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Synthesis, antitubercular evaluation and molecular docking studies of phthalimide bearing 1,2,3-triazoles

Pramod S. Phatak[a], Rajubai D. Bakale[a], Sambhaji T. Dhumal[b], Lalita K. Dahiwade[c], Prafulla B. Choudhari[c], Vagolu Siva Krishna[d], Dharmarajan Sriram[d], and Kishan P. Haval[a]

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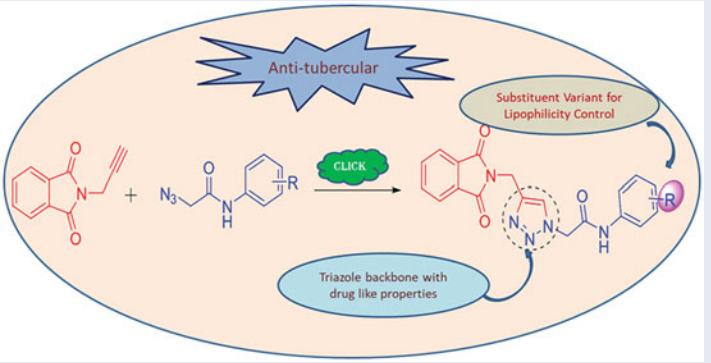
ABSTRACT

In a search for safer and potent antitubercular agents, here a library of newly substituted dioxoisoindolinylmethyl-triazolyl-*N*-phenylacetamide derivatives (**5a–l**) has been synthesized via click chemistry approach. All synthesized compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB). Among the screened compounds, **5d**, **5e**, **5h,** and **5l** showed good antitubercular activity. The compounds **5d** and **5l** have shown very effective antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB) with MIC 12.5 μg/mL. All the newly synthesized compounds were thoroughly characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectral data. We further performed exploratory docking studies on the crystal structure of *Mycobacterium tuberculosis enoyl reductase* to demonstrate the mechanism of antitubercular activity.

GRAPHICAL ABSTRACT



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KEYWORDS
Antitubercular activity; click chemistry; molecular docking study; N-phenylacetamide; phthalimide; 1,2,3-triazole

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Introduction

According to the World Health Organization (WHO) report on TB, the diseases, namely tuberculosis (TB) caused by the pathogen *Mycobacterium tuberculosis* (MTB) is one of the most deadliest infectious disease. As per Global Tuberculosis Report-2018, it is the leading cause due to a single infectious agent and its percentage is above HIV/AIDS.[1] Drug-Resistant TB is a major issue of public health. In 2017, WHO estimated that about 558,000 people in the world having TB are resistant to first-line drug rifampicin (RR-TB) and 82% having multi-drug resistant TB (MDR-TB). Treatment for drug-sensitive TB takes up to 2 months and for drug-resistant TB, it may take up to 24 months.[2] So, there is an urgent need to search for new drugs and their strategies for effective treatment. *Mycobacterium tuberculosis* has a unique cell wall made up of mycolic acids, which are highly lipophilic one. These mycolic acids are the major hurdle for antimycobacterial drug action. Mycolic acids are synthesized in the *Mycobacterium* via fatty acid biosynthesis process. Enoyl-ACP reductase is an important enzyme of the type II fatty acid synthase (FAS-II) system in *Mycobacterium*. This enzyme has no homologs in the mammalian system, so it deserves full credentials to act as an utilizable antitubercular target.

The heterocyclic compounds containing phthalimide core are the biologically active species which shows α-glucosidase inhibition,[3] antimalarial,[4] anti-inflammatory,[5] antimicrobial, anti-oxidant, [6] and anti-angiogenic[7] activities. Phthalimide when coupled with other heterocyclic groups like sulfonamide group, aminoquinoline, etc. also shows *in vitro* antitubercular activities.[8–11] Azoles are the important class of nitrogen-containing heterocycles that shows very good biological activities such as antifungal, antibacterial, antimalarial, anti-inflammatory, and antitubercular.[12,13] Particularly, 1,2,3-triazole is an important class of heterocyclic compounds, which has attracted increasing attention in medicinal chemistry and drug discovery (Figure 1).[14–16] 1,2,3-Triazoles are synthesized by "Click Chemistry" approach, which was firstly reported by Sharpless and research group.[17] 1,2,3-Triazole derivatives are endowed with numerous therapeutic activities, such as antimicrobial,[18] acidic corrosion inhibitor for steel,[19] SGLT2 inhibitor,[20] histone deacetylase 1 inhibitor,[21] α-glucosidase inhibitor,[22] and antitubercular.[23]

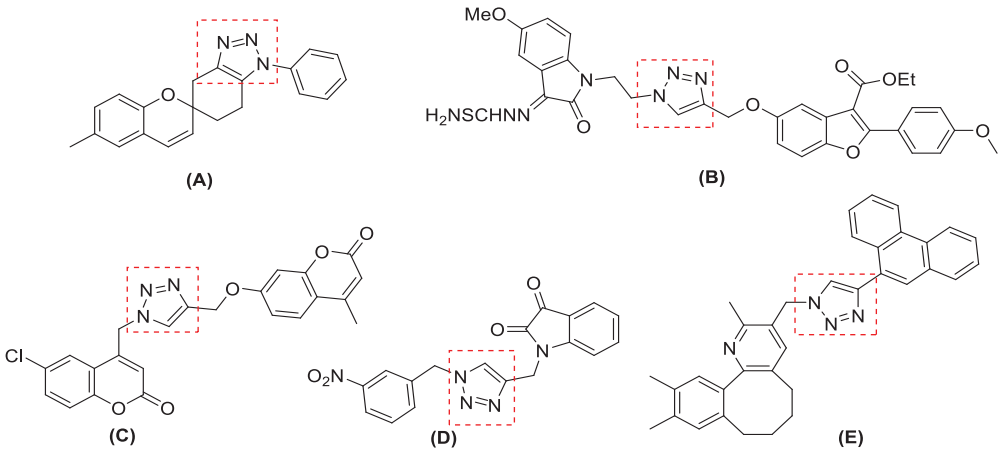


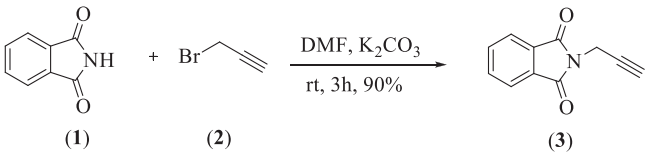
Figure 1. Some representative examples of 1,2,3-triazoles having antitubercular activity.

Results and discussions

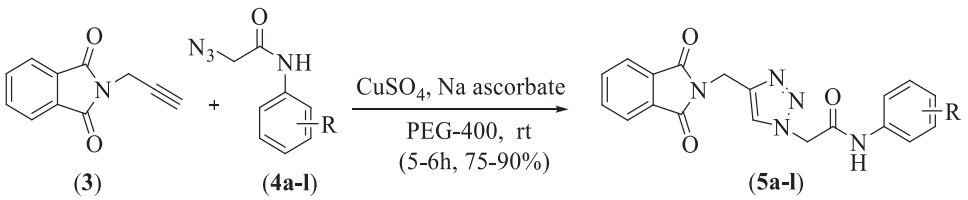
Chemistry

Considering the urgent need for preparing a library of new antitubercular agents and highly impressed by the antitubercular activities displayed by 1,2,3-triazoles, here we thought worthwhile to design and synthesize newly substituted 1,2,3-triazoles bearing phthalimide and acetyl phenoxy acetamide scaffolds in a single molecular framework with the hope to obtain better antimycobacterial activity. Herein, we have reported new dioxoisoindolinylmethyl-triazolyl-*N*-phenylacetamides **(5a-l)** via "Click Chemistry" approach. All the synthesized derivatives were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and determined their MIC (minimum inhibitory concentration) values. Molecular docking study and *in silico* ADME predictions of the synthesized compounds have been performed and results are incorporated.

In the present study, we have reported the synthesis of substituted 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a–l**) starting from phthalimide via click chemistry approach. Firstly, we performed the reaction of phthalimide **(1)** and propargyl bromide **(2)** in the presence of K_2CO_3 in DMF at room temperature to obtain 2-(prop-2-ynyl)isoindoline-1,3-dione (**3**) (Scheme 1) with 90% yield.[24–26] The structure of 2-(prop-2-ynyl)isoindoline-1,3-dione (**3**) was confirmed by spectral data. Further, the reaction of compound 2-(prop-2-ynyl)isoindoline-1,3-dione (**3**) and freshly prepared substituted *N*-phenyl acetamides **(4a–l)** were carried out in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in PEG-400 at room temperature and to furnish the corresponding substituted 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a–l**) with 75–90% yields (Scheme 2). The physical data of 1,2,3-triazoles is incorporated in Table 1.



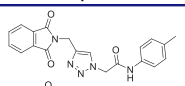
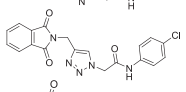
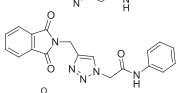
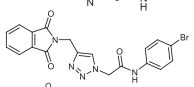
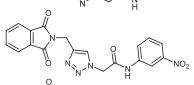
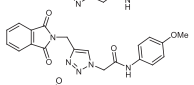
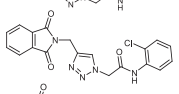
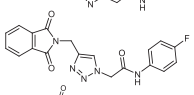
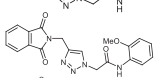
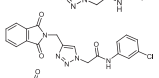
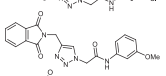
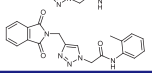
Scheme 1. Synthesis of 2-(prop-2-ynyl)isoindoline-1,3-dione (**3**).



5a : R = 4-CH_3, **5b** : R = 4-Cl, **5c** : R = H, **5d** : R = 4-Br,
5e : R = 3-NO_2, **5f** : R = 3-OCH_3, **5g** : R = 2-Cl, **5h** : R = 4-F,
5i : R = 2-OCH_3, **5j** : R = 3-Cl, **5k** : R = 3-OCH_3, **5l** : R = 2-CH_3

Scheme 2. Synthesis of substituted 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a–l**).

Table 1. Physical data and MIC values of substituted 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-l**).

Entry	Compounds	M. P. (°C)	Yield (%)	MIC (μg/mL)
5a		240–242	90	>25
5b		270–272	80	>25
5c		255–257	85	>25
5d		270–272	80	**12.5**
5e		290–291	85	**25**
5f		205–207	90	>25
5g		240–243	75	>25
5h		250–252	80	**25**
5i		200–202	90	>25
5j		250–252	85	>25
5k		210–211	90	>25
5l		235–237	85	**12.5**

MIC values of isoniazid and rifampicin are 0.1 and 0.2 μg/mL, respectively. The bold values indicates the better MIC values of compounds 5d, 5e, 5h and 5l as comparative to other remaining compounds.

All the newly synthesized compounds have been characterized using their IR, ^{1}H NMR, ^{13}CNMR, and HRMS spectral data. In IR spectrum of compound (**5a**), the characteristic peak at 1540 cm^{-1} indicates the presence of C=N bond. The ^{1}H NMR spectrum of compound (**5a**) displays a singlet at δ 2.32 ppm due to the CH_3 attached to the aromatic ring. The characteristic peaks of two singlets at δ 5.02 and 5.23 ppm confirms the presence of two CH_2 groups. The singlet at δ 7.96 ppm confirms the presence of 1,2,3-triazole ring in compound (**5a**). The three characteristic peaks in the ^{13}CNMR spectrum of (**5a**) in the upfield region at δ 28.26, 31.83, and 51.47 ppm confirm the presence of one CH_3 and two CH_2 carbons, respectively. The signals observed at δ 162.41 and 166.23 ppm clearly indicates the presence of two carbonyl groups of *N*-phenylacetamide and phthalimide, respectively. The HRMS spectrum further strengthens the structure assigned to 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(*p*-tolyl)acetamide (**5a**) as it displays $[M+H]^{+}$ ion peak at *m/z* 376.1410 for the molecular formula $C_{20}H_{17}N_5O_3$.

Antitubercular activity

The inoculum was prepared from fresh LJ medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase [OADC]), adjusted to OD_{590} 1.0, and diluted 1:20; 100 µl was used as an inoculum. Each drug stock solution was thawed and diluted in 7H9-S at four-fold, the final highest concentration tested. Serial two-fold dilutions of each drug were prepared directly in a sterile 96-well microtiter plate using 100 µl 7H9-S. A growth control containing no antibiotic and a sterile control was also prepared on each plate. Sterile water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed in plastic bags, and incubated at 37 °C in a normal atmosphere. After 7 days of incubation, 30 µl of Alamar blue solution was added to each well and the plate was re-incubated overnight. A change in color from blue (oxidised state) to pink (reduced) indicated the growth of bacteria and the MIC was defined as the lowest concentration of drug that prevented this change in color.[27] The compounds **5d**, **5e**, **5h,** and **5l** showed notable antitubercular activity with MIC values 12.5, 25, 25, and 12.5 μg/mL, respectively (Table 1). It has been observed that the compounds having 4-bromo (**5d**) or 2-methyl (**5l**) substituents on aromatic ring are showing very good antitubercular activities. Also, 3-nitro (**5e**) or 4-fluoro (**5h**) substituents are useful for possessing antitubercular activities.

Docking analysis

Docking analysis was utilized to predict the mechanism of action of the designed derivatives for antimycobacterial potential. All the molecules exhibited binding energies in the range of -92.69 to - 112.27 kcal/mol. Most active molecules (**5d)** exhibited hydrogen bond interactions with TYR158 and MET199, showed aromatic interaction with TYR158, hydrophobic interaction with MET199, TYR158 and Van der Waals interactions with PHE97, MET98, MET103, GLY104, PHE149, PRO156, ALA157, TYR158, MET161, ILE202, LEU207, ALA211, ILE215 (Figure 2). The compound (**5l)** showed hydrogen bond interactions with TYR158 showed aromatic interaction with TYR158 and PHE149 hydrophobic interaction with GLY96, PHE97, MET98, MET161, MET199, and Vander Waals interactions with PHE97, MET98, MET103, GLY104, PHE149, PRO156, ALA157, TYR158, MET161, ILE202, LEU207, ALA211, ILE215 (Figure 3). The compound (**5e**) showed hydrogen bond interactions with TYR158, GLY104, showed aromatic interaction with PHE149, TYR158 hydrophobic interaction with PHE149, LYS165, PRO193, MET199, LEU218, and Van der Waals interactions with GLY96, PHE97, MET98, MET103, GLY104, PHE149, PRO156, ALA157, TYR158, MET161, ALA198, ILE202, LEU207, ALA211, and ILE215 (Figure 4). The compound (**5h**) showed hydrogen bond interactions with TYR158, showed aromatic interaction with PHE149, TYR158 hydrophobic interaction with PHE149, PRO193, and Van der Waals interactions with PHE97, MET98, MET103, GLY104, PHE149, PRO156, ALA157, TYR158, MET161, ALA198, ILE202, LEU207, ALA211, and ILE215 (Figure 5).

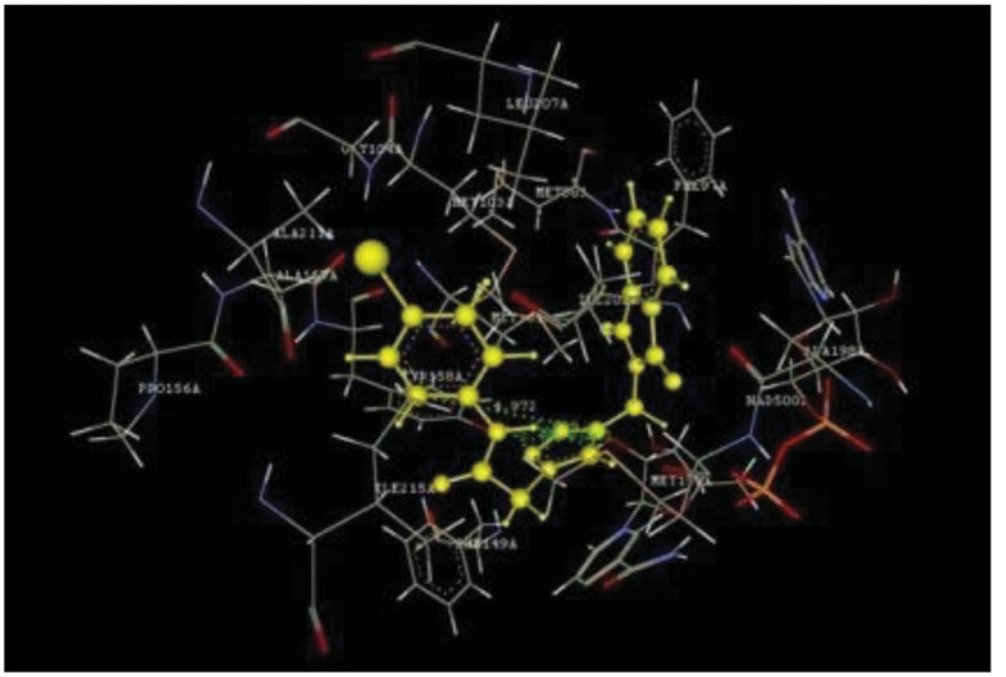


Figure 2. Binding mode of **5d** into the active site of InhA predicted by molecular docking.

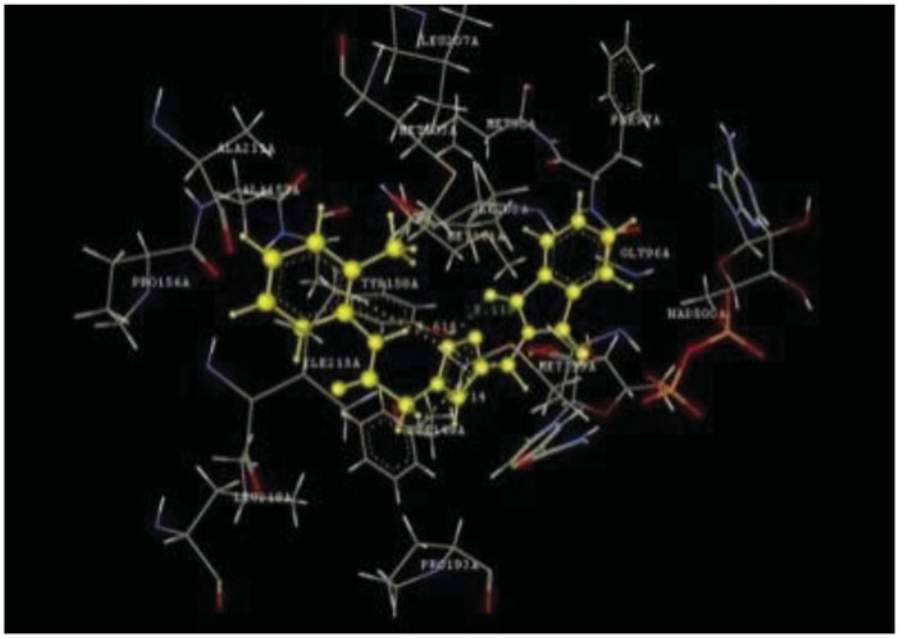


Figure 3. Binding mode of **5l** into the active site of InhA predicted by molecular docking.

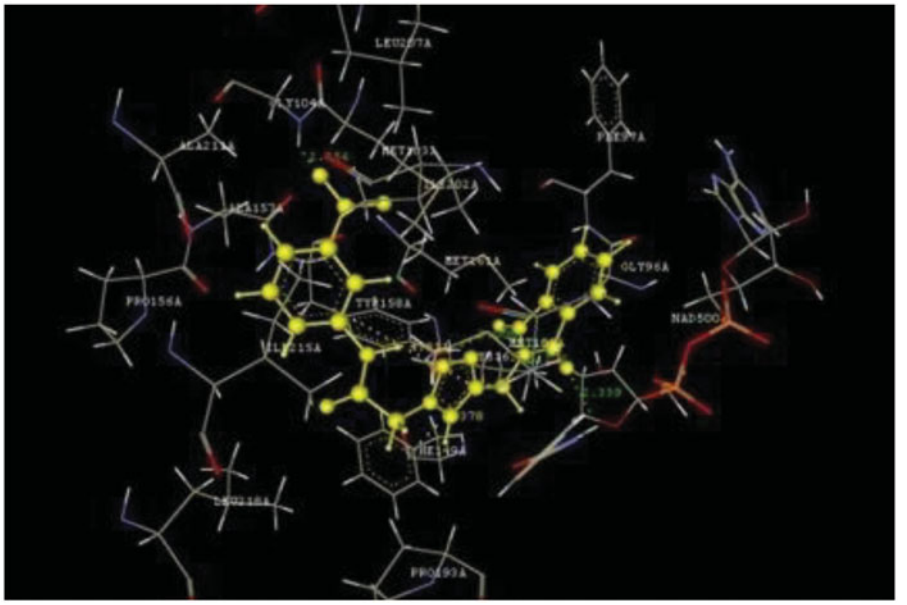


Figure 4. Binding mode of **5e** into the active site of InhA predicted by molecular docking.

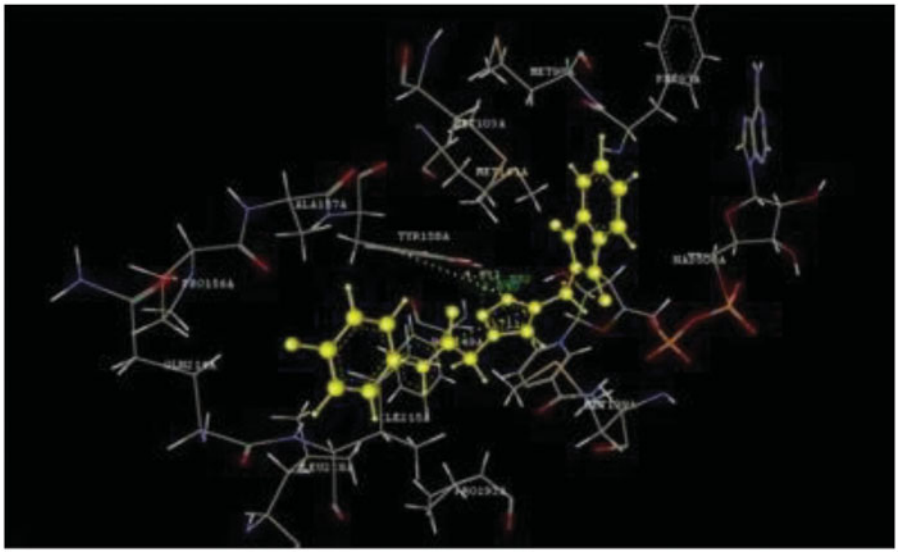


Figure 5. Binding mode of **5h** into the active site of InhA predicted by molecular docking.

ADME prediction

ADME prediction of all the synthesized molecules is predicted using Swiss ADME portal. All the molecules showed excellent physicochemical parameters with low Lipinski violation, which is desirable for the oral absorption of drug candidates (Table 2). All synthesized derivatives showed good physicochemical properties, which are infusing the ADME properties.

Table 2. Physicochemical property prediction of substituted 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-l**).

Entry	Mol. Wt.	Rotatable bonds	H-bond acceptors	H-bond donors	LOGP	Bioavai-lability Score
5a	375.38	6	5	1	2.35	0.55
5b	395.80	6	5	1	2.22	0.55
5c	361.35	6	5	1	2.06	0.55
5d	440.25	6	5	1	2.60	0.55
5e	406.35	7	7	1	1.55	0.55
5f	391.38	7	6	1	2.51	0.55
5g	395.80	6	5	1	2.62	0.55
5h	379.34	6	6	1	2.17	0.55
5i	391.38	7	6	1	2.58	0.55
5j	395.80	6	5	1	2.28	0.55
5k	391.38	7	6	1	2.39	0.55
5l	375.38	6	5	1	2.36	0.55

Conclusions

In conclusion, we have reported a series of newly substituted dioxoisoindolinylmethyl-triazolyl-*N*-phenylacetamide derivatives by 1,3-dipolar cycloaddition of the alkyne (**3**) and substituted phenyl acetamides (**4a-l**). Amongst the synthesized 1,2,3-triazoles, the compounds **5d**, **5e**, **5h,** and **5l** have displayed notable antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv. Molecular docking study indicates that all the molecules are binding to the *enoylreductase* of the *Mycobacterium tuberculosis*. We think the results obtained herein will provide a strong platform for structure-based optimization of these newly identified 1,4-disubstituted 1,2,3-triazole derivatives as antitubercular agents.

Experimental

The chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra (KBr pellets) were recorded on Bruker FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard and chemical shifts are in δ (ppm). ^{13}C NMR spectra were recorded on a Bruker DRX-75 MHz NMR in $CDCl_3$ + DMSO-d_6. High-resolution mass spectra (HRMS) were obtained using the Agilent 6520 (Q-TOF) ESI-HRMS instrument. The purity of the title and intermediate compounds was checked by thin-layer chromatography (TLC).

Synthesis of 2-(prop-2-yn-1-yl)isoindoline-1,3-dione (3)

A mixture of phthalimide (**3**) (0.01 mol), propargyl bromide (0.01 mol), and K_2CO_3 (0.02 mol) was stirred in DMF at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. The solid obtained was filtered, washed with water, and recrystallized from ethanol.

Yield: 90%, M.P.: 151–153 °C; White Solid. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 3.17 (s, 1H), 4.43 (d, J = 3 Hz, 2H), 7.78–7.83 (m, 2H), 7.85–7.90 (m, 2H).

General procedure for the synthesis of 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamides (5a-l)

2-(Prop-2-yn-1-yl)isoindoline-1,3-dione (**3**) (0.01 mol) and substituted *N*-phenylacetamides (**4a-l**) (0.01 mol) were stirred in the presence of $CuSO_4.5H_2O$ (20 mol%) and sodium ascorbate (20 mol%) in PEG-400. The progress of the reactions was monitored by TLC. After completion of reactions (5–6 h), the reaction mixtures were poured in ice cold water. The products obtained were filtered, washed with water, and recrystallized from ethanol.

2-(4-((1,3-Dioxoisoindolin-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(*p*-tolyl)acetamide (5a): Yield: 90%, M.P.: 240–242 °C; White Solid; IR (KBr) ν cm^{-1}: 3270, 3147, 3052, 2333, 1692, 1667, 1540, 1396, 1335, 1091, 818, 711; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 2.32 (s, 3H), 5.02 (s, 2H), 5.23 (s, 2H), 7.12 (d, J = 9 Hz, 2H), 7.47(d, J = 9 Hz, 2H), 7.74–7.78 (m, 2H), 7.83–7.87 (m, 2H), 7.96 (s, 1H), 10.01 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ ppm = 28.26, 31.83, 51.47, 118.51, 122.11, 123.69, 128.08, 130.70, 132.18, 133.13, 134.53, 141.17, 162.41, 166.23; HRMS $(ESI)^+$ calcd. for $C_{20}H_{17}N_5O_3$ $[M+H]^+$: 376.1365 and found 376.1410.

Docking analysis

Molecular docking analysis was performed to predict the possible mode of action of the synthesized triazole derivatives. Crystal structure of *Mycobacterium tuberculosis enoylreductase* (INHA) complexed with *N*-(3-chloro-2-methylphenyl)-1-cyclohexyl- 5-oxopyrrolidine-3-carboxamide (PDB ID: 4TZT) was *enoylreductase* downloaded from the free protein database www.rcsb.org. Crystal structure of the download was refined via removal of the water and addition of the hydrogen atoms so that native geometry of the protein is achieved. Ligands were prepared in Vlife engine module and optimized via the Merck molecular force field. Biopredicta module of the V life MDS 4.3 was utilized for docking analysis.[28–32] ADME of the synthesized derivatives was predicted from the free online server http://www.swissadme.ch. [33–35]

Supporting material to this article containing spectral data, ^{1}H and ^{13}C NMR spectrums and docking images of synthesized compounds are available for the authorized users.

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