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ORIGINAL PAPER

Synthesis of benzo-fused spiropiperidines through a regioselective free radical-mediated cyclization as key step: a suitable alternative towards the lead σ-1 receptor ligand L-687384

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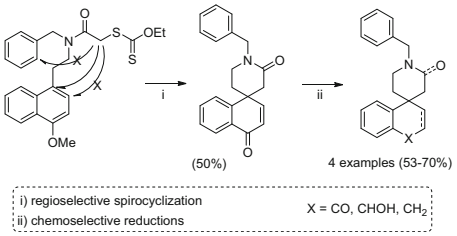
Abstract The synthesis of four novel benzo-fused spiropiperidines and the lead σ-1 receptor ligand L-687384 through a xanthate-mediated free radical spirocyclization as key step is described. Furthermore, the key free radical-based cyclization was computationally studied by means of the density functional theory approach at the UB3LYP/6-311+G(d) level to understand the regioselectivity because there are three possible closure pathways and only the benzo-fused spiropiperidines (*ipso* products) were experimentally found.

Graphical abstract



Keywords Radicals · Spirocompounds · Microwave-assisted synthesis · Density functional theory · Chemoselectivity · Reductions

Introduction

The spiropiperidine is the core of several compounds showing interesting pharmaceutical properties [1]. For example, BL-1743 (**1**) is a strong anti-influenza A virus agent interacting with the transmembrane protein M2 [2]. Moreover, various benzo-fused spiropiperidines display a wide range of outstanding pharmacological activities [3], for example, the lead σ-2 receptor ligand **2** ($IC_{50}^{[\sigma\text{-}2]} = 0.9$ nM) [4]. In the same context, the benzo-fused spiropiperidine L-687384 (**3a**) is a lead agonist of the σ-1 receptor ($IC_{50}^{[\sigma\text{-}1]} = 3.8$ nM) [5], inhibitor of the *Schistosoma mansoni* larvae [6] and inhibitor of the induced morphine cAM overdose ($IC_{50} = 14.58$ μM) [7]. Furthermore, it has been documented that various structural analogs of **3a** show strong analgesic activity [8]. Thus, based on the high interest in medicinal chemistry of benzo-fused spiropiperidine containing compounds, the objective of this work is to disclose the synthesis of the series **3a–3e** (Fig. 1).

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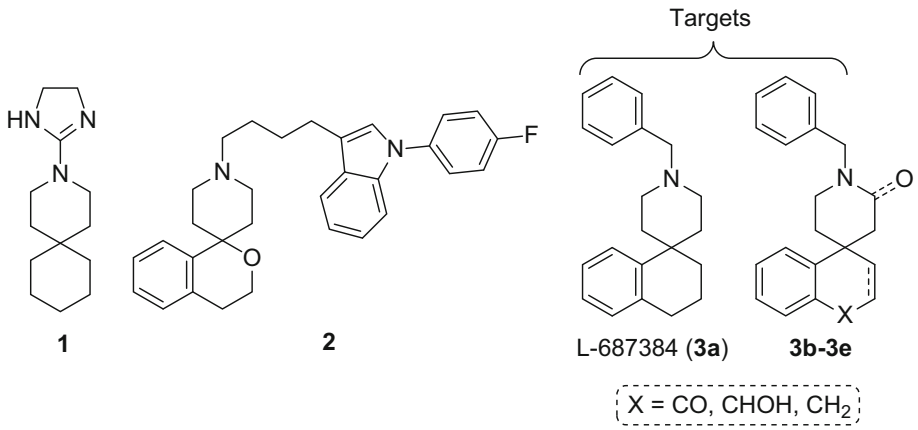


Fig. 1 Spiropiperidine **1**, benzo-fused spiropiperidine **2**, and the synthesis targets **3a–3e**

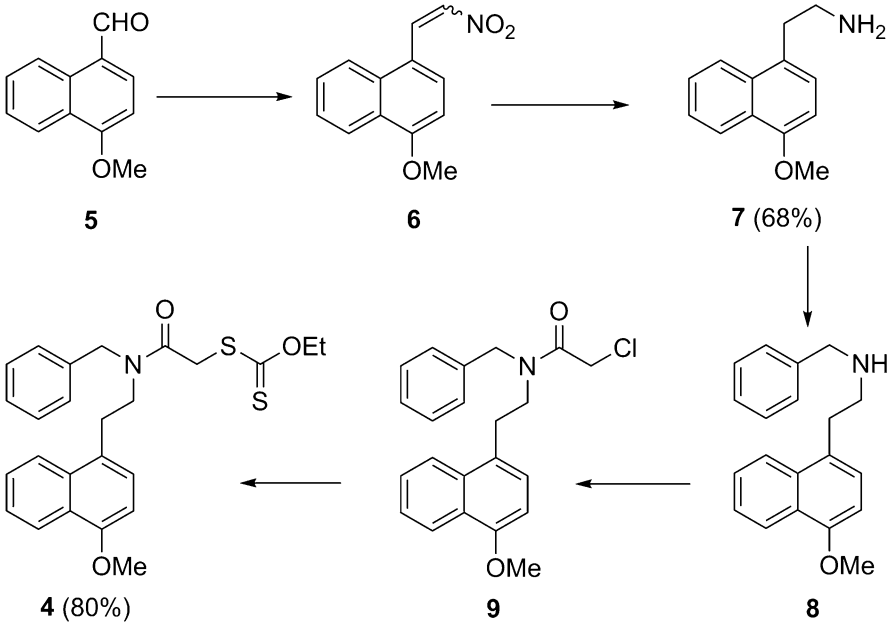
Several synthesis methods to construct the spiropiperidine framework have been reported in which the key step was either, tandem ring closing metathesis [9, 10], Mannich-type intramolecular cyclization [11], Pd-catalyzed domino Heck/cyanation [12], intramolecular Michael addition [13], tandem semi-pinacol rearrangement alkyne/aldehyde metathesis [14], or free radical-mediated spirocyclization [15, 16]. Only three reports describe the synthesis of the benzo-fused spiropiperidine L-687384 (**3a**), in which the construction of the spirocenter was the key step [5, 17, 18]. Moreover, we reported an efficient method to synthesize a set of novel spiropyrrolidinones through a xanthate-mediated free radical *ipso* cyclization in *p*-OMe-substituted phenyl-π systems including only one example in a *p*-OMe-substituted naphthyl-π system [19]. These free radical additions on aromatic systems with different stereoelectronic nature involve the use of dilauroyl peroxide (DLP) as free radical chain reaction initiator and as oxidation agent [20]. It is noteworthy that *ortho* [21–30] and *ipso* additions [15, 31–33] of free radicals to phenyl-π systems have been reported, but those to naphthyl-π systems are practically unexplored. In this context, the main hypothesis of this work is that the synthesis of L-687384 (**3a**) and the four novel benzo-fused spiropiperidines **3b–3e** could be accomplished using a strategy based on a xanthate-mediated free radical cyclization as key step.

Results and discussion

The synthesis started with the preparation of the xanthate **4**, which is the key precursor for the free radical-based cyclization. The commercially available 4-methoxynaphthaldehyde (**5**) condensed with nitromethane through a Henry reaction to give the α,β-unsaturated nitro compound **6**, which after an in situ olefin reduction gave the 4-methoxynaphthyl-1-ethanamine (**7**) yielding 68 % per two steps. Then, the latter reacted with benzaldehyde through a reductive amination to give the secondary amine **8** in quantitative yield, which was in situ N-acylated with chloroacetyl chloride to give **9**. Finally, **9** in situ undergoes a S_N2 with the potassium ethyl xanthogenate salt to afford the xanthate **4** yielding 80 % per three steps (Scheme 1).

Starting from the xanthate **4**, which is the precursor of the carbamoylmethyl radical **10**, we performed the cyclization using DLP as both, chain reaction initiator and oxidant, DCM as solvent, and microwaves as heat source to afford the benzo-fused spiropiperidine **3b** in 50 % yield. This modest conversion might be due to a regioselective cyclization just from the radical **10** because there are three possible closure pathways: *ipso* addition to the naphthyl-π system towards the benzo-fused spiropiperidine **3b** (Path *a*), *ortho* addition to the naphthyl-π system towards the naphthyl-azepinone **14** (Path *b*), and *ortho* addition to the phenyl-π system towards the *N*-(naphthylethyl)isoquinolinone **15** (Path *c*). However, the benzo-fused spiropiperidine **3b** was isolated exclusively. Based on a TLC after 30 min of reaction, we assume the formation of by-products **14** and **15** at least in traces because two small spots were visualized besides the one for the product **3b**. However, we unfortunately could not isolate them maybe due to their decomposition in either work-up or purification process. This might be attributed to the stability of the intermediates **11–13**. The most stable of these is the spiroallyl radical **11** because it has more canonic forms (5) than the cyclohexadienyl radical **13** (3) and one of them is stabilized by the OMe group. On the contrary, despite the naphthyl-type radical **12** has an equal amount of canonic forms than **11**, none of them is stabilized by the OMe group. Additionally, the regioselectivity in the cyclization process from the carbamoylmethyl radical **4** might be also attributed to ring stability factors in the corresponding final products **3b** and **14–15** because the *ipso* closure pathway *a* involves the formation of a stable six-membered ring, while *ortho* closure pathway *b* would involve the formation of a less stable

Scheme 1



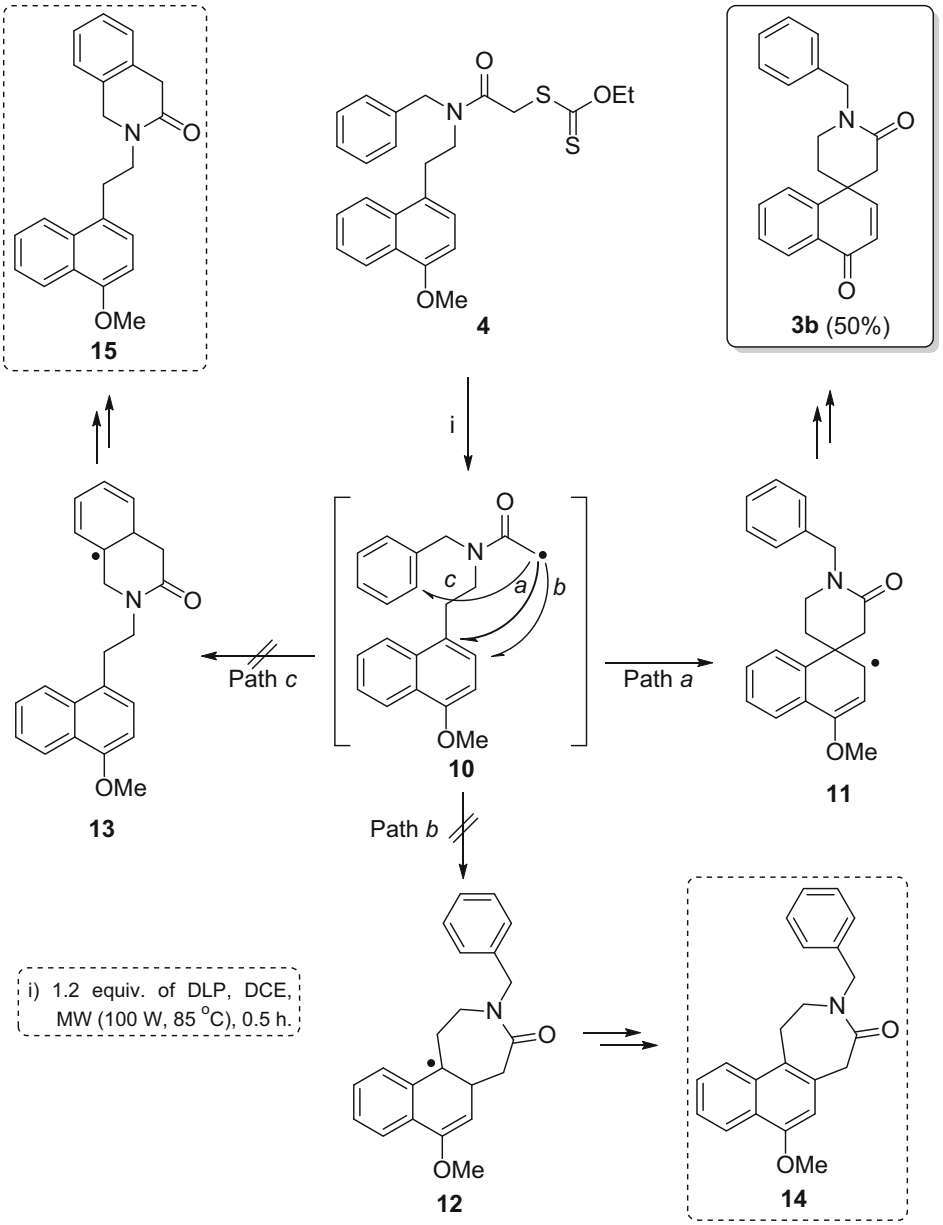
seven-membered ring. In the same context, despite pathway *c* would lead to a six-membered ring in the *N*-(naphthylethyl)isoquinolinone **15**, the high fluxionality makes it the less kinetically favored regioisomer (Scheme 2).

Thus, to test the above-mentioned hypotheses, we performed DFT-based calculations at the UB3LYP/6-311+G(d) level of theory (see the Supporting information for further details). As can be seen in Fig. 2, the pathway *a* is more kinetically favorable than pathways *b* and *c*. This reaction step presents an energy barrier of 3.7 kJ mol^{-1} lower than that of path *c* and 18.9 kJ mol^{-1} lower than that of path *b*. This means that the cyclization via the path *a* is five times faster than path *c* and one hundred times faster than path *b*. With respect to the stability of the intermediates **11–13**, it can be seen that the spiroallyl radical **11** is 13.2 kJ mol^{-1} lower than that of the naphthyl-type radical **12** and 21.5 kJ mol^{-1} lower than that of the cyclohexadienyl radical **13**. It means that the radical **11**, which conducts to the benzo-fused spiropiperidine **3b**, is formed through the most exothermic process (ca. −41.1 kJ mol^{-1}) among the three possible closure pathways (Fig. 2).

Based on these calculations, we can get more information which allows understanding the regioselectivity of the free radical cyclization. For example, despite the $TS_{[10\rightarrow13]}$ has an energy barrier of only 3.7 kJ mol^{-1} higher than that of $TS_{[10\rightarrow11]}$, the radical intermediate **13** has 21.5 kJ mol^{-1} more than the spiroallyl radical **11**. As it was mentioned above, this is due to the presence of a *p*-OMe group in the intermediate **11**, which stabilize the free radical by resonance. Thus, clearly **15**, which would come from the radical intermediate **13** should be obtained in low yields or not. Moreover, the naphthyl-azepinone **14**, which would come from the radical intermediate **12,** also should be obtained in low yields or not because the pathway *b* would involve the formation of the less kinetically favored TS. Thus, the calculations revealed that the benzo-fused spiropiperidine **3b** coming from the spiroallyl radical **11** must be the major regioisomer.

Finally, with the intention of preparing a series of novel benzo-fused spiropiperidines including the σ-1 receptor ligand L-687384, the aza-spirocompound **3b** was subjected to conventional $LiAlH_4$ reductive conditions using microwaves as heat source. Under these conditions, the two novel products **3c** and **3d** were obtained in 53 and 10 % yields. Interestingly, the major product **3c** retained the carbonyl-ketone group while both, the carbonyl-amide and the α,β-unsaturated ketone double bond were reduced. This outcome might be understood in terms of the initial chemoselective reduction of the α,β-unsaturated ketone double bond by the hydride in a 1,4-attack leading to the formation of a putative lithium oxy-aluminum enolate, which might be hydrolyzed to ketone **3c** in the work-up procedure. Also interestingly, when the reduction of the benzo-fused spiropiperidine **3b** was carried out using a mixture of $LiAlH_4$/CuI (2:4 equiv./equiv.) in THF, the analog **3e** was obtained in 53 % yield through a chemospecific reduction of the α,β-unsaturated ketone double bond. A further experiment was conducted from the compound **3b** with an excess of $LiAlH_4$ for directly accessing

Scheme 2



to the hydroxylated analog **3d** as the sole product with 68 % yield. On this way, reduction of the ketone group in compound **3c** towards the hydroxylated analog **3d** was carried out in quantitative yield. Finally, the synthesis of the bioactive benzo-fused spiropiperidine L-687384 was accomplished in a straightforward manner upon reduction of the carbonyl group in compound **3c** under Wolff-Kishner standard conditions in 70 % yield (Scheme 3).

All products were characterized using spectroscopic methods (H and C NMR, IR, and HRMS). Additionally, an adequate crystal for the X-ray diffraction analysis of the key benzo-fused spiropiperidine **3b** was obtained (CCDC 1022815; Fig. 3).

In conclusion, we herein described the synthesis of a series of benzo-fused spiropiperidines in which the spiro-center construction was the key step. This work is a contribution in the field of intramolecular free radical additions to naphthyl-π systems. It was computationally confirmed that the free radical cyclization on aromatic systems occurs through a regioselective process. This methodology can be considered as a suitable alternative for preparing compounds having the benzo-fused spiropiperidine framework, such as the observed in the lead agonist of

the σ-1 receptor L-687384 (**3a**), because nowadays, there are not many available methods for this purpose. In the same context, the prepared compounds **3b–3e** might be taken as the starting points for future SAR studies due to the high interest in medicinal chemistry of this class of spiro compounds.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on either Bruker Avance III (300 MHz) or Varian Unity (300 MHz) spectrometers. The solvent for the NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for ^{1}H NMR spectra is respect to TMS at 0.0 ppm. Internal reference for ^{13}C NMR spectra is $CDCl_3$ at 77.0 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). IR spectra were acquired on a Bruker Tensor 27 spectrophotometer. The absorbance peaks are reported in reciprocal centimeters ($\bar{\nu}$/cm^{-1}). High-resolution mass spectra were acquired on a Jeol SX-102A spectrophotometer. The ionization method was FAB+ and the spectral data were recorded via the TOF method. Microwave-assisted reactions were performed on a CEM Discover™ Synthesis Unit with a monomodal open vessel mode. Reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography purifications were performed using silica gel (230–400 mesh) and a mixture of solvents (hexanes, AcOEt, MeOH, and Et_3N) in different proportions as the mobile phase. Cold DCM was used as recrystallization media. All starting materials were purchased from Sigma-Aldrich and were used without further purification. The solvents were distilled and dried according to standard procedures.

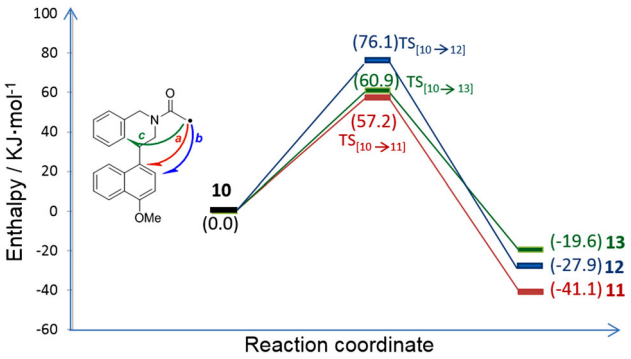
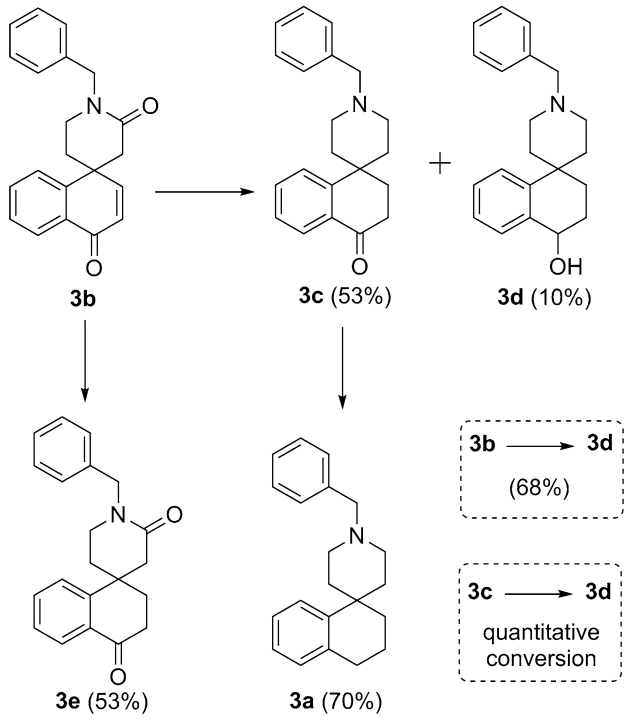


Fig. 2 Energy profile calculated at the UB3LYP/6-311+G(d) level for the cyclizations of the carbamoylmethyl radical **10**

Scheme 3



2-(4-Methoxynaphthalen-1-yl)ethan-1-amine (**7**, $C_{13}H_{14}NO$)

To a stirred solution of 6.0 g 4-methoxy-1-naphthaldehyde (**5**, 32.2 mmol, 1.0 equiv.) in 65.0 cm^3 nitromethane, 3.7 g ammonium acetate (48.3 mmol, 1.5 equiv.) was added and the resulting mixture was stirred for 3 h at 80 °C. The mixture was diluted in 100.0 cm^3 water and extracted with 100.0 cm^3 ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The crude was concentrated until dryness to give 1-methoxy-4-(2-nitrovinyl)naphthalene (**6**), which was used in the next step without further purification. Thus, a solution of **6** in 32.0 cm^3 THF was added to a stirred solution of 2.4 g $LiAlH_4$ (64.4 mmol, 2.0 equiv.) in 161.0 cm^3 THF at 0 °C and the resulting mixture was heated at reflux for 6 h. After this, 6.0 cm^3 water was added dropwise. Then, a solution of 6.0 cm^3 NaOH (4 N) was added. Finally, 19.0 cm^3 water was added to the solution and the resulting mixture was filtered through a Celite pad and the filtrate was concentrated until dryness. The new crude was purified by silica gel column chromatography (EtOAc/MeOH/Et_3N, 50:50:0.1, v/v/v) to afford 5.0 g 2-(4-methoxynaphthalen-1-yl)ethan-1-amine (**7**) (68 % per two steps) as a pale yellow oil. $R_f = 0.25$ (AcOEt/MeOH, 4:6, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 2H, NH_2), 3.04-3.18 (m, 4H, 2 CH_2), 3.99 (s, 3H, OCH_3), 6.75 (d, $J = 9.0$ Hz, 1H,

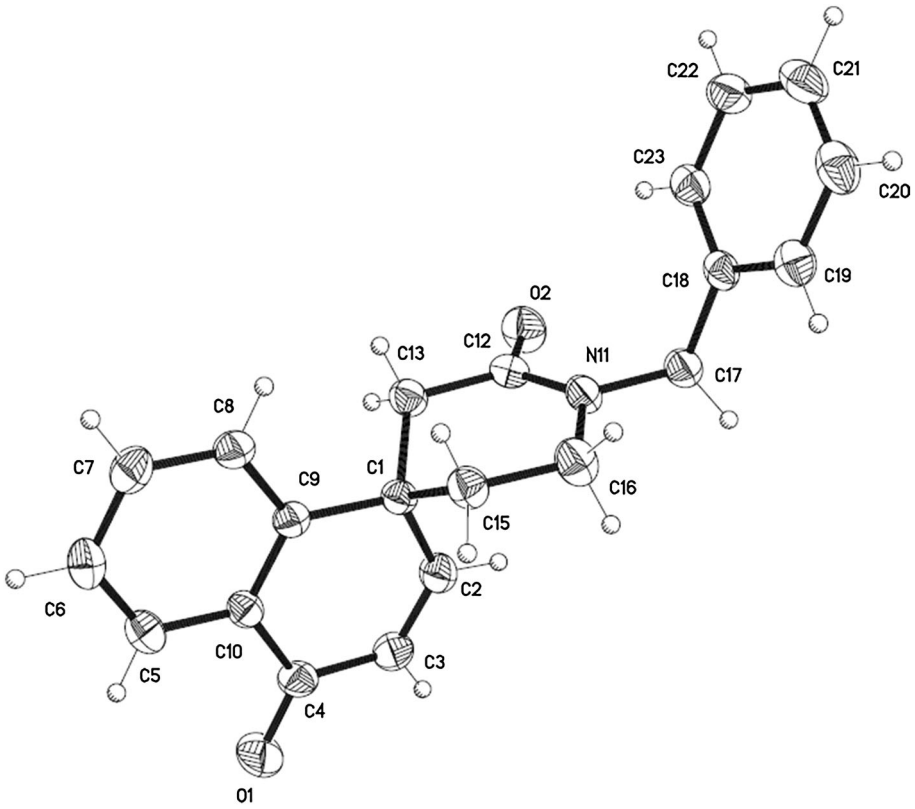


Fig. 3 ORTEP diagram for the compound **3b**

ArH), 7.25 (d, $J = 9.0$ Hz, 1H, ArH), 7.46–7.57 (m, 2H, ArH), 7.99 (d, $J = 9.0$ Hz, 1H, ArH), 8.33 (dd, $J = 1.5$, 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 36.7$, 42.8, 55.4, 103.2, 122.6, 123.5, 124.8, 125.9, 126.3, 126.4, 127.5, 132.6, 154.3 ppm; FT-IR (ATR): $\bar{\nu} = 1{,}391$, 1,586, 2,936, 3,361 cm^{-1}; HRMS: *m/z* calcd. for $C_{13}H_{15}NO^+$ ($[MH]^+$) 202.1232, found 202.1230.

S-[2-[Benzyl[2-(4-methoxynaphthalen-1-yl)ethyl]amino]-2-oxoethyl] O-ethyl carbonodithioate (**4**, $C_{25}H_{26}NO_3S_2$) To a stirred solution of 2.6 g 2-(4-methoxynaphthalen-1-yl)ethan-1-amine (**7**, 13.0 mmol, 1.0 equiv.) in 65.0 cm^3 MeOH, 2.5 cm^3 benzaldehyde (13.0 mmol, 1.0 equiv.) and 1.3 g molecular sieves (4 Å) were added and the resulting mixture was stirred for 2 h at room temperature. Then, the solution was cooled to 0 °C and 1.2 g $NaBH_4$ (32.6 mmol, 2.5 equiv.) was added. The reaction mixture was stirred for 1 h at 0 °C and then it was filtered through a Celite pad and the filtrate was concentrated until dryness. The crude was dissolved in 25.0 cm^3 AcOEt and washed with 2 × 80.0 cm^3 water. Then, the organic layer was dried over Na_2SO_4 and concentrated until dryness to afford *N*-benzyl-2-(4-methoxynaphthalen-1-yl)ethan-1-amine (**8**), which was used in the next step without further purification.

Thus, to a stirred solution of **8** in 65.0 cm^3 DCM, 1.6 g chloroacetyl chloride (14.3 mmol, 1.1 equiv.) and 1.4 g triethylamine (14.3 mmol, 1.1 equiv.) were added and the resulting mixture was stirred for 2 h at 0 °C. Then, the solvent was evaporated and the crude was dissolved in 25.0 cm^3 AcOEt and washed with 2 × 80.0 cm^3 water. Then, the organic layer was dried over Na_2SO_4 and concentrated until dryness to afford the *N*-benzyl-2-chloro-*N*-[2-(4-methoxynaphthalen-1-yl)ethyl]acetamide (**9**), which was used in the next step without further purification.

Thus, to a stirred solution of **9** in 25 cm^3 MeOH, 3.1 g potassium ethyl xanthogenate salt (19.6 mmol, 1.5 equiv.) was added and the resulting mixture was stirred for 3 h at room temperature. Then, the solvent was evaporated and the crude was dissolved in 25.0 cm^3 AcOEt and washed with 2 × 20.0 cm^3 water. Then, the organic layer was dried over Na_2SO_4 and concentrated until dryness. The new crude was purified by silica gel column chromatography (hexanes/AcOEt, 7:3, v/v) to give 4.71 g of a mixture of two rotamers (1:1) *S*-[2-[benzyl[2-(4-methoxynaphthalen-1-yl)ethyl]amino]-2-oxoethyl] *O*-ethyl carbonodithioate (**4**) (80 % per three steps) as a pale yellow oil. $R_f = 0.35$ (hexanes/AcOEt, 8:2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$–1.43 (m, 6H, 2 CH_3), 3.23-3.27 (m, 4H, 2 CH_2), 3.63–3.69 (m, 4H, 2 CH_2), 3.88 (s, 2H, CH_2), 3.98 (s, 6H, 2 OCH_3), 4.10 (s, 2H, CH_2), 4.42 (s, 4H, 2 CH_2), 4.58–4.67 (m, 4H, 2 CH_2), 6.71 (dd, $J = 3.0$, 6.0 Hz, 2H, ArH), 7.12–

7.36 (m, 10H, ArH), 7.42–7.56 (m, 4H, ArH), 7.80 (d, 2H, $J = 6.0$ Hz, ArH), 8.02 (d, 2H, $J = 6.0$ Hz, ArH), 8.26–8.32 (m, 2H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$, 30.7, 31.8, 39.4, 39.8, 48.3, 49.2, 52.9, 55.6, 70.6, 103.5, 122.6, 122.8, 123.1, 123.8, 125.1, 125.2, 125.6, 125.9, 126.1, 126.7, 126.8, 126.9, 127.0, 127.3, 127.7, 127.9, 128.4, 128.7, 129.0, 132.3, 132.8, 136.3, 137.1, 154.6, 155.0, 167.0, 213.9, 214.0 ppm; FT-IR (ATR): $\bar{\nu} = 1{,}055$, 1,225, 1,586, 1,647, 2,936 cm^{-1}; HRMS: *m/z* calcd. for $C_{25}H_{27}NO_3S_2^+$ ($[MH]^+$) 454.1511, found 454.1508.

1′-Benzyl-4H-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3b**, $C_{21}H_{19}NO_2$)

To a stirred solution of 2.1 g *S*-[2-[benzyl[2-(4-methoxynaphthalen-1-yl)ethyl]amino]-2-oxoethyl] *O*-ethyl carbonodithioate (**4**, 4.7 mmol, 1.0 equiv.) in 23.0 cm^3 1,2-DCE, 2.24 g DLP (5.6 mmol, 1.2 equiv.) was added in six cycles (0.2 equiv./cycle) of MW heating conditions (100 W, 85 °C, 5 min) and then the solvent was removed until dryness. The crude was purified by silica gel column chromatography (AcOEt/hexanes, 1:1, v/v) to afford 744.8 mg 1′-benzyl-4*H*-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3b**) (50 %) as colorless crystals (CCDC 1022815). $R_f = 0.33$ (hexanes/AcOEt, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.84$–1.92 (m, 1H, 1 H of CH_2), 2.23-2.33 (m, 1H, 1 H of CH_2), 2.61 (dd, $J = 2.4$, 17.4 Hz, 1H, 1 H of CH_2), 3.05 (d, $J = 17.4$ Hz, 1H, 1 H of CH_2), 3.39–3.43 (m, 2H, NCH_2), 4.73 (dd Δ_{AB}, $J = 14.4$, 32.7 Hz, 2H, NCH_2), 6.47 (d, $J = 10.5$ Hz, 1H, CH), 6.99 (d, $J = 10.2$ Hz, 1H, CH), 7.29 (m, 7H, ArH), 7.54–7.60 (m, 1H, ArH), 8.19 (dd, $J = 1.5$, 7.9 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 35.5$, 39.5, 42.8, 44.3, 50.3, 125.8, 127.3, 127.7, 127.9, 128.5, 128.9, 129.0, 131.0, 133.2, 136.7, 146.3, 150.1, 167.6, 183.9 ppm; FT-IR (ATR): $\bar{\nu} = 1{,}225$, 1,596, 1,661, 2,966 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{20}NO_2^+$ ($[MH]^+$) 318.1494, found 318.1497.

*1′-Benzyl-2,3-dihydro-4H-spiro[naphthalene-1,4′-piperidin]-4-one (**3c**, $C_{21}H_{22}NO$) and 1′-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4′-piperidin]-4-ol* (**3d**, $C_{21}H_{24}NO$)

Procedure A To a stirred solution of 150.0 mg 1′-benzyl-4*H*-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3b**, 0.47 mmol, 1.0 equiv.) in 2.0 cm^3 THF at 0 °C, a solution of 24.0 mg $LiAlH_4$ (0.94 mmol, 2.0 equiv.) in 5.0 cm^3 THF was added. The resulting mixture was MW heated (100 W, 60 °C) for 10 min. Then, 0.6 cm^3 water and 0.6 cm^3 NaOH (4 N) were sequentially added and the new solution was filtered through a Celite pad and concentrated until dryness. The crude was purified by silica gel column chromatography (hexanes/AcOEt/Et_3N, 50:50:0.1, *v/v/v*) to afford 76.0 mg 1′-benzyl-2,3-dihydro-4*H*-spiro[naphthalene-1,4′-piperidin]-4-one (**3c**) (53 %) and 14.4 mg 1′-benzyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4′-piperidin]-4-ol (**3d**) (10 %) as a mixture of the reduction reaction.

Procedure B To a stirred solution of 150.0 mg 1′-benzyl-4*H*-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3b**, 0.47 mmol, 1.0 equiv.) in 2.0 cm^3 THF at 0 °C, a solution of 24.0 mg $LiAlH_4$ (0.94 mmol, 2.0 equiv.) in 5.0 cm^3 THF was added. The resulting mixture was MW heated (100 W, 60 °C) for 10 min. Then, a second solution of 12.0 mg $LiAlH_4$ (0.47 mmol, 1.0 equiv.) in 2.0 cm^3 THF was added at 0 °C and the resulting mixture was MW heated (100 W, 60 °C) for 10 min. Then, 0.6 cm^3 water and 0.6 cm^3 NaOH (4 N) were sequentially added and the new solution was filtered through a Celite pad and concentrated until dryness. The crude was purified by silica gel column chromatography (hexanes/AcOEt/Et_3N, 20:80:0.1, v/v/v) to afford 98.2 mg 1′-benzyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4′-piperidin]-4-ol (**3d**) (68 %).

Procedure C To a stirred solution of 50.0 mg 1′-benzyl-2,3-dihydro-4*H*-spiro[naphthalene-1,4′-piperidin]-4-one (**3c**, 0.16 mmol, 1.0 equiv.) in 2.0 cm^3 THF at 0 °C, a solution of 6.0 mg $LiAlH_4$ (0.24 mmol, 1.5 equiv.) in 1.0 cm^3 THF was added. The resulting mixture was MW heated (100 W, 60 °C) for 10 min. Then, 0.3 cm^3 water and 0.3 cm^3 NaOH (4 N) were sequentially added and the new solution was filtered through a Celite pad and concentrated until dryness. The crude was purified by silica gel column chromatography (hexanes/AcOEt/Et_3N, 20:80:0.1, *v/v/v*) to afford 49.7 mg 1′-benzyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4′-piperidin]-4-ol (**3d**) (quantitative yield).

1′-Benzyl-2,3-dihydro-4H-spiro[naphthalene-1,4′-piperidin]-4-one (**3c**, $C_{21}H_{22}NO$)

Pale yellow oil; $R_f = 0.57$ (hexanes/AcOEt, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.67$–1.72 (m, 2H, CH_2), 2.13–2.23 (m, 4H, 2 CH_2), 2.31–2.39 (m, 2H, CH_2), 2.62–2.67 (m, 2H, NCH_2), 2.77–2.87 (m, 2H, NCH_2), 3.60 (s, 2H, NCH_2), 7.23–7.38 (m, 6H, ArH), 7.52–7.61 (m, 2H, ArH), 8.02 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.3$, 33.8, 35.4, 36.0, 49.4, 63.4, 125.5, 126.5, 127.4, 128.3, 129.3, 132.0, 134.1, 138.2, 151.8, 198.4 ppm; FT-IR (ATR): $\bar{\nu} = 1{,}597$, 1,685, 2,806, 2,923 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{23}NO^+$ ($[MH]^+$) 306.1858, found 306.1864.

1′-Benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4′-piperidin]-4-ol (**3d**, $C_{21}H_{24}NO$)

Pale yellow oil; $R_f = 0.28$ (hexanes/AcOEt, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$–1.63 (m, 2H, CH_2), 1.74–2.37 (m, 8H, 4 CH_2), 2.74–2.81 (m, 2H, CH_2), 3.59 (s, 2H, NCH_2), 4.72 (t, $J = 6.0$ Hz, 1H, CH), 7.17–7.44 (m, 8H, ArH), 7.53 (dd, $J = 3.0$, 9.0 Hz, 1H, ArH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 28.0, 35.5, 37.8, 38.3, 49.5, 49.6, 63.6, 68.8, 126.2, 127.0, 127.1, 128.3, 129.3, 138.3 139.0, 145.2 ppm; FT-IR (ATR): $\bar{\nu}$ = 1,451, 1,733, 2,927, 3,027, 3,359 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{25}NO^+$ ($[MH]^+$) 308.2014, found 308.2004.

1′-Benzyl-2,3-dihydro-4H-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3e**, $C_{21}H_{20}NO_2$)

To a stirred solution of 30.0 mg 1′-benzyl-4*H*-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3b**, 0.09 mmol, 4.0 equiv.) in 1.5 cm^3 THF at 0 °C, a solution of 7.0 mg $LiAlH_4$ (0.185 mmol, 2.0 equiv.) and 71.0 mg CuI (0.378 mmol, 4.0 equiv.) in 1.0 cm^3 THF was added. The resulting mixture was stirred for 30 min. Then, 0.6 cm^3 water and 0.6 cm^3 NaOH (4 N) were sequentially added and the new solution was filtered through a Celite pad and concentrated until dryness. The crude was purified by silica gel column chromatography (hexanes/AcOEt, 1/1, v/v) to give 62.6 mg 1′-benzyl-2,3-dihydro-4*H*-spiro[naphthalene-1,4′-piperidine]-2′,4-dione (**3e**) (53 %) as a colorless oil. R_f = 0.45 (hexanes/AcOEt, 3:2, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–2.01 (m, 2H, CH_2), 2.08–2.23 (m, 2H, CH_2), 2.62 (d, J = 18.0 Hz, 1H, 1 H of CH_2), 2.70–2.75 (m, 2H, CH_2), 2.84 (d, J = 18.0 Hz, 1H, 1 H of CH_2), 3.02–3.11 (m, 1H, 1 H of CH_2), 3.20–3.28 (m, 1H, 1 H of CH_2), 4.66 (dd, Δ_{AB}, J = 12, 36 Hz, 2H, NCH_2), 7.17 (d, J = 9.0 Hz, 1H, ArH), 7.26–7.37 (m, 6H, ArH), 7.41–7.47 (m, 1H, ArH), 8.02 (dd, J = 1.5, 7.8 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.3, 33.4, 34.0, 36.8, 43.8, 43.9, 50.2, 125.6, 127.5, 127.7, 128.1, 128.4, 128.7, 131.5, 134.0, 136.8, 147.7, 168.6, 197.0 ppm; FT-IR (ATR): $\bar{\nu}$ = 1,639, 1,682, 2,926 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{21}NO_2^+$ ($[MH]^+$) 320.1651, found 320.1654.

1′-Benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4′-piperidine] (L-687384, **3a**, $C_{21}H_{25}N$)

To a solution of 30.0 mg 1′-benzyl-2,3-dihydro-4*H*-spiro[naphthalene-1,4′-piperidin]-4-one (**3c**, 0.09 mmol, 1.0 equiv.) in 2.0 cm^3 diethyleneglycol/EtOH (1/1, v/v), 1.0 cm^3 hydrazine hydrate (0.98 mmol, 10.0 equiv.) was added and the mixture was heated at 150 °C for 1 h. Then, 28.0 mg KOH (0.49 mmol, 5.5 equiv.) was carefully added and the new mixture was heated at 220 °C for 3 h. After this, the temperature was decreased to rt. Then, 50.0 cm^3 AcOEt and 30.0 cm^3 water were added. Then, the organic layer was separated and the aqueous phase was extracted with 2 × 30.0 cm^3 AcOEt. The organic layers were combined, washed with excess of brine and dried over Na_2SO_4. The solvent was evaporated until dryness and the crude was immediately purified by silica gel column chromatography (hexanes/AcOEt/Et_3N, 80:20:0.1, *v/v/v*) to afford 18.3 mg 1′-benzyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4′-piperidine] L-687384 (**3a**) (70 %) as a colorless oil. R_f = 0.66 (hexanes/AcOEt, 4:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.61 (m, 2H, CH_2), 1.70-1-77 (m, 2H, CH_2), 1.81–1.86 (m, 2H, CH_2), 2.10–2.20 (m, 2H, CH_2), 2.26–2.35 (m, 2H, CH_2), 2.74–2.78 (m, 4H, 2 CH_2), 3.59 (s, 2H, NCH_2), 7.03–7.40 (m, 8H, ArH), 7.52 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 30.9, 31.0, 35.4, 38.5, 49.6, 63.6, 125.4, 125.9, 127.0, 127.1, 128.2, 129.0, 129.3, 137.4, 138.6, 145.4 ppm (NMR data are consistent with the literature [5]); FT-IR (ATR): $\bar{\nu}$ = 1,447, 1,490, 2,803, 2,926 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{25}N^+$ ($[MH]^+$) 292.2065, found 292.2070.

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