Supporting Information

Aminothiazole-featured pirinixic acid derivatives as dual 5-lipoxygenase and microsomal prostaglandin E_2 synthase-1 inhibitors with improved potency and efficiency *in vivo*

Thomas Hanke[†], Friederike Dehm[§], Stefanie Liening[§], Sven-Desiderius Popella[§], Jonas Maczewsky[§&], Max Friedel Pillong[&], Jens Kunze[&], Christina Weinigel[¶], Dagmar Barz[¶], Astrid Kaiser[†], Mario Wurglics[†], Michael Lämmerhofer[$], Gisbert Schneider[&], Lidia Sautebin[&], Manfred Schubert-Zsilavecz,[†] Oliver Werz[§*]*

Contents:

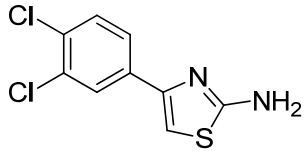
I Chemistry: 1H and 13C-NMR values of intermediates and final products, mass spectrometry and combustion analysis

The synthesis of the chlorinated ethyl [(pyrimidin-2-yl)sulfanyl] acetate derivatives (step I and II in scheme 1 in article) has been described before.[1,2] The 2-aminothiazoles were partially synthesized (step III in scheme 1), all other 2-aminothiazoles were purchased by Sigma Aldrich, Alfa Aesar, Acros Organics or Maybridge.

Step III: Synthesis of the 2-aminothiazoles (synthesis of compounds **21c–25c**):

To a solution of the corresponding 2-bromoacetophenone derivatives (E1, 1 equiv) in 25 ml methanol was added thiourea (1.5 equiv) and the solution was stirred 3h at room temperature. The solvent was evaporated under reduced pressure. The crude product was suspended in a 5 per cent $NaHCO_3$ solution and extracted with dichloromethane (3 times 25 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was further purified by column chromatography on silica gel (*n*-hexane - ethyl acetate).

Characterization of 4-(3,4-dichlorophenyl)-1,3-thiazol-2-amine (**21c**):

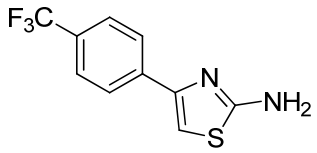


Synthesis Step III; E1: 2-bromo-1-(3,4-dichlorophenyl)ethanone (656 mg; 2.45 mmol), thiourea (279 mg; 3.67 mmol); Product: slightly yellow solid; yield: 97% (0.58 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 7.16 (s, 2H, -NH_2), 7.24 (s, 1H, thiazole-H_5), 7.63 (d, 1H, Ph-H_5, J = 7.50 Hz), 7.79 (dd, 1H, Ph-H_6, J = 7.50 Hz), 8.02 (s, 1H, Ph-H_2). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 103.75 (thiazole-C_5), 125.48 (Ph-C_6), 127.10 (Ph-C_2), 129.20 (Ph-

C_5), 130.65 (Ph-C_3), 131.21 (Ph-C_1), 135.39 (Ph-C_4), 147.15 (thiazole-C_4), 168.40 (thiazole-C_2). **MS (ESI+):** m/e = 244.6 $[M + H]^+$.

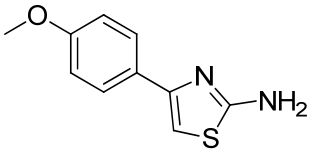
Characterization of 4-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (**22c**):



Synthesis Step III; E1: 2-bromo-1-[4-(trifluoromethyl)phenyl]ethanone (547 mg; 2.05 mmol), thiourea (234 mg; 3.07 mmol); Product: slightly yellow solid; yield: 95% (0.49 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 7.14 (s, 2H, -NH_2), 7.24 (s, 1H, thiazole-H_5), 7.71 (d, 2H, Ph-H_3/H_5, J = 9.00 Hz), 8.00 (d, 2H, Ph-H_2/H_6, J = 9.00 Hz). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 104.30 (thiazole-C_5), 125.39 (-CF$_3$), 125.96 (Ph-C_4), 126.92 (Ph-C_3/C_5), 127.34 (Ph-C_2/C_6), 138.54 (Ph-C_1), 148.26 (thiazole-C_4), 168.42 (thiazole-C_2). **MS (ESI+):** *m/e* = 244.7 $[M+H]^+$

Characterization of 4-(4-methoxyphenyl)-1,3-thiazol-2-amine (**25c**):

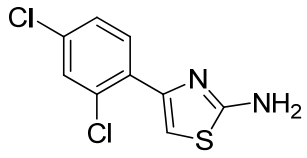


Synthesis Step III; E1: 2-bromo-1-(4-methoxyphenyl)ethanone (888 mg; 3.88 mmol), thiourea (443 mg; 5.82 mmol); Product: slightly yellow solid; yield: 81% (0.64 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 3.76 (s, 3H, -O-CH_3), 6.81 (s, 1H, thiazole-H_5), 6.92 (d, 2H, Ph-H_3/H_5, J = 7.50 Hz), 6.96 (s, 2H, -NH_2), 7.72 (d, 2H, Ph-H_2/H_6, J = 7.50 Hz). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 55.05 (O-CH$_3$), 99.40 (thiazole-C_5), 113.80 (Ph-C_3/C_5),

126.81 (Ph-C_2/C_6), 127.75 (Ph-C_1), 149.63 (thiazole-C_4), 158.51 (Ph-C_4), 168.10 (thiazole-C_2). **MS (ESI+):** *m/e* = 206.8 $[M+H]^+$

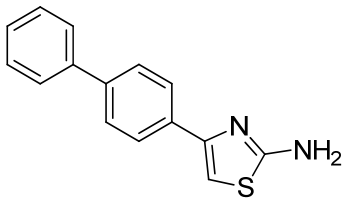
Characterization of 4-(2,4-dichlorophenyl)-1,3-thiazol-2-amine (**23c**):



Synthesis Step III; E1: 2-bromo-1-(2,4-dichlorophenyl)ethanone (656 mg; 2.45 mmol), thiourea (279 mg; 3.67 mmol); Product: slightly yellow solid; yield: 60% (0.36 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 7.11 (s, 3H, thiazole-H_5, -NH_2), 7.45 (dd, 1H, Ph-H_5, ^3J = 8.54 Hz), 7.64 (d, 1H, Ph-H_3, ^4J = 2.14 Hz), 7.87 (d, 1H, Ph-H_6, ^3J = 8.54 Hz). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 106.97 (thiazole-C_5), 127.29 (Ph-C_5), 129.62 (Ph-C_1), 131.28 (Ph-C_6), 131.99 (Ph-C_3), 132.28 (Ph-C_2), 132.32 (Ph-C_4), 145.16 (thiazole-C_4), 167.26 (thiazole-C_2). **MS (ESI+):** m/e = 244.7 $[M + H]^+$.

Characterization of 4-(biphenyl-4-yl)-1,3-thiazol-2-amine (**24c**):



Synthesis Step III; E1: 1-(biphenyl-4-yl)-2-bromoethanone (1090 mg; 3.96 mmol), thiourea (453 mg; 5.94 mmol); Product: yellow solid; yield: 86% (0.86 g).

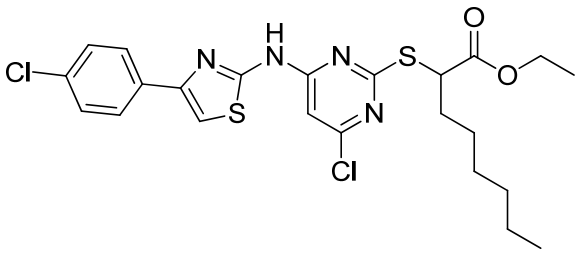
^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 7.06 (s, 3H, thiazole-H_5, -NH_2), 7.35 (t, 1H, Biph-H'_4, J = 7.50 Hz), 7.46 (t, 2H, -Biph-H'_3/H'_5, J = 7.50 Hz), 7.65–7.71 (m, 4H, -Biph-H_3/H_5/H'_2/H'_6), 7.89 (d, 2H, Ph-H_2/H_6, J = 9.00 Hz). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 101.72 (thiazole-C_5), 126.05 (-Biph-C_3/C_5), 126.39 (-Biph-C'_2/C'_6), 126.64 (-Biph-C_1/C_6),

127.33 (-Biph-C'_4), 128.90 (-Biph-C'_3/C'_5), 134.00 (-Biph-C_1), 138.64 (-Biph-C'_1), 139.68 (-Biph-C_4), 149.43 (thiazole-C_4), 168.17 (thiazole-C_2). **MS (ESI+):** *m/e* = 253.9 $[M+H]^+$

Step IV: Buchwald-Hartwig Amination (synthesis of compounds **6d–31d**):

The chlorinated ethyl [(pyrimidin-2-yl)sulfanyl] acetate derivatives (E1, 1 equiv), the corresponding 2-aminothiazole (E2, 1.2 equiv), Xantphos (0.06 equiv) and Na_2CO_3 (1.4 equiv) were dissolved in toluene (8 ml) in a three neck round bottom flask, which was three times evacuated and backfilled with argon before adding the $Pd_2(dba)_3$ (0.02 equiv) and water (20 ml). The mixture was heated at 90°C for 18h. The reaction mixture was cooled to room temperature and diluted with THF. The organic layer was separated from the water layer, filtered over celite and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane – ethyl acetate) and finally recrystallized in *n*-hexane – ethyl acetate.

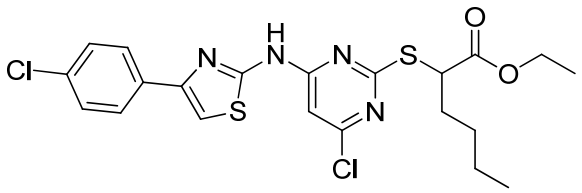
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**6d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (804 mg; 2.28 mmol), E2: 4-(4-chlorophenyl)-1,3-thiazol-2-amine (576 mg; 2.73 mmol), $Pd_2(dba)_3$ (42 mg; 0.04 mmol), Xantphos (80 mg; 0.14 mmol), Na_2CO_3 (339 mg; 3.19 mmol); Product: white solid; yield: 66% (0.80 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-CH_3, J = 6.56 Hz), 1.19 (t, 3H, O-ethyl-CH_3, J = 7.13 Hz), 1.25–1.41 (m, 8H, hexyl-CH_2), 1.81–2.02 (m, 2H, hexyl-CH_2), 4.15 (q, 2H, O-ethyl-CH_2, J = 7.07 Hz), 4.60 (t, 1H, S-CH, J = 7.07 Hz), 6.82 (s, 1H, Pyr-H_5), 7.50 (d, 2H, Ph-$H_{3/5}$, J = 8.60 Hz), 7.78 (s, 1H, thiazole-H_5), 7.93 (d, 2H, Ph-$H_{2/6}$, J = 8.60 Hz), 12.23 (s, 1H, -NH). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.79 (hexyl-CH$_3$), 13.95 (O-ethyl-CH$_3$), 21.87 (hexyl-CH$_2$), 26.30 (hexyl-CH$_2$), 28.06 (hexyl-CH$_2$), 30.84 (hexyl-CH$_2$), 31.33 (hexyl-CH$_2$), 46.99 (S-CH), 61.08 (O-ethyl-CH$_2$), 102.07 (Pyr-C_5), 109.30 (thiazole-C_5), 127.33 (Ph-$C_{2/6}$), 128.72 (Ph-$C_{3/5}$), 132.28 (Ph-C_4), 132.98 (Ph-C_1), 147.98 (thiazole-C_4), 157.72 (Pyr-C_4), 157.87 (Pyr-C_2), 169.59 (-COOEt), 170.86 (Pyr-C_6). **MS (ESI+)**: m/e = 525.5 [M].

Characterization of ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]hexanoate (**7d**):

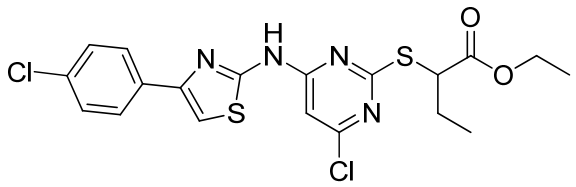


Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]hexanoate (1010 mg; 3.12 mmol), E2: 4-(4-chlorophenyl)-1,3-thiazol-2-amine (787 mg; 3.74 mmol), $Pd_2(dba)_3$ (63 mg; 0.07 mmol), Xantphos (108 mg; 0.19 mmol), Na_2CO_3 (473 mg; 4.46 mmol); Product: yellow solid; yield: 27% (0.42 g).

^{1}H-NMR (400.13 MHz, $(CD_3)_2SO$) δ: 0.88 (t, 3H, butyl-CH_3, J = 8.0 Hz), 1.20 (t, 3H, ethyl-CH_3, J = 8.0 Hz), 1.31–1.42 (m, 4H, butyl-CH_2), 1.86–1.99 (m, 2H, S-CH-CH_2), 4.15 (q, 2H, ethyl-CH_2, J = 8.0 Hz), 4.60 (t, 1H, S-CH, J = 8.0 Hz), 6.82 (s, 1H, Pyr-H_5), 7.51 (d, 2H, Ph-$H_{3/5}$, J = 8.0 Hz), 7.80 (s, 1H, thiazole-H_5), 7.92 (d, 2H, Ph-$H_{2/6}$, J = 8.0 Hz), 12.22 (s, 1H, -

N*H*). **^{13}C-NMR (100.61 MHz, $(CD_3)_2SO$)** δ: 13.65 (butyl-*C*H_3), 13.98 (O-ethyl-*C*H_3), 21.65 (butyl-*C*H_2), 28.59 (butyl-*C*H_2), 31.03 (butyl-*C*H_2), 47.02 (S-*C*H), 61.12 (O-ethyl-*C*H_2), 102.04 (Pyr-C_5), 109.36 (thiazole-C_5), 127.35 (Ph-$C_{2/6}$), 128.76 (Ph-$C_{3/5}$), 132.31 (Ph-C_1), 132.98 (Ph-C_4), 148.00 (thiazole-C_4), 157.66 (Pyr-C_6), 157.79 (Pyr-C_4), 169.63 (-*C*OOEt), 170.90 (Pyr-C_2). **MS (ESI+):** m/e = 497.5 $[M+H]^+$.

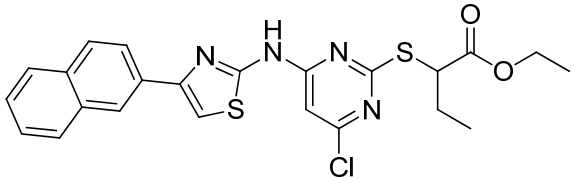
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoate (**8d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]butanoate (1244 mg; 4.21 mmol), E2: 4-(4-chlorophenyl)-1,3-thiazol-2-amine (1065 mg; 5.05 mmol), $Pd_2(dba)_3$ (77 mg; 0.08 mmol), Xantphos (146 mg; 0.25 mmol), Na_2CO_3 (625 mg; 5.90 mmol); Product: yellow solid; yield: 19% (0.37 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 1.03 (t, 3H, ethyl-C*H*$_3$, *J* = 7.5 Hz), 1.21 (t, 3H, ethyl-C*H*$_3$, *J* = 7.5 Hz), 1.91–1.99 (m, 2H, ethyl-C*H*$_2$), 4.17 (q, 2H, ethyl-C*H*$_2$, *J* = 7.5 Hz), 4.58 (t, 1H, S-C*H*, *J* = 7.5 Hz), 6.83 (s, 1H, Pyr-*H*5), 7.51 (d, 2H, Ph-3,5-*H*, *J* = 10.0 Hz), 7.80 (s, 1H, thiazole-*H*5), 7.94 (d, 2H, Ph-2,6-*H*, *J* = 10.0 Hz), 12.23 (s, 1H, N*H*). **^{13}C-NMR (100.61 MHz, $(CD_3)_2SO$)** δ: 11.30 (ethyl-*C*H_3), 14.00 (O-ethyl-*C*H_3), 24.91 (ethyl-*C*H_2), 48.49 (S-*C*H), 61.14 (O-ethyl-*C*H_2), 102.05 (Pyr-C_5), 109.41 (thiazole-C_5), 127.36 (Ph-C_2 + -C_6), 128.77 (Ph-C_3 + -C_5), 132.32 (Ph-C_1), 132.99 (Ph-C_4), 148.01 (thiazole-C_4), 157.69 (Pyr-C_4), 157.79 (Pyr-C_2), 169.68 (-*C*OOEt), 170.73 (Pyr-C_6). **MS (ESI+):** *m/e* = 469.5 $[M+H]^+$.

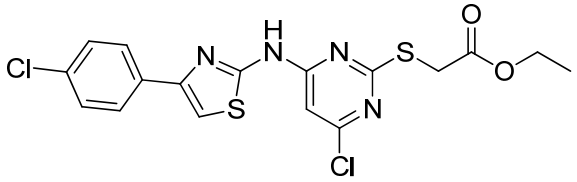
Characterization of ethyl 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoate (**9d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]butanoate (300 mg; 1.02 mmol), E2: 4-(naphthalene-2-yl)-1,3-thiazol-2-amine (276 mg; 1.22 mmol), $Pd_2(dba)_3$ (19 mg; 0.02 mmol), Xantphos (35 mg; 0.06 mmol), Na_2CO_3 (151 mg; 1.42 mmol); Product: yellow oil; yield: 81% (0.39 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 1.03 (t, 3H, ethyl-C*H*$_3$, *J* = 7.37 Hz), 1.21 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.08 Hz), 1.90–2.06 (m, 2H, ethyl-C*H*$_2$), 4.17 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.09 Hz), 4.59 (t, 1H, S-C*H*, *J* = 6.93 Hz), 6.84 (s, 1H, Pyr-*H*5), 7.49–7.56 (m, 2H, Naph-*H*-6,7), 7.87 (s, 1H, thiazole-*H*5), 7.91–7.98 (m, 3H, Naph-*H*-3,5,8), 8.06 (d, 1H, Naph-*H*4, *J* = 7.06 Hz), 8.44 (s, 1H, Naph-*H*1), 12.28 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 11.31 (ethyl-*C*H$_3$), 14.02 (O-ethyl-*C*H$_3$), 24.94 (ethyl-*C*H$_2$), 48.51 (S-*C*H), 61.15 (O-ethyl-*C*H$_2$), 102.05 (Pyr-*C*$_5$), 109.36 (thiazole-*C*$_5$), 123.94 (Naph-*C*$_3$), 124.30 (Naph-*C*$_1$), 126.18 (Naph-*C*$_6$), 126.53 (Naph-*C*$_7$), 127.60 (Naph-*C*$_5$), 128.17 (Naph-*C*$_8$), 128.28 (Naph-*C*$_4$), 131.57 (Naph-*C*$_2$), 132.55 (Naph-*C*$_{4a}$), 133.12 (Naph-*C*$_{8a}$), 149.15 (thiazole-*C*$_4$), 157.73 (Pyr-*C*$_6$), 157.77 (Pyr-*C*$_4$), 169.71 (-*C*OOEt), 170.75 (Pyr-*C*$_2$). **MS (ESI-):** *m/e* = 483.3 $[M-H]^-$

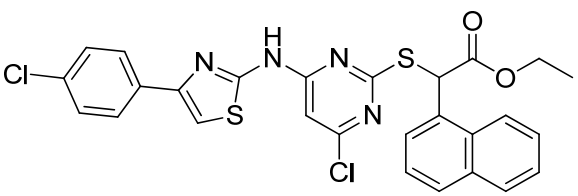
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]acetate (**10d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]acetate (700 mg; 2.62 mmol), E2: 4-(4-chlorophenyl)-1,3-thiazol-2-amine (662 mg; 3.14 mmol), $Pd_2(dba)_3$ (48 mg; 0.05 mmol), Xantphos (91 mg; 0.16 mmol), Na_2CO_3 (389 mg; 3.67 mmol); Product: white solid; yield: 45% (0.52 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 1.19 (t, 3H, O-ethyl-C*H*$_3$, *J* = 6.00 Hz), 4.12 (q, 2H, O-ethyl-C*H*$_2$, *J* = 6.00 Hz), 4.15 (s, 2H, S-C*H*$_2$), 6.80 (s, 1H, thiazole-*H*5), 7.50 (d, 2H, Ph-3,5-*H*, *J* = 9.00 Hz), 7.78 (s, 1H, Pyr-*H*5), 7.93 (d, 2H, Ph-2,6-*H*, *J* = 9.00 Hz), 12.20 (s, 1H, N*H*). **^{13}C-NMR (100.61 MHz, $(CD_3)_2SO$)** δ: 14.05 (O-ethyl-*C*H$_3$), 32.96 (S-*C*H$_2$), 61.15 (O-ethyl-*C*H$_2$), 101.82 (Pyr-*C*$_5$), 109.29 (thiazole-*C*$_5$), 127.36 (Ph-*C*$_2$ + -*C*$_6$), 128.74 (Ph-*C*$_3$ + -*C*$_5$), 132.30 (Ph-*C*$_1$), 132.97 (Ph-*C*$_4$), 148.01 (thiazole-*C*$_4$), 157.68 (Pyr-*C*$_4$), 157.79 (Pyr-*C*$_2$), 168.39 (-*C*OOEt), 170.15 (Pyr-*C*$_6$). **MS (ESI+):** *m/e* = 441.4 $[M+H]^+$

Characterization of ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]-2-(naphthalen-1-yl)acetate (**11d**):

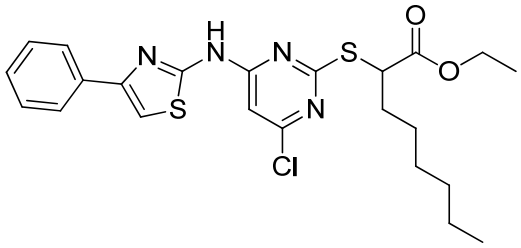


Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]-2-(naphthalene-1-yl)acetate (1030 mg; 2.62 mmol), E2: 4-(4-chlorophenyl)-1,3-thiazol-2-amine (662 mg; 3.14

mmol), $Pd_2(dba)_3$ (48 mg; 0.05 mmol), Xantphos (91 mg; 0.16 mmol), Na_2CO_3 (389 mg; 3.67 mmol); Product: white solid; yield: 58% (0.85 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 1.12 (t, 3H, ethyl-C*H*$_3$, *J* = 7.07 Hz), 4.09–4.25 (m, 2H, ethyl-C*H*$_2$), 6.46 (s, 1H, S-C*H*), 6.88 (s, 1H, Pyr-*H*$_5$), 7.49 (d, 2H, Ph-*H*$_{3/5}$, *J* = 8.62 Hz), 7.53–7.70 (m, 4 H, Naph- *H*$_{2/3/6/7}$), 7.76 (s, 1H, thiazole-*H*$_5$), 7.92 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.62 Hz), 8.02 (t, 2H, Naph- *H*$_{4/5}$, *J* = 8.00 Hz), 8.20 (d, 1H, Naph- *H*$_8$, *J* = 8.26 Hz), 12.29 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.97 (O-ethyl-*C*H$_3$), 49.14 (S-*C*H), 61.99 (O-ethyl-*C*H$_2$), 102.38 (Pyr-*C*$_5$), 109.41 (thiazole-*C*$_5$), 123.09 (Naph-*C*$_1$), 125.73 (Naph-*C*$_3$), 126.46 (Naph-*C*$_7$), 126.96 (Naph-*C*$_8$), 127.29 (Naph-*C*$_6$), 127.41 (Ph-*C*$_{2/6}$), 128.82 (Ph-*C*$_{3/5}$), 129.10 (Naph-*C*$_4$), 129.51 (Naph-*C*$_5$), 129.88 (Naph-*C*$_2$), 130.42 (Naph-*C*$_{4a}$), 132.39 (Ph-*C*$_1$), 132.99 (Ph-*C*$_4$), 133.72 (Naph-*C*$_{8a}$), 148.09 (thiazole-*C*$_4$), 157.82 (Pyr-*C*$_6$), 157.96 (Pyr-*C*$_4$), 169.54 (Pyr-*C*$_2$), 169.63 (-*C*OOEt). **MS (ESI+):** *m/e* = 567.6 [M]

Characterization of ethyl 2-({4-chloro-6-[(4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (**12d**):

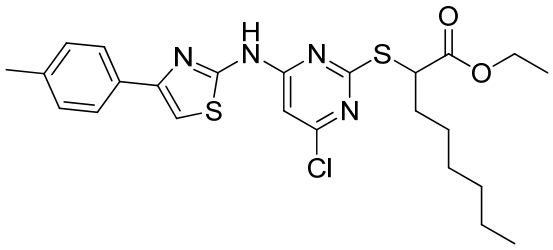


Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (900 mg; 2.56 mmol), E2: 4-phenyl-1,3-thiazol-2-amine (542 mg; 3.07 mmol), $Pd_2(dba)_3$ (47 mg; 0.05 mmol), Xantphos (89 mg; 0.15 mmol), Na_2CO_3 (380 mg; 3.59 mmol); Product: white solid; yield: 50% (0.63 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.86 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.20 (t, 3H, O-ethyl-C*H*$_3$, *J* = 5.00 Hz), 1.23-1.43 (m, 8H, hexyl-C*H*$_2$), 1.84-2.02 (m, 2H, hexyl-C*H*$_2$), 4.17

(q, 2H, O-ethyl-CH_2, J = 7.50 Hz), 4.62 (t, 1H, S-CH_2, J = 7.50 Hz), 6.84 (s, 1H, thiazole-*H*5), 7.35 (t, 1H, Ph-H_4, J = 7.50 Hz), 7.46 (t, 2H, Ph-3,5-*H*, J = 7.50 Hz), 7.74 (s, 1H, Pyr-*H*5), 7.93 (d, 2H, Ph-2,6-*H*, J = 7.50 Hz), 12.22 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.81 (hexyl-*C*H_3), 13.96 (O-ethyl-*C*H_3), 21.90 (hexyl-*C*H_2), 26.32 (hexyl-*C*H_2), 28.08 (hexyl-*C*H_2), 30.86 (hexyl-*C*H_2), 31.32 (hexyl-*C*H_2), 46.98 (S-*C*H), 61.10 (O-ethyl-*C*H_2), 102.00 (Pyr-C_5), 108.60 (thiazole-C_5), 125.63 (Ph-C_4), 127.85 (Ph-C_2 + -C_6), 128.72 (Ph-C_3 + -C_5), 134.09 (Ph-C_1), 149.24 (thiazole-C_4), 157.58 (Pyr-C_4), 157.69 (Pyr-C_2), 169.63 (-*C*OOEt), 170.90 (Pyr-C_6). **MS (ESI+):** *m/e* = 491.7 $[M+H]^+$

Characterization of ethyl 2-[(4-chloro-6-{[4-(4-methylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**13d**):

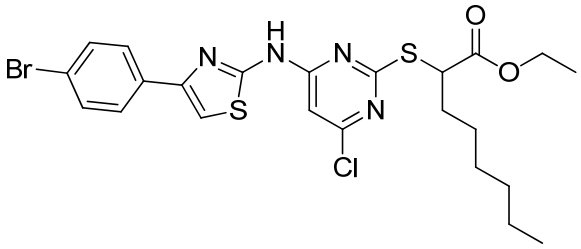


Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (800 mg; 2.28 mmol), E2: 4-(4-methylphenyl)-1,3-thiazol-2-amine (520 mg; 2.73 mmol), $Pd_2(dba)_3$ (42 mg; 0.05 mmol), Xantphos (79 mg; 0.14 mmol), Na_2CO_3 (338 mg; 3.19 mmol); Product: white solid; yield: 46% (0.53 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-CH_3, J = 7.50 Hz), 1.20 (t, 3H, O-ethyl-CH_3, J = 7.50 Hz), 1.23-1.42 (m, 8H, hexyl-CH_2), 1.84-2.01 (m, 2H, hexyl-CH_2), 2.34 (s, 3H, Ph-CH_3), 4.16 (q, 2H, O-ethyl-CH_2, J = 7.50 Hz), 4.61 (t, 1H, S-C*H*, J = 7.50 Hz), 6.83 (s, 1H, thiazole-*H*5), 7.26 (d, 2H, Ph-3,5-*H*, J = 7.50 Hz), 7.65 (s, 1H, Pyr-*H*5), 7.81 (d, 2H, Ph-2,6-*H*, J = 7.50 Hz), 12.19 (s, 1H, -N*H*). ^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$) δ: 13.82 (hexyl-*C*H_3), 13.96 (O-ethyl-*C*H_3), 20.76 (Ph-*C*H_3), 21.90 (hexyl-*C*H_2), 26.31 (hexyl-*C*H_2),

28.07 (hexyl-CH_2), 30.85 (hexyl-CH_2), 31.32 (hexyl-CH_2), 46.97 (S-*C*H), 61.11 (O-ethyl-CH_2), 101.97 (Pyr-C_5), 107.72 (thiazole-C_5), 125.57 (Ph-C_1), 129.28 (Ph-C_2 + -C_6), 131.44 (Ph-C_3 + -C_5), 137.18 (Ph-C_4), 149.32 (thiazole-C_4), 157.47 (Pyr-C_4), 157.67 (Pyr-C_2), 169.61 (-*C*OOEt), 170.91 (Pyr-C_6). MS (ESI+): *m/e* = 505.6 $[M+H]^+$

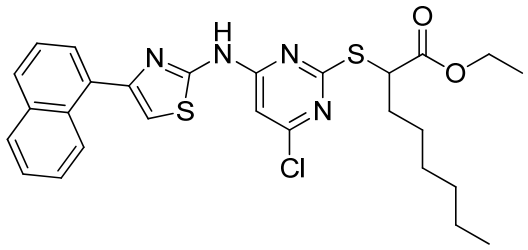
Characterization of ethyl 2-[(4-{[4-(4-bromophenyl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (**14d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (350 mg; 1.00 mmol), E2: 4-(4-bromophenyl)-1,3-thiazol-2-amine (305 mg; 1.20 mmol), $Pd_2(dba)_3$ (18 mg; 0.02 mmol), Xantphos (35 mg; 0.06 mmol), Na_2CO_3 (148 mg; 1.39 mmol); Product: white solid; yield: 38% (0.22 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-CH_3, *J* = 9.00 Hz), 1.19 (t, 3H, O-ethyl-CH_3, *J* = 6.00 Hz), 1.21-1.45 (m, 8H, hexyl-CH_2), 1.81-1.99 (m, 2H, hexyl-CH_2), 4.14 (q, 2H, O-ethyl-CH_2, *J* = 6.00 Hz), 4.59 (t, 1H, S-C*H*, *J* = 9.00 Hz), 6.81 (s, 1H, thiazole-*H*5), 7.64 (d, 2H, Ph-3,5-*H*, *J* = 9.00 Hz), 7.80 (s, 1H, Pyr-*H*5), 7.86 (d, 2H, Ph-2,6-*H*, *J* = 9.00 Hz), 12.23 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-CH_3), 13.97 (O-ethyl-CH_3), 21.90 (hexyl-CH_2), 26.32 (hexyl-CH_2), 28.08 (hexyl-CH_2), 30.86 (hexyl-CH_2), 31.29 (hexyl-CH_2), 46.99 (S-*C*H), 61.11 (O-ethyl-CH_2), 102.03 (Pyr-C_5), 109.46 (thiazole-C_5), 120.91 (Ph-C_4), 127.64 (Ph-C_2 + -C_6), 131.67 (Ph-C_3 + -C_5), 133.30 (Ph-C_1), 148.03 (thiazole-C_4), 157.64 (Pyr-C_4), 157.75 (Pyr-C_2), 169.62 (-*C*OOEt), 170.89 (Pyr-C_6). **MS (ESI-):** *m/e* = 569.7 $[M-H]^-$

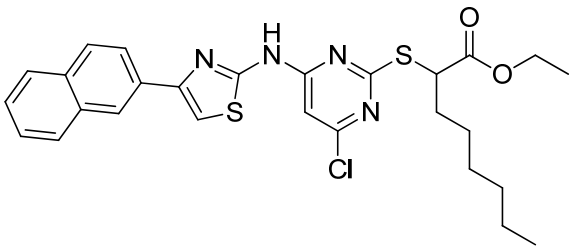
Characterization of ethyl 2-[(4-chloro-6-{[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**15d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (650 mg; 1.85 mmol), E2: 4-(naphthalen-1-yl)-1,3-thiazol-2-amine (502 mg; 2.22 mmol), $Pd_2(dba)_3$ (34 mg; 0.04 mmol), Xantphos (64 mg; 0.11 mmol), Na_2CO_3 (275 mg; 2.59 mmol); Product: white solid; yield: 58% (0.58 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 5.00 Hz), 1.19 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.26–1.43 (m, 8H, hexyl-C*H*$_2$), 1.85–2.02 (m, 2H, hexyl-C*H*$_2$), 4.15 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.62 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, thiazole-*H*5), 7.53 (s, 1H, Pyr-*H*5), 7.54–7.60 (m, 3H, Naph-3,6,7-*H*), 7.72 (d, 1H, Naph-2-*H*, *J* = 6.78 Hz), 7.95–8.01 (m, 2H, Naph-4,5-*H*), 8.40 (m, 1H, Naph-*H*8), 12.26 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-*C*H$_3$), 13.98 (O-ethyl-*C*H$_3$), 21.92 (hexyl-*C*H$_2$), 26.33 (hexyl-*C*H$_2$), 28.10 (hexyl-*C*H$_2$), 30.88 (hexyl-*C*H$_2$), 31.35 (hexyl-*C*H$_2$), 47.01 (S-*C*H), 61.12 (O-ethyl-*C*H$_2$), 102.01 (Pyr-*C*$_5$), 112.40 (thiazole-*C*$_5$), 125.44 (Naph-*C*$_2$), 125.79 (Naph-*C*$_7$), 125.95 (Naph-*C*$_6$), 126.24 (Naph-*C*$_3$), 127.16 (Naph-*C*$_4$), 128.26 (Naph-*C*$_8$), 128.48 (Naph-*C*$_5$), 130.52 (Naph-*C*$_{8a}$), 132.47 (Naph-*C*$_{4a}$), 133.48 (Naph-*C*$_1$), 149.36 (thiazole-*C*$_4$), 157.30 (Pyr-*C*$_4$), 157.75 (Pyr-*C*$_2$), 169.67 (-*C*OOEt), 170.92 (Pyr-*C*$_6$). **MS (ESI-):** *m/e* = 539.9 $[M-H]^-$

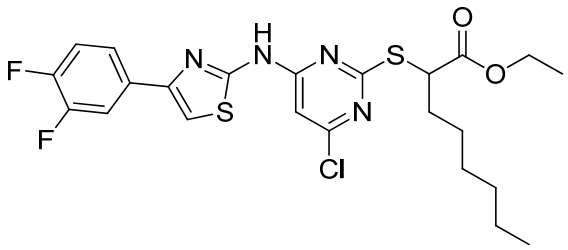
Characterization of ethyl 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**16d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-(naphthalen-2-yl)-1,3-thiazol-2-amine (309 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 55% (0.34 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.19 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.22–1.44 (m, 8H, hexyl-C*H*$_2$), 1.83–2.00 (m, 2H, hexyl-C*H*$_2$), 4.15 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.15 Hz), 4.60 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, Pyr-*H*5), 7.48–7.56 (m, 2H, Naph-6,7-*H*), 7.86 (s, 1H, thiazole-*H*5), 7.90–7.98 (m, 3H, Naph-3,5,8-*H*), 8.06 (d, 1H, Naph-*H*4), 8.44 (s, 1H, Naph-*H*1), 12.28 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-*C*H$_3$), 13.98 (O-ethyl-*C*H$_3$), 21.90 (hexyl-*C*H$_2$), 26.32 (hexyl-*C*H$_2$), 28.07 (hexyl-*C*H$_2$), 30.86 (hexyl-*C*H$_2$), 31.33 (hexyl-*C*H$_2$), 47.01 (S-*C*H), 61.11 (O-ethyl-*C*H$_2$), 102.03 (Pyr-*C*$_5$), 109.32 (thiazole-*C*$_5$), 123.92 (Naph-*C*$_3$), 124.27 (Naph-*C*$_1$), 126.17 (Naph-*C*$_6$), 126.51 (Naph-*C*$_7$), 127.58 (Naph-*C*$_5$), 128.14 (Naph-*C*$_8$), 128.27 (Naph-*C*$_4$), 131.54 (Naph-*C*$_2$), 132.53 (Naph-*C*$_{4a}$), 133.09 (Naph-*C*$_{8a}$), 149.13 (thiazole-*C*$_4$), 157.71 (Pyr-*C*$_4$), 157.75 (Pyr-*C*$_2$), 169.65 (-*C*OOEt), 170.90 (Pyr-*C*$_6$). **MS (ESI-):** *m/e* = 539.9 [M-H]$^-$

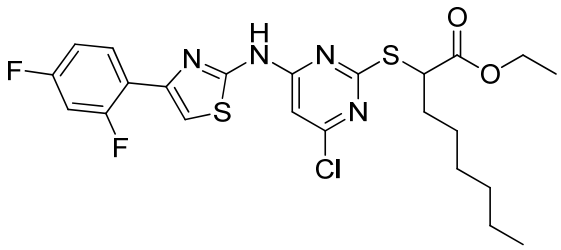
Characterization of ethyl 2-[(4-chloro-6-{[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**17d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-(3,4-difluorophenyl)-1,3-thiazol-2-amine (290 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 65% (0.40 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.20 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.25–1.42 (m, 8H, hexyl-C*H*$_2$), 1.81–2.01 (m, 2H, hexyl-C*H*$_2$), 4.16 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.60 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, Pyr-*H*5), 7.52 (dd, 1H, Ph-*H*$_5$), 7.77 (m, 1H, Ph-*H*$_2$), 7.83 (s, 1H, thiazole-*H*$_5$), 7.88–7.97 (m, 1H, Ph-*H*$_6$), 12.22 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.81 (hexyl-*C*H$_3$), 13.96 (O-ethyl-*C*H$_3$), 21.90 (hexyl-*C*H$_2$), 26.32 (hexyl-*C*H$_2$), 28.07 (hexyl-*C*H$_2$), 30.86 (hexyl-*C*H$_2$), 31.29 (hexyl-*C*H$_2$), 47.00 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 102.04 (Pyr-*C*$_5$), 109.66 (thiazole-*C*$_5$), 114.45 (Ph-*C*$_2$), 117.89 (Ph-*C*$_5$), 122.36 (Ph-*C*$_6$), 131.80 (Ph-*C*$_1$), 147.02 (thiazole-*C*$_4$), 147.68 (Ph-*C*$_4$), 150.93 (Ph-*C*$_3$), 157.62 (thiazole-*C*$_2$), 157.76 (Pyr-*C*$_4$), 157.81 (Pyr-*C*$_2$), 169.60 (-*C*OOEt), 170.88 (Pyr-*C*$_6$). **MS (ESI+):** *m/e* = 527.8 $[M+H]^+$

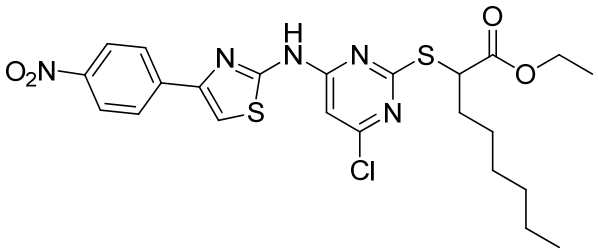
Characterization of ethyl 2-[(4-chloro-6-{[4-(2,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**18d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-(2,4-difluorophenyl)-1,3-thiazol-2-amine (289 mg; 1.36 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 23% (0.14 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.18 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.24–1.43 (m, 8H, hexyl-C*H*$_2$), 1.81–1.99 (m, 2H, hexyl-C*H*$_2$), 4.14 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.56 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.82 (s, 1H, Pyr-*H*5), 7.20 (m, 1H, Ph-*H*$_3$), 7.37 (m, 1H, Ph-*H*$_5$), 7.56 (s, 1H, thiazole-*H*$_5$), 8.05 (m, 1H, Ph-*H*$_6$), 12.21 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-*C*H$_3$), 13.98 (O-ethyl-*C*H$_3$), 21.92 (hexyl-*C*H$_2$), 26.33 (hexyl-*C*H$_2$), 28.10 (hexyl-*C*H$_2$), 30.88 (hexyl-*C*H$_2$), 31.29 (hexyl-*C*H$_2$), 47.03 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 102.07 (Pyr-*C*$_5$), 104.67 (Ph-*C*$_3$), 111.97 (Ph-*C*$_5$), 112.49 (thiazole-*C*$_5$), 118.65 (Ph-*C*$_1$), 130.36 (Ph-*C*$_1$), 142.17 (thiazole-*C*$_4$), 157.25 (thiazole-*C*$_2$), 157.68 (Pyr-*C*$_4$), 157.82 (Pyr-*C*$_6$), 158.87 (Ph-*C*$_2$), 162.18 (Ph-*C*$_4$), 169.62 (-*C*OOEt), 170.91 (Pyr-*C*$_2$). **MS (ESI+):** *m/e* = 527.9 $[M+H]^+$

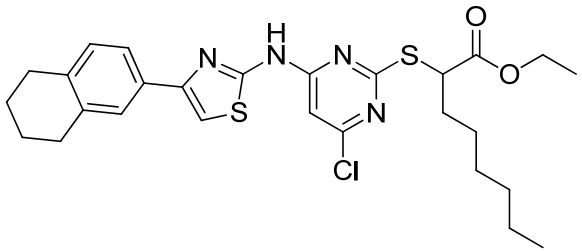
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-nitrophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**19d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (295 mg; 0.83 mmol), E2: 4-(4-nitrophenyl)-1,3-thiazol-2-amine (223 mg; 1.01 mmol), $Pd_2(dba)_3$ (15 mg; 0.02 mmol), Xantphos (15 mg; 0.05 mmol), Na_2CO_3 (125 mg; 1.18 mmol); Product: yellow solid; yield: 45% (0.20 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.86 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.18–1.23 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.27–1.43 (m, 8H, hexyl-C*H*$_2$), 1.84–1.99 (m, 2H, hexyl-C*H*$_2$), 4.17 (q, 2H, O-ethyl-C*H*$_2$, J = 7.50 Hz), 4.59 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, Pyr-*H*5), 8.09 (s, 1H, thiazole-*H*$_5$), 8.18 (d, 2H, Ph-*H*$_2$/*H*$_6$, *J* = 10.00 Hz), 8.32 (d, 2H, Ph-*H*$_3$/*H*$_5$, *J* = 10.00 Hz), 12.32 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.84 (hexyl-*C*H$_3$), 13.99 (O-ethyl-*C*H$_3$), 21.92 (hexyl-*C*H$_2$), 26.34 (hexyl-*C*H$_2$), 28.09 (hexyl-*C*H$_2$), 30.88 (hexyl-*C*H$_2$), 31.29 (hexyl-*C*H$_2$), 47.05 (S-*C*H), 61.13 (O-ethyl-*C*H$_2$), 102.14 (Pyr-*C*$_5$), 113.08 (thiazole-*C*$_5$), 124.21 (Ph-*C*$_3$/*C*$_5$), 126.51 (Ph-*C*$_2$/*C*$_6$), 140.08 (Ph-*C*$_1$), 146.48 (Ph-*C*$_4$), 147.06 (thiazole-*C*$_4$), 157.66 (Pyr-*C*$_4$), 157.86 (Pyr-*C*$_2$), 158.19 (thiazole-*C*$_2$), 169.63 (-*C*OOEt), 170.89 (Pyr-*C*$_6$). **MS (ESI-):** *m/e* = 535.1 $[M-H]^-$

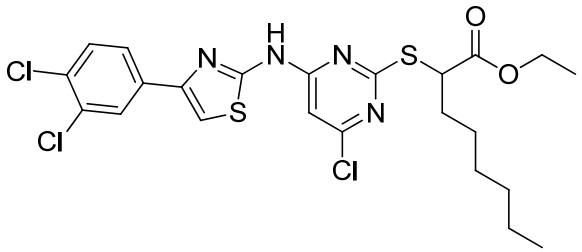
Characterization of ethyl 2-[(4-chloro-6-{[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**20d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-amine (315 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 39% (0.25 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.25 Hz), 1.18 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.21–1.40 (m, 8H, hexyl-C*H*$_2$), 1.74 (m, 4H, naphthyl-*H*$_6$/*H*$_7$), 1.84–1.96 (m, 2H, hexyl-C*H*$_2$), 2.75 (m, 4H, naphthyl-*H*$_5$/*H*$_8$), 4.14 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.59 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.79 (s, 1H, Pyr-*H*5), 7.09 (d, 1H, Naph-*H*$_4$, *J* = 7.50 Hz), 7.59 (m, 3H, Naph-*H*$_1$/*H*$_3$, thiazole-*H*$_5$), 12.17 (s, 1H, -N*H*). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 13.81 (hexyl-*C*H$_3$), 13.97 (O-ethyl-*C*H$_3$), 21.89 (hexyl-*C*H$_2$), 22.69 (Naph-*C*$_6$/*C*$_7$), 26.32 (hexyl-*C*H$_2$), 28.07 (hexyl-*C*H$_2$), 28.57 (Naph-*C*$_5$), 28.86 (Naph-*C*$_8$), 30.86 (hexyl-*C*H$_2$), 31.37 (hexyl-*C*H$_2$), 47.00 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 101.96 (Pyr-*C*$_5$), 107.52 (thiazole-*C*$_5$), 122.88 (Naph-*C*$_3$), 126.24 (Naph-*C*$_4$), 129.24 (Naph-*C*$_1$), 131.42 (Naph-*C*$_1$), 136.49 (Naph-*C*$_{4a}$), 136.81 (Naph-*C*$_{8a}$), 149.52 (thiazole-*C*$_4$), 157.39 (thiazole-*C*$_2$), 157.71 (Pyr-*C*$_4$/*C*$_2$), 169.66 (-*C*OOEt), 170.90 (Pyr-*C*$_6$). **MS (ESI-):** *m/e* = 544.2 $[M-H]^-$

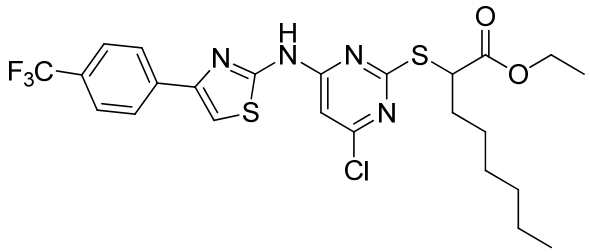
Characterization of ethyl 2-[(4-chloro-6-{[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**21d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-(3,4-dichlorophenyl)-1,3-thiazol-2-amine (335 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 71% (0.45 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.86 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.20 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.27–1.42 (m, 8H, hexyl-C*H*$_2$), 1.84–1.98 (m, 2H, hexyl-C*H*$_2$), 4.16 (q, 2H, O-ethyl-C*H*$_2$, *J* = 6.67 Hz), 4.59 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.82 (s, 1H, Pyr-*H*$_5$), 7.72 (d, 1H, Ph-*H*$_5$, *J* = 7.50 Hz), 7.90 (d, 1H, Ph-*H*$_6$, *J* = 7.50 Hz), 7.94 (s, 1H, thiazole-*H*$_5$), 8.15 (s, 1H, Ph-*H*$_2$), 12.32 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-*C*H$_3$), 13.96 (O-ethyl-*C*H$_3$), 21.89 (hexyl-*C*H$_2$), 26.31 (hexyl-*C*H$_2$), 28.05 (hexyl-*C*H$_2$), 30.85 (hexyl-*C*H$_2$), 31.29 (hexyl-*C*H$_2$), 47.02 (S-*C*H), 61.11 (O-ethyl-*C*H$_2$), 102.09 (Pyr-*C*$_5$), 110.07 (thiazole-*C*$_5$), 125.66 (Ph-*C*$_6$), 127.32 (Ph-*C*$_2$), 130.09 (Ph-*C*$_5$), 131.01 (Ph-*C*$_3$), 131.55 (Ph-*C*$_1$), 134.65 (Ph-*C*$_4$), 146.60 (thiazole-*C*$_4$), 157.64 (Pyr-*C*$_6$), 157.82 (Pyr-*C*$_4$), 157.93 (thiazole-*C*$_2$), 169.63 (-*C*OOEt), 170.87 (Pyr-*C*$_2$). **MS (ESI-):** *m/e* = 557.4 $[M-H]^-$

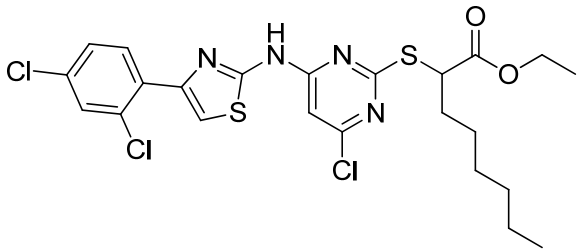
Characterization of ethyl 2-{[4-chloro-6-({4-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoate (**22d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 4-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (334 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 65% (0.42 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-C*H*$_3$, *J* = 6.25 Hz), 1.20 (t, 3H, O-ethyl-C*H*$_3$, *J* = 6.25 Hz), 1.23–1.43 (m, 8H, hexyl-C*H*$_2$), 1.81–2.04 (m, 2H, hexyl-C*H*$_2$), 4.16 (q, 2H, O-ethyl-C*H*$_2$, J =6.67 Hz), 4.60 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, Pyr-*H*$_5$), 7.82 (d, 2H, Ph-*H*$_2$/*H*$_6$, *J* = 7.50 Hz), 7.96 (s, 1H, thiazole-*H*$_5$), 8.14 (d, 2H, Ph-*H*$_3$/*H*$_5$, *J* = 7.50 Hz), 12.29 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.80 (hexyl-*C*H$_3$), 13.96 (O-ethyl-*C*H$_3$), 21.89 (hexyl-*C*H$_2$), 26.31 (hexyl-*C*H$_2$), 28.07 (hexyl-*C*H$_2$), 30.85 (hexyl-*C*H$_2$), 31.30 (hexyl-*C*H$_2$), 47.01 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 102.06 (Pyr-*C*$_5$), 111.21 (thiazole-*C*$_5$), 125.73 (-*C*F$_3$), 126.19 (Ph-*C*$_4$), 127.65 (Ph-*C*$_3$/$_5$), 128.07 (Ph-*C*$_2$/$_6$), 137.81 (Ph-C1), 147.63 (thiazole-*C*$_4$), 157.67 (Pyr-*C*$_6$), 157.80 (Pyr-*C*$_4$), 157.98 (thiazole-*C*$_2$), 169.63 (-*C*OOEt), 170.88 (Pyr-*C*$_2$). **MS (ESI-):** *m/e* = 557.5 $[M-H]^-$

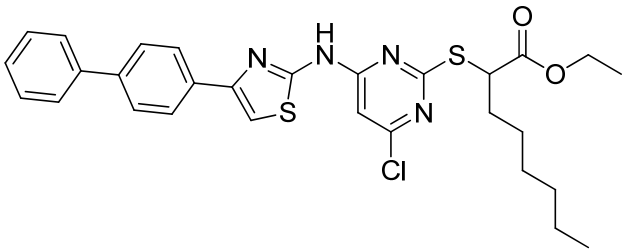
Characterization of ethyl 2-[(4-chloro-6-{[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**23d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (300 mg; 0.85 mmol), E2: 4-(2,4-dichlorophenyl)-1,3-thiazol-2-amine (251 mg; 1.03 mmol), $Pd_2(dba)_3$ (16 mg; 0.02 mmol), Xantphos (30 mg; 0.05 mmol), Na_2CO_3 (127 mg; 1.20 mmol); Product: yellow oil; yield: 34% (0.13 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-CH_3, J = 7.50 Hz), 1.17–1.23 (t, 3H, O-ethyl-CH_3, J = 7.50 Hz), 1.25–1.43 (m, 8H, hexyl-CH_2), 1.84–2.02 (m, 2H, hexyl-CH_2), 4.16 (q, 2H, O-ethyl-CH_2, J =6.67 Hz), 4.60 (t, 1H, S-CH, J = 7.50 Hz), 6.83 (s, 1H, Pyr-H_5), 7.55 (dd, 1H, Ph-H_5, ^3J = 8.50 Hz), 7.74 (d, 1H, Ph-H_3, ^4J = 2.15 Hz), 7.76 (s, 1H, thiazole-H_5), 7.90 (d, 1H, Ph-H_6, J = 8.50 Hz), 12.26 (s, 1H, -NH). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.81 (hexyl-CH$_3$), 13.95 (O-ethyl-CH$_3$), 21.90 (hexyl-CH$_2$), 26.30 (hexyl-CH$_2$), 28.07 (hexyl-CH$_2$), 30.86 (hexyl-CH$_2$), 31.28 (hexyl-CH$_2$), 47.01 (S-CH), 61.10 (O-ethyl-CH$_2$), 102.04 (Pyr-C_5), 113.90 (thiazole-C_5), 127.57 (Ph-C_5), 129.78 (Ph-C_1), 131.76 (Ph-C_6), 131.79 (Ph-C_3), 132.25 (Ph-C_2), 132.90 (Ph-C_4), 144.82 (thiazole-C_4), 157.00 (thiazole-C_2), 157.66 (Pyr-C_4), 157.81 (Pyr-C_2), 169.62 (-COOEt), 170.89 (Pyr-C_6). **MS (ESI-):** *m/e* = 557.2 $[M-H]^-$

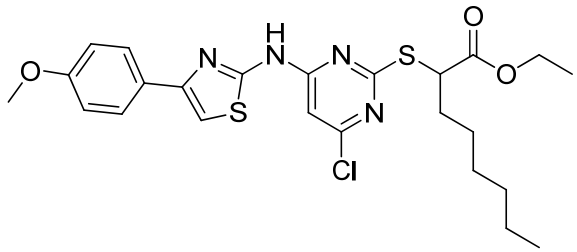
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-phenylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**24d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (300 mg; 0.85 mmol), E2: 4-(4-phenylphenyl)-1,3-thiazol-2-amine (259 mg; 1.03 mmol), $Pd_2(dba)_3$ (16 mg; 0.02 mmol), Xantphos (30 mg; 0.05 mmol), Na_2CO_3 (127 mg; 1.20 mmol); Product: white solid; yield: 36% (0.18 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.37 Hz), 1.18 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.31 Hz), 1.23–1.43 (m, 8H, hexyl-C*H*$_2$), 1.80–2.00 (m, 2H, hexyl-C*H*$_2$), 4.16 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.07 Hz), 4.60 (t, 1H, S-C*H*, *J* = 7.07 Hz), 6.83 (s, 1H, Pyr-*H*$_5$), 7.36 (t, 1H, Biph-*H*‘$_4$, *J* = 7.25 Hz), 7.47 (t, 2H, Biph-*H´*$_3$/*H´*$_5$, *J* = 7.34 Hz), 7.70–7.76 (m, 4H, Biph-*H*$_3$/*H*$_5$/*H´*$_2$/*H´*$_6$), 7.78 (s, 1H, thiazole-*H*$_5$), 8.00 (d, 2H, Biph-*H*$_2$/*H*$_6$, *J* = 8.42 Hz), 12.21 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-*C*H$_3$), 13.97 (O-ethyl-*C*H$_3$), 21.90 (hexyl-*C*H$_2$), 26.32 (hexyl-*C*H$_2$), 28.08 (hexyl-*C*H$_2$), 30.86 (hexyl-*C*H$_2$), 31.34 (hexyl-*C*H$_2$), 47.00 (S-*C*H), 61.11 (O-ethyl-*C*H$_2$), 102.03 (Pyr-*C*$_5$), 108.81 (thiazole-*C*$_5$), 126.21 (Biph-*C*$_3$/*C*$_5$), 126.47 (Biph-*C´*$_2$/*C´*$_6$), 126.95 (Biph-*C*$_2$/*C*$_6$), 127.51 (Biph-*C´*$_4$), 128.94 (Biph-*C´*$_3$/*C´*$_5$), 133.20 (Biph-*C*$_1$), 139.38 (Biph-*C´*$_1$), 139.52 (Biph-*C*$_4$), 148.88 (thiazole-*C*$_4$), 157.65 (thiazole-*C*$_2$), 157.71 (Pyr-*C*$_4$), 157.74 (Pyr-*C*$_2$), 169.64 (-*C*OOEt), 170.90 (Pyr-*C*$_6$). **MS (ESI+):** *m/e* = 567.3 $[M+H]^+$

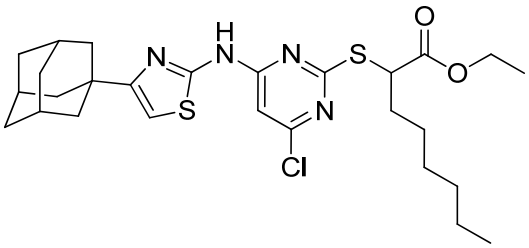
Characterization of ethyl 2-[(4-chloro-6-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (**25d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (300 mg; 0.85 mmol), E2: 4-(4-methoxyphenyl)-1,3-thiazol-2-amine (211 mg; 1.03 mmol), $Pd_2(dba)_3$ (16 mg; 0.02 mmol), Xantphos (30 mg; 0.05 mmol), Na_2CO_3 (127 mg; 1.20 mmol); Product: white solid; yield: 74% (0.33 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 6.53 Hz), 1.19 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.08 Hz), 1.23–1.44 (m, 8H, hexyl-C*H*$_2$), 1.80–2.03 (m, 2H, hexyl-C*H*$_2$), 3.79 (s, 3H, -O-C*H*$_3$), 4.15 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.06 Hz), 4.61 (t, 1H, S-C*H*, *J* = 6.99 Hz), 6.82 (s, 1H, Pyr-*H*$_5$), 7.00 (d, 2H, Ph-*H*$_{3/5}$, *J* = 8.89 Hz), 7.55 (s, 1H, thiazole-*H*$_5$), 7.84 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.85 Hz), 12.17 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.89 (hexyl-*C*H$_3$), 14.03 (O-ethyl-*C*H$_3$), 21.97 (hexyl-*C*H$_2$), 26.38 (hexyl-*C*H$_2$), 28.14 (hexyl-*C*H$_2$), 30.92 (hexyl-*C*H$_2$), 31.39 (hexyl-*C*H$_2$), 47.02 (S-*C*H), 55.17 (-O-*C*H$_3$), 61.17 (O-ethyl-*C*H$_2$), 102.02 (Pyr-*C*$_5$), 106.63 (thiazole-*C*$_5$), 114.13 (Ph-*C*$_{3/5}$), 126.98 (Ph-*C*$_1$), 127.03 (Ph-*C*$_{2/6}$), 149.19 (thiazole-*C*$_4$), 157.46 (thiazole-*C*2), 157.62 (Pyr-*C*$_6$), 157.71 (Pyr-*C*$_4$), 159.06 (Ph-*C*$_4$), 169.67 (-*C*OOEt), 170.96 (Pyr-*C*$_2$). **MS (ESI+):** *m/e* = 521.83 $[M+H]^+$

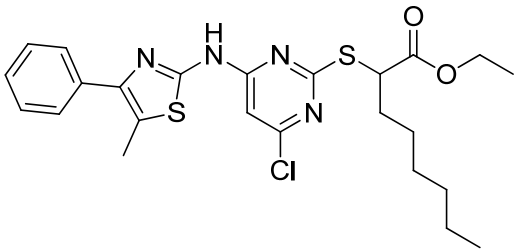
Characterization of ethyl 2-[(4-{[4-(adamantan-1-yl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (**26d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (250 mg; 0.71 mmol), E2: 4-(adamantan-1-yl)-1,3-thiazol-2-amine (200 mg; 0.85 mmol), $Pd_2(dba)_3$ (13 mg; 0.01 mmol), Xantphos (25 mg; 0.04 mmol), Na_2CO_3 (106 mg; 1.00 mmol); Product: yellow oil; yield: 66% (0.26 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.00 Hz), 1.18 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.10 Hz), 1.23–1.39 (m, 8H, hexyl-C*H*$_2$), 1.71–2.03 (m, 17H, hexyl-C*H*$_2$, Adamantyl-*H*$_{2/3/4/5/6/7/8/9/10}$), 4.13 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.09 Hz), 4.60 (t, 1H, S-C*H*, *J* = 7.14 Hz), 6.76 (s, 2H, Pyr-*H*$_5$, thiazole-*H*$_5$), 12.04 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.85 (hexyl-*C*H$_3$), 13.98 (O-ethyl-*C*H$_3$), 21.93 (hexyl-*C*H$_2$), 26.33 (hexyl-*C*H$_2$), 27.92 (Adamantyl-*C*$_{3/5/7}$), 28.11 (hexyl-*C*H$_2$), 30.89 (hexyl-*C*H$_2$), 31.39 (hexyl-*C*H$_2$), 35.89 (Adamantyl-*C*$_{4/6/10}$), 36.33 (Adamantyl-*C*$_{2/8/9}$), 41.62 (Adamantyl-*C*$_1$), 46.93 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 101.78 (Pyr-*C*$_5$), 105.18 (thiazole-*C*$_5$), 156.84 (thiazole-*C*$_2$), 157.54 (Pyr-*C*$_6$), 157.70 (Pyr-*C*$_4$), 161.03 (thiazole-*C*$_4$), 169.64 (-*C*OOEt), 170.94 (Pyr-*C*$_2$). **MS (ESI+):** *m/e* = 549.88 $[M+H]^+$

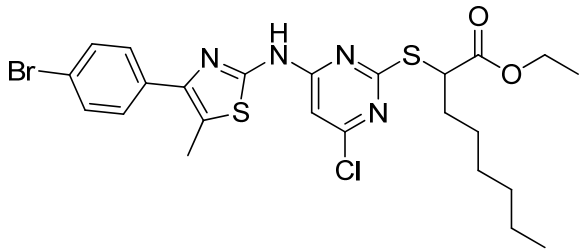
Characterization of ethyl 2-({4-chloro-6-[(5-methyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (**27d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 5-methyl-4-phenyl-1,3-thiazol-2-amine (260 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: white solid; yield: 45% (0.26 g).

^{1}H-NMR (250.13 MHz, ($CDCl_3$) δ: 0.81 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.21 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.24–1.42 (m, 8H, hexyl-C*H*$_2$), 1.77–1.99 (m, 2H, hexyl-C*H*$_2$), 2.48 (s, 3H, methyl-thiazol-C*H*$_3$), 4.15 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.50 (t, 1H, S-C*H*, *J* = 7.50 Hz), 5.47 (s, 1H, Pyr-*H*5), 7.26 (t, 1H, Ph-*H*$_4$, J = 7.50 Hz), 7.36 (t, 2H, Ph-*H*$_3$/*H*$_5$, *J* = 7.50 Hz), 7.57 (d, 2H, Ph-*H*$_2$/*H*$_6$, *J* = 7.50 Hz). **^{13}C-NMR (75.44 MHz, (CD_3)$_2$SO)** δ: 11.79 (thiazole-*C*H$_3$), 13.83 (hexyl-*C*H$_3$), 13.96 (O-ethyl-*C*H$_3$), 21.90 (hexyl-*C*H$_2$), 26.38 (hexyl-*C*H$_2$), 28.05 (hexyl-*C*H$_2$), 30.88 (hexyl-*C*H$_2$), 31.42 (hexyl-*C*H$_2$), 46.91 (S-*C*H), 61.09 (O-ethyl-*C*H$_2$), 101.78 (Pyr-*C*$_5$), 121.70 (thiazole-*C*$_5$), 127.32 (Ph-*C*$_4$), 127.91 (Ph-*C*$_2$ + -*C*$_6$), 128.37 (Ph-*C*$_3$ + -*C*$_5$), 134.62 (Ph-*C*$_1$), 144.58 (thiazole-*C*$_4$), 153.55 (thiazole-*C*$_2$), 157.53 (Pyr-*C*$_4$), 157.62 (Pyr-*C*$_2$), 169.56 (-*C*OOEt), 170.93 (Pyr-*C*$_6$). **MS (ESI-):** *m/e* = 503.9 [M-H]$^-$

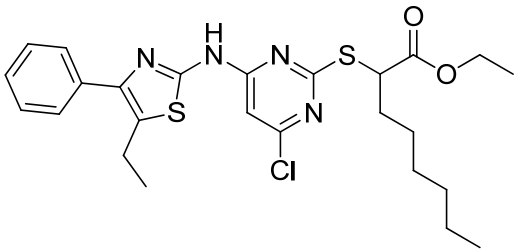
Characterization of ethyl 2-[(4-{[4-(4-bromophenyl)-5-methyl-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (**28d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (407 mg; 1.16 mmol), E2: 4-(4-bromophenyl)-5-methyl-1,3-thiazol-2-amine (368 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (168 mg; 1.59 mmol); Product: white solid; yield: 50% (0.34 g).

^{1}H-NMR (250.13 MHz, ($CDCl_3$) δ: 0.81 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.22 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.24–1.42 (m, 8H, hexyl-C*H*$_2$), 1.78–2.00 (m, 2H, hexyl-C*H*$_2$), 2.44 (s, 3H, methyl-thiazol-C*H*$_3$), 4.15 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.49 (t, 1H, S-C*H*, *J* = 5.00 Hz), 5.65 (s, 1H, Pyr-*H*5), 7.42 (d, 2H, Ph-*H*$_2$/*H*$_6$, *J* = 10.00 Hz), 7.49 (d, 2H, Ph-*H*$_3$/*H*$_5$, *J* = 10.00 Hz). **^{13}C-NMR (75.44 MHz, (CD_3)$_2$SO)** δ: 12.00 (thiazole-*C*H$_3$), 14.05 (hexyl-*C*H$_3$), 14.22 (O-ethyl-*C*H$_3$), 22.55 (hexyl-*C*H$_2$), 27.09 (hexyl-*C*H$_2$), 28.87 (hexyl-*C*H$_2$), 31.55 (hexyl-*C*H$_2$), 31.90 (hexyl-*C*H$_2$), 47.83 (S-*C*H), 61.52 (O-ethyl-*C*H$_2$), 101.40 (Pyr-*C*$_5$), 122.15 (thiazole-*C*$_5$), 122.87 (Ph-*C*$_4$), 129.95 (Ph-*C*$_2$/*C*$_6$), 132.08 (Ph-*C*$_3$/*C*$_5$), 133.28 (Ph-*C*$_1$), 143.51 (thiazole-*C*$_4$), 156.42 (Pyr-*C*$_4$), 156.77 (Pyr-*C*$_2$), 159.23 (thiazole-*C*$_2$), 170.52 (Pyr-*C*$_6$), 172.02 (-*C*OOEt). **MS (ESI-):** *m/e* = 582.1 $[M-H]^-$

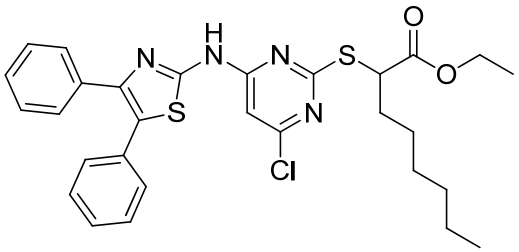
Characterization of ethyl 2-({4-chloro-6-[(5-ethyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (**29d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 5-ethyl-4-phenyl-1,3-thiazol-2-amine (279 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: yellow oil; yield: 85% (0.50 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (m, 3H, hexyl-C*H*$_3$), 1.20 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.50 Hz), 1.23–1.41 (m, 11H, hexyl-C*H*$_2$, ethyl-thiazol-C*H*$_3$), 1.85–1.99 (m, 2H, hexyl-C*H*$_2$), 2.94 (q, 2H, ethyl-thiazol-C*H*$_2$, *J* = 7.50 Hz), 4.17 (q, 2H, O-ethyl-C*H*$_2$, *J* = 7.50 Hz), 4.71 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.78 (s, 1H, Pyr-*H*5), 7.37 (t, 1H, Ph-*H*$_4$, *J* = 7.10 Hz), 7.47 (t, 2H, Ph-*H*$_3$/*H*$_5$, *J* = 7.50 Hz), 7.62 (d, 2H, Ph-*H*$_2$/*H*$_6$, J = 7.50 Hz), 12.09 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.80 (hexyl-*C*H$_3$), 13.94 (O-ethyl-*C*H$_3$), 16.27 (Thiazol-CH$_2$-*C*H$_3$), 19.85 (Thiazol-*C*H$_2$-CH$_3$), 21.88 (hexyl-*C*H$_2$), 26.30 (hexyl-*C*H$_2$), 28.06 (hexyl-*C*H$_2$), 30.87 (hexyl-*C*H$_2$), 31.60 (hexyl-*C*H$_2$), 46.84 (S-*C*H), 61.10 (O-ethyl-*C*H$_2$), 101.77 (Pyr-*C*$_5$), 127.46 (thiazole-*C*$_5$), 128.03 (Ph-*C*$_2$/*C*$_6$), 128.40 (Ph-*C*$_3$/*C*$_5$), 129.46 (Ph-*C*$_4$), 134.74 (Ph-*C*$_1$), 144.12 (thiazole-*C*$_4$), 153.89 (thiazole-*C*$_2$), 157.66 (Pyr-*C*$_4$/*C*$_6$), 169.65 (-*C*OOEt), 170.93 (Pyr-*C*$_2$). **MS (ESI+):** *m/e* = 520.0 $[M+H]^+$

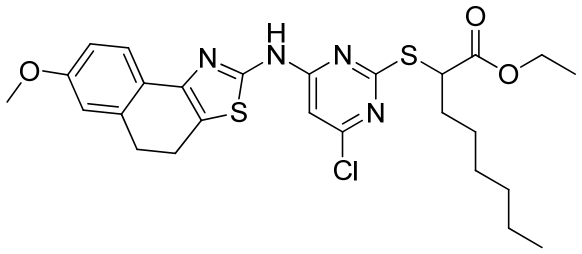
Characterization of ethyl 2-({4-chloro-6-[(4,5-diphenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (**30d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (396 mg; 1.13 mmol), E2: 4,5-diphenyl-1,3-thiazol-2-amine (341 mg; 1.35 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (39 mg; 0.07 mmol), Na_2CO_3 (178 mg; 1.58 mmol); Product: yellow oil; yield: 23% (0.15 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.80 (t, 3H, hexyl-C*H*$_3$, *J* = 6.71 Hz), 1.13 (t, 3H, O-ethyl-C*H*$_3$, *J* = 7.09 Hz), 1.17–1.39 (m, 8H, hexyl-C*H*$_2$), 1.81–1.97 (m, 2H, hexyl-C*H*$_2$), 4.04–4.17 (m, 2H, O-ethyl-C*H*$_2$), 4.65 (t, 1H, S-C*H*, *J* = 7.22 Hz), 6.80 (s, 1H, Pyr-*H*5), 7.30–7.47 (m, 10H, Ph-*H*), 12.30 (s, 1H, -N*H*). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 13.76 (hexyl-*C*H$_3$), 13.85 (O-ethyl-*C*H$_3$), 21.81 (hexyl-*C*H$_2$), 26.33 (hexyl-*C*H$_2$), 28.01 (hexyl-*C*H$_2$), 30.78 (hexyl-*C*H$_2$), 31.58 (hexyl-*C*H$_2$), 46.85 (S-*C*H), 61.06 (O-ethyl-*C*H$_2$), 102.08 (Pyr-*C*$_5$), 126.05 (thiazole-*C*$_5$), 127.77 (Ph´-*C*$_4$), 128.00 (Ph-*C*$_4$), 128.25 (Ph´-*C*$_{2/6}$), 128.35 (Ph-*C*$_{2/6}$), 128.91 (Ph´-*C*$_{3/5}$), 129.19 (Ph-*C*$_{3/5}$), 131.59 (Ph-*C*$_1$), 134.44 (Ph´-*C*$_1$), 144.13 (thiazole-*C*$_4$), 155.41 (thiazole-*C*$_2$), 157.57 (Pyr-*C*$_6$), 157.81 (Pyr-*C*$_4$), 169.68 (-*C*OOEt), 170.84 (Pyr-*C*$_2$). **MS (ESI+):** *m/e* = 567.70 $[M+H]^+$

Characterization of ethyl 2-{[4-chloro-6-({7-methoxy-4,5-dihydronaphtho[1,2-d][1,3]thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoate (**31d**):



Synthesis Step IV; E1: ethyl 2-[(4,6-dichloropyrimidin-2-yl)sulfanyl]octanoate (400 mg; 1.14 mmol), E2: 7-methoxy-4H,5H-naphtho[1,2-d][1,3]thiazol-2-amine (317 mg; 1.37 mmol), $Pd_2(dba)_3$ (21 mg; 0.02 mmol), Xantphos (40 mg; 0.07 mmol), Na_2CO_3 (169 mg; 1.59 mmol); Product: brown solid; yield: 30% (0.19 g).

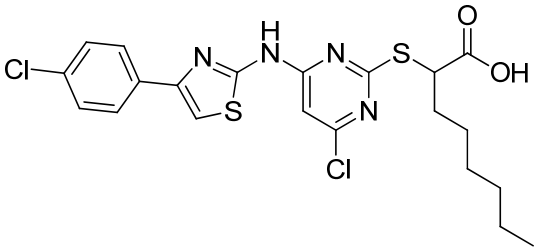
^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.94 (t, 3H, hexyl-CH_3, J = 7.50 Hz), 1.29 (t, 3H, O-ethyl-CH_3, J = 6.25 Hz), 1.35–1.50 (m, 8H, hexyl-CH_2), 1.92–2.09 (m, 2H, hexyl-CH_2), 3.02–3.08 (m, 4H, Naph-$H_{4/5}$), 3.86 (s, 3H, O-CH_3), 4.25 (q, 2H, O-ethyl-CH_2, J = 6.67 Hz), 4.67 (t, 1H, S-CH, J = 7.50 Hz), 6.89–6.97 (m, 3H, Pyr-H_5, Naph-$H_{6/8}$), 7.67 (d, 1H, Naph-H_9, J = 7.50 Hz), 12.21 (s, 1H, N-H). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.84 (hexyl-CH$_3$), 13.98 (O-ethyl-CH$_3$), 20.69 (Naph-C_4), 21.92 (hexyl-CH$_2$), 26.39 (hexyl-CH$_2$), 28.06 (hexyl-CH$_2$), 28.55 (Naph-C_5), 30.90 (hexyl-CH$_2$), 31.41 (hexyl-CH$_2$), 46.97 (S-CH), 55.07 (O-CH$_3$), 61.10 (O-ethyl-CH$_2$), 101.88 (Pyr-C_5), 111.84 (Naph-C_8), 114.02 (Naph-C_6), 121.59 (thiazole-C_5), 123.24 (Naph-C_9), 124.00 (Naph-C_{9a}), 136.52 (Naph-C_{5a}), 143.83 (thiazole-C_4), 155.58 (thiazole-C_2), 157.49 (Pyr-C_4), 157.64 (Pyr-C_2), 158.46 (Naph-C_7), 169.57 (-COOEt), 170.93 (Pyr-C_6). **MS (ESI-):** *m/e* = 546.1 $[M-H]^-$

Step V: Ester hydrolysis (synthesis of compounds **6–31**):

To a solution of the corresponding esters (E1, 1 equiv) in THF (10 ml) was added LiOH*H_2O (5 equiv) dissolved in Water (2 ml). The reaction stirred 24 h at 45°C. The solvent was

evaporated under reduced pressure and the residue was solved in water and a small amount of methanol. The water layer was acidified by 2N HCl and the resulting precipitate was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was finally recrystallized by ethyl acetate.

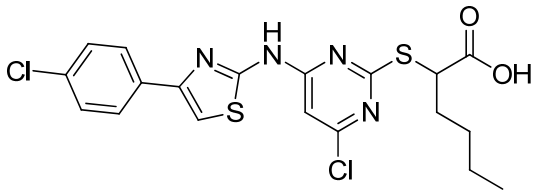
Characterization of 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**6**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (580 mg; 1.10 mmol), LiOH*H_2O (138 mg; 3.31 mmol); Product: white solid; yield: 65% (0.36 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.54 Hz), 1.26–1.42 (m, 8H, hexyl-C*H*$_2$), 1.80–2.03 (m, 2H, hexyl-C*H*$_2$), 4.59 (t, 1H, S-C*H*, *J* = 6.96 Hz), 6.81 (s, 1H, Pyr-*H*$_5$), 7.50 (d, 2H, Ph-*H*$_{3/5}$, *J* = 8.60 Hz), 7.78 (s, 1H, thiazole-*H*$_5$), 7.92 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.60 Hz), 12.21 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-*C*H$_3$), 21.92 (hexyl-*C*H$_2$), 26.35 (hexyl-*C*H$_2$), 28.18 (hexyl-*C*H$_2$), 30.92 (hexyl-*C*H$_2$), 31.76 (hexyl-*C*H$_2$), 47.32 (S-*C*H), 101.90 (Pyr-*C*$_5$), 109.33 (thiazole-*C*$_5$), 127.35 (Ph-*C*$_{2/6}$), 128.75 (Ph-*C*$_{3/5}$), 132.30 (Ph-*C*$_4$), 132.99 (Ph-*C*$_1$), 147.98 (thiazole-*C*$_4$), 157.68 (Pyr-*C*$_4$), 157.81 (Pyr-*C*$_2$), 170.10 (Pyr-*C*$_6$), 172.21 (-*C*OOH). **MS (ESI-):** m/e = 495.6 $[M-H]^-$

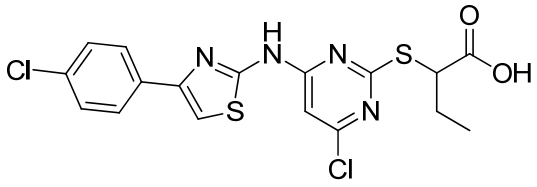
Characterization of 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]hexanoic acid (**7**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]hexanoate (370 mg; 0.74 mmol), LiOH*H_2O (94 mg; 2.23 mmol); Product: white solid; yield: 74% (0.26 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.86 (t, 3H, butyl-C*H*$_3$, *J* = 7.50 Hz), 1.28–1.44 (m, 4H, butyl-C*H*$_2$), 1.87–1.99 (m, 2H, S-CH-C*H*$_2$), 4.57 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.80 (s, 1H, Pyr-*H*$_5$), 7.49 (d, 2H, Ph-*H*$_{3,5}$, *J* = 8.76 Hz), 7.78 (s, 1H, thiazole-*H*5), 7.92 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.76 Hz), 12.19 (s, 1H, N*H*). **^{13}C-NMR (69.90 MHz, $(CD_3)_2SO$)** δ: 13.69 (butyl-*C*H$_3$), 21.73 (butyl-*C*H$_2$), 28.62 (butyl-*C*H$_2$), 31.42 (butyl-*C*H$_2$), 47.23 (S-*C*H), 101.94 (Pyr-*C*$_5$), 109.34 (thiazole-*C*$_5$), 127.36 (Ph-*C*$_2$/*C*$_6$), 128.76 (Ph-*C*$_3$/*C*$_5$), 132.32 (Ph-*C*$_1$), 132.99 (Ph-*C*$_4$), 148.00 (thiazole-*C*$_4$), 157.69 (Pyr-*C*$_6$), 157.83 (Pyr-*C*$_4$), 170.05 (Pyr-*C*$_2$), 172.22 (-*C*OOH). **MS (ESI+):** *m/e* = 469.3 $[M+H]^+$

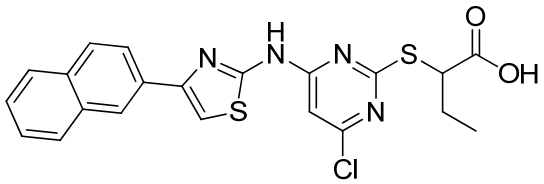
Characterization of 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoic acid (**8**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoate (304 mg; 0.65 mmol), LiOH*H_2O (136 mg; 3.24 mmol); Product: slightly yellow solid; yield: 89% (0.25 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 1.03 (t, 3H, ethyl-CH_3, J = 7.50 Hz), 1.95–2.10 (m, 2H, ethyl-CH_2), 4.59 (t, 1H, S-CH, J = 5.00 Hz), 6.83 (s, 1H, Pyr-H_5), 7.52 (d, 2H, Ph-$H_{3,5}$, J = 7.50 Hz), 7.81 (s, 1H, thiazole-H_5), 7.94 (d, 2H, Ph-$H_{2,6}$, J = 7.50 Hz), 12.22 (s, 1H, -NH), 13.04 (s, 1H, -COOH). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 11.23 (ethyl-CH$_3$), 25.20 (ethyl-CH$_2$), 48.67 (S-CH), 101.93 (Pyr-C_5), 109.35 (thiazole-C_5), 127.36 (Ph-C_2/C_6), 128.76 (Ph-C_3/C_5), 132.32 (Ph-C_1), 133.00 (Ph-C_4), 148.01 (thiazole-C_4), 157.71 (Pyr-C_4), 157.84 (Pyr-C_2), 170.08 (Pyr-C_6), 172.00 (-COOH). **MS (ESI-):** *m/e* = 439.6 [M-H]$^-$

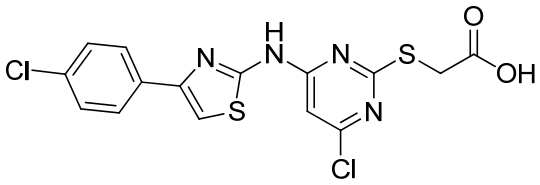
Characterization of 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoic acid (**9**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]butanoate (394 mg; 0.81 mmol), LiOH*H_2O (170 mg; 4.05 mmol); Product: yellow solid; yield: 94% (0.35 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 1.04 (t, 3H, ethyl-CH_3, J = 7.36 Hz), 1.91–2.07 (m, 2H, ethyl-CH_2), 4.60 (t, 1H, S-CH, J = 6.74 Hz), 6.84 (s, 1H, Pyr-H_5), 7.49–7.56 (m, 2H, Naph-$H_{6,7}$), 7.87 (s, 1H, thiazole-H_5), 7.91–7.98 (m, 3H, Naph-$H_{3,5,8}$), 8.06 (d, 1H, Naph-H_4, J = 7.05 Hz), 8.44 (s, 1H, Naph-H_1), 12.27 (s, 1H, -NH), 13.01 (s, 1H, -COOH). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 11.27 (ethyl-CH$_3$), 25.23 (ethyl-CH$_2$), 48.70 (S-CH), 101.94 (Pyr-C_5), 109.33 (thiazole-C_5), 123.95 (Naph-C_3), 124.30 (Naph-C_1), 126.19 (Naph-C_6), 126.53 (Naph-C_7), 127.60 (Naph-C_5), 128.17 (Naph-C_8), 128.29 (Naph-C_4), 131.57 (Naph-C_2), 132.55 (Naph-C_{4a}), 133.12 (Naph-C_{8a}), 149.13 (thiazole-C_4), 157.74 (Pyr-C_6), 157.82 (Pyr-C_4), 170.11 (Pyr-C_2), 172.06 (-COOH). **MS (ESI-):** *m/e* = 455.3 [M-H]$^-$

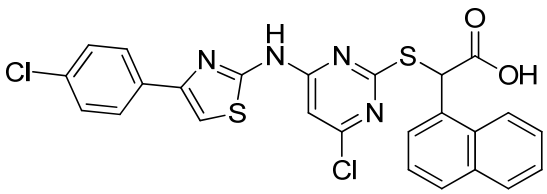
Characterization of 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]acetic acid (**10**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]acetate (125 mg; 0.28 mmol), LiOH*H_2O (36 mg; 0.85 mmol); Product: white solid; yield: 56% (0.07 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 4.09 (s, 2H, S-CH_2), 6.79 (s, 1H, thiazole-H_5), 7.49 (d, 2H, Ph-$H_{3,5}$, J = 7.50 Hz), 7.76 (s, 1H, Pyr-H_5), 7.92 (d, 2H, Ph-$H_{2,6}$, J = 7.50 Hz), 12.18 (s, 1H, N*H*), 12.84 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 33.20 (S-*C*H_2), 101.70 (Pyr-C_5), 109.35 (thiazole-C_5), 127.35 (Ph-$C_{2/6}$), 128.75 (Ph-$C_{3/5}$), 132.28 (Ph-C_1), 132.97 (Ph-C_4), 147.94 (thiazole-C_4), 157.64 (Pyr-C_6), 157.84 (Pyr-C_4), 169.59 (-*C*OOH), 170.45 (Pyr-C_2). **MS (ESI-):** *m/e* = 411.3 $[M-H]^-$

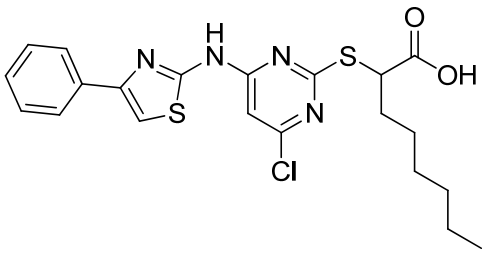
Characterization of 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]-2-(naphthalen-1-yl)acetic acid (**11**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]-2-(naphthalen-1-yl)acetate (300 mg; 0.53 mmol), LiOH*H_2O (67 mg; 1.59 mmol); Product: slightly yellow solid; yield: 43% (0.13 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 6.44 (s, 1H, S-C*H*), 6.87 (s, 1H, Pyr-H_5), 7.49 (d, 2H, Ph-$H_{3/5}$, J = 8.53 Hz), 7.55–7.68 (m, 4 H, Naph-$H_{2/3/6/7}$), 7.75 (s, 1H, thiazole-H_5), 7.92 (d, 2H, Ph-$H_{2/6}$, J = 8.53 Hz), 8.00 (t, 2H, Naph-$H_{4/5}$, J = 9.43 Hz), 8.20 (d, 1H, Naph-H_8, J = 8.26 Hz), 12.26 (s, 1H, -N*H*), 13.37 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 49.57 (S-*C*H), 102.21 (Pyr-C_5), 109.37 (thiazole-C_5), 123.28 (Naph-C_1), 125.63 (Naph-C_3), 126.27 (Naph-C_7), 126.98 (Naph-C_8), 127.02 (Naph-C_6), 127.37 (Ph-$C_{2/6}$), 128.77 (Ph-$C_{3/5}$), 128.99 (Naph-C_4), 129.13 (Naph-C_5), 130.54 (Naph-C_2), 131.13 (Naph-C_{4a}), 132.34 (Ph-C_1), 132.98 (Ph-C_4), 133.66 (Naph-C_{8a}), 148.01 (thiazole-C_4), 157.77 (thiazole-C_2), 157.86 (Pyr-C_6), 157.95 (Pyr-C_4), 169.79 (Pyr-C_2), 170.79 (-*C*OOH). **MS (ESI-):** *m/e* = 537.8 $[M-H]^-$

Characterization of 2-({4-chloro-6-[(4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoic acid (**12**):

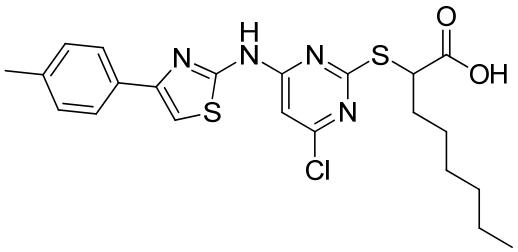


Synthesis Step V; E1: ethyl 2-({4-chloro-6-[(4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (600 mg; 1.22 mmol), LiOH*H_2O (154 mg; 3.66 mmol); Product: white solid; yield: 7% (0.04 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-CH_3, J = 7.50 Hz), 1.27–1.44 (m, 8H, hexyl-CH_2), 1.85–2.02 (m, 2H, hexyl-CH_2), 4.61 (t, 1H, S-C*H*, J = 7.50 Hz), 6.83 (s, 1H, Pyr-H_5), 7.34 (t, 1H, Ph-H_4, J = 7.50 Hz), 7.46 (t, 2H, Ph-$H_{3,5}$, J = 7.50 Hz), 7.74 (s, 1H, thiazole-H_5), 7.93 (d, 2H, Ph-$H_{2,6}$, J = 7.50 Hz), 12.23 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-*C*H_3), 21.91 (Hexyl-*C*H_2), 26.33 (Hexyl-*C*H_2), 28.18 (Hexyl-*C*H_2), 30.91 (Hexyl-*C*H_2), 31.81 (Hexyl-*C*H_2), 47.42 (S-*C*H), 101.84 (Pyr-C_5), 108.56

(thiazole-C_5), 125.63 (Ph-C_4), 127.85 (Ph-$C_{2/6}$), 128.72 (Ph-$C_{3/5}$), 134.10 (Ph-C_1), 149.21 (thiazole-C_4), 157.71 (Pyr-C_6), 157.77 (Pyr-C_4), 170.17 (Pyr-C_2), 172.23 (-*C*OOH). **MS (ESI+):** *m/e* = 463.4 $[M+H]^+$

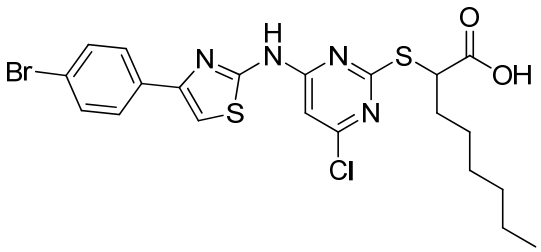
Characterization of 2-[(4-chloro-6-{[4-(4-methylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**13**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-methylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (312 mg; 0.62 mmol), LiOH*H_2O (77 mg; 1.85 mmol); Product: slightly yellow solid; yield: 49% (0.14 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-CH_3, *J* = 7.50 Hz), 1.27–1.44 (m, 8H, hexyl-CH_2), 1.85–2.05 (m, 2H, hexyl-CH_2), 2.34 (s, 3H, Ph-CH_3), 4.61 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.83 (s, 1H, Pyr-H_5), 7.26 (d, 2H, Ph-$H_{3/5}$, *J* = 7.50 Hz), 7.65 (s, 1H, thiazole-H_5), 7.82 (d, 2H, Ph-$H_{2/6}$, *J* = 7.50 Hz), 12.20 (s, 1H, -N*H*), 13.02 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexylhexyl-*C*H_3), 20.77 (Ph-*C*H_3), 21.92 (hexylhexyl-*C*H_2), 26.34 (hexylhexyl-*C*H_2), 28.16 (hexylhexyl-*C*H_2), 30.90 (hexyl-*C*H_2), 31.70 (hexyl-*C*H_2), 47.17 (S-*C*H), 101.87 (Pyr-C_5), 107.71 (thiazole-C_5), 125.58 (Ph-C_1), 129.29 (Ph-$C_{2/6}$), 131.44 (Ph-$C_{3/5}$), 137.18 (Ph-C_4), 149.29 (thiazole-C_4), 157.69 (Pyr-C_6), 157.74 (Pyr-C_4), 170.01 (Pyr-C_2), 172.24 (-*C*OOH). **MS (ESI+):** *m/e* = 477.8 $[M+H]^+$

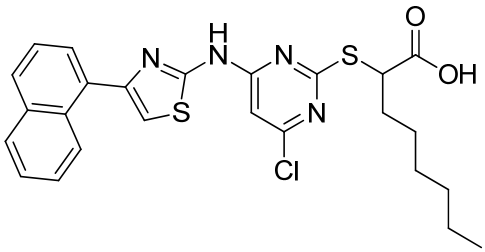
Characterization of 2-[(4-{[4-(4-bromophenyl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoic acid (**14**):



Synthesis Step V; E1: ethyl 2-[(4-{[4-(4-bromophenyl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (200 mg; 0.35 mmol), LiOH*H_2O (44 mg; 1.05 mmol); Product: slightly yellow solid; yield: 26% (0.05 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 6.67 Hz), 1.26–1.42 (m, 8H, hexyl-C*H*$_2$), 1.83–2.00 (m, 2H, hexyl-C*H*$_2$), 4.59 (t, 1H, S-C*H*, *J* = 6.74 Hz), 6.81 (s, 1H, Pyr-*H*$_5$), 7.64 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.39 Hz), 7.79 (s, 1H, thiazole-*H*$_5$), 7.86 (d, 2H, Ph-*H*$_{3/5}$, *J* = 8.39 Hz), 12.22 (s, 1H, -N*H*), 12.98 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.87 (hexyl-*C*H$_3$), 21.96 (hexyl-*C*H$_2$), 26.38 (hexyl-*C*H$_2$), 28.21 (hexyl-*C*H$_2$), 30.95 (hexyl-*C*H$_2$), 31.75 (hexyl-*C*H$_2$), 47.30 (S-*C*H), 101.93 (Pyr-*C*$_5$), 109.45 (thiazole-*C*$_5$), 120.95 (Ph-*C*$_4$), 127.69 (Ph-*C*$_{2/6}$), 131.71 (Ph-*C*$_{3/5}$), 133.35 (Ph-*C*$_1$), 148.06 (thiazole-*C*$_4$), 157.70 (Pyr-*C*$_6$), 157.85 (Pyr-*C*$_4$), 170.11 (Pyr-*C*$_2$), 172.25 (-*C*OOH). **MS (ESI-):** *m/e* = 539.8 $[M-2H]^{2-}$

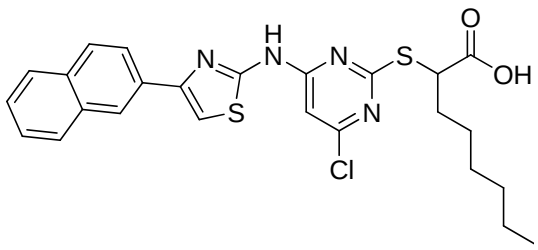
Characterization of 2-[(4-chloro-6-{[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**15**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (400 mg; 0.74 mmol), LiOH*H_2O (155 mg; 3.70 mmol); Product: slightly yellow solid; yield: 90% (0.34 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 6.58 Hz), 1.27–1.45 (m, 8H, hexyl-C*H*$_2$), 1.86–2.03 (m, 2H, hexyl-C*H*$_2$), 4.64 (t, 1H, S-C*H*, *J* = 6.85 Hz), 6.84 (s, 1H, Pyr-*H*$_5$), 7.54 (s, 1H, thiazole-*H*$_5$), 7.54–7.61 (m, 3H, Naph-*H*$_{3,6,7}$), 7.72 (d, 1H, Naph-*H*$_2$, *J* = 7.13 Hz), 7.96–8.01 (m, 2H, Naph-*H*$_{4,5}$), 8.39–8.42 (m, 1H, Naph-*H*$_8$), 12.26 (s, 1H, -N*H*), 13.00 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.89 (hexyl-*C*H$_3$), 21.98 (hexyl-*C*H$_2$), 26.39 (hexyl-*C*H$_2$), 28.23 (hexyl-*C*H$_2$), 30.97 (hexyl-*C*H$_2$), 31.76 (hexyl-*C*H$_2$), 47.23 (S-*C*H), 101.96 (Pyr-*C*$_5$), 112.41 (thiazole-*C*$_5$), 125.50 (Naph-*C*$_2$), 125.85 (Naph-*C*$_7$), 126.00 (Naph-*C*$_6$), 126.29 (Naph-*C*$_3$), 127.21 (Naph-*C*$_4$), 128.31 (Naph-*C*$_8$), 128.53 (Naph-*C*$_5$), 130.57 (Naph-*C*$_{8a}$), 132.52 (Naph-*C*$_{4a}$), 133.53 (Naph-*C*$_1$), 157.80 (Pyr-*C*$_6$), 157.83 (Pyr-*C*$_4$), 170.12 (Pyr-*C*$_2$), 172.30 (-*C*OOH). **MS (ESI-):** *m/e* = 511.8 $[M-H]^-$

Characterization of 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**16**):

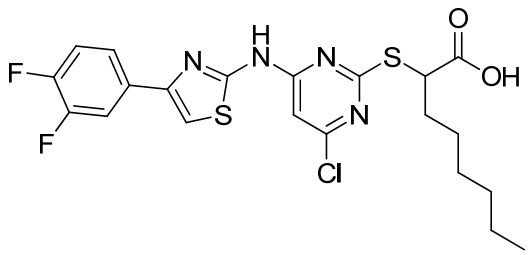


Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (309 mg; 0.57 mmol), LiOH*H_2O (119 mg; 2.86 mmol); Product: slightly yellow solid; yield: 58% (0.17 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.26–1.48 (m, 8H, hexyl-C*H*$_2$), 1.86–2.03 (m, 2H, hexyl-C*H*$_2$), 4.63 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.85 (s, 1H,

Pyr-H_5), 7.50–7.58 (m, 2H, Naph-$H_{6,7}$), 7.89 (s, 1H, thiazole-H_5), 7.92–8.00 (m, 3H, Naph-$H_{3,5,8}$), 8.08 (d, 1H, Naph-H_4, J = 7.50 Hz), 8.46 (s, 1H, Naph-H_1), 12.30 (s, 1H, -N*H*), 13.03 (s, 1H, -COO*H*). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-CH_3), 21.92 (hexyl-CH_2), 26.37 (hexyl-CH_2), 28.17 (hexyl-CH_2), 30.92 (hexyl-CH_2), 31.74 (hexyl-CH_2), 47.23 (S-CH), 101.94 (Pyr-C_5), 109.27 (thiazole-C_5), 123.95 (Naph-C_3), 124.30 (Naph-C_1), 126.16 (Naph-C_6), 126.50 (Naph-C_7), 127.59 (Naph-C_5), 128.15 (Naph-C_8), 128.26 (Naph-C_4), 131.58 (Naph-C_2), 132.55 (Naph-C_{4a}), 133.12 (Naph-C_{8a}), 149.15 (thiazole-C_4), 157.75 (Pyr-C_6), 157.82 (Pyr-C_4), 170.08 (Pyr-C_2), 172.22 (-COOH). **MS (ESI-):** *m/e* = 511.8 $[M-H]^-$

Characterization of 2-[(4-chloro-6-{[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**17**):

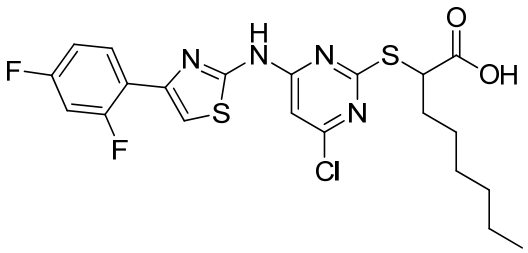


Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (301 mg; 0.57 mmol), LiOH*H_2O (120 mg; 2.86 mmol); Product: yellow solid; yield: 87% (0.25 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-CH_3, J = 7.50 Hz), 1.27–1.44 (m, 8H, hexyl-CH_2), 1.85–2.00 (m, 2H, hexyl-CH_2), 4.60 (t, 1H, S-C*H*, J = 7.50 Hz), 6.83 (s, 1H, Pyr-H_5), 7.52 (dd, 1H, Ph-H_5), 7.77 (m, 1H, Ph-H_2), 7.83 (s, 1H, thiazole-H_5), 7.88–7.97 (m, 1H, Ph-H_6), 12.21 (s, 1H, -N*H*), 12.99 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-CH_3), 21.92 (hexyl-CH_2), 26.34 (hexyl-CH_2), 28.15 (hexyl-CH_2), 30.90 (hexyl-CH_2), 31.66 (hexyl-CH_2), 47.19 (S-CH), 101.93 (Pyr-C_5), 109.65 (thiazole-C_5), 114.45 (Ph-C_2), 117.90 (Ph-C_5), 122.35 (Ph-C_6), 131.81 (Ph-C_1), 147.02 (thiazole-C_4), 147.69 (Ph-C_4),

150.94 (Ph-C_3), 157.63 (thiazole-C_2), 157.82 (Pyr-C_6), 157.84 (Pyr-C_4), 170.00 (Pyr-C_2), 172.21 (-*C*OOH). **MS (ESI-):** *m/e* = 497.12 $[M-H]^-$

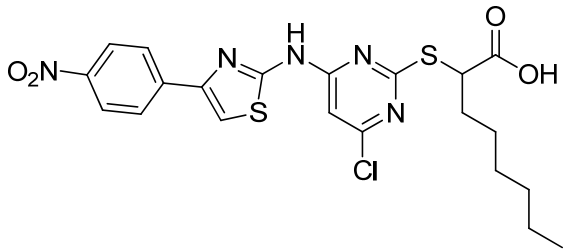
Characterization of 2-[(4-chloro-6-{[4-(2,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**18**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(2,4-difluorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (92 mg; 0.18 mmol), LiOH*H_2O (37 mg; 0.87 mmol); Product: yellow solid; yield: 86% (0.08 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.25–1.41 (m, 8H, hexyl-C*H*$_2$), 1.82–1.99 (m, 2H, hexyl-C*H*$_2$), 4.57 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.82 (s, 1H, Pyr-H_5), 7.20 (m, 1H, Ph-H_3), 7.37 (m, 1H, Ph-H_5), 7.56 (s, 1H, thiazole-H_5), 8.05 (m, 1H, Ph-H_6), 12.19 (s, 1H, -N*H*), 12.95 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.85 (hexyl-*C*H$_3$), 21.96 (hexyl-*C*H$_2$), 26.36 (hexyl-*C*H$_2$), 28.20 (hexyl-*C*H$_2$), 30.95 (hexyl-*C*H$_2$), 31.67 (Hexyl-*C*H$_2$), 47.24 (S-*C*H), 101.98 (Pyr-C_5), 104.69 (Ph-C_3), 111.99 (Ph-C_5), 112.49 (thiazole-C_5), 118.68 (Ph-C_1), 130.38 (Ph-C_1), 142.17 (thiazole-C_4), 157.28 (thiazole-C_2), 157.70 (Pyr-C_6), 157.88 (Pyr-C_4), 158.88 (Ph-C_2), 162.19 (Ph-C_4), 170.03 (Pyr-C_2), 172.24 (-*C*OOH). **MS (ESI-):** *m/e* = 497.9 $[M-H]^-$

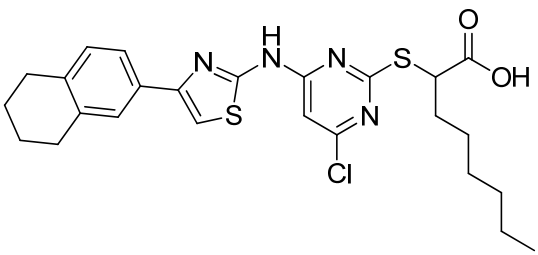
Characterization of 2-[(4-chloro-6-{[4-(4-nitrophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**19**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-nitrophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (170 mg; 0.32 mmol), LiOH*H_2O (108 mg; 2.57 mmol); Product: yellow solid; yield: 88% (0.14 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.26–1.43 (m, 8H, hexyl-C*H*$_2$), 1.87–1.99 (m, 2H, hexyl-C*H*$_2$), 4.58 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.82 (s, 1H, Pyr-*H*$_5$), 8.09 (s, 1H, thiazole-*H*$_5$), 8.17 (d, 2H, Ph-*H*$_{2/6}$, *J* = 10.00 Hz), 8.32 (d, 2H, Ph-*H*$_{3/5}$, *J* = 10.00 Hz), 12.31 (s, 1H, -N*H*), 13.00 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.85 (hexyl-*C*H$_3$), 21.94 (hexyl-*C*H$_2$), 26.36 (hexyl-*C*H$_2$), 28.17 (hexyl-*C*H$_2$), 30.92 (hexyl-*C*H$_2$), 31.65 (hexyl-*C*H$_2$), 47.25 (S-*C*H), 102.03 (Pyr-*C*$_5$), 113.08 (thiazole-*C*$_5$), 124.24 (Ph-*C*$_3$/*C*$_5$), 126.53 (Ph-*C*$_2$/*C*$_6$), 140.01 (Ph-*C*$_1$), 146.50 (Ph-*C*$_4$), 147.07 (thiazole-*C*$_4$), 157.68 (Pyr-*C*$_6$), 157.92 (Pyr-*C*$_4$), 158.22 (thiazole-*C*$_2$), 170.04 (Pyr-*C*$_2$), 172.21 (-*C*OOH). **MS (ESI-):** *m/e* = 506.9 $[M-H]^-$

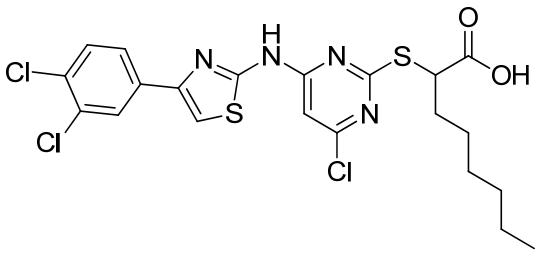
Characterization of 2-[(4-chloro-6-{[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**20**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (228 mg; 0.42 mmol), LiOH*H_2O (145 mg; 3.46 mmol); Product: yellow solid; yield: 45% (0.10 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 6.25 Hz), 1.26–1.42 (m, 8H, hexyl-C*H*$_2$), 1.75 (m, 4H, naphthyl-*H*$_{6/7}$), 1.86–1.98 (m, 2H, hexyl-C*H*$_2$), 2.73–2.76 (m, 4H, naphthyl-*H*$_{5/8}$), 4.60 (t, 1H, S-C*H*, *J* = 6.25 Hz), 6.79 (s, 1H, Pyr-*H*$_5$), 7.10 (d, 1H, Naph-*H*$_4$, *J* = 7.50 Hz), 7.60 (m, 3H, Naph-*H*$_{1/3}$, thiazole-*H*$_5$), 12.18 (s, 1H, -N*H*), 12.96 (s, 1H, -COO*H*). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 13.84 (hexyl-*C*H$_3$), 21.93 (hexyl-*C*H$_2$), 22.70 (Naph-*C*$_{6/7}$), 26.35 (hexyl-*C*H$_2$), 28.18 (hexyl-*C*H$_2$), 28.58 (Naph-*C*$_5$), 28.87 (Naph-*C*$_8$), 30.92 (hexyl-*C*H$_2$), 31.74 (hexyl-*C*H$_2$), 47.20 (S-*C*H), 101.86 (Pyr-*C*$_5$), 107.52 (thiazole-*C*$_5$), 122.88 (Naph-*C*$_3$), 126.25 (Naph-*C*$_4$), 129.25 (Naph-*C*$_1$), 131.41 (Naph-*C*$_1$), 136.48 (Naph-*C*$_{4a}$), 136.80 (Naph-*C*$_{8a}$), 149.47 (thiazole-*C*$_4$), 157.41 (thiazole-*C*$_2$), 157.70 (Pyr-*C*$_6$), 157.75 (Pyr-*C*$_4$), 170.05 (Pyr-*C*$_2$), 172.24 (-*C*OOH). **MS (ESI-):** *m/e* = 516.0 $[M-H]^-$

Characterization of 2-[(4-chloro-6-{[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**21**):

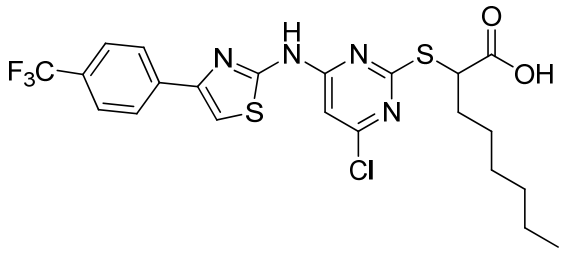


Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (162 mg; 0.29 mmol), LiOH*H_2O (60 mg; 1.43 mmol); Product: slightly yellow solid; yield: 44% (0.07 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.85 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.25–1.44 (m, 8H, hexyl-C*H*$_2$), 1.84–2.02 (m, 2H, hexyl-C*H*$_2$), 4.59 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.81 (s, 1H,

Pyr-H_5), 7.71 (d, 1H, Ph-H_5, J = 7.50 Hz), 7.90 (dd, 1H, Ph-H_6, J = 7.50 Hz), 7.93 (s, 1H, thiazole-H_5), 8.15 (s, 1H, Ph-H_2), 12.23 (s, 1H, -N*H*), 13.00 (s, 1H, -COO*H*). **^{13}C-NMR (62.90 MHz, $(CD_3)_2SO$)** δ: 13.82 (hexyl-*C*H_3), 21.92 (hexyl-*C*H_2), 26.35 (hexyl-*C*H_2), 28.16 (hexyl-*C*H_2), 30.91 (hexyl-*C*H_2), 31.71 (hexyl-*C*H_2), 47.27 (S-*C*H), 101.95 (Pyr-C_5), 110.64 (thiazole-C_5), 125.66 (Ph-C_6), 127.33 (Ph-C_2), 130.09 (Ph-C_5), 130.99 (Ph-C_3), 131.56 (Ph-C1), 134.68 (Ph-C_4), 146.63 (thiazole-C_4), 157.64 (Pyr-C_6), 157.88 (Pyr-C_4), 157.95 (thiazole-C_2), 170.07 (Pyr-C_2), 172.18 (-*C*OOH). **MS (ESI-):** *m/e* = 529.4 $[M-H]^-$

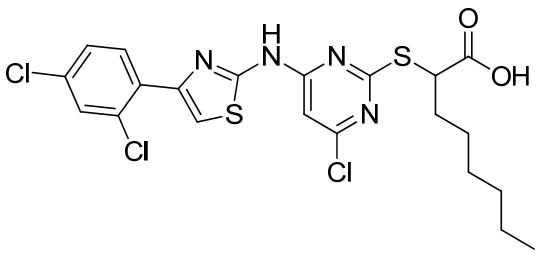
Characterization of 2-{[4-chloro-6-({4-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoic acid (**22**):



Synthesis Step V; E1: ethyl 2-{[4-chloro-6-({4-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoate (200 mg; 0.36 mmol), LiOH*H_2O (81 mg; 3.13 mmol); Product: slightly yellow solid; yield: 25% (0.05 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.81 (t, 3H, hexyl-CH_3, J = 6.37 Hz), 1.24–1.41 (m, 8H, hexyl-CH_2), 1.82–2.01 (m, 2H, hexyl-CH_2), 4.57 (t, 1H, S-C*H*, J = 7.50 Hz), 6.80 (s, 1H, Pyr-H_5), 7.78 (d, 2H, Ph-$H_{2/6}$, J = 8.47 Hz), 7.88 (s, 1H, thiazole-H_5), 8.09 (d, 2H, Ph-$H_{3/5}$, J = 8.47 Hz), 12.22 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 14.05 (hexyl-*C*H_3), 22.15 (hexyl-*C*H_2), 26.56 (hexyl-*C*H_2), 28.36 (hexyl-*C*H_2), 31.13 (hexyl-*C*H_2), 31.86 (hexyl-*C*H_2), 47.47 (S-*C*H), 102.18 (Pyr-C_5), 111.34 (thiazole-C_5), 125.93 (-*C*F_3), 126.45 (Ph-C_4), 127.93 (Ph-$C_{3/5}$), 128.36 (Ph-$C_{2/6}$), 137.99 (Ph-C_1), 147.89 (thiazole-C_4), 157.88 (thiazole-C_2), 158.17 (Pyr-C_6), 158.23 (Pyr-C_4), 170.26 (Pyr-C_2), 172.55 (-*C*OOH). **MS (ESI-):** *m/e* = 529.4 $[M-H]^-$

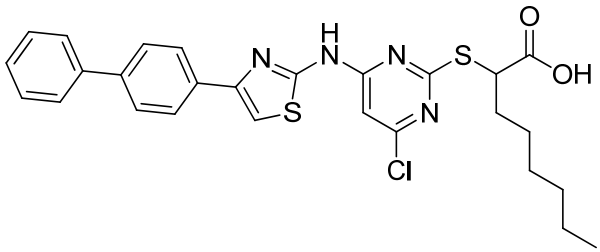
Characterization of 2-[(4-chloro-6-{[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**23**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(2,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (162 mg; 0.29 mmol), LiOH*H_2O (61 mg; 1.45 mmol); Product: yellow solid; yield: 91% (0.14 g).

^{1}H-NMR (300.03 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 6.70 Hz), 1.24–1.43 (m, 8H, hexyl-C*H*$_2$), 1.84–2.00 (m, 2H, hexyl-C*H*$_2$), 4.59 (t, 1H, S-C*H*, *J* = 6.93 Hz), 6.82 (s, 1H, Pyr-*H*$_5$), 7.53 (dd, 1H, Ph-*H*$_5$, ^3J = 8.61 Hz), 7.72 (d, 1H, Ph-*H*$_3$, ^4J = 2.15 Hz), 7.75 (s, 1H, thiazole-*H*$_5$), 7.89 (d, 1H, Ph-*H*$_6$, J = 8.50 Hz), 12.23 (s, 1H, -N*H*), 12.96 (s, 1H, -COO*H*).
^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$) δ: 13.85 (Hexyl-*C*H$_3$), 21.95 (Hexyl-*C*H$_2$), 26.35 (Hexyl-*C*H$_2$), 28.19 (Hexyl-*C*H$_2$), 30.94 (Hexyl-*C*H$_2$), 31.68 (Hexyl-*C*H$_2$), 47.23 (S-*C*H), 101.95 (Pyr-*C*$_5$), 113.90 (thiazole-*C*$_5$), 127.60 (Ph-*C*$_5$), 129.81 (Ph-*C*$_1$), 131.80 (Ph-*C*$_6$), 131.83 (Ph-*C*$_3$), 132.28 (Ph-*C*$_2$), 132.93 (Ph-*C*$_4$), 144.85 (thiazole-*C*$_4$), 157.03 (thiazole-*C*$_2$), 157.70 (Pyr-*C*$_6$), 157.89 (Pyr-*C*$_4$), 170.06 (Pyr-*C*$_2$), 172.23 (-*C*OOH). **MS (ESI-):** *m/e* = 531.0 $[M-H]^-$

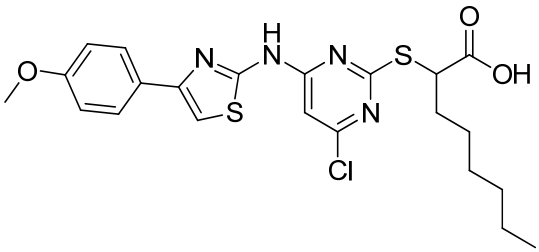
Characterization of 2-[(4-chloro-6-{[4-(4-phenylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**24**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-phenylphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (175 mg; 0.31 mmol), LiOH*H_2O (65 mg; 1.54 mmol); Product: yellow solid; yield: 81% (0.14 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.38 Hz), 1.23–1.42 (m, 8H, hexyl-C*H*$_2$), 1.83–2.00 (m, 2H, hexyl-C*H*$_2$), 4.60 (t, 1H, S-C*H*, *J* = 7.07 Hz), 6.82 (s, 1H, Pyr-*H*$_5$), 7.36 (t, 1H, Biph-*H*‘$_4$, *J* = 7.25 Hz), 7.47 (t, 2H, Biph-*H´*$_3$/*H´*$_5$, *J* = 7.34 Hz), 7.70–7.76 (m, 4H, Biph-*H*$_3$/*H*$_5$/*H´*$_2$/*H´*$_6$), 7.78 (s, 1H, thiazole-*H*$_5$), 8.00 (d, 2H, Biph-*H*$_2$/*H*$_6$, *J* = 8.42 Hz), 12.20 (s, 1H, -N*H*), 12.96 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexylhexyl-*C*H$_3$), 21.92 (hexylhexyl-*C*H$_2$), 26.34 (hexyl-*C*H$_2$), 28.16 (hexyl-*C*H$_2$), 30.91 (hexyl-*C*H$_2$), 31.71 (hexyl-*C*H$_2$), 47.19 (S-*C*H), 101.91 (Pyr-*C*$_5$), 108.77 (thiazole-*C*$_5$), 126.21 (Biph-*C*$_3$/*C*$_5$), 126.47 (Biph-*C´*$_2$/*C´*$_6$), 126.95 (Biph-*C*$_2$/*C*$_6$), 127.51 (Biph-*C´*$_4$), 128.94 (Biph-*C´*$_3$/*C´*$_5$), 133.20 (Biph-*C*$_1$), 139.38 (Biph-*C´*$_1$), 139.52 (Biph-*C*$_4$), 148.86 (thiazole-*C*$_4$), 157.68 (thiazole-*C*$_2$), 157.71 (Pyr-*C*$_6$), 157.79 (Pyr-*C*$_4$), 170.04 (Pyr-*C*$_2$), 172.23 (-*C*OOH). **MS (ESI-):** *m/e* = 537.1 $[M-H]^-$

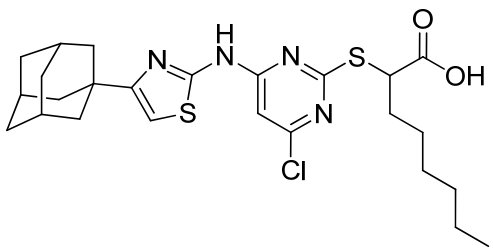
Characterization of 2-[(4-chloro-6-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoic acid (**25**):



Synthesis Step V; E1: ethyl 2-[(4-chloro-6-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}pyrimidin-2-yl)sulfanyl]octanoate (310 mg; 0.60 mmol), LiOH*H_2O (125 mg; 2.97 mmol); Product: yellow solid; yield: 85% (0.25 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.41 Hz), 1.26–1.42 (m, 8H, hexyl-C*H*$_2$), 1.83–2.00 (m, 2H, hexyl-C*H*$_2$), 3.79 (s, 3H, -O-C*H*$_3$), 4.60 (t, 1H, S-C*H*, *J* = 6.87 Hz), 6.81 (s, 1H, Pyr-*H*$_5$), 7.00 (d, 2H, Ph-*H*$_{3/5}$, *J* = 8.89 Hz), 7.56 (s, 1H, thiazole-*H*$_5$), 7.84 (d, 2H, Ph-*H*$_{2/6}$, *J* = 8.79 Hz), 12.18 (s, 1H, -N*H*), 13.00 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.88 (hexyl-*C*H$_3$), 21.97 (hexyl-*C*H$_2$), 26.39 (hexyl-*C*H$_2$), 28.21 (hexyl-*C*H$_2$), 30.96 (hexyl-*C*H$_2$), 31.75 (hexyl-*C*H$_2$), 47.20 (S-*C*H), 55.16 (-O-*C*H$_3$), 101.90 (Pyr-*C*$_5$), 106.59 (thiazole-*C*$_5$), 114.13 (Ph-*C*$_{3/5}$), 126.97 (Ph-*C*$_1$), 127.02 (Ph-*C*$_{2/6}$), 149.15 (thiazole-*C*$_4$), 157.49 (thiazole-*C*$_2$), 157.72 (Pyr-*C*$_6$), 157.77 (Pyr-*C*$_4$), 159.05 (Ph-*C*$_4$), 170.06 (Pyr-*C*$_2$), 172.28 (-*C*OOH). **MS (ESI-):** *m/e* = 491.3 $[M-H]^-$

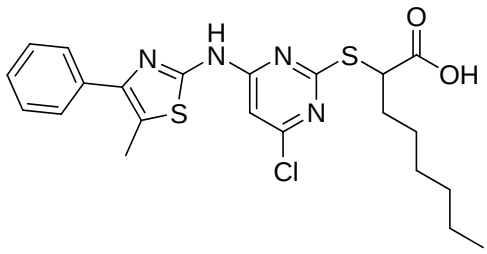
Characterization of 2-[(4-{[4-(adamantan-1-yl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoic acid (**26**):



Synthesis Step V; E1: ethyl 2-[(4-{[4-(adamantan-1-yl)-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (250 mg; 0.46 mmol), LiOH*H_2O (95 mg; 2.28 mmol); Product: white solid; yield: 82% (0.19 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 6.35 Hz), 1.24–1.41 (m, 8H, hexyl-C*H*$_2$), 1.72–2.03 (m, 17H, hexyl-C*H*$_2$, Adamantyl-*H*$_{2/3/4/5/6/7/8/9/10}$), 4.60 (t, 1H, S-C*H*, *J* = 6.91 Hz), 6.76 (s, 2H, Pyr-*H*$_5$, thiazole-*H*$_5$), 12.32 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.86 (hexyl-*C*H$_3$), 21.97 (hexyl-*C*H$_2$), 26.27 (hexyl-*C*H$_2$), 27.92 (Adamantyl-*C*$_{3/5/7}$), 28.46 (hexyl-*C*H$_2$), 31.07 (hexyl-*C*H$_2$), 32.66 (hexyl-*C*H$_2$), 35.83 (Adamantyl-*C*$_{4/6/10}$), 36.33 (Adamantyl-*C*$_{2/8/9}$), 41.58 (Adamantyl-*C*$_1$), 49.07 (S-*C*H), 101.23 (Pyr-*C*$_5$), 104.99 (thiazole-*C*$_5$), 157.12 (thiazole-*C*$_2$), 157.48 (Pyr-*C*$_6$), 157.75 (Pyr-*C*$_4$), 160.74 (thiazole-*C*$_4$), 171.26 (Pyr-*C*$_2$), 172.11 (-*C*OOH). **MS (ESI+):** *m/e* = 519.8 [M-H]$^-$

Characterization of 2-({4-chloro-6-[(5-methyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoic acid (**27**):

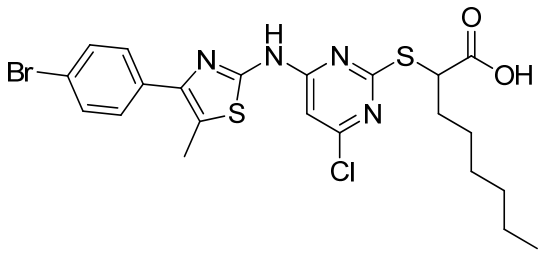


Synthesis Step V; E1: ethyl 2-({4-chloro-6-[(5-methyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (211 mg; 0.42 mmol), LiOH*H_2O (88 mg; 2.08 mmol); Product: yellow solid; yield: 54% (0.11 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 5.00 Hz), 1.19–1.42 (m, 8H, hexyl-C*H*$_2$), 1.86–2.00 (m, 2H, hexyl-C*H*$_2$), 4.57 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.75 (s, 1H, Pyr-*H*$_5$), 7.34 (t, 1H, Ph-*H*$_4$, *J* = 7.50 Hz), 7.45 (t, 2H, Ph- *H*$_{3/5}$, *J* = 7.50 Hz), 7.65 (d, 2H, Ph-*H*$_{2/6}$, *J* = 7.50 Hz), 12.04 (s, 1H, -N*H*), 12.97 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz,**

$(CD_3)_2SO$) δ: 11.79 (thiazole-*C*H_3), 13.83 (hexyl-*C*H_3), 21.92 (hexyl-*C*H_2), 26.44 (hexyl-*C*H_2), 28.14 (hexyl-*C*H_2), 30.93 (hexyl-*C*H_2), 31.77 (hexyl-*C*H_2), 47.17 (S-*C*H), 101.69 (Pyr-C_5), 121.62 (thiazole-C_5), 127.32 (Ph-C_4), 127.90 (Ph-C_2/C_6), 128.37 (Ph-C_3/C_5), 134.61 (Ph-C_1), 144.47 (thiazole-C_4), 153.65 (thiazole-C_2), 157.59 (Pyr-C_6), 157.66 (Pyr-C_4), 169.98 (Pyr-C_2), 172.24 (-*C*OOH). **MS (ESI-):** *m/e* = 477.62 $[M+H]^+$

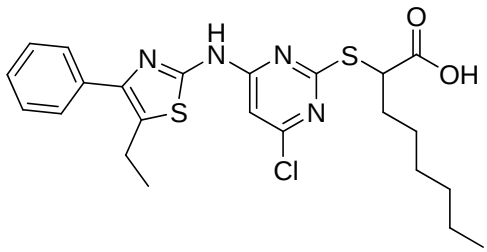
Characterization of 2-[(4-{[4-(4-bromophenyl)-5-methyl-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoic acid (**28**):



Synthesis Step V; E1: ethyl 2-[(4-{[4-(4-bromophenyl)-5-methyl-1,3-thiazol-2-yl]amino}-6-chloropyrimidin-2-yl)sulfanyl]octanoate (300 mg; 0.51 mmol), LiOH*H_2O (173 mg; 4.12 mmol); Product: white solid; yield: 78% (0.22 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.26–1.43 (m, 8H, hexyl-C*H*$_2$), 1.87–1.99 (m, 2H, hexyl-C*H*$_2$), 4.56 (t, 1H, S-C*H*, *J* = 7.50 Hz), 6.75 (s, 1H, Pyr-H_5), 7.61 (d, 2H, Ph-$H_{2/6}$, *J* = 10.00 Hz), 7.66 (d, 2H, Ph-$H_{3/5}$, *J* = 10.00 Hz), 12.07 (s, 1H, -N*H*), 12.97 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 11.79 (thiazole-*C*H_3), 13.85 (hexyl-*C*H_3), 21.94 (hexyl-*C*H_2), 26.46 (hexyl-*C*H_2), 28.16 (hexyl-*C*H_2), 30.95 (hexyl-*C*H_2), 31.78 (hexyl-*C*H_2), 47.24 (S-*C*H), 101.70 (Pyr-C_5), 120.54 (thiazole-C_5), 122.46 (Ph-C_4), 129.91 (Ph-C_2/C_6), 131.96 (Ph-C_3/C_5), 133.84 (Ph-C_1), 143.30 (thiazole-C_4), 153.81 (thiazole-C_2), 157.55 (Pyr-C_6), 157.72 (Pyr-C_4), 170.03 (Pyr-C_2), 172.24 (-*C*OOH). **MS (ESI-):** *m/e* = 553.9 $[M-H]^-$

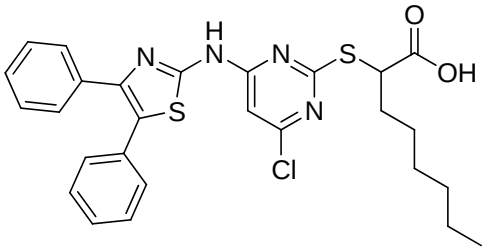
Characterization of 2-({4-chloro-6-[(5-ethyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoic acid (**29**):



Synthesis Step V; E1: ethyl 2-({4-chloro-6-[(5-ethyl-4-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (488 mg; 0.94 mmol), LiOH*H_2O (113 mg; 2.69 mmol); Product: white solid; yield: 87% (0.40 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.84 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.26–1.44 (m, 11H, hexyl-C*H*$_2$, ethyl-thiazol-C*H*$_3$), 1.84–2.02 (m, 2H, hexyl-C*H*$_2$), 2.92 (q, 2H, ethyl-thiazol-C*H*$_2$, *J* = 7.45 Hz), 4.67 (t, 1H, S-C*H*, *J* = 6.85 Hz), 6.76 (s, 1H, Pyr-*H*$_5$), 7.36 (t, 1H, Ph-*H*$_4$, *J* = 7.19 Hz), 7.46 (t, 2H, Ph-*H*$_{3/5}$, *J* = 7.35 Hz), 7.60 (d, 2H, Ph-*H*$_{2/6}$, J = 6.84 Hz), 12.06 (s, 1H, -N*H*), 12.97 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-*C*H$_3$), 16.30 (Thiazol-CH$_2$-*C*H$_3$), 19.88 (Thiazol-*C*H$_2$-CH$_3$), 21.93 (hexyl-*C*H$_2$), 26.41 (hexyl-*C*H$_2$), 28.17 (hexyl-*C*H$_2$), 30.94 (hexyl-*C*H$_2$), 31.87 (hexyl-*C*H$_2$), 47.14 (S-*C*H), 101.70 (Pyr-*C*$_5$), 127.48 (thiazole-*C*$_5$), 128.06 (Ph-*C*$_2$/*C*$_6$), 128.43 (Ph-*C*$_3$/*C*$_5$), 129.45 (Ph-*C*$_4$), 134.76 (Ph-*C*$_1$), 144.03 (thiazole-*C*$_4$), 154.02 (thiazole-*C*$_2$), 157.68 (Pyr-*C*$_6$), 157.70 (Pyr-*C*$_4$), 170.11 (Pyr-*C*$_2$), 172.29 (-*C*OOH). **MS (ESI-):** *m/e* = 491.19 [M]

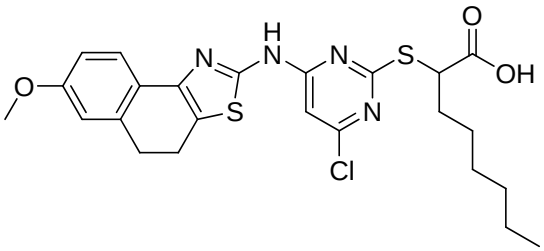
Characterization of 2-({4-chloro-6-[(4,5-diphenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoic acid (**30**):



Synthesis Step V; E1: ethyl 2-({4-chloro-6-[(4,5-diphenyl-1,3-thiazol-2-yl)amino]pyrimidin-2-yl}sulfanyl)octanoate (138 mg; 0.24 mmol), LiOH*H_2O (51 mg; 1.22 mmol); Product: white solid; yield: 66% (0.09 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.79 (t, 3H, hexyl-C*H*$_3$, *J* = 6.67 Hz), 1.16–1.36 (m, 8H, hexyl-C*H*$_2$), 1.81–1.97 (m, 2H, hexyl-C*H*$_2$), 4.60 (t, 1H, S-C*H*, *J* = 7.05 Hz), 6.79 (s, 1H, Pyr-*H*$_5$), 7.30–7.47 (m, 10H, Ph-*H*), 12.31 (s, 1H, -N*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.83 (hexyl-*C*H$_3$), 21.90 (hexyl-*C*H$_2$), 26.46 (hexyl-*C*H$_2$), 28.16 (hexyl-*C*H$_2$), 30.86 (hexyl-*C*H$_2$), 31.88 (hexyl-*C*H$_2$), 47.12 (S-*C*H), 101.98 (Pyr-*C*$_5$), 126.08 (thiazole-*C*$_5$), 127.82 (Ph´-*C*$_4$), 128.02 (Ph-*C*$_4$), 128.31 (Ph´-*C*$_{2/6}$), 128.41 (Ph-*C*$_{2/6}$), 128.93 (Ph´-*C*$_{3/5}$), 129.21 (Ph-*C*$_{3/5}$), 131.60 (Ph-*C*$_1$), 134.49 (Ph´-*C*$_1$), 144.19 (thiazole-*C*$_4$), 155.48 (thiazole-*C*$_2$), 157.58 (Pyr-*C*$_6$), 157.85 (Pyr-*C*$_4$), 170.14 (Pyr-*C*$_2$), 172.22 (-*C*OOH). **MS (ESI-):** *m/e* = 537.1 [M-H]$^-$

Characterization of 2-{[4-chloro-6-({7-methoxy-4*H*,5*H*-naphtho[1,2-d][1,3]thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoic acid (**31**):



Synthesis Step V; E1: ethyl 2-{[4-chloro-6-({7-methoxy-4*H*,5*H*-naphtho[1,2-d][1,3]thiazol-2-yl}amino)pyrimidin-2-yl]sulfanyl}octanoate (173 mg; 0.32 mmol), LiOH*H_2O (108 mg; 2.57 mmol); Product: yellow solid; yield: 15% (0.03 g).

^{1}H-NMR (250.13 MHz, $(CD_3)_2SO$) δ: 0.83 (t, 3H, hexyl-C*H*$_3$, *J* = 7.50 Hz), 1.25–1.41 (m, 8H, hexyl-C*H*$_2$), 1.85–1.97 (m, 2H, hexyl-C*H*$_2$), 2.88–2.96 (m, 4H, Naph-*H*$_{4/5}$), 3.76 (s, 3H, O-C*H*$_3$), 4.55 (t, 1H, S-C*H*, *J* = 6.25 Hz), 6.78–6.86 (m, 3H, Pyr-*H*$_5$, Naph-*H*$_{6/8}$), 7.57 (d, 1H, Naph-*H*$_9$, *J* = 7.50 Hz), 12.10 (s, 1H, N-*H*), 12.92 (s, 1H, -COO*H*). **^{13}C-NMR (75.44 MHz, $(CD_3)_2SO$)** δ: 13.85 (hexyl-*C*H$_3$), 20.69 (Naph-*C*$_4$), 21.94 (hexyl-*C*H$_2$), 26.45 (hexyl-*C*H$_2$), 28.16 (hexyl-*C*H$_2$), 28.55 (Naph-*C*$_5$), 30.95 (hexyl-*C*H$_2$), 31.78 (hexyl-*C*H$_2$), 47.20 (S-*C*H), 55.06 (O-*C*H$_3$), 101.81 (Pyr-*C*$_5$), 111.82 (Naph-*C*$_8$), 114.01 (Naph-*C*$_6$), 121.51 (thiazole-*C*$_5$), 123.24 (Naph-*C*$_9$), 123.97 (Naph-*C*$_{9a}$), 136.52 (Naph-*C*$_{5a}$), 143.72 (thiazole-*C*$_4$), 155.65 (thiazole-*C*$_2$), 157.55 (Pyr-*C*$_6$), 157.76 (Pyr-*C*$_4$), 158.45 (Naph-*C*$_7$), 169.97 (Pyr-*C*$_2$), 172.25 (-*C*OOH). **MS (ESI-):** *m/e* = 518.0 [M-H]$^-$

Combustion Analysis of tested compounds

	Expected				Found			
Compounds	C, %	H, %	N, %	S, %	C, %	H, %	N, %	S, %
6	50.70	4.46	11.26	12.89	50.49	4.41	11.18	13.05
7	48.62	3.87	11.94	13.66	48.79	3.94	12.06	13.50
8	46.26	3.20	12.69	14.53	46.01	3.35	12.69	14.41
9	55.20	3.75	12.26	14.03	54.83	3.73	11.97	13.94
10	43.59	2.44	13.56	15.52	43.37	2.53	13.31	15.39
11	55.66	2.99	10.39	11.89	55.44	3.05	10.31	11.73
12	54.47	5.01	12.10	13.85	54.21	5.08	11.97	13.57
13	55.39	5.28	11.74	13.44	55.35	5.45	11.79	13.53
14	46.54	4.09	10.34	11.83	46.48	4.16	10.06	11.80
15	58.52	4.91	10.92	12.50	58.29	5.01	10.71	12.57
16	58.52	4.91	10.92	12.50	58.23	4.92	10.84	12.63
17	50.55	4.24	11.23	12.85	50.60	4.39	11.15	12.55
18	50.55	4.24	11.23	12.85	50.23	4.12	11.03	12.51
19	49.65	4.36	13.79	12.62	49.68	4.34	13.53	12.45
20	58.07	5.65	10.83	12.40	57.85	5.64	10.54	12.30
21	47.42	3.98	10.53	12.06	47.42	4.14	10.25	11.99

22	49.76	4.18	10.55	12.08	49.37	4.12	10.33	11.84
23	47.42	3.98	10.53	12.06	47.68	4.08	10.20	12.31
24	60.15	5.05	10.39	11.90	60.27	5.16	10.02	11.95
25	53.59	5.11	11.36	13.01	53.50	5.09	11.05	12.62
26	57.62	6.38	10.75	12.31	57.37	6.27	10.45	12.36
27	55.39	5.28	11.74	13.44	55.51	5.43	11.49	13.18
28	47.53	4.35	10.08	11.54	47.72	4.40	9.77	11.27
29	56.25	5.54	11.41	13.06	56.22	5.52	11.19	13.35
30	60.15	5.05	10.39	11.90	59.96	5.14	10.12	11.57
31	55.53	5.24	10.79	12.35	55.49	5.16	10.49	12.10

II Figures S1-5

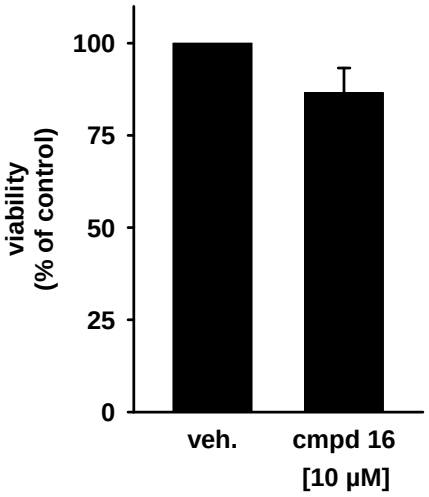


Figure S1. Effects of compound **16** on cellular integrity of PMNL. Cells were treated with 10 µM compound **16** for 1 h at 37 °C, stained with trypan blue and analysed by light microscopy. Data are given as mean ± S.E.M. obtained in 3 independent experiments.

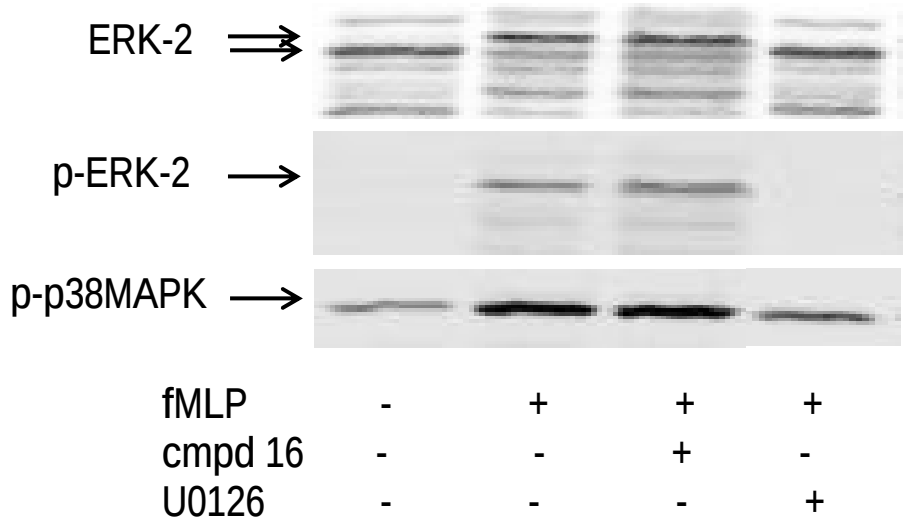


Figure S2. Effects of compound **16** on the activation of MAPK. Isolated PMNL were preincubated with compound **16** (10 µM) or U0126 (3 µM) at 37 °C for 10 min. Then fMLP (100 nM) was added and the reaction was stopped after 1.5 min. Total cell lsyates were analysed by Western blot for ERK-2, phospho-ERK-2 and phospho-p38MAPK. Data shown are representative for at least 3 independent experiments.

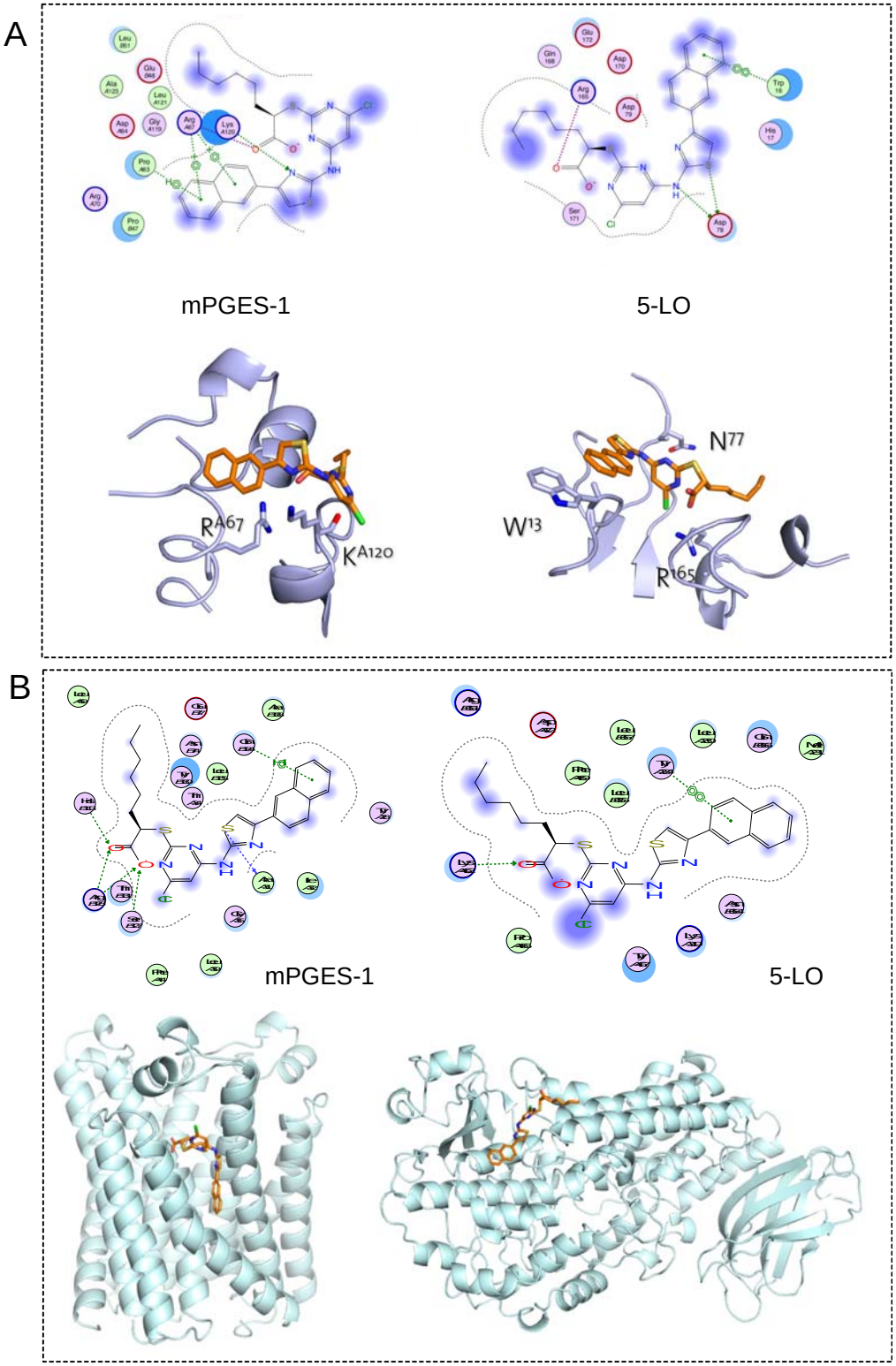


Figure S3. A) Automatically generated docking poses of compound **16**-*R* in the hypothetical most similar binding pockets found by PoLiMorph on the surfaces of mPGES-1 (PDB ID: 4al0) and 5-LO (PDB ID: 3o8y). Potentially interacting side-chains are highlighted (lower panel). **B)** Interaction plots for the automatically generated docking poses of compound **16**-*R* in the overall best matching binding pockets on the surfaces of mPGES-1 (PDB ID: 4al0) and 5-LO (PDB ID: 3o8y). Note that in the interaction plots for 5-LO the residue numbering is shifted compared to the literature standard (*e.g.* W13 is W16 in our plots).

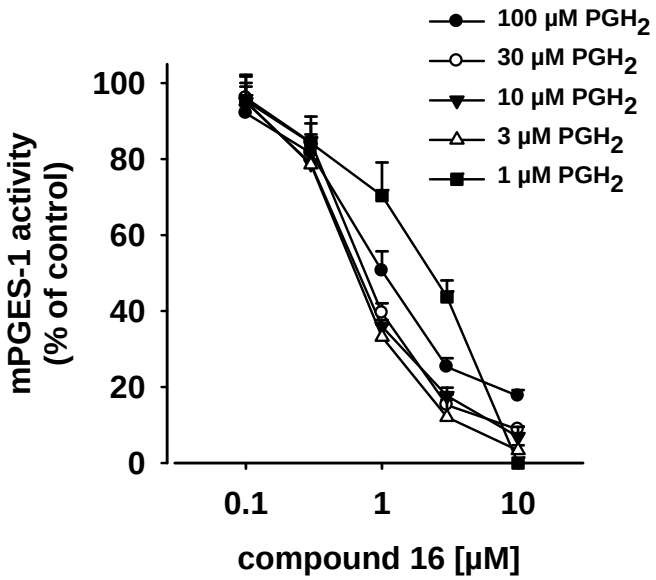
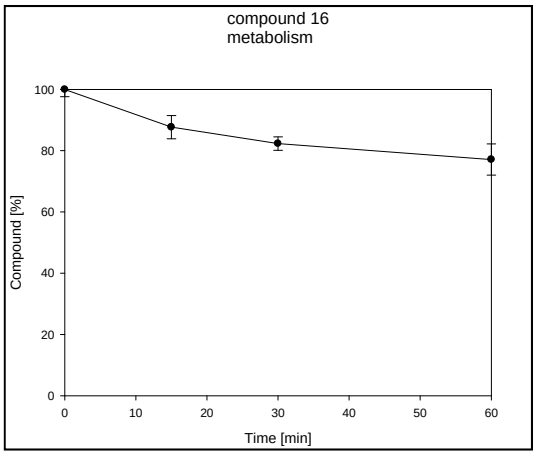
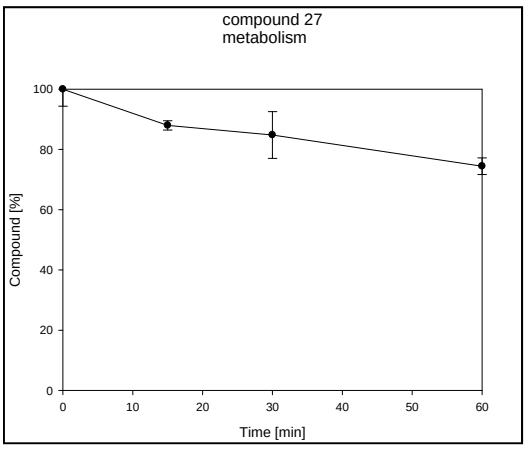


Figure S4. Inhibition of mPGES-1 activity by compound **16** at various substrate concentrations. Microsomal preparations of IL-1β stimulated A549 cells were preincubated with compound **16** or vehicle (0.5% DMSO) for 15 min at 4 °C and the reaction was started by addition of PGH_2 at the indicated concentrations. After 1 min at 4 °C the reaction was terminated. Data are expressed as percentage of control (100%), means ± S.E., n = 3.

A



B



C

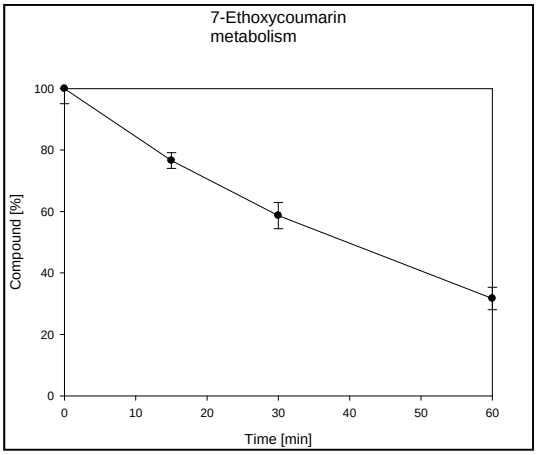


Figure S5. Metabolism of compound **16** (A), compound **27** (B) and 7-ethoxycoumarin (C) as reference compound. Compounds were treated with activated microsomes and measured at 0, 15, 30 and 60 minutes via HPLC. Data are given as mean ± S.E.M. obtained in 3 independent experiments.

III REFERENCES

(1) Hieke, M.; Ness, J.; Steri, R.; Dittrich, M.; Greiner, C.; Werz, O.; Baumann, K.; Schubert-Zsilavecz, M.; Weggen, S.; Zettl, H. Design, synthesis, and biological evaluation of a novel class of gamma-secretase modulators with PPARgamma activity. *J. Med. Chem.* **2010**, *53*, 4691–4700.

(2) Rau, O.; Syha, Y.; Zettl, H.; Kock, M.; Bock, A.; Schubert-Zsilavecz, M. Alpha-alkyl substituted pirinixic acid derivatives as potent dual agonists of the peroxisome proliferator activated receptor alpha and gamma. *Arch. Pharm. (Weinheim)*, **2008**, *341*, 191–195.