophenyl acetate (**163**)

was followed, using acetic anhydride (25.4g, 0.249mol), 3-chlorophenol (20g, 0.156mol),

and NaOH (10g, 0.249mol) in water (170ml). Work-up afforded 3-chlorophenyl acetate

(**164**) (19.7g, 74%), b.p. 103-105°C/13-15mmHg (lit.,[93] 105-107°C/13mmHg); ν_{max} (thin

film)/cm^{-1} 1775 (C=O); δ_H(60MHz;CDCl$_3$) 2.21 (3H, s, CH$_3$) and 6.9-7.4 (4H, m, ArH).

3-Fluorophenyl acetate (**165**).[93] -

The experimental procedure employed for the synthesis of 3-bromophenyl acetate (**163**)

was followed, using acetic anhydride (30.8ml, 0.329mol), 3-fluorophenol (26g, 0.232mol)

and NaOH (13.1g, 0.327mol) in water (220ml). Work-up afforded 3-fluorophenyl acetate

(165) (32.3g, 90%), b.p. 79-80°C/13-15mmHg (lit.,[262] 77-78°C/13mmHg); ν_{max} (thin

film)/cm^{-1} 1770 (C=O); δ_H(60MHz;CDCl$_3$) 2.3 (3H, s, CH$_3$) and 6.9-7.5 (4H, m, ArH).

4-Bromo-2-hydroxyacetophenone (167).[94] -

A mixture of 3-bromophenyl acetate (163) (10g, 0.046mol) and anhydrous aluminium

chloride (22.0g, 0.150mol) was heated at 180°C for 3 hours. 2M-HCl (100ml) was

added to the cooled reaction mixture, which was then steam distilled. The distillate was

extracted with chloroform (3 x 50ml) and the combined extracts were re-extracted with

0.5M-KOH (3 x 50ml). The alkaline extracts were washed with chloroform (2 x 40ml),

acidified and extracted with chloroform (3 x 40ml). The organic layer was dried (anhyd.

MgSO$_4$) and the solvent was evaporated to afford 4-bromo-2-hydroxyacetophenone (167)

(6.7g, 68%), m.p. 41-42°C (lit.,[94] 42-43°C); ν_{max} (thin film)/cm^{-1} *ca.* 3600-2500 (OH)

and 1640 (C=O); δ_H(60MHz;CDCl$_3$) 2.58 (3H, s, CH$_3$), 7.01 (1H, dd, *J* 1.8 and 8.5, 3-

H), 7.02 (1H, d, *J* 1.8, 5-H), 7.55 (1H, d, *J* 8.6, 6-H) and 12.3 (1H, s, OH).

4-Chloro-2-hydroxyacetophenone (168).[94] -

The experimental procedure employed for the synthesis of 4-bromo-2-

hydroxyacetophenone (167) was followed, using 3-chlorophenyl acetate (164) (15g,

0.088mol) and AlCl$_3$ (27.9g, 0.209mol). Work-up afforded 4-chloro-2-

hydroxyacetophenone (7) (10.1g, 67%), b.p. 119-121°C/*ca.* 13mmHg (lit.,[94] 121-

124°C/15mmHg); ν_{max} (thin film)/cm^{-1} *ca.* 3400-2700 (OH) and 1640 (C=O);

δ_H(60MHz;CDCl$_3$) 2.60 (3H, s, CH$_3$), 6.75-7.0 (2H, m, 3-H and 5-H), 7.5-7.75 (1H, m,

6-H) and 12.45 (1H, s, OH).

4-Fluoro-2-hydroxyacetophenone (**169**).[262] -

The experimental procedure used for the synthesis of 4-bromo-2-hydroxyacetophenone

(**167**) was followed, using 3-fluorophenyl acetate (**165**) (15g, 0.103mol) and AlCl$_3$ (30g,

0.226mol). Work-up afforded an oil which crystallised to give 4-fluoro-2-

hydroxyacetophenone (**169**) (13.2g, 83%), m.p. 22-23°C (lit.,[262] 24°C); ν_{max} (thin

film)/cm^{-1} *ca.* 3500-2500 (OH) and 1640 (C=O); δ_H(400MHz;CDCl$_3$) 2.55 (3H, s, CH$_3$),

6.54-6.60 (2H, m, 3-H and 5-H), 7.70 (1H, dd, *J* 6.5 and 8.7, 6-H) and 12.53 (1H, s,

OH).

2-Hydroxy-4-methoxyacetophenone (**170**).[96] -

A mixture of 2,4-dihydroxyacetophenone (29.4g, 0.193mol), dry acetone (300ml) and

dimethyl sulphate (Me$_2$SO$_4$) (18ml, 0.198mol) was refluxed over potassium carbonate

(30g) for 6 hours. After cooling, the solvent was evaporated off and excess Me$_2$SO$_4$

destroyed by addition of a 25% NH$_3$-ice mixture to the residue. The resulting mixture

was extracted with ethyl acetate (4 x 50ml). The ethereal solution was dried (anhyd.

MgSO$_4$) and the solvent was evaporated to give crude 2-hydroxy-4-methoxyacetophenone

(**170**) (22.4g, 70%), m.p. 46-48°C (lit.,[96] 48°C); δ_H(60MHz;CDCl$_3$) 2.55 (3H, s, CH$_3$),

3.85 (3H, s, OCH$_3$), 6.35-6.60 (2H, m, 3-H and 5-H), 7.60-7.75 (1H, d, *J* 9, 6-H) and

12.85 (1H, s, OH).

1-(4-Bromo-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **(177)**.[94] -

A cooled mixture of 60% KOH (90ml) was added to a cooled solution of 4-bromo-2-

hydroxyacetophenone **(167)** (8g, 0.036mol) and benzaldehyde (6.4g, 0.062mol) in EtOH

(100ml). The resulting mixture was then kept at 4°C for four days with occasional

shaking. The mixture was then diluted with H_2O (200ml) and acidified with dil. HCl. The

pecipitated product was collected at the pump and recrystallised from EtOH to give 1-(4-

bromo-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **(177)** (9.1g, 83%), m.p. 110-112°C

(lit.,[94] 115-116°C); ν_{max} (KBr)/cm^{-1} 1650 (C=O); δ_H(400MHz;CDCl$_3$) 7.06 (1H, dd, *J* 1.7

and 8.5, ArH), 7.20 (1H, d, *J* 1.9, ArH), 7.42-7.44 (3H, m, ArH), 7.54 (1H, d, *J* 15.5,

CH=CH), 7.63-7.65 (2H, m, ArH), 7.73 (1H, d, *J* 8.6, ArH), 7.91 (1H, d, *J* 15.4,

CH=CH) and 12.94 (1H, s, OH).

1-(4-Chloro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **(178)**.[94] -

The experimental procedure employed for the preparation of 1-(4-bromo-2-

hydroxyphenyl)-3-phenyl-2-propen-1-one **(177)** was followed, using 4-chloro-2- - ·

hydroxyacetophenone **(168)** (5g, 0.029mol), benzaldehyde (4g, 0.038mol), 60% KOH

(55ml) and EtOH (60ml). Work-up afforded 1-(4-chloro-2-hydroxyphenyl)-3-phenyl-2-

propen-1-one **(178)** (4.3g, 56%), m.p. 119-121°C (from EtOH) (lit.,[94] 124-125°C); ν_{max}

(KBr)/cm^{-1} 1650 (C=O); δ_H(60MHz;CDCl$_3$) 6.90-7.15 (2H, m, CH=CH), 7.4-8.0 (8H,

m, ArH) and 13.05 (1H, s, OH).

1-(4-Fluoro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one **(179)**.[94] -

The experimental procedure employed for the preparation of 1-(4-bromo-2-

hydroxyphenyl)-3-phenyl-2-propen-1-one (177) was followed, using 4-fluoro-2-

hydroxyacetophenone (169) (9g, 0.058mol), benzaldehyde (7.2g, 0.068mol), 60% KOH

(100ml) and EtOH (100ml). Work-up afforded 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-

propen-1-one (179) (9.5g, 68%), m.p. 102-104°C (from EtOH) ; ν_{max} (KBr)/cm^{-1} 1650

(C=O); δ_H(400MHz;CDCl$_3$) 6.62-6.72 (2H, m, ArH), 7.42-7.45 (3H, m, ArH), 7.55

(1H, d, J 15.4, CH=CH), 7.63-7.66 (2H, m, ArH), 7.89-7.93 (2H, m, CH=CH and

ArH) and 13.20 (1H, s, OH).

1-(2-Hydroxy-4-methoxyphenyl)-3-phenyl-2-propen-1-one (180).[263] -

Benzaldehyde (29.5ml, 0.290mol) and a 50% solution of NaOH (44ml) were added to a

solution of 2-hydroxy-4-methoxyacetophenone (170) (22g, 0.132mol) in EtOH (200ml).

The resulting mixture was shaken and allowed to stand for 24 hours at room temperature

and was then acidified with 2M-HCl and extracted with ether (Et$_2$O) (3 x 60ml). The

combined extracts were washed with 5% aq. NaHCO$_3$ (2 x 30ml), dried (anhyd. MgSO$_4$)

and the solvent was evaporated to afford a crude product which was recrystallised from

EtOH to give 1-(2-hydroxy-4-methoxyphenyl)-3-phenyl-2-propen-1-one (180) (22.6g,

67%), m.p. 101-102°C (lit.,[264] 105-106°C); ν_{max} (KBr)/cm^{-1} 1630 (C=O) and 1570

(CH=CH); δ_H(400MHz;CDCl$_3$) 3.84 (3H, s, OCH$_3$), 6.47-6.50 (2H, m, ArH), 7.40-7.43

(3H, m, ArH), 7.56 (1H, d, J 15.4, CH=CH), 7.62-7.65 (2H, m, ArH), 7.83 (1H, d, J

7.7, ArH), 7.87 (1H, d, J 15.5, CH=CH) and 13.41 (1H, s, OH).

1-(2-Hydroxyphenyl)-3-phenyl-2-propen-1-one (181).[94] -

A cooled solution of potassium hydroxide (KOH) (26.3g, 0.468mol) in H$_2$O (150ml) was

added to a cooled solution of 2-hydroxyacetophenone (26.5ml, 0.220mol) and

benzaldehyde (44.5ml, 0.439mol) in ethanol (300ml). The resulting mixture was then

kept at 4°C for four days with occasional shaking. The mixture was then diluted with

H_2O (200ml) and acidified with dil. HCl. The precipitated product was collected at the

pump and recrystallised from EtOH to give 1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one

(181) (25.7g, 52%), m.p. 85-86°C (lit.,[264] 87-88°C); ν_{max} (KBr)/cm^{-1} 1645 (C=O) and

1595 (CH=CH); δ_H(400MHz;CDCl$_3$) 6.94 (1H, t, ArH), 7.03 (1H, d, J 8.3, ArH), 7.42-

7.51 (3H, m, ArH), 7.64-7.66 (2H, m, ArH), 7.89-7.93 (2H, m, ArH) and 12.83 (1H, s,

OH).

3-(4-Bromophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (182).[94] -

The experimental procedure employed for the preparation of 1-(2-hydroxyphenyl)-3-

phenyl-2-propen-1-one (181) was followed, using 4-bromobenzaldehyde (5g, 0.027mol),

2-hydroxyacetophenone (4.8g, 0.035mol), 60% aq. KOH (43ml) and EtOH (47ml).

Work-up afforded 3-(4-bromophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (182) (4.2g,

51%), m.p. 148-149°C (from EtOH) (lit.,[92,265] 150°C); δ_H(400MHz;CDCl$_3$) 6.91-6.95

(1H, m, ArH), 6.70-7.04 (1H, m, ArH), 7.44-7.57 (4H, m, ArH), 7.62 (1H, d, J 15.5,

CH=CH), 7.64 (1H, d, J 15.9, ArH), 7.82 (1H, d, J 15.5, CH=CH), 7.89 (1H, dd, J

1.4 and 8.1, ArH) and 12.71 (1H, s, OH).

3-(4-Chlorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (183).[94] -

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)-3-phenyl-

2-propen-1-one (181) was followed, using 2-hydroxyacetophenone (30g, 0.220mol), 4-

chlorobenzaldehyde (25g, 0.176mol), 60% KOH (200ml) and EtOH (220ml). Work-up

afforded 3-(4-chlorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (**183**) (37.9g, 83%),

m.p. 145-147°C (from EtOH) (lit.,[92,265] 150°C); ν_{max} (KBr)/cm^{-1} 1650 (C=O);

δ_H(400MHz;CDCl$_3$) 6.92 (1H, t, ArH), 7.00 (1H, d, J 8.4, ArH), 7.37 (2H, d, J 7.4,

ArH), 7.47 (1H, t, ArH), 7.53-7.59 (3H, m, CH=CH and ArH), 7.81 (1H, d, J 15.4,

CH=CH), 7.86 (1H, d, J 8.0, ArH) and 12.74 (1H, s, OH).

3-(4-Fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (**184**).[94] -

The experimental procedure employed for the preparation of 1-(2-hydroxyphenyl)-3-

phenyl-2-propen-1-one (**181**) was followed, using 2-hydroxyacetophenone (5g, 0.037mol),

4-fluorobenzaldehyde (4g, 0.032mol), 60% aq. KOH (55ml) and EtOH (60ml). Work-up

afforded 3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (**184**) (4.51g, 58%),

m.p. 109-111°C (from EtOH) (lit.,[118] 118-119°C); ν_{max} (KBr)/cm^{-1} 1650 (C=O);

δ_H(400MHz;CDCl$_3$) 6.93 (1H, t, ArH), 7.01 (1H, d, J 8.3, ArH), 7.11 (2H, t, ArH),

7.46-7.50 (1H, m, ArH), 7.55 (1H, d, J 15.5, CH=CH), 7.61-7.65 (2H, m, ArH), 7.85

(1H, d, J 15.6, CH=CH), 7.89 (1H, d, J 1.2, ArH) and 12.77 (1H, s, OH).

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**185**).[94] -

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)-3-phenyl-

2-propen-1-one (**181**) was followed, using 2-hydroxyacetophenone (20g, 0.147mol), 4-

methoxybenzaldehyde (40g, 0.294mol), KOH (24.7g, 0.44mol) in H$_2$O (80ml) and EtOH

(400ml). Work-up afforded 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one

(**185**) (24g, 65%) m.p. 101-103°C (from EtOH) ; δ_H(400MHz;CDCl$_3$) 3.83 (3H, s,

OCH$_3$), 6.89-6.93 (3H, m, ArH), 7.00 (1H, d, J 7.8, ArH), 7.44-7.46 (1H, m, ArH),

7.50 (1H, d, J 15.4, CH=CH), 7.59 (2H, d, J 8.7, ArH), 7.87 (1H, d, J 15.4,

CH=CH), 7.89 (1H, dd, J 1.3 and 8.0, ArH) and 12.95 (1H, s, OH).

7-Bromo-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**186**).[94] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (**64**) was followed, using 1-(4-bromo-2-hydroxyphenyl)-3-phenyl-2-

propen-1-one (**177**) (7g, 0.023mol) and H$_3$PO$_4$ (28ml) in EtOH (300ml). Work-up

afforded 7-bromo-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**186**) (3.5g, 50%), m.p.

74-76°C (from EtOH) (lit.,[94] 79-80°C); ν_{max} (KBr)/cm^{-1} 1685 (C=O); δ_H(400MHz;CDCl$_3$)

2.90 (1H, dd, J 3.0 and 16.9, 3-H), 3.07 (1H, dd, J 13.0 and 16.9, 3-H), 5.40 (1H, dd,

J 3.0 and 13.0, 2-H), 7.19 (1H, dd, J 1.8 and 8.4, ArH), 7.26 (1H, d, J 1.76, ArH),

7.36-7.47 (5H, m, ArH) and 7.78 (1H, d, J 8.4, ArH).

7-Chloro-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**187**).[94] -

The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (**64**) was followed, using 1-(4-chloro-2-hydroxyphenyl)-3-phenyl-2-

propan-1-one (3g, 0.012mol), H$_3$PO$_4$ (13ml) and EtOH (150ml). Work-up afforded 7-

chloro-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**187**) (1.5g, 50%), m.p. 53-54°C

(from EtOH) (lit.,[94] 54-55°C); ν_{max} (KBr)/cm^{-1} 1690 (C=O); δ_H(400MHz,CDCl$_3$) 2.90

(1H, dd, J 3.0 and 17.0, 3-H), 3.07 (1H, dd, J 13.0 and 16.9, 3-H), 5.49 (1H, dd, J 3.0

and 13.0, 2-H), 7.03 (1H, dd, J 1.9 and 8.4, ArH), 7.08 (1H, d, J 1.9, ArH), 7.36-7.47

(5H, m, ArH) and 7.86 (1H, d, J 8.4, ArH); δ_C(100MHz;CDCl$_3$) 44.3 (C-2), 79.9 (C-3),

118.3, 119.5, 122.4, 126.1, 128.3, 128.8, 128.9, 138.2, 142.0 and 161.8 (ArC) and

190.8 (C-4).

7-Fluoro-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**188**).[94] -

The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (**64**) was followed, using 1-(4-fluoro-2-hydroxyphenyl)-3-phenyl-2-

propen-1-one (**179**) (10g, 0.041mol), H$_3$PO$_4$ (45ml) and EtOH (300ml). Work-up

afforded 7-fluoro-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**188**) (5.6g, 65%), m.p.

60°C (from EtOH); ν_{max} (KBr)/cm^{-1} 1698 (C=O); δ_H(400MHz;CDCl$_3$) 2.89 (1H, dd, J

3.0 and 16.9, 3-H), 3.07 (1H, dd, J 13.1 and 16.9, 3-H), 5.49 (1H, dd, J 3.0 and 13.1,

2-H), 6.72-6.79 (2H, m, ArH), 7.35-7.48 (5H, m, ArH) and 7.95 (1H, dd, J 6.6 and

8.7, ArH); δ_C(100MHz;CDCl$_3$) 44.2 (C-3), 80.1 (C-2), 104.9, 110.0, 117.9, 126.1,

128.8, 128.9, 129.5, 138.4, 163.1 and 167.5 (ArC) and 190.3 (C-4).

7-Methoxy-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**189**).[94] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (**64**) was followed, using 1-(2-hydroxy-4-methoxyphenyl)-3-phenyl-2-

propen-1-one (**180**) (5.3g, 0.021mol), H$_3$PO$_4$ (13.3ml) and EtOH (200ml). Work-up

afforded 7-methoxy-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**189**) (4g, 75%), m.p.

80-81°C (from EtOH) (lit.,[266] 91°C); ν_{max} (KBr)/cm^{-1} 1665 (C=O); δ_H(400MHz;CDCl$_3$)

2.82 (1H, dd, J 3.0 and 16.9, 3-H), 3.02 (1H, dd, J 13.2 and 16.9, 3-H), 3.82 (3H, s,

OCH$_3$), 5.46 (1H, dd, J 2.9 and 13.2, 2-H), 6.49 (1H, d, J 2.4, ArH), 6.61 (1H, dd, J

2.4 and 8.8, ArH), 7.35-7.48 (5H, m, ArH) and 7.86 (1H, d, J 8.8, ArH);

δ_C(100MHz;CDCl$_3$) 44.3 (C-3), 55.6 (OCH$_3$), 79.9 (C-2), 100.9, 110.2, 114.8, 126.1,

128.7, 128.8, 138.8, 163.5 and 166.2 (ArC) and 190.5 (C-4).

2-(4-Bromophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (190).[94] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (64) was followed, using 3-(4-bromophenyl)-1-(2-hydroxyphenyl)-2-

propen-1-one (182) (3g, 0.010mol), H$_3$PO$_4$ (12ml) and EtOH (250ml). Work-up afforded

2-(4-bromophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (190) (1.2g, 40%), m.p. 117-

118°C (from EtOH) (lit.,[265] 117°C); δ_H(400MHz;CDCl$_3$) 2.87 (1H, dd, J 3.1 and 16.8,

3-H), 3.02 (1H, dd, J 13.0 and 16.8, 3-H), 5.44 (1H, dd, J 3.0 and 13.0, 2-H), 7.03-

7.07 (2H, m, ArH), 7.35 (2H, d, J 8.3, ArH), 7.48-7.57 (3H, m, ArH) and 7.92 (1H,

dd, J 1.5 and 7.8, ArH); δ_C(100MHz;CDCl$_3$) 44.4 (C-3), 78.7 (C-2), 118.0, 120.8,

121.7, 122.6, 127.0, 127.7, 131.9, 136.2, 137.8 and 161.2 (ArC) and 192.1 (C-4).

2-(4-Chlorophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (191).[94] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (64) was followed, using 3-(4-chlorophenyl)-1-(2-hydroxyphenyl)-2-

propen-1-one (182) (10g, 0.039mol), H$_3$PO$_4$ (43ml) and EtOH (400ml). Work-up

afforded 2-(4-chlorophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (191) (3.2g, 32%), m.p.

87-88°C (from EtOH) (lit.,[267] 87°C); ν_{max} (KBr)/cm^{-1} 1700 (C=O); δ_H(400MHz;CDCl$_3$)

2.87 (1H, dd, J 3.0 and 16.8, 3-H), 3.03 (1H, dd, J 13.1 and 16.8, 3-H), 5.46 (1H, dd,

J 3.0 and 13.1, 2-H), 7.05 (2H, t, ArH), 7.38-7.43 (4H, m, ArH), 7.48-7.53 (1H, m,

ArH) and 7.92 (1H, dd, J 1.4 and 7.7, ArH); δ_C(100MHz;CDCl$_3$) 44.2 (C-3), 78.7 (C-2), 118.0, 120.8, 121.7, 127.0, 127.4, 128.9, 134.4, 136.1, 137.2 and 161.2 (ArC) and 191.2 (C-4).

2-(4-Fluorophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (**192**).[94] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**64**) was followed, using 3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one (**184**) (10g, 0.041mol), H$_3$PO$_4$ (43ml) and EtOH (400ml). Work-up afforded 2-(4-fluorophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (**192**) (3.4g, 34%), m.p. 70-71°C (from EtOH) (lit.,[118] 59-60°C); ν_{max} (KBr)/cm^{-1} 1698 (C=O);

δ_H(400MHz;CDCl$_3$) 2.87 (1H, dd, J 3.0 and 16.8, 3-H), 3.05 (1H, dd, J 13.2 and 16.8, 3-H), 5.46 (1H, dd, J 2.9 and 13.2, 2-H), 7.03-7.14 (4H, m, ArH), 7.43-7.52 (3H, m, ArH) and 7.92 (1H, dd, J 1.6 and 7.8, ArH); δ_C(100MHz;CDCl$_3$) 44.6 (C-3), 78.9 (C-2), 115.7, 118.0, 120.9, 127.1, 128.0, 134.6, 136.2, 161.4 and 162.8 (ArC) and 191.6 (C-4).

2,3-Dihydro-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**193**).[94] -

The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**64**) was followed, using 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**185**) (10g, 0.039mol), H$_3$PO$_4$ (44ml) and EtOH (500ml). Work-up afforded 2,3-dihydro-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**54**) (5.2g, 52%), m.p. 80-82°C (from EtOH) ; δ_H(400MHz;CDCl$_3$) 2.85 (1H, dd, J 2.8 and 16.8, 3-H), 3.09 (1H, dd, J 13.3 and 16.8, 3-H), 3.82 (3H, s, OCH$_3$), 5.42 (1H, dd, J 2.8 and 13.3, 2-H)

and 6.94-7.94 (8H, m, ArH); δ_C(100MHz;CDCl$_3$) 44.4 (C-3), 55.3 (OCH$_3$), 79.3 (C-2),

114.1, 118.1, 120.9, 121.4, 127.0, 127.7, 130.7, 136.0, 159.9 and 161.6 (ArC) and

192.1 (C-4).

1-(2-Aminophenyl)-3-phenyl-2-propen-1-one (**196**).[106,133] -

2-Aminoacetophenone (5g, 0.037mol) was added to a solution of benzaldehyde (3.9g,

0.037mol) in EtOH (30ml) containing NaOH (3 pellets) and the resulting mixture was

stirred at room temperature (*ca.* 25°C) for 24 hours. The precipitated product was

filtered and recrystallised from EtOH to afford 1-(2-aminophenyl)-3-phenyl-2-propen-1-

one (**196**) (4.8g, 58%), m.p. 70-72°C (lit.,[133] 71-72°C); ν_{max} (KBr)/cm^{-1} 3450-3300 (NH$_2$)

and 1645 (C=O); δ_H(400MHz;CDCl$_3$) 6.34 (2H, br s, NH$_2$), 6.61-6.79 (2H, m,

CH=CH) and 7.25-7.97 (9H, m, ArH); δ_C(100MHz;CDCl$_3$) 115.8, 117.2, 119.0, 123.1,

128.2, 128.8, 130.0, 130.9, 134.2, 135.2, 142.8, 150.9 (CH=CH and ArC) and 191.6

(C-1).

1-(2-Aminophenyl)-3-(4-bromophenyl)-2-propen-1-one (**197**).[133,134,268] -

The experimental procedure employed for the preparation of 1-(2-aminophenyl)-3-phenyl-

2-propen-1-one (**196**) was followed, using 2-aminoacetophenone (5g, 0.037mol), 4-

bromobenzaldehyde (6.8g, 0.037mol), EtOH (30ml) and NaOH (3 pellets). Work-up

afforded 1-(2-aminophenyl)-3-(4-bromophenyl)-2-propen-1-one (**197**) (9.7g, 87%), m.p.

94°C (from EtOH) ; ν_{max} (KBr)/cm^{-1} 3460-3310 (NH$_2$) and 1650 (C=O);

δ_H(400MHz;CDCl$_3$) 6.33 (2H, br s, NH$_2$), 6.61-6.72 (2H, m, CH=CH) and 7.25-7.87

(8H, m, ArH); δ_C(100MHz;CDCl$_3$) 115.8, 117.3, 119.1, 123.2, 128.2, 128.9, 130.1,

131.0, 134.3, 135.3, 142.9 and 150.9 (CH=CH and ArC) and 191.7 (C-1).

1-(2-Aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one (**198**).[133,134,268] -

The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (**196**) was followed, using 2-aminoacetophenone (5g, 0.037mol), 4-chlorobenzaldehyde (5.2g, 0.037mol), EtOH (30ml) and NaOH (3 pellets). Work-up afforded 1-(2-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-one (**93**) (6.91g, 74%), m.p. 81-82°C (from EtOH) (lit.,[91] 82-84°C); ν_{max} (KBr)/cm^{-1} 3480-3300 (NH$_2$) and 1640 (C=O); δ_H(400MHz;CDCl$_3$) 6.32 (2H, br s, NH$_2$), 6.67-7.84 (10H, m, CH=CH and ArH); δ_C(100MHz;CDCl$_3$) 115.9, 117.3, 118.9, 123.6, 129.1, 129.3, 130.9, 133.8, 134.4, 135.9, 141.4 and 151.1 (CH=CH and ArC) and 191.3 (C-1).

1-(2-Aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one (**199**).[133,134,268] -

The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (**196**) was followed, using 2-aminoacetophenone (5g, 0.037mol), 4-fluorobenzaldehyde (4.6g, 0.037mol), EtOH (30ml) and NaOH (3 pellets). Work-up afforded 1-(2-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one (**199**) (4.6g, 52%), m.p. 119-120°C (from EtOH) (lit.,[91] 119-121°C); ν_{max} (KBr)/cm^{-1} 3500-3300 (NH$_2$) and 1645 (C=O); δ_H(400MHz;CDCl$_3$) 6.31 (2H, br s, NH$_2$), 6.67-7.85 (10H, m, CH=CH and ArH); δ_C(100MHz;CDCl$_3$) 115.9, 116.0, 117.3, 119.0, 122.9, 130.0, 130.9, 131.5, 134.3, 141.6, 151.0, 163.8 (CH=CH and ArC) and 191.4 (C-1).

1-(2-Aminophenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**200**).[106,133] -

The experimental procedure employed for the synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (**196**) was followed, using 2-aminoacetophenone (5g, 0.037mol), 4-methoxybenzaldehyde (5g, 0.037mol), EtOH (30ml) and NaOH (3 pellets). Work-up afforded 1-(2-aminophenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**200**) (6g, 64%), m.p. 89-90°C (from EtOH) (lit., [269] 91-92°C); ν_{max} (KBr)/cm^{-1} 3450-3335 (NH$_2$) and 1645 (C=O); δ_H(400MHz;CDCl$_3$) 3.80 (3H, s, OCH$_3$), 6.34 (2H, br s, NH$_2$) and 6.66-7.85 (10H, m, CH=CH and ArH); δ_C(100MHz;CDCl$_3$) 55.2 (OCH$_3$), 114.2, 115.6, 117.1, 119.1, 120.7, 127.8, 129.8, 130.7, 133.9, 142.6, 150.8 and 161.2 (CH=CH and ArC) and 191.6 (C-1).

1-(2-Aminophenyl)-3-(4-nitrophenyl)-2-propen-1-one (**201**).[133,134,268] -

The experimental procedure employed for the preparation of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (**196**) was followed, using 2-aminoacetophenone (5g, 0.037mol), 4-nitrobenzaldehyde (5.6g, 0.037mol), EtOH (30ml) and NaOH (3 pellets). Work-up gave 1-(2-aminophenyl)-3-(4-nitrophenyl)-2-propen-1-one (**92**) (9.0g, 91%), m.p. 139-141°C (from EtOH) (lit.,[91] 140-142°C); ν_{max} (KBr)/cm^{-1} 3460-3350 (NH$_2$) and 1650 (C=O); δ_H(400MHz;CDCl$_3$) 6.39 (2H, br s, NH$_2$) and 6.69-8.26 (10H, m, CH=CH and ArH); δ_C(100MHz;CDCl$_3$) 115.9, 117.4, 118.5, 124.1, 127.0, 128.7, 130.9, 134.8, 139.6, 141.5, 148.3 and 151.3 (CH=CH and ArC) and 190.6 (C-1).

2-Phenyl-1,2,3,4-tetrahydro-4-quinolone (**202**).[133] -

A stirred mixture of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (**196**) (3g, 0.013mol), orthophosphoric acid (40ml) and glacial acetic acid (40ml) was boiled under reflux for 3

hours. The cooled mixture was poured into iced water and the resulting precipitate was

filtered, and then recrystallised from ethanol to afford 2-phenyl-1,2,3,4-tetrahydro-4-

quinolone (98) (1.5g, 52%), m.p. 149°C (lit.,[133] 149-150°C); ν_{max} (KBr)/cm^{-1} 3345 (NH)

and 1660 (C=O); δ_H(400MHz;CDCl$_3$) 2.76 (1H, dd, J 3.8 and 16.2, 3-H), 2.88 (1H, dd,

J 13.6 and 16.2, 3-H), 4.52 (1H, br s, NH), 4.74 (1H, dddd, J 3.8 and 13.6, 2-H), 6.71

(1H, d, J 8.2, ArH), 6.78 (1H, t, ArH), 7.31-7.46 (6H, m, ArH) and 7.87 (1H,d, J 7.9,

ArH); δ_C(100MHz;CDCl$_3$) 46.4 (C-3), 58.5 (C-2), 115.9, 118.4, 119.1, 126.6, 127.6,

128.5, 129.0, 135.4, 141.0 and 151.5 (ArC) and 193.2 (C-4).

2-(4-Bromophenyl)-1,2,3,4-tetrahydro-4-quinolone (203).[133,134] -

The experimental procedure employed for the preparation of 2-phenyl-1,2,3,4-tetrahydro-

4-quinolone (202) was followed, using 1-(2-aminophenyl)-3-(4-bromophenyl)-2-propen-1-

one (90) (8g, 0.026mol), orthophosphoric acid (50ml) and glacial acetic acid (50ml).

Work-up afforded 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4-quinolone (94) (2.8g, 35%),

m.p. 169-171°C (from EtOH) (lit.,[134] 171°C); ν_{max} (KBr)/cm^{-1} 3310 (NH) and 1645

(C=O); δ_H(400MHz;CDCl$_3$) 2.72 (1H, dd, J 4.3 and 16.2, 3-H), 2.80 (1H, dd, J 13.0

and 16.2, 3-H), 4.53 (1H, br s, NH), 4.69 (1H, dd, J 4.3 and 13.0, 2-H), 6.72 (1H, d, J

8.2, ArH), 6.79 (1H, t, ArH), 7.31-7.52 (5H, m, ArH) and 7.84 (1H, dd, J 1.4 and 7.9,

ArH); δ_C(100MHz;CDCl$_3$) 46.3 (C-3), 57.9 (C-2), 116.0, 118.7, 119.0, 122.2, 127.6,

128.3, 132.1, 135.5, 140.1 and 151.3 (ArC) and 192.8 (C-4).

2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone (204).[133] -

The experimental procedure employed for the synthesis of 2-phenyl-1,2,3,4-tetrahydro-4-

quinolone (202) was followed, using 1-(2-aminophenyl)-3-(4-chlorophenyl)-2-propen-1-

one (198) (6g, 0.024mol), H_3PO_4 (40ml) and acetic acid (40ml). Work-up afforded 2-(4-

chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone (97) (2.5g, 42%), m.p. 147°C (from EtOH)

(lit.,[265] 146°C); ν_{max} (KBr)/cm^{-1} 3320 (NH) and 1650 (C=O); δ_H(400MHz;CDCl$_3$) 2.73

(1H, dddd, J 1.6 and 4.3, 3-H), 4.22 (1H, dd, J 13.1 and 16.2, 3-H), 4.50 (1H, br s,

NH), 4.72 (1H, dd, J 4.2 and 13.1, 2-H), 6.72 (1H, d, J 8.2, ArH), 6.79 (1H, t, ArH),

7.32-7.86 (6H, m, ArH); δ_C(100MHz;CDCl$_3$) 46.4 (C-3), 57.9 (C-2), 115.9, 118.7,

119.1, 127.6, 128.0, 129.2, 134.2, 135.5, 139.5 and 151.3 (ArC) and 192.8 (C-4).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone (205).[133] -

The experimental procedure employed for the preparation of 2-phenyl-1,2,3,4-tetrahydro-

4-quinolone (202) was followed, using 1-(2-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-

one (199) (4.5g, 0.019mol), H_3PO_4 (40ml) and acetic acid (40ml). Work-up afforded 2-

(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone (205) (2.3g, 50%), m.p. 117-119°C

(from EtOH) (lit.,[265] 116-118°C); ν_{max} (KBr)/cm^{-1} 3320 (NH) and 1660 (C=O);

δ_H(400MHz;CDCl$_3$) 2.72 (1H, dd, J 4.0 and 16.4, 3-H), 2.82 (1H, dd, J 13.4 and 16.2,

3-H), 4.52 (1H, br s, NH), 4.71 (1H, dd, J 4.0 and 13.4, 2-H), 6.70-6.80 (2H, m,

ArH), 7.07 (2H, t, ArH), 7.31-7.43 (3H, m, ArH) and 7.85 (1H, dd, J 1.4 and 7.9,

ArH); δ_C(100MHz;CDCl$_3$) 46.4 (C-3), 57.8 (C-2), 115.8, 115.9, 118.5, 119.0, 127.5,

128.3, 135.5, 136.8 and 151.5 (ArC) and 193.1 (C-4).

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-4-quinolone (206).[133] -

The experimental procedure employed for the preparation of 2-phenyl-1,2,3,4-tetrahydro-

4-quinolone (**202**) was followed, using 1-(2-aminophenyl)-3-(4-methoxyphenyl)-2-propen-

1-one (**200**) (5.5g, 0.022mol), H_3PO_4 (25ml) and acetic acid (45ml). Work-up afforded

2-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-quinolone (**206**) (3.2g, 57%), m.p. 113-114°C

(from EtOH) (lit.,[265] 112-114°C); ν_{max} (KBr)/cm⁻¹ 3300 (NH) and 1645 (C=O);

δ_H(400MHz;CDCl$_3$) 2.71 (1H, dd, J 3.6 and 16.1, 3-H), 2.84 (1H, dd, J 14.0 and 16.1,

3-H), 3.81 (3H, s, OCH$_3$), 4.52 (1H, br s, NH), 4.65 (1H, dd, J 3.6 and 14.0, 2-H) and

6.61-7.86 (8H, m, ArH); δ_C(100MHz;CDCl$_3$) 46.5 (C-3), 55.3 (OCH$_3$), 57.9 (C-2),

114.3, 115.9, 118.3, 119.0, 127.6, 127.8, 133.1, 135.3, 151.6 and 159.6 (ArC) and

193.5 (C-4).

2-(4-Nitrophenyl)-1,2,3,4-tetrahydro-4-quinolone (**207**).[133,134] -

The experimental procedure employed for the preparation of 2-phenyl-1,2,3,4-tetrahydro-

4-quinolone (**202**) was followed, using 1-(2-aminophenyl)-3-(4-nitrophenyl)-2-propen-1-

one (**92**) (10g, 0.037mol), H_3PO_4 (50ml) and acetic acid (50ml). Work-up afforded 2-(4-

nitrophenyl)-1,2,3,4-tetrahydro-4-quinolone (**207**) (4.36g, 44%), m.p. 193-195°C (from

EtOH) (lit.,[134] 194°C); ν_{max} (KBr)/cm⁻¹ 3370 (NH) and 1675 (C=O); δ_H(400MHz;CDCl$_3$)

2.84 (2H, m, 3-H), 4.53 (1H, br s, NH), 4.89 (1H, dd, J 7.0 and 10.1, 2-H), 6.75-6.86

(2H, m, ArH), 7.36-7.40 (1H, m, ArH), 7.63-7.66 (2H, m, ArH), 7.88 (1H, dd, J 1.5

and 8.0, ArH) and 8.24-8.27 (2H, m, ArH); δ_C(100MHz;CDCl$_3$) 46.1 (C-3), 57.9 (C-2),

116.1, 119.2, 119.3, 124.3, 127.5, 127.7, 135.7, 148.0, 148.3 and 150.9 (ArC) and

191.8 (C-4).

4-Bromoepoxystyrene (**211**).[138] -

MCPBA (50%; 4.7g, 0.027mol) was added in small portions to a stirred solution of 4-bromostyrene (5g, 0.027mol) in CH_2Cl_2-phosphate buffer (the buffer was prepared by adding aqueous 0.1M Na_2HPO_4 to 0.1M NaH_2PO_4 until the pH was 8.0) (400ml; 1:1) at 0°C. After stirring for 5 hours at room temperature, more MCPBA (3g) was added. The mixture was stirred at room temperature overnight after which it was filtered and the organic layer separated, washed with $NaHCO_3$ and water and dried (anhydrous Na_2SO_4). The solvent was evaporated to give a residue which was purified by flash chromatography [elution with EtOAc-hexane (2:8)] to afford 4-bromoepoxystyrene (**211**) (3.89g, 72%); δ_H(400MHz;CDCl$_3$) 2.74 (1H, dd, J 2.5 and 5.4, CH$_2$), 3.13 (1H, dd, J 4.12 and 5.4, CH$_2$), 3.81 (1H, dd, J 2.6 and 3.8, CH), 7.14 (2H, d, J 8.4, 2-H and 6-H) and 7.46 (2H, d, J 8.4, 3-H and 5-H).

4-Chloroepoxystyrene (**212**).[138] -

The experimental procedure employed for the synthesis of 4-bromoepoxystyrene (**211**) was followed, using 4-chlorostyrene (6g, 0.043mol) and MCPBA (50%; 14.9g, 0.043mol). Work-up afforded a crude product which was purified by flash chromatography [elution with EtOAc-hexane (2:8)] to give 4-chloroepoxystyrene (**212**) (4.3g, 65%); δ_H(400MHz;CDCl$_3$) 2.72 (1H, dd, J 2.5 and 5.5, CH$_2$), 3.11 (1H, dd, J 4.6 and 5.4, CH$_2$), 3.79 (1H, dd, J 2.6 and 4.0, CH), 7.18 (2H, d, J 8.5, 2-H and 6-H) and 7.29 (2H, d, J 8.4, 3-H and 5-H); δ_C(100MHz;CDCl$_3$) 51.0 (CH$_2$), 51.6 (CH), 126.7, 128.5, 133.8 and 136.1 (ArC).

4-Fluoroepoxystyrene (**213**).[138] -

The experimental procedure employed for the synthesis of 4-bromoepoxystyrene (211)

was followed, using 4-fluorostyrene (4.5g, 0.037mol) and MCPBA (50%; 6.4g,

0.037mol). Work-up afforded a crude product which was purified by flash

chromatography [elution with EtOAc-hexane (2:8)] to give 4-fluoroepoxystyrene (213)

(2.4g, 49%); δ_H(400MHz;CDCl$_3$) 2.75-2.77 (1H, m, CH$_2$), 3.12-3.14 (1H, m, CH$_2$), 3.84

(1H, m, CH), 7.03 (2H, t, 2-H and 6-H) and 7.25 (2H, dd, J 5.8 and 8.2, 3-H and 5-H);

δ_C(100MHz;CDCl$_3$) 51.0 (CH$_2$), 51.7 (CH), 115.4 ($^2J_{CF}$ 22.1, C-3 and C-5), 127.1 ($^3J_{CF}$

9.1, C-2 and C-6), 133.3 ($^4J_{CF}$ 3.0, C-1) and 162.6 ($^1J_{CF}$ 246.5, C-4).

Attempted preparation of 4-methoxyepoxystyrene (214).[138] -

The experimental procedure employed for the synthesis of 4-bromoepoxystyrene (211)

was followed, using 4-methoxystyrene (4.5g, 0.034mol) and MCPBA (50%; 11.6g,

0.034mol). Work-up followed by flash chromatography gave two fractions:

(i) starting material, and

(ii) 4-methoxybenzaldehyde (identified by ^{1}H NMR, ^{13}C NMR and IR).

2-Mercaptobenzenemethanol (216).[144] -

Thiosalicylic acid (4.36g, 0.028mol) in dry THF (50ml) was added dropwise to a slurry

of LiAlH$_4$ (2g, 0.052mol) in THF (80ml) under nitrogen and the resulting mixture was

stirred for 24 hours. EtOAc (10ml) and then 10% aqueous H$_2$SO$_4$ (40ml) were added

dropwise and the mixture was filtered, separated, and the aqueous layer extracted with

EtOAc (2 x 30ml). The combined organic layer was washed with brine, dried (anhydrous

Na$_2$SO$_4$) and the solvent was evaporated to give an oil which later crystallised to afford 2-

mercaptobenzenemethanol (216) (2.61g, 65%), m.p. 32-33°C (lit.,[144] 31-32°C);

δ_H(400MHz;CDCl$_3$) 2.05 (1H, br s, OH), 3.66 (1H, s, SH), 4.71 (2H, s, CH$_2$), 7.15-

7.19 (2H, m, ArH) and 7.30-7.35 (2H, m, ArH); δ_C(100MHz;CDCl$_3$) 64.1 (CH$_2$), 126.2,

128.3, 128.6, 130.1, 131.3 and 138.7 (ArC).

2,3-Dihydro-2-phenyl-4H-benzothiopyran-4-one (220).[145,148,270] -

A mixture of 3-phenyl-3-thiophenylpropionic acid (13.0g, 0.050mol) and POCl$_3$ (60.0g,

0.390mol) was boiled under reflux for 20 minutes. The cooled reaction mixture was

added slowly to an ice-cold water bath (150ml) and the oily layer was separated. The

oily layer was dissolved in ethyl acetate (50ml) and was washed sequentially with 10%

aqueous NaOH (2 x 30ml) and water (2 x 30ml) and then dried (anhydrous MgSO$_4$). The

solvent was removed *in vacuo* and the product was purified by flash chromatography

(elution with benzene) to afford 2,3-dihydro-2-phenyl-4*H*-benzothiopyran-4-one (220)

(6.1g, 50.4%), m.p. 55-57°C (from CS$_2$-hexane) (lit.,[145] 55-56°C);ν_{max} (KBr)/cm^{-1} 1673

(C=O); δ_H(400MHz;CDCl$_3$) 3.20 (1H, dd, *J* 3.1 and 16.4, 3-H), 3.31 (1H, dd, *J* 13.0

and 16.4, 3-H), 4.72 (1H, dd, *J* 3.1 and 13.0, 2-H), 7.18-7.43 (8H, m, ArH) and 8.15

(1H, dd, *J* 1.0 and 8.0, ArH); δ_C(100MHz;CDCl$_3$) 45.5 (C-3), 46.7 (C-2), 125.2, 127.2,

127.4, 128.3, 128.4, 128.9, 129.2, 133.4, 138.4 and 142.1 (ArC) and 194.3 (C-4).

7-Bromo-3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (221).[26] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-1,5-

benzodioxepin-4-one (65) was followed, using 7-bromo-2,3-dihydro-2-phenyl-4*H*-1-

benzopyran-4-one (186) (0.4g, 1.32mmol), MCPBA (50%; 0.5g, 1.45mmol) and CH$_2$Cl$_2$

(20ml). Work-up and flash chromatography afforded 8-bromo-2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**221**) (0.25g, 59%); δ_H(400MHz;CDCl$_3$) 3.09-3.18 (2H, m, 3-H), 5.72 (1H, dd, J 5.9 and 7.1, 4-H), 7.06 (1H, d, J 8.6, 8-H), 7.19 (1H, d, J 2.3, 6-H), 7.30 (1H, dd, J 2.3 and 8.6, 9-H) and 7.35-7.42 (5H, m, PhH); δ_C(100MHz;CDCl$_3$) 38.4 (C-3), 83.6 (C-4), 118.4 (C-7), 121.7 (C-6), 126.0 (C-2' and C-6'), 127.3 (C-8), 128.7 (C-9), 128.9 (C-3' and C-5'), 129.2 (C-4'), 138.1 (C-9a), 144.7 (C-1'), 145.9 (C-5a) and 166.7 (C-2).

7-Chloro-3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (**222**).[26] -

The experimental procedure employed for the synthesis of 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) was followed, using 7-chloro-2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one (**187**) (0.7g, 3.0mmol), MCPBA (50%; 1.4g, 4.0mmol) and CH$_2$Cl$_2$ (50ml). Work-up and flash chromatography [elution with EtOAc-hexane (3:7)] afforded 7-chloro-3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (**222**) (0.5g, 60%); δ_H(400MHz;CDCl$_3$) 3.07-3.17 (2H, m, 3-H), 5.71 (1H, t, 4-H), 7.03 (1H, d, J 1.9, 8-H), 7.09-7.16 (2H, m, 9-H and 6-H) and 7.35-7.42 (5H, m, PhH); δ_C(100MHz;CDCl$_3$) 38.2 (C-3), 83.5 (C-4), 121.2 (C-6), 124.3 (C-8), 125.5 (C-9), 125.9 (C-2' and C-6'), 128.8 (C-3' and C-5'), 129.1 (C-4'), 131.0 (C-7), 138.0 (C-9a), 144.1 (C-1'), 145.6 (C-5a) and 166.6 (C-2).

7-Fluoro-3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (**223**).[26] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) was followed, using 7-fluoro-2,3-dihydro-2-phenyl-4H-1-

benzopyran-4-one (188) (0.5g, 2.0mmol), MCPBA (50%; 0.8g, 2.30mmol) and CH_2Cl_2

(50ml). Work-up and flash chromatography afforded 8-fluoro-2,3-dihydro-2-phenyl-1,5-

benzodioxepin-4-one (223) (0.35g, 67%); δ_H(400MHz;CDCl₃) 2.87 (1H, dd, J 3.0 and

16.9, 3-H), 3.05 (1H, dd, J 13.1 and 16.9, 3-H), 5.48 (1H, dd, J 3.0 and 13.1, 4-H),

6.71-6.77 (2H, m, 9-H and 8-H), 7.35-7.47 (5H, m, PhH) and 7.94 (1H, dd, J 6.6 and

8.6, 6-H).

4-(4-Bromophenyl)-3,4-dihydro-1,5-benzodioxepin-2-one (225).[26] -

The procedure employed for the preparation of 3,4-dihydro-4-phenyl-1,5-benzodioxepin-

2-one (65) was followed, using 2-(4-bromophenyl)-2,3-dihydro-4H-1-benzopyran-4-one

(190) (0.61g, 1.91mmol) and MCPBA (50%; 0.72g, 2.10mmol) in dry CH_2Cl_2 (20ml).

The mixture was refluxed for 72 hours. Work-up gave a crude product which was

purified by flash chromatography [elution with EtOAc-hexane (1:3)] to afford 4-(4-

bromophenyl)-3,4-dihydro-1,5-benzodioxepin-2-one (225) (0.5g, 78%), m.p. 115-117°C

(lit.,[26] 115-117°C); δ_H(400MHz;CDCl₃) 2.99 (1H, dd, J 6.7 and 13.4, 3-H), 3.16 (1H,

dd, J 5.9 and 13.4, 3-H), 5.65 (1H, t, 4-H), 7.02-7.04 (1H, m, 8-H), 7.13-7.16 (1H, m,

9-H), 7.17-7.20 (2H, m, 7-H and 6-H), 7.26 (2H, d, J 8.4, 2'-H and 6'-H) and 7.51

(2H, d, J 8.4, 3'-H and 5'-H); δ_C(100MHz;CDCl₃) 38.4 (C-3), 82.7 (C-4), 120.4 (C-6),

123.0 (C-4'), 124.0 (C-8), 125.9 (C-7), 126.6 (C-9), 127.8 (C-2' and C-6'), 131.9 (C-3'

and C-5'), 137.5 (C-9a), 145.0 (C-1'), 145.6 (C-5a) and 167.0 (C-4).

4-(4-Chlorophenyl)-3,4-dihydro-1,5-benzodioxepin-2-one (226).[26] -

The experimental procedure employed for the synthesis of 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (65) was followed, using 2-(4-chlorophenyl)-2,3-dihydro-4H-1-benzopyran-4-one (191) (0.23g, 0.88mmol), MCPBA (50%; 0.33g, 0.97mmol) and dry CH_2Cl_2 (50ml). Work-up and flash chromatography afforded 2-(4-chlorophenyl)-2,3-dihydro-1,5-benzodioxepin-4-one (226) (0.12g, 50%), m.p. 113-115°C (lit.,[26] 113-114°C); ν_{max} (KBr)/cm^{-1} 1745 (C=O); δ_H(400MHz;CDCl$_3$) 3.02 (1H, dd, J 6.9 and 13.3, 3-H), 3.17 (1H, dd, J 5.8 and 13.4, 3-H), 5.67 (1H, t, 4-H), 7.02-7.04 (1H, m, 8-H), 7.13-7.16 (1H, m, 7-H), 7.17-7.20 (2H, m, 9-H and 6-H) and 7.31-7.38 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H); δ_C(100MHz;CDCl$_3$) 38.4 (C-3), 82.7 (C-4), 120.5 (C-6), 124.0 (C-8), 125.9 (C-9), 126.6 (C-7), 127.5 (C-2' and C-6'), 129.0 (C-3' and C-5'), 134.9 (C-4'), 137.0 (C-1'), 145.0 (C-9a), 145.6 (C-5a) and 167.1 (C-2).

3,4-Dihydro-4-(4-fluorophenyl)-1,5-benzodioxepin-2-one (227).[26] -

The experimental procedure employed for the preparation of 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one (65) was followed, using 2,3-dihydro-2-(4-fluorophenyl)-4H-1-benzopyran-4-one (192) (3g, 12.3mmol), MCPBA (50%; 4.65g, 13.5mmol) and CH_2Cl_2 (50ml). Work-up afforded 2,3-dihydro-2-(4-fluorophenyl)-1,5-benzodioxepin-4-one (227) (1.77g, 60%), m.p. 125-127°C (lit.,[26] 125-127°C); ν_{max} (KBr)/cm^{-1} 1750 (C=O); δ_H(400MHz;CDCl$_3$) 3.03 (1H, dd, J 7.0 and 13.3, 3-H), 3.16 (1H, dd, J 5.8 and 13.3, 3-H), 5.68 (1H, t, 4-H), 7.01-7.03 (1H, m, 9-H), 7.06-7.11 (2H, m, 3'-H and 5'-H), 7.13-7.16 (1H, m, 7-H), 7.17-7.20 (2H, m, 8-H and 6-H) and 7.35-7.39 (2H, m, 2'-H and 6'-H); δ_C(100MHz;CDCl$_3$) 38.5 (C-3), 82.8 (C-4), 115.7 ($^2J_{CF}$ 22.1, C-3' and C-5'), 120.4 (C-6), 124.1 (C-9), 125.8 (C-8), 126.6 (C-7), 128.0 ($^3J_{CF}$ 9.1, C-2' and C-6'), 134.4

($^4J_{CF}$ 3.0, C-1'), 145.3 ($^1J_{CF}$ 59.4, C-4'), 161.7 (C-9a), 164.2 (C-5a) and 167.2 (C-2).

3,4-Dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one (**228**).[26] -

The experimental procedure employed for the preparation of 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) was followed, using 2,3-dihydro-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one (**193**) (0.6g, 2.4mmol), MCPBA (50%; 2.06g, 6.0mmol) and CH_2Cl_2 (20ml). The mixture was refluxed for 72 hours. Work-up and flash chromatography [elution with EtOAc-hexane (1:3)] afforded 2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzodioxepin-4-one (**228**) (0.36g, 56%), m.p. 120-121°C (lit.,[26] 121-122°C); ν_{max} (KBr)/cm^{-1} 1755 (C=O); δ_H(400MHz;CDCl$_3$) 3.08-3.10 (2H, m, 3-H), 3.81 (3H, s, OCH$_3$), 5.68 (1H, t, 4-H), 6.90 (2H, d, *J* 8.8, 3'-H and 5'-H), 6.97-6.99 (1H, m, 8-H), 7.11-7.14 (1H, m, 7-H), 7.15-7.18 (2H, m, 9-H and 6-H) and 7.28 (2H, d, *J* 8.8, 2'-H and 6'-H); δ_C(100MHz;CDCl$_3$) 38.4 (C-3), 55.3 (OCH$_3$), 83.2 (C-4), 114.1 (C-3' and C-5'), 120.3 (C-6), 124.4 (C-8), 125.6 (C-9), 126.4 (C-7), 127.6 (C-2' and C-6'), 130.6 (C-1'), 145.0 (C-9a), 145.7 (C-5a), 160.1 (C-4') and 167.6 (C-2).

3-Bromo-3-phenylpropionic acid (**231**). -

A mixture of cinnamic acid (20g, 0.14mol) and HBr (45% in AcOH) (138ml, 0.78mol) was heated at 70°C for 12 hours. The resulting mixture was quenched with ice-water and the resulting crystals were filtered and then recrystallised from ethanol to afford 3-bromo-3-phenylpropionic acid (**231**) (18.9g, 60%); δ_H(400MHz;CDCl$_3$) 3.27 (1H, dd, *J* 6.1 and 16.7, 2-H), 3.40 (1H, dd, *J* 8.9 and 16.7, 2-H), 5.38 (1H, dd, *J* 6.1 and 8.9, 3-H), 7.28-7.44 (5H, m, ArH) and 9.27 (1H, br s, OH); δ_C(100MHz;CDCl$_3$) 44.5 (C-2), 47.0 (C-3),

127.2, 128.8, 128.9 and 140.5 (ArC) and 175.6 (C-1).

2H-1,5-Benzodioxepin-2-one (**239**).[26] -

A mixture of chromone (2g, 0.014mol) and MCPBA (50%; 9.6g, 0.027mol) in dry

CH$_2$Cl$_2$ (50ml) was boiled under reflux for 48 hours. After cooling, the solvent was

evaporated and the residue was dissolved in EtOAc (50ml). The resulting solution was

washed with 10% aqueous NaHCO$_3$ (3 x 20ml), dried (anhydrous MgSO$_4$) and the solvent

was then evaporated. The residue was purified by flash chromatography [elution with

EtOAc-hexane (4:6)] to afford three fractions:

(i) starting material,

(ii) *2H-1,5-Benzodioxepin-2-one* (**239**) (0.1g, 4.4%), m.p. 150-152°C (Found: M$^+$

162.032. C$_9$H$_6$O$_3$ requires *M*, 162.032); ν_{max} (KBr)/cm^{-1} 1605 (C=O);

δ_H(400MHz;CDCl$_3$) 6.48 (1H, s, 3-H), 7.37-7.41 (1H, m, 7-H), 7.48 (1H, d, *J* 8.6,

9-H), 7.64-7.69 (1H, m, 8-H), 8.00 (1H, s, 4-H) and 8.25 (1H, dd, *J* 1.5 and 8.1, 6-H);

δ_C(100MHz;CDCl$_3$) 118.5 (C-3), 121.9 (C-6), 124.6 (C-8), 125.6 (C-9), 133.5 (C-7),

138.5 (C-4), 141.8 (C-9a), 156.3 (C-5a) and 173.4 (C-2); *m/z* 162 (M$^+$, 100%).

and

(iii) 2,3-epoxy-4*H*-1-benzopyran-4-one (**240**) (0.25g, 11%), m.p. 98-100°C (lit.,[171] 65-

66°C); δ_H(400MHz;CDCl$_3$) 2.66 (1H, d, *J* 2.4, 2-H), 3.69 (1H, d, *J* 2.4, 3-H), 7.05

(1H, dd, *J* 0.6 and 8.4, 8-H), 7.12-7.16 (1H, m, 6-H), 7.55 (1H, dddd, *J* 1.8, 7.3, 9.0

and 15.7, 7-H) and 7.88 (1H, dd, *J* 1.8 and 7.9, 5-H); δ_C(100MHz;CDCl$_3$) 55.3 (C-3),

77.2 (C-2), 118.0, 119.8, 123.3, 127.1, 136.2 and 155.4 (ArC) and 188.1 (C-4), and

3,4-Dihydro-4-phenyl-1,5-benzoxathiepin-2-one (**250**). -

METHOD 1

A mixture of 2-hydroxythiophenol (2g, 0.016mol), cinnamic acid (2.3g, 0.016mol) and

HBr (45% in AcOH) (10ml) was heated under reflux until most of the starting material

had reacted (checked by NMR). Ethyl acetate was added to the reaction mixture and the

resulting solution was washed with aqueous NaOH. The aqueous layer was acidified

(dilute HCl), extracted with EtOAc (2 x 30ml), dried (anhydrous MgSO$_4$) and the solvent

was evaporated *in vacuo* to give a residue which, together with a catalytic amount of

p-toluenesulphonic acid in toluene (150ml) was refluxed under Dean-Stark apparatus for

12 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc,

washed with aqueous NaOH and dried over anhydrous MgSO$_4$. The solvent was

evaporated and the residue was purified by flash chromatography [elution with EtOAc-

hexane (3:7) to afford two fractions:

(i) starting material, and

(ii) *3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one* (**250**) (0.35g, 9%), m.p. 94-95°C; ν_{max}

(KBr)/cm^{-1} 1770 (C=O); δ_H(400MHz;CDCl$_3$) 2.93-3.02 (2H, m, 3-H), 4.70 (1H, dd, *J*

7.2 and 9.5, 4-H), 7.17-7.29 (7H, m, ArH), 7.41-7.45 (1H, m, 8-H) and 7.54 (1H, dd, *J*

1.7 and 8.1, 6-H); δ_C(100MHz;CDCl$_3$) 40.0 (C-3), 50.3 (C-4), 120.3 (C-9), 121.6 (C-

1′), 126.3 (C-2′ and C-6′), 126.6 (C-4′), 128.2 (C-7), 128.9 (C-3′ and C-5′), 131.4 (C-

8), 136.4 (C-6), 141.8 (C-5a), 154.1 (C-9a) and 167.5 (C-2); *m/z* 256 (M$^+$, 10.1%) and

131 (100%).

METHOD 2

A mixture of 2-hydroxythiophenol (3g, 23.81mmol) and cinnamic acid (3.5g, 23.81mmol)

was heated at 150°C under N_2 until most of the acid had reacted (checked by NMR).

p-Toluenesulphonic acid (catalytic amount) and toluene were then added and the resulting

mixture was boiled under reflux in the Dean-Stark apparatus for 10 hours. The solvent

was evaporated and the residue taken up in EtOAc. The resulting solution was washed

with aqueous NaOH (3 x 30ml), dried (anhydrous $MgSO_4$) and the solvent was

evaporated. The residue obtained was purified by flash chromatography [elution with

EtOAc-hexane (2:8)] to give *3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one* (**250**) (1.5g,

24%).

Attempted preparation of 3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one (250).[145,270] -

A stirred mixture of cinnamic acid (10g, 0.067mol) and thiophenol (8g, 0.073mol) in

HBr-acetic acid (45%, 10g) was boiled under reflux for 9 hours. The cooled reaction

mixture was treated with water (300ml) and was then steam-distilled to remove the·

unreacted thiophenol. The hot aqueous layer was decanted and the oily residue was

washed twice with hot water. The residue was dissolved in chloroform (60ml) and dried

(anhyd. $MgSO_4$). The solvent was evaporated to afford 3-phenyl-3-thiophenylpropionic

acid (12.1g, 69%), m.p. 85-87°C (from hexane); ν_{max} (KBr)/cm^{-1} 3000 (OH) and 1705

(C=O); δ_H(400MHz;CDCl$_3$) 2.96 (1H, dd, J 8.1 and 13.9, 3-H), 3.01 (1H, dd, J 7.6 and

13.9, 3-H), 4.63 (1H, t, 4-H), 7.20-7.60 (10H, m, ArH) and 11.39 (1H, br s, OH);

δ_C(100MHz;CDCl$_3$) 40.6 (C-2), 48.6 (C-3), 127.6, 127.9, 128.4, 128.8, 133.4, 133.5

and 140.2 (ArC) and 177.0 (C-1).

4-(4-Bromophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **(251)**. -

The experimental procedure employed for the preparation of 3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one **(250)** was followed, using 2-hydroxythiophenol (2g, 0.016mol), 4-bromocinnamic acid (3.6g, 0.016mol) and HBr (10ml). Work-up and purification by flash chromatography [elution with EtOAc-hexane (3:7)] afforded two fractions:

(i) starting material, and

(ii) *4-(4-bromophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one* **(251)** (0.22g, 4%), m.p. 56-58°C (Found: M^+ 351.983. Calc. for $C_{15}H_{13}O_3BrS$: M, 351.977); ν_{max} (KBr)/cm^{-1} 1760 (C=O); δ_H(400MHz;CDCl$_3$) 2.92-3.04 (2H, m, 3-H), 4.72 (1H, dd, J 7.1 and 10.4, 4-H), 7.12 (2H, d, J 8.4, 3'-H and 5'-H), 7.25-7.29 (2H, m, 7-H and 9-H), 7.44 (2H, d, J 7.9, 2'-H and 6'-H), 7.47-7.51 (1H, m, 8-H) and 7.57 (1H, dd, J 1.7 and 8.2, 6-H); δ_C(100MHz;CDCl$_3$) 39.8 (C-3), 49.6 (C-4), 120.4 (C-9), 121.3 (C-4'), 122.1 (C-1'), 126.7 (C-7), 128.1 (C-3' and C-5'), 131.6 (C-8), 132.1 (C-2' and C-6'), 136.4 (C-6), 140.6 (C-5a), 154.1 (C-9a) and 167.1 (C-2); m/z 334 (M^+, 6.1%) and 209 (100%).

4-(4-Chlorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **(252)**. -

The experimental procedure employed for the preparation of 3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one **(250)** was followed, using 2-hydroxythiophenol (2g, 0.016mol), HBr (10ml) and 4-chlorocinnamic acid (2.9g, 0.016mol). Work-up followed by flash chromatography afforded two fractions:

(i) starting material, and

(ii) *4-(4-chlorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one* (**252**) (0.61g, 13%), m.p.

60-62°C (Found: M^+ 290.016. Calc. for $C_{15}H_{11}ClO_2S$: M, 290.017); ν_{max} (KBr)/cm^{-1}

1760 (C=O); δ_H(400MHz;CDCl$_3$) 2.95-3.04 (2H, m, 3-H), 4.74 (1H, dd, J 7.1 and 9.3,

4-H), 7.18 (2H, d, J 8.4, 3'-H and 5'-H), 7.25-7.30 (4H, m, 2'-H, 6'-H, 7-H and 9-H),

7.47-7.51 (1H, m, 8-H) and 7.56-7.59 (1H, m, 6-H); δ_C(100MHz;CDCl$_3$) 39.8 (C-3),

49.5 (C-4), 120.4 (C-9), 121.3 (C-5a), 126.7 (C-7), 127.7 (C-3' and C-5'), 129.1 (C-2'

and C-6'), 131.5 (C-8), 134.0 (C-4'), 136.3 (C-6), 140.1 (C-1'), 154.0 (C-9a) and 167.2

(C-2); m/z 290 (M^+, 7.7%) and 165 (100%).

4-(4-Fluorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one (**253**). -

The experimental procedure employed for the preparation of 3,4-dihydro-4-phenyl-1,5-

benzoxathiepin-2-one (**250**) was followed, using 2-hydroxythiophenol (2g, 0.016mol), 4-

fluorocinnamic acid (2.6g, 0.016mol) and HBr (10ml). Work-up followed by flash

chromatography [elution with EtOAc-hexane (3:7)] afforded two fractions:

(i) starting material, and

(ii) *4-(4-fluorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one* (**253**) (0.44g, 10%), m.p. 77-

80°C (Found: M^+ 270.046. Calc. for $C_{15}H_{11}FO_2S$: M, 270.046); ν_{max} (KBr)/cm^{-1} 1760

(C=O); δ_H(400MHz;CDCl$_3$) 2.95-3.04 (2H, m, 3-H), 4.75 (1H, dd, J 7.0 and 9.3, 4-H),

7.00 (2H, t, 3'-H and 5'-H), 7.21-7.23 (2H, m, 2'-H and 6'-H), 7.24-7.28 (2H, m, 7-H

and 9-H), 7.46-7.51 (1H, m, 8-H) and 7.58 (1H, dd, J 1.6 and 7.6, 6-H);

δ_C(100MHz;CDCl$_3$) 40.1 (C-3), 49.5 (C-4), 115.8 ($^2J_{CF}$ 22.1, C-3' and C-5'), 120.4 (C-

9), 121.4 (C-5a), 126.6 (C-7), 128.1 ($^3J_{CF}$ 8.1, C-2' and C-6'), 131.5 (C-8), 136.3 (C-6),

137.5 ($^4J_{CF}$ 3.0, C-1'), 154.1 (C-9a), 162.4 ($^1J_{CF}$ 247.5, C-4') and 167.3 (C-2); m/z 274

(M^+, 12.5%) and 149 (100%).

4-(4-Methoxyphenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one (**254**). -

The experimental procedure employed for the synthesis of 3,4-dihydro-4-phenyl-1,5-

benzoxathiepin-2-one (**250**) was followed, using 2-hydroxythiophenol (2g, 0.016mol),

HBr (10ml) and 4-methoxycinnamic acid (2.8g, 0.016mol). Work-up followed by flash

chromatography [elution with EtOAc-hexane (3:7)] afforded three fractions:

(i) starting material,

(ii) *4-(4-methoxyphenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one* (**254**) (0.2g, 4.4%);

δ_H(400MHz;CDCl$_3$) 2.99 (2H, d, J 12.7, 3-H), 3.78 (3H, s, OCH$_3$), 4.74 (1H, t, 4-H),

6.84 (2H, d, J 8.8, 3'-H and 5'-H), 7.16 (2H, d, J 8.7, 2'-H and 6'-H), 7.23-7.27 (2H,

m, 7-H and 9-H), 7.45-7.49 (1H, m, 8-H) and 7.58 (1H, dd, J 1.7 and 6.6, 6-H);

δ_C(100MHz;CDCl$_3$) 40.1 (C-3), 49.8 (OCH$_3$), 55.2 (C-4), 114.2 (C-3' and C-5'); 120.2

(C-9), 121.7 (C-5a), 126.5 (C-7), 127.5 (C-2' and C-6'), 131.2 (C-8), 133.8 (C-1'),

136.3 (C-6), 154.0 (C-9a), 159.3 (C-4') and 167.5 (C-2); m/z 286 (M^+, 11.1%) and 161

(100%).

(iii) *1-(2-hydroxyphenylthio)-1-(4-methoxyphenyl)ethane* (**255**) (0.24g, 5.2%) (Found: M^+

260.086. Calc. for C$_{15}$H$_{16}$O$_2$S: M, 260.087); ν_{max} (thin film)/cm^{-1} 3500-3300 (OH);

δ_H(400MHz;CDCl$_3$) 1.61 (3H, d, J 7.0, CH$_3$), 3.79 (3H, s, OCH$_3$), 4.09 (1H, q, CH),

6.68 (1H, s, OH), 6.78-6.82 (3H, m, ArH), 6.94 (1H, d, J 7.9, ArH), 7.11 (2H, d, J

8.6, ArH) and 7.22-7.27 (2H, m, ArH); δ_C(100MHz;CDCl$_3$) 21.5 (CH$_3$), 48.7 (OCH$_3$),

55.2 (CH), 113.8, 114.5, 118.0, 120.3, 128.1, 131.4, 134.4, 136.9, 157.4 and 158.9

(ArC); m/z 260 (M$^+$, 1.4%) and 135 (100%).

Attempted preparation of 3,4-dihydro-1,5-benzoxathiepin-2-one (257) : oxidation of 2,3-dihydro-4H-benzothiopyran-4-one (256). -

MCPBA (50%;, 6.9g, 0.020mol) was added slowly[1] to a solution of 2,3-dihydro-4H-

benzothiopyran-4-one (256) (3g, 0.018mol) in dry CH$_2$Cl$_2$ (50ml). [Thin layer

chromatography (TLC) showed the reaction to be complete after addition of MCPBA].

The solvent was evaporated and the residue was taken up in EtOAc (50ml). The resulting

solution was washed with aqueous NaHCO$_3$ (3 x 20ml), dried (anhydrous MgSO$_4$) and the

solvent was evaporated. The resulting residue was purified by flash chromatography

[elution with EtOAc-hexane (1:1)] to afford two fractions:

(i) 2,3-dihydro-4H-benzothiopyran-4-one 1-oxide (258) (2.28g, 70%) (Found: M$^+$

180.023. Calc. for C$_9$H$_8$O$_2$S: M, 180.025); ν_{max} (thin film)/cm^{-1} 1690 (C=O) and 1055

(SO); δ_H(400MHz;CDCl$_3$) 2.80-2.89 (1H, m, 3-H), 3.38-3.46 (3H, m, 2-H and 3-H),

7.61 (1H, t, 6-H), 7.71 (1H, t, 7-H), 7.82 (1H, d, J 7.7, 8-H) and 8.10 (1H, d, J 7.7, 5-

H); δ_C(100MHz;CDCl$_3$) 30.2 (C-3), 46.6 (C-2), 128.4, 128.8, 129.1, 132.0, 134.5 and

145.4 (ArC) and 191.9 (C-4); m/z 180 (M$^+$, 9.5%) and 152 (100%); and

---

[1]MCPBA must be added slowly, otherwise a violent exothermic reaction occurs with the
release of unpleasant fumes.

(ii) 2,3-dihydro-4H-benzothiopyran-4-one-1,1-dioxide (**259**) (0.81g, 23%), m.p. 131-132°C (from dilute AcOH) (lit.,[179] 131-133°C) (Found: M$^+$ 196.018. Calc. for $C_9H_8O_3S$: M, 196.019); ν_{max} (KBr)/cm^{-1} 1675 (C=O) and 1155 (SO$_2$); δ_H(400MHz;CDCl$_3$) 3.39 (2H, t, 3-H), 3.68 (2H, t, 2-H), 7.72 (1H, t, 6-H), 7.80 (1H, t, 7-H), 7.98 (1H, d, J 7.8, 8-H) and 8.09 (1H, d, J 7.8, 5-H); δ_C(100MHz;CDCl$_3$) 36.7 (C-3), 49.2 (C-2), 123.6, 128.7, 130.2, 133.3, 134.9 and 141.4 (ArC) and 190.1 (C-4); m/z 196 (M$^+$, 16.2%) and 104 (100%).

Note: When 1 equivalent of MCPBA was used, only 2,3-dihydro-4H-benzothiopyran-4-one-1-oxide was obtained.

Attempted oxidation of 2,3-dihydro-4H-benzothiopyran-4-one 1,1-dioxide (**259**) with MCPBA in CH$_2$Cl$_2$ resulted in recovery of the starting material.

2,3-Dihydro-3-phenyl-4,1-benzoxathiepin-5-one (**263**) *and 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one* (**266**). -

A mixture of thiosalicylic acid (1.0g, 6.5mmol), epoxystyrene (0.77g, 6.5mmol) and p-toluenesulphonic acid (0.03g) in benzene (50ml) was boiled in a Dean-Stark apparatus for 12 hours. After cooling, the solvent was evaporated and the residue was dissolved in EtOAc (50ml). The resulting solution was washed with aqueous NaHCO$_3$ (2 x 30ml), dried (anhydrous MgSO$_4$) and the solvent evaporated. The residue was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford two fractions:

(i) *2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one* (**263**) (0.43g, 26%), m.p. 38-40°C; ν_{max}

(thin film)/cm⁻¹ 1720 (C=O); δ_H(400MHz;CDCl₃) 3.29 (1H, dd, J 6.8 and 14.3, 2-H),

3.46 (1H, dd, J 6.0 and 14.3, 2-H), 5.74 (1H, dd, J 6.0 and 6.8, 3-H), 7.24-7.36 (6H,

m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 6-H and 8-H), 7.42 (1H, ddd, J 1.5, 7.6 and 15.2, 7-

H) and 8.14 (1H, dd, J 1.1 and 7.8, 9-H); δ_C(100MHz;CDCl₃) 40.6 (C-2), 83.3 (C-3),

124.1 (C-4'), 126.5 (C-8), 127.4 (C-5a or C-9a), 127.6 (C-6), 128.6 (C-3' and C-5'),

129.5 (C-2' and C-6'), 132.4 (C-9), 133.5 (C-7), 134.5 (C-5a or C-9a), 138.1 (C-1') and

163.7 (C-5); m/z 256 (M⁺, 21%) and 136 (100%); and

(ii) *2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one* (**266**) (0.12g, 7.2%);

δ_H(400MHz;CDCl₃) 3.93 (1H, dd, J 4.0 and 12.2, 3-H), 4.04 (1H, dd, J 7.6 and 12.2, 3-

H), 6.10 (1H, dd, J 4.0 and 7.6, 2-H), 7.17-7.45 (8H, m, ArH) and 8.12-8.14 (1H, m,

ArH); δ_C(100MHz;CDCl₃) 66.0 (C-3), 77.9 (C-2), 124.7 (C-4'), 125.9 (C-5a or C-9a),

126.7 (C-3' and C-5'), 128.5 (C-8), 128.7 (C-2' and C-6'), 131.0 (C-6), 131.9 (C-9),

132.7 (C-7), 136.8 (C-5a or C-9a), 138.2 (C-1') and 166.0 (C-5).

2,3-Dihydro-3-(4-bromophenyl)-4,1-benzoxathiepin-5-one (**261**) *and 2,3-dihydro-2-(4-*

bromophenyl)-4,1-benzoxathiepin-5-one (**264**). -

The experimental procedure employed for the preparation of 2,3-dihydro-3-phenyl-4,1-

benzoxathiepin-5-one (**263**) and 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one (**266**) was

followed, using thiosalicylic acid (0.58g, 3.77mmol), 4-bromoepoxystyrene (**211**) (0.7g,

3.77mmol) and a catalytic amount of *p*-toluene sulphonic acid (0.01g). Work-up followed

by flash chromatography [elution with EtOAc-hexane (4:6)] afforded two fractions:

(i) *2,3-dihydro-3-(4-bromophenyl)-4,1-benzoxathiepin-5-one* (**261**) (0.16g, 13%), m.p. 50-52°C (Found: **M**$^+$, 333.967. Calc. for $C_{15}H_{11}BrO_2S$: *M*, 333.966); ν_{max} (thin film)/cm^{-1} 1721 (C=O); δ_H(400MHz;CDCl$_3$) 3.20 (1H, dd, *J* 6.4 and 14.4, 2-H), 3.33 (1H, dd, *J* 6.1 and 14.4, 2-H), 5.66 (1H, t, 3-H), 7.12 (2H, d, *J* 8.3, 2'-H and 6'-H), 7.20-7.25 (2H, m, 6-H and 8-H), 7.37-7.41 (3H, m, 3'-H, 5'-H and 7-H) and 8.08 (1H, d, *J* 7.8, 9-H); δ_C(100MHz;CDCl$_3$) 40.0 (C-2), 82.9 (C-3), 121.6 (C-5a), 124.1 (C-9a), 126.7 (C-8), 127.6 (C-6), 131.3 (C-3' and C-5'), 131.8 (C-2' and C-6'), 132.6 (C-9), 133.5 (C-1'), 133.6 (C-7), 137.9 (C-4') and 163.6 (C-5); *m/z* 336 (**M**$^+$, 6%) and 165 (100%); and

(ii) *2,3-dihydro-2-(4-bromophenyl)-4,1-benzoxathiepin-5-one* (**264**) (0.02g, 2%); δ_H(400MHz;CDCl$_3$) 3.92 (1H, dd, *J* 4.0 and 12.2, 3-H), 4.02 (1H, dd, *J* 7.3 and 12.2, 3-H), 6.03 (1H, dd, *J* 4.0 and 7.3, 2-H), 7.16-7.21 (1H, m, 8-H), 7.30-7.34 (3H, m, 2'-H, 6'-H and 6-H), 7.48-7.52 (3H, m, 3'-H, 5'-H and 7-H) and 8.09 (1H, dd, *J* 1.3 and 7.4, 9-H).

2,3-Dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepin-5-one (**262**) *and 2,3-dihydro-2-(4-chlorophenyl)-4,1-benzoxathiepin-5-one* (**265**). -

The experimental procedure employed for the preparation of 2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one (**263**) and 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one (**266**) was followed, using thiosalicylic acid (3.4g, 22.08mmol), 4-chloroepoxystyrene (3g, 22.08mmol) and *p*-toluenesulphonic acid (0.05g). Work-up and purification by flash chromatography [elution with EtOAc-hexane (3:7)] afforded two fractions:

(i) *2,3-dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepin-5-one* (**262**) (0.5g, 8%), m.p. 30-

32°C (Found: M^+ 290.018. Calc. for $C_{15}H_{11}ClO_2S$: M, 290.017); ν_{max} (thin film)/cm^{-1}

1720 (C=O); δ_H(400MHz;CDCl$_3$) 3.25 (1H, dd, J 6.4 and 14.4, 2-H), 3.39 (1H, dd, J

6.1 and 14.4, 2-H), 5.70 (1H, t, 3-H), 7.21-7.24 (3H, m, 2'-H, 6'-H and 6-H), 7.26-

7.30 (3H, m, 3'-H, 5'-H and 8-H), 7.43 (1H, ddd, J 1.5, 7.6 and 15.2, 7-H) and 8.12

(1H, dd, J 1.1 and 7.8, 9-H); δ_C(100MHz;CDCl$_3$) 39.7 (C-2), 82.8 (C-3), 126.5 (C-8),

127.5 (C-6), 128.6 (C-3' and C-5'), 130.8 (C-2' and C-6'), 132.4 (C-9), 132.9 (C-4'),

133.3 (C-9a), 133.5 (C-7), 137.8 (C-1') and 163.6 (C-5); m/z 290 (M$^+$, 9%) and 165

(100%); and

(ii) *2,3-dihydro-2-(4-chlorophenyl)-4,1-benzoxathiepin-5-one* (**265**) (0.1g, 2%);

δ_H(400MHz;CDCl$_3$) 3.84 (1H, dd, J 4.0 and 12.2, 3-H), 3.94 (1H, dd, J 7.4 and 12.2, 3-

H), 5.97 (1H, dd, J 4.0 and 7.3, 2-H), 7.07-7.12 (2H, m, 6-H and 8-H), 7.24-7.35 (5H,

m, 2'-H, 3'-H, 5'-H, 6'-H and 7-H) and 8.02 (1H, dd, J 1.2 and 7.4, 9-H);

δ_C(100MHz;CDCl$_3$) 65.7 (C-3), 77.1 (C-2), 124.8 (C-8), 125.7 (C-5a), 128.1 (C-3' and

C-5'), 128.9 (C-2' and C-6'), 131.1 (C-6), 131.8 (C-9), 132.8 (C-7), 134.4 (C-4'); 135.4

(C-9a), 138.3 (C-1') and 165.8 (C-5).

2,3-Dihydro-3-(4-bromophenyl)-4,1-benzoxathiepine (**267**). -

A mixture of 2-mercaptobenzenemethanol (**216**) (1g, 7.0mmol), 4-bromoepoxystyrene

(**211**) (1.42g, 7.0mmol) and p-toluenesulphonic acid (0.03g) in benzene (50ml) was

heated under reflux in a Dean Stark apparatus for 72 hours. After cooling, the solvent

was evaporated and the oily residue was purified by flash chromatography [elution with

EtOAc-hexane (4:6)] to afford *2,3-dihydro-3-(4-bromophenyl)-4,1-benzoxathiepine* (**267**)

(1.05g, 47%), m.p. 42-44°C (Found: M^+ 319.988. Calc. for $C_{15}H_{13}BrOS$: M, 319.987);

δ_H(400MHz;CDCl$_3$) 3.06 (1H, dd, J 5.4 and 14.2, 2-H), 3.27 (1H, dd, J 7.1 and 14.2, 2-

H), 4.88 (2H, q, 5-H), 5.33 (1H, dd, J 5.5 and 7.1, 3-H), 6.96 (1H, dd, J 0.6 and 7.6,

8-H), 7.07 (1H, ddd, J 1.8, 7.6 and 14.4, 7-H), 7.09-7.14 (2H, m, 6-H and 9-H), 7.19

(2H, d, J 8.4, 3'-H and 5'-H) and 7.47 (2H, d, J 8.4, 2'-H and 6'-H);

δ_C(100MHz;CDCl$_3$) 41.4 (C-2), 69.7 (C-5), 81.7 (C-3), 120.8 (C-4'), 124.5 (C-7), 125.6

(C-8), 127.1 and 127.2 (C-6 and C-9), 129.4 (C-9a), 131.1 (C-3' and C-5'), 131.3 (C-2'

and C-6'), 131.5 (C-1') and 135.1 (C-5a); m/z 320 (M^+, 5%) and 151 (100%).

2,3-Dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepine (**268**). -

The experimental procedure employed for the preparation of 2,3-dihydro-3-(4-

bromophenyl)-4,1-benzoxathiepine (**267**) was followed, using 2-mercaptobenzenemethanol

(**216**) (1g, 7.0mmol), 4-chloroepoxystyrene (**212**) (1.10g, 7.0mmol) and *p*-toluene-

sulphonic acid (0.03g). Work-up followed by flash chromatography [elution with EtOAc-

hexane (4:6)] afforded *2,3-dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepine* (**268**) (0.83g,

43%); δ_H(400MHz;CDCl$_3$) 3.08 (1H, dd, J 5.5 and 14.2, 2-H), 3.28 (1H, dd, J 7.0 and

14.2, 2-H), 4.89 (2H, q, 5-H), 5.33 (1H, dd, J 5.5 and 7.0, 3-H), 6.96 (1H, dd, J 0.6

and 7.6, 9-H), 7.06 (1H, ddd, J 1.8, 7.6 and 14.4, 7-H), 7.09-7.17 (2H, m, 6-H and 8-

H), 7.24 (2H, d, J 8.5, 2'-H and 6'-H) and 7.32 (2H, d, J 8.5, 3'-H and 5'-H);

δ_C(100MHz;CDCl$_3$) 41.5 (C-2), 69.8 (C-5), 81.9 (C-3), 124.6 (C-7), 125.6 (C-9), 127.2

and 127.3 (C-6 and C-8), 128.4 (C-3' and C-5'), 129.5 (C-9a), 130.8 (C-2' and C-6'),

131.6 (C-4'), 132.7 (C-1') and 134.6 (C-5a); m/z 276 (M^+, 8.4%) and 151 (100%).

2,3-Dihydro-3-(4-fluorophenyl)-4,1-benzoxathiepine (**269**). -

The experimental procedure employed for the synthesis of 2,3-dihydro-3-(4-

bromophenyl)-4,1-benzoxathiepine (**267**) was followed, using 2-mercaptobenzenemethanol

(**216**) (1g, 7.0mmol), 4-fluoroepoxystyrene (**213**) (1g, 7.0mmol) and p-toluenesulphonic

acid (0.03g). Work-up and flash chromatography [EtOAc-hexane (3:7) as eluant]

afforded *2,3-dihydro-3-(4-fluorophenyl)-4,1-benzoxathiepine* (**269**) (0.96g, 53%);

δ_H(400MHz;CDCl$_3$) 3.06 (1H, dd, J 5.6 and 14.2, 2-H), 3.27 (1H, dd, J 6.9 and 14.2, 2-

H), 4.89 (2H, q, 5-H), 5.31 (1H, dd, J 5.7 and 7.0, 3-H), 6.96-7.10 (6H, m, ArH) and

7.24-7.28 (2H, m, ArH).

2,3-Dihydro-3-phenyl-4,1-benzoxathiepine (**270**). -

A mixture of 2-mercaptobenzenemethanol (**216**) (1g, 7.00mmol), epoxystyrene (0.86g,

7.00mmol) and p-toluenesulphonic acid (0.03g) in benzene (50ml) was heated under

reflux in a Dean-Stark apparatus for 72 hours. After cooling, the solvent was evaporated

and the oily residue was purified by flash chromatography [elution with EtOAc-hexane

(3:7)] to afford *2,3-dihydro-3-phenyl-4,1-benzoxathiepine* (**270**) (0.81g, 48%);

δ_H(400MHz;CDCl$_3$) 3.15 (1H, dd, J 5.8 and 14.1, 2-H), 3.39 (1H, dd, J 7.0 and 14.1, 2-

H), 4.93 (2H, q, 5-H), 5.41 (1H, dd, J 5.8 and 7.0, 3-H), 6.98 (1H, dd, J 0.6 and 7.7,

8-H), 7.08 (1H, ddd, J 2.0, 7.6 and 14.0, 7-H), 7.12-7.17 (2H, m, 6-H and 9-H), 7.32-

7.43 (5H, m, ArH); δ_C(100MHz;CDCl$_3$) 42.3 (C-2), 69.9 (C-5), 82.3 (C-3), 124.4 (C-7),

125.6 (C-8), 126.9 (C-4'), 127.1 (C-9), 127.3 (C-6), 128.3 (C-3' and C-5'), 129.4 (C-2'

and C-6'), 129.6 (C-9a), 131.9 (C-1') and 136.2 (C-5a); m/z 242 (M$^+$, 18.5%) and 151

(100%).

1-Acetyl-1,2,3,4-tetrahydro-2-phenyl-4-quinolone (**271**) *and 4-Acetoxy-1-acetyl-1,2-*

dihydro-2-phenylquinoline (**275**).[133] -

1,2,3,4-Tetrahydro-2-phenyl-4-quinolone (**202**) (2g, 8.97mmol) was refluxed in Ac_2O

(20ml) for 3 hours. After cooling, the reaction mixture was poured into iced water

(100ml). The resulting solution was extracted with EtOAc (3 x 30ml), dried (anhyd.

$MgSO_4$) and the solvent evaporated. The residue obtained was purified by flash

chromatography [elution with EtOAc-hexane (4:6)] to afford two fractions:

(i) 1-acetyl-1,2,3,4-tetrahydro-2-phenyl-4-quinolone (**271**) (0.21g, 9%), m.p. 167-168°C

(from EtOH) (lit.,[133] 166-167°C); δ_H(400MHz;$CDCl_3$) 2.42 (3H, s, OCH_3), 3.23 (1H, dd,

J 5.8 and 17.9, 3-H), 3.36 (1H, dd, *J* 1.8 and 18.0, 3-H), 6.46 (1H, br s, 2-H), 7.12-

7.23 (6H, m, ArH), 7.43-7.47 (1H, m, 7-H) and 7.92 (1H, dd, *J* 1.6 and 7.9, 5-H);

δ_C(100MHz;$CDCl_3$) 23.3 (CH_3), 42.6 (C-3), 54.7 (C-2), 125.09 (C-8), 125.5 (C-6),

126.1 (C-4a), 126.8 (C-3' andC-5'), 127.3 (C-4'), 127.6 (C-5), 128.6 (C-2' and C-6'),

134.4 (C-7), 137.9 (C-1'), 141.8 (C-8a) and 170.1 (C-4); *m/z* 265 (M^+, 49%) and 146

(100%); and

(ii) 4-acetoxy-1-acetyl-1,2-dihydro-2-phenylquinoline (**275**) (1.0g, 36%), m.p. 119-121°C

(from EtOH) (lit.,[133] 120-121°C); δ_H(400MHz;$CDCl_3$) 2.27 (3H, s, $COCH_3$), 2.35 (3H, s,

$OCOCH_3$), 6.07 (1H, d, *J* 6.6, 3-H), 6.71 (1H, br s, 2-H), 7.01 (1H, br s, ArH), 7.13-

7.24 (6H, m, ArH) and 7.33 (2H, d, *J* 6.6, ArH); δ_C(100MHz;$CDCl_3$) 20.8 ($COCH_3$),

22.8 ($OCOCH_3$), 53.0 (C-2), 117.5 (C-3), 121.7, 124.9, 125.4, 127.6, 127.8, 128.4,

135.4, 138.2 and 143.7 (ArC) and 168.7 and 170.1 ($COCH_3$ and $OCOCH_3$); *m/z* 307

(M^+, 15%) and 146 (100%).

1-Acetyl-1,2,3,4-tetrahydro-2-(4-bromophenyl)-4-quinolone (**272**) *and 4-Acetoxy-1-acetyl-*

1,2-dihydro-2-(4-bromophenyl)quinoline (**276**).[133] -

The experimental procedure employed for the preparation of 1-acetyl-1,2,3,4-tetrahydro-

2-phenyl-4-quinolone (**271**) and 4-acetoxy-1-acetyl-1,2-dihydro-2-phenylquinoline (**275**)

was followed, using 2-(4-bromophenyl)-1,2,3,4-tetrahydro-4-quinolone (**203**) (4.0g,

13.25mmol) and Ac_2O (50ml). Work-up followed by flash chromatography [EtOAc-

hexane (4:6)] afforded two fractions:

(i) *1-acetyl-1,2,3,4-tetrahydro-2-(4-bromophenyl)-4-quinolone* (**272**) (0.21g, 5%), m.p.

161-162°C (from EtOH) (Found: M^+ 343.023. Calc. for $C_{17}H_{14}BrNO_2$: *M*, 343.021);

ν_{max} (KBr)/cm^{-1} 1655 (NC=O) and 1695 (C=O); δ_H(400MHz;CDCl₃) 2.41 (3H, s,

OCH₃), 3.22 (1H, dd, *J* 5.6 and 18.1, 3-H), 3.29 (1H, dd, *J* 2.1 and 18.0, 3-H), 6.43

(1H, br s, 2-H), 7.03 (2H, d, *J* 8.1, 3'-H and 5'-H), 7.15-7.19 (2H, m, 6-H and 8-H),

7.30 (2H, d, *J* 8.3, 2'-H and 6'-H), 7.44-7.48 (1H, m, 7-H) and 7.91 (1H, dd, *J* 1.5 and

7.8, 5-H); δ_C(100MHz;CDCl₃) 23.3 (CH₃), 42.4 (C-3), 54.1 (C-2), 121.7, 125.0, 125.7,

125.9, 127.4, 128.5, 131.7, 134.5, 137.1 and 141.6 (ArC), 170.1 (C-4) and 192.7

(NCO); and

(ii) *4-acetoxy-1-acetyl-1,2-dihydro-2-(4-bromophenyl)quinoline* (**276**) (2.9g, 63%), m.p.

104-106°C (from EtOH) (Found: M^+ 385.033. Calc. for $C_{19}H_{16}NO_3Br$: 385.031); ν_{max}

(KBr)/cm^{-1} 1760 (OC=O) and 1655 (C=O); δ_H(400MHz;CDCl₃) 2.26 (3H, s, COCH₃),

2.35 (3H, s, OCOCH₃), 6.02 (1H, d, *J* 6.5, 3-H), 6.66 (1H, br s, 2-H), 6.99 (1H, br s,

8-H), 7.13-7.20 (3H, m, ArH), 7.23 (2H, d, *J* 8.1, ArH) and 7.32 (2H, d, *J* 8.5, ArH);

δ_C(100MHz;CDCl₃) 20.8 (COCH₃), 22.7 (OCOCH₃), 52.0 (br s, C-2), 116.7 (br s, C-8),

121.8, 121.9, 124.5, 124.8, 125.5, 128.5, 129.5, 131.5, 135.2, 137.2 and 144.0 (C-3

and ArC), 168.6 ($COCH_3$) and 170.1 ($OCOCH_3$); m/z 385 (M^+, 9.9%) and 146 (100%).

1-Acetyl-2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone (**273**) *and 4-Acetoxy-1-acetyl-*

1,2-dihydro-2-(4-chlorophenyl)quinoline (**277**).[133] -

The experimental procedure employed for the preparation of 1-acetyl-1,2,3,4-tetrahydro-

2-phenyl-4-quinolone (**271**) and 4-acetoxy-1-acetyl-1,2-dihydro-2-phenylquinoline (**275**)

was followed, using 2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone (**204**) (0.54g,

2.26mmol) and Ac_2O (10ml). Work-up followed by flash chromatography [elution with

EtOAc-hexane (4:6)] afforded two fractions:

(i) *1-acetyl-2-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-quinolone* (**273**) (0.25g, 39%), m.p.

168-170°C (from EtOH) (Found: M^+ 299.073. Calc. for $C_{17}H_{14}ClNO_2$: M, 299.071);

ν_{max} (KBr)/cm^{-1} 1655 (NC=O) and 1695 (C=O); δ_H(400MHz;$CDCl_3$) 2.41 (3H, s, CH_3),

3.22 (1H, dd, J 5.6 and 18.0, 3-H), 3.30 (1H, dd, J 2.0 and 18.0, 3-H), 6.46 (1H, br s,

2-H), 7.10 (2H, d, J 8.7, 3'-H and 5'-H), 7.15-7.20 (4H, m, 2'-H, 6'-H, 6-H and 8-H),

7.44-7.49 (1H, m, 7-H) and 7.92 (1H, dd, J 1.6 and 7.8, 5-H); δ_C(100MHz;$CDCl_3$) 23.3

(CH_3), 42.5 (C-3), 54.1 (br s, C-2), 125.0 (C-8), 125.7 (C-6), 126.0 (C-4a), 127.4 (C-

5), 128.2 (C-3' and C-5'), 128.8 (C-2' and C-6'), 133.6 (C-4'), 134.5 (C-7), 136.6 (C-

1'), 141.6 (C-8a), 170.1 (C-4) and 192.8 (NC=O); m/z 299 (M^+, 42.8%) and 146

(100%); and

(ii) *4-acetoxy-1-acetyl-1,2-dihydro-2-(4-chlorophenyl)quinoline* (**277**) (0.35g, 45%), m.p.

84-85°C (from EtOH) (Found: M^+, 341.083. Calc. for $C_{19}H_{16}NO_3Cl$: M, 341.082); ν_{max}

(KBr)/cm⁻¹ 1760 (OC=O) and 1655 (C=O); δ_H(400MHz;CDCl₃) 2.26 (3H, s, COCH₃),

2.35 (3H, s, OCOCH₃), 6.02 (1H, d, J 6.5, 3-H), 6.67 (1H, br s, 2-H), 6.98 (1H, br s,

8-H), 7.13-7.30 (7H, m, ArH); δ_C(100MHz;CDCl₃) 20.8 (COCH₃), 22.7 (OCOCH₃),

52.0 (br s, C-2), 116.5 (br s, C-8), 121.8, 124.5, 124.8, 125.6, 128.5, 128.6, 129.1,

133.7, 135.1, 136.7 and 144.0 (C-3, C-4 and ArC), 168.7 (COCH₃) and 170.2

(OCOCH₃); m/z 341 (M⁺, 18.1%) and 146 (100%).

1-Acetyl-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone (**274**) *and 4-Acetoxy-1-acetyl-1,2-dihydro-2-(4-fluorophenyl)quinoline* (**278**).[133] -

The experimental procedure employed for the preparation of 1-acetyl-1,2,3,4-tetrahydro-2-phenyl-4-quinolone (**271**) and 4-acetoxy-1-acetyl-1,2-dihydro-2-phenylquinoline (**275**) was followed, using 2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone (**205**) (1.3g, 5.39mmol) and Ac₂O (20ml). Work-up and flash chromatography afforded two fractions:

(i) *1-acetyl-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-quinolone* (**274**) (0.1g, 6.6%), m.p. 128-130°C (from EtOH) (Found: M⁺ 283.102. Calc. for C₁₇H₁₄FO₂N: M, 283.101); ν_{max} (KBr)/cm⁻¹ 1695 (NC=O) and 1665 (C=O); δ_H(400MHz;CDCl₃) 2.39 (3H, s, CH₃), 3.21 (1H, dd, J 5.6 and 18.0, 3-H), 3.28 (1H, dd, J 2.1 and 18.0, 3-H), 6.43 (1H, br s, 2-H), 6.83 (3H, t, 3'-H, 5'-H and 8-H), 7.08-7.16 (3H, m, 2'-H, 6'-H and 6-H), 7.41-7.45 (1H, m, 7-H) and 7.89 (1H, dd, J 1.6 and 7.8, 5-H); δ_C(100MHz;CDCl₃) 23.2 (CH₃), 42.5 (C-3), 54.0 (C-2), 115.4 ($^2J_{CF}$ 21.1, C-3'), 124.9 (C-8), 125.5 (C-6), 125.8 (C-4a), 127.2 (C-5), 128.4 ($^3J_{CF}$ 9.1, C-2'), 133.7 ($^4J_{CF}$ 3.0, C-1'), 134.4 (C-7), 141.5 (C-8a), 161.8 ($^1J_{CF}$ 246.5, C-4'), 170.0 (C-4) and 192.8 (NC=O); m/z 283 (M⁺, 44.3%) and 146 (100%); and

(ii) *4-acetoxy-1-acetyl-1,2-dihydro-2-(4-fluorophenyl)quinoline* (**278**) (0.97g, 55%), m.p.

72-74°C (from EtOH); ν_{max} (KBr)/cm^{-1} 1760 (OC=O) and 1655 (C=O);

δ_H(400MHz;CDCl$_3$) 2.26 (3H, s, COCH$_3$), 2.35 (3H, s, OCOCH$_3$), 6.02 (1H, d, J 6.6,

3-H), 6.69 (1H, br s, 2-H), 6.88 (2H, t, ArH), 6.99 (1H, br s, 8-H), 7.17-7.23 (3H, m,

ArH) and 7.33 (2H, dd, J 5.5 and 8.7, ArH); δ_C(100MHz;CDCl$_3$) 20.8 (COCH$_3$), 22.7

(OCOCH$_3$), 51.9 (C-2), 115.3 ($^2J_{CF}$ 21.1, ArC), 117.2 (C-3), 121.8, 124.6, 124.8, 125.5,

128.5, 129.6 ($^3J_{CF}$ 8.1), 133.9 ($^4J_{CF}$ 3.0), 135.2, 143.9 and 162.4 ($^1J_{CF}$ 246.5) (ArC),

168.7 (OC=O) and 170.1 (NC=O); m/z 325 (M$^+$, 19%) and 240 (100%).

1-Acetyl-2,3-dihydro-2-(4-bromophenyl)-1,4-benzodiazepin-5-one (**283**) *and 1-Acetyl-2,3-*

dihydro-2-(4-bromophenyl)-1,5-benzodiazepin-4-one (**280**).[133] -

A stirred solution of 1-acetyl-1,2,3,4-tetrahydro-2-(4-bromophenyl)-4-quinolone (**272**)

(0.7g, 2.03mmol) in trifluoroacetic acid (10ml) was treated dropwise with TMS-N$_3$

(0.35g, 3.0mmol) at room temperature under N$_2$. After stirring the mixture for 3 days,

the solvent was removed *in vacuo*, and the residue was purified by flash chromatography

[elution with EtOAc-hexane (3:2)] to afford three fractions:

(i) starting material,

(ii) *1-acetyl-2,3-dihydro-2-(4-bromophenyl)-1,4-benzodiazepin-5-one* (**283**) (0.03g, 2.1%)

(Found: M$^+$ 358.033. Calc. for C$_{17}$H$_{15}$BrN$_2$O$_2$: M, 358.032); δ_H(400MHz;CDCl$_3$) 1.79

(3H, s, CH$_3$), 3.31-3.39 (1H, m, 3-H), 3.42-3.49 (1H, m, 3-H), 5.95 (1H, dd, J 5.5 and

12.5, 2-H), 7.04-7.06 (1H, m, 9-H), 7.11 (2H, d, J 8.4, 3'-H and 5'-H), 7.42 (2H, d, J

8.4, 2'-H and 6'-H), 7.52-7.59 (2H, m, 6-H and 8-H), 7.64 (1H, t, NH) and 7.84-7.87

(1H, m, 7-H); δ_C(100MHz;CDCl$_3$) 23.0 (CH$_3$), 44.4 (C-3), 62.3 (C-2), 122.2 (C-5a),

129.0 (C-3' and C-5'), 129.3 (C-6), 130.2 (C-7), 130.3 (C-9), 131.8 (C-2' and C-6'),

132.4 (C-8), 133.0 (C-4'), 137.0 (C-1'), 137.1 (C-9a), 170.9 and 171.2 (C-5 and

NC=O); and

(iii) *1-acetyl-2,3-dihydro-2-(4-bromophenyl)-1,5-benzodiazepin-4-one* (**280**) (0.05g, 7%),

m.p. 240-242°C (from EtOH) (Found: M$^+$ 358.034. Calc. for C$_{17}$H$_{15}$BrN$_2$O$_2$: *M*,

358.032); ν_{max} (KBr)/cm^{-1} 1690 (COCH$_3$) and 1650 (C=O); δ_H(400MHz;CDCl$_3$) 1.74

(3H, s, CH$_3$), 2.62 (1H, dd, *J* 4.9 and 13.1, 3-H), 2.91 (1H, t, 3-H), 6.25 (1H, dd, *J* 4.9

and 13.8, 2-H), 7.07 (1H, dd, *J* 1.0 and 7.7, ArH), 7.12-7.28 (4H, m, ArH), 7.42-7.46

(3H, m, ArH) and 8.62 (1H, br s, NH); δ_C(100MHz;CDCl$_3$) 22.9 (CH$_3$), 39.0 (C-3),

60.4 (C-2), 122.0, 123.1, 126.6, 128.5, 129.7, 131.4, 131.8, 132.8, 136.3 and 139.0

(ArC), 170.2 and 172.2 (C-4 and NC=O); *m/z* 358 (M$^+$, 50%) and 119 (100%).

1-Acetyl-2,3-dihydro-2-(4-chlorophenyl)-1,4-benzodiazepin-5-one (**284**) *and 1-Acetyl-2,3-*

dihydro-(4-chlorophenyl)-1,5-benzodiazepin-4-one (**281**).[133] -

The experimental procedure employed for the preparation of 1-acetyl-2,3-dihydro-2-(4-

bromophenyl)-1,4-benzodiazepin-5-one (**283**) and 1-acetyl-2,3-dihydro-2-(4-bromophenyl)-

1,5-benzodiazepin-4-one (**280**) was followed, using 1-acetyl-2-(4-chlorophenyl)-1,2,3,4-

tetrahydro-4-quinolone (**273**) (0.24g, 0.8mmol), trifluoroacetic acid (10ml) and TMS-N$_3$

(0.15g, 1.3mmol). Work-up followed by flash chromatography afforded three fractions:

(i) starting material

(ii) *1-acetyl-2,3-dihydro-2-(4-chlorophenyl)-1,4-benzodiazepin-5-one* (**284**) (0.01g, 4%);

m.p. 83-84°C (from EtOH); δ_H(400MHz;CDCl$_3$) 1.80 (3H, s, CH$_3$), 3.34-3.48 (2H, m,

3-H), 5.97 (1H, dd, J 5.6 and 12.2, 2-H), 7.04-7.05 (1H, m, 9-H), 7.16-7.18 (3H, m,

3'-H, 5'-H and NH), 7.27 (2H, d, J 8.5, 2'-H and 6'-H), 7.52-7.59 (2H, m, 6-H and 8-

H) and 7.84-7.88 (1H, m, 7-H); δ_C(100MHz;CDCl$_3$) 23.1 (CH$_3$), 44.5 (C-3), 62.2 (C-2),

128.7 (C-3' and C-5'), 128.9 (C-2' and C-6'), 129.3 (C-6), 130.2 (C-7), 130.3 (C-9),

132.4 (C-8), 133.1 (C-5a), 134.1 (C-4'), 136.5 (C-1'), 137.1 (C-9a), 170.9* and 170.9*

(C-5 and COCH$_3$); and

(iii) *1-acetyl-2,3-dihydro-(4-chlorophenyl)-1,5-benzodiazepin-4-one* (**281**) (0.03g, 12%),

m.p. 132-134°C (from EtOH) (Found: M$^+$ 314.083. Calc. C$_{17}$H$_{15}$ClN$_2$O$_2$: M, 314.082);

ν_{max} (KBr)/cm^{-1} 1690 (COCH$_3$) and 1655 (C=O); δ_H(400MHz;CDCl$_3$) 1.74 (3H, s, CH$_3$),

2.63 (1H, dd, J 4.9 and 13.1, 3-H), 2.91 (1H, t, 3-H), 6.26 (1H, dd, J 4.9 and 13.8, 2-

H), 7.07 (1H, d, J 7.9, ArH), 7.19-7.29 (6H, m, ArH), 7.44 (1H, ddd, J 1.3, 7.7 and

15.4, ArH) and 8.43 (1H, br s, NH); δ_C(100MHz;CDCl$_3$) 22.9 (CH$_3$), 39.0 (C-3), 60.3

(C-2), 123.1, 126.6, 128.2, 128.8, 129.7, 131.5, 132.8, 133.9, 136.3 and 138.5 (ArC),

170.2 and 172.1 (C-4 and COCH$_3$).

N-*Butyl-3-(2-hydroxyphenoxy)-3-phenylpropanamide* (**287**). -

A mixture of 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) (0.5g, 2mmol) and

butylamine (0.2ml, 2mmol) was heated at 70°C for 1 hour. The resulting crude product

was purified by flash chromatography [elution with EtOAc-hexane (2:3)] to give N-*butyl-*

3-(2-hydroxyphenoxy)-3-phenylpropanamide (**287**) (0.36g, 55%), m.p. 106-107°C (Found:

M$^+$ 313.167. Calc. for C$_{19}$H$_{23}$NO$_3$: M, 313.168); δ_H(400MHz;CDCl$_3$) 0.90 (3H, t, CH$_3$),

1.26-1.35 (2H, m, 3'-H), 1.43-1.50 (2H, m, 2'-H), 2.63 (1H, dd, J 2.8 and 15.9, 2-H),

2.93 (1H, dd, *J* 10.0 and 15.9, 2-H), 3.24-3.36 (2H, m, 1'-H), 5.26 (1H, dd, *J* 2.8 and

10.0, 3-H), 5.68 (1H, br s, NH), 6.43-6.52 (2H, m, ArH), 6.86-6.94 (2H, m, ArH),

7.30-7.36 (5H, m, ArH) and 8.82 (1H, s, OH); δ_C(100MHz;CDCl$_3$) 13.6 (CH$_3$), 20.0 (C-

3'), 31.5 (C-2'), 39.6 (C-1'), 43.7 (C-2), 80.2 (C-3), 116.8, 119.0, 121.5, 124.7, 126.9,

128.4, 128.6, 140.0, 144.5 and 149.8 (ArC) and 170.9 (C-1); *m/z* 57 (100%) and 313

(M$^+$, 1.3%).

N-Butyl-3-(4-chlorophenyl)-3-(2-hydroxyphenoxy)propanamide (**288**). -

The experimental procedure employed for the preparation of *N*-butyl-3-(2-

hydroxyphenoxy)-3-phenylpropanamide (**287**) was followed, using 2-(4-chlorophenyl)-2,3-

dihydro-1,5-benzodioxepin-4-one (**226**) (0.5g, 1.9mmol) and butylamine (0.2ml,

~1.9mmol). Work-up and flash chromatography gave N-*butyl-3-(4-chlorophenyl)-3-(2-*

hydroxyphenoxy)propanamide (**288**) (0.41g, 65%), m.p. 84-86°C (Found: M$^+$ 347.128.

Calc. for C$_{19}$H$_{22}$NO$_3$^{35}Cl: *M*, 347.129); δ_H(400MHz;CDCl$_3$) 0.89 (3H, t, CH$_3$), 1.23-1.34

(2H, m, 3'-H), 1.42-1.49 (2H, m, 2'-H), 2.59 (1H, dd, *J* 2.7 and 15.9, 2-H), 2.90 (1H,

dd, *J* 2.6 and 15.9, 2-H), 3.21-3.33 (2H, m, 1'-H), 5.23 (1H, dd, *J* 2.6 and 10.1, 3-H),

5.90 (1H, br s, NH), 6.42 (1H, dd, *J* 1.1 and 8.0, ArH), 6.50-6.54 (1H, m, ArH), 6.87-

6.93 (2H, m, ArH), 7.24-7.31 (4H, m, ArH) and 9.57 (1H, s, OH); δ_C(100MHz;CDCl$_3$)

13.6 (CH$_3$), 19.9 (C-3'), 31.4 (C-2'), 39.6 (C-1'), 43.4 (C-2), 79.4 (C-3), 116.9, 119.2,

121.3, 124.8, 128.2, 128.8, 134.2, 138.5, 144.3 and 149.6 (ArC) and 170.8 (C-1); *m/z*

57 (100%) and 347 (M$^+$, 1.1%).

3-(4-Bromophenyl)-N-butyl-3-(2-hydroxyphenoxy)propanamide (**289**). -

The experimental procedure employed for the preparation of *N*-butyl-3-(2-

hydroxyphenoxy)-3-phenylpropanamide (**287**) was followed, using 2-(4-bromophenyl)-2,3-

dihydro-1,5-benzodioxepin-4-one (**225**) (0.5g, 1.56mmol) and butylamine (0.2ml,

1.57mmol). Work-up and flash chromatography afforded *3-(4-bromophenyl)*-N-*butyl-3-*

(2-hydroxyphenoxy)propanamide (**289**) (0.43g, 70%), m.p. 101-103°C; (Found: M^+

391.079. Calc. for $C_{19}H_{22}NO_3{}^{79}Br$: M, 391.078); δ_H(400MHz;CDCl$_3$) 0.89 (3H, t, CH$_3$),

1.29 (2H, sext, 3'-H), 1.46 (2H, quint, 2'-H), 2.59 (1H, dd, J 2.6 and 15.9, 2-H), 2.89

(1H, dd, J 10.0 and 15.9, 2-H), 3.22-3.37 (2H, m, 1'-H), 5.22 (1H, dd, J 2.5 and 10.0,

3-H), 5.81 (1H, br s, NH), 6.42 (1H, dd, J 1.1 and 7.9, ArH), 6.50-6.54 (1H, m, ArH),

6.87-6.94 (2H, m, ArH), 7.21 (2H, d, J 8.2, ArH), 7.46 (2H, d, J 8.2, ArH) and 8.91

(1H, br s, OH); δ_C(100MHz;CDCl$_3$) 13.6 (CH$_3$), 20.0 (C-3'), 31.4 (C-2'), 39.7 (C-1'),

43.4 (C-2), 79.5 (C-3), 116.9, 119.2, 121.4, 122.4, 124.9, 128.6, 131.8, 139.1, 144.3

and 149.7 (ArC) and 170.7 (C-1); m/z 57 (100%) and 393 (M^+, 1.2%).

Attempted alkylation of 4-aryl-3,4-dihydro-1,5-benzodioxepin-2-ones

Benzyl cinnamate (**293**). -

A solution of lithium diisopropylamide (LDA) [prepared by reacting diisopropylamine

(1.1ml, 7.53mmol) with BuLi (1.5M solution in hexane; 4.1ml, 6.67mmol) in dry THF

(10ml) under N$_2$ at *ca.* -78°C] was added dropwise to a mixture of 2,3-dihydro-2-phenyl-

1,5-benzodioxepin-4-one (**65**) (0.8g, 3.33mmol) and benzaldehyde (0.53g, 5mmol) in dry

THF (10ml) under N$_2$ at *ca.* -78°C. The reaction mixture was stirred for 2 hours at *ca.*

-78°C, left to warm to room temperature overnight, and then quenched by pouring into

ice - aq. NaHCO$_3$ (100ml). The resulting mixture was extracted with EtOAc (3 x 30ml)

and the combined extracts were dried (anhyd. Na$_2$SO$_4$). The solvent was evaporated and

the residue was chromatographed [preparative TLC on silica; elution with EtOAc-hexane

(3:7)] to give benzyl cinnamate (293)(0.35g, 44%); ν_{max} (thin film)/cm^{-1} 1713 (C=O);

δ_H(400MHz;CDCl$_3$) 5.12 (2H, s, CH$_2$), 6.35 (1H, d, J 16, PhCH=CH), 7.18-7.30 (8H,

m, ArH), 7.37-7.40 (2H, m, ArH) and 7.60 (1H, d, J 16, PhCH=CH);

δ_C(100MHz;CDCl$_3$) 66.3 (CH$_2$), 117.9 (PhCH=CH), 128.1, 128.2, 128.3, 128.6, 128.9,

130.3, 134.4 and 136.1 (ArC), 145.2 (PhCH=CH) and 166.6 (C=O); m/z 131 (100%)

and 238 (M$^+$, 21%).

4-Chlorobenzyl cinnamate (294).-

The experimental procedure employed for the synthesis of benzyl cinnamate (293) was

followed, using 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (65) (2g, 8.32mmol), 4-

chlorobenzaldehyde (1.75g, 12.48mmol) and LDA [Pr$^i_2$NH (2.6ml, 17.80mmol) with

BuLi (10.4ml, 16.9mmol) in dry THF (15ml)]. Work-up and flash chromatography

[elution with EtOAc-hexane (1:4)] afforded *4-Chlorobenzyl cinnamate* (294) (1g, 43%),

m.p. 49-50°C (Found: C, 70.8; H, 5.1. Calc. for C$_{16}$H$_{13}$ClO$_2$: C, 70.5; H, 4.8%); ν_{max}

(KBr)/cm^{-1} 1700 (C=O); δ_H(400MHz;CDCl$_3$) 5.11 (2H, s, CH$_2$), 6.37 (1H, d, J 16,

PhCH=CH), 7.25-7.32 (7H, m, ArH), 7.41-7.43 (2H, m, ArH) and 7.63 (1H, d, J 16,

PhCH=CH); δ_C(100MHz;CDCl$_3$) 65.5 (CH$_2$), 117.6 (PhCH=CH), 128.1, 128.8, 128.9,

129.6, 130.4, 134.2, 134.3 and 134.6 (ArC), 145.4 (PhCH=CH) and 166.6 (C=O); m/z

125 (100%), 272 (M$^+$, 10%).

4-Nitrobenzyl cinnamate (**295**).-

The experimental procedure employed for the preparation of benzyl cinnamate (**293**) was

followed, using 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) (0.5g, 2.08mmol), 4-

nitrobenzaldehyde (0.63g, 4.16mmol) and LDA [Pr^i_2NH (0.65ml, 4.70mmol) with BuLi

(2.60ml, 4.16mmol) in dry THF (10ml)]. Work-up and flash chromatography [elution

with EtOAc-hexane (1:4)] afforded *4-Nitrobenzyl cinnamate* (**295**) (0.21g, 36%), m.p.

103-104°C (Found: M^+ 283.083. Calc. for $C_{16}H_{13}NO_4$: M, 283.085); ν_{max} (KBr)/cm^{-1}

1706 (C=O); δ_H(400MHz;CDCl$_3$) 5.34 (2H, s, CH$_2$), 6.50 (1H, d, J 16, PhCH=CH),

7.38-7.41 (3H, m, ArH), 7.51-7.58 (4H, m, ArH), 7.76 (1H, d, J 16, PhCH=CH) and

8.22-8.25 (2H, m, ArH); δ_C(100MHz;CDCl$_3$) 64.8 (CH$_2$), 117.1 (PhCH=CH), 123.8,

128.2, 128.4, 129.0, 130.7, 134.1 and 143.4 (ArC), 146.1 (PhCH=CH), 147.8 (ArC)

and 166.4 (C=O); m/z 131 (100%) and 283 (M^+, 15%).

2,2-Dimethylpropyl cinnamate (**296**). -

The experimental procedure employed for the preparation of benzyl cinnamate (**293**) was

followed, using 2,3-dihydro-2-phenyl-1,5-benzodioxepin-4-one (**65**) (1g, 4.16mmol),

Bu^{t}CHO (0.72g, 8.32mmol) and LDA [Pr^i_2NH (1.3ml, 9.4mmol) with BuLi (5.2ml,

8.33mmol) in dry THF (15ml). Work-up and flash chromatography afforded *2,2-*

dimethylpropyl cinnamate (**296**) (0.9g, 50%) (Found: M^+ 218.131. Calc. for $C_{14}H_{18}O_2$:

M, 218.131); ν_{max} (thin film)/cm^{-1} 1706cm (C=O); δ_H(400MHz;CDCl$_3$) 0.99 (9H, s,

3xCH$_3$), 3.88 (2H, s, CH$_2$), 6.35 (1H, d, J 16, PhCH=CH), 7.24-7.29 (3H, m, ArH),

7.39-7.43 (2H, m, ArH) and 7.57 (1H, d, J 16, PhCH=CH); δ_C(100MHz;CDCl$_3$) 26.5

(CH$_3$C), 31.4 (CH$_3$$C$), 73.8 (CH$_2$), 118.3 (PhCH=$C$H), 128.0, 128.8, 130.1 and 134.5

(ArC), 144.5 (PhCH=CH) and 167.0 (C=O); m/z 131 (100%) and 218 (M$^+$, 8%).

Reaction of benzaldehyde with LDA. -

Benzaldehyde (2g, 18mmol) was added dropwise to a stirred solution of LDA [generated

from BuLi (1.5M; 5.5ml, 9mmol) and diisopropylamine (1.4ml, 10mmol)] in dry THF

(20ml) under N$_2$ at $ca.$ -40°C. After 1 hour the reaction mixture was allowed to warm to

room temperature overnight, and then quenched with ice-water, acidified (dilute HCl) and

extracted with EtOAc (3 x 20ml). The organic layer was dried (anhydr. Na$_2$SO$_4$) and the

solvent was evaporated to give a residue which was purified by flash chromatography

[elution with EtOAc-hexane (3:7)] to afford, in low yield, two products:

(i) N,N-diisopropylbenzamide ; δ_H(400MHz;CDCl$_3$) 1.24 (12H, br s, 4xCH$_3$), 3.59 (2H,

br s, 2xCH), 7.18-7.22 (2H, m, ArH) and 7.25-7.29 (3H, m, ArH); δ_C(100MHz;CDCl$_3$)

20.6 (4xCH$_3$), 48.0 (2x br s, 2xCH), 125.5 (C-3 and C-5), 128.3 (C-2 and C-6), 128.5

(C-4), 138.9 (C-1) and 171.0 (C=O), and

(ii) benzyl benzoate ; δ_H(400MHz;CDCl$_3$) 5.37 (2H, s, CH$_2$), 7.31-7.46 (7H, m, ArH),

7.53-7.58 (1H, m, ArH) and 8.06-8.09 (2H, m, ArH); δ_C(100MHz;CDCl$_3$) 66.7 (CH$_2$),

128.1, 128.2, 128.4, 128.6, 129.7, 130.2, 133.0 and 136.1 (ArC) and 166.4 (C=O).

Oxidation of 2,3-dihydro-2-phenyl-4H-benzothiopyran-4-one (220) with MCPBA. -

A mixture of 2,3-dihydro-2-phenyl-4H-benzothiopyran-4-one (220) (0.6g, 2.50mmol) and

MCPBA (50%; 1g, ~2.91mmol) in CH$_2$Cl$_2$ (30ml) was boiled under reflux for 1 hour.

The solvent was evaporated and the resulting residue was taken up in EtOAc (50ml),

washed with aqueous NaHCO$_3$ (3 x 20ml) and dried over anhydrous MgSO$_4$. The solvent

was evaporated and the residue was purified by flash chromatography [elution with

EtOAc-hexane (1:1)] to afford two fractions:

(i) 2,3-dihydro-2-phenyl-4H-benzothiopyran-4-one 1,1-dioxide (298) (0.24g, 35%); m.p.

153-154°C, (lit.,[272] 155°C); δ_H(400MHz;CDCl$_3$) 3.40 (1H, dd, J 3.3 and 17.8, 3-H),

3.95 (1H, dd, J 12.7 and 17.7, 3-H), 4.87 (1H, dd, J 3.3 and 12.8, 2-H), 7.42-7.48 (5H,

m, PhH), 7.74 (1H, ddd, J 1.4, 7.8 and 15.3, 6-H), 7.81 (1H, ddd, J 1.4, 9.0 and 15.2,

7-H), 8.05 (1H, dd, J 1.1 and 7.8, 8-H) and 8.16 (1H, dd, J 1.4 and 7.7, 5-H);

δ_C(100MHz;CDCl$_3$) 43.0 (C-3), 63.9 (C-2), 124.4, 128.0, 128.7, 129.1, 129.8, 129.9,

130.5, 133.3, 135.0 and 141.4 (ArC) and 190.8 (C-4); m/z 272 (M$^+$, 4.0%) and 104

(100%); and

(ii) 2,3-dihydro-2-phenyl-4H-benzothiopyran-4-one 1-oxide (297) (0.12g, 18%), m.p 147-

148°C (lit.,[272] 148-151°C).

2,3-Dihydro-3-phenyl-4,1-benzoxathiepin-5-one-1-oxide (299) *and 2,3-dihydro-3-phenyl-*

4,1-benzoxathiepin-5-one-1,1-dioxide (300). -

A mixture of 2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one (263) (0.66g, 2.58mmol)

and MCPBA (50%; 0.89g, 2.58mmol) in dichloromethane (10ml) was refluxed for 24

hours. The solvent was evaporated and the residue dissolved in EtOAc. The resulting

solution was washed with aq. NaHCO$_3$ (3 x 10ml) and then dried over anhydrous MgSO$_4$.

Evaporation of the solvent gave a residue which was purified by flash chromatography

[elution with EtOAc-hexane (1:1)] to give three fractions:

(i) starting material,

(ii) *2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one 1-oxide* (**299**) (0.11g, 15.7%), m.p.

90-91°C (Found: C, 64.50; H, 4.46. $C_{15}H_{12}SO_3$ requires: C, 66.14; H, 4.44%); ν_{max}

(KBr)/cm^{-1} 1740 (C=O); δ_H (400MHz;CDCl$_3$) 3.43-3.54 (2H, m, 2-H), 5.22 (1H, dd, *J*

7.0 and 8.1, 3-H), 7.28-7.34 (5H, m, ArH), 7.73-7.75 (3H, m, 7-H, 8-H and 9-H) and

8.23-8.25 (1H, m, 6-H); δ_C(100MHz;CDCl$_3$) 35.9 (C-2), 90.8 (C-3), 122.6 (C-1'), 127.6

(C-4'), 128.9 (C-3' and C-5'), 129.8 (C-2' and C-6'), 130.1 (C-9), 132.3 (C-6), 132.9

(C-5a), 134.0 (C-7), 134.7 (C-8), 139.1 (C-9a) and 161.2 (C-5); and

(iii) *2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one 1,1-dioxide* (**300**) (0.21g, 28.2%),

m.p. 65-67°C (Found: C, 61.50; H, 4.14. $C_{15}H_{12}SO_4$ requires: C, 62.47; H, 4.19%);

ν_{max} (KBr)/cm^{-1} 1675 (C=O); δ_H(400MHz;CDCl$_3$) 7.27-7.40 (5H, m, ArH), 7.64 (1H,

ddd, *J* 1.3, 7.6 and 15.2, 7-H), 7.82 (1H, ddd, *J* 1.2, 7.5 and 15.2, 8-H), 7.89 (1H, dd,

J 1.1 and 7.8, 9-H) and 8.08 (1H, dd, *J* 1.2 and 7.8, 6-H); δ_C(100MHz;CDCl$_3$) 35.7 (C-

2), 94.6 (C-3), 121.3 (C-1'), 125.4 (C-9), 127.6 (C-4'), 128.8 (C-3' and C-5'), 130.1

(C-2' and C-6'), 131.5 (C-7), 132.1 (C-6), 133.6 (C-5a), 135.2 (C-8), 145.2 (C-9a) and

160.8 (C-5).

2,3-Dihydro-3-phenyl-4,1-benzoxathiepine 1,1-dioxide (**302**). -

The same procedure employed for the synthesis of 2,3-dihydro-3-phenyl-1-sulfone-4,1-

benzoxathiepin-5-one (**300**) was followed, using 2,3-dihydro-3-phenyl-4,1-benzoxathiepine

(**270**) (1g, 4.0mmol), MCPBA (50%; 4.2g, 8.1mmol) and dichloromethane (30ml).

Work-up afforded two fractions:

(i) starting material, and

(ii) *2,3-dihydro-3-phenyl-4,1-benzoxathiepine 1,1-dioxide* (**302**) (0.77g, 70%), m.p. 81-82°C (Found: C, 65.06; H, 4.93. $C_{15}H_{14}SO_3$ requires: C, 65.65; H, 5.15%) (Found M^+ 274.064. Calc. for $C_{15}H_{14}SO_3$: M, 274.066); ν_{max} (KBr)/cm^{-1} 1290 (SO$_2$);

δ_H(400MHz;CDCl$_3$) 3.21 (1H, dd, J 10.0 and 14.6, 2-H), 3.44 (1H, dd, J 2.5 and 14.6, 2-H), 4.88 (1H, dd, J 2.6 and 9.8, 3-H), 4.94 (2H, dd, J 16.0 and 67.9, 5-H), 7.09-7.11 (1H, m, 6-H), 7.27-7.35 (5H, m, ArH), 7.46-7.55 (2H, m, 7-H and 8-H) and 7.94-7.97 (1H, m, 9-H); δ_C(100MHz;CDCl$_3$) 31.7 (C-2), 69.8 (C-5), 93.1 (C-3), 123.9 (C-9), 124.5 (C-6), 127.3 (C-4'), 128.6 (C-8), 128.7 (C-3' and C-5'), 129.6 (C-2' and C-6'), 132.4 (C-7), 134.8 (C-1'), 135.1 (C-9a) and 137.5 (C-5a).

3.3 KINETIC STUDY OF THE BAEYER-VILLIGER REACTION OF FLAVANONES

GENERAL PROCEDURE

The kinetic measurements were carried out as follows. The flavanone (0.17 mmol) and MCPBA (0.25 mmol) were accurately weighed into an NMR tube and CD_2Cl_2 (0.5 ml) was added with a syringe {in the case of compound **65**, substrate and MCPBA concentrations ([A] and [B] respectively) were varied to confirm the reaction order}. The tube was then immediately sealed with a septum. The mixture was shaken (time, $t = t_0$) and the first 400 MHz ^1H NMR spectrum of the reaction mixture was obtained as quickly as possible (at 303 $\pm$ 0.1 K). Subsequent spectra were acquired at 30 minute intervals over a period of $ca.$ 15 hours, using an automatic programme. The total acquisition time for each 32 scan spectrum was 2m 6s. The concentration changes were determined from the integrals for the methine proton signals of the flavanone substrate and the lactone product. All runs were carried out in duplicate and the spectra were calibrated relative to the CH_2Cl_2 signal at δ 5.31 ppm. The experimental data and the corresponding second-order plots for the various kinetic runs are summarised below, and typically gave straight line plots using the second-order equation:-

$$\frac{1}{(a-b)} \ln \frac{b(a-x)}{a(b-x)} = kt$$

where   a = initial concentration of flavanone
            b = initial concentration of MCPBA
            a-x = concentration of flavanone at time t
            b-x = concentration of MCPBA at time t

Kinetic data for reaction of compound 65

RUN 1

TIME	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol)
15	0.99	0.331	0.212	0.047
45	2.67	0.325	0.206	0.129
75	4.61	0.319	0.200	0.228
105	7.27	0.310	0.191	0.373
135	9.28	0.303	0.184	0.490
165	11.35	0.296	0.177	0.618
195	13.33	0.289	0.170	0.748
225	15.22	0.283	0.164	0.879
255	17.08	0.277	0.158	1.017
285	18.79	0.271	0.152	1.152
315	20.57	0.265	0.146	1.300
345	22.10	0.260	0.141	1.435
375	22.98	0.257	0.138	1.517
405	25.22	0.250	0.131	1.736
435	26.56	0.245	0.126	1.877
465	27.92	0.241	0.122	2.028
495	29.18	0.237	0.118	2.175
525	30.36	0.233	0.114	2.321
555	31.54	0.229	0.110	2.474
585	32.41	0.226	0.107	2.592
615	33.58	0.222	0.103	2.759
645	34.56	0.219	0.100	2.905
675	35.56	0.215	0.096	3.063
705	36.38	0.212	0.093	3.198
735	37.16	0.210	0.091	3.332
765	38.02	0.207	0.088	3.486
795	38.71	0.205	0.086	3.615
825	39.58	0.202	0.083	3.784
855	40.09	0.200	0.081	3.888
885	40.79	0.198	0.079	4.035

ACG9KIN5
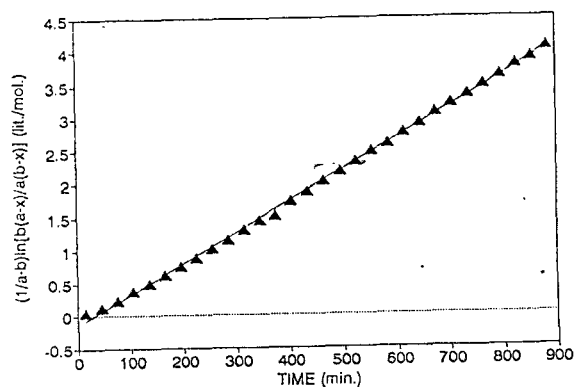
Regression Output:

Constant	-0.14949
Std Err of Y Est	0.040685
R Squared	0.998971
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.004717
Std Err of Coef.	0.000029

RUN 2

TIME	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol.)
13	1.29	0.330	0.211	0.061
43	4.56	0.319	0.200	0.225
73	6.91	0.311	0.192	0.353
103	9.08	0.304	0.185	0.478
133	11.17	0.297	0.178	0.606
163	13.18	0.290	0.171	0.738
253	18.68	0.272	0.153	1.143
283	20.28	0.266	0.147	1.275
313	21.87	0.261	0.142	1.415
343	23.37	0.256	0.137	1.554
373	24.83	0.251	0.132	1.697
403	26.13	0.247	0.128	1.831
433	27.4	0.242	0.123	1.969
463	28.65	0.238	0.119	2.112
493	29.83	0.234	0.115	2.254
523	30.93	0.231	0.112	2.394
553	32.02	0.227	0.108	2.538
583	33.04	0.224	0.105	2.680
613	34.03	0.220	0.101	2.825
643	34.97	0.217	0.098	2.969
673	35.91	0.214	0.095	3.120
703	36.71	0.211	0.092	3.254
733	37.45	0.209	0.090	3.383
763	38.25	0.206	0.087	3.528
793	38.99	0.204	0.085	3.668
823	39.59	0.202	0.083	3.786
853	40.28	0.199	0.080	3.927
883	40.94	0.197	0.078	4.067

ACG9KIN6
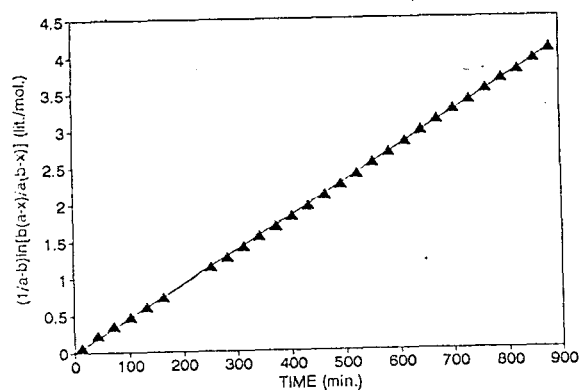
Regression Output:

Constant	-0.01074
Std Err of Y Est	0.016328
R Squared	0.999829
No. of Observations	28
Degrees of Freedom	26

X Coefficient(s)	0.004618
Std Err of Coef.	0.000012

223

Kinetic data for reaction of compound 65

RUN 1

ACG9KIN3

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln[b(a-x)/a(b-x)]$ (lit./mol)
18	2.21	0.164	0.426	0.052
48	6.51	0.157	0.419	0.158
78	11.58	0.148	0.410	0.293
108	15.66	0.141	0.403	0.409
138	19.49	0.135	0.397	0.525
168	23.41	0.128	0.390	0.651
198	27.03	0.122	0.384	0.776
228	30.41	0.116	0.378	0.901
258	33.68	0.111	0.373	1.028
288	36.91	0.105	0.367	1.163
318	40.00	0.100	0.362	1.301
348	42.74	0.096	0.358	1.430
378	45.37	0.091	0.353	1.562
408	48.07	0.087	0.349	1.707
438	50.50	0.083	0.345	1.845
468	52.81	0.079	0.341	1.984
498	54.97	0.075	0.337	2.122
528	57.06	0.072	0.334	2.263
558	58.99	0.068	0.330	2.402
588	61.11	0.065	0.327	2.563
618	62.70	0.062	0.324	2.691
648	64.38	0.059	0.321	2.834
678	66.20	0.056	0.318	2.997
708	67.67	0.054	0.316	3.137
738	69.23	0.051	0.313	3.294
768	70.62	0.049	0.311	3.442
798	72.05	0.046	0.308	3.603
828	73.33	0.044	0.306	3.755
858	74.52	0.042	0.304	3.905
888	75.62	0.040	0.302	4.050
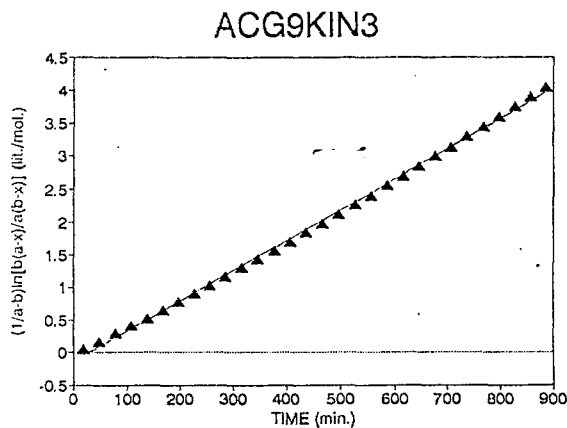
Regression Output:	
Constant	-0.13279
Std Err of Y Est	0.047614
R Squared	0.998534
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.004624
Std Err of Coef.	0.000033

RUN 2

ACG9KIN4

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln[b(a-x)/a(b-x)]$ (lit./mol)
16	2.57	0.163	0.425	0.061
46	9.72	0.151	0.413	0.243
76	15.15	0.142	0.404	0.395
106	20.36	0.133	0.395	0.554
136	25.22	0.125	0.387	0.715
166	29.84	0.117	0.379	0.881
196	33.96	0.110	0.372	1.042
226	37.88	0.104	0.366	1.208
256	41.70	0.097	0.359	1.383
286	45.22	0.091	0.353	1.558
316	48.36	0.086	0.348	1.726
346	51.80	0.080	0.342	1.926
376	54.49	0.076	0.338	2.095
406	57.17	0.072	0.334	2.276
436	59.92	0.067	0.329	2.476
466	62.01	0.063	0.325	2.640
496	64.45	0.059	0.321	2.845
526	66.51	0.056	0.318	3.032
556	68.27	0.053	0.315	3.202
586	70.19	0.050	0.312	3.401
616	71.57	0.047	0.309	3.554
646	73.31	0.045	0.307	3.759
676	74.90	0.042	0.304	3.960
706	76.22	0.040	0.302	4.139
736	77.17	0.038	0.300	4.274
766	78.65	0.036	0.298	4.498
796	79.67	0.034	0.296	4.663
826	80.88	0.032	0.294	4.871
856	82.14	0.030	0.292	5.104
886	82.76	0.029	0.291	5.226
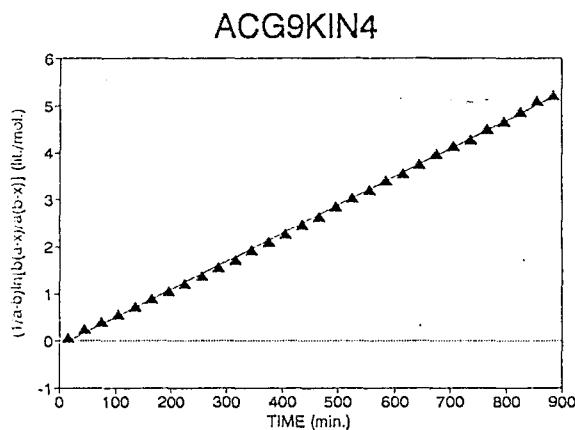
Regression Output:	
Constant	-0.11436
Std Err of Y Est	0.039782
R Squared	0.999391
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.005997
Std Err of Coef.	0.000028

224

Kinetic data for reaction of compound 65

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol)
14	1.90	0.327	0.425	0.045
44	5.83	0.314	0.412	0.143
74	9.58	0.301	0.399	0.243
104	13.15	0.289	0.387	0.345
134	16.64	0.278	0.376	0.453
164	19.97	0.266	0.364	0.563
194	23.03	0.256	0.354	0.672
224	26.01	0.246	0.344	0.785
254	28.77	0.237	0.335	0.897
284	31.42	0.228	0.326	1.011
344	36.29	0.212	0.310	1.243
374	38.43	0.205	0.303	1.354
404	40.61	0.198	0.296	1.475
434	42.49	0.192	0.290	1.585
464	44.39	0.185	0.283	1.702
494	46.06	0.180	0.278	1.811
524	47.70	0.174	0.272	1.923
554	49.18	0.169	0.267	2.029
584	50.58	0.165	0.263	2.135
614	51.79	0.161	0.259	2.23
644	52.97	0.157	0.255	2.327
674	53.95	0.153	0.251	2.41
704	54.94	0.150	0.248	2.497
734	55.91	0.147	0.245	2.585

ACG9KIN1
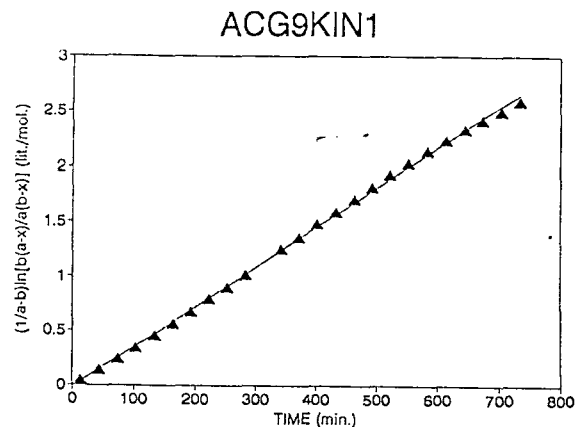
Regression Output:

Constant	-0.01657
Std Err of Y Est	0.026296
R Squared	0.999015
No. of Observations	24
Degrees of Freedom	22
X Coefficient(s)	0.003636
Std Err of Coef.	0.000024

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b)a-x)/a(b-x)] (lit./mol)
16	2.25	0.326	0.424	0.053
46	6.02	0.313	0.411	0.148
106	13.88	0.287	0.385	0.367
136	17.41	0.275	0.373	0.478
166	20.74	0.264	0.362	0.590
196	24.06	0.253	0.351	0.710
226	27.09	0.243	0.341	0.828
256	30.12	0.233	0.331	0.954
286	32.54	0.225	0.323	1.062
316	35.34	0.215	0.313	1.195
346	37.83	0.207	0.305	1.322
376	40.14	0.199	0.297	1.448
406	42.25	0.192	0.290	1.570
436	44.06	0.186	0.284	1.681
466	46.05	0.180	0.278	1.810
496	48.01	0.173	0.271	1.945
526	49.93	0.167	0.265	2.085
556	51.39	0.162	0.260	2.198
586	53.03	0.156	0.254	2.332
616	54.49	0.152	0.250	2.457
646	55.81	0.147	0.245	2.576
676	57.02	0.143	0.241	2.690
706	58.59	0.138	0.236	2.846
736	59.84	0.134	0.232	2.977
766	60.91	0.130	0.228	3.095
796	62.00	0.127	0.225	3.220
826	62.64	0.124	0.222	3.296
856	63.53	0.121	0.219	3.405
886	64.48	0.118	0.216	3.526

ACG9KIN2
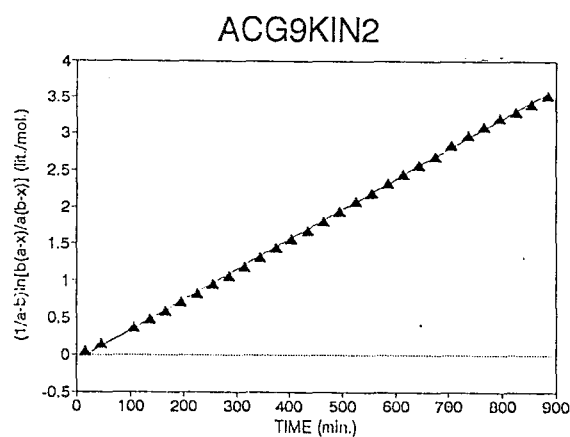
Regression Output:

Constant	-0.07837
Std Err of Y Est	0.025231
R Squared	0.999455
No. of Observations	29
Degrees of Freedom	27
X Coefficient(s)	0.004098
Std Err of Coef.	0.000018

Kinetic data for reaction of compound 221

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/b(a-x)] (lit./mol)
13	1.47	0.328	0.425	0.035
43	4.66	0.317	0.414	0.113
73	7.63	0.308	0.405	0.190
103	11.29	0.295	0.392	0.292
133	14.32	0.285	0.382	0.382
163	17.25	0.276	0.373	0.474
193	19.99	0.266	0.363	0.565
223	22.61	0.258	0.355	0.658
253	25.34	0.249	0.346	0.761
283	27.75	0.241	0.338	0.857
313	30.16	0.233	0.330	0.958
343	32.40	0.225	0.322	1.058
373	34.50	0.218	0.315	1.157
403	36.55	0.211	0.308	1.259
433	38.59	0.204	0.301	1.367
463	40.51	0.198	0.295	1.473
493	42.25	0.192	0.289	1.575
523	44.85	0.184	0.281	1.736
553	45.70	0.181	0.278	1.792
583	47.26	0.176	0.273	1.898
613	48.72	0.171	0.268	2.002
643	50.19	0.166	0.263	2.112
673	51.59	0.161	0.258	2.221
703	52.87	0.157	0.254	2.326
733	54.03	0.153	0.250	2.425
763	55.23	0.149	0.246	2.531
793	56.37	0.145	0.242	2.637
823	57.97	0.140	0.237	2.793
853	59.14	0.136	0.233	2.913
883	59.47	0.135	0.232	2.948

ACG22KIN1
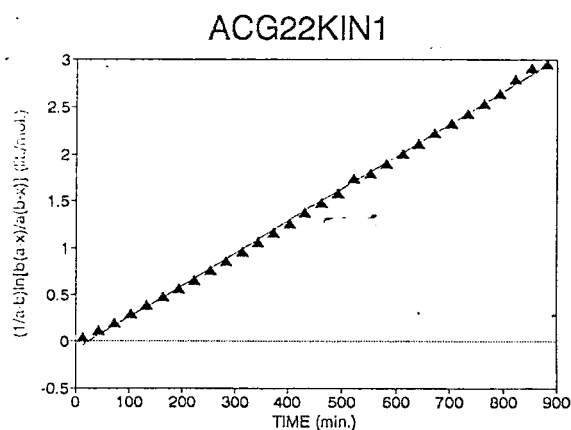
Regression Output:

Constant	-0.08581
Std Err of Y Est	0.032271
R Squared	0.998775
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.003429	
Std Err of Coef.	0.000023	

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol)
11	2.67	0.326	0.422	0.063
41	9.42	0.303	0.399	0.239
71	16.10	0.281	0.377	0.436
101	21.75	0.262	0.358	0.626
131	26.34	0.247	0.343	0.798
161	31.41	0.230	0.326	1.012
191	35.05	0.218	0.314	1.182
221	38.44	0.206	0.302	1.357
251	41.23	0.197	0.293	1.512
281	43.67	0.189	0.285	1.659
311	45.87	0.181	0.277	1.801
341	47.75	0.175	0.271	1.930
371	49.48	0.169	0.265	2.056
401	52.11	0.160	0.256	2.261
431	53.79	0.155	0.251	2.401
461	54.06	0.154	0.250	2.425
491	55.23	0.150	0.246	2.529
521	55.80	0.148	0.244	2.581
551	56.31	0.146	0.242	2.629
581	57.17	0.143	0.239	2.711
611	57.84	0.141	0.237	2.778
641	57.82	0.141	0.237	2.776
671	58.80	0.138	0.234	2.875
701	58.62	0.139	0.235	2.857
731	59.60	0.135	0.231	2.960

ACG22KIN2

Regression Output:

Constant	-0.08982
Std Err of Y Est	0.025366
R Squared	0.99922
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.003378	
Std Err of Coef.	0.000018	

226

Kinetic data for reaction of compound 224

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol)
12	2.43	0.325	0.421	0.058
42	9.49	0.301	0.397	0.242
72	15.67	0.281	0.377	0.424
102	20.39	0.265	0.361	0.581
132	26.07	0.246	0.342	0.791
162	30.17	0.233	0.329	0.961
192	33.89	0.220	0.316	1.131
222	37.18	0.209	0.305	1.296
252	39.81	0.200	0.296	1.438
282	42.68	0.191	0.287	1.605
312	44.81	0.184	0.280	1.739
342	48.13	0.173	0.269	1.965
372	49.28	0.169	0.265	2.049
402	51.44	0.162	0.258	2.216
432	53.68	0.154	0.250	2.402
462	53.95	0.153	0.249	2.425
492	54.32	0.152	0.248	2.458
522	53.69	0.154	0.250	2.403
552	54.51	0.151	0.247	2.475
582	54.30	0.152	0.248	2.456
612	54.16	0.153	0.249	2.444
642	54.02	0.153	0.249	2.431
672	54.24	0.152	0.248	2.451
702	53.99	0.153	0.249	2.429
732	54.00	0.153	0.249	2.430
762	53.99	0.153	0.249	2.429
792	54.12	0.153	0.249	2.440
822	54.15	0.153	0.249	2.443
852	54.28	0.152	0.248	2.454
882	53.99	0.153	0.249	2.429

ACG24KIN1
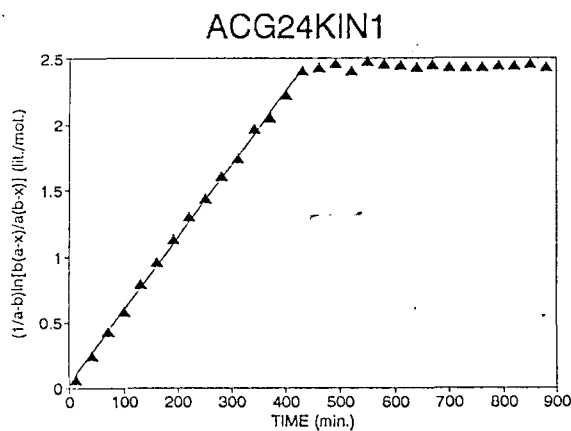
Regression Output:

Constant	0.034766
Std Err of Y Est	0.03161
R Squared	0.99831
No. of Observations	15
Degrees of Freedom	13

X Coefficient(s)	0.005519	
Std Err of Coef.	0.000063	

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/b(a-x)] (lit./mol)
11	2.67	0.326	0.422	0.063
41	9.42	0.303	0.399	0.239
71	16.10	0.281	0.377	0.436
101	21.75	0.262	0.358	0.626
131	26.34	0.247	0.343	0.798
161	31.41	0.230	0.326	1.012
191	35.05	0.218	0.314	1.182
221	38.44	0.206	0.302	1.357
251	41.23	0.197	0.293	1.512
281	43.67	0.189	0.285	1.659
311	45.87	0.181	0.277	1.801
341	47.75	0.175	0.271	1.930
371	49.48	0.169	0.265	2.056
401	52.11	0.160	0.256	2.261
431	53.79	0.155	0.251	2.401
461	54.06	0.154	0.250	2.425
491	55.23	0.150	0.246	2.529
521	55.80	0.148	0.244	2.581
551	56.31	0.146	0.242	2.629
581	57.17	0.143	0.239	2.711
611	57.84	0.141	0.237	2.778
641	57.82	0.141	0.237	2.776
671	58.80	0.138	0.234	2.875
701	58.62	0.139	0.235	2.857
731	59.60	0.135	0.231	2.960

ACG24KIN2

Regression Output:

Constant	0.066876
Std Err of Y Est	0.04901
R Squared	0.995963
No. of Observations	15
Degrees of Freedom	13

X Coefficient(s)	0.005529	
Std Err of Coef.	0.000098	

227

Kinetic data for reaction of compound 225

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b)a-x)/a(b-x)] (lit./mol)
12	1.58	0.328	0.425	0.037
42	5.15	0.316	0.413	0.126
72	9.77	0.300	0.397	0.249
102	12.98	0.290	0.387	0.341
132	16.45	0.278	0.375	0.448
162	19.95	0.267	0.364	0.564
192	23.01	0.256	0.353	0.673
222	25.89	0.247	0.344	0.782
252	28.84	0.237	0.334	0.902
282	31.61	0.228	0.325	1.022
312	34.00	0.220	0.317	1.133
342	36.41	0.212	0.309	1.252
372	38.65	0.204	0.301	1.370
402	41.32	0.195	0.292	1.520
432	43.53	0.188	0.285	1.653
462	45.41	0.182	0.279	1.773
492	47.34	0.175	0.272	1.904
522	49.40	0.168	0.265	2.052
552	52.19	0.159	0.256	2.269
582	53.88	0.154	0.251	2.411
612	55.30	0.149	0.246	2.537
642	56.72	0.144	0.241	2.670
672	58.30	0.139	0.236	2.826
702	58.45	0.138	0.235	2.841
732	59.78	0.134	0.231	2.981
762	60.80	0.131	0.228	3.093
792	61.90	0.127	0.224	3.219
822	63.81	0.121	0.218	3.452
852	63.69	0.121	0.218	3.437
882	64.74	0.117	0.214	3.573

ACG10KIN1
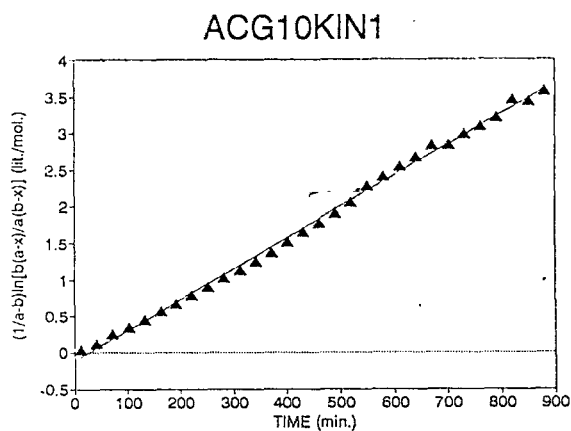
Regression Output:

Constant	-0.11962
Std Err of Y Est	0.060075
R Squared	0.997213
No. of Observations	30
Degrees of Freedom	28
X Coefficient(s)	0.004228
Std Err of Coef.	0.000042

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	(1/a-b)*ln[b(a-x)/a(b-x)] (lit./mol)
11	1.43	0.329	0.425	0.034
41	5.92	0.314	0.410	0.145
71	9.52	0.302	0.398	0.242
101	12.83	0.291	0.387	0.337
131	16.48	0.279	0.375	0.449
161	21.00	0.264	0.360	0.601
191	23.19	0.257	0.353	0.679
221	26.45	0.246	0.342	0.804
251	29.52	0.235	0.331	0.931
281	33.01	0.224	0.320	1.087
311	36.09	0.213	0.309	1.237
341	37.44	0.209	0.305	1.306
371	39.76	0.201	0.297	1.432
401	41.93	0.194	0.290	1.557
431	44.07	0.187	0.283	1.688
461	46.05	0.180	0.276	1.817
491	47.92	0.174	0.270	1.946
521	49.84	0.168	0.264	2.087
551	51.48	0.162	0.258	2.214
581	53.02	0.157	0.253	2.341
611	54.57	0.152	0.248	2.475
641	55.71	0.148	0.244	2.578
671	57.16	0.143	0.239	2.716
701	58.44	0.139	0.235	2.844
731	59.56	0.135	0.231	2.961
761	60.53	0.132	0.228	3.067
791	61.53	0.128	0.224	3.181
821	64.43	0.119	0.215	3.538
851	63.49	0.122	0.218	3.417
881	64.28	0.119	0.215	3.518

ACG10KIN2
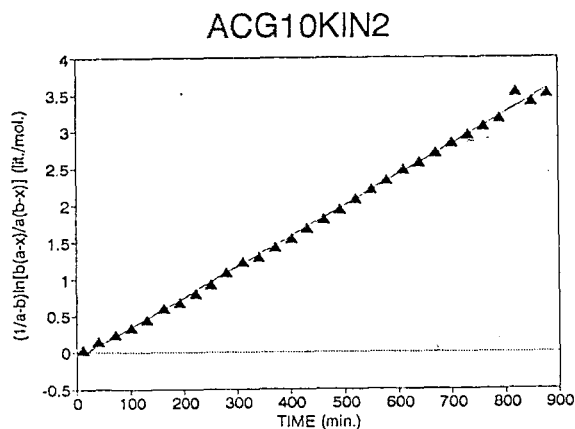
Regression Output:

Constant	-0.07791
Std Err of Y Est	0.048475
R Squared	0.998118
No. of Observations	30
Degrees of Freedom	28
X Coefficient(s)	0.004153
Std Err of Coef.	0.000034

228

Kinetic data for reaction of compound 226

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln[b(a-x)/a(b-x)]$ (lit./mol.)
11	1.72	0.328	0.424	0.040
41	6.41	0.313	0.409	0.158
71	10.67	0.298	0.394	0.274
101	14.57	0.285	0.381	0.389
131	18.33	0.273	0.369	0.509
161	21.89	0.261	0.357	0.632
191	25.25	0.250	0.346	0.757
221	28.45	0.239	0.335	0.885
251	31.70	0.228	0.324	1.027
281	34.47	0.219	0.315	1.156
311	37.16	0.210	0.306	1.291
341	39.69	0.201	0.297	1.428
371	42.01	0.194	0.290	1.561
401	44.31	0.186	0.282	1.703
431	46.42	0.179	0.275	1.841
461	48.37	0.172	0.268	1.978
491	50.20	0.166	0.262	2.114
521	51.93	0.161	0.257	2.250
551	53.62	0.155	0.251	2.391
581	55.18	0.150	0.246	2.529
611	56.58	0.145	0.241	2.660
641	58.06	0.140	0.236	2.805
671	59.35	0.136	0.232	2.938
701	60.49	0.132	0.228	3.062
731	61.71	0.128	0.224	3.201
761	62.77	0.124	0.220	3.327
791	63.81	0.121	0.217	3.457
821	64.30	0.119	0.215	3.520
851	65.11	0.117	0.213	3.627
881	65.93	0.114	0.210	3.740

ACG14KIN1
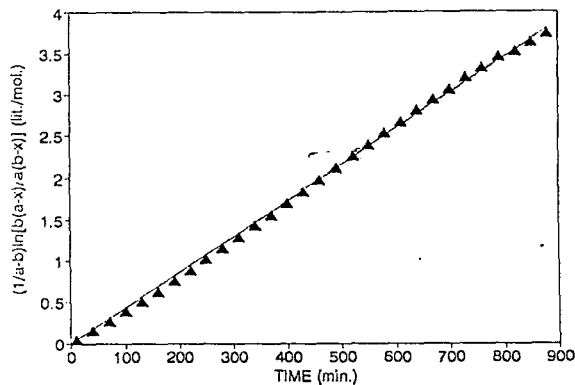
Regression Output:

Constant	0
Std Err of Y Est	0.042075
R Squared	0.998689
No. of Observations	30
Degrees of Freedom	29
X Coefficient(s)	0.00431
Std Err of Coef.	0.000015

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln[b(a-x)/a(b-x)]$ (lit./mol)
11	1.77	0.327	0.424	0.041
41	5.85	0.314	0.411	0.143
71	10.89	0.297	0.394	0.280
101	14.98	0.283	0.380	0.401
131	18.89	0.270	0.367	0.527
161	22.50	0.258	0.355	0.653
191	24.31	0.252	0.349	0.721
221	27.56	0.241	0.338	0.848
251	30.54	0.231	0.328	0.974
281	33.42	0.222	0.319	1.105
311	36.06	0.213	0.310	1.234
341	39.02	0.203	0.300	1.390
371	41.05	0.196	0.293	1.504
401	43.69	0.188	0.285	1.662
431	46.09	0.180	0.277	1.818
461	47.58	0.175	0.272	1.920
491	49.26	0.169	0.266	2.041
521	50.95	0.163	0.260	2.170
551	52.51	0.158	0.255	2.295
581	53.97	0.153	0.250	2.419
611	55.31	0.149	0.246	2.538
641	56.72	0.144	0.241	2.670
671	57.87	0.140	0.237	2.782
701	59.00	0.137	0.234	2.898
731	61.66	0.128	0.225	3.191
761	62.85	0.124	0.221	3.332
791	63.19	0.123	0.220	3.374
821	64.17	0.119	0.216	3.498
851	65.29	0.116	0.213	3.646
881	66.35	0.112	0.209	3.793

ACG14KIN2
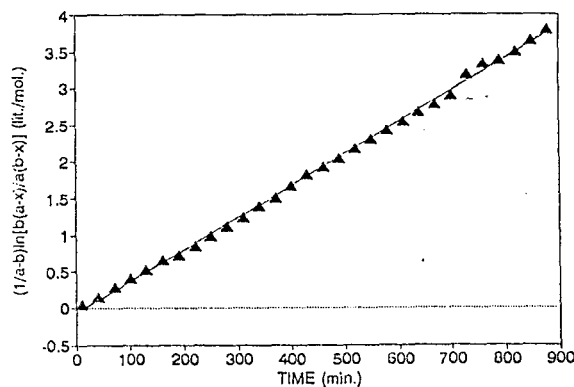
Regression Output:

Constant	-0.07102
Std Err of Y Est	0.044681
R Squared	0.998532
No. of Observations	30
Degrees of Freedom	28
X Coefficient(s)	0.004336
Std Err of Coef.	0.000031

229

Kinetic data for reaction of compound 228

RUN 1

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln\lvert b(a-x)/a(b-x)\rvert$ (lit./mol)
12	1.28	0.329	0.426	0.030
42	4.97	0.316	0.413	0.121
72	9.71	0.301	0.398	0.247
102	13.74	0.287	0.384	0.364
132	17.85	0.274	0.371	0.493
162	21.61	0.261	0.358	0.622
192	24.23	0.252	0.349	0.718
222	27.49	0.241	0.338	0.846
252	30.52	0.231	0.328	0.974
282	33.48	0.222	0.319	1.109
312	36.01	0.213	0.310	1.232
342	37.48	0.208	0.305	1.308
372	40.30	0.199	0.296	1.461
402	42.50	0.191	0.288	1.590
432	43.66	0.188	0.285	1.661
462	45.33	0.182	0.279	1.768
492	47.16	0.176	0.273	1.891
522	49.27	0.169	0.266	2.042
552	50.62	0.164	0.261	2.145
582	52.19	0.159	0.256	2.269
612	53.72	0.154	0.251	2.398
642	54.43	0.152	0.249	2.460
672	55.48	0.148	0.245	2.554
702	56.59	0.145	0.242	2.658
732	57.74	0.141	0.238	2.770
762	58.65	0.138	0.235	2.862
792	59.54	0.135	0.232	2.955
822	60.52	0.131	0.228	3.062
852	61.37	0.129	0.226	3.158
882	61.07	0.130	0.227	3.123

ACG64KIN1
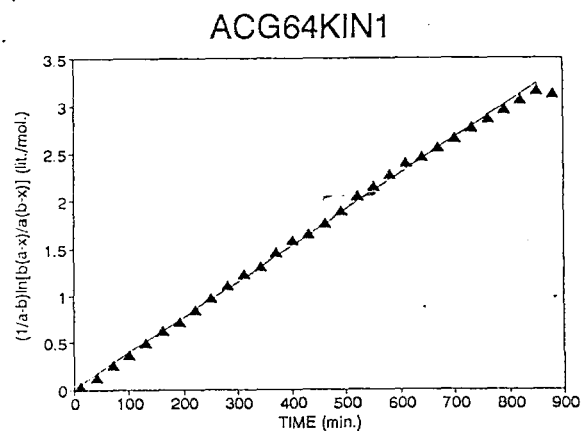
Regression Output:

Constant	0.013481
Std Err of Y Est	0.03939
R Squared	0.998399
No. of Observations	29
Degrees of Freedom	27

X Coefficient(s)	0.003782
Std Err of Coef.	0.000029

RUN 2

TIME (minutes)	%FORMATION	[A]	[B]	$(1/a-b)*\ln\lvert b(a-x)/a(b-x)\rvert$ (lit./mol)
13	2.17	0.326	0.423	0.051
43	8.51	0.305	0.402	0.214
73	13.56	0.288	0.385	0.359
103	18.43	0.272	0.369	0.512
133	22.27	0.259	0.356	0.646
163	25.90	0.247	0.344	0.782
193	30.00	0.233	0.330	0.951
223	33.25	0.222	0.319	1.098
253	36.10	0.213	0.310	1.237
283	38.80	0.204	0.301	1.378
313	41.21	0.196	0.293	1.513
343	43.47	0.188	0.285	1.649
373	45.52	0.181	0.278	1.780
403	47.45	0.175	0.272	1.911
433	49.25	0.169	0.266	2.041
463	50.92	0.163	0.260	2.168
493	52.44	0.158	0.255	2.290
523	53.88	0.154	0.251	2.411
553	55.02	0.150	0.247	2.512
583	56.21	0.146	0.243	2.622
613	57.37	0.142	0.239	2.733
643	58.63	0.138	0.235	2.860
673	59.48	0.135	0.232	2.949
703	60.69	0.131	0.228	3.081
733	61.57	0.128	0.225	3.181
763	62.38	0.125	0.222	3.276
793	63.13	0.123	0.220	3.367
823	63.86	0.120	0.217	3.459
853	64.84	0.117	0.214	3.586
883	65.49	0.115	0.212	3.674

ACG64KIN2
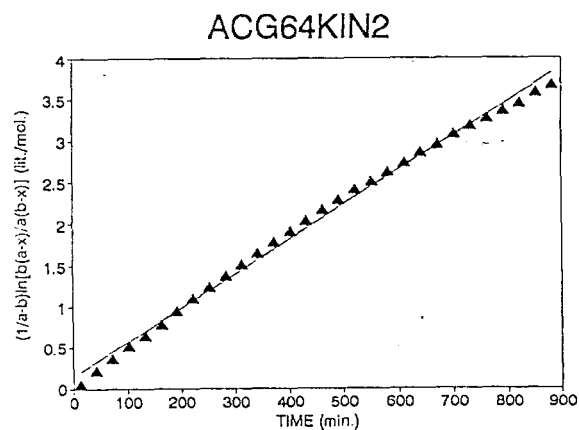
Regression Output:

Constant	0.147772
Std Err of Y Est	0.079961
R Squared	0.994902
No. of Observations	30
Degrees of Freedom	28

X Coefficient(s)	0.004156
Std Err of Coef.	0.000056

3.4   COMPETITION EXPERIMENTS

Materials and methods for radioreceptor binding assay.[250]

Fresh forebrains of Wister rats (supplied by the Biochemistry Department, Rhodes University) were homogenised gently in a 0.05M Tris-HCl buffer (pH 7.4) using a glass mortar and teflon pestle, followed by centrifugation at 20 000 rpm for 1 hour at 4°C. The supernatant containing cytosolic protein was decanted and the pellet was rehomogenised in Tris-HCl buffer. The protein concentration of the brain homogenates was determined by the Folin-Lowry method[250] as follows. A 1ml aliquot of protein sample was made up to 1.2ml with Tris-HCl buffer. To this was added 6ml of an alkaline solution prepared by mixing 1% $CuSO_4.5H_2O$ (1ml), 2% sodium tartrate (1ml) and 2% Na_2CO_3 in 0.1N NaOH (98ml). The mixture in the tube was left to stand at room temperature for 10 minutes. Folin reagent (0.3ml) was added into the tube which was then vortexed gently and left to stand for 30 minutes at room temperature, after which the absorbance was measured at 500nm. For the standard curve, protein standards containing 0-300μg of bovine serum albumin were assayed as above. A typical standard curve thus obtained is represented in figure 30. The final suspension was found to contain 2.25mg/ml protein. This was then diluted to a concentration of 1mg/ml protein for subsequent assay.

Binding assays were carried out in duplicate in a total volume of 250μl. In one set of tubes, various concentrations (0.5-150nM) of ^{3}H-diazepam[1] were incubated with the membranes (Table 28A). In another set of tubes, non-radioactive diazepam (100 fold excess) was added

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[1] ^{3}H-Diazepam (N-methyl-^{3}H); specific activity 83.0 Ci/mmol was obtained from New England Nuclear Research Products.

to the incubation medium containing the membranes and ^{3}H-diazepam (Table 28B) to determine non-specific binding. This was done to establish a saturation curve from which the K_D was determined. For competition studies, ^{3}H-diazepam at the K_D concentration was incubated with various concentrations ranging from 10^{-11} to 10^{-4}M of the test drug in every set of runs. Tubes were included for the duplicate determination of total binding (^{3}H-diazepam alone) and non-specific binding (^{3}H- and non-radioactive diazepam) (Table 29). In all cases the incubation mixtures were incubated at 25°C for 30 minutes. Following incubation, ice-cold Tris-HCl buffer (pH 7.4; 30ml) was rapidly added to each tube. The contents of each tube was rapidly filtered through Whatman GF/C glass fibre filters under negative pressure. The test tubes were rinsed with cold Tris-buffer (3.0ml), and the washings filtered. The filters were then washed with additional buffer (3ml) to remove any remaining unbound (free) ^{3}H-diazepam. The filters were shaken mechanically for 5 minutes in scintillation vials containing Scintillator 299™ (3ml). Bound ^{3}H-diazepam was estimated by conventional scintillation counting using a Beckman LS2800 instrument. The experimental data and the corresponding competition curves for various compounds obtained from these experiments are dealt with hereunder.
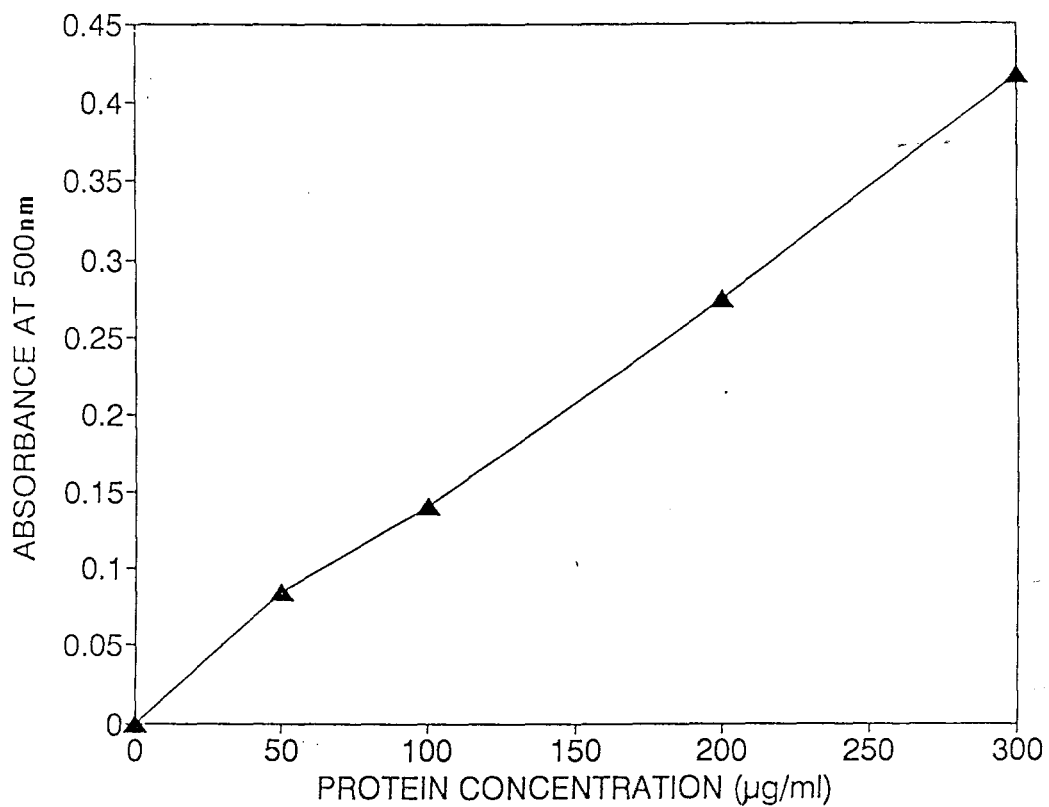
Protein Conc. (μg/ml)	Absorbance at 500nm
Blank	0
50	0.084
100	0.140
200	0.275
300	0.417

Figure 30. A typical protein standard curve.

Table 28. Composition of standards to assay the binding of ^{3}H-diazepam (^{3}H-DZP) on rat brain membranes.

A: Total binding (B_T)

^{3}H-DZP (nM)	Protein (1mg/ml) (μl)	Tris-HCl Buffer (μl)	^{3}H-DZP (μl)	50% EtOH (μl)	Vehicle (μl)
0.5	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 (1mg/ml) (μl)	Tris-HCl Buffer (μl)	^{3}H-DZP (μl)	50% EtOH (μl)	Vehicle (μl)
0.5	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
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	3.40	3.40	10.00
150.00	200.00	30.00	10.00	0.00	10.00

Table 29. Sample sets for competition studies using ^{3}H-DZP at K_D concentration, non-radioactive DZP and test drug at various concentrations (10^{-11}-10^{-4}M) in a total volume of 250μl.

	Protein (1mg/ml) (μl)	50% EtOH (μl)	Tris-HCl (μl)	^{3}H-DZP (μl)	DZP	Test Drug (μl)
B_T	200.00	20.00	20.00	10.00	-	-
B_{NS}	200.00	10.00	20.00	10.00	10.00	-
10^{-11}M	200.00	10.00	20.00	10.00	-	10.00
10^{-10}M	200.00	10.00	20.00	10.00	-	10.00
10^{-9}M	200.00	10.00	20.00	10.00	-	10.00
10^{-8}M	200.00	10.00	20.00	10.00	-	10.00
10^{-7}M	200.00	10.00	20.00	10.00	-	10.00
10^{-6}M	200.00	10.00	20.00	10.00	-	10.00
10^{-5}M	200.00	10.00	20.00	10.00	-	10.00
10^{-4}M	200.00	10.00	20.00	10.00	-	10.00
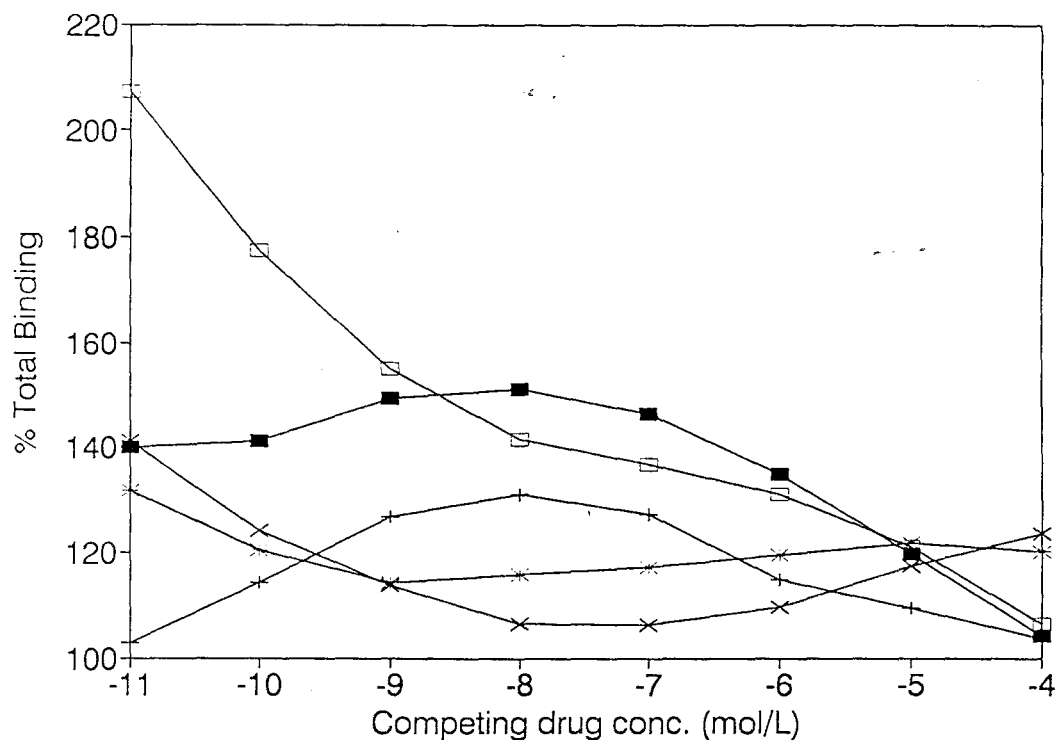
Figure 20. Competition curves for the 4-phenyl-1,5-benzodioxepinone derivatives.

Conc. (M)	% TOTAL BINDING				
	65 ■	222 *	225 +	226 x	228 □
10^{-11}	140	141.1	102.8	131.9	207.4
10^{-10}	141.1	124.0	114.2	120.5	177.5
10^{-9}	149.4	113.8	126.8	114.3	155.1
10^{-8}	151.2	106.6	131.1	115.8	141.6
10^{-7}	146.4	106.2	127.2	117.2	136.8
10^{-6}	135.1	109.8	115.0	119.5	131.2
10^{-5}	119.7	117.5	109.4	121.8	121.1
10^{-4}	104.2	123.6	103.8	106.5	106.5
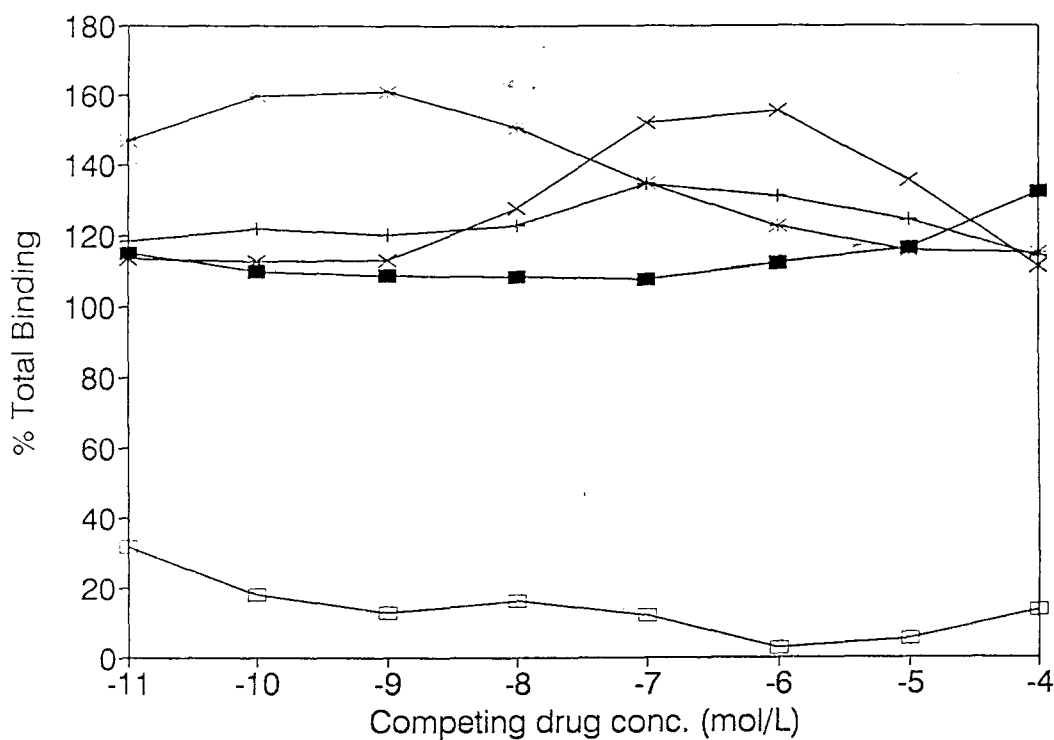
Figure 21. Competition curves for the 4-phenyl-1,5-benzoxathiepinone derivatives 250-254.

Conc. (M)	% TOTAL BINDING				
	250 ■	251 +	252 □	253 *	254 x
10^{-11}	115.3	118.5	31.6	146.9	113.4
10^{-10}	110.1	121.9	18.1	159.5	112.8
10^{-9}	108.9	120.4	13.0	160.9	113.2
10^{-8}	108.5	122.9	16.2	150.9	127.7
10^{-7}	112.3	134.5	12.0	135.0	152.0
10^{-6}	116.5	131.1	25.0	122.7	155.6
10^{-5}	132.2	124.4	5.4	115.7	135.7
10^{-4}	100.0	114.1	13.4	115.1	111.3
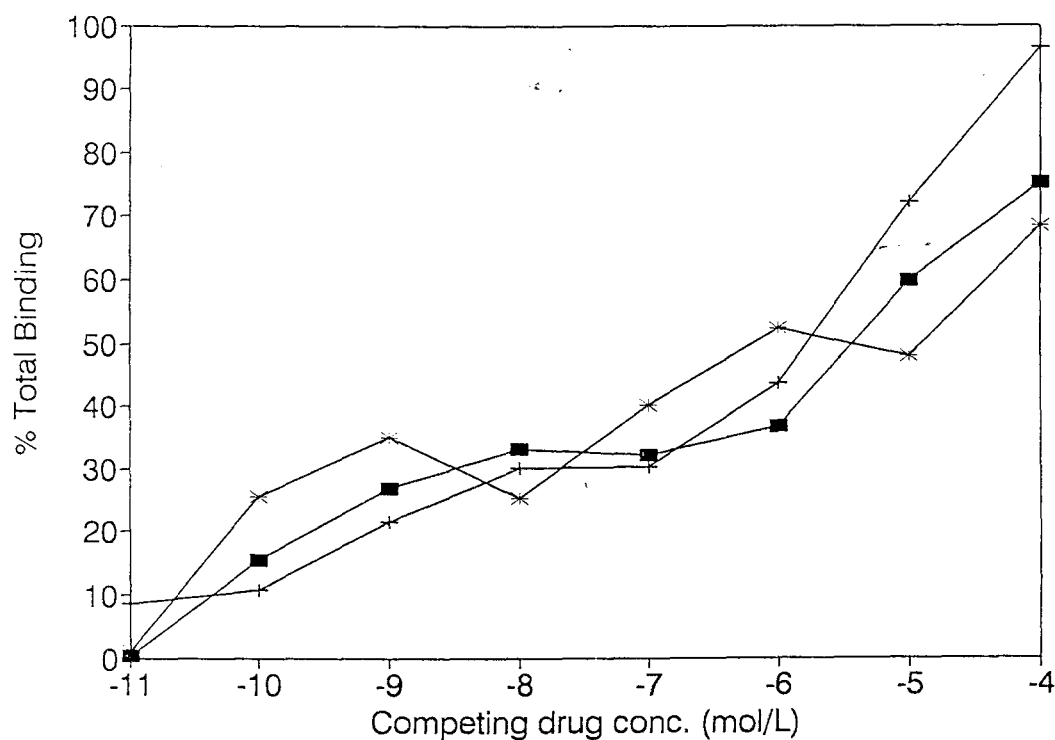
Figure 22.   Competition curves for   the 3-phenyl-4,1-benzoxathiepinone derivatives 261-263.

Conc. (M)	% TOTAL BINDING		
	261 *	262 +	263 ■
10^{-11}	1.1	8.6	0.2
10^{-10}	25.6	10.7	5.5
10^{-9}	35.0	21.5	26.9
10^{-8}	25.3	30.1	33.1
10^{-7}	40.3	30.3	32.2
10^{-6}	52.3	43.6	36.8
10^{-5}	48.0	72.1	59.8
10^{-4}	68.3	96.4	75.2
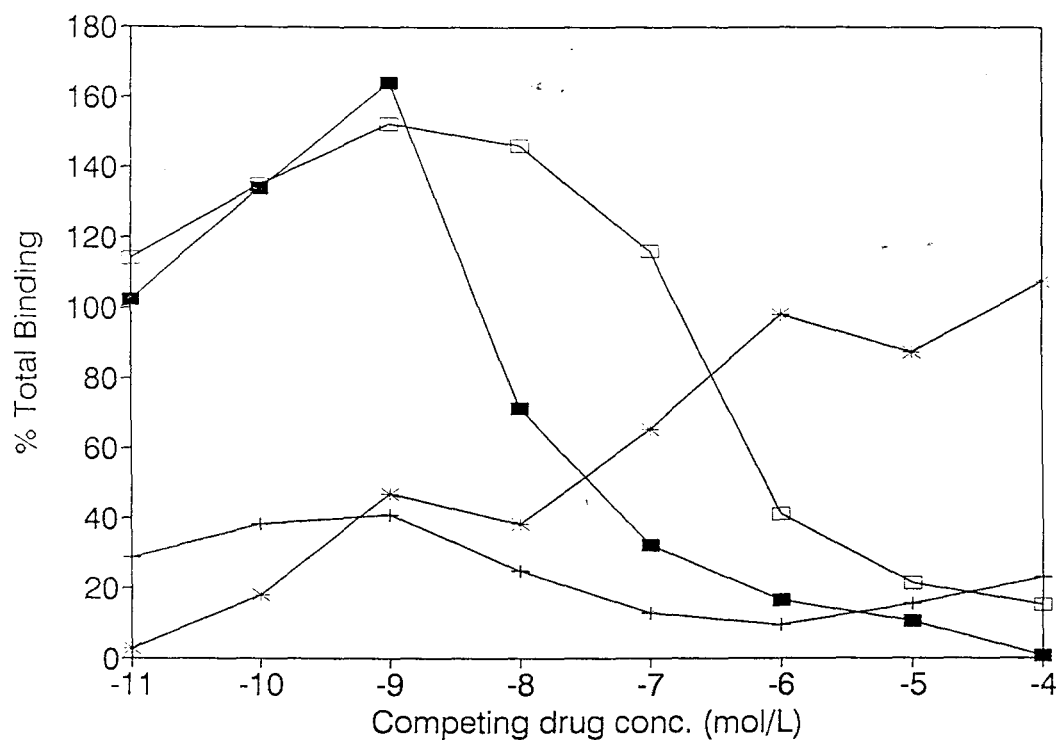
Figure 23.   Competition curves for the 3-phenyl-4,1-benzoxathiepine derivatives 267-270.

Conc. (M)	% TOTAL BINDING			
	267 *	268 +	269 □	270 ■
10^{-11}	2.7	28.5	114.1	102.5
10^{-10}	18.1	38.1	135.4	134.3
10^{-9}	47.1	40.8	152.4	164.2
10^{-8}	38.2	24.8	146.4	71.5
10^{-7}	65.4	13.0	116.1	32.3
10^{-6}	98.3	9.3	41.4	16.7
10^{-5}	87.3	15.4	21.4	10.3
10^{-4}	107.6	23.2	15.1	0.5

3.5   COMPUTER MODELLING

HYPERCHEM™, the molecular modelling package produced by Autodesk Inc., was used for computer modelling. Representative compounds from each series were constructed with the 2- or 3-phenyl substituent in either an axial or equatorial orientation. Energy minimisations were carried out using the Polak-Ribiere method (Tables 30-32). Although the energy minimised conformations obtained do not necessarily correspond to global minima, they do represent chemically reasonable arrangements which are consistent with other experimental data.

Table 30.   Minimum energies (kcal.mol⁻¹), total root-mean square gradient and the energy difference (ΔE/kcal.mol⁻¹) for "axial" and "equatorial" conformations of 4-phenyl-1,5-benzodiazepine analogues.
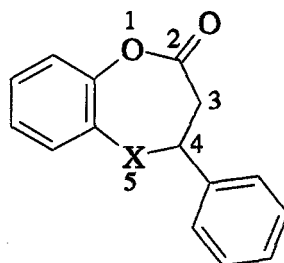
Compd.	X	Conformation[a]	Lowest Energies	Gradient	ΔE
65	O	Axial	8.689	0.097043	0.630
		Equatorial	8.059	0.094043	
250	S	Axial	11.537	0.095822	1.003
		Equatorial	10.534	0.093403	

[a] Refers to orientation of the 4-phenyl substituent.

Table 31: Minimum energies (kcal.mol^{-1}), total root-mean square gradient and energy difference (ΔE/kcal.mol^{-1}) for "axial" and "equatorial" conformations of 4,1-benzoxathiepinone analogues
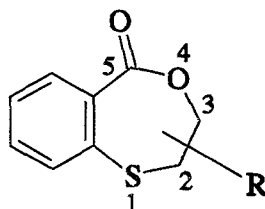
Compd.	R	Conformation[a]	Lowest Energies	Gradient	ΔE
266	2-ph	Axial	24.532	0.090731	4.594
		Equatorial	19.938	0.090108	
263	3-ph	Axial	23.317	0.095800	0.556
		Equatorial	22.761	0.095137	

[a] Refers to orientation of the 4-phenyl substituent.

Table 32. Minimum energies (kcal.mol^{-1}), total root-mean square gradient and the energy difference (ΔE/kcal.mol^{-1}) for "axial" and "equatorial" conformations of 3-phenyl-4,1-benzoxathiepine.
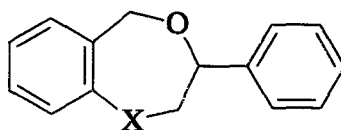
Compd.	Conformation[a]	Lowest Energies	Gradient	ΔE
270	Axial	6.583	0.088617	0.449
	Equatorial	6.134	0.092421	

[a] Refers to orientation of the 3-phenyl substituent.

3.6   X-RAY ANALYSIS

X-ray diffraction data were collected at the University of Natal, Pietermaritzburg. The

structures were solved for the author by direct methods using SHELXS-86,[274] and refined

using SHELX-76.[274] Crystal and collection data are summarised below, while the fractional

coordinates, anisotropic temperature factors, bond lengths, mean plane data and torsion

angles are tabulated in Appendix 1.

Table 33.   Crystal Data for 3,4-dihydro-4-(4-methoxyphenyl)-
1,5-benzodioxepin-2-one 228.[a]

Formula	$C_{16}H_{14}O_4$
Molar Mass	270.2826
Space group	$P2_1$, no. 4 (non-standard setting)
a(Å)	5.3700 (0.0018)
b(Å)	9.1922 (0.0011)
c(Å)	13.8950 (0.0028)
α	101.164 (0.013)
ß	90.0
γ	90.0
V(Å³)	672.91 (28)
F(000)	284.00
μ(cm⁻¹)	0.57
Number of reflections (2 < θ < 30°)	4045
Observed reflections [I > σ (I)]	3147
R,R$_W$	0.0812
N$_{parameters}$	187

[a] Estimated standard deviations in parentheses.

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Table 34.   Crystal Data for 3,4-dihydro-4-(4-chlorophenyl)-
1,5-benzoxathiepin-2-one 252.

Formula	$C_{15}H_{11}ClO_2S$
Molar Mass	290.7689
Crystal system	Monoclinic
Space group	C2/c
a(Å)	21.6639
b(Å)	4.6937
c(Å)	26.6021
α	90
ß	103.0921
γ	90
V(Å³)	2634
Z	8
D_c (g.cm⁻³)	1.463
F(000)	1200
μ(cm⁻¹)	3.85
Number of reflections (2 < θ < 30°)	3045
Observed reflections [I > σ (I)]	1824
R,R_W	0.0402, 0.0425
N_parameters	216
Weighting Scheme	w = 1 / [σ^2 (F) + 0.0006F²]

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APPENDIX 1: X-RAY CRYSTALLOGRAPHIC DATA

Table 35. Fractional coordinates (x10^4) for 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one 228 with e.s.d.'s in parentheses.

ATOM	X/a	Y/b	Z/c
O(1)	6413	-2138 (3)	2237 (2)
O(4)	8420 (9)	1239 (3)	4055 (2)
O(4′)	4275 (9)	3342 (3)	272 (2)
O(5)	9236 (9)	-1119 (3)	3932 (2)
C(2)	4504 (10)	-1068 (4)	2612 (2)
C(3)	4922 (10)	-425 (4)	3695 (3)
C(4)	7605 (10)	1 (4)	3896 (3)
C(5a)	8476 (10)	-2610 (4)	3670 (3)
C(6)	9364 (11)	-3567 (5)	4240 (3)
C(7)	8803 (12)	-5062 (5)	3968 (4)
C(8)	7360 (12)	-5567 (5)	3151 (4)
C(9)	6499 (12)	-4590 (4)	2586 (3)
C(9a)	7082 (11)	-3100 (4)	2843 (3)
C(1′)	4548 (10)	88 (4)	1970 (2)
C(2′)	6347 (10)	177 (4)	1266 (3)
C(3′)	6306 (10)	1177 (4)	675 (3)
C(4′)	4468 (10)	2244 (4)	803 (3)
C(5′)	2638 (11)	2214 (5)	1495 (3)
C(6′)	2662 (10)	1166 (4)	2077 (3)
C(10)	6084 (13)	3406 (6)	-461 (4)

Table 36: Bond angles (°), with e.s.d.'s in parentheses for 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one 228.

C(9a)- O(1)- C(2)	115.9 (3)
C(10) - O(4') - C(4')	118.3 (4)
C(5a) - O(5) - C(4)	120.6 (3)
C(3) - C(2) - O(1)	111.0 (3)
C(1') - C(2) - O(1)	106.5 (3)
C(1') - C(2) - C(3)	113.4 (3)
C(4) - C(3) - C(2)	111.2 (3)
O(5) - C(4) - O(4)	117.1 (4)
C(3) - C(4) - O(4)	126.0 (4)
C(3) - C(4) - O(5)	116.9 (3)
C(9a) - C(5a) - O(5)	121.3 (3)
C(9a) - C(5a) - C(6)	121.8 (3)
C(7) - C(6) - C(5a)	118.5 (4)
C(8) - C(7) - C(6)	120.3 (4)
C(9) - C(8) - C(7)	120.2 (4)
C(9a) - C(9) - C(8)	119.8 (4)
C(5a) - C(9a) - O(1)	120.5 (3)
C(9) - C(9a) - O(1)	120.2 (4)
C(9) - C(9a) - C(5a)	119.2 (4)
C(2') - C(1') - C(2)	122.7 (3)
C(6') - C(1') - C(2)	119.2 (3)
C(6') - C(1') - C(2')	118.1 (3)
C(3') - C(2') - C(1')	121.3 (4)
C(4') - C(3') - C(2')	119.8 (4)
C(3') - C(4') - O(4')	124.5 (4)
C(5') - C(4') - O(4')	116.1 (4)
C(5') - C(4') - C(3')	119.4 (3)
C(6') - C(5') - C(4')	121.0 (4)
C(5') - C(6') - C(1')	120.4 (4)

Table 37. Bond lengths (Å) with e.s.d.'s in parentheses for 3,4-dihydro-4-(4-methoxyphenyl)-1,5-benzodioxepin-2-one 228.

C(2) - O(1)	1.446 (5)
C(9a) - O(1)	1.381 (4)
C(4) - O(4)	1.199 (4)
C(4') - O(4')	1.364 (4)
C(10) - O(4')	1.481 (6)
C(4) - O(5)	1.360 (4)
C(5a) - O(5)	1.409 (4)
H(2) - C(2)	1.080
C(3) - C(2)	1.523 (5)
C(1') - C(2)	1.514 (5)
C(4) - C(3)	1.505 (5)
C(6) - C(5a)	1.379 (5)
C(9a) - C(5a)	1.372 (5)
C(7) - C(6)	1.386 (6)
C(8) - C(7)	1.379 (7)
C(9) - C(8)	1.382 (6)
C(9a) - C(9)	1.383 (5)
C(2') - C(1')	1.378 (5)
C(6') - C(1')	1.404 (5)
C(3') - C(2')	1.392 (5)
C(4') - C(3')	1.378 (5)
C(5') - C(4')	1.379 (5)
C(6') - C(5')	1.373 (5)
O(4') - C(10)	1.418 (6)

Table 38. Fractional coordinates (x10⁴) and isotropic thermal factors ($\mathring{A}^2$, x10³) for 3,4-dihydro-4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one 252.

ATOM	X/a	Y/b	Z/c	U$_{eq}$
Cl	3193	-172 (2)	2714	58
S	5692	-9884 (2)	3654	48
O(1)	5811 (1)	-10375 (6)	5111 (1)	80 (1)
O(2)	6501 (1)	-8487 (5)	4731 (1)	52
C(1)	3743 (1)	-2534 (6)	3066 (1)	42 (1)
C(2)	4274 (1)	-3231 (7)	2892 (1)	44 (1)
C(3)	4706 (1)	-5141 (7)	3169 (1)	43 (1)
C(4)	4619 (1)	-6333 (6)	3622 (1)	37 (1)
C(5)	4076 (1)	-5583 (7)	3786 (1)	50 (1)
C(6)	3640 (2)	-3702 (8)	3513 (1)	51 (1)
C(7)	5086 (1)	-8347 (6)	3955 (1)	39 (1)
C(8)	5401 (1)	-6910 (7)	4466 (1)	44 (1)
C(9)	5898 (1)	-8740 (8)	4793 (1)	52 (1)
C(10)	6641 (1)	-6948 (6)	4321 (1)	44 (1)
C(11)	7152 (1)	-5144 (7)	4448 (1)	56 (1)
C(12)	7358 (2)	-3774 (9)	4063 (2)	71 (1)
C(13)	7058 (2)	-4200 (9)	3558 (2)	72 (1)
C(14)	6537 (2)	-5997 (8)	3434 (1)	57 (1)
C(15)	6317 (1)	-7415 (6)	3817 (1)	42 (1)
H(1)	4319 (13)	-2415 (63)	2574 (11)	56 (9)*
H(2)	5053 (14)	-5652 (65)	3043 (12)	58 (9)*
H(3)	3998 (12)	-6364 (61)	4077 (11)	43 (8)*
H(4)	3295 (14)	-3284 (63)	3632 (10)	52 (8)*
H(5)	4857 (12)	-10043 (60)	4034 (10)	44 (8)*
H(6)	5075 (14)	-6454 (65)	4629 (11)	53 (8)*
H(7)	5585 (13)	-5107 (64)	4397 (10)	48 (8)*
H(8)	7367 (15)	-4908 (71)	4810 (13)	69 (10)*
H(9)	7723 (18)	-2624 (79)	4135 (14)	91 (13)*
H(10)	7179 (16)	-3275 (84)	3310 (13)	80 (12)*
H(11)	6333 (12)	-6391 (66)	3115 (11)	46 (8)*

* isotropic temperature factor $U_{eq} = (1/3) \, \Sigma_i \Sigma_j \, U_{ij} a_i^* a_j^* (a_i . a_j)$

Table 39. Interatomic angles (°) for 3,4-dihydro-4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one 252.

|			
C(7) - S - C(15)	102.7 (1)	C(9) - O(2) - C(10)	121.6 (2)
Cl - C(1) - C(2)	119.6 (2)	Cl - C(1) - C(6)	119.6 (2)
C(2) - C(1) - C(6)	120.7 (3)	C(1) - C(2) - C(3)	119.4 (3)
C(1) - C(2) - H(1)	118 (2)	C(3) - C(2) - H(1)	123 (2)
C(2) - C(3) - C(4)	121.3 (3)	C(2) - C(3) - H(2)	119 (2)
C(4) - C(3) - H(2)	120 (2)	C(3) - C(4) - C(5)	117.7 (3)
C(3) - C(4) - C(7)	123.9 (2)	C(5) - C(4) - C(7)	118.4 (2)
C(4) - C(5) - C(6)	121.8 (3)	C(4) - C(5) - H(3)	120 (2)
C(6) - C(5) - H(3)	118 (2)	C(1) - C(6) - C(5)	119.0 (3)
C(1) - C(6) - H(4)	122 (2)	C(5) - C(6) - H(4)	119 (2)
S - C(7) - C(4)	116.1 (2)	S - C(7) - C(8)	110.0 (2)
C(4) - C(7) - C(8)	110.3 (2)	S - C(7) - H(5)	103 (2)
C(4) - C(7) - H(5)	109 (2)	C(8) - C(7) - H(5)	108 (2)
C(7) - C(8) - C(9)	112.3 (3)	C(7) - C(8) - H(6)	106 (2)
C(9) - C(8) - H(6)	113 (2)	C(7) - C(8) - H(7)	110 (2)
C(9) - C(8) - H(7)	110 (2)	H(6) - C(8) - H(7)	106 (2)
O(1) - C(9) - O(2)	117.0 (3)	O(1) - C(9) - C(8)	125.1 (3)
O(2) - C(9) - C(8)	117.8 (3)	O(2) - C(10) - C(11)	115.6 (3)
O(2) - C(10) - C(15)	121.6 (3)	C(11) - C(10) - C(15)	122.5 (3)
C(10) - C(11) - C(12)	119.2 (3)	C(10) - C(11) - H(8)	119 (2)
C(12) - C(11) - H(8)	121 (2)	C(11) - C(12) - C(13)	120.3 (4)
C(11) - C(12) - H(9)	121 (2)	C(13) - C(12) - H(9)	118 (2)
C(12) - C(13) - C(14)	120.0 (4)	C(12) - C(13) - H(10)	121 (2)
C(14) - C(13) - H(10)	119 (2)	C(13) - C(14) - C(15)	120.9 (3)
C(13) - C(14) - H(11)	124 (2)	C(15) - C(14) - H(11)	115 (2)
S - C(15) - C(10)	122.3 (2)	S - C(15) - C(14)	120.5 (2)
C(10) - C(15) - C(14)	117.0 (3)		

Table 40. Interatomic distances (Å) for 3,4-dihydro-4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one 252.

|			
Cl - C(1)	1.738 (3)	S - C(7)	1.832 (3)
S - C(15)	1.761 (3)	O(1) - C(9)	1.189 (3)
O(2) - C(9)	1.356 (3)	O(2) - C(10)	1.397 (3)
C(1) - C(2)	1.373 (4)	C(1) - C(6)	1.375 (4)
C(2) - C(3)	1.382 (4)	C(2) - H(1)	0.95 (3)
C(3) - C(4)	1.380 (4)	C(3) - H(2)	0.92 (3)
C(4) - C(5)	1.389 (4)	C(4) - C(7)	1.516 (4)
C(5) - C(6)	1.374 (4)	C(5) - H(3)	0.91 (3)
C(6) - H(4)	0.90 (3)	C(7) - C(8)	1.533 (4)
C(7) - H(5)	0.99 (3)	C(8) - C(9)	1.493 (4)
C(8) - H(6)	0.93 (3)	C(8) - H(7)	0.97 (3)
C(10) - C(11)	1.374 (4)	C(10) - C(15)	1.384 (4)
C(11) - C(12)	1.367 (5)	C(11) - H(8)	0.98 (3)
C(12) - C(13)	1.369 (6)	C(12) - H(9)	0.94 (4)
C(13) - C(14)	1.388 (5)	C(13) - H(10)	0.88 (4)
C(14) - C(15)	1.387 (4)	C(14) - H(11)	0.88 (3)

Table 41. Anisotropic temperature factors ($Å^2$, $\times 10^3$) for 3,4-dihydro-4-(4-chlorophenyl)-1,5-benzoxathiepin-2-one 252.

| ATOM	U (11)	U (22)	U (33)	U (23)	U (13)	U (12)
Cl	57 (1)	56 (1)	57 (1)	9(1)	4(1)	13 (1)
S	49 (1)	40 (1)	53 (1)	-12 (1)	6 (1)	7 (1)
O(1)	70 (2)	105 (2)	63 (1)	43 (1)	10 (1)	-13 (2)
O(2)	45 (1)	58 (1)	49 (1)	16 (1)	2 (1)	-1 (1)
C(1)	44 (1)	35 (1)	44 (1)	-1 (1)	2 (1)	3 (1)
C(2)	47 (2)	45 (2)	39 (1)	2 (1)	9 (1)	0 (1)
C(3)	40 (1)	45 (2)	44 (1)	-5 (1)	12 (1)	0 (2)
C(4)	38 (1)	33 (1)	39 (1)	-4 (1)	6 (1)	-3 (1)
C(5)	51 (2)	54 (2)	48 (2)	13 (1)	18 (1)	6 (1)
C(6)	43 (2)	56 (2)	56 (2)	6 (2)	19 (1)	8 (2)
C(7)	38 (1)	36 (2)	43 (1)	-1 (1)	9 (1)	-2 (1)
C(8)	43 (2)	49 (2)	41 (1)	0 (1)	11 (1)	-1 (1)
C(9)	52 (2)	62 (2)	40 (1)	5 (2)	5 (1)	-9 (2)
C(10)	39 (1)	40 (2)	51 (2)	9 (1)	10 (1)	4 (1)
C(11)	42 (2)	52 (2)	71 (2)	5 (2)	6 (1)	-1 (2)
C(12)	47 (2)	68 (3)	101 (3)	17 (2)	24 (2)	-3 (2)
C(13)	68 (2)	71 (3)	92 (3)	28 (2)	48 (2)	15 (2)
C(14)	58 (2)	67 (2)	52 (2)	7 (2)	24 (2)	22 (2)
C(15)	41 (1)	38 (2)	50 (2)	1 (1)	13 (1)	9 (1)

APPENDIX II: ^{1}H NMR SPECTRA NOT INCLUDED IN TEXT
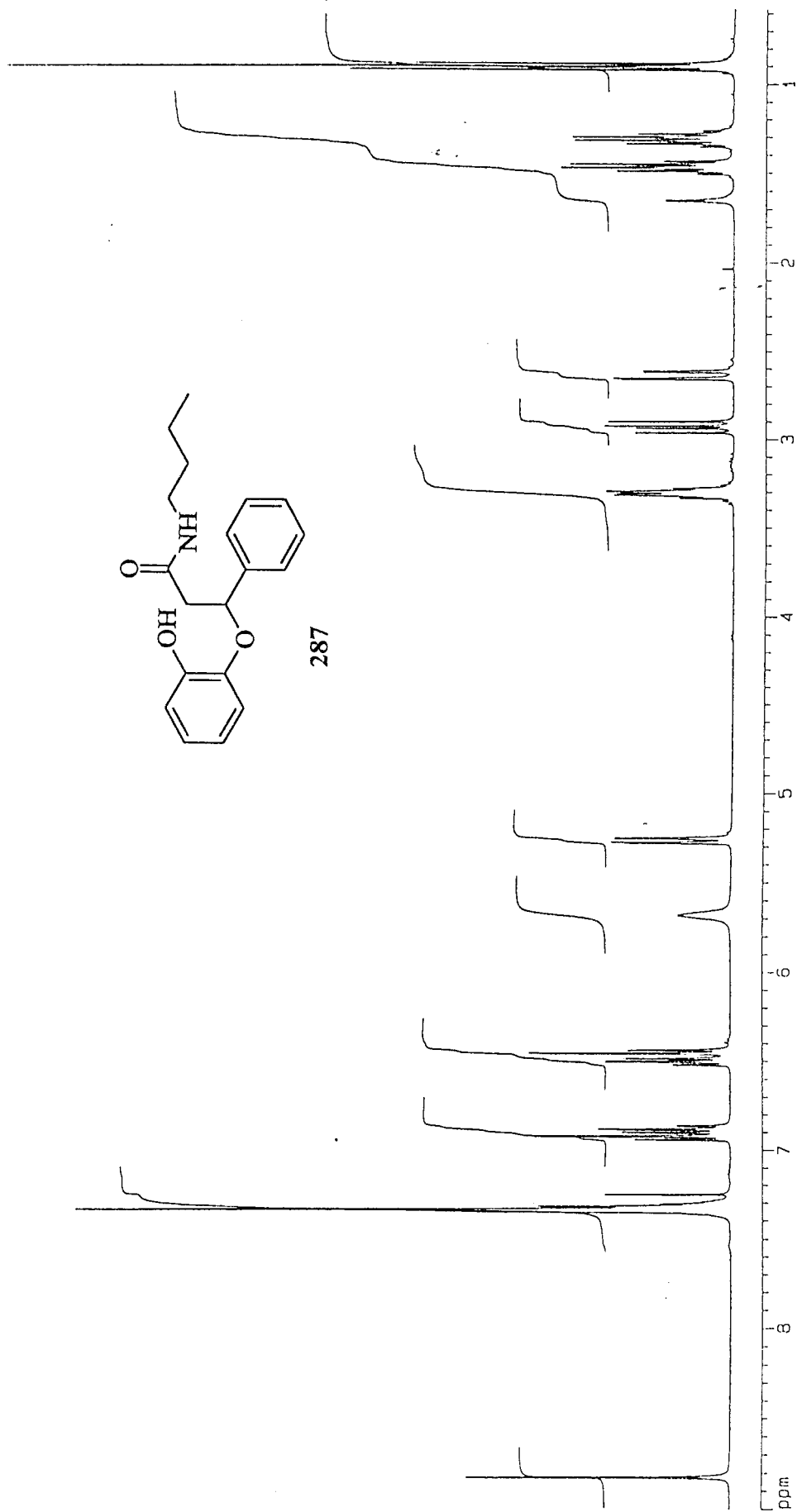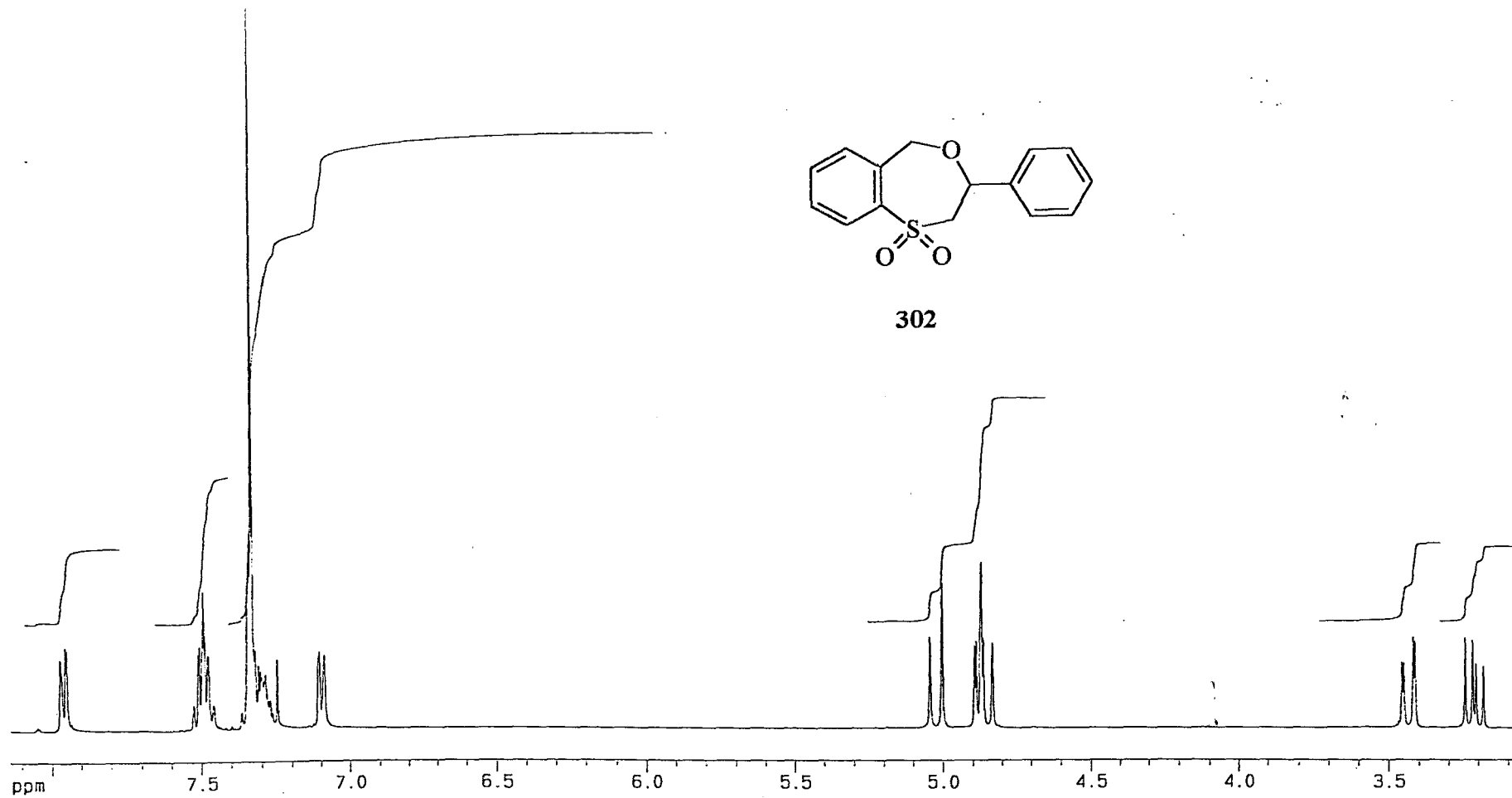
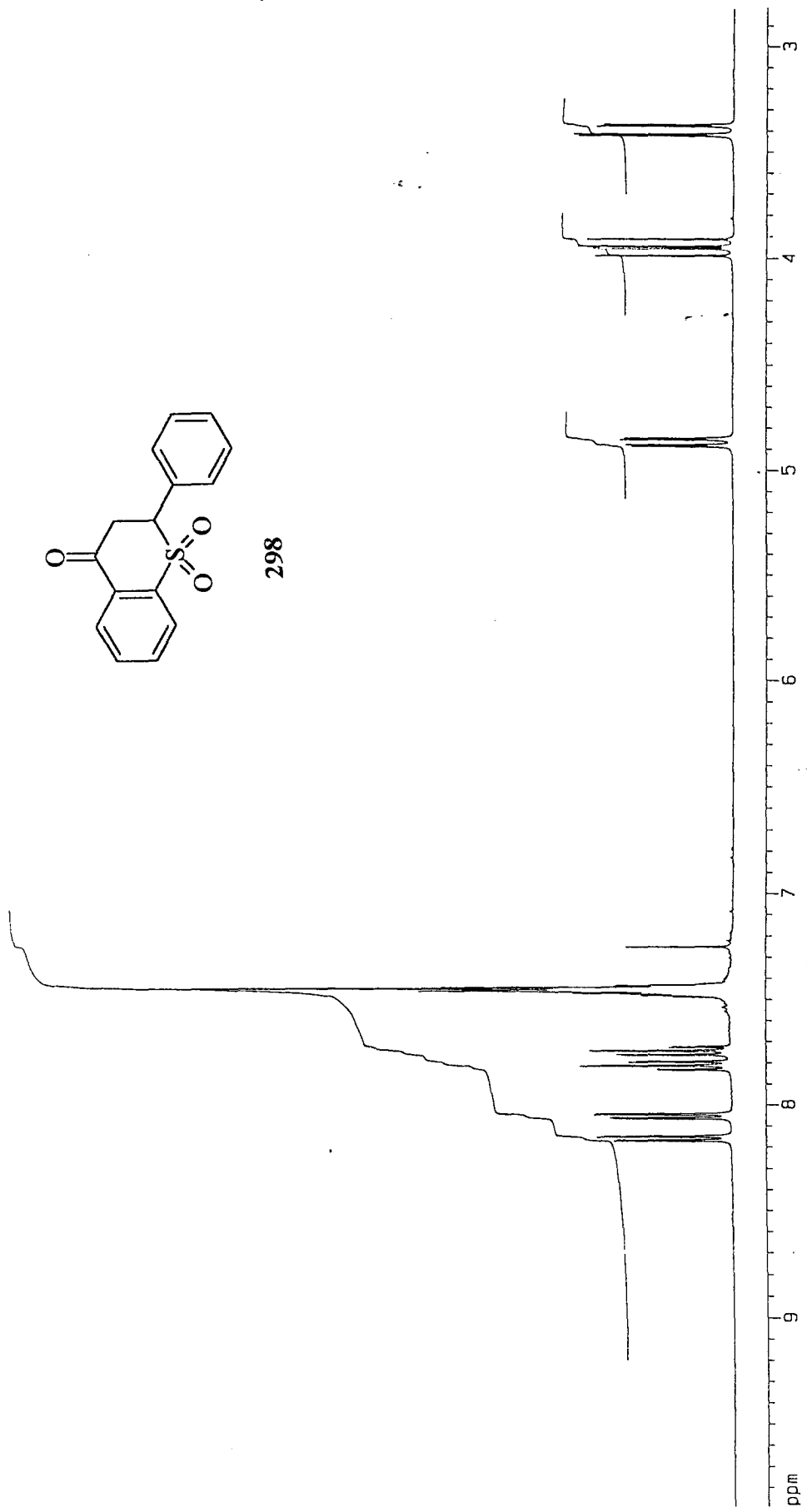Spectrum 2: *N*-Butyl-3-(2-hydroxyphen oxy)-3-phenylpropanamide **287**

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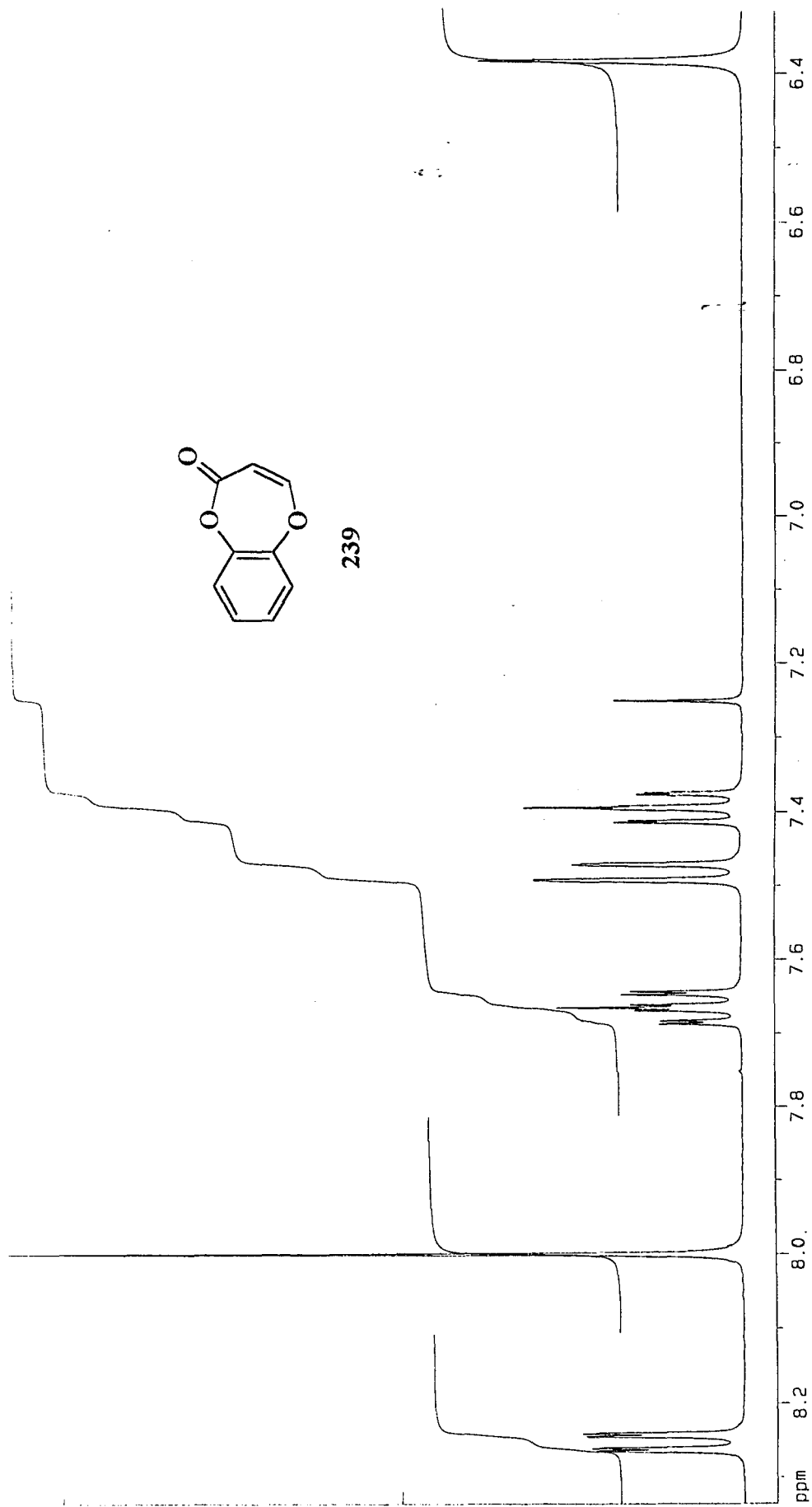
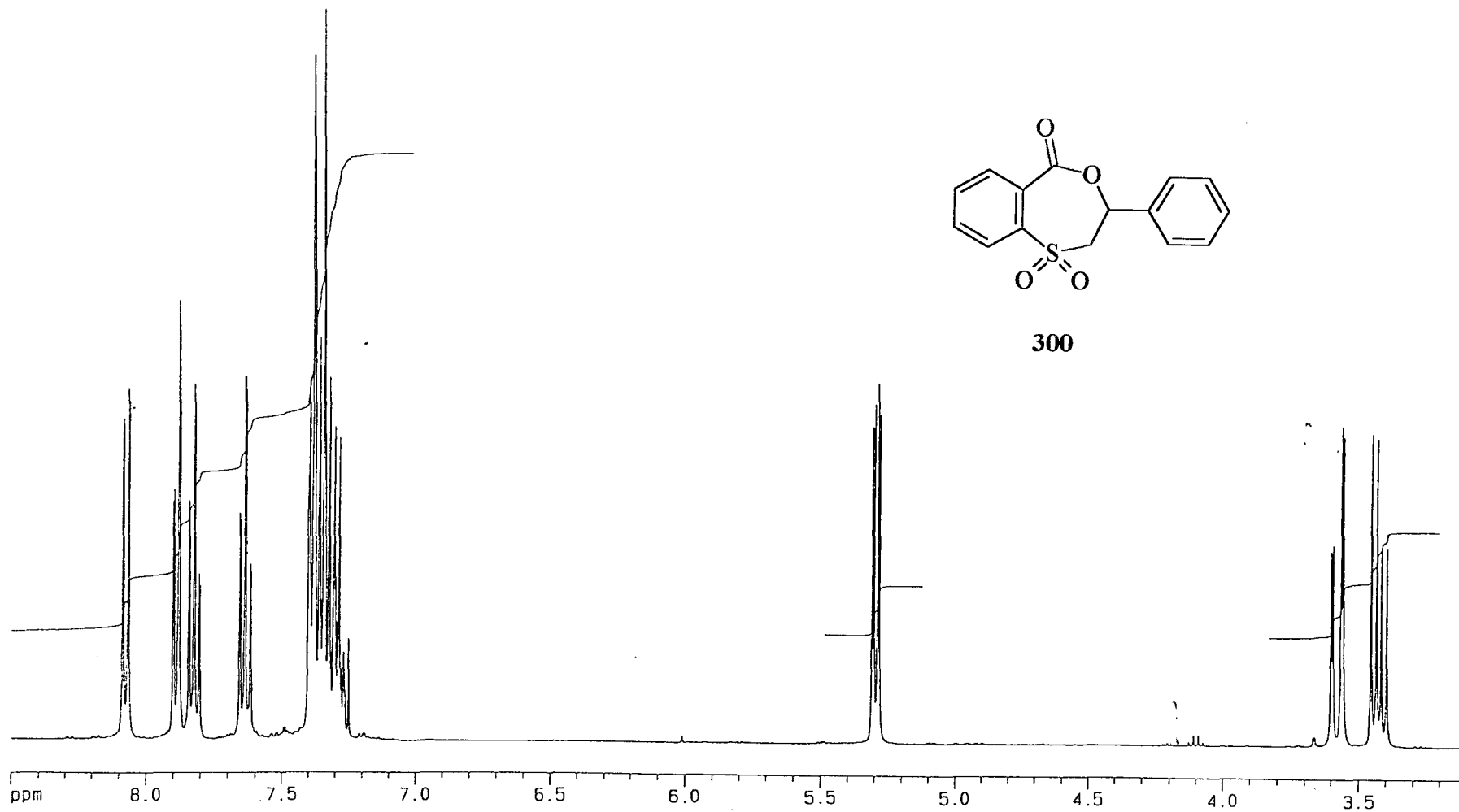Spectrum 1: 400 MHz ^{1}H NMR spectrum of 2*H*-1,5-benzodioxepin-2-one 239

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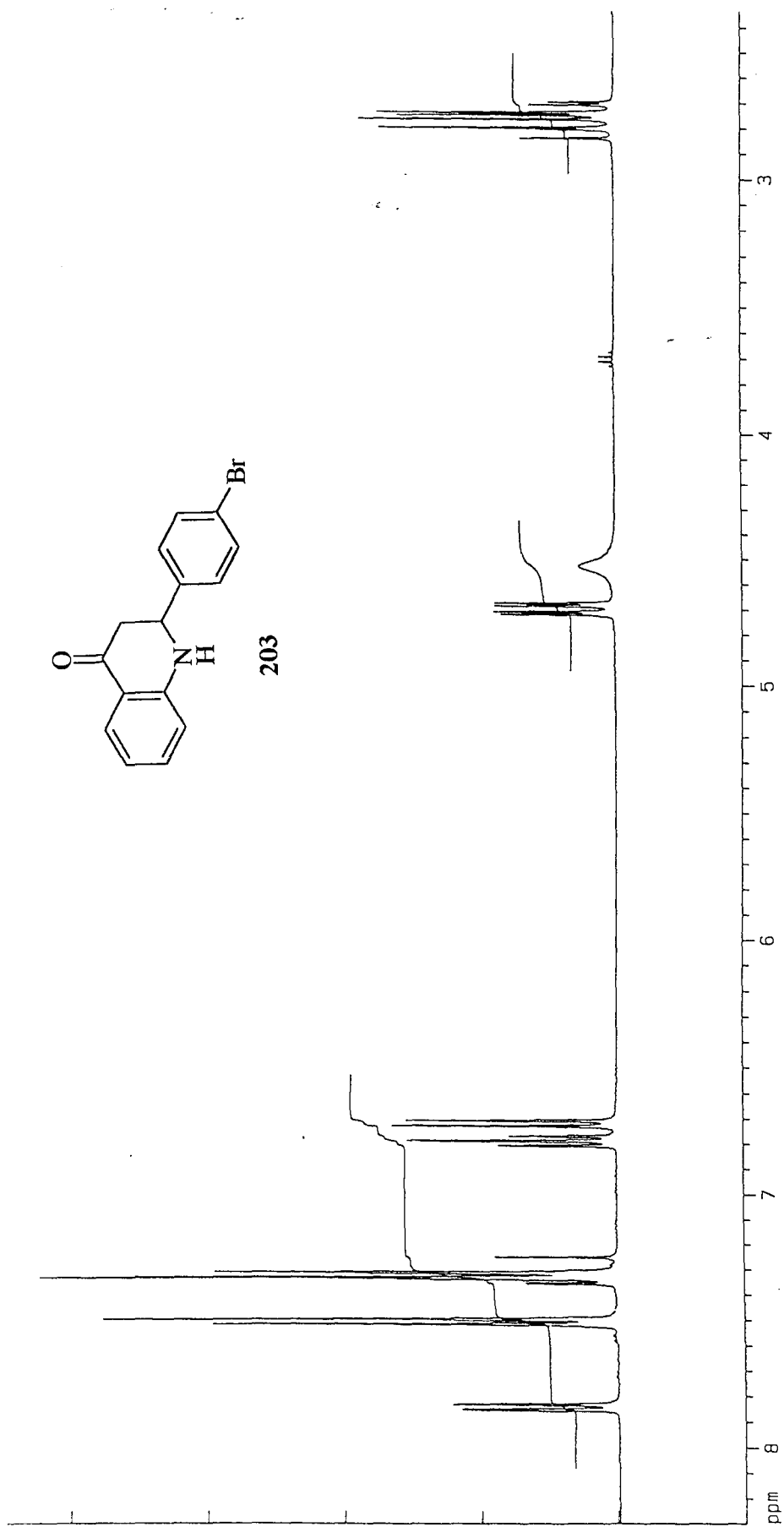
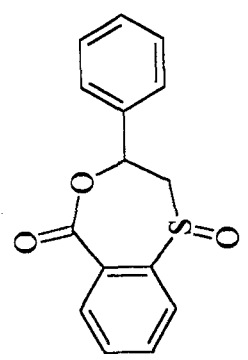Spectrum 3: 2-(4-Bromophenyl)-1,2,3,4-tetrahydro-4-quinolone **203**
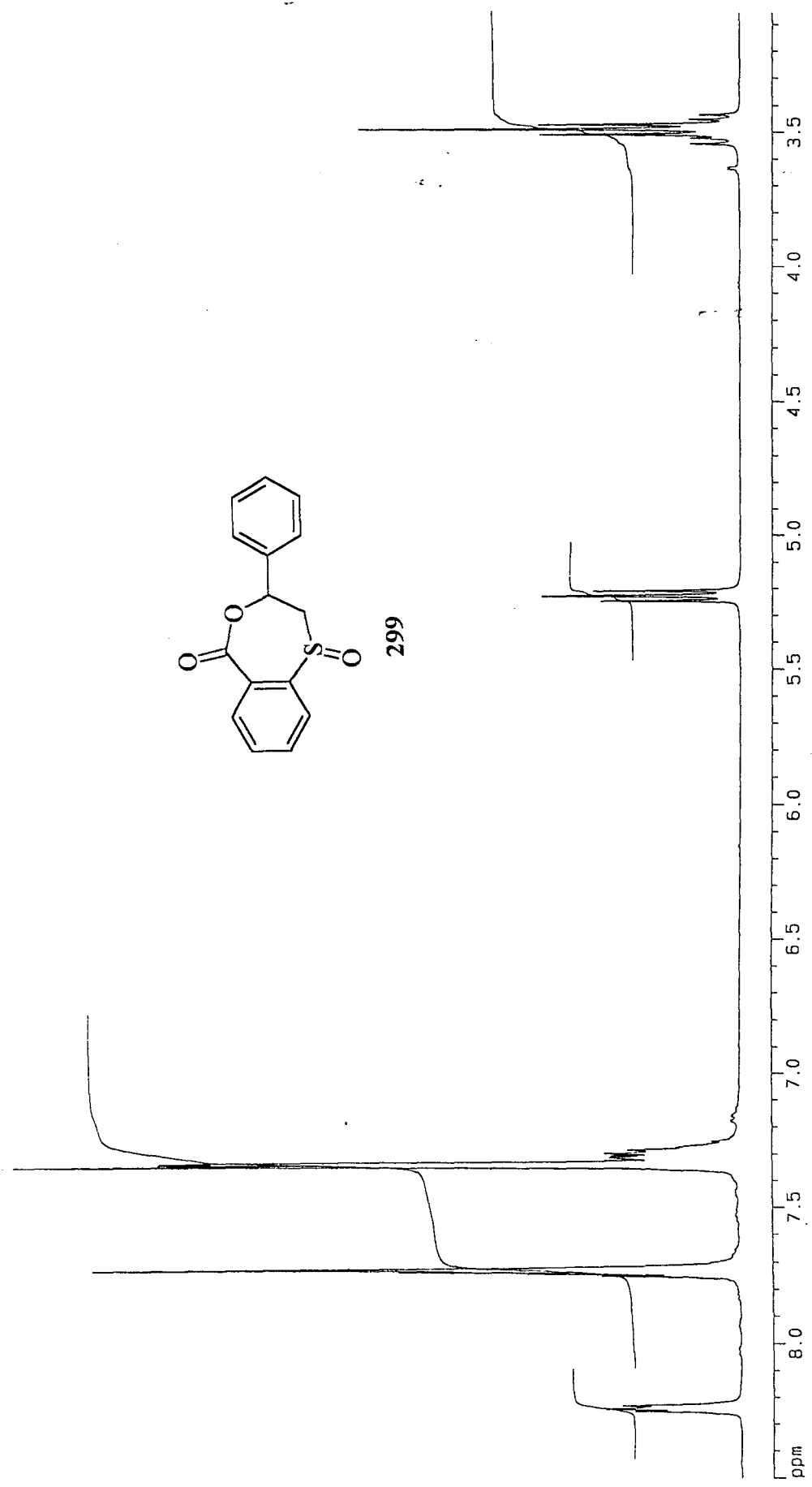
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Spectrum 4: 2,3-Dihydro-3-phenyl-4,1-benzoxathiepine 1,1-dioxide

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Spectrum 5: 2,3-Dihydro-2-phenyl-1-sulfone-*4H*-benzothiopyran-4-one 298

Spectrum 6: 2,3-Dihydro-3-phenyl-1-sulfone-4,1-benzoxathiepin-5-one 300

Spectrum 7: 2,3-Dihydro-3-phenyl-1-sulfoxide-4,1-benzoxathiepin-5-one 299

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