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The TosMIC Approach to 3-(Oxazol-5-yl) Indoles: Application to the Synthesis of Indole-Based IMPDH Inhibitors

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Abstract—A modified approach to the synthesis of 3-(oxazolyl-5-yl) indoles is reported. This method was applied to the synthesis of series of novel indole based inhibitors of inosine monophosphate dehydrogenase (IMPDH). The synthesis and the structure–activity relationships (SARs), derived from in vitro studies, for this new series of inhibitors is given.

Inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the de novo synthesis of guanosine nucleotides, catalyzes the irreversible NAD-dependent oxidation of inosine-5′-monophosphate (IMP) to xanthosine-5′-monophosphate (XMP).[1] Two distinct cDNA's encoding IMPDH have been identified and isolated. These transcripts labeled type I and type II are of identical size (514 amino acids).[2–4] IMPDH II activity is markedly upregulated in actively proliferating cell types including cancers and activated peripheral blood lymphocytes.[5]

CellCept® (mycophenolate mofetil, MMF), a prodrug of mycophenolic acid (MPA), has clinical utility due to its inhibition of IMPDH, for the treatment of transplant rejection. Dose-limiting gastrointestinal (GI) toxicity exhibited from administration of either MMF or MPA limits this drug's potential for treatment of other autoimmune disorders, such as psoriasis and rheumatoid arthritis.[6]

The formation of conjugates at either the carboxylic acid or phenolic residues of MPA, is implicated as a contributing factor in the poor therapeutic index observed for MMF.[7,8] Structurally related analogues, devoid of acid and phenolic functionalities, are reputed to have an improved therapeutic index with regard to dose limiting GI toxicity.[9,10] An alternative approach to IMPDH inhibition has been described by Pankiewicz.[11]

In recent reports, we have described a number of chemical changes intended to replace the urea linkage in **1** (Fig. 1).[9,12] For example, we have disclosed a new class of inhibitors of IMPDH, exemplified by BMS-337197.[9] This report describes our preliminary efforts directed at modification of the aniline moiety common to BMS-337197 and **1**.

Our strategy was to investigate an alternative spatial placement of the terminal oxazole moiety via replacement of phenyl residue (A) with a suitable molecular scaffold. Based on the reported protein/inhibitor crystallographic studies, key objectives would be (i) to maintain the hydrogen bond between the oxazole and

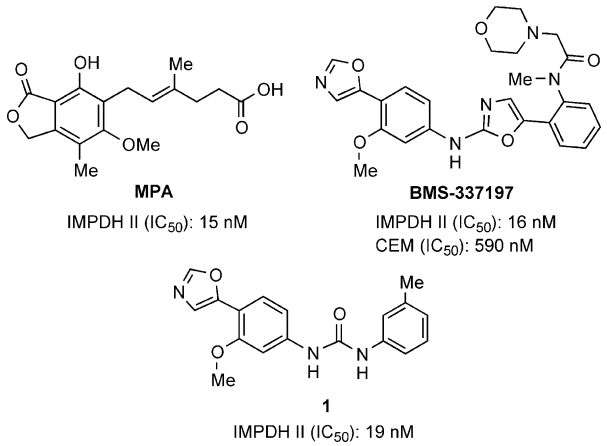

Figure 1. The chemical structures of MPA, BMS-337197 and **1**.

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the NH of Gly326 while maintaining the contribution to binding from inhibitor/protein interactions at the methyl binding pocket and (ii) preserve the hydrogen bond between the NH of the inhibitor and the carboxylate of Asp 274 (Fig. 2).[13] The use of an indole core offered the opportunity to suitably position the terminal oxazole residue and the flexibility to probe the methyl binding pocket.

Literature reports for the synthesis of 3-(oxazol-5-yl)indoles are sparse with the reported methods based upon the Schollkopf reaction of indole-3-carboxylates with isocyanomethyllithium.[14–16]

Tosylmethyl isocyanide (TosMIC) is a widely used reagent to prepare 5-substituted oxazoles from the corresponding aldehydes.[17] Consistent with a previous report, we have observed no reaction of the anion derived from TosMIC with either indole-3-carboxaldehyde or 6-nitro indole-3-carboxaldehyde.[18] The reaction of TosMIC with *N*-methyl-6-nitro indole-3-carboxaldehyde with potassium carbonate (reflux/MeOH) or DBN (DME/RT) as the base, gave us the corresponding 2-oxazoline (Table 1, **4**) as reported in the literature.[18] *However, we were surprised to find that the desired 3-(oxazol-5-yl) indole was isolated in 60% yield when the reaction was carried out at 80 °C in the presence of DBU* (Table 1, **5**). These results clearly indicate that as long as the nitrogen moiety of the indole is suitably derivatized the reaction with the anion of TosMIC will occur. Subsequent elimination of the tosyl group from the 2-oxazolines will depend on a variety of factors and the stability of the protecting group to the reaction conditions. These results are summarized in Table 1. As Table 1 indicates, reaction of TosMIC with an indole, the nitrogen of which is protected as a urea (Table 1, entry 10) and DBU at 80 °C leads to the formation of the desired 3-(oxazol-5-yl) indoles.[19] These optimized conditions were used to prepare a variety of substituted 3-(oxazol-5-yl) indoles (Table 2). Although the yields are moderate, this procedure offers an attractive alternative to the toxic and hazardous methyl

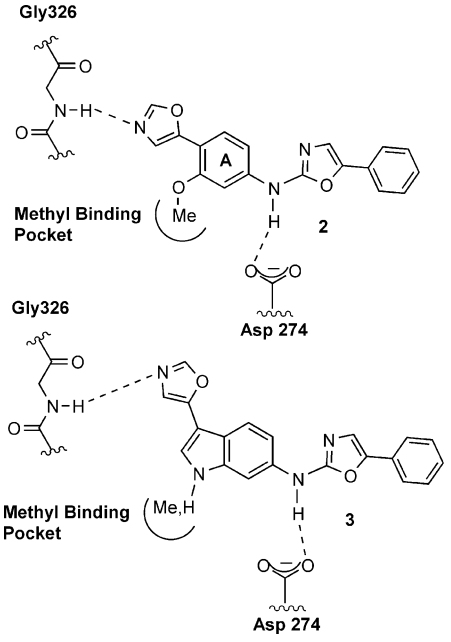
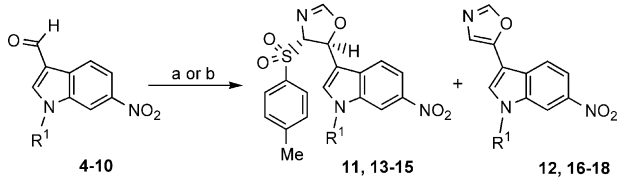


Figure 2. A comparison of binding modes for **2**, an analogue of BMS-337197 and an indole-based inhibitor, **3**.

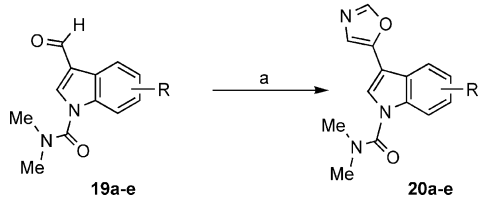
Table 1. Reaction of TosMIC with *N*-protected indoles



Entry	R^1	Rxn conditions	Product	Yield (%)
4	Me	a	11	37
5	Me	b	12	60
6	SO_2Me	a	13	75
7	SO_2Me	b	14 and 16	1:1[a]
8	CO_2Me	b	15 and 17	2:1[a]
9	$CONMe_2$	a	No Rxn[b]	
10	$CONMe_2$	b	18	46

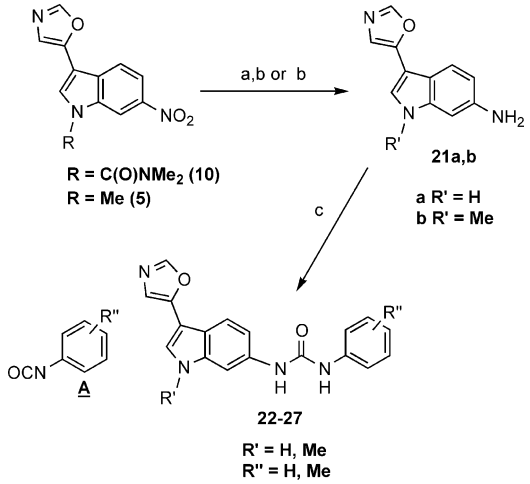
Reagents and conditions: (a) TosMIC, MeOH, K_2CO_3, 80 °C, 2.5 h; (b) TosMIC, DME, DBU, 80 °C, 2.5 h.
[a]Ratio of products based upon LC/MS analysis.

Table 2.

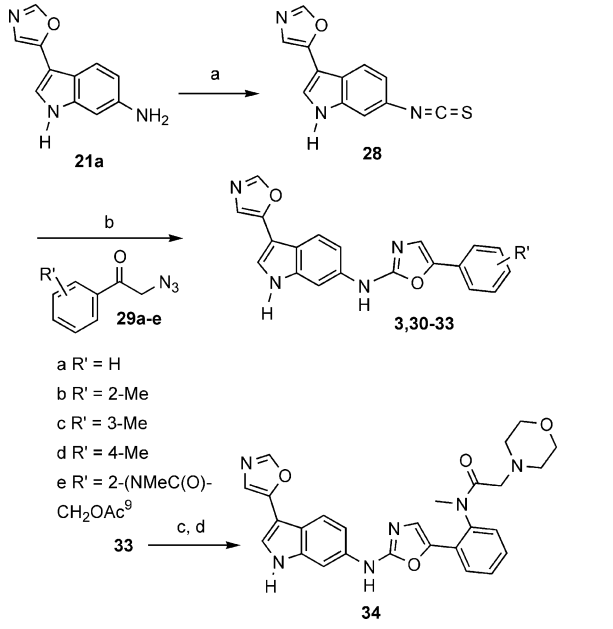


Entry	R	Yield (%)
19a	H	47
19b	5-OMe	41
19c	5-Br	51
19d	6-Me	40

Reagents and conditions: (a) TosMIC, DME, DBU, 80 °C, 2.5 h.



Scheme 1. Synthesis of **22**–**27**. Reagents and conditions: (a) K_2CO_3, MeOH, H_2O, 80 °C, 1.5 h, (84%); (b) H_2/Pd/C, MeOH (78%); (c) **A**, dioxane, 100 °C, (30–70%).



Scheme 2. Synthesis of **3**, **30**–**33**. Reagents and conditions: (a) 1,1′thiocarbonyldi-2(1H)-pyridone, CH_2Cl_2, rt, (96%); (b) **29a**–**d**, PPh_3, CH_2Cl_2, rt or dioxane 80 °C (50–60%); (c) LiOH, MeOH, H_2O, rt, (63%); (d) pyridine, MsCl, then morpholine (31%).

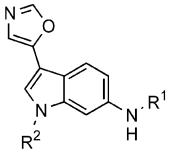
isocyanide in the synthesis of 3-(oxazol-5-yl) indoles.[20] This methodology was applied to a variety of indole based IMPDH inhibitors (Schemes 1 and 2).

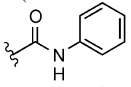
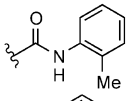
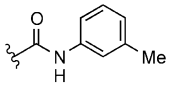
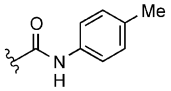
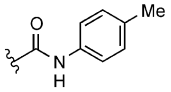
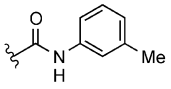
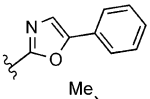
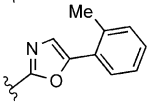
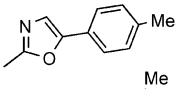
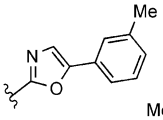
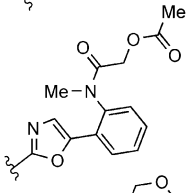
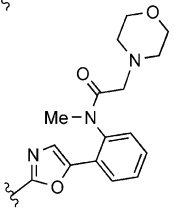
Table 3 reports the in vitro inhibitor potencies against IMPDH II for a series of inhibitors featuring 3-(oxazol-5-yl) indole derived analogues.

Replacement of the 3-oxazol-5-yl aniline moiety in urea **1** with 3-(oxazol-5-yl) indole, giving **22**, resulted in a minimal loss in potency. The potential for substitution about the phenyl ring was investigated through the incorporation of a methyl residue at the *ortho*, *meta* and *para* positions, **23**, **24**, and **25**. As Table 3 indicates there is an clear preference for substitution at the *ortho* and *para* over the *meta* postions. Surprisingly, methylation of the indole nitrogen of analogues **26** and **27** led to a considerable loss in potency. Based upon the binding model, this loss in binding affinity is likely due to steric repulsion and not due a disruption of a hydrogen bond to the NH. SAR in the 5-phenyl-2-aminooxazole series (**3**, **30**–**34**) suggests that the *ortho* position is most preferred. It is of interest to note that compound (**34**) which has the same morpholino side chain as BMS-337197 (Fig. 1) is significantly less potent in inhibiting the T-cell proliferation response in a CEM cell line (BMS-337197, CEM $IC_{50} = 590$ nM versus compound **34**, CEM $IC_{50} = 3.0$ μM).[21]

In summary, we have demonstrated that the 3-(oxazol-5-yl) indole group serves as a excellent replacement of the aniline moiety of the urea derivative (**1**) and BMS-337197 (Fig. 1) while maintaining potency. Efforts to improve the in vitro cell potency and evaluate the compounds in a T-cell mediated pharmacodynamic model are underway and will be reported in due course.

Table 3. SARs of the five-membered heterocyclic inhibitors of IMPDH



Compd	R^2	R^1	IMPDH II IC_{50} (μM)	CEM IC_{50} (μM)
1	NA	NA (UREA STD)	19	1.0
22	H		0.040	>10
23	H		0.035	9.7
24	H		0.20	>10
25	H		0.011	>10
26	Me		>5	NT
27	Me		>5	NT
3	H		0.093	>10
30	H		0.038	>10
31	H		0.205	>10
32	H		0.077	1.5
33	H		0.007	1.0
34	H		0.035	3.0

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19. General procedure for the preparation of 3-(oxazol-5-yl) indoles using TosMIC and DBU (e.g., entry 10 Table 1). Step A: To a solution of 6-nitroindole-3-carboxaldehyde (0.2 g, 1.05 mmol) in 3 mL of anhydrous DMF was added sodium hydride (0.042 g, 1.56 mmol) at 0 °C. The reaction mixture is warmed to room temperature over 10 min and dimethylcarbamyl chloride (144 μL, 1.56 mmol) was added. The reaction mixture was stirred at room temperature for 40 min. Water (10 mL) was added and the solid that separates out was filtered and dried (yield: 0.21 g, 76%). The ^{1}H NMR of the solid was consistent with the desired product (3-formyl-6-nitro-indole-1-carboxylic acid dimethylamide).

Step B: To 3-formyl-6-nitro-indole-1-carboxylic acid dimethylamide (0.1 g, 0.383 mmol) was added 1,2-dimethoxyethane (5 mL) followed by TosMIC (0.075 g, 0.383 mmol) and DBU (0.064 g, 0.42 mmol). The reaction mixture was heated at 80 °C for 90 min, cooled to room temperature and concentrated under reduced pressure. The residue that is obtained is purified by silica gel flash chromatography to yield 6-nitro-3-oxazol-5-yl-indole-1-carboxylic acid dimethylamide (0.054 g, 46%). ^{1}H NMR (DMSO-d_6): δ 8.6, (1H, s), 8.55 (1H, s), 8.5 (1H, s), 8.2 (m, 2H), 7.8 (1H, s), 3.1 (6H, s).
20. The main byproduct of the reaction is the parent indole-3-carboxaldehyde (15–20%) resulting from the clevage of the urea linkage under the reaction conditions (DBU/DME/80 °C).
21. See refs 9, 12 for details regarding the enzyme and cell assays.