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Highly Diastereoselective Cascade [5+1] Double Michael Reaction, a Route for the Synthesis of Spiro Thio-oxindoles

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Abstract

The first diastereoselective synthesis of spiro-thiooxindole is reported via Michael reaction between thiooxindoles and divinyl ketones. The reaction was conducted without any catalyst or additive under green conditions, i.e., ethanol as the solvent and room temperature. This study showed the art of governing regioselectivity in which novel spiro frameworks were generated in high yields. In addition to simple and column chromatography-free purification, the high diastereoselectivity makes this protocol very robust. The regio- and stereo- selectivity of the reaction has been discussed in light of the theoretical calculations, and molecular docking has been performed on the reaction products. Our method presents the first synthesis of *cis*-spiro thiooxindoles, which can be used to generate *cis*-spiro oxindoles. According to our docking studies, the latter demonstrates higher binding affinities towards the LdUMPS than corresponding *trans*-spiro oxindoles and may be utilized to develop new hit compounds for leishmaniasis treatment.

Keywords: Spiro-thiooxindole, Michael addition, Diastereoselective

Introduction

Oxindole scaffolds have been found as a vital pharmacophore,¹ encountered in natural products^{2,3} and pharmaceutical compounds. Inspired by the presence of spiro oxindole in several natural products such as gelsemine, chitosenine, spirotryprostatin B, and NITD609⁴⁻¹¹ (Figure 1), it is known that introducing a tetrahedral spiro carbon can further improve bioactivity by providing structural rigidity.¹²

Figure 1. Biologically active natural products with a spiro oxindole scaffold.

For this reason, there have been numerous efforts towards the synthesis of heterocycles containing spiro oxindole as the core structure.¹³⁻¹⁸ Among different methodologies that have been developed for the synthesis of spiro molecules,^{19,20} the Michael addition is one of the most robust.²¹⁻²⁴ Recently, the organocatalytic cascade Michael addition has emerged as an efficient strategy to provide spirocyclic oxindole structures in one-pot.²⁵⁻²⁹ For example, Wu *et al.* demonstrated a cascade [5+1] double-Michael addition between divinyl ketones and oxindoles³⁰ to afford spiro cyclohexanone oxindoles (scheme 1A). Later, Géant *et al.* applied tandem [5+1] double-Michael addition to obtaining spiro benzothiophenone cyclohexanone derivatives with high optical purity (Scheme 1B).³¹

Scheme 1. Comparison of different cascade [5+1] double Michael additions of divinyl ketones.

However, despite all previous efforts in the synthesis of spiro oxindoles with *trans* R¹ and R² groups, the synthesis of *cis*-spiro oxindoles has remained unexplored to the best of our knowledge. Since all previous biological studies have only focused on *trans*-spiro oxindoles, the *cis* isomer could be a demanding target for synthesis as it may further expand the biological activities of oxindoles. For example, Scala *et al.* discovered *trans*-spiro cyclohexanone oxindoles are efficient inhibitors that kill *Leishmania infantum* promastigotes and amastigotes without significant cytotoxic effects.³² More evidence for high activity of spiro oxindoles against leishmaniasis were confirmed later by Saha *et al.*³³ The

leishmaniasis are a group of diseases caused by protozoan parasites from more than 20 *Leishmania* species.³⁴ A better understanding of leishmaniasis was provided when French et al. demonstrated that *L. donovani* uridine 5'-monophosphate synthase (LdUMPS) is an essential enzyme for promastigotes viability and presented the crystal structure of the LdUMPS in complex with its product, UMP.³⁵ Their structural analysis revealed a tetrameric structure for LdUMPD with two dimeric OMPDC and two dimeric OPRT functional domains. As a result of this unusual structure, the oligomerization of LdUMPS is controlled by ligand binding at the OPRT active site.

Regarding the structure-activity relationship, we hypothesized a *cis*-spiro (thio)oxindole might have a higher affinity towards the OPRT domain of LdUMPS than the *trans* isomer. To test this initial idea, we first performed some docking studies and then introduced a method to synthesize *cis*-spiro cyclohexanone thiooxindoles. In the next step and in continuation of our previous works on oxindole chemistry,^{36,37} we employed thiooxindole to react with divinyl ketones. The highly diastereoselective [5+1] double Michael addition resulted in *cis*-spiro cyclohexanone thiooxindoles, which could be later converted to *cis*-spiro cyclohexanone oxindoles. Finally, density functional theory (DFT) was used to explain the reaction regioselectivity and stereoselectivity.

Result and discussion:

Table 1. Calculated binding energies (kcal mol⁻¹) of *trans/cis*-spiro (thio)oxindoles with OPRT domain of LdUMPS.

1	2	3	4
-7.30 kcal mol ⁻¹	-7.90 kcal mol ⁻¹	-6.80 kcal mol ⁻¹	-7.50 kcal mol ⁻¹

To gain an insight into the molecular determinants that can modulate the antagonistic activities of oxindole and thiooxindole, molecular docking studies were performed on *cis* and *trans* isomers. The results (Table 1), generated based on the crystal structure of the LdUMPS receptor, revealed that *cis*-spiro oxindole has the highest binding affinity towards LdUMPS active site. It binds to the OPRT domain of the LdUMPS receptor through interactions with Arg23, Phe54, Lys84, Asn138, Val175, Ser137, Pro199, Gln204, and Lys49 (figure 2, figure S1). The higher binding energy of *cis*-spiro oxindole compared with the *trans* isomer relies on steric hindrance between *trans*-(thio)oxindole and the active site. It seems electronic factors are responsible for higher activity of *trans*-oxindole in comparison with *trans*-thiooxindole.

Figure 2. Interaction between *cis*-spiro oxindole **2** with (A) OPRT domain of the LdUMPS (PDB ID: 2WNS) and (B) residual amino acids of the active site; Arg23, Phe54, Lys84, Asn138, Val175, Ser137, Pro199, Gln204, and Lys49. 4b. The figure is drawn using UCSF chimera 1.8 and AutoDock version 1.5.6.^{38,39}

Motivated by the initial docking results, which confirmed the importance of designing a robust synthetic method to provide *cis*-oxindole **2**, we therefore commenced the synthesis design. Since all previously applied Michael reactions on oxindole have far resulted in the *trans* isomer **1** formation, it was hypothesized replacing the carbonyl group of the oxindole with a thiocarbonyl group may introduce an intramolecular repulsion between the large lone pair electrons of sulfur and aryl π electrons. This could favor the formation of *cis* thiooxindole **4**, which after one extra step can be converted to *cis* oxindole **2**. The hypothesis was confirmed by theoretical calculations. The DFT computations (figure 3) demonstrated due to the electronic repulsion; the *cis* isomer **4** is more thermodynamically stable than *trans* isomer **3** (table S1). These results also explain why previous works on oxindole, where the *trans* isomer **1** is more stable than **2**, could only result in the *trans* isomer formation.

Figure 3. HOMO electronic cloud of (A) *cis*-spiro oxindole **2** and (B) *cis*-spiro thiooxindole **4**. The diffusive electronic cloud around the sulfur atom in thiooxindole makes the *cis* isomer more stable than the *trans* isomer. DFT calculations were performed using B3LYP/6-31+G(d) in the gas phase.

In the next step, thiooxindole derivatives were generated from the reaction of oxindole with P₂S₅ and sodium bicarbonate in dry THF. Dibenzal ketones were prepared through the condensation reaction of aldehyde and ketone in the presence of a suitable base and ethanol as the solvent. The [5+1] double Michel addition reaction was carried out on an equimolar mixture of freshly prepared thiooxindole **6** with divinyl ketone to provide single diastereoisomer **7** in high yield which was characterized through spectral analysis. The

regio and diastereoselectivity of this reaction were established by the aim of the one- and two-dimensional NMR. In ^1H -NMR, compound **7** displayed two doublets at δ 6.55 and 6.65 ppm, equivalent to 4 protons for each signal. This confirmed the *p*-ethoxyphenyl groups of the thiooxindole moiety exist at the *cis* position to each other. In the ^1H and ^{13}C -NMR spectra, no signal was observed related to other diastereoisomers. Further analysis by COSY, NOESY, and single-crystal X-ray diffraction, revealed that the aryl groups stand toward the phenyl part of thiooxindole.

However, the high regioselectivity of this reaction was a surprise as one could expect to observe the Michael addition on alpha carbon and sulfur atoms which results in the formation of an eight-member ring. To explain the observed regioselectivity, we used DFT calculations. Looking at the charge distribution (figure 4), we noticed the alpha carbon of thiooxindole has a more negative charge than sulfur – even after the first addition – and thus can act as a better nucleophile. Furthermore, the alpha carbon of thiooxindole **6** has a more negative charge than the alpha carbon of oxindole **5**. Accordingly, thiooxindole **6** is a better Michael donor than oxindole **5**. This trend is in agreement with the strong resonance between N and C=O in oxindole, whereas in thiooxindole there is a stronger resonance between the alpha carbon and C=S. Therefore, the charge distribution explains the formation of spiro structure over the eight-membered ring compounds.

Figure 4. Mulliken charge distribution on (A) N-methyl oxindole **5**, (B) N-methyl thiooxindole **6** and (C) the intermediate after the first Michael addition on N-methyl thiooxindole **6**. Calculations were performed using B3LYP/6-31G(d) in the gas phase.

Table 2. Optimization of the double Michael addition reaction condition ^s				
Entry	Base	Solvent	Temperature (°C)	Yield ^b (%)
1	K ₂ CO ₃ ^c	EtOH	23	21
2	K ₂ CO ₃	EtOH	23	81
3	K ₂ CO ₃ ^d	EtOH	23	56
4	-	EtOH	23	-
5	DABCO	EtOH	23	20
6	NaOH	EtOH	23	trace
7	K ₂ CO ₃	Toluene ^e	23	31 ^f

8	K ₂ CO ₃	THF	23	trace
9	K ₂ CO ₃	H ₂ O	23	trace
10	K ₂ CO ₃	MeOH	23	trace
11	K ₂ CO ₃	DCM	23	trace
12	K ₂ CO ₃	EtOH	reflux	36

^a 0.5 mmol thiooxindole (1.0 eq), 0.5 mmol dibenzal ketone (1.0 eq), 0.5 mmol base (1.0 eq), 20 mL solvent.
^b Isolated yield
^c 0.025 mmol base (0.5 eq) was used.
^d 0.5 mmol L-proline (1.0 eq) was used as an organocatalyst.
^e Mixture of *cis* and *trans* products was obtained.
^f Isolated yield of the *cis* product.

Delighted by these results, various optimization experiments were conducted to obtain the optimal reaction conditions using the reaction mentioned above as the model (table 2). The results showed K₂CO₃ accelerates the deprotonation step and thus promotes the reaction to proceed faster. The efficiency of this process could be further improved by increasing the amount of base up to 100 mol%. Exploring the effect of temperature showed that if the reaction was carried out in ethanol at the higher temperature (reflux), the yield of compound **7** would decrease. We also studied the effect of L-proline in the reaction, which resulted in a lower yield. Initially, it was expected L-proline would accelerate the reaction by forming dibenzal iminium intermediate. However, DFT calculations revealed the beta carbon of dibenzal iminium has less positive charge than the beta carbon of dibenzal ketone (figure S2), and thus the latter is a better Michael acceptor.

Scheme 2. Double Michael addition reaction of oxindole and thiooxindole on dibenzal ketones in ethanol and toluene.

In the next step, the role of the solvent on the reaction was surveyed. Toluene has been previously used to convert oxindole **5** to *trans*-spiro cyclohexanone oxindole **1** (scheme 2A) as an aprotic and apolar solvent. The same reaction condition on thiooxindole **6**, resulted in a mixture of *cis* and *trans* spiro products **3** and **4** (Scheme 2B). We, therefore, introduced a method using ethanol as a polar and protic solvent that produces *cis*-spiro cyclohexanone thiooxindole **3** as a single diastereomer (Scheme 2D). It is worth mentioning that treating the oxindole **5** under our reaction condition ended with a mixture of *cis* and *trans* spiro cyclohexanone oxindole (scheme 2C). Therefore, we concluded both solvent and substrate electronic structure are involved in the determination of reaction diastereoselectivity. To better understand these effects, conductor-like polarizable continuum model (CPCM)⁴⁰ was used in our DFT calculations. The theoretical results (figure S3) revealed *trans* configuration is more favorable in toluene, whereas the *cis* configuration can form easier in ethanol. This selectivity comes from the fact that the energy level of molecular orbitals and thus the repulsion between the chalcogen lone pair electrons and π electrons of aryl groups depends on the polarity of the solvent. Thus, the double Michael addition on oxindole in ethanol and on thiooxindole in toluene resulted in selective formation of **1** and **4**, respectively. However, when the reaction performed on oxindole in toluene and on thiooxindole in ethanol, the solvent and electronic effects became in conflict with each other, and a mixture of *cis* and *trans* isomers was obtained.

To further illustrate the scope of this reaction for the synthesis of complex heterocyclic spirothiooxindoles, N-methylthiooxindole and N-phenylthiooxindole with dibenzal ketones bearing electron-donating or withdrawing group were used. The obtained results are summarized in Table 3. The reaction furnished spiro framework as a single diastereomer and in moderate to good yield in all cases. Furthermore, we successfully scaled up the process and isolated >35g of compound **7** with 66% yield.

Table 3. Double Michael addition of thiooxindole on dibenzal ketone, reaction yield, and binding energies (kcal mol⁻¹) with OPRT domain of LdUMPS.

4 Yield: 72% -7.90 kcal mol ⁻¹	10 Yield: 62% -7.05 kcal mol ⁻¹
7 Yield: 81% -8.11 kcal mol ⁻¹	11 Yield: 79% -7.26 kcal mol ⁻¹

8 Yield: 69% -7.85 kcal mol ⁻¹	12 Yield: 20% -7.15 kcal mol ⁻¹
9 Yield: 21% -5.58 kcal mol ⁻¹	13 Yield: 15% -4.59 kcal mol ⁻¹

The potential of synthesized compounds as inhibitors of LdUMPS was then recognized by molecular docking (table 3). Our study showed that **7** fits better into the active site of the receptor. N-phenyl derivatives sterically intercut this fitting, and as a result, they have a lower binding affinity. Finally, we demonstrated it is possible to convert synthesized thiooxindoles into oxindole (scheme 3). Thus, our method opens a new window in the formation of biologically important *cis*-spiro oxindoles and *cis*-spiro thiooxindoles.

Scheme 3. Conversion of *cis*-spiro thiooxindole into *cis*-spiro oxindole

Conclusion:

In summary, we have introduced a robust synthetic strategy for diastereomerically-pure spiro (thio)oxindole via double Michael addition of thiooxindoles on dibenzal ketones. The reaction furnished corresponding spiro products in only one diastereomer. The regioselectivity and stereoselectivity of the reaction were discussed in light of the computational results. Molecular docking studies were performed on the reaction products, which demonstrated high binding affinities towards the OPRT domain of the LdUMPS receptor. Our reported protocol is catalyst-free, scalable, has mild reaction conditions, and there is no need to work-up and column chromatography. These advantages make this method a suitable candidate for synthesizing complex heterocyclic spiro (thio)oxindole systems in synthetic and medicinal chemistry.

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Experimental

General information

All materials used are commercially available and were purchased from Merck and used without any additional purification. ^1H NMR, ^{13}C NMR, and 2-D NMR spectra were recorded on a Bruker (Avance DRX-500) spectrometer using CDCl_3 or $\text{DMSO}-d_6$ as solvent at room temperature. Chemical shifts (δ) are given in parts per million (ppm) and are reported relative to residual solvent peaks: CDCl_3 (δ 7.26, δ 77.16 ppm), $\text{DMSO}-d_6$ (δ 2.50, δ 39.52 ppm). Coupling constants (J) are given in Hertz (Hz). FTIR spectra of samples were taken using an ABB Bomem MB-100 FTIR spectrophotometer. HRMS analyses were performed using a TOF mass analyzer on Mat95XP-Trap apparatus. X-ray crystallography was carried out through APEX II CCD BRUKER detector.

Computational studies

In all calculations, B3LYP DFT functional theory⁴¹ and 6-31G(d) basis set⁴² was used. Calculations were performed in the gas phase or solution by CPCM model and at 298.15 K. Conformer distribution was studied by Spartan,⁴³ and Gaussian09⁴⁴ was used for other calculations. The first frequency was utilized to assess whether structures were in the true optimized structure. The docking study was performed by using the Autodock 1.5.6. The size of the grid box was set to 20 Å. The enzyme structure was downloaded from the website protein data banks (PDB ID: 2WNS) and ligands optimized at 6-31G(d)-B3LYP level of theory by Gaussian. Auto Dock tools programs were used to visualize the complex in 3D. All single bonds of residue side chains inside the grid box were regarded as rotatable, and the docked ligand was allowed to rotate on all the single bonds and move flexibly within the grid box. The structural optimization was performed for 50,000 generations using a genetic algorithm.

General procedure for the synthesis of dibenzalketone

Preparation of dibenzal ketone from solid aldehyde: A mixture of LiClO_4 (5 mmol), Et_3N (5 mmol), ketone (5 mmol), and aldehyde (5 mmol) in 20 mL ethanol as solvent was stirred at room temperature. TLC monitored reaction completion. After the completion of the reaction, the solvent was removed by rotatory evaporation at reduced pressure, and the residue was washed by ethanol to afford the pure product.

Preparation of dibenzal ketone from liquid aldehyde: A mixture of NaOH (25 mmol), ketone (5 mmol), and aldehyde (5 mmol) in the mixture of $\text{H}_2\text{O}/\text{EtOH}$ (10:8) was stirred at room temperature for 10 minutes. Again, ketone (5 mmol) and aldehyde (5 mmol) were added to the reaction mixture. TLC monitored reaction completion. After the completion of the reaction, the solvent was removed by rotatory evaporation at reduced pressure, and the residue was washed by ethanol to afford the pure product.

1,5-Diphenyl-penta-1,4-dien-3-one:

Yellow solid, ^1H NMR (CDCl_3 , 500 MHz), δ 7.02 (2 H, d, $J = 15.9$ Hz), 7.42 (4 H, dd, $J = 5.0, 1.8$ Hz), 7.63 (6 H, dd, $J = 6.4, 3.1$ Hz), 7.75 (2 H,

d, $J = 15.9$ Hz). HRMS (ESI): m/z 234.1051 ($\text{M}^{++} \text{C}_{17}\text{H}_{14}\text{O}^{++}$ requires 234.1039). The spectroscopic data are consistent with those previously reported⁴⁵.

1,5-Di-*p*-tolyl-penta-1,4-dien-3-one: Yellow solid, ^1H NMR (CDCl_3 , 500 MHz), δ 2.35 (6 H, s), 7.09

(2 H, d, $J = 15.0$ Hz), 7.29 (4 H, d, $J = 7.5$ Hz, 2 H), 7.50 (4 H, d, $J = 7.5$ Hz), 7.92 (2 H, d, $J = 15.2$ Hz). HRMS (ESI): m/z 262.1385 ($\text{M}^{++} \text{C}_{19}\text{H}_{18}\text{O}^{++}$ requires 262.1352). The spectroscopic data are consistent with those previously reported⁴⁵.

1,5-Bis-(4-ethoxy-phenyl)-penta-1,4-dien-3-one: Yellow solid, ^1H NMR (CDCl_3 , 500 MHz), δ 1.44 (6 H, t, $J = 7.0$

Hz), 4.08 (4 H, q, $J = 7.0$ Hz), 6.92 (4 H, d, $J = 8.7$ Hz), 6.95 (2 H, d, $J = 15.9$ Hz), 7.56 (4 H, d, $J = 8.7$ Hz), 7.69 (2 H, d, $J = 15.8$ Hz). HRMS (ESI): m/z 322.1574 ($\text{M}^{++} \text{C}_{21}\text{H}_{22}\text{O}_3^{++}$ requires 322.1563). The spectroscopic data are consistent with those previously reported⁴⁵.

1,5-Bis-(4-nitro-phenyl)-penta-1,4-dien-3-one: Brown solid, ^1H NMR ($d_6\text{-DMSO}$, 500 MHz), δ 7.56 (2 H, d, $J =$

16.1 Hz), 7.93 (2 H, d, $J = 16.1$ Hz), 8.08 (4 H, d, $J = 8.5$ Hz), 8.31 (4 H, d, $J = 8.5$ Hz). HRMS (ESI): m/z 324.0749 ($\text{M}^{++} \text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_5^{++}$ requires 324.0746). The spectroscopic data are consistent with those previously reported⁴⁵.

General procedure for synthesizing thiooxindole

An oven-dried flask was charged with oxindole (3.7 mmol), dry THF (25 mL), and P_2S_5 (2.3 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, NaHCO_3 (7.5 mmol) was slowly added and stirred overnight. After removing the solvent by rotatory evaporation at reduced pressure, the residue was transferred into a 100-mL beaker. By adding 250 mL mixture of ice and water, a pale yellow solid appeared. The light yellow precipitate was washed with 10% solution of NaHCO_3 to remove unreacted oxindole and give the pure product.

1-methylindoline-2-thione (6): Yellow solid, ^1H NMR (CDCl_3 , 500 MHz), δ 7.32 (1 H, t, $J = 7.8$ Hz), 7.27 (1 H, d, $J = 7.8$ Hz), 7.16 (1 H, t, $J = 7.4$ Hz), 6.98 (1 H, d, $J = 7.8$ Hz), 4.09 (s, 2H), 3.61 (s, 3H). HRMS (ESI): m/z 163.0467 ($\text{M}^{++} \text{C}_9\text{H}_9\text{NS}^{++}$ requires 163.0450). The spectroscopic data are consistent with those previously reported⁴⁶.

1-phenylindoline-2-thione: brown solid, ^1H NMR (CDCl_3 , 500 MHz), δ 7.63 (2 H, t, $J = 7.6$ Hz), 7.55 (1 H, t, $J = 7.4$ Hz), 7.43 (2 H, d, $J = 7.5$ Hz), 7.38 (1 H, d, $J = 7.15$ Hz), 7.25 (1 H, t, $J = 7.5$ Hz), 7.20 (1 H, t, $J = 7.32$ Hz), 6.65 (1 H, d, $J = 7.7$ Hz), 4.32 (2 H, s). HRMS (ESI): m/z 225.0622 ($\text{M}^{++} \text{C}_{14}\text{H}_{11}\text{NS}^{++}$ requires 225.0607). The spectroscopic data are consistent with those previously reported⁴⁷.

General procedure for double Michael addition reaction

A mixture of thiooxindole (0.5 mmol), divinyl ketone (0.5 mmol), and K_2CO_3 (0.5 mmol) in 10 mL of ethanol was stirred at room temperature for about 24 hours.

Reaction completion was monitored by TLC using mobile phase (ethyl acetate/hexane; 1:6). After the completion of the reaction, since the product is insoluble in ethanol and diethyl ether, the purification was done by washing the crude reaction mixture with these solvents.

(1*s*,2*R*,6*S*)-1'-methyl-2,6-diphenyl-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**4**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 2.82 (2H, dd, *J* = 15.7, 4.0 Hz), 3.00 (3 H, s), 3.46 (2 H, t, *J* = 15.1 Hz), 4.14 (2H, dd, *J* = 14.6, 4.2 Hz), 6.63 (1H, d, *J* = 6.9 Hz), 6.82 (4 H, d, *J* = 7.5 Hz), 6.95 (4 H, d, *J* = 7.7 Hz), 7.32-7.38 (2H, m), 8.02-8.07 (1H, m). ¹³C NMR (CDCl₃, 125.8 MHz): δ 34.6, 43.7, 49.8, 67.6, 108.5, 125.5, 127.3, 127.5, 128.13, 128.5, 128.8, 129.5, 139.5, 146.9, 207.7, 208.5. HRMS (EI): *m/z* 397.1480 (M⁺• C₂₆H₂₃NOS⁺ requires 397.1495).

(1*s*,2*R*,6*S*)-2,6-bis(4-ethoxyphenyl)-1'-methyl-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**7**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 1.30 (6 H, t, *J* = 7.0 Hz), 2.75 (2H, dd, *J* = 15.6, 3.9 Hz), 3.00 (3 H, s), 3.39 (2 H, t, *J* = 15.1 Hz), 3.85 (4 H, q, *J* = 7.0 Hz), 4.06 (2H, dd, *J* = 14.3, 2.7 Hz), 6.45 (4 H, d, *J* = 8.7 Hz), 6.64 (1H, d, *J* = 6.9 Hz), 6.71 (4 H, d, *J* = 8.7 Hz), 7.32 (2H, quin, *J* = 7.6 Hz), 7.99 (1H, d, *J* = 7.3 Hz). ¹³C NMR (CDCl₃, 125.8 MHz): δ 14.7, 31.1, 45.0, 51.2, 63.1, 68.1, 110.0, 113.3, 123.2, 125.3, 128.8, 129.5, 129.7, 132.6, 146.2, 157.8, 204.7, 208.2. HRMS (EI): *m/z* 485.2015 (M⁺• C₃₀H₃₁NO₃S⁺ requires 485.2025).

(1*s*,2*R*,6*S*)-1'-methyl-2'-thioxo-2,6-di-*p*-tolylspiro[cyclohexane-1,3'-indolin]-4-one (**8**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 2.13 (6 H, s), 2.77 (2H, dd, *J* = 15.6, 4.1 Hz), 2.98 (3 H, s), 3.42 (2 H, t, *J* = 15.2 Hz), 4.09 (2H, dd, *J* = 14.5, 4.2 Hz), 6.62 (1H, d, *J* = 6.1 Hz), 6.68 (4 H, d, *J* = 8.0 Hz), 6.74 (4 H, d, *J* = 7.9 Hz), 7.31-7.41 (2H, m), 8.01 (1H, d, *J* = 7.2 Hz). ¹³C NMR (CDCl₃, 125.8 MHz): δ 20.8, 31.0, 44.9, 51.7, 67.8, 110.0, 123.2, 125.3, 128.1, 128.3, 128.7, 132.5, 134.6, 136.6, 146.2, 204.5, 208.1. HRMS (EI): *m/z* 425.1796 (M⁺• C₂₈H₂₇NOS⁺ requires 425.1813).

(1*s*,2*R*,6*S*)-1'-methyl-2,6-bis(4-nitrophenyl)-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**9**): Brown solid, ¹H NMR (CDCl₃, 500 MHz) δ 2.81 (2H, dd, *J* = 15.6, 3.2 Hz), 3.00 (3H, s), 3.47 (2H, t, *J* = 15.2 Hz), 4.13 (2H, dd, *J* = 14.5, 3.5 Hz), 6.76 (1H, d, *J* = 6.3 Hz), 7.59 – 7.58 (2H, m), 7.68 (4H, d, *J* = 8.5 Hz), 7.91 (4H, d, *J* = 8.5 Hz) 8.16 (1H, dd, *J* = 4.9, 1.9 Hz). ¹³C NMR (CDCl₃, 125.8 MHz): δ 34.6, 43.7, 49.8, 67.6, 108.5, 123.3, 125.5, 127.3, 128.5, 128.6, 129.5, 146.0 146.9, 149.0, 207.7, 208.5. HRMS (EI): *m/z* 487.1187 (M⁺• C₂₆H₂₁N₃O₅S⁺ requires 487.1202).

(1*s*,2*R*,6*S*)-1',2,6-triphenyl-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**10**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 2.85 (2H, d, *J* = 14.5 Hz), 3.50 (2 H, t, *J* = 15.0 Hz), 4.16 (2H, d, *J* = 14.1 Hz), 6.20 (3H, s), 7.32 (8 H, s), 7.53-7.56 (11H, m), 8.06 (1H, d, *J* = 7.3 Hz). ¹³C NMR (CDCl₃ and d₆-DMSO, 125.8 MHz): δ 43.3, 50.5, 66.6, 109.5, 112.5, 122.3, 125.8, 126.7, 127.3, 127.4, 127.4, 128.3, 130.6, 133.3, 135.1, 135.3, 145.6, 204.4, 208.4. HRMS (EI): *m/z* 459.1553 (M⁺• C₃₁H₂₅NOS⁺ requires 459.1657).

(1*s*,2*R*,6*S*)-2,6-bis(4-ethoxyphenyl)-1'-phenyl-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**11**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 1.34 (6H, s), 2.83 (2 H, d, *J* = 14.7), 3.48 (2 H, t, *J* = 15.0), 3.91 (4 H, s), 4.14 (2 H, d, *J* = 13.3), 6.19 (1H, d), 6.28 (2 H, s), 6.54 (4 H, d, *J* = 7.6), 6.81 (4 H, d, *J* = 7.4),

7.21 (1 H, t), 7.33 (4 H, s), 8.04 (1 H, d, *J* = 6.6). ¹³C NMR (CDCl₃, 125.8 MHz): δ 13.5, 43.5, 50.0, 61.8, 67.0, 109.5, 112.0, 122.4, 124.6, 125.9, 127.5, 127.7, 128.3, 128.4, 128.5, 130.7, 135.1, 145.6, 156.7, 204.7, 208.6. HRMS (EI): *m/z* 547.2187 (M⁺• C₃₅H₃₃NO₃S⁺ requires 547.2176).

(1*s*,2*R*,6*S*)-1'-phenyl-2'-thioxo-2,6-di-*p*-tolylspiro[cyclohexane-1,3'-indolin]-4-one (**12**): White solid, ¹H NMR (CDCl₃, 500 MHz), δ 2.23 (6H, s), 2.88 (2 H, d, *J* = 14.5 Hz), 3.53 (2H, t, *J* = 14.7 Hz), 4.18 (2H, d, *J* = 14.2 Hz), 6.23 (3H, s), 6.83 (8 H, dd, *J* = 25.0 Hz), 7.34 (5H, m), 8.08 (1H, d, *J* = 7.2 Hz). ¹³C NMR (CDCl₃ and d₆-DMSO, 125.8 MHz): δ 20.3, 44.0, 51.2, 67.3, 110.2, 113.2, 123.0, 126.5, 127.1, 128.0, 128.1, 128.3 129.0, 134.0, 135.8, 136.0, 146.4, 205.2, 207.1. HRMS (EI): *m/z* 487.1959 (M⁺• C₃₅H₃₃NO₃S⁺ requires 487.1970).

(1*s*,2*R*,6*S*)-2,6-bis(4-nitrophenyl)-1'-phenyl-2'-thioxospiro[cyclohexane-1,3'-indolin]-4-one (**13**): Brown solid, ¹H NMR (CDCl₃, 500 MHz) δ 2.95 (2H, dd, *J* = 15.5, 3.2 Hz), 3.60 (2H, t, *J* = 15.3 Hz), 4.26 (2H, dd, *J* = 14.5, 3.3 Hz), 6.72 (3H, s), 7.78 – 7.89 (5H, m), 7.98 (4H, d, *J* = 8.5 Hz), 8.01 (4H, d, *J* = 8.5 Hz) 8.15 (1H, dd, *J* = 4.4, 1.7 Hz). ¹³C NMR (CDCl₃, 125.8 MHz): δ 43.7, 49.8, 67.3, 112.7, 123.3, 125.4, 126.4, 127.4, 128.2, 128.6, 128.6, 129.1, 131.3, 139.4, 142.6, 146.0 149.0, 207.0, 208.5. HRMS (EI): *m/z* 549.1361 (M⁺• C₃₁H₂₃N₃O₅S⁺ requires 549.1358).

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