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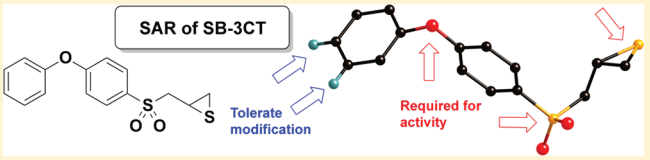
Structure–Activity Relationship for Thiirane-Based Gelatinase Inhibitors

Mijoon Lee, Masahiro Ikejiri, Dennis Klimpel, Marta Toth, Mana Espahbodi, Dusan Hesek, Christopher Forbes, Malika Kumarasiri, Bruce C. Noll, Mayland Chang, and Shahriar Mobashery*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States

Supporting Information

ABSTRACT: An extensive structure–activity relationship study with the template of 2-(4-phenoxyphenylsulfonylmethyl)thiirane (**1**), a potent and highly selective inhibitor for human gelatinases, is reported herein. Syntheses of 65 new analogues, each in multistep processes, allowed for exploration of key structural components of the molecular template. This study reveals that the presence of the sulfonylmethylthiirane and the phenoxyphenyl group were important for gelatinase inhibition. However, *para*- and some *meta*-substitutions of the terminal phenyl ring enhanced inhibitory activity and led to improve metabolic stability. This agrees with the result from metabolism studies with compound **1** that the primary route of biotransformation is oxidation, mainly at the *para* position of the phenyl ring and the α position of the sulfonyl group in the aliphatic side chain.



KEYWORDS: *Gelatinase, SAR, matrix metalloproteinases*

SB-3CT (compound **1**) is a potent and highly selective inhibitor of human gelatinases and a prototype for the thiirane class of matrix metalloproteinase (MMP) inhibitors.[1] Compound **1** has been evaluated in animal models of stroke and cancer metastasis, among others, and found to have protective effects on brain and antimetastatic properties in cancer.[2−6] The selectivity that this inhibitor exhibits is highly desirable, and when combined with the unique mechanism of action (Figure 1A),[7] it makes the thiirane class of gelatinase inhibitors of interest. To explore the properties of these molecules further, we undertook to prepare a large number of thiirane molecules based on the molecular template of the structure of SB-3CT for the purpose of establishing the structure–activity relationship (SAR; Figure 1B). First, we have looked at sulfone surrogates, such as sulfonamide, aminosulfone, and methylsulfone. We also have looked at sp^2-hybridized moieties such as ketone, oxime, and sulfoxide as replacements for the sulfone. The second direction of SAR was to evaluate the importance of the diphenyl ether moiety. We have explored methylene, carbonyl, methyl ether, and ester as connections between the two phenyl rings, but we have also explored direct connection between the two rings without any intervening moieties. Finally, substitution in the terminal rings was explored. Since this aspect proved to be fruitful for the generation of a series of active molecules, it was explored in greater depth. A point of interest for the modification of the terminal ring is the fact that it is also the site of both *in vitro* and *in vivo* metabolism of SB-3CT.[8,9] Avoiding major metabolism at this site, while retaining activity, would be beneficial to discovery of second-generation molecules.

Most of the compounds of Figure 1 were synthesized by the routes depicted in Scheme 1. The suitable synthetic route was chosen according to the property of the functional group to be introduced and the commercial availability of the starting material. When a given aromatic bromide was commercially available, the compound was subjected to route A, which consists of lithiation of arylbromide, which was then treated with sulfur to generate the corresponding thiolate.[10,11] The resulting thiolate was allowed to react with epichlorohydrin to give the corresponding complex more chlorohydrin, which was transformed to epoxide by treatment with base. Oxidation of the sulfide to sulfone with *m*-chloroperoxybenzoic acid, followed by oxygen-to-sulfur exchange using thiourea gave the desired thiirane molecules, such as **1**, **16**, **17**, and **30**. When suitable aniline derivatives were available, route B was used to incorporate the sulfonylmethylthiirane moiety. First, the amine was diazotized using isoamyl nitrite in the presence of acetic acid.[12] The resulting diazonium salt was converted to thioacetate,[13] which was subsequently subjected to a series of standard chemical transformations (basic hydrolysis, alkylation, epoxide ring formation, oxidation, and thiirane formation) to yield compounds of the types **9**, **10**, and **18**. When a desired phenol was commercially available, route C was generally pursued, which involves *O*-thiocarbamate formation, followed by thermal rearrangement to *S*-thiocarbamate.[1] *S*-Thiocarbamate was then hydrolyzed to the corresponding thiolate under basic conditions (route C/D).

When a suitable diphenyl ether was not commercially available—which was actually most of the times—it needed to be synthesized. Although there are many ways to construct the diphenyl ether,[14] three main methods were used in our work:

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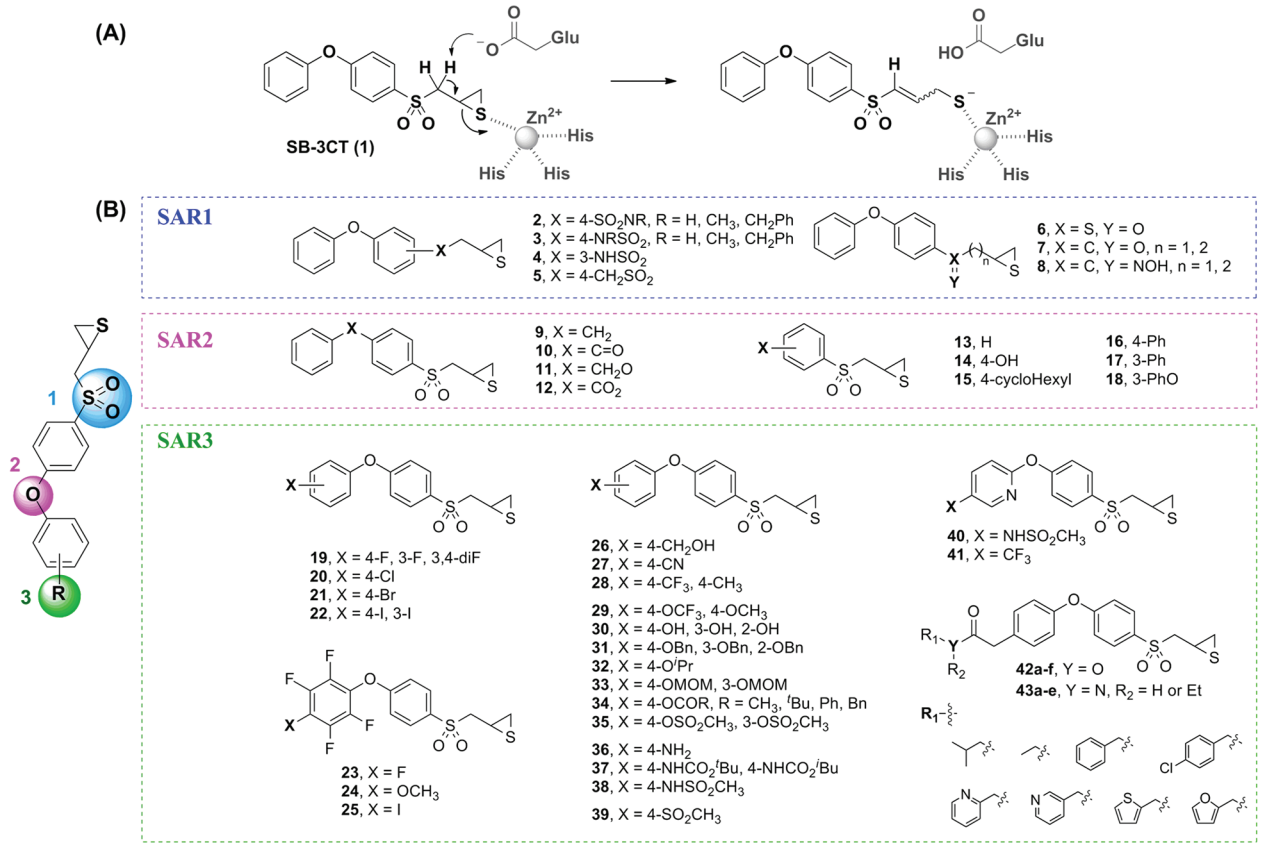
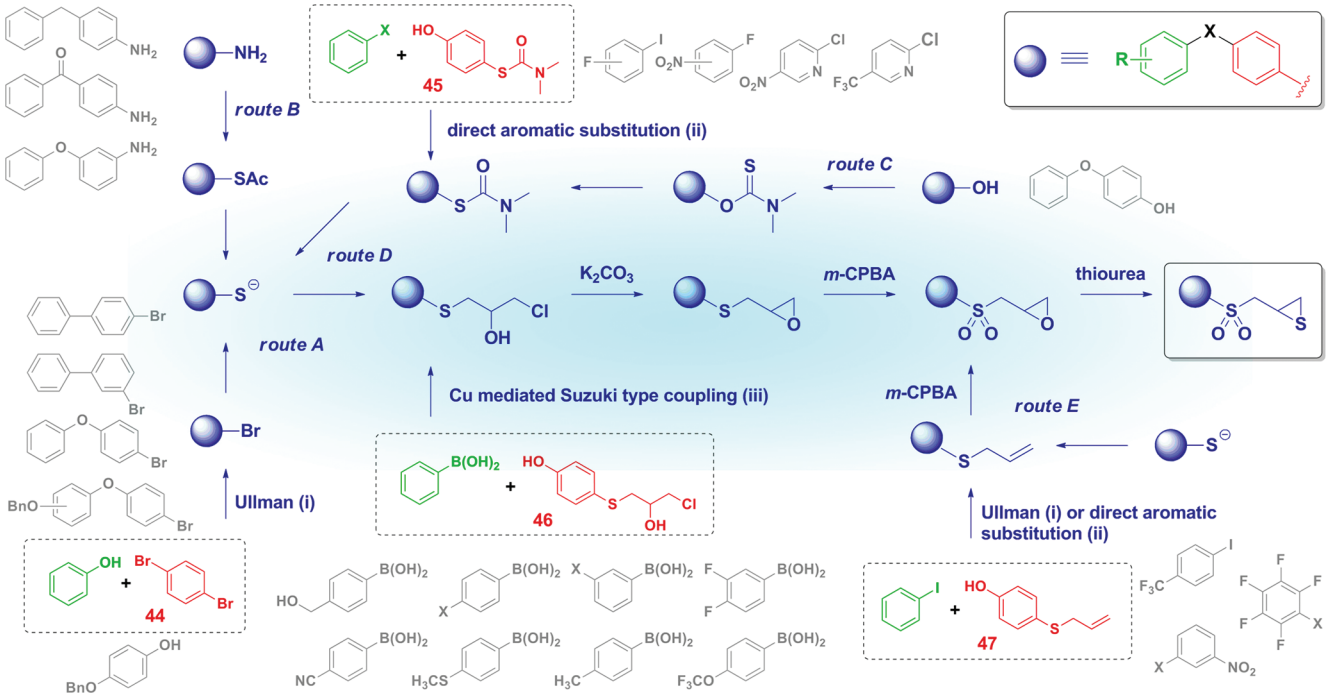


Figure 1. SAR of gelatinase inhibitors based on the structural template of SB-3CT (**1**).

Scheme 1[a]



[a]Reagents and conditions: (*route A*) *n*BuLi or Mg; S, THF; (*route B*) isoamyl nitrite, AcOH, 1,2-benzene disulfonylamide; KSAc, DMSO; (*route C*) thiocarbamoyl chloride, DABCO or *i*Pr$_2$EtN; 150−200 °C; (*route D*) KOH, reflux, MeOH; epichlorohydrin; (*route E*) *m*-CPBA; *Ullmann* (i) CuI, Cs_2CO_3, dimethylglycine·HCl, 90 °C, dioxane; *direct aromatic substitution* (ii) Cs_2CO_3, DMF or NaOH, DMF; *Cu mediated Suzuki type coupling* (iii) $Cu(OAc)_2$, Et_3N, 4 Å molecular sieves, CH_2Cl_2. All compounds were prepared as racemates.

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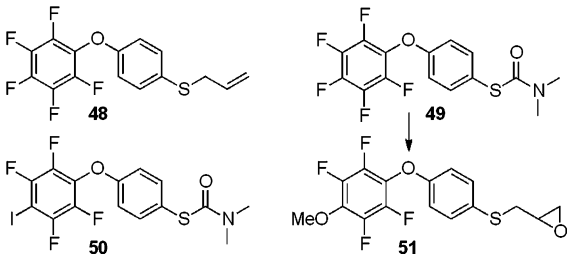
Ullmann condensation (using CuI as a catalyst),[15] Suzuki coupling conditions (using copper(II) acetate),[16,17] and direct aromatic substitution in the case of activated aromatic halide, such as hexafluorobenzene or 1-fluoro-4-nitrobenzene or 2-chloro-4-substituted pyridine derivatives under basic conditions. Four pairs of reagents for these couplings are given in the dotted square boxes in Scheme 1. Many aryl halides, phenols, and aryl boronic acids (colored in green) are commercially available, and they can constitute the terminal phenyl-ring component. We used four components for the middle ring (**44**−**47**, colored in red), with the exception of 1,4-dibromobenzene; the others were based on 4-hydroxythiophenol. Pathways A,[10,11,18] D,[19] and E[19−21] have been used previously by us in preparation of a handful of thiiranes that have been reported. These included syntheses of compounds **6**,[7] **14**,[22] **30**,[9,18] **35a**,[18] **36**,[19] **37a**,[19] **38**,[20] and **42**.[21] These compounds are included in the set of SAR-3 for side-by-side comparison with all the rest of the analogues. All compounds in this study were prepared as racemates, based on the fact that both enantiomers of SB-3CT showed the same inhibitory activity against gelatinases in a previous study.[10]

Certain derivatives obviously could be prepared by multiple routes, yet some target molecules were only accessible by a single set of reactions. For instance, SB-3CT (**1**) could be prepared by most of the routes described in Scheme 1. Aromatic halides would react readily with magnesium or *n*-BuLi to give the corresponding organometallic reagents, so route A is not appropriate for their synthesis. Instead, halogen-containing compounds (**19**−**22**) were prepared by a copper-catalyzed Suzuki-type coupling reaction[16,17] using the corresponding halogenated boronic acids. In the case of the pentafluorinated compound (**23**), it was obtained only when pentafluorinated compound (**48**) was subjected to route E. Several attempts using pentafluorophenyl boronic acid or 1-iodopentafluorobenzene under Ullmann condensation, or via route D using **49**, gave no product, or undesired compounds **50** or **51**. Details for the failed and successful attempts toward synthesis of pentafluorinated derivatives are given in the Supporting Information.



SAR-3 gave a series of compounds with various functional groups at the terminal ring. Among them were certain functionalities that gave a handle for further derivatization, such as −OH (**30**),[18] $-NH_2$ (**36**),[19] and $-CO_2H$ (**42**).[21] We have successfully demonstrated that incorporation of the methylsulfonyl moiety to the *p*-hydroxy- (**30a**) and NH_2-compounds (**36**) resulted in excellent gelatinase inhibitors.[18,20] In this study, we generated a series of esters and amides of compound **42**.[21] This series is based on the X-ray structures of gelatinases, which indicate that there is room for additional functionalities that can be incorporated into the carboxylic acid moiety in compound **42**. The synthesis of the ester-type inhibitors **42a**−**f** was achieved by an EDC-coupling reaction with the corresponding alcohol. The amid-type inhibitors **43a**−**e** were synthesized using pentafluorophenyl ester in the presence of the corresponding amine.

We prepared a total of 65 new compounds by the multistep reactions disclosed above for this SAR study of the thiirane inhibitors. These compounds were evaluated in a high-throughput manner with the purified catalytic domain of MMP-2 (also known as gelatinase A). Thiiranes serve as slow-binding inhibitors of gelatinases, which exhibit a time-dependence for enzyme inhibition. The mechanism of inhibition of gelatinases entails an enzyme-mediated reaction on the inhibitor, which results in potent inhibition by the product of this enzymic transformation.[7] As such, two measurements were taken in each case, one without preincubation and one with a 2-h preincubation of the enzyme with the inhibitor. If the slow-binding mechanism were to be operative, the enzyme activity remaining after preincubation should be less than that without it. First, the enzyme activity in the presence of 30 μM inhibitor was measured. At this concentration, SB-3CT (**1**), as a reference inhibitor, completely inhibits MMP-2 (0% activity remaining). Any compound that showed good inhibition at this concentration was further evaluated at 3 μM and at 300 nM by the same method. The blue bar graphs in Figure 2 showed MMP-2 inhibition of a limited set of compounds at [I] = 30 μM. The turquoise bar graphs in Figure 2 showed MMP-2 inhibition of the better inhibitors at inhibitor concentrations of 300 nM. The full set of analyses is given in the Supporting Information. This analysis established the SAR. The key SAR findings are as follows: (i) The sulfonylmethylthiirane is required for inhibition (cf. SAR-1). Any insertion of N or C atoms before or after the sulfone moiety leads to a loss of potency (**2**−**5**). Sulfone replacement by ketone, oxime, or sulfoxide (used as a diastereomeric mixture) resulted in poorer inhibitors of MMP-2 (**6**−**8**). All of the findings support our recently proposed mechanism that inhibition is due to the deprotonation of proton at the carbon α to the sulfone (Figure 1A).[7] All of the SAR-1 compounds have either less acidic α-methylenes, or the structure of the inhibitor bound in the active site of gelatinase would not poise it for the abstraction of proton by the enzyme. (ii) The diaryl ether would appear to be important for good inhibition (cf. SAR-2). Deletion of the terminal phenyl ring resulted in decreased gelatinase inhibition (**13** and **14**). Any additional atom (**11** and **12**) or deletion of the oxygen between the two aryl groups (e.g., biphenyl **16** and **17**) resulted in decreased gelatinase inhibition. The *para* substitution for the middle ring is important, as *m*-phenoxyphenyl (**18**) and *m*-biphenyl compounds (**17**) were generally poorer inhibitors than their *p*-substituted counterparts (**1** and **16**, respectively). Replacement of the terminal ring with the cyclohexyl group (**15**) followed the same trend with the rest of SAR-2 compounds. (iii) Substitution in the terminal phenyl ring is tolerated at the *para* and *meta* positions. All halogen substitutions show reasonable inhibitory potency, while potency decreased as the size of halogen increases. The same size-dependent trend was observed for other nonhalogen substituents. The alkoxy substituent is better than the corresponding alkyl substituent ($-OCF_3$ **29a** vs $-CF_3$ **28a**), while this trend reversed between derivatives with $-OCH_3$ **29b** vs $-CH_3$ **28b**. (iv) Replacement of the terminal phenyl ring with an electron-poor aromatic group leads to a loss of potency (tetra and penta fluorinated compounds, **23**−**25**). (v) The pyridine-containing compounds were generally poorer inhibitors than their phenyl counterparts (**40** vs **38** and **41** vs **28a**).

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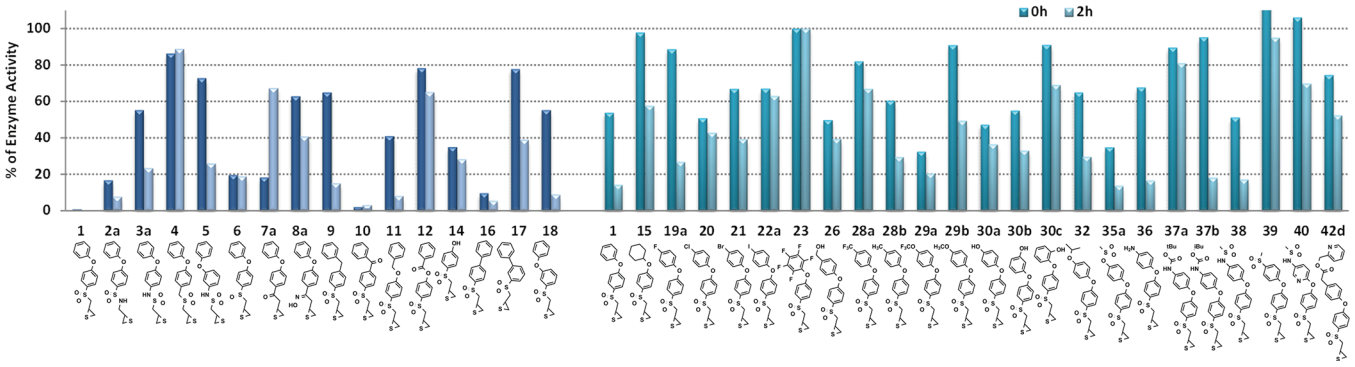


Figure 2. High-throughput screening of synthetic compounds at 30 μM (in blue) and at 300 nM (in turquoise) with MMP-2. The analyses for the full set of compounds are given in the Supporting Information.

Poor inhibition by tetra-/pentafluorinated compound or by pyridine containing compounds was initially difficult to explain. Computational docking and scoring of these molecules into the active site of MMP-2 illustrated that the terminal phenyl ring of the poor inhibitors **23** and **25** tends to extend into the solvent, whereas that for the good inhibitors gets embedded in the S1 loop (Figure S2 in the Supporting Information). This could be partially due to the larger footprint of the fluorinated terminal phenyl rings; however, as shown in other systems,[23,24] the distinct electrostatics of the fluorinated ring could also be a contributor, as it would influence interactions with the protein surface. We determined the X-ray crystal structures of selected compounds in the hope of shedding light on the activities of these inhibitors (Figure 3). There are no obvious structural points that stand out. The only discernible difference was that the sulfur atom in the thiirane ring of all three inactive compounds (A, B, and C in Figure 3) is pointing toward the middle phenyl ring, while that of active compounds (D, E, and F in Figure 3) is pointing away from the phenyl ring. If this difference has a mechanistic explanation for the inhibition outcome, it is not at the present obvious, as there exists freedom of rotation for the bonds in the sulfonylmethylthiirane moiety. The most likely explanation is that the structural modifications afford differential interactions in the MMP-2 active site that the existing X-ray structures cannot explain.

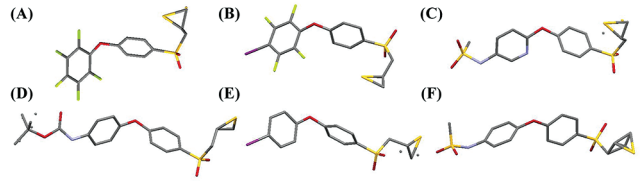
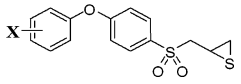


Figure 3. X-ray crystal structures of compounds **23** (A), **25** (B), **40** (C), **37a** (D), **22a** (E), and **38** (F) in the capped-stick representation.

Several of the most potent of the compounds were selected on the basis of the screening result and were further analyzed by detailed kinetics to document the mode of inhibition, to evaluate the dissociation constants, and to demonstrate the selectivity in inhibition of gelatinases (Table 1). These compounds inhibited MMP-2 invariably in the nanomolar range. The K_i values for MMP-9 were usually a few fold higher than those for MMP-2, but these molecules would appear to inhibit both gelatinases (MMP-2 and MMP-9). Several, such as compounds **19a**, **19b**, **22a**, **26**, **32**, **33a**, **36**, and **38a** include MMP-14 in their spectrum of inhibition. The inhibition of MMP-2, -9, and -14 was slow-binding in nature, consistent with

Table 1. Kinetic Parameters for Inhibition of MMPs by Selected Compounds, and Half-Lives for Metabolism



		K_i (μM)						
compd	X	MMP-1[a]	MMP-2[b]	MMP-3[a]	MMP-7[a]	MMP-9[b]	MMP-14[b]	half-life in rat liver S9 (min)
1[c]	*p*-H	206 ± 60	0.0139 ± 0.0004	15 ± 6	96 ± 41	0.6 ± 0.2	0.037 ± 0.003	4.4 ± 0.3
19a	*p*-F	NI[d] (20 μM)	0.061 ± 0.007	50% (20 μM)	9% (20 μM)	0.044 ± 0.005[a]	0.580 ± 0.140	3.7 ± 0.1
19b	*m*-F	7% (100 μM)	0.45 ± 0.1	27 ± 8	NI[d] (125 μM)	3.0 ± 0.3	0.19 ± 0.04	2.9 ± 0.2
22a	*p*-I	NI[d] (60 μM)	0.60 ± 0.11	18% (60 μM)	NI[d] (10 μM)	0.29 ± 0.07		7.2 ± 0.9
26	*p*-CH_2OH	205 ± 8	0.078 ± 0.013	4.1 ± 0.5	48.5 ± 5	0.390 ± 0.085	0.215 ± 0.012	13 ± 0.5
30a[c]	*p*-OH	128 ± 6	0.006 ± 0.003	2.2 ± 0.2	31.0 ± 4	0.160 ± 0.080	0.090 ± 0.050	23 ± 2
32	*p*-O*i*Pr	11% (50 μM)	0.30 ± 0.09	17 ± 4	30% (20 μM)	0.47 ± 0.10	0.28 ± 0.10	11 ± 1
33a	*p*-OMOM	6% (100 μM)	0.18 ± 0.05	12 ± 4	19% (75 μM)	0.16 ± 0.05	0.14 ± 0.04	7.7 ± 0.4
35a[c]	*p*-OMs	140 ± 7	0.023 ± 0.005	0.575 ± 0.030	18.2 ± 3	0.005 ± 0.005	0.145 ± 0.010	27 ± 2
36[c]	*p*-NH_2	10% (250 μM)	0.024 ± 0.015	23.4 ± 1.6	16% (250 μM)	0.87 ± 0.11	0.22 ± 0.02	11 ± 2, 50 ± 4
38a	*p*-OCF_3	3% (20 μM)	0.110 ± 0.040	14% (20 μM)	NI[d] (20 μM)	0.930 ± 0.090	5.08 ± 0.510	7.3 ± 0.3

[a]K_i is calculated from a Dixon plot as competitive inhibition. [b]K_i is calculated from the ratio of k_{off}/k_{on}. Slow-binding parameters (k_{off} and k_{on} values) are given in the Supporting Information. [c]Reported earlier, and given here for the sake of side-by-side comparison: **1**,[1] **30a**,[9] **35a**,[18] **36**.[19] [d]NI, no inhibition.

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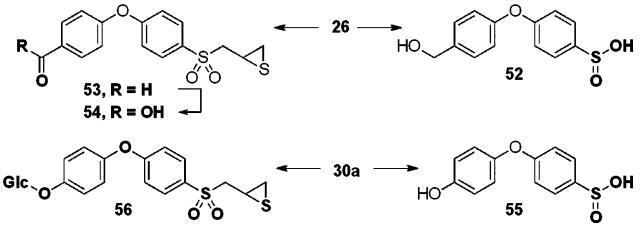
the mechanism that we have disclosed for the thiirane inhibitor class involving an enzyme-mediated reaction within the active site.[7] On the other hand, the entire set of compounds given in Table 1 were either not inhibitory or only poorly so for MMP-1, -3, and -7, as representatives of other classes of MMPs. In the few cases for which it was warranted that we evaluate the K_i values, the kinetic mechanism was linear competitive and not slow-binding inhibition. The slow-binding inhibition is the hallmark of the thiirane class of compounds for potent inhibition.[7]

Metabolic stability for compounds listed in Table 1 was evaluated in rat liver S9. SB-3CT (**1**) had a half-life of 4.4 ± 0.3 min. SB-3CT is primarily metabolized by oxidation at the *para* position of the terminal phenyl ring and at the methylene adjacent to the sulfone moiety to generate the sulfinic acid.[9] In general, addition of electron-withdrawing groups at the terminal phenyl ring decreased the half-life relative to that of SB-3CT, while electron-donating groups increased the half-life. Addition of fluorine at the *para* position (compound **19a**) decreased the half-life to 3.7 ± 0.1 min. Blocking the *para* position of the terminal phenyl ring prevented metabolism at that site; however, oxidation at the α-methylene to the sulfone group to give the corresponding sulfinic acid was the major metabolism pathway. Addition of electron-donating groups such as OCF_3 (compound **38a**) also blocked oxidation at the terminal phenyl ring and resulted in a lesser degree of oxidation at the α-methylene to the sulfone, thereby increasing the half-life to 7.3 ± 0.3 min. Incorporation of CH_2OH (**26**) increased the half-life to 13 ± 0.5 min. Three minor metabolites were observed: the sulfinic acid **52**, oxidation of the α-methylene to the hydroxyl group to generate the aldehyde **53**, and subsequent oxidation to the carboxylic acid **54**. The electron-donating group OH (compound **30a**) prolonged the half-life to 23 ± 2 min, as this compound was less likely to be metabolized to **55**. Another minor metabolite was conjugation with glucuronic acid to give **56**.



In this manuscript we have addressed the structure−function relationship for the template of the thiirane class of gelatinase inhibitors and we have explored the issue of metabolic stability and kinetic properties of a subset of these molecules. The molecular class has been versatile, with exhibited *in vivo* activity, which makes these molecules useful for future investigations of their activities in various animal models for disease.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data for representative compounds, and the crystallographic information files (CIFs) of compounds **22a**, **23**, **25**, **37a**, **38**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +1-574-631-2933. Fax: +1-574-631-6652.

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Notes

The authors declare no competing financial interest.

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