Synthesis and biological evaluation of Novel *N*-(3-(6-methyl-[1,2,4]triazolo [4,3-*b*]pyridazin-3-yl) aryl carboxamide and aryl sulfonamide derivatives

K. Thirumurugan*[a] N. Ramalakshmi,*[a] and J. Sembian Ruso[b]

[a]Department of Chemistry, Presidency College, Chennai -600005, India,
E-mail: thiruk2@yahoo.co.in: +919486455783 and
E-mail: rrama_subhar@yahoo.co.in: +919444958266
[b]M.R.G Arts College, Mannargudi, Tiruvarur District, Tamil Nadu, India
E-mail: sruso@rediffmail.com: +919751888652

Abstract:A novel derivatives of *N*-(3-6-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl)benzamide and sulphonamide were prepared from 3-(6-Methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl) aniline and these derivatives were subjected to preliminary antimicrobial activities against microorganism. All these compounds exhibit good to moderate activity.

Key words: 1,2,4 triazolopyridazine, sulphonamide, benazamide and antimicrobial activities.

Introduction

In the past few decades, the particular interest on synthesising the 1,2,4 triazole derivatives are due to their innumerable applications in various fields[1]. Remarkably, most of the 1,2,4-triazoles and their fused heterocyclic motifs are of specific interest in medicinal chemistry owing to their potential biological and pharmacological activities[2]. Besides, among the five membered heterocyclic the pyridazine is one such important heterocyclic compound because of its wide spectrum of usage in biological application as antimicrobial[3-8] anti-inflammatory[9-10] antiviral[11-12], anticancer[12], antitumor[13-14], antitubercular[15] activities, analgesic agents[16] and exhibit as potent chemo type for the selective inhibition of PDE4[17-18] and etc. In addition, the fused derivatives of pyridazine with other heterocyclic analogues such as triazolo, imidazolo and pyrazolo also have been reported for their broad biological properties as antibacterial, antidepressant, antiviral, antitumoral, anti-inflammatory agents, pesticides, herbicides, dyes, lubricant and analytical reagents[17-18].Further the recent literature reveals that the triazolopyridazine derivatives have also been reported for their potent HAV activity, c-Met kinase inhibitor, GABAA and adenine receptors[19].

Additionally, the amide and sulphonamide derivatives are found to be an important pharmacore which occupy major role in pharmacological applications as antimicrobial[20-21], antiviral[22], carbonic anhydrase inhibitory[23], and anti-cancer activities[24], HIV protease inhibitors[25], antimetabolite[26], cytotoxic activity[27-28], antibiotic[29], fatty acid amide hydrolase [FAAH] inhibitors[30], antimalaria[31] and antiproliferative[32].

Aspired by the above results, we have focused to synthesis a novel 1,2,4-triazolopyridazine derivatives containing amide and sulphonamide groups and are subjected against the bacterial strains (*Staphylococcus aureus* and *Bacillus subtilis*-gram positive, *Escherichia coli* and *Pseudomonas aeruginosa*-gram negative*)* and fungi (*A. flavus*, *A. Niger*, F. *oxysporum and C. albicans*) using the broth dilution method.

EXPERIMENTAL

All reagents were purchased from commercial suppliers and were used without purification. Melting points were determined in Buchi B-545melting point apparatus and were uncorrected. All ^{1}H NMR spectra were recorded on a Bruker Advance-400 & 300 NMR MHz spectrometer in DMSO-d_6 & $CDCl_3$ solution using TMS as an internal reference and all^{13}C NMR were recorded at 100 & 75MHz. Mass spectra were recorded on LC-MS-Agilent 1200 series. All these compounds were purified by flash column Chromatography using 230-400 mesh silica gels.

General Procedure for the synthesis of 3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)aniline : A mixture of compound **1** (1 mmol) and 10% Pd/C (0.22 mmol) in ethanol (5 mL) was heated at 50 ^{o}C followed by hydrazine hydrate (5 mmol) was slowly added. The reaction mass was cooled to ambient temperature and filtered through celite and concentrated to obtain a residue which was purified by column chromatography using hexane/ethyl acetate as eluent to furnish the desired triazolopyridazines **2** as off white solid.

General procedure for the synthesis of Substituted *N*-(3-6-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl)benzamide: A mixture of compound **2** (1 mmol), benzoyl chloride (1.2 mmol) and powdered sodium carbonate (1.2 mmol) in THF (5 mL) was stirred at ambient temperature for 6 h. The formation of benzamide

was checked by TLC and the reaction mixture was diluted with water and extracted with dichloromethane (2 x 25 mL), dried over anhydrous sodium sulfate and concentrated to obtain a residue which was purified by column chromatography using hexane/ethyl acetate as eluent to furnish the desired compound **4**.

4-Chloro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)benzamide:4a

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.54 (s, 1H, -CONH), 8.85 (s, 1H, ArH), 8.34-8.31 (d, *J* = 9.54 Hz, 1H, ArH), 8.04-8.00 (m, 1H, ArH), 7.97-7.90 (m, 3H, ArH), 7.59-7.52 (m, 3H, ArH), 7.34-7.31 (d, *J* = 9.54 Hz, 1H, ArH), 2.61 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 155.9, 144.7, 139.8, 136.9, 131.5, 130.1, 129.5, 128.9, 127.2, 124.9, 123.3, 122.9, 122.3, 119.5, 22.0 MS: m/z 364 (M^++1).

2-Fluoro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)benzamide:4b

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.65 (s, 1H, -CONH), 8.85 (s, 1H, ArH), 8.34-8.31 (d, *J* = 9.54 Hz 1H, ArH), 8.20-8.17 (d, *J* = 7.86 Hz, 1H, ArH), 7.90-7.87 (d, *J* = 7.95 Hz 1H, ArH), 7.72-7.76 (m, 1H, ArH), 7.76-7.55 (m, 2H, ArH), 7.39-7.31(m, 3H, ArH), 2.61 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 157.7, 155.9, 146.7, 144.7, 139.7, 133.1, 133.0, 130.4, 130.3, 129.7, 127.3, 125.0, 124.9, 123.3, 122.9, 121.6, 118.8, 116.8, 116.5, 22.0 MS: m/z 348 (M^++1).

4-Fluoro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)benzamide:4c

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.58 (s, 1H, -CONH), 8.85 (s, 1H, ArH), 8.34-8.28 (d, *J* = 9.54 Hz, 1H, ArH), 8.20-8.18 (d, *J* = 7.84 Hz, 1H, ArH), 8.10-8.06 (m, 2H, ArH), 7.97-7.95 (d, *J* = 7.95 Hz 1H, ArH), 7.60-7.56 (m, 1H, ArH), 7.40-7.32 (m, 3H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 164.6, 162.8, 155.4, 146.3, 144.2, 139.5, 131.2, 131.1, 130.5, 130.4, 129.0, 126.7, 124.4, 122.8, 122.3, 121.8, 119.0, 115.4, 115.2, 21.5 MS: m/z 348 (M^++1).

***N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)-4-(trifluoromethyl)benzamide:4d**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.71 (s, 1H, -CONH), 8.88 (s, 1H, ArH), 8.34-8.30 (d, *J* = 9.51 Hz, 1H, ArH), 8.22-8.17 (m, 3H, ArH), 7.98-7.93 (m, 3H, ArH), 7.61-7.56 (m, 1H, ArH), 7.34-7.31 (d, *J* = 9.57 Hz, 1H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 155.9, 146.7, 144.7, 139.7, 129.6, 129.1, 127.2, 125.9, 124.8, 123.3, 123.0, 122.5, 122.3, 119.5, 22.0 MS: m/z 398 (M^++1).

3, 4-Dichloro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)benzamide:4e

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.65 (s, 1H, -CONH), 8.85 (s, 1H, ArH), 8.34-8.32 (d, *J* = 9.52 Hz, 1H, ArH), 8.224-8.21 (m, 1H, ArH), 8.02 (s, 2H, ArH), 7.96-7.94 (m, 1H, ArH), 7.90-7.84 (m, 2H, ArH),7.61-7.57 (m, 1H, ArH), 7.35-7.32 (d, *J* = 9.56 Hz, 1H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 162.8, 155.4, 146.2, 144.2, 139.0, 137.9, 134.3, 132.2, 131.0, 129.1, 127.7, 126.5, 124.4, 122.8, 121.8, 119.0, 21.5 MS: m/z 399 (M^++1).

3, 4-Difluoro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)benzamide:4f

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.62 (s, 1H, -CONH), 8.85 (s, 1H, ArH), 8.34-8.31 (d, *J* = 9.52 Hz, 1H, ArH), 8.22-8.19 (m, 1H, ArH), 8.11-8.06 (m, 1H, ArH), 7.97-7.94 (m, 1H, ArH), 7.91-7.89 (m, 1H, ArH),7.66-7.5 (m, 2H, ArH), 7.34-7.32 (d, *J* = 9.56 Hz, 1H, ArH), 2.61 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 155.4, 152.8, 150.2, 150.2, 147.8, 146.3, 144.2, 139.2, 132.0, 129.1, 126.7, 125.4, 124.4, 122.9, 122.5, 119.0, 117.5, 117.3, 117.1, 21.5 MS: m/z 290 (M^++1).

2-Fluoro-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)-5-(trifluoromethyl) benzamide:4g

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.85 (s, 1H, -CONH), 8.84 (s, 1H, ArH), 8.35-8.33 (d, *J* = 9.54 Hz, 1H, ArH), 8.24-8.21 (m, 1H, ArH), 8.13-8.11 (m, 2H, ArH), 8.02-7.95 (m, 1H, ArH), 7.90-7.87 (m, 1H, ArH), 7.66-7.58 (m, 2H, ArH), 7.35-7.33 (d, *J* = 9.52 Hz, 1H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 161.5, 159.7, 155.4, 146.1, 144.3, 138.9, 129.8, 129.3, 127.5, 127.4, 126.9, 125.9, 124.9, 124.4, 122.9, 122.7, 122.2, 121.2, 117.8, 21.5 MS: m/z 417 (M^++1).

***N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)-1-naphthamide:4h**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.86 (s, 1H, -CONH), 8.31 (s, 1H, ArH), 8.22-8.19 (d, *J* = 9.52 Hz, 1H, ArH), 8.10-8.07 (m, 2H, ArH), 8.04-8.01 (m, 1H, ArH),7.99-7.95 (m, 2H, ArH), 7.82-7.79 (m, 1H, ArH), 7.65-7.56 (m, 4H, ArH), 7.35-7.33 (d, *J* = 9.52 Hz, 1H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 155.8, 146.8, 144.7, 140.1, 135.0, 133.6, 130.6, 130.1, 129.6, 128.8, 127.5, 127.3, 126.8, 126.0, 125.5, 124.9, 123.3, 122.8, 121.7, 118.9, 22.0 MS: m/z 395 (M^++1).

***N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)-2-naphthamide:4i**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.85 (s, 1H, -CONH), 8.92 (s, 1H, ArH), 8.63 (s, 1H, ArH), 8.34-8.31 (d, *J* = 9.52 Hz, 1H, ArH), 8.22-8.19 (d, *J* = 7.83 Hz, 1H, ArH), 8.11-7.99 (m, 5H, ArH), 7.67-7.57 (m, 3H, ArH), 7.34-7.31 (d, *J* = 9.52 Hz, 1H, ArH), 2.62 (s, 1H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 155.8, 146.9, 144.7, 140.1, 134.8, 132.6, 132.5, 129.5, 129.4, 128.6, 128.5, 128.3, 128.1, 127.3, 127.2, 125.0, 124.9, 132.3, 132.7, 122.2, 119.5, 22.0, MS: m/z 395 (M^++1).

4-Butyl-*N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)-benzamide:4j

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.41 (s, 1H, -CONH), 8.87-8.86 (d, *J* = 1.72 Hz, 1H, ArH), 8.32-8.29 (d, *J* = 9.52 Hz, 1H, ArH), 8.18-8.15 (d, *J* = 7.89 Hz, 1H, ArH), 7.98-7.88 (m, 4H, ArH), 7.58-7.53 (m, 1H, ArH), 7.35-7.30 (m, 3H, ArH), 2.66-2.60 (m, 5H, -CH_2, ArCH_3), 1.61-1.51(m, 2H, -CH_2), 1.61-1.51(m, 2H, -CH_2), 1.35-1.30 (m, 2H, -CH_2), 0.86-0.95 (m, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 155.8, 146.9, 144.7, 140.1, 132.7, 129.4, 128.7, 128.2, 127.1, 124.8, 123.3, 122.6, 122.2, 119.5, 33.5, 33.3, 22.1, 22.0, 14.1, MS: m/z 386 (M^++1).

***N*-(3-(6-methyl [1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)phenyl)cyclobutanecarboxamide:4k**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.98 (s, 1H, -CONH), 8.68-67 (m, 1H, ArH), 8.35-8.32 (d, *J* = 9.52 Hz, 1H, ArH), 8.12-8.8.10 (m, 1H, ArH), 8.18-8.15 (d, *J* = 7.89 Hz, 1H, ArH), 7.84-7.81 (m, 1H, ArH), 7.54-7.50 (m, 1H, ArH), 7.35-7.33 (d, *J* = 9.52 Hz, 1H, ArH), 3.30 (m, 1H, -CH), 2.63 (s, 3H, -CH_3), 2.51-2.49 (m, 2H, -CH_2), 2.28-2.23 (m, 2H, -CH_2), 2.15-2.13 (m, 1H, -CH), 1.97-1.94 (m, 1H, -CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 155.3, 146.3, 144.2, 139.7, 129.0, 126.6, 124.4, 122.8, 121.5, 120.5, 117.7 24.5, 21.5, 17.7 MS: m/z 308 (M^++1).

General procedure for the synthesis of Substituted *N*-(3-6-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl)benzenesulphonamide: A mixture of compound **2** (1 mmol), arylsulfonyl chloride (1.2 mmol) and potassium acetate (2.1 mmol) in ethanol (5 mL) was stirred at rt for 6 h. The formation of sulfonamide was checked by TLC and the reaction mixture was diluted with water and extracted with dichloromethane (2 x 25 mL), dried over anhydrous sodium sulfate and concentrated to obtain a residue which was purified by column chromatography using hexane/ethyl acetate as eluent to furnish the desired compound **3**.

3-bromo-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3a

Off white solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.68 (s, 1H, -SO_2NH), 8.33-8.22 (m, 2H, ArH), 8.12-8.10 (d, *J* = 7.86 Hz, 1H, ArH), 7.96 (s,1H, ArH), 7.82-7.77 (m, 2H, ArH), 7.52-7.45 (m, *J* = 1H, ArH), 7.31-7.23 (m, 2H, ArH), 2.67 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 146.1, 144.8, 141.7, 138.2, 136.4, 132.1, 130.3, 129.5, 127.7, 126.1, 124.9, 123.4, 123.1, 122.6, 121.9, 118.7, 21.9 MS: m/z 445 (M^++1).

4-Chloro-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3b

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.69 (s, 1H, -SO_2NH), 8.35-8.30 (m, 2H, ArH), 8.13-8.11 (d, *J* = 7.88 Hz, 1H, ArH), 7.83-7.81 (dd, *J* = 1.76 Hz, 2H, ArH), 7.65-7.63 (dd, *J* = 1.76 Hz 2H, ArH), 7.50-7.46 (m, 1H, ArH), 7.35-7.33 (d, , *J* = 9.52 Hz, 1H, ArH),7.27-7.25 (m, 1H, ArH), 2.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 146.2, 144.8, 138.6, 138.3, 130.3, 130.0, 129.0, 127.7, 124.9, 123.4, 123.2, 121.8, 118.8, 21.9 MS: m/z 400 (M^++1).

2-Fluoro-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3c

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.93 (s, 1H, -SO_2NH), 8.33-8.29 (m, 2H, ArH), 8.10-8.08 (d, *J* = 7.84 Hz, 1H, ArH), 7.90-7.86 (m, 1H, ArH), 7.69-7.63 (m, 2H, ArH), 7.48-7.26 (m, 5H, ArH), 2.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 155.9, 146.2, 144.8, 138.1, 136.5, 130.9, 130.2, 127.4, 127.2, 125.4, 124.9, 123.0, 121.2, 118.3, 117.9, 117.7, 21.9 MS: m/z 384 (M^++1).

4-Fluoro-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3d

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.62 (s, 1H, -SO_2NH), 8.35-8.31 (m, 2H, ArH), 8.12-8.10 (d, *J* = 7.80 Hz, 1H, ArH), 7.90-7.87 (m, 2H, ArH), 7.50-7.46 (m, 1H, ArH), 7.42-7.31 (m, 2H, ArH), 7.29-7.22 (m, 2H, ArH), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 155.5, 155.1, 145.8, 144.4, 144.0, 138.0, 135.7, 129.8, 129.2, 127.2, 124.4, 123.0, 122.7, 118.3, 116.7, 116.5 MS: m/z 384 (M^++1).

4-Methoxy-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3e

Off white solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.46 (s, 1H, -SO_2NH), 8.34-8.33 (m, 2H, ArH), 8.30-8.06 (d, *J* = 7.88 Hz, 1H, ArH), 7.77-7.75 (d, *J* =8.88 Hz, 2H, ArH), 7.47-7.46 (m, 1H, ArH), 7.35-7.31 (m, 1H, ArH), 7.26-7.24 (m, 1H, ArH), 7.06-7.04 (d, *J* = 8.92 Hz, 2H, ArH), 2.62 (s, 3H, -OCH_3), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 155.5, 144.9, 144.3, 138.5, 131.0, 129.7, 128.9, 127.2, 124.5, 123.0, 122.3, 120.8, 117.8, 114.5, 55.6, 21.5 MS: m/z 396 (M^++1).

***N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)-2-(trifluoromethoxy)benzenesulfonamide: 3f**

Off white solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.84 (s, 1H, -SO_2NH), 8.33-8.26 (m, 2H, ArH), 8.10-8.08 (d, *J* = 10.52 Hz, 1H, ArH), 8.03-7.99 (m, 1H, ArH), 7.76-7.70 (m, 1H, ArH), 7.55-7.43 (m, 3H, ArH), 7.33-7.30 (d, *J* = 12.72 Hz,1H, ArH), 7.26-7.23 (m, 1H, ArH), 2.62 (s, 3H, -OCH_3), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 157.8, 144.8, 138.1, 16.0, 131.4, 130.1, 127.9, 12.6, 124.9, 123.4, 123.0, 121.5, 121.3, 118.4 21.5 MS: m/z 450 (M^++1).

2-Chloro-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)-4-(trifluoromethoxy)benzenesulfonamide: 3g

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, -SO_2NH), 8.34-8.27 (m, 3H, ArH), 8.14-8.11 (d, *J* = 11.92 Hz, 2H, ArH), 7.93-7.91 (d, *J* = 7.76 Hz, 1H, ArH), 7.51-7.49 (m, 1H, ArH), 7.35-7.33 (m, 1H, ArH), 7.30-7.28 (m, 2H, ArH), 7.26-7.23 (m, 1H, ArH), 2.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 146.1, 144.8, 140.9, 137.5, 134.4, 132.9, 132.4, 130.3, 129.5, 127.8, 125.4, 124.9, 123.4, 123.3, 121.3, 118.4, 21.9 MS: m/z 468 (M^++1).

4-Cyano-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)benzenesulfonamide: 3h

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 1H, -SO_2NH), 8.33-8.28 (m, 2H, ArH), 8.09-8.05 (m, 2H, ArH), 7.91-7.87 (m, 1H, ArH), 7.55-7.43 (m, 2H, ArH), 7.34-7.27 (m, 2H, ArH), 2.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 146.1, 144.8, 139.0, 137.7, 135.6, 134.7, 130.8, 130.3, 129.3, 127.7, 124.9, 123.4, 123.1, 121.1, 118.1, 21.9 MS: m/z 391 (M^++1).

***N*-Methyl-4-*N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl)sulfomyl)benzamide: 3i**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.45 (s, 1H, -SO_2NH), 10.25 (s, 1H, -$CONHCH_3$), 8.32-8.25 (m, 2H, ArH), 8.07-8.05 (m, 1H, ArH), 7.75-7.66 (m, 4H, ArH), 7.46-7.41 (m, 1H, ArH), 7.33-7.30 (d, *J* = 12.72 Hz, 1H, ArH), 7.25-7.22 (m, 1H, ArH), 2.01 (s, 3H, CH_3), 2.59 (s, 3H, -$NHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 155.9, 146.3, 144.7, 143.6, 138.8, 133.3, 130.1, 128.4, 127.6, 124.9, 123.4, 122.8, 121.5, 119.0, 118.5 155.9, 24.5, 21.9 MS: m/z 423 (M^++1)

***N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)quinolone-6- sulphonamide: 3j**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.55 (s, 1H, -SO_2NH), 9.14 (s, ArH), 8.52-8.46 (m, 1H, ArH), 8.27-7.39 (m, 1H, ArH), 8.29-8.22 (m, 3H, ArH), 7.96-7.92 (m, 1H, ArH), 7.72-7.76 (m, 2H, ArH), 7.33-7.20 (m, 3H, ArH), 2.58 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 151.9, 146.3, 144.7, 143.2, 138.88, 137.4, 135.6, 134.8, 132.6, 129.7, 128.8, 127.3, 126.0, 124.8, 123.3, 123.1, 122.6, 121.3, 118.4, 21.9 MS: m/z 417 (M^++1).

***N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)naphthalene-2-sulphonamide: 3k**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.01 (s, 1H, -SO_2NH), 8.79-8.77 (d, *J* = 8.60 Hz, 1H, ArH,), 8.31-8.28 (m, 2H, ArH), 8.23-8.19 (m, 1H, ArH), 8.06-8.04 (d, *J* = 8.16 Hz, 1H, ArH), 8.00-7.98 (d, *J* = 7.84 Hz, 1H, ArH), 7.77-7.73 (m, 1H, ArH), 7.67-7.58 (m, 2H, ArH), 7.39-7.30 (m, 1H, ArH), 7.20 (d, *J* = 2.08, Hz, ArH), 7.18 (d, *J* = 1.36, Hz, ArH), 2.56 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 144.7, 138.5, 135.0, 134.2, 130.4, 130.1, 129.5, 128.6, 127.8, 127.5, 127.4, 124.8, 124.6, 123.4, 122.4, 120.4, 117.5, 21.9 MS: m/z 416 (M^++1)

***N*-(3-(6-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)cyclohexane sulphonamide: 3l**

White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.12 (s, 1H, -SO_2NH), 8.95-8.94 (t, *J* = 5.12 Hz, 1H, ArH,), 8.70-8.69 (m, *J* = 9.52 Hz 1H, ArH), 8.35-8.32 (d, *J* = 9.52 Hz, 1H, ArH), 8.10-8.08 (d, 1H, *J* = 7.88 Hz, 1H, ArH), 7.83-7.81 (m, 1H, ArH), 7.52-7.48 (m, 1H, CH), 7.63-7.34 (d, 1H, ArH), 2.62 (s, 1H, -CH_3), 2.50-2.37 (m, 1Hz, -CH), 1.84-1.74 (m, 4H, -CH_2CH_2H), 1.45-1.42 (m, 2H, -CH_2), 1.32-1.20 (m, 4H, -CH_2CH_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 155.9, 146.8, 144.6, 142.4, 140.3, 129.5, 127.0, 127.0, 124.7, 123.5, 122.0, 121.0, 118.2, 45.3, 42.6, 29.5, 25.6, 22.0 MS: m/z 416 (M^++1)

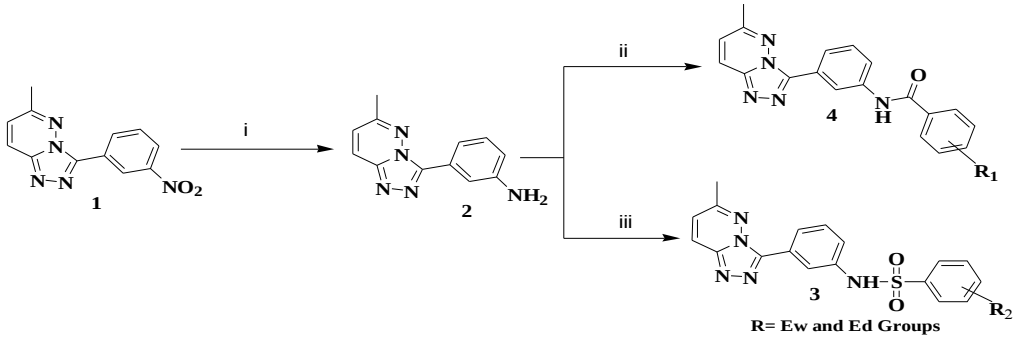
RESULTS AND DISCUSSION

The compound **1** was synthesised according to the procedure described in the literature [33]. The compound **1** on treatment with 10% Pd/C and hydrazine hydrate under heating afforded the compound **2** as off white solid. The intermediate **2** was subsequently treated with benzoylchloride and sulfonylchloride bearing various substitutions to furnish the derivatives **3** and **4** in quantitatively. This reaction involves in mild condition, short reaction time, easy work up and purification to deliver excellent yields.

Twenty three compounds were synthesised and their structure was confirmed by NMR and mass spectroscopy. All the synthesized compounds **3a-3l** and **4a-4k** were screened for their *in vitro* antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtiis*) and Gram-negative (*Escherichia* coli and *Pseudomonas aeruginosa*) bacteria strains using broth dilution method for determination of MIC.[9] This activity was compared to a well-known commercial antibiotic, such as ampicillin. The screening results revealed that the compound **3a-3k** and **4a-4l** exhibited strong to moderate activity against the tested organism. On the basis of the incubation zone, the compound **3d, 3e, 3j** and **4b, 4d, 4f** displayed strong activity against the tested organism whereas the compound **3a, 3b, 3c,** and **4c, 4h, 4i and 4j** displayed good to moderate activities towards the tested antibacterial strains. The enhanced activities of the tested compounds could be attributed to the presence of fluoro and methoxy substituent on the phenyl ring. These results are summarised in Table 3 &4. All the twenty three compounds were also subjected to their antifungal activities against the fungi namely, *A. flavus*, *A. Niger*, F. *oxysporum and C. albicans.*

Fluconazole was used as standard for the comparison of antifungal activity of the compounds **3** and **4.** This result indicated that almost all the compounds have moderate to good antifungal activity against the tested fungi. The compound **3d**, **3e**, **4b**, **4c**, and **4f** were found to have maximum inhibition against fungi, *A. flavus*, *A. Niger*, F. *oxysporum and C. albicans* (Table 4).

Scheme 1



i) Pd/c 10% , $NH_2NH_2.H_2O$, EtOH; 50° C; ii) ArCOCl, Na_2CO_3, THF; iii) $ArSO_2Cl$, KOAc, EtOH, RT

Table.1 Derivatives of aryl sulfonamide (3a-3l)

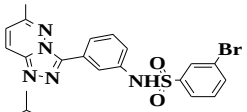
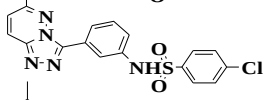
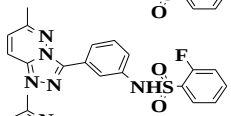
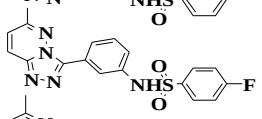
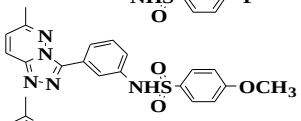
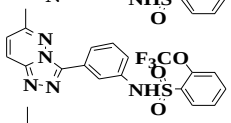
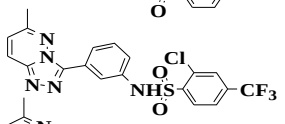
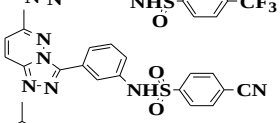
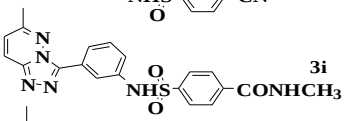
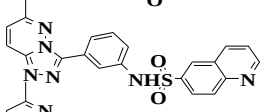
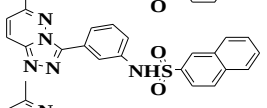
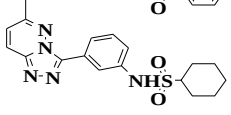
Entry	Structure	Product	Mp (ºC)	Yiled (%)
1		**3a**	310-315	**82**
2		**3b**	325-326	**75**
3		**3c**	340-341	**85**
4		**3d**	342-343	**76**
5		**3e**	295-297	**87**
6		**3f**	335-338	**80**
7		**3g**	305-307	**78**
8		**3h**	350-352	**82**
9		**3i**	329-333	**87**
10		**3j**	355-356	**82**
11		**3k**	302-303	**83**
12		**3l**	219-228	**86**

Table.2 Derivatives of aryl carboxamide (4a-4k)

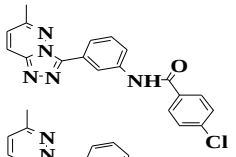
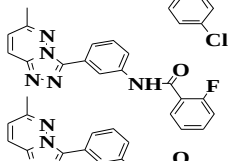
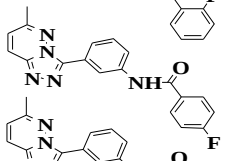
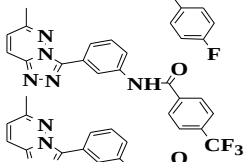
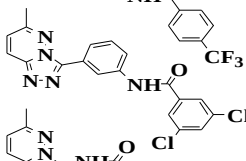
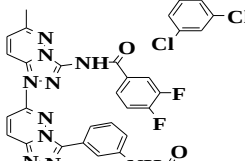
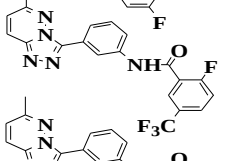
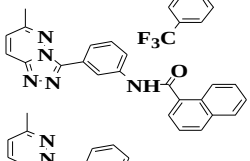
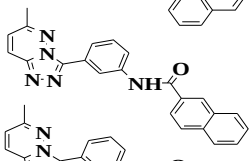
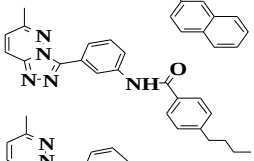
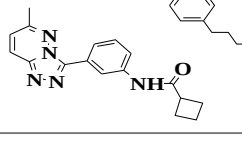
Entry	Structure	Product	Mp (^{o}C)	Yiled (%)
1		**4a**	223-225	**78**
2		**4b**	268-269	**82**
3		**4c**	229-232	**80**
4		**4d**	249-250	**79**
5		**4e**	202-204	**85**
6		**4f**	203-205	**76**
7		**4g**	219-220	**81**
8		**4h**	203-205	**83**
9		**4i**	250-251	**86**
10		**4j**	193-195	**77**
11		**4k**	210-211	**75**

Table 3. In vitro antibacterial screening results of the tested compounds 3a-3l and 4a-4k

Compounds	Inhibition zone diameter (mm/mg sample)			
	S. aureus	B. subtiis	E. coli	P. aeruginosa
3a	9	11	10	10.5
3b	9	10	10	9
3c	8	8.5	9	8
3d	**10**	**13.5**	**13**	**11.8**
3e	**11**	**13**	**12.7**	**10.7**
3f	6	7	8	8
3g	6	5	6	6
3h	6	7	7	6
3i	5	4	5	4
3j	**11.7**	**12.5**	**12.6**	**12**
3k	6	7	5	4
3l	5	7	6	15
4a	6	7	6	6.5

4b	**11**	**12.7**	**12**	**12**
4c	8	9	8	9
4d	**11.6**	**12**	**12**	**10.5**
4e	5	6	6	4
4f	**11**	**13**	**12**	**11.6**
4g	6	7	6	5.5
4h	8	9	8	7
4i	9	8.5	9	8.5
4j	4	4	5	
4k	8	9	7	9
Amphicilin	**12**	**14**	**14**	**12**

Table 4. In vitro antifungal screening results of the tested compounds 3a-3l and 4a-4k.

Compounds	Mycelial growth of inhibition (%)			
	A. flavus	A. niger	F. oxysporum	*C*. albicans
3a	44.2	55.8	58.3	48.5
3b	45.5	49.2	56.4	49.5
3c	54.4	47.9	52.8	50.2
3d	**67.5**	**72.3**	**77.3**	**64.5**
3e	**66.2**	**75.3**	**66.2**	**69.4**
3f	43.3	52.8	54.8	55.8
3g	55.4	58.6	55.7	58.4
3h	58.6	59.7	60.8	61.2
3i	46.7	55.9	61.2	48.5
3j	48.7	48.8	63.5	47.6
3k	49.4	55.3	59.7	48.6
3l	55.7	48.7	60.4	49.6
4a	56.8	49.2	58.9	48.8
4b	**68.5**	**73.4**	**67.6**	**66.5**
4c	**67.3**	**70.5**	**73.4**	**69.4**
4d	44.7	65.3	61.3	58.6
4e	48.5	62.5	62.3	55.7
4f	**65.8**	**70.6**	**66.7**	**68.9**
4g	64.2	56.9	59.5	57.6
4h	62.3	57.8	57.6	50.2
4i	45.7	59.2	58.2	53.9
4j	46.8	60.8	48.6	59.6
4k	41.2	63.8	47.5	58.5
Flucanozole	**72**	**80**	**75**	**78**

Conclusion

In conclusion, we have synthesized a novel series *N*-(3-6-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl)benzamide and sulphonamide derivatives were prepared from 3-(6-Methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)phenyl) aniline. All newly synthesized compounds were tested for their antimicrobial activities and showed fairly to good activities against the bacteria and fungi. However, in whole series, a few compounds possess potent antimicrobial activity. We conclude that additional improvement of the framework is proceeding to increase the efficacy and specificity by structural enhancements and variation.

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