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Development of a series of novel *o*-phenylenediamine-based indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors

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ABSTRACT

A novel series of *o*-phenylenediamine-based inhibitors of indoleamine 2,3-dioxygenase (IDO) has been identified. IDO is a heme-containing enzyme, overexpressed in the tumor microenvironment of many cancers, which can contribute to the suppression of the host immune system. Synthetic modifications to a previously described diarylether series resulted in an additional degree of molecular diversity which was exploited to afford compounds that demonstrated significant potency in the HeLa human cervical cancer IDO1 assay.

Indoleamine 2,3-dioxygenase is a heme-containing enzyme that catalyzes the initial and rate limiting step in the tryptophan (Trp)/kynurenine (Kyn) pathway. Activation of this pathway promotes the formation of Kyn and other bioactive metabolites which leads to a local environment depleted of Trp.[1] This process blocks T cell activation, increases the conversion of naïve T cells into regulatory T cells and induces T cell cycle arrest and apoptosis, thereby decreasing the presence of effector T cells. These effects result in a dampening of the immune response which can lead to tumor progression and recurrence. Indeed, the critical role that the immune system plays in the development and progression of tumors necessitated its inclusion in the update to Hanahan and Weinberg's seminal paper detailing the hallmarks of cancer.[2,3] The importance of utilizing the immune system to curtail the aberrant growth of cells can further be seen in the development and early success observed with immuno-oncology drugs in clinical trials, such as checkpoint inhibitors targeting CTLA-4 (ipilumamab[4]), PD-1 (nivolumab,[5] pembrolizumab[6]) and PD-L1 (atezolizumab[7]).

IDO is overexpressed in the tumor microenvironment of many cancers. Increased expression of IDO has been reported in numerous tumor types including: colon, lung, prostate, ovarian, acute myeloid leukemia, colorectal and endometrial and is often associated with decreased survival.[8] Inhibition of IDO has been shown to behave synergistically when used in combination with therapies[9] which target immune checkpoints, and as such several IDO inhibitors have advanced into clinical and pre-clinical trials (Fig. 1).[10–12]

Herein, we describe the synthesis and structure-activity relationships of novel *o*-phenylenediamine-based IDO inhibitors.

We have previously disclosed potent indoleamine 2,3-dioxygenase inhibitors containing a diaryl ether motif (Fig. 2).[13] A critical element common to all key analogs in that paper was the presence of a biphenyl carboxylic acid. This feature, and the lack of an obvious heme-coordinating element, distinguished these compounds from other IDO inhibitors in the literature. The inclusion of a heme-binding group had been common among inhibitors subsequent to the disclosure of two crystal structures of IDO1 in 2006.[14] Those X-ray structures showed 4-phenylimidazole bound to IDO1 with the phenyl ring located within a deep hydrophobic pocket and the imidazole coordinated to the heme iron.

In this paper additional efforts to define the structural features required for potency in this series will be disclosed. As in our previous work, we used a cellular assay of kynurenine production to

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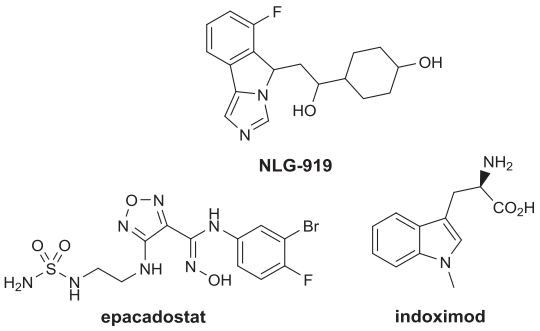


Fig. 1. IDO inhibitors in clinical trials.

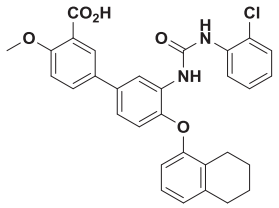
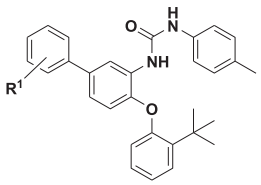


Fig. 2. Previously disclosed IDO inhibitor.

drive the SAR studies.[15] This decision was made with the understanding that by nature of utilizing a cell-based assay, structural changes that impact potency may not be entirely due solely to binding affinity, but may also reflect on other factors, including cell penetration. In the assay used for this work, we induced the expression of IDO1 with interferon-γ in the HeLa human cervical cancer line. It is thought that the kynurenine produced in this system is largely generated by IDO1. Our initial studies examined the placement of the critical carboxylic acid. The data from that exercise demonstrated a clear preference for the acid to be presented in the 2-position of the biphenyl (Table 1).

With the positioning of the acidic group established, efforts to replace the *t*-butylphenoxy were undertaken (Table 2). Replacement of oxygen with nitrogen afforded the potential to modulate the potency of this series through an additional point of substitution. Additionally, that nitrogen offered the possibility of addressing potential downstream issues, such as metabolic stability and pharmacokinetic profile, through an overall reduction in lipophilicity. Direct substitution of O with NH, however, resulted in nearly a 10-fold loss in potency (**1** to **4**). Capping the nitrogen with a methyl group resulted in a further drop in IDO1 activity. Compound **6**, wherein the aromatic ring was saturated to a cyclohexyl group, provided an analog equipotent to the initial *t*-butylanilino derivative. Interestingly, methylation of the nitrogen in this context

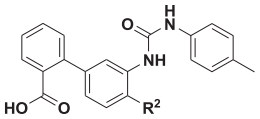
Table 1
SAR of the acidic moiety R^1.

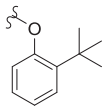
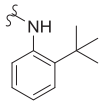
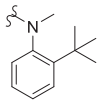
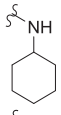
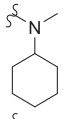
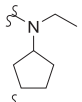
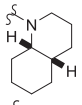
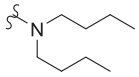
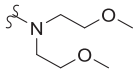
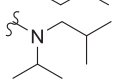
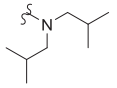
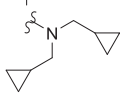


Compound	R^1	HeLa IC_{50} (μM)[a]
1	2-CO_2H	0.070 ± 0.031
2	3-CO_2H	>1.00
3	4-CO_2H	>1.00

[a] For determinations where n ≥ 2, standard deviation is given.

Table 2
SAR of the amine group R^2.



Compound	R^2	HeLa IC_{50} (μM)[a]
1		0.070 ± 0.031
4		0.600
5		> 1.00
6		0.504 ± 0.057
7		0.014 ± 0.001
8		0.023
9		0.159 ± 0.017
10		0.045
11		>1.00
12		0.042
13		0.013 ± 0.004
14		0.348

[a] For determinations where n ≥ 2, standard deviation is given.

afforded a 36-fold boost in potency in compound **7**. Changes to the ring size of the cycloalkyl group (C-3 through C-7), as exemplified by compound **8**, had little impact on the activity of this series. Internalization of the nitrogen into a ring, as with *cis*-decahydroquinoline **9**, resulted in a 10-fold drop in potency. The activity observed with the opening up of the ring system to afford a dialkyl species, as with di-*N*-butyl derivative **10**, in concert with the obliteration of activity observed with the more polar bis-methoxyethyl amine **11**, was suggestive of a preference for substituents which could occupy distinct lipophilic binding pockets. Incorporating branched aliphatic amines proved to be a way to improve IDO1 potency without negatively impacting the overall molecular weight of these compounds. Example **12** proved equipotent to compound **10**, while reducing the overall carbon count. Altering