INTRODUCTION

During the past few decades, enormous amount of research was devoted to study the biological activity of thioureas and its cyclic analogues[1,2] and it was found that the thiourea moiety, either in open form or incorporated in heterocyclic rings, was found in many therapeutic agents that exhibited unprecedented biological activities such as anticancer,[3] antiviral,[4] antimicrobial,[5] antioxidant,[6] antimalarial,[7] anti-inflammatory[8] and antithyroid activities.[9]

Some heterocyclic thiourea analogues have been reported as a new class of potent non-nucleoside inhibitors of human viruses Reverese Transcriptase ($NNRTI_S$).[10]

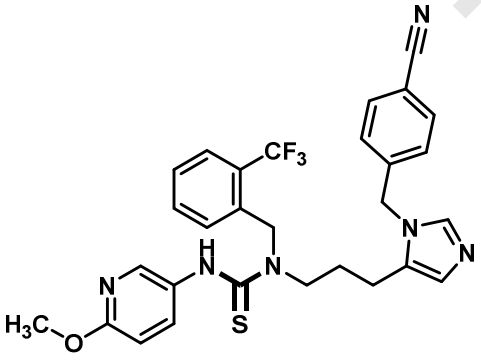
Moreover, thiourea derivatives are used as herbicides,[11] insecticides[12] and have many industrial applications such as corrosion inhibitors,[13] catalysts for organic synthesis[14] and as chelating agents for transition metals.[15]

1.1. Biological and medicinal significance of thiourea derivatives

1.1.1. Anticancer thiourea derivatives

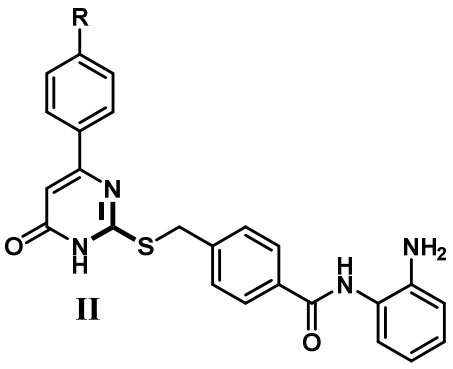
Globally, cancer has been a major health problem since the beginning of the 21st century. It is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.[16] Although an upsurge in the search for new antitumor chemotherapeutic agents has recently been observed, the survival rate of patients still remains low. Based on the GLOBOCAN 2012 estimates,[17] about 14.1 million new cancer cases worldwide and 8.2 million cancer deaths are estimated to have occurred in 2012. Therefore, the need for identification of novel chemical entities which may serve as leads for designing new antitumor agents with better potency, selectivity and safety profile remains critically important.

The thiourea derivative YH3945 (**I**), a selective and potent inhibitor of farnesyl-protein transferase, is being developed for the treatment of cancer.[18]

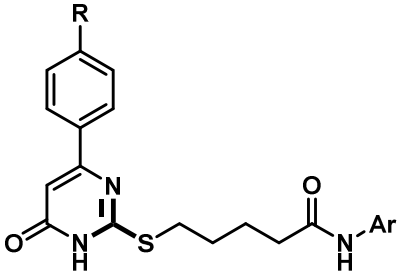


I

Two series of pyrimidine derivatives incorporating thiourea moiety in their skeleton **II**, **III** were synthesized as potential anticancer agents. The majority of these derivatives displayed good growth inhibitory activity against human leukemia cell line (U937) through inhibition of histone deacetylase (HDAC).[19]



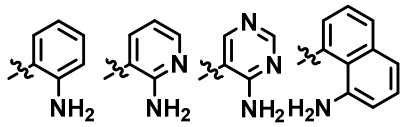
II



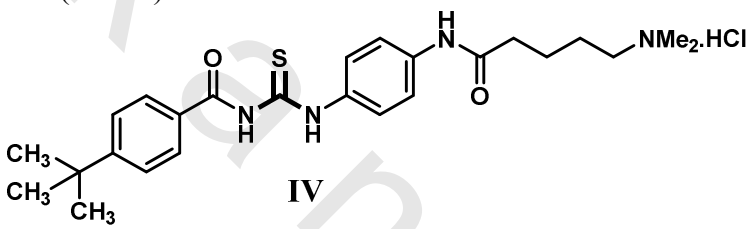
III

R = H, C_6H_5

Ar =

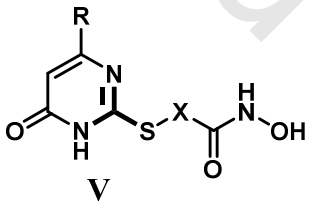


Tenovin-6 (**IV**), a sirtuin inhibitor, has been evaluated for antitumor activity against seven gastric cancer cell lines and was found to induce cell apoptosis in all cell lines by activation of death receptor 5 (DR5). It also exerted a slight to moderate synergistic cytotoxicity against gastric cell lines when used in combination with docetaxel or 7-ethyl-10-hydroxycamptothecin (SN-38).[20]



IV

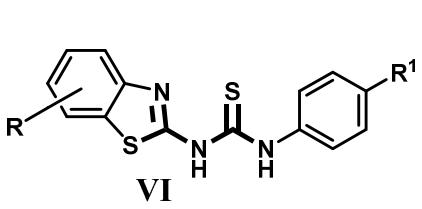
The pyrimidine hydroxyamides **V** were reported to exhibit potent HDAC inhibitory effect at nanomolar concentrations with antiproliferative activity against human leukemic myeloblast cell line (HL-60).[21]



V

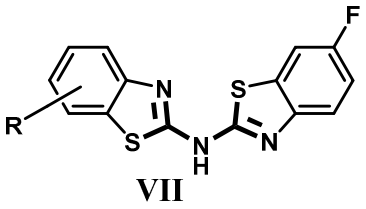
R = H, CH_3, C_3H_7(*n*), C_6H_5, $C_6H_5CH_2CH_2$
X = CH_2CH_2, CH=CH

It has been reported that both thiourea derivatives and benzothiazoles have DNA topoisomerase inhibitory effect.[22,23] Based on this fact, benzothiazolyl thioureas **VI** and *N*-bis-benzothiazoles **VII** were synthesized and evaluated for their anticancer activity. Both exhibited significant antiproliferative activity against human leukemic monoblast cell line (U937) and mouse melanoma cell line (B16-F10), Nevertheless, these compounds showed comparatively less cytotoxicity towards human acute monocytic leukemia cell line (THP-1).[24]



VI

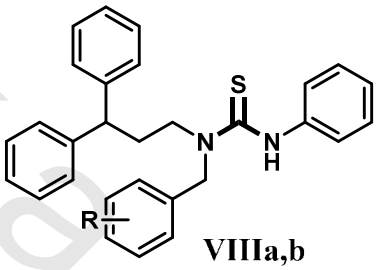
R= H, 6-F, 6-OEt
R^1= H, Cl, F



VII

R= 6-F, 6-OEt

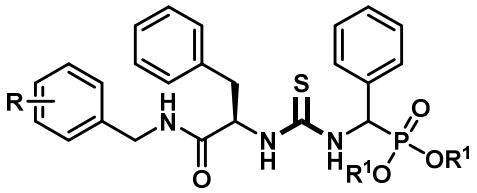
A series of *N*-3,3-diphenylpropyl-*N*-(4-substituted benzyl)-*N′*-phenylthioureas was synthesized and evaluated as potential DNA topoisomerases I and II-α inhibitors. Among them, compounds **VIIIa,b** showed both high topoisomerase inhibition and high anti-proliferative effect against human acute myelocytic leukemia cell line (K562) with IC_{50} values 14 (±1) and 16 (±1) μM, respectively.[22]



VIIIa,b

VIIIa: R= 4-$N(CH_3)_2$
VIIIb: R= 3,4-OCH_2O

A series of pseudo-peptide thioureas containing α-aminophosphonate moiety has been synthesized and evaluated for their anticancer activities against prostate (PC3), breast (Bcap37) and gastric (BGC823) human cancer cell lines. Among them, compounds **IXa-c** were identified as potent growth inhibitors.[25]

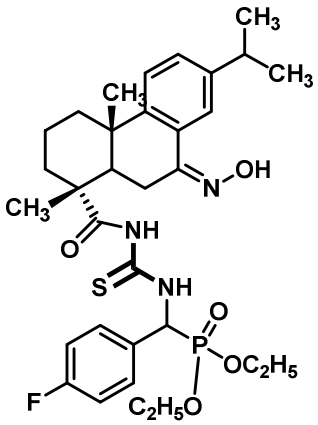


IXa-c

IXa: R= 4-F, R^1= *iso*-C_3H_7
IXb: R= H, R^1= C_2H_5
IXc: R= 2-F, R^1= C_2H_5

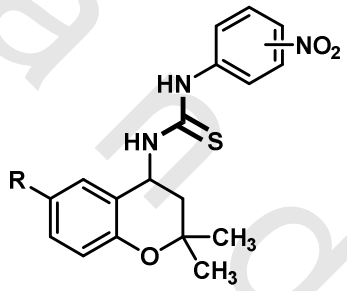
In addition, a series of thiourea α-aminophosphonate derivatives containing dehydroabietic acid structure was designed and synthesized as antitumor agents. Their growth inhibitory activities against lung (NCI-H460 and A549), liver (HepG2) and ovarian (SKOV3) human cancer cell lines were estimated using *in vitro* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The screening results revealed that many compounds exhibited moderate to high levels of antitumor activities against the tested cancer

cell lines. The mechanism of compound **X**, which exhibited good growth inhibition against all the four cell lines, was preliminarily investigated and revealed that it can induce cell apoptosis in A549 cell line.[26]



X

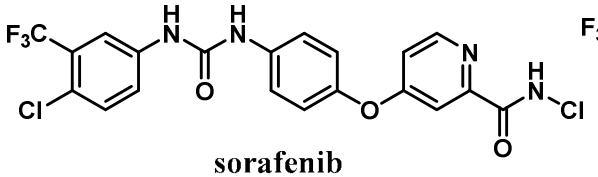
N-Aryl-*N'*-(chroman-4-yl)thioureas were synthesized and examined for their *in vitro* effects on the growth of three human high-grade glioma cell lines: U373, T98G, and Hs683. Significant *in vitro* growth inhibitory activity was observed with 2,2-dimethyl-chroman-type nitro-substituted phenylthioureas, compounds **XI**.[27]



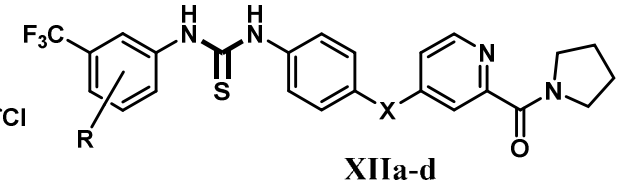
XI

R= Cl, Br

Two series of diarylthiourea derivatives were designed and synthesized as sorafenib analogues, an oral multi-kinase inhibitor. They were evaluated for their antiproliferative activities against prostate (PC3), colon (HCT116) and breast (MDA-MB-231) human cancer cell lines. Compounds **XIIa-d** demonstrated inhibitory activities against all three cell lines. Series B was more potent than series A, which suggests that the thioether moiety is optimal for the antiproliferative activity. The effect of the terminal substituents on the tail phenyl ring was also investigated and was found that presence of electron-donating group may decrease the inhibitory activity of the compounds.[28]



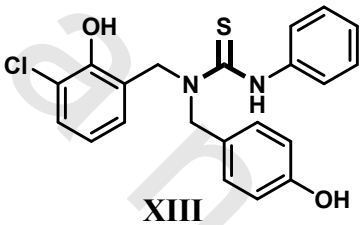
sorafenib



XIIa-d

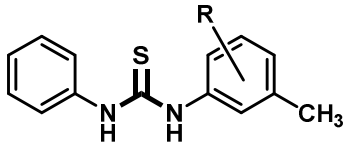
ID	Series	X	R
XIIa	A	O	5-CF_3
XIIb	A	O	4-Cl
XIIc	B	S	5-CF_3
XIId	B	S	4-Cl

A series of *N*-(4-substituted benzyl)-*N*-(3-substituted-2-hydroxybenzyl)-*N′*-phenyl-thioureas were synthesized and evaluated as potential epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) kinase inhibitors. These compounds displayed good EGFR and HER-2 inhibitory activity especially compound **XIII** which demonstrated significant EGFR and HER-2 inhibitory activity with IC_{50} values 0.08 and 0.35 μM for EGFR and HER-2, respectively.[29]



XIII

Diphenylthiourea derivatives **XIVa,b** have been synthesized and evaluated for antitumor activities against human breast adenocarcinoma cell line (MCF-7) using *in vitro* MTT assay. Compound **XIVa** exhibited better inhibitory activities (IC_{50}: 2.56 μg/ml) than **XIVb** (IC_{50}: 9.11 μg/ml). The telomerase inhibitory potency of both compounds was examined and the results revealed that both of them displayed potent telomerase inhibitory effect with IC_{50} values 1.8 and 15.6 μg/ml, respectively. This suggests that their antiproliferative effect was related to their telomerase inhibitory activities.[30]



XIVa,b

XIVa: R=2-CH_3, XIVb: R=3-CH_3

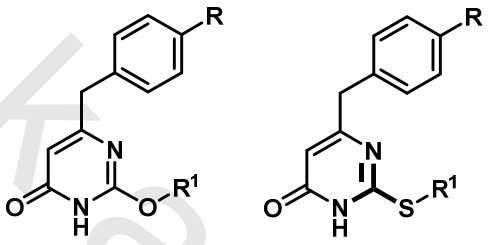
1.1.2. Antiviral thiourea derivatives

Viruses are recurrent socio-economical and health problems each year worldwide. Viral infections may be life threatening or debilitating such as those caused by Human Immunodeficiency Virus (HIV), hepatitis B (HBV), hepatitis C (HCV) and herpes viruses. Although many antiviral drugs with therapeutic values in treating some viral diseases have been successfully developed, it is difficult to find medicines that are selective only for viruses

without affecting the host cells. Thus, there remains a clear medical need to develop novel effective antiviral drugs that are selective enough to prevent viral replication without injury of the hosts.

Dihydroalkyloxybenzyloxopyrimidines (DABOs) **XV** and their sulfanyl analogues (S-DABOs) **XVI** were discovered as a potent and selective NNRTIs. The structure-activity studies led to the synthesis of several more potent derivatives and revealed that the presence of bulky substituents, such as sec-butyl, cyclopentyl, and cyclohexyl, at position-2 is essential for activity.[31]

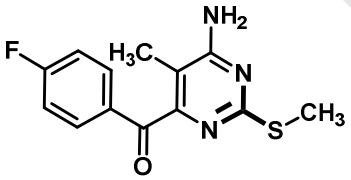
The S-DABOs analogues **XVI** were found to be more potent and selective against HIV than their DABO derivatives **XV**.[31] Alkylation at N-3 or replacing C=O with C=S at the position-4 led to inactive compounds.[32]



XV **XVI**

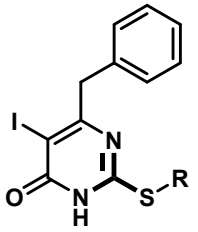
R= H, CH_3
R^1= alkyl or cycloalkyl

The 6-arylcarbonyl S-DABO analogue **XVII** was evaluated for cytotoxicity and anti-HIV-1 activity and was identified as potential lead compound with low cytotoxicity and submicromolar activity on human leukemic T cell line (MT-4) infected with both HIV-1 and clinically relevant mutants.[33]



XVII

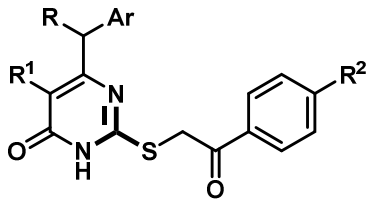
It has been reported that the C-5 iodo-S-DABO analogues **XVIII** showed HIV RT inhibitory activity at low micromolar range with IC_{50} values 0.18-3.03 μM.[34]



XVIII

R= $PhCH_2CH_2$, $PhCH_2CH_2CH_2$,
3-$CH_3C_6H_4CH_2$, 2-Naphthylmethyl

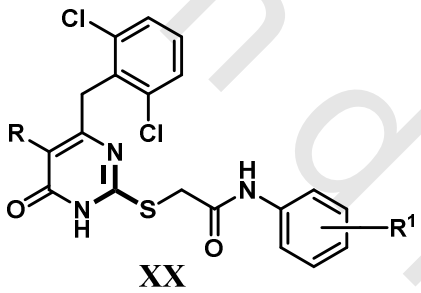
In addition, the 2-arylcarbonylmethylsulfanyl analogues **XIX** have been synthesized and evaluated for their *in vitro* anti-HIV activities in MT-4 cells. Most of these compounds showed moderate to potent activities against wild-type HIV-1 with an IC_{50} ranging from 0.01 to 8.97 μM.[35]



XIX

R = H, C_6H_5
R^1 = CH_3, C_2H_5
R^2 = H, OCH_3
Ar = 2-Br-C_6H_5, 3-Br-C_6H_5, 4-Br-C_6H_5, 3-OH-C_6H_5, 3,5-$(CF_3)_2$-C_6H_4 2,6-Cl_2-C_6H_4, 1-Naphthyl

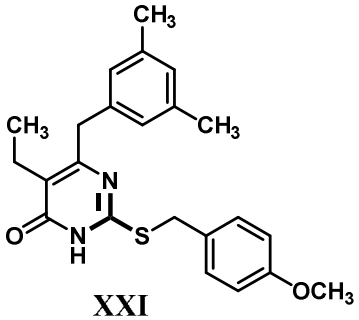
Furthermore, a series of 2-arylaminocarbonylmethylsulfanyl analogues **XX** was evaluated for anti-HIV activities in MT-4 cells. Most of these compounds showed moderate to potent activities against wild-type HIV-1 with IC_{50} values ranging from 0.18 μM to 4.48 μM.[36]



XX

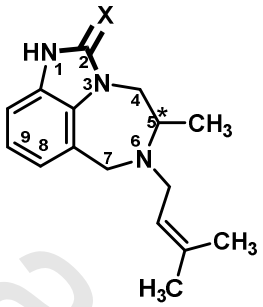
R= H, CH_3
R^1= 4-OCH_3, 4-Cl, 4-Br, 4-NO_2, 3,4-$(OCH_3)_2$, 3,4-F_2, 3,4 Cl_2

Moreover, a series of 5-alkyl-6-(substituted benzyl)-2-[(substituted benzyl) sulfanyl]pyrimidin-4(3*H*)-ones have been synthesized and evaluated for their *in vitro* activities against HIV-1 and HIV-2 in MT-4 cell cultures. The majority of the tested compounds showed moderate to good activities against HIV-1. Among them, compound **XXI** exhibited the most potent anti-HIV-1 activity.[37]



XXI

Tetrahydroimidazobenzodiazepinone (TIBO) derivatives **XXII** are a class of highly potent and specific inhibitors of HIV-1 replication in nanomolar concentrations which are 10^4-10^5 times lower than their cytotoxic concentrations. The unprecedented specificity of these compounds is due to an interaction with a RT-associated process.[38]



XXII

X= O, S or Se

In the imidazole part of TIBO structure, it has been found that replacement of the carbonyl oxygen with sulfur or selenium increased in the activity.[39]

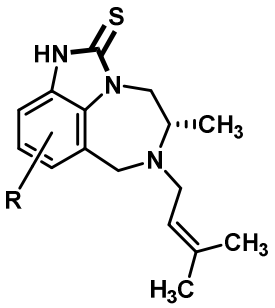
Substitutions at the diazepine ring have been also investigated. The 5-mono-methyl-substituted analogues and 7-mono-methyl-substituted analogues were the most active in the series.[40]

It was found that a methyl substituent at position-5 and a thione at position-2, gave a very potent inhibitor of HIV-1 (R82150) **XXIIIa**.[38]

In addition, substitution at the aromatic part of the TIBO structure has been investigated. Various substituents at position-8 gave compounds having improved activity compared with the parent compound.[40]

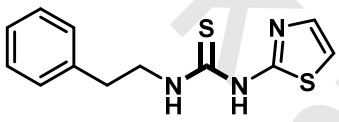
Introducing a chloro substituent at position-9 gave a compound (R82913) **XXIIIb** that had a 10-fold increase in activity, but also an increase in cytotoxicity.[38]

Changing chloro substituent from position-9 to position-8 afforded a more potent compound (R86183) (tivirapine) **XXIIIc** which has been subjected to clinical Phase I testing.[41]

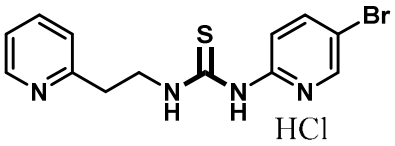


XXIIIa: R=H, XXIIIb: R=9-Cl
XXIIIc: R=8-Cl

The phenethylthiazolylthiourea (PETT) compounds are a class of potent HIV NNRTIs.[42] The lead compound of this class was LY73497 **XXIV**. Optimization of this lead compound gave 1-(5-bromopyridin-2-yl)-3-[2-(pyridin-2-yl)ethyl]thiourea hydrochloride (LY3000-46:HCl; trovirdine; Medivir) **XXV**, which has been selected for clinical trials.[42,43]

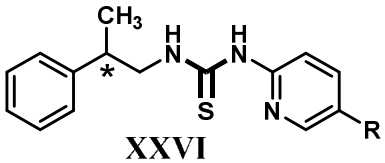


XXIV



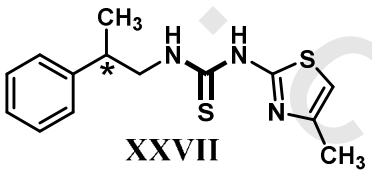
XXV

Chiral derivatives of several substituted halopyridyl and thiazolyl PETT derivatives were synthesized as HIV-1 NNRTIs. All the R isomers showed potent anti-HIV activity and inhibited the replication of the HIV-1 in peripheral blood mononuclear cells (PBMCs) at nanomolar concentrations whereas their S enantiomers were substantially less potent. The lead compounds **XXVI** and **XXVII** were further tested against the NNRTI resistant HIV strains and were several logs more potent than the standard NNRTI nevirapine.[44]



XXVI

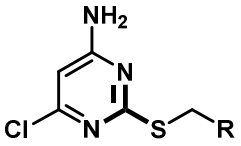
R= Cl, Br



XXVII

It has been reported that pyrimidine thioethers **XXVIII** displayed potent inhibitory activity against the P236L mutant RT, which renders HIV-1 resistant to delavirdine.[45,46]

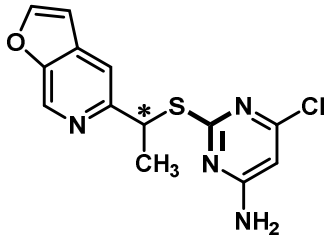
SAR studies revealed that oxidation of the sulfur atom or its replacement with oxygen or nitrogen decreased or abolished the activity. In addition, derivatives with amino or methylene in place of the sulfur are essentially inactive. Moreover, replacement of the chloro substituent at the pyrimidine ring with trifluoromethyl group gave a compound slightly less potent, whereas its replacement with other electron withdrawing groups (e.g. CN, COOEt) decreased the activity.[50]



XXVIII

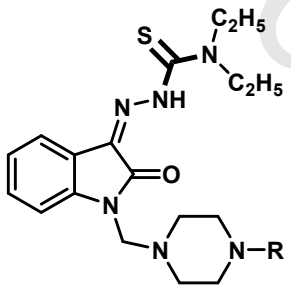
R= -CH=CH-C_6H_4, -CH=CHCONMe_2, -CH=CHCONEt_2, 3-CH_3-C_6H_4, 3-OCH_3-C_6H_4, 3-Br-C_6H_4, 2-naphthyl

Further study within pyrimidine thioether compounds have led to the development of furo[2,3-*c*]pyridylsulfanylpyrimidines which have broad activity against several NNRTI-resistant variants of HIV-1. Intensive evaluation of this class led to the selection of PNU-142721 (**XXIX)** as candidate for clinical development.[47]



XXIX

A series of 2-{1-[(4-aryl)piperazin-1-yl]methyl-2-oxoindolin-3-ylidene}-*N*,*N*-diethyl-hydrazinecarbothioamides **XXXa-c** was synthesized and evaluated for anti-HIV activity against HTLV-IIIB strain in human leukemic T cell line (CEM). Three compounds showed significant anti-HIV activity with IC_{50} values in the range of 2.62–3.40 μM. Compound **XXXb** exhibited the highest activity with an IC_{50} value 2.62 μM and a selectivity index (SI) 17.41, while not being cytotoxic to the cell line at a LC_{50} value of 44.90 μM.[48]

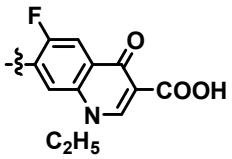


XXXa-c

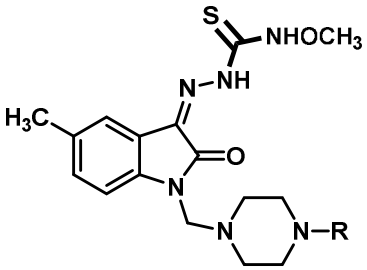
XXXa: R= $CH_2C_6H_5$

XXXb: R= 3-CF_3-C_6H_4

XXXc: R=



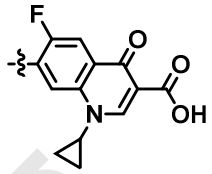
A series of 5-methyl-2-{1-[(4-aryl)piperazin-1-yl]methyl-2-oxoindolin-3-ylidene}-*N*-methoxyhydrazinecarbothioamides **XXXIa,b** were synthesized and evaluated for their anti-HIV and antitubercular activities. Compound **XXXIa** displayed promising activity against the replication of HIV-1 cells (IC_{50} 1.69 μM) and also proved effective in inhibiting the growth of both log phase (MIC 3.30 μM) and starved (MIC 12.11 μM) *Mycobacterium tuberculosis* cultures. Compound **XXXIb** inhibited isocitrate lyase enzyme that has a pivotal role in persistent Tuberculosis (TB) with 63.44% inhibition at 10 mM.[49]



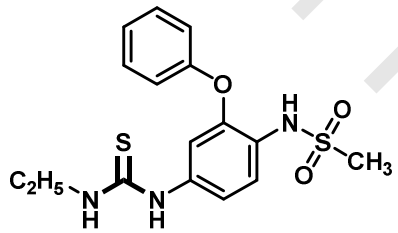
XXXIa,b

XXXIa: R= 4-ClC$_6$H$_4$

XXXIb: R=

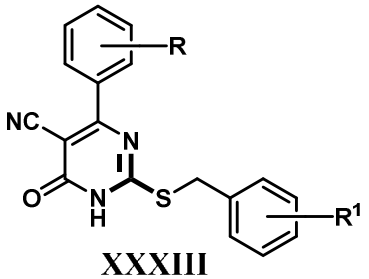


A series of thioureas bearing *N*-(2-phenoxyphenyl)-methanesulfonamide moiety have been synthesized and evaluated against HIV-1 (IIIB) and HIV-2 (ROD) strains in MT-4 cells. Compound **XXXII** was able to block HIV replication with almost 100% maximum protection at 125 μg/ml, and IC_{50} values 54.9 μg/ml and 65.9 μg/ml against HIV-1 and HIV-2, respectively.[50]



XXXII

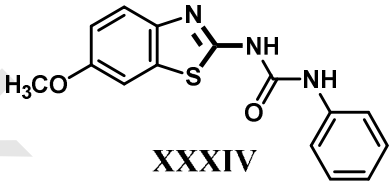
On the other hand, the 5-cyano-6-aryl-2-substituted benzylsulfanylpyrimidin-4(3*H*)-ones derivatives **XXXIII** showed good anti-HCV activity with IC_{50} values ranging from 7.1 to 33 μM against HCV nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase. The structure-activity relationship (SAR) studies suggest that the free NH of the pyrimidine ring seems to be necessary for the inhibitory activity, the para-substitutions at both aryl and benzyl groups led to a two fold increase in the activity while a combination of the para-substitution at the aryl group and an ortho-substitution at the benzyl moeity led to a five fold increase in the activity.[51]



XXXIII

R = Mono and dihalo, CF_3, CH_3, C_3H_7
R^1= Br, NO_2, CH_3, OCH_3

In addition, Frentizole **XXXIV** is a nontoxic antiviral and immunosuppressive agent used clinically in rheumatoid arthritis and systemic lupus erythematosus.[52]



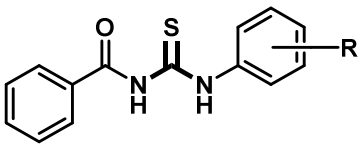
XXXIV

1.1.3. Antioxidant thiourea derivatives

Reactive oxygen species (ROS), known as mediators of intracellular signaling cascades, are chemically reactive molecules containing oxygen. Most living organisms can produce ROS and metabolize excessive ones by normal physiological processes. However, sometimes these efficient protecting systems could be disrupted by external factors (smoke, alcohol, diet and some drugs) or aging.[53] Accumulation of excessive ROS can damage lipids, proteins, carbohydrates, and DNA in cells, leading to oxidative stress, loss of cell function, and ultimate apoptosis or necrosis. The continuous overproduction of ROS and/or the decrease in antioxidant defenses, may contribute to the development of several diseases such as cancer, rheumatoid arthritis, transplanted organ rejection, atherosclerosis, sepsis and aging.[54] Therefore, exploring antioxidant chemicals that can scavenge ROS may be of great value in preventing the onset and propagation of oxidative stress.

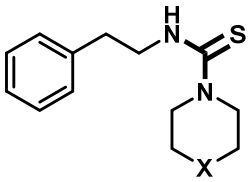
Literature review revealed that many thiourea derivatives possess antioxidant activities.

Two series of *N*-(arylthiocarbamoyl)benzamides **XXXV** and heterocyclic based thiourea derivatives **XXXVI** were synthesized and evaluated for antioxidant activity using lipid peroxidation inhibition assay. Among the tested compounds, *p*-OH or *p*-OCH_3 substituted benzamides and thioureas containing morpholine or piperidine nuclei showed the highest inhibition of lipid peroxidation.[55]



XXXVa,b

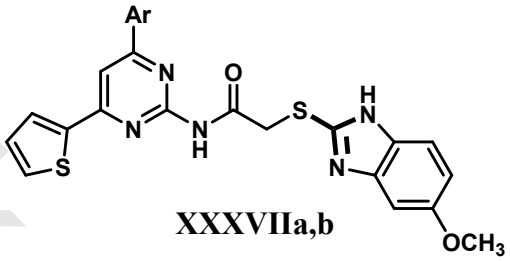
R=OH, OCH_3



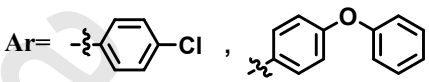
XXXVIa,b

X=CH_2, O

A series of substituted (2-benzimidazol-2-yl)sulfanyl]-*N*-(pyrimidin-2-yl)acetamide derivatives were synthesized and evaluated for their *in vitro* antioxidant activities using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay. Compounds **XXXVIIa,b** showed good antioxidant activity comparable to ascorbic acid standard.[56]

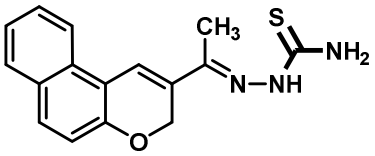


XXXVIIa,b

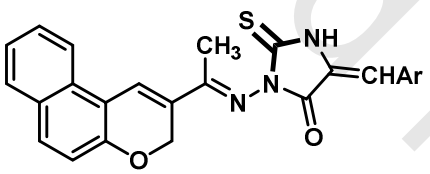


Ar=

A series of benzocoumarin derivatives that also incorporated thiourea moiety were synthesized and evaluated for their *in vitro* antioxidant activities using DPPH free radical scavenging assay. Compounds **XXXVIII-XL** showed moderate to good antioxidant activity.[57]

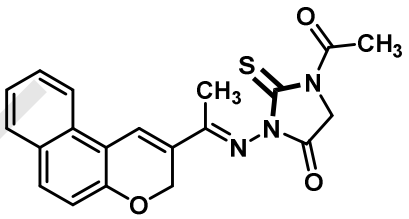


XXXVIII



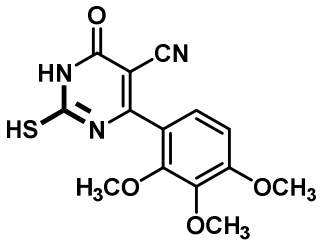
XXXIX

Ar= C_6H_5, 4-OH-C_6H_4



XL

In addition, a series of dihydropyrimidinecarbonitriles that also incorporated thiourea moiety in their skeleton was synthesized and evaluated for *in vitro* antioxidant activity by measuring of hydrogen peroxide scavenging, nitric oxide radical scavenging and lipid peroxidation inhibition. The results revealed that some of the tested compounds showed moderate to good antioxidant activity. Compound **XLI** showed good antioxidant activity as compared with standard ascorbic acid by scavenging of both hydrogen peroxide and nitric oxide radicals.[58]



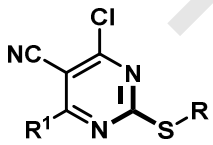
XLI

1.1.4. Antimicrobial thiourea derivatives

Antimicrobial drugs are essential for the treatment of a number of infectious diseases caused by different microorganisms. However, antimicrobial resistance makes it harder to eliminate infections from the body as existing drugs become less effective. As a result, discovery and development of new antimicrobial drugs are urgently needed to combat the growing threat of drug-resistant microbes.

A careful review in literature revealed that many thiourea derivatives are reported as potent antimicrobials against different types of microbes.

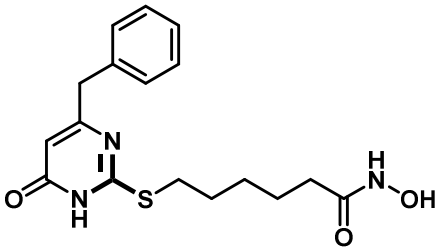
A series of alkyl or aralkylsulfanylpyrimidine derivatives **XLII** were synthesized and evaluated for their antimicrobial activity. Some derivatives exhibited potent activity against *Mycobacterium tuberculosis,* while others demostrated antibacterial activity against *Pseudomonas aeuroginosa* and *Escherichia coli*. Moreover, most of the tested compounds were found highly active against *Aspergillus fumigatus* and *Trichophyton mentagrophytes*.[59,60]



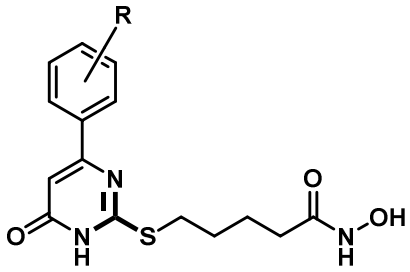
XLII

R= CH_3, C_2H_5, C_3H_7(*n*), 4-Cl-$C_6H_4CH_2$
R^1= SCH_3, C_6H_5, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 3-F-C_6H_4,
4-F-C_6H_4, 2,4-F_2-C_6H_3, 2-thienyl, 2-furyl

Furthermore, pyrimidine hydroxamates **XLIII** and **XLIVa-c** were discovered as HDAC inhibitors, able to reduce acquired antifungal resistance and trailing growth in *Candida albicans*. Compounds **XLIVb,c** were more potent than suberoylanilide hydroxamic acid (SAHA), a well-known HDAC inhibitor, in reducing the Candida growth. More interestingly, compounds **XLIVb,c** as well as SAHA were able to inhibit the fluconazole induced resistance in Candida cultures.[61]



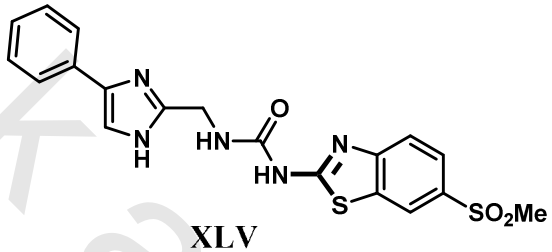
XLIII



XLIVa-c

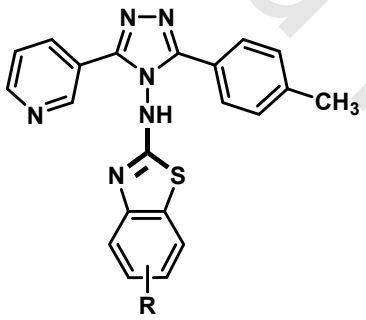
XLIVa: R=H, XLIVb: R=3-Cl, XLIVc: R=4-Cl

The phenylimidazole derivative **XLV** has been reported to possess antibacterial activity against *Streptococcus pneumoniae* through inhibition of an enoyl-acyl carrier protein reductase termed fabK which catalyzes the final and rate-limiting step of bacterial fatty acid biosynthasis and is only present in *Streptococcus pneumoniae.*[62]



XLV

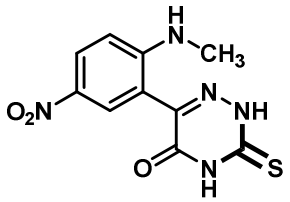
In addition, Patel *et al*.[63] synthesized a series of *N*-(1,2,4-triazol-4-yl)benzothiazol-2-amine derivatives which was evaluated for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* and antimicrobial activity against various bacteria and fungi. Compounds **XLVI** showed promising antimicrobial and antitubercular activites. Some Compounds showed better antitubercular activity compared with standard rifampicin.



XLVI

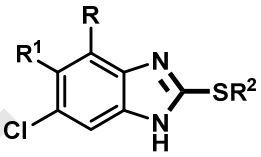
R = 6-F, 6-Br, 6-NO_2, 6-CH_3, 4-CH_3, 4-NO_2, 5,6-Cl_2

Synthesis of some substituted thioxotriazinone derivatives were reported by Pandeya *et al.*[64] and tested for their antibacterial activity against 20 strains of Gram positive and Gram negative bacteria. Among the tested compounds, compound X**LVII** showed good antibacterial activity in comparison to the standard sulphamethoxazole and was found to be most active against *Helicobacter pyloria*.



XLVII

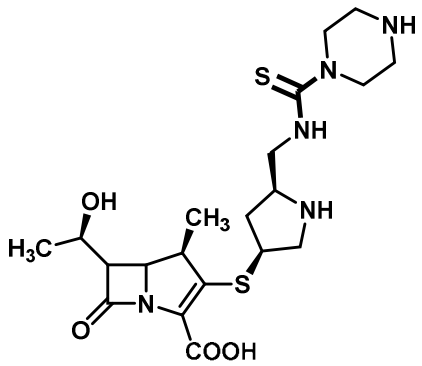
A series of aralkylsulfanyl substituted benzimidazole derivatives **XLVIII** was synthesized and evaluated for antibacterial and antiprotozoal activities. Compounds **XLVIIIa-d** exhibited antibacterial activity against nosocomial strains of *Stenotrophomonas malthophilia* with MIC ranging from 50 to 400 μg/ml and an activity comparable to that of metronidazole (MIC >400 μg/ml) against Gram positive and Gram negative bacteria. Compound **XLVIIIe** showed the most distinct antiprotozoal activity against *Entamoeba histolytica* and *Giardia duodenalis* with MIC 25 μM for both.[65]



XLVIIIa-e

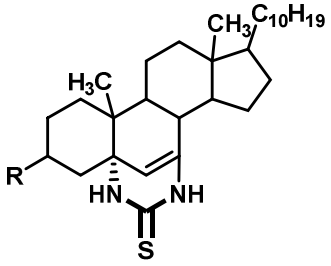
XLVIIIa: R=H, R^1=Cl, R^2=$CH_2CH_2N(CH_3)_2$
XLVIIIb: R=H, R^1=Cl, R^2=$CH_2CH_2N(C_2H_5)_2$
XLVIIIc: R=H, R^1=Cl, R^2=$CH_2CH_2CH_2N(CH_3)_2$
XLVIIId: R=Cl, R^1=H, R^2=$CH_2CH_2N(CH_3)_2$
XLVIIIe: R=H, R^1=Cl, R^2=*p*-nitrobenzyl

A series of 1β-methylcarbapenems having thiourea moieties was reported. Their *in vitro* antibacterial activities against both Gram positive and Gram negative bacteria were tested and the effect of substitution on the pyrrolidine ring was investigated. Compound **XLIX** showed the most potent antibacterial activity. It displayed superior or similar activities to meropenem against Gram positive bacteria, and to imipenem against Gram negative bacteria. In addition, It was found to be two to four times more active than the standards meropenem and imipenem against *Pseudomonas cepacia*.[66]



XLIX

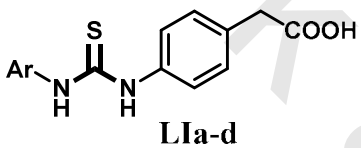
Steroidal thiourea derivatives have been synthesized and evaluated for their antibacetrial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium* and *Escherichia coli*. Compounds **La,b** were better antibacterial agents as compared with standard chloramphenicol.[67]



La,b

La: R = CH_3COO, Lb: R= Cl

Two series of substituted phenylthioureas **LI, LII** were synthesized and evaluated for antifungal and larvicidal activities. Compounds **LIa,b** and **LIIa** demonstrated selective good activity against *Phomopis obscurans* while compound **LIa** showed a good level of activity against *Phomopis viticola.* Compounds **LIb and LIIb,c** showed the highest toxicity against *Aedes aegypti* larvae with LC_{50} ranging from 67.9 to 165.6 ppm. Compounds **LIb-c** showed good biting deterrent activity. Compound **LIb** showed the highest activity with a proportion not biting (PNB) value 0.75.[68]



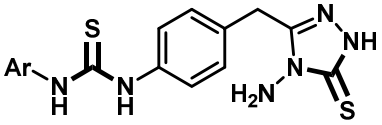
LIa-d

LIa: Ar=2,6-Cl_2-C_6H_3

LIb: Ar=4-CH_3S-C_6H_4

LIc: Ar=4-NO_2-C_6H_4

LId: Ar=2,4,6-Cl_3-C_6H_2



LIIa-c

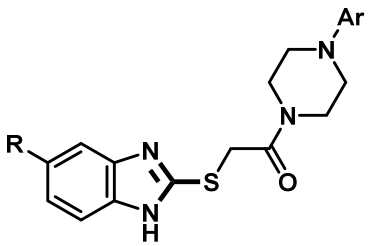
LIIa: Ar=2,4,6-Cl_3-C_6H_2

LIIb: Ar=4-CF_3-C_6H_4

LIIc: Ar=4-NO_2-C_6H_4

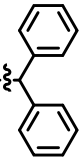
1.1.5. Antiparasitic thiourea derivatives

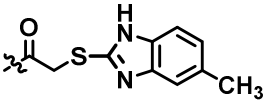
Mavrova and co-workers[69] synthesized 1*H*-benzimidazol-2-ylsulfanylacetyl-piperazine derivatives **LIII** and screened them for anthelminthic activity. Most of the synthesized compounds exhibited higher activity than albendazole towards *Trichinella spiralis*. Compounds **LIIIa-c** exhibited activities ranging from 96 to 100%. Compounds **LIIIa,b,d** were the most active towards *Syphacia obvelata* with activities ranging from 73 to 77%.



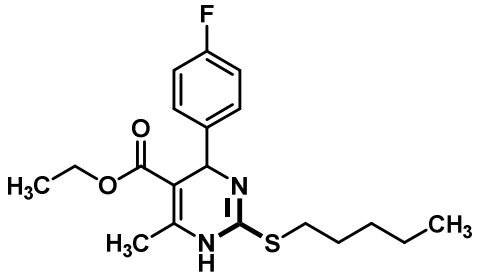
LIIIa-d

LIIIa: R= H, Ar= 4-Cl-C_6H_4 **LIIIb: R= CH_3, Ar= 4-Cl-C_6H_4**

LIIIc: R= CH_3, Ar= 

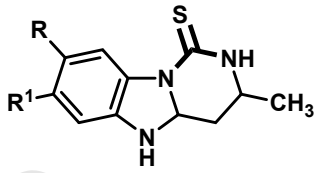
LIIId: R= CH_3, Ar= 

In addition, the alkylsulfanyl-1,4-dihydropyrimidine **LIV** showed promising *in vitro* and *in vivo* antifilarial activity against adult parasites of human lymphatic filarial parasite *Brugia malayi*.[70]



LIV

Furthermore, a series of substituted tetrahydrothioxopyrimido[1,6-*a*]benzimidazole derivatives was synthesized and evaluated for antiamoebic activity. Compounds **LV** showed good *in vitro* antiamoebic activity against *Entamoeba histolytica* with IC_{50} values ranging from 1.82 to 3.56 μM compared with the reference drug metronidazole with IC_{50} 1.22 μM.[71]

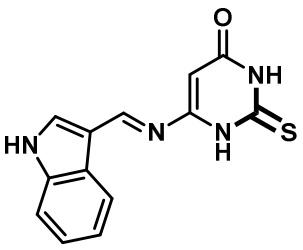


LV

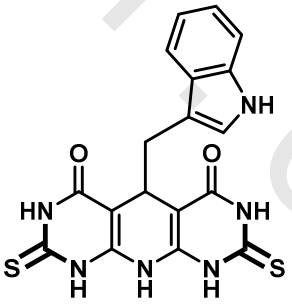
R = H, CH_3, COOH
R^1= H, CH_3

1.1.6. Anti-inflammatory thiourea derivatives

A series of pyrimidine derivatives was synthesized and evaluated for anti-inflammatory activity using carrageenan-induced rat paw oedema assay. The 6-{[(1*H*-indol-3-yl)methylene]amino}-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **LVI** and the 5-substituted-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-4,6(1*H*,5*H*)-dione **LVII** displayed more potent anti-inflammatory activity than ibuprofen.[72]

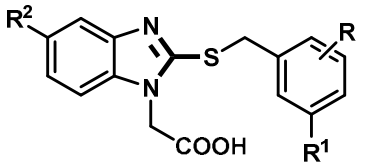


LVI



LVII

A high-throughput screening campaign has been made by J. Pothier *et al.*[73] to search for potent and selective chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells (CRTh2 receptor) antagonists which could be useful in the treatment of asthma and other inflammatory diseases such as allergic rhinitis. The study resulted in synthesizing a series of sulfanylbenzimidazole compounds from which compounds **LVIII** showed promising activity.

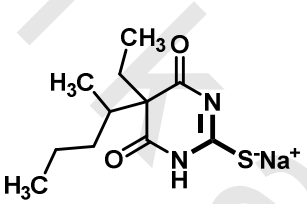


LVIII

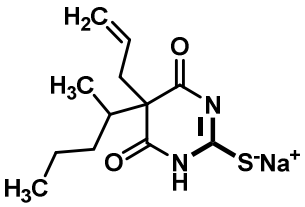
R= 2-$COOCH_3$, 3-OCH_3, 4-OCH_3, 4-$COOCH_3$
R^1= H, OCH_3, OC_2H_5, OC_3H_7(*n*)
R^2= H, F, CF_3, NO_2

1.1.7. CNS activity of thiourea derivatives

The sodium salts of the highly potent ultra short acting barbiturates, thiopental **LIX** and thiamylal **LX** are currently used as general anesthetics in short operations and for the induction of inhalation anesthesia.[74,75]

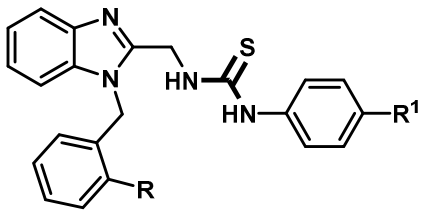


LIX



LX

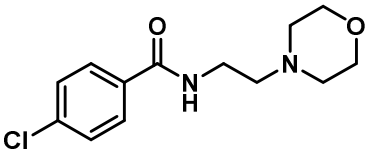
Siddiqui *et al.*[76] synthesized a number of 1-{[(substituted benzyl)benzimidazol-2-yl]methyl}thiourea derivatives. The compounds were screened for their anticonvulsant activity in *intraperitoneal* maximal electroshock (*ip* MES) and *subcutaneous* pentylene-tetrazole (*sc* PTZ) induced seizure models and were compared with the standard drug phenytoin. Majority of the tested compounds exhibited significant activity against both animal models. Compounds **LXI** displayed the most promising activity.



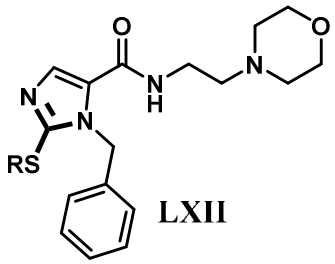
LXI

R= H, Cl
R^1= CH_3, OCH_3

On the other hand, Hadizadeh *et al.*[77] synthesized a series of moclobemide analogues and evaluated their antidepressant activity using forced swimming test in mice. Compounds **LXII** were found to be 10 fold more potent than moclobemide.



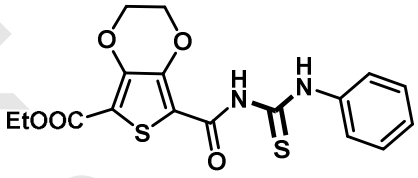
Moclobemide



LXII

R=CH_3, C_2H_5, $CH_2C_6H_5$

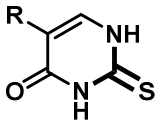
A series of 3,4-ethylenedioxythiophene derivatives linked to phenylthiourea was synthesized and screened for their anticonvulsant activity using three different models; *ip* MES, *sc* PTZ, and Minimal Clonic Seizure (6 Hz) models and evaluated for their neurotoxicity in rotorod model. Compound **LXIII** emerged as lead with no neurotoxicity at the maximum dose of 300 mg/kg of body weight.[78]



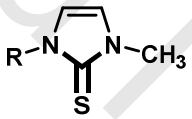
LXIII

1.1.8. Miscellaneous activities of thiourea derivatives

Thionamides are the most important class of antithyroid compounds used in nondestructive therapy of hyperthyroidism.[79] The most clinically useful thionamides are the five- and six-membered heterocyclic derivatives of thiourea **LXIVa,b,**[9,79-81] **LXVa,b**.[79]



LXIVa,b

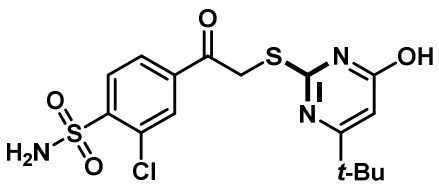


LXVa,b

LXIVa (propylthiouracil)**: R= *n*-C_3H_7**
LXIVb (iodothiouracil)**: R= I**

LXVa (Methimazole)**: R= H**
LXVb (Carbimazole)**: R= $COOCH_2CH_3$**

A series of benzenesulfonamide derivatives, bearing pyrimidine moieties that incorporates thiourea in its skeleton, were synthesized as carbonic anhydrases (CA) inhibitors. Compound **LXVI** had potent and highly selective affinity towards CA isoform I.[82]



LXVI