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SYNTHESIS OF NOVEL IMIDAZOLE–PYRAZOLE–TRIAZOLE HYBRIDS, BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES

V. Punia[1], P. Periwal[1], S. Sehrawat[2], S. Rohilla[1], V. Verma[1,✉], V. Singh[3], and M. Bhatia[3]

[1]Department of Chemistry, Guru Jambheshwar University of Science & Technology, Hisar-125001, (Haryana) India

[2]Department of Physics, Deenbandhu Chotu Ram University of Science & Technology, Murthal-131039, (Haryana) India

[3]Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar-125001, (Haryana) India

✉Corresponding author: vikas_chem_pu@yahoo.com

ABSTRACT

A series of novel imidazole-pyrazole-triazole hybrids (8a-8h) was developed through a sequential synthetic approach involving copper-catalysed azide alkyne cycloaddition followed by the Debus-Radziszewski imidazole synthesis. The structures of all compounds were confirmed by several spectroscopic techniques such as NMR and FTIR. The synthesized molecules were evaluated for their antimicrobial efficacy against a spectrum of Gram-positive (*S. aureus, B. subtilis*) and Gram-negative bacteria (*E. coli, P. aeruginosa*), along with fungal pathogens. IC_{50} values were also calculated for antioxidant properties. Many of the new imidazole derivatives displayed remarkable activity, with several derivatives notably going beyond the antimicrobial potency of the parent scaffolds with MIC values as low as 0.0163 µmol/mL and 0.0161 µmol/mL. Particularly, compounds 8a, 8d and 8f demonstrated pronounced bioactivity across multiple strains. For more insight into their mode of action, molecular docking analyses and druglikeness-related parameters were observed, revealing strong interactions with microbial enzyme active sites, thereby validating their therapeutic potential. This work highlights the potential of imidazole-pyrazole-triazole hybrids as promising scaffolds for the development of biologically active molecules. The integration of synthesis, biological evaluation, and molecular docking study provides useful insights for future drug discovery and rational design in medicinal chemistry.

Keywords: Imidazole, Pyrazole, Hybrids, Antifungal Activity, Antibacterial Activity, Molecular Docking.

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INTRODUCTION

Historically, heterocyclic scaffolds have held a prominent position in drug development due to their structural versatility and biological relevance, and the most influential N-heterocycles are imidazole, pyrazole, and triazole. Imidazole is a five-membered aromatic heterocycle that easily participates in hydrogen bonding and metal coordination, making it suitable for binding biological macromolecules. Imidazole derivatives demonstrate good stability, solubility, and cell permeability, which are important for drug design. Imidazole, in particular, exhibits a wide range of therapeutic actions, including antimicrobial[1,2], antitubercular[3], antiviral[4], anticancer[5], and antioxidant[6] properties. Pyrazole is a highly adaptable heterocyclic ring belonging to the azole family, characterized by its planar geometry and strong electron-withdrawing tendencies, which promote favourable interactions with diverse biological receptors.[7,8] Pyrazole derivatives have been extensively studied for their broad pharmacological spectrum, displaying noteworthy anti-Alzheimer 's[9], antioxidant[10], anticancer[11], anti-inflammatory[12], and antiviral [13] effects. Triazoles, particularly the 1,2,3-triazole isomer, exhibit exceptional chemical stability and metabolic persistence while forming strong dipole and hydrogen-bonding interactions.[14] The triazole derivatives have also demonstrated a wide array of biological properties, including antibacterial[15], antifungal[16], anticancer[17], antioxidant[18], antiviral[19], antiepileptic[20], and antitubercular activities[21], largely

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due to their high affinity for key biological targets. Because of their high binding affinity for microbial enzymes and membrane transporters, triazoles are frequently used as linker units in hybrid drug molecules. Nitrogen-containing heterocycles thus remain central to modern research across pharmaceutical, agrochemical, and biochemical fields. With the increasing problem of drug resistance and reduced efficacy of existing therapeutics, there is a need for novel heterocyclic hybrid molecules with enhanced biological potency.

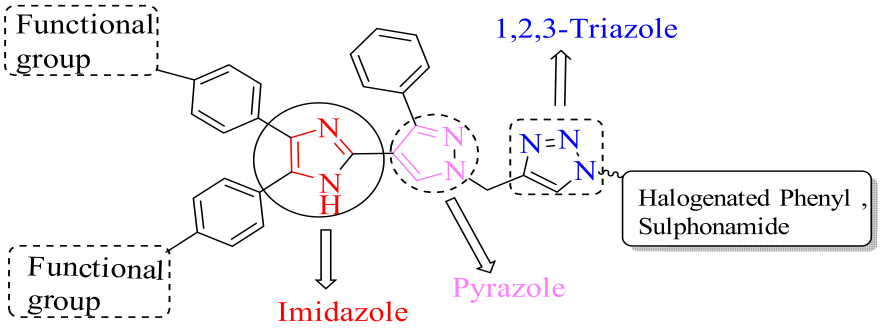


Fig.-1: Design Strategy of the Synthesized Molecules 8a-8h

Inspired by these observations, our work was focused on designing and synthesising tribrid molecules incorporating imidazole, pyrazole, and triazole units within a single chemical framework (Fig.-1). The synthesis strategy employed a sequence of click chemistry and Debus–Radziszewski reactions to assemble the hybrid scaffolds. Furthermore, molecular docking studies were carried out to investigate the interaction behaviour of these compounds with microbial enzymes at the molecular level. Developing novel therapeutic agents contributes to improving disease management and supports the objective of Sustainable Development Goal 3 (Good Health and Well-being).

EXPERIMENTAL

Materials and Methods

All chemicals and reagents used in this study were procured directly from Sigma Aldrich and Alfa-Aesar and used without further purification. The melting points of the synthesized compounds were measured using the open capillary method. Structural characterisation was performed using a Bruker Avance III NMR spectrometer. Dimethylsulfoxide-*d6* (DMSO-*d6*) was used as the solvent, with reference chemical shifts at δ 2.50 ppm for ^{1}H NMR and δ 39.50 ppm for ^{13}C NMR.

General Procedure for Synthesis of 3-phenyl-1-(prop-2-yn-1-yl)-1H-pyrazole-4-carbaldehyde (3)

3-Phenyl-1H-pyrazole-4-carbaldehyde (1, 1 mmol) was dissolved in DMF, and K_2CO_3 (1 mmol) was then added to the solution. The mixture was stirred for 20–30 minutes, after which propargyl bromide (2, 1 mmol) was introduced. Stirring was continued at room temperature, and the progress of the reaction was tracked by TLC. Once the reaction was complete, the mixture was poured into ice-cold water, leading to the formation of a precipitate, which was subsequently isolated by filtration.[22]

General Procedure for Synthesis of 4-(1H-imidazol-2-yl)-3-phenyl-1-(prop-2-yn-1-yl)-1H-pyrazole compounds (5a-5d

Compounds (5a–5d) were prepared via the condensation of 3-phenyl-1-(prop-2-yn-1-yl)-1H-pyrazole-4-carbaldehyde (3, 1 mmol) with 1,2-dicarbonyl compounds (4, 1 mmol) in the presence of ammonium acetate (7 mmol) using glacial acetic acid under reflux conditions. The reaction progress was monitored by TLC employing a hexane: ethyl acetate solvent system. Upon completion, the reaction mixture was slowly poured onto crushed ice with continuous stirring. After 30 minutes, the formed solid was collected by filtration, washed twice with water, and dried under reduced pressure.[23]

General Procedure for Synthesis of Organic Azides (7a-7b)

Organic azides (7a–7b) were synthesized from the corresponding anilines (6a–6b, 1 mmol) by treatment with concentrated HCl. A saturated aqueous solution of sodium nitrite (2 mmol) was then added dropwise at 0–5 °C, and the mixture was stirred for 30 minutes. Subsequently, an aqueous solution of sodium azide

(2 mmol) was introduced while maintaining the same temperature. Stirring was continued for 4–5 hours at 0–5 °C. After completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.[24]

General Procedure for Synthesis of Imidazole-Pyrazole-Linked 1,2,3-Triazole Compounds (8a-8h)
Imidazole-pyrazole alkynes (5a-5d) (1 mmol) were stirred with substituted azides (7a-7b) (1 mmol) in the presence of copper sulphate pentahydrate (0.10 mmol) and sodium ascorbate (0.20 mmol) using DMF: H_2O (7:3) as solvent at 50 ℃ temperature for 7 hours. After completion of the reaction, which was monitored through TLC, cold aqueous ammonia solution was added to the reaction mixture and extracted twice with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulphate and then dried under vacuum to obtain imidazole-pyrazole-linked 1,2,3-triazole compounds[25] (8a-8h).

Biological Evaluation
The antimicrobial activities were carried out by standard serial dilution protocols approved by the Clinical and Laboratory Standards Institute (CLSI)[26] as reported by S. Punia *et al.*[27] The synthesized compounds (8a-8h) were assessed for their *in vitro* antioxidant activity using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay. Absorbance was recorded at 517 nm using a UV-Visible spectrophotometer. Ascorbic acid was used as the standard reference antioxidant for comparison.

Druglikeness of Target Compounds
SwissADME, an online platform, was used to predict the drug-likeness and bioavailability-related parameters (http://www.swissadme.ch/).[28]

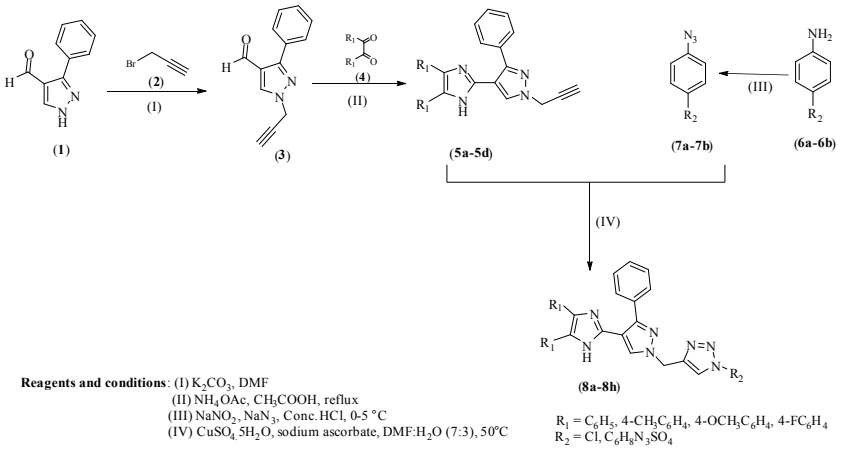
Molecular Docking Analysis
This study employed AutoDock Vina for molecular docking simulations to evaluate the binding properties of the synthesized compounds against the target proteins.[29,30] The crystal structures (PDB IDs: 2UV0[31]; 4Z69 (Human serum albumin complexed with palmitic acid and diclofenac) were retrieved from the Protein Data Bank (www.rcsb.org). The synthesized compounds were drawn in MarvinSketch[32], saved in MOL2 format, and energy minimised using the MMFF94 force field before being converted to PDBQT format using AutoDock tools.[33] The resulting binding poses were visualised and analysed in PyMOL and Discovery Studio Visualizer (BIOVIA, Discovery Studio Visualizer).

RESULTS AND DISCUSSION

Chemistry
Initially, the synthesis of 3-phenyl-1-(prop-2-yn-1-yl)-*1H*-pyrazole-4-carbaldehyde (3) was achieved using a nucleophilic substitution reaction. In this method, the precursor 3-phenyl-1*H*-pyrazole-4-carbaldehyde (3) was reacted with derivatives of 1,2-diketone (4) in the presence of ammonium acetate in refluxing conditions in acetic acid. It results in different substituents of pyrazole-imidazole alkyne (5a-5d). Simultaneously, different aniline derivatives (6a-6b) react with sodium azide and sodium nitrite in the presence of hydrochloric acid using ethyl acetate as a solvent to give azide (7a-7b). This is done by keeping the reaction mixture in an ice bath. These substituents of imidazole-pyrazole alkyne (5a-5d) were used to form imidazole-pyrazoles linked 1,2,3-triazole compounds (8a-8h) using each of the synthesised azides (Scheme). The synthesized compounds' structures were analysed using a suite of analytical techniques, including ^{1}H NMR, ^{13}C NMR, FTIR and HRMS.[34]

Antimicrobial Evaluation
The antimicrobial evaluation of the synthesized compounds (8a-8h) was done against four bacterial strains and three fungal strains. The results have been mentioned in Table-1. Against *P. aeruginosa*, compounds 8d, 8f, and 8h demonstrated potent inhibition (MIC = 0.0211, 0.0163 and 0.0161 µmol/mL, respectively). In the case of *E. coli*, superior activity was observed for 8b and 8d, displaying a MIC value of 0.0429 and 0.0423 µmol/mL. Against *A. niger*, the most effective agents were 8f with an MIC of 0.0653 µmol/mL. For *R. oryzae* and *C. albicans*, the highest activity was observed for 8d with an MIC value of 0.0423 µmol/mL, comparable to the standard drug, fluconazole (MIC 0.0408 µmol/mL). Structure-activity correlation revealed that halogen substitution at R_1 and the presence of sulfonyl groups

at R_2 (particularly benzene sulfonyl) synergistically enhanced antifungal potency, likely due to increased lipophilicity, membrane penetration, and improved binding to fungal targets. These findings suggest that strategic incorporation of electron-withdrawing halogens with sulfonyl functionalities offers a promising scaffold for broad-spectrum antifungal development.



Scheme-1: Imidazole-pyrazole Linked 1,2,3-triazole Compounds (8a-8h) using Click Reaction

Table-1: *In Vitro* Antibacterial, Antifungal and Antioxidant Evaluation of Synthesized Compound (8a-8h)

Compounds	R_1	R_2	Antibacterial evaluation MIC (µmol/mL)				Antifungal evaluation MIC (µmol/mL)			Antioxidant
			P. aeruginosa	*E. coli*	*B. subtilis*	*S. aureus*	*A. niger*	*R. oryzae*	*C. albicans*	IC_{50} value
8a	H	Cl	0.0902	0.1804	0.0902	0.0110	0.1804	0.0451	0.1804	0.0325
8b	CH_3		0.1717	0.0429	0.0858	0.0429	0.0858	0.1717	0.0858	0.0480
8c	OCH_3		0.0407	0.0814	0.0407	0.1628	0.1628	0.0814	0.1628	0.0725
8d	F		0.0211	0.0423	0.0423	0.0847	0.0847	0.0423	0.0423	0.0158
8e	H	$C_6H_8N_3SO_4$	0.0678	0.0678	0.0678	0.1357	0.1357	0.1357	0.1357	0.0665
8f	CH_3		0.0163	0.1307	0.0653	0.1307	0.0653	0.0653	0.0653	0.0669
8g	OCH_3		0.0627	0.0627	0.0627	0.0627	0.1254	0.1254	0.1254	0.0326
8h	F		0.0161	0.0647	0.1294	0.0647	0.1294	0.0647	0.1294	0.0129
Norfloxacin	--	--	0.0391	0.0391	0.0391	0.0195	--	--	--	--
Fluconazole	--	--	--	--	--	--	0.0408	0.0408	0.0408	--
Ascorbic Acid	--	--	--	--	--	--	--	--	--	0.0152

Antioxidant Activity

Table-1 reports the IC_{50} values (µmol/ml) for the antioxidative activity of all the synthesized compounds (8a-8h) compared to the standard, Ascorbic 8h gives the lowest IC_{50} of 0.0129 µmol/mL, which surpasses the standard, ascorbic acid (0.0152 µmol/mL). The pattern suggested that a fluoro substituent provided very strong antioxidant action.

Druglikeness of Target Compounds

The Absorption Distribution Metabolism Excretion (ADME) analysis (Table-2) of the hybrids is done to know about the pharmacokinetics and toxicity of compounds, and it reveals several encouraging features that support their potential as bioactive candidates.[35] Their rotatable bond counts (7–14) indicate an adequate degree of conformational flexibility, allowing adaptability in biological environments and possible target binding.[36] Importantly, most compounds maintain TPSA values between 77–96 Å² (8a-8d), which lie within the optimal window for membrane permeability and oral absorption. A particularly notable feature is the higher bioavailability scores observed for molecule 8c (0.55), making it especially promising for oral drug development. Collectively, these molecules combine structural diversity, strong aromatic frameworks conducive to stable binding, and manageable synthetic feasibility.

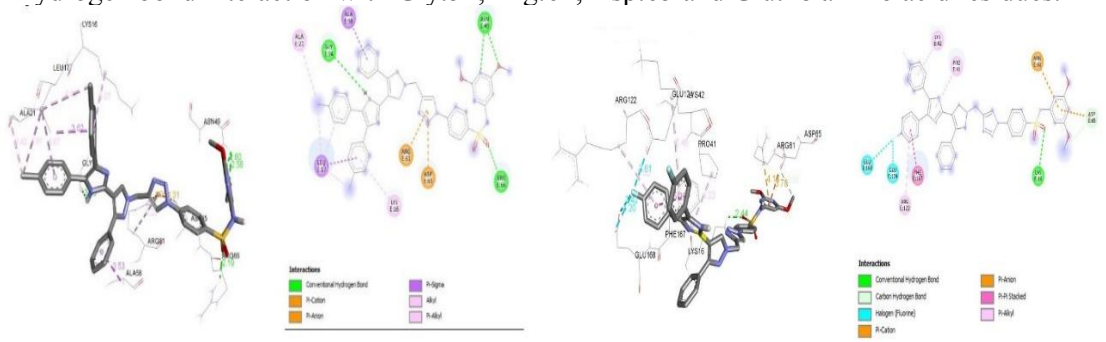
Table-2: Drug-likeness and Bioavailability-Related Parameters of Synthesized Compounds (8a-8h) as Predicted by SwissADME

Compounds	MW	nON	nOHNH	nRotB	TPSA	Lipinski violations	Veber violations	PAINS alerts	Brenk alerts	BA Score	SA score
8a	554.04	4	1	7	77.21	2	0	1	0	0.17	4.26
8b	582.10	4	1	7	77.21	2	0	1	0	0.17	4.51
8c	614.10	6	1	9	95.67	1	0	1	0	0.55	4.53
8d	590.02	6	1	7	77.21	2	0	1	0	0.17	4.25
8e	736.80	10	2	12	176.00	2	2	1	0	0.17	5.25
8f	764.85	10	2	12	176.00	2	2	1	0	0.17	5.50
8g	796.85	12	2	14	194.46	2	2	1	0	0.17	5.55
8h	772.78	12	2	12	176.00	2	2	1	0	0.17	5.23

*MW: Molecular Weight, nON: H-bond acceptors, nOHNH: H-bond donors, nRotB: number of rotatable bonds, TPSA: Topological Polar Surface Area, BA Score: Bioavailability Score, SA Score: Synthetic Accessibility Score

Molecular Docking

The synthesized compounds (8a-8h) exhibited binding energy ranging from -7.4 to -8.8 kcal/mol (PDB:2UV0) and -10.1 to -14.3 kcal/mol (PDB:4Z69) for their respective proteins (Table-3). The most active compounds 8f and 8h displayed various binding interactions with PDB:2UV0, as presented in Table-4 and Fig.-2. The least active compound 8b displayed a hydrogen bond, pi-anion, carbon-hydrogen, pi-donor hydrogen bond, alkyl and pi-alkyl interactions with Asp:65, Glu:62, Gln:24, Gly:54, Arg:66, Ile:52, Ala:58, Leu:17 and Ala:21 amino acid residues. Pi-Pi stacked and pi-sigma interactions were not observed. The standard compound norfloxacin created one hydrogen bond, pi-cation, pi-anion, carbon-carbon-hydrogen bond interaction with Gly:54, Arg:61, Asp:65 and Glu:48 amino acid residues.



8f 8h

Fig.-2: 3D and 2D Binding Interactions of Compound 8f and 8h with PDB: 2UV0

Table-3: Binding Affinity (kcal/mol) of Synthesized Compounds (8a-8o) with their Respective Targets

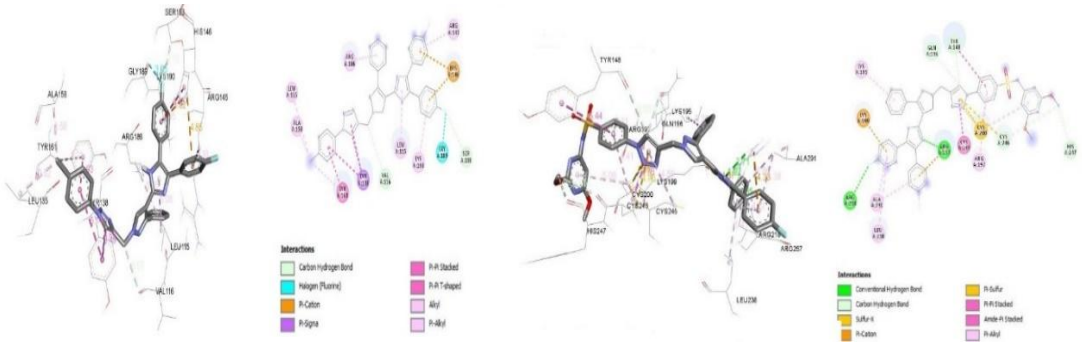
Compound	PDB: 2UV0	PDB: 4Z69
8a	-8.2	-12.6
8b	-7.9	-12.6
8c	-7.4	-11.3
8d	-8.6	-11.4
8e	-7.8	-13.2
8f	-8.3	-13.6
8g	-7.3	-10.1
8h	-7.9	-12.6
Norfloxacin	-5.5	-
Ascorbic acid	-	-5.4

Table-4: Binding Interactions of the Most Active Compounds with Respective Targets

Compound	Functional Group	Types of interactions	Amino acid residues	Bond Length(Å)
8h (Antibacterial activity) (PDB:2UV0)	O of SO_2NH	Hydrogen bond	Lys:16	2.44
	C of OCH_3 of dimethoxypyrimidin-4-yl	Carbon-hydrogen bond	Asp:65	3.55

	Dimethoxypyrimidin-4-yl ring	Pi-cation Pi-anion	Arg:61 Asp:65	4.16 3.70
	4-Florosubstituted phenyl ring	Pi-pi stacked	Phe:167	5.26
	4-Florosubstituted phenyl rings	Two pi-alkyl	Arg:122 Lys:42	5.30 5.46
	F of 4-Florosubstituted phenyl ring	Two halogen bonds	Glu:168 Glu:124	3.42 3.61
	Imidazol-2-yl ring	Pi-alkyl	Pro:41	4.23
8f (Antibacterial activity) (PDB:2UV0)	O of SO_2NH	Hydrogen bond	Arg:66	2.19
	N of Dimethoxypyrimidin-4-yl ring	Hydrogen bond	Asn:49	2.60
	O of the Dimethoxypyrimidin-4-yl ring	Hydrogen bond	Asn:49	2.56
	H of Imidazol-2-yl ring	Hydrogen bond	Gly:54	3.00
	1,2,3-triazol-1-yl ring	Pi-cation and Pi-anion	Arg:61, Asp:65	4.05, 4.35
	p-Tolyl ring linked to imidazol-2-yl ring	Pi-sigma	Leu:17	3.62
	Phenyl ring linked to pyrazol-1-yl	Pi-sigma	Ala:58	3.53
	p-Tolyl ring linked to imidazol-2-yl ring	Pi-alkyl	Ala:21, Leu:17, Lys:16	4.67, 5.01, and 5.29

The most active compounds 8d and 8h displayed hydrogen bond, pi-cation, pi-anion, pi-pi-stacked, pi-pi T-shaped, pi-sulfur, alkyl and pi-alkyl interactions with PDB:4Z69 as presented in Table-5 and Fig.-3. Compound 8c displayed hydrogen bond, hydrophobic and pi-cation and pi-sulfur interactions with Arg:218, Cys:245, Tyr:148, Lys:199, Cys:200, Ala:291, Leu:238 and Arg:197 amino acid residues. The standard compound ascorbic acid Leu:481 and Gly:2017 residues and carbon-hydrogen bond interaction with Ser:202 amino acid residue.



8d 8h

Fig.-3: 3D and 2D Binding Interactions of Compound 8d and 8h with PDB: 4Z69

The significant antibacterial, antifungal, and antioxidant activities observed for the synthesized imidazole-pyrazole-triazole derivatives highlight their potential as promising therapeutic candidates. In particular, compounds such as 8a and 8d exhibited strong activity against pathogenic microorganisms, suggesting their possible role in tackling infectious diseases and the growing challenge of antimicrobial resistance. These findings therefore align with the goals of Sustainable Development Goal 3: Good Health and Well-being, which promotes the development of effective treatments and strategies to control infectious diseases and enhance global health.

CONCLUSION

In conclusion, new imidazole-pyrazole-triazole scaffolds (8a-8h) were synthesized. All the synthesized (8a-8h) compounds successfully exhibited multifunctional bioactivity across antibacterial, antifungal and

antioxidant assays. In the antimicrobial evaluation tests, compound 8a showed the highest potency against *S. aureus* with an MIC value of 0.0110 µmol/mL and compound 8d (MIC 0.0423 µmol/mL) was found to be most active against *R. oryzae* and *C. albicans*. In antioxidant evaluation, the fluoro-substituted compound 8h demonstrated the lowest IC_{50}(0.0129 µmol/mL). The structure–activity relationship (SAR) emerging from this work suggested that introducing a strongly electron-withdrawing fluoro group at R_1 in conjunction with a sulfonyl-containing R_2 enhances combined antimicrobial and antioxidant properties. Furthermore, docking studies of compounds 8d, 8f and 8h displayed their binding interactions with PDB:2UV0 and PDB:4Z69. Drug-likeness properties of all the synthesized compounds were predicted, and the presence of sulfonyl sidechains and moderate lipophilicity helps in achieving balanced drug-like profiles. Overall, this study demonstrates a clear design paradigm for synthesising lead compounds with enhanced antimicrobial and antioxidant activities and supports the objectives of Sustainable Development Goal 3 (Good Health and Well-being) by contributing to the development of potential therapeutics against infectious diseases.

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CONFLICT OF INTERESTS

The authors declared that there is no conflict of interest in our manuscript.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

V. Punia http://orchid.org/0000-0001-5645-2805
P. Periwal http://orchid.org/0009-0000-4735-0401
S. Sehrawat http://orchid.org/0000-0002-1697-8463
S. Rohilla http://orchid.org/0000-0002-1697-8463
V. Verma http://orchid.org/0000-0002-6648-1877
V. Singh http://orchid.org/0000-0003-3056-8919
M. Bhatia http://orchid.org/0000-0003-4568-7582

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