Synthesis, characterization, *in silico* molecular docking study and biological evaluation of 5-(phenylthio) pyrazole based polyhydroquinoline core moiety

Nirav H. Sapariya*, Beena K. Vaghasiya, Rahul P. Thummar, Ronak D. Kamani, Kirit H. Patel, Parth Thakor\textsuperscript{b}, Sampark S. Thakkarc, Arabinda Ray\textsuperscript{c} and Dipak K. Raval

\textsuperscript{a}Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar- 388 120, Gujarat, India

\textsuperscript{b}B. R. Doshi School of Biosciences, Sardar Patel Maidan, Bakrol-Vadai Road, Satellite Campus, Sardar Patel University, Vallabh Vidyanagar -388120, Gujarat, India

\textsuperscript{c}Department of Advanced Organic Chemistry, P. D. Patel Institute of Applied Sciences (PDPIAS), Charotar University of Science & Technology (CHARUSAT), Changa-388421, Gujarat, India

*Corresponding author. Tel.: +91-02692-226856 - Ext. - 211; Fax: +91-02692 236475.

E-mail: nir.sapariya@gmail..com, dipanalka@yahoo.com

Supplementary Information
6.1.1. General procedure for the synthesis of 3-methyl-5-substituted phenylthio-1-phenyl-1H-pyrazole-4-carbaldehydes (3a-c)

5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 1 (1 mmol), substituted thiophenols 2a–c (1 mmol) and anhydrous potassium carbonate (2.5 mmol) in dimethyl formamide (10 mL) were charged in a 100 mL round bottom flask equipped with a mechanical stirrer and a condenser. The reaction mixture was heated at 90 °C for 2 h and the progress of the reaction was monitored by TLC. After the completion of reaction as confirmed by the TLC, the reaction mixture was poured in to 100 mL ice water. The solid separated was filtered, washed thoroughly with water, dried and recrystallized from hot ethanol (10 mL) to obtain 3a-c.

6.1.1.1 5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3a)
Yield 83 %; m.p. 241-243 °C; ¹H NMR (400 MHz, DMSO- d₆): δ 2.49 (s, 3H, CH₃ of pyrazole ), 7.05-7.53 (m, 9H, Ar–H), 9.96 (s, 1H, -CHO) ; ¹³C NMR (100 MHz, DMSO- d₆) δ: 13.8, 123.1, 126.3, 129.5, 129.6, 130.0, 130.3, 132.5, 133.0, 138.1, 138.3, 151.2, 186.2.

6.1.1.2 3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazole-4-carbaldehyde (3b)
Yield 87 %; m.p. 225-227 °C; ¹H NMR (400 MHz, DMSO- d₆): δ 2.34 (s, 3H, CH₃ of benzene ring ), 2.47 (s, 3H, CH₃ of pyrazole ), 7.07-7.62 (m, 9H, Ar–H), 9.73 (s, 1H, -CHO) ; ¹³C NMR (100 MHz, DMSO- d₆) δ: 13.5, 21.3, 114.6, 119.9, 126.2, 128.6, 129.3, 137.9, 139.2, 141.8, 149.2, 191.0.

6.1.1.3 5-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3c)
Yield 79 %; m.p. 214-216 °C; ¹H NMR (400 MHz, DMSO- d₆): δ 2.47 (s, 3H, CH₃ of pyrazole ), 7.07-7.48 (m, 9H, Ar–H), 10.02 (s, 1H, -CHO) ; ¹³C NMR (100 MHz, DMSO- d₆) δ: 13.8, 117.0, 117.2, 122.9, 126.4, 129.0, 129.6, 131.8, 131.9, 138.2, 139.5, 151.0, 160.7, 163.2, 186.3.

6.1.2. General procedure for the synthesis of substituted 3-((substituted)amino)-5,5-dimethylcyclohex-2-enone (6a-c).

1,3-Dimedone 4 (10 mmol), fluoro substituted amine 5a–c (10 mmol) and methanol (10 mL) with catalytic amount of acetic acid were charged in a 100 mL round bottom flask equipped with a mechanical stirrer. The reaction mixture was stirred at room
temperature for 2 h. After the completion of reaction (checked by TLC), the separated substituted enhydrazinoketones 6a–c were filtered and washed with methanol to obtain the pure solid product.

6.1.3. General procedure for the synthesis of 2-amino-4-(5-((substituted phenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(phenylamino)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8a–p)

A 50 mL round bottom flask, fitted with a reflux condenser, was charged with a mixture of 3-methyl-5-substituted phenylthio-1-phenyl-1H-pyrazole-4-carbaldehydes (3a–c) (1 mmol), malononitrile 7a or ethylcyanoacetate 7b or cyanoacetamide 7c (1 mmol), substituted enaminones 6a–c (1 mmol), and catalytic amount of piperidine (2-3 drops) in ethanol (10 mL). The mixture was heated under reflux for 1-3 h and the progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and stirred magnetically for further 10 min. The solid mass separated was collected by filtration, washed well with ethanol (10 mL) and crystallized from hot chloroform. The physicochemical and spectroscopic characterization data of the synthesized compounds 8a–p are given below.

6.1.3.1. 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8a)

Yield 81%; m.p. 213-215 °C; IR (KBr, ν_max, cm⁻¹): 3472 & 3332 (asym. & sym. str. of –NH₂), 2180 (C≡N str.), 1652 (C=O str.), 1367 (–CH₃ str.), 769 (C–S–C thioether str.);¹H NMR (400 MHz, DMSO-d₆): δ 0.73 (s, 3H, CH₃), 0.86 (s, 3H, CH₃), 1.04-1.92 (m, 4H, 2 × CH₂), 2.44 (s, 3H, CH₃ of pyrazole), 4.75 (s, 1H, CH), 5.24 (bs, 2H, -NH₂), 6.89-7.45 (m, 13H, Ar–H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 12.22, 27.63, 27.88, 31.76, 40.81, 49.09, 58.24, 109.24, 116.99, 117.22, 121.66, 124.93, 126.66, 127.46, 127.66, 128.59, 128.88, 130.24, 131.54, 132.08, 132.11, 132.83, 134.73, 138.88, 147.79, 150.44, 151.00, 161.02, 163.48, 194.80; ESI-MS (m/z): 609.1 (M⁺), 611.1 (M+2); Anal. Calcd (%) for C₃₄H₂₉ClFN₅OS: C, 66.93; H, 4.79; N, 11.48. Found: C, 66.89; H, 4.73; N, 11.42.
6.1.3.2. Ethyl 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8b)

Yield 79%; m.p. 224-226 °C; IR (KBr, $\nu_{\text{max}}$, cm$^{-1}$): 3475 & 3342 (asym. & sym. str. of –NH$_2$), 2193 (C≡N str.), 1663 (C=O str.), 1373 (–CH$_3$ str.), 764 (C–S–C thioether str.);$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.70 (s, 3H, CH$_3$), 0.85 (s, 3H, CH$_3$), 1.09-1.36 (m, 4H, 2 × CH$_2$), 1.87 (m, 3H, CH$_3$), 2.55 (s, 3H, CH$_3$ of pyrazole), 4.01 (m, 2H, CH$_2$), 5.93 (s, 1H, -CH), 6.56 (bs, 2H, NH$_2$), 6.68-7.30 (m, 13H, Ar–H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.45, 14.67, 25.88, 27.19, 28.26, 31.77, 40.81, 49.29, 58.31, 76.43, 111.95, 117.02, 117.25, 124.84, 125.39, 126.25, 127.41, 128.53, 129.61, 132.26, 134.50, 135.65, 138.98, 142.98, 145.11, 152.59, 160.92, 163.37, 168.78, 194.81; ESI-MS (m/z): 656.2(M$^+$), 658.1 (M+2); Anal. Calcd (%) for C$_{36}$H$_{34}$ClFN$_4$O$_3$S: C, 65.79; H, 5.21; N, 8.53. Found: C, 65.74; H, 5.18; N, 8.49.

6.1.3.3. 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (8c)

Yield 73%; m.p. 198-200 °C; IR (KBr, $\nu_{\text{max}}$, cm$^{-1}$): 3440 & 3354 (asym. & sym. str. of –NH$_2$), 2213 (C≡N str.), 2193 (C=O str.), 1373 (–CH$_3$ str.), 764 (C–S–C thioether str.); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.71 (s, 3H, CH$_3$), 0.87 (s, 3H, CH$_3$), 1.39-2. 11 (m, 4H, 2 × CH$_2$), 2.51 (s, 3H, CH$_3$ of pyrazole), 4.91 (s, 1H, CH), 6.00 (s, 2H, NH$_2$), 6.79-7.41 (m, 15H, Ar–H and CONH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.33, 14.67, 25.88, 27.19, 28.26, 31.55, 40.13, 49.17, 109.11, 116.93, 117.23, 121.56, 124.97, 126.76, 127.43, 127.69, 128.60, 128.83, 130.21, 131.57, 132.16, 132.20, 132.85, 134.75, 138.80, 147.82, 150.43, 151.03, 161.64, 163.86, 171.13, 194.73; ESI-MS (m/z): 627.1(M$^+$), 629.1 (M+2); Anal. Calcd (%) for C$_{34}$H$_{31}$ClFN$_5$O$_2$S: C, 65.79; H, 5.21; N, 8.53. Found: C, 65.06; H, 4.93; N, 11.11.

6.1.3.4. 2-amino-1-(4-fluorophenyl)-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8d)

Yield 73 %; m.p. 198-200 °C; IR (KBr, $\nu_{\text{max}}$, cm$^{-1}$): 3400 & 3354 (asym. & sym. str. of –NH$_2$), 2213 (C≡N str.), 2193 (C=O str.), 1369 (–CH$_3$ str.), 776 (C–S–C thioether str.); 762 (C-Cl stretching ); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.71 (s, 3H, CH$_3$), 0.87 (s, 3H, CH$_3$), 1.39-2. 11 (m, 4H, 2 × CH$_2$), 2.51 (s, 3H, CH$_3$ of pyrazole), 4.91 (s, 1H, CH), 6.00 (s, 2H, -NH$_2$), 6.79-7.41 (m, 15H, Ar–H and CONH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.33, 27.64, 27.85, 31.55, 40.13, 49.17, 109.11, 116.93, 117.23, 121.56, 124.97, 126.76, 127.43, 127.69, 128.60, 128.83, 130.21, 131.57, 132.16, 132.20, 132.85, 134.75, 138.80, 147.82, 150.43, 151.03, 161.64, 163.86, 171.13, 194.73; ESI-MS (m/z): 627.1(M$^+$), 629.1 (M+2); Anal. Calcd (%) for C$_{34}$H$_{31}$ClFN$_5$O$_2$S: C, 65.06; H, 4.93; N, 11.11. Found: C, 65.06; H, 4.93; N, 11.11.
Yield 84%; m.p. 201-203 °C; IR (KBr, νmax, cm⁻¹): 3433 & 3324 (asym. & sym. str. of \(-\text{NH}_2\)), 2190 (C≡N str.), 1658 (C=O str.), 1363 (–CH₃ str.), 761 (C–S–C thioether str.); ¹H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 0.69 (s, 3H, CH₃), 0.85 (s, 3H, CH₃), 1.35-1.99 (m, 4H, 2 \(\times\) CH₂), 2.15 (s, 3H, CH₃ of benzene ring), 2.43 (s, 3H, CH₃ of pyrazole), 4.72 (s, 1H, CH), 5.23 (s, 2H, -NH₂), 6.75-7.40 (m, 13H, Ar–H); ¹³C NMR (100 MHz, DMSO-\(d_6\)) δ: 12.36, 20.79, 27.56, 28.12, 28.56, 32.44, 41.45, 49.45, 58.19, 109.56, 117.12, 118.24, 125.61, 125.67, 127.57, 128.39, 129.84, 130.58, 131.94, 132.06, 135.23, 135.25, 139.05, 147.61, 150.28, 150.90, 161.15, 163.55, 193.88; ESI-MS (m/z): 589.2(M⁺); Anal. Calcd (%) for C₃₅H₃₂F₅N₅OS: C, 71.28; H, 5.47; N, 11.88. Found: C, 71.32; H, 5.43; N, 11.84.

6.1.3.5. Ethyl 2-amino-1-(4-fluorophenyl)-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8e).

Yield 76%; m.p. 205-207 °C; IR (KBr, νmax, cm⁻¹): 3453 & 3330 (asym. & sym. str. of \(-\text{NH}_2\)), 2223 (C≡N str.), 1673 (C=O str.), 1351 (–CH₃ str.), 771 (C–S–C thioether str.); ¹H NMR (400 MHz, CDCl₃): \(\delta\) 0.79 (s, 3H, CH₃), 0.93 (s, 3H, CH₃), 1.25-1.47 (m, 4H, 2 \(\times\) CH₂), 1.99 (s, 3H, CH₃ of benzene ring), 2.21 (s, 3H, CH₃), 2.73 (s, 3H, CH₃ of pyrazole), 4.16 (m, 2H, CH₂), 5.14 (s, 1H, CH), 6.05 (bs, 2H, -NH₂), 6.61-7.55 (m, 13H, Ar–H); ¹³C NMR (100 MHz, CDCl₃) δ: 12.66, 14.80, 20.78, 26.28, 28.14, 28.54, 32.43, 41.60, 50.02, 59.33, 113.42, 124.98, 125.34, 125.50, 127.21, 128.28, 128.32, 128.70, 129.6, 129.71, 132.23, 132.92, 133.60, 134.02, 134.91, 136.73, 149.21, 149.86, 151.68, 170.06, 196.02; ESI-MS (m/z): 636.2(M⁺); Anal. Calcd (%) for C₃₇H₃₇F₅N₄O₃S: C, 69.79; H, 5.86; N, 8.80. Found: C, 69.75; H, 5.82; N, 8.84.

6.1.3.6. 2-amino-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1-(4-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8f).

Yield 72%; m.p. 221-223 °C; IR (KBr, νmax, cm⁻¹): 3471 & 3337 (asym. & sym. str. of \(-\text{NH}_2\)), 2197 (C≡N str.), 1654 (C=O str.), 1358 (–CH₃ str.), 781 (C–S–C thioether str.); ¹H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 0.71 (s, 3H, CH₃), 0.84 (s, 3H, CH₃), 1.01-2.03 (m, 4H, 2 \(\times\) CH₂), 2.13 (s, 3H, CH₃ of benzene), 2.51 (s, 3H, CH₃ of pyrazole), 4.69 (s, 1H, CH), 5.73 (s, 2H, -NH₂), 6.82-7.53 (m, 13H, Ar–H); ¹³C NMR (100 MHz, DMSO-\(d_6\)) δ: 12.30, 20.79, 20.88, 27.58, 28.13, 28.60, 32.43, 41.50, 49.43, 58.10, 109.53, 117.13, 118.23,
6.1.3.7. **Ethyl 2-amino-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1-(4-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8g)**

Yield 80%; m.p. 199-201 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)) 3462 & 3329 (asym. & sym. str. of \(-\text{NH}_2\)), 2191 (C≡N str.), 1679 (C=O str.), 1359 (–CH\(_3\) str.), 770 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 0.75 (s, 3H, CH\(_3\)), 0.91 (s, 3H, CH\(_3\)), 1.21-1.43 (m, 4H, 2 × CH\(_2\)), 1.93 (s, 3H, CH\(_3\) of benzene ring), 2.23 (q, 3H, CH\(_3\)), 2.78 (s, 3H, CH\(_3\) of pyrazole), 4.36 (m, 2H, CH\(_2\)), 5.43 (s, 1H, CH), 6.13 (bs, 2H, -NH\(_2\)), 6.63-7.57 (m, 13H, Ar–H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \( \delta \): 12.43, 14.60, 20.67, 20.89, 25.89, 27.17, 28.30, 31.70, 40.82, 49.32, 58.32, 76.62, 111.98, 117.07, 117.29, 124.88, 125.39, 126.23, 127.43, 128.57, 128.77, 129.60, 132.25, 134.52, 135.67, 138.95, 148.96, 149.53, 152.61, 160.93, 163.39, 168.75, 194.86; ESI-MS (m/z): 686.2(M\(^+\)); Anal. Calcd (%) for C\(_{38}\)H\(_{37}\)F\(_3\)N\(_5\)O\(_3\)S : C, 66.46; H, 5.43; N, 8.16. Found: C, 66.50; H, 5.47; N, 8.20.

6.1.3.8. **2-amino-1-(2,4-difluorophenyl)-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8h)**

Yield 79%; m.p. 217-219 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)) 3481 & 3343 (asym. & sym. str. of \(-\text{NH}_2\)), 2187 (C≡N str.), 1662 (C=O str.), 1372 (–CH\(_3\) str.), 755 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 0.68 (s, 3H, CH\(_3\)), 0.81 (s, 3H, CH\(_3\)), 1.32-1.95 (m, 4H, 2 × CH\(_2\)), 2.17 (s, 3H, CH\(_3\) of benzene ring), 2.48 (s, 3H, CH\(_3\) of pyrazole), 4.81 (s, 1H, CH), 5.38 (s, 2H, -NH\(_2\)), 6.71-7.53 (m, 12H, Ar–H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \( \delta \): 12.35, 20.78, 27.55, 28.23, 28.63, 32.42, 41.53, 49.40, 58.12, 109.54, 117.17, 118.27, 125.56, 125.66, 127.58, 128.41, 129.85, 130.56, 131.96, 132.13, 132.38, 135.23, 135.28, 139.07, 147.63, 150.28, 150.89, 161.14, 163.53, 194.03; ESI-MS (m/z): 607.2(M\(^+\)); Anal. Calcd (%) for C\(_{35}\)H\(_{31}\)F\(_2\)N\(_5\)OS : C, 69.17; H, 5.14; N, 11.52. Found: C, 69.13; H, 5.10; N, 11.56.
6.1.3.9. Ethyl 2-amino-1-(2,4-difluorophenyl)-7,7-dimethyl-4-(3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8i)

Yield 73 %; m.p. 216-218 °C; IR (KBr, νmax, cm⁻¹): 3463 & 3342 (asym. & sym. str. of –NH₂), 2213 (C≡N str.), 1680 (C=O str.), 1367(--CH₃ str.), 775 (C–S–C thioether str.); ¹H NMR (400 MHz, DMSO-d₆): δ 0.66 (s, 3H, CH₃), 0.74 (s, 3H, CH₃), 1.07-1.14 (m, 4H, 2 × CH₂), 1.82 (s, 3H, CH₃ of benzene ring), 2.13 (s, 3H, CH₃), 2.55 (s, 3H, CH₃ of pyrazole), 4.02 (m, 2H, CH₂), 4.91 (s, 1H, -CH), 6.51 (s, 2H, NH₂), 6.57-7.59 (m, 12H, Ar–H); ¹³C NMR (100 MHz, DMSO-d₆): δ: 12.67, 14.85, 20.81, 26.30, 28.17, 28.50, 32.42, 41.63, 50.07, 59.36, 109.10, 113.45, 125.01, 125.32, 125.53, 127.12, 128.17, 128.27, 128.73, 128.98, 129.77, 132.24, 132.95, 133.67, 134.05, 134.96, 136.75, 149.23, 149.82, 151.65, 170.02, 195.97; ESI-MS (m/z): 654.2(M⁺), 658.1 (M+2); Anal. Calcd (%) for C₃₇H₃₆F₂N₄O₃S: C, 67.87; H, 5.54; N, 8.56. Found: C, 67.91; H, 5.50; N, 8.52.

6.1.3.10. 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,4-difluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8j)

Yield 75 %; m.p. 210-212 °C; IR (KBr, νmax, cm⁻¹): 3481 & 3341 (asym. & sym. str. of –NH₂), 2191 (C≡N str.), 1660 (C=O str.), 1361 (–CH₃ str.), 766 (C–S–C thioether str.); ¹H NMR (400 MHz, CDCl₃): δ 0.87 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 1.69-1.87 (m, 4H, 2 × CH₂), 2.65 (s, 3H, CH₃ of pyrazole), 3.60 (s, 2H, -NH₂), 4.95 (s, 1H, -CH), 6.75-7.49 (m, 12H, Ar–H); ¹³C NMR (100 MHz, CDCl₃) δ: 12.40, 27.64, 27.95, 28.13, 28.45, 32.37, 40.54, 49.80, 58.87, 110.70, 112.13, 121.78, 127.33, 127.53, 127.62, 127.81, 127.96, 128.45, 128.51, 128.81, 129.18, 132.93, 133.33, 135.03, 137.02, 147.83, 150.97, 151.43, 162.12, 163.97, 195.59; ESI-MS (m/z): 627.1 (M⁺), 629.1 (M+2); Anal. Calcd (%) for C₃₄H₂₈ClF₂N₅OS: C, 65.01; H, 4.49; 6.05; N, 11.15. Found: C, 65.05; H, 4.45; 6.05; N, 11.11

6.1.3.11. Ethyl 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,4-difluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8k)
Yield 78 %; m.p. 213-215 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)): 3480 & 3347 (asym. & sym. str. of \(-\text{NH}_2\)), 2217 (C≡N str.), 1668 (C=O str.), 1365 (–CH₃ str.), 769 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta 0.87 \) (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 1.46-1.51 (m, 4H, 2 × CH₂), 1.55 (s, 3H, CH₃), 2.73 (s, 3H, CH₃ of pyrazole), 4.16 (m, 2H, CH₂), 5.15 (s, 1H, –CH), 5.92 (s, 2H, –NH₂), 6.64-7.41 (m, 12H, Ar–H); \(^13\)C NMR (100 MHz, CDCl₃) \( \delta \): 12.26, 14.78, 26.26, 28.14, 28.44, 32.36, 40.62, 50.03, 59.52, 110.23, 111.90, 117.68, 117.83, 125.19, 125.32, 126.27, 127.50, 128.37, 128.61, 129.07, 132.80, 134.00, 135.60, 138.13, 148.87, 149.67, 152.43, 161.11, 163.41, 168.71, 194.89; ESI-MS (m/z): 674.1(M⁺), 676.1 (M+2); Anal. Calcd (%) for C₃₆H₃₃ClF₂N₄O₃S: C, 64.04; H, 4.93; N, 8.30. Found: C, 64.08; H, 4.97; N, 8.34.

6.1.3.12. 2-amino-4-(5-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,4-difluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (8l)

Yield 81 %; m.p. 201-203 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)): 3477 & 3342 (asym. & sym. str. of \(-\text{NH}_2\)), 2188 (C≡N str.), 1653 (C=O str.), 1366 (–CH₃ str.), 760 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta 0.77(s, 3H, CH_3) \), 0.91 (s, 3H, CH₃), 1.33-2.23 (m, 4H, 2 × CH₂), 2.53 (s, 3H, CH₃ of pyrazole), 5.02 (s, 1H, CH ), 6.11 (s, 2H, -NH₂), 6.73-7.51 (m, 14H, Ar–H and CONH₂); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \( \delta \): 12.34, 27.64, 27.80, 31.57, 41.07, 49.19, 109.12, 111.03, 116.95, 117.27, 121.63, 125.01, 125.24, 126.79, 127.54, 127.75, 128.61, 128.86, 130.22, 131.59, 132.23, 132.35, 132.88, 134.73, 138.89, 147.85, 150.40, 151.09, 161.67, 163.89, 171.17, 194.87; ESI-MS (m/z): 645.1(M⁺), 647.1 (M+2); Anal. Calcd (%) for C₃₄H₃₃ClF₂N₅O₂S: C, 63.20; H, 4.68; N, 10.84. Found: C, 63.24; H, 4.64; N, 10.83.

6.1.3.13. 2-amino-1-(4-fluorophenyl)-4-(5-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,4-difluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8m)

Yield 83 %; m.p. 227-228 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)): 3472 & 3342 (asym. & sym. str. of –NH₂), 2190 (C≡N str.), 1662 (C=O str.), 1368 (–CH₃ str.), 756 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta 0.84 \) (s, 3H, CH₃), 0.86 (s, 3H, CH₃), 1.63-1.88 (m, 4H, 2 × CH₂), 2.59 (s, 3H, CH₃ of pyrazole), 3.77 (s, 2H, -NH₂), 4.99 (s, 1H, CH), 6.82-7.46 (m, 13H, Ar–H); \(^13\)C NMR (100 MHz, CDCl₃)
δ: 12.46, 27.60, 28.15, 28.55, 32.41, 41.68, 49.84, 109.17, 115.99, 116.21, 117.63, 117.85, 125.69, 127.70, 128.44, 128.53, 131.50, 132.14, 132.23, 132.80, 134.67, 138.85, 147.64, 149.73, 149.98, 160.95, 163.40, 194.87; ESI-MS (m/z): 593.2 (M⁺); Anal. Calcd (%) for C₃₄H₂₉F₂N₅OS: C, 68.78; H, 4.92; N, 11.80. Found: C, 68.74; H, 4.88; N, 11.84.

6.1.3.14. Ethyl 2-amino-1-(4-fluorophenyl)-4-(5-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8n)

Yield 71 %; m.p. 231-233 °C; IR (KBr, νmax, cm⁻¹): 3418 & 3362 (asymp. & sym. str. of –NH₂), 2203 (C≡N str.), 1667 (C=O str.), 1372 (–CH₃ str.), 763 (C–S–C thioether str.); ¹H NMR (400 MHz, CDCl₃): δ 0.83 (s, 3H, CH₃), 0.92 (s, 3H, CH₃), 1.15-1.31 (m, 4H, 2 × CH₂), 1.62 (t, 3H, CH₃), 2.75 (s, 3H, CH₃ of pyrazole), 4.17 (m, 2H, CH₂), 5.17 (s, 1H, -CH), 6.69-7.35 (m, 15H, Ar–H and –NH₂); ¹³C NMR (100 MHz, CDCl₃) δ: 12.68, 14.81, 28.12, 28.57, 32.43, 41.86, 50.07, 59.63, 113.60, 117.52, 117.63, 125.88, 127.97, 128.13, 128.89, 129.06, 132.07, 132.23, 139.35, 149.67, 150.03, 151.73, 153.46, 158.93, 161.26, 162.07, 164.87, 170.03, 195.93; ESI-MS (m/z): 640.2(M⁺); Anal. Calcd (%) for C₃₆H₃₄F₂N₄O₃S: C, 67.48; H, 5.35; N, 8.74. Found: C, 67.44; H, 5.39; N, 8.78.

6.1.3.15. 2-amino-1-(4-fluorophenyl)-4-(5-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8o)

Yield 72 %; m.p. 209-211 °C; IR (KBr, νmax, cm⁻¹): 3414 & 3381 (asym. & sym. str. of –NH₂), 2192 (C≡N str.), 1670 (C=O str.), 1367 (–CH₃ str.), 764 (C–S–C thioether str.); ¹H NMR (400 MHz, DMSO-d₆): δ 0.72 (s, 3H, CH₃), 0.81 (s, 3H, CH₃), 1.01-1.89 (m, 4H, 2 × CH₂), 2.51 (s, 3H, CH₃ of pyrazole), 4.69 (s, 1H, CH), 5.36 (bs, 2H, -NH₂), 6.83-7.79 (m, 13H, Ar–H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 12.31, 20.89, 27.60, 28.17, 28.63, 32.45, 41.53, 49.44, 58.13, 109.56, 117.02, 118.25, 125.61, 125.68, 127.63, 128.50, 129.84, 130.53, 131.95, 132.23, 135.21, 135.29, 139.13, 147.60, 150.28, 150.90, 161.15, 163.48, 193.91; ESI-MS (m/z): 593.2 (M⁺); Anal. Calcd (%) for C₃₄H₂₉F₂N₅OS: C, 68.78; H, 4.92; N, 11.80 Found: C, 68.74; H, 4.96; N, 11.84.
6.1.3.16. Ethyl 2-amino-4-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1-(4- (trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8p)

Yield 79%; m.p. 229-231 °C; IR (KBr, \( \nu_{\text{max}}, \text{cm}^{-1} \)): 3483 & 3339 (asym. & sym. str. of –NH\(_2\)), 2217 (C≡N str.), 1673 (C=O str.), 1363 (–CH\(_3\) str.), 760 (C–S–C thioether str.); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 0.74 (s, 3H, CH\(_3\)), 0.93 (s, 3H, CH\(_3\)), 1.13-1.37 (m, 4H, 2 × CH\(_2\)), 1.59 (t, 3H, CH\(_3\)), 2.73 (s, 3H, CH\(_3\) of pyrazole), 4.19 (m, 2H, CH\(_2\)), 5.33 (s, 1H, -CH), 6.63-7.47 (m, 15H, Ar–H and –NH\(_2\)); \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)) \( \delta \): 12.65, 14.85, 20.86, 28.15, 28.60, 32.47, 41.85, 50.11, 59.67, 113.61, 118.55, 118.17, 125.94, 127.99, 128.15, 128.91, 129.06, 132.10, 133.19, 139.33, 149.69, 150.11, 151.65, 153.49, 159.03, 161.21, 162.13, 164.80, 169.97, 195.78; ESI-MS (m/z): 690.2(M\(^+\)); Anal. Calcd (%) for C\(_{37}\)H\(_{34}\)F\(_4\)N\(_4\)O\(_3\)S: C, 64.34; H, 4.96; N, 8.11. Found: C, 64.38; H, 4.92; N, 8.15.
$^1$H NMR spectra of compound 3a
$^1$H NMR spectra of compound 3c
$^1$H NMR spectra of compound 8a
$^1$H NMR spectra of compound 8b
$^1$H NMR spectra of compound 8c
$^1$H NMR spectra of compound 8d
\[ ^1 \text{H NMR spectra of compound 8e} \]
$^1$H NMR spectra of compound 8i
$^1$H NMR spectra of compound 8j
$^1$H NMR spectra of compound 8k
$^1$H NMR spectra of compound 8m
$^1$H NMR spectra of compound 8n
$^{13}$C NMR spectra of compound 8a
$^{13}$C NMR spectra of compound 8b
$^{13}$C NMR spectra of compound 8d
$^{13}$C NMR spectra of compound 8e
$^{13}$C NMR spectra of compound 8j
$^{13}$C NMR spectra of compound 8k
$^{13}$C NMR spectra of compound 8m
$^{13}$C NMR spectra of compound 8n
Mass spectrum of compound 8a
Mass spectrum of compound 8b
Mass spectrum of compound 8c
Mass spectrum of compound 8d