

Davis–Beirut Reaction: Route to Thiazolo-, Thiazino-, and Thiazepino-2*H*-indazolesKelli M. Farber,[†] Makhlu J. Haddadin,[‡] and Mark J. Kurth^{*,†}[†]Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States[‡]Department of Chemistry, American University of Beirut, Beirut, 1107 2020 Lebanon

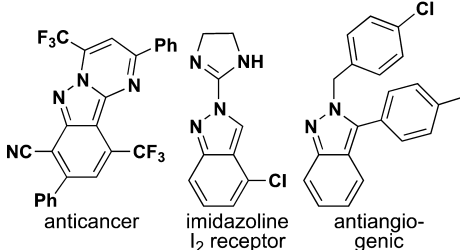
S Supporting Information

ABSTRACT: Methods for the construction of thiazolo-, thiazino-, and thiazepino-2*H*-indazoles from *o*-nitrobenzaldehydes or *o*-nitrobenzyl bromides and *S*-trityl-protected 1°-aminothioalkanes are reported. The process consists of formation of the requisite *N*-(2-nitrobenzyl)(tritylthio)-alkylamine, subsequent deprotection of the trityl moiety with TFA, and immediate treatment with aq. KOH in methanol under Davis–Beirut reaction conditions to deliver the target thiazolo-, thiazino-, or thiazepino-2*H*-indazole in good overall yield. Subsequent *S*-oxidation gives the corresponding sulfone.

INTRODUCTION

2*H*-Indazoles are of considerable interest due to their medicinal chemistry applications, which include anticancer,^{1,2} imidazoline I₂ receptor,³ and antiangiogenic⁴ activities (Figure 1a).

(a) 2*H*-Indazoles of medicinal chemistry interest:



(b) example Davis–Beirut reaction:

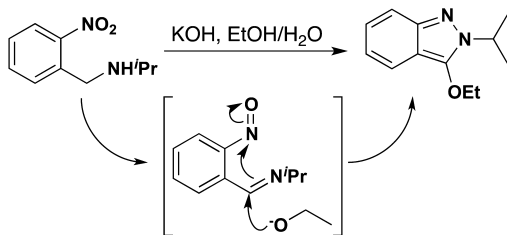


Figure 1. (a) Bioactive 2*H*-indazoles. (b) A typical Davis–Beirut reaction proceeding through the proposed nitrosoimine intermediate.⁶

Addressing this need, we recently developed the Davis–Beirut reaction,^{5–16} which is characterized by a noteworthy *N,N*-bond forming heterocyclization step, for the construction of a wide variety of 2*H*-indazoles and indazolones (Figure 1b).

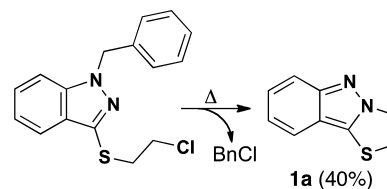
In connection with ongoing research activities addressing cystic fibrosis (CF),^{17,18} our interest in the development of myeloperoxidase inhibitors^{19,20} led us to explore introduction of a thioether moiety at C3 of the 2*H*-indazole scaffold. While

attempts to employ RSH in the base-mediated Davis–Beirut reaction failed, we have found that a thiol tethered to the 1°-aminoalkane^{7,21} used in the reductive amination step to construct the *o*-nitrobenzylamine intermediate (in turn, prepared from the appropriate *o*-nitrobenzaldehyde or *o*-nitrobenzyl bromide precursor) can deliver C3 *S*-substituted 2*H*-indazoles. We report here the details of this investigation.

RESULTS AND DISCUSSION

Sulfur-containing molecules are quite relevant in medicine and in human biology.^{22–25} Thioethers also offer an intriguing point of diversification through easy access to higher oxidation states at sulfur. The potential of sulfur-containing 2*H*-indazoles piqued the interest of Corsi and Palazzo, leading them to develop a limited and somewhat circuitous route to thiazoloindazole **1a** that proceeds by pyrolysis of 1-benzyl-3-((2-chloroethyl)thio)-1*H*-indazole (Scheme 1; 40% yield).²⁶ Attempts to employ external thiols under a variety of Davis–Beirut reaction conditions (generally ⁱPrOH + EtSH + aq. KOH) failed to deliver the thioether-containing 2*H*-indazole (e.g., the 2*H*-indazole in Figure 1b where the –OEt moiety would be replaced with the sought after –SEt). These reaction attempts resulted primarily in nitroaryl reduction²⁷ to the

Scheme 1. Thiazolo-2*H*-indazole **1a** by Pyrolysis of 1-Benzyl-3-((2-chloroethyl)thio)-1*H*-indazole



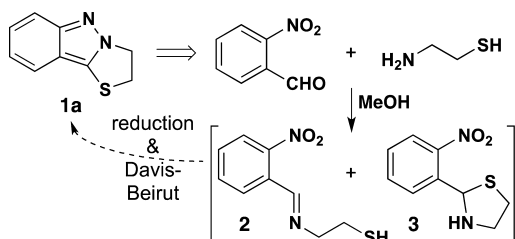
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corresponding aniline with only trace formation of the thia-containing 2*H*-indazole.

With this setback as a backdrop, we decided to explore the formation of 2,3-dihydrothiazolo[3,2-*b*]indazole (**1a**; Scheme 2) from 2-nitrobenzaldehyde and cysteamine before abandon-

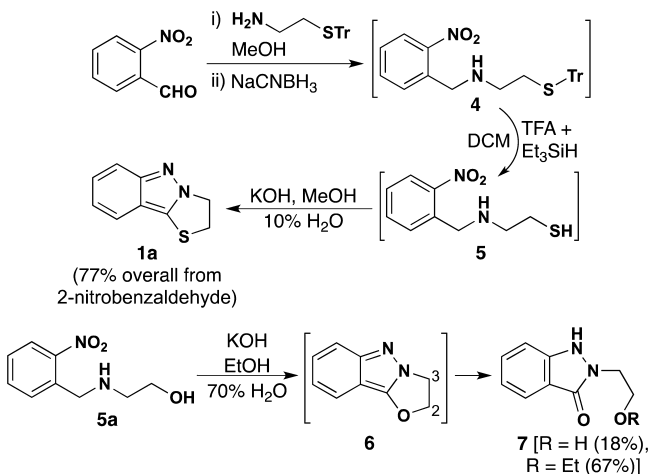
Scheme 2. Unwanted Aminoal Formation using 2-Aminoethanethiol



ing the thia-based Davis-Beirut reaction. Condensation of these two commercially available reagents in methanol provided the requisite imine **2**, but LCMS analysis of the reaction mixture indicated the formation of a second product that was determined to be thioaminal **3**. Varied reaction times, reaction conditions, and solvents (MeOH and *i*PrOH) all resulted in **3** being the major product. Also, attempts at reduction of this crude mixture of **2** and **3** (NaCNBH₃ in MeOH), followed immediately by the Davis-Beirut reaction, resulted in a complex mixture of products (TLC).

These difficulties led us to pursue an alternate route wherein the sulfur moiety was initially protected. While there are a number of effective thiol-protecting groups, trityl protection was selected for all of the aminothiols employed in this study for three reasons (i) the *S*-trityl group is easy to deprotect; (ii) the *S*-trityl group is stable to reductive amination conditions; and (iii) the UV activity of the *S*-trityl protected aminothiols, as well as their markedly different solubility characteristics, makes them easier to isolate and manipulate than their unprotected analogues. In the event (Scheme 3), 2-nitrobenzaldehyde in methanol reacted quickly with 2-(tritylthio)ethanamine (synthesized from cysteamine-HCl and trityl chloride in DMF)²⁸ to give an imine intermediate (not isolated) and subsequent addition of sodium cyanoborohydride delivered **4**. This crude *o*-nitrobenzylamine was treated with TFA and triethylsilane²⁹ in methylene chloride to cleave the trityl protecting group (\rightarrow **5**),

Scheme 3. Davis-Beirut Route to Thiazolo-2*H*-indazole **1a**

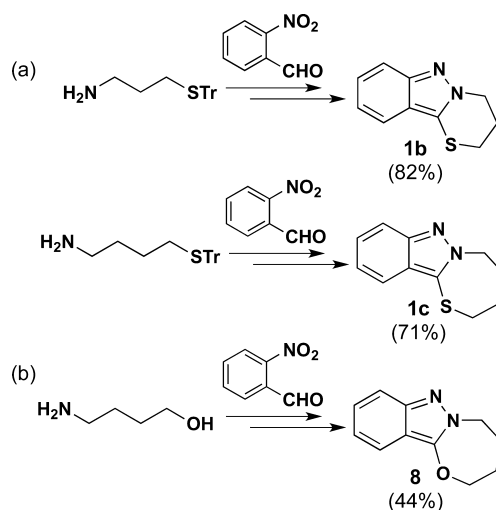


and then the resulting crude thiol was immediately (to minimize disulfide formation) subjected to the Davis-Beirut reaction—treatment with KOH in methanol plus 10% water at 90 °C—to deliver **1a** in 77% overall yield from 2-nitrobenzaldehyde.

It is interesting to note that Davis-Beirut reaction on the alcohol analogue of **5** (–SH replaced with –OH, **5a**) leads transiently to 2,3-dihydrooxazolo[3,2-*b*]indazole (**6**), but base-mediated opening of the dihydrooxazolo ring under the reaction conditions produces 1*H*-indazol-3(2*H*)-one **7**.¹² While this ring-opening of **6** can be avoided by increasing steric hindrance at the electrophilic –CH₂– through placement of alkyl substituents at the C2 and/or C3 positions of **6** and by conducting the heterocyclization at 60 °C,¹² these modifications are not required in the formation of thiazoloindazole **1a**.

With the gratifying result of **4** leading to stable **1a** in hand, we next set out to prepare homologues (Scheme 4a) of **1a** with

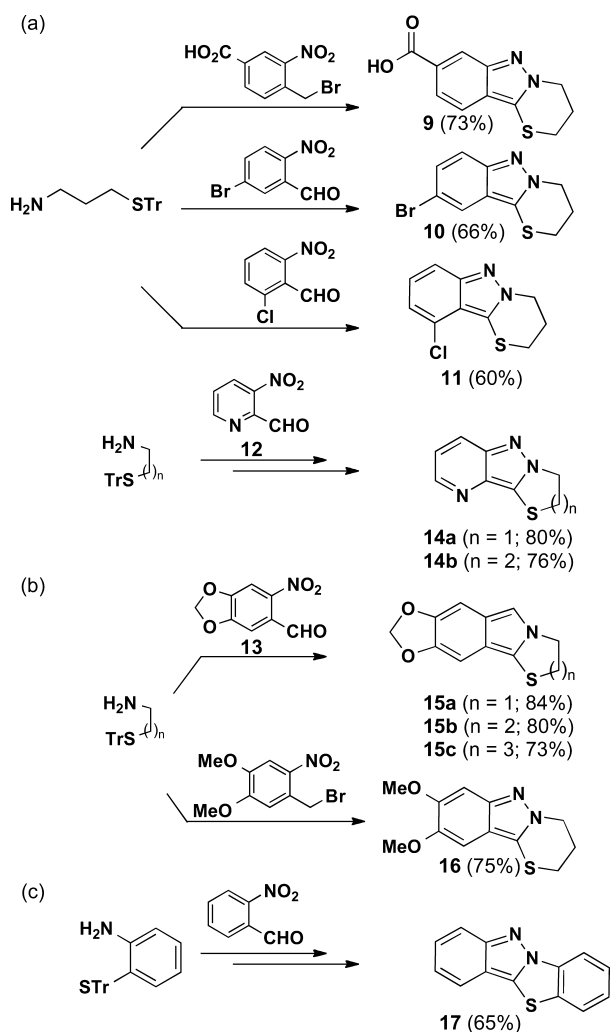
Scheme 4. (a) Thiazino and Thiazepino Analogues of **1a. (b) Oxazepino Analogue of **1c****



six- (thiazino; **1b**) and seven-membered (thiazepino; **1c**) sulfur-containing heterocycles. Applying Scheme 3 sequence of reactions to 3-(tritylthio)propan-1-amine delivered thiazinoindazole **1b** in 82% overall yield, whereas 4-(tritylthio)butan-1-amine delivered **1c** in 71% overall yield. This last result led us to prepare the unknown oxygen analogue of **1c** for comparison (e.g., **8**; Scheme 4b), which we obtained from 4-aminobutan-1-ol (\rightarrow **8**) in 44% overall yield. Indeed, we observe that the *O*-analogues of **1a**, **1b**, and **1c** are obtained in lower yield than the corresponding *S*-analogues: *O*-analogues of **1a–c** in 24% (see **6** in Scheme 3), 84%, and 44% yields (respectively) vs *S*-analogues **1a–c** in 77%, 82%, and 71% yields (respectively).¹²

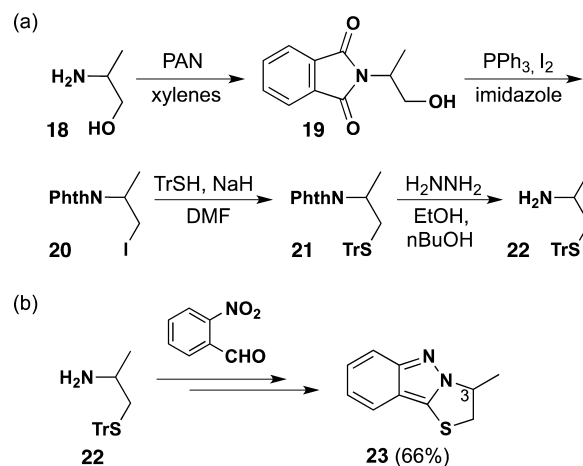
Next, the scope of the sulfur-based Davis-Beirut reaction was expanded to include substituents on the carbocyclic ring of these 2*H*-indazoles. These thia-based Davis-Beirut reactions proceed well with both electron-withdrawing (–COOH \rightarrow **9**, –Br \rightarrow **10**, –Cl \rightarrow **11**, and pyridyl \rightarrow **14a,b**; Scheme 5a) and electron-donating (–OCH₂O– \rightarrow **15a–c** and 8,9 di-OMe \rightarrow **16**; Scheme 5b) substituents as well as with both *o*-nitrobenzaldehyde and *o*-nitrobenzyl bromide precursors (Scheme 5a–c). Also, substitution *ortho* to the aldehyde does not dramatically affect the reaction (*ortho*-Cl \rightarrow **11**). *o*-Nitrobenzaldehydes can also be replaced with heteroaryl nitroaldehydes (e.g., **12** and **13**) to give interesting sulfur-

Scheme 5. Versatility of the Thia-Based Davis–Beirut Reaction



containing heteroaryl analogues (**14a,b** and **15a–c**) in good yields. Benzo-fused analogue **17** was synthesized via trityl-protected 2-aminothiophenol (Scheme 5c).³⁰ In earlier unpublished work, we found that the oxygen analogue of **17** (e.g., where “S” is replaced with “O”) was not similarly accessible with 2-aminophenol; 2-(3-methoxy-2*H*-indazol-2-yl)phenol was formed instead.

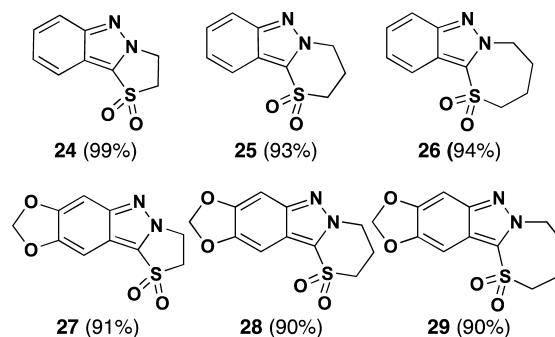
Diverse aminothiols are not readily available, and the literature provides few examples of diverse *S*-trityl aminoalkanes. Therefore, the method devised to prepare the *S*-trityl aminoalkanes employed in this study is presented in Scheme 6a (exemplified with the preparation of **22**; note that 2-(tritylthio)ethanamine,²⁸ 3-(tritylthio)propan-1-amine,³¹ and 4-(tritylthio)butan-1-amine³¹ were prepared as reported in the literature). Since the protecting group used for the amine must be orthogonally removed vis-à-vis the *S*-trityl protecting group, phthalimide protection was selected as both its introduction [amine + phthalic anhydride (PAN) in refluxing xylenes] and its deprotection (phthalimide + hydrazine monohydrate) are well established *S*-trityl-compatible protocols. From the requisite amino alcohol, amine protection (**18** → **19**; 80%), alcohol-to-iodide conversion (**19** → **20**; 76%),³² *S*-alkylation with triphenylmethanethiol (**20** → **21**; 55%), and hydrazinolysis (**21** → **22**; 44%) delivers the targeted *S*-trityl

Scheme 6. (a) Route to *S*-Trityl Aminoalkanes (Exemplified with **22**). (b) Synthesis of an Alkyl-Substituted Thiazoloindazole **23**

aminoalkane. *DL*-1-(Tritylthio)propan-2-amine (**22**) was subsequently employed in the Davis–Beirut sequence with *o*-nitrobenzaldehyde (imine formation and reduction, trityl cleavage, and then aq. KOH in MeOH) to deliver **23**—the C3 methyl analogue of **1a**—in 66% yield (Scheme 6b).

Having successfully introduced a thia moiety into the 2*H*-indazole scaffold, a contrast between these thia- (cf., **1a**) and oxo-bridged (cf., **6**) systems in terms of Davis–Beirut reaction yields is informative. In fact, whereas some 2,3-dihydrooxazolo-[3,2-*b*]indazoles (cf., **6**) and 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*b*]indazoles (e.g., oxa analogues of **1b**) exhibit base and light sensitivity, the thia-2*H*-indazoles reported here are quite stable. Also, while the oxo analogues can generally undergo further reaction with the alcohol solvent to form indazolones (cf., **6** → **7** in Scheme 3), the sulfur analogues reported here do not—even at higher reaction temperatures and extended reaction times.

It is also noteworthy that oxo-2*H*-indazole functionalization is generally limited to conversion to the corresponding indazolone, whereas thia-2*H*-indazoles present new diversification pathways via, for example, *S*-oxidation to the corresponding sulfone. Indeed, as summarized in Figure 2, oxidation³³ of the thioether moiety in these thiazolo-, thiazino-, and thiazepino-2*H*-indazoles with Na₂WO₄·2H₂O/30% aq. H₂O₂/EtOAc leads cleanly and in high yield to the corresponding sulfones (**24–29**).

Figure 2. Sulfones obtained by oxidation of the corresponding thia-2*H*-indazoles.

CONCLUSION

In summary, we have shown that the Davis–Beirut reaction affords thiazolo-, thiazino-, and thiazepino-2*H*-indazoles from *o*-nitrobenzaldehyde and *S*-trityl-protected 1°-aminoalkanes in good yields. The process consists of reductive amination of the *o*-nitrobenzaldehyde-derived imine, *S*-trityl deprotection, and immediate refluxing with aqueous base in methanol. The resulting thia-2*H*-indazoles are generally more stable than the corresponding oxo-2*H*-indazoles, and they can also be oxidized to the corresponding sulfones.

EXPERIMENTAL SECTION

General Experimental. All solvents and reagents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography was carried out on precoated plates (Silica gel 60 F₂₅₄, 0.50 mm thickness) and visualized with UV light. Flash chromatography was performed with 60 Å, 35–70 mm silica gel. Concentration refers to rotary evaporation under reduced pressure.

¹H NMR spectra were recorded at 600 MHz at ambient temperature with DMSO-*d*₆, MeOD-*d*₄, or CDCl₃ as solvents. ¹³C NMR spectra were recorded at 150 MHz at ambient temperature with DMSO-*d*₆, MeOD-*d*₄ or CDCl₃ as solvents. Data for ¹H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet), coupling constant (Hz), integration. Chemical shifts are reported in parts per million relative to DMSO-*d*₆ (¹H, δ 2.50; ¹³C, δ 39.52), MeOD-*d*₄ (¹H, δ 3.31; ¹³C, δ 49.99), or CDCl₃ (¹H, δ 7.26; ¹³C, δ 77.16). Infrared spectra were recorded on an ATI-FTIR spectrometer. High-resolution mass spectra were acquired on an LTQ Orbitrap XL mass spectrometer equipped with an electrospray ionization source operating in the positive ion mode. Samples were introduced into the source via loop injection at a flow rate of 200 μ L/min, in a solvent system of 1:1 acetonitrile:water with 0.1% formic acid.

General Procedure A: Preparation of Thiazolo-, Thiazino-, and Thiazepino-2*H*-indazoles. 2-Nitrobenzaldehyde (1.1 equiv) was dissolved in MeOH (0.4 M). The requisite *S*-trityl-protected aminothioalkane (1.0 equiv) was added, and the solution was stirred until TLC showed consumption of the starting amine. NaCNBH₃ (2.0 equiv) was added portionwise, and the solution was stirred until consumption of the imine was observed. The solution was evaporated, and the resulting residue was redissolved in methylene chloride. The organic layer was washed twice with 1 M HCl, dried over Na₂SO₄, filtered, and concentrated to ~10 mL. An equal volume of TFA was added, followed by addition of triethylsilane (3.0 equiv). This solution was left to stir for 30 min and then concentrated (care was taken to vent the rotary evaporator to nitrogen to prevent disulfide formation). To the remaining residue was added MeOH (0.1 M), KOH (15 equiv), and 10% v/v H₂O. The solution was heated at reflux in a 90 °C oil bath for 3–6 h. Upon reaction completion, the MeOH was evaporated and the remaining aqueous mixture was partitioned with EtOAc. The aqueous layer was extracted with EtOAc twice, and the resulting organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification with silica gel chromatography provided the desired indazole.

2,3-Dihydrothiazolo[3,2-*b*]indazole (1a). Prepared from 216 mg (0.68 mmol) of 2-(tritylthio)ethan-1-amine using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided 1a as a white amorphous solid in 77% yield (92 mg); ¹H NMR (600 MHz, CDCl₃) δ 7.60 (dt, *J* = 8.9, 1.0 Hz, 1H), 7.47 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.25 (ddd, *J* = 8.4, 6.6, 1.0 Hz, 1H), 7.00 (ddd, *J* = 8.4, 6.6, 0.9 Hz, 1H), 4.67 (t, *J* = 7.6 Hz, 2H), 3.97 (t, *J* = 7.6 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 154.0, 133.1, 126.6, 120.8, 120.0, 118.0, 116.1, 50.4, 34.4. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₉H₈N₂SH 177.0486; Found 177.0482.

3,4-Dihydro-2*H*-[1,3]thiazino[3,2-*b*]indazole (1b). Prepared from 200 mg (0.60 mmol) of 3-(tritylthio)propan-1-amine using General Procedure A. Purification by silica gel chromatography (20 \rightarrow

50% EtOAc in hexanes) provided 1b as an amorphous tan solid in 82% yield (94 mg). ¹H NMR (600 MHz, CDCl₃) δ 7.58 (m, 1H), 7.49 (m, 1H), 7.27 (m, 1H), 6.99 (m, 1H), 4.55 (app. t, *J* = 6.4 Hz, 2H), 3.23 (app. t, *J* = 6.4 Hz, 2H), 2.54 (app. p, *J* = 6.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 147.8, 127.0, 120.2, 119.8, 119.2, 117.0, 105.2, 48.8, 25.2, 24.8. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₀H₁₀N₂SH 191.0643; Found 191.0648.

2,3,4,5-Tetrahydro-[1,3]thiazepino[3,2-*b*]indazole (1c). Prepared from 199 mg (0.57 mmol) of 4-(tritylthio)butan-1-amine using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided 1c as an amorphous solid in 71% yield (83 mg). ¹H NMR (600 MHz, CDCl₃) δ 7.68 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.65 (dt, *J* = 8.5, 1.1 Hz, 1H), 7.33 (ddt, *J* = 8.8, 6.8, 1.1 Hz, 1H), 7.14 (ddt, *J* = 8.5, 6.8, 1.0 Hz, 1H), 4.84 (m, 2H), 2.78 (m, 2H), 2.25 (m, 2H), 1.90 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 144.6, 128.5, 126.5, 124.0, 123.1, 120.4, 116.2, 53.7, 34.1, 32.2, 26.7. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₁H₁₂N₂SH 205.0778; Found 205.0772.

2,3,4,5-Tetrahydro-[1,3]oxazepino[3,2-*b*]indazole (8). 4-Amino-1-butanol (160 mg, 1.8 mmol) and 2-nitrobenzaldehyde (250 mg, 1.65 mmol) were dissolved in ^tPrOH (5 mL) and stirred until TLC showed consumption of the starting material. NaCNBH₃ (310 mg, 4.94 mmol) was added portionwise, and the mixture was stirred for 20 min, at which time TLC showed consumption of the imine. Isopropanol (10 mL) was added to the solution. KOH (1.40 g, 25 mmol) was dissolved in a portion of water (2 mL) and added to the ^tPrOH solution, which changed to a dark orange color. This solution was heated at 60 °C for 8 h. The organic layer was washed twice with water and once with brine, dried over Na₂SO₄, filtered, and concentrated. Purification by silica gel chromatography (50% EtOAc in hexanes) provided 8 as a tan amorphous solid in 44% yield (142 mg). ¹H NMR (600 MHz, CDCl₃) δ 7.54 (dt, *J* = 8.5, 1.2 Hz, 1H), 7.49 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H), 6.97 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 4.51 (m, 2H), 4.20 (m, 2H), 2.16 (m, 2H), 1.96 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 148.4, 146.8, 126.5, 120.3, 118.9, 117.1, 110.0, 74.6, 52.8, 31.7, 26.1; HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₁H₁₂N₂O 189.1028; Found 189.1027.

3,4-Dihydro-2*H*-[1,3]thiazino[3,2-*b*]indazole-8-carboxylic acid (9). 4-(Bromomethyl)-3-nitrobenzoic acid (150 mg, 0.54 mmol, 1.0 equiv) and DIPEA (0.250 mL, 1.40 mmol, 2.5 equiv) were dissolved in MeOH. 3-(Tritylthio)propan-1-amine (480 mg, 1.40 mmol, 2.5 equiv) was dissolved in MeOH and added dropwise over 6 h to the stirring benzyl bromide solution. After addition was complete, the solution was left to stir overnight. The solvent was evaporated, and the remaining residue was redissolved in 10 mL of methylene chloride. To this solution was added 10 mL of TFA, followed quickly by addition of triethylsilane (0.225 mL, 1.40 mmol, 2.5 equiv). The solution was left to stir for 30 min. The solvent was evaporated, and the residue was redissolved in MeOH. KOH (484 mg, 8.63 mmol, 15 equiv) was dissolved in 10% v/v water and added to the MeOH solution. This mixture was heated at reflux in a 90 °C bath for 4 h. After the solution cooled, the MeOH was evaporated and EtOAc was added to the remaining aqueous residue. The aqueous layer was extracted once with EtOAc and then acidified. The aqueous layer was then extracted twice more with EtOAc (these extracts were not combined with the first). The organic layer was then washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification by silica gel chromatography (AcOH in 99% EtOAc \rightarrow 1% AcOH, 10% EtOH in 89% EtOAc) provided 9 as an amorphous pale yellow solid in 73% yield (98 mg). IR (neat) ν_{max} 3250, 1740 cm⁻¹; ¹H NMR (600 MHz, DMSO) δ 12.04 (s, 1H), 8.17 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 4.53 (app. t, *J* = 5.9 Hz, 2H), 3.33 (app. t, *J* = 5.5, 5.5 Hz, 2H), 2.57 (app. p, *J* = 6.3 Hz, 2H); ¹³C NMR (150 MHz, DMSO) δ 167.7, 146.0, 128.9, 124.6, 120.8, 119.7, 119.2, 48.8, 24.3, 23.9; HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₁H₁₀N₂O₂SH 235.0541; Found 235.0540.

9-Bromo-3,4-dihydro-2*H*-[1,3]thiazino[3,2-*b*]indazole (10). Prepared from 132 mg (0.40 mmol) of 3-(tritylthio)propan-1-amine using General Procedure A. Purification by silica gel chromatography (50% EtOAc in hexanes) provided 10 as a yellow amorphous solid in

66% yield (70 mg). ^1H NMR (600 MHz, CDCl_3) δ 7.79 (s, 1H), 7.55 (d, J = 9.3 Hz, 1H), 7.32 (d, J = 9.3 Hz, 1H), 4.44 (dd, J = 8.3, 7.1 Hz, 2H), 3.66 (app. t, J = 6.2 Hz, 2H), 2.10 (app. p, J = 7.1 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 147.1, 129.5, 122.9, 122.3, 122.2, 119.0, 115.1, 62.0, 29.4, 27.1; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{BrN}_2\text{SH}$ 268.9748; Found 268.9739.

10-Chloro-3,4-dihydro-2H-[1,3]thiazino[3,2-*b*]indazole (11). Prepared from 200 mg (0.60 mmol) of 3-(tritylthio)propan-1-amine using General Procedure A. Purification by silica gel chromatography (50% EtOAc in hexanes) provided **11** as a tan amorphous solid in 60% yield (81 mg). ^1H NMR (600 MHz, CDCl_3) δ 7.44 (d, J = 8.7 Hz, 1H), 7.12 (dd, J = 8.7, 7.2 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 4.51 (app. t, J = 6.1 Hz, 2H), 3.18 (m, 2H), 2.49 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 148.7, 127.1, 126.0, 125.7, 120.0, 118.5, 115.6, 49.2, 25.2, 24.0; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{ClN}_2\text{SH}$ 225.0253; Found 225.0253.

2,3-Dihydrothiazolo[3',2':1,5]pyrazolo[4,3-*b*]pyridine (14a). Prepared from 198 mg (0.62 mmol) of 2-(tritylthio)ethan-1-amine using General Procedure A. Purification by silica gel chromatography (50 \rightarrow 70% EtOAc in hexanes) provided **14a** as an orange amorphous solid in 80% yield (88 mg). ^1H NMR (600 MHz, CDCl_3) δ 8.47 (dt, J = 4.1, 1.2 Hz, 1H), 7.95 (dt, J = 8.8, 1.2 Hz, 1H), 7.19 (ddd, J = 8.8, 4.1, 1.2 Hz, 1H), 4.72 (app. t, J = 7.7 Hz, 2H), 4.00 (app. t, J = 7.7 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 146.8, 134.6, 133.2, 126.4, 121.8, 105.2, 51.1, 34.4; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_7\text{N}_3\text{SH}$ 178.0439; Found 178.0444.

3,4-Dihydro-2H-pyrido[3',2':3,4]pyrazolo[5,1-*b*][1,3]thiazine (14b). Prepared from 200 mg (0.60 mmol) of 3-(tritylthio)propan-1-amine using General Procedure A. Purification by silica gel chromatography (50 \rightarrow 70% EtOAc in hexanes) provided **14b** as an amorphous yellow solid in 76% yield (87 mg). ^1H NMR (600 MHz, CDCl_3) δ 8.45 (dt, J = 4.1, 0.5 Hz, 1H), 7.92 (dt, J = 8.8, 0.5 Hz, 1H), 7.19 (ddd, J = 8.8, 4.1, 0.5 Hz, 1H), 4.56 (app. t, J = 4.9 Hz, 2H), 3.27 (m, 2H), 2.57 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 146.1, 140.9, 136.5, 126.5, 125.1, 122.2, 49.3, 24.8, 24.5; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_9\text{N}_3\text{SH}$ 192.0595; Found 192.0605.

7,8-Dihydro-[1,3]dioxolo[4,5-*f*]thiazolo[3,2-*b*]indazole (15a). Prepared from 211 mg (0.66 mmol) of 2-(tritylthio)ethan-1-amine using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided **15a** as a tan solid in 84% yield (122 mg). mp decomposed at 250 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 6.87 (s, 1H), 6.66 (s, 1H), 5.93 (s, 2H), 4.55 (app. t, J = 7.6 Hz, 2H), 3.88 (app. t, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 151.3, 149.4, 144.8, 132.1, 111.1, 101.0, 95.0, 94.8, 50.2, 34.5; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{SH}$ 221.0384; Found 221.0384.

8,9-Dihydro-7H-[1,3]dioxolo[4,5-*f*][1,3]thiazino[3,2-*b*]indazole (15b). Prepared from 201 mg (0.60 mmol) of 3-(tritylthio)propan-1-amine using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided **15b** as a tan amorphous solid in 80% yield (113 mg). ^1H NMR (600 MHz, CDCl_3) δ 7.03 (s, 1H), 6.77 (s, 1H), 6.06 (s, 2H), 4.75 (app. t, J = 5.9 Hz, 2H), 3.27 (m, 2H), 2.55 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 154.0, 146.7, 137.7, 133.6, 114.0, 102.6, 95.4, 91, 47.6, 24.6, 22.9; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{SH}$ 235.0541; Found 235.0523.

7,8,9,10-Tetrahydro-[1,3]dioxolo[4,5-*f*][1,3]thiazepino[3,2-*b*]indazole (15c). Prepared from 180 mg (0.52 mmol) using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided **15c** as an amorphous solid in 73% yield (94 mg). ^1H NMR (600 MHz, CDCl_3) δ 6.91 (s, 1H), 6.82 (s, 1H), 5.93 (s, 2H), 4.64 (m, 2H), 2.69 (m, 2H), 2.18 (m, 2H), 1.82 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 149.1, 145.7, 144.5, 126.7, 120.3, 101.0, 95.3, 94.2, 53.6, 34.4, 32.5, 27.4; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{SH}$ 249.0697; Found 249.0698.

8,9-Dimethoxy-3,4-dihydro-2H-[1,3]thiazino[3,2-*b*]indazole (16). 1-(Bromomethyl)-4,5-dimethoxy-2-nitrobenzene (276 mg, 1 mmol, 1.0 equiv) and DIPEA (0.521 mL, 3 mmol, 3.0 equiv) were dissolved in MeOH. 3-(Tritylthio)propan-1-amine (666 mg, 2 mmol, 2 equiv) was dissolved in MeOH and added dropwise over 6 h to the

stirring benzyl bromide solution. After addition was complete, the solution was left to stir overnight. The solvent was evaporated, and the remaining residue was redissolved in 10 mL of methylene chloride. To this solution was added 10 mL of TFA, followed quickly by addition of triethylsilane (0.470 mL, 3 mmol, 3.0 equiv). The solution was left to stir for 30 min. The solvent was evaporated, and the residue was redissolved in MeOH. KOH (841 mg, 15 mmol 15 equiv) was dissolved in 10% v/v water and added to this MeOH solution. The mixture was heated at reflux in a 90 $^\circ\text{C}$ bath for 4 h. After the solution cooled, MeOH was evaporated and EtOAc was added to the remaining aqueous residue. The aqueous layer was extracted once with EtOAc and then acidified. The aqueous layer was then extracted twice more with EtOAc (these extracts were not combined with the first). The organic layer was then washed with brine, dried over Na_2SO_4 , filtered, and concentrated. Purification by silica gel chromatography (10% EtOH in EtOAc) provided **16** as an amorphous yellow solid in 75% yield (188 mg). ^1H NMR (600 MHz, MeOD) δ 6.84 (s, 1H), 6.73 (s, 1H), 4.40 (app. t, J = 5.9 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.25 (dd, J = 8.0, 3.2 Hz, 2H), 2.49 (m, 2H); ^{13}C NMR (150 MHz, MeOD) δ 153.6, 148.1, 145.0, 125.6, 119.3, 117.3, 114.7, 98.1, 96.0, 56.6, 56.4, 25.8; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{SH}$ 251.0854; Found 251.0848.

Benzo[4,5]thiazolo[3,2-*b*]indazole (17). Prepared from 178 mg (0.49 mmol) of 2-(tritylthio)aniline using General Procedure A. Purification by silica gel chromatography (50% EtOAc in hexanes) provided **17** as an amorphous solid in 65% yield (71 mg). ^1H NMR (600 MHz, CDCl_3) δ 8.35 (d, J = 8.2 Hz, 1H), 7.87 (m, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 162.4, 153.6, 149.0, 135.9, 132.4, 131.8, 131.0, 128.0, 126.6, 125.9, 124.5, 123.9, 121.6; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_8\text{N}_2\text{SH}$ 225.0486; Found 225.0482.

2-(1-Hydroxypropan-2-yl)isoindoline-1,3-dione (19). DL-alaninol (1.00 g, 13.30 mmol, 1 equiv) and phthalic anhydride (2.37 g, 16.00 mmol, 1.2 equiv) were dissolved in xylenes and heated at 140 $^\circ\text{C}$ for 3 h. The solution was concentrated, and the resulting solid was purified by silica gel chromatography (20% EtOAc in hexanes) to give the desired phthalimido alcohol. Isolated in 80% yield (2.18 g). Spectral data were in accordance with literature values.³⁴

2-(1-Iodopropan-2-yl)isoindoline-1,3-dione (20). Triphenylphosphine (2.55g, 9.70 mmol, 2 equiv) and imidazole (67 mg, 0.99 mmol, 0.2 equiv) were dissolved in dry methylene chloride. Iodine (2.50g, 9.84 mmol, 2 equiv) was added, and the solution was left to stir for 10 min. **19** (1.00 g, 4.87 mmol, 1 equiv) was dissolved in dry methylene chloride and added dropwise over 20 min. After addition, the solution was left to stir overnight. The solution was concentrated and then redissolved in EtOAc. The organic layer was washed with saturated sodium thiosulfate and brine, dried over Na_2SO_4 , filtered, and concentrated. Purification by column chromatography (5% EtOAc in hexanes) provided the desired product. Isolated in 76% yield (1.16g). Spectral data were in accordance with literature values.³⁵

2-(1-(Tritylthio)propan-2-yl)isoindoline-1,3-dione (21). Trityl mercaptan (965 mg, 3.50 mmol, 1.1 equiv) was dissolved in dry DMF and cooled to 0 $^\circ\text{C}$. Sodium hydride (60% dispersion in mineral oil, 152 mg, 3.80 mmol, 1.2 equiv) was added, and the solution was stirred for 20 min. **20** (1.00 g, 3.17 mmol, 1 equiv) was dissolved in dry DMF and added dropwise to the stirring solution over 10 min. After addition, the reaction was allowed to warm to room temperature and tracked by TLC to completion. The solution was partitioned between water and EtOAc. The organic layer was washed with water, dried over Na_2SO_4 , filtered, and concentrated. Purification by silica gel chromatography (30% EtOAc in hexanes) provided **21** as a white amorphous solid in 55% yield (809 mg). IR (neat) ν_{max} 1711, 1600 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.79 (m, 2H), 7.69 (m, 2H), 7.38–7.20 (m, 15H), 4.08 (m, 1H), 3.12 (dd, J = 12.2, 9.8 Hz, 1H), 2.51 (dd, J = 12.2, 9.8 Hz, 1H), 1.30 (d, J = 6.9, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.1, 144.7, 134.0, 132.0, 129.7, 128.0, 126.8, 123.3, 67.1, 46.9, 35.4, 18.8; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{NO}_2\text{SH}$ 464.1684; Found 464.1680.

3-Methyl-1-(tritylthio)butan-2-amine (22). Isoindolinedione **21** (500 mg, 1.07 mmol, 1.0 equiv) was suspended in a 4:1 solution of EtOH:BuOH. To this solution was added hydrazine monohydrate (6.0 equiv). The mixture was heated at reflux overnight. Upon cooling, a white precipitate formed. The precipitate was filtered off, and the filtrate was concentrated. The resulting residue was redissolved in chloroform, and the solution was left to stir for 1 h. The resulting precipitate was filtered off, and the filtrate was concentrated. Purification of the residue by silica gel chromatography (10% EtOAc in methylene chloride \rightarrow 10% MeOH in methylene chloride) provided **22** as a white crystalline solid in 44% yield (160 mg). mp 151–153 °C; IR (neat) ν_{\max} 3379 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.32–7.28 (m, 15H), 2.60 (m, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 144.9, 129.5, 128.5, 127.2, 66.4, 48.6, 46.6, 22.0. HRMS (ESI) m/z : $[\text{M}-\text{CPh}_3+\text{H}]^+$ calcd for $\text{C}_3\text{H}_9\text{NSH}$ 92.0534; Found 92.0524.

3-Methyl-2,3-dihydrothiazolo[3,2-*b*]indazole (23). Prepared from 160 mg (0.47 mmol) of **22** using General Procedure A. Purification by silica gel chromatography (20 \rightarrow 50% EtOAc in hexanes) provided **23** as an amorphous yellow solid in 66% yield (60 mg). ^1H NMR (600 MHz, CDCl_3) δ 7.46 (d, J = 9.0 Hz, 2H), 7.20 (m, 1H), 6.89 (m, 1H), 5.58 (m, 1H), 4.66 (ddd, J = 9.5, 8.3 Hz, 1H), 4.17 (dd, J = 9.5, 8.0 Hz, 1H), 1.71 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 153.7, 151.4, 126.8, 119.4, 119.0, 117.6, 101, 85.4, 52.7, 20.9. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{SH}$ 191.0643; Found 191.0644.

General Procedure B: Preparation of Sulfones. The indazole (1.0 equiv) was dissolved in EtOAc to 0.8 M. $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (0.1 equiv) was dissolved in a small amount of water and added to the EtOAc solution. A solution of 30% hydrogen peroxide (3.0 equiv) was added dropwise. After addition, the mixture was stirred until starting material was consumed (tracked by LCMS and TLC). The solution was cooled to 0 °C, and saturated sodium bisulfite (2 mL) was added dropwise. The solution was extracted with EtOAc, and then the organic layer was dried over Na_2SO_4 , filtered, and concentrated.

2,3-Dihydrothiazolo[3,2-*b*]indazole 1,1-Dioxide (24). Prepared from **1a** (50 mg, 0.28 mmol) by General Procedure B. Note that the sulfone precipitated out of solution and was analyzed without further purification. Sulfone **24** was isolated as a white amorphous solid in 99% yield (58 mg). IR (neat) ν_{\max} 1305, 1124 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.83 (dd, J = 8.5, 0.9 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.83, 7.43 (ddd, J = 8.8, 6.8, 1.0 Hz, 1H), 7.33 (ddd, J = 8.5, 6.8, 0.8 Hz, 1H), 5.01 (dd, J = 7.3, 6.1 Hz, 2H), 4.15 (dd, J = 7.3, 6.1, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 153.2, 131.1, 127.8, 125.5, 118.7, 118.6, 115.6, 55.3, 46.3; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{SH}$ 209.0384; Found 209.0385.

3,4-Dihydro-2H-[1,3]thiazino[3,2-*b*]indazole 1,1-Dioxide (25). Prepared from **1b** (50 mg, 0.26 mmol) by General Procedure B. Sulfone **25** was isolated as an off-white crystalline solid in 93% yield (53 mg). mp decomposed at 250 °C; IR (neat) ν_{\max} 1342 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.93 (dd, J = 8.5, 0.9 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.38 (ddd, J = 8.5, 6.8, 0.9 Hz, 1H), 7.29 (ddd, J = 7.5, 7.0, 0.9 Hz, 1H), 4.64 (dd, J = 6.3, 5.6 Hz, 2H), 3.55 (dd, J = 6.3, 5.6 Hz, 2H), 2.83 (app. p, J = 5.9 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 147.3, 130.7, 127.6, 125.3, 119.3, 119.2, 117.9, 51.2, 49.6, 21.3; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{SH}$ 223.0541; Found 223.0531.

2,3,4,5-Tetrahydro-[1,3]thiazepino[3,2-*b*]indazole 1,1-Dioxide (26). Prepared from **1c** (50 mg, 0.25 mmol) by General Procedure B. Sulfone **26** was isolated as an off-white amorphous solid in 94% yield (54 mg). IR (neat) ν_{\max} 1342, 1124 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.11 (dt, J = 8.6, 1.1 Hz, 1H), 7.75 (d, J = 8.6, 1.0 Hz, 1H), 7.38 (ddd, J = 8.7, 6.7, 1.1 Hz, 1H), 7.31 (ddd, J = 8.5, 6.7, 1.0 Hz, 1H), 4.96 (dd, J = 6.1, 5.8 Hz, 2H), 3.39 (dd, J = 6.1, 5.8 Hz, 2H), 2.35 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 147.1, 127.1, 125.8, 123.6, 119.8, 118.2, 105.2, 56.1, 54.8, 27.5. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{SH}$ 237.0697; Found 237.0681.

7,8-Dihydro-[1,3]dioxolo[4,5-*f*]thiazolo[3,2-*b*]indazole 9,9-Dioxide (27). Prepared from **15a** (50 mg, 0.23 mmol) by General

Procedure B. Sulfone **27** was isolated as a light tan amorphous solid in 91% yield (52 mg). IR (neat) ν_{\max} 1328 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 7.21 (s, 1H), 7.17 (s, 1H), 6.12 (s, 2H), 4.93 (td, J = 6.5, 1.0 Hz, 2H), 4.34 (td, J = 6.5, 1.0 Hz, 2H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 149.4, 149.2, 147.5, 130.7, 109.9, 101.8, 95.0, 93.3, 55.0, 46.2. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_4\text{SH}$ 253.0283; Found 253.0277.

8,9-Dihydro-7H-[1,3]dioxolo[4,5-*f*][1,3]thiazino[3,2-*b*]indazole 10,10-Dioxide (28). Prepared from **15b** (50 mg, 0.21 mmol) by General Procedure B. Sulfone **28** was isolated as a tan amorphous solid in 90% yield (51 mg). IR (neat) ν_{\max} 1320 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.15 (s, 1H), 6.97 (s, 1H), 6.02 (s, 2H), 4.54 (app. t, J = 6.0 Hz, 2H), 3.52 (dd, J = 6.3, 5.5 Hz, 2H), 2.81 (app. p, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 150.3, 148.2, 145.0, 130.4, 115.7, 101.7, 95.5, 94.4, 51.2, 49.2, 21.4. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_4\text{SH}$ 267.0439; Found 267.0437.

7,8,9,10-Tetrahydro-[1,3]dioxolo[4,5-*f*][1,3]thiazepino[3,2-*b*]indazole 11,11-Dioxide (29). Prepared from **15c** (50 mg, 0.20 mmol) by General Procedure B. Sulfone **29** was isolated as a yellow amorphous solid in 90% yield (54 mg). IR (neat) ν_{\max} 1350 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.28 (s, 1H), 6.94 (s, 1H), 6.00 (s, 1H), 4.79 (dd, J = 5.6, 1.2 Hz, 2H), 3.34 (app. t, J = 6.3 Hz, 2H), 2.34 (m, 2H), 2.00 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 149.8, 148.5, 144.3, 130.0, 120.2, 101.6, 95.0, 94.3, 56.2, 54.3, 27.6, 24.2. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4\text{SH}$ 281.0596; Found 281.0590.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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