Int. J. Bio-Inorg. Hybr. Nanomater., Vol. 3, No. 4 (2014), 231-238
ISSN Print: 2251-8533
ISSN Online: 2322-4142

International Journal of Bio-Inorganic Hybrid Nanomaterials

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

Mohammad Javad Taghizadeh[1*], Abdollah Javidan[2]

[1] *Ph.D., Department of Chemistry, Imam Hossein University, Tehran, Iran*
[2] *Associate Professor, Department of Chemistry, Imam Hossein University, Tehran, Iran*

Received: 20 August 2014; Accepted: 25 October 2014

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, ^{1}HNMR, ^{13}CNMR 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-

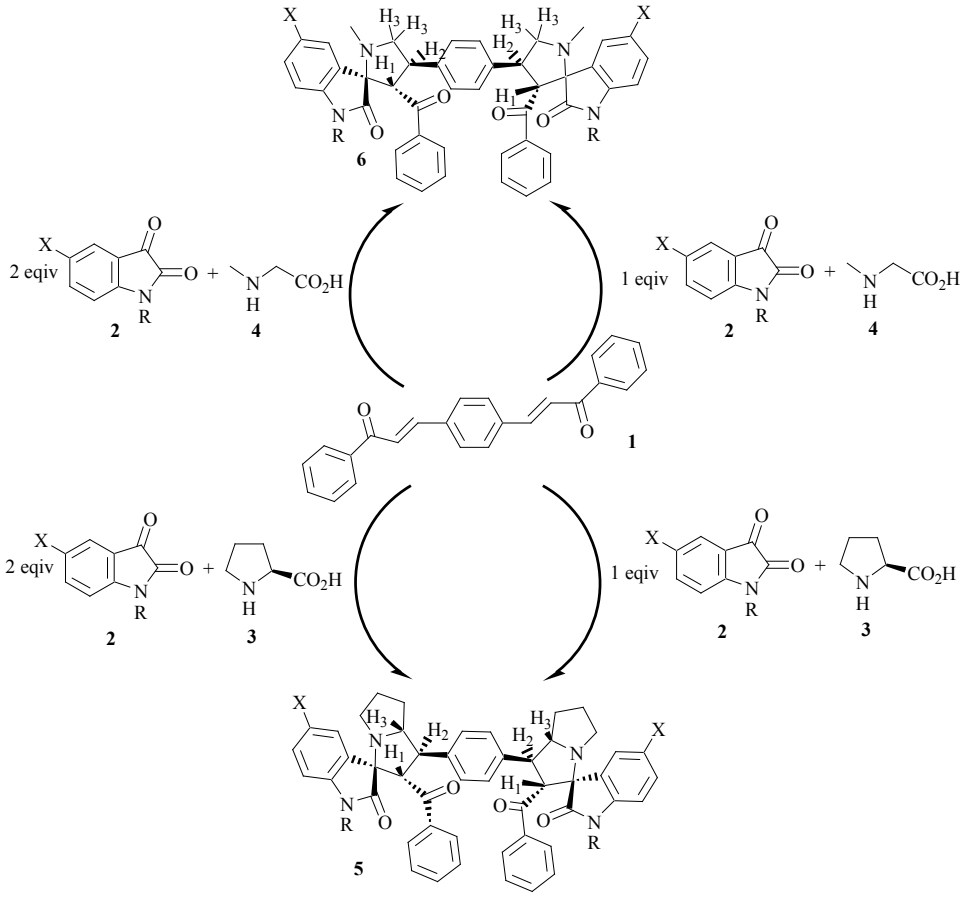
(*) Corresponding Author - e-mail: mohammadjavadtaghizadeh31@yahoo.com

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, ^{1}HNMR, ^{13}CNMR and Mass spectral data. Ob-

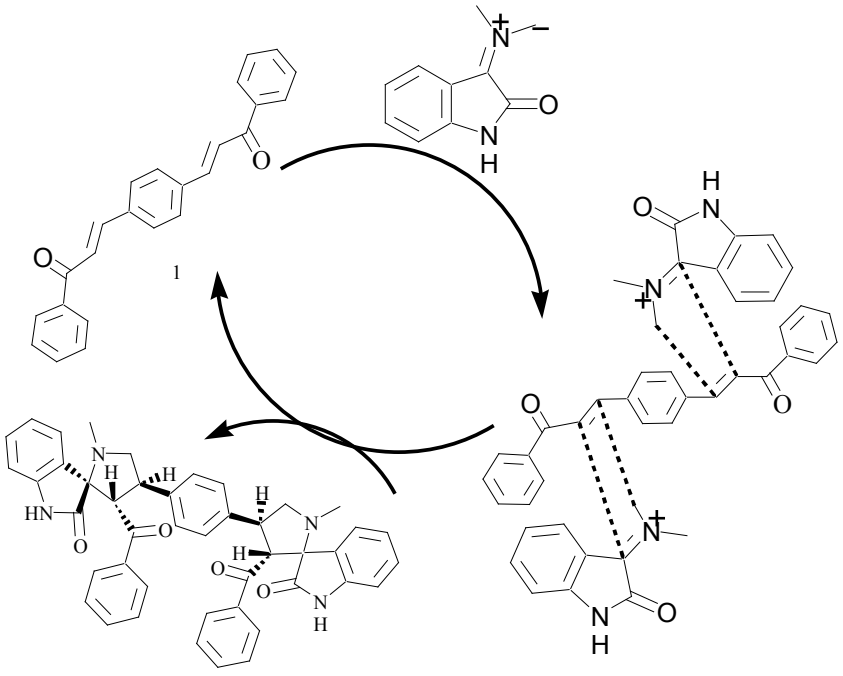


Scheme 1: *Synthesis of bis-spirooxindolo(pyrrolizidines/pyrrolidines).*

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 ^{13}CNMR spectra of 5g and two characteristic singlet at about (60.8 and 65.3) in the ^{13}CNMR 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 ^{1}HNMR, ^{13}CNMR, IR, Mass, HMQC, and COSY NMR experiments. For example, the ^{1}HNMR 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 ^{1}HNMR spectrum of 6g exhibits a multiplet signal at $\delta = 3.64$ ppm and a doblet 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 H_3 and H_2 in the ROESY spectrum shows that the H_2 hydrogen could be trans to H_3. But an intense contour between H_1 and H_3 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 ^{1}HNMR 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, H_1 dishilder than H_2 and H_3 is the location, according to Scheme 1, while the other regioisomer H_2 dishilder than H_2 and H_3 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, ^{13}CNMR spectra were measured with a Bruker DRX-250 AVANCE instrument with $CDCl_3$ 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 cm^3 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)-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'- pyrrolizin] -2-one (5a, $C_{48}H_{42}N_4O_4$) M.P.: 345°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.27-2.06 (m, 4CH_2), 2.58-2.63 (m, 2CH_2), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 27.7, 31.2, 48.0 (6CH_2), 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'-pyrrolizin]-2-one (5b, $C_{48}H_{40}Br_2N_4O_4$) M.P.: 335°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.26-2.05 (m, 4CH_2), 2.57-2.63 (m, 2CH_2), 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); ^{13}CNMR (75 MHz, $CDCl_3$); 27.8, 31.1, 47.9 (6CH_2), 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'-pyrrolizin]-2-one (5c, $C_{48}H_{40}N_6O_8$ M.P.: 318°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.28-2.06 (m, 4CH_2), 2.57-2.63 (m, 2CH_2), 3.85 (t, J = 9 Hz, 2H-2), 4.21 (m, 2CH), 4.58 (d, J = 9Hz, 2H-1), 6.75-7.49 (m, Ar-H), 8.38 (s, 2NH) ppm; ^{13}CNMR (75 MHz, $CDCl_3$); 27.7, 31.2, 48.0 (6CH_2), 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, $C_{50}H_{46}N_4O_4$) M.P.: 333°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.28-2.06 (m, $4CH_2$), 2.57-2.63 (m, $2CH_2$), 3.58 (s, $2NCH_3$), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 27.7, 31.2, 48.0 ($6CH_2$), 42.4 ($2NCH_3$), 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, $C_{50}H_{44}Br_2N_4O_4$) M.P.: 357°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.28-2.06 (m, $4CH_2$), 2.57-2.63 (m, $2CH_2$), 3.57 (s, $2NCH_2$), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 27.7, 31.2, 48.0 ($6CH_2$), 42.4 ($2NCH_3$), 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, $C_{50}H_{44}N_6O_8$) M.P.: 296°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.27-2.05 (m, $4CH_2$), 2.57-2.64 (m, $2CH_2$), 3.50 (s, $2NCH_3$), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 26.3, 27.3, 30.0 ($6CH_2$), 42.9 ($2NCH_3$), 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, $C_{52}H_{50}N_4O_4$) M.P.: 288°C; ^{1}HNMR (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, $2CH_2$), 3.66 (q, J = 7.5 Hz, $2CH_2$), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 12.3 ($2CH_3$), 27.1, 30.2, 31.3 ($6CH_2$), 35.4 ($2NCH_2$), 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, $C_{52}H_{48}Br_2N_4O_4$) M.P.: 303°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.07 (t, J = 7.5 Hz, $2CH_3$), 1.69-2.03 (m, $4CH_2$), 2.53-2.60 (m, $2CH_2$), 3.66 (q, J = 7.5 Hz, $2CH_2$), 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; ^{13}CNMR (75 MHz, $CDCl_3$); 12.3 ($2CH_3$), 27.1, 30.2, 31.6 ($6CH_2$), 35.4 ($2NCH_2$), 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, $C_{52}H_{48}N_6O_8$) M.P.: 328°C;

^{1}HNMR (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, 2H-2), 4.19 (m, 2CH), 4.57 (d, J = 10 Hz, 2H-1), 6.69-7.49 (m, Ar-H) ppm; ^{13}CNMR (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 (2C=O), 194.7 (2C=O) ppm; IR (KBr): V= 1672, 1699 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, $C_{44}H_{38}N_4O_4$) M.P.: 292°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16 (s, $2NCH_3$), 3.43(d, J = 10 Hz, 4H-3) 3.64 (m, 2CH), 4.14(d, J = 10 Hz, 2H-1), 6.63-7.55 (m, Ar-H), 8.84(s, 2NH) ppm; ^{13}CNMR (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 (2C=O), 195.9 (2C=O) ppm; IR (KBr): V= 1675, 1702, 3421 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, $C_{44}H_{36}Br_2N_4O_4$) M.P.: 281°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16 (s, $2NCH_3$), 3.44 (d, J = 10 Hz, 4H-3), 3.63(m, 2CH), 4.16 (d, J = 10 Hz, H-1), 6.63-7.55 (m, Ar-H), 8.84(s, 2NH) ppm; ^{13}CNMR (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 (2C=O), 195.9 (2C=O) ppm; IR (KBr): V= 1669, 1697, 3291 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, $C_{44}H_{36}N_6O_8$) M.P.: 277°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16 (s, $2NCH_3$), 3.43 (d, J = 10 Hz, 4H-3), 3.64(m, 2CH), 4.14 (d, J = 10 Hz, H-1), 6.63-7.55 (m, Ar-H), 8.84(s, 2NH) ppm; ^{13}CNMR (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 (2C=O), 195.9 (2C=O) ppm; IR (KBr): V=1665, 1705, 3421 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, $C_{46}H_{42}N_4O_4$) M.P.: 309°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16(s, $2NCH_3$), 3.14(s, $2NCH_3$), 3.43 (d, J = 10 Hz, 4H-3), 3.65(m, 2CH), 4.14(d, J = 10 Hz, 2H-1), 6.60-7.57 (m, Ar-H) ppm; ^{13}CNMR (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(2C=O), 195.9 (2C=O) ppm; IR (KBr): V= 1666, 1698 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, $C_{46}H_{40}Br_2N_4O_4$) M.P.: 285°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16 (s, $2NCH_3$), 3.15 (s, $2NCH_3$), 3.43 (d, J = 10 Hz, 4H-3), 3.65 (m, 2CH), 4.14 (d, J = 10 Hz, 2H-1), 6.63-7.65 (m, Ar-H) ppm; ^{13}CNMR (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 (2C=O), 196.1 (2C=O) ppm; IR (KBr): V= 1675, 1704 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, $C_{46}H_{40}N_6O_8$) M.P.: 323°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.16 (s, $2NCH_3$), 3.14 (s, $2NCH_3$), 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; ^{13}CNMR (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, 127.4, 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, $C_{48}H_{46}N_4O_4$) M.P.: 289°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.07 (t, J = 7.5 Hz, $2CH_3$), 2.15(s, $2NCH_3$), 3.44 (d, J = 10 Hz, 4H-3), 3.64 (m, 2CH), 3.69 (q, J = 7.5 Hz, $2CH_2$), 4.14(d, J = 10 Hz, 2H-1), 6.63-7.55 (m, Ar-H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$); 12.3 ($2CH_3$), 35.2 ($2NCH_3$), 35.5 ($2NCH_2$), 43.7 ($2CH_2$), 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, $C_{48}H_{44}Br_2N_4O_4$) M.P.: 315°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.06 (t, J = 7.5 Hz, $2CH_3$), 2.16(s, $2NCH_3$), 3.43(d, J = 10 Hz, 4H-3), 3.63(m, 2CH), 3.69 (q, J = 7.5 Hz, $2CH_2$), 4.13(d, J = 10 Hz, 2H-1), 6.65-7.49 (m, Ar-H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$); 12.3 ($2CH_3$), 35.2 ($2NCH_3$), 35.4 ($2NCH_2$), 43.9 ($2CH_2$), 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, $C_{48}H_{44}N_6O_8$) M.P.: 296°C; ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.06 (t, J = 7.5 Hz, $2CH_3$) 2.16 (s, $2NCH_3$), 3.43(d, J = 10 Hz, 4H-3), 3.64 (m, 2CH), 3.64 (q, J = 7.5 Hz, $2CH_2$), 4.14 (d, J = 10 Hz, 2H-1), 6.63-7.55 (m, Ar-H), 8.84 (s, 2NH) ppm; ^{13}CNMR (75 MHz, $CDCl_3$); 12.1 ($2CH_3$), 35.2 ($2NCH_3$), 35.5 ($2NCH_2$), 43.9 ($2CH_2$), 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.

REFERENCES

1. Orru R.V.A., Greef M., *Synthesis*, **10** (2003), 1471.
2. Balme G., Bossharth E., Monteiro N., *Eur. J. Org. Chem.*, **21** (2003), 4101.
3. Brase S., Gil C., Knepper K., *Bioorg. Med. Chem.*, **10** (2002), 2415.
4. Domling A., Ugi I., *Angew Chem., Int. Ed.*, **39** (2000), 3168.
5. Weber L., *Drug Discov. Today*, 7 (2002), 143.
6. Domling A., *Curr. Opin. Chem. Biol.*, **6** (2002), 306.
7. Ana G.N., Delgado J., Cecilia P., Marcaccini S., Carlos F.M., *Tetrahedron Lett.*, **46** (2005), 23.
8. Yavari I., Bayat M.J., Sirouspour M., Souri S., *Tetrahedron Lett.*, **66** (2010),7995.
9. Ugi I., Deomling A., Werner B.J., *Heterocycl.*

Chem., **37** (2000), 647.
10. Kappe C.O., *Eur. J. Med. Chem.*, **35** (2000), 1043.
11. Guarna A., Occhiato E.G., Macheeti F., Giacomelli V., *J. Org. Chem.*, **64** (1999), 4985.
12. Ling Y.Z., Li J.S., Liu Y., Kato K., Klus G.T., Brodie A., *J. Med. Chem.*, **40** (1994), 3297.
13. Kozyr A.V., Chenko L.P., Kolesnikow A.V., Zelenova N.A., *Immunol Lett.*, **80** (2002), 41.
14. Daly J.W., Spande T.W., Whittaker N., Highet R.J., Feigl D., Noshimori N., Tokuyama T., Meyers C.W., *J. Nat. Prod.*, **46** (1986), 210.
15. R.J. Molineux, 1987. *In Alkaloids: Chemical and Biological Perspective*, S.W. Pelletier (Ed.); Wiley: New York, Chapter 1.
16. Fujimori S., Jap P.A., *Chem. Abstr.*, **112** (1990), 98409.
17. Waldmann H., *Synlett*, (1995), 133.
18. J.W.R. Daly, 1998. *In Alkaloids*, G.A. Cordell (Ed.); Academic Press: New York.
19. Carroll W.A., Grieco P., *J. Am. Chem. Soc.*, **115** (1993), 1164.
20. Early W.G., Oh T., Overman L.E., *Tetrahedron*, **44** (1988), 3785.
21. Ban Y., Taga N., Oishi T., *Chem. Pharm. Bull.*, **24** (1976), 736.
22. Ban Y., Seto M., Oishi T., *Chem. Pharm. Bull.,* **23** (1975), 2605.
23. Ban Y., Taga N., Oishi T., *Tetrahedron Lett.*, **2** (1974), 187.
24. Okita T., Isobe M., *Tetrahedron*, **50** (1994), 11143.
25. Rosenmond P., Hosseini-Merescht M., Bub C., *Leibigs Ann. Chem.,* **2** (1994), 151.
26. Kornet M.J., Thio A.P., *J. Med. Chem.*, **19** (1976), 892.
27. R. Huisgen, 1984. *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa (Ed.); Vols. 1 and 2, Wiley, NewYork.
28. O. Tsuge, S. Kanemasa, 1989. *Advances in Heterocyclic Chemistry*, A.R. Katritzky (Ed.); Academic Press, San Diego.
29. Kang T.H., Matsumoto K., Todha M., Murakami Y., Takayama H., Kitajima M., Aimi N., Watanabe H., *Eur. J. Pharmacol.*, **444** (2002), 39.
30. Dideberg O., Lamotte-Brasseur J., Dupont L., Campsteyn H., Vermeire M., Angenot L., *Acta Crystallogr. Sect B*, **33** (1977), 1796.
31. Angenot L., *Plantes medicales et phytotherapie*, **12** (1978), 123.
32. Chou C.H., Gong C.L., Chao C.C., Lin C.H., Kwan C.Y., Hsieh C.L., Leung Y.M., *J. Nat. Prod.*, **72** (2009), 830.