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Tetrahydroisoquinoline based sulfonamide hydroxamates as potent matrix metalloproteinase inhibitors

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Abstract—The synthesis and MMP inhibitory activity of a series of tetrahydroisoquinoline based sulfonamide hydroxamates are described. In nine MMPs tested, most of the compounds display potent inhibition activity except for MMP-7. Some subtle isozyme selectivity is observed by varying the substituents at the 6- and 7-positions and aromatic ring of arylsulfonyl groups.

1. Introduction

The matrix metalloproteinases (MMPs) are an increasing family of zinc-dependent enzymes that degrade the major components of the extracelluar matrix. This family of enzymes includes the collagenases, stromelysins, and gelatinases. MMPs are necessary for tissue remodeling and the healing cascade under normal physiological conditions.[1] However overactivation of MMPs has been linked to the accelerated breakdown of connective tissues associated with pathological disease states including arthritis, tumor invasion and metastasis, periodontal disease, and multiple sclerosis.[2] Consequently much attention has been directed to discovery of orally active MMP inhibitors with understanding their abilities to treat a number of disease states.[2]

Representative by AG-3340,[3] CGS-27023A,[4] PGE-4410186[5] and WAY-170523,[6] many amino acids derived sulfonamide hydroxamates have been discovered as potent MMP inhibitors.[3–8] These compounds contain a hydroxamic acid group that is capable of chelating the active-site Zn(II) ion of MMPs thereby expressing their inhibition activities. Although several acyclic amino acids derived inhibitors has reached low nM range potency,[4,6,7] a considerable amount of effort has been invested in designing the inhibitors possessing a central, conformationally constrained heterocycle as the backbone.[3,5,8] The goal was to explore if this modification would improve the potency, selectivity toward different MMP isozymes, as well as the pharmacological properties. Considered 1,2,3,4-tetrahydroisoquinoline-1-carboxylates were a class of conveniently available amino acids,[9] we began to use them to synthesize a class of tetrahydroisoquinoline embodied sulfonamide hydroxamates **1**. Logically, these compounds possessed necessary elements as the MMP inhibitors like AG-3340, while their conformational rigidity resulted from their fused ring, as well as the additional space at the aromatic part of the tetrahydroisoquinoline unit, might result in different selectivity for MMPs.[10]

2. Chemical synthesis

As outlined in Scheme 1, synthesis of the designed compounds **1** started from protection of 3-hydroxybenzaldehyde or isovanillin with benzyl bromide and subsequent condensation with nitromethane to afford the olefins **2**. Reduction of **2** with LAH followed by hydrogenation catalyzed by Pd/C provided the amines **3**. Pictet–Spengler reaction of **3** with glyoxylic acid in ethanol gave the cyclized product, which was esterified with methanolic hydrogen chloride to produce amino esters **4**.[9] Treatment of **4** with a suitable sulfonyl chloride provided the sulfonamides **5**. Direct conversion of esters **5** to the corresponding hydroxamates was reached with hydroxylamine hydrochloride under basic condi-

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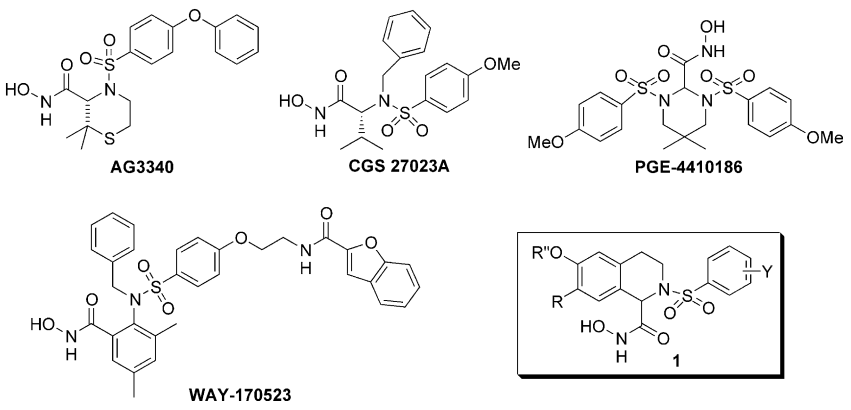
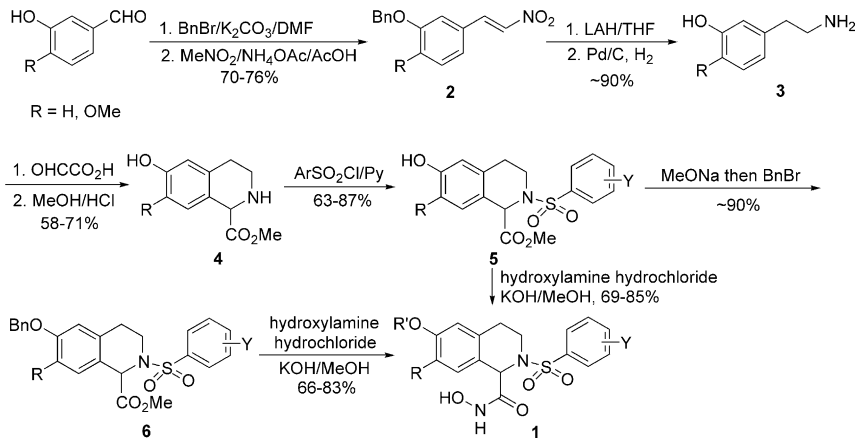


Scheme 1.



Scheme 2.

tion furnished the target molecules bearing a 6-hydroxyl group. Alternatively, alkylation of the 6-hydroxyl group of **5** with benzyl bromide yielded the esters **6**, which were treated with hydroxylamine hydrochloride mediated by potassium hydroxide afforded the target molecules with 6-benzoxyl groups (Scheme 2).

3. Preparation of MMPs and inhibition assay

The encoded catalytic MMP sequence was amplified from the full-length gene and cloned into the pGEMEX-1 plasmid, individually. After sequence confirmation, the recombinant plasmid was transformed into the BL21 (DE3) strain for expression. The target catalytic domains of MMPs (MMP-1, 2, 7, 9, 12, 14, 15, 16 and 26) were purified and refolded as previous described.[11–17]

The typical inhibition assay was carried out in 100 μL reaction system containing 50 mM Tris–HCl, pH 7.5, 10 mM $CaCl_2$, 10 μM $ZnCl_2$, 100 μM TPL, 1 mM DTNB, 2% DMSO and MMPs (5 nM for MMP-1, 10 nM for MMP-2, 1 μM for MMP-7, 15 nM for MMP-9, 5 nM for MMP-12, 300 nM for MMP-14, 10 nM for MMP-15, 10 nM for MMP-16, 10 nM for MMP-26) with different concentration of compounds. The enzymatic rate was recorded at 412 nm for 2 min. Each measurement was done in triplicate to ensure statistically significant results. For comparison, a known potent MMP inhibitor, galardin[18] was used for standard drug.

4. Biological results and discussion

As summarized in Table 1, most compounds displayed potent inhibition activities for selected MMPs but marked difference in potency and selectivity was observed for analogues with the different substituents at the 6 and 7 positions and arylsulfonyl groups. For 6-hydroxy substituted analogues, compound **1b** was much potent than **1a** or **1c** (compare entries 1–3), which indicated that a critical space at the 4′-position of **1** might be necessary for interaction of inhibitors with enzymes. A different selectivity pattern was seen for different substituents at the aromatic ring of the sulfonyl group. For example, analogues with 4′-amino group or 2′,5′-dichloro groups showed selectivity preferred to MMP-2 and MMP-12 but less potent for MMP-1, while 4′-nitro substituted derivative was very potent inhibitor for MMP-1 (compare entries 4–6). For compounds bearing a 6-benzoxyl group, although **1g** and **1i** displayed better activity in comparison with the corresponding compounds with 6-hydroxyl group **1a** and **1c**, the fact that **1h** and **1j** were less potent than **1b** and **1f**, respectively, illustrated that switch hydroxyl to benzyloxy group at the 6-position can either increase or decrease the activity of **1**. Similar results were noticed when a 7-methoxy group was introduced (compare entries 1,7 and 11; 3, 9 and 12). These results demonstrated that the space at the 6- and 7-positions of these inhibitors may play some role for activity. Noteworthy is that **1i** showed highest

Table 1. IC_{50} values for inhibition of MMPs by compounds **1** (μM)

Entry	Compd	MMP-1	MMP-2	MMP-7	MMP-9	MMP-12	MMP-14	MMP-15	MMP-16	MMP-26
1	**1a** (R′=R=Y=H)	6.319	0.430	N.A.[a]	0.335	0.421	1.102	0.218	0.184	0.858
2	**1b** (R′=R=H, Y=4′-Me)	0.152	0.018	10.50	0.040	0.029	0.052	0.019	0.021	0.097
3	**1c** (R′=R=H, Y=4′-OMe)	15.02	0.724	N.A.	4.10	7.689	3.108	0.621	1.677	7.508
4	**1d** (R′=R=H, Y=4′-NH_2)	13.19	0.150	N.A.	0.248	0.191	0.835	0.385	0.202	0.492
5	**1e** (R′=R=H, Y=4′-NO_2)	0.041	0.076	21.42	0.258	0.059	0.521	0.126	0.177	0.791
6	**1f** (R′=R=H, Y=2′-Cl, 5′-Cl)	N.A.	0.853	21.38	1.882	0.170	4.613	1.789	1.839	7.903
7	**1g** (R′=Bn, R=Y=H)	0.452	0.024	7.136	0.035	0.057	0.039	0.017	0.035	1.453
8	**1h** (R′=Bn, R=H, Y=4′-Me)	0.462	0.033	12.04	0.130	0.072	0.062	0.044	0.056	2.046
9	**1i** (R′=Bn, R=H, Y=4′-OMe)	0.088	0.016	2.424	0.03	0.057	0.034	0.004	0.022	0.744
10	**1j** (R′=Bn, R=H, Y=2′-Cl, 5′-Cl)	N.A.	1.099	N.A.	3.118	0.931	20.82	7.303	4.633	N.A.
11	**1k** (R′=H, R=OMe, Y=H)	0.595	0.027	10.69	0.10	0.065	0.867	0.029	0.040	0.146
12	**1m** (R′=H, R=OMe, Y=4′-OMe)	0.123	0.026	3.192	0.046	0.020	0.068	0.006	0.016	0.086
13	Galardin	0.006	0.007	—	0.015	0.013	0.023	0.006	0.008	0.017

[a] N.A.: no activity up to 50 μM.

potency (4 nM), which implies that the 4′-methoxy group is favored for inhibition of MMP-15. This conclusion is further supported by that the other two 4′-methoxy substituted compounds **1c** and **1n** also displayed better selectivity to MMP-15 (entries 3 and 12). Existing additional hydrogen bonding or having a suitable space at the 4′-position is proposed for explaining this phenomenon.

5. Summary

As a summary, we have found some tetrahydroisoquinoline embodied sulfonamide hydroxamates were potent inhibitors for MMPs. Some isozyme selectivity was observed for compounds possessing suitable substituents. A detailed explanation for these subtle differences using computer modeling, as well as the design of more selective compounds based upon this information are actively pursued in our laboratory and will report in due course.

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