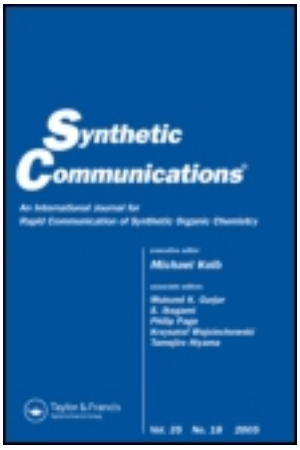

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Preparation of Saccharin Derivatives of Amino Acids as Potential Peptidomimetic Building Blocks

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Preparation of Saccharin Derivatives of Amino Acids as Potential Peptidomimetic Building Blocks

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Abstract: We present a useful route for the preparation of saccharin derivatives of amino acids. Sixteen new compounds, saccharin-derived amino acids, were synthesized, all of them bearing additional functional groups either at the 5- or 6-position of the saccharin skeleton, thus rendering the compounds more amenable to functionalization.

Keywords: Amino acid, bidentate ligands, oxidative cyclization, peptidomimetic, Saccharin

INTRODUCTION

Saccharin, 1,2-benzisothiazole-3-one-1,1-dioxide, is a well-known heterocyclic compound and has been used as a sweetener in the form of its sodium salt since 1885. Yet it is also a heterocycle of pharmaceutical importance, being a key structural element of certain CNS-active drugs.[1] It has attracted more and more attention after the synthesis of enzyme-activated inhibitors of serine proteases based on the saccharin scaffold was reported.[2–4] Another report revealed derivatives of saccharin as human leukocyte elastase inhibitors.[5] Since then, it has been widely incorporated into a variety of biologically active compounds. A recent

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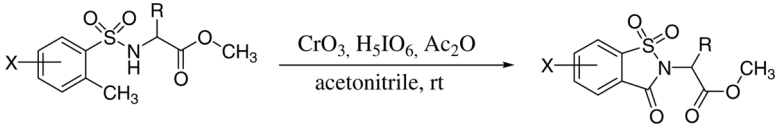
report also utilized the saccharin scaffold as part of the imidomethyl prodrug of certain phenolic drugs.[6]

Various methods for constructing the saccharin ring system have already been devised.[1,7–10] Most of these are difficult to carry out, and their yields are poor. Saccharines were prepared by reacting the sodium salt of saccharin with different halogenocompounds.[11–14] In the cases where halogenoderivatives of amino acids were used, racemization occurred during the reaction.[15] A similar but successful attempt made use of 3,3-dichloro-3*H*-benz[c][1,2]oxathiol 1,1-dioxide as a versatile substrate for reaction with amino acids.[15]

Since most of the published procedures are limited to the preparation of alkyl and alkoxy substituted saccharins, we overcame this problem by providing a novel route toward disubstituted saccharins capable of being incorporated into larger molecules as peptidomimetic building blocks. Based on the report of the successful cyclization of *N*-alkyl-*o*-methylarenesulfonamides to saccharin derivatives, utilizing the H_5IO_6-CrO_3 oxidation system,[16] we present a route to *N*-substituted saccharins obtained by CrO_3-catalyzed oxidation of the corresponding sulfonamide derivatives of various amino acids.

We designed those compounds by combining the saccharin moiety and amino acid moiety, using the latter's *N*-terminal as part of the saccharin heterocycle. Similar compounds have already been published by other research groups,[11,15] but our compounds allow for further derivatization at different parts of the molecule, that is at the benzene moiety of the saccharin heterocycle as well as at the *C*-terminus of the attached amino acid. The different substituents at the 6- and 5-positions of the saccharin scaffold render the final compounds more amenable to subsequent chemical manipulation, because the nitro group can easily be converted to an amino group, aryl bromides and aryl fluorides allow for cross-coupling reactions and aromatic nucleophilic substitutions, respectively, and the methoxy group can be easily deprotected.

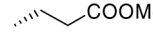
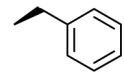
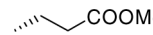
Herein we describe the synthesis and properties of 16 new saccharin derivatives of amino acids, in which their *N*-terminals are used as nitrogens of saccharin moieties (depicted in Scheme 1 and Table 1). The



1 2-5

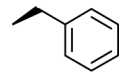
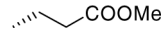
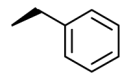
Scheme 1.

Table 1. Saccharin derivatives obtained via Scheme 1

Entry	1	Product	R	X	Yield (%)
1	**1a**	**2a**	H	6-NO_2	25
2	**1b**	**2b**		6-NO_2	27
3	**1c**	**2c**		6-NO_2	8
4	**1d**	**2d**		6-NO_2	9
5	**1e**	**2e**		6-NO_2	15
6	**1f**	**2f**		6-NO_2	—
7	**1g**	**3a**	H	6-Br	28
8	**1h**	**3b**		6-Br	33
9	**1i**	**3c**		6-Br	—
10	**1j**	**3d**		6-Br	—
11	**1k**	**3e**		6-Br	13

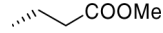
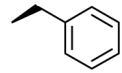
(*Continued*)

Table 1. Continued

Entry	1	Product	R	X	Yield (%)
12	**1l**	**3f**		6-Br	—
13	**1m**	**4a**	H	6-F	37
14	**1n**	**4b**		6-F	40
15	**1o**	**4c**		6-F	17
16	**1p**	**4d**		6-F	16
17	**1q**	**4e**		6-F	14
18	**1r**	**4f**		6-F	—
19	**1s**	**5a**	H	5-MeO	17
20	**1t**	**5b**		5-MeO	23
21	**1u**	**5c**		5-MeO	—

(*Continued*)

Table 1. Continued

Entry	1	Product	R	X	Yield (%)
22	**1v**	**5d**		5-MeO	—
23	**1x**	**5e**		5-MeO	16
24	**1y**	**5f**		5-MeO	—

synthesized compounds constitute a set of potentially useful peptidomimetic building blocks susceptible to further functionalization. Their preparation is simple and rapid. In addition, the products are easy to purify by extraction and washing, without the need for further purification. However, the chemical nature of the starting sulfonamides limits the yields of the reactions to a moderate level.

RESULTS AND DISCUSSION

Although sulfonylated derivatives of primary amines were successfully oxidized according to the published procedure,[16] in our case sulfonylated amino acids were used as the starting material. The reaction conditions therefore had to be altered and optimized to enable a smooth course of the oxidation, hence affording the desired products.

Because longer reaction times are required for substrates with halogen or electron-withdrawing substituents, a higher catalyst loading was used to shorten the reaction times and improve yields. At a loading of 5 mol% CrO_3, the reaction did not proceed either at room temperature or when heated to reflux, which prompted us to raise the catalyst loading to 20 mol%. Under those conditions, the reaction was still not completed at room temperature in 24 h; however, heating the mixture overnight under reflux afforded the desired product. Optimal conditions were realized when employing 50 mol% CrO_3, which brought about ready entry to the saccharin nucleus at room temperature in 2 h.

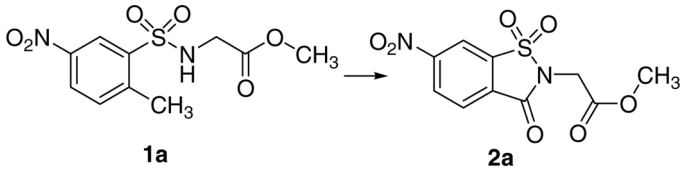
Table 2. Optimization of the reaction with respect to the solvent, catalyst loading, and temperature[a]

Solvent	ε^b	Catalyst loading (mol% CrO_3)	T	Yield (%)
Acetonitrile	37.5	5	Rt	No product detected
Acetonitrile	37.5	5	Reflux	No product detected
Acetonitrile	37.5	20	Rt	Not determined
Acetonitrile	37.5	20	Reflux	15
Acetonitrile	37.5	50	Rt	25
Ethyl acetate	6.0	50	Rt	No product detected
1,2-Dichloroethane	10.3	50	Rt	<10
Dioxane	2.2	50	Rt	No product detected
Acetic acid	6.2	50	Rt	18
Acetone	20.7	50	Rt	No product detected
DMF	36.7	50	Rt	No product detected

[a]Reaction conditions: 1 equiv. of sulfonamide **1a**, 7 equiv. of periodic acid, 7 equiv. of acetic acid anhydride, 5, 20, or 50 mol% CrO_3, 20 ml of solvent.
[b]Dielectric constant.

In a previous report, acetonitrile, was chosen as the most appropriate solvent because of the poor solubility of CrO_3 in most other organic solvents.[17] Therefore, test reactions were performed using more polar solvents in attempts to improve the solubility of CrO_3 and thus improve the yield (Table 2 and Scheme 2). Our findings confirmed that acetonitrile is indeed the solvent of choice for this reaction, although acetic acid also proved useful.

The relatively low yields can be ascribed mostly to the great extent of the competitive side reaction, that is, oxidation of the α-CH of the *N*-alkyl group, which is greatly influenced by the group attached to the ß-position relative to the nitrogen atom.[18] We concluded that the presence of electron-accepting and electron-withdrawing groups within individual amino acids determines the extent of the side reaction.



1a **2a**

Scheme 2.

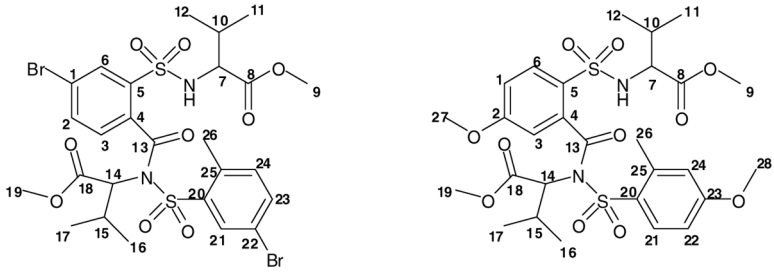


Figure 1. Dimers formed via an intermolecular oxidation.

In the cases of *L*- and *D*-Val derivatives of 6-Br (**1i**, **1j**) and 5-MeO series (**1u**, **1v**), none of the expected products could be isolated; instead, dimers were formed by an intermolecular oxidation (shown in Fig. 1). These dimeric structures were fully assignated using ^{1}H NMR, ^{13}C NMR, NMR correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra, which made it feasible to address another aspect of this reaction, that is, the retention of chiral configuration of starting amino acid derivatives. The absence of racemization under the reaction conditions was unambiguously shown by fully assignated proton and ^{13}C NMR spectra of the aforementioned dimeric structures. The spectra did not show any duplication of resonance signals, indicating that the isolated products were not a mixture of diastereomers. These results, as well as the determined specific rotations of the final compounds, led us to the assumption that the stereochemistry of the starting compounds was not compromised.

Additionally, none of the desired products (**2f**, **3f**, **4f**, and **5f**) could be generated by oxidation of the sulfonylated *L*-Phe derivatives, thus indicating the great extent of the competitive side reaction resulting from the contribution of the benzylic group attached to the α-*C* of phenylalanine.

CONCLUSION

To summarize, we report a novel route for the preparation of saccharin derivatives of amino acids. Sixteen new compounds, saccharin-derived amino acids, were synthesized using this method, which is tolerant of a variety of functional groups. The additional functional groups at the

5- and 6-position of the saccharin skeleton make the compounds more amenable to derivatization, which gives this procedure advantages over currently available methods.

EXPERIMENTAL

Chemicals from Aldrich Chemical Co. and Fluka were used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck silica-gel (60 F 254) plates (0.25 mm). The components were visualized with ultraviolet light and charred with 20% sulphuric acid in ethanol and ninhydrin. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectra were recorded on a Bruker Avance DPX_{300} spectrometer in $CDCl_3$ solution with TMS as the internal standard. IR spectra were obtained on a Perkin-Elmer 1600 Fourier transfer-infrared spectroscopy (FT-IR) spectrometer. Microanalyses were performed on a 240 C Perkin-Elmer CHN analyzer. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer. Optical rotation was determined on a Perkin-Elmer polarimeter 1241 MC using a 1-dm cell.

General Procedure for the Preparation of Saccharins from Sulfonylated Amino Acids (1a–y) and Characterization of Products

Periodic acid (7.0 mmol) was suspended in 20 mL of acetonitrile, and the mixture was stirred vigorously for 45 min. Chromium trioxide (0.5 mmol) and acetic acid anhydride (7.0 mmol) were then added, and the solution was cooled to 0 °C. The addition of sulfonylated amino acid (1.0 mmol) followed, and the reaction mixture was stirred at 0 °C for another half an hour, when the mixture was allowed to warm to room temperature. After 2 additional hours of stirring, the oxidation was complete, as indicated by TLC on the basis of the corresponding starting sulfonylated amino acid. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL). The solids were removed by filtration and rinsed with another portion of ethyl acetate (30 mL). The organic phase was extracted with a saturated solution of sodium thiosulfate ($Na_2S_2O_3$) (2×20 mL), 1 M NaOH solution (3×20 mL), water (2×10 mL), and brine (20 mL) and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude product was obtained, which needed no further purification.

Methyl 2-(6-Nitro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)acetate (**2a**)

Yellow solid; Mp 134–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.83 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 8.31 (d, 1H, J = 8.4 Hz, Ar-H^4), 8.71 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz, Ar-H^5), 8.80 (d, 1H, J = 1.8 Hz, Ar-H^7); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 38.30 (CH_2), 52.08 (CH_3), 116.28 (C-7), 126.01 (C-5), 128.46 (C-4), 130.22 (C-3a), 137.92 (C-7a), 150.70 (C-6), 155.71 (C-3), 164.71 (CO). MS (EI) m/z: 301 $(MH)^+$; IR (KBr, cm^{-1}): 1762, 1735, 1617, 1542, 1448, 1418, 1354, 1316, 1215, 1186, 1110, 1064, 994, 961, 906, 889, 862, 777, 732, 715, 692, 660, 629, 595, 582, 560, 518. Anal. calcd. for $C_{10}H_8N_2O_7S \times 0.5$ 0.5 H_2O (%): C, 38.84; H, 2.93; N, 9.06. Found: C, 38.55; H, 2.79; N, 9.03.

Methyl (2*S*)-2-(6-Nitro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)propanoate (**2b**)

Yellow solid; Mp 123–125 °C; $[\alpha]_D$ − 25.1 (c 1.95, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.90 (d, 3H, J = 7.2 Hz, C$\underline{H}_3$-CH), 3.79 (s, 3H, CH_3), 4.89 (q, 1H, J = 7.5 Hz, CH), 8.28 (d, 1H, J = 8.4 Hz, Ar-H^4), 8.69 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz, Ar-H^5), 8.76 (d, 1H, J = 1.8 Hz, Ar-H^7); MS (EI) m/z: 315 $(MH)^+$; IR (KBr, cm^{-1}): 1734, 1636, 1540, 1465, 1345, 1294, 1246, 1222, 1187, 1110, 1092, 1049, 994, 974, 912, 879, 847, 736, 700, 665, 644, 584, 529. Anal. calcd. for $C_{11}H_{10}N_2O_7S$ (%): C, 42.04; H, 3.21; N, 8.91. Found: C, 42.20; H, 3.26; N, 8.86.

Methyl (2*S*)-2-(6-Nitro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-3-methylbutanoate (**2c**)

Beige solid; Mp 136–139 °C; $[\alpha]_D$ −58.6 (c 1.40, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.05 (d, 3H, J = 6.9 Hz, C$\underline{H}_3$CH), 1.20 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$CH), 2.81–2.95 (m, 1H, C$\underline{H}$CH$_3$), 3.77 (s, 3H, CH_3O), 4.41 (d, 1H, J = 9.3 Hz, NHC$\underline{H}$), 8.29 (d, 1H, J = 8.4 Hz, Ar-H^4), 8.69 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz, Ar-H^5), 8.76 (d, 1H, J = 1.8 Hz, Ar-H^7); MS (EI) m/z: 343 $(MH)^+$; IR (KBr, cm^{-1}): 3434, 1754, 1728, 1636, 1542, 1438, 1355, 1290, 1274, 1248, 1194, 1139, 1047, 993, 889, 858, 732, 661, 584, 526. HRMS calcd. for $C_{13}H_{14}N_2O_7S$ m/z: 343.0600 $(MH)^+$; Found: 343.0608.

Methyl (2*R*)-2-(6-Nitro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-3-methylbutanoate (**2d**)

Beige solid; mp 136–139 °C; $[\alpha]_D$ + 51.8 (c 2.15, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.05 (d, 3H, J = 6.9 Hz, C$\underline{H}_3$CH), 1.20

(d, 3H, $J = 6.6$ Hz, C$\underline{H}_3$CH), 2.81–2.95 (m, 1H, C$\underline{H}$CH$_3$), 3.77 (s, 3H, CH$_3$O), 4.41 (d, 1H, $J = 9.3$ Hz, NHC$\underline{H}$), 8.29 (d, 1H, $J = 8.1$ Hz, Ar-H^4), 8.69 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.8$ Hz, Ar-H^5), 8.77 (d, 1H, $J = 1.8$ Hz, Ar-H^7); MS (EI) m/z: 343 (MH)$^+$; IR (KBr, cm^{-1}): 1728, 1634, 1542, 1355, 1290, 1274, 1249, 1194, 1139, 1048, 993, 890, 732, 661, 584, 526. HRMS calcd. for $C_{13}H_{14}N_2O_7S$ m/z: 343.0600 (MH)$^+$; Found: 343.0603.

Dimethyl (2*R*)-2-(6-Nitro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)pentanedioate (**2e**)

Green oil; $[\alpha]_D + 57.6$ (c 1.70, C$\underline{H}_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 2.48–2.78 (m, 4H, 2 × C$\underline{H}_2$), 3.69 (s, 3H, CH$_3$O), 3.79 (s, 3H, CH$_3$O), 4.89–4.94 (m, 1H, NHC$\underline{H}$), 8.28 (d, 1H, $J = 8.4$ Hz, Ar-H^4), 8.69 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, Ar-H^5), 8.77 (d, 1H, $J = 1.8$ Hz, Ar-H^7); MS (EI) m/z: 386 M$^+$; IR (NaCl, cm^{-1}): 3462, 3102, 2956, 2290, 1738, 1612, 1543, 1438, 1351, 1290, 1263, 1241, 1190, 1109, 1081, 1031, 982, 886, 862, 821, 778, 732, 663, 585. Anal. calcd. for $C_{14}H_{14}N_2O_9S$ (%): C, 43.52; H, 3.65; N, 7.25. Found: C, 43.75; H, 3.91; N, 7.03.

Methyl 2-(6-Bromo-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)acetate (**3a**)

Brown solid; mp 135–137 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 3.81 (s, 3H, CH$_3$O), 4.45 (s, 2H, CH$_2$), 7.95 (d, 1H, $J = 7.8$ Hz, Ar-H^4), 7.99 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz, Ar-H^5), 8.09 (d, 1H, $J = 1.5$ Hz, Ar-H^7); MS (EI) m/z: 335 (MH)$^+$; IR (KBr, cm^{-1}): 1740, 1636, 1415, 1338, 1298, 1227, 1178, 1077, 1000, 959, 896, 877, 843, 761, 715, 689, 665, 626, 592, 520. Anal. calcd. for $C_{10}H_8BrNO_5S$ (%): C, 35.94; H, 2.41; N, 4.19. Found: C, 35.97; H, 2.45; N, 4.22.

Methyl (2*S*)-2-(6-Bromo-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)propanoate (**3b**)

Beige solid; mp 117–119 °C; $[\alpha]_D -20.7$ (c 2.85, CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 1.86 (d, 3H, $J = 7.5$ Hz, C$\underline{H}_3$-CH), 3.77 (s, 3H, CH$_3$O), 4.83 (q, 1H, $J = 7.5$ Hz, NHC$\underline{H}$), 7.91 (d, 1H, $J = 8.1$ Hz, Hz, Ar-H^4), 7.97 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, Ar-H^5), 8.06 (d, 1H, $J = 1.5$ Hz, Ar-H^7); MS (EI) m/z: 349 (MH)$^+$; IR (KBr, cm^{-1}): 3453, 3086, 1745, 1730, 1585, 1457, 1437, 1398, 1345, 1324, 1283, 1237, 1185,

1139, 1085, 986, 898, 852, 763, 702, 672, 627, 596, 589, 571, 522. Anal. calcd. for $C_{11}H_{10}BrNO_5S$ (%): C, 37.95; H, 2.89; N, 4.02. Found: C, 37.73; H, 2.83; N, 4.19.

Dimethyl (2*R*)-2-(6-Bromo-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)pentanedioate (**3e**)

White solid; mp 117–120 °C; $[\alpha]_D + 81.9$ (*c* 2.15, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.42–2.75 (m, 4H, $2 \times CH_2$), 3.69 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 4.76–4.89 (m, 1H, NHC<u>H</u>), 7.92 (d, 1H, $J = 8.1$ Hz, Ar-H^4), 7.98 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, Ar-H^5), 8.06 (d, 1H, $J = 1.5$ Hz, Ar-H^7); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 23.69 (β-CH_2), 30.09 (γ-CH_2), 41.16 (CH), 51.84 (CH_3), 53.22 (CH_3), 124.36 (C-7), 125.67 (C-3a), 126.71 (C-4), 130.23 (C-6), 137.81 (C-5), 139.03 (C-7a), 158.36 (C-3), 167.93 (CO), 172.54 (CO). MS (EI) *m/z*: 360 (M-59)$^+$; IR (KBr, cm^{-1}): 3439, 1753, 1735, 1636, 1586, 1457, 1437, 1397, 1345, 1323, 1243, 1184, 1132, 1086, 1029, 1000, 983, 967, 905, 855, 826, 776, 760, 670, 640, 586, 572, 524. Anal. calcd. for $C_{14}H_{14}BrNO_7S$ (%): C, 40.01; H, 3.36; N, 3.33. Found: C, 39.91; H, 3.28; N, 3.42.

Methyl 2-(6-Fluoro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-acetate (**4a**)

White solid; mp 81–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.81 (s, 3H, CH_3O), 4.45 (s, 2H, CH_2), 7.54 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, Ar-H^5), 7.64 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.1$ Hz, Ar-H^7), 8.12 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.5$ Hz, Ar-H^4); MS (EI) *m/z*: 273 M$^+$; IR (KBr, cm^{-1}): 3473, 1740, 1636, 1481, 1445, 1412, 1341, 1308, 1288, 1264, 1221, 1177, 1058, 1008, 953, 892, 867, 852, 764, 728, 705, 660, 617, 594, 527, 494, 458. Anal. calcd. for $C_{10}H_8FNO_5S$ (%): C, 43.96; H, 2.95; N, 5.13. Found: C, 43.98; H, 2.97; N, 5.10.

Methyl (2*S*)-2-(6-Fluoro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)propanoate (**4b**)

White solid; mp 78–80 °C; $[\alpha]_D - 30.6$ (*c* 2.45, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (d, 3H, $J = 7.5$ Hz, C<u>H</u>$_3$-CH), 3.78 (s, 3H, CH_3O), 4.84 (q, 1H, $J = 7.5$ Hz, NHC<u>H</u>), 7.52 (dt, 1H, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, Ar-H^5), 7.61 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 2.1$ Hz, Ar-H^7), 8.08 (dd, 1H, $J_1 = 8.7$ Hz, $J_2 = 4.5$ Hz, Ar-H^4); ^{13}C NMR

(75 MHz, $CDCl_3$): δ (ppm) = 15.14 (CH_3), 50.35 (CH), 53.53 (CH_3O), 109.55 (d, $J = 26.7$ Hz, C-7), 122.64 (d, $J = 23.0$ Hz, C-5), 123.52 (d, $J = 2.9$ Hz, C-3a), 128.40 (d, $J = 9.5$ Hz, C-4), 140.49 (d, $J = 9.2$ Hz, C-7a), 158.25 (C-3), 166.78 (d, $J = 260.5$ Hz, C-6), 169.29 (CO). MS (EI) m/z: 288 $(MH)^+$; IR (KBr, cm^{-1}): 1734, 1636, 1600, 1484, 1341, 1288, 1258, 1230, 1171, 1126, 1090, 1043, 991, 947, 875, 843, 774, 762, 708, 670, 656, 590, 558, 534, 504, 474. Anal. calcd. for $C_{11}H_{10}FNO_5S$ (%): C, 45.99; H, 3.51; N, 4.88. Found: C, 45.99; H, 3.29; N, 4.96.

Methyl (2*S*)-2-(6-Fluoro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-3-methylbutanoate (**4c**)

White solid; mp 77–80 °C; $[\alpha]_D - 54.4$ (c 1.60, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.04 (d, 3H, $J = 6.9$ Hz, $C\underline{H}_3CH$), 1.18 (d, 3H, $J = 6.6$ Hz, $C\underline{H}_3CH$), 2.81–2.93 (m, 1H, $C\underline{H}CH_3$), 3.75 (s, 3H, CH_3O), 4.38 (d, 1H, $J = 9.3$ Hz, $NHC\underline{H}$), 7.52 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, Ar-H^5), 7.61 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 2.1$ Hz, Ar-H^7), 8.09 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.5$ Hz, Ar-H^4); MS (EI) m/z: 316 $(MH)^+$; IR (KBr, cm^{-1}): 1734, 1636, 1488, 1351, 1280, 1264, 1172, 1139, 1042, 1011, 923, 874, 853, 792, 763, 703, 668, 628, 615, 589, 544, 527. Anal. calcd. for $C_{13}H_{14}FNO_5S \times 0.1\ H_2O$ (%): C, 49.24; H, 4.51; N, 4.42. Found: C, 49.64; H, 4.54; N, 4.40.

Methyl (2*R*)-2-(6-Fluoro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-3-methylbutanoate (**4d**)

White solid; mp 77–80 °C; $[\alpha]_D + 65.4$ (c 2.80, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.04 (d, 3H, $J = 6.9$ Hz, $C\underline{H}_3CH$), 1.19 (d, 3H, $J = 6.6$ Hz, $C\underline{H}_3CH$), 2.81–2.93 (m, 1H, $C\underline{H}CH_3$), 3.75 (s, 3H, CH_3O), 4.38 (d, 1H, $J = 9.3$ Hz, $NHC\underline{H}$), 7.52 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, Ar-H^5), 7.61 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 2.1$ Hz, Ar-H^7), 8.09 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.5$ Hz, Ar-H^4); MS (EI) m/z: 316 $(MH)^+$; IR (KBr, cm^{-1}): 1734, 1636, 1489, 1350, 1280, 1172, 1139, 1040, 994, 923, 876, 850, 794, 764, 668, 628, 615, 591, 544, 526. Anal. calcd. for $C_{13}H_{14}FNO_5S \times 0.1\ H_2O$ (%): C, 49.24; H, 4.51; N, 4.42. Found: C, 49.22; H, 4.36; N, 4.32.

Dimethyl (2*R*)-2-(6-Fluoro-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)pentanedioate (**4e**)

Yellow oil; $[\alpha]_D + 82.6$ (c 1.90, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.50–2.75 (m, 4H, $2 \times CH_2$), 3.69 (s, 3H, CH_3O), 3.78 (s, 3H,

CH_3O), 4.84–4.90 (m, 1H, NHCH), 7.53 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, Ar-H^5), 7.61 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 2.1$ Hz, Ar-H^7), 8.09 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.5$ Hz, Ar-H^4); MS (EI) m/z: 360 $(MH)^+$; IR (NaCl, cm^{-1}): 3448, 3102, 2956, 2362, 1735, 1601, 1508, 1485, 1438, 1343, 1286, 1261, 1174, 1079, 1030, 865, 820, 764, 670, 590. Anal. calcd. for $C_{14}H_{14}FNO_7S$ (%): C, 46.80; H, 3.93; N, 3.90. Found: C, 47.32; H, 4.12; N, 4.13.

Methyl 2-(5-Methoxy-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)acetate (**5a**)

Orange solid; mp 86–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.81 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3OAr), 4.44 (s, 2H, CH_2), 7.34 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, Ar-H^6), 7.51 (d, 1H, $J = 2.4$ Hz, Ar-H^4), 7.84 (d, 1H, $J = 8.4$ Hz, Ar-H^7); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 38.96 (CH_2), 52.89 (CH_3O), 56.30 (CH_3OAr), 108.76 (C-4), 121.82 (C-6), 122.74 (C-7), 129.30 (C-7a), 129.63 (C-3a), 158.75 (C-3), 164.55 (C-5), 166.38 (CO). MS (EI) m/z: 285 M^+; IR (KBr, cm^{-1}): 1760, 1636, 1484, 1438, 1375, 1337, 1313, 1228, 1186, 1137, 1060, 1021, 966, 877, 846, 828, 763, 698, 584, 572, 504, 495. Anal. calcd. for $C_{11}H_{11}NO_6S$ (%): C, 46.31; H, 3.89; N, 4.91. Found: C, 46.57; H, 4.00; N, 4.72.

Methyl (2*S*)-2-(5-Methoxy-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)propanoate (**5b**)

Orange solid; mp 115–118 °C; $[\alpha]_D - 20.5$ (*c* 2.20, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.85 (d, 3H, $J = 7.5$ Hz, CH_3-CH), 3.77 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3OAr), 4.81 (q, 1H, $J = 7.5$ Hz, NHCH), 7.32 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, Ar-H^6), 7.47 (d, 1H, $J = 2.4$ Hz, Ar-H^4), 7.80 (d, 1H, $J = 8.7$ Hz, Ar-H^7); MS (EI) m/z: 299 M^+; IR (KBr, cm^{-1}): 1741, 1720, 1607, 1484, 1435, 1324, 1294, 1263, 1244, 1179, 1159, 1092, 1068, 1056, 1022, 986, 951, 928, 907, 882, 859, 837, 780, 769, 701, 667, 604, 573, 536. Anal. calcd. for $C_{12}H_{13}NO_6S$ (%): C, 48.16; H, 4.38; N, 4.68. Found: C, 48.16; H, 4.32; N, 4.47.

Dimethyl (2*R*)-2-(5-Methoxy-1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)pentanedioate (**5e**)

Yellow oil; $[\alpha]_D + 69.7$ (*c* 1.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.48–2.75 (m, 4H, $2 \times CH_2$), 3.69 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3OAr), 4.80–4.85 (m, 1H, NHCH), 7.33 (dd,

1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, Ar-H^6), 7.48 (d, 1H, $J = 2.4$ Hz, Ar-H^4), 7.81 (d, 1H, $J = 8.4$ Hz, Ar-H^7); MS (EI) m/z: 372 $(MH)^+$; IR (NaCl, cm^{-1}): 3448, 3099, 2954, 2291, 1735, 1604, 1508, 1485, 1437, 1335, 1299, 1246, 1185, 1139, 1071, 1044, 1015, 879, 832, 804, 763, 696. Anal. calcd. for $C_{15}H_{17}NO_8S \times 0.5\ H_2O$ (%): C, 47.36; H, 4.77; N, 3.68. Found: C, 47.51; H, 4.47; N, 3.40.

Methyl (2*S*)-2-({[5-Bromo-2-({[(5-bromo-2-methylphenyl)sulfonyl]-[(1*S*)-1-(methoxycarbonyl)]-2-methylpropyl]amino}carbonyl)phenyl]-sulfonyl}amino)-3-methylbutanoate (**6a**)

Yellow solid; mp 72–76 °C; $[\alpha]_D - 47.2$ (*c* 3.20, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.88–0.93 (m, 6H, CH_3-11 and CH_3-12), 1.04 (d, 3H, $J = 6.6$ Hz, CH_3-16), 1.18 (d, 3H, $J = 6.6$ Hz, CH_3-17), 1.97–2.09 (m, 1H, CH-10), 2.62 (s, 3H, CH_3-26), 2.80–2.92 (m, 1H, CH-15), 3.51 (s, 3H, CH_3-9), 3.68–3.73 (m, 1H, CH-7), 3.75 (s, 3H, CH_3-19), 4.37 (d, 1H, $J = 9.6$ Hz, CH-14), 5.14 (d, 1H, $J = 10.2$ Hz, SO_2NH), 7.18 (d, 1H, $J = 8.1$ Hz, H-24), 7.56 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, H-23), 7.91–7.99 (m, 2H, H-2 and H-3), 8.06–8.07 (m, 2H, H-6 and H-21);^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 17.52 (C-11), 18.84 (C-12), 19.70 (C-17), 19.83 (C-26), 20.66 (C-16), 28.23 (C-15), 31.58 (C-10), 52.30 (C-9), 52.74 (C-19), 60.31 (C-14), 61.08 (C-7), 119.37 (C-22), 124.20 (C-21), 125.55 (C-1), 126.72 (C-3), 130.07 (C-4), 132.06 (C-6), 134.01 (C-24), 135.66 (C-23), 136.41 (C-25), 137.71 (C-2), 138.90 (C-5), 139.21 (C-20), 158.21 (C-13), 168.01 (C-18), 171.75 (C-8); MS (ESI) m/z: 763 $(MNa)^+$; IR (KBr, cm^{-1}): 3468, 1756, 1734, 1715, 1636, 1586, 1448, 1348, 1325, 1276, 1254, 1182, 1167, 1139, 1078, 1063, 1015, 990, 921, 892, 874, 845, 822, 763, 708, 662, 603, 585, 527. Anal. calcd. for $C_{26}H_{32}Br_2N_2O_9S_2 \times 2\ H_2O$ (%): C, 40.22; H, 4.67; N, 3.61. Found: C, 39.98; H, 4.24; N, 3.63.

Methyl (2*R*)-2-({[5-Bromo-2-({[(5-bromo-2-methylphenyl)sulfonyl]-[(1*R*)-1-(methoxycarbonyl)]-2-methylpropyl]amino}carbonyl)phenyl]-sulfonyl}amino)-3-methylbutanoate (**6b**)

Yellow solid; mp 72–76 °C; $[\alpha]_D + 56.7$ (*c* 1.20, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.88–0.93 (m, 6H, CH_3-11 and CH_3-12), 1.04 (d, 3H, $J = 6.6$ Hz, CH_3-16), 1.18 (d, 3H, $J = 6.6$ Hz, CH_3-17), 1.97–2.08 (m, 1H, CH-10), 2.62 (s, 3H, CH_3-26), 2.80–2.92 (m, 1H, CH-15), 3.51 (s, 3H, CH_3-9), 3.68–3.77 (m, 1H, CH-7), 3.75 (s, 3H, CH_3-19), 4.37 (d, 1H, $J = 9.6$ Hz, CH-14), 5.14 (d, 1H, $J = 10.2$ Hz, SO_2NH), 7.18 (d, 1H, $J = 8.1$ Hz, H-24), 7.56 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, H-23), 7.91–7.99 (m, 2H, H-2 and H-3), 8.05–8.07 (m, 2H, H-6 and H-21); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 17.53 (C-11), 18.86 (C-12), 19.72 (C-17),

19.85 (C-26), 20.68 (C-16), 28.25 (C-15), 31.61 (C-10), 52.33 (C-9), 52.77 (C-19), 60.35 (C-14), 61.10 (C-7), 119.40 (C-22), 124.22 (C-21), 125.58 (C-1), 126.73 (C-3), 130.09 (C-4), 132.10 (C-6), 134.03 (C-24), 135.69 (C-23), 136.43 (C-25), 137.72 (C-2), 138.93 (C-5), 139.25 (C-20), 158.23 (C-13), 168.04 (C-18), 171.78 (C-8); MS (ESI) m/z: 763 $(MNa)^+$; IR (KBr, cm^{-1}): 3478, 2970, 1757, 1734, 1714, 1586, 1438, 1349, 1325, 1276, 1253, 1182, 1167, 1139, 1078, 1063, 1015, 990, 922, 892, 874, 845, 825, 800, 763, 708, 698, 663, 603, 585, 527. Anal. calcd. for $C_{26}H_{32}Br_2N_2O_9S_2 \times H_2O$ (%): C, 41.17; H, 4.52; N, 3.69. Found: C, 40.98; H, 4.15; N, 3.88.

Methyl (2*S*)-2-{[5-Methoxy-2-({[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}sulfonyl)benzoyl][(4-methoxy-2-methylphenyl)sulfonyl]amino}-3-methylbutanoate (**7a**)

Brown oil; $[\alpha]_D - 80.5$ (c 1.55, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.86–0.90 (m, 6H, CH_3-11 and CH_3-12), 1.04 (d, 3H, $J = 6.6$ Hz, Hz, CH_3-16), 1.18 (d, 3H, $J = 6.6$ Hz, CH_3-17), 1.94–2.04 (m, 1H, CH-10), 2.63 (s, 3H, CH_3-26), 2.83–2.94 (m, 1H, CH-15), 3.50 (s, 3H, CH_3-9), 3.60–3.66 (m, 1H, CH-7), 3.75 (s, 3H, CH_3-19), 3.84 (s, 3H, CH_3-28), 3.95 (s, 3H, CH_3-27), 4.35 (d, 1H, $J = 9.3$ Hz, CH-14), 5.06 (d, 1H, $J = 9.9$ Hz, SO_2NH), 6.74–6.79 (m, 2H, H-22 and H-24), 7.32 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, H-1), 7.48 (d, 1H, $J = 2.4$ Hz, H-3), 7.79–7.89 (m, 2H, H-6 and H-21); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 17.61 (C-11), 18.86 (C-12), 19.71 (C-16), 20.56 (C-26), 20.71 (C-17), 28.21 (C-15), 31.57 (C-10), 52.21 (C-9), 52.67 (C-19), 55.47 (C-28), 56.31 (C-27), 60.08 (C-14), 60.96 (C-7), 108.67 (C-3), 110.44 (C-24), 117.94 (C-22), 121.88 (C-1), 122.55 (C-6), 129.15 (C-20 or C-4), 129.16 (C-4 or C-20), 129.44 (C-5), 132.15 (C-21), 139.86 (C-25), 158.96 (C-13), 162.84 (C-23), 164.54 (C-2), 168.33 (C-18), 172.08 (C-8); MS (ESI) m/z: 665 $(MNa)^+$; IR (NaCl, cm^{-1}): 3304, 3099, 2967, 1737, 1602, 1570, 1508, 1485, 1465, 1436, 1391, 1337, 1298, 1247, 1187, 1135, 1069, 1043, 1015, 935, 868, 829, 763, 720, 665. Anal. calcd. for $C_{28}H_{38}N_2O_{11}S_2 \times H_2O$ (%): C, 50.90; H, 6.10; N, 4.24. Found: C, 50.85; H, 5.82; N, 4.71.

Methyl (2*R*)-2-{[5-Methoxy-2-({[(1*R*)-1-(methoxycarbonyl)-2-methylpropyl]amino}sulfonyl)benzoyl][(4-methoxy-2-methylphenyl)-sulfonyl]amino}-3-methylbutanoate (**7b**)

Brown oil; $[\alpha]_D + 86.7$ (c 1.35, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.86–0.90 (m, 6H, CH_3-11 and CH_3-12), 1.04 (d, 3H, $J = 6.6$ Hz, Hz, CH_3-16), 1.18 (d, 3H, $J = 6.6$ Hz, CH_3-17), 1.93–2.04 (m, 1H,

CH-10), 2.63 (s, 3H, CH_3-26), 2.82–2.94 (m, 1H, CH-15), 3.50 (s, 3H, CH_3-9), 3.60–3.65 (m, 1H, CH-7), 3.75 (s, 3H, CH_3-19), 3.84 (s, 3H, CH_3-28), 3.95 (s, 3H, CH_3-27), 4.35 (d, 1H, $J = 9.3$ Hz, CH-14), 5.06 (d, 1H, $J = 9.9$ Hz, SO_2NH), 6.74–6.79 (m, 2H, H-22 and H-24), 7.32 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, H-1), 7.48 (d, 1H, $J = 2.4$ Hz, H-3), 7.79–7.89 (m, 2H, H-6 and H-21); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 17.59 (C-11), 18.84 (C-12), 19.69 (C-16), 20.54 (C-26), 20.69 (C-17), 28.19 (C-15), 31.55 (C-10), 52.19 (C-9), 52.65 (C-19), 55.45 (C-28), 56.29 (C-27), 60.06 (C-14), 60.94 (C-7), 108.65 (C-3), 110.42 (C-24), 117.92 (C-22), 121.86 (C-1), 122.53 (C-6), 129.13 (C-20 or C-4), 129.14 (C-4 or C-20), 129.42 (C-5), 132.13 (C-21), 139.84 (C-25), 158.94 (C-13), 162.82 (C-23), 164.52 (C-2), 168.31 (C-18), 172.06 (C-8); MS (ESI) m/z: 665 $(MNa)^+$; IR (NaCl, cm^{-1}): 3304, 3099, 2967, 1737, 1602, 1570, 1508, 1485, 1465, 1436, 1391, 1337, 1298, 1247, 1187, 1135, 1069, 1043, 1015, 935, 868, 829, 763, 720, 665. Anal. calcd. for $C_{28}H_{38}N_2O_{11}S_2$ H_2O (%): C, 50.90; H, 6.10; N, 4.24. Found: C, 50.96; H, 5.92; N, 4.58.

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