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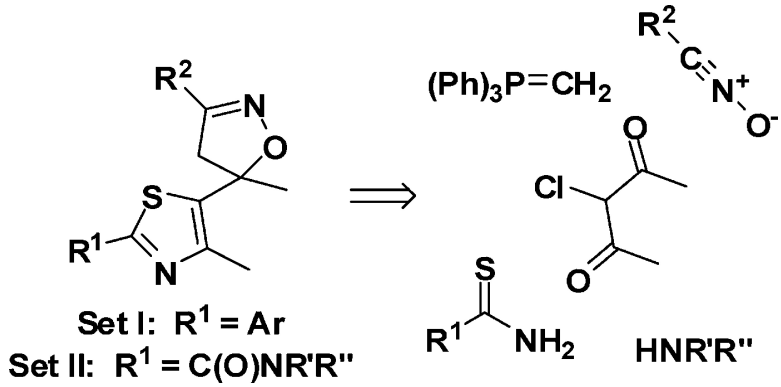


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# Synthesis of 5-(Thiazol-5-yl)-4,5-dihydroisoxazoles from 3-Chloropentane-2,4-dione

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Condensation of 3-chloropentane-2,4-dione with thioamides gives 1-(thiazol-5-yl)ethanones and subsequent Wittig olefination, followed by nitrile oxide 1,3-dipolar cycloaddition to the resulting prop-1-en-2-yl moiety, delivers racemic 5-(thiazol-5-yl)-4,5-dihydroisoxazoles. When this thiazole and isoxazoline diheterocyclic scaffold has a carboethoxy substituent at C2 of the thiazole ring, aminolysis provides for effective diversification. A 50-member library of various 5-(thiazol-5-yl)-4,5-dihydroisoxazoles is reported.

## Introduction

Heterocyclic compounds are widely used as medicines, agrochemicals, and probes for biological chemistry research. This utility is derived, in large part, from the specific interactions small heterocyclic compounds have with the macromolecules that mediate physiological functions. Indeed, six of the top seven small molecule drugs contain heterocycles.[1] Compared to monoheterocycles, fused or linked diheterocyclic scaffolds with two heteroatom-containing rings might be expected to afford additional binding opportunities as well as extended options for diversification.

Herein, we present the synthesis of a novel 5-(thiazol-5-yl)-4,5-dihydroisoxazole scaffold (**5,** referred to here as a thiazoloisoxazoline, Figure 1), as well as two strategies to diversify this diheterocyclic core (sets I and II). Thiazoles and 4,5-dihydroisoxazoles (i.e., isoxazolines), the component substructures of scaffold **5**, are known to elicit a variety of biological effects.

For example, thiazoles are an important motif in compounds with anticancer,[2] antifungal,[3] antibiotic,[4] and antiviral activities,[5] and isoxazoline-containing small molecules are known to educe anti-inflammatory,[6] herbicidal,[7] and fungicidal effects.[8] Metabolic processing of the isoxazoline moiety has also been exploited in an antedrug application.[9] The combination of these two heterocycles into a C5,C5-tethered scaffold should impart distinct and interesting characteristics as a consequence of this unique diheterocycle's higher functionality density and distinctive heteroatom array. Despite this potential, we are aware of only two reports of the thiazoloisoxazoline ring system (i.e., **5**).[10,11]

## Results and Discussion

Our general approach to thiazoloisoxazoline scaffold **5** is outlined in Scheme 1. Bis-functional thiazole **3** was prepared in two steps. Step one employed the Hantzsch procedure[12] [consisting of condensation of 3-chloropentane-2,4-dione with thiobenzamide (→ **2**{*1*}, 94%),[13] 4-chlorothiobenzamide (→ **2**{*2*}, 92%),[14] or ethyl 2-amino-2-thioxoacetate (→ **2**{*3*}, 63%)][15] to deliver the thiazole ring. Step two consisted of Wittig olefination of the ethanone moiety in **2**, which conveniently provided the 5-(prop-1-en-2-yl) moiety required for isoxazoline formation (**3** → **5**).

Set I, a collection of twenty thiazoloisoxazolines, was prepared by nitrile oxide 1,3-dipolar cycloadditions to 5-(prop-1-en-2-yl)thiazoles **3**{*1*} and **3**{*2*}. The requisite oximes were prepared via known literature procedures[16,17] and formed in situ nitrile oxides under Huisgen conditions[18] that, upon reacting with alkene **3**{*1*−*2*}, gave racemic cycloadduct **5**. There is ample literature precedent for 5,5- instead of 4,4-disubstituted isoxazoline formation from 1,1-disubstituted alkenes.[19] In diheterocycle **5**, proton NMR analysis of the isoxazoline C4 methylene AB quartet was particularly informative and, based on comparisons to similar systems as well as computational results,[20] established that these isoxazoline heterocycles are 5,5-disubstituted. This diversification at $R^1$ (two examples {*1*−*2*}) and $R^2$ (ten examples {*1*−*10*}) produced the twenty analogs delineated in Table 1. Each crude cycloadduct was subsequently dissolved in $CH_3CN/H_2O$/DMSO and purified by HPLC.

Set II, a collection of thirty 5-(2-carboxamidothiazol-5-yl)-4,5-dihydroisoxazoles, was prepared by nitrile oxide 1,3-dipolar cycloadditions to 5-(prop-1-en-2-yl)thiazole **3**{*3*}. The initial attempt to convert **2**{*3*} to **3**{*3*} failed when a THF solution of ethyl 5-acetyl-4-methylthiazole-2-carboxylate (**2**{*3*}) was added to chilled $Ph_3P{=}CH_2$ in THF. Fortunately, the addition of the chilled ylide to a THF solution of **2**{*3*} at 0 °C delivered ethyl 4-methyl-5-(prop-1-en-2-yl)thiazole-2-carboxylate (**3{*3*}**) in 70% yield.

Next, 3-nitrobenzaldehyde oxime (→ **5**{*3*,*11*}, 47%), nicotinaldehyde oxime (→ **5**{*3*,*10*}, 44%), and benzaldehyde oxime (→ **5**{*3*,*1*}, 64%) introduced diversity at the $R^2$ position by way of the nitrile oxide 1,3-dipolar cycloaddition (three examples *1*, *10*, and *11*). With 4,5-dihydroisoxazoles **5**{*3*, *1*, *10*, or *11*} in hand, two options for ester → amide diversification were explored: direct aminolysis by reaction of the ester with amines (step 4 in Scheme 2) and ester → acid, followed by amide formation (steps 5 and 6 in Scheme

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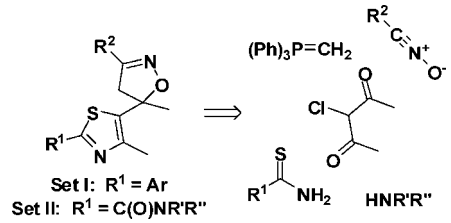



**Figure 1.** Thiazoloisoxazoline (**5**) ⇒ reagents.

**Scheme 1.** Synthesis of the Racemic Thiazoloisoxazoline Core

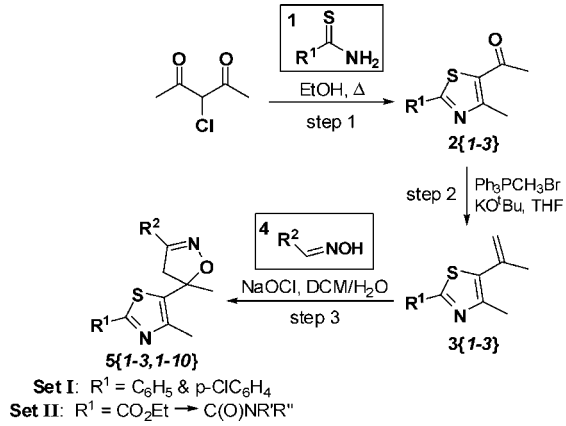
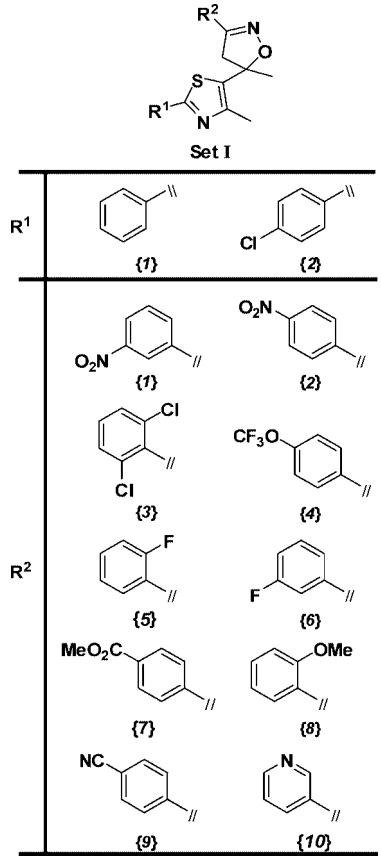



**Table 1.** $R^1$ {*1*−*2*} and $R^2$ {*1*−*10*} Diversity for Set I




2). Although the direct aminolysis strategy worked (for example, **5**{*3*,*1*} + benzylamine → 80%), the acid−amine coupling strategy proved to be generally more reliable.

That said, care must be exercised in the preparation of these acids to avoid decarboxylation to **7**{*1*}. Specifically,

**Scheme 2.** Synthesis of Racemic Carboxamidothiazoloisoxazolines

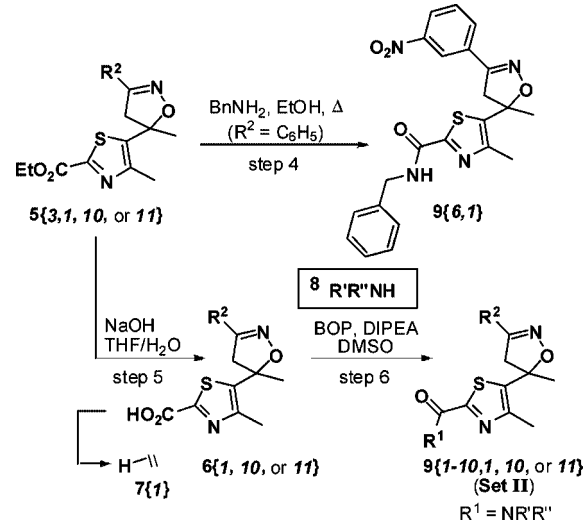
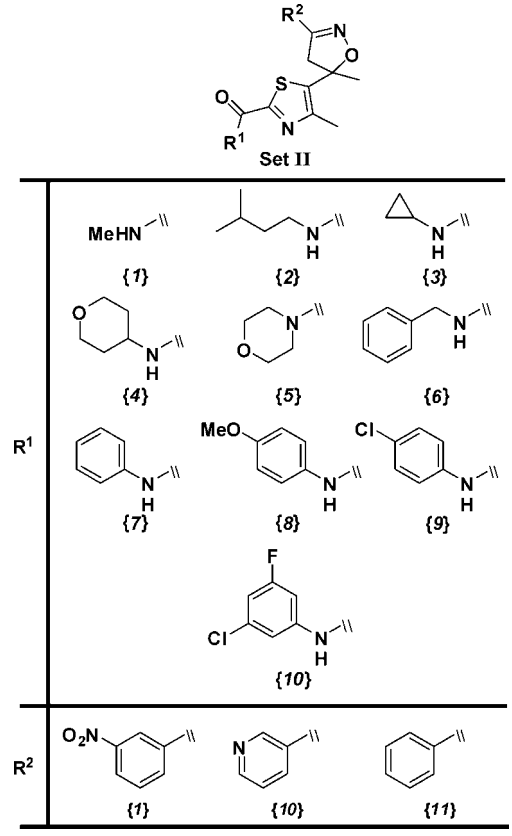



**Table 2.** $R^1$ {*1*−*10*} and $R^2$ {*1*, *10*, *11*} Diversity for Set II




the reaction temperature must be lowered to 0 °C prior to base neutralization with dilute aqueous HCl (→ pH 6) of the **5**{*3*, *1*, *10*, or *11*} → **6**{*1*, *10*, or *11*} reaction mixtures. This result was surprising in light of Sarodnick's decarboxylation of thiazoles under refluxing HBr.[21] With this precaution put into practice, free acids **6**{*1*, *10*, or *11*} were obtained in nearly quantitative yield from the saponification of esters **5**{*3*, *1*, *10*, or *11*} with aqueous sodium hydroxide in THF. Finally, acid → amide conversion with the ten amines depicted in Table 2 {*1*−*10*} delivered thiazoloisoxazoline set II.

In conclusion, two strategies for diversification of the 5-(thiazol-5-yl)-4,5-dihydroisoxazole scaffold have been developed, which led to a 50-member library of diheterocyclic thiazoloisoxazolines. Key steps included thiazole formation by the Hantzsch procedure, Wittig olefination, nitrile oxide 1,3-dipolar cycloaddition, and ester aminolysis. Compounds will be biologically evaluated as part of our collaboration with the National Institute of General Medical Sciences (NIGMS) to create pilot-scale diversity libraries.

## Experimental Section

**General Procedures.** All chemicals were purchased from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (silica gel 60, F254) and visualized with UV light. Flash chromatography was performed with silica gel 60 (230−400 mesh). NMR spectra ($^1$H at 300, 400, and 600 MHz; $^{13}$C at 75, 100, and 150 MHz) were recorded in $CDCl_3$ or DMSO-$d_6$, and chemical shifts are expressed in parts per million relative to internal TMS or solvent. LC/MS specifications are as follows: electrospray (+) ionization, mass range 100−900 Da, 20 V cone voltage, and Xterra MS $C_{18}$ column (2.1 mm × 50 mm × 3.5 $\mu$m). Preparative HPLC specifications are as follows: 15 mL/min flow rate, Xterra Prep MS $C_{18}$ OBD column (19 mm × 100 mm) and dual wavelength absorbance detector. Melting points were determined with an EZ-Melt automated melting point apparatus (Stanford Research Systems).

All aldoximes used in the syntheses are known compounds. 2,6-Dichlorobenzaldoxime was commercially available. All other oximes were prepared from reaction of the corresponding aldehyde with hydroxylamine hydrochloride using standard published procedures.[15,16] All reactions were performed under a nitrogen atmosphere. Dry solvents were used where indicated.

**General Procedure for Thiazole Synthesis: 1-(4-Methyl-2-phenylthiazol-5-yl)ethanone (2{*1*}).** To a solution of thiobenzamide (6.00 g, 43.7 mmol) in ethanol (50 mL) was added 3-chloro-2,4-pentanedione (4.96 mL, 43.7 mmol), and the resulting solution was warmed to reflux for 6 h, at which time TLC showed the reaction was complete. The reaction mixture was concentrated by rotary evaporation, and 1 M sodium hydroxide and EtOAc were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to deliver the product as a light brown solid (8.95 g, 94% yield). A small portion of the product was purified for analytical purposes: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.00−7.98 (m, 2H), 7.57−7.51 (m, 3H), 2.71 (s, 3H), 2.57 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 190.7, 168.6, 158.2, 132.20, 132.17, 131.5, 129.5, 126.6, 30.5, 18.3; $C_{12}H_{11}NOS$, ESI-MS *m*/*z* 218 $(M + H)^+$. Purity was determined to be 96% by HPLC analysis.

**Method A for Olefin Synthesis: 4-Methyl-2-phenyl-5-(prop-1-en-2-yl)thiazole (3{*1*}).** Methyltriphenylphosphonium bromide (2.96 g, 8.28 mmol) was dissolved in dry THF (10 mL) and cooled in an ice bath. Potassium *tert*-butoxide (8.83 mL of a 1.0 M solution in THF, 8.83 mmol) was added, and the reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature for 30 min, and warmed to reflux for 1 h. The reaction mixture was cooled in an ice bath, and a solution of **2**{*1*} (0.60 g, 2.76 mmol) in dry THF (10 mL) was added. The mixture was removed from the ice bath and warmed to reflux for 3 h, at which time TLC showed the reaction was complete. The reaction mixture was diluted with water, concentrated by rotary evaporation, and extracted with EtOAc (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification by flash chromatography (EtOAc/hexane 1:4) gave the pure product as a pale yellow oil (0.540 g, 91% yield). A small portion of the product was purified for analytical purposes: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.91−7.90 (m, 2H), 7.44−7.39 (m, 3H), 5.29−5.28 (m, 1H), 5.21 (s, 1H), 2.55 (s, 3H), 2.16 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 164.1, 148.9, 135.8, 134.1, 133.6, 130.0, 129.0, 126.5, 116.8, 25.3, 17.2; $C_{13}H_{13}NS$, ESI-MS *m*/*z* 216 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis.

**Method B for Olefin Synthesis: Ethyl 4-methyl-5-(prop-1-en-2-yl)thiazole-2-carboxylate (3{*3*}).** Methyltriphenylphosphonium bromide (12.4 g, 33.6 mmol) was dissolved in dry THF (90 mL) and cooled to 0 °C. Potassium *tert*-butoxide (42.0 mL of a 1.0 M solution in THF, 42.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature with stirring for 15 min and then heated to reflux for 2 h. TLC indicated the disappearance of starting material after 2 h. The suspension was cooled to 0 °C and added via syringe to a solution of **2**{*3*} (5.72 g, 26.9 mmol) in THF (90 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, at which time TLC showed the reaction was complete. The mixture was then concentrated by rotary evaporation, and water (100 mL) and EtOAc (100 mL) were added. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification by flash chromatography (EtOAc/hexane 1:9) afforded **3**{*3*} (4.10 g, 70%) as a yellow oil: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 5.36 (s, 1H), 5.27 (s, 1H,), 4.45 (q, $J$ = 7.2 Hz, 2H), 2.55 (s, 3H), 2.14 (s, 3H), 1.41 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.4, 153.5, 150.7, 140.9, 135.1, 118.6, 62.5, 25.1, 17.4, 14.4; $C_{10}H_{13}NO_2$, ESI-MS *m*/*z* 212 $(M + H)^+$. Purity was determined to be 100% by HPLC analysis.

**General Procedure for Isoxazoline Synthesis: 3-(2-Methoxyphenyl)-5-methyl-5-(4-methyl-2-phenylthiazol-5-yl)-4,5-dihydroisoxazole (5{*1*,*8*}).** Compound **3**{*1*} (0.054 g, 0.25 mmol) and 2-methoxybenzaldehyde oxime (0.076 g, 0.50 mmol) were dissolved in dichloromethane (2 mL) and cooled in an ice bath. Bleach (laboratory grade, 5.65%, 2.5 mL) was added dropwise, and the reaction mixture was stirred overnight. Water (2 mL) and dichloromethane (2 mL) were added, and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. Purification by preparative HPLC gave **5**{*1*,*8*} (0.047 g, 52% yield) as a light brown solid: mp 59−62 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90−7.88 (m, 2H), 7.75 (dd, $J$ = 7.6, 1.6 Hz, 1H), 7.55−7.48 (m, 3H),

7.41 (dt, $J = 7.6$, 1.6 Hz, 1H), 7.01−6.93 (m, 2H), 3.86 (s, 3H), 3.81 (d, $J = 17.6$ Hz, 1H), 3.71 (d, $J = 17.2$ Hz, 1H), 2.61 (s, 3H); $C_{21}H_{20}N_2O_2S$, ESI-MS *m/z* 365 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis.

**General Procedure for Carboxylic Acid Synthesis: 4-Methyl-5-(5-methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)thiazole-2-carboxylic acid (6{*11*}).** Compound **5**{*3*,*11*} (0.420 g, 1.27 mmol) was dissolved in THF/water (1:1, 10 mL), and sodium hydroxide (0.056 g, 1.40 mmol) was added at room temperature. The reaction mixture was stirred until disappearance of the starting material was confirmed by TLC after 18 h. The solution was cooled to 0 °C and neutralized with 0.05 M HCl until a pH of 6 was reached. Concentration by rotary evaporation, followed by lyophilization, gave a powder that was treated with chloroform to leach the free acid. Filtration of the solution and concentration by rotary evaporation gave **6**{*11*} (0.372 g, 97% yield): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 7.68−7.77 (m, 2H), 7.44−7.42 (m, 3H), 3.71 (d, $J = 17.4$ Hz, 1H), 3.63 (d, $J = 17.4$ Hz, 1H), 2.33 (s, 3H), 1.68 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 167.7, 161.8, 156.7, 146.7, 138.4, 130.3, 129.2, 128.9, 126.7, 85.0, 47.4, 27.7, 16.2; $C_{15}H_{14}N_2O_3S$, ESI-MS *m/z* 303 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis.

**5-Methyl-5-(4-methylthiazol-5-yl)-3-(3-nitrophenyl)-4,5-dihydroisoxazole (7{*1*}).** Following the General Procedure for Carboxylic Acid Synthesis using **5**{*3*,*1*} and acidifying with 2 M HCl produced a precipitate that was filtered and dried in a vacuum oven at 65 °C overnight to give **7**{*1*} (1.10 g, 94% yield): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1H), 8.41 (t, $J = 2.4$ Hz, 1H), 8.29−8.27 (m, 1H), 8.10 (dt, $J = 6.6$, 1.2 Hz, 1H), 7.62 (t, $J = 7.8$ Hz, 1H), 3.67 (d, $J = 16.8$ Hz, 1H), 3.60 (d, $J = 16.8$ Hz, 1H), 2.54 (s, 3H), 1.89 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 155.2, 152.7, 148.6, 143.7, 139.9, 132.4, 130.5, 130.3, 125.4, 121.8, 85.8, 48.0, 27.8, 14.5; $C_{18}H_{18}N_4O_4S$, ESI-MS *m/z* 304 $(M + H)^+$. Purity was determined to be 100% by HPLC analysis.

**General Procedure for Amide Synthesis: 4-Methyl-5-(5-methyl-3-(pyridin-3-yl)-4,5-dihydroisoxazol-5-yl)-N-phenylthiazole-2-carboxamide (9{*7*,*10*}).** Compound **6**{*10*} (0.032 g, 0.11 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 0.077 g, 0.17 mmol), and DIPEA (0.040 mL, 0.23 mmol) were dissolved in DMSO (0.5 mL) and stirred for 15 min. Aniline (0.012 g, 0.13 mmol) was added, and the reaction mixture was stirred at room temperature overnight. After 18 h when TLC showed the reaction to be complete, the product was precipitated by the dropwise addition of water, centrifuged, and collected by vacuum filtration. Purification by preparative HPLC gave **9**{*7*,*10*} (0.024 g, 65% yield): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.99 (s, 1H), 8.95 (d, $J = 1.8$ Hz, 1H), 8.76 (dd, $J = 5.4$, 1.8 Hz, 1H), 8.58 (dt, $J = 8.4$, 1.8 Hz, 1H), 7.76−7.74 (m, 1H), 7.68 (dd, $J = 9.0$, 1.2 Hz, 2H), 7.38−7.35 (m, 2H), 7.17−7.14 (m, 1H), 3.69 (d, $J = 16.8$ Hz, 1H), 3.65 (d, $J = 16.8$ Hz, 1H), 2.53 (s, 3H), 1.92 (s, 3H); $C_{20}H_{18}N_4O_2S$, ESI-MS *m/z* 379 $(M + H)^+$. Purity was determined to be 100% by HPLC analysis.

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**Supporting Information Available.** Detailed synthetic experimental procedures, $^1$H and $^{13}$C NMR and LCMS spectra for precursors **2**{*1*−*3*}, **3**{*1*−*3*}, **5**{*3*,*1*, *10*, or *11*}, **6**{*1*, *10*, or *11*}, and **7**{*1*}, as well as $^1$H NMR and LCMS spectra for representative library members are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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