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# A multicomponent approach in the discovery of indoleamine 2,3-dioxygenase 1 inhibitors: Synthesis, biological investigation and docking studies

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ABSTRACT

Indoleamine 2,3-dioxygenase plays a crucial role in immune tolerance and has emerged as an attractive target for cancer immunotherapy. In this study, the Passerini and Ugi multicomponent reactions have been employed to assemble a small library of imidazothiazoles that target IDO1. While the *p*-bromophenyl and the imidazothiazole moieties have been kept fixed, a full SAR study has been performed on the side-chain, leading to the discovery of nine compounds with sub-micromolar $IC_{50}$ values in the enzyme-based assay. Compound **7d**, displaying a α-acyloxyamide substructure, is the most potent compound, with an $IC_{50}$ value of 0.20 μM, but a low activity in a cell-based assay. Compound **6o**, containing a α-acylaminoamide moiety, shows an $IC_{50}$ value of 0.81 μM in the IDO1-based assay, a full biocompatibility at 10 μM, together with a modest inhibitory activity in A375 cells. Molecular docking studies show that both **7d** and **6o** display a unique binding mode in the IDO1 active site, with the side-chain protruding in an additional pocket C, where a crucial hydrogen bond is formed with Lys238. Overall, this work describes an isocyanide based-multicomponent approach as a straightforward and versatile tool to rapidly access IDO1 inhibitors, providing a new direction for their future design and development.

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Indoleamine 2,3-dioxygenase 1 (IDO1) is an intracellular heme-containing enzyme that catalyzes the oxidation of L-tryptophan (L-Trp) to *N*-formyl-L-kynurenine (NFK), the first and rate-limiting step along the kynurenine pathway.[1] There is a growing body of evidence supporting that IDO1 plays a crucial role in pathological immune escape.[2] Notably, in cancer IDO1 contributes to immunosuppression in tumor microenvironment and its overexpression is correlated with tumor progression, invasiveness and reduced overall survival.[2a] It has been largely demonstrated in animal models that IDO1 inhibition can break an acquired immune tolerance, significantly increasing the immunological responses induced by various chemotherapeutic drugs and immunotherapeutic agents. Overall, these results clearly suggest that IDO1 represents a promising therapeutic target in cancer immunotherapy.[3]

Since the discovery of 4-phenylimidazole as a weak IDO inhibitor in 1989,[4] the search for small-molecule inhibitors has been intensely pursued both in academia and in pharmaceutical companies and a number of structurally heterogeneous compounds have been discovered.[5] Nevertheless, among the thousands of compounds reported in the scientific and patent literature as IDO inhibitors, to date only five molecules have reached human clinical trials, confirming that the translation of *in vitro* to *in vivo* IDO inhibition is a big challenge.[6] Besides indoximod,[7] epacadostat[8] and GDC-0919,[9] very recently PF-06840003[10] and BMS-986205[11] have entered Phase I clinical trials.

In 2014 the imidazothiazole compounds **1** and **2** were reported by Tojo et al. (Fig. 1A)[12] displaying $IC_{50}$ values of 1.9 μM and 77 nM, respectively, in an enzyme-based assay. The crystal structure of the complex IDO1/**1** was described (Fig. 1B), demonstrating that the nitrogen of the imidazole ring is bound to the heme iron and the tolyl group is located in pocket A of the active site. Interestingly, a shift of Phe226 occurs and the resulting induced fit in pocket B allows for the allocation of the *p*-chlorophenyl ring adjacent to Phe226. In contrast, **2** showed an improved inhibitory activity: indeed, the rigid urea moiety allows the *p*-cyanophenyl group to interact with both Phe226 (π-π interaction) and Arg231 (electrostatic interaction). Surprisingly, despite the promising inhibitory activity on the purified enzyme, no inhibition was detectable when we prepared and tested compound **2** in a cell-based assay at concentration of 10 μM.

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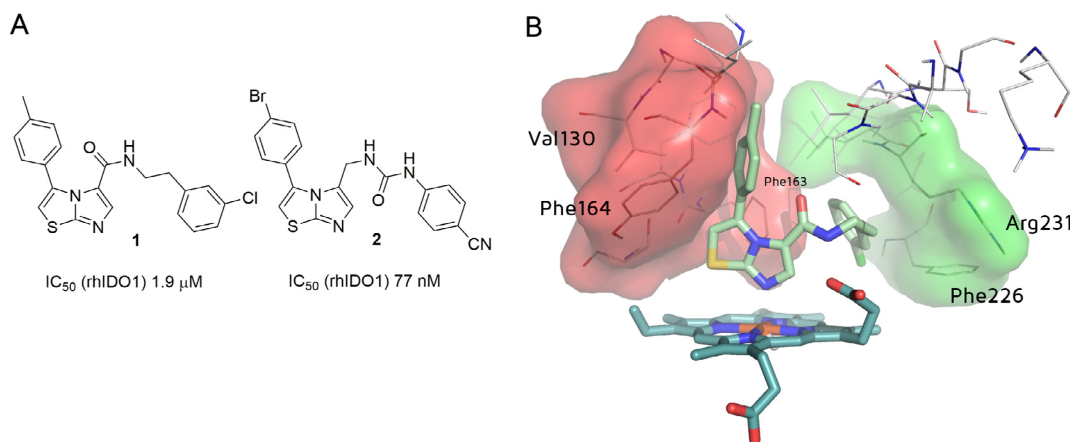


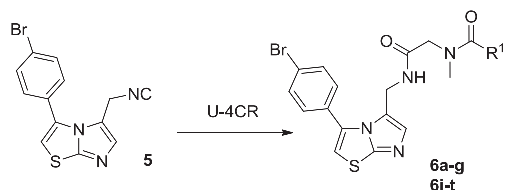

**Fig. 1.** (A) Structure of imidazothiazole compounds **1** and **2**. (B) Compound 1 bound to IDO1 (PDB code: 4PK6). Heme is depicted as cyan sticks and compound **1** as pale green sticks. Red surface: pocket A; green surface: pocket B.

Hence, the peculiar profile of this class of molecules prompted us to investigate the synthesis and the biological evaluation of a range of imidazothiazoles displaying a modified side chain, with the aim of both finding new analogues with an improved cellular activity against IDO1 and probing interactions with the active site aminoacids.

For the synthesis of a first series of compounds we exploited the Ugi multicomponent reaction,[13] which allows for the rapid and versatile generation of imidazothiazoles displaying different α-acylaminoamides in the side chain.

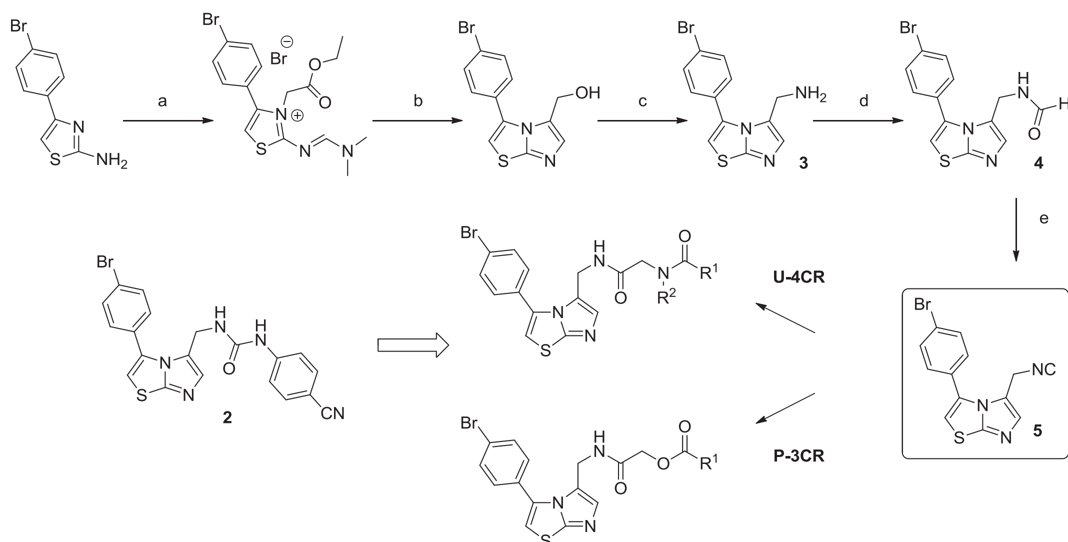
Starting from the required amine **3** described in literature,[12] the isocyanide **5** was prepared by formylation with ethyl formate followed by dehydration in the presence of phosphorous oxychloride and triethylamine (Scheme 1).

With the isocyanide **5** in our hand, we performed the Ugi reaction with aqueous methylamine as the amine component and formalin as the carbonyl partner, in order to minimize the steric hindrance in the side chain and allow for the penetration in the deep and tight pocket B of IDO active site. As a proof of principle, acetic acid, different substituted benzoic acids and phenylacetic acid were used (Scheme 2). Products **6a**–**g** precipitated from the reaction mixture as white solids and were obtained simply by filtration.




**Scheme 2.** Reagents and conditions: 37% aqueous formaldehyde solution, 40% aqueous methylamine solution, R1-COOH, $CH_3OH$.

As phenylacetic acid gave the best enzymatic inhibitory activity (see Table 1), we decided to evaluate whether the substitution of the methyl on the nitrogen of **6g** with a hydrogen would have improved the inhibitory activity. It is well known how difficult is to use ammonia in the Ugi reaction, especially when coupled with the highly reactive formaldehyde as the carbonyl compound, due to a number of possible side reactions.[14] Indeed, when 33% aqueous ammonium hydroxide was used, no product was afforded, even when the less nucleophilic 2,2,2-trifluoroethanol[15] was employed as solvent instead of methanol. Even the use of 2,4-dimethoxybenzylamine as ammonia equivalent and the subse-




**Scheme 1.** Reagents and conditions: (a) (I) DMF-DMA, DMF, 80 °C, 99%; (II) ethyl bromoacetate, 80 °C, 76%; (b) (I) DBU, DMF, 60 °C, 99%; (II) $LiAlH_4$, dry THF, 0 °C, 81%; (c) (I) DPPA, DBU, DMF, 60 °C, 67%; (II) $PPh_3$, $H_2O$, THF, 45 °C, 96%; (d) HCOOEt, reflux, 99%; (e) $POCl_3$, TEA, dry $CH_2Cl_2$, −30 °C, 77%.

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