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# The Development of New Carboxylic Acid-Based MMP Inhibitors Derived from a Cyclohexylglycine Scaffold

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**Abstract**—A series of carboxylic acids was prepared based on cyclohexylglycine scaffolds and tested for potency as matrix metalloproteinase (MMP) inhibitors. Detailed SAR for the series is reported for five enzymes within the MMP family, and a number of inhibitors such as compound **18** display low nanomolar potency for MMP-2 and MMP-13, while selectively sparing MMP-1 and MMP-7. 

## Introduction

It has long been postulated that the aberrant overexpression of matrix metalloproteinase enzymes (MMPs) may play a pivotal role in the progression of many pathological disease states where tissue turnover plays a key role.[1] These include osteoarthritis,[2] cancer,[3] congestive heart failure,[4] and others. Thus, considerable interest has been directed toward the direct inhibition of the MMPs. The majority of inhibitor scaffolds that have been disclosed contain a hydroxamic acid moiety which contributes key binding interactions to the active site zinc atom. The progression of these compounds in clinical trials has been hampered, however, by the emergence of musculoskeletal syndrome (MSS). Following a widespread hypothesis that this may be the result of broad spectrum inhibition of the MMP family, a wave of disclosures then followed which described the development of selective hydroxamate MMPIs which typically spared MMP-1 and MMP-7.[5]

Recently, significant interest has been directed toward selective MMPIs that contain a carboxylic acid moiety as a zinc binding element and this effort is benchmarked by BAY-129566 and disclosures by Warner–Lambert[6] and Shionogi (Fig. 1).[7] Both series of compounds contain a biaryl moiety that inserts into the P1′ pocket of MMP enzymes and effectively selects against shallow pocket enzymes such as MMP-1 and -7.

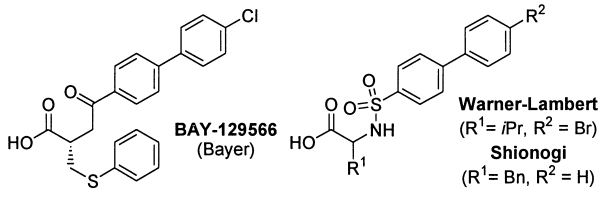


**Figure 1.** Other carboxylic acid based MMP-inhibitors.

We sought to design and target carboxylic acid inhibitors that would specifically allow interactions with the S2 pocket of the enzyme and minimize the high protein binding issues reported for BAY-129566.[2] We were encouraged upon the realization of very potent piperidinyl glycine-based inhibitors,[8] and chose to follow this lead with some substituted cyclohexylglycine analogues which we have previously shown to be synthetically accessible.[9] Herein, we communicate the synthesis and

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biological data for a series of novel 1,3- and 1,4-cyclohexylglycine-based inhibitors which exhibit selective inhibition of MMP-2 and MMP-13 while sparing MMP-1 and MMP-7.

## Chemistry

We recently described an application of the Kazmaier–Claisen rearrangement reaction, which provided an enantio- and stereoselective method for the synthesis of 4-hydroxy-cyclohexylglycines and alanines.[9] We have also been able to construct the 4-substituted cyclohexyl glycines in six steps from 4-hydroxyphenyl glycine **1** (Scheme 1), which is commercially available in either enantiomeric form as well as in racemic form.[10] Glycine **1** was efficiently hydrogenated in the presence of Raney nickel and subsequent sulfonylation and Williams esterification gave **2** as a 2:1 mixture of unassigned *cis* and *trans* isomers. The methoxybiphenylsulfonyl group was used as the P1′ substituent of choice based on earlier data acquired with a related, propargyl glycine scaffold.[11] The alcohol moiety in **2** proved to be inert to Mitsunobu displacement, mesylate formation and alkylation; however, oxidation with Jones' reagent provided ketone **3**, which could be further functionalized via ketal formation and reductive amination type events. Saponification of the methyl ester with LiOH then revealed the desired carboxylic acid inhibitors.

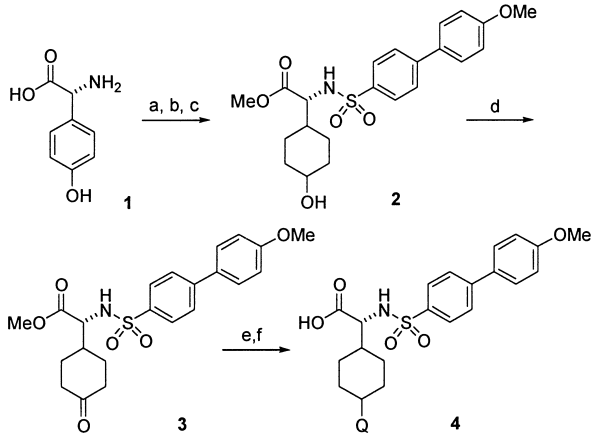
The related 3-substituted cyclohexyl glycines were prepared via Michael reaction with glycine imine **6** to give **7** (Scheme 2) as an inseparable mixture of two diastereomers. Therefore, the data reported herein were gathered with racemates which were often mixtures of diastereomers; however, Corey and co-workers have reported the enantioselective (200:1) and diastereoselective (25:1) Michael addition of 2-cyclohexenone to *tert*-butylglycinate benzophenone imine under chiral phase transfer catalysis (PTC) conditions,[12] which may provide a solution to this diastereomer issue in future work. Cleavage of the imine in **7** with citric acid[13] followed by sulfonamide formation[14] provided ketone **8**. Ketone derivatization followed by ester hydrolysis yielded the desired carboxylic acid inhibitors **9**.

Ketones **3** and **8** were most easily functionalized via standard ketal formation conditions or by reductive amination with primary amines, which gave ~2:1 mixtures of diastereomers that were typically carried forward without separation. Reductive amination ($RNH_2$, $NaCNBH_3$, NaOAc, AcOH, MeOH, rt) of **3** and **8** with benzylamine, methylamine, aniline, and ethanolamine, provided access to various secondary amines. Acylation or sulfonylation of the secondary amines was accomplished with acetyl chloride, mesityl chloride, and methoxyethyl chloroformate ($+Et_3N$, $CH_2Cl_2$, rt). Oxime **28** was formed by addition of $MeONH_3Cl$ ($+$NaOAc, dioxane/MeOH/$H_2O$, rt) to **8**. Ketals **12** and **21** were formed from 1,3-propane diol and ethylene glycol, respectively, and either $BF_3{\cdot}Et_2O$ or PTSA.

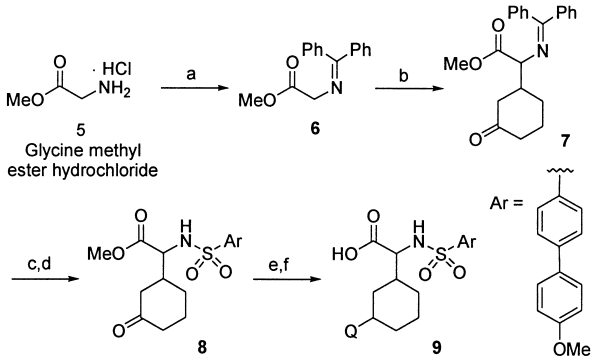
## Results and Discussion

All compounds were tested as diastereomeric mixtures for the inhibition of various MMP enzymes and plasma protein binding. The data are summarized in Table 1. Both 1,4- and 1,3-substituted cyclohexyl glycines demonstrated similar selectivity profiles, which seemed to vary only slightly from one analogue to another. Extremely potent binding was observed with MMP-2 and MMP-13 whereas MMP-1 and MMP-7 were spared by roughly three orders of magnitude. Stromelysin (MMP-3) was inhibited with moderate potency.

The absolute potencies of the inhibitors varied somewhat depending upon the nature of the substituent. This is consistent with binding interactions that were documented for a related set of piperidinyl glycines.[8] A more pronounced substituent effect was noted in the binding characteristics of the molecules with serum albumen. We hoped to target delivery of the molecules to the synovial fluid and anticipated that we could not tolerate protein binding >95%. There were isolated examples of

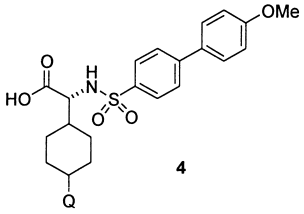



**Scheme 1.** Reagents and conditions: (a) Raney Ni, $H_2$ (100 psi), 3 N NaOH, $H_2O$, 80 °C, 3 days; (b) $NaHCO_3$, 4′-methoxy-4-biphenylsulfonyl chloride, dioxane/$H_2O$; (c) MeOH, $SOCl_2$, 65% (three steps); (d) Jones' reagent, acetone, 95%; (e) ketone derivatization conditions (see text); (f) LiOH, $H_2O$/MeOH/THF (1:2:4), rt, 18–48 h.




**Scheme 2.** Reagents and conditions: (a) benzophenone imine, $CH_2Cl_2$, rt, 4 h, quant; (b) LDA, CuI, THF, −78 °C, 45 min; then α,β-unsaturated ketone, −78 °C→rt, 18 h (e.g., 2-cyclohexen-1-one, 85%; 3-methyl-2-cyclohexen-1-one, 35%); (c) citric acid, $H_2O$, THF, rt, 5 h; (d) 4′-methoxy-4-biphenylsulfonyl chloride, $NaHCO_3$, dioxane/$H_2O$ (1:1), rt, 18 h, 85% (two steps); (e) ketone derivatization conditions (see text); (f) LiOH, $H_2O$/MeOH/THF (1:2:4), rt, 18–48 h.

**Table 1.** MMP enzyme inhibition and plasma protein binding data for 1,4-cyclohexylglycine and 1,3-cyclohexylglycine derivatives

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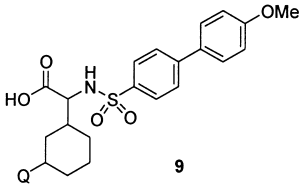


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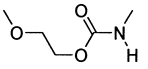
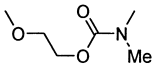
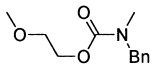
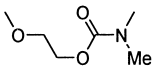
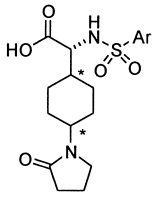
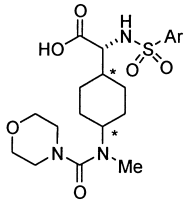
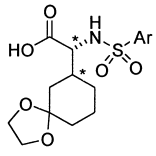
| Compound | General structure | Q | $IC_{50}$ (nM)[a] | | | | | Protein binding (%) |
|---|---|---|---|---|---|---|---|---|
| | | | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | |
| **10** | **4** | –H | 4350 | 8 | 2150 | 15,147 | 43 | 99.7 |
| **11** | **4** | =O | 8950 | 47 | 4700 | > 10,000 | 200 | — |
| **12** | **4** |  | 4999 | 7 | 2320 | 24,061 | 36 | 96.5 |
| **13** | **4** |  | 4183 | 5 | 520 | 9128 | 17 | 94.2 |
| **14** | **4** |  | 9829 | 14 | 600 | 7069 | 22 | 97.7 |
| **15** | **4** |  | 8270 | 12 | 1340 | 20498 | 26 | 99.3 |
| **16** | **4** |  | 6728 | 7 | 783 | > 10,000 | 21 | 87.8 |
| **17** | **4** |  | 284 | 0.6 | 26 | 845 | 0.8 | 98.5 |
| **18** | **4** |  | 4785 | 1 | 98 | 3307 | 1 | 99.0 |
| **19** | **4** |  | 22,927 | 41 | 5660 | > 10,000 | 64 | 90.1 |
| **20** | **9** | –OH | 5370 | 13 | 1610 | 7960 | 54 | — |
| **21** | **9** |  | 3780 | 9 | 630 | > 10,000 | 13 | 98.9 |
| **22** | **9** |  | 2190 | 5 | 250 | 5470 | 8 | 99.8 |
| **23** | **9** |  | 7960 | 15 | 860 | > 10,000 | 67 | — |
| **24** | **9** |  | 7910 | 12 | 500 | 4450 | 32 | 99.4 |
| **25** | **9** |  | 5350 | 6 | 210 | 6340 | 16 | — |
| **26** | **9** |  | 4660 | 17 | 560 | > 10,000 | 29 | 99.4 |
| **27** | **9** |  | 4730 | 8 | 230 | > 10,000 | 11 | 97.6 |

**Table 1 (*continued*)**

| Compound | General structure | Q | $IC_{50}$ (nM)[a] | | | | | Protein binding (%) |
|---|---|---|---|---|---|---|---|---|
| | | | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | |
| **28** | **9** |  | 4130 | 9 | 1250 | >10,000 | 21 | 99.7 |
| **29** | **9** |  | 4110 | 3 | 320 | 5150 | 7 | — |
| **30** | **9** |  | 5960 | 10 | 410 | 8540 | 11 | 97.6 |

[a]All in vitro inhibition assays were performed as described previously;[11] standard deviations for enzyme assays were typically ±30% of the mean or less.

**Table 2.** Comparison of MMP-13 inhibition and plasma protein binding data for *cis* versus *trans* cyclohexylglycine derivatives

| Compd | Configuration | Structure | MMP-13 $IC_{50}$ (nM) | Protein binding (%) |
|---|---|---|---|---|
| **31** | *cis* |  | 100 | 84.0 |
| **32** | *trans* | | 37 | 99.2 |
| **33** | *cis* |  | 81 | 83.1 |
| **34** | *trans* | | 21 | 95.5 |
| **35** | *cis* |  | 13 | 99.3 |
| **36** | *trans* | | 17 | 99.0 |

diastereomeric mixtures that met this requirement including **13**, **16**, and **19**, but we observed significant variabilities between isolated diasteromers as noted in Table 2. Despite the promising profiles of some inhibitors including **31**, **33**, and **34**, none of the compounds in this series has shown in vivo activity in the rat iodoacetate model of osteoarthritis. We are continuing to optimize characteristics of the carboxylate inhibitors to provide in vivo activity.

## Conclusion

We have reported a novel series of substituted cyclohexylglycine carboxylic acid MMP inhibitors. These inhibitors were highly selective inhibitors of MMP-2 and MMP-13 while sparing MMP-1 and MMP-7. Based on the overall profile described so far, this novel series bears the potential of producing multiple orally active as well as selective MMP inhibitors. We hope to report some of these promising data in the future.

## References and Notes

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