Discovery and in vivo evaluation of potent dual CYP11B2 (aldosterone synthase) and CYP11B1 inhibitors

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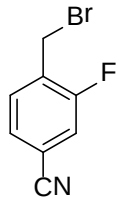
SUPPORTING INFORMATION

Contents include synthetic procedures for the preparation of **7n** and corresponding analytical data. The analytical data for other representative compounds is also included herein.

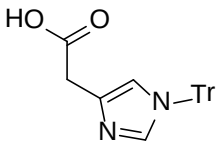
General. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Low-resolution mass spectra were recorded using an Agilent 1100 series LC-MS spectrometer. The absolute configuration was only established for **7n**. In general single enantiomer compounds were obtained by chiral semi-prep HPLC under the described conditions with the noted retention times (tR). The first eluting enantiomer is noted as *ent-1*, while the second is *ent-2*. The purity of all compounds was ≥ 95%, unless otherwise noted.

Compound 4 (R_2 = F; R_3 = CN). 4-Bromomethyl-3-fluorobenzonitrile.



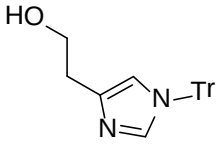
3-Fluoro-4-methylbenzonitrile (20 g, 148 mmol), NBS (31.6 g, 178 mmol) and benzoyl peroxide (1.8 g, 7.4 mmol) were taken up in carbon tetrachloride (490 mL) and refluxed for 2.5 h. The mixture was then allowed to cool to room temperature and was filtered. The filtrate was concentrated and purified via flash column chromatography (0-5% EtOAc/hexanes) to give 4-(bromomethyl)-3-fluorobenzonitrile (17.7g, 56%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.53 (t, *J*=7.30 Hz, 1 H) 7.43 - 7.48 (m, 1 H) 7.38 (dd, *J*=9.09, 1.52 Hz, 1 H) 4.49 (s, 2 H).

2-(1-Trityl-1H-imidazol-4-yl)acetic acid (cas # 168632-03-9).



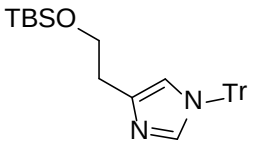
Trityl chloride (51 g, 0.18 mol) is added to a suspension of (1*H*-imidazol-4-yl)acetic acid hydrochloride (25 g, 0.15 mol) in pyridine (500 mL). This is stirred at room temperature for 16 h, at the end of which MeOH (150 mL) is added. This solution is stirred at room temperature for 1 h. Solvents are evaporated and the residue is taken up in CH_2Cl_2 and washed with 1 M aqueous citric acid solution (2X) and brine. The organic phase is dried over anhydrous Na_2SO_4 and evaporated to give a sticky residue which when taken up in diethyl ether and evaporated gave the product as a white solid that is used without further purification. MS (ESI) *m/z* 368.9 (M+H) (Procedure adapted from *J. Org. Chem.* 1993, *58*, 4606, also prepared in WO2003013526)

2-(1-Trityl-1H-imidazol-4-yl)ethanol (cas # 127607-62-9).



2-(1-Trityl-1*H*-imidazol-4-yl)acetic acid (65 g, 0.17mol) is suspended in THF (400 mL) and cooled to 0 °C. To this is added BH_3·THF solution (350 mL, 1.0 M). The clear solution obtained is stirred at 0 °C for 30 min before warming to room temperature until LCMS indicated completion of the reaction. The solution is cooled again to 0 °C and quenched carefully with water (250 mL). The resulting solution is diluted with EtOAc (300 mL) and transferred to a separatory funnel and the aqueous layer is extracted with EtOAc. The organic phase is dried over anhydrous Na_2SO_4 and evaporated to give a sticky residue which is taken up in ethanolamine (800 mL) and heated to 90 °C for 2 h. The reaction is transferred to a separatory funnel, diluted with EtOAc (1 L) and washed with water (3 X 600 mL). The organic phase is dried over anhydrous Na_2SO_4 and evaporated to give 2-(1-trityl-1*H*-imidazol-4-yl)-ethanol as a white solid that is used as is without further purification. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 - 7.39 (m, 10 H) 7.08 - 7.17 (m, 6 H) 6.60 (s, 1 H) 3.88 (t, *J*=5.68 Hz, 2 H) 2.75 (t, *J*=5.56 Hz, 2 H); MS (ESI) *m/z* 354.8 (M+H). (prepared by alternate method in *J. Med. Chem.* 1996, 39(19), 3806)

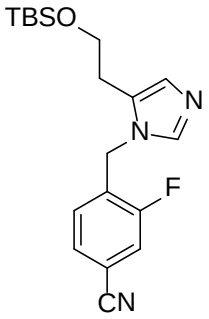
Compound 3 (n = 1). 4-(2-((tert-Butyldimethylsilanyl)oxy)ethyl)-1-trityl-1H-imidazole.



2-(1-Trityl-1*H*-imidazol-4-yl)ethanol (20 g, 56.5 mmol) is dissolved in CH_2Cl_2 (500 mL). To this is added imidazole (11.5 g, 169 mmol) and *tert*-butyldimethylsilylchloride (10.2 g, 67.8 mmol). The solution is stirred at room temperature until LCMS indicated the reaction is complete. The solution is partitioned between CH_2Cl_2 and aqueous saturated $NaHCO_3$. The organic layer is washed further with aqueous saturated $NaHCO_3$ and brine. The organic phase is dried over anhydrous Na_2SO_4 and evaporated to give an oil that is purified via flash column chromatography (EtOAc/hexanes 3:7) to give 4-(2-((*tert*-Butyldimethylsilanyl)oxy)ethyl)-1-trityl-1*H*-imidazole as a white solid.

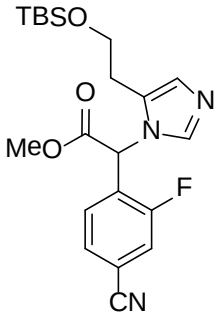
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 - 7.37 (m, 10 H) 7.15 (dd, *J*=6.19, 2.91 Hz, 6 H) 6.64 (s, 1 H) 3.87 (t, *J*=6.69 Hz, 2 H) 2.77 (t, *J*=6.69 Hz, 2 H) 0.85 (s, 9 H) 0.00 (s, 6 H)MS (ESI) *m/z* 469.3 (M+H).

Compound 5. 4-((5-(2-((tert-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile.



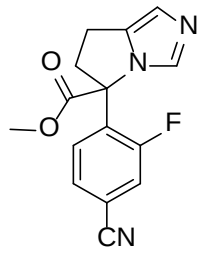
4-(2-((*tert*-Butyldimethylsilanyl)oxy)ethyl)-1-trityl-1*H*-imidazole (15.6 g, 33.3 mmol) and 4-(Bromomethyl)-3-fluorobenzonitrile (10.7 g, 50 mmol) are dissolved in MeCN (230 mL) and CH_2Cl_2 (35 mL), and stirred at room temperature for 30 h. Et_2NH (26 mL) and MeOH (200 mL) are then added and the solution is warmed 80 °C for 1 h. The solution is evaporated to dryness and the residue purified via flash column chromatography (EtOAc/hexanes 1:5 → EtOAc) to give 4-((5-(2-((*tert*-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile (9 g, 75%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (s, 1 H) 7.41 (m, 2 H) 6.94 (s, 1 H) 6.77 (t, *J*=7.71 Hz, 1 H) 5.29 (s, 2 H) 3.77 (t, *J*=6.44 Hz, 2 H) 2.65 (t, *J*=6.32 Hz, 2 H) 0.86 (s, 9 H) 0.00 (s, 6 H).

Methyl 2-(5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate.



4-((5-(2-((*tert*-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile (9 g, 25.1 mmol) is dissolved in anhydrous THF (170 mL) and stirred at -78 ^oC before a THF solution of LHMDS (45.1 mL, 1.0 M) is added dropwise over 15 min. After 30 min, methyl cyanoformate (2.09 mL, 26.32 mmol) is added dropwise over 10 min and the solution is left at -78 ^oC for 2 h. The excess LHMDS is quenched with aqueous saturated NH_4Cl and the mixture is allowed to warm to room temperature. The mixture is then diluted with EtOAc and washed with aqueous saturated NH_4Cl (2X). Organic is dried (Na_2SO_4) and evaporated. The crude residue is purified via flash column chromatography (EtOAc/hexanes 3:10 → EtOAc) to give Methyl 2-(5-(2-((*tert*-butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate (9.4 g, 90%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 (s, 1 H) 7.41 - 7.51 (m, 2 H) 7.13 (t, *J*=7.58 Hz, 1 H) 6.90 (s, 1 H) 6.43 (s, 1 H) 3.84 (s, 3 H) 3.72 - 3.81 (m, 2 H) 2.60 - 2.79 (m, 2 H) 0.87 (s, 9 H) 0.15 (s, 6 H).

Compound 11. Methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate.

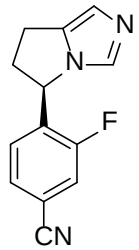


Methyl 2-(5-(2-((*tert*-butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate (9.4 g, 22.54 mmol) in THF (170 mL) is cooled to 0 °C before a solution of HCl in 1,4-dioxane (28.2 mL, 4.0 M, 112.8 mmol) is added. Mixture is allowed to warm to room temperature and stirred for 1 h. The solution is concentrated to dryness. CH_2Cl_2 is added and removed again to give the crude alcohol, methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-hydroxyethyl)-1H-imidazol-1-yl)acetate that is used without further purification.

The crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-hydroxyethyl)-1H-imidazol-1-yl)acetate (22.54 mmol) is dissolved in CH_2Cl_2 (200 mL) and stirred at 0 °C before Et_3N (20 mL, 143.5 mmol) and methanesulfonyl chloride (2 mL, 25.7 mmol) are added. After completion of the reaction, the solution is partitioned between CH_2Cl_2 and aqueous saturated $NaHCO_3$. The organic layer is dried (Na_2SO_4) and evaporated to give the crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-((methylsulfonyl)oxy)ethyl)-1H-imidazol-1-yl)acetatethat is used without further purification.

The crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-((methylsulfonyl)oxy)ethyl)-1H-imidazol-1-yl)acetate (22.5 mmol) is dissolved in MeCN (550 mL) and to it is added K_2CO_3 (9.35 g, 67.6 mmol), NaI (10.14 g, 67.6 mmol) and Et_3N (9.4 mL, 67.2 mmol). The reaction is stirred at 80 °C for 35 h. The mixture is filtered. Solid is rinsed with CH_2Cl_2. The filtrate is concentrated and purified via flash column chromatography (EtOAc / CH_2Cl_2 2:3 → EtOAc) to give methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylate (4 g, 62% in 3 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (s, 1 H) 7.40 - 7.42 (m, 1 H) 6.85 (s, 1 H) 6.74 (t, *J*=7.96 Hz, 1 H) 3.84 (s, 3 H) 3.63 - 3.78 (m, 1 H) 2.97 - 3.06 (m, 1 H) 2.66 - 2.82 (m, 2 H).

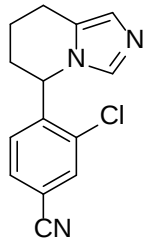
Compound 7n. (+)-(R)-4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluorobenzonitrile.



Methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylate (0.7 g, 2.46 mmol) is dissolved in THF/EtOH 2:1 (42 mL) and to it is added 2M LiOH (2.46 mL, 4.92 mmol). The mixture is stirred at room temperature for 1.5 h before being neutralized to pH 7-8 with 6M HCl and Et_3N. The solution is evaporated to slurry to give acid, 5-(2-fluoro-4-cyanophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid that is used without further purification.

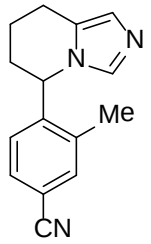
5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid(2.46 mmol) is dissolved in EtOH (100 mL) and heated at 80 °C in sealed tube for 3 h. The solution is evaporated and residue partitioned between CH_2Cl_2 and aqueous saturated $NaHCO_3$. The organic layer is dried (Na_2SO_4) and evaporated to give *racemic* 4-(6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-5-yl)-3-fluorobenzonitrile. Resolution of the enantiomers of the title compound is achieved by chiral HPLC using ChiralPak AS-H column with a MeCN mobile phase to give the (*S*)-enantiomer (tR = 16.7 min) and the (*R*)-enantiomer (**7n**) (tR = 22.5 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.45-2.55 (m, 1 H), 2.84-2.98 (m, 2 H), 3.10-3.23 (m, 1 H), 5.67 (dd, *J*=8.1, 4.3 Hz, 1 H), 6.78-6.84 (m, 1 H), 6.84 (s, 1H), 7.36 (s, 1 H), 7.38-7.45 (m, 2 H); MS (ESI) *m/z* 228 (M+H); $[\alpha]_D^{20}$ = +185.9.

Compound 6a. (racemic)-3-Chloro-4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile.



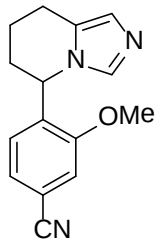
^{1}H NMR (400 MHz, Methanol-d$_4$) δ 1.74-1.85 (m, 2 H), 2.07-2.17 (m, 1 H), 2.33-2.44 (m, 1 H), 2.81-2.91 (m, 1 H), 2.91-3.00 (m, 1 H), 5.92 (d, J=5.3 Hz, 1 H), 6.76 (dd, J=8.1 Hz, 1 H), 6.82 (s, 1 H), 7.35 (s, 1 H), 7.65 (dd, J=8.1, 1.5 Hz, 1 H), 7.89-7.95 (m, 1 H); MS (ESI) *m/z* 258.1, 260.1 (M+H).

Compound 6b. (racemic)-3-Methyl-4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile.



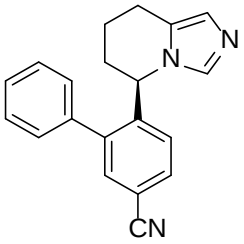
^{1}H NMR (400 MHz, Methanol-d$_4$) δ 1.77-1.89 (m, 2 H), 1.91-2.00 (m, 1 H), 2.29-2.39 (m, 1 H), 2.45 (s, 3 H), 2.86-2.93 (m, 2 H), 5.71 (t, J=6.1 Hz, 1 H), 6.77 (d, J=8.1 Hz, 1 H), 6.81 (s, 1 H), 7.29 (s, 1 H), 7.49 (d, J=8.1 Hz, 1 H), 7.61 (s, 1 H); MS (ESI) *m/z* 238.1 (M+H).

Compound 6c. (racemic)-3-Methoxy-4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile.



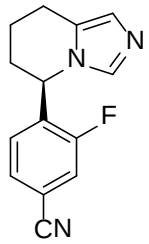
^{1}H NMR (400 MHz, Methanol-d_4) (HCl salt) δ 1.85-1.95 (m, 1 H), 1.95-2.04 (m, 1 H), 2.18-2.28 (m, 1 H), 2.31-2.41 (m, 1 H), 2.99 (s, 2 H), 3.88-3.94 (m, 3 H), 5.85-5.92 (m, 1 H), 7.09 (d, J=7.8 Hz, 1 H), 7.32-7.41 (m, 2 H), 7.48 (s, 1 H), 8.53 (s, 1 H); MS (ESI) *m/z* 254.1 (M+H).

Compound 7a. (eutomer)-6-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)-[1,1'-biphenyl]-3-carbonitrile.



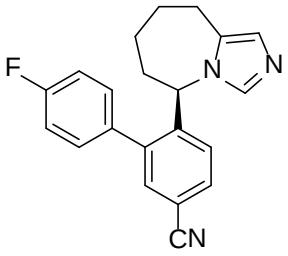
Resolution of the enantiomers of the title compound is achieved by Chiral HPLC using the ChiralPak AD column with a 20% IPA/Hexane mobile phase. ^{1}H NMR (400 MHz, Chloroform-d) δ 1.50-1.66 (m, 1 H), 1.73-1.83 (m, 1 H), 1.83-1.95 (m, 1 H), 1.95-2.16 (m, 1 H), 2.68-2.95 (m, 2 H), 5.28 (dd, J=8.5, 5.2 Hz, 1 H), 6.83 (s, 1 H), 7.01-7.15 (m, 2 H), 7.27-7.35 (m, 2 H), 7.43-7.54 (m, 3 H), 7.58 (s, 1 H), 7.62 (d, J=8.3 Hz, 1 H); MS (ESI) *m/z* 300 (M+H).

Compound 7c. (ent-2)-3-Fluoro-4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile.



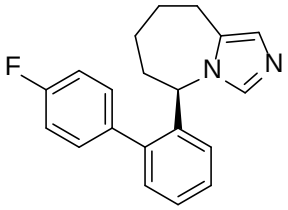
Resolution of enantiomers is achieved by chiral HPLC using ChiralPak AS-H column and 30 IPA:hexane to give enantiomer-1 (tR = 24 min) and enantiomer-2 (**7c**) (tR = 30 min). ^{1}H NMR (400 MHz, Methanol-d_4) (HCl salt) δ 1.88-1.98 (m, 1 H), 2.02-2.11 (m, 1 H), 2.14-2.24 (m, 1 H), 2.39-2.47 (m, 1 H), 2.92-3.00 (m, 1 H), 3.02-3.09 (m, 1 H), 5.83 (dd, J=9.1, 5.3 Hz, 1 H), 7.37-7.39 (m, 1 H), 7.42 (dd, J=10.4, 8.8 Hz, 1 H), 7.67 (dd, J=6.8, 2.0 Hz, 1 H), 7.86-7.90 (m, 1 H), 8.65 (s, 1 H); MS (ESI) *m/z* 242.1 (M+H).

Compound 7d. (ent-2)-4'-Fluoro-6-(6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)-[1,1'-biphenyl]-3-carbonitrile.



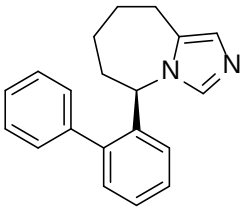
Resolution of the enantiomers of the title compound is achieved by chiral HPLC using the ChiralPak IA column with a 20% IPA:hexane mobile phase to give enantiomer-1 (tR = 17.6 min) and enantiomer-2 (**7d**) (tR = 23.0 minutes). ^{1}H NMR (400 MHz, Chloroform-d) δ 1.40-1.57 (m, 2 H), 1.77-1.92 (m, 2 H), 1.94-2.04 (m, 2 H), 2.43 (dd, J=15.0, 9.7 Hz, 1 H), 2.85 (dd, J=15.4, 7.3 Hz, 1 H), 5.13 (dd, J=7.5, 3.2 Hz, 1 H), 6.83 (s, 1 H), 6.92 (s, 1 H), 7.01-7.12 (m, 4 H), 7.51 (d, J=8.3 Hz, 1 H), 7.63 (d, J=1.8 Hz, 1 H), 7.75 (dd, J=8.1, 1.8 Hz, 1 H).

Compound 7e. (ent-2)-5-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepine.



Resolution enantiomers of the above compound is achieved by chiral HPLC using the ChiralPak AS column with a 15% IPA:hexane mobile phase to give enantiomer-1 (tR = 9.3 min) and enantiomer-2 (**7e**) (tR = 11.6 minutes). 1H NMR (400 MHz, Chloroform-d) δ 1.34-1.56 (m, 2 H), 1.81-1.99 (m, 2 H), 2.02-2.09 (m, 2 H), 2.28-2.41 (m, 1 H), 2.89 (dd, J=15.2, 6.6 Hz, 1 H), 4.98-5.05 (m, 1 H), 6.79 (s, 1 H), 6.90 (s, 1 H), 7.02 (d, J=7.6 Hz, 4 H), 7.28-7.34 (m, 1 H), 7.39-7.52 (m, 3 H); MS (ESI) m/z 307 (M+H).

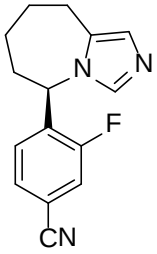
Compound 7f. (ent-2)-5-([1,1'-Biphenyl]-2-yl)-6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepine.



Resolution of the enantiomers of is achieved by chiral HPLC using the ChiralPak AS column with a 20% IPA:hexane mobile phase to give enantiomer-1 (tR = 7.5 min) and enantiomer-2 (**7f**) (tR = 10.8 minutes). ^{1}H NMR (400 MHz, Chloroform-d) δ 1.35-1.56 (m, 2 H), 1.80-

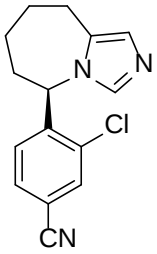
1.89 (m, 1 H), 1.89-1.98 (m, 1 H), 1.99-2.08 (m, 2 H), 2.28-2.41 (m, 1 H), 2.87 (dd, *J*=15.3, 6.2 Hz, 1 H), 5.05-5.15 (m, 1 H), 6.80 (br s, 1 H), 6.97 (br s, 1 H), 7.03-7.10 (m, 2 H), 7.31-7.36 (m, 4 H), 7.40- 7.48 (m, 3 H);); MS (ESI) *m/z* 289 (M+H).

Compound 7g. (ent-1)-3-Fluoro-4-(6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)benzonitrile.



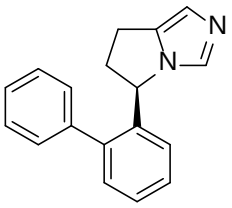
Resolution of the enantiomers is achieved by chiral HPLC using the ChiralPak IA column with a 20% IPA:hexane mobile phase to give enantiomer-1 (**7g**) (tR = 18.2 min) and enantiomer-2 (tR = 20.3 minutes). ^{1}H NMR (400 MHz, Chloroform-d) δ 1.38-1.67 (m, 2 H), 1.72-1.93 (m, 2 H), 1.96-2.14 (m, 1 H), 2.44-2.74 (m, 2 H), 2.97 (dd, *J*=15.4, 6.3 Hz, 1 H), 5.73 (dd, *J*=6.1, 2.8 Hz, 1 H), 6.80-6.94 (m, 2 H), 7.23 (s, 1 H), 7.39-7.42 (m, 1 H), 7.43 (s, 1 H); MS (ESI) *m/z* 256 (M+H).

Compound 7h. (ent-2)-3-Chloro-4-(6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)benzonitrile.



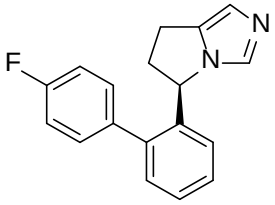
Resolution of the enantiomers is achieved by chiral HPLC using the ChiralPak IA column with a 20% IPA:hexane mobile phase to give enantiomer-1 (tR = 24.0 min) and enantiomer-2 (**7h**) (tR = 29.0 minutes). ^{1}H NMR (400 MHz, Chloroform-d) δ 1.50-1.87 (m, 4 H), 1.97-2.19 (m, 1 H), 2.42-2.61 (m, 1 H), 2.67-2.85 (m, 1 H), 2.85-3.00 (m, 1 H), 5.71 (dd, *J*=7.2, 2.7 Hz, 1 H), 6.83 (s, 1 H), 6.98 (s, 1 H), 7.17 (d, *J*=8.1 Hz, 1 H), 7.56 (dd, *J*=8.1, 1.5 Hz, 1 H), 7.72 (d, *J*=1.5 Hz, 1 H); MS (ESI) *m/z* 272, 274 (M+H).

Compound 7j. (ent-2)-5-([1,1'-Biphenyl]-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole.



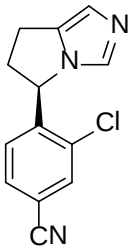
Resolution of the is achieved by chiral HPLC using ChiralPak AD column and 13% IPA:hexane to give enantiomer-1 (tR = 9.1 min) and enantiomer-2 (**7j**) (tR = 12.4 min). ^{1}H NMR (400 MHz, Methanol-d_4) (TFA salt) δ 2.65-2.74 (m, 1 H), 3.00 (ddd, *J*=15.6, 10.8, 8.5 Hz, 2 H), 3.09-3.19 (m, 1 H), 5.67-5.73 (m, 1 H), 7.08-7.14 (m, 1 H), 7.27 (s, 1 H), 7.32-7.41 (m, 3 H), 7.42-7.50 (m, 5 H), 8.66 (s, 1 H); MS (ESI) *m/z* 261.3 (M+H).

Compound 7k. (ent-2)-5-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole.



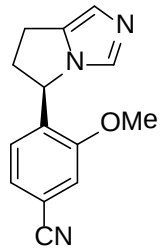
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AD column and 13% IPA:hexane to give enantiomer-1 (tR = 9.6 min) and enantiomer-2 (**7k**) (tR = 12.6 min). ^{1}H NMR (400 MHz, Chloroform-d) (HCl salt) δ 2.68-2.79 (m, 1 H), 2.95-3.06 (m, 2 H), 3.13-3.22 (m, 1 H), 5.55 (app t, *J*=7.6 Hz, 1 H), 6.96 (dd, *J*=7.6, 1.5 Hz, 1 H), 7.13 (s, 1 H), 7.18 (app t, *J*=8.6 Hz, 2 H), 7.27-7.32 (m, 2 H), 7.33-7.38 (m, 1 H), 7.40-7.49 (m, 2 H), 8.01 (s, 1 H); MS (ESI) *m/z* 279.1 (M+H).

Compound 7l. (ent-2)-3-Chloro-4-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)benzonitrile.



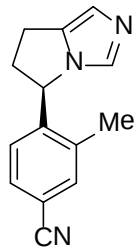
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak IA column with a 70% EtOAc:hexane mobile phase to give the enantiomer-1 (tR = 22.4 min) and enantiomer-2 (**7l**) (tR = 41.9 min. ^{1}H NMR (400 MHz, Chloroform-d) (TFA salt) δ 2.60-2.73 (m, 1 H), 3.08-3.20 (m, 2 H), 3.22-3.36 (m, 1 H), 6.04 (dd, *J*=7.6, 5.8 Hz, 1 H), 6.91 (d, *J*=8.1 Hz, 1 H), 7.24 (s, 1 H), 7.61 (d, *J*=8.1 Hz, 1 H), 7.81 (d, *J*=1.5 Hz, 1 H), 8.53 (s, 1 H);). MS (ESI) *m/z* 244.2, 246.2 (M+H).

Compound 7m. (ent-2)-4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-methoxybenzonitrile.



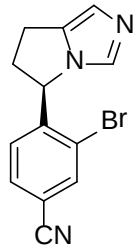
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AS-H column with a 1% EtOH:MeCN mobile phase to give enantiomer-1 (tR = 16.7 min) and enantiomer-2 (**7m**) (tR = 25.7 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.34-2.45 (m, 1 H), 2.77-2.93 (m, 2 H), 3.02-3.14 (m, 1 H), 3.93 (s, 3 H), 5.68 (dd, *J*=8.1, 4.0 Hz, 1 H), 6.65 (d, *J*=7.8 Hz, 1 H), 6.82 (s, 1 H), 7.15 (s, 1 H), 7.19 (d, *J*=7.8 Hz, 1 H), 7.35 (s, 1 H); MS (ESI) *m/*z 240 (M+H).

Compound 7o. (ent-2)-4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-methylbenzonitrile.



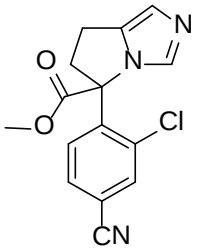
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AS-H column and 9:1 hexane/EtOH to give enantiomer-1 (tR = 84 min) and enantiomer-2 (**7o**) (tR = 104 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.33-2.42 (m, 1 H), 2.43 (s, 3 H), 2.84-2.95 (m, 2 H), 3.07-3.18 (m, 1 H), 5.54 (dd, *J*=8.1, 4.8 Hz, 1 H), 6.65 (d, *J*=8.1 Hz, 1 H), 6.83 (s, 1 H), 7.32 (s, 1 H), 7.41 (d, *J*=8.1 Hz, 1 H), 7.50 (s, 1 H); MS (ESI) *m/*z 224.0 (M+H).

Compound 7p. (ent-2)-3-Bromo-4-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)benzonitrile.



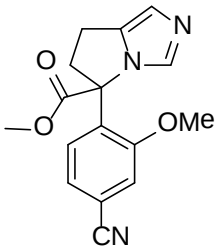
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AS-H column with a 25% IPA:hexane mobile phase to give enantiomer-1 (tR = 44.0 min) and enantiomer-2 (**7p**) (tR = 66.0 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.39-2.51 (m, 1 H), 2.77-2.98 (m, 2 H), 3.15-3.29 (m, 1 H), 5.71 (dd, *J*=8.3, 3.8 Hz, 1 H), 6.62 (d, *J*=8.1 Hz, 1 H), 6.86 (s, 1 H), 7.38 (s, 1 H), 7.52 (dd, *J*=8.1, 1.5 Hz, 1 H), 7.91 (s, 1 H); MS (ESI) *m/z* 288, 290 (M+H).

Compound 12a. (ent-2)-5-(2-Chloro-4-cyanophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid methyl ester.



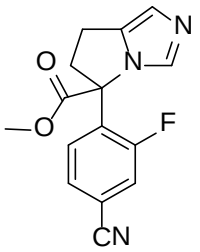
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AS column with a 15% IPA:hexane mobile phase to give enantiomer-1 (tR = 51.8 min) and enantiomer-2 (**12a**) (tR = 63.2 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.64-2.76 (m, 2 H), 2.97-3.06 (m, 1 H), 3.84 (s, 3 H), 3.86-3.93 (m, 1 H), 6.56 (d, *J*=8.1 Hz, 1 H), 6.87 (s, 1 H), 7.50 (obs d, *J*=8.1 Hz, 1 H), 7.52 (s, 1H), 7.73 (s, 1 H); MS (ESI) *m/z* 302.2, 304.2 (M+H).

Compound 12b. (ent-2)-Methyl 5-(4-cyano-2-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate.



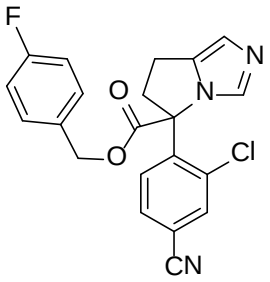
Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak AD column with a 30% IPA:hexane mobile phase to give enantiomer-1 (tR = 31.6 min) and enantiomer-2 (**12b**) (tR = 41.7 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.55-2.65 (m, 1 H), 2.66-2.76 (m, 1 H), 2.92-3.02 (m, 1 H), 3.63-3.74 (m, 1 H), 3.77 (s, 3 H), 3.90 (s, 3 H), 6.60 (d, *J*=8.1 Hz, 1 H), 6.81 (s, 1 H), 7.16 (d, *J*=1.3 Hz, 1 H), 7.21 (dd, *J*=8.1, 1.5 Hz, 1 H), 7.51 (s, 1 H); MS (ESI) *m/z* 298 (M+H).

Compound 12c. (ent-2)-Methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate.



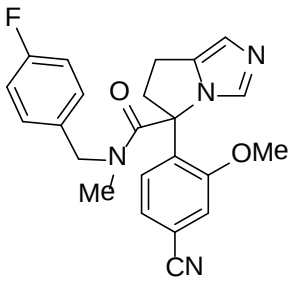
Resolution of the enantiomers of the title compound is achieved by chiral HPLC using ChiralPak AS column with a 20% IPA:hexane mobile phase to give enantiomer-1 (tR = 61.4 min) and enantiomer-2 (**12c**) (tR = 73.8 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.63-2.79 (m, 2 H), 2.92-3.03 (m, 1 H), 3.61-3.73 (m, 1 H), 3.81 (s, 3 H), 6.72 (app t, *J*=8.0 Hz, 1 H), 6.80 (s, 1 H), 7.36-7.43 (m, 2 H), 7.53 (s, 1 H); MS (ESI) *m/*z 286 (M+H).

Compound 14a. (ent-1)-4-Fluorobenzyl 5-(2-chloro-4-cyanophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate.



Resolution of the enantiomers is achieved by chiral HPLC using ChiralPak IA column and 3:7 *i*-PrOH/hexanes to give enantiomer-1 (**14a**) (tR = 39.2 min) and enantiomer-2 (tR = 60.3 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.68-2.80 (m, 2 H), 2.99-3.09 (m, 1 H), 3.84-3.91 (m, 1 H), 5.22 (ABq, *J*=11.9 Hz, 2 H), 6.56 (d, *J*=8.3 Hz, 1 H), 6.92 (s, 1 H), 7.01-7.08 (m, 2 H), 7.23-7.28 (m, 2 H), 7.50 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.57 (s, 1 H), 7.70 (d, *J*=1.5 Hz, 1 H); MS (ESI) *m/z* 396.1, 398.1 (M+H).

Compound 14b. (ent-2)-5-(4-Cyano-2-methoxyphenyl)-N-(4-fluorobenzyl)-N-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxamide.



Resolution enantiomers of the title compound is achieved by chiral HPLC using ChiralPak AD column with a 6:4 EtOH/hexane mobile phase to give enantiomer-1 (tR = 30.2 min) and enantiomer-2 (**14b**) (tR = 36.0 min). ^{1}H NMR (400 MHz, Chloroform-d) δ 2.60 (s, 3 H), 2.76-2.88 (m, 2 H), 2.95-3.04 (m, 1 H), 3.57-3.69 (m, 1 H), 3.74 (s, 3 H), 4.43 (d, *J*=14.4 Hz, 1 H), 4.58-4.70 (m, 1 H), 6.79 (s, 1 H), 6.86-6.94 (m, 1 H), 6.96-7.05 (m, 2 H), 7.10 (s, 1 H), 7.19-7.25 (m, 3 H), 7.55 (s, 1 H); MS (ESI) *m/z* 405.2 (M+H).

Assay protocols for measuring cellular aldosterone synthase activity and enzymatic CYP19 activity.

Human adrenocortical carcinoma NCI-H295R cell line is obtained from American Type Culture Collection (Manassas, VA). Insulin/transferrin/selenium (ITS)-A supplement (100x), DMEM/F-12, antibiotic/antimycotic (100x), and fetal calf serum (FCS) are purchased from Gibco (Grand Island, NY). Anti-mouse PVT scintillation proximity assay (SPA) beads and NBS 96-well plates are obtained from Amersham (Piscataway, NJ) and Corning (Acton, MA), respectively. Solid black 96-well flat bottom plates are purchased from Costar (Corning, NY). Aldosterone and angiotensin (Ang II) are purchased from Sigma (St. Louis, MO). D-[1,2,6,7-^{3}H(N)]aldosterone was acquired from PerkinElmer (Boston, MA). Nu-serum was a product of BD Biosciences (Franklin Lakes, NJ). The NADPH regenerating system, dibenzylfluorescein (DBF), and human aromatase supersomes® are obtained from Gentest (Woburn, MA).

For *in vitro* measurement of aldosterone activity, human adrenocortical carcinoma NCI-H295R cells are seeded in NBS 96-well plates at a density of 25,000 cells/well in 100 µl of a growth medium containing DMEM/F12 supplemented with 10% FCS, 2.5% Nu-serum, 1 µg ITS/ml, and 1x antibiotic/antimycotic. The medium is changed after culturing for 3 days at 37 ^{o}C under an atmosphere of 5% CO_2/95% air. On the following day, cells are rinsed with 100 µl of DMEM/F12 and incubated with 100 µl of treatment medium containing 1 µM Ang II and a compound at different concentrations in quadruplicate wells at 37 ^{o}C for 24 hr. At the end of incubation, 50 µl of medium is withdrawn from each well for measurement of aldosterone production by an RIA using mouse anti-aldosterone monoclonal antibodies.

Measurement of aldosterone activity can also be performed using a 96-well plate format. Each test sample is incubated with 0.02 µCi of D-[1,2,6,7-^{3}H(N)]aldosterone and 0.3 µg of anti-aldosterone antibody in phosphate-buffered saline (PBS) containing 0.1% Triton X-100, 0.1% bovine serum albumin, and 12% glycerol in a total volume of 200 µl at room temperature for 1 hr. Anti-mouse PVT SPA beads (50 µl) are then added to each well and incubated overnight at room temperature prior to counting in a Microbeta plate counter. The amount of aldosterone in each sample is calculated by comparing with a standard curve generated using known quantities of the hormone.

To measure aromatase activity, the human aromatase assay is performed in 96-well flat bottom plates according to a published protocol (Stresser, D. M.; Turner, S. D.; McNamara, J.; Stocker, P.; Miller, V. P.; Crespi, C. L.; Patten, C. J. *A high-throughput screen to identify inhibitors of aromatase (CYP19),* Anal Biochem. 2000, 2, 427–430) with minor modifications. Briefly, 10 µl of an NADPH regenerating system containing 2.6 mM $NADP^+$, 6.6 mM glucose 6-phosphate, 6.6 mM $MgCl_2$, and 0.8 U/ml glucose-6-phosphate dehydrogenase in 50 mM potassium phosphate, pH 7.4, is pre-incubated with the test compound at a desired concentration at 30 ^{o}C for 10 min in a total volume of 100 µl. Afterwards, 4 pmol of human aromatase, 20 µg of control microsomal protein, and 4 µM DBF in 100 µl of 50 mM potassium phosphate, pH 7.4, is added to each well and incubated at 30 ^{o}C for 90 min. The reaction is terminated by the addition of 75 µl of 2 N NaOH to each well. After 2 hr, the product, fluorescein, is measured by a fluorimeter using excitation and emission wavelengths of 485 and 538 nm, respectively.

Full concentration-response curves of the test compound are performed at least 3 times. The IC_{50} values are derived using a non-linear least squares curve-fitting program from Microsoft XLfit.