Synthesis and antiviral activity of sulfonohydrazide and 1,3,4-oxadiazole derivatives of 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*] quinazoline

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A series of new 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline substituted benzenesulfonohydrazide and 1,3,4-oxadiazole derivatives has been synthesised and characterised using spectral techniques. The antiviral activity of these compounds against an avian paramyxovirus (APMV-1) has been screened and the results show that some of the compounds possess good antiviral activity

Keywords: pyrazolo[5,1-*b*]quinazoline, sulfonohydrazide, 1,3,4-oxadiazole, antiviral

One of the important and largest classical divisions of organic chemistry is heterocyclic chemistry and it is well established that the majority of the biologically active substances contain heterocyclic rings, specifically pyrazoles and pyrimidines. Among them, pyrazolopyrimidinones are a series of isomeric heterocyclic compounds with well-known biological activity and their scaffold is found in many pharmaceuticals, for example zaleplon[1] and indiplon,[2] and in pesticides such as pyrazophos.[3] These compounds act as a kinase inhibitor with unexpected anti-proliferative activity against cells, including tumour cells in xenograft tumour models; hence, pyrazolopyrimidinone or a suitable salt or pro-drug is useful for the treatment of individuals suffering from a cancer or other proliferative disorder or disease.[4–6] Pyrazolopyrimidinone derivatives are also used to inhibit a guanosine 3′,5′-cyclic phosphate phosphodiesterase in the treatment of sexual dysfunction and in the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.[7] Sulfonohydrazide derivatives are pharmaceutically active compounds that show inhibitory activity of the JNK (Jun-Kinase) function and are hence used in the treatment or prevention of disorders of the autoimmune and neuronal systems.[8] It has been reported that a 1,3,4-oxadiazole ring attached to pyrazolopyrimidinones shows inhibitory activity against PAS kinase.[9,10] Hence, it is presumed that a pyrazolopyrimidinone ring with sulfonohydrazides or 1,3,4-oxadiazoles will possess significant biological activity.

Newcastle disease virus (NDV) is an economically important paramyxovirus that infects 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. To date, there is no approved drug against NDV. Ribavirin, a well-known broad-spectrum antiviral drug is approved for treatment of respiratory syncytial virus (RSV), a human paramyxovirus that causes severe lower respiratory tract infections in children.[11] However, 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.[12,13] All these factors highlight the importance of developing novel antiviral drugs. Therefore, the main objective of this study was to synthesise 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline-3-carbohydrazide (**1**) and its sulfonyl (**2**) and 1,3,4-oxadiazole (**3**) derivatives, and screen their antiviral activity against an avian paramyxovirus (APMV-1).

Results and discussion

The overall route adopted for the synthesis of 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline-3-carbohydrazide (**1**) is shown in Scheme 1. Commercially available ethyl cyanoacetate (**4**) reacted with trimethyl orthoformate in the presence of *p*-toluene sulfonic acid in acetic anhydride gave ethyl (*Z*)-2-cyano-3-methoxyacrylate (**6**), which on treatment with hydrazine hydrate in ethanol undergoes cyclisation to yield ethyl 5-amino-1*H*-pyrazole-4-carboxylate (**7**). Methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (**9**) was synthesised according to a literature procedure from

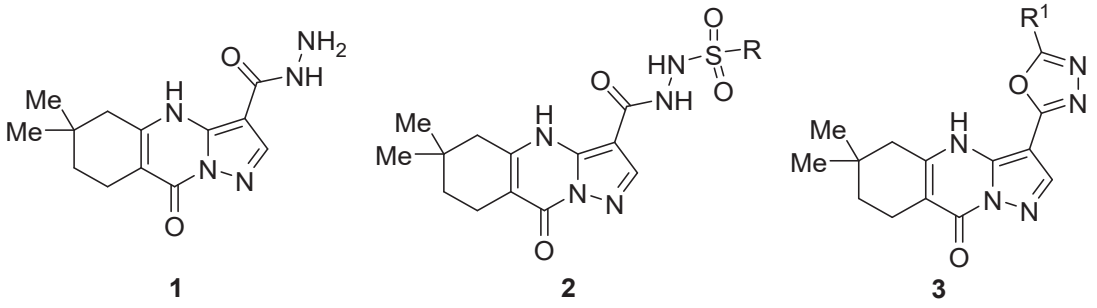

Fig. 1 Structures of hydrazide **1** and sulfonyl (**2**) and 1,3,4-oxadiazole (**3**) derivatives.

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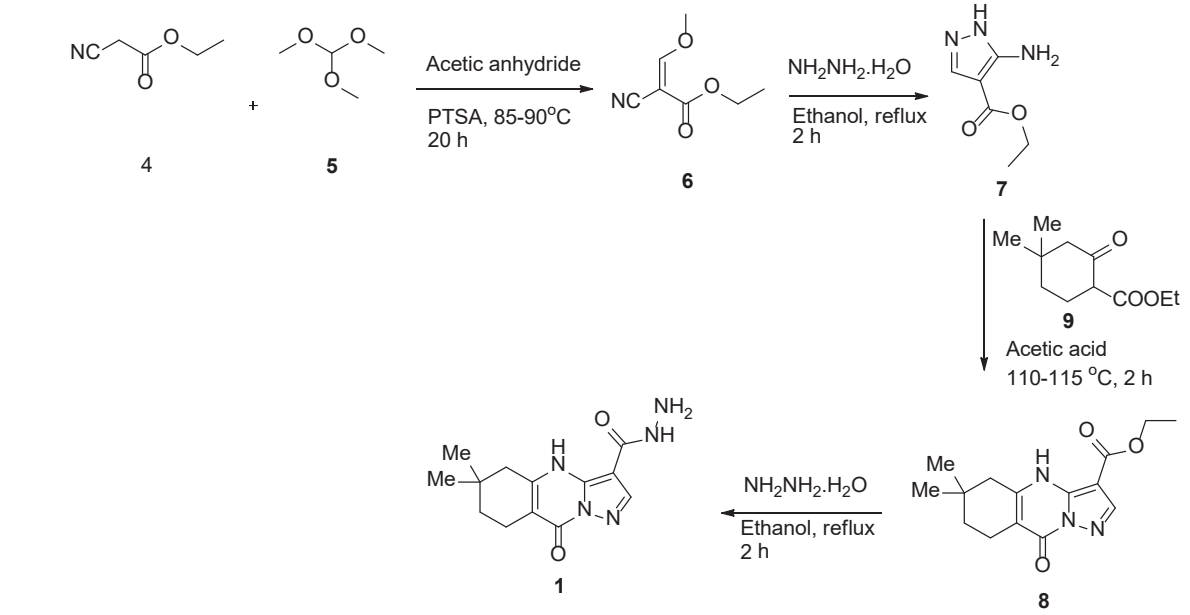
3,3-dimethyl cyclohexanone and dimethyl carbonate in the presence of sodium hydride in THF.[14,15] The intermediate **7** undergoes cyclisation with **9** in acetic acid to provide ethyl 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*] quinazoline-3-carboxylate (**8**), which on treatment with hydrazine hydrate in ethanol undergoes a nucleophilic substitution reaction to yield compound **1** (Scheme 1).

Benzene sulfonyl derivatives **2a**–**c** were prepared from compound **1** by treatment with the corresponding substituted benzene sulfonyl chloride (Scheme 2). The structures of the compounds **2a**–**c** were confirmed by ^{1}H and ^{13}C NMR, LCMS and IR spectra. Similarly, 1,3,4-oxadiazole derivatives **3a**–**c** were also synthesised by treating compound **1** with the corresponding substituted benzoyl chlorides followed by cyclisation using DCC (Scheme 2). The structures of compounds **3a**–**c** were also confirmed using ^{1}H and ^{13}C NMR, LCMS and IR spectra.

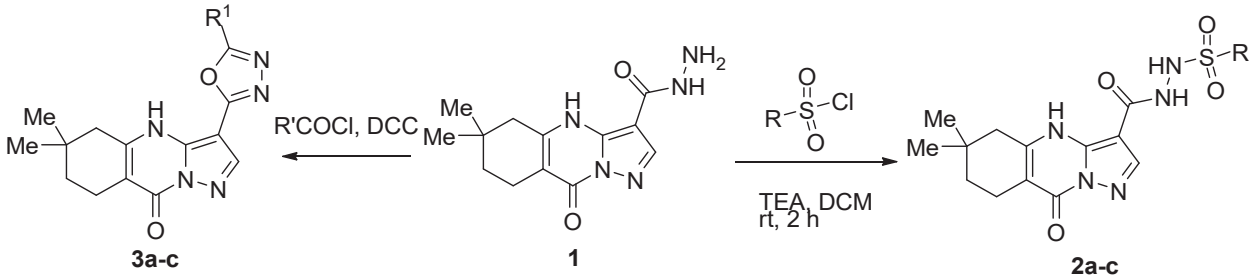
The antiviral evaluation of compounds **2a**–**c** and **3a–c** was carried out in African green monkey kidney and Vero cell lines. To test the antiviral activity, these compounds were initially screened by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as described in the literature.[16] The maximum non-cytotoxic concentration (MNCC), at which no significant changes were detected in the 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 (Newcastle disease virus, APMV-1). The well-known antiviral drug ribavirin was used for comparing the antiviral potential of the test compounds.

The MNCC of ribavirin was 31.25 μg mL^{-1}. The 50% cytotoxic concentration (CC50: dose that inhibited growth by 50% compared with untreated cells) of ribavirin was 400 μg mL^{-1}, and 32% viral plaque reduction was observed at a ribavirin dosage of 31.25 μg mL^{-1}. Monolayers of Vero cells in a 24-well plate were incubated with five different concentrations of the test compounds (0.1, 0.01, 0.001, 0.0001 and 0.00001 M) for 1 h. The cells were washed three times with PBS and then infected with a known dose of Newcastle disease virus for 1 h. The cells were again washed three times with PBS and overlaid with methyl cellulose media. The cells were incubated at 37 °C with 5% CO_2 for 5 d. The cells were observed every day during the incubation period. On the fifth 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 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 on compound treatment compared with untreated NDV infected cells, which were defined as 100%. The results obtained are shown in Table 1.

The results indicated that the test compounds **2a**–**c**, **3a** and **3c** showed antiviral activity by inhibiting the plaque formation by 56, 45, 5, 13 and 38%, respectively, at the minimum test



Scheme 1 Synthesis of compound **1**.



3a: 4-fluoro phenyl;
3b: 4-chloro phenyl
3c: 3,5-dimethyl phenyl

2a: 2-fluoro phenyl;
2b: 2-chloro phenyl
2c: 4-chloro phenyl

Scheme 2 Synthesis of compounds **2a–c** and **3a–c** from compound **1**.

Table 1 Antiviral activity of compounds **2a–c** and **3a–c** against APMV-1

Compound	Test concentration at which antiviral activity was observed/M	Plaque percentage of test virus concentration/%	Plaque reduction/%
2a	0.00001	44	56
2b	0.01	55	45
2c	0.1–0.00001	95	5
3a	0.0001	87	13
3b	0.1–0.00001	105	None
3c	0.00001	62	38
Ribavirin	0.0001	68	32

dose when compared with infected untreated controls. Test compound **3b** did not show any antiviral activity at the tested concentrations. Among the compounds under investigation, sulfonohydrazide derivatives showed relatively higher antiviral activity than the oxadiazole analogues, especially compound **2a**, which showed the highest antiviral activity. Surprisingly, it was observed that the oxadiazole **3b** did not show any activity, and 4-chlorophenyl substituted sulfonohydrazide **2c** and 4-fluorophenyl substituted oxadiazole **3a** showed very poor antiviral activity whereas 2-chlorophenyl substituted sulfonohydrazide **2b** showed activity equivalent to **2a**. The structural modification caused by changing the substituents in the phenyl ring in both sulfonohydrazides (R) and oxadiazoles (R^1) has a wide impact on the antiviral activity of the prepared compounds, especially *para*-substitution of the phenyl ring, which deactivated the antiviral efficacy in both series.

Conclusion

Sulfonohydrazide (2a–c) and 1,3,4-oxadiazole (3a–c) derivatives of 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydro pyrazolo[5,1-*b*]quinazoline were synthesised, characterised and screened for antiviral activity. The antiviral screening results suggested the prospective use of sulfonohydrazide derivatives for therapeutic purposes not only against NDV in birds but also against other paramyxoviruses infecting humans and animals. The real challenges ahead are to test their *in vivo* antiviral activity and to study their pharmacokinetics, which will help in developing them as potential antiviral drugs.

Experimental

All the chemicals used in the study are commercially available and high-purity grade (Aldrich or Merck, India). The solvents were of reagent grade and used as supplied commercially. TLC experiments were performed on alumina-backed silica gel 40F254 plates (Merck, Germany). The plates were illuminated under UV light (254 nm) and treated with $KMnO_4$. Melting points were determined using a melting point apparatus (B-540 Buchi, Germany) without corrections. All ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz or Bruker 400 MHz spectrometer. Molecular masses of unknown compounds were checked by LCMS 6200 series Agilent Technology. 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 Bruker Alpha FTIR 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 Flash 1112EA apparatus and Eager Xperience software.

Ethyl (Z)-2-cyano-3-methoxyacrylate (**6**)

To a stirred solution of ethyl cyanoacetate (25 g, 0.22 mol) in trimethyl orthoformate (36.5 mL, 0.33 mol), acetic anhydride (16 mL, 0.18 mol) and *p*-toluene sulfonic acid (0.5 g, 0.02 w/w) were added. The resultant solution was heated to 85–90 °C and stirred for 20 h. After reaction completion, the reaction mass was concentrated completely and the crude product was purified by methyl *t*-butyl ether slurry to obtain the desired product compound **6** as: Brown solid; yield 85%; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32–1.36 (t, 3H, J_1 = 7.2 Hz, J_2 = 5.4 Hz), 4.12 (s, 3H), 4.30 (q, 2H, J = 9.6 Hz), 7.94 (s, 1H); LCMS (ESI) *m/z* for $C_7H_9NO_3$: 156.2 Da ($[M + H]^+$). Anal. calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03; found: C, 54.14; H, 5.89; N, 9.01%.

*Ethyl 5-amino-1*H*-pyrazole-4-carboxylate* (**7**)

To a stirred solution of compound **6** (10 g, 0.06 mol) in ethanol (10 mL), hydrazine hydrate (9.4 mL, 0.19 mol) was added slowly at 25–30 °C. The reaction mass was heated to reflux and stirred for 2 h. After reaction completion, the reaction mass was concentrated and extracted with ethyl acetate (80 mL) and washed with water (2 × 40 mL) and brine solution (30 mL), and then dried over anhydrous sodium sulfate and concentrated completely to obtain the desired product compound **7** as: Yellow solid, yield 70%; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32–1.41 (m, 3H), 4.25–4.37 (m, 2H), 5.79 (bs, 3H, NH_2), 7.74 (s, 1H); LCMS (ESI) *m/z* for $C_6H_9N_3O_2$: 156.10 Da ($[M + H]^+$). Anal. calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08; found: C, 46.44; H, 5.87; N, 27.10%.

Methyl 4,4-dimethyl-2-oxocyclohexane-1-carboxylate (**9**)

A solution of dimethyl carbonate (3.3 mL, 0.039 mol) and NaH (1.24 g, 0.052 mol) in THF (24 mL) was heated to 80 °C for 30 min. Then 3,3-dimethylcycloheaxanone (2.0 g, 0.016 mol) was added and stirred for 2.5 h under nitrogen atmosphere. After reaction completion, the reaction mass was cooled to about 0 °C, quenched with methanol (10 mL), followed by water (25 mL), and the resultant mixture was acidified to about pH 1 with 3 M HCl. The compound was extracted with dichloromethane, dried over sodium sulfate and concentrated to afford compound **9** as:[15] Pale yellow liquid; yield 85%; ^1H NMR (400 MHz, DMSO-d_6): δ 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 = 6.3Hz, J_2 = 6 Hz), 3.71 (s, 3H), 12.09 (s, 1H, enol–OH); IR (ATR) (υ cm^{-1}): 821, 1065, 1231, 1441, 1617, 1657, 1712, 1746, 2922, 2952; LCMS (ESI) *m/z* for $C_{10}H_{16}O_3$: 184.9 Da ($[M + H]^+$).

*Ethyl-6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline-3-carboxylate* (**8**)

To a stirred solution of **7** (5 g, 0.032 mol) in acetic acid (50 mL), **9** (5.9 g, 0.032 mol) was added and the mixture was heated to 110–115 °C and stirred for 2 h. After reaction completion (monitored by TLC), the reaction mass was cooled to 20–25 °C. The solid obtained was collected by filtration and washed with water (35 mL) to afford the desired product compound **8** as: Off-white solid; yield 74%; ^1H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 6H), 1.28–1.32 (t, 2H, J_1 = 7.2 Hz, J_2 = 7.2 Hz), 1.47–1.51 (t, 2H, J_1 = 6.4 Hz, J_2 = 6.4 Hz), 2.44–2.49 (m, 2H), 2.58 (s, 2H), 2.27–4.32 (q, 2H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.3, 19.2, 27.4, 28.9, 33.7, 59.7, 95.6, 105.0, 142.6, 142.9, 147.3, 155.7, 161.7; FTIR (υ cm^{-1}): 777, 1101, 1511, 1597, 1634, 1686, 2929, 3212; LCMS (ESI) *m/z*: 289.0 Da ($[M+H]^+$). Anal. calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52; found: C, 62.25; H, 6.69; N, 14.50%.

*6,6-Dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline-3-carbohydrazide* (**1**)

To a stirred solution of **8** (25 g, 0.086 mol) in ethanol (250 mL), hydrazine hydrate (8.5 mL, 0.173 mol) was added slowly at 25–30 °C. The reaction mass was heated to reflux and stirred for 2 h. After reaction completion (monitored by TLC), the reaction mass was concentrated and extracted with ethyl acetate (200 mL), washed with water (2 × 100 mL) and brine solution (100 mL), and then dried over anhydrous sodium sulfate and concentrated completely to obtain the desired product compound **1**, which was used in the next step with any purification, as: Yellow solid; LCMS (ESI) *m/z* for $C_{15}H_{19}N_5O_2$: 274.0 Da ($[M - H]^+$).

Synthesis of sulfonohydrazides (**2a–c**)*; general procedure*

To a stirred solution of **1** (1.0 equiv.) in DCM (15 vol.), triethyl amine (2.5 equiv.) was added slowly at 10–15 °C and the mixture was stirred for 10 min at the same temperature. To this reaction mixture, the

corresponding sulfonyl chloride (**a**–**c**) (0.9 equiv.) was added slowly for about 5 min at 10–15 °C. The reaction mass temperature was raised to about 25 °C and stirred for 2 h. After reaction completion (monitored by TLC), the reaction mass was quenched with 5% sodium bicarbonate solution (6 vol.), extracted into DCM (10 vol.), washed with water (5 vol.) and brine solution (5 vol.), and then dried over anhydrous sodium sulfate and concentrated completely to obtain the desired products **2a**–**c** as solids.

N'-*(6,6-Dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazoline-3-carbonyl)-2-fluorobenzenesulfonohydrazide* (**2a**): Off-white solid; yield 78%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 6H), 1.22 (s, 4H), 1.46 (s, 4H), 7.3–7.34 (m, 1H), 7.39–7.44 (m, 1H), 7.68–7.7 (m, 1H), 7.78–7.82 (m, 1H), 8.29 (s, 1H), 10.12 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 27.9, 29.4, 96.6, 105.1, 117.6–117.9, 124.9, 127.9, 130.6, 136.1–136.2, 141.2, 142.9, 147.8, 156.2, 158.1, 160.6, 161.4; IR (ATR) (υ cm^{-1}): 829, 1198, 1300, 1597, 1634, 1686, 1817, 2961, 3147, 3367; LCMS (ESI) *m/z*: 434.3 Da ([M + H]$^+$). Anal. calcd for $C_{19}H_{20}FN_5O_4S$: C, 52.65; H, 4.65; N, 16.16; S, 7.40; found: C, 52.61; H, 4.69; N, 16.15; S, 7.43%.

*2-Chloro-*N'*-(6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydro-pyrazolo[5,1-*b*]quinazoline-3-carbonyl)benzenesulfonohydrazide* (**2b**): Off-white solid; yield 85%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 6H), 1.44–1.47 (t, 2H, J_1 = 6.4 Hz, J_2 = 6.4 Hz), 2.41–2.44 (t, 2H, J_1 = 6.0 Hz, J_2 = 6.0 Hz), 3.16 (s, 2H), 4.1 (bs, 1H), 7.45–7.5 (m, 1H), 7.3–7.34 (m, 1H), 7.39–7.44 (m, 1H), 7.61–7.67 (m, 1H), 7.98–8.0 (m, 1H), 8.29 (s, 1H), 10.0 (s, 1H), 10.3 (s, 1H); 11.4 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 27.9, 29.3, 34.2, 96.8, 105.1, 127.8, 131.3, 132.1, 132.3, 134.7, 137.8, 141.3, 142.9, 147.9, 156.2, 161.5; IR (ATR) (υ cm^{-1}): 861, 1045, 1297, 1597, 1641, 1686, 2929, 3181, 3371, 3628; LCMS (ESI) *m/z*: 450.4 Da ([M + H]$^+$). Anal. calcd for $C_{19}H_{20}ClN_5O_4S$: C, 50.72; H, 4.48; N, 15.57; S, 7.13; found: C, 50.70; H, 4.51; N, 15.54; S, 7.14%.

*4-Chloro-*N'*-(6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydro-pyrazolo[5,1-*b*]quinazoline-3-carbonyl)benzenesulfonohydrazide* (**2c**): Off-white solid; yield 76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 6H), 1.44–1.48 (t, 2H, J_1 = 6.4 Hz, J_2 = 6.8 Hz), 2.41–2.45 (t, 2H, J_1 = 6.0 Hz, J_2 = 6.0 Hz), 3.28 (s, 2H), 4.1 (bs, 1H), 7.62–7.65 (m, 2H), 7.81–7.83 (d, 1H, J = 8.8 Hz), 8.3 (s, 1H), 10.0 (s, 1H), 10.3 (s, 1H); 11.4 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.7, 27.9, 29.3, 34.2, 96.6, 105.1, 129.7, 129.8, 138.3, 141.3, 147.8, 156.2; IR (ATR) (υ cm^{-1}): 734, 1168, 1327, 1597, 1628, 1682, 2927, 3181, 3246, 3574; LCMS (ESI) *m/z*: 450.0 Da ([M + H]$^+$). Anal. calcd for $C_{19}H_{20}ClN_5O_4S$: C, 50.72; H, 4.48; N, 15.57; S, 7.13; found: C, 50.71; H, 4.52; N, 15.55; S, 7.11%.

Synthesis of 1,3,4-oxadiazoles (**3a**–**c**)*; general procedure*

To a solution of **1** (10 mol) in DMF (6 vol.), dicyclohexylcarbodiimide (15 mol) was added under inert atmosphere at about 5 °C. The resultant solution was stirred for 1 h at the same temperature. To this solution, the corresponding acid chloride (10 mol) was added and stirred for 30 min. Then the reaction mass was slowly brought to ambient temperature followed by heating to 110 °C for 10 h. After reaction completion (monitored by TLC), the reaction mass was poured into ice cold water and the precipitated side product (dicyclohexyl urea) was separated out by filtration and washed with ethyl acetate (10 vol.). Layers were separated and the aqueous layer was back extracted with ethyl acetate (10 vol.). The combined organic layer was washed with brine, dried over with sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography using ethyl acetate–hexanes in a gradient manner to obtain the desired products **3a**–**c** as solids.

*3-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-6,6-dimethyl-5,6,7,8-tetrahydropyrazolo[5,1-*b*]quinazolin-9(4*H*)-one* (**3a**): Off-white solid; yield 62%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 6H), 1.72–1.79 (m, 2H), 2.86 (s, 2H), 2.88–2.92 (m, 2H), 7.48–7.52 (m, 2H), 8.14–8.17 (m ,2H), 8.91 (s, 1H); IR (ATR) (υ cm^{-1}): 751, 851, 1479, 1496, 2924, 2950, 3438; LCMS (ESI) *m/z*: 378 Da ([M – H]$^+$). Anal. calcd for $C_{20}H_{18}FN_5O_2$: C, 63.32; H, 4.78; N, 18.46; found: C, 63.30; H, 4.82; N, 18.44%.

*3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-6,6-dimethyl-5,6,7,8-tetrahydropyrazolo[5,1-*b*]quinazolin-9(4*H*)-one* (**3b**): Off-white solid; yield 56%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 6H), 1.44–1.48 (t, 2H, J_1 = 6.4 Hz, J_2 = 6.8 Hz), 2.41–2.45 (t, 2H, J_1 = 6.0 Hz, J_2 = 6.0 Hz), 3.28 (s, 2H), 4.1 (bs, 1H), 7.62–7.65 (m, 2H), 7.81–7.83 (d, 1H, J = 8.8 Hz), 8.91 (s, 1H), 12.03 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.7, 27.9, 29.3, 34.2, 96.6, 105.1, 129.7, 129.8, 138.3, 141.3, 147.8, 156.2; IR (ATR) (υ cm^{-1}): 751, 851, 1479, 1496, 1634, 2859, 2950, 3438; LCMS (ESI) *m/z*: 396.0 Da ([M + H]$^+$). Anal. calcd for $C_{20}H_{18}ClN_5O_2$: C, 60.68; H, 4.58; N, 17.69; found : C, 60.65; H, 6.15; N, 17.70%.

*3-(5-(3,5-Dimethylphenyl)-1,3,4-oxadiazol-2-yl)-6,6-dimethyl-5,6,7,8,-tetrahydropyrazolo[5,1-*b*]quinazolin-9(4*H*)-one* (**3c**): Off-white solid; yield 66%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0 (s, 6H), 1.52–1.55 (m, 2H), 2.39 (s ,6H), 2.49–2.5 (m, 2H), 2.62 (s, 2H), 7.27 (s, 1H), 7.75 (s, 2H), 8.47 (s, 1H), 12.0 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 27.9, 29.4, 88.9, 124.6, 133.7; IR (ATR) (υ cm^{-1}): 635, 1194, 1582, 1612, 1701, 2935, 3431; LCMS (ESI) *m/z*: 390.1 Da ([M + H]$^+$). Anal. calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98; found: C, 67.82; H, 6.04; N, 17.95%.

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Electronic Supplementary Information

The ESI is available from:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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