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A Three-Component 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylide for Synthesis of New Bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) Derivatives

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ABSTRACT

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry. A comparative study of the synthesis of new bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) ring systems by the cycloaddition of azomethine ylides generated by a decarboxylative route from sarcosine/proline and isatin with the bis-chalcone using various conditions is described. As part of our endeavor to synthesize new bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) derivatives containing two spiro carbons which often enhances the biocidal profile or may create new medicinal properties remarkably. Herein we report the facile synthesis of bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) derivatives, in a highly regio- and stereoselective manner through 1,3-dipolar cycloaddition reaction of bis-dipolarophiles with the 1,3-dipole generated from isatin derivatives and secondary amino acids (L-proline or sarcosine). The structures of cycloaddition products were assigned by IR, ¹HNMR, ¹³CNMR and Mass spectral data.

Keyword: Azomethine ylides; Bis-dipolarophiles; Bis-spiro-oxindolo(pyrrolizidines/pyrrolidines); Sarcosine; Proline.

1. INTRODUCTION

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry [1–4]. The MCR strategy offers significant advantages over conventional linear-type synthesis because of its flexible, convergent, and atom-efficient nature [5, 6]. One-pot, multi-component reactions continue to be of

interest in the synthesis of poly-substituted nitrogen heterocycles owing to the fast assembly of the same without the isolation of unstable intermediates [7–10]. Hence, a feasible method for the generation of biologically active nitrogen containing heterocycles through MCRs has attracted great attention over the past decades [11–13]. Functionalized pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skel-

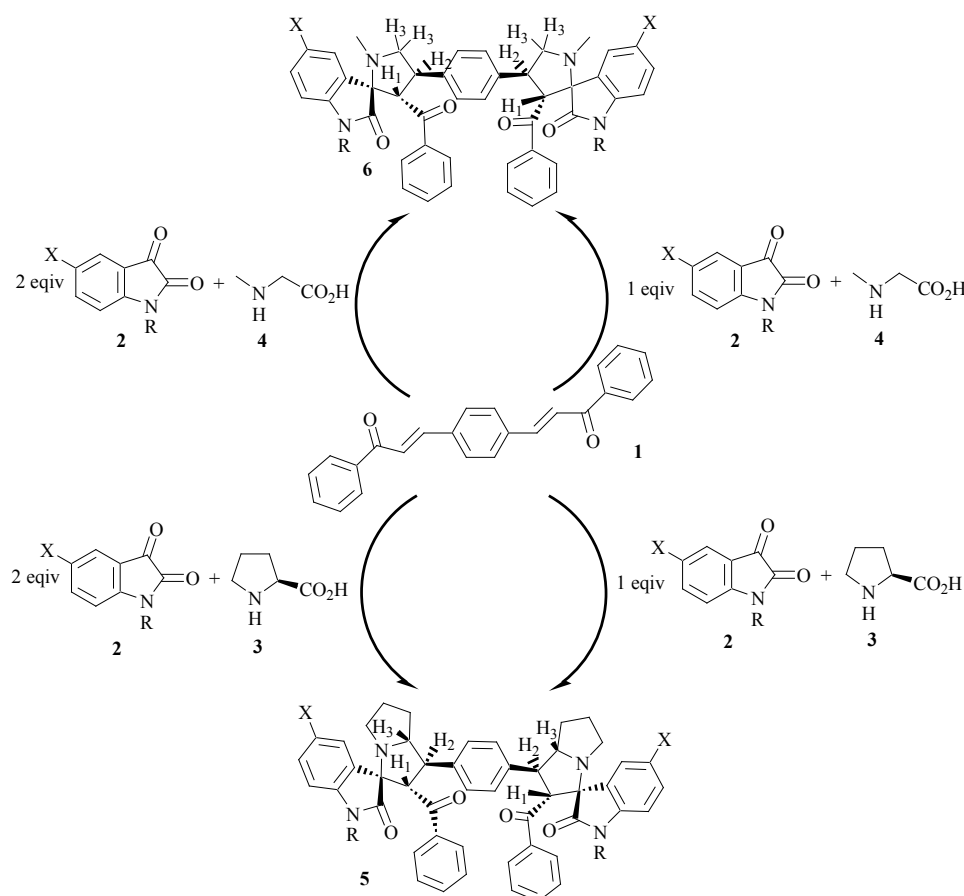
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etons for numerous alkaloids and pharmacologically important compounds [14–18]. Gelesmine, pseudotabersonine, formosanine, isoformosanine, morroniside and mitraphylline are some of the alkaloids containing spirooxindole ring systems [19–23]. Derivatives of spirooxindole find very wide biological applications as anti-microbials, anti-inflammatory, antitumourals, antibiotic agents and inhibitors of human NK-1 receptors [24–26]. 1,3-Dipolar cycloaddition reaction is an efficient method for the construction of heterocyclic units in a highly regio- and stereo-selective manner [27, 28]. As part of our endeavor to synthesize new bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) derivatives containing two spiro carbons which often enhances the biocidal profile or may create new medicinal properties remarkably. Herein we report the facile synthesis of bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) derivatives, in a highly regio- and stereoselective manner through 1,3-dipolar cycloaddition reaction of bis-dipolarophiles **1** with the 1,3-dipole generated from isatin derivatives and secondary amino acids (L-proline or sarcosine).

Based on the literature procedure [29–32], the (2E,2'E)-3,3'-(1,4-phenylene)bis(1-phenylprop-2-en-1-one) **1**, was easily prepared from reaction of terephthalaldehyde with acetophenone. Three component reactions between this bis-dipolarophile **1**, isatin derivatives (**2**) and L-proline (**3**) or sarcosine (**4**) carried out in ethanol at room temperature with excellent yields. Condensation of compounds **2** and **3** (or **4**) after decarboxylation leading to the non-stabilized azomethine ylides stereogenic centers in one step. But by using this strategy only diastereoisomer **5** (or **6**) were obtained purely in high total yield and high optical purity as shown by TLC, GC-MS and NMR analysis (Scheme 1). After this, other derivatives of this bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) were synthesized. The results are summarized in Table 1.

2. RESULTS AND DISCUSSION

The structures of cycloaddition products were assigned by IR, ¹HNMR, ¹³CNMR and Mass spectral data. Ob-



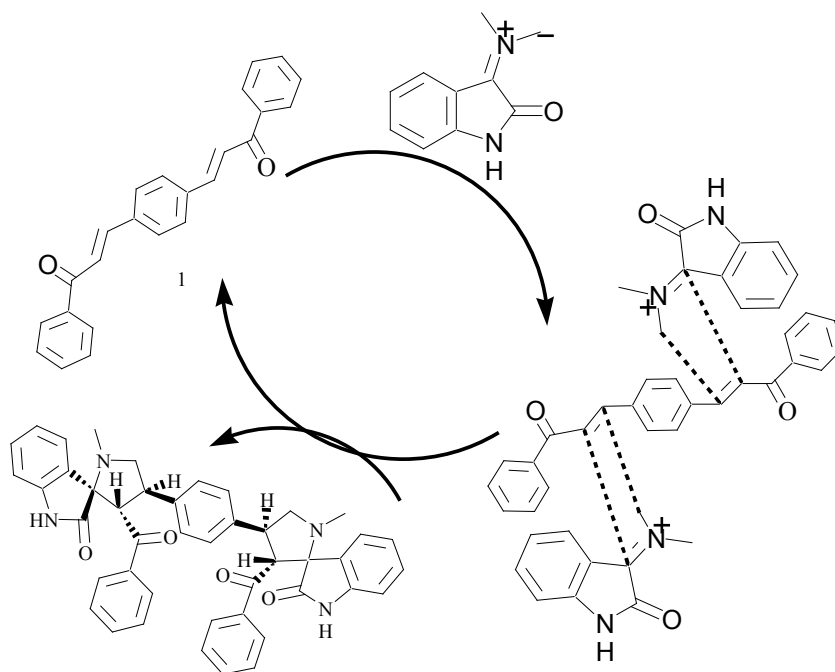
Scheme 1: Synthesis of bis-spirooxindolo(pyrrolizidines/pyrrolidines).

Table 1: Yield of compounds of 5 and 6.

5, 6	R	X	Yield (%)	
			5	6
A	H	H	93	87
B	H	Br	90	85
c	H	NO ₂	95	83
d	Me	H	95	85
e	Me	Br	94	87
f	Me	NO ₂	90	85
g	Et	H	95	85
h	Et	Br	90	80
i	Et	NO ₂	95	83

servation of three characteristic singlet at about (51.4, 66.2 and 72.4) in the ¹³CNMR spectra of 5g and two characteristic singlet at about (60.8 and 65.3) in the ¹³CNMR spectra of 6g is consistent with formation new pyrrolidine cyclic. The stereochemistry and the correct structure of this isomer and other derivatives were determined by ¹HNMR, ¹³CNMR, IR, Mass, HMQC, and COSY NMR experiments. For example,

the ¹HNMR spectrum of 5g exhibits a triplet signal at $\delta = 3.83$ ppm, a multiplet at $\delta = 4.19$ and a doublet at $\delta = 4.57$ ppm which are related to H-2, H-3 and H-1 protons respectively. The ¹HNMR spectrum of 6g exhibits a multiplet signal at $\delta = 3.64$ ppm and a doublet at $\delta = 4.14$ ppm which are related to H-2 and H-1 protons respectively. Also DEPT 135° of 5g showed signals, corresponding to three (CH) carbons that were direct-

**Scheme 2:** Suggestion mechanism for synthesis of bis-spiro oxindolopyrrolidines.

ly bonded to H-2, H-3 and H-1 in the region 51.4, 66.2 and 72.4 respectively. Stereochemistry of the 5a has been assigned from ROESY spectrum. Absence of any correlation between H₃ and H₂ in the ROESY spectrum shows that the H₂ hydrogen could be trans to H₃. But an intense contour between H₁ and H₃ shows these two hydrogen are cis to each other's. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in scheme 1. Absence of any vinyl-CH in the ¹H NMR spectrum shows that bis-spiro-oxindolo(pyrrolizidines/pyrrolidines) were synthesized. While our previous work mono-spiro-oxindolo(pyrrolizidines/pyrrolidines) were synthesized. According to the papers and chemical shifts of new proline ring formed, H₁ dishilder than H₂ and H₃ is the location, according to Scheme 1, while the other regioisomer H₂ dishilder than H₂ and H₃ is the location.

3. EXPERIMENTAL DETAIL

General melting points were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. ¹H, ¹³C NMR spectra were measured with a Bruker DRX-250 AVANCE instrument with CDCl₃ as solvent at 250.1 MHz. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an electron energy of 70 eV. isatin derivatives, proline, and sarcosine were obtained from Fluka (Buchs, Switzerland) and were used without further purification, and (2E,2'E)-3,3'-(1,4-phenylene)bis(1-phenylprop-2-en-1-one) were obtained via synthesis.

General procedure

To a magnetically stirred solution of isatin (1 mmol) and proline or sarcosine (1 mmol) in 10 cm³ ethanol, to this mixture (2E,2'E)-3,3'-(1,4-phenylene)-bis(1-phenylprop-2-en-1-one) (1 mmol) was added in one portion in room temperature. Then, the reaction mixture was stirred for 8 h. The solvent was then removed under reduced pressure. Recrystallization from ethyl acetate afforded.

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S),

7a'S)-2'-benzoyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one (5a, C₄₈H₄₂N₄O₄) M.P.: 345°C; ¹H NMR (300.1 MHz, CDCl₃); 1.27-2.06 (m, 4CH₂), 2.58-2.63 (m, 2CH₂), 3.86 (t, J = 9 Hz, 2H-2), 4.19 (m, 2CH), 4.58 (d, J = 9 Hz, 2H-1), 6.83-7.49 (m, Ar-H), 9.04 (s, 2NH) ppm; ¹³C NMR (75 MHz, CDCl₃); 27.7, 31.2, 48.0 (6CH₂), 52.5, 66.5, 72.6 (6CH), 74.1(2C), 125.4, 125.5, 127.0, 127.4, 129.6 (10CH), 128.3, 128.6, 128.8 (12CH), 122.5, 134.2, 139.8, 140.8 (8C), 181.7 (2C=O), 195.0 (2C=O) ppm; IR (KBr): V = 1659, 1706, 3420 cm⁻¹; MS (70 eV): m/z(%) = 738 (M⁺, 70), 528 (100), 337 (79), 200 (55).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-5-bromo-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-5-bromo-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one (5b, C₄₈H₄₀Br₂N₄O₄) M.P.: 335°C; ¹H NMR (300.1 MHz, CDCl₃); 1.26-2.05 (m, 4CH₂), 2.57-2.63 (m, 2CH₂), 3.85 (t, J = 9 Hz, 2H-2), 4.19 (m, 2CH), 4.59 (d, J = 9 Hz, 2H-1), 6.83-7.56 (m, Ar-H), 8.84 (s, 2NH); ¹³C NMR (75 MHz, CDCl₃); 27.8, 31.1, 47.9 (6CH₂), 52.5, 66.4, 72.6 (6CH), 74.1(2C), 125.4, 125.5, 127.4, 129.6 (8CH), 128.4, 128.6, 128.8 (12CH), 122.5, 134.2, 137.8, 139.8, 140.8 (10C), 180.5(2C=O), 195.0 (2C=O) ppm; IR (KBr): V = 1664, 1698, 3440 cm⁻¹; MS (70 eV): m/z(%) = 896, 898, 900 (M⁺, M⁺+2, M⁺+4, 27), 686 (100), 338 (75), 279 (65).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-5-nitro-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-5-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one (5c, C₄₈H₄₀N₆O₈) M.P.: 318°C; ¹H NMR (300.1 MHz, CDCl₃); 1.28-2.06 (m, 4CH₂), 2.57-2.63 (m, 2CH₂), 3.85 (t, J = 9 Hz, 2H-2), 4.21 (m, 2CH), 4.58 (d, J = 9 Hz, 2H-1), 6.75-7.49 (m, Ar-H), 8.38 (s, 2NH) ppm; ¹³C NMR (75 MHz, CDCl₃); 27.7, 31.2, 48.0 (6CH₂), 52.5, 66.5, 72.6 (6CH), 74.0 (2C), 125.4, 125.5, 127.4, 129.6 (8CH), 128.1, 128.6, 128.8 (12CH), 122.4, 134.2, 137.4, 139.5, 140.8 (10C), 181.6 (2C=O), 195.1 (2C=O) ppm; IR (KBr): V = 1676, 1700, 3420 cm⁻¹; MS (70 eV): m/z(%) = 828

(M⁺, 35), 618 (100), 338 (65), 245 (40).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-1-methyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5d, C₅₀H₄₆N₄O₄) M.P.: 333°C; ¹HNMR (300.1 MHz, CDCl₃); 1.28-2.06 (m, 4CH₂), 2.57-2.63 (m, 2CH₂), 3.58 (s, 2NCH₃), 3.85 (t, J = 9 Hz, 2H-2), 4.06 (m, 2CH), 4.41 (d, J = 9 Hz, 2H-1), 6.82-7.49 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 27.7, 31.2, 48.0 (6CH₂), 42.4 (2NCH₃), 52.5, 66.4, 72.6 (6CH), 74.1(2C), 125.4, 125.5, 127.1, 127.4, 129.6 (10CH), 128.3, 128.6, 128.8 (12CH), 122.4, 134.2, 139.7, 140.8 (8C), 181.4 (2C=O), 195.1 (2C=O) ppm; IR (KBr): V= 1674, 1697 cm⁻¹; MS (70 eV): m/z(%) = 766 (M⁺, 39), 556 (100), 338 (58), 214 (43).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-5-bromo-1-methyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-5-bromo-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5e, C₅₀H₄₄Br₂N₄O₄) M.P.: 357°C; ¹HNMR (300.1 MHz, CDCl₃); 1.28-2.06 (m, 4CH₂), 2.57-2.63 (m, 2CH₂), 3.57 (s, 2NCH₂), 3.85 (t, J = 9 Hz, 2H-2), 4.07 (m, 2CH), 4.41 (d, J = 9 Hz, 2H-1), 6.82-7.49 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 27.7, 31.2, 48.0 (6CH₂), 42.4 (2NCH₃), 52.5, 66.4, 72.7 (6CH), 74.1 (2C), 125.4, 125.5, 127.4, 129.6 (8CH), 128.3, 128.6, 128.8 (12CH), 122.4, 134.2, 137.2, 139.7, 140.8 (10C), 181.4(2C=O), 195.0 (2C=O) ppm; IR (KBr): V= 1681, 1703 cm⁻¹; MS (70 eV): m/z(%) = 924, 926, 928 (M⁺, M⁺+2, M⁺+4, 58), 338 (100), 293 (83).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-1-methyl-5-nitro-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-1-methyl-5-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5f, C₅₀H₄₄N₆O₈) M.P.: 296°C; ¹HNMR (300.1 MHz, CDCl₃); 1.27-2.05 (m, 4CH₂), 2.57-2.64 (m, 2CH₂), 3.50 (s, 2NCH₃), 3.73 (t, J = 9 Hz, 2H-2), 4.09 (m, 2CH), 4.36 (d, J = 9 Hz, 2H-1), 6.76-7.47 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 26.3, 27.3, 30.0 (6CH₂), 42.9 (2NCH₃), 48.3, 51.0, 63.4 (6CH), 71.4(2C), 125.3, 125.5, 127.3, 130.5

(8CH), 128.1, 128.6, 128.8 (12CH), 122.4, 134.2, 137.2, 139.7, 140.8 (10C), 181.4 (2C=O), 194.9 (2C=O) ppm; IR (KBr): V= 1676, 1698 cm⁻¹; MS (70 eV): m/z(%) = 856 (M⁺, 39), 646 (100), 338 (55), 259 (48).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-1-ethyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-1-ethyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5g, C₅₂H₅₀N₄O₄) M.P.: 288°C; ¹HNMR (300.1 MHz, CDCl₃); 1.06 (t, J = 7.5 Hz, 2CH₃), 1.67-2.03 (m, 4CH₂), 2.55-2.60 (m, 2CH₂), 3.66 (q, J = 7.5 Hz, 2CH₂), 3.83 (t, J = 10 Hz, 2H-2), 4.19 (m, 2CH), 4.57 (d, J = 10 Hz, 2H-1), 6.69-7.50 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 12.3 (2CH₃), 27.1, 30.2, 31.3 (6CH₂), 35.4 (2NCH₂), 47.2, 51.4, 65.2 (6CH), 72.4(2C), 125.5, 125.6, 127.4, 129.6, 130.5 (10CH), 128.5, 128.8, 129.0 (12CH), 122.4, 134.2, 137.6, 139.7 (8C), 178.4(2C=O), 194.7(2C=O) ppm; IR (KBr): V= 1664, 1703 cm⁻¹; MS (70 eV): m/z(%) = 794 (M⁺, 19), 584 (100), 338 (65), 228 (68).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-5-bromo-1-ethyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-5-bromo-1-ethyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5h, C₅₂H₄₈Br₂N₄O₄) M.P.: 303°C; ¹HNMR (300.1 MHz, CDCl₃); 1.07 (t, J = 7.5 Hz, 2CH₃), 1.69-2.03 (m, 4CH₂), 2.53-2.60 (m, 2CH₂), 3.66 (q, J = 7.5 Hz, 2CH₂), 3.83 (t, J = 10 Hz, 2H-2), 4.19 (m, 2CH), 4.57 (d, J = 10 Hz, 2H-1), 6.69-7.50 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 12.3 (2CH₃), 27.1, 30.2, 31.6 (6CH₂), 35.4 (2NCH₂), 47.1, 51.4, 65.2 (6CH), 72.1 (2C), 125.5, 125.6, 127.4, 129.6 (8CH), 128.5, 128.8, 129.0 (12CH), 122.3, 134.1, 135.4, 137.9, 139.7 (10C), 178.4(2C=O), 194.9 (2C=O) ppm; IR (KBr): V= 1666, 1705 cm⁻¹; MS (70 eV): m/z = 956, 958, 960 (M⁺, M⁺+2, M⁺+4, 66), 338 (100), 307 (76).

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(4-((1'S,2'R,3S,7a'S)-2'-benzoyl-1-ethyl-5-nitro-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-yl)phenyl)-1-ethyl-5-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5i, C₅₂H₄₈N₆O₈) M.P.: 328°C;

^1H NMR (300.1 MHz, CDCl_3); 1.06 (t, $J = 7.5$ Hz, 2CH_3), 1.67-2.03 (m, 4CH_2), 2.55-2.60 (m, 2CH_2), 3.64 (q, $J = 7.5$ Hz, 2CH_2), 3.83 (t, $J = 10$ Hz, $2\text{H}-2$), 4.19 (m, 2CH), 4.57 (d, $J = 10$ Hz, $2\text{H}-1$), 6.69-7.49 (m, Ar-H) ppm; ^{13}C NMR (75 MHz, CDCl_3); 12.3 (2CH_3), 27.1, 30.2, 31.3 (6CH_2), 35.5 (2NCH_2), 47.2, 51.4, 65.2 (6CH), 72.4 (2C), 125.5, 125.6, 127.4, 129.6 (8CH), 128.4, 128.8, 129.0 (12CH), 122.4, 134.1, 136.6, 137.6, 139.7 (10C), 179.7 ($2\text{C}=\text{O}$), 194.7 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1672, 1699\text{ cm}^{-1}$; MS (70 eV): $m/z = 884$ (M^+ , 28), 674 (100), 338 (45), 273 (80).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-1'-methylspiro[indoline-3,2'-pyrrolidin]-2-one (6a, $\text{C}_{44}\text{H}_{38}\text{N}_4\text{O}_4$) M.P.: 292°C ; ^1H NMR (300.1 MHz, CDCl_3); 2.16 (s, 2NCH_3), 3.43 (d, $J = 10$ Hz, $4\text{H}-3$), 3.64 (m, 2CH), 4.14 (d, $J = 10$ Hz, $2\text{H}-1$), 6.63-7.55 (m, Ar-H), 8.84 (s, 2NH) ppm; ^{13}C NMR (75 MHz, CDCl_3); 35.2 (2NCH_3), 43.9 (2CH_2), 60.8, 65.4 (4CH), 74.2 (2C), 125.3, 125.5, 127.1, 127.4, 129.6 (10CH), 128.7, 128.8, 129.4 (12CH), 122.5, 134.2, 139.8, 140.8 (8C), 180.6 ($2\text{C}=\text{O}$), 195.9 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1675, 1702, 3421\text{ cm}^{-1}$; MS (70 eV): $m/z = 686$ (M^+ , 55), 476 (100), 337 (67), 174 (82).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-5-bromo-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-5-bromo-1'-methylspiro[indoline-3,2'-pyrrolidin]-2-one (6b, $\text{C}_{44}\text{H}_{36}\text{Br}_2\text{N}_4\text{O}_4$) M.P.: 281°C ; ^1H NMR (300.1 MHz, CDCl_3); 2.16 (s, 2NCH_3), 3.44 (d, $J = 10$ Hz, $4\text{H}-3$), 3.63 (m, 2CH), 4.16 (d, $J = 10$ Hz, $2\text{H}-1$), 6.63-7.55 (m, Ar-H), 8.84 (s, 2NH) ppm; ^{13}C NMR (75 MHz, CDCl_3); 35.2 (2NCH_3), 43.9 (2CH_2), 60.8, 65.4 (4CH), 74.2 (2C), 125.3, 125.5, 127.4, 129.6 (8CH), 128.7, 128.8, 129.4 (12CH), 122.5, 134.2, 137.6, 139.8, 140.8 (10C), 180.6 ($2\text{C}=\text{O}$), 195.9 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1669, 1697, 3291\text{ cm}^{-1}$; MS (70 eV): $m/z = 844, 846, 848$ (M^+ , M^++2 , M^++4 , 88), 634 (78), 337 (100), 253 (80).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1'-methyl-5-nitro-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-1'-methyl-5-

nitrospiro[indoline-3,2'-pyrrolidin]-2-one (6c, $\text{C}_{44}\text{H}_{36}\text{N}_6\text{O}_8$) M.P.: 277°C ; ^1H NMR (300.1 MHz, CDCl_3); 2.16 (s, 2NCH_3), 3.43 (d, $J = 10$ Hz, $4\text{H}-3$), 3.64 (m, 2CH), 4.14 (d, $J = 10$ Hz, $2\text{H}-1$), 6.63-7.55 (m, Ar-H), 8.84 (s, 2NH) ppm; ^{13}C NMR (75 MHz, CDCl_3); 35.2 (2NCH_3), 43.9 (2CH_2), 60.8, 65.4 (4CH), 74.2 (2C), 125.3, 125.5, 127.4, 129.6 (8CH), 128.7, 128.8, 129.4 (12CH), 122.5, 134.2, 137.4, 139.8, 140.8 (10C), 180.6 ($2\text{C}=\text{O}$), 195.9 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1665, 1705, 3421\text{ cm}^{-1}$; MS (70 eV): $m/z = 776$ (M^+ , 26), 566 (100), 337 (42), 219 (70).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1,1'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-1,1'-dimethylspiro[indoline-3,2'-pyrrolidin]-2-one (6d, $\text{C}_{46}\text{H}_{42}\text{N}_4\text{O}_4$) M.P.: 309°C ; ^1H NMR (300.1 MHz, CDCl_3); 2.16 (s, 2NCH_3), 3.14 (s, 2NCH_3), 3.43 (d, $J = 10$ Hz, $4\text{H}-3$), 3.65 (m, 2CH), 4.14 (d, $J = 10$ Hz, $2\text{H}-1$), 6.60-7.57 (m, Ar-H) ppm; ^{13}C NMR (75 MHz, CDCl_3); 26.2 (2NCH_3), 35.2 (2NCH_3), 43.9 (2CH_2), 60.8, 65.4 (4CH), 74.2 (2C), 125.3, 125.5, 127.1, 127.4, 129.6 (10CH), 128.4, 128.8, 129.4 (12CH), 122.5, 134.2, 139.8, 140.9 (8C), 180.6 ($2\text{C}=\text{O}$), 195.9 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1666, 1698\text{ cm}^{-1}$; MS (70 eV): $m/z = 714$ (M^+ , 9), 504 (100), 337 (72), 188 (67).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-5-bromo-1,1'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-5-bromo-1,1'-dimethylspiro[indoline-3,2'-pyrrolidin]-2-one (6e, $\text{C}_{46}\text{H}_{40}\text{Br}_2\text{N}_4\text{O}_4$) M.P.: 285°C ; ^1H NMR (300.1 MHz, CDCl_3); 2.16 (s, 2NCH_3), 3.15 (s, 2NCH_3), 3.43 (d, $J = 10$ Hz, $4\text{H}-3$), 3.65 (m, 2CH), 4.14 (d, $J = 10$ Hz, $2\text{H}-1$), 6.63-7.65 (m, Ar-H) ppm; ^{13}C NMR (75 MHz, CDCl_3); 26.3 (2NCH_3), 35.1 (2NCH_3), 43.9 (2CH_2), 60.9, 65.3 (4CH), 73.8 (2C), 125.3, 125.5, 127.4, 129.6 (8CH), 128.2, 128.6, 128.8 (12CH), 123.2, 134.2, 137.6, 139.8, 140.9 (10C), 177.9 ($2\text{C}=\text{O}$), 196.1 ($2\text{C}=\text{O}$) ppm; IR (KBr): $\nu = 1675, 1704\text{ cm}^{-1}$; MS (70 eV): $m/z = 872, 874, 876$ (M^+ , M^++2 , M^++4 , 76), 660 (78), 337 (100), 267 (80).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1,1'-dimethyl-5-nitro-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-1,1'-dimethyl-

5-nitrospiro[indoline-3,2'-pyrrolidin]-2-one (6f, C₄₆H₄₀N₆O₈) M.P.: 323°C; ¹HNMR (300.1 MHz, CDCl₃); 2.16 (s, 2NCH₃), 3.14 (s, 2NCH₃), 3.43 (d, J = 10 Hz, 4H-3), 3.64 (m, 2CH), 4.16(d, J = 10 Hz, 2H-1), 6.63-7.50 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 26.2 (2NCH₃), 35.2 (2NCH₃), 43.9 (2CH₂), 60.8, 65.4, (4CH), 74.2 (2C), 125.3, 125.5, 127.4, 129.6 (8CH), 128.6, 128.8, 129.4 (12CH), 122.4, 134.2, 137.4, 139.8, 140.8 (10C), 181.6 (2C=O), 195.8 (2C=O) ppm; IR (KBr): V= 1669, 1698 cm⁻¹; MS (70 eV): m/z = 804 (M⁺, 14), 594 (100), 337 (47), 233 (75).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1-ethyl-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-1-ethyl-1'-methylspiro[indoline-3,2'-pyrrolidin]-2-one (6g, C₄₈H₄₆N₄O₄) M.P.: 289°C; ¹HNMR (300.1 MHz, CDCl₃); 1.07 (t, J = 7.5 Hz, 2CH₃), 2.15(s, 2NCH₃), 3.44 (d, J = 10 Hz, 4H-3), 3.64 (m, 2CH), 3.69 (q, J = 7.5 Hz, 2CH₂), 4.14(d, J = 10 Hz, 2H-1), 6.63-7.55 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 12.3 (2CH₃), 35.2 (2NCH₃), 35.5 (2NCH₂), 43.7 (2CH₂), 60.8, 65.3 (4CH), 74.1(2C), 125.3, 125.5, 127.3, 127.4, 129.6 (10CH), 128.5, 128.7, 128.9 (12CH), 122.4, 134.2, 139.8, 140.8 (8C), 180.6 (2C=O), 195.7 (2C=O) ppm; IR (KBr): V= 1664, 1703 cm⁻¹; MS (70 eV): m/z = 742 (M⁺, 88), 532 (100), 337 (92), 202 (37).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-5-bromo-1-ethyl-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-yl)phenyl)-5-bromo-1-ethyl-1'-methylspiro[indoline-3,2'-pyrrolidin]-2-one (6h, C₄₈H₄₄Br₂N₄O₄) M.P.: 315°C; ¹HNMR (300.1 MHz, CDCl₃); 1.06 (t, J = 7.5 Hz, 2CH₃), 2.16(s, 2NCH₃), 3.43(d, J = 10 Hz, 4H-3), 3.63(m, 2CH), 3.69 (q, J = 7.5 Hz, 2CH₂), 4.13(d, J = 10 Hz, 2H-1), 6.65-7.49 (m, Ar-H) ppm; ¹³CNMR (75 MHz, CDCl₃); 12.3 (2CH₃), 35.2 (2NCH₃), 35.4 (2NCH₂), 43.9 (2CH₂), 61.3, 65.4, (4CH), 74.2 (2C), 125.3, 125.5, 127.4, 129.6 (8CH), 128.6, 128.8, 129.3 (12CH), 122.5, 134.2, 137.6, 139.8, 140.8 (10C), 178.9 (2C=O), 195.4 (2C=O) ppm; IR (KBr): V= 1669, 1700, cm⁻¹; 900, 902, 904 (M⁺, M⁺+2, M⁺+4, 78), 690 (49), 337 (100), 281 (55).

(2'R,3'S,4'R)-3'-benzoyl-4'-(4-((3'R,4'S)-3'-benzoyl-1-ethyl-1'-methyl-5-nitro-2-oxospiro[indoline-

3,2'-pyrrolidine]-4'-yl)phenyl)-1-ethyl-1'-methyl-5-nitrospiro[indoline-3,2'-pyrrolidin]-2-one (6i, C₄₈H₄₄N₆O₈) M.P.: 296°C; ¹HNMR (300.1 MHz, CDCl₃); 1.06 (t, J = 7.5 Hz, 2CH₃) 2.16 (s, 2NCH₃), 3.43(d, J = 10 Hz, 4H-3), 3.64 (m, 2CH), 3.64 (q, J = 7.5 Hz, 2CH₂), 4.14 (d, J = 10 Hz, 2H-1), 6.63-7.55 (m, Ar-H), 8.84 (s, 2NH) ppm; ¹³CNMR (75 MHz, CDCl₃); 12.1 (2CH₃), 35.2 (2NCH₃), 35.5 (2NCH₂), 43.9 (2CH₂), 60.7, 65.4 (4CH), 74.1 (2C), 125.4, 125.5, 127.2, 129.6 (8CH), 128.7, 128.8, 129.4 (8CH), 122.5, 134.2, 137.4, 139.7, 140.7 (10C), 181.2 (2C=O), 195.9 (2C=O) ppm; IR (KBr): V= 1664, 1703, 1721 cm⁻¹; MS (70 eV): m/z(%) = 832 (M⁺, 34), 622 (100), 337 (58), 247 (70).

4. CONCLUSIONS

In conclusion, we introduced a small library of new bis-spirooxindolo(pyrrolizidines/pyrrolizines) through a one-pot three component reaction between available isatin derivatives, (proline/sarcosine) and bis-chalcone in mild condition and environmentally friendly solvent of aqueous ethanol, in high yield. The structure of the products was elucidated using IR, Mass, one and two dimensional NMR techniques.

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