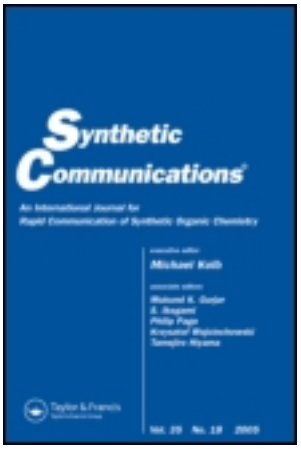

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Lipophilic δ-Amino Acid Conjugates from 4-Alkoxy-dithionaphthoic Acids

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Accepted author version posted online: 09 Nov 2011.Published online: 29 May 2012.

To cite this article: Anna C. Worth , Catherine E. Needham , Donald B. Franklin & Andrew J. Lampkins (2012): Facile Synthesis of Lipophilic δ-Amino Acid Conjugates from 4-Alkoxy-dithionaphthoic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:18, 2694-2706

To link to this article: http://dx.doi.org/10.1080/00397911.2011.565142

Synthetic Communications®, 42: 2694–2706, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.565142

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FACILE SYNTHESIS OF LIPOPHILIC δ-AMINO ACID CONJUGATES FROM 4-ALKOXY-DITHIONAPHTHOIC ACIDS

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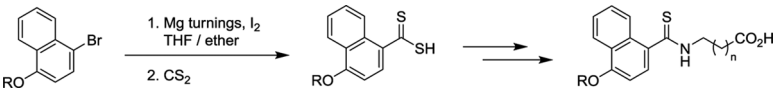
GRAPHICAL ABSTRACT



Abstract *Novel 4-alkoxy-dithionaphthoic acids were prepared and shown to be valuable synthons for* **δ***-amino acid conjugates. These dithioacids are efficiently synthesized and purified, stable to storage, and easily derivatized to facilitate thioacylation chemistry. To this end, we have demonstrated dithionaphthoic acids (**6**) to successfully undergo coupling with both protected and* un*protected amino acids, giving rise to stable thioamide conjugates (**8** and **9**).*

Keywords Bioconjugates; dithioacid; naphthalene; thioacylation; thioamide coupling

INTRODUCTION

The design of drug molecules and medicinal peptides whose biological target(s) lie within the central nervous system (CNS) poses a unique set of bioavailability challenges.[1] Unless directly administered (i.e., intracranial or epidural injection) into the CNS, these compounds must not only contend with normal metabolic processes but also penetrate the blood–brain barrier (BBB), a semipermeable barrier evolved to keep xenobiotics and toxins from reaching the brain. As such, many CNS disorders have either no or inadequate treatment modalities, including disorders whose pathology has been elucidated and biological targets identified [i.e., matrix metalloproteinase (MMP) -2, -9, and -12 in the progression of cerebral aneurysms,[2] prolyl oligopeptidase (POP) in schizophrenia and bipolar disorder,[3]

Received January 24, 2011.

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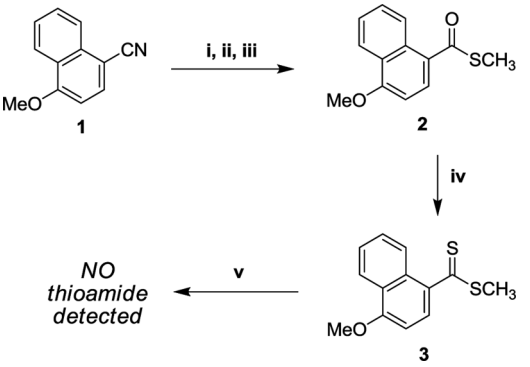
β-secretase in Alzheimer's disease,[4] and calpain in multiple sclerosis,[5] to name a few]. A focus area within our research is the directed synthesis of broadly applicable, metabolically stable scaffolds onto which precise customization would lead to novel families of druggable, biologically active peptide mimics that penetrate the CNS.

The two fundamental chemical moieties utilized to begin carrying out this task are a donor–acceptor 1,4-disubstutited naphthalene and a thioamide. To the former, a flat, rigid naphthalene system of this nature provides a lipophilic core with fluorescent properties that facilitate in vitro detection and assay development.[6] In addition, this core is synthetically accessible and readily amenable to further manipulation toward targeted derivatives. To the latter, a thioamide is isosteric to a traditional oxygenated amide (or peptide) group, more lipophilic, and potentially more stable to in vivo hydrolysis and protease-mediated cleavage.[7] Taken together, these two chemical accessories can dramatically influence the bioavailability and/or pharmacodynamics of any conjugate or agent containing this scaffold. Medicinal peptides, for instance, are ideal for this technology because their polar (oftentimes zwitterionic) nature and susceptibility to rapid in vivo degradation often limits their utility as pharmaceuticals.[8] As such, we envision amino acid conjugates of 4-alkoxy-naphthalene-1-thioamides to display (1) improved metabolic stability and (2) enhanced lipophilicity for preferential distribution into the CNS.

In this article, we describe a practical synthesis of new 4-alkoxy-dithionaphthoic acids, featuring a scalable and chromatography-free Grignard acylation using carbon disulfide. Further, we demonstrate the utility of this synthon by preparing thioamide-derived δ-peptide conjugates as scaffolds for drug discovery applications. The described preparations are user-friendly, amenable to scale-up, ideal for combinatorial synthesis, and broadly applicable to a wide variety of practitioners.

RESULTS AND DISCUSSION

Our initial attempt at preparing suitably functionalized naphthalenes reactive toward aminolysis focused upon 4-alkoxy-dithiomethylnaphthylates. We envisioned these scaffolds as suitable for thioamide ligation reactions and constructed a small family of derivatives in four to six efficient steps, depending upon the phenoxy substituent. A representative synthesis illustrating the preparation of methoxy derivative **3** is shown in Scheme 1. 4-Methoxy-naphthonitrile (**1**) was first saponified and converted to the acid chloride before nucleophilic acyl substitution with sodium methane thiolate afforded thiomethylester **2** in good yield. Lawesson's reagent was then employed to prepare the corresponding dithioester (**3**). While this reaction was oftentimes sluggish (typically taking 2–3 days in refluxing toluene), it provided consistently good yields of dithiomethylester product for every alkoxy substrate we prepared. However, in all cases, we were unable to observe any thioamide product—reactions were monitored via thin layer chromatography (TLC) and gas chromatography/mass spectrometry (GC/MS), and only starting material spots/peaks were observed even when reactions were allowed to stir for up to 14 days—when these dithiomethylnaphthylates were treated with primary or secondary aliphatic amines, even in the presence of standard acylation catalysts (e.g., dimethylaminopyridine, triethylamine, etc.). These results were surprising because thioacylations of amines using electron-rich benzoyl dithiomethylates are known to occur,



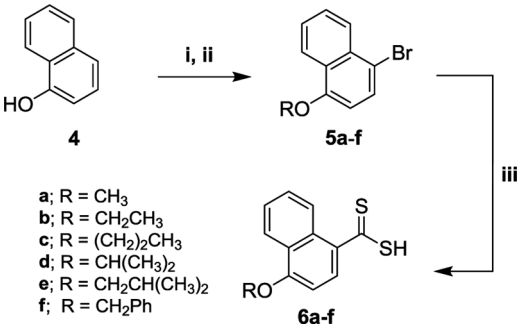
Scheme 1. Reagents and conditions: (i) NaOH, aqueous EtOH, reflux; (ii) $SOCl_2$, reflux; (iii) CH_3SNa, DMAP, THF/DMF; (iv) Lawesson's reagent, toluene, reflux; (v) 1° or 2° aliphatic amines, DMAP, THF/DMF.

albeit slowly (up to 10 days in some cases) and in moderate yields.[9] Thus, 4-alkoxy-dithiomethylnaphthylates such as **3** likely undergo aminolysis at even slower rates, rendering them essentially unreactive for practical synthetic purposes.

To generate more reactive thioacylating agents, we utilized dithionaphthoic acid groups and customized them for this chemistry. This functional group can be easily modified to esters that rapidly undergo aminolysis and similar nucleophilic acylation reactions. We envision this coupling reaction to be ideal for generating large families of thioamide peptide mimics combinatorially because it can be performed using the amino terminus of functionalized amino acids or polypeptide chains under extremely mild conditions. While a variety of methods exist for creating thioamides, the vast majority are not suitable for preparing bioconjugates of this nature. Perhaps the most widely utilized method is treatment of traditional oxygenated amides with thionating reagents such as phosphorus pentasulfide or Lawesson's reagent.[10] However, a selective conversion is oftentimes difficult in polyfunctionalized molecules with multiple carbonyl-containing functional groups. Other commonly employed methods (such as the Willgerodt–Kindler reaction[11] or alkylation of isothiocyanates[12]) typically employ harsh conditions (e.g., sustained elevated temperatures, acid catalysis, highly reactive reagents or intermediates, etc.) unsuitable for conjugating potentially labile biomolecules to a fixed scaffold. Thus, we believe 4-alkoxy-dithionaphthoic acids to be key synthons in preparing novel, functionalized thionaphthalene conjugates of this type.

We began our synthesis of 4-alkoxy-dithionaphthoic acids by bromination and subsequent etherification of 1-napthol (Scheme 2).[13] These alkyl ethers (**5**) were prepared to determine the optimal combination of pharmacodynamic properties (e.g., absorption, half-life, etc.) and CNS penetration of the resulting naphthalene conjugates. Factors affecting these key parameters, including molecular weight, ClogP, molecular volume and flexibility, and polar surface area, can be carefully modulated by variance of this alkyl group.

Bromo-ethers **5** were then converted to Grignard reagents and quenched with carbon disulfide to afford dithionaphthoic acids **6**. This protocol was found superior to others attempted (in situ thioacylation of organolithium or Gilman cuprate

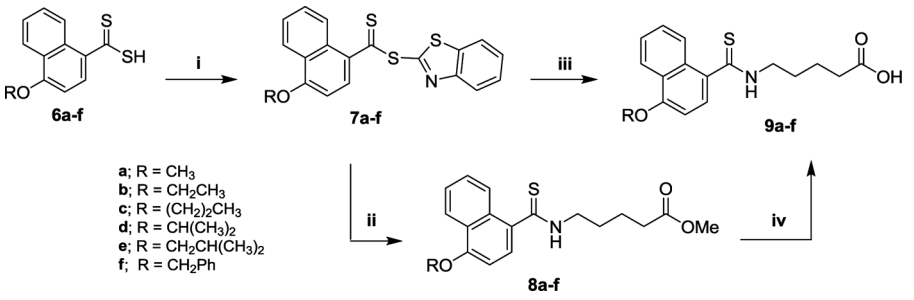


Scheme 2. Reagents and conditions: (i) NBS, CH_3CN; (ii) RI, K_2CO_3, CH_3CN; (iii) (1) Mg turnings, I_2, THF/ether (2); CS_2.

nucleophiles instead of Grignard reagents), and gave consistent, scalable (50 mg to 5 g) yields in our hands. Furthermore, this reaction does not require chromatographic purification, as a series of simple acid/base extractions efficiently separate the (blood-red) dithioacid products from the neutral organic starting materials and by-products.

These 4-alkoxy-dithionaphthoic acids (**6**) were then treated with mercaptobenzothiazole disulfide to give dithiazoyl esters (**7**, Scheme 3). These esters are extremely reactive thioacylating agents, in contrast to dithiomethylates **3** (*vide supra*), yet are stable for months in ambient conditions[14].

We have shown that dithioesters **7** readily undergo aminolysis with amino acid derivatives. When these dithioesters (**7**) are treated with protected amino acids (such as 5-amino methylvalerate, shown) the resulting thioamides (**8**) are generated in reasonable (54–76%) yield. The methyl esters within **8** can be selectively hydrolyzed in the presence of thioamides to generate thioacylated amino acids **9** in excellent yields. In addition, treatment of **7** with *un*protected amino acids also resulted in thioamide coupling in moderate, albeit reproducible, yields. This functional group specificity allows for direct thioacylation of the amino terminus within highly functionalized polypeptides or mimics thereof, facilitating expedited syntheses and diminished usage of protecting groups.



Scheme 3. Reagents and conditions: (i) MBTS, PPh_3, toluene/THF; (ii) 5-amino-methylvalerate HCl, DMAP, CH_2Cl_2/DMF; (iii) 5-aminovaleric acid, ultrasonication, DMF; (iv) NaOH, H_2O/THF.

CONCLUSION

In conclusion, we have developed a short, scalable synthesis for 4-alkoxydithionaphthoic acids which can be readily coupled to the amino terminus of (both protected and unprotected) δ-amino acids by way of a thioamide bond. We are currently evaluating the bioavailability and CNS permeability of this novel class of molecules and are investigating functionalized derivatives designed as selective agents toward Alzheimer's disease and other neurodegenerative disorders. The results of these investigations will be presented in due course.

EXPERIMENTAL

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified. Tetrahydrafuran (THF), toluene, CH_2Cl_2, and dimethylformamide (DMF) were degassed in 16 L drums and passed through two sequential purification columns (activated alumina; molecular sieves for DMF) under a positive argon atmosphere. Thin-layer chromatography (TLC) was performed on aluminum sheets with visualization with ultraviolet (UV) light or staining. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Brüker (ARX series) spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS; 0.00 ppm). Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), sept (septet), b (broad), and m (multiplet). Mass (MS) spectra were recorded on a ThermoElectron LCQ Deca XP MAX LC-MS.

S-Methyl-4-methoxynaphthalene-1-carbothioate, 2

To a solution of nitrile **1** (1.00 g, 5.46 mmol) and ethanol (95%, 40 mL) in a thick-walled pressure tube was added 6 N sodium hydroxide (20 mL). The reaction vessel was then sealed and heated to 100–120 °C, and the mixture was stirred rapidly overnight. After cooling to rt, the ethanol was removed in vacuo, and the remaining aqueous residue was acidified with concentrated HCl to pH < 3 and extracted with EtOAc (50 mL $\times$ 3). The combined organic extracts were washed with water and brine, dried with $MgSO_4$, and concentrated to afford the crude naphthoic acid (1.10 g, 5.44 mmol), which was dissolved in $SOCl_2$ (25 mL) and heated to reflux for 2 h. The solvent was then removed in vacuo. The remaining crude brown residue was then dissolved in dry THF (25 mL) and slowly added to a solution of sodium methane thiolate (0.57 g, 8.16 mmol), triethylamine (2 mL), dry THF (25 mL), and dry DMF (5 mL) in a round-bottomed flask. The resulting solution was allowed to stir under a blanket of argon overnight. The reaction mixture was then diluted with methylene chloride and washed with 10% aqueous. HCl, water, and brine. After drying over $MgSO_4$, the organic layer was evaporated and purified using flash chromatography (2:1 hexanes/methylene chloride eluent system) to afford **2** (1.027 g, 81% from **1**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ2.52 (s, 3H), 4.04 (s, 3H), 6.78 (d, $J = 8.4$ Hz, 1H), 7.50–7.64 (m, 2H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.31 (d, $J = 8.1$ Hz, 1H), 8.68 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ12.4, 55.6, 102.0,

121.9, 125.0, 125.4, 125.7, 127.5, 128.3, 129.8, 130.5, 158.9, 193.2. MS (ESI) calcd. for $C_{13}H_{12}O_2S$ $(M)^-$ 232.06, found 232.22.

S-Methyl-4-methoxynaphthalene-1-carbodithioate, 3

Lawesson's reagent (2.61 g, 6.47 mmol) was added to a solution of **2** (500 mg, 2.15 mmol) in dry toluene (80 mL), and the resulting mixture was heated to reflux for 2 days under argon. Upon cooling to rt, the solid was removed via filtration and rinsed with toluene. The filtrate was concentrated, and the remaining residue was purified using flash chromatography (5:3 hexanes/methylene chloride eluent system) to afford **3** (404 mg, 76%) as a red solid: ^{1}H NMR ($CDCl_3$) δ2.83 (s, 3H), 4.03 (s, 3H), 6.77 (d, $J = 7.8$ Hz, 1H), 7.46–7.55 (m, 3H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.29 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ20.9, 55.4, 102.1, 121.8, 124.7, 125.0, 125.4, 127.1, 130.4, 137.9, 156.7, 231.2. MS (ESI) calcd. for $C_{13}H_{12}OS_2$ $(M)^-$ 248.03, found 248.28.

General Procedure for Alkylating 4-Bromo-1-naphthol

An alkyl halide (24.1 mmol) was added to a stirring suspension of 4-bromonaphthol (5.68 mmol) and K_2CO_3 (17.1 mmol) in acetonitrile (40 mL). After stirring at room temperature for 30 min, the reaction was warmed to 60 °C overnight. Upon cooling to rt, the reaction was quenched with water and the acetonitrile evaporated. The crude residue was dissolved in dichloromethane and sequentially washed with water, 0.5 M NaOH, and brine. The organic layer was then dried over $MgSO_4$, filtered, evaporated, and purified using flash chromatography (hexanes/dicholoromethane 15:1).

4-Bromo-1-methoxynaphthalene, 5a. Colorless oil, yield = 91%. ^{1}H NMR ($CDCl_3$) δ3.95 (3H, s), 6.60 (1H, d, $J = 8.4$ Hz), 7.60 (2H, m), 7.70 (1H, d, $J = 8.4$ Hz), 8.30 (2H, m). ^{13}C NMR ($CDCl_3$) δ55.9, 104.9, 113.6, 122.5, 126.2, 127.1, 127.2, 128.3, 129.8, 132.8, 155.5.

4-Bromo-1-ethoxynaphthalene, 5b. Colorless solid, yield = 88%. ^{1}H NMR ($CDCl_3$) δ1.44 (t, $J = 6.9$ Hz, 3H), 3.98 (q, $J = 6.9$ Hz, 2H), 6.46 (d, $J = 8.4$ Hz, 1H), 7.42–7.55 (m, 3H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ14.3, 63.4, 104.8, 112.5, 122.1, 125.4, 126.3, 126.5, 127.2, 129.1, 132.0, 154.1

4-Bromo-1-propoxynaphthalene, 5c. Colorless solid, yield = 91%. ^{1}H NMR ($CDCl_3$) δ1.05 (t, $J = 7.5$ Hz, 3H), 1.83 (sext, $J = 7.5$ Hz, 2H), 3.89 (t, $J = 6.3$ Hz, 2H), 6.47 (d, $J = 8.4$ Hz, 1H), 7.41–7.54 (m, 3H), 8.11 (d, $J = 8.4$ Hz, 1H), 8.26 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ10.7, 22.5, 69.7, 105.1, 112.8, 122.5, 125.7, 126.7, 126.9, 127.6, 129.5, 132.4, 154.6.

4-Bromo-1-isopropoxynaphthalene, 5d. Colorless solid, yield = 69%. ^{1}H NMR ($CDCl_3$) δ1.40 (d, $J = 6.0$ Hz, 6H), 4.65 (sept, 6.0 Hz, 1H), 6.63 (d, $J = 8.4$ Hz, Hz, 1H), 7.43–7.61 (m, 3H), 8.12 (d, $J = 8.4$ Hz, 1H), 8.27 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ21.6, 70.2, 106.5, 112.4, 122.4, 125.3, 126.4, 127.2, 127.4, 129.1, 132.3, 153.1.

4-Bromo-1-isobutoxynaphthalene, 5e. Colorless oil, yield = 71%. ^{1}H NMR ($CDCl_3$) δ 1.09 (d, $J = 6.9$ Hz, 6H), 2.20 (m, $J = 6.6$ Hz, 1H), 3.81 (d, $J = 6.6$ Hz, 2H), 6.58 (d, $J = 8.1$ Hz, 1H), 7.48–7.7.60 (m, 3H), 8.14 (d, $J = 9.0$ Hz, 1H), 8.30 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 18.9, 27.9, 74.1, 104.7, 112.4, 122.0, 125.3, 126.3, 126.5, 127.2, 129.0, 132.0, 154.2. MS (ESI) calcd. for $C_{14}H_{15}BrO$ $(M)^+$ 278.03, found 278.12.

4-Bromo-1-benzyloxynaphthalene, 5f. Colorless solid, yield = 79%. ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 2H), 6.75 (d, $J = 8.4$ Hz, 1H), 7.41–7.78 (m, 8H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.37 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 70.3, 106.0, 113.5, 122.7, 126.3, 129.8, 126.9, 127.4, 127.9, 128.0, 128.8, 129.5, 132.5, 136.8, 154.2.

General Procedure for Grignard Reaction of 5 with CS_2

A solution of **5** (4.12 mmol) dissolved in THF (3 mL) under argon was added to magnesium turnings (7.38 mmol) in flame-dried glassware covered with dry ether (1 mL). A crystal of iodine was then added, and the suspension warmed to reflux with stirring for 3 h to facilitate Grignard initiation/formation. Upon cooling to room temperature, carbon disulfide (13 mmol) was added dropwise, and the resulting mixture was allowed to stir overnight. The reaction was then poured onto ice (30 g) and diluted with hexanes (20 mL). The (red) aqueous layer was separated, acidified with 3 M HCl, and extracted with ether. The organic extracts were pooled, dried over $MgSO_4$, and concentrated to dryness. No further purification was necessary.

4-Methoxy-dithionaphthoic acid, 6a. Red oil that solidified upon standing, yield = 64%. ^{1}H NMR ($CDCl_3$)δ 3.96 (s, 3H), 6.66 (br, 1H), 6.67 (d, $J = 8.1$ Hz, 1H), 7.44–7.56 (m, 2H), 7.69 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.1$ Hz, 1H), 8.46 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 55.7, 102.2, 122.1, 125.2, 125.5, 125.8, 127.7, 129.7, 138.7, 157.7, 229.1. MS (ESI) calcd. for $C_{12}H_9OS_2$ $(M-H)^-$ 233.02, found 233.27.

4-Ethoxy-dithionaphthoic acid, 6b. Red oil that solidified upon standing, yield = 64%. ^{1}H NMR ($CDCl_3$)δ 1.56 (t, $J = 6.9$ Hz, 3H), 4.23 (q, $J = 6.9$ Hz, 2H), 6.70 (br, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 7.48–7.60 (m, 2H), 7.73 (d, $J = 8.1$ Hz, 1H), 8.33 (d, $J = 8.1$ Hz, 1H), 8.50 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 14.7, 64.1, 103.0, 122.4, 125.3, 125.7, 125.8, 126.1, 127.8, 129.9, 138.6, 157.3, 229.2. MS (ESI) calcd. for $C_{13}H_{13}OS_2$ $(M+H)^+$ 249.03, found 249.21.

4-Propoxy-dithionaphthoic acid, 6c. Red oil that solidified upon standing, yield = 62%. ^{1}H NMR ($CDCl_3$) δ 1.14 (t, $J = 7.5$ Hz, 3H), 1.96 (sext, $J = 7.5$ Hz, 2H), 4.13 (t, $J = 6.3$ Hz, 2H), 6.70 (br, 1H), 6.72 (d, $J = 8.1$ Hz, 1H), 7.48–7.61 (m, 2H), 7.73 (d, $J = 8.4$ Hz, 1H), 8.34 (d, $J = 8.1$ Hz, 1H), 8.51 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 10.8, 22.6, 70.1, 103.0, 122.4, 125.4, 125.8, 125.9, 126.2, 127.8, 130.0, 138.7, 157.5, 229.2. MS (ESI) calcd. for $C_{14}H_{13}OS_2$ $(M-H)^-$ 261.05, found 261.20.

4-Isopropoxy-dithionaphthoic acid, 6d. Red oil that solidified upon standing, yield = 72%. ^{1}H NMR ($CDCl_3$) δ 1.48 (d, $J = 6.0$ Hz, 6H), 4.82 (sept, $J = 6.0$ Hz, 1H), 6.71 (br, 1H), 6.76 (d, $J = 8.1$ Hz, 1H), 7.48–7.62 (m, 2H), 7.76 (d, $J = 8.4$ Hz,

1H), 8.34 (d, $J = 8.4$ Hz, 1H), 8.52 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.0, 70.7, 104.1, 122.7, 125.3, 125.7, 126.2, 126.4, 127.8, 130.1, 138.4, 156.3, 229.1. MS (ESI) calcd. for $C_{14}H_{13}OS_2$ $(M - H)^-$ 261.05, found 261.14.

4-Isobutoxy-dithionaphthoic acid, 6e. Red oil that solidified upon standing, yield = 79%. ^{1}H NMR ($CDCl_3$) δ 1.13 (d, $J = 6.6$ Hz, 6H), 2.27 (m, $J = 6.6$ Hz, 1H), 3.94 (d, $J = 6.3$ Hz, 2H), 6.70 (br, 1H), 6.72 (d, $J = 8.1$ Hz, 1H), 7.46–7.61 (m, 2H), 7.74 (d, $J = 8.1$ Hz, 1H), 8.34 (d, $J = 8.4$ Hz, 1H), 8.51 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 19.4, 28.3, 74.7, 102.9, 122.3, 125.3, 125.8, 125.8, 126.1, 127.7, 129.9, 138.6, 157.4, 229.1. MS (ESI) calcd. for $C_{15}H_{15}OS_2$ $(M - H)^-$ 275.06, found 275.24.

4-Benzyloxy-dithionaphthoic acid, 6f. Red oil that solidified upon standing, yield = 68%. ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 2H), 6.69 (br, 1H), 6.79 (d, $J = 8.1$ Hz, Hz, 1H), 7.35–7.60 (m, 7H), 7.79 (d, $J = 8.1$ Hz, 1H), 8.37 (d, $J = 8.4$ Hz, 1H), 8.48 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 70.2, 103.5, 122.2, 125.1, 125.5, 125.6, 125.8, 127.1, 127.6, 128.0, 128.5, 129.7, 136.1, 138.9, 156.6, 229.0. MS (ESI) calcd. for $C_{18}H_{15}OS_2$ $(M + H)^+$ 311.05, found 311.21.

General Procedure for Dithiazoyl Ester Synthesis from Dithioacids 6

A THF (5 mL) solution of **6** (0.262 mmol) was added dropwise to a stirring suspension of 2,2′-dithiobis[benzothiazole] (0.210 mmol) and triphenylphosphine (0.210 mmol) in toluene (5 mL). After being heated to reflux for 2 h, the reaction was cooled to room temperature. The reaction mixture was then washed with dilute HCl solution and water and evaporated under reduced pressure. The crude residue was purified using flash chromatography (hexanes/dichloromethane 1:1). Trace amounts of PPh_3 were removed by dissolving the resulting orange solid in a minimal amount of CH_2Cl_2 and precipitating with cold hexanes. The red filtrate was concentrated to afford pure dithiazoyl ester.

1-(2-Benzothiazolyl)-4-methoxy-dithionaphthylate, 7a. Red solid, yield = 68%. ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 6.83 (d, $J = 8.1$ Hz, 1H), 7.42–7.61 (m, 2H), 7.70-7.77 (m, 2H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 8.33 (d, $J = 9.3$ Hz, 1H), 8.47 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 55.9, 102.4, 121.6, 122.3, 123.7, 124.9, 126.1, 126.6, 128.0, 128.4, 128.6, 131.5, 132.2, 132.3, 136.5, 152.3, 158.1, 160.1, 224.2. MS (ESI) calcd. for $C_{19}H_{14}NOS_3$ $(M + H)^+$ 368.02, found 367.91.

1-(2-Benzothiazolyl)-4-ethoxy-dithionaphthylate, 7b. Red solid, yield = 57%. ^{1}H NMR ($CDCl_3$) δ 1.58 (t, $J = 6.9$ Hz, 3H), 4.27 (q, $J = 6.9$ Hz, 2H), 6.79 (d, $J = 8.4$ Hz, 1H), 7.44–7.47 (m, 2H), 7.69–7.75 (m, 2H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), 8.14 (d, $J = 7.2$ Hz, 1H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.46 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 14.7, 64.2, 103.0, 121.6, 122.4, 123.7, 124.9, 126.0, 126.2, 126.6, 126.9, 128.0, 130.8, 131.5, 133.5, 136.3, 136.5, 152.3, 157.6, 224.2. MS (ESI) calcd. for $C_{20}H_{16}NOS_3$ $(M + H)^+$ 382.03, found 382.11.

1-(2-Benzothiazolyl)-4-propoxy-dithionaphthylate, 7c. Red solid, yield = 70%. ^{1}H NMR ($CDCl_3$) δ 1.15 (t, $J = 7.5$ Hz, 3H), 1.99 (sext, $J = 7.5$ Hz,

2H), 4.17 (t, $J = 6.3$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 1H), 7.47–7.55 (m, 2H), 7.69–7.76 (m, 2H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.97 (d, $J = 7.5$ Hz, 1H), 8.15 (d, $J = 7.2$ Hz, 1H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.47 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 10.7, 22.5, 70.1, 103.0, 121.6, 122.3, 123.7, 124.9, 126.0, 126.2, 126.6, 126.9, 128.4, 128.6, 131.5, 132.2, 132.3, 152.3, 157.7, 160.0, 224.2. MS (ESI) calcd. for $C_{21}H_{18}NOS_3$ $(M + H)^+$ 396.05, found 396.21.

1-(2-Benzothiazolyl)-4-isopropoxy-dithionaphthylate, 7d. Red solid, yield = 77%. ^{1}H NMR ($CDCl_3$) δ 1.45 (d, $J = 6.0$ Hz, 6H), 4.79 (sept, $J = 6.0$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 7.42–7.48 (m, 2H), 7.69–7.79 (m, 2H), 7.80 (d, $J = 8.1$ Hz, Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 8.14 (d, $J = 7.8$ Hz, 1H), 8.33 (d, $J = 8.4$ Hz, 1H), 8.47 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$)δ 22.0, 70.8, 104.1, 121.3, 121.7, 122.7, 123.7, 124.9, 126.0, 126.3, 127.1, 128.0, 128.5, 128.7, 131.6, 132.2, 132.4, 152.3, 156.7, 224.1. MS (ESI) calcd. for $C_{21}H_{18}NOS_3$ $(M + H)^+$ 396.05, found 396.33.

1-(2-Benzothiazolyl)-4-isobutoxy-dithionaphthylate, 7e. Red solid, yield = 58%. ^{1}H NMR ($CDCl_3$) δ 1.15 (d, $J = 6.6$ Hz, 6H), 2.30 (m, $J = 6.6$ Hz, 1H), 3.98 (d, $J = 6.3$ Hz, 2H), 6.80 (d, $J = 8.1$ Hz, 1H), 7.40–7.61 (m, 2H), 7.70–7.78 (m, 2H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 8.37 (d, $J = 7.5$ Hz, 1H), 8.48 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.4, 28.4, 74.8, 103.0, 121.6, 122.3, 123.7, 124.9, 126.0, 126.2, 126.6, 128.0, 128.4, 128.6, 130.9, 131.5, 132.3, 136.5, 152.3, 157.7, 224.1. MS (ESI) calcd. for $C_{22}H_{20}NOS_3$ $(M + H)^+$ 410.06, found 410.32.

1-(2-Benzothiazolyl)-4-benzyloxy-dithionaphthylate, 7f. Red solid, yield = 62%. ^{1}H NMR ($CDCl_3$)δ 5.33 (s, 2H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.40–7.63 (m, 9H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 8.41 (d, $J = 8.4$ Hz, 1H), 8.47 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 70.5, 103.7, 121.7, 122.5, 123.8, 124.9, 126.0, 126.2, 126.6, 127.4, 128.1, 128.3, 128.4, 128.8, 130.9, 132.2, 136.3, 136.6, 136.7, 152.3, 157.1, 160.1, 224.2. MS (ESI) calcd. for $C_{25}H_{18}NOS_3$ $(M + H)^+$ 443.05, found 443.22.

General Procedure for Coupling Dithiazoyl Esters 7 with 5-Amino-methylvalerate

A mixture of **7** (0.545 mmol), 5-amino-methylvalerate HCl (0.599 mmol) and DMAP (0.654 mmol) was added DMF (3 mL) and dichloromethane (3 mL). The resulting solution was allowed to stir overnight. The solvent was then evaporated, and the crude residue was dissolved in dichloromethane (50 mL) and washed with dilute HCl and water. The organic layer was then concentrated to dryness, and the product purified using flash chromatography (hexanes/ethyl acetate 3:1) to afford pure thioamide **8**.

Methyl-5-(4-methoxynaphthalene-1-thioamido)pentanoate, 8a. Colorless oil, yield = 73%. ^{1}H NMR ($CDCl_3$) δ 1.74–1.85 (m, 4H), 2.40 (t, $J = 6.6$ Hz, 2H), 3.65 (s, 3H), 3.90 (q, $J = 6.9$ Hz, 2H), 4.01 (s, 3H), 6.76 (d, $J = 7.8$ Hz, 1H), 7.45–7.55 (m, 3H), 7.70 (br, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 8.28 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.2, 27.5, 33.4, 45.8, 51.6, 55.7, 102.9, 122.4, 124.6, 125.4, 125.6, 125.6, 127.4, 130.1, 134.5, 156.5, 173.8, 200.5. MS (ESI) calcd. for $C_{18}H_{22}NOS_3$ $(M + H)^+$ 332.12, found 332.28.

Methyl-5-(4-ethoxynaphthalene-1-thioamido)pentanoate, 8b. Colorless solid, yield = 55%. ^{1}H NMR ($CDCl_3$) δ1.56 (t, $J = 6.9$ Hz, 3H), 1.78 (m 4H), 2.40 (t, $J = 6.9$ Hz, 2H), 3.66 (s, 3H), 3.89 (q, $J = 6.9$ Hz, 2H), 4.22 (q, $J = 6.9$ Hz, 2H), 6.74 (d, $J = 8.1$ Hz, 1H), 7.47–7.55 (m, 3H), 7.70 (br, 1H), 8.11 (d, $J = 7.2$ Hz, 1H), 8.32 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.7, 22.2, 27.5, 33.4, 45.8, 51.6, 64.0, 103.6, 122.5, 124.5, 125.5, 125.5, 125.7, 127.4, 130.1, 134.2, 155.8, 173.8, 200.6. MS (ESI) calcd. for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.14, found 346.26.

Methyl-5-(4-propoxynaphthalene-1-thioamido)pentanoate, 8c. Colorless oil, yield = 76%. ^{1}H NMR ($CDCl_3$) δ 1.13 (t, $J = 7.5$ Hz, 3H), 1.77 (m, 4H), 1.95 (sext, 7.5 Hz, 2H), 2.38 (t, $J = 6.9$ Hz, 2H), 3.64 (s, 3H), 3.87 (q, $J = 6.9$ Hz, 2H), 4.10 (t, $J = 6.6$ Hz, 2H), 6.73 (d, $J = 8.1$ Hz, 1H), 7.44–7.54 (m, 3H), 7.73 (br, 1H), 8.10 (d, $J = 7.2$ Hz, 1H), 8.32 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 10.8, 22.3, 22.6, 27.5, 33.4, 45.9, 51.7, 69.9, 103.6, 122.5, 124.6, 125.5, 125.6, 125.7, 127.4, 130.2, 134.2, 155.9, 173.8, 200.6. MS (ESI) calcd. for $C_{20}H_{26}NO_3S$ $(M + H)^+$ 360.16, found 360.32.

Methyl-5-(4-isopropoxynaphthalene-1-thioamido)pentanoate, 8d. Colorless oil, yield = 54%. ^{1}H NMR ($CDCl_3$) 1.45 (d, $J = 6.0$ Hz, 6H), 1.79 (m, 4H), 2.40 (t, $J = 6.6$ Hz, 2H), 3.65 (s, 3H), 3.90 (q, $J = 6.6$ Hz, 2H), 4.77 (sept, $J = 6.0$ Hz, Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 7.43–7.54 (m, 3H), 7.68 (br, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 8.30 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.0, 27.5, 29.7, 33.4, 45.8, 51.6, 70.5, 105.1, 122.8, 124.5, 125.4, 125.6, 126.4, 127.3, 130.3, 134.0, 154.8, 173.8, 200.7. MS (ESI) calcd. for $C_{20}H_{26}NO_3S$ $(M + H)^+$ 360.16, found 360.41.

Methyl-5-(4-isobutoxynaphthalene-1-thioamido)pentanoate, 8e. Colorless solid, yield = 76%. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, $J = 6.9$ Hz, 6H), 1.78 (m, 4H), 2.29 (m, $J = 6.9$ Hz, 1H), 2.39 (t, $J = 6.9$ Hz, 2H), 3.64 (s, 3H), 3.88 (q, $J = 6.6$ Hz, 2H), 3.90 (d, $J = 6.3$ Hz, 2H), 6.72 (d, $J = 8.1$ Hz, 1H), 7.44–7.54 (m, 3H), 7.71 (br, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 8.33 (d, $J = 7.8$ Hz, 1H).^{13}C NMR ($CDCl_3$) δ19.2, 22.1, 27.3, 28.2, 33.2, 45.7, 51.5, 74.5, 103.4, 122.3, 124.4, 125.3, 125.4, 125.6, 127.2, 130.0, 134.0, 155.8, 173.6, 200.4. MS (ESI) calcd. for $C_{21}H_{28}NO_3S$ $(M + H)^+$ 374.17, found 374.31.

Methyl-5-(4-benzyloxynaphthalene-1-thioamido)pentanoate, 8f. Colorless oil, yield = 61%. ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 4H), 2.38 (t, $J = 6.6$ Hz, 2H), 3.64 (s, 3H), 3.87 (q, $J = 6.6$ Hz, 2H), 5.26 (s, 2H), 6.80 (d, $J = 8.1$ Hz, 1H), 7.35–7.56 (m, 8H), 7.71 (br, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.37 (d, $J = 6.9$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.2, 27.4, 33.3, 45.8, 51.6, 70.2, 104.2, 122.4, 124.6, 125.2, 125.6, 127.2, 127.4, 128.0, 128.6, 130.2, 134.6, 136.6, 155.3, 173.7, 200.3. MS (ESI) calcd. for $C_{24}H_{26}NO_3S$ $(M + H)^+$ 408.16, found 408.18.

General Procedure for Preparing Thioamide-Derived Amino Acids 9

Method A. A suspension of **7** (0.27 mmol), 5-amniovaleric acid (0.30 mmol), and DMF (5 mL) in a sealed vial was allowed to sonicate for 3 h. The solvent was then evaporated, and the crude residue was dissolved in dichloromethane (50 mL) and washed with dilute HCl and water. The organic layer was then concentrated

to dryness, and the product was purified via flash chromatography (0–3% MeOH in CH_2Cl_2) to afford pure **9**.

Method B. A solution of **8** (0.27 mmol) in THF (3 mL) and 1 M NaOH (2 mL) was allowed to stir at 50 °C for 3 h. The organic solvent was then removed in vacuo and the aqueous residue was acidified with concentrated. HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated, and purified using flash chromatography (0–3% MeOH in CH_2Cl_2) to afford pure **9**.

5-(4-Methoxynaphthalene-1-thioamido)pentanoic acid, 9a. Colorless solid, yield = 63% (Method A), 96% (Method B). ^{1}H NMR (DMSO-d_6) δ1.58–1.73 (m, 4H), 2.29 (br, 2H), 3.31 (br, 2H), 3.99 (s, 3H), 6.98 (m, 1H), 7.55 (m, 3H), 8.02–8.41 (m, 2H), 10.48 (br, 1H), 12.14 (br, 1H). ^{13}C NMR (DMSO-d_6) δ 21.8, 28.3, 33.0, 44.9, 55.5, 102.8, 121.2, 124.2, 125.2, 125.9, 126.7, 129.6, 130.7, 134.2, 155.6, 174.1, 197.7. MS (ESI) calcd. for $C_{17}H_{20}NO_3S$ $(M+H)^+$ 318.11, found 318.40.

5-(4-Ethoxynaphthalene-1-thioamido)pentanoic acid, 9b. Colorless solid, yield = 68% (Method A), 98% (Method B). ^{1}H NMR (20:1 $CDCl_3$/DMSO-d_6) δ 1.52 (t, J = 6.9 Hz, 3H), 1.73–1.82 (m, 4H), 2.34 (t, J = 8.1 Hz, 2H), 3.82 (t, J = 6.3 Hz, 2H), 4.19 (q, J = 6.9 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 7.38–7.49 (m, 3H), 8.05 (d, J = 8.4 Hz, 1H), 8.25, (d, J = 8.1 Hz, 1H), 9.60 (br, 1H).^{13}C NMR (20:1 $CDCl_3$/DMSO-d_6) δ 14.5, 22.2, 27.0, 33.5, 45.7, 63.7, 103.5, 122.0, 124.8, 124.8, 125.1, 125.2, 126.8, 130.1, 134.5, 154.9, 175.2, 199.2. MS (ESI) calcd. for $C_{18}H_{22}NO_3S$ $(M+H)^+$ 332.12, found 332.38.

5-(4-Propoxynaphthalene-1-thioamido)pentanoic acid, 9c. Colorless solid, yield = 64% (Method A), 96% (Method B). ^{1}H NMR (20:1 $CDCl_3$/DMSO-d_6) δ 1.13 (t, J = 7.5 Hz, 3H), 1.76–1.81 (m, 4H), 1.95 (sext, J = 6.3 Hz, 2H), 2.37 (t, J = 6.9 Hz, 2H), 3.85 (br, 2H), 4.12 (br, 2H), 6.78 (d, J = 8.1 Hz, 1H), 7.41–7.54 (m, 3H), 8.07 (d, J = 7.8 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 9.70 (br, 1H).^{13}C NMR (20:1 $CDCl_3$/DMSO-d_6)δ 10.7, 22.4, 22.4, 27.1, 33.7, 45.9, 69.8, 103.6, 122.1, 125.0, 125.3, 125.4, 127.0, 130.3, 134.6, 155.2, 175.3, 199.3. MS (ESI) calcd. for $C_{19}H_{24}NO_3S$ $(M+H)^+$ 346.14, found 346.22.

5-(4-Isopropoxynaphthalene-1-thioamido)pentanoic acid, 9d. Colorless solid, yield = 57% (Method A), 97% (Method B). ^{1}H NMR ($CDCl_3$) δ1.45 (d, J = 6.0 Hz, 6H), 1.85 (m, 4H), 2.49 (t, J = 6.3 Hz, 2H), 3.95 (q, J = 6.3 Hz, 2H), 4.76 (sept, J = 6.0 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 7.27–7.53 (m, 3H), 7.78 (br, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 12.01 (br, 1H).\$^{13}$C NMR ($CDCl_3$) δ 22.0, 27.5, 29.7, 33.5, 45.9, 70.5, 105.0, 112.3, 121.3, 122.7, 124.6, 125.6, 127.2, 130.0, 140.3, 154.7, 179.2, 190.9. MS (ESI) calcd. for $C_{19}H_{24}NO_3S$ $(M+H)^+$ 346.14, found 346.28.

5-(4-Isobutoxynaphthalene-1-thioamido)pentanoic acid, 9e. Colorless solid, yield = 55% (Method A), 95% (Method B). ^{1}H NMR (20:1 $CDCl_3$/DMSO-d_6) δ 1.09 (d, J = 6.6 Hz, 6H), 1.73–1.81 (m, 4H), 2.23 (m, J = 6.6 Hz, 1H), 2.33 (t, J = 9.3 Hz, 2H), 3.82–3.89 (m, 4H), 6.73 (d, J = 6.0 Hz, 1H), 7.37–7.49 (m, 3H), 8.05 (d, J = 7.2 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 9.60 (br, 1H).

^{13}C NMR (20:1 $CDCl_3$/DMSO-d_6) δ 19.3, 22.4, 27.1, 28.2, 33.7, 45.9, 74.6, 103.6, 122.0, 125.0, 125.3, 125.4, 125.4, 127.0, 130.3, 134.6, 155.2, 175.4, 199.3. MS (ESI) calcd. for $C_{20}H_{26}NO_3S$ $(M+H)^+$ 360.16, found 360.34.

5-(4-Benzyloxynaphthalene-1-thioamido)pentanoic acid, 9f. Colorless solid, yield = 69% (Method A), 97% (Method B). ^{1}H NMR (DMSO-d_6) δ 1.56–1.77 (m, 4H), 2.29 (t, J = 7.5 Hz, 2H), 3.74 (q, J = 6.9 Hz, 2H), 5.36 (s, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.30–7.7.45 (m, 4H), 7.52–7.56 (m, 4H), 7.98–8.01 (m, 1H), 8.25–8.28 (m, 1H), 10.48 (t, J = 5.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 22.1, 26.7, 33.3, 45.1, 69.5, 104.8, 121.6, 124.3, 124.7, 125.0, 125.6, 126.9, 127.3, 127.8, 128.5, 130.0, 134.7, 136.9, 153.7, 174.3, 197.9. MS (ESI) calcd. for $C_{23}H_{24}NO_3S$ $(M+H)^+$ 394.14, found 394.28.

ACKNOWLEDGMENTS

This research was supported by an award from the Research Corporation for Science Advancement and Samford University. A. C. W. was supported by an Alabama Power Fellowship. The authors also thank Mike Jablonsky (University of Alabama, Birmingham) and Brian Gregory (Samford University) for use of their spectroscopic equipment facilities.

REFERENCES

1. Su, Y.; Sinko, P. J. Drug delivery across the blood–brain barrier: Why is it difficult? How to measure and improve it? *Expert Opin. Drug Deliv.* **2006**, *3*, 419–435.
2. Aoki, T.; Kataoka, H.; Ishibashi, R.; Nozaki, K.; Hashimoto, N. Cathepsin, B. K, and S are expressed in cerebral aneurysms and promote the progression of cerebral aneurysms. *Stroke* **2008**, *39*, 2603–2610
3. Tarrago, T.; Sabido, E.; Kogan, M.; De Oliveira, E.; Giralt, E. Primary structure, recombinant expression, and homology modeling of human brain prolyl oligopeptidase, an important therapeutic target in the treatment of neuropsychiatric diseases. *J. Pept. Sci.* **2005**, *11*, 283–287.
4. Citron, M. β-secretase as a target for the treatment of Alzheimer's disease. *J. Neurosci. Res.* **2002**, *70*, 373–379.
5. Imam, S. A.; Guyton, M. K.; Haque, A.; Vandenbark, A.; Tyor, W. R.; Ray, S. K.; Banik, N. L. Increased calpain correlates with Th1 cytokine profile in PBMCs from MS patients. *J. Neuroimmunol.* **2007**, *190*, 139–145.
6. (a) Chakraborty, C.; Hsu, C. H.; Wen, Z. H.; Lin, C. S. Recent advances of fluorescent technologies for drug discovery and development. *Curr. Pharm. Des.* **2009**, *15*, 3552–3570; (b) Sapsford, K. E.; Berti, L.; Medintz, I. L. Materials for fluorescence resonance energy transfer analysis: Beyond traditional donor–acceptor combinations. *Angew. Chem. Int. Ed.* **2006**, *45*, 4562–4588.
7. Bardi, R.; Piazzesi, A. M.; Toniolo, C.; Jensen, O. E.; Omar, R. S.; Senning, A. Molecular and crystal structures of three monothiated analogues of the terminally blocked ala-aib-ala sequence of peptaibol antibiotics. *Biopolymers* **1988**, *27*, 747–761.
8. Gentilucci, L.; De Marco, R.; Cerisoli, L. Chemical modifications designed to improve peptide stability: Incorporation of non-natural amino acids, pseudo-peptide bonds, and cyclization. *Curr. Pharm. Des.* **2010**, *16*, 3185–3203.

9. (a) Farina, C.; Pellegata, R.; Pinza, M.; Pifferi, G. Research on alkoxythiobenzamides, III: Synthesis of new 3,4,5-trimethoxythiobenzamides and related thiomorpholides with potential antisecretory and antiulcer activity. *Arch. Pharm.* **1981**, *314*, 108–117; (b) Csomós, P.; Fodor, L.; Sohár, P.; Bernáth, G. Synthesis of thiazino[6,5-*b*]indole derivatives, analogues of the phytoalexin cyclobrassinin: A new method for preparation of 3-aminomethylindole. *Tetrahedron* **2005**, *61*, 9257–9262
10. Ozturk, T.; Ertas, E.; Mert, O. Use of Lawesson's reagent in organic synthesis. *Chem. Rev.* **2007**, *107*, 5210–5278.
11. Brown, E. V. The Willgerodt reaction. *Synthesis* **1975**, 358–375.
12. Dell, C. P. Thionoamides and their selenium and tellurium analogues. In *Comprehensive Organic Functional Group Transformations*; A. R. Katritzky, O. Meth-Cohn, C. W. Rees (Eds.); Pergamon: Oxford, 1995, vol. 5, pp. 565–628.
13. (a) Suzuki, Y.; Takeuchi, K.; Kodomari, M. Regioselective halogenation and dimerization of alkoxynaphthalenes with alumina- or Kieselguhr-supported copper(II) halides. *J. Chem. Res., Synop.* **1997**, *11*, 426–427; (b) Lorz, E.; Baltzly, R. *N,N*-Disubstituted amidines, III: 4-Alkoxy-α -naphthamidines. *J. Am. Chem. Soc.* **1951**, *73*, 93–5; (c) Bringmann, G.; Goetz, R.; Harmsen, S.; Holenz, J.; Walter, R. Acetogenic isoquinoline alkaloids, LXXXII: Biomimetic total synthesis of michellamines A–C. *Liebigs Ann. Chem.* **1996**, *12*, 2045–2058; (d) Imanzadeh, G. K.; Zamanloo, M. R.; Eskandari, H.; Shayesteh, K. A new ring bromination method for aromatic compounds under solvent-free conditions with NBS/Al_2O_3. *J. Chem. Res.* **2006**, *3*, 151–153.
14. Yeo, S. K.; Choi, B. G.; Kim, J. D.; Lee, J. H. A convenient method for the synthesis of thiobenzamide derivatives and O-thiobenzoates by use of 2-benzothiazolyl dithiobenzoate as effective thiobenzoylation reagent. *Bull. Korean Chem. Soc.* **2002**, *23*, 1029–1030.