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Synthesis and SAR study of a novel series of dopamine receptor agonists

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ABSTRACT

The synthesis of a novel series of dopamine receptor agonists are described as well as their in vitro potency and efficacy on dopamine D_1 and D_2 receptors. This series was designed from pergolide and (4a*R*,10a*R*)-1-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]quinolin-6-ol (PHBQ) and resulted in the synthesis of (2*R*,4a*R*,10a*R*)-2-methylsulfanylmethyl-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (compound **27**), which has a D_1 and D_2 receptor profile similar to that of the most recently approved drug for Parkinson's disease, rotigotine.

1. Introduction

Parkinson's disease (PD) is a disorder in which the neurons that produce dopamine (Fig. 1) are degrading.[1] Dopamine receptor agonists (DRA) are used to treat the symptoms of this disease by substituting for dopamine, either as a mono-therapy or, as the disease is progressing to more severe stages, in combination with L-DOPA or apomorphine. Five subtypes of the dopamine receptors are known and they can be divided into two subclasses, 'D_1 like' (D_1 and D_5) and 'D_2 like' (D_2, D_3 and D_4).[1] Common for all DRA indicated for PD is their high selectivity for D_2 and D_3 receptors, and their low-to-neglectible interaction with D_1 receptors. Dopamine, coming from the precursor drug L-DOPA, and apomorphine displays a more balanced D_1/D_2 ratio when compared to the DRA and are both considered gold standard PD pharmacotherapies.[2]

Recently, rotigotine (Fig. 1) was approved for the treatment of PD as well.[3–5]

In vitro, rotigotine mimic the profiles of dopamine and apomorphine to some extent, displaying activity as an agonist at both D_2 and D_3 receptors as well as D_1 receptors. However, rotigotine still displays a preference for D_2 and D_3 receptors,[4] and when compared to apomorphine and dopamine itself, a relative more potent D_1 receptor component would be required in a putative improved version of rotigotine.

Furthermore, rotigotine is a phenolic amine which suffer from the same poor oral bioavailability and rapid clearance from the circulation as other phenolic amines.[6] Consequently, rotigotine has been formulated as a transdermal patch[4,5] to avoid first pass metabolism and secure bioavailability. Rotigotine also contains a thiophene which is a structural alert.[7,8]

The two octahydro-benzo[*g*]quinolines MHBQ and PHBQ (Fig. 1) from Sandoz,[9] have earlier been published as dopamine D_2-like receptor agonists, whereas pergolide has been published as a mixed D_1 and D_2 receptor agonist. We used these scaffolds as inspiration for a novel series of putative DRA with the aim of finding compounds with more balanced, apomorphine-like receptor profiles as compared to rotigotine and without the thiophene structural alert. Thus, we set out to synthesize an improved version of rotigotine by the synthesis and evaluation of a novel set of ligands designed as outlined above.

2. Results and discussion

2.1. Chemistry

The novel DRAs **6a–10a** (Table 1) were prepared in the following manner. Racemic azido alcohol **1** was prepared from naphthalen-1-ol as described in the literature (Scheme 1).[10] The procedure was slightly modified, and lithium was used instead of sodium in the Birch reduction of the naphthalen-1-ol. The hydroxy group was methylated using dimethyl sulfate, and the epoxide was prepared using *m*-CPBA as described in the literature.[10] It was possible

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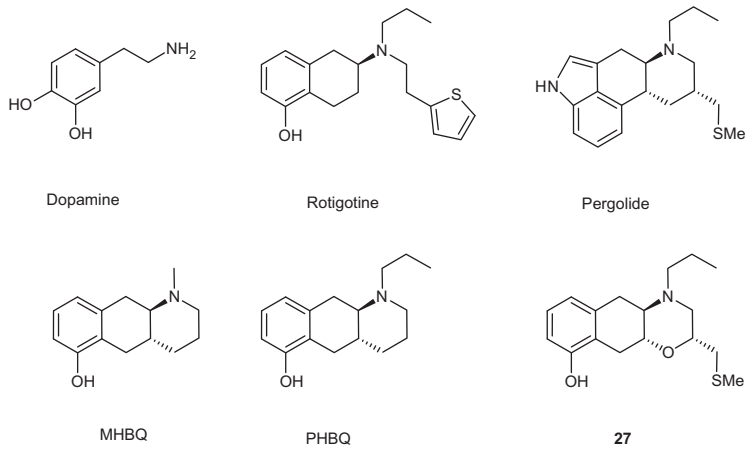
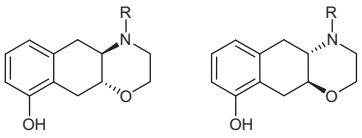


Figure 1. Structures of dopamine and the dopamine receptor agonists (DRA) rotigotine, Pergolide, MHBQ, PHBQ and **27**.

to use this procedure on a 0.3 mol scale in 66% isolated yield. Compound **1** was then prepared by reacting this epoxide with sodium azide under acidic conditions and then separating the two regioisomeric azido alcohols by crystalization.[10] Compound **1** was reduced to **2** by catalytic hydrogenation and then reacted with chloro-acetyl chloride to give **3**. The lactam **3** was reduced with lithium aluminum hydride (LAH), and the resulting morpholine was protected with a Boc group to yield **4**. Compound **4** was separated into its two enantiomers **4a** and **4b** by chiral supercritical fluid chromatography (SFC on a chiral phase). The Boc group was removed to produce **5a** (Scheme 2), which was converted into **8a**–**10a** by alkylation followed by deprotection with L-selectride under microwave conditions. The microwave conditions were convenient because deprotection of methyl aryl ethers with L-selectride, without electron withdrawing substituents, usually takes two days in refluxing THF.[11] It was not possible to prepare **8a**–**10a** with BBr_3 because using this method, the morpholine ring was also cleaved. Compound **6a** was prepared from **4a** by reducing the Boc group with LAH under microwave conditions and then cleaving the methyl group as described above. Compound **7a** was prepared from **4a** by reductive amination after deprotection. Compounds **6a**–**10a** were precipitated as their HCl salts. The HCl salt of the enantiomer **10b** was prepared in a similar manner from **4b** and a single crystal for X-ray was obtained (see Supplementary data). The configuration of **10b** was determined to be the (4a*S*, 10a*S*), whereas **6a**–**10a** have the opposite configuration.

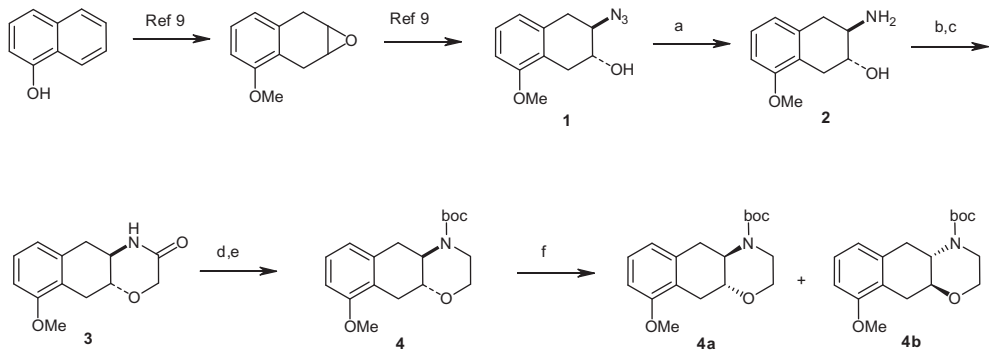
The novel DRA **19**–**27** (Table 2) were prepared in the following manner. Compounds **11a** and **11b** were prepared from racemic **2**

Table 1
Data for reference compounds and **6a**–**10a**, **10b**

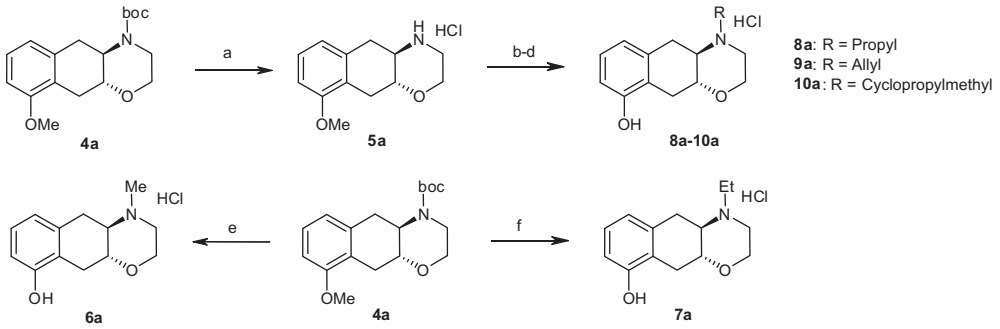


	R	D_1 EC_{50} (%eff)	D_2 EC_{50} (%eff)	D_1/D_2	H.Mic (L/min)	H.Hep (L/min)	*c*Log*D*	PSA	MPO
Dopamine	Figure 1	39 (100)	36 (100)	1	nd	nd	nd	nd	nd
Rotigotine	Figure 1	28 (110)	0.7 (110)	40	3.7	16	2.8	23.5	3.3
MHBQ	Figure 1	>10000	25 (94)	—	1.2	6.9	1.0	23.5	4.5
PHBQ	Figure 1	83 (95)	0.17 (96)	488	nd	nd	1.9	23.5	4.0
6a		>10000	4 (94)	—	0.2	3.4	1.2	32.7	5.5
7a		120 (85)	0.8 (120)	150	0.7	20	1.6	32.7	5.5
8a		150 (89)	0.14 (110)	1071	0.8	6.9	2.2	32.7	5.4
9a		330 (87)	1.1 (87)	66	0.9	11	2.0	32.7	5.5
10a		>10000	18 (99)	—	0.9	9.8	2.1	32.7	5.4
10b		>10000	1400 (90)	—	nd	nd	2.1	32.7	5.4

Values from efficacy assays (EC_{50}) is in nM and % efficacy is relative to dopamine. Calculated polar surface area (PSA) is topological PSA and calculated lipophilicity (*c*Log*D*) is at pH 7.4. In vitro CL_{int} are determined in human microsomes (H.Mic) and human hepatocytes (H.Hep).



Scheme 1. Reagents and conditions: (a) Pd/C, H_2 (45 psi), EtOH; (b) Chloroacetyl chloride, Et_3N, THF; (c) NaH, TBAI, THF; (d) $LiAlH_4$, THF; (e) Boc_2O, Et_3N, THF; (f) SFC separation.



Scheme 2. Reagents and conditions: (a) HCl, Ether, MeOH; (b) **8a**: (i) Propyliodide, K_2CO_3, DMF, 55 °C, (ii) L-selectride, THF, (iii) HCl/ether/MeOH; (c) **9a**: (i) allylbromide, K_2CO_3, DMF, 55 °C, (ii) L-selectride/THF, (iii) HCl/ether/MeOH; (d) **10a**: (i) cyclopropylmethylbromide, K_2CO_3, DMF, 55 °C, 5 h, (ii) L-selectride/THF, (iii) HCl/Ether/MeOH; (e) **6a**: (i) $LiAlH_4$/THF, (ii) L-selectride, THF, (iii) HCl/Ether/MeOH; (f) **7a**: (i) L-selectride, THF, microwave, 100 °C, (ii) HCl, ether, MeOH, (iii) acetaldehyde, $NaBH_3CN$, MeOH; (iv) HCl, ether, MeOH.

by Boc protection of the amine and separation of the enantiomers using SFC on a chiral phase (Scheme 3). The Boc group was removed after the separation using HCl in diethyl ether and MeOH as solvent to afford the pure enantiomers as the HCl salts. **11a** was alkylated with propionyl chloride to yield **12**. Compound **12** was alkylated with either (*S*)- or (*R*)-epichlorohydrine, and the intermediate was treated with base to yield a mixture of **13** and **14**, which were separated by chromatography.[12] Surprisingly, upon treatment of **11a** with either (*S*)- or (*R*)-epichlorhydrin the same diastereoisomers were observed in both cases depending on the site of attack of the nucleophile. Compounds **13** and **14** could independently be tosylated to give intermediates **15** and **16** (Scheme 4). The tosyl group was then displaced with different nucleophiles to afford compounds **19** to **27**. Finally, the methoxy group was cleaved with either L-selectride under microwave conditions (as described above) or with thiophenol and KF in DMA.

Compounds **25** and **27** were precipitated as their HCl salts whereas **19**–**24** and **26** were prepared and tested as the free bases. The absolute stereochemistry was determined by X-ray crystallography of a single crystal from the HCl salt of **27** (see Supplementary data), and the configuration was found to be (2*R*,4a*R*,10a*R*).

The references compounds MHBQ and PHBQ were prepared as described in the Supplementary data.

2.2. In vitro functional potencies at dopamine receptors and SAR considerations

In vitro functional potencies and efficacies of the novel compounds and key reference compounds were determined by measuring compound induced changes in cAMP in CHO cells expressing either the human D_1 or D_2 receptor (Tables 1 and 2).

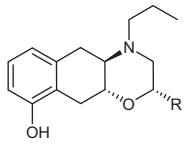
We first prepared the close analogues **6a** of MHBQ and **8a** of PHBQ. Compound **6a** was 6 times more potent on D_2 than MHBQ, whereas the EC_{50}'s on D_1 were >1000 nM for both compounds. On the contrary, **8a** was equipotent to PHBQ on both D_1 and D_2. In general, the *N*-alkyl structure–activity relationship (SAR) on the D_2 receptor within our series is similar to the SAR described for the known benzo[*g*]quinoline series, exemplified by MHBQ and PHBQ.[9] In short, the potency increases from methyl to propyl but the cyclopropylmethyl is apparently too large since the EC_{50} of **10a** is approximately 20 times weaker than **7a**–**9a**, and this confirms that the *N*-alkyl binding pocket probably is small.[9]

Hence, a relative small number of *N*-alkyl analogues were prepared and no real optimization of the D_1/D_2 ratio could be obtained by this strategy. The synthesis of analogues with a substituent at the 2 position was then pursued (Table 2), and we incorporated small lipophilic substituents at the 2 position. This is in agreement with a D_2 homology model recently published, which shows lipophilic residues Trp 386 and Phe 389 to be close to this position.[13]

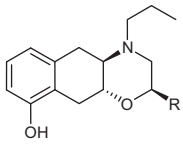
Compounds **19**–**27** were prepared in low to moderate yields and the absolute configuration of a crystal of the HCl salt of **27** were determined by X-ray crystallography (Supplementary data). Compounds **19**, **21**, **23**, **25**, and **27** have the (2*R*,4a*R*,10a*R*) configuration, while **20**, **22**, **24** and **26** are the corresponding-2-epimers, having the (2*S*, 4a*R*,10a*R*) configuration.

The compounds **20**, **22**, **24** and **26** with the 2*S* configuration are more selective D_2 receptor agonists, when compared to their 2*R* counterparts, because of their relative weaker D_1 receptor agonisms.

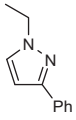
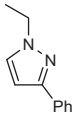
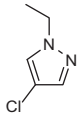
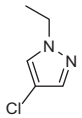
Table 2
Data for **19–27**



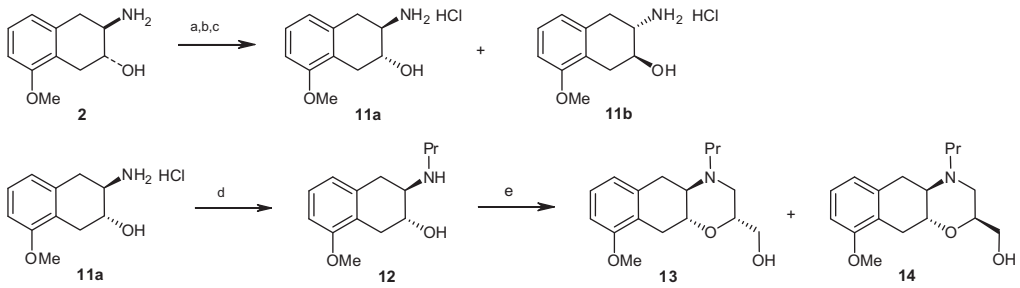
19, 21, 23, 25, 27



20, 22, 24, 26

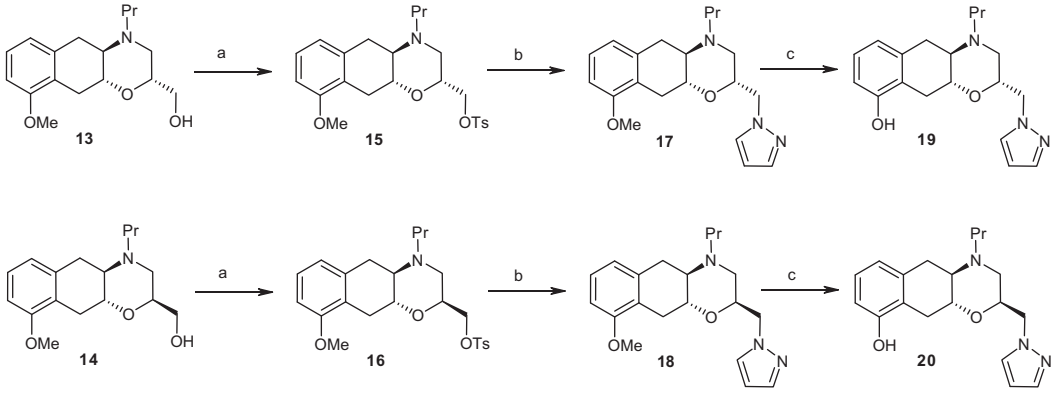
R =		D_1 EC_{50} (%eff)	D_2 EC_{50} (%eff)	D_1/D_2	H.Mic. (L/min)	H.Hep. (L/min)	*c*Log*D*	PSA	MPO
19		89 (90)	1.5 (99)	59	2.5	9.8	2.1	50.5	5.8
20		210 (88)	1.0 (95)	210	nd	nd	2.1	50.5	5.8
21		360 (90)	13 (98)	28	nd	nd	4.2	50.5	3.7
22		3900 (110)	33 (99)	118	nd	nd	4.2	50.5	3.7
23		150 (96)	1.7 (96)	88	2.5	8.4	1.4	63.4	5.8
24		230 (71)	0.5 (110)	460	nd	nd	1.4	63.4	5.8
25		74 (85)	2.1 (98)	35	16	14	2.9	50.5	5.2
26		400 (94)	3.5 (99)	114	nd	nd	2.9	50.5	5.2
27		19 (93)	0.6 (96)	32	13	14	3.2	32.7	4.8

Values from efficacy assays (EC_{50}) is in nM and % efficacy is relative to dopamine. Calculated polar surface area (PSA) is topological PSA and calculated lipophilicity (*c*Log*D*) is at pH 7.4. In vitro CL_{int} are determined in human microsomes and human hepatocytes.



Scheme 3. Reagents and conditios: (a) Boc_2O; (b) SFC separation; (c) HCl; (d) (i) propionyl chloride, (ii) $LiAlH_4$; (e) *S*(−)-epichlorohydrin or *R*(+)-epichlorohydrin.

Compound **27** incorporates a small methyl sulfide group in the 2 position (as in pergolide) and is the strongest D_1 receptor agonists among the novel DRAs. Compound **27** shows similar potency and efficacy on D_1 (19 nM, 93%) and D_2 (0.6 nM, 96%) receptors as rotigotine (D_1 (28 nM, 110%) and D_2 (0.7 nM, 110%)). However, compound **27** is predicted to be a better CNS drug than rotigotine based on MPO scores[8] and is devoid of any structural alerts.



Scheme 4. Reagents and conditions: (a) tosylchloride, pyridine, 4 h rt; (b) pyrazole, NaH, DMF, 130 °C, 0.5 h; (c) thiophenol, KF, DMA, microwave, 100 °C; compounds **21**–**27** (Table 1) were prepared in a similar manner.

Table 3
In vivo rat metabolism for rotigotine, **6a** and **7a**, $N = 5$

	Clp (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)	F (%)
Rotigotine	5.5	9.7	2	<5
6a	5.5	1.9	1	<5
7a	2.3	1.0	0.3	<5

Recently a D_1 receptor homology model was published,[14] and our data could help to refine this model further.

2.3. Metabolism

As the clinical use of most of the DRA's are hampered by frequent daily dosing due to a high metabolic clearance, the metabolic stability of novel DRA ligands is an important selection criteria. Thus, the intrinsic clearance (Clint) in human microsomes (H.Mic) and human hepatocytes (H.Hep) was determined for the new ligands and the reference compounds as well (see Tables 1 and 2). We found a high microsomal Clint, well over the liver blood flow of 1.4 L/min for all the tested compounds. An even higher Clint were seen using hepatocytes, which in addition to microsomes harbors conjugation enzymes catalyzing, for example, glucuronidation of the free hydroxyl group in the molecules. Except for a modest improvement of Clint for **6a**, which did not meet the desired pharmacological profile, all compounds showed high Clint values in excess of the liver blood flow, indicating similar high metabolic clearances and thus no apparent improvement of metabolic stability.

The in vivo PK parameters in rats dosed po and iv at 0.5 and 1.0 mg/kg for Rotigotine, **6a** and **7a** are shown in Table 3. The iv clearance and volume of distribution for **6a** (Clp = 5.5, Vss = 1.9) and **7a** (Clp = 2.3, Vss = 1.0) resulted in short half-life's and low bioavailabilities for both **6a** ($T_{1/2}$ = 1 h, F <5%) and **7a** ($T_{1/2}$ = 0.3 h, F <5%). Rotigotine showed higher Vss (9.7), but similar high clearence (5.5), resulting in short half-life's and low bioavailability for Rotigotine ($T_{1/2}$ = 2 h, F <5%). Because of these low bioavailabilities and short half-life's for **6a** and **7a**, and the high in vitro clearence for these compounds (Tables 1 and 2) no further in vivo PK parameters were measured for compound **8a**–**10a** and **19**–**27**. In case one of these compounds should be progressed into humans, alternative routes of administration, such as, for example, transdermal or subcutaneous administration, should be invistigated.

3. Conclusion

The *N*-alkyl DRAs **6a**–**10a** were prepared in good yields and all displayed relative potent D_2 receptor agonism, whereas the *N*-ethyl (**7a**) and the *N*-propyl (**8a**) analogues also displayed some potency at the D_1 receptor. Therefore, the *N*-propyl group was chosen as the *N*-substituent in the corresponding 2-substituted naphthooxazine analogues **19**–**27**. In general, these compounds were synthesized in low to moderate yield. The absolute configuration of **27** was determined by X-ray crystallography to be the (2*R*,4a*R*,10a*R*) configuration.

In short, compound **27** shows similar in vitro potency and efficacy on both D_1 and D_2 receptors as does rotigotine, and the hepatic clearance of the two compounds are also similar. However, compound **27** has no thiophene structural alert and may also have better CNS-drug like properties if this can be reliably predicted in this series via calculated MPO scores (4.8 vs 3.3, Table 2).[8]

4. Experimental

4.1. Chemistry

Reactions were generally performed under either argon or nitrogen gas in dry solvents. Organic extracts were dried over anhydrous sodium or magnesium sulfate and filtered before the solvents were removed under reduced pressure (described as 'dried and concentrated'). Microwave-assisted reactions were performed with Emrys Optimizer from Personal Chemistry operating at 2450 MHz, in sealed vials (described as 'using microwave heating') with internal pressure below 20 bar. An increasing amount of etylacetate in heptane was used for silica gel chromatography, unless otherwise noted. Hydrogenations were performed on a standard Parr shaker at rt under a hydrogen pressure of 1–3 bar. Tetrahydrofuran (THF), *N*,*N*′-dimethylformamide (DMF), *N*,*N*′-dimethylacetamide (DMA) dimethylsulphoxide (DMSO), *N*-methylpyrrolidone (NMP), 1,4-dioxane (dioxane), toluene, pyridine, acetonitrile (MeCN), dichloromethane (DCM) and 1,2-dichloroethane (DCE) were dried over 4 Å MS and were HPLC grade. Methanol (MeOH) and cyclohexane were also HPLC grade. 96% Ethanol (EtOH), 99.8% ethanol (abs EtOH), ethyl acetate (EtOAc), diethylether (ether) and heptane were technical grade. Thin layer chromatography was performed on Merck 60 F_{254} silica gel plates. The spots were visualized using a UV lamp operating at 254 nm. Melting points were measured on a Buchi 535 apparatus. NMR spectra were recorded either on a Bruker 600-Avance-III spectrometer equipped with a 5 mm TCI cryoprobe operating at 600 MHz for ^{1}H and 151 MHz for ^{13}C, or using a Bruker DRX-500 spectrometer equipped with a 5 mm QNP probe operating at 511 MHz for ^{1}H and 126 MHz for ^{13}C. Chemical shifts are reported in ppm. TMS was used as internal references for H NMR in $CDCl_3$, and residual $CHCl_3$ (δ = 77.1) for C NMR. As internal references

for NMR in DMSO-d_6, were residual DMSO used (δ = 2.50 for H NMR, and δ = 39.5 for C NMR). Coupling constants are in hertz. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. LC–MS data were obtained on a PE Sciex API150EX instrument equipped with an ion spray source and Shimadzu LC-8A/SLC-10A LC system: column, 30 mm × 4.6 mm Waters Symmmetry C18 column with 3.5 μm particle size; solvent system, A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.03) (TFA = trifluoroacetic acid); method, linear gradient elution with 90% A to 100% B in 2.4 min and then 10% B in 0.4 min, with a flow rate of 3.3 mL/min. Total time including equilibration was 2.8 min. Injection volume was 10 μL from a Gilson 215 autosampler. The purity of compounds submitted for biological testing were in all cases ⩾95% as determined using evaporative light scattering detection (ELSD) and ⩾95% using UV detection (254 nm) unless noted otherwise. Preparative LC–MS were performed on a PE Sciex API150EX instrument equipped with an ion spray source and Shimadzu LC-8A/SLC-10A LC system: column, 50 mm × 10 mm Waters Symmetry C18 column with 5 μm particle size; solvent system, A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.03); method, linear gradient elution with 90% A to 100% B in 7 min and then 10% B in 1 min, with a flow rate of 5.7 mL/min. Injection volume was 0–300 μL from a Gilson 233XL autosampler. HRMS spectra were obtained on a Bruker Daltonic MicroTOF with internal calibration using ESI in positive mode. Chiral compounds were resolved by chiral super critical fluid chromatography (SFC) on a Berger SFC multigram II instrument equipped with a Chiralpak AD 21.2 mm × 250 mm column. Solvent system: CO_2/EtOH/Et_2NH (70:29.9:0.1) or as specified below. The method consisted of a constant gradient with a flow rate of 50 mL/min. The fraction collection was performed by UV 230 nm detection.

4.1.1. Racemic *trans*-3-azido-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol (1)

To a solution of naphthalen-1-ol (8.65 g, 60.0 mmol) in abs. EtOH (10 mL) under nitrogen, was added NH_3(l) (60 mL) at −78 °C. Li (2.07 g, 300 mmol) was added in small portions over 5 min. After 65 min abs. EtOH (50 mL) was added after which the mixture was quenched with ice-cold water (100 mL), acidified with 12 M HCl, and extracted with ether (2 × 150 mL). The combined organic phases were washed with brine, dried and concentrated to give 9.38 g (>100%) of the intermediate alkene as a light red solid. GS/MS: *m*/*z* 146 (79%). Dimethylsulfate (28.4 g, 225.4 mmol) was added to a stirred suspension of this alkene (9.38 g, 64.2 mmol), K_2CO_3 (32.1 g, 232 mmol) and acetone (108 mL). The mixture was refluxed for 2.5 h, cooled to rt, dried and concentrated. Ether (100 mL) and half satd $NaHCO_3$ (100 mL) was added. The phases were separated, and the aqueous phase was extracted with more ether (2 × 100 mL). The combined organic phases were washed with brine, dried and concentrated to give 18 g of a light brown oil. The remaining dimethylsulfate was distillated off at 30–33 °C (0.3 mbar). Yield: 7.01 g (68%) of the methylated intermediate as a light red oil. GS/MS: *m*/*z* 160 (78%). mCPBA (11.89 g, 68.89 mmol) was added in small portions to a stirred solution of the intermediate (7.01 g, 43.76 mmol) in DCM (110 mL) at 0 °C. The mixture was stirred for 5 h at rt. The reaction was quenched by adding 2 M NaOH (140 mL) at 0 °C, and the phases were separated. The organic phase was filtered through silica gel using EtOAc/heptane (0–50%) as eluent. Yield: 4.99 g (65%) of 3-methoxy-1a,2,7,7a-tetrahydronaphtho[2,3-*b*]oxirene as a dark yellow solid. LC/MS: UV: 87.4%; MH^+: 177.0. The product was recrystallized from heptane/EtOH (4/1). Yield: 2.64 g (34%) as colorless crystals. Mp 48–9 °C. R_f: 0.49 (EtOAc); LC/MS: UV: 97.4%; MH^+: 176.9. ^{1}H NMR ($CDCl_3$) δ 2.80 (d, 1H), 3.15 (d, 1H), 3.30 (d, 1H), 3.45 (m, 3H), 3.80 (s, 3H), 6.65 (t, 2H) 7.10 (t, 1H). ^{13}C NMR ($CDCl_3$) δ 157.7, 132.9, 127.2, 121.9, 120.6, 108.2, 55.7, 52.2, 51.9, 29.9, 23.5. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.65; H, 6.94. This epoxide (13.99 g, 79.39 mmol) was dissolved in DMSO (300 mL). NaN_3 (41.29 g, 635.15 mmol) was suspended in DMSO (300 mL), and concentrated H_2SO_4 (11.67 g, 119.1 mmol) was dissolved in DMSO (133 mL). The solutions and suspensions were combined and stirred for 23 h at 60 °C. To the mixture was added EtOAc (1.0 L) and water (1.5 L). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic phases were washed with brine, dried and concentrated to give 19.66 g of the two isomers as a red solid. The regioisomers were separated by fractional crystallization in toluene (100 mL) where **1** precipitated. Yield: 4.61 g (27%) of **1** as colorless crystals, mp 143–144 °C (lit.[8] mp 145–147 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (b, 1H), 2.55 (dd, 1H), 2.85 (dd, 1H), 3.20 (dd, 1H), 3.35 (dd, 1H), 3.70 (m, 1H), 3.80 (s, 3H), 3.85 (m, 1H), 6.70 (m, 2H), 7.15 (t, 1H). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.27; H, 6.14; N, 18.94.

4.1.2. Racemic-*trans*-9-methoxy-4a,5,10,10a-hexahydro-4*H*-naphtho[2,3-*b*][1,4]oxazine-3-one (3)

Compound **1** (4.61 g, 21 mmol) was dissolved in abs EtOH (350 mL) and 10% Pd/C (490 mg) was added under an argon atmosphere. The mixture was hydrogenated at 2.5 bar overnight. The crude mixture was filtered through Celite, concentrated, and dried in vacuo to give racemic *trans*-3-amino-8-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ol (**2**) as a white solid. Yield: 4.15 g (96%). This material was dissolved in THF (200 mL) and cooled in an ice-bath. Et3 N (5.04 mL, 36 mmol) and then chloroacetyl chloride (2.32 mL, 29.2 mmol) in THF (11 mL) was added over 2 min. The mixture was stirred for 2 h at rt. EtOAc (400 mL) and 1 M HCl (400 mL) were added and the layers were separated. The organic layer was washed with brine, dried (MgSO4), filtered and concentrated to give 6.01 g of a brown solid. This intermediate was dissolved in THF (200 mL) and 60% NaH dispersion (1.25 g, 31 mmol) was added slowly at rt and the solution was stirred 3 h at rt. The solution was subsequently quenched by adding 6 M HCl (5.2 mL) and 3 precipitated. The product **3** was filtered off and washed several times with ether, then water and finally ether again, and then dried in vacuo. Yield: 3.14 g (60%) of 3 as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.41 (dd, 1H), 2.64 (t, 1H), 2.99 (dd, 1H), 3.10 (dd, 1H), 3.43 (m, 1H), 3.66 (m, 1H), 3.77 (s, 3H), 4.10 (m, 1H), 6.72 (d, 1H), 6.81 (d, 1H), 7.15 (t, 1H), 8.35 (s, 1H).

4.1.3. Racemic *trans*-9-methoxy-2,3,4a,5,10,10a-hexahydro-naphtho[2,3-*b*][1,4]oxazine-4-carboxylic acid *tert*-butyl ester (4)

1 M LAH in THF (15 mL, 15 mmol) was added dropwise to a stirred solution of compound **4** (1.61 g, 6.90 mmol) in THF (83 mL). The mixture was stirred for 3 h at rt. The solution was quenched with ice-cold water and ether was added. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried and concentrated to give an yellow oil. This intermediate was dissolved in THF (70 mL), and Et_3N (1.45 mL, 10.4 mmol) and Boc_2O (1.52 g, 7.0 mmol) were added, before the mixture was stirred for 3 days at rt. The solution was concentrated and the crude product was purified by silica gel chromatography (eluent: increasing amount of EtOAc in heptanes). Yield: 1.45 g (66%) of **4** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.42 (dd, 1H), 2.72 (dd, 1H), 3.17 (dd, 1H), 3.52–3.65 (m, 4H), 3.72 (m, 1H), 3.76 (s, 3H), 3.82 (m, 1H), 3.99 (m, 1H), 6.59 (d, 1H), 6.64 (d, 1H), 7.04 (t, 1H).

4.1.4. Resolution of racemic *trans*-9-methoxy-2,3,4a,5,10,10a-hexahydro-naphtho[2,3-*b*][1,4]oxazine-4-carboxylic acid *tert*-butyl ester (resolution of compound 4 into compounds 4a and 4b)

Compound **4** (1.38 g, 43 mmol) was resolved by chiral SFC on a Berger SFC multigram II instrument equipped with a Chiralpak AD 21.2 × 250 mm column. Solvent system: CO_2/EtOH/Et_2NH (70:29.9:0.1) Method: constant gradient with a flow rate of 50 mL/min. Fraction collection was performed by UV at 230 nm detection. Fast eluting enantiomer (4a*S*, 10a*S* enantiomer; compound **4b**): 0.622 g (45%) as a white solid. Mp = 89–90 °C. α_D +190.1 (*c* 0.25, MeOH). Slow eluting enantiomer (4a*R*,10a*R* enantiomer; compound **4a**): 0.633 g (46%) as a white solid. Mp = 89–90 °C. α_D −184.8 (*c* 0.25, MeOH).

4.1.5. (4a*R*,10a*R*)-9-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine hydrochloride (5A)

To a stirred solution of compound **4a** (545 mg, 1.71 mmol) in MeOH (11 mL) was added HCl (14 mL, 5 M in ether). After stirring for 45 min, the mixture was concentrated. Yield: 418 mg (96%) of intermediate **5a** as a white solid. Mp dec >280 °C; LC/MS: ELSD: 99.6%; UV: 99.2%; MH^+: 220.2. NMR data identical to the data reported for intermediate **5b**. Anal. Calcd for $C_{13}H_{17}NO_2$ HCl: C, 61.05; H, 7.09; N, 5.48. Found: C, 60.93; H, 7.26; N, 5.42.

4.1.6. (4a*S*,10a*S*)-9-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine hydrochloride (5b)

To a stirred solution of compound **4b** (543 mg, 1.71 mmol) in MeOH (11 mL) was added HCl (14 mL, 5 M in ether). After stirring for 45 min, the mixture was concentrated. Yield: 436 mg (100%) of intermediate **5b** as a white solid. Mp dec >280 °C; LC/MS: ELSD: 98.7%; UV: 93.7%; MH^+: 220.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (dd, 1H), 3.00–3.20 (br m, 4H), 3.30 (m, 1H), 3.75 (s, 3H), 3.90 (m, 2H), 4.00 (dd, 1H), 6.75 (d, 1H), 6.80 (d, 1H), 7.15 (t, 1H), 9.75 (b, 1H). ^{13}C NMR (DMSO-d_6) δ: 157.0, 133.3, 127.6, 121.6, 120.8, 108.6, 73.2, 63.1, 55.7, 54.3, 43.2, 31.4, 29.1. Anal. Calcd for $C_{13}H_{17}NO_2$·HCl: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.11; H, 7.25; N, 5.41.

4.1.7. (4a*R*,10a*R*)-4-Methyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol hydrochloride (6a)

Compound **4a** was dissolved in dry THF (5 mL). LAH (1 M in THF, 1.5 mL, 1.5 mmol) was added dropwise at rt and the solution was heated to 90 °C for 15 min using microwave heating. After cooling to rt, MeOH (0.3 mL) and ice-cold water (10 mL) was slowly added, and the product was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried and concentrated to give 107 mg intermediate (TLC: R_f = 0.19 (EtOAc)). L-selectride (1 M in THF, 4.6 mL, 4.6 mmol) was added at rt to this intermediate (107 mg). The solution was heated to 100 °C for 6 h using microwave heating. After cooling to 0 °C, ice-cold water (25 mL) and satd $NaHCO_3$ (10 mL) were slowly added, and the product was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine, dried, and concentrated. The crude product was purified by silica gel chromatography. The free base was dissolved in MeOH (1 mL) and precipitated as the HCl salt using 5 M HCl in ether (1.5 mL). Yield: 49 mg of **6a** as a white solid. Mp dec >280 °C; LC/MS: ELSD: 99.0%, UV: 100.0%, MH^+: 220.3. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (dd, 1H), 2.85 (s, 3H), 3.05–3.20 (br m, 2H), 3.25 (m, 1H), 3.35–3.50 (br m, 2H), 3.95–4.05 (br m, 3H), 6.60 (d, 1H), 6.65 (d, 1H), 7.00 (t, 1H), 9.55 (s, 1H), 11.30–11.40 (b, 1H). Anal. Calcd for $C_{13}H_{17}NO_2$·HCl: C, 61.05; H, 7.09; N, 5.48. Found: C, 60.46; H, 7.18; N, 5.28. α_D −122.9° (*c* 0.5, DMSO).

4.1.8. (4a*R*,10a*R*)-4-Ethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol hydrochloride (7a)

L-selectride (1 M in THF, 18 mL, 18 mmol) was added dropwise at rt to a solution of compound **4a** (577 mg, 1.8 mmol) in THF (5 mL). The solution was heated to 100 °C for 6 h using microwave heating. After cooling to 0 °C, ice-cold water (125 mL) and satd $NaHCO_3$ (50 mL) were slowly added, and the product was extracted with ether (3 × 75 mL). The combined organic phases were washed with brine, dried, and concentrated. The residue was purified by silicagel chromatography to give (4a*R*,10a*R*)-9-hydroxy-2,3,4a,5,10,10a-hexahydro-naphtho[2,3-*b*][1,4]oxazine-4-carboxylic acid *tert*-butyl ester as a white solid. Yield: 297 mg (54%). Mp: 203–205 °C. 141 mg, (0.46 mmol) of this material was dissolved in MeOH (4 mL) and HCl (5 M in Et_2O) was added. The solution was stirred for 45 min at rt and concentrated. The residue was dissolved in abs EtOH (2.3 mL). $NaCNBH_3$ (129 mg, 1.9 mmol), acetic acid (0.3 mL) and acetaldehyde (0.16 mL, 2.8 mmol) were added and the solution was heated to 90 °C for 15 min using microwave heating. After cooling to 0 °C, ice-cold water (25 mL) and satd $NaHCO_3$ (10 mL) were slowly added, and the product was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine, dried and concentrated. The crude product was purified by chromatography to give 49 mg. The product was dissolved in MeOH (1 mL) and HCl (1.5 mL, 5 M in ether) was added. The generated HCl salt was isolated and dried in vacuo. Yield of **7a**: 38 mg (31%) as a white solid. Mp dec >280 °C; LC/MS: ELSD 99%, UV 100%. MH^+: 234.1**.** ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.25 (t, 3H), 2.40 (dd, 1H , 3.05–3.20 (br m, 4H), 3.35–3.50 (m, 3H), 4.00–4.10 (br m, 3H), 6.60 (d, 1H), 6.65 (d, 1H), 7.00 (t, 1H), 9.55 (s, 1H), 11.45–11.55 (b, 1H). Anal. Calcd for $C_{14}H_{19}NO_2$·HCl: C, 61.31; H, 7.53; N, 5.11. (1/4H_2O) Found: C, 61.69; H, 7.57; N, 5.12. α_D: −116.6° (*c* 0.5, DMSO).

4.1.9. (4a*R*,10a*R*)-4-*n*-Propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol hydrochloride (8a)

K_2CO_3 (176 mg, 1.50 mmol) and *n*-propyl iodide (375 mg, 2.2 mmol) were added to a stirred solution of **5a** (100 mg, 0.39 mmol) in DMF (9 mL). The mixture was stirred at 55 °C for 3 h. Water (20 mL) was added and the product was extracted into ether (3 × 10 mL). The combined organic phases were washed with brine and satd NH_4Cl, dried and concentrated to give (4a*R*,10a*R*)-9-methoxy-4-*n*-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3*b*][1,4]oxazine as a white solid. Yield: 93 mg. LC/MS (method 25): RT 0.58 min, ELSD 100%, UV 92%. TLC: R_f = 0.51 (EtOAc). The L-selectride de-protection procedure described for **6a** was followed to give example **8a**. Yield: 61 mg (55%) as a white solid. Mp dec >300 °C; LC/MS: ELSD 100%, UV 98%. MH^+: 248.2**.** ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (t, 3H), 1.73 (m, 2H), 2.40 (dd, 1H), 3.00 (m, 1H), 3.10–3.20 (br m, 4H), 3.35–3.50 (br m, 2H), 4.05 (m, 3H), 6.60 (d, 1H), 6.65 (d, 1H), 7.00 (t, 1H), 9.55 (s, 1H), 11.30–11.40 (b, 1H); Anal. Calcd for $C_{15}H_{21}NO_2$·HCl·0.25H_2O: C, 62.48; H, 7.88; N, 4.86. Found: C, 62.71; H, 7.99; N, 5.05. α_D −109.3 (*c* 0.5, DMSO).

4.1.10. (4a*R*,10a*R*)-4-Allyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol hydrochloride (9a)

K_2CO_3 (202 mg, 1.46 mmol) and allyl bromide (0.21 mL, 300 mg, 2.48 mmol) were added to a stirred solution of **5a** (115 mg, 0.45 mmol) in DMF (10 mL). The mixture was stirred at 55 °C for 5 h. Water (20 mL) and satd $NaHCO_3$ (10 mL) were added and the product was extracted into ether (3 × 20 mL). The combined organic phases were washed with brine, dried and concentrated to give (4a*R*,10a*R*)-4-allyl-9-methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3*b*][1,4]oxazine as a white solid. Yield:

117 mg. LC/MS (method 25): RT 0.97 min, ELSD 97%, UV 48%. MH^+: 260.3. The L-selectride de-protecting procedure described for compound **6a** was followed to give **9a**. Yield: 28 mg (21%) as a white solid. Mp dec >280 °C; LC/MS: ELSD 99%, UV 96%. MH^+: 246.2. ^1H NMR (500 MHz, DMSO-d_6) δ 2.40 (dd, 1H), 3.10–3.20 (br m, 3H), 3.40 (m, 1H), 3.45 (dd, 1H), 3.75 (m, 1H), 4.00–4.10 (br m, 4H), 5.55 (d, 1H), 5.65 (d, 1H), 6.05 (m, 1H), 6.60 (d, 1H), 6.65 (d, 1H), 7.00 (t, 1H), 9.55 (s, 1H), 11.65–11.75 (b, 1H). Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl \cdot 0.25H_2O$: C, 62.93; H, 7.22; N, 4.89. Found: C, 62.53; H, 7.48; N, 4.71. α_D −115.4° (*c* 0.5, DMSO).

4.1.11. (4a*R*,10a*R*)-4-Cyclo-propylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3*b*][1,4]oxazin-9-ol hydrochloride (10a)

K_2CO_3 (176 mg, 1.27 mmol) and cyclopropylmethyl bromide (0.21 mL, 292 mg, 2.16 mmol) were added to a stirred solution of intermediate **5a** (100 mg, 0.39 mmol) in DMF (9 mL). The mixture was stirred at 55 °C for 3 h. Water (20 mL) and satd $NaHCO_3$ (10 mL) was added and the product was extracted into ether (3 × 20 mL). The combined organic phases were washed with brine, dried and concentrated to give (4a*R*,10a*R*)-4-cyclopropylmethyl-9-methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3*b*][1,4]oxazine as a white solid. Yield: 107 mg. LC/MS: ELSD 100%, UV 92%. MH^+: 274.3. The L-selectride deprotection procedure described for example **6a** was followed to give **10a**. Yield: 79 mg (72%) as a white solid. Mp dec >280 °C; LC/MS: ELSD 99%, UV 98%. MH^+: 260.2. ^1H NMR (500 MHz, DMSO-d_6) δ 0.45 (m, 2H), 0.65 (m, 2H), 1.15 (m, 1H), 2.40 (dd, 1H), 3.05–3.20 (br m, 3H), 3.25 (m, 1H), 3.35–3.45 (br m, 2H), 3.70 (d, 1H), 4.00–4.10 (br m, 3H), 6.60 (d, 1H), 6.65 (d, 1H), 7.00 (t, 1H), 9.55 (s, 1H), 11.10–11.20 (b, 1H). α_D −109.5° (*c* 0.5, DMSO).

4.1.12. (4a*S*,10a*S*)-4-Cyclo-propylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol hydrochloride (10b)

The procedure described for example **10a** was followed starting from intermediate **5b** (100 mg, 0.39 mmol) to give (4a*S*,10a*S*)-4-cyclopropylmethyl-9-methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho [2,3*b*] [1,4]oxazine. Yield: 107 mg. LC/MS: ELSD 99%, UV 90%. MH^+: 274.1.

The L-selectride deprotection procedure described for **6a** was followed to give **10b**. Yield: 73 mg as a white solid. Mp dec >280 °C; LC/MS: ELSD 99%, UV 96%. MH^+: 260.2. ^1H NMR data identical to the data reported for example **10a**. Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64,48; H, 7.52; N, 4.70. Found: C, 64.32; H, 7.66; N, 4.64. α_D +114.9° (*c* 0.5, DMSO-d_6).

4.1.13. Racemic *trans*-3-hydroxy-5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid *tert*-butyl ester (Boc-2)

Compound **2** (7.36 g, 38.1 mmol) was dissolved in THF (175 mL), and Et_3N (7.7 mL, 5.58 g, 55 mmol) and Boc_2O (7.74 g, 35.5 mmol) were added. The mixture was stirred at rt overnight and concentrated. The crude product was purified by silica gel chromatography to afford 6.90 g (62%) of Boc-**2** as a white solid.

4.1.14. Resolution of racemic *trans*-3-hydroxy-5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid *tert*-butyl ester (resolution of Boc-2 into Boc-2A and 2B)

Boc-**2** (13 g, 44 mmol) was resolved by chiral SFC on a Berger SFC multigram II instrument equipped with a Chiralpak AD 21.2 × 250 mm column. Solvent system: CO_2/EtOH/Et_2NH (70:29.9:0.1) Method: constant gradient with a flow rate of 50 mL/min. Fraction collection was performed by UV 230 nm detection. Fast eluting enantiomer (2S, 3S enantiomer; Boc-**2B**): 5.14 g (40%) as a white solid. Mp = 161–162 °C. Slow eluting enantiomer (2*R*,3*R* enantiomer; Boc-**2A**): 5.17 g as a white solid. Mp = 161–162 °C.

4.1.15. (2*R*,3*R*)-3-Amino-8-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ol (compound 11A)

To a stirred solution of Boc-**2A** (7.19 g, 24.5 mmol) in MeOH (100 mL) was added HCl (99 mL, 2 M in ether). After stirring for two hours the solution was filtered to afford compound **11A** as a white solid. Yield: 5.05 g (90%). LC/MS: ELSD 97.0%, UV 100%. MH^+: 194.1. $_D$ −105.5° (*c* 0.25, MeOH) ^1H NMR (500 MHz, DMSO-d_6) δ: 2.41 (dd, 1H), 2.95 (dd, 1H), 3.09–3,17 (m, 3H), 3.77 (s, 3H), 3.87 (m, 1H), 5.75 (1, 1H), 6.71 (d, 1H), 6.79 (d, 1H), 7.13 (t, 1H), 8.32 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 157.0, 133.8, 127.3, 122.7, 120.7, 108.3, 67.2, 55.7, 52.3, 32.6, 31.9.

4.1.16. (2*S*,3*S*)-3-Amino-8-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ol (compound 11B)

This material was synthesized from Boc-**2B** (7.44 g, 25.4 mmol) in a similar manner as described for compound **11A**. Yield: 5.34 g (91%) of compound **11B** as a white solid. LC/MS: ELSD 100%, UV 100%. MH^+: 194.1. α_D +104,6 (*c* 0.25, MeOH). NMR data identical to the data reported for compound **11A**.

4.1.17. (2*R*,3*R*)-8-Methoxy-3-propylamino-1,2,3,4-tetrahydro-naphthalen-2-ol (12)

Propionylchlorid (0.60 mL, 6.90 mmol) and Et_3N (1.80 mL, 12.9 mmol) were added to a stirred solution of compound **11a** (1.50 g, 6.5 mmol) suspended in THF (15.0 mL, 185 mmol). The solution was stirred for 20 min. LAH (1 M in THF, 10 mL) was added dropwise under stirring at rt. and the reaction mixture were heated to 90 °C for 20 min using microwave heating. The solution was quenched by pouring it into wet Na_2SO_4. The mixture was diluted with THF (50 mL), filtered over dry Na_2SO_4 and concentrated. Yield: 1.21 g (81%) of **12** as an oil. LC/MS: ELSD: 100%; UV: 100%; MH^+ 235.9. ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7,6 Hz, 3H), 1.43–1.52 (m, 2H), 2.37–2.51 (m, 3H), 2.61–2.68 (m, 1H), 2.74–2.80 (m, 1H), 3.14 (dd, *J* = 4.93, *J* = 16.0, 1H), 3.22–3.29 (dd, *J* = 16.9, *J* = 5.9, 1H), 3.56–3.63 (m, 1H), 3.73 (s, 1H), 6.60 (d, *J* = 8.05, 1H), 6.62 (d, *J* = 7.89, 1H), 7.03 (t, *J* = 7.86, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.7 136.4, 127.0, 123.8, 121.2, 107.7, 71.0, 59.8, 55.7, 49.5, 35,7, 32.1, 24.1, 12.2.

4.1.18. ((2*S*,4a*R*,10a*R*)-9-Methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-2-yl)-methanol (14) and ((2*R*,4a*R*,10a*R*)-9-methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-2-yl)-methanol (13)

S-(+)-Epichlorohydrin (1.22 mL, 15.5 mmol) was added to a stirred solution of compound **12** (751 mg, 3.20 mmol) dissolved in 1,2-DCE (3.2 mL). The reaction mixture was refluxed at 120 °C overnight, and concentrated. NaOH (8.7 mL, 2 M) was added to this intermediate (392 mg) and the mixture was refluxed at 130 °C overnight. The solution was allowed to cool, and THF (17.5 mL) was added. The phases were separated and the organic phase washed with brine (5 mL) and concentrated. The crude product was purified by silica gel chromatography to afford 116 mg (13%) of **14** and 76 mg (8%) of **13**.

Compound **14** LC/MS: ELSD: 100.0%; UV: 90.4%; MH^+ 291.8. ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.48, 3H), 1.38–1.59 (m, 2H), 2.09–2.15 (m, 1H), 2.30–2.40 (m, 1H), 2.59 (dd, *J* = 15.86, *J* = 11.69, 1H), 2.65 (dd, *J* = 11.87, *J* = 3.99, 1H), 2.99 (d, *J* = 11.81, 1H), 3.11 (t, *J* = 5.59, 1H), 3.14 (t, *J* = 5.14, 1H), 3.74 (s, 3H), 3.83–3.92 (m, 2H), 4.07–4.14 (m, 2H), 6.60 (d, *J* = 8.21, 1H), 6.63 (d, *J* = 7.86, 1H), 7.04 (t, *J* = 8.03, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.5 135.5, 127.1, 123.4, 121.1, 107.7, 72.4, 72.3, 67.0, 60.9, 55,7, 55.1, 53.2, 33.9, 30.7, 19.1, 12.3.

Compound **13** LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 291.8. ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7,3 Hz, 3H), 1.45–1.59 (m, 2H), 2.24–2.32 (m, 3H), 2.43 (dd, J = 16.9, J = 10.6, 1H), 2.60 (dd, J = 11.8, J = 15.4, 1H), 2.73 (m, 1H), 2.79 (d, J = 11.18, 1H), 3.10–3.19 (m, 2H), 3,55 (dd, J = 6.35, J = 11.64, 1H), (3.58–3.66 (m, 2H), 3.74 (s, 3H), 3.78 (br s, 1H), 6.61 (d, J = 8.21, 1H), 6.66 (d, J = 7.92, 1H), 7.05 (t, J = 7.88, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.5 135.8, 127.1, 123.4, 121.2, 107.7, 76.9, 76.0, 64.7, 60.9, 55,7, 55.6, 53.4, 33.9, 30.1, 18.7, 12.4.

4.1.19. Toluene-4-sulfonic acid (2*S*,4a*R*,10a*R*)-9-methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naptho[2,3-*b*][1,4]oxazin-2-ylmethyl ester (15)

Compound **15** was synthesized from **13** (294 mg, 1.01 mmol) as described for **16**. Yield: 330 mg (73%) of compound **15** as yellow/brown oil. LC/MS: ELSD: 100.0%; UV: 29.6%; MH^+ 446.0. ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7,34 Hz, 3H), 1.39–1.59 (m, 2H), 2.16 (t, J = 10.89, 1H), 2.21–2.34 (m, 2H), 2.37 (dd, J = 17.40, J = 6.52, 1H), 2.47 (s, 3H), 2.60 (dd, J = 15.01, J = 11.89, 1H), 2.71–2.81 (m, 1H), 2.61–2.68 (m, 1H), 2.89 (d, J = 12.13, 1H), 3.10 (dd, J = 16.91, J = 5.81, 1H), 3.17 (dd, J = 11.25, J = 4.90, 1H), 3.55 (dd, J = 15.76 J = 9.46, 1H), 3.82 (s, 3H), 3.87–3.94 (m, 1H), 4.04 (dd, J = 10.30, J = 4.92, 1H), 4.10 (dd, J = 10.30, J = 5.35, 1H), 6.68 (d, J = 8.17, 1H), 6.72 (d, J = 7.56, 1H), 7.12 (t, J = 7.91, 1H), 7.37 (d, J = 7.84, 2H), 7.83 (d, J = 8.12, 2H).

4.1.20. Toluene-4-sulfonic acid (2*R*,4a*R*,10a*R*)-9-methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naptho[2,3-*b*][1,4]oxazin-2-ylmethyl ester (16)

TsCl (343 mg, 1.80 mmol) was added to a solution of **14** (116 mg, 0.40 mmol) in pyridine (5.5 mL, 68 mmol). The solution was stirred at rt for 4 h and quenched by addition of water (0.4 mL). EtOAc (18.0 mL) and satd $NaHCO_3$ (7.4 mL) were added. The phases were separated and the organic phase extracted with satd $NaHCO_3$ (7.4 mL) and washed with brine, and concentrated. The crude product was purified by silica gel chromatography to afford 118 mg (quantitative) of **16**. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 446.0. Mp: 139.3–141.6. Anal. Calcd for $C_{23}H_{29}NO_5S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 64.67; H, 7.18; N, 3.02. ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7,44 Hz, 3H), 1.30–1.48 (m, 2H), 2.11–2.17 (m, 1H), 2.21–2.27 (mm, 1H), 2.26 (s, 3H), 2.31 (dd, J = 16.65, J = 5.98, 1H), 2.45 (dd, J = 16.15, J = 4.57, 1H), 2.51 (dd, J = 12.15, J = 8.08, 1H), 2.61–2.68 (m, 1H), 2.78 (d, J = 12.15, 1H), 2.92 (dd, J = 16.77, J = 11.22, 1H), 3.09 (dd, J = 16.05, J = 10.88, 1H), 3.18–3.24 (m, 1H), 3.81 (s, 3H), 4.03–4.09 (m, 1H), 4.31 (dd, J = 10.34, J = 6.08, 1H), 4.52 (dd, J = 10.34, J = 7.76, 1H), 6.66 (d, J = 8.15, 1H), 6.67 (d, J = 7.87, 1H), 7.09 (t, J = 7.90, 1H), 7.28 (d, J = 7.98, 2H), 7.82 (d, J = 7.98, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.4, 145.3, 135.6, 133.2, 130.2, 128.5, 127.1, 123.2, 121.2, 107.6, 71.3, 70.8, 68.4, 61.6, 55.7, 54.6, 51.5, 33.8, 30.1, 21.8, 19.1, 12.2.

4.1.21. (2*R*,4a*R*,10a*R*)-9-Methoxy-4-propyl-2-pyrazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine (17)

Compound **17** was synthesized from compound **15** as described for **18** from **16**. Yield: 20 mg (59%) of compound **17** as a white solid. LC/MS: ELSD: 100.0%; UV: 100.0%; MH+ 328.0. Anal. Calcd for $C_{20}H_{28}N_3O_2Cl{\cdot}2H_2O$: C, 58.00; H, 7.73; N, 10.14. Found: C, 58.47; H, 7.39; N, 10.04. ^1H NMR (500 MHz, DMSO-d_6) δ 0.95 (t, J = 7,34 Hz, 3H), 1.63–1.81 (m, 2H), 2.39 (dd, J = 16.71, J = 10.83, 1H), 2.90–3.06 (mm, 2H), 3.07–3.19 (m, 2H), 3.30–3.40 (m, 3H), 3.48 (dd, J = 16.03, J = 5.34, 1H), 3.65 (s, 1H) 3.76 (s, 3H), 4.08–4.16 (m, 1H), 4.29 (dd, J = 14.32, J = 6.74, 1H), 4.39 (dd, J = 14.32, J = 4.29, 1H), 4.43–4.49 (m, 1H), 6.28 (t, J = 2.04, 1H), 6.76 (d, J = 7.93, 1H), 6.82 (d, J = 8.21, 1H), 7.17 (t, J = 8.00, 1H), 7.50 (d, J = 1.89, 1H), 7.74 (d, J = 2.23, 1H).

4.1.22. (2*S*,4a*R*,10a*R*)-9-Methoxy-4-propyl-2-pyrazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine (18)

NaH (5.0 mg, 0.18 mmol) was added to a solution of **16** (42 mg, 0.09 mmol) and pyrazol (18.4 mg, 0.27 mmol) in DMF (1.0 mL). The solution was heated at 130 °C for 30 min using microwave conditions. The reaction was quenched with brine (10 mL) and EtOAc (10 mL) was added. The phases were separated and the organic phase washed with additional brine and concentrated. The product was purified by silica gel chromatography. Yield: 33 mg (95%) of compound **18** as an oil. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 328.0. Anal. Calcd for $C_{20}H_{28}N_3O_2Cl{\cdot}3.5H_2O$: C, 54.42; H, 7.90; N, 9.52. Found: C, 54.35; H, 7.57; N, 9.25. ^1H NMR (500 MHz, DMSO-d_6) δ 0.95 (t, J = 7,34 Hz, 3H), 1.67–1.82 (m, 2H), 2.33 (dd, J = 16.80, J = 10.21, 1H), 2.99–3.08 (mm, 2H), 3.32–3.52 (m, 7H), 3.77 (s, 3H), 4.35–4.42 (m, 1H), 4.44–4.51 (m, 1H), 4.69 (dd, J = 14.29, J = 6.06, 1H), 5.13 (dd, J = 14.33, J = 9.29, 1H), 6.27 (t, J = 1.87, 1H), 6.78 (d, J = 7.60, 1H), 6.82 (d, J = 7.98, 1H), 7.18 (t, J = 7.78, 1H), 7.50 (d, J = 1.70, 1H), 7.92 (d, J = 2.08, 1H).

4.1.23. (2*R*,4a*R*,10a*R*)-4-Propyl-2-pyrazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (19)

Compound **19** was synthesized from **17** as described for **20** from **18**. Yield: 7.5 mg (29%) of compound **19** as an oil. ^1H NMR (500 MHz, DMSO-d_6) δ 0.96 (t, J = 7,27 Hz, 3H), 1.54–1.67 (m, 1H), 1.70–1.82 (m, 1H) 2.41 (dd, J = 16.92, J = 10.69, 1H), 2.51 (br s, 1H), 2.85 (t, J = 13.90, 2H), 2.97–3.14 (m, 2H), 3.34–3.71 (m, 3H), 3.92–3.99 (m, 1H), 4.25–4.42 (m, 3H), 6.29 (s, 1H), 6.60 (dd, J = 7.45, 1H), 6.66 (d, J = 7.66, 1H), 6.99 (t, J = 7.89, 1H), 7.51 (s, 1H), 7.75 (d, J = 1.53, 1H); HRMS C19H26N3O2 [M+H$^+$] calcd 328.2020, found 328.2011.

4.1.24. (2*S*,4a*R*,10a*R*)-4-Propyl-2-pyrazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (20)

KF and thiophenol were added to **18** (21 mg, 0.06 mmol) dissolved in DMA. The reaction mixture was heated to 210 °C for 1 h using microwave heating, and then concentrated. The resulting mixture was purified with silica gel chromatography (eluent: 0–5% MeOH in EtOAc) and **20** was further purified by HPLC. Yield: 12 mg (60%) of **20** as an oil. ^1H NMR (500 MHz, DMSO-d_6) δ 0.77 (t, J = 7,27 Hz, 3H), 1.41–1.62 (m, 2H), 2.14 (dd, J = 16.67, J = 10.24, 1H), 2.31 (br s, 1H), 2.77–2.94 (m, 3H), 3.19–3.32 (m, 4H), 3.38 (d, J = 13.28, 3H), 4.15 (dd, J = 16.23, J = 10.05, 1H), 4.22–4.34 (m, 2H), 4.70 (dd, J = 14.11, J = 9.45 1H), 6.09 (s, 1H), 6.43 (dd, J = 7.62, 1H), 6.48 (d, J = 7.99, 1H), 6.81 (t, J = 7.62, 1H), 7.31 (s, 1H), 7.63 (s, 1H); HRMS $C_{19}H_{26}N_3O_2$ [M+H$^+$] calcd 328.2020, found 328.2016.

4.1.25. (2*R*,4a*R*,10a*R*)-2-(3-Phenyl-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (21)

NaH (4.3 mg, 0.18 mmol) was added to a solution of **15** (42 mg, 0.09 mmol) and 3-phenyl-pyrazol (38.9 mg, 0.27 mmol) in DMF (1 mL). The solution was heated at 130 °C for 30 min using microwave heating. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and EtOAc (15 mL) was added. The phases were separated and the organic phase extracted with $NaHCO_3$ (10 mL) and concentrated. Yield: 60 mg of the crude intermediate (2*R*,4a*R*,10a*R*)-9-methoxy-2-(3-phenyl-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine. LC/MS: ELSD: 99.9%; UV: 71.5%; MH^+ 418.1. This intermediate was dissolved in DMA (6.3 mL), and KF (11 mg, 0.18 mmol) and thiophenol (0.07 mL, 0.68 mmol) were added. The solution was heated at 210 °C for 1 h using microwave heating. The mixture was purified

by silica gel chromatography and then HPLC. Yield of **21**: 16 mg (22%). LC/MS: ELSD: 97.5%; UV: 85.6%; MH^+ 404.3. ^1H NMR (500 MHz, DMSO-d_6) δ 0.79 (t, J = 7,16 Hz, 3H), 1.57–1.69 (m, 1H), 1.70–1.84 (m, 1H), 2.44 (dd, J = 16.74, J = 10.37, 1H), 2.51 (br s, 2H), 2.55 (s, 1H), 2.87 (dd, J = 14.88, J = 12.08, 1H), 3.00–3.09 (m, 1H), 3.12 (dd, J = 16.57, J = 6.15, 1H) (s, 1H) 3.73 (d, J = 12.23, 3H), 3.99 (m, 1H), 4.31–4.48 (m, 3H), 6.61 (d, J = 7.60, 1H), 6.67 (d, J = 8.00, 1H), 6.77 (d, J = 2.13, 1H), 6.99 (t, J = 7.74, 1H), 7.31 (t, J = 7.27, 1H), 7.41 (t, J = 7.55, 1H), 7.79–7.83 (m, 3H), 9.67 (br s, 1H). HRMS $C_{25}H_{30}N_3O_2$ [M+H$^+$] calcd 404.2333, found 404.2339.

4.1.26. (2*S*,4a*R*,10a*R*)-2-(3-Phenyl-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (22)

Compound **22** was synthesized from **16** as described for **21** from **15**. Yield: 66 mg of the crude intermediate (2*S*,4a*R*,10a*R*)-9-methoxy-2-(3-phenyl-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine. LC/MS: ELSD: 91.9%; UV: 79.7%; MH^+ 418.1. Yield: 5 mg (8%) of compound **22** as an oil. LC/MS: ELSD: 100.0%; UV: 88.7%; MH^+ 404.3. ^1H NMR (500 MHz, DMSO-d_6) δ 0.79 (t, J = 7,22 Hz, 3H), 1.39–1.65 (m, 2H), 2.16 (dd, J = 16.74, J = 10.37, 1H), 2.32 (br s, 2H), 2.36 (s, 1H), 2.80–2.98 (m, 3H), 3.11–3.47 (m, 3H), 4.10–4.30 (m, 1H), 4.31–4.40 (m, 1H), 4.76 (dd, J = 15.23, J = 11.56 3.58, 1H), 6.45 (d, J = 7.82, 1H), 6.49 (d, J = 7.48, 1H), 6.57 (d, J = 2.25, 1H), 6.82 (t, J = 7.80, 1H), 7.12 (t, J = 7.33, 1H), 7.22 (t, J = 7.62, 2H), 7.62 (d, J = 7.33, 2H), 7.73 (d, J = 1.89, 1H), 9.43 (br s, 1H). HRMS $C_{25}H_{30}N_3O_2$ [M+H$^+$] calcd 404.2333, found 404.2330.

4.1.27. (2*R*,4a*R*,10a*R*)-4-Propyl-2-[1,2,3]triazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol TFA salt (23)

Compound **15** (42 mg, 0.09 mmol) dissolved in DMF (1.0 mL) was added to a mixture of 1*H*-[1,2,4]Triazole (18.7 mg, 0.27 mmol) and NaH (4.3 mg, 0.18 mmol). The solution was heated at 130 °C for 30 min using microwave heating. The reaction was quenched with satd NaHCO3 (10 mL), and EtOAc (15 mL) was added. The phases were separated and the organic phase washed with NaHCO3 (10 mL) and concentrated. Yield: 18 mg of the crude intermediate (2*R*,4a*R*,10a*R*)-9-methoxy-4-propyl-2-[1,2,3]triazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine). The L-selectride de-protecting procedure described for **6a** was followed to give **23**. Yield of **23**: 1.7 mg as a white oil. LC/MS: ELSD 100%, UV 100%. MH^+ = 329.5.

4.1.28. (2*S*,4a*R*,10a*R*)-4-Propyl-2-[1,2,3]triazol-1-ylmethyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (24)

Compound **24** was synthesized from **16** as described for **23** from **15**, except that the deprotection was achieved with the thiophenol method. Yield: 2.6 mg (14.1%) of compound **24** as a white solid. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 342.1.

4.1.29. (2*R*,4a*R*,10a*R*)-2-(4-Chloro-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (25)

Compound **15** (42 mg, 0.09 mmol) dissolved in DMF (1.0 mL) was added to a mixture of 4-chloro-1*H*-pyrazole (27.8 mg, 0.27 mmol) and NaH (4.3 mg, 0.18 mmol). The solution was heated at 130 °C for 30 min using microwave heating. The reaction was quenched with satd $NaHCO_3$ (10 mL), and EtOAc (15 mL) were added. The phases were separated and the organic phase extracted with $NaHCO_3$ (10 mL) and concentrated. Yield 13 mg (38%) of the intermediate (2*R*,4a*R*,10a*R*)-2-(4-chloro-pyrazol-1-ylmethyl)-9-methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine as a white solid. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 376.3; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (br s, 3H), 1.73 (br s, 1H), 1.99 (br s, 1H), 2.51 (dd, J = 9.25, J = 16.47, 1H), 2.97–3.44 (m, 7H), 3.83 (s, 3H), 3.94 (m, 1H), 4.51 (br s, 1H), 4.80 (br s, 1H), 5.57 (br s, 1H), 6.72 (d, J = 8.21, 2H), 7.17 (br s, 1H), 7.52 (s, 1H), 8.23 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.3 138.3, 132.3, 131.2, 128.1, 121.2, 121.0, 110.9, 108.4, 69.5, 68.5, 62.9, 55.8, 55.5, 51.7, 49.2, 30.1, 29.8, 16.5, 11.8. This intermediate (8 mg, 0.02 mmol) was dissolved in DMA (0.7 mL) in a vial. KF (~2 equiv) and thiophenol (0.01 mL) were added and the vial was sealed. The reaction mixture was heated to 220 °C for 1 h. and the solvent was evaporated off. The resulting mixture was purified with silica gel chromatography using 0–100% (EtOAc in heptane) and HPLC. Yield: 2.6 mg (26%) of **25** as an oil. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 362.4. ^1H NMR (500 MHz, DMSO-d_6) δ 0.95 (t, J = 7,26 Hz, 3H), 1.55–1.68 (m, 1H), 1.69–1.81 (m, 1H), 2.40 (dd, J = 16.60, J = 10.62, 1H), 2.51 (br s, 1H), 2.82–3.05 (m, 2H), 3.10 (dd, J = 16.71, J = 5.83, 1H), 3.25–3.72 (m, 2H), 3.95 (d, J = 5.99, 1H), (dd, J = 15.78, J = 10.27, 1H), 4.24–4.40 (m, 3H), 4.44–4.50 (m, 1H), 6.60 (d, J = 7.67, 1H), 6.66 (d, J = 7.67, 1H), 6.99 (t, J = 7.82, 1H), 7.61 (s, 1H), 7.99 (s, 1H); 9.66 (br s, 1H). HRMS $C_{19}H_{25}Cl_1N_3O_2$ [M+H$^+$] calcd 362.1630, found 362.1628.

4.1.30. (2*S*,4a*R*,10a*R*)-2-(4-Chloro-pyrazol-1-ylmethyl)-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol (26)

Compound **26** was synthesized from **16** as described for **25** from **15**. Yield: 43 mg of the intermediate (2*R*,4a*R*,10a*R*)-2-(4-chloro-pyrazol-1-ylmethyl)-9-methoxy-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine: 43 mg as an oil. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 376.1; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7,20 Hz, 3H), 1.69–1.83 (m, 1H), 1.88–2.04 (m, 1H), 2.50 (dd, J = 17.01, J = 10.40, 1H), 2.57 (dd, J = 18.94, J = 9.44, 1H), 2.90 (br s, 2H), 3.21 (dd, J = 15.56, J = 4.75, 1H), 3.29 (t, J = 11.30, 1H), 3.37 (dd, J = 17.08, J = 6.31, 1H), 3.54 (d, J = 11.18, 1H), 3.67 (t, J = 13.14, 1H), 3.84 (s, 3H), 4.29–4.41 (m, 2H), 4.55–4.66 (m, 1H), 4.91 (d, J = 8.33, 1H), 6.69 (d, J = 7.74, 1H), 6.72 (d, J = 8.17, 1H), 6.82 (d, J = 8.21, 1H), 7.15 (t, J = 8.00, 1H), 7.44 (s, 1H), 7.52 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.3 138.6, 132.3, 129.6, 128.0, 121.4, 121.0, 111.0, 108.4, 73.7, 70.6, 62.3, 55.8, 54.9, 54.6, 52.4, 30.1, 29.9, 16.4, 11.6. Yield of the product **(26)**: 6.4 mg (19%) as an oil. LC/MS: ELSD: 100.0%; UV: 100.0%; MH^+ 362.4; ^1H NMR (500 MHz, DMSO-d_6) δ 0.96 (t, J = 7,27 Hz, 3H), 1.57–1.81 (m, 2H), 2.32 (dd, J = 16.32, J = 10.42, 1H), 2.51 (br s, 1H), 2.93–3.06 (m, 3H), 3.42–3.60 (br s, 4H), 4.30 (dd, J = 15.78, J = 10.27, 1H), 4.39 (dd, J = 14.50, J = 4.50, 1H), 4.44–4.50 (m, 1H), 4.89 (dd, J = 14.32, J = 10.32 1H), 6.63 (d, J = 7.67, 1H), 6.67 (d, J = 7.67, 1H), 7.00 (t, J = 7.82, 1H), 7.61 (s, 1H), 8.10 (s, 1H); 9.67 (br s, 1H). HRMS $C_{19}H_{25}Cl_1N_3O_2$ [M+H$^+$] calc 362.1630, found 362.1624.

4.1.31. (2*R*,4a*R*,10a*R*)-2-Methylsulfanylmethyl-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol Hydrochloride (27)

Compound **15** (300 mg, 0.67 mmol) was dissolved in DMF (37.0 mL) under an argon atmosphere. Sodium methyl sulfide (142 mg, 2.02 mmol) and 18-crown-6 (178 mg, 0.67 mmol) were added to a vial and the solution was afterwards transferred to the vial. The solution was heated in the sealed vial to 110 °C for 30 min under microwaves. The reaction was quenched with satd $NaHCO_3$ (50 mL), and EtOAc (80 mL) were added. The phases were separated and the organic phase washed with additional satd $NaHCO_3$ (20 mL) and concentrated in vacou. The crude product was purified by silica gel chromatography (eluent 0–100% EtOAc in heptanes). Yield 60 mg (28%) of the intermediate (2*R*,4a*R*,10a*R*)-9-methoxy-2-methylsulfanylmethyl-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine as an oil. LC/MS (method 350): ELSD: 100%; UV: 100%; MH^+ 322.3;

R_t = 0.58. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.48 Hz, 3H), 1.43–1.62 (m, 2H), 2.12–2.22 (m, 4H), 2.26–2.39 (m, 2H), 2.43–2.58 (m, 2H), 2.59–2.67 (m, 1H), 2.70 (dd, J = 12.72 Hz, J = 4.89 Hz, 1H), 2.74–2.84 (m, 1H), 3.09 (d, J = 11.25 Hz, 1H), 3.16–3.29 (m, 2H), 3.60–3.68 (m, 1H), 3.79 (s, 3H), 3.85 (br s, 1H), 6.66 (d, J = 7.82 Hz, 1H), 6.72 (d, J = 6.85 Hz, 1H), 7.11 (t, J = 7.09 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 157.6, 135.8, 127.0, 123.6, 121.2, 107.6, 77.2, 75.3, 60.6, 56.5, 55.7, 55.6, 46.5, 37.7, 34.0, 30.1, 29.8, 20.7, 17.1, 12.4. This intermediate (50 mg, 0.16 mmol) was dissolved in DMA (7.3 mL) in a vial. KF (~2 equiv) and benzenethiol (0.80 mL, 0.80 mmol) were added and the vial was sealed. The reaction mixture was heated to 230 °C for 1 h. and the solvent was evaporated off. The resulting mixture was purified with silica gel chromatography using (eluent 0–50% EtOAc in heptanes) and HPLC. Yield: 26 mg (54%) of (2*R*,4a*R*,10a*R*)-2-mercaptomethyl-4-propyl-3,4,4a,5,10,10a-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-9-ol as an oil. This oil was dissolved in a minimum amount of MeOH and HCl in ether was slowly added to afford 14 mg (26%) of precipitated **27**. LC/MS (Method 111): ELSD: 100%; UV: 100%; MH^+ 308.3. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.96 (t, J = 6,36 Hz, 3H), 1.63–1.84 (m, 2H), 2.17 (s, 3H), 2.34–2.44 (m, 1H), 2.71 (d, J = 3.42 Hz, 2H), 2.96–3.10 (m, 3H), 3.11–3.19 (m, 1H), 3.42–3.49 (m, 1H), 3.64 (d, J = 11.74 Hz, 1H), 4.07 (br s, 1H), 4.21 (br s, 1H), 6.61 (d, J = 7.34 Hz, 1H), 6.67 (d, J = 7.82 Hz, 1H), 6.99 (t, J = 7.34 Hz, 1H), 9.55 (br s, 1H), 10.93 (br s, 1H).

4.2. Experimental for receptor pharmacology

4.2.1. D_1 cAMP assay

The ability of the compounds to stimulate the D_1 receptor mediated cAMP formation in CHO cells stably expressing the human recombinant D_1 receptor was measured as follows. Cells were seeded in 96-well plates at a concentration of 11,000 cells/well 3 days prior to the experiment. On the day of the experiment the cells were washed once in preheated G buffer (1 mM $MgCl_2$, 0.9 mM $CaCl_2$, 1 mM IBMX (3-*i*-butyl-1-methylxanthine) in PBS (phosphate buffered saline)) and the assay was initiated by addition of 100 μL of test compound diluted in G buffer. The cells were incubated for 20 min at 37 °C and the reaction was stopped by the addition of 100 μL S buffer (0.1 M HCl and 0.1 mM $CaCl_2$) and the plates were placed at 4 °C for 1 h. 68 μL N buffer (0.15 M NaOH and 60 mM NaOAc) was added and the plates were shaken for 10 min. 60 μL of the reaction were transferred to cAMP FlashPlates (DuPont NEN) containing 40 μL 60 mM Sodium acetate pH 6.2 and 100 micro-L IC mix (50 mM Sodium acetate pH 6.2, 0.1% sodium azide, 12 mM $CaCl_2$, 1% BSA (bovine serum albumin) and 0.15 micro-Ci/mL ^{125}I-cAMP) were added. Following an 18 h incubation at 4 °C the plates were washed once and counted in a Wallac TriLux counter.

4.2.2. D_2 cAMP assay

The ability of the compounds to stimulate the D_2 receptor mediated inhibition of cAMP formation in CHO cells transfected with the human D_2 receptor was measure as follows. Cells were seeded in 96 well plates at a concentration of 8000 cells/well 3 days prior to the experiment. On the day of the experiment the cells were washed once in preheated G buffer (1 mM $MgCl_2$, 0.9 mM $CaCl_2$, 1 mM IBMX in PBS) and the assay was initiated by addition of 100 μL of a mixture of 10 μM forskolin and test compound in G buffer. The cells were incubated 20 min at 37 °C and the reaction was stopped by the addition of 100 μL S buffer (0.1 M HCl and 0.1 mM $CaCl_2$) and the plates were placed at 4 °C for 1 h. 68 μL N buffer (0.15 M NaOH and 60 mM Sodium acetate) were added and the plates were shaken for 10 min. 60 μL of the reaction were transferred to cAMP FlashPlates (DuPont NEN) containing 40 μL 60 mM NaOAc pH 6.2 and 100 μL IC mix (50 mM NaOAc pH 6.2, 0.1% sodium azide, 12 mM $CaCl_2$, 1% BSA and 0.15 micro-Ci/mL ^{125}I-cAMP) were added. Following an 18 h incubation at 4 °C the plates were washed once and counted in a Wallac TriLux counter.

The standard deviation of the pEC50's were below 0.27 for all compounds tested.

4.3. Experimental for in vitro stability determination

4.3.1. In vitro stability in human liver microsomes

The stability of compounds in liver microsomes is determined by the $T_{½}$ method, that is, we measure the disappearance of 1 μM drug over time by LCMS. Using 0.5 mg/mL of microsomal protein (liver microsomes from several donors pooled to obtain an average enzyme content) in a NADPH generating system (1.3 mM NADP, 3.3 mM glucose 6-phosphate and 0.4 U/mL glucose 6-phosphate dehydrogenase), 3.3 mM MgCl2, 0.1 M Potassium phosphate buffer (pH 7.4), in a total volume of 100 μL, and stopping the incubations at time points 0, 5, 15, 30 and 60 min with 1:1 v/v acetonitrile. The $T_{½}$ is scaled to the metabolic competence of a whole liver using 45 mg microsome/g liver, 20 g liver/kg and Std. weight 70 kg.

4.3.2. In vitro stability in human hepatocytes

The stability of compounds in hepatocytes is determined by the $T_{½}$ method, that is, we measure the disappearance of 1 μM drug over time by LCMS. We use pooled hepatocytes from 10 donors (male and female). Cells are thawed in 37 °C water bath, live cells counted and seeded in a total of 100 μL in Dulbecco's modified Eagle medium (high glucose) with 5 mM hepes buffer in 96 well plates. 500.000 cells/mL are used for human hepatocytes. Incubations are started after 15 min of preincubation and stopped at time points 0, 30, 60, 90 and 120 min for human hepatocytes. The $T_{½}$ is scaled to the metabolic competence of a whole liver using scaling factors are 120 million cells per gram of liver, 20 g liver per kg and standard weight of /70 kg for human,

4.4. Experimental for in vivo pharmacokinetics in rats

In vivo pharmacokinetics was studied in rats following single intravenous (0.5 mg/kg) or oral (1 mg/kg) administration of compounds. Serial blood samples were collected at various time points up to 6 h after dosing. In vivo pharmacokinetic parameters were obtained following compartmental modeling. Bioanalysis of samples were analyzed by liquid chromatography coupled to a tandem mass spectrometer (LCMS/MS, Waters QuattroMicro, Manchester, U.K.).

4.5. Experimental for X-ray determination

X-ray crystal structure determinations were performed as follows. The crystal of the compounds was cooled to 120 K using a Cryostream nitrogen gas cooler system. The data were collected on a Siemens SMART Platform diffractometer with a CCD area sensitive detector. The structures were solved by direct methods and refined by full-matrix least-squares against F^2 of all data. The hydrogen atoms in the structures could be found in the electron density difference maps. The non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were at calculated positions using a riding model with O–H = 0.84, C–H = 0.99–1.00, N–H = 0.92–0.93 Å. For all hydrogen atoms the thermal parameters were fixed [U(H) = 1.2 U for attached atom]. The Flack x-parameters are in the range 0.0(1)–0.05(1), indicating that the absolute structures are correct. Programs used for data collection, data reduction and absorption were SMART, SAINT and SADABS [cf. '*SMART* and *SAINT*, *Area Detector Control and Integration Software*', Version 5.054,Bruker Analytical X-ray Instruments Inc., Madison, USA

(1998), Sheldrick '*SADABS*, *Program for Empirical Correction of Area Detector Data*' Version 2.03, University of Göttingen, Germany (2001)]. The program SHELXTL [cf. Sheldrick '*SHELXTL*, *Structure Determination Programs*', Version 6.12, Bruker Analytical X-ray Instruments Inc., Madison, USA (2001)] was used to solve the structures and for molecular graphics.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.11.012.

References and notes

1. *Therapy of Parkinson's Disease*; Pahwa, R., Lyons, K. E., Koller, W. C., Eds., 3rd ed.; Marcel Dekker, Inc., 2004. ISBN 0-8247-5455-7.
2. Millan, M. J.; Maiofiss, L.; Cussac, D.; Audinot, V.; Boutin, Jean-A.; Newman-Tancredi, A. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 791.
3. Horn, A. S.; Tepper, P.; van der Weide, J.; Watanabe, M.; Grigoriadis, D.; Seeman, P. *Pharm. Weekbl. Sci. Ed.* **1985**, *7*, 208.
4. Scheller, D.; Ullmer, C.; Berkels, R.; Gwarek, M.; Lübbert, H. *Enaunyn Schmiedebergs Arch. Pharmacol.* **2009**, *379*, 73.
5. Perez-Lloret, S.; Rascol, O. *CNS Drugs* **2010**, *24*, 941.
6. Blagg, J.; Allerton, C. M.; Batchelor, D. V.; Baxter, A. D.; Burring, D. J.; Carr, C. L.; Cook, A. S.; Nichols, C. L.; Phipps, J.; Sanderson, V. G.; Verrier, H.; Wong, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6691.
7. Stepan, A. F.; Walker, D. P.; Bauman, J.; Price, D. A.; Baillie, T. A.; Kalgutkar, A. S.; Aleo, M. D. *Chem. Res. Toxicol.* **2011**, *24*, 1345.
8. Wager, T.; Hou, X.; Verhoest, P. R.; Villalobos, A. *ACS Chem. Neurosci.* **2010**, *1*, 435.
9. Seiler, M. P.; Markstein, R.; Walkinshaw, M. D.; Boelsterli, J. J. *Mol. Pharmacol.* **1989**, *35*, 643.
10. Nozulak, J.; Vigouret, J. M.; Jaton, A. L.; Hofmann, A.; Dravid, A. R.; Weber, H. P.; Kalkman, H. O.; Walkinshaw, M. D. *J. Med. Chem.* **1992**, *35*, 480.
11. Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727.
12. Buriks, R. S.; Lovett, E. G. *J. Org. Chem.* **1987**, *52*, 5247.
13. Malo, M.; Brive, L.; Luthman, K.; Svensson, P. *ChemMedChem* **2012**, *7*, 471.
14. Malo, M.; Brive, L.; Luthman, K.; Svensson, P. *ChemMedChem* **2012**, *7*, 483.