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Publication date:
2011

Document Version
Early version, also known as pre-print

[Link to publication](#)

Citation for published version (HARVARD):

Dolusic, E, Larrieu, P, Blanc, S, Moineaux, L, Sapunarcic, F, Pouyez, J, Colette, D, Fraser, G, Stroobant, V, Pilotte, L, Colau, D, Frère, J-M, Masereel, B, Van den Eynde, B, Wouters, J & Frédérick, R 2011, 'Indole-pyridinyl-ethanones as novel inhibitors of indoleamine-2,3 dioxygenase (IDO), a promising target for anti-cancer immunotherapy' 47th RICT: Drug Discovery and Selection., Lyon, France, 6/07/11, pp. Book of Abstracts, 47èmes RICT, 6-8 juillet 2011, Lyon, France, IS08, p. 136.

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Indole-pyridinyl-ethanones as Novel Inhibitors of Indoleamine 2,3-Dioxygenase (IDO), a Promising Target for Anti-Cancer Immunotherapy



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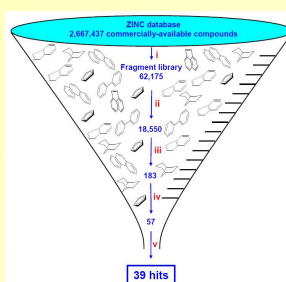
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Introduction. Immunotherapy is a promising novel strategy for cancer therapy. However, this approach showed a limited efficacy *in vivo* because cancer cells can develop mechanisms allowing tumors to resist or escape immune rejection.

IDO (EC 1.13.11.52), a heme dioxygenase, is expressed constitutively in many human tumors and its role in a tumoral immune resistance mechanism has been proved,¹ justifying the interest in IDO inhibitors.²

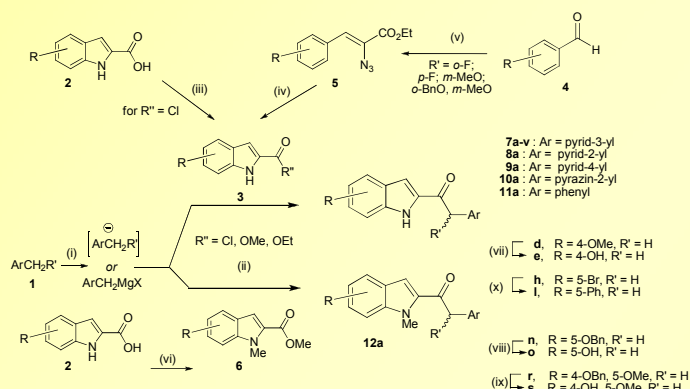
Aim of the Work. We sought to develop a novel series of IDO inhibitors starting with a virtual screening of a database of commercially-available compounds.



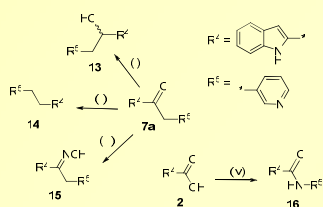
Virtual screening. Based on recent results such as structural findings³ and rational design of IDO inhibitors,⁴ we applied virtual screening of the ZINC database (<http://zinc.docking.org>) for the discovery of new inhibitors (Figure 1). The most promising candidates were purchased and tested *in vitro*. 1-(1*H*-Indol-2-yl)-2-pyridin-3-yl-ethanone (**7a**; IC₅₀ = 65 μM) was selected for pharmacomodulation (Schemes 1 and 2 and Table 1).

Figure 1. IDO Virtual screening flowchart. (i) fragment library, (ii) goldscore > 50, (iii) Cscore ≥ 4, (iv) visual analysis and selection, (v) really commercially-available.

Synthesis



Scheme 1. General synthetic scheme for indol-2-yl ethanones.⁵ Reagents and conditions: (i), LDA, THF / hexanes, -78 to 0°C, 1 h; (ii) THF / hexanes, 0°C to r.t., 16-24 h; (iii) SOCl₂, Δ, 15 min; (iv), hexane, 200°C (μW), 5 min; (v), N₃CH₂CO₂Et, NaOEt, EtOH, -10 to 4°C, 1.5 - 20 h; (vi), MeI, K₂CO₃, DMF, 80°C, 5 days; (vii), AlCl₃, CH₂Cl₂, 0°C to r. t., 24 h; (viii), HCO₂NH₄, Pd black, MeOH, r. t., 1 h; (ix) H₂ (1 atm), 3% Pd/C, EtOH, r. t., 45 min; (x) Ph(OH)₂, Pd(PPh₃)₄, K₂CO₃, EtOH/toluene 1/1, Δ, 20 h.



Scheme 2. Synthesis of compounds bearing different linker groups. Reagents and conditions: (i) HCO₂NH₄, Pd black, MeOH, r. t., 3 days; (ii), H₂NNH₂, KOH, (CH₂OH)₂, μW, 1h then aq. NH₄Cl; (iii), NH₂OH·HCl, pyridine, EtOH, μW (120°C), 30 min; (iv), SOCl₂, Δ, 15 min then 3-aminopyridine, DIPEA, THF, 0°C → r. t., 30 min.

Conclusion. The synthesis and SAR of a novel series of IDO inhibitors are described.

Starting from the lead compound **7a** (IC₅₀ = 65 μM) identified through a virtual screening procedure, up to a 5-fold improvement in *in vitro* potency could be achieved by introducing small substituents in the 5- and 6-positions of the indole nucleus. Most modifications of the aromatic moieties are tolerated. On the contrary, the presence of an iron chelating group on the linker seems to be mandatory, as corroborated by the docking experiments (Fig. 2). A number of compounds are also moderately active in the *in vivo* assay, thus opening possibilities for further pharmacological evaluation.

References. [1] Uyttenhove, C. *et al*, *J. Nat Med* **2003**, *9*, 1269-1274; [2] Macchiarulo *et al*, *Inflamm. Res.* **2009**, *37*, 219-229; [3] Sugimoto H. *et al*, *PNAS* **2006**, *103*, 2611-2616. [4] Röhrig, U. *et al*, *J. Med. Chem.* **2010**, *53*, 1172-1189; [5] Sundberg, R. *et al*, *J. Org. Chem.* **1978**, *43*, 4859-4865. This work is supported in part by the FNRS and Biowin (CANTOL : Convention n° 5678).

Table 1. Biological evaluation

compound	R	R'	enzymatic assay	
			IC ₅₀ (μM)	cell assay inh. % @ 20 μM
7a	H	H	65	13
7b	3-Br	H	>100	NI
7c	4-F	H	153	12
7d	4-OCH ₃	H	58	NI
7e	4-OH	H	83	NI
7f	5-F	H	36	24
7g	5-Cl	H	25	24
7h	5-Br	H	18	NI
7i	5-CH ₃	H	87	21
7j	5-OCH ₃	H	49	-
7k	5-NO ₂	H	>100	NI
7l	5-Ph	H	96	NI
7m	5-OCF ₃	H	13	12
7o	5-OH	H	37	NI
7p	6-F	H	43	NI
7q	7-OCH ₃	H	82	-
7r	4-OBn, 5-OCH ₃	H	>100	NI
7s	4-OH, 5-OCH ₃	H	63	11
7t	4,6-diCl	H	139	NI
7u	4,6-di(OCH ₃)	H	45	toxic
7v	H	CH ₃	141	NI
8a	H	H	37	10
9a	H	H	>100	NI
10a	H	H	26	NI
11a	H	H	29	NI
12a	H	CH ₃	34	NI
13	H	H	>100	NI
14	H	H	>100	NI
15	H	H	>100	25
16	H	-	94	NI

NI = no inhibition

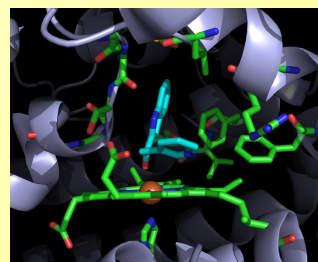


Figure 2. Docking of compound **7a** inside the IDO active site showing interaction of the carbonyl oxygen with the heme iron