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ARTICLE

Design, Synthesis and Biological Screening of Novel 1,2,4-Triazoles Employing Suzuki-Miyaura Coupling Reaction

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ABSTRACT

The present work describes the synthesis and biological evaluation of substituted 1,2,4-triazole derivatives. Synthesis is carried out by the condensation reaction of benzothiamide derivative with 2,2,2-trifluoroacetohydrazide to give 1,2,4-triazole, which was further modified by N-alkylation and Suzuki–Miyaura coupling reaction. Furthermore, the characterization of the product is carried out by elemental analysis and spectral analysis. Products were evaluated for their *in vitro* biological assay for antibacterial activity against various bacterial standard strains, *i.e. Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes*-MTCC-443, two Gram-negative bacteria *Escherichia coli* MTCC-442, *Pseudomonas aeruginosa*-MTCC-441 and three fungal strains *Candida albicans* MTCC-227, *Aspergillus niger* MTCC-282, *Aspergillus clavatus* MTCC-1323 at different concentrations and the results were compared with standard drugs.

KEYWORDS

Triazole, Methylation, N-Butylation, Suzuki–Miyaura coupling, Solvent, Spectroscopy.

INTRODUCTION

A literature survey revealed that various 1,2,4-triazole derivatives display significant biological activities such as bactericidal [1], diuretic [2], fungicidal [3], herbicidal [4], insecticidal and acaricidal [5], plant growth regulator [6], anticancer [7], 5-lipoxygenase inhibitors [8] and anti-HIV [9], antileshmanial [10], antitumor [11] activities. Platinum(II) complexes comprising 1,2,4-triazoles as ligands show antitumor activity similar to cisplatin [12]. Furthermore, ruthenium(III) complexes of 1,2,4-triazoles are promising as potential drugs in anticancer treatment as alternative to the approved platinum-based anticancer drugs [13]. 1,2,4-Triazoles such as rizatriptan as agents for acute treatment of migraine headaches are commercially available drugs [14]; however, they are still a topic of intensive research [1].

Keeping in mind the pharmacological applications of this class of compounds and with a view to further assess the pharmacological profile of this class of compounds, the present section incorporates synthesis of 30 novel analogues of 1,2,4-triazole derivatives.

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EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots visualization was made with UV light (254 and 365 nm) or with an iodine vapour. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using the KBr pellet method. Mass spectra were recorded on the Shimadzu GCMS-QP-2010 model using a direct injection probe technique. ^{1}H NMR and ^{13}C NMR were determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analyses of all the synthesized compounds were carried out on the Elemental Vario EL III Carlo Erba 1108 model and the results are in agreement with the structures assigned.

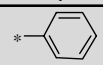
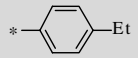
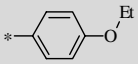
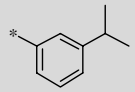
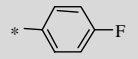
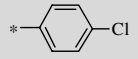
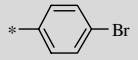
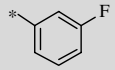
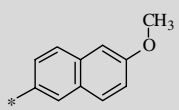
General procedure: In the first step, 4-bromobenzothioamide (Int-1) was prepared from 4-bromobenzonitrile by stirring with sodium hydrogen sulphide and magnesium chloride in DMF, which followed by methylation afforded the S-methyl benzothioamide derivative (Int-2). The condensation of Int-2 and 2,2,2-trifluoroacetohydrazide at 150 °C in DMF afforded 3-(4-bromophenyl)-5-(trifluoromethyl)-1*H*-1,2,4-triazole (Int-3) in good yield, which was subjected to N-butylation at 100 °C in DMF presence of K_2CO_3 base to afford 3-(4-bromophenyl)-1-butyl-5-(trifluoromethyl)-1*H*-1,2,4-triazole (Int-4). In the final step, (Int-4) was subjected to the Suzuki–Miyaura reaction with various arylboronic acids in the presence of palladium catalyst, TBAB, K_2CO_3 and DMF:water as a solvent at 120 °C to afford the final product 3-([1,1'-biphenyl]4-yl)-1-butyl-5-(trifluoro methyl)-1*H*-1,2,4-triazole **(P116)** in moderate to high yield (**Scheme-I**). The structures of all the newly substituted triazole derivatives were identified by mass, IR, ^{1}H NMR, ^{13}C spectroscopy and their physico-chemical data is given in Table-1.

1-Butyl-3-(4'-ethyl[1,1'-biphenyl]-4-yl)-5-(trifluoromethyl)-1*H*-1,2,4-triazole (P 117): Yield = 85 %, m.p. 137–139 °C; IR (KBr, ν_{max}, cm^{-1}): 3088, 2960, 2877, 1438, 1340, 1166, 1123, 893 ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.66–1.01 (t, 6H), 1.25–1.44 (m, 4H), 1.88–1.95 (m, 2H), 4.14–4.22 (t, 2H), 7.54–7.56 (d, 4H, Ar–H), 7.95–7.97 (d, 2H, Ar–H); ^{13}C NMR ($CDCl_3$) δ:14.55, 15.71, 19.78, 28.95, 33.59, 50.12, 122.13, 125.33, 128.12, 132.12, 138.46, 142.14, 142.82, 143.20, 143.44, 161.37; MS (*m/z*): 373, Anal. calcd. for $C_{21}H_{22}N_3F_3$: C, 67.55; H, 5.94; F, 15.26; N, 11.25 %; Found: C, 67.05; H, 5.71; F, 14.97; N, 11.02 %.

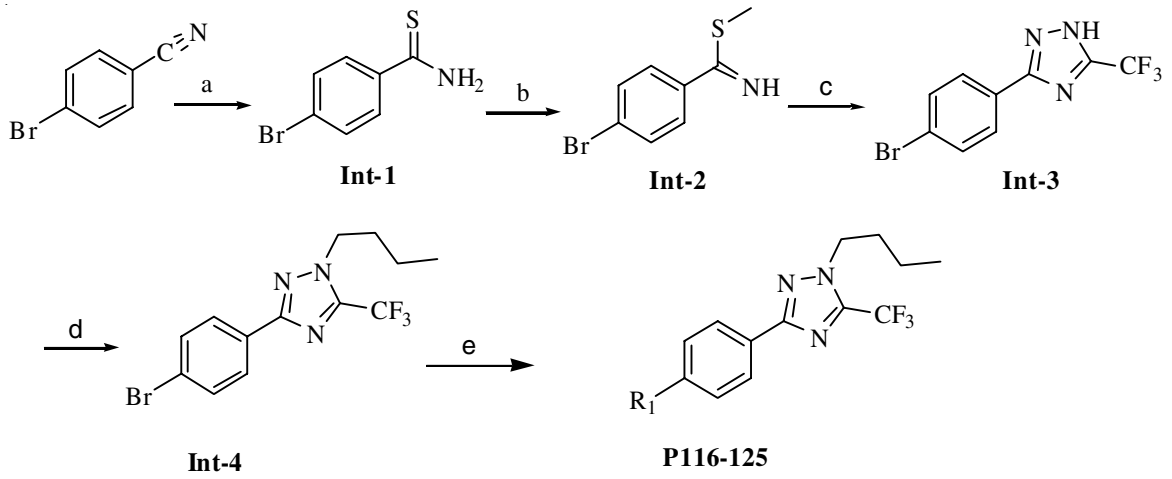
1-Butyl-3-(4'-ethoxy[1,1'-biphenyl]-4-yl)-5-(trifluoromethyl)-1H-1,2,4-triazole (P118): Yield = 79 %, m.p. 139–141 °C; IR (KBr, ν_{max}, cm^{-1}): 3036, 2962, 2875, 1599, 1510, 1431, 1338, 1259, 1166, 1128, 839, 510; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.95–0.99 (t, 3H), 1.26–1.29 (t, 3H), 1.33–1.42 (m, 2H), 1.89–1.91 (m, 2H), 2.67–2.73 (q, 2H), 4.18-4.22 (t, 2H), 7.29–7.31 (d, 2H, Ar–H), 7.60–7.62 (d, 2H), 7.72–7.74 (d, 2H), 7.89–7.91 (d, 2H, Ar–H); 13C NMR ($CDCl_3$) δ: 13.8, 14.8, 19.9, 30.8, 44.6, 64.7, 113.2, 114.9, 128.0, 128.4, 128.5, 129.6, 136.5, 156.4, 160.0, 164.0; MS (*m/z*): 375, Anal. calcd. for $C_{21}H_{22}N_3OF_3$: C, 64.77; H, 5.69; F, 14.64; N, 10.79; O, 4.11 %; Found: C, 64.11; H, 5.60; F, 14.22; N, 10.42; O, 4.03 %.

3-(4'-Bromo[1,1'-biphenyl]-4-yl)-1-butyl-5-(trifluoromethyl)-1*H*-1,2,4-triazole (P122): Yield = 91 %, m.p. 135–137 °C; IR (KBr, ν_{max}, cm^{-1}): 2960, 2870, 1602,1600, 1462, 1307, 1168, 1217, 889, 589 ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.96–1.00(t, 3H), 1.20–1.36 (m, 2H), 1.94–2.05 (m, 2H),

TABLE-1
PHYSICAL PARAMETERS

Compounds	Substituents	R_1	m.f.	m.w.	m.p. (°C)	Yield (%)	R_f
P116	4-Br		$C_{19}H_{18}N_3F_3$	345	131-133	89	0.58
P117	4-Br		$C_{21}H_{22}N_3F_3$	373	137-139	85	0.63
P118	4-Br		$C_{20}H_{20}N_3OF_3$	375	139-141	79	0.61
P119	4-Br		$C_{22}H_{24}N_3F_3$	389	157-159	77	0.64
P120	4-Br		$C_{19}H_{17}N_3F_4$	363	129-131	83	0.55
P121	4-Br		$C_{19}H_{17}N_3ClF_3$	380	151-152	78	0.57
P122	4-Br		$C_{19}H_{17}N_3BrF_3$	424	135-137	91	0.58
P123	4-Br		$C_{19}H_{17}N_3F_4$	363	131-133	81	0.59
P124	4-Br		$C_{17}H_{16}N_3SF_3$	351	145-147	86	0.66
P125	4-Br		$C_{24}H_{22}N_3OF_3$	346	176-178	77	0.59

TLC solvent system R_f: Ethyl acetate:Hexane – 4:6.



R_1 = Various substituted boronic acid

Reagents & Conditions: (a) MgC_2, NaSH and DMF at room temperature for 2 h; (b) MeI, diethyl ether at 0 °C to room temperature for 10 h; (c) Trifluoromethylaceto hydrazide in DMF reflux for 6 h; (d) *n*-Butyl bromide, K_2CO_3, DMF reflux for 3 h; (e) Aryl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, TBAB in DMF/water at 120 °C for 3 h.

Scheme-I

4.20–4.23 (t, 2H), 7.2–7.24 (d, 2H, Ar–H), 7.62–7.64 (d, 2H, Ar–H), 7.86–7.88 (d, 2H, Ar–H), 8.00–8.20 (d, 2H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 13.8, 19.9, 30.9, 44.7, 122.0, 126.02, 128.40, 129.01, 132.25, 137.50, 142.08, 142.97, 143.20, 162.05, 163.0 MS (*m/z*): 424, Anal. calcd. for $C_{19}H_{17}N_3BrF_3$: C, 53.79; H, 4.04; Br, 18.83; F, 13.43; N, 9.90 %; Found: C, 52.78; H, 3.97; Br, 18.62; F, 13.05; N, 9.53 %.

RESULTS AND DISCUSSION

All the synthesized compounds **(P116–P125)** were tested for their antibacterial and antifungal activity (MIC) *in vitro* by the broth dilution method [15-17] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes*-MTCC-443, two Gram-negative bacteria *Escherichia coli* MTCC-442, *Pseudomonas aeruginosa*-MTCC-441 and three fungal strains *Candida albicans* MTCC-227, *Aspergillus niger* MTCC-282, *Aspergillus clavatus* MTCC-1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs (Table-2). The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards [15].

Conclusion

In the present article, we report the synthesis, spectral studies, antibacterial and antifungal activities of a novel series of 1,2,4-

TABLE-2
MICROBIAL ACTIVITIES OF SYNTHESIZED COMPOUNDS

Compounds	Minimum inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	Staphylococcus aureus MTCC-96	*Streptococcus pyogenes* MTCC-443	*Escherichia coli* MTCC-442	*Pseudomonas aeruginosa* MTCC-441	*Candida albicans* MTCC-227	*Aspergillus niger* MTCC-282	*Aspergillus clavatus* MTCC-1323
P116	1000	250	500	250	1000	250	100
P117	62.5	100	250	100	500	250	100
P118	500	1000	1000	100	>1000	>1000	250
P119	1000	250	500	250	1000	250	100
P120	250	500	500	250	>1000	500	250
P121	1000	250	500	250	1000	250	100
P122	250	500	500	250	>1000	500	250
P123	62.5	100	250	100	500	250	100
P124	500	1000	1000	100	>1000	>1000	250
P125	62.5	100	100	200	500	250	100
Ampicillin	250	100	100	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	50	50	25	25	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Griseofulvin	–	–	–	–	500	100	100

triazole scaffold. The preliminary *in vitro* biological activities revealed that compounds **P117, P123** and **P124** exhibited moderate antibacterial activities. The results obtained from antimicrobial susceptibility testing are depicted in Table-2.

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