Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 547–551

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Quinolone-Based IMPDH Inhibitors: Introduction of Basic Residues on Ring D and SAR of the Corresponding Mono, Di and Benzofused Analogues

T. G. Murali Dhar,* Scott H. Watterson, Ping Chen, Zhongqi Shen, Henry H. Gu, Derek Norris, Marianne Carlsen, Kristin D. Haslow, William J. Pitts, Junqing Guo, John Chorba, Catherine A. Fleener, Katherine A. Rouleau, Robert Townsend, Diane Hollenbaugh and Edwin J. Iwanowicz*

Bristol-Myers Squibb PRI, Princeton, NJ 08543-4000, USA

Received 14 August 2002; accepted 1 October 2002

Abstract—The synthesis and the structure–activity relationships (SAR) of analogues derived from the introduction of basic residues on ring D of quinolone–based inhibitors of IMPDH are described. This led to the identification of compound **27** as a potent inhibitor of IMPDH with significantly improved aqueous solubility over the lead compound **1**.

The identification and development of inhibitors of inosine monophosphate dehydrogenase (IMPDH) activity, with reduced GI-related disorders common for CellCept®, has been an active area of research.[1,2] In the accompanying communication,[3] we have described our efforts in designing quinolone-based inhibitors of IMPDH. Although compounds with good enzyme and cell potency were identified in this series, poor physicochemical properties, particularly aqueous solubility, were an issue limiting the progression of these compounds for in vivo studies. For example, the aqueous solubilty of our lead compound **1** (Fig. 1) was 0.001 mg/mL.[4]

In this communication, we describe the synthesis and the structure–activity relationships of mono-substituted, di-substituted and benzofused analogues derived from the introduction of basic residues on the D-ring. This led to the identification of potent compounds with significantly improved aqueous solubility. In the previous communication, we have shown that small liphophillic residues at the 3- and 4-positions on the D-ring are tolerated. On the other hand, small polar functionality may provide compounds with a more favorable physio-

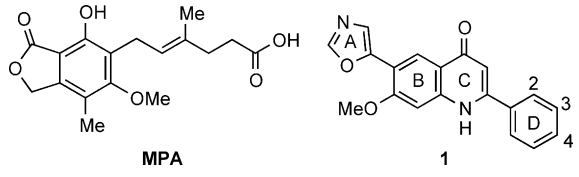


Figure 1. Chemical structures of MPA and quinolone **1**.

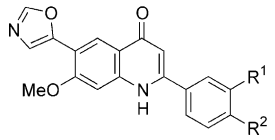
chemical profile, but at a cost in binding affinity.[3] Additionally, unlike mycophenolic acid analogues where the carboxylic acid functionality is a requirement for high potency, we have found that the introduction of acid functionality results in a reduction of binding affinity, regardless of whether the acid residue is positioned to mimic the MPA/IMPDH interaction[5] or directed toward solvent to enhance aqueous solubility. Notably, in previous classes of IMPDH inhibitors, introduction of basic residues has enhanced aqueous solubility while maintaining or improving cell potency.[1,6] We were interested in exploring whether a similar trend would hold for the quinolone-based series of inhibitors, and our results are summarized in Tables 1–3.

The synthetic pathways utilized in the preparation of these compounds are outlined in Schemes 1–5. Compounds **2**–**10** in Table 1 were synthesized employing the

*Corresponding authors. Tel.: +1-609-252-4158; fax: +1-609-252-6804; e-mail: dharm@bms.com; (T. G. M. Dhar), tel.: +1-609-252-5416; e-mail: iwanowie@bms.com (E. Iwanoowicz).

0960-894X/03/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00945-9

Table 1. SAR of bis-substituted phenyl analogues



I

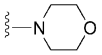
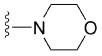
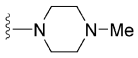
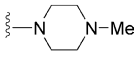
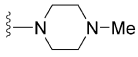
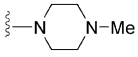
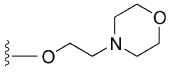
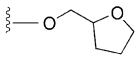
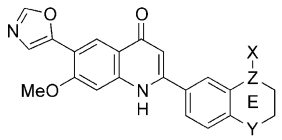
Compd	R^1	R^2	IMPDH II IC_{50}, μM	CEM IC_{50}, μM
MPA	NA	NA	0.014	0.39
2		H	<0.005	—
3	H		0.021	1.1
4		Me	0.005	0.65
5		H	0.016	1.7
6	H		0.053	2.2
7		Me	0.026	1.1
8		OMe	0.140	10
9		H	0.025	2.7
10		Me	0.015	0.78
11		Me	<0.005	0.60
12		Me	<0.005	0.71

Table 2. SAR of 6,6-fused analogues



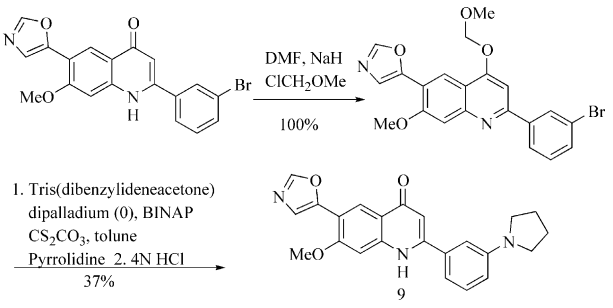
II

Compd	X	Y	Z	IMPDH II IC_{50}, μM	CEM IC_{50}, μM
13	=O	CH_2	C	<0.010	0.52
14	OH	CH_2	CH	0.083	3.4
15		CH_2	CH	0.015	0.37
16		O	CH	0.021	0.72
17		O	CH	0.033	1.4
18	Ac	O	N	0.014	1.3

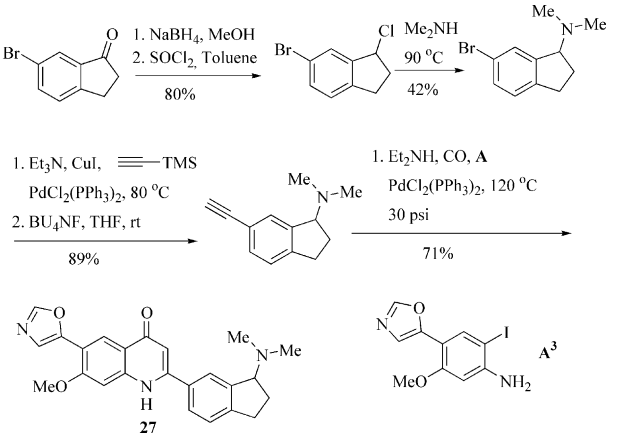
Buchwald protocol[7] on an appropriately substituted bromoquinolone.[3] A representative example is outlined in Scheme 1. Compounds **11** and **12** were synthesized in an analogous fashion by alkylation of the corresponding quinolone phenol.

Representative examples for the synthesis of the indane-quinolone series of IMPDH inhibitors (Table 3) are outlined in Schemes 2–5.[8] Compounds **13** and **16–18** (Table 2) were prepared in a manner analogous to the sequence outlined in Schemes 2 and 3 starting from the triflate derivative of 7-hydroxytetralin-1-one,[9] 6-bromo-tetrahydrobenzopyran-4-one, and 6-bromo-4-*N*-acetyl benzoxazine,[10] respectively. Compounds **14** and **15** were prepared from **13** as outlined in Scheme 6.

The in vitro inhibitory potencies of compounds, fashioned with a basic residue, against IMPDH II are outlined in Table 1. The basic residues are attached to the terminal phenyl moiety (D-ring). Combinations evaluating the effects of the introduction of a second substituent (Me- and MeO-) were also explored. Introduction of a morpholino (**2**) or *N*-methyl piperzinyl (**5**) residue at the 3-position of the D-ring was preferential to the corresponding analogues substituted at the 4-position (**3** and **6**). As reported in the accompanying communication, substitution at the 3- and 4- positions was the preferred bis-substitution pattern. The introduction of a methyl residue at the 4-position of analogues fashioned with a basic residue at the 3-position led to analogues of similar potency. This can be seen in the comparison of **2**, **5**, and **9** with **4**, **7**, and **10**, respectively. Introduction of a methoxy residue at the 4-position in combination with

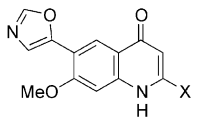


Scheme 1.

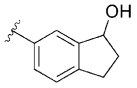
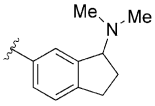
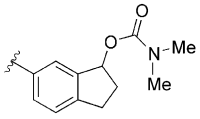
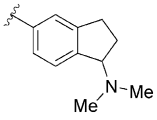
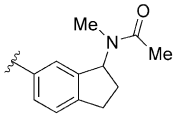
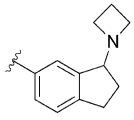
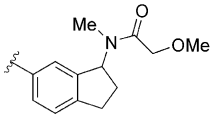
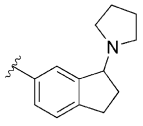
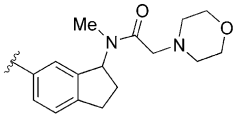
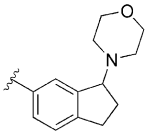
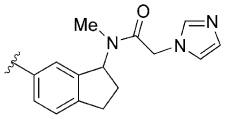
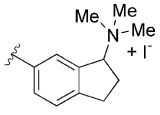
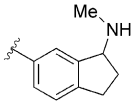
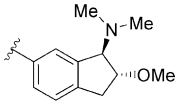
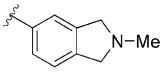


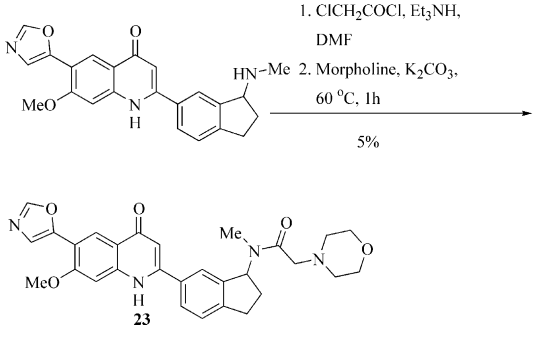
Scheme 2.

Table 3. SAR of 6,5-fused analogues

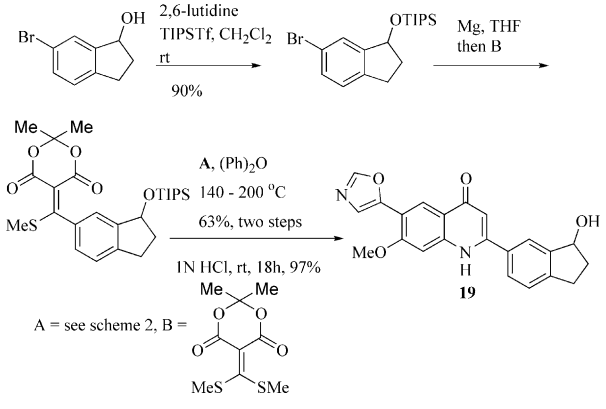


III

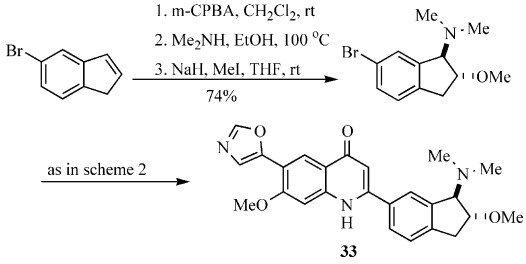
Compd	X	IMPDH II IC_{50}, μM	CEM IC_{50}, μM	Compd	X	IMPDH II IC_{50}, μM	CEM IC_{50}, μM
19		0.028	3.1	**27**		0.006	0.29
20		0.011	—	**28**		0.055	4.1
21		0.018	1.1	**29**		0.006	0.80
22		0.012	1.1	**30**		0.013	0.67
23		0.018	1.8	**31**		0.020	1.1
24		0.068	> 10	**32**		0.030	> 10
25		0.012	1.6	**33**		0.015	0.70
26		0.014	1.1				



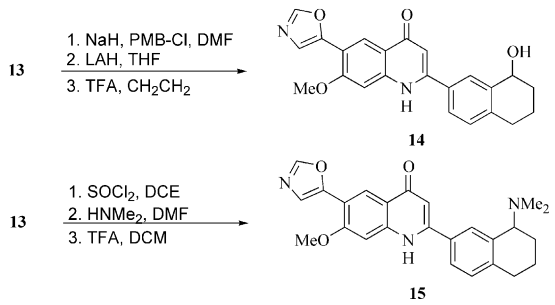
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

an *N*-methyl piperazinyl residue at the 3-position led to an almost 10-fold loss in potency (**3** vs **8**). Compounds **11** and **12** were fashioned with a basic residue and a lipophilic moiety, respectively tethered to the 3-postion via an ether linkage. Both analogues were highly potent inhibitors against IMPDH II and showed comparable potency in the CEM proliferation assay.[11]

Although potent compounds were obtained in the monosubstituted and disubstituted series, cell potency was less than optimal. Synthetic studies were expanded through the formation of an additional ring fused to the D-ring at positions 3 to 4 with the aim of maintaining enzyme activity while improving on cell potency. Since substitution at the 3-postition of the D-ring gave compounds which were 3- to 4-fold more potent than the corresponding 4-substituted analogues (compounds **2**, **3** and **5**, **6**, Table 1), most of our efforts were focussed on introducing substituents at position 1 of the benzofused analogues. The SAR of the 6,6 and 6,5 benzofused analogues are summarized in Tables 2 and 3.

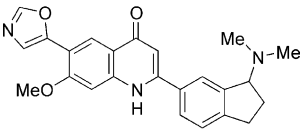
Table 2 reports the in vitro IC_{50} values of analogues based on a fused six-membered ring addition. Ketone **13**, a potent inhibitor of IMPDH II and T cell proliferation, showed the potential of this strategy. Modification to enhance aqueous solubility through the addition of polar functionality led to potent analogues. Oxygen introduction within the E-ring gave less potent analogues, similar to what was observed for the introduction of an oxygen atom in the bis-substituted examples (Table 1).

In addition to fusing a six-membered ring to the D-ring, we also chose to investigate analogues based on a five-membered system, as summarizes in Table 3. Early efforts focused on the modification of the indane system at the 1-position. As is evident in Table 3, this structural class led to very potent inhibitors of IMPDH II. The fact that basic and charged residues (imidazole **24** and trimethylammonium salt **32**) are tolerated in this region may indicate that groups anchored off the 1-position of the indane ring are directed toward solvent accessible regions of the protein.[12] The iso-indole derivative **26** is a potent inhibitor of IMPDH II but is only a micromolar inhibitor of T-cell proliferation, as judged by the CEM assay. From Tables 1–3, it is clear that the *N*,*N*-dimethylamino indane derivative **27** is the most potent compound with respect to the inhibition of IMPDH II ($IC_{50}=6$ nM; IMPDH I $IC_{50}=27$ nM) and the T-cell proliferation response in a CEM cell line ($IC_{50}=0.29$ μM). More importantly, **27** has significantly improved aqueous solubility (0.45 mg/mL) when compared to compound **1** (0.001 mg/mL).[4] The position of attachment of the dimethylamino moiety at the 1-position of the indane ring is clearly important since the isomeric 3-substituted dimethylamino indane **28** is 9 fold less potent than **27** and is only a modest inhibitor of the T-cell proliferation response.

The enantiomers of compound **27** were separated using a CHIRALPAK® AS column, and their potency against IMPDH II enzyme and in T-cell proliferation assays was established. As Table 4 indicates, both compounds were very potent inhibitors of IMPDH II. However, isomer A demonstrated a 2–3-fold improvement in inhibiting the proliferation of T-cells as judged by the CEM and PBL assays.[12]

In summary, analogue **34** has been identified as the lead compound in the quinolone series of IMPDH inhibitors. Determination of the absolute stereochemistry of the dimethylamino group and in vivo evaluation of in a T-cell mediated pharmacodynamic model is in progress and will be reported in due course.

Table 4.



34, 35

Compd	Enantiomer	IMPDH II IC_{50}, μM	CEM IC_{50}, μM	PBMC IC_{50}, μM
VX-497	NA	0.010	0.49	0.17
MPA	NA	0.014	0.39	0.06
34	A	<0.005	0.27	0.12
35	B	<0.005	0.55	0.32

References and Notes

1. Dhar, T. G. M.; Shen, Z.; Guo, J.; Liu, C.; Watterson, S. H.; Gu, H. H.; Pitts, W. J.; Fleener, C. A.; Rouleau, K. A.; Sherbina, N. Z.; McIntyre, K. W.; Witmer, M. R.; Tredup, J. A.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Cheney, D. L.; MacMaster, J. F.; Miller, L. M.; Berry, K. K.; Harper, T. W.; Barrish, J. C.; Hollenbaugh, D. L.; Iwanowicz, E. J. *J. Med. Chem.* **2002**, *45*, 2127.

2. Bjarnason, I. *Transplant. Proc.* **2001**, *33*, 3241.
3. Watterson, S. H.; Carlsen, M.; Dhar, T. G. M.; Shen, Z.; Pitts, W. J.; Guo, J.; Gu, H. H.; Norris, D.; Chorba, J.; Chen, P.; Cheney, D.; Fleener, C. A.; Rouleau, K.; Hollenbaugh, D. H.; Iwanowicz, E. J. *Bioorg. Med. Lett.* **2002** (see communication).
4. We thank Mr. Ravi Tejwani of discovery pharmaceutics, Bristol-Myers Squibb for determining the solubility's of compounds **1** and **27**.
5. Jones, D. F.; Mills, S. D. *J. Med. Chem.* **1971**, *14*, 305.
6. For an excellent discussion on the effect of a basic residue to aid solubility and absorption refer to Van de Waterbeemd, H.; Smith, D. A.; Beaumont, K.; Walker, D. K. *J. Med. Chem.* **2001**, *44*, 1313.
7. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
8. Cornelius, L. A. M.; Combs, D. W. *Synthetic Communications* **1994**, *24*, 2777.
9. Gerlach, U.; Wollmann, T. *Tetrahedron Lett.* **1992**, *33*, 5499.
10. Nugiel, D. A.; Kim, J.; Cornelius, L.; Chang, C. H.; Jadhav, P. K.; Holler, E. R.; Klabe, R. M.; Lee, B. T.; Cordova, B.; Garber, S.; Reid, C.; Lounge, K. A.; Gorey-Feret, L. J.; Lam, G. N.; Seitz, S. T. *J. Med. Chem.* **1997**, *40*, 1465.
11. The IMPDH II inhibition assay and the CEM, PBMC proliferation protocols are outlined in ref 1.
12. Sintchak, M. D.; Nimmesgern, E. *Immunopharmacology* **2000**, *47*, 163.