Medicinal Chemistry Research (2022) 31:1209–1223
https://doi.org/10.1007/s00044-022-02909-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Discovery of novel, selective, functionalized 5-(2-(5-arylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-γ-butyrolactone sigma-2 ligands

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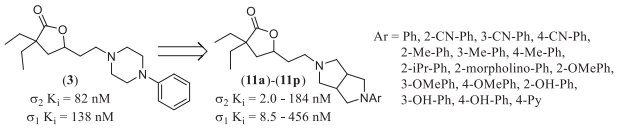
Received: 14 January 2022 / Accepted: 7 May 2022 / Published online: 18 May 2022

Abstract

The sigma-2 (σ_2) receptor was recently identified as the Transmembrane Protein 97 (TMEM97, also known as MAC30 (Meningioma-associated protein)). This protein has been linked to diseases and conditions such as Niemann-Pick disease, schizophrenia, neuropathic pain, traumatic brain injury, cancer, drug addiction, and Alzheimer's disease. The therapeutic utility of σ_2 ligands is under investigation in numerous laboratories and on-going clinical trials. Herein, we report the identification of a series of novel 5-(2-(5-arylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-γ-butyrolactone and their evaluation using in vitro σ_2 and sigma-1 (σ_1) assays to determine their σ_1/σ_2 selectivity profiles, as well as a series of in vitro ADME assays.

Graphical abstract



Keywords Sigma-2 · Sigma-1 · Sigma receptor · γ-butyrolactone

Introduction

The observation by W. R. Martin et. al. that Morphine, ketocyclazocine, and SKF-100047 produced different responses in chronic spinal dogs led them to propose that each compound was interacting with a different pharmacological target. They designated the three targets the μ-opioid receptor (morphine type, MOR), the κ-opioid receptor (ketocyclazocine type, KOR), and the σ-opioid receptor (SKF-100047 like) [1]. It was eventually determined that two enantiomers of SKF-100047 engage different targets. While (-)-SKF-100047 interacts with MOR and KOR to elicit an opioid-type response, (+)-SKF-100047 produces a non-opioid response through the sigma receptor (σR) [2, 3]. There are two sub-types of this receptor, designated sigma-1 (σ_1) and sigma-2 (σ_2) [4]. Crystal structure for both have been reported [5, 6], but date no natural ligands have been identified.

It was recently demonstrated that σ_2 is identical to the protein designated Transmembrane Protein 97 (TMEM97, also known as MAC30 (Meningioma-associated protein)) [7]. This protein is present in the endoplasmic reticulum (ER) and lysosomes where it binds to cholesterol [8] and has been linked to Niemann-Pick disease [9], schizophrenia

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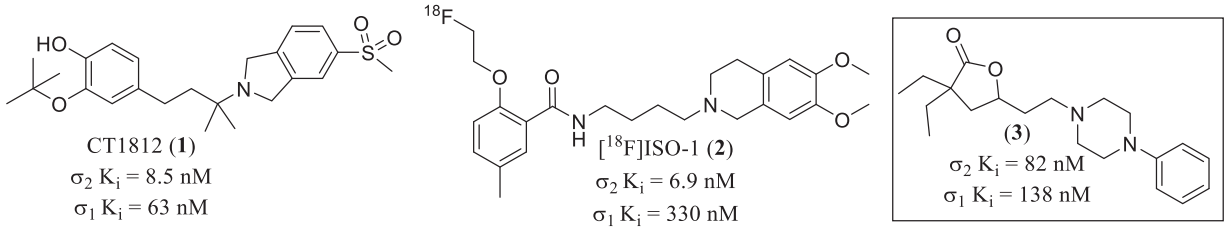


Fig. 1 Structures of CT1812 (**1**), [^{18}F]ISO-1 (**2**), and (**3**)

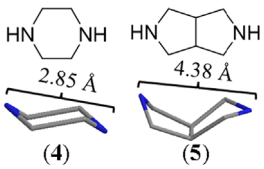


Fig. 2 Piperazine (**4**) and octahydropyrrolo[3,4-c]pyrrole (**5**) shape and size comparison

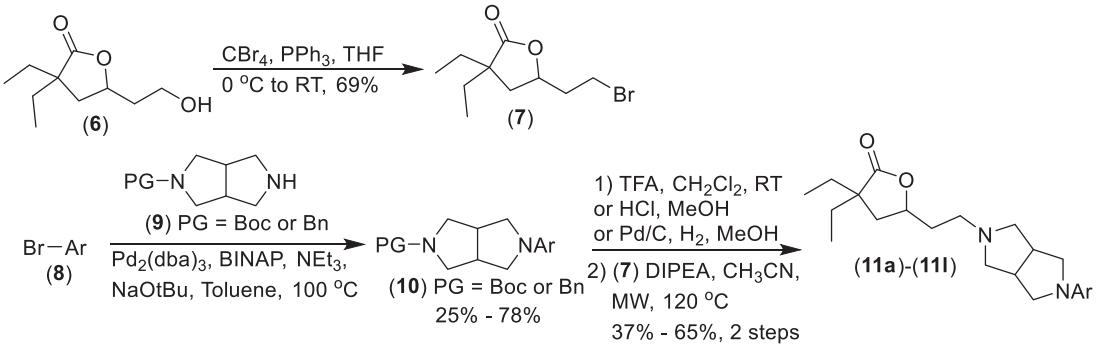
[10], neuropathic pain [11, 12], traumatic brain injury [13], cancer [14, 15], drug addiction [16], and Alzheimer's disease [17, 18]. The recent disclosure that σ_2 ligands can prevent the synaptotoxic impact of Aβ oligomers (AβO, oligomers of Aβ42) on neurons by blocking their interactions with neuronal receptors suggests that σ_2 may be a viable therapeutic target for the treatment of Alzheimer's disease [19]. The clinical candidate CT1812 (**1**, Fig. 1), a high affinity σ_2 ligand ($K_i = 8.5$ nM) that is moderately selectivity for σ_2 over σ_1 (σ_1 $K_i = 63$ nM) and has demonstrated efficacy in the hAPP Swe/Ldn mouse model of Alzheimer's disease, is currently undergoing phase 2 trials and will test this possibility [20]. Separately, the utility of this target in the diagnosis and treatment of breast cancer is currently under clinical investigation using [^{18}F]ISO-1 (**2**, Fig. 1), a radioligand with high σ_2 affinity (σ_2 $K_i = 6.9$ nM). This compound displayed a high level of σ_1/σ_2 selectivity (σ_1 $K_i = 330$ nM, $\sigma_1/\sigma_2 = 47.8$) [21]. Other σ_2 ligands have also produced positive results in animal models of pain [11, 22], depression, anxiety, [23], and drug addiction [16].

The possible utility of σ_2 ligands in numerous disease states prompted us to launch a program focused on the identification of novel σ_2 ligands. We recently reported a series of functionalized γ-butyrolactone σ_2 ligands typified by (**3**, Fig. 1). This compound demonstrated moderate σ_2 affinity ($K_i = 82$ nM) as well as affinity for the related protein σ_1 (K_i = 138 nM) [24]. As part of an effort to expand this series of novel σ_2 ligands, we opted to explore potential piperazine bioisosteres. We specifically focused on replacing the piperazine ring (**4**) with a octahydropyrrolo [3,4-c]pyrrole moiety (**5**) [25]. As noted in Fig. 2, these ring systems are similar in that they are both diamines, but their 3-dimensional shapes and the distance between the amines of each ring are substantially different. While the piperazine ring (**4**) exists in a standard chair configuration and has a nitrogen/nitrogen interatomic distance of 2.85 Å, the octahydropyrrolo[3,4-c]pyrrole ring system (**5**) exists in a distorted chair configuration and has a much larger nitrogen/nitrogen interatomic distance (4.38 Å). In addition, while the piperazine (**4**) nitrogen loan pairs of electrons are oriented parallel to each other and close enough to interact through space, this is not the case with the octahydropyrrolo [3,4-c]pyrrole ring system (**5**). The loan pairs of electrons in the later ring system are oriented away from each other and farther apart, which limits through space interactions. We hypothesized that these differences could lead to altered σ_2 affinity and selectivity for σ_2 over σ_1. The synthesis, characterization, and evaluation of a series of 5-(2-(5-arylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-γ-butyrolactone as potential selective σ_2 ligands will be presented.

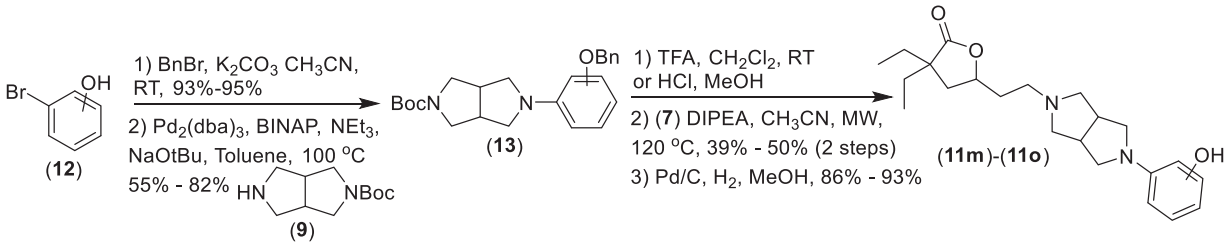
Results and discussion

Synthesis of target compounds is described in Schemes 1–3. The synthesis of (**11a**)–(**11l**) (Scheme 1) begins with the known alcohol (**6**) [24] which was Scheme 1: Synthesis of (11a)–(11l) converted to the corresponding bromide (**7**) with CBr_4 and PPh_3 in THF. Separately, aryl bromide (**8**) was reacted with Boc- or benzyl protect octahydropyrrolo [3,4-c]pyrrole (**9**) under Buchwald conditions to provide the protected aryl octahydropyrrolo[3,4-c]pyrrole (**10**). Deprotection of (**10**) either under acidic conditions (TFA/CH_2Cl_2 or HCl/MeOH) or via hydrogenation provided the free amine which was then reacted with (**7**) under basic conditions and with microwave heating to provide final target compounds (**11a**)–(**11l**).

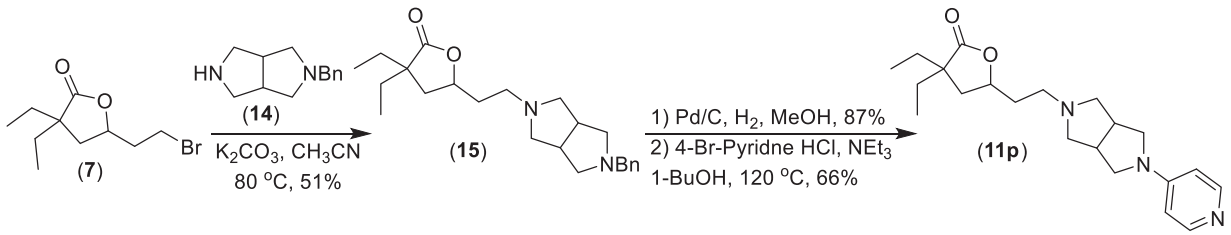
The three phenolic targets, (**11m**)–(**11o**), were prepared according to the methods described in Scheme 2. Bromophenol (**12**) was initially converted to the benzyl ether under basic conditions, and the resulting product was reacted with Boc-protect octahydropyrrolo[3,4-c]pyrrole (**9**) under Buchwald conditions to provide aryl octahydropyrrolo[3,4-c]pyrrole (**13**). Removal of the Boc-group under acidic conditions (TFA/CH_2Cl_2 or HCl/MeOH), provided the corresponding free amine which was reacted with (**7**) under basic condition and then subjected to Pd/C catalyzed hydrogenation to provide target compounds (**11m**)–(**11o**).



Scheme 1 Synthesis of (**11a**)–(**11l**)



Scheme 2 Synthesis of (**11m**)–(**11o**)



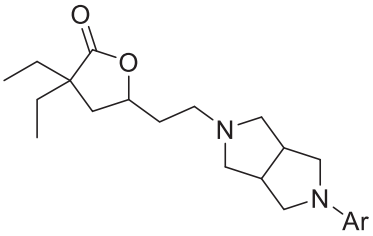
Scheme 3 Synthesis of (**11p**)

The pyridine analog (**11p**) was prepared according to the method of Scheme 3. Bromide (**7**) was reacted with benzyl protected octahydropyrrolo[3,4-c]pyrrole (**14**) under basic conditions to provide (**15**). Removal of the benzyl protecting group via hydrogenation provided the free amine, which was then reacted with 4-Br-pyridine HCl under basic conditions to provide the target compound (**11p**).

Table 1 describe the in vitro binding (K_i at σ_1 and σ_2), physicochemical properties (MW, TPSA, LogP), solubility, and CYP450 activity (3A4, 2D6, 2C9) of (**11a**)–(**11p**). All of the compounds are consistent with Lipinski's rule of 5 (MW, cLogP) and have acceptable water solubility (60–200 µM). In addition, TPSA and cLogP of the compounds are in a range that is indicative of BBB penetration (TPSA < 90, cLogP = 2–4) [26] except for (**11h**) whose cLog is outside of this range (cLogP = 4.8).

The structure activity analysis of this series begins with a comparison of the piperazine parent compound (**3**) with the corresponding octahydropyrrolo[3,4-c]pyrrole analog (**11a**). This biosiosteric replacement led to a >20-fold increase in σ_2 affinity (**11a** σ_2 $K_i = 3.5$ nM) and a smaller increase in σ_1 affinity (**11a** σ_1 $K_i = 31$ nM, 8.9-fold selectivity). Incorporation of a cyano substituent in the 2-, 3-, or 4-positions (**11b**-**11d**) produced compounds with similar σ_2 affinity (σ_2 $K_i = 6.8$, 7.0, and 9.6 nM respectively), but σ_1 affinity also increased (σ_1 $K_i = 20$, 22, and 22 nM respectively) and selectivity decreased to 3.1–2.3-fold. Replacing the cyano substituents with a CH_3 (**11e**-**11g**) once again produced compounds with high affinity for σ_2 ($K_i = 2.4$, 3.7, and 8.3 nM respectively), but selectivity over σ_1 diverged. While the 2-CH_3 analog (**11e**) exhibit low selectivity for σ_2 over σ_1 (σ_1 $K_i = 8.5$ nM, 3.5-fold selectivity), the 3-CH_3 analog (**11f**) and 4-CH_3 analog (**11g**) were substantially more selective. In each case, >10-fold selectivity for σ_2 over σ_1 was observed (**11f** σ_1 $K_i = 39$ nM, **11g** σ_1 $K_i = 86$ nM). Interestingly, increasing the size of the substituent in the 2-position by replacing the CH_3 with an isopropyl group (**11h**) led to increased σ_2 selectivity. Binding affinity at σ_2

Table 1 In vitro screening and physicochemical properties data for (**11a**)–(**11p**)



Entry	Ar	MW	TPSA	cLogP	σ_2 K_i (nM)	σ_1	σ_1/σ_2	Sol μM	CYP2C9 IC_{50} (nM)	CYP2D6	CYP3A4
3[a]	Ph	330	33	3.5	82	138	1.7	200	10000	10000	10000
11a	Ph	356	33	3.7	3.5	31	8.9	200	10000	8020	7540
11b	2-CN-Ph	381	57	3.4	6.8	20	2.9	197	10000	1850	1270
11c	3-CN-Ph	381	57	3.4	7.0	22	3.1	178	10000	3780	2540
11d	4-CN-Ph	381	57	3.4	9.6	22	2.3	151	10000	10000	2290
11e	2-Me-Ph	371	33	3.9	2.4	8.5	3.5	177	10000	1020	4420
11f	3-Me-Ph	371	33	3.9	3.7	39	10.5	194	10000	5020	3480
11g	4-Me-Ph	371	33	3.9	8.3	86	10.4	177	10000	6970	1530
11h	2-iPr-Ph	398	33	4.8	2.0	31.6	15.8	63	10000	300	974
11i	2-morpholino-Ph	441	45	3.1	6.3	47	7.5	121	10000	395	1000
11j	2-OMePh	386	42	3.6	6.5	261	40.2	191	10000	947	2030
11k	3-OMePh	386	42	3.6	25	48	1.9	200	10000	10000	7940
11l	4-OMePh	386	42	3.6	22	61	2.8	190	10000	10000	2060
11m	2-OH-Ph	372	53	3.3	11	98	8.9	154	10000	900	1760
11n	3-OH-Ph	372	53	3.3	36	58	1.6	170	10000	9870	4450
11o	4-OH-Ph	372	53	3.3	184	456	2.5	177	10000	5560	500
11p	4-Py	357	46	2.4	29	171	5.9	200	10000	7570	3040

[a]Piperazine analog

was maintained ($K_i = 2.0$ nM), but σ_1 potency decreased by >3-fold (σ_1 $K_i = 31.6$ nM) in comparison to the 2-CH_3 (**11e**) analog and selectivity increased (15.8-fold). Incorporation of a morpholine ring in the 2-position (**11i**) also provided a high affinity σ_2 ligand ($K_i = 6.3$ nM), and σ_1 potency decreased ($K_i = 47$ nM).

Incorporation of a methoxy (**11j**-**11l**) or a hydroxy (**11m**-**11o**) moiety on the benzene ring led to divergent results. Lower σ_2 affinity was observed when a methoxy moiety was placed in the 3- or 4-positions (**11k**, **11l**, σ_2 $K_i = 25$ and 22 nM respectively) and selectivity over σ_1 was low (1.9-fold and 2.8-fold). The 2-OMe analog (**11j**), on the other hand, remained a single digit nM ligand for σ_2 ($K_i =$ 6.5 nM), but σ_1 affinity drop significantly ($K_i = 261$ nM) and as a result, this compound is the most selective in this set (>40-fold). The 3-OH (**11n**) and 4-OH (**11o**) analogs had lower σ_2 affinity (K_i = 36, 184 nM) and were less selective for σ_2 over σ_1 (1.6-fold, 2.5-fold) than the 2-OH analog (**12m**, σ_2 $K_i = 11$ nM, σ_1 $K_i = 98$ nM). Lastly, the 4-pyridine analog (**11p**) was ~8-fold less potent at σ_2 ($K_i =$ 29 nM) than the corresponding phenyl analog (**11a**) and less selective for σ_2 over σ_1 (σ_1 $K_i = 171$ nM, 5.9-fold selectivity).

An assessment of the binding interactions that support σ_2 binding of our compounds was facilitated by the availability of a crystal structure of σ_2 [6]. Docking of (**3**) in the σ_2 binding site identified in these crystal structures (Fig. 3, left) suggests that this compound forms multiple, significant interaction with the surrounding amino acids. Specifically, our analysis indicates the formation of an ionic interaction between Asp^{29} and the aliphatic piperazine nitrogen of (**3**), a π-cation interaction between Tyr^{147} and the same piperazine nitrogen, and a π-π interaction between Phe^{66} and the benzene ring of (**3**). Similar interactions were observed when (**11a**) was docked into the same model (Fig. 3 center), but in this case, the increase size of the octahydropyrrolo[3,4-c]pyrrole moiety allows the benzene ring of (**11a**) to form an additional π-π interaction with Tyr^{147}. This binding interaction is not available to (**3**) and may explain the 10-fold increase in activity observed when the piperazine of (**3**) is replaced with an octahydropyrrolo[3,4-c]pyrrole in (**11a**).

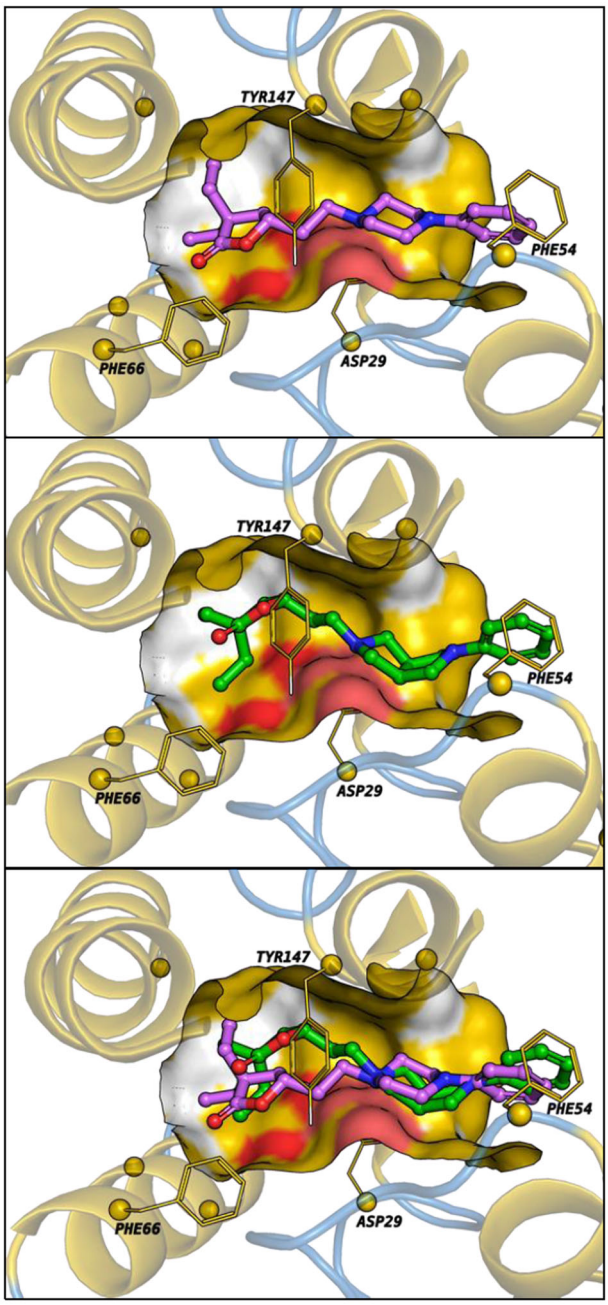


Fig. 3 In silico model of (**3**) and (**11a**) in binding site identified in crystal structure of σ_2 (PDB: 7M96) [6]. Top: (**3**) in binding pocket. Middle (**11a**) in binding pocket. Bottom: Overlay of (**3**) and (**11a**) in binding pocket

We also assessed our compounds' ability to inhibit the key metabolic enzymes CYP2C9, CYP2D6, and CYP3A4. Inhibition of these enzymes can lead to drug/drug interactions that create significant risks to patients [27]. All of the compounds described had little affinity for CYP2C9 ($IC_{50} > 10{,}000$ nM), but there was a clear SAR present with respect of CYP2D6 and CYP3A4. While none of the compounds were strong inhibitors of CYP2D6, analogs with substituents in the 2-position (**11b**, **11e**, **11h-11j**, and **11m**) were notably more potent inhibitors of this enzyme (CYP2D6 $IC_{50} =$ 300–1,850 nM) than the remaining analogs (CYP2D6 $IC_{50} =$ 3,780 to 10,000 nM). Similarly, moderate to weak inhibition of CYP3A4 was observed (CYP3A4 $IC_{50} = 500$ to 7940 nM). In this instance, however, compounds containing a substituent in either the 2-position or 4-position where more potent CYP3A4 inhibitor than the corresponding 3-position analogs. The 2-OMe analog (**11j**, CYP3A4 $IC_{50} = 2{,}030$ nM) and 4-OMe analog (**11l**, CYP3A4 $IC_{50} = 2{,}060$), for example, were both more potent CYP3A4 inhibitors than the corresponding 3-OMe analog (**11k**, CYP3A4 $IC_{50} = 7940$ nM). The 2-Me analog (**12e**, CYP3A4 $IC_{50} = 4{,}420$ nM) is a notable exception to this trend, as it has CYP3A4 potency similar to that observed with the 3-Me analog (**11f**, CYP3A4 $IC_{50} = 3{,}480$ nM). while the 4-Me analog (**11g**, CYP3A4 $IC_{50} = 1{,}530$ nM) is a more potent CYP3A4 inhibitor.

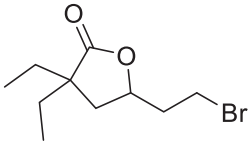
Conclusion

In summary, we have demonstrated that octahydropyrrolo [3,4-c]pyrrole is a viable bioisosteric replacement for the piperazine ring in our functionalized γ-butyrolactone series of σ_2 ligands. This change produces a significant increase in σ_2 affinity and led to the identification of compounds with up to 40-fold σ_1/σ_2 selectivity (**11j**, σ_2 $K_i = 6.5$ nM, σ_1 $K_i =$ 261 nM). All of the compounds examined demonstrated adequate to excellent aqueous solubility (60–200 μM), and physicochemical properties (MW, TPSA, cLogP) within drug-like space. Future studies will be focused on determining mouse liver microsomal stability of the compounds described and related analogs in an effort to identify highly potent, selective, novel σ_2 binder that are suitable for in vivo pharmacokinetic and efficacy studies.

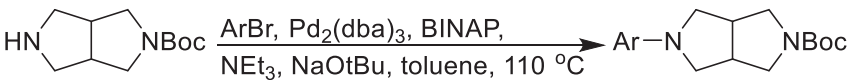
Experimental methods and materials

Reagents were purchased from Fisher Scientific, VWR International, Sigma Aldrich, and Combi-Blocks, Inc. Chromatographic purification of compounds (normal phase and reverse phase) was carried out on a Teledyne Isco Combiflash RF system. ^{1}H-NMR and ^{13}C spectra were obtained on a Bruker 400-MHz NMR. Chemical shift values (δ values) were reported in ppm relative to TMS. For multiplicity, s = singlet, d = doublet, t = triplet, m = multiplet. Purity (%) and mass spectral data were determined with a Waters Agilent 1200 HPLC/MS (Zorbax SB-C18, 2.1 × 30 mm, 3.5 μm, 100% water/0.1% formic acid to 100% acetonitrile/0.1% formic acid over 4.0 min, 1.0 mL/min.) with a diode array detector from 210–400 nm and Agilent 6130 quadrupole MS. All compounds were purified to 95% purity or greater as

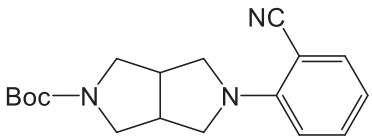
determined by HPLC/MS and ^{1}H-NMR. Melting points were recorded on a capillary melting point apparatus.



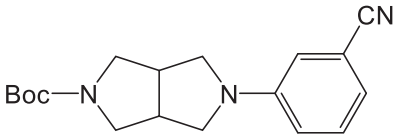
Synthesis of 5-(2-bromoethyl)-3,3-diethyldihydrofuran-2 (3H)-one (**7**): To a solution of 3,3-diethyl-5-(2-hydroxyethyl)dihydrofuran-2(3H)-one (8.03 g, 43.0 mmol, 1 eq.) in tetrahydrofuran (143 mL) was added triphenylphosphine (16.94 g, 64.6 mmol, 1.5 eq.). The resulting solution was cooled to 0 °C and carbon tetrabromide (21.44 g, 64.6 mmol, 1.5 eq.) was added in one portion. The reaction was allowed to stir at 22 °C overnight. The reaction mixture was diluted with ether and filtered and concentrated onto Celite in vacuo and further purified by column chromatography (ethyl acetate/hexanes, 0–30%, solid load) (7.36 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ4.60 (m, 1H), 3.53 (dd, $J = 5.5$, 7.6 Hz, 2H), 2.27–2.07 (m, 3H), 1.82 (dd, $J = 9.3$, 13.0 Hz, 1H), 1.69–1.57 (m, 4H), 0.93 (dt, $J = 7.5$, 25.7 Hz, 6H).



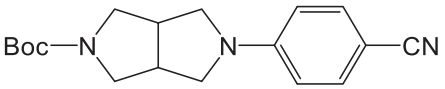
General procedure A: synthesis of tert-butyl 5-aryl-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate: To a solution of 2, 6- diazaspiro[3.3] heptane- 2- carboxylic acid tert- butyl ester hemioxylate (0.300 g, 1.23 mmol, 1.1 eq.) and an aryl bromide (1.12 mmol, 1.0 eq.) in anhydrous toluene (14 mL) under a nitrogen atmosphere was added the following material: $Pd_2(dba)_3$ (0.030 g, 2.5 mol %), BINAP (0.0450 g, 1.5/Pd), triethylamine (0.125 g, 1.23 mmol, 1.1 eq.) and NaOtBu (0.355 g, 3.69 mmol, 3.3 eq.). The resulting mixture was heated to 110 °C and stirred overnight under nitrogen. The reaction mixture was cooled to room temperature and then filtered through a plug of Celite. The collected filtrate was concentrated under vacuum to give a crude residue that was further purified by column chromatography (hexanes/ethyl acetate, 0–30%).



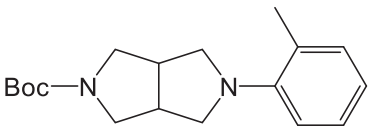
Synthesis of tert-butyl 5-(2-cyanophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10b**): The title compound was prepared according to general procedure A using 2-bromobenzonitrile (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.39 (dd, J = 1.6, 7.8 Hz, 1H), 7.30 (m, 1H), 6.66 (t, $J = 7.5$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 3.80 (m, 2H), 3.61 (m, 2H), 3.52 (m, 1H), 3.44 (m, 1H), 3.28 (m, 2H), 2.95 (b, 2H), 1.42 (s, 9H); MS (LC/MS, $M + H^+$): m/z 314.2.



Synthesis of tert-butyl 5-(3-cyanophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10c**): The title compound was prepared according to general procedure A using 3-bromobenzonitrile (25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 1H), 6.88 (d, $J =$ 7.5 Hz, 1H), 6.71-6.64 (m, 2H), 3.62 (m, 2H), 3.49 (m, 2H), 3.31 (m, 1H), 3.23 (m, 1H), 3.16 (dd, J = 3.9, 9.7 Hz, 2H), 2.99 (b, 2H), 1.42 (s, 9H); MS (LC/MS, $M + H^+$): m/z 314.2.

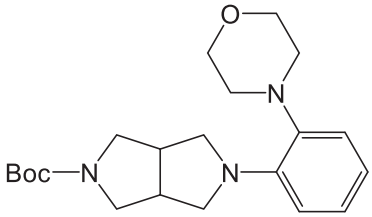


Synthesis of tert-butyl 5-(4-cyanophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10d**): The title compound was prepared according to general procedure A using 4-bromobenzonitrile (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, $J = 8.9$ Hz, 2H), 6.41 (d, $J =$ 8.9 Hz, 2H), 3.57 (m, 2H), 3.50 (m, 2H), 3.26 (m, 1H), 3.21–3.06 (m, 3H), 2.95 (b, 2H), 1.37 (s, 9H); MS (LC/MS, $M + H^+$): m/z 314.2.

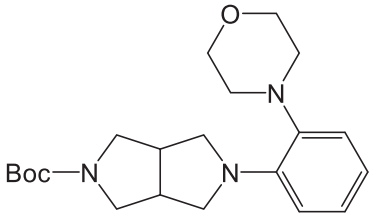


Synthesis of tert-butyl 5-(o-tolyl)hexahydropyrrolo [3,4-c]pyrrole-2(1H)-carboxylate (**10e**): The title compound was prepared according to general procedure A using 1-bromo-2-methylbenzene (63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.10 (m, 2H), 6.96-6.89 (m, 2H), 3.69 (b, 2H), 3.36 (b, 2H), 3.18 (b, 2H), 3.05 (b, 2H), 2.91 (b, 2H), 2.33 (s, 3H), 1.52 (s, 9H); MS

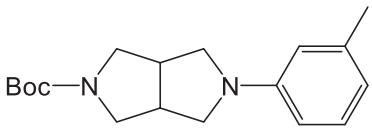
(LC/MS, $M + H^+$): m/z 303.2



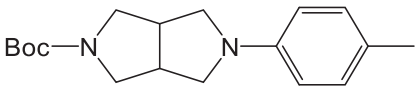
Synthesis of 2-benzyl-5-(2-isopropylphenyl)octahydropyrrolo[3,4-c]pyrrole (**10f**): The title compound was prepared according to general procedure A using 1-bromo-2-isopropylbenzene except that the product was purified by column chromatography (dichloromethane/MeOH, 0–5%) (78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.33 (m, 6H), 7.32-7.11 (m, 3H), 3.77 (s, 2H), 3.65 (sept, $J = 6.9$ Hz, 1H), 3.15 (m, 2H), 3.09-2.99 (m, 4H), 2.96 (m, 2H), 2.47 (dd, $J = 4.9$, 8.8 Hz, 2H), 1.39 (d, $J = 6.9$ Hz, 9H); MS (LC/MS, $M + H^+$): m/z 321.2.



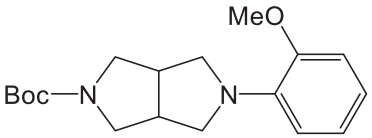
Synthesis of tert-butyl 5-(2-morpholinophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10g**): The title compound was prepared according to general procedure A using 4-(2-bromophenyl)morpholine (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-6.89 (m, 3H), 6.85 (d, $J =$ 7.8 Hz, 1H), 3.85 (t, $J = 4.5$ Hz, 4H), 3.62 (b, 2H), 3.48–3.21 (m, 6H), 3.04 (t, $J = 4.5$ Hz, 4H), 2.92 (b, 2H), 1.48 (s, 9H); MS (LC/MS, $M + H^+$): m/z 374.2.



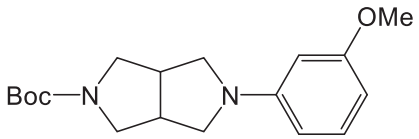
Synthesis of tert-butyl 5-(m-tolyl)hexahydropyrrolo [3,4-c]pyrrole-2(1H)-carboxylate (**10h**): The title compound was prepared according to general procedure A using 1-bromo-3-methylbenzene (76.5% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 7.5$ Hz, 1H), 6.46-6.37 (m, 2H), 3.68 (b, 2H), 3.52 (b, 2H), 3.42 (m, 1H), 3.29 (m, 1H), 3.23 (m, 2H), 2.97 (b, 2H), 2.38 (s, 3H), 1.54 (s, 9H); MS (LC/MS, $M + H^+$): m/z 303.2.



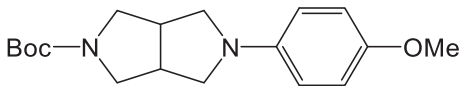
Synthesis of tert-butyl 5-(p-tolyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10i**): The title compound was prepared according to general procedure A 1-bromo-4-methylbenzene (65.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, $J = 8.1$ Hz, 2H), 6.52 (d, $J = 8.5$ Hz, 2H), 3.68 (m, 2H), 3.57 (b, 2H), 3.42 (m, 1H), 3.28 (m, 1H), 3.21 (m, 2H), 3.00 (b, 2H), 2.30 (s, 3H), 1.51 (s, 9H); MS (LC/MS, $M + H^+$): m/z 303.2.



Synthesis of tert-butyl 5-(2-methoxyphenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10j**): The title compound was prepared according to general procedure A using 1-bromo-2-methoxybenzene (78.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91–6.78 (m, 3H), 6.76–6.67 (m, 1H), 3.80 (s, 3H), 3.61 (b, 2H), 3.45 (b, 2H), 3.40-3.22 (m, 2H), 3.14 (b, 2H), 2.90 (b, 2H), 1.46 (s, 9H); MS (LC/MS, $M + H^+$): m/z 319.2.

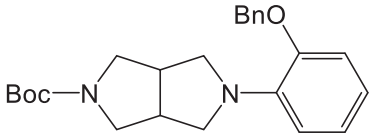


Synthesis of tert-butyl 5-(3-methoxyphenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10k**): The title compound was prepared according to general procedure A using 1-bromo-3-methoxybenzene (64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, $J = 8.1$ Hz, 1H), 6.29 (dd, $J =$ 2.2, 8.1 Hz, 1H), 6.18 (dd, $J = 1.8$, 8.1 Hz, 1H), 6.10 (t, $J =$ 2.2 Hz, 1H), 3.79 (s, 3H), 3.63 (m, 2H), 3.50 (m, 2H), 3.37 (m, 1H), 3.30–3.11 (m, 3H), 2.95 (b, 2H), 1.48 (s, 9H); MS (LC/MS, $M + H^+$): m/z 319.2.

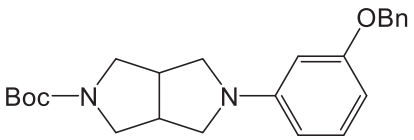


Synthesis of tert-butyl 5-(4-methoxyphenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**10l**): The title compound was prepared according to general procedure A using 1-bromo-4-methoxybenzene (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, $J = 9.0$ Hz, 2H), 6.50 (d, $J =$

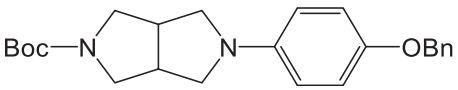
9.0 Hz, 2H), 3.73 (s, 3H), 3.62 (m, 2H), 3.48-3.29 (m, 3H), 3.23 (m, 1H), 3.12 (dd, $J = 3.5$, 9.3 Hz, 2H), 2.93 (b, 2H), 1.46 (s, 9H); MS (LC/MS, $M + H^+$): m/z 319.2.



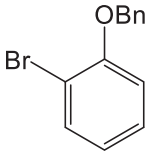
Synthesis of tert-butyl 5-(2-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate: The title compound was prepared according to general procedure A using 1-(benzyloxy)-2-bromobenzene (82% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 4H), 7.20 (m, 1H), 6.79 (m, 2H), 6.72 (m, 1H), 6.65 (m, 1H), 4.94 (s, 2H), 3.50 (b, 2H), 3.33 (m, 2H), 3.27–3.02 (m, 3H), 2.76 (b, 2H), 1.35 (s, 9H); MS (LC/MS, $M + H^+$): m/z 395.2.



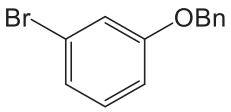
Synthesis of tert-butyl 5-(3-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate: The title compound was prepared according to general procedure A using 1-(benzyloxy)-3-bromobenzene (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.34 (m, 1H), 7.17 (t, $J = 8.2$ Hz, 1H), 6.39 (dd, $J = 1.7$, 8.0 Hz, 1H), 6.23 (m, 2H), 5.08 (s, 2H), 3.66 (m, 2H), 3.53 (m, 2H), 3.40 (m, 1H), 3.33–3.14 (m, 3H), 2.99 (b, 2H), 1.49 (s, 9H); MS (LC/MS, $M + H^+$): m/z 395.2.



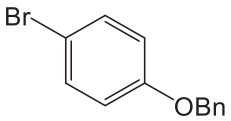
Synthesis of tert-butyl 5-(4-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate: The title compound was prepared according to general procedure A 1-(benzyloxy)-4-bromobenzene (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.34 (m, 1H), 6.95 (d, $J = 9.0$ Hz, 2H), 6.54 (d, $J = 8.8$ Hz, 2H), 5.03 (s, 2H), 3.67 (b, 2H), 3.47 (b, 2H), 3.40 (m, 1H), 3.28 (m, 1H), 3.18 (dd, $J = 3.4$, 9.3 Hz, 2H), 2.99 (b, 2H), 1.50 (s, 9H); MS (LC/MS, $M + H^+$): m/z 395.2.



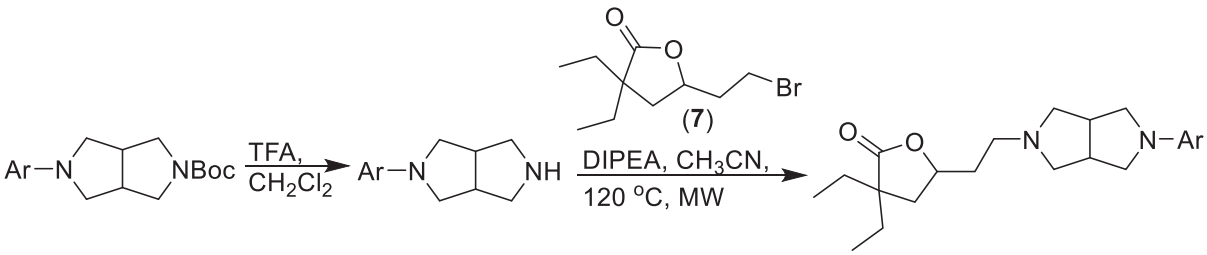
General procedure B: Synthesis of 1-(benzyloxy)-2-bromobenzene: To a solution of 2-bromophenol (1.0 g, 5.78 mmol, 1.01 eq.) in acetonitrile (14 mL) was added benzyl bromide (0.975 g, 5.7 mmol, 1.0 eq.) and K_2CO_3 (1.09 g, 7.87 mmol, 1.38 eq.). This mixture was allowed to stir at 22 °C overnight. The reaction was filtered and concentrated under vacuum to give a crude residue that was further purified by column chromatography (hexanes/ethyl acetate, 0–10%) (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, $J = 1.6$, 7.8 Hz, 1H), 7.51 (m, 2H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.35 (m, 1H), 7.29–7.22 (m, 1H), 6.97 (dd, $J = 1.2$ 8.3 Hz, 1H), 6.88 (td, $J = 1.3$, 7.6 Hz, 1H), 5.19 (s, 2H).



Synthesis of 1-(benzyloxy)-3-bromobenzene: The title compound was prepared according to general procedure B using 3-bromophenol (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.34 (m, 5H), 7.23–7.10 (m, 3H), 6.95 (m, 1H), 5.08 (s, 2H).



Synthesis of 1-(benzyloxy)-4-bromobenzene: The title compound was prepared according to general procedure B using 4-bromophenol (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.33 (m, 7H), 6.91 (d, $J = 9.1$ Hz, 2H), 5.08 (s, 2H).

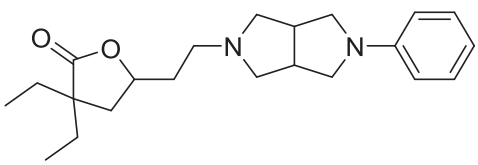


General procedure C: Synthesis of 3,3-diethyl-5-aryl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-ones: To a solution of tert-butyl 5-aryl-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (1.62 mmol, 1 eq.) in methylene chloride (4 mL) at 0 °C was added trifluoroacetic acid (2 mL). The reaction was allowed to stir at 22 °C for 30 minutes before being diluted with MeOH and concentrated under vacuum to afford the product as a TFA salt. The salt was then suspended in sat. $NaHCO_3$ solution and the free based product was extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentration in vacuo to afford 2-aryl-octahydropyrrolo[3,4-c]pyrrole as a free base which was used without further purification.

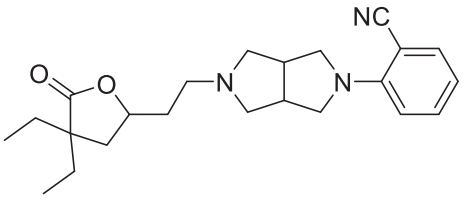
Next, a mixture of 5-(2-bromoethyl)-3,3-diethyldihydrofuran-2(3H)-one (**7**) (0.075 g, 0.301 mmol, 1 eq.), acetonitrile (3 mL), the 2-arl-octahydropyrrolo[3,4-c]pyrrole (0.361 mmol, 1.2 eq.) and N,N-diisopropylethyl amine (0.116 g, 0.903 mmol, 3 eq.) was microwaved at 120 °C for 4 h. The resulting solution was concentrated under vacuum to give a crude residue that was purified by column chromatography (methanol/dichloromethane, 0–10%) to provide the 3,3-diethyl-5-aryl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one.

General procedure D: Synthesis of 3,3-diethyl-5-aryl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-ones: To a solution of tert-butyl 5-aryl-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (1.62 mmol, 1 eq.) in MeOH (1.25 mL) at 0 °C was added 1 M methanolic HCl (3.75 mL). The reaction was allowed to stir at 22 °C overnight before being diluted with MeOH and concentrated under vacuum to afford the product as a HCl salt which was used without further purification.

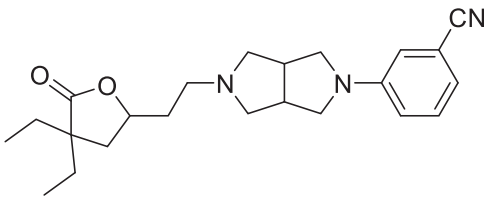
Next, a mixture of 5-(2-bromoethyl)-3,3-diethyldihydrofuran-2(3H)-one (**7**) (0.075 g, 0.301 mmol, 1 eq.), acetonitrile (3 mL), the 2-arl-octahydropyrrolo[3,4-c]pyrrole (0.361 mmol, 1.2 eq.) and N,N-diisopropylethyl amine (0.116 g, 0.903 mmol, 3 eq.) was microwaved at 120 °C for 4 h. The resulting solution was concentrated under vacuum to give a crude residue that was purified by column chromatography (methanol/dichloromethane, 0–10%) to provide the 3,3-diethyl-5-aryl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one.



Synthesis of 3,3-diethyl-5-(2-(5-phenylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11a**): The title compound was prepared according to general procedure C except 2-phenyloctahydropyrrolo[3,4-c]pyrrole was acquired from a commercial source rather than prepared from the Boc-protected analog (58% yield, HPLC purity: 98.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (m, 2H), 6.64 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 4.37 (m, 1H), 3.29 (t, J = 8.1 Hz, 2H), 3.08 (dt, J = 2.7, 9.3 Hz, 2H), 2.92–2.79 (b, 2H), 2.78–2.65 (m, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.32 (dd, J = 4.0, 8.9 Hz, 2H), 2.02 (dd, J = 6.7, 13.1 Hz, 1H), 1.87–1.61 (m, 3H), 1.51 (q, J = 7.3 Hz, 4H), 0.81 (dt, J = 7.5, 13.9 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 148.5, 128.8, 116.4, 113.4, 75.3, 60.1, 54.2, 50.8, 47.7, 40.8, 36.7, 34.3, 28.2, 27.5, 8.5, 8.4. MS (LC/MS, M + H$^+$): m/z 357.2.

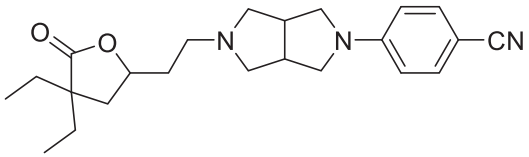


Synthesis of 2-(5-(2-(4,4-diethyl-5-oxotetrahydrofuran-2-yl)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzonitrile (**11b**): The title compound was prepared according to general procedure D using tert-butyl 5-(2-cyanophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (50% yield, HPLC purity: 99.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.5, 7.6 Hz, 1H), 7.36 (m, 1H), 6.81–6.68 (m, 2H), 4.45 (m, 1H), 3.62 (m, 2H), 3.45 (td, J = 2.0, 8.6 Hz, 2H), 2.92 (b, 2H), 2.74 (m, 2H), 2.63–2.53 (m, 2H), 2.52–2.46 (m, 2H), 2.11 (dd, J = 6.8, 13.0 Hz, 1H), 1.94–1.70 (m, 3H), 1.58 (qd, J = 2.6, 7.4 Hz, 4H), 0.88 (dt, J = 7.3, 14.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.9, 148.2, 133.0, 131.9, 118.2, 116.2, 114.7, 95.2, 72.9, 57.0, 52.9, 48.5, 45.7, 38.5, 36.8, 34.6, 26.2, 25.5, 6.4, 6.3. MS (LC/MS, M + H$^+$): m/z 382.2.

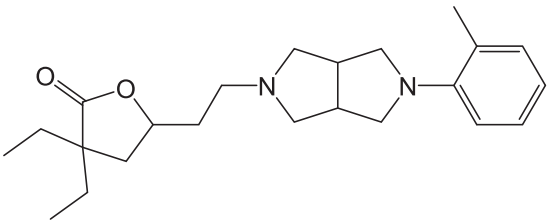


Synthesis of 3-(5-(2-(4,4-diethyl-5-oxotetrahydrofuran-2-yl)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzonitrile (**11c**): The title compound was prepared according to general procedure D using tert-butyl 5-(3-cyanophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (57% yield, HPLC purity: 98.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.82–6.75 (m, 2H), 4.44 (m, 1H), 3.44 (t, J = 8.7 Hz, 2H), 3.15 (dt, J = 3.8, 9.4 Hz, 2H), 2.98 (b, 2H), 2.73 (m, 2H), 2.57 (t, J = 7.0 Hz, 2H), 2.50 (dd, J = 3.1, 9.1 Hz, 2H), 2.10 (dd, J = 6.8, 12.9 Hz, 1H), 1.94–1.70 (m, 3H), 1.59 (q, J = 7.3 Hz, 4H), 0.89 (dt, J = 5.4, 14.9 Hz, 6H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 148.2, 130.0, 119.4, 119.2, 117.7,

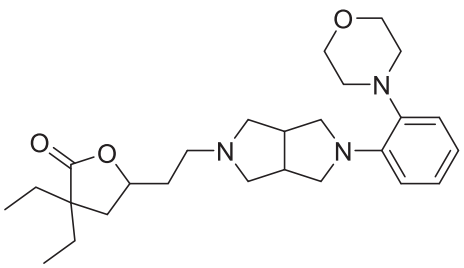
115.5, 111.7, 75.2, 60.0, 54.1, 50.6, 47.8, 40.8, 36.7, 34.1, 28.2, 27.6, 8.5, 8.4. MS (LC/MS, $M + H^+$): m/z 382.2.



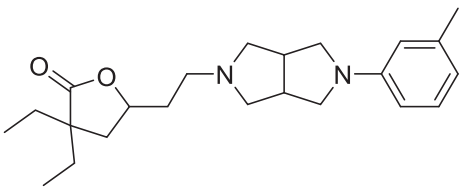
Synthesis of 4-(5-(2-(4,4-diethyl-5-oxotetrahydrofuran-2-yl)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzonitrile (**11d**): The title compound was prepared according to general procedure C using tert-butyl 5-(4-cyanophenyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (37% yield, HPLC purity: 99.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $J = 8.9$ Hz, 2H), 6.54 (d, $J = 8.7$ Hz, 2H), 4.44 (m, 1H), 3.55 (t, $J = 9.0$ Hz, 2H), 3.23 (dt, $J = 3.6$, 9.9 Hz, 2H), 3.00 (b, 2H), 2.72 (m, 2H), 2.64–2.50 (m, 4H), 2.10 (dd, $J = 6.7$, 13.1 Hz, 1H), 1.94–1.71 (m, 3H), 1.59 (q, $J = 7.5$ Hz, 4H), 0.89 (dt, $J = 5.1$, 14.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 150.2, 133.2, 120.5, 112.8, 112.6, 75.4, 59.8, 55.1, 50.6, 47.8, 40.6, 36.6, 34.5, 28.1, 27.6, 8.6, 8.4. MS (LC/MS, $M + H^+$): m/z 382.2.



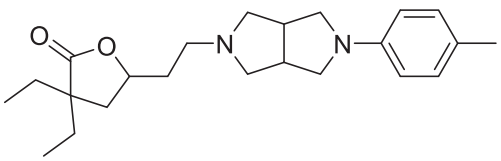
Synthesis of 3,3-diethyl-5-(2-(5-(o-tolyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11e**): The title compound was prepared according to general procedure C using tert-butyl 5-(o-tolyl)hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (62% yield, HPLC purity: 99.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (m, 2H), 6.96 (m, 2H), 4.50 (m, 1H), 3.08-2.92 (m, 6H), 2.86 (b, 2H), 2.60 (t, $J = 6.9$ Hz, 2H), 2.37–2.24 (m, 5H), 2.14 (dd, $J = 6.7$, 13.0 Hz, 1H), 1.99–1.75 (m, 3H), 1.64 (m, 4H), 0.94 (dt, $J = 7.4$, 18.1 Hz, 6H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 147.6, 130.9, 130.6, 126.4, 122.0, 117.7, 74.9, 59.1, 55.5, 50.5, 47.8, 40.5, 36.6, 34.5, 28.2, 27.5, 18.8, 8.5, 8.4. MS (LC/MS, $M + H^+$): m/z 371.2.



Synthesis of 3,3-diethyl-5-(2-(5-(2-morpholinophenyl) hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11g**): The title compound was prepared according to general procedure D using tert-butyl 5-(2-morpholinophenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (52% yield, HPLC purity: 98.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–6.94 (m, 3H), 6.91-6.83 (m, 1H), 4.49 (m, 1H) 3.85 (t, $J = 4.7$ Hz, 4H), 3.68-3.42 (m, 4H), 3.22–2.84 (m, 10H), 2.61 (b, 2H), 2.30 (b, 1H), 2.19 (dd, $J = 6.7$, 13.2 Hz, 1H), 2.05–1.90 (m, 1H), 1.84 (dd, $J = 9.3$, 13.2 Hz, 1H), 1.67–1.56 (m, 4H), 0.91 (dt, $J = 7.3$, 16.5 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.8, 143,2, 141.8, 122.9, 121.7, 118.3, 117.7, 74.5, 66.5, 58.8, 53.2, 50.3, 49.9, 48.5, 47.8, 40.1, 36.5, 28.2, 27.6, 8.5, 8.4. MS (LC/MS, $M + H^+$): m/z 442.2.

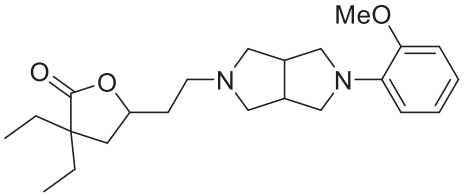


Synthesis of 3,3-diethyl-5-(2-(5-(m-tolyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11h**): The title compound was prepared according to general procedure C using tert-butyl 5-(m-tolyl)hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (46% yield, HPLC purity: 98.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 7.4$ Hz, 1H), 6.53–6.45 (m, 2H), 4.47 (m, 1H), 3.37 (m, 2H), 3.18 (dt, $J = 2.8$, 9.4 Hz, 2H), 2.95 (b, 2H), 2.86 (m, 2H), 2.59 (t, $J = 7.0$ Hz, 2H), 2.41 (dd, $J = 4.0$, 8.9 Hz, 2H), 2.33 (s, 3H), 2.12 (dd, $J = 6.6$, 13.0 Hz, 1H), 1.97–1.73 (m, 3H), 1.62 (q, $J = 7.5$ Hz, 4H), 0.92 (dt, $J = 7.5$, 14.8 Hz, 6H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.6, 147.2, 136.4, 127.3, 116.0, 112.8, 109.4, 73.9, 58.8, 52.9, 49.4, 46.4, 39.5, 35.4, 34.3, 26.9, 26.2, 20.1, 7.1, 7.0. MS (LC/MS, $M + H^+$): m/z 371.2.

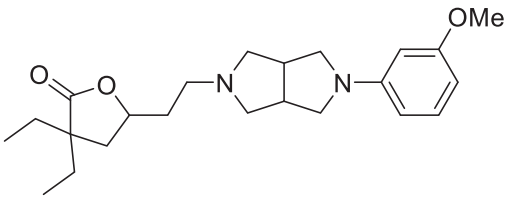


Synthesis of 3,3-diethyl-5-(2-(5-(p-tolyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl) dihydrofuran-2(3H)-one (**11i**): The title compound was prepared according to general procedure C using tert-butyl 5-(p-tolyl)hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (43% yield, HPLC purity: 99.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, $J = 8.4$ Hz, 2H), 6.45 (d, $J = 8.4$ Hz, 2H), 4.32 (m, 1H), 3.17 (m, 2H), 2.99 (dt, $J =$

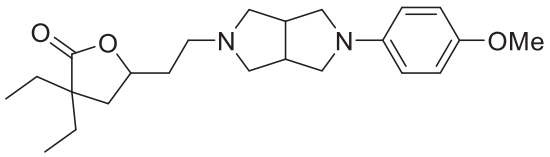
3.0, 9.2 Hz, 2H), 2.78 (b, 2H), 2.70 (m, 2H), 2.42 (t, J = 6.9 Hz, 2H), 2.42 (dd, J = 4.0, 8.8 Hz, 2H), 2.11 (s, 3H), 2.97 (dd, J = 6.8, 13.0 Hz, 1H), 1.81–1.57 (m, 3H), 1.45 (q, J = 7.2 Hz, 4H), 0.76 (dt, J = 7.5, 14.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 146.6, 129.3, 125.2, 113.8, 75.1, 59.8, 54.2, 50.6, 47.8, 40.7, 36.7, 34.9, 28.2, 27.5, 20.0, 8.5, 8.4. MS (LC/MS, M + H$^+$): m/z 371.2.



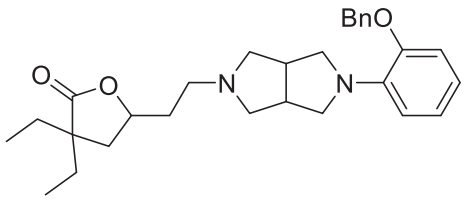
Synthesis of 3,3-diethyl-5-(2-(5-(2-methoxyphenyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11j**): The title compound was prepared according to general procedure C using 2-(2-methoxyphenyl)octahydropyrrolo[3,4-c]pyrrole (65% yield, HPLC purity: 98.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83–6.61 (m, 4H), 4.34 (m, 1H), 3.71 (s, 3H), 3.23 (q, J = 7.5 Hz, 2H), 2.86 (m, 2H), 2.72 (b, 2H), 2.58 (b, 2H), 2.44 (m, 2H), 2.31 (dt, J = 3.2, 8.8 Hz, 2H), 1.98 (dd, J = 6.8, 13.1 Hz, 1H), 1.84-1.73 (m, 1H), 1.73–1.58 (m, 2H), 1.47 (qd, J = 1.5, 7.5 Hz, 4H), 0.77 (dt, J = 7.3, 15.8 Hz, 6H), ^{13}C NMR (101 MHz, DMSO) δ 179.9, 150.9, 138.7, 120.9, 120.7, 116.7, 111.9, 75.2, 59.4, 55.4, 55.3, 50.7, 47.8, 40.6, 36.7, 34.7, 28.2, 27.6, 8.5, 8.4. MS (LC/MS, M + H$^+$): m/z 387.2.



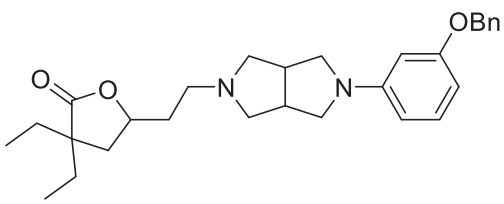
Synthesis of 3,3-diethyl-5-(2-(5-(3-methoxyphenyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11k**): The title compound was prepared according to general procedure C using tert-butyl 5-(2-methoxyphenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (53% yield, HPLC purity: 99.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 8.2 Hz, 1H), 6.30 (m, 2H), 6.20 (t, J = 2.2 Hz, 1H), 4.46 (m, 1H), 3.79 (s, 3H), 3.38 (t, J = 8.2 Hz, 2H), 3.17 (dt, J = 3.0, 9.5 Hz, 2H), 2.94 (b, 2H), 2.86–2.77 (m, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.42 (dd, J = 3.9, 9.0 Hz, 2H), 2.11 (dd, J = 6.8, 13.0 Hz, 1H), 1.95–1.72 (m, 3H), 1.61 (qd, J = 1.5, 7.5 Hz, 4H), 0.91 (dt, J = 7.4, 14.8 Hz, 6H); DMSO-d_6, DMSO) δ 179.9, 160.1, 149.7, 129.5, 106.3, 101.9, 99.3, 75.3, 60.2, 54.7, 54.4, 50.8, 47.8, 40.8, 36.7, 34.4, 28.2, 27.5, 8.5, 8.4. MS (LC/MS, M + H$^+$): m/z 387.2.



Synthesis of 3,3-diethyl-5-(2-(5-(4-methoxyphenyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11l**): The title compound was prepared according to general procedure C using tert-butyl 5-(4-methoxyphenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (52% yield, HPLC purity: 99.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 4.46 (m, 1H), 3.76 (s, 3H), 3.28 (m, 2H), 3.10 (dt, J = 3.2, 9.1 Hz, 2H), 2.92 (b, 2H), 2.84 (b, 2H), 2.63-2.51 (m, 2H), 2.39 (dd, J = 4.0, 8.7 Hz, 2H), 2.11 (dd, J = 6.8, 13.0 Hz, 1H), 1.97–1.71 (m, 3H), 1.61 (qd, J = 1.3, 7.4 Hz, 4H), 0.91 (dt, J = 7.3, 14.8 Hz, 6H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 151.3, 143.4, 114.8, 114.4, 75.3, 60.2, 55.2, 55.1, 50.8, 47.8, 41.0, 36.7, 34.5, 28.2, 27.5, 8.5, 8.4. MS (LC/MS, M + H$^+$): m/z 387.2.

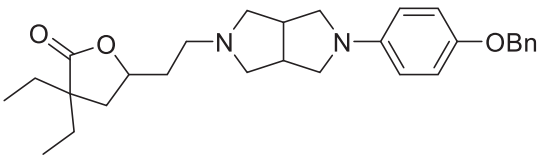


Synthesis of 5-(2-(5-(2-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2(3H)-one: The title compound was prepared according to general procedure D using tert-butyl 5-(2-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.29 (m, 5H), 7.01–6.86 (m, 3H), 6.81 (dd, J = 1.4, 7.7 Hz, 1H), 5.03 (s, 2H), 4.43 (m, 1H), 3.61 (b, 2H), 3.36 (t, J = 10.6 Hz, 2H), 3.17–2.97 (m, 3H), 2.91 (td, J = 5.3, 12.2 Hz, 1H), 2.86–2.73 (m, 2H), 2.58–2.37 (m, 2H), 2.30 (m, 1H), 2.17 (dd, J = 6.7, 13.1 Hz, 1H), 1.92–1.73 (m, 2H), 1.61 (q, J = 7.4 Hz, 4H), 0.91 (dt, J = 7.0, 13.9 Hz, 6H), MS (LC/MS, M + H$^+$): m/z 463.2.

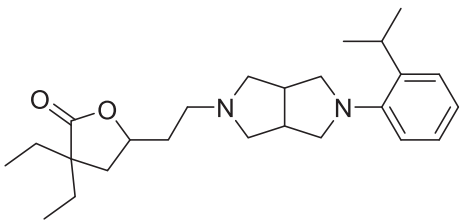


Synthesis of 5-(2-(5-(3-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2(3H)-one: The title compound was prepared according to general procedure D using tert-butyl 5-(3-

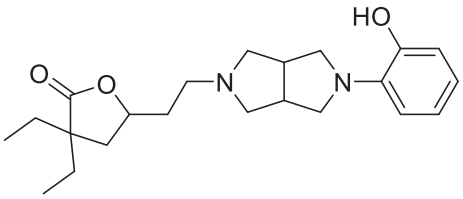
(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2H), 7.33–7.26 (m, 2H), 7.26–7.20 (m, 1H), 7.05 (m, 1H), 6.29 (dd, $J = 1.7$, 8.1 Hz, 1H), 6.24–6.18 (m, 2H), 4.96 (s, 2H), 4.37 (m, 1H), 3.28 (m, 2H), 3.08 (dt, $J =$ 2.9, 9.3 Hz, 2H), 2.93–2.81 (m, 2H), 2.81–2.69 (m, 2H), 2.50 (t, $J = 7.2$ Hz, 2H), 2.33 (dd, J 3.9, 8.9 Hz, 2H), 2.02 (dd, $J = 6.7$, 13.0 Hz, 1H), 1.87–1.63 (m, 3H), 1.52 (qd, $J = 1.2$, 7.4 Hz, 4H), 0.82 (dt, J = 7.4, 14.9 Hz, 6H). MS (LC/MS, $M + H^+$): m/z 463.2.



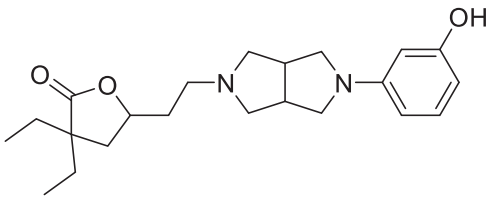
Synthesis of 5-(2-(5-(4-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2(3H)-one: The title compound was prepared according to general procedure D using tert-butyl 5-(4-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.31–7.25 (m, 2H), 7.24–7.18 (m, 1H), 6.81 (d, $J = 9.0$ Hz, 2H), 6.55 (d, $J = 9.0$ Hz, 2H), 4.92 (s, 2H), 4.37 (m, 1H), 3.19 (m, 2H), 3.01 (dt, $J = 3.1$, 9.3 Hz, 2H), 2.89–2.80 (m, 2H), 2.80–2.70 (m, 2H), 2.48 (t, $J =$ 6.9 Hz, 2H), 2.29 (dd, J 3.9, 8.6 Hz, 2H), 2.02 (dd, $J = 6.7$, 13.1 Hz, 1H), 1.87–1.62 (m, 3H), 1.52 (q, $J = 7.3$ Hz, 4H), 0.82 (dt, $J = 7.5$, 14.5 Hz, 6H). MS (LC/MS, $M + H^+$): m/z 463.2.



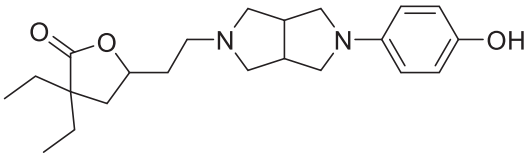
Synthesis of 3,3-diethyl-5-(2-(5-(2-isopropylphenyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11f**): To a dry round bottom flask, 0.04 g of 10% Pd/C (20% wt) was added and wet with a small amount of ethyl acetate. Following, a solution of 2-benzyl-5-(2-isopropylphenyl)octahydropyrrolo[3,4-c]pyrrole (0.20 g, 0.624 mmol, 1 eq.) in MeOH (2.1 mL) was added slowly to the Pd/C containing round bottom flask. This system was then flushed 3x with H_2, using a balloon filled with H_2. The reaction was allowed to stir under 1 atm H_2 for five days at room temperature. The Pd/C was removed via filtration through a plug of Celite. The filtrate was concentrated under vacuum to afford a crude oil of 2-(2-isopropylphenyl)octahydropyrrolo[3,4-c]pyrrole which was used in the next step without further purification. The second step of the sequence was then performed according to general procedure (A) (52% yield, HPLC purity: 99.1%). (^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, $J = 1.5$, 7.4 Hz, 1H), 7.10–6.90 (m, 3H), 4.43 (m, 1H), 3.38 (sept, $J =$ 6.9 Hz, 1H), 3.01–2.84 (m, 4H), 2.83–2.66 (m, 4H), 2.52 (t, $J = 6.8$ Hz, 2H), 2.19 (m, 2H), 2.06 (dd, $J = 6.8$, 13.1 Hz, 1H), 1.91–1.67 (m, 3H), 1.63-1.44 (m, 4H), 1.15 (d, $J =$ 6.9 Hz, 6H), 0.86 (dt, $J = 7.3$, 19.3 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 180.0, 146.7, 143.4, 126.1, 126.0, 123.5, 119.2, 75.3, 59.6, 58.2, 51.0, 47.8, 41.3, 36.8, 34.5, 28.3, 27.6, 26.4, 23.9, 8.5, 8.4. MS (LC/MS, $M + H^+$): m/z 399.2.



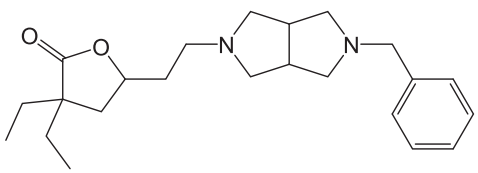
General Procedure E: Synthesis of 3,3-diethyl-5-(2-(5-(2-hydroxyphenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl) ethyl)dihydrofuran-2(3H)-one (**11m**): To a dry round bottom flask, 0.013 g of 10% Pd/C (20% wt) was added and wet with a small amount of ethyl acetate. Following, a solution of 5-(2-(5-(2-(benzyloxy)phenyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2 (3H)-one (0.065 g, 0.140 mmol, 1 eq.) in MeOH (1.5 mL) was added slowly to the Pd/C containing round bottom flask. This system was then flushed 3x with H_2, using a balloon filled with H_2. The reaction was allowed to stir under 1 atm H_2 for overnight at room temperature. The Pd/C was removed via filtration through a plug of Celite. The filtrate was concentrated under vacuum to give a crude residue that was first purified by column chromatography (methanol/dichloromethane, 0–10%) (86% yield, HPLC purity: 99.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J $= 1.3$, 7.8 Hz, 1H), 7.05 (td, $J = 1.3$, 7.7 Hz, 1H), 6.93 (dd, $J = 1.3$, 8.1 Hz, 1H), 6.85 (td, $J = 1.4$, 7.7 Hz, 1H), 4.52 (m, 1H), 3.12–3.00 (m, 2H), 2.98–2.74 (m, 6H), 2.65 (t, $J =$ 7.3 Hz, 2H), 2.58–2.46 (m, 2H), 2.16 (dd, $J = 6.7$, 13.1 Hz, 1H), 2.00–1.76 (m, 3H), 1.64 (q, $J = 7.5$ Hz, 4H), 0.95 (dt, $J = 7.4$, 22.8 Hz, 6H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.6, 147.4, 136.0, 119.4, 117.8, 115.8, 113.9, 73.8, 58.1, 53.9, 49.3, 46.4, 39.3, 35.3, 32.9, 26.8, 26.2, 7.1, 7.0. MS (LC/MS, $M + H^+$): m/z 373.2.



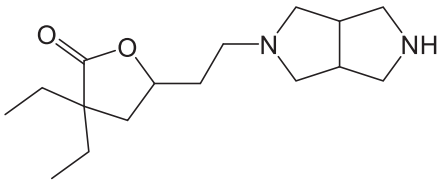
Synthesis of 3,3-diethyl-5-(2-(5-(3-hydroxyphenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11n**): The title compound was prepared according to general procedure E using 5-(2-(5-(3-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydro furan-2(3H)-one (88% yield, HPLC purity: 99.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (t, $J = 8.1$ Hz, 1H), 6.00 (td, $J = 1.8$, 7.6 Hz, 2H), 5.91 (t, $J = 2.3$ Hz, 1H), 4.24 (m, 1H), 3.18-3.05 (m, 2H), 2.97 (d, $J = 9.2$ Hz, 2H), 2.83–2.64 (m, 4H), 2.44 (t, $J = 7.3$ Hz, 2H), 2.25 (m, 2H), 1.91 (dd, $J = 6.7$, 13.1 Hz, 1H), 1.77–1.53 (m, 3H), 1.40 (q, $J = 7.4$ Hz, 4H), 0.70 (dt, $J = 7.4$, 15.6 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.9, 157.9. 149.8, 129.4, 104.8, 104.0, 100.5, 75.3, 60.2, 54.3, 50.8, 47.8, 40.8, 36.7, 34.2, 28.2, 27.5, 8.5, 8.4. MS (LC/MS, $M + H^+$): m/z 373.2.



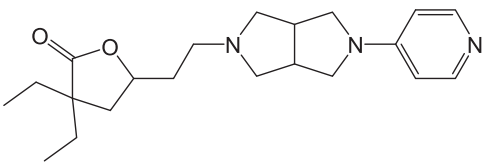
Synthesis of 3,3-diethyl-5-(2-(5-(4-hydroxyphenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one trifluoroacetate (**11o**): The title compound was prepared according to general procedure E using 5-(2-(5-(4-(benzyloxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2(3H)-one and the reaction time was extended to 3 days. A second purification was also conducted via column chromatography on a C18 column. (acetonitrile /H_2O, 0–100%, w/ 0.1% TFA) (93% yield, HPLC purity: 98.9%). ^{1}H NMR (400 MHz, MeOD) δ 6.78-6.67 (m, 4H), 4.54 (m, 1H), 3.69 (b, 2H), 3.45 (dd, $J = 7.2$, 9.6 Hz, 2H), 3.40–3.09 (m, 6H), 2.98 (m, 2H), 2.28 (dd, $J = 6.7$, 13.2 Hz, 1H), 2.20–1.97 (m, 2H), 1.91 (dd, $J = 9.4$, 13.2 Hz, 1H), 1.74–1.52 (m, 4H), 0.94 (dt, $J = 5.0$, 14.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.7, 149.7, 141.7, 115.7, 115.5, 74.2, 58.9, 54.7, 50.6, 47.8, 40.1, 36.4, 31.9, 28.2, 27.5, 8.4, 8.3., MS (LC/MS, $M + H^+$): m/z 373.2.



Synthesis of 5-(2-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydro furan-2(3H)-one (**15**): A solution of 5-(2-bromoethyl)-3,3-diethyldihydrofuran-2(3H)-one (0.400 g, 1.53 mmol, 1 eq.), acetonitrile (8 mL), 2-benzyloctahydropyrrolo[3,4-c]pyrrole (0.340 g, 1.68 mmol, 1.1 eq.) and K_2CO_3 (1.05 g, 7.65 mmol, 5 eq.) was heated and stirred at 80 °C for 24 hours. The resulting mixture was then filtered and concentrated under vacuum to give a crude residue that was further purified by column chromatography (methanol/dichloromethane, 0–10%) (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.14 (m, 4H), 7.14–7.06 (m, 1H), 4.38 (m, 1H), 3.46 (s, 2H), 2.64–2.48 (m, 6H), 2.48–2.38 (m, 2H), 2.28–2.13 (m, 4H), 2.02 (dd, $J = 6.8$, 13.0 Hz, 1H), 1.87–1.59 (m, 3H), 1.58–1.44 (m, 4H), 0.83 (dt, $J = 7.3$, 21.4 Hz, 6H); MS (LC/MS, $M + H^+$): m/z 371.2.



Synthesis of 3,3-diethyl-5-(2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one: A mixture of 5-(2-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)-3,3-diethyldihydrofuran-2(3H)-one (540 mg, 1.46 mmol, 1 eq.), Pd/C (108 mg, 20% wt) and MeOH (5.0 mL) was stirred at 22 °C under 1 atm of H_2 (filled balloon) for three days. The mixture was filtered through a plug of Celite, washed with MeOH (50 mL) and concentrated under vacuum to give a crude product that was used in following steps without further purification (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (m, 1H), 2.83 (b, 1H), 2.69 (m, 2H), 2.55-2.39 (m, 4H), 2.33 (m, 2H), 2.26 (t, $J = 7.0$ Hz, 2H), 2.14 (dd, $J = 1.7$, 9.0 Hz, 2H), 1.91 (dd, $J = 6.7$, 13.0 Hz, 1H), 1.71–1.47 (m, 3H), 1.45–1.32 (m, 4H), 0.69 (dt, $J = 7.4$, 19.2 Hz, 6H); MS (LC/MS, $M + H^+$): m/z 281.2



Synthesis of 3,3-diethyl-5-(2-(5-(pyridin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (**11p**): A solution of 3,3-diethyl-5-(2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)dihydrofuran-2(3H)-one (0.180 g, 0.642 mmol, 1 eq.), 1-butanol (6.4 mL), 4-bromopyridine hydrochloride (0.249 g, 1.28 mmol, 2.0 eq.) and triethylamine (0.325 g, 3.21 mmol, 5 eq.) was heated and stirred at 120 °C for 24 h. The resulting solution was concentrated under vacuum to give a crude residue that was further purified by column chromatography (methanol/dichloromethane, 0–10%, w/ 0.1% NH_4OH) (66% yield, HPLC purity: 99.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, $J = 1.4$, 3.5 Hz, 2H), 6.32 (dd, $J = 1.5$, 3.5 Hz, 2H), 4.37 (m, 1H), 3.45 (dd, $J = 8.3$, 9.2 Hz, 2H), 3.12 (dt, $J =$

3.4, 9.9 Hz, 2H), 2.90 (m, 2H), 2.62 (m, 2H), 2.50 (t, J = 7.4 Hz, 2H), 2.46 (m, 2H), 2.02 (dd, J = 6.8, 13.0 Hz, 1H), 1.85-1.61 (m, 3H), 1.52 (q, J = 7.5 Hz, 4H), 0.82 (dt, J = 5.7, 13.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.7, 152.3, 149.7, 110.2, 74.9, 60.3, 54.7, 50.9, 47.4, 40.9, 36.8, 34.5, 28.3, 27.7, 8.5, 8.4. MS (LC/MS, M + H^+): m/z 358.2

Computational values and docking studies

TPSA and cLogP values were calculated using the Dotmatics software suite (Dotmatics LLC The Old Monastery, Windhill Bishops, Stortford Herts, CW23 2ND UK). Docking studies and analysis were conducted using Schrodinger's Glide and Pymol software packages (Schrodinger Inc.1540 Broadway, 24th Floor, New York, NY 10036). Briefly, the crystal structure of sigma-2 receptor bound to a dihydroquinolinone derivative was obtained from the protein data bank (PDD ID: 7M96). The protein structure was prepared by adding missing atoms, adjusting the bond orders, filling in missing side chains and completing missing loops [29–33]. Water molecules beyond 4A of the ligand were deleted. The tautomerization and protonation states of the amino acids at pH of 7.4 were enumerated to adjust the hydrogen bonding network. Then, the protein structure was minimized using OPLSe force-field and charges. The receptor grid was generated by using Glide [34–37]. The center of the grid was defined based on the bound ligand coordinates. A van der Waals scaling factor of 0.8 was used to add some flexibility during the docking step. The ligands were prepared for docking by LigPrep [38]. The docking was carried out by Glide standard precision algorithm.

Sigma-1 and sigma-2 competitive radioligand-binding studies

Competitive binding assays were conducted by the Psychoactive Drug Screening Program (PDSP) at The University of North Carolina, Chapel Hill under the direction of Professor Bryan Roth [28]. Assay conditions can be found in the PDSP assay protocol book at https://pdsp.unc.edu/pdspweb/content/UNC-CH%20Protocol%20Book.pdf.

Aqueous solubility assay

Compounds were assessed for their solubility at pH 7.4 using the commercially available Millipore MultiScreenTM Solubility filter system (Millipore, Billerica, MA). Analysis was performed by liquid chromatography tandem mass spectrometry (LC/MS/MS).

Cytochrome P450 inhibition assay

Compounds were assessed for their ability to inhibit human cytochrome P450 3A4 using testosterone as a substrate and LC/MS/MS analysis, while the 2D6 and 2C9 assays use fluorescent substrates and Envision plate reader analysis. Expressed enzymes was used to minimize non-specific binding and membrane partitioning issues [39].

Acknowledgements K_i determinations for compound binding to Sigma-1, and Sigma-2 were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP web site https://pdsp.unc.edu/ims/investigator/web/. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. TPSA and cLogP values were generated using the Dotmatics software suite (Dotmatics LLC The Old Monastery, Windhill Bishops, Stortford Herts, CW23 2ND UK).

Compliance with ethical standards

Conflict of interest BEB and DJC both have equity interests in Praeventix LLC, which have been reviewed and approved by Temple University in accordance with its conflict of interest policies. Questions regarding this interest may be directed to the Temple University Conflict of Interest Program. No other author has reported conflicts of interest to disclose at the time of publication.

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