Bioorganic Chemistry 86 (2019) 34–38

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

# Imidazolo and tryptophan-imidazolo hybrid derived ureas/thioureas as potent bioactive agents – SAR and molecular modelling studies

H.K. Kumara, R. Suhas, D.M. Suyoga Vardhan, M. Shobha, D. Channe Gowda*

*Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysuru 570 006, Karnataka, India*

ARTICLE INFO

*Keywords:*
Imidazole
Trp
Antioxidant
Antimicrobial
Anti-inflammatory
Molecular docking

ABSTRACT

Herein, we used an imidazole derivative (IMD) which showed promising antibacterial, antifungal and antioxidant properties in our earlier investigation. Prompted by this, we converted IMD to hydrazide (IMH) by hydrazinolysis which was derivatized to various ureas (**3–7**) and thioureas (**8–12**). On the other hand, IMH was conjugated to Boc-Trp-OH as it has been shown in the past that hybridization of two molecules produced promising biologically active compounds. Boc of the conjugate was removed and further converted into several urea (**14–18**) and thiourea (**19–23**) derivatives. All the title compounds so also the starting materials and intermediates were assessed for potential biological applications. The results showed that compounds **3, 4, 8, 9, 14, 15, 19** and **20** were excellent antioxidants as revealed by DPPH, DMPD and ABTS assays. Further, certain analogues like **5–7, 10–12, 16–18** and **21–23** were found to be potent antimicrobials against pathogenic bacteria and fungi whereas good anti-inflammatory activity was obtained for molecules **5–7, 10–12, 16–18** and **21–23**. All together, derivatives of the conjugates have shown superior activity over non-conjugated compounds and the former have exhibited potent activity against standard drugs in all the assays. In a quest to understand the binding interactions of the compounds with active site of *tyrosine kinase* (PDB ID: 2HCK), *glucosamine-6-phosphate (GlcN-6-P) synthase* (PDB ID: 2VF5) and *cyclooxygenase-2* (PDB ID: 1CX2) enzymes, the correlation studies were conducted using molecular modelling which showed good receptor binding interactions with several amino acids of the enzymes. Overall, the current investigation may be considered for the discovery of lead compound(s) for treating multiple disorder conditions using singular molecular entity.

## 1. Introduction

The limitations of many monotherapies can be overcome by attacking the disease system on multiple fronts [1]. Multi-target therapeutics can be more efficacious and less vulnerable to adaptive resistance because the biological system is less able to compensate for the action of two or more drugs simultaneously. Indeed, multi-component drugs are now standard in therapeutic areas such as cancer, diabetes and infectious diseases; paradoxically composed of agents that were initially developed as single-target drugs. Unfortunately, the standard approach of combining monotherapies at the clinical stage limits the number of drug pairs that can be tested and bypasses the opportunity to find therapeutically relevant interactions between novel targets [2]. Over several years, imidazole and their derivatives has attracted much attention of medicinal chemists because of their potential to generate new chemotherapeutic agents. They have wide range of biological activities which has been well documented in the literature [3,4] which prompted us to work on this core. On the other hand, urea/thiourea derivatives display a wide range of biological activities including antimicrobial, antidiabetic, antituberculosis and anticancer properties [5–7].

Molecular hybridization as a drug discovery strategy involves the rational design of new chemical entities by the fusion of two molecules, both active compounds and/or pharmacophoric units recognized and derived from known bioactive molecules [8]. Owing to this, our research group has enormously contributed to the field of 'conjugation' of bioactive molecules, particularly amino acids/peptides with that of heterocycles and a step forward, derivatization of the conjugates [9–12] that led to the identification of several promising candidates for further studies. To this end, we planned to use imidazole derivative (IMD, **1**) that demonstrated good therapeutic profile in our earlier investigation [13]. Initially we performed hydrazinolysis of IMD to obtain IMH (**2**)

*Abbreviations:* DPPH, 1,1-diphenyl-2-picryl-hydrazyl; DMPD, *N,N*-dimethyl-*p*-phenylenediamine; ABTS, 2,2-azinobis-(3-ethylbenzothiazoline-6-sufonic acid); EDCI, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride; HOBt, *N*-hydroxybenzotriazole; NMM, *N*-methylmorpholine; TFA, trifluoroacetic acid

* Corresponding author.
*E-mail address:* dchannegowda@yahoo.co.in (D. Channe Gowda).

https://doi.org/10.1016/j.bioorg.2019.01.027
Received 20 July 2018; Received in revised form 8 October 2018; Accepted 16 January 2019
Available online 18 January 2019
0045-2068/ 

which was converted into urea and thiourea derivatives. In the second instance, we wanted to verify the effect of amino acid conjugation on IMH so also their ureas and thioureas. Among the amino acids, Trp was used as it is aromatic, heterocyclic, possess acid-base character due to the presence of indole ring and importantly it exhibits varied kinds of biological activities. Due to the multifaceted properties of Trp, it was conjugated to IMH at the N-terminus region. We designed the ureas and thioureas in such a way that they had both electron donating (EDG) as well as withdrawing groups (EWG) so that their effect on the biological activities could also be understood well. The ureas and thioureas of both conjugated and non-conjugated compounds along with the initial reactants and the intermediates were assessed for their potentiality to exhibit biological activities *viz.,* antioxidant, antimicrobial and anti-inflammatory. On the top of this, knowledge about binding or interaction of the compounds with that of receptor is highly desirable to understand the drug-receptor concept. In this sense, molecular docking of the title compounds was performed on different enzymes of all the aforesaid assays.

## 2. Results and discussion

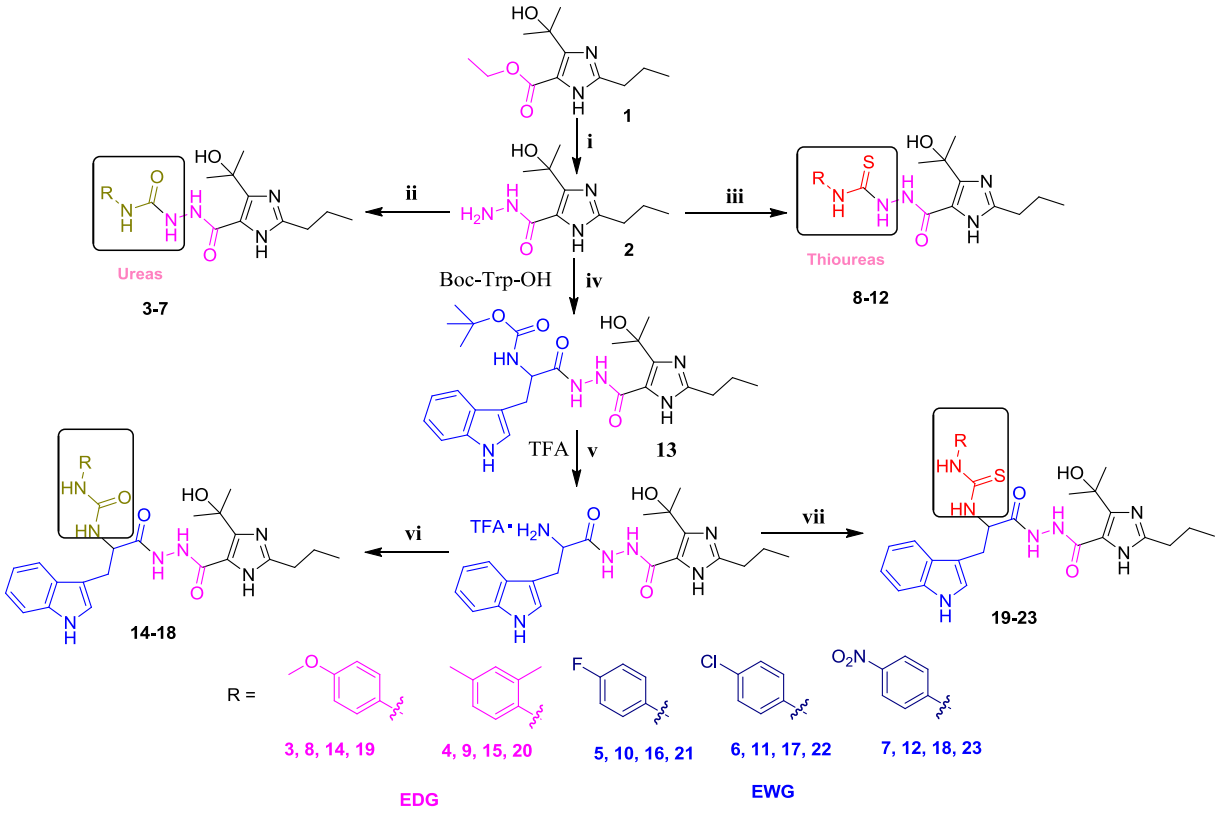
### 2.1. Chemistry

Synthesis of the desired compounds was achieved according to the steps illustrated in the Scheme 1. IMD was synthesized by literature known methods with slight modification [14,15]. This was treated with excess of hydrazine hydrate to get IMH which was reacted with different substituted phenyl isocyanates/phenyl isothiocyanates to obtain respective ureas (**3–7**) and thioureas (**8–12**). Next, IMH and Boc-Trp-OH were conjugated using EDCI/HOBt as coupling agents and NMM as base to get Boc-Trp-IMH (**13**). **13** was debocked using TFA and reacted as above to get respective ureas (**14–18**) and thioureas (**19–23**). All the compounds were obtained in good yields. The structures of all the newly synthesized compounds were confirmed by IR, $^{1}$H NMR, $^{13}$C NMR and mass spectral analyses. IMH showed bands at 3276 $cm^{-1}$ for $-NH_2$ and 3196 $cm^{-1}$ for $-NH$ in IR spectra whereas in PMR, peaks appeared at $\delta$ 9.06 for $-NH$ and 4.42–4.32 for $-NH_2$ which indicated the hydrazinolysis of the ester. Further, presence of peak at $\delta$ 10.24 ($-NH$) and absence at $\delta$ 4.42–4.32 ($NH_2$) confirmed the conjugation of IMH with Trp. The formation of urea and thiourea was confirmed by the presence of IR bands at 1685–1665 $cm^{-1}$ and 2035–2015 $cm^{-1}$ and peaks at $\delta$ 8.68–7.58 ($-NH-CO-NH-$) and 9.75–9.45 ($-NH-CS-NH-$) in PMR respectively. The presence of all requisite peaks and absence of extraneous peaks in PMR and CMR confirmed the structures. Further, the mass values obtained were in good agreement with the structures assigned (physical data, structures and spectral data are provided in Tables S1 and S2).

### 2.2. Biological activities

#### 2.2.1. Antioxidant activity

Biological results ($IC_{50}$/mm) of the compounds are presented in the Table 1. The radical scavenging properties of the compounds was assessed by DPPH [16], DMPD [17] and ABTS [18] assays. Ascorbic acid (AA) and gallic acid (GA) were used as reference standards for comparison. Initially, IMD and IMH were subjected to radical scavenging activity which showed poor results. Ureas (**3–7**) and thioureas (**8–12**) of IMH showed good antioxidant properties. The conjugation of Trp with IMH enhanced the radical scavenging ability of Boc-Trp-IMH which may be due to the presence of indole ring [19]. There was a drastic enhancement in the activity when N-terminus Trp was converted into urea (**14–18**) and thiourea (**19–23**) derivatives. It was found that the substituents present on phenyl ring of final compounds play an important role in increasing the potentiality of the molecules to scavenge




**Scheme 1.** Synthesis of urea and thiourea derivatives of IMH and Trp-IMH. Reagent and conditions: (i) $NH_2NH_2{\cdot}H_2O$, ethanol, reflux, 16 h; (ii) $R-C_6H_4-N=C=O$, THF, 0 °C to rt, 8 h; (iii) $R-C_6H_4-N=C=S$, THF, 0 °C to rt, 8 h; (iv) EDCI/HOBt, NMM, 0 °C to rt, overnight; (v) TFA, 45 min, rt; (vi) $R-C_6H_4-N=C=O$, DMF, NMM, 0 °C to rt; (vii) $R-C_6H_4-N=C=S$, DMF, NMM, 0 °C to rt.

**Table 1**
Biological activities of the title compounds.

| Entry | Antioxidant activity $IC_{50}$ (μg/mL)[a] | | | Antibacterial activity (mm)[a] | | Antifungal activity (mm)[a] | | Anti-inflammatory activity $IC_{50}$ (μg/mL)[a] |
|---|---|---|---|---|---|---|---|---|
| | DPPH | DMPD | ABTS | *E. coli* | *S. aureus* | *F. moniliforme* | *E. coli* | |
| 1 | > 300 | > 300 | > 300 | 05 ± 0.35 | 04 ± 0.26 | NA | 05 ± 0.35 | > 300 |
| 2 | > 300 | > 300 | > 300 | 07 ± 0.38 | NA | 06 ± 0.35 | 07 ± 0.38 | 285 ± 2.65 |
| 3 | 45 ± 1.25 | 40 ± 1.54 | 55 ± 1.56 | 14 ± 0.45 | 15 ± 0.42 | 18 ± 0.25 | 14 ± 0.45 | 125 ± 0.75 |
| 4 | 50 ± 1.56 | 45 ± 1.97 | 60 ± 1.85 | 15 ± 0.28 | NA | 14 ± 0.26 | 15 ± 0.28 | 180 ± 0.64 |
| 5 | 75 ± 0.97 | 80 ± 1.54 | 65 ± 1.29 | 24 ± 0.45 | 22 ± 0.15 | 25 ± 0.35 | 24 ± 0.45 | 60 ± 0.80 |
| 6 | 65 ± 1.78 | 85 ± 2.08 | 70 ± 1.67 | 22 ± 0.30 | 19 ± 0.18 | 21 ± 0.26 | 22 ± 0.30 | 55 ± 0.90 |
| 7 | 90 ± 1.56 | 100 ± 2.98 | 85 ± 0.56 | 28 ± 0.22 | 30 ± 0.35 | 26 ± 0.24 | 28 ± 0.22 | 35 ± 2.20 |
| 8 | 35 ± 1.56 | 30 ± 1.87 | 40 ± 1.50 | 12 ± 0.26 | 10 ± 0.69 | 14 ± 0.38 | 12 ± 0.26 | 100 ± 2.35 |
| 9 | 40 ± 1.65 | 40 ± 1.69 | 50 ± 1.52 | 12 ± 0.12 | NA | 14 ± 0.59 | 12 ± 0.12 | 140 ± 0.64 |
| 10 | 65 ± 2.10 | 70 ± 2.06 | 60 ± 2.50 | 20 ± 0.32 | 18 ± 0.44 | 19 ± 0.59 | 20 ± 0.32 | 50 ± 0.54 |
| 11 | 50 ± 1.65 | 70 ± 1.56 | 60 ± 1.65 | 19 ± 0.86 | 17 ± 0.66 | 18 ± 0.59 | 19 ± 0.86 | 40 ± 1.20 |
| 12 | 75 ± 1.75 | 80 ± 1.85 | 70 ± 1.70 | 26 ± 0.59 | 25 ± 0.59 | 24 ± 0.59 | 26 ± 0.59 | 30 ± 0.45 |
| 13 | 250 ± 1.26 | 265 ± 2.67 | 285 ± 2.35 | 10 ± 0.15 | 12 ± 0.95 | NA | 10 ± 0.15 | 250 ± 2.59 |
| 14 | 35 ± 1.65 | 30 ± 1.11 | 45 ± 1.50 | 17 ± 0.45 | 16 ± 0.64 | 19 ± 0.56 | 17 ± 0.45 | 100 ± 1.85 |
| 15 | 45 ± 1.25 | 40 ± 1.20 | 60 ± 1.36 | 16 ± 0.65 | NA | 16 ± 0.75 | 16 ± 0.65 | 150 ± 2.64 |
| 16 | 65 ± 2.36 | 70 ± 1.35 | 60 ± 1.25 | 26 ± 0.95 | 23 ± 0.38 | 27 ± 0.65 | 26 ± 0.95 | 50 ± 1.50 |
| 17 | 60 ± 1.98 | 75 ± 2.15 | 65 ± 1.06 | 23 ± 0.48 | 21 ± 0.75 | 21 ± 0.25 | 23 ± 0.48 | 45 ± 1.20 |
| 18 | 80 ± 1.05 | 100 ± 1.56 | 80 ± 1.45 | 30 ± 0.79 | 30 ± 0.68 | 28 ± 0.12 | 30 ± 0.79 | 20 ± 0.67 |
| 19 | 25 ± 1.45 | 20 ± 1.01 | 30 ± 1.98 | 14 ± 0.65 | 12 ± 0.31 | 14 ± 0.32 | 14 ± 0.65 | 80 ± 1.05 |
| 20 | 35 ± 2.01 | 30 ± 1.26 | 45 ± 1.27 | 13 ± 0.12 | NA | 17 ± 0.56 | 13 ± 0.12 | 120 ± 1.65 |
| 21 | 55 ± 1.22 | 70 ± 1.65 | 55 ± 1.28 | 22 ± 0.35 | 20 ± 0.45 | 22 ± 0.50 | 22 ± 0.35 | 50 ± 1.20 |
| 22 | 40 ± 1.20 | 65 ± 1.55 | 50 ± 1.89 | 20 ± 0.64 | 19 ± 0.89 | NA | 20 ± 0.64 | 35 ± 0.95 |
| 23 | 75 ± 2.26 | 75 ± 1.85 | 65 ± 1.65 | 28 ± 0.69 | 25 ± 0.75 | 26 ± 0.45 | 28 ± 0.69 | 25 ± 0.52 |
| **AA** | 45 ± 1.16 | 55 ± 1.65 | 45 ± 1.29 | – | – | – | – | – |
| **GA** | 40 ± 1.10 | 50 ± 1.36 | 45 ± 1.36 | – | – | – | – | – |
| **SM** | – | – | – | 16 ± 0.65 | 13 ± 0.56 | – | – | – |
| **BS** | – | – | – | – | – | 15 ± 0.59 | 13 ± 0.85 | – |
| **IM** | – | – | – | – | – | – | – | 55 ± 2.01 |
| **IP** | – | – | – | – | – | – | – | 50 ± 1.26 |

AA = Ascorbic acid, GA = Gallic acid; SM = Streptomycin, BS = Bavistin; IM = Indomethacin, IP = Ibuprofen; NA = No Activity, '–' = not analyzed.
[a] Values are mean of three determinations, the ranges of which are < 5% of the mean in all cases.

generated radicals effectively. Compounds **3, 4, 8, 9, 14, 15, 19** and **20** having EDGs namely, $OCH_3$ and $CH_3$ neutralized the generated free radical most effectively [20] and the $IC_{50}$ values were less than the standards in all the three assays. Contrarily, analogues **5–7, 10–12, 16–18** and **21–23** bearing EWGs like F, Cl and $NO_2$ slightly decreased radical scavenging potentiality which is in slight contrast to the literature [21,22]. The ureas and thioureas of Trp-IMH dominated over ureas and thioureas of IMH which can be attributed to the presence of Trp moiety which shows radical scavenging property [23]. In common, thioureas exhibited high antioxidant property over ureas (thiourea > urea) which is in accordance with earlier observation [22].

### 2.2.2. Antimicrobial activity

*In vitro* antimicrobial activity was done by agar well diffusion method [24,25] in which streptomycin (SM) and bavistin (BS) served as standard drugs for antibacterial and antifungal studies respectively. IMD showed very less antimicrobial property whereas IMH gave slightly enhanced activity which may be due to more polar nature, sterics, acid/base behavior and hydrogen-bonding. This would help the molecules to interact or penetrate more through the cell membranes of microbes and there by inactivating them [11]. The conjugation of Trp with IMH enhanced the antimicrobial properties. A drastic improvement in the activity was observed when **2** and **13** were converted into urea and thiourea derivatives. The electronic property of the compounds is found to have close relationship with the biological activity. Compounds bearing EWGs (F, Cl and $NO_2$ **5–7, 10–12, 16–18** and **21–23**) exhibited superior activity in comparison with the standards which is in good agreement with the earlier article [12]. On the other hand, compounds having EDGs ($OCH_3$ and $CH_3$ **3, 4, 8, 9, 14, 15, 19** and **20**) showed moderate activity against all the strains tested [26,27]. Among the series of compounds, urea derivatives exhibited superior activity over thiourea derivatives and this could be due to the electronegativity of oxygen atom and also its more interactive nature with the membrane receptor [28]. As SAR is concerned, it was suggestive that electron withdrawing groups ($NO_2$ > F > Cl > $OCH_3 \geq CH_3$) favor antimicrobial properties. Further, same trend of activity was observed for both antibacterial and antifungal studies.

### 2.2.3. Anti-inflammatory activity

Human erythrocyte suspension was used to screen the anti-inflammatory activity of the compounds by employing literature known method [29] in which indomethacin (IM) and ibuprofen (IP) were used as standards. It was observed that nature of the substituent on phenyl ring of ureas and thioureas was found to have strong relevance to the biological activities [30]. According to the results, compounds **5–7, 10–12, 16–18** and **21–23** bearing functionalities like F, Cl, and $NO_2$ were found to be suitable to obtain high potency. The presence of strong EWG has positive effect on anti-inflammatory activity. Compounds bearing EDGs *viz.* $OCH_3$ and $CH_3$ have exhibited moderate anti-inflammatory activity since the presence of EDGs reduce the anti-inflammatory potency [20].

## 2.3. Molecular docking studies

The accumulation of ROS, including hydrogen peroxide, superoxide, and the hydroxyl radical, could regulate the transduction of signals from the membrane to the nucleus via the modulation of cellular enzymatic activity by oxidation and reduction [31]. Among the enzymes modified by oxidative stress, protein kinases and phosphatases serve as important regulators of cellular signaling pathways [32]. Excessive generation of ROS has been shown to activate multiple protein kinases. In this sense, molecular docking was performed on active site of *tyrosine kinase* (PDB ID: 2HCK) with synthesized ligands (**1–23**) in order to determine the possible binding interaction of highly potent antioxidant

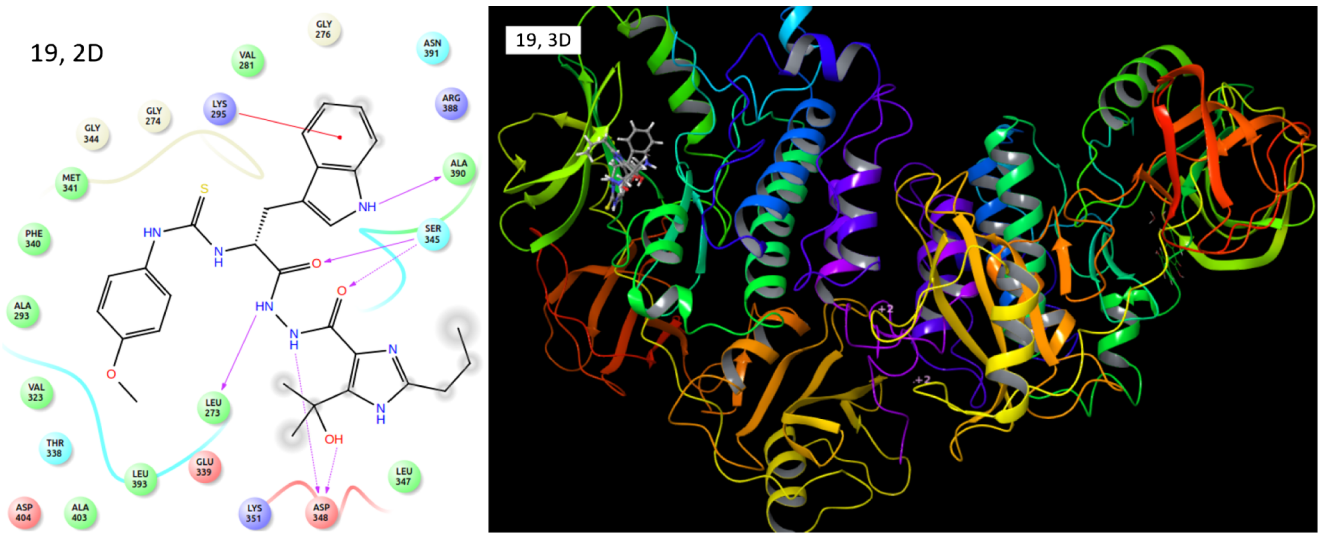



**Fig. 1.** 2D and 3D images of compound 19 with 2HCK.

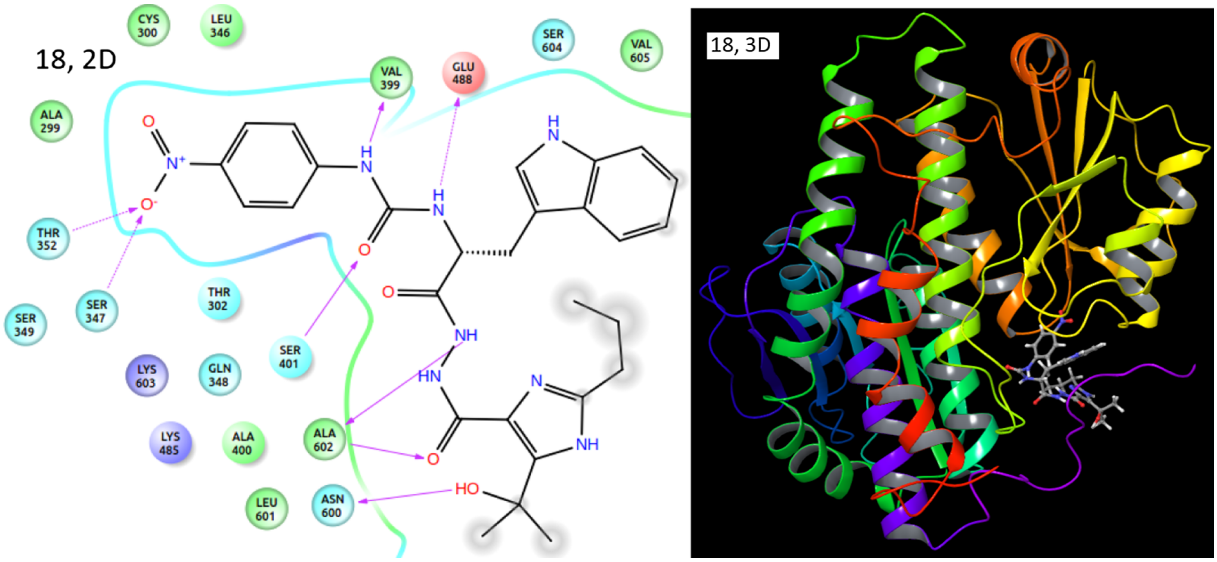



**Fig. 2.** 2D and 3D images of compound 18 with 2VF5.

molecules in the series. Most of the compounds showed good docking score and interaction with different amino acids residues and are tabulated in **S3**. Compounds **3, 4, 8, 9, 14, 15, 19** and **20** having EDGs ($OCH_3$ and $CH_3$) occupied highest docking scores among the series of compounds [33]. To our delight, results of the docking study obtained are in concordant with *in vitro* data. The binding interactions (2D and 3D) of **19** have been displayed in Fig. 1 and it showed hydrogen bonding with Leu 273, Asp 348, Asp 348, Ser 345, Ser 345 and Ala 390; also π-cation interaction with Lys 295. The docking images of **3, 8** and **14** were provided in Fig. S1.

*GlcN-6-P synthase* is the member of amidotransferase subfamily of enzymes. It, catalysing the first committed step in a pathway leading to the eventual formation of uridine 5′-diphospho-N-acetyl-D-glucosamine (UDP-GlcNAc), is an essential building block of bacterial and fungal cell wall. UDP-GlcNAc is an important point of metabolic control in biosynthesis of amino sugar-containing macromolecules [34,35]. Hence, molecular docking was conducted with active site of *GlcN-6-P Synthase* (PDB ID: 2VF5). It showed good binding interaction with surrounded amino acid residues. The docking score and the interacting amino acids are tabulated in **S4**. Most of the synthesized compounds exhibited well established bond with one or more amino acids in the receptor active pocket of 2VF5 protein. The potentiality of the compounds as antimicrobial agents was determined based on docking score. The docking score with 2VF5 protein ranging from −9.517 to −6.095, the highest negative value indicates best docked ligand to the targeted site. Compounds **5–7, 10–12, 16–18** and **21–23** bearing EWGs showed good interactions with active pockets. The 2D and 3D images of **18** is shown in Fig. 2 and it showed hydrogen bonding with Thr 352, Ser 347, Val 399, Glu 488, Asn 600, Ala 602 and Ser 401. The docking images of **7, 12** and **23** were provided in Fig. S2.

Cyclooxygenase (COX) enzymes catalyze a key step in the conversion of arachidonate to PGH2, the immediate substrate for a series of cell specific prostaglandin and thromboxane synthases. NSAIDs such as ibuprofen and indomethacin exert their effects through inhibition of COX [36]. Owing to this point, we conducted docking studies on crystal structure of *cyclooxygenase-2* (PDB ID: 1CX2). Most of the compounds exhibited good docking score and different kinds of interactions with amino acids residues are tabulated in **S5**. The molecules **5–7, 10–12, 16–18** and **21–23** with EWGs on phenyl ring exhibited good interaction with amino acid residues and occupy highest docking scores. Molecular docking studies showed an interacting map of *cyclooxygenase-2* with **21** is shown in Fig. 3 and it showed hydrogen bonding with Asp 87 and Asp 87. The docking images of **5, 10** and **16** were provided in Fig. S3.

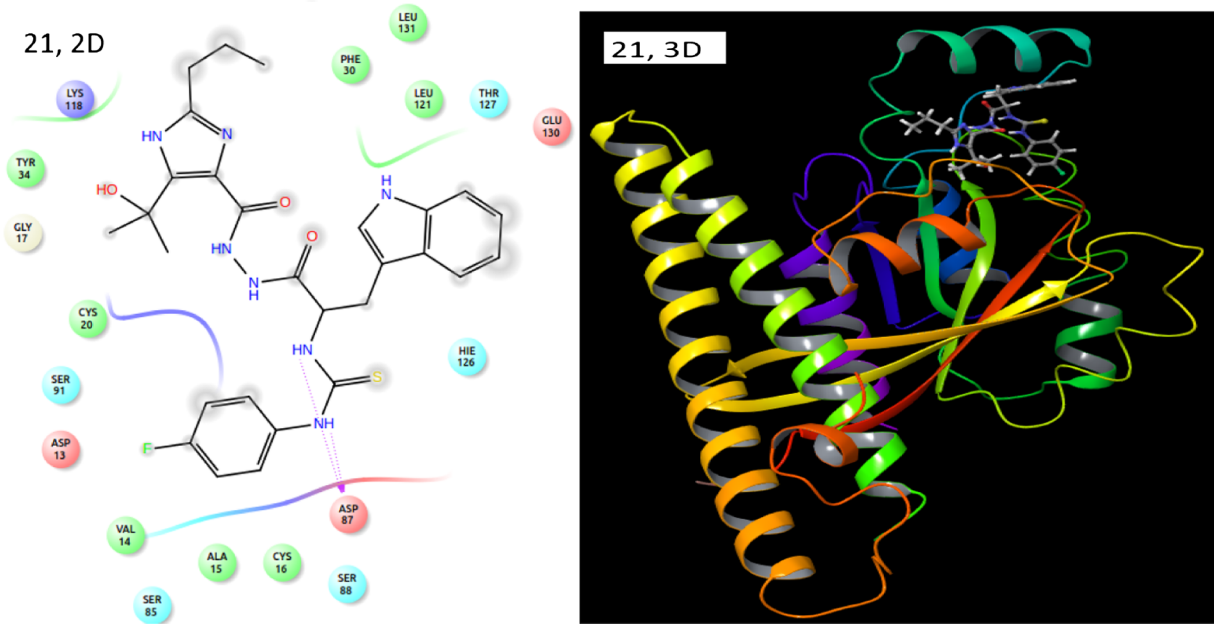



**Fig. 3.** 2D and 3D images of compound 21 with 1CX2.

## 3. Conclusions

To conclude, this is a hitherto first of its kind imidazole derivative conjugated Trp and their ureas and thioureas as a novel class of bioactive compounds, which have potential as antioxidant, anti-microbial and anti-inflammatory agents. Thus, the singular molecular framework having multitasking potentiality to cure multiple diseases should be looked as fore front in drug discovery. Molecular docking studies on active site of *tyrosine kinase* (PDB ID: 2HCK), *glucosamine-6-phosphate (GlcN-6-P) synthase* (PDB ID: 2VF5) and *cyclooxygenase-2* (PDB ID: 1CX2) revealed good binding interaction. The correlation between molecular docking studies and biological assays suggested that compounds bearing EDGs ($OCH_3$ and $CH_3$) were excellent antioxidants whereas those substituted with EWGs (F, Cl and $NO_2$) were excellent antimicrobial and anti-inflammatory agents.

## Acknowledgements

The authors gratefully acknowledge Department of Science and Technology (DST), New Delhi for awarding Inspire Fellowship, University Grant Commission (UGC), New Delhi for awarding BSR Faculty Fellowship and UGC-Post Doctoral Fellowship (PDFSS). We also acknowledge DST-Purse and Computer Science department (HPC Lab) for providing instrumentation facility and docking facility respectively.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.01.027.

## References

[1] C.T. Keith, A.A. Borisy, B.R. Stockwell, Nat. Rev. Drug Discov. 4 (2005) 71–78.
[2] J.L. Hartman, B. Gravik, L. Hartwell, Science 291 (2001) 1001–1004.
[3] Z. Ling, P. Xin-Mei, L.V.D. Guri, G. Rong-Xia, Z. Cheng-He, Med. Res. Rev. 34 (2014) 340–437.
[4] N. Rani, A. Sharma, G.K. Gupta, Randhir Singh, Mini-Rev. Med. Chem. 13 (2013) 1812–1835.
[5] H.M. Faidallah, K.A. Khan, A.M. Asiri, J. Fluor. Chem. 132 (2011) 131–137.
[6] R.S. Upadhayaya, G.M. Kulkarni, N.R. Vasireddy, J.K. Vandavasi, S.S. Dixit, V. Sharma, et al., Bioorg. Med. Chem. 17 (2009) 4681–4692.
[7] S. Saeed, N. Rashid, P.G. Jones, M. Ali, R. Hussain, Eur. J. Med. Chem. 45 (2010) 1323–1331.
[8] E.M. Guantai, K. Ncokazi, T.J. Egan, J. Gut, P.J. Rosenthal, P.J. Smith, et al., Bioorg. Med. Chem. 18 (2010) 8243–8256.
[9] H.K. Kumara, D.C. Gowda, Int. J. Pept. Res. Ther. 23 (2017) 259–267.
[10] H.K. Kumara, R. Suhas, D.M.S. Vardhan, J.S. Kumar, D.C. Gowda, Med. Chem. Res. 27 (2018) 1504–1516.
[11] G.P. Suresha, R. Suhas, W. Kapfo, D.C. Gowda, Eur. J. Med. Chem. 46 (2011) 2530–2540.
[12] R. Suhas, S. Chandrashekar, D.C. Gowda, Eur. J. Med. Chem. 48 (2012) 179–191.
[13] B.J. Ullas, P.G. Chandrashekar, R. Suhas, K.P. Rakesh, P. Avinash, D.C. Gowda, J. Chem. Appl. Biochem. 2 (2015) 116–123.
[14] K.S. Babu, A.R. Tagore, G.S. Reddy, G. Venkateswarlu, P.P. Reddy, R.V. Anand, ARKIVOC 2 (2010) 292–302.
[15] B.J. Ullas, P.G. Chandrashekara, R. Suhas, S.M. Anil, D.C. Gowda, Int. J. Chem. Pharm. Sci. 4 (2013) 79–87.
[16] L. Blois, Nature 181 (1958) 1199–1200.
[17] I. Glucin, Innov. Food. Sci. Emerg. Technol. 11 (2010) 210–218.
[18] R. Re, N. Pellegrini, A. Proteggente, A. Pannala, M. Yang, C. Rice-Evan, Free Radic. Biol. Med. 26 (1999) 1231–1237.
[19] A. Perez-Gonzalez, L. Munoz-Rugeles, J.R. Alvarez-Idaboy, RSC Adv. 4 (2014) 56128–56131.
[20] K.P. Rakesh, H.M. Manukumar, D.C. Gowda, Bioorg. Med. Chem. Lett. 25 (2015) 1072–1077.
[21] H. Sudhamani, S.K.T. Basha, S. Adam, S. Madhusudhana, A. Usha Rani, Res. Chem. Intermed. 43 (2017) 103–120.
[22] M.V.B. Reddy, D. Srinivasulu, K. Peddanna, C. Apparao, P. Ramesh, Synth. Commun. 45 (2015) 2592–2600.
[23] O.K. Bitzer-Quintero, A.J. Davalos-Marın, G.G. Ortiz, A.R. Angel Meza, B.M. Torres-Mendoza, R.G. Robles, et al., Biomed. Pharmacother. 64 (2010) 77–81.
[24] C. Perez, M. Paul, P. Bazerque, Acta Biol. Med. Exp. 56 (1990) 113–115.
[25] I. Singh, V.P. Singh, Phytomorphology 50 (2000) 151–157.
[26] Y. Ozkay, Y. Tunali, H. Karaca, I. Isikdag, Eur. J. Med. Chem. 45 (2010) 3293–3298.
[27] G. Gomathi, R. Gopalakrishnan, Mater Sci. Eng. C. 64 (2016) 133–138.
[28] B. Bano, Kanwal, K.K. Mohammed, A. Lodhi, U. Salar, F. Begum, et al., Bioorg. Chem. 80 (2018) 129–144.
[29] U.A. Shinde, A.S. Phadke, A.M. Nair, A.A. Mungantiwar, V.J. Dikshit, M.N. Saraf, Fitoterapia 70 (1999) 251–257.
[30] A.P. Keche, G.D. Hatnapure, R.H. Tale, A.H. Rodge, S.S. Birajdar, V.M. Kamble, Bioorg. Med. Chem. Lett. 22 (2012) 3445–3448.
[31] S.G. Rhee, Science 312 (2006) 1882–1883.
[32] C.M. Krejsa, G.L. Schieven, Environ. Health Perspect. 106 (1998) 1179–1184.
[33] H.K. Kumara, R. Suhas, D.M. Suyoga Vardhan, M. Shobha, D.C. Gowda, RSC Adv. 8 (2018) 10644–10653.
[34] S. Milewski, Biochim. Biophys. Acta 1597 (2002) 173–192.
[35] A. Teplyakov, G. Obmolova, M.A. Badet-denisot, B. Badet, Protein Sci. 8 (1999) 596–602.
[36] A. Palomer, F. Cabre, J. Pascual, J. Campos, M.A. Trujillo, A. Entrena, et al., J. Med. Chem. 45 (2002) 1402–1411.