RESEARCH OBJECTIVES

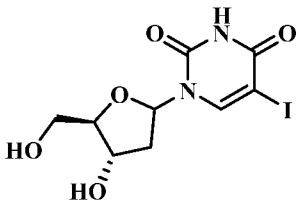
The development of new therapeutic agents is becoming the major interest in many academic and industrial research laboratories all over the world with the aim to discover new more potent chemotherapeutic agents, with higher specificity and reduced toxicity than the existing ones.

As shown in the introductory part, the thiourea moiety, either in open form or incorporated in heterocyclic ring systems, was found in many therapeutic agents. Several substituted thiourea derivatives proved to be effective against several pathogenic microorganisms and beneficial in improving various physiological disorders.

Pyrimidine derivatives have a great biological and medicinal significance. Their therapeutic efficacy is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis such as dihydrofolate reductase (DHFR), thymidylate synthetase (TS) and thymidine phosphorylase (TP).[83] Large array of pyrimidine derivatives possess a variety of pharmacological properties. These properties include anticancer,[21,84,85] antiviral,[86-88] antimicrobial,[89,90] and antiparasitic[91,92] activities.

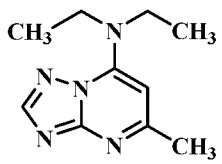
Literature survey revealed that many pyrimidine derivatives have gained clinical applications as flucytosine, idoxuridine and 5-fluorouracil (5-FU).[93]

5-FU: X=O
Flucytosine: X=NH



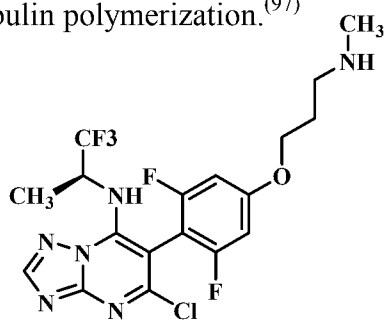
Idoxuridine

1,2,4-Triazolopyrimidine is one of the most important ring systems that has drawn the attention for its diverse biological activities.[94,95] For example, the triazolopyrimidine, trapidil acts as a platelet-derived growth factor antagonist.[96]



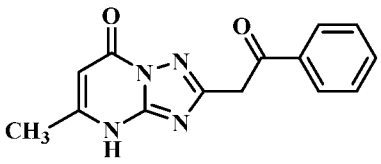
Trapidil

Furthermore, cevipabulin (TTI-237) and its analogues were proved to be potent anticancer agents that promote tubulin polymerization.[97]



Cevipabulin (TTI-237)

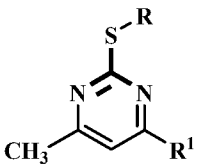
The new antibiotic essramycin, the first isolated 1,2,4-triazolo[1,5-*a*]pyrimidine natural product, was reported to exhibit broad-spectrum antibacterial properties.[98]



Essramycin

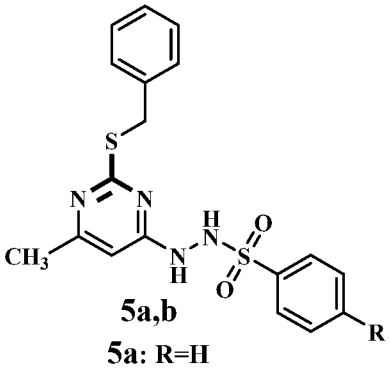
Enlightened by these findings, the objectives of the present investigation were directed towards the synthesis of various substituted pyrimidine and triazolopyrimidine derivatives linked to thiourea moiety.

A series of various substituted sulfanylpyrimidines was designed to incorporate thiourea moiety within the ring structures (**4-6, 13a-f, 16-18**). The substitution pattern was varied to include different functions in order to achieve SAR.



4: R = $-CH_2C_6H_5$, $R^1 = NHNH_2$

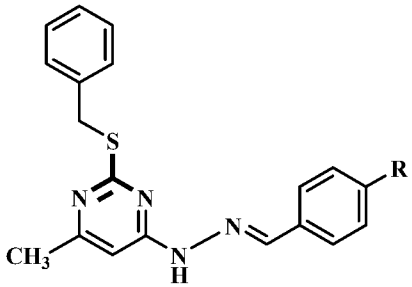
16: R = $-CH_2COC_6H_5$, R^1= Cl



5a,b

5a: R=H

5b: R=CH_3

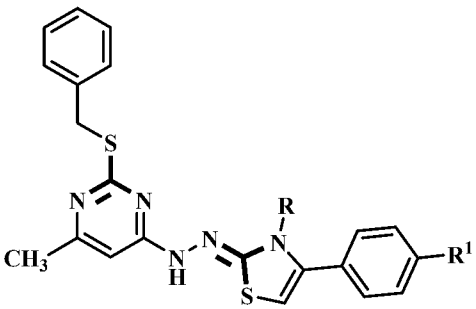


6a-c

6a: R=H

6b: R=Cl

6c: R=Br



13a-f

13a: R = CH_2-CH=CH_2, R^1 = H

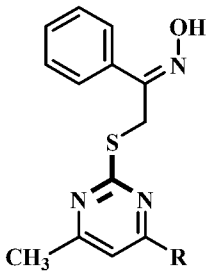
13b: R = CH_2-CH=CH_2, R^1 = Br

13c: R = CH_2-CH=CH_2, R^1 = CH_3

13d: R = C_6H_5, R^1 = H

13e: R = C_6H_5, R^1 = Br

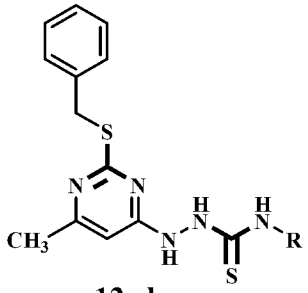
13f: R = C_6H_5, R^1 = CH_3



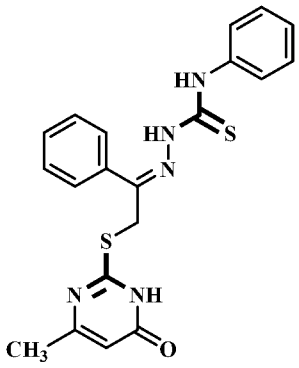
17: R= Cl

18: R= $NHNH_2$

Some compounds were also designed to incorporate sulfanylpyrimidine linked to thiourea moiety through various atoms spacer (**12**, **19**).



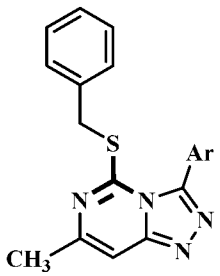
12a,b



19

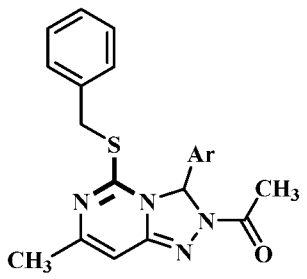
12a: R=CH_2-CH=CH_2
12b: R= C_6H_5

In addition, a series of substituted sulfanyltriazolopyrimidines (**7-11, 14**) were planned to be synthesized in order to investigate the effect of structural variation on the anticipated biological effect.



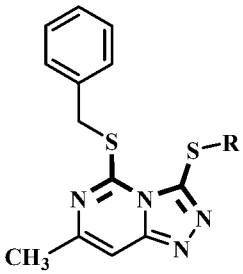
7a-c, 14

7a: Ar = C_6H_5
7b: Ar = 4-ClC_6H_4
7c: Ar = 4-BrC_6H_4
14: Ar = NH-C_6H_5



8a-c

8a: Ar=C_6H_5
8b: Ar=4-ClC_6H_4
8c: Ar=4-BrC_6H_4



9, 10a,b, 11

9: R =H
10a:R = CH_3
10b:R = $CH_2C_6H_5$
11: R = $CH_2COC_6H_5$