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Synthesis and Antiproliferative Activity of the Ring System [1,2]Oxazolo[4,5-*g*]indole

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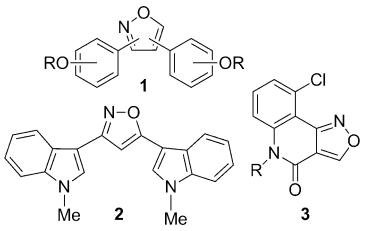
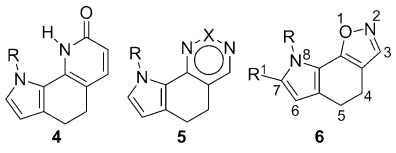
The [1,2]oxazole nucleus is found in many drugs with antitumor activity. Among these, the class of diaryl[1,2]oxazoles of type **1** has been widely studied and has shown very promising results.[1–3] In particular, some compounds were prepared as *cis*-restricted combretastatin A-4 (CA-4) analogues, in which the [1,2]oxazole ring mimics the *cis*-alkenyl bridge of natural CA-4, with the intent of stabilizing the active *cis* orientation. Some derivatives showed strong growth inhibitory activities against human cancer cell lines and the ability to induce G_2/M-phase cell-cycle arrest. In some cases higher antitubulin activity than CA-4 was observed.

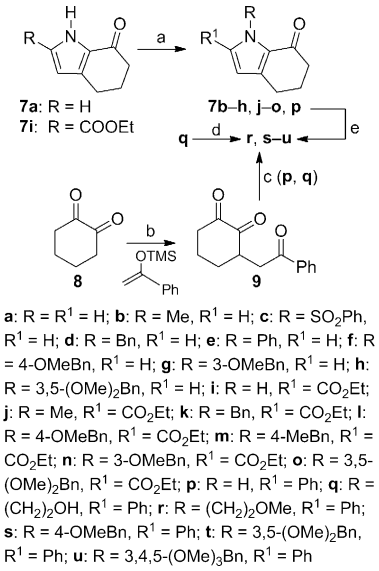


3,5-Bis(3′-indolyl)[1,2]oxazoles **2**, recently reported by us as analogues of nortopsentins A–C, exhibited in vitro cytotoxicity in the micromolar range.[4] Moreover, 4-phenyl[1,2]oxazoles emerged in very recent studies as inhibitors of bromodomain–histone interactions, having antiproliferative and anti-inflammatory properties.[5] Among polycondensed compounds, some tricyclic [1,2]oxazoles of type **3** have been described as selective inhibitors of multidrug-resistance protein (MRP1).[6]

We have already reported the synthesis of indole-containing heterocyclic systems in which a six-membered ring, in particular, a pyridine-2(1*H*)-one[7,8] (**4**) and pyrimidine ring[9] (**5**), is annelated to the indole moiety to produce compounds with interesting antitumor activity. In light of the promising properties that the [1,2]oxazole moiety confers to the molecules to which it is bound, we thought to cyclize the [1,2]oxazole ring on the indole moiety to obtain new tricyclic derivatives of type **6**.



Tetrahydroindol-7-ones **7a–f,i–m**, suitable substrates for our purpose, were prepared in 56–90% yields by a method previously reported by us (Scheme 1).[7–9] By using the same route,



Scheme 1. *Reagents and conditions*: a) NaH, DMF or THF, RT, 1 h then MeI or ArX (X = Cl or Br), RT or reflux, 2–4 h, 74–90%; for **7e**: K_2CO_3, *N*-methylpyrrolidone, N_2, RT, 1 h, then CuBr, RT 1 h, then PhI, reflux 4 h, 66%; b) CAN, MeCN, −35 °C→RT, 15 min, 60%;[10] c) for **7p**: $AcONH_4$, AcOH, RT, 48 h, 70%; for **7q**: $HO(CH_2)_2NH_2$, AcOH, reflux, 3 h, 60%; d) NaH, DMF, RT, 1 h then MeI, RT, 4 h, 70%; e) NaH, DMF, RT, 1 h then ArX (X = Cl or Br), RT or 50 °C, 6–48 h, 70–75%.

new tetrahydroindoles **7g,h,n,o** were prepared upon alkylation of the N-unsubstituted indolones **7a** and **7i** with substituted benzyl chlorides (74–90%). Additionally, to broaden the substitution pattern on the pyrrole ring of the novel ring system, the new tetrahydroindol-4-one **7p**, bearing a 2-phenyl functionality, was prepared by starting from the commercially available 1,2-cyclohexanedione **8** in two steps (Scheme 1). The first step involved the radical reaction between diketone **8** and trimethyl(1-phenylvinyloxy)silane as radical acceptor in the presence of excess ceric ammonium nitrate (CAN) as oxidizing agent to give the triketone **9** (60%).[10] The latter was cyclized in acetic acid with ammonium acetate to give the N-unsubstituted 2-phenyl derivative **7p** (70%), whereas reaction with ethanolamine furnished the tetrahydroindol-4-one **7q** (60%) carrying an ethanolic chain on the pyrrole nitrogen atom.

With this kind of substitution we intended to prepare compounds with increased water solubility. Methylation with iodo-

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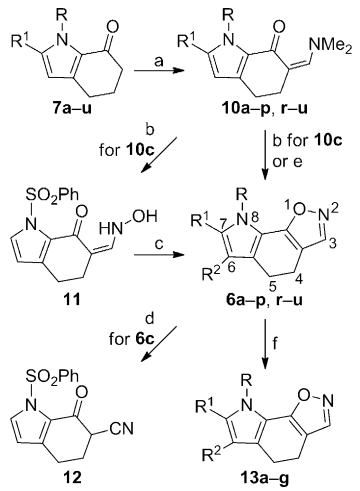
methane and sodium hydride as the base gave **7r** (70%). The NH derivative **7p** was subjected to alkylation on the pyrrole nitrogen atom using 4-methoxy-, 3,5-dimethoxy-, and 3,4,5-trimethoxybenzyl halides in the presence of sodium hydride as the base to yield the corresponding N-substituted tetrahydroindoles **7s**–**u** (70–75%).

α-Enaminoketones **10** (Scheme 2) were obtained in excellent yields (80–100%) by treating tetrahydroindoles **7** with the Bredereck reagent, *tert*-butoxy-bis-(dimethylamino)methane



Scheme 2. *Reagents and conditions*: a) TBDMAM, DMF, μW (150 W, $T = 190\,^{\circ}C$), 5 min–1 h, 60–100%; b) $NH_2OH{\cdot}HCl$, EtOH, 45 °C, 1.15 h, 50% (**6c**) and 42% (**11**); c) AcOH/MeOH (1:2), reflux, 40 min, 75%; d) KOH, EtOH, reflux, 30 min, 60% or TBAF, THF, RT, 24 h, 58%; e) NH_2OH, AcOH/MeOH (1:2), 40 °C→reflux, 40 min–2 h, 40–95%; f) NCS, DMF, RT, 16–24 h, 40–50%.

(TBDMAM), under microwave irradiation. Unfortunately, **10n** and **10o** were not obtained pure from the corresponding ketones after 15 min of irradiation. Purification by recrystallization or column chromatography was not possible, as compounds partially lost their enamino functionality, so they were used in the next step without purification. Moreover, **7q** did not react at all, so we could not isolate the corresponding enaminone, recovering the starting material.

In an attempt to establish a simple and versatile methodology for the synthesis of the new tricyclic ring system **6**, we used enaminoketones of type **10** as key intermediates for the annelation of the five-membered ring. Initially, we thought that we could start our project with the synthesis of the N-unsubstituted derivatives **6a** and **6i**, which could be further functionalized on the indole nitrogen atom with a variety of substituents. Thus, reaction of **10a** and **10i** with hydroxylamine hydrochloride as dinucleophile in ethanol at reflux as solvent yielded the desired [1,2]oxazoles **6a** (10%) and **6i** (83%). However, the low yield of **6a** argued against its synthetic pathway starting from this type of substrate. Access to **6a** was also possible via deprotection of the *N*-sulfonyl[1,2]oxazole **6c**. Thus, the *N*-sulfonyl enaminoketone **10c** was treated with hydroxylamine hydrochloride under the same reaction conditions described before. However, a mixture of the desired [1,2]oxazole **6c** (50%) and of the uncyclized intermediate **11** (42%) was obtained after prolonged heating. Such behavior underscored the mechanism of the ring closure, in which the nucleophilic nitrogen atom of hydroxylamine is responsible for the initial attack at the more electrophilic enamine carbon, but the subsequent ring closure did not take place quantitatively. Forced reaction conditions were required to afford the desired ring closure. In fact, by treating pure **11** with methanol and acetic acid under reflux, the corresponding [1,2]oxazole **6c** was obtained in very good yield (95%). Deprotection of the nitrogen atom of **6c** was attempted with a stoichiometric amount of potassium hydroxide in ethanol, or tetrabutylammonium fluoride (TBAF)[11] in THF, but unfortunately, even under mild conditions, we isolated *N*-phenylsulfonyl-substituted β-ketonitrile **12** (58–60%).

Surprisingly, the phenylsulfonyl substituent was never removed even on heating the mixture at reflux. Considering the poor stability of the [1,2]oxazole ring even under mild conditions, we turned to the use of enaminones, bearing the functional groups on the nitrogen atom, for the desired cyclization to [1,2]oxazoles. In this manner enaminones **10a**–**p**,**r**–**u** were allowed to react in methanol and acetic acid at reflux in the presence of a stoichiometric amount of hydroxylamine to give the desired [1,2]oxazoles **6a**–**p**,**r**–**u** (Table 1) in moderate to very good yields (10–90%). To further increase the pattern of substitution at the pyrrole ring, [1,2]oxazoles **6b**,**c**,**i**,**m**,**n**,**p**,**t**,

Table 1. Yields and melting points for [1,2]oxazolo[4,5-*g*]indoles **6a**–**p**,**r**–**m** and **13a**–**g** (see Schemes 1 and 2 for structures).

Substrate	Product	R	R^1	R^2	mp [°C][a]	Yield [%][b]
10a	**6a**	H	H	H	146–147	10
10b	**6b**	Me	H	H	84–85	67
10c, **11**	**6c**	SO_2Ph	H	H	134–135	50, 95
10d	**6d**	Bn	H	H	oil	52
10e	**6e**	Ph	H	H	oil	64
10f	**6f**	4-OMeBn	H	H	oil	30
10g	**6g**	3-OMeBn	H	H	oil	58
10h	**6h**	3,5-$(OMe)_2$Bn	H	H	103–104	45
10i	**6i**	H	CO_2Et	H	158–159	83
10j	**6j**	Me	CO_2Et	H	76–77	50
10k	**6k**	Bn	CO_2Et	H	127–128	65
10l	**6l**	4-OMeBn	CO_2Et	H	109–110	33
10m	**6m**	4-MeBn	CO_2Et	H	147–148	60
10n	**6n**	3-OMeBn	CO_2Et	H	112–113	55
10o	**6o**	3,5-$(OMe)_2$Bn	CO_2Et	H	120–122	40
10p	**6p**	H	Ph	H	176–177	60
10r	**6r**	$(CH_2)_2OMe$	Ph	H	oil	50
10s	**6s**	4-OMeBn	Ph	H	111–112	45
10t	**6t**	3,5-$(OMe)_2$Bn	Ph	H	135–136	90
10u	**6u**	3,4,5-$(OMe)_3$Bn	Ph	H	75–76	60
6b	**13a**	Me	Cl	H	75–76	40
6c	**13b**	SO_2Ph	Cl	H	oil	40
6i	**13c**	H	CO_2Et	Cl	175–176	50
6m	**13d**	4-MeBn	CO_2Et	Cl	139–140	45
6n	**13e**	3-OMeBn	CO_2Et	Cl	122–123	46
6p	**13f**	H	Ph	Cl	266–267	45
6t	**13g**	3,5-$(OMe)_2$Bn	Ph	Cl	oil	50

[a] Melting points reported were preformed on a Büchi–Tottoli capillary apparatus and are uncorrected. [b] Isolated yield after representative and were calculated after purification by flash chromatography. See the Supporting Information for full experimental procedures.

which were obtained in reasonable yields, were subjected to smooth chlorination with *N*-chlorosuccinimide to afford the chloro[1,2]oxazoles **13a**–**g** in moderate yields (40–50%).

All the synthesized compounds were submitted to the US National Cancer Institute (NCI) in Bethesda for cell-based antiproliferative screens. With the exception of the [1,2]oxazolo[4,5-*g*]indoles **6a**,**b**, all submitted [1,2]oxazolo indoles were selected for the one-dose (10^{-5} M) prescreening on the full panel of 60 human tumor cell lines divided into nine subpanels (leukemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast cancers).

Among these, eight compounds (**6h**,**k**,**n**,**o**,**t**,**u**, and **13e**,**g**) were selected for evaluation on the full panel at five doses (10^{-4}–10^{-8} M). All selected compounds gave positive GI_{50} values against all tested human cell lines with the exception of **6k**, **6t**, and **13g**, each of which were not responsive against one cell line (Table 2), respectively MCF7 and T47D of the breast cancer subpanel, and NCI-H322M of the non-small-cell lung cancer subpanel (Table 3).

Table 2. Overview of the antitumor screenings of **6h**,**k**,**n**,**o**,**t**,**u** and **13e**,**g**.

Compd	No. of cell lines[a] screened	positive	GI_{50} range [μM][b]	MG_MID[c]
6h	59	59	0.37–16.4	3.89
6k	59	58	0.88–52.4	5.13
6n	59	59	0.16–39.6	1.41
6o	54	54	0.03–31.1	0.25
6t	56	55	0.14–2.89	0.47
6u	59	59	0.25–46.5	1.35
13e	59	59	0.30–10.1	1.99
13g	59	58	2.15–50.0	7.08

[a] The number of cell lines *screened* and the number of cell lines in which the test compound gave a *positive* GI_{50} value. [b] The GI_{50} value is defined as the compound concentration causing 50% growth inhibition of tumor cells. [c] Mean graph mid-points (MG_MID).

An evaluation of the data listed in Table 3 indicates that the presence of a 3,5-dimethoxy-substituted benzyl moiety at the indole nitrogen (position 8) appears crucial for conferring good activity to the [1,2]oxazoloindole derivatives. In fact, the most active compounds were **6o** and **6t**, having mean graph mid-points (MG_MID) of 0.25 and 0.47 μM, respectively. Within the 3,5-dimethoxybenzyl series, when the ethoxycarbonyl substituent at position 7 (**6o**, MG_MID = 0.25 μM) was replaced by a phenyl group (**6t**), a slight decrease in activity was observed (MG_MID = 0.47 μM), whereas the corresponding unsubstituted derivative (**6h**) was significantly less active (MG_MID = 3.89 μM). Removal of the methoxy group from position 5 of the benzyl portion led to a substantial decrease in activity (compare **6o**, MG_MID = 0.25 μM, with **6n**, MG_MID = 1.41 μM, and **6h**, MG_MID = 3.89 μM, with **6g**, inactive). Moving the methoxy moiety from position 3 to 4 led to compounds devoid of activity. The introduction of a 4-methoxy group to generate a 3,5-dimethoxybenzyl derivative also led to a decrease in biological activity (compare **6t** and **7u**). Substitution at position 6 with a chloro group led to mixed results: in the 3-methoxy series (compare **6n** with **13e**), the chloro derivative maintained biological activity, whereas in the 3,5-dimethoxy series (compare **6t** with **13g**), a decrease in biological activity by more than one order of magnitude was observed.

Analysis of the GI_{50} values listed in Table 3 indicates that the most active compound, **6o**, was particularly effective against the leukemia subpanel. In fact, the calculated MG_MID value for the leukemia subpanel was higher than the overall cell lines MG_MID value (ΔMG_MID = 0.05 μM). The most sensitive cell lines were SR and K-562, having GI_{50} values in the nanomolar range, 50 and 60 nM, respectively. Compound **6o** was also highly selective against the colon cancer, ovarian cancer and CNS cancer subpanels, having subpanel MG_MID values at sub-micromolar levels, 0.25, 0.31 and 0.36 μM, respectively. Also in these subpanels the most sensitive cell lines showed GI_{50} values in the nanomolar range: KM12 of the colon cancer subpanel (90 nM), OVCAR-3 and NCI/ADR-RES of the ovarian cancer subpanel (40 and 80 nM, respectively), and SF-295 of the CNS cancer subpanel (60 nM). The same compound, however, got responses in the nanomolar range in other cell lines belonging to different subpanels: NCI-H522 of the non-small-cell lung cancer subpanel (50 nM), MDA-MB-435 of the melanoma subpanel (30 nM), A498 of the renal cancer subpanel (80 nM), and MCF-7 of the breast cancer subpanel (50 nM). Compound **6t**, which was slightly less active than **6o**, revealed selectivity against leukemia, colon cancer, and ovarian cancer subpanels, with MG_MID values at sub-micromolar levels (0.33, 0.35, and 0.44 μM, respectively), but in none of the cell lines reached the nanomolar range. In fact, it scored sub-micromolar figures in 51 out of 56 tested cell lines (93%) and in the remaining four cell lines, with the exception of the T-47D cell line, the response was at the low micromolar level.

The less active compounds **6u**, **6n**, and **13e**, however, exhibited MG_MID values of 1.35, 1.41, and 1.99 μM, respectively, showing in 30–50% of the tested cell lines GI_{50} values in the sub-micromolar range, and in the remaining cell lines, with some rare exceptions, the GI_{50} values remained in the low micromolar range.

In conclusion, reported a method for the synthesis of derivatives of the new ring system [1,2]oxazolo[4,5-*g*]indole. The antiproliferative activity exhibited by derivatives **6h**,**k**,**n**,**o**,**t**,**u** and **13e**,**g** against the totality of the NCI full panel of human tumor cell lines makes this class of compounds interesting for further studies. In particular, the potent activity of compounds **6o** and **6t** encourages the synthesis of new derivatives and makes them lead compounds for a new class of 3,5-dimethoxybenzyl[1,2]oxazolo[4,5-*g*]indoles with the aim of obtaining more potent antiproliferative agents.

Experimental Section

Full details of the protocols used to synthesize the compounds described and a brief summary of the US NCI cell-based antiproliferative screens are given in the Supporting Information.

Table 3. Inhibition of in vitro tumor cell growth by **6h**,**k**,**n**,**o**,**t**,**u** and **13e**,**g**.

Cell line	GI_{50} [μM][a]								Cell line	GI_{50} [μM][a]							
	6h	**6k**	**6n**	**6o**	**6t**	**6u**	**13e**	**13g**		**6h**	**6k**	**6n**	**6o**	**6t**	**6u**	**13e**	**13g**
Leukemia									***Melanoma cont.***								
CCRF-CEM	3.74	4.92	1.43	0.21	0.33	0.86	2.07	3.54	M14	2.39	3.69	0.43	0.16	0.32	0.47	2.07	4.22
HL-60(TB)	2.22	2.40	0.29	0.11	0.29	0.32	0.56	3.32	MDA-MB-435	0.37	0.88	0.22	0.03	0.14	0.25	0.30	2.26
K-562	0.59	2.48	3.43	0.06	0.32	0.36	0.39	3.08	SK-MEL-2	8.29	6.15	1.11	–	–	18.6	5.61	10.6
MOLT-4	4.09	4.73	1.16	0.56	0.40	0.97	3.48	3.43	SK-MEL-28	8.75	52.4	0.97	0.17	0.45	1.14	4.89	8.52
RPMI-8226	4.98	4.65	3.52	0.22	0.33	5.42	5.14	7.11	SK-MEL-5	2.75	2.97	0.59	0.12	0.34	0.88	1.24	5.50
SR	0.85	2.56	0.38	0.05	0.31	0.42	0.44	2.92	UACC-257	6.72	10.7	39.6	–	2.55	20.2	6.41	39.3
Non-small cell lung cancer									UACC-62	3.68	3.45	0.54	3.60	0.47	0.45	0.61	3.84
A549/ATCC	5.23	4.93	9.42	0.25	0.41	1.15	5.16	8.57	***Ovarian cancer***								
EKVX	4.30	5.65	9.10	0.38	0.41	1.39	3.05	4.97	IGROV1	7.44	4.98	0.78	0.22	0.48	2.64	1.23	4.89
HOP-62	4.40	5.30	0.86	0.46	0.49	2.37	2.89	44.0	OVCAR-3	2.99	3.06	0.38	0.04	0.21	0.37	0.38	4.63
HOP-92	4.25	5.24	10.5	–	2.89	12.7	9.25	50.0	OVCAR-4	16.4	7.69	9.6	0.45	0.60	3.12	6.46	6.57
NCI-H226	15.5	10.7	7.46	19.3	1.43	3.76	6.82	13.0	OVCAR-5	10.1	16.2	17.9	0.52	0.59	6.46	10.1	47.0
NCI-H23	3.89	6.37	3.42	0.33	0.49	2.57	3.55	6.15	OVCAR-8	4.81	7.19	10.3	0.40	0.53	5.38	7.27	15.9
NCI-H322M	7.75	11.7	4.99	0.49	0.31	46.5	3.53	>100	NCI/ADR-RES	1.95	2.01	0.30	0.08	0.30	0.33	0.50	2.58
NCI-H460	3.11	3.08	0.51	0.23	0.33	0.45	0.66	4.91	SK-OV-3	4.79	7.07	2.42	0.44	0.40	1.53	3.36	15.2
NCI-H522	3.57	1.96	0.24	0.05	0.18	0.29	0.35	2.15	***Renal cancer***								
Colon cancer									786-0	6.36	7.51	4.29	0.64	0.80	1.52	4.50	12.9
COLO 205	3.70	3.93	0.51	0.25	0.24	0.69	1.62	8.03	A498	1.16	1.55	0.16	0.08	0.16	0.27	0.38	2.96
HCC-2998	7.13	7.86	1.94	0.55	0.43	2.21	3.01	9.97	ACHN	5.54	5.84	2.66	2.22	0.83	0.96	4.54	9.31
4HCT-116	3.49	3.45	0.47	0.28	0.36	0.46	0.90	3.47	CAKI-1	2.79	3.24	–	0.16	0.35	0.57	1.85	5.24
HCT-15	3.03	3.58	0.52	0.20	0.39	0.64	0.84	4.84	RXF 393	5.20	6.88	1.72	0.15	0.24	1.36	2.88	5.96
HT29	3.17	3.23	0.37	–	–	0.45	0.80	3.71	SN12C	6.99	10.0	13.5	1.19	0.67	5.84	6.04	12.7
KM12	2.02	3.49	0.55	0.09	0.33	0.58	0.73	4.19	TK-10	8.04	14.4	7.51	0.57	0.99	7.70	6.59	26.5
SW-620	2.18	3.48	0.43	0.11	0.37	0.42	0.77	3.70	UO-31	6.09	4.32	1.91	6.63	0.54	3.23	3.36	4.16
CNS cancer									***Prostate cancer***								
SF-268	10.1	6.89	18.0	0.76	0.69	5.77	9.31	9.61	PC-3	11.0	9.68	5.19	–	–	3.62	5.39	7.12
SF-295	3.05	2.89	0.43	0.06	0.23	0.37	0.66	3.05	DU-145	3.99	11.4	2.27	0.25	0.32	1.73	2.42	26.6
SF-539	2.80	4.04	1.16	0.24	0.31	0.73	2.12	8.19	***Breast cancer***								
SNB-19	5.89	7.00	4.72	0.69	0.52	1.93	4.41	22.8	MCF7	2.20	>100	0.49	0.05	0.35	0.44	0.62	3.81
SNB-75	1.90	4.68	0.40	0.13	0.22	0.45	1.61	5.03	MDA-MB-231/ATCC	6.57	5.66	4.87	2.02	0.55	2.82	4.61	11.4
U251	4.43	4.73	0.91	0.25	0.44	0.95	4.75	6.20	HS 578T	2.38	2.75	0.74	0.21	0.26	0.51	1.21	3.71
Melanoma									BT-549	–	–	–	4.37	0.90	1.07	–	–
LOX IMVI	4.83	5.50	0.79	1.90	0.84	0.83	2.51	3.06	T-47D	3.69	4.66	0.61	31.1	>100	0.30	4.41	17.5
MALME-3M	4.25	6.28	0.57	–	–	18.4	0.64	4.16	MDA-MB-468	0.84	2.19	0.35	0.10	0.23	–	0.65	2.49

[a] Compound concentration causing 50% growth inhibition of tumor cells. Data were obtained from an in vitro disease-oriented tumor cell line screen by the US National Cancer Institute (NCI). Results of single experiments. See the Supporting Information for full experimental procedures.

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Keywords: antiproliferative activity · combretastatin A-4 · enaminoketones · hydroxylamine hydrochlorides · [1,2]oxazolo[4,5-*g*]indoles

[1] C.-M. Sun, L.-G. Lin, H.-J. Yu, C.-Y. Cheng, Y.-C. Tsai, C. Chu, Y.-H. Din, Y.-P. Chau, M.-J. Don, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1078 – 1081.

[2] J. Kaffy, R. Pontikis, D. Carrez, A. Croisy, C. Monneret, J.-C. Florent, *Bioorg. Med. Chem.* **2006**, *14*, 4067 – 4077.

[3] P. A. Brough, W. Aherne, X. Barril, J. Borgognoni, K. Boxall, J. E. Cansfield, K.-M. J. Cheung, I. Collins, N. G. M. Davies, M. J. Drysdale, B. Dymock, S. A. Eccles, H. Finch, A. Fink, A. Hayes, R. Howes, R. E. Hubbard, K. James, A. M. Jordan, A. Lockie, V. Martins, A. Massey, T. P. Matthews, E. McDonald, C. J. Northfield, L. H. Pearl, C. Prodromou, S. Ray, F. I. Raynaud, S. D. Roughley, S. Y. Sharp, A. Surgenor, D. L. Walmsley, P. Webb, M. Wood, P. Workman, L. Wright, *J. Med. Chem.* **2008**, *51*, 196 – 218.

[4] P. Diana, A. Carbone, P. Barraja, G. Kelter, H.-H. Fiebig, G. Cirrincione, *Bioorg. Med. Chem.* **2010**, *18*, 4524 – 4529.

[5] D. S. Hewings, M. Wang, M. Philpott, O. Fedorov, S. Uttarkar, P. Filippakopoulos, S. Picaud, C. Vuppusetty, B. Marsden, S. Knapp, S. J. Conway, T. D. Heightman, *J. Med. Chem.* **2011**, *54*, 6761 – 6770.

[6] B. H. Norman, J. M. Gruber, S. P. Hollinshead, J. W. Wilson, J. J. Starling, K. L. Law, T. D. Self, L. B. Tabas, D. C. Williams, D. C. Paul, M. W. Wagner, A. H. Dantzig, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 883 – 886.

[7] P. Barraja, L. Caracausi, P. Diana, A. Carbone, A. Montalbano, G. Cirrincione, P. Brun, G. Palù, I. Castagliuolo, F. Dall'Acqua, D. Vedaldi, A. Salvador, *Bioorg. Med. Chem.* **2010**, *18*, 4830 – 4843.

[8] *Photochemotherapeutic Heterocyclic Agents Having Antiproliferative and Antineoplastic Activity*, F. Dall'Acqua, G. Cirrincione, P. Barraja, A. Salvador, (Università Degli Studi di Padova and Università Degli Studi di Palermo, Italy), PCT Int. Appl. WO 2011/013159, **2011**; [*Chem. Abstr.* **2011**, *154*, 182251].

[9] P. Barraja, L. Caracausi, P. Diana, A. Montalbano, A. Carbone, A. Salvador, P. Brun, I. Castagliuolo, S. Tisi, F. Dall'Acqua, D. Vedaldi, G. Cirrincione, *ChemMedChem* **2011**, *6*, 1238 – 1248.

[10] M. Miura, N. Arai, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1437 – 1441.

[11] J. H. Liu, H. W. Chan, H. N. C. Wong, *J. Org. Chem.* **2000**, *65*, 3274 – 3283.

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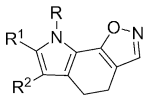
COMMUNICATIONS

Brand new ring: A series of 27 derivatives of the new ring system [1,2]oxazolo[4,5-*g*]indole were conveniently prepared and tested at the NCI for antiproliferative studies. Several of them showed good inhibitory activity toward all tested cell lines, reaching GI_{50} values generally at the micromolar and submicromolar levels and in some cases at nanomolar concentrations. The mean GI_{50} values, calculated on the full panel, were in the range 0.25–7.08 μM.



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Synthesis and Antiproliferative Activity of the Ring System [1,2]Oxazolo[4,5-*g*]indole

