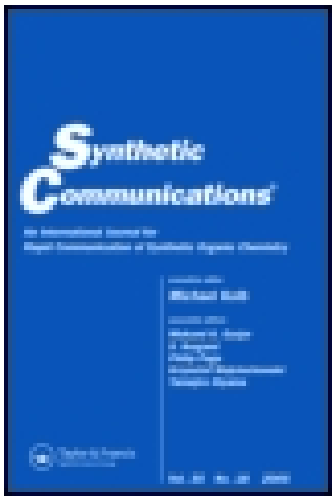

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Synthesis, Characterization, and Antimicrobial Potential of Some 1,4-Disubstituted 1,2,3-Bistriazoles

C. P. Kaushik[a], Krishan Kumar[a], Dharmendra Singh[b], S. K. Singh[c], Deepak Kumar Jindal[c] & Raj Luxmi[a]

[a] Department of Chemistry, Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India

[b] Centre for Research & Development, IPCA Lab Ltd., Kandivali, Mumbai, Maharashtra, India

[c] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India

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SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL POTENTIAL OF SOME 1,4-DISUBSTITUTED 1,2,3-BISTRIAZOLES

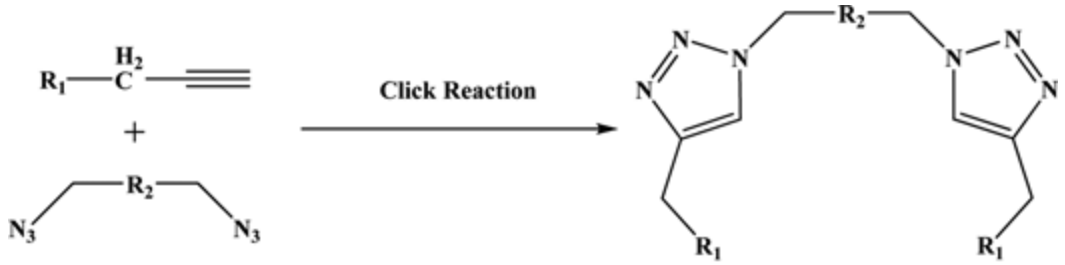
C. P. Kaushik[1], Krishan Kumar[1], Dharmendra Singh[2], S. K. Singh[3], Deepak Kumar Jindal[3] Raj Luxmi[1]

[1]Department of Chemistry, Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India, [2]Centre for Research & Development, IPCA Lab Ltd., Kandivali, Mumbai, Maharashtra, India, [3]Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India

Address Correspondence to: C. P. Kaushik, Email: kaushikcp@gmail.com

Abstract

A convenient synthesis of some new 1,4-disubstituted 1,2,3-bistriazoles ***(3a-3f, 4a-4f, 6a-6b, 7a-7b)*** *is reported via copper (I) catalyzed Huisgen 1,3-dipolar cycloaddition of various terminal alkynes with 1,4-bis(azidomethyl)benzene and 1,6-diazidohexane. The synthesized compounds were characterized by spectral techniques viz. IR,* ^{1}H *NMR,* ^{13}C *NMR, HRMS and tested in vitro for antimicrobial potential against* Bacillus subtilis, Staphylococcus aureus *(Gram positive bacteria),* Pseudomonas aeruginosa, Escherichia coli *(Gram negative bacteria),* Candida albicans *and* Aspergillus niger *(fungi). Among the synthesized 1,4-disubstituted 1,2,3-bistriazoles, compounds* ***6a***, ***6b*** *and* ***7b*** *displayed excellent antimicrobial potential against most of the tested strains.*



R_1 = Benzoate; p-Methylbenzoate; p-Methoxybenzoate; p-Nitrobenzoate; p-Fluorobenzoate; Acrylate; 1H-Benzotriazolyl; 1H-Benzimidazolyl. R_2 = p-C_6H_4- ; -$(CH_2)_4$-

Keywords Click reaction; 1,4-disubstituted 1,2,3-bistriazoles; Antibacterial activity; Antifungal activity

INTRODUCTION

N-heterocycles constitute a class of biologically active molecules owing to their key biological spectrum and applications as structural motif for designing of molecules of pharmaceutical interest.[1,2] Among these, triazoles are a versatile group of molecules present in numerous of life saving drugs.[3,4] Literature survey reveals that triazoles have immense chemotherapeutic importance as antiviral,[5] antimicrobial,[6,7] antimicobacterial,[8] anticancer,[9] antitripanosomal,[10] anti-HIV,[11] antimalarial,[12] analgesic,[13] anti-inflammatory,[14] antihypertensive,[15] anticonvulsant[16] and CNS depressant[17] agents. A review by Haider et al.[18] provides an excellent account of diverse biological activity spectrum associated with 1,2,3-triazole moiety.

Various methods are available for the synthesis of 1,2,3-triazoles,[19] however, the copper(I) catalyzed 1,3-dipolar cycloaddition of terminal alkynes with organic azides is one of the best method for regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[20]

This method was independently pioneered by Sharpless[21] and Meldal[22] in 2002 through dramatic modification in classical Huisgen 1,3-dipolar cycloaddition[23] reaction. This Sharpless-Meldal's pioneered reaction has been pointed out as one of the premier click reaction which attracted the chemist's interest with salient features like modularity, regioselectivity, high yields, purity and versatile chemical transformations. The significance of click reaction can also be revealed in synthesis of liquid crystals,[24] dendrimers,[25] triazolophanes,[26] peptidomimetics,[27] cyclic peptides,[28] nanotubes[29] and ionic receptors.[30]

Therefore, owing to widespread applications of triazoles, we focused the research work on synthesis and biological evaluation of 1,4-disubstituted 1,2,3-triazoles for the thirst of new potent antimicrobials. Earlier also, our research group synthesized 1,4-disubstituted 1,2,3-triazoles[31-36] having microbicidal activities. In continuation with our previous work, various 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** have been synthesized *via* copper(I) catalyzed click reaction of different terminal alkynes with 1,4-bis(azidomethyl)benzene and 1,6-diazidohexane. To the best of our knowledge, all the sixteen synthesized 1,4-disubstituted 1,2,3-bistriazoles are new. The synthesized bistriazoles were characterized by spectroscopic techniques like IR, ^{1}H NMR, ^{13}C NMR, HRMS and evaluated for their antimicrobial potential against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*.

RESULTS AND DISCUSSION

Chemistry

1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** were synthesized *via* Cu (I) catalyzed click reaction of various terminal alkynes with 1,4-bis(azidomethyl)benzene and 1,6-diazidohexane. 1,4-Bis(azidomethyl)benzene and 1,6-diazidohexane were prepared *in situ* by the reaction of sodium azide with 1,4-bis(bromomethyl)benzene and 1,6-dibromohexane, respectively.

Benzoic acid prop-2-ynyl ester and its derivatives **(1a-1e)** were synthesized[35,36] by reacting their corresponding aromatic acid chlorides with propargyl alcohol in dichloromethane using N,N-dimethylaminopyridine as base, whereas, propargyl acrylate **(1f)** was purchased from Sigma Aldrich. The ester linked terminal alkynes **(1a-1f)** were then reacted with 1,4-bis(bromomethyl)benzene and 1,6-dibromohexane in the presence of sodium azide, copper sulphate pentahydrate and sodium ascorbate in dimethylformamide-water to afford 1,4-disubstituted 1,2,3-bistriazoles **3a-3f** and **4a-4f**, respectively (Scheme 1).

The benzofused N-heteroaromatic alkynes **(5a-5b)** were synthesized by reacting benzotriazole/ benzimidazole with propargyl bromide in the presence of potassium carbonate using dimethylforamamide as solvent, as per literature procedure.[37] The synthesized alkynes **(5a-5b)** were then reacted with 1,4-bis(bromomethyl)benzene and 1,6-dibromohexane in the presence of sodium azide, copper sulphate pentahydrate, sodium ascorbate in dimethylformamide-water to furnish 1,4-disubstituted 1,2,3-bistriazoles **6a-6b** and **7a-7b**, respectively (Scheme 2).

The synthesized 1,4-disubstituted 1,2,3-bistriazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. The formation of triazoles was confirmed by the appearance of absorption band in the region 3153-3109 cm^{-1} in their IR spectra due to C-H stretching vibrations of triazole rings. In the ^{1}H NMR spectra, a characteristic singlet resonated in the region δ 7.95-8.32 was attributed to triazolyl protons present on the C-5 of the triazole rings. Moreover, in the ^{13}C NMR spectra of bistriazoles, signals appeared in the region δ 124.2-126.6 and δ 141.8-143.4 owing to C-5 and C-4 of the triazole rings also confirmed the formation of final products. The results obtained from high resolution mass spectral analysis were found in accordance with their calculated molecular mass.

Antibacterial Activity

All the synthesized 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** were tested *in vitro* for antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. Double strength nutrient broth was used as culture media. The antibacterial potential of bistriazoles was compared with standard drug, ciprofloxacin and their minimum inhibitory concentration (MIC) values were recorded in µmol/mL as shown in Table 1.

Antibacterial studies showed that the synthesized bistriazoles displayed average to excellent performance against tested bacterial strains. Compounds **4f**, **6a**, **6b** and **7b** (MIC 0.0643, 0.0497, 0.0249 and 0.0520 µmol/mL respectively) exhibited good antibacterial potential against *Bacillus subtilis*; compounds **3d**, **4d**, **6a**, **6b**, **7a** and **7b** (MIC 0.1670,

0.1728, 0.0994, 0.0998, 0.1036 and 0.1040 µmol/mL respectively) displayed significant activity against *Staphylococcus aureus*, whereas, compounds **6b**, **7a** and **7b** (MIC 0.0499, 0.0518 and 0.0520 µmol/mL respectively) have remarkable bactericidal efficacy against *Pseudomonas aeruginosa*, while in case of *Escherichia coli*, compounds **4d, 6a**, **6b**, **7a** and **7b** (MIC 0.0864, 0.0994, 0.0499, 0.1036 and 0.1040 µmol/mL respectively) emerged as good antibacterial agents.

Antifungal Activity

The 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** were screened for their *in vitro* antifungal activity against two fungal strains *i.e. Candida albicans* and *Aspergillus niger*. Fluconazole was used as reference compound and sabouraud dextrose broth as fungal culture media. The results were recorded in terms of MIC in µmol/mL of the compounds as displayed in Table 2.

Results of antifungal evaluation indicated that the synthesized bistriazoles exhibited excellent to moderate activity against tested fungal strains. Compounds **6a**, **6b** and **7b** (MIC 0.0497, 0.0499 and 0.0520 µmol/mL respectively) displayed noteworthy fungicidal potential against *Candida albicans*, while, compounds **3f**, **6a**, **6b** and **7b** (MIC 0.1224, 0.0994, 0.0499 and 0.1040 µmol/mL respectively) came out as potent antifungal agents against *Aspergillus niger*.

From the above antimicrobial evaluation, it has been shown that the presence of 1H-benzotriazolyl and 1H-benzimidazolyl moiety on methylene carbon attached to C_4 of the

triazole rings enhanced the antimicrobial potential of synthesized compounds against all tested bacterial and fungal species. Moreover, replacement of benzoyl group by p-nitrobenzoyl or acrylate also improved the microbicidal efficiency, although, displacement of benzoyl group by p-toluoyl or p-methoxybenzoyl group resulted into decrease in antimicrobial potency of the synthesized bistriazoles.

CONCLUSION

Presently, 1,4-disubstituted 1,2,3-bistriazoles were synthesized *via* copper(I) catalyzed click reaction of various terminal alkynes with 1,4-bis(azidomethyl)benzene and 1,6-diazidohexane. The synthesized bistriazoles were evaluated *in vitro* for antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Candida albicans* and *Aspergillus niger*. The compounds **6a**, **6b** against *Bacillus subtilis*; **6a**, **6b**, **7a** and **7b** against *Staphylococcus aureus*; **6b** against *Pseudomonas aeruginosa*; **4d, 6b** against *Escherichia coli* exhibited good antibacterial activity. Moreover, compounds **6a**, **6b** and **7b** appeared as better fungicidal agents against both tested fungal strains. In nutshell, antimicrobial activity reflects the compounds **6a**, **6b** and **7b** as good antimicrobial agents.

EXPERIMENTAL

Typical Procedure For Synthesis Of (1,1'-(1,4-Phenylenebis(Methylene))Bis(1H-1,2,3-Triazole-4,1-Diyl))Bis(Methylene)Dibenzoate (3a).

The synthesis[35,36] of benzoic acid prop-2-ynyl ester (**1a**) was carried out by reacting 0.23 mL of benzoyl chloride (2.0 mmol) with 0.14 mL of propargyl alcohol (2.4 mmol) using

245.0 mg of N,N-dimethylaminopyridine (2.0 mmol) as base in dry dichloromethane with continuous stirring at 10 ºC for 4 h. The compound **3a** was synthesized by reacting 263.96 mg of 1,4-bis(bromomethyl)benzene (**2**, 1.0 mmol) with 320.34 mg of benzoic acid prop-2-ynyl ester (**1a**, 2.0 mmol) using 195.03 mg of sodium azide (3.0 mmol), 24.97 mg of copper sulphate pentahydrate (0.1 mmol) and 80.0 mg of sodium ascorbate (0.4 mmol) in dimethylformamide : water (8+2 mL) with continuous stirring at 45 ºC for 12 h (Scheme 1).

Spectral Data

Appearance: white solid; Yield: 91%; m.p.: 198-202 ºC; FT-IR (KBr) ν_{max}/ cm^{-1}: 3111 (C-H str., triazole ring), 3062 (C-H str., aromatic ring), 1710 (C=O str., ester), 1600, 1521, 1446 (C=C str., aromatic ring), 1271 (C-O asym. str., ester), 1101 (C-O sym. str., ester); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.38 (s, 4H, NCH_2), 5.60 (s, 4H, OCH_2), 7.34 (s, 4H, Ar-H), 7.52 (t, 4H, Ar-H, *J*=7.2 Hz), 7.66 (t, 2H, Ar-H, *J*=7.2 Hz), 7.95 (d, 4H, Ar-H, *J*=7.2 Hz), 8.30 (s, 2H, C-H triazole); ^{13}C NMR (100 MHz, DMSO- d_6, δ, ppm): 52.9, 58.4, 125.4 (C_5 triazole), 128.9, 129.3, 129.7, 129.8, 134.0, 136.4, 142.6 (C_4 triazole), 165.9 (C=O ester); HRMS (*m*/*z*) calculated for $C_{28}H_{24}N_6O_4$ $[M+H]^+$: 509.1893. Found: 509.1930.

Typical Procedure For Synthesis Of 1,4-Bis((4-((1H-Benzo[D][1,2,3]Triazol-1-Yl)Methyl)-1H-1,2,3-Triazol-1-Yl)Methyl) Benzene (6a).

The 1-(prop-2-ynyl)-1H-benzo[d][1,2,3]triazoles (**5a**) was synthesized[37] by reacting 238.24 mg of 1H-benzo[d][1,2,3]triazole (2.0 mmol) with 0.21 mL of propargyl bromide

(2.4 mmol) using 552.0 mg of potassium carbonate (2.0 mmol) in dry dimethylforamamide with stirring at 15 ºC for 8 h. The compound **6a** was synthesized by reacting 263.96 mg of 1,4-bis(bromomethyl)benzene (**2**, 1.0 mmol) with 314 mg of 1-(prop-2-ynyl)-1H-benzo[d][1,2,3]triazole (**5a**, 2.0 mmol) using 195.03 mg of sodium azide (3.0 mmol), 24.97 mg of copper sulphate pentahydrate (0.1 mmol) and 80.0 mg of sodium ascorbate (0.4 mmol) in dimethylformamide : water (9+1 mL) with stirring at 35 ºC for 14 h (Scheme 2).

Spectral Data

Appearance: creamy white solid; Yield: 80%; m.p.: 232-236 ºC; FT-IR (KBr) ν_{max}/ cm^{-1}: 3136 (C-H str., triazole ring), 3064 (C-H str., aromatic ring), 2951 (C-H str., aliphatic), 1622, 1496, 1458 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.54 (s, 4H, NCH_2), 6.03 (s, 4H, NCH_2), 7.31 (d, 4H, Ar-H, *J*=8.0 Hz), 7.40 (t, 2H, Ar-H, *J*=7.6 Hz), 7.54 (t, 2H, Ar-H, *J*=7.6 Hz), 7.88 (d, 2H, Ar-H, *J*=8.4 Hz), 8.04 (d, 2H, Ar-H, *J*=8.4 Hz), 8.27 (s, 2H, C-H triazole); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.3, 52.9, 111.3, 119.6, 124.7 (C_5 triazole), 127.8, 128.8, 133.1, 136.3, 142.3 (C_4 triazole), 145.7; HRMS (*m*/*z*) calculated for $C_{26}H_{22}N_{12}$ $[M+H]^+$: 503.2124. Found: 503.2160.

Antimicrobial Activity

All synthesized 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** were evaluated for their *in vitro* antimicrobial potential against Gram-positive bacteria i.e. *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 7443); Gram-negative bacteria i.e. *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 1652) and

fungal strains i.e. *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 8189) using two fold serial dilution method.[38]

SUPPLEMENTAL MATERIAL

Full experimental detail, spectroscopic data and ^{1}H NMR, ^{13}C NMR, HRMS spectra of all newly synthesized 1,4-disubstituted 1,2,3-bistriazoles can be accessed on the publisher's website.

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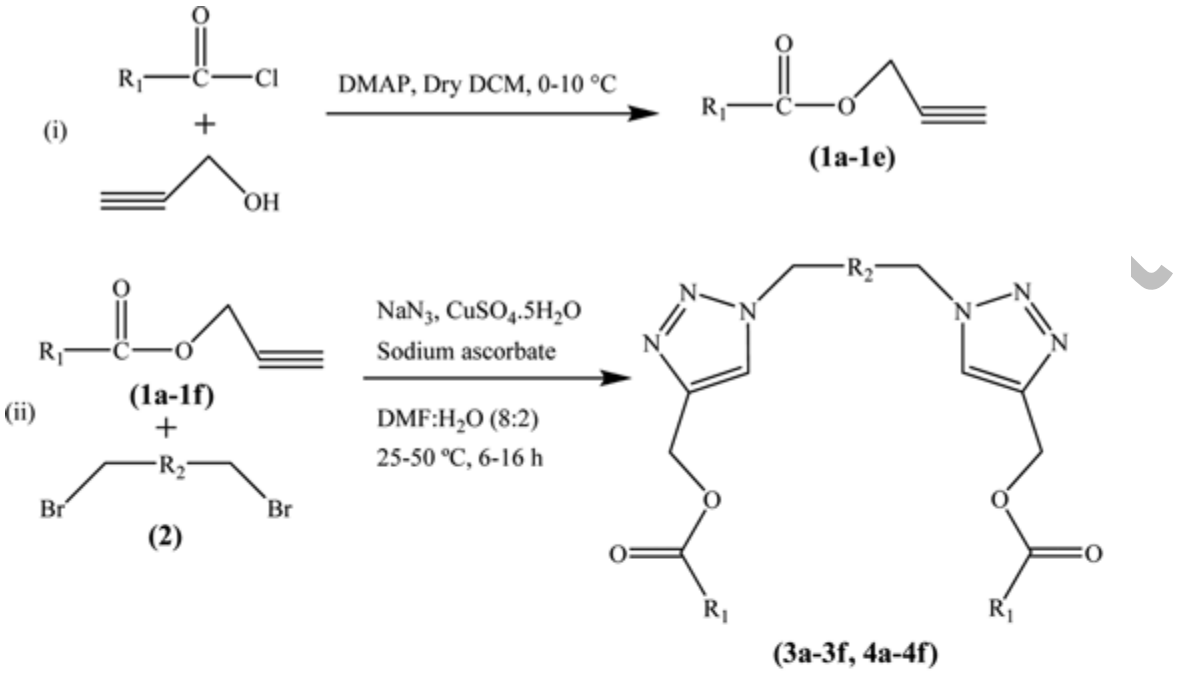
Table 1. Antibacterial activity of 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** in terms of MIC (μmol/mL)

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*Bacillus subtilis* (MTCC 441)	*Staphylococcus aureus* (MTCC 7443)	*Pseudomonas aeruginosa* (MTCC 424)	*Escherichia coli* (MTCC 1652)
3a	0.3933	0.9832	0.9832	0.4916
3b	0.3727	1.8636	0.9318	0.3727
3c	0.8794	0.8794	1.7588	0.4397
3d	0.0835	0.1670	0.1670	0.3342
3e	0.3673	0.9182	0.9182	1.8365
3f	0.1224	0.2448	0.1224	0.2448
4a	0.5117	0.5117	1.0234	1.0234
4b	0.4839	0.9678	0.9678	0.3871
4c	1.8228	1.8228	0.9114	1.8228
4d	0.0864	0.1728	0.0864	0.0864
4e	0.1906	0.3813	0.3813	0.9532
4f	0.0643	0.2574	0.1287	0.2574
6a	0.0497	0.0994	0.0994	0.0994
6b	0.0249	0.0998	0.0499	0.0499
7a	0.2072	0.1036	0.0518	0.1036
7b	0.0520	0.1040	0.0520	0.1040
Ciprofloxacin	0.0377	0.1509	0.0377	0.0754

Table 2. Antifungal activity of 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f, 6a-6b, 7a-7b)** in terms of MIC (µmol/mL)

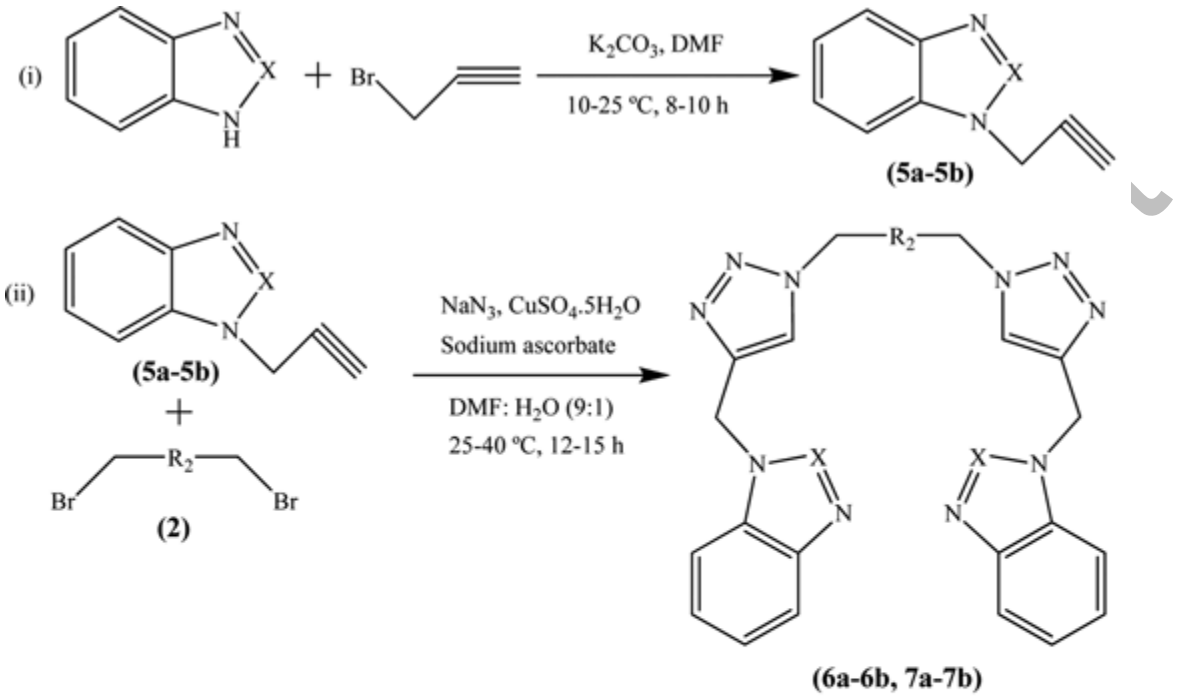
Compound	*Candida albicans* (MTCC 227)	*Aspergillus niger* (MTCC 8189)
3a	0.9832	0.9832
3b	0.9318	1.8636
3c	0.8794	0.3518
3d	0.4177	0.3342
3e	0.1836	0.3673
3f	0.1224	0.1224
4a	0.5117	0.5117
4b	0.9678	1.9358
4c	1.8228	1.8228
4d	0.1728	0.3457
4e	0.3813	0.4766
4f	0.1287	0.2574
6a	0.0497	0.0994
6b	0.0499	0.0499
7a	0.1036	0.2072
7b	0.0520	0.1040
Fluconazole	0.0408	0.0816

Scheme 1. Synthesis of ester linked 1,4-disubstituted 1,2,3-bistriazoles **(3a-3f, 4a-4f)**



Compound	R_1	R_2	Yield (%)
3a	C_6H_5-	1,4-C_6H_4-	91
3b	p- H_3C-C_6H_4-	1,4-C_6H_4-	82
3c	p-H_3CO-C_6H_4-	1,4-C_6H_4-	84
3d	p-NO_2-C_6H_4-	1,4-C_6H_4-	95
3e	p-F-C_6H_4-	1,4-C_6H_4-	93
3f	CH_2=CH-	1,4-C_6H_4-	73
4a	C_6H_5-	-$(CH_2)_4$-	87
4b	p- H_3C-C_6H_4-	-$(CH_2)_4$-	85
4c	p-H_3CO-C_6H_4-	-$(CH_2)_4$-	95
4d	p-NO_2-C_6H_4-	-$(CH_2)_4$-	96
4e	p-F-C_6H_4-	-$(CH_2)_4$-	72
4f	CH_2=CH-	-$(CH_2)_4$-	68

Scheme 2. Synthesis of 1,4-disubstituted 1,2,3-bistriazoles containing benzofused N-heteroaromatic functionalities **(6a-6b, 7a-7b)**



Compound	X	R_2	Yield (%)
6a	N	1,4-C_6H_4-	80
6b	CH	1,4-C_6H_4-	78
7a	N	-$(CH_2)_4$-	72
7b	CH	-$(CH_2)_4$-	75