© 2017 IJSRSET | Volume 3 | Issue 8 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section : Engineering and Technology

Synthesis of new 1,2,4-Triazole derivatives and their Antimicrobial Screening

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ABSTRACT

Present work illustrates synthesis and biological evaluation of substituted 1,2,4 trizole derivatives. Synthesis carried out by condensation reaction of benzothiamide derivative with 2,2,2-trifluoroacetohydrazide to give 1,2,4-triazole, which further modified by N-alkylation and Suzuki miyaura coupling reaction. Furthermore, the characterization of 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. S. pyogenes MTCC-442, S. aureus MTCC-96, E. coli MTCC-443, and B. subtilis MTCC-441 and antifungal activity against Aspergillus niger MTCC-282 and Candida albicans MTCC-227 at different concentrations, results were compared with standard drugs.

Keywords : Triazole, methylation, N-butylation, Suzuki-Miyaura coupling, solvent, spectroscopy

I. INTRODUCTION

Literature survey reveals that various 1,2,4-triazole derivatives display significant biological activities such as bactericidal,7 diuretic,8 fungicidal,9 herbicidal,10 insecticidal and acaricidal,11 plant growth regulator,12 anticancer,2 5-lipoxygenase inhibitors1 and anti-hiv,13 antileshmanial,14 antitumor15 activities. Platinum(II) complexes comprising 1,2,4-triazoles as ligands show antitumor activity similar to cis-platin.3 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.4 1,2,4-Triazoles such as rizatriptan as agents for acute treatment of migraine headaches are commercially available drugs;5 however, they are also still a topic of intensive research.[7]

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 thirty novel analogues of 1,2,4-triazole derivatives.

II. MATERIALS AND METHODS

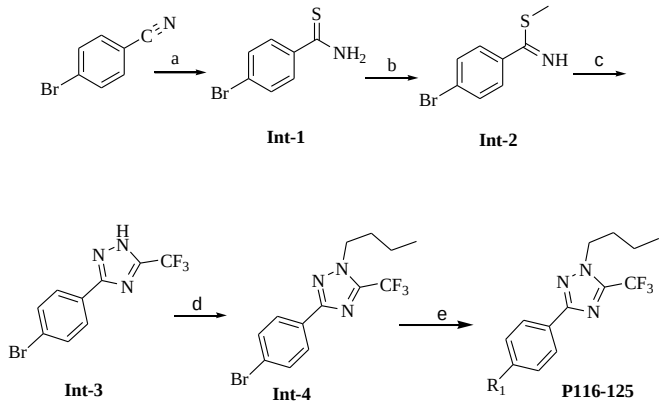
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by UV and iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using 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.

A. General Synthesis

In first step, 4-bromobenzothioamide (Int-1) was prepared from 4-bromobenzonitrile by stirring with sodium hydrogensulphide and magnesium chloride in DMF, which followed by methylation afforded the S-methyl benzothioamide derivative (Int-2). The condensation of S-methyl benzothioamide derivative (Int-2) and 2,2,2-trifluoroacetohydrazide at 150oC in DMF afforded 3-(4-bromophenyl)-5-(trifluoromethyl)-1H-1,2,4-triazole (Int-3) in good yield, which was subjected to N-butylation at 100oC in DMF presence of K_2CO_3 base to afford 3-(4-bromophenyl)-1-butyl-5-(trifluoromethyl)-1H-1,2,4-triazole (Int-4). In the final

step, (Int-4) was subjected to Suzuki-Miyaura reaction with various aryl boronic acids in the presence of palladium catalyst, TBAB, K_2CO_3 and DMF:water as a solvent at 120o C to afford the final products 3-([1,1'-biphenyl]4-yl)-1-butyl-5-(trifluoro methyl)-1H-1,2,4-triazole (P116-P125) in moderate to high yield. The structures of all newly substituted-triazole derivatives were identified by Mass, IR, ^{1}H NMR, ^{13}C spectroscopy.

B. Reaction Scheme



R_1= Various substituted Boronic acids

Reagents & Conditions: (a) $MgCl_2$, NaSH and DMF at r.t. for 2 h.,
(b) MeI , Diethyl ether at 0 ^{o}C to r.t. for 10 h.,
(c) trifluoromethylaceto hydrazide in DMF at reflux for 6 h.,
(d) n-Butyl Bromide, K_2CO_3, DMF at reflux for 3 h.,
(e) Aryl boroniacid, $Pd(PPh_3)_4$, K_2CO_3, TBAB in DMF/Water at 120^o C for 3 h.

Figure 2

C. Physical Parameters of Synthesized Compounds (Depicted Table 1.)

III. RESULTS AND DISCUSSION

A. Spectral Data

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) 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 $C_{21}H_{22}F_3N_3$: 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) 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); ^{13}C 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 $C_{21}H_{22}F_3N_3O$: 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) 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), 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 $C_{19}H_{17}BrF_3N_3$: 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%

B. Biological Evaluation

The synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method[16-18] 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, Aspergillusclavatus MTCC-1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. 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[16].

IV. CONCLUSIONS

In the present article, we report the synthesis, spectral studies, antibacterial and antifungal activities of a novel series of 1,2,4 triazole scaffold. The preliminary in vitro biological activities revealed that compounds **P17, P23** and **P24** exhibited moderate antibacterial activities. The results obtained from antimicrobial susceptibility testing are depicted in **Table2.**

Table 1

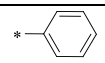
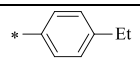
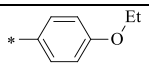
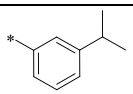
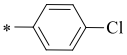
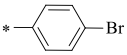
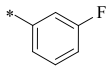
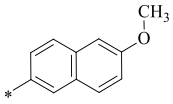
Code	R	R_1	MF	MW	MP	Yield	R_f
P16	4-Br		$C_{19}H_{18}F_3N_3$	345	131-133	89	0.58
P17	4-Br		$C_{21}H_{22}F_3N_3$	373	137-139	85	0.63
P18	4-Br		$C_{20}H_{20}F_3N_3O$	375	139-141	79	0.61
P19	4-Br		$C_{22}H_{24}F_3N_3$	389	157-159	77	0.64
P20	4-Br		$C_{19}H_{17}F_4N_3$	363	129-131	83	0.55
P21	4-Br		$C_{19}H_{17}ClF_3N_3$	380	151-152	78	0.57
P22	4-Br		$C_{19}H_{17}BrF_3N_3$	424	135-137	91	0.58
P23	4-Br		$C_{19}H_{17}F_4N_3$	363	131-133	81	0.59
P24	4-Br		$C_{17}H_{16}F_3N_3S$	351	145-147	86	0.66
P25	4-Br		$C_{24}H_{22}F_3N_3O$	346	176-178	77	0.59

Table 2, Antibacterial and antifungal activity of synthesized compounds.

Compounds	Minimum inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
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

V. REFERENCES

[1]. Mano, T.; Stevens, R. W.; Okumura, Y.; Kawai, M.; Okumura, T.; Sakakibara, M. *Bioorganic & medicinal chemistry letters* 2005, *15*, **2611.**

[2]. Matesanz, A. I.; Joie, C.; Souza, P. *Dalton Transactions* **2010**, *39*, 7059.

[3]. Shivarama Holla, B.; Veerendra, B.; Shivananda, M.; Poojary, B. *European journal of medicinal chemistry* **2003**, *38*, 759.

[4]. Groessl, M.; Reisner, E.; Hartinger, C. G.; Eichinger, R.; Semenova, O.; Timerbaev, A. R.; Jakupec, M. A.; Arion, V. B.; Keppler, B. K. *Journal of medicinal chemistry* **2007**, *50*, 2185.

[5]. Dahlof, C.; Lines, C. *Expert opinion on investigational drugs* **1999**, *8*, 671.

[6]. Sternfeld, F.; Baker, R.; Broughton, H. B.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Stanton, J. A.; Hargreaves, R. J. *Bioorganic & medicinal chemistry letters* **1996**, *6*, 1825.

[7]. Janam, S. R.; Kumar, S. D. *E-Journal of Chemistry* **2010**, 7, 37.

[8]. Kaplaushenko, A. G.; Panasenko, A. I.; Knysh, E. G.; Svintozelsky, A. A.; *Farmatsevtichnii Zhurnal (Kiev, Ukraine)* **2008**, 4, 57.

[9]. Xu, L.-z.; Zhang, S.-s.; Hu, Z.-q.; Jiao, K. *Chemical research in chinese universities* **2003**, *19*, 310.

[10]. Gyu, H. H.; Dal, N. G.; Yun, S. D.; Taek, H. I.; Seop, C. J.; Yeong, S. H.; Jin, C. S.; Hui, L. D.; Jin, K. G.; Mok, P. G. *Repub. Korean Kongkae Taeho Kongbo* **2009**, 34.

[11]. Hull Jr, J. W.; Romer, D. R.; Adaway, T. J.; Podhorez, D. E. *Organic Process Research & Development* **2009**, *13*, 1125.

[12]. Churilov, I. S.; Popkov, S. V.; Grishina, A. A.; Chembarova, E. V.; Mironova, O. Y.; *Khimicheskaya Promyshlennost Segodnya* **2008**, *8*, 31.

[13]. Rida, S. M.; El-Hawash, S. A.; Fahmy, H. T.; Hazzaa, A. A.; El-Meligy, M. M. *Archives of pharmacal research* **2006**, *29*, 826.

[14]. Van Der Meide, W. F.; Sabajo, L. O.; Jensema, A. J.; Peekel, I.; Faber, W. R.; Schallig, H. D.; Fat, R. F. *International journal of dermatology* **2009**, *48*, 52.

[15]. Qian, G.; Chun-ling, Z.; Wei-wei, F.; Ju-zheng, F. *Huaxi Yaoxue Zazhi* **2009**, *24*, 475.

[16]. National Committee for Clinical and Laboratory Standards, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, fourth ed. NCCLS, Villanova, Italy, 1997, *Document M 100-S7*. S100-S157.

[17]. D.H. Isenberg, Essential Procedure for Clinical Microbiology, American Society for Microbiology, Washington, (**1998).**

[18]. Zgoda, J. R.; Porter, J. R. *Pharmaceutical* ***Biology*** **2001**, *39*, 221.