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Syntheses of spiroindole melatonin analogues *via* 2-(indolin-3-ylidene)acetonitrile cycloadditions

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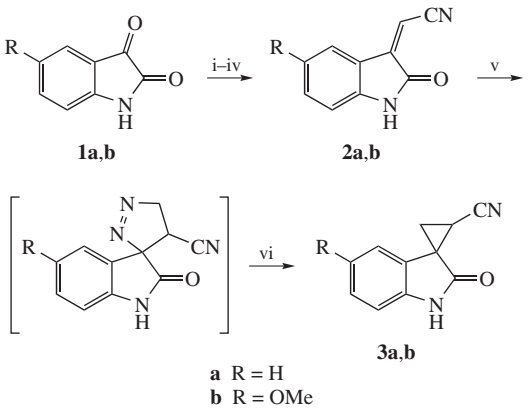
2-(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetonitriles were subjected to cycloaddition reactions at the double bond affording spiroindole melatonin analogues.

Spiroindole derivatives occupy a significant area within a variety of biologically active compounds. Spiroindole moiety is met in the molecules of physiologically active alkaloids,[1] antitumor agents,[2,3] anti-inflammatory drugs,[4] analgesics,[5] and cardiotonics.[6] Herein, we describe an original approach to 2′-oxo-1′,2′-dihydrospiro[cycloalkane-1,3′-indole]-2-carbonitriles from available 2-cyano-2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetic acid. We anticipate that the compounds obtained can be transformed into spiro analogues of melatonin [3-(2-acetylaminoethyl)-5-methoxy-1*H*-indole], an important neurohormone.[7–12]

Such spiro analogues of melatonin seem promising in view of conformational restriction[13] and 'umbrella effect'[14] concepts, which can provide more knowledge on the structure–activity relationship within this group of compounds.

To access the required spiroindole derivatives, we chose cycloaddition to the exocyclic double bond of 2-oxoindolylacetonitriles as the most promising strategy (*cf.* ref. 15), since these compounds can be readily obtained from inexpensive isatins **1** (Scheme 1, for experimental details, see Online Supplementary Materials). The choice of isatins **1a**,**b** relies on the requirements to the structure of melatoninergic ligands. The presence of methoxy group in the 5-position of indole moiety is necessary for the agonistic activity. However, some compounds based on unsubstituted indole are known to be efficient antagonist ligands for melatonin receptors.[16] The resulting compounds **2** and **4** were subjected to cycloaddition reaction.

Conventional methods of cyclopropanation[17–19] are mostly inapplicable to compounds with double bonds conjugated with electron-withdrawing groups. Herein, we tested the Corey–Chaykovsky reaction[20] and addition of diazonium compounds.[21] However, the Corey–Chaykovsky reaction turned unsuitable for our purpose. The addition of diazomethane[22,23] appeared to be appropriate (20-fold excess of CH_2N_2 without catalyst), the intermediate pyrazolines having been immediately decomposed upon reflux in toluene (see Scheme 1).



Scheme 1 *Reagents and conditions*: i, $NCCH_2COOH$, Et_3N, 1,4-dioxane, 4 h; ii, HCl aq.; iii, pyridine, 100 °C; iv, AcOH; v, diazomethane, Et_2O, 5 h; vi, toluene, 110 °C, 8 h.

The target cyclopropanes **3a**,**b** were isolated as isomeric mixtures in ratios of 5:2 and 3:1, respectively (^{1}H NMR spectroscopic data).

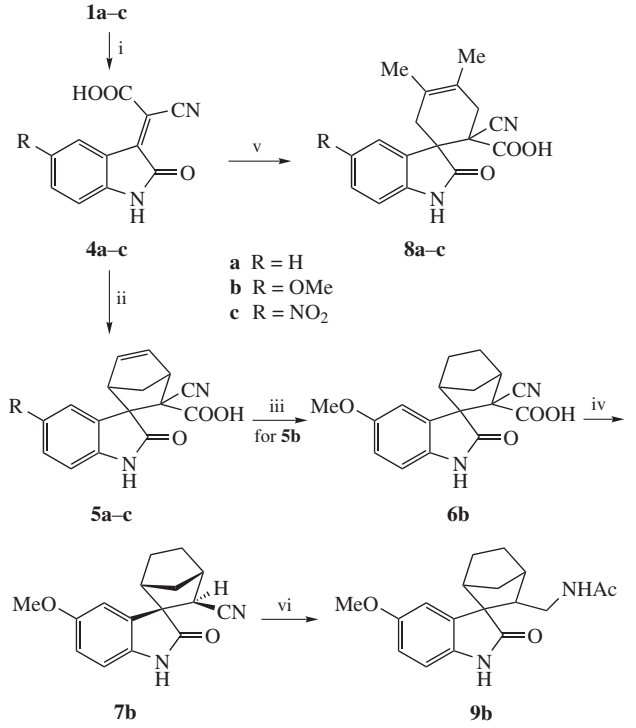
For the syntheses of the six-membered cyclic spiroindole scaffold, we used Diels–Alder [4+2]-cycloaddition (Scheme 2, Table 1).† We performed the [4+2]-cycloaddition to compounds **4** both in the absence and in the presence of ZnI_2. The adduct was obtained as a mixture of two diastereoisomers (NMR spectroscopic data), whose ratio was independent of the reaction conditions. The yield of the target compound **5** was slightly higher in the presence of ZnI_2 (see Table 1). The process was universal for substrates **4a–c** and various dienes providing high yields in the

Table 1 Yields of the Diels–Alder adducts (%).

Dienophile	Cyclopentadiene **5a–c**		2,3-Dimethylbutadiene **8a–c**	
	Without catalyst	ZnI_2	Without catalyst	ZnI_2
4a, R = H	83	—[a]	75	—[a]
4b, R = OMe	45	60	14	45
4c, R = NO_2	61	67	—[a]	53

[a] No reaction.

† *3-Cyano-5′-methoxy-2′-oxo-1′,2′-dihydrospiro{bicyclo[2.2.1]hept-5-ene-2,3′-indole}-3-carboxylic acid* **5b**. Method A: the reaction of **4b** (1 g, 4.1 mmol) and cyclopentadiene (1.7 ml, 0.02 mol) in ethanol (10 ml) gave light-brown product **5b**, yield 0.35 g (45%). Method B: the reaction of **4b** (3 g, 12.3 mol), ZnI_2 (0.3 g), and cyclopentadiene (5 ml, 0.06 mol) in acetonitrile (10 ml) gave light-brown product **5b** as an isomeric mixture (5:1 according to ^{1}H NMR), yield 2.3 g (60%). ^{1}H NMR (400.13 MHz, DMSO-d_6, major isomer) δ: 1.62 (d, 1H, *J* 9.9 Hz), 2.26 (d, 1H, *J* 9.6 Hz), 2.78 (s, 1H), 3.48 (s, 1H), 3.73 (s, 3H), 6.19 (dd, 1H, *J* 3.1 and 5.1 Hz), 6.44 (dd, 1H, *J* 3.1 and 5.1 Hz), 6.81 (s, 1H), 6.89 (d, 1H, *J* 2.2 Hz), 7.1 (d, 1H, *J* 2.0 Hz), 10.44 (s, 1H). ^{13}C NMR (400.13 MHz, DMSO-d_6, major isomer) δ: 39.85, 40.06, 52.45, 54.83, 56.01, 60.22, 109.95, 110.04, 113.65, 120.32, 131.14, 135.56, 135.77, 136.67, 154.79, 167.02, 175.55. IR (ν/cm^{-1}): 1470 [C(O)NH], 1490 [C(O)OH], 1640 (NH–C=O), 1740 [C(O)OH], 2260 (CN). HRMS (ESI), *m*/*z*: 309.0879 (M–H, δ 0.6 pm, calc. 309.0881), 333.0844 (M+Na, δ 0.6 pm, calc. 333.0846).



Scheme 2 *Reagents and conditions*: i, $NCCH_2COOH$, Et_3N, 1,4-dioxane, 4 h, then HCl aq.; ii, cyclopentadiene, EtOH, 78 °C; iii, $N_2H_4{\cdot}H_2O$, H_2O_2, 0–5 °C, methanol; iv, $EtO(CH_2)_2OH$, reflux, 2.5 h; v, 2,3-dimethylbutadiene, EtOH, reflux; vi, H_2 (1 atm), PtO_2, AcOH, Ac_2O, 25 °C, 4 h.

case of indole derivatives containing either electron-donating or electron-withdrawing groups in the 5-position of indole moiety.

Attempted decarboxylation of compound **5b** was accompanied by the retro-Diels–Alder fragmentation. To preserve the polycyclic skeleton, we performed the hydrogenation of its double bond by using diimide.‡ The decarboxylation of thus obtained compound **6b** gave product **7b** in high yield. The (*RS*,*RS*)-configuration of the spiro-center and nitrile group was confirmed by a signal of the HCCN proton at 2.82 ppm with *J* 4 Hz observed in the NMR spectrum. The *syn* position of the nonbornane bridge relative to the benzene ring in compound **7b** was determined by the NOE experiment (Figure S1, Online Supplementary Materials).

In the final step, hydrogenation of compound **7b** in AcOH/Ac_2O system in the presence of Adams catalyst[24] proceeded simultaneously with the acylation of the amino group (see Scheme 2). Product **9b** was identified by mass spectrometry.

To summarize, the developed strategy is versatile and can be used to synthesize various spirocyclic analogues of melatonin starting from simple reactants.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.09.003.

References

1 S.-L. Zhu, Sh.-J. Jia and Y. Zhang, *Tetrahedron*, 2007, **63**, 9365.
2 P. Kutschy, A. Salayová and Z. Curillová, *Bioorg. Med. Chem.*, 2009, **17**, 3698.
3 B. Lippa, G. Pan, M. Corbett, Ch. Li and G. S. Kauffman, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3359.
4 H. Sch. Eidam and P. A. Haile, *US Patent 2008/0318990 A1*, 2008.
5 Y. C. Tsai, J. P. Liou, R. Liao, C. Y. Cheng and P. L. Tao, *Bioorg. Med. Chem. Lett*., 1998, **8**, 1813.
6 D. W. Robertson, J. H. Krushinski and G. D. Pollock, *J. Med. Chem*., 1987, **30**, 824.
7 D. P. Zlotos, *Arch. Pharm. Chem. Life Sci*., 2005, **338**, 229.
8 D. X. Tan, R. J. Reiter and L. D. Chen, *Carcinogenesis*, 1994, **15**, 215.
9 M. A. Pappolla, Y. J. Chyan, B. Poeggeler, B. Frangione, G. Wilson, J. Chiso and R. J. Reiter, *J. Neural. Transm*., 2000, **107**, 203.
10 M. A. Pappolla, M. Sos, R. A. Omar, R. J. Bick, D. L. M. Hickson-Bick, R. J. Reiter, S. Efthimiopoulos and N. K. Robakis, *J. Neurosci.*, 1997, **17**, 1683.
11 S. M. Armstrong, *Experientia*, 1989, **45**, 932.
12 D. J. Kennaway and H. Wright, *Curr. Top. Med. Chem*., 2002, **2**, 199.
13 O. Uchikawa, K. Fukatsu, R. Tokunoh, M. Kawada, K. Matsumoto, Y. Imai, S. Hinuma, K. Kato, K. Nishikawa, K. Hirai, M. Miyamoto and S. Ohkawa, *J. Med. Chem*., 2002, **45**, 4222.
14 G. Spadoni, C. Balsamini, G. Diamantini, B. D. Giacomo, G. Tarzia, M. Mor, P. V. Plazzi, V. Lucini, R. Nonno, M. Pannacci, F. Fraschini and B. Stankov, *J. Med. Chem*., 1997, **40**, 1990.
15 M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya and G. I. Nikishin, *Mendeleev Commun*., 2012, **22**, 143.
16 Ch. Browning, I. Beresford, N. Fraser and H. Giles, *Br. J. Pharmacol.*, 2000, **129**, 877.
17 P. Tang and Y. Qin, *Synthesis*, 2012, **44**, 2969.
18 C. J. Thibodeaux, W. Chang and H. Lu, *Chem. Rev*., 2012, **112**, 1681.
19 F. Brackmann and A. de Meijere, *Chem. Rev*., 2007, **107**, 4493.
20 Yu. G. Gololobov, A. N. Nesmeyanov, V. P. Lysenko and I. E. Boldeskul, *Tetrahedron*, 1987, **43**, 2609.
21 H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev*., 2003, **103**, 977.
22 G. B. Bennett, R. B. Mason and M. J. Shapiro, *J. Org. Chem*., 1978, **43**, 4383.
23 F. Arndt, *Org. Synth*., 1943, **2**, 165.
24 N. A. Lozinskaya, S. E. Sosonyuk, M. S. Volkova, M. Yu. Seliverstov, M. V. Proskurnina, S. E. Bachurin and N. S. Zefirov, *Synthesis*, 2011, **2**, 273.

‡ *3-Cyano-5'-methoxy-2'-oxo-1',2'-dihydrospiro{bicyclo[2.2.1]heptane-2,3'-indole}-3-carboxylic acid* **6b**. A suspension of **5b** (1 g, 0.003 mol) in methanol (20 ml) was placed in a three-neck flask, and a 85% hydrazine hydrate solution (9.6 ml) was added. The mixture was cooled to 0–5 °C, and a 35% hydrogen peroxide solution (34 ml) was added within 4 h at a temperature below 30 °C. The mixture was kept overnight and then hydrochloric acid (15 ml) was added dropwise. The light-yellow precipitate that formed was washed with water (40 ml) and diethyl ether (15 ml) and dried. Yield 0.71 g (71%), mp 235–236 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.21 (m, 1H), 1.62 (m, 1H), 1.69 (d, 1H, *J* 10.3 Hz), 2.07 (m, 1H), 2.18 (m, 1H), 2.25 (m, 1H), 2.32 (m, 1H), 2.83 (d, 1H, *J* 10.8 Hz), 3.72 (s, 3H), 6.78 (d, 1H, *J* 8.3 Hz), 6.85 (dd, 1H, *J* 1.5 and 8.3 Hz), 7.1 (s, 1H), 10.50 (s, 1H). ^{13}C NMR (400.13 MHz, DMSO-d_6) δ: 22.41, 24.19, 39.90, 46.19, 49.98, 55.92, 57.58, 58.78, 109.98, 113.21, 113.31, 119.96, 133.07, 135.29, 154.90, 167.01, 176.01. IR (ν/cm^{-1}): 1490 [NHC(O)], 1500 [C(O)OH], 1640 [NHC(O)], 1740 [C(O)OH], 2250 (CN), 2440–2500 (OH) 3370 (NH). MS, *m*/*z*: 312 (M^+), 268 ($M^+ - CO_2$). Found (%): C, 64.39; H, 5.16; N, 8.86. Calc. for $C_{17}H_{16}N_2O_4{\cdot}^1/_4H_2O$ (%): C, 64.45; H, 5.25; N, 8.84.

5'-Methoxy-2'-oxo-1',2'-dihydrospiro{bicyclo[2.2.1]heptane-2,3'-indole}-3-carbonitrile **7b**. A mixture of **6b** (0.71 g, 2.3 mmol) and 2-ethoxyethanol (20 ml) was refluxed for 2.5 h and then concentrated. The product was recrystallized from a mixture of Pr^iOH and water (1:1); the yield 0.61 g (84%); mp 195–196 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 1.21 (m, 1H), 1.61 (m, 1H), 1.70 (d, 1H, *J* 11.3 Hz), 2.07 (m, 1H), 2.17 (s, 1H), 2.33 (m, 1H), 2.32 (d, 1H, *J* 10.6 Hz), 2.50 (s, 1H), 2.82 (d, 1H, *J* 4.0 Hz), 3.72 (s, 3H), 6.77 (d, 1H, *J* 8.3 Hz), 6.84 (dd, 1H, *J* 2.2 and 8.6 Hz), 7.09 (s, 1H), 10.50 (s, 1H). ^{13}C NMR (400.13 MHz, DMSO-d_6) δ: 22.45, 24.20, 40.53, 40.94, 46.24, 49.99, 57.55, 58.94, 109.97, 113.20, 113.22, 120.07, 133.12, 154.90, 166.97, 176.01. IR (ν/cm^{-1}): 1700 [C(O)NH], 2270 (CN), 3370 [C(O)NH]. MS, *m*/*z*: 268 (M^+), 253 (M^+–Me). Found (%): C, 71.40, H, 5.98; N, 10.50. Calc. for $C_{16}H_{16}N_2O_2$ (%): C, 71.62; H, 6.01; N, 10.44.

For experimental details, see Online Supplementary Materials.

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