Structural Optimization of Thiol-Based Inhibitors of Glutamate Carboxypeptidase II by Modification of the P1′ Side Chain

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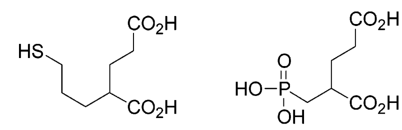
A series of thiol-based inhibitors containing a benzyl moiety at the P1′ position have been synthesized and tested for their abilities to inhibit glutamate carboxypeptidase II (GCP II). 3-(2-Carboxy-5-mercaptopentyl)-benzoic acid **6c** was found to be the most potent inhibitor with an IC_{50} value of 15 nM, 6-fold more potent than 2-(3-mercaptopropyl)pentanedioic acid (2-MPPA), a previously discovered, orally active GCP II inhibitor. Subsequent SAR studies have revealed that the phenoxy and phenylsulfanyl analogues of **6c**, 3-(1-carboxy-4-mercaptobutoxy)benzoic acid **26a** and 3-[(1-carboxy-4-mercaptobutyl)thio]benzoic acid **26b**, also possess potent inhibitory activities toward GCP II. In the rat chronic constriction injury (CCI) model of neuropathic pain, compounds **6c** and **26a** significantly reduced hyperalgesia following oral administration (1.0 mg/kg/day).

Introduction

Inhibitors of glutamate carboxypeptidase II (GCP II, EC 3.4.17.21) have shown efficacy in a variety of animal models of neurological diseases associated with glutamate excitotoxicity.[1,2] Recently, we found that 2-(3-mercaptopropyl)-pentanedioic acid (2-MPPA, Chart 1), the first reported orally available GCP II inhibitor, exhibits antinociceptive effects in a rat chronic constrictive injury (CCI) model of neuropathic pain following daily oral administration,[3] thereby potentially extending the therapeutic utility of GCP II inhibitors to multiple chronic disorders associated with glutamate excitotoxicity. Consequently, we found that the treatment of G93A FALS (familial amyotrophic lateral sclerosis) transgenic mice with 2-MPPA by oral administration resulted in statistically significant prolongation in median survival.[4] The discovery of 2-MPPA and its therapeutic utility in multiple animal models prompted us to further conduct structure−activity relationship (SAR) studies on thiol-based GCP II inhibitors.

Identifying more potent GCP II inhibitors using 2-MPPA as a template, however, posed a challenge because the metallopeptidase has been known to have a high degree of specificity for both substrates and inhibitors. Only two types of natural peptides are known as substrates for GCP II, *N*-acetylaspartylglutamate (NAAG) and folate poly-γ-glutamates. A common feature of these peptides is the presence of acidic residues including a C-terminal glutamate. Thus, most of the substrate-based GCP II inhibitors contain a glutarate (pentanedioic acid) moiety linked to a zinc binding group.[5] This core structure allows the compounds to interact with both the glutamate recognition site of the enzyme and the active site zinc atom(s), demonstrating a potent inhibitory effect. An attempt to further improve the inhibitory potency by modifying the glutarate moiety has not been vigorously pursued in the past because such a modification is expected to cause significant loss in potency. For instance, we have previously evaluated the influence of the P1′ side chain variability on the binding of 2-(phosphonomethyl)-pentanedioic acid (2-PMPA, Chart 1) and found that any alteration of the side chain greatly reduces GCP II inhibitory potency.[6]

Chart 1



Over the past decades, tremendous efforts have been made in identifying glutamate mimetics, particularly in the field of glutamate receptor agonists and antagonists.[7] A variety of compounds have been found to elicit affinity equal to or better than that of glutamate. Very recently, Miller's group reported the synthesis of conformationally constricted analogues containing a [1,2]oxazinane-3,6-dicarboxylic acid for the replacement of the terminal glutamate residue.[8] They found that IC_{50} values of these compounds for GCP II were comparable to the K_m value for NAAG. More recently, crystal structures of GCP II in complex with its inhibitors were determined at high resolution.[9] Crystallographic analysis revealed that the S1′ pocket filled with the glutarate moiety presents unoccupied hydrophobic space formed by the side chains of Leu428, Phe209, Lys699, and Tyr700. These new findings indicate that there is still an opportunity to improve the potency by modifying the P1′ side chain of 2-MPPA despite the presumed strict structural requirement at this part of the molecule for GCP II inhibition.

On the basis of synthetic feasibility, we have chosen to examine thiol-based GCP II inhibitors containing a carboxybenzyl group at the P1′ position as a substitute for a carboxyethyl group of 2-MPPA. In this paper, we describe the synthesis and biological evaluation of these new thiol-based analogues, leading to the discovery of a class of GCP II inhibitors superior to 2-MPPA in both in vitro and in vivo assessments.

Chemistry

The synthesis of P1′-carboxybenzyl-containing analogues of 2-MPPA is outlined in Scheme 1. The previously reported synthesis of 2-MPPA utilized monosubstituted Meldrum's acid **1** as a key intermediate,[3] which was coupled with methyl

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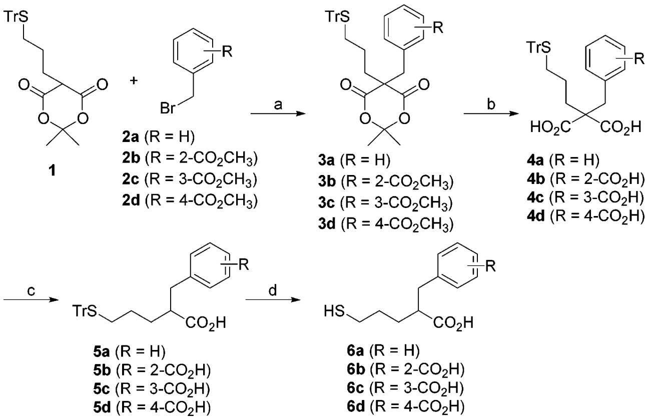
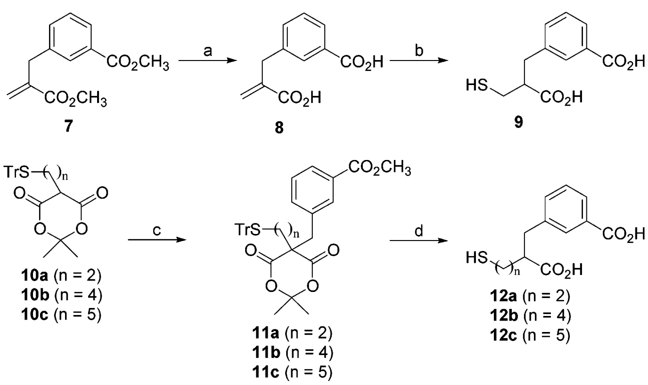
Scheme 1. Synthesis of Compounds **6a-d**[a]



[a] Reagents and conditions: (a) K_2CO_3, benzyltriethylammonium chloride, acetonitrile, 75 °C, 86% for **3a**, 76% for **3b**, 69% for **3c**,79% for **3d**; (b) 2.0 M NaOH−dioxane, 100 °C, 100% crude yield; (c) DMSO, 130 °C, 78% for **5a**, 51% for **5b**, 95% for **5c**, 85% for **5d**; (d) triisopropylsilane, TFA, dichloromethane, room temp, 85% for **6a**, 43% for **6b**, 89% for **6c**, 90% for **6d**.

Scheme 2. Synthesis of Compounds **9** and **12a−c**[a]



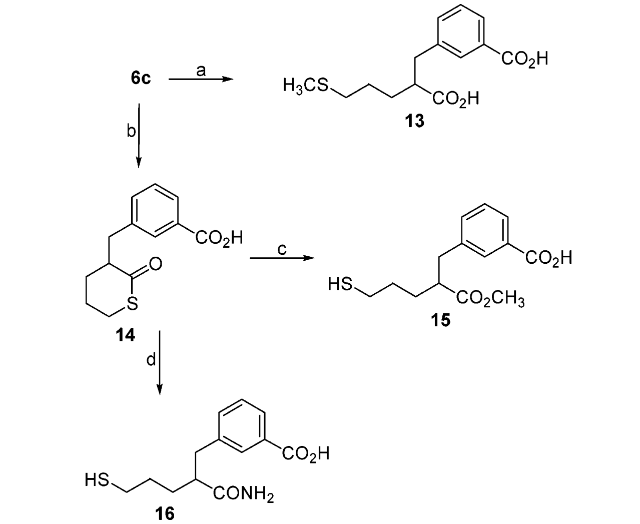
[a] Reagents and conditions: (a) 4.3 M NaOH−dioxane, room temp, quantitative yield; (b) (i) thiolacetic acid, dichloromethane, DMF, room temp; (ii) 4.3 M NaOH−dioxane, room temp, 86%; (c) methyl (3-bromomethyl)benzoate **2c**, K_2CO_3, benzyltriethylammonium chloride, acetonitrile, 75 °C, 54% for **11a**, 65% for **11b**, 88% for **11c**; (d) (i) 2.0 M NaOH−dioxane, 100 °C; (ii) DMSO, 130 °C; (iii) triisopropylsilane, TFA, dichloromethane, room temp, 80% for **12a**, 77% for **12b**, 86% for **12c**.

acrylate via Michael addition reaction. This type of coupling reaction with **1** can also be conducted using other relatively reactive electrophiles such as benzyl bromide as a substitute for methyl acrylate. Indeed, reaction of **1** and benzyl bromide **2a** gave disubstituted Meldrum's acid **3a** in 86% yield (Scheme 1). Hydrolysis of the acetonide ring of **3a** afforded diacid **4a**. Subsequent decarboxylation in DMSO and the removal of the trityl group by TFA/triisopropylsilane afforded **6a**. The same method was successfully applied to the synthesis of three carboxybenzyl analogues **6b−d** using the corresponding benzyl bromide **2b−d**, respectively.

Analogues of **6c** with various alkyl chain lengths were synthesized as illustrated in Scheme 2. The shortest analogue **9** was prepared from acrylate dieseter **7**.[10] Hydrolysis of the ester groups provided the corresponding diacid **8**. Addition of thiolacetic acid and the subsequent deacetylation gave **9**. Other analogues **12a−c** were synthesized using the same method as described for **6c** but starting with monosubstituted Meldrum's acids **10a−c**, respectively.

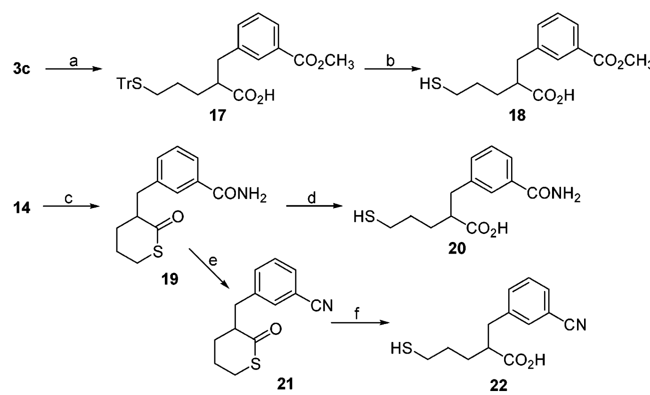
We have also synthesized various **6c** analogues where one of its key moieties was slightly modified. As shown in Scheme 3, the *S*-methyl derivative **13** was prepared by treating **6c** with methyl iodide under basic conditions. Compound **6c** was converted into the corresponding monomethyl ester **15** and amide **16** through methanolysis and aminolysis of **14**, respectively. As illustrated in Scheme 4, the methyl benzoate analogue **18** was prepared from the disubstituted Meldrum's acid **3c** while benzamide and benzonitrile analogues **20** and **22** were prepared from a common intermediate **19**.

Scheme 3. Synthesis of Compounds **13**, **15**, and **16**[a]



[a] Reagents and conditions: (a) iodomethane, sodium methoxide, methanol, room temp, quantitative yield; (b) 10-camphorsulfonic acid, toluene, reflux, 67%; (c) sodium methoxide, methanol, room temp, 83%; (d) 28% ammonium hydroxide, room temp, 87%.

Scheme 4. Synthesis of Compounds **18**, **20**, and **22**[a]

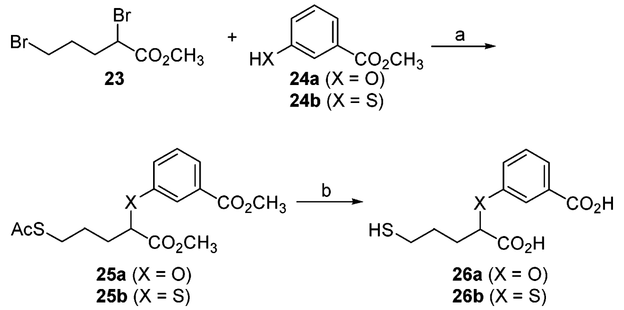


[a] Reagents and conditions: (a) (i) sodium hydroxide, water−dioxane, room temp; (ii) DMSO, 130 °C, 57%; (b) triisopropylsilane, TFA, dichloromethane, room temp, 53%; (c) ammonium chloride, diisopropylethylamine, HATU, DMF, room temp, 98%; (d) sodium hydroxide, THF−water, room temp, 87%; (e) oxalyl chloride, DMF, acetonitrile, 0 °C, 88%; (f) 1 M NaOH−THF, room temp, 89%.

Scheme 5 summarizes the synthesis of the ether and sulfide-containing analogues **26a** and **26b**. Methyl 2,5-dibromovalerate **23** was treated with **24a** or **24b** and subsequently with potassium thioacetate to give the penultimate precursor **25a** or **25b**, respectively. Base-mediated hydrolysis of the methyl esters and thioacetyl group afforded **26a** and **26b**.

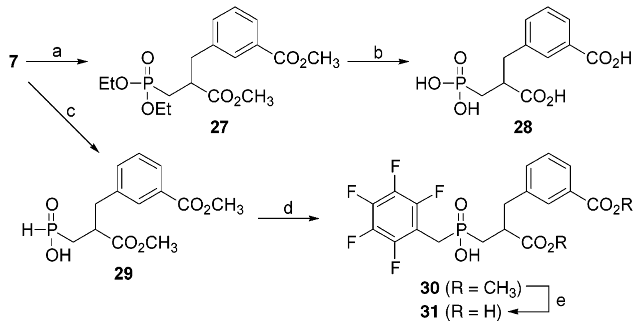
In addition, we synthesized analogues of **6c** in which its sulfhydryl group is substituted with other zinc-binding groups commonly used in metalloprotease inhibitors. As illustrated in Scheme 6, the synthesis of the phosphonate-based compound **28** involves the 1,4-addition of diethyl phosphite to acrylate dieseter **7** followed by hydrolysis of all the ester groups. The acrylate dieseter **7** also served as a starting material for the synthesis of the phosphinate-based compound **31** (Scheme 6).

Scheme 5. Synthesis of **26a** and **26b**[a]



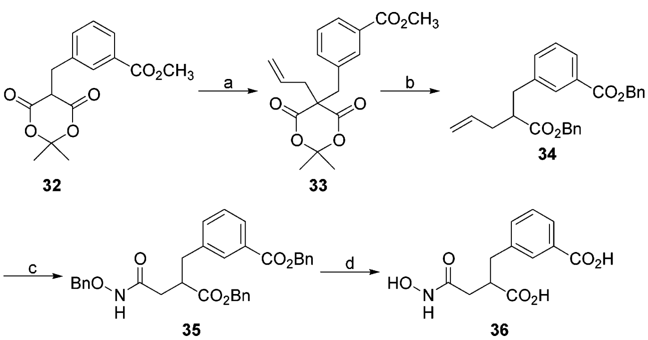
[a] Reagents and conditions: (a) (i) K_2CO_3, DMF; (ii) potassium thioacetate, DMF, 37% for **25a**, 68% for **25b**; (b) NaOH, dioxane−THF, room temp, 69% for **26a**, 86% for **26b**.

Scheme 6. Synthesis of **28** and **31**[a]



[a] Reagents and conditions: (a) diethyl phosphite, NaH, THF, room temp, 86%; (b) 12 M HCl, 100 °C, 79%; (c) BTSP, dichloromethane, room temp, 80%; (d) pentafluorobenzyl bromide, BSA, dichloromethane, 40 °C, 97%; (e) 12 M HCl, 100 °C, 15%.

Scheme 7. Synthesis of **36**[a]

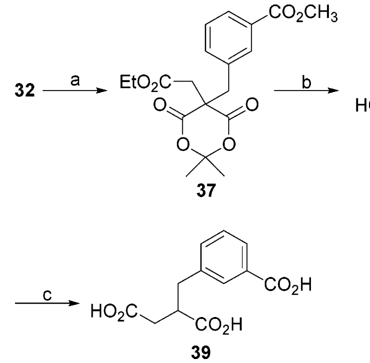


[a] Reagents and conditions: (a) K_2CO_3, benzyltriethylammonium chloride, allyl bromide, acetonitrile, 75 °C, 69%; (b) (i) 2 M NaOH−dioxane, 100 °C; (ii) DMSO, 130 °C; (iii) BnOH, EDC, DMAP, dichloromethane, room temp, 77% from **33**; (c) (i) RuO_2, $NaIO_4$, acetonitrile−water, room temp; (ii) $BnONH_2$·HCl, EDC, DIEA, DMAP, dichloromethane, room temp, 70%; (d) H_2 (21 psi), Pd/C, MeOH, room temp, 97%.

The treatment of **7** with bis(trimethylsilyl)phosphonite (BTSP) generated in situ from ammonium hypophosphite, chlorotrimethylsilane, and triethylamine afforded monosubstituted phosphinic acid **29**. Alkylation of **29** with pentafluorobenzyl bromide was successfully accomplished using a procedure similar to the one reported by Reiter's group,[11] providing disubstituted phosphinic acid **30**. A subsequent acidic hydrolysis of the two methyl ester groups gave the final product **31**.

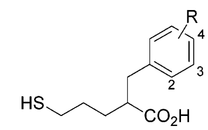
Synthesis of the hydroxamate-based compound **36** (Scheme 7) is similar to the method previously described.[12] Alkylation of **32** with allyl bromide gave the disubstituted Meldrum's acid **33**. The acetonide and methyl ester groups of **33** were hydrolyzed by treatment with sodium hydroxide in dioxane/water. Subsequent decarboxylation and condensation with benzyl alcohol afforded the dibenzyl ester **34**. Oxidation of the terminal olefin into a carboxylic acid, followed by coupling with benzyloxyamine gave the fully protected precursor **35**. The benzyl groups were removed by catalytic hydrogenolysis to yield the desired compound **36**.

Scheme 8. Synthesis of **39**[a]



[a] Reagents and conditions: (a) K_2CO_3, benzyltriethylammonium chloride, ethyl bromoacetate, acetonitrile, 65 °C, 60%; (b) 2 M NaOH, 100 °C, 100% crude yield; (c) DMSO, 130 °C, 68% from **37**.

Table 1. Inhibition of GCP II by Thiol-Based Inhibitors **6a-d**



compd	R	IC_{50} (nM)[a]
6a	H	1400 ± 600
6b	2-CO_2H	1700 ± 100
6c	3-CO_2H	15 ± 10
6d	4-CO_2H	63 ± 32

[a] Values are the mean ± SD of three or more independent experiments.

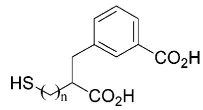
Compound **32** was also utilized in the synthesis of succinic acid-based inhibitor **39** as outlined in Scheme 8. Treatment of **32** with ethyl bromoacetate gave the disubstituted Meldrum's acid **37**. Subsequent hydrolysis and decarboxylation afforded the desired compound **39**.

Biological Results and Discussion

In Vitro GCP II Assay. The in vitro GCP II inhibitory potencies were measured using *N*-acetyl-L-aspartyl-[^{3}H]-L-glutamate as a substrate and human recombinant GCP II[13] as previously reported.[14] Table 1 summarizes the inhibitory effects of 2-benzyl-5-mercaptopentanoic acid **6a** and its carboxylated derivatives **6b**−**d**. The compound **6a** is more than 10-fold less potent than 2-MPPA in inhibiting GCP II. This was expected because the loss of one of the two carboxylates weakens the interaction with the glutamate recognition site of GCP II. Introduction of a carboxyl group onto the phenyl ring of **6a** had an effect on the inhibitory potency in a position-dependent manner. Ortho-substituted analogue **6b** was equally potent as **6a**, while the meta- and para-substituted analogues **6c** and **6d** exhibited significantly improved inhibitory potency in the GCP II assay with IC_{50} values of 15 and 63 nM, respectively. This is noteworthy because these two compounds are more potent GCP II inhibitors than 2-MPPA and represent the first successful attempt to improve the potency by modifying the glutarate moiety of the GCP II inhibitors.

To better understand the structure−activity relationship of this new class of thiol-based GCP II inhibitors, we selected the most potent inhibitor **6c** as a template for further structural modification. Table 2 summarizes the effect of carbon chain

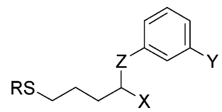
Table 2. Effect of Thioalkyl Chain Length on GCP II Inhibitory Potency



compd	n	IC_{50} (nM)[a]
7a	1	440 ± 180
7b	2	1100 ± 400
6c	3	15 ± 5
7c	4	390 ± 260
7d	5	190 ± 70

[a] Values are the mean ± SD of three or more independent experiments.

Table 3. Inhibition of GCP II by Analogues of **6c**



compd	R	X	Y	Z	IC_{50} (nM)[a]
6c	H	CO_2H	CO_2H	CH_2	15 ± 5
13	CH_3	CO_2H	CO_2H	CH_2	>20000
5c	Ph_3C	CO_2H	CO_2H	CH_2	>20000
15	H	CO_2CH_3	CO_2H	CH_2	730 ± 300
16	H	$CONH_2$	CO_2H	CH_2	640 ± 90
6a	H	CO_2H	H	CH_2	1400 ± 600
18	H	CO_2H	CO_2CH_3	CH_2	2700 ± 1700
20	H	CO_2H	$CONH_2$	CH_2	2200 ± 400
22	H	CO_2H	CN	CH_2	1800 ± 800
26a	H	CO_2H	CO_2H	O	14 ± 7
26b	H	CO_2H	CO_2H	S	32 ± 14

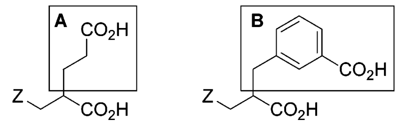
[a] Values are the mean ± SD of three or more independent experiments.

length of the mercaptoalkyl group on inhibitory potency. GCP II inhibitory potency of **7a**−**d** and **6c** toward GCP II was found to be dependent on the length of the mercaptoalkyl group. The compound **6c**, containing a mercaptopropyl group, is the most potent, and the shorter and longer mercaptoalkyl groups resulted in a significant loss of potency. A similar trend was observed in the previously reported SAR studies on the corresponding analogues of 2-MPPA.[3]

In addition, we have assessed the effect of minor modifications to the molecular structure of **6c** on the GCP II inhibitory potency. The results are summarized in Table 3. Blocking of the thiol group of **6c** resulted in complete loss of potency as shown by compounds **13** and **5c**. This can be attributed to the inability of these compounds to interact with the active site zinc atom(s). We also tested analogues where one of the two carboxylic groups in compound **6c** is replaced with methyl ester (compounds **15** and **18**), carboxamide (compounds **16** and **20**), or cyano group (compound **22**). Although the degree of effect was not as significant as that of the thiol-blocking, these compounds exhibited 40- to 180-fold decrease in GCP II inhibitory potency. These results clearly indicate that the thiol and the two carboxyl groups of **6c** play key roles in interacting with the active site of GCP II. Unlike these key functional groups, replacement of the benzyl carbon in **6c** with either an ether or sulfide linker was well tolerated, providing equally potent GCP II inhibitors **26a** and **26b** with IC_{50} values of 14 and 32 nM, respectively.

Our SAR analysis was extended to other zinc-binding groups to determine whether the same degree of improvement as with compound **6c** (6-fold greater potency than 2-MPPA) can be achieved with the previously reported classes of GCP II inhibitors such as phosphonate (2-PMPA), phosphinate **40**,[6] hydroxamate **41**,[12] and carboxylate **42**[12] by replacing their P1′ side chain from 2-carboxyethyl group (region A in Table 4) to 3-carboxybenzyl group (region B in Table 4). As summarized in Table 4, none of the four newly synthesized 3-carboxybenzyl group-containing compounds **28**, **31**, **36**, and **39** exhibited improvement in inhibitory potency over the parent 2-carboxyethyl group-containing counterparts. Instead, in three cases (2-PMPA to **28**, **40** to **31**, and **41** to **36**), the replacement with the 3-carboxybenzyl group resulted in significant loss of potency. These results demonstrate that the benefit of introducing a 3-carboxybenzyl group to the P1′ side chain is unique to the thiol-based GCP II inhibitors and does not necessarily apply to other classes of GCP II inhibitors.

Table 4. Effect of P1′ Substitution on GCP II Inhibitory Potency



compd	Z	P1′	IC_{50} (nM)[a]
2-MPPA	$HS(CH_2)_2$	A	90 ± 26[b]
6c		B	15 ± 5
2-PMPA	$(HO)_2OP$	A	0.30 ± 0.05[b]
28		B	120 ± 30
40	$(C_6F_5CH_2)(HO)OP$	A	82 ± 14[b]
31		B	2400 ± 700
41	HONOC	A	220 ± 40[b]
36		B	15000 ± 4000
42	HO_2C	A	20000 ± 2000[b]
39		B	15000 ± 5000

[a] Values are the mean ± SD of three or more independent experiments. [b] Values have been previously reported and are included herein for reference purposes.

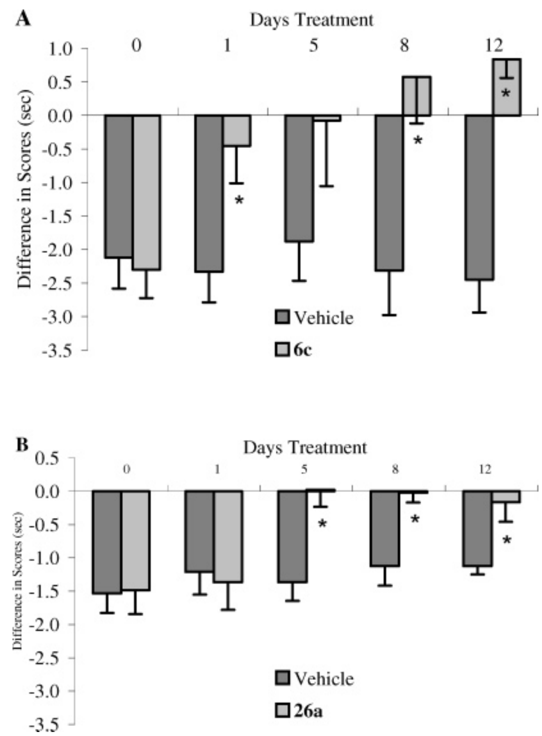


Figure 1. Antinociceptive effects of **6c** (A) and **26a** (B) in the rat chronic constriction injury (CCI) model of neuropathic pain. Both of these compounds were tested at 1.0 mg/kg/day by oral administration and significantly attenuated the CCI-induced hyperalgesic state relative to the vehicle-treated control (∗, $p < 0.05$).

Antinociceptive Effects of 6c in the Rat Chronic Constriction Injury (CCI) Model. We have subsequently tested the two most potent GCP II inhibitors **6c** and **26a** for their antinociceptive effects following oral administration (1.0 mg/kg/day) using the rat chronic constriction injury model of neuropathic pain.[15] As shown in Figure 1, both **6c** and **26a** significantly reduced thermal hyperalgesia relative to the vehicle-treated control on days 8 and 12. It should be noted that the effective doses for **6c** and **26a** are lower by an order of magnitude compared to that of 2-MPPA (10 mg/kg/day), presumably due to their improved potency toward GCP II. The results also suggest that both of these new thiol-based inhibitors are orally available and suitable for the treatment of chronic neuropathic pain.

Conclusions

Through the modifications of the P1′ side chain, we have successfully identified a new series of thiol-based GCP II inhibitors. Some of these compounds display in vitro potency superior to 2-MPPA. As represented by **6c** and **26a**, the improved potency was well-reflected in the subsequent assessment in the animal model of neuropathic pain, where these two compounds exhibited efficacy by daily oral dosing of 1.0 mg/kg, 10 times lower than the effective dose of 2-MPPA.

Relatively straightforward synthetic methods, combined with the easy availability of diverse benzyl bromides and phenols, allow us to expand our future SAR analysis to a wide variety of analogues within this class of GCP II inhibitors. In the meantime, further pharmacological characterizations of **6c** and **26a** are currently underway in various animal models of the neurological disorders associated with glutamate excitotoxicity.

Experimental Section

All reactions were performed under nitrogen. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Methyl 2,5-dibromovalerate **23** was obtained from AmeriBrom, Inc., Fort Lee, NJ. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra were recorded at 75 or 100 MHz. ^{31}P NMR spectra were recorded at 162 MHz. Elemental analysis results were obtained from Atlantic Microlabs, Norcross, GA.

3-[2,2-Dimethyl-4,6-dioxo-5-(3-tritylsulfanylpropyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (3c). To a solution of **1** (6.91 g, 15.0 mmol) and triethylbenzylammonium chloride (3.42 g, 15.0 mmol) in acetonitrile (75 mL) was added anhydrous K_2CO_3 (2.07 g, 15.0 mmol), and the suspension was stirred at 75 °C for 20 min. To the mixture was added a solution of methyl (3-bromomethyl)benzoate **2c** (4.12 g, 18.0 mmol) in acetonitrile (10 mL), and the resulting mixture was stirred at the same temperature for 5 h. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate (100 mL). The solution was washed with aqueous 5% $KHSO_4$ (100 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting solid residue was recrystallized from EtOAc/hexanes to provide 6.30 g of **3c** as a white solid (69% yield): ^{1}H NMR ($CDCl_3$) δ 0.66 (s, 3H), 1.12−1.35 (m, 2H), 1.50 (s, 3H), 1.98−2.07 (m, 2H), 2.17 (t, J = 7.2 Hz, 2H), 3.27 (s, 2H), 3.89 (s, 3H), 7.15−7.50 (m, 17H), 7.81 (bs, 1H), 7.88−7.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 29.1, 29.4, 31.3, 40.3, 43.3, 52.2, 57.0, 66.8, 105.8, 126.7, 127.9, 128.9, 129.1, 129.5, 130.8, 131.2, 134.8, 135.7, 144.7, 166.5, 168.3.

5-Benzyl-2,2-dimethyl-5-(3-tritylsulfanylpropyl)[1,3]dioxane-4,6-dione (3a). Compound **3a** was prepared as described for the preparation of **3c**, except benzyl bromide **2a** was used in place of **2c**: white powder (86% yield); ^{1}H NMR ($CDCl_3$) δ 0.60 (s, 3H), 1.15−1.32 (m, 2H), 1.49 (s, 3H), 1.96−2.07 (m, 2H), 2.15 (t, J = 7.2 Hz, 2H), 3.23 (s, 2H), 7.10−7.32 (m, 14H), 7.35−7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8, 29.4, 31.3, 40.3, 43.7, 57.3, 66.7, 105.8, 126.7, 127.8, 127.9, 128.8, 129.5, 130.3, 135.5, 144.7, 168.6.

2-[2,2-Dimethyl-4,6-dioxo-5-(3-tritylsulfanylpropyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (3b). Compound **3b** was prepared as described for the preparation of **3c**, except methyl (2-bromomethyl)benzoate **2b** was used in place of **2c**: beige powder (76% yield); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.15−1.28 (m, 2H), 1.51 (s, 3H), 1.95−2.04 (m, 2H), 2.11 (t, J = 7.3 Hz, 2H), 3.78 (s, 2H), 3.89 (s, 3H), 7.15−7.45 (18H), 7.72−7.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.7, 29.5, 31.3, 39.6, 39.8, 52.3, 56.3, 66.6, 105.5, 126.6, 127.6, 127.8, 129.4, 130.5, 131.5, 132.1, 132.4, 135.3, 144.6, 168.0, 168.4.

4-[2,2-Dimethyl-4,6-dioxo-5-(3-tritylsulfanylpropyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (3d). Compound **3d** was prepared as described for the preparation of **3c**, except methyl (4-bromomethyl)benzoate **2d** was used in place of **2c**: white powder (79% yield); ^{1}H NMR ($CDCl_3$) δ 0.66 (s, 3H), 1.16−1.32 (m, 2H), 1.50 (s, 3H), 1.96−2.08 (m, 2H), 2.16 (t, J = 7.3 Hz, 2H), 3.27 (s, 2H), 3.88 (s, 3H), 7.12−7.44 (m, 17H), 7.93 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.7, 29.2, 29.3, 31.3, 40.4, 43.3, 52.1, 56.9, 66.8, 105.8, 126.7, 127.9, 129.5, 129.6, 130.0, 130.5, 140.4, 144.7, 166.6, 168.3.

3-(2-Carboxy-5-tritylsulfanylpentyl)benzoic Acid (5c). A suspension of **3c** (6.10 g, 10.0 mmol) in 2.0 M NaOH (30 mL) and dioxane (10 mL) was stirred at 100 °C for 3 h. The resulting clear solution was concentrated, acidified to pH 1 by adding 1.0 M H_2SO_4, and extracted with EtOAc (100 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated to give 5.80 g of 2-(3-carboxybenzyl)-2-(3-tritylsulfanylpropyl)malonic acid **4c** as a crude material (100% crude yield). This material was dissolved in DMSO (15 mL), and the solution was stirred at 130 °C for 3 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL). The organic solution was washed with water (50 mL × 3) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residual material was recrystallized from EtOAc/hexanes to give 4.85 g of **5c** as a white solid (95% yield from **3c**): mp 196−197 °C; ^{1}H NMR (CD_3OD) δ 1.23−1.60 (m, 4H), 2.08−2.20 (m, 2H), 2.43−2.55 (m, 1H), 2.65−2.77 (m, 1H), 2.80−2.93 (m, 1H), 7.15−7.45 (m, 17H), 7.80−7.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 27.9, 32.8, 33.1, 39.4, 48.7, 66.1, 128.1, 129.3, 129.9, 131.2, 131.6, 132.4, 135.1, 142.6, 146.8, 170.3, 179.1. Anal. ($C_{32}H_{30}O_4S$) C, H, S.

2-Benzyl-5-tritylsulfanylpentanoic Acid (5a). Compound **5a** was prepared as described for the preparation of **5c**, except 5-benzyl-2,2-dimethyl-5-(3-tritylsulfanylpropyl)[1,3]dioxane-4,6-dione **3a** was used in place of **3c**: off-white solid (78% yield from **3a**); ^{1}H NMR ($CDCl_3$) δ 1.28−1.65 (m, 4H), 2.13 (t, J = 6.9 Hz, 2H), 2.45−2.59 (m, 1H), 2.66 (dd, J = 6.6, 13.6 Hz, 1H), 2.89 (dd, J = 8.1, 13.6 Hz, 1H), 7.07−7.32 (m, 15H), 7.35−7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.3, 31.0, 31.6, 37.9, 46.8, 66.5, 126.5, 126.6, 127.8, 128.4, 128.8, 129.6, 138.8, 144.9, 180.8.

2-(2-Carboxy-5-tritylsulfanylpentyl)benzoic Acid (5b). Compound **5b** was prepared as described for the preparation of **5c**, except 2-[2,2-dimethyl-4,6-dioxo-5-(3-tritylsulfanylpropyl)[1,3]dioxan-5-ylmethyl]benzoic acid methyl ester **3b** was used in place of **3c**: yellow solid (51% from **3b**); ^{1}H NMR (CD_3OD) δ 1.20−1.58 (m, 4H), 2.09 (t, J = 7.0 Hz, 2H), 2.51−2.64 (m, 1H), 3.03 (dd, J = 9.0, 13.1 Hz, 1H), 3.20 (dd, J = 6.0, 13.1 Hz, 1H), 7.12−7.29 (m, 11H), 7.30−7.40 (m, 7H), 7.91 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 27.5, 32.8, 33.0, 37.9, 40.4, 67.6, 127.6, 127.7, 128.8, 130.7, 131.3, 132.2, 132.8, 132.9, 142.5, 146.3, 170.7, 179.3.

4-(2-Carboxy-5-tritylsulfanylpentyl)benzoic Acid (5d). Compound **5d** was prepared as described for the preparation of **5c**, except 4-[2,2-dimethyl-4,6-dioxo-5-(3-tritylsulfanylpropyl)[1,3]dioxan-5-ylmethyl]benzoic acid methyl ester **3d** was used in place of **3c**: white solid (85% yield from **3d**); ^{1}H NMR ($CDCl_3$) δ 1.35−1.75 (m, 4H), 2.08−2.28 (m, 2H), 2.52−2.69 (m, 1H), 2.76 (dd, J = 5.3, 13.9 Hz, 1H), 2.91 (dd, J = 9.3, 13.9 Hz, 1H), 7.10−7.51 (m, 17H), 7.96 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.3, 31.3, 31.6, 37.8, 46.5, 66.6, 126.6, 127.6, 127.8, 129.0, 129.6, 130.4, 144.9, 145.3, 171.9, 180.9.

3-(2-Carboxy-5-mercaptopentyl)benzoic Acid (6c). To a solution of **5c** (4.85 g, 9.50 mmol) in dichloromethane (10 mL) were added trifluoroacetic acid (10 mL) and triisopropylsilane (1.90 g, 12.0 mmol). The dark solution gradually turned light-yellow. After the mixture was stirred for 30 min, the solvent was removed under reduced pressure and the residual material was partitioned between hexanes (60 mL) and 1.0 M NaOH (40 mL containing 200 mg of tris(2-carboxyethyl)phosphine hydrochloride). The aqueous layer was washed with hexanes (20 mL), acidified to pH 1 with 1 M H_2SO_4, and extracted with EtOAc (100 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residual material was recrystallized from EtOAc/hexanes to give 2.27 g of **6c** as a white solid (89% yield): mp 123−124 °C; ^{1}H NMR (CD_3OD) δ 1.54−1.77 (m, 4H), 2.43−2.53 (m, 2H), 2.58−2.72 (m, 1H), 2.83 (dd, J = 6.1, 13.5 Hz, 1H), 2.97 (dd, J = 8.8, 13.5 Hz, 1H), 7.32−7.48 (m, 2H), 7.81−7.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.7, 31.9, 32.9, 39.2, 48.4, 128.8, 129.5, 131.2, 132.0, 134.7, 141.3, 169.9, 178.8. Anal. ($C_{13}H_{16}O_4S$) C, H, S.

2-Benzyl-5-mercaptopentanoic Acid (6a) Compound **6a** was prepared as described for the preparation of **6c**, except 2-benzyl-5-tritylsulfanylpentanoic acid **5a** was used in place of **5c**. The crude material was purified by silica gel chromatography (EtOAc/hexanes, 1:1) to give **6a** as a colorless oil (85% yield): ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.9 Hz, 1H), 1.50−1.80 (m, 4H), 2.42−2.58 (m, 2H), 2.61−2.74 (m, 1H), 2.75 (dd, J = 7.1, 13.4 Hz, 1H), 3.00 (dd, J = 7.3, 13.4 Hz, 1H), 7.10−7.35 (m, 5H), 10.5−11.5 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 30.2, 31.5, 38.0, 46.8, 126.5, 128.5, 128.8, 138.7, 181.6. Anal. ($C_{12}H_{16}O_2S$) C, H, S.

2-(2-Carboxy-5-mercaptopentyl)benzoic Acid (6b). Compound **6b** was prepared as described for the preparation of **6c**, except 2-(2-carboxy-5-tritylsulfanylpentyl)benzoic acid **5b** was used in place of **5c**. The crude material was purified by silica gel chromatography (EtOAc/hexanes, 1:4 containing 1% AcOH) to give **6b** as a colorless oil (43% yield): ^{1}H NMR (CD_3OD) δ 1.55−1.81 (m, 4H), 2.41−2.57 (m, 2H), 2.67−2.80 (m, 1H), 3.09 (dd, J = 9.5, 12.6 Hz, 1H), 3.37 (dd, J = 5.5, 13.1 Hz, 1H), 7.24−7.37 (m, 2H), 7.44, (t, J = 7.3 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 24.7, 32.4, 32.8, 38.1, 48.3, 127.6, 131.3, 132.2, 132.8, 132.9, 142.5, 170.8, 179.4. Anal. ($C_{13}H_{16}O_4S$) C, H, S.

4-(2-Carboxy-5-mercaptopentyl)benzoic Acid (6d). Compound **6d** was prepared as described for the preparation of **6c**, except 4-(2-carboxy-5-tritylsulfanylpentyl)benzoic acid **5d** was used in place of **5c**: white solid (90% yield); mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.9 Hz, 1H), 1.57−1.88 (m, 4H), 2.53 (q, J = 6.7 Hz, 2H), 2.67−2.81 (m, 1H), 2.87 (dd, J = 6.2, 13.6 Hz, 1H), 3.05 (dd, J = 8.6, 13.7 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.2, 30.6, 31.4, 38.1, 46.6, 127.6, 129.0, 130.5, 145.2, 172.1, 181.2. Anal. ($C_{13}H_{16}O_4S$) C, H, S.

3-(2-Carboxyallyl)benzoic Acid (8). A solution of 3-(2-methoxycarbonylallyl)benzoic acid methyl ester **7**[10] (10.1 g, 43.1 mmol) in dioxane (50 mL) and 4.3 M NaOH (50 mL) was stirred at room temperature overnight. The solvents were removed under reduced pressure, and the residue was partitioned between aqueous 10% $KHSO_4$ (50 mL) and EtOAc (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give 8.90 g of **8** as a white solid (100% crude yield). This material was used in the next step without further purification: ^{1}H NMR (CD_3OD) δ 3.66 (s, 2H), 5.58 (s, 1H), 6.24 (s, 1H), 7.32−7.44 (m, 2H), 7.81−7.90 (m, 2H); ^{13}C NMR (CD_3OD) δ 38.7, 127.2, 128.7, 129.5, 131.1, 132.0, 134.7, 141.1, 141.8, 170.0.

3-(2-Carboxy-3-mercaptopropyl)benzoic Acid (9). To a solution of **8** (8.90 g, 43.1 mmol) in dichloromethane (50 mL) and DMF (15 mL) was added thiolacetic acid (6.2 mL, 86.2 mmol) at room temperature, and the mixture was stirred at room temperature for 2 days. The solvents were removed under reduced pressure, and the residue was partitioned between aqueous 10% $KHSO_4$ (60 mL) and EtOAc (75 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a colorless oil. This material was dissolved in dioxane (50 mL) and 4.3 M NaOH (50 mL), and the mixture was stirred at room temperature for 4 h. The solvents were removed under reduced pressure, and the residue was acidified to pH 2 with 1 M H_2SO_4 and taken up in EtOAc (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (EtOAc/hexanes, 1:2 containing 2% AcOH) to give 8.90 g of **9** as a white solid (86% from **7**): mp 104−106 °C; ^{1}H NMR (CD_3OD) δ 2.67 (d, J = 6.3 Hz, 2H), 2.78−2.90 (m, 1H), 2.94−3.05 (m, 2H), 7.34−7.48 (m, 2H), 7.82−7.90 (m, 2H); ^{13}C NMR (CD_3OD) δ 26.1, 37.8, 52.1, 129.0, 129.6, 131.3, 132.1, 134.7, 140.6, 169.8, 176.9. Anal. ($C_{11}H_{12}O_4S$) C, H, S.

2,2-Dimethyl-5-(2-tritylsulfanylethyl)[1,3]dioxane-4,6-dione (10a). Compound **10a** was prepared as previously described for the preparation of **1**,[3] except *S*-tritylmercaptoacetic acid was used in place of *S*-trityl-3-mercaptopropionic acid: white solid (93% yield); mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.75 (s, 3H), 2.04 (t, J = 6.5 Hz, 2H), 2.58 (t, J = 6.8 Hz, 2H), 3.60 (t, J = 6.0 Hz, 1H), 7.18−7.32 (m, 9H), 7.37−7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.5, 28.5, 29.3, 44.5, 66.9, 104.9, 126.8, 128.0, 129.5, 144.6, 164.9.

3-[2,2-Dimethyl-4,6-dioxo-5-(2-tritylsulfanyl-ethyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (11a). Compound **11a** was prepared as described for the preparation of **3c**, except 2,2-dimethyl-5-(2-tritylsulfanyl-ethyl)[1,3]dioxane-4,6-dione **10a** was used in place of **1**: white solid (54% yield); mp 154−156 °C (dec); ^{1}H NMR ($CDCl_3$) δ 0.62 (s, 3H), 1.25 (s, 3H), 2.03−2.11 (m, 2H), 2.17−2.25 (m, 2H), 3.23 (s, 2H), 3.88 (s, 3H), 7.17−7.39 (m, 17H), 7.75−7.80 (brs, 1H), 7.87−7.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.9, 29.0, 39.2, 43.0, 52.2, 56.9, 67.2, 105.8, 126.8, 128.0, 128.9, 129.1, 129.4, 130.7, 131.2, 134.8, 135.3, 144.4, 166.5, 167.7.

3-[2,2-Dimethyl-4,6-dioxo-5-(5-tritylsulfanylbutyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (11b). Compound **11b** was prepared as described for the preparation of **3c**, except 2,2-dimethyl-5-(5-tritylsulfanylbutyl)[1,3]dioxane-4,6-dione **10b** was used in place of **1** (65% yield): white solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 0.51 (s, 3H), 1.00−1.26 (m, 4H), 1.38 (s, 3H), 1.77−1.88 (m, 2H), 1.96 (t, J = 7.1 Hz, 2H), 3.14 (s, 2H), 3.73 (s, 3H), 6.98−7.28 (m, 17H), 7.66 (brs, 1H), 7.77 (dt, J = 6.3, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.4, 29.1, 29.4, 31.3, 40.7, 43.3, 52.2, 57.2, 66.6, 105.8, 126.6, 127.9, 128.9, 129.1, 129.6, 130.8, 131.3, 134.8, 135.8, 144.9, 166.6, 168.6.

3-[2,2-Dimethyl-4,6-dioxo-5-(5-tritylsulfanylpentyl)[1,3]dioxan-5-ylmethyl]benzoic Acid Methyl Ester (11c). Compound **11c** was prepared as described for the preparation of **3c**, except 2,2-dimethyl-5-(5-tritylsulfanylpentyl)[1,3]dioxane-4,6-dione **10c** was used in place of **1**: white foam (88% yield); ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 1.10−1.42 (m, 6H), 1.52 (s, 3H), 2.02−2.15 (m, 4H), 3.33 (s, 2H), 3.90 (s, 3H), 7.16−7.43 (m, 17H), 7.82−7.85 (m, 1H), 7.90−7.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.1, 28.6, 29.1, 29.3, 31.7, 41.0, 43.3, 52.2, 57.3, 66.5, 105.7, 126.5, 127.8, 128.9, 129.1, 129.6, 130.8, 131.2, 134.8, 135.8, 145.0, 166.5, 168.6.

3-(2-Carboxy-4-mercaptobutyl)benzoic Acid (12a). Compound **12a** was prepared in three steps from **11a** as described for the preparation of **6c** from **3c**: white solid (80% yield from **11a**); mp 124−126 °C; ^{1}H NMR (CD_3OD) δ 1.65−1.80 (m, 1H), 1.83−2.01 (m, 1H), 2.40−2.62 (m, 2H), 2.75−2.90 (m, 2H), 2.90−3.04 (m, 1H), 7.28−7.49 (m, 2H), 7.77−7.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 22.8, 37.5, 38.9, 47.5, 128.9, 129.5, 131.2, 132.0, 134.7, 141.0, 169.8, 178.3. Anal. ($C_{12}H_{14}O_4S$) C, H, S.

3-(2-Carboxy-6-mercaptohexyl)benzoic Acid (12b). Compound **12b** was prepared in three steps from **11b** as described for the preparation of **6c** from **3c** (77% yield from **11b**): white solid; mp 81−83 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.8 Hz, 1H), 1.40−1.79 (m, 6H), 2.51 (q, J = 7.5 Hz, 2H), 2.63−2.74 (m, 1H), 2.88 (dd, J = 6.0, 13.6 Hz, 1H), 2.99 (dd, J = 9.0, 13.6 Hz, 1H), 7.33−7.46 (m, 2H), 7.85−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.0, 31.3, 33.7, 38.1, 47.7, 128.5, 128.7, 129.4, 130.5, 134.4, 139.3, 172.2, 181.6. Anal. ($C_{14}H_{18}SO_4$) C, H, S.

3-(2-Carboxy-7-mercaptoheptyl)benzoic Acid (12c). Compound **12c** was prepared in three steps from **11c** as described for the preparation of **6c** from **3c**: white solid (86% yield from **11c**); mp 80−82 °C; ^{1}H NMR (CD_3OD) δ 1.26−1.47 (m, 4H), 1.47−1.72 (m, 4H), 2.45 (t, J = 7.0 Hz, 2H), 2.56−2.72 (m, 1H), 2.82 (dd, J = 5.9, 13.6 Hz, 1H), 2.95 (dd, J = 8.8, 13.5 Hz, 1H), 7.32−

7.48 (m, 2H), 7.81−7.93 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.8, 27.8, 29.1, 33.1, 34.9, 39.2, 48.8, 128.8, 129.5, 131.2, 132.0, 134.7, 141.4, 169.9, 179.1. Anal. ($C_{15}H_{20}O_4S$) C, H, S.

3-(2-Carboxy-5-methylsulfanylpentyl)benzoic Acid (13). To a solution of **6c** (2.00 g, 7.45 mmol) in methanol (20 mL) were added sodium methoxide (25 wt % solution in methanol, 6.5 mL) and iodomethane (0.51 mL, 8.20 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was partitioned between aqueous 10% $KHSO_4$ (30 mL) and EtOAc (50 mL). The organic layer was washed with saturated aqueous sodium thiosulfate (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to give 2.10 g of **13** as a white solid (quantitative yield): mp 72−74 °C; ^{1}H NMR (CD_3OD) δ 1.54−1.81 (m, 4H), 2.03 (s, 3H), 2.38−2.55 (m, 2H), 2.60−2.74 (m, 1H), 2.83 (dd, *J* = 5.9, 13.7 Hz, 1H), 2.97 (dd, *J* = 9.0, 13.7 Hz, 1H), 7.33−7.48 (m, 2H), 7.82−7.93 (m, 2H); ^{13}C NMR (CD_3OD) δ 15.2, 27.8, 32.2, 34.7, 39.2, 48.5, 128.8, 129.5, 131.2, 132.0, 134.7, 141.3, 169.9, 178.8. Anal. ($C_{14}H_{18}O_4S$) C, H, S.

3-(2-Oxotetrahydrothiopyran-3-ylmethyl)benzoic Acid (14). A solution of **6c** (5.12 g, 19.1 mmol) and 10-camphorsulfonic acid (0.50 g, 2.2 mmol) in toluene (30 mL) was refluxed for 6 h in a flask equipped with a Dean−Stark trap. The solvent was removed under reduced pressure, and the residual material was purified by chromatography (EtOAc/hexanes, 1:4). The resulting white solid was recrystallized from EtOAc/hexanes to give 3.20 g of **14** as a white solid (67% yield): ^{1}H NMR ($CDCl_3$) δ 1.55−1.69 (m, 1H), 1.89−2.01 (m, 2H), 2.03−2.14 (m, 1H), 2.72 (dd, *J* = 9.0, 13.6 Hz, 1H), 2.77−2.86 (m, 1H), 3.07−3.19 (m, 2H), 3.41 (dd, *J* = 4.0, 13.6 Hz, 1H), 7.38−7.48 (m, 2H), 7.93 (s, 1H), 7.98 (dd, *J* = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2, 27.4, 30.6, 36.3, 51.5, 128.3, 128.7, 129.4, 130.8, 134.8, 139.7, 172.2, 203.2.

3-(5-Mercapto-2-methoxycarbonylpentyl)benzoic Acid (15). To a solution of **14** (0.325 g, 1.30 mmol) in MeOH (3 mL) was added sodium methoxide (25 wt % solution in methanol, 0.3 mL). The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was partitioned between 10% $KHSO_4$ (30 mL) and EtOAc (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residual material was purified by chromatography (EtOAc/hexanes, 7:3 containing 1% AcOH) to give 0.308 g of **15** as a white solid (83% yield): mp 51−53 °C; ^{1}H NMR (CD_3OD) δ 1.51−1.80 (m, 4H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.64−2.77 (m, 1H), 2.85 (dd, *J* = 5.9, 13.5 Hz, 1H), 2.94 (dd, *J* = 9.0, 13.5 Hz, 1H), 3.57 (s, 3H), 7.33−7.44 (m, 2H), 7.79−7.89 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.7, 31.9, 32.8, 39.2, 48.5, 52.0, 128.9, 129.6, 131.1, 132.1, 134.6, 141.0, 169.8, 177.2. Anal. ($C_{14}H_{18}O_4S \cdot 0.2H_2O$) C, H, S.

3-(2-Carbamoyl-5-mercaptopentyl)benzoic Acid (16). A solution of **14** (0.42 g, 1.7 mmol) in 28% ammonium hydroxide (5 mL) was stirred at room temperature for 40 min. The reaction mixture was purged with nitrogen to remove excess ammonia and acidified to pH 4 with aqueous 10% $KHSO_4$. The product was extracted with EtOAc (25 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes to give 0.39 g of **16** as a white powder (87% yield): mp 163−165 °C; ^{1}H NMR (CD_3OD) δ 1.49−1.80 (m, 4H), 2.37−2.69 (m, 3H), 2.77 (dd, *J* = 5.7, 13.4 Hz, 1H), 2.91 (dd, *J* = 9.3, 13.4 Hz, 1H), 7.31−7.47 (m, 2H), 7.79−7.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.8, 32.3, 33.0, 39.8, 49.2, 128.7, 129.4, 131.3, 132.0, 134.8, 141.5, 169.9, 180.2. Anal. ($C_{13}H_{17}NO_3S$) C, H, N, S.

3-(2-Carboxy-5-tritylsulfanylpentyl)benzoic Acid Methyl Ester (17). To a solution of **3c** (0.43 g, 0.71 mmol) in water (3 mL) and dioxane (3 mL) was added sodium hydroxide (0.068 g, 1.70 mmol) at 0 °C, and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was acidified with 10% aqueous $KHSO_4$ (20 mL), extracted with EtOAc (25 mL), washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The residual material was dissolved in DMSO (1 mL) and heated at 130 °C for 1.5 h. After cooling, the reaction mixture was partitioned between 10% aqueous $KHSO_4$ (10 mL) and EtOAc (25 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (hexanes/EtOAc, 2:1 containing 1% AcOH) to give 0.210 g of **17** as a colorless oil (57% yield): ^{1}H NMR ($CDCl_3$) δ 1.15−1.60 (m, 4H), 2.00−2.20 (m, 2H), 2.50−2.62 (m, 1H), 2.72 (dd, *J* = 6.5, 13.8 Hz, 1H), 2.91 (dd, *J* = 8.6, 13.8 Hz, 1H), 3.90 (s, 3H), 7.16−7.44 (m, 17H), 7.79−7.83 (m, 1H), 7.85−7.96 (m, 1H).

3-(2-Carboxy-5-mercaptopentyl)benzoic Acid Methyl Ester (18). To a solution of **17** (0.21 g, 0.40 mmol) in dichloromethane (2 mL) were added triisopropylsilane (0.11 mL, 0.49 mmol) and trifluoroacetic acid (0.5 mL). The dark solution gradually turned light-yellow. After the mixture was stirred for 1.5 h, the solvent was removed under reduced pressure and the residual material was suspended in hexanes/EtOAc (95:5, 10 mL). The product was extracted with saturated aqueous $NaHCO_3$ (20 mL containing 10 mg of tris(2-carboxyethyl)phosphine hydrochloride). The aqueous layer was washed with hexanes (10 mL), acidified to pH 5 with 10% aqueous $KHSO_4$, and extracted with EtOAc (20 mL). The organic extract was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated to give 0.06 g of **18** as a colorless oil (53% yield): ^{1}H NMR (CD_3OD) δ 1.55−1.80 (m, 4H), 2.40−2.55 (m, 2H), 2.58−2.72 (m, 1H), 2.83 (dd, *J* = 6.1, 13.6 Hz, 1H), 2.96 (dd, *J* = 9.0, 13.6 Hz, 1H), 3.88 (s, 3H), 7.33−7.50 (m, 2H), 7.80−7.91 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.7, 31.9, 32.5, 39.2, 48.4, 52.6, 128.6, 129.6, 131.0, 131.4, 134.9, 141.5, 168.6, 178.8. Anal. ($C_{14}H_{18}O_4S$) C, H, S.

3-(2-Oxotetrahydrothiopyran-3-ylmethyl)benzamide (19). To a solution of **14** (1.61 g, 6.43 mmol) and ammonium chloride (0.35 g, 6.54 mmol) in DMF (12 mL) were added diisopropylethylamine (2.26 mL, 13.0 mmol) and HATU (2.75 g, 7.23 mmol) at 0 °C. The mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (30 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (25 mL), 10% $KHSO_4$ (20 mL), and brine (20 mL). The extract was dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes, and the recrystallized material was washed with water to remove any residual NaCl to give 1.57 g of **19** as a white solid (98% yield): ^{1}H NMR ($CDCl_3$) δ 1.52−1.70 (m, 1H), 1.86−2.15 (m, 3H), 2.71 (dd, *J* = 9.0, 13.2 Hz, 1H), 2.72−2.86 (m, 1H), 3.13 (t, *J* = 5.9 Hz, 2H), 3.37 (dd, *J* = 3.6, 13.2 Hz, 1H), 5.55−5.85 (brs, 1H), 5.95−6.25 (brs, 1H), 7.32−7.43 (m, 2H), 7.59−7.69 (m, 2H).

2-(3-Carbamoylbenzyl)-5-mercaptopentanoic Acid (20). A solution of **19** (0.16 g, 0.64 mmol) and sodium hydroxide (0.052 g, 1.3 mmol) in THF/water (1:1, 4 mL containing 30 mg of tris-(2-carboxyethyl)phosphine hydrochloride) was stirred at room temperature for 2 h. Additional sodium hydroxide (0.026 g, 0.65 mmol) was added, and the mixture was stirred for another 30 min. The reaction mixture was partitioned between aqueous 10% $KHSO_4$ (10 mL) and EtOAc (10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes to give 0.15 g of **20** as a white powder (87% yield): mp 137−139 °C; ^{1}H NMR (CD_3OD) δ 1.51−1.79 (m, 4H), 2.37−2.55 (m, 2H), 2.59−2.75 (m, 1H), 2.83 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.97 (dd, *J* = 8.8, 13.5 Hz, 1H), 7.30−7.44 (m, 2H), 7.63−7.73 (m, 2H); ^{13}C NMR (CD_3OD) δ 24.7, 31.9, 32.9, 39.3, 48.4, 126.7, 129.3, 129.6, 133.6, 135.0, 141.3, 172.4, 178.9. Anal. ($C_{13}H_{17}NO_3S$) C, H, N, S.

3-(2-Oxotetrahydrothiopyran-3-ylmethyl)benzonitrile (21). Oxalyl chloride (0.42 mL, 4.8 mmol) was slowly added to a solution of DMF (0.45 mL, 5.8 mmol) in acetonitrile (10 mL) at 0 °C. The resulting white suspension was stirred at 0 °C for 40 min. A solution of **19** (1.00 g, 4.01 mmol) in DMF (7 mL) was added to the mixture at 0 °C. After the mixture was stirred for 55 min, triethylamine (1.23 mL, 8.8 mmol) was added and the reaction mixture was concentrated under reduced pressure. The residual material was dissolved in EtOAc (30 mL), washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc, 1:1) to give 0.82 g of **21** as a colorless oil (88% yield): ^{1}H NMR ($CDCl_3$) δ 1.52−1.70 (m, 1H), 1.88−2.18 (m, 3H), 2.65−2.85 (m, 2H), 3.11 (dd, J = 5.0, 12.6 Hz, 1H), 3.18 (dd, J = 5.5, 12.6 Hz, 1H), 3.25−3.38 (m, 1H), 7.37−7.50 (m, 3H), 7.53 (dt, J = 6.8, 1.8 Hz, 1H).

2-(3-Cyanobenzyl)-5-mercaptopentanoic Acid (22). A solution of **21** (0.77 g, 3.3 mmol) in 1 M NaOH/THF (1:1, 20 mL containing 30 mg of tris(2-carboxyethyl)phosphine hydrochloride) was stirred at room temperature for 30 min. The reaction mixture was partitioned between aqueous 10% $KHSO_4$ (20 mL) and EtOAc (30 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc, 1:1 containing 1% AcOH) to give 0.74 g of **22** as a colorless oil (89% yield): ^{1}H NMR (CD_3OD) δ 1.54−1.80 (m, 4H), 2.40−2.57 (m, 2H), 2.58−2.72 (m, 1H), 2.85 (dd, J = 5.8, 13.5 Hz, 1H), 2.94 (dd, J = 9.3, 13.5 Hz, 1H), 7.40−7.60 (m, 4H); ^{13}C NMR (CD_3OD) δ 24.7, 32.0, 32.7, 38.8, 48.2, 113.3, 119.8, 130.5, 131.2, 133.6, 135.0, 142.7, 178.4. Anal. ($C_{13}H_{15}NO_2S{\cdot}0.3H_2O$) C, H, N, S.

3-(4-Acetylsulfanyl-1-methoxycarbonylbutoxy)benzoic Acid Methyl Ester (25a). To a solution of methyl 2,5-dibromovalerate **23** (22.00 g, 80.3 mmol) and methyl 3-hydroxybenzoate **24a** (10.18 g, 66.9 mmol) in DMF (80 mL) at room temperature was added K_2CO_3 (12.94 g, 93.7 mmol). The mixture was stirred at room temperature for 12 h and then at 70 °C for 1 h. To this reaction mixture was added potassium thioacetate (22.93 g, 200.8 mmol), and the mixture was stirred at 70 °C for another 1 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (1000 mL), washed with water (300 mL × 3) and brine (300 mL × 2), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography (EtOAc/hexanes, 1:9 to 1:4) to give 8.40 g of **25a** as a yellow oil (37% yield): ^{1}H NMR ($CDCl_3$) δ 1.73−1.88 (m, 2H), 2.01−2.08 (m, 2H), 2.32 (s, 3H), 2.93 (t, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.89 (s, 3H), 4.69 (t, J = 6.2 Hz, 1H), 7.07 (dd, J = 2.1, 8.0 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 28.5, 30.6, 31.4, 52.2, 52.3, 76.2, 115.9, 120.0, 123.0, 129.6, 131.7, 157.7, 166.6, 171.5,195.5.

3-(4-Acetylsulfanyl-1-methoxycarbonylbutylsulfanyl)-benzoic Acid Methyl Ester (25b). To a solution of 3-mercapto-benzoic acid methyl ester **24b** (0.71 g, 4.22 mmol) and K_2CO_3 (0.82 g, 5.91 mmol) in DMF (10 mL) was added methyl 2,5-dibromo-valerate **23** (1.50 g, 5.48 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (40 mL × 3). The combined extracts were washed with water (80 mL × 3) and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual material was dissolved in DMF (10 mL). Potassium thioacetate (0.79 g, 6.92 mmol) was added to the solution, and the mixture was stirred at 70 °C for 2 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (60 mL). The mixture was washed with water (50 mL × 3) and brine (60 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography (EtOAc/hexanes, 1:9 to 1:3) to give 1.03 g of **25b** as a yellow oil (68%). ^{1}H NMR ($CDCl_3$) δ 1.70−1.94 (m, 4H), 2.33 (s, 3H), 2.88 (t, J = 6.5 Hz, 2H), 3.68 (m, 4H), 3.93 (s, 3H), 7.40 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.1, 28.4, 30.4, 30.6, 50.1, 52.3, 52.3, 129.0, 129.0, 131.0, 133.8, 133.8, 137.1, 166.3, 172.1, 195.5.

3-(1-Carboxy-4-mercaptobutoxy)benzoic Acid (26a). A solution of **25a** (8.00 g, 23.5 mmol) in THF (60 mL) was purged of oxygen by bubbling nitrogen gas through the solution for 1 h. To the solution was added 3 M NaOH (47 mL), and the mixture was stirred at room temperature for 24 h. The reaction mixture was acidified to pH 2 with 1 M HCl and extracted with EtOAc (300 mL × 3). The combined extracts were washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. The residual oil was dissolved in ether, and the solution was slowly concentrated to precipitate 4.40 g of **26a** as a white solid (69% yield): mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.9 Hz, 1H), 1.99−1.83 (m, 2H), 2.22−2.11 (m, 2H), 2.63 (m, 2H), 4.76 (dd, J = 7.3, 5.0 Hz, 1H), 7.23 (m, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.49 (m, 1H), 7.72 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1, 29.6, 31.2, 75.5, 114.8, 122.1, 123.9, 129.9, 130.5, 157.6, 171.8, 177.1. Anal. ($C_{12}H_{14}O_5S$) C, H, S.

3-[(1-Carboxy-4-mercaptobutyl)thio]benzoic Acid (26b). A solution of **25b** (0.94 g, 2.64 mmol) and tris(2-carboxyethyl)-phosphine hydrochloride (0.76 g, 2.65 mmol) in THF (30 mL) was purged of oxygen by bubbling nitrogen gas through the solution for 1 h. To the solution was added 2 M NaOH (13 mL), and the mixture was stirred at room temperature for 24 h. The reaction mixture was acidified to pH 2 with 2 M HCl and extracted with ether (80 mL × 3). The combined extracts were washed with water (250 mL) and brine (250 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.65 g of **26b** as a white solid (86% yield): mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 8.0 Hz, 1H), 1.72−1.96 (m, 4H), 2.52−1.65 (m, 2H), 3.53 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.80 (dt, J = 7.6, 1.2 Hz, 1H), 8.07−8.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.1, 29.0, 31.4, 50.6, 129.3, 130.2, 131.4, 131.6, 137.8, 141.1, 171.4, 177.5. Anal. ($C_{12}H_{14}O_4S_2$) C, H, S.

3-[3-(Diethoxy-phosphoryl)-2-methoxycarbonylpropyl]benzoic Acid Methyl Ester (27). To a solution of **7** (0.19 g, 0.81 mmol) and diethyl phosphite (0.11 mL, 0.85 mmol) in THF (10 mL) was added sodium hydride (0.008 g, 60% dispersion in mineral oil) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 1 M HCl (30 mL) and extracted with EtOAc (30 mL × 2). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography (EtOAc/hexanes, 9:1) to give 0.26 g of **27** as a colorless oil (86% yield): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.83 (m, 1H), 2.19 (m, 1H), 2.92−3.10 (m, 3H), 3.59 (s, 3H), 3.88 (s, 3H), 3.95−4.09 (m, 4H), 7.32−7.35 (m, 2H), 7.82 (s, 1H), 7.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 16.3, 27.2 (d, J = 142.0 Hz), 39.0 (d, J = 12.3 Hz), 41.8 (d, J = 3.5 Hz), 51.8, 52.0, 62.1 (d, J = 6.5 Hz), 62.2 (d, J = 6.5 Hz), 128.5, 128.6, 130.6, 130.4, 134.0, 138.3, 166.9, 174.2.

3-(2-Carboxy-3-phosphonopropyl)benzoic Acid (28). A solution of **27** (0.24 g, 0.64 mmol) in 12 M HCl (8 mL) was stirred at 100 °C for 12 h. The reaction mixture was concentrated to dryness, and the residue was washed with ether and dried under vacuum to give 0.15 g of **28** as a white solid (79% yield): mp 205−207 °C; ^{1}H NMR (D_2O) δ 1.83−1.96 (m, 1H), 2.07−1.18 (m, 1H), 2.90−3.05 (m, 3H), 7.42 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.75 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H); ^{13}C NMR (D_2O) 27.9 (d, J = 136.5 Hz), 38.0 (d, J = 14.6 Hz), 41.8 (d, J = 3.8 Hz), 127.3, 128.1, 128.9, 129.2, 133.5, 137.8, 169.6, 177.5; ^{31}P NMR (D_2O) δ 27.4. Anal. ($C_{11}H_{13}O_7P$) C, H.

3-(3-Hydroxyphosphinoyl-2-methoxycarbonylpropyl)benzoic Acid Methyl Ester (29). To a suspension of ammonium hypophosphate (1.77 g, 21.4 mmol) in dichloromethane (30 mL) were added chlorotrimethylsilane (7.00 mL, 55.5 mmol) and triethylamine (7.14 mL, 51.2 mmol) while maintaining the temperature below 10 °C. A solution of **7** (1.00 g, 4.27 mmol) in dichloromethane (10 mL) was added to the mixture at a rate such that the temperature remained below 10 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 18 h. The reaction mixture was then quenched by the careful addition of 3 M HCl (50 mL) and diluted with dichloromethane (100 mL). The organic layer was washed with 3 M HCl (50 mL × 4) and H_2O (50 mL × 2) and concentrated to give 1.01 g of **29** as a light-yellow viscous oil (80% yield). This material was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.73−1.90 (m, 1H), 2.02−2.17 (m, 1H), 2.87−3.00 (m, 1H), 3.02−3.18 (m, 2H), 3.64 (s, 3H), 3.89 (s, 3H), 5.0−5.5 (br, 1H), 7.10 (d, J = 564.8 Hz, 1H), 7.30−7.38 (m, 2H), 7.81 (s, 1H), 7.87−7.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6 (d, J = 94.3 Hz), 36.9 (d, J = 12.3 Hz), 38.6, 50.2 (2C), 126.3, 126.8, 128.2, 128.6, 131.7, 136.0, 164.9, 171.9 (d, J = 5.4 Hz); ^{31}P NMR ($CDCl_3$) δ 35.2 (ddt, J = 15.9, 562.8, 13.9 Hz).

3-[3-(Hydroxylpentafluorophenylmethylphosphinoyl)-2-methoxycarbonylpropyl]benzoic Acid Methyl Ester (30). A solution of pentafluorobenzyl bromide (0.478 g, 1.83 mmol) and **29** (0.499 g, 1.66 mmol) in dichloromethane (10 mL) was purged with nitrogen for 30 min by bubbling a stream of nitrogen through the solution. To the solution was added *N*,*O*-bis(trimethylsilyl)acetamide (1.23 mL, 4.98 mmol), and the reaction mixture was stirred at 40 °C for 3 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 0.5 M HCl (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The viscous oil was then dissolved in methanol and concentrated to give 0.774 g of **30** as a colorless oil (97% yield). This material was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.74−1.88 (m, 1H), 2.07−2.24 (m, 1H), 2.86−3.20 (m, 3H), 3.15 (d, J = 16.2 Hz, 2H), 3.59 (s, 3H), 3.89 (s, 3H), 4.57 (s, 1H), 7.28−7.38 (m, 2H), 7.80 (s, 1H), 7.84−7.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1 (d, J = 89.0 Hz), 29.9 (d, J = 95.1 Hz), 39.2 (d, J = 11.5 Hz), 40.9 (d, J = 3.8 Hz), 50.7, 52.1 (d, J = 6.1 Hz), 128.2, 128.6, 130.1, 130.4, 133.6, 137.9, 135−152 (multiple fluoroaromatic peaks), 166.9, 174.1 (d, J = 6.1 Hz); ^{31}P NMR ($CDCl_3$) δ 49.3 (m).

3-[2-Carboxy-3-(hydroxypentafluorophenylmethylphosphinoyl)propyl]benzoic Acid (31). A solution of **30** (0.470 g, 0.98 mmol) in 12 M HCl (30 mL) was stirred at 100 °C for 12 h. The reaction solution was cooled to room temperature and concentrated in vacuo to dryness. The residual material was recrystallized from H_2O to give 0.058 g of **31** as a crystalline white solid (13% yield): mp 178−179 °C; ^{1}H NMR (DMSO-d_6) δ 1.80 (dt, J = 5.4, 14.9 Hz, 1H), 2.07 (ddd, J = 6.8, 12.6, 14.9 Hz, 1H), 2.86−3.08 (m, 3H), 3.20 (d, J = 15.2 Hz, 2H), 7.38−7.46 (m, 2H), 7.75−7.84 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 25.4 (d, J = 84.4 Hz), 30.4 (d, J = 93.6 Hz), 38.3 (d, J = 10.0 Hz), 40.8 (d, J = 3.1 Hz), 127.5, 128.5, 129.9, 130.8, 133−136 (multiple fluoroaromatic peaks), 133.6, 139.2, 167.3, 174.9 (d, J = 8.4 Hz); ^{31}P NMR (DMSO-d_6) δ 41.3 (m). Anal. ($C_{18}H_{14}F_5O_6P{\cdot}H_2O$) C, H.

3-(5-Allyl-2,2-dimethyl-4,6-dioxo[1,3]dioxan-5-ylmethyl)benzoic Acid Methyl Ester (33). To a solution of **32** (1.17 g, 4.0 mmol) and benzyltriethylammonium chloride (0.911 g, 4.0 mmol) in acetonitrile (30 mL) was added anhydrous K_2CO_3 (0.553 g, 4.0 mmol), and the suspension was stirred at 75 °C for 20 min. To the mixture was added allyl bromide (0.42 mL, 4.8 mmol), and the resulting mixture was stirred at the same temperature for 5 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL). The solution was washed with 1 M HCl (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residual material was purified by silica gel chromatography (EtOAc/hexanes, 1:10) to give 0.918 g of **33** as a white solid (69% yield): mp 57−59 °C; R_f = 0.32 (EtOAc/hexanes, 1:4); ^{1}H NMR ($CDCl_3$) δ 0.73 (s, 3H), 1.52 (s, 3H), 2.87 (d, J = 7.5 Hz, 2H), 3.36 (s, 2H), 3.88 (s, 3H), 5.21 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 5.69 (ddt, J = 9.9, 17.1, 7.5 Hz, 1H), 7.30−7.43 (m, 2H), 7.83 (s, 1H), 7.87−7.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.6, 43.5, 44.2, 52.2, 57.6, 105.9, 121.6, 129.0, 129.1, 130.4, 130.8, 131.1, 134.7, 135.5, 166.6, 168.1.

3-(2-Benzyloxycarbonylpent-4-enyl)benzoic Acid Benzyl Ester (34). A suspension of **33** (0.698 g, 2.10 mmol) in 2 M NaOH (10 mL) and dioxane (5 mL) was stirred at 100 °C for 3 h. The resulting clear solution was concentrated, acidified to pH 1 by adding 1 M HCl, and extracted with EtOAc (25 mL). The extract was dried over Na_2SO_4, filtered, and concentrated. The resulting white solid was dissolved in DMSO (10 mL), and the solution was stirred at 130 °C for 3 h. The reaction mixture was taken up in EtOAc (80 mL), washed with water (40 mL × 2), dried over Na_2SO_4, filtered, and concentrated to give 0.62 g of glassy liquid. This material was dissolved in dichloromethane (50 mL). To the solution of this material in dichloromethane (50 mL) were added EDC (0.959 g, 5.0 mmol), benzyl alcohol (0.541 g, 5.0 mmol), and DMAP (0.06 g, 0.5 mmol). The mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (80 mL). The organic solution was washed with 1 M HCl (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residual material was purified by chromatography (EtOAc/hexanes, 1:5) to give 0.670 g of **34** as a colorless oil (77% yield from **33**): ^{1}H NMR ($CDCl_3$) δ 2.22−2.35 (m, 1H), 2.35−2.48 (m, 1H), 2.77−2.91 (m, 2H), 2.99 (dd, J = 10.5, 15.1 Hz, 1H), 5.01 (s, 2H), 5.01−5.12 (m, 2H), 5.35 (s, 2H), 5.74 (ddt, J = 10.1, 17.0, 7.1 Hz, 1H), 7.13−7.22 (m, 2H), 7.26−7.48 (m, 10H), 7.85−7.95 (m, 2H).

3-(3-Benzyloxycarbamoyl-2-benzyloxycarbonylpropyl)benzoic Acid Benzyl Ester (35). To a solution of **34** (0.660 g, 1.59 mmol) in acetonitrile (30 mL) and water (30 mL) were added sodium periodate (2.74 g, 12.8 mmol) and a catalytic amount of ruthenium oxide. The mixture was stirred at room temperature for 20 h. The reaction mixture was filtered, and the filtrate was concentrated. The resulting aqueous solution was extracted with EtOAc (40 mL × 2), and the combined extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residual material was dissolved in dichloromethane (30 mL). To the solution were added EDC (0.268 g, 1.4 mmol), *O*-benzylhydroxylamine hydrochloride (0.208 g, 1.3 mmol), diisopropylethylamine (0.168 g, 1.3 mmol), and DMAP (0.012 g, 0.1 mmol). The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (80 mL). The organic solution was washed with 1 M HCl (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residual material was purified by silica gel chromatography to give 0.600 g of **35** as a colorless oil (70% yield from **34**): ^{1}H NMR ($CDCl_3$) δ 2.30 (dd, J = 4.6, 18.2 Hz, 1H), 2.60 (dd, J = 9.0, 18.2 Hz, 1H), 2.76 (dd, J = 9.0, 13.9 Hz, 1H), 3.04 (tt, J = 4.4, 9.0 Hz, 1H), 3.20 (dd, J = 4.6, 13.9 Hz, 1H), 4.67−4.73 (m, 2H), 5.03 (d, J = 10.1 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 5.35 (s, 2H), 7.22−7.48 (m, 18H), 7.85 (brs, 1H), 7.97 (dt, J = 7.3, 1.5 Hz, 1H).

3-(2-Carboxy-3-hydroxycarbamoylpropyl)benzoic Acid (36). To a solution of **35** (0.581 g, 1.08 mmol) in MeOH (30 mL) was added 100 mg of palladium on carbon (10%), and the mixture was shaken under hydrogen (21 psi) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residual material was dissolved in water and lyophilized to give 0.280 g of **36** as a glassy solid (97% yield): mp 163−165 °C (dec); ^{1}H NMR (CD_3OD) δ 2.40 (dd, J = 4.0, 17.9 Hz, 1H), 2.70 (dd, J = 8.2, 17.9 Hz, 1H), 2.96 (dd, J = 9.9, 14.9 Hz, 1H), 3.16−3.28 (m, 2H), 7.35−7.47 (m, 2H), 7.84−7.91 (m, 2H); ^{13}C NMR (CD_3OD) δ 31.5, 36.7, 39.5, 129.2, 129.8, 131.3, 134.1, 134.2, 139.0, 171.0, 173.8, 176.6; MS ES$^-$ *m*/*z* 266 (M − H)$^-$; MS ES$^+$ *m*/*z* 268 (M + 1)$^+$. Anal. ($C_{12}H_{13}NO_6$) H. C: calcd, 53.93; found, 55.09. N: calcd, 5.24; found, 6.35.

3-(5-Ethoxycarbonylmethyl-2,2-dimethyl-4,6-dioxo[1,3]dioxan-5-ylmethyl)benzoic Acid Methyl Ester (37). To a solution of **32** (0.877 g, 3.0 mmol) and benzyltriethylammonium chloride (0.683 g, 3.0 mmol) in acetonitrile (15 mL) was added anhydrous K_2CO_3 (0.415 g, 3.0 mmol), and the suspension was stirred at 65 °C for 20 min. To the mixture was added ethyl bromoacetate (0.551 g, 3.3 mmol), and the resulting mixture was stirred at the same temperature for 20 h. The solvent was removed under reduced pressure, and the residue was partitioned between aqueous 10% $KHSO_4$ (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL × 2). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes to give 0.680 g of **37** as a white solid (60% yield): ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.76 (s, 3H), 3.21 (s, 2H), 3.29 (s, 2H), 3.89 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.79 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 28.1, 28.6, 41.6, 44.9, 52.3, 52.4, 61.7, 107.5, 129.0, 129.6, 130.9, 131.0, 133.8, 134.6, 166.4, 167.7, 170.7.

2-Carboxy-2-(3-carboxybenzyl)succinic Acid (38). A suspension of **37** (0.570 g, 1.51 mmol) in 2 M NaOH (8 mL) was stirred at 100 °C for 3 h. The resulting clear reaction mixture was acidified to pH 1 by 1 M H_2SO_4 and extracted with EtOAc (25 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated to give 0.450 g of **38** (100% crude yield) as a colorless oil. This material was used in the next step without further purification: ^{1}H NMR (CD_3OD) δ 2.78 (s, 2H), 3.46 (s, 2H), 7.35−7.42 (m, 2H), 7.80−7.93 (m, 2H).

2-(3-Carboxybenzyl)succinic Acid (39). A solution of **38** (0.450 g, 1.51 mmol) in DMSO (6 mL) was stirred at 130 °C for 3 h. The solvent was removed under reduced pressure, and the residual oil was dissolved in EtOAc (25 mL). The organic solution was washed with water (25 mL × 3), dried over $MgSO_4$, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes to give 0.260 g of **39** as a white solid (68% yield from **37**): mp 188−190 °C; ^{1}H NMR (CD_3OD) δ 2.40 (dd, J = 4.9, 16.8 Hz, 1H), 2.60 (dd, J = 8.6, 16.9 Hz, 1H), 2.85−2.97 (m, 1H), 2.99−3.13 (m, 2H), 7.33−7.49 (m, 2H), 7.82−7.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 36.1, 38.4, 44.4, 129.1, 129.6, 131.4, 132.1, 134.8, 140.5, 169.8, 175.4, 177.6. Anal. ($C_{12}H_{12}O_6$) C, H.

Biological Studies. The GCP II assay was carried out as outlined previously.[14] The chronic constrictive injury models were performed following the procedure reported by Bennett's group.[15]

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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