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Synthesis of the new ring system 2-oxo-[1,4]oxazino[3,2-*e*]indole, heteroanalogue of Angelicin

Paola Barraja, Patrizia Diana, Alessandra Montalbano, Annamaria Martorana, Anna Carbone, Girolamo Cirrincione *

Dipartimento Farmacochimico, Tossicologico e Biologico Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

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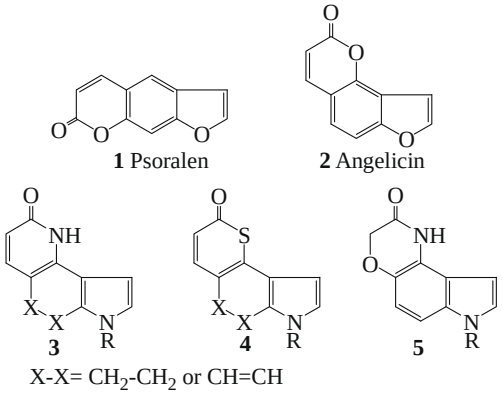
ABSTRACT

A convenient synthesis of the 2-oxo-[1,4]oxazino[3,2-*e*]indole ring system, an heteroanalogue of Angelicin, is reported. Our synthetic approach consisted of the annelation of the oxazine ring on the indole moiety using 4-amino-5-hydroxy indoles as building blocks. The antiproliferative activity of the new compounds either in the dark or under UVA irradiation was investigated.

Psoralen **1** and Angelicin **2**, linear and angular furocumarins, respectively, are photoactivable drugs which upon UVA light irradiation, intercalate into DNA and photobind with it.[1] Syntheses of their heteroanalogues were also reported.[2–4] With the aim of studying new photoreactive agents with enhanced antiproliferative activity and decreased side effects we have recently reported the synthesis of the new ring system pyrrolo[2,3-*h*]quinolin-2-one **3**. Some derivatives of such a system showed high phototoxicity (IC_{50} 0.4–16.4 μM) when compared with 8-methoxypsoralen (8-MOP) and Angelicin used as reference drugs.[5,6] Introduction of sulfur in place of the oxygen atom in the cumarin ring of Angelicin generally improves the interaction with DNA both in the dark and under UV light.[3]



In this light we studied the synthesis of the new ring system thiopyrano[2,3-*e*]indol-2-one **4** whose derivatives showed remarkable phototoxicity on human tumour cell lines with IC_{50} reaching in one case the nanomolar level.[7,8] On continuing our studies on photochemotherapeutic drugs we now propose the synthesis of the new ring system 2-oxo- [1,4]oxazino[3,2-*e*]indole **5**, which can be regarded as heteroanalogue of pyrroloquinolinones **3** where an additional oxygen atom replaces a carbon of the pyridone ring. The 1,4-benzoxazines have attracted special attention because of their natural occurrence and their variety of biological activities, such as analgesic,[9] antibiotic[10,11] and CNS depressant.[12] Moreover they find application as antitumour agents.[13,14] In our first attempts to synthesize the ring system we approached the classical Fischer cyclization on the preconstituted 6-hydrazono 1,4-benzoxazin-3-one **12b** (Scheme 1), which could have allowed the isolation of the desired 2-oxo-[1,4]oxazino[3,2-*e*]indole. In this light 2-amino-4-nitro phenol **6a** was reacted with freshly prepared chloride of fumaric acid monoethyl ester **7** in dioxane to give intermediate **8a** which undergoes ring closure in ethanol in the presence of potassium carbonate to produce the nitro benzoxazine **9a**. Catalytic reduction of this latter, gave in nearly quantitative yield the amino derivative **10**, which was subsequently subjected to diazotization with sodium nitrite in acetic acid to afford the diazonium salt **11**. Such a reaction mixture containing the diazonium species which showed the typical IR stretching for the diazo functionality at 2251 cm^{-1} was subjected to reduction with stannous chloride in hydrochloric acid but the expected hydrazine **12a** could not be isolated. This latter could not be obtained also by reduction of the diazonium salt with sodium bisulfite[15] or triphenylphosphine.[16] The hydrazine **12a**, upon reaction with acetone, could have led to the

* Corresponding author. Tel.: +39 0916161606; fax: +39 0916169999.
E-mail address: gcirrinc@unipa.it (G. Cirrincione).

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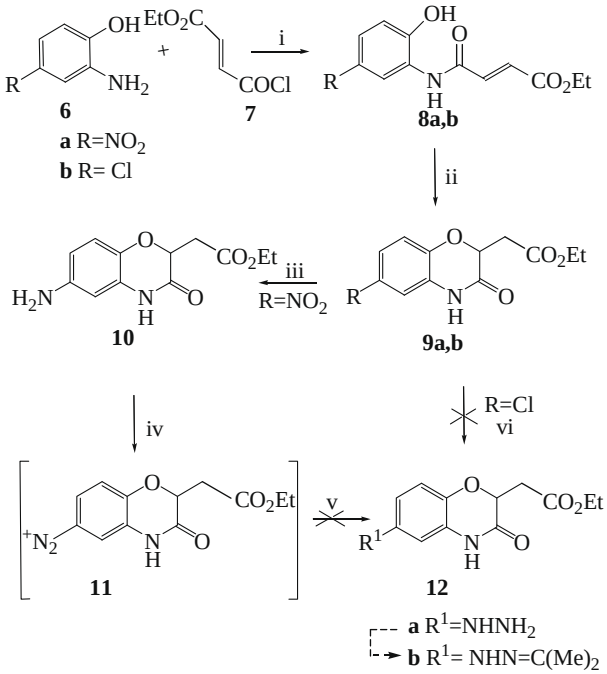
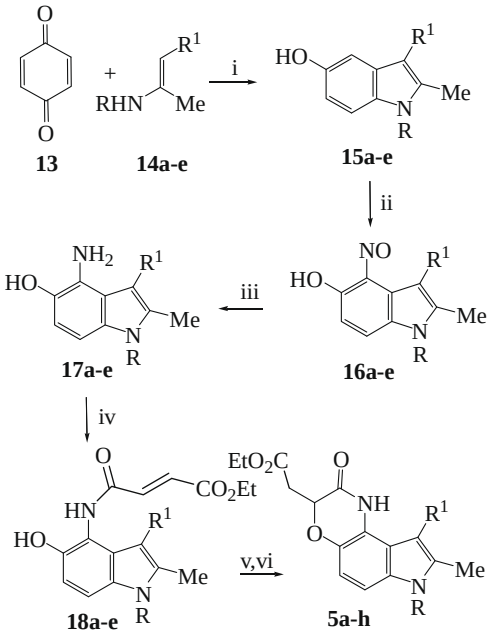


Scheme 1. Reagents and conditions: (i) $NaHCO_3$, dioxane, rt, 24 h, 80–90%; (ii) K_2CO_3, EtOH, reflux, 5 h, 75% (R = NO_2) or 60 °C, 3 h, 98% (R = Cl); (iii) H_2, Pd/C, EtOH, rt, 24 h, 98%; (iv) $NaNO_2$, 98% AcOH, 0 °C then rt, 1 h; (v) $SnCl_2$, 37% HCl; (vi) NH_2NH_2/DMF or NH_2NH_2, rt to reflux.



a R=Bn, R^1=CO_2Et; **b** R=Bn, R^1=CO_2Me; **c** R=Me, R^1=CO_2Et; **d** R=Me, R^1=CO_2Me; **e** R=Ph, R^1=CO_2Et; **f** R=Bn, R^1=CO_2H; **g** R=Me, R^1=CO_2H; **h** R=Ph, R^1=CO_2H.

Scheme 2. Synthesis of 2-oxo[1,4]oxazino[3,2-*e*]indoles **5a–h**. Reagents and conditions: (i) CH_3NO_2, rt, 24 h, 60–70%; (ii) TDA-1, $NaNO_2$, 90% AcOH, rt, 3 h, 65–80%; (iii) H_2, Pd/C, EtOH, rt, 24 h, 55–70%; (iv) **7**, $NaHCO_3$, dioxane, rt, 24 h, 70–90%; (v) K_2CO_3, EtOH, rt, 30 min, 65–82%; (vi) 15% KOH, EtOH, reflux, 40 min, 58–85%.

isolation of the corresponding hydrazone **12b** according to previously reported methods.[6,17] Then the chloro benzoxazine **9b** was prepared through the same route described for the nitro derivative (Scheme 1) using 2-amino-4-chlorophenol **6b** as the starting material. However the displacement of the chlorine atom with hydrazine to get **12a** failed. In fact under mild conditions such as stoichiometric amount of hydrazine in DMF, or using the nucleophile itself as the solvent at room temperature or at 40 °C, unreacted starting material was recovered. Whereas upon heating under reflux the reaction mixture with an excess of the nucleophile the benzoxazine ring underwent ring opening, to give 2-amino-4-chlorophenol **6b** as the main product.

These difficulties forced us to consider a different approach to the new ring system, which consisted of the annelation of the oxazine ring on the indole moiety. Thus key intermediates for our purpose were 4-amino-5-hydroxy indoles **17** bearing the functional groups in the suitable positions to annelate the benzoxazine moiety as depicted in the Scheme 2. The Nenitzescu synthesis involves the reaction between benzoquinones and β-aminocrotonates to produce 5-hydroxy indoles.[18] This reaction is generally carried out in ethanol, acetic acid, acetone or nitromethane.[19] We obtained the best yields of indoles **15a–e** starting from 1,4-benzoquinone **13**, ethyl β-aminocrotonates **14a–e** in nitromethane at room temperature (Scheme 2). Nitrosation of the hydroxy indole **15a** was initially carried out in refluxing AcOH and $NaNO_2$ (1:2) yielding a mixture of the 4-nitroso derivative **16a** (35%) and the corresponding 4,6-dinitroso derivative (15%). However the addition of the phase transfer catalyst tris-[2-(2-methoxy)ethyl]amine (TDA-1) in the reaction mixture produced excellent results. In fact the poor solubility of the starting hydroxy indoles was bypassed and smoother conditions could be used (such as room temperature and equimolecular ratio of $NaNO_2$), thus avoiding the undesirable dinitroso derivatives to be formed yielding the mono nitroso derivatives **16a–e** as main products. Reduction with H_2 and Pd on charcoal led to the hydroxy amino indoles **17a–e** which were generally obtained from the reaction mixture as grey solid upon partial evaporation of the solvent. Aminoindoles **17d** and **17e** are quite unstable, turning dark and making difficult any purification by chromatography or recrystallization. For this reason they were used in the next step without any further purification.

Reaction of **17a–e** with the freshly prepared chloride of fumaric acid monoethyl ester **7** in dioxane produced the α,β-unsaturated esters **18a–e** which easily cyclized in ethanol in the presence of potassium carbonate to give the desired **5a–e**.[20] Upon reaction in ethanolic potassium hydroxide of the latter, the acid derivatives **5f-h** were achieved, thus indicating that the carboxyester functionality at the 3 position undergoes hydrolysis yielding acid **5f** from either **5a** or **15b**, acid **5g** from either **5c** or **5d** and acid **5h** from **15e**.

All the new compounds were subjected to photobiological studies on cultured cell lines of human origin (HL-60, LoVo and NCTC 2546) at different concentrations and UVA doses (2.5, 3.25 J cm^{-2}), but they did not show any significant antiproliferative activity. Moreover the antiproliferative activity in the dark by the NCI of Bethesda was investigated. Only derivative **5a** showed modest activity with IC_{50} 1×10^{-5} M against the RPMI-8226 of the leukaemia panel, the HCT-116 of the colon cancer panel and BT-549 of the breast cancer panel cell lines.

In conclusion, we have reported a versatile method which allows the synthesis of derivatives of the new ring system 2-oxo[1,4]oxazino[3,2-*e*]indole.

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References and notes

1. Dall'Acqua, F.; Viola, G. In *Photobiology for the 21th century*; Coohil, T. P., Valenzeno, D. P., Eds.; Valdenmar: Overland Park, KS, 2001; p 325.

2. Jakobs, A. E.; Piette, J. *J. Photochem. Photobiol. B.* **1994**, *22*, 9–15.
3. Jakobs, A. E.; Piette, J. *J. Med. Chem.* **1995**, *38*, 869–874.
4. Rodighiero, P.; Guiotto, A.; Chilin, A.; Bordin, F.; Baccichetti, F.; Carlassare, F.; Vedaldi, D.; Caffieri, S.; Pozzan, A.; Dall'Acqua, F. *J. Med. Chem.* **1996**, *39*, 1293–1302.
5. Barraja, P.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G.; Viola, G.; Dall'Acqua, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2809–2811.
6. Barraja, P.; Diana, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Bioorg. Med. Chem.* **2006**, *14*, 8712–8728.
7. Barraja, P.; Sciabica, L.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G.; Disarò, S.; Basso, G.; Viola, G.; Dall'Acqua, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2291–2294.
8. Barraja, P.; Diana, P.; Montalbano, A.; Carbone, A.; Cirrincione, G.; Viola, G.; Salvador, A.; Vedaldi, D.; Dall'Acqua, F. *Bioorg. Med. Chem.* **2008**, *16*, 9668–9683.
9. Thuillier, G.; Laforest, J.; Bessin, P.; Bonnet, J.; Thuillier, J. *Eur. J. Med. Chem.* **1975**, *10*, 37–42.
10. Reusser, F. *J. Antibiot.* **1979**, *32*, 1186–1192.
11. Reusser, F. *Biochemistry* **1973**, *12*, 1136–1142.
12. Turk, C. F.; Krapcho, J.; Michel, I. M.; Weinryb, I. *J. Med. Chem* **1977**, *20*, 729–732.
13. Kimura, K.; Usui, Y.; Hattori, T.; Yamakawa, N.; Goto, H.; Usui, M.; Okada, S.; Shirato, K.; Tomoda, A. *Oncol. Rep.* **2008**, *19*, 3–10.
14. Ishihara, M.; Kawase, M.; Westman, G.; Samuelsson, K.; Motohashi, N.; Sakagami, H. *Anticancer Res.* **2007**, *27*, 4053–4057.
15. Mas, J. -M.; Rochin, C. PCT Int. Appl. WO 9724316, 1997; *Chem. Abstr.* **1997**, *127*, 108760.
16. Ray, P. C.; Medikonduri, S.; Ramanjaneyulu, G. S. PCT Int. Appl. WO 083320, 2007; *Chem. Abstr.* **2007**, *147*, 21894.
17. Rodighiero, P.; Chilin, A.; Pastorini, G.; Guiotto, A. *J. Heterocyc. Chem.* **1987**, *24*, 1041–1043.
18. Allen, G. R.; Pidacks, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 2536–2544.
19. Everett, S. A.; Naylor, M. A.; Barraja, P.; Swann, E.; Patel, K. B.; Stratford, M. R. L.; Hudnott, A. R.; Vojnovic, B.; Locke, R. J.; Wardman, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 2,* **2001**, 843–860.

20. Preparation of 2-oxo[1,4]oxazino[3,2-*e*]indoles **5a-e**: A mixture of **18a–e** (1.4 mmol) and K_2CO_3 (0.4 g, 2.8 mmol) in ethanol (10 mL) was stirred at room temperature for 30 min. The mixture was poured onto crushed ice and the solid was filtered off, dried and recrystallized from ethanol.

Data for ethyl 3-(2-ethoxy-2-oxoethyl)-7-benzyl-8-methyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylate **5a**: white solid; mp 166–167 °C; Yield 82%; IR ($CHBr_3$): 3181–3147 (NH), 1734 (CO), 1689 (CO), 1657 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.18 (3H, t, J = 7.3 Hz, CH_3), 1.36 (3H, t, J = 7.3 Hz, CH_3), 2.66 (3H, s, CH_3), 2.82–3.07 (2H, m, CH_2), 4.10 (2H, q, J = 7.3 Hz, CH_2), 4.36 (2H, q, J = 7.3 Hz, CH_2), 4.87–4.93 (1H, m, H-3), 5.52 (2H, s, CH_2), 6.85 (1H, d, J = 8.8 Hz, H-6), 7.02 (2H, d, J = 7.6 Hz, H-2′ and H-6′), 7.12 (1H, d, J = 8.8 Hz, H-5), 7.22–7.35 (3H, m, H-3′, H-4′ and H-5′), 11.61 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 13.0 (CH_3), 13.9 (CH_3), 14.1 (CH_3), 35.2 (CH_2), 46.2 (CH_2), 60.2 (CH_2), 60.7 (CH_2), 72.8 (CH), 102.9 (C), 105.1 (CH), 112.6 (CH), 114.4 (C), 119.0 (C), 126.0 (CH × 2), 127.4 (CH), 128.7 (CH × 2), 133.2 (C), 136.6 (C), 137.2 (C), 146.5 (C), 165.1 (CO), 167.1 (CO), 169.4 (CO). Anal. $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22. Found: C, 66.30; H, 6.15; N, 6.10.

Data for methyl 3-(2-ethoxy-2-oxoethyl)-7-benzyl-8-methyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylate **5b**: white solid; mp 170–171 °C; Yield 68%; IR ($CHBr_3$): 3221–3105 (NH), 1732 (CO), 1691 (CO), 1662 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.18 (3H, t, J = 7.4 Hz, CH_3), 2.65 (3H, s, CH_3), 2.82–3.07 (2H, m, CH_2), 3.89 (3H, s, CH_3), 4.09 (2H, q, J = 7.4 Hz, CH_2), 4.87–4.93 (1H, m, H-3), 5.52 (2H, s, CH_2), 6.85 (1H, d, J = 8.5 Hz, H-6), 7.00 (2H, d, J = 6.3 Hz, H-2′ and H-6′), 7.12 (1H, d, J = 8.5 Hz, H-5), 7.24–7.35 (3H, m, H-3′, H-4′ and H-5′), 11.58 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 13.0 (CH_3), 13.9 (CH_3), 35.2 (CH_2), 46.2 (CH_2), 51.9 (CH_3), 60.2 (CH_2), 72.8 (CH), 102.8 (C), 105.1 (CH), 112.6 (CH), 114.4 (C), 118.8 (C), 126.0 (CH × 2), 127.4 (CH), 128.7 (CH × 2), 133.2 (C), 136.6 (C), 137.2 (C), 146.5 (C), 165.1 (CO), 167.6 (CO), 169.4 (CO). Anal. $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.40; H, 5.25; N, 6.78.

Data for ethyl 3-(2-ethoxy-2-oxoethyl)-7,8-dimethyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylate **5c**: white solid; mp 141–142 °C; Yield 65%; IR ($CHBr_3$): 3255–3093 (NH), 1732 (CO), 1689 (CO), 1657 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.20 (3H, t, J = 7.3 Hz, CH_3), 1.36 (3H, t, J = 7.3 Hz, CH_3), 2.65 (3H, s, CH_3), 2.80–3.06 (2H, m, CH_2), 3.67 (3H, s, CH_3), 4.11 (2H, q, J = 7.3 Hz, CH_2), 4.33 (2H, q, J = 7.3 Hz, CH_2), 4.83–4.89 (1H, m, H-3), 6.86 (1H, d, J = 8.8 Hz, H-6), 7.11 (1H, d, J = 8.8 Hz, H-5), 11.60 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 12.9 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 30.2 (CH_3), 35.2 (CH_2), 60.2 (CH_2), 60.5 (CH_2), 72.8 (CH), 101.9 (C), 104.7 (CH), 112.2 (CH), 114.2 (C), 118.5 (C), 133.4 (C), 137.0 (C), 146.8 (C), 165.0 (CO), 167.1 (CO), 169.4 (CO). Anal. $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 61.12; H, 6.15; N, 7.18.

Data for methyl 3-(2-ethoxy-2-oxoethyl)-7,8-dimethyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylate **5d**: white solid; mp 144–145 °C; Yield 65%; IR ($CHBr_3$): 3255–2950 (NH), 1732 (CO), 1689 (CO), 1657 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.20 (3H, t, J = 7.3 Hz, CH_3), 2.65 (3H, s, CH_3), 2.80–3.06 (2H, m, CH_2), 3.64 (3H, s, CH_3), 3.85 (3H, s, CH_3), 4.11 (2H, q, J = 7.3 Hz, CH_2), 4.84–4.90 (1H, m, H-3), 6.84 (1H, d, J = 8.8 Hz, H-6), 7.08 (1H, d, J = 8.8 Hz, H-5), 11.60 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 12.9 (CH_3), 14.0 (CH_3), 30.2 (CH_3), 35.2 (CH_2), 51.7 (CH_3), 60.2 (CH_2), 72.8 (CH), 101.9 (C), 104.7 (CH), 112.2 (CH), 114.2 (C), 118.5 (C), 133.4 (C), 137.0 (C), 146.8 (C), 165.0 (CO), 167.1 (CO), 169.4 (CO). Anal. $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.10; H, 5.79; N, 7.50.

Data for ethyl 3-(2-ethoxy-2-oxoethyl)-7-phenyl-8-methyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylate **5e**: white solid; mp 142–144 °C; Yield 75%; IR ($CHBr_3$): 3232–3145 (NH), 1732 (CO), 1691 (CO), 1660 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.19 (3H, t, J = 7.3 Hz, CH_3), 1.37 (3H, t, J = 7.3 Hz, CH_3), 2.47 (3H, s, CH_3), 2.82–3.07 (2H, m, CH_2), 4.10 (2H, q, J = 7.3 Hz, CH_2), 4.38 (2H, q, J = 7.3 Hz, CH_2), 4.86–4.92 (1H, m, H-3), 6.47 (1H, d, J = 8.7 Hz, H-6), 6.82 (1H, d, J = 8.7 Hz, H-5), 7.45 (2H, d, J = 6.0 Hz, H-2′ and H-6′), 7.58–7.73 (3H, m, H-3′, H-4′ and H-5′), 11.59 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 14.0 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 35.2 (CH_2), 60.3 (CH_2), 60.9 (CH_2), 72.9 (CH), 103.6 (C), 105.0 (CH), 113.0 (CH), 114.2 (C), 118.8 (C), 128.2 (CH × 2), 129.5 (CH), 130.1 (CH × 2), 134.4 (C), 135.4 (C), 137.4 (C), 146.5 (C), 165.1 (CO), 167.2 (CO), 169.4 (CO). Anal. $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.28; H, 5.32; N, 6.38.

Data for 3-(2-ethoxy-2-oxoethyl)-7-benzyl-8-methyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylic acid **5f:** This compound was obtained by heating under reflux (40 min) an ethanolic solution (20 mL) of **5a** or **5b** (3 mmol) with 15% KOH (10 mL); white solid; mp 228–229 °C; Yield 80–85%, respectively; IR ($CHBr_3$): 3126–2884 (OH, NH), 1722 (CO), 1698 (CO), 1664 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 2.66 (3H, s, CH_3), 2.75–2.99 (2H, m, CH_2), 4.36 (2H, q, J = 7.1 Hz, CH_2), 4.83–4.88 (1H, m, H-3), 5.52 (2H, s, CH_2), 6.86 (1H, d, J = 8.8 Hz, H-6), 7.02 (2H, d, J = 6.0 Hz, H-2′ and H-6′), 7.12 (1H, d, J = 8.8 Hz, H-5), 7.25–7.36 (3H, m, H-3′, H-4′ and H-5′), 11.57 (1H, s, NH), 12.41 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 13.0 (CH_3), 14.1 (CH_3), 35.3 (CH_2), 46.2 (CH_2), 60.7 (CH_2), 73.0 (CH), 102.9 (C), 105.1 (CH), 112.7 (CH), 114.4 (C), 118.8 (C), 126.0 (CH × 2), 127.4 (CH), 128.8 (CH × 2), 133.2 (C), 136.6 (C), 137.3 (C), 146.5 (C), 165.3 (CO), 167.1 (CO), 171.0 (CO). Anal. $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.10; H, 4.90; N, 6.50.

Data for 3-(2-ethoxy-2-oxoethyl)-7,8-dimethyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylic acid **5g**: This compound was obtained by heating under reflux (40 min) an ethanolic solution (20 mL) of **5c** or **5d** (3 mmol) with 15% KOH (10 mL); white solid; mp 251–252 °C; Yield 68–70%, respectively; IR ($CHBr_3$): 3153–2911 (OH, NH), 1730 (CO), 1632 (CO), 1630 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.36 (3H, t, J = 6.5 Hz, CH_3), 2.61 (3H, s, CH_3), 2.71–2.99 (2H, m, CH_2), 3.63 (3H, s, CH_3), 4.30 (2H, q, J = 6.5 Hz, CH_2), 4.81–4.83 (1H, m, H-3), 6.85 (1H, d, J = 8.8 Hz, H-6), 7.06 (1H, d, J = 8.8 Hz, H-5), 11.57 (1H, s, NH), 12.57 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 12.8 (CH_3), 14.1 (CH_3), 30.1 (CH_3), 35.3 (CH_2), 60.6 (CH_2), 73.1 (CH), 101.9 (C), 104.6 (CH), 112.7 (CH), 114.2 (C), 118.6 (C), 133.4 (C), 137.1 (C), 146.7 (C), 165.3 (CO), 167.1 (CO), 171.1 (CO). Anal. $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.60; H, 5.45; N, 8.30.

Data for 3-(2-ethoxy-2-oxoethyl)-7-phenyl-8-methyl-2-oxo-1,2,3,7-tetrahydro[1,4]oxazino[3,2-e]indole-9-carboxylic acid **5h**: This compound was obtained by heating under reflux (40 min) an ethanolic solution (20 mL) of **5e** (3 mmol) with 15% KOH (10 mL); white solid; mp 224–226 °C; Yield 58%; IR ($CHBr_3$): 3408–2929 (OH, NH), 1697 (CO), 1656 (CO), 1637 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 2.40–2.52 (2H, m, CH_2), 2.45 (3H, s, CH_3), 4.34 (2H, q, J = 7.1 Hz, CH_2), 4.92–5.04 (1H, m, H-3), 6.43 (1H, d, J = 8.7 Hz, H-6), 6.78 (1H, d, J = 8.7 Hz, H-5), 7.44 (2H, d, J = 6.0 Hz, H-2′ and H-6′), 7.62–7.66 (3H, m, H-3′, H-4′ and H-5′), 11.47 (1H, s, NH), 12.49 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 14.0 (CH_3), 14.1 (CH_3), 37.6 (CH_2), 60.8 (CH_2), 74.5 (CH), 99.5 (C), 103.5 (C), 104.8 (CH), 113.3 (CH), 118.9 (C), 128.2 (CH × 2), 129.4 (CH), 130.0 (CH × 2), 134.2 (C), 135.4 (C), 137.6 (C), 146.3 (C), 166.5 (CO), 167.2 (CO), 167.3 (CO). Anal. $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.40; H, 4.70; N, 6.54.