HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2018 September 18.

Published in final edited form as:

J Org Chem. 2017 April 07; 82(7): 3844–3854. doi:10.1021/acs.joc.7b00440.

Thermal and Photoinduced Copper-Promoted C–Se Bond Formation: Synthesis of 2-Alkyl-1,2-benzisoselenazol-3(2*H*)-ones and Evaluation against *Mycobacterium tuberculosis*

Sandeep Thanna[†], **Christopher M. Goins**[†], **Susan E. Knudson**[‡], **Richard A. Slayden**[‡], **Donald R. Ronning**[†], and **Steven J. Sucheck**[*,†]

[†]Department of Chemistry and Biochemistry, The University of Toledo, 2801 W. Bancroft Street, Toledo, Ohio 43606, United States

[‡]Mycobacteria Research Laboratories, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado 80523, United States

Abstract

2-Alkyl-1,2-benzisoselenazol-3(2*H*)-ones, represented by ebselen (**1a**), are being studied intensively for a range of medicinal applications. We describe both a new thermal and photoinduced copper-mediated cross-coupling between potassium selenocyanate (KSeCN) and *N*-substituted *ortho*-halobenzamides to form 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones containing a C–Se–N bond. The copper ligand (1,10-phenanthroline) facilitates C–Se bond formation during heating via a mechanism that likely involves atom transfer (AT), whereas, in the absence of ligand, photoinduced activation likely proceeds through a single electron transfer (SET) mechanism. A library of 15 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones was prepared. One member of the library was azide-containing derivative **1j** that was competent to undergo a strain-promoted azide–alkyne cycloaddition. The library was evaluated for inhibition of *Mycobacterium tuberculosis* (*Mtb*) growth and *Mtb* Antigen 85C (*Mtb* Ag85C) activity. Compound **1f** was most potent with a minimal inhibitory concentration (MIC) of 12.5 μg/mL and an *Mtb* Ag85C apparent IC_{50} of 8.8 μM.

Abstract

[*]**Corresponding Author** steve.sucheck@utoledo.edu.

ASSOCIATED CONTENT

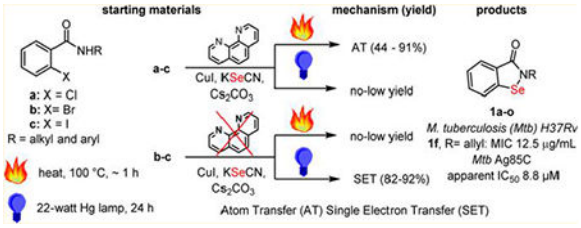
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:10.1021/acs.joc.7b00440.

^1H, ^{13}C NMR spectra for new compounds, compound **8** X-ray statistics, fluorescence studies, *Mtb* Ag85C study data, Alamar Blue assay (PDF) Crystallographic data for compound **8** (CIF)

Notes

The authors declare no competing financial interest.



■ INTRODUCTION

2-Phenyl-1,2-benzisoselenazol-3(2*H*)-one (**1a**), also called ebselen, EBS, PZ51, and DR3305 (Figure 1), is a lipid soluble organo-selenium compound that mimics glutathione peroxidase (GPx) activity and has the ability to inhibit some bacterial thioredoxin reductase systems (Figure 1).[1–3] EBS is being studied as a possible therapeutic agent for cancer,[4–8] bipolar disorder,[9] and for a rapidly expanding list of other indications.[10–14] Our interest was drawn to EBS due to our own efforts to identifying new *Mycobacterium tuberculosis (Mtb)* Ag85 inhibitors,[15–19] by reports of its activity against *Mtb* Ag85C[20] and drug-resistant *Mtb*.[21] In this work, we develop an efficient method to prepare libraries of 2-alkyl-1,2-benziso-selenazol-3(2*H*)-ones in order to identify a lead candidate to for the treatment of *Mtb* infection.

Our efforts lead us to evaluate the contributions of a number of groups with regard to the preparation of EBS and its derivatives. The first report was in 1924 by Lesser and Weiss who started from 2-(hydroxyselanyl)cyclohexane-1-carbonyl chloride.[22] Later, Welter et al. converted to anthranilic acid to 2,2′-diselanediyldibenzoic acid, followed by elaboration to EBS.[23–32] Further, *N*-substituted benzamides have been treated with *n*-butyl lithium, Se powder, and CuBr to produce this chemotype.[33–35] Kumar et al., accessed EBS using N-substituted *ortho*-halobenzamides catalytic CuI, 1,10-phenanthroline (**2**), Se powder, base, and heating for 8–36 h.[36,37] The same group later accessed EBS using KSeO^{t}Bu,[38] while Schinowski et al. used lithium diselenide and *N*-substituted *ortho*-iodobenzamides.[39] In this work, we report that EBS and its derivatives can be prepared in as little as 1 h using CuI, 1,10-phenanthroline (**2**), KSeCN (**3**), and *N*-substituted *ortho*-halobenzamides (**4a**–**c**) (Figure 1, eq 1). In addition, we report a second method which represents the first example of a low temperature photoinduced copper-mediated cross-coupling of (**4b**–**c**) with KSeCN (**3**) to form a C–Se bond, leading to the formation of EBS (Figure 1, eq 2).

The discovery of a photoinduced copper-mediated cross-coupling for C–Se bonds also lead us to evaluate some of the key contributions to copper-mediated cross-coupling chemistry. The origins of this chemistry can be traced back to the early 1900s where Ullmann and Goldberg introduced copper as a catalyst for C–C and C–N bond formation. Within the last 20 years, there has been a resurgence in the use of copper with the development of new methods to allow the formation of other types C–N, C–O, C–S and C–Se bonds.[40–43] The cross-coupling reactions reported to-date for C–Se bond formation require temperatures of greater than 100 °C.[36,43,44] However, we took note of the work of Fu and Peters who reported photoinduced Cu-catalyzed cross-couplings to form C–S[45] and C–N[46,47] bonds at

temperatures as low as 0 °C in seminal work which expanded the scope of Ullmann-type chemistry to thermally sensitive compounds.

Herein, we introduce ligand-directed thermal and photoinduced Cu-promoted cross-coupling methods to form C–Se bonds in which the presence of ligand favors thermal activation via a putative atom transfer (AT) mechanism, whereas the absence of ligand favors photoinduced activation, which proceeds through a putative single electron transfer (SET) mechanism (Scheme 1). In this work, the C–Se bond formation results in a putative selenocyanate **6** which cyclizes to the medicinally important ebselen (**1a**) and its congeners in a single step.

■ RESULTS

Thermal Activation.

We initially explored synthesis of 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones using reported conditions requiring 1,10-phenanthroline(phen)-CuI, Se-powder, potassium carbonate in combination with **4a** to afford **1a**; however, yields were modest in our hands after 30 h of heating (Table 1, entry 1).[36,37] We noted that diaryl selenides have been successfully synthesized using phen-CuI in combination with KSeCN.[48] On the basis of this observation, we surmised that the substitution of insoluble selenium power with KSeCN would produce an intermediate selenocyanate **6** that would cyclize to a selenazol-3(2*H*)-one under base-promoted conditions. Indeed, when we used aryl bromide **4b**, KSeCN, 0.2 equiv of phen-CuI, and 2.5 equiv of Cs_2CO_3, we obtained similar yields to entry 1 (Table 1) with a significantly reduced reaction time (Table 1, entry 2). Furthermore, the reaction was homogeneous and convenient to work up. Increasing the phen-CuI to 0.30 equiv improved the yield to 34% and 53% at 1 and 12 h reaction times, respectively (Table 1, entries 3 and 4), while increasing the catalyst loading to 1.0 equiv resulted in a 71% yield in 1 h (Table 1, entry 5). The chloride **4a** was less reactive, producing a 33% yield in 1.5 h under the same conditions (Table 1, entry 6), while the iodide **4c** reacted quickly to produce **1a** in 75% yield (Table 1, entry 7). Improved yields for the **4a** were obtained by switching the solvent to acetonitrile (Table 1, entry 8). Aryl bromide **4b** and aryl iodide **4c** were converted to **1a** using acetonitrile in 89% and 91% yields (Table 1, entries 9 and 10), respectively. DMSO could also be used as a solvent; however, yields were reduced (Table 1, entry 11). Further, we noted that 1,10-phenanthroline could be removed from the reaction to produce **1a**; however, the yields were reduced (Table 1, entry 12).

A library of 14 1,2-benzisoselenazol-3(2*H*)-ones was synthesized using this thermal method. The members of the library differ from each other at the nitrogen substituent (Table 2). Compounds **1a**, **1d**, **1h**, **1i**, and **1j** were prepared with a phenyl group or an *ortho*- or *para*-substituted phenyl group (i.e., substituents = fluoro, methoxy, or azide) as the nitrogen substituent. Compounds **1b**, **1c**, and **1e** contained a benzyl substituent, while compound **1f** possessed an allyl substituent. Aliphatic substituents were also tolerated as demonstrated by the preparation of compounds **1g**, **1m**, and **1n**, which contain aliphatic rings. Larger substituents were tolerated such as *tert*-butyl and adamantyl, as shown by the preparation of compounds **1k** and **1l**, respectively.

Photoinduced Activation.

We were intrigued by a report from Fu et al. that shows Ullmann-type reactions occur under photoinduced conditions in the absence of a copper ligand.[45] Therefore, we explored this possibility with KSeCN and aryl halides (**4a**–**c**) to form ebselen (**1a**). Table 3 shows our results using aryl bromide (**4b**) which affords **1a** in 89% using thermal conditions (entry 1). Replacing the heating with a 22 W (combined) Hg lamp (Figure S1) and cooling with ice for 2 h, following by warming to room temperature, afforded **1a** in 31% (Table 3, entry 2). A significant improvement in the yield to 82% occurred when the 1,10-phenanthroline ligand was removed from the reaction (Table 3, entry 3). This data supports a proposed mechanism in which a [(phen)CuI-(SeCN)] (**C**) complex is needed in the thermal activation method, however, not needed in the light activated case. The yield of the photoinduced reaction dropped to 60% and 0% when 10 and 0 mol % CuI were used (Table 3, entries 4 and 5, respectively). These results illustrate the requirement for copper(I). When the phen-free reaction was placed in the dark, a 6% yield was observed (Table 3, entry 6), indicating the importance of light. Removal of the base (Table 3, entry 7) resulted in no reaction. Ambient light was sufficient to generate a 21% yield (Table 3, entry 8). Use of a 250 W IR lamp produced a 63% yield; however, moderate heating (65–70 °C) was also involved (Table 3, entry 9). Finally, the combination of 10 mol % CuI and NaO^{t}Bu afforded a yield of 81%; however, the reaction time was extended to 48 h (Table 3, entry 10). Iodide **4c** was a superior substrate in the reaction; however, chloride **4a** was unreactive (Table 3, entries 11 and 12, respectively). The chemistry was also successful for alkyl amide **5o** which afforded ebselen derivative **1o** in 85% yield. An additional reaction was conducted using only the shortwave UV light (RPR-3000A lamp, 250–360 nm), indicating that the BLE-8T365 lamp (320–400 nm) was not needed for the reaction (Table 3, entry 14). In summary, the combination of light, a phen-free Cu(I) source, and base promoted efficient formation of ebselen (**1a**). This is the first report of a photoinduced copper-promoted C–Se–N bond forming reaction.

Copper Species Study.

We investigated the identity of possible copper complexes that might be present under thermal conditions by electrospray ionization mass spectrometry (ESI-MS). For the thermal case, a mixture of CuI, phen, KSeCN, and Cs_2CO_3 (1.0:1.0:1.2:2.5) in acetonitrile was heated to 70–80 °C for 1 h, followed by ESI-MS. Major cationic species were detected at *m*/*z*: 423.2 and 425.1, which correspond to $[(phen)_2Cu^{63}]^+$ and $[(phen)_2Cu^{65}]^+$ (**A**), respectively (Supporting Information, Figure S2). ESI-MS in the negative ion mode was inconclusive. For the photoinduced case, a mixture of CuI, KSeCN, and Cs_2CO_3 (1.0:2.2:1.2) in acetonitrile, which lacks phen, was irradiated with a 22 W (combined) Hg lamp at room temperature for 1 h. ESI-MS was inconclusive in the positive ion mode; however, the negative ion mode revealed major masses at *m*/*z*: 272, 274, and 276 that were assigned to the isotope envelope of $[Cu(SeCN)_2]^-$, i.e., $[Cu^{63}(Se^{80}CN)_2]^-$, $[Cu^{63}(Se^{80}CN)(Se^{78}CN)]^-$, and $[Cu^{65}(Se^{80}CN)_2]^-$ (**B**), respectively (Supporting Information, Figure S3). The absorption spectrum of the CuI, KSeCN, and Cs_2CO_3 (1.0:2.2:1.2) mixture was recorded after irradiation. The sample had a strong absorption band at 242 nm, and the sample exhibited a strong fluorescence emission at 338 nm after excitation at 242 nm (Supporting Information, Figure S4). The absorption spectra of a mixture of complex **B**

(0.91 μM) + **4b** (0.91 μM) and compound **4b** (0.91 μM) alone were obtained for characterization purposes (Supporting Information, Figure S5). To provide evidence of that photoexcited complex **B** can transfer energy to the substrate, substrate **4b** was titrated into complex **B** and the luminescence recorded, revealing strong concentration-dependent fluorescence quenching (Supporting Information, Figure S6).

Synthesis of Biotinylated 1,2-Benzisoselenazol-3(2*H*)-ones.

Our interest in 1,2-benzisoselenazol-3(2*H*)-ones was sparked by the cysteine-reactive nature of ebselen (**1a**) against an *Mtb* Ag85C[20] as well as reports of activity against other cysteine-containing enzymes.[49] New tools are needed to identify other possible cysteine-reactive targets within *Mtb* and other organisms. Our method development was driven in part by a desire to access **1j** which could potentially be used in combination with click chemistry as part of a long-term goal to identify cysteine-reactive enzymes and proteins. Once in hand, we investigated whether azide **1j** would undergo the copper-promoted azide–alkyne Huisgen cycloaddition (CuAAC). Thus, azide **1j** was treated with phenylacetylene (7) under standard CuAAC conditions. However, instead of forming the 1,2,3-triazole, phenylacetylene opened the selenazol-3(2*H*)-one ring to afford the isobaric dialkyl selenide (**8**). The formation of compound 8 was is confirmed by X-ray crystallography (Scheme 2). In retrospect, the identification of adduct **8** is not surprising since Cu(I) is known to form Cu-acetylides.[50] These intermediates can attack the Se atom in 1,2-benziso-selenazol-3(2*H*)-ones. To circumvent this problem, **1j** was treated with dibenzocyclooctyne-PEG_3-biotin (**9**) in THF to afford triazole **10** in 79% yield. Compound **10** may serve as a useful affinity-based tool for identification of enzymes with solvent exposed cysteines.

Mtb Growth and Enzyme Inhibition Studies.

The library of 16 1,2-benzisoselenazol-3(2*H*)-ones was screened against *Mtb* H_{37}Rv using a modified 96-well microplate Alamar blue assay (MABA) to determine minimal inhibitory concentrations (MICs). The MICs ranged from 12.5 to 100 μg/mL with the exception of compound **10**, which was less active (Table 4). The library was screened at 5 μM for the ability to covalently inhibit the activity of *Mtb* Ag85C using a previously reported fluorometric assay.[20] *Mtb* Ag85C is involved in the biosynthesis of the *Mtb* cell wall,[51] and EBS has been shown to inhibit *Mtb* Ag85C by forming a selenenylsulfide bond at Cys209.[20] On the basis of the activity of EBS, it was expected that some members of this library would behave similarly. The percent of *Mtb* Ag85C activity remaining after 40 min of incubation ranged from 15% to 80% for the library (Table 4;Supporting Information, Figure S7). The same assay[20] was used to determine the apparent IC_{50} ($app IC_{50}$) for each compound against *Mtb* Ag85C after 15 min of incubation. This assay revealed $app IC_{50}$ in the range of 0.54 to greater than 100 μM (Table 4; Supporting Information, Figure S8A and S8B).

■ DISCUSSION

Chemistry.

Different mechanisms have been proposed for the copper-catalyzed Ullmann-type reactions.[52–62] These include (i) oxidative addition—reductive elimination (OA-RE, Cu(I)/(III)),[57,63] (ii) single-electron transfer (SET, Cu(I)/(II)),[56] and (iii) atom transfer (AT, Cu(I)/(II)).[62] An

OA-RE cycle involves oxidative addition of Ar-X on $LCu^{I}(SeCN)$ to generate an $LCu^{III}(SeCN)ArX$ intermediate, which undergoes RE to form a C–Se coupled product. The work of Mitani,[64] Bethell,[65] Hartwig,[66] and Huffman[67] suggested the possible occurrence of Cu(III) species. However, more recent computational studies by Jones et al. suggest the energies required to access the Cu(III) species in the OA step are prohibitively high in comparison to energies required for key intermediates in SET and AT mechanisms.[68] We propose AT and SET mechanisms for the arylselenocyanate formation in Scheme 1. The AT mechanism involves transfer of the halide atom from aryl halide to a $(phen)Cu^{I}(SeCN)$ (**C**) complex, forming caged aryl radical (Ar·) and $(phen)Cu^{II}(SeCN)X$ complex (**D**). Complex (**D**) would couple to afford an arylselenocyanate **6** and $(phen)Cu^{I}X$ (**E**). Intermediate **E** can undergo ligand exchange to regenerated **C**, completing the cycle. Arylselenocyanate **6** can cyclize to form **1**. A photoinduced SET mechanism requires a radical-nucleophilic aromatic substitution ($S_{RN}1$) and involves photoexcitation of $[Cu^{I}(SeCN)_2]^{-}$ (**B**) to afford excited species $[Cu^{I}(SeCN)_2]^{-}*$ (**F**), which can undergoes SET to form a putative caged radical pair comprising $[Ar–X^{\bullet -}$ and $Cu^{II}(SeCN)_2]$ (**G**).[68] Intermediate **G** can couple to form arylselenocyanate **6** and $[Cu^{I}(SeCN)X]^{-}$ (**H**). Intermediate **H** can undergo ligand exchange to regenerate **B**, completing the catalytic cycle. The radicals generated in the SET and AT mechanisms are proposed to exist as caged radical pairs which rapidly convert to product; hence, they are not affected in the presence of radical quenchers.[69,70] EPR spectroscopy studies by Hida and co-workers on the reaction of haloanthraquinones and aminoethanol observed the short-lived radical species and Cu(II) species.[69,70] Similarly, Fu and Peters observed copper(II)-thiolate complexes during studies on photoinduced cross-coupling between aryl thiols and aryl halides.[71] We also note the order of reactivity of aryl halides for C–Se cross-coupling under the thermal and photoinduced conditions was I > Br > Cl, which parallels the reduction potentials of aryl halides (e.g., PhI −1.91 V, PhBr −2.43 V, PhCl −2.76 V)[72,73] and is opposite to the reactivity of aromatic nucleophilic substitution reaction. This also infers that the thermal reaction proceeds through a radical reaction.

The observed and proposed intermediates parallel what has been observed for the Cu-catalyzed cross-coupling of aryl halides with thiols both thermally and photoinduced. For the thermal case, Hartwig et al. used X-ray diffraction and solution phase characterization to observe copper complexes that exist as neutral three-coordinate trigonal planar complexes of $[(phen)Cu^{I}(phth)]$ in the solid state and as ionic complexes consisting of $[(phen)_2Cu^{I}]^{+}$ and $[Cu(phth)_2]^{-}$ in solution.[66] Hartwig et al. also isolated ionic complexes (e.g., $[(Me_2phen)_2$-$Cu]^{+}$ and $[Cu(OPh)_2]^{-}$) in the copper-catalyzed etherification of aryl halides and observed that the concentration of ionic complexes is higher in polar solvents.[66] We postulate the presence of a related neutral $[(phen)Cu^{I}(SeCN)]$ (**C**) intermediate in the thermally activated copper-promoted cross-coupling to form C–Se bonds. This adduct can form from the disproportionation reaction of $[(phen)_2Cu^{I}]^{+}$ (**A**) and $[Cu^{I}(SeCN)_2]^{-}$ (**B**) complexes. Our evidence for this intermediate is indirectly supported by the observation that addition of ligand increases the yield from 44% to 89% (Table 1, entries 11 and 9). Only the addition of ligand would allow for formation of a $[(phen)Cu^{I}(SeCN)]$ (**C**) or a related neutral (phen) complex. For the photoinduced case, Peters and Fu extensively investigated the cross-coupling between and thiols and aryl halides. They concluded that the $[Cu(SAr)_2]^{-}$ anion is the lone and active intermediate.[71] Similarly, we observed the related $[Cu(SeCN)_2]^{-}$ (**B**)

anion. EPR studies by Hida and coworkers on the photoinduced Cu-catalyzed cross-coupling of haloanthraquinones and aminoethanol identified short-lived radical species and Cu(II) species.[69,70] Similarly, Fu and Peters observed copper(II)-thiolate complexes (analogous to complex **G**) during studies on photoinduced cross-coupling between and thiols and aryl halides.[71] We set up experiments with and without 1,10-phenanthroline ligand. Under photoinduced activation, addition of ligand decreases yield from 82% to 31% (Table 3, entries 3 and 2), which is likely a result of a decrease in $[Cu^{I}(SeCN)_2]^-$ concentration, indicating $[Cu^{I}(SeCN)_2]^-$ as active catalyst. Our observations combined with the cited prior work suggests that the photoinduced Cu-promoted cross-coupling of arylhalides and KSeCN proceeds through an SET mechanism.

Biological.

Among the library, compound **1a**, **1c**, and **1f** showed the lowest MICs = 12.5 μg/mL against *Mtb* H37Rv and shared calculated LogP (cLogP) values in the range of 2.73–3.70. Compounds **1g**, **8**, and **10** showed MIC ≥ 50 μg/mL and shared cLogP values ≥ 4.60. The remainder of the compounds shared intermediate MICs and cLogP values. We suspect the most active compounds had cLogP values ideal for cell wall diffusion. Compounds **1a**, **1c**, and **1f** reduced *Mtb* Ag85C activity to 17%, 36%, and 15%, respectively, after 40 min of enzyme incubation (Table 4). Compounds **1g**, **1l**, **1m**, **1n**, **10** reduced *Mtb* Ag85C activity to 30%, 59%, 40%, 44%, and 61%, respectively. This reduction in compound activity between the two groups loosely correlates with the replacement of the phenyl group with an alkyl or the large biotinyl moiety in the case of **10**. The data suggest all the compounds were reacting with the exposed cysteine 209 on *Mtb* Ag85C; however, the phenyl-containing compounds accessed the reactive site better. This conclusion is supported by the *app*IC_{50} data which show all the compounds with the exception of **8** rapidly inactivate the enzyme at low concentrations.[74] The results are significant in light of limited progress that has been made identifying inhibitors of Ag85s. The few classes of compounds have been described which inhibit the Ag85s have been reviewed[75] and include thiophenes,[17,76] phosphonates,[77] sulfonates,[78] and derivatives of trehalose[51,79,80] and arabino-sides.[19,81] These earlier inhibitors demonstrated IC_{50s} in the mid to low μM range, whereas, in the current study, we identified inhibitors in the nM range.

CONCLUSIONS

An efficient Cu-promoted synthesis of 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones was discovered that involves the use of 1,10-phenanthroline, KSeCN, and *ortho*-halobenzamides. The method affords the products in as little as 1 h, which is significantly faster than similar chemistry using Se powder. As part of this study, the first example of a photoinduced Cu-promoted C–Se bond forming reaction was discovered that enabled the synthesis of ebselen (**1a**) at low temperatures upon irradiation with a 22 W (combined) Hg lamp. An atom transfer step and a 1,10-phenanthroline-Cu complex is proposed in the thermal mechanism, and a single electron transfer step is proposed for the photoinduced mechanism. The mechanisms are supported by the ESI-MS detection of $[(phen)_2CuI]^+$ (**A**) and $[CuI(SeCN)_2]^-$ (**B**) complexes. A library of 14 1,2-benzisoselenazol-3(2*H*)-ones was prepared in good yield using the thermal method. The library was evaluated for anti-*Mtb*

$H_{37}RV$ activity and the ability to inhibit a cysteine-containing *Mtb* Ag85C demonstrating different aspects of utility for the chemotype. As a result, new *Mtb* growth and enzyme inhibitors were identified. Due to the rapidly expanding medical applications for 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones, these methods are expected to facilitate the synthesis of new therapeutics.

EXPERIMENTAL SECTION

General Information.

All the starting materials were obtained from Acros Organics or Sigma-Aldrich. Unless specified, all the reactions are carried out under an atmosphere of nitrogen using a nitrogen balloon. All solvents were purchased form Fisher Scientific or Sigma-Aldrich. The solvents were purified by distillation and other standard methods. Reactions were monitored using thin-layer chromatography (TLC silica gel 62 F_{254}), and spots were observed by UV light. All photochemical reactions were carried out in a handmade cardboard box fitted with two bulbs with a combined output of 22 W (14 W Rayonet RPR-3000A lamp (spectral energy distribution wavelength range: 250–360 nm) + 8 W Spectronics Corp. BLE-8T365 (365 nm)). An Aminco Bowman II luminescence spectrometer was used for fluorimetry experiments. ^{1}H NMR and ^{13}C NMR and G-COSY were carried out using a Bruker Avance III 600 MHz or Varian Inova 600 MHz spectrometers. ^{1}H NMR and ^{13}C NMR were referenced to the $CDCl_3$ peak at 7.27 and 77.16, respectively. High resolution mass spectroscopy (HRMS) was performed on a micro mass Q-TOF2 instrument.

General Procedure for Thermal Activated Synthesis of Benzo-1,2-selenazol-3(2*H*)-one compounds, Table 1.

The starting benzamide (1 equiv), copper(I) iodide (1 equiv), 1,10-phenanthroline (1 equiv), cesium carbonate (2.5 equiv), and potassium selenocyanate (1.2 equiv) were suspended in solvent *N,N*-dimethylmethanamide or acetonitrile. The resulting red colored mixture was heated to 95–100 °C for 0.6–12 h. The reaction was cooled, diluted with 20.0 mL of ethyl acetate, and filtered, and the residue was washed with ethyl acetate. To the filtrate was added cold H_2O (20.0 mL), followed by extraction with 20.0 mL of ethyl acetate. This process was repeated thrice. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain a solid which was purified by flash column chromatography on silica gel (ethyl acetate–hexane) to obtain product 1,2-benzisoselenazol-3(2*H*)-one derivative.

Synthesis of 2-Phenylbenzo[*d*][1,2]selenazol-3(2*H*)-one (1a).[82]

2-Iodo-*N*-phenylbenzamide (400 mg, 1.24 mmol), copper(I) iodide (236 mg, 1.24 mmol), 1,10-phenanthroline (223 mg, 1.24 mmol), cesium carbonate (1011 mg, 3.10 mmol), potassium selenocyanate (214 mg, 1.49 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 45 min, 100 °C. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexanes) to obtained pure 2-phenylbenzo[*d*][1,2]selenazol-3(2*H*)-one **1a**. Yield 75% (256.2 mg), white solid; silica gel TLC R_f = 0.37 (3:7 ethyl acetate–hexanes); mp 182–183 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 1 H), 7.70–7.62 (m, 4 H), 7.49 (ddd, *J* = 2.3, 5.8, 7.9 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.32–7.28 (m, *J* =1.0, 1.0 Hz, 1 H) ; ^{13}C NMR (150.2

MHz, MeoD) δ 166.6, 139.7, 139.0, 132.2, 129.0, 128.0, 127.9, 126.7, 126.1, 125.5, 124.8; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{13}H_{17}NO_3Na$ 297.9747; Found 297.9748.

Synthesis of 2-(4-Methoxybenzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1b).

2-Iodo-*N*-(4-methoxybenzyl)benzamide (400 mg, 1.08 mmol), copper(I) iodide (207 mg, 1.08 mmol), 1,10-phenanthroline (196 mg, 1.08 mmol), cesium carbonate (888 mg, 2.72 mmol), potassium selenocyanate (188 mg, 1.30 mmol), and *N*,*N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexane) to obtain pure 2-(4-methoxybenzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1b**). Yield 63% (220.5 mg), white solid; silica gel TLC R_f = 0.1 (3:7 ethyl acetate–hexanes); mp 139–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 1 H), 7.59–7.54 (m, 9 H), 7.43 (ddd, *J* = 2.6, 5.6, 7.9 Hz, 1 H), 7.33–7.30 (m, *J* = 8.6 Hz, 8 H), 6.92–6.89 (m, 2 H), 4.96 (s, 2 H), 3.82 (s, 3 H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 167.1, 159.8, 139.3, 132.0, 130.3, 129.5, 129.0, 127.9, 126.3, 124.1, 114.3, 55.5, 48.4; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{15}H_{13}NO_2SeNa$ 342.0004; Found 342.0016.

2-(2-Methoxybenzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1c).

2-Iodo-*N*-(2-methoxybenzyl)benzamide (370 mg, 1.01 mmol), copper(I) iodide (192 mg, 1.01 mmol), 1,10-phenanthroline (182 mg, 1.01 mmol), cesium carbonate (821 mg, 2.52 mmol), potassium selenocyanate (174 mg, 1.20 mmol), and *N*,*N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. Purified by flash column chromatography on silica gel (25% ethyl acetate–hexane) to obtain pure product 2-(2-methoxybenzyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1c**). Yield 44% (141 mg), white solid; silica gel TLC R_f = 0.24 (3:7 ethyl acetate–hexanes); mp 169–170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 5 H), 7.58–7.56 (m, 10 H), 7.44–7.40 (m, *J* = 1.7 Hz, 11 H), 7.34 (dt, *J* =1.7, 7.8 Hz, 6 H), 6.99–6.91 (m, *J* = 0.9, 7.4, 7.4 Hz, 11 H), 5.07 (s, 2 H), 3.93 (s, 3 H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 157.6, 138.6, 131.9, 131.0, 130.0, 128.9, 127.6, 126.1, 125.7, 123.9, 121.0, 110.6, 55.4, 43.6; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{15}H_{13}NO_2SeNa$ 342.0009; Found 342.0017.

Synthesis of 2-(4-Methoxyphenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1d).[39]

2-Iodo-*N*-(4-methoxyphenyl)benzamide (400 mg, 1.13 mmol), copper(I) iodide (216 mg, 1.13 mmol), 1,10-phenanthroline (204 mg, 1.33 mmol), cesium carbonate (922 mg, 2.83 mmol), potassium selenocyanate (196 mg, 1.30 mmol), and *N*,*N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexane) to obtain pure product 2-(4-methoxyphenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1d**). Yield 67% (231 mg), pale yellow solid; silica gel TLC R_f = 0.25 (3:7 ethyl acetate–hexanes); mp 170–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (td, *J* = 0.9, 7.7 Hz, 1H), 7.65–7.68 (m, 2H), 7.46–7.53 (m, 3H), 6.94–6.98 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 166.1, 158.6, 137.9, 132.5, 131.7, 129.5, 127.6, 127.4, 126.6, 132.9, 114.7, 55.7; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{14}H_{11}NO_2SeNa$ 327.9847; Found 327.9858.

Synthesis of 2-Benzylbenzo[*d*][1,2]selenazol-3(2*H*)-one(1e).[36]

N-Benzyl-2-iodobenzamide (276 mg, 0.88 mmol), copper(I) iodide (156 mg, 0.82 mmol), 1,10-phenanthroline (148 mg, 0.82 mmol), cesium carbonate (667 mg, 2.04 mmol), potassium selenocyanate (142 mg, 1.20 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. Purified by flash column chromatography on silica gel (25% ethyl acetate–hexane) to obtain pure product 2-benzylbenzo[*d*][1,2]selenazol-3(2*H*)-one (**1e**). Yield 39% (90 mg), white solid; silica gel TLC R_f = 0.28 (3:7 ethyl acetate–hexanes); mp 130–132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.56–7.60 (m, *J* = 0.7 Hz, 2H), 7.44 (ddd, *J* = 2.7, 5.4, 7.9 Hz, 1h), 7.33–7.39 (m, 5H), 5.03 (s, 2H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 167.2, 138.0, 137.2, 132.0, 129.0, 128.9, 128.6, 128.4, 127.4, 126.3, 124.0, 49.0; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{14}H_{11}NOSeNa$ 311.9898; Found 311.9914.

Synthesis of 2-Allylbenzo[*d*][1,2]selenazol-3(2*H*)-one (1f).

2-Iodo-*N*-allylbenzamide (400 mg, 1.39 mmol), copper(I) iodide (267 mg, 1.39 mmol), 1,10-phenanthroline (251 mg, 1.39 mmol), cesium carbonate (1.135 g, 3.48 mmol), potassium selenocyanate (241 mg, 1.67 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 1.5 h, 100 °C. Purified by flash column chromatography on silica gel (25% ethyl acetate–hexane) to obtain pure product 2-allylbenzo[*d*][1,2]selenazol-x3(2*H*)-one (**1f**). Yield 39% (90 mg), white solid; silica gel TLC R_f = 0.28 (3:7 ethyl acetate–hexanes); mp 124–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (qd, *J* = 0.7, 7.9 Hz, 1 H), 7.67–7.64 (m, 1 H), 7.63–7.59 (m, 1 H), 7.45 (ddd, *J* = 1.0, 7.0, 7.9 Hz, 1 H), 5.99 (tdd, *J* = 6.3, 10.2, 16.9 Hz, 1 H), 5.44–5.31 (m, 2 H), 4.50 (td, *J* = 1.3, 6.4 Hz, 2 H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 167.1, 138.0, 133.7, 132.1, 129.0, 127.8, 126.3, 124.1, 119.5, 47.3; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{10}H_9NOSeNa$ 261.9742; Found 261.9755.

Synthesis of 2-(Cyclohexylmethyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1g).

N-(Cyclohexylmethyl)-2-iodobenzamide (200 mg, 0.58 mmol), copper(I) iodide (110 mg, 0.58 mmol), 1,10-phenanthroline (105 mg, 0.58 mmol), cesium carbonate (474.66 mg, 1.45 mmol), potassium selenocyanate (100 mg, 0.70 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 1.5 h, 100 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-(cyclohexylmethyl)benzo[*d*][1,2]-selenazol-3(2*H*)-one (**1g**) was obtained. Yield 63% (110 mg), off-white solid; silica gel TLC R_f = 0.59 (1:1 ethyl acetate–hexanes); mp 151–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 1 H), 7.66–7.59 (m, 2 H), 7.47–7.43 (m, 1 H), 3.73 (d, *J* = 7.0 Hz, 2 H), 1.82–1.73 (m, 5 H), 1.69 (d, *J* = 9.0 Hz, 1 H), 1.31–1.18 (m, 3 H), 1.12–1.03 (m, 2 H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 167.4, 137.8, 131.9, 128.9, 127.5, 126.2, 123.9, 59.5, 50.9, 39.1, 31.3, 30.6, 26.3, 25.7; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{14}H_{17}NOSeNa$ 318.0368; Found 318.0381.

Synthesis of 2-(4-Fluorophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1h).

N-(4-Fluorophenyl)-2-iodobenzamide (400 mg, 1.17 mmol), copper(I) iodide (335 mg, 1.76 mmol), 1,10-phenanthroline (317 mg, 1.79 mmol), cesium carbonate (995.56 mg, 2.93 mmol), potassium selenocyanate (203 mg, 1.40 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. After flash column chromatography on silica gel using 20% ethyl acetate

in hexanes as mobile phase, pure product 2-(4-fluorophenyl)benzo[*d*][1,2]-selenazol-3(2*H*)-one (**1h**) was obtained. Yield 52% (180 mg), white solid; silica gel TLC R_f = 0.15 (3:7 ethyl acetate–hexanes); mp 176–177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 3.7 Hz, 2H), 7.56–7.61 (m, 2H), 7.46–7.52 (m, 1H), 7.11–7.18 (m, *J* = 8.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 160.94 (d, *J* = 247.6 Hz), 137.47, 134.77 (d, *J* = 3.30 Hz), 132.6, 129.4, 127.49 (d, *J* = 7.7 Hz), 127.0, 126.6, 123.7, 116.2 (d, *J* = 22.0 Hz); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_8FNOSeNa$ 315.9647; Found 315.9657.

Synthesis of 2-(2-Fluorophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1i).

N-(2-Fluorophenyl)-2-iodobenzamide (400 mg, 1.17 mmol), copper(I) iodide (335 mg, 1.76 mmol), 1,10-phenanthroline (317 mg, 1.79 mmol), cesium carbonate (995.56 mg, 2.93 mmol), potassium selenocyanate (203 mg, 1.40 mmol), and *N,N*-dimethylmethanamide (4.0 mL), 1 h, 100 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-(2-fluorophenyl)benzo[*d*][1,2]-selenazol-3(2*H*)-one (**1i**) was obtained. Yield 35% (120 mg), off-white solid; silica gel TLC R_f = 0.24 (3:7 ethyl acetate–hexanes); mp 156–158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04–7.97 (m, *J* = 7.3 Hz, 2 H), 7.82–7.73 (m, 2 H), 7.54–7.49 (m, *J* = 1.7 Hz, 1 H), 7.43–7.39 (m, *J* = 1.7 Hz, 1 H), 7.38–7.31 (m, *J* = 1.2, 7.6 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 117.18 (d, *J* = 19.8 Hz), 122.1, 123.9, 125.11 (d, *J* = 3.3 Hz), 130.7, 130.9, 131.13 (d, *J* = 6.6 Hz), 132.7, 133.7, 158.44 (dd, *J* = 250.8, 1.0 Hz), 166.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_8FNOSeNa$ 315.9647; Found 315.9657.

Synthesis of 2-(4-Azidophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1j).

N-(4-Azidophenyl)-2-iodobenzamide (500 mg, 1.37 mmol), copper(I) iodide (262 mg, 1.37 mmol), 1,10-phenanthroline (247 mg, 1.37 mmol), cesium carbonate (1118 mg, 3.43 mmol), potassium selenocyanate (237 mg, 1.40 mmol), and *N,N*-dimethylmethanamide (5.0 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-(4-azidophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1j**) was obtained. Yield 20% (90 mg), brown solid; silica gel TLC R_f = 0.24 (3:7 ethyl acetate–hexanes); mp 169–170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (td, *J* = 0.9, 7.9 Hz, 1 H), 7.71–7.67 (m, 2 H), 7.66–7.63 (m, *J* = 8.8 Hz, 2 H), 7.51 (ddd, *J* = 3.7, 4.5, 7.9 Hz, 1 H), 7.14–7.09 (m, *J* = 8.8 Hz, 2 H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 165.8, 138.4, 137.4, 135.9, 132.7, 129.5, 127.2, 127.0, 126.7, 123.8, 119.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_8N_4OSeNa$ 338.9756; Found 338.9763.

Synthesis of 2-(*tert*-Butyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (1k).[39]

N-(*tert*-Butyl)-2-iodobenzamide (200.0 mg, 0.66 mmol), copper(I) iodide (126 mg, 0.66 mmol), 1,10-phenanthroline (119 mg, 0.66 mmol), cesium carbonate (538 mg, 1.65 mmol), potassium selenocyanate (114 mg, 0.79 mmol), and *N,N*-dimethylmethanamide (2.0 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-(*tert*-butyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1k**) was obtained. Yield 75% (125 mg), white solid; silica gel TLC R_f = 0.43 (3:7 ethyl acetate–hexanes); mp 137–139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (td, *J* = 1.1, 7.8 Hz, 1H), 7.56–7.60 (m, 2H), 7.40 (ddd, *J* = 1.7, 6.3, 8.0 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (151 MHz,

$CDCl_3$) δ 167.1, 137.0, 131.7, 130.2, 128.5, 126.1, 123.3, 59.0, 29.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{14}NOSe$ 256.0235; Found 256.0233.

Synthesis of 2-((3*R*,5*S*)-Adamantan-1-yl)benzo[*d*][1,2]-selenazol-3(2*H*)-one (1l).

N-((3*R*,5*S*)-Adamantan-1-yl)-2-iodobenzamide (400.0 mg, 1.04 mmol), copper(I) iodide (200 mg, 1.04 mmol), 1,10-phenanthroline (189 mg, 1.04 mmol), cesium carbonate (855 mg, 2.62 mmol), potassium selenocyanate (182 mg, 1.26 mmol), and *N*,*N*-dimethylmethanamide (4.0 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-((3*R*,5*S*)-adamantan-1-yl)benzo[*d*][1,2]selenazol-3(2*H*)-one (**1l**) was obtained. Yield 72% (250 mg), white solid; silica gel TLC R_f = 0.51 (3:7 ethyl acetate–hexanes); mp 215–217 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 1H), 7.59–7.58 (m, 1H), 7.57–7.54 (m, 1H), 7.41–7.38 (m, 1H), 2.43 (d, *J* = 2.4 Hz, 6H), 2.19 (s, 3H), 1.81–1.79 (m, 3H), 1.75–1.73 (m, 3H); ^{13}C NMR (150.2 MHz, $CDCl_3$) δ 166.8, 137.5, 131.5, 130.5, 128.5, 126.0, 123.4, 60.1, 41.7, 36.4, 30.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NOSe$ 334.0705; Found 334.0722.

Synthesis of 2-Cyclopentylbenzo[*d*][1,2]selenazol-3(2*H*)-one (1m).

N-Cyclopentyl-2-iodobenzamide (350.0 mg, 1.11 mmol), copper(I) iodide (211.6 mg, 1.11 mmol), 1,10-phenanthroline (200.2 mg, 1.11 mmol), cesium carbonate (905 mg, 2.77 mmol), potassium selenocyanate (192.1 mg, 1.33 mmol), and *N*,*N*-dimethylmethanamide (3.0 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-cyclopentylbenzo[*d*][1,2] selenazol-3(2*H*)-one (**1m**) was obtained. Yield 78% (232 mg), white solid; silica gel TLC R_f = 0.23 (3:7 ethyl acetate–hexanes); mp 119–120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03–8.05 (m, 1H), 7.62–7.64 (m, 1H), 7.57 (dt, *J* = 1.4, 7.6 Hz, 1H), 7.42 (ddd, *J* =1.0, 7.1, 7.9 Hz, 1H), (quin, *J* = 7.8 Hz, 1H), 2.17–2.27 (m, *J* = 1.6, 2.8 Hz, 2H), 1.81–1.90 (m, 1H), 1.69–1.75 (m, 2H), 1.61–1.68 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 137.5, 133.2, 131.7, 128.6, 126.2, 123.8, 55.9, 33.5, 24.2; HRMS (ESI-TOF) *m*/*z*xs: $[M + Na]^+$ Calcd for $C_{12}H_{13}NOSeNa$ 290.0055; Found 290.0058.

Synthesis of 2-Cyclohexylbenzo[*d*][1,2]selenazol-3(2*H*)-one (1n).[39]

N-Cyclohexyl-2-iodobenzamide (400.0 mg, 1.21 mmol), copper(I) iodide (231.6 mg, 1.22 mmol), 1,10-phenanthroline (219.1 mg, 1.21 mmol), cesium carbonate (990.3 mg, 3.04 mmol), potassium selenocyanate (210.2 mg, 1.45 mmol), and *N*,*N*-dimethylmethanamide (4.0 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 20% ethyl acetate in hexanes as mobile phase, pure product 2-cyclohexylbenzo[*d*][1,2]selenazol-3(2*H*)-one (**1n**) was obtained. Yield 85% (290 mg), white solid; silica gel TLC R_f = 0.27 (3:7 ethyl acetate–hexanes); mp 157–158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10–7.99 (m, 1 H), 7.64 (d, *J* = 7.9 Hz, 1 H), 7.57 (s, 1 H), 7.42 (s, 1 H), 4.53–4.45 (m, 1 H), 2.11 (dd, *J* = 2.0, 12.7 Hz, 2 H), 1.87 (d, *J* = 13.9 Hz, 2 H), 1.77–1.70 (m, 1 H), 1.50 (d, *J* = 13.0 Hz, 2 H), 1.40 (dd, *J* = 3.7, 11.7 Hz, 2 H), 1.25–1.16 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 137.9, 137.9, 131.7, 128.8, 126.2, 124.0, 53.8, 34.4, 25.6. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NOSe$ 282.0392; Found 282.0392.

Synthesis of *N*-(4-Azidophenyl)-2-((phenylethynyl)selanyl)-benzamide (8).

2-(4-Azidophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (100.0 mg, 0.32 mmol), copper(I) iodide (60.27 mg, 0.32 mmol), 1,10-phenanthroline (57.0 mg, 0.32 mmol), cesium carbonate (257.8 mg, 0.79 mmol), potassium selenocyanate (54.7 mg, 0.38 mmol), and *N*,*N*-dimethylmethanamide (1.5 mL), 1 h, 90 °C. After flash column chromatography on silica gel using 35% ethyl acetate in hexanes as mobile phase, pure product *N*-(4-azidophenyl)-2-((phenylethynyl)selanyl)benzamide (**8**) was obtained. Yield 71% (93.7 mg), brown solid; silica gel TLC R_f = 0.26 (3:7 ethyl acetate–hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 8.33 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.91 (s, 1H), 7.73 (dd, *J* = 1.3, 7.70 Hz, 1H), 7.62–7.67 (m, 2H), 7.55–7.59 (m, 3H), 7.37–7.42 (m, 4H), 7.05–7.10 (m, 2h); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 136.8, 135.5, 134.3, 132.8, 132.0, 131.0, 130.7, 128.7, 128.5, 126.7, 126.4, 123.4, 122.3, 119.8, 104.5, 73.8; HRMS (ESI-MS) *m*/*z*: $[M + Na]^+$ Calcd for $C_{21}H_{14}N_4OSeNa$ 441.02; Found 441.02.

Synthesis of *N*-(13,16-Dioxo-16-(3-(4-(3-oxobenzo[*d*][1,2]-selenazol-2(3*H*)-yl)phenyl)-3,9-dihydro-8*H*-dibenzo[*b*,*f*][1,2,3]-triazolo[4,5-*d*]azocin-8-yl)-3,6,9-trioxa-12-azahexadecyl)-5-((3a*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-pentanamide (10).

In a dried round-bottom flask, 2-(4-azidophenyl)benzo[*d*][1,2]selenazol-3(2*H*)-one (10.0 mg, 0.032 mmol) was dissolved in dry THF (0.5 mL) under a N_2 atmosphere and stirred for 5.0 min. Then, the solution of dibenzocyclooctyne-PEG_3-biotin (**9**, 22.32 mg, 0.032 mmol) was added and reaction mixture was stirred at room temperature for 12.0 h. After reverse phase column chromatography using H_2O as mobile phase, pure product compound **10** was obtained. Yield 79% (25.6 mg), ash color solid. Note: ^{1}H NMR integration values were not clear due to complexity of molecule, but C^{13} and HRMS were clear. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08–8.15 (m, 1H), 7.74–7.87 (m, 4H), 7.61–7.72 (m, 2H), 7.42–7.59 (m, 6H), 7.30–7.39 (m, 2H), 7.02–7.07 (m, 1H), 6.92–7.01 (m, 1H), 6.75 (s, 1H), 6.20–6.28 (m, 1H), 5.66–5.79 (m, 1H), 4.97–5.08 (m, 1H), 4.45–4.52 (m, 2H), 4.29–4.38 (m, 1H), 3.61 (br. s., 4H), 3.53–3.59 (m, 6H), 3.46–3.52 (m, 4H), 3.35–3.42 (m, 2H), 3.23–3.32 (m, 2H), 3.06–3.18 (m, 2H), 2.85–2.96 (m, 1H), 2.65–2.75 (m, 1H), 2.33–2.46 (m, 2H), 2.13–2.25 (m, 2H), 2.02 (s, 1H), 1.37–1.50 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 172.1, 172.0, 165.9, 163.1, 144.1, 143.2, 140.6, 140.3, 133.7, 132.9, 131.6, 131.2, 129.8, 129.3, 129.1, 128.7, 127.9, 127.8, 127.6, 127.5, 127.2, 126.7, 125.8, 125.5, 125.2, 124.9, 124.7, 124.2, 124.0, 70.3, 61.7, 59.9, 55.2, 52.2, 40.6, 39.3, 39.2, 39.2, 39.1, 35.6, 35.0, 30.7, 29.6, 27.9, 27.2, 25.4. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{50}H_{55}N_9O_8SSeNa$ 1044.2952; Found 1044.2976.

General Procedure for Photoinduced Synthesis of Benzo-1,2-selenazol-3(2*H*)-ones.

A borosilicate tube under an atmosphere of nitrogen was charged with aryl halide (1.0 equiv), CuI (1.0 equiv), KSeCN (2.5 equiv), Cs_2CO_3 (1.2 equiv), and acetonitrile (3.0 mL). The tube was sealed with a rubber septum, and the heterogeneous reaction mixture was cooled to 0 °C with vigorous stirring. The cooled tube was irradiated by the 22 W Hg lamps for 12–24 h. After the reaction was complete, it was filtered through Celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel, 30% ethyl acetate in hexanes.

Photoinduced Synthesis of 2-Phenylbenzo[*d*][1,2]selenazol-3(2*H*)-one (1a).

Using 2-iodo-*N*-phenylbenzamide (**4c**, 100 mg, 0.31 mmol), copper(I) iodide (59.0 mg, 0.31 mmol), cesium carbonate (121 mg, 0.37 mmol), potassium selenocyanate (112 mg, 0.78 mmol), and acetonitrile (3.0 mL), 16 h, 0 °C to room temperature. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexane) to obtain pure 2-phenylbenzo[*d*][1,2]selenazol-3(2*H*)-one (**1a**). Yield 92% (78.3 mg); silica gel TLC R_f = 0.37 (3:7 ethyl acetate–hexanes). Using 2-bromo-*N*-phenylbenzamide (**4b**, 100 mg, 0.36 mmol), copper(I) iodide (69.2 mg, 0.36 mmol), cesium carbonate (142 mg, 0.44 mmol), potassium selenocyanate (131 mg, 0.91 mmol), and acetonitrile (3.0 mL), 16 h, 0 °C to room temperature. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexane) to obtain pure 2-phenylbenzo[*d*][1,2]-selenazol-3(2*H*)-one (**1a**). Yield 87% (87.2 mg); silica gel TLC R_f = 0.37 (3:7 ethyl acetate–hexanes). Using 2-chloro-*N*-phenylbenzamide (**4a**, 100 mg, 0.31 mmol), copper(I) iodide (59.0 mg, 0.31 mmol), cesium carbonate (121 mg, 0.37 mmol), potassium selenocyanate (112 mg, 0.78 mmol), and acetonitrile (3.0 mL), 16 h, 0 °C to room temperature. Purified by flash column chromatography on silica gel (35% ethyl acetate–hexane) to obtain pure 2-phenylbenzo[*d*][1,2]-selenazol-3(2*H*)-one (**1a**). Yield < 5; silica gel TLC R_f = 0.37 (3:7 ethyl acetate–hexanes).

Photoinduced Synthesis of 2-Isobutylbenzo[*d*][1,2]-selenazol-3(2*H*)-one (1o).

2-Iodo-*N*-isobutylbenzamide (200 mg, 0.66 mmol), copper(I) iodide (126 mg, 0.66 mmol), cesium carbonate (258 mg, 0.79 mmol), potassium selenocyanate (237 mg, 1.65 mmol), and acetonitrile (3.0 mL), 32 h, 0 °C to room temperature. Purified by flash column chromatography on silica gel (30% ethyl acetate–hexane) to obtain pure 2-isobutylbenzo[*d*][1,2]selenazol-3(2*H*)-one (**1o**). Yield 85% (143.8 mg), white solid; silica gel TLC R_f = 0.39 (3:7 ethyl acetate–hexanes); mp 114–116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 1H), 7.62–7.66 (m, 1H), 7.57–7.62 (m, 1H), 7.43 (t, J = 7.3 Hz, 1H), 3.70 (d, J = 7.3 Hz, 2H), 2.05 (quind, J = 13.7 Hz, 1H), 1.00 (d, J = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 137.9, 132.0, 129.0, 127.6, 126.3, 124.0, 52.2, 30.1, 20.1; HRMS (ESI-MS) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{14}NOSe$ 256.0235; Found 256.0240.

Synthesis of Thermal Activated Copper Complex $[(phen)_2\text{-}Cu^I]$+ $[Cu^I(SeCN)_2]^-$ (A and B).

A 50.0 mL round-bottom flask (RBF) was charged with CuI (50 mg, 0.26 mmol), phen (47.3 mg, 0.26 mmol), KSeCN (95 mg, 0.65 mmol), Cs_2CO_3 (102.64 mg, 0.31 mmol), and acetonitrile (2.0 mL) under an atmosphere of N2. The resulting red colored reaction mixture was heated to 80 °C for 1.0 h, and then it was filtered through a plug of Celite to obtain copper complex **A** and **B**.

Synthesis of Copper Complex $[Cu^I(SeCN)_2]^-$ (B).

A borosilicate tube was charged with CuI (50 mg, 0.26 mmol), KseCN (95 mg, 0.65 mmol), Cs_2CO_3 (102.64 mg, 0.31 mmol), and acetonitrile (2.0 mL) under an atmosphere of N_2. The tube was sealed with a rubber septum, and the heterogeneous mixture was cooled to 0 °C. The cooled tube with reaction mixture was irradiated with a 22 W Hg lamp for 1 h, and then it was filtered through a short plug of Celite to obtain copper complex **B**.

Steady-State Fluorimetry Experiment on Copper Complex B.

A 26 μM solution of complex **B** in acetonitrile was excited using a Xe arc lamp (500 W) at 242 nm, and the right angle emission was detected at 338 nm (Figure S4).

Absorption Spectrum of Complex B, Mixture of B and 4b, and Compound 4b.

Copper complex $[CuI(SeCN)_2]^-$ (**B**) at 5.25 μM, complex **B** (5.25 μM) plus **4b** (0.91 μM), and compound **4b** (0.91 μM, alone) were prepared. The absorption spectra were then recorded (Figure S5).

Luminescence Quenching of Complex B.

2.0 mL of 5.25 μM copper complex $[CuI(SeCN)_2]^-$ (**B**) in acetonitrile was transferred into a standard quartz cuvette. The cuvette was placed in an Aminco Bowman II Spectrofluorometer, and complex **B** was excited at a wavelength of 242 nm. The emission spectrum was recorded, revealing an emission at 338 nm. Compound **4b** was added to the cuvette at concentrations of 0.72, 1.45, 2.18, and 2.90 μM, and the change in intensity of the emission spectra was recorded (Figure S6).

Procedure To Determine Percent *Mtb* A85C Active after 40 min of Incubation with Inhibitors.

Ag85C was expressed and purified as previously described.[83] The enzyme was reacted with 5 μM of 1,2-benzisoselenazol-3(2*H*)-one **1a**–**1n**, **8**, and **10** (10 mM DMSO stock) for 40 min at room temperature. The enzymatic activity of Ag85C, covalently modified with these analogues, was evaluated using a fluorometric assay previously described (Figure S7).[20] Briefly, resorufin butyrate was used as an acyl donor while trehalose was utilized as the acyl acceptor. All reactions were performed in 50 mM sodium phosphate (pH 7.5). Trehalose was dissolved in the reaction buffer to produce a 500 mM stock, while a 10 mM stock solution of resorufin butyrate was prepared using DMSO. The reactions were performed in triplicate at 37 °C on a Synergy H4 Hybrid Reader (BioTek) using 500 nM Ag85C, 4 mM trehalose, and 100 μM resorufin butyrate. Reactions are initiated through the addition of resorufin butyrate. Analysis of the data was carried out using Prism 5 software (Figure S7).

Procedure To Determine Apparent IC_{50} of 1,2-Benzisoselenazol-3(2*H*)-ones against *Mtb* Ag85C.

An apparent IC_{50} value for each 1,2-benzisoselenazol-3(2*H*)-one was obtained for *Mtb* Ag85C by varying the concentration of inhibitor, ranging from 40.0 μM to 312.0 nM (Figure S8A and S8B). Compounds were incubated with Ag85C for 15 min at room temperature. Enzymatic activity was assessed using the resourifin butyrate assay previously described. The apparent IC_{50} was calculated using the following equation: $IC_{50} = [(50 - A)(B - A)] \times (D - C) + C$,[84] where points were expressed in percent inhibition: (i) A = the point on the curve that is less than 50%, (ii) B = the point on the curve that is greater than or equal to 50%, (iii) C = the concentration of inhibitor that gives the A% inhibition, and (iv) D = the concentration of inhibitor that gives the B% inhibition (Figure S8A and S8B).

In Vitro *Mtb* Alamar Blue Assay (MABA).

Mtb H37Rv is a drug sensitive laboratory reference strain used in the MIC studies.[85] The bacteria were grown at 37 °C in Difco 7H9 Middlebrook liquid media (BD Biosciences, 271310) supplemented with 10% Middlebrook OADC Enrichment, 0.05% Tween (G-Biosciences, 786–519) and 0.2% Glycerol. A modified 96-well microplate Alamar Blue assay (MABA) was used to establish MIC values.[86] Briefly, compounds were solubilized in DMSO and were 2-fold serially diluted in 7H9 media (DMSO < or equal to 0.02% DMSO). Bacteria were grown to mid-log growth, diluted, and added to the wells with compounds. Cell and media controls were included in each plate. The plates were incubated at 37 °C for 6 days when Alamar blue was added to each well, and then the plate was incubated overnight (Alamar blue final concentration 0.001%). On day seven, the last well that showed no sign of growth and remained blue was considered the MIC for that compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The work was supported in part by a grant from the National Institutes of Health (Grant No. AI105084) to S.J.S. and D.R.R. We thank Kelly J. Lambright of the University of Toledo Instrumentation Center for assistance with X-ray crystallography on compound 8.

REFERENCES

(1). Müller A; Cadenas E; Graf P; Sies H Biochem. Pharmacol 1984, 33, 3235–3239. [PubMed: 6487370]

(2). Wendel A; Fausel M; Safayhi H; Tiegs G; Otter R Biochem. Pharmacol 1984, 33, 3241–3247. [PubMed: 6487371]

(3). Steinbrenner H; Steinbrenner H; Bilgic E; Steinbrenner H; Bilgic E; Alili L; Sies H; Brenneisen P Free Radical Res 2006, 40, 936–943. [PubMed: 17015273]

(4). Yan J; Guo Y; Wang Y; Mao F; Huang L; Li X Eur. J. Med. Chem 2015, 95, 220–229. [PubMed: 25817772]

(5). Xing F; Li S; Ge X; Wang C; Zeng H; Li D; Dong L Oral Oncol 2008, 44, 963–969. [PubMed: 18282784]

(6). Zeng H; Combs GF J. Nutr. Biochem 2008, 19, 1–7. [PubMed: 17588734]

(7). Sanmartín C; Plano D; Sharma AK; Palop JA Int. J. Mol. Sci 2012, 13, 9649–9672. [PubMed: 22949823]

(8). Huawei Z; Gerald FC, Jr. J. Nutr. Biochem 2008, 19, 1–7. [PubMed: 17588734]

(9). Singh N; Halliday AC; Thomas JM; Kuznetsova OV; Baldwin R; Woon ECY; Aley PK; Antoniadou I; Sharp T; Vasudevan SR; Churchill GC Nat. Commun 2013, 4, 1332. [PubMed: 23299882]

(10). Rusetskaya NY; Borodulin VB Biochemistry(Moscow, Russ. Fed.) 2015, 9, 45–57.

(11). Ding H; Wang T; Xu D; Cha B; Liu J; Li Y Biochem. Biophys. Res. Commun 2015, 460, 157–163. [PubMed: 25753204]

(12). Petronilho F; Florentino D; Silvestre F; Danielski LG; Nascimento DZ; Vieira A; Kanis LA; Fortunato JJ; Badawy M; Barichello T; Quevedo J Inflammation 2015, 38, 1394–1400. [PubMed: 25616904]

(13). Tan SM; Deliyanti D; Figgett WA; Talia DM; de Haan JB; Wilkinson-Berka JL Exp. Eye Res 2015, 136, 1–8. [PubMed: 25912997]

(14). Vichi S; Cortés-Francisco N; Caixach J Food Chem 2015, 175, 401–408. [PubMed: 25577098]
(15). Boucau J; Sanki AK; Sucheck SJ; Ronning DR 235th National Meeting Abstr. Pap. Am. Chem. Soc 2008, BIOL-058.
(16). Boucau J; Sanki AK; Voss BJ; Sucheck SJ; Ronning DR Anal. Biochem 2009, 385, 120–127. [PubMed: 18992216]
(17). Ibrahim DA; Boucau J; Lajiness DH; Veleti SK; Trabbic KR; Adams SS; Ronning DR; Sucheck SJ Bioconjugate Chem 2012 23, 2403–2416.
(18). Sanki AK; Boucau J; Ronning DR; Sucheck SJ Glycoconjugate J 2009, 26, 589–596.
(19). Sanki AK; Boucau J; Umesiri FE; Ronning DR; Sucheck SJ Mol. BioSyst 2009, 5, 945–956. [PubMed: 19668859]
(20). Favrot L; Grzegorzewicz AE; Lajiness DH; Marvin RK; Boucau J; Isailovic D; Jackson M; Ronning DR Nat. Commun 2013, 4, 2748. [PubMed: 24193546]
(21). Padiadpu J; Baloni P; Anand K; Munshi M; Thakur C; Mohan A; Singh A; Chandra N ACS Infect. Dis 2016, 2, 592–607. [PubMed: 27759382]
(22). Lesser R; Weiß R Ber. Dtsch. Chem. Ges. B 1924, 57, 1077–1082.
(23). Welter A; Christiaens L; Wirtz P; Nattermann A, und Cie. G.m.b.H., Fed. Rep. Ger. Patent EP0044453 (A2), 1982; p 30.
(24). Młochowski J; Kloc K; Syper L; Inglot AD; Piasecki E Eur. J. Org Chem 1993, 1993, 1239–1244.
(25). Fong MC; Schiesser CH Tetrahedron Lett 1995, 36, 7329–7332.
(26). Mlochowski J; Juchniewicz L; Kloc K; Gryglewski RJ; Jakubowski A; Inglot AD Eur. J. Org. Chem 1996, 1996, 1751–1755.
(27). Osajda M; Młochowski J Tetrahedron 2002, 58, 7531–7537.
(28). Wojtowicz H; Chojnacka M; Młochowski J; Palus J; Syper L; Hudecova D; Uher M; Piasecki E; Rybka M Farmaco 2003, 58, 1235–1242. [PubMed: 14630233]
(29). Kloc K; Maliszewska I; Mlochowski J Synth. Commun 2003, 33, 3805–3815.
(30). Wojtowicz H; Kloc K; Maliszewska I; Mlochowski J; Pietka M; Piasecki E Farmaco 2004, 59, 863–868. [PubMed: 15544790]
(31). Pietka-Ottlik M; Wojtowicz-Mlochowska H; Kolodziejczyk K; Piasecki E; Mlochowski J Chem. Pharm. Bull 2008, 56, 1423–1427. [PubMed: 18827382]
(32). Pietka-Ottlik M; Potaczek P; Piasecki E; Mlochowski J Molecules 2010, 15, 8214–8228. [PubMed: 21076388]
(33). Engman L; Hallberg AJ Org. Chem 1989, 54, 2964–2966.
(34). Chang T; Huang M; Hsu W; Hwang J; Hsu L Chem. Pharm. Bull 2003, 51, 1413–1416. [PubMed: 14646319]
(35). Zade SS; Panda S; Singh HB; Wolmershaeuser G Tetrahedron Lett 2005, 46, 665–669.
(36). Balkrishna SJ; Bhakuni BS; Chopra D; Kumar S Org. Lett 2010, 12, 5394–5397. [PubMed: 21053969]
(37). Balkrishna SJ; Bhakuni BS; Kumar S Tetrahedron 2011, 67, 9565–9575.
(38). Balkrishna SJ; Kumar S; Azad GK; Bhakuni BS; Panini P; Ahalawat N; Tomar RS; Detty MR; Kumar S Org. Biomol. Chem 2014, 12, 1215–1219. [PubMed: 24448734]
(39). Pacula AJ; Scianowski J; Aleksandrzak KB RSC Adv 2014, 4, 48959–48962.
(40). Ullmann F; Bielecki J Ber. Dtsch. Chem. Ges 1901, 34, 2174–2185.
(41). Ullmann F; Sponagel P Ber. Dtsch. Chem. Ges 1905, 38, 2211–2212.
(42). Lee C; Liu Y; Badsara SS Chem. - Asian J 2014, 9, 706–722. [PubMed: 24443103]
(43). Beletskaya IP; Ananikov VP Chem. Rev 2011, 111, 1596–1636. [PubMed: 21391564]
(44). Kumar AV; Reddy VP; Reddy CS; Rao KR Tetrahedron Lett 2011, 52, 3978–3981.
(45). Uyeda C; Tan Y; Fu GC; Peters JC J. Am. Chem. Soc 2013, 135, 9548–9552. [PubMed: 23697882]
(46). Ziegler D. l. T.; Choi J; Munoz-Molina JM; Bissember AC; Peters JC; Fu GC J.Am. Chem. Soc 2013, 135, 13107–13112. [PubMed: 23968565]

(47). Do H; Bachman S; Bissember AC; Peters JC; Fu GC J. Am. Chem. Soc 2014, 136, 2162–2167. [PubMed: 24446666]

(48). Beletskaya IP; Sigeev AS; Peregudov AS; Petrovskii PV; Khrustalev VN Chem. Lett 2010, 39, 720–722.

(49). Bender KO; Garland M; Ferreyra JA; Hryckowian AJ; Child MA; Puri AW; Solow-Cordero DE; Higginbottom SK; Segal E; Banaei N; Shen A; Sonnenburg JL; Bogyo M Sci. Transl Med 2015, 7, 306.

(50). Hein JE; Fokin VV Chem. Soc. Rev 2010, 39, 1302–1315. [PubMed: 20309487]

(51). Belisle JT; Vissa VD; Sievert T; Takayama K; Brennan PJ; Besra GS Science 1997, 276, 1420–1422. [PubMed: 9162010]

(52). Cohen T; Lewarchik RJ; Tarino JZJAm. Chem. Soc 1974, 96, 7753–7760.

(53). Cohen T; Cristea IJ Am. Chem. Soc 1976, 98, 748–753.

(54). Weingarten HJ. Org. Chem 1964, 29, 3624–3626.

(55). Aalten HL; van Koten G; Grove DM; Kuilman T; Piekstra OG; Hulshof LA; Sheldon RA Tetrahedron 1989, 45, 5565–5578.

(56). Bunnett JF; Kim JKJAm. Chem. Soc 1970, 92, 7463–7464.

(57). Jenkins CL; Kochi JK J. Am. Chem. Soc 1972, 94, 856–865.

(58). Litvak VV; Shein SM Zh. Org. Khim 1974, 10, 2360–2364.

(59). Bacon RGR; Hill HA O. J. Chem. Soc 1964, 1097–1107.

(60). Whitesides GM; Fischer WF, Jr.; San Filippo J, Jr.; Bashe RW; House HO J. Am. Chem. Soc 1969, 91, 4871–4882.

(61). Whitesides GM; Kendall PE J. Org. Chem 1972, 37, 3718–3725.

(62). Johnson CR; Dutra GA J. Am. Chem. Soc 1973, 95, 7783–7788.

(63). Kochi JK J. Am. Chem. Soc 1957, 79, 2942–2948.

(64). Mitani M; Kato I; Koyama KJ Am. Chem. Soc 1983, 105, 6719–6721.

(65). Bethell D; Jenkins IL; Quan PM J. Chem. Soc., Perkin Trans. 2 1985, 1789–1795.

(66). Tye JW; Weng Z; Johns AM; Incarvito CD; Hartwig JF J. Am. Chem. Soc 2008, 130, 9971–9983. [PubMed: 18597458]

(67). Huffman LM; Stahl SS J. Am. Chem. Soc 2008, 130, 9196–9197. [PubMed: 18582057]

(68). Jones GO; Liu P; Houk KN; Buchwald SL J. Am. Chem. Soc 2010, 132, 6205–6213. [PubMed: 20387898]

(69). Arai S; Hida M; Yamagishi T Bull. Chem. Soc. Jpn 1978, 51, 277–282.

(70). Arai S; Yamagishi T; Ototake S; Hida M Bull. Chem. Soc. Jpn 1977, 50, 547–548.

(71). Johnson MW; Hannoun KI; Tan Y; Fu GC; Peters JC Chem. Sci 2016, 7, 4091–4100. [PubMed: 28044096]

(72). Enemaerke RJ; Christensen TB; Jensen H; Daasbjerg K J. Chem. Soc., Perkin Trans. 2 2001, 1620–1630.

(73). Creutz SE; Lotito KJ; Fu GC; Peters JC Science 2012, 338, 647–651. [PubMed: 23118186]

(74). Goins CM; Dajnowicz SJ; Thanna S; Sucheck SJ; Parks JM; Ronning D R ACS Infect. Dis 2017, DOI: 10.1021/acsinfecdis.7b00003.

(75). Thanna S; Sucheck SJ MedChemComm 2016, 7, 69–85. [PubMed: 26941930]

(76). Warrier T; Tropis M; Werngren J; Diehl A; Gengenbacher M; Schlegel B; Schade M; Oschkinat H; Daffe M; Hoffner S; Eddine AN; Kaufmann SHE Antimicrob. Agents Chemother 2012, 56, 1735–1743. [PubMed: 22290959]

(77). Gobec S; Plantan I; Mravljak J; Wilson RA; Besra GS; Kikelj DBioorg. Med. Chem. Lett 2004, 14, 3559–3562. [PubMed: 15177473]

(78). Kovac A; Wilson RA; Besra GS; Filipic M; Kikelj D; Gobec S J. Enzyme Inhib. Med. Chem 2006, 21, 391–397. [PubMed: 17059171]

(79). Rose JD; Maddry JA; Comber RN; Suling WJ; Wilson LN; Reynolds RC Carbohydr. Res2002, 337, 105–120. [PubMed: 11814442]

(80). Wang J; Elchert B; Hui Y; Takemoto JY; Bensaci M; Wennergren J; Chang H; Rai R; Chang CWT Bioorg. Med. Chem 2004, 12, 6397–6413. [PubMed: 15556758]

(81). Sanki AK; Boucau J; Srivastava P; Adams SS; Ronning DR; Sucheck SJ. Bioorg. Med. Chem 2008, 16, 5672–5682.

(82). Fischer H; Dereu N Bull. Soc. Chim. Belg 1987, 96, 757–768.

(83). Favrot L; Lajiness DH; Ronning DR J. Biol. Chem 2014, 289, 25031–25040. [PubMed: 25028518]

(84). Optimization in Drug Discovery; Yan Z; Caldwell GW Eds.; Humana Press, 2014, ISBN: 978–1-62703–741-9.

(85). Knudson SE; Kumar K; Awasthi D; Ojima I; Slayden RA Tuberculosis 2014, 94, 271–276. [PubMed: 24746463]

(86). Kumar K; Awasthi D; Lee SY; Zanardi I; Ruzsicska B; Knudson S; Tonge PJ; Slayden RA; Ojima I J. Med. Chem 2011, 54, 374–381. [PubMed: 21126020]

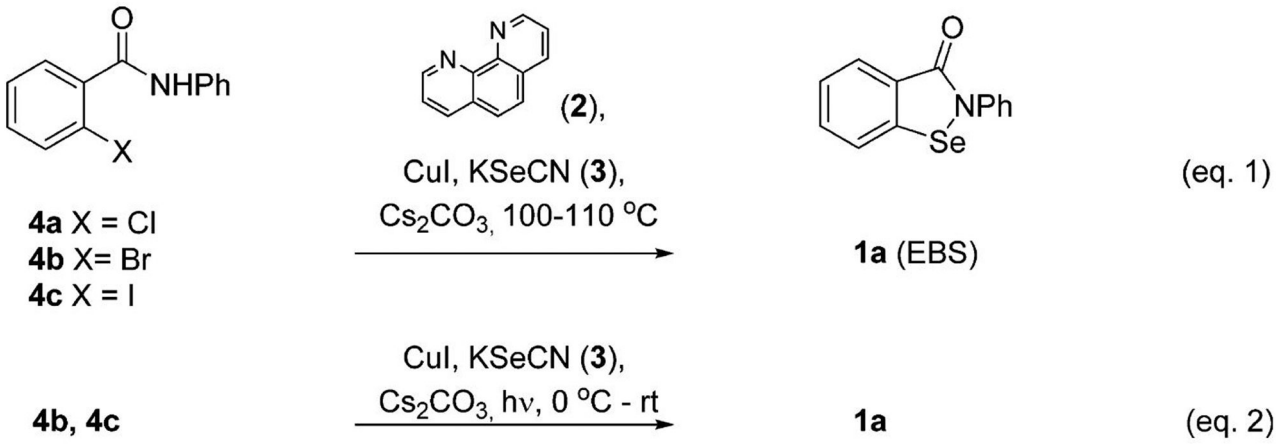
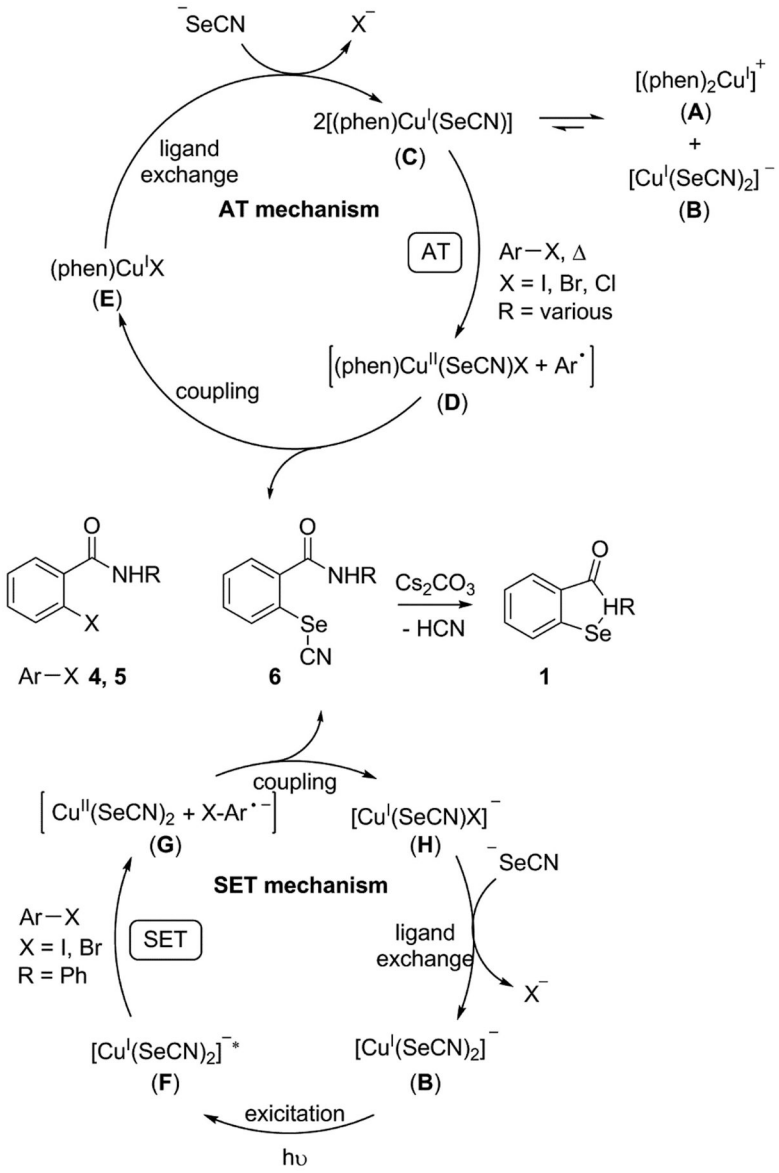


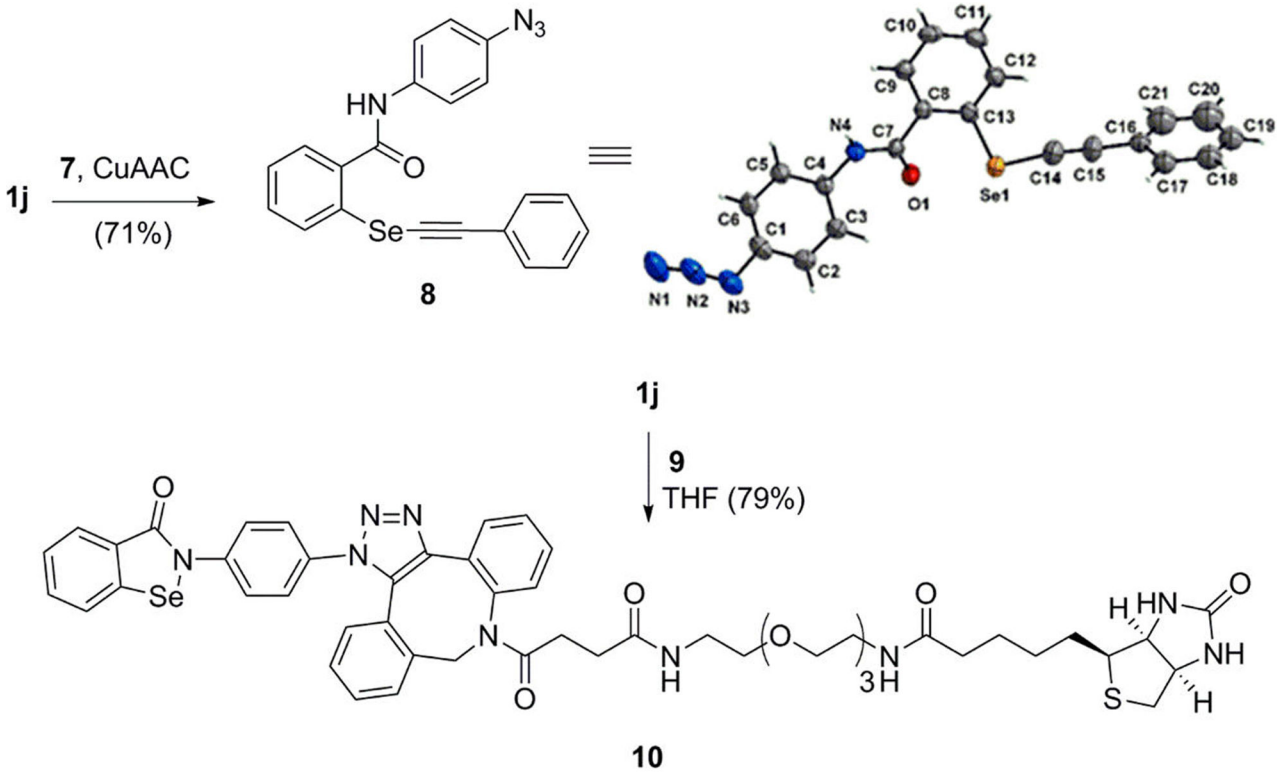
Figure 1.
Thermal (eq 1) and photoinduced (eq 2) preparation of ebselen (**1a**).



Scheme 1.

Proposed Cu-Promoted Mechanisms for Thermal and Photoinduced Synthesis of 2-Alkyl-1,2-benzisoselenazol-3(2*H*)-ones[a]

[a]AT = Atom transfer, SET = Single electron transfer.

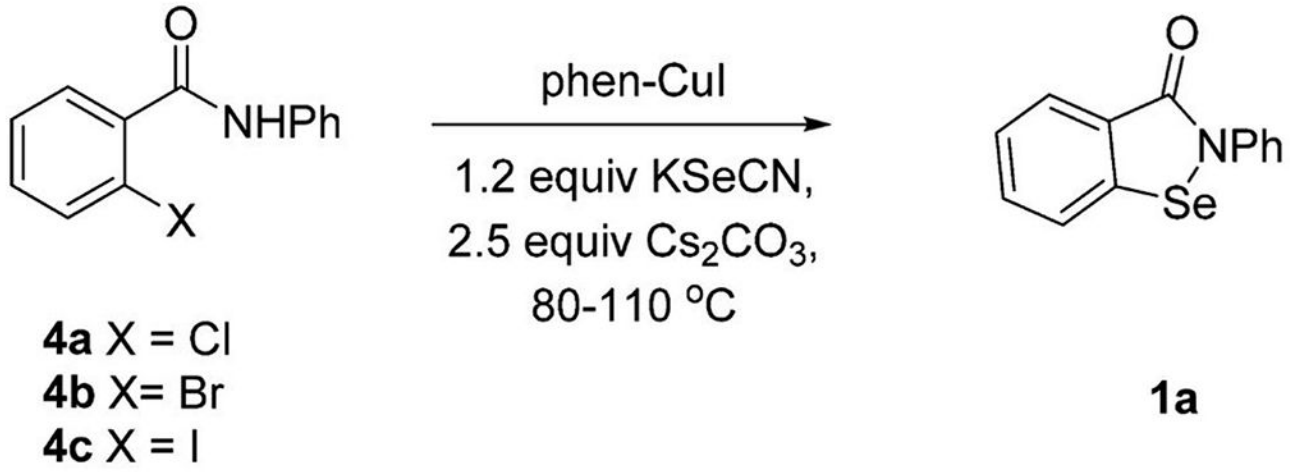


Scheme 2.

Synthesis of 2-Phenylbiotinyl-1,2-benzisoselenazol-3(2*H*)-one 10 and X-ray Crystal Structure of *N*-(4-Azidophenyl)-2-((phenylethynyl)selanyl)benzamide (8)

Table 1.

Optimization of Thermal Method to Produce 2-Phenyl-1,2-benzisoselenazol-3(2*H*)-one (1a)[a]



entry	aryl halide	phen-CuI (equiv)	solvent	temp (°C)	time (h)	yield (%)
1[b]	**4a**	0.25	DMF	110	30	20
2	**4b**	0.2	DMF	100	12	30
3	**4b**	0.3	DMF	100	1	34
4	**4b**	0.3	DMF	100	12	53
5	**4b**	1.0	DMF	100	1	71
6	**4a**	1.0	DMF	100	1.5	33
7	**4c**	1.0	DMF	100	0.6	75
8	**4a**	1.0	CH_3CN	80	1	48
9	**4b**	1.0	CH_3CN	82	12	89
10	**4c**	1.0	CH_3CN	80	12	91
11	**4b**	1.0	DMSO	100	1.5	44
12[c]	**4b**	1.0	CH_3CN	82	12	41

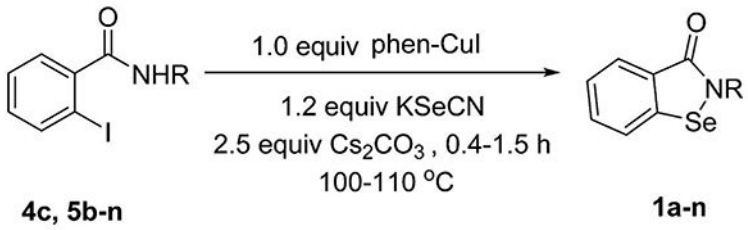
[a] Unless otherwise stated, 1.2 equiv of KSeCN and 2.5 equiv of Cs_2CO_3 were used.

[b] Conditions used for comparison = Se powder, K_2CO_3 (3.0 equiv), CuI (25 mol %), phen (25 mol %).[36]

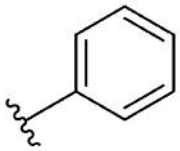
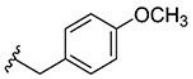
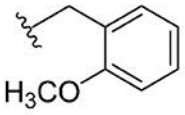
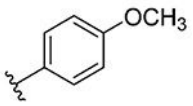
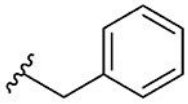
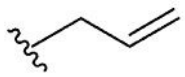
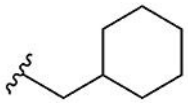
[c] No phen, ambient light. The temperatures reported were measured outside the reaction vessel.

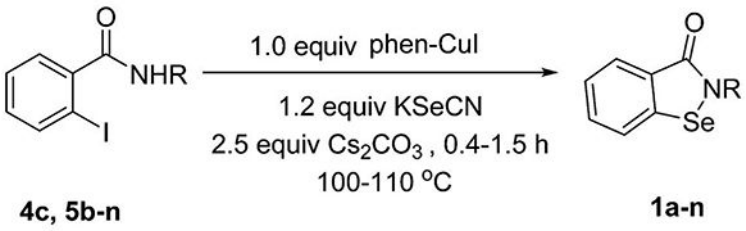
Table 2.

Thermal Synthesis of a 1,2-Benzisoselenazol-3(2*H*)-one Library

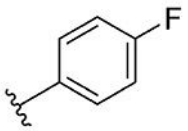
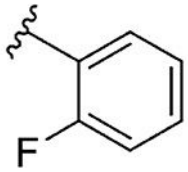
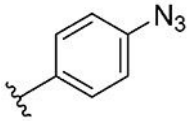
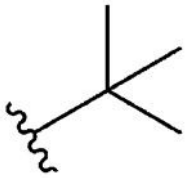
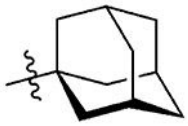
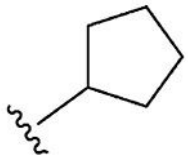


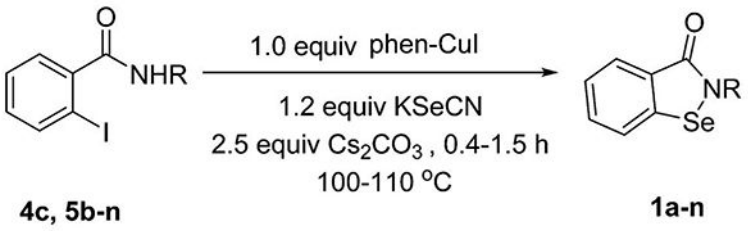
4c, 5b-n **1a-n**

entry	substrate	R	product, yield (%)
1	**4c**		**1a**, 91
2	**5b**		**1b**, 63
3	**5c**		**1c**, 44
4	**5d**		**1d**, 67
5	**5e**		**1e**, 39
6	**5f**		**1f**, 39
7	**5g**		**1g**, 63



4c, 5b-n **1a-n**

entry	substrate	R	product, yield (%)
8	**5h**		**1h**, 52
9	**5i**		**1i**, 35
10	**5j**		**1j**, 23
11	**5k**		**1k**, 75
12	**5l**		**1l**, 72
13	**5m**		**1m**, 78



4c, 5b-n **1a-n**

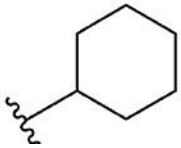
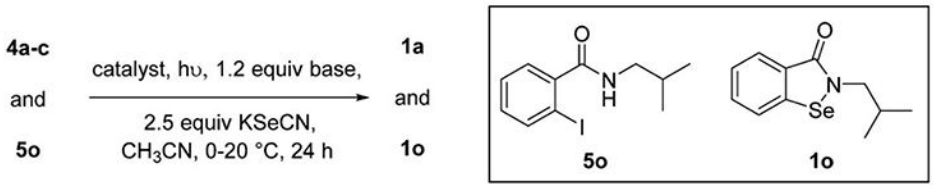
entry	substrate	R	product, yield (%)
14	**5n**		**1n**, 85

Table 3.

Optimization of Photoinduced Method To Produce 2-Phenyl-1,2-benzisoselenazol-3(2H)-ones[a]



entry	equiv, catalyst	halogen	energy	yield (%)
1	1.0, phen-CuI	**4b**	thermal reaction	**1a**: 89[b]
2	1.0, phen-CuI	**4b**	22 W Hg lamp	**1a**: 31
3	1.0, CuI	**4b**	22 W Hg lamp	**1a**: 82
4	0.1, CuI	**4b**	22 W Hg lamp	**1a**: 60[c]
5		**4b**	22 W Hg lamp	**1a**: N.R.
6	1.0, CuI	**4b**	dark	**1a**:6
7	1.0, CuI	**4b**	22 W Hg lamp	**1a**: N.R.
8	1.0, CuI	**4b**	ambient light	**1a**: 21
9	1.0, CuI	**4b**	250 W infrared lamp	**1a**: 63[d]
10	0.1, CuI	**4b**	22 W Hg lamp	**1a**: 81[c,e]
11	1.0, CuI	**4c**	22 W Hg lamp	**1a**: 92
12	1.0, CuI	**4a**	22 W Hg lamp	**1a**: N.R.
13	1.0, CuI	**5o**	22 W Hg lamp	**1o**: 85
14	1.0, CuI	**4b**	14 W Hg lamp	**1a**: 77[f]

[a]Unless otherwise stated, KSeCN (2.5 equiv) and Cs_2CO_3 (1.2 equiv) 24 h, and acetonitrile were used. Reactions were cooled for about 2 h and allowed to warm to room temperature (20 °C).

[b]Thermal activation = phen-CuI (1.0 equiv), KSeCN (1.2 equiv), Cs_2CO_3 (2.5 equiv), 12 h, 100–110 °C.

[c]48 h.

[d]Reaction reached 65–70 °C.

[e]NaOtBu (0.1 equiv). N.R = no reaction. 22 W is a combined wattage of two lamps.

[f]Reaction performed without BLE-8T365 (320–400 nm) lamp; only the 14 W Rayonet RPR-3000A lamp was used.

Table 4.

Activity of 2-Alkyl-1,2-benzisoselenazol-3(2*H*)-ones against *Mtb* H_{37}Rv and *Mtb* Ag85C

compound no.	cLogP[a]	MIC (μg/mL)	*Mtb* Ag85C activity (%)[b]	Ag85C *app*IC_{50} (μM)
1a	3.70	12.5	17 ± 3	5.12
1b	3.65	25	24 ± 17	0.54
1c	3.65	12.5	36 ± 4	28.6
1d	3.62	25	20 ± 4	1.2
1e	3.73	25	20 ± 10	6.5
1f	2.73	12.5	15 ± 2.0	8.8
1g	4.60	50	30 ± 16	5.3
1h	3.85	25	19 ± 2	0.72
1i	3.85	25	21 ± 7	1.0
1j	4.15	25	20 ± 4	1.1
1k	3.20	25	31 ± 12	1.5
1l	4.62	50	59 ± 14	25
1m	3.43	25	40 ± 17	4.1
1n	3.99	25	44 ± 15	3.7
8	5.76	100	80 ± 7	>100
10	5.26	N/A	61 ± 11	2.02

[a] clogP was calculated using ChemBioDraw Ultra 13.

[b] The percent activity of *Mtb* Ag85C was determined after treatment with 5 μM inhibitor and 40 min of preincubation. The activity was normalized to an untreated (uninhibited) control reaction. The error was calculated by performing each reaction in triplicate.