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Oxathiolene oxide synthesis via chelation-controlled addition of organometallic reagents to alkynols followed by addition of sulfur electrophiles and evaluation of oxathiolene oxides as anticarcinogenic enzyme inducers

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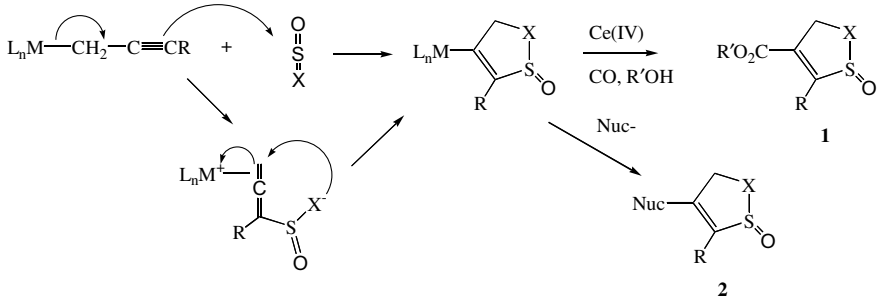
Abstract—A number of alkynols have been prepared by Sonogashira coupling of propargyl alcohol to aromatic halides. Chelation-controlled addition of organometallic nucleophiles to these alkynols was then effected followed by the addition of the sulfur electrophiles, sulfur dioxide or thionyl chloride. This methodology was used to prepare a number of oxathiolene oxides, which have been screened as NQO1 (quinone oxidoreductase) inducers.

1. Introduction

We have pursued the synthesis of unusual organosulfur compounds with biomedical science applications for over 15 years.[1,2] Transition-metal mediated 3 + 2 cycloaddition reactions have been used to prepare both the oxathiolene oxide (**1**, **2** X = O) and dithiolene oxide (**1**, **2** X = S) core structures.

We had recognized that these compounds (**1**, **2** X = S or O) were structurally similar to the five-member rings in dithiolethiones, and that the thiolene oxides could participate in both Michael additions and S_N2' reactions with soft nucleophiles. These structural and reactivity characteristics were found in many early chemopreventive agents[3–5] and we became interested in the synthesis of organosulfur compounds, which could subsequently be screened for this biological activity.

Chemoprevention of cancer involves the use of chemical agents either to retard or to block carcinogenesis.[6] These agents may affect the metabolism of xenobiotic



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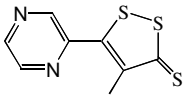
procarcinogens and this metabolism proceeds in two phases. In phase 1, procarcinogens are typically oxidized (cytochrome P-450) or reduced and this change many times increases their chemical reactivity. In phase 2, phase 1 metabolites are typically conjugated to biological nucleophiles or electrophiles, such as glutathione (glutathione S-transferases) or glucoronic acid (UDP-glucuronyl transferases). They can also be reduced in oxidation state or hydrolyzed, and rendered less reactive and hence less carcinogenic. A strategy for protection against carcinogenesis as well as other oxidative and electrophilic cellular damage involves inducing the genes, which code for the enzymes involved in phase 2 metabolism. The molecular mechanisms involved in phase 2 gene inductions are becoming better understood, as both the structure/activity relationships of known inducers and the molecular events involved in phase 2 gene induction are clarified.

The relative activities of phase 2 enzyme inducers are now most often initially screened using quinone oxidoreductase (NQO1) as the target enzyme in a murine hepatoma cell line (Hepa 1c1c7).[7] This assay is performed on living cells, and thus offers two advantages (1) it assesses not only phase 2 enzyme induction, but the contribution of cellular metabolic pathways that may enhance or diminish the efficacy of candidate chemopreventive agents; (2) it enables the simultaneous measurement of both phase 2 enzyme inducer activity and the toxicity of candidate agents. The ability to assess toxicity is critical, since the lack of toxicity is of major importance in compounds that ultimately will be administered as preventive agents (i.e., to healthy individuals). This assay does not answer questions about compound uptake and distribution in a whole animal or deal with questions about chronic versus acute toxicity in the liver or other organs, but it is a reasonable starting point for assessing chemoprotective ability. This screen relies on a simple spectrophotometric measurement of the reduction of a tetrazolium dye (3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyltetrazolium bromide, MTT) by the quinone oxidoreductase enzyme.[8,9] Relative strengths of phase 2 inducers are now typically presented as the concentrations of compound required to double the quinone oxidoreductase activity (CD values). The ready availability of mutant Hepa cell lines deficient in cytochrome P-450 activity and the aryl hydrocarbon receptor also makes it easy to screen compounds and determine if they are phase 1 and/or phase 2 (monofunctional or bifunctional) inducers.

Cruciferous vegetables, particularly those of the *Brassica* genus, contain a number of unusual organosulfur compounds that are excellent phase 2 inducers.[10] During the 1970s and 1980s, the related synthetic organosulfur compound Oltipraz (4-methyl-5-(2-pyrazinyl)-3*H*-1,2-dithiole-3-thione) (**3**) was being thoroughly investigated as an antischistosomal agent.[4,11] Oltipraz was extremely effective against schistosomiasis and also proved to be an excellent glutathione S-transferase and UDP-glucuronosyl transferase inducer. However, reports of paresthesia and fingertip pain following Oltipraz exposure, side effects, which were exacerbated by exposure to sunlight, led to the discontinuation of schistosomiasis trials of this compound.[4] The connection between unusual organosulfur compounds and cancer prevention was nevertheless established by the mid-1980s. This work also led to the identification of a number of other naturally occurring sulfur compounds, such as isothiocyanates (**4**) and disulfides (**5**) that function as phase 2 inducers.[10,12–16]



3

$CH_3S(O)(CH_2)_4NCS$

4

$CH_2{=}CHCH_2SSCH_2CH{=}CH_2$

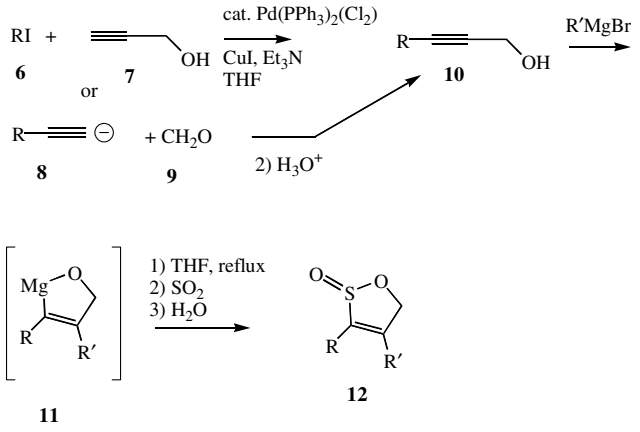
5

Similarities between the oxathiolene oxide nucleus and these organosulfur compounds led us to begin to explore the activity of oxathiolene oxides as candidate chemopreventive agents. Several compounds were prepared using the transition-metal mediated [3 + 2] cycloaddition chemistry described above and then were shown to elevate mRNA levels of glutathione S-transferase (GST), quinone oxidoreductase (NQO1) and ferritin H and L expression in a normal murine liver cell line, BNLCL.2.[17] Having verified that compounds containing the oxathiolene oxide nucleus could be nontoxic, anticarcinogenic enzyme inducers at both the mRNA and protein levels, we wanted to evaluate this class of compounds in more detail. We have begun to develop a nontransition-metal based synthetic route to the oxathiolene oxides that has proven convenient and general and we describe those synthetic studies herein. The NQO1 CD values of these compounds (along with their IC_{50}'s) in a normal murine liver cell line are reported here. A discussion of structure–activity relationships, which can be inferred from this initial set of compounds is also presented.

2. Results and discussion

2.1. Oxathiolene oxide synthesis

Chelation-controlled addition of Grignard reagents to alkynols (**10** to **12**) was first reported independently by both Richey and Eisch in 1969.[18,19] Duboudin and coworkers extended the addition chemistry during the



1970s and 1980s, showing that the intermediate magnesium chelate (**11**) could be trapped by a number of electrophiles including CO_2 and SO_2.[20–22] Subsequently, Fallis showed that the chelate can be trapped with aldehydes to prepare dienols and trapped with nitriles to make furans.[23–25] Fleming has also recently reported some related chelation-controlled conjugate additions using magnesium chelates.[26,27]

The 1982 Duboudin communication[22] reported two examples of the general type of reactions in which we were interested (**10** to **12**). They reported addition of ethyl and phenyl magnesium bromide to 3-phenyl-2-propyn-1-ol. We were interested in extending the Duboudin and co-workers[20–22] work to include alkynols substituted by a variety of aromatic rings containing a number of different substituents, which ranged from strongly electron donating to strongly electron withdrawing and we were interested in the possibility of using a much wider range of organometallic nucleophiles.

All the alkynols (**13**–**20**, **22**, **24** and **26**) used in this study were synthesized by Pd catalyzed cross coupling (Sonogashira coupling)[28] of propargyl alcohol to an aromatic halide. Isolated yields are generally quite high with the exception of the CF_3 substituted phenyl halides (**17** and **18**) and the phenyl bromide (**19**). Use of diisopropylamine rather than triethylamine improved isolated yields of some alkynols, primarily because the diisopropylamine proved easier to separate from the desired products by chromatography.[28] Heteroaromatics such as thiophenyl iodide (**21**) and bromide (**23**) participated in this cross coupling as did pyridinyl bromide (**25**).

In many cases, related Sonogashira couplings are synthetically easier to perform than these reactions involving aromatics halides and propargyl alcohol.[28] For most alkynes other than propargyl alcohol, these types of reactions are simply worked up by evaporating the reaction solvent and extracting the product into pentane. We found that the isolated yields of the product were routinely poor if we tried this with these propargyl alcohol coupled products. These reactions require an aqueous work up and extraction to obtain the yields reported. Trimethylsilyl protected propargyl alcohol (**27**) could be coupled and the product (**28**) extracted into pentane without workup. However, that product (**28**) still has to be deprotected prior to the cyclization chemistry presented below. While the overall yield of this two-step process to produce **15** was slightly higher (82% for **27** to **28** to **15** compared to 72% for the one-step process to **15** as shown in Table 1), the time and inconvenience of doing two manipulations rather than one did not cause us to routinely use the two-step route.

Following the preparation of the alkynols using the Sonogashira coupling, these compounds were then treated with organometallic nucleophiles followed by sulfur dioxide (Table 2). Several comments on this chemistry are in order. We found that the organometallic nucleophiles allyl and vinyl magnesium bromide in diethyl ether or tetrahydrofuran provided the highest yields of oxathiolene oxide products (Table 2, entries 1–8). Interestingly, if we instead used allyl or vinyl magnesium chloride, then the isolated yields of oxathiolene oxide were slightly lower and the crude product ^{1}H NMR spectra contained resonances that could be attributed

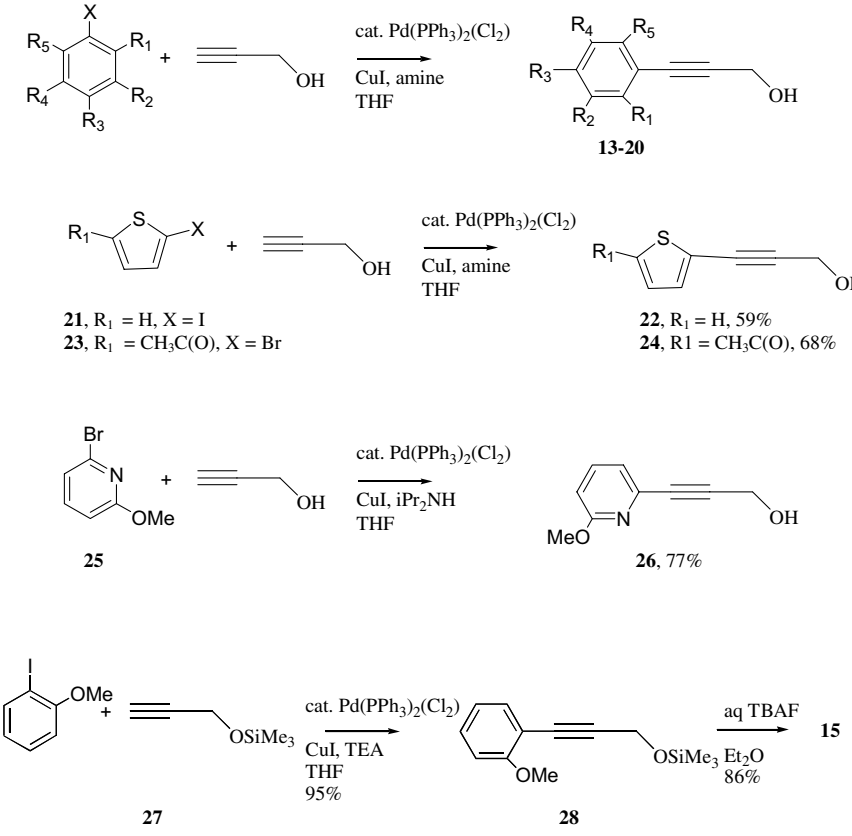


Table 1. Coupling of phenyl halides to propargyl alcohol

Entry	X	R_1	R_2	R_3	R_4	R_5	Amine	% Yield	Product
1	I	F	H	H	H	H	Et_3N	82	**13**
2	I	H	H	F	H	H	Et_3N	99	**14**
3	I	OMe	H	H	H	H	Et_3N	72	**15**
4	I	H	H	OMe	H	H	Et_3N	98	**16**
5	I	CF_3	H	H	H	H	Et_3N	43	**17**
6	I	H	H	CF_3	H	H	Et_3N	48	**18**
7	Br	OMe	H	OMe	H	H	iPr_2NH	29	**19**
8	I	H	H	*	H	H	iPr_2NH	91	**20**

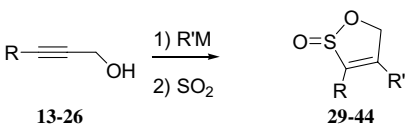
* = 

Table 2. Reactions of organometallic nucleophiles with substituted propargyl alcohols followed by SO_2 quench

Entry	Propargyl alcohol (R= or #)	R′M	%	Product #
1	R = Me	AllylMgBr	45	**29**
2	R = Ph	VinylMgBr	65	**30**
3	R = Ph	AllylMgBr	71	**31**
4	**16**	VinylMgBr	79	**32**
5	**15**	VinylMgBr	84	**33**
6	**14**	VinylMgBr	40	**34**
7	**13**	VinylMgBr	41	**35**
8	**22**	VinylMgBr	63	**36**
9	**20**	VinylMgBr	28[a]	**37**
10	R = Ph	$LiAlH_4$	32	**38**
11	R = Ph	MeMgBr (10% CuI)	42	**39**
12	R = Ph	PhMgBr (10% CuI)	40	**40**
13	**15**	EtMgBr (10% CuI)	26	**41**
14	R = 3-OMePh	EtMgBr (10% CuI)	51	**42**
15	R = Ph	EtMgBr (10% CuI)	47	**43**
16	R = Et	MeMgBr (10% CuI)	35	**44**

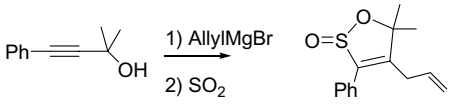
[a] This procedure starts with protected alkynol (**20**) and the isolated yield reported here is for nucleophilic addition and deprotection.

to alkenols, which would result from the protonation of **11**. For that reason, we concentrated on the use of magnesium bromides in the work reported here. Yields of oxathiolene oxides were generally lower when we tried to use alkyl or phenyl magnesium bromides (Table 2, entries 11–15). When 3-phenyl-2-propyn-1-ol was treated with methyl magnesium bromide without CuI, oxathiolene oxide (**39**) was present in less than 10% yield by crude product ^1H NMR. Instead, 3-phenyl-2-propyn-1-ol was recovered largely unreacted. Likewise, when 3-phenyl-2-propyn-1-ol, was treated with methyl magnesium bromide and 10% $ZnCl_2$, the crude product indicated a 3:1 mixture of unreacted alkynol to product (**39**). The isolated yield of **39** improved to 42% (Table 2, entry 11) with the use of catalytic CuI, so we routinely added 10% CuI with these types of Grignard reagents.



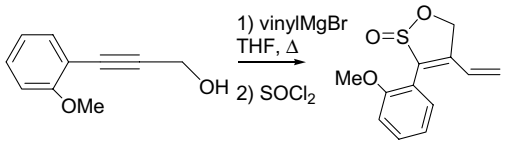
13-26 **29-44**

Most of the addition chemistry that we completed (Table 2) involved the use of primary propargyl alcohols as substrates. We purposefully avoided the use of secondary propargyl alcohols since they would react to form diastereomeric oxathiolene oxide pairs and we wanted to avoid this complication in the compounds we were screening. We did however, attempt this sequence with an achiral tertiary propargyl alcohol (**45**). The desired oxathiolene oxide (**46**) could be isolated and characterized by ^1H NMR and GC–MS but it proved unstable to chromatography and we were not able to completely characterize this product.

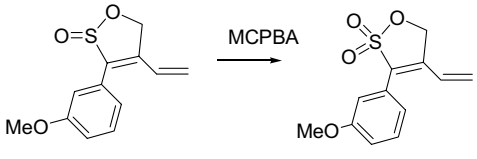


45 **46**

We also found that freshly distilled thionyl chloride ($SOCl_2$) can be used in place of SO_2, but the oxathiolene product yield is not as high. Alkynol (**22**) was first treated with vinyl magnesium bromide under the same conditions used for the SO_2 reactions. The solution was then cooled to −78 °C and freshly distilled thionyl chloride in THF was added and the solution was allowed to warm to 25 °C. The oxathiolene oxide (**33**) was produced but the isolated yield was only 30% here and it was 84% when SO_2 was used. Lastly, we also found that oxathiolene oxide (**42**) could be oxidized to an oxathiolene dioxide (**47**) in high yield.



15 **33**

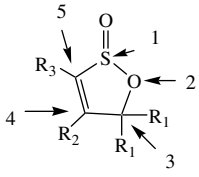


42 **47** (99%)

2.2. Oxathiolene oxides as NQO1 inducers

We had already established that the structurally related oxathiolene oxide nucleus was a promising phase 2 inducer, but the synthetic chemistry used to prepare the initial set of four test compounds was too cumbersome.[17] Hence, the simple synthetic route to these compounds outlined above was developed. This enabled the facile synthesis of a greater number of compounds with directed substitutions at defined locations in the oxathiolene oxide nucleus. The impact of these changes on biological function was studied by measuring NQO1 inducing ability and toxicity.

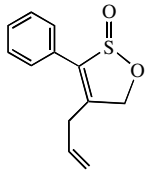
2.2.1. Preliminary structure–activity relationship data for oxathiolene oxides



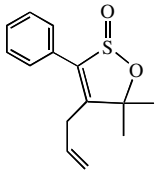
48

The atoms in the oxathiolene oxide nucleus are numbered as shown in structure **48**. Changes made to date at each position and their effect on NQO1 CD values will be discussed briefly. We start this discussion with changes made to the carbon containing core of the molecule. We should also note that Oltipraz (**3**) had a CD value of 6 μM in this same cell line.

2.2.1.1. Changes in the carbon core of 48. Oxathiolene oxides, which are unsubstituted at ring carbon number 3, such as **31**, are easiest to prepare, and compounds that were symmetrically disubstituted (such as **46**) at this position showed no advantage. Monosubstitution at carbon number 3 would introduce a second chiral centre (the sulfur is chiral in these molecules) and require separation and screening of the individual diastereomers. For that reason, we have avoided having a chiral centre at carbon 3 in our early work.

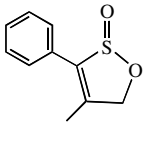


31
CD = 26.4 ±2 (N=3)
IC_{50} >160 (N = 4)

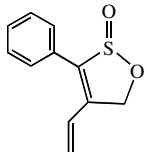


46
46.0 ± 8.5 (N=3)
73.1±23 (N = 4) conc = μM±SD

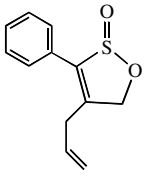
Changes at the number 4 position are controlled by the choice of the Grignard reagent we add to the alkynol. With commercially available Grignard reagents screened to date, the isolated yields of oxathiolene oxide product followed the trend of R_2 = vinyl > allyl > phenyl > methyl. At least with these simple, commercially available Grignards, CD values gave no clear indication that methyl (**39**), vinyl (**30**), allyl (**31**) or phenyl (**40**) was superior. We focused on 4 = vinyl for many of the changes investigated here initially at the 5 position, because yields for synthesis of the core ring structure were highest and the 4 = vinyl compounds had CD values comparable to, or better than, the other substituents. The IC_{50} value for this compound (**30**) was worrisome but we did not yet know if it would be a trend for 4 = vinyl compounds.



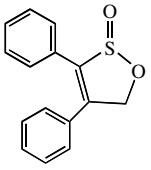
39
CD = 19.1 ± 11 (N=5)
IC_{50} >200 (N = 2)
conc = μM±SD



30
24.2 + 5 (N=3)
>134.4±10 (N = 3)

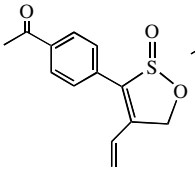


31
26.4 ±2 (N=3)
>160 (N = 4)

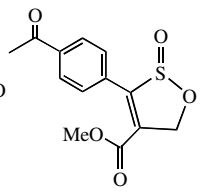


40
29.9±3 (N = 2)
87±32.5 (N = 2)

Having the 4 position substituted with an electron withdrawing group like carbomethoxy (**49**) showed no advantage, and synthesis of the compounds with 4 = carboalkoxy requires use of a synthetic procedure with considerably lower yields[2] than those obtained by using the sequence shown above to make **29**–**44**. However, the troubling IC_{50} seen for compound **30** became a problem for this new 4 = vinyl compound **37**, even though its CD was the lowest we had seen for the oxathiolene oxides.

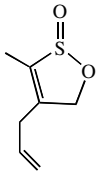


37
CD = 8.82 ± 1 (N=4)
IC_{50} 37±2 (N = 2)

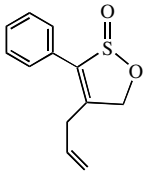


49
38.0 ± 6 (N=4)
70.5±10 (N = 2)

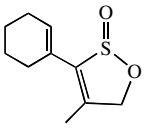
We also looked at alkyl versus aryl changes in the 5 position. 5-Phenyl compounds were considerably more active than 5-methyl (**31** vs **29**). The two compounds where the 5 position was substituted by a phenyl or cyclohexenyl (**39** and **50**) had CD values, which were within experimental error of one another. 5-Phenyl substituted compounds were easily made by Sonogashira coupling of aryl iodides or bromides to propargyl alcohol as we demonstrated above, so 5 = aryl offered some practical advantages from the synthetic point of view.



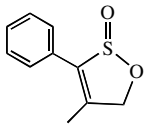
29
CD = 51.1 ± 3 (N=3)
IC_{50} >200 (N = 3)
conc = μM±SD



31
26.4 ± 2 (N=3)
>160 (N = 4)

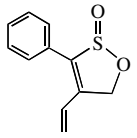


50
32.3 ± 10 (N=3)
>200 (N = 3)

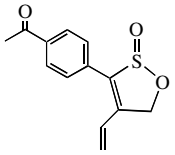


39
19.1 ± 10 (N=5)
>200 (N = 2)

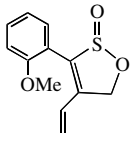
Since structure **30** seemed particularly promising among those discussed above, we made a few substituted aromatic and vinyl substituted oxathiolene oxide analogues of **30**. Three of these compounds, the acetyl phenyl (**37**), the 2-methoxyphenyl (**33**) and the thiophenyl (**36**) have CD values of less than 10. Unfortunately, the IC_{50} value for compound **30** that was starting to creep down became a trend for 4 = vinyl compounds (**37**, **33** and **36**).



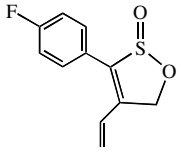
30
CD = 24.2±5 (N=3)
IC_{50} 134.4±10 (N = 3)
conc = μM±SD



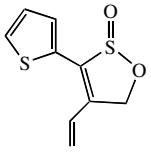
37
8.8±1 (N=4)
37±2 (N = 2)



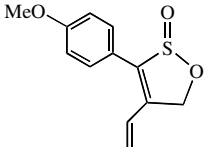
33
9.0±4 (N=5)
93.7±18 (N = 4)



34
CD = 21.7+1 (N = 3)
IC_{50} 99.4±2 (N = 2)
conc = μM±SD



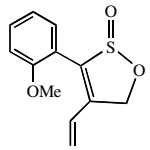
36
9.9+3 (N = 5)
69.7±14 (N = 3)



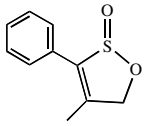
32
19.4+4 (N = 3)
85±21 (N = 3)

Switching from 4 = vinyl (**33**) back to 4 = methyl for some 5 = methoxyphenyl substituted compounds (**51** and **52**) solved the toxicity problem (IC_{50}'s back over 200 μM) but also brought CD values back up by a factor of 3.

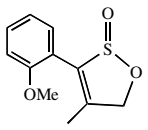
Lastly, changing the sulfur oxidation state (atom number 1) had little effect on the CD value in one of the cases we tested, as shown by **47**.



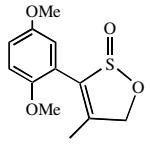
33
CD = 9.0±4 (N=5)
IC_{50} 93.7+18(N=4)
conc = μM±SD



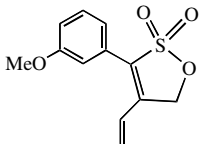
39
19.1+10 (N=5)
>200 (N = 3)



51
35.5±0.3 (N=2)
>200 (N=2)



52
29.6±3 (N=2)
>200 (N = 2)



47
CD=16.35±0.4 (N=2)
IC_{50}=72.5±36 (N=2)

3. Preliminary NQO1 screening conclusions

Talalay and co-workers have recently shown that there was a direct correlation between the energy of the highest occupied molecular orbital (or reduction potential) of a family of 30 phenylpropenoids and their NQO1 CD values.[29] In Table 3, we present calculated energies of the highest occupied molecular orbitals for the oxathiolene oxides screened here and their pCD values (log of 1/CD in M). To calculate HOMO energies (in eV) of the molecules studied, we used semiempirical AM1 quantum mechanical calculations carried out with the Spartan ES '04 program. The restricted Hartree Fock (RHF) formalism was also used in these calculations. The correlation that Talalay observed for the phen-

Table 3. Highest occupied molecular orbital energies, pCDs and compound numbers

E HOMO (eV)	pCD	Compound number
−8.63	4.529	**52**
−8.78	4.712	**32**
−8.95	4.45	**51**
−9.07	4.616	**30**
−9.07	5.004	**36**
−9.1	4.524	**40**
−9.1	4.664	**34**
−9.13	5.046	**33**
−9.16	4.337	**46**
−9.17	4.719	**39**
−9.18	4.578	**31**
−9.24	4.786	**47**
−9.28	5.055	**37**
−9.54	4.291	**29**

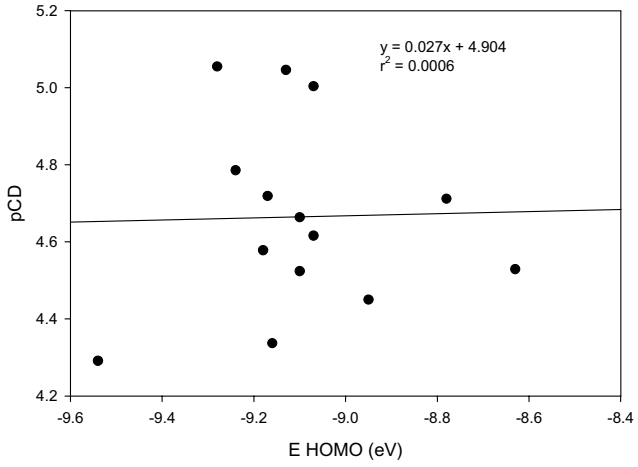


Figure 1. pCD of NQO1 induction by oxathiolene oxides versus E HOMO (eV).

ylpropenoids clearly does not extend into the oxathiolene oxides (Fig. 1). Thus, molecular parameters governing the activity of organosulfur inducers may be different from those for nonsulfur containing compounds, perhaps suggesting mechanistic differences in their mode of enzyme activation.

Although we know of no simple molecular parameter, which correlates with CD values reported here, we can offer some preliminary structure–activity conclusions based on this first test set of compounds. Heteroatom substituted or containing aromatics in the 5 position look promising (**33**, **36** and **37**). A vinyl group at the 4 position is good for inducing activity but bad for toxicity. Alkyl groups rather than alkenyl groups in the 4 position lower toxicity but also decrease inducing activity by a factor of 3. Sulfur oxidation state and substitution at the 3 position appear to have little effect on activity. It should also be noted that the three most active compounds in this study (**33**, **36** and **37**) all had CD values approaching that of Oltipraz (6 μM) in this cell line so we plan to continue this line of research. In the future, we plan to use this initial test set of compounds to develop a comparative molecular field analysis (CoMFA) model to help guide the synthesis of new molecules in this class.[30]

4. Summary

In conclusion, we have used Sonogashira coupling reactions to prepare a large number of aromatic substituted alkynols. We have extended the original Duboudin report that 3-phenyl-2-propynol would react with methyl and phenyl magnesium bromide followed by SO_2 quench to produce oxathiolene oxides. We find that this route works for a variety of primary alkynols. This synthetic sequence can also be used with tertiary alkynols but the oxathiolene oxides produced in that case are unstable. We find that allyl and vinyl magnesium bromide are superior to the analogous chlorides and that they are superior to alkyl and phenyl magnesium bromides. We find that alkyl magnesium bromides when used in combination with catalytic CuI are superior to the alkyl Grignards alone or in combination with catalytic Zn(+2). We find that $SOCl_2$ can be used as the sulfur electrophile but SO_2 is superior and oxathiolene oxides produced via this chemistry can be easily oxidized to oxathiolene dioxides. A number of new oxathiolene oxides with NQO1 CD values of less than 10 μM have been prepared using this chemistry. In the future, this first set of oxathiolene oxide screening and toxicity data will be used to develop a comparative molecular field analysis model to guide the development of new molecules in this class.

5. Experimental

5.1. General procedures

The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 300.13 MHz or a Bruker Avance 500 MHz spectrometer operating at 500.13 MHz. ^{13}C NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 75.48 MHz. All spectra were referenced to the residual proton or carbon signals of the respective deuterated solvents. All elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectrometry was performed at the Duke Mass Spectrometry Facility, Duke University in Durham, NC.

All reactions were carried out under an atmosphere of nitrogen. Ether, THF, hexane and methylene chloride were purchased from Fisher Scientific. Methylene chloride was distilled from CaH_2, ether, THF and pentane were distilled over Na/benzophenone. Water was deionized and distilled. Deuterated solvents were purchased from Cambridge Isotope Laboratories and dried over molecular sieves. Magnesium Sulfate, DMF, vinyl magnesium bromide, allyl magnesium bromide, ethyl magnesium bromide, phenyl magnesium bromide, 2-iodoanisole, 4-iodoanisole, 1-iodo-2-trifluoromethyl-benzene, 1-iodo-4-trifluoromethyl-benzene, 2-iodothiophene, 2-fluoroiodobenzene, 4-fluoroiodobenzene, 2-bromo-5-acetylthiophene, 2,5-dimethoxybromobenzene and sulfur dioxide were purchased from Aldrich Chemical Company and used as received. Diisopropyl amine and triethyl amine were purchased from Aldrich Chemical Company, treated with potassium hydroxide and distilled. Propargyl alcohol, 3-phenyl-2-propyn-1-ol, 2-butyn-1-ol and 3-[3-methoxyphenyl]-prop-2-yn-1-ol were purchased from GFS Chemicals and were used as received. *trans*-Dichloro-bis(triphenylphosphine)-palladium was purchased from Strem Chemicals and used as received. Copper iodide was purchased from Acros Organics and used as received.

5.2. General procedure for the Sonogashira reaction to form 3-aryl-2-propyn-1-ols

A round bottom flask was charged with haloaryl (1 equiv), 1% $Pd(PPh_3)_2Cl_2$, 2% CuI and DMF (20 mL). The solution was stirred and cooled to −20 °C using a CO_2/ethylene glycol bath. An amine (4.5 equiv) was added to the solution. Propargyl alcohol

(1.09 equiv) in THF (20 mL) was added dropwise. The solution was stirred at room temperature for 18 h and then was quenched by the addition of H_2O (30 mL). The mixture was then extracted with ethyl acetate (2×50 mL) and the extract was dried using $MgSO_4$. The solvent was removed by rotary evaporation and high vacuum. The product was obtained following chromatography on SiO_2 (1:1 ethyl acetate/hexane) and the solvent was removed by rotary evaporation followed by exposure to high vacuum conditions (1 mmHg) for 1–2 h.

5.3. 3-(2′-Fluorophenyl)-2-propyn-1-ol (13)

2-Fluoroiodobenzene (3.0 g, 13.51 mmol), $Pd(PPh_3)_2Cl_2$ (0.190 g, 0.27 mmol), CuI (0.103 g, 0.54 mmol) and THF (30 mL) were used along with triethyl amine (4.10 g, 40.51 mmol) and propargyl alcohol (0.838 g, 14.18 mmol). The reaction followed the procedure described above. The reaction produced **13** (1.65 g, 10.99 mmol, 82%) as an orange oil. Anal. Calcd for $C_9H_7F_1O_1$: C, 71.99; H, 4.70. Found: C, 71.83; H, 4.72. HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_9H_7F_1O_1$, 150.0481; found, 150.0476. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.77 (s, 1H), 4.52 (s, 2H), 7.05 (t, $J = 8.6$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 7.29 (m, 1H), 7.41 (dt, $J = 7.6$ Hz, $J = 1.7$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.92, 79.33, 92.59, 111.26 (d, $J = 16$ Hz), 115.64 (d, $J = 20.7$ Hz), 124.14, 130.40 (d, $J = 7.7$ Hz), 133.79, 163.03 (d, $J = 251.7$ Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −110.74.

5.4. 3-(4′-Fluorophenyl)-2-propyn-1-ol (14)

4-Fluoroiodobenzene (3.0 g, 13.51 mmol), $Pd(PPh_3)_2Cl_2$ (0.190 g, 0.27 mmol), CuI (0.103 g, 0.54 mmol) and THF (30 mL) were used along with triethyl amine (4.10 g, 40.51 mmol) and propargyl alcohol (0.838 g, 14.18 mmol). The reaction followed the procedure described above. The reaction produced **14** (2.01 g, 13.39 mmol, 99%) as an orange oil. HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_9H_7F_1O_1$, 150.0481; found, 150.0479. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 4.49 (s, 2H), 6.97 (m, 2H), 7.38 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.60, 84.65, 87.33, 115.81 (d, $J = 22.3$ Hz), 118.90, 133.80 (d, $J = 8.3$ Hz), 162.77 (d, $J = 249.4$ Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −111.02.

5.5. 3-(2′-Methoxyphenyl)-2-propyn-1-ol (15)

2-Iodoanisole (6.0 g, 25.64 mmol), $Pd(PPh_3)_2Cl_2$ (0.360 g, 0.51 mmol), CuI (0.195 g, 1.03 mmol) and THF (50 mL) were used along with triethyl amine (10 g, 98.13 mmol) and propargyl alcohol (5.30 g, 89.69 mmol). The solution turned to an orange-red colour after stirring for 20 min. The reaction followed the procedure described above. The reaction produced **15** (3.01 g, 19.11 mmol, 72%) as a yellow solid mp 48 °C. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.18; H, 6.31. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.73 (br s, 1H), 3.87 (s, 3H), 4.53 (d, $J = 5.7$ Hz, 2H), 6.88 (m, 2H), 7.28 (dt, 2H), 7.39 (dd, $J = 1.5$ Hz, $J = 7.7$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.91, 55.78, 82.00, 91.33, 110.63, 111.68, 120.48, 129.99, 133.82, 160.04.

5.6. 3-(4′-Methoxyphenyl)-2-propyn-1-ol (16)

4-Iodoanisole (6.0 g, 25.64 mmol), $Pd(PPh_3)_2Cl_2$ (0.360 g, 0.51 mmol) and CuI (0.195 g, 1.03 mmol) were used along with propargyl alcohol (5.30 g, 89.69 mmol). After 5 min of stirring, triethylamine (10 g, 98.13 mmol) was added to the solution. The solution turned a yellow-brown colour after stirring for 20 min. The reaction followed the procedure described above. The reaction yielded **16** (4.07 g, 25.09 mmol, 98%) as a yellow solid mp 52 °C. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.27; H, 6.29. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.43 (s, 1H), 3.79 (s, 3H), 4.62 (s, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 7.36 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.99, 55.52, 85.91, 86.01, 114.08, 114.17, 133.42, 159.97.

5.7. 3-(2′-Trifluoromethylphenyl)-2-propyn-1-ol (17)

1-Iodo-2-trifluoromethyl-benzene (5.0 g, 18.38 mmol), $Pd(PPh_3)_2Cl_2$ (0.258 g, 0.368 mmol), CuI (0.140 g, 0.735 mmol) and DMF (20 mL) were used along with triethyl amine (10 mL, 71.93 mmol) and propargyl alcohol (1.18 g, 19.97 mmol) in THF (20 mL). The reaction followed the procedure described above. The reaction yielded **17** (1.60 g, 7.99 mmol, 43%) as a yellow oil. Anal. Calcd for $C_{10}H_7F_3O_1$: C, 59.99; H, 3.53. Found: C, 59.78; H, 3.62. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.80 (s, 1H), 4.51 (s, 2H), 7.38 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 49.75, 79.78, 93.07, 121.00 (d, $J = 1.9$ Hz), 122.57, 124.75, 126.00 (q, $J = 5.2$ Hz), 128.43, 131.62, 134.30. ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −62.69.

5.8. 3-(4′-Trifluoromethylphenyl)-2-propyn-1-ol (18)

1-Iodo-4-trifluoromethyl-benzene (5.0 g, 18.38 mmol), $Pd(PPh_3)_2Cl_2$ (0.258 g, 0.368 mmol), CuI (0.140 g, 0.735 mmol) and DMF (20 mL) were used along with triethyl amine (10 mL, 71.93 mmol) and propargyl alcohol (1.18 g, 19.97 mmol) in THF (20 mL). The reaction followed the procedure described above. The reaction yielded **18** (1.75 g, 8.74 mmol, 48%) as an orange oil. Anal. Calcd for $C_{10}H_7F_3O_1$: C, 59.99; H, 3.53. Found: C, 59.73; H, 3.53. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 2.04 (s, 1H), 4.54 (s, 2H), 7.51 (apparent q, 4H, $J = 13.7$ Hz, $J = 8.6$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.37, 84.25, 89.64, 121.99, 125.20 (q, $J = 4.0$ Hz), 125.98, 126.32 (m), 129.98, 130.41. ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −63.28 (s).

5.9. 3-(2′,5′-Dimethoxyphenyl)-2-propyn-1-ol (19)

2,5-Dimethoxybromobenzene (1.05 g, 4.84 mmol), $Pd(PPh_3)_2Cl_2$ (0.032 g, 0.046 mmol), PPh_3 (0.024 g, 0.092 mmol), propargyl alcohol (0.408 g, 6.90 mmol) and diisopropyl amine (20 mL) were mixed and heated to 40 °C for 20 min, then CuI (0.018 g, 0.092 mmol) was added and the reaction was heated to 80 °C. The

solution turned a brown colour after stirring for 5 min. After 18 h, the reaction was stopped and allowed to cool to room temperature and worked up as described above. The reaction yielded **19** (0.282 g, 1.47 mmol, 29%) as a yellow solid mp 127–129 °C. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.22; H, 6.29. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 2.25 (s, 1H), 3.72 (s, 3H), 3.81 (s, 3H), 4.51 (br s, 2H), 6.78 (s, 1H), 6.81 (d, J = 2.9 Hz, 1H), 6.93 (d, J = 2.9 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 52.00, 55.98, 56.55, 82.02, 91.63, 112.057, 112.27, 116.11, 118.56, 153.35, 154.63.

5.10. 3-(4′-Methyl-[1,3]-dioxolanylphenyl)-2-propyn-1-ol (20)

2-(4-Iodo-phenyl)-2-methyl-[1,3]dioxolane (2.01 g, 6.93 mmol), $Pd(PPh_3)_2Cl_2$ (0.048 g, 0.070 mmol), PPh_3 (0.036 g, 0.140 mmol), propargyl alcohol (0.611 g, 10.34 mmol) and diisopropyl amine (40 mL) were mixed and heated to 40 °C for 20 min, then CuI (0.026 g, 0.140 mmol) was added to the solution and the temperature was increased to 80 °C. The solution turned a brown colour after stirring for 5 min. After 18 h, the reaction was stopped and allowed to cool to room temperature and worked up as described above. The reaction yielded **20** as an orange solid (1.03 g, 4.72 mmol, 68%) mp 47–51 °C. Anal. Calcd for $C_{13}H_{14}O_3C$, 71.54; H, 6.47. Found: C, 71.51; H, 6.43. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.61 (s, 3H), 3.74 (t, J = 5.9 Hz, 2H), 4.01 (t, J = 6.4 Hz, 2H), 4.47 (s, 2H), 7.40 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 27.62, 51.76, 64.70, 85.63, 87.59, 108.79, 122.29, 125.55, 128.46, 131.79, 132.01, 143.89.

5.11. 3-(2′-Thiophenyl)-2-propyn-1-ol (22)

2-Iodothiophene (6.0 g, 28.57 mmol), $Pd(PPh_3)_2Cl_2$ (0.401 g, 0.57 mmol), CuI (0.218 g, 1.14 mmol) and THF (100 mL) were used along with triethyl amine (13 g, 128.48 mmol). The green solution produced was treated with the dropwise addition of propargyl alcohol (1.71 g, 31.14 mmol) in THF (20 mL). The solution turned to an orange colour after stirring for 20 min. The reaction then followed the procedure described above. The reaction yielded **22** (2.34 g, 16.93 mmol, 59%) as a brown solid mp 87 °C Anal. Calcd for $C_7H_6S_1O_1$: C, 60.84; H, 4.38. Found: C, 60.58; H, 4.43. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.87 (s, 1H), 4.53 (s, 2H), 6.99 (dd, J = 4.1 Hz, J = 3.6 Hz, 1H), 7.24 (dd, J = 3.6 Hz, J = 0.9 Hz, 1H), 7.29 (dd, J = 3.5 Hz, J = 1.1 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 51.80, 79.16, 91.29, 122.58, 127.09, 127.54, 132.51.

5.12. 3-(5′-Acetyl-2′-thiophenyl)-2-propyn-1-ol (24)

2-Bromo-5-acetylthiophene (1.05 g, 5.12 mmol), $Pd(PPh_3)_2Cl_2$ (0.038 g, 0.054 mmol), PPh_3 (0.026 g, 0.096 mmol), propargyl alcohol (0.432 g, 7.31 mmol) and diisopropyl amine (20 mL) were heated to 40 °C for 20 min. CuI (0.019 g, 0.100 mmol) was added to the solution and the reaction was heated to 80 °C. The solution turned a brown colour after stirring for 5 min. After 18 h, the reaction was stopped and allowed to cool to room temperature and worked up as described above. The reaction yielded **24** (0.630 g, 3.50 mmol, 68%) as a brown solid mp 82 °C. Anal. Calcd for $C_9H_8S_1O_2$: C, 59.98; H, 4.47. Found: C, 60.46; H, 4.73. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.58 (s, 1H), 2.52 (s, 3H), 4.51 (s, 2H), 7.16 (d, J = 3.9 Hz, 2H), 7.52 (d, J = 3.9 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 26.76, 51.62, 78.42, 94.56, 130.42, 132.03, 132.92, 144.82, 190.21.

5.13. General procedure for addition reactions between propyn-1-ols and Grignards

A two-neck round bottom flask, equipped with a magnetic stirring bar, was charged with the 3-aryl-2-propyn-1-ol in THF (50 mL). The solution was treated with 3.2 equiv of the appropriate Grignard reagent. The reaction was heated to reflux for 18 h. The solution was cooled to room temperature, then to −78 °C and sulfur dioxide gas was condensed into the flask over 5 min. The brown solution turned to a yellow colour as the solution warmed to 25 °C over the next hour. The reaction was quenched by stirring the solution with aqueous ammonium chloride (30 mL of a saturated solution) and performing an aqueous ether extraction (3 × 50 mL ether). The extracted ether was washed with water and brine. The ethereal solution was dried using magnesium sulfate and the solvent removed by rotary evaporation. The residue was dissolved in a small amount of chloroform and treated with pentane until a precipitate formed. The precipitate was filtered and the solution was condensed to an oil using rotary evaporation. The product was obtained following chromatography on SiO_2 (ether) and removal of the solvent by rotary evaporation and high vacuum.

5.14. 4-Allyl-3-methyl-[1,2]-oxathiol-3-en-2-oxide (29)

2-Butyn-1-ol (2.0 g, 27.74 mmol) in THF (50 mL) was treated with allyl magnesium bromide (2 M in THF 22.2 mL, 44.4 mmol). The reaction was performed and worked up as described above. The reaction yielded **29** (1.98 g, 12.53 mmol, 45%) as a yellow oil. Anal. Calcd for $C_7H_{10}S_1O_2$: C, 53.15; H, 6.38. Found: C, 53.45; H, 6.55. HRMS (m/z): $[M+H]^+$ calcd for $C_7H_{10}S_1O_2$, 158.0401; found, 158.0399. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 2.00 (t, J = 2.2 Hz, 3H), 3.01 (d, J = 6.5 Hz, 2H), 5.01 (dq, J = 14.6 Hz, J = 2.2 Hz, 1H), 5.12 (m, 2H). 5.39 (dq, J = 14.7 Hz, J = 2.2 Hz, 1H), 5.74 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 9.08, 29.95, 83.42, 118.45, 132.60, 140.04, 140.50.

5.15. 3-Phenyl-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (30)

3-Phenyl-2-butyn-1-ol (1.03 g, 7.80 mmol) in THF (25 mL) was treated with vinyl magnesium bromide (24.1 mL of a 1.0 M solution, 24.1 mmol). The reaction was performed and worked up as described above. The reaction yielded **30** (0.984 g, 4.77 mmol, 65%) as a brown oil. Anal. Calcd for $C_{11}H_{10}S_1O_2$: C, 64.05; H, 4.89. Found: C, 63.85; H, 5.17. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.48 (d, J = 18.1 Hz, 1H), 5.49 (d, J = 14.1 Hz, 1H), 5.56 (d, J = 11.1 Hz, 1H), 5.85 (d,

J = 14.4 Hz, 1H), 6.57 (dd, J = 17.9 Hz, J = 10.9 Hz, 1H), 7.42 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 24.10, 81.83, 123.49, 127.23, 129.41, 129.61, 129.87 137.37, 144.53.

5.16. 4-Allyl-3-phenyl-[1,2]-oxathiol-3-en-2-oxide (31)

3-Phenyl-2-butyn-1-ol (2.0 g, 15.13 mmol) in THF (50 mL) was treated with allyl magnesium bromide (25 mL of a 2.0 M solution, 50 mmol). The reaction was performed and worked up as described above. The reaction yielded **31** (2.38 g, 10.80 mmol, 71%) as a yellow oil. Anal. Calcd for $C_{12}H_{12}S_1O_2$: C, 65.43; H, 5.49. Found: C, 65.93; H, 5.66. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 3.13 (t, J = 6.3 Hz, 2H), 5.17 (d, J = 11.4 Hz, 1H), 5.18 (d, J = 15.4 Hz, 1H), 5.24 (d, J = 15.4 Hz, 1H), 5.62 (d, J = 15.1 Hz, 1H), 5.83 (m, 1H), 7.64 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 30.66, 76.37, 83.93, 118.81, 128.42, 128.83, 128.99 129.25, 132.79, 141.88.

5.17. 3-[4′-Methoxyphenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (32)

3-(4′-Methoxyphenyl)-2-propyn-1-ol (**23**) in THF (25 mL) was treated with vinyl magnesium bromide (20 mL of a 1.0 M solution, 20 mmol). The reaction was performed using the procedure described above. The reaction yielded **32** (1.15 g, 4.87 mmol, 79%) as a yellow oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{12}S_1O_3$, 236.0507; found, 236.0507. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 3.82 (s, 3H), 5.45 (m, 2H), 5.54 (d, J = 11.0 Hz, 1H), 5.82 (d, J = 13.5 Hz, 1H), 6.55 (dd, J = 11.1 Hz, J = 14.1 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 55.60, 81.68, 114.73, 120.70, 122.83, 127.17, 130.82, 137.84, 145.75, 160.73.

5.18. 3-[2′-Methoxyphenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (33)

3-[2′-Methoxyphenyl]-2-propyn-1-ol (**22**) (0.100 g, 0.617 mmol) in THF (25 mL) was treated with vinyl magnesium bromide (1.98 mL of a 1.0 M solution, 1.98 mmol). The reaction was performed using the procedure described above. The reaction yielded **33** (0.122 g, 0.516 mmol, 84%) as a clear oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{12}S_1O_3$, 236.0507; found, 236.0499. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 3.84 (s, 3H), 5.38 (d, J = 14.1 Hz, 1H), 5.41 (d, J = 17.9 Hz, 1H), 5.47 (d, J = 11.1 Hz, 1H), 5.82 (d, J = 14.0 Hz, 1H), 6.46 (dd, J = 11.0 Hz, J = 17.9 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.31 (dd, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.39 (dt, J = 7.5 Hz, J = 1.7 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 55.85, 80.69, 111.26, 117.41, 121.18, 122.15, 127.61, 131.50, 132.64, 139.40, 144.95, 157.59.

5.19. 3-[4′-Fluorophenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (34)

3-[4′-Fluorophenyl]-2-propyn-1-ol (0.700 g, 4.66 mmol) in THF (25 mL) was treated with vinyl magnesium bromide (9.17 mL of a 1.0 M solution, 9.17 mmol). The reaction was performed using the procedure described above. The reaction yielded **34** (0.418 g, 1.86 mmol, 40%) as a brown oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{11}H_9F_1S_1O_2$, 224.0307; found, 224.0308. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.43 (m, 2H), 5.51 (d, J = 11.0 Hz, 1H), 5.78 (d, J = 14.4 Hz, 1H), 6.46 (dd, J = 11.0 Hz, J = 17.8 Hz, 1H) 7.08, (m, 2H), 7.39 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 81.62, 116.49 (d, J = 21.8 Hz), 123.65, 124.63, 126.78, 131.42 (d, J = 8.5 Hz), 139.32, 145.16, 164.61. ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −111.09 (s).

5.20. 3-[2′-Fluorophenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (35)

3-[2′-Fluorophenyl]-2-propyn-1-ol (**20**) (1.50 g, 9.99 mmol) in THF (50 mL) was treated with vinyl magnesium bromide (32.0 mL of a 1.0 M solution, 32.0 mmol). The reaction was performed using the procedure described above. The reaction yielded **35** (0.919 g, 4.10 mmol, 41%) as a brown oily product. Anal. Calcd for $C_{11}H_9F_1S_1O_2$: C, 58.92; H, 4.05. Found C, 58.89; H, 4.21. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.49 (m, 2H), 5.58 (d, J = 11.0 Hz, 1H), 5.85 (d, J = 14.4 Hz, 1H), 6.39 (ddd, J = 2 Hz, J = 11.0 Hz, J = 17.8 Hz, 1H), 7.20 (m, 2H), 7.41 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 81.32, 116.34 (d, J = 21.3 Hz), 123.63, 124.88, 126.15, 131.88 (d, J = 14.5 Hz), 134.91, 140.78, 141.63, 159.18, 160.17 (d, J = 249.9 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$ δ): −112.02 (s).

5.21. 3-[2′-Thiophenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (36)

3-[2′-Thiophenyl]-2-propyn-1-ol (**22**) (0.753 g, 5.29 mmol) in THF (25 mL) was treated with vinyl magnesium bromide (17 mL of a 1.0 M solution, 17 mmol). The reaction was performed using the procedure described above. The reaction yielded **36** (0.700 g, 3.27 mmol, 63%) as a brown solid mp 107–109 °C. Anal. Calcd for $C_9H_8S_2O_2$: C, 50.92; H, 3.80. Found C, 51.00; H, 3.93. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 5.56 (m, 2H), 5.62 (d, J = 11.0 Hz, 1H), 5.85 (d, J = 14.4 Hz, 1H), 6.88 (dd, J = 11.0 Hz, J = 17.6 Hz, 1H), 7.12 (dd, J = 3.6 Hz, J = 5.1 Hz, 1H), 7.33 (d, J = 3.6 Hz, 1H), 7.47 (dd, J = 1.0 Hz, J = 5.1 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 82.21, 123.70, 126.95, 128.15, 128.83, 129.32, 129.73, 137.24, 139.96.

5.22. 3-[4′-Acetylphenyl]-4-vinyl-[1,2]-oxathiol-3-en-2-oxide (37)

3-(4′-Methyl-[1,3]-dioxolanylphenyl)-2-propyn-1-ol (**20**) (0.819 g, 3.81 mmol) in THF (25 mL) was treated with vinyl magnesium bromide (12.02 mL of a 1.0 M solution, 12.02 mmol). The reaction was performed and worked up as described above. The reaction yielded **37** (0.260 g, 1.05 mmol, 28%) as a white solid mp 55–56 °C. HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{12}S_1O_3$, 248.0507; found, 248.0501. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 2.62 (s, 3H), 5.54 (d, J = 14.5 Hz, 1H), 5.54 (d,

J = 18.0 Hz, 1H), 5.63 (d, J = 11.0 Hz), 5.87 (d, J = 14.5 Hz, 1H), 6.58 (dd, J = 18.0 Hz, J = 11.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 27.15, 82.01, 124.63, 126.78, 129.29, 129.84, 132.22, 133.55, 137.89, 140.70, 197.75.

5.23. 3-Phenyl-[1,2]-oxathiol-3-en-2-oxide (38)

3-Phenyl-2-propyn-1-ol (0.506 g, 3.83 mmol) in THF (30 mL) was treated with lithium aluminum hydride (0.433 g, 11.41 mmol). The reaction was stirred for 5 h at room temperature. The solution was cooled to −78 °C and sulfur dioxide gas was condensed into the flask over 2 min. The solution turned to a yellow colour as the solution warmed to 25 °C over the next hour. The reaction was quenched by stirring with aqueous ammonium chloride (30 mL) and an aqueous ether extraction (3 × 50 mL ether) was performed. The extracted ether layers were washed with water and brine. The ethereal solution was dried using magnesium sulfate and the solvent removed by rotary evaporation. The solution was dissolved in a small amount of chloroform and treated with pentane until a precipitate formed. The precipitate was filtered and the solution was condensed to an oil using rotary evaporation. The product was obtained following chromatography on SiO_2 (ether) and removal of the solvent by rotary evaporation and high vacuum. The reaction yielded **38** (0.221 g, 1.23 mmol, 32%) as a yellow oil. Spectroscopically this product is identical to that previously reported by Duboudin and co-workers.[22]

5.24. General procedure for addition reactions between propyn-1-ols and alkyl Grignards catalyzed by CuI

A two-neck round bottom flask, equipped with a magnetic stirring bar, was charged with the appropriate Grignard reagent. The Grignard reagent was then treated with a 10% mass of copper iodide. Dry THF (20 mL) was added to the solution as the reaction was warmed from −20 to 0 °C over 2 h. The colour of the solution was yellow. At this point, 0.3125 equiv of the propyn-1-ol was added to the solution. The reaction was heated to reflux for 3–5 h. The solution was cooled to room temperature, then to −78 °C and sulfur dioxide gas was condensed into the flask over 5 min. The brown solution turned to a green colour as the solution warmed to 25 °C over the next hour. The reaction was quenched by stirring the solution with aqueous ammonium chloride (30 mL of a saturated solution) and performing an aqueous ether extraction (3 × 50 mL ether). The extracted ether layers were washed with water and brine. The ethereal solution was dried using magnesium sulfate and the solvent removed by rotary evaporation. The solution was dissolved in a small amount of chloroform and treated with pentane until a precipitate formed. The precipitate was filtered and the solution was condensed to an oil using rotary evaporation. The product was obtained following chromatography on SiO_2 (1:1 ethyl acetate/hexane) and removal of the solvent by rotary evaporation and high vacuum.

5.25. 4-Methyl-3-phenyl-[1,2]-oxathiol-3-en-2-oxide (39)

3-Phenyl-2-propyn-1-ol (0.515 g, 3.90 mmol), CuI (0.089 g, 0.47 mmol) and THF (30 mL) was treated with methyl magnesium bromide (9 mL, 6.43 mmol). The reaction was performed and worked up as described above to yield **39** (0.316 g, 1.63 mmol, 42%) as a yellow oil, spectroscopically identical to that previously reported.[31]

5.26. 3,4-Diphenyl-[1,2]-oxathiol-3-en-2-oxide (40)

Copper iodide (0.461 g, 2.42 mmol) and phenylmagnesium bromide solution (24.2 mL, 24.2 mmol) was diluted with THF (20 mL). The reaction followed the procedure described above with 3-phenyl-2-propyn-1-ol (1.04 g, 7.87 mmol) used as the propynol. The reaction produced **40** (0.806 g, 3.15 mmol, 40%) as a brown oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{12}S_1O_2$, 256.0558; found, 256.0553. Spectroscopically, this product was identical to that previously reported by Duboudin and co-workers.[22]

5.27. 3-[2′-Methoxyphenyl]-4-ethyl-[1,2]-oxathiol-3-en-2-oxide (41)

Copper iodide (0.136 g, 0.71 mmol) and ethylmagnesium bromide solution (7.5 mL, 7.5 mmol) were diluted with THF (20 mL). The reaction followed the procedure described above with 3-[2′-methoxyphenyl]-2-propyn-1-ol (**15**) (0.363 g, 2.24 mmol) being used as the propynol. The reaction yielded **41** (0.141 g, 0.59 mmol, 26%) as a brown oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}S_1O_3$, 238.0664; found, 238.0663. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.11 (t, J = 7.7 Hz, 3H), 2.37 (q, J = 7.7 Hz, 2H), 3.84 (s, 3H), 5.21 (d, J = 14.9 Hz, 1H), 5.61 (d, J = 14.9 Hz, 1H) 6.94 (m, 2H), 7.30 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 13.01, 20.27, 55.98, 82.80, 110.99, 117.85, 120.86, 131.18, 132.07, 141.57, 146.56, 157.76.

5.28. 4-Ethyl-3-[3′-methoxyphenyl]-[1,2]-oxathiol-3-en-2-oxide (42)

Copper iodide (0.047 g, 0.25 mmol) and ethylmagnesium bromide solution (7.9 mL, 7.9 mmol) were diluted with THF (20 mL). The reaction followed the procedure described above with 3-[3′-methoxyphenyl]-2-propyn-1-ol (0.407 g, 2.51 mmol) being used as the propynol. The reaction yielded **42** (0.305 g, 1.28 mmol, 51%) as a brown oil. HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}S_1O_3$, 238.0664; found, 238.0664. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 1.11 (t, J = 7.7 Hz, 3H), 2.37 (q, J = 7.7 Hz, 2H), 3.84 (s, 3H), 5.36 (d, J = 14.9 Hz, 1H), 5.77 (d, J = 14.9 Hz, 1H) 6.94 (m, 2H), 7.30 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 12.01, 20.43, 55.38, 76.8, 105.99, 115.01, 124.86, 130.18, 132.07, 141.57, 146.56, 157.76.

5.29. 4-Ethyl-3-phenyl-[1,2]-oxathiol-3-en-2-oxide (43)

Copper iodide (0.157 g, 0.82 mmol) and ethylmagnesium bromide solution (24 mL, 24 mmol) were diluted

with THF (50 mL). The reaction followed the procedure described above with 3-phenyl-2-propyn-1-ol (0.996 g, 7.54 mmol) being used as the propynol. The reaction yielded **43** (0.737 g, 3.54 mmol, 47%) as a yellow oil. Anal. Calcd for $C_{11}H_{12}S_1O_2$: C, 63.44; H, 5.81. Found C, 63.24; H, 6.06. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{12}S_1O_2$, 208.0558; found, 208.0554. ^1H NMR (300 MHz, $CDCl_3$ δ): 1.14 (t, $J = 7.7$ Hz, 3H), 2.43 (q, $J = 7.6$ Hz, 2H), 5.25 (d, $J = 15.1$ Hz, 1H), 5.65 (d, $J = 15.1$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 12.92, 19.39, 83.16, 128.66, 129.91, 128.92, 129.00, 143.42, 145.70.

5.30. 3-Ethyl-4-methyl-[1,2]-oxathiol-3-en-2-oxide (44)

Copper iodide (0.248 g, 1.30 mmol) and methylmagnesium bromide solution (28 mL, 20 mmol) were diluted with THF (30 mL). The reaction followed the procedure described above with 2-pentyn-1-ol (1.010 g, 12.01 mmol) being used as the alkynol. The reaction yielded **44** (0.608 g, 4.16 mmol, 35%) as a brown oil. HRMS (*m/z*): $[M+H]^+$ calcd for $C_6H_{10}S_1O_2$, 146.0402; found, 146.0397. ^1H NMR (300 MHz, $CDCl_3$ δ): 1.19 (t, $J = 7.6$ Hz, 3H), 1.86 (s, 3H), 2.44 (q, $J = 7.6$ Hz, 2H), 4.95 (dq, $J = 0.9$ Hz, $J = 14.5$ Hz, 1H), 5.39 (dq, $J = 0.9$ Hz, $J = 14.5$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 10.02, 13.08, 17.31, 84.06, 138.04, 144.97.

5.31. 4-Allyl-5,5-dimethyl-3-phenyl-[1,2]-oxathiol-3-en-2-oxide (46)

4-Phenyl-2-methyl-3-butyn-2-ol (**45**) (2.08 g, 12.98 mmol) in THF (100 mL) was treated with allyl magnesium chloride (2.0 M, 20 mL, 40 mmol). The reaction was performed as described above. The reaction yielded **46** as a yellow oil (1.92 g, 7.74 mmol, 62%). Unfortunately, the product decomposed upon attempted silica gel purification before complete spectroscopic data could be gathered. ^1H NMR (300 MHz, $CDCl_3$ δ): 1.82 (s, 3H), 1.84 (s, 3H), 3.18 (m, 2H), 5.07 (d, $J = 10.1$ Hz, 1H), 5.17 (d, $J = 17.1$ Hz, 1H), 5.95 (ddt, $J = 6.9$, $J = 10.1$ Hz, $J = 17.1$ Hz, 1H), 7.18, (m, 1H), 7.29 (m, 2H), 7.40 (m, 2H). GC–MS *m/z* (% relative intensity): 248 (11.5%, M^+), 217 (22.4%), 200 (18.8%), 199 (30.3%), 185 (14.1%), 169.1 (31.1%), 159 (19.4%), 154 (14.2%), 143 (27.2%), 142 (28.5%), 141 (54.9%), 128 (41.2%), 106 (18.3%), 105 (100%), 91 (15.9%), 77 (21.6%), 43 (27.2%).

5.32. 4-Ethyl-3-[3′-methoxyphenyl]-[1,2]-oxathiol-3-en-2,2-dioxide (47)

A round bottom flask was charged with **42** (0.305 g, 1.28 mmol), CH_2Cl_2 (30 mL) and MCPBA (0.240 g, 1.39 mmol). The solution was cooled to 0 °C prior to the addition of the MCPBA and then stirred 1 h. The reaction was quenched by the addition of aq Na_2CO_3 (15 mL). The product was extracted using CH_2Cl_2 (2×20 mL). The solution was dried using magnesium sulfate and the solvent removed by rotary evaporation. The product was obtained by column chromatography on silica gel using ether (100%) as the eluent. The reaction yielded **47** as a yellow oil (0.322 g, 1.27 mmol, 99%). Anal. Calcd for $C_{12}H_{14}S_1O_4$: C, 56.68; H, 5.55. Found C, 57.48; H, 5.56. ^1H NMR (300 MHz, $CDCl_3$ δ): 1.12 (t, $J = 7.7$ Hz, 3H), 2.45 (q, $J = 7.7$ Hz, 2H), 3.83 (s, 3H), 5.01 (s, 2H), 7.055 (m, 3H), 7.38 (t, $J = 7.8$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$ δ): 11.74, 20.76, 55.37, 71.09, 114.44, 115.86, 121.43, 126.97, 130.23, 130.86, 145.61, 159.95.

5.33. Cell culture

The murine hepatoma cell line, Hepa 1c1c7 (ATCC, 36) was maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Hepa 1c1c7 cells were cultured in α-MEM. The media was supplemented with 10% foetal bovine serum (Gem Cell) and 100 units/mL penicillin G sodium and 100 μg/mL streptomycin sulfate. The cell culture media and penicillin–streptomycin were obtained from Life Technologies.

5.34. Determination of NQO1 activity in Hepa 1c1c7 cells

NQO1 activity was measured as previously described (**40**) with minor modifications. Briefly, Hepa 1c1c7 cells were seeded in 96 well plates at a density of 1×10^4 cells/mL in 200 μL. After 24 h of growth, media was withdrawn and replaced with media that contained dilutions of the test compounds. Treatments for each individual experiment were performed in octuplicates. After growing Hepa 1c1c7 cells in the presence of test compounds for 48 h, NQO1 activity was determined by measuring spectrophotometrically the NADPH-dependent menadiol-mediated reduction of 3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to a blue formazan dye (**40**). Toxicity of the test compounds was assessed by the crystal violet staining assay (**40**), which was performed on 96 well plates that were seeded and treated at the same time as the plates for the NQO1 assay. The concentration required for doubling NQO1 activity (CD value) and the concentration at which cells are 50% viable (IC_{50}) were determined using the CALCUSYN program (Biosoft). Calculations of NQO1 fold induction are based on NQO1 specific activity, which was calculated as described (**40**).

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