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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antiviral study of 4-(7,7-dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl) morpholine derivatives

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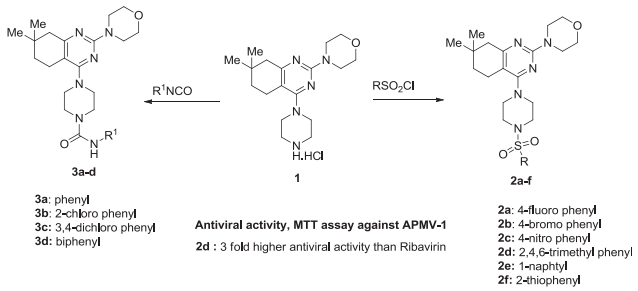
Abstract A series of 4-(7,7-dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine substituted sulfonamide and urea derivatives has been synthesized and characterized using spectral techniques. The antiviral activity of these compounds against an avian paramyxo virus (AMPV-1) was screened using MTT assay and found that one of the sulfonamide derivatives (**2d**) show three-fold higher antiviral activity than Ribavirin, a commercial antiviral drug substance.

Graphical abstract



Keywords Tetrahydroquinazoline · Piperazine · Morpholine · Avian paramyxo virus · Antiviral

Introduction

Heterocyclic chemistry is one of the important and largest classical divisions of organic chemistry, which deals with heterocyclic organic compounds (Katritzky et al. 1985; Joule and Mills 2008; Hepworth et al. 1995). Traditionally, majority of the biologically active substances possess heterocyclic rings; amongst pyrimidine template has an important significance. The pyrimidine ring occurs as a part structure of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), co-enzymes like folic acid, thiamine bromide, and riboflavin (Looper et al. 2005; Kobayashi et al. 1991; Skinner and Wunz 1951). Pyrimidine derivatives found useful in the treatment of cancer, myocardial interaction, and glaucoma (Noronha et al. 2008). Morpholine is another important organic heterocyclic compound seen as a part structure of several medicinal drugs along with pyrimidine template (Cano et al. 2010, 2013). 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 (Sekiya et al. 1980). 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 (Chou et al. 2013) and GATA modulator (Dibyendu et al. 2010). Piperazine is the most important heterocyclic compound present in many of the notable drugs, which act as anti-helmintic, anti-depressant, and anti-histamines (de Boer

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et al. 2001). It is presumed that molecules containing all these three heterocycles (pyrimidine, morpholine, and piperazine) as a part of their structures would exhibit promising biological activity. Amprenavir, tipranavir, and darunavir are commercially approved antiviral drugs which has sulfonamide functional group in its entity and trifluridine, mozenavir are few commercially available antiviral drugs which has urea functional group in its entity. Owing to the known antiviral properties of sulfonamides (Supuran et al. 2004; Scozzafava et al. 2003) and urea (Suresh Kumar et al. 2014) with above mentioned heterocyclic molecules (Izuru et al. 2012; Sudhakar Babu et al. 2015), compounds being prepared with above all heterocyclic hubs would expect to show enhanced biological activity.

In the recent evaluation towards antiviral research, study on Newcastle disease virus (NDV) (APMV-1) has been attractive area for virologists due to its oncolytic activity and its use as a vaccine vector for both animals and humans (Dmitriy and Peter 2012; Ravindra et al. 2009). NDV is economically important paramyxovirus that can infect more than 250 bird species. The disease onset is rapid with clinical signs appearing within 48 h. Currently used vaccines are not 100% protective and there is an unmet need to combat the disease through other strategies that include using antiviral drugs. As on date, there is no approved drug against NDV. Ribavirin, a well-known broad spectrum antiviral drug (Gilbert and Knight 1986) is approved for treatment of respiratory syncytial virus, a human paramyxovirus, which causes severe lower respiratory tract infections in children. Ribavirin is expensive and there are concerns about its efficacy. Furthermore, it is shown to have potential toxic effects on exposed individuals when administered via aerosol and the high cost (Hebert and Guglielmo 1990; Fackler et al. 1990). All these factors highlight the importance of developing novel antiviral drugs.

The main objective, therefore, of the present endeavor in the synthesis, characterization and antiviral screening against a NDV viz. an avian paramyxovirus (APMV-1) of newer heterocyclic compounds viz. 4-(7,7-dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl) morpholine (**1**), its sulfonamide (**2**) and urea (**3**) derivatives (Fig. 1). To our delight one of the sulfonamide derivative exhibited significant antiviral activity against African Green Monkey Kidney cell line.

Results and discussion

The overall protocol adopted for the synthesis of **1** is delineated in Scheme 1. 3,3-Dimethyl cyclohexanone (**4**) on treatment with dimethyl carbonate in the presence of sodium hydride in THF yielded methyl-4,4-dimethyl-2-oxocyclohexane-1-carboxylate (**5**), which underwent cyclization with *S*-methylisothiourea hemisulfate in water to give 7,7-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one(**6**) (Tetsuo et al. 1981; John et al. 2010). The intermediate 7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**7**) was synthesized from **6** by replacing the S-Me group with morpholine (Kengi et al. 2003). The conversion of **7** to **1** involves two nucleophilic replacement reactions, first replacement of hydroxy group by chloride group in the presence of $POCl_3$ to give **8** and then replacement of chloride group with piperazine (Selvakumar et al. 2017) (Scheme 1).

As depicted in Scheme 2 several new sulfonamide derivatives **2a–f** were synthesized from **1** by treating with corresponding substituted sulfonyl chlorides. Likewise, four urea derivatives **3a–d** were also synthesized from **1** by treating with respective phenyl substituted isocyanate derivatives. The structures of these compounds **2a–f** and **3a–d** were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance

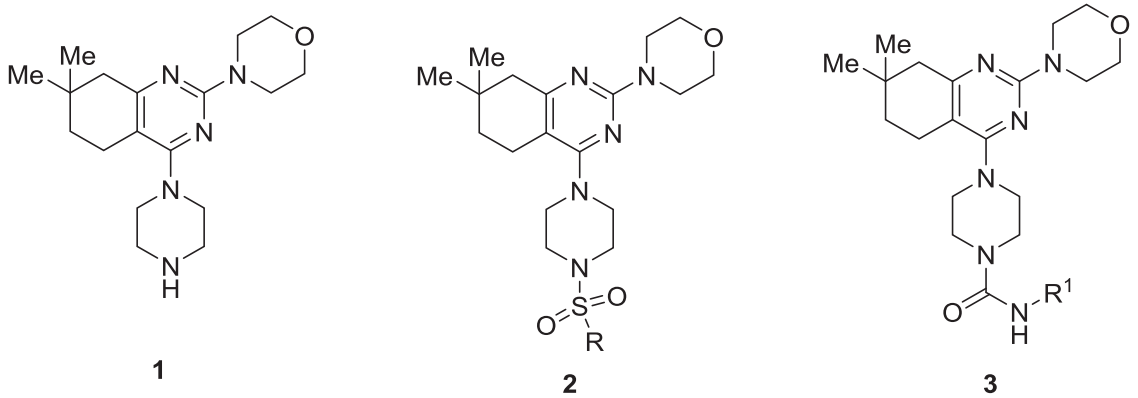
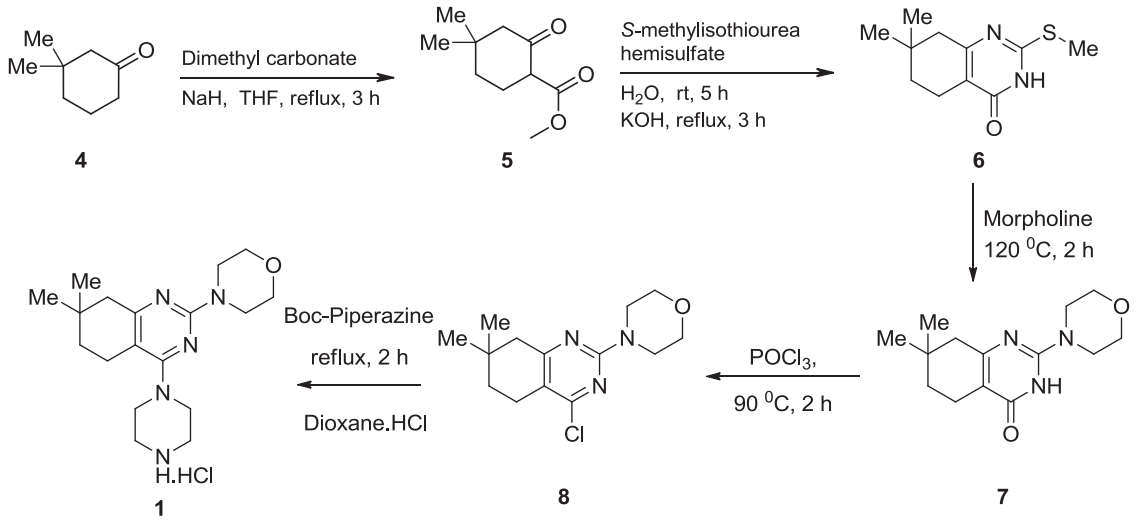
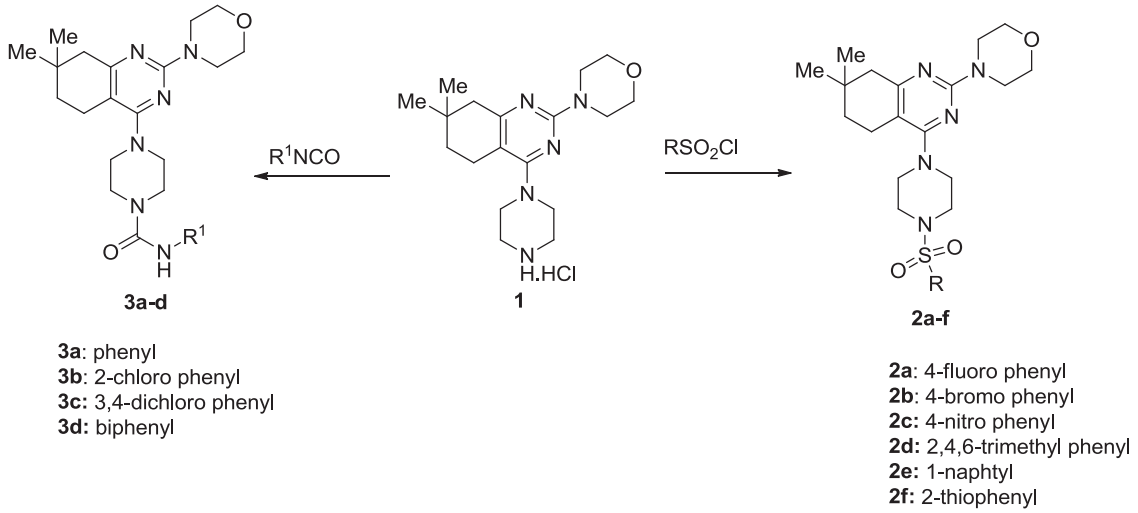


Fig. 1 Structures of 4-(7,7-dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**1**), sulfonamide (**2**), urea (**3**) derivatives



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



Scheme 2 Synthesis of sulfonamide (**2a–f**) and urea derivatives (**3a–d**) of **1**

(NMR), infrared (IR), and liquid chromatography mass spectrometry (LCMS) spectra.

The antiviral activity of these compounds was screened against African Green Monkey Kidney cell line, Vero cell line. To test the antiviral activity these compounds were initially screened by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as described in literature (Gerlier and Thomasset 1986). The maximum non-cytotoxic concentration (MNCC), 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 paramyxo virus, which is a NDV (APMV-1). A well-known antiviral drug, Ribavirin, was used for comparing the antiviral potential of the test compounds. The 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 400 µg/mL and 32% viral plaque reduction was observed by Ribavirin at dose of 31.25 µg/mL.

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 NDV 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_2 for 5 days. The cells were observed every day during the incubation period. On the 5th day, the overlay media was removed and the cells were fixed with cold methanol for 30 min. The cells were then stained with 1% crystal violet and air dried. The

Table 1 Antiviral activity of **2a–f** and **3a–d** against Vero cell line APMV-1

Compound numbers	Test concentration (M) at which antiviral activity was observed	Percentage of test virus concentration	Plaque reduction percentage
2a	0.001	79	21
2b	0.1–0.00001	80	None
2c	0.01	63	37
2d	0.001	16	84
2e	0.1–0.00001	90	None
2f	0.1–0.00001	115	None
3a	0.0001	63	37
3b	0.1–0.00001	233	None
3c	0.001	76	24
3d	0.1–0.00001	115	None
Ribavirin	0.0001	68	32

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 were defined as 100%. The results obtained are collected in Table 1.

The structural modification caused by changing the substituents in sulfonamide moiety (R) and urea moiety (R1) has a wide impact on anti-viral activity of the prepared compounds. While test compounds **2b**, **2e**, **2f**, **3b**, and **3d** did not show any antiviral activity at the tested concentrations, the test compounds **2a**, **2c**, **2d**, **3a**, and **3c** showed antiviral activity by inhibiting the plaque formation by 21, 37, **84**, 37, 24% respectively at the minimum test dose when compared to infected untreated controls. Interestingly, compound **2d** bearing trimethyl substituted phenyl ring contained sulfonamide derivative and compound **3a** bearing simple phenyl ring contained urea derivative displayed reasonably good activity compare to their other substituted phenyl analogs. However, sulfonamide derivative **2d** has shown higher antiviral activity than urea derivatives **3a**.

Conclusion

Herein, we have reported the novel synthesis of a series of 4-(7,7-dimethyl-4-(piperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine substituted sulfonamide derivatives (**2a–f**) and urea derivatives (**3a–d**). We have tested the antiviral activity of these compounds using MTT assay and amongst, one of the sulfonamide derivatives (**2d**) was found to be showed three-fold higher antiviral activity than that of commercial antiviral drug Ribavirin, which may become potential lead in antiviral drug development if the same or similar analogs are modified and studied further.

Experimental

All the chemicals used in the study are commercially available high purity grade (Aldrich or Merck, India). The solvents were of reagent grade and used as supplied commercially. Thin layer chromatography (TLC) experiments were performed on alumina-backed silica gel 40F254 plates (Merck, Darmstadt, 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 300 or 400 MHz NMR. Molecular masses of unknown compounds were checked by LCMS 6200 series Agilent Technology (Agilent, Bengaluru, India). Chemical shifts are reported in ppm (δ) with reference to internal standard tetramethylsilane. 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 Fourier transform infrared 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.

Compound **1** was prepared from commercially available 3,3-dimethyl cyclohexanone (**4**) over five steps using synthetic procedure previously reported by our research group (Skinner and Wunz 1951).

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

To a solution of **1** (0.01 mol) in THF (10 Vol), diisopropyl ethylamine (0.03 mol) was added at about 10 °C and stirred for 15 min. To this suspension, corresponding sulfonyl chloride (**a–f**) (0.01 mol) was added and stirred for 3 h at ambient temperature. Reaction completion was monitored by TLC, the reaction was quenched with 10% sodium bicarbonate solution and diluted with ethyl acetate. Organic layer separated was washed with 10% of citric acid solution and concentrated under reduced pressure. A few compounds were purified by column chromatography using a mixture of ethyl acetate-hexanes in silica gel to afford pure compounds.

4-(4-(4-((4-Fluorophenyl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2a**) Compound **2a** is an off-white solid. Yield: 75%, m. p:199–203 °C; ^{1}H NMR (400 MHz, dimethyl sulphoxide (DMSO)-d_6, δ ppm): 0.93 (s, 6H, CH_3-tetrahydroquinazoline), 1.37(m, 2H, CH_2-tetrahydroquinazoline), 2.31 (s, 2H,

CH_2-tetrahydroquinazoline), 2.34 (m, 2H, CH_2-tetrahydroquinazoline), 3.00 (s, 4H, CH_2-piperazine), 3.35 (s, 4H, CH_2-piperazine), 3.52–3.59 (m, 8H, CH_2-morpholine), 7.48–7.54 (m, 2H, CH-4-flurophenyl), 7.82–7.85 (m, 2H, CH-4-flurophenyl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.1 (tetrahydroquinazoline-C), 28.4 (tetrahydroquinazoline-C), 29.3 (tetrahydroquinazoline-C), 35.7 (tetrahydroquinazoline-C), 44.4 (tetrahydroquinazoline-C), 46.0 (piperazine-C), 46.4 (piperazine-C), 47.3(morpholine-C), 66.5 (morpholine-C), 106.5 (pyrimidine-C), 117.0–117.3 (4-flurophenyl-C), 131.1–131.6 (4-flurophenyl-C), 159.3 (pyrimidine-C), 163.9 (pyrimidine-C), 165.3–166.4 (4-flurophenyl-C); IR (ATR, υcm^{-1}): 1108 and 1163 (SO_2-symmetric-stretching), 1348 (SO_2-asymmetric-stretching), 1542 (NSO_2-bending), 1569 (NSO_2-bending), 2832, 2920; LCMS (ESI) *m/z*: 490.3 Da $[M + H]^+$; Anal. calcd for $C_{24}H_{32}FN_5O_3S$: C, 58.88; H, 6.59; N, 14.30; S, 6.55, found: C, 58.86; H, 6.60; N, 14.31; S, 6.54%.

4-(4-(4-((4-Bromophenyl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2b**) Compound **2b** is a white solid. Yield: 68%, m.p: 265–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.98 (s, 6H, CH_3-tetrahydroquinazoline), 1.39 (s, 2H, CH_2-tetrahydroquinazoline), 2.45 (m, 4H, CH_2-tetrahydroquinazoline), 3.07 (s, 4H, CH_2-piperazine), 3.67–3.69 (m, 8H, CH_2-morpholine), 3.79 (s, 4H, CH_2-piperazine), 7.67–7.7 (d, 2H, $J = 8.1$ Hz, CH-4-bromophenyl), 7.87–7.9 (d, 2H, $J = 8.1$ Hz, CH-4-bromophenyl); IR (ATR, υ cm^{-1}): 1107 and 1166 (SO_2-symmetric-stretching), 1262 (SO_2-asymmetric-stretching), 1615 (NSO_2-bending); LCMS (ESI) *m/z*: found: 550.3 Da $[M + H]^+$, Anal. calcd for $C_{24}H_{32}BrN_5O_3S$: C, 52.36; H, 5.86; N, 12.72; S, 5.82, found: C, 52.35; H, 5.89; N, 12.71; S, 5.81%.

4-(4-(4-((4-Nitrophenyl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2c**) Compound **2c** is a yellow color solid. Yield: 82%, m.p: 209–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.93 (s, 6H, CH_3-tetrahydroquinazoline), 1.24 (s, 2H, CH_2-tetrahydroquinazoline), 1.36 (m, 2H, CH_2-tetrahydroquinazoline), 2.3 (s, 4H, CH_2-piperazine), 2.34 (s, 2H, CH_2-tetrahydroquinazoline), 3.1 (s, 4H, CH_2-piperazine), 3.53–3.58 (s, 8H, CH_2-morpholine), 8.01–8.04 (d, 2H, $J =$ 8.4 Hz, CH-4-nitrophenyl), 8.44–8.47 (d, 2H, $J = 8.1$ Hz, CH-4-nitrophenyl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.1 (tetrahydroquinazoline-C), 28.4 (tetrahydroquinazoline-C), 28.8(tetrahydroquinazoline-C), 38.5 (tetrahydroquinazoline-C), 44.3 (tetrahydroquinazoline-C), 46.0 (piperazine-C), 46.4 (piperazine-C), 47.3 (morpholine-C), 66.4 (morpholine-C), 106.4 (pyrimidine-C), 125.2 (pyrimidine-C), 129.1 (4-nitrophenyl-C), 129.6 (4-nitrophenyl-C), 132.0 (4-nitrophenyl-C), 132.1 (4-nitrophenyl-C), 141.1 (4-nitrophenyl-C), 150.5 (4-nitrophenyl-C), 159.3 (pyrimidine-C), 165.3 (pyrimidine-C); IR (ATR, υ cm^{-1}):1110 and 1170 (SO_2-symmetric-stretching), 1349 (SO_2-asymmetric-stretching), 1417, 1529 (NSO_2-bending), 1567 (NSO_2-bending), 2851, 2919; LCMS (ESI) *m/z*: 517.3 Da $[M + H]^+$, Anal. calcd for $C_{24}H_{32}N_6O_5S$: C, 55.80; H, 6.24; N, 16.27; S, 6.21; found: C, 55.78; H, 6.27; N, 16.29; S, 6.20%.

4-(4-(4-((2,4,6-Trimethylphenyl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2d**) Compound **2d** is an off-white solid. Yield: 80%, m.p:192–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.97 (s, 6H, CH_3-tetrahydroquinazoline), 1.24 (s, 2H, CH_2-tetrahydroquinazoline), 1.42 (s, 2H, CH_2-tetrahydroquinazoline), 2.29 (s, 4H, CH_2-piperazine), 2.36 (s, 2H, CH_2-tetrahydroquinazoline), 2.57 (s, 9H, CH_3-aryl), 3.15 (s, 4H, CH_2-piperazine), 3.6 (s, 8H, CH_2-morpholine), 7.1 (s, 2H, CH-Aryl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 20.9 (tetrahydroquinazoline-C), 22.9 (trimethylphenyl-C), 23.2 (tetrahydroquinazoline-C), 35.4 (tetrahydroquinazoline-C), 39.1 (tetrahydroquinazoline-C), 44.3 (tetrahydroquinazoline-C), 44.9 (piperazine-C), 47.4 (morpholine-C), 66.1 (morpholine-C), 130.2 (trimethylphenyl-C), 132.4 (trimethylphenyl-C), 140.2 (trimethylphenyl-C); IR (ATR, υ cm^{-1}): 1102 and1150 (SO_2-symmetric-stretching), 1302 (SO_2-asymmetric-stretching), 1419, 1538 (NSO_2-bending), 1564 (NSO_2-bending), 2848, 2922; LCMS (ESI) *m/z*: 514.3 Da $[M + H]^+$, Anal. calcd for $C_{27}H_{39}N_5O_3S$: C, 63.13; H, 7.65; N, 13.63; S, 6.24; found: C, 63.15; H, 7.68; N, 13.65; S, 6.21%.

4-(4-(4-((naphthalen-1-yl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2e**) Compound **2e** is a pale-yellow solid. Yield: 63%, m.p: 187–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.91 (s, 6H, CH_3-tetrahydroquinazoline), 1.35 (m, 2H, CH_2-tetrahydroquinazoline), 2.28 (s, 2H, CH_2-tetrahydroquinazoline), 2.34 (s, 2H, CH_2-tetrahydroquinazoline), 3.19 (s, 4H, CH_2-piperazine), 3.31 (s, 4H, CH_2-piperazine), 3.46 (s, 4H, CH_2-morpholine), 3.55 (s, 4H, CH_2-morpholine), 7.69–7.73 (m, 3H, CH-naphthyl), 8.11–8.18 (m, 2H, CH-naphthyl), 8.3–8.33 (d, 1H, $J = 8.4$ Hz, CH-naphthyl), 8.68–8.71 (d, 1H, $J = 7.5$ Hz, CH-naphthyl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.8 (tetrahydroquinazoline-C), 28.4 (tetrahydroquinazoline-C), 28.8 (tetrahydroquinazoline-C), 35.4 (tetrahydroquinazoline-C), 38.5 (tetrahydroquinazoline-C), 44.3 (piperazine-C), 45.6 (piperazine-C), 47.6 (morpholine-C), 67.8 (morpholine-C), 106.5 (pyrimidine-C), 125.1 (pyrimidine-C), 127.5 (naphthyl-C), 128.7 (naphthyl-C), 129.1 (naphthyl-C), 129.6 (naphthyl-C), 130.8 (naphthyl-C), 132.3 (naphthyl-C), 134.4 (naphthyl-C), 135.2 (naphthyl-C), 159.3 (pyrimidine-C), 165.3 (pyrimidine-C); IR

(ATR, $\upsilon\,cm^{-1}$): 1128 (SO_2-symmetric-stretching), 1257 (SO_2-asymmetric-stretching), 1418, 1539 (NSO_2-bending), 1565 (NSO_2-bending), 1728, 2845, 2920 (aryl CH-stretching); LCMS (ESI) *m/z*: 522.3 Da $[M + H]^+$, Anal. calcd for $C_{28}H_{35}N_5O_3S$: C, 64.47; H, 6.76; N, 13.42; S, 6.15; found: C, 64.46; H, 6.79; N, 13.41; S, 6.16%.

4-(4-(4-((thiophen-2-yl)sulfonyl)piperazin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolin-2-yl)morpholine (**2f**) Compound **2f** is an off-white solid. Yield: 78%, m.p: 179–182 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.95 (s, 6H, CH_3-tetrahydroquinazoline), 1.39 (s, 2H, CH_2-tetrahydroquinazoline), 2.32 (s, 2H, CH_2-tetrahydroquinazoline), 2.37 (s, 2H, CH_2-tetrahydroquinazoline), 3.04 (s, 4H, CH_2-piperazine), 3.39 (s, 4H, CH_2-piperazine), 3.55–3.59 (s, 8H, CH_2-morpholine), 7.29–7.32 (t, 1H, $J = 3.9$ Hz, CH-thiophene), 7.65–7.66 (d, 1H, $J = 2.4$ Hz, CH-thiophene), 8.07–8.09 (d, 1H, $J = 4.2$ Hz, CH-thiophene); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.1(tetrahydroquinazoline-C), 28.4 (tetrahydroquinazoline-C), 29.3 (tetrahydroquinazoline-C), 35.7 (tetrahydroquinazoline-C), 39.3 (tetrahydroquinazoline-C), 44.4 (tetrahydroquinazoline-C), 46.0 (piperazine-C), 46.3 (morpholine-C), 47.2 (piperazine-C), 66.4 (morpholine-C), 106.5 (pyrimidine-C), 126.0 (thiophene-C), 128.8 (thiophene-C), 129.0 (thiophene-C), 133.7 (pyrimidine-C), 134.5 (pyrimidine-C), 165.3 (pyrimidine-C); IR (ATR, υ cm^{-1}): 1167 (SO_2-symmetric-stretching), 1263, 1350 (SO_2-asymmetric-stretching), 1502, 1537 (NSO_2-bending), 1566 (NSO_2-bending); LCMS (ESI) *m/z*: 478.2 Da $[M + H]^+$, Anal. calcd for $C_{22}H_{31}N_5O_3S_2$: C, 55.32; H, 6.54; N, 14.66; S, 13.43; found: C, 55.30; H, 6.56; N, 14.67; S, 13.45%.

*General synthetic procedure for synthesis of **3a–d***

To a solution of compound **1** (0.01 mol) in THF (10 volumes), Triethyl amine (0.03 mol) was added. After stirring the mixture for 15 min, corresponding isocyante (0.01 mol) was added and gradually heated to about 65 °C for 5 h. Reaction completion was monitored by TLC and reaction was quenched with water and product was extracted with ethyl acetate. The organic layer was washed with brine solution and concentrated under reduced pressure. Crude obtained was purified by column chromatography using a mixture of ethyl acetate-hexanes to afford pure urea derivatives **3a–d**.

4-(7,7-Dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)-N-phenylpiperazine-1-carboxamide (**3a**) Compound **3a** is an off-white solid. Yield: 86%, m.p: 205–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.03 (s, 6H, CH_3-tetrahydroquinazoline), 1.48–1.53 (t, 2H, $J = 6.3$ Hz, CH_2-tetrahydroquinazoline), 2.46 (s, 2H, CH_2-tetrahydroquinazoline), 2.49–2.53 (t, 2H, $J = 6.6$ Hz, CH_2-tetrahydroquinazoline), 3.42 (s, 4H, CH_2-piperazine), 3.63 (s, 4H, CH_2-piperazine), 3.72–3.75 (m, 8H, CH_2-morpholine), 6.39 (bs, 1H, NH-amide), 7–7.39 (m, 5H, aryl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.3 (tetrahydroquinazoline-C), 28.5 (tetrahydroquinazoline-C), 29.3 (tetrahydroquinazoline-C), 35.9 (tetrahydroquinazoline-C), 44.1 (tetrahydroquinazoline-C), 44.4 (piperazine-C), 46.6 (morpholine-C), 48.0 (piperazine-C), 66.5 (morpholine-C), 106.4 (pyrimidine-C), 118.6 (phenyl-C), 120.0 (phenyl-C), 122.2 (phenyl-C), 128.7 (phenyl-C), 129.2 (phenyl-C), 140.9 (phenyl-C), 155.5 (pyrimidine-C), 159.5 (pyrimidine-C), 165.1 (pyrimidine-C), 165.8 (C=O, urea); IR (ATR, υ cm^{-1}): 1236, 1445 (H–N–C stretching), 1539 (N–C–N stretching), 1567 (NH-stretching), 1635 (C=O, stretching), 3334 (NH- stretching); LCMS (ESI) *m/z*: 451.5 Da $[M + H]^+$, Anal. calcd for $C_{25}H_{34}N_6O_2$: C, 66.64; H, 7.61; N, 18.65; found: C, 66.64; H, 7.65; N, 18.64 %.

N-(2-chlorophenyl)-4-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl) piperazine-1-carboxamide (**3b**) Compound **3b** is an off-white solid. Yield: 76%, m.p: 212–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.04 (s, 6H, CH_3-tetrahydroquinazoline), 1.49–1.54 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz, CH_2-tetrahydroquinazoline), 2.47 (s, 2H, CH_2-tetrahydroquinazoline), 2.5–2.54 (t, 2H, $J_1 = 6$ Hz, $J_2 = 6.3$ Hz, CH_2-tetrahydroquinazoline), 3.42–3.46 (m, 4H, CH_2-piperazine), 3.65–3.7 (m, 4H, CH_2-piperazine), 3.72–3.76 (m, 8H, CH_2-morpholine), 6.95–7.01 (m, 1H, CH-2-chlorophenyl), 7.07 (s, NH), 7.24–7.3 (m, 1H, CH-2-chlorophenyl), 7.34–7.37 (m, 1H, CH-2-chlorophenyl), 8.21–8.25 (m, 1H, CH-2-chlorophenyl); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 21.8 (tetrahydroquinazoline-C), 28.0 (tetrahydroquinazoline-C), 28.9 (tetrahydroquinazoline-C), 35.4 (tetrahydroquinazoline-C), 43.7 (tetrahydroquinazoline-C), 44.0 (piperazine-C), 46.1 (morpholine-C), 47.5 (piperazine-C), 66.0 (morpholine-C), 105.9 (pyrimidine-C), 125.5 (2-chlorophenyl-C), 126.7 (2-chlorophenyl-C), 127.2 (2-chlorophenyl-C), 129.2 (pyrimidine-C), 155.0 (pyrimidine-C), 159.0 (pyrimidine-C), 164.6 (C=O, urea); IR (ATR, υ cm^{-1}): 1252, 1392 (H–N–C stretching), 1516 (N–C–N stretching), 1564 (NH-stretching), 1630 (C=O, stretching), 2847, 3343 (NH- stretching); LCMS (ESI) *m/z*: 485.8 Da $[M + H]^+$, Anal. calcd for $C_{25}H_{33}ClN_6O_2$: C, 61.91; H, 6.86; N, 17.33; found: C, 61.90; H, 6.90; N, 17.35.

N-(3,4-dichlorophenyl)-4-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperazine-1-carboxamide (**3c**) Compound **3c** is an off-white solid. Yield: 73%, m.p: 182–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.03 (s,

6H, CH_3-tetrahydroquinazoline), 1.48–1.53 (t, 2H, $J_1 = 6.0$ Hz, $J_2 = 6.3$ Hz, CH_2-tetrahydroquinazoline), 2.46–2.52 (m, 4H, CH_2-tetrahydroquinazoline), 3.41 (s, 4H, CH_2-piperazine), 3.62 (s, 4H, CH_2-piperazine), 3.72–3.75 (m, 8H, CH_2-morpholine), 6.53 (s, NH), 7.22–7.25 (d, 2H, $J =$ 8.7 Hz, CH-3,4-dichlorophenyl), 7.33–7.36 (d, 2H, $J = 8.7$ Hz, CH-3,4-dichlorophenyl), 7.64 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 22.3 (tetrahydroquinazoline-C), 28.4 (tetrahydroquinazoline-C), 29.3 (tetrahydroquinazoline-C), 35.9 (tetrahydroquinazoline-C), 44.0 (tetrahydroquinazoline-C), 44.4 (piperazine-C), 46.5 (morpholine-C), 47.9 (piperazine-C), 66.5 (morpholine-C), 106.4 (pyrimidine-C), 119.6 (3,4-dichlorophenyl-C), 120.8 (3,4-dichlorophenyl-C), 123.3 (3,4-dichlorophenyl-C), 130.6 (pyrimidine-C), 131.0 (3,4-dichlorophenyl-C), 141.3 (3,4-dichlorophenyl-C), 154.9 (3,4-dichlorophenyl-C), 159.4 (pyrimidine-C), 165.1 (pyrimidine-C), 165.7 (C=O, urea); IR (ATR, υ cm^{-1}): 1234, 1417 (H–N–C stretching), 1517 (N–C–N stretching), 1571 (NH-stretching), 1642 (C=O, stretching), 2850, 3261 (NH- stretching); (ESI) *m/z*: 519.5 Da $[M + H]^+$, Anal. calcd for $C_{25}H_{32}Cl_2N_6O_2$: C, 57.80; H, 6.21; N, 16.18, found: C, 57.78; H, 6.24; N, 16.15%.

N-([1,1′-Biphenyl]-4-yl)-4-(7,7-dimethyl-2-morpholino-5,6,7,8-tetrahydroquinazolin-4-yl)piperazine-1-carboxamide (**3d**) Compound **3d** is an off-white solid. Yield: 63%, m.p: 159–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):1.04 (s, 6H, CH_3-tetrahydroquinazoline), 1.49–1.54 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz, CH_2-tetrahydroquinazoline), 2.47 (s, 2H, CH_2-tetrahydroquinazoline), 2.5–2.54 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6$ Hz, CH_2-tetrahydroquinazoline), 3.42–3.46 (m, 4H, CH_2-piperazine), 3.65–3.7 (m, 4H, CH_2-piperazine), 3.72–3.76 (m, 8H, CH_2-morpholine), 6.95–7.01 (m, 1H, CH-biphenyl), 7.07 (s, NH), 7.24–7.3 (m, 1H, CH-biphenyl), 7.34–7.37 (m, 6H, CH-biphenyl), 8.21–8.25 (m, 1H, CH-biphenyl); ^{13}C NMR (75 MHz, DMSO-d_6), δ ppm: 21.8 (tetrahydroquinazoline-C), 28.8 (tetrahydroquinazoline-C), 29.3 (tetrahydroquinazoline-C), 35.4 (tetrahydroquinazoline-C), 38.7 (tetrahydroquinazoline-C), 44.0 (piperazine-C), 46.1 (morpholine-C), 47.5 (piperazine-C), 66.0 (morpholine-C), 105.9 (pyrimidine-C), 119.7 (biphenyl-C), 126.0 (biphenyl-C), 126.4 (biphenyl-C), 126.6 (biphenyl-C), 128.7 (biphenyl-C), 133.3 (pyrimidine-C), 139.9 (biphenyl-C), 140.0 (biphenyl-C), 155.0 (biphenyl-C), 159.0 (pyrimidine-C), 164.6 (pyrimidine-C), 165.3 (C=O, urea); IR (ATR, υ cm^{-1}): 1252, 1392 (H–N–C stretching), 1416 (H–N–C stretching), 1516 (N–C–N stretching), 1564 (NH-stretching), 1630 (C=O, stretching), 2847, 3343 (NH-stretching); LCMS (ESI) *m/z*: 527.9 Da $[M + H]^+$, Anal. calcd for $C_{31}H_{38}N_6O_2$: C, 70.70; H, 7.27; N, 15.96; found: C, 70.68; H, 7.25; N, 15.95%.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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