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RESEARCH ARTICLE

SYNTHESIS OF NEW [1,2,4] TRIAZOLO[4,3-*c*]QUINAZOLINE LINKED WITH PIPERAZINE SCAFFOLDS AS ANTIBACTERIAL AGENTS

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ABSTRACT

A series of new [1,2,4]triazolo[4,3-*c*]quinazoline linked with piperazine scaffolds 8(a-j) were synthesized and evaluated for their antibacterial activity against Gram-positive bacteria (*B. subtilis, S. aureus, M. luteus*), Gram-negative bacteria (*P. vulgaris, S. typhimurium, E. coli*). Antibacterial evaluation indicates, the compounds containing 2-chlorophenyl (8d) showed better activity against *S. aureus* and *M. Luteus*, 4-chlorophenyl (8e) showed better activity against Gram-positive and Gram-negative bacteria (except *E. coli)*. Similarly, compounds containing 4-nitrophenyl (8h) was active against all the tested strains *except S. Aureus*. The other compounds also exhibited considerable antibacterial activities.

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INTRODUCTION

Quinazolinone is an important pharmacophore and exhibits a wide spectrum of biological activities such as anticancer (Raghavendra, 2015), antimicrobial (Mishra, 1999), anticonvulsant (Jatav, 2007), antitubercular (Bhut, 2000), anti-inflammatory (Maggio, 2001), estrogenic (Murugan, 2000) and antiparkinsonism (Srivastava, 1987). Its derivatives have been approved as a drug including prazosin and doxazosine are used to treat benign prostatic hyperplasia and post traumatic stress disorder, erlotinib and gefitinib both are used for the curing of lung and pancreatic cancers, idelalisib and fenquizone have been shown to exhibit a broad spectrum of antimicrobial, antitumor, antifungal and cytotoxic activities, lapatinib has been displayed to be effective in combination therapy for breast cancer. Piperazine and substituted piperazines are important pharmacophores that can be found in many marketed drugs such as the Merck HIV protease inhibitor Crixivan (Vacca, 1994). Piperazinyl linked ciprofloxacin dimers reported as potent antibacterial agents against resistant strains (Kems, 2003), antimalarial agents (Ryckebusch, 2003) and potential antipsychotic (Yevich, 1986), antifungal (Upadhayaya, 2004), anti-inflammatory (Li, 2006), agonistic (Glase, 1997), dopamine D4 receptor agonist (Matulenko, 2004). Most of the drugs, such as norfloxacin and ciprofloxacin having piperazine nucleus showed broad spectrum activity of respiratory, urinary, gastrointestinal tracts, skin and soft tissue infection caused by either Gram-negative or Gram-positive bacteria (Hooper, 1999). Similarly, the applications of triazoles are increasingly found in all aspects of drug discovery, derivatives of triazole have been found to have antitubercular (Suresh Kumar, 2010), anti-HIV (Laazrek, 2001), anti-allergenic (Buckle, 1984), cytostatic (Delas Heras, 1979), virostatic (El-Etrawy, 2010), anti-cancer (Holla, 2003), anti-convulsant (Chen, 2007), analgesic (Almajan, 2009) and anti-inflammatory (Erhan, 2002) activities. Triazoles are also being studied for the treatment of obesity (Poulsen, 2008) and osteoarthritis (Joshua, 2003). There are number of drugs, which are containing triazole nucleus, such as Fluconazole (Yi, 2009), Isavuconazole (Pasqualott, 2010), Itraconazole (Alexander, 2010), Voriconazole (Smith, 2006), Pramiconazole (Geria, 2008), and Posaconazole (Schiller, 2008), that have been used for the treatment of fungal infections. Inspired by the biological properties of quinazolinone, piperazine and triazole derivatives, and in continuation of our research on biologically active heterocycles (Nagaraj, 2017, 2018, 2020) it was thought of interest to couple quinazolinone, piperazine and triazole to a single structure for enhancing biological activity. The present investigation deals with the synthesis of new [1,2,4]triazolo[4,3-*c*]quinazoline linked with piperazine scaffolds 8(a-j) to study their effect on bacterial strains.

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MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

2-Phenyl-3,4-dihydro-4-quinazolinone (2): To a stirred solution of anthranilamide **1** (0.01 mol) in absolute ethanol (10 mL), benzaldehyde (0.011 mol) and iodine (0/011 mol) was added and continued the stirring for about 15 min. The completion of the reaction was checked by TLC ($CHCl_3$: MeOH, 8:2) and *poured the reaction mixture in water (25 mL).* The resulting precipitate was filtered and washed with sodium thiosulphate solution (5%) and then with water and recrystalized from acetonitrile to get pure compound 2 as light yellow solid in 91% yield. IR (KBr) ν_{max}: 3341 (N-H), 3032 (CH-Ar), 1686 (C=O), 1612 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30 (d, J = 7.4 Hz, 2H, ArH), 7.50 (d, J = 7.4 Hz, 2H, ArH), 7.75-8.00 (m, 5H, ArH), 12.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 119.7, 124.6, 125.3, 126.0, 127.9, 128.7, 129.0, 130.2, 132.8, 141.5, 144,4, 160.8; MS: *m/z* 208, 223 (M^++1).

4-Chloro-2-phenylquinazoline (3): To a stirred thionyl chloride (20 mL), compound **2** (0.01 mol) in portions and DMF (5 mL) dropwise was added and refluxed the mixture at 80 ^{o}C for 3 h. After completion of reaction, the mixture was cooled and excess thionyl chloride was removed under reduced pressure. The residue obtained was dissolved in DCM (60 mL) and washed with a saturated solution of sodium carbonate thrice and dried. The solid obtained was recrystallized from ethanol to give compound **3** as brown solid in 78% yield. IR (KBr) ν_{max}: 3045 (CH-Ar), 1618 (C=N), 1605 (C=C), 689 (C-Cl) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.57-7.65 (m, 4H, ArH), 7.85-7.89 (m, 2H, ArH), 8.16-8.20 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.6, 125,0, 127.5, 128.6, 128.9, 129.1, 130.8, 133.8, 135.2, 149.8, 152.8, 161.3; MS: *m/z* 117, 205, 223, 237, 241 (M^++1).

5-Phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-amine (4): A mixture of compound **3** (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (20mL) was refluxed for 8 h. The reaction mixture was cooled to room temperature and the solid separated, was filtered off, dried, and purified by coloumn chromatography (silica gel 60-120 mesh) using ethylacetate and *n*-hexane (3:2) as an eluent to afford the pure compound 4 as brown solid with yield 62%. IR (KBr) ν_{max}: 3414, 3361 (NH_2), 3028 (CH-Ar), 1610 (C=N), 1607 (C=C) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.17 (s, 2H, NH_2), 7.50-7.62 (m, 5H, ArH), 7.78-7.90 (m, 1H, ArH), 8.15-8.63 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.3, 125.0, 126.9, 127.1, 128.6, 129.2, 131.2, 132.4, 136.5, 143.4, 150.7, 153.0, 155.1; MS: *m/z* 261 (M^++1).

5-Phenyl-3-piperazino[1,2,4]triazolo[4,3-*c*]quinazoline (7): To a solution of compound **6** (0.011 mol) in xylene (15 mL), compound 4 (0.01 mol) and *p*-toluenesulphonic acid (PTSA) (3%) was added and then heated the mixture to reflux at 140-145 ^{o}C for 12-24 h. After the completion of the reaction, crystalized the product by cooling to rt and purified by recrystallization to give pure compouns **7**. IR (KBr) ν_{max}: 3332 (N-H), 3032 (CH-Ar), 1612 (C=N), 1605 (C=C), 1472 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.35-3.40 (m, 4H, piperazine-H), 3.55-3.60 (m, 4H, piperazine-H), 5.70 (s, 1H, NH), 7.20-7.60 (m, 5H, ArH), 7.70-7.91 (m, 3H, ArH), 8.10 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.8, 49.5, 121.8, 123.4, 126.7, 127.0, 127.9, 128.3, 129.9, 132.8, 135.5, 141.5, 151.8, 155.8, 163.2; MS: *m/z* 330 (M^+).

General procedure for the synthesis of Phenyl[4-(5-aryl [1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8): To a solution of corresponding carboxylic acid (0.01 mol) in DCM (20 mL), *N*-hydroxybenzotriazole-HOBt (0.01 mol), 4-dimethylaminopyridine-DMAP (0.01 mol) and *N*,*N*-dicyclohexylcarbodiimide-DCC (0/011 mol) was added and stirred at room temperature for 30 min. To this reaction mixture, a solution of compound **7** (0.01 mol) in 10 mL CH_2Cl_2 was added and continued the stirring for 20 h at rt. Filtered the reaction mixture and washed with saturated aq. $NaHCO_3$ and 1 mol/L HCl, and dried by anhy. Mg_2SO_4 and then concentrated the solution in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-pettrolium ether (1:5) to give corresponding compounds 8(a-j).

Phenyl[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl) piperazino]methanone (8a): IR (KBr) ν_{max}: 3028 (CH-Ar), 1701 (C=O), 1614 (C=N), 1602 (C=C), 1454 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6):δ 3.40-3.50 (m, 4H, piperazine-H), 3.90-4.00 (m, 4H, piperazine-H), 7.32-7.55 (m, 10H, ArH), 7.80-7.90 (m, 3H, ArH), 8.10 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.2, 49.0, 122.4, 123.4, 125.6, 127.0, 127.8, 128.2, 128.9, 129.1, 130.7, 131.9, 132.2, 133.8, 137.0, 144.7, 150.9, 155.1, 159.3, 167.5; MS: *m/z* 434 (M^+).

(4-Methylphenyl)[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8b): IR (KBr) ν_{max}: 3029 (CH-Ar), 2871 (CH-Ali), 1698 (C=O), 1611 (C=N), 1601 (C=C), 1453 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.55 (s, 3H, CH_3), 3.35-3.40 (m, 4H, piperazine-H), 3.87-3.95 (m, 4H, piperazine-H), 8.95-7.10 (m, 4H, ArH), 7.35-7.50 (m, 5H, ArH), 7.82-7.91 (m, 3H, ArH), 8.12 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.6, 44.3, 48.7, 122.3, 123.6, 126.5, 127.2, 127.9, 128.4, 128.9, 129.2, 129.9, 131.4, 132.6, 137.1, 141.4, 145.5, 151.0, 155.4, 158.2, 167.1; MS: *m/z* 448 (M^+).

(4-Methoxyphenyl)[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8c): IR (KBr) ν_{max}: 3034 (CH-Ar), 2981 (CH-Ali), 1705 (C=O), 1615 (C=N), 1603 (C=C), 1451 (C-N), 1071 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 3.36-3.45 (m, 4H, piperazine-H), 3.90-4.00 (m, 4H, piperazine-H), 7.30-7.50 (m, 9H, ArH), 7.80-7.90 (m, 3H, ArH), 8.12 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 57.3, 43.4, 49.1, 115.4, 123.1, 123.9, 126.7, 127.2, 128.2, 128.9, 129.2,

130.2, 131.4, 132.5, 136.8, 143.5, 150.1, 154.7, 158.5, 159.6, 166.1; MS: *m/z* 465 (M^++1).

(2-Chlorophenyl)[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8d): IR (KBr) ν_{max}: 3037 (CH-Ar), 1710 (C=O), 1610 (C=N), 1605 (C=C), 1451 (C-N), 689 (C-Cl) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.30-3.40 (m, 4H, piperazine-H), 3.80-3.85 (m, 4H, piperazine-H), 7.10-7.15 (m, 3H, ArH), 7.30-7.58 (m, 6H, ArH), 7.70-7.85 (m, 3H, ArH), 8.09 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.4, 48.6, 121.9, 123.5, 125.8, 126.7, 127.2, 127.9, 128.0, 128.9, 129.0, 130.5, 131.2, 132.4, 133.1, 135.1, 136.8, 143.5, 149.2, 154.4, 158.7, 165.2; MS: *m/z* 468 (M^+).

(4-Chlorophenyl)[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanon (8e): IR (KBr) ν_{max}: 3022 (CH-Ar), 2954 (CH-Ali), 1699 (C=O), 1606 (C=N), 1610 (C=C), 1452 (C-N), 687 (C-Cl) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.42-3.50 (m, 4H, piperazine-H), 3.95-4.00 (m, 4H, piperazine-H), 7.15 (d, J = 7.6 Hz, 2H, ArH), 7.31-7.58 (m, 7H, ArH), 7.75-7.85 (m, 3H, ArH), 8.15 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.3, 48.2, 122.1, 124.1, 126.9, 127.1, 128.0, 128.9, 129.0, 129.9, 131.2, 132.4, 133.0, 135.4, 136.5, 143.8, 149.3, 154.4, 158.4, 166.1; MS: *m/z* 468 (M^+).

(4-Hydroxyphenyl)[4(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8f): IR (KBr) ν_{max}: 3349 (O-H), 3039 (CH-Ar), 1704 (C=O), 1611 (C=N), 1605 (C=C), 1457 (C-N), 1081 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.36-3.40 (m, 4H, piperazine-H), 3.85-3.90 (m, 4H, piperazine-H), 5.26 (s, 1H, OH), 7.00 (d, J = 7.6 Hz, 2H, ArH), 7.30-7.50 (m, 7H, ArH), 7.80-7.85 (m, 3H, ArH), 8.07 (d, *J* = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.1, 48.7, 114.9, 122.5, 123.9, 127.5, 128.0, 128.2, 128.4, 128.9, 129.3, 130.1, 131.4, 135.9, 143.5, 148.7, 154.3, 158.8, 154.0, 166.1; MS: *m/z* 451 (M^++1).

(2-Hydroxyphenyl)[4(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8g): IR (KBr) ν_{max}: 3345 (O-H), 3031 (CH-Ar), 1697 (C=O), 1610 (C=N), 1607 (C=C), 1459 (C-N), 1082 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.40-3.45 (m, 4H, piperazine-H), 3.90-3.95 (m, 4H, piperazine-H), 5.18 (s, 1H, OH), 7.05-7.10 (m, 2H, ArH), 7.30-7.52 (m, 7H, ArH), 7.75-7.80 (m, 3H, ArH), 8.05 (d, *J* = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.9, 48.8, 118.1, 120.8, 121.9, 122.0, 123.2, 126.9, 127.1, 127.4, 127.9, 129.3, 130.6, 131.5, 133.1, 136.9, 144.1, 149.4, 153.9, 155.0, 158.4, 168.1; MS: *m/z* 451 (M^++1).

(4-Nitrophenyl)[4-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino]methanone (8h): IR (KBr) ν_{max}: 3042 (CH-Ar), 1702 (C=O), 1613 (C=N), 1601 (C=C), 1522 (N=O), 1455 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.36-3.40 (m, 4H, piperazine-H), 3.70-3.80 (m, 4H, piperazine-H), 7.30-7.50 (m, 5H, ArH), 7.75-7.85 (m, 7H, ArH), 8.11 (d, *J* = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.8, 49.2, 123.1, 123.9, 123.6, 126.9, 127.8, 128.0, 128.9, 129.5, 130.7, 131.4, 137.1, 143.8, 144.0, 147.3, 149.7, 154.4, 158.2, 165.1; MS: *m/z* 479 (M^+).

[4-(5-Phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino](3-pyridyl)methanone (8i): IR (KBr) ν_{max}: 3044 (CH-Ar), 1696 (C=O), 1619 (C=N), 1610 (C=C), 1455 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.33-3.40 (m, 4H, piperazine-H), 3.86-3.92 (m, 4H, piperazine-H), 7.27-7.52 (m, 6H, ArH), 7.81-7.90 (m, 4H, ArH), 8.06 (d, *J* = 8.1 Hz, 1H, ArH), 8.50-8.60 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.9, 49.1, 123.5, 123.9, 127.1, 127.9, 128.0, 128.9, 130.3, 130.9, 131.8, 132.4, 133.1, 136.8, 141.7, 145.8, 148.7, 151.1, 154.2, 157.4, 167.4; MS: *m/z* 435 (M^+).

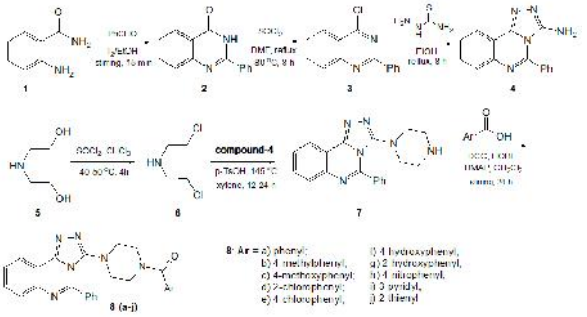
[4(5-Phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)piperazino](2-thienyl)methanone (8j): IR (KBr) ν_{max}: 3036 (CH-Ar), 1704 (C=O), 1611 (C=N), 1608 (C=C), 1456 (C-N), 1030 (C-S-C) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.39-3.48 (m, 4H, piperazine-H), 3.86-3.95 (m, 4H, piperazine-H), 7.05-7.10 (m, 2H, ArH), 7.28-7.56 (m, 6H, ArH), 7.75-7.86 (m, 3H, ArH), 8.11 (d, *J* = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.3, 49.1, 122.0, 123.8, 127.0, 127.8, 128.1, 129.0, 129.7, 130.4, 131.0, 131.9, 132.5, 135.8, 136.4, 144.1, 151.2, 153.4, 158.5, 166.2; MS: *m/z* 441 (M^++1).

RESULTS AND DISCUSSION

The anthranilamide 1 on reaction with benzaldehyde in the presence of iodine in ethyl alcohol at stirring for 15 minutes to yield 2-phenyl-3,4-dihydro-4-quinazolinone 2, which on chlorination with thionyl chloride in DMF at reflux for 3 h, gave 4-chloro-2-phenylquinazoline 3. The compound 3 on cyclo condensation with thiosemicarbazide in ethyl alcohol at reflux for 8 h, furnished the 5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-amine 4 in good yields. The compound 4 when reacted with compound 6, in the presence of p-TsOH in xylene at 145 ^{o}C for 12-24 h, afforded the 5-phenyl-3-piperazino[1,2,4]triazolo[4,3-*c*]quinazoline 7, which on reaction with corresponding aryl/heteryl carboxylic acid using HOBt, DMAP and DCC in DCM solvent at room temperature for 20 h to afford the corresponding phenyl[4-(5-aryl[1,2,4]triazolo [4,3-*c*]quinazolin-3-yl) piperazino] methanone 8(a-j) in good yields (Scheme 1). The structure of compounds was established from their IR, MS and NMR spectral analyses.

IR spectrum of **2,** the absorption bands due to C=O and NH are appeared at 1686, 3341 cm^{-1}. The C=N absorption band appeared at 1612 cm^{-1}. Its ^{1}H NMR spectra, the aromatic protons of both phenyl groups were appeared as a multiple at δ 7.30-8.00 and NH proton of quinazolinone ring appeared as singlet at δ 12.4 ppm. Its ^{13}C NMR specta, the signals of quinazolinone ring appeared at δ 124.6, 141.5, 144.4, 160.8, ppm. In the IR spectrum of **3,** the absorption bands appeared at 1618 (C=N), 1605 (C=C) and 689 (C-Cl) cm^{-1}. Its ^{1}H NMR spectrum, the signals appeared for the protons of aromatic ring in the range of at δ 7.57-8.20.

Its ^{13}C NMR specta, the signals appeared for quinazolinone ring at δ 116.6, 149.8, 152.8 and 161.3 ppm. In the IR spectrum of 4, the absorption bands appeared at 3414, 3361 (NH_2), 1610 (C=N) cm^{-1}. Its ^{1}H NMR spectrum, the signals appeared for the protons of aromatic ring in the range of at δ 7.50-8.63 and the protons of NH_2 group appeared as a singlet at δ 5.17 ppm, Its ^{13}C NMR specta, the signals appeared for quinazolinone ring at δ 123.3, 143.4, 155.1 and the signals of triazole ring at δ 150.7, 153.0 ppm.



Scheme 1. Schematic route for the synthesis of compounds 8(a-j)

The IR spectrum of 7, the absorption bands corresponding to NH and C=N appeared at 3332 and 1612 cm^{-1}. Its ^{1}H NMR spectrum, the signals for methylene protons of piperazine appeared as multiplets at δ 3.35-3.40 and 3.55-3.60 ppm integrating four protons in each, the signal at δ 5.70 as singlet for one proton is assigned to NH, the other aromatic protons appeared in the range of 7.20-8.10 for nine protons. Its ^{13}C NMR spectra, showed the signals of piperazine ring at δ 47.8 and 49.5 ppm, the quinazoline ring carbons at δ 123.4, 141.5 and 151.8 ppm, the triazole ring carbons at δ 155.8 and 63.2 ppm. The other signals were observed at the expected region. The IR spectra of compounds 8a, C=O and C=N absorption bands appeared at 1701 1614 cm^{-1} respectively. Its proton NMR spectra, showed the signals for protons of piperazine ring at δ 3.40-3.50 and 3.90-4.00 ppm, the other aromatic protons appeared at the expected region. Its ^{13}C NMR spectra, showed the signals of piperazine at δ 44.2, 49.0, the triazole ring at δ 155.1, 167.5 ppm.

ANTIBACTERIAL ACTIVITY: The *in vitro* antibacterial activity of compounds **8(a-j)** were evaluated against Gram +ve bacteria (*Bacillus subtilis, Staphylococcus aureus, Micrococcus luteus*) and Gram -ve bacteria (*Proteus vulgaris, Salmonella typhimurium, Escherichia coli*) by broth dilution method (Villanova, 1982).

The lowest concentration required to arrest the growth of acteria was regarded as the minimum inhibitory concentration (MIC, µg/mL) was determined for all the compounds and presented in **Table 1**. All assays included the solvent and reference controls, Ampicillin was used as standard drug. The investigation of antibacterial screening data revealed that all the tested compounds exhibited interesting biological activity, however, with a degree of variation.

Table 1: Antibacterial activity of compounds 8(a-j)

Compound	Minimum inhibitory concentration (MIC μg/mL)					
	B. subtilis	*S. aureus*	*M. luteus*	*P. vulgaris*	*S. typhimurium*	*E. coli*
8a	6.23	25.0	12.5	25.0	25.0	25.0
8b	6.25	12.5	3.12	25.0	12.5	12.5
8c	1.56	6.25	12.5	6.25	---	---
8d	3.12	1.56	1.56	6.25	6.25	25.0
8e	1.56	1.56	1.56	3.12	3.12	25.0
8f	6.25	12.5	6.25	25.0	---	---
8g	12.5	25.0	12.5	12.5	12.5	25.0
8h	1.56	3.12	1.56	3.12	1.56	12.5
8i	12.5	6.25	12.5	25.0	12.5	25.0
8j	6.25	12.5	12.5	6.25	25.0	---
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.5

Note: – indicates, strains are resistant to the compound >25 «g/mL conc.

Antibacterial evaluation of compounds 5(a-j) indicates, that these compounds showed considerable inhibition towards all the tested bacteria. Amongst them, compounds containing 2-chloroyphenyl (8d), 4-chlorophenyl (8e) and 4-nitrophenyl (8h) groups on piperazine ring showed considerable activity against tested bacterial strains. Compound, 8d showed better activity against *S. aureus* and *M. Luteus*, compound (8e) showed better activity against Gram-positive and Gram-negative bacteria (except *E. coli)*. Similarly, compounds containing 4-nitrophenyl (8h) was active against all the tested strains *except S. Aureus*. The other compounds also exhibited considerable antibacterial activities.

CONCLUSION

A series of new [1,2,4]triazolo[4,3-*c*]quinazoline linked with piperazine scaffolds **8(a-j)** were synthesized and evaluated for their antibacterial activity against various Gram positive and Gram negative bacterial strains. Antibacterial evaluation indicates, the compounds containing 2-chlorophenyl (**8d)** showed better activity against *S. aureus* and *M. Luteus*, 4-chlorophenyl (**8e**) showed better activity against Gram-positive and Gram-negative bacteria (except *E. coli)*. Similarly, compounds containing 4-nitrophenyl (**8h)** was active against all the tested strains *except S. Aureus*. The other compounds also exhibited considerable antibacterial activities and emerged as potential molecules for further development.

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