Pergamon

Tetrahedron 58 (2002) 9075–9079

TETRAHEDRON

A facile entry into a new class of spiroheterocycles: synthesis of dispiro[oxindolechromanone/ flavanone/tetralone]pyrroloisoquinoline ring systems

G. Subramaniyan,[a] R. Raghunathan[a,*] and M. Nethaji[b]

[a]*Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India*
[b]*Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560 012, India*

Received 12 March 2002; revised 9 August 2002; accepted 5 September 2002

Abstract—A series of novel dispiroheterocyclic systems have been synthesized by the cycloaddition of a new azomethine ylide generated by the decarboxylative route from tetrahydroisoquinoline-3-carboxylic acid and isatin with various dipolarophiles containing exocyclic double bond such as 3-arylidene-4-chromanone, 3-arylidene-4-flavanone and 2-arylidenetetrahydro-1-naphthalenone in moderate to good yield. The regio and stereochemistry of the title compounds was established by single crystal X-ray structure and spectroscopic techniques.

1. Introduction

The 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins offers a convenient one step route for the construction of a variety of complex pyrrolidine derivatives with stereogenic centers, because the reaction is usually concerted.[1–3] Highly substituted pyrrolidines have gained much prominence, since they form the central skeleton of many natural products.[4] Spirooxindole ring systems are the central skeleton for numerous alkaloids and pharmacologically important compounds. Hence, there has been renewed interest in the synthesis of such interesting compounds. Gelsemine, pseudotabersonine, morroniside, formosanine, isoformosanine and mitraphylline are some of the alkaloids containing spirooxindole ring systems.[5,6] Of particular interest, spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids like horsifiline, spirotryprostatine A and B, elacomine etc.[7] The derivatives of spirooxindole find very wide biological applications as antimicrobial, antitumoral, antibiotic agents and inhibitors of human NK-1 receptor etc.[8a–c] Recently the total synthesis of spirotryprostatine[8d] and the asymmetric synthesis of (−)-horsifiline[8e] have been reported. In continuation of our studies of the synthesis of novel heterocyclic systems through cycloaddition reactions,[9–11] we herein report a facile synthesis of dispiroheterocycles containing the spirooxindole ring system through the regioselective cycloaddition reaction of azomethine ylides with unusual dipolarophiles such as 3-arylidene-4-chromanone, 3-arylidene-4-flavanone and 2-arylidene-1,2,3,4 tetrahydro-1-naphthalenone.

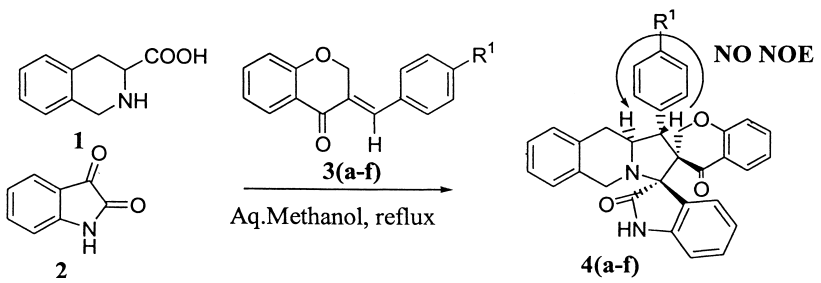
2. Results and discussion

Azomethine ylides can be generated by a number of methods of which the decarboxylation route offers a convenient method for the synthesis of substituted pyrrolidines.[12] In this method an aldehyde and a secondary amino acid are condensed to generate the reactive intermediate which is then trapped by dipolarophiles. This method was studied recently using simple amino acids like sarcosine and proline with good chemical yield.[13] However, substitution of proline by pipecolinic acid gave only poor yield.[14] In some cases, these reactions were reported to be unsuccessful.[15] Here we have chosen tetrahydroisoquinoline-3-carboxylic acid, isatin and various dipolarophiles containing an exocyclic double bond for our studies. The required (*E*)-3-arylidene-4-chromanones were prepared by the acid catalyzed reaction of 4-chromanone with various benzaldehydes and the products were assigned *E*-configuration on the basis of their NMR spectra, in accordance with the literature.[16] The reaction of tetrahydroisoquinoline-3-carboxylic acid with isatin in boiling aqueous methanol leads to the formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reactions with (*E*)-3-arylidene-4-chromanones to give a single cycloadduct, in a one pot three component process, as evidenced by thin layer chromatography and mass spectral studies (Scheme 1) (Table 1). The reaction afforded a series of novel dispiroheterocycles **4** containing the oxindole ring system

Keywords: cycloaddition; azomethine ylide; dispiroheterocycles.

* Corresponding author. Tel.: +91-44-2351269; fax: +91-44-2352494; e-mail: ragharaghunathan@yahoo.com

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01130-4



Scheme 1.

by a regio and stereo controlled cycloaddition of the azomethine ylide to the exocyclic double bond of 3-arylidene-4-chromanone in all cases.

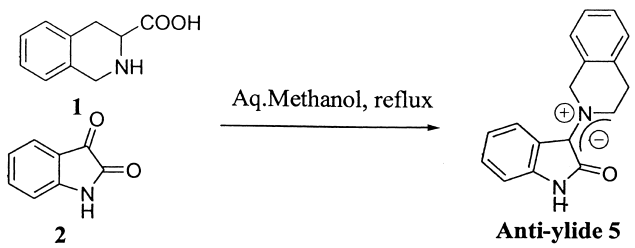
Control of the relative stereochemistry at the spiro centre observed. Presumably, an *anti*-ylide (**5**)[14,17] (Scheme 2) is involved in the transition state which adds to arylidene-chromanone to give the observed products. Formation of the *syn*-ylide is not observed due to the unfavorable steric repulsion between the carbonyl oxygen of the oxindole ring and the isoquinoline. The regio and stereochemical outcome of the cycloaddition was determined by single crystal X-ray structure of the cycloadduct (**4c**).[18] The X-ray structure of (**4c**) reflects that the cycloaddition proceeds via *endo*-transition state.[17] The possibility of the other isomer forming via an *exo*-transition state was ruled out by NOE studies. For example in the case of (**4a**), irradiation of the C_1 benzylic proton at δ 4.84 did not cause any enhancement of the signal for the C_{10a} proton at δ 4.37. The structure and regiochemistry of the cycloadducts (**4a**–**f**) have also been confirmed by spectroscopic data. For example the IR spectrum of (**4a**) showed two carbonyl peaks at 1689 and 1712 cm^{-1} which corresponds to the chromanone and oxindole ring carbonyls, respectively. The ^1H NMR spectrum of (**4a**) of the benzylic proton exhibited a doublet at δ 4.84 which clearly shows the regiochemistry of the cycloaddition reaction. There is no evidence for formation of the other regioisomer. If the other regioisomer was formed then the ^1H NMR spectrum would give a singlet for the benzylic proton. The signals in the ^{13}C NMR spectrum at 72.08 and 74.83 ppm correspond to two spiro carbons. The signals in the ^{13}C NMR spectrum at 191.62 and 177.89 ppm indicate the presence of the chromanone and oxindole ring carbonyls. Moreover the presence of a molecular ion peak at *m/z* 498(M^+) in the mass spectrum of (**4a**) confirms the formation of the cycloadduct. Identical results were obtained with other derivatives of the benzylidene chromanones (Fig. 1).

In order to establish the generality of this cycloaddition reaction, we extended the methodology to other dipolarophiles containing exocyclic double bond such as (*E*)-3-arylidene-flavan-4-one (**6a**–**c**) (Scheme 3) and (*E*)-2-arylidene-tetrahydonaphthalene-1-one (**8a**–**d**) (Scheme 4). These dipolarophiles reacted with isatin and tetrahydroisoquinoline-3-carboxylic acid in refluxing aqueous methanol to give a series of cycloadduts in moderate to good yield (Table 2). The structure and regiochemistry of the cycloadducts were similar to those obtained from (*E*)-3-arylidene-4-chromanone and this was confirmed by spectroscopic data.

Thus, an efficient synthesis of novel dispiroheterocycles containing the oxindole ring has been accomplished by 1,3-dipolar cycloaddition methodology.

Table 1. 1,3-Dipolar cycloaddition of 1,3 dipole **5** with 3-arylidene-4-chromanone (**3a**–**f**)

Entry	Substrate	R^1	Time (h)	Products	Yield (%)
1	**3a**	H	5	**4a**	69
2	**3b**	Cl	7	**4b**	71
3	**3c**	OMe	5.5	**4c**	62
4	**3d**	Me	5.5	**4d**	73
5	**3e**	NO_2	9	**4e**	71
6	**3f**	NMe_2	6	**4f**	75



Scheme 2.

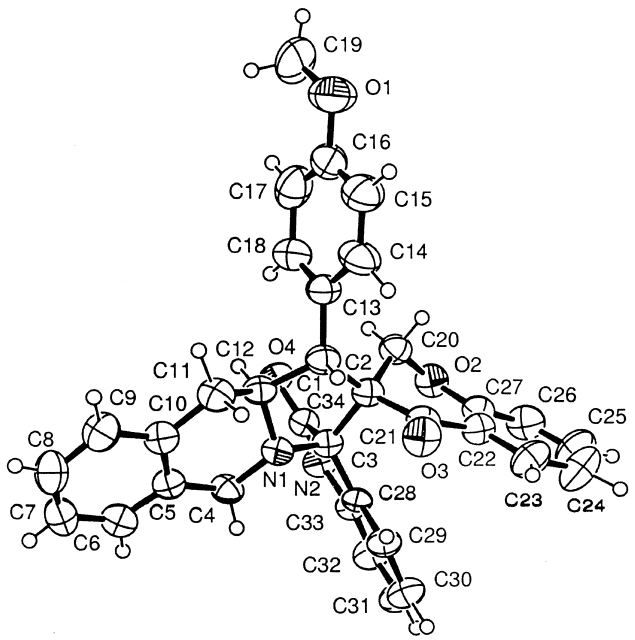
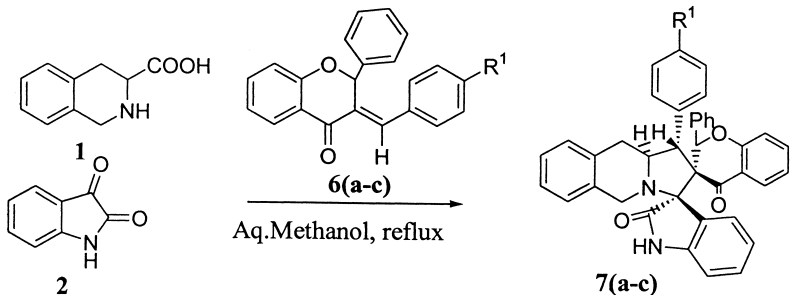
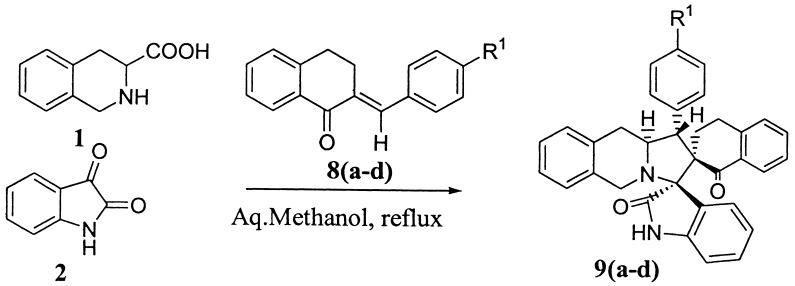


Figure 1. ORTEP diagram of **4c**.



Scheme 3.



Scheme 4.

Table 2. 1,3-Dipolar cycloaddition of 1,3 dipole **5** with 3-arylidene-4-flavanones (**6a**–**c**) and 2-arylidenetetrahydro-1-naphthalenone (**8a**–**d**)

Entry	Substrate	R^1	Time (h)	Products	Yield (%)
1	**6a**	H	8	**7a**	78
2	**6b**	Cl	11	**7b**	61
3	**6c**	OMe	14	**7c**	76
4	**8a**	H	10.5	**9a**	81
5	**8b**	Cl	18	**9b**	79
6	**8c**	OMe	16	**9c**	69
7	**8d**	Me	11	**9d**	71

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on SHIMADZU FT-IR 8300 instrument. Mass spectra were recorded on JEOL DX 303 HF spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on JEOL 400 and 100 MHz, respectively. Elemental analyses were carried out on PERKIN–ELMER 240 B instrument. The starting materials (*E*)-3-arylidene-flavan-4-one[19] and (*E*)-2-arylidene-naphthalene-1-one[20] were prepared according to literature procedures.

3.2. General procedure for the cycloaddition reaction of the azomethine ylide generated from tetrahydro-isoquinoline-3-carboxylic acid and isatin with various dipolarophiles

A mixture of isatin (1 mmol), tetrahydroisoquinoline-3-carboxylic acid (1.01 mmol) and a dipolarophile (1.01 mmol) in aqueous methanol (10 mL) was refluxed for the time shown in Tables 1 and 2. The solvent was then evaporated to dryness in vacuo and the residue chromatographed on silica gel using hexane–ethylacetate (5:1) as eluent to give the cycloadducts.

3.2.1. 1,2,3,5,10,10a-Hexahydro-1-phenyl-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo [1,2-*a*] isoquinoline (4a). Yield 0.34 g (69%) colorless solid, mp 178–179°C; [Found: C, 79.35; H, 5.35; N, 5.71. $C_{33}H_{26}N_2O_3$ requires C, 79.5; H, 5.26, N, 5.62%]; IR (KBr): 1689, 1712, 3365 cm^{-1}; ^{1}H NMR: 2.97 (d, *J*=6.8 Hz, 2H), 3.51 (d, *J*=11.3 Hz, 1H, OCH_2), 3.44 (d, *J*=14.4 Hz, 1H, NCH_2), 3.81 (d, *J*=14.4 Hz, 1H, NCH_2), 4.37 (m, 1H), 4.58 (d, *J*=11.3 Hz, 1H, OCH_2), 4.84 (d, *J*=12.2 Hz, 1H), 6.52– 7.64 (m, 17 H), 8.31 (s, NH); ^{13}C NMR: 35.42, 47.64, 51.32, 58.77, 59.47, 72.08, 74.83, 109.03, 116.53, 121.09, 122.32, 125.71, 125.98, 126.16, 126.45, 127.09, 127.91, 128.84, 128.93, 129.19, 131.08, 133.34, 133.40, 133.53, 134.39, 135.15, 140.89, 161.02, 177.89, 191.62; CIMS *m*/*z*: 498(M^+).

3.2.2. 1,2,3,5,10,10a-Hexahydro-1-(4-chlorophenyl)-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (4b). Yield 0.38 g (71%) colorless solid, mp 238–239°C; [Found: C, 74.25; H, 4.58; N, 5.15. $C_{33}H_{25}ClN_2O_3$ requires C, 74.36; H, 4.73, N, 5.26%]; IR (KBr): 1689, 1712, 3359 cm^{-1}; ^{1}H NMR: 2.97 (d, *J*=6.8 Hz, 2H), 3.51 (d, *J*=10.9 Hz, 1H, OCH_2), 3.45 (d, *J*=14.2 Hz, 1H, NCH_2), 3.81 (d, *J*=14.2 Hz, 1H, NCH_2), 4.37 (m, 1H), 4.59 (d, *J*=10.9 Hz, 1H, OCH_2), 4.85 (d, *J*=12.7 Hz, 1H), 6.47– 7.64 (m, 16 H), 8.52 (s, NH); ^{13}C NMR: 35.42, 47.64, 51.31, 53.41, 58.75, 59.47, 72.07, 74.89, 109.12, 116.53, 121.09, 122.32, 125.71, 125.99, 126.16, 126.45, 127.06, 127.91, 128.83, 128.91, 129.20, 131.09, 133.34, 133.39, 133.51, 134.41, 135.16, 140.98, 161.00, 178.19, 191.63; CIMS *m*/*z*: 532(M^+).

3.2.3. 1,2,3,5,10,10a-Hexahydro-1-(4-methoxyphenyl)-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (4c). Yield 0.33 g (62%) colorless solid, mp 191–192°C; [Found: C, 77.42; H, 5.25; N, 5.22. $C_{34}H_{28}N_2O_4$ requires C, 77.25; H, 5.34, N, 5.30%]; IR (KBr): 1679, 1712, 3344 cm^{-1}; ^{1}H NMR: 2.98 (d,

J=7.8 Hz, 2H), 3.53 (d, J=11.3 Hz, 1H, OCH_2), 3.45 (d, J=14.2 Hz, 1H, NCH_2), 3.83 (d, J=14.2 Hz, 1H, NCH_2), 3.78 (s, 3H), 4.38 (m, 1H), 4.56 (d, J=11.3 Hz, 1H, OCH_2), 4.89 (d, J=12.2 Hz, 1H), 6.48– 7.64 (m, 16H), 8.25 (s, NH, 1H); ^{13}C NMR: 35.48, 47.69, 51.24, 55.18, 58.89, 59.36, 72.17, 74.80, 109.02, 113.99, 116.51, 120.93, 121.17, 122.22, 125.59, 126.07, 126.25, 126.44, 127.07, 127.57, 127.86, 128.91, 129.05, 130.66, 133.60, 133.68, 134.97, 141.01, 158.89, 161.02, 178.29, 191.89; CIMS *m/z*: 528(M^+).

3.2.4. 1,2,3,5,10,10a-Hexahydro-1-(4-methylphenyl)-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (4d). Yield 0.37 g (73%) colorless solid, mp 234–235°C; [Found: C, 79.55; H, 5.64; N, 5.32. $C_{34}H_{28}N_2O_3$ requires C, 79.67; H, 5.51, N, 5.47%]; IR (KBr): 1681, 1712, 3354 cm^{-1}; ^{1}H NMR: 2.32 (s, 3H), 2.99 (d, J=6.8 Hz, 2H), 3.44 (d, J=13.9 Hz, 1H, NCH_2), 3.51 (d, J=11.2 Hz, 1H, OCH_2), 3.83 (d, J=13.9 Hz, 1H, NCH_2), 4.28 (m, 1H), 4.53 (d, J=11.2 Hz, 1H, OCH_2), 4.89 (d, J=12.2 Hz, 1H), 6.58–7.67 (m, 16H), 8.33 (s, NH); ^{13}C NMR: 36.41, 48.60, 52.52, 59.91, 60.03, 73.08, 75.53, 109.68, 117.41, 121.82, 122.11, 123.16, 126.51, 126.98, 127.33, 128.12, 128.82, 129.84, 129.94, 130.26, 133.05, 133.45, 134.54, 134.62, 135.86, 138.06, 161.95, 178.56, 192.69; CIMS *m/z*: 512(M^+).

3.2.5. 1,2,3,5,10,10a-Hexahydro-1-(4-nitrophenyl)-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (4e). Yield 0.38 g (71%) colorless solid, mp 176–177°C; [Found: C, 72.79; H, 4.57; N, 7.59. $C_{33}H_{25}N_3O_5$ requires C, 72.92; H, 4.64, N, 7.73%]; IR (KBr): 1685, 1710, 3348 cm^{-1}; ^{1}H NMR: 2.97 (d, J=6.8 Hz, 2H), 3.44 (d, J=14.2 Hz, 1H, NCH_2), 3.52 (d, J=11.0 Hz, 1H, OCH_2), 3.81 (d, J=14.2 Hz, 1H, NCH_2), 4.35 (m, 1H), 4.54 (d, J=11.0 Hz, 1H, OCH_2), 4.89 (d, J=12.2 Hz, 1H), 6.57–7.68 (m, 16H), 8.53 (s, NH); ^{13}C NMR: 35.43, 47.69, 51.72, 58.92, 59.79, 71.96, 74.95, 109.12, 116.61, 121.36, 122.48, 125.66, 125.91, 126.31, 126.50, 127.14, 128.00, 128.94, 129.40, 130.78, 133.03, 133.36, 134.42, 135.41, 140.77, 161.02, 177.44, 191.30; CIMS *m/z*: 543(M^+).

3.2.6. 1,2,3,5,10,10a-Hexahydro-1-(4-*N*,*N*-dimethylphenyl)-2-(spiro-3^1-chroman-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (4f). Yield 0.40 g (75%) colorless solid, mp 174–175°C; [Found: C, 77.45; H, 5.66; N, 7.83. $C_{35}H_{31}N_3O_3$ requires C, 77.61; H, 5.77, N, 7.76%]; IR (KBr): 1679, 1712, 3358 cm^{-1}; ^{1}H NMR: 2.93 (s, 6H), 2.96 (d, J=8.8 Hz, 2H), 3.56 (d, J=11.2 Hz, 1H, OCH_2), 3.43 (d, J=13.9 Hz, 1H, NCH_2), 3.82 (d, J=13.9, NCH_2), 4.35 (m, 1H), 4.50 (d, J=11.2 Hz, 1H, OCH_2), 4.89 (d, J=12.2 Hz, 1H), 6.66– 7.62 (m, 16H), 8.03 (s, 1H, NH); ^{13}C NMR: 35.57, 40.52, 47.73, 51.28, 59.10, 59.13, 72.29, 74.69, 108.83, 112.59, 116.51, 120.82, 121.26, 122.20, 125.54, 126.03, 126.44, 127.17, 127.86, 128.96, 133.83, 134.88, 140.92, 149.83, 161.07, 178.02, 192.05; CIMS *m/z*: 541(M^+).

3.2.7. 1,2,3,5,10,10a-Hexahydro-1-phenyl-2-(spiro-3^1-flavan-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (7a). Yield 0.44 g (78%) colorless solid, mp 228–229°C; [Found: C, 81.65; H, 5.18; N, 4.74. $C_{39}H_{30}N_2O_3$ requires C, 81.51; H, 5.26, N, 4.87%]; IR (KBr): 1684, 1708, 3349 cm^{-1}; ^{1}H NMR: 2.95 (dd, J=11.3, 3.4 Hz, 1H), 3.19 (dd, J=10.7, 3.4 Hz, 1H), 3.50 (d, J=14.4 Hz, 1H, NCH_2), 3.81 (d, J=14.4 Hz, 1H, NCH_2), 4.34 (m, 1H), 4.66 (d, J=8.8 Hz, 1H), 6.19–7.88 (m, 23H), 8.95 (s, NH); ^{13}C NMR: 35.33, 48.20, 53.00, 63.95, 64.55, 78.50, 83.68, 109.21, 117.47, 121.02, 121.91, 123.93, 125.51, 125.83, 126.06, 126.37, 126.48, 126.51, 127.15, 127.53, 127.71, 127.80, 128.96, 129.15, 129.84, 133.58, 134.12, 135.39, 135.48, 138.26, 140.93, 158.05, 178.59, 193.06; CIMS *m/z*: 574(M^+).

3.2.8. 1,2,3,5,10,10a-Hexahydro-1-(4-chlorophenyl)-2-(spiro-3^1-flavan-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (7b). Yield 0.37 g (61%) colorless solid, mp 198–199°C; [Found: C, 76.73; H, 4.69; N, 4.71. $C_{39}H_{29}ClN_2O_3$ requires C, 76.90; H, 4.80, N, 4.60%]; IR (KBr): 1689, 1712, 3356 cm^{-1}; ^{1}H NMR: 2.93 (dd, J=3.4, 11.8 Hz, 1H), 3.14 (dd, J=3.4, 10.4 Hz, 1H), 3.45 (d, J=14.2 Hz, 1H, NCH_2), 3.80 (d, J=14.2 Hz, 1H, NCH_2), 4.32 (m, 1H), 4.62 (d, J=9.8 Hz, 1H), 6.14–7.88 (m, 22H), 8.32 (s, 1H); ^{13}C NMR: 35.34, 48.24, 52.09, 63.96, 64.49, 78.48, 83.78, 109.28, 114.18, 117.58, 120.98, 121.90, 121.99, 124.01, 125.89, 126.05, 126.38, 126.45, 127.17, 127.56, 127.84, 128.97, 129.12, 130.15, 133.66, 134.22, 135.37, 135.88, 140.86, 158.09, 178.29, 193.24; CIMS *m/z*: 608(M^+).

3.2.9. 1,2,3,5,10,10a-Hexahydro-1-(4-methoxyphenyl)-2-(spiro-3^1-flavan-4^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (7c). Yield 0.45 g (76%) colorless solid, mp 232–233°C; [Found: C, 79.29; H, 5.47; N, 4.72. $C_{40}H_{32}N_2O_4$ requires C, 79.45; H, 5.33, N, 4.63%]; IR (KBr): 1685, 1710, 3357 cm^{-1}; ^{1}H NMR: 2.91 (dd, J=11.7, 3.4 Hz, 1H), 3.13 (dd, J=10.2, 3.4 Hz, 1H), 3.45 (d, J=14.2 Hz, 1H, NCH_2), 3.60 (s, 3H), 3.74 (d, J=14.2 Hz, 1H, NCH_2), 4.24 (m, 1H), 4.54 (d, J=8.3 Hz, 1H), 6.08–7.25 (m, 22H), 8.55 (s, NH); ^{13}C NMR: 35.35, 48.23, 52.09, 55.06, 64.02, 64.32, 78.44, 83.83, 109.10, 113.11, 117.51, 120.99, 121.90, 124.01, 125.49, 125.85, 126.04, 126.37, 126.44, 127.18, 127.55, 127.82, 128.98, 129.12, 129.73, 130.17, 133.65, 134.22, 135.36, 135.71, 140.84, 158.07, 178.38, 193.13; CIMS *m/z*: 604(M^+).

3.2.10. 1,2,3,5,10,10a-Hexahydro-1-phenyl-2-(spiro-2^1-tetrahydronaphthalene-1^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (9a). Yield 0.40 g (81%) colorless solid, mp 188–189°C; [Found: C, 82.44; H, 5.60; N, 5.58. $C_{34}H_{28}N_2O_2$ requires C, 82.33; H, 5.68, N, 5.64%]; IR (KBr): 1682, 1712, 3378 cm^{-1}; ^{1}H NMR: 1.42 (m, 1H), 2.42–2.51 (m, 2H), 2.96–3.12 (m, 3H), 3.38 (d, J=14.4 Hz, 1H, NCH_2), 3.68 (d, J=14.4 Hz, 1H, NCH_2), 4.35 (m, 1H), 4.68 (d, J=9.3 Hz, 1H), 6.61–7.97 (m, 17H), 8.35 (s, NH); ^{13}C NMR: 25.80, 30.16, 35.74, 47.75, 55.73, 59.82, 60.14, 76.39, 76.68, 77.00, 77.32, 109.32, 122.54, 125.47, 126.04, 126.23, 126.39, 126.94, 127.68, 127.82, 128.23, 128.32, 128.97, 129.11, 132.57, 132.92, 133.72, 134.22, 138.54, 140.60, 143.06, 178.04, 197.82; CIMS *m/z*: 496(M^+).

3.2.11. 1,2,3,5,10,10a-Hexahydro-1-(4-chlorophenyl)-2-(spiro-2^1-tetrahydronaphthalene-1^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (9b). Yield 0.42 g (79%) colorless solid, mp 237–238°C; [Found: C, 76.82;

H, 5.35; N, 6.59. $C_{34}H_{27}ClN_2O_2$ requires C, 76.90; H, 5.28, N, 6.68%]; IR (KBr): 1691, 1710, 3368 cm^{-1}; ^1H NMR: 1.43 (m, 1H), 2.38–2.50 (m, 2H), 2.98–3.12 (m, 3H), 3.39 (d, J=14.6 Hz, NCH_2), 3.66 (d, J=14.6 Hz, NCH_2), 4.29 (m, 1H), 4.66 (d, J=9.3 Hz, 1H), 6.59–7.99 (m, 16H), 8.93 (s, NH); ^{13}C NMR: 25.92, 30.45, 35.82, 47.90, 55.23, 59.76, 60.62, 76.67, 76.87, 77.18, 77.50, 109.71, 122.76, 125.74, 125.98, 126.29, 126.53, 126.57, 127.89, 128.47, 128.56, 129.14, 129.43, 132.33, 132.93, 133.74, 134.18, 137.34, 140.84, 143.13, 178.59, 197.86; CIMS m/z: 530(M^+).

3.2.12. 1,2,3,5,10,10a-Hexahydro-1-(4-methoxyphenyl)-2-(spiro-2^1-tetrahydronaphthalene-1^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (9c). Yield 0.36 g (69%) colorless solid, mp 242–243°C; [Found: C, 79.91; H, 5.66; N, 5.41. $C_{35}H_{30}N_2O_3$ requires C, 79.82; H, 5.74, N, 5.32%]; IR (KBr): 1681, 1725, 3357 cm^{-1}; ^1H NMR: 1.43 (m, 1H), 2.39–2.51 (m, 2H), 2.99– 3.13 (m, 3H), 3.35 (d, J=14.4 Hz, 1H, NCH_2), 3.65 (s, 3H), 3.69 (d, J=14.4 Hz, 1H, NCH_2), 4.32 (m, 1H), 4.68 (d, J=9.3 Hz, 1H), 6.59–7.96 (m, 16H), 8.93 (s, NH); ^{13}C NMR: 26.16, 30.49, 36.07, 48.09, 55.40, 55.49, 60.11, 60.69, 67.68, 77.64, 78.32, 91.55, 109.56, 122.81, 125.77, 126.33, 126.45, 126.54, 126.71, 128.00, 128.14, 128.59, 129.31, 129.37, 130.82, 131.99, 132.86, 133.29, 134.12, 134.63, 140.96, 143.44, 158.84, 178.23, 198.34; CIMS m/z: 526(M^+).

3.2.13. 1,2,3,5,10,10a-Hexahydro-1-(4-methylphenyl)-2-(spiro-2^1-tetrahydronaphthalene-1^1-one)-3-(spiro-3^{11}-indolino)-pyrrolo[1,2-*a*]isoquinoline (9d). Yield 0.36 g (71%) colorless solid, mp 251–252°C; [Found: C, 82.21; H, 5.85; N, 5.39. $C_{35}H_{30}N_2O_2$ requires C, 82.33; H, 5.92, N, 5.49%]; IR (KBr): 1685, 1710, 3357 cm^{-1}; ^1H NMR: 1.44 (m, 1H), 2.33 (s, 3H), 2.48 (m, 2H), 2.80–3.08 (m, 3H), 3.38 (d, J=14.2 Hz, 1H, NCH_2), 3.68 (d, J=14.2 Hz, 1H, NCH_2), 4.34 (m, 1H), 4.65 (d, J=9.3 Hz, 1H), 6.61–7.96 (m, 16H), 8.49 (s, NH); ^{13}C NMR: 21.08, 25.82, 30.14, 35.74, 47.76, 55.38, 59.78, 60.12, 76.41, 76.68, 77.00, 77.32, 109.33, 122.54, 125.45, 126.03, 126.13, 126.27, 126.39, 127.68, 127.80, 128.30, 128.97, 129.08, 130.68, 132.55, 132.95, 133.75, 134.30, 135.39, 136.50, 140.63, 141.09, 178.19, 127.92; CIMS m/z: 510(M^+).

Acknowledgements

G. S. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowship. Financial support from CSIR and UGC is gratefully acknowledged.

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