International Letters of Chemistry, Physics and Astronomy
ISSN: 2299-3843, Vol. 68, pp 10-17
doi:10.18052/www.scipress.com/ILCPA.68.10
2016 SciPress Ltd, Switzerland

Submitted: 2016-02-25
Revised: 2016-04-02
Accepted: 2016-06-30
Online: 2016-07-19

Synthesis, Characterization and Antimicrobial Activities of some Novel 3-(4-Bromobenzyl)-5-(Thiophen-2-yl)-4H-1,2,4-Triazol Derivatives

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Keywords: Triazole derivatives, 3,4,5-trisubstituted-1,2,4-triazol, thiophene derivatives, Antimicrobial activities.

ABSTRACT. A convenient and promising synthesis of 4-(alkyl/aryl)- 3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol was carried out by the reaction of 2-(4-bromobenzyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole with different aliphatic/aromatic primary amine without any solvent. The newly synthesized compound were characterized by ^{1}H NMR, IR and Mass spectroscopy and also screened for their antimicrobial activity against various strains of bacteria and fungi.

1. INTRODUCTION

Now a days research is concentrated towards the introduction of new and safe therapeutic agents of pharmaceutical use. The nitrogen containing heterocycles are found in most of the pharmaceutical compounds. In past years various substituted triazole derivatives were synthesized and found to possess remarkable medicinal and biological properties.

Triazoles are 5-membered rings, which contain two carbon and three nitrogen atoms. The triazoles are show isomeric forms depend upon the position of nitrogen atoms [1]. Fisher was synthesized first time the parent compound triazole in 1878 [31]. The name triazole was first given to the carbon-nitrogen ring system $C_2N_3H_3$ by Bladin in 1885 [3, 4]. In the world over 0.2 million 1,2,4-triazole derivatives have been reported in the literature [2]. Two structural isomeric triazoles are known, the 1,2,3-(1,2,5) as osotriazole and the 1,2,4-(1,3,4)- known as triazole. Both the form are exists in two dissimilar tautomeric forms. The different isomers are characterized by the position of the nascent hydrogen. Thus 1,2,4-triazoles are exist in two forms i.e. 1*H* and 4*H* [5]. Out of the two triazoles 1, 2, 4- triazole has wide variety of activity [6]. 1,2,4-Triazoles are important five-member heterocycles, involved in a broad range of industrial applications such as agrochemicals, corrosion inhibitor, dyes, optical brighteners and biologically active agents [7].

The 1,2,4- triazole derivatives of clinically significance includes **Rizatriptan**(1) [8] as an anantimigraine agent, **Trazodone**(2) [9,10] as an antidepressant, **Dapiprazole**(3) [11] as a miotic agent, Ribavirin(4) [12] as an antiviral agent, **Israpafant**(5) [13] as an antiasthmatic, **Lotrifen**(6) [14] as an abortifacient and **Rilmazafone**(7) [15] as a potent sedative and hypnotic agent. Some 1,2,4- triazole derivatives are also found to be useful as potent antiestrogens, most common examples which are **Anastrozole**(8) [16], **vorozole**(9) [17] and **letrozole**(10) [18,19]. Many potent antifungal derivatives exhibited antifungal activity is attributed to the presence of triazole ring system. Most common examples of triazole containing antifungal derivatives include **Fluconazole**(11) [20], **Voriconazole**(12) [21] and **Itraconazole**(13) [22]. The triazole derivatives also used as potent hypnotic agents. This type of derivatives are fused triazole at 1,2-position of 1,4-benzodiazepines to give **Estrazolam**(14) [23], **Triazolam**(15) [24] and **Alprazolam**(16) [25]. The triazole derivatives also used as anti diabetic[29] like **Sitagliptin**(17) [26, 27], anti HIV agent like Maraviroc(18) [28], anticancer agents [30],antioxident [32] and antibacterial [33].

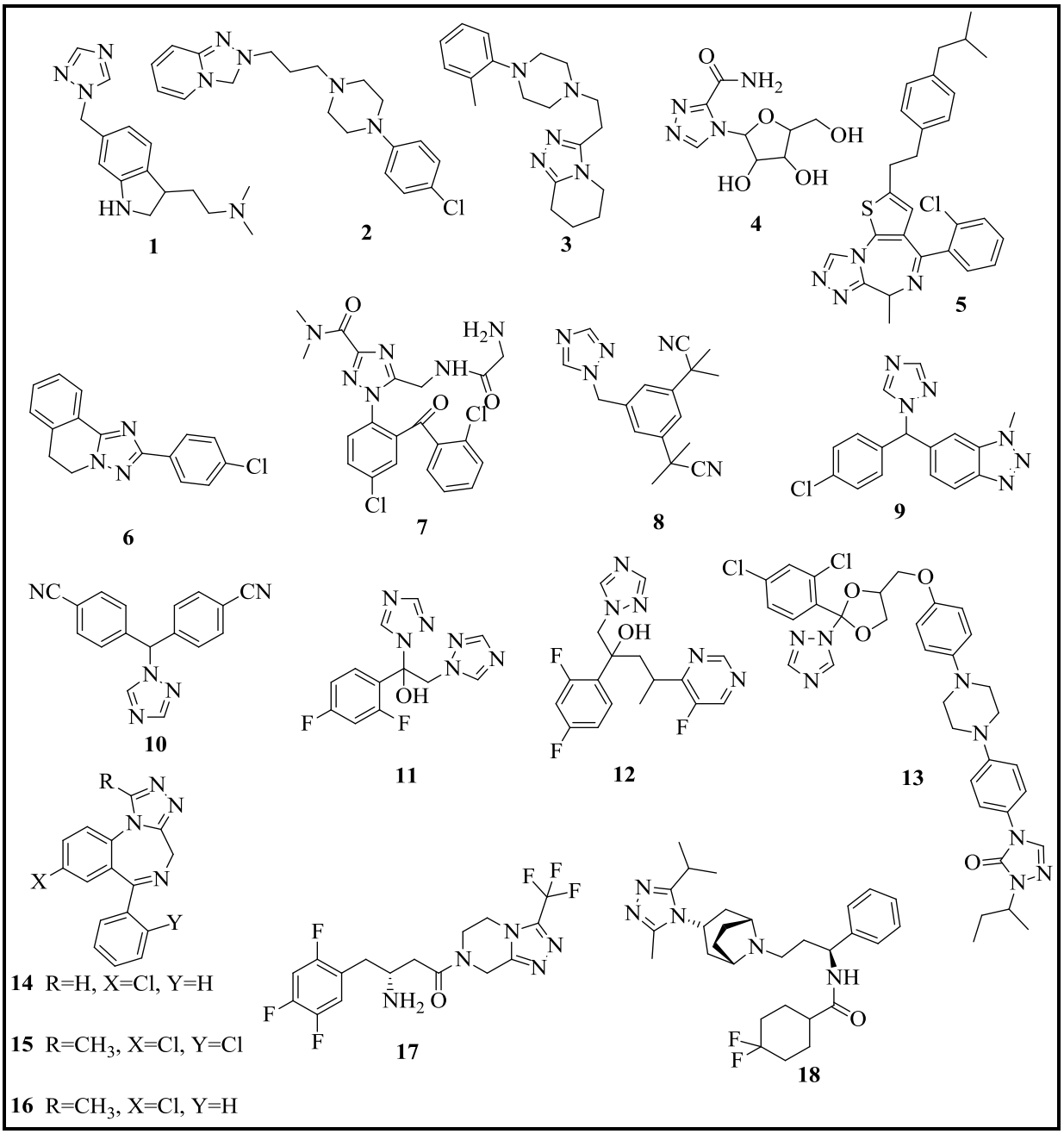

Figure 1: Triazole derivatives as theraputic agents

We have synthesized novel 3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol derivatives by condensation of oxadiazole and primary amine. The newly synthesized compounds were characterized by IR, Mass and ^{1}H NMR spectroscopy. All the synthesized compounds were evaluate for their antimicrobial activity.

2. EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. The progress of the reaction was monitored by analytical TLC on precoated plates (silica gel 60, F254) and visualized with UV light. Melting points were determined using open capillary tube and are uncorrected. Flash column chromatography was performed with silica gel 60 (60-120 mesh). NMR spectra were recorded using DMSO-d^6 as a solvent on a Bruker 400 MH_z and chemical shifts are expressed in parts per million (ppm) related to internal standard TMS. Infrared spectra were determined on a Shimadzu IR Affinity-1S. The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 100-800 Da, 20-V cone voltage, and Xterra MS C_{18} column (2.1 mm x 50 mm x 3.5 µm).

Preparation of Methyl 2-(4-bromophenyl)acetate (2).
To a stirred suspension of 4-bromo phenyl acetic acid (60.0 g, 279.0 mmol) in dry methanol (300 ml, 5T), concentrated sulfuric acid (5.46 g, 55.8 mmol) was added drop wise after 5 minutes. The resultant solution was stirred for 2 hours at reflux temperature, and then solvent was evaporated under vacuum. The product was dissolved in water and extracted with dichloromethane (120 ml × 2). The combined organic layers were washed with 5% sodium bicarbonate solution (300 ml) followed by water (300 ml), brine (300 ml) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give analytical pure product (55.0 g, Yield: 87 %).

Preparation of 2-(4-bromophenyl)acetohydrazide (3).
To a stirred cooled (ice bath) solution of methyl 2-(4-bromophenyl)acetate (50.0 g, 218.2 mmol) in isopropyl alcohol (500 ml, 10T), hydrazine hydride (21.84 g, 436.5 mmol) was added drop wise. The obtained solution was stirred at 10-20^{o}C for 1-2 hours. White solid product was precipitate after some time. The product was isolated by filtration and washed with isopropyl alcohol (100 ml x 2) to give pure product as a white solid (45 g Yield: 95 %), mp 140-145^{o}C.

Preparation of 2-(4-bromobenzyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (5).
To a mixture of 2-(4-bromophenyl)acetohydrazide (40.0 g, 174.61 mmol) and thiophene-2-carboxylic acid (24.61 g, 192.1 mmol), Phosphorus oxychloride (40 ml, 1.0T) was added drop wise. The obtained solution was stirred at 70-80°C for 4-6 hours (monitored by TLC), then poured onto crushed ice (400 g), and adjust pH 7.0 with 15% potassium bicarbonate solution, the product was isolated by filtration and washed with water (80 ml X 4) to give impure product. The impure product was recrystalize in isopropyl alcohol (200 ml, 5T) to give pure product as off white solid (40.0 g, Yield: 71.4 %).

General procedure for the preparation of 4-Substituted-3-(4-bromobenzyl)-5-(thiophen -2-yl)-4H-1,2,4-triazole (6a-o)
A mixture of 2-(4-bromobenzyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (1.0 g, 3.1 mmol) and different aliphatic/aromatic primary amine (2.8 mmol) was heated at 120-140 oC for 8-15 hours. The progress of the reaction was monitored by TLC. After the completion of reaction cool the reaction mass at room temperature. The obtained residue was dissolved in ethyl acetate (10.0 ml) and cool the solution at 0-10 oC. pH =1-2 was adjusted by hydrogen chloride in ethyl acetate. The reaction mass was stirred for 15-20 minutes, then the product was isolated by filtration and wash by ethyl acetate (1 ml X 3) to give the pure product. The product was dry at 50-55oC to give analytical pure product (Yield: 60-85 %).

Preparation of 2-(3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)ethanol (8)
A mixture of 2-(4-bromobenzyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (20.0 g, 62.26 mmol) and ethanol amine (12.7 g, 186.8 mmol) was heated at 120-140 oC for 15 hours. The progress of reaction was monitored by TLC. After completion of the reaction, cool the reaction mass at room temperature. The ethyl acetate (60 ml) was added to the residue and stirred for 30 minutes, the resultant solid was filtered to give impure product. The product was recrystalized in methanol to give pure product as light yellow solid (13.94 g Yield 61.7 %).

General preparation of ester derivatives of 2-(3-(4-bromobenzyl) -5-(thiophen-2-l)-4H-1,2,4-triazol-4-yl)ethanol (9a-j)
To a stirred cooled (ice bath) solution of different aliphatic/aromatic carboxylic acid (3.3 mmol), EDC.HCl (0.8g, 4.1 mmol) and HOBT (0.4 g, 2.7 mmol) in dimethylformamide (5 ml), the solution of 2-(3-(4-bromobenzyl)-5-(thiophen-2-l)-4H-1,2,4-triazol-4-yl)ethanol (1.0 g, 2.7 mmol) in dimethyl formamide (5 ml) was added drop wise. The obtained solution was stirred at 50-60oC for 8-10 hours (monitored by TLC), then poured onto water (50 ml) and extracted with ethyl acetate (10 ml X 3). Combine ethyl acetate layers were wash with water (10 ml X 3), followed by brine solution (10 ml) and dried over anhydrous sodium sulfate. The solvent was removed in vacuum to give impure product. The product was purified by column chromatography in ethyl acetate and cyclohexane to give pure product (Yield 50-70 %).

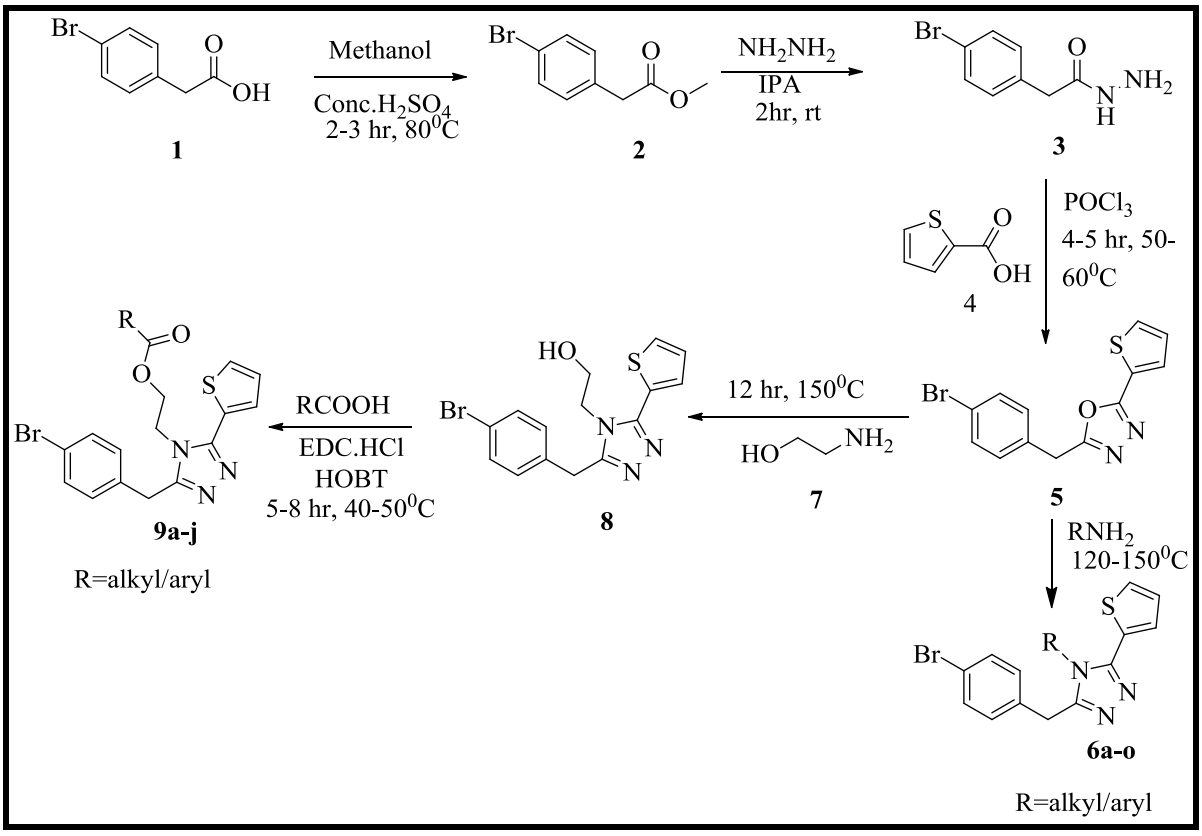

Figure 2: Reaction Scheme for 6a-o and 9a-j

3-(4-bromobenzyl)-4-(4-fluorophenethyl)-5-(thiophen-2-yl)-4H-1,2,4-triazole(6b):
Light yellow; mp; 190; Yield: 64 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ=2.752-2.785 (t, 2H), 4.219-4.223 (d, 2H), 4.395 (s, 2H), 7.043-7.063 (d, 4H), 7.279-7.300 (d, 3H), 7.550-7.571 (d, 2H), 7.675 (s, 1H), 7.905 (s, 1H), ppm; **MS**: m/z 442.1 (M(Br^{79})+H)$^+$ 444.1 (M(Br^{81})+H)$^+$; **IR cm^{-1}**: 3032.10, 2970.38, 2833.43, 1653.00, 1595.13, 1489.05, 1226.73, 721.38

3-(4-bromobenzyl)-4-butyl-5-(thiophen-2-yl)-4H-1,2,4-triazole(6h):
Cream solid; mp:163;Yield: 75 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ=0.725-0.761 (t, 3H), 1.151-1.243 (m, 2H), 1.330-1.407 (m, 2H), 4.140-4.157 (d, 2H), 4.396 (s, 2H), 7.284-7.309 (m, 3H), 7.337-7.357 (d, 2H), 7.737 (s, 1H), 7.936 (s, 1H) ppm; **MS**: m/z 376.2 (M(Br^{79})+H)$^+$ 378.2 (M(Br^{81})+H)$^+$; **IR cm^{-1}**: 3012.91, 2970.38, 2866.22, 1668.43, 1595.13, 1489.05, 1228.66, 821.68, 719.45

3-(4-bromobenzyl)-4-(4-chlorophenyl)-5-(thiophen-2-yl)-4H-1,2,4-triazole(6d):
Off-white solid; mp:210;Yield: 80 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ= 3.978-4.004 (d, 2H), 6.980-7.033 (m, 4H), 7.404-7.489 (m, 4H), 7.609-7.663 (m, 3H), ppm; **MS**: m/z 430.0 (M(Br^{79})+H)$^+$ 432.0 (M(Br^{81})+H)$^+$; **IR cm^{-1}**: 3034.03, 2970.38, 2835.36, 1653.00, 1570.06, 1489.05, 1226.73, 775.38, 721.38

2-(3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)ethyl-2-(4-bromophenyl) acetate (9b)
White solid; mp:157;Yield: 58 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ = 3.435 (s, 2H), 4.204-4.270 (t, 4H), 4.489 (s, 2H), 7.058-7.079 (d, 2H), 7.269-7.274 (d, 3H), 7.452-7.473 (d, 2H), 7.526-7.546 (d, 2H), 7.679-7.695 (d, 1H), 7.855-7.878 (t, 1H) ppm; **MS:** m/z 560.0 (M(Br^{79})+H)$^+$ 562.0 (M(Br^{81})+H)$^+$; **IR cm^{-1}:** 3030.17, 2931.80, 1722.43, 1489.05, 1232.51, 1010.70, 854.47, 721.38

2-(3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)ethyl acetate (9e)
White solid; mp:160; Yield: 64 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ = 1.774 (s,3H), 4.143-4.160 (q, 2H), 4.278-4.337 (t, 2H), 4.427-4.488 (m, 2H), 7.235-7.333 (m, 3H), 7.535-7.563 (t, 2H), 7.639-7.650 (m, 1H), 7.692-7.809 (t, 1H), ppm; **MS:**m/z 405.9 (M(Br^{79})+H)$^+$ 407.9 (M(Br^{81})+H)$^+$; **IR cm^{-1}:** 3032.10, 2951.09, 1734.01, 1489.05, 1228.66, 1010.70, 854.47, 721.38

2-(3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)ethyl pivalate (9f)
Off-white solid; mp:132;Yield: 57 %. **^{1}H NMR** (400 MHz, DMSO-d^6): δ = 0.934 (s, 9H), 4.150-4.163 (d, 2H), 4.322-4.364 (d, 2H), 4.539-4.575 (d, 2H), 7.263-7.322 (m, 3H), 7.537-7.579 (q, 2H), 7.724-7.785 (m, 1H), 7.834-7.886 (m, 1H), ppm; **MS:** m/z 448.4 $(M(Br^{79})+H)^+$ 450.4 $(M(Br^{81})+H)^+$; **IR cm^{-1}:** 3016.67, 2970.38, 1716.65, 1489.05, 1228.66, 1010.70, 856.39, 719.

Table 1: Physical Data of Compound 6a-o

Compound	R	Color	M.P.(°C)	Yield (%)
6a	3,4-Difluoro benzyl	Orange	190	85
6b	4-Fluoro phenyl ethyl	Light yellow	212	64
6c	Benzyl	Cream	180	72
6d	p-Chloro phenyl	Off white	210	80
6e	2-Nitro phenyl	Yellow	155	85
6f	Phenyl	Gray	220	78
6g	4-Fluoro benzyl	Orange	186	70
6h	n-butyl	Cream	163	75
6i	4-Methoxy phenyl	Gray	176	68
6j	Ethanol	Light yellow	179	79
6k	Thiophene-2-ethyl	Gray	185	82
6l	3-Methyl butanoic acid	Gray	207	73
6m	Methyl	Off white	164	68
6n	Ethyl	Off white	170	76
6o	Propyl	Off white	174	80

Table 2: Physical Data of Compound 9a-j

Compound	R	Color	M.P.(°C)	Yield (%)
9a	Phenyl	Cream	165	65
9b	p-Bromo benzyl	White	157	58
9c	Thiophene	White	115	60
9d	4-methyl phenyl	Light yellow	80	69
9e	Methyl	White	160	64
9f	Tertiary butyl	Off white	132	57
9g	4-Chloro phenyl	White	92	50
9h	Admantone	Dull orange	85	55
9i	4-Nitro phenyl	Light yellow	168	56
9j	n-butane	Off white	128	64

Table 3: Antibacterial and antifungal activity of compound 6a-o and 9a-j

Compounds	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
	B. megaterium	*S.aureus*	*E.coli*	*P. Aeruginosa*	*A. niger*	*A. flavus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
6a	1000	1000	500	500	500	1000
6b	1000	1000	1000	1000	1000	1000
6c	1000	1000	1000	1000	1000	500
6d	1000	1000	1000	1000	1000	1000
6e	250	1000	1000	1000	250	250
6f	1000	125	125	125	500	500

6g	1000	1000	1000	1000	500	500
6h	125	250	500	1000	1000	1000
6i	1000	1000	1000	1000	1000	1000
6j	500	1000	500	500	1000	1000
6k	500	500	1000	1000	1000	500
6l	1000	1000	500	500	500	1000
6m	1000	250	1000	500	1000	1000
6n	1000	1000	1000	500	500	500
6o	1000	1000	500	1000	500	500
9a	250	500	250	250	250	250
9b	250	125	125	250	125	125
9c	125	1000	125	125	500	500
9d	250	500	500	500	250	250
9e	250	250	125	250	250	250
9f	125	125	125	125	125	125
9g	1000	1000	1000	1000	1000	500
9h	500	250	250	500	1000	250
9i	125	250	1000	1000	1000	1000
9j	500	1000	500	1000	1000	500

2. 1. RESULTS AND DISCUSSION

Various methodologies and process have been described for the synthesis of 1,2,4-triazol. During the study of literature on triazole we found that 1,3,4-oxadiazole are versatile intermediate or scaffold for the synthesis of 1,2,4-triazole. Thus, we first synthesised 1,3,4-oxadiazole corresponding to our target molecule.

4-bromo phenyl acetic acid **1** was reacted with methanol in the presence of catalytic conc.sulphuric acid to give Methyl 2-(4-bromophenyl)acetate **2** which was then converted in to 2-(4-bromophenyl)acetohydrazide **3** by reaction with hydrazine hydride in isopropyl alcohol at 25-35 °C. The product was then reacted with thiophene-2-carboxylic acid **4** in phosphorus oxychloride at 70-80°C to give 2-(4-bromobenzyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole **5** scaffold. The oxadiazole scaffold was reacted with different substitutes aromatic or aliphatic amine to give different novel 3-(4-bromobenzyl)-4-alkyl/aryl-5-(thiophen-2-yl)-4H-1,2,4-triazole **6**. These new compounds were purified by crystallization in appropriate solvent. All the reactions were smooth, and provided the products in the range of 60-85% yield.

Also the oxadiazole scaffold was reacted with ethanol amine **7** to give 2-(3-(4-bromobenzyl)-5-(thiophen-2-l)-4H-1,2,4-triazol-4-yl)ethanol **8** scaffold. This scaffold **8** was reacted with different substitutes aromatic and aliphatic carboxylic acid in the presence of EDC.HCl and HOBT to give different novel 2-(3-(4-bromobenzyl)-5-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)ethyl alkylate/arylate **9**. These new compounds were purified by column chromatography in silicagel.

The newly synthesized derivatives were evaluated for their in vitro antibacterial activity against gram negative *Escherichia coli* and *Pseudomonas aeruginosa*, gram positive *Staphylococcus aureus* and *Bacillus megaterium* and antifungal activity against *Aspergillus niger* and *Aspergillus flavus* by micro broth dilution method. The standard strains used for screening antibacterial and antifungal activities were procured from Atmiya Institute of Pharmacy in-vitro testing Laboratory, Rajkot, Gujarat, India. The MIC values are given in **Table-3**. The standard drugs used for antibacterial activity were Streptomycin, Ampicillin and Nystatin for antifungal activity. 1000 µg/mL, 500 µg/mL, 250 µg/mL, 125 µg/mL and 62.5 µg/mL, concentrations of the synthesized drugs were taken.

3. CONCLUSION

An efficient method was described for preparation of 3-(4-bromobenzyl)-5-(thiophen-2-yl)-4*H*-1,2,4-triazol derivatives in good yield and the structure of synthesized compounds was determined by IR, ^{1}H NMR, and LC-Mass spectroscopic analysis.

All the synthesized compounds were evaluated for their antimicrobial activity. The investigation of antimicrobial and antifungal screening data revealed that compound 9a, 9b, 9d, 9e and 9f are broad spectrum drug which can inhibit the growth of gram positive, gram negative bacteria and fungi and 6a, 6b, 9h and 9i are active against gram positive bacteria. Whereas rest of the compounds is also potent drug, gives narrow spectrum action against pathogenic microbes.

Acknowledgement

The authors are thankful to UGC for financial support under the scheme of Innovative PG Program and also to Atmiya in-vitro Testing Laboratory, Yogidham, Rajkot for antimicrobial activity studies.

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