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AN EFFICIENT SYNTHESIS, CHARACTERIZATION AND BIOACTIVITY OF BENZIMIDAZOLE LINKED TRIAZOLES

Asghar Jafar Khan and Abdul Rahim Abdul Sami *

Department of Chemistry, Milliya Arts, Scince & Mangement Science College, Beed - 431122, Maharashtra, India.

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Triazoles, Benzimidazoles, Biological activity

Correspondence to Author:
Abdul Rahim Abdul Sami

Research Scholar,
Department of Chemistry,
Milliya Arts, Scince & Mangement Scince College, Beed - 431122, Maharashtra, India.

E-mail: phychemmax@gmail.com

ABSTRACT: A series of benzimidazole-linked triazoles hybrids (4a-4u) have been synthesized by simple cyclization, followed by amide coupling and click reaction starting from o-phenylene diamines as substrates with 4-formylbenzioc acid, propargylamine and followed by treatment with aryl azides. The structure of synthesized compounds (4a-4u) was confirmed by spectral techniques. The prepared compounds were screened by the agar well diffusion method against both Gram-positive bacteria (*S. aureus, B. subtilis, M. luteus and B. megatherium*) as well as Gram-negative bacteria (*E. coli, K. pneumoniae, S. typhi and S. paratyphi*). Analysis of antibacterial activity profile of synthesized compounds revealed that compounds (4a) and (4c) exhibited prominent activity against all tested Gram positive and Gram-negative microbes.

INTRODUCTION: Since last decade there is considerable interest in the development of novel hybrid drug like molecules that include two pharmacophores in a single molecule in order to improve the efficacy of such compounds [1, 2]. Benzimidazole which is a privileged heterocycle, attached to other heterocyclic moieties including fused rings resulted in compounds to give hybrid compound with enhanced pharmacological profile. Wonderful demands for novel bioactive molecules are continuously growing in the market [3]. In the present scenario, development of better drugs in shorter times have always been challenge for medicinal chemists. However, synthesis of new molecules, combining high activity, drug likeness and good pharmacokinetic properties is equally fascinating [4].

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There are two types of triazoles *viz.* 1,2,3 triazoles and 1,2,4 triazoles. 1,2,3-Triazole moieties are attractive one because of their high stability, tendency to form hydrogen bonding up surges their solubility which favour binding towards biomolecular targets in the cell [5-9]. Its structural simplicity, ease of synthesis and pohavet cytotoxic properties in low nanomolar range has made it greatly pursued scaffold for the development of antimicrobial agents, some of the potent hybrid molecules that have been recently developed as new antibacterial agents were obtained by the combination of different pharmacophores [10-19]. The promising biological activity exhibited by these hybrid molecules [20-22] prompted us to develop some newer hybrid molecules by linking the triazole pharmacophore with benzimidazole scaffold with a view to enhance their antimicrobial activity [23-25]. Thus, a series of novel class of triazole-benzimidazole hybrids (4a–4u) has been synthesized and evaluated for their antimicrobial activity.

MATERIALS AND METHODS: O-Phenylenediamines, 4-formylbenzoic acid,

propargylamine, aryl azides, and all solvents were procured from commercially available sources and used without further purification. Standard microbiological media were used for antibacterial activity assays.

Synthesis of Benzimidazole-Linked Triazole Hybrids (4a-4u): The compounds were synthesized through a multi-step process.

Cyclization: o-Phenylenediamines were reacted with 4-formylbenzoic acid under suitable conditions to form benzimidazole intermediates.

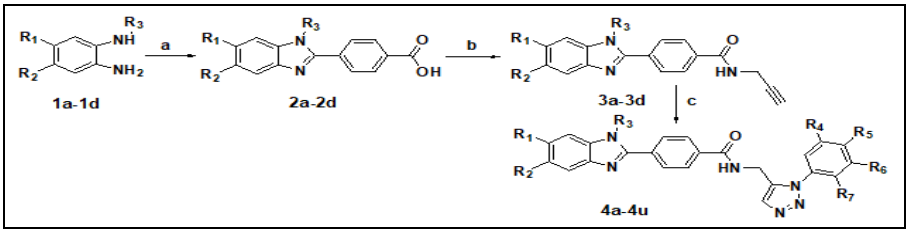
Amide Coupling: The benzimidazole intermediates were coupled with propargylamine to yield propargylated benzimidazole derivatives.

Click Reaction: The propargylated derivatives were treated with aryl azides under click chemistry conditions to obtain the final benzimidazole-linked triazole hybrids (4a-4u).

Antibacterial Activity Screening: The synthesized compounds (4a-4u) were evaluated for their antibacterial activity using the agar well diffusion method.

RESULT AND DISCUSSION: A series of benzimidazole linked triazole hybrids (4a-4u) were prepared by following the conventional synthetic procedures (Scheme 1). A condensation reaction between different o-phenylenediamine and 4-formylbenzioc acidgive rise benzimidazole linked carboxylic acids (2a-2u) which on coupling with propargylamine in presence of EDCI/HOBT furnished the terminal alkynes (3a-3d).

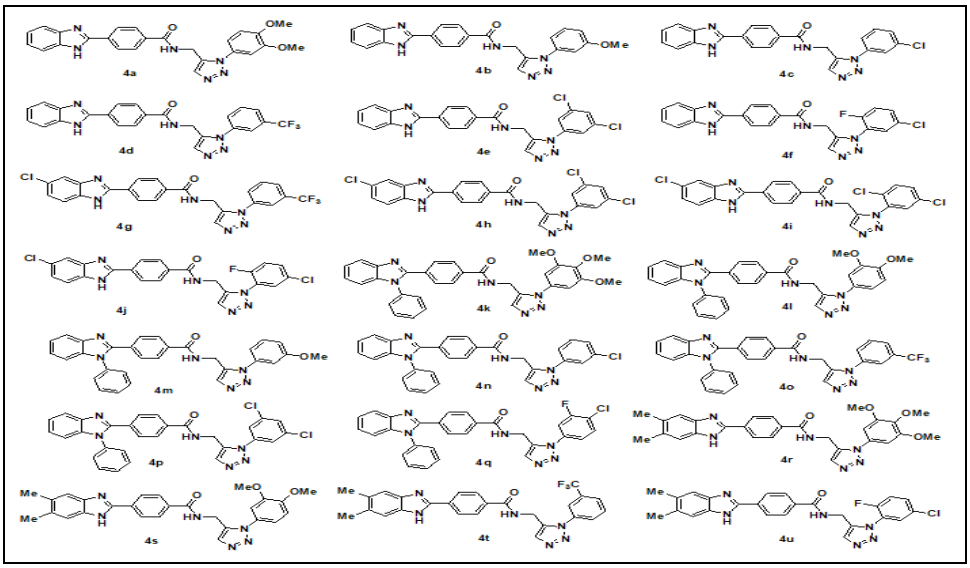
The final compounds (4a-4u) were prepared by a simple click reaction between these terminal alkynes (3a-3d) and aromatic azides. Structures of the final compounds were confirmed from their spectral data.



SCHEME 1: CONVENTIONAL SYNTHETIC PROCEDURES

Where R_1 = H, Cl and Me; R_2= H and Me; R_3= Ph; R_4; R_5, R_6 and R_7 can be H, MeO, Ph, Cl and CF_3

Reagent and Conditions: (a) 4-formylbenzioc acid, MeOH, 60 ^oC, 2-3 hr. (b) Propargylamine, EDCI, HOBt, DMF, at 0^oC to r.t (c) Aryl Azides, $CuSO_4.5H_20$, Sodium ascorbate, tBuOH: H_2O (1:1), rt, 3-4 hr.

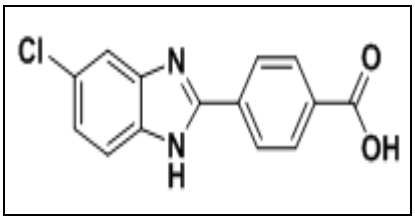


SYNTHESISED BENZIMIDAZOLE LINKED TRIAZOLES

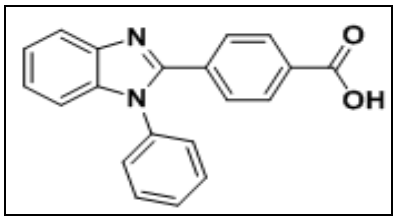
Experimental Section: All Chemicals used in this work were purchased from Aldrich and Merck chemical companies and used without purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (200, 400, 500 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are expressed in ppm relative to internal standard TMS. Multiplicities of NMR signals are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m). ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector.

General Procedure for the Synthesis of Benzimidazoles Acids (2a-2d): *O*-phenylenediamines (1a-1d) (0.025 mol) and 4-formyl benzoic acid (0.025 mol) in 100ml methanol was stirred at 60 ^{o}C for 2-3 hr. Completion of reaction was monitored by TLC. After completion, reaction cool down to room temperature then solid observed. It was filtered and washed with hexane. Yield: 83%, white solid (2a-2d).

4-(1*H*-benzo[d]imidazol-2-yl) benzoic acid (2b): White solid, yield 85%; ^{1}H NMR (300 MHz, DMSO-d_6). δ 8.27 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.07, 152.25, 133.93, 133.39, 130.36, 129.67, 127.20, 127.04, 123.19; ESI-MS: 273 $(M+H)^{+}$.

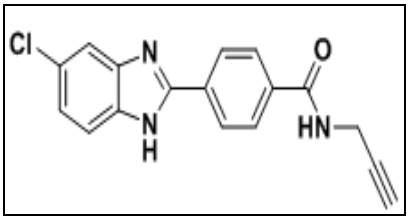


4-(1-phenyl-1*H*-benzo[d]imidazol-2-yl) benzoic acid (2d): White solid, yield 90%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.58 (t, *J* = 8.7 Hz, 3H), 7.47–7.41 (m, 2H), 7.34 (dd, *J* = 9.7, 8.3 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.24, 151.33, 142.96, 137.55, 136.61, 134.20, 131.89, 130.60, 129.74, 129.66, 129.48, 127.92, 124.30, 123.49, 120.08, 111.10; ESI-MS: 315 $(M+H)^{+}$.



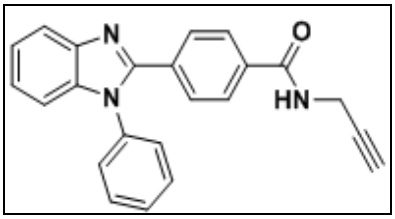
General Procedure for the Synthesis of Bbenzimidazoles Amides (3a-3d): Benzoic acid derivative (2a-2d) (0.025 mol) was taken in 100 ml RBF in DMF solvent and EDCI (1.2 Eq) and HOBt was added at r.t to this solution and stirred for 15 minutes. Finally, propargyl amine was added to the mixture and reaction mixture was kept for overnight. Completion of reaction was monitored by TLC. After completion, reaction cool down to room temperature and water and ethyl acetate work up followed by rota-evaporation provide the crude, the crude product was purified by column chromatography to give product (3a-3d). Yield: 83%, white solid.

4-(5-chloro-1*H*-benzo[d]imidazol-2-yl)-N-(prop-2-yn-1-yl) benzamide (3b): White solid, yield 90%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.33 (s, 1H), 9.10 (t, J = 5.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.65 (s, 2H), 7.32 – 7.22 (m, 1H), 4.10 (dd, J = 5.3, 2.3 Hz, 2H), 3.15 (t, J = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.34, 151.70, 134.90, 132.20, 127.97, 126.46, 122.75, 81.15, 72.91, 28.58; ESI-MS: 310 $(M+H)^{+}$.



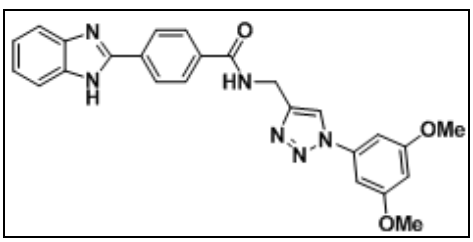
4-(1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-(prop-2-yn-1-yl) benzamide (3d): White solid, yield 90%; ^{1}H NMR (500 MHz, DMSO) δ 9.00 (t, *J* = 5.5 Hz, 1H), 7.82 (dd, *J* = 6.8, 1.8 Hz, 3H), 7.63 – 7.54 (m, 5H), 7.47 – 7.43 (m, 2H), 7.33 (dtd, *J* = 14.9, 7.2, 1.2 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 4.05 (dd, *J* = 5.5, 2.5 Hz, 2H), 3.13 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.72,

151.45, 143.02, 137.58, 136.72, 134.84, 132.99, 130.59, 129.55, 129.45, 128.00, 127.73, 124.17, 123.41, 120.04, 111.06, 81.61, 73.42, 40.64, 40.43, 40.22, 40.01, 39.81, 39.60, 39.39, 29.04; ESI-MS: 352 $(M+H)^+$.

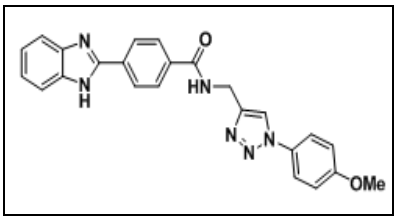


General Procedure for the Synthesis of Compounds (4a-4u): Compound (**3a-3d)** (0.025mol) and different aryl azides (0.025mol) in 5 ml [H_2O: tBuOH] solvent was taken with catalytic amount of $CuSO_4.\ 5H_2O$ and Sodium ascorbate and stirred for 3-4 hrs. Completion of reaction was checked by TLC. After rotary evaporation, reaction mixture neutralized with $NaHCO_3$ and water (10ml) and chloroform (20ml) were added and the aqueous layer was extracted with chloroform (2 x 25 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation to afford crude product which was further purified by column chromatography using ethyl acetate and hexane as solvent system.

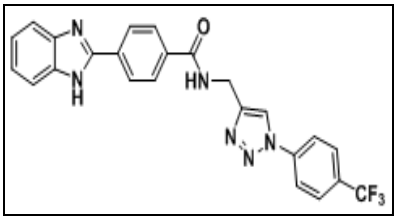
4-(1*H* - benzo[d] imidazol-2-yl) - N-((1 - (3, 5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl) benzamide (4a): White solid (75%); M.P.: 244-246 ^oC; ^1H NMR (300 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.77 (s, 1H), 8.34 (s, 1H), 8.04 (s, 2H), 7.80 (s, 1H), 7.62 (s, 1H), 7.27 (d, *J* = 24.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 3H), 6.58 (s, 1H), 4.63 (s, 2H), 3.80 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.73, 161.12, 138.04, 133.47, 133.13, 129.28, 127.86, 126.14, 123.85, 121.92, 103.84, 100.19, 98.20, 55.63, 34.94; HRMS (ESI) calculated for $C_{25}H_{23}O_3N_6$ $(M+H)^+$ 455.1826; found: 455.1818.



4-(1*H* - benzo[d] imidazol-2-yl) – N - ((1 - (4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl) benzamide (4b): White solid (78%); M.P.: 126-128 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.2 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 5.5, 3.4 Hz, 1H), 7.59 (dd, *J* = 8.7, 4.3 Hz, 3H), 7.53 (dd, *J* = 5.6, 3.3 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.26 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.77 (d, *J* = 5.3 Hz, 2H), 3.86 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 161.30, 160.32, 153.38, 143.81, 133.13, 129.16, 127.54, 126.02, 124.59, 122.39, 121.93, 121.61, 119.58, 116.06, 53.85, 38.48; HRMS (ESI) calculated for $C_{24}H_{21}O_2N_6$ $(M+H)^+$ 425.1720; found: 425.1717.

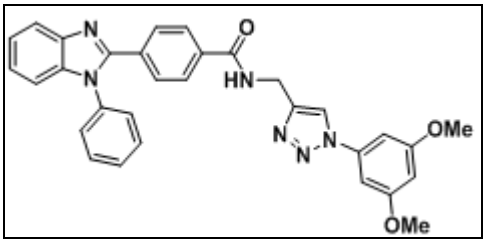


4-(1*H*-benzo[d] imidazol-2-yl) – N - ((1-(4-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl) methyl) benzamide (4d): White solid (69%); M.P.: 136-138 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.88 (s, 1H), 8.24 (t, *J* = 7.4 Hz, 3H), 8.03 (s, 2H), 7.80 (d, *J* = 12.3 Hz, 4H), 7.62 (s, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 4.66 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.67, 165.36, 139.52, 137.07, 135.45, 133.44, 131.22, 130.71, 130.28, 127.88, 126.06, 125.33, 124.98, 123.75, 121.71, 116.45, 111.77, 34.92; HRMS (ESI) calculated for $C_{24}H_{18}ON_6F_3$ $(M+H)^+$ 463.1488; found: 463.1484.

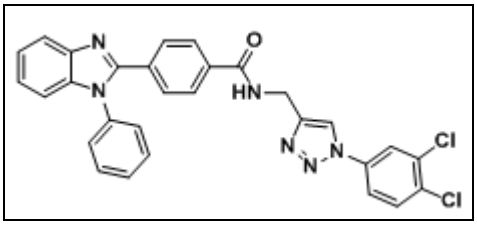


N-((1-(3,5-dimethoxyphenyl)-1H-1, 2, 3-triazol-4-yl) methyl)-4-(1-phenyl-1H-benzo[d]imidazol-2-yl) benzamide (4l): White solid (73%); **M.P.:** 116-118 ^oC; ^1H NMR (300 MHz, DMSO-D_6) δ 9.15 (s, 1H), 8.71 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 3H), 7.57 (d, *J* = 7.2 Hz, 5H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.39 – 7.17 (m, 3H), 7.06 (s, 2H), 6.58 (s, 1H), 4.58 (d, *J* = 4.6 Hz, 2H), 3.81 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.96, 161.51, 142.81, 138.39,

136.59, 134.56, 132.94, 130.05, 129.58, 128.87, 127.35, 127.16, 123.87, 123.34, 121.10, 119.97, 110.65, 100.79, 98.96, 55.75, 35.32; HRMS (ESI) calculated for $C_{31}H_{27}O_3N_6$ $(M+H)^+$ 531.2139; found: 531.2134.



N-((1-(3,4-dichlorophenyl)-1H-1, 2, 3-triazol-4-yl)methyl)-4-(1-phenyl-1H-benzo[d]imidazol-2-yl) benzamide (4p): White solid (82%); M.P.: 118-120 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.89 (s, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 1.2 Hz, 2H), 7.52 – 7.47 (m, 3H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.26 (s, 2H), 4.76 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.00, 136.62, 135.93, 134.38, 134.06, 133.03, 131.50, 130.07, 129.64, 128.89, 127.36, 127.09, 123.91, 123.38, 122.31, 120.88, 120.00, 119.42, 110.65, 35.33; HRMS (ESI) calculated for $C_{29}H_{21}ON_6Cl_2$ $(M+H)^+$ 539.1148; found: 539.1153.



Antimicrobial Activity: Antibacterial properties from the synthesized benzimidazoles based triazole conjugates **(4a-4u)** was screened by the agar well diffusion method against both Gram-positive bacteria (*S. aureus, B. subtilis, M. luteus* and *B. megatherium*) as well as Gram-negative bacteria (*E. coli, K. pneumoneae, S. typhi* and *S. paratyphi*). Before analysing the activity, all microorganisms were brought to synchronized growth by inoculating them in nutrient broth and subsequently incubating for 18 hours and used for further activity studies. In brief, nutrient agar medium is prepared, autoclaved and poured in a sterile petri plate under sterile environment.

After solidification, 50 µL (106CFU/mL) of test bacterial culture were inoculated and spread uniformly by sterile spreader and wells were made on agar plate by sterile cork borer. A 100 µg/mL stock solution of test compounds and standard drug streptomycin were prepared using DMSO (Dimethyl sulfoxide) as a solvent. The streptomycin was used as standard as well as positive control whereas neat DMSO was used as negative control. 100 µL of the test samples, streptomycin and DMSO were loaded individually in separate wells. The plates were incubated at 37°C for 18 hours and the zone of inhibition measured by using calibrated scale and expressed in mm.

These results clearly indicate that compounds **(**4a-4u) displayed significant activity with a high degree of variation. Analysis of antibacterial activity profile of synthesized compounds revealed that compounds (4a) and (4c) exhibited prominent activity against all tested Gram positive and Gram-negative microbes **Table 1** suggesting similar growth inhibitory potential like that of streptomycin.

TABLE 1: ANTIBACTERIAL ACTIVITIES OF COMPOUNDS BY THE AGAR WELL DIFFUSION METHOD DATA REPRESENTED AS ZONE OF INHIBITION (MM)

Compound	*S. aureus*	*B. subtilis*	*M. luteus*	*B. megatherium*	*E. coli*	*K. pneumonia*	*S. typhi*	*S. Para typhi*
4a	22	19	20	20	18	22	12	14
4b	14	13	14	17	15	15	13	16
4c	20	11	16	16	15	16	0	15
4d	14	15	15	11	14	12	16	13
4e	16	16	13	0	0	12	11	10
4f	15	12	10	9	16	13	15	0
4g	13	12	0	11	11	0	16	7
4h	10	13	7	15	0	11	12	14
4i	0	0	8	16	11	0	12	16
4j	7	0	11	12	18	13	13	15
4k	11	--	--	-	--	--	-	--

4l	15	0	14	0	14	17	10	14
4m	11	11	15	11	9	0	17	16
4n	10	16	15	16	13	8	11	15
4o	8	0	0	0	0	0	0	0
4p	16	11	11	12	14	13	11	11
4q	11	0	0	0	0	0	0	0
4r	0	--	--	--	--	--	--	--
4s	9	8	9	8	11	11	9	10
4t	0	8	8	0	9	0	0	8
4u	10	9	8	0	0	8	9	10
Streptomycin	23	24	26	21	24	23	20	22

" --" : not tested.

In view of the above results, further evaluation is under progress to understand the required concentration essential for complete inhibition of growth of selected microbial strain i.e., MIC.

CONCLUSION: Benzimidazoles linked triazole hybrids **(4a-4u)** have been synthesized by simple cyclization, followed by amide coupling and click reaction starting from *o*-phenylene diamines as substrates. Further, these compounds were evaluated for their anti-microbial activity by using the agar well diffusion method. Most of the compounds were found to be significant in view of inhibition in the range between 8-25mm against both Gram-positive and Gram-negative bacterial strains. Based on this primary result, further studies are under progress.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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