Bis-Michael Acceptors as Novel Probes to Study the Keap1/Nrf2/ARE Pathway

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Supporting Information

ABSTRACT: Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator that promotes the transcription of cytoprotective genes in response to oxidative/electrophilic stress. Various Michael-type compounds were designed and synthesized, and their potency to activate the Keap1/Nrf2/ARE pathway was evaluated. Compounds bearing two Michael-type acceptors proved to be the most active. Tether length and rigidity between the acceptors was crucial. This study will help to understand how this feature disrupts the interaction between Keap1 and Nrf2.

INTRODUCTION

Oxidative/electrophilic stress (OES) is the consequence of an abnormal production of reactive oxygen and nitrogen species and/or electrophiles in the cells.1 OES stress is linked to over 200 diseases and conditions such as cancers, diabetes, pulmonary infections, and neurodegenerative disorders. The Keap1/Nrf2/ARE pathway plays a central role in the cellular response to OES because the antioxidant response element (ARE) is an essential component of the cellular antioxidant defense and is under the transcriptional control of nuclear factor erythroid 2-related factor 2 (Nrf2).2−4

Because Kelch like ECH associated protein 1 (Keap1) regulates Nrf2-mediated transcription, the former is recognized as a therapeutic target with high potential. Indeed, the genes targeted by the Keap1/Nrf2/ARE pathway are involved in the synthesis and conjugation of glutathione and antioxidant proteins and enzymes.5 Understanding the Keap1/Nrf2/ARE pathway has thus become extremely important and the focus of drug discovery programs recently initiated by several research groups.6−18

In the basal state, Nrf2 is sequestered in the cytosol via its interaction with a Keap1 dimer. When this Keap1−Nrf2 complex binds to the Keap1-dependent E3-ubiquitin ligase (Cullin 3), Nrf2 is then degraded by the proteasome and the Keap1 dimer is free to bind to a newly translated Nrf2. This maintains low concentrations of free Nrf2 in the nucleus and transcription of genes related to ARE at basal levels. When Keap1 is targeted by small molecules, the conformation of the Keap1 dimer is modified and its interactions with Nrf2 are tighter. Accordingly, the ubiquitination of Nrf2 is stopped and newly synthesized Nrf2 can accumulate in the nucleus and turn on the expression of cytoprotective genes. According to Dinkova-Kostova et al., this mode of action is proper to electrophilic inducers.19

Keap1 comprises five domains: (1) the N-terminal region, (2) the broad complex, tramtrack, bric-a-brac (BTB) domain (exposing Cys151, responsible for the formation of the Keap1 dimer), (3) the intervening region (IVR, exposing Cys273, Cys288, and six others), (4) the Kelch repeat domain (responsible for the recognition of Nrf2), and (5) the C-terminal region.20 Among strategies used to disrupt the Keap1−Nrf2 interaction, noncovalent protein−protein interaction inhibitors have recently been reported.6−10 Several crystal structures reveal that these molecules target the binding site of Nrf2 on Keap1 (Kelch repeat domain).7−10 Another strategy consists of using electrophiles from synthetic or natural sources.11−18 The latter proved particularly successful (Figure 1) and are believed to target some of the cysteine (Cys) residues of Keap1. Among them, Cys151 (BTB domain) as well

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as Cys273 and Cys288 (IVR domain) appear to be the most sensitive to electrophiles.21

Despite potential toxicity issues associated with off-target interactions, covalent drugs nonetheless offer certain advantages over traditional drugs such as low administration doses and frequency, selectivity, and potentially longer action times.22,23 Most of the time, covalent drugs are designed in a way that a warhead reacts irreversibly with the targeted host. This renders off-target interactions hard to circumvent except by modulating the reactivity of the warhead. We decided to tackle this issue in a completely different way: because Keap1 offers a unique profile with its multicysteine domains, we rather opted to design new agonists bearing two moderately reactive reversible cysteine acceptors. Dual cysteine trapping should significantly increase the target residence time: once the first cysteine is anchored, trapping of a second cysteine becomes a kinetically favored intramolecular process that should also be thermodynamically beneficial due to enthalpy gain and weak entropy variation. Proper distance and/or nature of the acceptors, combined with traditional secondary noncovalent interactions, should provide selectivity to either the BTB or the IVR domains for these new agonists. Herein, we report the synthesis of series of single and double Michael-type acceptor compounds and their biological evaluation toward the Keap1/Nrf2/ARE pathway. For the first time, a systematic study of the effect of the length and rigidity of the tether between the Michael acceptors, as well as the effect of the electrophilicity of these acceptors, offers new insight into how this therapeutic target reacts to multielectrophile compounds.24

**SYNTHESIS**

**Single-Electrophilic Compounds.** α,β′-Unsaturated β-dicarbonyl compounds were synthesized in three to four steps from the corresponding ketones. First, the methoxycarbonylation of monoprotected cyclohexane-1,4-dione 1 gave the β-ketoester 2 (Scheme 1). Upon deprotonation with two equivalents of LDA, the resulting dianion was reacted with a series of electrophiles.25 Finally, selenation and oxidative elimination26 generated the Michael acceptors 3 and 4.27,28

To vary the lipophilicity of the compounds, the same sequence was applied to the gem-dimethyl analogue 5 (Scheme 2).

![Scheme 1](image1)

**Scheme 1**

```
1 → 2
     \( R = \text{Me} (32\%) \)
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*Reagents and conditions: (a) \( \text{NaH, Me}_2\text{CO}_3, \text{reflux} \); (b) LDA, R-I, rt; (c) PhSeBr, pyridine, CH\(_2\)Cl\(_2\), 0 °C; (d) \( \text{H}_2\text{O}_2, \text{CH}_2\text{Cl}_2, 0 \) °C.

2. For β-ketoesters bearing an unsaturation (cf. compounds 10 and 12), final oxidation gave best results using DDQ.

![Scheme 2](image2)

**Scheme 2**

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5 → 7
     \( R = \text{H} (57\%) \)
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*Reagents and conditions: (a) \( \text{NaH, KH, Me}_2\text{CO}_3, \text{THF, reflux} \); (b) LDA, R-X, rt; (c) PhSeBr, pyridine, CH\(_2\)Cl\(_2\), 0 °C; (d) \( \text{H}_2\text{O}_2, \text{CH}_2\text{Cl}_2, 0 \) °C; (e) DDQ, 1,4-dioxane, rt.

![Figure 1](image3)

**Figure 1.** Electrophilic modulators of the Keap1/Nrf2/ARE pathway.

To study the influence of the ester portion, trans-esterification29 of 6 using allyl alcohol or tert-butanol as the solvent gave mixtures of esters. After oxidation, 7 and 18 or 7 and 19, respectively, could be isolated (Scheme 3). We also prepared the corresponding acid 20 by hydrolysis of unsaturated keto-ester 7.30

To test the influence of the electrophilicity of the Michael acceptor, several variations were made (Scheme 4). First, a reduction of 7 in Luche conditions afforded the alcohol 21.30 Chloro- and iodoenones 23 and 24 were prepared using known procedures.31,32 Morita–Baylis–Hillman reaction on 22 with paraformaldehyde gave the allylic alcohol 25.33 Further transesterification afforded 26.34 Classic methoxycarbonylation of enone 22 provided keto-ester 27, which, upon α-methylation, afforded 28 as a racemic mixture.35 On the
other hand, oxidation of keto-ester 27 by selenium dioxide gave dienone 29.\textsuperscript{36}

**Bis-Electrophilic Compounds.** To attach two Michael acceptors on the same molecule and assess the influence of rigidity on activity, we used tethers of different lengths (1–4 carbons, 31, 32) and rigidity (alkane, alkene 33, and alkyne 34, Scheme 5). These tethers were incorporated by bis-alkylation with the dianion of 6. No significant amount of single alkylation biproducts was observed. The ensuing tandem oxidations afforded the desired products 30–34, albeit in low yield. A series of compounds bearing a dioxolane instead of the gem-dimethyl was also prepared for comparison (35, 36). Finally, an unsymmetrical bis-electrophilic compound 37 was obtained by oxidation of 26 with DDQ.

**RESULTS AND DISCUSSION**

**ARE Inducing Activity and Cytotoxicity.** To evaluate the ARE-inducing activity, all compounds, at concentrations ranging from 0 to 100 μM, were incubated with ARE-Luc-transfected human embryonic kidney cells (HEK-293T) for 24 h. Sulforaphane (10 μM) was used as a positive control. Also, NAD(P)H:quinone oxidoreductase (NQO1) induction was measured by quantitative polymerase chain reaction (qPCR) in RAW 264.7 cells using sulforaphane as a positive control. In addition, cytotoxicity was evaluated for each molecule in a lactate dehydrogenase (LDH) assay in HEK-293T cells. The data are reported as mean ± SEM based on three separated experiments.

**Lipophilicity As an Off-Target Indicator.** Compounds lacking any substitution at the C4 position (see 7, with two hydrogens instead of gem-dimethyl) were too electrophilic.
Difficulties in their isolation and purification compromised the validity of their evaluation.

To counterbalance for the level of reactivity of these electrophiles, steric hindrance around C4 was increased. We chose commercially available ketone 1 as a starting point for comparison. Analouges with a dioxolane moiety (3, 4, 35, and 36) showed moderate activity and significant toxicity at the higher concentrations (Figure 2).

We hypothesized that toxicity was due to the hydrophilicity associated with the dioxolane moiety. 14,37 To test this hypothesis, we increased the compounds’ lipophilicity. Replacing the dioxolane with a gem-dimethyl provided an increased activity with no toxicity even at high concentrations (e.g., 7). Further exploration of the substitution at C6 was essential to generate unambiguous biological data (Table 1). The single electrophiles showed better activities at 100 μM (compounds 7–12), with no apparent toxicity. They were much more lipophilic than their dioxolane analogues according to their clogP values, which tends to support our hypothesis.

**Importance of Electrophilicity.** To induce the transcription of genes controlled by ARE, a first cysteine nucleophilic addition to the electrophilic compounds has to occur. Analogues 7–12 suggest that unsaturated keto esters are indeed suitable electrophiles to study Keap1 reactivity. Replacement of the methyl ester by larger groups (allyl 18 or t-Bu 19) gave a slight increase in activity, although accompanied by increased toxicity, whereas the corresponding acid (20) retained most of the activity. Replacement of the methyl ester by a chloride (23) had no significant effect, but the iodide derivative (24) was not reactive enough. This effect was also observed with other poor electrophiles, such as those lacking the ketone (21) or the ester (25, 26, and 28), with the exception of compound 27. This comes as a surprise because it is hard to evaluate the combined participation of the carbonyls in 27 while we expected 29 to be much more potent. 38

**Boost in Activity with a Second Michael Acceptor.** To take advantage of the numerous cysteine residues of Keap1, 39 we tested compounds with two Michael-type acceptors. Right

<table>
<thead>
<tr>
<th>Table 1. Fold-Induction of ARE-Luciferase Gene Expressiona</th>
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aSulforaphane has a fold-induction of 9.80 ± 1.00 at 10 μM. b% Mortality evaluated in the LDH assay are reported when over 5%. cPredicted values by ChemDraw 12.0.

Figure 2. (A) Fold induction of ARE-luciferase gene expression; (B) % cell mortality induced by compounds 3, 4, 35, 36, and 7 at 10, 20, 50, and 100 μM, respectively.
away, this second class of molecules turned out to be very potent (30, 31, and 38), with an astonishing 167-fold increase from 7 to 31 at 10 μM (Figure 3). Even though solubility and toxicity became an issue at higher concentrations, the study of similar compounds provided new insights about the target. First, the addition of a second unsaturated keto-ester enhanced the fold-induction drastically. Second, the spatial position between the two electrophilic parts is important to modulate activity. Indeed, going from a simple methylene (30) to a propane linker (31) resulted in a ca. 70-fold increase (at 20 μM), whereas an additional factor 2 was gained with a butane tether (32).

So far, it was not clear whether the tether length optimization reflected an optimal distance between the two Michael acceptors for reaction with two cysteine residues in the binding site or the result of a gain in hydrophobic interactions. To answer this, we decided to rigidify the tether. From butane (32) to E-butene (33) to butyne (34) tethers, increased rigidity resulted in a significant increase in activity, with compound 34 being the best compound so far (50-fold-induction at only 1 μM). These results strongly suggest an optimal distance and conformation between the Michael acceptors for interaction with Keap1.

These results raise the question whether the second Michael acceptor on 30–34 acts as a cysteine trap. It turns out that the Michael acceptors on these molecules are similar to the αβ′-unsaturated β-cyanoketone of CDDO, which was co-crystallized in the BTB domain of Keap1. We have thus docked our molecules in the crystal structure and set the distance between the nucleophilic sulfur and the electrophilic carbon to 1.8 Å as in CDDO. Interestingly, there is no other cysteine residue in the active site of the BTB domain that could act as a partner for a second nucleophilic addition. In return, the ketone and the ester functions were able to make hydrogen bonds with other residues in the active site and within the electronic density area. Hence, in the absence of a crystal of Keap1 with any of compounds 30–34, we cannot answer the question on the nature of the interaction of the second Michael acceptor with Keap1. As suggested by docking, it could be a H-bond in the BTB domain but it could also be that these molecules rather target the IVR region. Unfortunately, this region of Keap1 has not been crystallized yet and we cannot answer this hypothesis clearly at this point.

**Added Functionality Reduces Activity.** To prove whether only an H-bond acceptor is needed in addition to the electrophile, we installed different chemical functions (13–17). None of these compounds showed activity. Even 17 is particularly inactive, although it presents a distance between the ester side chain and the Michael-type acceptor that resembles the distance between Michael-type acceptors in 30. Having H-bond acceptors on the side chain (14–17) is even more detrimental than simple alkyl side chains (8, 10–12), suggesting that this part of the molecule also plays a role in lipophilic interactions with the active site.

**NQO1 Expression.** Michael-type acceptors are listed as pan assay interference compounds (PAINS). To address this eventuality in the case of the present class of molecules, we measured the expression of NQO1, a Nrf2 positively regulated gene, by qPCR in RAW 264.7 cells for sulforaphane and 14 compounds of interest at 10 μM (Table S1, Supporting Information). We observed the same tendencies as those observed in the luciferase ARE reported assay (Figure 4).

![Figure 3. Docking of 31 in BTB domain of Keap1 using PyMol and NRGsuite.](image)

![Figure 4. Fold induction of NQO1 expression by sulforaphane (SFN), compounds 8, 17, 27, 32, 33, and 34 at 2, 5, and 10 μM.](image)

Indeed, an aliphatic side chain (8) is preferred over a functionalized one (17), the addition of a Michael acceptor enhances activity (cf. 8 and 32), and an increased rigidity between Michael acceptors is beneficial (cf. 32, 33, and 34). This confirms that the observed activity is indeed dependent on the Nrf2 pathway and not on a promiscuous activity. Moreover, these Michael acceptors are much more potent than the naturally occurring sulforaphane.

**CONCLUSION**

In this study, we report herein the synthesis and biological evaluations of 32 Michael acceptors toward the Keap1/Nrf2/ARE pathway for the transcription of antioxidant cellular responses. This study gives several insights on how reversible covalent modulators interact with Keap1. The electrophilic part of the molecule has to be sufficiently lipophilic to show some activity. Furthermore, the electrophile has to be powerful enough to react with the targeted cysteine, an essential element in the design of Keap1 ligands to stop the ubiquitination and subsequent degradation of Nrf2. The 1-methoxy carbonyl-3,3-dimethylcyclohex-2-enone motif answered these two criteria. Addition of a second Michael acceptor had a crucial impact on activity, up to a 50-fold-induction at only 1 μM. The distance between the Michael acceptors as well as the rigidity of the tether were optimized to generate our best compound (34) in this family.

Our results suggest that the role of the second Michael acceptor is unlikely to be a hydrogen bond acceptor as none of the compounds with heteroatoms at the end of the side chain showed activity. We could hypothesize that the second Michael acceptor rather serves as a second cysteine trap. This remains to be proven, but the consequences of such a hypothesis, should it
turn out to be true, are of high importance. Indeed, trapping of several cysteine residues would imply that the BTB domain is not the target but probably the IVR region of Keap1.

We believe our study will serve to increase the understanding of this target toward the generation of new drug leads. Our data also highlight the importance to design appropriate electrophiles toward covalent drug. Investigations on the nature and exact role of the second electrophile are in progress, and the results will be published in due course.

**Experimental Section**

**Biology: Cell lines.** Human embryonic kidney 293 cells (HEK-293T; ATCC CRL-1573) and the murine macrophage cell line (RAW 264.7; ATCC TIB-71) were obtained from American Type Culture Collection (Manassas, VA). Cells were cultured using standard methods at 37 °C in 5% CO2–95% air in Dulbecco’s Modified Eagle Medium (DMEM) (Wisent, Canada) supplemented with 10% fetal bovine serum (FBS), antibiotics (streptomycin at 100 μg/mL and penicillin at 100 U/mL), 5% sodium pyruvate, 5% nonessential amino acids, and 2 mM t-glutamine (complete DMEM).

**Luciferase Assays.** The day before transfection, human embryonic kidney HEK 293T cells (1×105) were plated in 24-well tissue-culture-treated plates. Cells were transiently transfected with 0.05 μg of ARE-luc (Nrf2 response element) plasmid using FuGENE6 transfection reagent (Promega, Madison, WI; E2691). The day after transfection, cells were treated with Keap1 ligands at different concentrations or with sulfonamide at 10 μM. After 24 h, cell lysates were then assayed for luciferase activity using the luciferase assay system from Promega (E1500).

**Real-Time PCR Analyses.** RAW 264.7 cells were treated with 2, 5, and 10 μM of different compounds or with 10 μM of sulfonamide for 5 h. Total RNA was then extracted using Ribozol reagent according to the manufacturer’s protocol. A total of 500 ng of the resulting RNA was then reverse transcribed using iScript reverse transcription supermix for the reverse transcriptase quantitative PCR (RTqPCR) kit (Bio-Rad). Real-time PCR was performed with the iQ SYBR green supermix (Bio-Rad). Amplification plots were generated using the Rotorgene 6000 Application software version 1.7 (Corbett Research), and fold induction was calculated using the threshold cycle (ΔΔCt) method and using 18S expression for normalization.

**Cell Viability Assay.** The cytotoxicity of Keap1 ligands on cells was determined using the LDH assay. Brieﬂy, HEK 293T cells were treated with increasing concentrations of Keap1 ligands. After 24 h, supernatants were collected and cells were lysed in Triton 1%. To measure lactate dehydrogenase (LDH) activity, buffer containing (+)-lactic acid and nicotinamide adenine dinucleotide (NAD) (Sigma-Aldrich; L-1750 and N7004, respectively) was added to the supernatant and the cells lysate, followed by measurement of absorbance at 340 nm.

**Chemistry: General.** All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a dry nitrogen or argon atmosphere. THF was distilled from Na and benzophenone under nitrogen immediately prior to use. 1,4-Dioxane was distilled from Na and benzophenone under argon and kept on 4 Å molecular sieves. DCMS, MeOH, tolune, i-Pr2NH, Et3N, and pyridine were dried from CaH2 under nitrogen at atmospheric pressure immediately prior to use. All other required fine chemicals were used directly without purification. All reference to “water” correspond to deionized water. All references to “brine” refer to a saturated aqueous sodium chloride solution. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. All new compounds showed chemical purity of ≥95% as assessed by 1H NMR. All NMR spectra were recorded on an AV300 Bruker (300 MHz for 1H and 75 MHz for 13C) or an AS400 variable (400 MHz for 1H and 100 MHz for 13C). Chemical shifts are referenced to δ 7.26 signal of CHCl3 (1H NMR) and 77.16 signal of CDCl3 (13C NMR) as internal standards for deuterated chloroform and to δ 0.30 signal of CH3Cl (1H NMR) and δ 3.53 signal of CD2Cl2 (13C NMR) as internal standards for deuterated DCM. Data for proton spectra are reported as follows: chemical shift in ppm (multiplicity (singlet, doublet (d), triplet (t), quartet (q), and multiplet (m))), integration, coupling constants [Hz]. Carbon spectra were recorded with complete proton decoupling, and the chemical shifts are reported in ppm. High-resolution mass spectrometry data were obtained by the ESI-Q-TOF (maXis). TLC was conducted with precoated 60 Å 250 μm silica gel plates with F-254 indicator and visualized using a combination of UV and potassium permanganate staining. Flash column chromatography was performed using silica gel (230–400 mesh). IR spectra were recorded with a FTIR instrument by applying substrates neat.

**General Procedure**

**Synthesis of compound (1).** A solution of 3 (2.86 mmol) in THF (1.0 mL) was added dropwise to a suspension of NaH (60% in oil, 1.54 g, 38.4 mmol) in Me2CO (10 mL) at rt. The reaction was heated to reflux for 4 h, then cooled to 0 °C. Saturated aq NH4Cl (30 mL) was added, and the usual workup (EtOAc; brine) and purification (5–15% EtOAc in hexanes) afforded compound 2 (3.81 g, 93%) as a pale-yellow oil. Spectral data was consistent with that previously reported.

**Synthesis of compound (2).** A solution of 1 (3.0 g, 19.2 mmol) in Me2CO (20 mL) was added dropwise to a suspension of NaH (60% in oil, 1.54 g, 38.4 mmol) in Me2CO (10 mL) at rt. The reaction was heated to reflux for 4 h, then cooled to 0 °C. Saturated aq NH4Cl (30 mL) was added, and the usual workup (EtOAc; brine) and purification (5–15% EtOAc in hexanes) afforded compound 3 (2.81 g, 93%) as a pale-yellow oil. Spectral data was consistent with that previously reported.
Methyl 9-Methyl-8-oxo-1,4-dioxaspiro[4.5]dec-6-ene-7-carboxylate (4). Following the procedure used to prepare 3, 2 (0.30 g, 2.35 mmol) was treated with LDA (4.99 mmol) and iodomethane (0.16 mL, 2.57 mmol) then quenched with saturated aq NH₄Cl (15 mL) and water (2 mL). The usual workup (EtOAc) and purification (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoester (278.5 mg confirmed by mass spectrometry) as a pale-yellow oil. The latter was treated with pyridine (0.11 mL, 1.36 mmol) and PhSeBr (319.4 mg, 1.35 mmol) then quenched with 1 N aq HCl (10 mL). The usual workup (EtOAc) and purification (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoester (303.4 mg, 39% over two steps) as a colorless oil. Spectral data was consistent with that previously reported.44

Methyl 5,5-Dimethyl-1-oxacyclohexane-carboxylate (5). Following the procedure used to prepare 2, 5 (9.6 g, 76 mmol) was treated with NaH (60% in oil, 12.2 g, 305 mmol), Me₂CO₃ (16.0 mL, 190 mmol), and KH (30% in oil, catalytic amount) and then quenched with aq 3 M AcOH (120 mL) and poured into brine (100 mL). The usual workup (EtOAc; 5 × 100 mL) followed by distillation (<1 Torr, 74–76 °C) afforded 6 (10.1 g, 72%) as a colorless oil. Spectral data was consistent with that previously reported.44

Methyl 3,3-Dimethyl-6-oxocyclohex-1-enecarboxylate (6). Following the procedure used to prepare 3, 6 (102.6 mg, 0.56 mmol) was treated with pyridine (60 μL, 0.74 mmol) and PhSeBr (163.5 mg, 0.69 mmol). The usual workup (CH₃Cl) gave the corresponding phenylselenyl-β-ketoester. The latter was treated with aq H₂O₂ (50 wt %, 0.5 mL), and then water (4 mL) and CH₃Cl (10 mL) were added. The usual workup (CH₃Cl saturated aq NaHCO₃; brine; aq NaCl; brine) afforded pure 7 (319.4 mg, 44 mg) as a pale yellow oil.41

1H NMR (CDCl₃, 400 MHz, δ ppm) 7.58 (d, 2H, J = 7.2 Hz), 7.39 (t, 1H, J = 7.3 Hz), 7.30 (t, 2H, J = 7.5 Hz), 3.85 (m, 4H), 3.64 (s, 3H), 3.06 (m, 1H), 2.50 (d, 1H, J = 3.8, 13.7 Hz), 2.15 (d, 1H, J = 13.7 Hz), 1.99 (m, 1H), 1.83 (t, 1H, J = 13.4 Hz), 1.13 (d, 3H, J = 6.5 Hz).13C NMR (CDCl₃, 100 MHz) δ ppm 170.17, 138.79, 129.71, 128.56, 116.67, 96.97, 94.30, 93.43, 43.51, 40.75, 14.86. HRMS (ESI-Q-Tof) calc'd for C₁₇H₂₀O₅SeNa 407.0369, found 407.0371. IR (neat) = 2958, 2921, 2848, 1723, 1686, 1587, 1459 cm⁻¹.

Following the procedure used to prepare 3, 6 (21.58 mg, 0.17 mmol) was treated with LDA (2.34 mmol) and iodomethane (80 μL, 1.29 mmol) and then quenched with aq 1 N HCl (10 mL). The usual workup (EtOAc) and purification (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoester (150.0 mg, confirmed by mass spectrometry) as a yellow oil. The latter (100.0 mg, 0.50 mmol) was treated with pyridine (50 μL, 0.62 mmol) and PhSeBr (140.1 mg, 0.59 mmol) and then quenched with 1 N aq HCl (5 mL). The usual workup (CH₃Cl; aq 1 N HCl; brine) gave the corresponding phenylselenyl-β-ketoester as a yellow oil. Following the procedure used to prepare 6 (58.4 mg, 39% over two steps) as a yellow oil.13C NMR (CDCl₃, 100 MHz) δ ppm 170.17, 138.79, 129.71, 128.56, 116.67, 96.97, 94.30, 93.43, 43.51, 40.75, 14.86. HRMS (ESI-Q-Tof) calc'd for C₁₇H₂₀O₅SeNa 407.0369, found 407.0371. IR (neat) = 2958, 2921, 2848, 1723, 1686, 1587, 1459 cm⁻¹.

Methyl 3,3,5-Trimethyl-6-oxocyclohex-1-enecarboxylate (7). Following the procedure used to prepare 3, 6 (21.58 mg, 0.17 mmol) was treated with LDA (2.34 mmol) and iodomethane (80 μL, 1.29 mmol) and then quenched with aq 1 N HCl (10 mL). The usual workup (EtOAc) and purification (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoester (150.0 mg, confirmed by mass spectrometry) as a yellow oil. The latter (100.0 mg, 0.50 mmol) was treated with pyridine (50 μL, 0.62 mmol) and PhSeBr (140.1 mg, 0.59 mmol) and then quenched with 1 N aq HCl (5 mL). The usual workup (CH₃Cl; aq 1 N HCl; brine) gave the corresponding phenylselenyl-β-ketoester as a yellow oil. Following the procedure used to prepare 6 (58.4 mg, 39% over two steps) as a yellow oil. Spectral data was consistent with that previously reported.45

Methyl 5-Allyl-3,3-dimethyl-6-oxocyclohex-1-enecarboxylate (8). Following the procedure used to prepare 3, 6 (210.3 mg, 1.10 mmol) was treated with LDA (2.40 mmol) and allyl bromide (0.15 mL, 1.73 mmol) and then quenched with aq 1 N HCl (10 mL). The usual workup (EtOAc) and purification (10% EtOAc in hexanes) afforded 8 (19.8 mg, 34% over two steps) as a yellow oil.1H NMR (CDCl₃, 400 MHz) δ ppm 7.25 (d, 1H, J = 2.0 Hz), 3.79 (s, 3H), 2.46 (m, 1H), 1.90 (m, 2H), 1.65 (t, 1H, J = 13.7 Hz), 1.29 (m, 9H), 1.24 (s, 3H), 1.20 (s, 3H), 0.87 (t, 3H, J = 6.7 Hz).13C NMR (CDCl₃, 100 MHz) δ ppm 170.97, 167.59, 163.13, 130.24, 52.35, 43.59, 41.83, 33.91, 31.87, 30.36, 29.53, 29.03, 26.88, 25.40, 22.77, 14.24. HRMS (ESI-Q-Tof) calc'd for C₂₁H₂₂O₂Na 289.1774, found 289.1784. IR (neat) ν 2955, 2925, 2875, 1745, 1719, 1686 cm⁻¹.
β-ketoester (176.8 mg conﬁrmed by mass spectrometry) as a yellow oil. Following the procedure used to prepare 8, alkylated β-ketoester (98.0 mg, 0.44 mmol) was treated with DDQ (159.7 mg, 0.70 mmol) and K2CO3 (165.7 mg, 1.20 mmol) in 1,4-dioxane and then quenched with water (10 mL). The usual workup (EtOAc; brine) and puriﬁcation (10% EtOAc in hexanes) afforded 12 (44.7 mg, 34% over two steps) as a white solid.1 H NMR (CDCl3, 400 MHz) δ (ppm) 7.34 (d, 1H, J = 2.2 Hz), 3.80 (s, 3H), 2.69 (dd, 1H, J = 3.0, 16.6 Hz), 2.15 (ddd, 1H, J = 2.2, 4.4, 17.0 Hz), 1.86 (t, 1H, J = 13.6 Hz), 1.32 (s, 3H), 1.25 (s, 3H). HRMS (ESI-Q-Tof) calculated for C10H18F2O3Na: 246.0944, found 246.0945 IR (ν max) ν 2957, 2929, 1734, 1684, 1275, 1256, 1218 cm−1.

Methyl 3,3-Dimethyl-6-oxo-5-(2-oxo)propyl)cyclohex-1-ene-carboxylate (16). Following the procedure used to prepare 3, 6 (801.1 mg, 4.35 mmol) was treated with LDA (9.62 mmol) and chloroacetonitrile (0.69 mL, 8.67 mmol) and then quenched with HCl (1 N, 30 mL). The usual workup (EtOAc; brine) and puriﬁcation (5% EtOAc in hexanes) gave the corresponding allyl β-ketoester (215.4 mg conﬁrmed by mass spectrometry) as an orange oil. The latter was treated with pyridine (0.33 mL, 3.56 mmol) and PhSeBr (680.1 mg, 2.88 mmol) and then quenched with HCl (5 mL). The usual workup (CH2Cl2; saturated NaHCO3; brine) and puriﬁcation (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoester (93.5 mg) as a yellow oil. The latter was treated with aq H2O2 (50 wt %, 0.5 mL, 8.65 mmol), and then water (5 mL) was added. The usual workup (CH2Cl2; saturated NaHCO3; brine) and puriﬁcation (20–30% EtOAc in hexanes) afforded 16 (37.8 mg, 4% over two steps) as a white solid. The IR (ν max) ν 2957, 2933, 2917, 2870, 1745, 1717, 1716, 1684, 1546 cm−1.

**Materials and Methods**

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afforded 18 (78.8 mg, 32% over two steps) as an orange oil. 1H NMR (CDCl3, 300 MHz) δ (ppm) 7.34 (1H, 5.9H, 1.06 mg, 3.88, dd, 1H, J = 1.5, 3.0, 17.2 Hz), 5.26 (ddd, 1H, J = 1.3, 2.6, 10.4 Hz), 4.70 (dt, 2H, J = 1.4, 5.7 Hz), 2.53 (2H, J = 6.8 Hz, 1.89) (t, 2H, J = 6.78 Hz, 1.23 (s, 6H). 13C NMR (CDCl3, 75 MHz) δ (ppm) 194.40, 164.58, 164.36, 131.99, 130.24, 118.76, 65.88, 35.59. 35.35, 33.64, 27.51. HRMS (ESI-Q-ToF) calc for C9H12O3Na+ 231.0996, found 231.0933. IR (neat) ν 2962, 1740, 1714, 1686, 1267, 1224 cm⁻¹.

**Tert-Butyl 3,3-Dimethyl-6-oxocyclohex-1-enecarboxylate (19).** Following the procedure used to prepare 18, 6 (204.7 mg, 1.11 mmol) was treated DMAP (200.7 mg, 1.64 mmol) and 4 Å molecular sieves (365.8 mg) in CH2Cl2 (5.0 mL) for 1 h, cooled to rt, diluted with Et2O (10 mL), washed with H2O (10 mL), dried over anhyd Na2SO4, evaporated in vacuo, and then treated with NaH (60% in oil, 505.5 mg, 12.6 mmol) and Me2CO3 (28). A solution of 23 (1.6 g, 12.9 mmol) was heated for 1 h, cooled to rt, diluted with Et2O (10 mL) and then was added dropwise to a solution of 24 (250.1 mg, 1.88 mmol) in THF (2.0 mL + 2.0 mL for rinsing). The mixture was stirred for 20 h, and then quenched with aq 1 N HCl (10 mL). The usual workup (CH2Cl2; aq 1 N HCl; aq NaHCO3 and purification (5% EtOAc in hexanes) afforded 25 (351.6 mg, 75%) as a yellow oil. Spectral data was consistent with that previously reported.46

2-(Hydroxymethyl)-4,4-dimethylcyclohex-2-ene (26). A solution of 22 (1.6 g, 12.9 mmol) in THF (2.0 mL + 2.0 mL for rinsing) was added to a mixture of paraformaldehyde (194.6 mg, 6.4 mmol) and imidazole (441.6 mg, 6.5 mmol) in 1 N NaHCO3 (25.6 mL) and THF (2.4 mL) at rt. The mixture was stirred for 50 h and then quenched with aq 1 N HCl (25 mL). The usual workup (CH2Cl2) and purification (10−30% EtOAc in hexanes) afforded 4,4-dimethylcyclohex-2-ene (548.2 mg, 4.4 mmol) and 25 (453.8 mg, 35% corrected) as a colorless oil. Spectral data was consistent with that previously reported.46

**Methyl 5,5-dimethyl-2-oxocyclohexanecarboxylate (27).** Following the procedure used to prepare 22, 24 (534.0 mg, 4.30 mmol) was treated with NaH (60% in oil, 505.5 mg, 12.6 mmol) and Me2CO3 (1.6 mL, 20.2 mmol) in refluxing 1,4-dioxane (3 mL) overnight and then quenched with water (2 mL) and aq 3 M AcOH (2 mL). The usual workup (EtO) and purification (5% EtOAc in hexanes) gave 27 (265.9 mg, 34%) as a yellow oil. The spectral data was consistent with that previously reported.46

**Methyl 5,5-Trimethyl-2-oxocyclohex-3-enecarboxylate (28).** Liodomethane (30 μL, 0.48 mmol) was added dropwise to a solution of 27.545 mg, 0.30 mmol) in acetone (3.0 mL) at 0 °C, followed by K2CO3 (115.0 mg, 0.83 mmol). The resulting mixture was stirred overnight at 40 °C, was allowed to cool down to rt, and the solvent was removed under vacuum. Aq 1 N HCl (5 mL) was added, and the usual workup (CH2Cl2; brine) and purification (5% EtOAc in hexanes) afforded 28 (31.7 mg, 54%) as a yellow oil. The spectral data was consistent with that previously reported.46
to afford pure 29 (50.0 mg, 49%) as a yellow oil. Spectral data was consistent with that previously reported.  

**Dimethyl 5,5'-Methylenebis(3,3-dimethyl-6-oxyocyclohex-1-ene-carboxylate)** (30). Following the procedure used to prepare 3, 6 (400.5 mg, 2.17 mmol) was treated with LDA (4.80 mmol) and dibromomethane (105 μL, 1.30 mmol) and then quenched with saturatedaq 1 N HCl (20 mL). The usual workup (EtOAc; brine) and purification (10% EtOAc in hexanes) gave the corresponding alkylated β-ketoster (374.8 mg confirmed by mass spectrometry) as an orange oil. The latter (102.3 mg, 0.27 mmol) was treated with pyridine (70 μL, 0.87 mmol) and PhSeBr (192.9 mg, 0.82 mmol) and then quenched withaq 1 N HCl (3 mL). The usual workup (CH₂Cl₂; saturatedaq NaHCO₃; brine) gave the corresponding ω-substituted β-ketoester (106.5 mg, 0.47 mmol) in 1,4-dioxane and then quenched with saturatedaq NaN₂CO₃ (10 mL). The mixture was poured into brine (10 mL). The usual workup (EtOAc; brine) and purification (10–30% EtOAc in hexanes) gave a yellow solid that was triturated in Et₂O to obtain 33 (12.9 mg, 13% over two steps) as a white solid; mp = 126–128 °C.  

**1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.72 (d, 2H, J = 2.2 Hz), 5.43 (m, 3H), 3.79 (s, 6H), 2.54 (4H, 2.08 (m, 2H), 1.85 (m, 2H), 1.61 (td, 2H, J = 3.7, 13.6 Hz), 1.23 (m, 6H), 1.19 (s, 6H).**  

**13C NMR (CDCl₃, 75 MHz) δ (ppm) 196.19, 196.16, 165.61, 163.55, 130.08, 130.05, 129.95, 52.35, 43.53, 43.51, 41.39, 41.37, 33.96, 33.95, 32.33, 32.31, 30.33, 25.34. HRMS (ESI-Q-Tof) calc'd for C₂₃H₂₄O₆Na 439.2091, found 439.2094. IR (neat) ν 2936, 1717, 1674, 1273, 1252 cm⁻¹.  

**Dimethyl 5,5'-But-2-ene-1,4-diylibis(3,3-dimethyl-6-oxyocyclohex-1-ene-carboxylate)** (34). Following the procedure used to prepare 3, 6 (214.7 mg, 1.17 mmol) was treated with LDA (2.04 mmol), freshly distilled HMHA (200 μL, 1.15 mmol), and 1,4-dichloro-2-butyne (64.3 mg, 0.65 mmol) and then quenched withaq 1 N HCl (10 mL). The usual workup (EtOAc; brine) and purification (5% EtOAc in hexanes) gave the corresponding alkylated β-ketoster (127.4 mg confirmed by mass spectrometry) as a yellow oil. Following the procedure used to prepare 8, alkylated β-ketoster (121.4 mg, 0.29 mmol) was treated with DDQ (150.1 mg, 0.66 mmol) in 1,4-dioxane and then quenched with saturatedaq NaN₂CO₃ (10 mL). The usual workup (EtOAc; brine) and purification (20–40% EtOAc in hexanes) gave a brown residue that was triturated in Et₂O to afford 34 (17.5 mg, 8% over two steps) as a light-brown solid; mp = 132–134 °C.  

**1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.51 (d, 2H, J = 2.1 Hz), 3.78 (s, 6H), 2.68 (m, 4H, 2.27 (m, 2H), 2.11 (m, 2H), 1.75 (t, 2H, J = 13.7 Hz), 1.26 (s, 6H), 1.23 (s, 6H).**  

**13C NMR (CDCl₃, 75 MHz) δ (ppm) 194.89, 194.87, 165.36, 165.34, 164.22, 164.15, 129.71, 129.67, 79.25, 79.24, 52.35, 43.19, 43.17, 42.11, 42.19, 33.97, 30.27, 25.33, 19.16. HRMS (ESI-Q-Tof) calc'd for C₂₄H₂₄O₆Na 447.1395, found 447.1388. IR (neat) ν 2956, 1731, 1670, 1281, 1255 cm⁻¹.  

**Bis(methoxy) 8-oxo-1,4-diazoisoquinolin[4,5]-dec-6-en-7-carboxylate** Methylenne (35). Following the procedure used to prepare 3, 2 (1967.6 mg, 0.92 mmol) was treated with LDA (1.93 mmol) and dibromomethane (32 μL, 0.46 mmol) and then quenched withaq 1 N HCl (10 mL) and water (2 mL). The usual workup (EtOAc; brine) and purification (30% EtOAc in hexanes) gave the corresponding alkylated β-ketoster (26.3 mg confirmed by mass spectrometry) as a pale-yellow solid; mp = 148–150 °C. The latter (47.5 mg, 0.11 mmol) was treated with pyridine (50 μL, 0.62 mmol) and PhSeBr (107.6 mg, 0.46 mmol) and then quenched withaq 1 N HCl (3 mL). The usual workup (CH₂Cl₂; 1 N HCl) and purification (20–40% EtOAc in hexanes) gave the corresponding phenylsilyl-β-ketoster (37.7 mg, 13% over 2 steps) as a white solid. The latter (23.1 mg, 0.03 mmol) was treated withaq H₂O₂ (50 wt %, 0.05 mmol), and then water (1 mL) was added. The usual workup (CH₂Cl₂; saturatedaq NaHCO₃; brine) and purification (30% EtOAc in hexanes) afforded 35 (64.3 mg, 53% over two steps) as a white solid; mp = 84–86 °C.  

**1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.25 (d, 2H, J = 2.1 Hz), 3.79 (s, 6H), 2.48 (m, 2H), 1.89 (m, 4H), 1.65 (td, 2H, J = 0.9, 13.9 Hz), 1.34 (m, 6H), 1.25 (s, 6H), 1.20 (s, 6H).**  

**13C NMR (CDCl₃, 75 MHz) δ (ppm) 196.97, 196.75, 163.59, 163.17, 130.22, 52.34, 43.51, 41.90, 33.92, 30.35, 29.05, 27.17, 27.14, 25.40. HRMS (ESI-Q-Tof) calc'd for C₂₂H₂₂O₅Na 429.2210, found 429.2214. IR (neat) ν 2936, 1717, 1675, 1259, 1237 cm⁻¹.  

**(E)-Dimethyl 5,5'-But-2-ene-1,4-diylibis(3,3-dimethyl-6-oxyocyclohex-1-ene-carboxylate)** (33). Following the procedure used to prepare 3, 6 (2013.0 mg, 1.09 mmol) was treated with LDA (2.50 mmol) and (2E)-1,4-dibromobut-2-ene (146.7 mg, 0.69 mmol) and then quenched withaq 1 N HCl (10 mL). The usual workup (EtOAc; brine) and purification (10% EtOAc in hexanes) gave the corresponding alkylated β-ketoster (201.9 mg confirmed by mass spectrometry) as a yellow oil. Following the procedure used to prepare 8, alkylated β-ketoster (80.9 mg, 0.21 mmol) was treated with DDQ (106.5 mg, 0.47 mmol) in 1,4-dioxane and then quenched with saturatedaq NaN₂CO₃ (10 mL). The mixture was poured into brine (10 mL). The usual workup (EtOAc; brine) and purification (10–20% EtOAc in hexanes) gave the corresponding
aldehydes (3.7 mg confirmed by mass spectrometry) as a colorless oil. A solution of PhSeCl (100 mg, 0.56 mmol) in CH₂Cl₂ (1.0 mL) was treated with pyridine (39 μL, 0.48 mmol) at rt for 30 min, and then with a solution of the aldehydes (4.5 mg, 0.12) in CH₂Cl₂ (1.0 mL) at rt for 8 h. CH₂Cl₂ (4 mL), water (1 mL), and 1 N aqueous HCl (1 mL) were added, and layers were separated. The usual workup (CH₂Cl₂; brine) and purification (0–20% EtOAc in hexanes) afforded the corresponding phenylselenyl-β-ketoester (62.7 mg confirmed by mass spectrometry, 38% over 2 steps) as a pale-yellow solid. A solution of the latter (60.5 mg, 0.08 mmol) in CH₂Cl₂ (1.0 mL) was treated with aqueous H₂O₂ (30 wt %, 0.04 mL). Water (5 mL) was added, and the usual workup (CH₂Cl₂; brine) afforded 37 (37.1 mg, quant) as a white solid; mp = 138–140 °C. H NMR (CDCl₃, 300 MHz) δ (ppm) 7.06 (d, 2H, J = 1.9 Hz), 4.18–3.95 (m, 8H), 3.81 (s, 6H), 2.83–2.66 (m, 1H), 2.22 (d2, 2H, J = 13.5, 4.7, 2.0 Hz), 2.13–1.99 (m, 2H), 1.97–1.77 (m, 2H), 1.49–1.32 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 198.17, 194.52, 164.79, 157.47, 148.05, 132.80, 110.0, 97.2 mg, 0.32 mmol) in 1,4-dioxane (2.0 mL). The solution was stirred at reflux for 4 h and allowed to cool down to rt. Water (10 mL) was added, and then the usual workup (EtOAc; brine) and purification (10–20% EtOAc in hexanes) afforded 37 (72.9 mg, 75%) as a white solid; mp = 40–42 °C. H NMR (CDCl₃, 300 MHz) δ (ppm) 7.32 (app s, 1H), 6.84 (app s, 1H), 4.85 (d, 2H, J = 1.3 Hz), 2.51 (m, 4H), 1.88 (m, 4H), 1.22 (s, 6H), 1.19 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 199.07, 194.52, 164.79, 157.47, 154.39, 130.30, 126.32, 35.59, 35.36, 34.56, 34.33, 33.75, 27.90. HRMS (ESI-Q-ToF) calc'd for C₁₈H₂₀O₄Na 327.1567, found 327.1565. IR (neat) ν 2956, 2891, 1741, 1683, 1436, 1260 cm⁻¹.

**ABBREVIATIONS USED**

Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; HEK, human embryonic kidney; ROS, reactive oxygen species; NNS, reactive nitrogen species; FDA, food and drug administration; BTB, broad complex, tramtrack, bric-a-brac; IVR, intervening region; LDA, lithium diisopropylamine; DDQ, 2,3-dichloro-5,6-dicyano-p-benzoquinone; LDH, lactate dehydrogenase; SEM, standard error of the mean; GSH, glutathione; clogP, calculated partition coefficient

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**Author Contributions**

L.J.D. synthesized new compounds, H.T. tested for biological activity, L.J.D., G.B., and E.M. designed compounds, H.T. and M.R. designed biological experiments, and all authors reviewed and approved manuscript contents. All authors have given approval to the final version of the manuscript.

**Notes**

The authors declare no competing financial interest.

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**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b01132.

NQO1 induction data, LDH assay data, NMR spectra for new compounds (PDF)

Molecular formula strings (CSV)


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(24) Several reports stress the importance of having two electrophilic sites on a molecule to improve its activity toward the Keap1/Nrf2/ARE pathway. However, none of these reports systematically evaluated the length and rigidity of the spacer between these electrophiles, or the effect of the electrophilicity of the acceptors. See ref 12. See also: (a) Dinkova-Kostova, A. T.; Massiah, M. A.; Bozak, R. E.; Hicks, R. J.; Talalay, P. Potency of Michael Reaction Acceptors as Inducers of Enzymes That Protect against Carcinogenesis Depends on Their Reactivity with Sulphydryl Groups. *Proc. Natl. Acad. Sci. U. S. A.* 2001, 98, 3404−3409. (b) Turpaev, K.; Ermolenko, M.; Cresteil, T.; Drapier, J. C. Benzylidenemalononitrile Compounds as Activators of Cell Resistance to Oxidative Stress and Modulators of Multiple Signaling Pathways. A Structure−activity Relationship Study. *Biochem. Pharmacol.* 2011, 82, 535−547.


(27) With a 1,1-dicarbonyl, these Michael acceptors are often referred to as Nazarov acceptors.

(28) It should be noted that, due to the instability of final compounds 3 and 4, purification had to be performed after selenation. Oxidation furnished clean products.


(34) As suggested by Satoh et al., hydrophilic electrophiles are more readily to react with the cysteine of glutathione (GSH) because of its hydrophilic microenvironment. Depletion of GSH could explain the activity we observed: on one hand, Nrf2 transcription might be activated to restore normal GSH concentration. On the other hand, the compound would also be more inclined to react with Keap1 owing to depletion of GSH pool. See ref 14.

(35) In fact, Honda reported 29 with COMe=CN as a very potent modulator of Keap1/Nrf2. See ref 11.


(37) Several reports stress the importance of having two electrophilic sites on a molecule to improve its activity toward the Keap1/Nrf2/ARE pathway. However, none of these reports systematically evaluated the length and rigidity of the spacer between these electrophiles, or the effect of the electrophilicity of the acceptors. See ref 12. See also: (a) Dinkova-Kostova, A. T.; Massiah, M. A.; Bozak, R. E.; Hicks, R. J.; Talalay, P. Potency of Michael Reaction Acceptors as Inducers of Enzymes That Protect against Carcinogenesis Depends on Their Reactivity with Sulphydryl Groups. *Proc. Natl. Acad. Sci. U. S. A.* 2001, 98, 3404−3409. (b) Turpaev, K.; Ermolenko, M.; Cresteil, T.; Drapier, J. C. Benzylidenemalononitrile Compounds as Activators of Cell Resistance to Oxidative Stress and Modulators of Multiple Signaling Pathways. A Structure−activity Relationship Study. *Biochem. Pharmacol.* 2011, 82, 535−547.


(27) With a 1,1-dicarbonyl, these Michael acceptors are often referred to as Nazarov acceptors.