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Diaryl and Heteroaryl Sulfides: Synthesis via Sulfenyl Chlorides and Evaluation as Selective Anti-Breast-Cancer Agents

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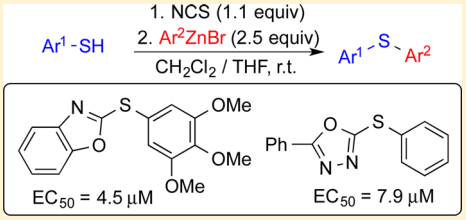
Supporting Information

ABSTRACT: A mild protocol for the synthesis of diaryl and heteroaryl sulfides is described. In a one-pot procedure, thiols are converted to sulfenyl chlorides and reacted with arylzinc reagents. This method tolerates functional groups including aryl fluorides and chlorides, ketones, as well as N-heterocycles including pyrimidines, imidazoles, tetrazoles, and oxadiazoles. Two compounds synthesized by this method exhibited selective activity against the MCF-7 breast cancer cell line in the micromolar range.



INTRODUCTION

Diaryl thioethers, and particularly those containing heterocyclic moieties, are a common structural motif in natural products and medicinal agents (Figure 1). For example, thioethers have

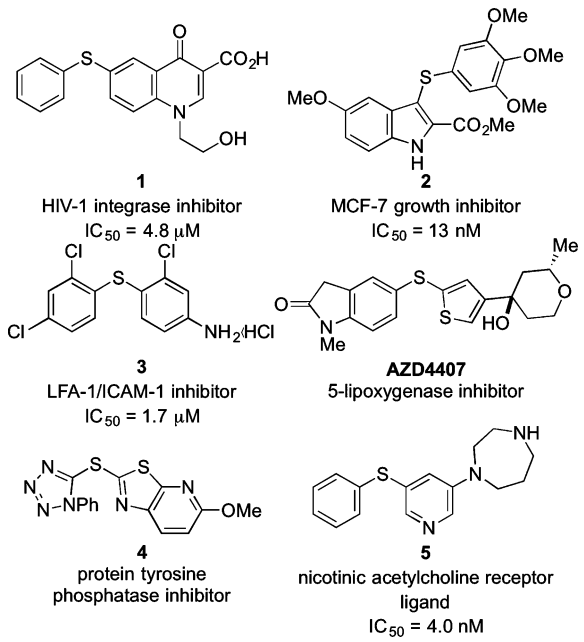


Figure 1. Representative bioactive diaryl sulfides.

therapeutic potential for treatment of HIV,[1] breast cancer,[2] inflammatory diseases,[3,4] diabetes,[5] and Alzheimer's disease.[6] Despite their abundance, until recently few general methods were available for their synthesis under mild conditions that would tolerate sensitive heterocycles. In this manuscript, we report synthesis of diaryl sulfides by in situ formation of highly reactive sulfenyl chlorides and subsequent trapping with arylzinc reagents. A series of heterocyclic diaryl thioethers were designed and prepared as combretastatin A-4 analogues; two of these compounds demonstrated micromolar activity against the MCF-7 breast cancer cell line.

In the past two decades, there have been numerous advances in the synthesis of this class of compounds, and particularly in the field of metal-catalyzed carbon−sulfur bond formation (Figure 2a). Copper- and palladium-catalyzed cross-coupling

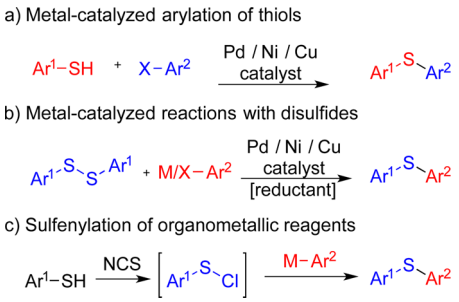


Figure 2. Strategies for the synthesis of diaryl sulfides.

reactions offer a broad scope of reactivity; however, these methods often require elevated temperatures.[7−9] Mechanism-based reaction design has been employed to accelerate transformations such that they occur under milder reaction conditions. For example, the Fu and Peters laboratories disclosed a copper-catalyzed, photoinduced synthesis of diaryl sulfides that proceeds at 0 °C.[10]

An umpolung approach employs electrophilic sulfur reagents (Figure 2b and c). Recent reports detail reactions of disulfides with aryl iodides, boronic acids, or silanes in the presence of stoichiometric reducing agents (Figure 2b).[11−14] Sulfenyl chlorides are used less frequently, likely due to their instability.

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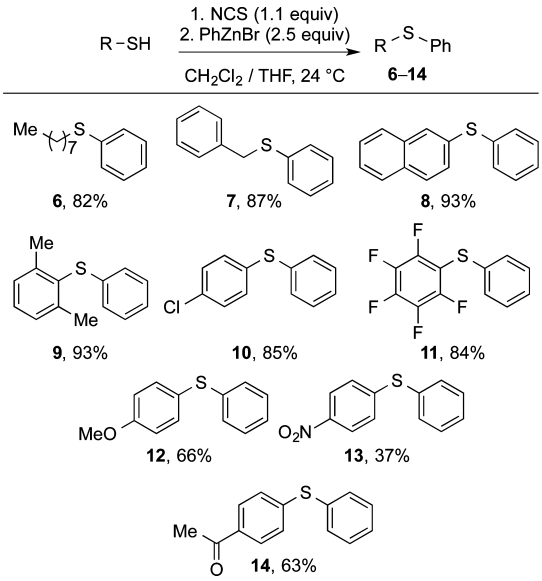
Schlosser and co-workers demonstrated reactions of indoles with sulfenyl chlorides prepared in situ.[15] The high reactivity of sulfenyl chlorides allows the reaction to occur at 0 °C. Recently, expansion of the scope of this reaction to include Grignard reagents was reported by Lee and co-workers (Figure 2c).[16] Contemporaneously, on the basis of our work with *N*-chloroamines,[17,18] we developed sulfenylation of organozinc reagents as a functional-group tolerant[19] strategy for synthesis of diaryl sulfides.

RESULTS AND DISCUSSION

A variety of in situ-formed alkyl and aryl sulfenyl chlorides react with phenylzinc bromide to afford the respective thioethers in good yields (Scheme 1). Substrates containing ortho-

Scheme 1. Reactivity of Alkyl and Aryl Thiols[a]

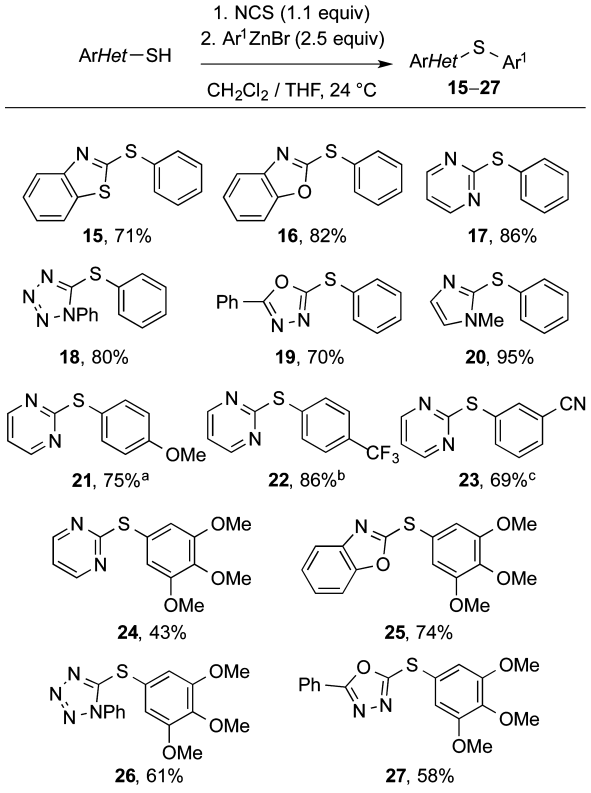


[a]Isolated yields after silica gel chromatography.

disubstituted aryl rings pose a significant challenge for most metal-catalyzed methods, yet our reaction conditions furnish **9** in 93% yield. Halogenation, and particularly fluorination, is well tolerated. Electron-rich thiols such as 4-methoxy thiophenol are competent in the transformation, although the desired product **12** is afforded in slightly diminished yield due to competitive formation of diaryl disulfide. 4-Nitrothiophenol proved to be a challenging substrate, as it is prone to decomposition under the reaction conditions, thus affording **13** in a modest yield. One benefit of using aryl zinc reagents in contrast to aryl Grignard reagents is the increased functional group compatibility. For example, 1-(4-mercapto-phenyl)-ethanone reacted smoothly to provide desired diaryl sulfide **14** with no observed competitive addition to the ketone.

In an effort to ensure that our method is compatible with the sensitive heterocyclic moieties frequently found in bioactive compounds, we examined several heteroaromatic thiols (Scheme 2). A broad range of heterocycles react with phenylzinc bromide to provide good to excellent yields of the corresponding sulfides, including benzothiazole, benzoxazole, pyrimidine, tetrazole, oxadiazole, and imidazole functional groups (**15**–**20**). Notably, when phenylmagnesium bromide was used instead of phenylzinc bromide, compounds **15**, **16**, and **20** were obtained in diminished yields (65, 57, and 59%

Scheme 2. Reactivity of Heteroaryl Thiols[d]



[a]Used (4-OMe)C_6H_4MgBr. [b]Used (4-F)C_6H_4MgBr. [c]Used (3-CN)-C_6H_4MgBr. [d]Isolated yields after silica gel chromatography.

respectively). Furthermore, both electron-rich and electron-poor Grignard reagents react smoothly to afford the desired thioether products in good yields (**21** and **22**, respectively). *meta*-Cyanophenylmagnesium reagent is well-tolerated, affording **23** in good yield.

We sought to synthesize combretastatin A-4[20,21] analogues using our method since it tolerates a diverse range of heterocycles and would further SAR studies of these compounds. Diaryl sulfide analogues of combretastatin containing N-heterocyclic moieties have been reported to be active against MCF-7 breast cancer cell lines (e.g., **2**).[2,22−25] We examined reactions of a variety of heteroaryl sulfides with 3,4,5-trimethoxyphenylzinc bromide, biasing our small library of analogues toward inclusion of the 3,4,5-trimethoxyphenyl scaffold, a privileged motif commonly found in anticancer compounds that target microtubules.[26,27] We were pleased to see that the corresponding arylzinc bromide reacts with a variety of in situ-formed heteroaryl sulfenyl chlorides to afford the respective trimethoxyphenyl-substituted thioethers in modest to good yields (**24**−**27**).

Having synthesized a variety of combretastatin A-4 analogues, we set out to evaluate these compounds for anti-breast-cancer activity. Select products from Schemes 1 and 2 were tested for anticancer activity against the MCF-7 breast cancer cell line relative to the normal MCF-10A stromal cell line using a proliferation-based procedure (Figure 3).[28] Results are compared to activity of the estrogen receptor antagonist, faslodex (ICI 182,780).[29,30] Two compounds demonstrated selective inhibition of cancer cell proliferation. Diaryl sulfide **25**, containing benzoxazole and 3,4,5-trimethoxyphenyl moieties, was a potent inhibitor of MCF-7 cell proliferation (EC_{50} = 4.5

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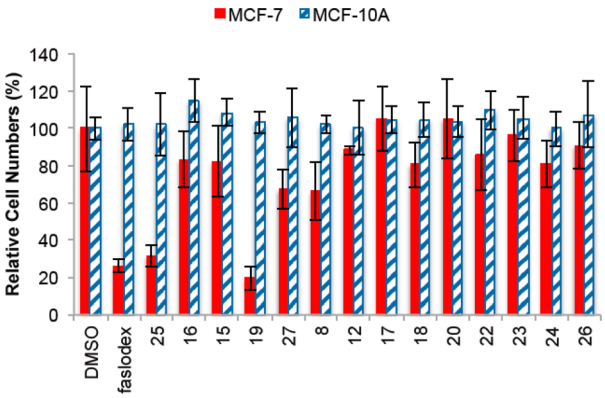

Figure 3. Evaluation of diaryl sulfides for anti-breast-cancer activity. Anti-breast-cancer activity of compounds at 10 μM screened against breast cancer (MCF-7) and normal breast cell lines (MCF-10A). Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anticancer activity for that compound. All data are normalized to the DMSO vehicle control.

μM). In comparison, the simple phenyl analogues **16** and **15** were inactive. In contrast, trimethoxyphenyl-containing thioether **27** performed poorly, while its phenyl analogue **19** was a more potent cell proliferation inhibitor (EC_{50} = 7.9 μM).

CONCLUSION

We have developed a mild and efficient protocol for the synthesis of alkyl and diaryl sulfides. This method tolerates a wide array of heterocyclic moieties and is amenable to the construction of highly functionalized diaryl and diheteroaryl sulfides. Biological studies of select compounds have identified two promising inhibitors of MCF-7 breast cancer cell proliferation. Future efforts will focus on using this methodology to create a larger library of functionalized heterocyclic sulfides and investigating their biological activity against a broad range of cancer cell lines.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under an atmosphere of N_2 using glassware that was either oven- or flame-dried prior to use. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were degassed with argon and then passed through two 4 × 36 in. columns of anhydrous neutral A-2 alumina (8 × 14 mesh; activated under a flow of argon at 350 °C for 12 h) to remove H_2O. ^{1}H NMR spectra were recorded on 500 MHz (500 MHz ^{1}H, 125.7 MHz ^{13}C) or 400 MHz (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), quartet (q), multiplet (m), apparent singlet (ap s), and apparent doublet (ap d)], coupling constants [Hz], integration. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 °C. Infrared spectra (thin film or neat) are reported in terms of frequency of absorption (cm^{-1}). Melting points (mp) are uncorrected. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ solution. Flash chromatography was performed using silica gel 60 Å (170−400 mesh) from Fisher Scientific.

Phenylmagnesium bromide[31] and phenylzinc bromide[32] were prepared according to reported procedures. 4-(Trifluoromethyl)-phenylmagnesium bromide and 4-methoxyphenylmagnesium bromide were prepared from their respective halide precursors in THF. 3-Cyanophenylmagnesium bromide was prepared by magnesium-halogen exchange with isopropylmagnesium bromide in the presence of LiCl.[33] Molarities of organomagnesium and organozinc reagents were determined by titration.[33] *N*-Chlorosuccinimide (NCS) was recrystallized from benzene and stored in an amber vial for up to two weeks.

General Procedure A for Sulfenylation of Arylzinc Reagents. To a solution of NCS (0.073 g, 0.55 mmol) in DCM (1.0 mL) was added thiol (0.50 mmol), and the solution was stirred for 30 min in the absence of direct light. The solution was taken up using a Teflon needle and added dropwise to a solution of arylzinc reagent in THF (1.25 mmol). Upon completion, as judged by TLC, the reaction mixture was quenched with MeOH and concentrated in vacuo, and the residue was adsorbed onto 3 mL of silica gel and purified by flash column chromatography.

General Procedure B for Sulfenylation of Arylmagnesium Reagents. To a solution of NCS (0.073 g, 0.55 mmol) in DCM (1.0 mL) was added thiol (0.50 mmol), and the solution was stirred for 30 min in the absence of direct light. The solution was taken up using a Teflon needle and added dropwise to a solution of arylmagnesium reagent in THF (1.25 mmol). Upon completion, as judged by TLC, the reaction mixture was quenched with MeOH and concentrated in vacuo, and the residue was adsorbed onto 3 mL of silica gel and purified by flash column chromatography.

Octyl(phenyl)sulfane (6). Title compound was prepared according to general procedure A from octane thiol (0.087 mL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3% EtOAc in hexanes) afforded the title compound as a colorless oil (0.091 g, 82%). Spectral data were consistent with reported values:[34] TLC R_f = 0.7 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 4H), 7.15 (t, J = 7.0 Hz, 1H), 2.91 (t, J = 7.3 Hz, 2H), 1.68−1.61 (m, 2H), 1.42 (m, 2H), 1.27 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 128.9 (2C), 125.7, 33.7, 31.9, 29.31, 29.27 (2C), 29.0, 22.8, 14.2.

Benzyl(phenyl)sulfane (7). Title compound was prepared according to general procedure A from benzyl mercaptan (0.059 mL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3% EtOAc in hexanes) afforded the title compound as a colorless oil (0.087 g, 87%). Spectral data were consistent with reported values:[35] TLC R_f = 0.5(10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 9H), 7.16 (t, J = 7.2 Hz, 1H), 4.10 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 136.5, 129.9, 128.95, 128.94, 128.6, 127.3, 126.4, 39.1.

2-Napthyl(phenyl)sulfane (8). Title compound was prepared according to general procedure A from thio-2-naphthol (0.080 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3% EtOAc in hexanes) afforded the title compound as a colorless oil (0.110 g, 93%). Spectral data were consistent with reported values:[34] TLC R_f = 0.6 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75−7.66 (m, 3H), 7.44−7.34 (m, 5H), 7.28−7.18 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 133.9, 133.1, 132.4, 131.0, 130.0, 129.3, 129.0, 128.8, 127.8, 127.5, 127.1, 126.7, 126.3.

2,6-Dimethylphenyl(phenyl)sulfane (9). Title compound was prepared according to general procedure A from 2,6-dimethylthiophenol (0.069 mL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3% EtOAc in hexanes) afforded the title compound as a colorless oil (0.100 g, 93%). Spectral data were consistent with reported values:[36] TLC R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.14 (m, 5H), 7.04 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 7.6 Hz, 2H), 2.42 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 138.1, 130.6, 129.4, 129.0, 128.6, 125.8, 124.7, 22.0.

4-Chlorophenyl(phenyl)sulfane (10). Title compound was prepared according to general procedure A from 4-chlorobenzenethiol (0.072 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3%

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EtOAc in hexanes) afforded the title compound as a colorless oil (0.094 g, 85%). Spectral data were consistent with reported values:[34] TLC R_f = 0.7 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 4H), 7.28−7.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 134.8, 133.1, 132.1, 131.4, 129.5, 129.4, 127.6.

(Perfluorophenyl)(phenyl)sulfane (11). Title compound was prepared according to general procedure A from pentafluorothiophenol (0.067 mL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (3% EtOAc in hexanes) afforded the title compound as a colorless crystalline solid (0.114 g, 84%). Spectral data were consistent with reported values:[37] TLC R_f = 0.6 (5% EtOAc in hexanes); mp 45−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.32−7.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7 (m), 146.7 (m), 143.2 (m), 141.2 (m), 139.0 (m), 136.9 (m), 133.1, 130.7, 129.6, 128.1, 109.1 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.9 (dd, J = 24.7 Hz, 7.0 Hz, 2F), −151.6 (t, J = 20.9 Hz, 1F), −160.6 (td, J = 22.2 Hz, 6.7 Hz, 2F); IR (neat) 1482, 1093, 971 cm^{-1}; HRMS (TOF MS CI+) m/z calcd for $C_{12}H_5F_5S$ $(M)^+$ 276.0032, found 276.0025.

(4-Methoxyphenyl)(phenyl)sulfane (12). Title compound was prepared according to general procedure A from 4-methoxybenzenethiol (0.062 mL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (10% EtOAc in hexanes) afforded the title compound as a colorless oil (0.071 g, 66%). Spectral data were consistent with reported values:[34] TLC R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 2H), 7.22−7.11 (m, 5H), 6.87 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 138.7, 135.4, 129.0, 128.2, 125.8, 124.3, 115.0, 55.3.

(4-Nitrophenyl)(phenyl)sulfane (13). Title compound was prepared according to general procedure A from 4-nitrobenzenethiol (0.082 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (10% EtOAc in hexanes) afforded the title compound as a colorless oil (0.042 g, 37%). Spectral data were consistent with reported values:[34] TLC R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dt, J = 9.6 Hz, J = 2.2 Hz, 2H), 7.53 (m, 2H), 7.46 (m, 3H), 7.18 (dt, J = 9.6 Hz, J = 2.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 145.4, 134.8, 130.5, 130.1, 129.7, 126.7, 124.1.

4-Phenylsulfanylacetophenone (14). Title compound was prepared according to general procedure A from 1-(4-sulfanylphenyl)-ethan-1-one (60 μL, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 2.6 mL). Purification by flash column chromatography (5% EtOAc in hexanes) afforded the title compound as a pale yellow solid (0.072 g, 63%). Spectral data were consistent with reported values:[38] TLC R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.5 Hz, 2H), 7.50−7.47 (m, 2H), 7.40−7.38 (m, 3H), 7.20 (d, J = 8.5 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 145.0, 134.5, 134.0, 132.1, 129.8, 129.0, 128.9, 127.5, 26.5; IR (neat) 2922, 1677, 1589, 690 cm^{-1}.

2-Phenylthiobenzothiazole (15). Title compound was prepared according to general procedure A from 2-mercaptobenzothiazole (0.084 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (0.087 g, 71%). Compound **15** was also prepared from PhMgBr according to general procedure B to afford 65% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were consistent with reported values:[39] TLC R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.72 (m, 2H), 6.63 (d, J = 8.0 Hz, 1H), 7.52−7.43 (m, 3H), 7.38 (m, 1H), 7.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 154.0, 135.6, 135.4, 130.6, 130.01, 129.98, 126.2, 124.4, 122.0, 120.9.

2-Phenylthiobenzoxazole (16). Title compound was prepared according to general procedure A from 2-mercaptobenzoxazole (0.076 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (0.093 g, 82%). Compound **16** was also prepared from PhMgBr according to general procedure B to afford 57% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were consistent with reported values:[39] TLC R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.59 (m, 1H), 7.47−7.42 (m, 3H), 7.39 (m, 1H), 7.27−7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 152.0, 142.1, 134.5, 130.0, 129.8, 127.3, 124.5, 124.4, 119.2, 110.2.

2-(Phenylthio)pyrimidine (17). Title compound was prepared according to general procedure A from 2-mercaptopyrimidine (0.056 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (20% EtOAc in hexanes) afforded the title compound as a colorless oil (0.081 g, 86%). Spectral data were consistent with reported values:[40] TLC R_f = 0.3 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 5.0 Hz, 2H), 7.63 (m, 2H), 7.44 (m, 3H), 6.95 (t, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 157.7, 135.4, 129.45, 129.43, 129.3, 117.1.

1-Phenyl-5-(phenylthio)-1*H*-tetrazole (18). Title compound was prepared according to general procedure A from 1-phenyl-1*H*-tetrazole-5-thiol (0.089 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (30% EtOAc in hexanes) afforded the title compound as a colorless crystalline solid (0.102 g, 80%): TLC R_f = 0.4 (30% EtOAc in hexanes); mp 129−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.53 (m, 7H), 7.42−7.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 134.0, 133.7, 130.5, 130.1, 129.86, 129.85, 126.9, 124.5; IR (neat) 3067, 2922, 1498, 1412, 1389, 1240 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{13}H_{10}N_4S$ $(M + Na)^+$ 277.0524, found 277.0524.

2-Phenyl-5-(phenylthio)-1,3,4-oxadiazole (19). Title compound was prepared according to general procedure A from 5-phenyl-1,3,4-oxadiazaole-2-thiol (0.089 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (20−50% EtOAc in hexanes) afforded the title compound as a white solid (0.089 g, 70%). Spectral data were consistent with reported values:[41] TLC R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 7.0 Hz, 2H), 7.67 (m, 2H), 7.51−7.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 162.9, 133.7, 131.9, 129.9, 129.8, 129.1, 127.1, 126.8, 123.5.

1-Methyl-2-(phenylthio)-1*H*-imidazole (20). Title compound was prepared according to general procedure A from 2-mercapto-1-methylimidazole (0.057 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (10% EtOAc in hexanes) afforded the title compound as a colorless oil (0.081 g, 95%). Compound **20** was also prepared from PhMgBr according to general procedure B to afford 59% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were consistent with reported values:[39] TLC R_f = 0.2 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.18−7.13 (m, 4H), 7.06 (d, J = 1.0 Hz, 1H), 3.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 135.0, 130.2, 129.3, 128.0, 126.6, 123.9, 33.9.

2-(4-Methoxyphenylthio)pyrimidine (21). Title compound was prepared according to general procedure B from 2-mercaptopyrimidine (0.056 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and (4-OMe)PhMgBr (1.3 mmol, 1.8 mL). Purification by flash column chromatography (20−30% EtOAc in hexanes) afforded the title compound as a white solid (0.082 g, 75%). Spectral data were consistent with reported values:[40] TLC R_f = 0.4 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 4.4 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 6.95 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 160.6, 157.6, 137.1, 120.0, 116.8, 114.9, 55.4.

2-(4-(Trifluoromethyl)phenylthio)pyrimidine (22). Title compound was prepared according to general procedure B from 2-mercaptopyrimidine (0.056 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and (4-CF_3)PhMgBr (1.3 mmol, 2.1 mL). Purification by flash column chromatography (10−30% EtOAc in hexanes) afforded the title compound as a colorless oil (0.110 g, 86%): TLC R_f = 0.6 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.8 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.02 (t, J =

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4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 157.8, 135.1, 134.6 (ap d, J = 1.4 Hz, 1C), 131.1 (q, J = 32.8 Hz, 1C), 126.1 (q, J = 3.7 Hz, 1C), 124.0 (q, J = 272.4 Hz, 1C), 117.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0; IR (thin film) 3039, 2927, 1566, 1389, 1329, 1170, 1122 cm^{-1}; HRMS (TOF MS CI+) m/z calcd for $C_{11}H_7F_3N_2S$ (M + H)$^+$ 257.0360, found 257.0353.

3-(Pyrimidin-2-ylthio)benzonitrile (23). Title compound was prepared according to general procedure B from 2-mercaptopyrimidine (0.056 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and (3-CN)PhMgBr (1.3 mmol, 2.3 mL). Purification by flash column chromatography (10−30% EtOAc in hexanes) afforded the title compound as a white solid (0.074 g, 69%): TLC R_f = 0.4 (30% EtOAc in hexanes); mp 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.4 Hz, 2H), 7.95 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 157.7, 139.2, 138.3, 132.5, 131.7, 129.8, 118.1, 117.7, 113.4; IR (thin film) 3066, 2927, 2231, 1560, 1379, 1182 cm^{-1}; HRMS (TOF MS CI+) m/z calcd for $C_{11}H_7N_3S$ (M + H)$^+$ 214.0439, found 214.0433.

2-(3,4,5-Trimethoxyphenylthio)pyrimidine (24). Title compound was prepared according to general procedure A from 2-mercaptopyrimidine (0.056 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and 3,4,5-trimethoxyphenylzinc bromide (1.3 mmol, 2.8 mL). Purification by flash column chromatography (20−50% EtOAc in hexanes, 1% Et_3N) afforded the title compound as a white solid (0.059 g, 43%): TLC R_f = 0.1 (30% EtOAc in hexanes); mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.8 Hz, 2H), 6.99 (t, J = 4.8 Hz, 1H), 6.88 (s, 2H), 3.90 (s, 3H), 3.87 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 157.8, 153.6, 139.2, 123.8, 117.1, 112.4, 61.0, 56.3; IR (neat) 2945, 2851, 1547, 1375, 1117 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{13}H_{14}N_2O_3S$ (M+Na)$^+$ 301.0623, found 301.0616.

2-(3,4,5-Trimethoxyphenylthio)benzoxazole (25). Title compound was prepared according to general procedure A from 2-mercaptobenzoxazole (0.076 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and 3,4,5-trimethoxyphenylzinc bromide (1.3 mmol, 2.8 mL). Purification by flash column chromatography (5−15% EtOAc in hexanes, 1% Et_3N) afforded the title compound as a white solid (0.117 g, 74%): TLC R_f = 0.4 (30% EtOAc in hexanes); mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.6 Hz, J = 5.6 Hz, 1H), 7.44 (dd, J = 8.8 Hz, J = 6.0 Hz, 1H), 7.27 (m, 2H), 6.94 (s, 2H), 3.90 (s, 3H), 3.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 153.8, 152.0, 142.1, 139.8, 124.54, 124.45, 121.2, 119.2, 112.0, 110.2, 61.0, 56.4; IR (neat) 2931, 2837, 1489, 1451, 1406, 1232, 1129, 1121 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{15}NO_4S$ (M + Na)$^+$ 340.0620, found 340.0620.

1-Phenyl-5-(3,4,5-trimethoxyphenylthio)-1*H*-tetrazole (26). Title compound was prepared according to general procedure A from 1-phenyl-1*H*-tetrazole-5-thiol (0.089 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and 3,4,5-trimethoxyphenylzinc bromide (1.3 mmol, 2.8 mL). Purification by flash column chromatography (30−50% EtOAc in hexanes, 1% Et_3N) afforded the title compound as a white solid (0.105 g, 61%): TLC R_f = 0.3 (30% EtOAc in hexanes); mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 5H), 6.78 (s, 2H), 3.86 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.8, 139.9, 133.8, 130.5, 129.9, 124.7, 120.7, 111.7, 61.0, 56.4; IR (neat) 3042, 2951, 2860, 1585, 1408, 1231, 1125 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{16}N_4O_3S$ (M + Na)$^+$ 367.0841, found 367.0836.

2-Phenyl-5-(3,4,5-trimethoxyphenylthio)-1,3,4-oxadiazole (27). Title compound was prepared according to general procedure A from 5-phenyl-1,3,4-oxadiazaole-2-thiol (0.089 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol) and 3,4,5-trimethoxyphenylzinc bromide (1.3 mmol, 2.8 mL). Purification by flash column chromatography (5−25% EtOAc in hexanes, 1% Et_3N) afforded the title compound as a white solid (0.100 g, 58%): TLC R_f = 0.3 (30% EtOAc in hexanes); mp 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 6.8 Hz, 2H), 7.51 (m, 3H), 6.93 (s, 2H), 3.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 163.3, 153.9, 139.8, 132.0, 129.2, 126.9, 123.6, 121.0, 111.5, 61.1, 56.5; IR (neat) 3009, 2943, 2850, 1582, 1463, 1128 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{17}H_{16}N_2O_4S$ (M +Na)$^+$ 367.0728, found 367.0722.

General Procedures for Biological Experiments. Biological experiments were performed according to a modified procedure by Sigman et al.[28]

Materials. The following reagents were obtained from commercial sources as indicated: Dulbecco's Modified Eagle's Medium (DMEM)/high glucose containing 4.5 g/L glucose and 4.0 mM L-glutamine (HyClone); fetal bovine serum (FBS), heat-inactivated (Omega Scientific); L-glutamine, 200 mM (Gibco); penicillin/streptomycin solution 50× (Mediatech); DMEM/Ham's Nutrient Mixture F12 containing 2.5 mM L-glutamine, 3151 mg/L dextrose, and 55 mg/L sodium pyruvate (Sigma-Aldrich); horse serum (Sigma-Aldrich); 50 μM hydrocortisone solution (Sigma-Aldrich); human insulin solution (Sigma-Aldrich); cholera toxin (Sigma-Aldrich); human Epidermal Growth Factor (EGF), recombinant (Sigma-Aldrich); 0.25% Trypsin-EDTA (Gibco); nuclease-free sterile water (Fisher Scientific); molecular biology grade DMSO (Sigma-Aldrich); ICI 182,780 (faslodex) (Tocris Bioscience).

Cell Lines and Culture Conditions. MCF-7 cells were maintained in DMEM/high glucose supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with MCF-7 cells were performed in DMEM/high glucose supplemented with 2% FBS, L-glutamine, and penicillin/streptomycin. MCF-10A cells were maintained in standard medium according to a modified recipe by Brugge et al.:[42] DMEM/F12 supplemented with 5% horse serum, 10 μg/mL of human insulin, 0.5 μg/mL of hydrocortisone, 10 ng/mL of EGF, 100 ng/mL of cholera toxin, and penicillin/streptomycin. Experiments with MCF-10A cells were performed in the same medium.

Evaluation of Compounds against MCF-7 Cells. MCF-7 cells were centrifuged in 1× PBS for 20 min, and then the pellet was resuspended in DMEM supplemented with 10% FBS and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 1500 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well of DMEM supplemented with 10% FBS, and grown for 24 h in 5% CO_2 at 37 °C. The compounds (including the faslodex positive control) were dissolved in molecular biology grade DMSO to achieve a 3.5 mM stock solution and then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 3.5 mM stock solutions were subsequently diluted to a final concentration of 10 μM in DMEM supplemented with 2% FBS. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

After 24 h of growth, the cells were treated by replacing the normal media with fresh media containing the individual compounds or vehicle control (day 0). The outer rows of wells were not used to eliminate the possibility of effects due to evaporation of media. The cells were incubated with compound for 48 h and then treated again by aspirating the media and adding fresh media containing the compounds and controls (day 2). This procedure was repeated after an additional 48 h (day 4). After incubating a final 24 h, the 96-well plates were rinsed with 1× PBS, blotted dry, and then frozen at −78 °C overnight (day 5). On day 6, cell proliferation was measured using the fluorescence-based CyQUANT Cell Proliferation Assay Kit (Invitrogen).

Fluorimetry analysis was performed according to a modified procedure by McGowan et al.[43] Cells were stained with 200 μL/well of 1× CyQUANT GR dye in cell lysis buffer for 10 min in the dark at room temperature and quantified by fluorimetry at 535 nm with 485 nm excitation. The fluorescence values were normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 6 wells per compound.

Evaluation of Compounds against MCF-10A Cells. MCF-10A cells were centrifuged in 1× PBS for 20 min, and then the pellet was resuspended in DMEM/F12 and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 9000 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well of DMEM/F12, and grown for 24 h in 5% CO_2 at 37 °C. The 3.5 mM stock solutions of compound in

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DMSO were subsequently diluted to a final concentration of 10 μM in DMEM/F12. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

Addition of compounds was performed as specified above for days 0–6. Fluorimetry analysis was performed as specified above for MCF-7 cells, with the exception of staining MCF-10A cells with 200 μL/well of 5× CyQUANT GR dye in cell lysis buffer for 10 min in the dark at room temperature before quantification by fluorimetry. The fluorescence values were normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 6 wells per compound.

Dose–Response of Compounds 19 and 25. MCF-7 cells were centrifuged in 1× PBS for 20 min, and then the pellet was resuspended in DMEM supplemented with 10% FBS and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 1500 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well of DMEM supplemented with 10% FBS, and grown for 24 h in 5% CO_2 at 37 °C. The compounds **19** and **25** were dissolved in molecular biology grade DMSO to achieve a 42 mM stock and then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 42 mM stock solutions in DMSO were subsequently diluted to 120 μM in DMEM supplemented with 2% FBS and then serially diluted to achieve 10 different concentrations. Additionally, the corresponding DMSO vehicle controls for each concentration were serially diluted using the same medium.

Addition of compounds was performed as specified above for days 0–6. Fluorimetry analysis was performed as specified above for the evaluation of compounds against MCF-7 cells. The fluorescence values were normalized to the DMSO vehicle controls corresponding to each concentration. The normalized values were plotted as an average ± standard deviation of 4 wells per concentration, and these data were analyzed using the dose–response nonlinear regression fitting function (log[inhibitor] vs response with variable slope (four parameters)).

■ ASSOCIATED CONTENT

Supporting Information

Dose–response curves and spectroscopic data 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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