Stereospecific Synthesis of 5-Substituted 2-Bisarylthiocyclopentane Carboxylic Acids as Specific Matrix Metalloproteinase Inhibitors

Thierry Le Diguarher,[†] Anne-Marie Chollet,[†] Marc Bertrand,[‡] Philippe Hennig,[†] Eric Raimbaud,[†] Massimo Sabatini,[†] Nicolas Guilbaud,[†] Alain Pierré,[†] Gordon C. Tucker,[†] and Patrick Casara*,[†]

Institut de Recherches Servier, 125 chemin de Ronde, 78290 Croissy sur Seine, France, and Technologie Servier, 25-27 rue E. Vignat, 45007 Orléans, France

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The synthesis and structure−activity relationship (SAR) studies of a series of cyclopentane carboxylic acid matrix metalloproteinase (MMP) inhibitors are described. Potent and specific MMP-2, -3, -9, -13 inhibitors were obtained by regio- and stereoselective substitutions at positions 2 and 5 on the cyclopentane ring. Compounds **2a** and **2e** are active in the mouse B16−F10 metastasis model and display very good pharmacokinetic parameters.

Introduction

Matrix metalloproteinases (MMPs) are a class of zinc-dependent proteolytic enzymes involved in the turnover of extracellular matrix.[1] Upregulation of MMPs has been associated with various pathologies including arthritis (MMP-1, -3, -13)[2] and cancer (MMP-2, -9).[3] Inhibition of these enzymes is recognized as a potentially valuable therapeutic approach. Among the compounds that are, or have been, in clinical development, are those active against a spectrum of MMPs (CGS 27023A[4] and trocade[5] for arthritis; marimastat,[6] prinomastat,[7] and BMS-275291[8] for cancer), and those selective for MMP-13 (RS-130830[9] for arthritis) or MMP-2 and -9 (ABT-518[10] for cancer). We recently described a series of bisarylthioethers as tetrahedral analogues of the substrate transition-state. For example, **1**[11] is a very potent and specific inhibitor of MMP-2, -3, -9, and -13. However, this compound has only modest bioavailability (<30%), a fact attributed to the presence of the hydroxamate function. Conformational analysis of **1** modeled in the three-dimensional structure of MMP-2 (Figure 1) suggested that the P1 and P1′ groups adopt a trans/trans orientation relative to the zinc binding group. This is in agreement with the previously reported X-ray crystal structure of a cyclic sulfonamide inhibitor bound to stromelysin.[12] Therefore, the synthesis of the corresponding (1,2-trans, 1,5-trans) 2,5-disubstituted cyclopentane carboxylic acid **2** was proposed with the expectation that, without the hydroxamate, the pharmacokinetic parameters would be improved (Scheme 1). Such an approach has been previously demonstrated in various sulfonamide series.[13] To potentially improve potency, an extensive investigation of substitutions at P1/P2 and P1′P′1 in **2** was also proposed.

Chemical Methods

An attractive retrosynthetic approach for a rapid SAR study was to obtain **2** from the synthon **4**. This would allow independent variation of R_3 (P1′) and X (P1) starting from a common precursor (Scheme 2). Synthon

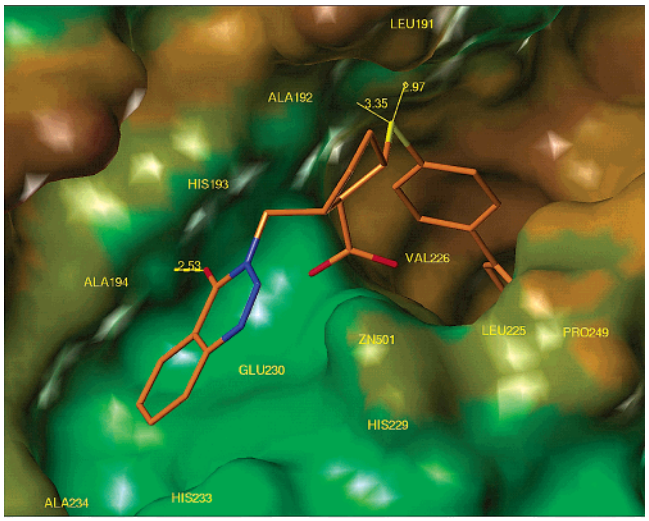

Figure 1. All structures were modeled in SYBYL 6.8[28] using standard bond lengths and angles. The whole protein, including the zinc, calcium, and water molecules, was kept fixed in aggregate. All the hydrogen atoms were added on the crystal structure of the enzyme and their geometries were optimized using the MMFF94s Merck force field.[29] Each compound **2** was then docked manually in this binding cavity and its conformation was fully optimized with MMFF94s to obtain the best zinc chelation and S1′−S2 protein interactions. The side chains of the amino acid residues of the active site in close contact with the ligands were allowed to change their conformations depending on the ligands docked.

4 could be obtained by sequential Michael additions starting from 5-hydroxy-2-cyclopentene carboxylate **6**. The first addition introduces a functional carbon side chain by addition/elimination to give **5**. The second stereoselectively forms a thioether bond by trans addition. It was considered that the trans relative stereochemistry of the 1,5-substitutions in **4** might be favored by thermodynamic control, a possibility allowed by retro-Michael elimination of any initially formed trans 2,5-addition product. The carboxycyclenol **6** was prepared by a double Wittig−Horner reaction between diethylphosphonoacetate *tert*-butylester and succinaldehyde, generated in situ from dimethoxyfuran[14,15] (Scheme 3). Homologation at C5 was achieved by 1,4-addition of 1,3-dithiane anion[16] to the acetyl derivative **7** giving the addition/β-elimination adduct **8**. Since the

* Corresponding author. Institut de Recherches Servier. Chemin de Ronde, Croissy sur Seine, France. Fax: 33.1.55.72.24.7078290. Tel: 33.1.55.72.23.61125. E-mail: patrick.casara@fr.netgrs.com.
[†] Institut de Recherches Servier.
[‡] Technologie Servier.

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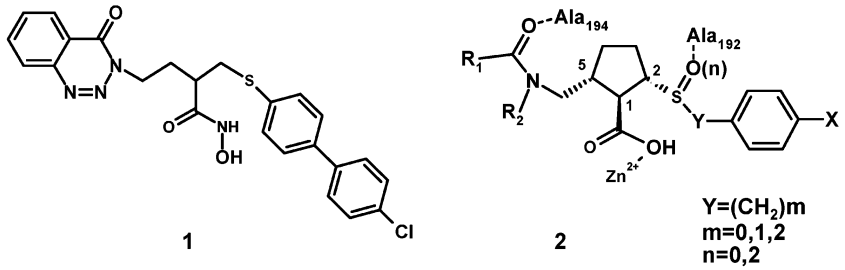
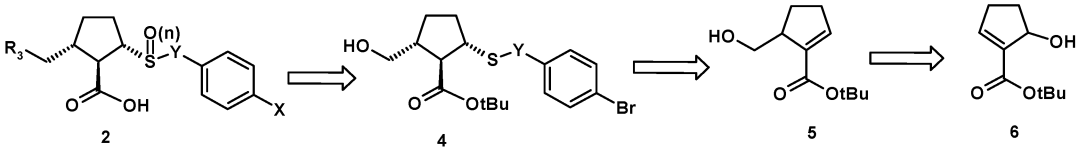
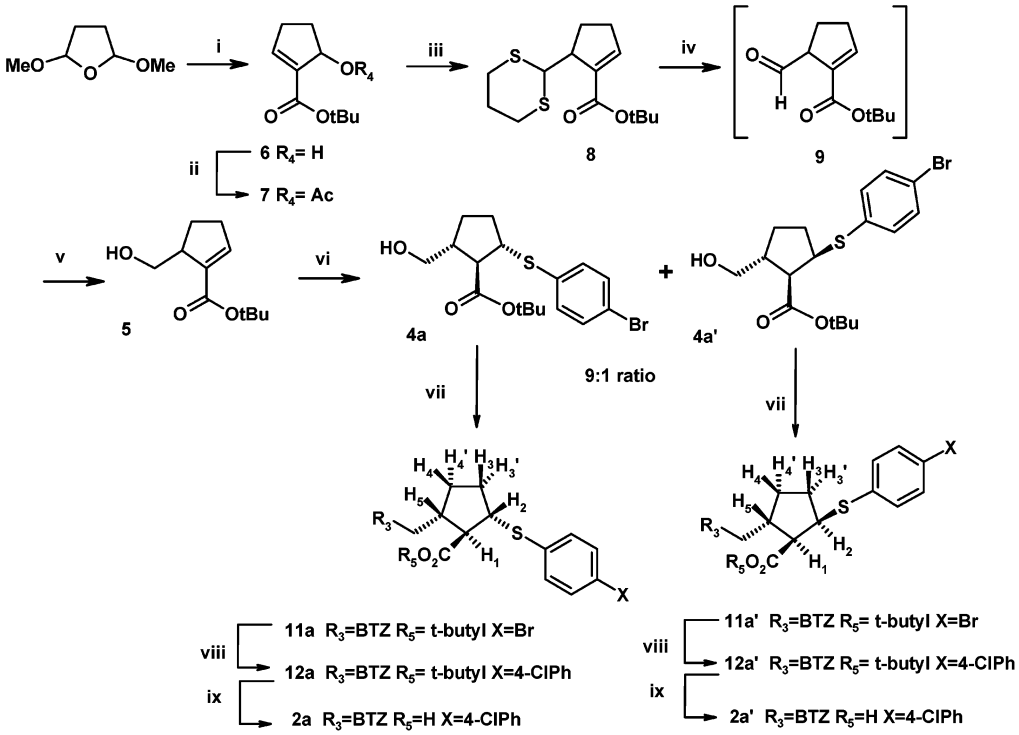
Scheme 1



Scheme 2



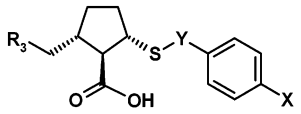
Scheme 3[a]



[a] i: (a) HCl, 1 N; (b) $OP(OEt)_2CH_2CO_2tBu$, K_2CO_3, H_2O; (c) Ac_2O, pyridine, rt. ii: dithiane, LDA, THF, −78 °C. iii: HgO, $HgCl_2$, acetone/H_2O. iv: $LiAlH(OCH(Et)_3)_3$, THF, −78 °C. v: 4-BrPhSH, piperidine, reflux, 5 h. vii: PPh_3, DIAD, BTZH, THF, 0 °C-rt. viii: *p*-ClPhSnBu$_3$, $Pd(PPh_3)_4$, LiCl, toluene, reflux, 12 h. ix: TFA, CH_2Cl_2, 0 °C-rt, 18 h.

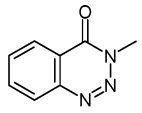
conditions for removal of the dithiane were incompatible with a thioether, it was necessary to cleave the dithiane prior to the second Michael addition. The aldehyde **9** so obtained[17] was immediately reduced to provide the primary alcohol **5**, thus minimizing the potential for isomerization of the double bond. With **5** in hand, the key Michael reaction with 4-bromophenylthiol could be investigated. Under thermodynamic conditions (piperidine/reflux), the desired trans/trans adduct **4a** was obtained as the major product. Surprisingly, the cis/trans stereoisomer **4a′** resulting from cis Michael addition was also isolated. The corresponding trans/cis stereoisomer, preferentially obtained by cuprate addition to 2-silyloxy cyclopentene carboxylates,[18] was undetectable. The diastereoisomers, **4a** and **4a′**, were subsequently used in parallel for elaboration of the side chains P1 and P1′. Previous work had shown that in **1**, 4-oxobenzo[*d*]1,2,3-triazin-3-yl (BTZ) and *p*-chlorobiphenyl are well accepted at P1 and P1′, respectively. These groups were therefore selected for inclusion in our first targets aimed at validating our conformational hypothesis.[19] The *p*-chlorophenyl group was introduced by Stille coupling between 4-chlorophenyl tri-*n*-butyltin and **4a** or **4a′** to give compounds **11a** and **11a′**, respectively.[20] The BTZ moiety was then introduced under Mitsunobu conditions to give **12a** and **12a′**, respectively.[21] Acidic hydrolysis of the *tert*-butyl esters **12a** and **12a′** afforded the carboxylic acids **2a** and **2a′**, respectively (Table 1). The relative configurations at C1, C2, and C5 were confirmed by NOESY experiments. Separation of the enantiomers of **2a** was carried out by preparative chiral HPLC to provide (1*R*,2*S*,5*R*)-**2a** and

Table 1. Structures and Biological Activities of Derivatives **2a** to **2m**[a]



				MMP IC_{50} nM except for 1				
no.	R_3	Y	X	1(IC_{50} μM)	2	3	9	13
Marimastat				0.0015 ± 0.0005 (2)	1.8 ± 0.3 (3)	25 ± 10 (5)	1.6 ± 0.1 (4)	3.4 ± 2.4 (3)
CGS27023A				0.096 ± 0.015 (14)	15 ± 2 (14)	14 ± 3 (14)	10 ± 1 (15)	12 ± 2 (7)
Trocade				(K_i) 7	154	527	58	3.4
Prinomastat				0.048 ± 0.023 (3)	0.5 ± 0.2 (4)	1.1 ± 0.4 (3)	0.2 ± 0.1 (3)	1.5 ± 0.6 (4)
1				> 10 (2)	0.06 ± 0.03 (3)	10 ± 2 (3)	0.5 ± 0.4 (3)	1.2 ± 0.5 (4)
2a	BTZ[a]	bond	4-Cl(C_6H_4)	12 ± 5 (3)	63 ± 21 (2)	235 ± 12 (2)	93 ± 24 (3)	168 ± 104 (2)
(1*R*,2*S*,5*R*)−**2a**	BTZ	bond	4-Cl(C_6H_4)	3.1 ± 0.4 (3)	18 ± 7 (3)	98 ± 23 (2)	43 ± 16 (3)	28 ± 17 (3)
(1*S*,2*R*,5*S*)−**2a**	BTZ	bond	4-Cl(C_6H_4)	67 ± 29 (2)	743 ± 189 (3)	5.2 ± 1.8 × 10^3 (2)	3.0 ± 1.2 × 10^3 (3)	1.9 ± 1.2 × 10^3 (3)
2a′	BTZ	bond	4-Cl(C_6H_4)	> 100 (2)	849 ± 222 (2)	3.3 ± 0.1 × 10^3 (2)	2.9 ± 0.2 × 10^3 (2)	5.0 ± 07 × 10^3 (2)
2b	Phth.	bond	C_6H_5	0.093 (1)	24 ± 9 (2)	278 ± 44 (4)	76 ± 12 (2)	66 (1)
2c	Phth	CH_2	C_6H_5	> 100 (2)	2.8 ± 0.4 × 10^3 (2)	3.0 ± 0.3 × 10^3 (2)	3.8 ± 0.9 × 10^3 (2)	15 ± 8 × 10^3 (2)
2d	Phth	$(CH_2)_2$	C_6H_5	45 ± 1 (2)	46 ± 16 (3)	26 ± 4 (3)	12 ± 6 (3)	162 ± 17 (3)
2e	Phth	$(CH_2)_2$	4-F(C_6H_4)	6 (1)	62 ± 10 (3)	60 ± 17 (2)	26 ± 1 (2)	248 ± 28 (3)
2f	Phth.	$(CH_2)_2$	4-Cl(C_6H_4)	50 ± 34 (2)	73 ± 17 (5)	45 ± 13 (6)	13 ± 5 (5)	129 ± 20 (5)
2g	BTZ	$(CH_2)_2$	4-Cl(C_6H_4)	> 70 (2)	106 ± 5 (2)	62 ± 20 (2)	24 ± 6 (2)	391 ± 36 (2)
2h	BTZ	bond	4-SMe(C_6H_4)	> 10 (2)	5 ± 2 (2)	21 (1)	4 ± 2 (2)	13 ± 2 (2)
2i	BTZ	bond	4-CN(C_6H_4)	> 10 (2)	13 ± 1 (2)	5 (1)	24 ± 1 (2)	11 ± 1 (2)
2j	BTZ	bond	4-pyridyl	> 36 (2)	176 ± 82 (2)	1.2 ± 1.0 × 10^3 (2)	341 ± 4 (2)	275 ± 103 (2)
2k	BTZ	bond	2-thiazolyl	> 100 (2)	> 8 × 10^3 (2)	> 100 × 10^3 (2)	> 6 × 10^3 (2)	> 100 × 10^3 (2)
2l	BTZ	bond	2-benzo-thiazolyl	> 1 (2)	829 ± 36 (2)	8 × 10^3 (1)	661 (1)	417 (1)
2m	BTZ	bond	4-triazolyl	> 100 (2)	> 100 × 10^3 (2)	> 100 × 10^3 (2)	> 100 × 10^3 (2)	> 100 × 10^3 (2)

[a] (n) number of experiments. [b]

BTZ= 

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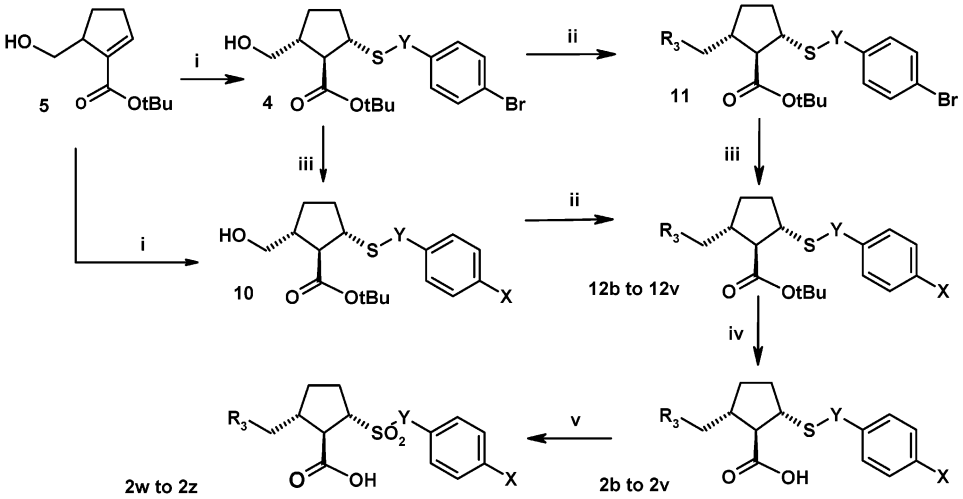
Scheme 4: Preparation of Compounds **2b** to **2z**[a]

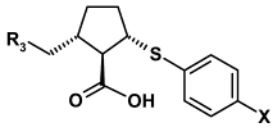


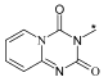
[a] i: 4-(Br or X)PhYSH, piperidine, reflux, 2 h. ii: PPh_3, DIAD, R_3H, THF, 0 °C-rt or (a) TsCl, pyridine; (b) R_3K or R_3Na, DMF, Δ. iii: $XSnBu_3$, $Pd(PPh_3)_4$, LiCl, toluene, Δ, 12 h. iv: TFA, CH_2Cl_2, 0 °C-rt, 18 h. v: dimethyldioxirane, acetone, 0 °C-rt.

(1*S*,2*R*,5*S*)-**2a**. The absolute stereochemistry of (1*R*,2*S*, 5*R*)-**2a** (corresponding to structure **2a** in Scheme 3) is inferred on the basis of its potent MMP activity and molecular modeling of the compound docked in the MMP-2 active site (see below).

As previously described, various cyclic imides such as a BTZ or phthalimido at P1 increase activity,[11,19] while biaryl substitution at P1′ improves selectivity versus MMP-1.[22] We thus sought to elaborate **5** with a variety of such groups. Intermediate compounds **12** could be synthesized via different routes (Scheme 4). Introduction of the P1′ residue could be achieved by Stille coupling to **4** as described above, or by direct reaction of **5** with available biarylthiolates. The P1 moieties were incorporated starting from **4** or **10** by Mitsunobu reaction or by tosylate displacement to obtain **11** or **12**, respectively. Stille reaction of **11** also gave rise to compounds **12**. Compounds **12b** to **12v**, obtained via these different routes, were then converted to the corresponding carboxylic acids **2b** to **2v** by acidic hydrolysis (Tables 1 and 2). Oxidation of selected thioethers to the corresponding sulfones (**2w**−**z**) was carried out by treatment of **2d**−**2g** with dimethyl dioxirane (Table 3).

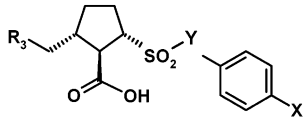
Table 2. Structures and Biological Activities of Derivatives **2n** to **2v**[a]



#	R_3	X	1(IC_{50} μM)	MMP IC_{50} nM			
				2	3	9	13
2n		4-Cl(C_6H_4)	70 ± 16 (3)	572 ± 56 (2)	9.4 ± 3.0 x 10^3 (3)	3.3 ± 1.1 x 10^3 (3)	3.1 ± 0.9 x 10^3 (2)
2o		4-Cl(C_6H_4)	2.1 ± 0.1 (2)	13 ± 1 (2)	474 (1)	35 ± 3 (2)	80 ± 16 (2)
2p		4-Cl(C_6H_4)	10 (3)	25 ± 2 (2)	184 ± 84 (3)	37 ± 5 (3)	32 ± 11 (2)
2q		4-Cl(C_6H_4)	> 10 (2)	9 ± 1 (2)	134 (1)	30 ± 4 (2)	27 ± 10 (2)
2r		4-Cl(C_6H_4)	6.6 ± 0.7 (2)	130 ± 47 (2)	21 (1)	642 ± 153 (2)	682 ± 173 (2)
2s		4-Cl(C_6H_4)	4.4 ± 0.9 (2)	20 ± 12 (2)	216 ± 203 (2)	62 ± 30 (2)	133 ± 64 (2)
2t		4-Cl(C_6H_4)	> 10 (2)	1.7 ± 0.4 x 10^3 (2)	18 ± 8 x 10^3 (2)	3.8 ± 0.2 x 10^3 (2)	5.1 ± 0.9 x 10^3 (2)
2u		4-SMe(C_6H_4)	63 ± 38 (2)	14 ± 2 (2)	305 ± 201 (2)	16 ± 7 (2)	195 ± 150 (2)
2v		4-CN(C_6H_4)	> 1 (2)	20 ± 8 (2)	103 (1)	31 ± 7 (2)	31 ± 4 (2)

[a] (n) number of experiments.

Table 3. Structures and Biological Activities of Derivatives **2w** to **2z**[a]



				MMP IC_{50} nM except for 1				
no.	R_3	Y	X	1(IC_{50} μM)	2	3	9	13
2w	BTZ	bond	4-Cl(C_6H_4)	> 100 (2)	83 ± 4 (2)	694 ± 54 (2)	512 ± 82 (3)	1.8 ± 0.5 × 10^3 (2)
2x	phthalyl.	$(CH_2)_2$	4-F(C_6H_4)	5.9 ± 2.0 (2)	76 ± 34 (2)	316 (1)	47 ± 4 (2)	296 ± 39 (2)
2y	phthalyl.	$(CH_2)_2$	4-Cl(C_6H_4)	5.4 ± 1.2 (2)	76 ± 32 (2)	64 (1)	39 ± 1 (2)	808 ± 292 (2)
2z	BTZ	$(CH_2)_2$	4-Cl(C_6H_4)	> 100 (2)	383 ± 90 (2)	253 ± 82 (3)	132 ± 8 (2)	2.8 ± 1.4 × 10^3 (2)

[a] (n) number of experiments.

Results and Discussion

The inhibitory activities of compounds **2** were examined against a panel of MMPs, and the results were compared to those for clinical reference compounds (Table 1). A main goal of this work was to study the influence of ring constraint on MMPs inhibition in comparison with the acyclic series.[11] The stereoisomer **2a** was found to be much more active against MMP-2, -3, -9, and -13 than the diastereoisomer **2a′**, corroborating our conformational analysis, and justifying further exemplification. Also, as would be expected, one of the enantiomers of **2a** was much more active than the other. On the basis of molecular modeling (see below), the active enantiomer was assigned the (1*R*,2*S*,5*R*) configuration. Almost all the other cyclic carboxylic acids analogues of **2a** gave IC_{50} values for MMP-2, -3, -9, and -13 in the sub-1 μM range, thereby showing significant improvements in activity compared to the corresponding compounds in the acyclic series (IC_{50} > 1 μM).

In the cyclic series, the length of the spacer Y is critical and must be either a bond or a two-carbon chain. A methylene Y spacer is deleterious to MMP inhibition as shown by a comparison of compounds **2b**, **2c**, and **2d**. This result, which was also observed in the ether acyclic series,[19] is in agreement with our conformational analysis showing that a bond or a two-carbon chain

confers the same spatial orientation to the biaryl P1′ group. However, with an ethylene spacer, para substitution on the terminal phenyl ring significantly decreased MMP-13 activity due to steric hindrance at P1′ (compare **2b** with **2e** and **2f** or **2a** with **2g**). Therefore, further variations at P1′ were made only with Y as a bond, since there is more space available for further substitution.

All compounds showed very good selectivity against MMP-1, as was the case seen in the ether series.[19] Replacement of the 4-chlorophenyl ring of **2a** with the heteroaryl groups 4-pyridyl (**2j**), 2-thiazolyl (**2k**), 2-benzothiazolyl (**2l**), and 4-triazolyl (**2m**) increased IC_{50} values across the board by 1 or 2 orders of magnitude. In contrast, substantial improvement in potency was obtained by replacing the 4′-chloro of **2a** by either a 4′-methylthio (**2h**) or a 4′-cyano (**2i**) group. In these cases, IC_{50} values for MMP-2, -3, -9, and -13 are shifted into the nanomolar range. These results illustrate once again the preference of MMPs for lipophilic interactions at P1′.[23]

In the sulfone series (**2w**−**z**), activities were not significantly different from those of the corresponding thioethers, with the exception of an unexplained loss of MMP-13 activity for **2w** and **2z**. Therefore, 4-chlorobiphenylthioether at P1′ was maintained to enhance the interactions at P1.

Cyclic amide or imide functions at P1 are critical for activity in the acyclic series.[11,19] We therefore examined the SAR at P1 by replacing the triazino ring of **2a** with various heterocycles (compounds **2n**−**t**, Table 2). Except for the hydantoin **2n**, modification of the triazino ring (compounds **2o**−**q**) either maintained or slightly improved MMPs affinity compared to **2a**. Whereas modifications of the benzo ring as in **2r** and **2t** were not tolerated, the potency of the thienyl analogue (**2s**) was not altered significantly. No improvement of potency was observed by replacing the para chloro substituent of **2q** with methylthio or a cyano to give **2u** and **2v**, respectively.

Using molecular modeling calculations, we attempted to explain the above results. Because there is a high degree of sequence homology between the catalytic domain of MMP-3 and those of MMP-2 and -9, one of the crystal structures of MMP-3, PDB code 1QIB, was used to generate a three-dimensional model of the MMP-2 active site. All structures were modeled in SYBYL 6.8.[24] using standard bond lengths and angles. The whole protein, including the zinc, calcium, and water molecules, was kept fixed in aggregate. All the hydrogen atoms were added on the crystal structure of the enzyme, and their geometries were optimized using the MMFF94s Merck force field.[25] Each compound **2** was then docked manually in this binding cavity, and its conformation was fully optimized with MMFF94s to obtain the best zinc chelation and S1′−S2 protein interactions. The side chains of the amino acid residues of the active site in close contact with the ligands (Figure 1) were allowed to change their conformations depending on the ligands docked.

One of the most active compounds (1*R*,2*S*,5*R*)-**2a** is shown in Figure 1 for visualization. Only the assigned configuration (1*R*,2*S*,5*R*) fits into this model, thereby establishing the absolute sterochemistry. The calculated distances of the sulfur atom and the carbonyl of the triazine moiety are compatible with hydrogen bonding interaction with the amide proton of Ala192/Leu191 and Ala194 respectively (shown by yellow lines in Figure 1). The same interaction can be obtained for the sulfones **2w** to **2z** but with hydrogen bonding to the oxygen atoms of the sulfone. This model explains the preferred orientation of the side chain in S1′ and the lack of activity of **2c** against MMP-2 compared to **2b** and **2d** (which is due to the bend of the methylene of **2c**). Additionally, the sterically demanding azepine ring of **2t** does not allow a fit in this model, in agreement with its complete lack of activity.

Table 4. In Vitro PK Parameters and Inhibition of B16F10 Melanoma in Mice

			no. of metastases (% control)					
			mg/kg i.p.				mg/kg p.o.	
no.	MF % R/H	A%	25	50	100	200	100	200
2a	74/100	95	45	39	30	TOX	70	74.5
2e	55/62	90			32.5	24.5	72	68
2f	43/61	94			96	43	69	64.5
2g	76/63	91			51	31	65	80
2y	58/91	92			78	109	NT	NT

Pharmacological Evaluation. In vitro pharmacokinetic parameters were considered in selecting compounds for further pharmacological evaluation. Rat and human hepatic microsomes (R and H in Table 4) were used to estimate metabolic stability and first pass metabolism (MF %), whereas Caco-2 cell permeability was used to measure in vitro absorption (A %). More favorable results were achieved in this carboxylic acid series than in the previous hydroxamate series.[19] Selected compounds with MF values over 60% and A values over 90% were considered as good candidates for further in vivo studies (Table 4). For preliminary evaluation of their antitumor activity, these compounds were tested in mice against the B16F10 melanoma, an experimental metastasis model.[26]

In this model, **2a**, **2e**, and **2g** administered intraperitoneally (i.p.) led to significant dose-dependent reductions in the number of metastases (>60% at 200 mg; Table 4) and marked reductions of their size (100% inhibition of the occurrence of metastases with diameter over 1 mm; data not shown).

Compound **2a**, found to be toxic at the highest dose, was active at 25 and 50 mg/kg i.p., reducing by 55 and 60% the number of metastases, respectively. Following oral administration, **2a** was only marginally active, without a clear dose-dependent effect (Table 4). The excellent in vivo pharmacokinetic parameters of **2a** and **2e** confirmed their potential for further pharmacological evaluation (Table 5).

A preliminary evaluation of the enantiomers of compound **2a** showed that the biological activities are concentrated in the (1*R*,2*S*,5*R*)-enantiomer. The profile is comparable to those for the hydroxamates **CGS 27023A** and trocade but with better selectivity versus MMP-1 (Table 1). The establishment of an enantiospecific synthesis for the production of (1*R*,2*S*,5*R*)-**2a** starting from a single enantiomer of **6** is in progress.

Conclusion

In summary, we have described a stereoselective synthesis of a series of 2,5-disubstituted cyclopentane

Table 5. Pharmacokinetics in Mice[a] of Compounds **2a** and **2e**

	2a				**2e**			
route	dose mg/kg	C_{max} μg/mL	$t_{1/2}$ (h)	F (%)	dose mg/kg	C_{max} μg/mL	$t_{1/2}$ (h)	F (%)
i.v.	5	40	3.4		5	40	3.5	
i.p.	50	203	4	100	50	130	4	100
p.o.	50	93	3	69	50	107	4	93

[a] Compounds were administrated as a solution in Tween 80/H_2O at 4% (i.p. and p.o.) or at 0.4% (i.v.).

carboxylic acids as potent MMP-2, -3, -9, -13 inhibitors having selectivity against MMP-1. In these rigidified molecules, 1,2- and 1,5-trans configurations are required for activity, in agreement with our initial conformational analysis. By conformational restriction and by establishing better interactions at S1 and S1′, these carboxylic acid derivatives partially overcome their lower innate binding to zinc compared to the corresponding acyclic hydroxamate analogues. Furthermore, selected compounds from the series show significant improvements in pharmacokinetic parameters relative to the hydroxamates. On the basis of their in vivo activities in a mouse metastasis model and their good oral bioavailabilities, compounds (1*R*,2*S*,5*R*)-**2a** and **2e** were identified as suitable candidates for further development.

Experimental Section

Chemistry General Techniques. Unless otherwise noted, all reactions were carried out under a nitrogen or argon atmosphere using anhydrous conditions. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material unless otherwise stated.

All reagents were purchased in the highest available commercial quality and were used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.2-mm Merck silica gel plates. Ultraviolet light, phosphomolybdic acid, and *p*-anisaldehyde were used for visualization.

Preparative flash chromatography separations were carried out on Kiesegel 60 (0.04−0.063 mm) Merck silica gel.

Reverse phase HPLC analysis was performed on an Agilent 1100 instrument using a Xtera Waters column with detection at 210 nm using a H_2O/CH_3CN + 0.1% TFA gradient over 15 min.

NMR spectra were recorded on a Bruker DPX 200 or 300 instrument as indicated, calibrated using TMS as an internal reference. For compounds **2a** and **2a′**, additional experiments were carried out on a Bruker Avance 400 MHz spectrometer equipped with a BBI 5 mm grad z probe.

The following abbreviations are used to indicate multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; b, broad.

IR spectra were recorded on a Brucker Vector 22 spectrophometer.

Electrospray mass spectra were recorded in a positive mode on a Finnigan TSQ 7000 spectrophometer, by infusion at 15 μL/min of a 0.1 mg/mL sample solution in a mixture of CH_3CN/H_2O (3/1:v/v).

***tert*-Butyl 5-Hydroxycyclopent-2-enecarboxylate (6).** A mixture 2,5-dimethoxydihydrofuran (26.4 mL, 0.204 mol) in 0.5 M aq. HCl (200 mL) was heated to reflux until dissolution was complete. The reaction mixture was cooled to room temperature and neutralized with saturated aq. $KHCO_3$. To this mixture was added a solution of K_2CO_3 (1.41 g, 0.008 mol) in water (10 mL) and then diethylphosphonoacetate *tert*-butyl ester (40.5 mL, 0.204 mol). The resulting mixture was stirred 24 h at room temperature and extracted with EtOAc. The organic phase was washed with saturated aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated to give the title compound as a yellow oil which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.8 (m, 1H, C=C*H*), 5.05 (m, 1H, C*H*OH), 2.9−2.6 (m, 2H, CH_2-CHOH), 2.3−2.5 (m, 2H, C=CHCH_2), 1.5 (s, 9H, *tBu*). IR: V_{max} 3400; 1708 cm^{-1}.

***tert*-Butyl 5-Acetylcyclopent-1-enecarboxylate (7).** To a solution of compound **6** (37.6 g, 0.204 mol) in CH_2Cl_2 (100 mL) at 0 °C was added pyridine (50 mL, 0.612 mol) and then acetic anhydride (38.5 mL, 0.408 mol). The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was taken up in EtOAc and washed with 1 M aq. HCl and saturated aq. K_2CO_3. The solution was dried over Na_2SO_4 and concentrated. Flash chromatography (gradient of EtOAc/heptane, 5:95) gave compound **7** (46.15 g, 27.5% 2 steps). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.0 (m, 1H, C=C*H*), 6.0 (m, 1H, C*H*OAc), 2.85−2.2 (m, 3H, C*H*CH_2CHOAc), 1.95 (d, 1H, C*H*CH_2CHOAc), 2.05 (s, 3H, O*Ac*), 1.5 (s, 9H, *tBu*). IR: V_{max} 1737−1715 cm^{-1}.

***tert*-Butyl 5-(1,3-Dithianyl)cyclopent-1-enecarboxylate (8).** To a solution of 1,3-dithiane (6.85 g, 57 mmol) in THF (75 mL) at −78 °C was added dropwise a solution of *n*-BuLi (35.7 mL, 1.6 M, 57 mmol) in THF. The reaction mixture was stirred at −78 °C over 1.5 h and added to a mixture of **7** (12.75 g, 47.5 mmol) and CuI (9.05 g, 47.5 mmol) in THF (150 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 5 h, quenched with saturated aq. NH_4Cl, and allowed to warm to room temperature. The reaction mixture was filtered through Celite and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (gradient of EtOAc in petroleum ether) gave compound **8** (10.9 g, 80%) as a cream powder. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.8 (m, 1H, C=C*H*), 4.8 (d, 1H, SC*H*S), 3.4 (m, 1H, C*H* CHS_2), 3.1−2.9 (m, 2H, C=CHCH_2), 2.8−2.6 (m, 2H, C=CHCH_2CH_2), 2.6−2.4 (m, 4H, SCH_2), 2.1(m, 2H, SCHCH_2CH_2S)0.1.55 (s, 9H, *tBu*). IR: V_{max} 1704 cm^{-1}. Anal. ($C_{14}H_{22}O_2S_2$): C, H, S.

***tert*-Butyl 5-Formylcyclopent-1-enecarboxylate (9).** A solution of dithiane **8** (7.8 g, 27.2 mmol) in acetone (50 mL) was added to a mixture of $HgCl_2$ (17.74 g, 65.3 mmol) and HgO (7.07 g, 32.6 mmol) in acetone/H_2O (85:15, 175 mL), at room temperature. The reaction mixture was stirred at room temperature for 48 h, filtered through Celite, and washed with acetone/CH_2Cl_2. The organic layer was concentrated and the residue was diluted petroleum ether. The resulting solution was filtered and evaporated to provide crude **9** (5 g, 90%) as a yellow oil which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.7 (d, 1H, C*H*O), 6.8 (m, 1H, C=C*H*CH$_2$), 3.7 (m, 1H, C*H*CHO), 2.5 (m, 2H, C=CHCH_2CH_2), 2.2 (m, 2H, C=CHCH_2CH_2), 1.45 (s, 9H, *tBu*). IR: V_{max} 1708−1673 cm^{-1}.

***tert*-Butyl 5-Hydroxymethylcyclopent-1-enecarboxylate (5).** To a suspension of $LiAlH_4$ (3.3 g, 86.6 mmol) in THF (500 mL) was added dropwise 3-ethyl-3-pentanol (36.6 mL, 260 mmol) maintaining the reaction mixture at 40 °C. After complete addition, the reaction mixture was stirred at 50 °C for 1 h, and at room temperature overnight. The mixture was then transferred to a solution of **9** (17 g, 86.6 mmol) in THF (500 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, carefully quenched with saturated aq. NH_4Cl (500 mL), and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (gradient of EtOAc in petroleum ether) gave **5** (17.2 g, 93%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.8 (m, 1H, C=C*H*), 3.8 (m, 1H, O*H*), 3.6 (d, 2H, CH_2OH), 3.11 (m, 1H, C*H*CH_2OH), 2.45 (m, 2H, C=CHCH_2), 2.1 (m, 2H, CH_2-CHCH_2OH), 1.55 (s, 9H, *tBu*). IR: V_{max} 3400, 1706−1686, 1626 cm^{-1}. Anal. ($C_{11}H_{18}O_3$): C, H.

***tert*-Butyl 2-(4-Bromophenylthio)-5-hydroxymethylcyclopentanecarboxylate (4a, 4a′).** To a stirred mixture of **5** (6.6 g, 33 mmol) in piperidine (75 mL) was added 4-bromothiophenol (12.6 g, 66.5 mmol). The mixture was heated to reflux for 5 h and then concentrated in vacuo. The residue was diluted with cold water (500 mL), acidified with aq. 1 N HCl (500 mL), and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (gradient of EtOAc in petroleum ether) gave **4a** (5 g, 39%) and **4a′** (0.65 g, 5%). **4a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.5−7.3 (2d, 4H, *Ph*), 4.65 (t, 1H, O*H*), 3.77 (q, 1H, C*H*S), 3.42−3.38 (m, 2H, CH_2OH), 2.33 (t, 1H, C*H*CO$_2$), 2.2 (m, 1H, C*H*CH$_2$OH), 2.15−1.8 (m, 2H, CH_2CHCH$_2$OH), 1.8−1.6 (m, 2H, CH_2CHS), 1.55 (s, 9H, *tBu*). IR: V_{max} 3395, 1714 cm^{-1}. **4a′**: ^{1}H NMR (400 MHz, DMSO d6): δ 7.45−7.2 (2d, 4H, *Ph*), 4.0−3.45 (m, 3H, CH_2OH, C*H*S), 2.95−2.35 (2m, 1H, C*H*CO$_2$), 2.7−2.35 (2m, 1H, C*H*CH$_2$OH), 2.25−1.3 (m, 4H, CH_2CHCH$_2$OH, CH_2CHS), 1.9 (m, 1H, O*H*), 1.5 (s, 9H, *tBu*). IR: V_{max} 3425, 1719, 1686 cm^{-1}. MH$^+$(386).

***tert*-Butyl 2-[2-(4-Bromophenyl)ethylthio]-5-hydroxymethylcyclopentane-carboxylate (4b).** Compound **4b** (2.3 g, 55%) was prepared from **5** (2 g, 10 mmol) and 4-bromophenylethanethiol (4.38 g, 20 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.4−7.05 (2d, 4H, *Ph*), 6.15 (t, 1H, O*H*), 3.62 (m, 2H, CH_2OH), 3.45 (q, 1H, C*H*S), 2.85−2.8 (m, 4H, CH_2CH_2S), 2.4 (t, 1H, C*H*CO$_2$), 2.35 (m, 1H, C*H*CH$_2$OH), 2.10−1.65 (m, 2H, CH_2-CHCH$_2$OH), 1.9−1.6 (m, 2H, CH_2CHS), 1.55 (s, 9H, *tBu*).

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-hydroxymethylcyclopentane-carboxylate (10a and 10a′).** Compound **10a** (3 g, 38%) was prepared from **5** (3.7 g, 18.5 mmol) and 4-chlorobiphenylthiol (6.15 g, 28 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.7−7.4 (2d, 8H, *PhPh*), 4.65 (s, 1H, O*H*), 3.8 (q, 1H, C*H*S), 3.4 (m, 2H, CH_2OH), 2.35 (t, 1H, C*H*CO$_2$), 2.2 (q, 1H, C*H*CH$_2$OH), 2.15−1.6 (m, 4H, CH_2CH_2), 1.32 (s, 9H, *tBu*). IR: V_{max} 3332, 1719, 1593 cm^{-1}. Compound **10a′** (0.3 g, 4%) was obtained in the experiment described above. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.7−7.4 (2d, 8H, *PhPh*), 4.65 (s, 1H, O*H*), 3.9 (q, 1H, C*H*S), 3.32 (m, 2H, CH_2OH), 2.95 (t, 1H, C*H*CO$_2$), 2.48 (q, 1H, C*H*CH$_2$OH), 2.15−1.6 (m, 4H, CH_2CH_2), 1.32 (s, 9H, *tBu*). IR: V_{max} 3318, 1720, 1593 cm^{-1}.

***tert*-Butyl 2-Biphenylthio-5-hydroxymethylcyclopentanecarboxylate (10b).** To a mixture of **4a** (3 g, 7.8 mmol) in toluene (100 mL) at room temperature was added sequentially tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.23 mmol), a solution of Na_2CO_3 (1.8 g, 1.7 mmol) in water (10 mL), and a solution of phenyl boric acid (1.04 g, 8.5 mmol) in a minimum volume of EtOH. The reaction mixture was heated to reflux for 12 h and then concentrated in vacuo. The residue was diluted with EtOAc, washed with brine, dried over Na_2-SO_4, and concentrated. Flash chromatography (gradient of EtOAc in petroleum ether) gave compound **10b** (2.15 g, 72.5%). ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.6−7.4 (m, 9H, *PhPh*), 3.65 (m, 2H, CH_2OH), 3.45 (m, 1H, C*H*S), 2.5 (t, 1H, C*H*CO$_2$), 2.35 (m, 1H, C*H*CH$_2$OH), 2.05−1.8 (m, 2H, CH_2CHCH$_2$OH), 1.9 (m, 1H, C*H*CH$_2$OH), 1.8−1.55 (m, 2H, CH_2CHS), 1.45 (s, 9H, *tBu*). IR: V_{max} 3300, 1720 cm^{-1}.

***tert*-Butyl 2-Biphenylmethylthio-5-hydroxymethylcyclopentanecarboxylate (10c).** Compound **10c** (2.4 g, 60%) was prepared from **5** (2 g, 10 mmol) and biphenylmethanethiol (4.04 g, 21 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.6−7.4 (2m, 9H, *PhPh*), 3.8 (s, 2H, PhCH_2S), 3.65 (m, 2H, CH_2OH), 3.4 (s, 2H, C*H*S), 2.5−2.25 (2m, 2H, C*H*CO$_2$; C*H*CH$_2$OH), 2.2−1.6 (2m, 4H, CH_2CH_2), 1.9 (t, 1H, O*H*), 1.8−1.6 (m, 2H, CH_2CHS), 1.4 (s, 9H, *tBu*). IR: V_{max} 3533, 1714 cm^{-1}.

***tert*-Butyl 2[2-(4′-Chlorobiphenyl)-ethylthio)]-5-hydroxymethyl cyclo-pentanecarboxylate (10d).** Compound **10d** (2.3 g, 50%) was prepared from **5** (2.07 g, 10.4 mmol) and 2-[2-(4′-chlorobiphenyl)ethanethiol (5.2 g, 21 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.5−7.25 (m, d, 8H, *PhPh*), 3.65 (m, 2H, CH_2-OH), 3.5 (s, 1H, C*H*S), 2.9 (m, 2H, CH_2CH_2S), 2.45−1.6 (m, 6H, C*H*CO$_2$, C*H*CH$_2$OH, CH_2CH_2), 1.9 (t, 1H, O*H*), 1.45 (s, 9H, *tBu*). IR: V_{max} 3335, 1719 cm^{-1}.

***tert*-Butyl 2-(4′-Methylthiobiphenylthio)-5-hydroxymethyl cyclopentane Carboxylate (10e).** Compound **10e** (3.1 g, 30%) was prepared from **4a** (1 g, 2.4 mmol) and 4-methylthiophenyl boric acid (0.44 g, 2.6 mmol) according to the same procedure used for preparing **10b**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.5−7.35 (m, d, 8H, *PhPh*), 3.95 (q, 1H, C*H*S), 3.65 (m, 2H, CH_2OH), 2.5 (s, t, 4H, C*H*CO$_2$, CH_3S), 2.35 (m, 1H, C*H*CH$_2$OH), 2.3−1.5 (m, 4H, CH_2CH_2), 1.55 (s, 1H, O*H*), 1.4 (s, 9H, *tBu*). IR: V_{max} 3226, 1719 cm^{-1}. Anal. ($C_{24}H_{30}O_3S_2$): C, H, S.

***tert*-Butyl 2-(4′-Cyanobiphenylthio)-5-hydroxymethylcyclopentane Carboxylate (10f).** Compound **10f** (0.9 g, 28%) was prepared from **5** (1.5 g, 7.56 mmol) and (4′-cyanobiphenyl)thiol (3.2 g, 15 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.8−7.6−7.45 (m, d, 8H, *PhPh*), 4.0 (q, 1H, C*H*S), 3.65 (m, 2H, CH_2OH), 2.5 (t, 1H, C*H*CO$_2$), 2.4 (m, 1H, C*H*CH$_2$OH), 2.25−1.5 (m, 4H, CH_2CH_2), 1.6 (s, 1H, O*H*), 1.45 (s, 9H, *tBu*). IR: V_{max} 3483, 2227, 1721, 1607 cm^{-1}.

***tert*-Butyl 2-(4-Pyridin-4-ylphenylthio)-5-hydroxymethyl Cyclopentane Carboxylate (10g).** Compound **10g** (0.98 g, 97%) was prepared from **4a** (1 g, 2.6 mmol) and 4-pyridinyl boric acid (0.42 g, 3.4 mmol) according to the same procedure used for preparing **10b**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.7 (d, 2H, o-*Py*), 7.6−7.4 (m, 6H, *m-Py Ph*), 4.0 (q, 1H, C*H*S), 3.65 (m, 2H, CH_2OH), 2.55 (t, 1H, C*H*CO$_2$), 2.4 (m, 1H, C*H*CH$_2$-OH), 2.3−1.5 (m, 4H, CH_2CH_2), 1.6 (s, 1H, O*H*), 1.45 (s, 9H, *tBu*). IR: V_{max} 3278, 1721 cm^{-1}.

***tert*-Butyl 2-(4-Thiazol-2-ylphenylthio)-5-hydroxymethylcyclopentane Carboxylate (10h).** Compound **10h** (0.425 g, 14.5%) was prepared from **5** (1.5 g, 7.56 mmol) and 4-(thiazol-2-yl)phenylthiol (2.95 g, 15 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.9−7.45−7.35 (m, 2d, 6H, *Phthiazol*), 4.0 (q, 1H, C*H*S), 3.15 (m, 2H, CH_2OH), 2.5 (t, 1H, C*H*CO$_2$), 2.4 (q, 1H, C*H*CH$_2$OH), 2.25−1.5 (m, 5H, CH_2CH_2, O*H*), 1.45 (s, 9H, *tBu*). IR: V_{max} 3285, 1707 cm^{-1}. Anal. ($C_{20}H_{25}NO_3S_2$): C, H, N.

***tert*-Butyl 2-(4-benzothiazol-2-ylphenylthio)-5-hydroxymethyl cyclopentane Carboxylate (10i).** Compound **10i** (0.24 g, 11%) was prepared from **5** (1 g, 5.04 mmol) and 4-(benzothiazol-2-yl)phenylthiol (1.84 g, 7.56 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.15−7.5 (m, 8d, 6H, *PhPh*), 4.6 (s, 1H, O*H*), 3.9 (q, 1H, C*H*S), 3.4 (m, 2H, CH_2OH), 2.35 (q, 1H, C*H*CO2), 2.3 (q, 1H, C*H*CH$_2$OH), 2.25−1.56 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 3303, 1717 cm^{-1}.

***tert*-Butyl 2-(4-[1,2,4]Triazol-4-ylphenylthio)-5-hydroxymethyl cyclopentanecarboxylate (10j).** Compound **10j** (0.38 g, 16%) was prepared from **5** (1.2 g, 6 mmol) and 4-[1,2,4]triazol-4-ylphenylthiol (1.6 g, 9 mmol) according to the same procedure used for preparing **4a**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 9.1 (s, 2H, *triazine*), 7.65−7.3 (2d, 4H, *Ph*), 4.7 (s, 1H, O*H*), 3.85 (q, 1H, C*H*S), 3.4 (m, 2H, CH_2OH**),** 2.4 (t,1H, C*H*CO$_2$), 2.2 (m, 1H, C*H*CH$_2$OH), 1.85−1.65 (m, 4H, CH_2CH_2), 1.4 (s, 9H, *tBu*). IR: V_{max} 3345, 1719 cm^{-1}.

***tert*-Butyl 2-(4-Bromophenylthio)-5-[2-(4-oxo-4H-benzo-[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentanecarboxylate (11a).** To a mixture of triphenylphosphine (13.4 g, 25.8 mmol) and diisopropyl azodicarboxylate (5.22 g, 25.8 mmol) in anhydrous THF (100 mL) at 0 °C was added a solution of compound **4a** (5 g, 12.9 mmol) and benzotriazine (3.9 g, 25.8 mmol) in anhydrous THF (50 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 18 h. After concentrating in vacuo, the residue was diluted with diisopropyl ether. The precipitate was removed by filtration and the filtrate was concentrated. Compound **11a** (5.7 g, 85.6%) was obtained by flash chromatography (gradient of EtOAc in petroleum ether). ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.3−8.15 (2d, 2H, *o-Phtriazine*), 8.0−7.7 (2m, 2H, *m-Phtriazine*), 7.4−7.25 (d, m, 4H, *Ph*), 4.55 (t, 2H, NCH_2), 3.85 (m, 1H, C*H*S), 2.9 (m, 1H, C*H*CO$_2$), 2.65 (m, 2H, C*H*CH$_2$N), 2.25−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1714, 1683 cm^{-1}.

***tert*-Butyl 2-(4-Bromophenylthio)-5-[2-(4-oxo-4H-benzo-[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentanecarboxylate (11a′).** Compound **11a′** (0.65 g, 75.4%) was prepared from **4a′** (0.65 g, 1.67 mmol) and benzotriazine (0.5 g, 3.35 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4−8.15 (2d, 2H, *o-Phtriazine*), 8.0−7.75 (2m, 2H, *m-Phtriazine*), 7.4−7.25 (2d, 4H, *Ph*), 4.7−4.4 (m, 2H, NCH_2), 3.85 (m, 1H, C*H*S), 3.25 (m, 2H, C*H*CH_2N), 3.15 (m, 1H, C*H*CO_2), 2.25−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1727, 1683 cm^{-1}.

***tert*-Butyl 2-[2-(4-Bromophenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentanecarboxylate (11b).** Step 1: *tert*-Butyl 2-(4-bromophenylethylthio)-5-tosyloxymethylcyclopentanecarboxylate. To a solution of compound **4b** (2.3 g, 5.5 mmol) in CH_2Cl_2 (50 mL) at room temperature was added sequentially pyridine (1.8 mL, 23 mmol), and tosyl chloride (1.26 g, 6.64 mmol). The reaction mixture was stirred 5 days and then concentrated. The residue was diluted with EtOAc and washed with dilute aq. 1 N HCl, 1 N saturated aq. $NaHCO_3$, and brine. The organic layer was concentrated and the residue (1.73 g, 55%) was used in the next step without further purification. Step 2: Preparation of **11b**. A mixture of *tert*-butyl 2-(4-bromophenylethylthio)-5-tosyloxymethyl cyclopentane-carboxylate (1.73 g, 3 mmol), 18-C-6 (2.4 g, 9 mmol), and potassium phthalimide (1.7 g, 9.1 mmol) in DMF (75 mL) was heated for 12 h at 40 °C. The reaction mixture was diluted with water and extracted several times with EtOAc. The combined organic layers were concentrated and the residue was purified by flash chromatography (heptane/EtOAc; 9:1) to give the title compound (1.3 g, 79%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9−7.75 (m, 4H, *Pht*), 7.4 (d, 2H, *o-Ph*), 7.1 (d, 2H, *m-Ph*), 4.0−3.7 (m, 2H, CH_2N), 3.4 (m, 1H, C*H*S), 2.9−2.6 (m, 5H, C*H*CH_2N, CH_2CH_2S), 2.45 (m, 1H, C*H*CO_2), 2.2−1.65 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1775, 1708 cm^{-1}.

***tert*-Butyl 2-[2-(4′-Chlorobiphenylthio)]-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12a).** To a solution of compound **11a** (5.7 g, 0.011 mol) in toluene (150 mL) at room temperature was added sequentially 4-chlorophenyl tri-*n*-butyltin (8.86 g, 22 mmol), tetrakis (triphenylphosphine) palladium(0) (0.6 g, 0.5 mmol), and lithium chloride (1.5 g, 35 mmol). The reaction mixture was heated to reflux for 18 h and then concentrated. The residue was taken up in heptane and extracted several times with acetonitrile. The combined organic layers were concentrated and the residue was purified by flash chromatography (heptane/EtOAc; 9:1) to give **12a** (4.5 g, 74.3%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4−8.2 (2d, 2H, *o-Phtriazine*), 7.9−7.8 (2m, 2H, *m-Phtriazine*), 7.5−7.25 (d, m, 8H, *Ph*), 4.6 (t, 2H, NCH_2), 3.85 (m, 1H, C*H*S), 2.9 (m, 1H, C*H*CO_2), 2.7 (m, 1H, C*H*CH_2N), 2.2−1.7 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1724, 1683 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{30}H_{30}N_3O_3S^{35}Cl$): calcd.: 570.1594; found: 570.1592.

***tert*-Butyl 2[2-(4′-Chlorobiphenylthio)]-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12a′).** Compound **12a′** (0.3 g, 43.5%) was prepared from **11a′** (0.65 g, 1.25 mmol) and 4-chlorophenyl tri-*n*-butyltin (1 g, 2.5 mmol) according to the same procedure used for preparing **12a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4−8.15 (2d, 2H, *o-Phtriazine*), 8.0−7.75 (2m, 2H, *m-Phtriazine*), 7.45 (m, 8H, *Ph*), 4.7−4.4 (dd, 2H, NCH_2), 3.9 (m, 1H, C*H*S), 3.4−3.1 (m, 2H, C*H*CO_2, C*H*CH_2N), 2.35−1.9−1.6 (3m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). HRMS [M+Na]$^+$, *m/z*, ($C_{30}H_{30}N_3O_3S^{35}Cl$): calcd.: 570.1594; found: 570.1600.

***tert*-Butyl 2-Biphenylthio-5-(phthalimidomethyl)-cyclopentane Carboxylate (12b).** Step 1: *tert*-Butyl 2-biphenylthio-5-tosyloxymethylcyclopentanecarboxylate. The title compound (2.62 g, 87%) was prepared according to the procedure of **11b**, Step 1 using **10b** (2.15 g, 5.6 mmol), pyridine (1.8 mL, 22.4 mmol) and tosyl chloride (3.2 g, 16.8 mmol) in CH_2Cl_2 (50 mL). The crude product was used in the next step without further purification. Step 2: **12b**. Compound **12b** (2.52 g, 80%) was prepared according to the procedure of **11b**, Step 2, using *tert*-butyl 2-biphenylthio-5-tosyloxymethylcyclopentanecarboxylate (2.65 g, 4.9 mmol), 18-C-6 (3.9 g, 15 mmol), and potassium phthalimide (2.7 g, 14.7 mmol) in DMF (50 mL). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85−7.7 (m, 4H, *Pht*), 7.6−7.3 (m, 9H, *PhPh*), 3.65 (m, 2H, CH_2OH), 3.9 (m, 1H, C*H*S), 3.9−3.7 (AB, 2H, CH_2N), 2.65 (m, 1H, C*H*CH_2N), 2.55 (m, 1H, C*H*CO_2), 2.2−1.6 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1774, 1722, 1703 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{31}H_{31}NO_4S$): calcd.: 536.1872; found: 536.1871.

***tert*-Butyl 2-Biphenylmethylthio-5-(phthalimidomethyl)-cyclopentane Carboxylate (12c).** Step 1: *tert*-Butyl 2-biphenylmethylthio-5-tosyloxymethylcyclopentanecarboxylate. The title compound (1.7 g, 50%) was prepared according to the procedure of **12b**, Step 1, using **10c** (2.4 g, 6 mmol) and tosyl chloride (3.2 g, 16.8 mmol). It was used in the next step without further purification. Step 2: **12c**. Compound **12c** (1.2 g, 74%) was prepared according to the procedure of **12b**, Step 2 using *tert*-butyl 2-biphenylmethylthio-5-tosyloxymethylcyclopentane carboxylate (1.7 g, 0.003 mol) and potassium phthalimide (1.7 g, 0.0092 mol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9 (m, 4H, *Pht*), 7.65−7.4 (m, 9H, *PhPh*), 3.85 (s, 2H, PhCH_2S), 3.65 (m, 2H, CH_2N), 3.2 (m, 1H, C*H*S), 2.6 (m, 1H, C*H*CH_2N), 2.4 (m, 1H, C*H*CO_2), 2.15−1.5 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1774, 1721, 1704 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{32}H_{33}NO_4S$): calcd.: 550.2028; found: 550.2046.

***tert*-Butyl 2-[2-(Biphenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentane Carboxylate (12d).** Compound **12d** (0.7 g, 56%), a white crystalline solid (mp 87 °C), was prepared according to the same procedure used for preparing **12a** using **11b** (1.3 g, 2.3 mmol), phenyl tri-*n*-butyltin (1.5 mL, 4.6 mmol), tetrakis (triphenylphosphine) palladium(0) (0.115 g, 0.1 mmol), and LiCl (0.29 g, 6.9 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85−7.7 (m, 4H, *Pht*), 7.6−7.3 (m, 9H, *PhPh*), 3.77 (m, 2H, CH_2N), 3.5 (m, 1H, C*H*S), 2.9 (m, 4H, PhCH_2CH_2S), 2.65 (m, 1H, C*H*CH_2N), 2.5 (m, 1H, C*H*CO_2), 2.2−1.6 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1775, 1709 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{32}H_{35}NO_4S$): calcd.: 564.2185; found: 564.2192.

***tert*-Butyl 2-[2-(4′-Fluorobiphenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentane Carboxylate (12e).** Compound **12e** (2.13 g, 62%) was prepared from **11b** (3.36 g, 6.2 mmol) and 4-fluorophenyl tri-*n*-butyltin (4.76 g, 12.4 mmol) according to the same procedure used for preparing **12a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9−7.7 (m, 4H, *Pht*), 7.5−7.25 (m, 8H, *PhPh*), 3.9−3.7 (dd, 2H, CH_2N), 3.45 (m, 1H, C*H*S), 2.9 (m, 4H, PhCH_2CH_2S), 2.65 (m, 1H, C*H*CH_2N), 2.5 (m, 1H, C*H*CO_2), 2.2−1.6 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1775, 1709 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{33}H_{34}NO_4SF$): calcd.: 582.2097; found: 582.2090.

***tert*-Butyl 2-[2-(4′-Chlorobiphenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentane Carboxylate (12f).** Compound **12f** (1.93 g, 59%) was prepared from **11b** (3.36 g, 6.2 mmol) and 4-chlorophenyl tri-*n*-butyltin (4.96 g, 12.4 mmol) according to the same procedure used for preparing **12a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9−7.7 (m, 4H, *Pht*), 7.5−7.25 (m, 8H, *PhPh*), 3.9−3.7 (2dd, 2H, CH_2N), 3.45 (m, 1H, C*H*S), 2.9 (m, 4H, PhCH_2CH_2S), 2.65 (m, 1H, C*H*CH_2N), 2.5 (m, 1H, C*H*CO_2), 2.2−1.6 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1775, 1709 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{33}H_{34}N_3O_3S^{35}Cl$): calcd.: 598.1795; found: 598.1795.

***tert*-Butyl 2-[2-(4′-Chlorobiphenyl)ethylthio]-5-[2-(4-oxo-4H-benzo[*d*][1,2,3] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12g).** Compound **12g** (0.37 g, 57.5%) was prepared from **10d** (0.5 g, 1.12 mmol) and benzotriazine (0.33 g, 2.23 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.3−8.15 (2d, 2H, *o-Phtriazine*), 8.2−7.9 (2m, 2H, *m-Phtriazine*), 7.75−7.45 (m, d, 8H, *PhPh*), 4.45 (d, 2H, NCH_2), 3.3 (m, 1H, C*H*S), 2.85 (m, 5H, C*H*CO_2, SCH_2CH_2), 2.5 (m, 1H, C*H*CH_2N), 2.2−1.5 (3m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1720, 1684 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{32}H_{34}N_3O_3S^{35}Cl$): calcd.: 598.1907; found: 598.1909.

***tert*-Butyl 2-(4′-Methylthiobiphenylthio)- 5-[2-(4-oxo-4H-benzo[*d*][1,2,3] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12h).** Compound **12h** (0.235 g, 58.5%) was prepared from **10e** (0.3 g, 0.71 mmol) and benzotriazine (0.21 g, 1.43

mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.35−8.15 (2d, 2H, *o-Phtriazine*), 8−7.7 (2m, 2H, *m-Phtriazine*), 7.5−7.3 (m, d, 8H, *PhPh*), 4.55 (m, 2H, NCH_2), 3.95 (q, 1H, C*H*S), 2.9 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.5 (s, 3H, SCH_3), 2.2−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1720, 1682 cm^{-1}. Anal. ($C_{31}H_{33}N_3O_3S_2$): C, H, N, S.

***tert*-Butyl 2-(4′-Cyanobiphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12i).** Compound **12i** (0.425 g, 60%) was prepared from **10f** (0.545 g, 1.33 mmol) and benzotriazine (0.4 g, 2.7 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4−8.2 (2d, 2H, *o-Phtriazine*), 8.15−7.95 (2m, 2H, *m-Phtriazine*), 7.9−7.75−7.5 (3d, 8H, *PhPh*), 4.5 (m, 2H, NCH_2), 3.9 (q, 1H, C*H*S), 2.85 (q, 1H, C*H*CH$_2$N), 2.6 (t, 1H, C*H*CO$_2$), 2.3−1.6 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 2233,1721, 1686 cm^{-1}. Anal. ($C_{31}H_{30}N_4O_3S$): C, H, N, S.

***tert*-Butyl 2-(4-Pyridin-4-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12j).** Compound **12j** (0.74 g, 56.6%) was prepared from **10g** (1 g, 2.54 mmol) and benzotriazine (0.75 g, 5.1 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.65 (d, 2H, *o-Py*), 8.35−8.15 (2d, 2H, *o-Phtriazine*), 7.95−7.8 (2t, 2H, *m-Phtriazine*), 7.8−7.5 (m, 6H, *m-PyPh*), 4.55 (m, 2H, NCH_2), 4.0 (q, 1H, C*H*S), 3.0 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.2−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). HRMS [M+H]$^+$, *m/z*, ($C_{29}H_{30}N_4O_3S$): calcd.: 515.2117; found: 515.2103.

***tert*-Butyl 2-(4-Thiazol-2-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12k).** Compound **12k** (0.41 g, 72.5%) was prepared from **10h** (0.425 g, 1.1 mmol) and benzotriazine (0.32 g, 2.2 mmol) according to the same procedure used for preparing **11a.** $_1$H NMR (200 MHz, $CDCl_3$): δ 8.35−8.2 (2d, 2H, *o-Phtriazine*), 8.1−7.95 (2t, 2H, *m-Phtriazine*), 7.8−7.45−7.35 (3d, 6H, *Phthiazol*), 4.55 (m, 2H, NCH_2), 4.0 (q, 1H, C*H*S), 3.0 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.3−1.8 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1720, 1678 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{27}H_{28}N_4O_3S_2$): calcd.: 543.1501; found: 543.1495.

***tert*-Butyl 2-(4-benzothiazol-2-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12l).** Compound **12l** (0.26 g, 50%) was prepared from **10i** (0.4 g, 0.9 mmol) and benzotriazine (0.27 g, 1.8 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4−7.3 (md, 12H, *PhPh, Phtriazine*), 4.7−4.4 (m, 2H, NCH_2), 4.05 (q, 1H, C*H*S), 2.9 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.3−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1715, 1693, 1677 cm^{-1}.

***tert*-Butyl 2-(4-[1,2,4]Triazol-4-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12m).** Compound **12m** (0.33 g, 65%) was prepared from **10j** (0.38 g, 1 mmol) and benzotriazine (0.3 g, 2 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.5 (s, 2H, *triazine*), 8.4−8.2 (2d, 2H, *o-Phtriazine*), 8.0−7.8 (2t, 2H, *m-Phtriazine*), 7.55−7.3 (2d, 4H, *Ph*), 4.6 (m, 2H, NCH_2), 4.0 (q, 1H, C*H*S), 2.95 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.3−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1720, 1680 cm^{-1}. Anal. ($C_{26}H_{28}N_6O_3S$): C, H, N, S.

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-ylmethyl]-cyclopentane Carboxylate (12n).** Compound **12n** (0.52 g, 80%) was prepared from **10a** (0.5 g, 1.2 mmol) and 1,5,5-trimethylhydantoin (0.25 g, 1.8 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.65−7.5 (2dd, 8H, *PhPh*), 3.85 (q, 1H, C*H*S), 3.50 (m, 2H, CH_2N), 2.8 (s, 3H, NCH_3), 2.45 (m, 2H, C*H*CH$_2$O, C*H*CO$_2$), 2.15−1.4 (2m, 4H, CH_2CH_2), 1.35. (s, 9H, *tBu*), 1.3 (s, 6H, 2CH_3). IR: V_{max} 1769, 1714 cm^{-1}. HRMS [M+Na]$^+$, *m/z*, ($C_{29}H_{36}N_2O_4S^{35}Cl$): calcd: 565.1904; found: 565.1908.

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(saccharin-2-ylmethyl)cyclopentane Carboxylate (12o).** Step 1: *tert*-Butyl 2-(4′-chlorobiphenylthio)-5-mesyloxymethyl cyclopentane carboxylate. The title compound (1.05 g, 88%) was obtained according to the procedure of **12b**, step 1, using **10a** (1 g, 2.4 mmol) and mesyl chloride (0.275 g, 2.4 mmol). It was purified by flash chromatography (heptane/EtOAc; 9:1). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.7−7.55 (2d, 8H, *PhPh*), 4.25 (d, 2H, CH_2O), 3.85 (q, 1H, C*H*S), 3.20 (s, 3H, C*H*SO$_2$), 2.50 (m, 2H, C*H*CH$_2$O, C*H*CO$_2$), 2.20−1.60 (2m, 4H, CH_2CH_2), 1.35 (s, 9H, *tBu*). IR: V_{max} 1717 cm^{-1}. Anal. ($C_{24}H_{29}ClO_5S$): C, H, S, Cl. Step 2: Preparation of **12o**. Compound **12o** (0.22 g, 35%) was prepared according to the procedure of **12b**, step 2 using the compound from step 1 (0.52 g, 1.06 mmol), and saccharin sodium salt (0.65 g, 3.2 mmol). ^{1}H NMR (200 MHz, DMSO d6): δ 8.1−7.9 (m, 4H, *Ph*SO$_2$), 7.8−7.4 (2m, 12H, *PhPh*), 385 (q, 1H, C*H*S), 3.8 (m, 2H, CH_2N), 2.65 (m, 1H, C*H*CH$_2$N), 2.6 (m, 1H, C*H*CO$_2$), 2.2−1.75 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 1730, 1593, 1340, 1181 cm^{-1}. MNH$_4^+$(601).

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(3-oxo-[1,2,4]-triazolo[4,3-a]pyridin-2-ylmethyl)]-cyclopentane Carboxylate (12p).** To a solution of*tert*-butyl 2-(4′-chlorobiphenylthio)-5-mesyloxymethyl-cyclopentanecarboxylate (1.6 g, 3.20 mmol) (obtained in step 1 of the synthesis of **12o**) in DMF (25 mL) was added 15C-5 (0.7 g, 3.17 mmol), 3-oxo-[1,2,4]triazolo-[4,3-a]pyridine (0.43 g, 3.17 mmol) and NaH (60%, 0.127 g, 3.17 mmol). The reaction mixture was heated for 12 h at 40 °C. It was then diluted with water and extracted several times with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (heptane:EtOAc; 3:2) to give the title compound (0.29 g, 46%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.85 (d, 1H, *o-Py*), 7.75−7.4 (2m, 8H, *PhPh*), 7.2−6.65 (2m, 3H, *m-pPy*), 4.0 (m, 2H, NCH_2), 3.85 (m, 1H, C*H*S), 2.8−2.55 (2m, 2H, C*H*CH$_2$N, C*H*CO$_2$), 2.3−1.5 (m, 4H, CH_2CH_2), 1.2 (s, 9H, *tBu*). IR: V_{max} 1718, 1639, 1596 cm^{-1}.

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(2,4-dioxo-2H-pyrido[1,2-a][1,3,5] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12q).** Compound **12q** (0.38 g, 67%) was prepared from **10a** (0.42 g, 1 mmol) and 2,4-dioxo-2H-pyrido[1,2-a][1,3,5]-triazine (0.33 g, 2 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.5−7.85−7.1−6.95 (2d, m, t, 4H, *Py*), 7.65−7.5 (2d, 8H, *PhPh*), 4.2−3.85 (2dd, 2H, NCH_2), 3.8 (q, 1H, C*H*S), 2.65 (q, 1H, C*H*CH$_2$N), 2.5 (t, 1H, C*H*CO$_2$), 2.2−1.6 (m, 4H, CH_2CH_2), 1.2 (s, 9H, *tBu*). IR: V_{max} 1727, 1667, 1651 cm^{-1}. Anal. ($C_{30}H_{30}ClN_3O_4S$): C, H, N, S, Cl.

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(4-oxo-4,7-dihydro-(N-tritylimidazo) [4,5-d][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12r).** Compound **12r** (0.53 g, 85%) was prepared from **10a** (0.335 g, 0.8 mmol) and 4-oxo-4,7-dihydro-(*N*-tritylimidazo)[4,5-d][1,2,3]triazine (0.6 g, 1.6 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5−7.3−7.2 (m, 24H, *trityl*, *PhPh* NC*H*N), 4.6−4.4 (2d, 2H, NCH_2), 3.9 (q, 1H, C*H*S), 2.85 (q, 1H, C*H*CH$_2$N), 2.55 (t, 1H, C*H*CO$_2$), 2.1−1.75 (m, 4H, CH_2CH_2), 1.35 (s, 9H, *tBu*). IR: V_{max} 1718. [M1+Na]$^+$ 560 (M-trityl), [M2+H−H$_2$O]$^+$ 243 (trityl$^+$).

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(4-oxo-4-H-thieno-[3,2-d][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylate (12s).** Compound **12s** (0.95 g, 86%) was prepared from **10a** (0.84 g, 2 mmol) and 4-oxo-4-H-thieno[3,2-d][1,2,3]triazine (0.61 g, 4 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.9−7.65 (2d, 2H, C*H* = C*H*S), 7.6−7.3 (d, s, 8H, *PhPh* NC*H*N) 4.8−4.5 (2d, 2H, NCH_2), 3.95 (q, 1H, C*H*S), 2.9 (q, 1H, C*H*CH$_2$N), 2.7 (t, 1H, C*H*CO$_2$), 2.2−1.7 (m, 4H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1721, 1672. HRMS [M+Na]$^+$, *m/z*, ($C_{28}H_{28}N_2O_4S_2{}^{35}Cl$): calcd: 576.1158; found: 576.1188.

***tert*-Butyl 2-(4′-Chlorobiphenylthio)-5-(3-oxo-6,7,8,9-tetrahydro-5H-[1,2,4] triazolo[4,3-a]azepin-2-ylmethyl)]-cyclopentane Carboxylate (12t).** Compound **12t** (0.2 g, 26%) was prepared from **10a** and 3-oxo-6,7,8,9-tetrahydro-5H-[1,2,4]-triazolo[4,3-a]azepine (0.66 g, 4.3 mmol) according to the same procedure used for preparing **12p**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.65−7.45 (2d, 8H, *PhPh*), 4.55 (q, 1H, C*H*S), 3.70 (m, 2H, NCH_2), 3.15 (dd, 2H, CH_2NCO), 2.75 (m, 1H, C*H*CO$_2$), 2.65

(m, 2H, CH_2C=N), 2.45 (m, 1H, C*H*CH_2N), 2.00−1.6 (m, 10H, CH_2CH_2), 1.25 (s, 9H, *tBu*). IR: V_{max} 1728, 1705 cm^{-1}. Anal. ($C_{30}H_{36}ClN_3O_3S$): C, H, N, S, Cl.

***tert*-Butyl 2-(4′-Methylthiobiphenylthio)-5-(2,4-dioxo-2H-pyrido[1,2-a][1,3,5] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12u).** Compound **12u** (0.78 g, 97%) was prepared from **10e** (0.6 g, 1.4 mmol) and 2,4-dioxo-2H-pyrido[1,2-a][1,3,5]triazine (0.45 g, 2.8 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, DMSO d6): δ 8.45−7.85−7.1−6.75 (2d, m, t 4H, *Py*), 7.65−7.3 (2d, 8H, *PhPh*), 4.4−4.1 (m, 2H, NCH_2), 3.9 (q, 1H, C*H*S), 2.85 (q, 1H, C*H*CH_2N), 2.65 (t, 1H, C*H*CO_2), 2.55 (s, 2H, SCH_3), 2.3−1.7 (m, 4H, CH_2CH_2), 1.35 (s, 9H, *tBu*). HRMS [M+H]$^+$, *m*/*z*, ($C_{31}H_{33}N_3O_4S_2$): calcd: 576.1991; found: 576.1991.

***tert*-Butyl 2-(4′-Cyanobiphenylthio)-5-(2,4-dioxo-2H-pyrido[1,2-a][1,3,5] triazin-3-ylmethyl)]-cyclopentane Carboxylate (12v).** Compound **12v** (0.5 g, 40%) was prepared from **10f** (0.88 g, 2.25 mmol) and 2,4-dioxo-2H-pyrido[1,2-a]-[1,3,5]triazine (0.7 g, 4.3 mmol) according to the same procedure used for preparing **11a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.45−7.15−6.75 (4m, 3H, *Py*), 7.8−7.35 (2d, 9H, *PyPhPh*), 4.2 (m, 2H, NCH_2), 3.9 (m, 1H, C*H*S), 2.8 (m, 1H, C*H*CH_2N), 2.65 (m, 1H, C*H*CO_2), 2.3−1.5 (m, 4H, CH_2CH_2), 1.3 (s, 9H, *tBu*). IR: V_{max} 2225, 1719, 1680, 1645 cm^{-1}. MH$^+$(555).

2[2-(4′-Chlorobiphenylthio)]-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2a). To a solution of **12a** (4.5 g, 8.2 mmol) in CH_2Cl_2 (200 mL) at room temperature was added dropwise trifluoroacetic acid (TFA; 12.5 mL). The reaction mixture was stirred 24 h and then concentrated in vacuo. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc/AcOH; 97:2:1) to give, after lyophilisation from acetonitrile/water, **2a** (3.5 g, 87.5%) as a beige powder. ^{1}H/^{13}C NMR (400 MHz, DMSO-d_6): δ 12.5−12 (m, 1H, CO_2H), 8.25/125.5 (d, 1H, *o-Phtriazine*), 8.18/128.8 (d, 1H, *o′-Phtriazine*), 8.08/136.5 (td, 1H, *p-Phtriazine*), 7.92/133.8 (td, 1H, *m-Phtriazine*), 7.68/129.2, 7.62/128.0, 7.62/128.0 (3d, 8H, *PhPh*), 4.5/53.5 (d, 2H, NCH_2), 3.90/49.5 (m, 1H C*H*S), 2.85/44.0 (m, 1H, C*H*CH_2N), 2.60/55.0 (t, 1H, C*H*CO_2), 2.18/1.70//34.0 (m, 2H, C3H_2), 1.90/1.70//29.5 (m, 2H, C4H_2). In a NOESY experiment on **2a**, positive Overhauser effects were observed between H-1 (δ = 2.6) and H-3 (δ = 2.18−17), between H-1 and H-4 (δ = 1.9−17), between H-2 (δ = 2.85) and H-4, between H-2 and H-5 (δ = 3.9) and between H-3 and H-5 in agreement with a trans/trans relative conformation. IR: V_{max} 3400−2400, 1723, 1680 cm^{-1}. Anal. ($C_{26}H_{22}ClN_3O_3S$): C, H, N, S, Cl.

2[2-(4′-Chlorobiphenylthio)]-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-yl methyl)]-cyclopentanecarboxylic Acid (2a′). Compound **2a′** (0.195 g, 76%) was prepared from **12a′** (0.285 g, 0.52 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H/^{13}C NMR (400 MHz, DMSO-d_6): δ 12.2 (m, 1H, CO_2H), 8.28/125.3 (d, 1H, *o-Phtriazine*), 8.18/129.0 (d, 1H, *o′-Phtriazine*), 8.08/136.5 (td, 1H, *p-Phtriazine*), 7.92/133.5 (td, 1H, *m-Phtriazine*), 7.68/129.0, 7.60/128.0, 7.42/130.5 (3d, 8H, *PhPh*), 4.55/4.40//53.5 (2dd, 2H, NCH_2), 4.10/50.5 (m, 1H C*H*S), 3.05/41.5 (m, 1H, C*H*CH_2N), 3.15/53.5 (t, 1H, C*H*CO_2), 2.22/1.78//33.2 (m, 2H, C3H_2), 2.05/1.55//27.5 (m, 2H, C4H_2). In a NOESY experiment on **2a′**, positive Overhauser effects were observed between H-1 (δ = 3.15) and H-3 (δ = 2.22−178), between H-1 and H-4 (δ = 2.05), between H-2 (δ = 4.1) and H-4 and between H-3 and H-5 (δ = 3.9) in agreement with a cis/trans relative conformation. IR: V_{max} 3100−2500, 1723, 1696 cm^{-1}. Anal. ($C_{26}H_{22}ClN_3O_3S$): C, H, N, S, Cl.

Separation of the Enantiomers of 2[2-(4′-chlorobiphen-ylthio)]-5-[2-(4-oxo-4H-benzo[*d*] [1,2,3]triazin-3-yl-methyl)]-cyclopentane Carboxylic Acid ((1*R*,2*S*,5*R*) and (1*S*,2*R*,5*S*)-2a). The enantiomeric mixture **2a** (0.4 g) was separated by preparative HPLC using a Chiralpack column (eluant EtOH/TFA; 1000/1) and an UV detector at 210 nM to give: Peak 1: (1*R*,2*S*,5*R*)-**2a** (0.16 g, elution time 27.30 min), optical purity > 98% e.e. $[\alpha]_D$ = +57.5°(*c* = 9.99; DMSO). ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.25 (m, 1H, CO_2H), 8.3−7.95 (3m, 4H, o,*m-Phtriazine*), 7.65−7.45 (2m, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 3.95 (q, 1H, C*H*S), 2.85 (q, 1H, C*H*CH_2N), 2.6 (m, 1H, C*H*CO_2), 2.25−1.6 (m, 4H, CH_2CH_2). Anal. ($C_{26}H_{22}ClN_3O_3S$): C, H, N, S, Cl. IR: V_{max} 3100−2600, 1724, 1652 cm^{-1}. Peak: (1*S*, 2*R*, 5*S*)-**2a** (0.06 g, elution time 31.93 min), optical purity 89% e.e. ^{1}H NMR: comparable to (1*R*,2*S*,5*R*)-**2a**. IR: V_{max} 2800−1900, 1700, 1656 cm^{-1}. MH$^+$(492); MNH$_4^+$-(509).

2-Biphenylthio-5-(phthalimidomethyl)-cyclopentane Carboxylic Acid (2b). Compound **2b** (1.12 g, 90%) was prepared from **12b** (1.4 g, 5.15 mmol) in CH_2Cl_2 (100 mL) and TFA (3.5 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.85 (m, 4H, *Pht*), 7.7−7.3 (m, 9H, *PhPh*), 3.8 (m, 1H, C*H*S), 3.65 (m, 2H, CH_2N), 2.55 (m, 1H, C*H*CH_2N), 2.45 (m, 1H, C*H*CO_2), 2.15−1.9 (m, 2H, CH_2CHS), 1.9−1.55 (m, 2H, CH_2CH_2CHS). IR: V_{max} 3400−2400, 1725−1705, 1711 cm^{-1}. Anal. ($C_{27}H_{23}NO_4S$): C, H, N. MH$^+$(458); MNH$_4^+$(475).

2-Biphenylmethylthio-5-phthalimidomethylcyclopentane Carboxylic Acid (2c). Compound **2c** (1.1 g, 97%) was prepared from **12c** (1.2 g, 2.3 mmol) and TFA (3.5 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO d6): δ 7.9 (m, 4H, *Pht*), 7.65−7.4 (m, 9H, *PhPh*), 3.85 (s, 2H, PhCH_2S), 3.7 (dd, 2H, CH_2N), 3.3 (m, 1H, C*H*S), 2.65 (m, 1H, C*H*CH_2N), 2.4 (m, 1H, C*H*CO_2), 2.1−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3200−2400, 1774, 1707 cm^{-1}. Anal. ($C_{28}H_{25}NO_4S$): C, H, N, S.

2-Biphenylethylthio-5-(phthalimidomethyl)-cyclopentane Carboxylic Acid (2d). Compound **2d** (0.51 g, 88%) was prepared from **12d** (0.65 g, 1.2 mmol) and TFA (1.85 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.2 (m, 1H, CO_2H), 7.85 (m, 4H, *Pht*), 7.6−7.25 (m, 9H, *PhPh*), 3.65 (m, 2H, CH_2N), 3.4 (m, 1H, C*H*S), 2.8 (m, 4H, PhCH_2CH_2S), 2.65 (m, 1H, C*H*CH_2N), 2.4 (m, 1H, C*H*CO_2), 2.2−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3200−2300, 1773, 1707 cm^{-1}. Anal. ($C_{29}H_{27}NO_4S$): C, H, N, S.

2-[2-(4′-Fluorobiphenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentane Carboxylic Acid (2e). Compound **2e** (1.62 g, 86%) was prepared from **12e** (2.13 g, 3.8 mmol) and TFA (5.9 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.9−7.65 (m, 4H, *Pht*), 7.5−7.1 (m, 8H, *PhPh*), 4.0−3.7 (m, 2H, CH_2N), 3.55 (m, 1H, C*H*S), 3.0−2.5 (m, 6H, PhCH_2CH_2S, C*H*CH_2N, C*H*CO_2), 2.3−1.6 (m, 4H, CH_2CH_2). IR: V_{max} 3500−3000, 1771, 1706, 1682 cm^{-1}. Anal. ($C_{29}H_{26}FNO_4S$): C, H, N. MH$^+$(503).

2-[2-(4′-Chlorobiphenyl)ethylthio]-5-(phthalimidomethyl)-cyclopentane Carboxylic Acid (2f). Compound **2f** (1.67 g, 96%) was prepared from **12f** (1.93 g, 3.35 mmol) and TFA (5.2 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.3−11.3 (m, 1H, CO_2H), 7.85 (m, 4H, *Pht*), 7.7−7.35 (m, 8H, *PhPh*), 3.7 (m, 2H, CH_2N), 3.4 (m, 1H, C*H*S), 2.85 (m, 4H, PhCH_2CH_2S), 2.65 (m, 1H, C*H*CH_2N), 2.4 (m,1H, C*H*CO_2), 2.2−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3400−2400, 1773, 1723−1695 cm^{-1}. Anal. ($C_{29}H_{26}ClNO_4S$): C, H, N, S, Cl.

2-[2-(4′-Chlorobiphenyl)ethylthio]-5-[2-(4-oxo-4H-benzo-[*d*][1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2g). Compound **2g** (0.27 g, 86%) was prepared from **12g** (0.35 g, 0.6 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.15 (m, 1H, CO_2H), 8.25 (2d, 2H, *o-Phtriazine*), 8.1−7.95 (2t, 2H, *m-Phtriazine*), 7.55−7.7−7.3 (AB, 3d, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 3.4 (q, 1H, C*H*S), 2.85 (m, 5H, SCH_2CH_2, C*H*CO_2), 2.55 (m, 1H, C*H*CH_2N), 2.2−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2300, 1720, 1683 cm^{-1}. Anal. ($C_{28}H_{26}ClN_3O_3S$): C, H, N, S, Cl.

2-(4′-Methylthiobiphenylthio)-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2h). Compound **2h** (0.175 g, 83%) was prepared from **12h** (0.235 g, 0.42 mmol) and TFA (0.65 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.3 (m, 1H, CO_2H), 8.25 (2d, 2H, *o-Phtriazine*), 8.15−7.95 (2t, 2H, *m-Phtriazine*), 7.65−7.5−7.3 (2m, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 3.3 (q, 1H, C*H*S) 2.85 (q, 1H, C*H*CH_2N), 2.65 (t, 1H, C*H*CO_2), 2.5 (s, 3H, SCH_3), 2.3−1.7 (m, 4H, CH_2CH_2).

IR: V_{max} 3300−2300, 1718, 1658 cm^{-1}. Anal. ($C_{27}H_{25}N_3O_3S_2$): C, H, N, S. MH$^+$(504).

2-(4′-Cyanobiphenylthio)-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]-triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2i). Compound **2i** (0.24 g, 63%) was prepared from **12i** (0.425 g, 0.8 mmol) and TFA (1.2 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.35 (m, 1H, CO_2H), 8.25 (2d, 2H, *o-Phtriazine*), 8.05−7.85 (2t, 2H, *m-Phtriazine*), 7.85−7.65−7.5 (m, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 4.0 (q, 1H, CHS) 2.85 (q, 1H, $CHCH_2N$), 2.65 (t, 1H, $CHCO_2$), 2.3−1.6 (m, 4H, CH_2CH_2). IR: V_{max} 3200−2400, 2224, 1709, 1678 cm^{-1}. Anal. ($C_{27}H_{22}N_4O_3S$): C, H, N, S. MH$^+$(483).

2-(4-Pyridin-4-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylic Acid (2j). Compound **2j** (0.26 g, 40%) was prepared from **12j** (0.74 g, 1.4 mmol) and TFA (1.2 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.4 (m, 1H, CO_2H), 8.65 (m, 2H, *o-Py*), 8.25−8.2 (2d, 2H, *o-Phtriazine*), 8.07−7.9 (2t, 2H, *m-Phtriazine*), 7.75−7.45 (m, 6H, *o-PyPh*), 4.5 (d, 2H, NCH_2), 4.0 (q, 1H, CHS) 2.85 (m, 1H, $CHCH_2N$), 2.6 (t, 1H, $CHCO_2$), 2.2−1.7 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2300, 2224, 1681, 1606 cm^{-1}. Anal. ($C_{25}H_{22}N_4O_3S$): C, H, N, S. MH$^+$(459).

2-(4-Thiazol-2-ylphenylthio)-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2k). Compound **2k** (0.21 g, 57%) was prepared from **12k** (0.74 g, 1.4 mmol) and TFA (1.2 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.1 (m, 1H, CO_2H), 8.5−8.4 (2d, 2H, *o-Phtriazine*), 8.3−8.05 (t, m, 5H, *m-Phtriazine*, *m-Ph*, *thiazol*), 7.9 (d, 1H, *thiazol*), 7.65 (d, 2H, *o-Ph*), 4.7 (d, 2H, NCH_2), 4.2 (q, 1H, CHS), 3.1 (m, 1H, $CHCH_2N$), 2.85 (t, 1H, $CHCO_2$), 2.4−1.9 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2300, 2224, 1682 cm^{-1}. Anal. ($C_{23}H_{20}N_4O_3S_2$): C, H, N, S. MH$^+$(465).

2-(4-Benzothiazol-2-ylphenylthio)-5-[2-(4-oxo-4H-benzo-[*d*][1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2l). Compound **2l** (0.1 g, 92%) was prepared from **12l** (0.12 g, 0.2 mmol) and TFA (0.5 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.4 (m, 1H, CO_2H), 8.3−7.4 (m, 12H, *PhPh Phtriazine*), 4.55 (d, 2H, NCH_2), 4.05 (q, 1H, CHS), 2.9 (m, 1H, $CHCH_2N$), 2.7 (t, 1H, $CHCO_2$), 2.4−1.6 (m, 4H, CH_2CH_2). IR: V_{max} 2800−1800, 1714, 1681 cm^{-1}. Anal. ($C_{27}H_{22}N_4O_3S_2$, 0.2 H_2O): C, H, N, S. MH$^+$(515).

2-(4-[1,2,4]Triazol-4-ylphenylthio)-5-[2-(4-oxo-4H-benzo-[*d*][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylic Acid (2m). Compound **2m** (0.2 g, 68%) was prepared from **12m** (0.33 g, 0.65 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.35 (m, 1H, CO_2H), 9.1 (s, 2H, *triazine*), 8.25 (m, 2H, *o-Phtriazine*), 8.1−7.95 (2t, 2H, *m-Phtriazine*), 7.65−7.55 (m, 4H, *Ph*), 4.5 (d, 2H, NCH_2), 4.0 (q, 1H, CHS), 2.65 (m, 1H, $CHCH_2N$), 2.6 (t, 1H, $CHCO_2$), 2.3−1.6 (m, 4H, CH_2CH_2). IR: V_{max} 2800−1800, 1692 cm^{-1}. Anal. ($C_{22}H_{20}N_6O_3S$): C, H, S, N:calcd, 18.74; found, 18.11. MH$^+$(449).

2-(4′-Chlorobiphenylthio)-5-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-ylmethyl]-cyclo pentane Carboxylic Acid (2n). Compound **2n** (0.27 g, 58%) was prepared from **12n** (0.52 g, 0.96 mmol) and TFA (1.4 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.65−7.45 (2m, 8H, *PhPh*), 3.7−3.2 (m, 3H, CHS CH_2N), 2.75 (s, 3H, NCH_3), 3.0−2.3 (m, 2H, $CHCH_2N$, $CHCO_2$), 2.2−1.1 (2m, 4H, CH_2CH_2), 1.3 (s, 6H, $2CH_3$). HPLC (gradient and isocratic systems) purity > 98.5%. HR/ESIMS Calcd for $C_{25}H_{27}ClN_2O_4S$ M_r 487.1458 (MH$^+$), found 487.1473.

2-(4′-Chlorobiphenylthio)-5-(saccharin-2-ylmethyl)-cyclopentane Carboxylic Acid (2o). Compound **2o** (0.15 g, 83%) was prepared from **12o** (0.2 g, 0.35 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO d6): δ, 8.05−7.85 (2m, 4H, $PhSO_2$), 7.5−7.3 (m, 8H, *PhPh*), 4−3.8 (m, 3H, NCH_2, CHS), 2.9 (m, 1H, $CHCH_2N$), 2.75 (t, 1H, $CHCO_2$), 2.4−1.7 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2300, 1732, 1702, 1383, 1336 cm^{-1}. Anal. ($C_{26}H_{22}ClNO_5S$, 0.15 $(ipr)_2O$): C, H, N, S:calcd, 11.78; found, 11.13. MH$^+$(526).

2-(4′-Chlorobiphenylthio)-5-(3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2-ylmethyl)]-cyclopentane Carboxylic Acid (2p). Compound **2p** (0.15 g, 49%) was prepared from **12p** (0.28 g, 0.47 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.3 (m, 1H, CO_2H), 7.85 (d, 1H, *o-Py*), 7.75−7.55−7.35 (2d, m, 8H, *PhPh*), 7.15−6.55 (2m, 3H, *m-pPy*), 3.95 (m, 2H, NCH_2), 3.9 (m, 1H, CHS), 2.75−2.55 (2m, 2H, $CHCH_2N$, $CHCO_2$), 2.25−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 2700−2400, 1723, 1667, 1643, 1594 cm^{-1}. Anal. ($C_{25}H_{22}ClN_3O_3S$): H, N, C: calcd, 62.56; found, 61.86, S: calcd, 6.68; found, 6.20. MH$^+$(480).

2-(4′-Chlorobiphenylthio)-5-(2,4-dioxo-2H-pyrido[1,2-a][1,3,5]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2q). Compound **2q** (0.265 g, 78%) was prepared from **12q** (0.38 g, 0.674 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.45 (m, 1H, CO_2H), 8.45−7.85−7.05−6.95 (2d, m, t, 4H, *Py*), 7.65−7.45 (2d, 8H, *PhPh*), 4.2−4.0 (m, 2H, NCH_2), 3.9 (m, 1H, CHS), 2.7 (m, 1H, $CHCH_2N$), 2.5 (t, 1H, $CHCO_2$), 2.3−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2400, 1747, 1712, 1684, 1636 cm^{-1}. Anal. ($C_{26}H_{22}ClN_3O_4S$): H, N, S, Cl, C: calcd, 61.47; found, 60.98. MH$^+$(508).

2-(4′-Chlorobiphenylthio)-5-(4-oxo-4,7-dihydro-imidazo-[4,5-d][1,2,3]triazin-3-ylmethyl)]-cyclopentane Carboxylic Acid (2r). Compound **2r** (0.12 g, 40%) was prepared from **12r** (0.51 g, 0.653 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 14.5−12.5 (m, 2H, NH, CO_2H), 8.7 (s, 1H, $NCHN$), 7.85−7.6 (2dd, 8H, *PhPh*), 4.75 (d, 2H, NCH_2), 4.15 (q, 1H, CHS), 3.1 (q, 1H, $CHCH_2N$), 2.85 (t, 1H, $CHCO_2$), 2.5−1.9 (m, 4H, CH_2CH_2). IR: V_{max} 3196, 2800−2400, 1721, 1692 cm^{-1}. Anal. ($C_{23}H_{20}ClN_5O_3S$): C, H, N, S, Cl. M$^+$Na$^+$(504).

2-(4′-Chlorobiphenylthio)-5-(4-oxo-4-H-thieno[3,2-d]-[1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2s). Compound **2s** (0.65 g, 77%) was prepared from **12s** (0.925 g, 1.7 mmol) and TFA (1.5 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.35 (m, 1H, CO_2H), 8.45−7.9 (2d, 2H, $CH=CHS$), 7.65−7.5 (2d, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 3.9 (q, 1H, CHS), 2.85 (q, 1H, $CHCH_2N$), 2.6 (t, 1H, $CHCO_2$), 2.3−1.6 (m, 4H, CH_2CH_2). IR: V_{max} 2800−2300, 1703, 1680 cm^{-1}. Anal. ($C_{24}H_{20}ClN_3O_3S_2$): H, N, S, Cl, C: calcd, 57.88; found, 57.29. MH$^+$-(498).

2-(4′-Chlorobiphenylthio)-5-(3-oxo-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a] azepin-2-ylmethyl)]-cyclopentane Carboxylic Acid (2t). Compound **2t** (0.13 g, 73%) was prepared from **12t** (0.2 g, 0.36 mmol) and TFA (1 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.5 (m, 1H, CO_2H), 7.65−7.55 (2d, 8H, *PhPh*), 4.65 (q, 1H, CHS), 3.65 (m, 2H, NCH_2), 3.4−3.15 (dd, 2H, CH_2NCO), 2.9 (t, 1H, $CHCO_2$), 2.7 (m, 2H, $CH_2C{=}N$), 2.45 (m, 1H, $CHCH_2N$), 2.15−1.6 (m, 10H, CH_2CH_2). IR: V_{max} 3400, 2600, 1728, 1666 cm^{-1}. Anal. ($C_{26}H_{28}ClN_3O_3S$): H, N, S, Cl, C: calcd, 62.70; found, 62.10. MH$^+$(498).

2-(4′-Methylthiobiphenylthio)-5-(2,4-dioxo-2H-pyrido-[1,2-a][1,3,5]triazin-3-ylmethyl)]-cyclopentane Carboxylic Acid (2u). Compound **2u** (0.2 g, 28.5%) was prepared from **12u** (0.78 g, 1.35 mmol) and TFA (2 mL) according to the same procedure used for preparing **2a.** The compound was crystallized as the hemisodium salt. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.35 (m, 1H, CO_2H), 8.45−7.85−7.05−6.95 (2d, m, t, 4H, *Py*), 7.5−7.3 (2d, 8H, *PhPh*), 4.2−3.8 (m, 3H, NCH_2, CHS), 2.7 (q, 1H, $CHCH_2N$), 2.5 (m, 4H, $CHCO_2$, SCH_3), 2.3−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 2900−1900, 1746, 1711, 1683 cm^{-1}. Anal. ($C_{27}H_{25}N_3O_4S_2$,0.5Na): C, H, N, S, Na. MH$^+$(520) M$^+$Na$^+$(542).

2-(4′-Cyanobiphenylthio)-5-(2,4-dioxo-2H-pyrido[1,2-a]-[1,3,5]triazin-3-yl methyl)]-cyclo pentanecarboxylic acid (2v). Compound **2v** (0.195 g, 43.5%) was from **12v** (0.5 g, 0.9 mmol) and TFA (1.4 mL) according to the same procedure used for preparing **2a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.4 (m, 1H, CO_2H), 8.45−7.85−7.05−7.0 (2d, m, t, 4H, *Py*), 7.7−7.5 (2d, 8H, *PhPh*), 4.2−3.9 (m, 3H, NCH_2, CHS), 2.7 (q, 1H,

C*H*CH_2N), 2.5 (t, 1H, C*H*CO_2), 2.3−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 2800−1800, 2226, 1735, 1704, 1678, 1636 cm^{-1}. Anal. ($C_{27}H_{22}N_4O_4S$,0.15 H_2O): C, H, N, S. MH^+(499).

2-(4′-Chlorobiphenylsulfonyl)-5-[2-(4-oxo-4H-benzo[*d*]-[1,2,3]triazin-3-yl methyl)]-cyclopentane Carboxylic Acid (2w). To a solution of **2a** (0.2 g, 0.46 mmol) in CH_2Cl_2/MeOH (4:1, 12.5 mL) at 0 °C, was added in three portions a solution of dimethyldioxirane (6.5 mL) in acetone (20 mL). The reaction mixture was stirred at room temperature for 12 h and then concentrated. The residue was taken up in water, acidified to pH 2 with 1 N aq. HCl, and extracted several times with EtOAc. The organic phases were dried over Na_2SO_4 and concentrated to give **2w** (0.185 g, 87%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.5 (m, 1H, CO_2H), 8.25 (m, 2H, *o-Phtriazine*), 8.2−7.9 (2m, 2H, *m-Phtriazine*), 7.95−7.8−7.65 (2m, 8H, *PhPh*), 4.55 (d, 2H, NCH_2), 4.1 (m, 1H, C*H*S), 3.1 (t, 1H, C*H*CO_2), 2.8 (m, 1H, C*H*CH_2N), 2.2−1.65 (m, 4H, CH_2CH_2). IR: V_{max} 3500−2400, 1721, 1687, 1637, 1310, 1143 cm^{-1}. Anal. ($C_{26}H_{22}ClN_3O_5S$): C, H, N, S, Cl.

2-[2-(4′-Fluorobiphenyl)ethylsulfonyl]-5-(phthalimidomethyl)- cyclopentane Carboxylic Acid (2x). Compound **2x** (0.53 g, 80%) was prepared using **2e** (0.625 g, 1.24 mmol), dimethyldioxirane (25 mL), and acetone (50 mL) according to the same procedure used for preparing **2w**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.8 (m, 1H, CO_2H), 7.9−7.65 (m, 4H, *Pht*), 7.5−7.35−7.25 (m, 8H, *PhPh*), 3.95 (m, 1H, C*H*S), 3.7 (t, 2H, CH_2N), 3.5−3.05 (m, 4H, PhCH_2CH_2S), 3.0 (t, 1H, C*H*CO_2), 2.65 (m, 1H, C*H*CH_2N), 2.3−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3400−2500, 1769, 1733, 1686, 1604, 1360, 1150 cm^{-1}. Anal. ($C_{29}H_{26}FNO_6S$): C, H, N. MH^+(534).

2-[2-(4′-Chlorobiphenyl)ethylsulfonyl]-5-(phthalimidomethyl)- cyclopentane Carboxylic Acid (2y). Compound **2y** (0.53 g, 98%) was prepared using **2f** (0.5 g, 0.96 mmol) and dimethyldioxirane (20 mL) according to the same procedure used for preparing **2w**. ^{1}H NMR (200 MHz, DMSO d6): δ 12.7 (m, 1H, CO_2H), 7.9−7.8 (m, 4H, *Pht*), 7.7−7.4 (m, 8H, *PhPh*), 4.0 (m, 1H, C*H*S), 3.75 (m, 2H, CH_2N), 3.5−3.05 (m, 4H, PhCH_2CH_2S), 3.0 (m, 1H, C*H*CH_2N), 2.6 (m, 1H, C*H*CO_2), 2.2−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3300−2800, 1770, 1694, 1304, 1152 cm^{-1}. Anal. ($C_{29}H_{26}ClNO_6S$): C, H, N, S, Cl. MNH_4^+(569).

2-[2-(4′-Chlorobiphenyl)ethylsulfonyl)]-5-[2-(4-oxo-4H-benzo[*d*][1,2,3]triazin −3-ylmethyl)]-cyclopentane Carboxylic Acid (2z). Compound **2z** was prepared using **2g** (0.15 g, 0.29 mmol), dimethyldioxirane (12 mL) and acetone (20 mL) according to the same procedure used for preparing **2w**. The residue was purified by flash chromatography (CH_2Cl_2:MeOH; 98:2) to give **2z** (0.07 g, 43.7%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.5 (m, 1H, CO_2H), 8.25−8.2 (m, 2H, *o-Phtriazine*), 8.2−7.9 (2d, 2H, *m-Phtriazine*), 7.6−7.45 (2dd, 8H, *PhPh*), 4.5 (d, 2H, NCH_2), 4.0 (m, 1H, C*H*S), 3.4 (m, 2H, CH_2S), 3.1−2.9 (t, 3H, PhCH_2, C*H*CO_2), 2.8 (m, 1H, C*H*CH_2N), 2.3−1.5 (m, 4H, CH_2CH_2). IR: V_{max} 3600−2400, 1721, 1682, 1377, 1124 cm^{-1}. HPLC (gradient and isocratic systems) purity >98.5%. HR/ESIMS Calcd for $C_{28}H_{26}ClN_3O_5S$ M_r 552.1360 (MH^+), found 552.1415.

Enzyme Assays. Human pro-MMPs were dissolved in Novex developing buffer (Cat. No LC2671) at the following concentrations: MMP-1 (Calbiotech) at 1.25 μg/mL; MMP-2 and MMP-9 (Boehringer) at 300 and 200 mU/mL, respectively; MMP-3 (AbCys) at 1 μg/mL and MMP-13 (Pr G. Murphy, University East Anglia) at 2 μg/mL. Pro-enzymes were activated by 2 mM *p*-aminophenilmercuric acetate (APMA, Sigma) at 37 °C for 30 min (MMP-1, -2, -9) or 1 h (MMP-3, -13). Activation was stopped by transferring the samples to ice. Inhibitors were dissolved in dimethyl sulfoxide (DMSO) at 10^{-2} M, then serially diluted (1/10) in developing buffer at concentrations from 10^{-4} to 10^{-13} M. Fluorogenic substrates were purchased from Bachem. Substrate for MMP-3 was (7-methoxycoumarine-4-yl)-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2.[27] Substrate for MMP-1, -2, -9, -13 was Dnp-Pro-Cha-Gly-Cys(ME)-His-Ala-Lys(Nma)-NH_2.[28] They were dissolved in DMSO at 10^{-2} and 2×10^{-3} M, respectively, then diluted to 2×10^{-4} M in water. Assays were performed in 96-well plates by adding to each well 70 μL of developing buffer, 10 μL of inhibitor (or buffer for the control) and 10 μL of enzyme (or buffer for the blank). Each point was run in duplicate and each inhibitor was assayed at least twice. After a 30 min preincubation at 37 °C, 10 μL of substrate was added and the plates were incubated for 6 h at 37 °C. Reading was then performed by a Spectrofluor Plus fluorimeter (Tecan), set at excitation and emission wavelengths of 340 and 440 nm, respectively. Substrate degradation in the presence of inhibitor at a given concentration was calculated as % fluorescence of control wells. IC_{50} of each product on each enzyme was calculated by EXCEL software using 3 points in the central linear range of fluorescence inhibition.

In Vivo Antitumor Activity. B16-F10 is a variant of the murine melanoma B16 selected for its enhanced ability to form experimental lung metastases.[29] B16-F10 cells were purchased from the National Cancer Institute and were maintained by successive passages in vitro. For animal experiments, tumor cells were collected and inoculated into the tail vein of $B_6D_2F_1$ mice in a volume of 200 μL PBS containing 0.5% foetal calf serum (2×10^5 cells/mouse, 7 mice per experimental group). Anti-metastatic compounds were administered i.p. or p.o. to animals 1 h before the i.v. inoculation of tumor cells, and then every day for 3 days (four administrations). For metastasis evaluation, mice were killed on day 11 by cervical dislocation, and lungs were removed, rinsed extensively in PBS, and fixed in Bouin's fluid. The black pigmented metastases of up to 2 mm in diameter were easily detected by the naked eye. Following dissection of each lung into five lobes, both the total number of metastases and the number of metastases of diameter ≥ 1 mm were scored by two investigators in a double-blind manner. Results are expressed as % of the mean numbers of metastases (total and ≥ 1 mm diameter) per lung of treated animals versus control.

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