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Synthesis and Biological Value of Thiouracils and Fused Thiouracils (A review)

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ABSTRACT

A literature survey revealed that the thiouracil derivatives and their condensed heterocycles have occupied a marked position as synthon for various biologically active compounds. They have a wide range of therapeutic uses that include anti-cancer, anti-microbial, molluscicidal, anti-leishmanial, anti-oxidant, anti-viral as anti-HIV and anti-HCV, and anti-thyroid activities. Numerous methods for the synthesis of thiouracils offer enormous scope in the field of medicinal chemistry. The review article aims to review the work reported for the synthesis and the biological activities of thiouracils and fused thiouracils from the past to recent years.

Key Words: *Thiouracils, Fused thiouracils, Synthesis, Biological activities*

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INTRODUCTION

Heterocyclic compounds are those cyclic compounds whose ring contain besides carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. Heterocyclic compounds, bearing atoms of at least two different elements as a member of its ring have attracted considerable attention in the development of pharmacologically active molecules and advanced organic materials. Pyrimidine ring is the building unit of DNA and RNA which explains the fact that pyrimidine derivatives and related fused heterocycles exhibit diverse pharmacological activities. Another important class of pyrimidine is 2-thiopyrimidine (2-TP) and its derivatives. 2-Thiouracil (**TU**), which is a sulfur-containing uracil, a six membered simple aromatic ring comprises of carbon, two nitrogen atoms at positions 1 and 3, sulfur and oxygen **(Figure 1).**

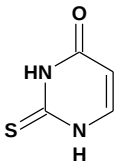


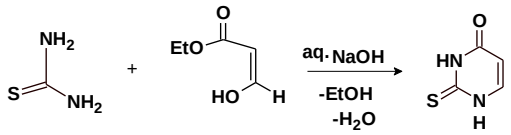
Figure 1. Structure of 2-thiouracil

There are two established antithyroid drugs, 6-propyl-2-thiouracil and 6-methyl-2-thiouracil. Thio derivatives of pyrimidine bases including 2-thiouracil, 6-methyl-2-thiouracil, and 2-thiocytosine are minor components of t-RNA, and furthermore, they have contributed remarkably to biological, pharmacological, and medicinal chemistry. Among the pyrimidine containing heterocycles, thiouracils are potential therapeutics as antiviral, anticancer and antimicrobial agents. For example, S-alkylation and N-alkylation products have been recently reported as novel antibacterial, cytotoxic agents and unique HIV reverse transcriptase inhibitors. Moreover, a literature survey revealed that the thiouracil derivatives and their condensed heterocycles have occupied a marked position in the design and synthesis of novel chemotherapeutic agents with remarkable antitumor, HCV inhibitors and antimicrobial activities. During the last two decades, several thiouracil derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. In the light of the aforementioned facts, and in continuation for our interest in the synthesis of biologically active heterocyclic compounds, we report herein the main aspects of the synthesis and the biological value of these heterocycles from the past to recent years.

1. Synthesis of thiouracils

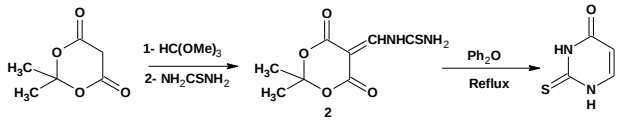
1.1. 2-Thiouracil

The thiouracil system is constructed either via cyclocondensation of carbonyl compound with thiourea or by introducing thiourea residues into the structure of carbonyl compounds, followed by cyclization of intermediate thio ureides. According to the first synthetic pathway, 2-Thiouracil **1** was prepared by condensation of the enol form of ethyl formyl acetate as its sodium salt with thiourea. This reaction was reported [1] by Wheeler and Liddle.



1

2-Thiouracil 1 can be also synthesized (with a 70% yield) using two-stage process, whereby Meldrum's acid is heated with trimethyl orthoformate and thiourea, after which the intermediate thio ureid **2** is subjected to thermolysis in diphenyl ether [2].



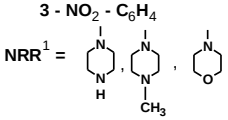
2 1

1. 2. 2-Substituted thiouracils

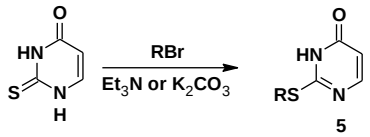
In 2010, Basavaraja *et al.*[3] reported that piperazine and morpholine linked to thiouracil derivatives **4** were prepared via reaction of methylated thiouracil **3** with heterocyclic secondary amines like piperazine, N-methylpiperazine and morhpoline.

3 4

Ar = C_6H_5 ,4 - Cl -C_6H_4 , 4 -OCH_3 - C_6H_4 , 3 - NO_2 - C_6H_4

NRR^1 = 

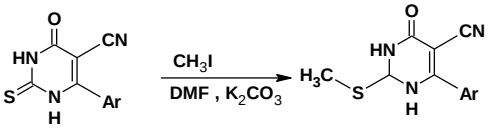
In 2011, Supaluk *et al.* [4] reported the synthesis of S-substituted thiouracils **5** through the alkylation of 2-thiouracil with alkylating agents (R -Br) in base catalysis (Et_3N or K_2CO_3).



5

R = $CH_2C_6H_{11}$,$CH_2C_6H_5$, s -C_4H_9 , n - C_4H_9 , 1 - adamantyl

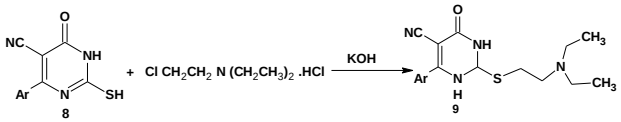
In 2013, Fadi *et al.*[5] reported the methylation of 2-thiouracils **6** with methyl iodide, K_2CO_3 in dry DMF.



6 7

Ar = C_6H_5 ,4-Cl -C_6H_4

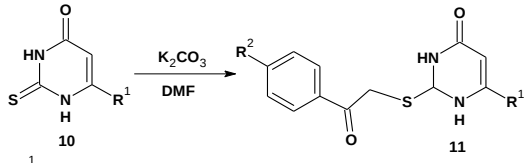
In the same year, Ahmed *et al.*[6] reported the reaction of 2-thiouracils **8** with the hydrochloride salt of diethyl-aminoethyl chloride in KOH to obtain 2-(diethyl amino) ethy-2-thiouracil derivatives **9**.



8 9

Ar = C_6H_5 , 4 -NO_2 -C_6H_4

In 2016, Dong *et al.*[7] reported the synthesis of thiouracils **11** by S-alkylation of the 6-substituted 2-thiouracils **10** with the appropriate substituted phenacyl halides in the presence of anhydrous K_2CO_3.

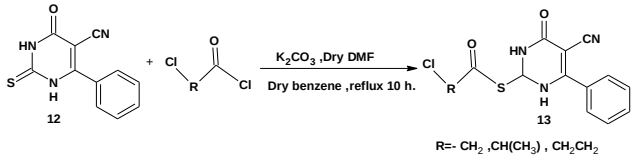


10 11

R^1 =CH_3 ,NH_2

R^2 = Cl, NO_2 ,CH_3 ,OCH_3

In the same year, Makaram *et al.* [8] reported the reaction of 4-oxo-6-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile (**12**) with chloroacetyl chloride, 2-chlororopionyl chloride, and 3-chloropropionyl chloride in dry benzene using K_2CO_3 as a base to obtain S-chloro alkanethioates **13**.

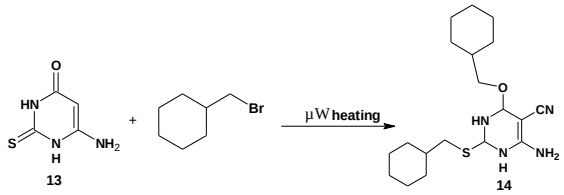


12 13

R=- CH_2 ,$CH(CH_3)$, CH_2CH_2

Alkylation of 6-amino-2-thioxo-2,3-dihydro-pyrimidin-4(*1H*)-one **14** was performed using

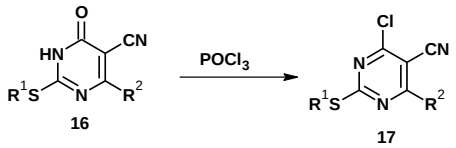
(bromomethyl)-cyclohexane to enable the concomitant alkylation at the 2- and 4-positions. The use of microwave heating (μW) afforded the desired product **15** in 16 min at140°C. This reaction was reported [9] by C. Daniela *et al* in 2016.



13 14

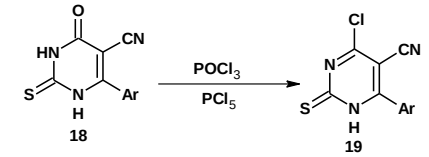
1.3. 4-Substituted thiouracils

Conversion of 2-thiouracil derivatives **16, 18** to their corresponding 4-chloro analogs **17, 19** using phosphorus oxychloride has been reported [10-13] or it can be performed using phosphorus oxychloride / phosphorus pentachloride mixture [14,15].



16 17

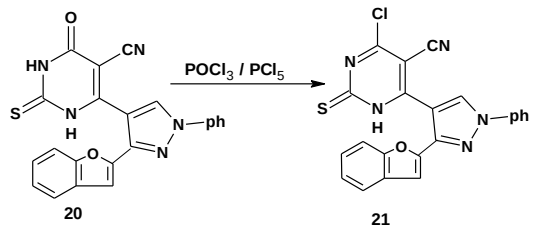
R^1 = CH_3 , C_2H_5 , C_3H_7,$CH_2C_6H_5$
R^2 = 2-C_4H_3S , 2-C_4H_3O , 3-F-C_6H_4 , C_6H_5, 4-NO_2-C_6H_4 , 2-C_4H_3O



18 19

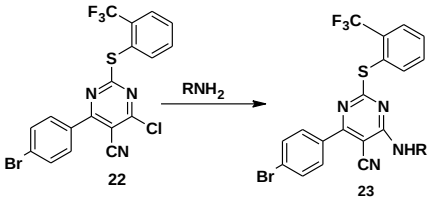
Ar = C_6H_5 ,2-OCH_3 -C_6H_4 ,2-CH_3-C_6H_4, 3,4,5 -$(OCH_3)_3$ -C_6H_2 , 4-F-C_6H_4, 4-Br -C_6H_4 ,4-N$(CH_3)_2$ -C_6H_4

In 2011, Magdy *et al*.[16] reported the synthesis of 6-(3-(benzofuran-2-yl)-1-phenyl-*1H*-pyrazol-4-yl)-4-chloro-1,2-dihydro-2-thioxopyrimidine-5- carbonitrile (**21)** by reaction of 2-thiouracil derivative **20** with $POCl_3/PCl_5$ in boiling water bath.



20 21

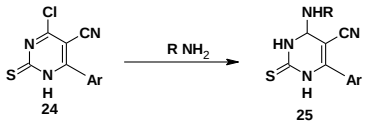
In 2006, Ding *et al*.[17] reported the synthesis of a series of 6-(4-bromophenyl)-5-cyano-4-alkylamino thiouracil derivatives **23** from 4-chloro-2-thiouracil **22** and different amines.



22 23

R = 2 -(3 - OCH_3 -C_6H_4) - CH_2CH_2 ,
2 -(3,4 - $(OCH_3)_2$ - C_6H_3) - CH_2CH_2,
4 -$(NHCH_3)$ -C_5H_{10} N

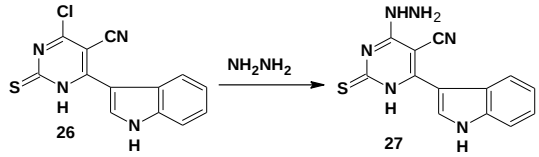
In 2011, Mosaad *et al.*[15] reported that a series of 4-alkylamino-2-thiouracils **25** was prepared via reaction of 4-chloro-2-thiouracils **24** with different amines.



24 25

R = 4-$COCH_3$ - C_6H_4, 2- COOH-C_6H_4, 4-antipyryl
Ar = 4-F-C_6H_4, 4-Br-C_6H_4, 4-N$(CH_3)_2$ -C_6H_4, 3,4,5-$(OCH_3)_3$-C_6H_3

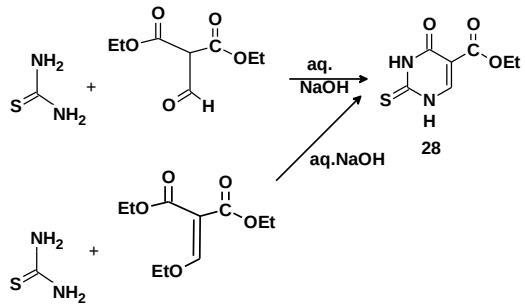
In 2014, Mosaad *et al*.[18] reported the synthesis of 4-hydrazino derivatives **27** by reaction of the appropriate chloropyrimidine **26** with 99% hydrazine hydrate in methanol.



26 27

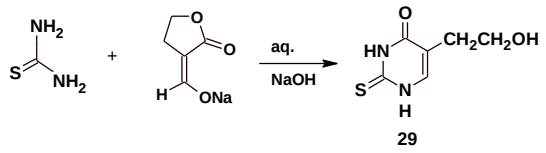
1.4. 5-Substituted thiouracils

In 1942, Ballard and Johnson [19] reported the formation of 5-ethoxycarbonyl-2-thiouracil (**28)** via the reaction of diethoxycarbonyl acetaldehyde (Diethyl α-formyl malonate) and ethyl α-ethoxycarbonyl-β-ethoxyacrylate, independently with thiourea.



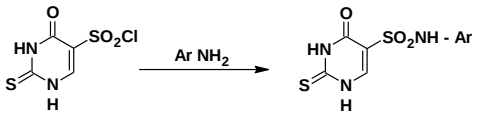
28

In 1964, Fissekis *et al.*[20] reported that 5-(2-hydroxyethyl)-2-thiouracil **(29)** was prepared by refluxing thiourea with the aqueous solution of the sodium salt of α-formylbutyro lactone in its enolate form.



29

In 2002, Omar *etal.*[21] reported the reaction of 2-thiouracil-5-sulphonyl chloride (**30)** with a series of amines giving certain sulphonamides **31.**

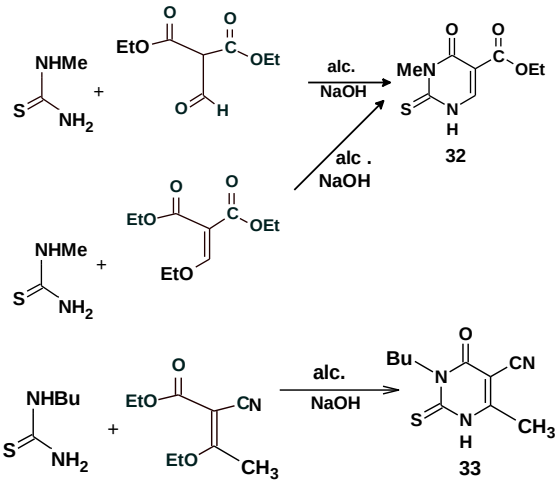


30 31

Ar = C_6H_5 ,4-CH_3-C_6H_4,4-Cl-C_6H_4, 4-Br-C_6H_4 ,3-F-C_6H_4 ,3,5-$(Cl)_2$-C_6H_3 , 5-Cl-C_6H_3-2-CH_3 , 2,4-$(Cl)_2$ - C_6H_3

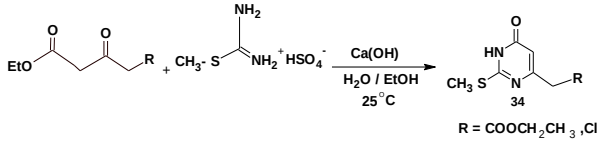
1.5. 3, 5-Disubstituted thiouracils

In 1956, Whitehead and Traverso[22] prepared 5-ethoxycarbonyl-3-methyl-2-thiouracil **(32)** and 3-butyl-5-cyano-6-methyl-2-thiouracil **(33)** by condensation of N-methyl thiourea and its butyl homologue with diethoxycarbonyl acetaldehyde (diethyl α-formylmalonate) or ethyl α-ethoxycarbonyl-β-ethoxyacrylate to give **32** or with ethyl α-ethoxy ethylidene cyanoacetate to give **33**.



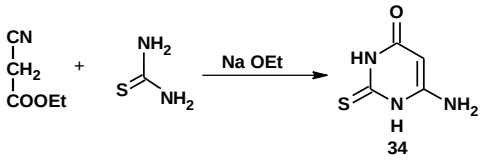
1.6. 6-Substituted thiouracils

In 1999, Maurizio *et al.*[23] reported the synthesis of thiouracil derivatives **34** via reaction of acetone dicarboxylic acid diethyl ester or ethyl-γ-chloroacetoacetate independently with S-methyl thiourea hydrogen sulphate in presence of calcium hydroxide.



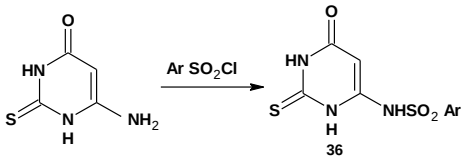
R = $COOCH_2CH_3$,Cl

In 2010, Mosaad *et al.*[24] reported the reaction of ethyl cyanoacetate with thiourea in sodium ethoxide to prepare 6-amino-2-thioxo-2, 3-dihydro-*1H*-pyrimidine-4-one (**35**).



34

In 2015, Mosaad *et al.*[13] reported the reaction 6-Amino-2-thiouracil with benzene sulfonyl chloride and 4-toluene sulfonyl chloride in presence of pyridine as an acid binder to give sulfonamides **36**.

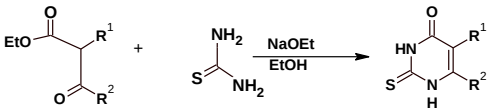


36

Ar = C_6H_5 , 4-CH_3 -C_6H_4

1.7. 5, 6- Disubstituted thiouracils

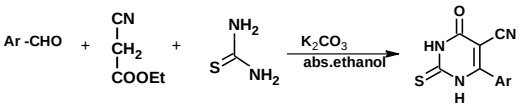
In 1997, Antonello and his co-workers [25] reported the preparation of a series of 5 and 6-disubstituted thiouracils **37** by condensation of β-oxo esters with thiourea in alcoholic sodium ethoxide.



37

R^1 = H ,CH_3
R^2 = $C_6H_5CH_3CH_2$,2-CH_3-C_6H_4 , 1-CH_2-$C_{10}H_7$,2-CH_2- C_{10} H_7, C_6H_5 - SCH_2

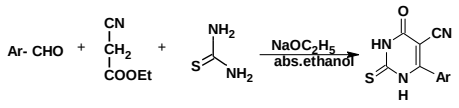
Many authors [26-28] reported the formation of 5-cyano-6-aryl-2-thiouracils **38** via cyclocondensation of aromatic aldehydes, thiourea, and ethylcyanoacetate in absolute ethanol /anhy. K_2CO_3.



38

Ar = C_6H_5 ,$CH_2CH_2C_6H_5$, 4-OCH_3-C_6H_4 ,4-Cl-C_6H_4, 4-Br-C_6H_4 , 4-F- C_6H_4, 4-CH_3- C_6H_4 , 3-NO_2- C_6H_4, 3-Cl-C_6H_4,3- Br-C_6H_4

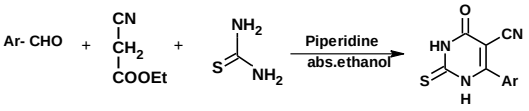
6-Aryl-5- cyano-2- thiouracils could be also obtained [14,15,29] by the reaction of ethyl cyanoacetate, thiourea and aromatic aldehyde in ethanol using sodium ethoxide / ethanol.



38

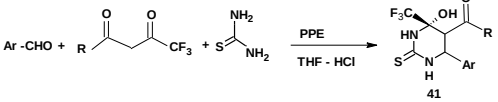
Ar =C_6H_5 ,2-(OCH_3)C_6H_4 ,2-CH_3-C_6H_4, 4-$N(CH_3)_2C_6H_4$,3,4-$(OCH_3)_2C_6H_4$, 3,4,5$(OCH_3)_3C_6H_2$, 4-FC_6H_5 , 4-Br C_6H_4 , 3 -Indolyl

A series of pyrimidine-2-thione derivatives **40-42** were prepared via a Biginelli-type multicomponent reaction between aldehyde, (ethyl cyano acetate or ethyl trifluoroaceto acetate or isopropylacetoactate) and thiourea in piperidine [30], polyphosphate ester (PPE) [31] or strontium chloride hexahydrate [32,33].



40

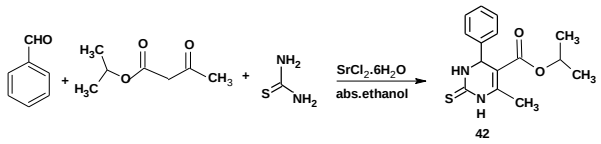
Ar =4-OCH_3-C_6H_4,4-Cl- C_6H_4, 3-Cl-C_6H_4



41

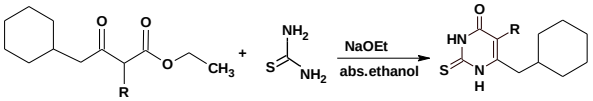
Ar = C_6H_5 ,4-F-C_6H_4,4-OCH_3-C_6H_4 , 2-Br-C_6H_4,3-OH-C_6H_4 ,3-CN-C_6H_4

R = 2 -C_4H_3S, 2-C_4H_3O, OCH_2CH_3 ,OCH_3



42

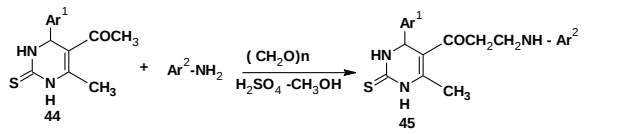
In 2011, Yan-Ping *et al*,[34] reported the synthesis of a novel dihydro-alkylsulfanyl-cyclohexyl-oxopyrimidines **43** through the reaction of β-keto esters and thiourea in sodium ethoxide.



43

R =CH_3 ,CH_2CH_3 ,$CH(CH_3)_2$

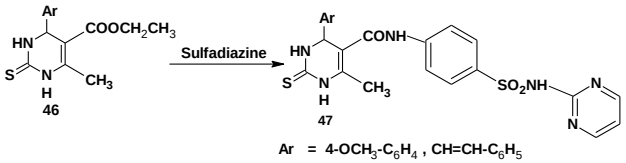
In 2012, Mosaad *et al*.[35] reported the synthesis of a series of mannich bases **45** via the reaction of 5-acetyl-6-methyl-2-thiouracils **44** with paraformaldehyde and primary aromatic amines.



Ar^1 = C_6H_5 ,4-OCH_3 -C_6H_4,CH=CH- C_6H_5

Ar^2 = C_6H_5 ,4- OCH_3 - C_6H_4

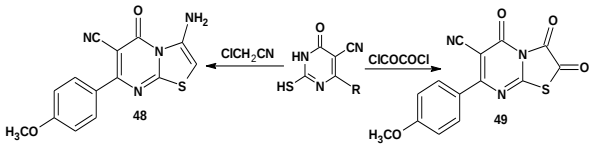
Reaction [36] of 5-ethoxycarbonyl-6-methyl-2-thiouracils **46** with sulfadiazine in DMF gave sulphonamides **47**.



Ar = 4-OCH_3-C_6H_4 , CH=CH-C_6H_5

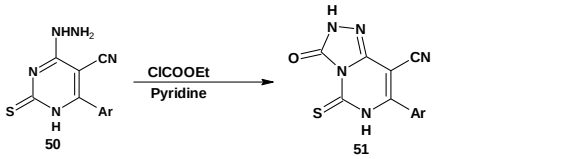
2. Synthesis of fused thiouracils

In 2009, Mohamed *et al* [37], reported the reaction of 6-aryl-5-cyano-2-thiouracil with chloroacetonitrile in boiling ethanol containing triethylamine to afford 3-aminothiazolo pyrimidine **48**; whereas the reaction of thiouracil with dioxalyl chloride gave 2,3,5-trioxothiazolopyrimidine **49**.



48 49

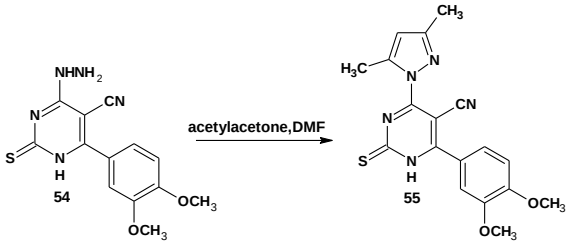
Omar *et al*, [14,29] reported the reaction of the hydrazinyl derivatives **50** with ethylchloroformate in refluxing pyridine to afford the desired triazolopyrimidine derivatives **51.**



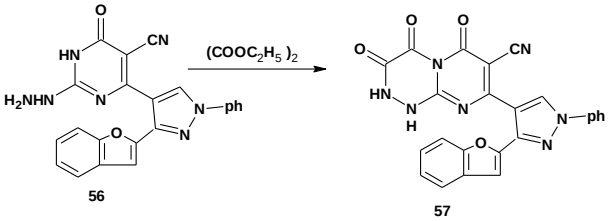
Ar = 2 - (OCH_3) -C_6H_4 ,3,4-$(OCH_3)_2$ -C_6H_3

The preparation of 7-(2-methoxyphenyl)-5-thioxo-5,6-dihydro [1,2,4] triazolo[4,3-*c*] - pyrimidine-8-carbonitrile (**53)** from 4-hydrazino pyrimidine **52** and trimethyl orthoformate by heating under reflux was reported[14].

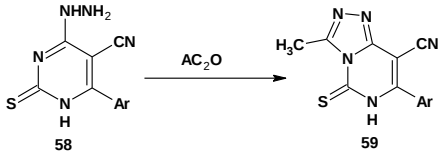
In 2012, Omar *et al*,[29] reported cyclocondensation of hydrazinyl derivative **54** with acetyl acetone in refluxing DMF for preparation of 6-(3,4-dimethoxyphenyl)-4-(3,5-dimethyl-*1H*-pyrazol-1-yl)-2-thioxo-1,2-dihydro-pyrimidine-5-carbonitrile (**55)**.



Magdy and associates[16] reported the synthesis of 1,3,4,6-tetrahydro-3,4,6- trioxo-*2H*-pyrimido [2,1-*c*]-[1,2,4] triazine-7-carbonitrile (**57)** via cyclocondensation of hydrazino pyrimidine derivative **56** with diethyloxalate in absolute ethanol.

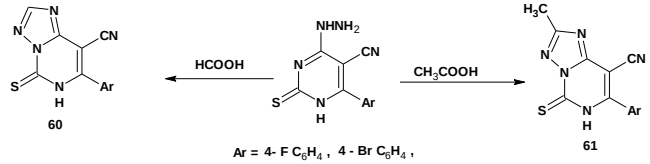


In 2013, Mosaad *et al*.[38] presented that the 4-hydrazinopyrimidine derivatives **58** has also been used as key starting material for the preparation of triazolopyrimidines **59** by the reaction with acetic anhydride.



Ar =3,4,5(OCH3)3C6H2 , 4-FC6H4 , 4-Br C6H4 ,3 -Indolyl

Triazolo[1,5-*c*]-pyrimidine **60** and 2-methyl triazolo[1,5-*c*]-pyrimidine **61** were prepared via the reaction of hydrazino derivatives with formic acid or acetic acid. This reaction was reported [38,18] by Mosaad *et al* in 2013 and 2014.

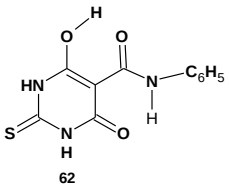


Ar = 4- F C6H4 , 4 - Br C6H4 , 3,4,5 (OCH3)3 C6H2, 3-indolyl

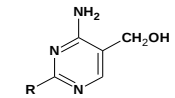
3. Biological significance of 2-thiouracils and fused thiouracils

3.1. Anti-cancer activity

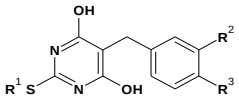
Merbarone® **62**, a topoisomerase II inhibitor acting on the catalytic site, active against both fast and slow growing cancers. Merbarone®, showed antitumor activity[39] against the murine L1210 leukemia model as well as against B16 melanoma and M5076 sarcoma22 (optimum dose range 50-100 mg/kg).



A series of 2-S-substituted thiouracil derivatives has been reoported for antitumer activity[40-42]. For example, methioprim **63**, ethioprim **64** and benzylthioprim **65** and **66**.

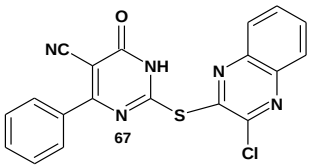


63: R=CH3S
64: R=C2H5S
65: R=C6H5CH2S

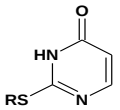


R1 = 4 -CH2C6H4OCH3 , 4 -CH2C6H4O-CH(CH3)2CH2 , CH2C(CH3)=CH2 , CH2C6H3(3-CH3-4-OC3H7-iso)
R2 =H,CH3
R3 = H,OCH(CH3)2

Thiouracil quinoxaline hybrids **67** demonstrated chemopreventive effect[44] against carcinogenesis on Raji cells.

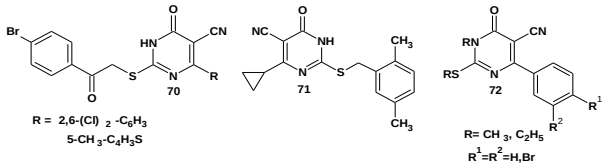


2-S-alkylated thiouracil **68** selectively exhibited cytotoxic activity against murine leukemia cell line (P388cell) and 1-adamantylthiopyrimidine **69** displayed cytotoxic activity [4] against many cell lines. Significant activity of **69** was observed against multidrug-resistant small cell lung cancer cell line (H69AR) with the IC_{50} of 35.0 mg/mL, whereas the control drug; etoposide showing the IC_{50} of 30.0 mg/mL.

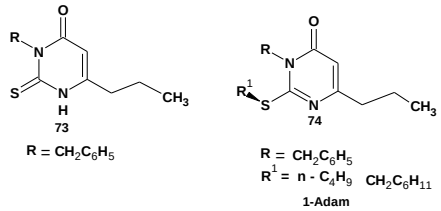


68 : R=CH2C6H5
69 : R=1- Adam

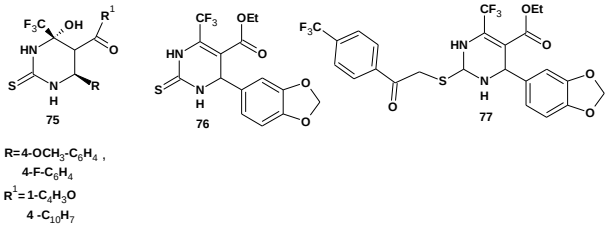
Functionalized S-alkylated 6-aryl-5-cyano-2-thiouracils **70** displayed potent growth inhibitory effect [44] toward non-small cell lung cancer (HOP-92) and leukemia (MOLT-4) cell lines, respectively. Compound **71** may possess specific biological properties[45], including potent antagonist of Epac protein at therapeutic target of cancer and **72** displayed promising anticancer activity [28] against leukaemia, non-small cell lung, melanoma, and renal cancer.



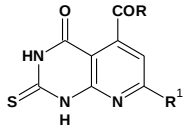
6-Propylthiouracils **73, 74** are novel cytotoxic agents [46], the adamantly derivative is the most potent cytotoxic against multi drug-resistant small cell lung cancer cell line (H69AR).



A series of trifluoromethylated-2-thioxopyrimidines **75-77** were synthesized and They showed highly potent and selective anticancer activity[31] against colon cancer cell line (COLO 320 HSR).



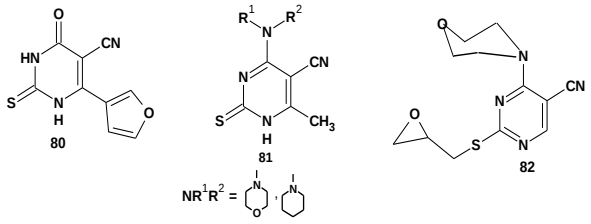
7-Phenyl-5-(thiophene-2-carbonyl)-2-thioxo-2,3-dihydro-1H-pyrido [2,3-*d*] pyrimidin-4-one (**78)** and ethyl 7-(4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate (**79)** showed moderate activity [47] against lung carcinoma cell line (H460).



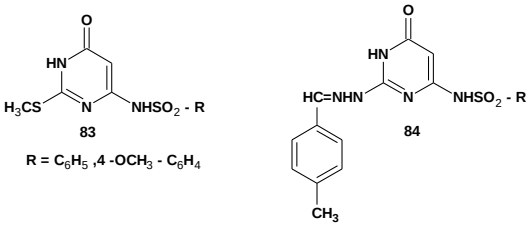
78 : R= 2 -C4H3S ,R1 = C6H5

79 : R= OC2H5 ,R1 = 4 -OCH3 -C6H4

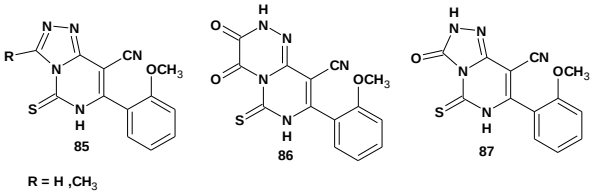
Some novel 2-thiouracil-5-carbonitrile derivatives **80-82** showed promising anticancer activity[5] against many cell lines. Compound **80** exhibited potential growth inhibition activity against most of the tested subpanel tumor cell lines. It showed promising activity toward several cell lines of Non-Small Cell Lung cancer (EKVX, HOP-62, HOP-92, NCI-H23, and NCI-H322M).



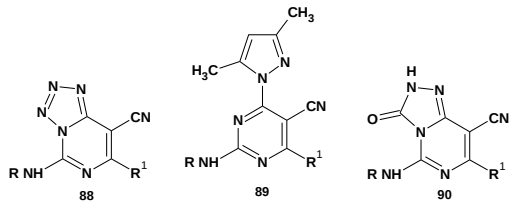
Thiouracil derivatives **83, 84** revealed antiproliferative activity[13] against human colon (HT-29) and breast (MCF-7) cell lines.



The fused 5-cyano-2-thiouracil derivatives **85-87** induced a significant growth inhibition[14] towards liver cancer (HEPG2) cell line in comparison to 5-flurouracil after treatment with IC_{50} values (ranged from 3.74 to 8.48 µg/ml concentrations) for each compound while the IC_{50} value for 5-flurouracil was 5µg/ml concentration.

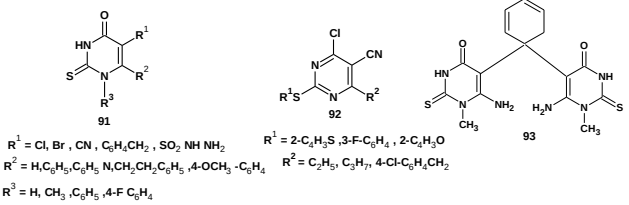


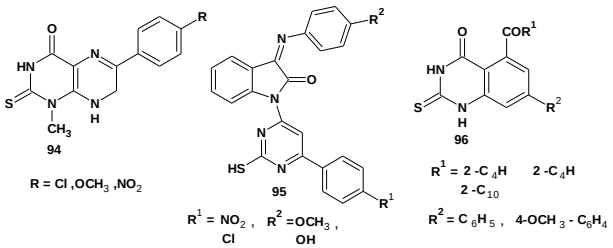
A novel series of 5-cyano-2-thiouracil derivatives **88-90** were designed as potential cyclic-dependant kinase 2 inhibitors [29] (CDK2) against human cervix carcinoma (Hela cell lines**)**.



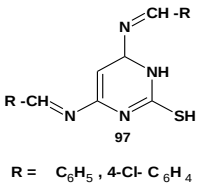
3.2. Anti-microbial activity

In various communication articles [10,47-52], thiouracils having formula **(91-96)** were reported to be useful as anti- infective agents as antibacterial and antifungal.

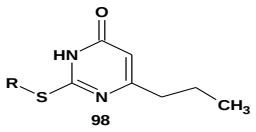




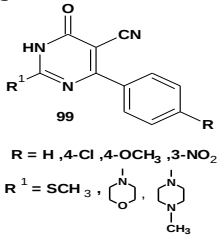
Thiouracil derivatives,4,6-bis-(benzyldidene-amino)-1,3,4-tri-hydropyrimidine-2-thiones **(97)**, revealed promising antimicrobial activity[53].



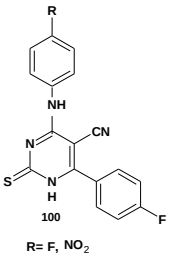
It is demonstrated that the thiouracil analogs **98** is a novel antibacterial. It exerts potent activity [46] against *B.catarrhalis* with MIC of 32 µg/mL.



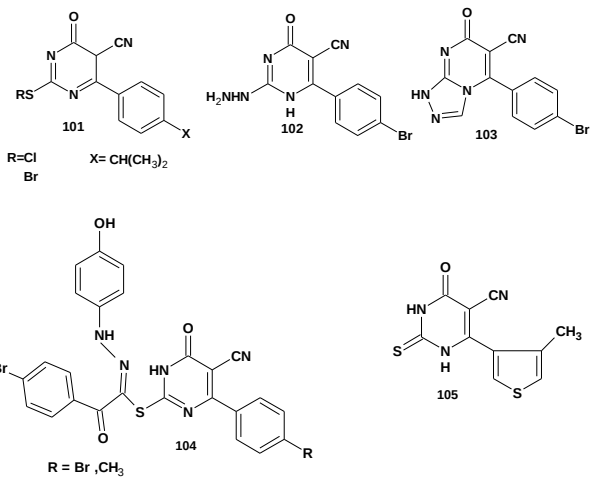
A series of 6-aryl-5-cyano-2-thiouacils **99** exhibited moderate antibacterial activity [3] against *Staphylococcus aureus* and *Bacillus subtilis* and significant antifungal activity against *Candida albicans* and *Asperigillus niger*.



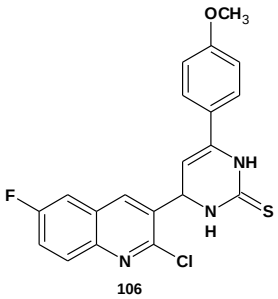
Thiouracil derivatives **100** were found to be potent [27] against *Mycobacterium tuberculosis*.



Thiouracil derivatives **101** showed significant activity against *staphylococcus aureus*, while compounds**102, 103** displayed moderate inhibitory activity [28] against *Candida albicans*. Moreover, compounds **104** possessed superior antibacterial activity against the gram positive bacteria *S.aureus* and *B.subtilis* compared to the reference drug Amoxicillin. Moreover, compound **105** was found to be broad spectrum antimicrobial agent[44] and it also exhibit promising antifungal activity against *C.albicans*.

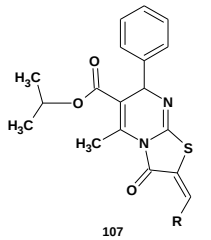


4-(2-Chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-3,4-dihydropyimidine-2(1*H*)-thione **(106)** has a significant antibacterial activity [54] against *S.aureus*, *Klebsiella aerogenes* and *Proteus microbialis*.



Isopropyl2-(4-substitutedbenzylidene)-5-methyl-3-oxo-7-phenyl-3,7-diydro-2*H*-thiazolo[3,2-*a*]-

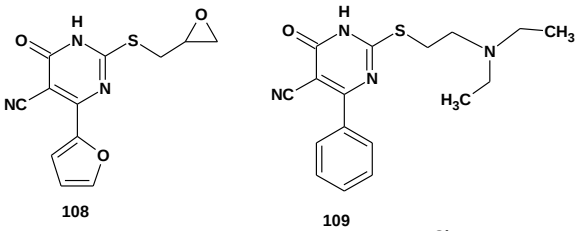
pyrimidine-6-carboxylate derivatives **107** showed potent antimicrobial activity [33] against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, *Penicillium marneffei* and *Trichophyton mentagrophytes*.



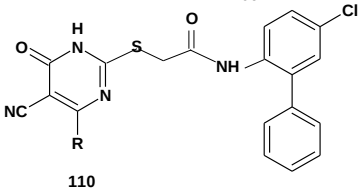
107

R = C_6H_4 ,4-Br-C_6H_4 ,4-NO_2-C_6H_4
4-OCH_3 -C_6H_4 ,4- $N(CH_3)_2$ -C_6H_4

Novel 2-thiouracil-5-carbonitrile derivatives **108-110** showed broad spectrum antimicrobial activity [6] against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Shigella flexneri* and *Candida albicans*.

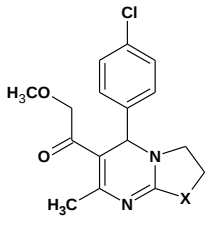


108 109



110

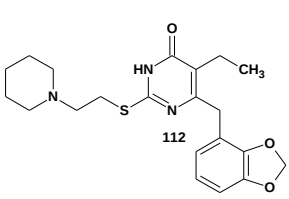
Thiouracil derivatives **111** were found to have significant antimicrobial activity[55] against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and antifungal *Aspergillus niger* and *Candida albicans* comparable to the standard drugs Ciprofloxacin and Fluconazole.



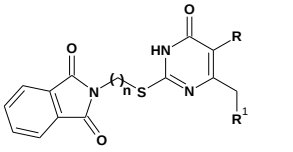
111

X = N ,S

Thiopyrimidine **112** showed promising antimicrobial activity towards *B. subtilis*, *C. albicans*, and *A. niger*, while compounds **113** and **114** were found active against *A.niger* and *B.cereus*, respectively. Compound **115** (MIC value = 0.0524 µmol/cm3) exhibited an interesting antimicrobial profile with dual antibacterial (against *S. aureus*) and antifungal (against *C. albicans*) effects [56].

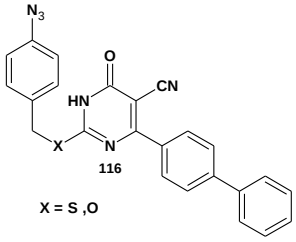


112



113 : R=CH_3, R^1 =3,4 - $(OCH_3)_2$, n = 2
114 : R=CH_3 , R^1=$C_7H_5O_2$, n = 3
115 : R =CH_2CH_3 , R^1=$C_7H_5O_2$, n = 3

4-Oxo-5-cyano thiouracils **116** showed good antimicrobial activity [57] against *Escherichia coli* mutant strain, NR698 and evaluated as SecA inhibitors. Protein translocation is essential for bacterial survival and the most important translocation mechanism is the secretion (Sec) pathway in which Sec A is a central core driving force. Thus targeting Sec A is a promising strategy for developing novel antibacterial therapeutics.

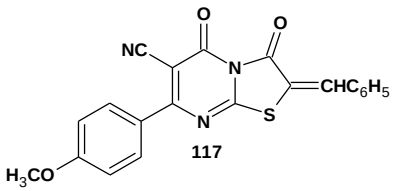


116

X = S ,O

3.3 Molluscicidal activity

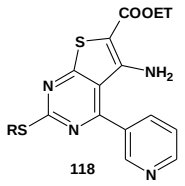
Fused thiouracil **117** posses significant molluscicidal activity [37] towards *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni*.



117

3.4. Anti-leishmanial activity

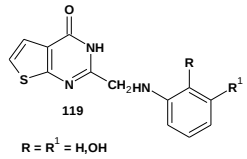
3-Amino-2-carboethoxy-6-substitutedthio-4-(3-pyridyl) thieno [2,3-*d*] pyrimidines **(118)** found to have a significant antileishmanial activity[58] against *L.donovani promastigotes*.



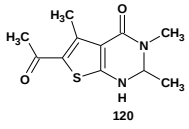
R = CH_3 ,C_2H_5 ,CH_2=CH_2
$C_6H_5CH_2$, 4-OCH_3 -$C_6H_4CH_2$

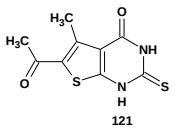
3.5. Antioxidant activity.

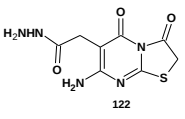
The antioxidant activity of fused thiouracil derivatives was reported. Compound **119** showed good antioxidant activity[59] (DPPH Scavenging method) compared to BHT (Butylated Hydroxy Toluene) as reference, IC_{50}=234,184,132; respectively. The significant antioxidant activity [60,61] of compounds **120-124** were reported because they protect DNA from damage.

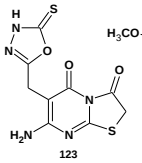


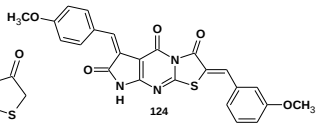
R = R^1 = H,OH



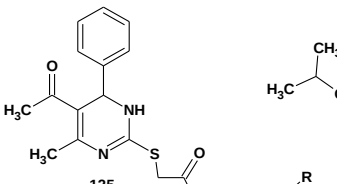




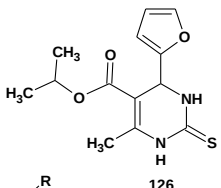




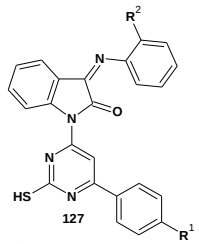
A series of 2-dihydropyrimidine-2(1H)-thiones **125** proved to have significant antioxidant activities compared to ascorbic acid [62]. Compound **126** showed promising antioxidant activity [63].



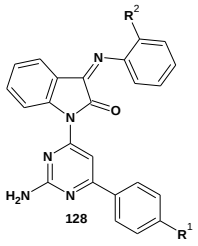
R = 4-Cl,3-Br ,4-Br ,3-NO_2 ,4-NO_2



A series of novel 1-(2-mercapto-6-(substituted phenyl) pyrimidine-4-yl)-3-(2-substituted phenyl imino) indolin-2-ones (**127)** and 1-(2 amino-6-(substituted phenyl)pyrimidine-4-yl)-3-(2-substituted phenyl imino) indolin-2-ones (**128)** were synthesized and showed more promising antioxidant activity [53] in comparison to standard, butylated hydroxy toluene.

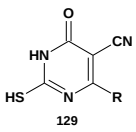


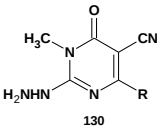
R^1= OH, OCH_3
R^2 = NO_2 , Cl



R^1 = OCH_3
R^2 = NO_2, Cl

Thiouracil derivatives **129** and **130** have shown more promising antioxidant activity [64] as compared to standard, ascorbic acid.

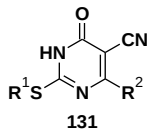




R = C_6H_5 , 3-OCH_3 -C_6H_4 , 2,3,4 - $(OCH_3)_3$ -C_6H_2

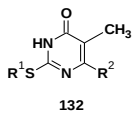
3.6. Anti-viral activity

A series of 5-cyano-2-thiouracil derivatives **131** was synthesized by Ram *etal* and reported as antiviral [26] against herpes simplex.

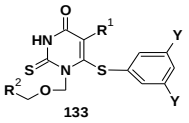


R^1 = C_2H , $C_6H_5CH_2$, n - C_4H_9
R^2 = 4-Cl -C_6H_5 , 4-$(CH_3)_2NC_6H_4$,
2 - Thienyl

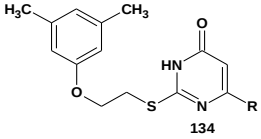
The reverse transcriptase (RT) of human immunodeficiency Type 1(HIV-1RT) is one of the main targets for drugs used in the treatment of AIDS, several RT inhibitors have been developed and approved by food and drug administration organization (FDA) . A series of 5-substituted-2- thiouracils of general formula **132-135** was reported as HIV-1 inhibitor [65-67].



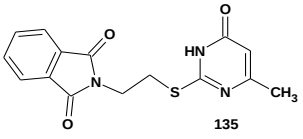
R^1 = 2,4-F-C_6H_4 , 4 -Cl -C_6H_4
4 -OCH_3- C_6H_4, C_6H_5
R^2 = 2,6-F-$CH_2C_6H_4$



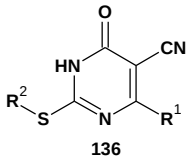
R^1 =C_2H_5 , i-propyl
R^2 = CH_3 , CH_2OH ,C_6H_5
Y = H ,CH_3



R = $CH_2C_6H_4$,CH_2(2,6 -$F_2C_6H_3$)



A series of 5-cyano-6-aryl-2-thiouracil derivatives **136** showed antiviral activity[17,68] against hepatitis C viral NS5B RNA-dependant RNA polymerase (anti-HCV). It's noteworthy to mention here that this is the same mechanism as the famous new Sovaldi drug.

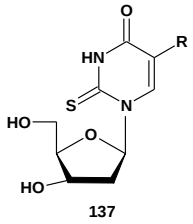


136

R^1 = 4- Br C_6H_4 , 2,4- F- C_6H_3 , 2,4 -Cl-C_6H_3 , 2- CH_3 - C_6H_3 , 4-BrC_6H_4, 2,4 -F-C_6H_4

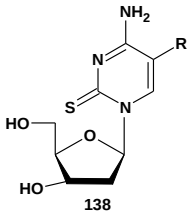
R^2 = 3 -NO_2 - $C_6H_4CH_2$, 3,5 -OCH_3- $C_6H_3CH_2$, 3 - CH_3 - $C_6H_4CH_2$, 2- Br - $C_6H_4CH_2$, $CH_3(CH_2)_4$, 2 -Br -C_6H_4

A series of 2-thiouracil nucleosides **137,138** showed potent and selective antiviral activities [69,70] against herpes simplex virus (HSV), varicella-zoster virus (VZV) and human cytomegalovirus (HCMV).



137

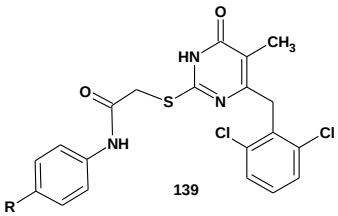
R = CH_3 ,I,$CH_2CH_2CH_3$



138

R = I , CH_2CH_3 ,CH_2CH_2CH

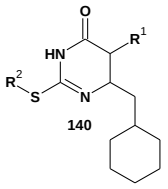
A series of novel 2-(phenylaminocarbonyl methylthio)-6-(2,6-dichlorobenzyl)-pyrimidin-4(*3H*)-ones **139** have been evaluated for their anti-HIV activities [71] and showed promising activities against wild-type HIV-1. Among them, the most potent HIV-1 inhibitor was 4-bromophenyl derivative (EC_{50} = 0.18 ± 0.06lM), which was more effective than the reference drugs Nevirapine and Efavirenz.



139

R = Cl ,Br ,NO_2 ,3 -F ,4 -F

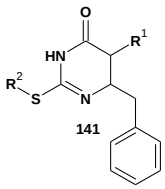
A novel dihydro-aryl/alkylsulfanyl-cyclohexylmethyl-oxopyrimidines (S-DACOs) **140**, **141** were evaluated with C8166 cells infected by the HIV-1IIIB *in vitro*, using Nevirapine (NVP) and Zidovudine (AZT) as positive control and showed potent anti-HIV activities [34,72].



140

R^1 = $CH(CH_3)_2$ - , CH_2CH_3

R^2 = (4 - OCH_3)C_6H_4 $COCH_2$, $C_6H_4COCH_2$, $C_6H_4CH_2$, $C_6H_4COCH_2$



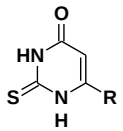
141

R^1 = I , Br

R^2 = $C_6H_5CH_2$, $C_6H_5CH_2$ CH_2 , $C_6H_5CH_2CH_2$, $(OCH_3)C_6H_4CH_2$

3.7. Anti-thyroid agents

2-Thiouracil derivatives are useful clinically as antithyroids. A huge number of compounds structurally related to 2-thiouracil have been evaluated for antithyroid activity but probably the most widely used compounds for the treatment of hyperthyroidism [73] are 6-propyl-2-thiouracil (**142)** and 6-methyl-2-thiouracil (**143)**.



	R
142	- CH_2CH_2 CH_3
143	- CH_3

Conflict of Interest: The authors declare that they don't have any conflict of interest.

REFERENCES

1. Wheeler, H. L.; Liddle, L. M. Researches on pyrimidines: synthesis of uracol-3-acetic acid. *J. Amer. Chem. Soc.* **1908**, *40*, 358-550.
2. Cassis, P.; Tapia, R and Volderrama, J. A. New synthesis of uracil and 2-thiouracil. *Synth. Commun.* **1984,** *14* (10), 961-965.
3. Basavaraja, H. S.; Jayadevaiah, K. V.; Mumtaz, M.H.; Vijay, K. M.; Basavaraj, P. Synthesis of novel piperazine and morpholine linked substituted pyrimidine derivatives as antimicrobial agents. *J. Pharm. Sci. Res*. **2010**, *2* (1), 5-12.
4. Supaluk, P.; Apilak, W.; Chanin, N.; Maneekarn, C.; Nirun, S.; Somsak, R.; Virapong, P. Synthesis and structure reactivity relationship of 2-thiopyrimidine-4-one analogs as antimicrobial and anticancer agents. *Eur.J. Med. Chem*. **2011**, *46*, 738-742.
5. Fadi, M. A.; Gary, A. P.; Bernard, D. G.; Adam, B. K.; Joshua, C. C. Synthesis of some dihydropyrimidine-based compounds bearing-pyrazoline moiety and evaluation of their antiproliferative activity. *Eur. J. Med. Chem*. **2013**, *70*, 273-279.

6. Ahmed, M. F, Nargues, S. H.; Khadiga, A. I.; Ahmed, M. M. H.; Marwa, T. M. S. Synthesis, biological evaluation and molecular docking studies of some pyrimidine derivatives. *Eur. J. Med. Chem*. **2013**, *66*, 276- 295.
7. Dong, C.; Zhi-Hua, Z.; Yu, C.; Xin-Jia, Y.; Shi-Ti, Z.; Liang-Jing, Z.; Li-Hong, M.; Fang, L.; Bing-Jie ,F. Synthesis of some new thiazolo[3,2-a]pyrimidine derivatives and screening of their *invitro* antibacterial and antitubercular activities. *Med. Chem. Res.* **2016**, *25*, 292-302.
8. Makaram, M. S.; Azza, T. T.; Hala, B. E.; Eman, A. E. Synthesis of novel S -acyl and S-alkylpyrimidinone derivatives as potential cytotoxic agents. *Res. Chem. Intermed.* **2016**, doi: 10.1007/s11164-016-2487-x.
9. Daniela, C.; Konstantin, C.; Stefano, G.; LanZ, W.; Bernard, T. G.; Cline, C.; Roberta, F. Synthesis and biological evaluation of N^2-Substituted 2,4-diamino-6-cyclohexyl methoxy-5-nitrosopyrimidines and related 5-cyano-NNO-azoxy derivatives as Cyclin-Dependent Kinase2(CDK2) Inhibitors. *Chem. Med. Chem*. **2016,** *11*, 1705-1708.
10. Agarwal, N.; Sirvastava, P.; Raghuwanshi, K.; Upadhyay, D. N.; Siha, S.; Shukla, P. K.; Vishnu, J.R. Chloropyrimidines as new class of antimicrobial agents. *Bioorg. Med. Chem*. **2002**, 10, 869-874.
11. Kuppast, B.; Katerina, S.; George, L.; Hesham, F. Synthesis of substituted pyrimi-dines as corticotropin releasing factor (CRF) receptor ligands. *Eur. J. Med. Chem*, **2014**, *78*, 1-9.
12. Shuang-Xi, G.; Yuan-Yuan, Z.; Fen-Er, C.; Erik, D.C.; Jan, B.; Christophe, P. Structural modification of diarylpyrimidine derivatives as HIV-1 reverse transcriptase inhibitors. *Med.Chem.Res*. **2015**, *24*, 220-225.
13. Mosaad, S. M.; Samir, M. A.; Omar, A.F.; Wietrzyk, J.; Milczarek, M.; Soliman, A. M. Synthesis of new pyrimidine derivatives and their antiproliferative activity against selected human cancer cell lines. *Res. Chem. Intermed.* **2015**, *41*, 1789-1801.
14. Omar, A. F.; Zeid, I.F.; Haiba, M.E.; Soliman, A.M.; Abd-Elmoez, S.I.; El-Serwy, W. S. Synthesis, antibacterial and anticancer evaluation of some pyrimidine derivatives. *World. J. Chem.* **2009**, *4* (2), 127-132.
15. Mosaad, S. M.; Samir, M. A.; Naglaa, M. A. Synthesis and antimicrobial evaluation of some 6-aryl-5-cyano-2-thiouracil derivatives. *Acta. Pharm.* **2011**, *61*, 171-185.
16. Magdy, E.; Somia, S.A.; Mogeda, E.H.; Mohamed, A. K. Synthesis, antitumor activity and molecular docking study of novel benzofuran-2-yl pyrazole pyrimidine derivatives. *Acta Poloniae Pharmaceutic (Drug Research)*. **2011** ,*68* (3), 357-373.
17. Ding, Y.; Girardet, J.; Smith, K. L.; Larson, G.; Prigaro, B.; Wu, J. Z.; Yao, N. Parallel synthesis of 5-cyano-6-aryl-2-thiouracil derivatives as inhibitors for hepatitis C viral NS5B RNA-dependent RNA polymerase. *Bioorg. Chem*. **2006**, *34*, 26-38.
18. Mosaad, S. M.; Mahmoud, M.Y.; Naglaa, M. A. Novel indolyl-pyrimidine derivatives: synthesis, antimicrobial and antioxidant evaluations. *Med. Chem. Res*. **2014**, doi: 10.1007/s00044-014-0916-1.
19. Ballard, E.; Johnson, T.B. Synthesis of derivatives of pyrmidine-5-carboxylic acid. *J. Amer. Chem. Soc*. **1942**, *64*, 794-798.
20. Fissekis, J. D.; Myles, A.; Brown, G.B. Synthesis of 5-hydroxyalkylpyrimdines from lactones. *J. Org. Chem* .**1964**, *29*, 2670-2675.
21. Omar, A. F.; Wafaa, M..; Hisham, H.R.; Samir, M. A.; Mosaad. S. M. Synthesis of new 2-thiouracil-5-sulfonamide derivatives with biological activity. *Arch. Pharm. Res*. **2002**, *25* (3), 258- 269.
22. Whitehead, C. W., Traverso, J. Synthesis of 2-thiocytosines and thiouracils. *J. Amer. Chem. Soc*. **1956**, *78*, 52-94.
23. Maurizio, B.; Occhionero, F.; Nicoletti,R.; Mastro-marino,P.; Saladino, R. Synthesis and biological evaluation of 2-methoy- and 2-methylthio-6-{(2-alkylamino)ethyl]-4-(3H)-pyrimidinones with anti-rubella virus activity .*J. Bioorg. Med. Chem* .**1999**, *7* (9), 1925-1931.
24. Mosaad, S. M.; Samir, M. A.; Amira, I. S. Synthesis of certain pyrimidine derivatives as antimicrobial agents and anti-inflammatory agents. *Molecules*.**2010**, *15*, 1882-1890.
25. Antonello, M.; Marino, A.; Gianluca, S.; Silvana, Q.; Silivio, M.; Antonella, D.M.; Franca, S.; Monica, P. L.C. Dihydro(alkylthio)(naphthylmethyl)oxo-pyrimidines: novel non-nucleoside reverse transcriptase inhibitors of the S-DABO series. *J. Med. Chem.***1997,** *40*, 1447-1454.
26. Ram, V. J.; Vanden, B. D. A.; Vlietinck, A.J. Syntheses and activities of novel pyrimidines derived from 5-cyano-6-aryl2-thiouracil. *Liebigs. Ann. Chem*. **1987**, *5*, 797-801.
27. Chitre, T. S.; Bothara, K. G.; Patil, S.M.; Asgaonkar, K. D.; Nagappa, S.; Kathiravan, M. K. Design, Synthesis, Docking and Anti-mycobacterial activity of some novel thiouracil derivatives as thymidine monophoshate kinase (TMPKmt) inhibitors. *Inter. J. Res. Pharm. Biomed. Sci*. **2011**, *2* (2), 616-623.
28. Azza, T. T.; Amira, A. H. Novel pyrimidinone derivatives: synthesis, antitumor and antimicrobial evaluation. Chem. Pharm. Bull.2012, 60 (4), 521-530.
29. Omar, A.F.; Mohamed, A. H. I.; Manal, M. A.; Khaled, A.M. A.; Aisha, A. K. R. Novel 2-thiopyrimidine derivatives as CDK2 inhibitors: molecular modeling, synthesis, and anti-tumor

activity evaluation. *Med. Chem. Res*. **2012**, doi: 10.1007/s00044-012-0051-9.
30. Alessandro, S.; Kristein, V. B.; Steven, D. J.; Thierry, L.; Jean, H.; Jef, R.; Mark, W.; Piet, H. Synthesis of a 2,4,6-trisubstituted 5-cyano-pyrimidine library and evaluation of its immunosuppressive activity in a mixed lymphocyte reaction assay. *Bioorg. Med. Chem*. **2013**, *21* (5), 1209-1218.
31. Oluropo, C.A.; Olugbeminiyi, O. F.; Adamson, S.F.; Lewis, E.M.; Cosmas, O. O. Synthesis and in vitro cytotoxicity evaluation of some fluorinated hexahydropyrimidine derivatives. *Bioorg. Med. Chem. Lett*, **2011**, *21*, 989-992.
32. Chitra, S.; Devanathan, D.; Pandiarajan, K. Synthesis and in vitro microbiological evaluation of novel4-aryl-5-isopropoxycarbonyl-6-methyl-3,4-dihydropyrimidinones. *Eur. J. Med. Chem*. **2010**, *45*, 367-371.
33. Kotaiah, Y.; Hari, K. N.; Naga, R. K.; Rao, C.V.; Jonnalagadda, S. B.; Maddila, S. Synthesis and biological evaluation of novel isopropyl 2-thiazolopyrimidine-6-carboxylate derivatives. *J. Korean Chem. Soc*. **2012**, *56* (1), 68-73.
34. Yan-Ping, H.; Jin, L.; Shui-Shuan, Z.; Cong, L.; Christopher, C. L.; Chun-Sheng, Z.; Da-Xiong, L.; De-Hua, Z.; Hua, W.; Qing-Qing, C.; Yong-Tang, Z. Synthesis and biological evaluation of novel dihydro-aryl/alkylsulfanyl-cyclohexylmethyl-oxopyrimidines (S-DACOs) as high active anti-HIV agents. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 694-697.
35. Mosaad, S. M.; Samir, M. A.; Yasser, M.Z.; Zainab, M. New theopyrimidine derivatives of expected anti-inflammatory. Pharmacophore. 2012, 3 (1), 62-75.
36. Mosaad, S. M.; Waleed, M.H.; Samar, S.F.; Zainab, M.M.; Ross, P.M.; Gerhard, S.; David, L. O. Synthesis and kinetic testing of tetrahydropyrimidine-2-thione and pyrrole derivatives as inhibitors of the metallo-b-lactamase from klebsiella pneumonia and pseudomonas aeruginosa. *Chem .Biol .Drug .Des*. **2012**, *80*, 500-515.
37. Mohamed, A.; Mohamed, A.; Magdy, S.; Kamelia, E.; Mortta, E. A convenient synthesis of some new bioactive diheterocylic thioether and thiazolopyrimidine derivatives. *Acta. Chim. Slov.* **2009**, *56*, 852-859.
38. Mosaad, S. M.; Mahmoud, M.Y.; Naglaa, M. A. Synthesis, antimicrobial, antioxidant activities of novel 6-aryl-5-cyanothiouracil derivatives. *Eur. J. Med. Chem.* **2013**, 69, 591-600.
39. Angelo, R.; Andre, S.; Silvia, S.; Olga, B.; Francesco, B.; Alessandra, P.; Maria, E.M.; Valeria, M.; Paolo, L. C.; Roberta. L. Synthesis and antiproliferative activity of basic thioanalogues of merbarone. *Bioorg. Med. Chem*. **2003**, *11*, 2575-589.
40. James, F.H.; Robert, G.; Paul, S.; Howard, T. Inhibition of Tumor Growth in Mice by a Series of 2-Substituted Thiopyrimidines. *Cancer Res*. **1958**, *18*, 776-780.
41. Grigoryan, L.A.; Kaldrikyan, M.A.; Melik-Ogandzhanyan, R.G.; Arsenyan, F.G. Synthesis and antitumor activity of new 2-thio and 2-amino-substituted pyrimidines. *J. Pharm. Che*m. **2011**, *5* (3), 137-140.
42. Grigoryan, L. A.; Kaldrikyan, M.A.; Melik-Ogandzhanyan, R.G.; Arsenyan, F.G.; Stepanyan ,G. M.; Garibdzhanyan, B. G. Synthesis and antitumor activity of 2-S- substituted pyrimidine derivatives. *J. Pharm. Chem.* **2005**, *39* (9), 468 -47.
43. Galal, S.A.; Abdelsamie, A.S.; Tokuda, H.; Suzuki, N.; Lida, A.; El-Hefnawi, M. M .; Ramadan, R.A.; Atta, M.H.E .; El Diwani, H.I. Synthesis, cancer chemopreventive activity and molecular docking study of novel quinoxaline derivatives. *Eur. J.Med. Chem*. **2011**, *46*, 327-340.
44. Azza, T. T.; Sahar, M. A. Synthesis and bioactivity evaluation of new 6-aryl-5-cyano thiouracils as potential antimicrobial and anticancer agents. *Molecules* **2012**, 17, 9868-9886.
45. Chen, H.; Tsalkova, T.; Mei, F.C.; Hu, Y.; Cheng, X.; Zhou, J. 5-Cyano-6-oxo-1,6- dihydro-pyrimidines as potent antagonists targeting exchange proteins directly activated by c.AMP. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4038- 4043.
46. Supaluk, P.; Nirun, S.; Ratchanok, P.; Supin, T.; Somsak, R. Virapong, P. Synthesis and Novel Bioactivities of Substituted 6-Propylthiouracils. *Eur. J. Sci. Res.* **2009**, *36* (2), 236-245.
47. Nadia, R.M.; Manal, M.T.; Yasser, M. A .; Mohamed ,H.E .Utility of 6-amino-2-thiouracil as a precursor for the synthesis of bioactive pyrimidine derivatives. *Bioorg. Med. Chem*. **2007**, *15*, 6227-623
48. Omar, A.F.; Samir, M.A.; Mosaad, S. M. Synthesis of new 2-thiouracil-5-sulphonamide derivatives with antibacterial and antifungal activity. *Arch. Pharm. Res.* **2005**. 28, 1205 - 1212.
49. Shaker. Y.; Sahera, F. M. 6-Amino-2-thio- and 6-Aminouracils as Precursors for the Synthesis of antiviral and antimicrobial methylene bis (2-thiouracils), tricyclic pyrimidines, and 6-alkylthiopurine-2-ones. *Monatsh.fur.Chemie*. **2008**, *139*, 161-168.
50. Yogesh, P.; Gaurav, P.; Ijaj, T.; Vaibhav, C.; Kirt, K.; Shital, N.; Bhanudas, K. Microwave assisted synthesis of new N1-substituted 5-cyano-pyrimidine derivatives as potent antimicrobial agents, *J. Korean Chem. Soc*. **2008**, *52* (1), 30-35.
51. Shaker Y.; Fatmah, A.; Sahera, F.M. Syntheis, antiviral and antimicrobial activities of new substituted thioxanthines and thiolumazines .*J. Appl. Sci. Res*. **2009**, 5 (11), 844-1852.

52. Prasenjit, M.; Soma, J; Lakshmi, K. K. Syntheis of novel mercapto-pyrimidine and amino-pyrimidine of indoline-2-one as potential antioxidant & antibacterial agents. *Pharma. Res*. **2010**, *3*, 17-26.
53. Hayam, H.S.; Ahmed, .H.S.; Aymn, E.R. Synthesis and biological evaluation of some pyrimidine, pyrimido 2,1- b 1,3 thiazine and thiazolo 3,2- a pyrimidine derivatives , *Acta Pharm*. **2006**, *56* ,231-244.
54. Balujas, S.; Kacchadia, N.; Chanda, S. Thiopyrimidine derivatives: synthesis and antibacterial activity. *J. Pharm. Chem*. **2012**, *46* (2), 117-121.
55. Malik, N.; Priyanka, D.; Prabhakar, K.V.; Anurag, K. Design, synthesis, and biological evaluation of thiourea and guanidine derivatives of pyrimidine-6-carboxylate. *Res.Chem Intermed*.**2014**, doi: 10.1007/s11164-014-1871-79.
56. Attia, M. I.; Amany, L.K.; Nasser, R. E. Antimicrobial pyrimidinones II: synthesis and antimicrobial evaluation of certain novel 5,6-disubstituted 2-(substituted amino) alkylthio pyrimidin-4(3H)-ones. *Monatsh. Chem*. **2014**, *145*, 1825-1837.
57. Chaudhary, A. S.; Jinshan, J.; Weixuan, C.; Phang, C.; Tai, B. W. Design, syntheses and evaluation of 4-oxo-5-cyano thiouracils as Sec A inhibitors . *Bioorg. Med. Chem.* **2015**, *23* (1), 105-117.
58. Singh, D.N.; Verma, N.; Pathak, L.P. Synthesis and antileishmanial activity of some new substituted imidazolo [3, 2-c] pyrimidines and thieno [2, 3-d] pyrimidines. *J. Ind. Council Chem*.**2010**, *27* (2), 140-144.
59. Madhurani, R. B.; Narendra, S. C.; Nargund, L. V.G. Synthesis of 2, 3-disubstituted thieno (2, 3-d) pyrimidines for antibacterial and pharmacological activity. *Der.Pharma Chemica*. **2011**, *3* (4), 238-244.
60. Ameen, A. A.; Mohamed, M. Y.; Hoda, A. R. H. Synthesis, antioxidant, antitumor activities of some new thiazolo pyrimidines, pyrrolo thiazolo pyrimidines and triazolo pyrrolo thiazolo pyrimidines derivatives. *J. Chin. Chem. Soc* .**2011**, *58*, 41- 48.
61. Ameen, A.A.; Mohamed, F.E.; Farid, A.B. Design and synthesis of novel thiophenes carbohydrazide, thienopyrazole and thienopyrimidine derivatives as antioxidant and antitumor agents. *Acta Pharm*. **2010**, *60*, 311-323.
62. Rajasekaran, S.; Gopal, K.R.; Sanjay, P.P.N.; Alook, K. A. Design, Synthesis and Biological Activity of Substituted Dihydropyrimidine-2-(1H)-thiones. *Inter. J. Pharm. Tech. Res*. **2011**, *3* (2), 626-631.
63. Mansouri ,M.; Movahedian, A.; Rostami, M.; Fassihi, A. Synthesis and antioxidant evaluation of 4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate ester. *Res. Pharma. Sci*. **2012**, *7* (4), 257-264.
64. Bhalgat, C. M., Irfan, M.A.; Ramesh, B.; Ramu , G . Novel pyrimidine and its triazole fused derivatives: Synthesis and investigation of antioxidant and anti-inflammatory activity. *Arab. J. Ch*em .**2014**, *7*, 986-993.
65. Novikov, M. S.; Ozero, A.A.; Sim, O.G.; Buckheit, R.W. Synthesis and anti-HIV-1 activity of 2-[2-(3,5-dimethyphenoxy-ethylthio]pyrimidin-4(3H)-ones. *Chemistry of Heterocyclic Compounds* .**2004**, *40* (1), 37-42.
66. Navrotskii, M. B. Synthesis and anti-HIV-1 activity of new derivatives of 6-(arylmethyl)-2-[(Cyclohexylmethyl)-thio]-4(3H)-pyrimidinone and 6-(arylmethyl)-2- {[(methylthio)methyl]thio}-4(3H)-pyrimidinone . *Pharma. Chem. J*. **2004**, *38* (9), 480-482.
67. Claudi,M., Fabrizio,M .; Jose,A.; Imma,C.; Giovanni, M.; Reynel , C.; Maurizio, B,; Federico, C. Synthesis and biological investigation of S-aryl-S-DABO derivatives as HIV-1 inhibitors . *Bioorg. Med. Lett* .**2006**, *16*, 3541-3544.
68. Ramesh, L. S.; Ganesh, K. D.; Sanket, D. H.; Prashant, D. L. 3D-QSAR analysis of 5-cyano-6-aryl-2-thiouracil as inhibitors of Hepatitis C viral NS5B RNA–dependent RNA polymerase , *Der Pharma Chemica*, **2011**, *3* (2), 88-95.
69. Shigeta, S.; Mori, S.; Kira, T .; Takahashi, K.; Kodama, E.; Konno, K.; Nagata, T .; Kato, H.; Wakayama, T.; Koike, N .; Saneyoshi, M. Anti-herpes virus activities and cytotoxicity activity of 2-thiopyrimidine nucleoside analogues in vitro. *Antiviral Chemistry and Chemotherapy*.**1999**, *10*, 195-209.
70. Shigeta, S.; Mori, S.; Watanabe, F.; Takahashi, K.; Nagata, T.; Koike, N.; Wakayama, T.; Saneyoshi, M. Synthesis and antiherpes virus activities of 5-alkyl- 2-thiopyrimidine nucleoside analogues. *Antiviral Chemistry and Chemotherapy*. **2002**, *13*, 67-82.
71. Mingyan, Y.; Xinyon, L.; Zhenyu, L.; Shuai, L.; Christophe, P.; Erik, D. C. Synthesis and biological evaluation of novel 2-(substituted phenylamino-carbonylmethylthio)-6-(2,6-dichlorobenzyl)-pyrimidin-4(3H)-ones as potent HIV-1 NNRTIs. Bioorg. Med. Chem. **2009**, *17*, 7749-7754.
72. Hua, Q.; Chang, L.; Ying, G.; Ruiping, W.; Jianfang, Z.; Liying, M.; Zhili, Z.; Xiaowei, W.; Yuxin, C.; Junyi, L. Synthesis and biological evaluation of novel C5 halogen-functionalized S - as potent HIV-1 non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem*. **2010**, *18*, 3231-3237.
73. Jain, K. S.; Chitre, T. S.; Miniyar, P. B.; Kathiravan, M. K.; Bendre, V. S.; Veer, V. S.; Shahane, S. R.; Shishoo, C. J. Biological and medicinal significance of pyrimidines. *Current Science*. **2006**, *90* (6), 793-803.