Novel and potent dopamine D_2 receptor (D_2R) Go-protein biased agonists

Alessandro Bonifazi,[†O] Hideaki Yano,[‡O] Adrian M. Guerrero,[†] Vivek Kumar,[†]

Alexander F. Hoffman[§], Carl R. Lupica[§], Lei Shi,[‡] Amy Hauck Newman[†,*]

[†] *Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States*

[‡] *Computational Chemistry and Molecular Biophysics Unit, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States*

[§] *Electrophysiology Research Section, Cellular Neurobiology Research Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States*

[*]Corresponding author:

Phone: (443)-740-2887. Fax: (443)-740-2111.

E-mail: anewman@intra.nida.nih.gov

[O]These authors contributed equally to this work

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CHEMISTRY

PAM **2** was prepared by amide coupling between racemic 2-methylindoline and thionyl chloride activated benzo[d]thiazole-2-carboxylic acid, as reported in Scheme 1A. Compound **9** (Scheme 1B) was also prepared by reacting benzo[d]thiazole-2-carboxylic acid with 4-aminobutanol and 1,1'-carbonyldiimidazole (CDI) to afford the intermediate amide alcohol **23**. **23** was then converted into the corresponding bromine analogue **24** via an Appel reaction before being inserted in the *N*-5 position of **sumanirole**[1-2] by nucleophilic substitution, carried out in a sealed vessel, at a high temperature and in the absence of base. The absence of organic or inorganic base was necessary to minimize intra-molecular cyclization of **24** and/or the more favorable **sumanirole** *N*-1 alkylation.[2] Similarly, **10** was prepared starting from (±)-2-methylindoline to obtain the intermediate **25** by amidation with 4-bromobutanoic acid followed by **sumanirole** *N*-5 alkylation (Scheme 1C). **Sumanirole** *N*-5 alkylation with bromoalkane intermediates produced moderate to low yields, thus reductive amination was used to successfully obtain *N*-5 regio-specificity in almost quantitative yields. **11** (diastereomeric mixture) and its **(*R*,*S*)-12** and **(*R*,*R*)-13** single enantiomers were prepared, as depicted in Scheme 1D, starting from the commercially available (±)-, (*S)*- or (*R)*-2-methylindoline, respectively. The indoline nitrogen was reacted with phosgene and 4-aminobutanol to afford the alcohol intermediates, which were then oxidized to the corresponding aldehydes with Dess-Martin periodinane (DMP) and conjugated to **sumanirole** in the *N*-5 position via sodium triacetoxyborohydride-mediated reductive amination. Diastereomeric excess and purity of the final resolved diastereoisomers were determined via chiral HPLC, in comparison with the diastereomeric mixture (HPLC chromatograms; Figure S1), using methods described in detail in the experimental section. Finally, compound **8**, presenting

the benzothiazole ring substituted in position 5 as the SP, was prepared following Scheme 1E. Amidation of the activated benzo[d]thiazole-5-carboxylic acid, followed by oxidation of the terminal alcohol to the corresponding aldehyde and consequent reductive amination led to the desired product. In Schemes 2 and 3 the synthetic routes to obtain the bivalent analogues embedding the 1,2,3,4 tetrahydroquinoline PP are shown. Specifically, Cbz- protected (*R*)-3-amino-1-methoxy-3,4-dihydroquinolin-2(1H)-one, a key intermediate isolated from the enantiospecific **sumanirole** synthesis,[1] was deprotected and dialkylated with two *n*-propyl substituents (**35**) before being reduced in the presence of borane dimethylsulfide complex and subsequently *N*-substituted with *N*-(4-bromobutyl)-1H-indole-2-carboxamide[1] to obtain **14**. In order to synthesize the mono-propyl analogue **17**, **34** was first reacted with propionyl chloride and then reduced to obtain the *n*-propyl secondary amine intermediate **38** which was readily alkylated with *N*-(4-bromobutyl)-1H-indole-2-carboxamide. The benzothiazole- and 2-methylindoline-containing analogues depicted in Scheme 3 were prepared from the intermediates **23** and **26**, respectively. **23** was oxidized to the corresponding aldehyde and from the subsequent reductive amination with *N*-methyl-1,2,3,4-tetrahydroquinolin-3-amine[1] both mono- and di-substituted products **15** and **18** were isolated. Compound **16** was obtained from alkylation of *N*-methyl-1,2,3,4-tetrahydroquinolin-3-amine with **40** under basic conditions.

Compound 19, presenting a *trans*-cyclopropyl ring in the connecting linker, was prepared according to the multistep approach described in Scheme 4. The preparation of the *trans*-cyclopropyl linker was slightly modified from what was previously reported,[3] allowing an overall higher yield synthesis with intermediates that were easily analyzed by chiral HPLC (methods in the experimental section) to confirm the retention of stereochemistry throughout the entire synthetic route (chiral HPLC analyses of intermediate **42** and final product **19** in Figures

S2 and S3). In detail, commercially available predominantly *trans* ethyl 2-formylcyclopropane-1-carboxylate was reacted first with nitromethane in the presence of lithium tert-butoxide, then with methanesulfonyl chloride and triethylamine to generate the pure *trans* nitro-olefin **42** in almost quantitative yield, over two steps. **42** was analyzed in chiral HPLC to confirm the formation of the sole *trans* racemic mixture (Figure S2) in 50:50 enantiomeric ratio. Simultaneous reduction of both the nitro-olefin and the ester functional groups with lithium aluminum hydride yielded intermediate **43**, which was then reacted with indole-2-carboxylic acid to afford **44**. Both **43** and **44** showed spectroscopic data identical to the same intermediates prepared previously, via a different synthetic approach.[3] Finally, oxidation of the primary alcohol and reductive amination with **sumanirole** led to final product **19**. **19** was analyzed in chiral HPLC to confirm the lack of racemization during the synthetic steps and the formation of the pure *trans*-cyclopropyl racemic mixture. Indeed, the chiral HPLC chromatogram (Figure S3) shows the existence of only the two cyclopropyl *trans* enantiomers (enantiomeric ratio 47:53), despite the potential formation of eight total stereoisomers that could have occurred in the case of an undesired racemization at the cyclopropyl or at the **sumanirole** scaffold. Thus, these data confirmed the stereospecificity of this alternative synthetic route. **20**, differing from **19** only due to the shift of the cyclopropyl ring one methylene unit farther from the PP and closer to the SP, was prepared as described in Scheme 5. *Trans*-**48** was obtained following the procedure by Kumar et al.,[3] which described in detail the isolation of the *trans* cycloproyl methanamino-O-pyranil protected intermediate **46**. Finally, alcohol **48** was oxidized and coupled with **sumanirole** to obtain **20**. **20** was analyzed by chiral HPLC, analogously to **19**, to confirm the lack of racemization and the presence of only the *trans*-cyclopropyl enantiomeric mixture (Figure S4, enantiomeric ratio 49:51).

1[1,2] (G-protein D_2R biased full agonist) was resynthesized, in high yield, via a slightly modified synthetic procedure, where the final coupling step between **sumanirole** in *N*-5 position and the *N*-(4-bromobutyl)-1H-indole-2-carboxamide was obtained by reductive amination in presence of the corresponding aldehyde (*N*-(4-oxobutyl)-1*H*-indole-2-carboxamide), sodium triacetoxyborohydride, and catalytic amount of acetic acid. All the obtained spectroscopic data where consistent with the previously published ones.[1]

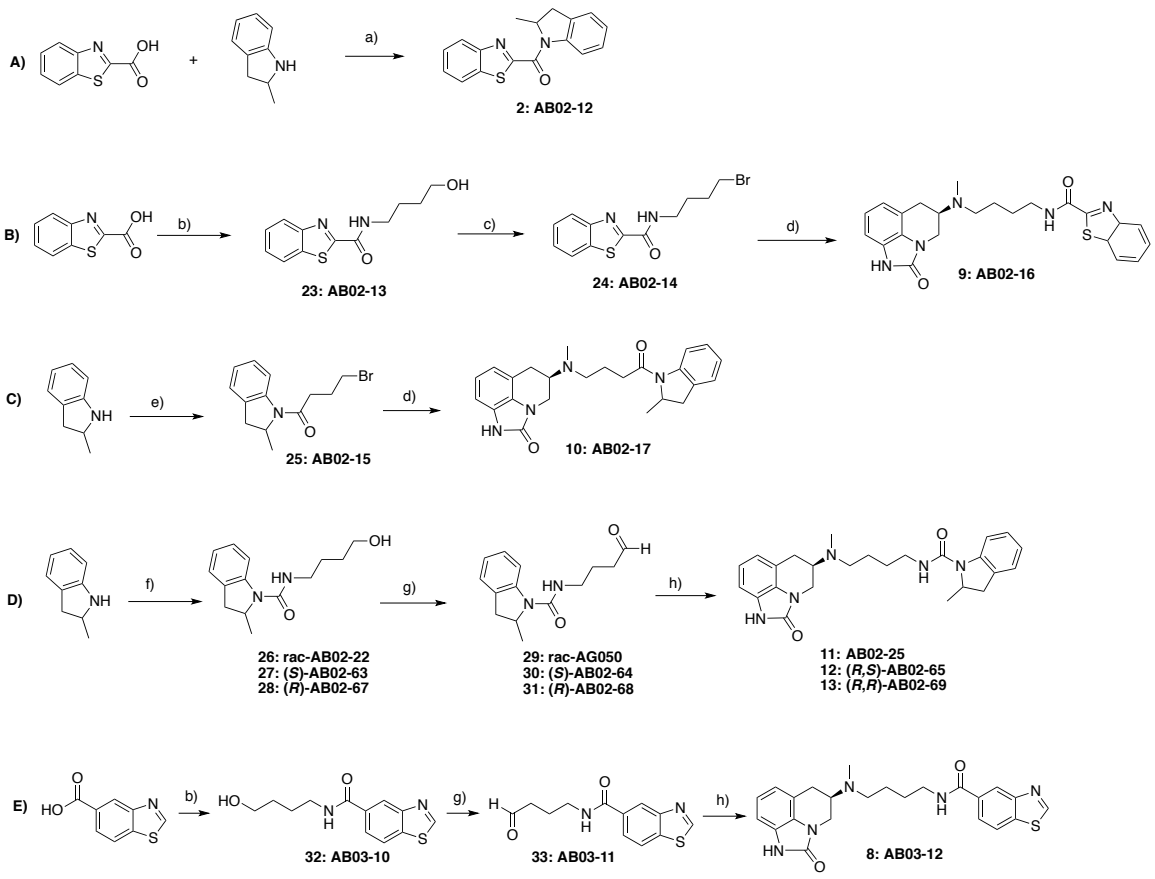
Experimental Methods

All chemicals and solvents were purchased from chemical suppliers unless otherwise stated, and used without further purification. All melting points were determined on an OptiMelt automated melting point system and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 instrument. Proton chemical shifts are reported as parts per million (δ ppm) relative to tetramethylsilane (0.00 ppm) as an internal standard. Coupling constants are measured in Hz. Chemical shifts for ^{13}C NMR spectra are reported as parts per million (δ ppm) relative to deuterated $CHCl_3$ or deuterated MeOH ($CDCl_3$ 77.5 ppm, CD_3OD 49.3 ppm). Chemical shifts, multiplicities and coupling constants (*J*) have been reported and calculated using Vnmrj Agilent-NMR 400MR or MNova 9.0 software. Gas chromatography-mass spectrometry (GC/MS) data were acquired (where obtainable) using an Agilent Technologies (Santa Clara, CA) 6890N GC equipped with an HP-5MS column (cross-linked 5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) and a 5973 mass-selective ion detector in electron-impact mode. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively, and the oven temperature gradient used was as follows: the initial temperature (100 °C) was held

for 3 min and then increased to 295 °C at 15 °C/min over 13 min, and finally maintained at 295 °C for 10 min. All column chromatography was performed using a Teledyne Isco CombiFlash RF flash chromatography system and silica gel (Merck, 230-400 mesh, 60Å) or preparative thin layer chromatography (silica gel, Analtech, 1000 μm). Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree with ± 0.4% of calculated values (table S1). HRMS (mass error less than 5 ppm) and MS/MS fragmentation analysis were performed on a LTQ-Orbitrap Velos (Thermo-Scientific, San Jose, CA) coupled with an ESI source in positive ion mode to confirm the assigned structures and regiochemistry. HPLC analysis was performed using an Agilent system coupled with DAD (Diode Array Detector). Separation of the analyte, purity and enantiomeric/diastereomeric excess determinations were achieved at 40 ^{o}C using one of the following different methods (the specific method used for each compound is mentioned in the detailed reaction description). **Method A)**: Agilent Poroshell 120 EC-C18 (4.6 x 50 mm, 2.7 μm) column. The mobile phase used (0.5 mL/min flow rate) was composed of 0.1% acetic acid in H_2O and acetonitrile with gradient elution, starting with 10% (organic) linearly increasing to 60% up to 5 min, maintaining at 60% (5-15 min) and re-equlibrating to 10%. The total run time was 20 min. **Method B)**: Chiralcel OD (Daicel Corporation CPI Company) column (4.6 x 50 mm, 3 μm). The mobile phase used (0.5 mL/min flow rate) was composed of 0.1% diethylamine in 2-propanol and hexanes with gradient elution, starting with 10% of 2-propanol linearly increasing to 20% up to 5 min, maintaining at 20% (5-20 min) and re-equilibrating to 10%. The total run time was 25 min. **Method C)**: Chiralcel OZ-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile phase used (0.5 mL/min flow rate) was composed of 10% 2-propanol in hexanes with isocratic elution. The total run time was 60 min. **Method D)**: Chiralpak AD-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile

phase used (0.5 mL/min flow rate) was composed of 0.1% diethylamine in 2-propanol and hexanes with gradient elution, starting with 20% of 2-propanol linearly increasing to 30% up to 15 min, maintaining at 30% (15-160 min) and re-equilibrating to 20%. The total run time was 170 min. **Method E)** Chiralpak AD-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile phase used (1.0 mL/min flow rate) was composed of 40% 2-propanol (in presence of 0.1% diethylamine) in hexanes with isocratic elution. The total run time was 60 min. Optical rotations were determined using a Jasco DIP-370 polarimeter. Unless otherwise stated, all the compounds were evaluated to be >95% pure on the basis of combustion analysis, NMR, GC-MS, and HPLC-DAD.

Scheme 1.



a) $SOCl_2$, DCM, DMF, TEA; b) 1,1-CDI, 4-aminobutanol, THF; c) PPh_3, CBr_4, ACN; d) **sumanirole**, DMF, 100 ^oC, sealed vessel; e) $SOCl_2$, DCM, TEA, 4-bromobutanoic acid; f) $COCl_2$, 4-aminobutanol, THF, TEA; g) DMP, DCM, from 0 ^oC to RT; h) **sumanirole**, $Na(OAc)_3BH$, AcOH, DCE.

Benzo[d]thiazol-2-yl(2-methylindolin-1-yl)methanone (2). To a solution of benzo[d]thiazole-2-carboxylic acid (1.0g, 5.6 mmol) in dichloromethane (50 mL) at room temperature, was added a solution of thionyl chloride (1.0g, 1.6 mL, 8.4 mmol) in *N*,*N*-dimethylformamide (2 mL).

Reaction was heated to reflux for 3 hours, before cooling to room temperature and concentrating under reduced pressure to afford the crude acid chloride. Residue was dissolved in DCM, and to the stirring solution was added 2-methylindoline (0.74g, 5.6 mmol), followed by triethylamine (1.6 ml, 11.5 mmol), and the reaction allowed to stir overnight at room temperature. Upon completion, reaction mixture was then washed with a 10% aqueous solution of Na_2CO_3. The organic phase was dried over anhydrous Na_2SO_4. Filtration and removal of solvent under vacuum afforded the crude product which was subsequently purified via Combiflash chromatography, eluting with 10% EtOAc in hexanes to afford **2** as a white solid. After washing with a 10% solution of diethyl ether in hexanes, product was dried via vacuum filtration to a constant weight **(0.246 g/ 15% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.18 – 8.09 (m, 1H), 8.03 – 7.95 (m, 1H), 7.53 (dtd, *J* = 20.6, 7.2, 1.3 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.09 (br s, 1H), 3.52 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.79 (d, *J* = 15.6 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.64, 153.66, 141.76, 136.53, 131.64, 127.50, 126.75, 126.50, 125.17, 124.85, 121.91, 118.95, 56.70, 36.60, 22.49 ppm. GC-MS (EI) 294.1 *m/z* (M+). Anal. ($C_{17}H_{14}N_2OS \cdot 0.25H_2O$) C, H, N. M.p.: 133-134 °C

N-(4-Hydroxybutyl)benzo[d]thiazole-2-carboxamide (23). To a stirring solution of benzo[d]thiazole-2-carboxylic acid (1.0g, 5.6 mmol) in tetrahydrofuran (20 mL) at room temperature, was added 1,1'-carbonyldiimidazole (1.0g, 6 mmol), followed by dropwise addition of *N*,*N*-dimethylformamide (2 mL) to solubilize any undissolved solids. 4-aminobutan-1-ol (0.5g, 0.517 mL, 5.6 mmol) was subsequently added dropwise into solution, and the reaction allowed to stir overnight at room temperature. Reaction was concentrated under vacuum to

afford the crude product which was purified via Combiflash chromatography, eluting with 100% EtOAc to afford the desired compound as a viscous yellow oil **(0.586 g/ 42% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.76 (t, *J* = 6.2 Hz, 1H), 7.41 (dtd, *J* = 25.6, 7.6, 1.2 Hz, 2H), 3.66 (t, *J* = 6.2 Hz, 2H), 3.48 (q, *J* = 6.6 Hz, 2H), 3.17 (s, 1H), 1.80 – 1.57 (m, 4H) ppm.

N-(4-Bromobutyl)benzo[d]thiazole-2-carboxamide (24). To a stirring solution of **23** (0.5g, 2 mmol) in anhydrous acetonitrile (10 mL) at room temperature and under inert atmosphere, was added triphenylphosphine (0.8 g, 3 mmol), followed by carbon tetrabromide (1.0g, 3 mmol). Reaction was heated to reflux, and allowed to proceed for 4 hours. Upon completion of the reaction, solvent was stripped under vacuum and precipitated solids were resuspended in a 2N aqueous solution of NaOH. This aqueous solution was subsequently extracted 3x with EtOAc and the combined organic fractions were then dried over anhydrous Na_2SO_4. Filtration and removal of solvent under reduced pressure afforded the crude alkyl bromide, which was then purified via Combiflash chromatography, eluting with EtOAc:Hexanes (2:8) to afford the desired product as a pale red solid **(0.381 g / 61% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.96 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 3.60 – 3.42 (m, 4H), 2.06 – 1.92 (m, 2H), 1.90 – 1.79 (m, 2H) ppm.

(R)-N-(4-(Methyl(2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)butyl)benzo[d]thiazole-2-carboxamide (9). **24** (0.124 g, 0.4 mmol) and **sumanirole** (0.100 g, 0.4 mmol) were charged to a sealed vessel and solubilized in *N,N*-dimethylformamide (10 mL). Reaction was heated to approximately 100°C, and allowed to proceed with vigorous

stirring for two hours. Upon completion of the reaction, solvent was concentrated under vacuum, and the remaining residue purified by preparatory thin-layer chromatography, eluting with MeOH:chloroform (5:95) to afford the desired product (**0.051g, 29% yield**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.03 – 7.84 (m, 3H), 7.54 – 7.40 (m, 2H), 7.01 – 6.79 (m, 3H), 4.26 – 4.17 (m, 1H), 3.61 – 3.41 (m, 3H), 3.26 (tt, *J* = 9.9, 4.7 Hz, 1H), 3.04 – 2.79 (m, 2H), 2.71 – 2.56 (m, 2H), 2.41 (s, 3H), 1.82 – 1.56 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.23, 159.93, 154.93, 152.88, 137.03, 127.30, 126.69, 126.55, 126.07, 124.12, 122.36, 121.41, 119.73, 118.46, 107.33, 57.55, 53.44, 39.85, 38.15, 27.19, 26.92, 25.30 ppm. HRMS (ESI positive) calculated 436.1802; found 436.1814 ($+H^+$). $[\alpha]_D^{23}$: 0.83 (0.120 g/100 mL in MeOH). Anal. ($C_{23}H_{25}N_5O_2S \cdot 1.5H_2O$) C, H, N. M.p.: 63 °C (dec.)

4-Bromo-1-(2-methylindolin-1-yl)butan-1-one (25). To a stirring solution of 4-bromobutanoic acid (2.5 g, 1.6 mL, 15 mmol) in dichloromethane (50 mL) at room temperature, was added thionyl chloride (2.7 g, 1.65 mL, 22.7 mmol) and the reaction heated to reflux for three hours. Reaction mixture was then stripped of solvent under vacuum, and the residue resuspended with the dropwise addition of a solution of 2-methylindoline (2.0 g, 15 mmol) in dichloromethane (50 ml). Once addition was complete, triethylamine (5 mL, 35.8 mmol) was added to the reaction mixture, and stirred overnight at room temperature. The reaction mixture was subsequently decanted into a separatory funnel and washed with a 10% Na_2CO_3 solution, followed by a 10% HCl solution. The organic phase was then dried over anhydrous Na_2SO_4, before filtering and concentrating under vacuum to afford the crude bromide. Crude material was then purified by Combiflash chromatography, eluting with EtOAc:Hexanes (2:8) to afford the desired product **(3.56 g, 84% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.6 Hz,

2H), 7.02 (t, *J* = 7.4 Hz, 1H), 4.58 – 4.49 (m, 1H), 3.74 – 3.66 (m, 2H), 3.41 (dd, *J* = 16.0, 9.0 Hz, 1H), 2.69 (dtd, *J* = 29.6, 14.9, 14.3, 6.6 Hz, 3H), 2.31 – 2.17 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 3H) ppm.

(5R)-5-(Methyl(4-(2-methylindolin-1-yl)-4-oxobutyl)amino)-5,6-dihydro-4H imidazo[4,5,1-ij]quinolin-2(1H)-one (10). Compound **25** (0.112 g, 0.4 mmol) and **sumanirole** (0.100 g, 0.4 mmol) were charged to a sealed vessel and solubilized in *N,N*-dimethylformamide (10 mL). Reaction was heated to approximately 100°C, and allowed to proceed with vigorous stirring for two hours. Upon completion of the reaction, solvent was concentrated under vacuum, and the remaining residue purified by preparatory thin-layer chromatography, eluting with MeOH:chloroform (10:90) to afford the desired product as a mixture of diastereoisomers **(0.04 g, 20% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.08 – 6.88 (m, 2H), 6.88 – 6.78 (m, 2H), 4.52 (s, 1H), 4.16 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.62 – 3.45 (m, 1H), 3.42 (d, *J* = 18.5 Hz, 1H), 3.25 – 3.19 (m, 1H), 2.98 – 2.80 (m, 3H), 2.79 – 2.61 (m, 4H), 2.41 (s, 3H), 2.00 – 1.91 (m, 2H), 1.29 (br s, 3H) ppm. An analytical sample was converted into the corresponding maleate salt. ^{13}C NMR (101 MHz, CD_3OD) δ 171.33, 168.77, 133.61, 126.76, 126.70, 126.59, 124.55, 123.95, 122.16, 122.13, 122.09, 119.40, 118.03, 114.26, 107.98, 107.75, 65.46, 58.48, 56.16, 54.43, 38.48, 38.19, 37.33, 37.32, 36.93, 35.75, 32.15, 26.14, 22.77, 21.29, 20.04, 19.67, 14.00 ppm. HPLC-DAD Method A (R_t: 6.099 min; purity 93.3%). HRMS (ESI positive) calculated 405.2285; found 405.2295 ($+H^+$).

N-(4-Hydroxybutyl)-2-methylindoline-1-carboxamide (26). To a stirring solution of 2-methylindoline (2.0 g, 15 mmol) and triethylamine (~5 eq.) in anhydrous tetrahydrofuran (50

mL) cooled to 0 °C and under inert atmosphere, was added dropwise a solution of phosgene (6 mL, 15% wt. in toluene) in anhydrous tetrahydrofuran (10 mL). After stirring for 1 hour at 0°C, a solution of 4-aminobutan-1-ol (1.3 g, 1.344 mL, 15 mmol) and triethylamine (~5 eq.) in tetrahydrofuran (10 mL) was added dropwise into the reaction, and allowed to warm to room temperature overnight with stirring. Reaction was subsequently concentrated under vacuum and resuspended in H_2O before extracting repeatedly with dichloromethane. Organic fractions were then combined together and dried over anhydrous Na_2SO_4. Filtration and solvent removal under vacuum afforded the crude alcohol, which was purified via Combiflash chromatography, eluting with 100% EtOAc to afford the desired product as a yellow oil **(0.850 g / 23% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.90 (td, *J* = 7.4, 1.0 Hz, 1H), 5.10 (s, 1H), 4.38 (ddt, *J* = 10.7, 6.5, 3.2 Hz, 1H), 3.69 (t, *J* = 5.8 Hz, 2H), 3.36 (ddd, *J* = 11.8, 9.4, 6.3 Hz, 3H), 2.60 (dd, *J* = 15.6, 1.9 Hz, 1H), 2.03 (s, 1H), 1.66 (pd, *J* = 6.7, 1.6 Hz, 4H), 1.32 – 1.21 (m, 3H) ppm.

(S)-N-(4-Hydroxybutyl)-2-methylindoline-1-carboxamide (27). Compound was prepared following the synthetic procedure described for **26** starting from (2*S*)-methylindoline. Observed spectroscopic data collected for **27** identical to that observed for **26.**

(R)-N-(4-Hydroxybutyl)-2-methylindoline-1-carboxamide (28). Compound was prepared following the synthetic procedure described for **26** (2*R*)-methylindoline. Observed spectroscopic data collected for **28** identical to that observed for **26.**

2-Methyl-N-(4-oxobutyl)indoline-1-carboxamide (29). To a well stirring solution of **26** (0.782 g, 3.15 mmol) in dichloromethane (32 mL), was added Dess-Martin Periodinane (1.536 g, 3.62 mmol) and the reaction stirred for 1 hour at room temperature. The reaction mixture was washed with 10% $NaHCO_3$ and the organic phase dried over anhydrous Na_2SO_4. Filtering and concentrating under vacuum afforded the crude aldehyde as a peach colored oil which was purified via Combiflash chromatography, eluting with 100% EtOAc to afford the desired product as a colorless oil **(0.470 g, 60% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.20 – 7.07 (m, 2H), 6.91 (qd, *J* = 7.5, 1.1 Hz, 1H), 5.03 (br s, 1H), 4.43 – 4.24 (m, 2H), 3.44 – 3.30 (m, 3H), 2.66 – 2.55 (m, 2H), 1.92 (p, *J* = 6.9 Hz, 2H), 1.41 – 1.21 (m, 3H) ppm.

(S)-2-Methyl-N-(4-oxobutyl)indoline-1-carboxamide (30). Compound was prepared following the synthetic procedure described for **29**, starting from **27**. Observed spectroscopic data collected for **30** identical to that observed for **29.**

(R)-2-Methyl-N-(4-oxobutyl)indoline-1-carboxamide (31). Compound was prepared following the synthetic procedure described for **29**, starting from **28**. Observed spectroscopic data collected for **31** identical to that observed for **29.**

2-Methyl-N-(4-(methyl((R)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)butyl)indoline-1-carboxamide (11). To a stirring solution of **sumanirole** (0.3 g, 1.47 mmol) in 1,2-dichloroethane (20 mL) at room temperature was added glacial acetic acid (catalytic, 5 drops), followed by the dropwise addition of **29** (0.418 g, 1.69 mmol) in 1,2-

dichloroethane (10 mL). After 15 minutes of continued stirring, $NaBH(OAc)_3$ (0.470 g, 2.21 mmol) was added in one portion and the reaction allowed to stir overnight at room temperature. Reaction was subsequently quenched with the addition of solid K_2CO_3 and allowed to stir for 5 minutes before filtering and concentrating under vacuum to afford the crude product as a viscous dark green oil. Crude material was purified by Combiflash chromatography, eluting with MeOH:DCM (15:85) to afford the desired product as a foamy white solid **(0.46 g, 72% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.66 (dq, *J* = 7.8, 1.1 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.01 – 6.83 (m, 4H), 4.90 (t, *J* = 5.6 Hz, 1H), 4.47 – 4.34 (m, 1H), 4.18 (dd, *J* = 12.1, 4.5 Hz, 1H), 3.56 (dd, *J* = 12.0, 10.2 Hz, 1H), 3.49 (s, 1H), 3.44 – 3.32 (m, 3H), 3.22 (tt, *J* = 9.7, 4.8 Hz, 1H), 2.99 – 2.91 (m, 2H), 2.73 – 2.56 (m, 3H), 2.40 (s, 3H), 1.64 – 1.55 (m, 3H), 1.30 (dd, *J* = 6.4, 1.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.74, 154.64, 142.33, 129.93, 127.51, 127.25, 125.73, 125.19, 121.95, 121.56, 119.97, 118.55, 114.74, 107.26, 57.30, 55.19, 53.69, 40.27, 40.03, 38.06, 36.32, 27.93, 26.77, 25.04, 21.01 ppm. HPLC-DAD Method B (diastereoisomer A R_t: 10.679 min; diastereoisomer B R_f: 13.854 min. purity >99%; dr 49:51); method E (diastereoisomer A R_t: 13.992 min; diastereoisomer B R_f: 31.393 min. purity 95.9%; dr 49:51). The free base was converted into the corresponding oxalate salt. HRMS (ESI positive) calculated 434.2551; found 434.2562 ($+H^+$). $[\alpha]_D^{23}$: -8.00 (0.125 g/100 mL in MeOH). Anal. ($C_{25}H_{31}N_5O_2 \cdot 1.25C_2H_2O_4 \cdot 1.25H_2O$) C, H, N M.p.: 118 °C (dec.)

(S)-2-Methyl-N-(4-(methyl((R)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)butyl)indoline-1-carboxamide (12). Compound was prepared following the synthetic procedure described for **11**, starting from **30**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.89 (ddd, *J* = 19.2, 16.5, 7.9 Hz, 4H), 4.91 (t, *J* = 5.7

Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 1H), 4.17 (dd, *J* = 12.1, 4.2 Hz, 1H), 3.61 – 3.43 (m, 2H), 3.38 (dd, *J* = 15.7, 8.9 Hz, 3H), 3.20 (dq, *J* = 9.7, 5.1, 4.7 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.63 (td, *J* = 15.6, 14.4, 6.2 Hz, 3H), 2.39 (s, 3H), 1.62 (d, *J* = 14.4 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.75, 154.64, 142.35, 129.91, 127.51, 127.36, 125.90, 125.19, 121.93, 121.42, 119.83, 118.50, 114.74, 107.21, 57.40, 55.18, 53.72, 40.32, 40.09, 38.14, 36.32, 27.94, 26.84, 25.20, 21.00 ppm. HPLC-DAD Method B (R_t: 11.410 min. purity 89.2%, de >99%). The free base was converted into the corresponding oxalate salt. $[\alpha]_D^{23}$: 3.333 (0.120 g/100 mL). Anal. ($C_{25}H_{31}N_5O_2 \cdot 2C_2H_2O_4 \cdot 1.5H_2O$) C, H, N. M.p.: 52 °C (dec.). A sample of the oxalate salt was free based and analyzed via HPLC-DAD method E (R_t: 14.491 min. purity >99%, de >99%).

(R)-2-Methyl-N-(4-(methyl((R)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)butyl)indoline-1-carboxamide (13). Compound was prepared following the synthetic procedure described for **11**, starting from **31**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 2H), 7.01 – 6.83 (m, 4H), 4.87 (s, 1H), 4.46 – 4.34 (m, 1H), 4.17 (dd, *J* = 11.9, 4.3 Hz, 1H), 3.61 – 3.47 (m, 2H), 3.44 – 3.29 (m, 3H), 3.22 (dt, *J* = 9.9, 4.8 Hz, 1H), 2.96 (m, 2H), 2.73 – 2.57 (m, 3H), 2.40 (s, 3H), 1.63 – 1.56 (m, 3H), 1.31 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.71, 154.37, 142.34, 129.92, 127.51, 127.34, 125.66, 125.19, 121.93, 121.48, 119.98, 118.54, 114.73, 107.12, 57.35, 55.19, 53.72, 40.28, 40.05, 38.08, 36.32, 27.93, 26.84, 25.11, 21.03 ppm. HPLC-DAD Method B (R_t: 14.468 min. purity 99.1%, de >99%). The free base was converted into the corresponding oxalate salt. $[\alpha]_D^{23}$: -20.0 (0.115 g/ 100 mL). Anal. ($C_{25}H_{31}N_5O_2 \cdot 1.5C_2H_2O_4 \cdot H_2O$) C, H, N. M.p.: 93 °C (dec.). A

sample of the oxalate salt was free based and analyzed via HPLC-DAD method E (R_t: 32.314 min. purity >99%, de >99%).

N-(4-Hydroxybutyl)benzo[d]thiazole-5-carboxamide (32)

Compound was prepared following the synthetic procedure described for **23** starting from benzo[*d*]thiazole-5-carboxylic acid (0.3 g, 1.7 mmol). The crude product was used in the next step without further purification.

N-(4-Oxobutyl)benzo[d]thiazole-5-carboxamide (33)

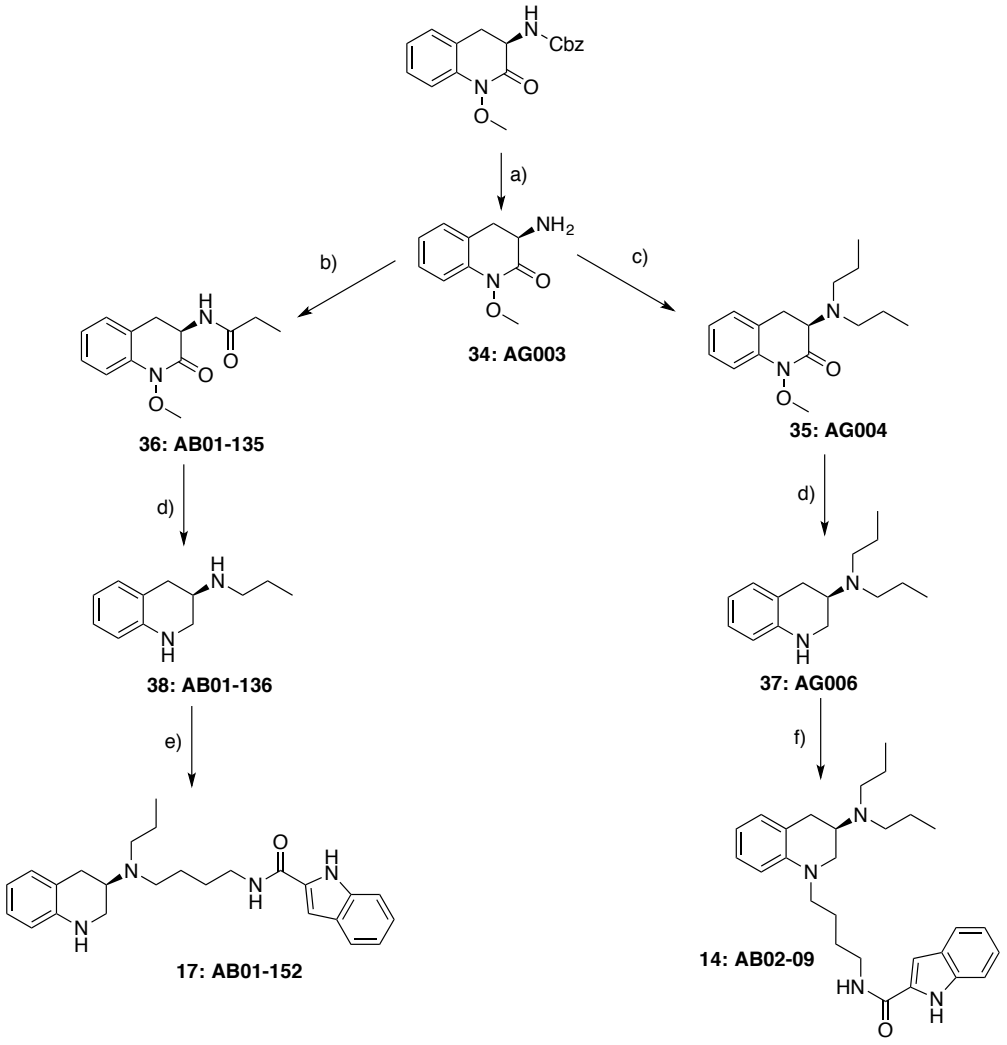
Compound was prepared following the synthetic procedure described for **29** starting from **32** (0.12 g, 0.5 mmol). Crude material was purified by Combiflash chromatography, eluting with 100% EtOAc to afford the desired product as yellow oil (**0.06 g, 48% yield**).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, *J* = 1.1 Hz, 1H), 9.07 (d, *J* = 2.1 Hz, 1H), 8.41 (dd, *J* = 78.8, 1.5 Hz, 1H), 8.15 – 7.50 (m, 2H), 6.73 (br s, 1H), 3.61 – 3.40 (m, 2H), 2.64 (td, *J* = 6.8, 1.1 Hz, 2H), 1.99 (p, *J* = 6.8 Hz, 2H).

(R)-N-(4-(Methyl(2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)butyl)benzo[d]thiazole-5-carboxamide (8)

Compound was prepared following the synthetic procedure described for **11** starting from **sumanirole** (0.022 g, 0.1 mmol) and **33** (0.022g , 0.09 mmol). Crude material was purified by Combiflash chromatography, eluting with 10% CMA ($CHCl_3$:MeOH:NH_4OH 9:1:0.1) to afford the desired product as yellow oil (**69% yield**).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.49 (dd, *J* = 1.7, 0.6 Hz, 1H), 8.15 – 7.73 (m, 3H), 7.08 – 6.64 (m, 4H), 4.14 (dd, *J* = 12.1, 4.2 Hz,

1H), 3.76 – 3.39 (m, 2H), 3.27 – 3.11 (m, 1H), 2.94 (d, *J* = 7.3 Hz, 2H), 2.65 (dt, *J* = 13.0, 6.6 Hz, 2H), 2.56 – 2.24 (m and s, 1H and 3H), 1.84 – 1.47 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.04, 155.27, 154.12, 153.08, 136.66, 133.45, 127.45, 125.59, 124.48, 122.13, 121.76, 121.40, 119.96, 118.41, 106.99, 57.28, 53.65, 40.04, 40.00, 38.19, 29.69, 27.25, 27.03, 25.25. The free base was converted into the corresponding oxalate salt. $[\alpha]_D^{23}$: -12.173 (0.115 g/100 mL). Anal. ($C_{23}H_{25}N_5O_2S \cdot C_2H_2O_4 \cdot 3H_2O$) C, H, N. M.p.: 113 °C (dec)

Scheme 2.



a) $Pd(OH)_2/C$, H_2, EtOH, 50 psi, 12-24 hrs; b) propionyl chloride, DCM, TEA; c) propionaldehyde, $Na(OAc)_3BH$, AcOH, THF; d) $BH_3{\cdot}(CH_3)_2$, THF, from 0 ^oC to reflux; e) *N*-(4-bromobutyl)-1*H*-indole-2-carboxamide, K_2CO_3, DMF, 100 ^oC, sealed vessel; f) *N*-(4-bromobutyl)-1*H*-indole-2-carboxamide, DME, DIPEA, 100 ^oC, sealed vessel.

(R)-3-Amino-1-methoxy-3,4-dihydroquinolin-2(1H)-one (34). Benzyl (R)-(1-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(methyl)carbamate (6.55 g, 20 mmol) was added as a viscous

amber oil into a hydrogenation vessel and solubilized with anhydrous ethanol (200 mL). $Pd(OH)_2$ on carbon (0.5 g, 0.712 mmol) was added carefully to the solution and gently shaken to ensure submersion in the solvent. The reaction mixture was subsequently placed in a Parr hydrogenation apparatus and pressurized under H_2 gas (50 psi). Reaction was allowed to proceed with vigorous mechanical shaking overnight at room temperature. After 24 hours, reaction was removed from hydrogenation apparatus and the reaction mixture filtered through celite and concentrated under vacuum to afford the crude material as a viscous oil. Crude product was purified by Combiflash chromatography, eluting with MeOH:DCM (15:85) to afford the *N*-methoxylated lactam as the major product **(3.6 g, 93.3% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 2H), 7.20 (m, 1H), 7.11 – 7.01 (m, 1H), 3.91 (s, 3H), 3.46 (dd, *J* = 3.1, 1.0 Hz, 1H), 3.10 (dd, *J* = 15.3, 6.0 Hz, 1H), 2.85 (t, *J* = 14.3 Hz, 1H), 2.06 (br s, 2H) ppm.

(R)-N-(1-Methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propionamide (36). To a well stirring solution of **34** (5.5 g, 18.5 mmol) in dichloromethane (40 mL) at room temperature, was added dropwise a solution of propionyl chloride (4.0 g, 3.77 mL, 24 mmol) in dichloromethane (10 mL). Reaction was allowed to proceed over the following 12 hours at this temperature. Reaction mixture was then concentrated under vacuum and purified by Combiflash chromatography, eluting with MeOH:Chloroform (1:99) to afford the desired product **(4.5 g, 97% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 1H), 7.19 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.09 (m. 1H), 6.61 (br s, 1H), 4.58 (ddd, *J* = 14.3, 6.1, 5.2 Hz, 1H), 3.90 (s, 3H), 3.48 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.53 (m, 1H), 2.31 (qd, *J* = 7.6, 1.3 Hz, 2H), 1.27 – 1.09 (m, 3H) ppm.

(R)-N-Propyl-1,2,3,4-tetrahydroquinolin-3-amine (38). To a solution of **36** (4.10 g, 16.5 mmol) in anhydrous tetrahydrofuran (50 mL) under inert atmosphere and cooled to 0°C, was added dropwise a solution of $BH_3 \cdot THF$ (15 mL, 10 M soln.). Reaction was slowly warmed to room temperature over 1 hour with continued stirring, and subsequently heated to reflux overnight. Upon completion, reaction was quenched with the dropwise addition of MeOH at 0°C until no further gas evolution was detected. Reaction mixture was then concentrated under vacuum to afford the desired crude product used in the next step without further purification.

(R)-N-(4-(Propyl(1,2,3,4-tetrahydroquinolin-3-yl)amino)butyl)-1H-indole-2-carboxamide (17). To a stirring solution of **38** (0.173 g, 0.9 mmol) and K_2CO_3 (0.3 g, 2.1 mmol) in *N,N*-dimethylformamide (5 mL) at room temperature, was added dropwise a solution of *N*-(4-bromobutyl)-1*H*-indole-2-carboxamide[2] (0.21 g, 0.7 mmol) in *N,N*-dimethylformamide (5 mL). Reaction was stirred at this temperature for the following 12 hours, and then heated gently to 100°C for an additional hour. Upon completion, the reaction mixture was filtered and concentrated under vacuum to afford the crude material which was purified by Combiflash chromatography, eluting with MeOH:Chloroform (15:85) to afford the desired product **(0.096 g, 34% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 7.63 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.42 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.06 – 6.91 (m, 2H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.72 – 6.56 (m, 1H), 6.50 (ddd, *J* = 21.2, 8.3, 1.2 Hz, 1H), 6.32 (br s, 1H), 3.80 (m, 1H), 3.49 (q, *J* = 6.6 Hz, 2H), 3.41 – 3.31 (m, 1H), 3.24 – 3.00 (m, 1H), 2.87 – 2.68 (m, 2H), 2.67 – 2.41 (m, 4H), 2.15 (q, *J* = 7.6 Hz, 2H), 1.73 – 1.39 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.48, 144.30, 136.08, 130.85, 130.54, 129.92, 127.66, 127.15, 126.82, 124.40, 121.86, 120.87, 120.61, 118.04, 117.26, 113.84, 111.85,

101.60, 54.11, 52.61, 50.18, 45.38, 44.14, 41.68, 39.58, 32.63, 29.76, 27.57, 26.22, 21.87, 11.80 ppm. The free base was converted into the corresponding oxalate salt. HRMS (ESI positive) calculated 405.26489; found 405.26477 ($+H^+$). $[\alpha]_D^{23}$:-9.565 (0.115 g/100 mL in MeOH). Anal. ($C_{25}H_{32}N_4O \cdot 1.25C_2H_2O_4 \cdot 0.5H_2O$) C, H, N M.p.: 88-92 °C

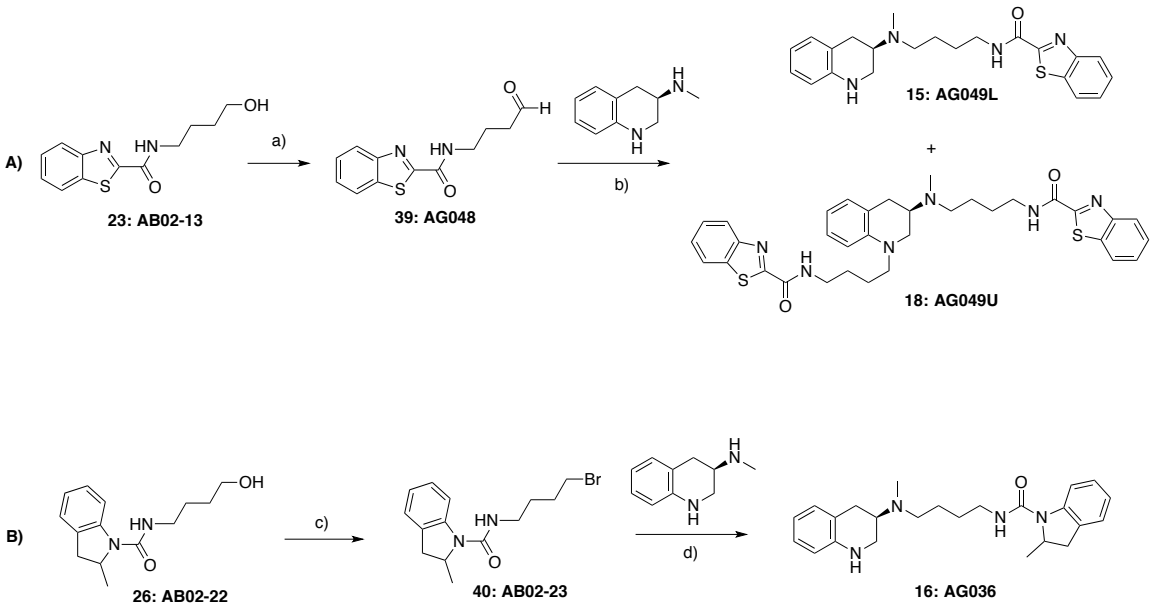
(R)-3-(Dipropylamino)-1-methoxy-3,4-dihydroquinolin-2(1H)-one (35). To a well stirred solution of **34** (3.6 g, 18.7 mmol) in tetrahydrofuran (25 mL) at room temperature, was added propionaldehyde (3.26 g, 4.03 mL, 56.2 mmol) along with acetic acid (0.28 g, 0.27 mL, 4.6 mmol), and finally $NaBH(OAc)_3$ (13.1 g, 84.6 mmol). An additional 25 mL of tetrahydrofuran was subsequently added to rinse, and the reaction stirred at room temperature overnight. Reaction was quenched with the dropwise addition of a saturated Na_2CO_3 solution, and subsequently extracted 3x with 50 mL portions of dichloromethane. Organic fractions were then combined together, dried over anhydrous Na_2SO_4, before filtering and concentrating under reduced pressure. Crude material was used in the next step without further purification.

(R)-N,N-Dipropyl-1,2,3,4-tetrahydroquinolin-3-amine (37). To a solution of **35** (1.3 g, 4.7 mmol) in anhydrous tetrahydrofuran (50 mL) under inert atmosphere and cooled to 0°C, was added dropwise a solution of $BH_3 \cdot THF$ (5 mL, 10 M soln.). Reaction was slowly warmed to room temperature over 1 hour with continued stirring, and subsequently heated to reflux overnight. Upon completion, reaction was quenched with the dropwise addition of MeOH until no further gas evolution was detected. Reaction mixture was then concentrated under vacuum to afford the desired crude product as a viscous yellow oil in sufficient purity as to advance to the following synthetic **(1.00 g, 86% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (t, *J* = 7.8 Hz, 2H),

6.62 (td, *J* = 7.4, 1.2 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 3.14 (d, *J* = 9.4 Hz, 2H), 2.83 (d, *J* = 7.2 Hz, 2H), 2.57 – 2.48 (m, 4H), 1.68 (d, *J* = 10.7 Hz, 1H), 1.68 (s, 1H), 1.48 (p, *J* = 7.3 Hz, 2H), 1.00 – 0.89 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 6H) ppm.

(R)-N-(4-(3-(Dipropylamino)-3,4-dihydroquinolin-1(2H)-yl)butyl)-1H-indole-2-carboxamide (14). Compound **37** (0.1 g, 0.4 mmol), along with *N*-(4-bromobutyl)-1*H*-indole-2-carboxamide[2] (0.15 g, 0.5 mmol), and diisopropylethylamine (0.742 g, 1 mL, 5.74 mmol) were charged to a sealed vessel and solubilized in 1,2-dimethoxyethane (20 mL). Reaction was then heated to approximately 80°C, and allowed to proceed with vigorous stirring overnight. Upon completion of the reaction, solvent was concentrated under vacuum and the remaining residue purified by Combiflash chromatography, eluting with MeOH:chloroform (5:95). Semi pure material isolated was further purified by two iterations of preparatory thin-layer chromatography, eluting with MeOH:chloroform: NH_4OH (5:95:1) to afford the desired product **(0.0134g, 7% yield).).** ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 9.71 (br s, 1H), 7.61 (d, *J* = 8.0, 1H), 7.41 (d, *J* =8.0 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.12 – 6.95 (m, 3H), 6.83 (br s, 1H), 6.60 – 6.56 (m, 2H), 3.64 – 3.61 (m, 1H), 3.49 (m, 2H), 3.31 – 3.22 (m, 5H), 2.81 (br d, *J* = 7.9 Hz, 2H), 2.55 – 2.35 (m, 3H), 1.82 – 1.33 (m, 8H), 0.88 (td, *J* = 7.3, 4.0 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$ + CD_3OD) δ 161.81, 144.83, 136.18, 129.70, 127.52, 127.35, 124.29, 121.84, 120.43, 116.36, 111.86, 110.78, 62.52, 52.66, 49.87, 49.66, 49.44, 49.23, 39.28, 34.74, 21.19, 23.72, 18.85, 13.80, 11.68 ppm. HPLC-DAD Method A (R_t: 8.214 min; purity 94.2%). HRMS (ESI positive) calculated 447.31184; found 447.31402 ($+H^+$). $[\alpha]_D^{23}$:9.091 (0.055 g/100 mL in MeOH).

Scheme 3.



a) DMP, DCM, from 0 ^{o}C to RT; b) $Na(OAc)_3BH$, AcOH, DCE; c) PPh_3, CBr_4, ACN; d) K_2CO_3, ACN, 60 ^{o}C.

N-(4-Oxobutyl)benzo[d]thiazole-2-carboxamide (39). To a stirring solution of **23** (0.5 g, 1.9 mmol) in dichloromethane (20 mL) at room temperature was added Dess-Martin Periodinane (0.974 g, 2.3 mmol) and allowed to proceed over the following 1 hour. Upon completion, reaction mixture was diluted in dichloromethane and washed with a 10% aqueous solution of $NaHCO_3$. Organic fraction was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the crude aldehyde as a viscous oil. Crude product was subsequently purified via Combiflash chromatography, eluting with EtOAc:Hexanes (1:1) to afford the desired product as a cloudy, viscous oil **(0.495 g, 99%).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.13 – 8.03 (m, 1H), 7.98 (ddd, *J* = 8.0, 4.3, 1.1 Hz, 2H), 7.61 – 7.46 (m, 1H), 3.62 – 3.51 (m, 2H), 2.62 (td, *J* = 7.2, 1.1 Hz, 2H), 2.06 – 1.97 (m, 2H) ppm.

(R)-N-(4-(Methyl(1,2,3,4-tetrahydroquinolin-3-yl)amino)butyl)benzo[d]thiazole-2-carboxamide (15) and (R)-N-(4-(3-((4-(Benzo[d]thiazole-2-carboxamido)butyl)(methyl)amino)-3,4-dihydroquinolin-1(2H)-yl)butyl)benzo[d]thiazole-2-carboxamide (18). To a well stirring solution of (*R*)-*N*-methyl-1,2,3,4-tetrahydroquinolin-3-amine (0.353 g, 2.17 mmol) in 1,2-dichloroethane (45 mL) was added acetic acid (5 drops, catalytic*), followed by the dropwise addition of a solution of **39** (0.540 g, 2.17 mmol) in 1,2-dichloroethane (5 mL). This was allowed to stir at room temperature for the following 15 minutes before the addition of $NaBH(OAc)_3$ (0.691 g, 3.26 mmol). The reaction was subsequently allowed to proceed over the following 85 hours. Upon completion, reaction was transferred to a separatory funnel and washed 3x with a 10% aqueous solution of $NaHCO_3$. Organic fraction was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the crude products as a pale orange oil. Purification via Combiflash chromatography was conducted in gradient from 0 to 15% MeOH in DCM, and two distinct fractions were collected and concentrated under vacuum to afford two regioisomeric products as amber colored oils.

18 (77.6 mg, 5.69 % yield) eluted first. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.89 (m, 3H), 7.78 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.58 – 7.41 (m, 2H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.10 – 7.01 (m, 1H), 7.01 – 6.85 (m, 2H), 6.57 (dt, *J* = 20.3, 7.7 Hz, 2H), 3.54 (q, *J* = 6.5 Hz, 5H), 3.51 – 3.40 (m, 2H), 3.40 – 3.25 (m, 2H), 3.06 – 2.94 (m, 2H), 2.94 – 2.81 (m, 2H), 2.58 (s, 3H), 1.75 (d, *J* = 6.4 Hz, 8H) ppm. free base was converted into the corresponding oxalate salt. ^{13}C NMR (101 MHz, dmso) δ 165.11, 162.73, 159.96, 159.83, 153.13, 144.64, 136.52, 129.97, 127.54, 127.31, 124.31, 123.46, 118.81, 117.03, 111.79, 109.99, 57.53, 53.20, 51.78, 50.61, 49.04, 48.23, 37.17, 26.86, 26.48, 26.46, 22.96, 21.40 ppm. $[\alpha]_D^{23}$:-

9.231 (0.130g/100 mL in MeOH). HRMS (ESI positive) calculated 627.26; found 627.26 ($+H^+$). Anal. ($C_{34}H_{38}N_6O_2S_2 \cdot 3C_2H_2O_4$) C, H, N

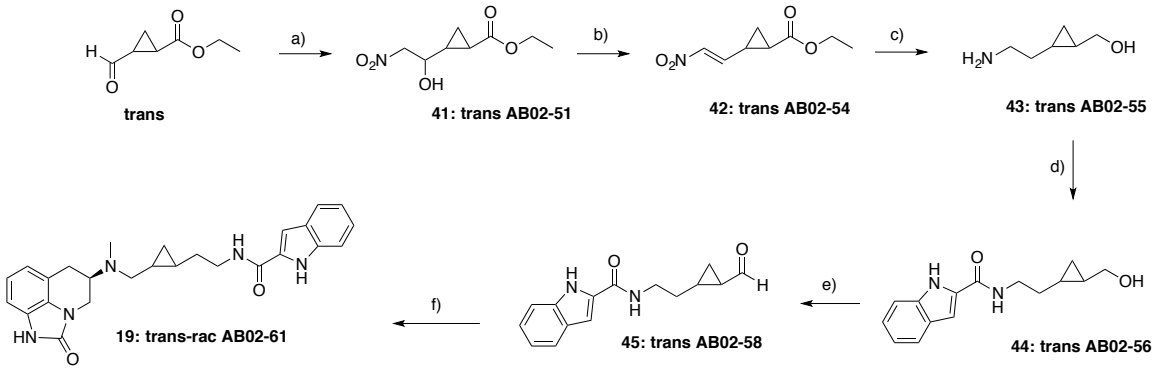
15 (45.3 mg, 5.28 % yield) eluted second. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.56 – 7.43 (m, 1H), 7.29 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 8.3 Hz, 1H), 3.90 (br s, 1H), 3.76 – 3.64 (m, 3H), 3.62 – 3.46 (m, 3H), 3.17 – 3.06 (m, 3H), 2.74 (s, 3H), 1.99 – 1.91 (m, 2H), 1.77 (dt, *J* = 21.6, 10.7 Hz, 2H) ppm. Free base was converted into the corresponding oxalate salt. ^{13}C NMR (101 MHz, dmso) δ 165.11, 163.12, 159.95, 153.14, 144.72, 136.52, 129.84, 127.54, 127.30, 124.33, 123.46, 117.17, 117.02, 114.27, 65.35, 57.75, 53.15, 41.01, 39.02, 37.03, 27.55, 26.50, 21.32, 15.61 ppm. $[\alpha]_D^{23}$:-11.0 (0.100 g/100 mL in MeOH). HRMS (ESI positive) calculated 395.19; found 395.19 ($+H^+$). Anal. ($C_{22}H_{26}N_4OS \cdot 2.5C_2H_2O_4 \cdot 1.5H_2O$) C, H, N. M.p.: 83 °C (dec.)

N-(4-bromobutyl)-2-methylindoline-1-carboxamide (40). Compound was prepared following the synthetic procedure described for **24** starting from **26** (0.850 g, 3.42 mmol). Crude product was partially purified via Combiflash chromatography, eluting with EtOAc:Hexanes (gradient from 20% to 60% EtOAc in hexanes), and used in the next step without any further purification.

2-Methyl-N-(4-(methyl((R)-1,2,3,4-tetrahydroquinolin-3-yl)amino)butyl)indoline-1-carboxamide (16). **40** (0.257 g. 0.83 mmol) along with (*R*)-*N*-methyl-1,2,3,4-tetrahydroquinolin-3-amine (0.154 g, 0.95 mmol) were added to a sealed vessel and suspended in acetonitrile (5 mL). Solubilization was induced with vigorous stirring and gentle heating (65 – 85 °C) in an oil bath. Reaction was allowed to proceed over the following 3 hours, before heating was removed. Reaction mixture was basified by the addition of solid K_2CO_3 (5 to 10 equivalents), filtered and

concentrated under vacuum to afford the crude product as an amber colored oil. Crude material was purified via Combiflash chromatography in gradient from 5 to 10% MeOH in Chloroform to afford the desired product as an off-white solid **(25.8 mg, 7.95% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.05 – 6.87 (m, 3H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 4.56 – 4.47 (m, 1H), 3.68-3.24 (m, 5H), 3.03 (m, 4H), 2.62 (s and m, 3H and 1H), 1.98-1.56 (m, 4H), 1.30 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.85, 143.52, 142.49, 129.83, 129.66, 127.54, 127.46, 125.10, 121.94, 118.41, 115.01, 114.50, 57.20, 55.02, 53.70, 38.99, 37.39, 36.42, 27.38, 21.04, 15.26 ppm. $[\alpha]_D^{23}$: -10.909 (0.055 g/100 mL in MeOH). HRMS (ESI positive) calculated 393.2646; found 393.2657 ($+H^+$). Anal. ($C_{24}H_{32}N_4O \cdot 0.5CHCl_3 \cdot 1.5CH_3OH$) C, H, N. M.p.: 47-48 °C

Scheme 4.



a) tBuOLi, tBuOH, CH_3NO_2, THF; b) MsCl, TEA, DCM; c) LAH, THF; d) Indole-2-carboxylic acid, HOBt, EDC, THF; e) DMP, DCM, from 0 ^oC to RT; f) **sumanirole**, $Na(OAc)_3BH$, AcOH, DCE.

Trans-ethyl 2-(1-hydroxy-2-nitroethyl)cyclopropane-1-carboxylate (41). To a solution of ethyl 2-formylcyclopropane-1-carboxylate (predominantly trans) (1.0 g, 7 mmol) in tetrahydrofuran/t-BuOH (10 mL, 1:1 ratio), cooled to 0 °C in an ice bath, was added dropwise nitromethane (0.641 g, 10.5 mmol). After 5 minutes of stirring, lithium tert-butoxide (0.112 g) was added cautiously to the reaction and allowed to stir at room temperature for the following 3 hours. Upon completion, the reaction was diluted with a saturated aqueous solution of NH_4Cl, and the mixture extracted with dichloromethane. Organic fractions were combined together and dried over anhydrous Na_2SO_4, before filtering and drying under vacuum to afford the desired product without further purification **(1.32 g, 92.3% yield).** ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 – 4.36 (m, 2H), 4.23 – 4.04 (m, 2H), 3.99 (q, *J* = 7.0 Hz, 1H), 2.90 – 2.84 (br s, 1H), 1.77 – 1.67 (m, 1H), 1.55 (m, 1H), 1.33 – 1.16 (m, 4H), 1.16 – 0.99 (m, 1H) ppm.

Trans-ethyl (E)-2-(2-nitrovinyl)cyclopropane-1-carboxylate (42).

To a well stirring solution of **41** (8.291 g, 40.8 mmol) and methanesulfonyl chloride (7.01 g, 4.74 mL, 61.2 mmol) in dichloromethane (100 mL) under inert atmosphere and submerged in a 0 °C ice bath, was added dropwise a solution of triethylamine (10.322 g, 14.227 mL, 102 mmol) in dichloromethane (50 mL). Reaction was allowed to warm to room temperature with stirring over the following 18 hours. Upon completion, reaction mixture was concentrated under vacuum and subsequently diluted in H_2O. This aqueous mixture was extracted with diethyl ether, and the organic fraction combined together and dried over anhydrous Na_2SO_4, before filtering, and concentrating under vacuum to afford the crude product as a yellow oil. Crude material was purified twice via Combiflash chromatography, first eluting in gradient from 0 to 90% EtOAc in Hexanes, and semi-pure material re-purified, eluting in gradient from 0 to 24% EtOAc in Hexanes. Finally, the purified racemic mixture was quantitated by chiral HPLC. HPLC-DAD Method C (Enantiomer A R_t: 30.379 min; Enantiomer B R_t: 37.560 min; purity 99.9%; er 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 13.2 Hz, 1H), 6.74 (dd, *J* = 13.2, 10.6 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.6 Hz, 2H), 2.23 – 2.10 (m, 1H), 1.97 (m, 1H), 1.66 (dtd, *J* = 8.6, 5.4, 3.2 Hz, 1H), 1.38 – 1.14 (m, 4H) ppm.

Trans-(2-(2-aminoethyl)cyclopropyl)methanol (43). Lithium aluminum hydride (0.4 g, 10.37 mmol) was charged to a round bottom flask under inert atmosphere and cooled to 0 °C in an ice bath before being cautiously suspended with the dropwise addition of anhydrous tetrahydrofuran (30 mL). To this stirring suspension was added dropwise a solution of **42** (0.640 g, 3.46 mmol) in anhydrous tetrahydrofuran (10 mL), and the reaction allowed to warm to room temperature with vigorous stirring over following 18 hours. Upon completion of the reaction, excess hydride

was quenched via the dropwise addition of MeOH, followed by 2N aqueous solution of NaOH. Anhydrous Na_2SO_4 was added into stirring solution to remove excess water, and solids were removed via filtration over Celite. Filtrate was concentrated under vacuum to afford the crude desired amino alcohol used in the next step without further purification (**0.386 g, 97% yield**).

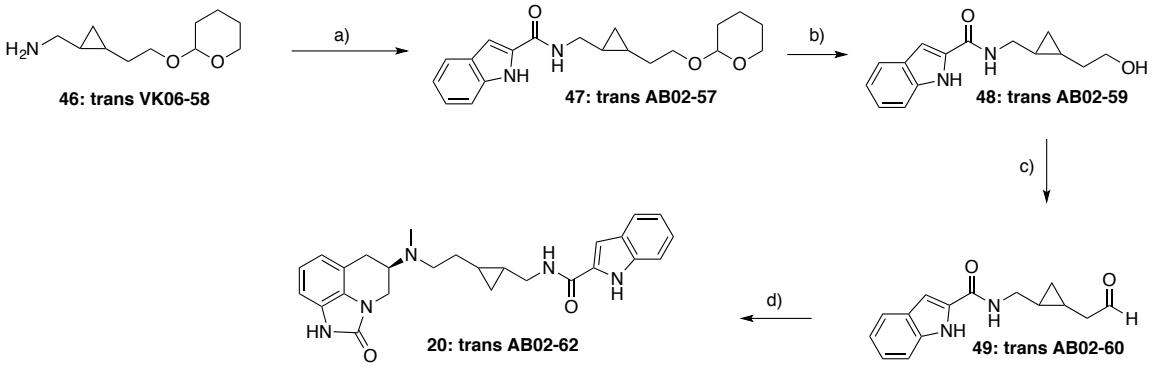
Trans-N-(2-(2-(hydroxymethyl)cyclopropyl)ethyl)-1H-indole-2-carboxamide (44). As previously described,[3] to a stirring solution of 1H-indole-2-carboxylic acid (0.391 g, 2.4 mmol) in a 1:1 mixture of THF:DCM (20 mL) cooled to 0 °C in an ice bath, was added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.548 g, 2.8 mmol) and Benzotriazol-1-ol (0.356 g, 2.6 mmol). After 30 minutes of stirring at 0 °C, a solution of **43** (0.250 g, 2.2 mmol) in dichloromethane (10 mL) was added dropwise, followed by the dropwise addition of *N*,*N*-diisopropylethylamine (0.397 g, 0.535 mL, 3 mmol) into the reaction mixture and allowed to stir overnight warming to room temperature. Upon reaction completion, solvent was stripped under vacuum and resultant residue diluted in EtOAc. Organic phase was washed with a 20% aqueous solution of $NaHCO_3$, before drying over anhydrous Na_2SO_4, filtering, and concentrating under reduced pressure. Crude material was purified via Combiflash chromatography, eluting with EtOAc:Hexanes (4:6) to afford the desired product **(0.275 g, 49% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (m, 1H), 7.63 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.41 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.36 (m, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (m, 2H), 4.06 – 3.75 (m, 2H), 3.49 – 3.22 (m, 1H), 3.01 (dd, *J* = 11.0, 9.5 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.17 – 1.03 (m, 1H), 0.96 (dq, *J* = 9.0, 4.6 Hz, 1H), 0.70 (tt, *J* = 9.4, 4.3 Hz, 1H), 0.40 (ddt, *J* = 16.7, 8.4, 5.0 Hz, 2H) ppm.

Trans-N-(2-(2-formylcyclopropyl)ethyl)-1H-indole-2-carboxamide (45). As previously described,[3] to a stirring solution of **44** (0.280 g, 1.1 mmol) in dichloromethane (15 mL) at 0 ^{o}C was added Dess-Martin Periodinane (0.583 g, 1.38 mmol) and allowed to proceed over the following 1 hour at room temperature. Upon completion, reaction mixture was diluted in dichloromethane and washed with a 10% aqueous solution of $NaHCO_3$. Organic fraction was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the crude aldehyde. Crude product was subsequently purified via Combiflash chromatography, eluting with EtOAc:Hexanes (1:1) to afford the desired product as a viscous oil **(0.119 g, 43% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 9.10 (d, *J* = 5.2 Hz, 1H), 7.65 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.45 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.34 – 7.23 (m, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.84 (dd, *J* = 2.2, 0.9 Hz, 1H), 6.37 (s, 1H), 3.60 (q, *J* = 6.7 Hz, 2H), 1.80 – 1.67 (m, 3H), 1.46 (m, 1H), 1.36 (dt, *J* = 9.0, 4.6 Hz, 1H), 1.00 (ddd, *J* = 8.1, 6.4, 4.7 Hz, 1H) ppm.

Trans-N-(2-(2-((methyl((R)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)methyl)cyclopropyl)ethyl)-1H-indole-2-carboxamide (19). To a stirring solution of **sumanirole** (0.083 g, 0.41 mmol) in 1,2-dichloroethane (10 mL), was added Acetic Acid (5 drops, catalytic), followed by the dropwise addition of **45** (0.120 g, 0.47 mmol) in 1,2-dichloroethane (5 mL). After stirring for 30 minutes, $NaBH(OAc)_3$ (0.130 g, 0.61 mmol) was added slowly into the reaction and allowed to stir overnight at room temperature. Upon completion, reaction was quenched with the addition of 0.1 g of K_2CO_3, filtered and concentrated under vacuum to afford the crude product which was purified by Combiflash chromatography, eluting with MeOH:chloroform (1:9) to afford the desired product **(89 mg, 49% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 18.5 Hz, 1H), 8.92 (s, 1H), 7.61 (d, *J* =

8.2 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.11 (tdd, *J* = 7.0, 3.8, 1.0 Hz, 1H), 7.00 – 6.90 (m, 1H), 6.90 – 6.77 (m, 3H), 6.59 – 6.51 (m, 1H), 4.18 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.63 – 3.47 (m, 3H), 3.25 (m, 1H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.60 – 2.39 (s and m, 3H and 2H), 1.65 – 1.52 (m, 2H), 0.76 (m, 1H), 0.61 (m, *J* = 7.2 Hz, 1H), 0.46 – 0.35 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.70, 154.52, 154.53, 136.32, 136.30, 136.31, 130.85, 130.83, 127.58, 127.30, 127.29, 125.73, 124.37, 121.81, 121.51, 120.57, 119.91, 119.92, 118.42, 118.35, 111.99, 107.22, 106.56, 102.00, 101.97, 58.62, 58.41, 57.33, 57.22, 39.90, 39.73, 38.66, 38.61, 33.59, 33.54, 27.31, 27.16, 17.58, 17.11, 17.05, 15.92, 10.83, 10.73, ppm. HPLC-DAD Method D (diastereoisomer A R_t: 114.571 min; diastereoisomer B R_t: 138.375 min; purity 97.7%; dr 50:50). The free base was converted into the corresponding oxalate salt. $[\alpha]_D^{23}$: 4.545 (0.110 g/100 mL in MeOH). HRMS (ESI positive) calculated 444.2394; found 444.2384 ($+H^+$). Anal. ($C_{26}H_{29}N_5O_2 \cdot 2C_2H_2O_4$) C, H, N. M.p.: 113 °C (dec.)

Scheme 5.



a) Indole-2-carboxylic acid, HOBt, EDC, THF; b) 10% HCl in H_2O, THF; c) DMP, DCM, from 0 ^oC to RT; d) **sumanirole**, $Na(OAc)_3BH$, AcOH, DCE.

Trans-N*-((2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)cyclopropyl)methyl)-1*H*-indole-2-carboxamide *(47). As previously described,[3] to a stirring solution of 1H-indole-2-carboxylic acid (1 g, 6.2 mmol) in tetrahydrofuran (20 mL) cooled to 0 °C in an ice bath, was added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.39 g, 7.24 mmol) and Benzotriazol-1-ol (0.977 g, 7.24 mmol). After 30 minutes of stirring at 0 °C, a solution of **46** (1.03 g, 5.17 mmol) in tetrahydrofuran (20 mL) was added dropwise, followed by the dropwise addition of *N*,*N*-diisopropylethylamine (0.397 g, 0.535 mL, 3 mmol) into the reaction mixture and allowed to stir overnight warming to room temperature. Upon reaction completion, solvent was stripped under vacuum and resultant residue diluted in EtOAc. Organic phase was washed with a 20% aqueous solution of $NaHCO_3$, before drying over anhydrous Na_2SO_4, filtering, and concentrating under reduced pressure. Crude material was purified via Combiflash chromatography, eluting with EtOAc:Hexanes (3:7) to afford the desired product as a mixture of diasteroisomers **(0.285 g, 17% yield).** ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.44 (dq, J =

8.4, 1.0 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.94 (ddd, *J* = 13.8, 2.2, 0.9 Hz, 1H), 6.58 – 6.51 (m, 1H), 4.61 (ddd, *J* = 22.1, 5.1, 2.6 Hz, 1H), 4.02 – 3.78 (m, 2H), 3.69 – 3.46 (m, 3H), 3.14 (dddd, *J* = 16.7, 13.3, 8.2, 4.7 Hz, 1H), 2.07 – 1.31 (m, 8H), 0.80 (m, 2H), 0.57 – 0.38 (m, 2H) ppm.

Trans-N*-((2-(2-hydroxyethyl)cyclopropyl)methyl)-1*H*-indole-2-carboxamide *(48). As previously described,[3] to a stirring solution of **47** (0.3 g, 0.88 mmol) in tetrahydrofuran (6 mL) at room temperature, was added dropwise a 10% aqueous solution of HCl and allowed to stir overnight. Upon completion, reaction was diluted with water and extracted with EtOAc. Organic fractions were combined together, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Crude material was purified by Combiflash chromatography, eluting in gradient from 60 to 80% EtOAc in Hexanes to afford the desired product **(0.199 g, 88% yield).** ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 7.60 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.23 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.14 (m, 1H), 6.93 (br s, 1H), 3.77 (m, 3H), 2.95 – 2.83 (m, 1H), 1.79 (dq, *J* = 14.3, 5.3 Hz, 1H), 1.53 – 1.45 (br s, 1H), 1.27 – 1.07 (m, 1H), 0.77 (dtt, *J* = 30.4, 9.0, 4.5 Hz, 2H), 0.42 (ddt, *J* = 37.7, 8.3, 5.0 Hz, 2H) ppm.

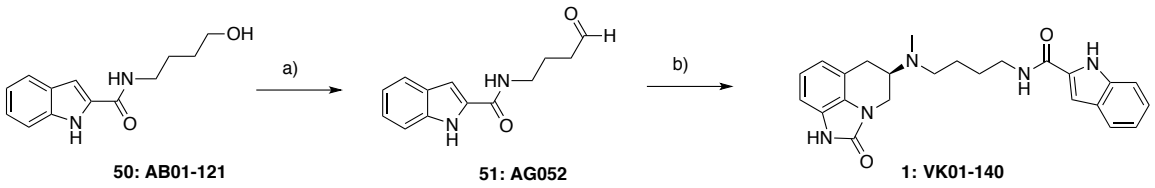
Trans-N-((2-(2-oxoethyl)cyclopropyl)methyl)-1H-indole-2-carboxamide (49). As previously described,[3] to a stirring solution of **48** (0.2 g, 0.77 mmol) in dichloromethane (15 mL) at room temperature and opened to atmosphere was added Dess-Martin Periodinane (0.408 g, 0.96 mmol) and allowed to proceed over the following 1 hour. Upon completion, reaction mixture was diluted in dichloromethane and washed with a 10% aqueous solution of $NaHCO_3$. Organic fraction was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the

crude aldehyde. Crude product was subsequently purified via Combiflash chromatography, eluting with EtOAc:Hexanes (1:1) to afford the desired product **(0.179 g, 90% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 9.35 (s, 1H), 7.71 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.61 (br s, 1H), 7.44 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.14 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.10 (dd, *J* = 19.5, 3.8 Hz, 1H), 2.69 (ddd, *J* = 13.6, 9.8, 2.6 Hz, 1H), 2.14 – 2.01 (m, 1H), 0.90 – 0.75 (m, 2H), 0.68 (dt, *J* = 8.3, 5.3 Hz, 1H), 0.53 (dt, *J* = 8.3, 5.3 Hz, 1H) ppm.

Trans-N-((2-(2-(methyl((R)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-5-yl)amino)ethyl)cyclopropyl)methyl)-1H-indole-2-carboxamide (20). To a stirring solution of **sumanirole** (0.123 g, 0.61 mmol) in 1,2-dichloroethane (10 mL), was added Acetic Acid (5 drops, catalytic), followed by the dropwise addition of **49** (0.180 g, 0.7 mmol) in 1,2-dichloroethane (5 mL). After stirring for 30 minutes, $NaBH(OAc)_3$ (0.193 g, 0.91 mmol) was added slowly into the reaction and allowed to stir overnight at room temperature. Upon completion, reaction was quenched with the addition of solid K_2CO_3, filtered and concentrated under vacuum to afford the crude product which was purified by Combiflash chromatography, eluting with MeOH:chloroform (1:9) to afford the desired product **(96 mg, 37% yield).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.90 (br s, 1H), 7.59 (t, *J* = 8.9 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.30 – 7.21 (m, 1H), 7.10 (dd, *J* = 8.1, 7.0 Hz, 1H), 6.95 (dq, *J* = 7.6, 4.0 Hz, 1H), 6.91 – 6.79 (m, 3H), 6.56 (br s, 1H), 4.13 (ddd, *J* = 36.2, 12.1, 4.2 Hz, 1H), 3.70 – 3.48 (m, 2H), 3.34 – 3.15 (m, 2H), 2.95 (dd, *J* = 11.4, 6.8 Hz, 2H), 2.75 – 2.57 (m, 1H), 2.42 – 2.32 (s and m, 3H and 1H), 1.55 (m, 1H), 1.25 (m, 1H), 0.89 (m, 1H), 0.73 (m, 1H), 0.54 – 0.42 (m, 1H), 0.38 (td, *J* = 7.9, 4.0 Hz, 1H) ppm. HPLC-DAD Method D (diastereoisomer A R_t: 117.044 min; diastereoisomer B R_t: 129.707 min; purity 90.2%; dr 48:52). The free base was converted into the corresponding

oxalate salt. ^{13}C NMR (101 MHz, d_6-DMSO) δ 163.60, 161.44, 153.75, 136.81, 132.33, 127.51, 127.22, 126.81, 123.58, 121.79, 121.35, 120.05, 119.35, 116.03, 115.65, 112.66, 107.30, 105.04, 102.83, 57.86, 57.76, 55.80, 54.58, 53.89, 42.79, 37.57, 32.46, 29.12, 26.25, 25.14, 18.79, 17.85, 17.66, 15.04, 10.54 ppm. $[\alpha]_D^{23}$: -13.571 (0.140 g/100 mL in MeOH). HRMS (ESI positive) calculated 444.2394; found 444.2381 ($+H^+$). Anal. ($C_{26}H_{29}N_5O_2 \cdot 2C_2H_2O_4 \cdot 1.25H_2O$) C, H, N. M.p.: 55 °C (dec.)

Scheme 6.



50: AB01-121 51: AG052 1: VK01-140

a) DMP, DCM, from 0 ^{o}C to RT; b) **sumanirole**, $Na(OAc)_3BH$, AcOH, DCE.

***N*-(4-oxobutyl)-1*H*-indole-2-carboxamide (51)**

To a stirring solution of **50**[2] (0.5 g, 2.15 mmol) in dichloromethane (25 mL) at 0 ^{o}C was added Dess-Martin Periodinane (1.05 g, 2.48 mmol) and allowed to proceed over the following 1 hour at room temperature. Upon completion, reaction mixture was diluted in dichloromethane and washed with a 10% aqueous solution of $NaHCO_3$. Organic fraction was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the crude aldehyde. Crude product was partially purified via Combiflash chromatography, eluting with EtOAc:Hexanes (1:1), and used in the next step without any further purification.

(*R*)-*N*-(4-(methyl(2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)amino)butyl)-1*H*-indole-2-carboxamide (1)

To a stirring solution of **sumanirole** (0.285 g, 1.40 mmol) in 1,2-dichloroethane (18 mL), was added Acetic Acid (5 drops, catalytic), followed by the dropwise addition of **51** (0.370 g, 1.6 mmol) in 1,2-dichloroethane (10 mL). After stirring for 30 minutes, $NaBH(OAc)_3$ (0.445 g, 2.1 mmol) was added slowly into the reaction and allowed to stir overnight at room temperature. Upon completion, reaction was quenched with the addition of solid K_2CO_3, filtered and concentrated under vacuum to afford the crude product which was purified by Combiflash

chromatography, eluting with MeOH:chloroform (15:85) to afford the desired product **(0.359 g, 61.3% yield).** ^{1}H and ^{13}C NMR chemical shifts were consistent with previously reported data.[1] The free base was converted into the corresponding oxalate salt. HRMS (ESI positive) calculated 418.22; found 418.22 ($+H^{+}$), error -1.5ppm. Anal. ($C_{24}H_{27}N_5O_2 \cdot C_2H_2O_4 \cdot H_2O$), calculated C 59.42, H 5.95, N 13.33; found C 59.68, 6.10, 13.14. A sample of the oxalate salt was free based and analyzed via HPLC-DAD: Chiralpak AD-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile phase used (1 mL/min flow rate) was composed of 0.1% diethylamine in 2-propanol and hexanes with gradient elution, starting with 30% of 2-propanol linearly increasing to 40%. Maximum absorbance was observed at λ 280 nM. Purity and enatiomeric excess were determined to be >95% and >99%, respectively.

Table S1: Microanalysis, Mass Spectroscopy and HPLC-DAD data

Compounds	Calculated			Found		
	C%	**H%**	**N%**	**C%**	**H%**	**N%**
2	68.32	4.89	9.37	68.58	4.81	9.42
	GC-MS (EI) 294.1 *m/z* (M+)					
8	51.81	5.74	12.08	51.62	5.35	11.96
9	59.72	6.10	15.14	59.73	5.71	14.88
	HRMS = 436.1802 ($+H^+$)			HRMS = 436.1814 ($+H^+$) HRMS = 458.1634 ($+Na^+$)		
10	HRMS = 405.2285 ($+H^+$)			HRMS = 405.2295 ($+H^+$) HRMS = 427.2113 ($+Na^+$)		
	HPLC-DAD = purity 93.3%					
11	58.09	6.38	12.32	58.48	6.28	12.17
	HRMS = 434.2551 ($+H^+$)			HRMS = 434.2562 ($+H^+$)		
	HPLC-DAD = figures S1A and S1B					
12	54.37	5.98	10.93	54.55	5.89	10.54
	HPLC-DAD = figures S1A and S1B					
13	57.33	6.19	11.94	57.66	6.40	11.83
	HPLC-DAD = figures S1A and S1B					
14	HRMS = 447.31184 ($+H^+$)			HRMS = 447.31402 ($+H^+$)		
	HPLC-DAD = purity 94.2%					
15	50.15	5.30	8.66	50.15	5.17	8.47
	HRMS = 395.19 ($+H^+$)			HRMS = 395.19 ($+H^+$)		

16	62.42	7.76	11.20	62.31	7.33	10.80
	HRMS = 393.2649 ($+H^+$)			HRMS = 393.2657 ($+H^+$)		
17	62.78	6.80	10.65	63.09	6.55	10.56
	HRMS = 405.26489 ($+H^+$)			HRMS = 405.26447 ($+H^+$)		
18	53.56	4.94	9.37	53.66	5.16	8.99
	HRMS = 627.26 ($+H^+$)			HRMS = 627.26 ($+H^+$)		
19	57.78	5.33	11.23	57.38	5.70	11.29
	HRMS = 444.2394 ($+H^+$)			HRMS = 444.2384 ($+H^+$)		
	HPLC-DAD = figures S3					
20	55.77	5.54	10.84	55.46	5.54	11.18
	HRMS = 444.2394 ($+H^+$)			HRMS = 444.2381 ($+H^+$)		
	HPLC-DAD = figures S4					

Table S2. D_2-Mediated Gi and Go activation, cAMP inhibition and β-arrestin2 recruitment[a]

D2s-BRET Constructs		Quinpirole	Sumanirole[b]	1[b]	2	8	9	11	12	13	19	20
Gi1 activation (10 min)	Emax (%)	100.0 ± 6.0	133.0 ± 7.5	93.4 ± 5.5	16.2 ± 6.1	86.7 ± 4.3	108.7 ± 8.0	110.9 ± 6.8	65.5 ± 6.6	67.8 ± 6.0	49.1 ± 2.9	93.4 ± 5.5
	EC50 (nM)	86.7 ± 29.7	543.3 ± 216.4	124.7 ± 60.5	0.5 ± 0.5	103.3 ± 29.8	1,166.8 ± 382.8	66.5 ± 23.7	812.8 ± 353.7	222.3 ± 100.2	174.6 ± 58.0	124.7 ± 60.5
GoA activation (10 min)	Emax (%)	100.0 ± 5.3	94.8 ± 2.9	66.4 ± 4.1	29.3 ± 5.8	89.2 ± 6.4	82.7 ± 7.4	86.1 ± 6.1	67.3 ± 6.7	68.9 ± 6.1	69.5 ± 4.0	66.4 ± 4.1
	EC50 (nM)	37.2 ± 12.7	74.8 ± 17.8	1.1 ± 0.9	200.4 ± 147.3	6.2 ± 2.9	136.8 ± 61.8	30.1 ± 13.1	115.3 ± 56.3	0.8 ± 0.4	18.4 ± 6.8	1.1 ± 0.9
cAMP inhibition (10 min)	Emax (%)	100.0 ± 11.7	114.1 ± 2.2	95.9 ± 3.3	24.2 ± 14.1	95.3 ± 9.4	80.1 ± 13.2	72.9 ± 14.1	96.8 ± 11.7	88.7 ± 11.3	44.2 ± 3.2	95.9 ± 3.3
	EC50	13.9 ± 8.5	32.2 ± 5.4	0.3 ±	26.5 ±	7.2 ± 4.1	96.1 ±	67.6 ±	78.5 ±	76.7 ±	17.1 ±	0.3 ± 0.1

(nM)	0.1	26.3	65.1	50.6	44.8	45.2	7.6	

[a]Potency (expressed as EC50) and efficacy values (%, normalized to quinpirole Emax) for hD_2R expressed in HEK293 cells. The values represent the arithmetic mean ± SEM of at least three independent experiments, each performed in triplicate. [b]Data previously reported[2]

Table S3. [^{3}H]-(*R*)-(+)-7-OH-DPAT radioligand competition binding data on D_4R

Compounds	**D_4R**
	K_i ± SEM (nM)
Sumanirole	1610 ± 297
1	899 ± 154
11	30.9 ± 2.61
(*R*,*S*)-12	25.5 ± 3.18
(*R*,*R*)-13	44 ± 5.95
19	1490 ± 142
20	1320 ± 110

The values represent the arithmetic mean from at least three independent experiments, each performed in triplicate. The competition experiments were performed in the presence of 3 nM [^{3}H]-(*R*)-(+)-7-OH-DPAT, similarly to what previously described,[4] and membrane preparations from HEK293 cells expressing hD_4R (final concentration of proteins in the experiment ~30-60 μg/well). IC_{50} values for each compound were determined from dose-response curves and K_i values were calculated using the Cheng-Prusoff equation;[5] K_d values for [^{3}H]-(*R*)-(+)-7-OH-DPAT were determined via separate homologous competitive binding experiments using cold (±)-7-OH-DPAT.

Table S4. Off-target binding for **1**[a]

Binding Assay Results for 1			
Receptor [^{3}H]Ligand	**IC_{50} (nM)**	**K_i (nM) ± SEM**	**Hill Slope ± SEM**
DA D_1 [^{3}H]SCH23390	>9200[*]	>7900[*]	[*]
$5HT_{1A}$ [^{3}H]8-OH-DPAT	137 ± 29	127 ± 27	-0.63 ± 0.07
$5HT_{2A}$ [^{3}H]5-HT	1,940 ± 410	1,440 ± 260	-1.06 ± 0.18
$5HT_{2C}$ [^{3}H]5-HT	3,080 ± 390	2,440 ± 270	-0.75 ± 0.04

[*]If some experiments yielded Ki, values less than 10 μM and other experiments yielded Ki, values greater than 10 μM, the latter experiments were assigned a value of 10 μM and averages calculated. The actual value is greater than that average and no standard error is reported. No Hill slope or SEM was calculated due to the low affinity of the compound

[a]Data were obtained through the NIDA Addiction Treatment Discovery Program contract (ADA151001) with Oregon Health & Science University.

Table S5. Off-target binding for **11**[a]

Binding Assay Results for 11			
Receptor [^{3}H]Ligand	**IC_{50} (nM)**	**K_i (nM) ± SEM**	**Hill Slope ± SEM**
DA D_1 [^{3}H]SCH23390	>10 μM[*]	>10 μM[*]	[*]
$5HT_{1A}$ [^{3}H]8-OH-DPAT	25.6 ± 3.0	23.7 ± 2.8	-0.48 ± 0.01
$5HT_{2A}$ [^{3}H]5-HT	4,120 ± 740	3,090 ± 490	-0.70 ± 0.10
$5HT_{2C}$ [^{3}H]5-HT	>10 μM[*]	>10 μM[*]	[*]

*No Hill slope or SEM was calculated due to the low affinity of the compound. [a]Data were obtained through the NIDA Addiction Treatment Discovery Program contract (ADA151001) with Oregon Health & Science University.

Table S6. Off-target binding and functional data for **(*R*,*R*)-13**[a]

Binding Assay Results for (*R*,*R*)-13			
Receptor [^{3}H]Ligand	**IC_{50} (nM)**	**K_i (nM) ± SEM**	**Hill Slope ± SEM**
DA D_1 [^{3}H]SCH23390	>10 μM*	>10 μM*	*
$5HT_{1A}$ [^{3}H]8-OH-DPAT	35.8 ± 4.4	33.2 ± 4.0	-0.51 ± 0.01
$5HT_{2A}$ [^{3}H]5-HT	3,700 ± 1,000	2,710 ± 670	-0.71 ± 0.04
5HT2C [^{3}H]5-HT	>10 μM*	>10 μM*	*

*No Hill slope or SEM was calculated due to the low affinity of the compound. [a]Data were obtained through the NIDA Addiction Treatment Discovery Program contract (ADA151001) with Oregon Health & Science University.

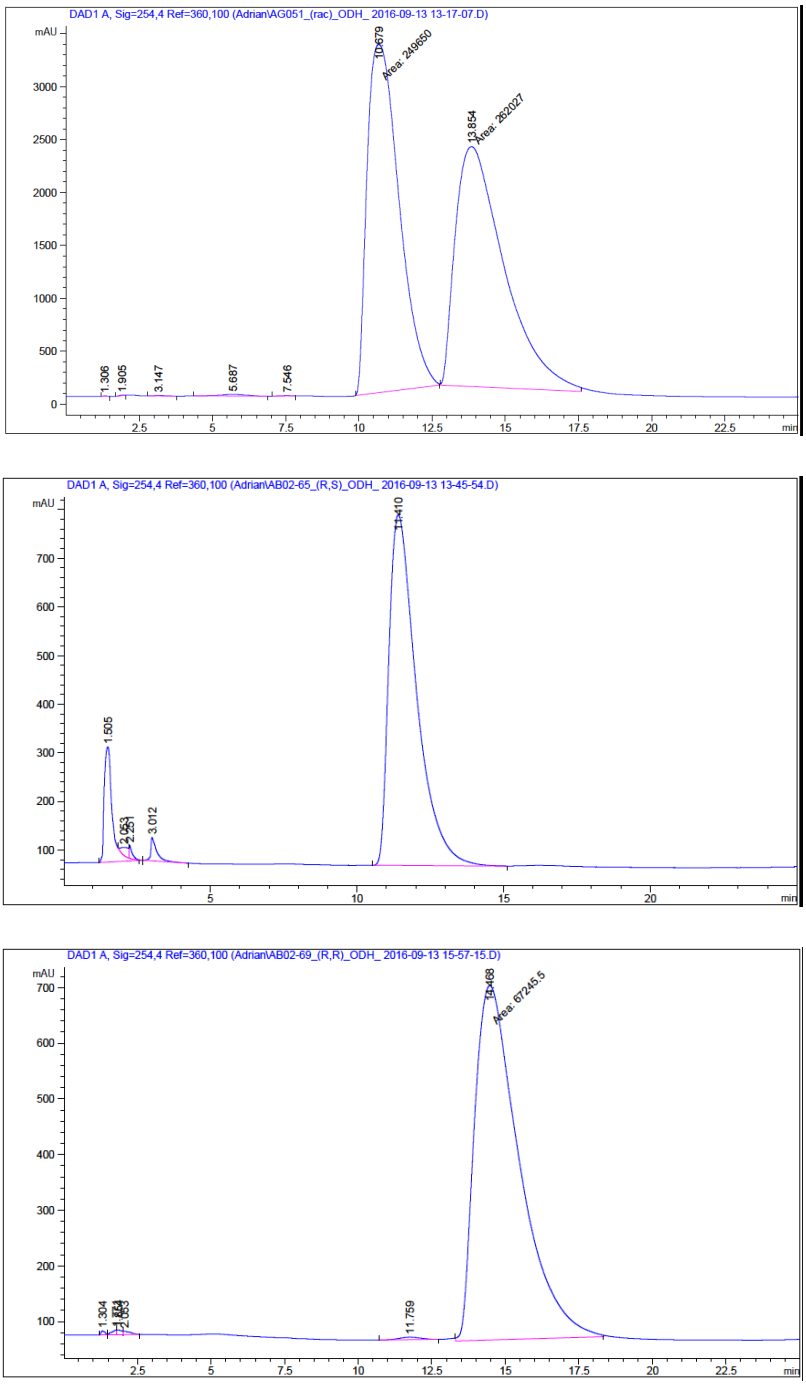


Figure S1A. 11, (*R*,*S*)-**12** and (*R*,*R*)-**13** – Chiral HPLC resolution OD (5 cm)

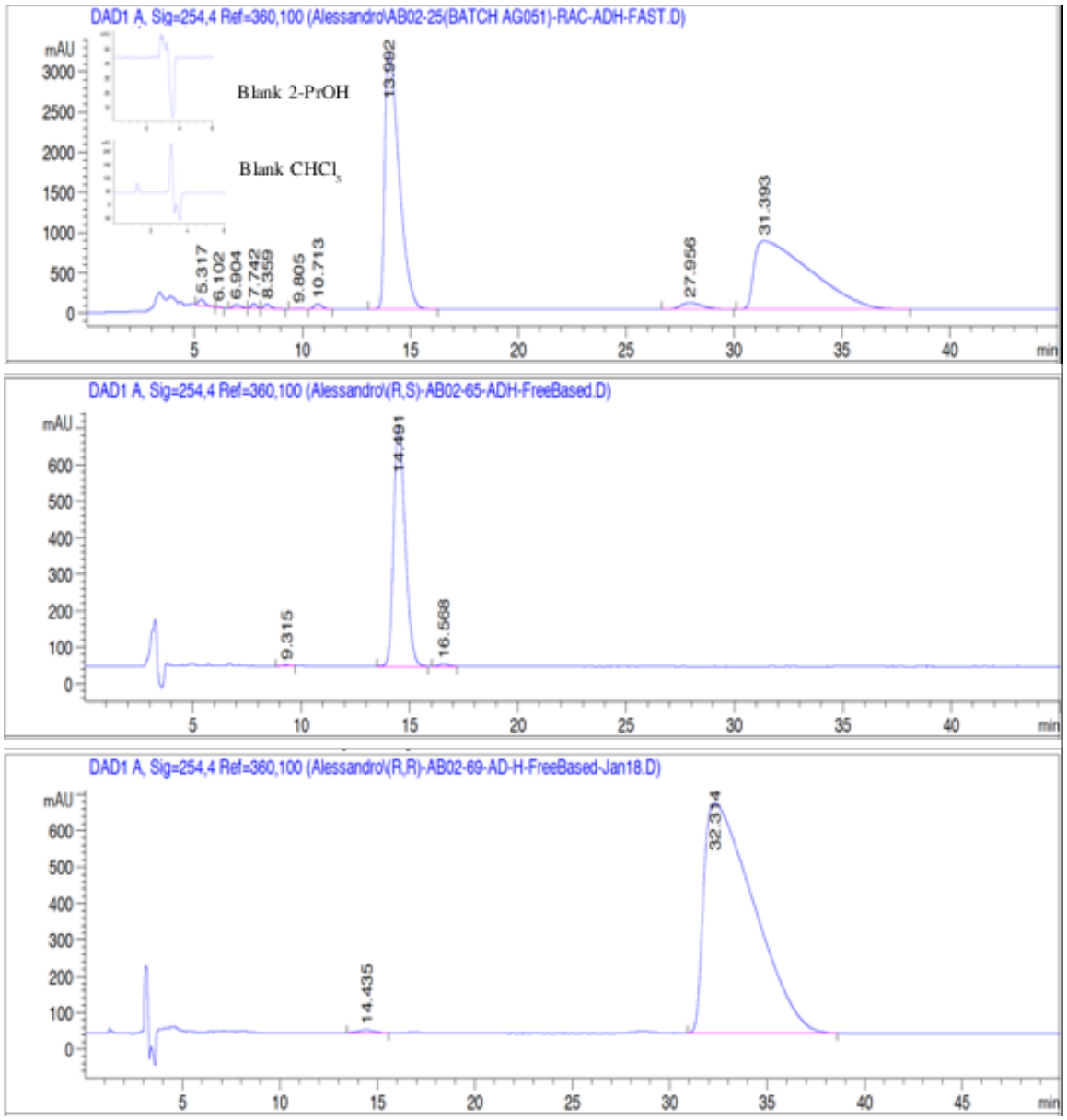


Figure S1B. 11, (*R*,*S*)-**12** and (*R*,*R*)-**13** – Chiral HPLC resolution AD-H (25 cm). In the top-left corner of the first panel are reported the blank chromatograms of 2-PrOH and $CHCl_3$ used to dissolve the samples.

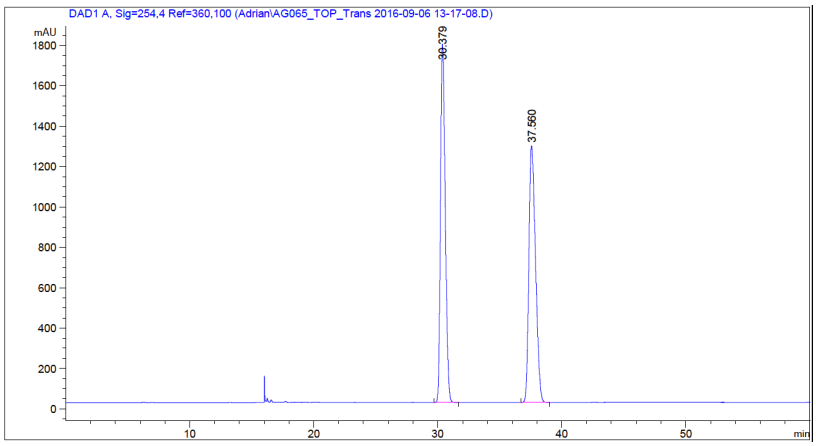


Figure S2. **42** – Chiral HPLC resolution OZ-H (25 cm)

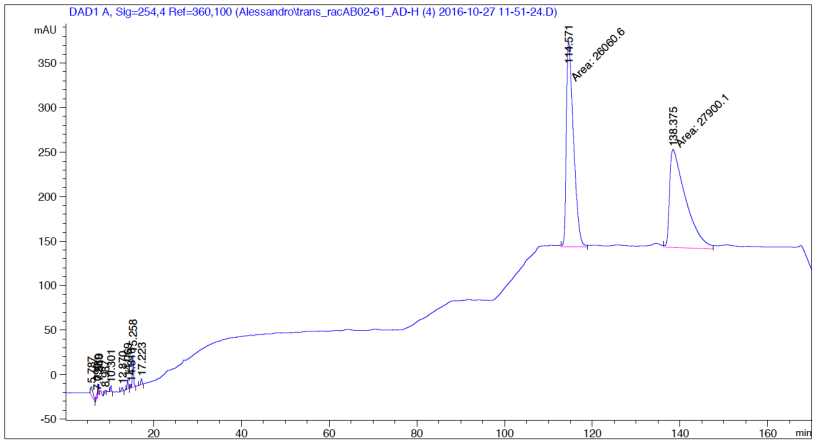


Figure S3. *trans*-**19** - Chiral HPLC resolution AD-H (25 cm)

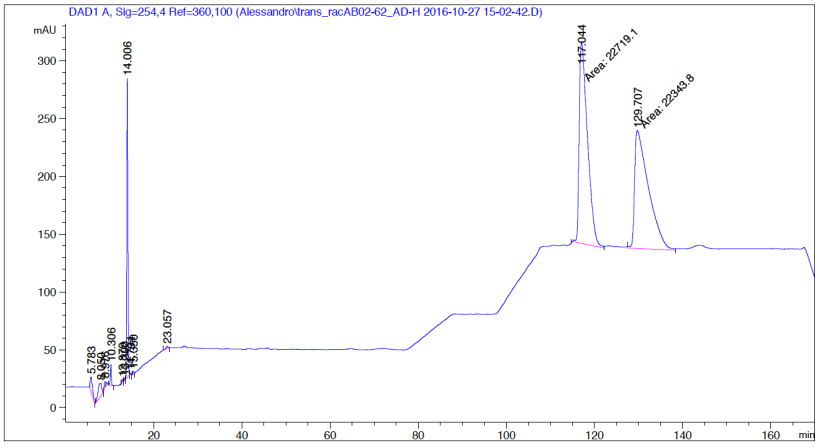


Figure S4. *trans*-**20** - Chiral HPLC resolution AD-H (25 cm)

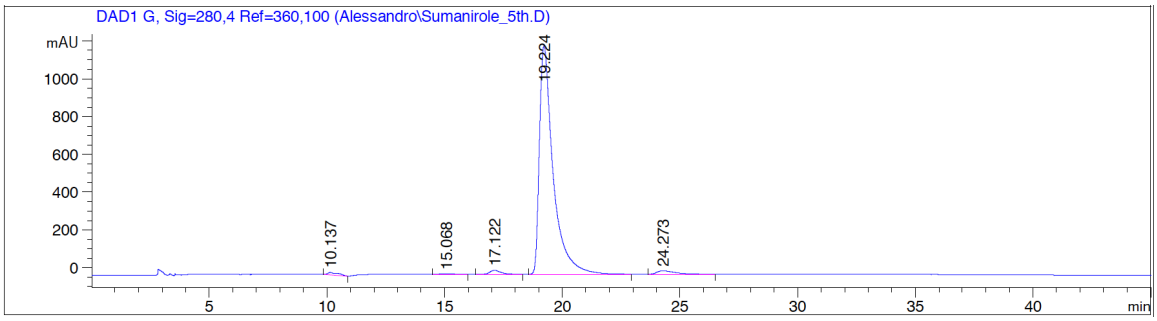


Figure S5. Sumanirole - Chiralpak AD-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile phase used (1 mL/min flow rate) was composed of 0.1% diethylamine in 2-propanol and hexanes with isocratic elution (10% of 2-propanol). Maximum absorbance was observed at λ 280 nM and enantiomeric excess was >99%.

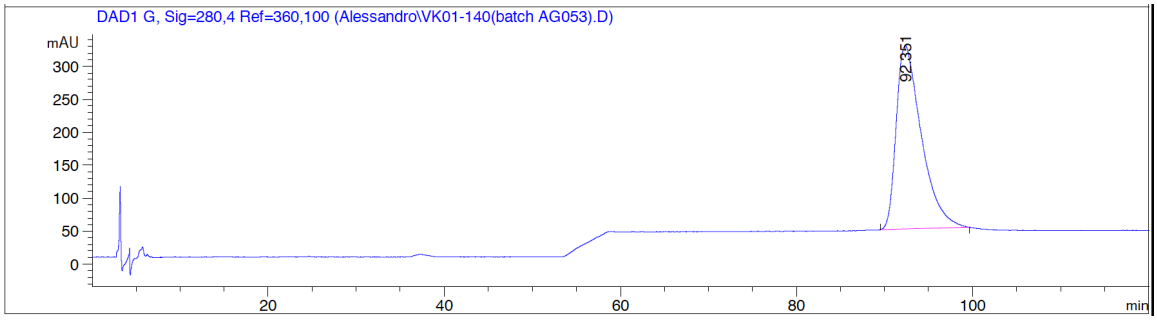


Figure S6. **1** - Chiralpak AD-H (Daicel Corporation CPI Company) column (4.6 x 250 mm, 5 μm). The mobile phase used (1 mL/min flow rate) was composed of 0.1% diethylamine in 2-propanol and hexanes with gradient elution, starting with 30% of 2-propanol linearly increasing to 40%. Maximum absorbance was observed at λ 280 nM and enantiomeric excess was >99%.

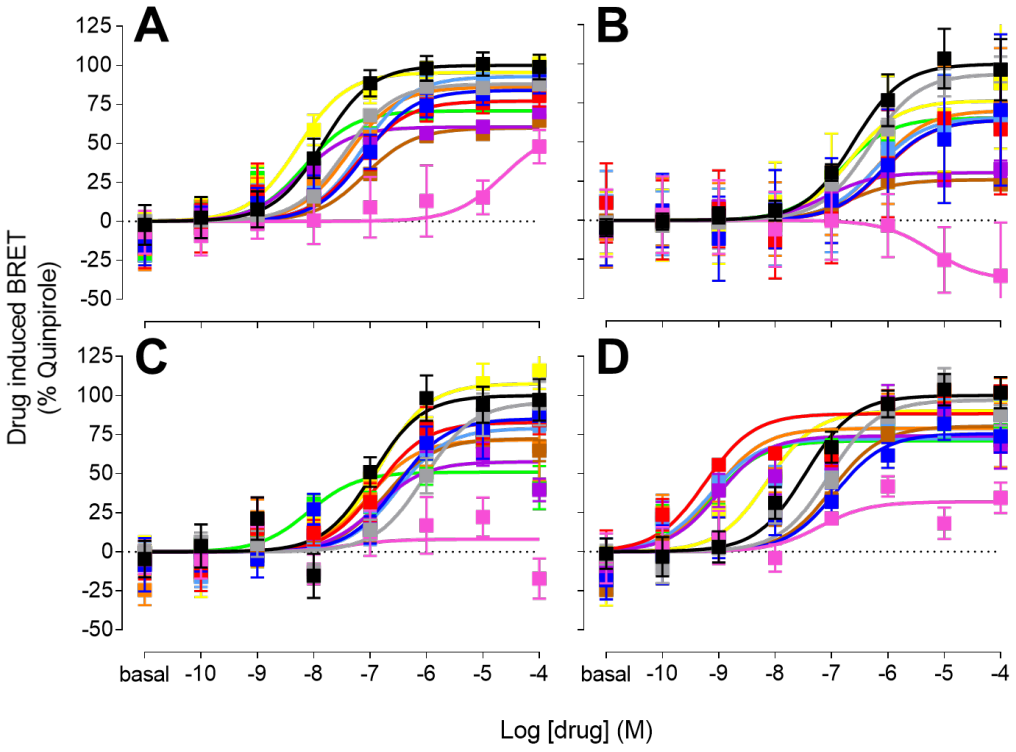


Figure S7. Dose response curves (normalized to quinpirole $E_{max)}$ used for **table 2**. **A.** cAMP inhibition, **B**. β-arrestin 2 recruitment, **C**. Gi1 activation, and **D**. GoA activation (Black – quinpirole, gray – **sumanirole**, magenta – **2**, blue – **9**, red – **11**, purple – **19**, brown – **20**, light blue – **12**, orange – **13**, yellow – **8**, green – **1**). Curves are fitted to a monophasic sigmoidal dose response. The error bars represent S.E.M.

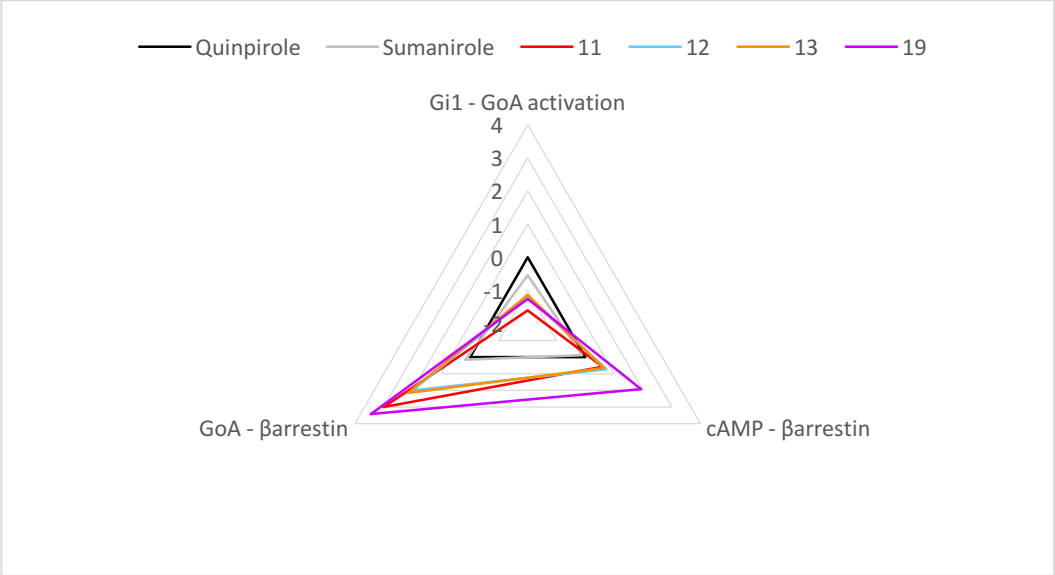


Figure S8. Bias factor values, taken from table 3, represented as web of bias, similarly to what previously shown by Klein Herenbrink C. et al.[6] Bias factors in logarithmic scale for D_2-Mediated Gi vs. Go activation, cAMP inhibition vs. β-arrestin2 recruitment, and Go activation vs. β-arrestin2 recruitment.

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