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Design and Synthesis of New Indanol-1,2,3-triazole Derivatives as Potent Antitubercular and Antimicrobial Agents

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ABSTRACT

In a search of new antitubercular agents, herein we have reported a series of new thirty-two indanol-1,2,3-triazole derivatives. The synthesized compounds were screened for their *in vitro* antitubercular and antimicrobial activities. Among the screened compounds, most of the compounds have displayed good antitubercular activity against *Mycobacterium tuberculosis* H37Rv. The compound **5g** has been identified as potent antitubercular agent with MIC value 1.56 μM. The most active compounds of the series were further studied for their cytotoxicity against HEK 293 cells using MTT assay and found to be nontoxic. In addition, ten compounds were shown good antimicrobial activities against both antibacterial and antifungal pathogens. A molecular docking study against *Mycobacterial enoyl-ACP-reductase* (InhA) was performed to gain an insight into the molecular mechanism of antitubercular action. The pharmacokinetic parameters of these compounds were studied and displayed acceptable drug-likeness score.

Keywords: 1,2,3-Triazoles, Antitubercular Activity, Antimicrobial Activity, Click Chemistry, Molecular Docking Study, ADME Prediction.

The world is facing many health problems.[1] As per Global Tuberculosis Report-2019, tuberculosis (TB) is among the top ten reasons of death worldwide.[2] It is a communicable disease and infected by the bacillus *Mycobacterium tuberculosis*. It gets spread when people who are sick with TB expel bacteria into the air; for example, by coughing. It normally affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB).[3] The one-fourth of the world's

population is infected with *M. tuberculosis*. The drug-resistant tuberculosis and co-infection with HIV are two leading health concerns about the tuberculosis. It is observed that the control of tubercular spread has become one of the main health concern in the world.[4] As constrained treatment options for multi-drug resistant (MDR-TB) and extensively drug resistant (XDR-TB) are available, TB research community is facing the challenge of synthesizing new anti-TB drugs with novel modes of action.[5] According to the WHO, resistance to the most effective first-line antibiotic rifampicin for tuberculosis, occurred in approximately six lacks cases in 2017. Among these cases, approximately 82% were resistant to multiple treatment options. Since the discovery of Rifampicin (RIF) 40 years ago, only few promising anti-TB drugs have been invented.[6]Hence, it is an urgent requirement to design and synthesis of new antitubercular and antimicrobial agents.[7]

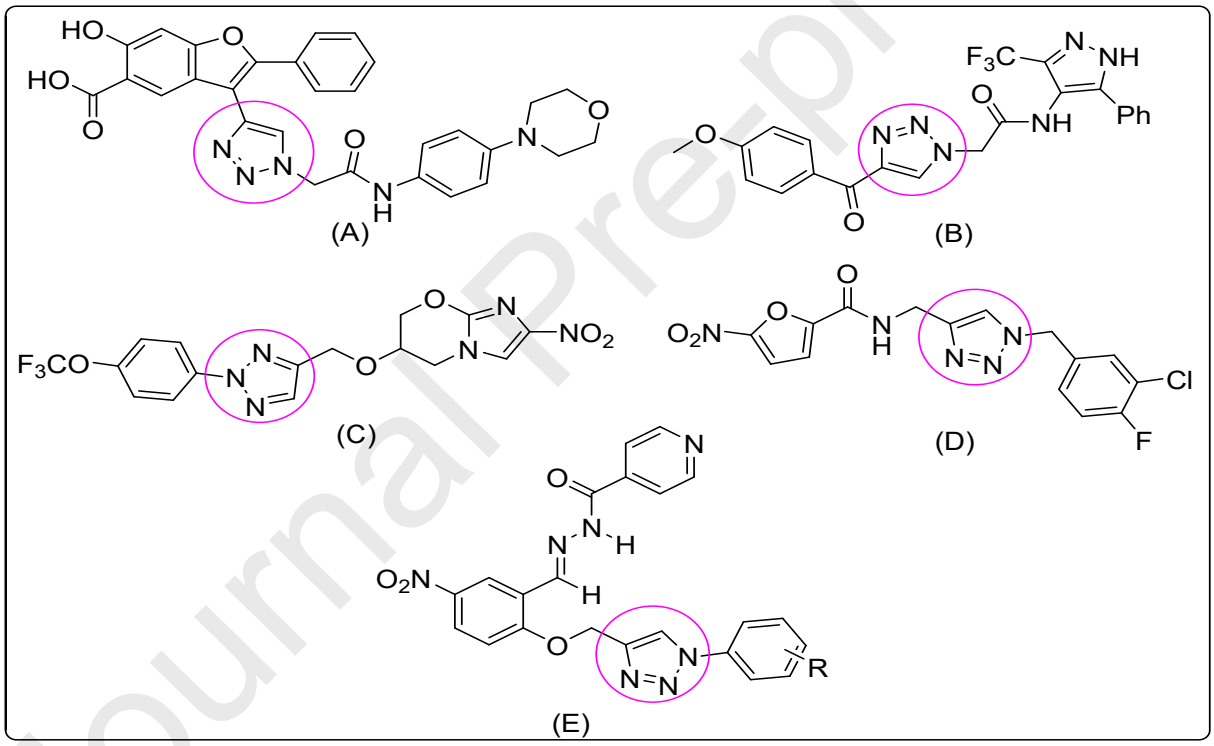


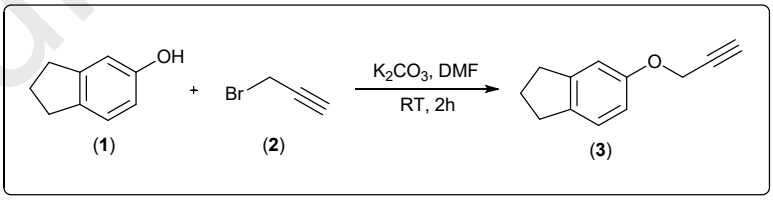
Fig.1. Representative 1, 2, 3-triazole derivatives having antitubercular activity

Indanol derivatives are endowed with various biological activities such as antiviral, insecticidal, hypotension, anti-inflammatory, CNS depressant, antimicrobial, anti-HIV, antagonistic, antihypertensive, and antitubercular.[8-13] Similarly, the 1,2,3-triazole derivatives are important target molecules for the researchers worldwide due their pharmaceutical applications.[14] It includes anti-tubercular,[15] antifungal,[16] α-glycosidase inhibitors,[17] antibacterial, anti-allergic and anti-HIV.[18] Molecular hybridization is a classical approach for the design of new bioactive

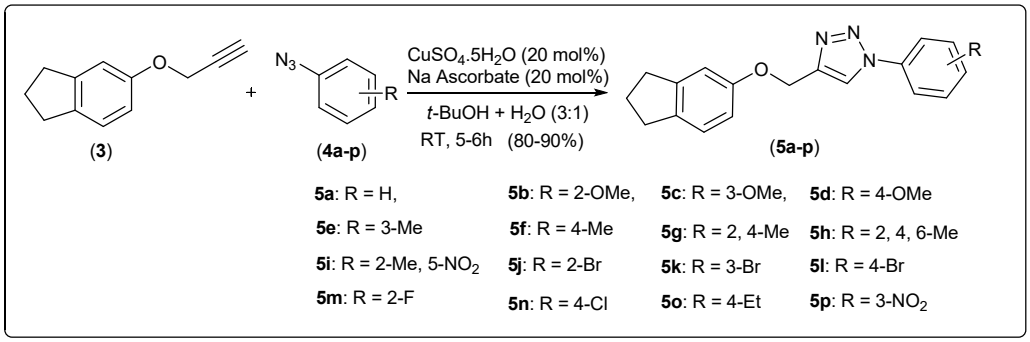
compounds.[19, 20] This molecular hybridized compounds could have more solubility and oral bioavailability in some extents. In literature, many 1,2,3-triazole derivatives coupled with another moieties are reported.[21, 22] Triazole based antitubercular agent **A** (I-A09) (**Fig.1**) is under pre-clinical trials.[23] The compound **B** (**Fig.1**) from the novel 3-trifluromethyl pyrazolo-1,2,3-triazole hybrids emerged as the most promising antitubercular agent with lowest cytotoxicity.[24] 1-aryl-4-linked 1,2,3-triazole based compound **C** (**Fig.1**) identified potent new candidate with improved aqueous solubility.[25] The compound **D** (**Fig.1**) from the 5-nitrofuran triazole conjugates showed promising antitubercular activity.[26] Isoniazid embedded triazole compound **E** (**Fig.1**) exhibited potent antitubercular activity with low cytotoxicity.[27]

In continuation of our ongoing research on synthesis of new antitubercular and antimicrobial agents,[28, 29] herein we have synthesized new indanol-1,2,3-triazole derivatives (**5a-p** & **7a-p**) by employing click chemistry approach. The synthesized compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB). In addition, *in vitro* antimicrobial activities were also evaluated.

The reaction sequence followed for the synthesis of indanol-1,2,3-triazole derivatives (**5a-p** & **7a-p**) is as shown in **Scheme 1** to **3**. In the first step, the key intermediate 5-(prop-2-ynyloxy)-2,3-dihydro-1*H*-indene (**3**) was synthesized by propargylation of 5-indanol (**1**) in the presence of potassium carbonate in DMF at room temperature with 85% yield. The click reactions of 5-(prop-2-ynyloxy)-2,3-dihydro-1*H*-indene (**3**) and freshly prepared substituted phenyl azides (**4a-p**) were performed in the presence of copper acetate and sodium ascorbate to give the corresponding 4-(2,3-dihydro-1*H*-inden-5-yloxy)methyl)-1-phenyl-1*H*-1,2,3-triazole derivatives (**5a-p**) with 80-90% yields.

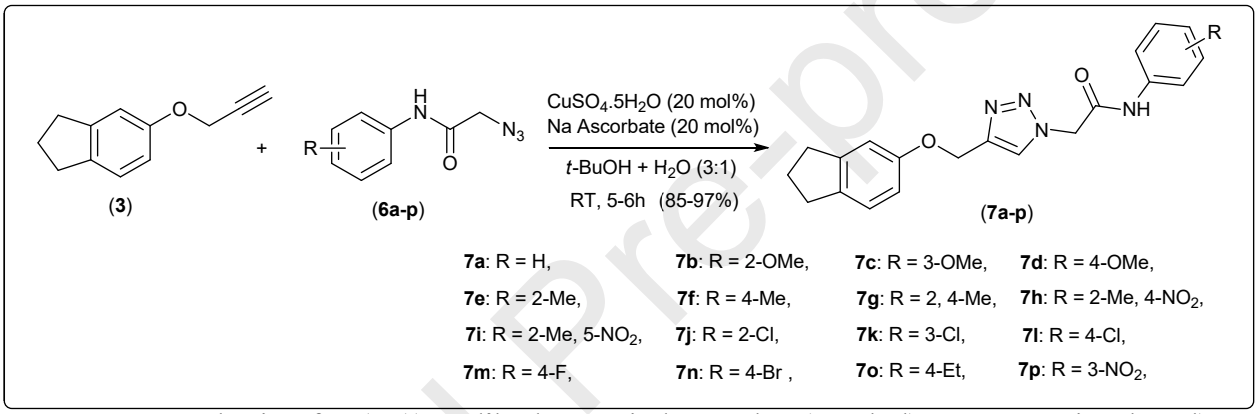


Scheme 1. Synthesis of 5-(prop-2-ynyloxy)-2,3-dihydro-1*H*-indene (**3**)



Scheme 2. Synthesis of 4-((2,3-dihydro-1*H*-inden-5-yloxy)methyl)-1-phenyl-1*H*-1,2,3-triazole derivatives (**5a-p**)

Similarly, the click reactions of 5-(prop-2-ynyloxy)-2,3-dihydro-1*H*-indene (**3**) and freshly prepared substituted 2-azido*N*-phenylacetamides (**6a-p**) were afforded the corresponding 2-(4-((2,3-dihydro-1*H*-inden-5-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide derivatives (**7a-p**) with 85-97% yields. The structures of newly synthesized indanol-1,2,3-triazole derivatives (**5a-p** & **7a-p**) were assigned by their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.



Scheme 3. Synthesis of 2-(4-((2,3-dihydro-1*H*-inden-5-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide derivatives (**7a-p**)

The indanol-1, 2, 3-triazole derivatives (**5a-p**) and (**7a-p**) were evaluated for their i*n vitro* antitubercular activity against *Mycobacterium tuberculosis H37Rv* strain.[30,31] These compounds have displayed excellent antitubercular activity compared to first line antitubercular drugs, ciprofloxacin and ethambutol (**Table 1**). The compound **5g** with 2, 4-dimethyl substituted benzene ring has displayed excellent antitubercular activity with MIC value 1.56 µM, which is more potent than ethambutol and equivalent to another standard drug, ciprofloxacin. The three compounds **5h**, **5j** and **5m** having 2, 4, 6-trimethyl, 2-bromo and 2-flouro substituted benzene ring, respectively were shown significant antitubercular activity with MIC value 6.25 µM. The compound **7b** with 2-methoxy phenyl acetamido moiety has shown good antitubercular activity against *Mycobacterium tuberculosis H37Rv* strain with MIC value 6.25 µM. The four compounds **5b**, **5c**, **5e** and **5i** having 2-methoxy, 3-methoxy, 3-methyl and 2-methyl, 5-nitro substituted benzene ring, respectively were displayed noticeable antitubercular activity with MIC value 12.5 µM. The

compounds **5a** and **5d** having benzene ring and 4-methoxy substituted benzene ring respectively showed good antitubercular activity with MIC value 25 µM (**Table 1**). It has been observed that the phenyl-1,2,3-triazole derivatives (**5a-p**) were displayed better antitubercular activity than the phenylacetamido-1,2,3-triazole derivatives (**7a-p**). These obtained results will be useful for further identification of more potent antitubercular agents.

The indanol-1,2,3-triazole derivatives **5a**, **5b**, **5c**, **5d**, **5e**, **5g**, **5h**, **5i**, **5j**, **5m** and **5b** were found to be most active against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. The *in vitro* cytotoxicity of active indanol-1,2,3-triazole derivatives were assessed by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay against growth inhibition of HEK 293 (Human Embryonic Kidney) cells at 25 µM concentration (**Table 1**).[32,33] It has been observed that these active indanol-1, 2, 3-triazole derivatives does not exhibit strong cytotoxicity towards the HEK 293 (Human Embryonic Kidney).

Table 1. MIC values and cytotoxicity activities of indanol-1, 2, 3-triazole derivatives

Compound	MIC against Mtb H37Rv strain (µM)	% Inhibition Cytotoxicity at 25 µM
5a	25	23.39
5b	12.5	19.81
5c	12.5	25.78
5d	25	21.09
5e	12.5	23.44
5f	>25	ND
5g	1.56	19.86
5h	6.25	16.56
5i	12.5	26.53
5j	6.25	16.51
5k	>25	ND
5l	>25	ND
5m	6.25	20.97
5n	>25	ND
5o	>25	ND
5p	>25	ND
7a	>25	ND
7b	6.25	23.35
7c	>25	ND
7d	>25	ND
7e	>25	ND
7f	>25	ND

7g	>25	ND
7h	>25	ND
7i	>25	ND
7j	>25	ND
7k	>25	ND
7l	>25	ND
7m	>25	ND
7n	>25	ND
7o	>25	ND
7p	>25	ND
Ciprofloxacin	1.56	ND
Ethambutol	3.125	ND
ND : Not determined		

All the newly synthesized indanol-1, 2, 3-triazole derivatives were evaluated for their *in vitro* antimicrobial activities by using agar well diffusion method.[34,35] The antibacterial screening was executed against Gram-positive *S. aureus*, *B. cereus*, *B. subtilis* and Gram-negative *E. aerogenes*, *E. coli*, *S. typhi*, *P. aeruginosa*, *S. boydii*, *S. abony* pathogens. The antifungal screening was executed against *A. niger*, *C. albicans* and *S. cerevisiae* fungal pathogens. Among the screened indanol-1, 2, 3-triazole derivatives, **5d**, **5g**, **5i**, **5j**, **5k**, **5p**, **7a**, **7b**, **7k** and **7p** were shown excellent antimicrobial activities (**Table 2**). The minimum inhibitory concentration (MIC) values were determined for the most active indanol-1, 2, 3-triazole derivatives. (**Table 3**).

Table 2. Antimicrobial activity of synthesized indanol-1, 2, 3-triazole derivatives

Compounds	**Antibacterial pathogens**									**Antifungal pathogens**		
	S. aureus	***B. cerus***	***B. subtilis***	***E. aerogenes***	***E. coli***	***S. typhi***	***P. aeruginosa***	***S. boydii***	***S. abony***	***A. niger***	***C. albicans***	***S. cerevisiae***
5a	07	--	--	--	--	--	--	--	--	--	12	08
5b	10	--	--	--	--	--	--	--	--	--	10	--
5c	12	--	--	--	10		09	13	11		12	--
5d	08	05	10	09	10	08	12	11	12	06	11	05
5e	06	--	--	--	--	--	--	--	--	--	10	13
5f	--	--	--	--	--	--	--	--	--	--	12	--
5g	07	10	10	10	12	12	13	11	09	10	11	12
5h	--	--	--	--	--	--	--	--	--	--	--	--
5i	13	12	12	11	11	11	09	11	09	06	15	06
5j	16	09	10	12	11	11	13	12	13	07	09	10
5k	19	10	17	16	15	08	14	20	14	06	14	07
5l	--	--	--	--	08	--	--	--	--	--	11	07

5m	15	--	--	--	--	--	--	--	--	--	09	10
5n	08	--	--	--	--	--	--	--	--	--	10	08
5o	07	--	--	--	--	--	--	--	--	--	13	
5p	08	13	12	14	12	08	11	10	08	06	12	07
7a	23	12	12	16	11	12	10	11	11	09	13	12
7b	12		10	13	10	12	08	12	11	10	12	10
7c	--	--	--	--	--	--	--	15	--	--	--	--
7d	--	--	--	--	--	--	--	--	--	--	--	--
7e	--	--	--	--	--	--	--	11	--	--	--	--
7f	08	--	--	--	--	--	--	--	--	--	12	--
7g	--	--	--	--	--	--	--	13	--	--	--	--
7h	--	--	--	--	--	--	--		--	--	--	--
7i	--	--	--	12	--	--	09	09	--	--	--	--
7j	--	--	--	--	--	--	--		--	--	--	--
7k	10	10	12	12	13	13	09	11	07	08	10	05
7l	08	--	--	--	--	--	--	--	--	--	15	10
7m	13	--	--	--	--	--	--	11	--	--	13	--
7n	--	--	--	12	--	--	05	13	--	--	--	12
7o	--	--	--	--	--	--	--	11	--	--	--	--
7p	10	12	11	10	10	10	06	10	10	05	10	09
Tetracycline	29	33	32	33	29	33	32	34	32	NA	NA	NA
Fluconazole	NA	NA	NA	NA	NA	NA	NA	NA	NA	30	30	30
(--) : Inactive; NA : Not applicable												

Table 3. MIC values of the most potent indanol-1, 2, 3-triazole derivatives (µg/mL)

Compounds	**Pathogens**					
	S. aureus	***E. aerogenes***	***S. boydii***	***A. niger***	***C. albicans***	***S. cerevisiae***
5d	160	130	70	180	80	210
5g	150	75	55	70	60	50
5i	50	60	60	155	40	150
5j	90	120	140	170	130	110
5k	100	150	130	190	100	160
5p	165	70	90	220	125	180
7a	140	80	130	170	85	110
7b	120	95	150	170	180	210
7k	135	110	140	190	165	230
7p	140	145	140	220	150	135
Tetracycline	20	30	20	NA	NA	NA
Fluconazole	NA	NA	NA	08	25	12

NA: Not applicable

In order to investigate the probable mechanism by which the synthesized indanol-1, 2, 3-triazole derivatives can exhibit the antitubercular activity and to establish an SAR based on the results of *in vitro* assay, molecular docking study against the critical mycobacterial target *enoyl-ACP-reductase* (InhA) was performed. In the absence of available resources to perform the enzyme-based assays, molecular docking has received significant importance to find the targets for different ligands and their associated thermodynamic interactions that direct the inhibition of the pathogen. Mycobacterial *enoyl-ACP-reductase* (InhA), an enzyme contributing to mycolic acids biosynthesis, has been recognized as a promising target of novel antitubercular drugs. Mycolic acids are very long chain (C_{74}-C_{90}) α-alkyl β-hydroxy fatty acids covalently linked to arabino-galactan that form the major components of the mycobacterial cell envelope providing them protection from antibiotics and are also found responsible for mycobacterial virulence.[36] The biosynthesis of mycolic acids is catalyzed by two enzyme systems namely, fatty acid synthase I (FAS I) that produces the shorter chain fatty acids and fatty acid synthase II (FAS II) which is involved in elongation of fatty acids chain. InhA catalyzes the *trans*-enoyl reduction which is the final step of FAS II pathway. Inhibition of *enoyl-ACP-reductase* (InhA) disrupts the integrity of mycobacterial cell wall *via* inhibiting mycolic acid biosynthesis and remains a most promising approach towards antitubercular drug design. In addition, triazole containing heterocycles have shown the potential to inhibit InhA which encouraged the selection of this target to gauze the binding affinity of the title compounds towards this crucial cell wall target.[37, 38]

A molecular docking study have shown that the compounds occupied an energetically favorable position in the active site cavity of InhA with varying level of affinities at the co-ordinates close to the co-crystallized ligand. They have created good to moderate docking scores ranging from -8.95 (glide binding energy of -51.716 kcal/mol) for the active compound to -7.072 (glide energy -40.444 kcal/mol) for a moderately active one with an average docking score of -7.677 (glide energy -43.953 kcal/mol). The binding arrangement and thermodynamic interaction of compounds **5b**, **5c**, **5e**, **5h**, **5i**, **5j**, **5m** and **7b** with InhA enzyme is given in supplementary material (**Table S1, Figures S75-S82**). These binding affinity scores were found to be in harmony with the experimentally observed antitubercular activity. To achieve more insight into binding pattern and types of

thermodynamics interactions guiding the anchoring of these ligands into the target, a per-residue interaction analysis between the InhA enzyme and these compounds was performed.

The most active indanol-1, 2, 3-triazole derivative **5g** produced the highest docking score of -8.95 with a Glide binding energy of -51.716kcal/mol (**Table S1**). The lowest energy docked conformation of **5g** showed that it is deeply embedded into the active pocket of InhA (**Fig. 2**), which can be explained in terms of significant bonded and non-bonded interactions with amino acid residues lining the active site. The per-residue interaction analysis showed that the two scaffolds i.e. the indanol and triazole showed a well-balanced network of favorable steric interactions with the active site residues. The triazole nucleus portrayed very closed van der Waals interactions with Leu218 (-2.986 kcal/mol), Ile215 (-3.283 kcal/mol), Ile202 (-2.825 kcal/mol), Pro193 (-2.884 kcal/mol), Gly192 (-2.974 kcal/mol), Ala191 (-2.958 kcal/mol), Ala157 (-2.853 kcal/mol), Pro156 (-2.943 kcal/mol), Met155 (-2.888 kcal/mol), Met103 (-3.192 kcal/mol), while phenyl substituted 1,2,3-triazole scaffold showed similar type of interactions with Met199 (-3.516 kcal/mol), Ala198 (-2.878 kcal/mol), Thr196 (-2.976 kcal/mol), Ile194 (-2.796 kcal/mol), Met161 (-3.132 kcal/mol), Tyr158 (-3.666 kcal/mol), Phe149 (-3.14 kcal/mol), Asp148 (-2.876 kcal/mol), Met147 (-2.816 kcal/mol), Met98 (-2.879 kcal/mol), Phe97 (-2.924 kcal/mol), Gly96 (-2.956 kcal/mol), Ile95 (-2.973 kcal/mol), Ser94 (-2.477 kcal/mol), Ile21 (-2.775 kcal/mol), Ser20 (-2.995 kcal/mol) residues. The enhanced binding affinity of **5g** is also attributed to relatively lesser but prominent electrostatic interactions observed with Met199 (-2.994 kcal/mol), Lys165 (-4.835 kcal/mol), Tyr158 (-2.953 kcal/mol), Met147 (-2.967 kcal/mol), Gly96 (-2.914 kcal/mol) and Ser20 (-2.993 kcal/mol) residues. The binding of **5g** was stabilized by hydrogen bond and a pi-pi stacking interaction. The nitrogen atom of the triazole ring formed a close hydrogen bond with Tyr158 (2.30Å). The same triazole ring also showed a prominent pi-pi stacking interaction with Tyr158 (1.992Å). Such hydrogen-bonding and the pi-pi (π-π) stacking interactions serve as "anchor" to guide the ligand into the active site of enzyme and facilitate the steric and electrostatic interactions.

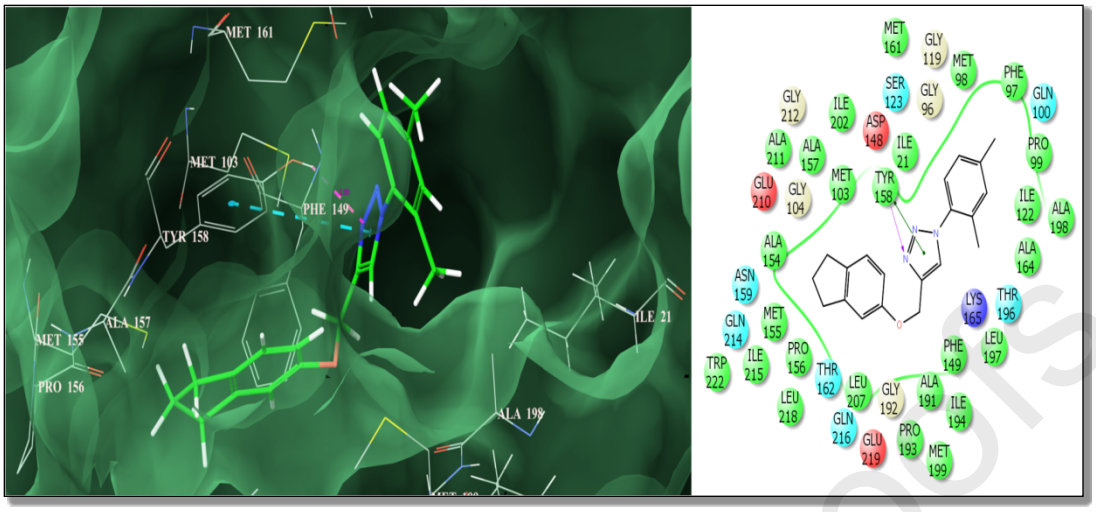


Fig. 2. Binding mode of compound **5g** into the active site of mycobacterial enoyl ACP reductase (InhA)

Overall, these results of the molecular docking study and specially the per-residue ligand interaction analysis have shown that the indanol and triazole nucleus act synergistically to attach with the active site of InhA and the substitutions around these scaffolds improve the binding affinity. These results suggest that indanol-1, 2, 3-triazole derivatives have significant affinity for this crucial mycobacterial target InhA and qualify this dimeric scaffold as a promising initiation point for structure-based lead optimization. In *silico* ADME properties of newly synthesized compounds were studied. The results obtained indicate the good % ABS ranging from 69.36-95.21 and acceptable drug-likeness score (Supplementary material, **Table S2**).

In summary, a series of new thirty-two indanol-1, 2, 3-triazole derivatives were synthesized *via* click chemistry approach. The synthesized compounds were evaluated for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv. The compound **5g** has been identified as an excellent antitubercular agent. It has antitubercular activity with an equivalent to the standard drug, ciprofloxacin having the MIC value 1.56µM. Whereas, the other ten compounds, **5a**, **5b**, **5c**, **5d**, **5e**, **5h**, **5i**, **5j**, **5m** and **7b** have exhibited good antitubercular activity with MIC values ranging from 1.56-12.5µM. The active antitubercular indanol-1, 2, 3-triazole derivatives were evaluated for their cytotoxic effects against HEK 293 (Human Embryonic Kidney) cells. These derivatives did not exhibited cytotoxicity towards the HEK 293 cells (Human Embryonic Kidney). In addition, indanol-1, 2, 3-triazole derivatives **5d**, **5g**, **5i**, **5j**, **5k**, **5p**, **7a**, **7b**, **7k** and **7p** has shown good *in vitro* antimicrobial activities. A molecular docking study was

performed to investigate the mode of action of indanol-1, 2, 3-triazole derivatives. These compounds have displayed a high affinity towards the active site of *Mycobacterial enoyl-ACP-reductase (InhA)* enzyme. In *silico* ADME properties of these newly synthesized compounds were studied. It has been indicated the acceptable drug-likeness score. We feel that the inspiring results obtained will be a good platform for identification of new potent antitubercular and antimicrobial agents.

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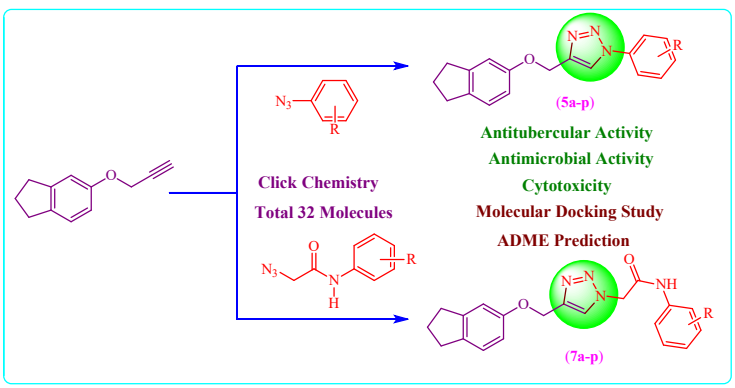
Supplementary Material

Supplementary material to this article containing ^{1}H NMR, ^{13}C NMR and HRMS spectrums of new compounds are available for the authorized users.

Graphical abstract



- Efficient synthesis of new thirty-two indanol-1,2,3-triazole derivatives
- Potent antitubercular and antimicrobial activities
- Non-toxic to mammalian cell
- Molecular docking study
- In silico ADME prediction for drug-likeness