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1,2,3-Triazoles as inhibitors of indoleamine 2,3-dioxygenase 2 (IDO2)

Ute F. Röhrig,[a] Somi Reddy Majjigapu,[a,b] Daniela Caldelari,[a] Nahzli Dilek,[a] Patrick Reichenbach,[c] Kelly Ascencao,[a] Melita Irving,[c] George Coukos,[c,d] Pierre Vogel,[b,c] Vincent Zoete[a*], Olivier Michielin[a,c,d*]

[a] Molecular Modeling Group, SIB Swiss Institute for Bioinformatics, CH-1015 Lausanne, Switzerland

[b] Laboratory of Glycochemistry and Asymmetric Synthesis, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

[c] Ludwig Center for Cancer Research of the University of Lausanne, CH-1066 Epalinges, Switzerland

[d] Department of Oncology, University of Lausanne and Centre Hospitalier Universitaire Vaudois (CHUV), CH-1011 Lausanne, Switzerland

* Corresponding authors

E-mail: Vincent.Zoete@sib.swiss (V.Z.), Olivier.Michielin@sib.swiss (O.M.)

Abstract

Indoleamine 2,3-dioxygenase 2 (IDO2) is a potential therapeutic target for the treatment of diseases that involve immune escape such as cancer. In contrast to IDO1, only a very limited number of inhibitors have been described for IDO2 due to inherent difficulties in expressing and purifying a functionally active, soluble form of the enzyme. Starting from our previously discovered highly efficient 4-aryl-1,2,3-triazole IDO1 inhibitor scaffold, we used computational structure-based methods to design inhibitors of IDO2 which we then tested in cellular assays. Our approach yielded low molecular weight inhibitors of IDO2, the most active displaying an IC_{50} value of 51 µM for mIDO2, and twofold selectivity over hIDO1. These compounds could be useful as molecular probes to investigate the biological role of IDO2, and could inspire the design of new IDO2 inhibitors.

Keywords

indoleamine 2,3-dioxygenase; cancer immunotherapy; molecular modeling; cellular assays; tryptophan metabolism

The kynurenine pathway of tryptophan metabolism is not only implicated in neurodegenerative diseases and neurological disorders,[1] but it also plays a central role in tumor-induced immunosuppression.[2,3] Indoleamine 2,3-dioxygenase 1 (IDO1, EC 1.13.11.52) and tryptophan 2,3-dioxygenase (TDO, EC 1.13.11.11), which catalyze the initial and rate-limiting step of the kynurenine pathway, are expressed by tumor cells to escape a potentially effective immune response. *In vivo* studies demonstrate that administration of IDO1 and TDO inhibitors improve the efficacy of anticancer therapies.[4]

The role of the more recently discovered IDO1 paralogue indoleamine 2,3-dioxygenase 2 (IDO2)[5-7] remains unclear due to ambiguous experimental findings. According to recent work, human IDO2 is weakly expressed in the liver, testis, and thyroid, but in contrast to previous reports,[8,9] not in different tumors.[2] IDO2 knockout mice show a normal development except for defects in IDO1-mediated T-cell regulation and inflammatory responses.[10,11] Two commonly occurring single nucleotide polymorphisms in the coding region of human IDO2 lead to more than 25% of humans having a non-functional IDO2 enzyme.[5] In enzymatic assays, IDO2 shows a low affinity for L-Trp and a low turnover rate,[7,12-14] which might be attributed to the artificial reducing cofactors (ascorbate and methylene blue) routinely used in these assays. This hypothesis is backed by the observation that the alternative cofactors cytochrome b5 and cytochrome P450, increase the affinity and the turnover rate of IDO2 for L-Trp.[12] However, also in a cellular context IDO2 expression does not influence the Trp/Kyn ratio at physiological Trp concentrations. Thus, it is not unambiguously established if IDO2 protects tumors against immune rejection in vivo, and if inhibitors of the enzyme will be of therapeutic benefit.[15-17]

As the exact role of IDO2 is still under investigation, it is critical to develop pharmacological probes that inhibit its enzymatic function. Many IDO1 inhibitors have been described[18] but very few have been developed against IDO2. This may be due to the inherent difficulties in expressing and purifying enzymatically active human IDO2. Despite its first description in 2007,[5-7] the group from the University of Sydney working most actively on characterizing IDO2 published its first report using purified hIDO2 in 2014.[14] Meanwhile, scientists from Amgen Inc. noted in 2011 that “recombinant human IDO2 was challenging to express and purify,”[13] and their report does not describe a single IDO2 inhibitor, except for the previously known unspecific compounds 1-methyl-L-tryptophan (L-1MT) and necrostatin-1. They found the enzymatic IC_{50} value of the classic IDO1 inhibitor L-1MT to be identical for hIDO1 and hIDO2 (35 μM).[13] To date only one study describes inhibitors selective for IDO2 over IDO1 and TDO.[19] In this study, the authors screened a library of 640 FDA-approved drugs in cellular assays on mIDO1 and mIDO2 and found 12 compounds that displayed better IC_{50} values for mIDO2 than for mIDO1. However, lower inhibition of mIDO1 could be due to the fact that this assay is no longer in its linear phase after 16

h of incubation (see Figure S1 in Supplementary Material). In summary, IDO2 is a challenging target for the development of inhibitors of its enzymatic function, and the current limited understanding of its activities warrants further investigation.

Here, we have used our expertise in the design of 4-aryl-1,2,3-triazoles as IDO1 inhibitors[20,21] to address the challenge of discovering IDO2 inhibitors. We previously found that all synthesized 1,2,3-triazole compounds were very selective for IDO1 over TDO and that none of them were toxic up to a concentration of 100 μM.[22] The most active compound, MMG-0358, displayed an excellent ligand efficiency of -0.72 kcal/mol/atom and a cellular IC_{50} value of 77 nM on hIDO1. Similar to previous reports, we found that soluble human IDO2, which we tried producing and purifying from both mammalian and bacterial expression systems (HEK-293T and BL21pLysS cells, respectively), was enzymatically inactive. In addition, we found that even in transiently transfected cells human IDO2 was inactive. Mouse IDO2, however, as well as human IDO1 were both enzymatically active in transiently transfected HEK-293 cells. We therefore performed cellular assays for hIDO1 and for mIDO2 to determine the activity, selectivity, and cytotoxicity of triazole compounds. Mouse IDO2 shares 72% overall sequence identity with human IDO2, and 100% sequence identity in the active site. The disadvantages of cellular assays with respect to enzymatic assays are not only their higher experimental complexity, but also the impossibility to match the cellular activity of a compound to its binding affinity for a specific target, because many other factors like off-target binding, cellular permeability, and toxicity play important roles in final functional read-outs. An important advantage, whereas, of cellular assays is that active compounds, having overcome such obstacles (cell penetration etc.), presumably hold strong potential for *in vivo* activity. Overall, we found that 1,2,3-triazole compounds occupying only the A-pocket above the heme distal site of IDO were highly selective for IDO1 and nontoxic, while compounds occupying both the A and the B pocket towards the entrance of the active site[21] were generally more active on IDO2 than on IDO1, some of these without cell cytotoxicity.

The structure of the active site for hIDO2 differs from the one of hIDO1 by four amino acid side chains: Tyr126 in hIDO1 is replaced by His130 in IDO2, Cys129 by Leu133, Phe164 by Ile168, and Ser167 by Thr171. This results in an about 15% larger volume of the A pocket for hIDO2 (Figure 1).

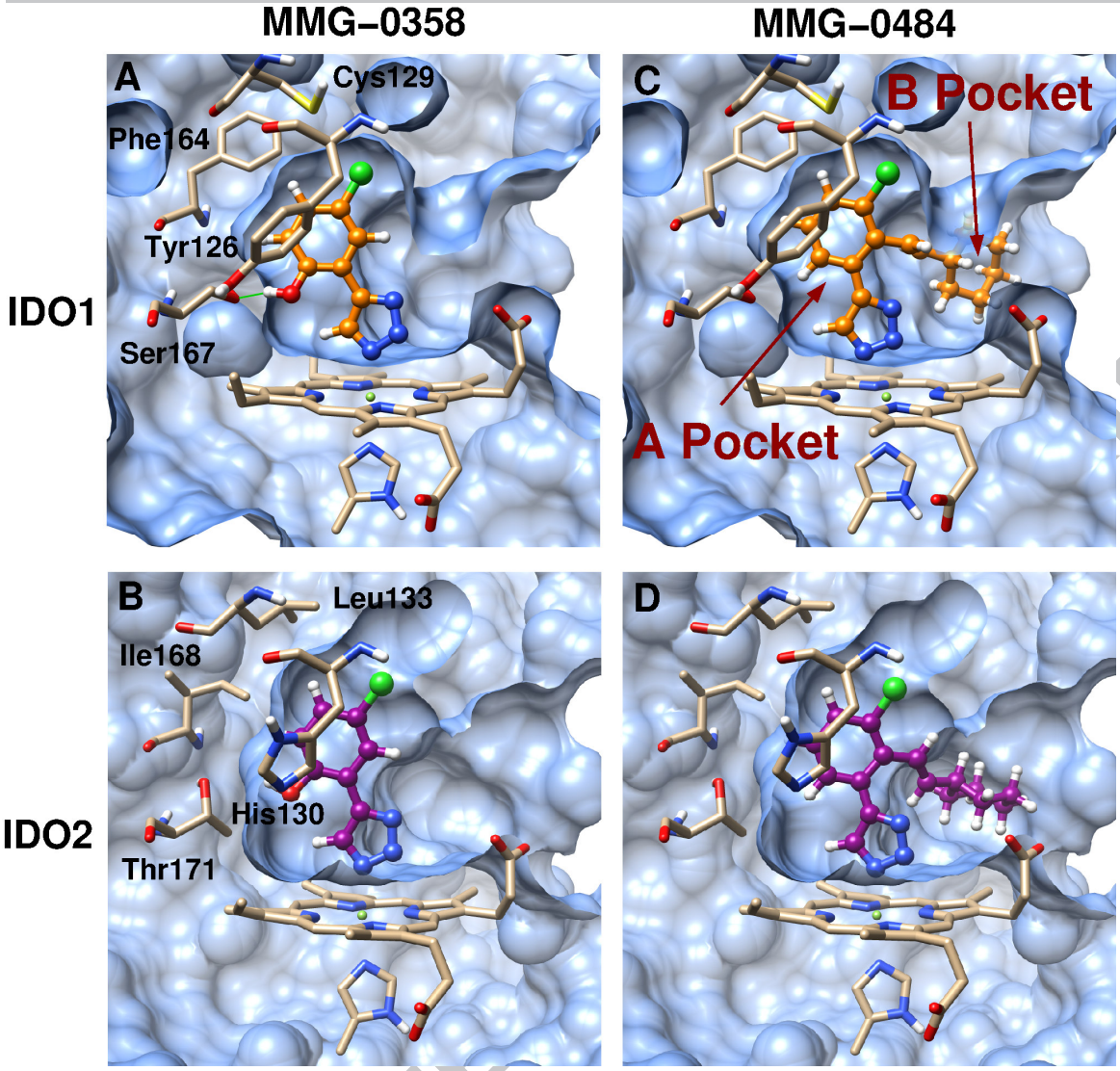
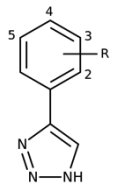


Figure 1: Active site structures of hIDO1 and hIDO2, with calculated binding modes of compound **6** (MMG-0358) and **12g** (MMG-0484). Pocket A and B are highlighted in part (C). The highly potent IDO1 inhibitor MMG-0358 shows a decreased shape complementarity and the loss of a hydrogen bond in IDO2. MMG-0484 shows similar interactions with IDO1 and IDO2.

We tested some of our previously developed 4-phenyl-1,2,3-triazole compounds with different substitutions on the phenyl ring[20] for their inhibitory activity on hIDO1 and on mIDO2 in transfected cells (Table 1). In agreement with our earlier results, these compounds display low cytotoxicity and a strong inhibition of IDO1, except for the *p*-chloride substituted compound **5**, probably due to unfavorable steric interactions. As expected, this compound is slightly more active on mIDO2 due to a larger binding pocket, while all other compounds are much weaker inhibitors of mIDO2. The reason for this decreased activity is not clear but could be due to a less favorable shape complementarity, as depicted in Figure 1. The bigger subpocket in *meta* position of the phenyl ring visible in the

model of IDO2 (Figure 1B and D) could not be exploited by a CF_3 or an isopropyl substituent (data not shown). However, the best inhibitor of hIDO1, MMG-0358 (**6**, Figure 1A and 1B) with a cellular IC_{50} value of 77 nM,[20] is also the best inhibitor of mIDO2, albeit more than three orders of magnitude weaker at 120 µM. This decreased activity could be due to the loss of the hydrogen bond to Ser167 in IDO1.

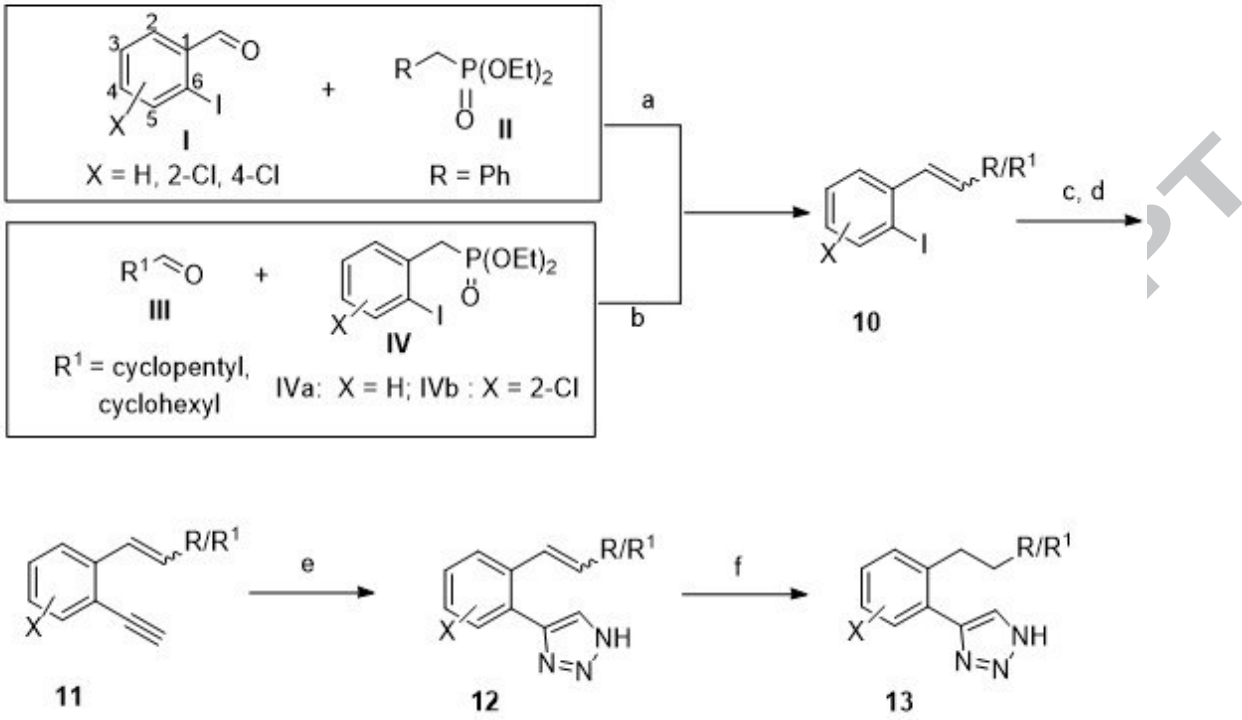
Table 1: Cellular tests with triazoles filling only the A-pocket. All compounds were tested at a concentration of 200 µM. *only one experiment.



Compd	R	Tox [%]	Inh(hIDO1) [%]	Inh(mIDO2) [%]
1	-	5.3 ± 4.3	93 ± 1	1 ± 1
2	2-OH	0.2 ± 0.4	96 ± 2	14 ± 7
3	2-Cl	0.2 ± 0.9	83 ± 2	4 ± 6
4	3-Cl	0 ± 0.5	95 ± 3	2 ± 4
5	4-Cl	2 ± 2.5	9 ± 13	27*
6	2-OH, 5-Cl	0 ± 0.6	98 ± 1	43 ± 7

We subsequently addressed the challenge of designing triazole compounds occupying both the A and the B pocket in order to increase their activity on IDO2. As shown in Figure 1B, the *ortho* position on the phenyl ring provides a favorable access point to the B pocket. In IDO2, the access seems to be facilitated with respect to IDO1, as evident from the more relaxed conformation of the aliphatic chain with respect to IDO1 (compare Figure 1D vs. 1C). The evaluated compounds (Table 2) were chosen based on their favorable docking results and their synthetic accessibility. Synthetic routes are shown in Scheme 1. In general, iodo styrene compounds were synthesized from the corresponding benzyl phosphonates and aldehydes.[23-25] These were transformed to ethylyl styrene derivatives applying the Sonogashira coupling reaction.[26,27] The N-unsubstituted 1,2,3-triazoles were obtained by the method developed by Yamamoto and co-workers, which involves the reaction of ethynyl derivatives with $TMSN_3$.[28] Compounds **13a-f** were synthesized by reduction of the corresponding unsaturated compound with $FeCl_3 \bullet 6H_2O/N_2H_4 \bullet H_2O$ at 80 °C.[29]

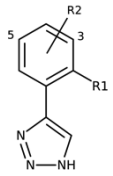
Scheme 1.*



*Reagents, conditions, and yields: (a) NaHMDS, THF, 0 °C - RT, THF, 12-14 h, 60-70%, (b) t-BuOK, THF, 0 °C - RT, THF, 3h, 45-55%, (c) TMSA, $PdCl_2(PPh_3)_2$, Et_3N, CuI, dioxane, 45 °C, 5 h (d) KF, MeOH, rt, 3 h, for 2 steps 75-90%; (e) $TMSN_3$, CuI, DMF/ MeOH (9:1), 100 °C, 10-12 h, 60-75%, (f) $FeCl_3.6H_2O$, $N_2H_4.H_2O$, EtOH, 80 °C, 24h, 60-65%.

Surprisingly, in cellular assays for hIDO1 and mIDO2 inhibition, some of these compounds were very cytotoxic (Table 2). This finding is important for the future design of IDO2 inhibitors as cell death might be mistaken for selectivity over IDO1. Indeed, the incubation time necessary for the IDO2 assay is 3 times longer than the one for hIDO1, leading to increased cell death and reduced tryptophan degradation. In contrast to other studies, we measured cell death on the same cells on which tryptophan degradation was measured, providing a direct link between cytotoxicity and kynurenine production. The structure-cytotoxicity relationship of the triazole compounds with B-pocket extension is unclear with all substituents in 2, 3 and 5-position of the phenyl ring contributing to individual cytotoxicities.

Table 2: Cellular tests for triazoles filling both A and B pockets. All compounds were tested at a concentration of 200 µM.



Compd	R1	R2	Tox [%]	Inh (hIDO1) [%]	Inh (mIDO2) [%]
9	-benzyl		0 ± 0	84 ± 3	80 ± 1
12b	-CH=CH-phenyl	3-Cl	57.9 ± 9.6	32 ± 6	97 ± 0
12g	-CH=CH-cyclohexyl	3-Cl	5.4 ± 8.9	56 ± 2	65 ± 4
13a	-CH_2CH_2-phenyl		3.7 ± 2.5	58 ± 6	90 ± 2
13b	-CH_2CH_2-phenyl	3-Cl	70.8 ± 4.5	76 ± 20	94 ± 1
13c	-CH_2CH_2-phenyl	5-Cl	51.6 ± 16.9	70 ± 7	97 ± 1
13d	-CH_2CH_2-cyclopentyl		35.1 ± 17	74 ± 3	89 ± 3
13e	-CH_2CH_2-cyclohexyl		72.3 ± 2.7	77 ± 10	95 ± 2
13f	-CH_2CH_2-cyclopentyl	3-Cl	21.5 ± 3.6	71 ± 3	90 ± 10
16	-CH_2-CH-OH-phenyl		0 ± 0	28 ± 1	47 ± 3

Compound **16** was not further explored in spite of its low cytotoxicity because it showed low activity against mIDO2. This compound contains a hydroxyl group in the linker to the B-pocket extension, which according to its docked pose cannot form a hydrogen bond with the active site. However, we determined cellular IC_{50} values (Table 3) for active compounds displaying low cytotoxicity. Compound **13a** confers the lowest IC_{50} value on mIDO2 (51 µM) and twofold higher activity on mIDO2 as compared to hIDO1 (100 µM). Compound **9** displays 1.5-fold selectivity with an IC_{50} value of 70 µM on mIDO2 and 105 µM on hIDO1. Compound **12g** inhibits both hIDO1 and mIDO2 with an IC_{50} value of about 100 µM. In conclusion, we discovered three novel 1,2,3-triazole compounds with B-pocket extensions that are not cytotoxic and inhibit IDO2 at micromolar concentrations.

Table 3: Cellular IC_{50} values on hIDO1 and mIDO2 for compounds with low cytotoxicity. *only one experiment.

Compd	IC_{50} hIDO1 [μM]	IC_{50} mIDO2 [μM]	Selectivity Ratio
6	0.09 ± 0.03	120*	0.0008
9	105 ± 7	70 ± 20	1.5
12g	110 ± 10	110 ± 10	1.0
13a	100 ± 20	51 ± 8	2.0

Conclusions

We describe the discovery of new 1,2,3-triazole compounds occupying both the A and the B pockets of the IDO active site, which inhibit IDO2 more strongly than IDO1. Since developing an enzymatic assay for IDO2 is problematic and because many factors influence the activities measured in the cellular assays, it will be challenging to further optimize the active compounds. However, their micromolar activity is on a par with the activity of the widely used yet completely unselective IDO1/IDO2 inhibitor L-1MT.[13] In summary, we believe that the noncytotoxic 1,2,3-triazole compounds may serve as useful molecular probes for investigating the biological role of IDO2 in healthy tissues and tumors, and could inspire the design of new IDO2 inhibitors.

Supplementary Material

Document file with materials and methods, supplementary figures, and synthetic procedures (PDF).

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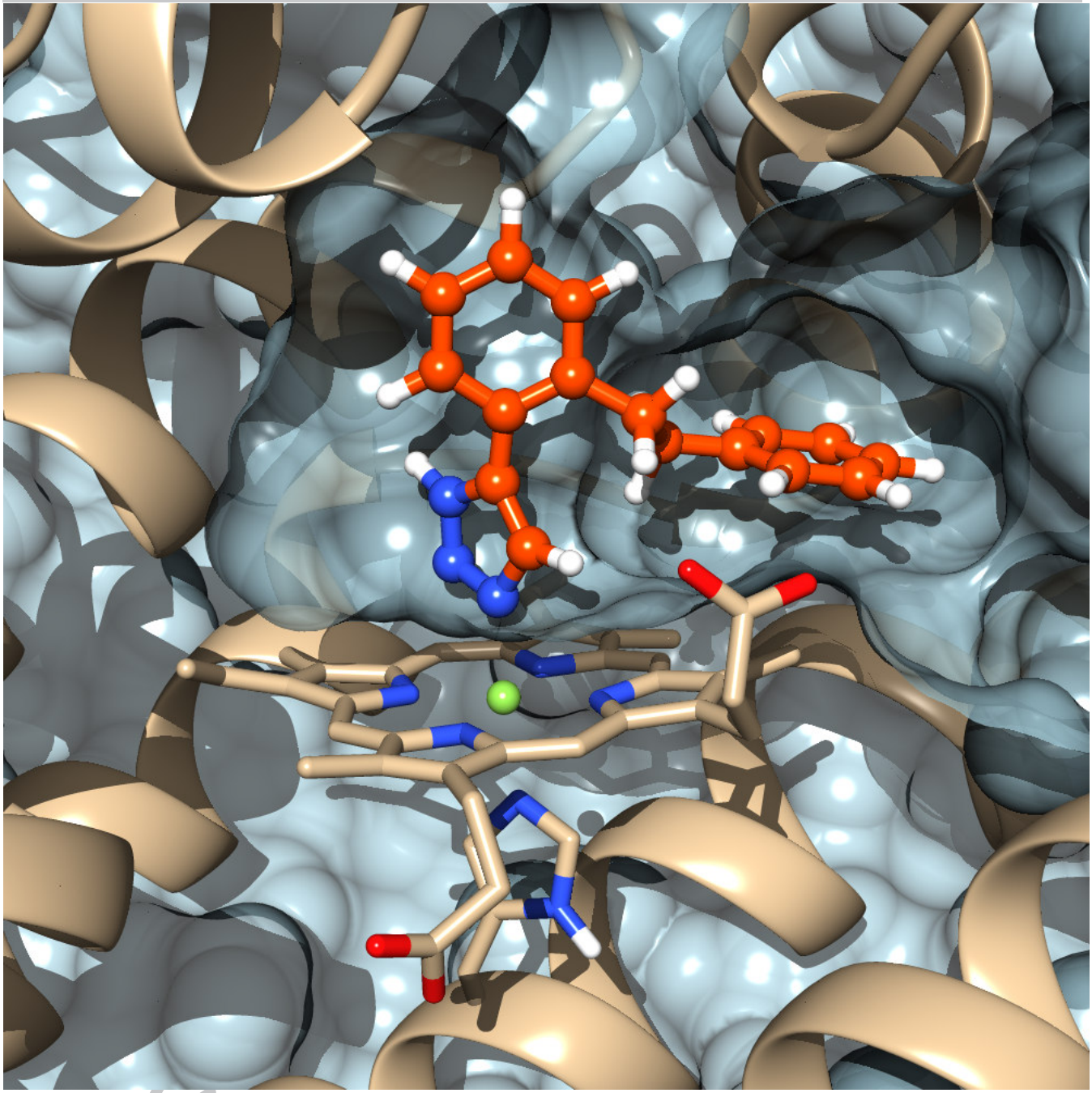

1,2,3-Triazoles as inhibitors of indoleamine 2,3-dioxygenase 2 (IDO2)

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[a] Molecular Modeling Group, SIB Swiss Institute for Bioinformatics, CH-1015 Lausanne, Switzerland

[b] Laboratory of Glycochemistry and Asymmetric Synthesis, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

[c] Ludwig Center for Cancer Research of the University of Lausanne, CH-1066 Epalinges, Switzerland

[d] Department of Oncology, University of Lausanne and Centre Hospitalier Universitaire Vaudois (CHUV), CH-1011 Lausanne, Switzerland

* Corresponding authors

E-mail: Vincent.Zoete@sib.swiss (V.Z.), Olivier.Michielin@sib.swiss (O.M.)

Highlights

- IDO2 is a potential target in cancer immunotherapy
- 4-Aryl-1,2,3-triazoles were synthesized and tested in cellular assays for mIDO2 inhibition
- Best compound has an IC_{50} value of 51 µM for mIDO2, twofold selectivity over hIDO1, and is not cytotoxic