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The Gabriel–Colman Rearrangement in Biological Systems: Design, Synthesis and Biological Evaluation of Phthalimide and Saccharin Derivatives as Potential Mechanism-Based Inhibitors of Human Leukocyte Elastase, Cathepsin G and Proteinase 3

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Abstract—The results of a structure–activity relationship study focusing on the interaction of a series of phthalimide and saccharin derivatives with leukocyte elastase, cathepsin G and proteinase 3 are described. The phthalimide derivatives were found to be inactive while some of the saccharin derivatives were found to be fair inhibitors of these enzymes.

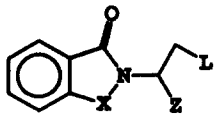
Introduction

Proteolytic enzymes are involved in a range of important cellular functions including tissue remodelling, fibrinolysis, fertilization, phagocytosis, digestion and blood coagulation. An increasing body of evidence suggests that some of these enzymes play a key role in disease states.[1] For example, the neutrophil-derived serine proteinases human leukocyte elastase (HLE), cathepsin G (Cath G) and proteinase 3 (PR 3) have been implicated in various inflammatory diseases such as pulmonary emphysema,[2] cystic fibrosis,[3] inflammatory bowel disease,[4] psoriasis[5] and others.[6] The clinical significance of these enzymes has provided the impetus behind efforts aimed at modulating the aberrant activity of these enzymes through the use of low molecular weight inhibitors.[7–9]

Inhibitors of HLE, Cath G and PR 3 that have been described recently include 3-oxo-1,2,5-thiadiazolidine and isothiazolidin-3-one 1,1-dioxides,[10,11] β-lactams and azetidinone derivatives,[12,13] succinimide[14–16] and isocoumarin[17] derivatives, haloenol and ynenol lactones[18,19] and others.[20,21] Herein we present an account of a structure–activity relationship study related to the development of phthalimide and saccharin-derived mechanism-based inhibitors (I) of these enzymes, the design of which is based on the Gabriel–Colman rearrangement.[22,23]

Chemistry

The synthesized compounds are listed in Tables 1 and 2. The physical and spectral properties of the synthesized compounds are found in Table 3.

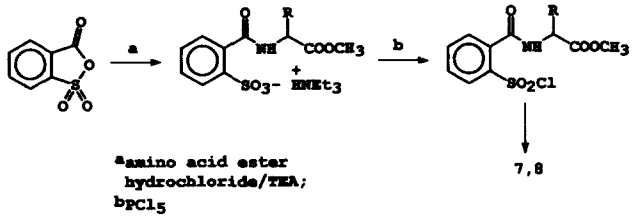


(I)

Compounds **1**, **2** and **3** were synthesized by the sequential addition of carbonyl diimidazole, triethylamine and the appropriate amino acid ester hydrochloride salt to phthalic acid. Compound **2** was formed during the synthesis of compound **1**. Compounds **4** and **5** were prepared by oxidizing compound **3** with *m*-chloroperbenzoic acid. Compounds **7** and **8** were prepared according to Scheme 1. Compounds **6**, **9**, **10** and **16** were synthesized as described previously.[24] Alkylation of phthalimide and saccharin with (α-bromomethyl)acrylate yielded compounds **11** and **13**, respectively. Compound **12** was isolated during the synthesis of compound **8** as a mixture of conformational isomers. Alkylation of saccharin with phenyl chloromethylsulfide yielded **14**. Oxidation of **14** gave compounds **15** and **16**. Chlorination of methyl (2-thiophenoxy)ethanoate with *N*-chlorosuccinimide,[25] followed by alkylation with saccharin, yielded **17**. Subsequent oxidation of **17** with *m*-chloroperbenzoic acid yielded compounds **18** and **19**.

Biochemical Studies

Human leukocyte elastase (HLE), cathepsin G and proteinase 3 were assayed as described previously.[14–16,26] The apparent pseudo first-order inactivation rate constants were determined from the slopes of the



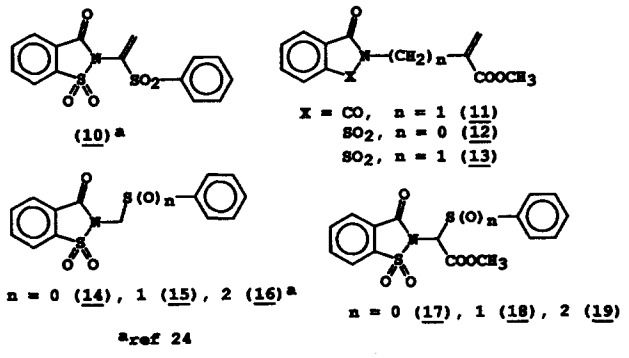
Scheme 1. Synthesis of compounds 7 and 8.

Table 1. Derivatives of compound I

Compound	X	Z	L
1[a,b]	CO	$COOCH_3$	OH
2[a,b]	CO	$COOCH_3$	imidazole
3[c]	CO	$COOCH_3$	SCH_2Ph
4[d]	CO	$COOCH_3$	$SOCH_2Ph$
5[c]	CO	$COOCH_3$	SO_2CH_2Ph
6[a,b]	CO	SO_2Ph	F
7[a]	SO_2	$COOCH_3$	H
8[c]	SO_2	$COOCH_3$	SCH_2Ph
9[a,b]	SO_2	SO_2Ph	F

[a]Racemic; [b]Ref. 24; [c](S) isomer; [d]diastereomeric mixture.

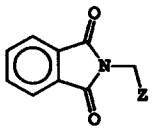
Table 2



semilogarithmic plots of ln (E_t/E_o) versus t, where E_t/E_o is the amount of active enzyme remaining after time t, and expressed in terms of the apparent second-order inactivation rate constants, k_{obs}/[I] M^{-1} s^{-1} (Table 4).

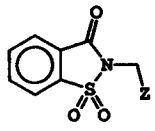
Results and Discussion

The Gabriel–Colman rearrangement is a little-studied reaction involving an alkoxide-induced ring opening of a saccharin or phthalimido ester or ketone that is followed by a prototropic shift and subsequent ring closure to yield a substituted benzothiazine or isoquinoline derivative.[22,23] Based on what is known about the mechanism of this rearrangement, we hypothesized that derivatives of phthalimide and saccharin that embody in their structures appropriate recognition and reactivity elements may function as mechanism-based inhibitors of the aforementioned serine proteinases.[24] Major objectives of our work in this area aimed at assessing the relative importance of the various structural elements in compounds I–III in terms of their ability to bind productively to the active site of a target proteinase, and gaining insight about the delicate interplay between chemical reactivity and geometric and charge complementarity for activity.



(II)

Z = COOEt, COOBzl, COPh, COCH=CHPh, CN, PO(OEt)2, NO2, S(O)nPh, n = 0-2.



(III)

Z = COOEt, COOBzl, COPh CN, PO(OEt)2, SPh.

A series of phthalimide derivatives **II** was initially synthesized and investigated for their inhibitory activity toward HLE and Cath G. None of these compounds interacted with the enzymes in a time-dependent manner, irrespective of the nature of Z.[20] Based on the known chemistry of saccharin and its derivatives,[27] as well as early work by Zimmerman and coworkers,[28] a series of saccharin derivatives **III** was prepared and their interaction with HLE, Cath G and PR 3 was investigated. An active compound was obtained with Z = SO_2Ph (compound **16**, Table 4), while the rest of the compounds were found to be inactive. In general, only saccharin derivatives with Z = SO_2R, OOCR, F or Cl were found to possess inhibitory activity.[20,29]

The incubation of compound **16** with PR 3, for example, led to progressive loss of enzymatic activity (Fig. 1). The enzyme regained about 10% of its activity after 24 h, suggesting that the observed inhibition arises from the slow deacylation of a relatively stable acyl enzyme. The interaction of HLE and Cath G with compound **16** was similar to that of PR 3, namely, **16** appears to function as an alternate substrate inhibitor (Table 4).

Based on these initial observations, we attempted to probe further the interaction of saccharin derivatives with these serine proteinases using additional compounds based on structure **I** (Table 1) and related derivatives (Table 2). The amino acid-derived phthalimide (**1–6**) and saccharin (**7** and **8**) derivatives were found to be inactive. Compound **9** was found to inhibit PR 3 and Cath G but had minimal activity toward HLE. Furthermore, compound **10** was found to inhibit all three enzymes, while compound **12** was inactive. Taken together, these observations suggest an absolute requirement for an SO_2 group for the manifestation of inhibitory activity. The reaction of compound **10** with imidazole at room temperature is instantaneous and complete upon mixing the reactants, as evidenced by NMR, suggesting that His-57 might readily react with a putative Michael acceptor generated at the active site of the enzyme. The X-ray crystal structure of **10** is shown in Figure 2. It is possible that favorable binding interactions involving the SO_2 group(s) may account in part for the inhibitory activity of this compound.[30] The

Table 3. Physical constants and spectral data of inhibitors

Compound	mp °C	NMR ppm	MF (anal.)
1	oil	3.65 (*s*, 1H), 3.80 (*s*, 3H), 4.22 (*d*, 2H), 5.05 (*t*, 1H), 7.5 (*dd*, 1H), 7.88 (*dd*, 2H)	$C_{12}H_{11}NO_5$ (C, H, N)
2	115–117	3.8 (*s*, 3H), 4.8 (*dd*, 2H), 5.25 (*dd*, 1H), 6.95 (*d*, 2H), 7.4 (*s*, 1H), 7.75 (*dd*, 2H), 7.85 (*dd*, 2H)	$C_{15}H_{13}N_3O_4$ (C, H, N)
3	76–77	3.27 (*dd*, 2H), 3.71 (*s*, 2H), 3.72 (*s*, 3H), 4.98 (*dd*, 1H), 7.3 (*m*, 5H), 7.6 (*dd*, 2H), 7.88 (*dd*, 2H)	$C_{19}H_{17}NO_4S$ (C, H, N)
4	47–48	3.35 (*m*, 1H), 3.65 (*m*, 1H), 3.75 (*s*, 3H), 4.05 (*t*, 2H), 5.4 (*m*, 1H), 7.45(*m*, 5H), 7.73 (*dd*, 2H), 7.87 (*dd*, 2H)	$C_{19}H_{17}NO_5S$ (C, H, N)
5	167–169	3.75 (*s*, 3H), 3.82 (*d*, 2H), 4.3 (*dd*, 2H), 5.5 (*dd*, 1H), 7.4 (*m*, 5H), 7.73 (*dd*, 2H), 7.88 (*dd*, 2H)	$C_{19}H_{17}NO_6S$ (C, H, N)
6	190–191	5.3 (*m*, 1H), 5.48 (*m*, 1H), 5.67 (*dd*, 1H), 7.6 (*m*, 2H), 7.7 (*m*, 1H), 7.8 (*m*, 2H), 7.9 (*dd*, 2H), 8.0 (*dd*, 2H)	$C_{16}H_{12}NO_4SF$ (C, H, N)
7	115–118	1.85 (*d*, 3H), 3.85 (*s*, 3H), 5.2 (q, 1H), 8.16 (*m*, 3H), 8.4 (*d*, 1H)	$C_{11}H_{11}NO_5$ (C, H, N)
8	oil	3.4 (*d*, 2H), 3.85 (*s*, 3H), 3.9 (*s*, 2H), 4.8 (*t*, 1H), 7.3–7.5 (*m*, 5H), 7.9–8.1(*m*, 3H), 8.2(*d*,1H)	$C_{17}H_{15}NO_5S_2$ (C, H, N)
9	oil	5.25 (*m*, 1H), 5.4 (*m*, 1H), 5.6 (*m*, 1H), 5.6–5.75 (*m*, 3H), 7.9–8.1 (*m*, 6H)	$C_{15}H_{12}FNS_2O_5$ (C, H, N)
10	150–152	4.46 (*d*, 1H), 7.01 (*d*, 1H), 7.54–7.74 (*m*, 3H), 7.84–8.13 (*m*, 6H)	$C_{15}H_{11}NO_5S_2$ (C, H, N)
11	oil	3.8 (*s*, 3H), 4.6 (*s*, 2H), 5.6 (*d*, 1H), 6.35 (*d*, 1H), 7.8 (*dd*, 2H), 7.85 (*dd*, 2H)	$C_{13}H_{11}NO_4$ (C, H, N)
12	131–132	3.85 (*s*, 3H), 6.37 (*d*, 1H), 6.79 (*d*, 1H), 7.86–8.00 (*m*, 3H), 8.12 (*m*, 1H)	$C_{11}H_9NO_5S$ (C, H, N)
13	71–72	3.81 (*s*, 3H), 4.65 (*s*, 2H), 5.92 (*d*, 1H), 6.45 (*d*, 1H), 7.82–7.95 (*m*, 3H), 8.11 (*dd*, 1H)	$C_{12}H_{11}NO_5S$ (C, H, N)
14	66–67	5.3 (*s*, 2H), 7.2–7.6 (*m*, 5H), 7.9–8.2 (*m*, 3H), 8.0 (*d*, 1H)	$C_{14}H_{11}NO_3S_2$ (C, H, N)
15	124.5–127	4.8 (*dd*, 2H), 7.6 (*m*, 3H), 7.8–8.1 (*m*, 6H)	$C_{14}H_{11}NO_4S_2$ (C, H, N)
16	167–168	5.0 (*s*, 2H), 7.5–8.1 (*m*, 9H)	$C_{14}H_{11}NO_5S_2$ (C, H, N)
17	142–143	3.85 (*s*, 3H), 5.96 (*s*, 1H), 7.35 (*m*, 3H) 7.68 (*m*, 2H), 7.86 (*m*, 3H), 8.06 (*m*, 1H)	$C_{16}H_{13}NO_5S_2$ (C, H, N)
18	115–117	3.85 (*s*, 3H), 5.50 (*s*, 1H), 7.58 (*m*, 3H), 7.95 (*m*, 5H), 8.14 (*m*, 1H)	$C_{16}H_{13}NO_6S_2$ (C, H, N)
19	186–187	3.85 (*s*, 3H), 5.84 (*s*, 1H), 7.60 (*m*, 2H), 7.70 (*m*, 1H), 7.92 (*m*, 3H), 8.10 (*m*, 3H)	$C_{16}H_{13}NO_7S_2$ (C, H, N)

Table 4. Inhibition of human leukocyte elastase, proteinase 3 and cathepsin G

Compound	$k_{obs}/[I]$ M^{-1} s^{-1}		
	HLE	PR 3	Cath G
9	a	110	60
10	70	110	80
16	570	180	10
18	NA[b]	170	NA[b]
19	NA[b]	80	NA[b]

[a]Alternate substrate.
[b]No activity at an [inhibitor]/[enzyme] ratio of 200 and a 10 min incubation period.

inhibitory activity of **10** probably involves acylation of the active site serine, followed by a slow deacylation process and/or a 'double hit' mechanism as illustrated in Figure 3. Definitive resolution of these questions will have to await the results of further experimentation.

Small structural changes, such as (a) extending the (phenylsulfonyl)vinyl moiety by one carbon (**13**), (b) replacing the SO_2Ph group with a $COOCH_3$ group (**12**), and (c) using a phthalimide derivative (**11**), led to inactive compounds.

As noted earlier, when Z = COOR (structures **II** and **III**), the compounds were inactive. In contrast, when Z = SO_2Ph, active compounds are obtained in the saccharin series and inactive compounds in the phthalimide series. Interestingly, a saccharin derivative containing both functionalities (**19**) inhibited only PR 3. The corresponding sulfoxide derivative (**18**) was also active toward PR 3 but not toward HLE or Cath G.

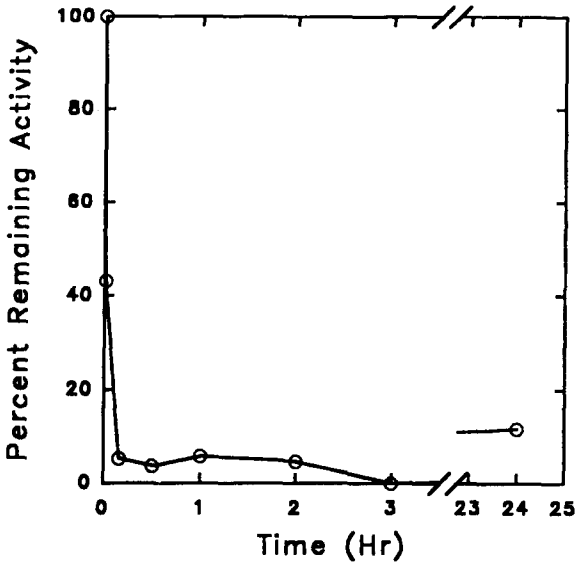


Figure 1. PR 3 (373 nM) was incubated with inhibitor **16** (37.3 μM) in 0.1 M phosphate buffer, pH 6.5. Aliquots were withdrawn at the indicated time intervals and assayed for enzymatic activity using Boc-L-Ala-*p*-nitrophenol (20 mM in CH_3CN).

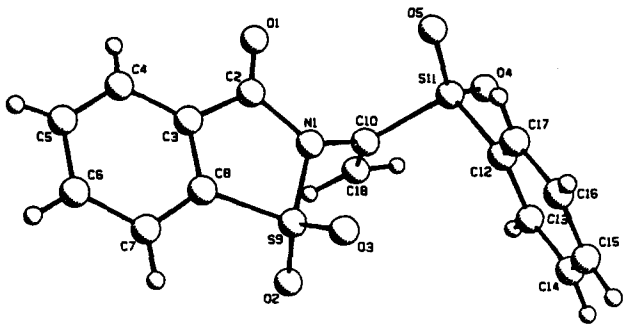


Figure 2. X-Ray crystal structure of compound **10**.

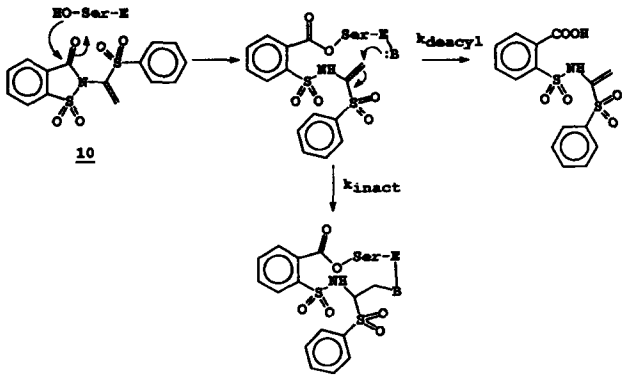


Figure 3. Postulated mechanism of action of compound **10**.

These results suggest that while the active sites of HLE and PR 3 are strikingly similar,[30,31] nevertheless, subtle differences in the make up of their active sites influence greatly the mode of binding of low molecular weight compounds, which may explain in part the observed differences in behavior of these compounds.

In conclusion, the inhibitory activity of phthalimide and saccharin derivatives **I–III** towards the serine proteinases HLE, Cath G and PR 3 has been investigated. Ongoing studies aimed at optimizing inhibitory activity and elucidating the mechanism of action of these compounds are currently in progress and will be reported in due course.

Experimental

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. The infrared and NMR spectra of the synthesized compounds were recorded on a Perkin–Elmer 1330 infrared spectrophotometer and a Varian XL-300 NMR spectrometer, respectively. A Hewlett–Packard diode array UV-vis spectrophotometer was used in the enzyme assays and inhibition studies. Human leukocyte elastase was purchased from Elastin Products Company, Owensville, MO. Human leukocyte cathepsin G was obtained from Athens Research and Technology Co., Athens, GA. Human leukocyte proteinase 3 was isolated as previously described.[25] Methoxysuccinyl Ala-Ala-Pro-Val *p*-nitroanilide, methoxysuccinyl Ala-Ala-Pro-Phe *p*-nitroanilide and Boc-L-Ala *p*-nitrophenol were purchased from Sigma Chemical Co., St. Louis. The IUPAC names of the synthesized compounds were obtained using AUTONOM 1.1 (Beilstein Informationssysteme GmbH, Frankfurt, Germany).

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-hydroxy-propionic acid methyl ester 1 and 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-imidazol-1-yl propionic acid methyl ester 2

Carbonyl diimidazole (8.92 g, 55 mmol) was added portionwise to a solution of phthalic acid (4.15 g, 25 mmol) in 100 mL dry THF. The solution was refluxed for 30 min. Triethylamine (2.52 g, 25 mmol) and (DL) serine methyl ester hydrochloride (3.88 g, 25 mmol) were then added and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was taken up in ethyl acetate (200 mL). The organic layer was washed with 5% hydrochloric acid, 5% sodium bicarbonate and water and dried over anhydrous sodium sulfate. The solvent was removed to give 1.42 g crude product which was purified by column chromatography, (hexane: methylene chloride gradient), yielding compound **1** (0.92 g, 15% yield) as a colorless oil. The acidic extract was neutralized with 5% sodium bicarbonate and extracted with ethyl acetate (2 × 50 mL). Removal of the solvent *in vacuo* yielded pure compound **2** (4.2 g, 60% yield).

3-Benzylsulfanyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester 3

Carbonyl diimidazole (1.53 g, 11 mmol) was added to a solution of phthalic acid (1.66 g, 10 mmol) in 75 mL dry THF. The solution was refluxed for 15 min, then triethylamine (1.01 g, 10 mmol) and *S*-benzyl-L-cysteine methyl ester hydrochloride (2.62 g, 10 mmol)

were added. Refluxing was continued for another 15 min. The reaction mixture was cooled to room temperature, carbonyl diimidazole (1.53 g, 11 mmol) was added and stirring was continued overnight. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150 mL). The organic layer was washed with 5% hydrochloric acid, 5% sodium bicarbonate and water, then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* yielded 3.0 g (85% yield) of compound **3**.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylmethanesulfinyl-propionic acid methyl ester ***4***

m-Chloroperbenzoic acid (0.37 g, 2.14 mmol) was added to an ice-cold solution of compound **3** (0.7 g, 1.95 mmol) in 10 mL methylene chloride, and the solution was stirred overnight at room temperature. The mixture was filtered and the filtrate was washed with 5% sodium bicarbonate (2 × 25 mL), dried over anhydrous sodium sulfate and evaporated, yielding compound **4** (0.6 g, 82% yield).

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylmethanesulfonyl-propionic acid methyl ester ***5***

Compound **5** was prepared using the same procedure as that used in the preparation of compound **4** with two equivalents of *m*-chloroperbenzoic acid (1.7 g, 87% yield).

*2-(1,1,3-Trioxo-1,3-dihydro-benzo[*d*]isothiazol-2-yl)-propionic acid methyl ester* ***7***

A solution of (DL) alanine methyl ester hydrochloride (2.0 g, 14 mmol), 2-sulfobenzoic acid anhydride (1.65 g, 7 mmol) and triethylamine (7.6 g, 36 mmol) in dry ethyl acetate (50 mL) was refluxed for 2 h using a Dean–Stark trap. The solvent was removed on a rotary evaporator and a vacuum pump. The viscous residue was mixed with phosphorus pentachloride (2.89, 14 mmol) and heated to 80 °C for 2 h. The resulting brown oil was taken up in ethyl acetate (100 mL), washed with water (100 mL) and dried over calcium chloride. Removal of the solvent *in vacuo* left an oily product which was purified by column chromatography using a mixture of hexane:ethyl acetate (7:3) as eluents (0.6 g, 16% yield).

*3-Benzylsulfanyl-2-(1,1,3-trioxo-1,3-dihydro-benzo[*d*]-isothiazol-2-yl)-propionic acid methyl ester* ***8*** *and 2-(1,1,3-trioxo-1,3-dihydro-benzo[*d*]isothiazol-2-yl)-acrylic acid methyl ester* ***12***

A solution of *S*-benzyl-L-cysteine methyl ester hydrochloride (2.0 g, 76 mmol) 2-sulfobenzoic acid anhydride (1.55 g, 84 mmol), and triethylamine (6.52 g, 65 mmol) in dry ethyl acetate (75 mL) was refluxed for 2 h using a Dean–Stark trap. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. Phosphorus pentachloride (1.59 g, 75 mmol) was added to the viscous residue and the mixture was heated to 90 °C for 2 h. The reaction mixture was cooled to room temperature, taken up in ethyl acetate (75 mL) and washed with water (100 mL), 5% sodium bicarbonate (2 × 75 mL) and water (75 mL) and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a crude product which was purified by flash chromatography (hexane:ethyl acetate, 7:3), yielding compound **8** (0.33 g, 11% yield) and **12** (0.05 g). The latter was obtained as a mixture of conformational isomers which were separated by flash chromatography.

Compound **8** was also prepared by reacting 2-(carbomethoxy)-benzene sulfonyl chloride with the amino acid ester hydrochloride salt and triethylamine in toluene.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-acrylic acid methyl ester ***11***

Potassium phthalimide (54 mmol) was added to a solution of α-(bromomethyl)acrylate (50 mmol) in 50 mL dry DMF. The reaction mixture was stirred at room temperature overnight, poured into 200 mL ice-cold water and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was evaporated *in vacuo*, leaving a crude product which was purified by flash chromatography (8.7 g, 71% yield).

*2-(1,1,3-Trioxo-1,3-dihydro-benzo[*d*]isothiazol-2-ylmethyl)-acrylic acid methyl ester* ***13***

Sodium saccharin (3.0 g, 14.4 mmol) was added to a stirred solution of α-(bromomethyl)acrylate (1.41 g, 7.9 mmol) in 10 mL dry DMF at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, 2 h at room temperature and then poured into ice-cold water. The resulting precipitate was collected and washed with hexane (1.80 g, 81% yield).

*1,1-Dioxo-2-phenylsulfanylmethyl-1,2-dihydro-benzo[*d*]-isothiazol-3-one* ***14***

Saccharin sodium salt (5 g, 24.4 mmol) and chloromethylphenyl sulfide (3.87 g, 24.4 mmol) were combined and heated at 130 °C for 40 min. The residue was taken up in ethyl acetate (100 mL) and washed with water (2 × 50 mL), saturated sodium bicarbonate (40 mL) and water (50 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a clear oil which crystallized from hexane (2.05 g, 28% yield). Further purification yielded compound **14**, mp 66–67 °C.

*2-Benzenesulfinylmethyl-1,1-dioxo-1,2-dihydro-benzo-[*d*]isothiazol-3-one* ***15***

Compound **14** (3.05 g, 10 mmol) in 100 mL methylene chloride was treated with *m*-chloroperbenzoic acid (2.87 g) and kept at 0 °C for 10 h. Work-up yielded **15** (2.44 g, 80% yield), mp 124.5–129 °C.

*2-Benzenesulfonylmethyl-1,1-dioxo-1,2-dihydro-benzo-[*d*]isothiazol-3-one* ***16***

Compound **14** (5.5 g, 18 mmol) in 100 mL methylene chloride was mixed with *m*-chloroperbenzoic acid (7.78

g, 2.5 eq.) and stirred overnight. The mixture was filtered and the filtrate was washed with 5% sodium bicarbonate (3 × 100 mL) and dried. Evaporation of the solvent yielded pure **16** (5.38 g, 89% yield), mp 167–168 °C.

Phenylsulfanyl-(1,1,3-trioxo-1,3-dihydro-benzo[d]isothiazol-2-yl)acetic acid methyl ester 17

A solution of saccharin (5.49 g, 30 mmol), methyl 2-chloro-2-(thiophenoxy)ethanoate (5.42 g, 25 mmol), triethylamine (3.03 g, 30 mmol) and acetonitrile (25 mL) was refluxed for 24 h. The solvent was removed *in vacuo*, the residue was taken up in ethyl acetate (100 mL) and washed with 5% aqueous HCl (2 × 25 mL) and 5% aqueous sodium bicarbonate (2 × 35 mL) and dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography, yielding pure **17** (1.76 g, 19% yield).

2-Benzenesulfinylmethyl-1,1-dioxo-1,2-dihydro-benzo-[d]isothiazol-3-one 18

A solution of compound **17** (0.30 g, 0.83 mmol) and *m*-chloroperbenzoic acid (0.19 g of 60%) in 10 mL methylene chloride was stirred overnight. Work-up yielded compound **18** (0.10 g, 32%) yield).

Compound **19** was obtained using a similar procedure (0.15 g, 38% yield).

Crystallography

Crystals of compound **10** crystallized with space group symmetry Pbca. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu K_α radiation and a 12 kW rotating anode generator. Cell constants determined were a = 14.733 (1) A, b = 28.053 (3) A, c = 7.3091 (3) A, and V = 3020.9 (4) A. For Z = 8 and F.W. = 349.38, the calculated density is 1.536 g cm^{-3}. A total of 2326 reflections were collected. The linear absorption coefficient for Cu K_α is 33.8 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.92 to 1.16. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1872 observed reflections ($I > 0.01\ \sigma(I)$) and 252 variable parameters and converged with unweighted and weighted agreement factors of $R = 0.043$ and $R_w = 0.067$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.28 and –0.32 e^-/A^3, respectively. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation.

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