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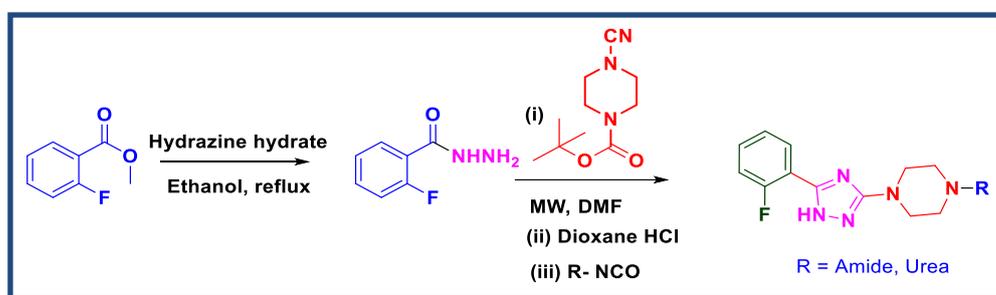
Microwave Assisted Synthesis of 3, 5-Disubstituted 1, 2, 4-Triazole Based Piperazine Amide and Urea Derivatives

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Abstract: We reported here the microwave assisted synthesis of 3,5-disubstituted 1,2,4-triazole based piperazine amide and urea derivatives with very good yield under mild reaction conditions.



How to cite this paper: Vaithiyalingam, D., Nelson, M., Chinnamadhayan, M., & Ayyanar, S. (2021). Microwave Assisted Synthesis of 3, 5-Disubstituted 1, 2, 4-Triazole Based Piperazine Amide and Urea Derivatives. *Online Journal of Chemistry*, 1(1), 7–17. DOI: 10.31586/ojc.2021.010102. Retrieved from <https://www.scipublications.com/journal/index.php/ojc/article/view/39>

Received: June 2, 2021
Accepted: July 16, 2021
Published: July 17, 2021



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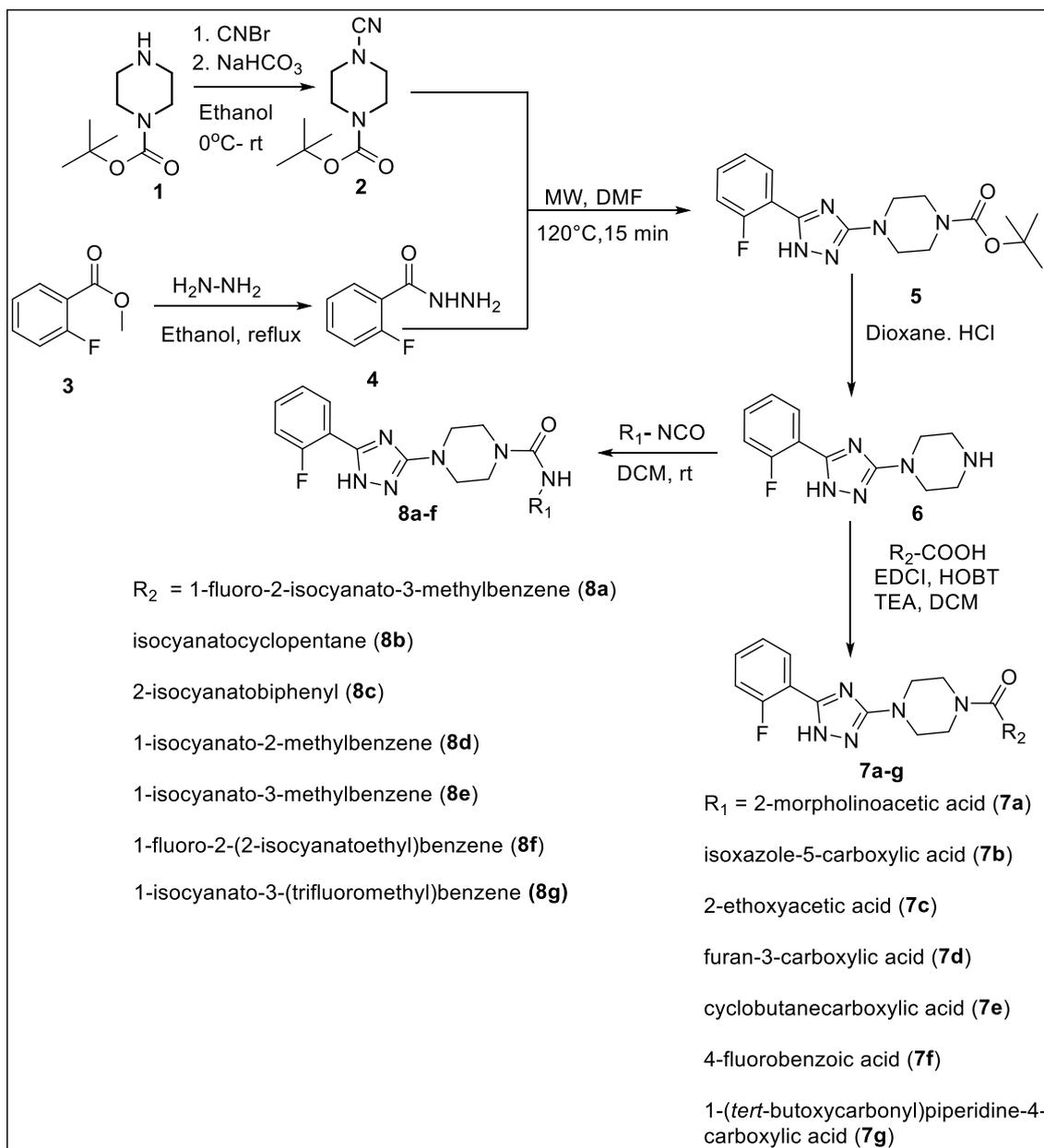
Keywords: Triazole, piperazine, urea, microwave

1. Introduction

Substituted 1,2,4-triazole and its derivatives have gained a considerable interest of the medicinal chemist in search for the new drugs. Because 1,2,4-triazoles are key skeletons of many biologically active molecules and exhibits versatile applications like pesticides, medicines, organocatalysts and functional materials [1,2]. Based on the high importance of this scaffold, the development of methods for its synthesis has been a focus in organic chemistry [3]. Previously, 1,2,4-triazole derivatives were prepared from the *N*-acyl amidrazones obtained from hydrazines and carboxylic acid derivatives by intramolecular cyclization [4]. However, the major drawback of this method is tedious synthetic procedures and low yields. Therefore, the development of a simple and efficient procedure to prepare 1,2,4-triazole derivatives is still essential. Recently, the transition-metal catalyzed synthesis of 1,2,4-triazoles from readily available starting materials were reported with low yield and harsh conditions [5]. Subsequently, Yeung synthesized 1,2,4-triazoles using a convenient and efficient one-pot synthesis of by condensation of nitriles and hydrazides in presence of base [6]. In 2009, Nagasawa's group reported copper-catalyzed synthesis of 1,2,4-triazole derivatives via coupling of amidines with nitriles [7], which was the first example of the synthesis of 1,2,4-triazole derivatives using transition-metal. In 2014, Huang group report the synthesis of trisubstituted 1,2,4-triazole by a new 1,3-dipolar cycloaddition between oxime and hydrazonoyl chloride under basic condition [8]. In the same year, Beifuss's group reported the synthesis of symmetrically substituted 3,5-diaryl-1,2,4-triazoles using a novel and efficient copper-catalyzed reaction between imidates and ammonium carbonate [9]. A more recent report has shown that nitriles and

hydroxylamine can also form 1,2,4-triazoles [10]. Kalita *et al.*, have developed iodine mediated metal free synthesis of symmetrical and unsymmetrical 3,5-disubstituted-1*H*-1,2,4-triazole derivatives from amidines and imidates [11].

Here, we report the direct reaction between piperazine substituted nitrile and hydrazide under microwave condition for the efficient synthesis of the intermediate (3,5-substituted 1,2,4-triazoles) with good yield and very less reaction time (Scheme 1). Further, we synthesized a series of various urea derivatives with the use of this intermediate.



Scheme 1. Synthetic route of 3,5-substituted 1,2,4-triazole based urea and amide derivatives.

2. Experimental section

2.1. Materials and methods

All the chemicals and reagents were used in this work as an analytical grade. N-BOC piperazine, cyanogen bromide, 2-fluoro methyl benzoate, 2-isocyanato 1,1-biphenyl, 2-

fluoro isocyanate, 3-methyl isocyanate, 3-methyl isocyanate, 1-fluoro-2-isocyanato-3-propyl benzene, 4-chloro phenyl isocyanate, 2-chloro phenyl isocyanate and 4-methoxy phenyl isocyanate were purchased from Sigma Aldrich. Isocyanatocyclopentane, cyclohexyl isocyanate 1-Naphthyl isocyanate, 3-trifluoromethyl phenyl isocyanate were purchased from Alfa Aesar and copper sulphate, hydrazine hydrate and sodium bicarbonate were obtained from Merck and all the solvents were obtained from laboratory grade.

The melting points were measured in open capillary tubes and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard, CDCl_3 and DMSO-d_6 as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ -scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethyl acetate as an eluent.

2.2. Preparation of tert butyl 1-cyano piperazine carboxylate (2)

To a stirred solution of N-bocpiperazine (9 g, 0.048 mol) and NaHCO_3 (4.05 g, 0.048 mol) in ethanol (60 mL), was added cyanogen bromide (6.10 g, 0.0576 mol) portion wise at 0°C . The reaction mixture was stirred at room temperature for about 4 h. After completion of reaction, ethanol was concentrated under reduced pressure, water was added into the residue (40 mL), extracted with ethyl acetate (2 x 40 mL), washed with brine (20 mL) dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Yield: 9.2 g (90.7 %) white solid; m.p. $119\text{--}122^\circ\text{C}$; $R_f = 0.60$ (UV active, 20% EtOAc in hexane); $^1\text{H-NMR}$ (300 MHz, CDCl_3) $\delta = 3.54\text{--}3.51$ (t, 4H), 1.46-1.46 (m, 9H); MS: m/z $[\text{M}^+]$ 212.30

2.3. Preparation of 2-fluorobenzohydrazide (4)

To a stirred solution of methyl 2-fluorobenzoate **3** (6 g, 0.038 mol) in ethanol, was added hydrazine hydrate (2.87 g, 0.057 mol) drop wise and gradually heated to 90°C and maintained for 5 h. After completion of reaction, the solvent was removed under reduced pressure. The solid was formed, filtered and washed with minimum amount of water. Yield: 5.5 g (94%) as off-white solid; m. p. $105\text{--}107^\circ\text{C}$; $R_f = 0.40$ (UV active, 50% EtOAc in hexane); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) $\delta = 9.51$ (s, 1H), 7.56-7.47 (m, 2H), 7.29-7.22 (m, 2H), 4.52 (s, 2H); IR (film) $\nu = 3305, 3198, 1646, 694\text{ cm}^{-1}$; MS: m/z $[\text{M}^+]$ 155.30.

2.4. Preparation of intermediate (5)

The mixture of 2-fluoro benzohydrazide **4** (2.5 g, 0.016 mol) and compound **2** (3.77 g, 0.017 mol) were dissolved in DMF and kept in a microwave at 120°C for about 15 mins. After completion of reaction, reaction mixture was concentrated under reduced pressure to remove DMF and added water, extracted with ethyl acetate (40 mL), washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the compound was purified by silica gel (60–120 mesh) using pet ether and ethyl acetate as eluent. Yield: 5.1 g (92.0 %) off white solid; m. p. $118\text{--}119^\circ\text{C}$; $R_f = 0.40$ (UV active, 20% EtOAc in hexane); $^1\text{H-NMR}$ (300 MHz, MeOD-d_4) $\delta = 7.95\text{--}7.91$ (d, 1H), 7.49-7.46 (d, 1H), 7.31-7.22 (m, 2H), 3.45-3.43 (m, 4H), 2.96-2.94 (m, 4H), 1.41 (s, 9H); MS: m/z $[\text{M}^+]$ 348.00.

2.5. Preparation of 4-[5-[2-fluorophenyl]-1H-1,2,4-triazol-3-yl]piperazine (6)

To a stirred solution of intermediate **5** (4.0 g, 0.011 mol) in dioxane (30 mL), was added dioxane.HCl at 0°C and Stirred for 30 mins at room temperature. After completion of the reaction, the reaction mass was concentrated under reduced pressure. The salt was basified to $\text{pH} = 9$ by adding 25 mL of water and 10 % NaHCO_3 Solution and extracted with ethyl acetate (2 X 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (60-120 mesh size) using pet ether and ethyl acetate as eluent. Yield: 2.5 g. (89.0%), off white solid; m. p. $120\text{--}122^\circ\text{C}$; $R_f = 0.20$ (UV active, 50% EtOAc in hexane); $^1\text{H-NMR}$ (300 MHz,

MeOD- d_4) δ = 7.95-7.91 (d, 1H), 7.49-7.46 (d, 1H), 7.31-7.22 (m, 2H), 3.45-3.43 (m, 4H), 2.96-2.94 (m, 4H); IR (film) ν = 3277, 3207, 3126, 2952, 2837, 1587, 1520, 767 cm^{-1} ; MS: m/z [M⁺] 248.00.

2.6. Preparation of amide derivatives (7a-g)

General procedure

To the well stirred mixture of corresponding carboxylic acid (1.1 eq), EDCI.HCl (1.2 eq) and HOBT (1.2 eq) in DCM, were added triethylamine followed by addition of intermediate **6** at 0°C and the reaction mixture was stirred for room temperature for 3 h. After completion of reaction, water was added to reaction mixture. The solid formed was filtered, washed with water, and dried under reduced pressure. The crude was purified by column chromatography using silica gel 230-400 mesh to get compounds **7a-g**.

2.7. 1-(4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-2-morpholinoethanone (7a)

Off white solid; R_f = 0.50 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 10.79 (s, 1H), 8.22-8.18 (m, 1H), 7.46-7.42 (m, 1H), 7.33-7.73 (m, 1H), 7.29-7.19 (m, 1H), 3.77-3.73 (m, 8H), 3.57-3.50 (m, 4H), 3.25 (s, 2H), 2.56-2.55 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 167.8, 161.3, 158.9, 131.6, 131.6, 129.8, 129.6, 129.6, 125.0, 116.0, 115.8, 115.3, 66.8, 61.6, 53.4, 47.1, 46.6, 45.1, 41.3; IR(film) ν = 3431, 3202, 2919, 2852, 1631, 1531, 1480, 755 cm^{-1} ; MS: m/z [M⁺]: 375.20.

2.8. (4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)(isoxazol-5-yl)methanone (7b)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 10.81 (s, 1H), 8.36-8.35 (d, 1H), 8.23-8.19 (m, 1H), 7.46-7.42 (m, 1H), 7.33-7.19 (m, 2H), 6.84-6.84 (m, 1H), 3.95-3.88 (m, 4H), 3.67-3.62 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 165.2, 163.6, 161.4, 156.9, 150.2, 131.8, 131.7, 129.5, 125.1, 115.6, 107.8, 47.1, 46.4, 46.1, 42.4; IR(film) ν = 3099, 2847, 16939, 1593, 1531, 1487, 1421, 1256, 778 cm^{-1} ; MS: m/z [M⁺]: 343.00.

2.9. 2-Ethoxy-1-(4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)ethanone (7c)

Off white solid; R_f = 0.40 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 10.70 (s, 1H), 8.22-8.18 (m, 1H), 7.47-7.41 (m, 1H), 7.32-7.23 (m, 1H), 7.21-7.18 (m, 1H), 4.21 (s, 2H), 3.78-3.76 (m, 2H), 3.69-3.68 (m, 2H), 3.63-3.59 (m, 2H), 3.57-3.54 (m, 4H), 1.28-1.24 (t, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 168.1, 165.1, 161.4, 158.9, 150.0, 131.7, 129.6, 125.0, 115.8, 70.4, 66.8, 46.9, 46.5, 44.7, 41.3, 15.0; IR(film) ν = 3093, 2978, 2850, 1654, 1594, 1530, 1493, 779 cm^{-1} ; MS: m/z [M⁺]: 334.00.

2.10. (4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)(furan-3-yl)methanone (7d)

Off white solid; R_f = 0.35 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 10.68 (s, 1H), 8.22-8.18 (m, 1H), 7.75-7.75 (m, 1H), 7.47-7.42 (m, 2H), 7.33-7.18 (m, 2H), 6.59-6.59 (m, 1H), 3.84-3.75 (m, 4H), 3.60 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 164.0, 161.4, 158.9, 143.5, 143.0, 131.7, 131.3, 129.6, 125.0, 120.8, 116.0, 115.8, 110.0, 46.9, 46.7, 44.6, 42.1; IR(film) ν = 3132, 2846, 1617, 1531, 1487, 1436, 751 cm^{-1} ; MS: m/z [M⁺]: 342.00.

2.11. cyclobutyl(4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)methanone (7e)

Off white solid; R_f = 0.35 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 10.68 (s, 1H), 8.22-8.17 (m, 1H), 7.45-7.32 (m, 1H), 7.30-7.23 (m, 1H), 7.21-7.18 (m, 1H), 3.78-3.75 (m, 2H), 3.52-3.49 (m, 6H), 3.34-3.30 (m, 1H), 2.42-2.37 (m, 2H), 2.21-2.12 (m, 2H), 2.00-1.90 (m, 2H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 173.3, 164.7, 161.3, 158.3, 150.12,

131.6, 129.6, 124.9, 115.7, 46.8, 46.5, 44.4, 41.0, 37.1, 25.0, 24.9, 17.8; IR(film) ν = 3195, 2940, 2860, 1622, 1531, 1438, 1221, 754 cm^{-1} ; MS: m/z [M⁺]: 330.10.

2.12. (4-Fluorophenyl)(4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)methanone (7f)

Off white solid; R_f = 0.50 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 10.62 (s, 1H), 8.22-8.17 (m, 1H), 7.49-7.42 (m, 4H), 7.32-7.27 (m, 1H), 7.24-7.10 (m, 2H), 3.91-3.58 (m, 8H); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ = 169.7, 165.1, 164.7, 162.2, 161.4, 158.9, 150.1, 131.7, 131.5, 129.6, 129.4, 125.1, 116.0, 115.8, 115.1, 115.0, 46.7, 46.5, 116.0, 115.8, 115.1, 46.7, 46.5, 44.3, 41.3; IR(film) ν = 3423, 3206, 2922, 2856, 1611, 1532, 1566, 756 cm^{-1} ; MS: m/z [M⁺]: 370.00.

2.13. Tert-butyl 4-(4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazine-1-carbonyl)piperidine-1-carboxylate (7g)

Off white solid; R_f = 0.40 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 10.62 (s, 1H), 8.22-8.18 (m, 1H), 7.45-7.43 (m, 1H), 7.33-7.27 (m, 1H), 7.23-7.18 (m, 1H), 4.19-4.12 (m, 1H), 3.78-3.66 (m, 4H), 3.55-3.52 (m, 4H), 2.81-2.69 (m, 4H), 1.79-1.73 (m, 4H), 1.47(s, 9H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 173.1, 165.0, 161.4, 158.9, 154.7, 150.0, 131.8, 129.6, 125.1, 125.0, 116.0, 115.1, 79.6, 60.3, 47.1, 46.6, 44.9, 43.4, 41.2, 38.4, 28.4, 21.0, 14.1; IR(film) ν = 3453, 3095, 2975, 2856, 1736, 1692, 1635, 1532, 755 cm^{-1} ; MS: m/z [M⁺]: 459.00.

2.14. Preparation of urea derivatives (8a-g)

General procedure

To a well stirred mixture of corresponding intermediate **6** (1.0 eq) and triethylamine (2.0 eq) in DCM were added various isocyanate (1.1 eq) at 0°C and the reaction mixture was stirred for room temperature for about 3 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure to remove DCM. The crude product was purified by column chromatography using silica gel 230-400 mesh to get compounds **8a-g**.

2.15. N-(2-fluoro-6-methylphenyl)-4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazine-1-carboxamide (8a)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 13.12 (s, 1H), 8.17 (s, 1H), 7.95-7.91 (m, 1H), 7.45 (s, 1H), 7.34-7.29 (m, 2H), 7.21-7.12 (m, 2H), 6.88-6.83 (m, 1H), 3.57-3.41 (m, 4H), 3.36-3.25 (m, 4H), 2.23 (s, 3H); IR (film) ν = 3251, 3078, 2923, 2855, 1743, 1635, 1598, 1523, 753 cm^{-1} ; MS: m/z [M⁺]: 399.20.

2.16. N-cyclopentyl-4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazine-1-carboxamide (8b)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 12.83 (s, 1H), 7.92 (s, 1H), 7.26-7.25 (m, 3H), 6.35 (s, 1H), 3.94-3.88 (m, 4H), 3.40-3.35 (m, 4H), 1.80-1.74 (m, 2H), 1.64-1.59 (m, 2H), 1.49-1.40 (m, 4H); IR (film) ν = 3284, 2957, 2863, 1621, 1529, 1483, 1255 cm^{-1} ; MS: m/z [M⁺]: 359.30.

2.17. N-(biphenyl-2-yl)-4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl)piperazine-1-carboxamide (8c)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 12.83 (s, 1H), 8.11-8.06 (d, 1H), 7.93-7.91 (d, 1H), 7.51 (m, 1H), 7.38-7.28 (m, 1H), 3.39-3.32 (m, 4H), 3.32-3.29 (m, 4H); MS: m/z [M⁺]: 443.30.

2.18. 4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)-N-m-tolylpiperazine-1-carboxamide (8d)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, MeOD): δ = 7.95 (s, 1H), 7.52 (s, 1H), 7.3-7.15 (m, 5H), 3.68 (m, 4H), 3.51 (m, 4H), 2.30 (s,

3H); IR (film) ν = 3267, 2914, 2831, 1639, 1537, 1484, 1451, 1300, 1248, 817 cm^{-1} ; MS: m/z [M⁺]: 381.40.

2.19. 4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)-N-o-tolylpiperazine-1-carboxamide (8e)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 13.01 (s, 1H), 9.47-9.45 (m, 1H), 8.17-7.96 (d, 1H), 7.96-7.92 (m, 1H), 7.45-7.27 (m, 4H), 7.19-7.11 (m, 1H), 7.06-7.02 (m, 1H), 3.59-3.41 (m, 4H), 3.40-3.34 (m, 4H), 2.02 (s, 3H); IR (film) ν = 3278, 2922, 2853, 1634, 1534, 1523, 1491, 1330, 1255, 994, 752 cm^{-1} ; MS: m/z [M⁺]: 381.00.

2.20. N-(2-fluorophenethyl)-4-(5-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl) piperazine-1-carboxamide (8f)

Off white solid; R_f = 0.45 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ = 13.12 (s, 1H), 7.94-7.90 m, 1H), 7.46-7.25 (m, 3H), 7.24-7.10 (m, 2H), 6.79-6.76 (m, 1H), 3.40-3.24 (m, 4H), 3.22-3.19 (m, 4H), 2.78-2.69 (m, 2H), 2.49-2.49 (m, 2H); IR(film) ν = 3322, 2924, 2854, 1617, 1539, 1487, 1451, 1261, 1225, 754 cm^{-1} ; MS: m/z [M⁺]: 413.00.

2.21. 4-(5-(2-Fluorophenyl)-1H-1,2,4-triazol-3-yl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide (8g)

Off white solid; R_f = 0.47 (UV active, 10% CHCl_3 in MeOH); $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 13.01 (s, 1H), 9.47-9.45 (m, 1H), 8.17-7.96 (d, 1H), 7.96-7.92 (m, 1H), 7.45-7.27 (m, 4H), 7.19-7.11 (m, 1H), 7.06-7.02 (m, 1H), 3.59-3.41 (m, 4H), 3.40-3.34 (m, 4H); IR (film) ν = 3278, 2922, 2853, 1634, 1534, 1523, 1491, 1330, 1255, 994, 752 cm^{-1} .

3. Results and discussion

Based on above initial information's, we planned to optimize the reaction condition of intermediate 5. The reaction between nitrile (4) and hydrazide (3) was used to identify the reaction parameters that would provide optimal results. As presented in Table 1, to improve yields and demonstrate the methodology. To this effort, we decided to evaluate the various solvents and bases with microwave heating conditions.

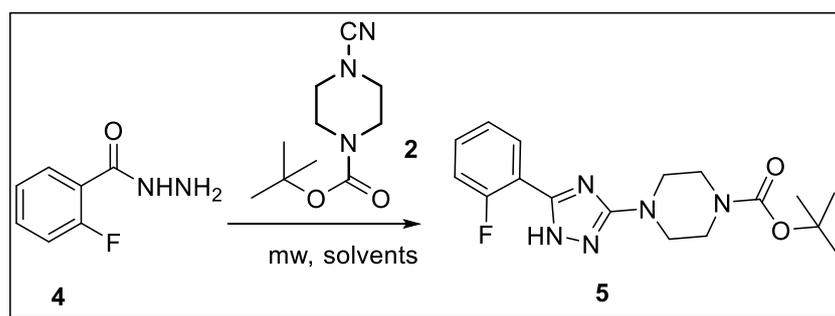


Table 1. Results of the reaction of nitrile with hydrazide under different conditions.

S. No.	Solvents	Mw (°C)	Time (mins)	Yield (%)
1.	Ethanol	90	60	25
2.	Butanol	90	50	40
3.	Tert-butanol	90	30	50
4.	Xylene	120	30	60
5.	DMF	120	15	92
6.	DMSO	150	20	75

Further, we examined different the reaction condition of synthesis of intermediate **5** with convention heating and it compared as shown in Table 2.

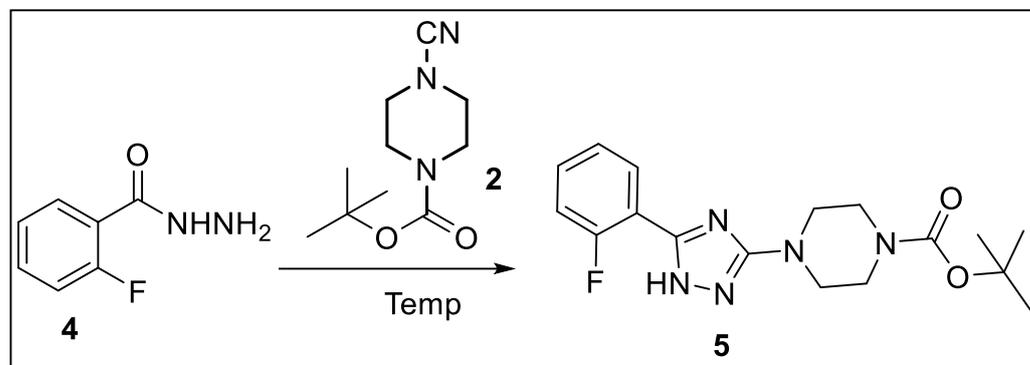


Table 2. Results of the reaction of nitrile with hydrazide under different conditions.

S no	Solvents	Conventional heating		MW	
		Temp (°C)	Yield (%)	Temp (°C)	Yield (%)
1.	Ethanol	90	-	90	20
2.	Butanol	90	10	90	40
3.	Tert-butanol	90	25	90	50
4.	Xylene	120	30	120	60
5.	DMF	120	50	120	92
6.	DMSO	150	40	150	75

Based on the above results, we comparing the conventional heating with microwave condition, MW mediated reactions are the best method for the synthesis of intermediate **5** without using any base or metal. In this method, it takes only few minutes to complete the reaction and it offers good yield with easy work up, when compared to conventional heating method.

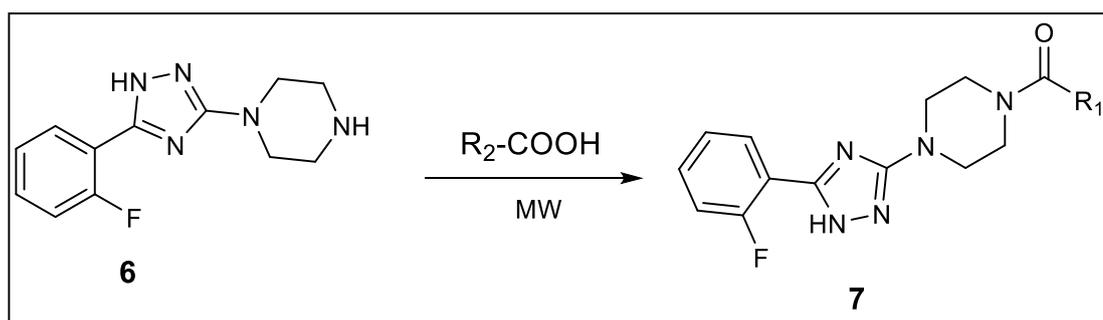
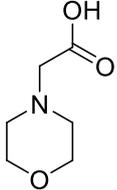
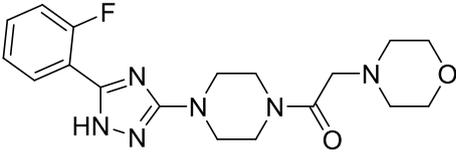
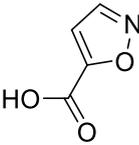
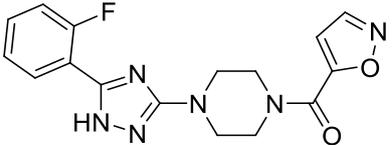
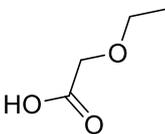
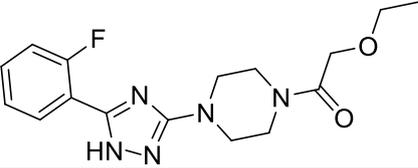
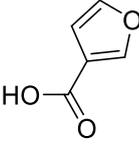
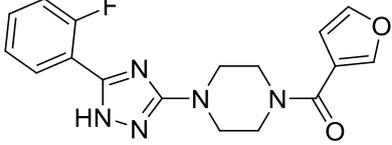
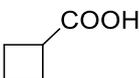
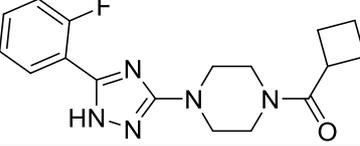
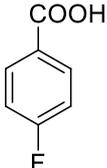
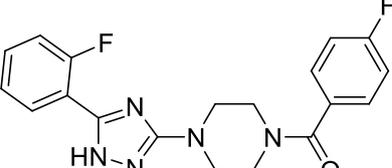
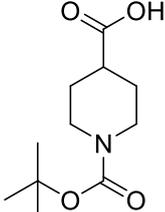
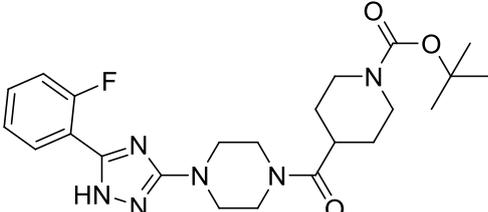
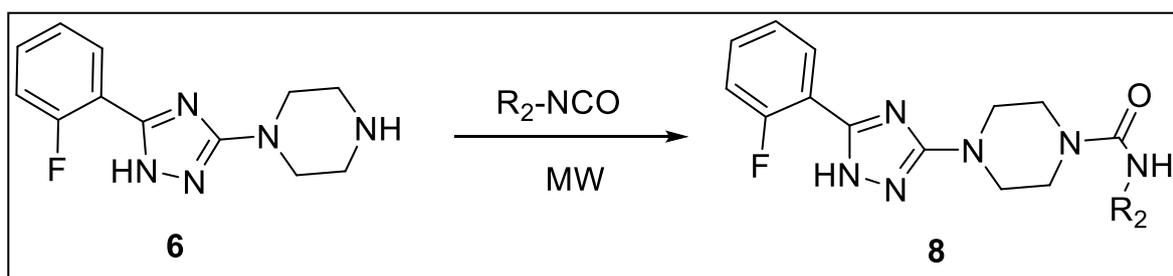


Table 3. Results of the reaction of intermediate **6** with various carboxylic acids.

S. No	Acids	Amide derivatives	Product code	Yield (%)
1.			7a	80
2.			7b	78
3.			7c	87
4.			7d	85
5.			7e	89
6.			7f	90
7.			7g	88

Further, the intermediate **6** reactions with various isocyanates to give urea derivatives with electron donating and electron withdrawing substituents in the aromatic [12-17]. As shown in Table 4, both electron donating and electron withdrawing substituents on phenyl rings does not affect the reaction, and the corresponding reactions proceeded smoothly to afford the desired products with excellent yield in shorter reaction time.

**Table 4.** Results of the reaction of intermediate **6** with various isocyanates.

S. No	Isocyanates	Urea derivatives	Product code	Yield (%)
1.			8a	97
2.			8b	94
3.			8c	95
4.			8d	98
5.			8e	99
6.			8f	90

7.			8g	96
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4. Conclusion

We synthesized piperazine linked 3,5-disubstituted 1,2,4-triazole intermediate that proceeds by the direct reaction of a nitrile and a hydrazide in microwave irradiation without using any base and solvents. The obtained triazole derivatives as an intermediate for preparing some urea and amide derivatives using their corresponding isocyanates and carboxylic acids through coupling reaction to give very good yield (up to 99 %) in very short time.

Acknowledgement

We acknowledge the financial support of the Department of Science and Technology, CERI, (Grant No. DST/TM/CERI/C130(G)), DST-SERB, extramural major research (Grant No. EMR/2015/000969), Council of Scientific and Industrial Research (CSIR) HRDG, New Delhi (Gant No. 01(2901)/17/EMR-II). Also, we thank DST-PURSE and UGC-UPE programs for providing instrumental facility.

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