INCB24360 (Epacadostat), a Highly Potent and Selective Indoleamine-2,3-dioxygenase 1 (IDO1) Inhibitor for Immuno-oncology

Eddy W. Yue, Richard Sparks, Padmaja Polam, Dilip Modi, Brent Douty, Brian Wayland, Brian Glass, Amy Takvorian, Joseph Glenn, Wenyu Zhu, Michael Bower, Xiangdong Liu, Lynn Leffet, Qian Wang, Kevin J. Bowman, Michael J. Hansbury, Min Wei, Yanlong Li, Richard Wynn, Timothy C. Burn, Holly K. Koblish, Jordan S. Fridman, Tom Emm, Peggy A. Scherle, Brian Metcalf, and Andrew P. Combs*  
Incyte Corporation, 1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States  

ABSTRACT: A data-centric medicinal chemistry approach led to the invention of a potent and selective IDO1 inhibitor 4f, INCB24360 (epacadostat). The molecular structure of INCB24360 contains several previously unknown or underutilized functional groups in drug substances, including a hydroxyamidine, furazan, bromide, and sulfamide. These moieties taken together in a single structure afford a compound that falls outside of “drug-like” space. Nevertheless, the in vitro ADME data is consistent with the good cell permeability and oral bioavailability observed in all species (rat, dog, monkey) tested. The extensive intramolecular hydrogen bonding observed in the small molecule crystal structure of 4f is believed to significantly contribute to the observed permeability and PK. Epacadostat in combination with anti-PD1 mAb pembrolizumab is currently being studied in a phase 3 clinical trial in patients with unresectable or metastatic melanoma.

KEYWORDS: Epacadostat, INCB24360, IDO1, data-centric medicinal chemistry, immuno-oncology

The central tenet of cancer immunotherapy is that the immune system can be induced to recognize and eliminate malignant cells within the human body. The harnessing of our innate immune system to treat a wide variety of cancers has been proposed for decades. The recent unprecedented durable responses observed in melanoma patients when treated with anti-CTLA4 mAb (ipilimumab),1 and more recently anti-PD1 mAb (pembrolizumab and nivolumab)2 therapies have provided the first clinical validation for this novel immune mediated mechanism of action for cancer therapy (immuno-oncology or I-O). Cancer therapy is currently undergoing a paradigm shift toward identifying agents (mAb and small molecules) that afford restoration and/or activation of the immune system, often in combination strategies.3−6

Indoleamine-2,3-dioxygenase-1 (IDO1) was first shown by Munn and Mellor to play an immunomodulatory role in fetal protection from the maternal immune system.7 Multiple tumor types, including melanoma, ovarian, and colon, overexpress IDO1 and are believed to subvert this immunomodulatory mechanism and promote tolerance local to the cancer.8,9 Since Munn and Mellor’s seminal research, numerous articles have appeared further validating IDO1 as a therapeutic target for cancer immunotherapy, including studies with si-RNA,10 IDO null mice,11,12 and small molecule inhibitors 1-methyltryptophan 1 (1-MT)13 and hydroxyamidine 2 (5l)14 (Figure 1).15 Notably, IDO1 null mice16 or IDO1 inhibitors in combination with anti-PD1 mAbs have shown synergy in efficacy models.17 These studies provide strong support for the clinical testing of IDO1 inhibitors in combination with anti-PD1 mAbs and anti-PDL1 mAbs to improve the observed low response rates while maintaining their remarkable durability.

IDO1, IDO2, and tryptophan 2,3-dioxygenase (TDO) are members of the heme containing myoglobin family of enzymes and oxygen transporter proteins that catalyze the initial and rate-limiting enzymatic step in the kynurenine biochemical pathway for the metabolism of the essential amino acid tryptophan to N-
formylkynurenine. IDO1 is expressed throughout the body where it can be locally up-regulated in response to inflammation and infection by cytokines, such as interferon gamma (IFN-γ). IDO1 overexpression is associated with several diseases, but most convincingly implicated in cancer. IDO1 induction in dendritic cells may suppress T-cell responses and promote tolerance through either direct effects on T-cells mediated by tryptophan depletion or cytotoxic effects on T-cells from tryptophan metabolites, such as quinolinic acid and kynurenic acid. The role of IDO2 in immunomodulation is less well understood, as there are functionally inactive polymorphisms occurring in approximately 50% of the examined population with only recent correlations to cancer. Conversely, TDO is predominantly expressed in the liver where it is responsible for the homeostasis of tryptophan levels throughout the body in response to dietary intake. Though there is recent evidence that TDO is upregulated in some tumor microenvironments, the vast majority of research supports the predominant role of IDO1 in regulating the immune response. A selective IDO1 inhibitor was therefore desired to avoid potential untoward toxicities associated with altering global tryptophan levels through TDO inhibition.

We previously reported the discovery of a hydroxyamidine hit with micromolar potency from a high throughput screen of our internal collection (>300,000 compounds) that was rapidly improved to a proof-of-concept (PoC) lead (2 or previously reported as S1). Compound 2 demonstrated nanomolar potency in our IDO1 biochemical and cellular assays and excellent selectivity over TDO, but poor oral bioavailability in rodent pharmacokinetics (PK). The PoC study with 2 demonstrated single agent efficacy in a B16-GMCSF mouse melanoma model, although it required subcutaneous dosing due to the compounds short in vivo half-life. In comparison to 1-MT, the first and only other confirmed competitive IDO1 inhibitor (IDO1 IC50 ≈ 34 μM) reported at the time of this research, hydroxyamidine lead 2 provided an excellent starting point for our medicinal chemistry program. We report herein the further optimization of the PoC lead 2 to afford our clinical candidate INCB24360, epacadostat, a highly potent and selective IDO1 inhibitor with good oral bioavailability across multiple species.

An in-depth analysis of the ADME factors that may be limiting the oral bioavailability of this novel chemotype was undertaken. The metabolism studies revealed that the oxygen of the hydroxyamidine was subject to phase two glucuronidation in vivo and was the major metabolic pathway for the hydroxyamidine class of compounds. Two in vitro clearance counter screens using liver S9 fractions were established to test our compounds’ susceptibility to glucuronidation (P2) alone and to P450-mediated metabolism plus glucuronidation (P1 + P2). Metabolic profiling of our previously reported meta-substituted phenyl derivatives of 3 did not provide significant improvements in P2 stability. The meta-Br-phenyl 3a was identified as a slightly more potent IDO1 inhibitor in a HeLa cellular assay compared to the meta-Cl-phenyl 2 and was therefore incorporated into most subsequent compounds within our structure–activity relationship (SAR) studies (Table 1). Replacement of the furazan by a variety of heterocycles was also investigated and revealed that the furazan was essential for potent IDO1 inhibition. It was hypothesized that substitution at the C3 position of the furazan might disrupt binding to the proximal glucuronidase active site through a steric and/or electronic clash and thus diminish the propensity of the hydroxyamidine to be glucuronidated. Synthesis of secondary 3-amino-furazans and was therefore incorporated into most subsequent

Table 1. Selected SAR of Furazan (3)

| cmpd | X | R  | IDO IC50 (nM) | HeLa IC50 (nM) | P2 Cl | P1 + P2 Cl |
|------|---|----|--------------|----------------|-------|-----------|
| 2    | Cl | NH2| 75           | 19             | >2.2  | >2.2      |
| 3a   | Br | NH2| 50           | 10             | >2.2  | 1.4       |
| 3b   | Br | NHMe| 100         | 14             | >2.2  | >2.2      |
| 3c   | Br | NMe2| >5000        | >5000          | >2.2  | >2.2      |
| 3d   | Br | NHEt| 180          | 35             | 1.4   | >2.2      |
| 3e   | Br | NHBn| 230          | 280            | 2.1   | >2.2      |

Rat IntCl (L/h/kg). Rat hepatic blood flow = 3.3 L/h/kg.

Initial SAR at the 3-amino position of the furazan demonstrated that a variety of secondary amino substituents, such as 3b and 3d, were tolerated in the biochemical and cellular assays, but did not improve the in vitro measured P2 clearance (Table 1). The tertiary amino derivatives, such as 3c, were inactive. Extension of the secondary amino side-chain to a variety of larger, more hydrophobic substituents, such as benzyl derivative 3e, maintained similar biochemical potency, and provided the initial evidence that C3 substituents on the furazan are projected into a solvent exposed region (see Figures S8 and S9) when bound to IDO1. Unfortunately, no improvements in in vitro clearance were observed and cellular activity was severely diminished, presumably due to the high protein binding (3e: fapp < 0.5%) of these lipophilic compounds. In an attempt to reduce the protein binding and restore the potent cellular activity, a series of polar side-chains at C3 of the amino-furazan were designed and synthesized. The addition of polar capping groups to an amino-ethyl C3 substituent provided a highly potent series of IDO1 inhibitors 4a–g (Table 2).

The similar biochemical potencies of these polar inhibitors 4d–g compared to nonpolar analog 3e suggest that the improvements
HeLa IC₅₀ values were both highly potent IDO1 inhibitors and demonstrated increased potency and near identical mouse PK for the two closely related analogs (Figure 2). An immune-mediated mechanism-of-action for 4f was supported by a parallel study in immune-compromised mice (nu/nu) in which no difference in tumor growth inhibition was observed between 4f treated and control animals. Based on these findings, the bromo analog 4f was fully profiled in vitro and in vivo (Table 4). In vitro characterization demonstrated 4f is a highly potent IDO1 inhibitor in cells (HeLa IC₅₀ = 7.4 nM) and in an IFN-γ induced whole blood (WB) assay (IC₅₀ = 125 nM). Absolute selectivity (>1,000-fold) was observed over the related dioxygenases, TDO and IDO2. In addition, 4f was clean in in vitro toxicology studies, including the hERG patch clamp, PXR, Cyp inhibition, and CEREP panel of over 50 receptors and enzymes (see Supporting Information).

Table 2. Selected SAR of Amino-Furazan (4)

Table 3. Comparisons of Bromo (4f) vs Chloro (4g)

![Diagram](https://example.com/diagram.png)
in IDO null mice (∼400 nM kynurenine). TDO metabolism is believed to be responsible for the observed baseline levels of kynurenine in these studies. Similar PK/PD correlations were observed in dogs and cynomolgous monkeys. Allometric scaling using in vivo and in vitro ADME data to cover the WB IC50 at trough resulted in a predicted oral dosing of 4f in humans of 50 mg twice-a-day.

Evaluation of the physiochemical and calculated properties of 4f confirmed the molecular structure to be outside of classical “drug-like” space, including Lipinski’s rule-of-five (1) (>5 HBD; 4f = 6 and >10 HBD + HBA; 4f = 11) and Veber’s permeability rules (2) (PSA < 140 Å2; 4f PSA = 163 Å2) (Table 2). Contrary to the predicted low permeability of these compounds based on their high polar surface area (PSA) and large number of hydrogen bond donors (HBD), these molecules maintained moderate permeability in the Caco-2 assay. The good permeability and oral bioavailability of 4f is attributed to the two intramolecular hydrogen bonds observed in the crystal structure of 4f (Figure 4).

One hydrogen bond exists between the aniline NH and the oxygen of the hydroxyamidine and the second between the imino nitrogen of the hydroxyamidine and the furazan C3 NH. This network of hydrogen bonds not only reduces the effective polarity of the compound and thus increases its permeability but also stabilizes the typically high energy cis-conformation of the amidine. This is critical since our SAR and modeling is consistent with 4f existing in the cis-conformation for binding to IDO1 (Figure 5). Further supporting evidence that 4f is significantly less polar (~8-fold) than predicted from its calculated properties is provided by the comparison of the calculated LogP (cLogP) versus the measured LogD (@ pH 7.4) values of 2.3 and 1.5, respectively. We subscribe to the principle that ligand efficiency (LE), a measure of the free energy of binding per atom, and lipophilic ligand efficiency (LLE = pIC50 – cLogP) provide a more meaningful characterization of the quality of a clinical candidate. The calculated LE and LLE based on the HeLa cell assay, 0.46 and 6.6, respectively, for 4f are nearly ideal.

Preclinical 28-day IND toxicity studies in mice and dogs demonstrated 4f is well-tolerated, in accord with the high selectivity observed in the in vitro profiling data. No adverse findings were identified in any parameter (clinical observations and pathology, histopathology, body weight, food consumption), and there were no signs of autoimmunity. A maximum tolerated dose (MTD) was not established at doses up to 2000 mg/kg/d in mice and 500 mg/kg/d in dogs. Plasma levels of 4f achieved multiples of the WB IC50 at trough during these safety studies. The FDA granted a clinical safe starting dose of 960 mg based on these IND safety study results.

In summary, a potent and selective IDO1 inhibitor 4f (INCB24360, epacadostat) was invented through a series of SAR studies primarily focused on improving the PK by reducing the rate of glucuronidation while maintaining cell potency. A data-centric medicinal chemistry approach was taken, and therefore calculated properties and/or perceived “drug-likeness” did not dictate the design of new molecules. Ultimately, INCB24360 4f was identified as a novel chemotype containing several previously unidentified and/or underutilized substituents (furazan, hydroxyamidine, sulfamide, bromide) in known drug substances. INCB24360 4f proved to be efficacious in rodent models of melanoma and well-tolerated in preclinical IND toxicity studies. Epacadostat (INCB24360) 4f in combination with anti-PD1 mAb, pembrolizumab, is currently being tested in a pivotal trial for the treatment of patients with unresectable or metastatic melanoma.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00391.

**Table 4. PK Profile of INCB24360 (4f) Across Species**

| species | CI (L/h/kg) | Vss (L/kg) | iv (h) | AUC (µM-h) | Po F (%) | Po t1/2 (h) |
|---------|-------------|------------|--------|------------|---------|------------|
| rat     | 1.1         | 2.0        | 1.4    | 1.3        | 11      | 2.2        |
| dog     | 0.5         | 0.7        | 3.1    | 29         | 59      | 4.9        |
| cyno    | 0.8         | 1.8        | 3.3    | 9.3        | 33      | 2.7        |

Figure 3. INCB24360 (4f) PK/PD in mice.

Figure 4. Crystal structure of INCB24360 (4f). Intramolecular hydrogen bonds stabilize the cis-conformation.

Figure 5. Model of INCB24360 (4f) bound to IDO1. The hydroxyl of the requisite hydroxyamidine forms a coordinate covalent bond with the ferrous iron of the heme, while the m-Br-phenyl group binds deep into the active site (pocket A) of IDO1. The aminoethyl-sulfamide substituent projects out of the active site toward solvent (pocket B). IDO1 crystal structure used in the modeling was PDB entry 4PK5.
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