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Discovery of Hydroxyamidine Derivatives as Highly Potent, Selective Indoleamine-2,3-dioxygenase 1 Inhibitors

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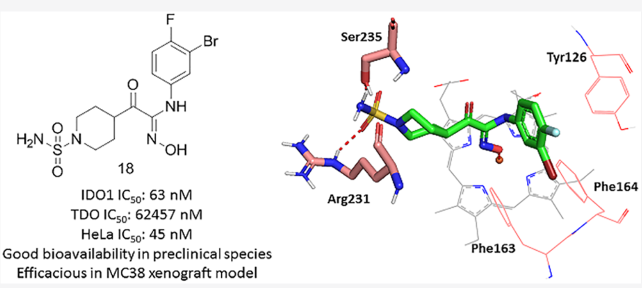
ABSTRACT: In this study, a series of novel hydroxyamidine derivatives were identified as potent and selective IDO1 inhibitors by structure-based drug design. Among them, compounds **13−15** and **18** exhibited favorable enzymatic and cellular activities. Compound **18** showed improved bioavailability in mouse, rat, and dog (F% = 44%, 58.8%, 102.1%, respectively). With reasonable *in vivo* pharmacokinetic properties, compound **18** was further evaluated in a transgenic MC38 xenograft mouse model. The combination of compound **18** with PD-1 monoclonal antibody showed a synergistic antitumor effect. These data indicated that compound **18** as a potential cancer immunotherapy agent should warrant further investigation.



KEYWORDS: *IDO1, cancer immunotherapy, hydroxyamidine derivatives, lead optimization, structure-based drug design, bioisostere*

Over the past two decades, immunotherapy has been transformed into a mainstream treatment method with great potential for a variety of cancers.[1] However, there are occasions where the immune system cannot effectively control the development of tumors due to immune tolerance. Indoleamine 2,3-dioxygenase 1 (IDO1), an immune regulatory enzyme, plays an important role in regulating the immune system through the control of the kynerenine pathway.[2−4]

IDO1 is a heme-containing monomeric enzyme that controls the rate-limiting step of catabolizing tryptophan to *N*-kynurenine along the kynurenine pathway, which is responsible for local immunosuppression.[5−7] Plenty of studies indicate that the abnormal expression of IDO1 is related to tumor cells evading the immune system. IDO1 can oxidize and destroy tryptophan, which is an important amino acid for T cell activation. In this way, T cells lose the ability to kill tumors. In principle, blocking IDO1 can active T-cells and promote the immune system to kill cancer cells. Therefore, IDO1 is an attractive target for cancer immunotherapy.[8]

Epacadostat (INCB-24360) is developed as a selective IDO1 inhibitor. It has been used with checkpoint modulators for cancer treatment in clinical studies and showed an early sign of benefit in phase I/II trials.[9−11] However, epacadostat in combination with pembrolizumab in the ECHO-301 phase III trial has failed to increase the overall and progression-free survival when compared to pembrolizumab alone.[12] The disappointing phase III results have cooled down the research interest in the IDO1 inhibitors. However, IDO1 related therapy is still a promising field, as evidenced by multiple ongoing clinical trials from several companies.[13,14] For example, an IDO1 inhibitor from Bristol-Myers Squibb, BMS-986205, is currently in an active phase 3 trial in Muscle Invasive Bladder Cancer (MIBC).[15]

The crystal structure of IDO1 in complex with epacadostat was published in 2018 with a PDB entry of 6E40,[16] which opens the door for structure-based design of novel IDO1 inhibitors. In this crystal structure, epacadostat is positioned in the active pocket by three key contacts: (1) a $\pi-\pi$ interaction between its substituted phenyl ring and the residue Tyr126; (2) a hydrogen bond formed by sulfamide and Arg231; (3) a dative bond formed between the *N*-hydroxylamidine oxygen and the heme iron (Figure 1). The furazan ring is often found in pyrotechnic compounds and propellants but is rarely used in medicines.[17] Up to now, most medchem efforts have been focused on optimizing the hydroxyamidine motifs as well as the halogenated phenyl region.[18−22] The sulfamide side chain and core modification especially the furazan ring replacement remain to be explored. So, herein, we describe our work that

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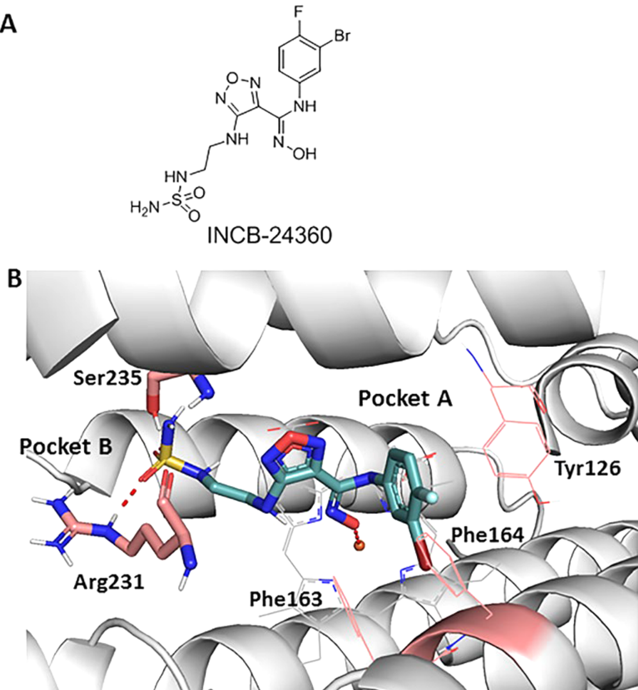

Figure 1. (A) Hydroxyamidine derivative as IDO1 inhibitor; (B) INCB-24360 (navy) binding mode in the crystal structure (PDB 6E40).

has led to the identification of novel IDO1 inhibitors by bioisosteric replacements of the furazan group, as well as the alternative groups to the sulfamide side chain.

We designed a set of electron-withdrawing carbonyl groups to replace the furazan ring (compounds **1−6**; the synthesis route of compounds **1−6** is shown in Schemes S1−S6), aiming to keep the acidity of the hydroxylamidine group. Subsequently, biological assays were employed to evaluate the biological activities of compounds **1−6,** including enzymatic assays with purified recombinant human IDO1/TDO proteins and cellular IDO1 inhibition assays using HeLa cell lines. As shown in Table 1, compound **1** with thiazole substitution exhibited the best enzymatic activity (IDO1 IC_{50} = 51 nM) among those designs. It showed micromolar level activity in the HeLa cell line, which could be related to the membrane permeability of the compound. Compounds **2−4** with aromatic or heterocyclic aromatic substitutions also showed less potencies compared to epacadostat in enzymatic and cellular assays. Compound **5** with saturated six-member ring showed a modest enzymatic activity, and the best cellular activity among the designed compounds. As shown by the structure−activity relationship (SAR) data of compound **6**, the carbonyl group of compound **5** was quite important for its enzymatic and cellular potencies.

A molecular modeling study was carried out to further understand the SAR of these compounds. It was well-known that the interaction between the deprotonated oxygen and the heme iron is important for biological activity.[18,19] So we hypothesized that the oxygen of the *N*-hydroxyamidine was in the deprotonated state and the heme iron was in its ferrous state (Fe^{2+}). Compounds **1−6** were docked into the binding pocket using MOE.[23,24] A commonly used docking score in MOE, GBVI/WSA dG[28] alone, could not be used to distinguish actives from inactives (Table 1). Then, the pK_a values[25] of the heme interaction oxygens from each compounds were calculated; these are shown in Table 1. The calculated pK_a values showed some correlation with the enzymatic activity. All the activities were similar to that of the reference compound except compound **3** which might be due to suboptimal binding reflected in the weaker docking score.

Based on the enzymatic and cellular data, as well as the calculated pK_a, compound **5** was selected as the starting point for the next round SAR study. A series of cyclohexane substitutions were designed and synthesized (Table 2, compounds **7−10**, Schemes S7−S10), none of them showed improved enzymatic potency. As inspired by our previous work,[26] substituted piperidinyls were investigated (Table 2). Weak electron-withdrawing substitutions such as benzene (compound **11**, Scheme S11) and benzaldehyde (compound **12**, Scheme S12) showed similar potencies in IDO1 enzymatic assays as compound **5**, with reduced cellular potencies. Interestingly, the phenylformamide substitution (compound **13**, Scheme S13) showed 3-fold increase in the enzymatic potency compared to compound **5**. Further substitution at the para-position with 1-methylpyrazol-4-yl (compound **14**, Scheme S14) resulted in a 10-fold and a 4-fold increase in the enzymatic and cellular potencies, respectively. The benzylformamide substitution (compound **15**, Scheme S15) and the sulfonyl substitution (compound **18**, Scheme 1) showed similar potency levels in both enzymatic and cellular assays as compound **14.**

To further analyze binding poses of the designed compounds, we also performed molecular modeling studies on compound **14** and **18**. As shown in Figure 2, both compounds shared a similar binding pose in the pocket A. As a result, the deprotonated oxygen of the *N*-hydroxylamidine was positioned to bind the heme iron similarly as epacadostat. In the pocket B, compound **18** formed the aformentioned hydrogen bond with the residue Arg231 (Figure 2B). Interestingly, a significant cation−π interaction was formed at a distance of 2.47 Å between the Arg231 and the phenyl group in compound **14** (Figure 2A). Cation−π interactions were quite common in proteins, protein−ligands and protein−DNA complexes, and important for protein folding, molecular recognition and catalysis.[29] Thus, it was reasonable to expect that the similar cation-π interactions in the pocket B could contribute to the improvement of binding potencies in compounds, **13−16.**

To further evaluate the ADMET properties of compounds **13−15** and **18**, we profiled them in CYP and hERG inhibition assays. As shown in Table S2, all the compounds except **15** had clean CYP and hERG profiles. In addition to compound **18**, we selected the most potent compound **14** for further *in vivo* studies among the compounds forming cation−π interactions. Two animal models (rat and dog) were used to evaluate the pharmacokinetics of those two compounds. As listed in Table 3, compound **14** showed poor oral pharmacokinetics in dog, while compound **18** had a better profile and good oral exposure in both species.

The synthesis route and *in vitro* and *in vivo* Profile for compound **18** are shown in Scheme 1 and Table 4. *In vitro* data indicated that compound **18** was a highly potent and selective IDO1 inhibitor with clean CYP and hERG profiles. Its pharmacokinetic profiles in animal models (mouse, rat, and dog) demonstrated an increased oral exposure and bioavailability from mouse, rat, to dog (F = 44%, 58%, and 102.1%, respectively). Meanwhile, compared with epacadostat, compound **18** exhibited a superior pharmacokinetic profile in a

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Table 1. SAR of the Furazan Ring Replacement Groups with Charge and pK_a Data

Compd	R	IDO1 IC_{50} (nM)[a]	TDO IC_{50} (nM)[a]	HeLa IC_{50} (nM)[a]	GBVI/WSA dG Score	pKa[b]
Epacadostat (INCB-24360)		26	>100000	5	-6.0	5.45
1		51	11808	1772	-6.1	5.93
2		117	63091	272	-5.8	6.45
3		467	>100000	1677	-5.5	5.88
4		410	79985	1428	-5.5	7.19
5		132	79348	63	-6.3	6.20
6		497	>100000	578	-6.0	10.50

[a]Values are expressed as the mean of at least two independent determinations. [b]pK_a was calculated using JChem For Excel.[27,28]

nonrodent species (dog) with lower clearance and better bioavailability. Compound **18** had the potential to show better pharmacokinetic profile in humans than epacadostat.

To further understand the mechanism of action, the *in vivo* pharmacodynamics (PD) study of compound **18** was carried out in a mouse model. After administrated orally to C57 mice (300 mg/kg single dose), compound 18 was able to reduce the level of kynurenine down to 87.8% at 2 h after dosing (Figure 3). The concentration change of kynurenine was proportional to the exposure level of the compound.

The antitumor effects of compound **18** in combination with PD-1 antibody were further evaluated using the MC38 tumor growth inhibition model in *h*PD-1 transgenic mice. Due to the lower exposure seen in mice, higher doses of compound **18** were used to match the exposure level of epacadostat. As shown in Figure 4, Oral treatment of compound **18** combined with PD-1 antibody (PD-1, 3 mg/kg, ip, qod ×8; compound **18**, 300 or 600 mg/kg, po, bid ×14) showed good dose-dependent tumor growth inhibition (150 mg/kg, TGI = 60.3%; 300 mg/kg, TGI = 71.7%; 600 mg/kg, TGI = 86.8%). The PD-1 combo treatment groups with 300 or 600 mg/kg compound **18** showed better antitumor efficacy compared to either PD-1 alone (3 mg/kg, ip, qod ×8, TGI = 57.3%) or the combination usage of epacadostat and PD-1 (PD-1, 3 mg/kg, ip, qod ×8; epacadostat, 100 mg/kg, po bid ×14, TGI = 66.9%). No body weight losses were observed in all the treatment groups.

In summary, we developed a series of novel hydroxyamidine based IDO1 inhibitors using the structure-based drug design approach. Among these derivatives, compounds **14** and **18** showed favorable enzymatic and cellular activities against IDO1, which indicated that the carbonyl group could be used as a bioisostere replacement for the furazan ring in drug design. As compound **14** showed a poor dog PK, further in vivo studies were focused on compound **18**. In the transgenic MC38 xenograft model, compound **18** was orally efficacious in combination with PD-1 monoclonal antibody and showed a synergistic antitumor effect. Together with the increased bioavailability from rodent to larger nonrodent animals, these *in vivo* PD and efficacy studies demonstrated that compound **18** warrant further investigation as a potential add-on cancer immunotherapy agent to PD-1 antibody.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00443.

Biological assays, pharmacokinetic assays, *in vivo* efficacy study, experimental procedures, and analytical data for compound **18** (PDF)

Table 2. Structure−Activity Relationship Data of Cyclohexane and Piperidine Substituted Hydroxylamidine

Compd	R	IDO1 IC_{50} (nM)[a]	TDO IC_{50} (nM)[a]	HeLa IC_{50} (nM)[a]
7		198	58738	21
8		102	>100000	291
9		150	>100000	197
10		80	80960	204
11		149	>100000	1019
12		106	>100000	281
13		40	57970	54
14		14	>100000	15
15		43	89770	28
16		24	>100000	262
17		98	65721	150
18		63	62457	45

[a]Values are expressed as the mean of at least two independent determinations.

Scheme 1. Synthesis of Compound 18[a]

[a]Reagents and conditions: (a) SeO_2, 1,4-dioxane, 80 °C, 16 h; (b) $NH_2OH·HCl$, K_2CO_3, CH_3OH, rt, 2 h; (c) NCS, DMF, rt, 16 h; (d) 3-bromo-4-fluoroaniline, EtOH, rt, 3 h; (e) 4 M HCl in 1,4-dioxane, 2 h; (f) *tert*-butyl chlorosulfonylcarbamate, Et_3N, DCM, 0 °C, 1 h; (g) 4 M HCl in 1,4-dioxane, MeOH, rt, 1 h.

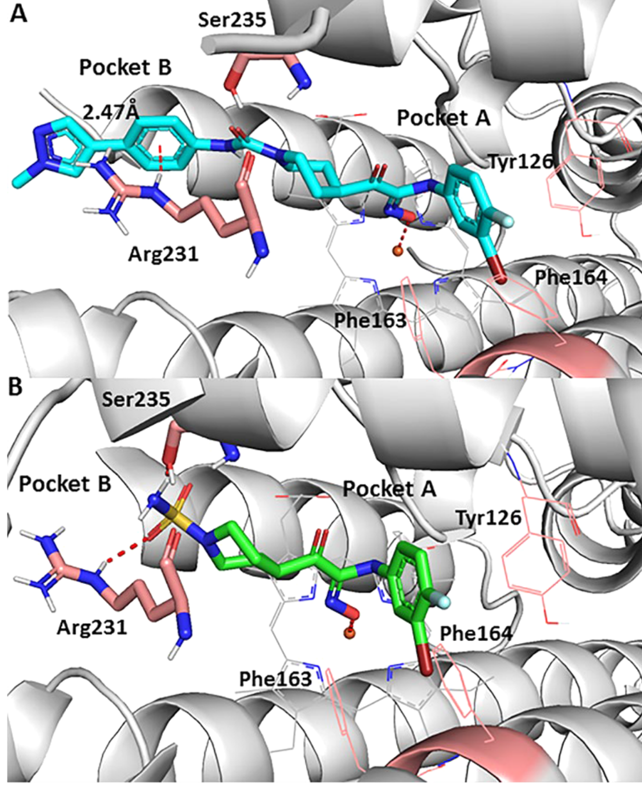

Figure 2. Molecular docking of active compounds binding to the IDO1 active site (PDB code: 6E40). (A) Compound **14** (cyan); (B) compound **18** (purple).

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Table 3. Oral Pharmacokinetic Profiles of Compound 14 and 18

	rat PK@3mg/kg			dog PK@2mg/kg		
compd	C_{max} (ng/mL)	AUC (ng/mL·h)	$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC (ng/mL·h)	$t_{1/2}$ (h)
14	173	1034	5.08	140	255	1.10
18	179	1527	6.14	742	3633	3.04

Table 4. Profiling of Compound 18

assay	18	INCB-24360 (epacadostat)
enzymatic IDO1 IC_{50} (nM)	63	26
enzymatic TDO IC_{50} (nM)	62 457	>10 000
cellular HeLa IC_{50} (nM)	45	5.3
CYP inhibition (1A2, 2C9, 2C19, 2D6, 3A4)	>10uM	>10uM
hERG	>30 uM	>30 uM
PPB (rat/dog/human)	92.4%/96.0%/96.4%	97.0%/97.5%/98.5%
liver microsome stability (rat/human) $T_{1/2}$ (min)	93.4/348.7	73.1/293
mouse PK@3mg/kg		
C_{max} (ng/mL)	127	253
AUC (ng/mL·h)	358	1016
$t_{1/2}$ (h)	1.21	2.41
Cl (μL/min/mg)	61.2	49.2
bioavailability (F%)	44%	44%
rat PK@3mg/kg		
C_{max} (ng/mL)	179	133
AUC (ng/mL·h)	1527	807
$t_{1/2}$ (h)	6.14	2.73
Cl (μL/min/mg)	16.7	29
bioavailability (F%)	58.8%	55%
dog PK@2mg/kg		
C_{max} (ng/mL)	742	245
AUC (ng/mL·h)	3633	676
$t_{1/2}$ (h)	3.04	5.03
Cl (μL/min/mg)	9.3	36.6
bioavailability (F%)	102.1%	50%

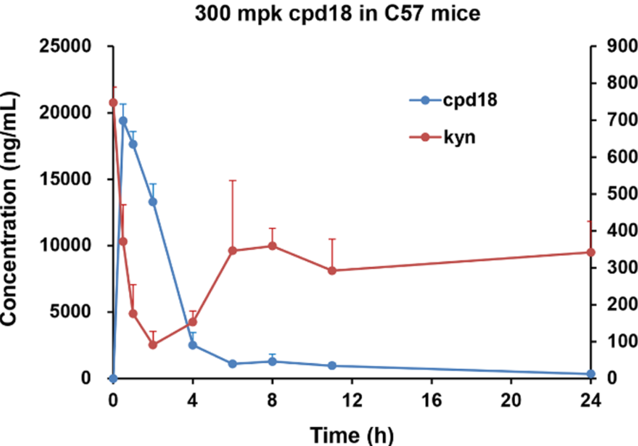

Figure 3. Kynurenine reduction of oral administration of compound **18** in the C57 mouse model.

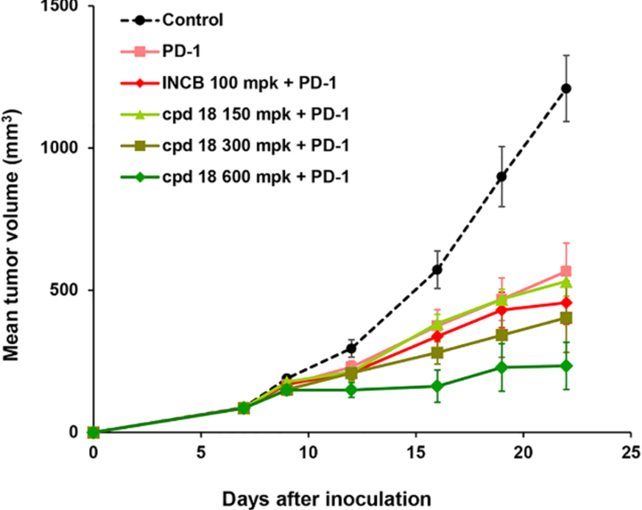

Figure 4. Efficacy study of compound **18** in combination with PD-1 monoclonal antibody in the MC38 xenograft model in hPD-1 transgenic mice.

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

IDO1, Indoleamine 2, 3-dioxygenase 1; TDO1, tryptophan 2,3-dioxygenase 1; MOE, Molecular Operating Environment; PD-1, programmed death 1; DMHH, *N*,*O*-dimethylhydroxylamine hydrochloride; DMAP, 4-dimethylaminopyridine; DCM, dichloromethane; NCS, *N*-chlorosuccinimide; EDC, 3-(ethyliminomethylideneamino)-*N*,*N*-dimethylpropan-1-amine; THF, tetrahydrofuran; DMF, dimethylformamide; SAR, structure−activity relationship; CYP, cytochrome p450 enzyme; hERG, human ether-a-go-go-related gene; PPB, plasma protein bonding; PK, pharmacokinetic; po, orally; ip, intraperitoneally; bid, twice daily; qod, every other day; TGI, tumor growth inhibition.

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