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Facile synthesis, antimicrobial evaluation and molecular docking studies of pyrazole-imidazole-triazole hybrids

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ABSTRACT

A series of eighteen pyrazole-imidazole-triazole hybrid (2-(4-((2-(substituted-1H-pyrazol-1-yl)-4-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(substituted)phenylacetami- de) **(6a-6r)** are synthesized through click reaction between in situ generated 2-azido-N-substituted acetamide and N-propargylated pyrazole-imidazole derivatives which in turn has been obtained regioselectively from 1-(1H-imidazol-2-yl)-1H-pyrazole and propargyl bromide. The structure of synthesized compounds **(6a-6r)** was confirmed by various spectroscopic studies (1D and 2D NMR, FT-IR, HRMS) and evaluated for antimicrobial activity. The compound **6m** demonstrated excellent potency for *A. niger* (MIC value 0.0064 µmol/mL); even better than that of the reference drug Fluconazole (MIC value 0.0112 µmol/mL). Further, the binding conformation of most active compounds was ascertained by molecular docking studies.

1. Introduction

Among nitrogen containing heterocycles, pyrazole, imidazole and triazole show innumerable chemical, biological, agrochemical and pharmacological properties. Some documented imidazole-pyrazole hybrid exhibited anticancer, [1] antibacterial, [2] antifungal, [3] anti-tubercular [4] and antidiabetic activities [5]. Imidazole-triazole hybrid displayed a number of application in medicinal chemistry [6–10]. Triazole-pyrazole hybrid demonstrated a broad spectrum of pharmacological array such as anti-tubercular, [11] antifungal, [12] antibacterial, [13] antidiabetic [14] antitumor [15] etc. Some clinically approved drugs containing pyrazole, imidazole as a nuclear framework are Celecoxib (anti-inflammatory), Phenylbutazone (antipyretic and analgesic), Rimonabant (anti-obesity), Clotrimazole (antifungal), clonidine (antihypertensive), flumazenil (GABAA receptor antagonist). Numerous drugs bearing triazole moieties available in market are e.g. Fluconazole (antifungal), Cefatrizine (antibiotic), Tazobactum (beta-lactamase inhibitor) etc. A series of pyrazolylimidazole derivatives **(A, Fig. 1)** was designed, synthesized and evaluated for antimicrobial activity by Menozzi et al., 2004.[16] Results reported indicate that compounds show excellent inhibitory effect on pathogenic strain of yeast and gram (+) bacteria *viz.* S. aureus, superior to standard drug, Bifonazole. The synthesized series was also evaluated for their antitubercular activity also and found to exhibit good activity. In 2016, Negi et al., [17] described the designing and synthesis of a novel series of 1,2,3-triazole-metronidazole hybrid **(B, Fig. 1)** and evaluated against a panel of 30 MRSA strains. Most of the synthesized compounds were active even at the concentration at which reference drug ofloxacin was inactive. Recently, a group of researchers (Faidallach *et al.*, 2018) [18] found to show the promising antibacterial activity by a family of amide linked triazole derivatives **(C, Fig. 1)**. Prompted by pharmacological importance of imidazole, pyrazole and 1,4-disubstituted-1,2,3-triazole scaffold and on account of our interest for synthesizing biological potent compounds, it was thought to amalgamate these three moieties in a single molecule via molecular hybridization approach.

By using click reaction, a novel series of pyrazole-imidazole-triazole hybrids (**6a-6r**) was synthesized. The synthesized hybrids were characterized by 1D and 2D NMR, ^{13}C NMR and HRMS spectroscopic techniques. The synthesized derivatives were examined for their antimicrobial activity against four bacterial strains and two fungal strains. Further, to study the mode of action and binding affinity of synthesized derivatives, docking analysis was carried out against *E. coli* and *C. albicans.*

2. Results and discussion

2.1. Chemistry

The synthesis of imidazole amide linked 1,2,3-triazoles **(6a-6r)** is depicted in **Scheme 2.** At first, 1-(5-Phenyl-1H-imidazol-2-

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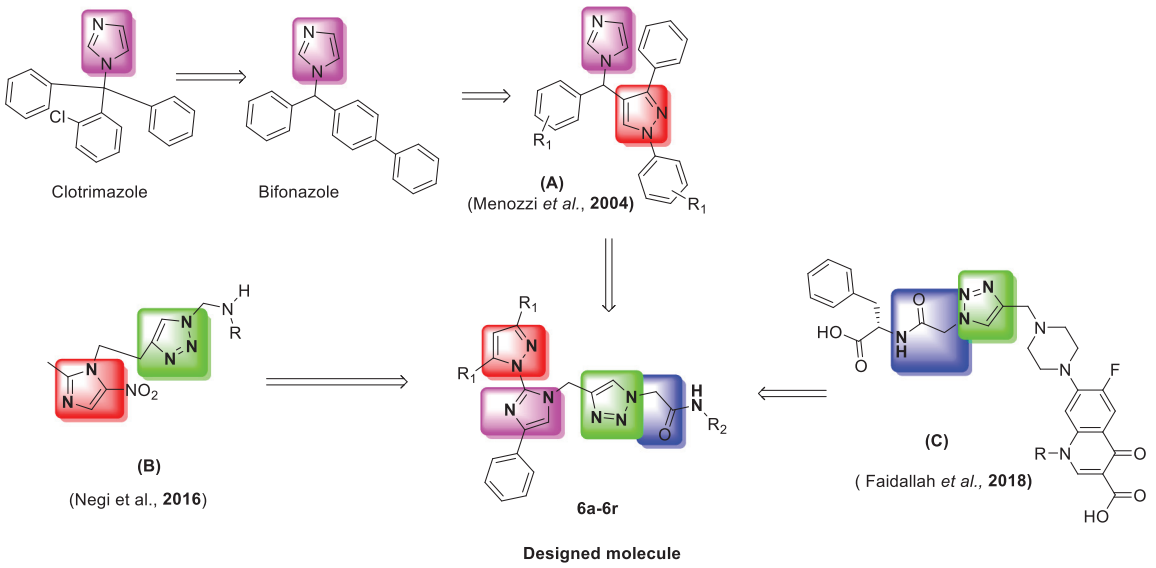
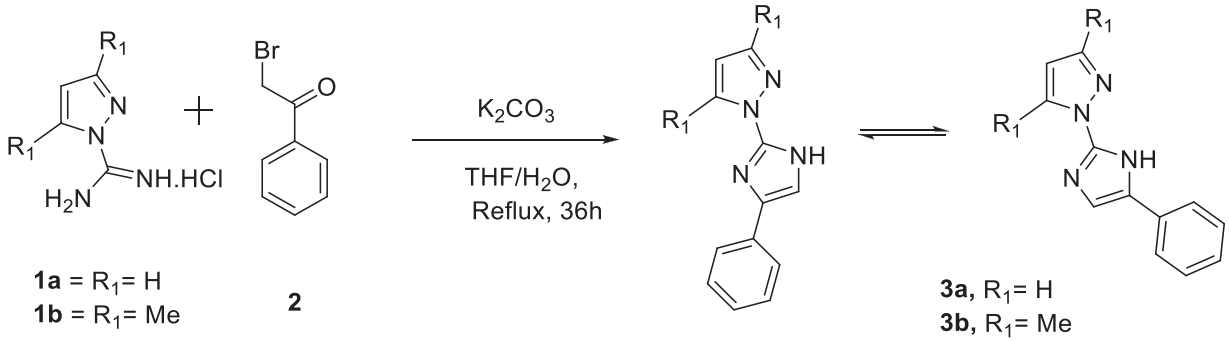


Fig. 1. Representative pyrazole-imidazole, imidazole-triazole, pyrazole-triazole hybrid and designing of pyrazole-imidazole-triazole hybrid.



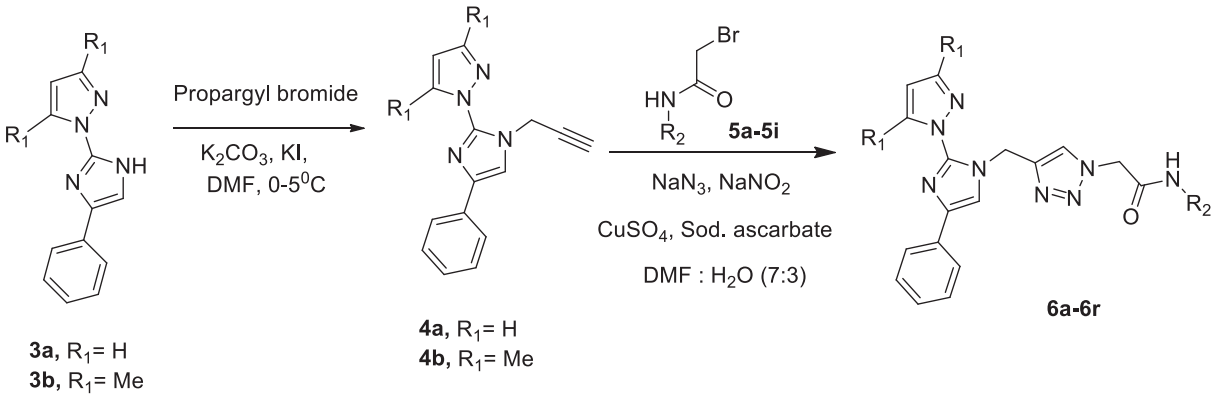
Scheme 1. Synthesis of pyrazolylimidazole compounds **3a** and **3b.**

yl)-1H-pyrazole **(3a)** and 3,5-Dimethyl-1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole **(3b)** were prepared by formerly described route. [19] It involves the [3+2] cyclo-condensation reaction of 1H-pyrazole-1-carboximidamide hydrochloride **(1a)** and 3,5-dimethyl-1H-pyrazole-1-carboximidamide nitrate **(1b)** respectively**,** with 2-bromo-1-phenylethanone (**2a)** in presence of potassium carbonate by using THF:water (5:1) (**Scheme 1**). Cyclization of carboxamidine **(1a, 1b)** moiety to imidazole ring **(3a-3b)** was demonstrated by the appearance of a D_2O exchangeable broad singlet at 12.81-12.59 ppm (N-**H** of imidazole, (S.I. file).) and another singlet at 7.56-7.59 ppm (imidazole ring proton), in ^{1}H NMR spectrum of compound **3a** and **3b** (S.I. file) In addition, the compounds displayed 5 aromatic protons assuring phenyl ring in the molecule.

Then, the propargylated imidazole derivatives, 1-(5-phenyl-1-(prop-2-yn1-yl-1H-imidazole-2-yl)-1H-pyrazole **(4a)** and 3,5-dimethyl-1-(4-phenyl-1-(prop-2-yn-1-yl)-1H-imidazol-2-yl)-1H-pyrazole **(4b)** were regioselectively obtained by treating the corresponding pyrazolylimidazole **(3a, 3b)** with propargyl bromide in presence of potassium carbonate at 0-5ºC in the presence of dimethylformamide (DMF) [20]. In FTIR of compound **4a** and **4b** the band at 2360-2365 cm^{-1} was due to alkyne (**C≡C)** str. ^{1}H NMR of these compound (**4a-4b)** in DMSO (S.I. file). displayed two characteristic signals in span of δ 3.46-3.47 (t, 1H, ≡**CH)** and δ 5.14-4.87 ppm (d, 2H, NC**H**$_2$) along-with disappearance of N-**H** peak. Appearance of a High field singlet at δ 36.77 ppm in ^{13}C NMR of compound **4a-4b** (S.I. file) was assigned to N**C**H$_2$ while the comparatively low field singlets at 76.72 and 76.54 ppm to alkyne **C (C≡C).** These findings evident the alkylation of compound **3a, 3b** by propargyl bromide.

Further, 2-bromo-N-(substituted)acetamide **(5a-5i)** were synthesized by reacting the corresponding substituted aniline analogues and bromoacetyl bromide in dichloromethane using potassium carbonate (**Scheme 2**) [21]. Finally, targeted compounds 1,4-disubstituted 1,2,3-triazole incorporated imidazole derivatives **(6a-6r)** were prepared by Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of alkyne and *in situ* generated azide from 2-bromo-N-(substituted)acetamide and sodium azide (**Scheme 2**) [21].

Formation of target compounds **6a-6r** were ascertained by the presence of two bands in IR due to amide I (1600–1620 cm^{-1}) and amide II (1680-1695 cm^{-1}). Further, the triazole ring formation in **6a-6r** was confirmed by the characteristic 1,2,3-triazole ring (-CH) signal in the span of 7.90 to 8.07 ppm in the ^{1}H NMR spectra in place of 3.46-3.47 (t, 1H, ≡**CH)** peak of alkyne. In ^{13}C NMR (S.I. file), a confirmatory sign of ring closure of alkyne was the appearance of tertiary carbon of triazole ring around **δ** 125.15 to 124.62 in compounds **6a-6r.** Other important signals were the characteristics NH peak at δ 10.01 to 10.74 and one singlets due to imidazole ring proton at δ 7.80 to 7.83. Another singlet for imidazole-triazole bridged and triazole-anilide bridged methylene group ring appeared in the region of δ 5.20 to 5.50 and δ 5.28 to 5.58 respec-



Compound	R_1	Compound	R_1	Compound	R_2
6a	H	**6j**	CH_3	**5a/6a/6j**	4-$OMeC_6H_4$
6b	H	**6k**	CH_3	**5b/6b/6k**	4-$CH_3C_6H_4$
6c	H	**6l**	CH_3	**5c/6c/6l**	3-Cl-2-$CH_3C_6H_3$
6d	H	**6m**	CH_3	**5d/6d/6m**	4-ClC_6H_4
6e	H	**6n**	CH_3	**5e/6e/6n**	2-3-$(Cl)_2C_6H_3$
6f	H	**6o**	CH_3	**5f/6f/6o**	3-4-$(Cl)_2IC_6H_3$
6g	H	**6p**	CH_3	**5g/6g/6p**	3-FC_6H_4
6h	H	**6q**	CH_3	**5h/6h/6q**	2-$NO_2C_6H_4$
6i	H	**6r**	CH_3	**5i/6i/6r**	1-$C_{10}H_7$

Scheme 2. Synthesis of imidazole amide linked 1,2,3-triazole hybrids (**6a-6r**).

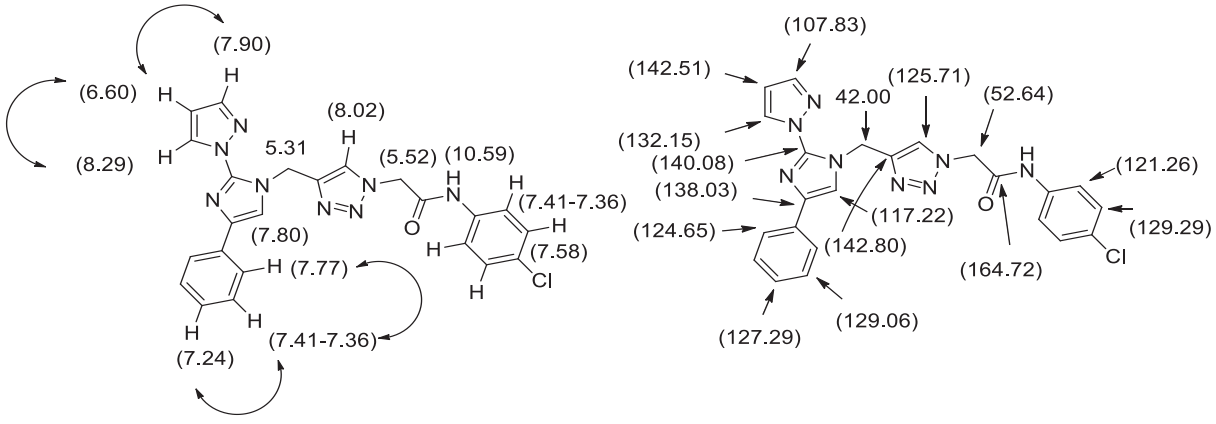


Fig. 2. ^{1}H NMR and ^{13}C NMR signals and COSY correlation of compound **6d.**

tively. In ^{13}C NMR spectra of the compounds (S.I. file)., signal due to quaternary carbon of the triazole ring appeared at δ 143.30 to 140.11. The carbonyl carbon appeared at δ 163.97 to 181.86. The assignment of peaks of ^{1}H and ^{13}C spectra were confirmed by correlating them with different correlation spectroscopy like COSY (Correlation Spectroscopy), HSQC (Heteronuclear Single-Quantum Coherence) and HMBC (Heteronuclear multiple Bond Correlation. The mass spectra (S.I. file) of the compounds showed signals because of $[M^+]$ and $[M^++1]$ ions, which were in good agreement with their calculated values.

The proton and carbon assignment in NMR of compound **6d** was identified by 1D and 2D-NMR e.g. COSY (correlation spectroscopy), HSQC and HMBC (**Fig. 2**), (S.I. file).

In FTIR of compound **6d**, the band at 1602.85 and 1687.71 $cm^{-1}$was due to (amide I) and (amide II) str. The ^{1}H NMR spectrum of imidazole derivative **6d** exhibited singlets at δ 10.59 **(1H)** ppm for N-**H**, 5.30 **(2H)** ppm for NC**H**$_2$, 5.51 **(2H)** ppm NC**H**$_2$CO, 8.02 **(1H)** ppm for C-H of triazole ring and 7.86 **(1H)** ppm for C-**H** of imidazole ring.

In ^{13}C NMR spectrum of **6d**, signals at δ 52.64 and 42.00 ppm were assigned to acetoamide (**C**H$_2$CONH) group and methylene (**C**H$_2$) group respectively, whereas (**C**ONH) absorbed at δ 164.73 ppm. DEPT-135 spectra established that the peak at δ 52.64 ppm and 42.00 ppm were observed due to secondary carbon of acetoamido (**C**H$_2$CO**NH**) and methylene (**C**H$_2$) groups respectively.

The connectivity of all hydrogen atoms in **6d**, through intervening bond was established by COSY (Correlation Spectroscopy). Signal at δ 6.60 (t, J = 2.0, Hz, 1H) ppm show mutual correlation with δ 8.29 (d, 1H, J = 2.4 Hz) and 7.90 (d, J = 1.4 Hz, 1H) ppm. Signal splitting and J value justified that these signals are due to pyrazole C_4-**H**, C_3-**H** and C_5-**H** respectively. Similarly, correlation of signal at δ 7.38 (d, J = 8.0 & 7.6 Hz) ppm with signals at 7.24 and 7.78 ppm with triplet multiplicity with integration of 2H and in ^{1}H NMR support our assignment of these signals to the imidazole ring linked phenyl ring. Two singlets at 8.02 and 7.85 ppm which do not show correlation with other signals were assigned to triazole ring H and imidazole ring **H**.

Table 1
In vitro antibacterial evaluation of synthesized compounds **6a-6r** (MIC in µmol/mL).

Compound	R_1	R_2	E. coli	S. aureus	B. subtilis	P. aeruginosa
6a	H	4-$OMeC_6H_4$	0.0275	0.0550	0.0550	0.0275
6b	H	4-$CH_3C_6H_4$	0.0142	0.0285	0.0285	0.0142
6c	H	3-Cl-2-$CH_3C_6H_3$	0.0264	0.0528	0.0528	0.0264
6d	H	4-ClC_6H_4	0.0136	0.0272	0.0272	0.0136
6e	H	2-3-$(Cl)_2C_6H_3$	0.0126	0.0243	0.0243	0.0126
6f	H	3-4-$(Cl)_2C_6H_3$	0.0126	0.0252	0.0252	0.0126
6g	H	3-FC_6H_4	0.0071	0.0282	0.0282	0.0071
6h	H	2-$NO_2C_6H_4$	0.0133	0.0266	0.0266	0.0133
6i	H	1-$C_{10}H_7$	0.0132	0.0264	0.0264	0.0132
6j	Me	4-$OMeC_6H_4$	0.0518	0.0259	0.0259	0.0518
6k	Me	4-$CH_3C_6H_4$	0.0267	0.0534	0.0534	0.0267
6l	Me	3-Cl-2-$CH_3C_6H_3$	0.0254	0.0254	0.0254	0.0254
6m	Me	4-ClC_6H_4	0.0128	0.0064	0.0064	0.0128
6n	Me	2-3-$(Cl)_2C_6H_3$	0.0118	0.0236	0.0236	0.0118
6o	Me	3-4-$(Cl)_2C_6H_3$	0.0118	0.0238	0.0238	0.0118
6p	Me	3-FC_6H_4	0.0133	0.0133	0.0133	0.0133
6q	Me	2-$NO_2C_6H_4$	0.0126	0.0252	0.0252	0.0126
6r	Me	1-$C_{10}H_7$	0.0248	0.0496	0.0496	0.0248
Ciprofloxacin	-	-	**0.0047**	**0.0047**	**0.0047**	**0.0047**

The Carbon-hydrogen correlations were established by analyzing HSQC (Hetero-nuclear Single-Quantum Coherence Spectroscopy) spectrum of compound **6d.** HSQC revealed the assignment of carbon signals at δ 142.51, 132.15, 125.71, 124.65, 117.21, 107.83, 52.64, 42.00 because the key correlation was δ 8.29 → 132.15, 8.02 → 125.71 (triazole 3°**C**), 7.90 → 107.83, 7.80 (imidazole ring **H**) → 117.22, 7.77 → 124.65, 7.58 →129.29, 7.39 → 129.06, 7.38 → 129.29, 7.24 → 127.29, 6.60 → 142.51, 5.30 (C**H**$_2$) → 42.00 (N**C**H$_2$), 5.52 (C**H**$_2$) → 52.64 (CO**C**H).

HMBC (Hetero-nuclear Multiple Bond Correlation) established the connectivity of hydrogen with other carbon through multiple bond correlation of signals. HMBC gives the information of carbon atoms having three and two bonds coupling with hydrogens. HMBC experiment established the assignment of quaternary carbon signals through two bond correlation at 142.80, 138.03, 137.75, 133.83 and 127.84. The above assignment was confirmed through the correlation of signals at δ 8.02→142.80 (triazole ring 4° carbon); 8.29 → 132.15, 107.83 and 142.51; 7.90 → 107.83, 132.15 and 142.51; 7.80 → 117.22, 140.08 and 138.03; 7.77→124.65, 127.29 & 138.03; 6.60 →132.15; 7.39 →124.65 & 129.06; 7.24→124.65 ppm. Displacement of correlation by the signal at of δ 5.31 and 5.52 with 125.71 in HMBC spectroscopy support the orientation of methylene bridges with respect to triazole ring.

Mass spectrometery also assured the structure of compound **6d** by observation of the molecular ion peak; HRMS (m/z) calculated for $C_{23}H_{19}ClN_8O$: 458.1444, found $[M+1]^+$: 459.1486.

2.2. Antimicrobial assay

The synthesized hybrid were tested for their antimicrobial activity against bacterial (*Staphylococcus aureus* MTCC 6538P, *Bacillus subtilis* ATCC 6633, *Escherichia coli* MTCC 1652, *Pseudomonas aeruginosa* ATCC 27853), fungus (*Aspergillus niger*) and yeast (*Candida albicans* ATCC 10231). The antibacterial assays were performed in accordance with the procedures outlined by Clinical and Standards Institute (CLSI) (Wayne, 2012) [22]. The antibacterial assays were completed by serial dilution method and Minimum Inhibitory Concentrations were determined in µmol/mL) through a stock solution of 100 µg/mL. From this solution, through serial dilution technique concentration of 50 - 3.12 µg/ mL was attained in other test tube. Each experiment was accompanied by a positive control containing broth, pathogen and a known inhibitory compound (Ciprofloxacin); a negative control containing broth and pathogen. The test tubes were incubated for 24 hours at 37°C with agitation and then observations were documented visually. The test tubes containing minimum concentration of the synthesized hybrid in which there is no visual growth is considered as MIC.

2.2.1. Antibacterial activity

All the synthesized hybrid **4a-4b** and **6a-6r** were screened for in vitro antimicrobial activity against four bacterial strains, namely *B. subtilis, S. aureus, E. coli, P. aeruginosa* and two fungal strains *C. albicans* and *A. niger*. Results of antibacterial activity are presented in **Table 1** and **Fig. 3.** The hybrid exhibited substantial efficacy against the tested bacterial strains in the range of 0.0064-0.0550 µmol/mL. The compound **6m** showed excellent activity against *B. subtilis* and *S. aureus* with MIC value of 0.0064 µmol/mL. The hybrid **6e (**MIC 0.0126 µmol/mL**), 6f (**MIC 0.0126 µmol/mL**), 6m (**MIC 0.0128 µmol/mL**), 6n (**MIC 0.0118 µmol/mL**), 6o (**MIC 0.0118 µmol/mL) and **6q (**MIC 0.0126 µmol/mL) displayed promising antibacterial activity on gram negative bacteria viz. *E. coli* and *P. aeruginosa.* Among the synthesized hybrid, **6e** (0.0243 µmol/mL), **6n** (0.0236 µmol/mL), **6o** (0.0238 µmol/mL) and **6p** (0.0133 µmol/mL) exhibited moderate efficacy against the tested gram positive bacteria *B. subtilis* and *S. aureus*.

The compound **6g** displayed highest activity towards *E. coli* and *P. aeruginosa* with MIC value of 0.0071 µmol/mL. Further, compound **6l** (MIC, 0.0254 µmol/mL) and **6p** (MIC, 0.0133 µmol/mL) showed similar activity against all the tested bacterial strains. As evident from the activity data, generally, hybrid with halogen group on anilide ring displayed enhanced bactericidal potential against all the tested strains. Compounds bearing dichloro group on anilide ring were found more potent than the monochlorinated derivatives. Further, it has been also observed that the synthesized derivatives show higher activity against gram (-) than gram (+) bacteria. Moreover, in most of cases, presence of methyl group on pyrazole ring enhance the activity against the bacterial strains. In compounds **6a-6i** replacement of methoxy and Me group by Cl at para position of N-phenyl ring leads to increase in activity against all the tested bacterial strains. However, in compounds **6j-6r** trend of activity among the para substituted analogues is Cl> OMe> Me.

2.2.2. Antifungal activity

Antifungal activity results of the tested hybrid are depicted in **Table 2** and **Fig. 4.** The hybrid displayed significant antifungal activity against the tested fungal strains with (MIC 0.0064 - 0.1008 µmol/mL). The derivative, **6m** (MIC, 0.0064 µmol/mL) was found almost two fold more active against *A. niger* than the reference drug Fluconazole (MIC, 0.0102 µmol/mL). Among the synthesized hybrid, **6a** (MIC, 0.0136 µmol/mL), **6d** (MIC, 0.0136

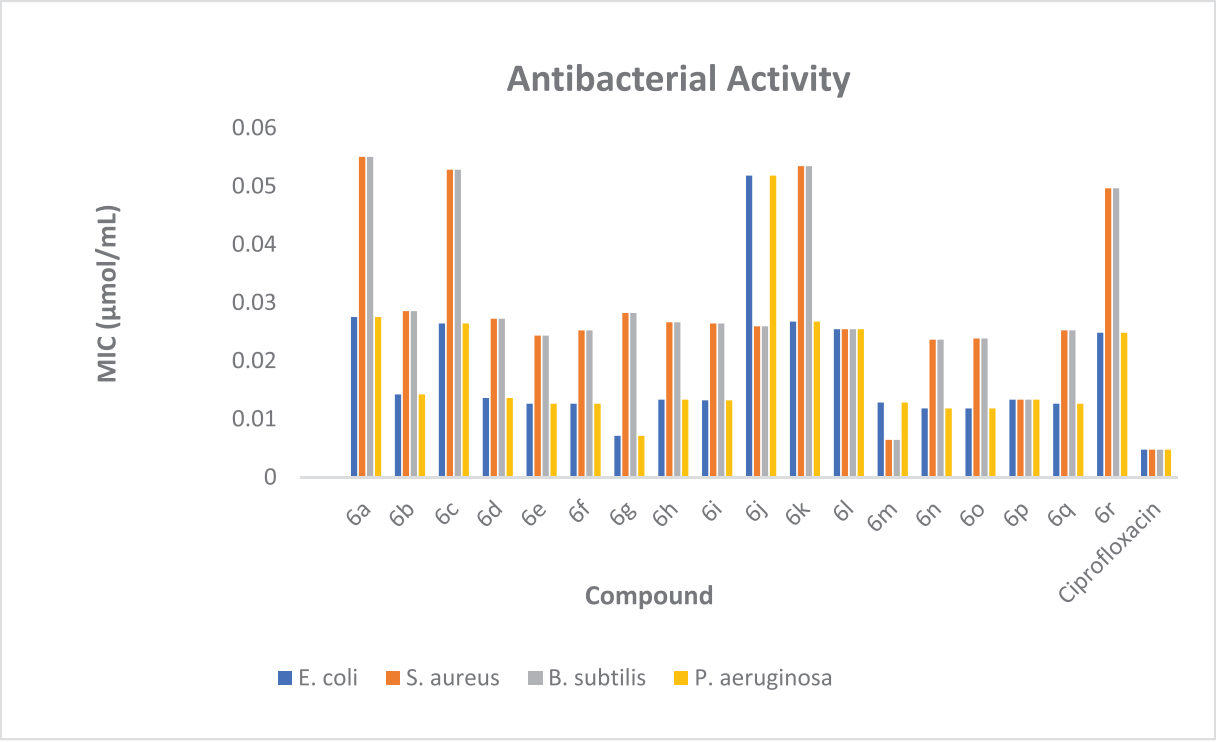


Fig. 3. *In vitro* antibacterial evaluation of synthesized hybrids **6a-6r** (MIC in µmol/mL).

Table 2
In vitro antifungal evaluation of synthesized compounds **6a-6r** (MIC in µmol/mL).

Compound	R_1	R_2	*C. albicans*	A. *nigar*
6a	H	4-$OMeC_6H_4$	0.0272	0.0136
6b	H	4-$CH_3C_6H_4$	0.1140	0.0570
6c	H	3-Cl-2-$CH_3C_6H_3$	0.0528	0.0264
6d	H	4-ClC_6H_4	0.0272	0.0136
6e	H	2-3-$(Cl)_2C_6H_3$	0.0504	0.0252
6f	H	3-4-$(Cl)_2C_6H_3$	0.0504	0.0252
6g	H	3-FC_6H_4	0.0282	0.0141
6h	H	2-$NO_2C_6H_4$	0.0864	0.0432
6i	H	1-$C_{10}H_7$	0.0528	0.0264
6j	Me	4-$OMeC_6H_4$	0.0259	0.0129
6k	Me	4-$CH_3C_6H_4$	0.0534	0.0267
6l	Me	3-Cl-2-$CH_3C_6H_3$	0.0508	0.0254
6m	Me	4-ClC_6H_4	0.0246	0.0064
6n	Me	2-3-$(Cl)_2C_6H_3$	0.0848	0.0236
6o	Me	3-4-$(Cl)_2C_6H_3$	0.0848	0.0238
6p	Me	3-FC_6H_4	0.0266	0.0133
6q	Me	2-$NO_2C_6H_4$	0.1008	0.0514
6r	Me	1-$C_{10}H_7$	0.0496	0.0248
Fluconazole	-	-	**0.0056**	**0.0112**

µmol/mL), **6g** (MIC, 0.0141 µmol/mL), **6j** (MIC, 0.0129 µmol/mL) and **6p** (MIC, 0.0133 µmol/mL) exhibited promising activity against *A. niger*. However, compounds **6e, 6f, 6i, 6k, 6l, 6n, 6o** and **6r** exhibited moderate activity with MIC value 0.0252, 0.0252, 0.0264, 0.0267, 0.0252, 0.0236, 0.0238 and 0.0248 µmol/Ml on *A. niger*. The hybrid **6a** (MIC, 0.0272 µmol/mL), **6d** (MIC, 0.0272 µmol/mL), **6g** (MIC, 0.0282 µmol/mL), **6j** (MIC, 0.0259 µmol/mL), **6m** (MIC, 0.0246 µmol/mL) and **6p** (MIC, 0.0266 µmol/mL) were found to show significant efficacy on tested strain of *C. albicans*. From the above results, it can be summarized that triazole derivatives bearing Cl and OMe group at anilide ring has been shown good activity as compared to strong electron withdrawing NO_2 against the tested fungal strains. Among the synthesized series, most of derivatives bearing methyl group at pyrazole ring displayed higher activity than the **H** analogues. Moreover, the synthesized hybrid were found to show higher potency against *A. niger* than *C. albicans*.

2.3. Drug likeness of the target compounds

The physicochemical properties of hybrid were evaluated by using Lipinski's rule of five, which act as a filter for drug likeness and to regulate their pharmacokinetic parameters. Some important properties to determine drug likeness were calculated by Molinspiration property calculator (https://www.molinspiration.com) are presented in Table 3. The pharmacokinetic parameters comprise distribution, metabolism, absorption and excretion from the human body. The value of milogP (octanol-water partition coefficient) of all hybrid is less than 5.0 (2.797 to 4.334) showing their high affinity and excellent permeability across the lipid bilayers of biological membranes. The sum of -OH and -NH groups showed that the hydrogen bond donor is less than 5.0 (1 for all). Therefore, the number of violations to the Lipinski's rule of five is zero, confirming their easy binding to receptors. The molecular weight less than 500 for most of derivatives indicate easy absorption, diffusion and transportation. The value of total polar surface area (TPSA) was less than 160Å^2 (95.45 Å^2 to 141.27 Å^2) which presented it to be a good predictor of transport properties like blood barrier penetration, intestinal absorption etc. The mathematical equation of %ABS is equal to 109-(0.345 x TPSA) [23]. All the hybrid molecules exhibited good absorption (%ABS = 58.27 to 70.89 and the numbers of rotational bonds are less than 10 (i.e. 9) except for **6h** and **6q**, thus confirming their good flexibility. According to Lipinski's rule of five, any molecule violating more than one of these rule decrease the activity and selectivity of a drug like compound to make unlikely orally-active for human beings. It is clear from the above discussion that parameters of all the compounds were within the limits of Lipinski's rule of five with violation number equal to zero except for **6h, 6k, 6n, 6o, 6q** and **6r** thereby passing the criteria for good oral bioavailability.

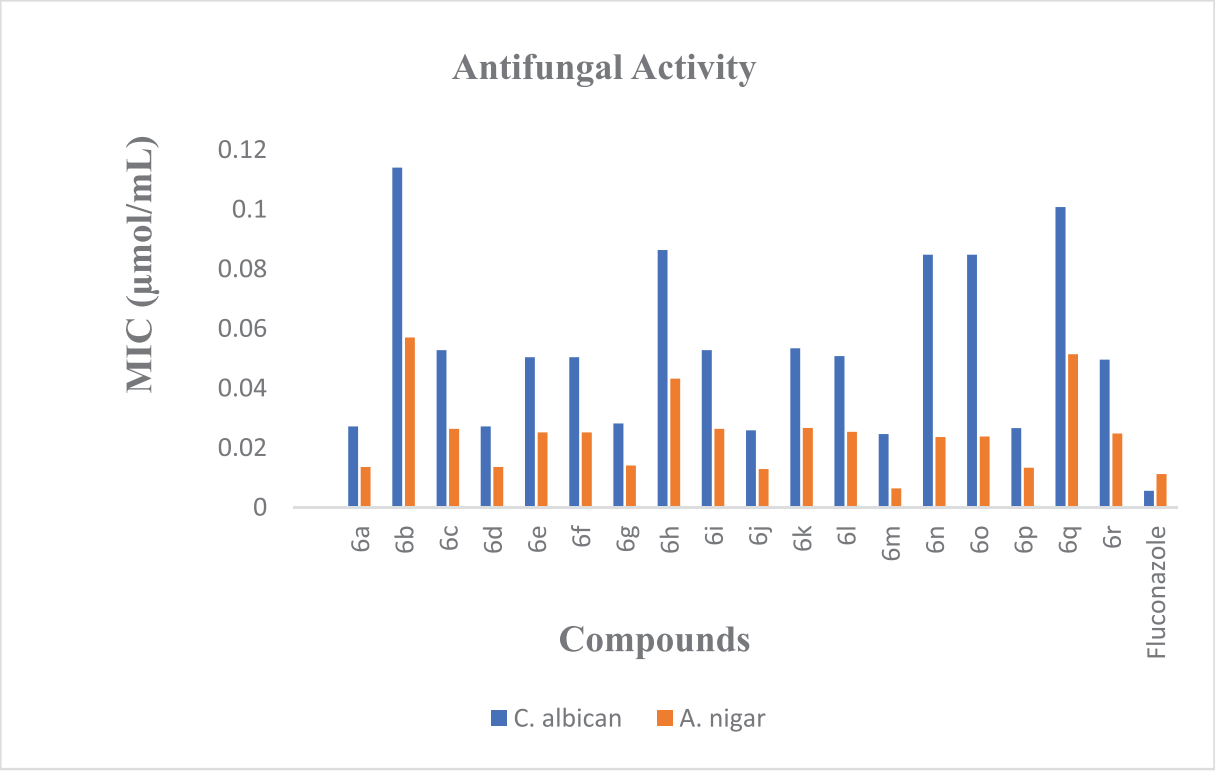


Fig. 4. *In vitro* antifungal evaluation of synthesized compounds **6a-6r** (MIC in µmol/mL).

Table 3
Molecular Property Engine of the synthesized compounds **6a-6r.**

Compound	S+logP	S+logD	MlogP	MWt	HBDH	M_NO	T_PSA	Rule Of 5	Rule Of 5_Code
6a	2.175	2.175	2.797	454.49	1	10	104.68	0	<None>
6b	2.604	2.604	3.528	438.49	1	9	95.45	0	<None>
6c	2.843	2.843	3.736	472.94	1	9	95.45	0	<None>
6d	2.578	2.577	3.528	458.91	1	9	95.45	0	<None>
6e	3.089	3.087	3.736	493.35	1	9	95.45	0	<None>
6f	2.921	2.92	3.736	493.35	1	9	95.45	0	<None>
6g	2.448	2.447	3.423	442.45	1	9	95.45	0	<None>
6h	2.307	2.285	3.755	469.46	1	12	141.27	1	LP, NO
6i	3.441	3.44	3.94	474.52	1	9	95.45	0	<None>
6j	2.832	2.832	3.209	482.54	1	10	104.68	0	<None>
6k	3.681	3.679	4.142	521.41	1	9	95.45	1	LP, Mw
6l	3.258	3.257	3.94	466.54	1	9	95.45	0	<None>
6m	3.225	3.225	3.94	486.96	1	9	95.45	0	<None>
6n	3.497	3.497	4.142	500.99	1	9	95.45	1	LP, Mw
6o	3.571	3.57	4.142	521.41	1	9	95.45	1	LP, Mw
6p	2.98	2.979	3.839	470.51	1	9	95.45	0	<None>
6q	2.946	2.926	4.174	497.51	1	12	141.27	2	LP, NO
6r	4.034	4.034	4.334	502.58	1	9	95.45	2	LP, Mw

2.4. Docking studies

The hybrid **6g** and **6m** have been identified as being more active against bacteria and fungi. These were therefore docked into the productive site of DNA gyrase region of the *E. coli* and sterol 14 alpha demethylase of *C. albicans* respectively using docking tool Autodock Vina. The DNA gyrase sterol 14 alpha demethylase x-ray crystal structures were acquired from the protein database (PDB: 1KZN and 5TZ1), and the docking guidelines were selected. The findings were presented with Discovery Studio Visualizer Application 2017 R2.

The minimum energy combinations of both hybrid **6g** and **6m** with the active site residues of DNA gyrase and sterol 14 alpha demethylase respectively, represented in Figs. 5 and 6 are supported by multiple forms of connections at the binding site.

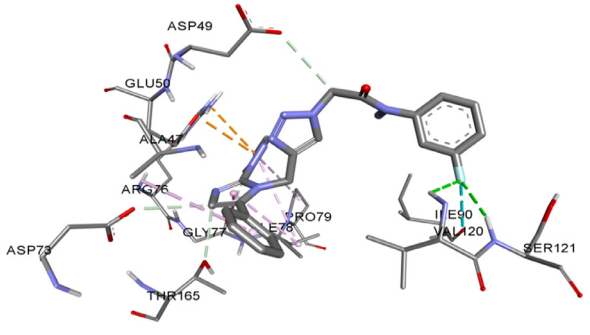


Fig. 5. Binding interactions of hybrid **6g** in binding site of *E. coli* DNA gyrase.

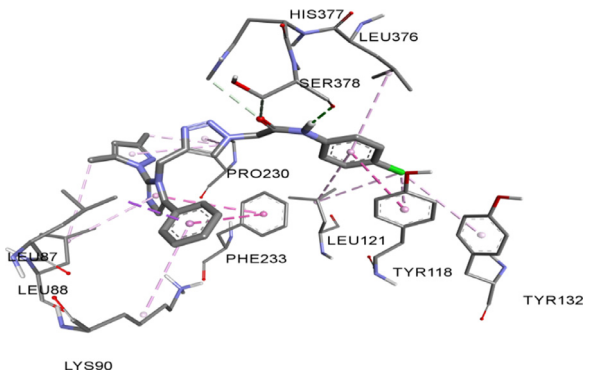


Fig. 6. Binding interactions of hybrid **6m** in binding site of *C. albicans* 14 alpha demthylase.

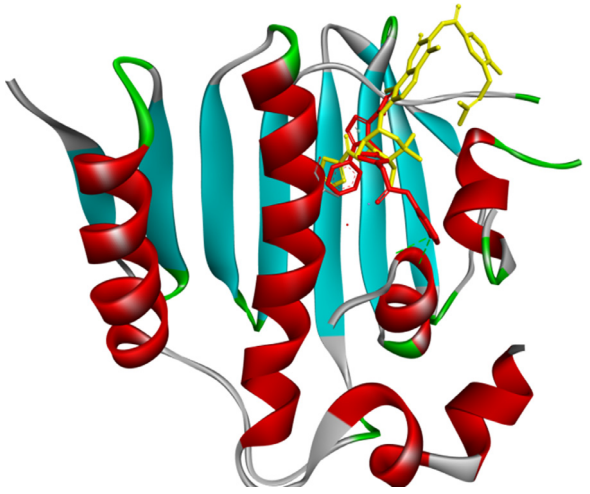


Fig. 7. Hybrid **6g** (red) and cocrystallized ligand CBN (yellow) along with cartoon representation of *E. coli* DNA Gyrase.

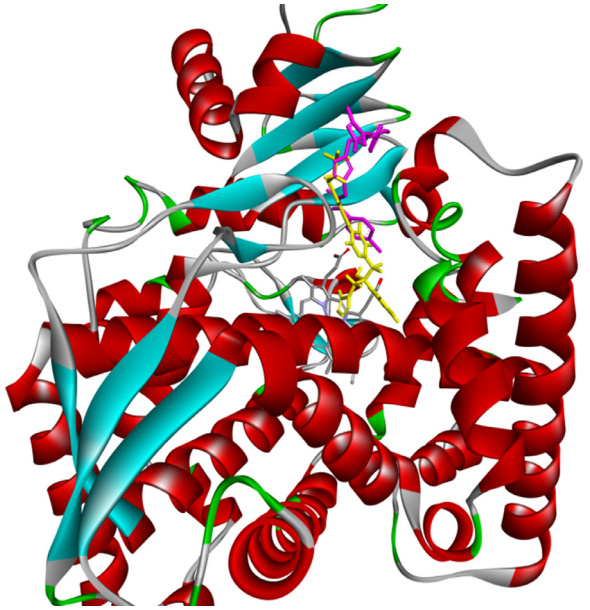


Fig. 8. Hybrid **6m** (pink) and co-crystallized ligand (yellow) along with cartoon representation of *C. albicans* Sterol 14 alpha demethylase.

Ironically, fluorine atoms played a significant part in molecular affixation of compound **6g**. By acting as an accepter, the fluorine atom located at position 3 of the phenyl ring linked to amide nitrogen rendered hydrogen bonds with Val120 and Ser121. In addition, the fluorine atom formed halogen bond with Ile90. Asp49, Asp73, Gly77 and Thr165 formed carbon hydrogen bonds with different parts of the molecule. Pi-anion contacts with imidazole ring were developed by Glu50 while Arg76 succeeded in making pi-cation contacts this ring. In addition, the binding affinity of compound **6g** was -9.5 kcal/mol, more comparable to the binding affinity of co-crystallized CBN ligand (-9.3 kcal/mol). These observations validated that hybrid **6g** efficiently inhibits the enzyme (**Fig. 5**).

The NH part of the amide linkage of hybrid **6m** created a hydrogen bond with Ser378. Chlorophenyl ring was engaged in pi-pi stacked interactions with Tyr118 while imidazole and phenyl ring attached to it stacked against Phe233 via pi-pi interactions. This phenyl ring also made pi-sigma interaction with Leu87. Carbonyl oxygen built carbon hydrogen bond with His377. **Figs. 7** and **8** displays the carton diagram of DNA gyrase and Sterol 14 alpha demethylase along with their docked and co-crystallized ligand respectively.

3. Conclusion

Conclusively, a novel series of pyrazole-limidazole-triazole hybrid was synthesized by using multistep synthetic route in which 1,2,3-triazole was synthesized in last step from N-propargylated pyrazolylimidazole derivatives and 2-bromo-*N*-(substituted)acetamide by click reaction in DMF/H_2O with good yield. Structure of synthesized compounds was confirmed by employing different spectroscopic methods. The synthesized hybrids were assessed for *in vitro* antimicrobial assay. The hybrid **6g** and **6m** show highest activity against *E. coli* (MIC 0.0071, 0.0064 µmol/mL respectively) and *P. aeruginosa* (MIC 0.0071, 0.0064 µmol/mL respectively). Overall the compounds were found to be more active against *A. niger* than *C. albicans*. Compound **6m** was found almost two fold more active than the standard drug against *A. niger*.

4. Materials and method

4.1. Experimental

4.1.1. General

In present study, chemicals were procured from Alfa-Aesar /Sigma Aldrich and used as such without further purification. To detect the melting point of synthesized compounds, open capillary method was used. Standard literature procedures were used for drying the solvents. To perform thin layer chromatography (TLC), pre-coated Merck silica gel (SIL G/UV_{254}, ALUGRAM) plates were used in ethyl acetate: hexane mixture solvent system followed by observing spots under UV light (254 nm). The spectrum for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were taken in dimethylsulfoxide-$\mathbf{d_6}$ by Bruker Avance III. The chemical shifts of DMSO for ^{1}H (δ 2.50 ppm) and ^{13}C (δ 39.50 ppm) were used as reference. Coupling constant values are given in Hertz. Peaks splitting patterns in ^{1}H NMR are reported as follow: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; t, triplet; bt, broad triplet; m, multiplet. The IR spectra of synthesized compounds were recorded on Shimazdu IR Affinity-I using KBr powder as a standard in the region of 4000-400 cm^{-1}. The high resolution mass spectra (HRMS) were recorded by Mass spectrometer Esquire 3000 with ESI resource.

*4.1.2. General method of synthesis of 1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole **(3a)** and 3,5-dimethyl-1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole **(3b)***

1H-Pyrazole-1-carboximidamide hydrochloride **(1a, 1mmol)** was dissolved in 10 ml of the mixture of tetrahydrofuran and water (5:1) and clamped with the reflux condenser. Potassium carbonate (**2.5 mmol**) was added in small portions. Then a solution of 2-bromo-1-phenylethanone **(2, 1.2 mmol)** in tetrahydrofuran was constantly added drop wise *via* pressure equalizing funnel over a period of 20 minutes while refluxing. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of reaction, crude product was filtered and purified with the help of column chromatography (60-120 mesh silica, hexane/ethylacetate 90/10). Compound **3b** was prepared by the same procedure from 3,5-dimethyl-1H-pyrazole-1-carboximidamide nitrate.

*4.1.2.1. 1-(5-Phenyl-1H-imidazol-2-yl)-1H-pyrazole **(3a)**.* White floppy solid; mp: 158-160°C; ^{1}H NMR (400 MHz, DMSO): δ = 12.81 (s, 1H, N-**H**, D_2O exchangeable), 8.40 (bs, 1H, pyrazole C_5-**H**), 7.82 – 7.83 (m, 2H, phenyl C_2-**H,** C_6-**H**), 7.80 (bs, 1H, pyrazole C_3-**H**), 7.59 (s, 1H, imidazole **H**), 7.37 (t, *J* = 7.6, Hz, 2H, phenyl C_3-**H**, C_5-**H**), 7.22 (t, *J* = 7.6, 7.2 Hz, 1H, phenyl C_4-**H**), 6.58 (t, J = 2.4, 2.0, 1H, pyrazole C_4-**H**); ^{13}C NMR (100 MHz, DMSO): δ = 141.89, 141.77, 138.78, 134.56, 128.93, 128.42, 126.83, 124.70, 112.39, 108.25 **ppm**; IR (KBr, $\boldsymbol{\nu}_{max}$/cm^{-1}): 3445.30 (N-H str.); HRMS: m/z Cacld. (M + H)$^+$ for $C_{12}H_{10}O_4$: 211.0978 found 211.0975.

*4.1.2.2. 3,5-Dimethyl-1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole **(3b)**.* Light Yellow solid; mp: 193-194°C; ^{1}H NMR (400 MHz, DMSO): δ = 12.59 (s, 1H, N-**H**, D_2O exchangeable), 7.80 (d, *J* = 7.6 Hz, 2H, phenyl C_2-**H**, C_6-**H** (3,5-Dimethyl-1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole), 7.56 (bs, 1H, imidazole **H**), 7.36 (t, *J* = 7.6 Hz, 2H, phenyl C_3-**H**, C_5-**H**), 7.21 (t, *J* = 7.6, 7.2 Hz, 1H, phenyl C_4-**H**), 6.12 (s, 1H, pyrazole C_4-**H**), 2.60 (s, 3H, C**H**$_3$), 2.23 (s, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, DMSO): δ = 149.41, 141.87, 140.86, 138.64, 134.83, 128.89, 126.66, 124.62, 111.78, 108.11, 13.71, 13.05 **ppm**; IR (KBr, $\boldsymbol{\nu}_{max}$/cm^{-1}): 3439.09 (N-H str.); HRMS: m/z Cacld. (M + H)$^+$ for $C_{14}H_{14}N_4$: 239.1291 found 239.1293.

*4.1.3. General method of synthesis of substituted-1-(4-phenyl-1-(prop-2-yn-1-yl)-1H-imidazol-2-yl)-1H-pyrazole **(4a-4b):***

To a solution of pyrazolylimidazole (**3a-3b,** 1 mmol) in 15 mL dimethylformamide, potassium carbonate (4 mmol) was added and stirred for 10 minutes. Propargyl bromide (1.2 mmol) was added dropwise and reaction mixture was stirred at 0-5°C for 4-5 h. The workup of reaction was done with ice cold water and compound was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield **4a-4b**. The synthesized compounds were purified with Ethyl acetate: Hexane (9:1).

*4.1.3.1. 1-(5-Phenyl-1-(prop-2-yn-1-yl-1H-imidazole-2-yl)-1H-pyrazole **(4a)**.* White colour, yield: 74 %, M.P.: 50-55°C, ^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, *J* = 2.4 Hz, 1H, pyrazole C_3-**H**), 7.90 (d, *J* = 1.6 Hz, 1H, pyrazole C_5-**H**), 7.84 (s, 1H, imidazole ring **H**), 7.81 (d, *J* = 7.6 Hz, 2H, imidazole C_4-phenyl C_2-C_6 **H**), 7.40 (t, *J* = 7.6, 8.0 Hz, 2H, imidazole C_4-phenyl C_3-C_5 **H**), 7.26 (t, *J* = 7.2, 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.61 (t, *J* = 2.0, 2.0 Hz, 1H, pyrazole C_4-**H**), 5.14 (d, *J* = 2.4 Hz, 2H, methylene **H**), 3.46 (t, *J* = 2.4,2.4 Hz, 1H, alkenyl **H**).^{13}C NMR (101 MHz, DMSO) δ142.60, 139.91, 138.04, 133.74, 131.85, 139.08, 127.38, 124.73, 116.96, 107.88, 78.54, 76.72, 36.77. IR (KBr, $\boldsymbol{\nu}_{max}$/cm^{-1}): 3253.91(C-H str.of alkyne), 3047.53(aromatic C-H), 2920.23 (aliphatic C-H), 2856.53, 2360.87 (alkyne C-H str.) 1564.27 and 1544.98 (C=N and C=C), 1217.08.

*4.1.3.2. 3,5-Dimethyl-1-(4-phenyl-1-(prop-2-yn-1-yl)-1H-imidazol-2-yl)-1H-pyrazole **(4b)**.* White colour; yield: 80 %, mp: 70-75°C; ^{1}H NMR (400 MHz, DMSO) δ: 7.85 (s, 1H, imidazole ring **H**), 7.79 (d, *J* = 7.1 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.39 (t, *J* = 7.7 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.26 (t, *J* = 7.4 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.15 (s, 1H, pyrazole C_4-**H**), 4.86 (d, 2H, J = 2.4 Hz, methylene **H**), 3.47 (t, 1**H**, J = 2.5, ≡C-**H**), 2.29 (s, 3H, **CH$_3$**), 2.22 (s, 3H, **CH$_3$**). ^{13}C NMR (101 MHz, DMSO) δ 150.25, 142.84, 139.10, 138.28, 133.95, 129.08, 127.32, 124.70, 116.56, 107.19, 78.28, 76.64, 36.00, 13.84, 11.7 **ppm**. IR (KBr, $\boldsymbol{\nu}_{max}$/cm^{-1}): 3255.91(C-H str. of alkyne), 3048.53(aromatic C-H), 2922.23 (aliphatic C-H), 2858.53, 2365.87 (alkyne bond str.) 1565.27 and 1545.98 (C=N and C=C), 1227.08. HRMS: m/z (M + H)+ Cacld. for $C_{17}H_{16}N_4$: 277.1375 found 277.1455.

*4.1.4. General method of synthesis of 2-bromo-N-(substituted)acetamide **(5a-5i)***

2-Bromo-N-(substituted)acetamide **5a-5i** were synthesized by earlier reported method [21]. Substituted aniline (1mmol) and bromo acetyl bromide (1.5 mmol) were stirred with potassium carbonate in dichloromethane at 0-10 °C for 3-4 hours. After completion of reaction ice cold water was added to reaction mixture. Layer of dichloromethane was separated and dried over anhydrous Na_2SO_4. The excess of solvent was removed under reduced pressure and the obtained compound was purified from chloroform.

*4.1.5. General method of synthesis of 2-(4-((2-(substituted-1H-pyrazol-1-yl)-4-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(substituted)phenylacetamide **(6a-6r)***

In a round-bottomed flask, a mixture of N-propargylated pyrazolylimidazole **4a-4b** (1.4 mmol), 2-bromo-*N*-(substituted)acetamide **5a-5i** (1.4 mmol) and sodium azide (2.8 mmol) was taken in dimethylformamide/water (7:3), copper sulphate pentahydrate (14 mol %) and sodium ascorbate (28 mol %) were added and reaction mixture was stirred for 8-10 hours at 60°C. The reaction progress was monitored by TLC. After the completion of reaction, workup was done by adding ammonia solution and product was extracted with ethyl acetate (50 mL ×3). The ethyl acetate layer was washed with brine solution and dried using anhydrous Na_2SO_4. The solution was concentrated under reduce pressure and residue was purified by recrystallization with $CHCl_3$. The desired products pyrazole-imidazole-triazole hybrids **6a-6r** were isolated in good yields.

*4.1.5.1. N-(4-Methoxyphenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide **(6a)**.* White colour, yield: 54%, M.P.:124-126°C, ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H, amide N-**H**), 8.29 (d, *J* = 2.8 Hz, 1H, pyrazole C_3-**H**), 8.01 (s, 1H, triazole ring **H**), 7.90 (d, *J* = 2.0 Hz, 1H, pyrazole C_5-**H**), 7.80 – 7.77 (m, 3H, imidazole C_4-phenyl C_2/C_6-**H** and imidazole ring **H**), 7.47 (d, *J* = 8.8 Hz, 2H, 4-methoxyphenyl ring C_2/C_6-H), 7.38 (t, *J* = 7.6 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.24 (t, *J* = 7.6, 8.4 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.90 (d, *J* = 4.8 Hz, 2H, 4-methoxyphenyl ring C_3/C_5-H), 6.60 (t, J = 2.4, 2.0, 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 3.72 (s, 3H, OC**H**$_3$).^{13}C NMR (100 MHz, DMSO) δ 163.98 (**C**OCH$_2$), 156.01, 142.75, 142.49, 140.09, 138.03, 133.87, 132.15, 131.91, 129.05, 127.27, 125.67, 124.66, 121.24, 117.21, 114.47, 107.81 (aromatic ring **C**), 55.63, 52.61 (COCH$_2$), 42.02 (**C**H$_2$). IR (KBr, υ_{max}) = 3290 (N-H Str.), 3147 (C–H str., triazole), 3003 (C–H str., aromatic), 1687 (C=O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{24}H_{22}N_8O_2$: 455.1938 found 455.1948.

*4.1.5.2. 2-(4-((5-Phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide **(6b)**.* Green

colour, yield: 58%, M.P.:148-150°C, ^{1}H NMR (400 MHz, DMSO) δ 10.34 (s, 1H, amide N-**H**), 8.30 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.02 (s, 1H, triazole ring **H**), 7.96 (bs, 1H), 7.91 (bd, J = 1.2 Hz, 1H, pyrazole C_5-**H**), 7.80 (s, 1H, imidazole ring **H**), 7.46 (dd, J = 4.0 Hz, 3H), 7.38 (t, J = 7.6, 7.2 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.25 (t, J = 7.6, 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 7.13 (dd, J = 4.0 Hz, 2H), 6.60 (t, J = 2.0, 2.4 Hz, 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.27 (s, 2H, C**H**$_2$), 2.26 (s, 3H, C**H**$_3$). IR (KBr, υ_{max}) = 3295 (N-H Str.), 3136 (C–H str., triazole), 3037 (C–H str., aromatic), 1699 (C = O str.), 1610 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{24}H_{21}N_8O$: 467.1989 found 467.2298. Due to poor solubility ^{13}C NMR of compound is not available.

4.1.5.3. N-(3-Chloro-2-methylphenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6c)***. Brown colour, yield: 74%, M.P.:155-156°C, ^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H, amide N-**H**), 8.29 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.02 (s, 1H, triazole ring **H**), 7.90 (d, J = 1.2 Hz, 1H, pyrazole C_5-**H**), 7.80 (s, 1H, imidazole ring **H**), 7.77 (bd, J = 7.2 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.40 – 7.30 (m, 4H, imidazole C_4-phenyl C_3/C_5-**H and** 1H of 2-methyl-3-chlorophenyl ring), 7.26 – 7.20 (m, 2H, imidazole C_4-phenyl C_4-H and 2H of 2-methyl-3-chlorophenyl ring), 6.60 (t, J = 2.4, 2.0 Hz 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.36 (s, 2H, C**H**$_2$), 2.24 (s, 3H, C**H**$_3$).^{13}C NMR (100 MHz, DMSO) δ 164.97 (**C**OCH$_2$), 142.58, 140.11, 138.08, 137.12, 134.34, 133.66, 132.14, 130.93, 129.12, 127.47, 127.41, 127.06, 125.70, 124.82, 124.67, 117.18, 107.93 (aromatic ring **C**), 52.26 (COCH$_2$), 41.90 (**C**H$_2$), 15.42. IR (KBr, υ_{max}) = 3251 (N-H Str.), 3135 (C–H str., triazole), 3030 (C–H str., aromatic), 1695 (C=O str.), 1622 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+Cacld. for $C_{24}H_{21}ClN_8O$: 473.9369 found 473.1600.

4.1.5.4. N-(4-Chlorophenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6d)***. Brown colour, yield: 84%, M.P.:124-126°C, ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H, amide N-**H**), 8.29 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.02 (s, 1H, triazole ring **H**), 7.90 (d, J = 1.4 Hz, 1H, pyrazole C_5-**H**), 7.80 (s, 1H, imidazole ring **H**), 7.77 (d, J = 7.3 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.58 (d, J = 8.8 Hz, 2H, 4-chlorophenyl C_3/C_5-**H**), 7.41 – 7.36 (m, 4H, imidazole C_4-phenyl C_3/C_5-**H** and 4-chlorophenyl C_2/C_6-**H**), 7.24 (t, J = 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.60 (t, J = 2.0, Hz 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.31 (s, 2H, C**H**$_2$).^{13}C NMR (100 MHz, DMSO) δ 164.73 (**C**OCH$_2$), 142.80, 142.51, 138.03, 137.75, 133.83, 132.15, 129.29, 129.06, 127.84, 127.29, 125.71, 124.65, 121.26, 117.21, 107.83 (aromatic ring **C**), 52.64 (COCH$_2$), 42.00 (**C**H$_2$). IR (KBr, υ_{max}) = 3251 (N-H Str.), 3135 (C–H str., triazole), 3030 (C–H str., aromatic), 1695 (C=O str.), 1622 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+Cacld. for $C_{23}H_{19}ClN_8O$: 459.1443 found 459.1486.

4.1.5.5. N-(2,3-Dichlorophenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6e)***. White colour, yield: 74%, M.P.:130-132°C, ^{1}H NMR (400 MHz, DMSO) δ 10.20 (s, 1H, amide N-**H**), 8.29 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.02 (s, 1H, triazole ring **H**), 7.90 (d, J = 1.6 Hz, 1H, pyrazole C_5-**H**), 7.80 (s, 1H, imidazole ring **H**), 7.77 (d, J = 7.2 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.71 (dd, J = 8.4 Hz, 1H, 2,3-dichlorophenyl ring H), 7.49 (dd, J = 8.0 Hz, 1H, 2,3-dichlorophenyl ring H), 7.37 (dd, J = 16 Hz, 3H, imidazole C_4-phenyl C_3/C_5-**H** and 2,3-dichlorophenyl ring **H**), 7.24 (t, J = 7.2 Hz, 1**H**, imidazole C_4-phenyl C_4-**H**), 6.60 (t, J = 2.0, 2.4 Hz 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.42 (s, 2H, C**H**$_2$).^{13}C NMR (100 MHz, DMSO) δ 165.32 (**C**OCH$_2$), 142.85, 142.60, 140.12, 138.10, 136.25, 133.61, 132.47, 132.14, 129.13, 128.63, 127.72, 127.44, 125.77, 124.95, 124.68, 117.17, 107.96 (aromatic ring **C**), 52.33 (COCH$_2$), 41.86 (**C**H$_2$). IR (KBr, υ_{max}) = 3241 (N-H Str.), 3125 (C–H str., triazole), 3020 (C–H str., aromatic), 1670 (C=O str.), 1640 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{23}H_{18}Cl_2N_8O$: 493.1053 found 493.1080.

4.1.5.6. N-(3,4-Dichlorophenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6f)***. White colour, yield: 66%, M.P.:145-147°C, ^{1}H NMR (400 MHz, DMSO) δ 10.74 (s, 1H, amide N-**H**), 8.30 (d, J = 2.0 Hz, 1H, pyrazole C_3-**H**), 8.03 (s, 1H, triazole ring **H**), 7.93 (d, J = 2.0 Hz, 1H, pyrazole C_5-**H**), 7.91 (s, 1H, 2,3-dichlorophenyl C_2-H), 7.80 (s, 1H, imidazole ring **H**), 7.78 (d, J = 7.6 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.60 (d, J = 8.8 Hz, 1H, 2,3-dichlorophenyl ring H), 7.47 (dd, J = 8.8 Hz, 1H, 2,3-dichlorophenyl ring H), 7.38 (t, J = 7.6 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.24 (t, J = 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.60 (t, J = 1.6, 2.0 Hz, 1H, pyrazole C_4-**H**), 5.52 (s, 2H, COC**H**$_2$), 5.33 (s, 2H, C**H**$_2$).^{13}C NMR (100 MHz, DMSO) δ 165.08 (**C**OCH$_2$), 140.11, 138.54, 138.09, 133.52, 132.16, 131.64, 131.29, 129.16, 127.48, 126.04, 125.80, 124.67, 121.11, 119.92, 117.17, 108.01 (aromatic ring **C**), 52.53 (COCH$_2$), 41.82 (**C**H$_2$). IR (KBr, υ_{max}) = 3255 (N-H Str.), 3136 (C–H str., triazole), 3037 (C–H str., aromatic), 1693 (C=O str.), 1618 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{23}H_{18}C_{l2}N_8O$: 493.1053 found 493.1352.

4.1.5.7. N-(3-Fluorophenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6g)***. White colour, yield: 60%, M.P.:168-170°C, ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H, amide N-**H**), 8.24 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 7.99 (s, 1H, triazole ring **H**), 7.88 (d, J = 1.6 Hz, 1H, pyrazole C_5-**H**), 7.75 (bd, J = 9.2 Hz, 3H, imidazole C_4-phenyl C_2/C_6-**H** and **imidazole ring H**), 7.49 (bd, J = 11.6 Hz, 1H. imidazole ring **H**), 7.40 – 7.33 (m, 3H), 7.24 (t, J = 7.6 Hz, 1H, imidazole C_4-phenyl C_5-**H**), 6.94-6.6.89 (m, 1H,), 6.58 (t, J = 2.0 Hz, 1H, pyrazole C_4-**H**), 5.49 (s, 2H, COC**H**$_2$), 5.28 (s, 2H, C**H**$_2$).^{13}C NMR (100 MHz, DMSO) δ 164.91 (**C**OCH$_2$), 142.61, 140.27, 140.16, 140.11, 138.07, 133.58, 132.15, 129.14, 127.45, 125.77, 124.67, 117.17, 115.58, 107.97, 106.77, 106.50 (aromatic ring **C**), 79.36, 52.57 (COCH$_2$), 41.85 (**C**H$_2$). IR (KBr, υ_{max}) = 3282 (N-H Str.), 3130 (C–H str., triazole), 3045 (C–H str., aromatic), 1695 (C = O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{23}H_{19}FN_8O$: 445.3539 found 445.3578.

4.1.5.8. N-(2-Nitrophenyl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6h)***. Yellow colour, yield: 63%, M.P.: 145-150°C, ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H, amide N-**H**), 8.28 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.00-7.97 (m, 2H, imidazole ring **H** and triazole ring **H**), 7.90 (d, J = 1.2 Hz, 1H, pyrazole C_5-**H**), 7.78 – 7.67 (m, 5H, imidazole C_4-phenyl C_2/C_6-**H**), 7.44 – 7.36 (m, 3H), 7.24 (t, J = 7.6, 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.59 (t, J = 2.0 Hz, 1H, pyrazole C_4-**H**), 5.51 (s, 2H, COC**H**$_2$), 5.38 (s, 2H, C**H**$_2$). IR (KBr, υ_{max}) = 3292 (N-H Str.), 3140 (C–H str., triazole), 3035 (C–H str., aromatic), 1691 (C=O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{23}H_{19}N_9O_3$: 470.1684 found 470.1594.

4.1.5.9. N-(Naphthalen-1-yl)-2-(4-((5-phenyl-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6i)***. Grey colour, yield: 85%, M.P.:180-182°C, ^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H, amide N-**H**), 8.30 (d, J = 2.4 Hz, 1H, pyrazole C_3-**H**), 8.13 (bd, J = 8.8 Hz, 1H, α-naphthyl ring **H**), 8.07 (s, 1H, triazole ring **H**), 7.96 (bd, J = 7.6 Hz, 1H, α-naphthyl ring **H**), 7.91 (d, J = 2.0 Hz, 1H, pyrazole C_5-**H**), 7.81 (s, 2H), 7.78 (bd, J = 8.8 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.70 (d, J = 7.6 Hz, 1H, α-naphthyl ring **H**), 7.60 – 7.56 (m, 2H, α-naphthyl ring **H**), 7.50 (t, J = 8.0 Hz, 1H, α-naphthyl ring **H**), 7.38 (t, J = 7.2, 8.0 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.24 (t, J = 7.2, 7.6 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.59 (t, J = 2.0, 1H, pyrazole C_4-**H**), 5.53 (s, 2H, COC**H**$_2$), 5.50 (s, 2H, C**H**$_2$).^{13}C NMR (100 MHz, DMSO) δ 167.60 (**C**OCH$_2$), 142.49, 138.06, 134.17, 133.25, 132.15, 129.04, 128.63,

128.16, 127.26, 126.60, 126.44, 126.16, 126.03, 124.67, 123.02, 122.25, 122.01, 117.21, 107.80 (aromatic ring **C**), 51.69 (COCH$_2$), 44.04 (**C**H$_2$). IR (KBr, υ_{max}) = 3340 (N-H Str.), 3136 (C–H str., triazole), 3057 (C–H str., aromatic), 1732 (C=O str. amide), 1666 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{27}H_{22}N_8O$: 475.1989 found 475.2025.

4.1.5.10. 2-(4-((2-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide ***(6j)***. Grey colour, yield: 53%, M.P.:140-142°C, ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H, amide N-**H**), 7.95 (s, 1H, triazole ring **H**), 7.82 (s, 1H, imidazole ring **H**), 7.76 (d, J = 8.0 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.48 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl ring C$_2$/C$_6$-H), 7.38 (t, J = 7.6 Hz, 2H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H**), 7.24 (t, J = 6.8, 7.2 Hz, 1H, imidazole C$_4$-phenyl C$_4$-**H**), 6.90 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl ring C$_3$/C$_5$-H), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.26 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 3.72 (s, 3H, OC**H**$_3$), 2.24 (s, 3H, C**H**$_3$), 2.20 (s, 3H).^{13}C NMR (100 MHz, DMSO) δ 163.97 (**C**OCH$_2$), 156.04, 150.12, 143.03, 142.57, 139.30, 138.27, 134.12, 131.95, 129.05, 127.20, 125.55, 124.65, 121.25, 116.84, 114.50, 107.03 (aromatic ring **C**), 55.65 (O **C**H$_3$), 52.64 (COCH$_2$), 41.40 (**C**H$_2$), 13.85, 11.57. IR (KBr, υ_{max}) = 3290 (N-H Str.), 3147 (C–H str., triazole), 3003 (C–H str., aromatic), 1687 (C=O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+Cacld. for $C_{26}H_{26}N_8O_2$: 483.2251 found 483.2733.

4.1.5.11. 2-(4-((2-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide ***(6k)***. Grey colour, yield: 65%, M.P.: 210-212°C, ^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H, amide N-**H**), 7.97 (s, 1H, triazole ring **H**), 7.81 (s, 1H, imidazole ring **H**), 7.75 (d, J = 7.7 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.39 – 7.30 (m, 4H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H** and 2H of 2-metnyl-3-chlorophenyl ring), 7.25-7.19 (m, 2H, imidazole C$_4$-phenyl C$_4$-**H** and 2-metnyl-3-chlorophenyl ring **H**), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.37 (s, 2H, COC**H**$_2$), 5.24 (s, 2H, C**H**$_2$), 2.24 (s, **6** H, C**H**$_3$), 2.19 (s, 3H, C**H**$_3$).^{13}C NMR (100 MHz, DMSO) δ 165.73 (**C**OCH$_2$), 150.25, 143.13, 139.27, 138.25, 137.45, 134.32, 133.15, 132.95, 130.61, 129.04, 128.56, 128.29, 127.43, 124.62, 123.21, 116.82, 107.01 (aromatic ring **C**), 53.25 (COCH$_2$), 41.40 (**C**H$_2$), 15.51, 13.86, 11.57. IR (KBr, υ_{max}) = 3271 (N-H Str.), 3136 (C–H str., triazole), 3059 (C–H str., aromatic), 1691 (C=O str.), 1612 (N-H bending) cm^{-1}. Due to poor solubility HRMS of compound cannot be reported.

4.1.5.14. N-(3-Chloro-2-methylphenyl)-2-(4-((2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6l)***. Brown colour, yield: 74%, M.P.:134-136°C,^{1}H NMR (400 MHz, DMSO) δ 10.18 (s, 1H, amide N-**H**), 7.97 (s, 1H, triazole ring **H**), 7.81 (s, 1H, imidazole ring **H**), 7.76 (bd, J = 7.2 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.71 (dd, J = 8.4 Hz, 1H, 2,3-dichlorophenyl ring **H**), 7.49 (dd, J = 8.0 Hz, 1H, 2,3-dichlorophenyl ring **H**), 7.35-7.39 (m, 3H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H** and 2,3-dichlorophenyl ring **H**), 7.24 (t, J = 7.2, 7.6 Hz, 1H, imidazole C$_4$-phenyl C$_4$-**H**), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.43 (s, 2H, COC**H**$_2$), 5.29 (s, 2H, C**H**$_2$), 2.24 (s, 3H, C**H**$_3$), 2.19 (s, 3H, C**H**$_3$).^{13}C NMR (100 MHz, DMSO) δ 165.28 (**C**OCH$_2$), 150.55, 143.30, 142.60, 139.17, 138.35, 133.75, 132.49, 129.16, 128.63, 127.76, 127.43, 126.72, 126.05, 125.66, 124.92, 124.65, 116.87, 107.10 (aromatic ring **C**), 52.30 (COCH$_2$), 41.15 (**C**H$_2$), 15.51, 13.68, 11.32. IR (KBr, υ_{max}) = 3241 (N-H Str.), 3125 (C–H str., triazole), 3020 (C–H str., aromatic), 1670 (C=O str.), 1640 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{26}H_{25}ClN_8O$: 521.0261 found 521.1909.

4.1.5.13. N-(4-Chlorophenyl)-2-(4-((2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6m)***. White colour, yield: 64%, M.P.:124-126°C, ^{1}H NMR (400 MHz, DMSO) δ 10.58 (s, 1H, amide N-**H**), 7.96 (s, 1H, triazole ring **H**), 7.82 (s, 1H, imidazole ring **H**), 7.76 (d, J = 7.2 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.59 (d, J = 8.9 Hz, 2H, 4-chlorophenyl C$_3$/C$_5$-**H**), 7.38 (t, J = 8.0, 8.8 Hz, 4H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H** and 4-chlorophenyl C$_2$/C$_6$-**H**), 7.24 (t, J = 7.2 Hz, 1H, imidazole C$_4$-phenyl C$_4$-**H**), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.31 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 2.24 (s, 3H, C**H**$_3$), 2.19 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, DMSO) δ 181.26 (**C**OCH$_2$), 150.93, 146.45, 137.81, 129.31, 129.06, 125.59, 124.64, 122.58, 121.25, 117.81, 116.87, 116.28, 115.73, 115.24, 107.02 (aromatic ring **C**), 47.27 (COCH$_2$), 41.41 (**C**H$_2$), 13.85, 11.57. HRMS: m/z (M + H)+Cacld. for $C_{25}H_{23}ClN_8O$: 487.2216 found 487.2256.

4.1.5.11. N-(2,3-Dichlorophenyl)-2-(4-((2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6n)***. White colour, yield: 67%, M.P.:160-162°C, ^{1}H NMR (400 MHz, DMSO) δ 10.36 (s, 1H, amide N-**H**), 7.96 (s, 1H, triazole ring **H**), 7.83 (s, 1H, imidazole ring **H**), 7.76 (d, J = 7.6 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.45 (d, J = 8.0 Hz, 2H, 4-methylphenyl C$_2$/C$_6$-H), 7.38 (t, J = 7.6, 7.2 Hz, 2H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H**), 7.24 (t, J = 7.2, 6.8 Hz, 1H, imidazole C$_4$-phenyl C$_4$-**H**), 7.13 (d, J = 7.6 Hz, 2H, 4-methylphenyl C$_3$/C$_5$-H), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.28 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 2.25 (s, 3H, C**H**$_3$), 2.24 (s, 3H, C**H**$_3$), 2.19 (s, 3H, C**H**$_3$).^{13}C NMR (100 MHz, DMSO) δ 164.25 (**C**OCH$_2$), 150.12, 143.02, 142.58, 139.27, 138.25, 136.34, 134.11, 133.23, 129.75, 129.07, 127.21, 125.59, 124.63, 119.66, 116.85, 107.03 (aromatic ring **C**), 52.67 (COCH$_2$), 41.40 (**C**H$_2$), 20.91, 13.86, 11.57. IR (KBr, υ_{max}) = 3241 (N-H Str.), 3125 (C–H str., triazole), 3020 (C–H str., aromatic), 1670 (C=O str.), 1640 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{25}H_{22}Cl_2N_8O$: 483.2751 found 483.2733.

4.1.5.15. N-(3,4-Dichlorophenyl)-2-(4-((2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamide ***(6o)***. White colour, yield: 64%, M.P.:160-162°C, ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H, amide N-**H**), 7.97 (s, 1H, triazole ring **H**), 7.93 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H, imidazole ring **H**), 7.76 (d, J = 7.2 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.60 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 8.8 Hz, 1H), 7.38 (t, J = 7.2, 8.0 Hz, 2H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H**), 7.24 (t, J = 7.2,7.6 Hz, 1H, imidazole C$_4$-phenyl C$_4$-**H**), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.33 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 2.24 (s, 3H, C**H**$_3$), 2.20 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, DMSO) δ 165.11 (**C**OCH$_2$), 150.37, 143.17, 142.62, 139.22, 138.70, 138.31, 133.89, 131.63, 131.34, 129.13, 127.35, 125.63, 124.64, 121.04, 119.87, 116.85, 107.07 (aromatic ring **C**), 52.59 (COCH$_2$), 41.25 (**C**H$_2$), 13.75, 11.43. IR (KBr, υ_{max}) = 3235 (N-H Str.), 3126 (C–H str., triazole), 3035 (C–H str., aromatic), 1690 (C=O str.), 1620 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+Cacld. for $C_{25}H_{22}C_{l2}N_8O$: 521.1366 found 521.1908.

4.1.5.16. 2-(4-((2-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-fluorophenyl)acetamide ***(6p)***. White colour, yield: 74%, M.P.:138-140°C, ^{1}H NMR (400 MHz, DMSO) δ 10.66 (s, 1H, amide N-**H**), 7.97 (s, 1H, triazole ring **H**), 7.82 (s, 1H, imidazole ring **H**), 7.76 (bd, J = 7.2 Hz, 2H, imidazole C$_4$-phenyl C$_2$/C$_6$-**H**), 7.58 – 7.52 (m, 1H), 7.41 – 7.35 (m, 3H, imidazole C$_4$-phenyl C$_3$/C$_5$-**H** and 1**H** of 3-fluorophenyl ring), 7.30 – 7.22 (m, 2H, imidazole C$_4$-phenyl C$_4$-H and 3-fluorophenyl ring), 6.95-6.90 (m, 1H), 6.11 (s, 1H, pyrazole C$_4$-**H**), 5.32 (s, 2H, COC**H**$_2$), 5.25 (s, 2H, C**H**$_2$), 2.24 (s, 3H, C**H**$_3$), 2.20 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, DMSO) δ 164.82 (**C**OCH$_2$), 163.77, 161.36, 150.36, 143.16, 142.59, 139.23, 138.31, 133.91, 131.10, 129.12, 127.33, 125.62, 124.64, 116.86, 115.45, 111.01, 110.79, 107.06 (aromatic ring **C**), 52.59 (COCH$_2$), 41.26 (**C**H$_2$), 13.75, 11.42. IR (KBr, υ_{max}) = 3292 (N-H Str.), 3140 (C–H str., triazole), 3035 (C–H

str., aromatic), 1691 (C=O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{25}H_{23}FN_8O$: 471.2052 found 471.2372.

*4.1.5.17. 2-(4-((2-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide **(6q)**.* White colour, yield: 83%, M.P.:151-153°C, ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H, amide N-**H**), 7.99 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H, triazole ring **H),** 7.80 (s, 1H, imidazole ring **H**), 7.75 (d, J = 8.0 Hz, 3H), 7.70 (t, J = 8.5 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.23 (t, J = 7.0 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.11 (s, 1H, pyrazole C_4-**H**), 5.39 (s, 2H, $COCH_2$), 5.24 (s, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO) δ 165.32 ($COCH_2$), 142.82, 142.51, 140.10, 138.04, 134.66, 133.85, 132.15, 130.77, 129.06, 127.28, 126.39, 126.00, 125.73, 125.53, 124.67, 117.19, 107.83 (aromatic ring **C**), 52.44 ($COCH_2$), 40.58 (CH_2), 21.22, 14.55. IR (KBr, υ_{max}) = 3292 (N-H Str.), 3140 (C–H str., triazole), 3035 (C–H str., aromatic), 1691 (C=O str.), 1614 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+Cacld. for $C_{25}H_{23}N_9O_3$: 498.1924 found 498.2516.

*4.1.5.18. 2-(4-((2-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-phenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(naphthalen-1-yl)acetamide **(6r)**.* Grey colour, yield: 84%, M.P.:170-172°C, ^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H, amide N-**H**), 8.14 (d, J = 8.8 Hz, 1H, α-naphthyl ring **H**), 8.02 (s, 1H, triazole ring **H**), 7.97 (bd, J = 7.2 Hz, 1H, α-naphthyl ring **H**), 7.83 (s, 1H, imidazole ring **H**), 7.80 (d, J = 8.0 Hz, 1H, naphthylene ring **H**), 7.76 (bd, J = 7.2 Hz, 2H, imidazole C_4-phenyl C_2/C_6-**H**), 7.70 (d, J = 7.2 Hz, 1H, α-naphthyl ring **H**), 7.63–7.54 (m, 2H, α-naphthyl ring **H**), 7.50 (t, J = 7.6, 8.0 Hz, 1H, α-naphthyl ring **H**), 7.38 (t, J = 7.6 Hz, 2H, imidazole C_4-phenyl C_3/C_5-**H**), 7.24 (t, J = 7.6, 7.2 Hz, 1H, imidazole C_4-phenyl C_4-**H**), 6.11 (s, 1H, pyrazole C_4-**H**), 5.51 (s, 2H, $COCH_2$), 5.26 (s, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO) δ 165.46 ($COCH_2$), 150.13, 143.03, 142.63, 139.30, 138.28, 134.18, 134.11, 133.16, 129.06, 128.67, 128.00, 127.21, 126.65, 126.48, 126.18, 126.04, 125.64, 124.64, 123.02, 121.99, 116.85, 107.02 (aromatic ring **C**), 52.58 ($COCH_2$), 41.43 (CH_2), 13.86 (CH_3), 11.57 (CH_3). IR (KBr, υ_{max}) = 3340 (N-H Str.), 3136 (C–H str., triazole), 3057 (C–H str., aromatic), 1732 (C=O str. amide), 1666 (N-H bending) cm^{-1}. HRMS: m/z (M + H)+ Cacld. for $C_{29}H_{26}N_8O$: 503.2808 found 503.2811.

4.2. Antimicrobial evaluation

The antimicrobial activities were carried out by standard serial dilution following the procedure as reported by S. Chauhan et al. [8].

4.3. Molecular docking analysis

The 3D chemical structure of hybrid was made with Marvin sketch [24] and protein preparation part was accomplished with UCSF Chimera [25]. Docking studies were carried out using Autodock Vina [26] and Discovery studio [27] was used for visualization of results, (Table 3).

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Suman Punia: Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Vikas Verma:** Conceptualization, Methodology, Supervision, Writing - original draft. **Devinder Kumar:** Methodology, Investigation, Visualization. **Ashwani Kumar:** Software, Data curation. **Laxmi Deswal:** Formal analysis, Investigation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2020.129216.

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