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A facile expeditious one pot synthesis and antifungal evaluation of disubstituted 1,2,3-triazole with two amide linkages

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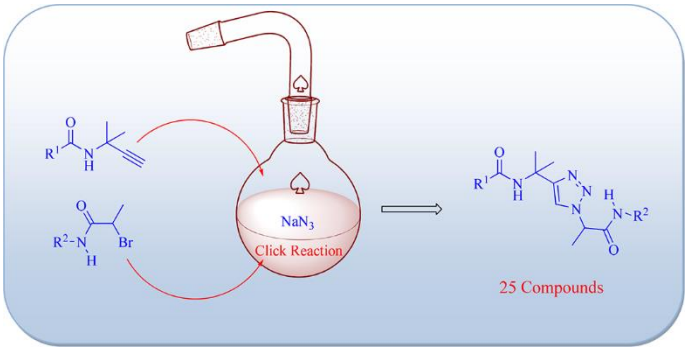
Abstract

A library of twenty five amide linked 1,4-disubstituted 1,2,3-triazoles have been prepared through a facile expeditious synthetic protocol involving Cu(I) mediated cyclization of *N*-(2-methylbut-3-yn-2-yl)aromatic amides and *in situ* generated 2-azido-*N*-substituted propanamides. Structures of newly synthesized compounds (**5a**–**5y**) were confirmed by analytical techniques like FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS. *In vitro* antifungal activity was also examined

against two fungal strains *Candida albicans* and *Aspergillus niger* by serial dilution method. The compounds **5m** and **5w** exhibited appreciable potent activity.

Graphical Abstract



KEYWORDS: 1,3-dipolar cycloaddition, 1,4-disubstitued 1,2,3-triazoles, antifungal activity, synthesis

Introduction

The triazoles constitute a class of heterocyclic compounds, which attracted the attention of medicinal chemists due to broad spectrum pharmaceutical applications. Molecules with 1,2,3-triazole entity possess anti-HIV,[1,2] anticancer,[3–5] anti-oxidant,[6,7] antibacterial,[8–10] antifungal,[11–13] antimalarial,[14–16] antitubercular,[17,18] anti-phytopathogenic[19] and anti-inflammatory[20] activities. Further, the triazole also shows several applications in material science,[21,22] bioconjugation,[23] polymer chemistry[24] and as high performance organic coatings.[25] The most remarkable features of 1,2,3-triazoles are its stability towards metabolic degradation and capablity of hydrogen bonding in living system which favors effective binding to biomolecule targets leading to appreciable biological activity.[26]

The usual method for the synthesis of disubstituted 1,2,3-triazoles through 1,3-dipolar cycloaddition of organic azides and terminal alkynes resulting to 1,4- and 1,5- isomers was initially induced by Huisgen.[27] The major limitations of this non-catalyzed pathway are high temperature condition and poor regioselectivity in products. To overcome these drawbacks Sharpless[28] and Meldal[29] introduced the Cu (I) catalyst for synthesis of substituted 1,2,3-triazoles which yields only single isomer i.e. 1,4-disubstituted 1,2,3-triazole under milder reaction conditions. Some other synthetic protocols for triazoles using nominal reaction conditions have also been reported.[30–32]

Though, in continuation of our previous work on synthesis of substituted 1,2,3-triazoles[33] we synthesized twenty five new amide linked compounds from *N*-(2-methylbut-3-yn-2-yl)aromatic amides, 2-bromo-*N*-substituted propanamides and sodium azide using copper sulphate pentahydrate as a catalyst and characterized by analytical techniques.

Further, fungal infections constitute a worldwide health problem and the number of diseases caused by pathogenic fungi is observed in humans and plants.[34,35] These infections are difficult to treat and have remarkable impacts on the crops, and often lead to significant yield reduction and economic losses in agriculture. The search for newer antifungal agents continues due to the rapid development of the resistance among fungi to the existing antimicrobial agents. In continue to this antifungal evaluation of synthesized compounds was carried out against two fungal strains viz. *C. albicans* and *A. Niger*.

Result and discussion

Chemistry

Herein we reported three component Cu (I) catalyzed one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles with two amide linkages from the reaction of 2-bromo-*N*-substituted propanamide, *N*-(2-methylbut-3-yn-2-yl) aromatic amide and sodium azide in dimethylforamide-water. *N*-(2-methylbut-3-yn-2-yl)aromatic amides **(2)** were synthesized from reaction of aromatic acid chloride **(1)** and 2-methylbut-3-yn-2-amine in the presence of 4-dimethylaminopyridine (DMAP). 2-Bromo-*N*-substituted propanamides **(4)** were synthesized from reaction of 2-bromopropanoyl bromide and aromatic amines **(3)** in the presence of potassium carbonate. The targeted disubstitited triazoles (**5a**–**5y**) were synthesized by reaction of 2-azido-*N*-substituted propanamide (generated *in situ* from reaction between 2-bromo-*N*-substituted propanamide (**4**) and sodium azide) with *N*-(2-methylbut-3-yn-2-yl)aromatic amide **(2)** in the presence of copper sulphate pentahydrate and sodium ascorbate using DMF:water as solvent.

The structures of synthesized triazoles (**5a**–**5y**) were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. In IR spectra of all the compounds characteristic absorption band observed at 3199–3132 cm^{-1} due to C–H stretching of triazole ring, 3394–3315 cm^{-1} and 3284–3207 cm^{-1} due to N-H stretching of amide linkages, 1716–1674 cm^{-1} and 1647–1618 cm^{-1} were due to C = O stretching of amide bonds.

^{1}H NMR spectra of compounds displayed two characteristic singlets in the range of δ 11.28–10.34, δ 8.72–8.14 were due to N-H protons and singlet at δ 8.16–8.01 was due to triazolyl proton. Aromatic protons appeared in the range of δ 8.30–6.90 and a single proton attached to N_1 of triazole ring appeared as quartet in range of δ 5.79–5.47. In ^{13}C NMR spectra a characteristic signal of C = O appeared in range of δ 168.8–167.2 and δ 166.5–164.9. C–4 and C–5 of triazoles ring appeared at δ 153.5–153.2 and δ 121.0–120.7 respectively. HRMS spectral

analysis of synthesized compounds was found in accordance with the theoretically predicted molecular masses.

Antifungal activity

The synthesized 1,4-disubstituted 1,2,3-triazoles (**5a**-**5y**) were examined for *in vitro* antifungal activity against two fungal strains – *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) using serial dilution method.[36] Fluconazole was used as a standard drug. The minimum inhibitory concentration (MIC) values were presented in µmol/mL (**Table 1**).

Results indicated that some of the synthesized compounds possess appreciable activity. The Compounds **5h**, **5j**, **5l**, **5m**, **5o, 5w** showed better activity in case of *C. albicans* with MIC, 0.0552, 0.0546, 0.0552, 0.0536, 0.0530 and 0.0302 µmol/mL respectively. In case of *A. niger* the compounds **5h**, **5l**, **5m**, **5o, 5w, 5y** showed moderate to good activity as evident the MIC, 0.0276, 0.0276, 0.0134, 0.0265, 0.0151 and 0.0288 µmol/mL respectively.

The activity results revealed that presence of electron withdrawing group, i.e. nitro displayed good antifungal efficiency while naphthyl group on nitrogen atom of amide linkage showed potent antifungal activity. Triazoles having thienyl moiety exhibited good activity in case of *A. niger* in comparison to furyl moiety, where as triazoles having thienyl and nitro group exhibited remarkable antifungal efficiency in comparison with the reference.

Conclusion

In summary, we have reported the one pot facile synthesis of a library of amide linked 1,4-disubstituted 1,2,3-triazoles from the click reaction of *N*-(2-methylbut-3-yn-2-yl)aromatic amide and 2-azido-*N*-substituted propanamides (synthesized *in situ* from reaction of 2-bromo-*N*-

substituted propanamides and sodium azide). The synthesized compounds were characterized by various analytical techniques viz. FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS. Antifungal evaluation of compounds was carried out by two fungal strains *C. albicans* and *A. niger*. The compound **5m** and **5w** exhibited persuasive activity.

Experimental

Material and methods

All chemicals used in the synthesis were purchased from Alfa-Aesar, Sigma-Aldrich, Hi-media, Qualigens and used without purification. The progress of the reactions was monitored by thin layer chromatography. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a SHIMADZU IR AFFINITY-I FT-IR spectrophotometer using KBr powder and the values are expressed in cm^{-1}. The ^{1}H and ^{13}C NMR spectra of the synthesized molecules were recorded at 400 MHz and 100 MHz, respectively, using Bruker Avance II 400 MHz NMR spectrometer in DMSO-d_6 solvent, and the chemical shifts were expressed in δ and coupling constants (J) in Hz. Splitting patterns were indicated as s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quartet, m: multiplet. HRMS were obtained on Waters Micromass Q-Tof Micro (ESI) spectrophotometer and values were quoted in *m/z*.

Typical procedure for the synthesis of N-(2-(1-(1-oxo-1-(phenylamino)propan-2-yl)-1H-1,2,3-triazol-4-yl)propan-2-yl)benzamide

The starting reactant *N*-(2-methylbut-3-yn-2-yl)benzamide (**2a**) was synthesized from reaction of benzoyl chloride (1.0 mmol) and 2-methylbut-3-yn-2-amine in the presence of 4-

dimethylaminopyridine (DMAP) in dry dichloromethane with continuous stirring at 0–10 ºC for 3–4 h. 2-Bromo-*N*-phenyl propanamide (**4a**) was synthesized by drop wise addition of 2-bromopropanoyl bromide (1.2 mmol) to aniline (1.0 mmol) using dichloromethane as solvent in the presence of potassium carbonate at 0–5 ºC for 15–20 minutes. Further for synthesis of *N*-(2-(1-(1-oxo-1-(phenylamino)propan-2-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzamide (**5a**), 2-bromo-*N*-phenyl propanamide (1.0 mmol) was dissolved in dimethylformamide in a round bottom flask, aqueous sodium azide (3.0 mmol) was added and stirred for 30 min at 40–50 ºC. To the above mixture *N*-(2-methylbut-3-yn-2-yl)benzamide (1.0 mmol), aqueous copper sulphate pentahydrate (0.1 mmol) and sodium ascorbate (0.4 mmol) were added and stirring was continued for 12 h at same temperature. After completion of reaction, ice cold water was added to reaction mixture. Precipitated product was filtered and washed with ammonia solution and then with water. Crude product was washed with ethyl acetate and dried under vacuum to get desired product (**5a**) in good yield.

N-(2-(1-(1-oxo-1-(phenylamino)propan-2-yl)-1H-1,2,3-triazol-4-yl)propan-2-yl)benzamide

Yield 83% as white solid; m.p.164–168 ºC; IR (KBr), ν (cm^{-1}): 3394, 3253 (N-H amide str.), 3124(C-H str. triazole), 3041(C-H str. aromatic ring), 2983(C-H str., aliphatic), 1681, 1635 (C = O str. amide); ^{1}H NMR (400 MHz, DMSO): δ 10.48 (s, 1H, N-H amide), 8.32 (s, 1H, N-H amide), 8.06 (s, 1H, C-H triazole), 7.83 (d, 2H, ArH, J = 8.0 Hz), 7.60 (d, 2H, ArH, J = 8.0 Hz), 7.51 (t, 1H, ArH, J = 8.0 Hz), 7.44 (t, 2H, ArH, J = 8.0 Hz), 7.33 (t, 2H, ArH, J = 8.0 Hz), 7.10 (t, 1H, ArH, J = 8.0 Hz), 5.52 (q, 1H, J = 8.0 Hz), 1.77 (d, 3H, J = 8.0 Hz), 1.74 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 167.7, 166.4, 153.4, 138.8, 135.8, 131.4, 129.1, 128.5, 127.9, 124.4,

120.7, 119.9, 59.2, 51.5, 28.9, 18.3. HRMS [M + H] + for $C_{21}H_{23}N_5O_2$ calc: 378.1852, found:. 378.1925.

General procedure for in vitro Antifungal activity

The newly synthesized 1,4-disubstituted 1,2,3-triazoles (**5a**–**5y**) were studied for antifungal activity against *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) by serial dilution method using a stock solution of 100 µg/mL concentration. Sabouraud dextrose was employed as culture media. Dimethylsulfoxide was used as solvent control. Fluconazole was used as standard drug for fungal activity assay. The stock solutions of the test compounds and standard drug were serially diluted to get the concentration of 50–3.12 µg/mL and then inoculated with suspension of respective microorganism in sterile saline. The inoculated test tubes were incubated at 25 ºC in case of *C. albicans* for 48 h and at 25 ºC for 120 h in case of *A. niger*. Antifungal potential of synthesized triazoles was assessed in terms of minimum inhibitory concentration of microbial growth.

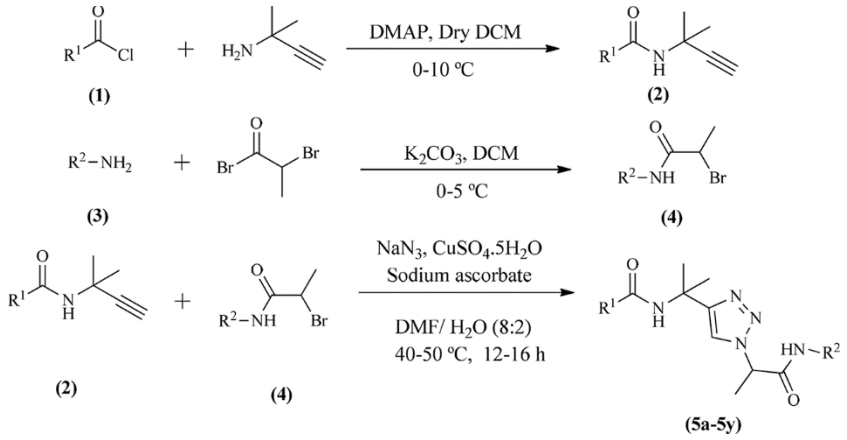
References

Table 1. Antifungal activity of 1,4-disubstituted 1,2,3-triazoles (**5a**–**5y**) (MIC in μmol/mL)

Compound	*C. albicans* (MTCC 227)	*A. niger* (MTCC 282)
5a	0.1324	0.0662
5b	0.0613	0.0613
5c	0.0591	0.0591
5d	0.0632	0.0632
5e	0.0584	0.0584
5f	0.0613	0.0613
5g	0.0571	0.0571
5h	0.0552	0.0276
5i	0.0587	0.0587
5j	0.0546	0.0546
5k	0.0591	0.0591
5l	0.0552	0.0276
5m	0.0536	0.0134
5n	0.0566	0.0283
5o	0.0530	0.0265
5p	0.0680	0.0340

5q	0.0628	0.0314
5r	0.0606	0.0303
5s	0.0648	0.0324
5t	0.0598	0.0299
5u	0.0650	0.0325
5v	0.0582	0.0291
5w	0.0302	0.0151
5x	0.0622	0.0311
5y	0.0576	0.0288
Fluconazole	0.0408	0.0102

Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles (5a–5y).



Compound No.	R^1	R^2	Reaction Time (h)	Yield %
5a	C_6H_5	C_6H_5	12	83
5b	C_6H_5	4-$CH_3OC_6H_4$	14	91
5c	C_6H_5	4-$NO_2C_6H_4$	12	87
5d	C_6H_5	4-FC_6H_4	16	82
5e	C_6H_5	α-$C_{10}H_7$	16	78
5f	4-$CH_3OC_6H_4$	C_6H_5	12	84
5g	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	15	92
5h	4-$CH_3OC_6H_4$	4-$NO_2C_6H_4$	16	84
5i	4-$CH_3OC_6H_4$	4-FC_6H_4	12	87
5j	4-$CH_3OC_6H_4$	α-$C_{10}H_7$	14	81

5k	4-$NO_2C_6H_4$	C_6H_5	13	88
5l	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	12	86
5m	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	14	92
5n	4-$NO_2C_6H_4$	4-FC_6H_4	15	89
5o	4-$NO_2C_6H_4$	α-$C_{10}H_7$	15	84
5p	C_4H_3O	C_6H_5	14	86
5q	C_4H_3O	4-$CH_3OC_6H_4$	16	83
5r	C_4H_3O	4-$NO_2C_6H_4$	13	88
5s	C_4H_3O	4-FC_6H_4	12	84
5t	C_4H_3O	α-$C_{10}H_7$	15	91
5u	C_4H_3S	C_6H_5	14	90
5v	C_4H_3S	4-$CH_3OC_6H_4$	14	88
5w	C_4H_3S	4-$NO_2C_6H_4$	13	92
5x	C_4H_3S	4-FC_6H_4	14	94
5y	C_4H_3S	α-$C_{10}H_7$	16	86