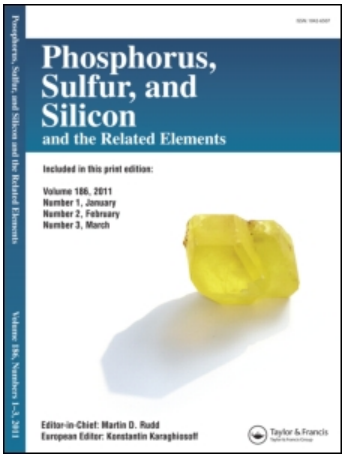

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The Utility of Diaryl Sulfides and Diaryl Sulfones in Heterocyclic Synthesis [1993-2003]

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The Utility of Diaryl Sulfides and Diaryl Sulfones in Heterocyclic Synthesis [1993–2003]

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The present review selectively describes the work, generally, reflecting the recent current state of knowledge about the utility of diaryl sulfides and diaryl sulfones in heterocyclic synthesis while emphasizing important development methods, main reactions, and their applications.

Keywords

A) INTRODUCTION

On surveying the literature, focusing on the last decade, it was found that a considerable work dealing with the chemistry, uses, and applications of diaryl sulfides and diaryl sulfones containing different heterocyclic and other organic moieties have been published. Generally it was reported that the main aim of the majority of the published studies is to evaluate the exchangeable intra and inter relationships between the basic molecules, i.e. diphenyl sulfide and diphenyl sulfone derivatives from one side and certain bonded organic heterocyclic moieties (isolated or condensed) on the other side and their mutual effects on the reactions and biological activities of the resulting combined molecules.

Diaryl sulfides and diaryl sulfones are not only the key structural elements of the most widely employed class of antibacterial drugs,[1–3] but also act as building blocks in certain polymers commonly used in moulding, coating, adhesive membranes, composite matrices, and engineering thermoplastics.[4–7]

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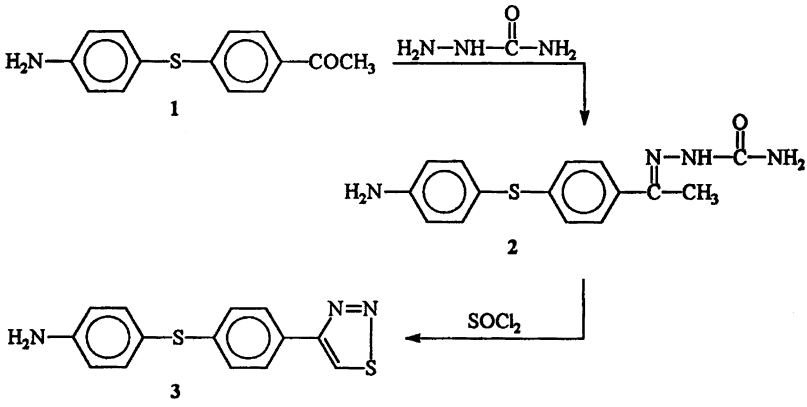
B) DIARYL SULFIDES IN HETEROCYCLIC SYNTHESIS

The reported synthetic routes can be classified into the following types:

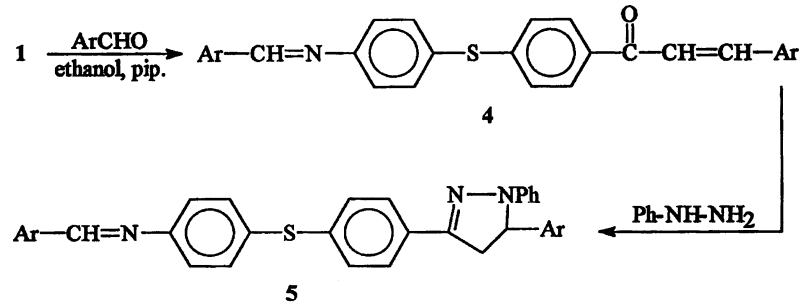
1) Diaryl Sulfides in Heterocyclic Synthesis Based on the Introduction of Ph-S-Ph Group in a Heterocyclic Ring

Preparation of diaryl sulfides containing thiadiazoles, pyrazolines, isoxazolines, and pyrimidines:

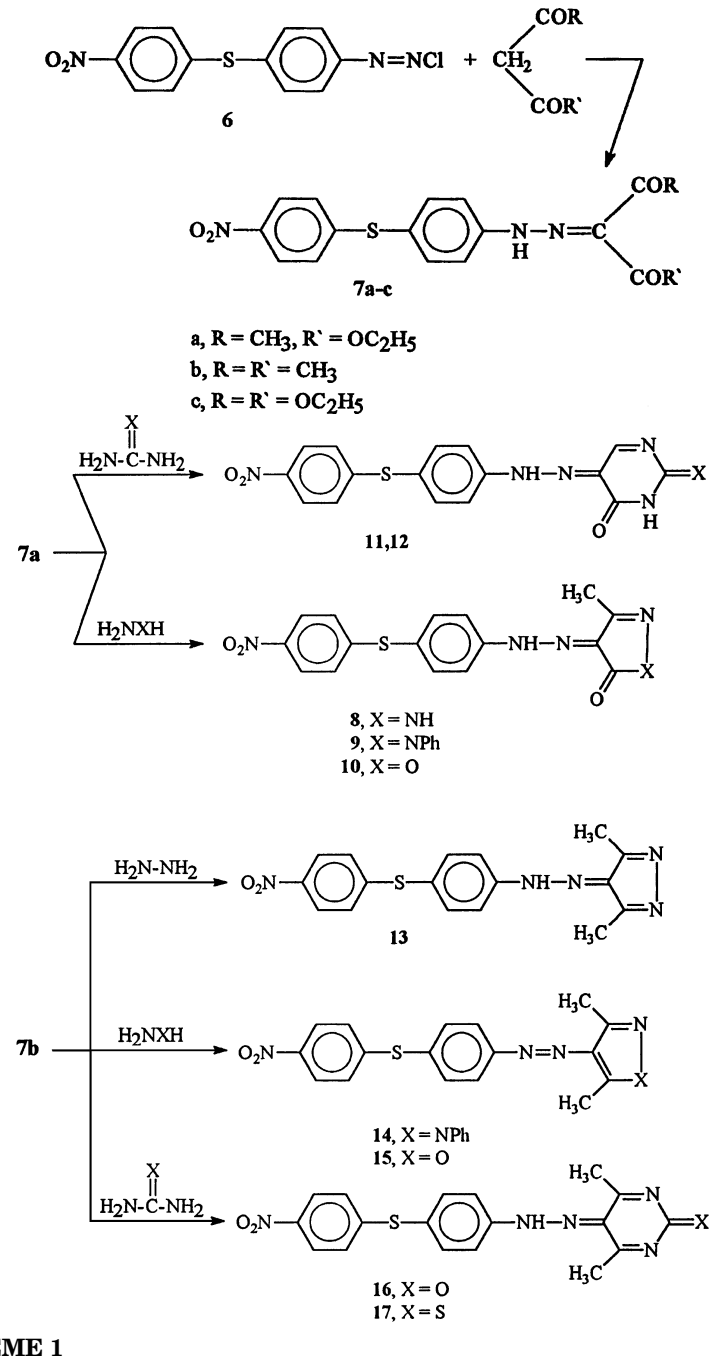
4-Amino-4′-acetyl diphenyl sulfide **1** reacted with semicarbazide to give the respective semicarbazone **2** which upon reaction with thionyl chloride gave 1,2,3 thiadiazole derivative[8] **3**.



On the other side, compound **1** condensed with aromatic aldehydes in presence of piperidine to give the sulfide **4**, which upon reaction with phenylhydrazine gave 1-phenyl-Δ^2-pyrazoline derivatives[9] **5**.



Ar = Ph, 4-MeOC$_6$H$_4$-, 4-CH$_3$-C$_6$H$_4$, 4-O$_2$N-C$_6$H$_4$, 4-Cl-C$_6$H$_4$-

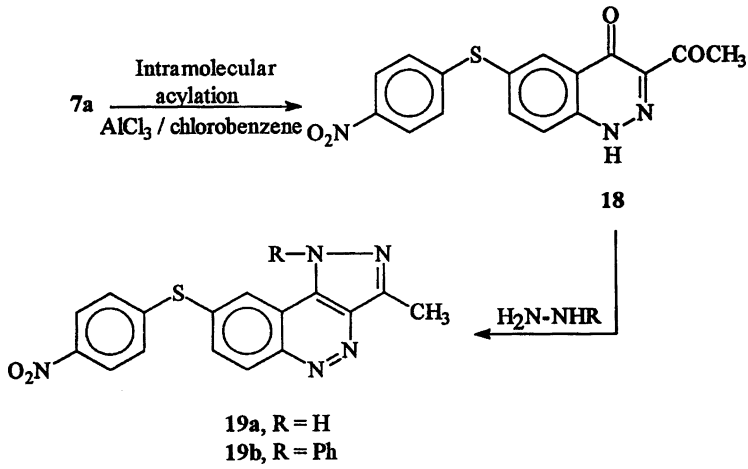


SCHEME 1

Also, the diazonium salt of 4-amino-4′-nitro diphenyl sulfide[10] **6** was coupled with active methylene compounds, namely, ethyl acetoacetate, acetylacetone, and diethyl malonate to give the corresponding aryl-hydrazones **7a–c**. One of the resulting hydrazones **7a** underwent condensation with hydrazine hydrate, phenylhydrazine, hydroxylamine, urea, and thiourea to give pyrazolines **8**, **9**, isoxazoline **10** and pyrimidine derivatives **11** and **12**, respectively. Similar reactions of arylhydrazone **7b** with hydrazines, hydroxylamine, urea and thiourea yielded the corresponding pyrazoles **13**, **14**, isoxazole **15** and pyrimidine derivatives **16**, **17** (Scheme 1).

2) Diaryl Sulfides in Heterocyclic Synthesis Based on the Introduction of PhS-, RS- and Heterocyclic-S-Groups in a Benzoheterocyclic Systems and/or Other Fused Heterocyclic Systems

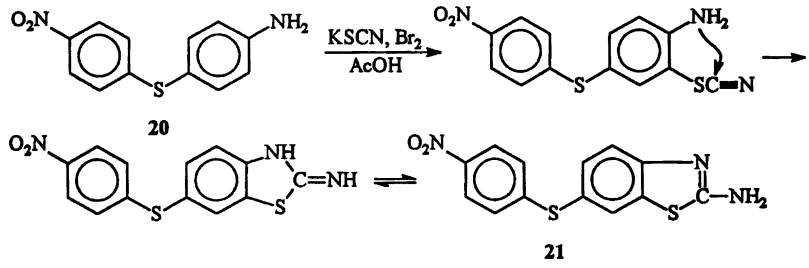
i) The intramolecular cyclization of the former arylhydrazone **7a** with $AlCl_3$ in chlorobenzene gave 6-arylthio-1*H*-cinnoline-4-one **18** which in turn, reacted with hydrazine hydrate or phenylhydrazine to give pyrazolo[4,3-*c*]cinnoline derivatives **19**.



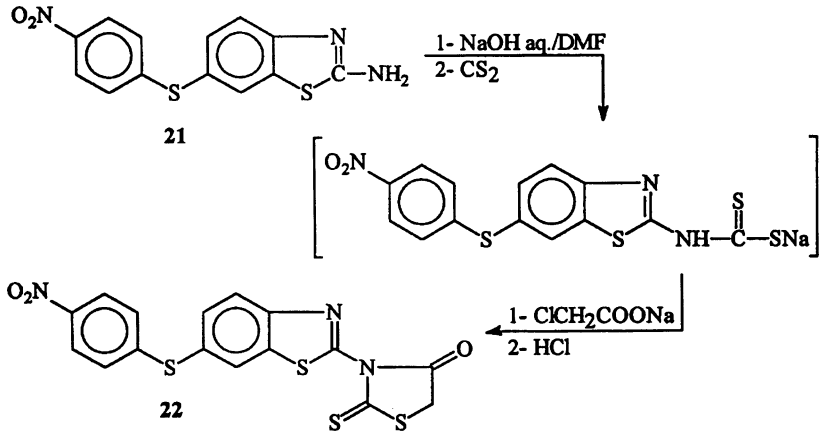
19a, R = H
19b, R = Ph

ii- 2-Amino-6-[(p-nitrophenyl)thio]benzothiazole **21** was prepared by thiocyanation of 4-amino-4′-nitrodiphenylsulfide[11] **20**.

Compound **21** was allowed to react with carbon disulfide in concentrated aqueous sodium hydroxide and *N*,-*N*-dimethylformamide as a solvent, to form the sodium salt of the dithiocarbimidic acid, which was alkylated *in situ* with sodium chloroacetate and



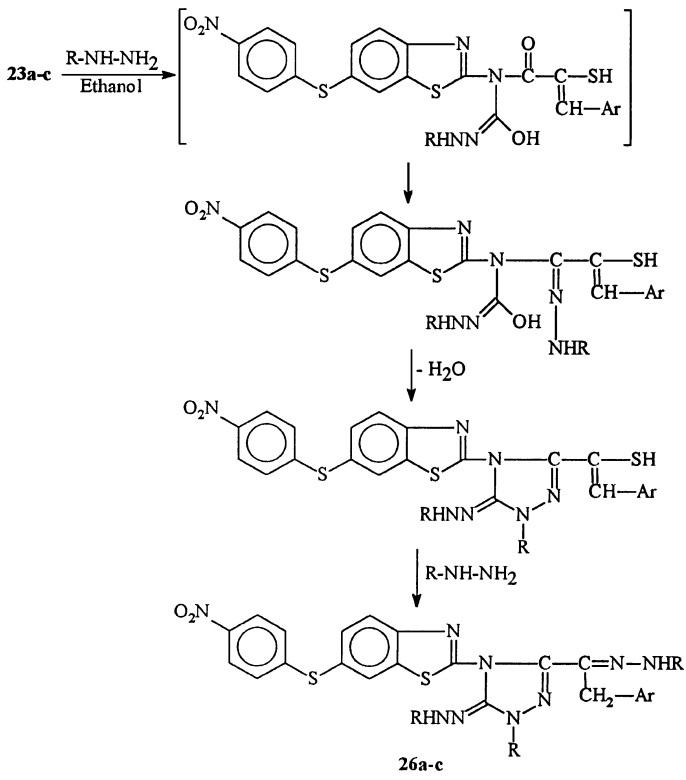
treated with hot concentrated hydrochloric acid to give rhodanine **22**.



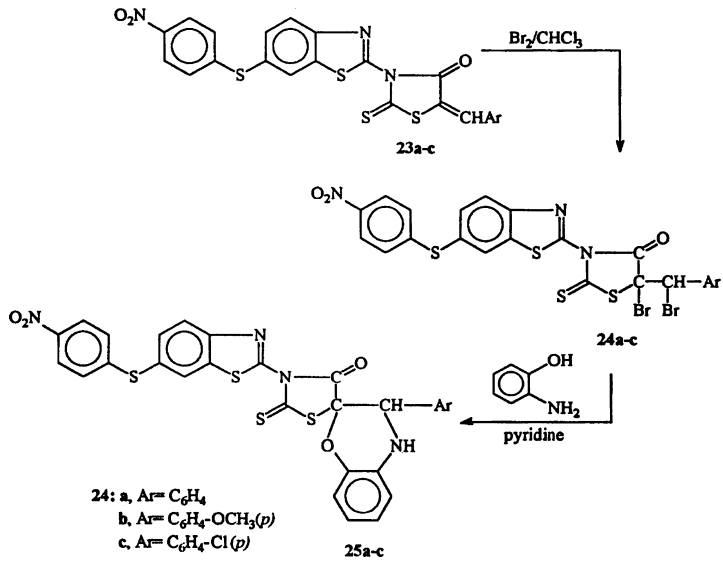
Compound **22** was easily condensed with aromatic aldehydes at the active methylene group to give 5′-arylidine rhodanine **23**. Bromination of **23a–c** in chloroform gave 5′-α,β-dibromoarylidine rhodanines **24**, which reacted with *o*-aminophenol to produce spiroheterocyclic compounds[11] **25**.

Treatment of 5-arylidine rhodanines **23a–c** with hydrazine hydrate or phenylhydrazine in ethanol resulted in ring cleavage leading to the formation of the azine compounds **26a–c** (Scheme 2)[11].

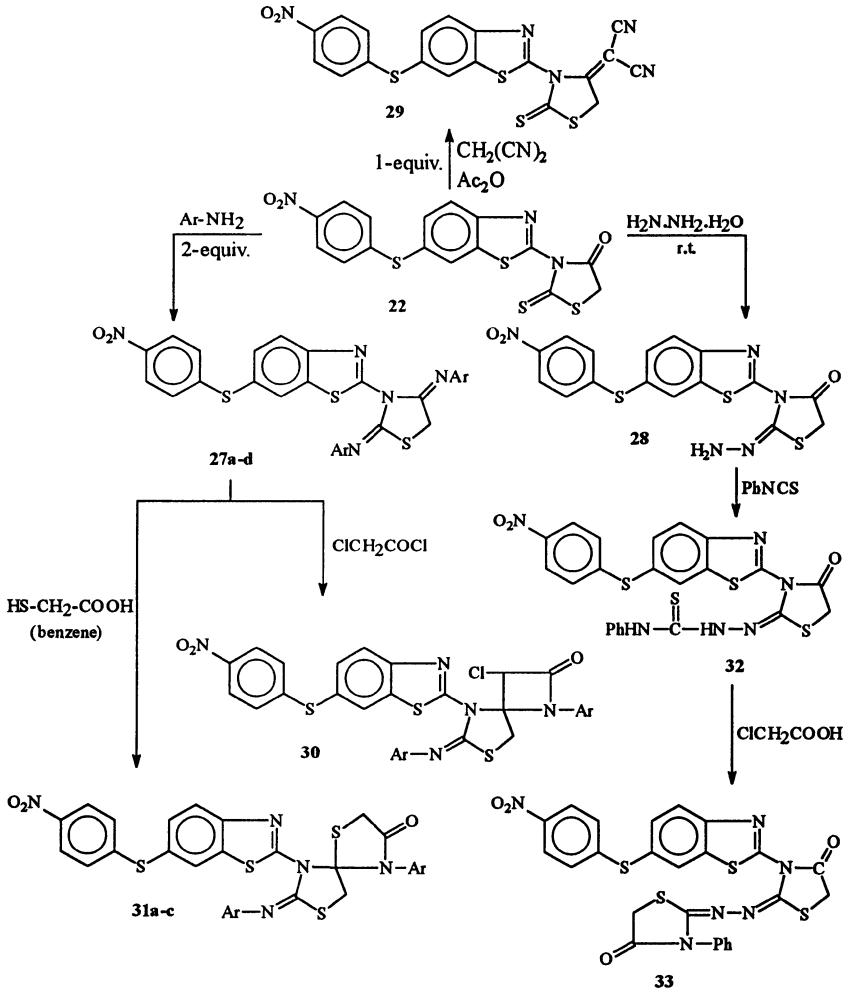
ii) Compound **22** was also used as a precursor for the synthesis of another series of hetorocyclic compounds.[12] Thus, compound **22** was easily condensed with two equivalents of aromatic amines to give the corresponding 2,4-diaryliminothiazolidine **27a–d**. Also, the reaction of **22** with hydrazine hydrate at room temperature gave the hydrazono derivative **28**. In contrast, compound **22** was reacted with malononitrile to afford thiazolidinethione **29**. Compound **27a–d** underwent cycloaddition reaction with chloroacetylchloride or with



SCHEME 2



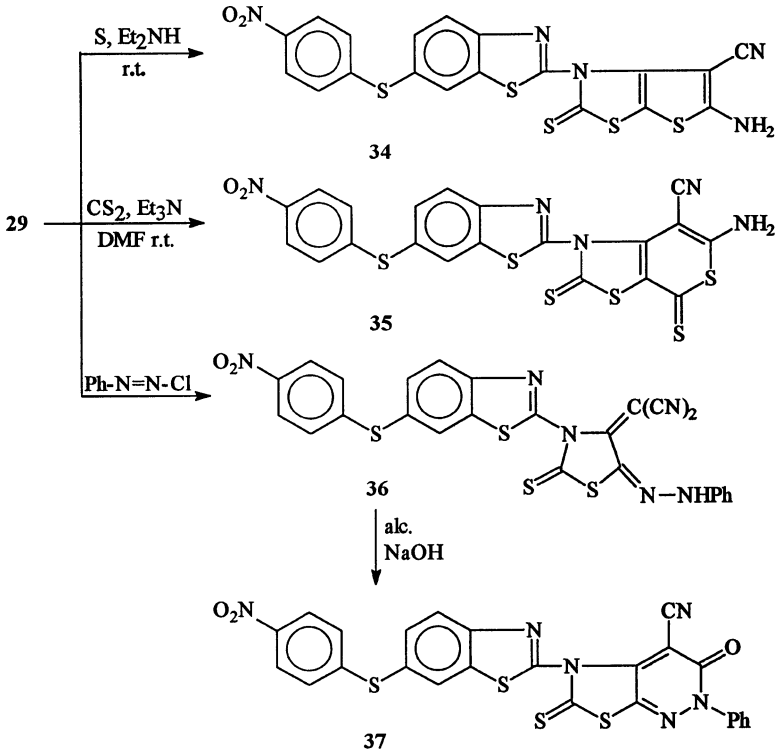
thioglycolic acid to give the corresponding spiro compounds **30a–d** and **31a–d** respectively. The hydrazono compound **28** reacted with phenyl isothiocyanate to give the corresponding thiosemicarbazone **32**. The latter compound **32** underwent cyclocondensation reaction with chloroacetic acid to yield compound[12] **33** (Scheme 3).



SCHEME 3

Compound **29** was reacted with sulfur in ethanol in presence of diethylamine or with carbon disulfide in dimethylformamide DMF and triethylamine to give the corresponding *o*-aminocyanothiophene **34** and thiopyranthione **35** respectively.

Benzene diazonium chloride was coupled with **29** to form the phenylhydrazone derivative **36**. This latter compound was easily cyclized in alcoholic NaOH solution to give the thiazolo-pyridazine derivative[12] **37** (Scheme 4).

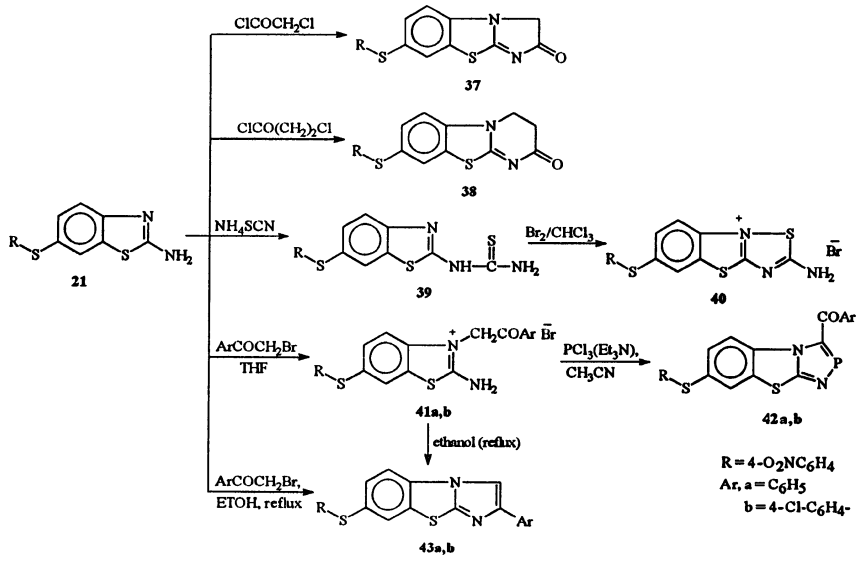


SCHEME 4

iii) 2-Amino-6-[(*p*-nitrophenyl)thio]benzothiazole **21** was also used in building fused heterocyclic rings related to benzothiazole.[13]
Thus, compound **21** underwent cyclocondensation reaction with chloroacetyl chloride or *β*-chloropropionyl chloride in refluxing ethanol to give imidazo[2,1-*b*]benzothiazole **37** and pyrimido[2,1-*b*]benzothiazole **38**. On the other hand, the interaction of ammonium thiocyanate with the hydrochloride salt of **21** gave 1-[6-[(*p*-nitrophenyl)thio]benzothiazol-2-yl]thiourea **39**, which on its treatment with bromine in chloroform yielded[1,2,4]thiadiazolo-[3,2-*b*]benzothiazolium bromide[13] **40**.

Treatment of **21** with *p*-substituted phenacyl bromides in tetrahydrofuran (THF) yielded 2-amino-3-phenacyl-6-[(*p*-

nitrophenyl)thio]benzothiazolium bromides **41a**,**b**. Compounds **41a**,**b** reacted with phosphorus trichloride and triethylamine in acetonitrile to form benzothiazolo[3,2-*d*][1,2,4]diazaphosphole **42a**,**b**. Also, compounds **41a**,**b** underwent cyclization, on heating with ethanol to give the corresponding imidazo[2,1-*b*]benzothiazoles[13] **43a**,**b** (Scheme 5).

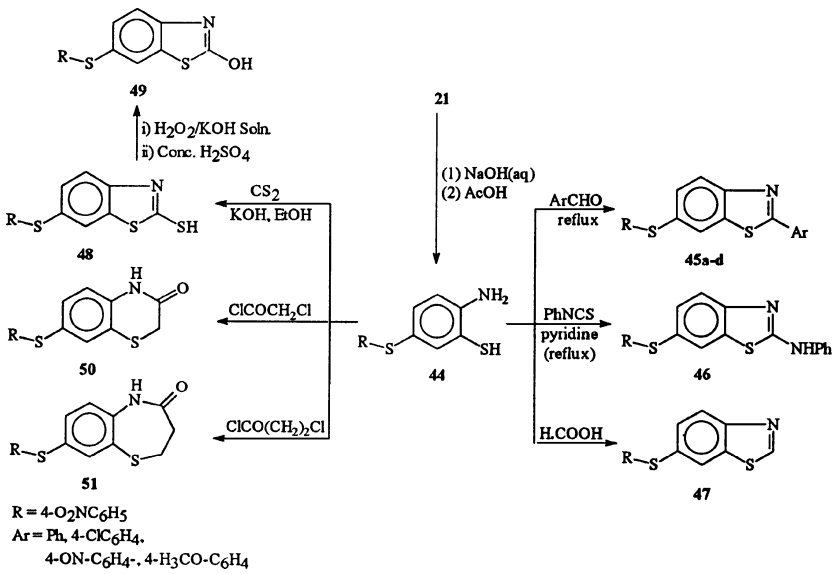


SCHEME 5

4-Amino-3-mercapto-4′-nitro diphenyl sulfide **44** was prepared by a hydrolytic fission of compound **21** and was used as precursor in the synthesis of other arylsulfidobenzothiazole derivatives,[13] through its reaction with aromatic aldehydes, phenyl isothiocyanate, formic acid, and carbon disulfide in ethanolic potassium hydroxide solution to form the corresponding benzothiazole derivatives **45a–d**, **46**, **47** and **48**; respectively. Selective oxidation of 2-mercaptobenzothiazole **48** using H_2O_2 in KOH solution followed by acidification with conc. H_2SO_4 furnished the 2-hydroxybenzo-thiazole **49**.[13]

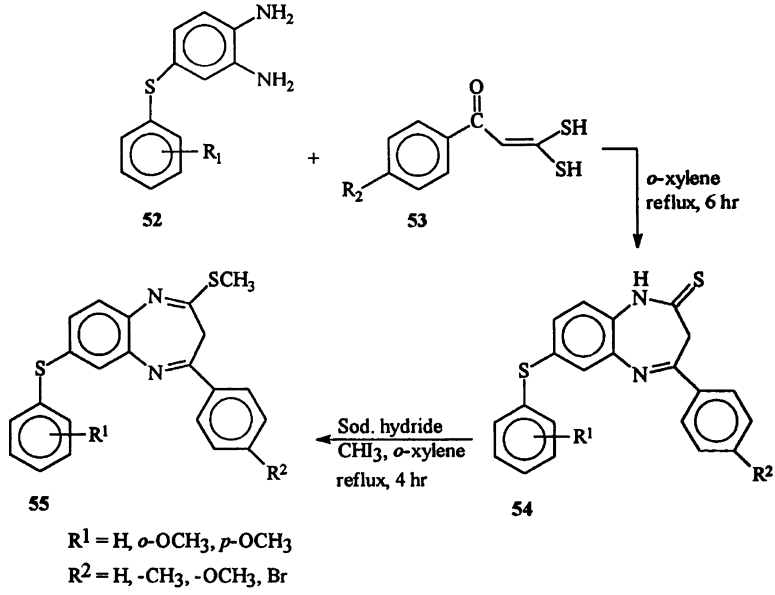
The reaction of **44** with chloroacetyl chloride in ethanolic NaOH solution or chloropropionyl chloride in dry pyridine gave the corresponding 2*H*[1,4]benzothiazin-3(4*H*)one **50**, 2,3-dihydro[1,5]benzothiazepin-4(5*H*) one[13] **51** (Scheme 6).

iv) Synthesis of 2-methylthio-3*H*-4-(*p*-substitutedphenyl)-7-[(*o*-, and *p*-substituted)phenylthio]-1,5-benzodiazepines[14] **55** was achieved by the reaction of 3,4-diminodiphenyl sulfides **52** with

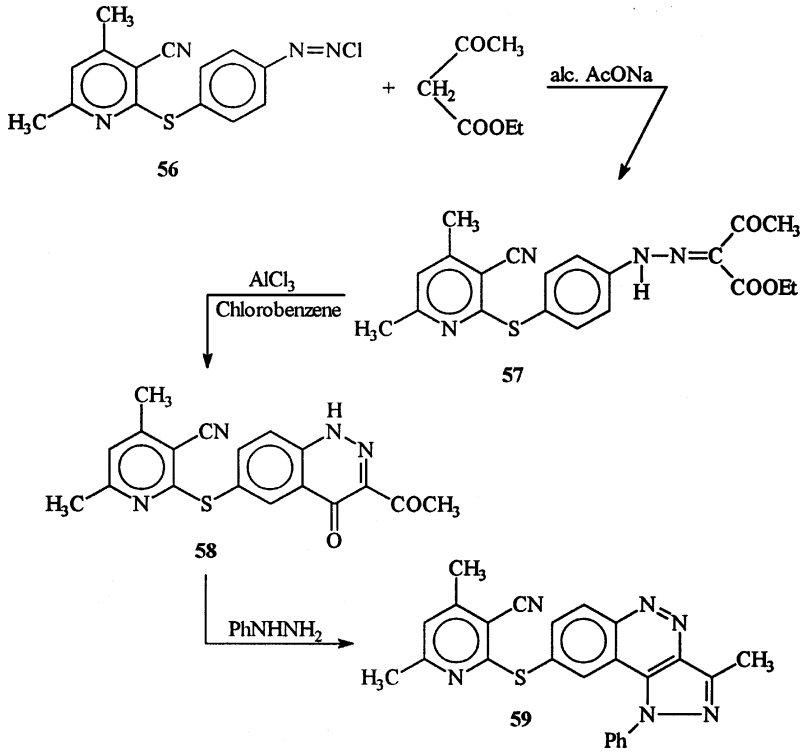


SCHEME 6

3,3-dimercapto-1-(*p*-substitutedphenyl)-2-propen-1-one **53** in anhydrous ortho-xylene. The 1*H*-1,5-benzodiazepine-2-thiones **54** have been obtained, which on treatment with sodium hydride and methyl iodide afforded the compound **55**.



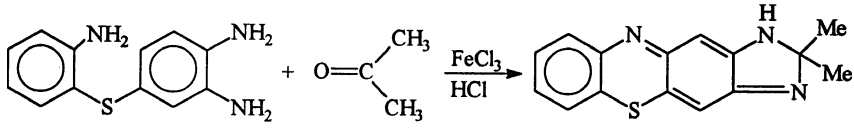
v) Coupling reaction of diazotized 4-aminophenyl-3′-cyano-4′,6′-dimethyl pyrid-2′-yl sulfide **56** with ethyl acetoacetate resulted in the formation of the corresponding hydrazone **57**. The hydrazone **57** underwent intramolecular acylation with anhydrous $AlCl_3$ in chlorobenzene to give the 1*H*-cinnoline-4-one **58**. Interaction of **58** with phenylhydrazine led to the formation of 1*H*-pyrazolo[4,3-*c*]cinnoline[15] **59** (Scheme 7).



SCHEME 7

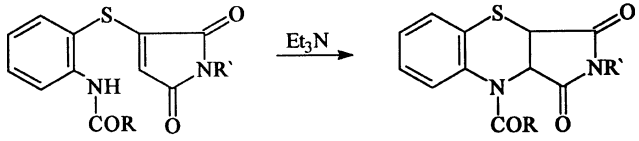
3) Diaryl Sulfides in Heterocyclic Synthesis Based on Intramolecular Cyclization of Diaryl Sulfide Derivatives

i) 2,2-Dimethyl-1,2-dihydroimidazo[4,5-*b*]phenothiazine[16] **61** was prepared by cyclocondensation reaction of triamino diphenyl sulfide **60** with acetone in the presence of $FeCl_3$ and mineral acid.



60 61

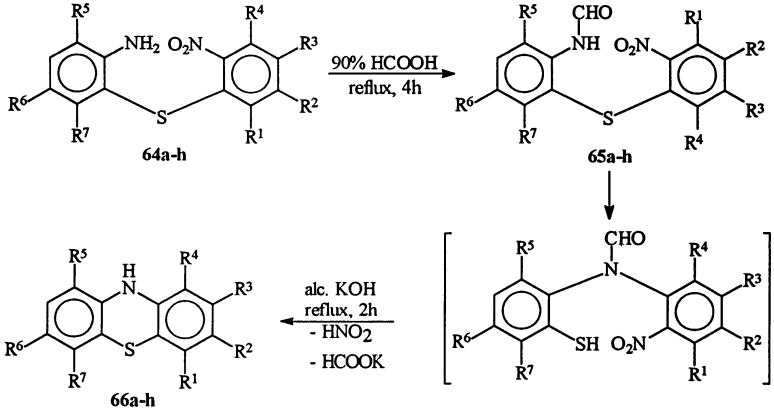
ii) When *N*-substituted 2-[(2-acylaminophenyl)thio]maleimides **62** were treated with a week base such as Et_3N it gave 4-acyl-2,3-dihydrobenzothiazine-2,3-dicarboximides[17] **63** *via Michael*-type intramolecular cyclization.



62 63

R	R`
Me	Me, El, Ph, CH_2Ph
Ph, CH_2Br	Me

iii) New phenothiazine drugs of varying structural complicity were synthesized *via Smile* rearrargement of 2-formamido-2′-nitro substituted diphenyl sulfide **65** (Scheme 8).[18–25]

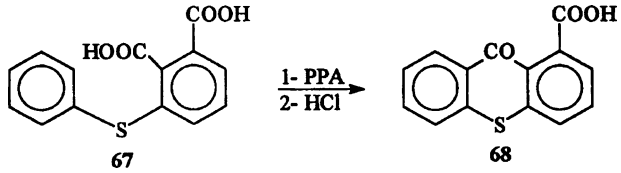


64a-h 65a-h 66a-h

a, $R^1 = R^2 = R^3 = R^6 = H$, R^2 = H, NO_2, CO_2H, Cl, Br, R^5 = Me, R^7 = Cl
b, $R^1 = R^2 = R^3 = R^4 = R^7 = H$, $R^5 = R^6$ = Cl
c, $R^1 = R^2 = R^4 = R^6 = H$, R^3 = H, Br, Cl, O_2N, F_3C, MeO, CO_2H; $R^5 = R^7$ = Cl
d, $R^1 = R^3 = R^4 = R^7 = H$, R^2 = H, Me, halo, methoxy; R^5 = Me, R^6 = Cl
e, R^1 = CO_2H, H, Cl, CF_3, Br, NO_2, OMe; $R^2=R^3=R^4=R^5=R^7$ = H, R^6 = PhO
f, $R^1 = R^2 = R^4 = R^7$ = H; R^3 = H, CO_2H; R^5 = Me, R^6 = F
g, $R^1 = R^3 = R^4 = R^7$ = H; R^5 = Me, R^2 = Br, R^6 = F
h, $R^1 = R^3 = R^5 = R^7$ = H; $R^2 = CF_3$, $R^4 = NO_2$, R^6 = Br.

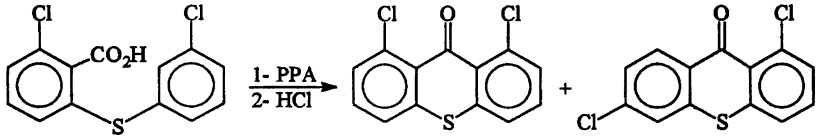
SCHEME 8

iv) Reaction of 3-phenylthio-1,2-benzenedicarboxylic acid **67** with polyphosphoric acid (PPA) gave 96% thioxanthone-1-carboxylic acid[26] **68**.



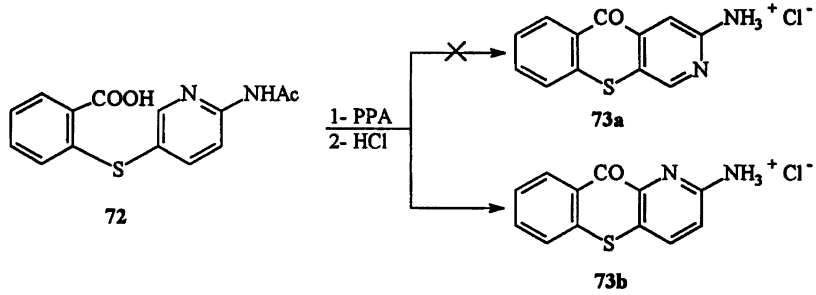
67 **68**

Meanwhile, cyclization of chlorinated (phenylthio)benzoic acid **69** gave a mixture of 1,8- and 1,6-dichloro-9*H*-thioxanthen-9-one **70** and **71**, respectively.[27]



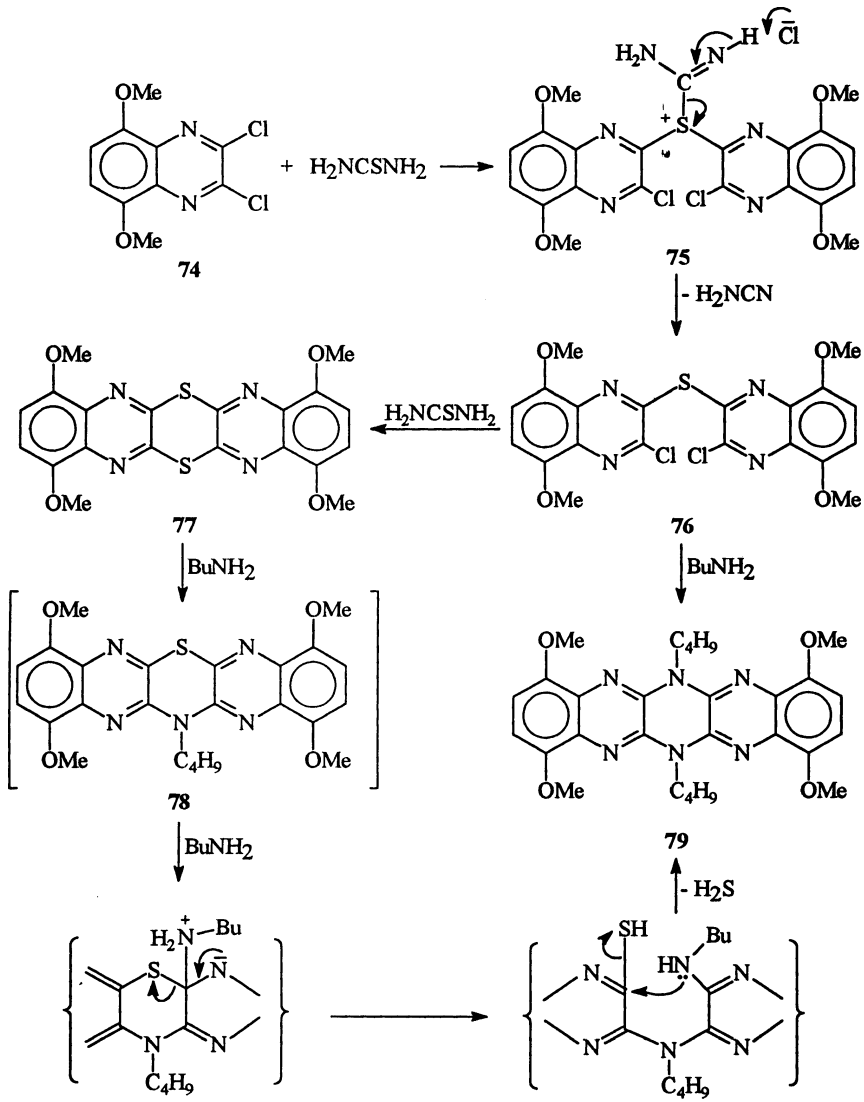
69 **70** **71**

v) Also, 2-(6-acetamido-3-pyridylthio)benzoic acid **72** was converted to 2-amino-9*H*-azathioxanth-9-one hydrochloride[28] **73b** upon *Friedel-Crafts* intramolecular ring closure. Although, two different isomers, **73a** and **73b**, could be expected, only the regioisomer **73b** was obtained.



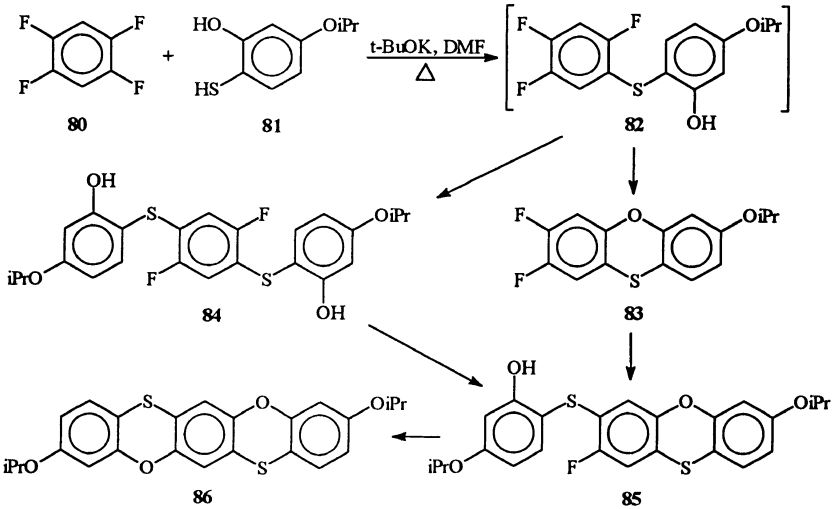
72 **73a** **73b**

vi) When 2,3-dichloroquinoxaline **74** was treated with an equimolecular amount of thiourea, it gave the sulfide **76** which is an intermediate in the formation of the dithiine[29] **77**, through its reaction with thiourea, and **76** was thought to be formed from the isothiouronium salt **75**. Also, reaction of sulfide **76** with butylamine gave the hexaaza penta cycle **79** (Scheme 9).



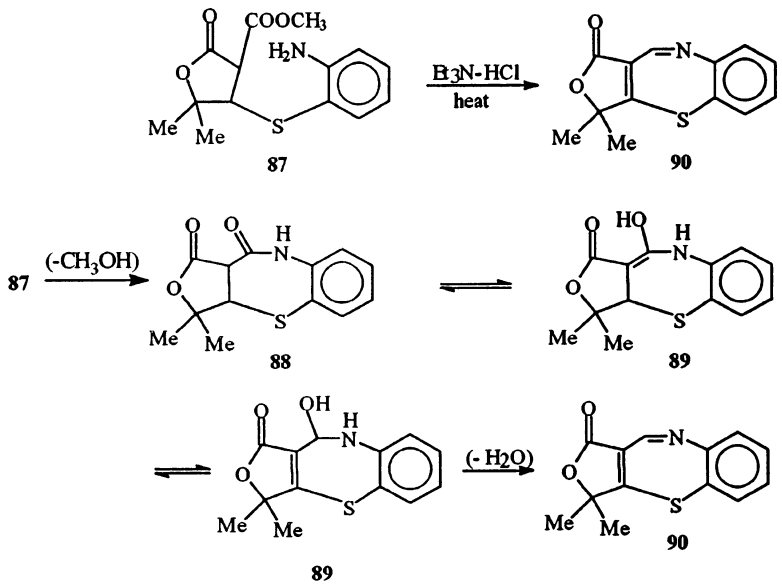
SCHEME 9

vii) 3,10-Diisopropoxy-5,12-dioxa-7,14-dithiapentacene[30] **86** was synthesized from a base-mediated cyclization of 1,2,4,5-tetrafluorobenzene **80** with the strong nucleophile mainly 5-isopropoxy-2-mercaptophenol **81** which form compound **86**. Through the formation of sulfide intermediates **82**, **84**, **85** (Scheme 10).



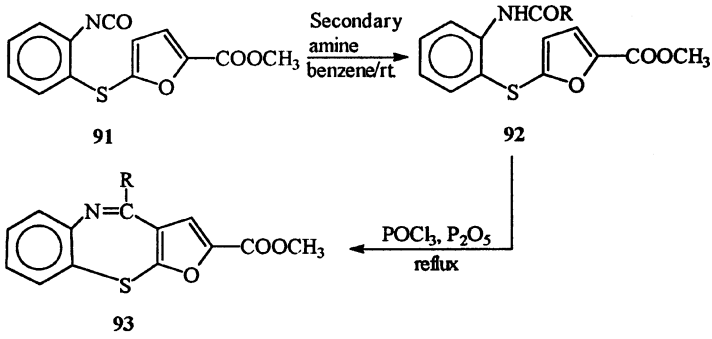
SCHEME 10

viii) Heating of 3-(2-aminophenylthio)-2-methoxycarbonyl-4-methyl-2-penten-4-olide **87** with triethylamine hydrochloride gave 3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one[31,32] **90** through the steps outlined in Scheme 11.



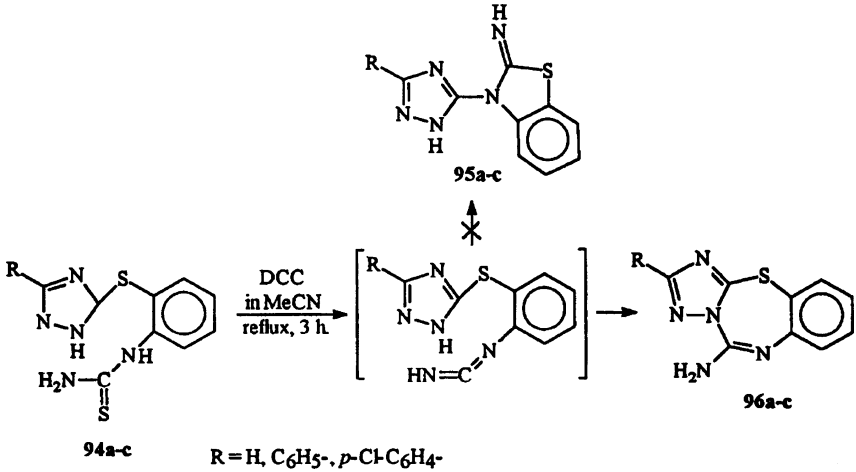
SCHEME 11

ix) The reaction of methyl 5-(2-isocyanato phenylthio)-2-furan carboxylate **91** with cyclic amines gave corresponding ureas **92**, which on *Bischler-Napieralski* reaction gave the furobenzothiazepines[33] **93**.



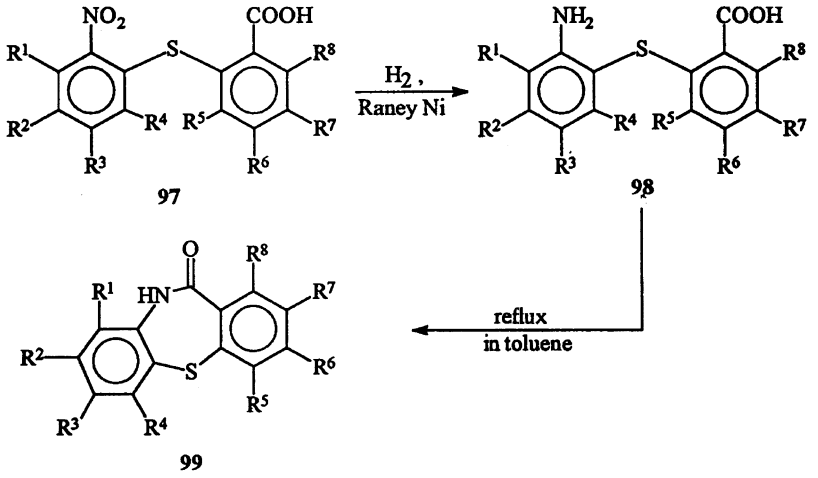
R = 4-methylpiperazino, morpholino, piperidino, pyrrolidino

x) Synthesis of triazoles **95a–c** from the reaction of *N*-({2-[3-aryl-(1*H*-1,2,4-triazol-5-yl)]thio}phenyl)thioureas **94** with dicyclohexacarbidiimide (DCC) in CH_3CN *via* the *Smile*-type rearrangement was attempted. However, 1,2,4-triazolo[5,1-*b*]-1,3,5-benzothiadiazepin-5-yl amine derivatives[34] **96** were obtained due to cyclo-desulfurization of thioureas **94**.



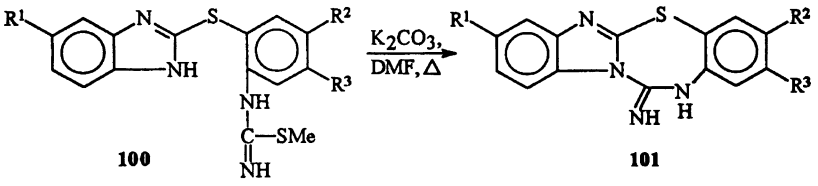
R = H, C_6H_5-, *p*-Cl-C_6H_4-

xi) Dibenzothiazepines[35] **99** were prepared by condensation of 2-chloronitrobenzene with thiosalycylic acid in *N*,*N*-dimethyl formamide using K_2CO_3 at 70° for 6 h. to give the sulfides **97** which on reduction by hydrogen using raney Ni as a catalyst and heated in refluxing toluene gave the dibenzothiazepines **99**.



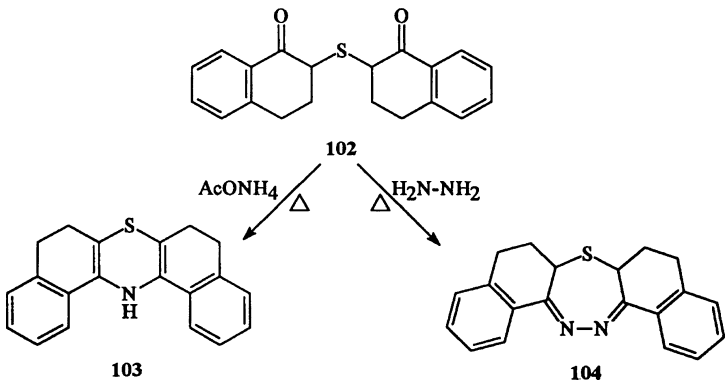
R^1-R^8 = H, (substituted)alkyl, alkoxy, alkyl carbonyl, aryl, aryloxy, arylcarbonyl.

xii) Cyclization of *N*-(benzimidazolyl thiophenyl)-S-methyl isothiourea derivatives 100 by heating with potassium carbonate in DMF furnished benzimidazo[2,1-*b*][1,3,5]benzothiadiazepine derivatives[36] **101**.



R^1 = H, Me ; R^2 = H, Cl ; R^3 = H, Cl, MeO, CF_3

xiii) Di(1-oxotetrahydronaphtyhl)sulfide **102** underwent cyclocondensation with ammonium acetate or hydrazine to give dibenzotetrahydrophenothiazine[37] **103** in 46% yield and ditetrahydronaphthothiadiazepine[37] **104** in 60% yield respectively.

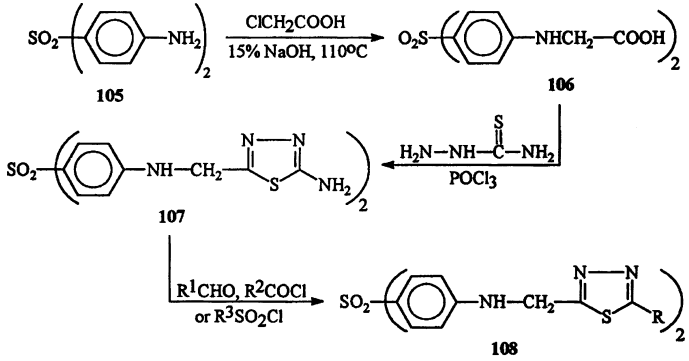


C) DIARYL SULFONES IN HETEROCYCLIC SYNTHESIS

The reported synthetic routes can be classified into the following types:

1) Diaryl Sulfones in Heterocyclic Synthesis Based on Introduction of Ph-SO_2-Ph Group in Heterocyclic Ring

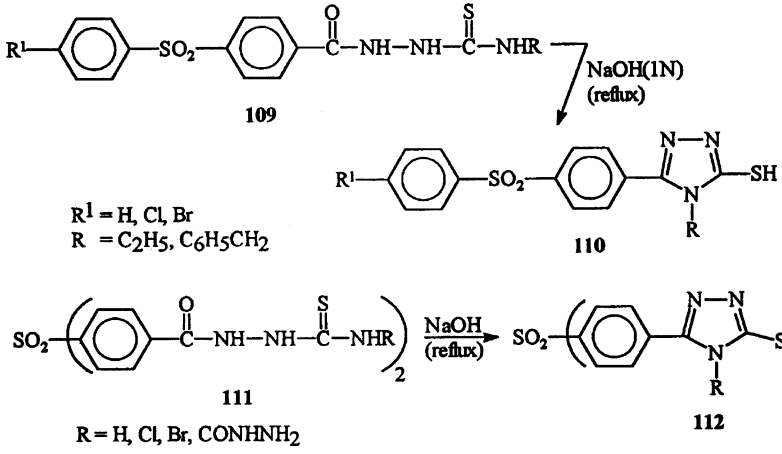
i) *P*, *p*′-Bis(2-substituted benzalamino/benzoylamino/sulfonamido-1,3,4-thiadiazol-5-yl-methylamine)diphenylsulfones[38] **108** were prepared starting from Diamino dipheyl sulfone **105** by its reaction with monochloroacetic acid to form *p*,*p*′-carboxy methylamino derivative **106**, which in turn underwent cyclocondensation with thiosemicarbazide to give *p*,*p*′-bis(2-amino-1,3,4-thiadiazole-5-yl-methylamino)-diphenyl sulfone **107**. The latter compound **107**



R (N=CHR[1]), R[1] = Ph, 4-HO-C_6H_4-, 4-$O_2NC_6H_4$-, etc.
R (NHCOR[2]), R[2] = Ph, 4-Cl-C_6H_4-, 2-naphthyl
R ($NHSO_2R^3$), R[3] = Ph, 4-HO-C_6H_4-, 4-O_2N-C_6H_4-

reacts with either R^1CHO, R^2COCl or R^3SO^2Cl to give the corresponding **108**.

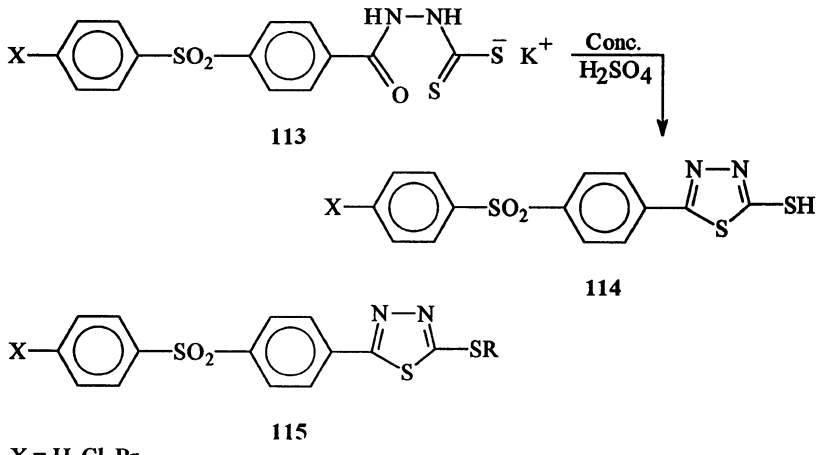
ii) Diphenyl sulfones incorporated with triazole ring **110** and **112** were prepared[39] by cyclizing thiosemicarbazides **109** or **111** in alkaline medium.



iii) The 2-mercapto-5-[*p*-(arylsulfonyl)phenyl]-1,3,4-thiadiazoles[40] **114** existing mainly in their thionic tautomeric form were synthesized by acid catalyzed cyclization of the corresponding potassium acyldithiocarbazinates **113** (Scheme 12). Various S-alkylmercapto-1,3,4-thiadiazoles **115** derived from **114** were obtained by two methods. The 2-mercapto-5-[*p*′-(bromophenylsulfonyl)phenyl]-1,3,4-thiadiazole **114** showed a dichotomous behaviour in alkylation, affording S-alkyl and *N*-alkyl derivatives.

Thus, compounds **114** react with chloroacetone, bromoacetophenone, methyl chloroacetate affording either mercaptosubstituted derivatives **116** or mixtures of **116** and N^3-substituted derivatives[41] **117**. These results were explained on the basis the ambident reactivity of nucleophiles derived from **114** using the principle of hard-soft acids-bases (HSAB).

iv) Treatment of *p*-hydrazinocarbonyl diphenyl sulfone **118** with carbon disulfide in alcoholic potassium hydroxide solution gave 5-*p*-phenylsulfophenyl-1,3,4-oxadiazole-2-thione **119**.[42] Reaction of compound **119** with formaldehyde and aromatic amines in ethanol gave 3-arylaminomethyl-5-*p*-phenylsulfophenyl-1,3,4-oxadiazole-2-thione **120**.[42]

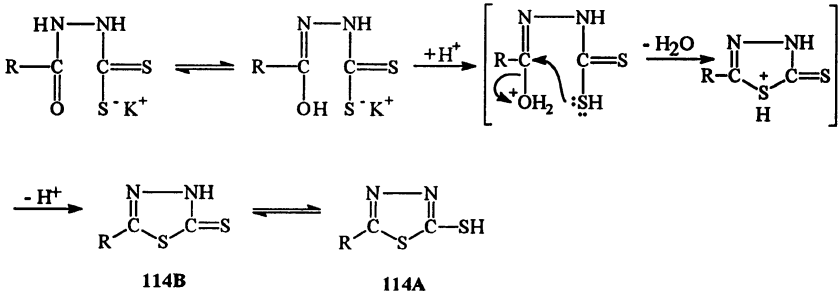


113

114

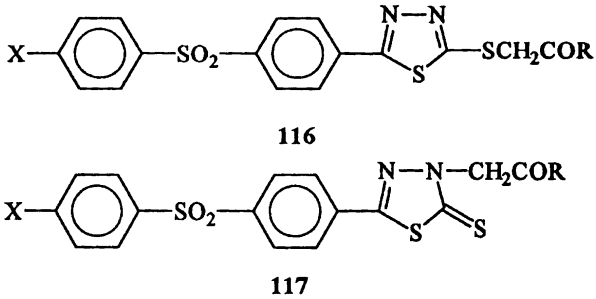
115

X = H, Cl, Br
R = Me, Et, CH_2Ph



114B 114A

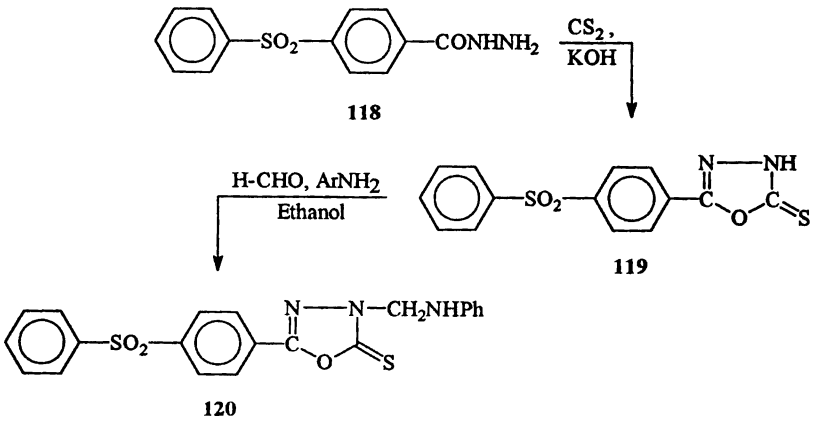
SCHEME 12



116

117

X = H, Cl, Br
R = Me, Et, CH_2Ph

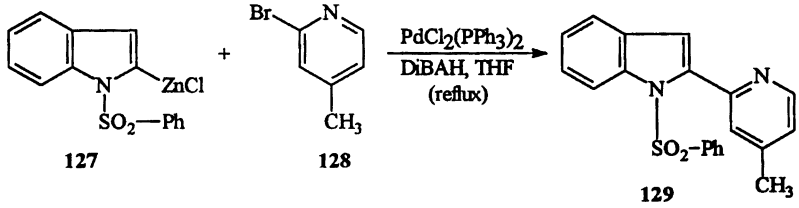


2) Diaryl Sulfones in Heterocyclic Synthesis with the Aim to Prepare Fused Heterocyclic-Heterocyclic Sulfones and Phenyl-Fused Heterocyclic Sulfones

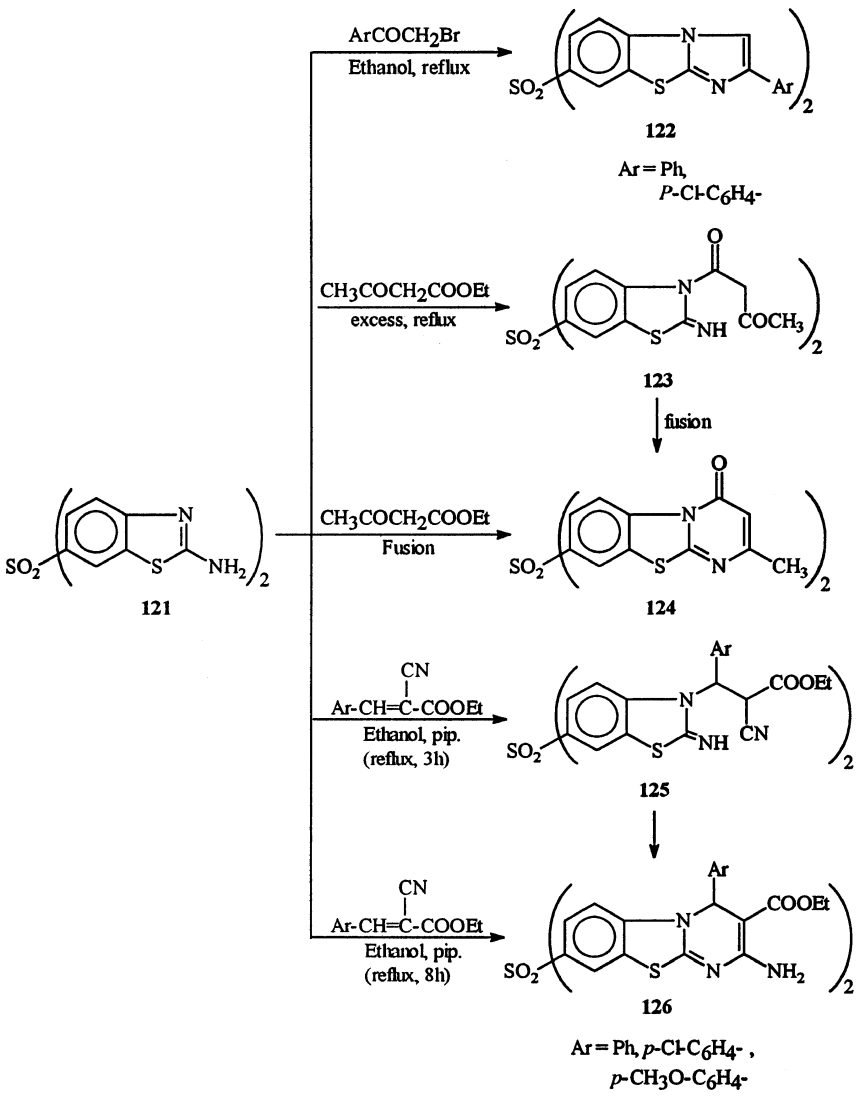
i) The reaction of Bis(2-aminobenzothiazol-6-yl)sulfone[43] **121** with phenacylbromides provided imidazobenzothiazol-7-yl sulfones **122**.[44]

Also, **121** underwent cyclocondensation reaction with active methylene esters (e.g., ethyl acetoacetate) or with arylidine active methylene esters and gave the corresponding pyrimido[2,1-*b*]-benzothiazole derivatives[44] **124**, **126** through the formation of intermediates **123** and **125**, respectively (Scheme 13).

ii) An efficient and facile method for the preparation of 2-(2-pyridyl)-indole[45] **129** was based on the palladium(o) catalyzed coupling of 1-(benzenesulfonyl)-2-indolylzinc chloride **127** with 2-bromo-4-methyl-pyridine **128**.

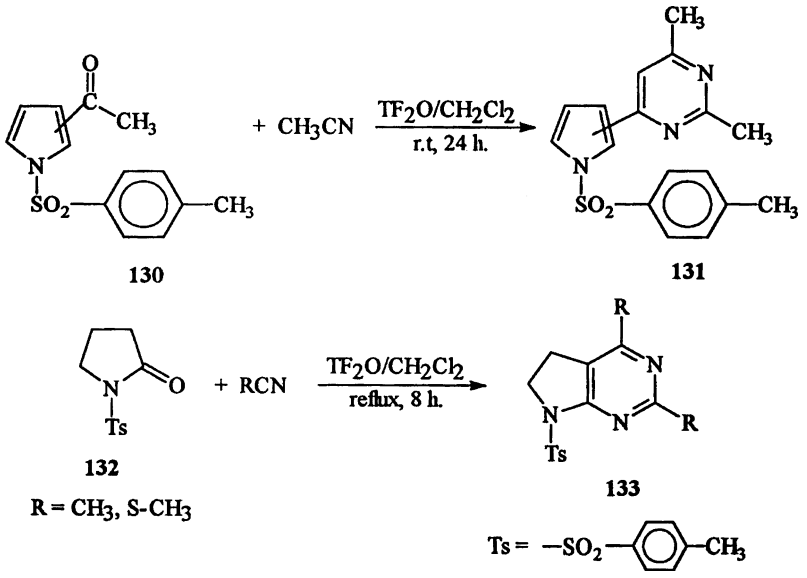


iii) *N*-tosyl-2- and 3-acetyl pyrroles 130 or *N*-tosyl-2-pyrrolidone **132** were cyclocondensed with cyano compounds in the presence of triflic anhydride (TF_2O) to yield heteroaryl pyrimidines **131** and **133**.[46]



SCHEME 13

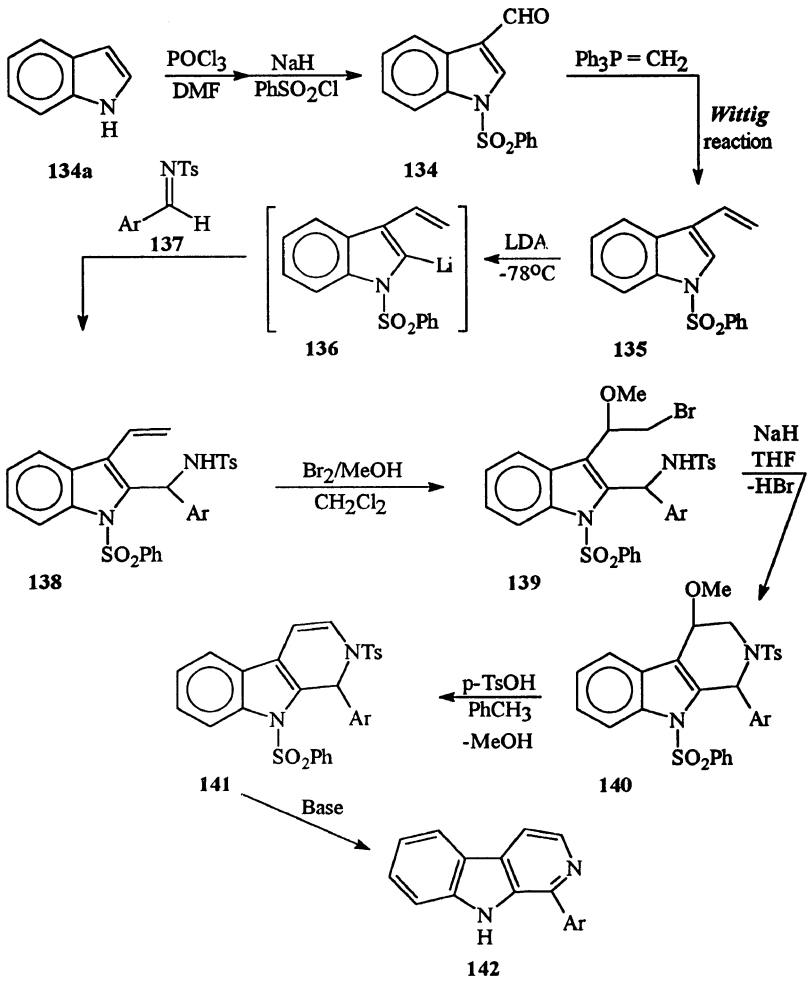
It is worth noting that the reaction of methyl 2-acetylpyrrole with acetonitrile led to *N*-trifly substituted pyrrole salts,[46] due to the electrophilic attack of TF_2O to the heterocyclic nitrogen. The authors have found that the reaction of *N*-protected analogues *N*-tosyl-2- and -3-acetyl pyrroles **130** with TF_2O afforded the derived 2,4-dimethyl-6-(*N*-tosy-2- or -3-pyrrolyl)pyrimidine **131**.



iv) A new synthetic route to β-carbolines[47] was described in which *N*-tosyladimines ArC(:NTs)H **137** [Ar = unsubstituted Ph] underwent attack by α-lithiated 3-alkenyl-1-(phenylsulfonyl)indoles **136** to give the corresponding sulfonamides **138**. These alkenylsulfonamides **138** were alkoxy brominated using Br_2 in methanol giving **139** then cyclized to tetrahydro-β-carbolines **140** upon treatment with sodium hydride. Treatment with TsOH in toluene gave dihydro-β-carbolines **141** by loss of methanol. Aromatization and loss of the phenyl sulfonyl protecting group was achieved by treatment with any of several bases to give compound **142** (Scheme 14).

v) Preparation of substituted pyrrolo[2,3-*c*]pyridine-5-carboxylate **145** *via Pictet-Spengler* reaction,[48] which was applied with the amine **143** by its treatment with one equivalent of an aqueous solution of formaldehyde and two equivalents of trifluoracetic acid in dichloromethane leading to the formation of tetrahydro-6-azaindole **144** (the product of *Pictet-Spengler* condensation). Dehydrogenation of the tetrahydro derivative **144** under the same conditions known to dehydrogenate tetrahydro-β-carboline derivatives gave 6-azaindole derivative **145**.

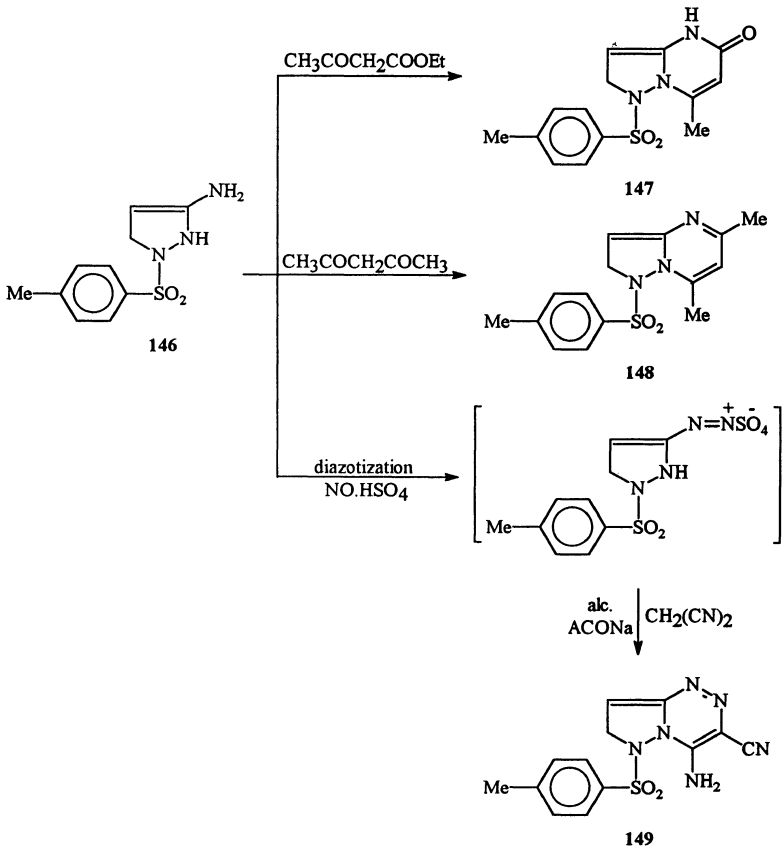
vi) Synthesis of 1-(*p*-tosyl)pyrazolo[1,5-*a*]pyrimidines[49] **147**, **148** was achieved by the interaction of 3-amino-1,5-dihydro-1-(*p*-tosyl)pyrazole **146** with active methylene compounds (e.g., ethyl acetoacetate or acetylacetone), while diazotization of compound



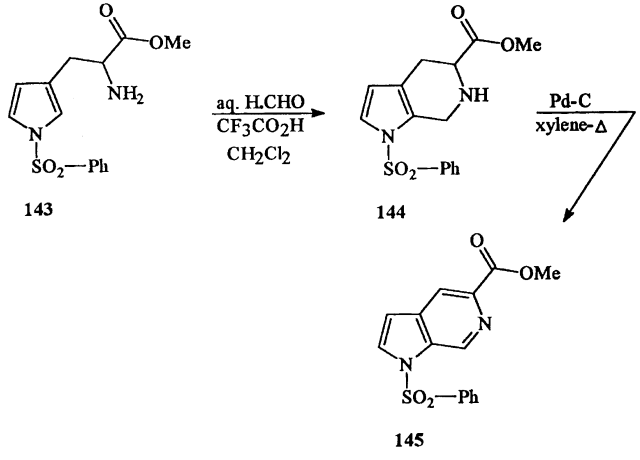
SCHEME 14

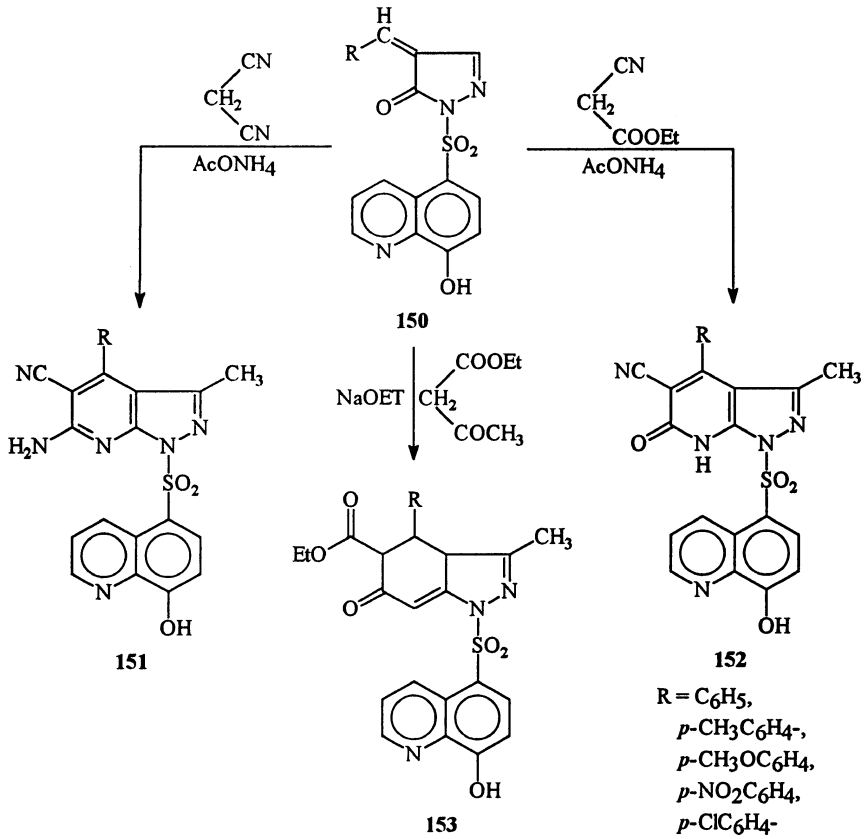
146 and subsequent coupling with bifunctionally active nitriles yielded the corresponding pyrazolo[5,1-*c*][1,2,4]triazine derivative **149** (Scheme 15).[49]

vii) A series of 5-sulfonyl-(nicotinonitriles, pyridones, and cyclohexenones)-8-hydroxyquinolines[50] **151**, **152**, and **153** have been synthesized by *Michael* condensation of arylidine (hydroxyquinolinyl sulfonyl) methyl pyrazolines **150** with malononitrile, ethyl cyanoacetate, and ethyl acetoacetate respectively (Scheme 16).



SCHEME 15

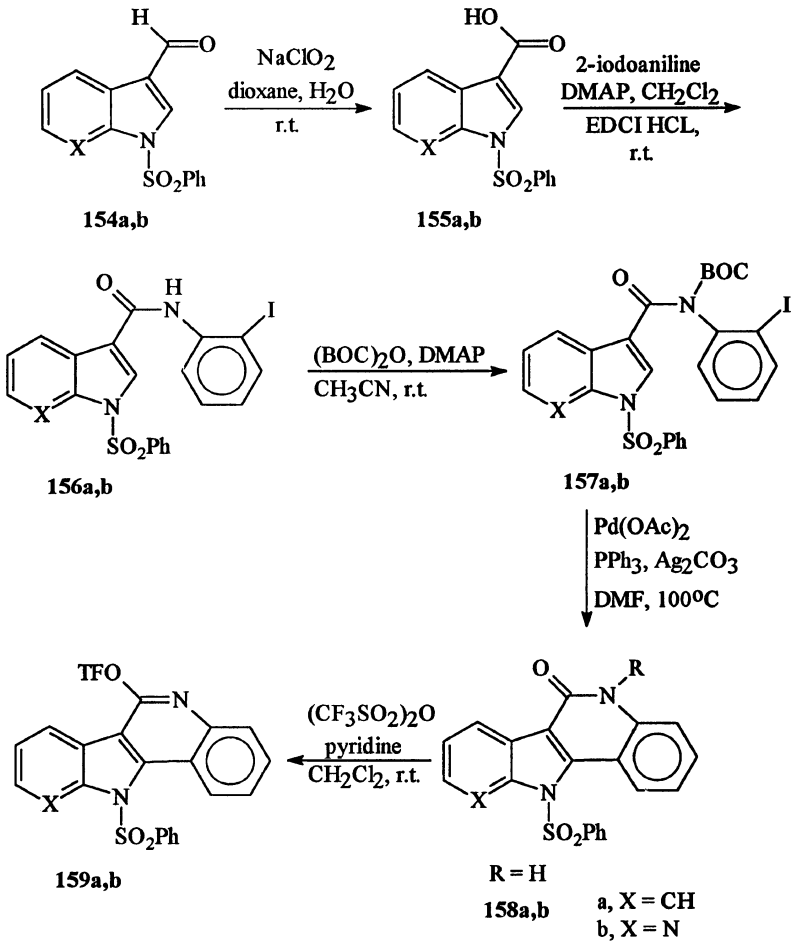




SCHEME 16

The condensation reaction of active nitriles with unsaturated ketones was carried out in the presence of ammonium acetate.[50,51]

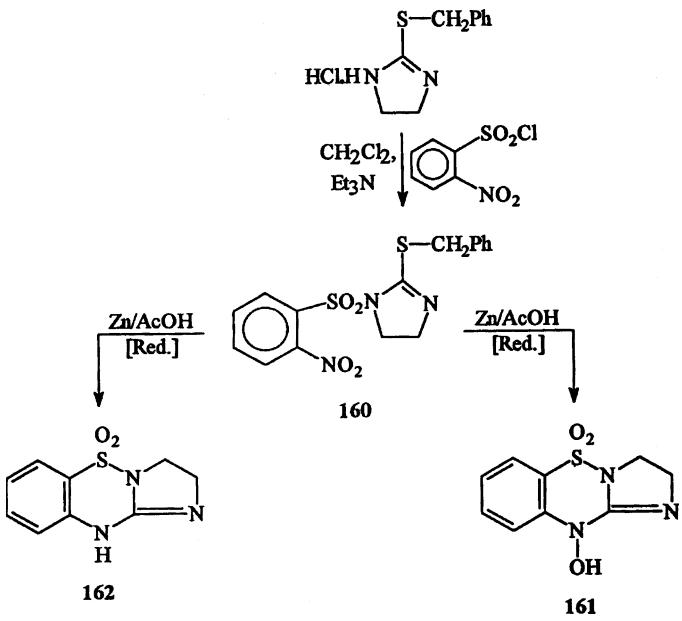
viii) Indolo[3,2-*c*]quinoline and pyrido[3′,2′:4,5]pyrrolo[3,2-*c*]quinoline derivatives[52] **159a**,**b** were prepared starting from 1-phenylsulfonyl3-formyl indole **154** by $NaClO_2$ oxidation, followed by amidification of **155a**,**b** with 2-iodoaniline in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI)/4-dimethylamino pyridine (DMAP) to give the corresonding amides **156a**,**b**, which underwent intramolecular *Heck* cyclization to give compounds **159a**,**b**. In order to prevent deiodination on the phenylring during *Heck* reaction, amides were protected with tert-butyl group (BOC) (Scheme 17).



SCHEME 17

3) Diaryl Sulfones in Heterocyclic Synthesis Based on Intramolecular Cyclization Reactions

i) The tricyclic *N*-hydroxyguanidine derivatives[53] **161** and **162**, were synthesized by sulfonation of 2-benzylthio-2-imidazolidine hydrochloride using 2-nitro benzenesulfonyl chloride giving the intermediate **160** which was reduced with zinc powder in acetic acid to give 10-*N*-hydroxy-1*H*-2,3-dihydroimidazo[1,2-*b*][1,2,4]benzothiadiazine-5,5-dioxide **161** and 2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]-benzothiadiazine-5,5-dioxide **162**.

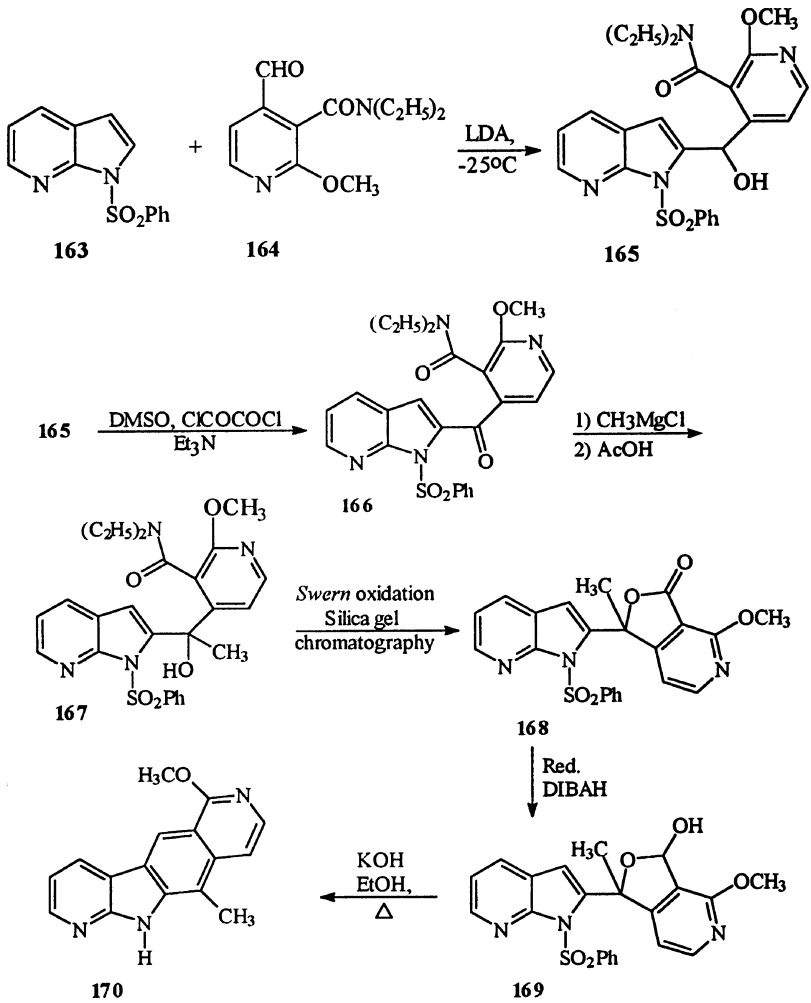


ii) Synthesis of 1-Methoxy-5-methyl-6*H*-pyride[3′,2′:4,5]pyrrolo[2,3-*g*]-isoquinoline[54] **170** was accomplished from *N*-benzenesulfonyl-2-substituted-1*H*-pyrrolo[2,3-*b*]pyridine **165** (prepared by condensation of the aldehydic compound **164** with the 2-lithio-7-azaindole **163** to give compound **165**) *via Swern* oxidation to give the ketone **166**, ketone **166** was treated with methyl magnesium chloride to give alcohol **167**, which underwent lactonization during its purification on silica gel, and the lactone **168** was reduced with (DIBAH) and afforded the lactol **169**. This compound was treated with KOH in refluxing ethanol to give the tetracyclic compound **170**. The sequence outlined in Scheme 18.

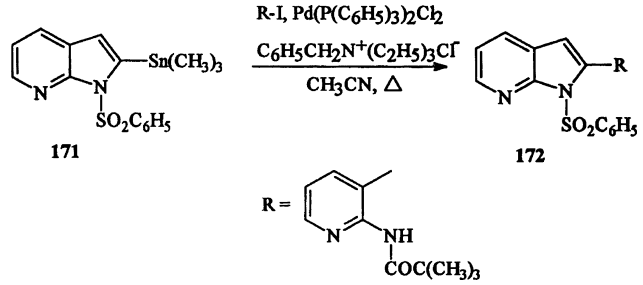
iii) Also, 2-substituted indoles were obtained *via* other metallic derivatives than the lithium species. *Suzuki* coupling reaction, between 2-(trimethylstannyl)-7-azaindole **171** and iodo derivative using $Pd(P(C_6H_5)_3)_2Cl_2$ and $C_6H_5CH_2N^+(C_2H_5)_3Cl^-$ as a catalyst to give 2-substituted-7-azaindoles **172**.

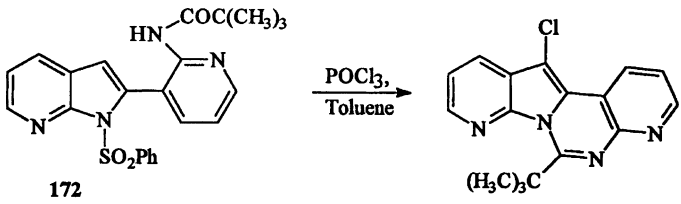
In order to obtain γ-carbolines,[54] compound **172** was treated with $POCl_3$ in toluene to perform *Bischler-Napieralski* cyclization which occured in 1-position rather than 3-position to give the tricyclic compound **173**.

iv) A new approach to fused [1,2-*a*]indoles[55] was based on intramolecular radical cyclization reaction involving ipso-substitution using



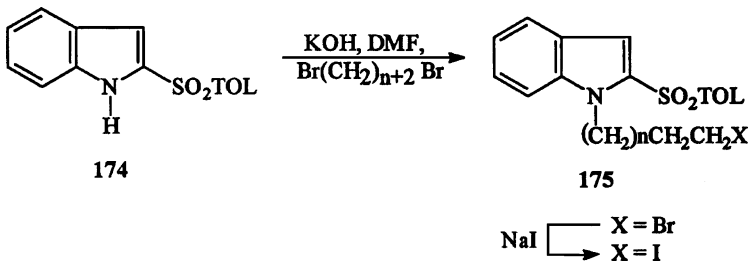
SCHEME 18





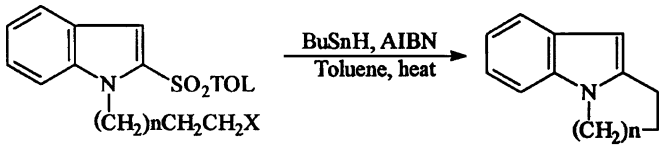
172 173

sulfones. The desired cyclization precursors were prepared from 2-toluene sulfonyl indole **174** by *N*-alkylation using the appropriate dibromo alkane, followed by SN^2 displacement with sodium iodide in acetone to give compound **175**.



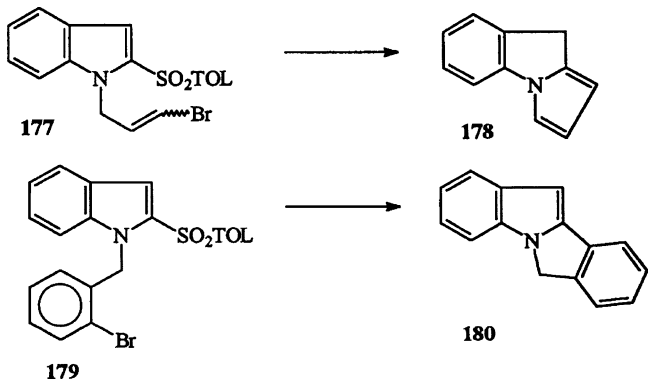
174 175

Treatment of bromide precursor **175** with tributyltin hydride (TBTH) under radical conditions led to compound **176**.



175 176

In case of vinyl and aryl radical cyclization, the *N*-alkylation of 2-[(4-methylphenyl)sulfornyl]indole **174** with either 1,3-dibromoprop-1-ene or 2-bromobenzylbromide led to the cyclization precursors **177**, **179**. When these compounds were subjected to the cyclization conditions, they gave the desired products **178** and **180**, respectively.[56]

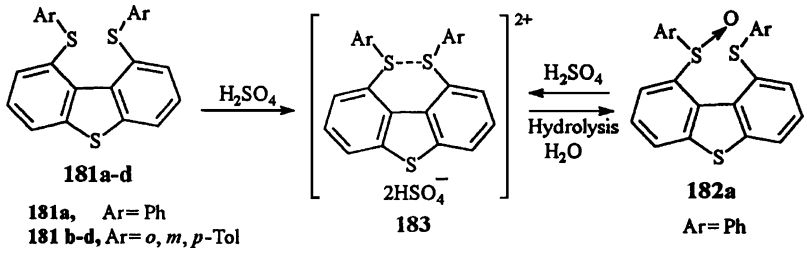


D) Syntheses Based on Reactions of Diaryl Sulfides Containing Heterocycles

The following are reported[57–74] chemical reactions of certain diaryl sulfides containing heterocyclic systems.

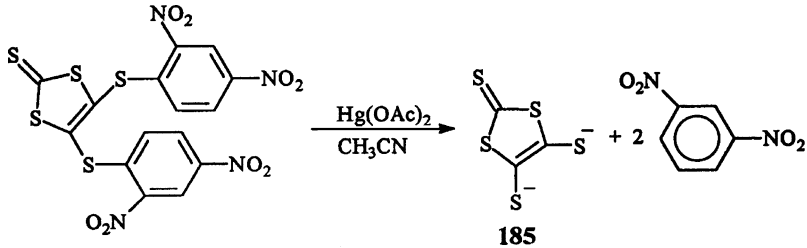
1) Effect of Concentrated Sulfuric Acid on the 1,9-Bis(arylthio)-dibenzothiophene

1,9-Bis(arylthio)dibenzothiophene **181** were oxidized to their monooxides **182** by an equimolar amount of *m*-chloroperbenzoic acid (mClPBA). The molecular structure of the diphenylthio derivatives indicates that the central thiophene ring is considerably distorted due to the sterric repultion between the two phenylthio groups attached to C_1 and C_9 but the distance between the two sulfur atoms is within *Van der walls* contact (3.70Å)[57] and two phenyl rings are located at antiorientation and are close to the dibenzothiophene ring. Compounds **181a**, **182a** were dissolved in concentrated sulfuric acid and generate the dithiocations[58,59] **183**. Hydrolysis of the dithiocations gave the corresponding sulfoxides **182a**.



2) Oxidation

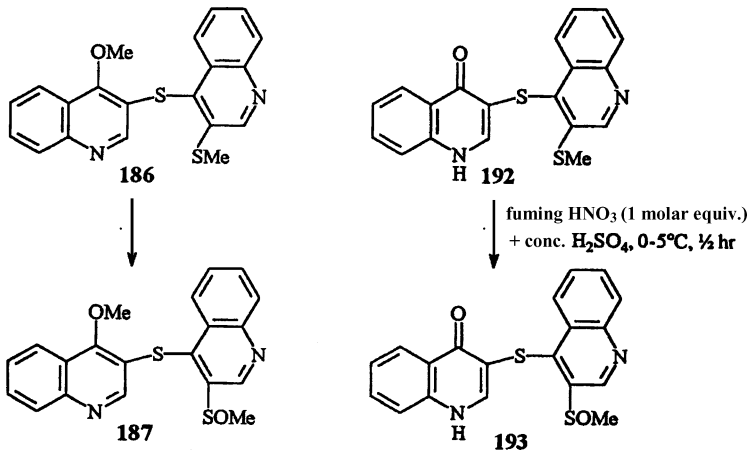
Oxidation of 4,5-bis (2,4-dinitrophenylthio)-1,3-dithiol-2-thione **184** with $Hg(OAc)_2$ in MeCN gave the dithiolate dianion[60] **185**. Both nitrobenzene rings of compound **184** are perpendicular to the dithiole ring forming donor-acceptor π-π type asymmetric configuration (according to the crystal structure of this compound).

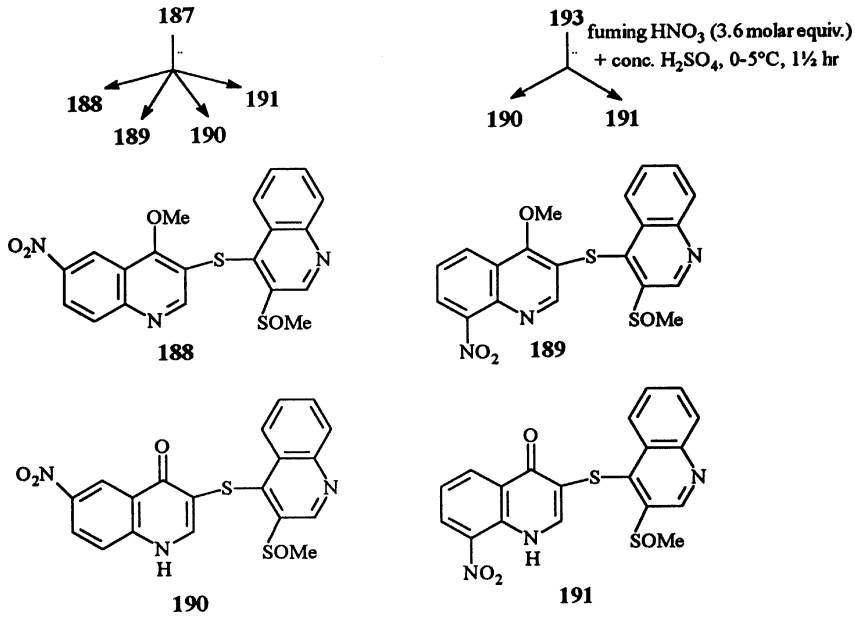


184 185

3) Nitration

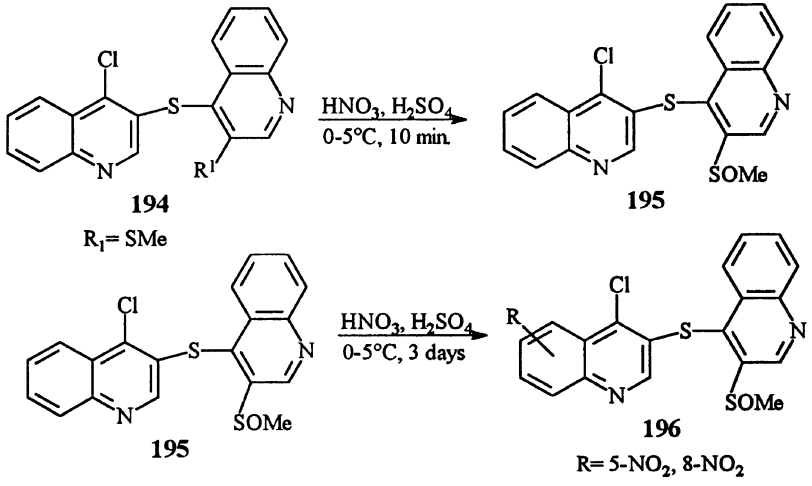
Reaction of 4-methoxy- or 1,4-dihydro-4-oxo-3-methylthio-3,4′-diquinolinyl sulfides **186**, **192** with a nitrating mixture ran as the 3′-methylthio group S-mono oxidation followed by C_6- and C_8-nitration[61] and led to the mixture composed of products **188**, **189**, **190**, and **191** in case of structure **186**, or compounds **190** and **191** in case of substrate **192** (Scheme 19).





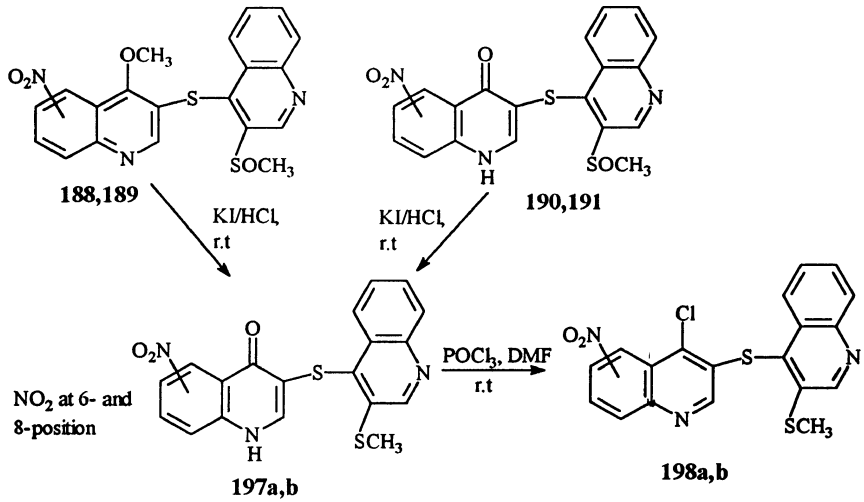
SCHEME 19

Meanwhile, reaction of 4-chloro-3′-methylthio-3,4′-diquinolinyl sulfide **194** with a nitrating mixture[62] proceeded *via* the 3′-methylthio group mono-oxidation and yielded 3′-methyl sulfinyl diquinolinyl sulfides **195** (Scheme 20).



SCHEME 20

Further treatment of **195** (R = -, R^1 = SOMe) with a nitrating mixture followed as C_5- and C_8-nitration and gave mixture of **196** (R = 5-NO_2, 8-NO_2, R^1 = SOMe). Treatment of 3′-methyl sulfinyl quinolines **188–191** with hydrochloric acid/potassium iodide causes reduction of the sulfoxide group to the sulfide group[62] yielding quinoline **197**, which was then be converted by reaction with phosphoryl chloride to 4-chloroquinolines **198a**,**b** (Scheme 21).

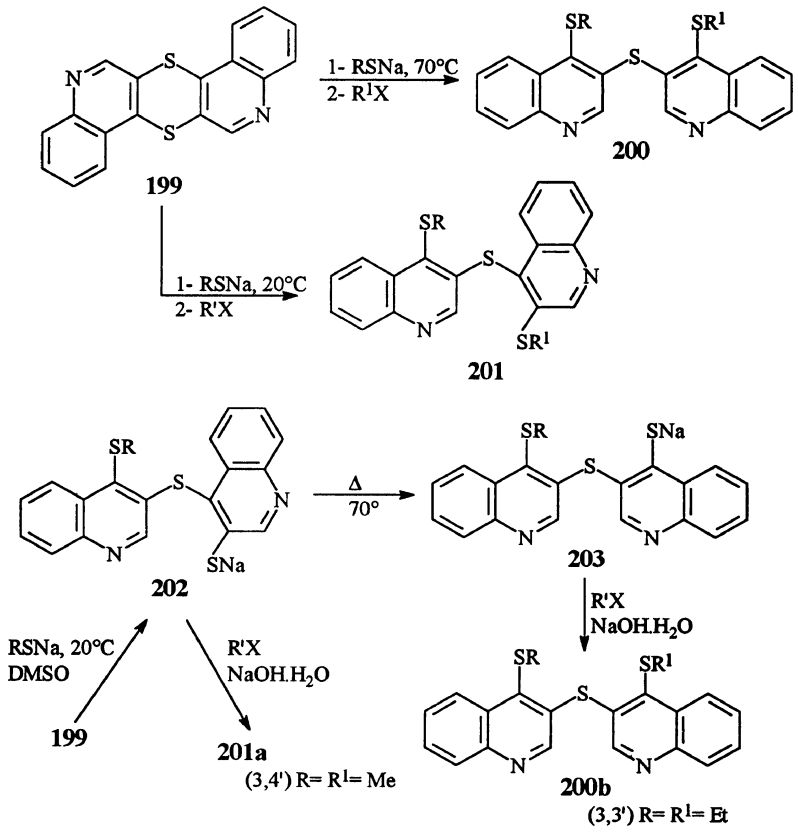


SCHEME 21

4) Smile Rearrangement

Reaction of thioquinanthrene **199** with sodium alkanethiolate at 70°C in dimethyl sulfoxide (DMSO) or DMF yielded 4,4′-dialkylthio-3,3′-diquinolinyl sulfides **200**, which resulted in the S–S type of the *Smiles* rearrangement[63] of primary reaction products (sodium 3-quinolinethiolates) **202**. When the reaction was carried out at 20°C the products were 3′,4-dialkyl thio-3,4′-diquinolinyl sulfides **201** (Scheme 22).

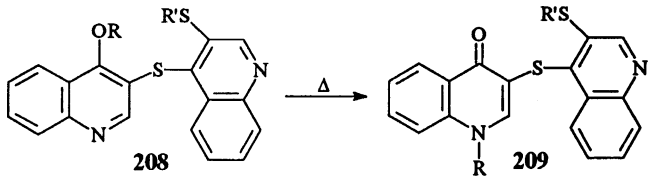
On the other hand, the reaction of thioquinanthrene **199** with sodium alkoxides and α,ω-dihaloalkanes,[64] lead to the formation of α,ω-bis[4-(4-methoxy-3-quinolinylthio)-3-quinolinylthio]alkanes **206**. The yield depended on the nature of α,ω-dihaloalkanes. The effect of α,ω-dihaloalkanes of the following types: XCH_2X (X = Cl, Br, I), $X(CH_2)_2X$ (X = Cl, Br, I), $Br(CH_2)_3Br$ and $Br(CH_2)_6Br$ was studied, and it was found that the yield of **205** increased when n = 2, 3, 6. 4-Alkoxy-3′-(ω-bromo-alkylthio)-3,4′-diquinolinyl sulfide **205** was prepared

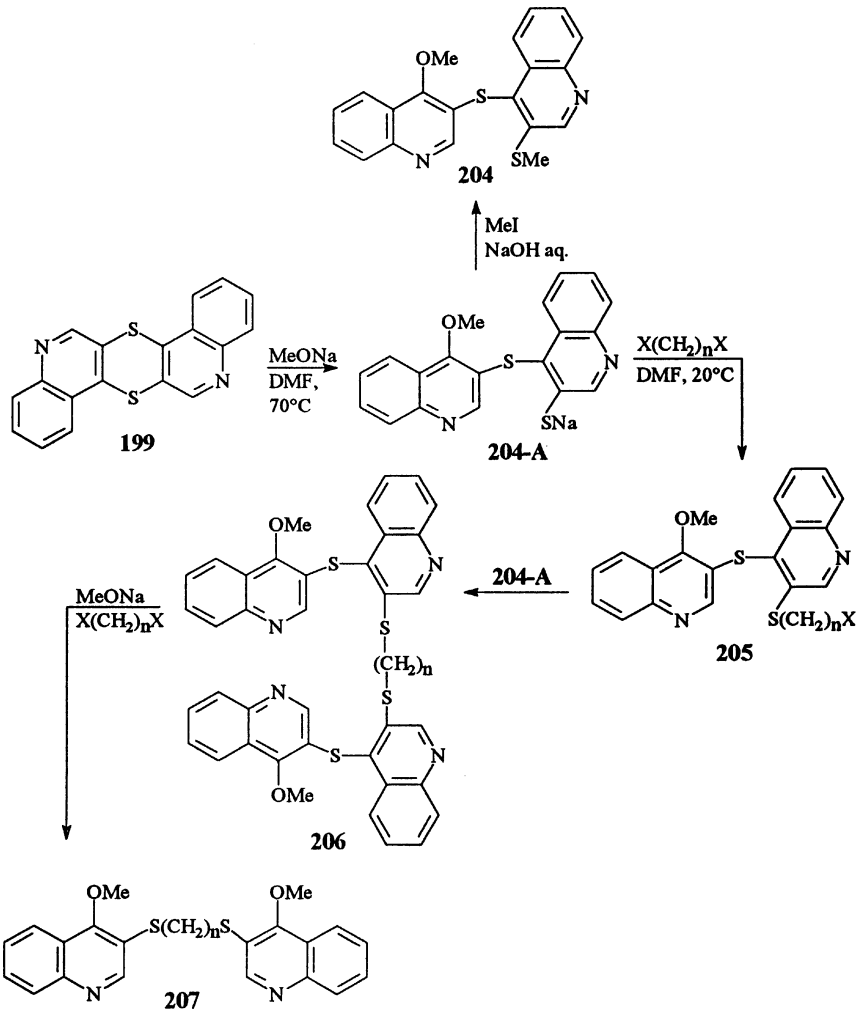


SCHEME 22

and transformed to α,ω-bis(4-alkoxy-3-quinolinyl-thio)alkanes **207** (Scheme 23).

4-Alkoxy-3′-alkylthio-3,4′-diquinolinly sulfides **208** underwent thermal rearrangement[65] to give 1-alkyl-1,4-dihydro-4-oxo-3′-alkylthio-3,4′-diquinolinyl sulfides **209**.



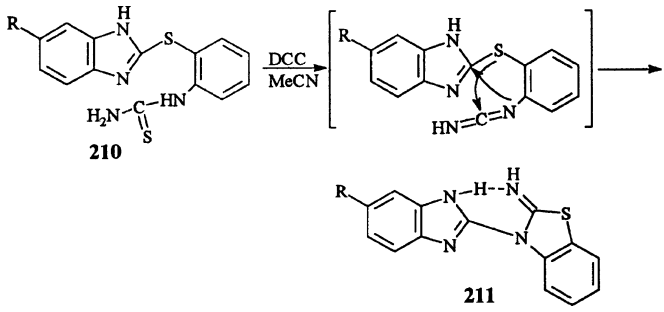


SCHEME 23

The reaction of *N*-[2-(1*H*-benzimidazol-2-ylthio)phenyl]thiourea **210** with DCC afforded the 2-imino-3-benzimidazolylbenzothiazolines[34,66] **211** *via* the *Smile*-type rearrangement (Scheme 24).

5) Nucleophilic Substitution Reaction

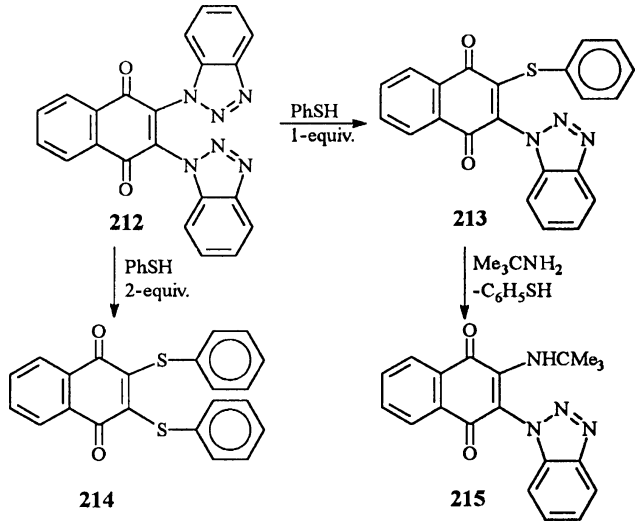
2,3-Bis(benzotriazol-l-yl)-1,4-naphthoquinone **212** reacted with one equivalent of thiophenol to give the (phenylthio)naphthoquinone[67] **213**,



R= H, C_6H_5-, 4-Cl-C_6H_4

SCHEME 24

while reaction with two equivalents of PhSH gave the bis(phenylthio)-naphthoquinone **214**. Reaction of **213** with $(CH_3)_3CNH_2$ gave compound **215** (Scheme 25).

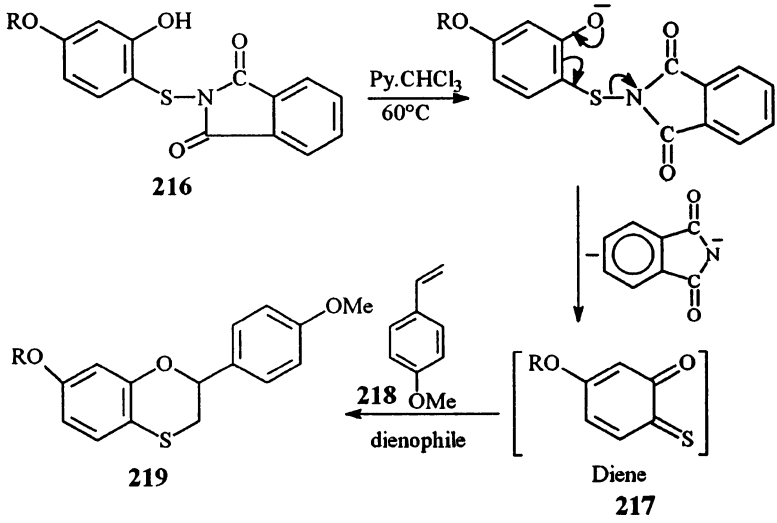


SCHEME 25

6) *Diels-Alder* Reaction

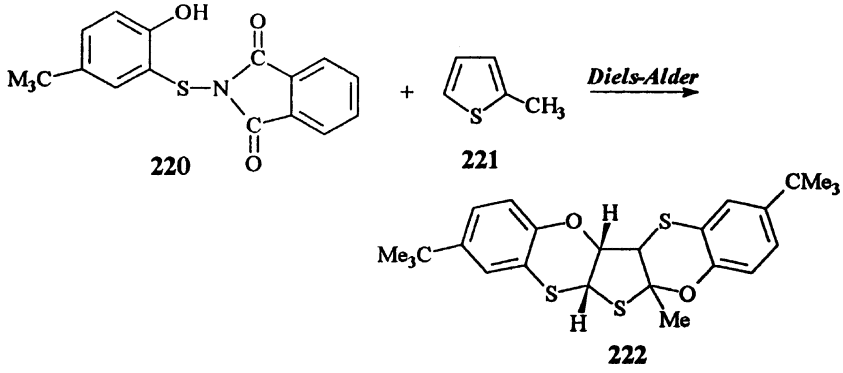
The reaction of *o*-hydroxy thiophthalimides **216** with pyridine (2 equiv.) and 2 equiv. of *p*-vinyl anisol **218** in chloroform at 60°C gave 1,4-benzoxathiin cyclo adducts[68] **219** *via Diels-Alder* reaction (Scheme 26).

A reasonable mechanism involved pyridine deprotonation of the hydroxyl group to give phenate which underwent phthalimide anion elimination with the formation of *o*-thioquinone **217**. This reactive



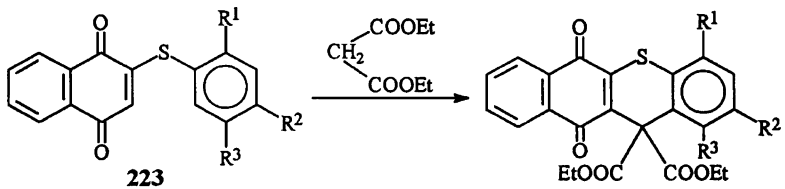
SCHEME 26

electron poor product was then trapped[69] by the electron rich alkene **218** to give **219** *via* an inverse electron demand *Diels-Alder* reaction. Also, *o*-thioquinone **220** underwent facile hetero *Diels-Alder* reaction[70] with cyclic dienes [e.g. 2-methylthiophene **221**] leading to thiophene bis[benzoxathiin] **222**.



7) Oxidative Free Radical Reaction

Reaction between 2-phenylthio-1,4-naphthoquinones **223** and diethyl malonate[71] was initiated by manganese(III) acetate to give 6,11-dihydro-6,11-dioxo-12*H*-5-thianaphthacenes **224**. This reaction was performed in various solvents, the best results were obtained in DMSO.



223

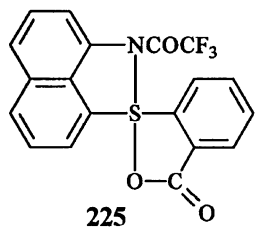
R^1 = H, Me, Cl, Br, COOEt
R^2 = H, Me, Br, OMe, F
R^3 = H, Me

224

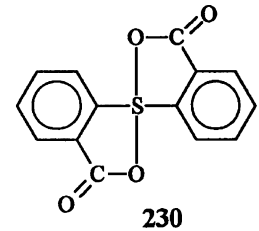
8) Formation of Spiroλ^4-Sulfanes

Spiro-λ^4-sulfanes[72,73] (earlier spiro sulfuranes), the stable organic analogues of the simple four-coordinated sulfur (IV) atom (e.g., SF_4 molecule) and reactions occurring at sulfur exhibiting trigonal-bipyrimidal configuration. Diaryl Spiro-λ^4-sulfanes with apical ligands of *o*-acyl, *o*-alkyl or *N*-acyl type were prepared from diaryl sulfides having two reactive groups (e.g., COOH, CH_2OH, NHAc, NHR) by oxidation (starting with s-halogenation).

The S(IV) [C, C, N, O] spirosulfuran[72] **225** and S(IV) [C, C, O, O]. spirosulfurane[74] **230** were prepared from sulfides using halogenating agents (e.g., *N*-choroarenesulfonamide or phenyliodoacetate).

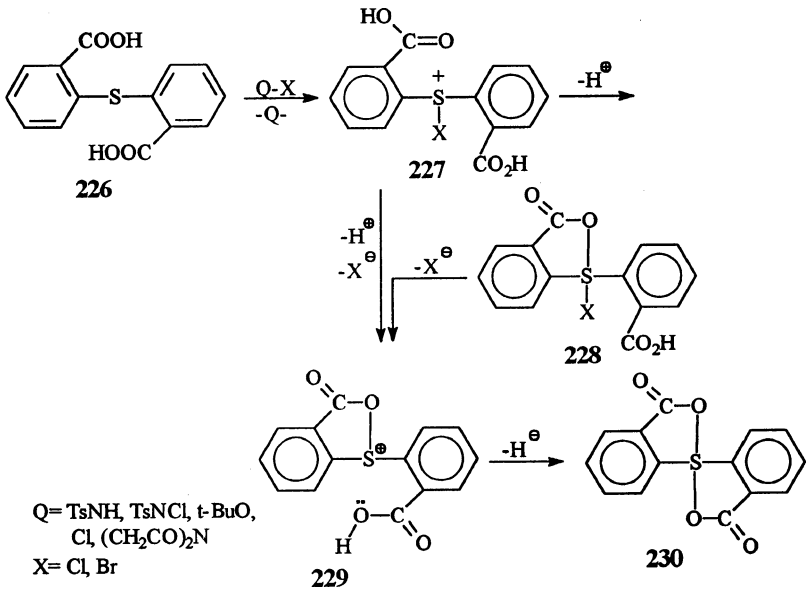


225



230

The interpretition of the formation of spiro sulfurane **230** from 2,2′-thiodibenzoic acid **226** depends on that, the halo sulfonium ion of the type **227** is formed as a reactive intermediate, and the *o*-carboxyl group stabilize the positive sulfonium center by polarized carbonyl *o*-atom. Due to the intramolecular nucleophilic attack of the *o*-carboxyl group, a cyclic acyloxysulfonium ion **229** may be formed from the halosulfonium ion **227**, presumably through a monocyclic halosulfurane intermediate **228**. The intermediate **229** is stablized by nucleophilic addition of the second ortho carboxyl group leading to a spiro sulfurane structure **230** (Scheme 27).



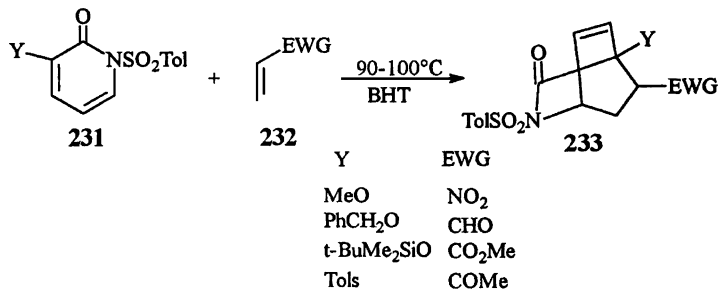
SCHEME 27

E) SYNTHESES BASED ON REACTIONS OF DIARYL SULFONES CONTAINING HETEROCYCLES

The following are reported[75–80] chemical reactions of certain diaryl sulfones containing heterocyclic systems.

1) *Diels-Alder* Reaction

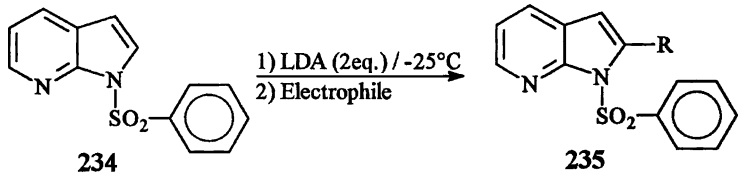
Captodative 3-oxy and 3-(tolylthio)-1-tosyl-2-pyridones **231** are shown to be reactive as nucleophilic dienes[75] undergoing *Diels-Alder* 2 + 4-cycloadditions with various electrophilic alkenes **232** under mild thermal conditions (90–100°C) and gave bicyclo lactam adducts **233**.



Y	EWG
MeO	NO_2
$PhCH_2O$	CHO
t-$BuMe_2SiO$	CO_2Me
Tols	COMe

2) Alkylation

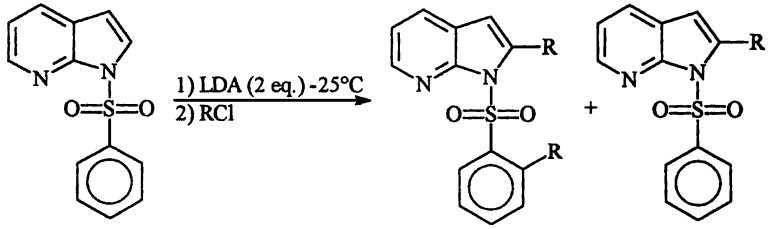
Lithiation of the two position of l-phenylsulfonyl-7-azaindole[76] **234** was performed with two equivalents of lithiumdiisopropylamide (LDA) at −25°C for 30 min and subsequent addition of various electrophiles led to the formation of the 2-alkyl-l-phenylsulfonyl-7-azaindole **235** but in low yield.



234 **235**

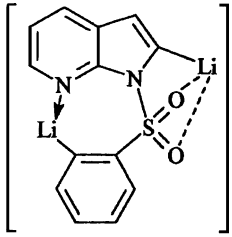
R= CH_3, *p*-(CH_3O-, H_3C-, Cl-, O_2N-), C_6H_5CHOH, COOH, CHO

The use of trimethylsillyl chloride or trimethyltin chloride as electrophiles led to the formation of two derivatives,[76] the disubstituted compounds **236**, and the monosubstituted compounds **237**.



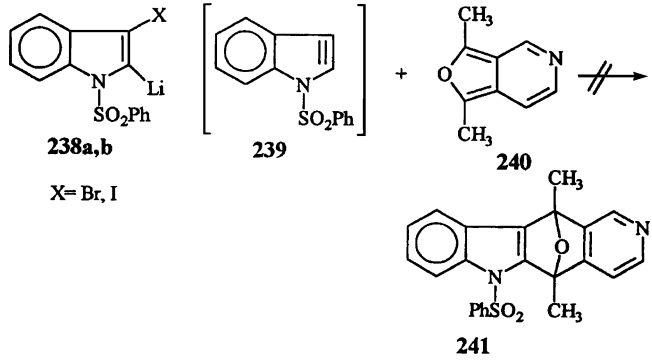
234 **236** **237**

A selective monosubstitution was performed, when the reaction was carried out with one equivalent of lithiumamide[77] or tert-butyllithium.[78] The dianionic intermediate [A] could be expected and the presence of the nitrogen atom in 7-position of 7-azaindole increases the stabilization of the anionic species leading to alkylation in the phenyl sulfonyl group itself.



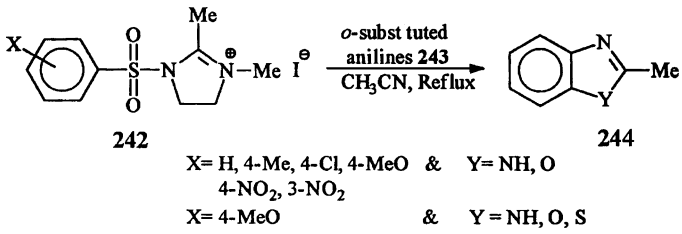
A

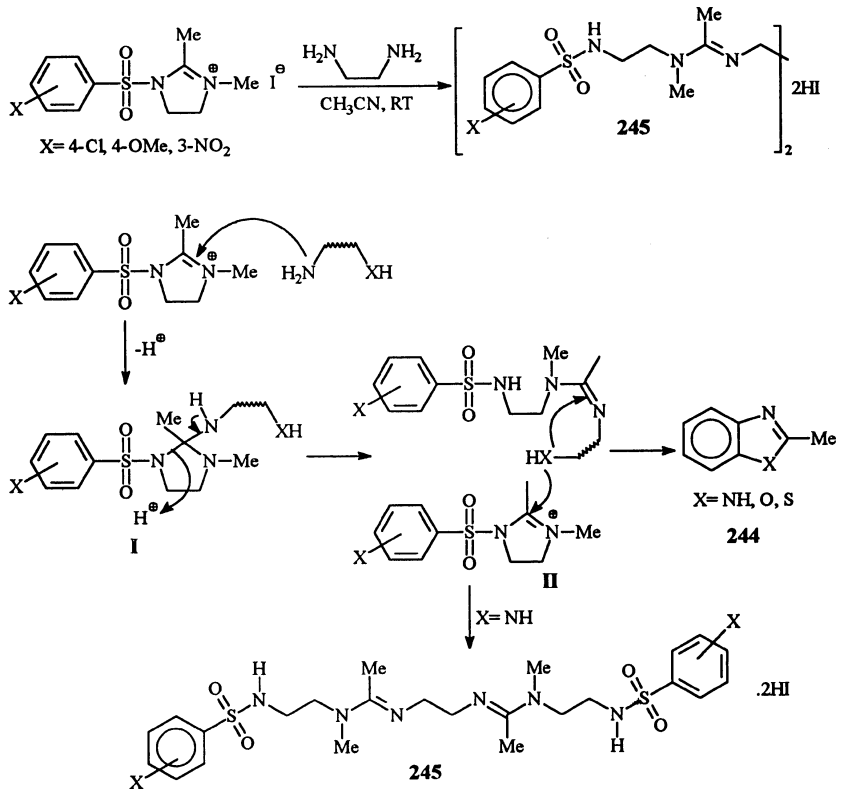
Attempts to generate and trap 1-phenylsulfonyl-2,3-indolyne **239** *via Diels-Alder* reaction[79] of 2-lithio-3-bromo-1-phenyl-sulfonyl indole **238a** and 2-lithio-3-iodo-1-phenylsulfonyl indole **238b** with 3,5-dimethylfuro[4,3-*c*]pyridine **240** to give the adduct **241** by heating the mixture at 50–60°C were unsuccessful. This is due to the remarkable stability of **238a**,**b** toward elimination which occurs under the reaction conditions.



3) Nucleophilic Substitution Reaction

Reaction of 1,2-dimethyl-3-arylsulfonyl-4,5-dihydro-3*H*-imidazol-l-ium iodides **242** with two types of bifunctional nucleophiles, namely ortho-substituted anilines (as aromatic nucleophiles) resulted in one-carbon unit transfer products: 2-methylbenzoxazoles, 2-methylbenzimidazoles and 2-methylbenzothiazoles **243** respectively, which mimics the one-carbon unit transfer reaction of N(5), N(10)-methyltetrahydrofolate coenzyme. The reaction of imidazolium salts **242** with ethylene diamine (as aliphatic nucleophile) exclusively produced the bis-addust **245**.[80] These different behaviors were explained with addition reaction mechanism (Scheme 28).





SCHEME 28

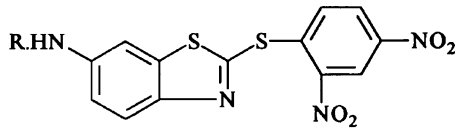
F) APPLICATIONS OF DIARYL SULFIDES AND DIARYL SULFONES CONTAINING HETEROCYCLES

The importance of diaryl sulfides and diaryl sulfones containing different heterocycles is due to their widest clinical application especially in the synthesis of drugs used in treatment of functional diseases. Also, they are useful as herbicides, insecticides, and agrochemical fungicides, in addition their important uses in various industrial fields. The following is an outline of some selected examples of these applications.

Biological Applications

1) As Antibacterial Agents

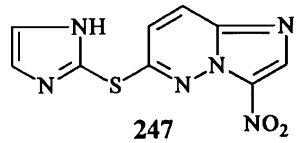
i) 6-Acetamido-2-(2,4-dinitrophenylthio)benzothiazole[81] **246** have antibacterial activity against gram-positive and gram-negative organisms.



246

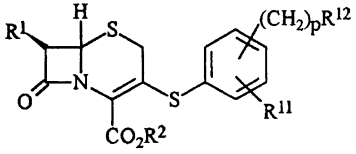
R= CH_3CO-

ii) Also, 7-[(1*H*-imidazol-2-yl)thio]-3-nitroimidazo[1,2-*b*]pyridazine[82] **247** was claimed to be effective against *Helicobacterium pylori* (*Campylobacter pyloridis*).



247

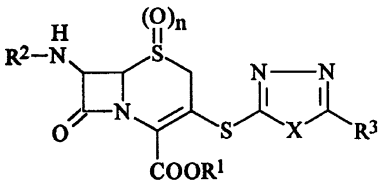
iii) Cephalosporin antibiotics: (7R)-7-(acylamino)-3-(aryhthio)-3-cephen-4-carboxylic acids[83] **248** exhibit antibiotic activity against a wide spectrum of organisms including those which are resistant to β-lactam antibiotics.



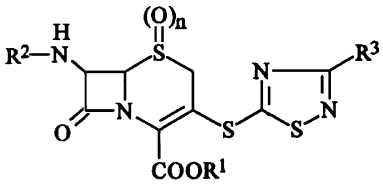
248

R^1= NHC(O)ZR^3, NR^4R^5;
Z= $CH_2(X)_m$, C(NOR^6), CH(OR^7), C(CHCO_2R^8), CH(NR^9R^{10}),
X= O, S; m= 0,1
R^2= H, alky, alkenyl, aryl, heterocycle, aralkyl, heteroalkyl
R^3= CN, alkyl, aryl heterocycle
$R^{4\text{-}7}$= H, alkyl, aryl, acyl
R= H, alkyl, aryl
R^9,R^{10}= H, alkyl, acyl, heterocycle
R^{11}= H, halogen
R^{12}= SR^{13}, R^{13}= ethyl, cycloalkyl

Cephalosporins[84,85] **249**, **250**, **251** are used for controlling methicillin-resistant *Staphylococcus aureus* (MRSA).

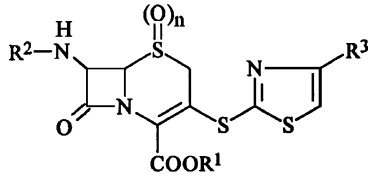


249



250

[X = O, S; R^1 = H, metal protecting groups, biohydrolyzable ester group, R^2 = phenylacetyl, Q; R^3 = pyridyl; 3,4-dihydroxyphenyl-3-hydroxy-4-pyridin-6-yl; *N*-methylpyridinium-3-yl; R^4 = protected amino; R^5 = H, Me, allyl, cycloalkyl methyl, cycloalkyl, 2-fluoroethyl, n = 0, 1].

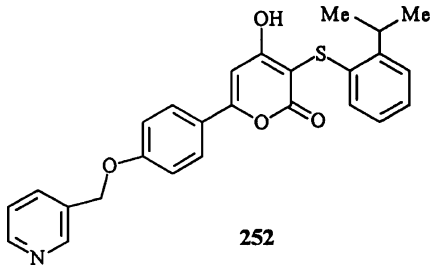


251

[R^1 = H, metal, protecting group, biohydrolyzable ester group; R^2 = phenyl acetyl, Q; R^3 = 3-pyridyl, N-methylpyridinium-3-yl, Ph, 2-thienyl; R^4 = protected amino; R^5 = H, Me, cycloalkyl, 2-fluoroethyl; n = 0, 1].

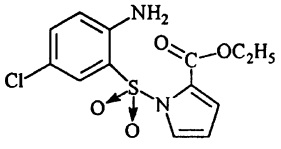
2) Antiviral Agents

i) Pyrone derivative[86] **252** was used as protease inhibitors and antiviral agents.

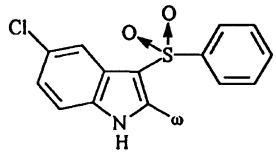


252

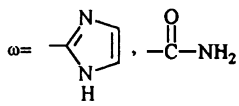
ii) Arylpyrrolyl and arylindolyl sulfones[87] **253** and **254** are used as anti-human immunodeficiency virus-type 1 (HIV-1).



253

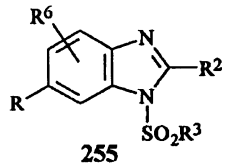


254



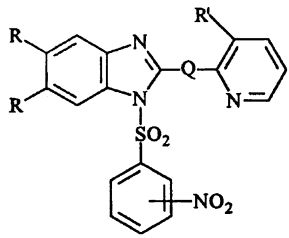
iii) 3-Benzimidazolyl-3-phenylacrylamides[88] **255** were also used by L.N. Jungheim et al.[88] as antiviral agents.

R= R^1ZC (:$CHCONR^4R^5$)
R^1= halo, OH, MeO, SO_2Me
R^2= H, (alkanoyl)amine
R^3= NMe_2, Ph
R^4, R^5= H, alkyl
R^6= H, halo, alkyl
Z= Unsubstituted-1,2-phenylene



255

iv) *N*-(benzenesulfonyl)benzimidazoles[89] **256a–c** showed potential antiviral activity against two RNA viruses at micromolar concentrations.

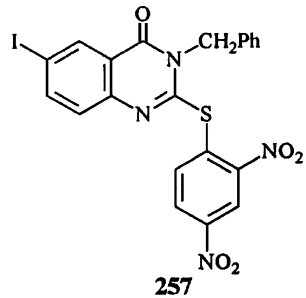


256a-c

a- R= H, Cl; R'= H, NO_2; Q= $(CH_2)_2$, SCH_2, S, NO_2
b- R= R'= H; Q= $(CH_2)_2$
c- R= Cl; R'= H; Q= $(CH_2)_2$

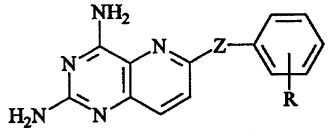
3) Antitumor Activity

i) A new compound of 4-(3*H*)-quinazolinone analogs[90] **257** bearing 6-iodo and 2-thioether functions proved to be a highly reactive as an anticancer agent.



257

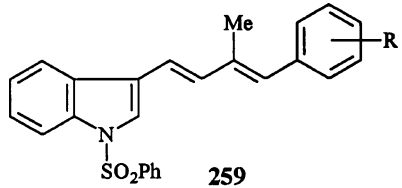
ii) 6-Substituted 2,4-diaminopyrido[3,2-*d*]pyrimidines[91] **258**, the analogs of piritrexim (PTX), were also used as antitumor agents.



258

R= 2-MeO, 4-MeO, 3,4-$(MeO)_2$, H, 4-Cl, 2,3-benzo;
Z= S, SO_2

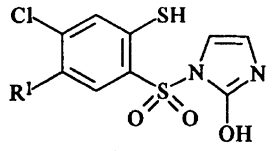
iii) 3-[3′-methyl-4′-(substituted phenyl)-1,3′-butadieneindole derivatives[92] **259** displayed different inhibitory effects as anticancer agents in-vitro. Besides, their inhibitory rate of anti-inflammation was 100% at 10^{-5} M.



259

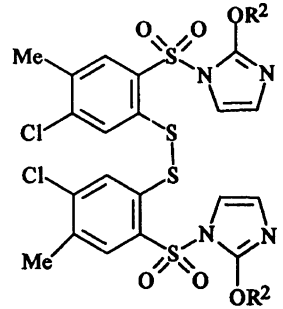
R= *p*-Cl, *m*-NO_2

iv) The [(chloromercaptophenyl)sulfonyl]imidazoles[93] **260** and bis-{[(aryloxyimidazolyl)sulfonyl]phenyl}sulfides[93] **261** exhibited weak, moderate or fairly high activity against some human tumor cell lines.



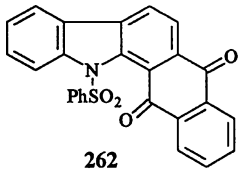
260

R^1 = Me, PhNHCO, 4-Me-C_6H_4NHCO, CO_2H, CO_2Me, CO_2Pr
R^2 = Ph, 3-Cl-C_6H_4, H_2N-C_6H_4

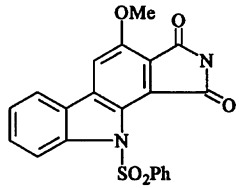


261

v) Coplanar [a]-annelated carbazoles[94] **262** and **263** showed significant cytotoxicity against K562 and RXF393 human tumor cell lines.



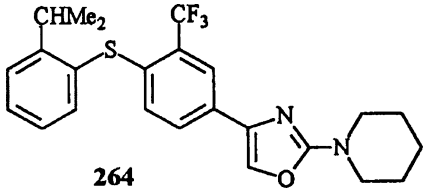
262



263

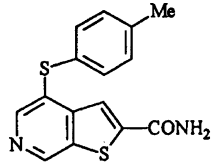
4) Antiinflammatory Agents

i) Arylphenylheterocyclyl sulfide derivatives[95] **264** are used for treating inflammatory and immune diseases, such as arthritis, asthma, inflammatory bowel disease, and so on.

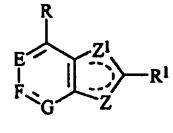


264

ii) Thienopyrimidine carboxamide[96] **265**, and its analogs **266** are used as cell-adhesion-inhibitory anti-inflammatory.



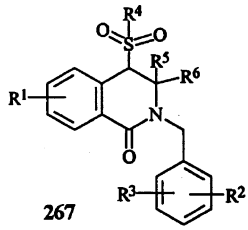
265



266

EFG= NCH=CH, -CHN=CH, -NCH=N, etc
R= Z^1R^2; R^1= Z^3R^3; R^2= H, halo, alkyl, alkoxy, aryl
R^3= H, R-, RO-, aryl, $CONH_2$
ZZ^1= $SO_{0\text{-}2}$; Z^2, Z^3 = bond, O, S

iii) 2-Benzyl-4-sulfonyl-4*H*-isoquinoline-1,3-diones[97] **267** are useful as anti-inflammatory agents.

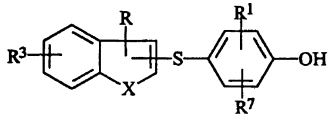


267

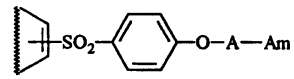
R^1=, halo, C_{1-4} alkyl, C_{1-4} alkoxy
R^2, R^3= H, halo, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy
R^4= C_{3-4} alkyl, CF_3CH_2, 2-thienyl, 2-naphtyl, (un) subsituted Ph
R^5= H; R^6= OH, or R^5R^6= O

5) As Cardiovascular Agents

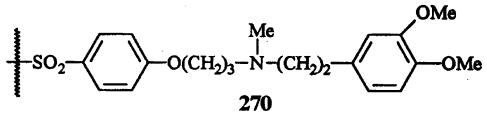
i) Hydroxy-4-benzenethio derivatives[98] **268** are used as intermeidates for preparation of aminoalkoxybenzenesulfonyl derivatives **269** and **270**, which are useful as cardiovascular agents.



268



269

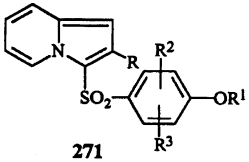


270

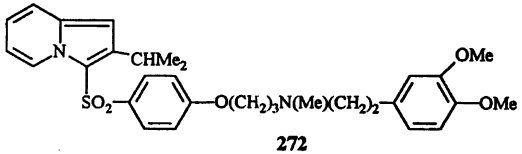
268, R^1, R^2= H, Me, Et, halo
R= alkyl, cycloalkyl, Ph
R^3= H, halo; X= O, S, NR^4; R^4= H, alkyl

269, [A= C_{2-5} alkylene or $CH_2CH(OH)CH_2$; Am= substituted amino

ii) Also, 3-(4-akloxyphenyl)sulfonyl indolizines[99] **271** are used as intermediates for cardiovascular agents **272**.



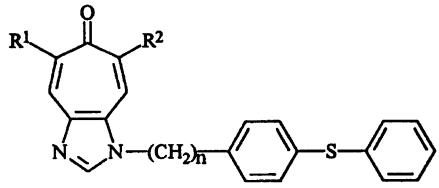
271



272

271, [R= H, C_{1-8} alkyl, C_{3-6} cycloalkyl, (substituted) Ph,
R^1= OH, protecting group, e.g., Me, CH_2Ph, C_{1-4} alkylsulfonyl,
C_{6-10} arylsulfonyl; R^2, R^3= H, Me, Halo]

iii) The use of 1-{[*p*-(phenylthio)phenyl]alkyl}-1,6-dihydro-1*H*-cycloheptimidazol-6-one derivatives[100] **273** are claimed for the treatment of cardiovascular disease.

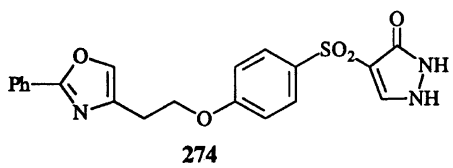


273

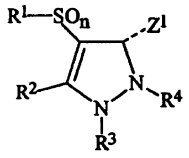
R^1, R^2= H, alkyl, cycloalkyl, alkylsufinyl, arylthio, etc.

6) As Anthihyperglycemic Agents

i) Sulfonylpyrazolones[101] **274**, sulphonylpyrazolines[101] **275** are used as hypoglycemic agent in treating hyperglycemia associated with non-insulin–dependent diabetes and for treating hyperlipidemia.



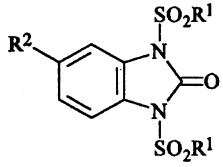
274



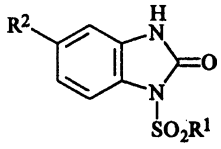
275

R^1-R^4= alkyl, aryl, aralkyl
Z^1= H, O, S, N, n= 0-2

ii) 1,3-Bis(arylsulfonyl)benzimidazolones[102] **276** and 1-arylsulfonylbenzimidazolones[102] **277** are useful as potential hypoglycemic agents.



276



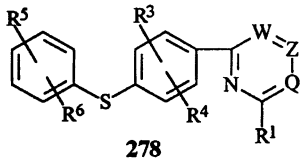
277

R^1 = 4-Me$C_6H_4SO_2$, 2-naphtyl-SO_2; R^2= H, NO_2

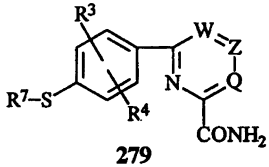
7) As Anticonvulsant Agents

Diaryl sulfides containing pyridines, pyrimidines, pyrazines, and triazines[103] **278** and **279** are useful for the treatment of neuronal damage following ischemia, the treatment of acute or chronic pain, as

antitimnitus agents, as anticonvulsants, as antimanic depressants, and as local anesthetics.



278

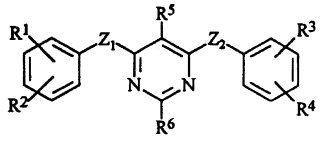


279

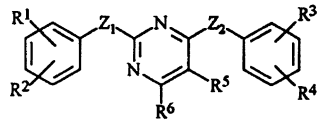
[Q, Z, W= CR^2, N; R^1= alky, H_2N, alkylthio, R^8CO, R^8SO_2, H_2NCO_2, 2-imidazolinyl, 3-pyrazolyl, R^2= H, alkyl, alkenyl, alkynyl, halo, HO, cycloalkyl, cyano, NH_2, RO, R^3, R^4, R^5, R^6= H, R-, Cl, -OH, NO_2, -NH_2, CN, ureido, azido, RO, CO_2H, R^7= R, R^8= R, R^9O, R^9= H, R.

8) As Anticoagulants

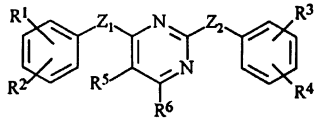
Aryl and heterocyclyl substituted primidines[104] **280a–c** demonstrated the selective ability to inhibit human factor Xa (the enzyme factor) and human thrombin, and are effective in treating a 70 Kg person at 100–500 mg/day and therefore are useful as anticoagulants.



280a



280b



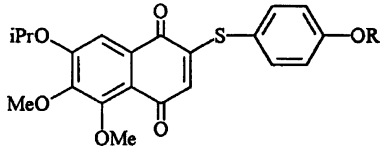
280c

Z_1= O, NR^7, CH_2O SO_n (n= 0-2)
Z_2= O, NR^7, OCH_2, SO_n (n= 0-2)
R^1, R^4= H, halo, alkyl
R^2= $C(NH)NH_2$, C(NH)NHOR, $C(NH)NHCOR^7$
R^3, R^5= H, halo, alkyl
R^6= (un)substituted aryl, aralkyl, heterocycl, etc.

9) Nerve Cell Death Inhibitors

Chromone derivatives[105] represented by general formula **281** wherein R represents a variety of substituents (e.g., carboxyalkyl, carboxylakenyl, alkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl,

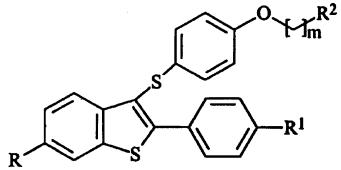
alkylsulfonylalkyl). Thus, when R = $CONMeCH_2CH_2OH$ at 50 μg/ml *in vitro* decreased cell death ratio from 100% to 32.67%.



281

10) Treatment of the Effects Associated with Post-Menopausal Syndrome

i) Benzothiophene derivatives[106,107] **282a**,**b** are useful for the inhibition of the various medical conditions associated with post-menopausal syndrome, such as osteoporosis and cardiovascular disease, as well as estrogen-dependent diseases including cancer of the breast, uterus, and cervix.

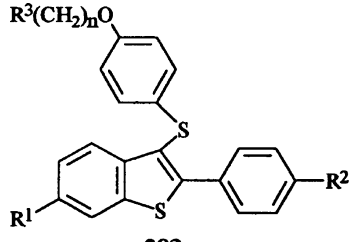


282a,b

282a; R, R^1= OH, halo, OPg (protecting group), m= 0-1
R^2= substituted C_{5-7} cycloalkyl, N-substituted pyrrolidin-2-yl, pyrrolidin-3-yl

282b; R, R^1= H, OH, halo, OPg; m= 0
R^2= CHR^3OR^4, CO_2R^5, $CHOHCH_2NR^6R^7$, heterocycle
R^3= H, CH_2OH; R^4= H, C_{1-6} alkyl, COR^8
R^5= H, C_{1-6} alkyl, aryl, R^6= H, C_{1-6} alkyl
NR^6R^7= 3,5-dimethylpiperidino, .., R^8= H, C_{1-6} alkyl, aryl

ii) Benzothiophene compounds[108] **283** are useful for inhibiting aortal smooth muscle profileration and are active for treatment of the effects of post-menopausal syndrome.

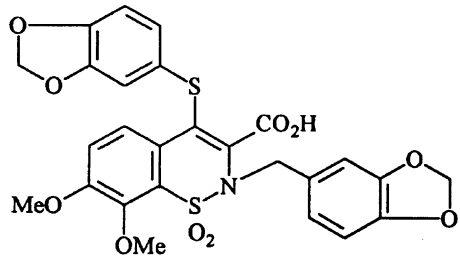


283

R^1 = H, OH, O (C_{1-6} alkyl); R^2 = H, OH, O (C_{1-4} alkyl), $OCOC_2H_5$, OCO (C_{1-6} alkyl), OSO_2 (C_2-C_6)alkyl, halo; R^3 = 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, . . . , n = 2–3.

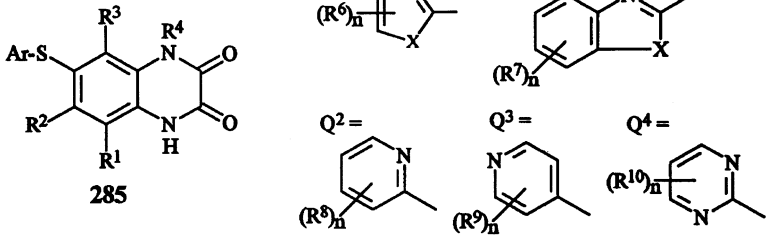
11) As Antagonists

i) Benzothiazin-1,1-dioxide[109] **284** is a new structural class of potent endothelin receptor antagonists.



284

ii) Arylthioquinoxaline derivatives[110] **285** showed antagonizing activity for glutamate receptors of central nervous cells in particular the glycine binding site of N-methyl-D-aspartate (NMDA) receptor and/or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.



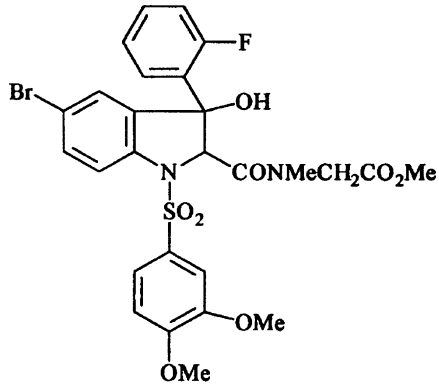
285

Ar= (un)substitited arom. heterocyclyl containing at least one N

R^1= H, halo, NO_2; R^2= H, halo, nitro, cyano, trihalomethyl

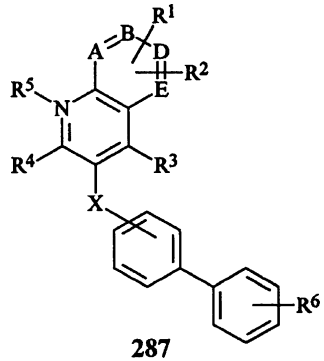
R^3= H, halo, NO_2; R^4= H, (un)substituted lower alkyl or cycloalkyl

iii) 1-Phenylsulfonyl-3-hydroxyindoline-2-carboxamides[111] **286** are used as vasopressin and oxytocin antagonists.



286

iv) Biphenyl-substituted quinoline and naphthyridines[112] **287** which are angiotensin II antagonists are also useful in the treatment of hypertension, congestive heart failure, and cardiac hypertrophy.

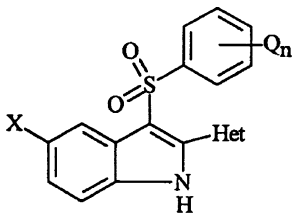


287

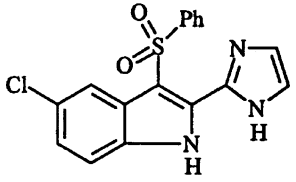
[A, B, D, E are each C atoms or only 1 of them may be a N atom]
R^1, R^2= H, (un)substituted C_{1-4} alkyl, haloalky, CN, NO_2, $-NH_2$
R^3= CO_2H, carboxylate ester, CH_2OH, CHO, $-CONH_2$, $CONHSO_2CF_3$
R^4= H, alkyl, alkenyl, alkynyl, cycloalkyl, Ph
R^5= an optional O atom. R^6= H, ester group, $NHSO_2CF_3$, $O_2S(OH)_2$, SO_3H, heterocycle, CO_2H. (X= O, CH_2, S, SO, SO_2, NH, CO)

12) As Reverse Transcriptase Inhibitors

i) 3-Substituted heterocyclic indoles[113] **288** are useful as inhibitors of HIV reverse transcriptase prevent or treat of HIV infections/ AIDS/ARC.

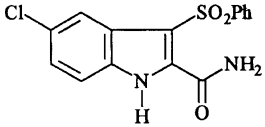


288



288a

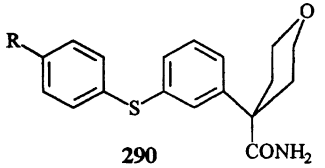
ii) Also, 5-chloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxamide[114] **289**, and analogs are HIV reverse transcriptase inhibitors and are claimed for the treatment of AIDS and ARC.



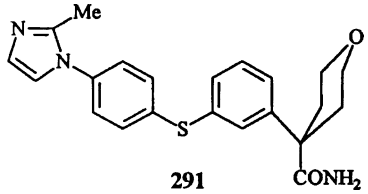
289

13) As 5-Lipoxygenase Inhibitors

i) Tetrahydro-4-[3-(4-heterocyclylphenylthio)phenyl]-2*H*-pyran-4- carboxamides[115,116] **290**, **291** are useful as 5-lipoxygenase inhibitors.



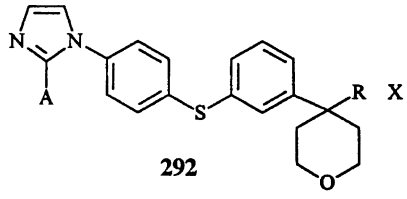
290



291

R = (un) substituted imidazolyl, pyrazolyl, benzimidazolyl, or benzopyrazolyl.

ii) Also, tetrahydro-4-[3-(4-imidazol-l-ylphenylthio)phenyl]-2*H*-pyran-4-carboxamides[117] **292** are used as 5-lipoxygenase inhibitors and are useful in the treatment or alleviation of inflammatory disease, allergy, and cardiovascular disease in mammals.

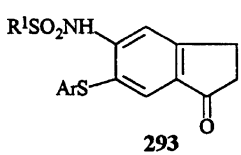


292

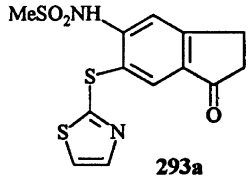
A= alkyl, aryl; R= $CONH_2$; X= CH_3SO_3H

14) As Cycloxygenase Inhibitors

i) *N*-(2,3-dihydro-1-oxo-1*H*-inden-5-yl)alkanesulfonamides[118] **293** are useful for the treatment of cycloxygenase-mediated diseases such as pain, fever, and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza, or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, and arthritis (including rheumatoid arthritis).



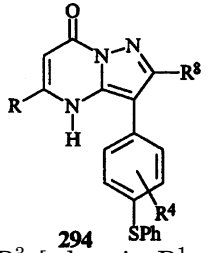
293



293a

Ar= aryl; R^1= alkyl, fluoroalkyl

ii) 4,7-dihydro-7-oxo-3-(4-phenylthiophenyl)pyrazolo[1,5-*a*]pyrimidines[119] **294** are used for inhibiting the formation of NO (nitrogen oxide) *in vivo* and are useful in treating an allergic disease asthma and atropic dermatitis.

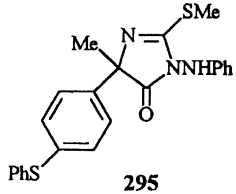


294

R = $(CH_2)_nC(R^1)(R^2)AR^3$ [wherein R^1 = H, lower alkyl; R^2 = H, lower alkoxy; R^3 = H, alkyl; R^4 = H, lower alkyl, lower alkoxy; R^8 = H, lower alkyl, lower alkoxy]; A = O, S; R^2R^3 = 5–6 membered heterocycle, n = 0–2.

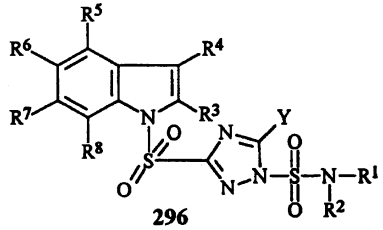
15) As Agrochemical Fungicides

i) *N*-aminoimidazolinone[120] **295** gave ≥75% control *Puccinia recondita* on wheat when sprayed at l g/L.



295

ii) Indolylsulfonyltriazole derivatives[121] **296** used as agrochemical fungicides. Compounds of this invention at 1000 ppm gave ≥80% control of Phytophthora in festans.

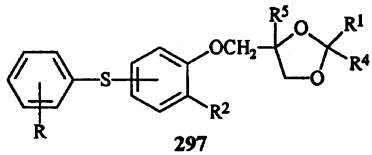


296

Y= halo, R^1, R^2= alkyl; R^3, R^4= H, alkyl; R^5-R^8= H, alkyl, etc.

16) As Pesticides

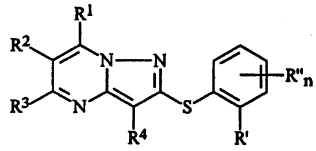
i) {[(phenylthio)phenoxy]methyl} dioxalanes[122] **297** are used as pesticides against white flies (*Bemisia tabaci*) and Aonidiella.



297

R= alky, halo, etc.; **R^1-R^3 = alkyl, halo, alkoxy, etc.**
R^4= H, alkyl, halo, etc. **R^5= H, alkyl**

ii) Pyrazolo[1,5-*a*]pyrimidines[123] **298** are useful as pesticides and agrochemical fungicides.

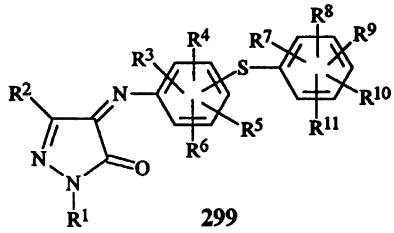


298

R^1= C(=CHOMe)CO_2Me, C(=CHOMe)CONHMe, C(=NOMe)CO_2Me, C(=NOMe)CONHMe, etc.
R'= 2-oxazolyl; 1,3,4-oxadiazol-2-yl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl
R"= CN, halo, (halo)alkyl, (halo)alkoxy, (halo)alkylthio, etc.
R^1,R^3= H, CN, -NO_2, -OH, -NH_2, halo, (halo)alkyl, aryl, etc.
R^2= H, halo, (halo)alkyl, aryl, aryloxy, heteroaryl, etc.
R^4= H, CN, NO_2, NO, halo, (halo)alkyl, etc.; n= 0 or 1.

17) As Insecticides

i) Pyrazoline derivatives[124] **299** are useful as pesticides and have insecticidal activity against immature *Aedes aegypti*.

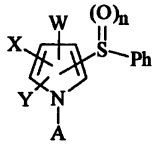


299

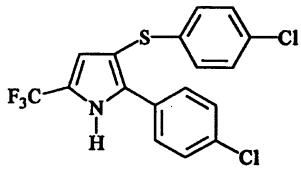
R^1, R^2= H, C_{1-4} (halo)alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, alkoxycarbonyl, aminocarbonylalkyl, Ph, etc.

R^3-R^{11}= H, halo, C_{1-4} (halo)alkyl, NO_2, CN, C_{1-4}(alkoxy), C_{1-4}(alkylthio) or their salts

ii) Arylthio, -sulfinyl and -sulfonyl pyrroles[125] **300** are useful for controlling insects, and compound **300a** showed 100% efficacy against southern Army worm at 300 ppm.



300

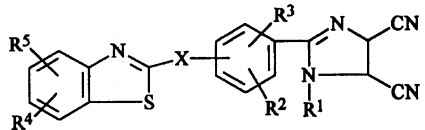


300a

X= (un)substituted phenyl, n= 0-2; W= halo, CN, NO_2, C_{1-4} (halo)alkyl

Y= H, halo, C_{1-4} haloalkyl; A= H, CN, C(O)(C_{1-6} alkyl), etc.

iii) [(Benzothiazolyl)thio]imidazoledinitriles[126] **301** are useful as insectides, they showed pharmacological activity against insects and representatives of the order Acarina that are harmful to animals and plants, as well as against helminths in warm-blooded animals.



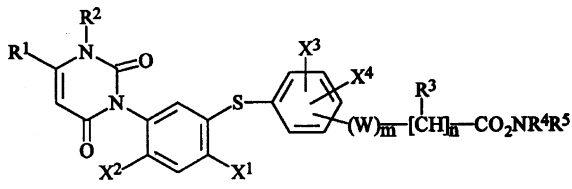
301

X= S, SO or SO_2 R^1= H, alkyl; R^2= H, halo, cyano, etc

R^3= H, halo alkyl, etc R^4, R^5= H, halo, NO_2, etc.

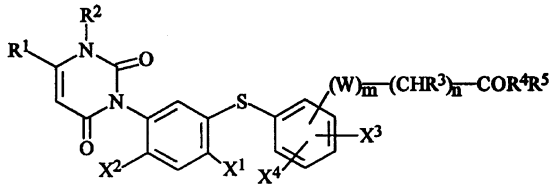
18) As Herbicides

i) Uracils[127,128] **302**, **303** are useful as herbicides.



302

W= O, S, imino, C_{1-3} alkylimino
R^1= C_{1-3} (halo)alkyl, R^2= C_{1-3} alkyl
R^3= H, C_{1-3} alkyl, X^1= halo, -CN, NO_2; X^2= H, halo
X^3, X^4= H, halo, C_{1-6} (halo)alkyl, C_{3-8} halo(lakenyl), CN, etc.
m= 0,1; n= 0-2; R^4, R^5= H, C_{1-6} (haloalkyl), CN, C_{1-6} alkyl, etc.

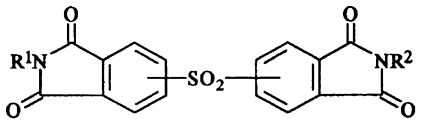


303

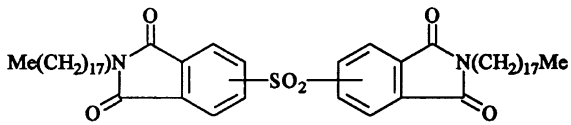
W= O, S, imino, Cl, contg. C_3 alkylimino.
Other substituents the same as comp. **302**.

19) Industrial Applications

i) Bisimide derivatives[129] **304a**,**b** are useful as additives for heat-resistant resins.



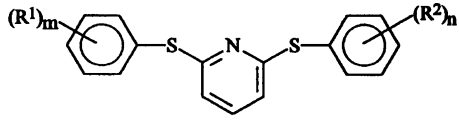
304a



304b

304a; R^1, R^2= alkyl

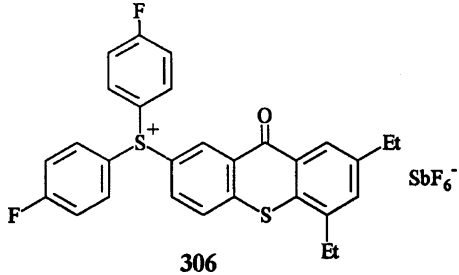
ii) 2,6-bis(phenylthio)pyridine derivatives[130] **305** are suitable as lubricants, lubricant additives, grease, and antioxidants which have excellent stability against heat and oxidation.



305

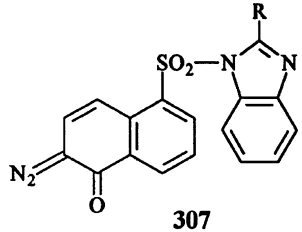
(R^1= R^2= halo, $C_{1\text{-}24}$ hydrocarbyl; m, n= 0-5)

iii) Thioxanthone sulfonium salts[131] **306** are used as photopolymerization initiators and when added by ratio equal 1.5 part to an energy ray curing composition containing 80 part celloxide 2021 (an alicyclic epoxy resin) and 20 part EHPE 3150 (an alicyclic epoxy resin) and was coated on an Alumenium test panel at 5 M thickness and irradiated with U. V. light using a high-pressure Hg lamp to give a cured coating film with complete transparancy, good stability and glass, and no odor.



306

iv) 1-(1,2-naphthoquinone-2-diazide-5-sulfonyl)-2-alkylbenzimidazoles[132] **307**, are useful as photosensitive materials.



307

R= $C_{5\text{-}9}$ alkyl

G) CONCLUSION

This article describes the role of diaryl sulfides and diaryl sulfones in heterocyclic syntheses, either by using one of the two aryl groups in building up an isolated or fused heterocyclic ring, or by using both of them in building three or more fused heterocyclic rings.

On the other hand, the sulfone group may be used as a good protecting group in the synthesis of fused heterocycles, or as a good leaving group in other heterocyclic syntheses using SN^2 substitution reaction. The importance of this class of compounds is due to their wide clinical and other biological applications in addition to their important uses in industrial fields.

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