The Three-Component Reaction between Isatin, α-Amino Acids, and Dipolarophiles

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3-Spiro[pyrrolidino-oxindoles] were prepared in high yields from a three-component reaction between isatin, an α-amino acid, and a dipolarophile. Both *N*-substituted and *N*-unsubstituted α-amino acids were used as the amine component.

Introduction

The pyrrolidino-2-spiro-3′-oxindole ring system can be found in several pharmacologically active alkaloids, such as horsfiline (**1**)[1] and spirotryprostatin B (**2**)[2,3] (Figure 1). Various strategies have been used to obtain these spiro compounds, such as oxidative rearrangement of β-carbolines and 1,3-dipolar addition. One class of powerful reagents to utilize in the 1,3-dipolar reaction are the azomethine ylides,[4] which are zwitterionic and are composed of one positively charged nitrogen atom and two terminal sp^2-hybridized carbon atoms. Evidence for the formation of a non-stabilized azomethine ylide, thermally generated from a condensation between sarcosine and benzophenone, was reported in 1970 by Rizzi.[5]

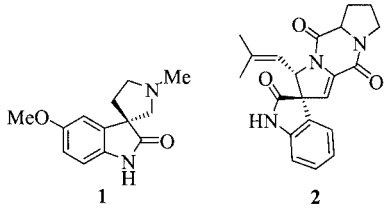
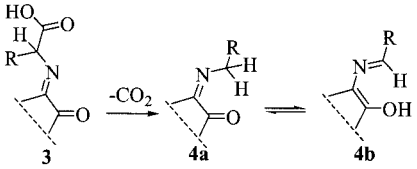


Figure 1. Horsfiline (**1**) and spirotryprostatin B (**2**)

It should be noted that the mechanisms of decarboxylative generation of azomethine ylides and the Strecker degradation[6,7] of α-amino acids resemble one another. When an α-amino acid derivative **6** (see Scheme 2) is condensed with a carbonyl compound, e.g., isatin (**5**), a betaine structure **7′** is formed that is in equilibrium with the corresponding ring-closed spiro oxazolidinone **7′′**. Tsuge et al.[8] have shown that the ring tautomer, the oxazolidinone, is an intermediate in the decarboxylative route to azomethine ylides, whereby carbon dioxide is expelled from the intermediates **7′′** to yield the azomethine ylides **8**, which will, in turn, react with suitable dipolarophiles, e.g., **9**. The Strecker degradation, however, does not proceed via spiro oxazolidinones **7′′**, but instead follows the mechanism outlined in Scheme 1. The α-amino acid is condensed with the 1,2-dicarbonyl compound (e.g., isatin) to yield an azomethinecarboxylic acid **3** that subsequently will lose carbon dioxide to give compound **4a**. Because of the presence of the neighboring carbonyl group, the enol **4b** can be formed with ease, and it is hydrolysed subsequently to the corresponding amino alcohol and the carbon skeleton of what was the α-amino acid finally becomes an aldehyde.



Scheme 1. Strecker degradation

Results and Discussion

We have condensed isatin **5** with a number of α-amino acid derivatives **6** (Scheme 2), such as sarcosine (**6a**), *N*-benzylglycine (**6b**), and thiazolidine-4-carboxylic acid (**6d**) in a methanol/water medium. A dipolarophile **9** was also

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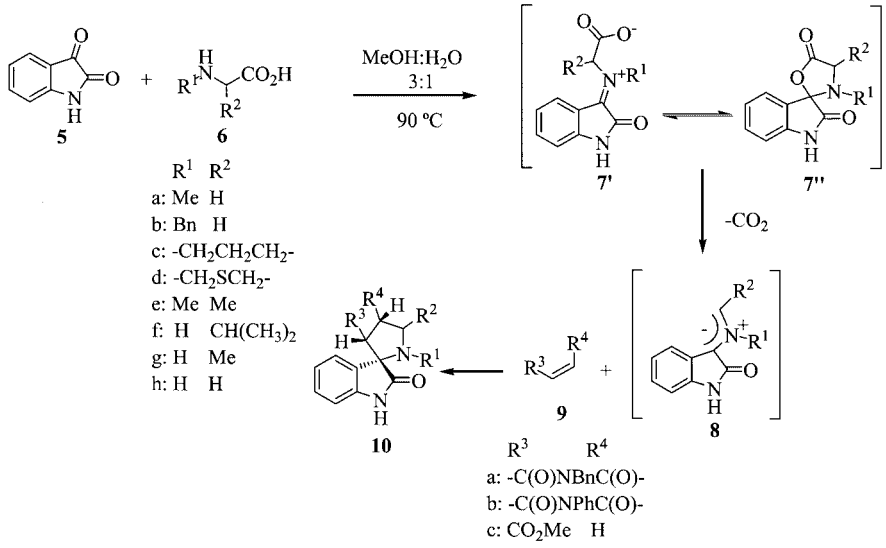


Scheme 2

added together with the isatin and the α-amino acid derivative. When the reaction mixture was heated to reflux (90 °C), the suspension dissolved and gas (CO_2) began to evolve after ca. 1 min. Loss of CO_2 from the oxazolidinones **7′′** proceeds via a stereospecific 1,3-cycloreversion to generate the anti-1,3-dipoles **8**, which is due to the fact that the oxazolidinones **7′′** are formed almost exclusively with trans stereochemistry.[9] By now, the anti-azomethine ylides **8** are formed and the 1,3-dipolar addition of the dipolarophiles **9** yield the pyrrolidine-2-spiro-3′-(2-oxindole)s **10**. After the reaction mixture had been heated under reflux for the stated time, the reactions were quenched in an ice/sat. aq. $NaHCO_3$ mixture; this medium was chosen because of the slight excess of the α-amino acid derivatives **6** that were used. In several cases we obtained a high yield of almost pure compounds. Solid products could be obtained, however, by allowing the reaction to reach room temperature, although a better yield was obtained when the reaction was quenched in an ice/sat. aq. $NaHCO_3$ mixture. All of the synthesized pyrrolidine-2-spiro-3′-oxindoles **10** are colorless, although the crude spiro-3-oxindoles were sometimes tinged with yellow.

Acyclic α-Amino Acid Derivatives

We conclude that the presence of NH bonds did not disturb the reaction because the use of *N*-methylisatin was not beneficial for the reaction when sarcosine (**6a**) and *N*-benzylmaleimide (**9a**) were used as partners. Changing from sarcosine (**6a**) to *N*-benzylglycine (**6b**) did not affect the yield either. Recrystallisation of the spiro compound **10ba** from acetonitrile yielded good single crystals and a rigid conformation of the solvate molecule (Figure 2). The molecular packing scheme, which is dominated by ordinary van der Waals contacts, is normal; the unit cell does not contain residual accessible solvate space for further solvent inclusion. Based on the X-ray structure (Figure 2), we deduced the stereochemistry of the pyrrolidine-2-spiro-3′-oxindoles **10** to be as denoted in Scheme 2, but the absolute stereochemistry can be assigned only to pyrrolidine-2-spiro-3′-oxindole **10ba**. Interestingly, proton H15 on carbon atom 4 in the oxindole moiety (i.e., C15 in Figure 2) is shifted upfield (δ = 6.17 ppm for compound **10ba**) when the dipolarophile is *N*-benzylmaleimide (**9a**) relative to compound **10bc** (δ = 6.91 ppm), which was formed when methyl acrylate (**9c**) was used as the dipolarophile. The reason for this upfield shift can be found in T-stacking of the phenyl ring from the former *N*-benzylmaleimide. This T-stacking orientation over proton H15 can be seen in Figure 2. On the other hand, when *N*-phenylmaleimide was incorporated in the structure, an upfield shift occurred (δ = 6.73 ppm for compound **10cb**), but the T-stacking is not that extensive because of the lack of a CH_2 group.

Cyclic α-Amino Acid Derivatives

In 2001, Azizian et al.[10] published a study of some reactions between proline (**6c**), isatin (**5**), and *N*-arylmaleimide **9** in refluxing ethanol, which are conditions that yielded the pyrrolidine-2-spiro-3′-oxindole derivatives **10**. When we utilized our conditions with isatin (**5**), proline (**6c**), and *N*-phenylmaleimide (**9b**), the same product was obtained in similar yields. The full carbon NMR spectroscopic data were not published, however, and we noticed discrepancies when we compared our carbon NMR spectroscopic data with the published ones. Azizian et al.[10] reported two signals, at δ = 142.4 and 141.7 ppm, whereas we detect only one signal in this vicinity, at δ = 141.5 ppm. The other two *ipso* signals resonate at δ = 124.9 and 132.1 ppm, respectively (not reported by Azizian).

Interestingly, the reactions involving proline were complete after only 0.5 h of heating under reflux, as compared with heating for 18 h under reflux when acyclic α-amino acid derivatives were used as the amine component. Shorter reaction times were also observed in the synthesis of the pyrrolidine-2-spiro-3′-oxindole (**10da**), i.e., when thiazolid-

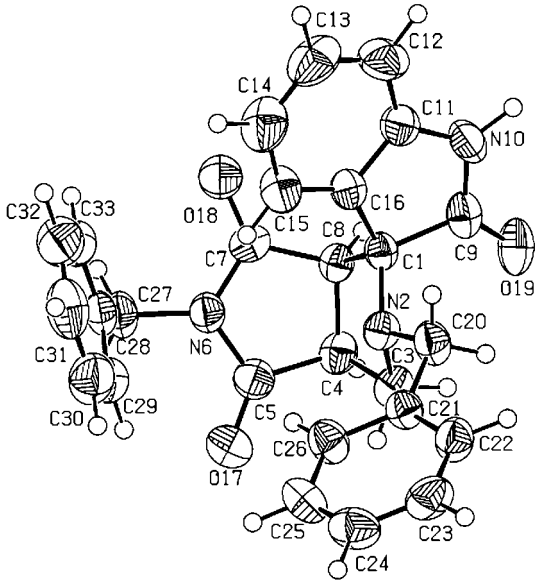


Figure 2. Molecular structure of **10ba** showing the atom numbering scheme; displacement ellipsoids of non-H atoms are drawn at the 50% probability level; H atoms are presented as small spheres of arbitrary radii; the acetonitrile solvate molecule is excluded

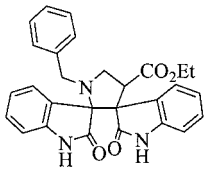
ine-4-carboxylic acid (**6d**) was used as the amine component. We believe that the extra ring pushes the equilibrium towards the spiro oxazolidinone **7′′**. This phenomenon is due to the fact that the substituents R^1 and R^2 will force compound **7′** to adopt a geometry close to that of the spiro oxazolidinone **7′′**. Hence, **7′′** is the prevailing tautomer when an extra ring is added the spiro oxazolidinone.

Compound **10da** was desulfurized using Raney nickel to yield the spiro compound **10ea**, which proved to be identical with the product formed from the three-component reaction between isatin (**5**), *N*-methylalanine (**6e**), and *N*-benzylmaleimide (**9a**).

Unsymmetrical Dipolarophiles

When methyl acrylate (**9c**) was used as dipolarophile and the azomethine ylide was generated from isatin (**5**) and *N*-benzylglycine (**6b**) and thiazolidine-4-carboxylic acid (**6d**), respectively, we obtained the pyrrolidine-2-spiro-3′-oxindoles **10bc** and **10dc**. Compound **10dc** has been reported by Pardasani et al.[11] as orange crystals melting at 180 °C. In our hands, however, we found that when compound **10dc** was recrystallized from ethanol, colorless crystals were obtained that melt at 197 °C. Compounds **10bc** and **10dc** are consistent with the observations made by Grigg et al.[12] and Pardasani[11] with regard to the regiochemistry.

Larger dipolarophiles, such as chalcones, have been used successfully in this three-component reaction.[13] When ethyl (3-methyleneoxindole)acetate[14] was used as the dipolarophile in the decarboxylative condensation between isatin (**5**) and *N*-benzylglycine (**6b**), we obtained the double-spiro compound **11** that has the same configuration as some related molecules (e.g., **12**) that were reported by Casaschi et al.[15]



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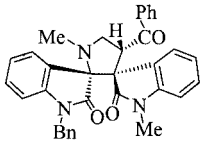

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N-Unsubstituted α-Amino Acids

Despite the fact that the decarboxylative condensation between isatin and *N*-substituted α-amino acids has been investigated thoroughly, the reaction between isatin and *N*-unsubstituted α-amino acids has not attracted much interest, most likely because it is believed that this reaction would lead to Strecker degradation of the α-amino acid. Interestingly, Grigg et al.[16] have described an imine formed in situ from valine (**6f**) and alloxane that resulted in a decarboxylative formation of an azomethine ylide, which was trapped by *N*-methylmaleimide. We performed a similar three-component reaction between isatin and three different α-amino acids, valine (**6f**), alanine (**6g**), and glycine (**6h**), together with *N*-benzylmaleimide (**9a**) as the dipolarophile. The pyrrolidine-2-spiro-3′-oxindoles **10fa**, **10ga**, and **10ha**, respectively, were obtained in good yields. The condensation between the amino acid and isatin followed the pathway outlined in Scheme 2 to yield, after decarboxylation, the azomethine ylide **8** that, in the presence of a dipolarophile, gave rise to the pyrrolidine-2-spiro-3′-oxindoles **10**. It is possible to generate an azomethine ylide via thermal tautomerisation of imines,[17] but in these reactions the azomethine ylide was not obtained by such a process.

Conclusions

In this study, we preformed 1,3-dipolar additions involving different dipolarophiles and an azomethine ylide prepared from the decarboxylative condensation between *N*-substituted α-amino acids and isatin. This reaction produces pyrrolidine-2-spiro-3′-oxindoles **10** in high yields. *N*-Unsubstituted α-amino acids, i.e., common α-amino acids, have also been used in this reaction to yield pyrrolidine-2-spiro-3′-oxindoles **10**. This high yielding reaction is believed to proceed by a mechanism similar to the Strecker degradation, where a transient 1,3-dipole is trapped by a dipolarophile, e.g., *N*-benzylmaleimide.

Experimental Section

General Remarks: All starting materials and solvents (PA grade) are commercially available and were used without further purification. NMR spectra were recorded in $CDCl_3$ solutions, unless otherwise stated, on a Bruker DPX 300 spectrometer, operating at 300 MHz for ^1H and 75 MHz for ^{13}C; δ values are reported in ppm and *J* values in hertz. IR spectra were recorded on a Perkin−Elmer 1600 FTIR instrument on using KBr tablets. Mass spectra were recorded

on a Micromass Platform II spectrometer, using the direct-inlet system operating in the electron impact (EI) mode at 70 eV. Only fragment peaks larger than 20% of the base peak are given. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined using a Buchi melting point B-545 apparatus and are uncorrected.

General Procedure for the Three-Component Reaction Yielding *N*-Me-10aa, 10aa, 10ba, 10ca, 10da, 10ea, 10fa, and 10ga: A suspension of isatin (10 mmol), DL-α-amino acid derivative (11 mmol) and *N*-benzylmaleimide (10 mmol) was heated under reflux at 90 °C in a mixture of methanol (30 mL) and water (10 mL). While under reflux, a clear solution was obtained and CO_2 was expelled. After the stated time, the reaction mixture was quenched by pouring it into a mixture of ice and sat. aq. $NaHCO_3$ (150 mL). The solid that formed was collected and washed thoroughly with water. Analytically pure samples were obtained by recrystallization from ethanol. Reflux times, yields, and melting points are given in Table 1.

Table 1. Reflux times, yields, and melting points of pyrrolidine-2-spiro-3′-oxindoles **10**

Compound	Time [h]	Yield [g, (%)]	M.p. [°C]
***N*-Me-10aa**	18	1.53, (82)	218−220
10aa	18	3.34, (92)	140−142
10ba	18	3.37, (77)	189−190
10cb	0.5	3.25, (87)	217−219
10da	2	3.83, (95)	186−188
10ea	18	2.99, (79)	218−219
10fa	2	3.65, (94)	207−208
10ga	18	3.43, (95)	212−213
10ha	2	1.35, (39)	195−196

4-Benzyl-1,6-dimethylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (*N*-Me-10aa): A suspension of *N*-methylisatin (5 mmol), sarcosine (5.5 mmol), and *N*-benzylmaleimide (5 mmol) was heated under reflux for 18 h in a mixture of methanol (15 mL) and water (5 mL) and then quenched according to the general description. IR (KBr): $\tilde{\nu}$ = 1703, 1613, 1469, 1469, 1370, 1343, 1181, 751 cm^{-1}. ^1H NMR: δ = 1.97 (s, 3 H), 3.15 (s, 3 H), 3.37 (d, *J* = 8.1 Hz, 1 H), 3.47−3.55 (m, 2 H), 3.73−3.78 (m, 1 H), 4.63 and 4.78 (AB q, *J* = 14.0 Hz, 2 H), 6.34 (d, *J* = 7.2 Hz, 1 H), 6.77−6.85 (m, 2 H), 7.24−7.27 (m, 1 H), 7.32−7.46 (m, 5 H) ppm. ^{13}C NMR: δ = 25.9 (q), 34.7 (q), 43.0 (t), 44.8 (d), 52.0 (d), 54.7 (d), 72.6 (s), 108.2 (d), 122.9 (d), 124.4 (s), 126.4 (d), 128.2 (d), 128.8 (d), 129.4 (d), 129.9 (d), 135.8 (s), 144.2 (s), 174.9 (s), 176.8 (s), 178.8 (s) ppm. MS (EI): *m*/*z* (%) = 375 (100) [M^+], 241 (31), 229 (24), 159 (28), 130 (20), 91 (61). $C_{22}H_{21}N_3O_3$ (375.43): calcd. C 70.38, H 5.64, N 11.19; found C 70.36, H 5.70, N 11.12.

4-Benzyl-1-methylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10aa): IR (KBr): $\tilde{\nu}$ = 3265, 1704, 1619, 1470, 1398, 1339, 1213, 1191, 1155, 755, 703 cm^{-1}. ^1H NMR: δ = 2.03 (s, 3 H), 3.48−3.53 (m, 3 H), 3.68−3.71 (m, 1 H), 4.64 and 4.79 (AB q, *J* = 14.0 Hz, 2 H), 6.30 (d, *J* = 7.5 Hz, 1 H), 6.68 (d, *J* = 7.8 Hz, 1 H) 6.75−6.80 (m, 1 H), 7.13−7.18 (m, 1 H), 7.31−7.47 (m, 5 H), 8.32 (s, 1 H) ppm. ^{13}C NMR: δ = 34.7 (q), 43.0 (t), 44.9 (d), 51.9 (d), 54.6 (t), 72.8 (s), 110.2 (d), 122.8 (d), 125.0 (s), 126.7 (d), 128.2 (d), 128.8 (d), 129.4 (d), 129.8 (d), 135.7 (s), 141.3 (s), 175.2 (s), 178.7 (s), 178.8 (s) ppm. MS (EI): *m*/*z* (%) = 361 (89) [M^+], 333 (35), 332 (100), 130 (23), 91 (59). $C_{21}H_{19}N_3O_3$ (361.40): calcd. C 69.79, H 5.30, N 11.63; found C 69.70, H 5.24, N 11.55.

1,4-Dibenzylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10ba): IR (KBr): $\tilde{\nu}$ = 1718, 1701, 1619, 1471, 1397, 1339, 1196, 753, 722, 698 cm^{-1}. ^1H NMR: δ = 3.21−3.32 (m, 2 H), 3.38 (d, *J* = 9.1 Hz, 1 H), 3.50−3.64 (m, 3 H), 4.62 and 4.87 (AB q, *J* = 14.0 Hz, 2 H), 6.17 (d, *J* = 7.4 Hz, 1 H), 6.71−6.76 (m, 2 H), 7.00−7.02 (m, 2 H), 7.13−7.19 (m, 1 H), 7.21−7.28 (m, 3 H), 7.40−7.52 (m, 5 H), 8.16 (s, 1 H) ppm. ^{13}C NMR: δ = 42.9 (t), 44.5 (d), 51.5 (t), 51.6 (d), 52.2 (t), 72.7 (s), 123.0 (d), 124.9 (s), 127.0 (d), 126.4 (d), 128.0 (d), 128.4 (d), 128.4 (d), 128.8 (d), 129.4 (d), 130.0 (d), 136.1 (s), 138.1 (s), 141.3 (s), 175.0 (s), 178.5 (s), 178.7 (s) ppm. MS (EI): *m*/*z* (%) = 437 (35) [M^+], 409 (21), 408 (37), 91 (100). $C_{27}H_{23}N_3O_3$ (437.50): calcd. C 74.12, H 5.30, N 9.60; found C 74.18, H 5.35, N 9.48.

X-ray Crystallography: Suitable crystals for the X-ray structure investigation of **10ba** were obtained by slow evaporation of an acetonitrile solution. The X-ray data was collected at room temperature with an Enraf−Nonius κ-CCD diffractometer[18] equipped with graphite monochromator and Mo-K_α radiation. The Denzo-SMN Software Package[19] was used to determine the unit cell and for reduction of the data sets. The structure was solved by direct methods and refined with a full-matrix least-squares method based on F^2, taking advantage of the MaXus software package.[20,21] The non-H atoms were refined anisotropically and the H atoms were placed in geometrically relevant positions after verification from late Fourier electron density calculations. All H atoms were supplied with fixed isotropic thermal displacement factors, U(iso) = 0.05 $Å^2$. No absorption correction was applied. Calculations to prepare material for publication were performed within Platon.[22] CCDC-211607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Crystal Data for 10ba: $C_{27}H_{23}O_3N_3{\cdot}C_2H_3N$, M_r = 437.50 + 41.05, space group: monoclinic, $P2_1/n$ (No. 14). Unit cell parameters: *a* = 9.681(1), *b* = 10.842(1), *c* = 24.238(1) Å, β = 90.92(1)°, *V* = 2543.7(4) $Å^3$, *Z* = 4. D_x = 1.250(1) g/cm^3, *F*(000) = 1008. μ(Mo-*Kα*) = 0.95 cm^{-1}. Crystal dimensions 0.17 × 0.17 × 0.26 mm. A total of 2161 independent reflections [$I > 3\sigma(I)$] were refined to give R = 0.045, R_w = 0.045 for 321 parameters {$w = 1/[\sigma^2{\cdot}F_o^2 + (0.0300)F_o^2]$}. $(\Delta/\sigma)_{max}$ = 0.0006, $\Delta\rho_{max}$ = 0.17 e·$Å^{-3}$, $\Delta\rho_{min}$ = −0.38 e·$Å^{-3}$, $\Delta\rho_{mean}$ = 0.04 e·$Å^{-3}$. GOF = 1.364.

4-Phenyl-1,6-propylidenepyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10cb): Recrystallization from methanol yielded analytically pure **10cb**. ^1H NMR: δ = 1.96−2.17 (m, 4 H), 2.54−2.64 (m, 2 H), 3.67 (t, *J* = 7.9 Hz, 1 H), 3.94 (d, *J* = 8.0 Hz, 1 H), 4.46−4.53 (m, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 6.98 (t, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 7.4 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.32−7.52 (m, 5 H), 8.41 (s, 1 H) ppm. ^{13}C NMR: δ = 24.1 (t), 26.2 (t), 45.1 (t), 46.0 (d), 55.9 (d), 65.4 (d), 69.8 (s), 110.6 (d), 122.5 (d), 124.9 (s), 126.4 (d), 127.2 (d), 128.8 (d), 129.4 (d), 130.0 (d), 132.1 (s), 141.5 (s), 174.7 (s), 175.8 (s), 178.5 (s) ppm.

5-Benzylpyrrolidino[3,4:3′4′]pyrrolo[1,2-*c*]thiazole-3-spiro-3′-(2-oxindole)-4,6-dione (10da): IR (KBr): $\tilde{\nu}$ = 3194, 1699, 1616, 1471, 1398, 1332, 1287, 1201, 752, 701 cm^{-1}. ^1H NMR: δ = 2.96−3.05 (m, 2 H), 3.26 and 3.46 (AB q, *J* = 6.0 Hz, 2 H), 3.58 (t, *J* = 7.9 Hz, 1 H), 3.86 (d, *J* = 8.2 Hz, 1 H), 4.52−4.58 (m, 1 H), 4.62 and 4.79 (AB q, *J* = 13.9 Hz, 2 H), 6.36 (d, *J* = 7.5 Hz, 1 H), 6.70 (d, *J* = 7.8 Hz, 1 H), 6.74−6.79 (m, 1 H), 7.15−7.21 (m, 1 H), 7.34−7.45 (m, 5 H), 8.56 (s, 1 H) ppm. ^{13}C NMR: δ = 29.6 (t), 43.0 (t), 44.1 (d), 45.5 (t), 56.5 (d), 67.3 (d), 68.3 (s), 110.5 (d),

123.0 (d), 123.8 (s), 126.8 (d), 128.4 (d), 128.9 (d), 129.3 (d), 130.2 (d), 135.5 (s), 140.9 (s), 174.4 (s), 175.1 (s), 178.0 (s) ppm. MS (EI): *m/z* (%) = 405 (65) [M$^+$], 344 (24), 104 (20), 91 (100), 77 (27). $C_{22}H_{19}N_3O_3S$ (405.48): calcd. C 65.17, H 4.72, N 10.36, S 7.91; found C 65.21, H 4.68, N 10.31, S 7.83.

4-Benzyl-1,6-dimethylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10ea): IR (KBr): ṽ = 1696, 1618, 1472, 1397, 1350, 1330, 1218, 1218, 1190, 759 cm^{-1}. ^{1}H NMR: δ = 1.32 (d, *J* = 6.5 Hz, 3 H), 1.96 (s, 3 H), 3.37 (d, *J* = 8.1 Hz, 1 H), 3.46 (t, *J* = 8.0 Hz, 1 H), 3.91−4.00 (m, 1 H), 4.63 and 4.79 (AB q, *J* = 14.0 Hz, 2 H), 6.47 (d, *J* = 7.5 Hz, 1 H), 6.70 (d, *J* = 7.7 Hz, 1 H), 6.81−6.86 (m, 1 H), 7.16−7.21 (m, 1 H), 7.29−7.45 (m, 5 H), 8.17 (s, 1 H) ppm. ^{13}C NMR: δ = 15.8 (q), 32.9 (q), 42.7 (t), 47.9 (d), 50.1 (d), 58.1 (d), 73.5 (s), 110.0 (d), 122.7 (d), 125.6 (s), 127.1 (d), 128.1 (d), 128.8 (d), 129.1 (d), 129.8 (d), 135.9 (s), 141.1 (s), 175.0 (s), 176.0 (s), 179.1 (s) ppm. MS (EI): *m/z* (%) = 375 (100) [M$^+$], 346 (58), 91 (55), 56 (33). $C_{22}H_{21}N_3O_3$ (375.43): calcd. C 70.38, H 5.64, N 11.19; found C 70.26, H 5.68, N 11.14.

4-Benzyl-6-isopropylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10fa): IR (KBr): ṽ = 3200, 2956, 1703, 1620, 1472, 1394, 1340, 1174, 755, 696, 610 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 1.24 (d, *J* = 6.4 Hz, 3 H), 2.02−2.12 (m, 2 H; 1 H disappears when sample is shaken with D_2O), 3.52−3.58 (m, 2 H), 3.94−3.99 (m, 1 H), 4.61 and 4.80 (AB q, *J* = 13.9 Hz, 2 H), 6.29 (d, *J* = 7.5 Hz, 1 H), 6.64 (d, *J* = 7.8 Hz, 1 H), 6.72 (t, *J* = 7.6 Hz, 1 H), 7.11−7.16 (m, 1 H), 7.31−7.48 (m, 5 H), 7.99 (s, 1 H) ppm. ^{13}C NMR: δ = 20.9 (q), 21.2 (q), 29.8 (d), 42.8 (t), 47.7 (d), 52.0 (d), 65.7 (d), 67.9 (s), 110.1 (d), 122.8 (s), 180.8 (s) ppm. MS (EI): *m/z* (%) = 389 (64) [M$^+$], 318 (35), 185 (55), 130 (21), 91 (100), 77 (20). $C_{23}H_{23}N_3O_3$ (389.46): calcd. C 70.93, H 5.95, N 10.79, found C 70.86, H 6.03, N 10.67.

4-Benzyl-6-methylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10ga): IR (KBr): ṽ = 1700, 1622, 1472, 1393, 699 cm^{-1}. ^{1}H NMR: δ = 1.37 (d, *J* = 6.5 Hz, 3 H), 2.04 (s, 1 H), 3.41−3.47 (m, 2 H), 4.42−4.51 (m, 1 H), 4.61 and 4.81 (AB q, *J* = 14.0 Hz, 2 H), 6.36 (d, *J* = 7.5 Hz, 1 H), 6.68 (d, *J* = 7.8 Hz, 1 H), 6.74−6.79 (m, 1 H), 7.13−7.18 (m, 1 H), 7.31−7.47 (m, 5 H), 8.15 (s, 1 H) ppm. ^{13}C NMR: δ = 16.9 (q), 42.7 (t), 49.0 (d), 52.0 (d), 53.4 (d), 68.6 (s), 110.1 (d), 122.7 (d), 126.4 (d), 126.5 (s), 128.2 (d), 128.9 (d), 129.2 (d), 129.8 (d), 136.0 (s), 140.6 (s), 174.9 (s), 175.8 (s), 180.6 (s) ppm. MS (EI): *m/z* (%) = 361 (100) [M$^+$], 333 (66), 172 (30), 131 (34), 130 (26), 118 (28), 104 (23), 91 (89). 77 (28), 65 (24). $C_{21}H_{19}N_3O_3$ (361.40): calcd. C 69.79, H 5.30, N 11.63; found C 69.71, H 5.33, N 11.56.

4-Benzylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10ha): IR (KBr): ṽ = 3369, 3338, 1697, 1620, 1472, 1395, 1338, 1167, 758, 694, 590 cm^{-1}. ^{1}H NMR: δ = 2.13 (br. s, 1 H), 3.47 (d, *J* = 8.1 Hz, 1 H), 3.59−3.67 (m, 2 H), 3.97−4.03 (m, 1 H), 4.61 and 4.79 (AB q, *J* = 13.9 Hz, 2 H), 6.24 (d, *J* = 7.5 Hz, 1 H), 6.68−6.73 (m, 2 H), 7.12−7.18 (m, 1 H), 7.34−7.47 (m, 5 H), 7.98 (s, 1 H) ppm. ^{13}C NMR: δ = 43.1 (t), 47.3 (d), 47.9 (t), 51.7 (d), 69.3 (s), 110.2 (d), 122.8 (d), 126.0 (d), 126.6 (s), 128.3 (d), 128.9 (d), 129.5 (d), 129.9 (d), 135.8 (s), 140.6 (s), 174.9 (s), 178.5 (s), 180.0 (s) ppm. MS (EI): *m/z* (%) = 347(26) [M$^+$], 320 (21), 319 (100), 185 (22), 158 (53), 131 (31), 130 (31), 91 (51). $C_{20}H_{17}N_3O_3$ (347.38): calcd. C 69.15, H 4.93, N 12.10; found C 69.16, H 4.90, N, 11.98.

4-Benzyl-1,6-dimethylpyrrolidino[3,4-*c*]pyrrole-2-spiro-3′-(2-oxindole)-3,5-dione (10ea): The thiazolidine oxindole **10da** (0.22 g, 0.5 mmol) was suspended in ethanol (100 mL). Raney nickel was added in a large excess and the mixture was treated with hydrogen at room temperature at 50 Psi in a Parr apparatus. After 16 h, the reaction mixture was filtered through a celite pad, which was washed thoroughly with ethanol, and the filtrate was evaporated to yield a light-brown solid (0.15 g, 73%). Recrystallization from ethanol yielded the analytically pure substance. M.p. 217−218 °C. IR (KBr): ṽ = 3598, 3529, 2980, 1694, 1617, 1472, 1398, 1281, 760, 702 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.17 (d, *J* = 6.5 Hz, 3 H), 1.84 (s, 3 H), 3.36 (d, *J* = 8.0 Hz, 1 H), 3.51 (t, *J* = 8.0 Hz, 1 H), 3.79−3.84 (m, 1 H), 4.55 and 4.64 (AB q, *J* = 14.8 Hz, 2 H), 6.38 (d, *J* = 7.4 Hz, 1 H), 6.70−6.76 (m, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 7.16−7.21 (m, 1 H), 7.31−7.41 (m, 5 H), 10.51 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 15.6 (q), 32.6 (q), 41.5 (t), 47.5 (d), 49.7 (d), 57.2 (d), 72.6 (s), 109.4 (d), 121.3 (d), 125.7 (s), 126.4 (d), 127.6 (d), 127.8 (d), 128.5 (d), 129.3 (d), 136.1 (s), 142.6 (s), 174.5 (s), 176.0 (s), 178.1 (s) ppm.

Methyl 1-Benzylpyrrolidine-2-spiro-3′-(2-oxindole)-3-carboxylate (10bc): A mixture of isatin (1.47 g, 10 mmol), *N*-benzylglycine (2.00 g, 12 mmol), and methyl acrylate (1.72 g, 20 mmol) in a methanol (30 mL) and water (10 mL) was heated under reflux at 90 °C. After 18 h at reflux, the reaction was quenched in ice/sat. aq. $NaHCO_3$ (100 mL) and then after 1 h the mixture was extracted with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvents were evaporated to yield an orange solid (2.31 g). Recrystallisation from acetone/water yielded compound **10bc** (1.26 g, 38%). Recrystallization from ethanol yielded the analytically pure substance. M.p. 168−169 °C. IR (KBr): ṽ = 3214, 2815, 1744, 1797, 1613, 1471, 1198, 1161, 756 cm^{-1}. ^{1}H NMR: δ = 2.25−2.36 (m, 1 H), 2.55−2.68 (m, 1 H), 3.07 (td, *J* = 8.7, 3.7 Hz, 1 H), 3.20−3.28 (m, 1 H), 3.24 (s, 3 H), 3.46 and 3.53 (AB q, *J* = 13.0 Hz, 2 H), 3.66 (t, *J* = 9.1 Hz, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 7.03−7.08 (m, 1 H), 7.17−7.28 (m, 7 H), 8.91 (s, 1 H) ppm. ^{13}C NMR: δ = 25.6 (t), 50.8 (t), 51.6 (q), 52.8 (d), 54.0 (d), 73.2 (s), 110.1 (d), 122.7 (d), 125.5 (d), 127.2 (d), 128.0 (s), 128.2 (s), 128.7 (d), 129.4 (d), 138.5 (s), 141.4 (s), 171,8 (s), 180.1 (s) ppm. MS (EI): *m/z* (%) = 336 (27) [M$^+$], 308 (20), 91 (100). $C_{20}H_{20}N_2O_3$ (336.39): calcd. C 71.41, H 5.99, N 8.33; found C 71.82, H 5.92, N 8.38.

Methyl Pyrrolidino[1,2-*c*]thiazole-3-spiro-3′-(2-oxindole)-4-carboxylate (10dc): A mixture of isatin (1.47 g, 10 mmol), thiazolidine-4-carboxylic acid (1.47 g, 11 mmol), and methyl acrylate (1.72 g, 20 mmol) in a methanol (30 mL) and water (10 mL) was heated under reflux for 2 h. The reaction mixture changed from an orange suspension to a clear solution, whereupon it was quenched as outlined in the general description. Compound **10dc** (2.11 g, 69%) was collected; recrystallisation from ethanol produced analytically pure **10dc**. M.p 196−198 °C (ref.[11] 180 °C). IR (KBr): ṽ = 3243, 1741, 1702, 1615, 1470, 1330, 1263, 1184, 748 cm^{-1}. ^{1}H NMR: δ = 2.25−2.36 (m, 1 H), 2.43−2.51 (m, 1 H), 2.98 (dd, *J* = 11.5, 2.6 Hz, 1 H), 3.14−3.24 (m, 1 H), 3.19 (s, 3 H), 3.47 and 3.92 (AB q, *J* = 10.7 Hz, 2 H), 3.71 (dd, *J* = 12.6, 6.9 Hz, 1 H), 4.26−4.34 (m, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 6.97−7.02 (m, 1 H), 7.22−7.28 (m, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 9.61 (s, 1 H) ppm. ^{13}C NMR: δ = 33.4 (t), 38.3 (t), 51.7 (q), 53.7 (d), 55.1 (t), 68.3 (d), 74.3 (s), 110.4 (d), 122.2 (d), 124.1 (s), 127.4 (d), 130.1 (d), 141.7 (s), 170.3 (s), 180.9 (s) ppm. MS (EI): *m/z* (%) = 304 (100) [M$^+$], 217 (69), 172 (22), 145 (26), 144 (23), 130 (25), 116 (22), 101 (43), 77 (29), 59 (32), 55(26). $C_{15}H_{16}N_2O_3S$ (304.37): calcd. C 59.19, H 5.30, N 9.20, S 10.54; found C 59.12, H 5.32, N 9.16, S, 10.60.

Ethyl 1′-Benzyl-2-oxindole-3-spiro-2′-pyrrolidine-3′-spiro-3′′-(2-oxindole)-4′-carboxylate (11): Isatin (0.37 g, 2.5 mmol) and benzylglycine (0.82 g, 5 mmol) were heated to 90 °C in a mixture of methanol

(21 mL) and water (7 mL). 3-Methyleneoxindole acetic acid ethyl ester (0.54 g, 2.5 mmol) was added and after 14 h the reaction was quenched in ice/sat. aq. $NaHCO_3$ mixture (100 mL). An off-white solid (1.09 g) was collected and recrystallized from ethanol to yield the double-spiro compound **11** (0.55 g, 46%). M.p. 288−291 °C (dec). IR (KBr): $\tilde{\nu}$ = 3358, 3263, 1756, 1724, 1620, 1469, 1188, 1154, 752 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 0.56 (t, *J* = 7.1 Hz, 3 H), 3.25−3.73 (m, 6 H), 4.49−4.54 (m, 1 H), 6.18 (d, *J* = 7.4 Hz, 1 H), 6.50−6.55 (m, 1 H), 6.67−6.71 (m, 2 H), 7.06−7.12 (m, 2 H), 7.23−7.40 (m, 6 H) 7.45 (d, *J* = 7.3 Hz, 1 H), 10.28 (s, 1 H), 10.43 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 13.1 (q), 45.9 (d), 49.7 (t), 52.7 (s), 59.9 (t), 60.71 (s),76.9 (s), 109.2 (d), 109.3 (d), 120.8 (d), 120.9 (d), 123.1 (s), 125.0 (d), 125.9 (d), 127.2 (d), 127.7 (s), 128.1 (d), 128.5 (d), 129.0 (d), 129.8 (d), 138.5 (s), 142.7 (s), 143.6 (s), 169.8 (s), 174.1 (s), 175.6 (s) ppm. MS (EI): *m*/*z* (%) = 467 (7) [M^+], 250 (52), 217 (32), 172 (24), 159 (80), 145 (40), 144 (29), 117 (34), 116 (46), 104 (20), 91 (100), 90 (20), 89 (43), 77 (24), 65 (20), 63 (22), 51 (20) $C_{28}H_{25}N_3O_4$ (467.53): calcd. C 71.93, H 5.39, N 8.99; found C 71.84, H 5.31, N 9.11.

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