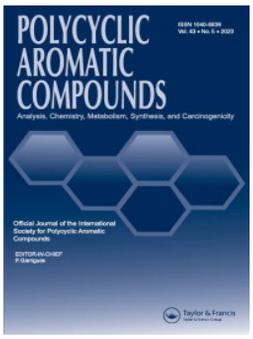

Polycyclic Aromatic Compounds

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpol20

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To cite this article: Sambhaji T. Dhumal, Tejshri R. Deshmukh, Kishan P. Haval, Vagolu Siva Krishna, Dharmarajan Sriram, Vijay M. Khedkar, Naziya N. M. A. Rehman, Prashant P. Dixit & Ramrao A. Mane (2023): Synthesis of New Amide Linked Biphenoloxy 1,2,3-Triazoles as Antitubercular and Antimicrobial Agents, Polycyclic Aromatic Compounds, DOI: 10.1080/10406638.2023.2225671

To link to this article: https://doi.org/10.1080/10406638.2023.2225671

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Synthesis of New Amide Linked Biphenoloxy 1,2,3-Triazoles as Antitubercular and Antimicrobial Agents

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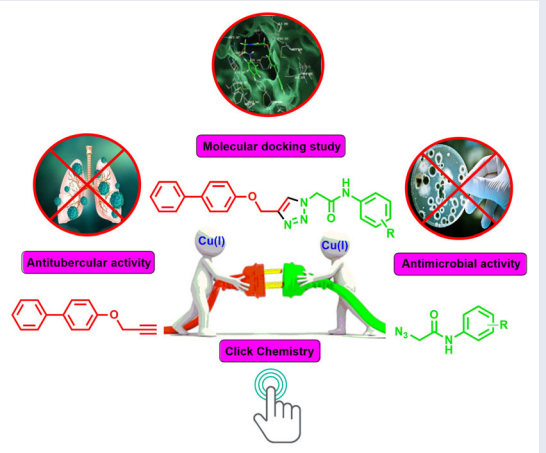
ABSTRACT

New 1,2,3-triazoles bearing biphenoloxymethyl and acetanilido moieties (**5a-5l**) have been synthesized, starting from 4-phenylphenol (**1**) following click chemistry approach. The synthesized compounds have been thoroughly characterized by their ^{1}H NMR, ^{13}C NMR and HRMS spectral data. These compounds were evaluated for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and antimicrobial activity against pathogenic microbia. Among the screened compounds, **5a** and **5i** have displayed notable antitubercular activity with MIC 25 μg/mL. Compounds **5a**, **5b**, **5c, 5 g**, **5i** and **5 l** have shown effective inhibition against most of tested pathogens. Molecular docking results of compounds **5a** and **5i** show the binding modes of the synthesized compounds into the active site of mycobacterial enoyl reductase. The synthesized compounds have also been analyzed for their ADME properties. By considering all these results, the present research work will offer a promising lead series for discovery of emerging potent antitubercular agents.



ARTICLE HISTORY
Received 18 September 2020
Accepted 9 June 2023

KEYWORDS
Antimicrobial activity; antitubercular activity; click chemistry; molecular docking; study; 1,2,3-triazole

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/10406638.2023.2225671.

Introduction

Tuberculosis (TB) is an infectious disease caused by pathogen, *Mycobacterium tuberculosis* (MTB).[1] Tuberculosis is now found in every corner of the globe and is the second largest infectious disease, creating severe public health problem. Tuberculosis primarily targets lungs and then other organs namely; intestine, meninges, bones, joints, and almost every other organ.[2] Despite its known etiology, tuberculosis still remains one of the most threatening health problems globally, claiming more than two million fatalities each year with almost nine million new cases.[3] The currently practised DOTS (Directly observed Treatment, short-term) therapy needs longer duration for treatment and therefore, the pathogenic strains, responsible for tuberculosis have acquired resistance to drugs.[4] New forms of tuberculosis like multi drug-resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB) and totally drug-resistant tuberculosis (TDR-TB) have emerged.[5] Therefore, most of the chemists focuses on the syntheses of library of new analogues of existing drugs or new chemical entities with hope to obtain better antitubercular activity.

In search of potent antitubercular agents, nitrogen-containing heterocycles particularly, 1,2,3-triazoles are gaining immense importance due to their broad spectrum applications in different areas such as bioconjugations, surface sciences, polymers, biochemical, supramolecular chemistry and pharmaceuticals.[6] Among the various 1,2,3-triazoles, 1,4-disubstituted-1,2,3-triazole derivatives have been receiving serious attention because of their diverse pharmacological activities such as antimicrobial,[7] antibacterial,[8] antitubercular,[9] antidiabetic,[10] anticancer,[11] and antiviral.[12] Literature survey also revealed that 1,2,3-Triazole and its derivatives have also been used as various enzyme inhibitors against histone deacetylase, alkaline phosphatase, cysteine protease and acetylcholinesterase.[6] 1,2,3-Triazole scaffold is an attractive prototype, as it is remarkably stable under oxidative/reductive conditions, enzymatic degradation and is capable to exhibit hydrogen bonding, dipole-dipole moments and π-stacking interactions.[13] These unique features of 1,2,3-triazole have increased its importance in the field of medicinal chemistry as they bind with the biological targets with high affinity due to its improved solubility.[14]

1,2,3-triazole is also reported as a core structural moiety in several important antifungal agents *viz*. Fluconazole, Itraconazole, Voriconazole and Ketoconazole.[15] These aforementioned broad and potent activities of triazole and its derivatives have established them as pharmacologically active scaffolds.

Owing to the therapeutic significance of 1,2,3-triazoles, in recent years a library of 1,2,3-triazoles have been synthesized and their antitubercular and antimicrobial activities reported.[16–19] Some molecules possessing antitubercular activity are shown in Figure 1.

Keeping in view the therapeutic significance of triazoles for developing new leads possessing excellent antitubercular and antimicrobial activities,[20–25] here, we have decided to design and synthesize the titled compounds, 2-(4-(([1,1′-biphenyl]-4-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-5l**) and to evaluate them for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and antimicrobial activity against potent bacterial and fungal pathogens.

Experimental

General

Chemicals and solvents were procured from Merck and S. D. fine chem. Melting points were determined in open capillary and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (GF 254) using UV light to visualize the course of the reactions. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Bruker Avance 300–500 (FT-NMR) and Bruker DRX-300 instruments, respectively, using $CDCl_3$ and DMSO-d_6 as solvent.

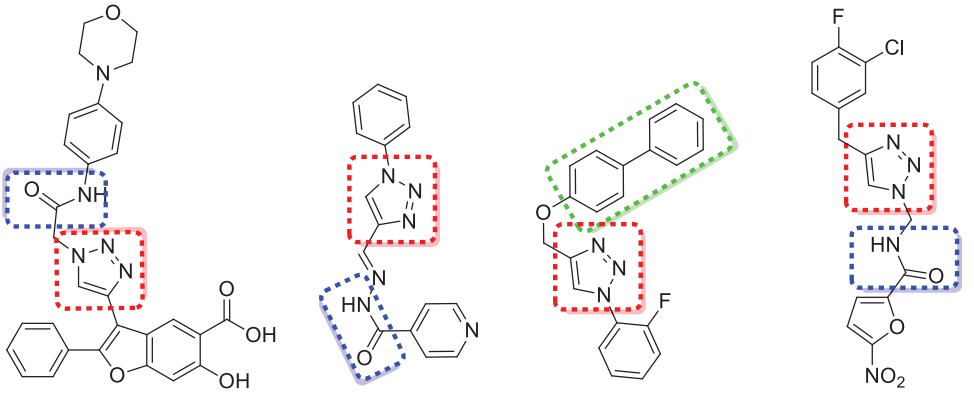


Figure 1. 1,2,3-triazoles containing Bioactive molecules.

Chemical shifts are reported in δ ppm with TMS as internal standard. High-resolution mass spectra (HRMS) were obtained using the Agilent 6520 (Q-TOF) ESI-HRMS instrument. Routine monitoring of reaction was performed by TLC using 0.25 mm E. Merck precoated silica gel TLC plates (60 F254) hexane:ethyl acetate as eluent.

Synthesis of 4-(prop-2-yn-1-yloxy)-1,1′-biphenyl (1)[18]

Off white solid, yield 82%, M.P.: 83–85 °C.

General procedure for the synthesis of 2-(4-(([1,1′-biphenyl]-4-loxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamides (5a-5l)

In a round bottom flask, 4-(prop-2-yn-1-yloxy)-1,1′-biphenyl (**1**) (0.0024 mol) and freshly prepared substituted 2-azido-*N*-phenylacetamides (**2a-2l**) (0.0024 mol) were stirred in presence of copper sulfate (20 mol%) and sodium ascorbate (20 mol%) in PEG-400: H_2O (1:1). The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: hexane (3:7) as solvents. After stirring for 4h, the reaction mass was poured in ice cold water. The obtained solid was filtered, washed with water and crystalized from ethanol:DMF.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (5a)

White solid, yield 93%, M.P.: 240–241 °C; IR (KBr) cm^{-1}: 3390, 2870, 2354, 1665, 1365, 1225, 1032, 852, 691; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 5.23 (s, 2H, NCH_2), 5.36 (s, 2H, OCH_2), 7.07–7.63 (m, 14H, merged signals, Ar-H), 8.28 (s, 1H, triazolyl-H), 10.46 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 52.8 (NCH_2), 61.7 (OCH_2), 115.8, 119.8, 124.9, 126.8, 126.8, 127.3, 128.3, 129.4, 129.4, 133.4, 139.0, 140.4, 143.1, 156.3, 164.7 (C = O); HRMS $(ESI)^+$ calcd. for $C_{23}H_{21}N_4O_2$ $[M+H]^+$: 385.1620, found 385.1130.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-tolyl)acetamide (5b)

White solid, yield 90%, M.P.: 260–262 °C; IR (KBr) cm^{-1}: 3250, 2980, 2354, 1670, 1604, 1492, 1224, 996, 745, 562; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 2.24 (s, 3H, CH_3), 5.23 (s, 2H, NCH_2), 5.41 (s, 2H, OCH_2), 7.11–7.62 (m, 13H, merged signals, Ar-H), 8.28 (s, 1H, triazolyl-H), 9.79 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 18.4 (CH_3), 52.6 (NCH_2), 61.7 (OCH_2), 115.8, 125.3, 126.1, 126.6, 126.8, 126.8, 127.3, 128.3, 129.4, 131.0, 132.2, 133.5,

136.1, 140.7, 143.1, 158.3, 164.9 (C = O); HRMS (ESI)$^+$ calcd. for $C_{24}H_{23}N_4O_2$ $[M+H]^+$: 399.1776, found 399.1818.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-tolyl)acetamide (5c)

White solid, yield 89%, M.P.: 210–211 °C; IR (KBr) cm^{-1}: 3351, 2972, 2361, 1662, 1586, 1348, 1214, 1028, 728, 580; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm = 2.28 (s, 3H, CH_3), 5.23 (s, 2H, NCH_2), 5.34 (s, 2H, OCH_2), 6.90–7.63 (m, 13H, merged signals, Ar-H), 8.27 (s, 1H, triazolyl-H), 10.38 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ ppm = 21.7 (CH_3), 49.2 (NCH_2), 61.7 (OCH_2), 115.7, 117.0, 120.8, 125.1, 126.8, 127.2, 127.3, 128.3, 129.3, 129.4, 133.5, 138.7, 138.9, 140.4, 143.7, 158.3, 164.7 (C = O); HRMS (ESI)$^+$ calcd. for $C_{24}H_{23}N_4O_2$ $[M+H]^+$: 399.1776, found 399.1824.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-tolyl)acetamide (5d)

Off white solid, yield 92%, M.P.: 240–242 °C; IR (KBr) cm^{-1}: 3136, 2868, 2361, 1661, 1496, 1214, 1028, 1006, 819, 506; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm = 2.26 (s, 3H, CH_3), 5.23 (s, 2H, NCH_2), 5.35 (s, 2H, OCH_2), 7.13–7.64 (m, 13H, merged signals, Ar-H), 8.28 (s, 1H, triazolyl-H), 10.40 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ ppm = 21.0 (CH_3), 52.8 (NCH_2), 61.7 (OCH_2), 115.7, 119.8, 126.8, 126.9, 127.3, 128.4, 129.5, 129.9, 133.4, 133.4, 136.4, 140.3, 143.1, 158.3, 164.5 (C = O); HRMS (ESI)$^+$ calcd. for $C_{24}H_{23}N_4O_2$ $[M+H]^+$: 399.1776, found 399.1794.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-chlorophenyl)acetamide (5e)

White solid, yield 87%, M.P.: 224–225 °C; IR (KBr) cm^{-1}: 3146, 2960, 2354, 1668, 1593, 1261, 1168, 1045, 790, 685, 556; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm = 5.25 (s, 2H, NCH_2), 5.48 (s, 2H, OCH_2), 7.15–7.78 (m, 13H, merged signals, Ar-H), 8.28 (s, 1H, triazolyl-H), 10.02 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ ppm = 52.6 (NCH_2), 61.7 (OCH_2), 115.8, 126.5, 126.8, 126.8, 126.9, 127.3, 128.1, 128.3, 129.4, 130.2, 133.5, 134.8, 140.4, 143.2, 143.4, 158.3, 164.5 (C = O); HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}ClN_4O_2$ $[M+H]^+$: 419.1230, found 419.1276.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-chlorophenyl) acetamide (5f)

White solid, yield 85%, M.P.: 165–168 °C; IR (KBr) cm^{-1}: 3146, 2970, 2354, 1679, 1598, 1377, 1220, 1168, 1022, 824, 528; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm = 5.25 (s, 2H, NCH_2), 5.40 (s, 2H, OCH_2), 7.09–7.80 (m, 13H, merged signals, Ar-H), 8.30 (s, 1H, triazolyl-H), 10.69 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ ppm = 52.6 (NCH_2), 70.2 (OCH_2), 115.6, 118.1, 119.2, 124.0, 126.6, 126.7, 127.2, 128.2, 129.2, 131.1, 133.3, 133.6, 140.2, 140.2, 143.0, 158.1, 165.1 (C = O); HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}ClN_4O_2$ $[M+H]^+$: 419.1230, found 419.1273.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-chlorophenyl)acetamide (5 g)

Pale yellow solid, yield 92%, M.P.: 225–227 °C; IR (KBr) cm^{-1}: 3252, 2945, 2361, 1668, 1605, 1504, 1377, 1220, 1168, 1022, 824, 528; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm = 5.24 (s, 2H, NCH_2), 5.37 (s, 2H, OCH_2), 7.15–7.64 (m, 13H, merged signals, Ar-H), 8.28 (s, 1H, triazolyl-H), 10.61 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ ppm = 57.5 (NCH_2), 75.1 (OCH_2), 120.5, 126.2, 131.5, 131.7, 132.1, 132.6, 132.9, 133.1, 134.2, 134.2, 138.2, 142.6, 145.1, 163.0, 169.7 (C = O); HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}ClN_4O_2$ $[M+H]^+$: 419.1230, found 419.1279.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-methoxyphenyl) acetamide (5h)

White solid, yield 86%, M.P.: 192–194 °C; IR (KBr) cm^{-1}: 3306, 2937, 2354, 1674, 1598, 1502, 1220, 999, 790, 533; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.73 (s, 3H, OCH_3), 5.23 (s, 2H, NCH_2), 5.36 (s, 2H, OCH_2), 6.66–7.63 (m, 13H, merged signals, Ar-H), 8.29 (s, 1H, triazolyl-H), 10.47 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 55.6, 61.7 (NCH_2), 70.4 (OCH_2), 105.6, 109.9, 112.1, 115.7, 126.8, 126.9, 127.3, 128.3, 129.4, 130.3, 133.5, 140.2, 143.2, 158.3, 160.2, 164.2 (C = O); HRMS (ESI)$^+$ calcd. for $C_{24}H_{22}N_4O_3$ $[M+H]^+$: 415.1725, found 415.1782.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl) acetamide (5i)

Off white solid, yield 91%, M.P.: 242–244 °C; IR (KBr) cm^{-1}: 3203, 3134, 2354, 1668, 1604, 1523, 1220, 1040, 795, 533; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.73 (s, 3H, OCH_3), 5.23 (s, 2H, NCH_2), 5.33 (s, 2H, OCH_2), 6.90–6.93 (d, 2H, J = 8Hz, Ar-H), 7.15–7.17 (d, 2H, J = 8Hz, Ar-H), 7.49–8.28 (m, 9H, merged signals, Ar-H), 8.32 (s, 1H, triazolyl-H), 10.37 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 57.7, 61.6 (NCH_2), 79.7 (OCH_2), 114.6, 115.7, 121.4, 126.8, 127.3, 128.4, 129.5, 132.1, 133.4, 140.3, 143.0, 156.1, 158.3, 164.2 (C = O); HRMS (ESI)$^+$ calcd. for $C_{24}H_{22}N_4O_3$ $[M+H]^+$: 415.1725, found 415.1768.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)acetamide (5j)

Off white solid, yield 88%, M.P.: 223–225 °C; IR (KBr) cm^{-1}: 3146, 2971, 2354, 1668, 1502, 1231, 1027, 824, 790, 533; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 5.23 (s, 2H, NCH_2), 5.36 (s, 2H, OCH_2), 7.15–7.70 (m, 13H, merged signals, Ar-H), 8.32 (s, 1H, triazolyl-H), 10.55 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 52.7 (NCH_2), 61.7 (OCH_2), 115.7, 116.2, 121.6, 121.7, 126.8, 126.8, 127.3, 128.3, 129.4, 133.4, 140.3, 143.1, 158.3, 164.7 (C = O); HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}FN_4O_2$ $[M+H]^+$: 403.1526, found 403.1568.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-bromophenyl)acetamide (5k)

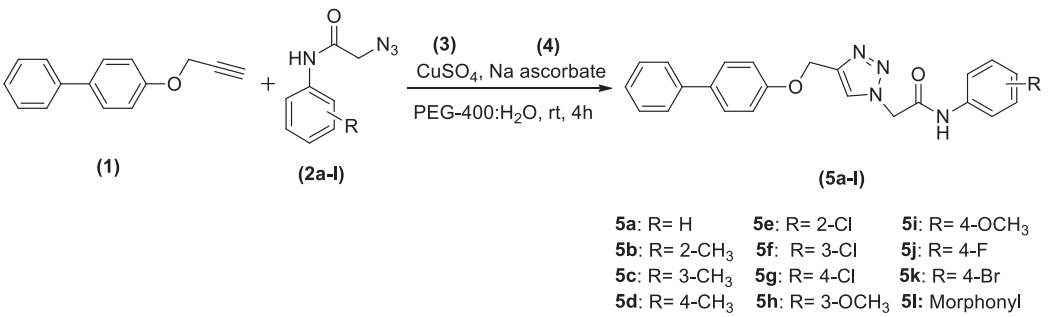
Pale yellow solid, yield 89%, M.P.: 222–223 °C; IR (KBr) cm^{-1}: 3150, 2966, 2354, 1668, 1604, 1372, 1226, 1034, 830, 790, 539; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 5.23 (s, 2H, NCH_2), 5.37 (s, 2H, OCH_2), 7.14–7.63 (m, 13H, merged signals, Ar-H), 8.29 (s, 1H, triazolyl-H), 10.65 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 52.8 (NCH_2), 61.6 (OCH_2), 115.7, 116.0, 121.8, 126.8, 126.8, 127.3, 128.3, 129.5, 132.3, 133.4, 138.3, 140.3, 143.1, 158.3, 165.0 (C = O); HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}BrN_4O_2$ $[M+H]^+$: 463.0725 and found 463.0770.

2-(4-(([1,1′-Biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-1-morpholino ethanone (5 l)

Green solid, yield 80%, M.P.: 268–270 °C; IR (KBr) cm^{-1}: 3152, 2983, 2356, 1668, 1598, 1220, 1068, 998, 790, 558; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.46–3.47 (m, 2H, morphinyl ring-H), 3.51–3.54 (m, 2H, morphinyl ring-H), 3.58–3.59 (m, 2H, morphinyl ring-H), 3.64–3.65 (m, 2H, morphinyl ring-H), 5.21 (s, 2H, NCH_2), 5.49 (s, 2H, OCH_2), 7.13–7.63 (m, 9H, merged signals, Ar-H), 8.13 (s, 1H, triazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 45.3, 51.2 (NCH_2), 61.8 (OCH_2), 66.5, 115.8, 126.8, 126.9, 127.3, 128.3, 129.4, 133.4, 140.4, 143.0, 158.3, 165.0 (C = O); HRMS (ESI)$^+$ calcd. for $C_{21}H_{23}N_4O_3$ $[M+H]^+$: 379.1725, found 379.1773.

Results and discussion

A convenient synthetic path has been developed to obtain the titled compounds, 2-(4-(([1,1′-biphenyl]-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-5l**), starting from



Scheme 1. Synthesis of new 2-(4-(([1,1′-biphenyl]-4-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-5l**).

4-phenylphenol by following click chemistry. 4-Phenylphenol has been condensed with propargyl bromide in the presence of K_2CO_3 in DMF to afford desired starting material biphenyloxymethyl ethyne (**1**). It was then allowed to interact with substituted 2-azido-*N*-phenylacetamides **(2a-2l)** in the presence of $CuSO_4$ **(3)** and sodium ascorbate **(4)** as catalyst in PEG-400: H_2O (1:1) for 4 h to yield the cyclo addition titled products, 2-(4-(([1,1′-biphenyl]-4-loxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-5l**) (Scheme 1) with better to excellent yields. The physical data of the compounds (**5a-5l**) is recorded in Table 1.

These synthesized compounds were thoroughly characterized by their ^{1}H NMR, ^{13}C NMR and HRMS spectral data. The IR spectrum of compound **5a** has shown characteristic peak at 1566 cm^{-1} which corresponds to the C = N bond. The ^{1}H NMR spectrum of one of the representative compound **5a** displays peaks at δ 5.23, 5.36, 8.28 and 10.46 ppm, as four singlets due to the NCH_2, OCH_2, triazolyl-H and amido-NH, respectively, and a multiplet in the region δ 7.07 to 7.63 ppm due to the merged signals of 14 aromatic-H. The presence of three characteristics carbon signals are observed at δ 52.8, 61.7 and 164.7 ppm in ^{13}C NMR spectrum of compound **5a**, owing to the signals of NCH_2, OCH_2 and amido carbon group, respectively. The HRMS spectrum of compound 2-(4-(([1,1′-biphenyl]-4-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide **5a** showing $[M+H]^+$ ion peak at m/z 385.1130 for its molecular formula $C_{23}H_{20}N_4O_2$, confirming the formation of a 1,2,3-triazole ring. The detailed experimental procedures and spectral data of all the new compounds (**5a-5l**) are given in the supplementary materials.

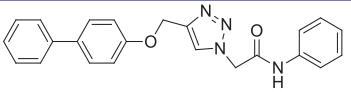
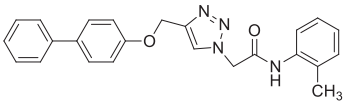
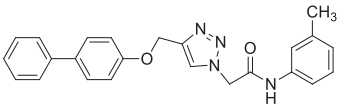
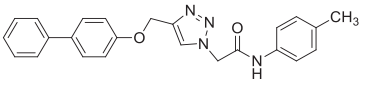
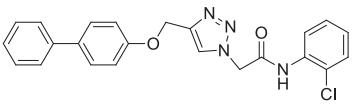
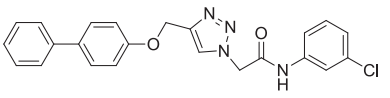
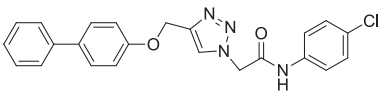
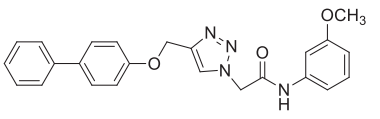
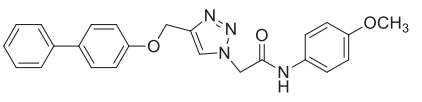
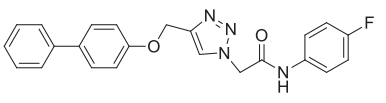
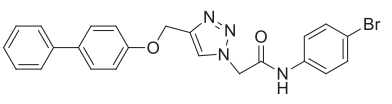
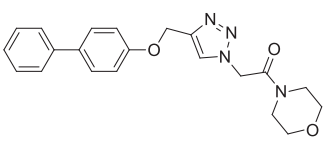
Antitubercular activity

The newly synthesized compounds (**5a-5l**) were evaluated for their *in vitro* antitubercular evaluation against *Mycobacterium tuberculosis* H_{37}Rv. It is evident from Table 1 that most of synthesized compounds have shown moderate antitubercular activity compared to standard drug, rifampicin. Among the newly synthesized compounds **5a** and **5i** were found to be active against *Mycobacterium tuberculosis* H_{37}Rv. The compound **5a** have phenyl acetamido moiety shown MIC 25 µg/mL. The compound **5i** with 4-methoxy phenyl acetamido moiety has also displayed moderate inhibitory activity with MIC 25 µg/mL.

Antimicrobial activity

The antimicrobial activity of the synthesized compounds (**5a-5l**) was evaluated against potent bacterial and fungal pathogens. The antimicrobial activity of the synthesized compounds was determined by the agar well diffusion method.[26] Fluconazole and tetracycline were used as internal references for antifungal and antibacterial activities, respectively. Among the synthesized compounds, **5a**, **5b**, **5c**, **5 g, 5i** and **5 l** have shown effective inhibition against all pathogens. Activity

Table 1. Physical data and antitubercular activity of newly synthesized compounds (**5a-5l**).

Compound	Structures	M. P. (o C)	Yields (%)	MIC (μg/mL)
5a		240–241	93	25
5b		260–262	90	>25
5c		210–211	89	>25
5d		240–242	92	>25
5e		224–225	87	>25
5f		165–168	85	>25
5g		225–227	92	>25
5h		192–194	86	>25
5i		242–244	91	25
5j		223–225	88	>25
5k		222–223	89	>25
5l		268–270	80	>25

MIC values of Isoniazid and Rifampicin is 0.1 and 0.2 μg/mL, respectively.

of compounds **5b** and **5 g** against *E. coli*, *S. typhi* and *S. boydii* was noteworthy. Compound **5l** also showed good activity against *S. boydii* and *S. cerevisiae*. Compound **5l** was found to be active against fungal pathogens, *S. cervisiae* and *C. albicans* (Table 2).

Table 2. Antibacterial and antifungal activities of synthesized 1,2,3-triazoles (**5a-5l**).

Compounds→Bacterial Pathogens↓	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Tetracycline as Standard (mm)
S. typhi ATCC 9207	26	16	12	06	02	01	14	06	06	03	03	10	33
E. aerogenes ATCC 13048	15	06	10	01	00	10	15	02	05	00	01	06	29
B. subtilis ATCC 6633	07	05	13	00	00	00	09	01	04	00	00	06	32
B. cereus ATCC 1177	12	05	14	01	03	08	20	06	10	01	00	05	33
P. aerogenosa ATCC 9027	05	06	09	02	00	01	10	00	09	02	01	06	32
S. abony NCTC 6017	07	07	12	02	00	05	13	02	06	00	02	06	32
E. coli ATCC 8739	16	09	08	01	01	10	14	00	05	02	03	05	29
S. aureus ATCC 6538	06	06	10	03	03	02	14	08	05	01	00	13	29
S. boydii ATCC 12034	05	11	13	02	00	15	23	03	14	02	00	15	34
Compounds→Fungal Pathogens↓	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	**Fluconazole as Standard (mm)**
S. cerevisiae ATCC 9763	05	07	06	01	01	00	15	02	06	01	02	15	30
A. niger ATCC 16404	08	06	05	02	00	03	06	01	04	01	01	04	30
C. albicans ATCC 10231	06	06	06	00	02	02	05	00	07	01	00	13	30

Diameter of zone of inhibition is given in millimeters (mm).

Table 3. MIC Values in μg/mL of most potent compounds.

Compounds → Pathogens↓	5a	5b	5c	5g	5i	5l	Tetracycline	Fluconazole
S. typhi	60	80	150	120	350	320	20	NA
B. subtilis	340	450	220	300	900	450	35	NA
B. cereus	170	460	170	70	280	530	30	NA
E. coli	110	230	280	160	600	550	25	NA
S. aureus	530	490	330	150	570	190	20	NA
S. boydii	600	180	230	40	130	140	20	NA
S. cerevisiae	550	510	650	130	340	130	NA	12
A. niger	410	620	850	470	850	630	NA	08
C. albicans	560	610	720	520	370	290	NA	30

NA: Not applicable.

Minimum inhibitory concentration (MIC)

In this present study, the MIC was determined for the most potent selected antimicrobial compounds **5a**, **5b**, **5c**, **5 g**, **5i** and **5 l**. MIC was deduced by following the method and guidelines of Clinical and Laboratory Standard Institute (CLSI). The results are recorded in Table 3.

Docking analysis

Promising level of anti-tubercular activities demonstrated by the two compounds **5a** and **5i** in the *in vitro* cell-based assay prompted us to perform molecular docking studies to elucidate their plausible mechanism of antitubercular activity, which could serve as potential starting points for structure-based lead optimization. Mycobacterial enoyl-ACP-reductase (FabI/ENR/InhA) plays a crucial role in the fatty acids elongation cycle, a step essential for mycolic acid biosynthesis through the mycobacterial type II fatty acid biosynthesis pathway.[20] Mycolic acids are very long chain α-alkyl β-hydroxy fatty acids (C74-C90) covalently linked to arabino-galactan which forms the major component of the mycobacterial cell wall. These acids provide protection from commonly used antibiotics, and are also significantly responsible for mycobacterial virulence. Inhibition of InhA efficiently helps to kill *Mycobacterium tuberculosis* under aerobic and anaerobic conditions by blocking the biosynthesis of this vital cell wall component i.e. mycolic acid and consequential cell lysis.[27] Furthermore, literature survey demonstrated the potential of triazolyl scaffolds to inhibit mycobacterial InhA. This encourages the selection of target to evaluate the binding affinity of titled compounds toward the crucial cell wall.[28–32] Molecular docking study

was carried out using the standard protocol implemented in the GLIDE (Grid-based Ligand Docking with Energetics) module of the Schrodinger molecular modeling package[33] to predict the binding modes of **5a** and **5i** into the active site of InhA.[34–37] Firstly, the molecular docking protocol was validated by extracting the co-crystallized ligand from the protein complex and re-docked into the active site. An overlay of the docked pose over the X-ray conformation showed that molecular docking protocol could reproduce the experimental binding mode with an RMSD of less than 0.1 Å (Figure S1 in supporting information).

From the ensuing docked conformations, it is observed that both the triazole analogues (**5a** - Figure 2 and **5i** - Figure 3) are deeply embedded into the active site of InhA with significant affinity (docking score: −8.957 (**5a**) and −8.594 (**5i**)) engaging in multiple bonded and non-bonded interactions with the residues lining the active site. Interestingly, they could accommodate well at the same site as the co-crystallized ligand with similar network of non-bonded and bonded interactions (Figure S2 in supporting information). Quantitative estimates of the per-residue interactions (Table 4 in supporting information) reveal that both compounds are stabilized within the active site through an extensive network of significant Van der Waals interactions with Leu218, Ile215, Ile194, Pro193, Ala191, Tyr158, Ala157, Met155 and Met103 residues *via* biphenyl-4-yloxy methyl component while the 1,2,3-triazole nucleus showed similar interactions

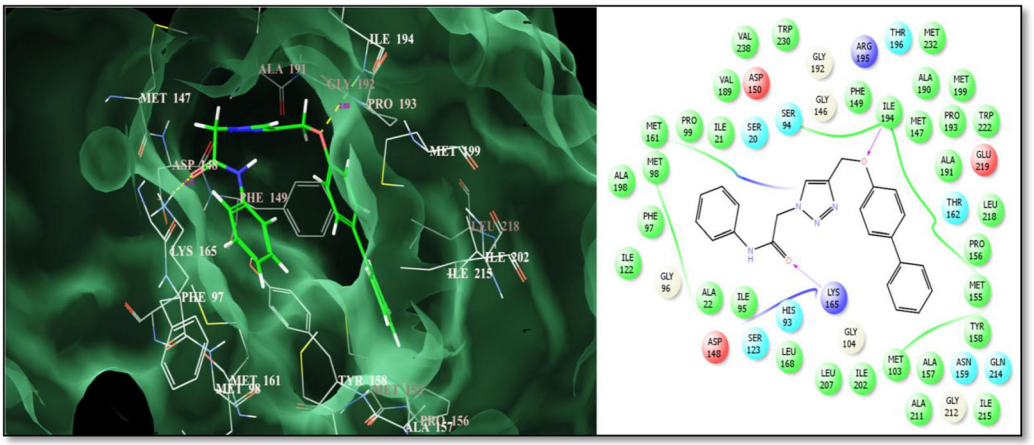


Figure 2. Binding mode of compound **5a** into the active site of mycobacterial enoyl reductase (InhA).

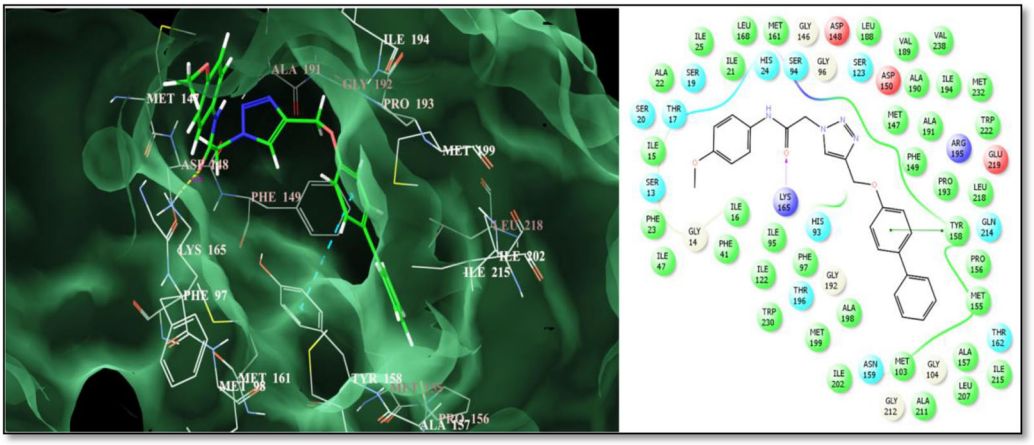


Figure 3. Binding mode of compound **5i** into the active site of mycobacterial enoyl reductase (InhA).

with Met199, Gly192, Phe149, Met147 and Ser94 residues. The *N*-phenyl acetamide side chain in compound **5a** and *N*-(4-methoxyphenyl) acetamide side of compound **5i** have shown significant Van der Waals interactions with Lys165, Met161, Asp148, Phe97, Gly96, Ile95, Ile21, Ser20 and Gly14 residues lining the active site of InhA. The enhanced binding affinity of these two compounds were also attributed to an equally significant array of electrostatic interactions observed with Glu220, Glu219, Glu210, Gly209, Gly192, Ala191, Lys165, Pro156 and Ser94 residues. These balanced set of steric and electrostatic interactions were major determinants in the binding of **5a** and **5i** to the active sites of InhA, which were further complimented by prominent hydrogen-bonding interactions observed between the amide oxygen (-CONH-) and Lys 165 residue. Compound **5a** showed an additional hydrogen bond with Ile94 through the ether linkage (-O-) while compound **5i** has displayed a close pi-pi (π- π) stacking interactions between the biphenyl component and the Tyr158 residue contributing additionally to the stability of **5a** and **5i** within the active site of InhA. These hydrogen-bonding and the pi-pi (π-π) stacking interactions serve as 'anchor' to guide the 3D orientation of ligand into the active site and facilitate the steric and electrostatic interactions with the enzyme. These results suggest that biphenyloxy tethered amide linked 1,2,3-triazoles possess promising binding affinity toward this crucial Mtb target InhA providing scope for structure-based lead optimization.

In silico ADME prediction

Good efficacy and an acceptable ADME (absorption, distribution, metabolism and excretion) profile are the most important properties of any successful drug. ADME properties prediction is one of the widely known pharmacokinetic parameters for the prediction of the oral bioavailability of any drug. Therefore, here we have predicted the in *silico* ADME properties of the newly synthesized 2-(4-(([1,1′-biphenyl]-4-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-5l**).

In this study, we have calculated the aforementioned properties and Lipinski's rule of five[38] of newly synthesized compounds using Molinspiration online property calculation toolkit.[39] A compound is considered an orally active drug as well as obeys the Lipinski's rule of five if there is only one violation observed out of the following four criteria's: miLog P (octanol-water partition coefficient) $\leq$5, molecular weight $\leq$500, number of hydrogen bond acceptors $\leq$10 and number of hydrogen bond donors $\leq$5. Other than this absorption (% ABS) of all the derivatives of the series was calculated by the formula,[40]

$$\% \text{ ABS} = 109 - (0.345 \times \text{TPSA})$$

Table 4. Pharmacokinetic parameters for *in silico* ADME prediction of 1,2,3-triazoles (**5a-5l**).

Entry	% ABS[a]	TPSA[b] (A^2)	n-ROTB[c]	MV[d]	MW[e]	miLogP[f]	n-ON[g]	n-OH NH[h]	Lipinski violations[i]	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	–
5a	85.18	69.05	7	331.66	384.43	5.37	5	1	0	0.49
5b	85.18	69.05	7	345.19	398.46	6.21	5	1	0	0.77
5c	85.18	69.05	7	345.19	398.46	6.24	5	1	0	0.32
5d	85.18	69.05	7	345.19	398.46	6.05	5	1	0	0.42
5e	85.18	69.05	7	349.54	418.88	6.34	5	1	0	0.93
5f	85.18	69.05	7	349.54	418.88	6.37	5	1	0	0.49
5g	85.18	69.05	7	357.20	418.88	5.59	6	1	1	1.02
5h	81.99	78.28	8	357.20	414.46	5.43	6	1	0	0.34
5i	81.99	78.28	8	341.52	414.46	5.84	5	1	0	0.20
5j	85.18	69.05	7	381.34	402.42	7.00	5	1	0	0.78
5k	85.18	69.05	7	348.46	463.33	5.69	5	1	1	0.62
5l	85.18	69.05	6	353.39	378.42	5.85	5	1	0	0.34

[a]Percentage Absorption; [b]Topographical polar surface area; [c]Number of rotatable bonds; [d]Molecular volume; [e]Molecular Weight; [f]Lipophilicity; [g]No. of hydrogen bond acceptors; [h]No. of hydrogen bond acceptors; [i]Number of violations.

Furthermore, the drug-likeness model score (a collective property of physicochemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) of synthesized compounds (**5a-5l**) were computed by MolSoft software.[41]

It was observed from Table 4 that most of the predictions were within the acceptable range. All the synthesized compounds exhibited very good % ABS ranging from 81.99 to 85.18% and results are shown in Table 4. Drug likeness score were also calculated in order to achieve biological activity of compound. Most of the compounds from the synthesized series showed positive drug likeness score. Results showed that the compounds possess average to good potential for the development as orally active drug molecules.

Conclusions

New 1,2,3-triazoles bearing biphenoloxymethyl and acetanilido moieties (**5a-5l**) have been successfully synthesized with good yields by following click chemistry. All the synthesized compounds were evaluated for their *in vitro* antimicrobial activity against nine and three different strains of bacterial and fungal pathogens, respectively. The bioactivity results shows that compounds **5a**, **5b**, **5c**, **5 g**, **5i** and **5 l** exhibited effective inhibition against various screened pathogens. In addition to this, we have also screened all the compounds for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Among the series, compounds **5a** and **5i** were acts as active antitubercular agent with MIC value 25 µg/mL. Furthermore, molecular docking investigation supports the most active compounds, which provides a valuable insight into the plausible mechanism of antitubercular action. Moreover, ADME properties of the synthesized compounds have shown good drug-like properties and therefore, the newly synthesized compounds can be acts as potent therapeutic agents.

Acknowledgments

Authors are grateful to Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad for antitubercular evaluation. One of the authors, STD is grateful to U.G.C., New Delhi, India for financial assistance in the form of NET Senior Research Fellowship. Authors also acknowledge Schrodinger Inc. for providing the academic license for GLIDE program to carry out the molecular docking studies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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