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A facile synthesis of chromeno[3,4-*c*]spiropyrrolidine-oxindoles via 1,3-dipolar cycloadditions

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ABSTRACT

A facile one-pot synthesis of chromene bearing novel spiropyrrolidine-oxindoles has been accomplished by the [3+2]-cycloaddition reaction of 3-acetyl-2*H*-chromen-2-ones with azomethine ylides derived in situ from isatin or *N*-methyl isatin with sarcosine.

1. Introduction

The intramolecular [3+2] cycloaddition of azomethine ylides has been used widely to construct complex cyclic systems from relatively simple precursors.[1] This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms complex ring systems with regio- and stereocontrol.[2] Azomethine ylides are a class of powerful reagents used in [1,3]-dipolar cycloaddition reactions, which in general afford a range of pharmacologically important heterocyclic compounds.[3]

The abundance of naturally occurring chromene and chromane derivatives, and their interesting physiological properties along with the known selective dopamine D3 receptor antagonist action of some benzopyrano[3,4-*c*]pyrrolidine derivatives has gained a vital place in the field of heterocyclic chemistry.[4] Synthesis of heterocyclic compounds containing the chromeno[3,4-*c*]pyrrole and spiropyrrolidine-oxindole motifs seemed to be interesting due to their widespread known biological activities. 3′-Spiropyrrolidine-oxindoles and their derivatives such as horsfiline, elacomine, alstonisine and spirotryprostatin B have become important synthetic targets as these structural frameworks form the core units of many naturally occurring molecules that possess significant biological activities (Fig. 1).[5] Some spiropyrrolidine-oxindole derivatives are potential antileukaemic and anticonvulsant agents[6] and possess antiviral and local anaesthetic activities.[7]

As a part of our own interest in cycloaddition reactions,[8] we report herein the facile synthesis of novel chromeno[3,4-*c*]spiropyrrolidine-oxindoles via the one-pot, three-component condensation of 3-acetyl-2*H*-chromen-2-ones **1a**–**c** with the azomethine ylide generated in situ from isatin or *N*-methyl isatin.

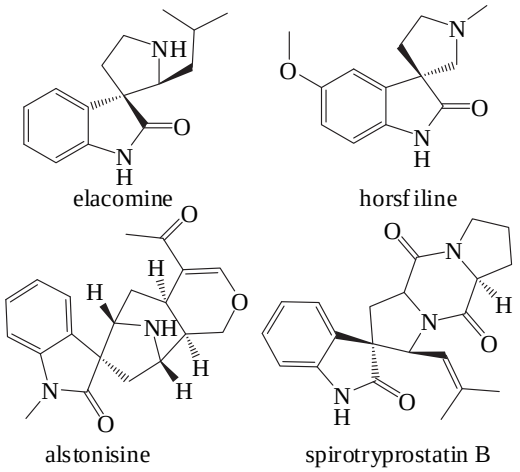

Figure 1. 3,3′-Pyrrolidinyl-spirooxindole-type natural products.

2. Results and discussion

3-Acetyl-2*H*-chromen-2-one **1a**–**c** and sarcosine were treated with isatin or *N*-methyl isatin in toluene. The reactions smoothly went to completion when the mixture was heated to reflux for 24 h. After evaporation of the solvent and recrystallization of the crude products from CH_3CN, **2a**–**f** were obtained in good yields (Scheme 1). The results are shown in Table 1. Identification of the

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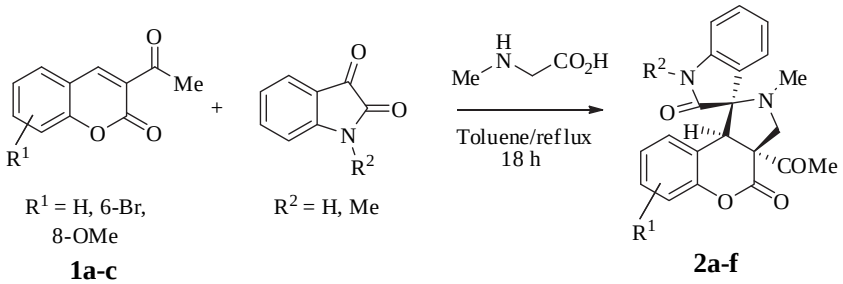


R^1 = H, 6-Br, 8-OMe

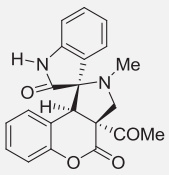
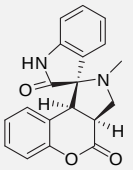
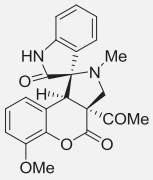
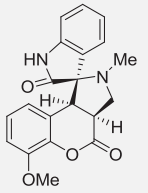
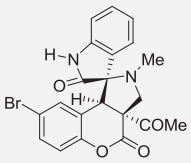
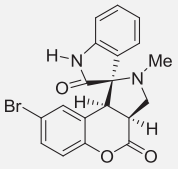
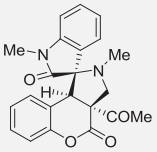
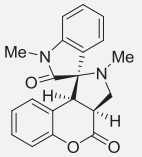
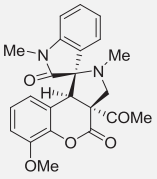
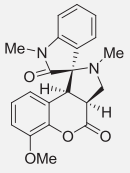
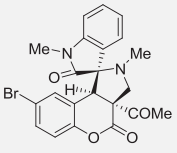
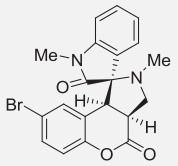
1a-c

R^2 = H, Me

2a-f

Scheme 1. Synthesis of chromeno[3,4-*c*]spiropyrrolidine-oxindoles **2a**–**f**.

Table 1
Reaction results for the synthesis of chromeno[3,4-*c*]spiropyrrolidine- oxindoles **2a**–**f** and **3a**–**f**

Compound	R^1	R^2	Yield (%)	Structure[a,c,d]	Compound	Yield (%)	Structure[b,c,d]
2a	H	H	68		**3a**	80	
2b	8-OMe	H	75		**3b**	90	
2c	6-Br	H	80		**3c**	87	
2d	H	CHMe	68		**3d**	83	
2e	8-OMe	Me	75		**3e**	79	
2f	6-Br	Me	73		**3f**	86	

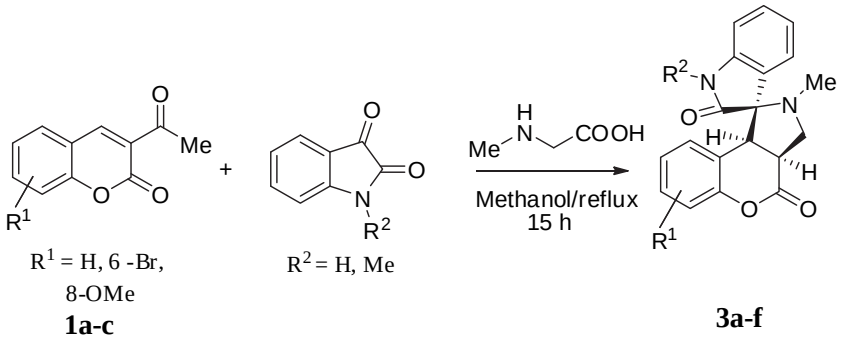
[a] All reactions were carried out using 2 mmol of 3-acetyl coumarins **1a**–**c** with isatin or *N*-methy isatin (2 mmol) in 30 mL of toluene under reflux for 18 h.
[b] All reactions were carried out using 2 mmol of 3-acetyl coumarins **1a**–**c** with isatin or *N*-methy isatin (2 mmol) in 30 mL of methanol under reflux for 15 h.
[c] Yields of the pure products (**2a**–**f** and **3a**–**f**) obtained after recrystallization from acetonitrile and methanol, respectively.
[d] Structures were further confirmed by single-crystal X-ray analyses.

products was carried out by spectroscopic methods. For example, the ^{1}H NMR spectrum of **2a** showed two characteristic singlets at δ 2.06 (3H) and 2.42 (3H) due to COMe and NMe, respectively. Two doublets appeared at δ 3.82 (1H, J=10.5 Hz) and 4.00 (1H, J=10.5 Hz) for NCH_2 together with two singlets at δ 4.21 (1H) and 10.27 (1H) due to the PhCH and NH, respectively.

Product **3a**–**f** were surprisingly obtained when the reactions were carried out in methanol under reflux conditions for 15 h with subsequent recrystallization of the crude solids from methanol (Scheme 2). The results are presented in Table 1.

of **3a**–**f** is expected to occur from the same side that the acetyl group has been eliminated. Literature survey disclosed that deacetylation is a common process in disubstituted 1,3-diketones under basic methanol or ethanol conditions.[11]

The reactions were found to be highly regioselective leading to the formation of only one product **2a** (Fig. 4, **II**) and the formation of the other possible regioisomer **2a′** (Fig. 4, **I**) was not observed. This may be due to the unfavourable dipole–dipole repulsion between the carbonyl groups of oxindole and the dipolarophile (Fig. 4). Observation of similar results has been reported recently.[12]



Scheme 2. Synthesis of chromeno[3,4-*c*]spiropyrrolidine-oxindoles **3a**–**f**.

The regio- and stereochemical outcome of the cycloaddition reactions were unambiguously ascertained by single-crystal X-ray analysis of the cycloadducts **2a** (Fig. 2) and **3c** (Fig. 3).[9] Inspection of the results reveals that the [3+2] cycloaddition in methanol has been accompanied with deacetylation presumably via nucleophilic attack of methanol to COMe group.

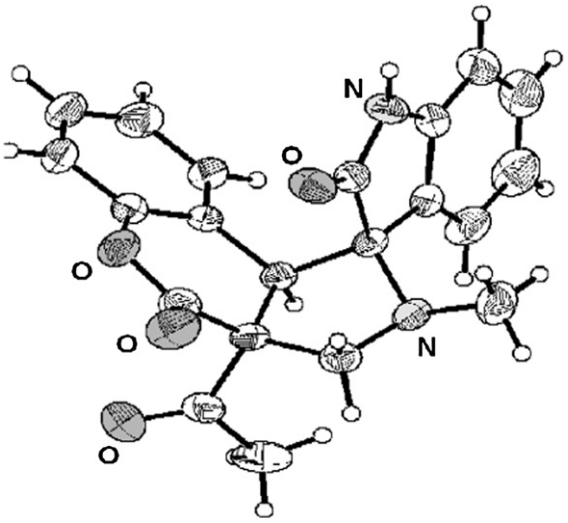


Figure 2. ORTEP diagram of compound **2a**.

To gain insight into the timing of deacetylation process, cycloaddition reactions of **1c** in toluene and methanol were monitored by TLC. The formation of **2c** was unequivocally evident in both solvents. Disappearance of **2c** and appearance of **3c** was then observed when reaction proceeded to completion in methanol. Comparison of Figures 1 and 2 reveals that the conversion of **2c** to **3c** occurs with retention of configuration. Obtaining products in base catalyzed H/D exchange reactions of ketones proceeding with retention of configurations has been explained by the formation of carbanion intermediates tightly connected to methanol hydrogens.[10] Therefore, subsequent addition of proton to carbanions derived by **2a**–**f** and formation

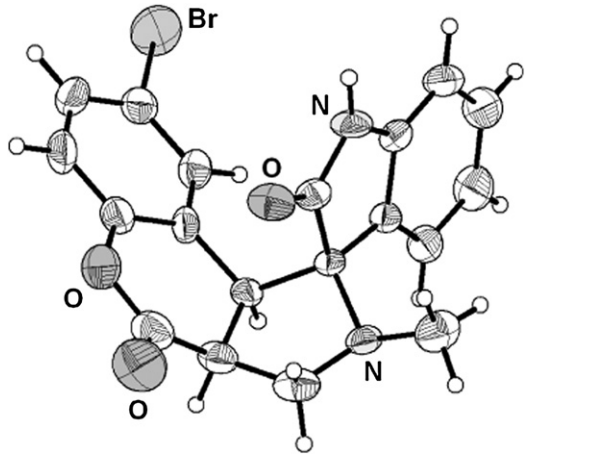


Figure 3. ORTEP diagram of compound **3c**.

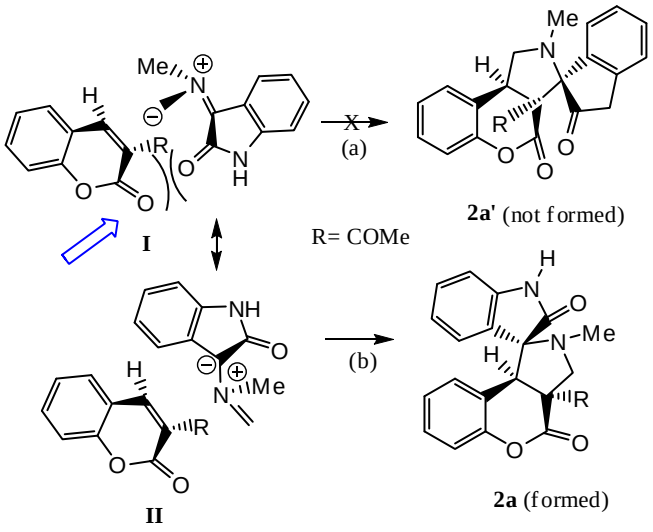


Figure 4. Transition state model evoked for the formation of **2a**.

The reactions have been found to be stereospecific. Cycloadducts **2a**–**f** and **3a**–**f** were obtained stereochemically pure, with no evidence in the NMR spectra or TLC of the crude products of any diastereoisomers. The *syn* stereochemical relation present between the –COMe and –H groups in the dipolarophiles **1a**–**c** is completely retained in the cycloadducts. Furthermore, the ring junction between the two fused rings of pyrrolidine and chromenon **3a**–**f** is always *cis* as confirmed by coupling constant of 9.1–9.4 Hz of –PhCH and X-ray crystallography.

3. Conclusions

In conclusion, we have found a diastereoselective three-component 1,3-dipolar cycloaddition reaction which gives a tricyclic fused chromeno[3,4-*c*]yrrolidine-oxindoles containing a spiro center with novel regioselectivities. Direct access to pure **2a**–**f** and **3a**–**f** in good to excellent yields simply by means of recrystallization method with no need to tedious chromatography procedure is an important aspect of MCRs, which deserves some considerations.

4. Experimental section

4.1. General information

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer; in cm^{-1}. ^1H- and ^{13}C NMR Spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^1H) and 125 MHz (^{13}C). Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN–O-Rapid Heraeus elemental analyzer (Wellesley, MA).

4.2. Representative procedure for the synthesis of chromeno [3,4-*c*]spiropyrrolidine-oxindole (2a)

A mixture of sarcosine (0.18 g, 2.0 mmol), 3-acetyl coumarin (0.38 g, 2.0 mmol) and isatin (0.29 g, 2.0 mmol) was heated to reflux in dry toluene (30 mL) containing molecular sieves (1.0 g, 4 Å) with stirring for 18 h. The progress of the reaction was followed by TLC. After completion, the mixture was filtered and the solvent was removed under reduced pressure. The residue was then recrystallized from CH_3CN to afford **2a**.

*4.2.1. 3a-Acetyl-1,2,3,3a-tetrahydro-2-methyl-spiro-[1,3]-chromeno [3,4-c]pyrrol-4(9bH)-one-oxindole (**2a**).* White solid, (0.49 g, 68%), mp 251–252 °C; [Found C, 69.37; H, 5.21; N, 7.57. $C_{21}H_{18}N_2O_4$ requires C, 69.60; H, 5.01; N, 7.73%]; ν_{max} (KBr) 1749, 1700 cm^{-1}; δ_H (500 MHz, DMSO) 2.06 (s, 3H, CO*Me*), 2.42 (s, 3H, N*Me*), 3.82 (d, 1H, *J* 10.5 Hz, NC*H*), 3.99 (d, 1H, *J* 10.5 Hz, NC*H*), 4.21 (s, 1H, PhC*H*), 6.29 (d, 1H, *J* 7.6 Hz, Ph), 6.75 (d, 1H, *J* 7.6 Hz, Ph), 6.84 (t, 1H, *J* 7.6 Hz, Ph), 7.03 (d, 1H, *J* 87.5 Hz, Ph), 7.17 (t, 1H, *J* 7.5 Hz, Ph), 7.23 (t, 1H, *J* 7.5 Hz, Ph), 7.32 (t, 1H, *J* 7.5 Hz, Ph), 7.56 (d, 1H, *J* 7.5 Hz, Ph), 10.27 (s, 1H, N*H*); δ_C (125 MHz, DMSO) 25.5, 35.5, 50.6, 59.9, 62.6, 77.9, 110.8, 116.7, 117.4, 123.4, 124.8, 125.5, 126.7, 128.5, 130.4, 131.0, 143.0, 151.0, 166.8, 177.4, 203.8; *m*/*z* (EI, 70 eV) 362 (2, M^+), 291 (25), 264 (22), 174 (100), 159 (82%).

*4.2.2. 3a-Acetyl-6-methoxy-1,2,3,3a-tetrahydro-2-methyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**2b**).* White solid, (0.59 g, 75%), mp 211–212 °C; [Found C, 67.12; H, 4.97; N, 7.01. $C_{22}H_{20}N_2O_5$ requires C, 67.34; H, 5.14; N, 7.14%]; ν_{max} (KBr) 1751, 1709 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.09 (s, 3H, CO*Me*), 2.39 (s, 3H, N*Me*), 3.67 (s, 3H, O*Me*), 3.86 (d, 1H, *J* 10.3 Hz, NC*H*), 4.09 (d, 1H, *J* 10.3 Hz, NC*H*), 4.21 (s, 1H, PhC*H*), 5.87 (d, 1H, *J* 7.5 Hz, Ph), 6.64–6.69 (m, 2H, Ph), 6.87 (d, 1H, *J* 7.5 Hz, Ph), 7.19 (t, 1H, *J* 7.5 Hz, Ph), 7.34 (t, 1H, *J* 7.5 Hz, Ph), 7.45 (d, 1H, *J* 7.5 Hz, Ph), 8.67 (s, 1H, N*H*); δ_C (125 MHz, $CDCl_3$) 26.4, 35.4, 50.8, 56.1, 60.7, 62.4, 78.2, 111.3, 111.9, 117.0, 119.2, 123.7, 124.4, 124.6, 126.7, 130.6, 140.1, 142.5, 147.5, 166.6, 178.6, 201.1; *m*/*z* (EI, 70 eV): 392 (3, M^+), 218 (50), 203 (55), 174 (100), 133 (20%).

*4.2.3. 3a-Acetyl-8-bromo-1,2,3,3a-tetrahydro-2-methyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**2c**).* White solid, (0.70 g, 80%), mp 106–107 °C; [Found: C, 57.01; H, 3.96; N, 6.11. $C_{21}H_{17}BrN_2O_4$ requires C, 57.16; H, 3.88; N, 6.35%]; ν_{max} (KBr) 1760, 1707 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.17 (s, 3H, CO*Me*), 2.45 (s, 3H, N*Me*), 3.90 (d, 1H, *J* 10.4 Hz, NC*H*), 4.15 (d, 1H, *J* 10.4 Hz, NC*H*), 4.19 (s, 1H, PhC*H*), 6.40 (s, 1H, Ph), 6.81 (d, 1H, *J* 7.7 Hz, Ph), 6.89 (d, 1H, *J* 7.7 Hz, Ph), 7.24 (d, 1H, *J* 6.8 Hz, Ph), 7.27 (t, 1H, *J* 6.8 Hz, Ph), 7.41 (t, 1H, *J* 7.5 Hz, Ph), 7.49 (d, 1H, *J* 7.5 Hz, Ph), 8.21 (s, 1H, N*H*); δ_C (125 MHz, $CDCl_3$) 26.3, 35.4, 50.5, 60.7, 62.3, 78.1, 111.0, 117.0, 118.3, 119.0, 124.2, 124.7, 128.6, 129.4, 130.8, 131.0, 142.5, 149.8, 166.4, 178.1, 200.9; *m*/*z* (EI, 70 eV) 440 (2, M^+), 290 (18), 253 (27), 174 (100), 105 (46%).

*4.2.4. 3a-Acetyl-1,2,3,3a-tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**2d**).* White solid, (0.51 g, 68%), mp 103–104 °C; [Found: C, 70.01; H, 5.13; N, 7.19. $C_{22}H_{20}N_2O_4$ (376.14): C, 70.20; H, 5.36; N, 7.44%]; ν_{max} (KBr) 1757, 1702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.15 (s, 3H, CO*Me*), 2.42 (s, 3H, N*Me*), 2.81 (s, 3H, N*Me*), 3.92 (d, 1H, *J* 10.3 Hz, NC*H*), 4.20 (d, 1H, *J* 10.3 Hz, NC*H*), 4.22 (s, 1H, PhC*H*), 6.25 (d, 1H, *J* 7.4 Hz, Ph), 6.73–6.77 (m, 2H, Ph), 7.02 (d, 1H, *J* 7.4 Hz, Ph), 7.19 (t, 1H, *J* 7.1 Hz, Ph), 7.29 (t, 1H, *J* 7.4 Hz, Ph), 7.40 (t, 1H, *J* 7.4 Hz, Ph), 7.53 (d, 1H, *J* 7.1 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 25.7, 26.5, 35.4, 51.1, 60.9, 62.6, 78.0, 108.8, 116.2, 117.6, 123.9, 124.5, 125.4, 126.3, 127.8, 129.8, 130.7, 145.2, 150.8, 167.0, 175.8, 201.3; *m*/*z* (EI, 70 eV) 376 (13, M^++1), 333 (11), 251 (6), 188 (100), 173 (25%).

*4.2.5. 3a-Acetyl-6-methoxy-1,2,3,3a-tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**2e**).* White solid, (0.60 g, 75%), mp 197–198 °C; [Found: C, 67.63; H, 5.72; N, 6.61. $C_{23}H_{22}N_2O_5$ requires C, 67.97; H, 5.46; N, 6.89%]; ν_{max} (KBr) 1761, 1700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.13 (s, 3H, CO*Me*), 2.42 (s, 3H, N*Me*), 2.84 (s, 3H, N*Me*), 3.83 (s, 3H, O*Me*), 3.89 (d, 1H, *J* 10.2 Hz, NC*H*), 4.21(d, 1H, *J* 10.2 Hz, NC*H*), 4.27 (s, 1H, PhC*H*), 5.84 (d, 1H, *J* 7.5 Hz, Ph), 6.69 (t, 1H, *J* 7.5 Hz, Ph), 6.73–6.75 (m, 2H, Ph), 7.15–7.28 (m 3H, Ph), 7.40 (t, 1H, *J* 7.5 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 25.8, 26.5, 35.3, 50.9, 56.3, 60.8, 62.4, 77.9, 108.7 112.0, 117.1, 119.0, 126.4, 128.6, 129.4, 130.3, 130.6, 140.3, 145.3, 147.7, 166.5, 175.7, 201.1; *m*/*z* (EI, 70 eV) 407 (5, M^++1), 363 (7), 203 (10), 188 (100), 173 (18%).

*4.2.6. 3a-Acetyl-8-bromo-1,2,3,3a-tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**2f**).* White solid, (0.67 g, 73%), mp 194–195 °C; [Found: C, 58.34; H, 4.12; N, 5.98. $C_{22}H_{19}BrN_2O_4$ requires C, 58.04; H, 4.21; N, 6.15%]; ν_{max} (KBr) 1745, 1706 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.17 (s, CO*Me*), 2.45 (s, N*Me*), 2.91 (s, N*Me*), 3.91 (d, 1H, *J* 10.3 Hz, NC*H*), 4.20–4.23 (m, 2H, NC*H* and PhC*H*), 6.64 (d, 1H, *J* 8.5 Hz, Ph), 6.76 (s, 1H, Ph), 6.83 (d, 1H, *J* 7.5 Hz, Ph), 7.02–7.08 (m, 2H, Ph), 7.27 (d, 1H, *J* 7.5 Hz, Ph), 7.32 (d, 1H, *J* 7.5 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 25.9, 26.4, 35.4, 50.5, 60.8, 63.4, 77.9, 109.0, 116.7, 118.4, 118.8, 119.2, 124.2, 124.4, 130.6, 131.0, 132.7, 145.1, 149.9, 172.2, 174.7, 200.9; *m*/*z* (EI, 70 eV) 454 (4, M^+), 412 (4), 236 (3), 188 (100), 173 (20%).

4.3. Representative procedure for the synthesis of spiropyrrolidine-oxindole annulated coumarin derivatives (3a)

A mixture of sarcosine (0.18 g, 2.0 mmol), 3-acetyl coumarin (0.38 g, 2.0 mmol) and isatin (0.29 g, 2.0 mmol) was heated to

reflux in methanol (30 mL) containing molecular sieves (1.0 g, 4 Å) with stirring for 15 h. After completion, the reaction was cooled and the solid was filtered and recrystallized from methanol to afford the **3a**.

*4.3.1. 1,2,3,3a-Tetrahydro-2-methyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**3a**).* White solid, (0.66 g, 80%), mp 255–256 °C; [Found: C, 71.01; H 5.24; N, 8.59. $C_{19}H_{16}N_2O_3$ requires C, 71.24; H, 5.03; N, 8.74%]; ν_{max} (KBr) 1751,1701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.17 (s, N*Me*), 3.57–3.59 (m, C*H*COO), 3.77 (m, 1H, NC*H*), 3.84 (d, 1H, *J* 9.5 Hz, NC*H*), 3.89 (d, 1H, *J* 9.1 Hz, PhC*H*), 6.26 (d, 1H, *J* 7.0 Hz, Ph), 6.70–6.73 (m, 2H, Ph), 6.91 (d, 1H, *J* 7.4 Hz, Ph), 7.11 (t, 2H, *J* 7.4 Hz, Ph), 7.24 (t, 1H, *J* 7.4 Hz, Ph), 7.35–7.37 (m, 1H, Ph), 9.08 (s, N*H*); δ_C (125 MHz, $CDCl_3$) 35.7, 38.5, 48.4, 56.4, 77.1, 110.7, 117.4, 123.2, 124.2, 128.1, 129.5, 130.2, 143.3, 151.4, 167.0, 177.4; *m*/*z* (EI, 70 eV) 320 (2, M^+), 264 (20), 222 (11), 174 (100), 159 (35%).

*4.3.2. 6-Methoxy-1,2,3,3a-tetrahydro-2-methyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole (**3b**).* White solid, (0.63 g, 90%), mp 249–250 °C; [Found: C, 68.34; H, 5.34; N, 8.12. $C_{20}H_{18}N_2O_4$ requires C, 68.56; H, 5.18; N, 8.00%]; ν_{max} (KBr) 1754, 1702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.19(s, 3H, N*Me*), 3.61–3.63 (m, 1H, C*H*COO), 3.80 (s, 3H, O*Me*), 3.82–3.84 (m, 1H, NC*H*), 3.92–3.97 (m, 2H, NC*H*, PhC*H*), 5.89 (d, 1H, *J* 7.0 Hz, Ph), 6.69–6.74 (m, 2H, Ph), 6.82 (d, 1H, *J* 7.6 Hz, Ph), 7.21 (t, 1H, *J* 7.6 Hz, Ph), 7.35 (t, 1H, *J* 7.6 Hz, Ph), 7.42 (br s, 1H, Ph), 7.90 (s, 1H, N*H*); δ_C (125 MHz, $CDCl_3$) 35.6, 38.2, 48.5, 56.2, 56.3, 76.9, 110.6, 11.8, 117.9, 119.4, 122.9, 123.8, 124.2, 127.0, 130.7, 140.7, 143.5, 147.6, 168.2, 177.9; *m*/*z* (EI, 70 eV) 350 (3, M^+), 294 (8), 236 (4), 174 (100), 159 (28%).

*4.3.3. 4-Bromo-1,2,3,3a-tetrahydro-2-methyl-spiro-[1,3]-chromeno [3,4-c]pyrrol-4(9bH)-one-oxindole (**3c**).* White solid, (0.70 g, 87%), mp 243–244 °C; [Found: C, 57.12; H, 3.99; N, 7.12. $C_{19}H_{15}BrN_2O_3$ requires C, 57.16; H, 3.79; N, 7.02%]; ν_{max} (KBr) 1766, 1702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.11 (s, 3H, N*Me*), 3.50–3.53 (m, 1H, C*H*COO), 3.76–3.78 (m, 2H, NCH_2), 3.83 (d, 1H, *J* 9.4 Hz, PhC*H*), 6.29 (s, 1H, Ph), 6.71 (d, 1H, *J* 7.7 Hz, Ph), 6.76 (d, 1H, *J* 8.7 Hz, Ph), 7.09 (t, 1H, *J* 7.5 Hz, Ph), 7.17 (d, 1H, *J* 8.7 Hz, Ph), 7.22 (t, 1H, *J* 7.7 Hz, Ph), 7.28 (d, 1H, *J* 5.1 Hz, Ph), 9.35 (s, 1H, N*H*); δ_C (125 MHz, $CDCl_3$) 35.6, 38.1, 48.1, 56.2, 77.0, 110.8, 111.8, 119.0, 119.4, 123.3, 124.2, 126.4, 130.5, 130.7, 132.3, 143.4, 150.5, 168.1, 178.0; *m*/*z* (EI, 70 eV) 399 (9, M^++1), 342 (7), 220 (5), 174 (100), 159 (17%).

*4.3.4. 1,2,3,3a-Tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]-pyrrol-4(9bH)-one-oxindole (**3d**).* White solid, (0.55 g, 83%), mp 110–111 °C; [Found: C, 71.57; H, 5.33; N, 8.19. $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N 8.38%]; ν_{max} (KBr) 1762, 1699, 1608 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.17 (s, 3H, N*Me*), 2.81 (s, 3H, N*Me*), 3.64 (m, 1H, C*H*COO), 3.85–3.91 (m, 2H, NCH_2), 3.98 (d, 1H, *J* 9.4 Hz, PhC*H*), 6.23 (d, 1H, *J* 7.2 Hz, Ph), 6.73–6.76 (m, 2H, Ph), 7.02 (d, 1H, *J* 7.9 Hz, Ph), 7.18 (t, 1H, *J* 7.3 Hz, Ph), 7.24 (t, 1H, *J* 7.3 Hz, Ph), 7.42 (t, 1H, *J* 7.9 Hz, Ph), 7.49 (d, 1H, *J* 7.3 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 25.7, 35.7, 38.6, 48.8, 56.5, 77.1, 108.7, 116.8, 117.7, 123.7, 124.0, 124.2, 126.8, 127.7, 129.6, 130.4, 145.4, 151.4, 168.7, 176.1; *m*/*z* (EI, 70 eV) 334 (5, M^+), 234 (5), 220 (4), 188 (100), 173 (40).

*4.3.5. 6-Methoxy-1,2,3,3a-tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole **3e**.* White solid, (0.58 g, 79%), mp 172–173 °C; [Found: C, 69.01; H, 5.37; N, 7.53. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%]; ν_{max} (KBr) 1752, 1697, 1610 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.15 (s, 3H, N*Me*), 2.83 (s, 3H, N*Me*), 3.61 (m, 1H, C*H*COO), 3.83 (s, 3H, O*Me*), 3.85–3.88 (m, 1H, NC*H*), 3.90 (m,1H, NC*H*), 3.95 (d, 1H, *J* 9.8 Hz, PhC*H*), 5.80 (d, 1H, *J* 7.6 Hz, Ph), 6.67 (t, 1H, *J* 7.4 Hz, Ph), 6.74 (t, 1H, *J* 7.4 Hz, Ph), 7.22 (t, 1H, *J* 7.4 Hz, Ph), 7.39 (t, 1H, *J* 7.6 Hz, Ph), 7.45 (d, 1H, *J* 7.4 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 25.8, 35.6, 38.3, 48.9, 56.3, 56.4, 76.9, 108.7, 112.0, 117.7, 119.0, 123.6, 123.7, 124.2, 126.9, 130.3, 140.9, 145.5, 147.9, 168.1, 176.0; *m*/*z* (EI, 70 eV) 364 (11, M^+), 250 (4), 218 (6), 188 (100), 173 (31%).

*4.3.6. 8-Bromo-1,2,3,3a-tetrahydro-2,3′-dimethyl-spiro-[1,3]-chromeno[3,4-c]pyrrol-4(9bH)-one-oxindole **3f**.* White solid, (0.71 g, 86%), mp 183–184 °C; [Found: C, 57.77; H, 4.51; N, 6.59. $C_{20}H_{17}BrN_2O_3$ requires C, 58.13; H, 4.15; N, 6.78%]; ν_{max} (KBr): 1762, 1669, 1605 cm^{-1}; δ_H (500 MHz, DMSO) 2.00 (s, 3H, N*Me*), 2.74 (s, 3H, N*Me*), 3.49–3.52 (m, 1H, C*H*COO), 3.80 (t, 1H, *J* 9.1 Hz, NC*H*), 3.85–3.89 (m, 1H, NC*H*), 3.96 (d, 1H, *J* 10.7 Hz, PhC*H*), 6.20 (br s, 1H, Ph), 6.97–6.99 (m, 2H, Ph), 7.25 (t, 1H, *J* 7.4 Hz, Ph), 7.38 (d, 1H, *J* 8.7 Hz, Ph), 7.45 (t, 1H, *J* 7.5 Hz, Ph), 7.50 (d, 1H, *J* 7.4 Hz, Ph); δ_C (125 MHz, DMSO) 26.4, 35.7, 45.9, 51.8, 54.8, 76.0, 109.1, 109.7, 117.5, 123.2, 124.7, 126.1, 128.8, 129.9, 130.9, 133.3, 144.4, 155.7, 172.3, 174.7; MS (EI, 70 eV): *m*/*z* (EI, 70 eV) 413 (2, M^++1), 329 (4), 314 (2), 188 (100), 173 (33%).

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