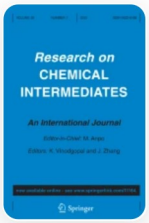
Exploring the antioxidant potential of bis-1,2,3-triazolyl-*N*-phenylacetamides

Published: 12 December 2022

Volume 49, pages 635–653, (2023) Cite this article



Research on Chemical Intermediates

Aims and scope

Submit manuscript

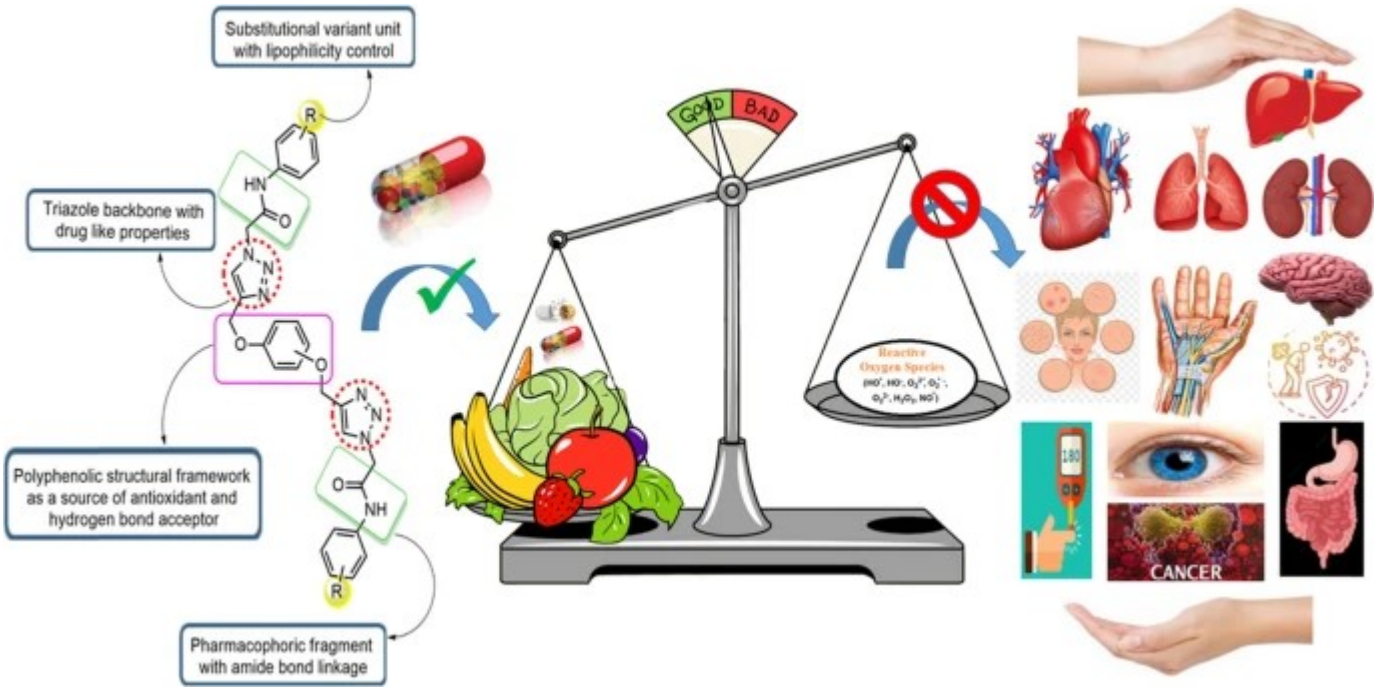
Tejshri R. Deshmukh, Vijay M. Khedkar, Jaiprakash N. Sangshetti & Bapurao B. Shingate

Abstract

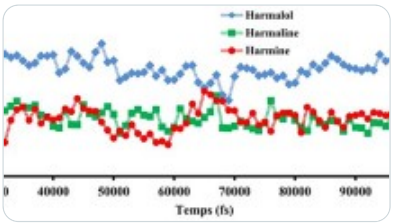
Oxidative stress causes an imbalance between formation and accumulation of reactive oxygen species in cells and tissue, leading to various chronic and degenerative illnesses, viz. aging, cataract, cancer, rheumatoid arthritis, autoimmune disorders, and cardiovascular and neurodegenerative diseases. In this study, we have screened a library of bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z) for their in vitro antioxidant activity via 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay. A detailed structure activity relationship study was

undertaken to identify the key substitution contributing to the antioxidant activity followed by molecular docking study against enzyme myeloperoxidase (MPO). Myeloperoxidase is a heterodimeric, cationic, and glycosylated heme enzyme, which gets released under increased oxidative stress producing neutrophil oxidant, hypochlorous acid having the capacity to modify various biomolecules by chlorination and/or oxidation of sulfhydryl groups in proteins causing their inactivation and promoting tissue damage. The in silico binding affinity study could shed light on the binding modes of these molecules and further identify the thermodynamic interactions with active site residues governing the binding affinity. This in silico study could provide a platform for structure-based optimization of bis-1,2,3-triazolyl-*N*-phenylacetamides as potential modulators of pro-oxidative tissue injury pertubated by the MPO/H_2O_2/HOCl/HOBr system. Here, the ultimate study results illustrated that most of the derivatives were more active than standard antioxidant agent. Hence, this study also serves a significant contribution in the discovery of potent antioxidants in future research.

Graphical Abstract



Similar content being viewed by others



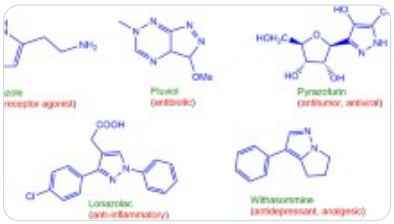
In vitro antioxidant activities of five β-carboline alkaloids, molecular docking, and...

Article | 07 March 2022

Antioxidant activities and molecular docking of 2-thioxobenzo[g]quinazoline derivatives

Article | Open access

09 April 2019



Environmentally benign synthesis of substituted pyrazoles as potent antioxidant agents,...

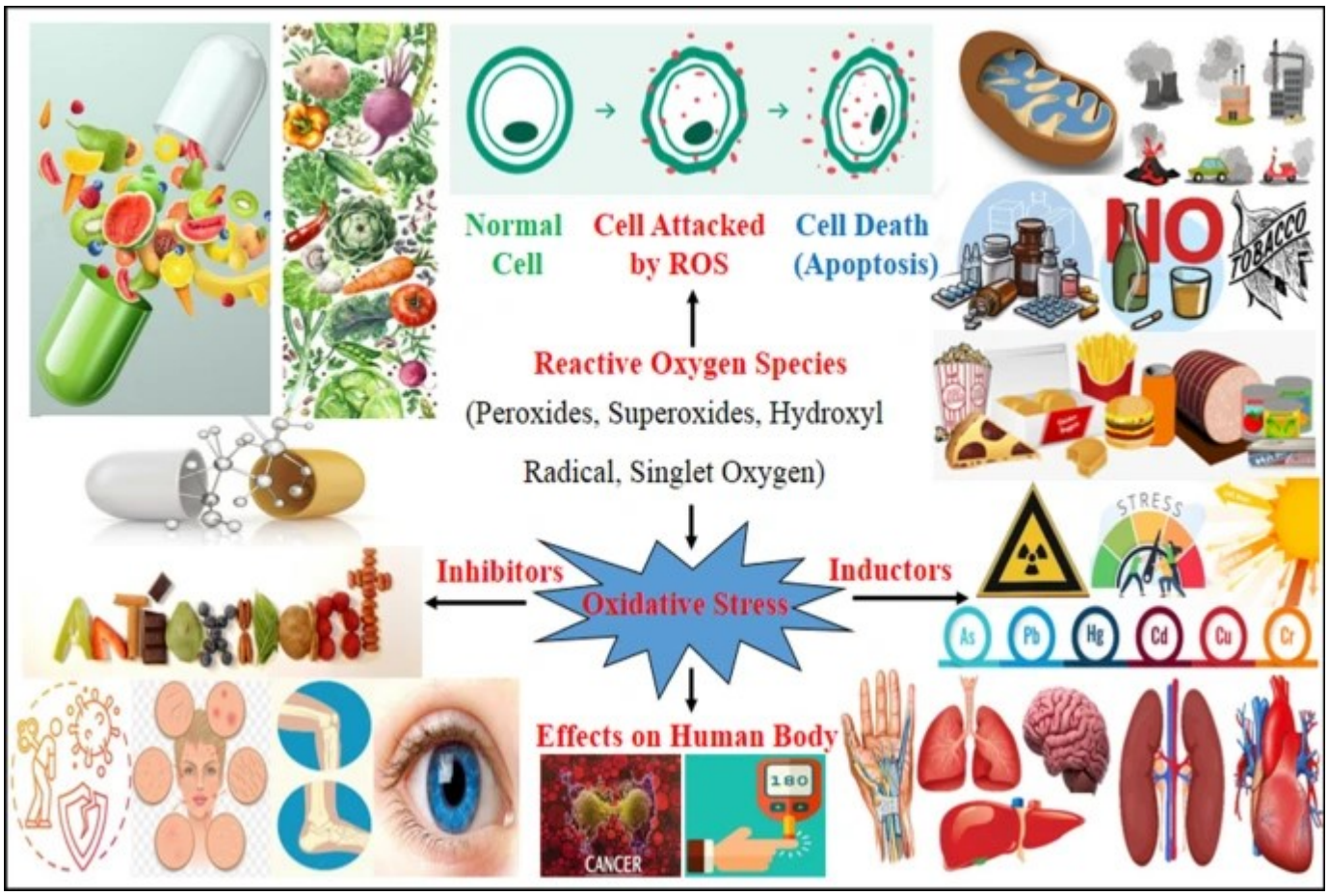
Article | 26 August 2020

Introduction

Reactive oxygen species (ROS) in the form of free radicals (superoxide, singlet oxygen, hydroxyl radical, and nitric oxide) and neutral molecules (hydrogen peroxide) induce damage of biological macromolecules (lipids, proteins, and DNA) under oxidative stress [1]. Thus, it leads to various diseases such as carcinogenesis, cell aging, drug-associated toxicity, inflammation, cardiovascular, and neurodegenerative diseases [2]. ROS are continuously produced as by-products of mitochondrial electron transport during cellular respiration in the body. ROS can also be generated from numerous endogenous sources such as peroxisomes, endoplasmic reticulum, inflammatory cytokinesis, and cyclooxygenase as well as exogenous sources such as consumption of drugs, tobacco, processed food, alcohol, synthetic solvents, heavy metals, UV irradiation, radioactive rays, ionizing radiations, smoking, and air pollution [3]. ROS are unstable species, which readily react with other molecules to achieve stability. While some radicals have essential roles in normal cell processes such as neural signal transduction, excessive free radical incursion can damage all components of the cell. Oxidative stress is the pro-oxidative state, when the ROS level exceeds the capability of defense mechanisms [4]. Figure 1 summarizes inhibitors and inductors of oxidative stress as well as

their effects on human body and cell apoptosis in a single framework.

Fig. 1



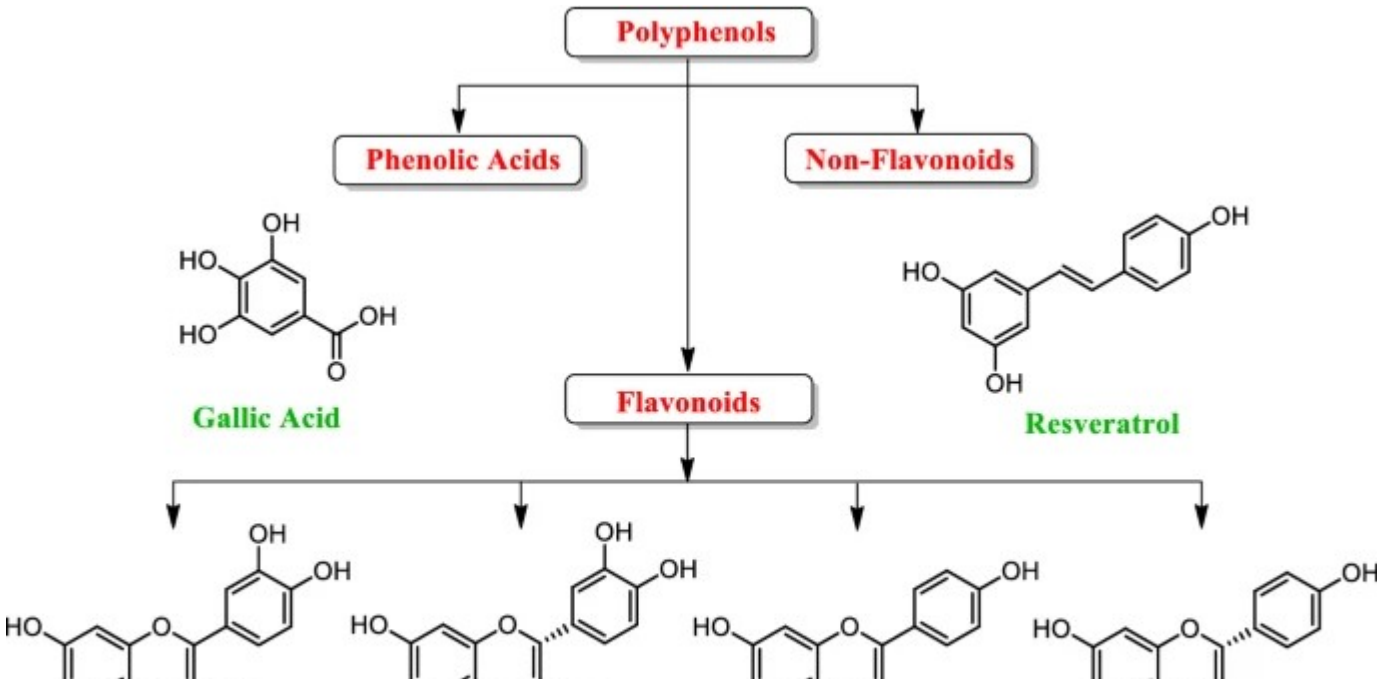
Pictorial presentation of inhibitors and inductors of oxidative stress as well as its effect on human body and cell apoptosis by the attack of ROS on normal cell

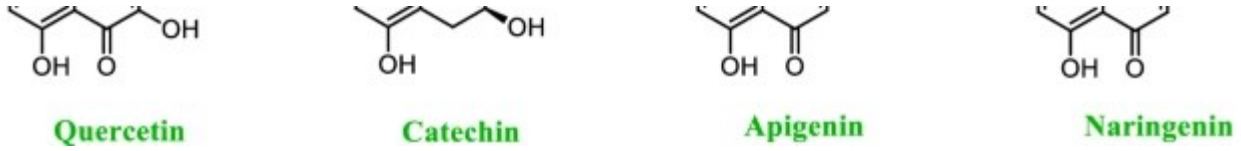
The human body has several mechanisms to counteract oxidative stress with the help of antioxidant defense systems. These are chemicals, which either naturally produce enzymes (endogenous antioxidants) in human body or are externally provided through foods and/or supplements (exogenous antioxidants) that can react with free radicals, terminate their chain reactions, and reduce ROS levels, by which damage to essential biomolecules can be prevented [5]. Myeloperoxidase (MPO) is an endogenous antioxidant, heterodimeric, cationic, and glycosylated heme enzyme, which is abundantly expressed in neutrophils, lesser extent in monocytes, and certain type of macrophages. Under increased oxidative stress, it produces

neutrophil oxidant, hypochlorous acid (HOCl) capable of modifying biomolecules by chlorination and/or oxidation of sulfhydryl groups in proteins causing their inactivation and promoting tissue damage. Evidence has emerged that MPO-derived oxidants contribute to major adverse events and that levels of MPO-derived chlorinated compounds are specific biomarkers for disease progression, which has attracted considerable interest in the development of therapeutically useful MPO inhibitors [6].

However, without exogenous antioxidant compounds, the endogenous antioxidant defense systems are incomplete. For this reason, there is a wide scope of research interest in the field of antioxidants and many compounds have been widely studied for their antioxidant activities, using various methodologies [7,8,9,10]. Dietary polyphenols are essentially included in our diet via vegetables, fruits, grains, cereals, spices, chocolates, and beverages [11,12,13]. It is a significant group of naturally occurring exogenous antioxidants [14]. But, synthetic polyphenols are an organic compound having one or more aromatic rings with one more than one hydroxyl groups in its structural skeleton. Therefore, for molecular designing or synthesis of antioxidant agents, polyphenolic group as a lead precursor is used to enhance the antioxidant activity [15,16,17]. There are several polyphenols such as gallic acid, resveratrol, quercetin, catechin, apigenin, and naringenin having better antioxidant activity as shown in Fig. 2.

Fig. 2

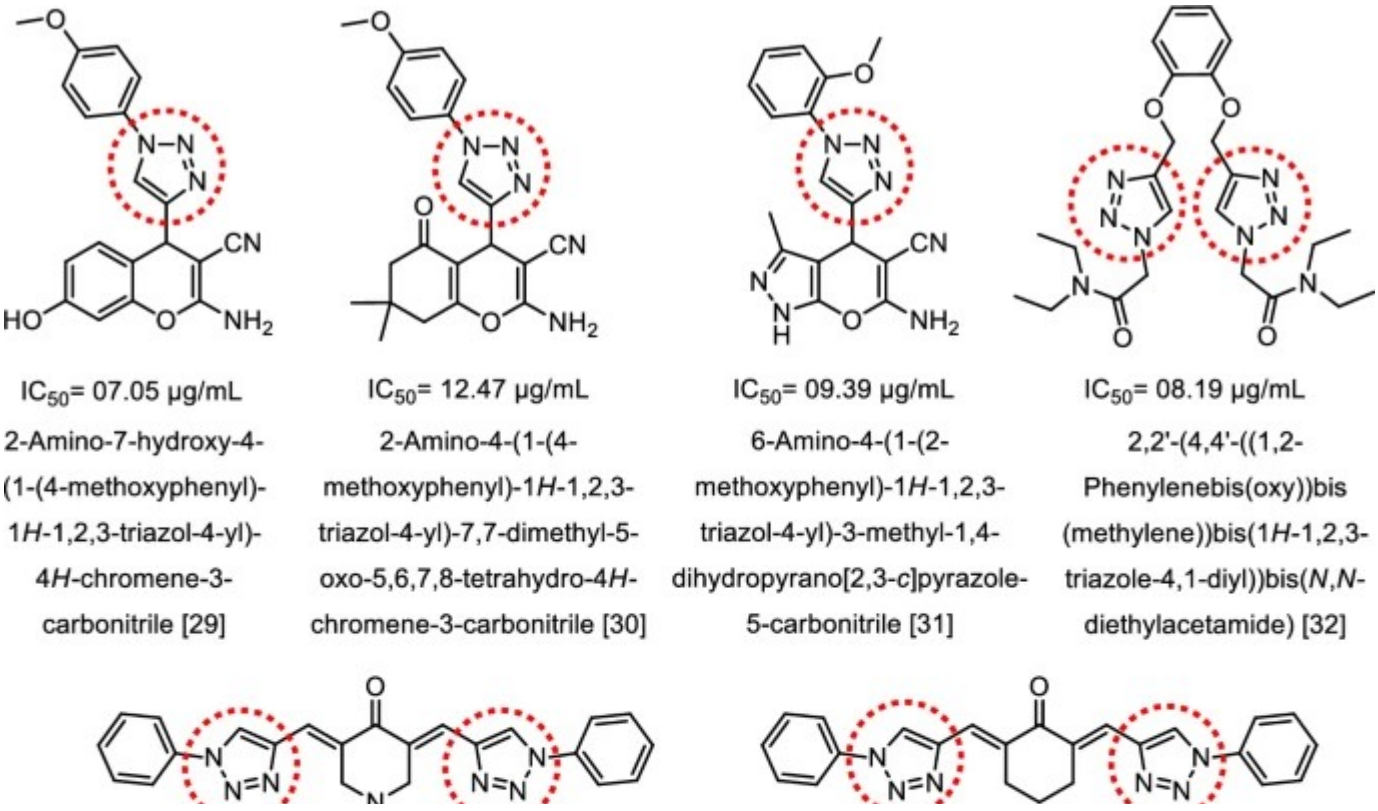


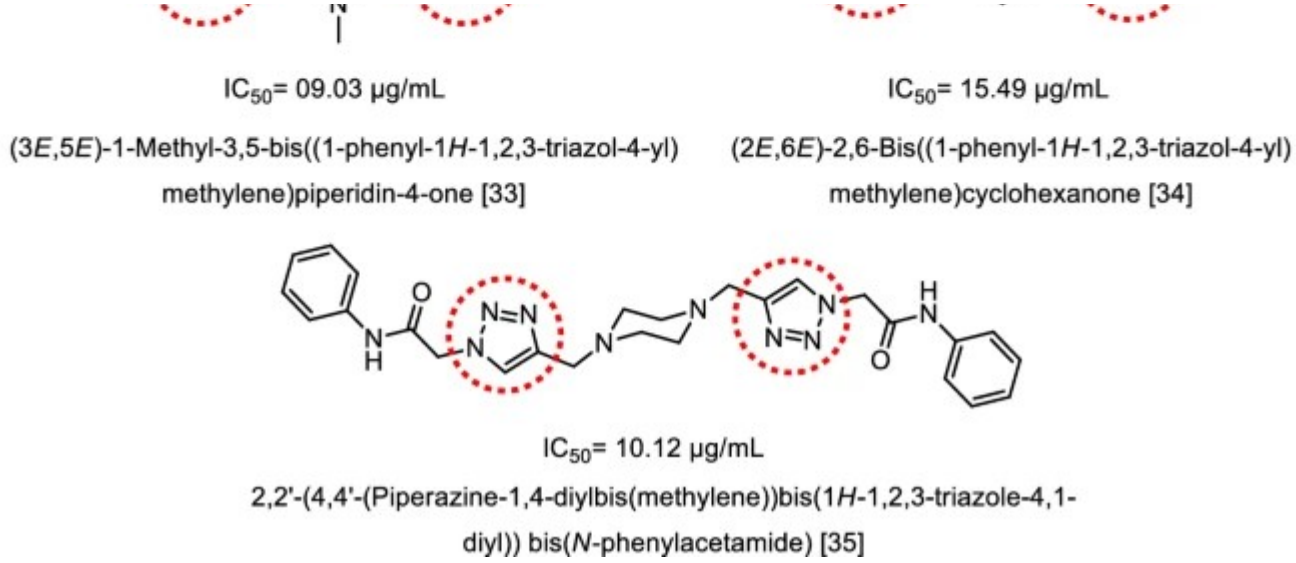


Chemical structures of some polyphenols having better antioxidant activity

Amide derivatives plays a vital role in biological activities. Most of researchers are fascinated to synthesize 1,4-disubstituted-1,2,3-triazoles as they act as a bioisostere of amide with high binding affinity toward biological targets [18]. Sharpless and Meldal [19, 20] regioselectively synthesized 1,4-disubstituted 1,2,3-triazoles by using copper (I)-catalyzed 1,3-dipolar cycloaddition reaction of terminal alkyne and azide with the help of click chemistry approach [21]. 1,2,3-Triazole hybrids displays various biological activities such as antifungal [22], antibacterial [23], antiviral [24], antitubercular [25], anticancer [26], anti-inflammatory [27], and antioxidant [28]. Recently, we have also reported various monomeric, dimeric, or bis-1,2,3-triazolyl derivatives with potent antioxidant activity [29,30,31,32,33,34,35]. Some of the most active antioxidants are represented in Fig. 3.

Fig. 3





Representative structures of 1,2,3-triazolyl hybrids having potent antioxidant activity

In view of the therapeutic significance of monomeric, dimeric, or bis-1,2,3-triazolyl derivatives as antioxidant agents and in continuation of our earlier research on bis-1,2,3-triazolyl-*N*-phenylacetamides synthesis [36, 37], herein, we would like to report the antioxidant activity of bis-1,2,3-triazolyl-*N*-phenylacetamides from polyphenols as a source of lead precursor with hope to obtain potent antioxidant agents. The in silico molecular docking is considered as complementary to the biological activity for predicting affinity and specificity for the selected therapeutic targets to facilitate drug discovery process [38]. In order to gain insight into their mechanism of action and to predict the biomolecular interactions, which contributed to their antioxidant activity, herein, we have also performed the in silico molecular docking study against enzyme myeloperoxidase.

Experimental section

Procedure for (evaluation of DPPH radical scavenging) antioxidant activity

The antioxidant activity of all the synthesized compounds (3a–z) has been assessed in vitro by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay [39], and the results were compared with standard synthetic antioxidant BHT (butylated hydroxytoluene). The

hydrogen atom or electron-donating ability of the compounds was measured from the bleaching of the purple colored methanol solution of 1,1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. Here, we have added the 1 mL of various concentrations of the test compounds (5, 10, 25, 50, and 100 mg/mL) in methanol to 4 mL of 0.004% (w/v) methanol solution of DPPH. The reaction mixture was incubated at 37 °C. The scavenging activity on DPPH was determined by measuring the absorbance at 517 nm after 30 min. All tests were performed in triplicate, and the mean values were entered. The percent of inhibition (*I* %) of free radical production from DPPH was calculated by a chain-breaking mechanism [40] using following equation:

$$ \% {\text{ of scavenging }} = \, \left[{\left({A_{{{\text{control}}}} - A_{{{\text{sample}}}} } \right)/\left({A_{{{\text{sample}}}} \times 100} \right)} \right] $$

where A_{control} is the absorbance of the control (DPPH radical without test sample), A_{sample} is the absorbance of the test sample (DPPH radical with test sample), and the control contains all reagents except the test samples.

Protocol for molecular docking study

Molecular docking studies have been performed using the *Glide* (grid-based ligand docking with energetics) module of the Schrödinger molecular modeling package (Schrödinger, LLC, New York, NY) [41] for the synthesized bis-1,2,3-triazolyl-*N*-phenylacetamides, which exhibited promising antioxidant activity, in order to find their preferred binding conformations in the biological target. With this purpose, the starting coordinates of the human myeloperoxidase enzyme (MPO) (PDB code: 4C1M) at a 2.0 Å resolution in complex with the inhibitor were retrieved from the Protein Data Bank [42] and refined using the *Protein Preparation Wizard.* This pre-processing involves deleting crystallographic water molecules, assignment of the correct bond orders and angles, creation of disulfide bonds, identification of atomic overlaps, and addition of hydrogen atoms corresponding to pH 7.0. Following assignment of appropriate charge and protonation state, finally the prepared enzyme structure was subjected to energy minimization to relieve the steric clashes among the residues, using OPLS-2005 force field until the average RMSD of the non-hydrogen atoms reached 0.3 Å. Next, the 3D structures of the ligands, i.e., bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z), were sketched with the *build* panel. Their geometries were refined

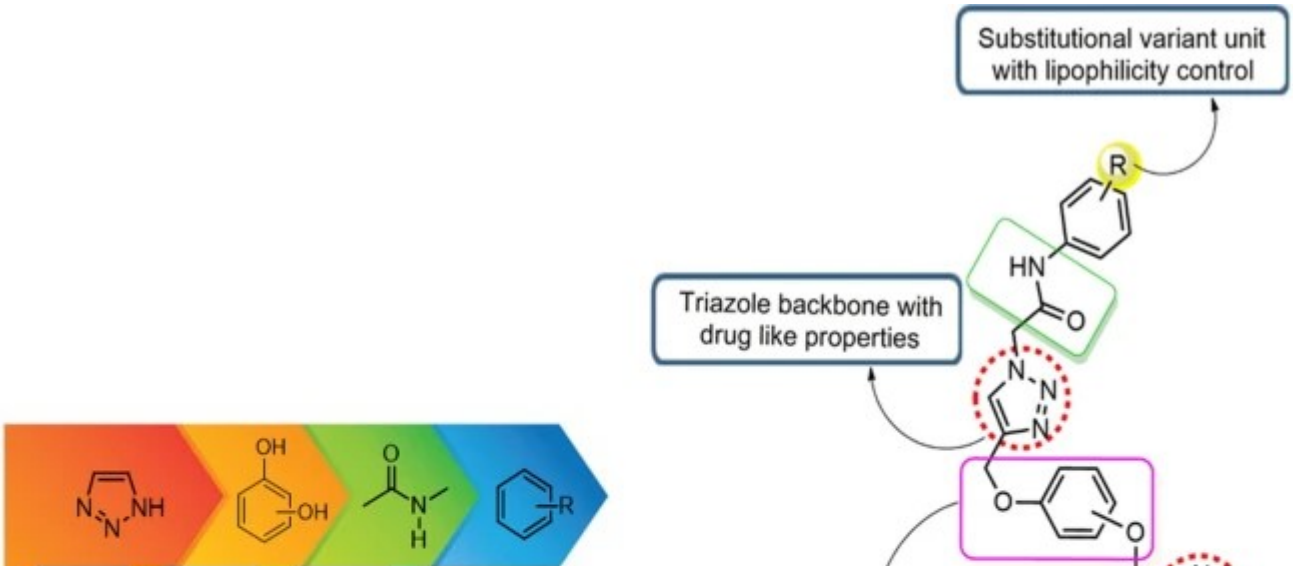
using *ligand preparation* panel in Maestro which involved addition of hydrogens, correction of chiralities and ionization states, generation of ring conformations, and adjusting the realistic bond lengths and angles. Following the assignment of the partial charges using the OPLS-2005 force field and their energy minimization, the shape and properties of the active site of myeloperoxidase (MPO) enzyme were characterized and set up for docking using the *receptor grid generation* panel. The panel uses the native ligand as the reference coordinate as it signifies the active site of a molecule. Followed by generation of a grid box of 12 × 12 × 12 Å around the centroid of the co-crystallized ligand, these energy minimized structures of ligands were subjected to docking against MPO enzyme using with extra precision (i.e., GlideXP) scoring function to gauze the enzyme–ligand binding affinities and mode of interaction. The docking poses generated for these ligands as output file were visualized through the Maestro's pose viewer utility and analyzed for the key thermodynamic interactions (bonded and nob-bonded) with the active site residues.

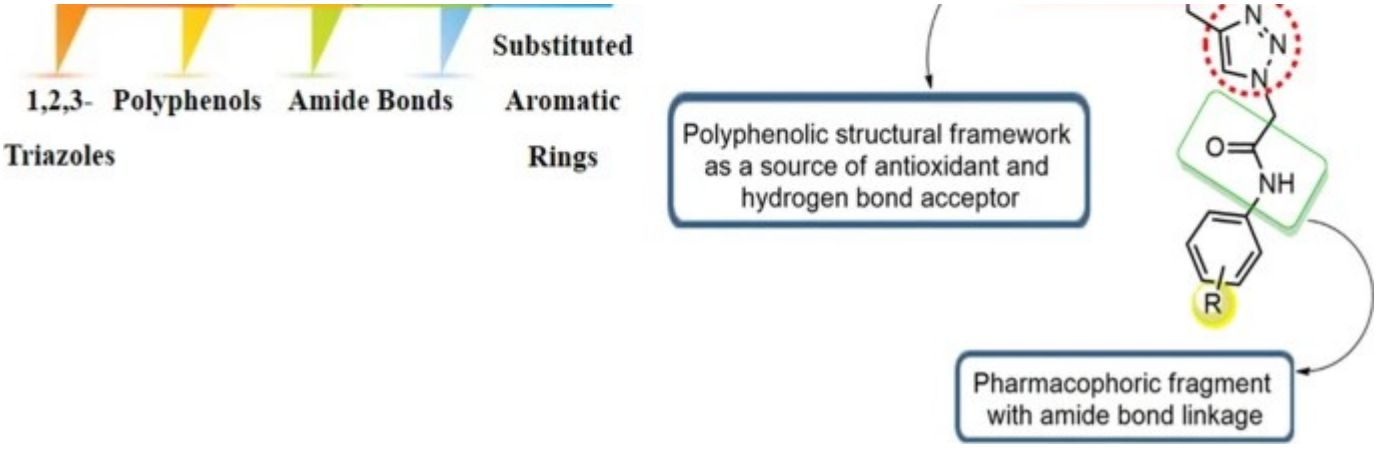
Results and discussion

Chemistry

The molecular structural framework of bis-1,2,3-triazolyl-*N*-phenylacetamides was originated designed by using molecular hybridization of pharmacophoric components such as 1,2,3-triazoles, polyphenol, amide bond, and substituted aromatic rings as shown in Fig. 4.

Fig. 4



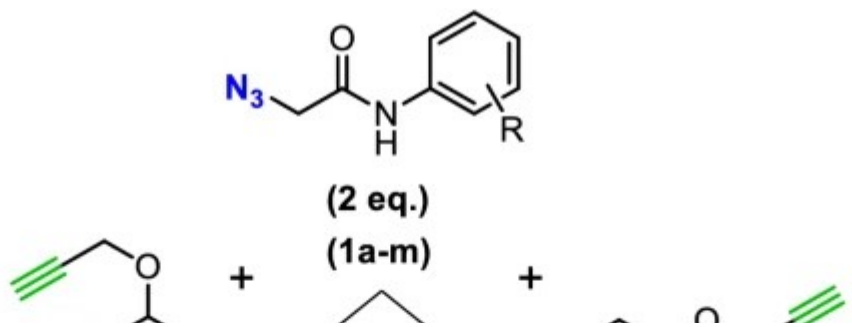


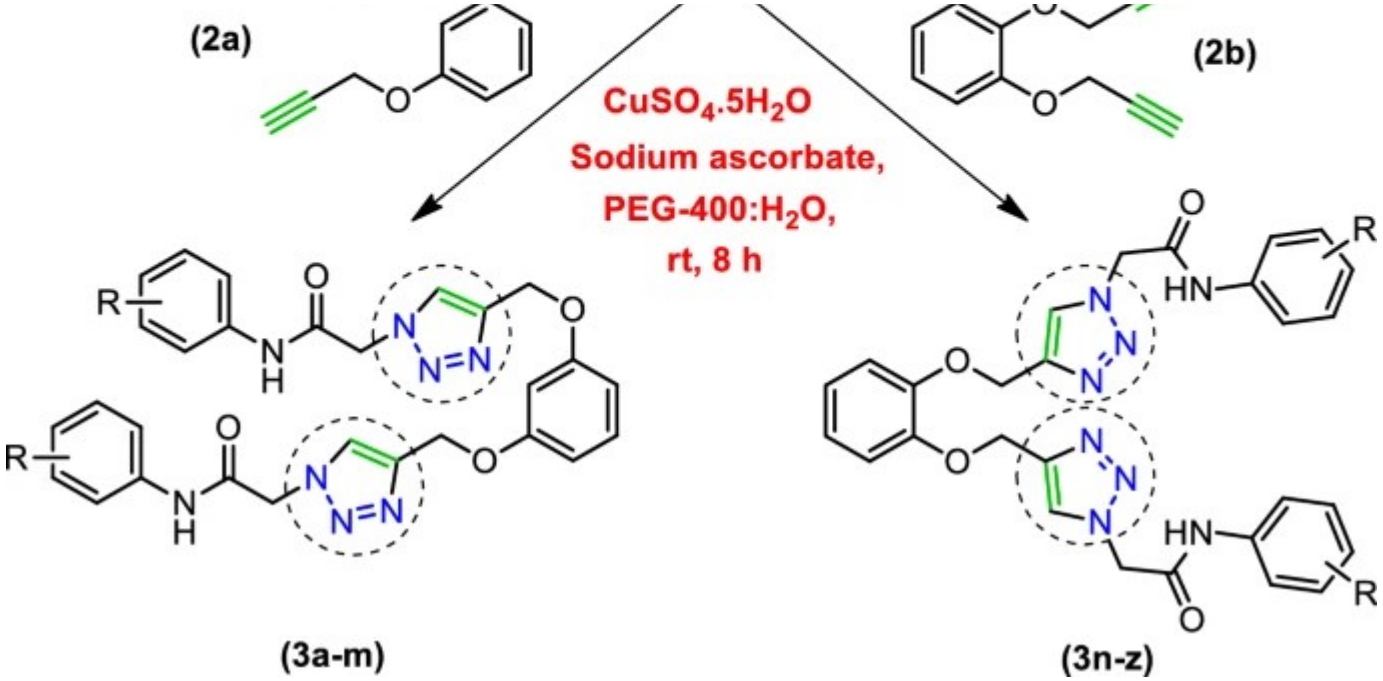
Molecular design strategy for the synthesis of bis-1,2,3-triazolyl-*N*-phenylacetamides

Therefore, the current molecular design was sketchily divided into four segments. The first one is symmetrically positioned 1,2,3-triazolyl units that shows drug-like properties and performs as the main backbone of the molecular design strategy. The second component is polyphenolic units of 1,2- or 1,3-diaryloxy moiety in the structural framework as a source of lead antioxidant and hydrogen bond acceptor. The next one is amide bonds, which play a vital role in the bioactive molecular designing. Lastly, substituted aromatic rings act as variant units to synthesize a library of bis-1,2,3-triazolyl-*N*-phenylacetamide derivatives that may enhance the bioactivity as well as control the lipophilicity.

As per above molecular designing strategy, we have already reported the synthesis of bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z) by using click chemistry approach via multi-step synthetic pathway [36] as demonstrated in Scheme 1 as well as characterized by various spectral analysis techniques such as ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry.

Scheme 1.





Synthesis of bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z) via click chemistry approach

Antioxidant activity

All the newly synthesized bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z) were evaluated for their in vitro antioxidant activity by using DPPH radical scavenging assay. Here, we have used butylated hydroxytoluene (BHT) as a standard antioxidant agent for the comparative study. All the obtained activity, lipophilicity factors, and molecular docking score results are collectively incorporated in Table 1.

Table 1 Antioxidant activity, lipophilicity factors, and docking score of compounds (3a–z)

According to bioactivity results from Table 1, we have observed that most of the synthesized compounds show excellent antioxidant activities with promising lower IC_{50} values as compared to the standard antioxidant agent BHT. According to DPPH assay, among all compounds of the series 14 hybrids show good to excellent radical scavenging activity than the standard antioxidant agent BHT specifically, 3a, 3b, 3f, 3h, 3j, 3k, 3l, 3m, 3n, 3o, 3s, 3t, 3u,

and 3w. The IC_{50} values of the active compounds were found to be in the range of 8.74–16.05 µg/mL, whereas an IC_{50} value of BHT is 16.47 µg/mL. It proves that the active compounds of the newly synthesized series were found to be more potent than the standard BHT used for comparative antioxidant activity study.

From Table 1, we observed that compounds 3o, 3n, 3s, 3t, and 3m displayed the highest radical scavenging activity than BHT with IC_{50} values 8.74, 9.12, 9.84, 10.03, and 10.11 µg/mL, respectively. Some more compounds such as 3a, 3w, 3b, 3k, and 3u show IC_{50} values 11.01, 11.44, 12.32, 12.85, and 13.32 µg/mL, respectively, whereas the compounds 3j, 3h, 3l, and 3f were also more potent than BHT with IC_{50} values 15.04, 15.17, 15.17, and 16.05 µg/mL, respectively. The remaining compounds 3c, 3d, 3e, 3g, 3i, 3p, 3q, 3r, 3v, 3x, 3y, and 3z had less antioxidant activity than BHT. But, when we compared the activity results of the synthesized compounds with our previously reported monomeric form of 1,2,3-triazolyl hybrids [43], it was observed that most of the compounds have shown excellent antioxidant activity.

The lipophilicity is one of the factors that enhance the eminence and therapeutic success of any drug molecules [44]. Every drug should pass through several biomembranes to reach at the targeted sites for its better in vitro action [45]. Lipophilicity is one of the physicochemical properties, which are based on the values of Log *P*/Clog. Therefore, to study the correlation of bioactivity of synthesized compounds with lipophilicity parameters such as Log *P* and Clog *P*, they were calculated using ChemBioDraw Ultra 12.0 software, and the results are included in Table 1. It was known that if the values of Log $P \leq 5$, then the compounds show better lipophilicity. It was found that all the synthesized compounds having values of Log *P* and Clog *P* are in acceptable range, that is, (≤ 5) 1.162–4.4824. Hence, all the compounds show excellent lipophilic properties that help to accelerate the rate of therapeutic success.

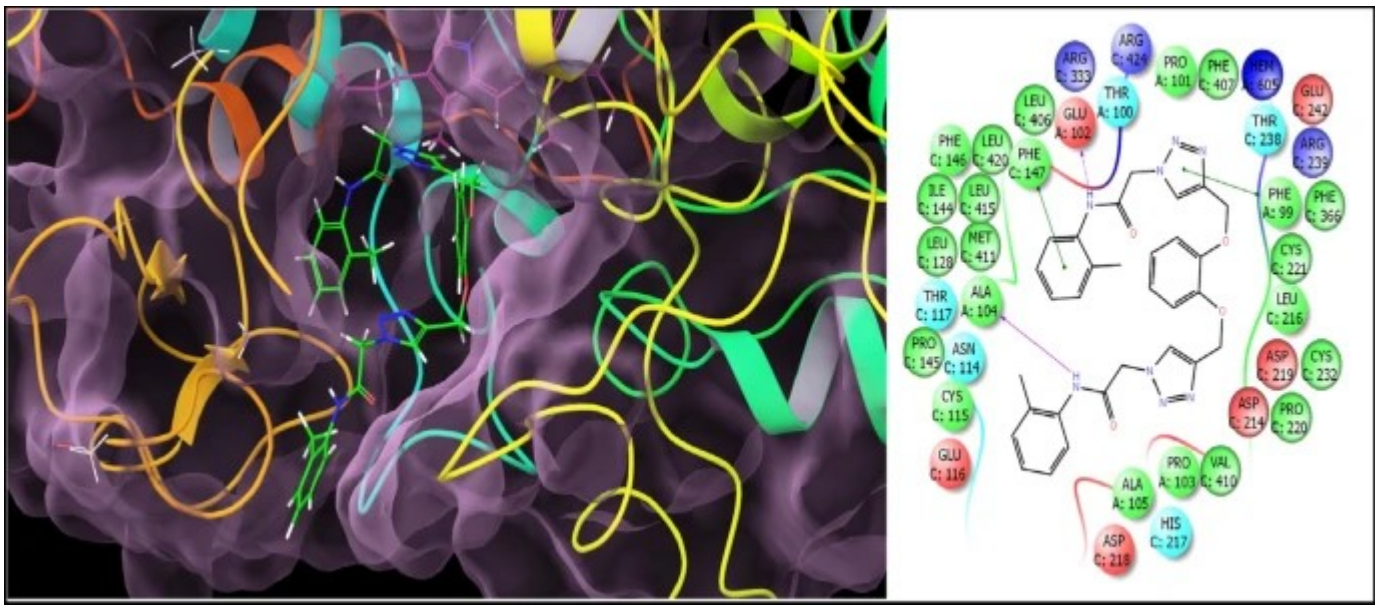
Molecular docking study

In order to validate the in vitro antioxidant activity of bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z), we investigated its mechanism of action from the viewpoint of in silico system. Docking simulation could position the compounds into the human myeloperoxidase enzyme (MPO) active site adequately to explain the probable reasons why the compounds have shown significant antioxidant activities. Their minimum energy docked conformations could

snuggly fit into the binding cavity of MPO at coordinates close to the co-crystallized ligand engaging in a network of favorable bonded and non-bonded interactions with the surrounding residues. The results were analyzed based on docking scores, binding energies along with the interactions between compounds and the key residues of MPO as summarized in Table 1.

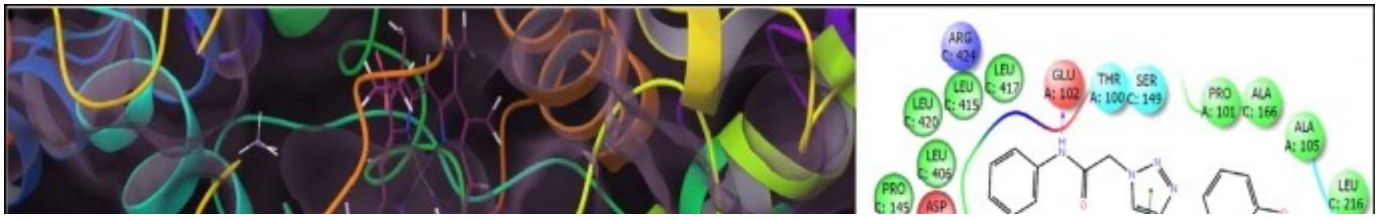
Here, we have discussed in detail the binding mode of the most active analogue 3o for the sake of brevity. The analysis of ligand–receptor complex based on the bonded and non-bonded interactions shows that compound 3o displayed a remarkable interaction with myeloperoxidase enzyme (Fig. 5).

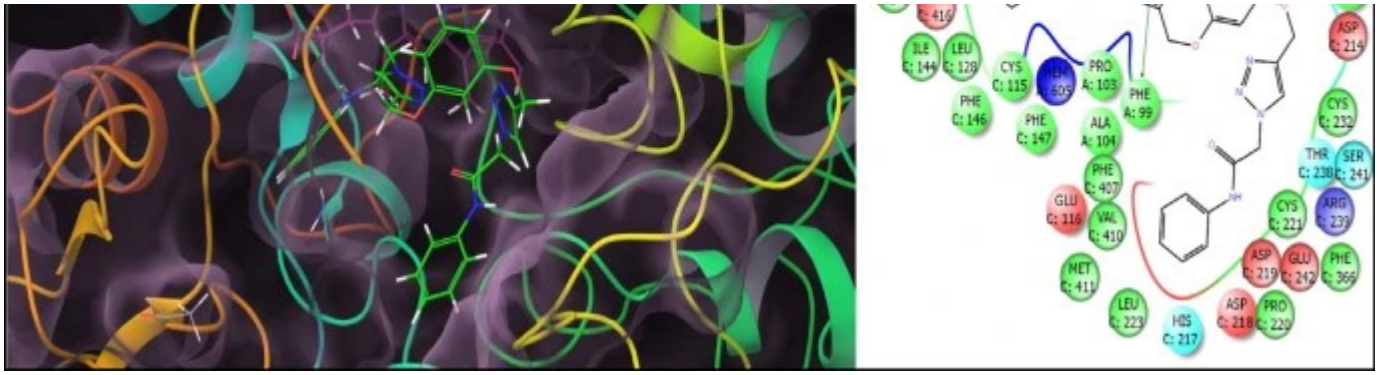
Fig. 5



Binding mode of 3o into the active site of myeloperoxidase (MPO)

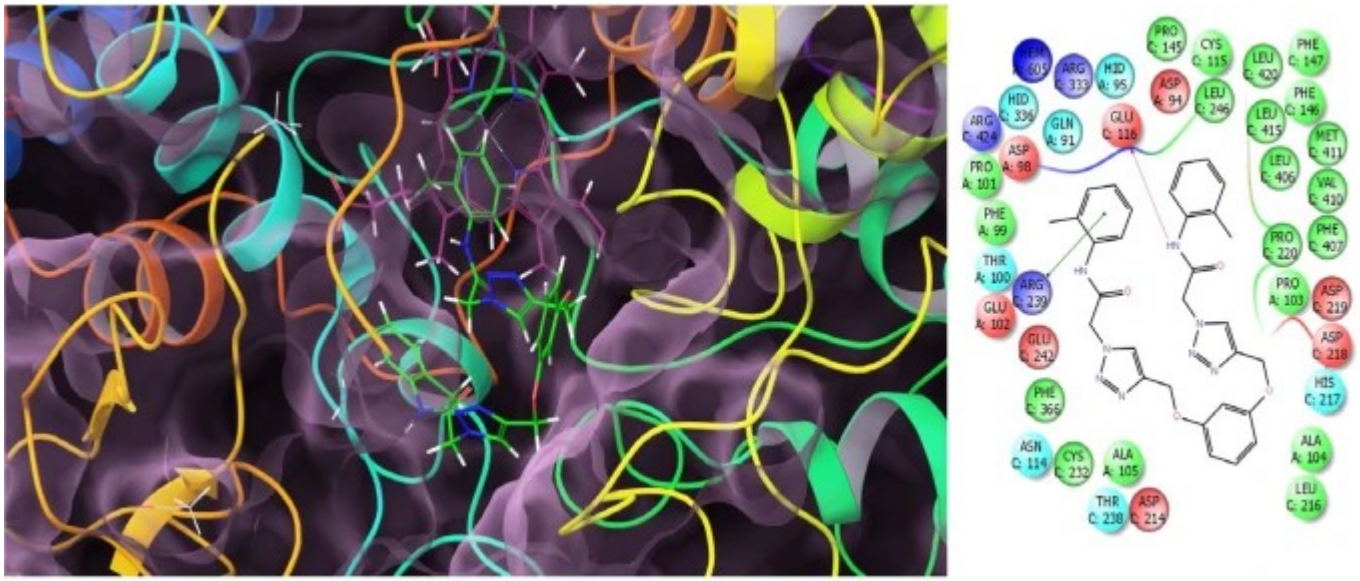
Fig. 6





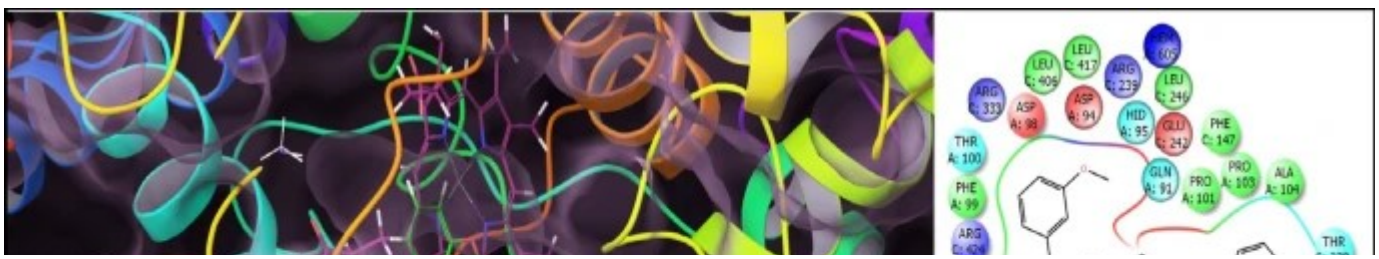
Binding mode of 3a into the active site of myeloperoxidase (MPO)

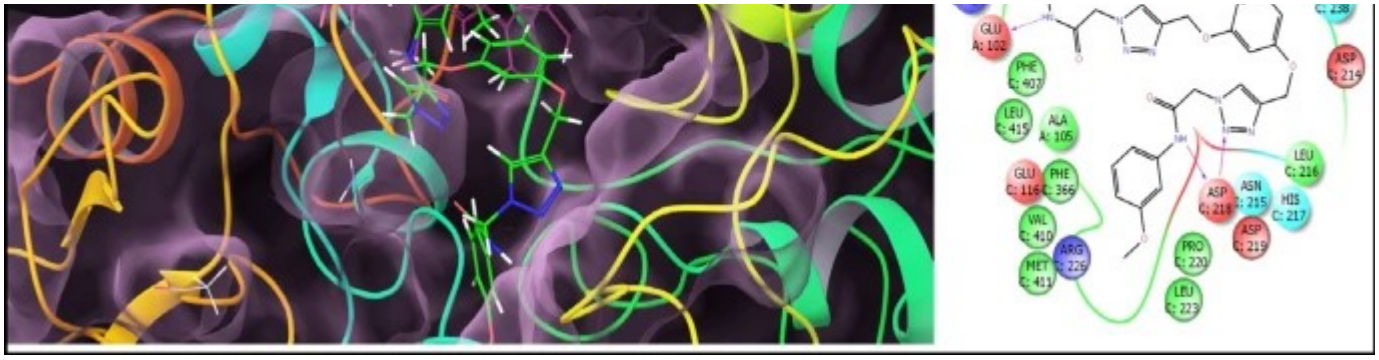
Fig. 7



Binding mode of 3b into the active site of Myeloperoxidase (MPO)

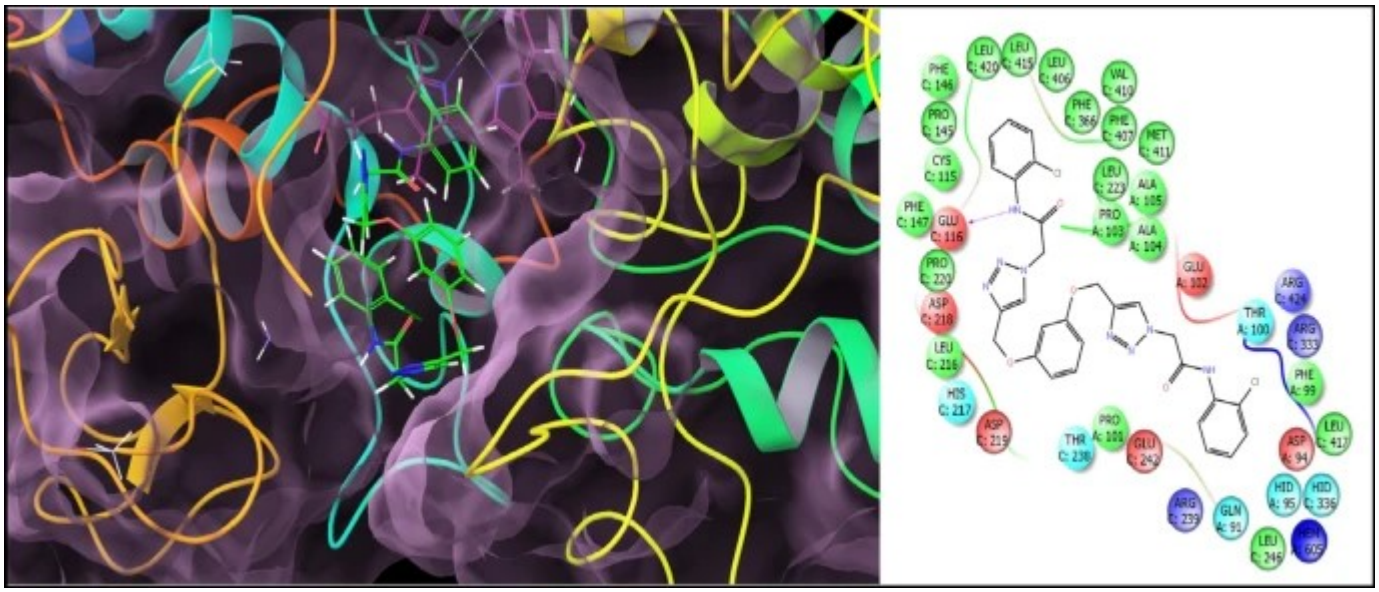
Fig. 8





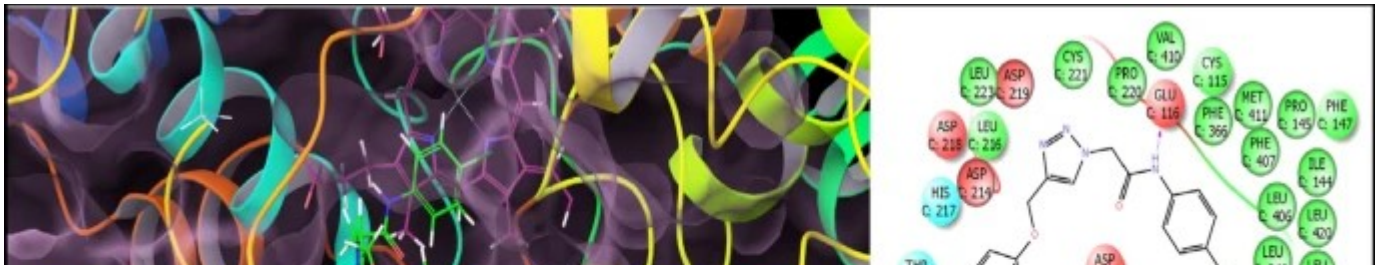
Binding mode of 3f into the active site of myeloperoxidase (MPO)

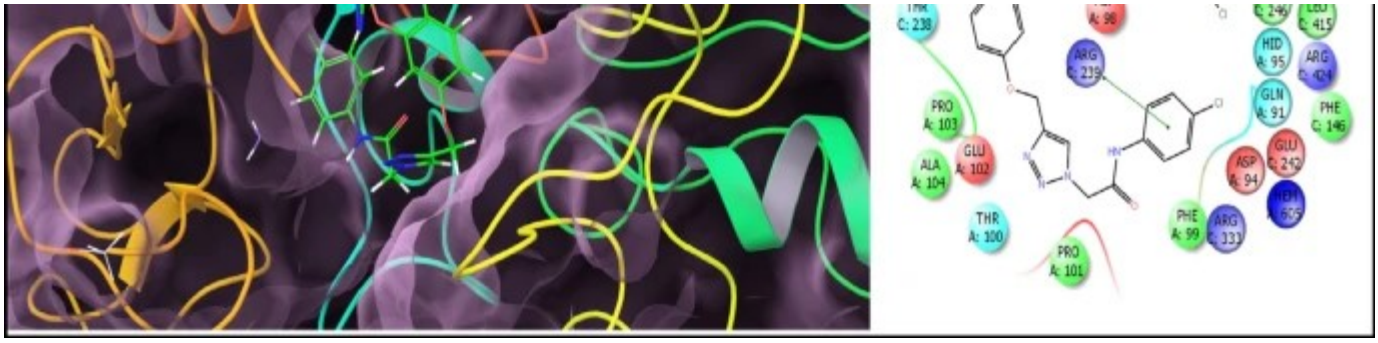
Fig. 9



Binding mode of 3 h into the active site of myeloperoxidase (MPO)

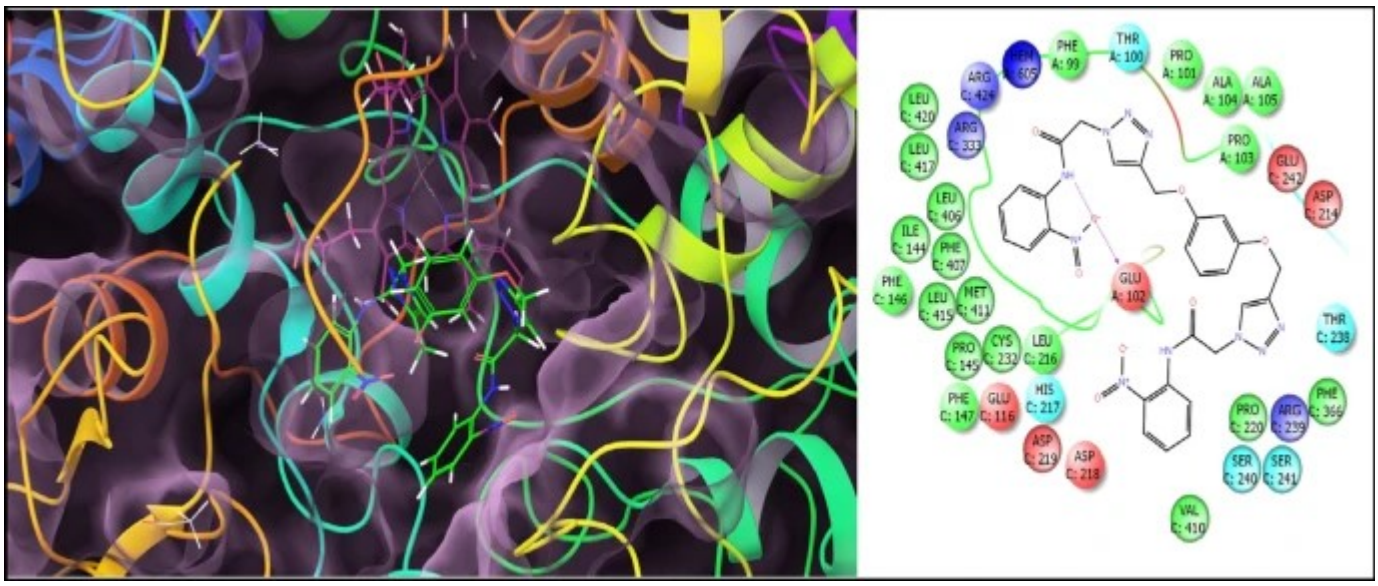
Fig. 10





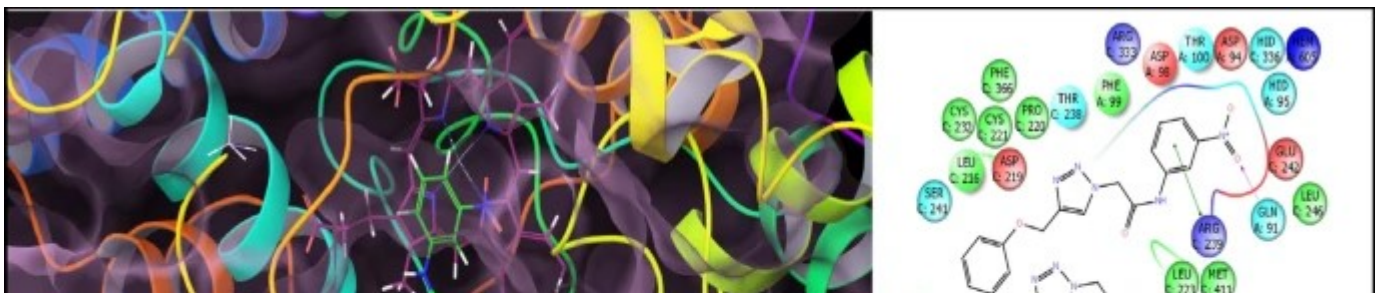
Binding mode of 3j into the active site of myeloperoxidase (MPO)

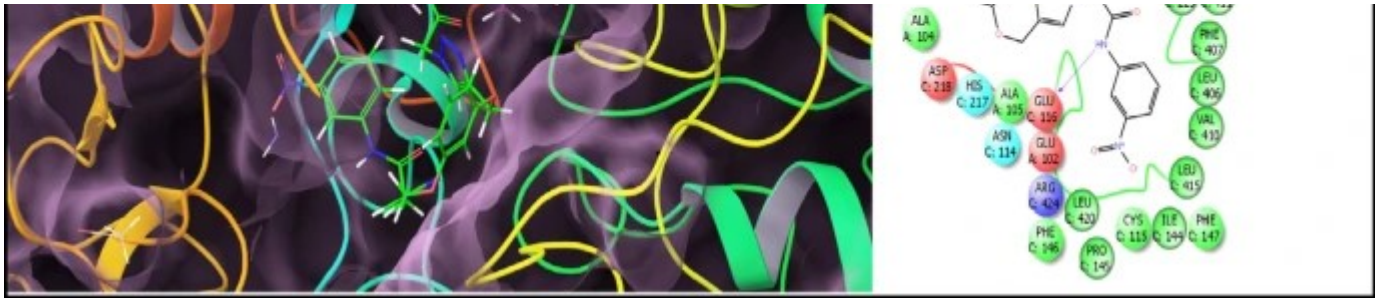
Fig. 11



Binding mode of 3k into the active site of myeloperoxidase (MPO)

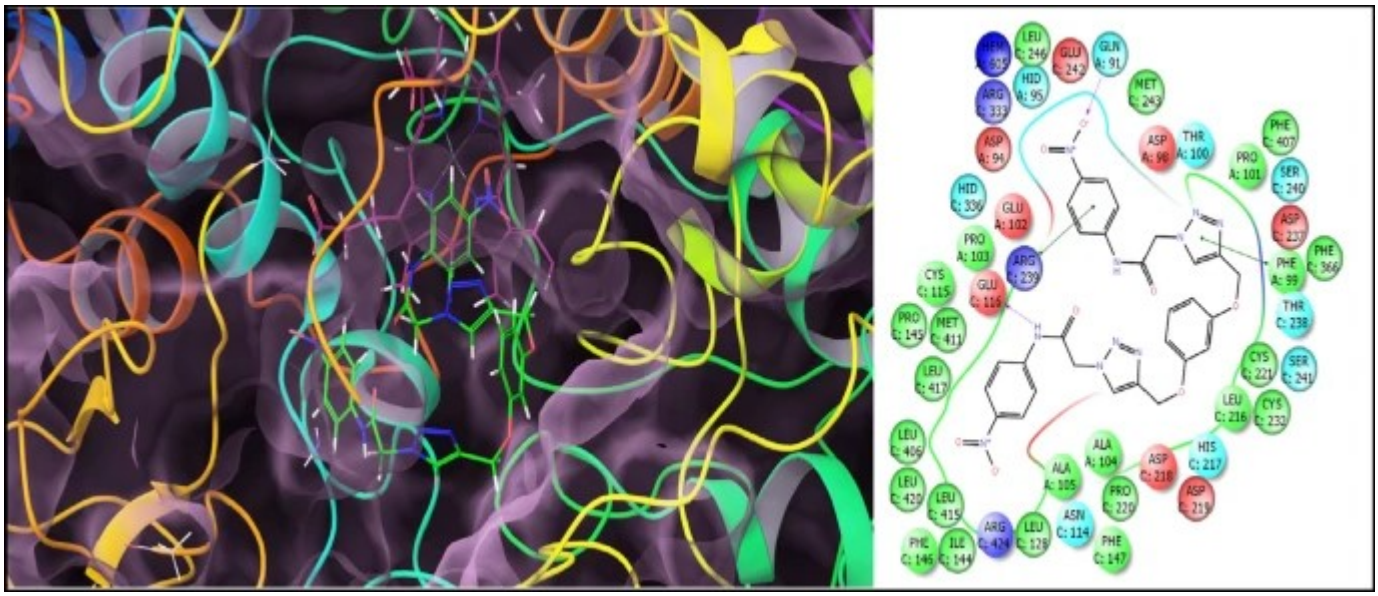
Fig. 12





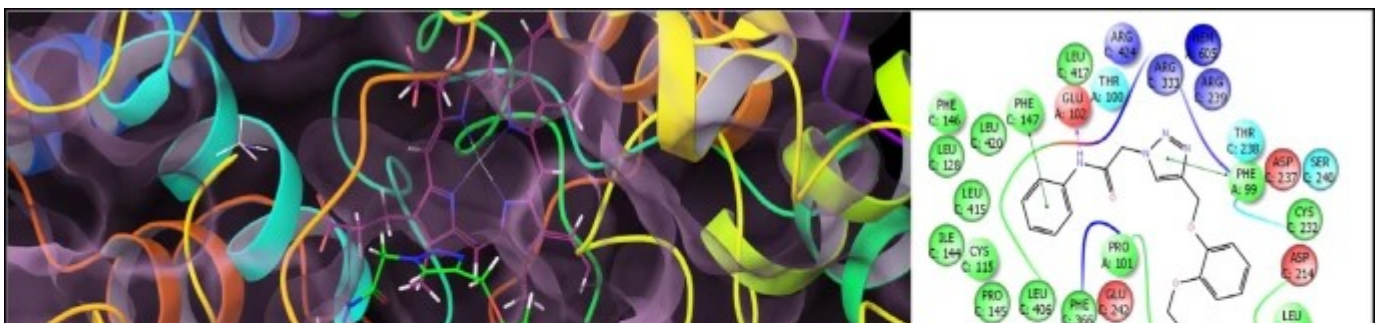
Binding mode of 3l into the active site of myeloperoxidase (MPO)

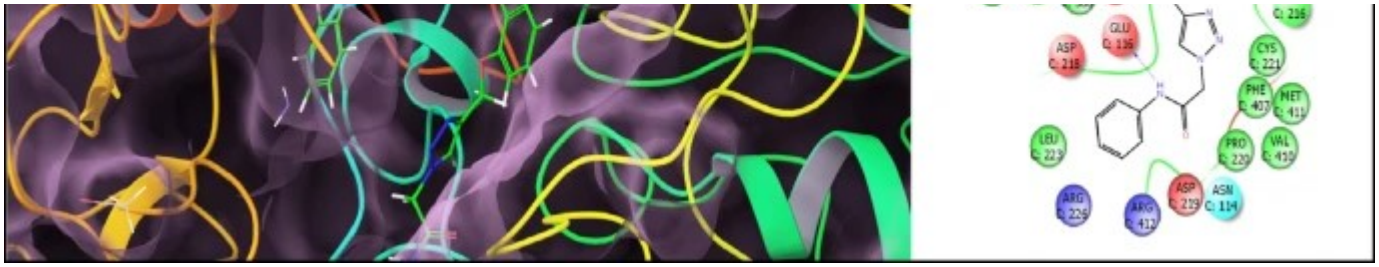
Fig. 13



Binding mode of 3m into the active site of myeloperoxidase (MPO)

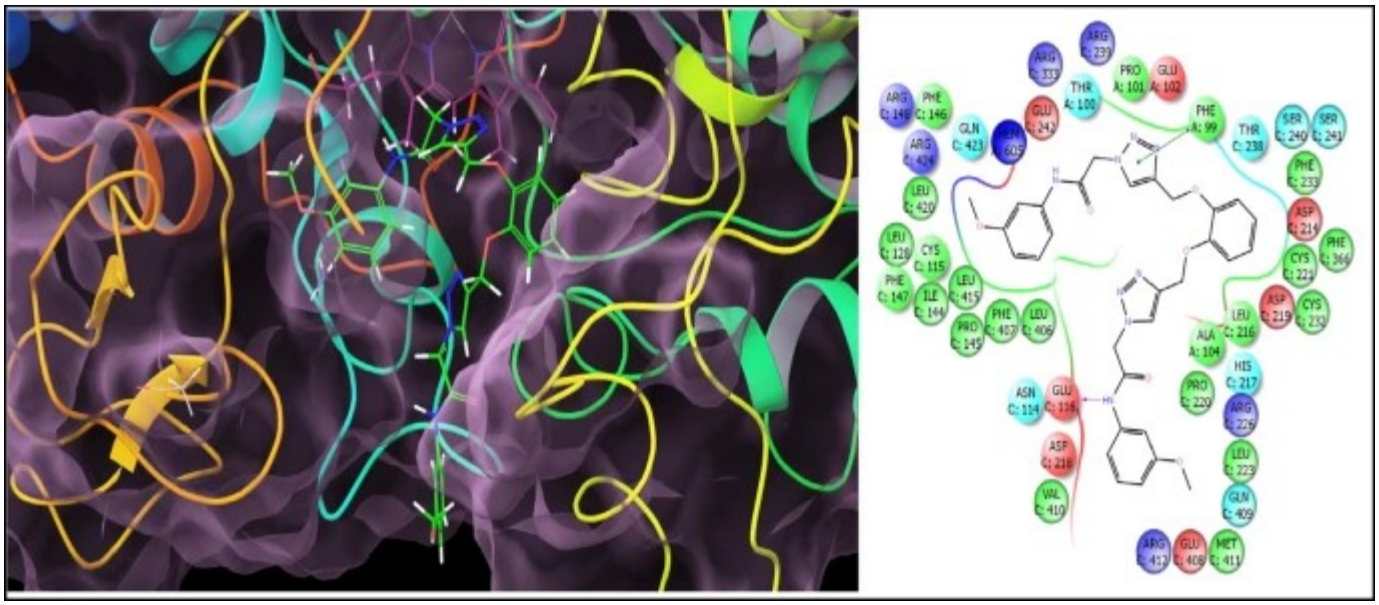
Fig. 14





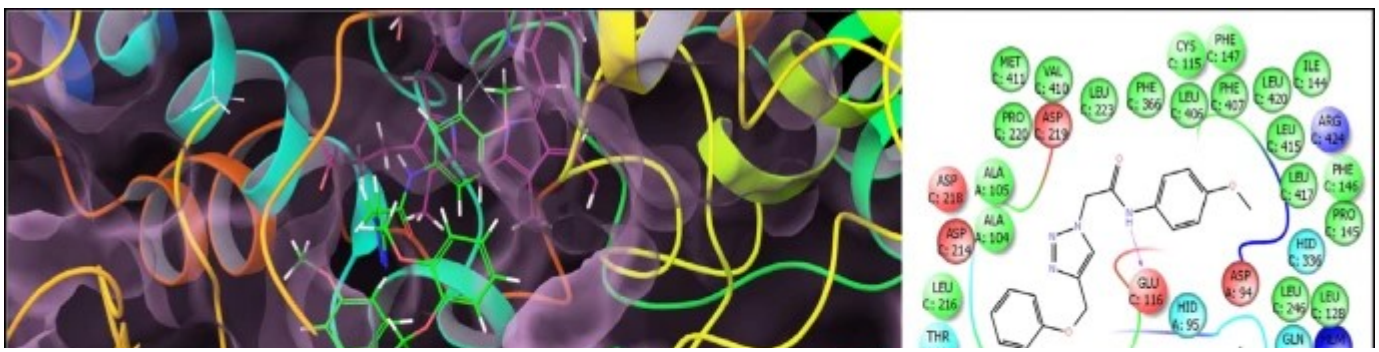
Binding mode of 3n into the active site of myeloperoxidase (MPO)

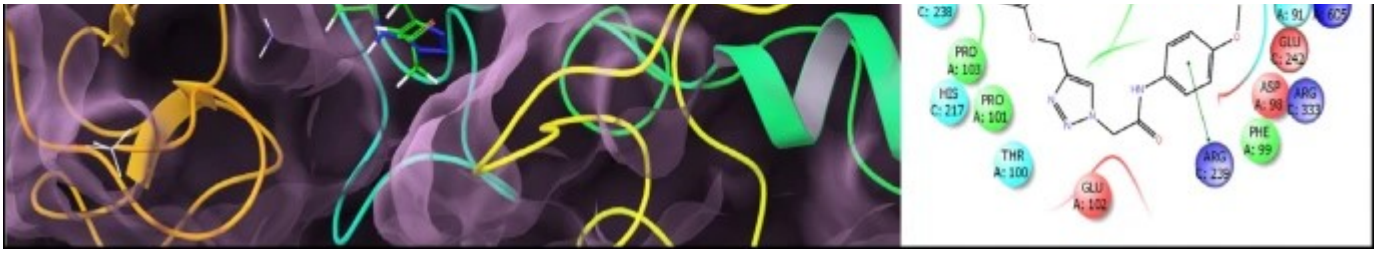
Fig. 15



Binding mode of 3s into the active site of myeloperoxidase (MPO)

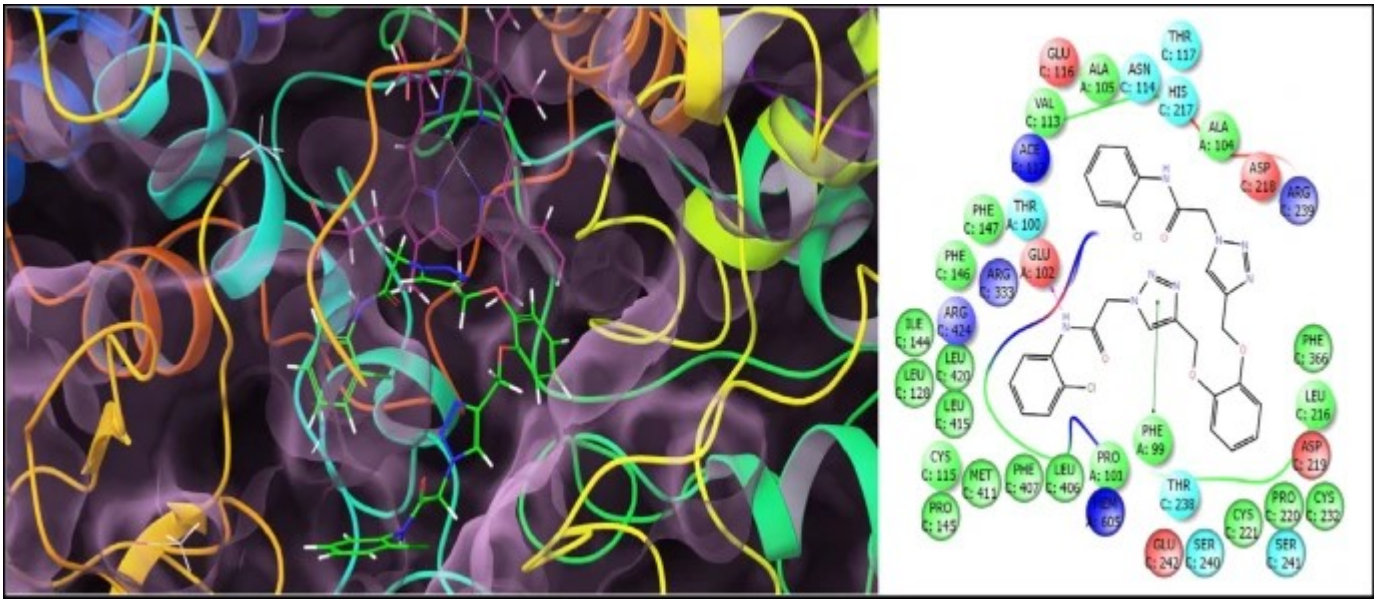
Fig. 16





Binding mode of 3t into the active site of myeloperoxidase (MPO)

Fig. 17



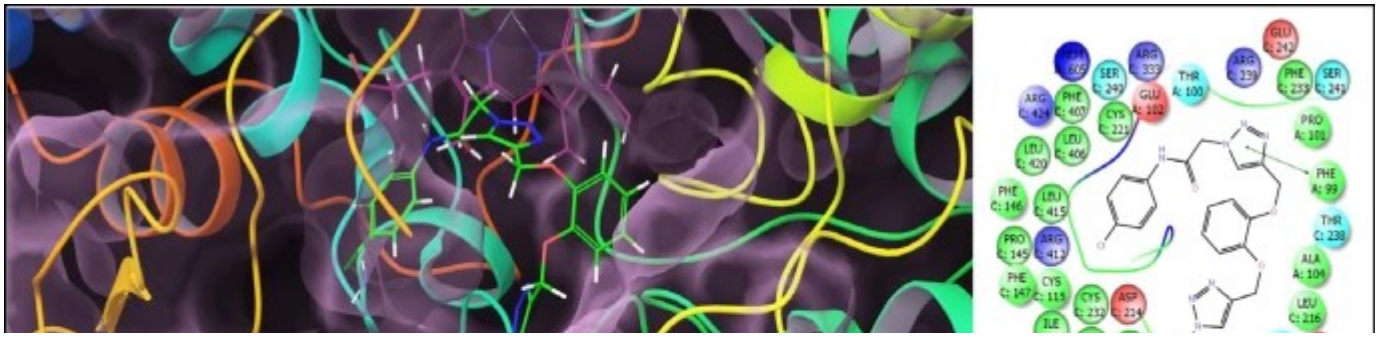
Binding mode of 3u into the active site of myeloperoxidase (MPO)

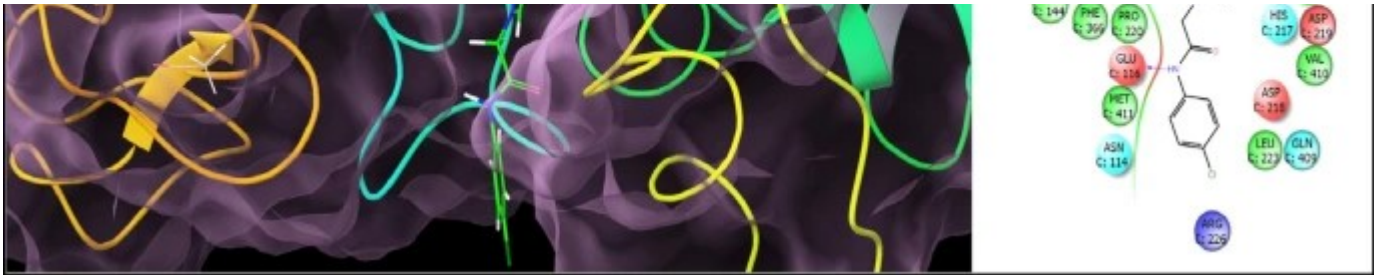
This compound exhibited the highest binding affinity producing a docking score of −8.898 and glide binding energy of − 63.637 kcal/mol. Compound was found to be positioned in the active site of MPO due to a network of significant van der Waals interactions observed between bis(oxy)bis(methylene)bis(1*H*-1,2,3-triazole-4,1-diyl)bis(*N*-(*o*-tolyl)acetamide) side chains and the Phe147 (−2.637 kcal/mol), Phe146 (− 1.501 kcal/mol), Pro145 (− 1.453 kcal/mol), Glu116 (− 2.644 kcal/mol), Asn114 (− 1.688 kcal/mol), Leu420 (− 1.18 kcal/mol), Leu415 (− 1.05 kcal/mol), Met411 (− 1.164 kcal/mol), Val410 (− 1.043 kcal/mol), Phe407 (− 1.473 kcal/mol), Pro220 (− 1.665 kcal/mol), Asp218 (− 4.709 kcal/mol), His217 (− 1.033 kcal/mol), Ala104 (− 3.456 kcal/

mol), Pro103 (− 1.036 kcal/mol), Glu102 (− 1.726 kcal/mol), Pro101 (− 1.13 kcal/mol), Thr100 (− 1.513 kcal/mol), and Phe99 (− 2.52 kcal/mol) residues lining the active site of MPO. Similarly, the central phenylene ring also showed a very promising van der Waals interactions with Hem605 (− 3.756 kcal/mol), Phe366 (− 1.823 kcal/mol), Arg239 (− 2.115 kcal/mol), Thr238 (− 2.249 kcal/mol), Leu216 (− 1.416 kcal/mol), and Asp98 (− 1.323 kcal/mol) residues. While these van der Waals interactions were found to be the major driving force behind the enhanced binding affinity, significant electrostatic interactions observed with Hem605 (− 2.851 kcal/mol), Glu116 (− 1.712 kcal/mol), Asp427 (− 1.039 kcal/mol), Arg239 (− 2.331 kcal/mol), Thr238 (− 1.416 kcal/mol), Asp219 (− 1.651 kcal/mol), Asp218 (− 1.957 kcal/mol), Ala104 (− 1.545 kcal/mol), Glu102 (− 1.451 kcal/mol), and Pro101 (− 1.034 kcal/mol) also contributed to the stability of the complex. Furthermore, compound 3o could also establish two hydrogen bonds through the amide function (-NHCO-) with Glu102 (1.758 Å) and Ala104 (2.483 Å) residues. Also two very close $\pi-\pi$ stacking interactions were observed with Phe99 (2.986 Å) and Phe147 (2.497 Å) residues through the triazole and phenyl ring, respectively. Such hydrogen-bonding and π-stacking interactions "*anchor*" the ligand to guide its orientation into the 3D space of the active site and facilitate the steric and electrostatic interactions.

Analysis of the docking scores and per-residue interactions for the potent molecules in the series showed that even they were engaged in a similar network of bonded and non-bonded interactions (Figs. 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18). In these figures, green lines observed on the right side indicate $\pi-\pi$ stacking interactions, while pink lines represent hydrogen-bonding interactions. A significant correlation was observed between their binding affinities and observed antioxidant activities. Based on their per-residue interaction analysis, a systematic point mutation can be carried out to optimize the scaffold for arriving at compounds with improved potency and selectivity.

Fig. 18





Binding mode of 3w into the active site of myeloperoxidase (MPO)

Conclusion

In conclusion, bis-1,2,3-triazolyl-*N*-phenylacetamides (3a–z) were synthesized and evaluated for their in vitro antioxidant activity by using DPPH radical scavenging assay. The bioactivity results revealed that out of 20 six derivatives of bis-1,2,3-triazolyl-*N*-phenylacetamides, 14 compounds possess more potent antioxidant activity than BHT with IC_{50} values ranging between 8.74 and 16.05 µg/mL. The compound 3o was found as most potent antioxidant agent among all the titled compounds with an IC_{50} value 8.74 µg/mL. The molecular docking studies showed a putative binding mode of the derivatives and their significant interactions with myeloperoxidase (MPO). The study concluded that the compounds with better binding affinity have displayed potent antioxidant activity. Therefore, it has offered an attractive lead series for the discovery of novel antioxidant agents and a powerful encouragement for further research in the same area.

Dedication

Dedicated to all teachers on the occasion of the National Teacher's Day (September 5, 2022).

Availability of data and materials

Not applicable.

References

1. E. Malle, P.G. Furtmüller, W. Sattler, C. Obinger, Br. J. Pharmacol. 152, 838 (2007)

Article CAS Google Scholar

2. N. Mihailovic, V. Markovic, I.Z. Matic, N.S. Stanisavljevic, Z.S. Jovanovic, S. Trifunovic, L. Joksovic, RSC Adv. 7, 8550 (2017)

Article CAS Google Scholar

3. M. Rudrapal, S.J. Khairnar, J. Khan, A.B. Dukhyil, M.A. Ansari, M.N. Alomary, F.M. Alshabrmi, S. Palai, P.K. Deb, R. Devi, Front. Pharmacol. 13, 806470 (2022)

Article CAS Google Scholar

4. E. Mentese, F. Yilmaz, N. Baltas, O. Bekircan, B. Kahveci, J. Enzyme Inhib. Med. Chem. 30, 435 (2015)

Article CAS Google Scholar

5. B. Halliwell, J.M.C. Gutteridge, *Free radicles in biology and medicine* (Oxford University Press, New York, 2015)

Book Google Scholar

6. S. Mandal, K. Shiva, K.P. Kumar, S. Goel, R.K. Patel, S. Sharma, R. Chaudhary, A. Bhati, N. Pal, A.K. Dixit, J. Pharm. Biol. Sci. 9, 88 (2021)

Article Google Scholar

7. J. Wang, H. Tang, B. Hou, P. Zhang, Q. Wang, B.L. Zhang, Y.W. Huang, Y. Wang, Z.M. Xiang,

C.T. Zi, X.J. Wang, J. Sheng, RSC Adv. 7, 54136 (2017)

Article CAS Google Scholar

8. S.K. Dangolani, F. Panahi, Z. Tavaf, M. Nourisefat, R. Yousefi, A.K. Nezhad, ACS Omega 3, 10341 (2018)

Article Google Scholar

9. A.K. Gupta, S. Kalpana, J.K. Malik, Indian J. Pharm. Sci. 74, 481 (2012)

Article CAS Google Scholar

10. L. Andonova, D.Z. Dimitrova, M. Georgieva, A. Zlatkov, Biotechnol. Biotechnol. Equip. 28, 1165 (2014)

Article Google Scholar

11. A. Abdülmelik, B. Ercan, A. Yusuf, T. Fikret, A. Hüseyin, K. Ömer, Iran. J. Chem. Chem. Eng. 37, 209 (2018)

Google Scholar

12. E. Bursal, R. Boğa, Prog. Nutr. 20, 167 (2018)

Google Scholar

13. E. Bursal, A. Aras, Ö. Kılıç, K. Buldurun, Nat. Prod. Res. 35, 4794 (2021)

Article CAS Google Scholar

14. R. Tsao, Nutrients 2, 1231 (2010)

Article CAS Google Scholar

15. R. Pulido, L. Bravo, F. Saura-Calixto, J. Agric. Food Chem. 48, 3396 (2000)

Article CAS Google Scholar

16. A. Scalbert, I.T. Johnson, M. Saltmarsh, Am. J. Clin. Nutr. 81, 215S (2005)

Article CAS Google Scholar

17. F. Shahidi, P. Ambigaipalan, J. Funct. Foods 18, 820 (2015)

Article CAS Google Scholar

18. D. Dheer, V. Singh, R. Shankar, Bioorg. Chem. 71, 30 (2017)

Article CAS Google Scholar

19. H.C. Kolb, K.B. Sharpless, Drug Discov. Today. 8, 1128 (2003)

Article CAS Google Scholar

20. C.W. Tornoe, C. Christensen, M. Meldal, J. Org. Chem. 67, 3057 (2002)

Article CAS Google Scholar

21. R.A. Brawn, M. Welzel, J.T. Lowe, J.S. Panek, Org. Lett. 12, 336 (2010)

Article CAS Google Scholar

22. R.G. Lima-Neto, N.N.M. Cavalcante, R.M. Srivastava, F.J.B. Mendonca, A.G. Wanderley,

R.P. Neves, J.V. dos Anjos, Molecules 17, 5882 (2012)

Article CAS Google Scholar

23. S.M.M. Lopes, J.S. Novais, D.C.S. Costa, H.C. Castro, A.M.S. Figueiredo, V.F. Ferreira, T.M.V.D.P. Melo, F.C. Silva, Eur. J. Med. Chem. 143, 1010 (2018)

Article CAS Google Scholar

24. I.E. Glowacka, J. Balzarini, A.E. Wroblewski, Eur. J. Med. Chem. 70, 703 (2013)

Article CAS Google Scholar

25. A.A. Ali, D. Gogoi, A.K. Chaliha, A.K. Buragohain, P. Trivedi, P.J. Saikia, P.S. Gehlot, A. Kumar, V. Chaturvedi, D. Sarma, Bioorg. Med. Chem. Lett. 27, 3698 (2017)

Article Google Scholar

26. A.S. Nipate, C.K. Jadhav, A.V. Chate, T.R. Deshmukh, A.P. Sarkate, C.H. Gill, ChemistrySelect 6, 5173 (2021)

Article CAS Google Scholar

27. T.W. Kim, Y. Yong, S.Y. Shin, H. Jung, K.H. Park, Y.H. Lee, Y. Lim, K.Y. Jung, Bioorg. Chem. 59, 1 (2015)

Article Google Scholar

28. M.F. Mady, G.E.A. Awad, K.B. Jorgensen, Eur. J. Med. Chem. 84, 433 (2014)

Article CAS Google Scholar

29. S.P. Khare, T.R. Deshmukh, J.N. Sangshetti, V.S. Krishna, D. Sriram, V.M. Khedkar, B.B. Shingate, ChemistrySelect 3, 13113 (2018)

Article CAS Google Scholar

30. S.P. Khare, T.R. Deshmukh, S.V. Akolkar, J.N. Sangshetti, V.M. Khedkar, B.B. Shingate, Res. Chem. Intermed. 45, 5159 (2019)

Article CAS Google Scholar

31. S.P. Khare, T.R. Deshmukh, J.N. Sangshetti, V.M. Khedkar, B.B. Shingate, Synth. Commun. 49, 2521 (2019)

Article CAS Google Scholar

32. T.R. Deshmukh, S.P. Khare, V.S. Krishna, D. Sriram, J.N. Sangshetti, O. Bhusnure, V.M. Khedkar, B.B. Shingate, J. Heterocycl. Chem. 56, 2144 (2019)

Article CAS Google Scholar

33. T.R. Deshmukh, S.P. Khare, V.S. Krishna, D. Sriram, J.N. Sangshetti, B.B. Shingate, Chem. Biol. Interface 9, 59 (2019)

CAS Google Scholar

34. T.R. Deshmukh, V.S. Krishna, D. Sriram, J.N. Sangshetti, B.B. Shingate, Chem. Pap. 74, 809 (2020)

Article CAS Google Scholar

35. T.R. Deshmukh, S.P. Khare, V.S. Krishna, D. Sriram, J.N. Sangshetti, V.M. Khedkar, B.B. Shingate, Synth. Commun. 50, 271 (2020)

Article CAS Google Scholar

36. T.R. Deshmukh, V.M. Khedkar, R.G. Jadhav, A.P. Sarkate, J.N. Sangshetti, S.V. Tiwari, B.B. Shingate, New J. Chem. 45, 13104 (2021)

Article CAS Google Scholar

37. T.R. Deshmukh, A.P. Sarkate, D.K. Lokwani, S.V. Tiwari, R. Azad, B.B. Shingate, Bioorg. Med. Chem. Lett. 29, 126618 (2019)

Article CAS Google Scholar

38. S. Ekins, J. Mestres, B. Testa, Br. J. Pharmacol. 152, 21 (2007)

Article CAS Google Scholar

39. M. Burits, F. Bucar, Phytother. Res. 14, 323 (2000)

Article CAS Google Scholar

40. E. Niki, Chem. Phys. Lipids. 44, 227 (1987)

Article CAS Google Scholar

41. R.A. Friesner, R.B. Murphy, M.P. Repasky, L.L. Frye, J.R. Greenwood, T.A. Halgren, P.C. Sanschagrin, D.T. Mainz, J. Med. Chem. 49, 6177 (2006)

Article CAS Google Scholar

42. http://www.rcsb.org/pdb

43. S.V. Akolkar, A.A. Nagargoje, V.S. Krishna, D. Sriram, J.N. Sangshetti, M. Damale, B.B. Shingate, RSC Adv. 7, 22080 (2019)

Article Google Scholar

44. J.A. Arnott, S.L. Planey, Expert Opin. Drug Discov. 7, 863 (2012)

Article CAS Google Scholar

45. A. Kokate, X. Li, B. Jasti, A.A.P.S. Pharm, Sci. Tech. 9, 501 (2008)

CAS Google Scholar

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004, (MH) India, for providing laboratory facility. We are also grateful to Schrodinger Inc. for GLIDE software to perform the molecular docking studies.

Funding

No funding was received.

Author information

Authors and Affiliations

Department of Chemistry, Dr. Babasaheb Ambedkar, Marathwada University, Aurangabad, Maharashtra, 431004, India
Tejshri R. Deshmukh & Bapurao B. Shingate

Department of Pharmaceutical Chemistry, School of Pharmacy, Vishwakarma University, Pune, Maharashtra, 411048, India
Vijay M. Khedkar

Y. B. Chavan College of Pharmacy, Rauza Bagh, Aurangabad, Maharashtra, 431001, India
Jaiprakash N. Sangshetti

Contributions

TRD performed the experimental work, prepared the graphical abstract, and wrote the manuscript. VMK carried out the molecular docking study. JNS performed the biological activity. The research and manuscript writing were reviewed and monitored under the guidance of BBS.

Corresponding author

Correspondence to Bapurao B. Shingate.

Ethics declarations

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare there is no conflict of interest.

Ethical approval

Not applicable.

Additional information

Dedicated to all teachers on the occasion of the National Teacher's Day (September 5, 2022).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary file1 (DOCX 24704 KB)

Rights and permissions

About this article

Cite this article

Deshmukh, T.R., Khedkar, V.M., Sangshetti, J.N. *et al.* Exploring the antioxidant potential of bis-1,2,3-triazolyl-*N*-phenylacetamides. *Res Chem Intermed* 49, 635–653 (2023). https://doi.org/10.1007/s11164-022-04915-2

Received	Accepted	Published
05 September 2022	03 December 2022	12 December 2022

Issue Date

February 2023

DOI
https://doi.org/10.1007/s11164-022-04915-2

Share this article

Anyone you share the following link with will be able to read this content:

Get shareable link

Keywords

Bis-1,2,3-triazolyl-*N*-phenylacetamides Click reaction Myeloperoxidase

Oxidative stress Molecular docking Antioxidant activity