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SYNTHESIS AND ANTI BACTERIAL EVALUATION OF NOVEL (4-(2-FLUORO-4-(1*H*-1,2,3,-TRIAZOL-1-YL)PHENYL)PIPERAZIN-1-YL)KETONE ANALOGUES

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ABSTRACT

Encouraged by the various pharmacological and biological importance on triazole hybrids in this work, we have designed a simple synthetic method for the synthesis of novel (4-(2-fluoro-4-(1*H*-1,2,3,-triazol-1-yl)phenyl)piperazin-1-yl)ketone derivatives (**7a-j)**, evaluated for *in vitro* antibacterial targets**.** The antibacterial screening outcomes revealed the prepared compounds showed good antibacterial activity. Among the synthesized compounds **7d, 7i,** and **7j** displayed noteworthy anti-bacterial activity. The tetrazole hybrid **7j** exhibited superior inhibition of *Enterobacter aerogenes* and *Bacillus subtilis* pathogens with MIC values of 113±0.68and 73±1.92µg/mL respectively. The molecule **7c** is most effective against *Enterobacter aerogenes, Bacillus subtilis* with consecutive MIC's of 128±1.88 µg/mL and 91±1.74 µg/mL.

KEYWORDS: Piperazine, Triazoles, Molecular hybridization, antibacterial activity.

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1. INTRODUCTION

N-heterocyclic compounds are widely distributed in nature and are essential components of numerous physiologically significant substances, including nucleic acids, vitamins, medications, agrochemicals and dyes [i]. In addition to the pharmaceutical industry, they are well-known in the rapidly expanding fields of organic and medicinal chemistry. In *N*-containing five member heterocyclic compounds triazoles are of immense significance owing to their extensive range of biological applications such as anti-tubercular[ii], anticonvulsant [iii], antiviral [iv], antimicrobial [v], anti-diabetic [vi], anti-proliferative [vii], anti-inflammatory [viii], antioxidant [ix], anti-plasmodial and anti-malarial activities [x] and anti-urease [xi] activities.

Triazoles give organisms a variety of biological activities through their easy interaction with proteins, enzymes, and receptors [xii-xiii]. Numerous medicinal scaffolds have made extensive

use of their derivatives. In clinical practice, for example, the fluconazole (1990), antifungals itraconazole (1992), and voriconazole (2002) are frequently used. Ribavirin (2003) is a wide-spectrum anti-viral drug utilized in the hepatitis treatment. Rizatriptan (1998) is a drug moiety used as an anti-migraine agent. The anticancer medications letrozole (1997), anastrozole (2000), talazoparib (2018), and vorozole (1984) contain tetrazole ring and are all very effective. Additionally, Tazobactam (1986) is frequently used in antibiotic therapy, Rufinamide (2008) has FDA approval for treating pediatric epilepsy, and Maraviroc (2007) is an anti-HIV medication [ivx] (Figure 1) also contain triazole ring in their structure.

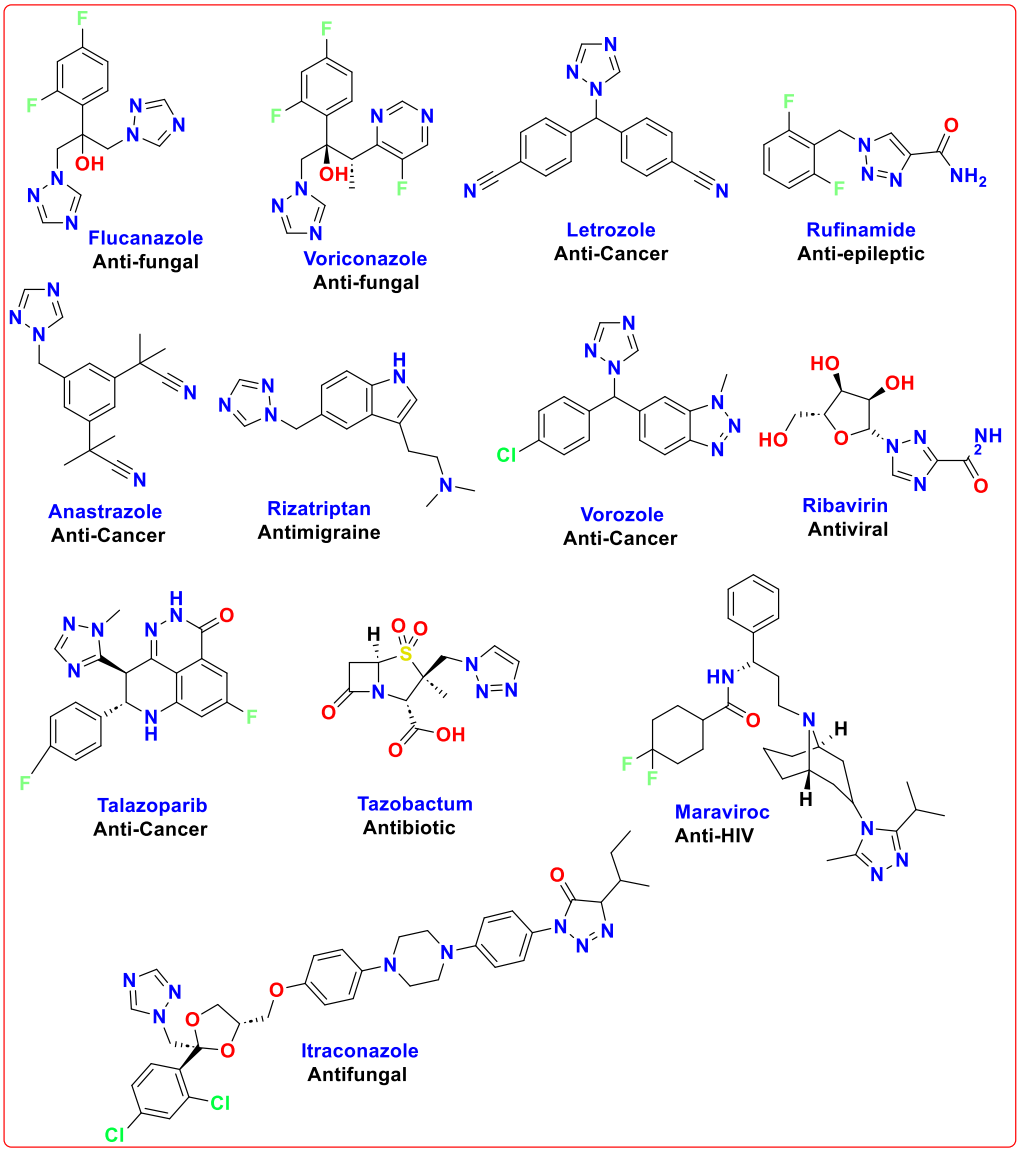


Fig. 1. Some bio-active compounds with triazole nucleus.

The synthesis and evaluation of a novel class of triazole-based hybrids and conjugates has demonstrated the potential of triazoles as linkers. These cutting-edge substances are being investigated as potential main candidates for a range of biological uses. Their efficiency covers a wide range, including their use as neuroprotective agents and as agents against cancer, bacteria, TB, viruses, diabetes, malaria, and leishmaniasis [xv].

Undoubtedly, nitrogen heterocyclic compounds represent the majority imperative structural scaffolds in pharmaceuticals, accounting for greater than 75% of FDA-endorsed drug molecules [i]. Piperazine heterocyclic with two nitrogen's is the 3rd largest in drug discovery, which found in various pharmacological agents with cardioprotective, anti-viral, anxiolytic, anti-depressant and anti-cancer activities. Additionally, it was an important constituent of numerous blockbuster drugs, such as *Sildenafil* (sold as *Viagra*), and *Imatinib* (marketed as *Gleevec*) [xvi-xvii]. In recent times, the bio applications of piperazine analogs have engrossed great research interest, with sundry biological properties such as antimicrobial[xviii], anti-fungal[xix], anti-inflammatory [xx] etc. Predominantly, the piperazine would be considered to be one of the most essential and substantial building blocks of many synthetic and natural anticancer agents [xxi] (Fig. 2).

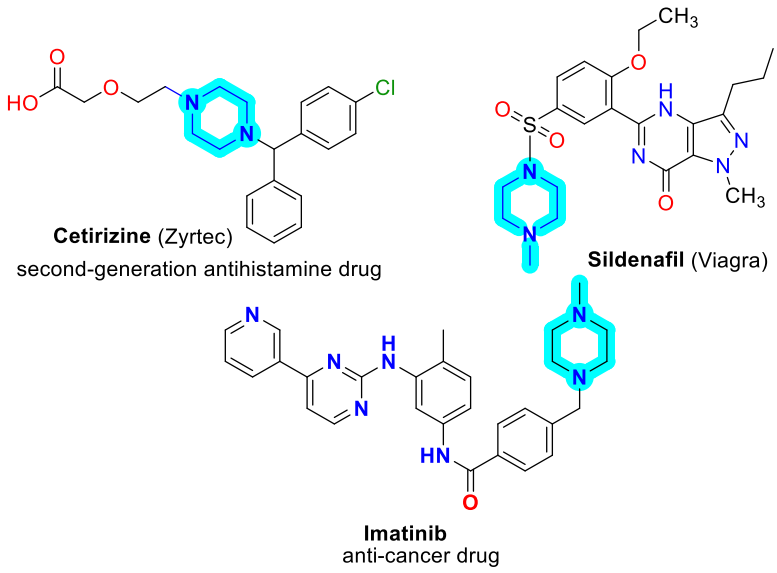


Fig.2. Drug molecules containing piperazine ring.

In case of drug candidates with piperazine ring the two heteroatom's advances the pharmacokinetic and pharmacological profile while the nitrogen atom locations work as both hydrogen bond acceptors/donors that optimize the receptor interactions and enhances the water solubility and bio-availability [xxii-xxiii]. Existence of extra nitrogen atoms permits the customization of the 3D geometry at the distal location of the pierazine ring, which is not easily accessible with the piperazine contiguous six-membered analogues like piperidines or morpholines. Therefore, it is not surprising that piperazine scaffold has been cited as a vital structure in design of a variety of bioactive motifs [xxii]. Piperazine analogues are best recognized for their extensive range of therapeutic properties, including anti-bacterial, antifungal, anticonvulsant, anti-depressant, antipsychotic, anthelmintic, antihypertensive, anti-malarial, anticancer, anti-inflammatory, and anti-HIV [xvi, xvii, xxii-xxiv] properties attributed mainly due to the existence of the extra nitrogen at the 4th location. Though, merely 20% of the piperazines presently employed in medicinal chemistry research have extra substituents on the piperazine carbons [xvi, xvii, xxii-xxiv] . It is evident that new, effective, and selective ways to access the carbon functionalization of the piperazine moiety are desirable in order to overcome the structural diversity, which actually impedes in medicinal chemistry applications in contrast to the archaic substitution prototypes at the N1-nitrogen [xxv-xxvii].

The present-day research in medicinal chemistry involves the wide use of pharmacophore hybridization strategy, to procure novel bioactive molecules with enhanced therapeutic properties, as hybridization of two or more dissimilar pharmacophores with consistent pharmacophore functions or with diverse modes of action often results in modified outcomes. Considering all the above aspects and in continuation of our previous efforts in synthesis of bio-active heterocycles [xxviii-xxix], in this present work we used the tactic towards design of a series of triazoles containing arylpiperazines hybrids using molecular hybridization strategy, and evaluated them against six clinically important bacterial strains together with both gram-negative and gram-positive class.

2. EXPERIMENTAL

2.1. Material and Methods

The chemicals have all been carried forward without additional purification; they were all bought from SRL-India, Merck, and Finar. Using a JASCO FT/IR-5300, IR spectra of KBr pellets were captured. We used $CDCl_3$ and DMSO as a solvent to record ^1H NMR spectras on a Varian 300 MHz spectrometer. Mass spectra were captured using the electro spray ionization (ESI) mode on an LC-MSD-Trap-SL device. Using silica gel plates that had already been coated, TLC was used to track each reaction (60F 254; Merck). Ten-to-twenty-fold excess (by weight) of the crude reaction product was used for column chromatography on 100–200 mesh silica gel (SRL, India). Over anhydrous sodium sulfate, the organic extracts were dried.

Synthesis of 3-fluoro-4-(piperazin-1-yl)benzenamine **(3) [**xxx-xxxi]: To the stirred solution of 16 grams (67.51 mmol) of 3-fluoro-4-iodobenzenamine **1** in 100 mL DMSO, 22.4 mg (10 mol %) $Pd(OAc)_2$, 10.5 grams (76 mmol) K_2CO_3 and 6grams (69.53mmol) Piperazine **2** were added and then heated to 60 °C for three hours. The after cooling to room temperature, the reaction mixture was diluted with 100 mL of water and then taken out using of ethyl acetate (3 X 100 mL). Later to obtain 3-fluoro-4-(piperazin-1-yl)benzenamine (**3**), the organic layer was removed, doused with 75 mL of brine solution, dried with Na_2SO_4, filtered, and concentrated *in vaccum.* White solid; Yield: 13 g, 82%; M.P: 124-126 °C.

Synthesis of 1-(4-azido-2-fluorophenyl)piperazine (**4**) [xxxii]: In a round-bottomed flask, 200 mg (2.14 mmol) of 3-fluoro-4-(piperazin-1-yl)aniline was dissolved in 4 mL of CH_3CN and cooled to 0°C in an ice bath. Next, 331 mg of (380 µL, 3.21 mmol) t-BuONO was added to this stirred mixture followed by the drop wise addition of 300 mg (340 µL, 2.56 mmol) of $TMSN_3$. The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to afford the product **4**, as a pale-yellow oil in 85 % yield.

Synthesis of 1-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazine (**5**) [xxxiii]: CuI (19 mg, 0.1 mmol), Sodium ascorbate (20 mg, 0.1 mmol), 1-(4-azido-2-fluorophenyl)piperazine (**4**) (0.5 mmol), CaC_2 (42 mg, 0.65 mmol), and MeCN–H_2O mixture (12 mL v/v = 2:1) were added to a flask. Then, at room temperature the mixture was stirred and TLC was used to track the reaction. Following the completion of the reaction, 6 % aq. HCl was used to neutralize the system to pH = 5, and the mixture was subsequently extracted using EtOAc (3 × 30 mL). After being separated, the organic layer was rinsed with water and allowed to sat. brine, then dried over anhydrous $NaSO_4$. Finally, the 1-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazine

(**5**) was obtained by column chromatography (silica gel, EtOAc–PE) using the crude product obtained from solvent evaporation.

*General procedure for the Synthesis of (4-(2-fluoro-4-(1H-1,2,3,-triazol-1-yl)phenyl)piperazin-1-yl)ketone derivatives **(7a-j):*** 149 milligrams (0.60 mmol) of *1-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazine* **(5)** was solvated in 10 mL THF and then cooled to 0 °C, next 18 milligrams (1.5 mmol) of DIPEA was added go after by 1.5 mmol acid chlorides **(6a-j)**. The overall mixture was stirred at R.T overnight and then it was quenched with H_2O and extracted thrice with 10mL ethyl acetate. Finally, the titled molecules **7a-j** were obtained after rinsing the organic with 10mL brine solution, drying with Na_2SO_4 and concentration in vacuum.

(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(phenyl)methanone **(7a):** Pale yellow solid; Yield: 83 %; M.P: 230-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.36(s, 1H), 7.27-6.90 (m, 4H, ArH), 7.57-7.32 (d, J = 7.5 Hz, 2H, ArH), 4.21(t, J = 4.8 Hz, 4H, CH_2), 3.53(t, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 155.2, 143.9, 138.8, 134.7, 132.4, 130.2, 124.9,123.9, 122.7,120.2, 118.9, 55.1, 47.3; IR (KBr, cm^{-1}): 3448, 3078, 2922, 2858, 1738, 1616, 1585, 1518, 1450, 1409, 1255, 866; m/z (ESI–MS) 352.18 $[M + H]^+$.
1-(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)-2-methylpropan-1-one **(7b):** Off white solid; Yield: 85 %; M.P: 190-192°C;.^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (s, 1H), 7.62-7.20 (m, 3H, ArH), 4.12 (t, J = 5.2 Hz, 4H, CH_2), 3.38 (t, J = 5.2 Hz, 4H, CH_2), 2.67(m, 1H, -$CH(CH_3)_2$), 1.3 (d, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 151.9, 136.5, 131.8, 128.5, 127.4, 124.4, 122.4, 108.9, 54.5, 44.5, 29.5,28.8, 28.1 ; IR (KBr, cm^{-1}): 3454, 3093, 2974, 2927, 2872, 1740, 1582, 1513, 1453, 1209, 938; m/z (ESI–MS) 318.21$[M + H]^+$.
(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(3-fluorophenyl)methanone (**7c**): Pale brown solid; Yield: 79%; M.P: 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.25 (s, 1H), 7.78-7.31 (m, 5H, ArH), 6.75-6.95 (m, 3H, ArH), 4.29 (t, J = 5.5 Hz, 4H, CH_2), 3.51 (t, J = 5.5 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.4, 155.4, 144.3, 142.9, 135.4, 134.6, 132.4, 128.6, 128.4, 127.3, 126.6, 124.8, 123.8, 122.9, 122.6, 46.3, 45.8; IR (KBr, cm^{-1}): 3434, 3040, 2923, 2852, 1656, 1607, 1534, 1482, 1391, 1255, 881; m/z (ESI–MS) 370.22 $[M + H]^+$.
1-(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)ethan-1-one **(7d)**:. Off white solid; Yield: 76 %; M.P: 218-220 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.56 (s, 1H), 7.23-7.65 (m, 3H, ArH), 4.13 (t, J = 4.8 Hz, 4H, CH_2), 3.54 (t, J = 4.8 Hz, 4H, CH_2), 2.43 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 151.3, 141.3, 132.9, 131.5, 124.3, 123.3, 122.7, 121.3, 51.6, 48.6, 45.2, 25.6; IR (KBr, cm^{-1}): 3445, 3066, 2962, 2911, 2890, 2856, 1730, 1699, 1614, 1580, 1518, 1449, 1382, 1302, 1257, 1161, 928; m/z (ESI–MS) 290.17$[M + H]^+$.
1-(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)-3,3-dimethylbutan-1-one **(7e):**. Pale yellow solid; Yield: 81%; M.P:157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 7.69-7.29 (m, 3H, ArH), 4.24 (d, J = 5.2 Hz, 4H, CH_2), 3.53 (t, J = 5.2 Hz, 4H, CH_2), 2.77 (s, 2H, CH_2), 1.18 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ:162.2, 154.8, 135.0, 134.9, 133.2, 127.9, 127.5, 122.8, 121.1, 52.2, 47.4, 46.5, 34.1, 25.5; IR (KBr, cm^{-1}): 3433, 3076, 2925, 2852, 1741, 1658, 1607, 1526, 1474, 1351, 1207, 917; m/z (ESI–MS) 346.27$[M + H]^+$.
(2-chlorophenyl)(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)methanone **(7f):** pale brown solid; Yield: 80%; M.P:.246-248 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.35 (s, 1H), 8.12-7.71(m, 5H, ArH), 7.21 (t, J = 8.5, 2H, ArH), 4.21 (d, J = 4.8 Hz, 4H, CH_2), 3.62 (t, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 151.8,142.2, 139.1, 135.8, 130.0, 129.9, 129.6, 128.9, 128.7, 124.2, 123.7, 122.3, 121.2, 120.7, 58.9, 55.8; IR (KBr, cm^{-1}): 3446, 3080, 2968, 2934, 1724, 1551, 1519, 1455, 1257, 1125, 943; ESI. MS: *m/z* 387.22 $(M+H)^+$.

(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(2-nitrophenyl)methanone **(7g):** Pale pink solid; Yield: 73%; M.P: 228-230 °C; ^{1}H NMR (400 MHz, DMSO) δ:9.35(s, 1H), 8.35 (d, J = 7.2 Hz, 2H, ArH), 7.97- 7.83 (t, J = 7.6 Hz, 2H, ArH), 7.45-7.67 (m, 3H, ArH), 7.3 (d, J = 7.6 Hz, 1H, ArH), 3.97 (t, J = 5.2 Hz, 4H, CH_2), 3.25 (t, J = 5.2 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 151.8, 142.2, 139.1, 135.8, 130.1, 129.8, 129.6, 129.0, 128.7, 124.2, 123.7, 122.5, 121.2, 120.7, 58.9, 45.8; IR (KBr, cm^{-1}): 3270, 3081, 2982, 2921, 2839, 1691, 1583, 1546, 1448, 1344, 1265, 1103, 936; m/z (ESI–MS) 397.18 $[M + H]^+$.

(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(2-hydroxyphenyl)methanone **(7h):** Off white solid; Yield: 83%; M.P: 272-274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.25(s, 1H), 7.48-7.15 (m, 3H, ArH), 7.78(m, 4H, ArH), 5.96 (s, 1H, OH), 4.11 (t, J = 4.8 Hz, 4H, CH_2), 3.34(t, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1, 160.9, 157.5, 155.4, 145.4, 144.1, 142.9, 132.3; 127.3.7, 124.9, 124.2, 123.9, 122.8, 121.3, 120.5, 54.9, 50.9; IR (KBr, cm^{-1}): 3415, 3100, 2927, 2866, 1731, 1703, 1617, 1590, 1517, 1476, 1233, 931; m/z (ESI–MS) 368.23$[M + H]^+$.

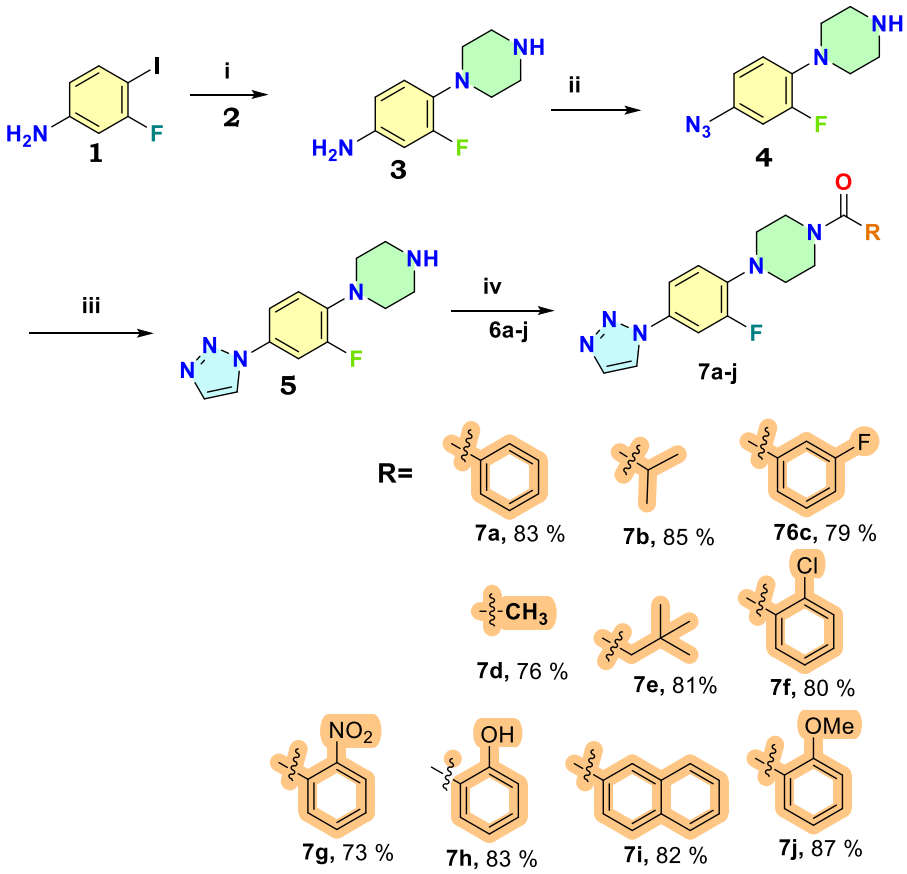
(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(naphthalen-2-yl)methanone **(7i):** Off white solid, Yield: 82%; M.P: 212-214 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.24 (s, 1H), 8.35 (d,2H, ArH), 7.89-7.47 (m, 6H, ArH), 7.31-7.22 (m, 1H, ArH), 4.15 (t, J = 4.8 Hz, 4H, CH_2), , 3.45(t, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 166.1, 157.5, 155.4, 147.5, 145.4, 144.1, 142.9, 132.3, 127.3, 124.8, 124.2, 123.9,122.6, 121.3, 120.4, 117.4, 115.4, 54.9, 51.0; IR (KBr, cm^{-1}): 3436, 3077, 2958, 2859, 1698, 1664, 1582, 1490, 1341, 1293, 1114, 940; m/z (ESI–MS) 402.21 $[M + H]^+$

(4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(2-methoxyphenyl)methanone **(7j)**: Off white solid; Yield: 87 %; M.P: 244-246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.45 (s, 1H), 7.90-7.79 (m, 2H, ArH), 7.65-6.98 (m, 5H, ArH), 4.12 (t, J = 4.8 Hz, 4H, CH_2), 4.03 (s, 3H, OCH_3), 3.47 (t, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 167.4, 144.3, 142.8, 135.4, 134.6, 132.4, 128.6, 128.4, 127.3, 126.6, 124.5, 122.4, 123.8, 122.6, 122.0, 121.3, 120.5, 55.0, 52.1, 46.3; IR (KBr, cm^{-1}): 3437, 3177, 2955, 2836, 1723, 1567, 1246, 1125, 1010, 923; m/z (ESI–MS) 382. 27 $[M + H]^+$.

3. RESULTS AND DISCUSSION

3.1. CHEMISTRY

The construction of (4-(2-fluoro-4-(1*H*-1,2,3,-triazol-1-yl)phenyl)piperazin-1-yl)ketones **7a-j** has been accomplished by the synthetic sequence pointed up in below scheme 1. In first step, the Cu catalyzed C-N cross coupling reaction of 3-fluoro-4-iodobenzenamine (**1**) with piperazine (**2**) in presence of Cs_2CO_3 base in DMSO at 110 °C for 4 h gave compound 3-fluoro-4-(piperazin-1-yl)benzenamine (**3**) in 80 % yield. Next, the reaction of amine **3** with $TMSN_3$ and ^{t}BuONO in CH_3CNa at room temperature for 4h directed to the construction of 1-(4-azido-2-fluorophenyl) piperazine (**4**) in 85 % yield. Next, the azide functionality of the intermediate **4** undergo electrocyclization using CaC_2, CuI, and Sodium ascorbate in MeCN/H_2O (2:1) at room temperature for 12 h provided the intermediate 1-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazine **5** in 85 % yield. Finally, coupling of intermediate **5** with diverse acid chlorides **6a-j** with DIPEA in THF between 0 °C to room temperature for about 12 h produced the consecutive amide derivatives **7a-j (**Scheme 2**)** in quantitative yields by adapting the protocol shown in **scheme 1**.



Scheme1. Synthesis of novel aryl piperazine tethered triazole derivatives **7a-j**.
Reagents and Conditions: (i) Piperazine (**2**), 10 mol % $Pd(OAc)_2$, K_2CO_3, DMSO, 60 °C, 3h; (ii) tBuONO (1.5 eq.),$TMSN_3$ (1.2 eq.), CH_3CN, r.t, 4h ; (iii) CaC_2 (1.3 eq.), CuI (0.3 eq.), Sodium ascorbate (0.3 eq.), $MeCN/H_2O$ (2:1), r.t, 6-18h (iv) THF, DIPEA, acid chlorides **5a-j**, rt, 7-12 h.

The formation of 3-fluoro-4-(piperazin-1-yl)benzenamine (**3**) was confirmed by mass spectrum of the compound showed a $(M+H)^+$ peak at 196.23 corresponding to molecular formula $C_{10}H_{14}FN_3$. In the ^{1}H-NMR spectrum of the intermediate **4,** proton signals at δ 7.26 ppm (multiplet, 2H) and δ 7.07 ppm (triplet, 1H) match up to the phenyl ring with 1,2,4-tri substitutions. The proton resonates at δ 4.80 ppm (brs, 2H), δ 3.89 ppm (triplet, 4H) and δ 3.17 ppm (triplet, 4H) correspond to the $–NH_2$, and $-N(CH_2)_2$ groups respectively. The IR spectra of the compound **4** contains distinctive absorption peaks at 3154, 1665 and peaks at 1340-1254 cm^{-1} designates the presence of as $–NH_2$, -C=N, -C-N aromatic functional groups respectively. High resolution mass spectra (HRMS) of the compound **4** gave a $(M+H)^+$ peak at 265.12 and corresponding to molecular formula $C_{11}H_{14}N_6OF$. Evidenced from the above spectral data, the intermediate **4** has been characterized as 1-(2-fluoro-4-(1*H*-tetrazol-1-yl)phenyl)piperazine.

Furthermore, in the characterization of title compound **7j,** the ^{1}H-NMR spectra of the compound **7j** showed proton signals at δ 9.21 ppm (doublet, 1H), 8.28 (ppm (doublet, 1H) indicates Ar -N=C-H protons *of* 1,2,3- triazole ring, δ 7.52-7.55 ppm (multiplet, 2H), δ 7.44 ppm (doublet, 1H), δ 7.18-7.15 ppm (multiplet, 1H), δ 6.89 ppm (doublet, 2H), corresponds to 1,2- substituted phenyl and 1, 2,4-trisubstitute phenyl rings. The proton signals δ 4.47 ppm

(triplet, 4H) δ 3.57ppm (triplet, 4H) represents the two -$N(CH_2)_2$ of piperazine ring and the signal at δ 4.14ppm (singlet, 3H) corresponds to -OCH_3 group. IR signals at 3100 (s), 2927 (s) cm^{-1} are of alkene and alkane –C–H stretchings. Bands at 1476(s) cm^{-1} in the IR spectra is because of *C=N* and at 1205 (m) cm^{-1} is of *N–N* stretchings. IR peak at 1703 cm^{-1} is of amide C=O stretching. Additionally, IR peaks at 1617(s), 1590 (m), and 1517 (w) cm^{-1} are of Ar–C=C stretching vibrations confirms the titled product **7j.** The molecular structure of the titled molecule **6j** is additionally authenticated by its ^{13}C NMR signals that discovered the existence of 16 diverse carbon atoms in that molecule.
The signals at δ 47.4 and 44.1 ppm were assigned to the carbons of *N*-methyenic functionality. The signals at δ 55.1 ppm stand for the –OCH_3 carbon. The peaks at δ 145.7 ppm and δ 167.4 ppm were of tetrazole and carbonyl carbons consecutively. Signal at 155.1 stand for the the aryl –C–F bond carbon. The peaks between 144.2–120.6 ppm can be allocated to the aromatic carbons of the compound (4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(2-methoxyphenyl)methanone (**7j**). The mass spectra of the compound showed a $(M+H)^+$ peak at 382.27 and corresponding to molecular formula $C_{20}H_{20}FN_5O_2$. The observed spectroscopic data characterized the title molecule **7j** as (4-(2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl)piperazin-1-yl)(2-methoxyphenyl)methanone. In the same way remaining title compounds of the series were also adequately characterized.

3.2. ANTI-BACTERIAL SCREENING

. The designed 4-(2-fluoro-4-(1*H*-1,2,3,-triazol-1-yl)phenyl)piperazin-1-yl)ketone derivatives (**7a-j)** were investigated for *in-vitro* anti-bacterial properties on the gram-negative bacterial strains *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* and gram-positive bacterial strains *Bacillus subtilis*, *Bacillus cerus*, *Staphylococcus aureus* by well diffusion method [xxxi]. Streptomycin was used as a standard antibacterial reference compound. The outcomes of antibacterial screening were tabulated in table 2 with zone of inhibition.

The antibacterial screening outcomes revealed that the titled compounds **7c, 7f, 7g, 7h**, **7i, and 7j** are active on all the six bacterial pathogens examined. The titled molecules (**7j**, **7c** and **7f)** exhibited potent inhibition against *Enterobacter aerogenes and Pseudomonas aeruginosa and Escherichia coli* strains with zone of inhibition values 18±0.5 to 27±1.3 mm. Similarly, the molecules **7j**, **7c**, and **7f** displayed fine inhibition on gram-positive pathogens *Staphylococcus aureus, Bacillus cerus,* and *Bacillus subtilis* with zone of inhibition values between with zone of inhibition values 8±1.8 to 26±1.1 mm.

Table 2. Antibacterial activity of the final compounds **7a-j** in Zone of inhibition (mm)

Molecule	***Microorganism***					
	Gram (–)			***Gram (+)***		
	E.aerogenes (-)	***P.aeruginosa (-)***	***E.Coli (-)***	***B.subtilis (+)***	***B. cerus (+)***	***S.aureus (+)***
6a	12±1.5	13±1.4	12±1.7	11±1.1	12±1.2	11± 0.9
6b	11±0.9	-	-	11±0.7	-	11±1.1
6c	23±1.3	24±1.4	18±1.5	23±1.8	22±1.4	19±1.4
6d	10±1.1	09±1.7	-	10±1.1	-	
6e	-	-	10±0.6	-	10±1.1	10±0.6
6f	23±0.4	23±1.5	18±0.8	22±1.1	21±0.7	18±1.8
6g	19±1.8	19±1.7	16±1.4	19±1.7	18±1.7	16±1.2
6h	19±1.1	18±1.8	16±0.7	18±1.8	18±1.1	16±0.8
6i	16±1.2	18±1.4	14±1.4	16±1.1	15±1.2	11±1.5
6j	27±1.3	26±1.4	20±1.4	26±1.1	25±1.2	21±1.6
Streptomycin	**33±2.5**	**32±2.1**	**29±1.9**	**32±2. 6**	**33±2.3**	**29±2.4**

-: No inhibition; Zone of inhibition diameter is presented in mm.

* Mean± Standard deviation of three replicates was expressed as results.

Table 3. MIC values of most potent titled compounds (µg/mL).

Entry	***E. aerogenes(-)***	***B. subtilis(+)***
7j	113±0.68	73±1.92
7c	128±1.88	91±1.74
7f	121±1.96	123±0.94
Streptomycin	**30**±0.59	**25**±0.32

After evaluation of zone of inhibition values, next molecules with prominent growth inhibition zones were further investigated for their minimum inhibitory concentration (MIC) value (µg/mL) by serial dilution technique and the outcomes were presented in table 2. The investigation outcomes specify that many of the examined molecules exhibited erratic inhibitory properties on bacterial strain growth. The MIC was calculated from Clinical and Laboratory Standard Institute (CLSI) method and guidelines (table 2). In present work, the MIC's was evaluated for the selected most effective **7j**, **7c**, and **7f** molecules. Compound **6j** exhibited excellent inhibition against *Enterobacter aerogenes* and *Bacillus subtilis* pathogens with MIC vales of 113±0.68µg/mL and 73±1.92µg/mL respectively. Moreover, the molecule **7c** exhibited good activity against the *Enterobacter aerogenes* and *Bacillus subtilis* pathogens by MIC values of 128±1.88µg/mL and 91±1.74µg/mL consecutively. Next, the compound **7f** showed good inhibition activity on *Bacillus subtilis with* MIC value of 123±0.94µg/mL and 121±1.96µg/mL against *Enterobacter aerogenes* Whereas the reference drug streptomycin show the MIC values of 30±0.59 µg/mL and **25**±0.32 µg/mL against the pathogens *Enterobacter aerogenes(-)* and *Bacillus subtilis(+)* correspondingly, indicating that the molecules **7j**, **7c**, and **7f** are less potent than reference streptomycin.

From the outcomes of the antibacterial investigation, it was assumed that (i) existence of an electron releasing unit at phenyl ring 2nd position in molecule **7j** is accountable for the potent activity on the examined bacterial pathogens; (ii) The +I effect of the units on phenyl ring

system is responsible for the antibacterial potency by augmenting the lipophilicity and consequently improve cell penetration rate; (iii) The location and nature of the substituted unit on the aryl ring effect the bacterial inhibiting capacity of the inspected molecules; (iv) The electron releasing units were accountable for their better antioxidant activities; (v) presence of halo units such as -F, -Cl on phenyl ring and napthyl ring are responsible for the activity of compounds **7c**, **7f** and **7i** respectively.

Procedure for antibacterial activity **[xxxi]**

Every compound was dissolved at a 1 mg/mL concentration in DMSO. In sterile Mueller Hinton medium, each one bacterium species was inoculated at 37 °C for a full day to build up inoculums. To get the turbidity to meet the 0.5 McFarland standards, the bacterial suspension was diluted with sterile saline. On sterile Mueller Hinton agar plates, a 200µL diluted suspension of each one pathogen was added inoculated. Next, in the agar medium, wells were punched. Each compound solution was divided into 100µL wells using a Micropipette. To assess its effectiveness against the pathogenic culture, a well was additionally filled with 100µL of DMSO solution without any compound. Then every petri dish was incubated at 37 °C for one day (24 h). Positive outcomes were regarded as a clear zone surrounding the well. Following the full incubation period, the produced compounds' antibacterial activity was assessed and noted the zone of inhibition in millimetre (mm).

4. CONCLUSION

In conclusion, a series of new (4-(2-fluoro-4-(1*H*-1,2,3,-triazol-1-yl)phenyl)piperazin-1-yl)ketone derivatives (**7a-j)** have been synthesized and characterized by mass, NMR, and IR spectral analysis. Further, the obtained molecules were evaluated in antibacterial studies. The *in vitro* antibacterial screening outcomes revealed that the molecules **7j**, **7f** and **7c** inhibited the majority anti-bacterial growth of all the tested pathogens. Further, the docking analysis indicated compounds **7j**, **7f** and **7c** showed highest binding energy. Moreover, *in silico* docking scores are in good correlation with the *in vitro anti-bacterial screening results* of the prepared molecules. As a result, medicinal chemists who work with antibacterial agents should consider the synthesized aryl-piperazine tethered triazole scaffolds as a potential, favorable alternative. However, further lead optimization is needed to get wide spectrum of activity.

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AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all the authors. The authors have given approval to the final version of the manuscript. VAN Satish, K. Johar, B. Manoj Kumar conceptualization, investigation, methodology, validation, writing; S N Murthy Boddapati and K.A. Emmanuel formal analysis, visualization, editing, and supervision.

CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

REFERENCES

i Kabir, E, Uzzama, M. A review on biological and medicinal impact of heterocyclic compounds. *Results in Chemistry*, **2022**, 4, 100606. https://doi.org/10.1016/j.rechem.2022.100606

Ii Druzhinin Boechat N, Ferreira VF, Ferreira SB, de Lourdes GFM, de CdSF BMM, Costa MD, Lourenço MC, Pinto AC, Krettli AU, Aguiar AC. Novel 1,2,3-triazole derivatives for use against Mycobacterium tuberculosis H37Rv (ATCC 27294) strain. J Med Chem 2011, 54(17):5988–5999. https://doi.org/10.1021/jm2003624

Iii Kadaba PK. Triazolines. 14. 1,2,3-Triazolines and triazoles, a new class of anticonvulsants. Drug design and structure-activity relationships. J Med Chem., 1988, 31(1):196–203. https://doi.org/10.1021/jm00396a032

iv Al-Soud YA, Al-Dweri MN, Al-Masoudi NA (2004) Synthesis, antitumor and antiviral properties of some 1,2,4-triazole derivatives. Farmaco 59(10):775– 783. https://doi.org/10.1016/j.farmac.2004.05.006 16.

v Zoumpoulakis P, Camoutsis C, Pairas G, Sokovic M, Glamoclija J, Potamitis C, Pitsas A (2012) Synthesis of novel sulfonamide-1,2,4-triazoles, 1,3,4- thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents. Biological evaluation and conformational analysis studies. Bioorg Med Chem 20(4):1569–1583. https://doi.org/10.1016/j.bmc.2011.12.031

vi De La Rosa M, Kim HW, Gunic E, Jenket C, Boyle U, Koh YH, Korboukh I, Allan M, Zhang W, Chen H, Xu W (2006) Tri-substituted triazoles as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase. Bioorg Med Chem Lett 16(17):4444–4449. https://doi.org/10.1016/j.bmcl.2006.06.048 11.

vii Padmavathi V, Sudhakar Reddy G, Padmaja A, Kondaiah P, Ali S (2009) Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4- thiadiazoles and 1,2,4-triazoles. Eur J Med Chem 44(5):2106–2112. https:// doi.org/10.1016/j.ejmech.2008.10.012

viii Labanauskas L, Udrenaite E, Gaidelis P, Brukstus A (2004) Synthesis of 5-(2-,3- and 4- methoxyphenyl)-4H-1,2,4-triazole-3-thiol derivatives exhibiting anti-inflammatory activity. Farmaco 59(4):255–259. https://doi.org/10.1016/j.farmac.2003.11.002

ix Shaikh MH, Subhedar DD, Arkile M, Khedkar VM, Jadhav N, Sarkar D, Shingate BB (2016) Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent. Bioorg Med Chem Lett 26(2):561–569. https://doi.org/10.1016/j.bmcl.2015.11.071

x Chu XM, Wang C, Wang WL, Liang LL, Liu W, Gong KK, Sun KL (2019) Triazole derivatives and their antiplasmodial and antimalarial activities. Eur J Med Chem 166:206–223. https://doi.org/10.1016/j.ejmech.2019.01.047

xi Khan I, Ali S, Hameed S, Rama NH, Hussain MT, Wadood A, Uddin R, Ul-Haq Z, Khan A, Ali S, Choudhary MI (2010) Synthesis, antioxidant activities and urease inhibition of some new 1,2,4-triazole and 1,3,4-thiadiazole derivatives. Eur J Med Chem 45(11):5200–5207. https://doi.org/10.1016/j.ejmech.2010.08.034

xii Dai, J.; Tian, S.; Yang, X.; Liu, Z. Synthesis Methods of 1,2,3-/1,2,4-Triazoles: A Review. *Front. Chem.* **2022**, *10*, 891484. https://doi.org/10.3389/fchem.2022.891484

xiii Rouzi, K.; Brandán, S.A.; El Houssni, I.; Poyraz, E.B.; Hassani, I.A.E.; Dege, N.; Abuelizz, H.A.; Oulmidi, A.; Bouatia, M.; Karrouchi, K. 4-Amino-5-(Pyridin-4-Yl)-4*H*-1,2,4-Triazole-3-Thiol as Potent Antimicrobial Agent: Synthesis, X-ray,

Antimicrobial Activity and Computational Studies. *J. Mol. Struct.* **2025**, *1320*, 139613. https://doi.org/10.1016/j.molstruc.2024.139613

xiv Khan, J.; Rani, A.; Aslam, M.; Maharia, R.S.; Pandey, G.; Nand, B. Exploring Triazole-Based Drugs: Synthesis, Application, FDA Approvals, and Clinical Trial Updates–A Comprehensive Review. *Tetrahedron* **2024**, *162*, 134122. https://doi.org/10.1016/j.tet.2024.134122

xv Bozorov, K.; Zhao, J.; Aisa, H.A. 1,2,3-Triazole-ContainingHybrids as Leads in Medicinal Chemistry: A Recent Overview. Bioorg. Med. Chem. 2019, 27 (16), 3511–3531. doi:10.1016/j.bmc.2019.07.005

xvi Vitaku, E., Smith, D.T., Njardarson, J.T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.*, *57*, 10257–10274. https://doi.org/10.1021/jm501100b

xvii Brunton, L., Chabner, B., Knollman, B. (2010). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacGraw-Hill: New York, NY, USA, 2010.

xviii Thriveni, K.S., Padmashali, B., Siddesh, M.B., Sandeep, C. (2014). Synthesis of Pyrimidine Incorporated Piperazine Derivatives and their Antimicrobial Activity. *Ind. J. Pharm. Sci.*,76, 332-338. 10.4103/0250-474X.139928

xix Radi, S., Toubi, Y., Hakkou, A., Souna, F., Himri, I., Bouka, M. (2012). Synthesis, Antibacterial andAntifungal Activities of Novel N,N'-bipyrazole Piperazine Derivatives. *Lett. Drug. Des. Discovery*, 9, 853-857. https://doi.org/10.2174/157018012803307941.

xx Batista, D.C., Silva, D.P.B., Florentino, I.F., Cardoso, C.S., Gonçalves, M.P., Valadares, M.C., Liao, L.M., Sanz, G., Vaz, B.G., Costa, E.A., Menegatti, R. (2018). Anti-inflammatoryeffect of a new piperazine derivative: (4-methylpiperazin-1-yl)(1-phenyl-1*H*-pyrazol-4-yl)methanone. *Inflammopharmacology*, 26, 217-226. https://doi.org/10.1007/s10787-017-0390-8.

xxi Al-Ghorbani, Md., Gouda, M.A., Baashen,Md., Alharbi, O., Almalki, F.A., Ranganatha, L.V. (2022) Piperazine Heterocycles as Potential Anticancer Agents: A Review. *Pharm. Chem. J*, 56, 29-37. https://doi.org/10.1007/s11094-022-02597-z

xxii Elliott, S. (2011). Current awareness of piperazines: Pharmacology and toxicology. *Drug Test. Anal.*, *3*, 430–438. doi: 10.1002/dta.307.

xxiii Shaquiquzzaman, M., Verma, G., Marella, A., Akhter, M., Akhtar, W., Khan, M.F., Tasneem, S., Alam, M.M. (2015). Piperazine scaffold: A remarkable tool in generation of diverse pharmacological agents. *Eur. J. Med. Chem.*, *102*, 487–529. https://doi.org/10.1016/j.ejmech.2015.07.026

xxiv Rathi, A.K., Syed, R., Shin, H.S., Patel, R.V. (2016). Piperazine derivatives for therapeutic use: A patent review (2010-present). *Expert Opin. Ther. Pat.*, *7*, 777–797. https://doi.org/10.1080/13543776.2016.1189902

xxv Zhang, R.H., Guo, H.Y., Deng, H., Li, J., Quanb, Z.S. (2021). Piperazine skeleton in the structural modification of natural products: A review. *J. Enzyme Inhib. Med. Chem.*, *36*, 1165–1197. https://doi.org/10.1080/14756366.2021.1931861

xxvi Blakemore, D.C., Castro, L., Churcher, I., Rees, D.C., Thomas, A.W., Wilson, D.M., Wood, A. (2018). Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.*, *10*, 383–394. https://doi.org/10.1038/s41557-018-0021-z

xxvii Cernak, T., Dykstra, K.D., Tyagarajan, S., Vachal, P., Krska, S.W. (2016). The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev., 45*, 546–576. https://doi.org/10.1039/C5CS00628G

xxviii Boddapati, S N M.; TALARI, S.; KOLA, A E.; Chalapaka, B. (2022). Synthesis of 2-aryl-5-(arylsulfonyl)-1,3,4-oxadiazoles as potent antibacterial andantioxidant agents," *Turkish Journal of Chemistry* 46(3),766-776. https://doi.org/10.55730/1300-0527.3366

xxix Saketi, J.M.R.; Boddapati, S.N.M.; M., R.; Adil, S.F.; Shaik, M.R.; Alduhaish, O.; Siddiqui, M.R.H.; Bollikolla, H.B. (2020). $Pd(PPh_3)_4$ Catalyzed Synthesis of Indazole Derivatives as Potent Anticancer Drug. *Appl. Sci.*, *10*, 3792. https://doi.org/10.3390/app10113792

xxx Viegas-Junior, C., Danuello, A., Bolzani, V.S., Eliezer J. Barreiro, Manssour Fraga, C.A. (2007). Molecular Hybridization: A Useful Tool in the Design of New Drug Prototypes. Current Medicinal Chemistry, 14(17), 1829-1852. http://dx.doi.org/10.2174/092986707781058805.

xxxi Phatak, P.S., Sathe, B.P., Dhumal, S.T., Rehman, N.N.M.A., Dixit, P.P., Khedkar, V.M., Haval K.P. (2019). Synthesis, antimicrobial evaluation and docking studies of substituted acetylphenoxymethyl-triazolyl-N-phenylacetamides. *J Heterocyclic Chem* 56,1928–1938. https://doi.org/10.1002/jhet.3568.

xxxii Barral, K., Moorhouse, A.D., J.E. Moses. Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages. *Org. Lett.* 2007, 9, 9, 1809–1811. https://doi.org/10.1021/ol070527h

xxxiii Yubo J., Chunxiang K., Qing Y.The Use of Calcium Carbide in the Synthesis of 1-Monosubstituted Aryl 1,2,3-Triazole via Click Chemistry. Synlett, **2009**, 19, 3163–3166. DOI: 10.1055/s-0029-1218346.

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