Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 295–299

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

General Synthesis of α-Substituted 3-Bisaryloxy Propionic Acid Derivatives as Specific MMP Inhibitors

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Received 11 August 2000; revised 23 October 2000; accepted 8 November 2000

Abstract—Modulations of α and aryl substitutions on 3-aryloxy propionic acid hydroxamates led to novel and potent inhibitors of MMP-2,3,9 and 13, and selectivity versus MMP-1.

Introduction

Matrix metalloproteinases (MMPs) are a class of zinc dependent proteolytic enzymes implicated in the degradation and regeneration of the extracellular matrix.[1] Upregulation of specific MMPs has been associated with various pathologies including arthritis (MMP-1,3,13),[2] and metastatic cancer (MMP-2,9),[3] and therefore inhibition of these enzymes has been recognized as a valuable therapeutic approach. Although numerous publications and patents have been issued in this field, few compounds — among them CGS 27023A[4] and Ro32-3555 (Trocade),[5] for arthritis, BB-2516 (Marimastat)[6] and AG3340 (Prinomastat)[7] for cancer — are in clinical development. They all are active on a large spectrum of MMPs, Prinomastat being the more selective with a 30-fold selectivity index for MMP-13 versus MMP-1 (Table 2). The needed degree of selectivity of MMP inhibitors is debatable. On one side, development of wide-spectrum inhibitors is suggested by contribution of several MMPs to a single disease. On the other, inhibitors aiming only at the enzyme that plays the major pathological role could reduce the risk of blocking matrix turnover in healthy tissues. As an example, side effects of Marimastat and even Prinomastat include joint pain stiffness.[8] This could be due to inhibition of MMP-1, which is expressed in both normal and diseased joints,[2,9] contrary from MMP-13, which seems to be specifically upregulated in arthritic cartilage.[2c] More specific inhibitors lacking MMP-1 activity would likely reduce these side effects. Since structural information is available only for MMP-1 and 3, the interactions of the MMP-substrate transition-state **1** or various inhibitors with MMP-2 and 9 have been proposed by conformational analysis of their active sites based on their sequence homology[10] (Scheme 1). Most of them mimicked only the right-hand side P′ of the substrate,[11] and all the attempts to integrate the left-hand part P were based on pseudo peptide structures.[12] We chose to combine both sides of the substrate in a non-peptide tetrahedral structure of general formula **3** or **4**, and included a carboxylate or hydroxamate, respectively, as a functional group chelating the zinc cofactor. The P′ part could be mimicked by a bisaromatic ether as a hydrophobic and hydrogen binding acceptor, since compound **2** showed significant inhibitory activities for all MMPs[13] (Table 2). Then, an alkylcyclic amide or imide could be envisaged for biologically stable replacement of the P side of the substrate.

Chemistry

A direct chemical access to this new class of compounds was possible neither by 1,4-addition of phenolate to substituted acrylate, due to rapid retro-Michael elimination, nor by reduction of 3-phenoxy-acrylate, due to partial reduction of the aromatic moiety. Therefore we decided to generate the carboxylic function from a precursor **5** by oxidation of a double bond after introduction of the

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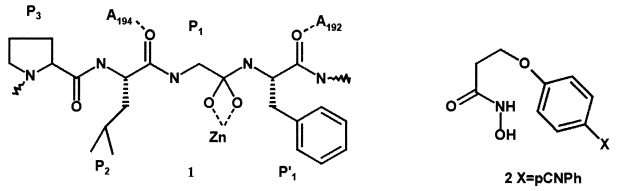
0960-894X/01/$ - see front matter
PII: S0960-894X(00)00646-6



Scheme 1.

two side chains. A retrosynthetic analysis based on a Claisen rearrangement led to 1,4-disubstituted 2-butene **7**. This type of synthon could be obtained either from the 1,4-dihalo or dihydroxy-2-butene, and this approach is attractive for a rapid SAR study, since P_1 and P'_1 substitutions could be exemplified independently from a common precursor **6** (Scheme 2).

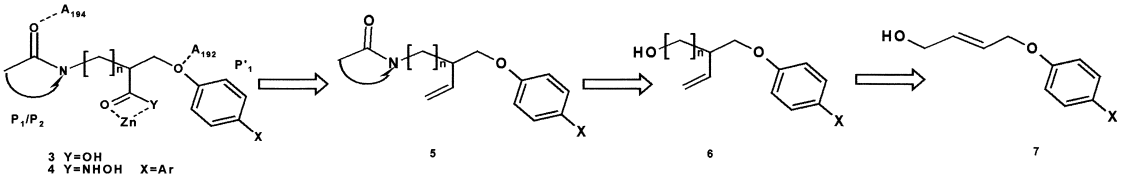
In order to explore diversity at the P location, the biphenylether was used as the P'_1 (X = Ph) surrogate. The starting alcohol **7a** was readily obtained in large quantities by sequential substitution of 1,4-dichloro-2-butene by potassium 4-phenylphenolate then ammonium tetrabutyl acetate and methanolysis in 51% overall yield. More general precursors were obtained by using 4-bromophenolate or 4-bromophenyl-phenolate in the first step to give **7b** and **7c**, respectively (Scheme 3).

With these disubstituted precursors **7** in hand, the Claisen rearrangement was achieved by heating at reflux in ethyl orthoacetate with acidic catalysis and distillation of the liberated alcohol to afford the esters **8** in high yields.[14] Reduction of the esters produced the synthons **6** ready to construct the inhibitors with the ethyl side chain ($n = 2$). In order to select the optimal P_1 chain length, the homologous synthon was obtain from **6a** by introduction of a cyanide function under the Mitsunobu conditions[15] followed by a reduction of the primary amine to give **9a** (Scheme 3).

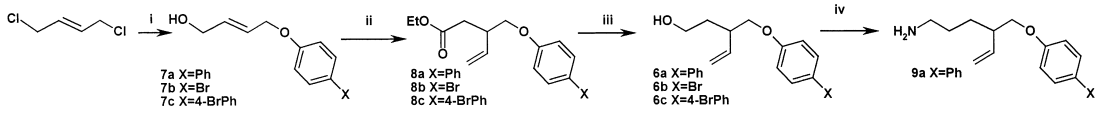
Investigation on the P_1 side

Previous work showed that a phthalimido group was well accepted at P_1[16] and therefore it was our model of choice for the determination of the optimal chain length. Substitution of the hydroxyl function of **6a** was carried out under the Mitsunobu reaction conditions with phthalimide in very good yield[17] to give **5a**. The amine in **9a** was functionalized with phthalimido-carboxylate to give the corresponding homologue **5b** in moderate yield.[18] Under classical conditions the oxidation of the double bond (e.g., $NaIO_4$; OsO_4; O_3)[19] was either unsuccessful or produced mixtures of the desired acid along with various oxidized intermediates in low yield. A sequential procedure using periodic acid to form the primary alcohol (with some acid) followed by Jones reagent to complete the transformation, afforded the acids **3a** and **3b** in reasonable yields. The direct conversion of the carboxylic acids into hydroxamates by coupling with hydroxylamine or by condensation of the acid chlorides with trimethylsilyl-hydroxylamine was never complete and separation from the starting material proved difficult. Indirect conversion (adapted from the protection of carboxylic acid by coupling with allyl[20] or benzylhydroxamate[21]) allowed subsequent purification of the intermediates before deprotection and afforded final products **4a** and **4b** in reasonable yield, as shown in Scheme 4.[22]

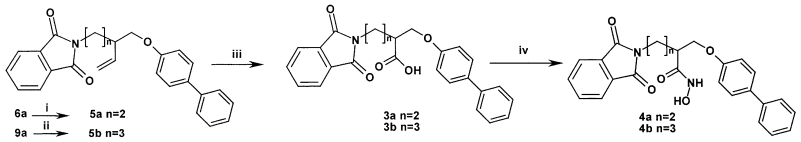
In order to optimize the P_1 interactions, a variety of analogues with various heterocycles replacing the terminal phthalimido group of **4a** were envisaged. They were prepared by a Mitsunobu substitution from **6a** to give **5c–f** in very good yield with the exception of the sac-



Scheme 2.



Scheme 3. (i) (a) K_2CO_3, 4-XPhOH, rt, 96 h; (b) N(nBu)$_4$OAc, acetone Δ; (c) MeOH, NaOH 2 M, rt 12 h (**7a**: 51%, **7b**: 47%, **7c**: 85%); (ii) $CH_3C(OEt)_3$, Δ, 12 h (**8a**: 87%, **8b**: 72%, **8c**: 73%); (iii) LAH, Et_2O, −78 °C, 48 h (**6a**: 95%, **6b**: 85%, **6c**: 95%); (iv) (a) PPh_3, DEAD, $(CH_3)_2C(OH)CN$, Et_2O, 68%; (b) LAH, Et_2O, 67%.



Scheme 4. (i) PPh_3, DEAD, PhtNH, rt (**5a**: 86%); (ii) $PhtNCO_2Et$, TEA, Δ (**5b**: 58%); (iii) (a) H_5IO_6, $RuCl_3$; (b) CrO_3, H_2SO_4 (**3a**: 34%, **3b**: 63%); (iv) (a) $H_2NOAllyl$, HCl, DIEA, HOBT, CH_2Cl_2, rt; (b) Bu_3SnH, $PdCl_2(PPh_3)$, CH_2Cl_2, rt (**4a**: 55%, **4b**: 18%).

Table 1. P_1 substitution: structures and yields of compounds **3-4-5** (**c** to **g**)

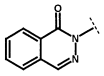
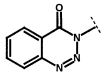
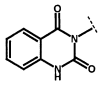
Z					
Compound	**5c**	**5d**	**5e**	**5f**	**5g**
i or ii %	>95	>95	43	>95	20
Compound	**3c**	**3d**	**3e**	**3f**	**3g**
iii %	60	56	61	52	64
Compound	**4c**	**4d**	**4e**	**4f**	**4g**
iv %	25	35	54	39	55

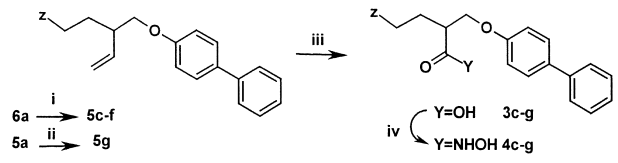
Table 2. Biological and pharmocokinetic data

	IC_{50} (nM)						IC_{50} (nM)						
No.	MMP1	MMP2	MMP3	MMP9	MMP13	No.	MMP1	MMP2	MMP3	MMP9	MMP13	MF%	A%
BB-2516[6]	1.5	1.8	25	1.6	3.4	**4c**	$>10^3$	36	71	199	84	17	—
CGS 27023A[4]	96	15	14	10	12	**4d**	$>10^4$	6	62	33	101	13	—
Ro 32-3555[5]	(Ki) 7	154	527	58	3.4	**4e**	$>10^5$	7	23	16	42	30	—
AG3340	48	0.5	1.1	0.2	1.5	**4f**	31	0.5	5	1	3	29	80
2	$>10^3$	49	47	655	64	**4g**	2850	24	69	25	65	52	—
4a	768	3	16	5	7	**4h**	74	0.1	3.2	0.6	0.016	35	75
4b	$>10^3$	82	313	221	485	**4i**	116	0.4	1.1	0.6	0.6	42	96
						13	9500	25	4.3	3.6	67	23	—

charine derivative **5e** as shown in Table 1. Since a quinazolinedione can not be introduced directly, the adduct **5g** was obtained after reduction of **5a**, amidation by isatoic anhydride and ring closure in the presence of triphosgene.[23] By using the oxidation protocol described above, the corresponding carboxylic acids were obtained and directly converted to their hydroxamates **4c–g** in moderate overall yields, as shown in Scheme 5 and in Table 1.

Investigation on the P_1' side

Based on crystallographic data showing that the S_1' enzyme site is a narrow pocket, shallower in MMP-1 than in the others MMPs (replacement of Arg by Leu), we sought an increase of the steric hindrance at this site to improve the selectivity index.[10] This could be achieved by introduction of a *para* chloro or cyano substitution on the terminal phenyl ring as previously described.[13,14] These P_1' terminal modifications were performed by substitution of a 4-bromophenyl starting either from **5h** or **5i** obtained after introduction of the triazino moiety on **6b** or **6c**, respectively. Then the 4-chlorophenyl moiety was introduced by a Stille reaction[24] on **5h** with 4-chlorophenylstannane, and cyanide substitution was achieved on **5i** with zinc cyanide.[25]



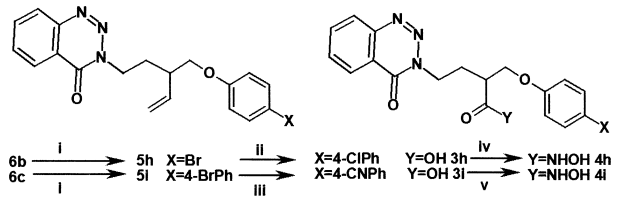
Scheme 5. (i) PPh_3, DIAD, ZH, THF, 0 °C–rt; (ii) (a) $NaBH_4$, *i*PrOH; (b) AcOH; (c) isatoic anhydride, DMF, rt −55 °C; (d) triphosgene, CH_2Cl_2, rt–reflux; (iii) H_5IO_6, $RuCl_3$. (B) CrO_3, H_2SO_4; (iv) (a) $H_2NOAllyl$, HCl, DIEA, HOBT, CH_2Cl_2, rt; (b) Bu_3SnH, $PdCl_2(PPh_3)$, CH_2Cl_2, rt.

According to the procedure described in Scheme 6, the double bonds were sequentially transformed into the corresponding carboxylic and hydroxamic acids to afford compounds **3h–i** and **4h–i**, respectively, as shown in Scheme 6.

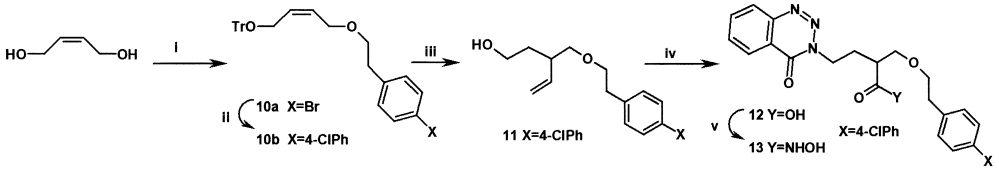
An alternative method to investigate the depth of the S_1' pocket was to introduce an ethyl-spacer between the oxygen atom and the first phenyl ring, in order to maintain the spatial orientation of the P_1' moiety.[12a] For production of the phenylethylether **10a**, it was necessary to monoprotect the *cis* butene-1,4-diol before the introduction of the 4-bromophenylethylalcohol, in order to control the mono substitution. By the procedure described above, the two side chains were built up and the double bond sequentially transformed into the corresponding carboxylic and hydroxamic acids to generate **12** and **13**, respectively, as shown in Scheme 7.

Biological and Pharmacokinetic Parameters Evaluation

The inhibitory activities of these compounds were examined against a panel of MMPs[26] and the results



Scheme 6. (i) PPh_3, DIAD, benzotriazine-4-one, THF, 0 °C–rt. (**5h**: 89% **5i**: 95%); (ii) (a) 4-ClPhSnBu_3, $Pd(PPh_3)_4$, toluene; (b) H_5IO_6, $RuCl_3$; (c) CrO_3, H_2SO_4 (**3h**: 35%); (iii) (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (b) H_5IO_6, $RuCl_3$; (c) CrO_3, H_2SO_4 (**3i**: 70%); (iv) (a) H_2N OAllyl, HCl, EDC, HOBT, NEt_3, CH_2Cl_2 rt; (b) Bu_3SnH, $PdCl_2(PPh_3)$, AcOH, CH_2Cl_2 (**4h**: 60%); (v) (a) H_2NOBn, EDC, HOBT, NEt_3, CH_2Cl_2, rt; (b) H_2, Pd/C (**4i**: 29%).



Scheme 7. (i) (a) TrCl, TEA, CH_2Cl_2, rt; (b) MsCl, TEA, CH_2Cl_2, rt; (c) NaH, 4-BrPh$(CH_2)_2$OH, THF, rt (10a: 32%); (ii) 4-ClPhSn$(Bu)_3$, $Pd(Ph_3)_4$, toluene, Δ, (10b: 48%); (iii) (a) HCO_2H, Et_2O; (b) $CH_3C(OEt)_3$, Δ, 12 h; (c) LAH, Et_2O (11: 65%); (iv) (a) PPh_3, DIAD, benzotriazine-4-one, THF, 0 °C rt; (b) H_5IO_6, $RuCl_3$; (c) CrO_3, H_2SO_4 (12: 55%); (v) (a) H_2NOAllyl, HCl, DIEA, HOBT, CH_2Cl_2, rt; (b) Bu_3SnH, $PdCl_2(PPh_3)$, CH_2Cl_2, rt (13: 36%).

were compared to the various clinical references (Table 2). The carboxylic acids **3a–i** and **12** displayed no significant activities (IC_{50} in the μM range; data not shown) and therefore they were no longer considered for further evaluation. Then hydroxamates **4a** and **4b** were compared and it appeared that the ethyl side-chain derivative was over 20-fold more potent than the propyl homologue on MMP-2,9 and 13 with already a better selectivity index versus MMP-1 than the reference compounds. It is noteworthy that **4a** was about 10-fold more potent on these enzymes than the non-substituted analogue **2**, illustrating the importance of P_1 interactions contribution.

The compounds **4c–g**, obtained by P_1 modification of **4a**, inhibited almost all of the targeted enzymes without notable differences. But if their IC_{50} values remained in the nM range, comparable to those of the reference compounds, an improved selectivity index versus MMP-1 for **4e** and **4g** was realized. In addition, it was interesting to note the remarkably low nM values of the triazino derivative **4f** coupled to a lower selectivity index versus MMP-1. The modification of the P_1' part of **4f** by substitution of the bisaryl moiety led to **4h** and **4i**, which showed a significant improvement in terms of IC_{50} values, especially for the MMP-2,9 and 13 (shift to the sub nM range), with an increased selectivity index versus MMP-1. The elongated analogue **13** also showed an expected increase of this selectivity compared to **4f** but with a slight decrease of potency, thus pointing at the limit of the P_1' modifications to balance activity and selectivity. None of these modifications affected the MMP-3 inhibition IC_{50}, remaining below 5 nM and comparable to **4f**, in keeping with the available space at this site in MMP-3.[10]

Some in vitro pharmacokinetic parameters (PK) were evaluated on selected compounds using hepatic microsomes to predict metabolic stability and first pass metabolism modelling metabolic bioavailability (MF%) and using Caco2 cell line monolayers permeability and in vivo transposition to predict absorption (A%) (Table 2). The hydroxamates **4h** and **4i**, despite intermediate metabolic stability corresponding to 35% and 42% of MF%, respectively, were comparable to the reference compounds[5b,7c] and better than most of the other hydroxamates. These two compounds are good candidates for further pharmacological evaluation with predicted permeability absorption of 75 and 96%, respectively.

Pharmacological Evaluation

In an in vitro model of MMP dependent cartilage lost,[27] **4i** was 10-fold more potent than **4h** to inhibit the degradation of proteoglycan with IC_{50} values of 0.01 and 0.1 μM, respectively. The better absorption of **4i** should compensate its relatively lower affinity for MMP-13, illustrating the importance of the PK parameters. In a preliminary evaluation of these compounds against the B16F10 melanoma, an experimental metastasis model in mice,[28] only compound **4i** showed a significant reduction of tumour burden (35 and 40% at 100 and 200 mg/kg ip, respectively). Identification and production of the corresponding active enantiomer of these compounds are in progress for further studies.

Conclusion

A synthetic access to 2-substituted-3-bisaryloxypropionic acid hydroxamates, a new class of transition state analogue inhibitors of MMPs was developed based on a Claisen rearrangement of 1,4-disubstituted-2-butene. Key synthons allowed independent optimization of P_1 and P_1' sides, leading to selective and very potent inhibitors of MMPs-2,3,9 and 13 and selective versus MMP-1, with acceptable predicted PK parameters. The activities of the selected compounds **4h** and **4i** were validated in cartilage degradation and metastasis models.

Acknowledgements

The authors wish to thank Christine Fouache, Delphine Peyroulan-Thorel, Marie Pacherie-Thomas and Christophe Lesur for excellent technical assistance and Solange Huet for excellent secretarial assistance.

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26. Human purified MMPs were purchased from Calbiochem (MMP-1), Boehringer (MMP-2,9), Valbiotech (MMP-3) and from Pr Murphy (U. East Anglia, MMP-13). Inhibition of MMPs, except MMP-3, was quantified as described previously (*Anal. Biochem.* **1993**, *212*, 58) by using the substrate Dnp-Pro-Cha-Gly-Cys(ME)-His-Ala-Lys(Nma)-NH_2 (Bachem) which is cleaved between amino acids Gly and Cys by APMA-activated MMPs. For MMP-3 assays, the following substrate is used: (7-methoxycoumarine-4-yl)-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 which is cleaved between Ala and Nva (reference M-2105 from Bachem) (*Biochemistry* **1992**, *31*, 12618). The fluorescent cleavage product was measured with a fluorometer (Spectrofluor Plus, Tecan) equipped with a combination of 340 and 440 nm filters for excitation and emission, respectively.
27. Adapted from *Biochem. Biophys. Res. Commun.* **2000**, *267*, 438; SO_4^{-} labeled cartilage explants were stimulated for 1 day with 10 ng/mL interleukin-1β (Sigma) in order to induce MMP production. Explants were then cultured for one extra day in the absence (control) or presence of 5×10^{-4} M APMA (MMP activator)±MMP inhibitors at concentrations ranging between 10^{-9} and 10^{-6} M ($n=8$/group). Proteoglycan degradation was quantified as % radioactivity released by each explant, and the effect of the products was calculated as % inhibition of APMA-induced, MMP-dependent degradation.
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