Electronic Supplementary Information

Asymmetric synthesis towards doxanthrine, a dopamine D1 full agonist

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**Experimental Section**

All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar) or nitrogen (N₂). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (100-200 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with Fₒ₅₄ indicator. The ¹H NMR spectra were recorded with a 400 MHz and ¹³C NMR spectra were recorded with a 100 MHz using CDCl₃ and DMSO-d₆. ¹H NMR chemical shifts are expressed in parts per million (δ) relative to CDCl₃ (δ = 7.26) and DMSO-d₆ (δ = 2.49); ¹³C NMR chemical shifts are expressed in parts per million (δ) relative to the CDCl₃ resonance (δ = 77.0) and DMSO-d₆ (δ = 39.7). High resolution mass spectra (HRMS) were measured with a QTOF I (quadrupole–hexapole TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface. D-Serine derived cyclic sulfamidate carboxylic acid 6 was prepared by following the literature procedure.¹

(R)-3-(tert-butoxycarbonyl)-1,2,3-oxathiazolidine-4-carboxylic acid 2,2-dioxide 6.¹

¹H NMR (400 MHz, d₆-DMSO): δ: 13.83 (br s, 1H), 4.98 (dd, J = 8.8, 3.4 Hz, 1H), 4.89 (m, 2H), 1.50 (s, 9H); (400 MHz, d₆-acetone): δ 5.04 (dd, J = 6.8, 1.8 Hz, 1H), 4.97 (dd, J = 9.6, 6.8 Hz, 1H), 4.88 (dd, J = 9.6, 1.8 Hz, 1H), 1.50 (s, 9H).

High resolution mass spectra (HRMS) were measured with a QTOF I (quadrupole–hexapole TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface. D-Serine derived cyclic sulfamidate carboxylic acid 6 was prepared by following the literature procedure.¹

Instead of EtOAc, hydrogenation was also carried out in MeOH. ¹H NMR of the crude sulfamidate 6 in d₄-MeOH showed better profile. ¹H NMR (400 MHz, d₄-MeOH): δ 4.91 (dd, J = 6.8, 1.6 Hz, 1H), 4.85 (dd, J = 9.5, 6.8 Hz, 1H, along with peak of HOD), 4.76 (dd, J = 9.5, 1.6 Hz), 1.52 (s, 9H). ¹³C NMR (100 MHz, d₄-MeOH): 170.34, 149.8, 86.7, 69.7, 59.1, 28.2. ELSD-MS (ESI): 266.0 [M-H]. [α]²⁵_D = + 24.3 (c 0.53, MeOH). HRMS (ESI): calcd for C₈H₁₃NNaO₇S 290.0310 m/z [M+Na]⁺, found 290.0310.

**Synthesis of (R)-2-tert-Butoxycarbonylamino-3-(3,4-dimethoxyphenoxy)-propionic acid 5:** To a stirring solution of 3,4-dimethoxy phenol (5.17 g, 33.56 mmol) in THF (100 ml), sodium hydride (60% in oil; 5.6 g, 129.68 mmol) was added portion wise at 0 °C and stirred at that temperature for 30 min. The reaction mass was cooled to -15 °C and a solution of sulfamidate carboxylic acid 6 (11.2 g, 41.97mmol) in THF (75 ml) was added
dropwise maintaining the temperature and stirred. After 2 h, reaction mixture was acidified (pH 2, monitored by pH paper) by addition of saturated NaHSO$_4$ solution and extracted with ethyl acetate (3x100 ml). Organic layer was separated, dried over Na$_2$SO$_4$ and evaporated to dryness under reduced pressure to get the crude product. The crude mass was purified by column chromatography to get the pure 3-aryloxyamino acid 5 (13.5 g, 94%) as a brown colour oily liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.96 (br s, 1H), 6.71 (d, $J$ = 8.7 Hz, 1H), 6.47 (s, 1H), 6.34 (d, $J$ = 8.5 Hz, 1H), 5.53 (d, $J$ = 8.5 Hz, 1H), 4.66 (d, $J$ = 8.1 Hz, 1H), 4.34 (d, $J$ = 7.7 Hz, 1H), 4.14 (dd, $J$ = 9.3, 2.9 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$: 174.3, 155.5, 152.6, 149.7, 143.9, 111.6, 103.9, 100.9, 77.3, 76.6, 68.5, 55.3, 55.7, 53.3, 28.1 (3C). FTIR ($\tilde{v}$; neat): 3442 (br), 2933, 1712, 1600, 1512, 1456, 1394, 1368, 1229, 1200, 1162, 1060, 1026, 970, 926, 840, 764, 623, 462; LC-MS (ESI): 340.3 [M-H]; HRMS (ESI): calculated for C$_{16}$H$_{22}$NNaO$_7$, 364.1372; found 364.1374. $[\alpha]_D^{25}$ = -33.1 (c 1.03, MeOH).

**Synthesis of (R)-2-Benzoxycarbonylamino-3-(3,4-dimethoxy-phenoxy)-propionic acid 5b:** To a stirring solution of (R)-2-tert-butoxycarbonylamino-3-(3,4-dimethoxy phenoxy)-propionic acid 5 (13.5 g, 39.5 mmol) in CH$_2$Cl$_2$ (70 ml) added TFA (70 ml) dropwise at 0 °C and stirred at rt for 30 min. The reaction mass was evaporated to dryness under reduced pressure and co-distilled with CHCl$_3$ to get TFA salt of de-Boc acid as an off-white solid. Triethyl amine (23.0 ml, 158.2 mmol) and N-(benzoyloxy carbonyloxy) succinimide (9.8 g, 39.54 mmol) were added to a solution of TFA salt of aryloxy amino acid in THF (270 ml) and water (90 ml) and stirred at rt for 12 h. Reaction mass was acidified with 1N HCl solution under cold condition and extracted with ethyl acetate. Organic layer was evaporated to dryness under reduced pressure and purified by column chromatography to get the N-Cbz protected aryloxy amino acid 5b (12.6 g, 85%) as a light brown oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.33-7.29 (m, 5H), 6.72 (d, $J$ = 8.7 Hz, 1H), 6.47 (s, 1H), 6.34 (dd, $J$ = 8.7, 1.7 Hz, 1H), 5.79 (d, $J$ = 8.4 Hz, 1H), 5.12 (s, 2H), 4.72 (m, 1H), 4.39 (d, $J$ = 8.4 Hz, 1H), 4.18 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$: 173.9, 156.1, 152.5, 149.8, 144.0, 135.8, 128.5 (3C), 128.2, 128.0, 111.6, 104.0, 101.0, 68.3, 67.3, 56.3, 55.8, 53.8. FTIR ($\tilde{v}$ cm$^{-1}$, neat): 3442 (br), 3431, 2960,
2928, 2853, 1716, 1601, 1512, 1601, 1280, 1201, 1162, 1024, 915, 999, 699, 618. LC-MS (ESI): 374 [M-H]; HRMS (ESI): calculated for C_{19}H_{21}NNaO_7 398.1216; found 398.1218. [α]_D^{25} = -24.1 (c 1.06, MeOH).

**Synthesis of [(R)-2-(3,4-Dimethoxy-phenoxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid benzyl ester 7:** N-methyl morpholine (5.8 ml, 52.7 mmol) and *iso*-butylchloroformate (3.7 ml, 28.77 mmol) were added to a stirring solution of N-Cbz amino acid 5b (9.0 g, 23.9 mmol) in CH_2Cl_2 (86 ml) at -15 °C and stirred for 20 min at this temperature followed by addition of N,O-dimethyl hydroxylamine hydrochloride (3.74 g, 38.0 mmol). After stirring for 30 min at -15 °C, the reaction mixture was allowed to rise to rt slowly. After 5 h, the reaction was quenched with water and extracted with CH_2Cl_2. Organic layer was separated and evaporated to dryness under reduced pressure and purified by column chromatography to get the pure Weinreb amide 7 (6.8 g, 68%) as a light brown oil. ^1^H NMR (400 MHz, CDCl_3): δ 7.33-7.29 (m, 5H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.50 (s, 1H), 6.37-6.35 (m, 1H), 5.80 (d, *J* = 7.7 Hz, 1H), 5.11-5.10 (m, 2H), 5.06-5.04 (m, 1H), 4.18 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.16 (s, 3H). ^1^C NMR (100 MHz, d_4-MeOH): δ 169.4, 155.8, 152.8, 149.7, 143.8, 136.1, 111.6, 104.0, 101.1, 68.2, 66.8, 61.4, 56.3, 55.7, 51.2. FTIR (v cm⁻¹; neat): 3442 (br), 3321, 2936, 2835, 1722, 1662, 1599, 1512, 1454, 1388, 1330, 1260, 1229, 1199, 1161, 1053, 1025, 989, 904, 836, 742, 699; LC-MS (ESI): 419 [M+H]^+; HRMS (ESI): calculated for C_{21}H_{26}N_2NaO_7 441.1638; found 441.1637. [α]_D^{25} = +8.8 (c 1.17, MeOH).

[(R)-1-(3,4-Dimethoxy-phenoxy)methyl]-2-oxo-2-oxo-2-tolyl ethyl]-carbamic acid benzyl ester 8 (procedure same as stated for 12): ^1^H NMR (400 MHz, MeOD): δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.27-7.17 (m, 7H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.26 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.33 (t, *J* = 3.9 Hz, 1H), 5.07 (s, 2H), 4.17 (dd, *J* = 15.0, 3.9 Hz, 2H), 3.73 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.35 (s, 3H). ^1^C NMR (100 MHz, MeOD): δ 201.4, 157.3, 153.4, 150.4, 144.3, 138.2, 136.7, 131.8 (2C), 131.5 (2C), 128.9, 128.0, 127.9, 127.7, 125.7, 114.2, 104.9, 101.2, 68.5, 66.7, 58.6, 56.1, 55.2, 19.5. HRMS (ESI): calculated for C_{26}H_{27}N_2NaO_8 472.1736; found 472.1739. [α]_D^{25} = +13.0 (c 0.99, CH_2Cl_2).
Synthesis of [(R)-1-(3,4-Dimethoxy-phenoxy)methyl]-2-hydroxy-2-o-tolyl-ethyl]-carbamic acid benzyl ester 4a: To a solution of ketone 7 (1.15 g, 2.55 mmol) in ethanol (20 ml) added NaBH₄ (0.095 g, 2.55 mmol) at 0 °C and stirred at room temp for 1 h. Reaction mass was quenched with saturated NH₄Cl solution, concentrated under reduced pressure. Obtained crude mass was dissolved in water and extracted with ethyl acetate. Organic layer was separated, dried over anhydrous Na₂SO₄, evaporated to dryness and purified by flash column chromatography to get the N-Cbz amino alcohol 4a (1.05 g, 91 %) as a brown liquid. ¹H NMR (400 MHz, MeOD): δ 7.47-7.45 (m, 1H), 7.35-7.33 (m, 4H), 7.25 (s, 1H), 7.20-7.12 (m, 3H), 5.63-5.55 (m, 1H), 5.34-5.27 (m, 1H), 5.09 (s, 2H), 4.11-4.07 (m, 2H), 3.98-3.95 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.34 (s, 3H). LC-MS (ESI): 452 [M+H]⁺

Synthesis of ((3S, 4R)-6,7-Dimethoxy-4-o-tolyl-chroman-3-yl)-carbamic acid benzyl ester 9: A solution of starting hydroxy compound (0.10 g, 0.22 mmol) and Bi(OTf)₃ (0.043 g, 0.066 mmol) in nitromethane (10 ml) was heated at 40 °C for 45 min. Reaction mass was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. Organic layer was separated, dried over sodium sulphate and filtered. The filtrate was concentrate under reduced pressure to get the crude which was purified by flash column chromatograpy to get the pure compound 9 as a light brown liquid (0.086 g, 90%). ¹H NMR (400 MHz, MeOD): δ 7.33-7.30 (m, 5H), 7.23 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 7.0 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.08 (d, J = 7.6 Hz, 1H), 6.48 (s, 1H), 6.32 (s, 1H), 5.35 (d, J = 8.4 Hz, 1H), 5.14(d, J = 12.0 Hz, 1H), 5.06(d, J = 12.0 Hz, 1H), 4.22 (br, 1H), 4.07 (d, J = 11.0 Hz, 1H), 4.03 (d, J = 8.3 Hz, 1H), 3.95 (d, J = 10.6 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 2.66 (s, 3H). ¹³C NMR (100 MHz, MeOD): δ 155.6, 149.2, 148.0, 144.3, 141.5, 136.6, 136.1, 130.6, 129.8, 128.5 (2C), 128.2 (2C), 128.1, 126.8, 125.9, 113.3, 100.3, 66.9, 63.7, 55.8, 56.2, 48.6, 43.6, 19.3. HRMS (ESI): calculated for C₂₆H₂₇NNaO₅ 456.1787; found 456.1785. [α]D₂₅ = -66.7 (c 1.14, CH₂Cl₂).

Synthesis of [(R)-2-(2-Benzzyloxyethyl-phenyl)-1-(3,4-dimethoxy-phenoxy)methyl]-2-oxo-ethyl]-carbamic acid benzyl ester 12: n-BuLi (6.5 ml, 2.2 M) was drop wise added to a stirred solution of 1-Benzzyloxyethyl-2-bromo-benzene 11 (4.24 g, 15.29 mmol) in THF (65 ml) at -78 °C and stirred at this temperature for 15 min. A pre-cooled
(-78 °C) solution of Weinreb amide 7 (2.0 g, 4.78 mmol) in THF (40 ml) was added to the reaction mixture and stirring was continued. After 45 min, reaction was quenched with saturated NH₄Cl solution, extracted with ethyl acetate. The organic layer was evaporated to dryness under reduced pressure and purified by flash column chromatography to get the pure ketone 12 (1.1 g, 40%) as a brownish yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.65 (m, 2H), 7.51 (m, 1H), 7.51-7.28 (m, 11H), 6.64 (d, J = 8.7 Hz, 1H), 6.32 (s, 1H), 6.18 (d, J = 8.7 Hz, 1H), 6.00 (d, J = 7.8 Hz, 1H), 5.45 (m, 1H), 5.12 (s, 2H), 4.83 (d, J = 13.5 Hz, 1H), 4.66 (d, J = 13.5 Hz, 1H), 4.48 (s, 2H), 4.20-4.19 (m, 1H), 4.13-4.10 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H). ¹³C NMR (100 MHz, MeOD): δ 202.3, 158.3, 154.4, 151.4, 145.3, 139.9, 139.4, 138.1, 137.2, 131.6, 129.6, 129.5, 129.4, 129.39, 129.31, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 114.1, 106.0, 102.4, 73.8, 71.1, 69.46, 67.32, 59.72, 57.67, 56.31. FTIR (ν cm⁻¹; neat): 3343 (br), 3031, 2936, 1717, 1601, 1510, 1455, 1382, 1343, 1282, 1200, 1161, 1068, 1027, 966, 909, 838, 741, 699. HRMS (ESI): calculated for C₃₃H₃₃NNaO₇ 578.2155; found 578.2154. [α]D₂₅ = +2.1 (c 1.0, CHCl₃).

**Synthesis of [(R)-2-(2-Benzylloxymethyl-phenyl)-1-(3,4-dimethoxy phenoxy methyl)-2-hydroxy-ethyl]-carbamic acid benzyl ester 13:** To a solution of ketone 12 (4.7 g, 8.5 mmol) in ethanol (50 ml) was added NaBH₄ (0.320 g, 8.5 mmol) at 0 ºC and stirred at rt for 1 h. Reaction mass was quenched with saturated NH₄Cl solution, concentrated under reduced pressure. Obtained crude mass was dissolved in water and extracted with ethyl acetate. Organic layer was separated, dried over Na₂SO₄ and filtered. The filtrate was evaporated to dryness and purified by flash column chromatography to get the N-Cbz amino alcohol 13 (4.3 g, 91%) as a pale yellow liquid. ¹H NMR (400 MHz, MeOD; major isomer): δ 7.62 (d, J = 7.6 Hz, 1H), 7.36-7.20 (m, 11H), 7.05-7.03 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.7, 2.4 Hz, 1H), 5.22 (d, J = 8.1 Hz, 1H), 4.90-4.76 (m, 3H), 4.66-4.57 (m, 3H), 4.26 (dd, J = 9.8, 5.1 Hz, 1H), 4.14-4.12 (m, 2H), 3.73 (s, 3H), 3.70 (s, 3H). ¹³C NMR (100 MHz, MeOD): δ 157.1, 154.4, 150.4, 144.0, 142.0, 138.2, 137.3, 135.4, 129.8, 128.8, 128.4 (2C), 128.3, 128.1(2C), 127.8 (2C), 127.7, 127.6 (2C), 127.3, 126.9, 113.3, 105.26, 101.53, 72.95, 70.87, 68.36, 67.97, 66.10, 56.65, 56.31, 55.40. FTIR (ν cm⁻¹; neat): 3413 (br), 3064, 2936, 1712, 1600,
1512, 1435, 1322, 1228, 1200, 1161, 1141, 1027, 939, 835, 743, 698, 612. LC-MS (ESI): 558 [M+H]+; HRMS (ESI): calculated for C_{33}H_{35}NNaO_{7} 580.2311; found 580.2314. \[\alpha\]D_{25} = -3.9 (c 1.01, CHCl₃).

Synthesis of N-\((R)-2-(2-Benzyloxymethyl-phenyl)-1-(3,4-dimethoxyphenoxymethyl)-2-hydroxy-ethyl\)-4-nitro-benzenesulfonamide 15: To the N-CBZ amino alcohol 13 (4.3 g, 7.7 mmol) in MeOH (40 ml) was added 10% Pd/C (0.450 g) and the reaction mixture was stirred under hydrogen balloon at rt for 1 h. Reaction mixture was filtered through celite bed, to remove the palladium charcoal, and the filtrate evaporated to get the crude product, which was immediately used for the next step.

To a solution of the crude product in CH₂Cl₂ (40 ml) was added Et₃N (3.2 ml, 23.1 mmol, 3.0 equiv) followed by nosyl chloride (1.87 g, 8.47 mmol, 1.1 equiv) under ice cold condition and the reaction mixture was stirred for 3 h at rt. The reaction was quenched with water (15 ml) and extracted with CH₂Cl₂ (3x40 ml) and evaporated to dryness. The crude mass was purified by flash column chromatography to get the N-nosyl amino alcohol 15 (4.4 g, 94%) as a pale yellow solid. \(^1\)H NMR (400 MHz, CDCl₃; major diastereomer): δ 7.90 (d, \(J = 8.6\) Hz, 2H), 7.48-7.31 (m, 7H), 7.15-6.88 (m, 5H), 6.77-6.73 (m, 1H), 6.45-6.39 (m, 2H), 5.05 (d, \(J = 8.7\) Hz, 1H), 4.77-4.65 (m, 2H), 4.46-4.29 (m, 3H), 4.12-4.08 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.56-3.55 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl₃): δ: 152.6, 149.8, 149.1, 145.6, 144.1, 140.3, 136.2, 134.1, 130.6, 130.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.6, 127.5, 126.3, 126.1, 111.9, 104.9, 100.8, 73.6, 70.6, 69.9, 69.0, 58.0, 56.3, 55.8. FTIR (v cm⁻¹; neat): 3495, 3106, 2925, 2856, 1604, 1513, 1452, 1405, 1348, 1281, 1260, 1228, 1200, 1164, 1091, 1048, 1027, 934, 911, 853, 763, 739, 700, 686, 614, 546, 465. LC-MS (ESI): 609 [M+H]+; HRMS (ESI): calculated for C_{31}H_{32}N₂NaO₈S 630.1726; found 630.1729.

Synthesis of N-\((3S, 4R)-4-(2-Benzyloxymethylphenyl)-6,7-dimethoxychroman-3-yl\)-4-nitro-benzenesulfonamide 18: A solution of Mesyl chloride (0.9 ml, 11.73 mmol, 1.7 equiv) in CH₂Cl₂ (10 ml) was drop-wise added to a mixture of alcohol starting material (4.2 g, 6.9 mmol) , Et₃N (1.7 ml, 12.42 mmol) in CH₂Cl₂ (25 ml) at 0 °C and stirred. After 3 h, it was quenched with water (10 ml) and extracted with CH₂Cl₂ (3x30 ml). Organic part was separated, washed with saturated NaHCO₃ solution, dried over sodium
sulphate. The filtrate was concentrated under reduced pressure to get the crude product as a light brown solid (4.70 g, >99%), which was used for the next step without any purification.

NaH (60% in oil; 0.552 g, 13.8 mmol) was added to a solution of crude O-mesityl compound 16 (4.7 g, 6.9 mmol) in THF (100 ml) at rt. The reaction mixture was heated at 50 °C for 4 h. Aqueous work-up followed by filtration through a short plug of silica afforded 3.0 g of orange yellow solid as a mixture of aziridine 17 and cyclized product 18.

To a solution of above mixture in ClCH₂CH₂Cl (60 ml) was added Cu(OTf)₂ (0.15 g) at rt and heated to 70 °C. After 2 h, it was evaporated under vacuum and a solution of saturated NaHCO₃ solution was added to it followed by extraction with ethyl acetate (2x60 ml). Organic part was separated, dried over Na₂SO₄ and evaporated under vacuum. The crude was purified by flash column chromatography to obtain 2.3 g of chroman 18 (56% over 3 steps) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, J = 8.5 Hz, 2H), 7.49-7.36 (m, 8H), 7.14 (d, J = 7.5 Hz, 1H), 7.07-7.03 (m, 1H), 6.70-6.67 (m, 1H), 6.41(d, J = 7.7 Hz, 1H), 6.37 (s, 1H), 5.67 (s, 1H), 4.86 (d, J = 12.2 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 10.0 Hz, 1H), 4.61 (dd, J = 10.6, 3.7 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 3.94 (d, J = 10.4 Hz, 1H), 3.82-3.77 (m, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 3.30 (m, 1H). ¹³C NMR (400 MHz, CDCl₃): δ: 149.2, 149.1, 148.6, 144.4, 143.6, 140.9, 135.9, 135.8, 130.6, 129.3, 129.0, 128.8 (3C),128.7, 128.5, 127.6 (2C), 127.2, 123.6 (2C), 114.2, 112.6, 100.2, 73.9, 70.3, 69.7, 56.3, 55.8, 54.3, 42.0. LC-MS (ESI): 589 [M-H].

HRMS (ESI): calculated for C₃₁H₃₀N₂O₈S 613.1620; found 613.1623. [α]D²⁵ = -47.2 (c 1.0, CHCl₃).

**Synthesis of (3S, 4R)-4-(2-Benzylxymethyl-phenyl)-6,7-dimethoxo-3-chroman-3-ylamine 19:** To a well stirred solution of N-nosyl aminochroman 18 (1.4 g, 2.37 mmol) in 24 ml of CH₃CN/DMSO (49:1) at 25 °C, 4-methoxythiophenol (1.0 g, 7.11 mmol) and K₂CO₃ (1.63 g, 11.85 mmol) were added and stirred. After 3 h, the solvent was concentrated under reduced pressure and the crude reaction mass was subjected to flash column chromatographic purification using 0–10% MeOH in CH₂Cl₂ as an eluent to obtain aminochroman 19 (0.84 g, 87%) as a colourless liquid. ¹H NMR (400 MHz,
CDCl$_3$): $\delta$ 7.40-7.30 (m, 6H), 7.24-7.20 (m, 2H), 6.95-6.92 (m, 1H), 6.44 (s, 1H), 6.15 (s, 1H), 4.71-4.57 (m, 4H), 4.13 (dd, $J$ = 10.8, 2.6 Hz, 1H), 4.08 (d, $J$ = 5.7 Hz, 1H), 3.84 (s, 3H), 3.81-3.78 (m, 1H), 3.55 (s, 3H), 3.23-3.19 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.7, 148.3, 143.6, 137.7, 136.3 (2C), 130.0, 129.4, 128.6, 128.4 (2C), 128.2 (2C), 127.9, 127.8, 126.6, 113.3, 100.1, 72.6 (2C), 70.4, 68.6, 56.23, 55.76, 51.29. FTIR (v cm$^{-1}$, neat): 3370, 3026, 2927, 2855, 1618, 1509, 1454, 1406, 1360, 1263, 1196, 1132, 1068, 1026, 984, 861, 834, 754, 700, 579. LC-MS (ESI): 406 [M+H]$^+$; HRMS (ESI): calculated for C$_{25}$H$_{27}$NO$_4$ 406.2013, found 406.2016. [$\alpha$]$_D^{25}$ = -48.0 (c 1.0, MeOH).

**Synthesis of (6a$S$, 12b$R$)-2,3-Dimethoxy-6a,7,8,12b-tetrahydro-6H-5-oxa-7-aza benzo-[c]phenanthrene (O-methyl doxanthrine) 20:** To a solution of amine O-benzyl compound 19 (0.6 g, 1.48 mmol) in acetic acid (2.5 mL) was added 10% of Pd-C (0.06 g, 10% w/w), and stirred under 1atm (H$_2$ balloon) for 7 h. The reaction mixture was filtered over celite bed using 150 mL of ethyl acetate and the volatiles were concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with aqueous saturated NaHCO$_3$ (30 mL). The organic part was separated and washed with brine, dried over anhydrous Na$_2$SO$_4$ and evaporated under vacuum to obtain 0.46 g of crude amino chroman having tethered alcohol functionality.

A solution of crude amino chroman alcohol (0.46 g, 1.46 mmol) in 1,4-dioxane (18.5 mL) and 12 N HCl (12 mL) was heated under reflux for 2 h. The reaction mixture was concentrated under reduced pressure to afford the intermediate chloride.

It was immediately dissolved in anhydrous 1,4-dioxane (33.5 mL) in which anhydrous potassium carbonate (7 g, 50.73 mmol, 40.0 equiv) was added and the mixture was heated at 80 °C for 1 h. The mixture was cooled to rt, poured into water and extracted with chloroform (3x15 mL). The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, concentrated under reduced pressure to get the crude mass which was purified by flash column chromatography (70% ethyl acetate in hexanes) to get O-methyl doxanthrine 20 (0.185 g, 42% in 2 steps) as an off-white solid. M.P. 138-140 °C; $^1$H NMR (400 MHz, $d_6$-DMSO): $\delta$ 7.46 (d, $J$ = 7.5 Hz, 1H), 7.28-7.19 (m, 3H), 6.96 (s, 1H), 6.54 (s, 1H), 4.18 (dd, $J$ = 9.8, 4.6 Hz, 1H), 3.91 (s, 2H), 3.85-3.80 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.81-2.78 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 151.5, 150.5, 144.5,
138.3, 138.0, 128.0, 127.6 (2C), 126.7, 115.7, 113.8, 103.4, 71.0, 57.5, 57.1, 56.5, 47.9, 41.5. FTIR (v cm⁻¹; neat): 3847, 3739, 3438, 3345, 2921, 2860, 2329, 1616, 1511, 1448, 1404, 1353, 1266, 1222, 1183, 1110, 1026, 977, 929, 877, 819, 743, 635, 563, 482. LC-MS (ESI): 298 [M+H]⁺; HRMS (ESI) : calculated for C₁₈H₂₀NO₃: 298.1438, found 298.1436. [α]D²⁵ = +76.2 (c 1.0, CH₂Cl₂).

Synthesis of (6aS,12bR)-6a,7,8,12b-Tetrahydro-6H-5-oxa-7-aza-benzo[c]-phenanthrene-2,3-diol (Doxanthrine 2): BBr₃(0.2 ml, 1M solution in CH₂Cl₂) was added to a solution of O-methyl doxanthrine 20 (0.030 g, 0.1 mmol) in CH₂Cl₂ (2ml) at ice cold condition and it was stirred at this temperature for 2 h. Reaction was quenched with methanol and extracted with CH₂Cl₂. Crude product (0.009 g, 30%) was triturated with ether to get doxantrine 2 as 60% of purity. Column chromatographic purification and preparative HPLC were not successful.

¹H NMR (400 MHz, MeOD): δ 7.57 (d, J = 7.0 Hz, 1H), 7.43-7.38 (m, 3H), 6.91 (s, 1H), 6.44 (s, 1H), 4.50 (d, J = 3.8 Hz, 2H), 4.46 (dd, J = 10.0, 4.3 Hz, 1H), 4.28 (d, J = 11.3 Hz, 1H), 4.08 (t, J = 10.5 Hz, 1H), 3.20 (dt, J = 11.3, 4.3 Hz, 1H). LC-MS (ESI): 270 [M+H]⁺.

Reference
D-Serine derived cyclic sulfamidate carboxylic acid

\[ \text{H NMR of compound 6 (400 MHz, Acetone-}d_6) \]

\[ \text{C NMR of compound 6 (100 MHz, MeOD)} \]

\[ \text{\textsuperscript{1}H NMR of compound 6 (400 MHz, Acetone-d}_6) \]

\[ \text{\textsuperscript{13}C NMR of compound 6 (100 MHz, MeOD)} \]
LCMS of compound 6
(R)-2-tert-Butoxycarbonylamino-3-(3,4-dimethoxy phenoxy)-propionic acid

$^1$H NMR of Compound 5 (400 MHz, CDCl₃)

$^{13}$C NMR of Compound 5 (100 MHz, CDCl₃)
LCMS of Compound 5
(R)-2-Benzyloxycarbonylamino-3-(3,4-dimethoxy-phenoxy)-propionic acid

\[ \text{1H NMR of Compound 5b (400 MHz, CDCl}_3\] \]

\[ \text{13C NMR of Compound 5b (100 MHz, CDCl}_3\] \]
LCMS of compound 5b
[(R)-2-(3,4-Dimethoxy-phenoxy)-1-(methoxy methylcarbamoyl)-ethyl]-carbamic acid benzyl ester

$^1$H NMR of Compound 7 (400 MHz, CDCl$_3$)

$^{13}$C NMR of Compound 7 (100 MHz, CDCl$_3$)
$^{13}$C NMR- APT of Compound 7 (100 MHz, CDCl$_3$)
[(R)-1-(3,4-Dimethoxy-phenoxyethyl)-2-oxo-2-phenyl ethyl]-carbamic acid benzyl ester

$^{1}H$ NMR of Compound 8 (400 MHz, MeOD)

$^{13}C$ NMR of Compound 8 (100 MHz, MeOD)
[(R)-1-(3,4-Dimethoxy-phenoxy)methyl]-2-hydroxy-2-o-tolyl ethyl]-carbamic acid benzyl ester

$^1$H NMR of Compound 4 (400 MHz, CDCl$_3$)
LCMS of Compound 4a
((3S, 4R)-6,7-Dimethoxy-4-o-tolyl-chroman-3-yl)-carbamic acid benzyl ester

$^1$H NMR of Compound 9 (400 MHz, CDCl$_3$)

$^{13}$C NMR of Compound 9 (400 MHz, CDCl$_3$)
LCMS of Compound 9

Exact Mass = 433
[(R)-2-(2-Benzyloxymethyl-phenyl)-1-(3,4-dimethoxy phenoxy methyl)-2-oxo-ethyl]-carbamic acid benzyl ester

$^1$H NMR of Compound 12 (400 MHz, CDCl$_3$)
H NMR of Compound 12 (400 MHz, MeOD)

C NMR of Compound 12 (400 MHz, MeOD)

1H NMR of Compound 12 (400 MHz, MeOD)

13C NMR of Compound 12 (400 MHz, MeOD)
LCMS of Compound 12

Exact Mass = 555
[(R)-2-(2-Benzyloxymethyl-phenyl)-1-(3,4-dimethoxy-phenoxymethyl)-2-hydroxy-ethyl]-carbamic acid benzyl ester

HPLC of Compound 13 (Mixture of Diastereoisomers)
LCMS of Compound 13
$^1$H NMR of Compound 13- Major isomer (400 MHz, MeOD)

$^{13}$C NMR of Compound 13- Major isomer (100 MHz, MeOD)
$^1$H NMR of Compound 13- Minor isomer (400 MHz, MeOD)

$^{13}$C NMR of Compound 13- Minor isomer (100 MHz, MeOD)
$N$-$[(R)-2-(2-Benzylxomethyl-phenyl)-1-(3,4-dimethoxy-phenoxymethyl)-2-hydroxy-ethyl]-4-nitro-benzenesulfonamide$

{^1}H$ NMR of Compound 15 (400 MHz, CDCl$_3$)

{^{13}}C$ NMR of Compound 15 (100 MHz, CDCl$_3$)
$^{13}$C NMR – APT of Compound 15 (100 MHz, CDCl$_3$)
LCMS of Compound 15
N-[(3S, 4R)-4-(2-Benzylxymethyl-phenyl)-6,7-dimethoxy-chroman-3-yl]-4-nitrobenzenesulfonamide

$^1$H NMR of Compound 18 (400 MHz, CDCl$_3$)

$^{13}$C NMR of Compound 18 (100 MHz, CDCl$_3$)
LCMS of Compound 18
(3S,4R)-4-(2-Benzoyloxymethyl-phenyl)-6,7-dimethoxy-chroman-3-ylamine

\(^1\text{H NMR of Compound 19 (400 MHz, DMSO-}d_6)\)

\(^1\text{H NMR of Compound 19 (400 MHz, D}_2\text{O exchange)}\)
$^1$H NMR of Compound 19 (400 MHz, CDCl$_3$)

$^{13}$C NMR of Compound 19 (100 MHz, CDCl$_3$)
LCMS of Compound 19

Exact Mass = 405
(6aS, 12bR)-2,3-Dimethoxy-6a,7,8,12b-tetrahydro-6H-5-oxa-7-aza benzo[c]phenanthrene

$^1$H NMR of Compound 20 (400 MHz, MeOD)
$^1$H NMR of Compound 20 (400 MHz, DMSO-$d_6$)

$^{13}$C NMR of Compound 20 (100 MHz, MeOD)
$^{13}$C NMR-APT of Compound 20 (100 MHz, MeOD)
LCMS of O-methyl doxanthrine 20
(6aS,12bR)-6a,7,8,12b-Tetrahydro-6H-5-oxa-7-aza-benzo[c]phenanthrene-2,3-diol [Doxanthrine]

$^1$H NMR of Doxanthrine 2 (400 MHz, MeOD)
LCMS of Compound 2