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# The spiropiperidine-3,3′-oxindole scaffold: a type II β-turn peptide isostere

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ABSTRACT

An unprecedented chiral spiropiperidine oxindole system was synthesized starting from enantiopure quaternary 3-aminooxindole and relying on a ring closing metathesis as the key step. This compound acts as an highly constrained Freidinger γ-lactam, adopting a type II β-turn conformation in solution, as assessed by modelling and spectroscopical studies.



## 1. Introduction

β-turns represent an important recognition element of peptides and proteins and are considered as initiation sites for protein folding.[1] Consequently, it is not surprising that a major challenge in the field of peptidomimetics is the design and synthesis of conformationally constrained analogues that mimic these essential secondary structural elements.[2] Nowadays, β-turn based pharmacophore design has become a central topic in medicinal chemistry.[3]

A general approach to the synthesis of peptidomimetic compounds involves the use of non-peptide building blocks, which enforce or stabilize a particular type of β-turn, when inserted into a peptide chain. A pioneer in this field is Freidinger, who developed dipeptide γ-, δ-, ε-lactams as constrained scaffolds to stabilize turn conformations.[4] In his approach, the lactam ring acts as the bridging element of the betagenic—$(i+1)$–$(i+2)$—central residue and can bring recognition groups for interaction with the receptor or enzyme active site. In particular, hydrophobic and aromatic moieties often play an important role in recognition and activation of receptors possessing lipophilic domains, and this is why many ligand mimics contain these elements.

In the course of a program directed towards the search for new methodologies to access pharmaceutically relevant heterocyclic scaffolds,[5] we recently developed a new protocol for the asymmetric synthesis of quaternary 3-aminooxindoles.[6] 3,3′-Disubstituted oxindoles are important targets in organic synthesis[7] due to their frequent occurrence in natural products[8] and biologically relevant molecules[9] (Fig. 1). Diverse oxindole derivatives were used as non-peptide scaffolds[10] in the search for peptidomimetics either as enzyme inhibitors or as ligands of G-protein-coupled receptors.[11]

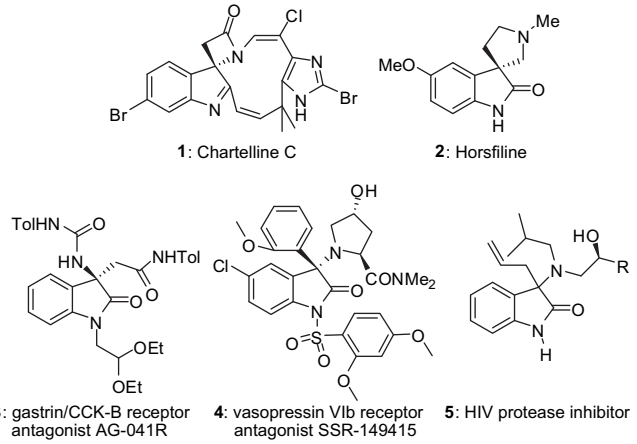


**Figure 1.** Representative 3,3′-disubstituted oxindole-containing natural products (**1** and **2**) and drugs (**3**–**5**).

For instance, in searching for new HIV-1 protease inhibitors that maintain their potencies against mutant strains of HIV, a series of novel oxyindole-derived HIV-1 protease inhibitors were designed and synthesized and the effects of substituents, spirocyclic rings

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and ring sizes on the activity have been investigated.[12] Besides, the oxindole framework is the essential feature of orally active non-peptide arginine-vasopressin receptor antagonists, such as SSR-149415 and of growth hormone secretagogue (ghrelin) receptors agonists.[13] At the end, the 3-aminooxindole structure is the key pharmacophore in compound AG-041R, a potent gastrin/CCK-B receptor antagonist.[14]

## 2. Results and discussion

The light of the relevance of the oxindole nucleus, mainly as key framework of non-peptidic ligands for G-protein-coupled receptors, we report here the synthesis of the spiropiperidine-3,3′-oxindole-based peptide isostere **6**, acting as a potent type II β-turn mimetic (Fig. 2). Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their structural implications on biological systems.[15] Compound **6** can be regarded as an highly constrained Freidinger γ-lactam, bearing a fused aromatic ring as recognition group and a spiropiperidine ring as further element of conformational restriction.

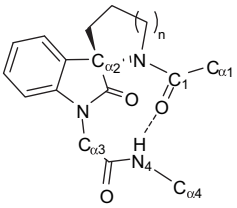



**Figure 2.** Parameters for the characterization of β-turn propensity of spirooxindole-based scaffolds.

The reverse turn mimicry ability of spirooxindole scaffolds was firstly evaluated by performing a computer-assisted[16] conformational analysis on compounds like **6**, as a function of the dimension of the spiro ring in position 3 of the oxindole skeleton. The computed main geometric features of β-turns are the interatomic distance $d\alpha$ ($C\alpha_1$–$C\alpha_4$), which should be less than 7 Å, the virtual torsion angle $\beta$ ($C_1$–$C\alpha_2$–$C\alpha_3$–$N_4$), which should be $|\beta|<30°$ and the possible presence of the characteristic hydrogen bond $C_1O\cdots HN_4$, that was estimated by means of the 'hydrogen bonds' function implemented in the software.[17] The computational procedure consisted in an unconstrained Monte Carlo/Energy Minimization conformational search using the molecular mechanics MMFF94 force field[18] in vacuo. For each compound only conformations within 6 kcal/mol of the global minimum were kept. Results are reported in Table 1 as percentage of conformers, which meet the requirements for a generic β-turn.

**Table 1**
MC/EM conformational analysis for spirooxindole-based scaffolds[a]

| *N* | No. of conf. <6 kcal/mol | % $d_\alpha$<7 Å | % $\|\beta\|$<30° | % H bond |
|---|---|---|---|---|
| 0 | 8 | 50 | 50 | 25 |
| 1 | 4 | 50 | 50 | 50 |
| 2 | 6 | 67 | 67 | 67 |
| 3 | 4 | 50 | 50 | 50 |

[a] Results are reported as percentage of conformers, which meet the indicated requirement.

The highest percentage of conformers having a β-turn geometry is achieved by oxindole **6**, bearing a spiropiperidine ring ($n$=2). For this structure, 67% of conformers have $d\alpha$<7 Å, $|\beta|$ <30° and also show a ten membered intramolecular hydrogen bond. According to definition of β-turn types, the analysis of the dihedral angle values of the amide backbone for the global minimum of **6**, ascribes this compound to a type II β-turn (Table 2). The same global minimum was found, both in vacuo and in water, the latter being implicitly represented by a solvation model.[19]

**Table 2**
Calculated values of selected geometrical parameters for the MM/MC lowest energy conformer of **6**

| Compd | $\Phi_{(i+1)}$; $\psi_{(i+1)}$ (deg) | $\Phi_{(i+2)}$; $\psi_{(i+2)}$ (deg) | $d(C\alpha_{(i)}\cdots C\alpha_{(i+3)})$ (Å) | $\beta$ (deg) |
|---|---|---|---|---|
| **6** | −52.00; 126.53 | 101.71; −30.37 | 5.472 | 9.65 |
| II β-turn (ideal) | −60; 120 | 80; 0 | 4.745 | −1.95 |

The similarity between **6** and a type II β-turn model was evaluated by superimposing their amide backbone. An alignment score of 0.95[20] was obtained, thus confirming the good ability of **6** to mimic such a secondary structure (Fig. 3).

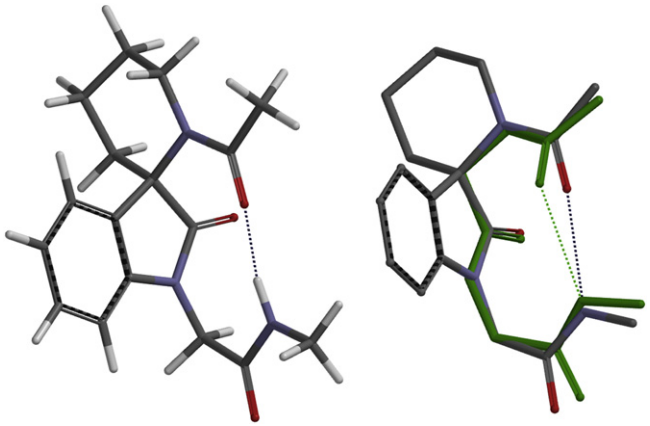
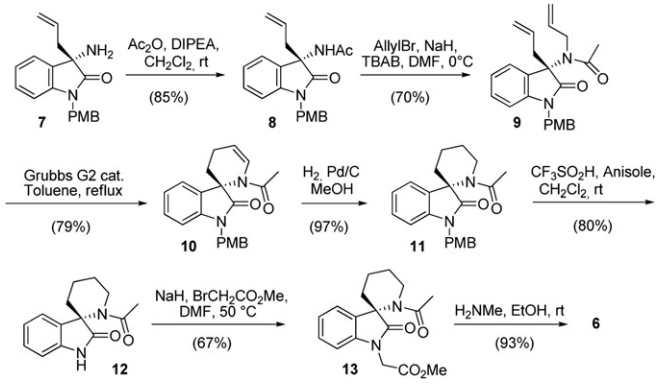


**Figure 3.** Lowest energy conformer for **6** obtained by MC/MM calculations. Superimposition with standard type II β-turn (in green) is shown.

On the basis of predictions from computational studies, we then focused our attention to the synthesis of compound **6**, according to the Scheme 1. We recently developed the diastereoselective Grignard addition of imines derived from isatine.[6] Following the described protocol, amine **7** could be obtained in good yield as a 3*S* single enantiomer. Acetylation of **7** with acetic anhydride to give **8**, followed by allylation of the amide nitrogen with allyl bromide, afforded diene **9** in good overall yields. Diene **9** was submitted to a ring closing metathesis reaction (RCM) with Grubbs' second generation catalyst in refluxing toluene.[21] The spirooxindole **10** was obtained in 79% yield after chromatographic purification. $^1$H NMR investigation revealed the metal-promoted shift to enamide of the newly formed double bond. Hydrogenation of the double bond to




**Scheme 1.**

give **11** was followed by removal of PMB protecting group with $CF_3SO_2H$/anisole. The resulting **12** was subjected to alkylation with methyl bromoacetate to afford **13**, and then treated with methylamine to give the desired tetrapeptide mimetic **6**.

The spiropiperidine oxindole **6** was fully characterized by means of 1D- and 2D-dimensional NMR spectroscopy. The study of conformational behaviour was conducted in $CDCl_3$, at 2.0 mM concentration to avoid intermolecular aggregation, in order to assess the presence of the intramolecular hydrogen bond.[22] The participation of the NH amide proton in intramolecular hydrogen bonding was first estimated by evaluation of its chemical shift value and of the temperature coefficient, recording five spectra from 303 K to 343 K with increments of 10 K. Downfield chemical shift value (7.80 ppm at 303 K) and small temperature coefficient (−3.6 ppb/K) were found, thus supporting the involvement of NH in an equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state. Besides, DMSO titration studies in $CDCl_3$ indicate that the chemical shift of NH in **6** is almost constant up to 30% of the hydrogen bond-acceptor solvent DMSO (chemical shift difference of 0.16 ppm in absolute value), thus confirming the presence of a rather stable intramolecular H-bonded conformation. From NMR spectra, a prevalent rotamer seems to be present for the acetyl–piperidine moiety; further, the NOESY experiment highlights a strong NOE interaction between the acetyl group and the N–$CH_2$ protons of the piperidine ring, only detectable in a H-bonded conformation similar to that shown in Figure 3. Finally, a further probe of a constrained conformation for **6** was derived from $^1$H NMR analysis of the AB system of the geminal glycyl residue,[23] comparing the chemical shift difference in $CDCl_3$ between the two α-protons, $\Delta\delta_{\alpha/\alpha'}$, in the case of non-hydrogen bonded compound **13** and in the case of hydrogen bonded compound **6**. This difference was found 0.72 ppm for **13** and 0.92 ppm for **6**, thus suggesting the strong preference of **6** for a turn state.

The FT-IR spectrum of a 2.0 mM solution of **6** in $CHCl_3$ showed a strong absorption band at 3350 $cm^{-1}$ for an hydrogen-bonded NH stretching together with a weak band at 3438 $cm^{-1}$ for the non-hydrogen-bonded NH stretching, in accordance with the prevalence of a conformational constrained state in this molecule.

## 3. Conclusions

In summary, we have prepared a spiropiperidine oxindole-based peptide isostere, with the purpose of exploring its conformational behaviour. The synthesis starts from a previously described enantiopure quaternary 3-aminooxindole and relies on a ring closing metathesis as the key step for attaining the spiropiperidine ring. Conformational analysis by means of modelling and NMR and IR spectroscopies assesses a type II β-turn conformation for this compound. Work is now underway to evaluate the application of this novel spirocyclic peptide isostere to the synthesis of β-turned ligands for G-protein-coupled receptors.

## 4. Experimental section

### 4.1. General methods

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were run under $N_2$, unless otherwise indicated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 $F_{254}$; spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). $^1$H and $^{13}$C NMR spectra were recorded using 300 and 400 MHz spectrometers. Chemical shifts ($\delta$) are expressed in ppm relative to TMS at $\delta$=0 ppm for $^1$H NMR and to $CDCl_3$ at $\delta$=77.16 ppm for $^{13}$C NMR. High-resolution MS spectra were recorded using a FT-ICR (Fourier Transform Ion Ciclotron Resonance) instrument, equipped with ESI source, or a standard MS instrument, equipped with EI source. IR spectra were recorded using a FTIR instrument.

*4.1.1. N-[(S)-3-Allyl-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-acetamide (**8**).* To a solution of amine **7** (70 mg, 0.23 mmol, 1 equiv) in dry $CH_2Cl_2$ (3 mL) at 0 °C and under nitrogen atmosphere, *i*-$Pr_2NEt$ (59 μL, 0.34 mmol, 1.5 equiv) and $Ac_2O$ (32 μL, 0.34 mmol, 1.5 equiv) were added. The solution was stirred for 2 h at room temperature before addition of 5% aq $H_3PO_4$ solution (5 mL). Then the aqueous layer was extracted twice with $CH_2Cl_2$ (10 mL). The collected organic phases were dried over $Na_2SO_4$ and evaporated under reduced pressure to afford **8** (65 mg, 85%) as a clear oil, which was used in the next step without any further purification. $R_f$=0.38 (EtOAc). $[\alpha]_D^{25}$ −32.6 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.35 (d, *J*=8.6 Hz, 2H), 7.22 (dd, *J*=7.5, 0.6 Hz, 1H), 7.16 (ddd, *J*=7.8, 7.5, 1.1 Hz, 1H), 7.03 (ddd, *J*=7.8, 7.5, 0.6 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 2H), 6.69 (d, *J*=7.8 Hz, 1H), 6.26 (s, 1H), 5.81 (ddt, *J*=17.3, 10.0, 7.5 Hz, 1H), 5.29 (dd, *J*=17.3, 1.4 Hz, 1H), 5.25 (br d, *J*=10.0 Hz, 1H), 4.96 (d, *J*=15.8 Hz, 1H), 4.93 (d, *J*=15.8 Hz, 1H), 3.79 (s, 3H), 2.70 (dd, *J*=13.4, 7.6 Hz, 1H), 2.54 (dd, *J*=13.4, 7.2 Hz, 1H), 2.00 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 176.0, 168.9, 158.9, 142.6, 130.3, 129.6, 128.7, 128.5 (2C), 127.8, 122.5, 122.4, 121.3, 114.1 (2C), 109.5, 60.7, 55.2, 43.6, 41.8, 22.7. HRMS (EI) calcd for $C_{21}H_{22}N_2O_3$ 350.1630, found 350.1626.

*4.1.2. N-Allyl-N-[(S)-3-allyl-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-acetamide (**9**).* A solution of **8** (80 mg, 0.23 mmol, 1 equiv), $Bu_4NBr$ (73 mg, 0.23 mmol, 1 equiv) and allyl bromide (96 μL, 1.14 mmol, 5 equiv) in dry DMF (5 mL) was stirred for 20 min at 0 °C under a nitrogen atmosphere. After that time, 95% NaH (16 mg, 0.68 mmol, 3 equiv) was added and the solution was stirred at room temperature for 1 h. The reaction was then diluted with water (10 mL) and extracted three times with ethyl acetate (15 mL). The organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure, to give a crude product, which was purified with flash chromatography (hexane/EtOAc 1:7) to afford **9** (62 mg, 70% yield), as a clear oil. $R_f$=0.31 (EtOAc). $[\alpha]_D^{25}$ −41.9 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.38 (d, *J*=8.7 Hz, 2H), 7.15 (d, *J*=7.2 Hz, 1H), 7.14 (ddd, *J*=7.7, 7.2, 0.9 Hz, 1H), 6.98 (ddd, *J*=7.7, 7.2, 0.6 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 6.65 (d, *J*=7.7 Hz, 1H), 6.07 (dddd, *J*=17.2, 10.6, 5.2, 4.0 Hz, 1H), 5.69 (d, *J*=17.2, 1H), 5.44 (d, *J*=10.6, 1H), 5.18 (ddt, *J*=17.1, 9.8, 7.0 Hz, 1H), 4.99 (d, *J*=17.1, 1H), 4.94 (d, *J*=16.1, 1H), 4.88 (d, *J*=9.8, 1H), 4.81 (d, *J*=16.1, 1H), 4.39 (ddt, *J*=18.8, 4.0, 1.9 Hz, 1H), 4.30 (ddt, *J*=18.8, 5.2, 1.6 Hz, 1H), 3.80 (s, 3H), 2.86 (dd, *J*=12.4, 7.0, 1H), 2.80 (dd, *J*=12.4, 7.0, 1H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 176.1, 170.8, 158.8, 143.4, 135.0, 134.3, 129.9, 129.2, 128.8 (2C), 128.3, 122.1, 121.6, 120.2, 117.6, 113.9 (2C), 108.8, 66.1, 55.2, 47.6, 43.7, 40.0, 22.5. HRMS (EI) calcd for $C_{24}H_{26}N_2O_3$ 390.1943, found 390.1956.

*4.1.3. (S)-1′-Acetyl-1-(4-methoxy-benzyl)-3′,4′-dihydro-spiro[indoline-3,2′-pyridin]-2-one (**10**).* To a solution of **9** (140 mg, 0.36 mmol, 1 equiv) in dry toluene (3 mL) under nitrogen atmosphere, second generation Grubbs' catalyst (31 mg, 10% mol) was added and the solution was heated to reflux for 24 h. The solution was then evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane/EtOAc 1:9) to afford **10** (100 mg, 79%), as a brown oil. $R_f$=0.31 (EtOAc). $[\alpha]_D^{25}$ −17.6 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.37 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=7.1 Hz, 1H), 7.16 (ddd, *J*=7.6, 7.1, 1.2 Hz, 1H), 6.97 (ddd, *J*=7.6, 7.1, 0.8 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 2H), 6.84 (dd, *J*=7.8, 1.4 Hz, 1H), 6.70 (d, *J*=7.6 Hz, 1H), 5.19 (br t, *J*=7.8 Hz, 1H), 4.99 (d, *J*=15.8 Hz, 1H), 4.92 (d, *J*=15.8 Hz, 1H), 3.80 (s, 3H), 2.43–2.35 (m, 1H), 2.34–2.25

(m, 2H), 2.19 (s, 3H), 1.77–1.70 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 176.2, 167.3, 158.9, 142.1, 131.1, 128.5 (3C), 128.1, 126.4, 122.5, 122.2, 114.1 (2C), 109.3, 106.3, 61.2, 55.2, 43.6, 31.2, 21.7, 18.0. HRMS (EI) calcd for $C_{22}H_{22}N_2O_3$ 362.1630, found 362.1622.

*4.1.4. (S)-1′-Acetyl-1-(4-methoxy-benzyl)spiro[indoline-3,2′-piperidin]-2-one (**11**).* To a solution of **10** (100 mg, 0.28 mmol, 1 equiv) in MeOH (5 mL), 10% Pd/C (10 mg) was added and the reaction was stirred at room temperature under a hydrogen atmosphere for 3 days. The suspension was then filtered through a pad of Celite and evaporated under reduced pressure to afford **11** (98 mg, 97%), as a pale yellow oil. $R_f$=0.47 (EtOAc). $[\alpha]_D^{25}$ −39.0 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.34 (d, *J*=8.6 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 1H), 7.14 (ddd, $J_1$=$J_2$=7.6 Hz, $J_3$=1.0 Hz, 1H), 6.96 (dd, $J_1$=$J_2$=7.6 Hz, 1H), 6.88 (d, *J*=8.6 Hz, 2H), 6.68 (d, *J*=7.6 Hz, 1H), 5.00 (d, *J*=15.6 Hz, 1H), 4.86 (d, *J*=15.6 Hz, 1H), 3.95 (dt, *J*=12.6, 5.1 Hz, 1H), 3.79 (s, 3H), 3.71–3.62 (m, 1H), 2.16–1.90 (m, 4H), 2.10 (s, 3H), 1.88–1.65 (m, 1H), 1.68 (dt, *J*=13.5, 4.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 177.7, 171.3, 159.5, 143.0, 132.3, 129.1 (3C), 128.7, 122.6, 122.4, 114.8 (2C), 110.0, 62.8, 55.8, 44.8, 44.2, 34.1, 24.4, 22.9, 17.6. HRMS (EI) calcd for $C_{22}H_{24}N_2O_3$ 364.1787, found 364.1792.

*4.1.5. (S)-1′-Acetylspiro[indoline-3,2′-piperidin]-2-one (**12**).* To a mixture of **11** (30 mg, 0.08 mmol, 1 equiv) and anisole (135 μL, 1.26 mmol, 15 equiv) in dry $CH_2Cl_2$ (2 mL), at 0 °C and under nitrogen atmosphere, $CF_3SO_2H$ (73 μL, 0.82 mmol, 10 equiv) was added and the reaction was stirred at room temperature for 3 h. The solution was then basified with saturated aq $NaHCO_3$ solution (5 mL) and extracted twice with $CH_2Cl_2$ (10 mL). The organic layer was separated, dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude was purified with flash chromatography (EtOAc), to afford **12** (16 mg, 80%), as a pale yellow oil. $R_f$=0.47 (EtOAc). $[\alpha]_D^{25}$ −12.4 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.55 (br s, 1H), 7.26 (d, *J*=7.5 Hz, 1H), 7.24 (dd, *J*=7.7, 7.5 Hz, 1H), 6.99 (dd, *J*=7.7, 7.5 Hz, 1H), 6.87 (d, *J*=7.7 Hz, 1H), 3.93 (dt, *J*=12.9, 4.8 Hz, 1H), 3.64 (ddd, *J*=12.9, 9.0, 5.3 Hz, 1H), 2.11 (s, 3H), 2.10–2.05 (m, 1H), 2.05–1.89 (m, 3H), 1.87–1.76 (m, 1H), 1.72 (dt, *J*=13.4, 4.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 178.4, 170.9, 140.4, 131.9, 128.3, 122.5, 121.9, 109.9, 62.2, 44.2, 33.2, 23.8, 22.4, 17.0. HRMS (EI) calcd for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1223.

*4.1.6. (S)-Methyl 2-(1′-acetyl-2-oxospiro[indoline-3,2′-piperidine]-1-yl)acetate (**13**).* To a solution of **12** (35 mg, 0.14 mmol, 1 equiv) in dry DMF (3 mL), NaH (7 mg, 0.28 mmol, 2 equiv) and methyl bromoacetate (27 μL, 0.28 mmol, 2 equiv) were added and the solution was stirred for 2 h at 50 °C. The reaction was then quenched with saturated aq $NH_4Cl$ solution (4 mL) and extracted twice with EtOAc (10 mL). The organic phase was then washed with brine (10 mL). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure, to afford **13** (31 mg, 67%), as a yellow oil, which was used in the next step without further purification. $R_f$=0.29 (EtOAc). $[\alpha]_D^{25}$ −48.7 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.30 (d, *J*=7.7 Hz, 1H), 7.27 (dd, *J*=7.9, 7.7 Hz, 1H), 7.03 (dd, *J*=7.9, 7.7 Hz, 1H), 6.74 (d, *J*=7.9 Hz, 1H), 4.91 (d, *J*=17.7 Hz, 1H), 4.20 (d, *J*=17.7 Hz, 1H), 3.93 (dt, *J*=12.9, 5.0 Hz, 1H), 3.78 (s, 3H), 3.70–3.61 (m, 1H), 2.12 (s, 3H), 2.10–1.88 (m, 4H), 1.87–1.80 (m, 1H), 1.77 (dt, *J*=14.0, 4.1 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 177.4, 171.5, 169.2, 142.5, 131.9, 128.9, 122.9 (2C), 108.8, 62.7, 53.0, 44.8, 42.1, 33.9, 24.3, 22.8, 17.5. HRMS (EI) calcd for $C_{17}H_{20}N_2O_4$ 316.1423, found 316.1431.

*4.1.7. (S)-2-(1′-Acetyl-2-oxospiro[indoline-3,2′-piperidine]-1-yl)-N-methylacetamide (**6**).* To a solution of **13** (26 mg, 0.08 mmol, 1 equiv) in dry ethanol (3 mL), under nitrogen atmosphere and at 0 °C, an 8 M solution of $MeNH_2$ in EtOH (3 mL) was added. After removing the cooling bath, the reaction mixture was stirred at room temperature overnight. The solution was then evaporated under reduced pressure affording pure **6** (20 mg, 93%), as a pale yellow foam. $R_f$=0.29 (EtOAc). $[\alpha]_D^{25}$ −17.0 (*c* 1.0, $CHCl_3$). FTIR $\nu_{max}$ ($CHCl_3$) 3438.46, 3350.71, 1669.09, 1644.98, 1601.59, 1467.56, 1380.78, 1096.33. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 7.73 (br s, 1H), 7.33–7.27 (m, 2H), 7.08 (ddd, *J*=8.0, 7.5, 1.0 Hz, 1H), 6.83 (dd, *J*=8.0, 0.9 Hz, 1H), 4.89 (d, *J*=17.2 Hz, 1H), 3.97 (d, *J*=17.2 Hz, 1H), 3.94 (dt, *J*=13.0, 5.0 Hz, 1H), 3.69 (dt, *J*=13.0, 7.4 Hz, 1H), 2.74 (d, *J*=4.7 Hz, 3H), 2.10 (s, 3H), 2.08–1.94 (m, 4H), 1.89–1.78 (m, 1H), 1.71 (dt, *J*=13.7, 4.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) 170.8, 167.6, 141.4, 130.8, 128.7, 122.8, 122.3, 108.6, 62.1, 44.1, 43.5, 32.6, 29.6, 26.1, 23.4, 22.3, 16.5. HRMS (EI) calcd for $C_{17}H_{21}N_3O_3$ 315.1583, found 315.1588.

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