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# Synthesis and Biological Assessment of New 1,2,4-Triazole Derivatives

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## Research Article

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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.

## INTRODUCTION

Literature survey reveals 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 *cis*-platin. [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 also still a topic of intensive research [15]. 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.

## EXPERIMENTAL

### 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 spotsvisualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GCMS-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. Elemental analyses of the all the synthesized compounds were carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreement with the structures assigned.

### General Procedure

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 150°C 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 100°C 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)

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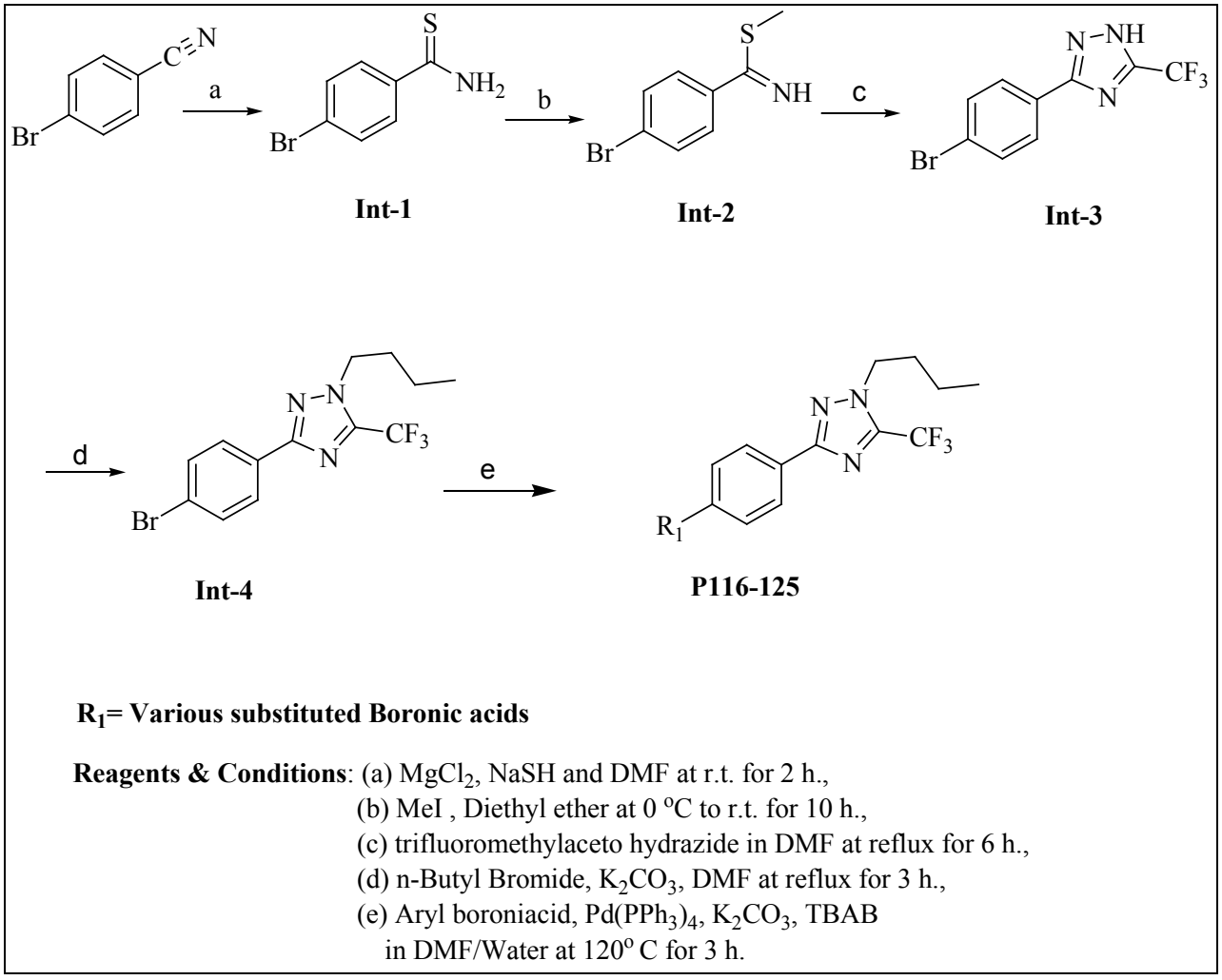
was subjected to Suzuki-Miyaura reaction with various aryl boronic acids in the presence of palladium catalyst, TBAB, $K_2CO_3$ and DMF:water as a solvent at 120°C to afford the final products 3-([1,1'-biphenyl]4-yl)-1-butyl-5-(trifluoro methyl)-1H-1,2,4-triazole **(P116-P125)** in moderate to high yield.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




**1-butyl-3-(4'-ethyl[1,1'-biphenyl]-4-yl)-5-(trifluoromethyl)-1H-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); 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 $C_{21}H_{22}F_3N_3O$: 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)-1H-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%

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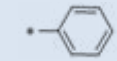
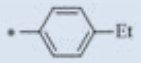
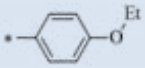
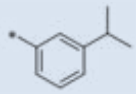
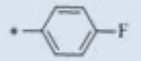
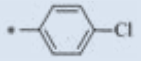
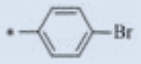
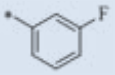
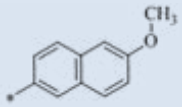
**Table 1.** Physical parameters TLC Solvent system Rf: Ethyl acetate:Hexane–4:6.

| Code | R | $R_1$ | M.F. | M.W. | M.P. | Yield | $R_f$ |
|---|---|---|---|---|---|---|---|
| P116 | 4-Br |  | $C_{19}H_{18}F_3N_3$ | 345 | 131-133 | 89 | 0.58 |
| P117 | 4-Br |  | $C_{21}H_{22}F_3N_3$ | 373 | 137-139 | 85 | 0.63 |
| P118 | 4-Br |  | $C_{20}H_{20}F_3N_3O$ | 375 | 139-141 | 79 | 0.61 |
| P119 | 4-Br |  | $C_{22}H_{24}F_3N_3$ | 389 | 157-159 | 77 | 0.64 |
| P120 | 4-Br |  | $C_{19}H_{17}F_4N_3$ | 363 | 129-131 | 83 | 0.55 |
| P121 | 4-Br |  | $C_{19}H_{17}ClF_3N_3$ | 380 | 151-152 | 78 | 0.57 |
| P122 | 4-Br |  | $C_{19}H_{17}BrF_3N_3$ | 424 | 135-137 | 91 | 0.58 |
| P123 | 4-Br |  | $C_{19}H_{17}F_4N_3$ | 363 | 131-133 | 81 | 0.59 |
| P124 | 4-Br |  | $C_{17}H_{16}F_3N_3S$ | 351 | 145-147 | 86 | 0.66 |
| P125 | 4-Br |  | $C_{24}H_{22}F_3N_3O$ | 346 | 176-178 | 77 | 0.59 |

## RESULTS AND DISCUSSION

All the synthesized compounds **(P116-P125)** 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, *Aspergillus clavatus* 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 results obtained from antimicrobial susceptibility testing are depicted in **Tables 1 and 2**.

**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 |

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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].

## CONCLUSION

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 P117, P123 and P124 exhibited moderate antibacterial activities.

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