RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 19454

Oxidative radical coupling of hydroquinones and thiols using chromic acid: one-pot synthesis of quinonyl alkyl/aryl thioethers†

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Received 17th February 2020
Accepted 11th May 2020

DOI: 10.1039/d0ra01519a

rsc.li/rsc-advances

An efficient, simple and practical protocol for one-pot sequential oxidative radical C–H/S–H cross-coupling of thiols with hydroquinones (HQs) and oxidation leading to the formation of quinonyl alkyl/aryl thioethers using H_2CrO_4 was developed. This cross-coupling of thiyl and aryl radicals offers mono thioethers in good to moderate yield and works well with a wide variety of thiols. Similarly, this method works well for coupling of 2-amino thiophenol and HQs to form phenothiazine-3-ones **5a–c**. C–S bond formation *via* thioether synthesis was observed using a chromium reagent for the first time. Theoretical studies on the pharmacokinetic properties of compounds **5a–c** revealed that due to drug-like properties, compound **5b** strongly binds with Alzheimer's disease (AD) associated AChE target sites.

Introduction

The quinonoid class of compounds finds applications in several fields such as synthetic chemistry,[1] medicinal chemistry,[2] natural products,[3] and functional materials.[4] The chemical reactivity and catalytic performance of quinones depends upon their electron-accepting character, redox behavior,[5] and the nature of functional group(s) present.[6] Hetero-functionalized quinones, especially quinonyl thioethers, display good structural stability,[7] and useful pharmaceutical[8] and other biological activities.[9] Around thirty-one currently marketed drugs are thioether derivatives (Fig. 1),[10] used for the treatment of cancer, HIV, diabetes, Alzheimer's, inflammatory diseases, *etc.* In the case of materials, the thioether group contributes to physical, electronic and surface properties.[11]

In general, number of methods known for C–S[12] bond formation *via* C–H functionalization only less compared to C–N or C–O bond formation. One of the potential reasons could be lack of transition metal catalysts and reagents that can tolerate sulfur poisoning. Classical approaches for the construction of C–S bond are the direct coupling of organic halides or acids with thiols/disulfides/arylsulfonyl halides and addition of thiols to unsaturated C–C bonds under free radical or metal (Mn, Fe, Ni, Cu, Ru, Rh, Pd, Ag and Cs) catalyzed conditions.[12]

A good number of methods are known for the introduction of the thioether group on quinones (Q–S–R). Aryl quinonyl thioethers (Q–S–R) were prepared by reaction of arylsulfonyl chlorides with quinone–CuI–PPh_3,[13a] aryl disulfides (R–S–S–R) with quinone–AgOAc–dpp[13b] and CuI catalyzed oxidative addition of aryl boronic acids,[14a] and aryl iodides with aryl thiols.[14b] We recently demonstrated I_2-DMSO[15] mediated thiomethylation (–SMe) of quinone. Moreover, the conjugate addition of thiol on quinone was demonstrated using CuI–O_2,[16] and $Co(OAc)_2$–O_2 (ref. 7) system.

Conjugate addition of thiols or its derivatives to quinones,[17] usually leads to a mixture of thiolated hydroquinones (HQs).[18] This followed by re-oxidation provides quinonyl thioethers. A popular method for synthesis of quinone is the oxidation of HQ. In direct conversion of HQs into quinonyl thioethers, two such transformations should take place in one pot. To the best of our knowledge, there are only two such reports known. In one case, carcinogenic S-alkylisothiouronium salt[19a] was used for thioalkylation and in another study, an enzyme laccase was used to catalyse thiol addition on naphthohydroquinone[19b] and HQ[19c,d] (Scheme 1). Formation of poly thioalkylated products and poor yield are the main drawbacks of the enzymatic reaction. C–S bond formation on HQ *via* oxidative radical cross-coupling (ORCC), to form quinonyl thioethers was seldom explored.

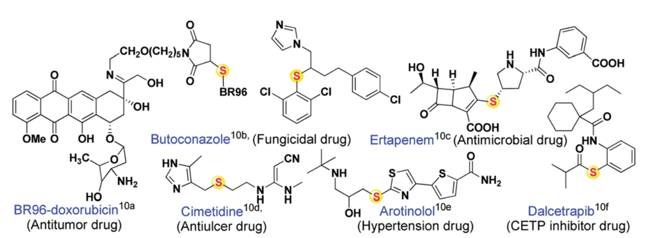

Fig. 1 Bioactive molecules containing a thioether linkage.

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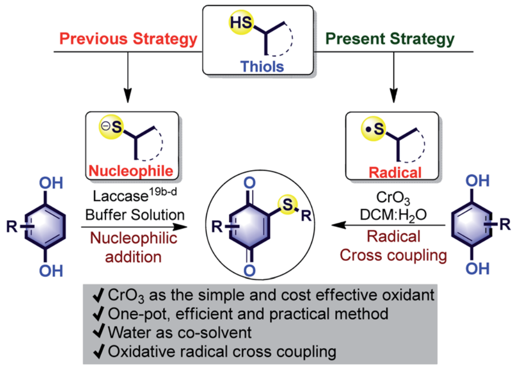
† Electronic supplementary information (ESI) available: Experimental, spectral data and copies of spectra. See DOI: 10.1039/d0ra01519a



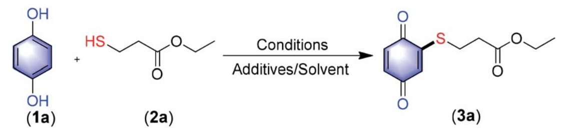
Scheme 1 Quinonyl thioethers from thiol and hydroquinone.

Chromium reagents are powerful oxidants which finds application in polymerization, aldol and Diels–Alder reactions.[20a] However, compared to other transition metals, its application in organic synthesis is undeveloped. To avoid poisonous effects due to contamination, chromium reagents are immobilized on zeolite.[20b] It is well known that chromic acid formed from CrO_3 dimerizes thiol oxidatively to form disulfides through thio radical,[20c] and also oxidizes hydroquinone to quinone.[20d] Based on this and in continuation of our research interest on C–H functionalization of quinones,[15,21] we hypothesized that HQ may undergo cross dehydrogenative oxidative radical cross-coupling (CDORCC) with thiol in the presence of CrO_3. CDORCC is highly advantageous because it is atom economic,[22] no need for pre-functionalization, and could be used for C–S bond forming reaction.[23] Under the present study, we observed the formation of quiononyl thioether in the presence of *in situ* generated chromic acid from CrO_3. To the best of our knowledge, this is the first example of C–S bond-forming reaction observed using a chromium reagent. Herein we present the results.

Result and discussion

To check our hypothesis, a solution of HQ (**1a**, 1.0 equiv.) and ethyl 3-mercaptopropanoate (**2a**, 1.5 equiv.) in DCM : H_2O (1 : 1 v/v, 4 mL) was treated with different oxidizing agents (1.0 equiv.) and the results are summarized in Table 1. In the case of oxidants such as $KMnO_4$, NBS, Na_2O_2 (entry 1) and iodine reagents like PIDA, PIFA, IBX or $NaIO_4$ (entry 2) the reaction failed to deliver the expected product **3a**. Interestingly, with $K_2S_2O_8$ (1.0 equiv., entry 3) both oxidation of HQ to quinone as well as C–S bond-forming reaction took place to afford the product **3a** in 10% isolated yield. Based on this encouraging result, we tried the same reaction using $(NH_4)_2S_2O_8$ (1.0 equiv., entry 4) and CrO_3 (1.0 equiv., entry 5), to get product **3a** in 20% and 30% respectively. Further, when 3.0 equiv. of CrO_3 (entry 5) was used the yield improved to 75%. However, with higher equivalents (3.0 equiv.) of $K_2S_2O_8$ (35%) and $(NH_4)_2S_2O_8$ (48%) the product **3a** was obtained in less isolated yield as compared with CrO_3 (entries 3–5). By decreasing (2.0 equiv., entry 6) or increasing (4.0 equiv., entry 6) the quantity of CrO_3 the yield did

Table 1 Optimization of reaction condition[a]



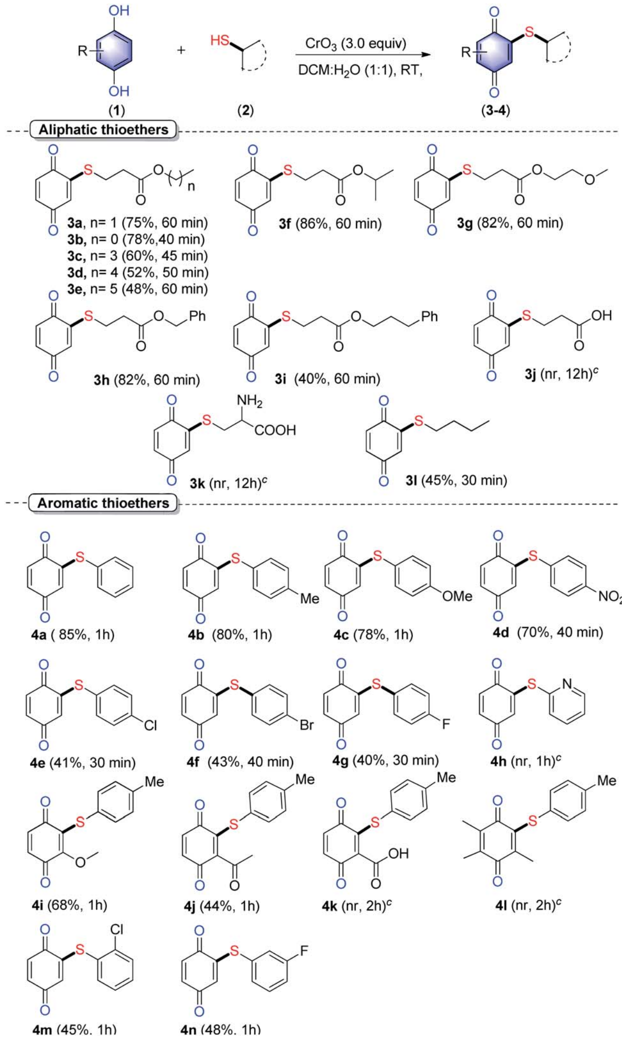
Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	$KMnO_4$/NBS/Na_2O_2	—	DCM : H_2O	NR
2	PIDA/PIFA/IBX/$NaIO_4$	—	DCM : H_2O	NR
3	$K_2S_2O_8$	—	DCM : H_2O	10/35[c]
4	$(NH_4)_2S_2O_8$	—	DCM : H_2O	20/48[c]
5	CrO_3	—	DCM : H_2O	30/75[c]
6	CrO_3	—	DCM : H_2O	68[d]/72[e]
7	CrO_3	—	DCM/H_2O	NR[c]/12[c]
8	CrO_3	—	DCE : H_2O	45[c]
9	CrO_3	—	ACN : H_2O	NR[c]
10	CrO_3	—	DMF : H_2O	NR[c]
11	CrO_3	TFA	DCM : H_2O	25[c]
12	CrO_3	*p*-TSA	DCM : H_2O	38[c]
13	CrO_3	H_2SO_4/HCl	DCM : H_2O	NR[c]
14	CrO_3–$(NH_4)_2S_2O_8$	—	DCM : H_2O	52[f]

[a] Reaction conditions: hydroquinone **1a** (1.0 mmol), thiol **2a** (1.5 mmol) oxidant (1 equiv.), additive (1 equiv.), solvent 1 : 1 ratio (4.0 mL) at rt for 1 h. [b] Isolate yield. [c] Oxidant (3.0 equiv.). [d] Oxidant (2.0 equiv.). [e] Oxidant (4.0 equiv.). [f] CrO_3 (0.1 equiv.) + $(NH_4)_2S_2O_8$ (3.0 equiv.); NR = no reaction.

not improve. Additionally, when the reaction was carried out with only DCM (no reaction) or H_2O (12%, entry 7), the result was not encouraging. This proves that solvent combinations are more favorable and water is essential for this reaction. Further, when the reaction was carried out in a combination of H_2O with various solvents such as DCE, DMF and ACN (Table 1, entries 8–10) the reaction yield diminished significantly. Finally, the effects of different acids as additive was evaluated.

When TFA (25%, entry 11) or *p*-TSA (38%, entry 12) was used the product **3a** was obtained only in very less yield. Furthermore, when HCl and H_2SO_4 were used as an additive, hydroquinone (**1a**) was simply converted into *p*-bezoquinone (**6a**) (entry 13). Finally, a catalytic amount of CrO_3 (0.1 equiv.) with $(NH_4)_2S_2O_8$ (3.0 equiv.) reaction was performed (entry 14), under this condition only 52% of desired product was obtained. The systematic screening study revealed that **1a** (1.0 equiv.), **2a** (1.5 equiv.) and CrO_3 (3.0 equiv.) in DCM : H_2O (1 : 1 v/v, 4 mL) at room temperature could be the optimum condition for oxidative direct C–S bond formation and synthesis of quinonyl thioethers from hydroquinone.

With the optimum condition in hand, substrate scope of various alkyl and aryl thiols was examined under the optimized reaction condition and the results are depicted in Scheme 2. The reaction of a series of linear long-chain (C1–C5) mercaptopropanoates (**2b**–**2e**) with HQ afforded corresponding thioethers **3b**–**3e** in good to moderate yield (75% to 48%). As the chain length of thioesters increased, the reactivity decreased. Mercaptopropanoate (**2f**) containing isopropyl group provided product **3f** in best isolated yield (85%). Similarly, mercaptopropanoates **2g**–**2h**,



Scheme 2 Scope of C–H/S–H cross-coupling between HQ and thiols.[a,b] [a]Reaction conditions: hydroquinone (1.0 equiv., 100 mg), thiol (1.5 equiv.), CrO_3 (3.0 equiv.), DCM : H_2O (4 mL, 1 : 1) at rt, [b]isolated yield; [c]expected product.

containing substituents such as 2-methoxyethyl (**2g**), benzyl (**2h**) and 3-phenylpropyl (**2i**) esters provided corresponding products **3g–3i** in 1 h in good to moderate (82–40%). As noted earlier, with an increase in chain length, the yield decreased. In the case of free acids, such as 3-mercaptopropanonic acid (**2j**), amino-3-sulfhydrylpropanoic acid (**2k**) the reaction failed to deliver the expected product **3j** and **3k.** Furthermore, simple thiols like butanethiol (**2l**) containing no ester group also reacted quickly with HQ to offer product **3l**, albeit in moderate yield (45%).

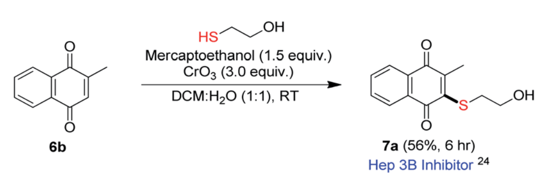
As the next part of our study, the suitability of various aryl thiols was examined. The unsubstituted thiophenol (**2m**) gave aryl thioether **4a** in a very good yield (85%). Similarly, thiophenols bearing electron-donating groups such as 4-Me (**2n**) and 4-OMe (**2o**) showed good reactivity and yielded corresponding aryl thioethers **4b** (80%) and **4c** (78%) in very good yield. The thiophenol **2p** containing electron-withdrawing 4-NO_2 group provided product **4d** in moderate yield 70%. However, thiophenols **2q–s**, substituted with deactivating substituents like 4-Cl, 4-Br, 4-F gave low to the moderate yield of desired products **4e–g** (40–43%). However, 2-mercaptopyridine (**2t**) failed to deliver the expected product **4h**. Further, the reaction of substituted hydroquinones with 4-methylthiophenol (**2n**) was examined. The 2-methoxy HQ (**1b**) and 2-acelyl HQ (**1c**) underwent reaction very smoothly to afford desired products in 68% (**4i**) and 44% (**4j**) respectively. HQ **1d** containing deactivating –COOH group and HQ **1e** containing highly substituted, 2,3,5-trimethyl failed to deliver the expected product (**4k–l**). Finally, the reactivity of *ortho* and *meta* substituted aryl thiol was also evaluated. Accordingly, 2-chlorothiophenol (**2u**) and 3-fluorothiophenol (**2v**) underwent reaction smoothly and the desired products **4m** and **4n** were obtained in 45% and 48% respectively. This result when combined with the result obtained from compounds **4e–f** reveals that the position of the substituent at *o*/*m*/*p* did not influence the reactivity of aromatic thiols much under this oxidative condition.

Having demonstrated the synthesis of mono derivatives of quinonyl thioether in one pot using 1.5 equiv. of thiols, the effect of using a super stoichiometric quantity of thiols was examined (Scheme 3). Interestingly, when the reaction was carried out under standard condition using 3.0 equiv. aryl thiol **2n**, bis-thiolated product **4o** was obtained in 60% yield.

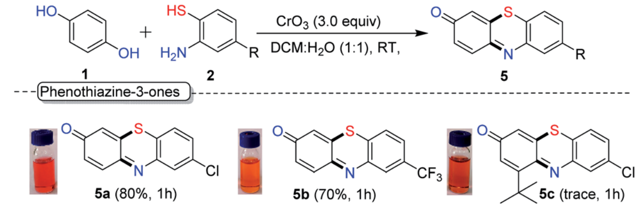
Vitamin K family consists of 2-methyl-1,4-naphthoquinone derivatives substituted with a long alkyl chain at 3-position. Thioether analogs of vitamin K were found to inhibit protein-tyrosine phosphatases and induce protein-tyrosine phosphorylation in a human hepatoma cell line (Hep3B).[24] Utility of our method for the synthesis of Hep3B inhibitor was examined (Scheme 4). Accordingly, under the optimized condition, mercaptoethanol underwent reaction with menadione (**6b**) to provide corresponding product **7a**, a Hep3B inhibitor, in 56% (Scheme 4).[24]

As the next part of our study, we examined the reactivity of thiophenols with an additional functional group. Interestingly, under the optimal condition, when HQ was treated with 2-amino thiophenol derivatives **2w** and **2x**, we observed the formation of biologically important phenothiazines **5a** (–Cl) and **5b** (–CF_3) through tandem C–S and C–N bond formation and oxidation of hydroquinone to quinone in 80% and 70% yield

Scheme 3 One-pot C–H difunctionalization of HQ.



Scheme 4 Synthesis of Hep3B inhibitor.



Scheme 5 Domino reaction for phenothiazine-3-one. Reaction conditions: hydroquinone (1.0 equiv., 100 mg), 2-aminothiolphenol (1.5 equiv.), CrO_3 (3.0 equiv.), DCM : H_2O (4 mL, 1 : 1) at rt, isolated yield.

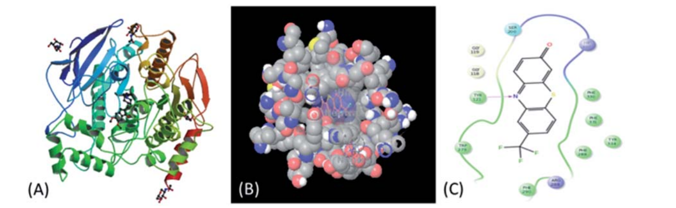


Fig. 2 (A) Acetylcholinesterase target; (B) 3D structure of protein–ligand interaction; (C) 2D structure of protein–ligand interaction.

respectively (Scheme 5). However, reaction with sterically substituted HQ (**1f**) provides the expected phenothiazines **5c** only in trace quantity.

In general, phenothiazines are excellent chromogenic molecules that find application as coloring agents.[25a] Moreover, this moiety is used as a common building block for the synthesis of pharmaceuticals including promazine drugs, anti-tubercular agents and cholinesterase inhibitors *etc.*[25b] The computer modeling of Absorption, Distribution, Metabolism, and Excretion (ADME) properties of compounds provides an idea about structure–property relationships and drug metabolism and pharmacokinetics (DMPK) properties based on the compound structure. *In silico* ADME-PK is applied at an early phase of the drug development process, in order to remove molecules with poor ADME-PK properties and leads to significant savings in research and development costs.

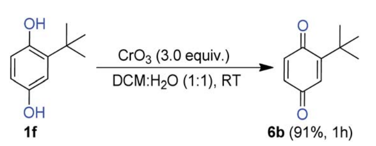
In this contest, we tried to understand ADME-PK properties of phenothiazine-3-one derivatives **5a–c** *in silicon* study was carried out using Swiss-ADME,[26] web tool (see ESI†). Results revealed that all compounds showed high gastrointestinal (GI) absorption, good blood–brain barrier (BBB) permeability and also compounds do not have P-glycoprotein (P-gp) permeability. The high lipophilicity (log $P_{o/w}$) and less skin permeation (log K_p) of compounds were observed in the range of 3.11 to 3.61 and −5.08 to −5.96 cm s^{-1} respectively. Furthermore, compounds **5a–c** showed inhibition of cytochrome P450 isomers such as CYP1A2, CYP2C19 and CYP2C9. In addition topological polar surface area (TPSA) of **5a–c** was found to 58.20 Å (≤140 Å), indicating that compounds have appropriate oral bioavailability (0.55). All compounds **5a–c** meet the criteria of drug-likeness assessment based on Lipinski, Ghose and Veber rules. The drug lead-likeness shows, compound **5b** with trifluromethyl (–CF_3) is the most druggable substance without any violation. A combination of fragment contributions and a complexity penalty of **5b** indicated good synthetic accessibility (2.81).

Further, to establish interaction mode with Alzheimer's disease (AD) associated AChE (Fig. 2A) target (PDB ID:1EVE) compound **5b** was selected and *in silico* docking studies of **5a** was performed by using Glide 10.7 Schrödinger[27] software (see ESI†). Compound **5b** exhibited G-score −7.30 kcal mol^{-1} and glide model score −44.18. Moreover, compound **5b** showed strong hydrophobic interaction (Fig. 2B and C) with the amino acid residue Tyr121. These results reveal that the compound **5b** strongly binds with the AChE active site. Thus compound **5b** has good potential to show AChE inhibition.

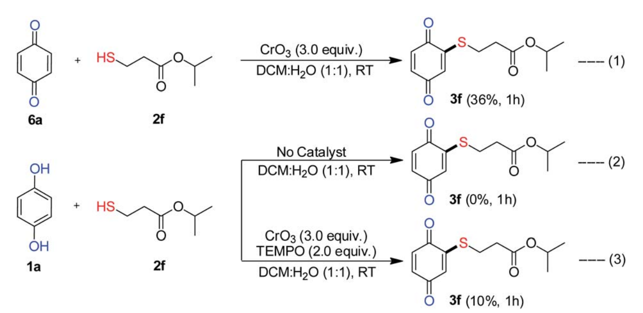
Next, we examined the conversion efficiency of hydroquinone to benzoquinone under optimized reaction conditions. The *tert*-butyl benzoquinone (**6b**) obtained in excellent yield 91%. It reveals that the optimized condition was suitable for the conversion of HQ to BQ (Scheme 6).

To gain an understanding of the plausible mechanism for the C–S coupling reaction, a series of control experiments were conducted (Scheme 7). The reaction of isopropyl 3-mercaptopropanoate (**2f**) with benzoquinone (**6a**) under optimal condition provided only product **3f** in low yield (36% equiv. 1), which is much less than the yield (86%, Scheme 2) obtained with hydroquinone (**1a**). This result indicated the benzoquinone may not the intermediate in the formation of product **3f** and a sequential oxidative C–H/S–H cross-coupling between HQ and thiol should have taken place. Furthermore, the reaction carried out in the absence of CrO_3 failed to deliver the desired product **3f** (equiv. 2), which revealed that, CrO_3 plays the role of oxidant in the oxidative cross-coupling reaction.

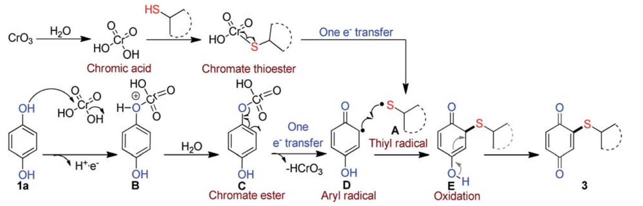
Additionally, to determine whether radical intermediate was involved, the reaction was carried out between **1a** and **2f** in the presence of radical scavenger TEMPO (2.0 equiv.). The yield of product **3f** decreased from 86% to 10% which clearly indicated that radical intermediates are involved in the reaction. Further, unlike the formation of poly thioalklylated quinones[18,19] in nucleophilic addition of thiol to quinones, under our reaction



Scheme 6 Conversion of HQ to BQ.



Scheme 7 Verification experiments for the mechanism.



Scheme 8 A Plausible mechanism.

conditions, only mono thioalkylated quinones were obtained. If it is radical cross-coupling the steric effect did not impact severely on the reactivity. From this view of point, we carried out the reaction with *o*/*m* substituted aryl thiophenol (Scheme 2, entry **4m–4n**) and desired products obtained in moderately. This result reveals that the steric hindrance did not much influence the reactivity. This clearly shows that no conjugate addition of thiol to quinone. The formation of thiyl radicals from thiol is known.[28] As it was mentioned earlier, without the presence of water (Table 1, entries 6 and 7) no reaction took place. Based on the verification experiments and background information, a plausible mechanism is proposed as shown in Scheme 8.

CrO_3 on reaction with water is expected to produce chromic acid, a powerful oxidant used in controlled oxidation of organic compounds. After the formation of chromate thioester by the reaction between thiol and chromic acid, it is expected to undergo one-electron transfer reaction to afford thiyl radical **A**. Similarly, hydroquinone is expected to form corresponding chromate ester **C** *via* deprotonation of intermediate **B**, which is then transformed into a phenoxy followed by semi-quinone radical **D** *via* oxidation. Further, thiyl radical **A** and semi-quinone radical **D** might undergo radical cross-coupling to form intermediate **E**, which reoxidizes to form more stable quinonyl thioether.

Conclusion

A simple and efficient method for oxidative radical C–H/S–H cross-coupling of hydroquinones with alkyl thiols/thiophenol/amino thiophenol to form quinonyl thioethers in mono-selective fashion under mild condition is demonstrated. A series of quinonyl alkyl/aryl thioethers and phenothiazines-3-ones were obtained in moderate to good yield at rt. To the best of knowledge, this is the first example of C–S bond formation using a chromium reagent such as H_2CrO_4. Furthermore, *in silico* analysis of ADME-PK properties of phenothiazines established that compound **5b** meets the criteria of drug and lead likeness and also posses good bioavailability. Moreover, it was also observed that compound **5b** strongly binds with Alzheimer's disease (AD) associated AChE target.

Experimental section

General information

All the reagents were purchased commercially and used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with Bruker 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, sep = septet, br = broad resonance. All the NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre-coated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and staining with I_2 on silica gel. High-resolution mass spectra (HRMS) were recorded on the Thermo Executive Plus spectrometer.

General method-A

To a slowly stirred solution of hydroquinone (1.0 equiv.) and a suitable thiols (1.5 equiv.) in DCM : H_2O (1 : 1, 4 mL), followed by which CrO_3 (3.0 equiv.) was added portion wise at room temperature. The progress of the reaction was monitored by TLC. Upon the complete consumption of starting materials it was diluted with ethyl acetate and water. The organic phase was separated, extracted with two or more times with ethyl acetate, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to get product. The disposal of chromic acid starts with adding H_2SO_4 or $CaCO_3$ to the aqueous phase (pH = 1). Further, solid $Na_2S_2O_3$ was added while stirring until the solution turns blue and cloudy. For MSDS information of CrO_3 (http://www.labchem.com/tools/msds/msds/LC13090.pdf).

Ethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3a). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2a** (182 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 162.0 mg, 75.0% yield, mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, J = 10.0 Hz, 1H), 6.63 (d, J = 10.0 Hz, 1H) 6.33 (s, 1H), 4.08–4.05 (q, 2H), 2.99–2.96 (t, 2H), 2.64–2.60 (t, 2H); 1.17–1.14 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 170.6, 151.8, 137.4, 136.1, 124.9, 61.0, 32.1, 24.9, 14.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{12}NaO_4S$: 263.0354; found: 263.0348.

Methyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3b). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2b** (162 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 160.2 mg, in 78.0% yield, mp 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, J = 10.0 Hz 1H), 6.65 (d, J = 10.0 Hz, 1H) 6.35 (s, 1H), 3.64 (s, 3H), 3.01–2.98 (t, 2H), 2.68–2.64 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 171.2, 151.8, 137.4, 136.1, 124.9, 52.1, 31.9, 24.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{10}NaO_4S$: 249.0197; found: 249.0200.

Butyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3c). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2c**

(220.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 144.8 mg, 60.0% yield, mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, J = 10.0 Hz, 1H), 6.68–6.65 (dd, J_1 = 10.0 Hz, J_2 = 10.0 Hz, 1H) 6.37 (s, 1H), 4.07–4.04 (t, 2H), 3.02–3.00 (t, 2H), 2.68–2.65 (t, 2H), 1.59–1.52 (m, 2H), 1.35–1.26 (m, 2H), 0.88–0.85 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 170.8, 151.9, 137.4, 136.1, 124.9, 65.4, 32.2, 30.5, 25.0, 19.0, 13.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{16}O_4S$: 268.0269; found: 268.0774.

Pentyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3d). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2d** (239.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 132.0 mg, 52.0% yield, mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, J = 10.0 Hz, 1H), 6.76 (d, J = 10.0 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H), 4.07–4.04 (t, 2H), 3.04–3.00 (t, 2H), 2.69–2.65 (t, 2H), 1.58 (s, 2H), 1.28 (d, 4H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 170.7, 151.9, 137.4, 136.1, 124.9, 65.4, 32.2, 28.2, 27.9, 25.1, 22.2, 13.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{18}NaO_4S$: 305.0823; found: 305.0824.

Hexyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3e). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2e** (258.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 127.9 mg, 48.0% yield, mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, J = 10.0 Hz, 1H), 6.72–6.69 (dd, J_1 = 10.0 Hz, J_2 = 10.0 Hz, 1H), 6.40 (s, 1H), 4.10–4.07 (t, 2H), 3.06–3.02 (t, 2H), 2.72–2.68 (t, 2H), 1.64–1.57 (m, 2H), 1.29 (s, 6H), 0.87–0.84 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 170.8, 152.0, 137.4, 136.1, 124.9, 65.4, 32.2, 31.4, 28.5, 25.5, 25.1, 22.5, 13.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{20}NaO_4S$: 319.0980; found: 319.0973.

Isopropyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio) propanoate (3f). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2f** (201.4 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 194.4 mg, 85.0% yield, mp 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 10.0 Hz, 1H), 7.01 (d, J = 10.0 Hz, 1H), 6.71 (s, 1H), 5.36–5.27 (m, 1H), 3.36–3.33 (t, 2H), 2.99–2.96 (t, 2H), 1.53–1.52 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.6, 170.2, 151.9, 137.4, 136.1, 124.9, 32.4, 29.6, 25.0, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{14}NaO_4S$: 277.0510; found: 277.0502.

2-Methoxyethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio) propanoate (3g). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2g** (223.1 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 199.5 mg, 82.0% yield, mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (d, J = 10.0 Hz, 1H), 6.50 (d, J = 10.0 Hz, 1H), 6.21 (s, 1H), 4.03–4.00 (t, 2H), 3.36–3.34 (t, 2H), 3.11 (s, 3H), 2.87–2.84 (t, 2H), 2.56–2.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.7, 183.6, 170.7, 151.6, 137.2, 136.0, 124.9, 70.0, 63.8, 58.6, 31.8, 24.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{14}NaO_4S$: 293.0460; found: 293.0451.

Benzyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (3h). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2h** (266.6 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 223.0 mg, 82.0% yield, mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.21 (m, 5H), 6.66 (d, J = 10.0 Hz, 1H), 6.58 (d, J = 10.0 Hz, 1H), 6.30 (s, 1H), 5.03 (s, 2H), 2.97–2.93 (t, 2H), 2.67–2.64 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.7, 170.7, 151.8, 137.4, 136.1, 135.5, 128.7, 128.5, 128.4, 66.9, 32.2, 24.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{14}NaO_4S$: 325.0510; found: 325.0514.

3-Phenylpropyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio) propanoate (3i). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2i** (304.6 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow semi solid, 118.8 mg, 40.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.16 (m, 5H), 6.80 (d, J = 10.0 Hz, 1H), 6.71 (d, J = 10.0 Hz, 1H), 6.41 (s, 1H), 4.16–4.13 (t, 2H), 3.05–3.01 (t, 2H), 2.71–2.66 (q, 4H), 1.99–1.96 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 183.7, 170.7, 151.9, 141.0, 137.4, 136.2, 128.5, 126.1, 124.9, 64.6, 32.2, 32.1, 30.0, 25.0; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{18}NaO_4S$: 353.0823; found: 353.0816.

2-(Butylthio)cyclohexa-2,5-diene-1,4-dione (3k). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2l** (122.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 79.5 mg, 45.0% yield, mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 10.0 Hz, 1H), 7.05–7.02 (dd, J_1 = 10.0 Hz, J_2 = 10.0 Hz, 1H), 6.69 (s, 1H), 3.10–3.06 (t, 2H), 2.06–1.99 (q, 2H), 1.85–1.77 (q, 2H), 1.28–1.25 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 183.8, 153.1, 137.4, 136.1, 124.7, 30.1, 29.2, 22.1, 13.5.

2-(Phenylthio)cyclohexa-2,5-diene-1,4-dione (4a). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2m** (150.0 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10, orange red solid, 150.0 mg, 85.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 5H), 6.83 (d, J = 10.4 Hz, 1H), 6.70–6.66 (dd, J_1 = 10.4 Hz, J_2 = 10.4 Hz, 1H), 5.88 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5, 183.9, 154.5, 137.5, 135.8, 135.6, 130.6, 130.4, 126.9, 125.9. The spectral data of the compound **4a** was complies with the values reported in the literature.[29]

2-(*p*-Tolylthio)cyclohexa-2,5-diene-1,4-dione (4b). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2n** (168.7 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange red solid, 165.6 mg, 80.0% yield; ^{1}H NMR

(400 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.81 (d, $J = 10.0$ Hz, 1H), 6.68–6.65 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1H), 5.87 (d, $J = 2.4$ Hz, 1H), 2.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.5$, 184.1, 154.9, 141.1, 137.5, 135.5, 131.2, 125.8, 123.2, 21.4. The spectral data of the compound **4b** was complies with the values reported in the literature.[29]

2-((4-Methoxyphenyl)thio)cyclohexa-2,5-diene-1,4-dione (4c). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2o** (190.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange red solid, 168.3 mg, 76.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$ (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 10.0$ Hz, 1H), 6.66–6.63 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1H), 5.84 (d, $J = 2.4$ Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.5$, 184.1, 161.5, 155.3, 137.5, 137.1, 135.9, 125.8, 116.9, 116.0, 55.5. The spectral data of the compound **4c** was complies with the values reported in the literature.[29]

2-((4-Nitrophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4d). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2p** (210.8 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as a yellow solid, 165.0 mg, 70.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.34$ (d, $J = 8.0$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 6.88 (d, $J = 10.0$ Hz, 1H), 6.74 (d, $J = 10.0$ Hz, 1H), 5.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.0$, 183.2, 152.3, 149.0, 137.5, 136.3, 135.9, 135.7, 126.7, 125.3, 124.1. The spectral data of the compound **4d** was complies with the values reported in the literature.[29]

2-((4-Chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4e). The reaction was carried out according to general method A using hydroquinone **1f** (100 mg, 0.60 mmol) and CrO_3 (180 mg, 1.8 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an yellow solid, 92.3 mg, 41.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.50–7.43 (dd, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, 2H), 6.85 (d, $J = 10.0$ Hz, 2H), 6.71–6.68 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1H), 5.87 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.3$, 183.8, 153.9, 137.5, 137.3, 136.9, 135.8, 130.7, 126.0, 125.3. The spectral data of the compound **4e** was complies with the values reported in the literature.[29]

2-((4-Bromophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4f). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2r** (255.5 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange solid, 113.8 mg, 43.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$–7.61 (m, 2H), 7.39–7.36 (m, 2H), 6.84 (d, $J = 10.0$ Hz, 1H), 6.72–6.68 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1H), 5.88 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.3$, 183.7, 153.8, 137.5, 137.2, 135.9, 133.7, 126.1, 126.0, 125.9, 125.6. The spectral data of the compound **4f** was complies with the values reported in the literature.[29]

2-((4-Fluorophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4g). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2s** (174.1 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange solid, 84.3 mg, 40.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.48 (q, 2H), 7.22–7.18 (t, 2H), 6.83 (d, $J = 10.0$ Hz, 1H), 6.71–6.68 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1H), 5.85 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 184.4, 183.9, 165.9, 162.9, 154.4, 137.9, 137.8, 137.5, 125.9, 117.9, 117.7. The spectral data of the compound **4g** was complies with the values reported in the literature.[29]

2-Methoxy-5-(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione (4i). The reaction was carried out according to general method A using hydroquinone **1b** (100 mg, 0.71 mmol), thiol **2n** (132.0 mg, 1.06 mmol) and CrO_3 (210.9 mg, 2.13 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange red solid, 125.8 mg, 68.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.0$, 2H), 7.28 (d, $J = 8.0$, 2H), 5.97 (s, 1H), 5.78 (s, 1H), 3.84 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.8$, 184.0, 178.8, 159.6, 157.0. 141.1, 135.5, 135.4, 131.2, 123.4, 107.6, 106.7, 56.6, 21.4.

2-Acetyl-3-(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione (4j). The reaction was carried out according to general method A using hydroquinone **1c** (100 mg, 0.65 mmol), thiol **2n** (122.3 mg, 0.98 mmol) and CrO_3 (193.0 mg, 1.95 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange red solid, 77.8 mg, 44.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (d, $J = 8.0$, 2H), 7.15 (d, $J = 8.0$, 2H), 6.79 (d, $J = 8.0$ 1H), 6.72 (d, $J = 8.0$, 1H), 2.35 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.8$, 183.5, 183.1, 145.4, 142.6, 139.9, 136.7, 136.5, 134.3, 130.3, 126.3, 31.3, 21.4.

2-((2-Chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4m). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2u** (197.0 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 101.3 mg, 45.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.52$–7.41 (m, 4H), 6.84 (d, $J = 10$, 1H), 6.72–6.69 (dd, $J_1 = 2.4$, $J_2 = 2.4$, 1H), 5.90 (d, $J_1 = 2.4$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.3$, 183.6, 153.6, 137.5, 135.9, 135.3, 133.8, 131.9, 130.9, 128.8, 126.1.

2-((2-Chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione (4n). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2v** (175.0 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as an orange yellow solid, 112.5 mg, 48.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$–7.51 (m, 2H), 7.29–7.23 (m, 2H), 6.85 (d, $J = 10$, 1H), 6.72–6.69 (dd, $J_1 = 2.4$, $J_2 = 2.4$, 1H), 5.88 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.3$, 183.7, 163.9, 161.4, 151.7, 137.5, 137.4, 135.9, 133.5, 133.4, 126.0, 125.9, 125.8, 117.2, 116.9, 114.2, 114.0.

2,6-Bis(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione (4o). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2n** (334.8 mg, 2.7 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10, to get the product as an orange red solid, 190.1 mg, 60.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.0$, 4H), 7.27–7.25 (t, 4H), 5.57 (s, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.4$, 181.3, 154.0, 141.1, 135.5, 131.2, 126.5, 123.5, 21.4.

8-Chloro-3*H*-phenothiazin-3-one (5a). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2u** (216.2 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as a red solid, 177.8 mg, 80.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.90$ (d, 1H), 7.60 (d, 1H), 7.44–7.37 (m, 2H), 6.95–6.75 (m, 1H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.4$, 147.5, 139.9, 139.7, 135.6, 134.6, 133.4, 133.1, 131.0, 125.9, 121.9, 120.5.

8-(Trifluoromethyl)-3*H*-phenothiazin-3-one (5b). The reaction was carried out according to general method A using hydroquinone **1a** (100 mg, 0.90 mmol), thiol **2v** (189.0 mg, 1.36 mmol) and CrO_3 (267 mg, 2.7 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as a red solid, 177.0 mg, 70.0% yield, mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (s, 1H), 7.67–7.54 (m, 3H), 6.97–6.76 (m, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 182.4, 147.8, 139.8, 139.1, 135.8, 134.1, 130.8, 130.7, 127.5, 126.9, 126.8, 125.8, 121.1.

2-(*tert*-Butyl)-8-chloro-3*H*-phenothiazin-3-one (5c). The reaction was carried out according to general method A using hydroquinone **1f** (100 mg, 0.60 mmol), thiol **2h** (143.5 mg, 0.90 mmol) and CrO_3 (178.2 mg, 1.8 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10, orange red solid, trace yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.85 (d, 1H), 7.50 (s, 1H), 7.14–7.33 (m, 2H), 6.66 (s, 1H), 1.38 (s, 9H).

2-(*tert*-Butyl)cyclohexa-2,5-diene-1,4-dione (6b). The reaction was carried out according to general method A using 2-(*tert*-butyl)benzene-1,4-diol **6b** (100 mg, 0.58 mmol), thiol **2w** (68.0 mg, 0.87 mmol) and CrO_3 (172.3 mg, 1.74 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as a yellow solid, 90.0 mg, 91.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.65$ (s, 2H), 6.56 (2, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.4$, 187.4, 156.0, 138.7, 135.0, 131.5, 35.3, 29.2, 29.0.

2-((2-Hydroxyethyl)thio)-3-methylnaphthalene-1,4-dione (7a). The reaction was carried out according to general method A using menadione **6b** (100 mg, 0.58 mmol), thiol **2w** (68.0 mg, 0.87 mmol) and CrO_3 (172.3 mg, 1.74 mmol). The reaction mixture was purified using eluent, hexane/ethyl acetate = 90 : 10 to get the product as a yellow solid, 80.5 mg, 56.0% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$–8.04 (m, 2H), 7.70–7.67 (t, 2H), 3.80–3.78 (t, 2H), 3.35–3.32 (t, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.3$, 181.6, 148.3, 145.7, 133.8, 133.5, 132.7, 132.0, 126.9, 126.7, 62.0, 37.3, 15.5. The spectral data of the compound **7a** was complies with the values reported in the literature.[24]

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

AKTP and SP thanks UGC-RFSMS, New Delhi for the award of the fellowship. We thank DST-FIST and DST-PURSE New Delhi, India for NMR and HRMS facilities at School of Chemistry, Bharathidasan University, Tiruchirappalli, India.

References

1 (*a*) G. A. Kraus and J. Mengwasser, *Molecules*, 2009, **14**, 2857–2861; (*b*) A. E. Wendlandt and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2015, **54**, 14638–14658; (*c*) B. Hosamani, M. F. Ribeiro, E. N. da Silva Junior and I. N. N. Namboothiri, *Org. Biomol. Chem.*, 2016, **14**, 6913–6931; (*d*) C. Song, X. Dong, H. Yi, C. W. Chiang and A. Lei, *ACS Catal.*, 2018, **8**, 2195–2199.
2 (*a*) P. R. Dandawate, A. C. Vyas, S. B. Padhye, M. W. Singh and J. B. Baruah, *Mini-Rev. Med. Chem.*, 2010, **10**, 436–454; (*b*) M. K. Hadden, S. A. Hill, J. Davenport, R. L. Matts and B. S. J. Blagg, *Bioorg. Med. Chem.*, 2009, **17**, 634–640.
3 (*a*) J. Madeo, A. Zubair and F. Marianne, *SpringerPlus*, 2013, **2**(139), 1–8; (*b*) S. Park, E. Yun, I. H. Hwanf, S. Yoon, D. E. Kim, M. Na, G. Y. Song and S. Oh, *Mar. Drugs*, 2014, **12**, 3231–3244; (*c*) M. Arai, T. Kawachi, H. Sato, A. Setiawan and M. Kobayashi, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3155–3157; (*d*) J. L. Bolton and T. Dunlap, *Chem. Res. Toxicol.*, 2017, **30**, 13–37; (*e*) P. A. Garcia, A. P. Hernández, A. S. Feliciano and M. A. Castro, *Mar. Drugs*, 2018, **16**(292), 1–51.
4 (*a*) V. J. Litchfield, R. B. Smith, A. M. Franklin and J. Davis, *Synth. Commun.*, 2008, **38**, 3447–3455; (*b*) S. Er, C. Suh, M. P. Marshaka and A. A. Guzik, *Chem. Sci.*, 2015, **6**, 885–893; (*c*) E. J. Son, J. H. Kim, K. Kim and C. B. Park, *J. Mater. Chem. A*, 2016, **4**, 11179–11202; (*d*) Y. Ding, Y. Li and G. Yu, *Chem*, 2016, **1**, 790–801; (*e*) O. Taran, *Front. Chem.*, 2017, **5**(49), 1–13.
5 (*a*) D. Sladic and M. J. Gasic, *Molecules*, 2006, **11**(1), 1–33; (*b*) N. E. Najjar, H. G. Muhtasib, R. A. Ketola, P. Vuorela, A. Urtti and H. Vuorela, *Phytochem. Rev.*, 2011, **10**, 353–370; (*c*) P. S. Guin, S. Das and P. C. Mandal, *Int. J. Electrochem.*, 2011, **816202**, 1–22.
6 (*a*) J. Fourie, C. J. Oleschuk, F. Guziec Jr, L. Guziec, D. J. Filterman, C. Monterrosa and A. Begleiter, *Canc. Chemother. Pharmacol.*, 2002, **49**, 101–110; (*b*) C. Frontana, A. V. Mayagoitia, J. Garza, R. Vargas and I. Gonzalez, *J. Phys. Chem. A*, 2006, **110**, 9411–9419; (*c*) L. Zhou, Y. Chen, X. Yang, Y. Su, W. Zhang and J. Xu, *Catal. Lett.*, 2008, **125**, 154–159; (*d*) X. Yang, Y. Wang, C. Zhang, T. Fang, L. Zhou, W. Zhang and J. Xu, *J. Phys. Org. Chem.*, 2011, **24**, 693–697.
7 W. Yu, P. Hjerrild, K. M. Jacobsen, H. N. Tobiesen, L. Clemmensen and T. B. Poulsen, *Angew. Chem., Int. Ed.*, 2018, **57**, 9805–9809 and references cited therein.
8 (*a*) K. Mozaina, C. L. Cantrell, A. B. Mims, A. R. Lax, M. R. Tellez and W. L. A. Osbrink, *J. Agric. Food Chem.*, 2008, **56**, 4021–4026; (*b*) C. K. Ryu, S. Y. Lee, N. Y. Kim, J. A. Hong, J. H. Yoon and A. Kim, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 427–430; (*c*) V. K. Tandon, S. Kumar, N. N. Mishra and P. K. Shukla, *Eur. J. Med. Chem.*, 2012,

56, 375–386; (*d*) A. Kacmaz, E. T. Acar, G. Atun, K. Kaya, B. D. Sigirci and F. Bagcigil, *ChemistrySelect*, 2018, **3**, 8615–8623; (*e*) H. Yıldırım, N. Bayrak, M. Yıldız, E. M. Kara, B. O. Celik and A. F. Tuyun, *J. Mol. Struct.*, 2019, **1195**, 681–688.

9 Z. Wang, E. C. Southwick, M. Wang, S. Kar, K. S. Rosi, C. S. Wilcox, J. S. Lazo and B. I. Car, *Cancer Res.*, 2001, **61**, 7211–7216.

10 (*a*) H. O. Sjögren, M. Isaksson, D. Willner, I. Hellström, K. E. Hellström and P. A. Cancer, *Res*, 1997, **57**, 4530–4536; (*b*) A. M. Keith Walker, A. C. Braemer, S. Hitt, R. E. Jones and T. R. Matthews, *J. Med. Chem.*, 1978, **21**, 840–842; (*c*) A. J. Sedman, *Am. J. Med.*, 1984, **76**, 109–114; (*d*) D. M. Livermore, A. M. Sefton and G. M. Scott, *J. Antimicrob. Chemother.*, 2003, **52**, 331–344; (*e*) X. Y. Zhang, G. S. Liu and J. Yuan, *Chin. J. Clin. Rehabil.*, 2013, **7**(24), 3340–3342; (*f*) T. F. Luscher, S. Taddei, J. C. Kaski, J. W. Jukema, D. Kallend, T. Munzel, J. J. P. Kastelein and J. E. Deanfield, *Eur. Heart J.*, 2012, **33**, 857–865.

11 (*a*) A. S. Thigpen, S. T. Nestor, R. A. O'Brien, S. Minkowicz, Y. Sheng, J. H. Davis Jr, K. N. West and A. Mirjafari, *New J. Chem.*, 2017, **41**, 1625–1630; (*b*) A. Bhadani and S. Singh, *Langmuir*, 2011, **27**(23), 14033–14044.

12 (*a*) T. Kondo and T. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205–3220 and references cited therein; ; (*b*) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Andy Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291–314 and references cited therein; For latest papers-; (*c*) W. H. Bao, C. Wu, J. T. Wang, W. Xia, P. Chen, Z. T. X. Xu and W. M. He, *Org. Biomol. Chem.*, 2018, **16**, 8403–8407; (*d*) G. S. Sorabad and M. R. Maddani, *Asian J. Org. Chem.*, 2019, **8**, 1–9; (*e*) W. H. Bao, Z. Wang, X. Tang, Y. F. Zhang, J. X. Tana, Q. Zhu, Z. Cao, Y. W. Lin and W. M. He, *Chin. Chem. Lett.*, 2019, **30**, 2259–2262; (*f*) L. Y. Xie, Y. L. Chen, L. Qin, Y. Wen, J. W. Xie, J. X. Tan, Y. Huang, Z. Cao and W. M. He, *Org. Chem. Front.*, 2019, **6**, 3950–3955.

13 (*a*) X. Yu, Q. Wu, H. Wan, Z. Xu, X. Xu and D. Wang, *RSC Adv.*, 2016, **6**, 62298–62301; (*b*) C. Zhang, J. Mc-Clure and C. J. Chou, *J. Org. Chem.*, 2015, **80**, 4919–4927.

14 (*a*) D. Wang, X. Yu, L. Wang, W. Yao, Z. Xu and H. Wan, *Tetrahedron Lett.*, 2016, **57**, 5211–5214; (*b*) D. Wang, X. Yu, W. Yao, W. Hu, C. Ge and X. Shi, *Chem. - Eur. J.*, 2016, **22**, 5543–5546.

15 S. Rajasekar, T. P. A. Krishna, N. Tharmalingam, A. Ilangovan and E. Mylonakis, *ChemistrySelect*, 2019, **4**, 2281–2287.

16 F. L. Zeng, X. L. Chen, S. Q. He, K. Sun, Y. Liu, R. Fu, L. B. Qu, Y. F. Zhao and B. Yu, *Org. Chem. Front.*, 2019, **6**, 1476–1480.

17 (*a*) V. K. Tandon and H. K. Maurya, *Tetrahedron Lett.*, 2009, **50**, 5896–5902; (*b*) V. K. Tandon, H. K. Maurya, S. Kumar, A. Rashid and D. Panda, *RSC Adv.*, 2014, **4**, 12441–12447.

18 (*a*) I. H. Spinner, W. D. Raper and W. Metanomski, *Can. J. Chem.*, 1963, **41**, 483–494; (*b*) A. R. Katritzky, D. Fedoseyenkoa, P. P. Mohapatraa and P. J. Steel, *Synthesis*, 2008, **5**, 777–787; (*c*) V. K. Tandona, D. B. Yadava, R. V. Singh, M. Vaisha, A. K. Chaturvedi and P. K. Shukla, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3463–3466; (*d*) D. E. Allgeier, S. A. Herbert, R. Nee, K. D. Schlecht and K. T. Finley, *J. Org. Chem.*, 2003, **68**, 4988–4990.

19 (*a*) Y. Lu, Y. Zhao, S. Wang, X. Wang, Z. Ge and R. Li, *RSC Adv.*, 2016, **6**, 11378–11381; (*b*) K. W. Wellington, G. E. Gordon, L. A. Ndlovu and P. Steenkamp, *ChemCatChem*, 2013, **5**, 1570–1577; (*c*) K. W. Wellington, R. Bokako, N. Raseroka and P. Steenkamp, *Green Chem.*, 2012, **14**, 2567–2576; (*d*) M. Schlippert, A. Mikolasch, V. Hahn and F. Schauer, *J. Mol. Catal. B Enzym.*, 2016, **126**, 106–114.

20 (*a*) X. Zeng and X. Cong, *Org. Chem. Front.*, 2015, **2**, 69–72; (*b*) M. Yadava and X. Qiang, *Chem. Commun.*, 2013, **49**, 3327–3329; (*c*) A. Levina, L. Zhang and P. A. Lay, *J. Am. Chem. Soc.*, 2010, **132**, 8720–8731; (*d*) M. Juaristi, J. M. Aizpurua, B. Lecea and C. Palomo, *Can. J. Chem.*, 1984, **62**, 2941–2944.

21 (*a*) A. Ilangovan, S. Saravanakumar and S. Malayappasamy, *Org. Lett.*, 2013, **15**(19), 4968–4971; (*b*) A. Ilangovan, A. Polu and G. Satish, *Org. Chem. Front.*, 2015, **12**, 1616–1620; (*c*) A. Polu and A. Ilangovan, *Tetrahedron Lett.*, 2018, **59**, 438–441; (*d*) T. P. A. Krishna, P. Sakthivel and A. Ilangovan, *Org. Chem. Front.*, 2019, **6**, 3244–3251; (*e*) P. Sakthivel, T. P. A. Krishna and A. Ilangovan, *Org. Biomol. Chem.*, 2020, **18**, 3027–3031.

22 Y. Hong, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016–9085 and references cited therein.

23 Z. Huang, D. Zhang, X. Qi, Z. Yan, M. Wang, H. Yan and A. Lei, *Org. Lett.*, 2016, **18**, 2351–2354.

24 Y. Nishikawa, Z. Wang, J. Kerns, C. S. Wilcox and B. I. Carr, *J. Biol. Chem.*, 1999, **274**, 34803–34810.

25 (*a*) V. Venkatraman, M. Foscato, V. R. Jensenb and B. K. Alsberg, *J. Mater. Chem. A*, 2015, **3**, 9851–9860; (*b*) Y. Liaoa, P. Jianga, S. Chena, F. Xiaoa and G. J. Deng, *RSC Adv.*, 2013, **3**, 18605–18608.

26 (*a*) A. Daina, O. Michielin and V. Zoete, *Sci. Rep.*, 2017, **7**, 42717; (*b*) T. Sander, J. Freyss, M. Von-Korff and C. Rufener, *J. Chem. Inf. Model.*, 2015, **55**, 460–473; (*c*) A. Daina and V. Zoete, *Curr. Med. Chem.*, 2016, **11**(11), 1117–1121.

27 J. R. Greenwood, D. Calkins, A. P. Sullivan and J. C. Shelley, *J. Comput. Aided Mol. Des.*, 2010, **24**, 591–604.

28 F. Denes, M. Pichowicz, G. Povie and P. Renaud, *Chem. Rev.*, 2014, **114**, 2587–2693 and cited therein.

29 D. Wang, X. Yu, L. Wang, W. Yao, Z. Xu and H. Wan, *Tetrahedron Lett.*, 2016, **57**, 5211–5214 and references cited therein.

