ANTIPROLIFERATIVE AND ANTIBACTERIAL ACTIVITY OF 3-ARYLBENZO[*g*]INDAZOLES FUNCTIONALIZED WITH NITRO AND AMINO GROUPS AT POSITION 6

Viviana Cuartas* [1,2], María del Pilar Crespo [3], Eva-María Priego [4], Leentje Persoons [5], Dirk Daelemans [5], María-José Camarasa [4], Braulio Insuasty [1,2] and María-Jesús Pérez-Pérez [4]

[1] Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A. A. 25360 Cali, Colombia. [2] Centre for Bioinformatics and Photonics-CIBioFI, Calle 13 No. 100-00, Edificio E20, No. 1069, Cali, Colombia. [3] Grupo de Biotecnología e Infecciones Bacterianas, Departamento de Microbiología, Universidad del Valle, Cali, Colombia. [4] Instituto de Química Médica (IQM-CSIC), Juan de la Cierva 3, 28006-Madrid, Spain. [5] KU Leuven Department of Microbiology, Immunology and Transplantation, Laboratory of Virology and Chemotherapy, Rega Institute for Medical Research, KU Leuven, Herestraat 49, 3000 Leuven, Belgium.

INTRODUCTION

Colchicine-site inhibitors based on combretastatin A-4 (**CA-4**) have been extensively studied as antimitotic and vascular disrupting agents [1]. Among the different approaches, the design and synthesis of conformationally restricted ligands have led to very potent inhibitors.

Indazoles are benzo-fused pyrazoles for which a broad range of biological properties have been described, including antiproliferative and antibacterial activities [2,3]. These fused tricyclic pyrazole derivatives are characterized by their conformational restriction.

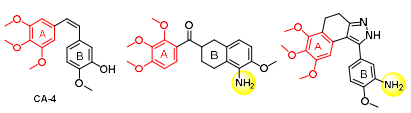
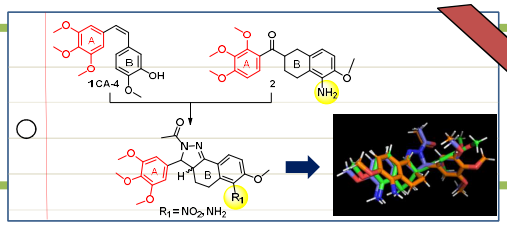


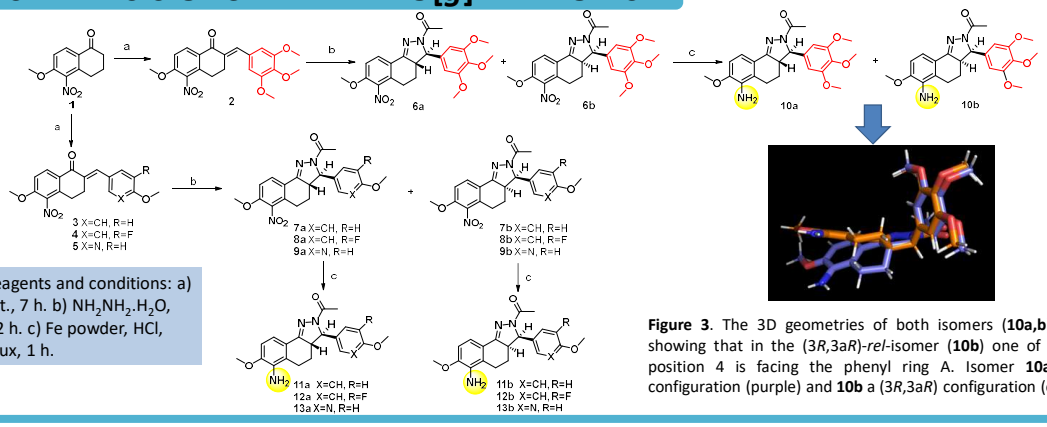
Figure 1. Combretastatin A-4 and *cis*-restricted analogues.

OBJETIVES

As part of our ongoing project on conformationally restricted ligands interacting at the colchicine binding site in tubulin [1], we have here designed and synthesized a novel series of tricyclic pyrazoline derivatives incorporating a nitro or an amino group at position 6 on the benzo[*g*]indazol ring and different aryl groups at position 3.



SYNTHESIS OF 3-ARYLBENZO[*g*]INDAZOLES



Scheme 1. Reagents and conditions: a) NaOH, EtOH, rt., 7 h. b) $NH_2NH_2.H_2O$, AcOH, reflux, 2 h. c) Fe powder, HCl, EtOH:H_2O, reflux, 1 h.

Figure 3. The 3D geometries of both isomers (**10a,b**) were optimized showing that in the (3*R*,3a*R*)-*rel*-isomer (**10b**) one of the hydrogens at position 4 is facing the phenyl ring A. Isomer **10a** has a (3*R*,3a*S*) configuration (purple) and **10b** a (3*R*,3a*R*) configuration (orange).

ANTIPROLIFERATIVE ACTIVITY

Table 1. Antiproliferative activity expressed in IC_{50} (μM)

	Capan-1	Hap1	HCT-116	NCI-H460	HL-60
6a	57.8±2.4	62.3±4.7	82.0±9.0	43.7±4.7	28.6±35.7
6b	42.9±12.3	61.0±6.6	>100	44.6±0.8	26.8±36.6
7a	40.8±5.0	39.3±4.8	29.9±9.0	**10.8±1.6**	30.9±14.8
7b	27.0±4.0	37.0±2.7	25.3±18.9	**11.8±1.6**	38.0±10.1
8a	42.9±1.6	24.9±11.8	26.9±4.8	**5.4±0.5**	42.5±0.5
8b	17.9±3.5	38.5±4.1	36.0±6.8	**14.9±2.9**	38.9±2.2
9a	73.4±26.6	38.9±0.4	36.5±1.2	30.9±10.0	42.7±3.9
9b	32.3±11.1	41.7±3.9	48.9±6.8	45.0±1.7	42.9±1.9
10a	30.3±9.0	46.2±2.7	45.2±2.6	36.6±10.4	52.5±16.3
10b	32.7±22.0	36.4±6.6	52.1±15.3	44.4±2.2	41.6±5.0
11a	45.1±20.6	39.2±7.3	43.5±6.0	42.1±7.5	55.9±20.8
11b	53.5±18.8	52.8±7.8	>100	54.1±4.6	44.8±27.6
12a	36.7±14.4	42.6±17.7	45.0±11.5	39.3±8.5	38.7±7.5
12b	42.6±3.9	42.6±20.3	66.1±31.3	33.7±10.88	65.9±20.2
13a	56.4±11.6	80.6±9.7	62.2±10.9	47.3±15.3	49.0±25.5
13b	60.7±1.7	54.9±5.0	80.6±9.7	43.9±9.6	65.8±17.1
Docetaxel (nM)	4.2±2.1	2.3±0.7	0.9±0.8	3.8±2.9	2.3±0.3
Stauroporine (nM)	0.7±0.2	0.4±0.1	0.10	1.5±0.4	7.4±1.7

Capan-1: pancreatic adenocarcinoma; *Hap1*: chronic myeloid leukemia; *HCT-116*: colorectal carcinoma; *NCI-H460*: lung carcinoma; *HL-60*: acute myeloid leukemia.
*IC_{50}: Concentration of each compound that inhibits 50% of cell proliferation.

ANTIBACTERIAL ACTIVITY

Table 1. Antibacterial activity of nitro derivatives expressed in MIC (μg/mL)

	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*N. gonorrhoeae* ATCC 49226
3	>1000	>1000	>1000	≥500
4	>1000	>1000	>1000	>1000
5	>1000	>1000	>1000	>1000
2	>1000	>1000	>1000	>1000
6a	>1000	>1000	>1000	≥500
6b	>1000	>1000	>1000	≥500
7a	>1000	>1000	>1000	≥500
7b	>1000	>1000	>1000	≥500
8a	>1000	>1000	>1000	**250***
8b	>1000	>1000	>1000	>1000
9a	>1000	>1000	>1000	≥500
9b	>1000	>1000	>1000	**62.5***

*Hemolytic capacity of 0% in human red blood cells (RBC).
None of the tested compounds was active against *S. aureus*, *E. coli* and *P. aeruginosa* (MIC ≥1000 μg/mL).

CONCLUSIONS

We have successfully synthesized a new series of benzo[*g*]indazole derivatives **6-13a,b** with the 6-nitro and 6-amino groups by cyclocondensation of 5-nitro benzylidene tetralones with hydrazine in acetic acid. All compounds were evaluated for their antiproliferative activity against selected cancer cell lines and some nitro-based indazoles have shown IC_{50} values between 5-10 μM against the lung carcinoma cell line *NCI-H460*. Moreover, compounds **8a** and **9b** have shown MIC values of 250 and 62.5 μg/mL against *N. gonorrhoeae* with no hemolytic activity in human red blood cells (RBC) suggesting low membrane interactions and toxicity.

Acknowledgments

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