An Efficient Synthesis of Spiro-oxindole Derivatives by Three-Component Reactions in Water

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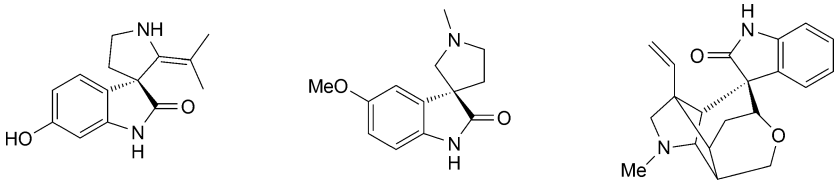
An efficient synthesis of (3*S*)-1,1′,2,2′,3′,4′,6′,7′-octahydro-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carbonitrile is achieved *via* a three-component reaction of isatin, ethyl cyanoacetate, and 1,2,3,4,5,6-hexahydro-2-(nitromethylidene)pyrimidine. The present method does not involve any hazardous organic solvents or catalysts. Also the synthesis of ethyl 6′-amino-1,1′,2,2′,3′,4′-hexahydro-9′-nitro-2-oxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carboxylates in high yields, at reflux, using a catalytic amount of piperidine, is described. The structures were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS data) and by elemental analyses. A plausible mechanism for this reaction is proposed (*Scheme 2*).

Introduction. – Multicomponent reactions (MCRs) and their improvement are of considerable interest in the current-day research. As a one-pot reaction, MCRs permit rapid access to combinatorial libraries of complex molecules especially in drug discovery [1]. The synthetic utility of such protocols becomes more significant, when the reactions are carried out in H_2O. The search for alternative reaction media to replace volatile, flammable, and often toxic solvents, commonly employed in organic synthesis, is also a priority for the development of 'green chemical processes' [2][3]. The heterocyclic spiro-oxindole ring system is a widely distributed structural framework present in a number of pharmaceuticals and natural products [4] such as gelsemine, horsfiline, and elacomine, *etc.* [3] (*Fig.*).

The unique structural array and the highly pronounced pharmacological activity displayed by the class of spiro-oxindole compounds have made them attractive synthetic targets [5]. Pyrido-pyrimidines and their oxo and thioxo derivatives are well-known pharmacophores in drug design, associated with a wide range of biological



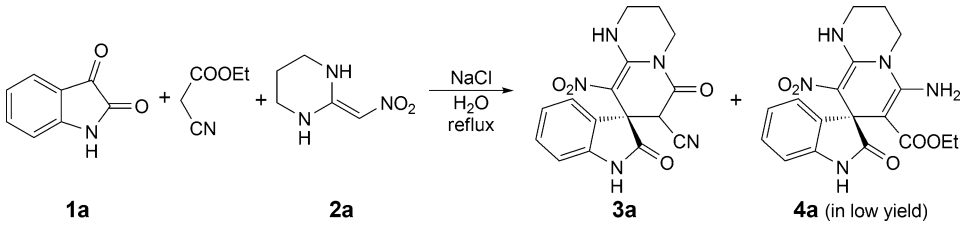
Elacomine Horsfiline Gelsemine

Figure. *Selected examples of natural products with spiro-linked oxindole motif*

properties [6–10]. Pyrido[1,2-*a*]pyrimidines have been described as analgesic, anti-allergic, antiasthmatic, and antipsychotic agents, and some examples are neutral HCl acceptors in organic synthesis [11].

A literature survey revealed that, although several methods have been reported for the synthesis of 6′-amino-1′,2′,3′,4′-tetrahydro-9′-nitro-2-oxospiro[indoline-3,8′-pyrido[1,2-*a*]pyrimidine]-7′-carbonitrile [12], so far, no report was available on the synthesis of (3*S*)-1,1′,2,2′,3′,4′,6′,7′-octahydro-9′-nitro-2,6′-dioxo-spiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carbonitrile. Based on our interest in the organic synthesis in aqueous medium [13] and continuation of our work on the synthesis of spiro-oxindole derivatives [14][15], we describe herein the one-pot, three-component reactions of isatin **1a**, ethyl cyanoacetate, and hexahydro-2-(nitromethylidene)pyrimidine **2a** in the presence of a catalytic amount of NaCl in H_2O for the formation of spiro-oxindoles of type **3** (*Scheme 1*).

Scheme 1. *Three-Component Synthesis of Spirooxindole* **3a**



1a **2a** **3a** **4a** (in low yield)

Results and Discussion. – Previously, we reported the efficient synthesis of 6′-amino-1′,2′,3′,4′-tetrahydro-9′-nitro-2-oxospiro[indoline-3,8′-pyrido[1,2-*a*]pyrimidine]-7′-carbonitrile using isatins, malononitrile, 1,1-bis(methylsulfanyl)-2-nitroethene and 1,*n*-diamines in EtOH in the presence of piperidine [12]. In the current work, we utilized ethyl cyanoacetate instead of malononitrile and studied the product formation, considering that the CN or the ester group can participate in the cyclization step, thus formation of two products is probable. Our initial experiment was focused on the three-component reaction of *N*-methyl isatin (=1-methyl-1*H*-indole-2,3-dione; **1b**), ethyl cyanoacetate, and hexahydro-2-(nitromethylidene)pyrimidine (**2a**) under different conditions (*Table 1*). Pyrimidines **2** were generated from the reaction between 1,1-bis(methylsulfanyl)-2-nitroethene and 1,*n*-diamines in refluxing MeCN [16].

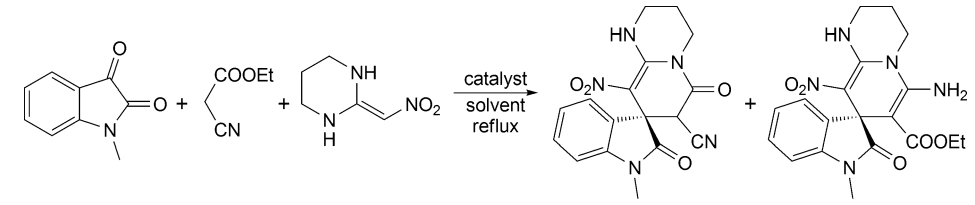
When piperidine and DABCO were used, the reaction led to the formation of **4b** as major product, as the result of cyclization through the attack to the CN group [12]. As shown in *Table 1*, utilizing NaCl as catalyst caused the ester group taking part in the cyclization, and, therefore, the yield of new spiro-oxindole **3b** increased, resulting in a 1:1 mixture **3b**/**4b**.

We next examined the substrate scope of the reaction by reacting ethyl cyanoacetate with isatin and *N*-methylisatins, and ketene aminals **2** (*Table 2*).

Also for the synthesis of spiro-oxindole **4**, the reaction was performed in H_2O, in the presence of a catalytic amount of piperidine. The results are compiled in *Table 3*.

A plausible mechanism for the formation of these spiro-oxindoles is outlined in *Scheme 2*. It is conceivable that, initially, intermediate **A** is formed *via* the *Knoevenagel*

Table 1. *Optimization of Reaction Conditions*

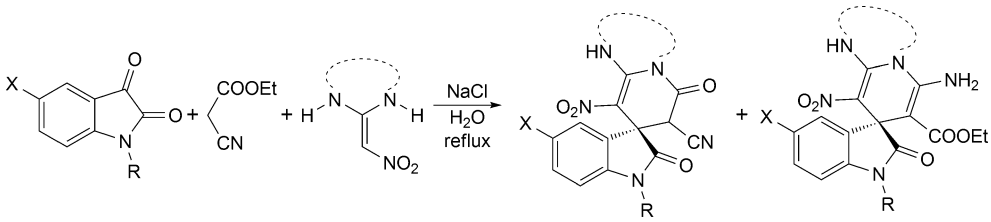


1b **2a** **3b** **4b**

Entry	Catalyst	Solvent	Yield of **3b** [%]	Yield of **4b** [%]
1	Piperidine	EtOH	20	60
2	Piperidine	H_2O	trace	60
3	Piperidine	MeCN	trace	20
4	NaCl	H_2O	48	48
5	DABCO[a])	EtOH	25	35

[a]) 1,4-Diazabicyclo[2.2.2]octane.

Table 2. *Results of the One-Pot, Three-Component Reaction*



1 **2** **3** **4**

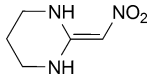
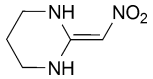
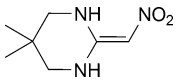
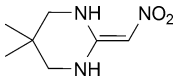
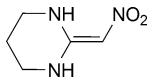
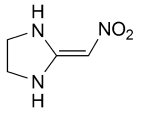
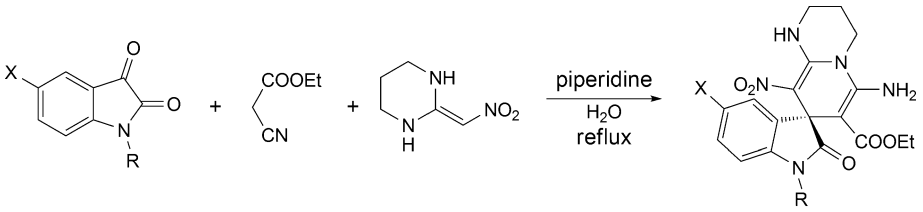
Substrate **2**		X	R	Time [h]	Product (yield [%])	
					3	**4**
	**2a**	H	H	3	**3a** (48)	**4a** (20)
	**2a**	H	Me	3	**3b** (48)	**4b** (48)
	**2b**	H	H	4	**3c** (46)	**4c** (30)
	**2b**	H	Me	4	**3d** (52)	**4d** (35)
	**2a**	Br	Me	5	**3e** (40)	**4e** (25)
	**2c**	H	H	8	**3f** (85)	**4f** (trace)

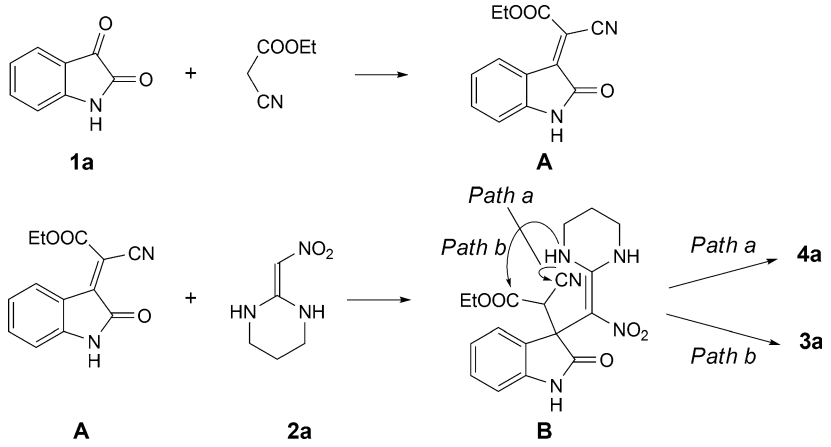
Table 3. *Synthesis of Spiro-oxindole* **4**



1 **2** **4**

Product **4**	X	R	Time [h]	Yield [%]
4g	NO_2	H	1	85
4b	H	Me	1	90

Scheme 2. *Proposed Mechanism of the Reaction*



condensation of isatin (**1a**) and ethyl cyanoacetate, followed by *Michael* addition of ketene aminal **2a** to afford intermediate **B** [12]. Intramolecular cyclization of **B** may proceed in two path ways. Attack of the NH group to the ester or CN group generate spiro-oxindole **3a** or **4a**, respectively.

In brief, a convenient and environmentally friendly one-pot, three-component reaction of readily available starting materials to give spiro-oxindole compounds has been developed.

Financial support of this work by the Tarbiat Modares University, Iran, is gratefully acknowledged.

Experimental Part

General. Isatin, ethyl cyanoacetate, amines, and 1,1-bis(methylsulfanyl)-2-nitroethene were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* instrument. IR Spectra: *NICOLET FT-IR 100* spectrometer; KBr pellets;

$\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-300 AVANCE* spectrometers; at 300 and 75 MHz, resp.; in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *FINNIGAN-MAT 8430* mass spectrometer; at an ionization potential of 70 eV; in m/z. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer for C, H, and N.

Synthesis of Compounds **3** (exemplified for **3a**). A mixture of *isatin* (*1*H-*indole-2,3-dione*; **1a**; 1 mmol), ethyl cyanoacetate ($NCCH_2COOEt$; 1 mmol), and *1,2,3,4,5,6-hexahydro-2-(nitromethylidene)pyrimidine* (**2a**; 1 mmol), in the presence of NaCl (30 mol-%) in H_2O (15 ml) was stirred at reflux for 3 h. After completion of the reaction (TLC), the mixture was filtered and purified using flash chromatography (FC) to afford the pure product **3a** in good yield, besides spiro-oxindole **4a**.

Synthesis of Compounds **4** (exemplified for **4b**). A mixture of N-*methylisatin* (**1b**; 1 mmol), $NCCH_2COOEt$ (1 mmol), and **2a** (1 mmol), in the presence of piperidine (one drop) in H_2O (15 ml) was stirred at reflux for 3 h. After completion of the reaction (TLC), the mixture was filtered, and the precipitate was washed with EtOH (4 ml) to afford the pure product **4b**.

*(3*S*)-1,1′,2,2′,3′,4′,6′,7′-Octahydro-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carbonitrile* (**3a**). Yield: 0.162 g (48%). Cream-colored powder. M.p. 269–271°. IR: 3425 and 3192 (2 NH), 1726 (NCO and NHCO), 1618 (C=C), 1494 and 1378 (NO_2). ^1H-NMR: 1.97–2.06 (*m*, 2 H); 3.42–3.54 (*m*, 2 H); 3.76–3.84 (*m*, 1 H); 3.94–4.02 (*m*, 1 H); 5.11 (*s*, 1 H); 6.88 (*d*, $^3J = 7.8$, 1 H), 6.94 (*t*, $^3J = 7.6$, 1 H), 7.12 (*d*, $^3J = 7.4$, 1 H), 7.27 (*t*, $^3J = 7.7$, 1 H); 10.89 (*s*, 1 H); 11.41 (*s*, 1 H). ^{13}C-NMR: 18.5; 40.7; 43.6; 50.5; 50.6; 106.4; 109.8; 112.6; 121.9; 123.2; 125.6; 129.8; 142.7; 151.5; 161.0; 174.7. EI-MS: 339 (5, M^+), 293 (40), 250 (35), 127 (67), 114 (45), 44 (96), 30 (100). Anal. calc. for $C_{16}H_{13}N_5O_4$ (339.31): C 56.64, H 3.86, N 20.64; found: C 56.59, H 3.80, N 20.68.

*(3*S*)-1,1′,2,2′,3′,4′,6′,7′-Octahydro-1-methyl-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-a]pyrimidine]-7′-carbonitrile* (**3b**). Yield: 0.149 g (45%). Cream-colored powder. M.p. 264–265°. IR: 3411, 3061 (2 NH), 1708 (NCO and MeNCO), 1624 (C=C), 1482 and 1347 (NO_2). ^1H-NMR: 1.97–2.05 (*m*, 2 H); 3.20 (*s*, 3 H); 3.47–3.53 (*m*, 2 H); 3.74–3.82 (*m*, 1 H); 3.93–3.98 (*m*, 1 H); 5.18 (*s*, 1 H); 7.03 (*t*, $^3J = 7.2$, 1 H); 7.12 (*d*, $^3J = 7.3$, 1 H); 7.19 (*d*, $^3J = 6.7$, 1 H); 7.39 (*t*, $^3J = 6.9$, 1 H); 11.41 (*s*, 1 H). ^{13}C-NMR: 18.5; 26.7; 40.8, 43.5; 50.1; 50.3; 106.2; 108.9; 112.5; 122.7; 122.9; 124.9; 130.1; 144.1; 151.5; 160.9; 173.3. EI-MS: 353 (21, M^+), 307 (34), 223 (47), 176 (48), 147 (88), 118 (100), 104 (51). Anal. calc. for $C_{17}H_{15}N_5O_4$ (353.33): C 57.79, H 4.28, N 19.82; found: C 57.74, H 4.35, N 19.88.

*(3*S*)-1,1′,2,2′,3′,4′,6′,7′-Octahydro-3′,3′-dimethyl-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-a]pyrimidine]-7′-carbonitrile* (**3c**). Yield: 0.176 g (48%). Orange powder. M.p. 254–255°. IR: 3413, 3314, (2 NH), 1724 (NCO and NHCO), 1630 (C=C), 1474 and 1345 (NO_2). ^1H-NMR: 1.06 (*s*, 6 H); 3.31 (*s*, 2 H); 3.68 (*q*, *AB* system, $^2J = 12.1$, 2 H); 5.42 (*s*, 1 H); 6.91 (*d*, $^3J = 7.7$, 1 H); 6.97 (*t*, $^3J = 7.7$, 1 H); 7.00 (*d*, $^3J = 6.8$, 1 H); 7.29 (*t*, $^3J = 6.8$, 1 H); 10.89 (*s*, 1 H); 11.34 (*s*, 1 H). ^{13}C-NMR: 23.0; 23.7, 28.9; 43.5; 50.3; 51.1; 51.5; 106.4; 109.9; 112.7; 122.0; 122.7; 125.7; 129.9; 142.7; 150.5; 161.3; 174.5. EI-MS: 367 (5, M^+), 311 (15), 242 (44), 197 (41), 170 (100), 142 (80), 114 (66). Anal. calc. for $C_{18}H_{17}N_5O_4$ (367.36): C 58.85, H 4.66, N 19.06; found: C 58.91, H 4.60, N 19.18.

*(3*S*)-1,1′,2,2′,3′,4′,6′,7′-Octahydro-1,3′,3′-trimethyl-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-a]pyrimidine]-7′-carbonitrile* (**3d**). Yield: 0.175 g (46%). Yellow powder. M.p. 264–266°. IR: 3420, 3061 (2 NH), 1709 (NCO and MeNCO), 1623 (C=C), 1484 and 1347 (NO_2). ^1H-NMR: 1.06 (*s*, 6 H); 3.21 (*s*, 3 H); 3.33 (*s*, 2 H); 3.68 (*q*, *AB* system, $^2J = 12.6$, 2 H); 5.51 (*s*, 1 H); 7.04 (*t*, $^3J = 6.9$, 1 H); 7.1 (*d*, $^3J = 7.8$, 1 H); 7.13 (*d*, $^3J = 7.8$, 1 H); 7.40 (*t*, $^3J = 7.1$, 1 H); 11.34 (*s*, 1 H). ^{13}C-NMR: 23.0; 23.8; 26.7; 28.9; 43.4; 50.2; 50.4; 50.5; 106.3; 108.9, 112.6; 122.5; 122.8; 124.9; 130.2; 144.1; 150.6; 161.2; 173.1. EI-MS: 381 (39, M^+), 335 (100), 320 (21), 224 (40), 209 (30), 155 (38), 41 (37). Anal. calc. for $C_{19}H_{19}N_5O_4$ (381.39): C 59.84, H 5.02, N 18.36; found: C 59.76, H 4.98, N 18.41.

*(3*S*)-5-Bromo-1,1′,2,2′,3′,4′,6′,7′-octahydro-1-methyl-9′-nitro-2,6′-dioxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-a]pyrimidine]-7′-carbonitrile* (**3e**). Yield: 0.156 g (43%). White powder. M.p. 280° (dec.). IR: 3396 and 3153 (2 NH), 1712 (NCO and MeNCO), 1689 (C=C), 1480 and 1331 (NO_2). ^1H-NMR: 1.95–2.12 (*m*, 2 H); 3.20 (*s*, 3 H); 3.63–3.67 (*m*, 2 H); 3.79–3.82 (*m*, 1 H); 3.98–4.02 (*m*, 1 H); 5.22 (*s*, 1 H); 7.11 (*d*, $^2J = 8.37$, 1 H); 7.49 (*s*, 1 H); 7.59 (*d*, $^2J = 8.23$, 1 H); 11.04 (*s*, 1 H). ^{13}C-NMR: 18.3; 26.8; 45.4; 50.1; 54.3; 55.1; 106.1; 110.8; 114.5; 116.3; 122.1; 126.1; 132.8; 143.6; 151.4; 160.7; 175.6. EI-MS: 418 (5), 399 (19), 334 (59), 264 (45), 176 (37), 155 (88), 110 (100). Anal. calc. for $C_{17}H_{14}BrN_5O_4$ (432.23): C 47.24, H 3.26, N 16.20; found: C 47.31, H 3.21, N 16.16.

*(7*S*)-1′,2,2′,3,5,6-Hexahydro-8-nitro-2′,5-dioxospiro[imidazo[1,2-*a*]pyridine-7(1*H*),3′-[3*H*]indole]-6-carbonitrile* (**3f**). Yield: 0.260 g (80%). Gray powder. M.p. 275–277°. IR: 3350 and 3195 (2NH), 1726 (NCO and NHCO), 1635 (C=C), 1480 and 1320 (NO_2). ^{1}H-NMR: 3.95 (*dd*, ^3J = 7.8, 2 H); 3.94 (*dt*, ^2J = 17.0, ^3J = 7.7, 1 H); 4.12 (*dt*, ^2J = 17.0, ^3J = 7.7, 1 H); 6.90 (*d*, ^3J = 7.5, 1 H); 6.96 (*t*, ^3J = 7.1, 1 H); 7.25 (*d*, ^3J = 6.5, 1 H); 7.28 (*t*, ^3J = 7.3, 1 H); 10.03 (*s*, 1 H); 10.95 (*s*, 1 H). ^{13}C-NMR: 43.6; 44.2; 44.4; 51.6; 104.2; 109.9; 112.7; 122.1; 123.3; 126.5; 130.1; 142.6; 151.9; 159.2; 174.7. EI-MS: 325 (1, M^+), 202 (3), 149 (8), 127 (61), 111 (100), 97 (6), 83 (51), 57 (52). Anal. calc. for $C_{15}H_{11}N_5O_4$ (325.28): C 55.39, H 3.41, N 21.53; found: C 55.43, H 3.49, N 21.48.

*Ethyl (3*R*)-6′-Amino-1,1′,2,2′,3′,4′-hexahydro-5,9′-dinitro-2-oxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carboxylate* (**4g**). Yield: 0.365 g (85%). Orange powder. M.p. 289–291°. IR: 3307, 3171 and 3025 (NH_2 and 2 NH), 1707 (MeCOO and NHCO), 1653 (C=C), 1522, 1480 and 1336 (NO_2), 1158 (C–O). ^{1}H-NMR: 0.84 (*t*, ^3J = 6.7, 3 H); 0.88–1.08 (*m*, 2 H); 3.28–3.44 (*m*, 2 H); 3.53.3.63 (*m*, 2 H); 3.72. (*q*, ^3J = 6.6, 2 H); 6.82 (*d*, ^3J = 8.4, 1 H); 7.75 (*s*, 1 H); 8.05 (*d*, ^3J = 8.4, 1 H); 8.33 (*s*, 2 H); 10.90 (*s*, 1 H); 12.09 (*s*, 1 H). ^{13}C-NMR: 13.1; 18.5; 48.9; 50.5; 52.9; 59.0; 77.6; 107.5; 108.7; 117.3; 125.0; 134.6; 141.4; 149.1; 151.1; 153.2; 167.7; 179.8. EI-MS: 411 (7), 287 (27), 215 (31), 141 (46), 125 (100), 114 (53). Anal. calc. for $C_{18}H_{18}N_6O_7$ (430.37): C 50.23, H 4.22, N 19.53; found: C 50.17, H 4.26, N 19.48.

*Ethyl (3*R*)-6′-Amino-1,1′,2,2′,3′,4′-hexahydro-1-methyl-9′-nitro-2-oxospiro[3*H*-indole-3,8′-[8*H*]pyrido[1,2-*a*]pyrimidine]-7′-carboxylate* (**4b**). Yield: 0.319 g (80%). Cream-colored powder. M.p. 267–268°. IR: 3450, 3277, 3158 (NH_2 and 2 NH), 1704 (MeCOO and NHCO), 1655 (C=C), 1475 and 1348 (NO_2), 1132 (C–O). ^{13}H-NMR: 0.74 (*t*, ^3J = 6.6, 3 H); 2.06–2.10 (*m*, 2 H); 3.06 (*s*, 3 H); 3.32–3.40 (*m*, 2 H); 3.67–3.85 (*m*, 4 H); 6.79–7.14 (*m*, 4 H); 8.22 (*s*, 2 H), 12.18 (*s*, 1 H). ^{13}C-NMR: 13.6; 19.3; 26.1; 43.0; 49.9; 56.3; 58.6; 78.6; 106.2; 109.6; 121.0; 122.2; 127.3; 132.5; 145.7; 149.9; 153.0; 168.0; 177.7. EI-MS: 399 (M^+, 8), 256 (100), 211 (39), 184 (78), 155 (65), 128 (29). Anal. calc. for $C_{19}H_{21}N_5O_5$ (399.40): C 57.14, H 5.30, N 17.53; found: C 57.19, H 5.23, N 17.61.

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Received August 8, 2014