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DIVERSE REACTIONS OF α/β-MERCAPTOALKANOIC ACIDS: IN THE SYNTHESES OF CONDENSED FUSED POLYCYCLIC HETEROCYCLES

(dedicated to late.**Dr. KALLAM ANJI REDDY**)

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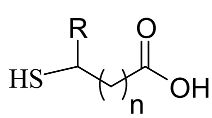
Abstract: This review describes the reactions of α/β-mercaptoalkanoic acids as building blocks for the synthesis of polyfunctional heterocycles with pharmacological interest. Annelated heterocycles have been prepared by the cyclocondensation reaction of α/β-mercaptoalkanoic acids with carbonyl function. This reaction takes place by nucleophilic addition, followed by cyclisation with elimination of water. The main objective of this survey is to provide a comprehensive account of the reactions of α/β-mercaptoalkanoic acids with carbonyl function, β-halovinylaldehydes, α-haloesters, hetero/aromatic halides, α-halonitriles, imines in building various heterocycles and examining their potential in developing better chemotherapeutic agents.

Keywords: 2-mercaptoacetic acid, β-mercaptopropanoic acid, cyclocondensation, spiro heterocycles.

1. INTRODUCTION

Voluminous literature on the utility of α/β-mercaptoalkanoic acids (**1a-e**), esters as a versatile synthon[1] in the preparation of condensed fused heterocycles has appeared in recent times. In spite of the fact that there appeared in literature reviews on reactions of these reagents (**1a-e**) with aldimines,[2] β-halovinylaldehydes,[3] a detailed account on the reactions with carbonyl group and other functionalities like α-haloesters, hetero/aromatic halides, α-halonitriles, imines, olefin, hydroxyl functional groups, is not reported till date. This necessitated us to review and highlight the current reactions in the field of polycyclic heterocycles.



1a-e

1	R	n
a	H	0
b	H	1
c	Me	0
d	CO_2H	1
e	Me_2	0

The present review is divided into 4 sections based on the nature of heterocycles formed or employed or the type of reaction used.

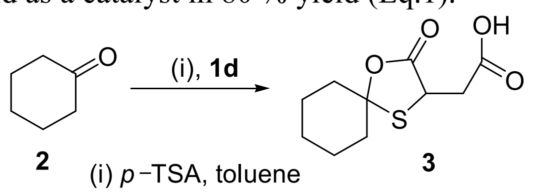
1. Spiroheterocycles
2. Heterocycles based on S_N-Ar mechanism
3. Conjugate addition to olefinic bonds
4. Miscellaneous

2. SPIROHETEROCYCLES

Spiro heterocyclic compounds are of interest in synthetic organic chemistry. Indeed, the presence of spiro carbon atom induces a relative steric strain and allows thermal, base or acid promoted rearrangement of these products. Thus they yield new and often unexpected heterocycles.[4-8] The cycloaddition between dipolarophiles bearing an exocyclic carbon-carbon double bond and appropriate 1,3-dipole is one of the best methods for the synthesis of bicyclic spiro compounds. The other method is the cyclocondensation of aldimines with bifunctional nucleophiles such as α/β-mercaptocarboxylic acids. Recent literature reports revealed the synthesis of some spiro heterocycles that have activity as herbicides and pesticides.[9] Photo and thermo chromic properties of spiro derivatives have been studied.[10, 11] From all of the foregoing facts, together with importance of thiophene derivatives, the syntheses of some spiro heterocyclic compounds were described.

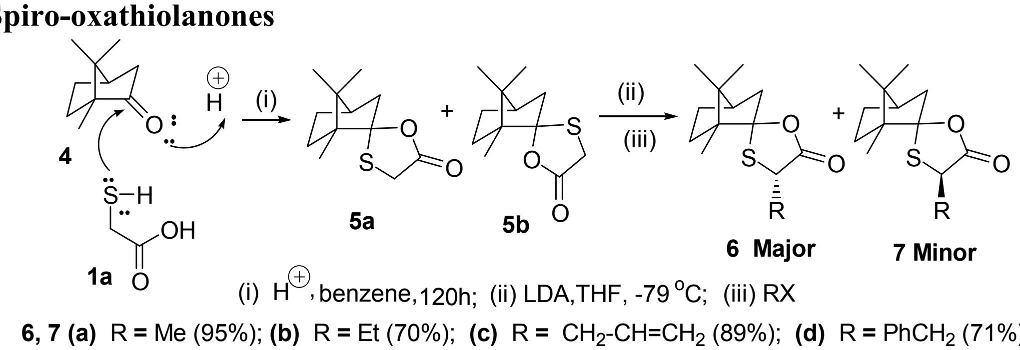
2.1. Spiro thioxa-4-one derivative

Pelter *et al.* [12] reported the synthesis of spirooxathiolanones (**3**) by the reaction of mercaptosuccinic acid and cyclohexanone (**2**) in toluene under azeotropic removal of water using *p*-toluenesulfonic acid as a catalyst in 80 % yield (Eq.1).



(Eq.1)

2.2. Spiro-oxathiolanones

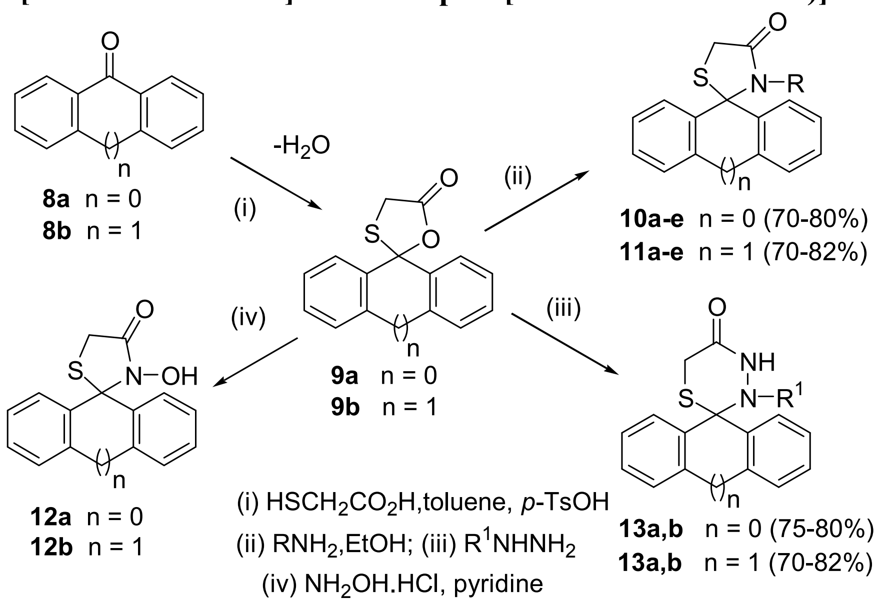


Scheme 1

The synthesis of optically active α-substituted thioglycolic acids has been reported by Liu and Chen [13] in recent years, which involves a self-reproduction of chirality from an optically active α-monosubstituted thioglycolic acid [14] or reaction of thiolates with an optically active α-hetero substituted acetic acid.[15] When a benzene solution containing R-(+)-camphor (**4**) and 2-mercaptoacetic acid **1a** in the presence of catalytic amount of *p*-tolunesulfonic acid was refluxed for 120 hours, two optically active oxathiolanones **5a** and **5b** were obtained [16] in a ratio 5.6 to 1 with a total yield of 95% (conversion 52%).

The preferential formation of 1,3-oxathiolan-5-one **5b** would be predicted by an *endo* attack on carbonyl carbon of camphor by the more nucleophilic sulfur atom of the 2-mercaptoacetic acid, followed by lactonization. The major oxathiolanone **5a** was deprotonated with lithium diisopropylamide in THF at -78 °C and alkylated with a variety of alkyl halides to yield monoalkylated products **6, 7** with excellent diastereoselectivity. The predicted stereochemistry of ketalization and alkylation were in agreement with X-ray crystallography result (Scheme 1).

2.3. Spiro [fluoren-oxathiolan]-one and Spiro [anthracen-oxathiolan)]-one



10,11 (**a**) R = C_6H_5; (**b**) R = $C_6H_5CH_2$; (**c**) R = *p*-MeC_6H_4

(**d**) R = *p*-$NO_2C_6H_4$; (**e**) R = *o*-pyridyl

13 (**a**) R^1 = H, n = 0; (**b**) R^1= $C_6H_5CH_2$, n = 0

14 (**a**) R^1 = H, n = 1; (**b**) R^1= $C_6H_5CH_2$, n = 1

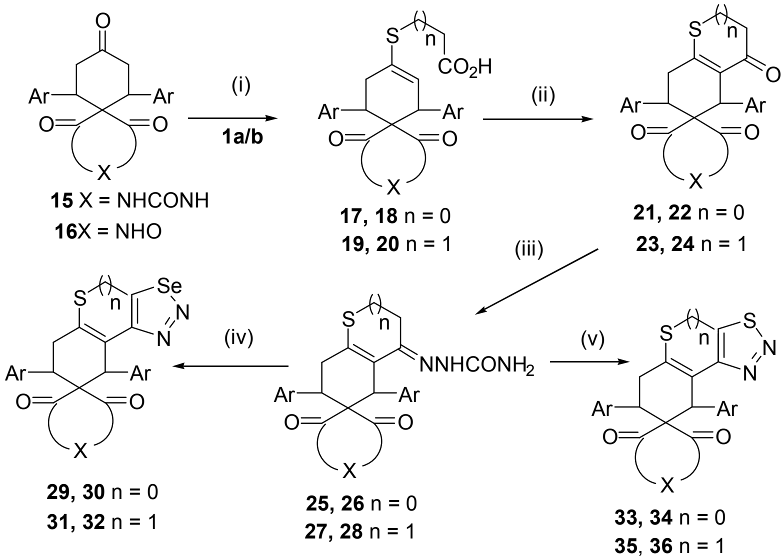
Scheme 2

Spiro derivatives exhibit interesting photochromic properties, biological activity and optical activity.[17] Thiazolidinones are known for their bactericidal, fungicidal, anti-inflammatory activity.[18] Hozien and Wareth [19] reported the synthesis of spirohetero-cycles related to thiazolidin-4-ones incorporated with fluorene and anthracene moieties. Reaction of 2-mercaptoacetic acidwith fluorenone (**8a**) and anthrone (**8b**) afforded spiro [fluorene-9, 2'-(1',3'-oxathiolan)]-5'-one **9a** and spiro [anthracene-9 (10*H*), 2'-(1',3'-oxathiolan)]-5'-one **9b**. The reaction of compound **8a** and **8b** with primary alkyl, arylamine and heterocyclic amines in absolute ethanol at reflux temperature gave spiro [fluorene-9,2'-thiazolidin]-3'-(aryl or heterocyclo/-4'-one (**10a-e**) and spiro[anthracene-9(10*H*)-2'-thiazolidin]-3'-(aryl or heterocyclo)-4'-one (**11a-e**) respectively. Reaction of **9a** and **9b** with hydroxylamine hydrochloride, hydrazine, in ethanol gave the corresponding spiro [flourene-9,2'-thiazolidin]-3'-(hydroxyl)-4'-one (**12a**) and spiro[anthracene-9(10*H*)-2'-thiazolidin]-3'-(hydro-xyl)-4'-one (**12b**), spirothiadiazinones (**13a,b, 14a,b**) (Scheme 2).

2.4. Spiro-tetrahydrothiochromeno-1,2,3-selena/thiadiazoles

Much emphasis has been placed on the synthesis of heterocyclic compounds resembling a steroidal moiety because of the interest in their chemical and physical properties.[20] The *gem*-

ester functionality of 2, 6-dimethyl-4-oxocyclohexan-1,1-dicarboxylates was found to be a useful one for the development of spiro-pyrimidinetriones, pyrazolidinediones and isoxazolidene-diones.[21] Bhaskara Reddy and Ramana Reddy [22] reported the synthesis of spiro-pyrimidine-triones having 1, 2, 3-selena/thiadiazole group in a rigid framework. The condensation of **15** and **16** with 2-mercaptoacetic acid **1a** and β-mercaptopropanoic acid **1b** in the presence of *p*-toluenesulfonic acid in benzene resulted in the corresponding thioacids **17-20** which, on cyclodehydration with phosphorous pentoxide, led to the formation of tricyclic ketones **21-24**.
The semicarbazones (**25-285**) of the tricylic ketones by oxidative cyclization with SeO_2 and Hurd-Mori reaction process with $SOCl_2$, furnished 6,8-diarylspiro[5,6,7,8-tetrahydrobenzo[4,5] thieno[3,2-*d*][1,2,3]selena/thiadiazole-7,5'-(hexahydropyrimidine)]2',4",6"-triones (**29**/**33**), 7,4'-[tetrahydroisoxazole]-3',5'-diones (**30**/**34**) and 7',9'-diaryl spiro [hexahydropyrimidine-5,8'-(6',7',8',9'-tetrahydro-4'*H*-thiochromene)[4,3-*d*][1,2,3] selena / thiadi-azoles]-2,4,6-triones (**31** /**35**) and [tetrahydro-isoxazole-4,8'-(6',7',8',9'-tetrahydro-4'*H*-thio-chromene)[4,3,-*d*] [1,2,3] selena/thiadizole]-3,5-diones (**32**/**36**) (Scheme 3).



(i) *p*-TSA/benzene; (ii) P_2O_5/benzene; (iii) $NH_2CONHNH_2$.HCl / NaOAc/MeOH
(iv) SeO_2/AcOH/60-70 °C; (v) $SOCl_2/CH_2Cl_2$; Ar = C_6H_5, 4-$MeOC_6H_4$
15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35 X = NHCONH
16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36 X = NHO

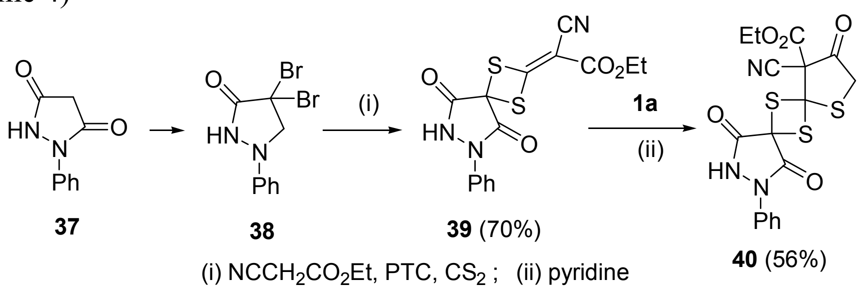
S.No	n	Ar	X	% Y
29a	0	C_6H_5	NHCONH	67
29b	0	4-$MeOC_6H_4$	NHCONH	62
30a	0	C_6H_5	NHO	64
30b	0	4-$MeOC_6H_4$	NHO	59
31a	1	C_6H_5	NHCONH	60
31b	1	4-$MeOC_6H_4$	NHCONH	63
32a	1	C_6H_5	NHO	57
32b	1	4-$MeOC_6H_4$	NHO	62

S.No	n	Ar	X	% Y
33a	0	C_6H_5	NHCONH	62
33b	0	4-$MeOC_6H_4$	NHCONH	63
34a	0	C_6H_5	NHO	55
34b	0	4-$MeOC_6H_4$	NHO	57
35a	1	C_6H_5	NHCONH	59
35b	1	4-$MeOC_6H_4$	NHCONH	55
36a	1	C_6H_5	NHO	58
36b	1	4-$MeOC_6H_4$	NHO	59

Scheme 3

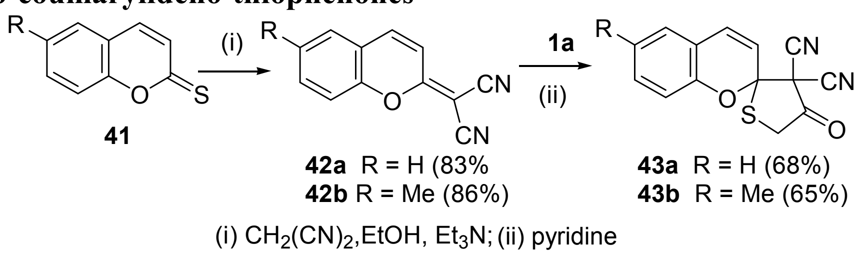
2.5. Spiro-pyrazolidinedione-dithietano-thiazolidinone

The 3,5-pyrazolidinediones have gained increasing importance in recent years owing to the medical use of 4-butyl-1,2-diphenyl-3,5-pyrazolinedione (butazalidin) in the treatment of rheumatoid arthritis.[23] Khodairy [24] reported the synthesis of fused spiro heterocyclic compounds containing a pyrazole moiety using PTC technique.[25] 4,4-dibromo-1-phenyl-pyrazolinedione [26] (**38**) was treated with CS_2 and active methylenes namely ethyl cyanoacetate under PTC conditions to afford the corresponding dithietane derivative **39**.[27] The reaction of dithietane **39** in pyridine with 2-mercaptoacetic acid gave the spiro derivatives of thiazolidinone **40** in 56% yield (Scheme 4)



Scheme 4

2.6. Spiro-coumarylideno-thiophenones

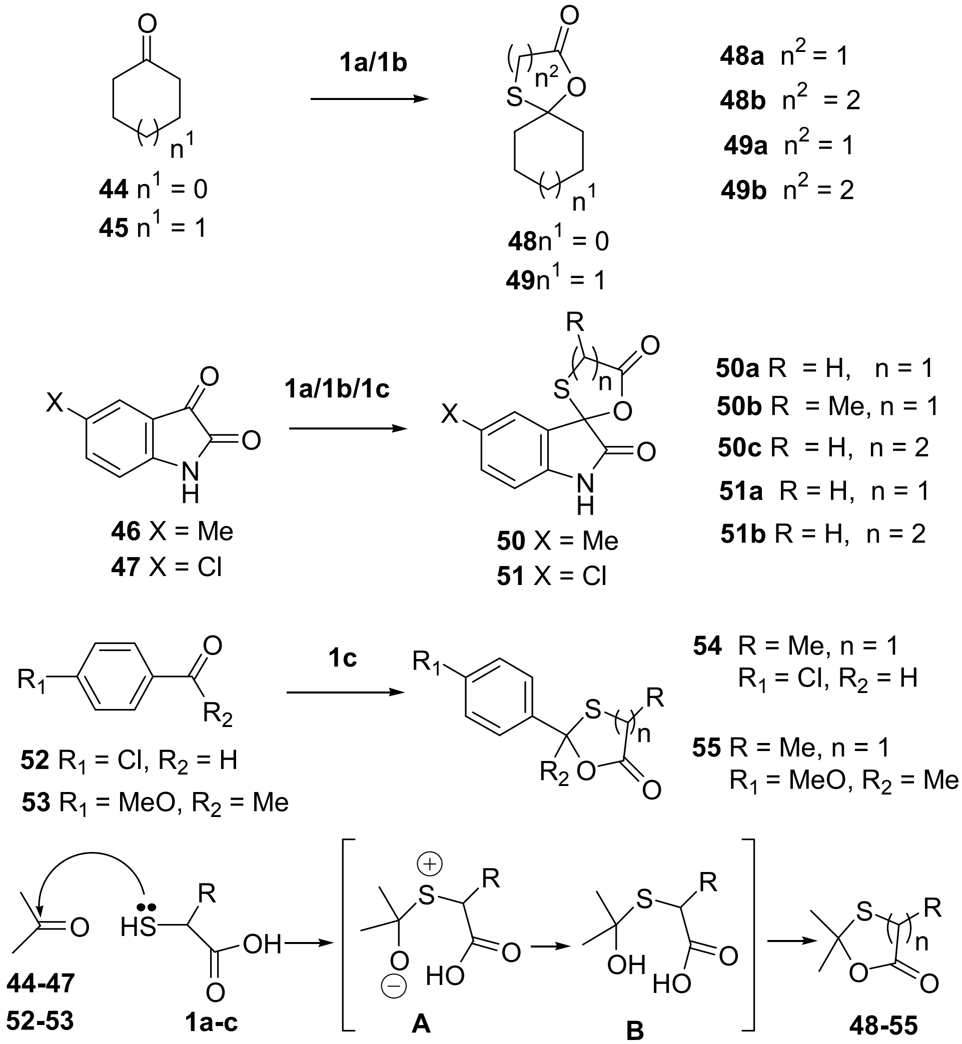


Scheme 5

α,β-unsaturated nitriles are versatile reagents extensively utilized in heterocyclic synthesis.[28] Coumarin derivatives are known for their physiological, anti-bacterial and antifungal properties.[29] Abdel Ghany *et al.* [30] reported the synthesis of spiro heterocyclic systems attached to coumarin nucleus by the addition of bidentates to 2-coumarylidene malononitrile derivatives. The reaction of thiocoumarin **41** with malononitrile in refluxing ethanol in presence of triethylamine as a catalyst gave 2-coumarylidenemalononitrile **42** in 83-86% yield. The reaction of compounds **42a, b** with mercaptoacetic acid **1a** [31] in refluxing pyridine gave the corresponding spiro thiophen-3-one derivatives **43a,b**. The postulated mechanism involves addition of the mercapto group on the ethylene bond followed by cylization *via* elimination of water molecule to afford the spiro compound (Scheme 5).

2.7. Spiro 1,3-oxathiolane

Development of organic solid state reaction has emerged as frontier area of research in synthetic organic chemistry.[32-34] The reactions are especially appealing because they have certain advantages, such as high efficiency, selectivity, mild reaction conditions,[35] and envi-ronmental acceptability.[36] This approach has been widely used in a variety of organic reactions.[37, 38] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole, spirooxathiolane heterocycles have made them attractive synthetic targets.[39-41]



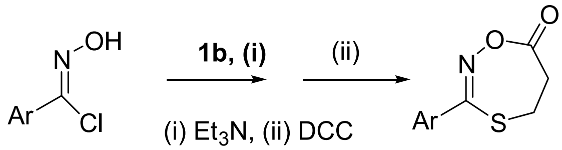
Scheme 6

Dandia *et al.* [42] have reported the synthesis of spiro 1, 3-oxathiolanes containinig different alicyclic / heterocyclic moieties (**48-53**). Cyclocondensation was performed using excess molar ratio of α/β-mercaptoalkanoicacids **1a-c** with carbonyl compounds such as cyclopentanone **44**, cyclohexanone **45**, substituted indoles **46,47**, by the solid state reaction at room temperature in 2-3 min after grinding the two reactants in agate mortar. The method was extended to reaction of aromatic aldehydes **52**/ ketones **530** giving 2-(substitutedaryl)-4-methyl-1,3-oxathiolane derivatives (**54-55**). This cyclocondensation reaction is a two step reaction. The first step involves nucleophilic attack of thiol group on carbon-oxygen double bond of carbonyl group giving the intermediate hydroxyl alkylthio acids (**A & B**) which on elimination of water gave the products (**48-55**) (Scheme 6).

3. HETEROCYCLES BASED ON S_N-AR MECHANISM (ADDITION-ELIMINATION PATH)

The chemistry of α/β-mercaptoalkanoic acids thus far has always been the subject of intense research efforts. Undoubtedly this is due to their synthetic potential and numerous applications associated with their chemistry.[1-3] As a consequence, α/β-mercaptoalkanoic acids and their esters have enjoyed a similar pronounced attention. Here we would like to report the reactions between α/β-mercaptoalkanoic acids and other reactive intermediates such as β-halovinylaldehydes,[43-46] α-haloesters,[47] hetero/aromatic halides,[48] α-halonitriles, imines which involves the formation of C-S bond by nucleophilic substitution followed by addition-elimination path [49,50] resulting in the formation of condensed five, six or seven member heterocycles. Derivatives prepared in this fashion relate to patents or experiments to develop potent heterocycles aiming at agrochemicals or drugs.

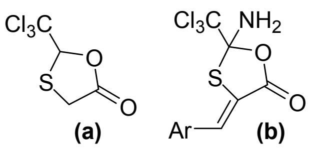
Johnson *et al.* [51] has reported the synthesis of 5,6-dihydro-7,-1,4, 2-oxathiazepin-7- one (**57**) by the reaction of hydroximoyl chloride (**56**) with β-mercaptopropionic acid **1b**, followed by cyclisation with DCC (Eq.2).



56 **57** Eq. 2

3.1. Oxathiolanones

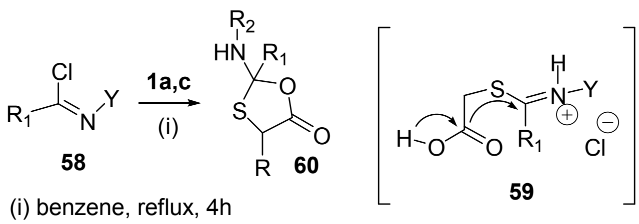
Imidoyl chlorides combine the properties of both acid chlorides and azomethines. They are reactive and versatile chemical agents that have found wide application in organic synthesis and in the study of chemical reactivity.[52] Trifluoroacetimidoyl chlorides are regarded as promising new building blocks for the synthesis of functionalized fluorine-containing compounds.[53]



(a) **Plant growth regulator**

(b) **Enzyme inhibitor**

Fig. 1



58 **60** **59**

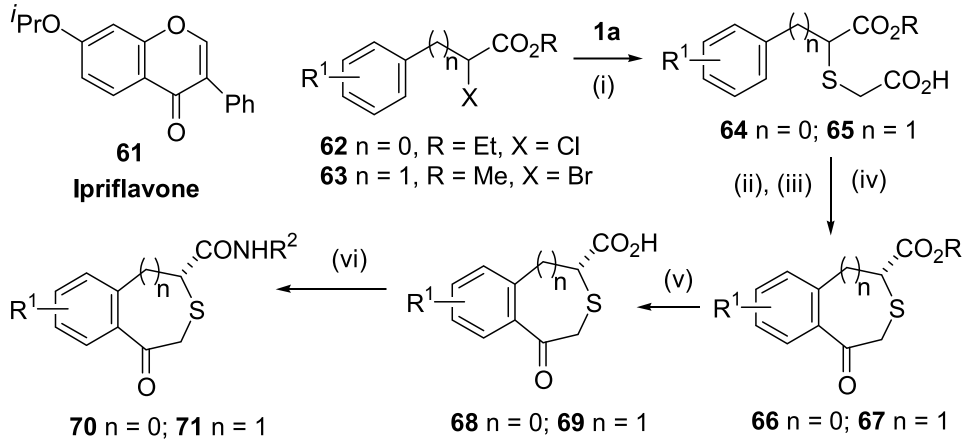
60	R	R_1	R_2	% Y
a	H	CF_3	$PhSO_2$	95
b	H	H	*p*-Ts	95
c	H	OH	$PhSO_2$	92
d	Me	OH	*p*-Ts	92

60	R	R_1	R_2	% Y
e	H	CF_3	CO_2Me	95
f	H	CF_3	C(O)Ph	95
g	H	CH_2F	$PhSO_2$	92

Scheme 7

The derivatives of 1,3-oxathiolanones have applications as fungicides, herbicides, growth regulators [54] (Figure **1a, b**). Onys'ko *et al.* [55] reported the synthesis of oxathiolanones, based on accessible fluoroacetimidoyl chlorides, activated by *N*-acyl-*O*-*N*-sulfonyl substituents. Heterocyclization of imidoyl chlorides **58** with ά-mercaptocarboxylic acids **1a, 1c** in benzene affords the corresponding oxathiolanones **60** in high yields. The unusually facile transformation of **58** to **60** most likely results from the highly electrophilic nature of imines **58** and from a beneficial five membered ring formation. It is quite possible that substitution of the chlorine atom by the thio-function is accompanied by far intramolecular ring closure of immonium salts of type **59**. The remarkable ease of heterocyclization can be explained by the high electrophilicity of the iminium *C*-atom (**59**) and the geometrically favorable location of the reactive centers [56] (Scheme 7).

3.2. 2-Benzothiopyran and 3-Benzothiepin Derivatives



(i) K_2CO_3 or Et_3N; (ii) $COCl_2$ or $SOCl_2$, DMF; (iii) $AlCl_3$ or $SnCl_4$; (iv) NaOR
(v) 2N KOH; (vi) R^2NH_2, DEPC, Et_3N

70	R^1	R^2
a	6-cyclohexyl	4-Cl-C_6H_4
b	6-cyclohexyl	4-Me-C_6H_4
c	6-cyclohexyl	2,5-$(EtO)_2$-C_6H_3
d	6-cyclohexyl	$C_6H_4[4\text{-}CH_2P(O)(OEt)_2]$
e	6-cyclohexyl methyl	$C_6H_4[4\text{-}CH_2P(O)(OEt)_2]$
f	6-(4-Cl)C_6H_4	$C_6H_4[4CH_2P(O)(OEt)_2]$
g	6,7-Me_2	3-pyridyl
h	6,7-Me_2	3-pyrazinyl

71	R^1	R^2
a	H	$C_6H_4(4CH_2P(O)(OEt)_2)$
b	7-Cl	$C_6H_4(4CH_2P(O)(OEt)_2)$
c	7-Me	$C_6H_4(4CH_2P(O)(OEt)_2)$
d	7,8-Me_2	$C_6H_4(4\text{-}P(O)(OEt)_2)$
e	7,8-$(MeO)_2$	$C_6H_4(4\text{-}P(O)(OEt)_2)$
f	7,8-$(MeO)_2$	$C_6H_4[4CH_2P(O)(OEt)_2)$
g	7,8-O-CH_2-CH_2-O	$C_6H_4[4CH_2P(O)(OEt)_2)$
h	7,8-O-CH_2- O	$C_6H_4[4CH_2P(O)(OEt)_2)$

Scheme 8

Ipriflavone (7-isopropoxyisoflavone) **61** enhanced bone-like tissue formation *in vitro* due to stimulation of differentiation of rat bone marrow stromal cells into osteoblasts.[57] 2-Benzothiopyran-1-carboxamide derivatives were found to increase cellular alkaline phosphotase (ALP) activity, in cultures of rat bone marrow stromal cells. Oda and co-workers [58] reported the synthesis of 2-benzothiopyran-1-carboxamide derivatives (**70**) and the ring expanded 3-benzothiepin-2-carboxamide derivatives (**71**) starting from α-haloesters (**62**, **63**) as described in scheme **8**.

The sulfides **64, 65** were prepared by coupling of **62** or **63** with α-mercaptocarboxylic acids in the presence of a base. The sulfides (**64, 65**) were converted into acyl chlorides and cyclised by intramolecular Friedel-Crafts reaction to give esters (**66, 67**), which were then hydrolysed to provide carboxylic acids (**68, 69**). The amides (**70, 71**) were prepared by coupling reaction of **68** or **69** with amines [59] (R^2NH_2). The intramolecular cyclization of the sulfides **64, 65** gave a mixture of *cis* and *trans* products **66, 67**, which were treated with alkoxide to afford the more stable trans form as a single product (Scheme 8).

The synthesized compounds **70a-h, 71a-h** were screened for biological activity. The ALP activity of these 3-benzothiepin derivatives bearing a 4-(dialkoxyphosphoryl methyl) phenyl group on the 2-carboxamide moiety such as **71f** and **71h** exhibited significant improvements of activity compared to ipriflavone. The effect of compounds (10^{-5} M) on ALP activity in the culture of rat bone marrow stromal cell line MC3T3-E1 was evaluated according to the method of Maniatopoulos *et al.* [60] and expressed as the ratio value compared to the control group (n = 5-10). This study revealed that **71h** enhanced the effect of bone morphogenic protein.

3.3. 2-[Mercapto(cyano)methylene]-1, 2, 3, 4-tetrahydroquinazolin-4-ones

Quinazolin-4-ones have received considerable attention in the literature of pharmaceutical chemistry.[61] Fleischer *et al.* [62] reported the synthesis of substituted 2[mercapto(cyano)-methylene]-1,2,3,4-tetrahydroquinazolin-4-ones **74** as a part of program aimed at the development of potent *N*-methyl-D-aspartic acid antagonists. The reaction of Quinazolinones [63] (**72**) and *N*-bromosuccinimide in acetonitrile at room temperature gave the bromoquinazolinones (**73**) in 73% yield. The reaction of **73** with thiolactic acid **1c** in methanol gave mercaptoquinazolinone derivative **74** in 18% yield (Scheme 9).

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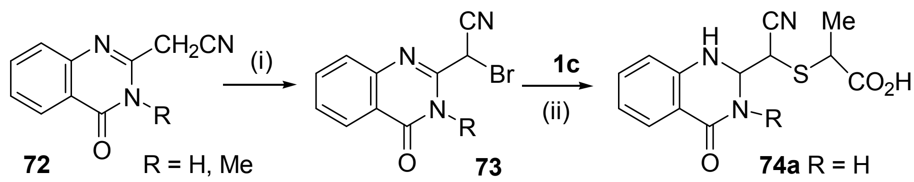


(i) NBS,MeCN;(ii) MeOH

Scheme 9

3.4. 3,4-Dihydro-2H-1,4-benzthiazine / 1,5-benzthiepine derivatives

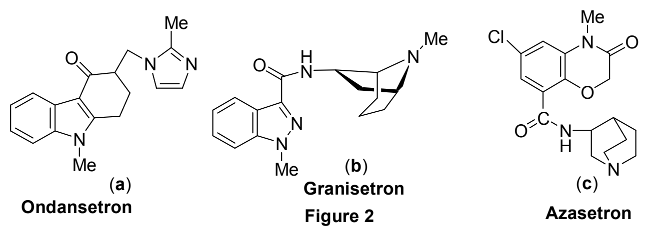
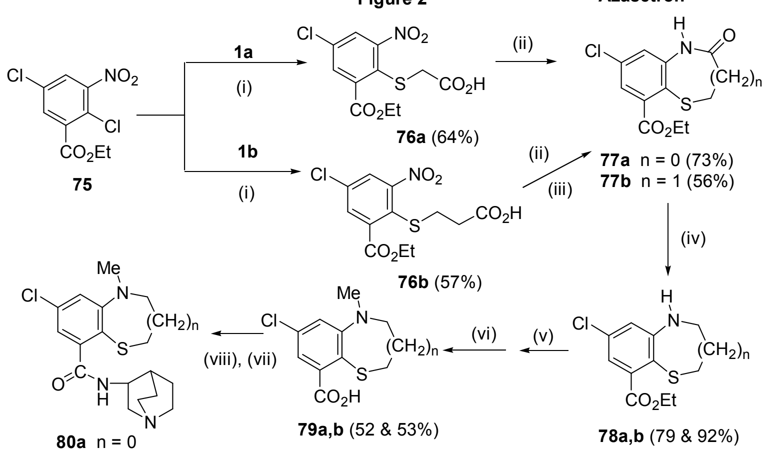


Figure 2



(i) $NaHCO_3$, EtOH; (ii) Fe, NH_4Cl, H_2O/DMF; (iii) H_3PO_4; (iv) $NaBH_4$,THF; $BF_3.Et_2O$; (v) MeI, K_2CO_3, DMF

(vi) NaOH; (vii) pivaloyl Chloride, Et_3N. EtOAc ; (viii) 3-amino-1-azabicyclo [2.2.2] octane

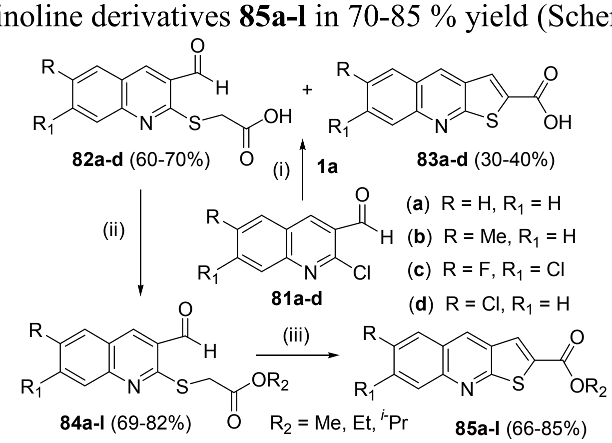
Scheme 10

Selective 5-HT_3 receptor antagonists exihibit potent antagonism of chemotherapy or radiation-induced emesis in humans, [64] ondansetron, [65] granisetron [66] and azasetron [67] (Fig. **2a-c**) have already been marketed for this indication. Kuroita and co-workers [68] reported the synthesis of benzthiazine-8-carboxamide and benzthiepine-9-carboxamide derivatives.

Commercially available 2, 5-dichloro-3-nitrobenzoic acid was converted into ethyl 2,5-dichloro-3-nitrobenzoate (**75**) by reaction with ethanol as per the methodology described by Spryskov's.[69] Thioethers **76a** and **76b** were prepared by coupling of **75** with mercapto acids **1a, b** respectively. The nitro group of **76a** was reduced with iron powder under a neutral condition of aqueous ammonium chloride, followed by spontaneous cyclization to afford **77a** with a desired ring system. Compound **76b** was reduced by the use of iron powder without spontaneous cyclization and cyclization with an acid catalyst provided **77b**. The amides **77a, 77b** were reduced to the amines **78a,b** in presence of sodium borohydride, boron trifluoride etherate and tetrahydrofuran by the Merkel's method [70] of selective reduction of an amide in the presence of an ester moiety. Compounds **78a** and **78b** were methylated at the 5-position with iodomethane in the presence of K_2CO_3, followed by hydrolysis with base to afford carboxylic acids **79a** and **79b** respectively. Compounds **79a** and **79b** were coupled with 3-amino-1-azabicyclo[2.2.2]octane to give **80a** and **80b** respectively (Scheme 10).

3.5. Thienoquinolines

The reaction of 3-formyl-2-chloroquinolines (**81a-d**) with 2-mercaptoacetic acidin the presence of sodium hydroxide in absolute ethanol afforded a mixture of uncyclised [3-formylquinolin-2-yl)thio]acetic acid (**82a-d**) in 60-70% yield and cyclised thieno[2,3-*b*]quinoline-2-carboxylic acids (**83a-d**) in a 30-40% yield respectively.[71] The uncyclised compounds **82a-d** on refluxing with $POCl_3$ in various alcoholic media gave [(3-formylquinolin-2-yl) thio] acetates **84a-l** in 68-82% yield. Cyclisation of quinolinylthioacetates **84a-l** under reflux conditions in DMF gave thieno[2,3-*b*]quinoline derivatives **85a-l** in 70-85 % yield (Scheme 11).



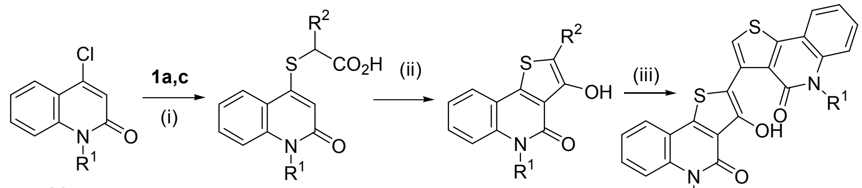
(i) NaOH, KI, EtOH, reflux ; (ii) $POCl_3$, R_2OH ; (iii) DMF, r.t

85	R	R_1	R_2	% Y
a	H	H	Me	85
b	Me	H	Me	76
c	F	Cl	Me	70
d	Cl	H	Me	72
e	H	H	Et	82
f	Me	H	Et	74

85	R	R_1	R_2	% Y
g	F	Cl	Et	69
h	Cl	H	Et	69
i	H	H	^{i}Pr	80
j	Me	H	^{i}Pr	76
k	F	Cl	^{i}Pr	66
l	Cl	H	^{i}Pr	70

Scheme 11

3.6. 3-Thienoquinolinyl-thienoquinolinones



86a-c **87a-f (90-96%)** **88a-f** **89a-c**

(i) MeOH, K_2CO_3, Et_3N, toluene; (ii) PPA,175-180 °C; (iii) Dil.HCl

88 (**a**) R^1 = Me, R^2 = H (70%); (**b**) R^1 = Et, R^2 = H (63%); (**c**) R^1 = Ph, R^2 = H (62%)
(**d**) R^1 = Me, R^2 = Me (70%); (**e**) R^1 = Et, R^2 = Me (64%); (**f**) R^1 = Ph, R^2 = Me (66%)

89 (**a**) R^1 = Me (68%); (**b**) R^1 = Et (67%); (**c**) R^1 = Ph (69%)

Scheme 12

Thienoquinolines are effective antipyretic, analgesic and anti-inflammatory agents [72] and also useful as herbicides and insecticides.[73] Few methods [74,75] are known for the synthesis of angularly fused thienoquinolinones in the literature. Gupta and Darbarwar [76] reported facile synthesis of thienoquinolines. 4-Chloro-1-substitutedquinolin-2(1*H*)-one **86a-c** were reacted with mercaptoacids (**1a, 1c**), in dry methanol in the presence of anhydrous K_2CO_3 and triethylamine under reflux conditions afforded 2-[1,2-dihydro-2-oxo-4-quinolinythio]-acetic/propionic acids **87a-f** in 90-96 % yield. The cyclodehydration of **87a-f** in polyphosphoric acid at 175-180 °C afforded 3-hydroxythieno[3,2-*c*]quinoline-1-substituted-4-(5*H*)-ones **88a-f** in 62-70 % yield. The compounds **88a-c** undergo aldol type condensation in aqueous acid medium resulting in the formation of 3-hydroxy-2-[4,5-dihydro-4-oxo-thieno[3,2,-*c*]quinolin-3-yl]thieno-[3,2-*c*] quinolin-4(5*H*)-ones (**89a-c**) in 67-69 % yield (Scheme 12).

3.7. Thiazino/thiazepinoquinolinecarboxylic acids

Synthetic fluoroquinolones [*e.g.* ciprofloxacin [77] (Fig. **3a**)] represent a successful achievement towards the design and development of potent antiinfective drugs.[78, 79] 1,4-benzothiazines derivatives are reported as excellent inhibitors of Nickel peptide deformylase (Ni-PDF) (Fig. **3b**) and showed improved antibacterial potency.[80, 81] 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one derivatives,[82-84] diltiazem [85] (Fig. **3c**) are of significant interest synthetically and pharmacologically. Huniti *et al.* [86-88] reported the synthesis of hybrid tricyclic system encompassing the structural features of both "fluoroquinoline" (rings A, B) and dihydro-1,4-benzothiazine/thiazepine-4-one (rings B,C). The reaction of 2,4-dichloro-5-fluoro-3-nitro-benzoyl chloride (**90**) with ethyl 3-(*N,N*-dimethylamine)acrylate (**91**) following the reported procedure [89] gave ethyl ester (**92**). The acid-catalysed hydrolysis of (**93**) gave 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxa-1,4-dihydroquinoline-3-carboxylic acid (**94**). The reaction between 7-Chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid [90] (**94**) and α/β-mercapto acids (**1a-d**), in aqueous acetone containing triethylamine afforded the corresponding acyclic precursors **95a-d** in 77-91 % yield (Scheme 13).

This reaction follows a nucleophile aromatic substitution 'S_N-Ar'(addition-elimination) path and is facilitated by the presence of the electron withdrawing C(6)-fluoro-, C(4)-keto and C(8)-nitro groups. Reduction of the 8-nitro compound **95** with sodium dithionite in aqueous potassium carbonate gave the respective 8-amino derivative **96**. The intermediate 8-amino derivatives **96** underwent lactamization upon heating with polyphosphoric acid (PPA) at 140-150 °C afforded the corresponding annulated products (**97**) in 68-75 % yield. The authors [86-88] have reported the synthesis of pyrido[3',2':4,5]thieno[2,3-*b*][1,4] thiazines (**99a-c**) in 74-84 % yield utilizing 2-

chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbo-xylic acid **97** as common synthon [91] by adopting the same methodology as discussed in the above scheme (Scheme 48). The compounds **96a-d** and **99a-c** were tested using 10 uM concentration against the panel of 60 human cancer cell lines used by the National Cancer Institute (NCI, USA). The more affected cell line was IGROVI (from ovarian cancer). The % growth inhibition at 10 uM was 76%, 64%, 65% and 88% for compounds **96a, 96c** and **99a, 99c** respectively.

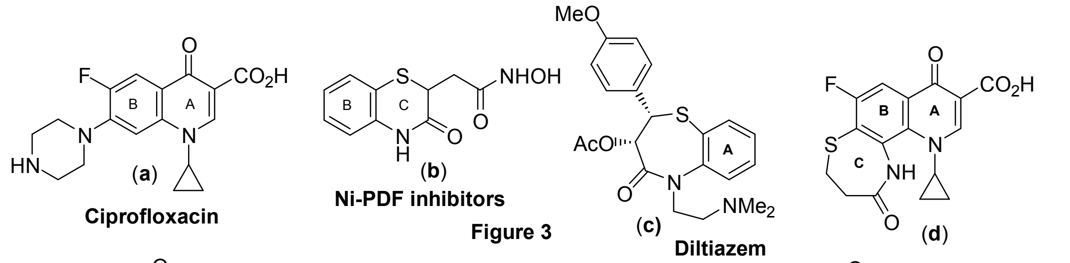
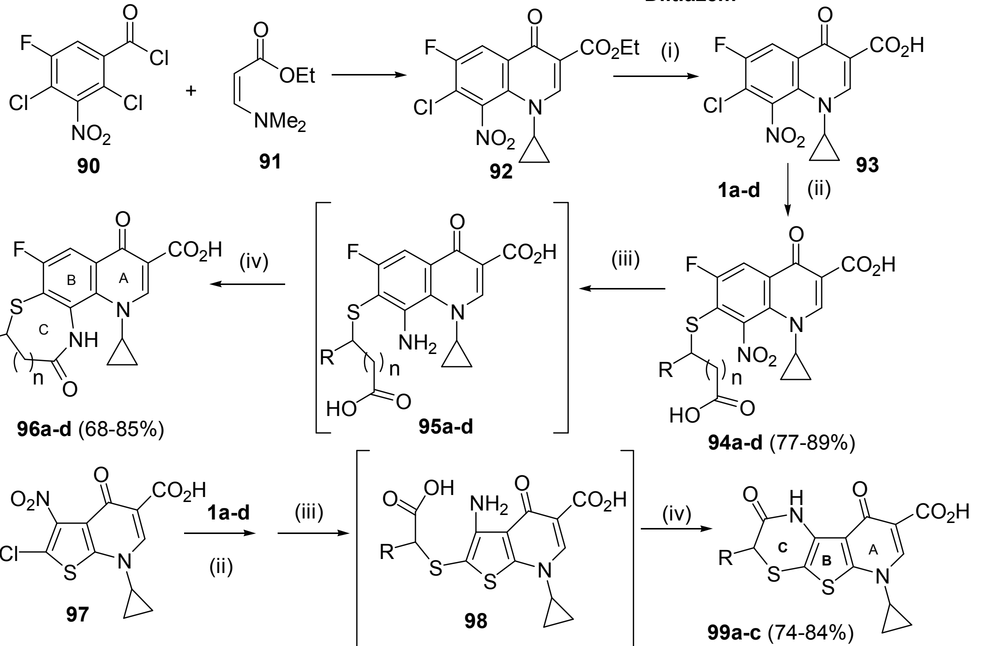


Figure 3



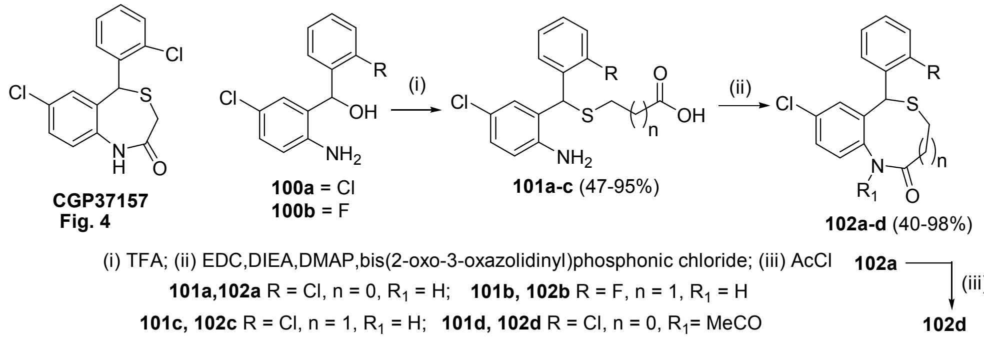
Scheme 13

(i) AcOH + H_2SO_4 ; (ii) aq.acetone, Et_3N ; (iii) $Na_2S_2O_4$,aq.K_2CO_3; (iv) PPA

(**a**) R = H, n= 0; (**b**) R = Me; n = 0; (**c**) R = CH_2CO_2H, n = 0; (**d**) R = H, n = 1

3.8. Benzothiazepines

Existing treatments for type II diabetes include insulin and modified insulins, insulin secretagogues (sulfonylureas and metiglinides), insulin sensitizers (thiazolidinediones and biguanides) and blockers of glucose uptake [92, 93] (acarbose and pramlintide). Compounds from different structural classes, such as CGP37157 [1,4-benzothiazepin-2-one] [Fig. **4**], diltiazem [1,5-benzothiazepin-2-one] and prenylamine and fendiline (both phenylalkylamines), have been reported to inhibit mitochondrial sodium-calcuim exchanger (*m*NCE) activity. The synthesis of benzothiazepinones described by Hirai *et al.* [94] requires 5 steps starting from 2-aminobenzophenones. Pei and co-workers [95] reported the synthesis of benzothiazepinones in two steps by 5-alkylation and cyclization. Benzhydrol **100a** was allowed to react with 3-mercaptopropionic acid in trifluoroacetic acid to give thioacid derivatives **101**. Cyclization of **101** using ethylene dichloride, diethylamine, 4-dimethylaminopyridine and bis(2-oxo-3oxazolidinyl)phosphonic chloride yielded the corresponding lactams **102** in 98% yield. The compounds **102a-d** were evaluated for their ability to inhibit *m*-NCE function, where in the exchanger-mediated Na^{+} / Ca^{2+} translocation in mitochondria in permeabilised cells was monitored by using a Ca^{2+} sensing fluorescence based assay. The 1,4-benzothiazepinone exhibited an IC_{50} of 1.4 μM which was comparable to the reported literature [96] value of 0.4 uM. Substituents on the 5-phenyl ring appeared to be crucial for *m*-NCE activity. The 1,5-benzothiazocinone **101a** exhibited an IC_{50} of 12.6 μM for *m*-NCE which indicates the potential of this lead as a drug candidate (Scheme 14).



(i) TFA; (ii) EDC,DIEA,DMAP,bis(2-oxo-3-oxazolidinyl)phosphonic chloride; (iii) AcCl

101a,102a R = Cl, n = 0, R_1 = H; **101b, 102b** R = F, n = 1, R_1 = H

101c, 102c R = Cl, n = 1, R_1 = H; **101d, 102d** R = Cl, n = 0, R_1= MeCO

Scheme 14

3.9. 2-Arylmethyl isoindol-1-ones

Tetracyclic systems, as in Figure **5** incorporating an isoindole moiety with its nitrogen atom as one of the two junction atoms are widely expanded. The isoindolo [1,2-*b*] [3] benzazepine (n = 2, m = 0, X = CH_2, ring D = benzene; Fig. **5**) belonging to the aporhoeadane alkaloid series is one example.[97] Pigeon and Decroix [98, 99] reported the synthesis of substituted isoindolones **104a-e** could be the precursors for the synthesis of tetracyclic isoindolobenzothiazoline **105** (X = S, n+m = 3). Hydroxylactam [100] **103a-e** [n = 0, 1; Ar = Ph, thien-2 (3)-yl] reacted with 2-mercaptoacetic acid **1a** under the acidic conditions gave the substitution products **104a-e** in 81-94% yield *via* a *N*-acyliminium ion. The acid derivative **104a** was treated with thionly chloride under reflux conditions of DCM for 2 hrs and the resulting acid chloride in presence of aluminium chloride as a catalyst at -5 °C gave the cyclic ketone (**105**) in 62 % yield (Scheme 15).

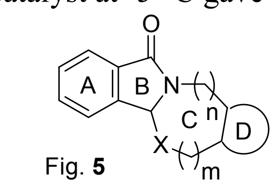
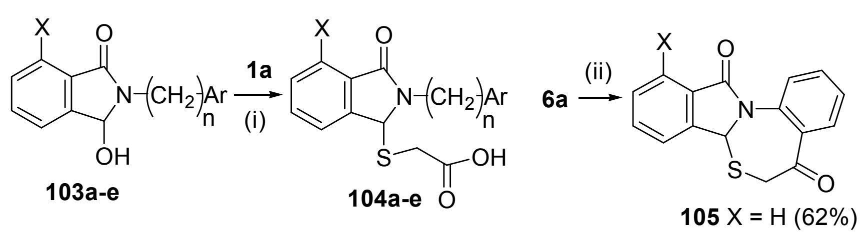


Fig. **5**

n = 0,1,2; m = 0,1,2

X = O,S,NH,CH_2

Ring D = benzene, thiophene



(i) AcOH, reflux; (ii) $SOCl_2$, CH_2Cl_2, $AlCl_3$, reflux

104 (**a**) Ar = Ph, X = H, n = 0 (81%); (**b**) Ar = Thien-2-yl, X = H, n = 1 (88%)

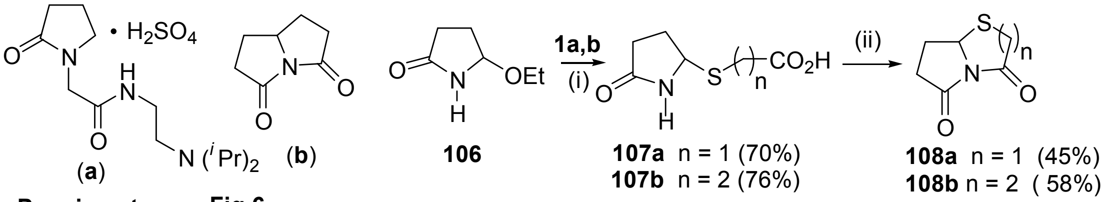
104 (**c**) Ar = Thien-3-yl, X = H, n = 1 (90%);(**d**) Ar = Ph, X = H, n = 1(94%); (**e**) Ar = Ph, X = NO_2, n = 1(56%)

Scheme 15

3.10. Dihydropyrrolo-thiazole-3,5-dione

Pramiracetam (CI-879) compound Fig. **6a,** was discovered to reverse electro-convulsive shock (ECS) induced amnesia in rodents and was found to possess congnition-enhancing activity in other paradigms.[101] The dihydro-1*H*-pyrrolizine-3,5 (2*H*,6*H*)-diones (Figure **6b**) have shown the reversal effects of ECS in mice over an extraordinarily broad dose range.[102] Butler *et al.* [103] reported the synthesis of cyclic imides of pyrrolidone derivatives. 5-Ethoxy-2-pyrrolidinone **106**

[104] on reaction with mercaptoacids **1a,b** at 70 °C for 24 h gave the 2/3-[5-oxo-(2-pyrrolidinyl)thio]acetic/propionic acids (**107a,b**) in 70-76 % yield. The reaction of thio acids (**107a,b**) with Ac_2O in acetic acid medium gave Dihydropyrrolo[2,1-*b*]thiazole-3,5 (2*H*, 6*H*)-dione **108a** and Dihydro-2*H*-pyrrolo[2,1-*b*][1,3]thiazole-4,6(3*H*,7*H*)-dione **108b** in 45-58 % yield (Scheme 16).



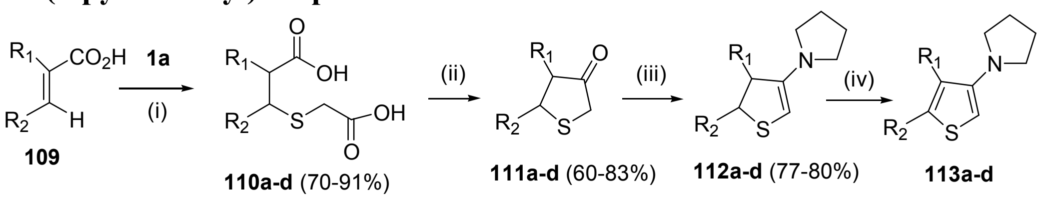
(i) 60-70 °C, 16-24 h; (ii) Ac_2O, AcOH

Scheme 16

4. CONJUGATE ADDITION TO OLEFINIC BOND

Carbon sulfur bond formation by conjugate addition of mercapto acids to α, β-unsaturated carbonyl compounds has versatile applications in chemistry and biology as it plays critical roles (i) in biosynthesis,[105] (ii) protection of the olefinic double bond of conjugated enones,[106] (iii) synthesis of bioactive compounds,[107] (iv) homoenolate anion equivalents [108] and (v) generation of β-acylvinyl cation.[109] The present review aims to highlight the application mercaptoacids in this field.

4.1. 3-(1-pyrrolidinyl)thiophenes



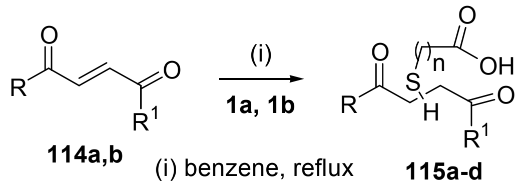
(i) Et_3N, 1,4-dioxane; (ii) Ac_2O, LiOAc ; (iii) pyrrolidine, *p*-TSA, benzene; (iv) diisopentyldisulfide, 200-250 °C

113 (**a**) R_1 = Me, R_2 = H (*14%); (**b**) R_1 = H, R_2 = Me (*15%)
(**c**) R_1 = H, R_2 = Ph (*27%);(**a**) R_1 = Ph, R_2 = Ph (*14%) * Overall yield

Scheme 17

Substituted 3-(1-pyrrolidinyl)-thiophenes undergo [2+2] cycloaddition reactions with dimethylacetylene dicarboxylate in a polar solvent to give thieno [3,2-*b*]pyrrolizines. Reinhoudt *et al.* [110] has reported the synthesis of alkyl- and aryl-substituted 3-(1-pyrrolidinyl)-thiophenes in four steps. The initial step is the addition of mercaptoacetic acid **1a** to α, β-unsaturated acid (**109**) in presence of triethylamine in 1,4-dioxane under reflux conditions and it gave the substituted 3-[(carboxymethyl)-thio]propanoic acids **110a-d** in 70-90% yield. Ring closure of the dicarboxylic acid **110a-d** in presence of acetic anhydride and lithium acetate as a catalyst at 120 °C afforded the substituted 4-oxotetrahydrothiophenes (**111a-d**) in 60-83 % yield. Condensation of the cyclic thioketones (**111a-d**) with pyrrolidine in presence of *p*-toluenesulfonic acid under azeotropic removal of water gave pyrrolidinyl-2,3-dihydrothiophenes (**112a-d**) in 77-80 % yield. The aromatization of the enamine (**112a-d**) in diisopentyldisulfide medium [111] at 200-250 °C following the methodology of Buiter *et al.* [112] gave 3-(1-Pyrrolidinyl)-thiophenes **113a-d** in 14-27 % overall yield (Scheme 17).

4.2. Long chain thioethers



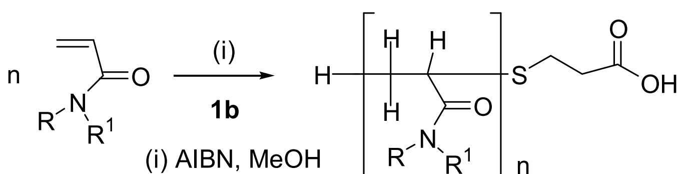
114a,b **115a-d**

114	R	R^1	n	% Y
a	Me-$(CH_2)_{11}$-	MeO-	-	--
b	Me-$(CH_2)_5$-	-$(CH_2)_2$-CO_2H	-	--
115	R	R^1	n	% Y
a	Me-$(CH_2)_{11}$-	MeO-	1	93
b	Me-$(CH_2)_{11}$-	MeO-	2	98
c	Me-$(CH_2)_5$-	-$(CH_2)_2$-CO_2H	1	95
d	Me-$(CH_2)_5$-	-$(CH_2)_2$-CO_2H	2	92

Scheme 18

Thioethers have been described as lubricants, additives, coatings, rubber substituents [113-115] and as intermediates for the preparation of wetting agents and detergents.[116] Thioethers are also capable of increasing thermal stability of polymers and rubbers. [117] Osman *et al.* [118] have reported the synthesis of sulfurated ethers of olefinic fatty acids. Methyl 4-oxo-*trans*-2-hexadecenoate (**114a**) and 9, 12-dioxo-*trans*-10-octadecenoic acid (**114b**) [119,120] were reacted with mercaptoacetic acid (**1a**) and 3-mercaptopropionic acid (**1b**) in benzene medium under reflux conditions to afford branched chain thioethers **115a-d** in 92-98 % yield. The addition products are of isomeric type in both cases (Scheme 18).

4.3. Telomerization Process



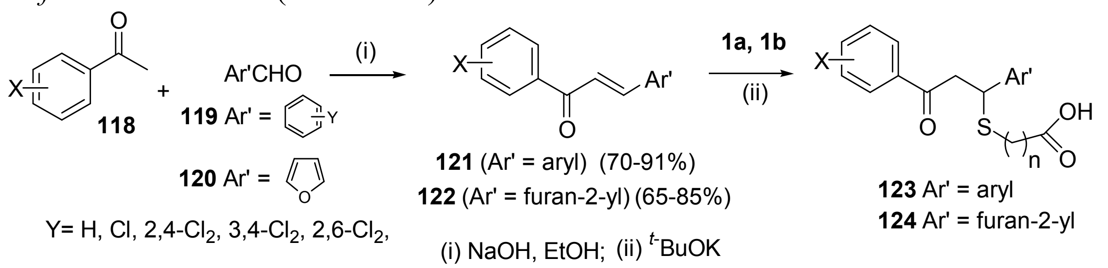
116 **117**

Scheme 19

3-Mercaptopropionic acid (3-MPA) is known as a versatile bifunctional chain transfer reagent in the telemerization of short oligomers for biotechnology application.[121] The dialkyl propenamide (**116**) undergoes telomerization process in presence of 3-mercaptopropionic acid, AIBN in methanol medium. AIBN is used as initiator to transform the thiol into radical and the isolated polymer (**117**) contains a single specific functional end group because of the high transfer activity of the 3-MPA. By the variation of the conc. of 3-MPA, the telomer length (**117**) is easily adjusted to a convenient molecular average weight (2000-2500 g/mol). Structures with a lower critical solution temperature [122] are often used for bioconjugates (Scheme 19).

4.4. Dihydrochalcones

The Claisen-Schmidt [123] condensation of substituted acetophenone (**118**), with substituted benzaldehyde (**119**), or furfural (**120**) in presence of sodium hydroxide and ethanol medium at room temperature gave chalcone derivative (**121, 122**) in 69-97 % yield. Ceylan *et al.* [124] and Albert Levai [125] have reported the reaction of chalcones (**121, 122**) with 2-mercaptoacetic acid**1a** or 3-mercaptopropionic acid **1b** in mild conditions. The Michael reaction of chalocones with mercapto acids occurs in presence of $^{t-}$BuOK (6 mmol) at room temperature without solvent in a short reaction time of 3-hours to give the desired 1,4-addition products (**123a-l; 124 a-j**). All the compounds showed antifungal activity. The dihydrochalcones **123a, e** was an especially active against *Aspergillus niger, Trichophyton mentagrophytes, Micosporum gypseum and Epidermophyton floccosum strains* (Scheme 20).



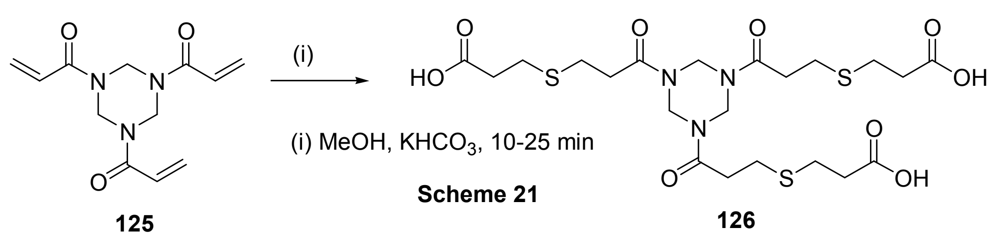
123	X	Ar'	n	% Y
a	H	C_6H_5	1	75
b	H	2-ClC_6H_4	1	74
c	H	4-ClC_6H_4	1	90
d	H	3,4-$Cl_2C_6H_3$	1	76
e	H	2,6-$Cl_2C_6H_3$	1	80
f	4-Cl	C_6H_5	1	68
g	4-Br	C_6H_5	1	79
h	H	C_6H_5	2	77
i	H	2-ClC_6H_4	2	60
j	H	4-ClC_6H_4	2	83
k	H	2,4-$Cl_2C_6H_3$	2	87
l	4-Cl	2,6-$Cl_2C_6H_3$	2	58

124	X	Ar'	n	% Y
a	2-MeO	Furan-2-yl	1	92
b	3-MeO	Furan-2-yl	1	88
c	4-MeO	Furan-2-yl	1	81
d	2-Cl	Furan-2-yl	1	94
e	3-Cl	Furan-2-yl	1	91
f	4-Cl	Furan-2-yl	1	85
g	2-Br	Furan-2-yl	1	77
h	3-Br	Furan-2-yl	1	83
i	4-Br	Furan-2-yl	1	93
j	2-OH	Furan-2-yl	1	86

Scheme 20

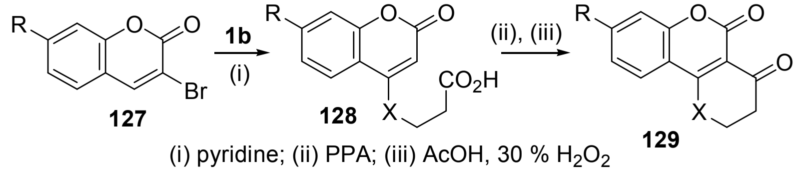
4.5. Tripodal thio ethers

1, 3, 5-triacryloyl hexahydro-1,3,5-triazine (TAT) is an inexpensive stable symmetrical synthon and is used extensively for the synthesis of tripodal thioethers compounds which are of value as chelating ligands,[126-128] and in nano particle assembly.[129-130] Son *et al.* [131] have reported the facile synthesis of functinalised tripodal thioether from ionic thiol-ene reactions of TAT. TAT (**125**) was reacted with 3-mercaptopropionic acid in presence of potassium bicarbonate and methanol to give the thioether **126** in 63 % yield. The triazine ring exists in the chair confirmation with the three 'arms ' pointing out toward the same side of the ring to create a bowl-like cavity, due to combination of intra- and intermolecular hydrogen bonding, the extended structure consists of a linear chain of dimeric capsules in which triazine rings constitute the ends of capsule [132] (Scheme 21).



Scheme 21

4.6. Thiopyrano-benzopyrano-4, 5-diones



(i) pyridine; (ii) PPA; (iii) AcOH, 30 % H_2O_2

129 (**a**) R = H, X = S (50%); (**b**) R = H, X = SO_2 (55%); (**c**) R = MeO, X = S (60%)
(**d**) R = MeO, X = SO_2 (45%); (**e**) R = EtO, X = S (50%); (**f**) R = EtO, X = SO_2 (58%)

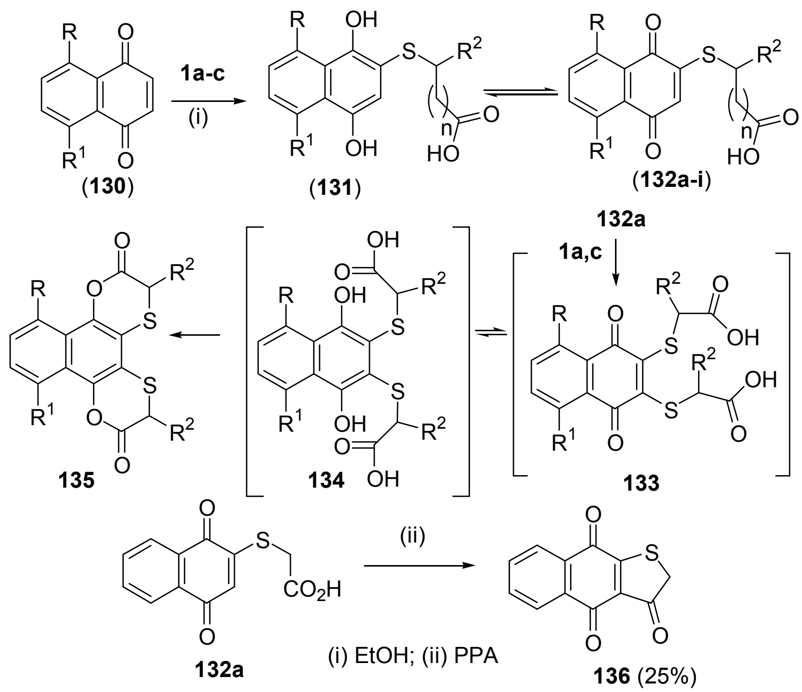
Scheme 22

Merchant *et al.* [133] have reported the reaction of 3-bromocoumarin derivatives **127** with β-mercaptopropionic acid in excess of pyridine under reflux conditions for 4-5-hours to yield the corresponding coumarinomercaptopropionic acids **128** in 50-60 % yield. The reaction has occurred at ‘4’ position instead of the expected ‘3’ position. The coumarinomercapto-propionic acids (**128**) were cyclised to the corresponding 2*H*, 4*H*, 5*H*, 3, 2, (*c*)-1-benzopyrano-4,5-diones in 50-60% yield. The above diones were oxidized with 30 % H_2O_2 in acetic acid at room temperature to yield appropriate sulfones (**129**) in 45-58 % yield (Scheme 22).

4.7. Naphtho-bis-1,4-oxathiin-2,7-diones

A number of benzoquinones, naphthoquinones were reported to exhibit antifungal activity.[134] Tandon *et al.* [135-140] have reported the reaction of 1,4-naphthoquinones (**130**) [141,142] with mercapto acids (**1a-c**) in ethanol at room temperature gave the S-(1,4-naphthoquinon-2-yl)mercapto acids (**131a-i**) in 40-80 % yield. The reaction of 1,4-naphtha-quinones **130** with two equivalents of 2-mercaptoacetic acid**1a,** thiolactic acid **1c**, however gave the tetracyclic oxathiin-diones (**135a,b**) in about 30-65 % yield. The mechanism of formation of (**135a,b**) from (**130**) and mercaptoalkanoic acids (**1a, 1c**) is shown in (Scheme 23).

The first step involves the addition of the anion of (**1a, 1c**) to form **131**, which disproportionate to the corresponding *S*-(1,4-naphthoquin-2-yl) mercaptoalkanoic acid (**132**). Compound **132a, b,** undergo further reaction with another molecule of (**1a, 1c**) to give **133a, 133b**. The latter aromatises to the dihydro form (**134a, b**) leading to facile dehydration resulting in the formation of **135a, b**. The preferential formation of **133b** to give **134b** may be due to the higher nucleophilicity of the sulfide anion of the thiolactic acid (**1c**) than 2-mercaptoacetic acid (**1a**). Moreover, the side chain in **133b** and **134b** may exist only in folded or cisoid confirmation to facilitate the formation of **135b**. The steric control observed [143] during the formation of **135b** in preference to **135a** facilitated intramolecular cyclodehydaration of **134b**. The uncyclised acid (**132a)** S-(1,4-naphthoquinon-2-yl)mercapto acetic acid on cyclisation with PPA at 100 °C afforded 2,3,4,9-tetrahydronaphtho[2,3,-*b*]thiophene-3,4,9-trione **136** in 25 % yield (Scheme 23). The evaluation of antifungal properties of compounds **259a-i** was conducted against various strains of pathogenic fungi, for example *C. albicans, C. neoformans, S. Schenckii, T. mentagraphytes, M. cannis* and *A. tumifaciens* according to the method of Dhar *et al.*,[144] The promising inhibitory effect of 1,4-naphthoquinones containing a sulfur atom attached to carboxylic group **132h** was pronounced against a number of fungi. MIC value of this compound was 3.12 ug/mL against *C. albicans*, *T. mentagraphytes* and *M.cannis*, where as it holds 1.56 ug/mL MIC value against *C. neoformans* and 25.0 ug/mL aginst *A. tumifaciens*. The activity of this compound against all the fungi is more when compared with amphotericin B and miconazole



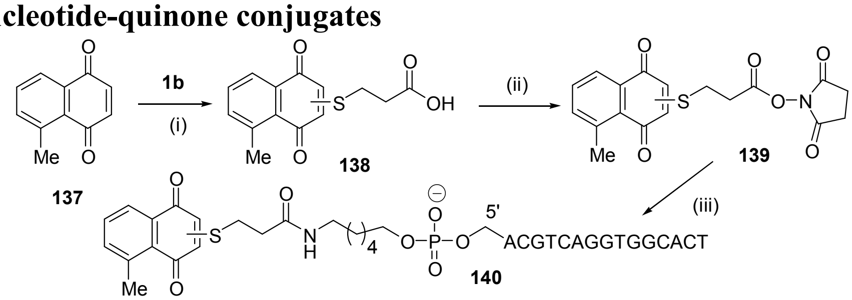
130 (**a**) R = R^1 = H; (**b**) R = R^1 = OH; (**c**) R = OH, R^1 = Cl

135a R = R^1= R^2 = H (30%); **135b** R = R^1 = H ; R^2 = Me (65%)

132	R	R^1	R^2	n	% Y
a	H	H	H	0	40
b	H	H	Me	0	60
c	OH	OH	H	0	60
d	OH	OH	Me	0	80
e	OH	Cl	H	0	45
f	OH	Cl	Me	0	50
g	H	H	H	1	43
h	OH	OH	H	1	61
i	OH	Cl	H	1	35

Scheme 23

4.8. Oligonucleotide-quinone conjugates



(i) 70 % EtOH, 4 ^oC; (ii) *N*-hydroxysuccinamide, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide, DMF
(iii) oligo-$(CH_2)_6NH_2$, 3-(*N*-morpholino)propanesulfonic acid, pH 7.5, 50% DMF, 4 ^oC

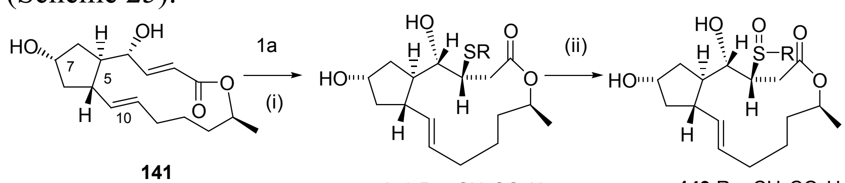
Scheme 24

Naphthaquinone based oligonucleotides are known to sensitize the selective oxidation of thymine and serve as the basis for *in-vivo* application of specific modification of DNA. [145-147] Rokita & Chatterjee [148] reported the condensation reaction of 3-mercaptopropionic acid **1b** with 5-methyl-1,4-naphthoquinone (**137**) in 70 % ethanol at 4 °C to provide a convenient method for attaching a sequence-directing oligonucleotide. The products of this reaction, two inseperable regioisomers [149] (**138**) were carried together throughout the sequence. Treatment of this acid

(**138**) with *N*-hydroxysuccinimide in presence of 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide yielded the activated succinimidyl ester **139**. This was subsequently used to acylate a hexamethyleneamino linking arm that was coupled to the 5'-terminus of an olignucleotide 15 bases in length. The oligonucleotide with linker (**140**) preparation is based on standard procedure of solid-phase phosphoramidite chemistry (Scheme 24).

4.9. Brefeldin A sulfide Derivative

Brefeldin A is a macrolide antibiotic first isolated from the fungus *Penicillium decumbens*.[150] Brafeldin A possesses a number of interesting biological properties of potential therapeutic interest, including antitumor and antiviral effects.[151] However, the potential clinical use of Brefeldin A is severly limited by its undesirable pharmacokinetic properties including negligible bioavailability after oral administration and rapid clearence from blood plasma after intravenous administration.[152] To make Brefeldin A prodrug water soluble compounds Argade *et al.* [153] reported the synthesis of sulfide derivatives of Brefeldin A by Michael addition of thiols to the α, β-unsaturated lactone system present in **141**. Brefeldin A was reacted with mercaptoacetic acid in aqueous methanol in the presence of Proton Sponge [1,8-(bisdimethylamino)naphthalene] to give thiol addition product **142**. The reaction occurred readily and was found to be highly diasteroselective. The R configuration at C-3 in these products was assigned on the basis of the X-ray.[154] The sulfide **142** was oxidized to sulfoxide **143** by oxidation with *m*-chloroperbenzoic acid in chloroform in 68% yield. The greater solubility of Brefeldin A (thioether) **143** (40 mg/mL) when compared to Brefeldin A (**141**) (2.8 mg /mL) indicates its potential for better formulation (Scheme 25).



141 **142** R = CH_2CO_2H **143** R = CH_2CO_2H

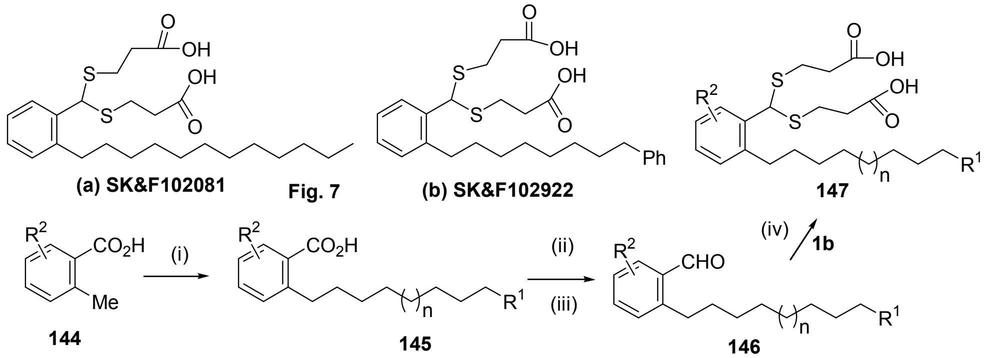
(i) aq. MeOH, 1,8-(bisdimethylamino)naphthalene; (ii) *m*-CPBA, $CHCl_3$

Scheme 25

5. MISCELLANEOUS HETEROCYCLES

5.1. Dithianonanedioic acids

5-(2-dodecylphenyl)-4,6-dithianonedioc acid (Fig. **7a**, SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithiaanonedioic acid (Fig. **7b**, SK&F 102922) [155] prototypes of a class of selective leukotriene antagonists having improved potency and an increased duration of action. Perchonock *et al.* [156] have reported the synthesis of alkynyl- and aryldithiaalkanedioic acids ("dithioacetals") for evaluation of leukotriene antagonist activity. The disubstituted aryls (**144**) were alkylated with appropriate alkyl halides in presence of *n*-butyl lithium, tetrahedron, di-isopropylamine to give corresponding 2-dodecyl/octyl, 5 or 6-substituted acids (**145**). The acids on reduction with borane followed by subsequent oxidation with pyridinium chlorochromate in DCM gave the alkoxy substituted benzaldehydes (**146**). Reaction of (**146**) with 3-mercaptopropionic acids using boron trifluoride etherate as catalyst afforded aryldithiaalkanodioic acids (**147**) (Scheme 26).



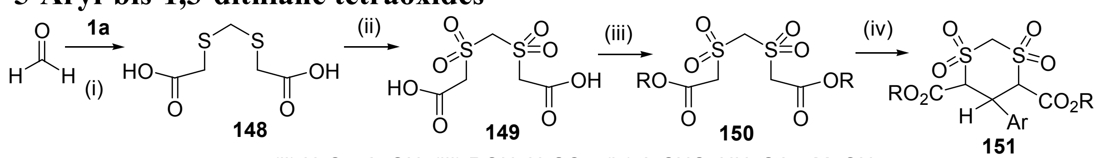
(i) Me $(CH_2)_{10}$-Br / Ph-$(CH_2)_7$-Br; BuLi, THF, DIPA; (ii) BH_3, THF; (iii) PCC, MDC; (iv) $BF_3.Et_2O$

147	R^1	R^2	n
a	Me	H	4
b	Me	6-Me	4
c	Me	5-OH	3
d	Me	5-MeO	3
e	Me	5-Br	3

147	R^1	R^2	n
f	Me	5-NO_2	3
g	Me	H	3
h	Ph	H	0
i	Ph	5-CF_3	0

Scheme 26

5.2. 5-Aryl-bis-1,3-dithiane tetraoxides



(i) HCl, H_2O ; (ii) H_2O_2, AcOH; (iii) ROH, H_2SO_4; (iv) ArCHO, NH_4OAc, MeOH

150a R =Me (90%); **150b** R = Et (85%)

151 (**a**) R = Me, Ar = C_6H_5 (35%); (**b**) R = Me, Ar = 2-ClC_6H_4 (45%); (**c**) R = Me, Ar = 4-MeC_6H_4 (30%)

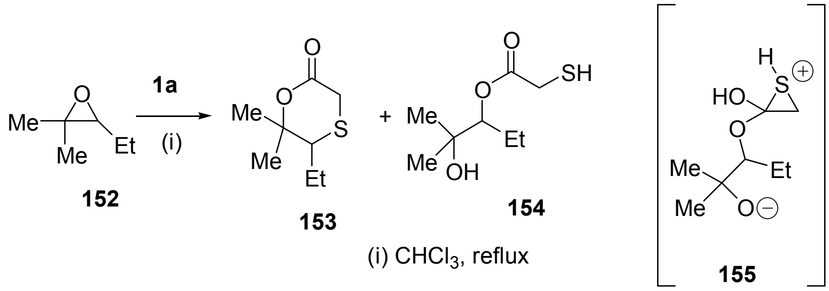
(**d**) R = Me, Ar = 4-MeOC_6H_4 (35%); (**e**) R = Et, Ar = C_6H_5 (40%); (**f**) R = Et, Ar = 2-ClC_6H_4 (35%)

Scheme 27

1,3-dithianes are well known reagents in organic synthesis.[157, 158] Most of the dithianes are prepared from propane-1,3-dithiol [159] and aldehydes or ketones and therefore possess substituents at the 2-position only. Balaiah and Prema [160] reported the synthesis of 1,3-dithianes which have substituents at other positions *via* condensation process. The reaction of paraformaldehyde and mercaptoacetic acid **1a** in presence of conc. HCl at 100 ºC gave methylene dithio-diacetic acid (**148**), in 75-80 % yield. The oxidation of (**148**) with hydrogen peroxide in acetic acid at 25-30 ºC gave the *bis*-sulfone (**149**) in 85 % yield. The esterification of acid **149** with alcohol gave the disulfone diester (**150**) in 85-90 % yield. The dimethyl or diethylmethylene-*bis*-sulfonyl acetate **150** was condensed with aromatic aldehydes in presence of ammonium acetate in ethanol gave the 1,3-dithiane tetraoxide (**151**). The six membered ring compounds were formed instead of eight membered rings because of their greater stability and ease of formation (Scheme 27).

5.3 Thiolactone

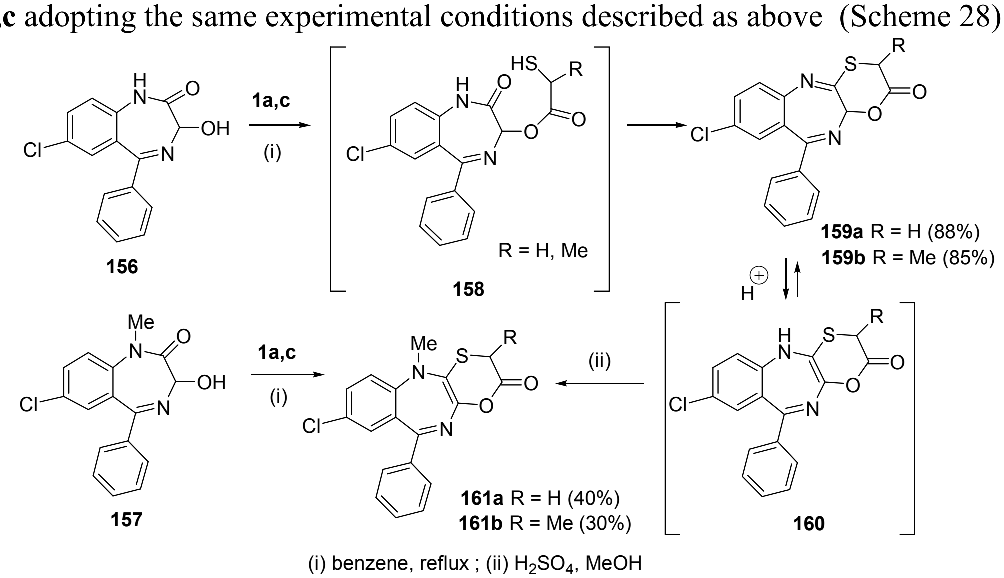
Nucleophilic addition of mercaptoacetic acid **1a** with 2,3-epoxy-2-methylpentane (**152**) in chloroform under reflux conditions was reported [161]to give a 3:4 mixture of thiolactone (**153**) and the hydroxy acetate (**154**). The formation of hydroxy acetate was explained through (the anchimeric assisted formation of) cyclic sulfonium ion intermediate [162] (**155**) (Eq. **3**).



Eq. **3**

5.4. 1, 4-oxathianobenzodiazepine-2-ones

The reaction of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**156**) (oxazepam) with mercaptocarboxylic acids **1a,c** in anhydrous benzene under reflux conditions undergoes different cyclofunctionalisation route [163, 164] to give [1,4]-oxathiano [5,6-*b*][1,4]-benzodiazepine-2-ones (**159**) in 85-88% yield.[165] The reaction of tricyclic oxathia-2-ones **159** with methanol and sulfuric acid gave the *N*-methyl derivative (**336**) in 30-40 % yield. The formation of compounds (**159**) and (**161**) was shown in Scheme 28. This involves an initial esterification of 3-OH to give the unstable thioester intermediate (**158**) which through acid promoted cyclization and subsequent elimination of water leads to to the formation of (**159**). The reaction with H_2SO_4 / MeOH allows the shift of the tautomeric imine-enamine equilibrium towards the enamine form (**160**) allowing the *N*-methylation to give derivatives (**161**), which could also be obtained by directly reacting *N*-methyloxazepam **157** with mercaptocarboxylic acids **1a,c** adopting the same experimental conditions described as above (Scheme 28).[163-165]



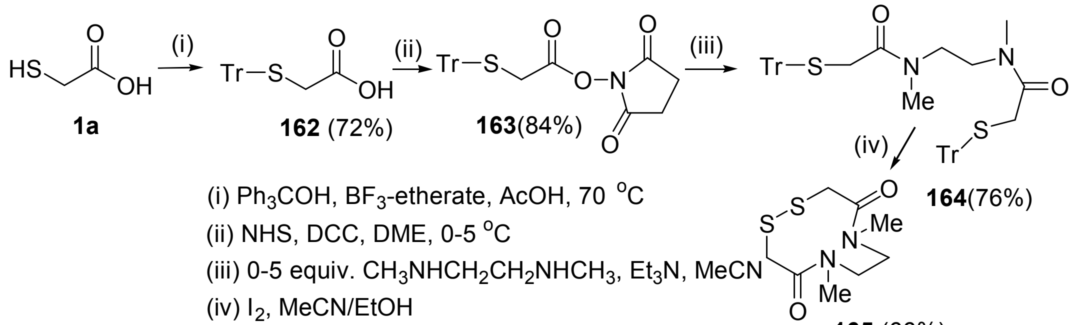
(i) benzene, reflux ; (ii) H_2SO_4, MeOH

Scheme 28

5.5. 10-Membered diamide disulfide ring

Structures similar to *N,N'*-ethylene *bis*-(2-thioacetamide) are frequent precursors to complexing reagents for technetium and have been used extensively in Tc-based radioimaging work both at research and clinical levels.[166,167] Maharaj *et al.* [168] reported the synthesis of cyclic diamide disulfides which can be used as lipophilic, bifunctional DADS chelators for Tc radio imaging.

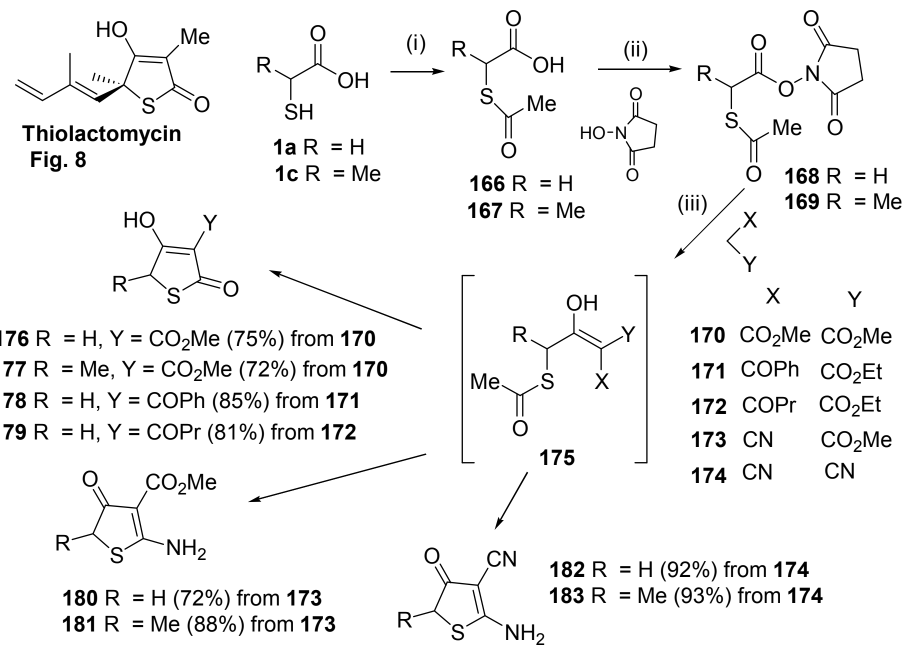
The 10 membered heterocycle **165** was synthesized from 2-mercaptoacetic acid and *N,N'*-dimethylethylenediamine in four steps in 30% overall yield (Scheme 29).
Tritylation of 2-mercaptoacetic acid under Lewis acid catalysis readily afforded the 2-(Triphenymethy)thioacetic acid **162**, which was subsequently reacted with 1,3-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) to give the activated succinimidoyl ester **163**. Treatment of two equivalents of **163** with *N,N'*-dimethyl-ethylenediamine in 1,2-dimethoxyethane, allowed for the acylation of both nitrogens and the formation of *N*,*N'*-{Dimethyl-*bis*[2-(triphenylmethyl)thioacetyl]}-ethylenediamine **164** in 76% yield. Deprotection of diamide **164** was effected with 1.1 equivalents of iodine in ethanol-acetonitrile and by maintaining high dilution conditions to preclude intermolecular disulfide formation, *in situ* intramolecular oxidative cyclization readily generated the monomeric 10 membered diamide disulfide **165** in 68% yield. The choice of the *S*-protecting group for thioacetic acid and the method for its cleavage were crucial for the efficiency of the synthesis. The *S*-protection by other means as arylthioethers, hemithioacetals or thioesters requires very harsh conditions that can lead to decomposition. This cyclic diamide disulfide exists in solution as a mixture of two *Z, Z* and one *Z, E* disulfide and amide ring conformers and has been characterized by nuclear Overhauser effect (*NOE*), ^{1}H-^{1}H, ^{1}H-^{13}C shift correlated 2D-NMR and molecular modeling studies (Scheme 29).



Scheme 29

5.6. Thiolactomycin analogues

Thiolactomycin (TLM, Fig. **8**), an antibiotic isolated from *Nocardia sp*., is a unique thiolactone containing molecule that exhibits potent *in vitro* activity against many pathogenic bacteria and *M.tuberculosis*.[169] Furthermore TLM and its analogues are attractive leads for new drugs against malaria.[170] Markopovlou *et al.* [171] have reported a one pot synthesis of thiotetronic ring system based on *C*-acylation/cyclization reaction between the activated esters and active methylene compounds. The synthesis involves first the reaction of mercapto acids **1a, c** with acetyl chloride in presence of 1,4-dioxane and triethyl amine at 0 °C to give *S*-acetylthioglycolic acids **166**,**167** in 90-95 % yield. The *N*-hydroxy succinimide esters of *S*-acetylthioglycolic acids **168**,**169** were prepared in 89-90 % yield by reaction of *S*-acetylthioglycolic acids with *N*-hydroxysuccinimide in presence of DCC and dichloromethane. The reaction of succinimidoyl esters of *S*-acetylthioglycolic acids **168**,**169** and active methylene esters **170-173** and malononitrile (**174**) in presence of NaH, THF at 0 °C afforded either the 3-substituted thiotetronic acids **176, 177, 178, 179** or 2-aminothiophenes **180, 181, 182, 183** *via* an intramolecular condensation mechanism. The reaction involves the non-isolable *C*-acylation intermediate **175** which undergoes an *in situ* cyclisation reaction resulting in the formation of highly functionalized thiophene derivatives (**176-183**) (Scheme 30).

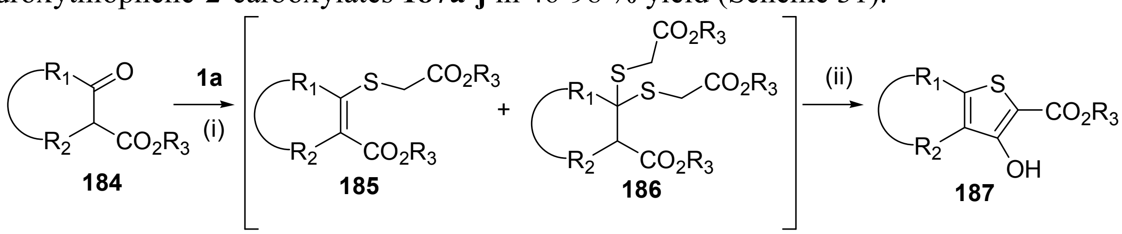


(i) AcCl, 1,4-dioxane, Et_3N, 0 °C ; (ii) DCC, CH_2Cl_2 ; (iii) 60 % NaH, THF, 0 °C

Scheme 30

5.7. 3-Hydroxythiophene-2-carboxylates

3-Thienyloxypropanolamines are known as β-adrenergic blocking agents.[172] Lissavetzky *et al.*[173] have reported the synthesis of bicyclic alkyl 3-hydroxythiophene-2-carboxylates as intermediates for the synthesis of 3-thienyloxypropanolamines by the modification of Fiesselmann procedure. The condensation reaction of linear or cyclic β-ketoesters **184** and two equivalents of 2-mercaptoacetic acidunder catalysis condition of dry HCl gas bubbling in alcoholic medium at -10 °C gave a mixture of diester **185** and triester **186.** The isolated crude product mixture of **185, 186** was subjected to cyclisation by treatment with the corresponding sodium alkoxide in alcoholic solution maintained under nitrogen atmosphere to give alkyl 3-hydroxythiophene-2-carboxylates **187a-j** in 46-98 % yield (Scheme 31).



(i) R_3OH, HCl, -10 °C, 1 h ; (ii) $NaOR_3$/ R_3OH. r.t. 24 h

187	R_1 R_2	R_3	% Y	187	R_1 R_2	R_3	% Y
a	$-(CH_2)_5-$	Et	86	f	$-(CH_2)_2-S-CH_2-$	Me	46
b	$-(CH_2)_5-$	Et	75	g	$-(CH_2)_3-S-$	Et	54
c	$-CH(Me)-(CH_2)_2-$	Me	91	h	$-CH_2-S-CH_2-S-$	Et	62
d	$-CH(Me)-(CH_2)_3-$	Me	87	i	$-CH_2-S-CH_2-$	Me	98
e	$-(CH_2)_2-CH(Me)-CH_2-$	Me	81	j	$-(CH_2)_2-S-$	Me	85

Scheme 31

6.CONCLUSIONS

The data presented in this review clearly demonstrate the high synthetic potential of α/β-Mercaptoalkanoic acids. Many biologically active heterocycles have been obtained based on reactions of these reagents and carbonyl compounds.

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