Synthesis and antiviral activity of 4-(7,7-dimethyl-4-[4-{N-aroyl/benzyl}1-piperazinyl]-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine derivatives

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Abstract

The synthesis of a series of 4-(7,7-dimethyl-4-[4-{N-aroyl/(het)aroyl/ benzyl}1-piperazinyl]-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine derivatives has been described. The antiviral activity of these compounds against avian paramyxovirus (APMV-1), which is a Newcastle disease virus has also been screened.

Keywords: Tetrahydroquinazoline, piperazine, morpholine, avian paramyxovirus, antiviral
Introduction

Heterocyclic chemistry is one of the largest classical divisions within organic chemistry,\textsuperscript{1-3} and its importance is highlighted by the frequency that heterocycles appear in biologically active compounds. Pyrimidines are well known heterocycles which appear in many natural products and are often key starting materials used in many drug discovery projects.\textsuperscript{4-6} A review of literature revealed that substituted pyrimidines have been used to synthesize a variety of protein kinase inhibitors (e.g., JAK, MAP kinase, tyrosine kinases and VEGF receptor) which are being employed in the treatment of a wide range of diseases such as cancers, inflammatory bowel disease and ocular neovascular diseases.\textsuperscript{7-8} 2-Morphilino- substituted pyrimidine derivatives have been used to treat diseases and disorders arising from abnormal cellgrowth, particularly which are associated with PI3 kinase such as cancer, immune disorders, viral infection and neurological disorders.\textsuperscript{9-11} Piperazine is also an important heterocyclic compound present in many of the notable anti-helmintic, anti-depressant and anti-histamines drugs.\textsuperscript{12} N-Aroyl-substituted piperazines attached to 4-(thiophen-2-ylmethyl)-2H-phthalazin-1-ones showed poly(ADP-ribose)polymerase-1 inhibition property.\textsuperscript{13} Recently, Wang et al. have reported that N-aroyl or N-benzyl-substituted piperazines attached to ubiquinones have antioxidant properties.\textsuperscript{14} Hence, it is presumed that molecules containing these heterocyclic hubs would exhibit promising biological activity. In the recent evaluation towards antiviral research, study on Newcastle disease virus (NDV) has been an attractive area for Virologists due to its economic importance. These viruses can infect more than 250 bird species and the disease onset is rapid with clinical signs appearing within 48 h.\textsuperscript{15,16} Further, currently used vaccines are not 100% protective and there is a definite need to combat the disease through other strategies that include using antiviral drugs. As on date, there is no approved drug against NDV and Ribavirin, a well-known broad spectrum antiviral drug is approved for treatment of respiratory syncytial virus, a human paramyxovirus.\textsuperscript{17} However, Ribavirin is costly, there are concerns about its efficacy and it is shown to have potential toxic effects on exposed individuals when administered via aerosol.\textsuperscript{18,19} Since pyrimidine template is present in various commercial antiviral drug substances such as Abacavir, Idoxuridine, Valganciclovir and Zidovudine, novel compounds that contain pyrimidine template are designed and screened for antiviral activity. Therefore, the main objective of the present endeavor is to synthesize 4-(7,7-dimethyl-4-{piperazin-1-yl}-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine 1 and its N-aroyl/(het) aroyl 2 and N-benzyl-substituted piperizine derivatives 3 and to screen their antiviral activity against a NDV viz. avian paramyxovirus (APMV-1).

![Figure 1. Structures of 1 and its N-aroyl/(het) aroyl 2 and N-benzyl-substituted piperizine derivatives 3.](image-url)
Results and Discussion

The synthesis of 4-(7,7-dimethyl-4-{piperazin-1-yl}-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (1) is described in Scheme 1. Commercially available 3,3-dimethyl cyclohexanone (6) on treatment with dimethyl carbonate in the presence of sodium hydride in THF gave methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (5). The intermediate 5 undergoes cyclization with S-methylisothiourea hemisulfate in water to provide 7,7-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6). 7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4(3H)-one (7) was synthesized from 6 by replacing the SMe group with morpholine. The synthesis of scaffold 4-(7,7-dimethyl-4-{piperazin-1-yl}-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (1) from 7 involves two nucleophilic replacement reactions, viz. initial replacement of hydroxy group by chloride group in the presence of POCl₃ to provide compound 8 and then replacement of chloride group with piperazine (Scheme 1).

Scheme 1. Synthesis of 4-(7,7-dimethyl-4-{piperazin-1-yl}-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (1).

The protocol employed for the synthesis of N-aryl 2a-g and N-benzyl-substituted piperizine 3a-f derivatives of 1 is depicted in Scheme 2. Several N-aryl-substituted piperizine derivatives 2a-g were prepared by treating 1 with corresponding substituted benzoyl chloride or heterocyclic acyl chloride a-g. Similarly N-benzyl-substituted piperizine 3a-f derivatives of 1 were synthesized via reductive amination of 1 by respective aryl aldehydes using sodium triacetoxyborohydride (STAB). The structures of these compounds 2a-g and 3a-f were confirmed by ¹H and ¹³C NMR and LCMS spectra.
Scheme 2. Synthesis of N-aroyl-substituted piperizines 2a-g and N-benzyl-substituted piperizines 3a-f from 1.

Antiviral activity
To test the antiviral activity of these compounds, they were initially screened by MTT assay\textsuperscript{23} in African Green Monkey Kidney cell line, Vero cell line. The maximum non-cytotoxic concentration, at which no significant changes were detected in cellular morphology of Vero cells was used as the highest test dose for testing the antiviral activity of the compounds by viral plaque reduction assay using an avian paramyxovirus (APMV-1). The commercially available antiviral drug, Ribavirin, was used for comparing the antiviral potential of the test compounds. The maximum non-cytotoxic concentration (MNCC), at which no significant changes were detected in cellular morphology of Vero cells, of Ribavirin was 31.25 µg/mL. The 50% cytotoxic concentration (CC50: dose that inhibited the growth by 50% compared to untreated cells) of Ribavirin was determined to be 400 µg/mL and 32% viral plaque reduction was observed by Ribavirin at dose of 31.25 µg/mL.

In a typical experiment, monolayers of Vero cells in 24-well plate were incubated with five different concentrations of test compounds (0.1, 0.01, 0.001, 0.0001 and 0.00001 M) for 1 h. The cells were washed with PBS thrice and then infected with a known dose of Newcastle disease virus for 1 h. The cells were washed again with PBS thrice and overlaid with methyl cellulose media. The cells were incubated at 37°C with 5% CO\textsubscript{2} for 5 days. During the incubation period the cells were observed every day. On the fifth day, the overlay media was removed, the cells were fixed with cold methanol for 30 min, then stained with 1% crystal violet and air dried. The number of plaques produced by viral infection was counted in each well. The percentage of plaque reduction was determined by calculating the reduction in the number of plaques upon compound treatment compared to untreated NDV infected cells which was defined as 100%. The results thus obtained are collected in Table 1.
Table 1. Antiviral activity of the compounds against APMV-1

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Test concentration (M) at which antiviral activity was observed</th>
<th>Percentage of test virus concentration</th>
<th>Plaque reduction percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>0.00001</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>2b</td>
<td>0.1 - 0.00001</td>
<td>115</td>
<td>None</td>
</tr>
<tr>
<td>2c</td>
<td>0.00001</td>
<td>96</td>
<td>6</td>
</tr>
<tr>
<td>2d</td>
<td>0.00001</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>2e</td>
<td>0.0001</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>2f</td>
<td>0.00001</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>2g</td>
<td>0.0001</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>3a</td>
<td>0.1 - 0.00001</td>
<td>103</td>
<td>None</td>
</tr>
<tr>
<td>3b</td>
<td>0.1 - 0.00001</td>
<td>94</td>
<td>None</td>
</tr>
<tr>
<td>3c</td>
<td>0.1 - 0.00001</td>
<td>210</td>
<td>None</td>
</tr>
<tr>
<td>3d</td>
<td>0.1 - 0.00001</td>
<td>80</td>
<td>None</td>
</tr>
<tr>
<td>3e</td>
<td>0.1 - 0.00001</td>
<td>115</td>
<td>None</td>
</tr>
<tr>
<td>3f</td>
<td>0.1 - 0.00001</td>
<td>95</td>
<td>None</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>0.0001</td>
<td>68</td>
<td>32</td>
</tr>
</tbody>
</table>

The results provided in the Table 1 indicated that the test compounds 2a and 2c-g showed antiviral activity by inhibiting the plaque formation by 22, 6, 25, 12, 28 and 17%, respectively at the minimum test dose when compared to infected untreated controls, while the compounds 2b and 3a-f did not show any antiviral activity at the tested concentrations. Also, the results suggested that N-aroyl/(het)aroyl derivatives showed antiviral activity, whereas N-benzyl analogues showed no such activity. It is evidently observed that presence of carbonyl group in N-aroyl/(het)aroyl derivatives may be responsible for the antiviral efficacy of these compounds. Among the compounds under investigation N-imidazolyl-substituted piperazine derivative 2f exhibited relatively a higher antiviral activity than the others.

Conclusions

In conclusion, we have reported the novel synthesis of a series of seven 4-(7,7-dimethyl-4-[4-{N-aroyl/(het)aroyl}-substituted 1-piperazinyl]-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine derivatives 2a-g and six 4-(7,7-dimethyl-4-[4-{N-benzyl}-substituted 1-piperazinyl]-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine derivatives 3a-f. Amongst, compounds 2d and 2f which had N-aroyl/(het)aroyl-substituted 1-piperazinyl scaffold showed antiviral activity against APMV-1, a Newcastle disease virus almost equal to marketed drug Ribavirin and further modification of this scaffold or N-aroyl/(het)aroyl substrate would definitely pose lead molecule towards antiviral therapeutics.

Experimental Section
General. All the chemicals used in the study are commercially available high purity grade (Aldrich or Merck, India). Commercially available reagent grade solvents were used as received. TLC experiments were performed on alumina-backed silica gel 40F254 plates (Merck, Germany). The plates were illuminated under UV (254 nm) and KMnO₄. Melting points were determined using a melting point apparatus (B-540 Buchi, Germany) without corrections. All ¹H and ¹³C NMR spectra were recorded on a Bruker 300 or 400 MHz instrument. Molecular masses of unknown compounds were checked by LCMS 6200 series Agilent Technology instrument. Chemical shifts are reported in ppm (δ) 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 FT-IR spectrometer (Bruker, Germany) 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 Eager xperience software.

Methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (5). 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 3M HCl and the product was extracted with dichloromethane, dried over sodium sulphate and concentrated under reduced pressure to afford methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (5).

Yield: 2.48 g; 85%, Pale yellow liquid. ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 0.91 (s, 6H), 1.32-1.36 (t, 2H, J₂ 6.3 Hz, J₂ 6 Hz), 2.03 (s, 2H), 2.17-2.19 (t, 2H, J₂ 6.3 Hz, J₂ 6 Hz), 3.71 (s, 3H), 12.09 (s, 1H, enol-OH); IR (ATR, υ cm⁻¹): 821, 1065, 1231, 1416, 1538, 1628, 1657, 1712, 1746, 2922, 2952; LCMS (ESI) m/z [M+H]⁺: 184.9 Da.

7,7-Dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6). To a stirred solution of potassium hydroxide (17 g, 0.298 mol) and S-methyl isothiouria hemisulfate (24.5 g, 0.176 mol) in water (125 mL), 5 (25 g, 0.135 mol) was added drop wise 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 precipitate. The solid was collected by filtration and dried under vacuum to give the desired compound 7,7-Dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6). Yield: 24.9 g; 82%, Pale yellow solid, mp 249-253°C; ¹H NMR (400 MHz, DMSO-d₆, δ 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, υ cm⁻¹): 1400, 1538, 1628, 1657, 1692, 2916, 3289; LCMS (ESI) m/z [M+H]⁺: 225.0 Da. Anal. Calcd for C₁₁H₁₆N₂OS: C, 58.90; H, 7.19; N, 12.49. Found: C, 59.12; H, 7.22; N, 12.68%.

7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4(3H)-one (7).

Compound 6 (5 g, 0.022 mol) was dissolved in morpholine (20 mL) and this mixture was 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). The solid obtained was collected by filtration and dried to afford 7.

Yield: 5.05 g; 86%, colorless solid, mp 244-248°C (methyl-t-butyl ether); ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 0.92 (s, 6H), 1.38-1.43 (t, 3H, J₂ 6.3 Hz, J₂ 6.8 Hz), 2.17 (s, 2H), 2.25-2.29 (t, 3H, J₁
6.3 Hz, J2 6.8 Hz), 3.47-3.5 (t, 4H, J1 6 Hz, J2 6.8 Hz), 3.6-3.63 (t, 4H, J1 6 Hz, J2 6.8 Hz), 11 (bs, NH); IR (ATR, c m\(^{-1}\)):1254, 1380, 1569, 1633, 2851, 3301; LCMS (ESI) m/z [M+H]\(^+\): 264.2 Da. *Anal. Calcd* for C\(_{14}\)H\(_{21}\)N\(_2\)O: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.96; H, 8.01; N, 16.13%.

**4-(4-Chloro-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (8).** To compound 7 (10 g, 0.035 mol), phosphorous oxychloride (45 mL, 0.029 mol) was added and heated at 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 brown crude material. The resultant mixture was co-distilled with toluene and diluted with ethyl acetate, thenquenched with sodium bicarbonate slowly under stirring by maintaining the temperature about 10°C. Layers were separated and organic layer was dried over sodium sulfate and concentrated to get 8. Yield: 7.9 g; 74%, pale yellow solid. mp 69-73°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\), \(\delta\) ppm): 0.94 (s, 6H), 1.53-1.59 (m, 3H, J1 8.8 Hz, J2 8.8 Hz), 2.44 (m, 4H), 3.62 (s, 8H); IR (ATR, \(\nu\) cm\(^{-1}\)):1257, 1316, 1440, 1513, 1578, 2846, 2949; LCMS (ESI) m/z [M+H]\(^+\): 282.1 Da. *Anal. Calcd* for C\(_{13}\)H\(_{20}\)ClN\(_2\)O: C, 59.67; H, 7.15; N, 14.91. Found: C, 59.92; H, 7.13; N, 15.08%.

**4-(7,7-Dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine, hydrochloride (1).** To a solution of 8 (25 g, 0.088 mol) in ethanol (125 mL), triethylamine (25 mL, 0.177 mol) and N-BOC piperazine (16.5 g, 0.088 mol) were added at about 25°C and the reaction mass was concentrated under vacuum to dryness. The residue was dissolved in dichloromethane (250 mL) and washed with 1.5 N HCl (100 mL). Organic layer was concentrated to afford off white solid which was further treated with dioxane in HCl (100 mL) and stirred for 2 h at about 10°C. Reaction completion was monitored by TLC and the reaction mixture was concentrated under reduced pressure to get thick syrup which was chased with methyl-t-butyl ether. Solid precipitated was stirred at about 25°C for 60 min and collected by filtration to afford compound 1. Yield: 21.2 g; 65%, Pale brown crystalline solid; mp 297-300°C (methyl-t-butyl ether); \(^1\)H NMR (400 MHz, DMSO-d\(_6\), \(\delta\) ppm): 1 (s, 6H), 1.41-1.45 (t, 2H, J 8 Hz, J2 7.2 Hz), 2.59 (m, 2H), 3.18 (s, 4H), 3.57 (s, 2H), 3.68-3.78 (m, 8H), 3.92 (s, 4H), 9.67 (bs, NH), 12.5 (bs); IR (ATR, \(\nu\) cm\(^{-1}\)): 1343, 1493, 1618; LCMS (ESI) m/z [M+H]\(^+\): 332.2 Da.

**General procedure for synthesis of 2a-g**

To a solution of 1 (0.001 mol) in dichloromethane (10 fold), triethylamine (0.003 mol) was added slowly under stirring at about 10°C. To this, corresponding benzoyl chloride a-g (0.0011 mol) was added and stirred for 60 min. Reaction completion was monitored by TLC. After completion, the reaction was quenched with 10% sodium bicarbonate solution and extracted with dichloromethane. Organic layer was washed with 10% of citric acid solution followed by brine solution. Organic layer was concentrated under reduced pressure and purified using column chromatography using ethyl acetate-hexanes to afford pure compounds 2a-g.

**4-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinoxin-4-yl)piperazin-1-yl][2-fluorophenyl]methanone (2a).** Compound 2a is a pale yellow color crystalline solid. Yield: 385 mg; 85%, mp 211-213°C (ethyl acetate-hexane); \(^1\)H NMR (400 MHz, DMSO-d\(_6\), \(\delta\) ppm): 0.82-0.84 (m, 2H), 0.95 (s, 6H), 1.42-1.44 (m, 2H), 2.33 (s, 2H), 3.25 (m, 2H), 3.56-3.58 (m, 8H), 3.75 (m, 2H), 7.28-7.34 (m, 2H), 7.41-7.50 (m, 2H); IR (ATR, \(\nu\) cm\(^{-1}\)):754, 1108, 1423, 1636, 1732, 2852, 2922; LCMS (ESI) m/z [M+H]\(^+\): 454.3 Da. *Anal. Calcd* for C\(_{25}\)H\(_{32}\)FN\(_2\)O: C, 66.20; H, 7.11; N, 15.44. Found: C, 66.45; H, 7.14; N, 15.22%.
(4-{7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl)-4-fluorophenyl)methanone (2b). Compound 2b is a beige color crystalline solid. Yield: 372 mg; 82%, mp 211-213°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.5 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6.0 Hz), 2.46 (m, 2H), 2.52 (s, 2H), 3.35 (s, 4H), 3.72-3.74 (m, 12H), 7.1-7.16 (t, 2H, $J_1$ 8.4 Hz, $J_2$ 8.7 Hz), 7.4-7.48 (q, 2H, $J_2$ 5.4 Hz); $^{13}$C NMR (75 MHz, DMSO-d$_6$, δ): 21.8, 27.9, 28.8, 35.4, 43.9, 46.1, 47.5, 66.0, 105.9, 115.2-115.4, 129.5-129.6, 132.0-132.1, 159.0, 164.7, 165.1, 168.2; IR (ATR, u cm$^{-1}$): 753, 850, 996, 1110, 1419, 1567, 1641, 2849; LCMS (ESI) m/z [M+H]$^+$: 454.3 Da. Anal. Calcd for C$_{28}$H$_{32}$FNO$_2$: C, 66.20; H, 7.11; N, 15.44. Found: C, 66.52; H, 7.08; N, 15.61.

(4-{7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl)-4-dimethylamino-phenyl)methanone (2c). Compound 2c is a pale brown powder. Yield: 311 mg; 65%, mp 183-186°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.48-1.53 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6 Hz), 2.46 (s, 2H), 2.47-2.52 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6 Hz), 3.02 (s, 6H), 3.34 (s, 4H), 3.72-3.75 (m, 12H), 6.68-6.71 (d, 2H, $J_2$ 8.7 Hz), 7.38-7.41 (d, 2H, $J_2$ 8.7 Hz); IR (ATR, u cm$^{-1}$): 1256, 1362, 1412, 1564, 1610, 2853, 2910. Anal. Calcd for C$_{27}$H$_{38}$N$_4$O$_2$: C, 67.75; H, 8.00; N, 17.56. Found: C, 67.42; H, 8.03; N, 17.72.

2-[2,4-Difluorophenyl]-1-{4-{7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl}ethan-1-one (2d). Compound 2d is a pale yellow crystalline solid. Yield: 374 mg; 77%, mp 140-143°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.48-1.53 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6.0 Hz), 2.46-2.5 (m, 4H), 3.3 (s, 4H), 3.61-3.64 (m, 2H), 3.7-3.76 (m, 12H), 6.8-6.9 (m, 2H), 7.26-7.34 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-d$_6$, δ): 22.3, 28.4, 29.3, 32.9, 35.8, 41.7, 44.4, 45.3, 46.5, 47.9, 48.1, 66.5, 103.6-104.1, 106.4, 111.3-111.5, 120.0-120.2, 133.1-133.3, 159.5-160.5, 162.2-162.9, 165.2, 165.7, 1682; LCMS (ESI) m/z [M+H]$^+$: 486.1 Da. Anal. Calcd for C$_{26}$H$_{32}$F$_2$N$_2$O$_2$: C, 64.31; H, 6.85; N, 14.42. Found: C, 64.18; H, 6.88; N, 14.64.

(4-{7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl)[quinolin-3-yl]methanone (2e). Compound 2e is a pale brown crystalline solid. Yield: 330 mg; 68%, mp 165-168°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.49-1.53 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6.0 Hz), 2.46 (s, 2H), 2.49-2.53 (t, 2H, $J_1$ 6.3 Hz, $J_2$ 6.0 Hz), 3.4 (s, 2H), 3.5 (s, 2H), 3.72-3.74 (m, 8H), 3.84 (s, 2H), 3.98-4.02 (m, 2H), 7.6-7.66 (m, 1H), 7.66-7.78 (m, 2H), 7.87-7.90 (d, 1H, $J$ 8.4 Hz), 8.1-8.14 (d, 1H, $J$ 8.4 Hz), 8.29-8.32 (d, 1H, $J$ 8.7 Hz); IR (ATR, u cm$^{-1}$): 1116, 1257, 1441, 1565, 1638, 2854, 2920; LCMS (ESI) m/z [M+H]$^+$: 487.0 Da. Anal. Calcd for C$_{28}$H$_{34}$N$_6$O$_2$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.42; H, 7.07; N, 17.03.
(4-{7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl)[1H-imidazol-1-yl]methanone (2f).

Compound 2f is a pale yellow crystalline solid. Yield: 365 mg; 86%, mp 205-208°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.48-1.53 (t, 2H, J1 6.3 Hz, J2 6.0 Hz), 2.46 (s, 2H), 2.49-2.53 (t, 2H, J1 6.6 Hz, J2 6.0 Hz), 3.42 (s, 4H), 3.63 (s, 4H), 3.72-3.75 (m, 8H), 6.39 (bs, NH), 7-7.39 (m, 5H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ: 22.2, 28.4, 29.3, 44.4, 46.0, 46.5, 47.6, 66.5, 106.3, 119.1, 129.3, 137.6, 150.8, 159.4, 165.3, 165.5; IR (ATR, υ cm$^{-1}$): 991, 1239, 1412, 1544, 1565, 1695, 2827; LCMS (ESI) m/z [M+H]$^+$: 426.1 Da. Anal. Calcd for C$_2$H$_3$N$_2$O$_2$: C, 62.10; H, 7.34; N, 23.04. Found: C, 62.10; H, 7.34; N, 23.04%.

[5-Bromopyridin-3-yl][4-{7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl}piperazin-1-yl]methanone (2g). Compound 2g is a pale-pink powder. Yield: 340 mg; 66%, mp 182-185°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.03 (s, 6H), 1.48-1.53 (t, 2H, J1 6.3 Hz, J2 6.0 Hz), 2.47-2.51 (m, 4H), 3.35 (s, 4H), 3.39 (s, 2H), 3.72-3.75 (m, 8H), 3.9 (s, 2H), 7.94 (s, 1H), 8.61 (s, 1H), 8.76 (s, 1H); IR (ATR, υ cm$^{-1}$): 996, 1253, 1412, 1536, 1566, 1627, 2850, 2923; LCMS (ESI) m/z [M+H]$^+$: 515.6 Da. Anal. Calcd for C$_2$H$_3$BrN$_5$O$_2$: C, 55.92; H, 6.06; N, 16.30. Found: C, 55.71; H, 6.09; N, 16.51%.

**General procedure for synthesis of 3a-f.** To a solution of 1 (0.001 mol) in THF (5 volumes), corresponding aryl aldehyde a-f (0.001 mol) was added at about 25°C. To the resultant mixture, sodium triacetoxy borohydride (0.0025 mol) was added in several lots and contents were stirred for 4 h to go for completion. After reaction completion by TLC, reaction was quenched with 10% sodium bicarbonate solution and product was extracted using ethyl acetate. Organic layer was dried over sodium sulfate and concentrated to get crude material which was further purified using column chromatography.

4-{4-[4-(2-Fluorobenzyl)piperazin-1-yl]-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl}morpholine (3a).

Compound 3a is a pale yellow crystalline solid. Yield: 316 mg; 72%, mp 138-142°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.02 (s, 6H), 1.45-1.49 (t, 2H, J1 6.3 Hz, J2 6.0 Hz), 2.45-2.49 (m, 4H), 2.64 (s, 4H), 3.41 (s, 4H), 3.69-3.74 (m, 10H), 7.03-7.09 (m, 1H), 7.12-7.17 (m, 1H), 7.25-7.28 (m, 1H), 7.45 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ: 22.4, 28.4, 29.3, 35.9, 44.4, 46.5, 48.0, 52.7, 66.5, 106.3, 115.3-115.7, 124.6-124.8, 129.6, 132.1, 159.5, 160.0, 162.5, 164.8, 165.7; IR (ATR, υ cm$^{-1}$): 748, 996, 1111, 1219, 1417, 1486, 1541, 1564, 2842; LCMS (ESI) m/z [M+H]$^+$: 440.1 Da. Anal. Calcd for C$_{25}$H$_{34}$FN$_5$O: C, 68.31; H, 7.80; N, 15.93. Found: C, 68.62; H, 7.76; N, 16.02%.

4-{4-[4-(3-Fluorobenzyl)piperazin-1-yl]-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl}morpholine (3b).

Compound 3b is a pale yellow crystalline solid. Yield: 325 mg; 74%, mp 127-131°C (ethyl acetate-hexane); $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 1.02 (s, 6H), 1.46-1.5 (t, 2H, J1 6.3 Hz, J2 6.0 Hz), 2.45-2.49 (m, 4H), 2.57 (s, 4H), 3.4 (s, 4H), 3.57 (s, 2H), 3.72-3.74 (m, 8H), 7.0-7.06 (m, 2H), 7.34-7.36 (m, 2H); IR (ATR, υ cm$^{-1}$): 786, 996, 1112, 1218, 1416, 1487, 1541, 1565, 2852, 2915; LCMS (ESI) m/z [M+H]$^+$: 440.1 Da. Anal. Calcd for C$_{25}$H$_{34}$FN$_5$O: C, 68.31; H, 7.80; N, 15.93. Found: C, 68.18; H, 7.83; N, 15.98%.
4-{4-[4-Bromo-2-fluorobenzyl]piperazin-1-yl}-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (3c). Compound 3c is a pale brown powder. Yield: 357 mg; 69%, mp 175-178°C (ethyl acetate); 1H NMR (300 MHz, CDCl3, δ ppm): 1.03 (s, 6H), 1.47-1.51 (t, 2H, J 6.3 Hz, J2 6.0 Hz), 2.47-2.51 (m, 4H), 2.53-4.26 (m, 4H), 3.4 (s, 4H), 3.63 (s, 2H), 3.75 (m, 8H), 6.87-6.88 (m, 1H), 7.28 (m, 1H), 7.48-7.53 (m, 1H); IR (ATR, υ cm–1): 992, 1106, 1364, 1481, 1546, 1570, 2920; LCMS (ESI) m/z [M+H]+: 520.9 Da. Anal. Calcd for C25H33BrFN6O: C, 58.05; H, 6.39; N, 13.42%. Found: C, 58.05; H, 6.39; N, 13.44%.

4-{4-[4-Chloro-3,6-difluorobenzyl]piperazin-1-yl}-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (3d). Compound 3d is a pale yellow solid. Yield: 364 mg; 74%, mp 151-154°C (ethyl acetate); 1H NMR (300 MHz, CDCl3, δ ppm): 1.02 (s, 6H), 1.45-1.5 (t, 2H, J 6.3 Hz, J2 6.0 Hz), 2.45-2.49 (m, 4H), 2.59 – 2.68 (m, 4H), 3.34 (s, 4H), 3.6-3.84 (m, 10H), 6.96- 7.03 (m, 1H), 7.06-7.14 (m, 1H); IR (ATR, υ cm–1): 992, 1107, 1365, 1473, 1546, 1570, 2920; Anal. Calcd for C25H32ClF2N6O: C, 61.03; H, 6.56; N, 14.23; O, 3.25; LCMS (ESI) m/z [M+H]+: 492.3 Da. Anal. Calcd for C25H32ClF2N6O: C, 61.03; H, 6.56; N, 14.23. Found: C, 60.89; H, 6.59; N, 14.42%.

4-{4-[4,6-Difluorobenzyl]piperazin-1-yl}-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (3e). Compound 3e is a pale yellow solid. Yield: 325 mg; 71%, mp 130-133°C (ethyl acetate-hexane); 1H NMR (300 MHz, CDCl3, δ ppm): 1.01 (s, 6H), 1.44-1.48 (t, 2H, J 2.6, 2.5 Hz, H2 6.0 Hz), 2.43-2.47 (m, 4H), 2.63 (s, 4H), 3.39 (s, 4H), 3.74-3.78 (m, 10H), 6.89-6.94 (m, 2H), 7.22-7.3 (m, 1H); 13C NMR (75 MHz, DMSO-d6) δ: 21.9, 27.9, 28.8, 35.4, 43.9, 46.1, 47.4, 48.1, 51.8, 66.0, 105.8, 111.2-111.5, 131-132, 147-148, 164.3; IR (ATR, υ cm–1): 997, 1111, 1224, 1426, 1467, 1541, 1568, 2834, 2920; LCMS (ESI) m/z [M+H]+: 458.1 Da. Anal. Calcd for C25H33F2N6O: C, 65.62; H, 7.27; N, 15.31. Found: C, 65.38; H, 7.23; N, 15.46%.

4-{4-[4,2-Dichlorobenzyl]piperazin-1-yl}-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (3f). Compound 3f is a colorless crystalline solid. Yield: 353 mg; 72%; mp 146-149°C (ethyl acetate); 1H NMR (300 MHz, CDCl3, δ ppm): 1.02 (s, 6H), 1.46-1.5 (t, 2H, J 6.3 Hz, J2 6.0 Hz), 2.46-2.5 (m, 4H), 2.5 (s, 4H), 3.38 (s, 4H), 3.64 (s, 2H), 3.73-3.74 (m, 8H), 7.23-7.28 (m, 1H), 7.28 (s, 1H), 7.47-7.49 (d, 1H, J = 8.4 Hz); 13C NMR (75 MHz, DMSO-d6) δ: 21.9, 28.0, 28.8, 35.4, 43.9, 46.1, 47.5, 52.5, 57.9, 66.0, 105.8, 127.1, 128.6, 132.1, 134.7, 164.4, 165.3; IR (ATR, υ cm–1): 994, 1108, 1363, 1499, 1545, 1571, 2846, 2903; LCMS (ESI) m/z [M+H]+: 494.0 Da. Anal. Calcd for C25H33Cl2N6O: C, 61.22; H, 6.78; N, 14.28. Found: C, 61.45; H, 6.73; N, 14.42%.

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