Supporting Information

Design, Synthesis, and Insecticidal Activity of 5,5-Disubstituted 4,5-Dihydropyrazolo[1,5-*a*]quinazolines as Novel Antagonists of GABA Receptors

Xunyuan Jiang,[†] Shuai Yang,[†] Ying Yan,[†] Fei Lin,[†] Ling Zhang,[‡] Weijing Zhao,[†] Chen Zhao[*,†] and Hanhong Xu[*,†]

[†]State Key Laboratory for Conservation and Utilization of Subtropical Agro-Bioresources and Key Laboratory of Natural Pesticide and Chemical Biology, Ministry of Education, South China Agricultural University, Guangzhou 510642, China

[‡]College of Life Science and Technology, Jinan University, Guangzhou 510632, China

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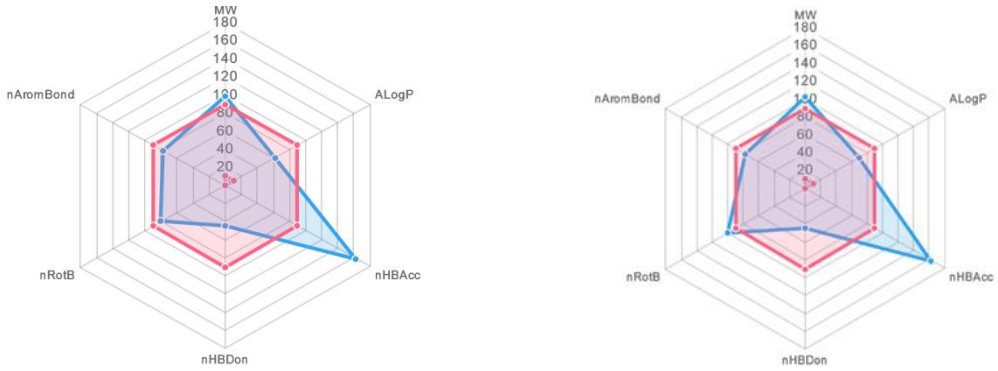
Table S1. Crystal data and structure refinement for compound **5d** (CCDC 1868709)

Item	Value
Empirical formula	$C_{24}H_{23}ClF_6N_4O_5S$
Formula weight	628.97
Temperature/K	292.5(3)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.0097(2)
b/Å	11.9031(2)
c/Å	21.7592(3)
α/°	90
β/°	97.315(2)
γ/°	90
Volume/Å^3	2828.33(8)
Z	4
Density (ρ_{calc}g/cm^3)	1.411
μ/mm^{-1}	2.602
F(000)	1224.0
Crystal size/mm^3	0.25 × 0.20 × 0.15
Radiation	CuKα (λ = 1.54184)
2θ range for cell determination/°	8.096 to 148.296
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-17 \le l \le 26$
Reflections collected	19730
Independent reflections	5629 [R_{int} = 0.0247, R_{sigma} = 0.0185]
Data / restraints / parameters	5629/105/423
Goodness-of-fit on F^2	1.356
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0882, wR_2 = 0.2837
Final R indices (all data)	R_1 = 0.0933, wR_2 = 0.2998
Largest diff. Peak/hole / eÅ^{-3}	1.15/-0.43

Figure S1. Sequence alignment results of the template sequence (PDB ID: 4COF) with M. domestica RDL (Q75NA5).

A platform InsectiPAD (http://chemyang.ccnu.edu.cn/ccb/database/InsectiPAD/) covers 495 approved insecticides and over 22200 related physicochemical properties. More importantly, it contains over 2900 qualitative analyses and 1500 quantitative scores for insecticides and provides comprehensive insecticide-likeness analysis for any compound. We employed the platform InsectiPAD to analyze the insecticide-likeness of compounds **5a** and **5b**. The radar plot of molecule properties was used to describe (Figure S2). The result of the qualitative analyses of compound **5a** exhibited that the values of MW and nHBAcc were out of the range of the insecticide-likeness limits. The result of the qualitative analyses of compound **5b** indicated that the values of MW, nRotB and nHBAcc were out of the range of the insecticide-likeness limits. Comparing the results of compounds **5a** and **5b**, the insecticide-likeness of compound **5a** is slightly better than compound **5b**. Also, the bee toxicity of compound **5a** was predicted using a free cloud platform BeeTox (http://beetox.cn), which develops a new DL model of deep graph attention convolutional neural networks to accurately classify and predict chemical poisoning of honey bees. Using prediction function in BeeTox to submit compound **5a**, and the predicted result showed that compound **5a** may be non-toxic to honey bee.

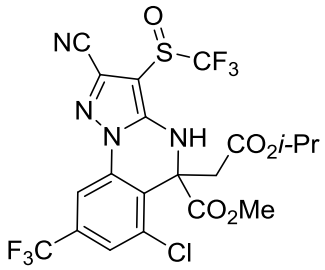


(a) **(b)**

Figure S2. Physicochemical properties of compounds **5a** and **5b**. A radar plot of molecule properties: log of the octanol−water partition coefficient (ALogP), molecular weight (MW), number of hydrogen bond acceptors (nHBAcc), number of hydrogen bond donors (nHBDon), number of rotatable bonds (nRotB) and number of aromatic bonds (nAromBond). The red area represents "good" property space for insecticidal bioavailability, and the blue hexagon represents values of the six calculated properties for compounds **5a** and **5b**. (a) Physicochemical properties of compound **5a**. (b) Physicochemical properties of compound **5b**.

Characterization data:

Methyl-6-chloro-2-cyano-5-(2-isopropoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7b):



dr = 80:20; white solid; 91% yield.

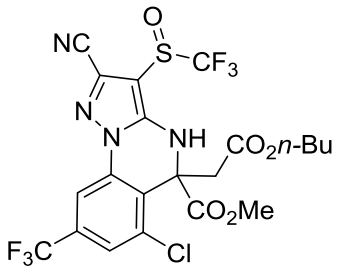
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 1.8 Hz, 1H, Ar–H), 7.58 (d, J = 1.9 Hz, 1H, Ar–H), 7.34 (brs, 0.8H, –NH–), 6.89 (brs, 0.2H, –NH–), 4.97 (p, J = 6.3 Hz, 0.8H, –O<u>CH</u>$(CH_3)_2$), 4.91 (p, J = 6.2 Hz, 0.2H, –O<u>CH</u>$(CH_3)_2$), 3.82 (s, 2.4H, –OCH_3), 3.81 (s, 0.6H, –OCH_3), 3.47 – 3.28 (m, 2H, –CH_2–), 1.18 (d, J = 6.2 Hz, 3H, –OCH<u>$(CH_3)_2$</u>), 1.11 (d, J = 6.3 Hz, 3H, –OCH<u>$(CH_3)_2$</u>).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.81, 168.20, 144.56, 134.19, 133.62 (q, J = 34.7 Hz), 133.27, 126.44 (q, J = 3.9 Hz), 125.67, 125.54 (q, J = 336.2 Hz), 123.69, 122.33 (q, J = 273.3 Hz), 111.69 (q, J = 3.8 Hz), 110.42, 94.05, 69.61, 61.79, 54.39, 41.71, 21.70, 21.62 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.43, 168.04, 144.48, 134.39, 133.62 (q, J = 34.7 Hz), 133.06, 126.44 (q, J = 3.9 Hz), 125.54 (q, J = 336.2 Hz), 125.53, 123.73, 122.33 (q, J = 273.3 Hz), 111.69 (q, J = 3.8 Hz), 110.42, 94.03, 69.53, 61.63, 54.48, 42.43, 21.57, 21.53 (minor diastereomer).

HRMS (ESI): calcd. for $C_{20}H_{14}ClF_6N_4O_5S$ $[M–H]^-$ 571.0278, found 571.0276.

Methyl-5-(2-butoxy-2-oxoethyl)-6-chloro-2-cyano-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7c):



dr = 80:20; white solid; 86% yield.

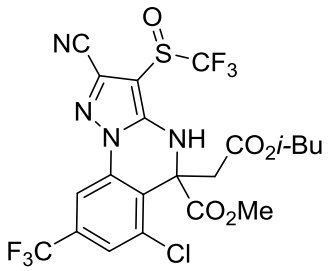
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 1.4 Hz, 0.2H, Ar–H), 8.13 (d, J = 1.3 Hz, 0.8H, Ar–H), 7.57 (d, J = 1.2 Hz, 1H, Ar–H), 6.82 (brs, 1H, –NH–), 4.10 – 3.98 (m, 2H, –$\underline{CH_2}CH_2CH_2CH_3$), 3.82 (s, 2.4H –$OCH_3$), 3.81 (s, 0.6H –$OCH_3$), 3.56 – 3.32 (m, 2H, –$CH_2$–), 1.56 – 1.47 (m, 2H, –$CH_2\underline{CH_2}CH_2CH_3$), 1.28 – 1.22 (m, 2H, –$CH_2CH_2\underline{CH_2}CH_3$), 0.89 (t, J = 7.4 Hz, 2.4H, –$CH_2CH_2CH_2\underline{CH_3}$), 0.88 (t, J = 7.4 Hz, 0.6H, –$CH_2CH_2CH_2\underline{CH_3}$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.40, 168.20, 144.61, 134.26, 133.58 (q, J = 34.6 Hz), 133.17, 126.41 (q, J = 3.8 Hz), 125.61, 125.51 (q, J = 336.1 Hz), 123.65, 122.33 (q, J = 273.4 Hz), 111.71 (q, J = 3.5 Hz), 110.42, 93.89, 65.62, 61.70, 54.40, 41.36, 30.46, 19.06, 13.70 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.09, 168.04, 144.55, 134.43, 133.58 (q, J = 34.6 Hz), 132.97, 126.35 (q, J = 4.2 Hz), 125.48, 125.46 (q, J = 336.1 Hz), 123.71, 122.36 (q, J = 273.3 Hz), 119.22, 111.56 (q, J = 3.6 Hz), 93.50, 65.47, 61.61, 54.48, 42.02, 30.33, 19.03, 13.64 (minor diastereomer).

HRMS (ESI): calcd. for $C_{21}H_{16}ClF_6N_4O_5S$ $[M–H]^-$ 585.0434, found 585.0421.

Methyl-6-chloro-2-cyano-5-(2-isobutoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7d):



dr = 65:35; white solid; 83% yield.

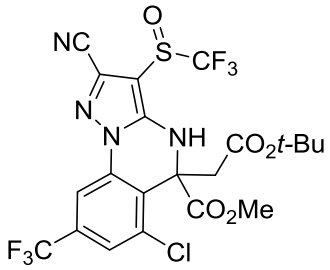
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 1.3 Hz, 0.35H, Ar–H), 8.16 – 8.11 (m, 0.65H, Ar–H), 7.59 (d, J = 1.2 Hz, 1H, Ar–H), 6.82 (brs, 1H, –NH–), 3.82 (s, 1.95H, –OCH_3), 3.81 (s, 1.05H, –OCH_3), 3.88 – 3.71 (m, 2H, –$O\underline{CH_2}CH(CH_3)_2$), 3.53 – 3.35 (m, 2H, –$CH_2$–), 1.88 – 1.80 (m, 1H, –$OCH_2\underline{CH}(CH_3)_2$), 0.85 (d, J = 6.7 Hz, 3.9H, –$OCH_2CH(\underline{CH_3})_2$), 0.85 (d, J = 6.7 Hz, 2.1H, –$OCH_2CH(\underline{CH_3})_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.38, 168.21, 144.71, 134.38, 133.67 (q, J = 34.9 Hz), 133.21, 126.36 (q, J = 3.7 Hz), 125.70, 125.58 (q, J = 336.4 Hz), 123.76, 122.38 (q, J = 273.3 Hz), 111.75 (q, J = 3.7 Hz), 110.40, 94.00, 71.73, 61.81, 54.34, 41.41, 27.68, 18.96, 18.95 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.13, 168.07, 144.63, 134.54, 133.65 (q, J = 34.7 Hz), 133.02, 126.43 (q, J = 3.9 Hz), 125.58, 125.51 (q, J = 336.5 Hz), 123.81, 122.41 (q, J = 273.1 Hz), 111.64 (q, J = 3.8 Hz), 110.52, 93.68, 71.63, 61.73, 54.42, 41.99, 27.63, 19.03, 18.92 (minor diastereomer).

HRMS (ESI): calcd. for $C_{21}H_{16}ClF_6N_4O_5S$ $[M–H]^-$ 585.0434, found 585.0423.

Methyl-5-[2-(tert-butoxy)-2-oxoethyl]-6-chloro-2-cyano-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7e):



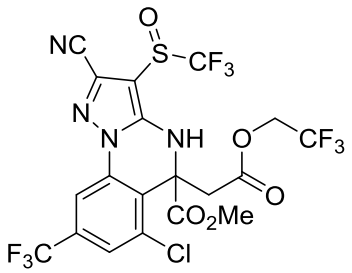
dr = 99:1; white solid; 61% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 1.8 Hz, 1H, Ar–H), 7.57 (d, J = 1.8 Hz, 1H, Ar–H), 6.96 (brs, 1H, –NH–), 3.80 (s, 3H, $–OCH_3$), 3.38 (q, J = 17.5 Hz, 2H, $–CH_2–$), 1.30 (s, 9H, $–C(CH_3)_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.11, 167.89, 144.37, 134.31, 133.38 (q, J = 34.7 Hz), 133.09, 126.36 (q, J = 3.7 Hz), 125.64, 125.45 (q, J = 336.1 Hz), 123.84, 122.37 (q, J = 273.2 Hz), 111.52 (q, J = 3.8 Hz), 110.45, 93.63, 82.84, 61.73, 54.41, 43.07, 27.82.

HRMS (ESI): calcd. for $C_{21}H_{16}ClF_6N_4O_5S$ $[M–H]^-$ 585.0434, found 585.0428.

Methyl-6-chloro-2-cyano-5-[2-oxo-2-(2,2,2-trifluoroethoxy)ethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7f):



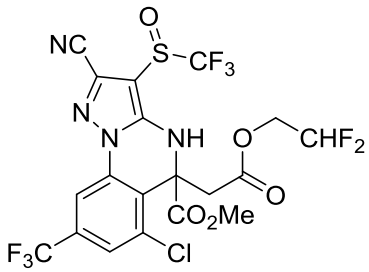
dr = 99:1; white solid; 85% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.7 Hz, 1H, Ar–H), 7.59 (d, J = 1.8 Hz, 1H, Ar–H), 6.80 (brs, 1H, –NH–), 4.47 – 4.26 (m, 2H, –O$\underline{CH_2}$CF3), 3.83 (d, J = 0.9 Hz, 3H, –OCH_3), 3.69 – 3.55 (m, 2H, –CH_2–).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.80, 167.77, 144.40, 134.44, 133.92 (q, J = 34.9 Hz), 133.08, 126.51 (q, J = 3.7 Hz), 125.64, 125.49 (q, J = 336.4 Hz), 123.05, 122.57 (q, J = 277.2 Hz), 122.34 (q, J = 273.4 Hz), 111.82 (q, J = 3.8 Hz), 110.30, 93.76, 61.44, 60.88 (q, J = 37.3 Hz), 54.64, 41.71.

HRMS (ESI): calcd. for $C_{19}H_9ClF_9N_4O_5S$ $[M–H]^-$ 610.9838, found 610.9840.

Methyl-6-chloro-2-cyano-5-[2-(2,2-difluoroethoxy)-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7g):



dr = 60:40; white solid; 71% yield.

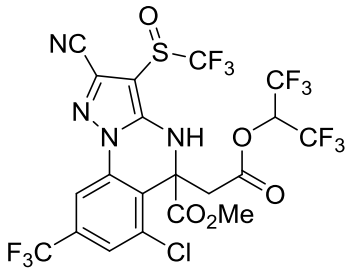
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.8 Hz, 0.6H, Ar–H), 8.14 (d, J = 2.1 Hz, 0.4H, Ar–H), 7.59 (d, J = 1.8 Hz, 1H, Ar–H), 7.28 (brs, 0.4H, –NH–), 6.92 (brs, 0.6H, –NH–), 5.87 (tdt, J = 54.7, 24.2, 3.9 Hz, 1H, –$OCH_2\underline{CH}F_2$), 4.31 – 4.12 (m, 2H, –$OCH_2\underline{CH}F_2$), 3.83 (s, 1.2H, –OCH_3), 3.82 (s, 1.8H, –OCH_3), 3.62 – 3.38 (m, 2H, –CH_2–).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.42, 167.88, 144.37, 134.37, 133.71 (q, J = 35.0 Hz), 132.98, 126.45 (q, J = 3.6 Hz), 125.56, 125.44 (q, J = 336.4 Hz), 123.17, 122.31 (q, J = 273.4 Hz), 112.14 (t, J = 241.6 Hz), 111.70 (q, J = 3.3 Hz), 110.36, 93.60, 62.95 (t, J = 28.9 Hz), 61.42, 54.60, 41.61 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.65, 168.06, 144.37, 134.19, 133.81 (q, J = 35.1 Hz), 133.16, 126.45 (q, J = 3.6 Hz), 125.73, 125.44 (q, J = 336.4 Hz), 123.17, 122.31 (q, J = 273.4 Hz), 112.26 (t, J = 241.7 Hz), 111.85 (q, J = 3.2 Hz), 110.36, 94.06, 63.10 (t, J = 29.3 Hz), 61.55, 54.55, 40.97 (minor diastereomer).

HRMS (ESI): calcd. for $C_{19}H_{10}ClF_8N_4O_5S$ $[M–H]^-$ 592.9933, found 592.9913.

Methyl-6-chloro-2-cyano-5-{2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-2-oxoethyl}-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7h):



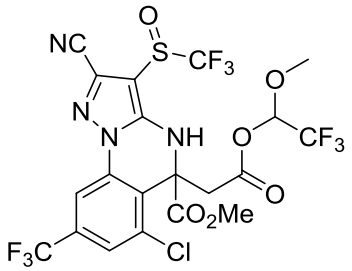
dr = 85:15; white solid; 59% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, J = 0.6 Hz, 1H, Ar–H), 7.66 (brs, 0.15H, –NH–), 7.61 (d, J = 0.6 Hz, 1H, Ar–H), 6.95 (brs, 0.85H, –NH–), 5.69 – 5.59 (m, 1H, –$CH(CF_3)_2$), 3.87 (s, 0.45H, –OCH_3), 3.84 (s, 2.55H, –OCH_3), 3.82 – 3.61 (m, 2H, –CH_2–).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.53, 166.51, 144.08, 134.25, 134.11 (q, J = 35.1 Hz), 133.04, 126.57 (q, J = 3.3 Hz), 125.69, 125.35 (q, J = 336.0 Hz), 122.40, 122.23 (q, J = 272.7 Hz), 120.07 (q, J = 281.0 Hz), 111.93 (q, J = 3.5 Hz), 110.24, 93.83, 66.92 (hept, J = 35.1 Hz), 61.19, 54.83, 41.46.

HRMS (ESI): calcd. for $C_{20}H_8ClF_{12}N_4O_5S$ $[M–H]^-$ 678.9712, found 678.9707.

Methyl-6-chloro-2-cyano-5-[2-oxo-2-(2,2,2-trifluoro-1-methoxyethoxy)ethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7i):

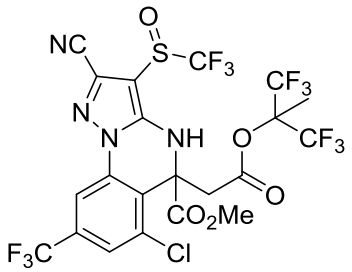


White solid; 51% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.9 Hz, 1H, Ar–H), 7.60 (d, J = 1.8 Hz, 1H, Ar–H), 7.08 (brs, 1H, –NH–), 5.93 – 5.73 (m, 1H, –O<u>CH</u>$(OCH_3)CF_3$), 3.83 (s, 3H, –OCH_3), 3.55 (s, 3H, –$OCH(O\underline{CH_3})CF_3$), 3.65 – 3.42 (m, 2H, –$CH_2$–).

HRMS (ESI): calcd. for $C_{20}H_{11}ClF_9N_4O_6S$ $[M–H]^-$ 640.9944, found 640.9955.

Methyl-6-chloro-2-cyano-5-{2-[(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy]-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (7j):



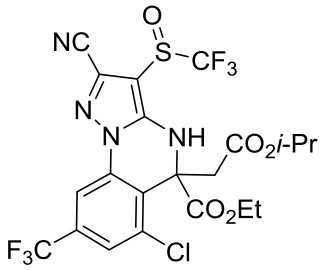
dr = 99:1; white solid; 23% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.8 Hz, 1H, Ar–H), 7.60 (d, J = 1.3 Hz, 1H, Ar–H), 6.87 (brs, 1H, –NH–), 3.83 (s, 3H, $–OCH_3$), 3.71 – 3.50 (m, 2H, $–CH_2–$), 1.87 (s, 3H, $–C(CF_3)_2\underline{CH_3}$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.70, 165.62, 144.20, 134.34, 133.90 (q, J = 34.9 Hz), 133.12, 126.57 (d, J = 3.7 Hz), 125.83, 125.46 (q, J = 336.0 Hz), 122.78, 122.33 (q, J = 273.4 Hz), 121.74 (q, J = 285.6 Hz), 111.92 (q, J = 3.8 Hz), 110.28, 94.01, 81.58 (p, J = 31.2 Hz), 61.47, 54.67, 42.48, 13.95.

HRMS (ESI): calcd. for $C_{21}H_{10}ClF_{12}N_4O_5S$ $[M–H]^-$ 692.9869, found 692.9871.

Ethyl-6-chloro-2-cyano-5-(2-isopropoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8b):



dr = 50:50; white solid; 84% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 1.9 Hz, 0.5H, Ar–H), 8.12 (d, J = 1.7 Hz, 0.5H, Ar–H), 7.57 (d, J = 1.8 Hz, 1H, Ar–H), 7.29 (brs, 0.5H, –NH–), 6.81 (brs, 0.5H, –NH–), 4.97 (p, J = 6.3 Hz, 0.5H, $–O\underline{CH}(CH_3)_2$), 4.91 (p, J = 6.3 Hz, 0.5H, $–O\underline{CH}(CH_3)_2$), 4.42 – 4.21 (m, 2H, $–O\underline{CH_2}CH_3$),

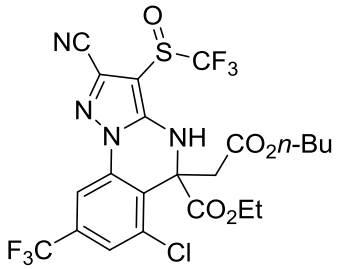
3.56 – 3.22 (m, 2H, –CH_2–), 1.28 – 1.22 (m, 3H, –$OCH_2\underline{CH_3}$), 1.16 (dd, *J* = 28.5, 6.2 Hz, 3H, –$OCH(\underline{CH_3})_2$), 1.10 (dd, *J* = 8.7, 6.3 Hz, 3H, –$OCH(\underline{CH_3})_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.48, 167.46, 144.52, 134.42, 133.52 (q, *J* = 34.6 Hz), 133.23, 126.33 (d, *J* = 4.0 Hz), 125.47, 125.47 (q, *J* = 336.4 Hz), 123.82, 122.34 (q, *J* = 273.3 Hz), 111.53 (q, *J* = 3.4 Hz), 110.46, 93.40, 69.49, 64.03, 61.77, 42.35, 21.58, 21.53, 13.91 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.86, 167.58, 144.57, 134.20, 133.42 (q, *J* = 34.4 Hz), 133.04, 126.39 (d, *J* = 4.0 Hz), 125.63, 125.55 (q, *J* = 336.3 Hz), 123.73, 122.37 (q, *J* = 273.2 Hz), 111.65 (q, *J* = 3.5 Hz), 110.45, 93.88, 69.57, 63.82, 61.86, 41.66, 21.71, 21.63, 13.85 (minor diastereomer).

HRMS (ESI): calcd. for $C_{21}H_{16}ClF_6N_4O_5S$ $[M–H]^-$ 585.0434, found 585.0416.

Ethyl-5-(2-butoxy-2-oxoethyl)-6-chloro-2-cyano-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8c):



dr = 50:50; white solid; 80% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.8 Hz, 0.5H, Ar–H), 8.12 (d, *J* = 1.7 Hz, 0.5H, Ar–H), 7.57 (s, 1H, Ar–H), 7.24 (s, 0.5H, –NH–), 6.79 (s, 0.5H, –NH–), 4.39 – 4.20 (m, 2H, –$O\underline{CH_2}CH_3$), 4.08 – 3.93 (m, 2H, –$\underline{CH_2}CH_2CH_2CH_3$), 3.56 – 3.30 (m, 2H, –$CH_2$–), 1.56 – 1.45 (m, 2H, –$CH_2\underline{CH_2}CH_2CH_3$), 1.32 – 1.26 (m, 2H, –$CH_2CH_2\underline{CH_2}CH_3$), 1.25 (t, *J* = 7.2 Hz, 3H, –$OCH_2\underline{CH_3}$), 0.88 (t, *J* = 7.4 Hz, 1.5H, –$CH_2CH_2CH_2\underline{CH_3}$), 0.88 (t, *J* = 7.4 Hz, 1.5H, –$CH_2CH_2CH_2\underline{CH_3}$).

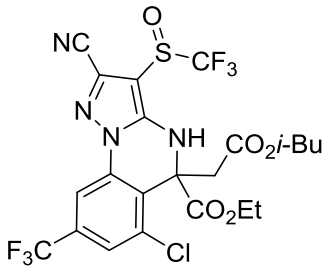
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.48, 167.59, 144.64, 134.28, 133.53 (q, *J* = 34.9 Hz), 132.98, 126.38 (q, *J* = 3.6 Hz), 125.60, 125.54 (q, *J* = 336.2 Hz), 123.81, 122.35 (q, *J* = 273.3 Hz), 111.69 (q, *J* = 3.8 Hz), 110.45, 93.77, 65.63, 63.84, 61.79, 41.96, 30.47, 19.08, 13.83, 13.71 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.16, 167.47, 144.62, 134.46, 133.43 (q, *J* = 34.6 Hz), 133.16, 126.31 (q, *J* = 4.2 Hz), 125.47 (q, *J* = 336.6 Hz), 125.43, 123.69, 122.38 (q, *J* = 273.2 Hz), 111.56

(q, *J* = 3.4 Hz), 110.45, 93.43, 65.48, 64.05, 61.76, 41.31, 30.41, 19.04, 13.89, 13.66 (minor diastereomer).

HRMS (ESI): calcd. for $C_{22}H_{18}ClF_6N_4O_5S$ $[M–H]^-$ 599.0591, found 599.0543.

Ethyl-6-chloro-2-cyano-5-(2-isobutoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8d):



dr = 50:50; white solid; 80% yield.

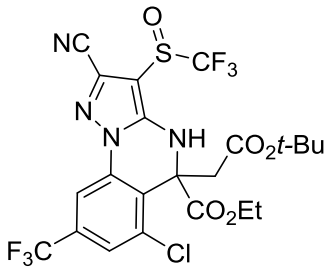
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.8 Hz, 0.5H, Ar–H), 8.12 (d, *J* = 1.7 Hz, 0.5H, Ar–H), 7.57 (d, *J* = 1.8 Hz, 1H, Ar–H), 7.25 (s, 0.5H, –NH–), 6.83 (s, 0.5H, –NH–), 4.44 – 4.19 (m, 2H, –O$\underline{CH_2}CH_3$), 3.86 – 3.71 (m, 2H, –O$\underline{CH_2}CH(CH_3)_2$), 3.58 – 3.33 (m, 2H, –$CH_2$–), 1.83 (ddt, *J* = 13.4, 9.8, 6.7 Hz, 1H, –$OCH_2\underline{CH}(CH_3)_2$), 1.25 (t, *J* = 7.1 Hz, 1.5H, –$OCH_2\underline{CH_3}$), 1.24 (t, *J* = 7.1 Hz, 1.5H, –$OCH_2\underline{CH_3}$), 0.85 (s, 3H, –$OCH_2CH(\underline{CH_3})_2$), 0.84 (s, 3H, –$OCH_2CH(\underline{CH_3})_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.24, 167.49, 144.65, 134.52, 133.49 (q, *J* = 34.8 Hz), 132.90, 126.26 (q, *J* = 3.9 Hz), 125.58, 125.46 (q, *J* = 336.4 Hz), 123.85, 122.35 (q, *J* = 273.3 Hz), 111.66 (q, *J* = 3.8 Hz), 110.46, 93.70, 71.66, 64.00, 61.78, 41.81, 27.62, 18.96, 18.95, 13.86 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.51, 167.60, 144.62, 134.33, 133.38 (q, *J* = 34.7 Hz), 133.09, 126.32 (q, *J* = 4.0 Hz), 125.54 (q, *J* = 336.0 Hz), 125.45, 123.71, 122.38 (q, *J* = 273.3 Hz), 111.56 (q, *J* = 3.8 Hz), 110.45, 93.44, 71.57, 63.81, 61.76, 41.20, 27.57, 18.97, 18.92, 13.81(minor diastereomer).

HRMS (ESI): calcd. for $C_{22}H_{18}ClF_6N_4O_5S$ $[M–H]^-$ 599.0591, found 599.0555.

Ethyl-5-[2-(tert-butoxy)-2-oxoethyl]-6-chloro-2-cyano-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8e):



dr = 70:30; white solid; 49% yield.

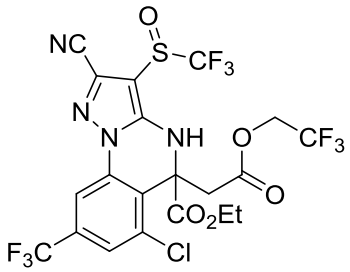
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 2.0 Hz, 1H, Ar–H), 7.57 (d, J = 1.9 Hz, 1H, Ar–H), 7.19 (brs, 0.3H, –NH–), 6.92 (brs, 0.7H, –NH–), 4.32 – 4.22 (m, 2H, –O$\underline{CH_2}CH_3$), 3.46 – 3.23 (m, 1.4H, –CH_2–), 3.39 – 3.25 (m, 0.6H, –CH_2–), 1.30 (s, 2.7H, –$C(CH_3)_2$), 1.32 (s, 6.3H, –$C(CH_3)_2$), 1.25 (t, J = 7.1 Hz, 0.9H, –$OCH_2\underline{CH_3}$), 1.24 (t, J = 7.1 Hz, 2.1H, –$OCH_2\underline{CH_3}$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.94, 167.53, 144.54, 134.45, 133.46 (q, J = 34.7 Hz), 133.24, 126.36 (q, J = 3.6 Hz), 125.72, 125.54 (q, J = 336.5 Hz), 124.06, 122.44 (q, J = 273.1 Hz), 111.57 (q, J = 3.8 Hz), 110.44, 93.75, 82.86, 63.92, 62.03, 43.19, 27.88, 13.91 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.25, 167.62, 144.68, 134.29, 133.55 (q, J = 34.9 Hz), 133.41, 127.13 (q, J = 3.4 Hz), 125.71, 125.54 (q, J = 336.5 Hz), 123.98, 122.44 (q, J = 273.1 Hz), 111.64 (q, J = 3.8 Hz), 110.42, 93.75, 82.94, 63.75, 62.13, 42.90, 27.94, 13.85 (minor diastereomer).

HRMS (ESI): calcd. for $C_{22}H_{18}ClF_6N_4O_5S$ $[M–H]^-$ 599.0591, found 599.0550.

Ethyl-6-chloro-2-cyano-5-[2-oxo-2-(2,2,2-trifluoroethoxy)ethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8f):



dr = 60:40; white solid; 85% yield.

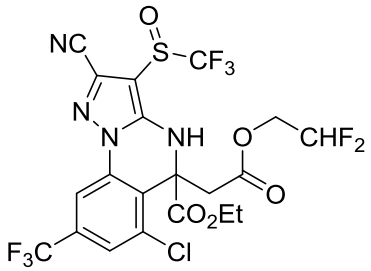
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.9 Hz, 0.6H, Ar–H), 8.14 (d, J = 1.6 Hz, 0.4H, Ar–H), 7.59 (d, J = 2.1 Hz, 1H, Ar–H), 7.18 (brs, 0.4H, –NH–), 6.84 (brs, 0.6H, –NH–), 4.48 – 4.22 (m, 2H, –O$\underline{CH_2}CF_3$), 4.36 – 4.23 (m, 2H, –O$\underline{CH_2}CH_3$), 3.71 – 3.46 (m, 2H, –CH_2–), 1.26 (t, J = 7.2 Hz, 1.2H, –$OCH_2\underline{CH_3}$), 1.25 (t, J = 7.1 Hz, 1.8H, –$OCH_2\underline{CH_3}$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.14, 167.34, 144.40, 134.24, 133.85 (q, J = 34.9 Hz), 133.15, 126.48 (q, J = 3.9 Hz), 125.67, 125.52 (q, J = 336.1 Hz), 123.05, 122.57 (q, J = 277.2 Hz), 122.29 (q, J = 273.2 Hz), 111.86 (q, J = 3.8 Hz), 110.35, 93.87, 64.12, 61.57, 60.99 (q, J = 37.1 Hz), 40.87, 13.81 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.85, 167.19, 144.41, 134.41, 133.76 (q, J = 34.8 Hz), 133.00, 126.42 (q, J = 4.7 Hz), 125.51, 125.44 (q, J = 336.1 Hz), 123.10, 122.54 (q, J = 277.1 Hz), 122.32 (q, J = 273.2 Hz), 111.75 (q, J = 3.9 Hz), 109.30, 93.55, 64.31, 61.50, 60.81 (q, J = 37.2 Hz), 41.56, 13.81 (minor diastereomer).

HRMS (ESI): calcd. for $C_{20}H_{11}ClF_9N_4O_5S$ $[M–H]^-$ 624.9995, found 624.9981.

Ethyl-6-chloro-2-cyano-5-[2-(2,2-difluoroethoxy)-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8g):



dr = 60:40; white solid; 63% yield.

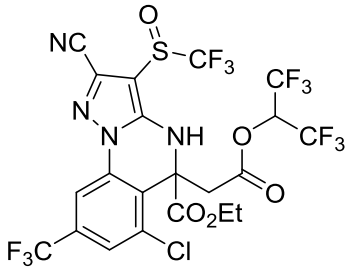
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 2.0 Hz, 0.6H, Ar–H), 8.14 (d, J = 1.7 Hz, 0.4H, Ar–H), 7.59 (d, J = 2.3 Hz, 1H, Ar–H), 5.88 (tdt, J = 54.7, 26.4, 3.9 Hz, 1H, –$OCH_2\underline{CH}F_2$), 4.40 – 4.27 (m, 2H, –$O\underline{CH_2}CHF_2$), 4.27 – 4.17 (m, 2H, –$O\underline{CH_2}CH_3$), 3.60 – 3.35 (m, 2H, –CH_2–), 1.25 (t, J = 7.1 Hz, 3H, –$OCH_2\underline{CH_3}$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.47, 167.27, 144.45, 134.38, 133.80 (q, J = 34.7 Hz), 133.02, 126.41 (q, J = 3.7 Hz), 125.51, 125.45 (q, J = 336.5 Hz), 123.21, 122.30 (q, J = 273.4 Hz), 112.15 (t, J = 241.7 Hz), 111.73 (q, J = 4.1 Hz), 110.37, 93.98, 64.26, 62.99 (t, J = 28.9 Hz), 61.59, 41.59, 13.88 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.72, 167.42, 144.39, 134.18, 133.70 (q, J = 34.4 Hz), 133.19, 126.49 (q, J = 3.7 Hz), 125.72, 125.53 (q, J = 336.4 Hz), 123.27, 122.02 (q, J = 273.4 Hz), 112.27 (t, J = 241.7 Hz), 111.84 (q, J = 3.9 Hz), 110.35, 93.55, 64.07, 63.15 (t, J = 29.4 Hz), 61.66, 40.96, 13.82 (minor diastereomer).

HRMS (ESI): calcd. for $C_{20}H_{12}ClF_8N_4O_5S$ $[M–H]^-$ 607.0089, found 607.0076.

Ethyl-6-chloro-2-cyano-5-{2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-2-oxoethyl}-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8h):



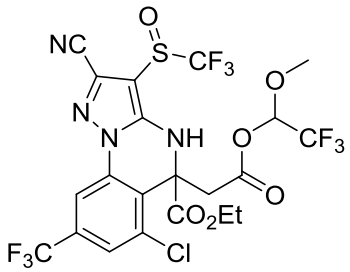
dr = 99:1; white solid; 46% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H, Ar–H), 7.61 (s, 1H, Ar–H), 6.94 (brs, 1H, –NH–), 5.63 (p, J = 5.9 Hz, 1H, –O<u>CH</u>$(CF_3)_2$), 4.40 – 4.22 (m, 2H, –O<u>CH_2</u>CH_3), 3.89 – 3.60 (m, 2H, –CH_2–), 1.28 – 1.23 (m, 3H, –OCH_2<u>CH_3</u>).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.96, 166.54, 144.14, 134.31, 134.03 (q, J = 34.9 Hz), 133.01, 126.49 (q, J = 3.5 Hz), 125.67, 125.38 (q, J = 335.4 Hz), 122.53, 122.24 (q, J = 273.4 Hz), 120.07 (q, J = 281.2 Hz), 111.90 (q, J = 3.7 Hz), 110.26, 93.76, 66.99 (hept, J = 34.5 Hz), 64.49, 61.35, 41.41, 13.87.

HRMS (ESI): calcd. for $C_{21}H_{10}ClF_{12}N_4O_5S$ $[M–H]^-$ 692.9869, found 692.9854.

Ethyl-6-chloro-2-cyano-5-[2-oxo-2-(2,2,2-trifluoro-1-methoxyethoxy)ethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8i):

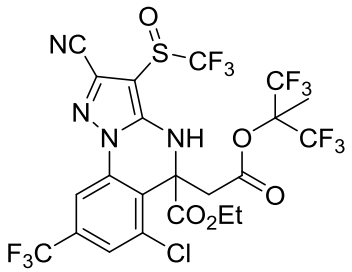


dr = 60:40; white solid; 36% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 1.8 Hz, 0.6H, Ar–H), 8.14 (d, J = 1.8 Hz, 0.4H, Ar–H), 7.60 (d, J = 2.3 Hz, 1H, Ar–H), 7.17 (s, 0.4H, –NH–), 7.05 (s, 0.6H, –NH–), 5.91 – 5.73 (m, 1H, –O<u>CH</u>(OCH_3)CF_3), 4.39 – 4.22 (m, 2H, –O<u>CH_2</u>CH_3), 3.66 – 3.58 (m, 1H, –CH_2–), 3.58 (s, 1.2H, –OCH(O<u>CH_3</u>)CF_3), 3.54 (s, 1.8H, –OCH(O<u>CH_3</u>)CF_3), 3.49 – 3.40 (m, 1H, –CH_2–), 1.26 (t, J = 7.2 Hz, 1.2H, –OCH_2<u>CH_3</u>), 1.25 (t, J = 7.1 Hz, 1.8H, –OCH_2<u>CH_3</u>).

HRMS (ESI): calcd. for $C_{21}H_{13}ClF_9N_4O_6S$ $[M–H]^–$ 655.0101, found 655.0142.

Ethyl-6-chloro-2-cyano-5-{2-[(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy]-2-oxoethyl}-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (8j):



dr = 60:40; white solid; 20% yield.

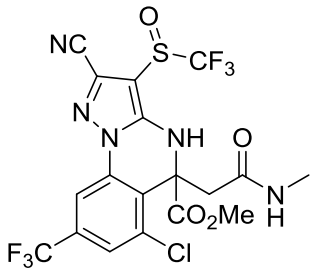
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, J = 1.3 Hz, 0.6H, Ar–H), 8.14 (d, J = 1.3 Hz, 0.4H, Ar–H), 7.60 (d, J = 2.3 Hz, 1H, Ar–H), 7.08 (s, 0.6H, –NH–), 6.86 (s, 0.4H, –NH–), 4.40 – 4.24 (m, 2H, –O<u>CH_2</u>CH_3), 3.76 – 3.50 (m, 2H, –CH_2–), 1.87 (s, 1.2H, –C(CF_3)$_2$<u>CH_3</u>), 1.87 (s, 1.8H, –C(CF_3)$_2$<u>CH_3</u>), 1.26 (t, J = 7.1 Hz, 1.2H, –OCH_2<u>CH_3</u>), 1.25 (t, J = 7.1 Hz, 1.8H, –OCH_2<u>CH_3</u>).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.22, 165.93, 144.27, 134.12, 133.89 (q, J = 34.4 Hz), 133.22, 126.48 (q, J = 3.6 Hz), 125.64, 125.49 (q, J = 336.1 Hz), 123.69 (q, J = 273.9 Hz), 122.78, 121.66 (q, J = 285.6 Hz), 112.92 (q, J = 3.5 Hz), 110.34, 93.89, 81.41 (p, J = 30.6 Hz), 64.17, 61.62, 41.99, 13.92, 13.82 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.06, 165.65, 144.16, 134.26, 133.80 (q, J = 34.7 Hz), 133.01, 129.35, 127.14 (q, J = 3.2 Hz), 125.49 (q, J = 336.1 Hz), 123.69 (q, J = 273.9 Hz), 121.66 (q, J = 285.6 Hz), 116.73, 111.85 (q, J = 4.4 Hz), 110.07, 93.74, 81.41 (p, J = 30.6 Hz), 64.28, 61.47, 42.28, 13.98, 13.88 (minor diastereomer).

HRMS (ESI): calcd. for $C_{22}H_{12}ClF_{12}N_4O_5S$ $[M–H]^–$ 707.0025, found 707.0023.

Methyl-6-chloro-2-cyano-5-[2-(methylamino)-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (9b):



dr = 70:30; white solid; 51% yield.

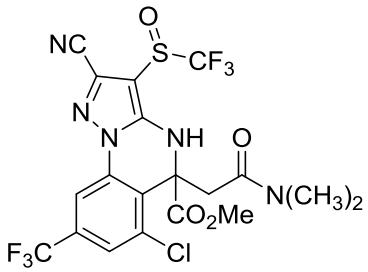
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 1.8 Hz, 0.7H, Ar–H), 8.12 (d, J = 1.8 Hz, 0.3H, Ar–H), 7.75 (brs, 0.3H, –NH–), 7.55 (d, J = 1.8 Hz, 0.3H, Ar–H), 7.54 (d, J = 1.8 Hz, 0.7H, Ar–H), 7.27 (brs, 0.7H, –NH–), 5.78 (t, J = 4.9 Hz, 0.3H, –NHCH_3), 5.76 (t, J = 4.7 Hz, 0.7H, –NHCH_3), 3.81 (s, 0.9H, –OCH_3), 3.78 (s, 2.1H, –OCH_3), 3.36 – 3.14 (m, 2H, –CH_2–), 2.73 (d, J = 4.8 Hz, 0.9H, –NHCH_3), 2.72 (d, J = 4.9 Hz, 2.1H, –NHCH_3).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.46, 168.35, 144.35, 134.30, 133.16 (q, J = 34.8 Hz), 132.51, 126.09 (q, J = 3.8 Hz), 125.66 (q, J = 336.4 Hz), 125.39, 124.18, 122.27 (q, J = 273.3 Hz), 111.54 (q, J = 3.8 Hz), 110.38, 93.58, 62.10, 54.18, 42.44, 26.21 (major diastereomer).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.58, 168.42, 144.43, 134.13, 133.10 (q, J = 34.6 Hz), 132.74, 126.17 (q, J = 3.9 Hz), 125.66 (q, J = 336.4 Hz), 125.60, 124.04, 122.22 (q, J = 273.3 Hz), 111.68 (q, J = 3.6 Hz), 110.33, 94.09, 62.22, 54.12, 42.10, 26.41 (minor diastereomer).

HRMS (ESI): calcd. for $C_{18}H_{11}ClF_6N_5O_4S$ $[M–H]^-$ 542.0124, found 542.0114.

Methyl-6-chloro-2-cyano-5-[2-(dimethylamino)-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (9c):



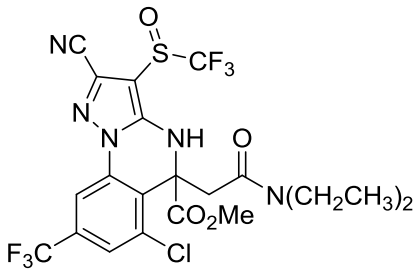
dr = 99:1; white solid; 69% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 1.8 Hz, 1H, Ar–H), 7.53 (d, J = 0.1 Hz, 1H, Ar–H), 3.79 (s, 3H, –OCH_3), 3.66 (d, J = 17.3 Hz, 1H, –CH_2–), 3.36 (d, J = 17.3 Hz, 1H, –CH_2–), 3.05 (s, 3H, –$N(CH_3)_2$), 2.86 (s, 3H, –$N(CH_3)_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.74, 167.98, 145.04, 134.76, 133.08 (q, J = 34.7 Hz), 132.38, 126.24 (q, J = 3.8 Hz), 125.45 (q, J = 336.5 Hz), 125.36, 124.68, 123.35 (q, J = 273.3 Hz), 111.65 (q, J = 3.7 Hz), 110.67, 93.58, 62.43, 54.36, 40.15, 37.46, 35.56.

HRMS (ESI): calcd. for $C_{19}H_{13}ClF_6N_5O_4S$ $[M–H]^-$ 556.0281, found 556.0266.

Methyl-6-chloro-2-cyano-5-[2-(diethylamino)-2-oxoethyl]-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (9d):



dr = 90:10; white solid; 66% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 1.8 Hz, 1H, Ar–H), 7.53 (d, J = 1.8 Hz, 1H, Ar–H), 7.39 (brs, 1H, –NH–), 3.79 (d, J = 7.9 Hz, 3H, –OCH_3), 3.62 (d, J = 17.1 Hz, 1H, –CH_2–), 3.40 – 3.28 (m, 4H, –CH_2– and –$N(\underline{CH_2}CH_3)_2$), 3.27 – 3.17 (m, 1H, –$N(\underline{CH_2}CH_3)_2$), 1.21 (t, J = 7.2 Hz, 3H, –$N(CH_2\underline{CH_3})_2$), 1.04 (t, J = 7.1 Hz, 3H, –$N(CH_2\underline{CH_3})_2$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.72, 167.09, 144.86, 134.67, 133.05 (q, J = 34.9 Hz), 132.37, 126.29 (q, J = 3.6 Hz), 125.51, 125.44 (q, J = 335.9 Hz), 124.70, 122.44 (q, J = 273.3 Hz), 111.68 (q, J = 3.5 Hz), 110.67, 93.74, 62.54, 54.29, 42.27, 40.54, 39.88, 14.20, 12.87.

HRMS (ESI): calcd. for $C_{21}H_{17}ClF_6N_5O_4S$ $[M–H]^-$ 584.0591, found 584.0573.