International Journal of Chemical Research and Development
www.chemicaljournal.in
Online ISSN: 2664-6560, Print ISSN: 2664-6552
Received: 30-05-2021; Accepted: 14-06-2021; Published: 29-06-2021
Volume 3, Issue 1, 2021, Page No. 20-25

Review on role of urea and thiourea derivatives of some heterocyclic Scaffold in drug design and medicinal chemistry

Shivakumara K N*, Sridhar B T
Assistant Professor, Department of Chemistry, Maharani Cluster University, Palace Road, Bangalore, Karnataka, India

DOI: https://doi.org/10.33545/26646552.2021.v3.i1a.23

Abstract
Compounds comprising urea and thiourea are progressively more used in drug design and medicinal chemistry to facilitate key drug-target communications and fine-tune crucial drug-like properties. Urea and thiourea represent privileged structures in medicinal chemistry. Certainly, these scaffolds encompass a common structure of a array of drugs and bioactive compounds artistic with a expansive range of beneficial and pharmacological properties. Herein, we provide an overview of urea and thiourea based medicinally important compounds, ranging from standard drugs to current medicinal chemistry developments.

Keywords: urea, thiourea, pharmacological activity

Introduction

Substituted ureas own broad spectra of biological activity [1], while the urea pharmacophore itself appears in many accepted drugs [2]. Urea derivatives are widely used because of their good pharmacological properties. For example, it has been reported as antimicrobial [3], anti-tuberculosis [4], antihyperglylcemic activity [5], anti-influenza activity [6], antitumor activity [7–9].

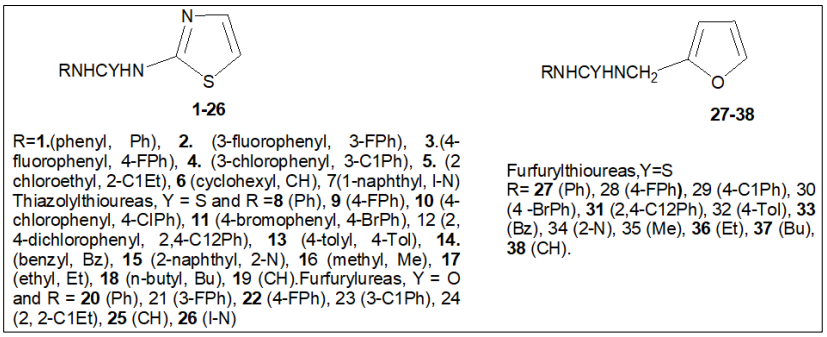
On the other end, thiourea and its derivatives are considered as crucial molecules for their varied applications, such as having high biological activity. The existence of two units of reactive primary amine groups has made urea and thiourea suitable precursors for synthesis of a large number of their derivatives, which are known to display a broad range of applications in the pharmaceutical industry owing to their biological activities, including their anticonvulsant [10], antibacterial [11–12] and anticancer properties [13].

Pharmacological activities

The urea and thiourea scaffold is extremely versatile and has been featured in a number of drugs, highlighting the importance of these moieties. The most important and recent studies have revealed that urea and thiourea derivatives have a broad spectrum of pharmacological activities which can be classified into the following categories

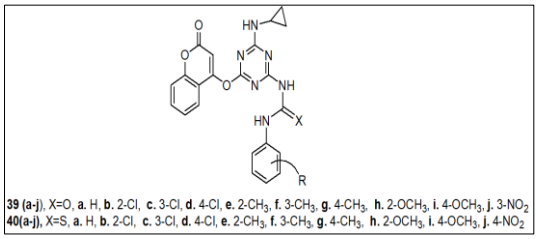
Antimicrobial activity

Yonova PA *et al* [14], synthesized thirty-eight N-substituted-N'-(2-thiazolyl and furfuryl) ureas and thioureas were prepared by reaction of 2-aminothiazole and 2-furfurylamine with the appropriate iso (thio) cyanate. All compounds were tested for herbicidal activity and selectivity on seedlings of wheat and cucumber. The phenylurea derivative of 2-aminothiazole 1 was 1.7-fold more and the 3-chlorophenylurea derivative of 2-furfurylamine 23 was equally as active as the standard diuron with respect to selective herbicidal activity. Out of 24 thioureas, four compounds (15, 16, 17, and 18) displayed the highest selective herbicidal activity and two other compounds (19 and 33) were almost equal to diuron activity. In general, the ureas and thioureas containing a 2-thiazole ring were more active than those containing a 2-furfuryl residue. The ureas and thioureas containing thiazole nuclei were found to possess high biological activity. The presence of fluoro- or chloro-phenyl substituents in these compounds increased the cytokinin-like activity and alkyl groups markedly increased the herbicidal activity.



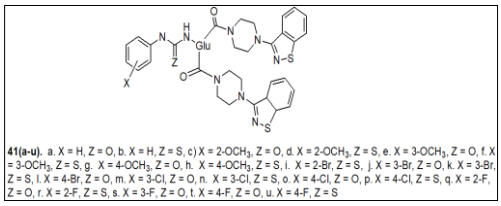
Scheme 1: Synthesis of Urea and Thiourea Derivatives of 2-aminothiazole and 2- furfurylamine.

Kaswala PB *et al* [15], have reported the synthesis of a series of urea and thiourea derivatives of s-triazine. All the synthesized compounds were characterized by using several physico-analytical techniques and were evaluated for their antibacterial activities against various Gram-positive and Gram-negative strains of bacteria. A few compounds showed good to superior *in vitro* antibacterial activity against S. aureus, B. subtilis, E. coli and P. aeruginosa respectively.



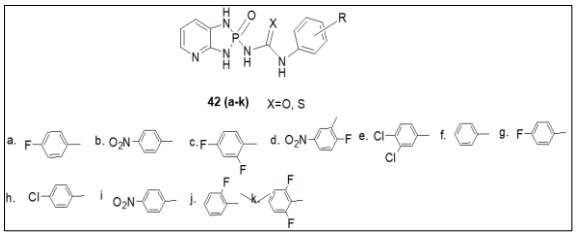
Scheme 2: General synthetic route for urea and thiourea derivatives of s-triazine.

D. C. Gowda *et al* [16], have synthesized several substituted urea/thiourea derivatives by the reaction of glutamic acid and 3-(1-piperazinyl)-1, 2-benzisothiazole with various substituted phenyl isocyanates/isothiocyanates. The novel compounds were confirmed on the basis of spectroanalytical methods. The antimicrobial activities were investigated against several pathogens by the agar well diffusion method and the micro dilution method. The study revealed that the compounds containing fluoro and bromo as substituents showed promising antimicrobial activity.



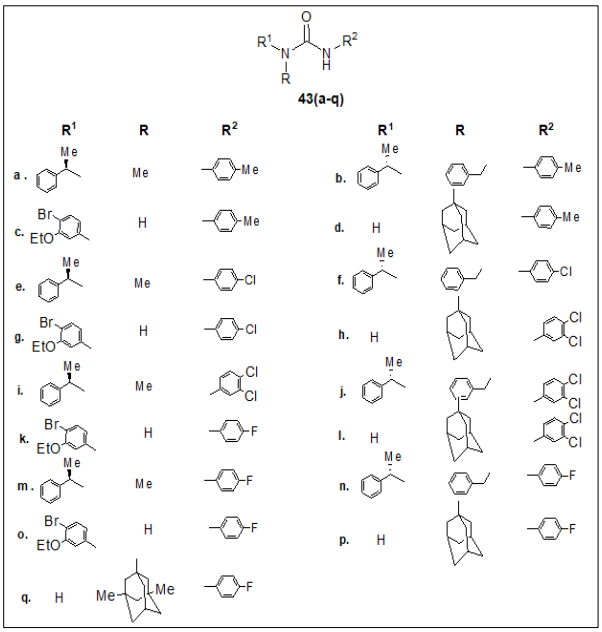
Scheme 3: Synthesis of N-terminal substituted amino acid conjugated urea/thiourea derivatives.

S. Devineni *et al* [17]., have been synthesized and characterized novel series substituted urea/thiourea derivatives, N-(substitutedphenyl)- N^1 -(2- oxo-2,3-dihydro-1H-2λ^5 -[1,3,2]diazaphospholo[4,5-b] pyridin-2-yl)ureas 42(a–e)/thioureas 42(f–k). The *in vitro* antimicrobial activity of the compounds was investigated, including minimum inhibitory concentration. Most of the thiourea-linked analogues exhibited good antimicrobial activity.



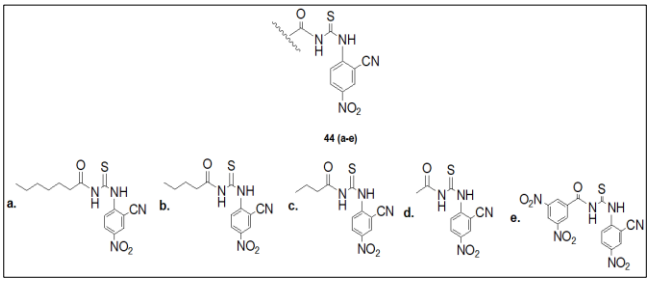
Scheme 4: Synthesis of substituted urea/thiourea derivatives, N-(substitutedphenyl)- N^1-(2-oxo-2,3-dihydro-1H-2λ^5 -[1,3,2]diazaphospholo[4,5-b] pyridin-2-yl)ureas 42(a-e)/thioureas/thioureas 42(f–k).

A series of benzoylthiourea derivatives was synthesized, characterized and reported their antimicrobial activities by Arslan H *et al* [18], the compounds were studied by using a broth micro dilution method. The strains used for the study were E. faecalis, S. aureus, S. epidermidis, P. aeruginosa, E. coli, C. albicans, C. parapsilosis, C. krusei, and C. glabrata. Only a few thiourea derivatives showed moderate antibacterial activity, whereas no effect was recorded against the fungal strains.



Scheme 5: Synthesis of *N*-(arylcarbamothioyl) cyclohexanecarboxamide derivatives.

Thioureas are elegant building blocks in several five- and six-membered heterocyclic units. Larik *et al* [19]. have synthesized various alkyl/aryl thioureas. These newly synthesized compounds were evaluated for antimicrobial activity and showed significant antibacterial and antifungal activity. Furthermore, molecular docking studies were carried out to understand the binding mode of the inhibitors with the enzyme.

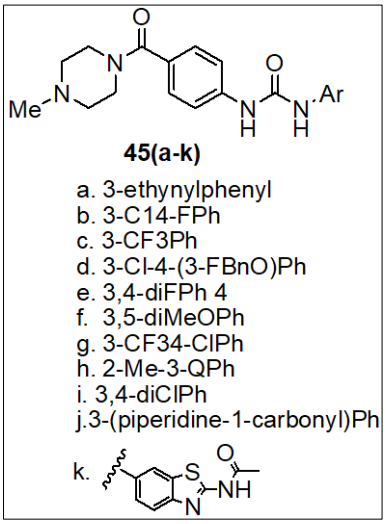


Scheme 6: Synthesis of various alkyl chain length bearing acyl and aryl thioureas 44(a-e).

Anticancer and antiproliferative activity

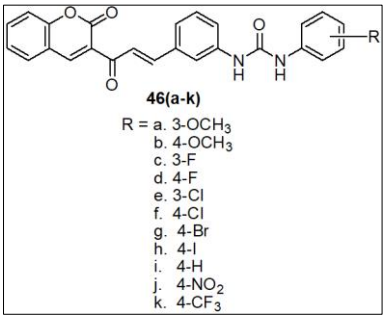
Eleven diarylurea derivatives bearing N-methylpiperazinyl moiety were synthesized by the reaction of isocyanate with arylamine and structures of 45(a–k) were elucidated by ^{1}H-NMR and MS by Wei Xuan *et al* [20]., The synthesized compounds were evaluated for their cytotoxic activities via MTT method against human lung adenocarcinoma epithelial cell line A549 and human

prostate carcinoma cell line PC_3. Compounds 45d and 45k displayed potent cytotoxic activity. The results suggested that the activities are considerably related to the substituent group at another phenyl ring.



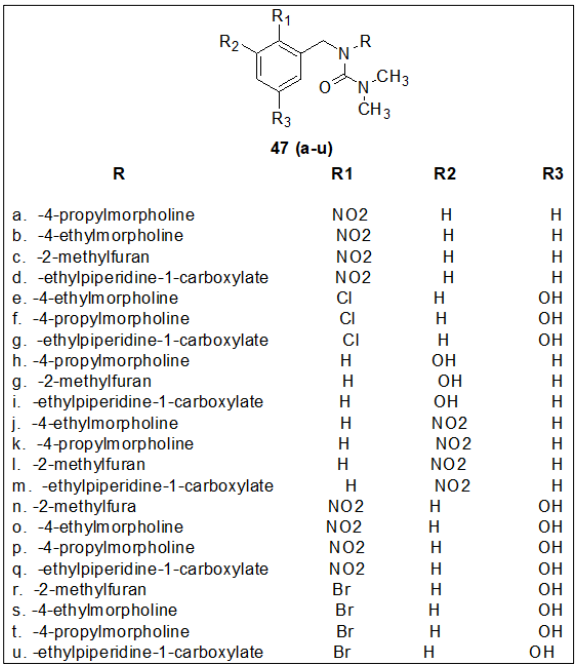
Scheme 7: Synthesis of diarylurea derivatives of N-methyl pierazine.

Kurt BZ *et al* [21], have reported the design and synthesis of coumarin derivatives bearing diversely substituted chalcone-urea moieties 46(a-k). The synthesized compounds screened for their *in vitro* antiproliferative activities against the cancer cell lines (H4IIE and HepG2). Additionally, the synthesized compounds were tested on a cell line that was not cancerous (CHO) and the damage, it could give to normal cells was determined. Among the synthesized compounds, 46k exhibited better inhibition of H4IIE compared to Sorafenib. 46j also showed better inhibition against HepG2 than Sorafenib. Therefore, 46k and 46j may be potent antitumor agents, representing a promising lead for further optimization.



Scheme 8: Synthesis of urea and thiourea derivatives of coumarin.

Lokwani D *et al* [22], have reported the study on quantitative structure–activity relationship (2D and 3D) have been carried out for establishing a correlation between the structural properties of benzyl urea derivatives and their anti-tumour activities. Finally, the most promising compounds from these screening were synthesized and biologically evaluated for their anti-cancer properties. Compound 1-(2, 4-dimethylphenyl)-3,3-dimethyl-1-(2-nitrobenzyl) urea (47d) showed significant anti-proliferative activity (at 100 µg/mL) in human cancer cell lines-T-cell leukemia (Jurkat J6), myelogenous leukemia (K562), and breast cancer (MCF-7) compared to reference standard 5-flurouracil. Therefore, the above study revealed that presence of electropositive group like NO_2 at phenyl ring at R_1 position and sterically bulky group at R_2 like 2, 4-dimethylphenyl position can help the benzyl urea pharmacophore for inhibiting the tumor cells.

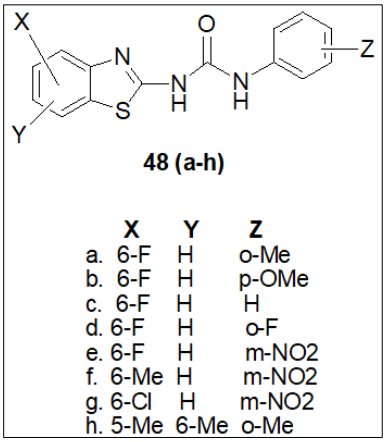


47 (a-u)

R	R1	R2	R3
a. -4-propylmorpholine	NO2	H	H
b. -4-ethylmorpholine	NO2	H	H
c. -2-methylfuran	NO2	H	H
d. -ethylpiperidine-1-carboxylate	NO2	H	H
e. -4-ethylmorpholine	Cl	H	OH
f. -4-propylmorpholine	Cl	H	OH
g. -ethylpiperidine-1-carboxylate	Cl	H	OH
h. -4-propylmorpholine	H	OH	H
g. -2-methylfuran	H	OH	H
i. -ethylpiperidine-1-carboxylate	H	OH	H
j. -4-ethylmorpholine	H	NO2	H
k. -4-propylmorpholine	H	NO2	H
l. -2-methylfuran	H	NO2	H
m. -ethylpiperidine-1-carboxylate	H	NO2	H
n. -2-methylfura	NO2	H	OH
o. -4-ethylmorpholine	NO2	H	OH
p. -4-propylmorpholine	NO2	H	OH
q. -ethylpiperidine-1-carboxylate	NO2	H	OH
r. -2-methylfuran	Br	H	OH
s. -4-ethylmorpholine	Br	H	OH
t. -4-propylmorpholine	Br	H	OH
u. -ethylpiperidine-1-carboxylate	Br	H	OH

Scheme 9: Synthesis of benzyl urea derivatives bearing various heterocyclic functionalities.

Kyeong Lee *et al* [23]., demonstrated the design and synthesis series of amide and urea derivatives of benzothiazole and evaluated for their antiproliferative profile in human SK-Hep-1 (liver), MDA-MB-231 (breast), and NUGC-3 (gastric) cell lines. Among them, compounds 48f, 48g and 48h had potent to moderate inhibitory activities. Further these compounds were investigated for their ability to inhibit Raf-1 activity.

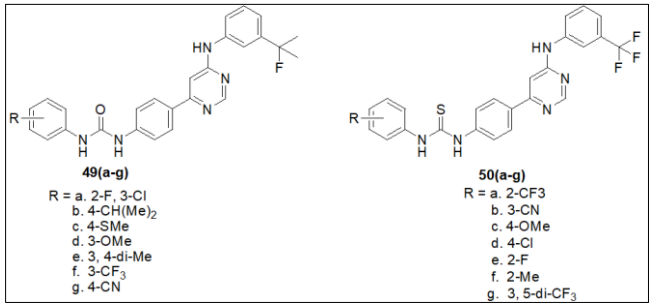


Scheme 10: Synthesis of amide and urea derivatives of benzothiazole.

Anti-inflammatory activity

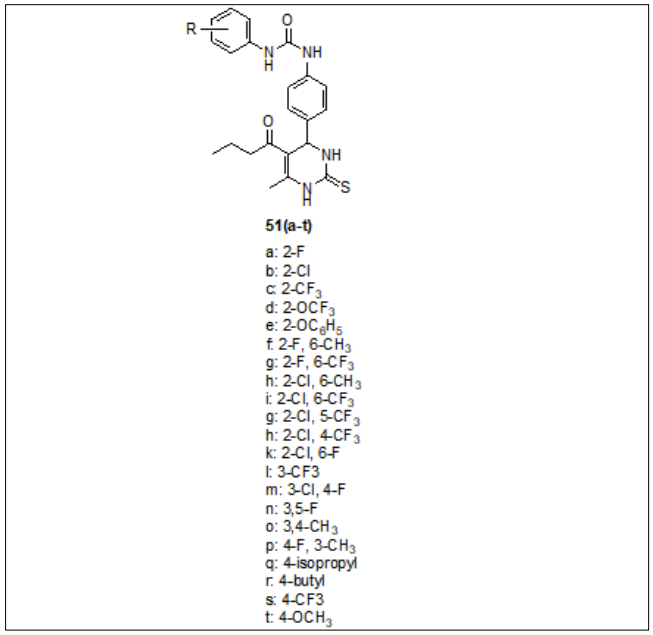
Keche AP *et al* [24], have synthesized and evaluated the anti-inflammatory of a novel series pyrimidine derivatives with aryl urea, aryl thiourea and aryl sulfonamide moieties. The compound

49a found to be promising anti-inflammatory agents. With few exceptions, overall it has been observed that the urea or thiourea moiety found to be favorable structural feature for the aninflmmatory activity. Thus the presence of functionalities such as F, CF_3, Cl and isopropyl on benzene ring of ureido or thioureido terminus found to have strong relevance to the anti-inflammatory activity and Isopropyl, CF_3, OCF_3, CN, and OMe etc at 2, 3 or 4-position on benzene ring of ureido, thioureido and sulfonamide terminus found to be effective.



Scheme 11: Synthesis of amide aryl urea, aryl thiourea and aryl sulfonamide derivatives of pyrimidine.

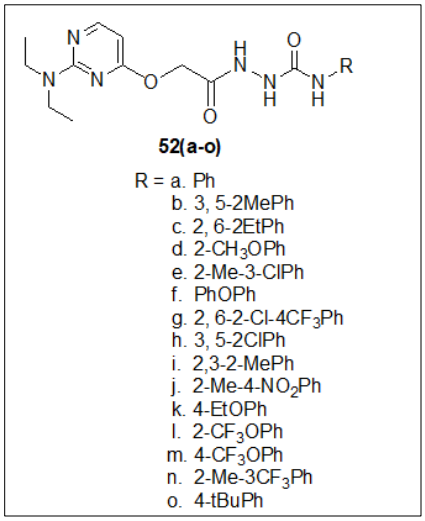
Tale RH *et al* [25], have synthesized a novel series of 3, 4-dihydropyrimidin-2(1H)-one urea derivatives of N-aryl urea inconvenient and atom economic and ecological manner and evaluated their anti-inflammatory activity. It was found that amongst all the compounds screened, compounds 51g and 51o showed promising anti-inflammatory activity against TNF-a and IL-6.



Scheme 12: Synthesis of amide aryl urea, aryl thiourea derivatives of pyrimidinone.

Insecticidal activity

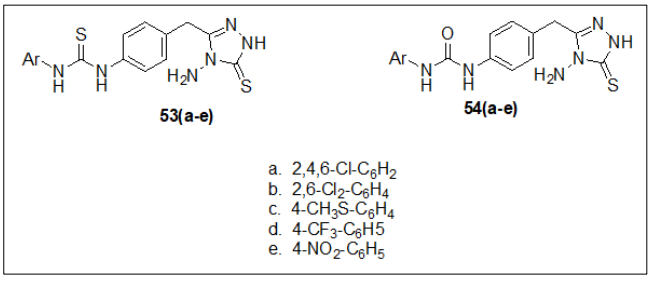
Liu XH *et al* [26], designed and synthesized a series of novel pyrimidine derivatives. Their structures were elucidated by ^{1}H NMR and MS spectroscopic techniques. Biological activities of these compounds were tested against *Aedes aegypti*. Many of them exhibited insecticidal activity against adult and larval mosquitoes. Compound 52d displayed relatively good activity to reach 70% mortality at 2 µg/mL. Furthermore, DFT (Density functional theory) calculations were established to study the structure-activity relationship of these novel compounds.



Scheme 13: Synthesis of amide, aryl urea derivatives of pyrimidine.

Miscellaneous activity

A series of novel thiourea and urea derivatives containing 1,2,4-triazole moieties were synthesized and evaluated for their antifungal and larvicidal activity by Kocyigit-Kaymakcioglu B *et al* [27], Triazole derivatives 53(a–e) and 54(a–e) were synthesized by reacting thiocarbohydrazide with thiourea and urea compounds respectively, in a 130–140 °C oil bath. The proposed structures of all the synthesized compounds were confirmed using elemental analysis, UV, IR, ^{1}H-NMR and mass spectroscopy. All compounds were evaluated for antifungal activity against plant pathogens, larvicidal and biting deterrent activity against the mosquito *Aedes aegypti* L. and *in vitro* cytotoxicity and anti-inflammatory activity against some human cell lines. *Phomopis* species were the most sensitive fungi to these compounds. Compound 53d was the most active derivative among the tested compounds in a larvicidal assay against *A. aegypti*. The comparison of antifungal and insecticidal activities of thiourea and urea derivatives showed that thiourea derivatives bearing 2, 6-dichlorophenyl, 2, 4, 6-trichlorophenyl, 4-nitophenyl, 4-trifluoromethylphenyl substituents were the active compounds. Thiourea compounds, 53a, 53d, and urea compound 54e show sufficient potential to warrant further modification to discover new antifungal and insecticidal molecules.



Scheme 14: Synthesis of thiourea and urea derivatives containing 1, 2, 4-triazole.

Conclusion

This review presented the diverse and potent pharmacological activities of the urea and thiourea derivatives of some of the heterocyclic compounds. The information provided in this manuscript can be useful for the further study of this scaffold in order to evaluate their biological potential in a better way and for development of further pharmacologically significant medicinal agents for the treatment of various diseases.

References

1. Vishnyakova TP, Golubeva IA, Glebova EV. Substituted Ureas-Methods of Synthesis and Applications, Russian Chemical Reviews,1985:54(3):249-261.
2. Mashkovskii MD, Lekarstvennye sredstva. [Drugs] 16th ed., Novaya Volna, Moscow, 2012, 1216. (in Russian).
3. Patil M, Noonikara-Poyil A, Joshi SD, Patil SA, Patil SA, Bugarin A. New Urea Derivatives as Potential Antimicrobial Agents: Synthesis, Biological Evaluation, and Molecular Docking Studies. Antibiotics,2019:8(4):178.
4. Upadhayaya RS, Kulkarni GM, Vasireddy NR, Vandavasi JK, Dixit SS, Sharma V *et al*. Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against Mycobacterium tuberculosis. Bioorganic Medicinal Chemistry,2009:17:4681-4692.
5. Ahmad S, Javed K, Rathish IG, Bano S, Alam MS. Synthesis, pharmacological evaluation and ligand-protein interaction study of hybrid urea and thiourea derivatives as antihyperglycemic agents, Phosphorus Sulfur Silicon Related Elements,2018:9(5):36-44.
6. Fedorova VA, Kadyrova RA, Slita AV, Muryleva AA, Petrova PR, Kovalskaya AV *et al*. Synthesis of Urea Derivatives of 9-Aminomethylcytisine, Chemistry of Natural Compounds,2020:56(6):1183-1185.
7. Lan J, Huang L, Lou H, Chen C, Liu T, Hu S *et al*. Design and synthesis of novel C14-urea-tetrandrine derivatives with potent anti-cancer activity. European Journal of Medicinal Chemistry,2018:143:1968-1980.
8. Abdelhaleem EF, Abdelhameid MK, Kassab AE, Kandeel MM. Design and synthesis of thienopyrimidine urea derivatives with potential cytotoxic and pro-apoptotic activity against breast cancer cell line MCF-7. European Journal of Medicinal Chemistry,2018:143:1807-1825.
9. Solomon VR, Pundir S, Lee H, Design and synthesis of 4-piperazinyl quinoline derived urea/thioureas for anti-breast cancer activity by a hybrid pharmacophore approach, Journal of Enzyme Inhibition and Medicinal Chemistry,2019:34(1):620-630.
10. Koçyigit-Kaymakçıoglu B, Rollas S, Korcegez E, Arıcıoglu F. Synthesis and Biological Evaluation of New N-substituted-N'-(3,5-di/1,3,5-trimethylpyrazole-4-yl)thiourea/urea Derivatives. European journal of pharmaceutical sciences,2005:26(1):97-103.
11. Wan Zullkiplee WSH, Abd Halim AN, Ngaini Z, Mohd Ariff MA, Hussain H. Bis-Thiourea Bearing Aryl and Amino Acids Side Chains and Their Antibacterial Activities. Phosphorus, Sulfur, and Silicon and the Related Elements,2014:189(6):832-838.
12. Wu J, Shi Q, Chen Z, He M, Jin L, Hu D. Synthesis and Bioactivity of Pyrazole Acyl Thiourea Derivatives. Molecules,2012:17(5):5139-5150.
13. Shing JC, Choi JW, Chapman, R, Schroeder MA, Sarkaria JN, Fauq A *et al*. A Novel Synthetic 1,3-Phenyl Bis-Thiourea Compound Targets Microtubule Polymerization to Cause Cancer Cell Death. Cancer Biology & Theraphy,2014:15(7):895-905.
14. Yonova PA, Stoilkova GM. Synthesis and Biological Activity of Urea and Thiourea Derivatives from 2-Aminoheterocyclic Compounds, Journal of Plant Growth Regulation,2005:23:280-291.
15. Kaswala PB, Chikhalia KH, Shah NK, Patel DP, Patel DH, Mudaliar GV. Design, synthesis and antimicrobial evaluation of s-triazinyl urea and thiourea derivatives, ARKIVOC,2009:(11):326-335.
16. Sharma A, Suhas R, Chandan S, Gowda DC. Novel Urea and Thiourea Derivatives of Thiazole Glutamic Acid Conjugate as Potential Inhibitors of Microbes and Fungi, Russian Journal of Bioorganic Chemistry,2013:39(6):656-664.
17. Devineni S, Golla M, Chamarthi NR, Meriga B, Saddala MS, Asupathri UR. 2-Amino-2,3-dihydro-1H-2k5-[1,3,2]diazaphospholo[4,5-b]pyridin- 2-one-based urea and thiourea derivatives: synthesis, molecular docking study and evaluation of anti-inflammatory and antimicrobial activities, Medicinal Chemistry Research,2016:25:751-768.
18. Ozer CK, Arslan H, Van Derveer D, Kulcu N. Synthesis and Characterization of *N*-(Arylcarbamothioyl)-cyclohexanecarboxamide Derivatives: The Crystal Structure of *N*-(Naphthalen-1-ylcarbamothioyl)cyclohexanecarboxamide, Molecules,2009:14:655-666.
19. Larik FA, Saeed A, Faisal M, Channar PA, Azam SS, Ismail H *et al*. Synthesis, molecular docking and comparative efficacy of various alkyl/aryl thioureas as antibacterial, antifungal and α-amylase inhibitors, Computational Biology and Chemistry,2018:77:193-198.
20. Wei X, Wen D, Hong-xiang H, San-qi Z. Synthesis and cytotoxic activity of diaryl urea derivatives with a 4-methylpiperazinylcarbonyl moiety, Medicinal Chemistry Research,2013:22:3857-3862.
21. Kurt BZ, Kandas NO, Dag A, Sonmez F, Kucukislamoglu M. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents, Arabian Journal of Chemistry,2017:13(1):1-10.
22. Lokwani D, Bhandari S, Pujari R, Shastri P, Shelke G, Pawar V. Use of Quantitative Structure–Activity Relationship (QSAR) and ADMET prediction studies as screening methods for design of benzyl urea derivatives for anti-cancer activity, Journal of Enzyme Inhibition and Medicinal Chemistry,2011:26(3):319-331.
23. Song EY, Kaur N, Park MY, Jin Y, Lee K, Kim G *et al*. Synthesis of amide and urea derivatives of benzothiazole as Raf-1 inhibitor. European Journal of Medicinal Chemistry,2008:43:1519-1524.
24. Keche AP, Hatnapure GD, Tale Rajesh H, Rodge AH, Birajdar SS, Kamble VM. A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: Synthesis,

anti-inflammatory and antimicrobial evaluation, Bioorganic & Medicinal Chemistry Letters,2012:22(10):3445-3448.
25. Tale RH, Rodge AH, Hatnapure GD, Keche AP. The novel 3,4-dihydropyrimidin-2(1H)-one urea derivatives of N-aryl urea: Synthesis, anti-inflammatory, antibacterial and antifungal activity evaluation, Bioorganic & Medicinal Chemistry Letters,2011:21:4648-4651.
26. Liu XH, Wang Q, Sun ZH, Wedge DE, Becnel JJ, Estep AS *et al*. Synthesis and insecticidal activity of novel pyrimidine derivatives containing urea pharmacophore against Aedes aegypti, Pest Management Science,2017:73(5):953-959.
27. Kocyigit-Kaymakcioglu B, Celen AO, Tabanca N, Ali A, Khan SI, Khan A IK *et al*. Synthesis and Biological Activity of Substituted Urea and Thiourea Derivatives Containing 1,2,4-Triazole Moieties, Molecules,2013:18(3):3562-3576.
28. Shaikh T. Role of chemistry in drug discovery and drug design. Int. J Adv. Chem. Res. 2021;3(1):16-18. DOI: 10.33545/26646781.2021.v3.i1a.30