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# Synthesis, characterization and in vitro antibacterial evaluation of 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxamide derivatives

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**Abstract** A series of six novel 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxamide derivatives has been synthesized and characterized using various spectral techniques ($^{1}$H and $^{13}$C NMR, LCMS, IR). The antibacterial activities of these compounds have been screened against nine different Gram-positive and Gram-negative bacterial strains. The results show that quinazoline derivatives containing thiazole ring **2a** and **2b** exhibit good antibacterial activity amongst the compounds under investigation.

**Keywords** Synthesis · Characterization · Tetrahydroquinazoline · Piperazine · Morpholine · Antibacterial

## Introduction

Heterocyclic chemistry is playing an important role in medicinal chemistry and serving as key templates for numerous therapeutic agents [1–3]. The majority of the biologically active substances contain heterocyclic rings. Among them, the pyrimidine scaffold is found in many natural products and the chemistry of pyrimidine derivatives play an important role in the field of drugs, agricultural chemicals, and many biological processes [4–6]. The pyrimidine derivatives show various biological activities including antitubercular, anti-inflammatory,

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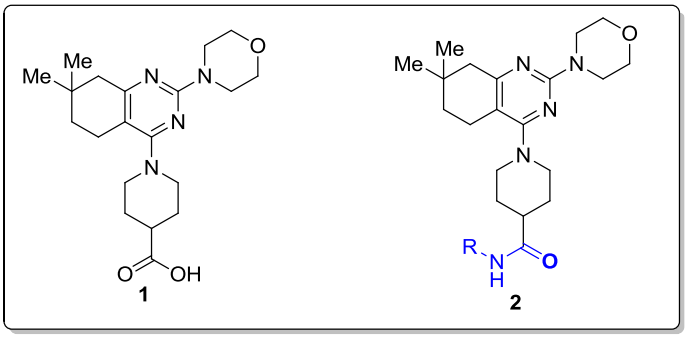
anticonvulsant, antimicrobial, antibacterial, antifungal, anticancer and analgesic [7–12]. 2-Morphilino-substituted pyrimidine derivatives have been used to treat diseases and disorders arising from abnormal cell growth, particularly those associated with PI3 kinase such as cancer, immune disorders, viral infection and neurological disorders [13–15]. A review of literature revealed that 2-(morpholin-4-yl)-5,6,7,8-tetrahydroquinazolin-4-amine derivatives were proved to show potent hypoglycemic activity [16]. Structure–Activity Relationship Study of 2-(morpholin-4-yl)-5,6,7,8-tetrahydroquinazolin-4-amine derivatives revealed its selective and potent inhibition of p97 ATPase [17] and GATA modulator [18]. Tricyclic ring containing morpholine, piperazine and pyrimidine were reported as fast-acting antimalarial agents [19] and histamine H4 receptor modulators [20]. Likewise, isonipecotic acid is one of the most important heterocyclic compounds found in many of the notable drugs, which act as antihelmintic, antidepressant and antihistamine [21].

Hence, it is presumed that molecules containing the 2-morphilino-substituted pyrimidine ring linked to isonipecotic acid along with extended amide would exhibit promising biological activity. Owing to the known biological properties of thiazole [22, 23], pyrimidine [4–6], hydrazine [24] and isoxazole [25] moieties, the amine group containing respective hetero molecules are used for preparing novel amide compounds which are expected to show enhanced biological activity. The main objective, therefore, of the present endeavor is the synthesis of 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxylic acid (**1**) and 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxamide derivatives (**2**) and screening the antibacterial activity of these compounds against Gram-positive and Gram-negative bacteria strains.

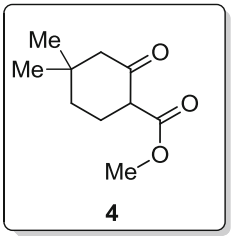



## Experimental

All the chemicals used in the study are ofcommercially available high-purity grade (Aldrich or Merck, India). The solvents were of commercially available reagent grade and used as supplied. TLC experiments were performed on alumina-backed silica gel 40F254 plates (Merck, Germany). The plates were illuminated under UV (254 nm) and $KMnO_4$. Melting points were determined using a melting point apparatus (B-540; Buchi, Germany) without corrections.

All $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker (Germany) 300 or 400 MHz NMR. Molecular masses of unknown compounds were checked by LCMS (6200 series; Agilent, India). Chemical shifts are reported in ppm ($\delta$) with reference to internal standard TMS. The signals are designated as follows: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), doublet of triplet (dt), multiplet (m), and broad singlet (bs). IR spectra were recorded using a Bruker Alpha FT-IR spectrometer (Bruker) using a diamond attenuated total reflectance (ATR) single reflectance module (24 scans). All reactions were carried out under a nitrogen/argon atmosphere unless otherwise stated. Elemental analysis was carried out with a Thermo Scientific, model Flash 1112EA apparatus and Eagar xperience software.

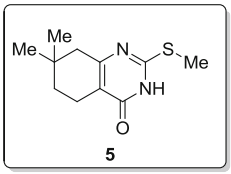
*Methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate* **(4)** Dimethyl carbonate (3.3 mL, 0.039 mol) and NaH (1.24 g, 0.052 mol) in THF (24 mL) were heated to about 80 °C for 30 min. Then, 3,3-dimethyl cyclohexanone (2.0 g, 0.016 mol) was added and stirred for 2.5 h under nitrogen atmosphere. After reaction completion by TLC (10% methanol in chloroform), the reaction mass was cooled to about 0 °C and methanol followed by water was added. Then, the resultant reaction mixture was acidified to pH 1 using 3 M HCl and the product was extracted with dichloromethane, dried over sodium sulfate and concentrated under reduced pressure to afford **4**. Yield: 85%, pale yellow liquid. $^{1}H$ NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 0.91 (s, 6H), 1.32–1.36 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz), 2.03 (s, 2H), 2.17–2.19 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz), 3.71 (s, 3H), 12.09 (s, 1H, enol-OH); IR (ATR, $\upsilon$ $cm^{-1}$): 821, 1065, 1231, 1441,1617, 1657, 1712, 1746, 2922, 2952; LCMS (ESI) m/z for $C_{10}H_{16}O_3$ $[M + H]^+$: 184.9 Da.



**4**

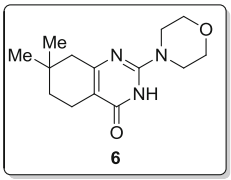
*7,7-Dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one* **(5)** To a stirred solution of potassium hydroxide (17 g, 0.298 mol) and *S*-methyl isothiourea hemisulfate (24.5 g, 0.176 mol) in water (125 mL), compound **4** (25 g, 0.135 mol) was added dropwise over 15 min at ambient temperature, stirred for 5 h and heated to about 100 °C for 3 h. After reaction completion by TLC (10% methanol in chloroform), the reaction mass was cooled to about 0 °C then acidified with acetic acid (about pH 5) to produce a precipitate. The solid was collected by filtration and dried under vacuum to give the desired compound **5**. Yield: 82%, pale yellow solid, m.p: 249–253 °C; $^{1}H$ NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 0.95 (s, 6H), 1.37–1.41 (t, 3H, $J = 6$ Hz), 2.17 (m, 4H), 3.33 (s, 2H), 7.59 (bs, NH); IR (ATR, $\upsilon$ $cm^{-1}$): 1400, 1538, 1628, 1657, 1692, 2916, 3289; LCMS (ESI) m/z $[M + H]^+$: 225.0 Da;

Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49; S, 14.29, Found: C, 58.91; H, 7.21; N, 12.48; S, 14.28%.



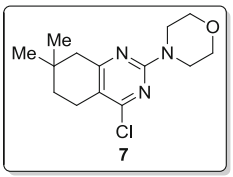

**5**

*7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4(3H)-one* **(6)** In a round-bottom flask, compound **5** (5 g, 0.022 mol) was dissolved in morpholine (20 mL) and heated to about 120 °C for 2 h. After reaction completion by TLC (10% methanol in chloroform), morpholine was removed completely under reduced pressure to give a crude mass which was stirred for 60 min in methyl-t-butyl ether (25 mL), and the solid obtained was collected by filtration and dried to afford compound **6**. Yield: 86%, white solid, m.p: 244–248 °C; $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 0.92 (s, 6H), 1.38–1.43 (t, 3H, $J_1 = 6.3$ Hz, $J_2 = 6.8$ Hz), 2.17 (s, 2H), 2.25–2.29 (t, 3H, $J_1 = 6.3$ Hz, $J_2 = 6.8$ Hz), 3.47–3.5 (t, 4H, $J_1 = 6$ Hz, $J_2 = 6.8$ Hz), 3.6–3.63 (t, 4H, $J_1 = 6$ Hz, $J_2 = 6.8$ Hz), 11 (bs, NH); IR (ATR, $\upsilon$ cm$^{-1}$): 1254, 1380, 1569, 1633, 2851, 3301; LCMS (ESI) m/z $[M + H]^+$: 264.3, found: 264.2 Da; Anal. Calcd for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96, Found: C, 63.84; H, 8.09; N, 15.95%.



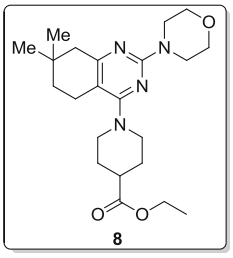

**6**

*4-(4-Chloro-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine* **(7)** To compound **6** (10 g, 0.035 mol), phosphorous oxychloride (45 mL, 0.029 mol) was added and heated to about 90 °C and stirred for 2 h. After reaction completion by TLC (10% methanol in chloroform), $POCl_3$ was removed completely under vacuum to give a brown crude material. The resultant mixture was co-distilled with toluene and diluted with ethyl acetate, then slowly quenched with sodium bicarbonate under stirring by maintaining the temperature at about 10 °C. Layers were separated and the organic layer was dried over sodium sulfate and concentrated to obtain compound **7**. Yield: 74%, off-white solid. m.p: 69–73 °C; $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 0.94 (s, 6H), 1.53–1.59 (m, 3H, $J_1 = 8.8$ Hz, $J_2 = 8.8$ Hz), 2.44 (m, 4H), 3.62 (s, 8H); IR (ATR, $\upsilon$ cm$^{-1}$): 1257, 1316, 1440, 1513, 1578, 2846, 2949; LCMS (ESI) m/z for $C_{14}H_{20}ClN_3O$ $[M + H]^+$: 282.1 Da.



7

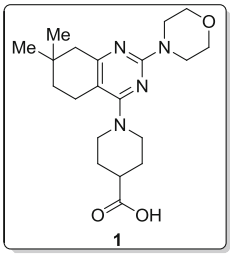
*Ethyl 1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl) piperidine-4-carboxylate* **(8)** To a solution of compound **7** (25 g, 0.088 mol) in ethanol (125 mL), triethylamine (0.177 mol) and ethyl isonipecotate (0.088 mol) were added at about 25 °C. The resultant reaction mixture was heated to about 120 °C for 5 h. After reaction completion, the reaction mixture was concentrated under reduced pressure to dryness and the concentrate was dissolved in dichloromethane and washed with 1 N HCl. The organic layer was concentrated under reduced pressure to afford compound **8**. Yield: 80%, off-white solid, m.p: 73–77 °C. $^{1}$H NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.98 (s, 6H), 1.18–1.22 (t, 3H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz), 1.39–1.48 (m, 2H), 1.65–1.68 (m, 2H), 1.86–1.89 (m, 2H), 2.27 (s, 2H), 2.32–2.45 (m, 2H), 2.79–2.87 (m, 2H), 3.56–3.59 (m, 8H), 3.68–3.72 (m, 2H), 4.04–4.1 (q, 2H, $J = 7.2$ Hz); IR (ATR, υ cm$^{-1}$):994, 1113, 1167, 1366, 1417, 1542, 1565, 1724, 2920, 2954; LCMS (ESI) m/z $[M + H]^+$: 403.5 Da; Anal. Calcd for $C_{22}H_{34}N_4O_3$: C, 65.64; H, 8.51; N, 13.92, Found: C, 65.65; H, 8.53; N, 13.90%.



8

*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxylic acid* **(1)** To a solution of compound **8** (25 g, 0.062 mol) in THF (200 mL), lithium hydroxide (0.124 mol) in water (75 mL) was added and heated to 45–50 °C for 4 h. After reaction completion, THF was removed completely under reduced pressure to afford a thick syrup which was diluted with water (150 mL) and ethyl acetate (150 mL). The organic layer was removed and the resultant aqueous layer was acidified to pH about 3 using 1 N HCl. The product was extracted using dichloromethane (2 × 100 mL) and concentrated under reduced pressure to afford compound **1**. Yield: 90%, off-white solid, m.p: 189–193 °C. $^{1}$H NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.99 (s, 6H), 1.38–1.45 (m, 2H), 1.6–1.67 (m, 2H), 1.85–1.89 (m, 2H), 2.32 (s, 2H), 2.43–2.5 (m, 5H), 2.78–2.86 (m, 2H), 3.57–3.71 (m, 10H), 12.1 (bs, 1H, OH-acid); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 21.9, 27.9, 28.8, 35.4, 43.9, 46.1, 47.1, 66.0, 105.8, 159.0, 164.2, 165.6, 175.8; IR (ATR, υ cm$^{-1}$): 991, 1110, 1413, 1537, 1612, 1709, 2846, 2919; LCMS (ESI) m/z $[M + H]^+$: 375.3 Da;

Anal. Calcd for $C_{20}H_{30}N_4O_3$: C, 64.15; H, 8.07; N, 14.96, Found: C, 64.14; H, 8.10; N, 14.95%.

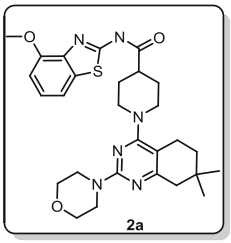


**1**

**General procedure for synthesis of compounds 2a–f**

To the solution of compound **1** (1 eqv.) in DMF (10 vol.), EDC.HCl (1.5 eqv.) and HOBT (0.4 eqv.) were added under nitrogen atmosphere at 25–30 °C. This mixture was stirred for 15 min and then the corresponding amine (**a–f**, 1 eqv.) followed by triethyl amine (2 eqv.) were added and the resultant reaction mixture was stirred for 4 h at 25–30 °C. After reaction completion, the reaction was quenched with 10% sodium bicarbonate (5 vol.) and the solid precipitated was collected by filtration, the wet cake was washed with water and dried to afford the desired product **2a–f**.

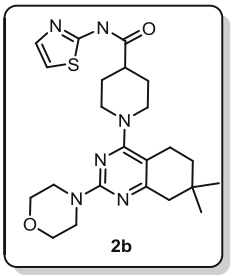
*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-(4-methoxybenzo[d]thiazol-2-yl)piperidine-4-carboxamide* **(2a)** Compound **2a** is an off-white solid. Yield: 72%, $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.82–0.84 (m, 2H), 0.98 (s, 6H), 1.42–1.45 (m, 2H), 1.62–1.72 (m, 2H), 1.89–1.93 (m, 2H), 2.32 (s, 2H), 2.72–2.85 (m, 2H), 3.57–3.59 (m, 8H), 3.8–3.84 (m, 2H), 3.9 (s, 3H), 6.96–6.99 (d, 2H, $J = 8.1$ Hz), 7.21–7.26 (t, 1H, $J_1 = 7.5$ Hz, $J_2 = 8.4$ Hz), 7.49–7.52 (d, 1H, $J = 7.8$ Hz), 12.5 (s, 1H, NH-amide); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 22.5, 28.5, 29.1, 31.7, 35.9, 42.2, 44.4, 46.6, 47.7, 56.2, 66.5, 106.4, 108.0, 113.9, 124.8, 133.2, 138.8, 152.2, 156.9, 159.5, 164.8, 166.0, 174.4; IR (ATR, $\upsilon$ cm$^{-1}$): 970, 1048, 1109, 1258, 1543, 1654, 1691, 2848, 2915; LCMS (ESI) m/z $[M + H]^+$: 537.5 Da; Anal. Calcd. for $C_{28}H_{36}N_6O_3S$: C, 62.66; H, 6.76; N, 15.66; S, 5.97, Found: C, 62.65; H, 6.77; N, 15.65; S, 5.95%.



**2a**

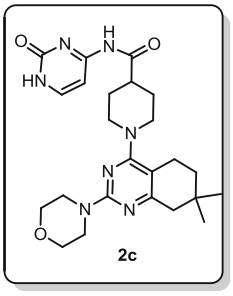
*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-(thiazol-2-yl)piperidine-4-carboxamide* **(2b)** Compound **2b** is an off-white solid. Yield: 82%, $^1$H

NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.95 (s, 6H), 1.42 (m, 2H), 1.7–1.73 (m, 2H), 1.88–1.91 (m, 2H), 2.32 (s, 2H), 2.72–2.88 (m, 2H), 3.56–3.59 (m, 8H), 3.79–3.84 (m, 2H), 9.15 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$:23.2, 28.0, 28.4, 31.2, 35.2, 36.2, 41.2, 45.1, 47.3, 65.9, 105.6, 111.9, 114.8, 117.7, 120.6, 149.1, 151.1, 158.2–159.2, 162.7, 163.5, 173.3; IR (ATR, $\upsilon$ cm$^{-1}$): 955, 1114, 1318, 1428, 1545, 1692, 2947; LCMS (ESI) m/z $[M + H]^+$: 458.5 Da; Anal. Calcd for $C_{23}H_{32}N_6O_2S$: C, 60.50; H, 7.06; N, 18.41; S, 7.02, Found: C, 60.49; H, 7.09; N, 18.40; S, 7.01%.



**2b**

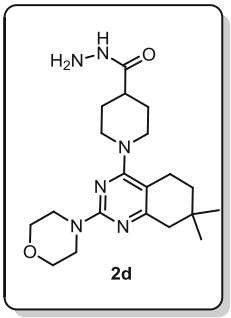
*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-(2-oxo-1,2-dihydropyrimidin-4-yl)piperidine-4-carboxamide* (2c) Compound **2c** is an off-white solid. Yield: 65%; $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.99 (s, 6H), 1.36–1.51 (m, 2H), 1.62–1.69 (m, 2H), 1.81–1.85 (m, 2H), 2.26 (s, 2H), 2.43–2.65 (m, 3H), 2.69–2.77 (m, 3H), 3.56–3.58 (m, 8H), 3.77–3.81 (m, 2H), 7.10–7.13 (d, 2H, $J = 7.2$ Hz), 7.79–7.81 (d, 2H, $J = 6.9$ Hz), 10.79 (bs, 1H, amide), 11.5 (bs, 1H, keto-enol); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 22.7, 27.5, 27.9, 34.7, 41.9, 44.6, 46.8, 65.3, 94.5, 105.1, 109.4–120.9, 148.2, 150.4, 152.2, 154.6, 157.5–159.0, 162.6, 163.0, 175.1; IR (ATR, $\upsilon$ cm$^{-1}$): 810, 1112, 1306, 1456, 1555, 1688, 1726, 2951; LCMS (ESI) m/z $[M + H]^+$: 468.7 Da; Anal. Calcd for $C_{24}H_{33}N_7O_3$: C, 61.65; H, 7.11; N, 20.97; Found: C, 61.65; H, 7.15; N, 20.99%.



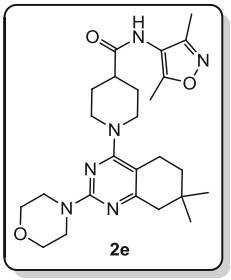
**2c**

*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carbohydrazide* **(2d)** Compound **2d** is a pale yellow solid. Yield: 77%; $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$ ppm): 0.94 (s, 6H), 1.40 (m, 2H), 1.65 (m, 4H), 2.3 (s, 2H), 2.4 (m, 2H), 2.71 (m, 2H), 3.55–3.58 (m, 8H), 3.76–3.80 (m, 2H),7.4 (bs, 2H, $NH_2$), 9.0 (bs, 1H, amide); IR (ATR, $\upsilon$ cm$^{-1}$): 975, 1112, 1420, 1540, 1566, 1636, 2818,

3316; LCMS (ESI) m/z $[M + H]^+$: 489.3 Da; Anal. Calcd for $C_{20}H_{32}N_6O_2$: C, 61.83; H, 8.30; N, 21.63; Found: C, 61.82; H, 8.34; N, 21.62%.

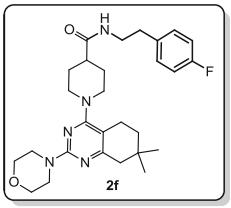



*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-(3,5-dimethylisoxazol-4-yl)piperidine-4-carboxamide* **(2e)** Compound **2e** is an off-white solid. Yield: 68%. $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.02 (s, 6H), 1.50–1.59 (m, 2H), 2.46 (S, 2H), 2.17 (s, 3H), 2.31 (s, 23H), 2.44 (s, 2H), 2.47–2.51 (m, 2H), 2.82–2.9 (m, 2H), 3.71–3.74 (m, 8H), 3.87–3.92 (m, 2H), 6.48 (s, 1H, amide); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 9.4, 10.7, 21.9, 24.3, 28.0, 28.4, 28.6, 28.8, 31.2, 35.5, 41.8, 44.0, 46.1, 47.2, 66.0, 105.8, 114.2, 157.4, 159.0, 162.0, 164.3, 165.6, 173.9; IR (ATR, $\upsilon$ $cm^{-1}$): 875, 1005, 1113, 1228, 1365, 1418, 1544, 1664, 1742, 2850, 2921, 3294; LCMS (ESI) m/z $[M + H]^+$: 469.3 Da; Anal. Calcd for $C_{25}H_{36}N_6O_3$: C, 64.08; H, 7.74; N, 17.93; Found: C, 64.10; H, 7.75; N, 17.91%.




*1-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-(4-fluorophenethyl)piperidine-4-carboxamide* **(2f)** Compound **3f** is an off-white solid. Yield: 86%; $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.02 (s, 6H), 1.48 (m, 2H), 1.82–1.84 (m, 4H), 2.18–2.23 (m, 1H), 2.44–2.48 (m, 4H), 2.80–2.82 (m, 4H), 3.52–3.54 (m, 2H), 3.71–3.75 (m, 10H), 7.02–7.04 (m, 2H), 7.14–7.16 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 22.4, 28.4, 28.8, 29.3, 34.6, 35.9, 42.5, 44.4, 46.6, 47.8, 66.5, 106.3, 115.2–115.4, 130.8–130.9, 136.0–136.1, 159.5, 160.0, 162.4, 164.7, 166.0, 174.5; IR (ATR, $\upsilon$ $cm^{-1}$): 824, 1000, 1110, 1223, 1527, 1566, 1646,

1742, 2921, 3359; LCMS (ESI) m/z $[M + H]^+$: 496.8 Da; Anal. Calcd for $C_{28}H_{38}FN_5O_2$: C, 67.85; H, 7.73; N, 14.13; Found: C, 67.84; H, 7.74; N, 14.12%.

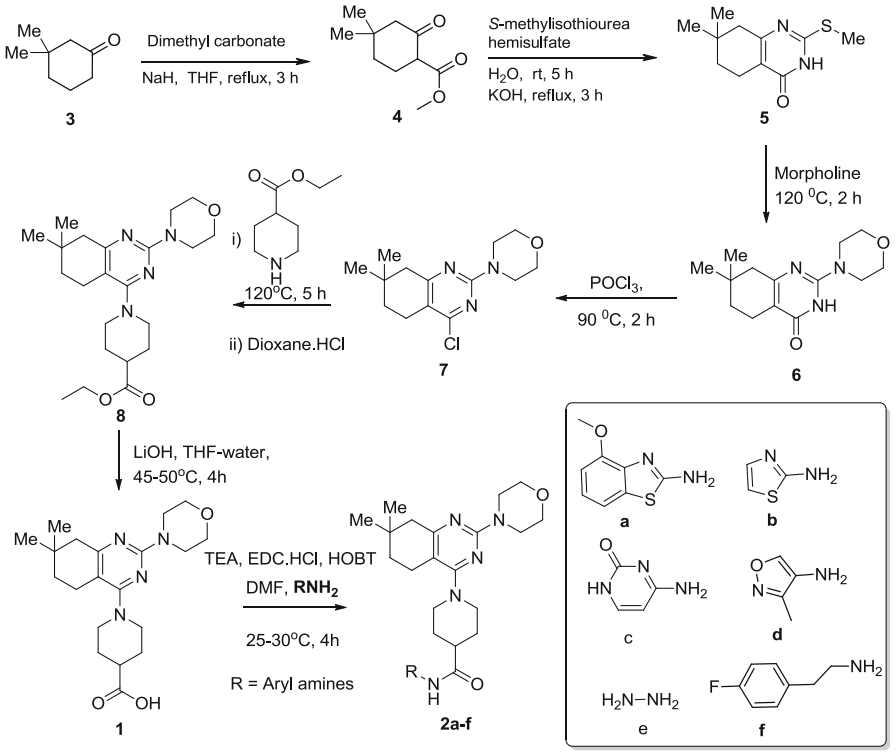



## Results and discussion

The protocol employed for the synthesis of 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxylic acid (**1**) and 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxamide derivatives (**2**) is shown in Scheme 1. Treatment of 3,3-dimethyl cyclohexanone (**3**) with dimethyl carbonate in the presence of sodium hydride in tetrahydrofuran provided methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (**4**) [26]. Compound **4** was coupled with *S*-methylisothiourea hemi sulfate in water to afford 7,7-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**5**) as a product. 7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**6**) was synthesized from **5** by replacing the SMe group with morpholine as reported earlier [20]. The synthesis of ethyl 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl) piperidine-4-carboxylate (**8**) from **6** involves two nucleouphilic replacement reactions, i.e. initial replacement of the hydroxyl group by chlorine in the presence of $POCl_3$ to provide (**7**) and then replacement of the chlorine group with ethyl isonipecotate. Hydrolysis of the intermediate **8** using lithium hydroxide yielded compound **1**.

Several amide derivatives (**2a**–**f**) were synthesized by treating **1** with corresponding amines ($RNH_2$, **a**–**g**) using TEA, EDC.HCl and HOBT in DMF. The structures of compounds **2a**–**f** were confirmed by using elemental analysis, IR (ATR), NMR and LCMS spectral techniques. The antibacterial activities of these compounds were screened against five Gram-positive and four Gram-negative bacterial strains.

All the newly synthesized compounds (**2a**–**f**) were evaluated for their in vitro antibacterial activity against human pathogens by means of a standard two-fold serial dilution method using agar media. The in vitro antibacterial activity was performed against five Gram-positive bacterial strains. *Staphylococcus aureus*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *E. faecalis* and *Bacillus subtilis* and four Gram-negative strains, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobactera erogenes* and *Moraxella catarrhalis.* In these studies, commercially available antibiotics Ciprofloxacin and Linezolid were used as reference standards. The results obtained are shown in Table 1. The results indicated that compounds **2a**, **2b** and **2c** exhibited good potency in inhibiting the growth of both Gram-positive bacteria and Gram-negative bacteria when used at a dose of 4–16 μg/mL. In




**Scheme 1** Synthesis of **2a–f**

general, compounds showing inhibition of at least 18 mm were considered to be active, and hence these compounds were further evaluated for their minimal inhibitory concentration (MIC). The in vitro antibacterial activity of the compounds **2a**, **2b** and **2c** against Gram-negative bacteria such as *E. coli*, *P. aeruginosa* and *Enterobactera erogenes* were found to be superior to the marketed drug Linezolid, but relatively less active when compared to Ciprofloxacin. It is interesting to note that the compounds **2a** and **2b** which contains thiazole ring system showed relatively higher activity as expected, due to the presence of the bioactive thiazole moiety [22, 23].

## Conclusion

In conclusion, the synthesis and characterization of a series of novel 1-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperidine-4-carboxamide derivatives (**2a–f**) have been reported. The antibacterial activities of these compounds were tested against good number of Gram-positive and Gram-negative bacterial strains. The results indicated that the thiazole ring containing quinazoline derivatives **2a** and **2b** showed good antibacterial activity amongst the compounds prepared, and

**Table 1** Anti-bacterial evaluation of **2a–f**

| Compound no. | Gram-positive strains MIC (μg/mL) | | | | | Gram-negative strains MIC (μg/mL) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* ATCC 29213 (MSSA) | *Staphylococcus aureus* ATCC 33591 (MRSA) | *Staphylococcus epidermidis* ATCC 700565 | *Enterococcus faecalis* ATCC 29212 | *Bacillus subtilis* ATCC 6633 | *Escherichia coli* ATCC 25922 | *Pseudomonas aeruginosa* ATCC 27853 | *Enterobacter aerogenes* ATCC 13048 | *Moraxella catarrhalis* ATCC 25238 |
| **2a** | >16 | 8 | >16 | 8 | >16 | 8 | 8 | 8 | 4 |
| **2b** | >16 | >16 | >16 | >16 | >16 | 8 | 8 | 4 | 8 |
| **2c** | >16 | 8 | >16 | >16 | >16 | >16 | >16 | 8 | 8 |
| **2d** | >16 | >16 | >16 | >16 | >16 | >16 | >16 | >16 | >16 |
| **2e** | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **2f** | >64 | >64 | >64 | >64 | >64 | >16 | >16 | >16 | >16 |
| Ciprofloxacin | 0.5 | 0.5 | >4 | 1 | 0.06 | <0.007 | 0.25 | 0.015 | 0.03 |
| Linezolid | 4 | 2 | 2 | 2 | 1 | >64 | >64 | >64 | 8 |

further modification of the quinazoline scaffold or the thiazole ring would definitely indicate lead molecules toward antibacterial therapeutics.

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