Electronic Supplementary Material (ESI) for MedChemComm.
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Supplementary material - Chemistry

Experimental section

The compounds named below were named using ACD/Name 9.04 from ACD/Labs.

All solvent and reagents used were of reagent grade purchased from commercial sources.

Purity and characterization of compounds were established by liquid chromatography–mass spectroscopy (LC-MS) and NMR analytical techniques (see method details below). Unless stated otherwise, the purities were above 95% for all reported compounds.

High resolution MS and purity was detected on a Waters LCTp ToF MS using electrospray ionization (ESI-MS). The LC inlet consisted of a Waters Acquity UPLC system, and the separation was performed on a Waters C18 XBridge at 45-50 °C. The separation was obtained with a 2-95% MeCN gradient over 3 min at pH 10 (40 mM NH3 and 5 mM H2CO3). A measure of related impurities was assessed at 210 nM.

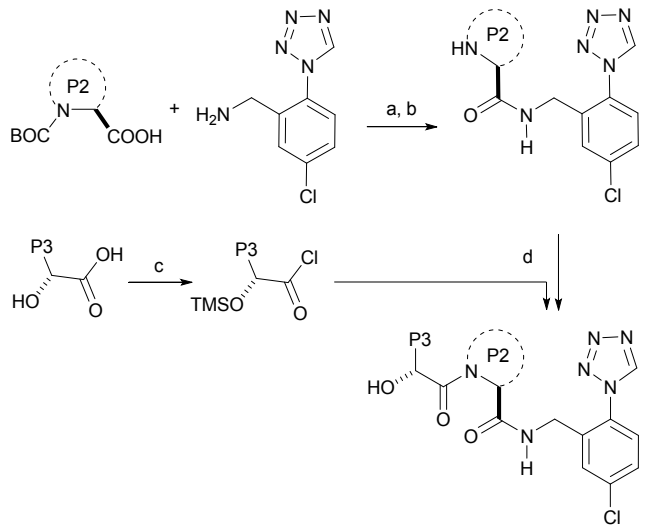
1H NMR were recorded on a Bruker Avance DPX400 (400 MHz), AV500 (500 MHz) or AV600 (600 MHz) and were determined in CHCl3-d, DMSO-d6 and MeOH-d4 with trimethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Chemical shifts are reported in ppm relative to solvent signal at 7.26 ppm (CHCl3), 2.50 ppm (DMSO) and 3.30 ppm (MeOH) and coupling constant (J) values are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak; bs, broad singlet.

Chiral separations were performed on Waters preparative HPLC system fitted with either Chiralpak AD, Chiralpak AS or Chiracel OD. The enantiomeric excess was determined using the same setup and detected by PDA at 240 nm. The final compounds were purified by RP-HPLC on a Waters Fraction Lynx system equipped with a ZQ MS detector. The columns used were Waters

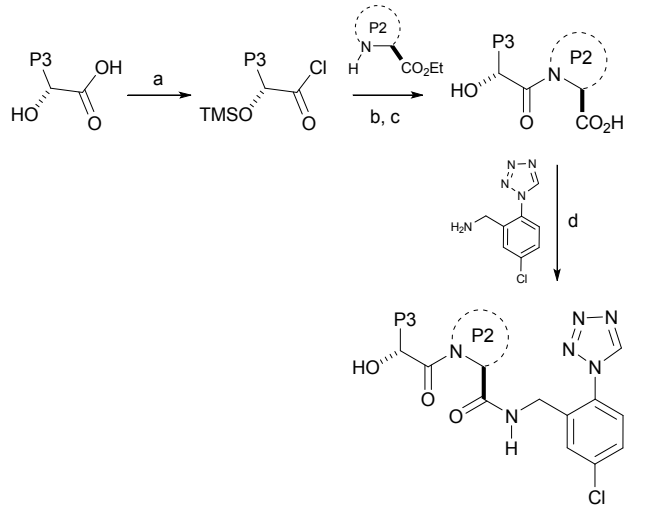
Xbridge C18 OBD 5 µm (pH 10, gradient 5-95% MeCN + 0.2% NH3) or Waters SunFire C18 OBD 5 µm (pH 3, gradient 5-95% MeCN + 0.1 M formic acid).

Compound synthesis

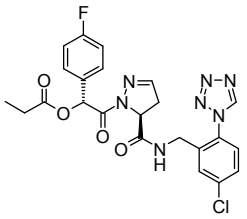
The compounds described in this article were synthesised using the methods depicted in scheme 1 or scheme 2.



Scheme 1. Synthesis of compounds containing P2 building blocks **6-12** and **14-23**. Reagents and conditions:
(a) HOBt, EDC, TEA, CH_2Cl_2, r.t.; (b) HCl (conc., aq.), MeOH, r.t.; (c) TMSCl, DMAP, pyridine, r.t., then DMF (cat.), CO_2Cl_2, CH_2Cl_2, 0 °C to r.t.; (d) pyridine, CH_2Cl_2, r.t., then MeOH.

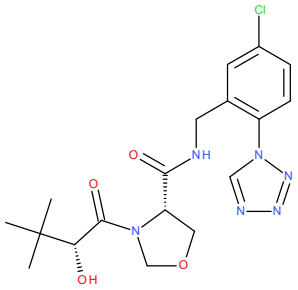


Scheme 2. Synthesis of compounds containing P2 building block **13**. Reagents and conditions:
(a) TMSCl, DMAP, pyridine, r.t., then DMF (cat.), CO_2Cl_2, CH_2Cl_2, 0 °C to r.t.; (b) pyridine, CH_2Cl_2, r.t., then MeOH; (c) LiBr, Et_3N, CH_3CN r.t.; (d) NMM, TBTU, EtOAc, r.t.



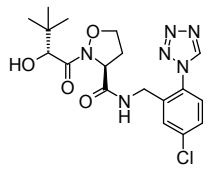
Compound 5, (1R)-2-[(5S)-5-{[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]carbamoyl}-4,5-dihydro-1H-pyrazol-1-yl]-1-(4-fluorophenyl)-2-oxoethyl propanoate

^{1}H NMR (500 MHz, ($CDCl_3$): δ 9.05 (s, 1H), 7.55 (m, 3H), 7.43 (m, 2H), 7.25 (s, 1H), 7.04 (m, 3H), 6.52 (s, 1H), 4.79 (dd, 1H), 4.22 (dd, 2H), 3.25 (ddd, 1H), 3.09 (ddd, 1H), 2.41 (m, 2H), 1.03 (t, 3H). HRMS (ESI) calculated for $C_{23}H_{21}ClFN_7O_4$ $(M+H)^+$, 514.1406 found 514.1405.



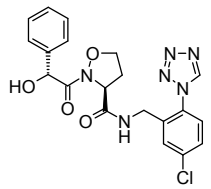
Compound 24, (4S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]oxazolidine-4-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) mixtures of rotamers: δ 9.08 (s, 0.24H), 9.06 (s, 0.76H), 7.66 (s, 1H), 7.54 (br, 1H), 7.47 (d, 1H), 7.30 (br, 1H), 5.24 (d, 0.24H), 5.14 (d, 1.6H), 4.89 (d, 0.24H), 4.64 (t, 0.24H), 4.49 – 4.59 (m, 0.76H), 4.42 (d, 0.76H), 4.2 – 4.34 (m, 2H), 4.05 (t, 1H), 3.82 (dd, 1H), 3.39 (d, 0.24H), 3.24 (d, 0.76H), 1.02 (s, 7H), 0.93 (s, 2H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_4$ $(M+H)^+$, 423.1548 found 423.1557.



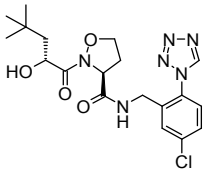
Compound 25, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-3,3-dimethylbutanoyl]isoxazolidine-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.73 (bt, 1H), 7.58 (d, 1H), 7.42 (dd, 1H), 7.25 (d, 1H), 4.75 (dd, 1H), 4.22-4.30 (m, 3H), 4.11-4.17 (ddd, 1H), 3.97 (q, 1H), 3.12 (bs, 1H), 2.77-2.88 (m, 1H), 2.40-2.50 (m, 1H), 0.94 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_4$ 423.1548 $(M+H)^+$, found 423.1552.



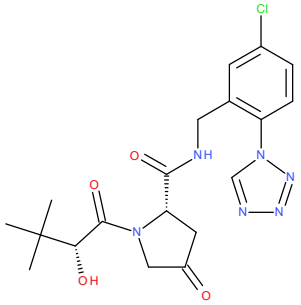
Compound 26, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-2-phenylacetyl]isoxazolidine-3-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.61 (d, 1H), 7.47 (bt, 1H), 7.44 (dd, 1H), 7.12-7.35 (m, 6H), 5.49 (d, 1H), 4.64 (dd, 1H), 4.22-4.33 (m, 2H), 4.20 (d, 1H), 3.81 (ddd, 1H), 2.64-2.72 (m, 1H), 2.52-2.62 (m, 1H), 2.22-2.31 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{20}ClN_6O_4$ 443.1234 $(M+H)^+$, found 443.1234.



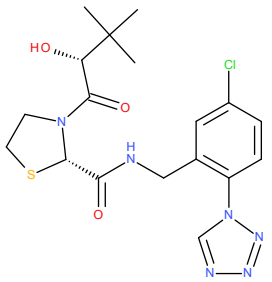
Compound 27, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-4,4-dimethylpentanoyl]isoxazolidine-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.59 (d, 1H), 7.44-7.50 (m, 2H), 7.27 (d, 1H), 4.69 (dd, 1H), 4.63 (dd, 1H), 4.27 (d, 2H), 4.18 (ddd, 1H), 3.93 (q, 1H), 2.80-2.88 (m, 1H), 2.47-2.55 (m, 1H), 1.40 (d, 2H), 1.01 (s, 9H). HRMS (ESI) calculated for $C_{19}H_{26}ClN_6O_4$ 437.1704 $(M+H)^+$, found 437.1700.



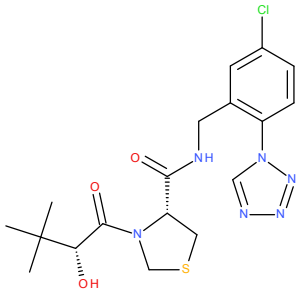
Compound 28, (2S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-1-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]-4-oxo-pyrrolidine-2-carboxamide

^{1}H NMR (500 MHz, CD_3OD) δ 9.54 (s, 1H), 7.7 – 7.81 (m, 1H), 7.55 (dd, 1H), 7.49 (d, 1H), 4.88 (dd, 1H), 4.27 – 4.38 (m, 2H), 4.08 – 4.18 (m, 2H), 3.96 (s, 1H), 2.86 – 2.98 (m, 1H), 2.43 (d, 1H), 0.99 (d, 9H). HRMS (ESI) calculated for $C_{19}H_{24}ClN_6O_4$ 435.1548 $(M+H)^+$, found 435.1536.



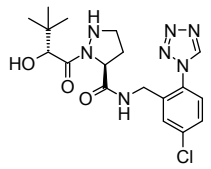
Compound 29, (2S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]thiazolidine-2-carboxamide

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.66 (d, 1H), 7.40 (dd, 1H), 7.24 (s, 1H), 7.04 (t, 1H), 5.61 (s, 1H), 4.26 (dd, 1H), 4.16 (dd, 1H), 4.09 (q, 1H), 3.89 – 4.02 (m, 3H), 3.33 (dt, 1H), 3.06 (dt, 1H), 0.92 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_3S$ 451.1319 $(M+H)^+$, found 451.132.



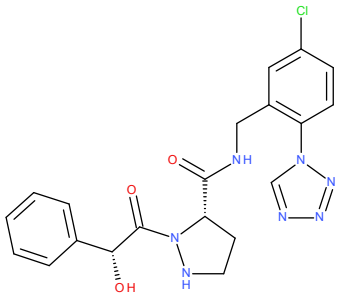
Compound 30, (4R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]thiazolidine-4-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, 1H), 7.69 (d, 1H), 7.49 (d, 1H), 7.30 (s, 1H), 7.19 (s, 1H), 4.96 (dd, 1H), 4.77 (d, 1H), 4.57 (d, 1H), 4.31 (tt, 2H), 4.1 – 4.16 (m, 1H), 3.54 (dd, 1H), 3.05 – 3.18 (m, 2H), 1.04 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_3S$ 439.1319 $(M+H)^+$, found 439.1310.



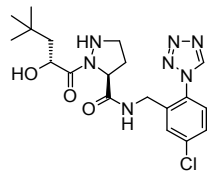
Compound 31, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-3,3-dimethylbutanoyl]pyrazolidine-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.68 (bt, 1H), 7.59 (d, 1H), 7.47 (dd, 1H), 7.28 (d, 1H), 4.62 (dd, 1H), 4.46 (dd, 1H), 4.37 (d, 1H), 4.28 (dd, 1H), 4.10-4.25 (m, 2H), 3.30-3.37 (m, 1H), 2.78-2.88 (m, 1H), 2.54-2.64 (m, 1H), 2.25-2.33 (m, 1H), 0.97 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{25}ClN_7O_3$ 422.1707 $(M+H)^+$, found 422.1708.



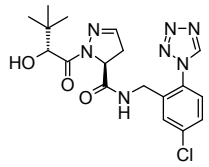
Compound 32, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-2-phenylacetyl]pyrazolidine-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.69 (bt, 1H), 7.61 (d, 1H), 7.45 (dd, 1H), 7.35-7.38 (m, 2H), 7.25-7.33 (m, 4H), 5.61 (d, 1H), 4.51 (d, 1H), 4.42 (t, 1H), 4.35 (dd, 1H), 4.18-4.26 (m, 2H), 3.01-3.08 (m, 1H), 2.25-2.35 (m, 1H), 2.14-2.17 (m, 2H). HRMS (ESI) calculated for $C_{20}H_{21}ClN_7O_3$ 442.1394 $(M+H)^+$, found 442.1418.



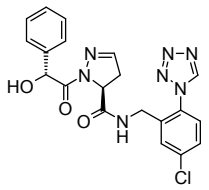
Compound 33, (3S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-2-[(2R)-2-hydroxy-4,4-dimethylpentanoyl]pyrazolidine-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.64 (bt, 1H), 7.59 (d, 1H), 7.46 (dd, 1H), 7.28 (d, 1H), 4.69 (dd, 1H), 4.52 (t, 1H), 4.40 (dd, 1H), 4.18 (dd, 1H), 3.33 (dd, 1H), 2.75 (ddd, 1H), 2.46-2.56 (m, 1H), 2.27-2.37 (m, 1H), 1.46 (dd, 1H), 1.35 (dd, 1H), 1.01 (s, 9H). HRMS (ESI) calculated for $C_{19}H_{27}ClN_7O_3$ 436.1864 $(M+H)^+$, found 436.1881.



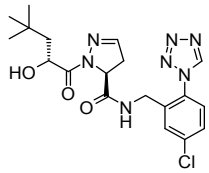
Compound 34, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-3,3-dimethylbutanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.91 (bt, 1H), 7.58 (d, 1H), 7.43 (dd, 1H), 7.25 (d, 1H), 7.03 (s, 1H), 4.87 (dd, 1H), 4.63 (s, 1H), 4.20-4.30 (m, 2H), 3.56 (dd, 1H), 3.15 (bs, 1H), 2.99 (dd, 1H), 0.93 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{23}ClN_7O_3$ 420.1551 $(M+H)^+$, found 420.1534.



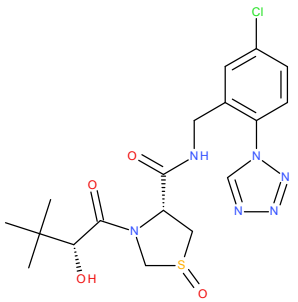
Compound 35, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-2-phenylacetyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, CD_3OD): δ 9.56 (s, 1H), 7.75 (d, 1H), 7.57 (dd, 1H), 7.50 (d, 1H), 7.43-7.47 (m, 2H), 7.23-7.33 (m, 3H), 7.00 (bs, 1H), 5.88 (s, 1H), 4.59 (dd, 1H), 4.27 (q, 2H), 3.13 (ddd, 1H), 2.86 (ddd, 1H). HRMS (ESI) calculated for $C_{20}H_{19}ClN_7O_3$ 440.1238 $(M+H)^+$, found 440.1246.



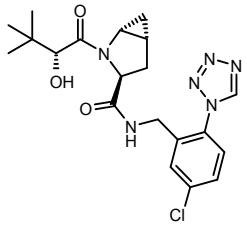
Compound 36, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-4,4-dimethylpentanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.05 (s, 1H), 7.89 (bt, 1H), 7.61 (d, 1H), 7.46 (dd, 1H), 7.28 (d, 1H), 7.05 (s, 1H), 4.89 (ddd, 1H), 4.83 (dd, 1H), 4.27 (d, 2H), 3.55 (ddd, 1H), 3.16 (d, 1H), 3.06 (ddd, 1H), 1.53 (dd, 1H), 1.40 (dd, 1H), 1.01 (s, 9H). HRMS (ESI) calculated for $C_{19}H_{25}ClN_7O_3$ 434.1707 $(M+H)^+$, found 434.1702.



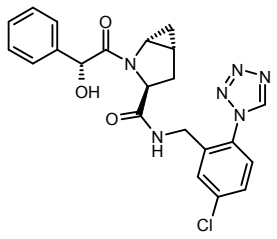
Compound 37, (4R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]-1-oxo-1,3-thiazolidine-4-carboxamide

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.74 (t, 1H), 7.62 (d, 1H), 7.43 (dd, 1H), 7.26 (s, 1H), 6.10 (dd, 1H), 5.26 (d, 1H), 4.34 (dd, 1H), 4.06 – 4.17 (m, 1H), 4.03 (s, 2H), 3.91 (d, 1H), 3.15 – 3.29 (m, 2H), 0.93 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_4S$ 455.1268 $(M+H)^+$, found 455.1256.



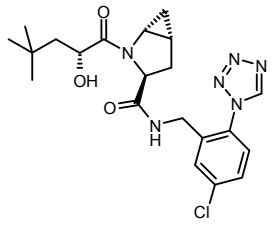
Compound 38, (1R,3S,5R)-2-((R)-2-Hydroxy-3,3-dimethyl-butyryl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.22 (s, 1H), 7.71 (d, 1H), 7.50 (dd, 1H), 7.41 (d, 1H), 7.06 (m, 1H), 4.20 (s, 1H), 4.14 (m, 3H), 3.61 (m, 1H), 2.18 (m, 2H), 1.81 (m, 1H), 0.98 (s, 9H), 0.94 (m, 1H), 0.53 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1760.



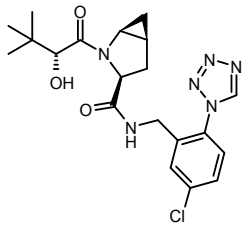
Compound 39, (1R,3S,5R)-2-((R)-2-Hydroxy-2-phenyl-acetyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.59 (d, 1H), 7.55 (m, 1H), 7.36 (dd, 1H), 7.26-7.21 (m, 6H), 5.30 (s, 1H), 4.29 (dd, 1H), 4.17 (d, 2H), 3.21 (m, 1H), 2.33 (m, 1H), 1.84 (m, 1H), 1.68 (m, 1H), 0.39 (m, 1H), -0.49 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{21}ClN_6O_3$ 453.1442 $(M+H)^+$, found 453.1474.



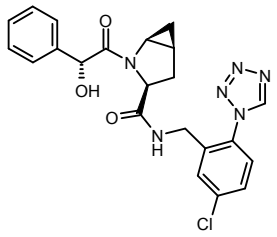
Compound 40, (1R,3S,5R)-2-((R)-2-Hydroxy-4,4-dimethyl-pentanoyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.20 (s, 1H), 7.69 (d, 1H), 7.51 (dd, 1H), 7.41 (d, 1H), 7.04 (m, 1H), 4.59 (t, 1H), 4.15 (m, 3H), 3.41 (m, 1H), 3.33 (d, 1H), 2.20 (m, 1H), 1.81 (m, 2H), 1.26 (dd, 1H), 1.03 (s, 9H), 0.97 (m, 1H), 0.55 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O_3$ 447.1911 $(M+H)^+$, found 447.1884.



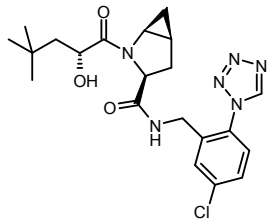
Compound 41, (1S,3S,5S)-2-((R)-2-Hydroxy-3,3-dimethyl-butyryl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.20 (s, 1H), 7.68 (d, 1H), 7.50 (dd, 1H), 7.41 (d, 1H), 7.28 (m, 1H), 4.64 (dd, 1H), 4.20 (m, 2H), 4.05 (dd, 1H), 3.70 (m, 1H), 2.37 (m, 1H), 2.01 (dd, 1H), 1.66 (m, 1H), 1.13 (m, 1H), 0.99 (s, 9H), 0.69 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1751.



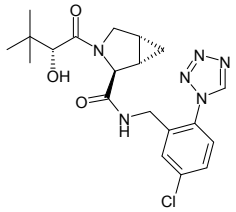
Compound 42, (1S,3S,5S)-2-((R)-2-Hydroxy-2-phenyl-acetyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.65 (d, 1H), 7.59 (m, 1H), 7.42 (dd, 1H), 7.35 (m, 5H), 7.26 (d, 1H), 5.31 (s, 1H), 4.73 (dd, 1H), 4.19 (ddd, 2H), 3.12 (m, 1H), 2.24 (m, 2H), 1.49 (m, 1H), 0.96 (m, 1H), 0.74 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{21}ClN_6O_3$ 453.1442 $(M+H)^+$, found 453.1475.



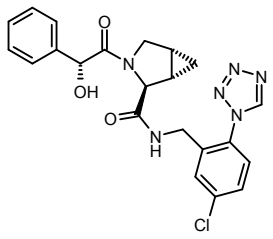
Compound 43, (1S,3S,5S)-2-((R)-2-Hydroxy-4,4-dimethyl-pentanoyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.19 (s, 1H), 7.69 (d, 1H), 7.51 (dd, 1H), 7.41 (d, 1H), 7.12 (m, 1H), 4.59 (dd, 1H), 4.48 (d, 1H), 4.19 (dd, 1H), 4.06 (dd, 1H), 3.38 (m, 1H), 2.42 (m, 1H), 1.96 (m, 1H), 1.66 (m, 1H), 1.62 (d, 1H), 1.42 (dd, 1H), 1.03 (s, 9H), 0.98 (m, 1H), 0.77 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O_3$ 447.1911 $(M+H)^+$, found 447.1870



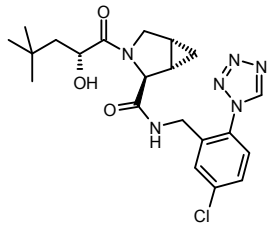
Compoun 44, (1S,2S,5R)-3-((R)-2-Hydroxy-3,3-dimethyl-butyryl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.60 (d, 1H), 7.43 (t, 1H), 7.41 (dd, 1H), 7.25 (d, 1H), 4.50 (s, 1H), 4.25 (dd, 1H), 4.18 (dd, 1H), 3.91 (d, 1H), 3.79 (d, 1H), 3.75 (dd, 1H), 3.08 (d, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 0.94 (s, 9H), 0.75 (m, 1H), 0.21 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1757.



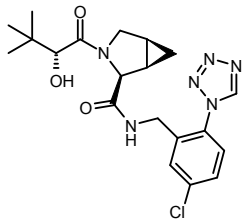
Compound 45, (1S,2S,5R)-3-((R)-2-Hydroxy-2-phenyl-acetyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN) for the major rotamer: δ 9.22 (s, 1H), 7.66 (d, 1H), 7.52 (dd, 1H), 7.43 (d, 1H), 7.40-7.19 (m, 6H), 5.08 (s, 1H), 4.41 (s, 1H), 4.21 (m, 2H), 3.59 (dd, 1H), 3.31 (d, 1H), 1.49 (m, 2H), 0.53 (m, 1H), -0.41 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{21}ClN_6O_3$ 453.1442 $(M+H)^+$, found 453.1440.



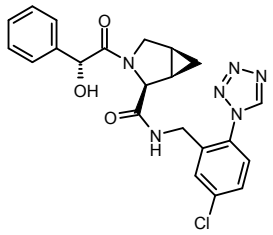
Compound 46, (1S,2S,5R)-3-((R)-2-Hydroxy-4,4-dimethyl-pentanoyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN) for the major rotamer: δ 9.19 (s, 1H), 7.64 (d, 1H), 7.50 (dd, 1H), 7.41 (d, 1H), 7.14 (m, 1H), 4.32 (s, 1H), 4.20 (m, 3H), 3.70 (dd, 1H), 3.58 (d, 1H), 1.65 (m, 1H), 1.56 (m, 1H), 1.39 (d, 1H), 1.29 (dd, 1H), 0.99 (s, 9H), 0.77 (m, 1H), 0.18 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O_3$ 447.1911 $(M+H)^+$, found 447.1878.



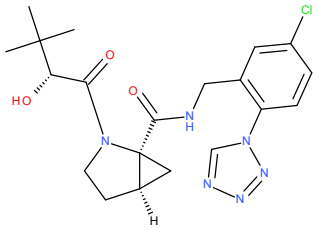
Compound 47, (1R,2S,5S)-3-((R)-2-Hydroxy-3,3-dimethyl-butyryl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.22 (s, 1H), 7.80 (d, 1H), 7.49 (dd, 1H), 7.41 (d, 1H), 6.92 (m, 1H), 4.35 (d, 1H), 4.15 (d, 2H), 3.84 (m, 2H), 3.76 (d, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 0.94 (s, 9H), 0.71 (m, 1H), 0.66 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1754.



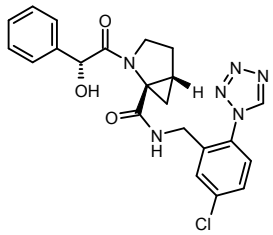
Compound 48, (1R,2S,5S)-3-((R)-2-Hydroxy-2-phenyl-acetyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.23 (s, 1H), 7.80 (d, 1H), 7.52 (dd, 1H), 7.44-7.32 (m, 6H), 6.97 (m, 1H), 5.04 (d, 1H), 4.34 (d, 1H), 4.19 (m, 2H), 3.60 (d, 1H), 3.04 (m, 1H), 1.79 (m, 1H), 1.55 (m, 1H), 0.64 (m, 2H). HRMS (ESI) calculated for $C_{22}H_{21}ClN_6O_3$ 453.1442 $(M+H)^+$, found 453.1441.



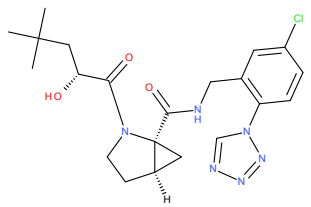
Compound 49, (1S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-2-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]-2-azabicyclo[3.1.0]hexane-1-carboxamide

^{1}H NMR (500 MHz, CD_3OD) δ 9.56 (s, 1H), 7.77 (d, 1H), 7.53 (dd, 1H), 7.47 (d, 1H), 4.18 – 4.37 (m, 2H), 3.93 – 4.06 (m, 2H), 3.31 (dt, 1H), 2.36 (td, 1H), 1.93 – 2.05 (m, 2H), 1.83 – 1.93 (m, 1H), 0.99 (s, 9H), 0.91 – 0.94 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{26}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1737.



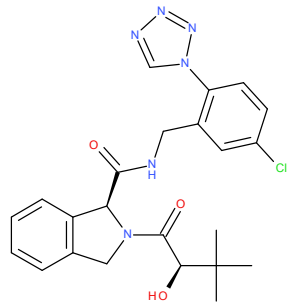
Compound 50, (1*S*,5*R*)-*N*-[5-chloro-2-(1*H*-tetrazol-1-yl)benzyl]-2-[(2*R*)-2-hydroxy-2-phenylacetyl]-2-azabicyclo[3.1.0]hexane-1-carboxamide

^{1}H NMR (500 MHz, cd_3cn) δ 9.27 (s, 1H), 7.83 (d, 1H), 7.17 – 7.63 (m, 8H), 5.12 (s, 1H), 4.34 (dd, 1H), 4.12 (dd, 1H), 3.63 – 3.87 (m, 2H), 3.25 (dd, 1H), 2.06 – 2.2 (m, 1H), 1.86 (ddd, 2H), 1.31 – 1.43 (m, 1H), 0.65 (t, 1H). HRMS (ESI) calculated for $C_{22}H_{21}ClN_6O_3$ 453.1449 $(M)^+$, found 453.1442.



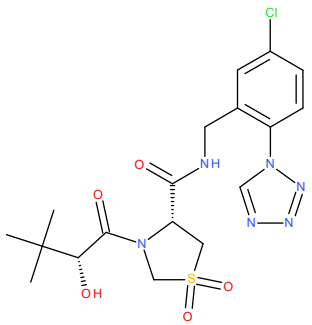
Compound 51, (1S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-2-[(2R)-2-hydroxy-4,4-dimethyl-pentanoyl]-2-azabicyclo[3.1.0]hexane-1-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.71 (d, 1H), 7.44 (d, 1H), 7.23 – 7.35 (m, 2H), 4.18 – 4.42 (m, 3H), 3.96 (q, 1H), 3.59 (t, 1H), 2.32 – 2.45 (m, 1H), 2.19 (q, 1H), 2.00 (dd, 1H), 1.85 (q, 1H), 1.42 (dd, 1H), 1.23 (d, 1H), 1.02 (s, 9H), 0.81 – 0.92 (m, 2H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O_3$ 447.1911 $(M+H)^+$, found 447.1917



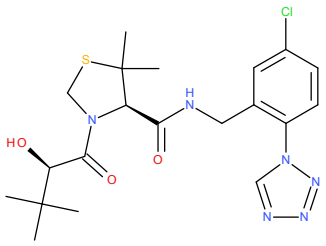
Compound 52, (1S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-2-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]isoindoline-1-carboxamide

^{1}H NMR (400 MHz, CD_3OD) δ 9.37 – 9.56 (m, 1H), 7.63 (d, 1H), 7.4 – 7.53 (m, 2H), 7.32 (dq, 4H), 5.52 (d, 1H), 4.98 – 5.19 (m, 2H), 4.01 – 4.31 (m, 3H), 1.02 (s, 9H). HRMS (ESI) calculated for $C_{23}H_{26}ClN_6O_3$ 469.1755 $(M+H)^+$, found 469.1737.



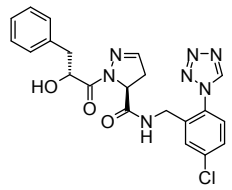
Compound 53, (4R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]-1,1-dioxo-1,3-thiazolidine-4-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.67 (d, 1H), 7.51 (dd, 1H), 7.41 (t, 1H), 7.32 (d, 1H), 5.4 – 5.48 (m, 1H), 5.33 (s, 1H), 5.27 – 5.33 (m, 1H), 4.32 – 4.39 (m, 2H), 4.24 (dd, 1H), 4.04 (s, 1H), 3.77 (dd, 1H), 3.34 – 3.42 (m, 1H), 1.00 (s, 9H). HRMS (ESI) calculated for $C_{18}H_{24}ClN_6O_5S$ 471.1217 $(M+H)^+$, found 471.1235.



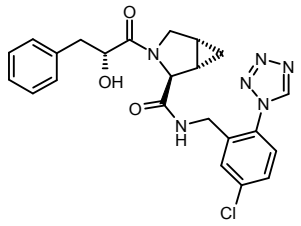
Compound 54, (4R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3,3-dimethyl-butanoyl]-5,5-dimethyl-thiazolidine-4-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.69 (s, 1H), 7.36 – 7.43 (m, 1H), 7.23 (d, 1H), 6.76 (s, 1H), 4.91 (d, 1H), 4.73 (d, 1H), 4.37 (dd, 1H), 4.27 (s, 1H), 4.12 (dd, 1H), 4.00 (s, 1H), 3.00 (s, 1H), 1.51 (s, 3H), 1.35 (s, 3H), 0.97 (s, 9H). HRMS (ESI) calculated for $C_{20}H_{28}ClN_6O_3S$ 467.1632 $(M+H)^+$, found 467.1635.



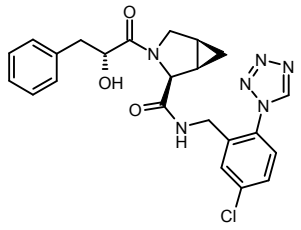
Compound 55, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-3-phenylpropanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, CD_3OD): δ 9.54 (s, 1H), 7.73 (s, 1H), 7.55 (d, 1H), 7.48 (d, 1H), 7.15-28 (m, 5H), 7.03 (s, 1H), 5.05 (bs, 1H), 4.58-4.65 (m, 1H), 4.25 (q, 2H), 3.13-3.23 (m, 1H), 3.01-3.08 (m, 1H), 2.82-2.93 (m, 2H). HRMS (ESI) calculated for $C_{21}H_{21}ClN_7O_3$ 454.1394 $(M+H)^+$, found 454.1381.



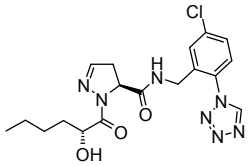
Compound 56, (1S,2S,5R)-3-((R)-2-Hydroxy-3-phenyl-propionyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.59 (d, 1H), 7.45 (dd, 1H), 7.34-7.19 (m, 7H), 4.45 (s, 1H), 4.42 (t, 1H), 4.29 (dd, 1H), 4.19 (dd, 1H), 3.63 (dd, 1H), 3.38 (d, 1H), 2.92 (d, 1H), 1.79 (m, 1H), 1.62-1.58 (m, 2H), 0.68 (m, 1H), -0.20 (m, 1H). HRMS (ESI) calculated for $C_{23}H_{23}ClN_6O_3$ 467.1598 $(M+H)^+$, found 467.1562.



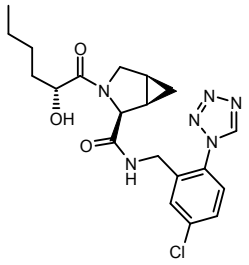
Compound 57, (1R,2S,5S)-3-((R)-2-Hydroxy-3-phenyl-propionyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.75 (d, 1H), 7.43 (dd, 1H), 7.32-7.19 (m, 6H), 6.34 (m, 1H), 4.34-4.24 (m, 4H), 3.62 (d, 1H), 3.18 (dd, 1H), 2.96 (dd, 1H), 2.88 (dd, 1H), 1.87 (m, 1H), 1.59 (m, 1H), 0.74 (m, 2H). HRMS (ESI) calculated for $C_{23}H_{23}ClN_6O_3$ 467.1598 $(M+H)^+$, found 467.1589.



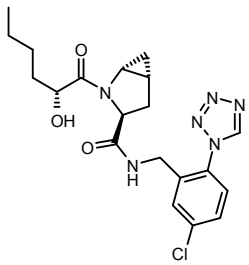
Compound 58, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxyhexanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (600 MHz, CD_3CN): δ 9.19 (s, 1H), 7.69 (d, 1H), 7.54 (dd, 1H), 7.44 (d, 1H), 7.30 (br. t, 1H), 7.04 (br. t, 1H), 4.68-4.63 (m, 2H), 4.25-4.13 (m, 2H), 3.29 (d, 1H), 3.20-3.14 (dd, 1H), 2.99-2.94 (dd, 1H), 1.76-1.69 (m, 1H), 1.55-1.48 (m, 1H), 1.42-1.28 (m, 4H), 0.91 (t, 3H), HRMS (ESI) calculated for $C_{18}H_{22}ClN_7O_3$ 420.1551 $(M+H)^+$, found 420.1556.



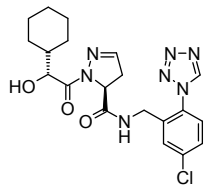
Compound 59, (1S,4S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxyhexanoyl]-3-azabicyclo[3.1.0]hexane-4-carboxamide

^{1}H NMR (400 MHz, CD_3CN) for the major rotamer: δ 9.21 (s, 1H), 7.64 (d, 1H), 7.50 (dd, 1H), 7.41 (d, 1H), 7.17 (m, 1H), 4.34 (s, 1H), 4.24-4.12 (m, 3H), 3.69 (dd, 1H), 3.62 (d, 1H), 1.65-1.54 (m, 3H), 1.41-1.28 (m, 5H), 0.89 (m, 3H), 0.77 (m, 1H), 0.15 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1751.



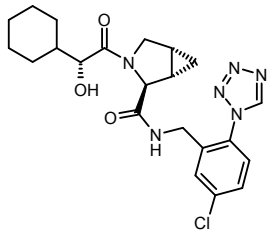
Compound 60, (1R,3S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-4-[(2R)-2-hydroxyhexanoyl]-4-azabicyclo[3.1.0]hexane-3-carboxamide

^{1}H NMR (400 MHz, CD_3CN): δ 9.21 (s, 1H), 7.68 (d, 1H), 7.49 (dd, 1H), 7.41 (d, 1H), 7.12 (m, 1H), 4.46 (dd, 1H), 4.14 (m, 3H), 3.44 (m, 1H), 2.26-2.09 (m, 2H), 1.82 (m, 2H), 1.57 (m, 1H), 1.40-1.31 (m, 4H), 0.96-0.89 (m, 4H), 0.52 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_3$ 433.1755 $(M+H)^+$, found 433.1735.



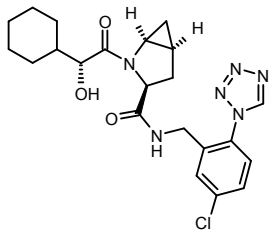
Compound 61, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-cyclohexyl-2-hydroxyacetyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.92 (bt, 1H), 7.61 (d, 1H), 7.44 (dd, 1H), 7.28 (d, 1H), 7.05 (s, 1H), 4.85 (dd, 1H), 4.58 (d, 1H), 4.26 (d, 2H), 3.50 (ddd, 1H), 3.09 (ddd, 1H), 2.80 (bs, 1H), 1.43-1.76 (m, 6H), 1.06-1.36 (m, 5H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_7O_3$ 446.1707 $(M+H)^+$, found 446.1739.



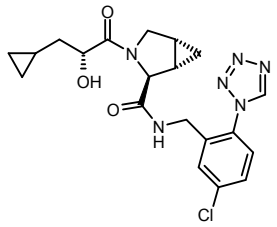
Compound 62, (1S,2S,5R)-3-((R)-2-Cyclohexyl-2-hydroxy-acetyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.59 (d, 1H), 7.43 (dd, 1H), 7.36 (m, 1H), 7.26 (d, 1H), 4.50 (s, 1H), 4.24 (ddd, 2H), 4.01 (d, 1H), 3.66 (m, 2H), 1.83-1.13 (m, 13H), 0.82 (m, 1H), 0.10 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{27}ClN_6O_3$ 459.1911 $(M+H)^+$, found 459.1911.



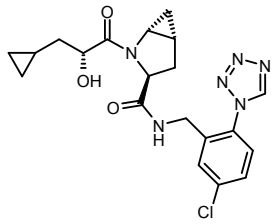
Compound 63, (1S,3S,5S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-4-[(2R)-2-cyclohexyl-2-hydroxy-acetyl]-4-azabicyclo[3.1.0]hexane-3-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H), 7.31 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.42 (dd, *J* = 8.9 Hz, *J* = 3.4 Hz, 1H), 4.31 (d, *J* = 4.0 Hz, 1H), 4.22 (d, *J* = 5.8 Hz, 2H), 3.35 (m, 1H), 2.58 (m, 1H), 2.05-1.08 (m, 14H), 0.50 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{27}ClN_6O_3$ 459.1911 (M+H)+, found 459.1923.



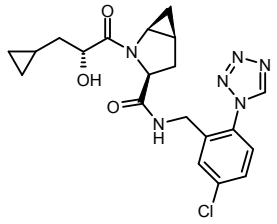
Compound 64, (1S,2S,5R)-3-((R)-3-Cyclopropyl-2-hydroxy-propionyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.60 (d, 1H), 7.45 (dd, 1H), 7.27 (m, 1H), 7.20 (m, 1H), 4.50 (s, 1H), 4.26 (m, 3H), 3.68 (dd, 1H), 3.59 (d, 1H), 1.86 (m, 1H), 1.70 (m, 1H), 1.59 (m, 1H), 1.36 (m, 1H), 0.83 (m, 2H), 0.51 (m, 2H), 0.10 (m, 3H). HRMS (ESI) calculated for $C_{20}H_{23}ClN_6O_3$ 431.1598 $(M+H)^+$, found 431.1628.



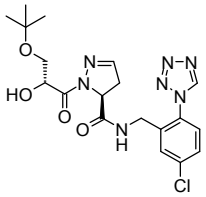
Compound 65, (1R,3S,5R)-2-((R)-3-Cyclopropyl-2-hydroxy-propionyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.61 (d, 1H), 7.45 (dd, 1H), 7.25 (m, 2H), 4.59 (dd, 1H), 4.44 (dd, 1H), 4.25 (m, 2H), 3.33 (m, 1H), 2.69 (m, 1H), 1.95 (m, 2H), 1.76 (m, 1H), 1.51 (m, 1H), 1.08 (m, 1H), 0.92 (m, 1H), 0.50 (m, 3H), 0.10 (m, 2H). HRMS (ESI) calculated for $C_{20}H_{23}ClN_6O_3$ 431.1598 $(M+H)^+$, found 431.1587.



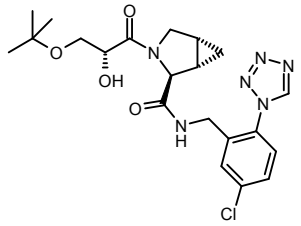
Compound 66, (1S,3S,5S)-2-((R)-3-Cyclopropyl-2-hydroxy-propionyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.60 (m, 1H), 7.57 (d, 1H), 7.44 (dd, 1H), 7.26 (d, 1H), 4.74 (dd, 1H), 4.59 (dd, 1H), 4.21 (m, 2H), 3.37 (m, 1H), 2.61 (dd, 1H), 2.17 (m, 1H), 1.72 (m, 2H), 1.53 (m, 1H), 0.91 (m, 1H), 0.76 (m, 2H), 0.53 (m, 2H), 0.11 (m, 2H). HRMS (ESI) calculated for $C_{20}H_{23}ClN_6O_3$ 431.1598 $(M+H)^+$, found 431.1592.



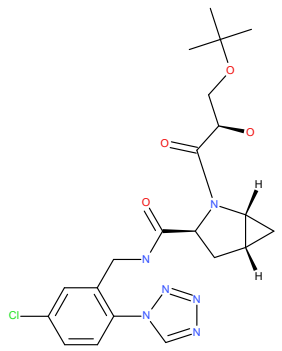
Compound 67, (5S)-1-[(2R)-3-*tert*-Butoxy-2-hydroxypropanoyl]-*N*-[5-chloro-2-(1H-tetrazol-1-yl)benzyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.92 (br. t, 1H), 7.59 (d, 1H), 7.47 (dd, 1H), 7.28 (d, 1H), 7.06 (s, 1H), 4.90 (d, 1H), 4.89 (dd, 1h), 4.33-4.21 (m, 2H), 3.69-3.62 (m, 2H), 3.65-3.58 (m, 1H), 3.07-2.98 (m, 1H), 1.13 (s, 9H), HRMS (ESI) calculated for $C_{19}H_{24}ClN_7O_4$ 450.1660 $(M+H)^+$, found 450.1680.



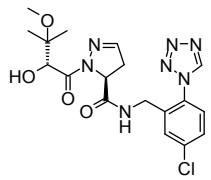
Compound 68, (1S,2S,5R)-3-((R)-3-tert-Butoxy-2-hydroxy-propionyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.58 (d, 1H), 7.45 (dd, 1H), 7.26 (m, 2H), 4.58 (s, 1H), 4.34 (m, 1H), 4.24 (m, 2H), 4.07 (d, 1H), 3.58 (m, 2H), 3.37 (t, 1H), 1.85 (m, 1H), 1.65 (m, 1H), 1.17 (s, 9H), 0.76 (m, 1H), 0.27 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O4$ 463.1860 $(M+H)^+$, found 463.1860.



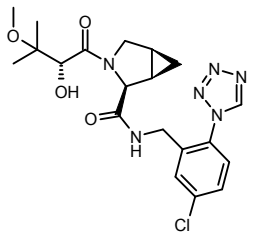
Compound 69, (1R,3S,5R)-2-((R)-3-tert-Butoxy-2-hydroxy-propionyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H), 7.26 (m, 2H), 4.61 (m, 1H), 4.50 (dd, *J* = 8.8 Hz, *J* = 2.9 Hz, 1H), 4.24 (m, 2H), 3.66 (m, 2H), 3.43 (m, 1H), 2.71 (m, 1H), 2.01-1.89 (m, 2H), 1.20 (s, 9H), 1.08 (m, 1H), 0.61 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}ClN_6O4$ 463.1860 (M+H)+, found 463.1879.



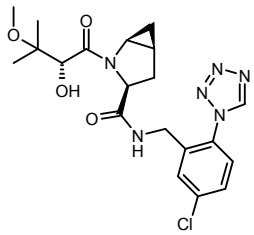
Compound 70, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-3-methoxy-3-methylbutanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (600 MHz, $CDCl_3$): ca 3:2 mixture of diastereomers, data for major isomer: δ 9.02 (s, 1H), 7.91 (bt, 1H), 7.53 (d, 1H), 7.40 (dd, 1H), 7.25 (d, 1H), 7.01 (s, 1H), 4.75-4.93 (m, 2H), 4.10-4.25 (m, 2H), 3.17 (s, 3H), 2.95-3.60 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H). HRMS (ESI) calculated for $C_{18}H_{23}ClN_7O_4$ 436.1497 (M+H)+, found 436.150.



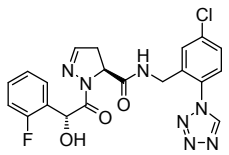
Compound 71, (1R,2S,5S)-3-(2-Hydroxy-3-methoxy-3-methyl-butyryl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 8.99 (s, 1H), 7.78 (d, 1H), 7.43 (dd, 1H), 7.25 (m, 1H), 6.10 (m, 1H), 4.41 (d, 1H), 4.31 (dd, 1H), 4.23 (dd, 1H), 4.16 (dd, 1H), 3.97 (d, 1H), 3.67 (d, 1H), 3.19 (s, 3H), 3.15 (d, 1H), 1.89 (m, 1H), 1.71 (m, 1H), 1.28 (s, 3H)m, 1.13 (s, 3H), 0.75 (m, 2H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_4$ 449.1704 $(M+H)^+$, found 449.1700.



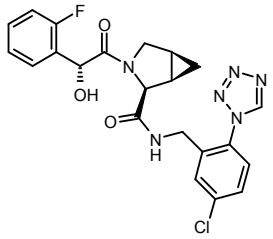
Compound 72, (1S,3S,5S)-2-(2-Hydroxy-3-methoxy-3-methyl-butyryl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 9.01 (s, 1H), 7.59 (m, 2H), 7.43 (dd, 1H), 7.25 (m, 1H), 4.80 (dd, 1H), 4.35 (s, 1H), 4.19 (d, 2H), 4.07 (m, 1H), 3.22 (s, 3H), 2.57 (dd, 1H), 2.21 (m, 1H), 1.64 (m, 1H), 1.35 (s, 3H)m, 1.14 (s, 3H), 0.69 (m, 2H). HRMS (ESI) calculated for $C_{20}H_{25}ClN_6O_4$ 449.1704 $(M+H)^+$, found 449.1692.



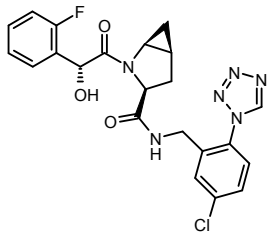
Compound 73, (3S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-2-[(2R)-2-(2-fluorophenyl)-2-hydroxy-acetyl]-3,4-dihydropyrazole-3-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) for the most potent isomer: δ 9.00 (s, 1H), 7.81 (br. t, 1H), 7.62 (d, 1H), 7.47 (dd, 1H), 7.35 (ddd, 1H), 7.31-7.27 (m, 2H), 7.10 (dd, 1H), 7.02 (dd, 1H), 6.91 (br. s, 1H), 5.96 (d, 1H), 4.81 (dd, 1H), 4.29(d, 2H), 4.08 (d, 1H), 3.53 (dddd, 1H), 2.98-2.87 (m, 1H), HRMS (ESI) calculated for $C_{20}H_{18}ClFN_7O_3$ 458.1143 $(M+H)^+$, found 458.1136.



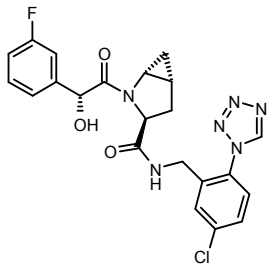
Compound 74, (1S,4S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-(2-fluorophenyl)-2-hydroxy-acetyl]-3-azabicyclo[3.1.0]hexane-4-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 9.13 (s, 1H), 7.80 (d, 1H), 7.42 (dd, 1H), 7.33-7.25 (m, 3H), 7.16-7.05 (m, 2H), 6.87 (m, 1H), 5.36 (s, 1H), 4.37 (d, 1H), 4.28 (d, 2H), 3.65 (d, 1H), 3.07 (m, 1H), 1.83 (m, 1H), 1.59 (m, 1H), 0.86 (m, 1H), 0.72 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{20}ClFN_6O_3$ 471.1348 $(M+H)^+$, found 471.1349.



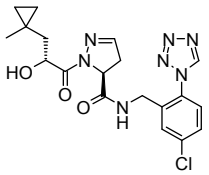
Compound 75, (1S,3S,5S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-4-[(2R)-2-(2-fluorophenyl)-2-hydroxy-acetyl]-4-azabicyclo[3.1.0]hexane-3-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 9.04 (s, 1H), 7.65 (d, 1H), 7.45 (dd, 1H), 7.41-7.31 (m, 3H), 7.27 (d, 1H), 7.19-7.08 (m, 2H), 5.67 (d, 1H), 4.73 (dd, 1H), 4.33 (d, 1H), 4.27 (dd, 1H), 4.20 (dd, 1H), 3.13 (m, 1H), 2.40 (dd, 1H), 2.19 (m, 1H), 1.54 (m, 1H), 0.91 (m, 1H), 0.78 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{20}ClFN_6O_3$ 471.1348 $(M+H)^+$, found 471.1342.



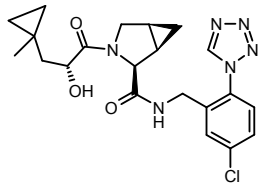
Compound 76, (1R,3S,5R)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-4-[(2R)-2-(3-fluorophenyl)-2-hydroxy-acetyl]-4-azabicyclo[3.1.0]hexane-3-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 8.95 (s, 1H), 7.57 (d, 1H), 7.47 (dd, 1H), 7.32-7.26 (m, 2H), 7.11-6.97 (m, 4H), 5.31 (s, 1H), 4.59 (dd, 1H), 4.24 (dd, 1H), 4.14 (dd, 1H), 2.90 (m, 1H), 2.64 (m, 1H), 2.03 (dd, 1H), 1.81 (m, 1H), 1.10 (m, 1H), 0.61 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{20}ClFN_6O_3$ 471.1348 $(M+H)^+$, found 471.1331.



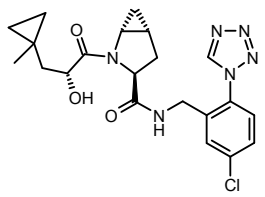
Compound 77, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-3-(1-methylcyclopropyl)propanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.90 (bt, 1H), 7.61 (d, 1H), 7.47 (dd, 1H), 7.29 (d, 1H), 7.06 (s, 1H), 4.97 (ddd, 1H), 4.84 (dd, 1H), 4.28 (d, 2H), 3.61 (ddd, 1H), 3.17 (d, 1H), 3.04 (ddd, 1H), 1.70 (dd, 1H), 1.47 (dd, 1H), 1.16 (s, 3H), 0.20-0.42 (m, 4H). HRMS (ESI) calculated for $C_{19}H_{23}ClN_7O_3$ 432.1551 $(M+H)^+$, found 432.1541.



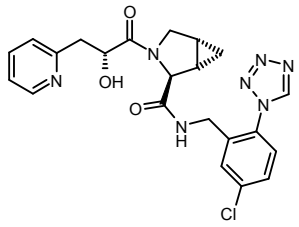
Compound 78, (1R,2S,5S)-3-[(R)-2-Hydroxy-3-(1-methyl-cyclopropyl)-propionyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.73 (d, 1H), 7.39 (dd, 1H), 7.26 (d, 1H), 6.98 (broad m, 1H), 4.38 (d, 1H), 4.30-4.15 (m, 3H), 3.79 (d, 1H), 3.73-3.67 (m, 1H), 3.40 (broad s, 1H), 1.96-1.90 (m, 1H), 1.80-1.73 (m, 1H), 1.64 (dd, 1H), 1.32 (dd, 1H), 1.11 (s, 3H), 0.84-0.74 (m, 2H), 0.48-0.38 (m, 1H), 0.36-0.31 (m, 1H), 0.28-0.21 (m, 2H). HRMS (ESI) calculated for $C_{21}H_{25}ClN_6O_3$ 445.1755 $(M+H)^+$, found 445.1749.



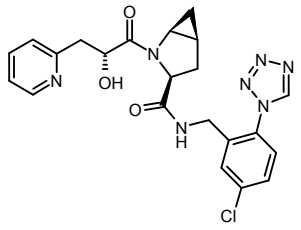
Compound 79, (1R,3S,5R)-2-[(R)-2-Hydroxy-3-(1-methyl-cyclopropyl)-propionyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.61 (d, 1H), 7.44 (dd, 1H), 7.31 (t, 1H), 4.67 (m, 1H), 4.41(dd, 1H), 2.68-2.61 (m, 1H), 2.03-1.97 (m, 1H), 1.97-1.90 (m, 1H), 1.86 (dd, 1H), 1.34 (dd, 1H), 1.17 (s, 3H), 1.13-1.06 (m, 1H), 0.54-0.48 (m, 2H), 0.40-0.35 (m, 1H), 0.31-0.26 (m, 2H). HRMS (ESI) calculated for $C_{21}H_{25}ClN_6O_3$ 445.1755 $(M+H)^+$, found 445.1739.



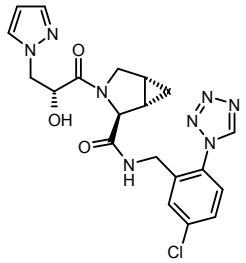
Compound 80, (1R,4S,5S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3-(2-pyridyl)propanoyl]-3-azabicyclo[3.1.0]hexane-4-carboxamide

^{1}H NMR (600 MHz, CD_3OD) δ 9.55 (s, 1H), 8.47 (d, 1H), 8.36 (d, 0.28H), 7.74 (td, 0.72H), 7.69 (d, 0.72H), 7.62 (d, 0.28H), 7.55 (dd, 0.72H), 7.48 (d, 0.72H), 7.45 (d, 0.28H), 7.33 (d, 0.72H), 7.28 (dd, 0.72H), 7.25 (d, 0.28H), 7.22 (dd, 0.28H), 4.80 (s, 0H), 4.65 (dd, 0.72H), 4.49 (dd, 0.28H), 4.39 (s, 0.72H), 4.18 – 4.32 (m, 2H), 3.92 (d, 0.28H), 3.81 (dd, 0.72H), 3.76 (d, 0.72H), 3.53 (dd, 0.28H), 2.92 – 3.12 (m, 2H), 1.66 (dq, 1H), 1.60 (dq, 0.28H), 1.54 (td, 0.72H), 0.78 – 0.84 (m, 0.28H), 0.76 (td, 0.72H), 0.16 – 0.22 (m, 0.28H), -0.03 (q, 0.72H). HRMS (ESI) calculated for $C_{22}H_{22}ClN_7O_3$ 468.1549 $(M+H)^+$, found 468.1551.



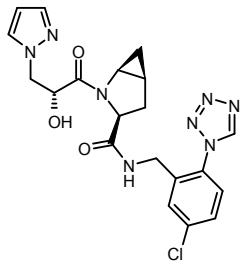
Compound 81, (1S,3S,5S)-2-((R)-2-Hydroxy-3-pyridin-2-yl-propionyl)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9.54 (s, 1H), 8.49 (d, 1H), 7.91 (m, 1H), 7.77 (s, 1H), 7.69 (dt, 1H), 7.58-7.53 (m, 2H), 7.33 (d, 1H), 7.20 (m, 1H), 4.87 (m, 1H), 4.75 (dd, 1H), 4.28 (dd, 1H), 4.19 (dd, 1H), 3.79 (m, 1H), 3.23 (dd, 1H), 3.06 (dd, 1H), 2.39 (m, 1H), 2.11 (dd, 1H), 1.66 (m, 1H), 1.01 (m, 1H), 0.75 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{22}ClN_7O_3$ 468.1551 $(M+H)^+$, found 468.1539.



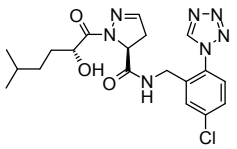
Compound 82, (1R,4S,5S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-3-[(2R)-2-hydroxy-3-pyrazol-1-yl-propanoyl]-3-azabicyclo[3.1.0]hexane-4-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 8.95 (s, 1H), 8.17 (s, 1H), 7.91 (s, 1H), 7.60 (d, 1H), 7.47 (dd, 1H), 7.28-7.26 (m, 1H), 6.96 (m, 1H), 4.58 (m, 1H), 4.47-4.17 (m, 5H), 3.78 (dd, 1H), 3.71 (d, 1H), 1.83 (m, 1H), 1.71 (m, 1H), 0.83 (m, 1H), 0.25 (m, 1H). HRMS (ESI) calculated for $C_{19}H_{20}ClN_9O_3$ 458.1456 $(M+H)^+$, found 458.1440.



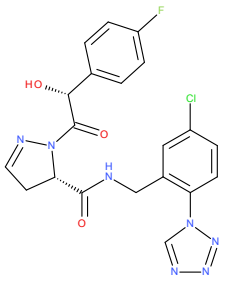
Compound 83, (1S,3S,5S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-4-[(2R)-2-hydroxy-3-pyrazol-1-yl-propanoyl]-4-azabicyclo[3.1.0]hexane-3-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) for the most potent isomer: δ 9.03 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 7.60 (d, 1H), 7.44-7.40 (m, 2H), 7.26 (d, 1H), 4.86 (m, 1H), 4.70 (dd, 1H), 4.52 (dd, 1H), 4.44 (dd, 1H), 4.17 (d, 2H), 3.46 (m, 1H), 2.39 (dd, 1H), 2.28 (m, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 0.86-0.77 (m, 2H). HRMS (ESI) calculated for $C_{19}H_{20}ClN_9O_3$ 458.1456 $(M+H)^+$, found 458.1429.



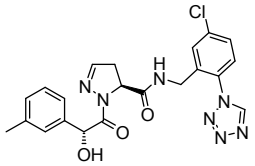
Compound 84, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-5-methylhexanoyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.86 (br. t, 1H), 7.60 (d, 1H), 7.47 (dd, 1H), 7.29 (d, 1H), 7.07 (s, 1H), 4.87(dd, 1H), 4.74 (br. t, 1H), 4.28 (d, 2H), 3.61 (dd, 1H), 3.20 (d, 1H), 3.06 (dd, 1H), 1.78-1.69 (m, 1H), 1.61-1.50 (m, 2H), 1.40-1.29 (m, 2H), 0.89 (t, 6H), HRMS (ESI) calculated for $C_{19}H_{24}ClN_7O_3$ 434.1707 $(M+H)^+$, found 434.1703.



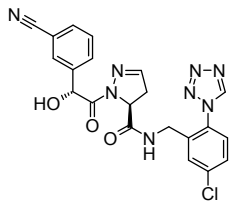
Compound 85, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-(4-fluorophenyl)-2-hydroxyacetyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

1H NMR (600 MHz, CD_3CN) δ 2.93 (ddd, 1H), 3.10 (ddd, 1H), 4.15-4.19 (m, 2H), 4.25 (dd, 1H), 4.60 (dd, 1H), 5.73-5.76 (m, 1H), 6.97-6.99 (m, 1H), 7.07-7.10 (m, 2H), 7.28-7.30 (m, 1H), 7.42-7.46 (m, 3H), 7.54-7.56 (m, 1H), 7.71 (d, 1H), 9.20 (s, 1H). HRMS (ESI) calculated for $C_{20}H_{18}ClFN_7O_3$ 458.1143 $(M+H)^+$, found 458.1141.



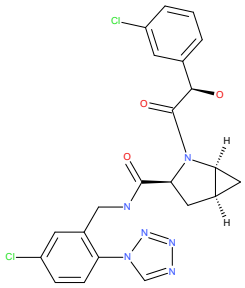
Compound 86, (5S)-*N*-[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]-1-[(2R)-2-hydroxy-2-(3-methylphenyl)acetyl]-4,5-dihydro-1H-pyrazole-5-carboxamide

^{1}H NMR (500 MHz, $CDCl_3$) for the most potent isomer: δ 9.00 (s, 1H), 7.83 (t, 1H), 7.62 (d, 1H), 7.46 (dd, 1H), 7.27-7.16 (m, 4H), 7.11-7.07 (m, 1H), 6.95 (s, 1H), 5.77 (s, 1H), 4.74 (dd, 1H), 4.28 (d, 2H), 4.02 (br., 1H), 3.49 (dd, 1H), 2.91 (m, 1H), 2.32 (s, 3H), HRMS (ESI) calculated for $C_{21}H_{20}ClN_7O_3$ 454.1394 $(M+H)^+$, found 454.1407.



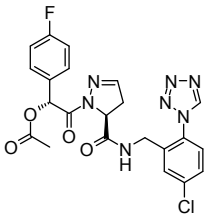
Compound 87, (3S)-N-[[5-chloro-2-(tetrazol-1-yl)phenyl]methyl]-2-[(2R)-2-(3-cyanophenyl)-2-hydroxy-acetyl]-3,4-dihydropyrazole-3-carboxamide

^{1}H NMR (400 MHz, CD_3CN) for the most potent isomer: δ 9.19 (s, 1H), 7.64-7.78 (m, 4H), 7.43-7.57 (m, 3H), 7.27 (bt, 1H), 7.00 (s, 1H), 5.80 (d, 1H), 4.60 (dd, 1H), 4.30 (d, 1H), 4.25 (dd, 1H), 4.16 (dd, 1H), 3.10 (ddd, 1H), 2.92 (ddd, 1H). HRMS (ESI) calculated for $C_{21}H_{18}ClN_8O_3$ 465.1190 $(M+H)^+$, found 465.1185.



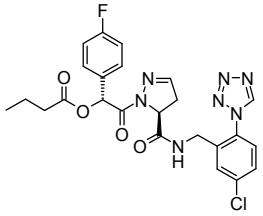
Compound 88, (1S,3S,5S)-2-[(R)-2-(3-Chloro-phenyl)-2-hydroxy-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 5-chloro-2-tetrazol-1-yl-benzylamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.47 (dd, J = 8.5 Hz, J = 2.2 Hz, 1H), 7.39-7.25 (m, 6H), 5.30 (s, 1H), 4.76 (dd, J = 10.5 Hz, J = 2.4 Hz, 1H), 4.29 (dd, J = 15.5 Hz, J = 6.2 Hz, 1H), 4.20 (dd, J = 15.5 Hz, J = 5.7 Hz, 1H), 3.11 (m, 1H), 2.42 (dd, J = 13.3 Hz, J = 2.6 Hz, 1H), 2.21 (m, 1H), 1.57 (m, 1H), 0.93 (m, 1H), 0.79 (m, 1H). HRMS (ESI) calculated for $C_{22}H_{20}Cl_2N_6O_3$ 487.1052 $(M+H)^+$, found 487.1055.



Compound 89, [(1R)-2-[(5S)-5-[[5-Chloro-2-(tetrazol-1-yl)phenyl]methylcarbamoyl]-4,5-dihydropyrazol-1-yl]-1-(4-fluorophenyl)-2-oxo-ethyl] acetate

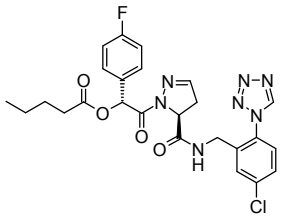
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.60 (d, 1H), 7.53 (m, 2H), 7.46 (dd, 1H), 7.43 (bt, 1H), 7.28 (d, 1H), 7.06 (m, 2H), 7.02 (bt, 1H), 6.53 (s, 1H), 4.81 (dd, 1H), 4.27 (dd, 1H), 4.18 (dd, 1H), 3.30 (ddd, 1H), 3.11 (ddd, 1H), 2.13 (s, 3H), HRMS (ESI) calculated for $C_{22}H_{19}ClFN_7O_4$ 500.1249 $(M+H)^+$, found 500.1267.



Compound 90, (1R)-2-[(5S)-5-{[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]carbamoyl}-4,5-dihydro-1H-pyrazol-1-yl]-1-(4-fluorophenyl)-2-oxoethyl butanoate

^{1}H NMR (500 MHz, $(CH_3)_2SO$*): δ 9.80 (s, 1H), 8.49 (t, 1H), 7.67 (1H), 7.60 (m, 2H), 7.45 (m, 2H), 7.18 (t, 2H), 7.15 (s, 1H), 6.59 (s, 1H), 4.54 (dd, 1H), 4.20 (dd, 1H), 4.05 (dd, 1H), 3.14 (dd, 1H), 2.31 (m, 2H), 1.50, (m, 2H), 0.83 (t, 3H),

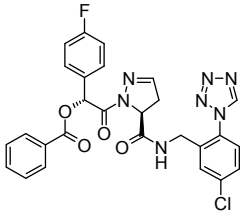
HRMS (ESI) calculated for $C_{24}H_{23}ClFN_7O_4$ $(M+H)^+$, 528.1563 found 528.1573.



Compound 91, (1R)-2-[(5S)-5-{[5-Chloro-2-(1H-tetrazol-1-yl)benzyl]carbamoyl}-4,5-dihydro-1H-pyrazol-1-yl]-1-(4-fluorophenyl)-2-oxoethyl pentanoate

^{1}H NMR (500 MHz, $(CH_3)_2SO$*): δ 9.80 (s, 1H), 8.49 (t, 1H), 7.67 (1H), 7.60 (m, 2H), 7.45 (m, 2H), 7.19 (t, 2H), 7.15 (s, 1H), 6.58 (s, 1H), 4.54 (dd, 1H), 4.20 (dd, 1H), 4.05 (dd, 1H), 3.14 (dd, 1H), 2.73 (dd, 1H), 2.33 (m, 2H), 1.45, (m, 2H), 1.24 (m, 2H), 0.80 (t, 3H),

HRMS (ESI) calculated for $C_{25}H_{25}ClFN_7O_4$ $(M+H)^+$, 542.1719 found 542.1719.



Compound 92, [(1R)-2-[(5S)-5-[[5-Chloro-2-(tetrazol-1-yl)phenyl]methylcarbamoyl]-4,5-dihydropyrazol-1-yl]-1-(4-fluorophenyl)-2-oxo-ethyl] benzoate

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.86 (d, 2H), 7.64 (m, 2H), 7.59 (m, 1H), 7.55 (d, 1H), 7.50 (bt, 1H), 7.42 (t, 2H), 7.36 (dd, 1H), 7.23 (d, 1H), 7.12-7.05 (m, 3H), 6.77 (s, 1H), 4.81 (dd, 1H), 4.28 (ddd, 2H), 3.27 (ddd, 1H), 3.13 (ddd, 1H), HRMS (ESI) calculated for $C_{27}H_{21}ClFN_7O_4$ 562.1406 $(M+H)^+$, found 562.1390.

Supplementary material – Biology

Ethical statement

All animal experiments were approved by the Local Ethics Committee on Animal Experiments in Göteborg, Sweden. The studies were performed according to the animal ethics protocol number 183-2005 and 9-2006.

Determination of Thrombin Inhibition with a Chromogenic, Robotic Assay. The thrombin inhibitor potency is measured with a chromogenic substrate method, in a Plato 3300 robotic microplate processor (Rosys AG, CH-8634 Hombrechtikon, Switzerland), using 96-well, half volume microtitre plates (Costar, Cambridge, MA, USA; Cat No 3690). Stock solutions of test substance in DMSO (72 µL), 0.1 - 1 mmol/L, are diluted serially 1:3 (24 + 48 µL) with DMSO to obtain ten different concentrations, which are analyzed as samples in the assay. 2 µL of test sample is diluted with 124 µL assay buffer, 12 µL of chromogenic substrate solution (S-2366, Chromogenix, Mölndal, Sweden) in assay buffer and finally 12 µL of α-thrombin solution (Human α-thrombin, Sigma Chemical Co. or Hematologic Technologies) in assay buffer, are added, and the samples mixed. The final assay concentrations are: test substance 0.00068 - 133 µmol/L, S-2366 0.30 mmol/L, α-thrombin 0.020 NIHU/mL. The linear absorbance increment during 40 minutes incubation at 37 °C is used for calculation of percentage inhibition for the test samples, as compared to blanks without inhibitor. The IC_{50} value, corresponding to the inhibitor concentration which causes 50% inhibition of the thrombin activity, is calculated from a log concentration vs. % inhibition curve.

Determination of Activated Partial Thromboplastin Time (APTT). APTT is determined in pooled normal human citrated plasma with the reagent PTT Automated 5 manufactured by Stago. The inhibitors are added to the plasma (10 µL inhibitor solution to 90 µL plasma) and incubated with the APTT reagent for 3 minutes followed by the addition of 100 µL of calcium chloride solution (0.025 M) and APTT is determined by use of the coagulation analyzer KC10 (Amelung) according to the instructions of the reagent producer. The clotting time is expressed as absolute values (seconds) as well as the ratio of APTT without inhibitor (APTT0) to APTT with inhibitor (APTTi). The latter ratios (range 1-0) are plotted against the concentration of inhibitor (log transformed) and fitted to sigmoidal dose-response curves according to the equation $y = a/[1+(x/IC_{50})s]$ where: a = maximum range, i.e. 1; s = slope of the dose-response curve; and IC_{50} = the concentration of inhibitor that doubles the clotting time. The calculations are processed on a PC using the software program GraFit Version 3, setting equation equal to: Start at 0, define end = 1 (Erithacus Software, Robin Leatherbarrow, Imperial College of Science, London, UK).

Thrombin Clotting Time (TCT). TCT was measured by adding 25 ⍰l of citrated rat plasma to the coagulometer (Amelung KC10A micro, Lemgo , Germany). After a 1 min incubation period at 37°C, 50 ⍰l of Thrombin10 (Diagnostica Stago, Asniéres, France) dissolved in 10 ml H2O, was added and the time to coagulation measured.

Tolerability studies in mice

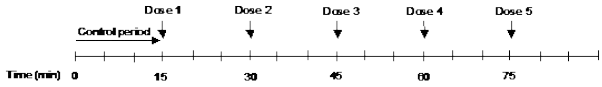
Rats and mice were housed and acclimatised under standards conditions for at least 5 days prior to experiments.

1. Preparation

The mouse was anaesthetized with penthobarbital natrium (100 mg/kg to 120 mg/kg, Apoteksbolaget, Umeå, Sweden) and tracheotomized (Polyethylene, PE 90) to facilitate spontaneuos breathing. A catheter (Polyethylene, PE 50 connected to PE 10) was inserted in the left carotid artery for continuous infusion of penthobarbital (10 to 25 mg/kg/h) and measurement of arterial blood pressure (BP) and heart rate (HR). A catheter (Polyethylene, PE 25 connected to PE 10) was inserted in the left jugular vein for administration of drugs or vehicle. Respiration rate (RESP) was measured with a thermoelement inserted in the trachal catheter. A bipolar electrocardiogram (ECG) was recorded from skin electrodes. Signals were recorded with a computer system (PharmLab 3.0.1, AstraZeneca R&D Mölndal, later upgraded to versions 5.0 and 6.0). The body temperature was maintained at ⍰38°C throughout the experiment by external heating.

2. Experimental protocol

The protocol is schematically represented below. The experiment was initiated with a 15 min control period for registration of basal values. Increasing doses of drugs were administrated intravenously with an interval of 15 min. The drugs were injected with a Hamilton syringe (50 µL) over a period of 30 (to 120) s.



3. Data analysis

First sign was classified as any reaction on HR, BP, RESP or ECG following drug administration, the lethal dose was classified as the dose the mouse did not survive. If the mouse survived the highest dose, the result was described as more than (>) the given dose.

Determination of kinetic solubility. Each compound was dissolved in 100 µL DMSO (concentration: 5 or 10 mM) on a mother plate. 10 µL of each solution was transferred to a precipitation plate and diluted with 3x330 µL buffer, pH 6.8. The buffer was prepared by adding 2.665 g of 2-Morpholinoethanesulphonic acid monohydrate (MES) to 500 mL HBSS stock solution (Gibco) and titrating the pH to 6.8 with 10 M NaOH. The precipitation plate was shaken on a flat bed shaker for 16 hours. 400 µL of each solution was transferred to an 8x12 Whatman GF/B well filter placed on top of a vacuum manifold. Immediately after the filter was filled, vacuum was applied and the samples were filtered onto the filtration plate. From the mother plate, compound solutions were also transferred to a standard plate, where the sample was diluted using an organic solvent suitable for the compound (EtOH, MeCN, etc.). One, two or three standards might be used, the concentration of the first standard was always set as a hundredfold dilution from the mother plate concentration. The filtration plate and standard plate were analysed by LC-UV/MS to determine the solubility. UV detection was used for quantitation and MS data was used for confirmation of compound identity.