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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Investigation of the monoamine oxidase inhibition properties of benzoxathiolone derivatives

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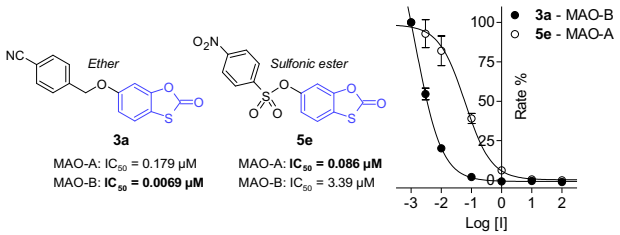
Abstract

The treatment of neuropsychiatric and neurodegenerative disorders such as depression and Parkinson's disease represent significant challenges in healthcare. Enzymes that metabolise neurotransmitter amines are important drug targets for these disorders and inhibitors of these enzymes have played key roles as therapeutic agents. For example, inhibitors of monoamine oxidase (MAO) A have been used for decades as antidepressant agents and act by inhibiting the central metabolism of serotonin and noradrenaline, while MAO-B inhibitors conserve central dopamine supply and have been used to treat Parkinson's disease. Literature reports that benzoxathiolone derivatives act as potent MAO inhibitors with specificity for the MAO-B isoform. To expand on these findings, the present study synthesised series of benzoxathiolone derivatives and investigated their human MAO inhibition properties. The results showed that the benzoxathiolone derivatives were potent MAO inhibitors, with the most potent compounds exhibiting IC_{50} values of 0.083 and 0.086 µM (**4d** and **5e**) and 0.0069 and 0.0066 µM (**3a** and **3b**) for MAO-A and MAO-B, respectively. Compounds **4d** and **5e** are significantly more potent MAO-A inhibitors compared to those reported previously. It may be concluded that benzoxathiolone derived compounds may act as future leads for the development of new treatments for depression and Parkinson's disease.

Graphical Abstract



Keywords Tioxolone · Benzoxathiolone · Neurodegenerative disorder · Enzyme inhibition · Monoamine oxidase · MAO

Abbreviations

DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
MAO	monoamine oxidase
NMR	nuclear magnetic resonance
SD	standard deviation
SI	selectivity index
TLC	thin layer chromatography

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00044-023-03042-w.

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Introduction

The monoamine oxidase (MAO) enzymes are important targets for the treatment of neuropsychiatric and

neurodegenerative disorders such as depression and Parkinson's disease [1]. MAO regulates the levels of neurotransmitter amines in the central and peripheral tissues by catalysing the oxidation of the α-carbon and thereby terminating the pharmacological action of the neurotransmitter [2]. Two isoforms of MAO exist, MAO-A and MAO-B, which are products of separate genes [3, 4]. Although the two isoforms have a high degree of similarity with respect to their amino acid sequences, three-dimensional structures and structures of their active sites, they display different substrate specificities. Serotonin is a specific substrate for MAO-A while the exogenous amines, 2-phenethylamine and benzylamine, are specific MAO-B substrates [1]. Overlap in substrate specificity also occurs with the catecholamines dopamine, noradrenaline, and adrenaline, as well as the dietary amines tryptamine and tyramine acting as substrates for both MAO isoforms.

Based on the role of MAO-A in the metabolism of serotonin, noradrenaline and dopamine, MAO-A inhibitors have been used for decades to treat depression [5–7]. The mechanism of action of MAO-A inhibitors is based on the monoamine hypothesis of depression which proposes that reduced monoamine neurotransmitter levels or monoamine mediated neurotransmission may lead to depression [8]. MAO-B inhibitors in turn, are established agents in the treatment of Parkinson's disease where they inhibit the metabolism of dopamine [9]. Degeneration of the nigrostriatal neuronal pathways results in depletion of striatal dopamine and is responsible for the motor symptoms in Parkinson's disease. To restore striatal dopamine, MAO-B inhibitors are frequently combined with levodopa, the metabolic precursor of dopamine. It is noteworthy that MAO-B has also been linked to neuronal damage in Parkinson's disease. The MAO catalytic cycle generates hydrogen peroxide as by-product, and if this occurs in vulnerable tissues such as the substantia nigra, hydrogen peroxide may be converted to reactive species such as the highly damaging hydroxyl radical [10, 11]. If cellular antioxidants are not able to remove these species, they may interact with, and damage cell components and contribute to neurodegeneration [10]. The finding that MAO-B density increases in the brain with ageing further supports a role for MAO-B inhibitors as potential neuroprotective agents in age-related disorders such as Parkinson's disease [12]. Hydrogen peroxide generated by the MAO catalytic cycle in cardiac tissue may also be of medicinal importance. MAO-A in cardiac tissue is a source of hydrogen peroxide which has been linked to oxidative damage and mitochondrial injury of the heart muscle [13, 14]. Based on this observation, it has been proposed that MAO-A inhibitors may have a future therapeutic role in heart disease.

Currently, the MAO-B specific inhibitors selegiline, rasagiline and safinamide are approved for the treatment of Parkinson's disease [1, 15, 16]. Selegiline and rasagiline are propargylamine compounds and mechanism-based irreversible inhibitors of MAO-B while safinamide is a reversible and competitive inhibitor. These compounds have good safety profiles. MAO-A inhibitors that are currently approved for the treatment of depression and anxiety disorders include phenelzine, isocarboxazid, tranylcypromine and moclobemide [1, 17, 18]. While reversible inhibitors such as moclobemide have good safety profiles, irreversible inhibitors (e.g., phenelzine, isocarboxazid and tranylcypromine) have been associated with serious adverse effects and may cause a potentially fatal hypertensive crisis if ingested with tyramine-rich food [19, 20]. This is known as the 'cheese effect' and occurs when the MAO-A mediated first-pass metabolism of tyramine within the digestive system is irreversibly inhibited. Tyramine enters the systemic circulation, which leads to the release of noradrenaline from adrenergic neurons and an increase in blood-pressure. Dietary restrictions are thus recommended when irreversible MAO-A inhibitors are prescribed [20].

The discovery of MAO inhibitors is an active area of research and is pursued in both the academia and industry [21]. Based on an academic interest in the discovery of MAO inhibitors with potentially useful inhibition properties and isoform specificities, the present study synthesised series of benzoxathiolone derivatives and investigated their human MAO inhibition properties. Benzoxathiolones have been reported to potently inhibit MAO-B. For example, compounds **1** and **2** inhibit human MAO-B with half maximal inhibitory concentration (IC_{50}) values of 0.003 and 0.004 μM, respectively (Fig. 1). Although these compounds are MAO-B specific inhibitors, potent inhibition of MAO-A has also been found. In this respect, **1** and **2** inhibit human MAO-A with IC_{50} values of 0.189 and 0.424 μM, respectively [22]. To expand on the reported study, this study will synthesise benzoxathiolones substituted on C6, with the substituent linked by an ether (**3a**–**n**), ester (**4a**–**g**) or sulfonic ester (**5a**–**j**) (Table 1).

Results and discussion

Chemistry

This study aimed to synthesise benzoxathiolone derivatives that are substituted on C6, with the substituent linked by an ether (**3a**–**n**), ester (**4a**–**g**) or sulfonic ester (**5a**–**j**). The benzoxathiolone derivatives were synthesised according to a modification of a literature method (Fig. 2) [22]. 6-Hydroxy-1,3-benzoxathiol-2-one (tioxolone, **8**) and a suitable alkyl halide were stirred in a mixture of K_2CO_3 and N,N-dimethylformamide (DMF) (or ethanol for **3g**) to produce the required ether derivatives (**3a**–**n**). The ester

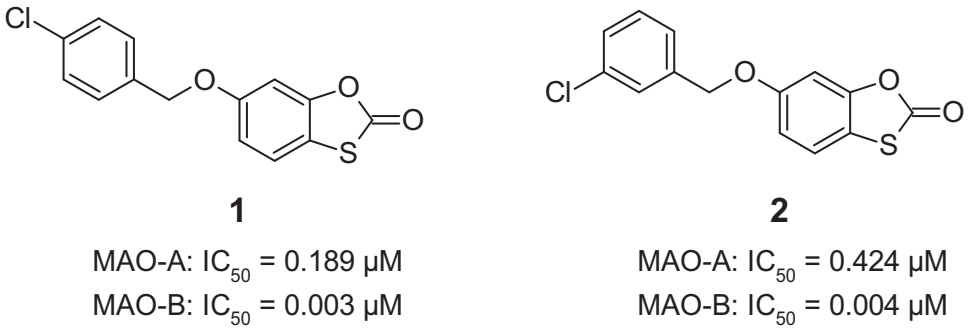


Fig. 1 The structures of benzoxathiolone derivatives that have been reported to inhibit MAO

(**4a**–**g**) and sulfonic ester (**5a**–**j**) derivatives were similarly synthesised by reaction of tioxolone with an acyl chloride and sulfonyl chloride, respectively. This simple method is a one-step reaction in which 3 different classes of electrophilic reagents (alkyl halide, acyl chloride, sulfonyl chloride) were used to produce the 3 series. Interestingly, three disubstituted and one trisubstituted derivative were also produced during the development of the synthetic conditions (Table 2). Disubstituted derivatives (**6a**–**c**) were obtained in reactions of tioxolone with an alkyl halide where ethanol was used as solvent. For this reason, ethanol was replaced with DMF as solvent, and the temperature of the reactions was reduced. However, a trisubstituted derivative (**7**) still formed under these conditions, without producing the desired monosubstituted product. The di- and trisubstituted products likely occur when the monosubstituted benzoxathiolone is again alkylated at the thiol (Fig. 3). After the addition of a water molecule in a concerted reaction, carbon dioxide is eliminated to yield the disubstituted compounds. This may be followed by alkylation of the hydroxyl to give the trisubstituted compound. It may be mentioned that the reaction between tioxolone and 5-bromopentanoyl chloride yielded the di-alkylated product **4d**. For the reaction between tioxolone and 3-chloropropionyl chloride, **4e** was obtained which indicated elimination of the 3-chloro under the reaction conditions.

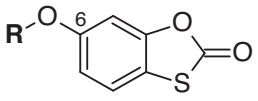
The benzoxathiolone derivatives were synthesised with yields in the following ranges: **3a**–**n**, 5–38%; **4a**–**g**, 4–68%; **5a**–**j**, 5–80%; **6a**–**c**, 5–37% and **7**, 18%. Each compound was characterised by nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectrometry (HRMS) to confirm the proposed structure. Incomplete crystallisation may have contributed to the relatively low yields in some instances. The purities of the synthesised compounds were estimated by high performance liquid chromatography (HPLC) analysis. For most compounds, the purities were >90%. The following compounds however displayed estimated purities of less than 90%: **3h** (88%), **3j** (71%), **4d** (89%) and **5e** (78%). Compound **5b** yielded two peaks with approximately equal areas (57 and 40%). NMR and HRMS, however, support the proposed structure which suggests that **5b** may have decomposed prior or during HPLC analysis. It should be noted that potential instability of **5b** may have affected the results of the MAO inhibition studies discussed below. For all the compounds that were analysed, the ppm deviation was within 5 ppm with the exception of **5e, 5f** and **5g**. In conjunction, the NMR and HRMS data supported the structures that were proposed for the synthesised compounds.

IC_{50} values for the inhibition of MAO

The MAO inhibition potencies of the series of benzoxathiolone derivatives were evaluated by measuring IC_{50} values for the in vitro inhibition of recombinant human MAO-A and MAO-B. For both MAO isoforms, kynuramine served as substrate and the MAO-generated product of kynuramine oxidation, 4-hydroxyquinoline, was measured by fluorescence spectrophotometry [23, 24]. Examples of sigmoidal plots for the inhibition of MAO are shown in Figs. 4 and 5.

The IC_{50} values are given in Table 3 and show that the benzoxathiolone derivatives are indeed inhibitors of both MAO-A and MAO-B. All compounds that were evaluated exhibited inhibition. For MAO-A, the most potent inhibition was observed for **4d** ($IC_{50} = 0.083\,\mu M$) and **5e** ($IC_{50} = 0.086\,\mu M$). Interesting structure-activity relationships are apparent for MAO-A inhibition. (a) Among the ether derivatives, six compounds (**3a**, **b**, **e**, **f**, **h**, **j**) had $IC_{50} < 1\,\mu M$. The weakest inhibition was observed with compound **3n** ($IC_{50} = 57.9\,\mu M$), which shows that a relatively long linker chain is not suitable for MAO-A inhibition. It is also noticeable that the compounds substituted with aliphatic chains (**3c**, **d**) were weak MAO-A inhibitors which demonstrates the requirement for an aromatic ring system (e.g., phenyl). Comparing **3b** vs. **3h** and **3e** vs. **3g**, it may be concluded that *para* substitution of the benzyloxy ring is more favourable for MAO-A inhibition compared to *meta* substitution. (b) The di- and trisubstituted derivatives (**6a**–**c**, **7**) were weak MAO-A inhibitors, which demonstrates the requirement for the benzoxathiolone moiety and

Table 1 The structures of the benzoxathiolone derivatives that were synthesised and investigated in this study



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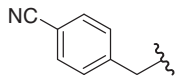
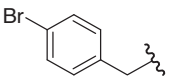
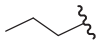
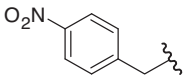
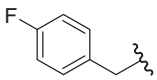
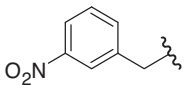
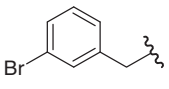
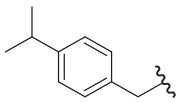
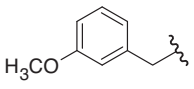
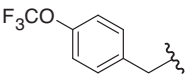
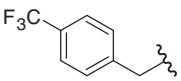
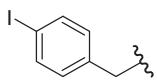
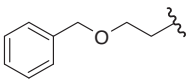
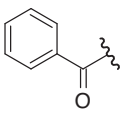
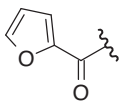
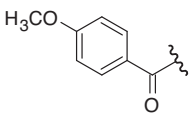
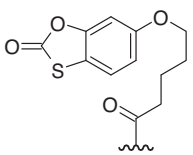
 **3a**
 **3b**
 **3c**
 **3d**
 **3e**
 **3f**
 **3g**
 **3h**
 **3i**
 **3j**
 **3k**
 **3l**
 **3m**
 **3n**
 **4a**
 **4b**
 **4c**
 **4d**
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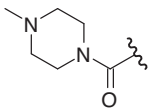
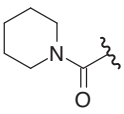
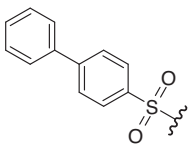
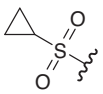
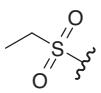
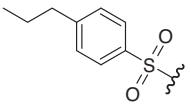
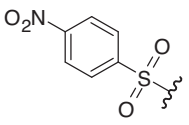
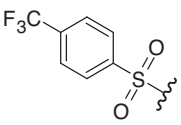
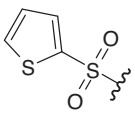
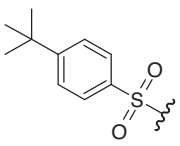
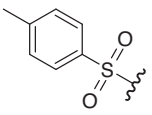
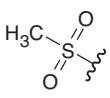
 **4f**
 **4g**
 **5a**
 **5b**
 **5c**
 **5d**
 **5e**
 **5f**
 **5g**
 **5h**
 **5i**
 **5j**

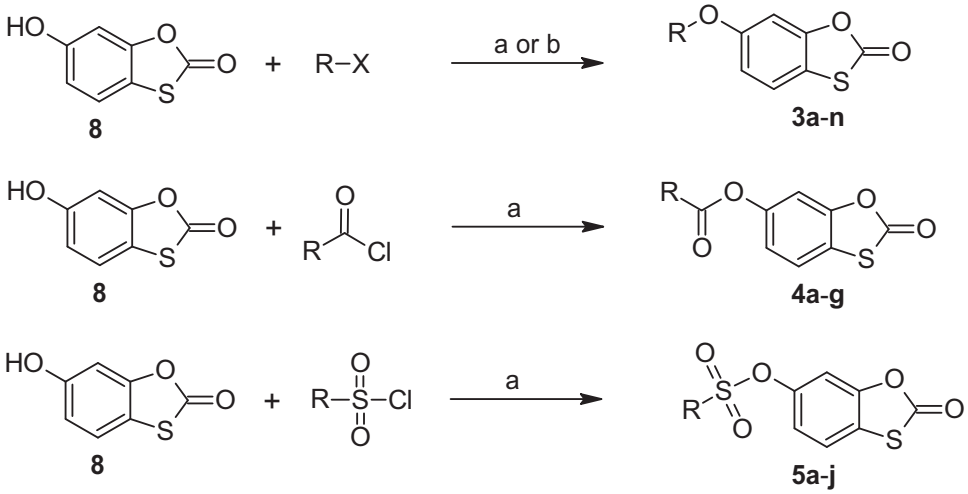
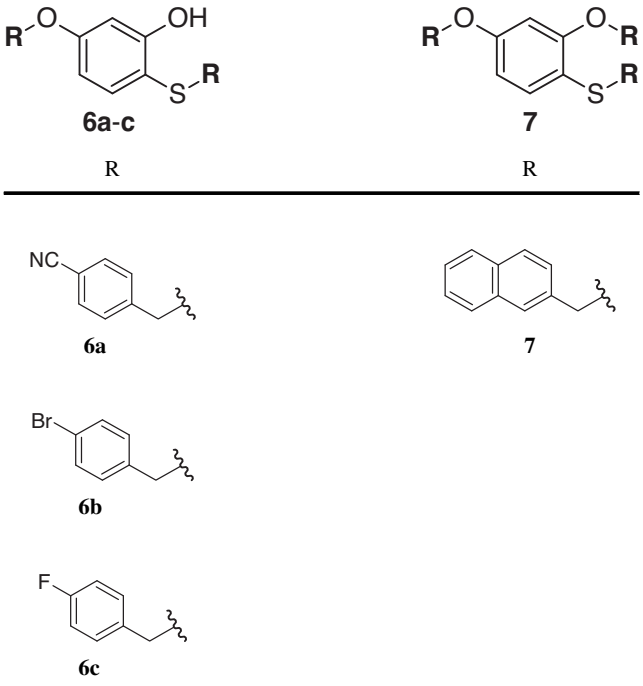


Fig. 2 Synthetic route for the synthesis of benzoxathiolone derivatives. Key: (a) DMF, K_2CO_3, rt, 24 h; (b) ethanol, K_2CO_3, reflux, 24 h

Table 2 The structures of the di- (**6a–c**) and trisubstituted derivatives (**7**)



the limitations of the available space within the MAO-A active site. (c) Among the ester derivatives, five compounds (**4a–e**) exhibited $IC_{50} < 1$ μM. It is noteworthy that **4d** which is double-substituted with benzoxathiolone is a potent MAO-A inhibitor. The piperazine and piperidine derivatives (**4f**, **g**) also were weak MAO-A inhibitors. (d) Among the sulfonic ester derivatives, seven compounds (**5b–g**, **i**) had $IC_{50} < 1$ μM. Weaker MAO-A inhibition was recorded for **5a** and **5h**, the derivatives with the bulkiest substituents among this series. Interestingly, very small substituents (e.g., **5j**) also produced weak MAO-A inhibition. (e) The most potent MAO-A inhibitors of this study (**4d**, **5e**) are ester and sulfonic ester derivatives, respectively, which demonstrates the suitability for MAO-A inhibition of these classes of compounds. (f) Compounds **3e**, **4e**, **5b**, **5c**, **5e** and **5g** may be highlighted selective MAO-A inhibitors (SI < 0.1) that display good potency for MAO-A ($IC_{50} < 1$ μM).

For MAO-B, the most potent inhibition was observed for **3a** ($IC_{50} = 0.0069$ μM) and **3b** ($IC_{50} = 0.0066$ μM). Interesting structure-activity relationships are apparent for MAO-B inhibition. (a) Among the ether derivatives, twelve compounds (**3a–c**, **f–n**) exhibited $IC_{50} < 1$ μM. Interestingly, the ethoxy substituted compound **3d** was not a MAO-B inhibitor while the propoxy substituted **3c** possessed good inhibition ($IC_{50} = 0.556$ μM). This shows that the substituent should be larger than an ethoxy to produce MAO-B inhibition. Larger substituents (e.g., **3a–b**, **f–n**) than the propyloxy leads to even more potent MAO-B inhibition. Interestingly, the *para*-nitrobenzyloxy substituted compound **3e** ($IC_{50} = 5.12$ μM) was a much weaker MAO-B inhibitor compared to the *meta* substituted homologue **3g** ($IC_{50} = 0.086$ μM). The *para*- and *meta*-bromobenzyloxy substituted compounds **3b** ($IC_{50} = 0.0066$ μM) and **3h** ($IC_{50} = 0.011$ μM), however, were both potent MAO-B inhibitors. (b) With the exception of **6c**, the di- and trisubstituted derivatives (**6a–b**, **7**) were moderate to weak MAO-B inhibitors. As for MAO-A, larger compounds such as these may not fit well into the MAO-B active site. Compound **6c** with the smallest substituent on the benzyloxy ring (e.g., fluorine) is the only compound that potently inhibits MAO-B among these series. (c) Among the ester derivatives, five compounds (**4a–d**, **g**) presented with $IC_{50} < 1$ μM. As for MAO-A, **4d** which is double-substituted with benzoxathiolone is a good potency MAO-B inhibitor. The acrylate substituted derivative (**4e**) had weak MAO-B inhibition, which again demonstrates the

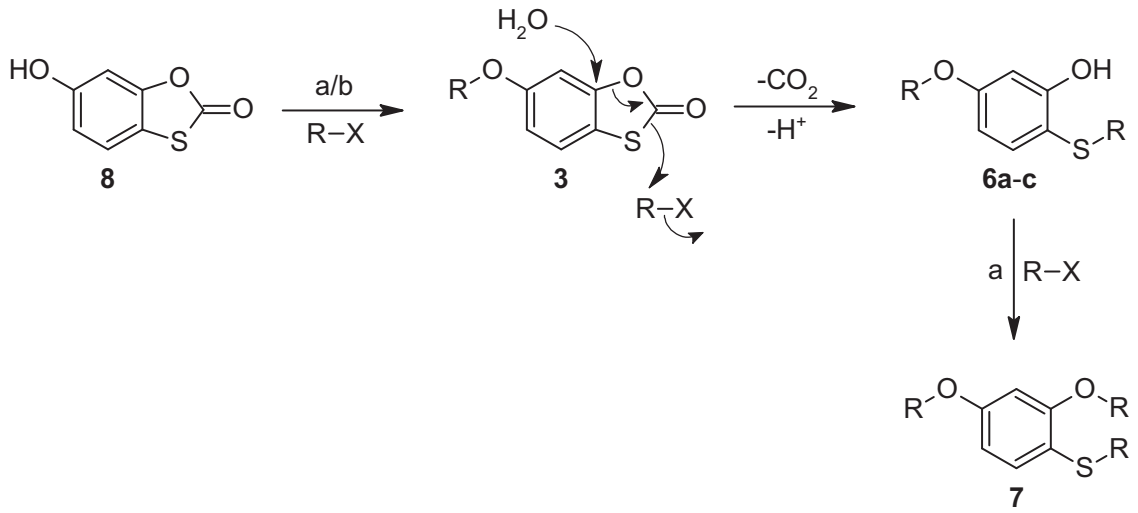


Fig. 3 A proposed mechanism by which the di- (**6a**–**c**) and trisubstituted derivatives (**7**) are formed upon alkylation of tioxolone. Key: (a) DMF, K_2CO_3, rt, 24 h; (b) ethanol, K_2CO_3, reflux, 24 h

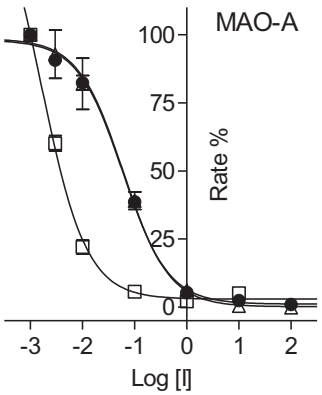


Fig. 4 Graphs of MAO-A catalytic activity versus inhibitor concentration (log[I]) for **4d** (circles), **5e** (triangles) and harmine (squares)

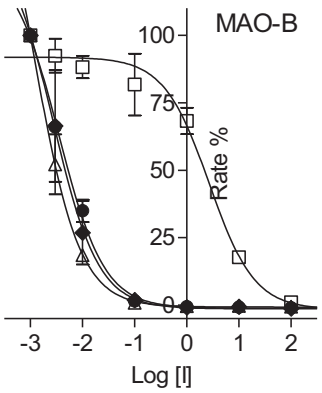


Fig. 5 Graphs of MAO-B catalytic activity versus inhibitor concentration (log[I]) for **3a** (diamonds), **3b** (circles), **3f** (triangles) and curcumin (squares)

requirement for a larger substituent for MAO-B inhibition. (d) Among the sulfonic ester derivatives, only two compounds (**5d**, **h**) had $IC_{50} < 1$ μM. Interestingly, these are the two derivatives with larger aliphatic chains (propyl and isobutyl) substituted on the side chain phenyl ring. CF_3 and methyl substitution (e.g., **5f**, **i**) also yielded more potent MAO-B inhibition compared to the other sulfonic ester derivatives considered. This result shows that larger lipophilic substituents on the side chain phenyl ring is favourable for MAO-B inhibition. Smaller substituents as observed with **5c** and **5j** yielded weak MAO-B inhibition. (e) The most potent MAO-B inhibitors of this study (**3a**, **b**) are ether derivatives, which demonstrates the suitability for MAO-B inhibition of this class of compounds. (f) Compounds **3l** and **3n** may be highlighted as selective MAO-B inhibitors (SI > 350) that display good potency for MAO-B ($IC_{50} < 0.15$ μM).

Conclusions

The study investigated series of benzoxathiolones substituted on C6, with the substituent linked by an ether (**3a**–**n**), ester (**4a**–**g**) or sulfonic ester (**5a**–**j**). During the development of the synthetic conditions, disubstituted derivatives (**6a**–**c**) as well as a trisubstituted derivative (**7**) were obtained. All compounds were examined for their ability to inhibit, in vitro, the activities of MAO-A and MAO-B. The benzoxathiolones were found to be potent MAO inhibitors with **4d** and **5e** exhibiting IC_{50} values of 0.083 and 0.086 μM, respectively, for the inhibition of MAO-A. Compounds **3a** and **3b** were the most potent MAO-B inhibitors with IC_{50} values of 0.0069 and 0.0066 μM, respectively. These potencies are remarkable when considering that the reference inhibitors harmine and safinamide inhibit MAO-A and MAO-B with IC_{50} of 0.0041 and 0.048 μM, respectively [25]. It may be

Table 3 The IC_{50} values (μM) for the inhibition of MAO by the benzoxathiolone derivatives

	IC_{50} (μM)[a]		
	MAO-A	MAO-B	SI[b]
3a	0.179 ± 0.003	0.0069 ± 0.0002	26
3b	0.297 ± 0.019	0.0066 ± 0.001	45
3c	3.21 ± 0.455	0.556 ± 0.245	5.8
3d	7.02 ± 0.846	–	–
3e	0.199 ± 0.030	5.12 ± 1.79	0.039
3f	0.399 ± 0.028	0.008 ± 0.002	50
3g	1.35 ± 0.004	0.086 ± 0.014	16
3h	0.477 ± 0.034	0.011 ± 0.003	43
3i	3.30 ± 0.601	0.028 ± 0.004	118
3j	0.155 ± 0.010	0.014 ± 0.0003	11
3k	1.71 ± 0.059	0.015 ± 0.001	114
3l	9.87 ± 3.40	0.011 ± 0.00001	897
3m	1.63 ± 0.089	0.016 ± 0.0004	102
3n	57.9 ± 3.65	0.150 ± 0.005	386
4a	0.410 ± 0.040	0.025 ± 0.001	16
4b	0.803 ± 0.012)	0.369 ± 0.027	2.2
4c	0.670 ± 0.056	0.018 ± 0.001	37
4d	0.083 ± 0.012	0.797 ± 0.052	0.10
4e	0.837 ± 0.060	13.5 ± 2.383	0.062
4f	31.7 ± 5.51	4.30 ± 0.134	7.4
4g	1.23 ± 0.040	0.093 ± 0.0004	13
5a	11.6 ± 0.382	28.9 ± 2.62	0.40
5b	0.725 ± 0.032	15.6 ± 4.87	0.046
5c	0.981 ± 0.148	28.9 ± 2.41	0.034
5d	0.148 ± 0.025	0.199 ± 0.009	0.74
5e	0.086 ± 0.002	3.39 ± 0.090	0.025
5f	0.177 ± 0.001	1.34 ± 0.138	0.13
5g	0.612 ± 0.008	10.5 ± 0.184	0.058
5h	4.55 ± 0.238	0.401 ± 0.035	11
5i	0.328 ± 0.008	1.35 ± 0.205	0.24
5j	3.84 ± 0.088	26.6 ± 7.106	0.14
6a	16.7 ± 0.983	5.32 ± 3.39	3.1
6b	77.5 ± 4.63	14.9 ± 0.841	5.2
6c	15.3 ± 0.014	0.416 ± 0.024	37
7	82.8 ± 31.8	2.46 ± 1.78	34
Curcumin[c]	2.75 ± 0.172	2.58 ± 0.217	1.1
Harmine[c]	0.0041 ± 0.00007	–	–

[a]All values are given as the mean ± standard deviation (SD)of triplicate measurements

[b]SI is the selectivity index and is calculated as IC_{50}(MAO-A)/IC_{50}(MAO-B)

[c]Reference inhibitor

concluded that benzoxathiolone derivatives are in general good leads for the design and development of MAO-A and MAO-B inhibitors. Such compounds may find application in the therapy of depressive illness and Parkinson's disease.

Benzoxathiolones substituted on C6 with an ether-linked substituent have been previously investigated as MAO inhibitors [22]. The reported study found that benzoxathiolones are potent MAO-B inhibitors with IC_{50} values ranging from 0.003 to 0.051 μM. Two of the reported benzoxathiolones were potent MAO-A inhibitors with IC_{50} values of 0.189 and 0.424 μM. The results of the present study are similar, with the ether derivatives (**3a–n**) exhibiting IC_{50} values as low as 0.0066 μM. Potent MAO-A inhibition was also observed among **3a–n** with the most potent inhibitor exhibiting an IC_{50} of 0.155 μM (**3j**). However, this is the first report of the MAO inhibition properties of ester and sulfonic ester derivatives of benzoxathiolone. Two highly potent MAO-A inhibitors were discovered among these compounds, **4d** ($IC_{50} = 0.083$ μM) and **5e** ($IC_{50} = 0.086$ μM). These inhibitors are superior compared to the ether derivatives. Good potency MAO-B inhibitors were also present among the ester and sulfonic ester derivatives, with the most potent compounds in these classes being **4c** ($IC_{50} = 0.018$ μM) and **5d** ($IC_{50} = 0.199$ μM), respectively. In contrast to the ether compounds, none of the ester and sulfonic ester derivatives inhibited MAO-B with an $IC_{50} < 0.01$ μM.

Experimental

Materials and instrumentation

Solvents and general laboratory chemicals were obtained from ACE Chemicals (Johannesburg, South Africa) while the reagents that were used for the chemical syntheses were obtained from Sigma-Aldrich. Deuterated dimethyl sulfoxide (DMSO-*d6*) for NMR spectroscopy was obtained from Merck. All the reagents used for the biology component of this study, including enzymes and substrates were obtained from Sigma-Aldrich. For the MAO inhibition studies, fluorescence intensities were recorded with a Varian Cary Eclipse fluorescence spectrophotometer (Agilent Technologies) and a SpectraMax iD3 multi-mode microplate reader (Molecular Devices).

Nuclear magnetic resonance spectroscopy: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 600 spectrometer at frequencies of 600 MHz and 150 MHz, respectively. All measurements were conducted in DMSO-*d6*. Chemical shifts (δ) are reported in parts per million (ppm) and were referenced to the solvent signal at 2.5 and 39.5 ppm for ^{1}H and ^{13}C NMR, respectively. Multiplicities are abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). The coupling constant *J* are reported in Hz.

Mass spectrometry: HRMS was conducted with a Bruker MicroTOF Q II mass spectrometer.

Chromatography: Column chromatography was performed with high-purity grade silica gel (pore size 60 Å, 70–230 mesh, 63–200 µm) from Sigma Aldrich, and thin layer chromatography (TLC) was performed with silica gel sheets (60 F_{254}) from Merck. Dichloromethane was used as the mobile phase for column chromatography, while a mixture of ethyl acetate and hexane (1:4) was used for TLC.

Purity by HPLC: To determine the purities of synthesised compounds, HPLC analyses were conducted with a Shimadzu Nexera-I LC 2040 C 3D Plus HPLC system equipped with a quaternary pump and a Shimadzu Nexera-I LC 2040 C 3D Plus series diode array detector. HPLC grade acetonitrile (Merck) and Milli-Q water (Millipore) were used for the chromatography. A Venusil XBP C18 column (4.60 × 150 mm, 5 µm) was used for the separation and the mobile phase consisted at the start of each run of 50% acetonitrile and 50% water. The flow rate was set to 0.8 mL/min. At the start of each run, a solvent gradient programme was initiated. The composition of the acetonitrile in the mobile phase was increased linearly from 50 to 100% over a period of 6 min and then lowered to 50% at 10 min. Each HPLC run lasted 13 min and a period of 5 min was allowed for equilibration between runs. A volume of 2 µL of solutions of the test compounds (1 mg/mL) was injected into the HPLC system, and the eluent was monitored at a wavelength of 300 nm. The test compounds were dissolved in either acetonitrile or methanol.

Synthetic procedures

Two methods for the syntheses of the benzoxathiolone derivatives were used. Method A was used for the majority of the compounds (**3a–f**, **3h–n**, **4a–g**, **5a–j**, **7**) while Method B was used for the synthesis of four compounds (**3g**, **6a–c**). Method A: In a round bottom flask, 6-hydroxy-1,3-benzoxathiol-2-one (**8**, 5 mmol), the appropriate alkyl halide, acyl chloride or sulfonyl chloride (7.5 mmol) and K_2CO_3 (10 mmol) were added to anhydrous DMF (10 mL). The reaction mixture was stirred at room temperature for 24 h. Ethanol was subsequently added to the reaction and the contents of the flask were filtered by vacuum filtration and the filtrate was allowed to evaporate. Ethanol was added to the residue and the resulting solution was allowed to recrystallise. The crystals were collected by filtration and dried *in vacuo* to obtain the desired derivatives.

Method B: In a round bottom flask, 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol), the appropriate alkyl halide (7.5 mmol) and K_2CO_3 (10 mmol) were added to absolute ethanol (10 mL). The reaction mixture was stirred under reflux at 80 °C for 24 h. Dichloromethane was subsequently added to the reaction mixture and the contents of the flask were filtered by vacuum filtration and the filtrate was allowed to evaporate. A mixture of ethanol and dichloromethane was added to the residue and the solution was allowed to recrystallise. The crystals were collected by filtration and dried *in vacuo* to obtain the desired derivatives. These methods have been adapted from the reported procedure [26].

4-({[2-Oxobenzo(d)(1,3)oxathiol-6-yl]oxy}methyl)benzonitrile (**3a**): The title compound (cream to white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-(bromomethyl)benzonitrile. Yield: 545 mg (38%), mp: 135–138 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.88 (d, J = 8.3 Hz, 2H, H-4', H-6'), 7.66 – 7.64 (m, 3H, H-4, H-3', H-7'), 7.27 (d, J = 2.5 Hz, 1H, H-7), 7.04 (dd, J = 8.8, 2.5 Hz, 1H, H-5), 5.27 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.23 (C-2), 158.47 (C-6), 148.93 (C-7a), 142.71 (C-2'), 132.92 (C-4', C-6'), 128.64 (C-3', C-7'), 124.43 (C-4), 119.16 (C-5'), 114.05 (C-8'), 113.41 (C-5), 111.13 (C-3a), 99.96 (C-7), 69.37 (C-1'). Purity: 98%. HRMS-ESI *m/z* $[MH]^+$ 284.0382 (Calc. for $C_{15}H_{10}NO_3S$: 284.0376).

6-[(4-Bromobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3b**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-bromo-4-(bromomethyl)benzene. Yield: 624 mg (37%), mp: 130–134 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.65 (d, J = 8.8 Hz, 1H, H-4), 7.60 (d, J = 8.4 Hz, 2H, H-4', H-6'), 7.43 (d, J = 8.4 Hz, 2H, H-3', H-7'), 7.26 (d, J = 2.5 Hz, 1H, H-7), 7.02 (dd, J = 8.8, 2.5 Hz, 1H, H-5), 5.14 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.27 (C-2), 158.64 (C-6), 148.93 (C-7a), 136.40 (C-2'), 131.89 (C-4', C-6'), 130.41 (C-3', C-7'), 124.39 (C-4), 121.62 (C-5'), 113.80 (C-3a), 113.49 (C-5), 99.94 (C-7), 69.53 (C-1'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 336.9542 (Calc. for $C_{14}H_{10}BrO_3S$: 336.9529).

6-Propoxybenzo(d)(1,3)oxathiol-2-one (**3c**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-bromopropane. Yield: 284 mg (27%), mp: 66-67 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.62 (d, J = 8.7 Hz, 1H, H-4), 7.16 (d, J = 2.5 Hz, 1H, H-7), 6.94 (dd, J = 8.8, 2.5 Hz, 1H, H-5), 3.96 (t, J = 6.5 Hz, 2H, H-1'), 1.77 – 1.70 (m, 2H, H-2'), 0.98 (t, J = 7.4 Hz, 3H, H-3'). ^{13}C NMR (151 MHz, DMSO) δ 170.36 (C-2), 159.28 (C-6), 149.00 (C-7a), 124.28 (C-4), 113.15 (C-5), 113.10 (C-3a), 99.41 (C-7), 70.19 (C-1'), 22.33 (C-2'), 10.78 (C-3'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 211.0432 (Calc. for $C_{10}H_{11}O_3S$: 211.0423).

6-Ethoxybenzo(d)(1,3)oxathiol-2-one (**3d**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and iodoethane. Yield: 366 mg (37%), mp: 80–85 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.62 (d, J = 8.7 Hz, 1H, H-4), 7.15 (d, J = 2.5 Hz, 1H, H-7), 6.93 (dd, J = 8.7, 2.5 Hz, 1H, H-5), 4.06 (q, J = 7.0 Hz, 2H, H-1'), 1.33 (t, J = 7.0 Hz, 3H, H-2'). ^{13}C NMR (151 MHz, DMSO) δ

170.35 (C-2), 159.11 (C-6), 148.99 (C-7a), 124.29 (C-4), 113.12 (C-3a, C-5), 99.37 (C-7), 64.37 (C-1'), 14.90 (C-2'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 197.0275 (Calc. for $C_9H_9O_3S$: 197.0267).

6-[(4-Nitrobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3e**): The title compound (red-brown powder) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-nitrobenzene. Yield: 180 mg (12%), mp: 135–140 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.27 (d, $J = 8.7$ Hz, 2H, H-4', H-6'), 7.73 (d, $J = 8.7$ Hz, 2H, H-3', H-7'), 7.67 (d, $J = 8.7$ Hz, 1H, H-4), 7.29 (d, $J = 2.5$ Hz, 1H, H-7), 7.06 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.34 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.24 (C-2), 158.42 (C-6), 148.93 (C-7a), 147.58 (C-5'), 144.81 (C-2'), 128.84 (C-3', C-7'), 124.47 (C-4), 124.11 (C-4', C-6'), 114.12 (C-3a), 113.45 (C-5), 99.99 (C-7), 69.13 (C-1'). Purity: 94%. HRMS-ESI *m/z* $[M]^+$ 303.0202 (Calc. for $C_{14}H_9NO_5S$: 303.0196).

6-[(4-Fluorobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3f**): The title compound (white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-fluorobenzene. Yield: 345 mg (25%), mp: 125–130 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.65 (d, $J = 8.7$ Hz, 1H, H-4), 7.60 (d, $J = 8.4$ Hz, 2H, H-4', H-6'), 7.42 (d, $J = 8.4$ Hz, 2H, H-3', H-7'), 7.26 (d, $J = 2.5$ Hz, 1H, H-7), 7.02 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.14 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.28 (C-2), 158.63 (C-6), 148.92 (C-7a), 136.40 (C-2'), 131.89 (C-3', C-7'), 130.41 (C-4', C-6'), 124.39 (C-4), 121.62 (C-5'), 113.80 (C-3a), 113.48 (C-5), 99.93 (C-7), 69.53 (C-1'). Purity: 98%. HRMS-ESI *m/z* $[MH]^+$ 277.0338 (Calc. for $C_{14}H_{10}FO_3S$: 277.0329).

6-[(3-Nitrobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3g**): The title compound (mustard-yellow crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-3-nitrobenzene. Yield: 158 mg (10%), mp: 228–230 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.28 (t, $J = 2.1$ Hz, 1H, H-3'), 8.18 (dd, $J = 8.2$, 1.6 Hz, 1H, H-5'), 7.89 (d, $J = 7.7$ Hz, 1H, H-7'), 7.69 (t, $J = 7.9$ Hz, 1H, H-6'), 7.07 (d, $J = 8.4$ Hz, 1H, H-4), 6.24 (d, $J = 2.7$ Hz, 1H, H-7), 6.08 (dd, $J = 8.5$, 2.7 Hz, 1H, H-5), 5.19 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 167.78 (C-2), 161.14 (C-6), 147.82 (C-7a), 140.05 (C-4'/C-2'), 136.03 (C-7'), 133.78 (C-4), 129.98 (C-6'), 122.49 (C-5'), 121.67 (C-3'), 113.16 (C-3a), 105.21 (C-5), 102.01 (C-7), 67.46 (C-1'). Purity: 98%. HRMS-ESI *m/z* $[MH]^+$ (Calc. for $C_{14}H_{10}NO_5S$: 304.0274).

6-[(3-Bromobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3h**): The title compound (cream-white granules) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-bromo-3-(bromomethyl)benzene. Yield: 88 mg (5%), mp: 103–106 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.68 (s, 1H, H-3'), 7.65 (d, $J = 8.7$ Hz, 1H, H-4), 7.55 (d, $J = 8.0$ Hz, 1H, H-5'), 7.47 (d, $J = 7.7$ Hz, 1H, H-7'), 7.37 (t, $J = 7.8$ Hz, 1H, H-6'), 7.28 (d, $J = 2.5$ Hz, 1H, H-7), 7.04 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.17 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.28 (C-2), 158.59 (C-6), 148.93 (C-7a), 139.75 (C-2'), 131.31 (C-4), 131.18 (C-3'), 130.80 (C-5'), 127.19 (C-6'), 124.41 (C-7'), 122.20 (C-4'), 113.88 (C-3a), 113.43 (C-5), 99.94 (C-7), 69.34 (C-1'). Purity: 88%. HRMS-ESI *m/z* $[MH]^+$ 336.9534 (Calc. for $C_{14}H_{10}BrO_3S$: 336.9529).

6-[(4-Isopropylbenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3i**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-isopropylbenzene. Yield: 336 mg (22%), mp: 127-130 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.64 (d, $J = 8.7$ Hz, 1H, H-4), 7.37 (d, $J = 8.1$ Hz, 2H, H-4', H-6'), 7.27 (d, $J = 8.2$ Hz, 2H, H-3', H-7'), 7.26 (d, $J = 2.6$ Hz, 1H, H-7), 7.02 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.10 (s, 2H, H-1'), 2.89 (hept, $J = 6.9$ Hz, 1H, H-8'), 1.20 (d, $J = 6.9$ Hz, 6H, H-9', H-10'). ^{13}C NMR (151 MHz, DMSO) δ 170.30 (C-2), 158.93 (C-6), 148.94 (C-7a), 148.77 (C-5'), 134.28 (C-2'), 128.51 (C-3', C-7'), 126.85 (C-4', C-6'), 124.34 (C-4), 113.50 (C-3a), 113.46 (C-5), 99.83 (C-7), 70.28 (C-1'), 33.66 (C-8'), 24.31 (C-9', C-10'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 301.0887 (Calc. for $C_{17}H_{17}O_3S$: 301.0893).

6-[(3-Methoxybenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3j**): The title compound (yellow granules) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-3-methoxybenzene. Yield: 388 mg (27%), mp: 68–70 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.64 (d, $J = 8.7$ Hz, 1H, H-4), 7.31 (t, $J = 8.1$ Hz, 1H, H-4'), 7.26 (d, $J = 2.5$ Hz, 1H, H-7), 7.02 (m, 3H, H-3', H-5', H-7'), 6.92 – 6.90 (m, 1H, H-5), 5.13 (s, 2H, H-1'), 3.76 (s, 3H, H-9'). ^{13}C NMR (151 MHz, DMSO) δ 170.30 (C-2), 159.83 (C-6'), 158.81 (C-6), 148.93 (C-7a), 138.49 (C-2'), 130.08 (C-4'), 124.34 (C-4), 120.32 (C-3'), 113.89 (C-7'), 113.77 (C-5'), 113.63 (C-3a), 113.48 (C-5), 99.90 (C-7), 70.21 (C-1'), 55.54 (C-9'). Purity: 71%. HRMS-ESI *m/z* $[MH]^+$ 289.0543 (Calc. for $C_{15}H_{13}O_4S$: 289.0529).

6-{[4-(Trifluoromethoxy)benzyl]oxy}benzo(d)(1,3)oxathiol-2-one (**3k**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-(trifluoromethoxy)benzene. Yield: 192 mg (11%), mp: 101–104 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.66 (d, $J = 8.7$ Hz, 1H, H-4), 7.60 (d, $J = 8.7$ Hz, 2H, H-4', H-6'), 7.40 (d, $J = 8.0$ Hz, 2H, H-3', H-7'), 7.28 (d, $J = 2.5$ Hz, 1H, H-7), 7.04 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.19 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.27 (C-2), 158.67 (C-6), 148.94 (C-5'), 148.45 (C-7a), 136.45 (C-4), 130.19 (C-2', C-3', C-7'), 124.40 (C-9'), 121.56 (C-4', C-6'), 113.83 (C-3a), 113.43 (C-5), 99.90 (C-7), 69.40 (C-1'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 343.0253 (Calc. for $C_{15}H_{10}F_3O_4S$: 343.0246).

6-{[4-(Trifluoromethyl)benzyl]oxy}benzo(d)(1,3)oxathiol-2-one (**3l**): The title compound (white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene. Yield: 321 mg (20%), mp: 110–111 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.78 (d, $J = 8.2$ Hz, 2H, H-4', H-6'), 7.69 (d, $J = 8.1$ Hz, 2H, H-3', H-7'), 7.66 (d, $J = 8.8$ Hz, 1H, H-4), 7.29 (d, $J = 2.5$ Hz, 1H, H-7), 7.05 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.28 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.25 (C-2), 158.55 (C-6), 148.94 (C-7a), 141.82 (C-2'), 128.61 (C-3', C-4', C-6', C-7'), 125.86 (C-5'), 125.84 (C-8'), 124.44 (C-4), 113.97 (C-3a), 113.45 (C-5), 99.95 (C-7), 69.42 (C-1'). Purity: 98%. HRMS-ESI *m/z* $[MH]^+$ 327.0286 (Calc. for $C_{15}H_{10}F_3O_3S$: 327.0297).

6-[(4-Iodobenzyl)oxy]benzo(d)(1,3)oxathiol-2-one (**3m**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-iodobenzene. Yield: 310 mg (16%), mp: 136–139 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.78 – 7.75 (m, 2H, H-4', H-6'), 7.64 (d, $J = 8.8$ Hz, 1H, H-4), 7.27 (d, $J = 8.3$ Hz, 2H, H-3', H-7'), 7.25 (d, $J = 2.5$ Hz, 1H, H-7), 7.01 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 5.12 (s, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.27 (C-2), 158.64 (C-6), 148.92 (C-7a), 137.74 (C-4', C-6'), 136.76 (C-2'), 130.45 (C-3', C-7'), 124.38 (C-4), 113.79 (C-3a), 113.49 (C-5), 99.93 (C-7), 94.60 (C-5'), 69.66 (C-1'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 384.9372 (Calc. for $C_{14}H_{10}IO_3S$: 384.9390).

6-[2-(Benzyloxy)ethoxy]benzo(d)(1,3)oxathiol-2-one (**3n**): The title compound (brown-white granules) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and [(2-bromoethoxy)methyl]benzene. Yield: 206 mg (14%), mp: 90–92 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.64 (d, $J = 8.8$ Hz, 1H, H-4), 7.38 – 7.33 (m, 4H, H-6', H-7', H-9', H-10'), 7.31 – 7.27 (m, 1H, H-8'), 7.20 (d, $J = 2.5$ Hz, 1H, H-7), 6.97 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 4.56 (s, 2H, H-4'), 4.19 (m, 2H, H-2'), 3.79 – 3.76 (m, 2H, H-1'). ^{13}C NMR (151 MHz, DMSO) δ 170.34 (C-2), 159.09 (C-6), 148.96 (C-7a), 138.71 (C-5'), 128.72 (C-7', C-9'), 128.01 (C-6', C-10'), 127.93 (C-8'), 124.33 (C-5), 113.40 (C-3a), 113.25 (C-4), 99.57 (C-7), 72.55 (C-4'), 68.49 (C-1'), 68.38 (C-2'). Purity: 94%. HRMS-ESI *m/z* $[MH]^+$ 303.0676 (Calc. for $C_{16}H_{15}O_4S$: 303.0686).

2-Oxobenzo(d)(1,3)oxathiol-6-yl benzoate (**4a**): The title compound (metallic light-brown crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and benzoyl chloride. Yield: 130 mg (10%), mp: 130–133 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.15 (dd, $J = 8.2$, 1.1 Hz, 2H, H-3', H-7'), 7.87 (d, $J = 8.6$ Hz, 1H, H-4), 7.78 (t, $J = 7.5$ Hz, 1H, H-5'), 7.65 – 7.61 (m, 3H, H-7, H-4', H-6'), 7.33 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5). ^{13}C NMR (151 MHz, DMSO) δ 169.82 (C-2), 164.89 (C-1'), 150.44 (C-6), 148.33 (C-7a), 134.73 (C-5'), 130.37 (C-3', C-7'), 129.49 (C-4', C-6'), 129.02 (C-2'), 124.45 (C-4), 120.43 (C-3a), 119.84 (C-5), 107.45 (C-7). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 273.0217 (Calc. for $C_{14}H_9O_4S$: 273.0216).

2-Oxobenzo(d)(1,3)oxathiol-6-yl furan-2-carboxylate (**4b**): The title compound (off-white powder) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and furan-2-carbonyl chloride. Yield: 887 mg (68%), mp: 160–163 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.13 (dd, $J = 1.6$, 0.7 Hz, 1H, H-4'), 7.86 (d, $J = 8.6$ Hz, 1H, H-4), 7.61 (m, 2H, H-7, H-6'), 7.30 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5), 6.83 (dd, $J = 3.6$, 1.7 Hz, 1H, H-5'). ^{13}C NMR (151 MHz, DMSO) δ 169.78 (C-2), 156.55 (C-1'), 149.62 (C-6), 149.36 (C-4'), 148.32 (C-7a), 143.12 (C-2'), 124.50 (C-4), 121.10 (C-5), 120.65 (C-3a), 119.75 (C-6'), 113.33 (C-7), 107.40 (C-5'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 263.0009 (Calc. for $C_{12}H_7O_5S$: 263.0009).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-methoxybenzoate (**4c**): The title compound (off-white powder) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-methoxybenzoyl chloride. Yield: 100 mg (7%), mp: 128–130 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.11 – 8.09 (m, 2H, H-3', H-7'), 7.85 (d, $J = 8.6$ Hz, 1H, H-4), 7.59 (d, $J = 2.2$ Hz, 1H, H-7), 7.29 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5), 7.15 – 7.13 (m, 2H, H-4', H-6'), 3.88 (s, 3H, H-9'). ^{13}C NMR (151 MHz, DMSO) δ 169.85 (C-2), 164.49 (C-5'), 164.39 (C-1'), 150.54 (C-6), 148.31 (C-7a), 132.62 (C-3', C-7'), 124.38 (C-4), 121.01 (C-2'), 120.20 (C-3a), 119.90 (C-5), 114.80 (C-4', C-6'), 107.49 (C-7), 56.15 (C-9'). Purity: 93%. HRMS-ESI *m/z* $[MH]^+$ 303.0333 (Calc. for $C_{15}H_{11}O_5S$: 303.0322).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 5-{[2-oxobenzo(d)(1,3)oxathiol-6-yl]oxy}pentanoate (**4d**): The title compound (white flakes) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 5-bromovaleryl chloride. Yield: 92 mg (4%), mp: 97-99 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.80 (d, $J = 8.6$ Hz, 1H, H-4"), 7.63 (d, $J = 8.7$ Hz, 1H, H-4), 7.41 (d, $J = 2.2$ Hz, 1H, H-7"), 7.19 (d, $J = 2.4$ Hz, 1H, H-7), 7.14 (dd, $J = 8.6$, 2.2 Hz, 1H, H-5"), 6.96 (dd, $J = 8.8$, 2.5 Hz, 1H, H-5), 4.07 (t, $J = 5.9$ Hz, 2H, H-5'), 2.70 (t, $J = 7.0$ Hz, 2H, H-2'), 1.85 – 1.80 (m, 4H, H-3', H-4'). ^{13}C NMR (151 MHz, DMSO) δ 171.98 (C-1'), 170.35 (C-2"), 169.80 (C-2), 159.17 (C-6"), 150.27 (C-7a"), 149.00 (C-6), 148.26 (C-7a), 124.37 (C-4"), 124.32 (C-4), 120.12 (C-3a"), 119.68 (C-5), 113.22 (C-3a), 113.21 (C-5"), 107.22 (C-7), 99.46 (C-7"), 68.33 (C-5'), 33.44 (C-2'), 28.18 (C-4'), 21.39 (C-3'). Purity: 89%. HRMS-ESI *m/z* $[MH]^+$ 419.0274 (Calc. for $C_{19}H_{15}O_7S_2$: 419.0254).

2-Oxobenzo(d)(1,3)oxathiol-6-yl acrylate (**4e**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 3-chloropropionyl chloride. Yield: 245 mg (22%), mp: 74-76 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.82 (d, $J = 8.6$ Hz, 1H, H-4), 7.51 (d, $J = 2.2$ Hz, 1H, H-7), 7.21 (dd, $J = 8.6$,

2.3 Hz, 1H, H-5), 6.57 (dd, $J = 17.3$, 1.2 Hz, 1H, H-3'), 6.43 (dd, $J = 17.3$, 10.4 Hz, 1H, H-2'), 6.20 (dd, $J = 10.4$, 1.2 Hz, 1H, H-3'). ^{13}C NMR (151 MHz, DMSO) δ 169.79 (C-2), 164.40 (C-1'), 150.02 (C-6), 148.29 (C-7a), 134.62 (C-4), 127.78 (C-3'), 124.43 (C-2'), 120.39 (C-3a), 119.63 (C-5), 107.24 (C-7). Purity: 100%. HRMS-ESI *m/z* $[MH]^+$ 223.0058 (Calc. for $C_{10}H_7O_4S$: 223.0060).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-methylpiperazine-1-carboxylate (**4f**): The title compound (brown-white flakes) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-methylpiperazine-1-carbonyl chloride. Yield: 454 mg (31%), mp: 146–150 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.76 (d, $J = 8.6$ Hz, 1H, H-4), 7.42 (d, $J = 2.3$ Hz, 1H, H-7), 7.14 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5), 3.58 (m, 2H, H-3'), 3.43 (m, 2H, H-7'), 2.37 (m, 4H, H-4', H-6'), 2.22 (s, 3H, H-8'). ^{13}C NMR (151 MHz, DMSO) δ 169.90 (C-2), 152.95 (C-1'), 151.07 (C-6), 148.16 (C-7a), 124.09 (C-4), 119.79 (C-5), 119.40 (C-3a), 107.29 (C-7), 54.64 (C-4'), 54.47 (C-6'), 46.16 (C-8'), 44.60 (C-3'), 44.08 (C-7'). Purity: 90%. HRMS-ESI *m/z* $[MH]^+$ 295.0745 (Calc. for $C_{13}H_{15}N_2O_4S$: 295.0747).

2-Oxobenzo(d)(1,3)oxathiol-6-yl piperidine-1-carboxylate (**4g**): The title compound (white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-piperidinecarbonyl chloride. Yield: 150 mg (11%), mp: 96–100 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.75 (d, $J = 8.6$ Hz, 1H, H-4), 7.40 (d, $J = 2.3$ Hz, 1H, H-7), 7.13 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5), 3.56 (m, 2H, H-7'), 3.41 (m, 2H, H-3'), 1.63 – 1.54 (m, 6H, H-4', H-5', H-6'). ^{13}C NMR (151 MHz, DMSO) δ 169.93 (C-2), 152.88 (C-1'), 151.23 (C-6), 148.16 (C-7a), 124.05 (C-4), 119.83 (C-5), 119.24 (C-3a), 107.31 (C-7), 45.58 (C-7'), 45.14 (C-3'), 25.88 (C-6'), 25.52 (C-4'), 24.10 (C-5'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 280.0634 (Calc. for $C_{13}H_{14}NO_4S$: 280.0638).

2-Oxobenzo(d)(1,3)oxathiol-6-yl (1,1'-biphenyl)-4-sulfonate (**5a**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and (1,1'-biphenyl)-4-sulfonyl chloride. Yield: 91 mg (5%), mp: 150-152 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.00 – 7.96 (m, 4H, H-3', H-4', H-6', H-7'), 7.80 (m, 1H, H-4), 7.78 (m, 2H, H-9', H-13'), 7.54 (m, 2H, H-10', H-12'), 7.49 (m, 1H, H-11'), 7.41 (d, $J = 2.3$ Hz, 1H, H-7), 7.05 (dd, $J = 8.7$, 2.3 Hz, 1H, H-5). ^{13}C NMR (151 MHz, DMSO) δ 169.47 (C-2), 148.35 (C-6), 148.26 (C-7a), 146.92 (C-8'), 138.22 (C-2'), 132.97 (C-4), 129.72 (C-10', C-12'), 129.58 (C-11'), 129.49 (C-9', C-13'), 128.40 (C-4', C-6'), 127.73 (C-3', C-7'), 124.94 (C-5'), 122.53 (C-3a), 119.72 (C-5), 107.53 (C-7). Purity: 96%. HRMS-ESI *m/z* $[MH]^+$ 385.0204 (Calc. for $C_{19}H_{13}O_5S_2$: 385.0199).

2-Oxobenzo(d)(1,3)oxathiol-6-yl cyclopropanesulfonate (**5b**): The title compound (cream-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and cyclopropanesulfonyl chloride. Yield: 870 mg (64%), mp: 105–106 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.89 (d, $J = 8.6$ Hz, 1H, H-4), 7.63 (d, $J = 2.3$ Hz, 1H, H-7), 7.37 (dd, $J = 8.6$, 2.4 Hz, 1H, H-5), 3.12 (m, 1H, H-2'), 1.21 (m, 2H, H-3'), 1.04 (m, 2H, H-4'). ^{13}C NMR (151 MHz, DMSO) δ 169.63 (C-2), 148.73 (C-6), 148.33 (C-7a), 124.90 (C-4), 122.21 (C-3a), 120.16 (C-5), 107.73 (C-7), 27.87 (C-2'), 6.57 (C-3', C-4'). Purity: 57/40%. HRMS-ESI *m/z* $[MH]^+$ 272.9886 (Calc. for $C_{10}H_9O_5S_2$: 272.9886).

2-Oxobenzo(d)(1,3)oxathiol-6-yl ethanesulfonate (**5c**): The title compound (cream-yellow crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and ethanesulfonyl chloride. Yield: 927 mg (71%), mp: 93–97 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.88 (d, $J = 8.7$ Hz, 1H, H-4), 7.61 (d, $J = 2.4$ Hz, 1H, H-7), 7.34 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5), 3.59 (q, $J = 7.3$ Hz, 2H, H-2'), 1.39 (t, $J = 7.3$ Hz, 3H, H-3'). ^{13}C NMR (151 MHz, DMSO) δ 169.61 (C-2), 148.41 (C-6), 148.39 (C-7a), 124.96 (C-4), 122.11 (C-3a), 119.97 (C-5), 107.52 (C-7), 45.22 (C-2'), 8.49 (C-3'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 260.9875 (Calc. for $C_9H_9O_5S_2$: 260.9886).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-propylbenzenesulfonate (**5d**): The title compound (metallic-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-propylbenzene-1-sulfonyl chloride. Yield: 996 mg (57%), mp: 79–84 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.81 – 7.79 (m, 2H, H-3', H-7'), 7.77 (d, $J = 8.7$ Hz, 1H, H-4), 7.51 (d, $J = 8.4$ Hz, 2H, H-4', H-6'), 7.31 (d, $J = 2.3$ Hz, 1H, H-7), 6.99 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5), 2.70 – 2.67 (m, 2H, H-8'), 1.65 – 1.59 (m, 2H, H-9'), 0.88 (t, $J = 7.3$ Hz, 3H, H-10'). ^{13}C NMR (151 MHz, DMSO) δ 169.45 (C-2), 150.90 (C-6), 148.38 (C-7a), 148.20 (C-5'), 131.62 (C-2'), 130.23 (C-4', C-6'), 128.88 (C-3', C-7'), 124.86 (C-4), 122.39 (C-3a), 119.71 (C-5), 107.45 (C-7), 37.40 (C-8'), 23.97 (C-9'), 13.85 (C-10'). Purity: 97%. HRMS-ESI *m/z* $[MH]^+$ 351.0341 (Calc. for $C_{16}H_{15}O_5S_2$: 351.0355).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-nitrobenzenesulfonate (**5e**): The title compound (mixed-brown powder) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-nitrobenzene-1-sulfonyl chloride. Yield: 261 mg (15%), mp: 196–200 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.46 (d, $J = 8.9$ Hz, 2H, H-4', H-6'), 8.18 (d, $J = 8.9$ Hz, 2H, H-3', H-7'), 7.81 (d, $J = 8.7$ Hz, 1H, H-4), 7.44 (d, $J = 2.4$ Hz, 1H, H-7), 7.05 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5). ^{13}C NMR (151 MHz, DMSO) δ 169.45 (C-2), 151.68 (C-6), 148.32 (C-7a), 148.02 (C-5'), 139.46 (C-2'), 130.63 (C-4', C-6'), 125.59 (C-3', C-7'), 125.12 (C-4), 123.02 (C-3a), 119.72 (C-5), 107.55 (C-7). Purity: 78%. HRMS-ESI *m/z* $[M]^+$ 352.9636 (Calc. for $C_{13}H_7NO_7S_2$: 352.9658).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-(trifluoromethyl)benzenesulfonate (**5f**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-(trifluoromethyl)benzene-1-sulfonyl

chloride. Yield: 322 mg (17%), mp: 121-124 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.14 (d, $J = 8.3$ Hz, 2H, H-4', H-6'), 8.08 (d, $J = 8.4$ Hz, 2H, H-3', H-7'), 7.80 (d, $J = 8.7$ Hz, 1H, H-4), 7.44 (d, $J = 2.4$ Hz, 1H, H-7), 7.05 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5). ^{13}C NMR (151 MHz, DMSO) δ 169.44 (C-2), 148.31 (C-6), 148.08 (C-7a), 138.25 (C-2'), 135.07 (C-4), 134.86 (C-5'), 129.95 (C-4', C-6'), 127.62/127.59 (C-3', C-7'), 125.05 (C-8'), 122.90 (C-3a), 119.69 (C-5), 107.55 (C-7). Purity: 90%. HRMS-ESI *m/z* $[M]^+$ 375.9657 (Calc. for $C_{14}H_7F_3O_5S_2$: 375.9682).

2-Oxobenzo(d)(1,3)oxathiol-6-yl thiophene-2-sulfonate (**5g**): The title compound (off-yellow crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and thiophene-2-sulfonyl chloride. Yield: 1056 mg (67%), mp: 80-85 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.25 (dd, $J = 5.0$, 1.4 Hz, 1H, H-5'), 7.85 (dd, $J = 3.9$, 1.4 Hz, 1H, H-3'), 7.81 (d, $J = 8.7$ Hz, 1H, H-4), 7.36 (d, $J = 2.3$ Hz, 1H, H-7), 7.31 (dd, $J = 4.9$, 3.9 Hz, 1H, H-4'), 7.03 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5). ^{13}C NMR (151 MHz, DMSO) δ 169.44 (C-2), 148.38 (C-6), 148.22 (C-7a), 138.18 (C-4), 137.47 (C-5'), 132.74 (C-2'), 129.13 (C-4'), 124.95 (C-3'), 122.76 (C-3a), 119.59 (C-5), 107.37 (C-7). Purity: 98%. HRMS-ESI *m/z* $[MH]^+$ 314.9426 (Calc. for $C_{11}H_7O_5S_3$: 314.9450).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-(tert-butyl)benzene-sulfonate (**5h**): The title compound (cream coloured crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-(tert-butyl)benzene-1-sulfonyl chloride. Yield: 1457 mg (80%), mp: 98–101 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.84 (d, $J = 8.6$ Hz, 2H, H-3', H-7'), 7.78 (d, $J = 8.7$ Hz, 1H, H-4), 7.71 (d, $J = 8.7$ Hz, 2H, H-4', H-6'), 7.33 (d, $J = 2.3$ Hz, 1H, H-7), 7.01 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5), 1.32 (s, 9H, H-9', H-10', H-11'). ^{13}C NMR (151 MHz, DMSO) δ 169.47 (C-2), 159.06 (C-5'), 148.36 (C-6), 148.23 (C-7a), 131.61 (C-2'), 128.70 (C-4', C-6'), 127.25 (C-3', C-7'), 124.88 (C-4), 122.38 (C-3a), 119.66 (C-5), 107.41 (C-7), 35.65 (C-8'), 31.09 (C-9', C-10', C-11'). Purity: 93%. HRMS-ESI *m/z* $[MH]^+$ 365.0508 (Calc. for $C_{17}H_{17}O_5S_2$: 365.0512).

2-Oxobenzo(d)(1,3)oxathiol-6-yl 4-methylbenzenesulfonate (**5i**): The title compound (white granules) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-methylbenzene-1-sulfonyl chloride. Yield: 607 mg (38%), mp: 123–124 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.77 (dd, $J = 8.5$, 4.1 Hz, 3H, H-3', H-7', H-4), 7.49 (d, $J = 8.1$ Hz, 2H, H-4', H-6'), 7.33 (d, $J = 2.3$ Hz, 1H, H-7), 6.98 (dd, $J = 8.7$, 2.3 Hz, 1H, H-5), 2.44 (s, 3H, H-8'). ^{13}C NMR (151 MHz, DMSO) δ 169.46 (C-2), 148.40 (C-6), 148.21 (C-7a), 146.61 (C-5'), 131.41 (C-2'), 130.82 (C-4', C-6'), 128.82 (C-3', C-7'), 124.87 (C-4), 122.39 (C-3a), 119.69 (C-5), 107.44 (C-7), 21.66 (C-8'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 323.0030 (Calc. for $C_{14}H_{11}O_5S_2$: 323.0042).

2-Oxobenzo(d)(1,3)oxathiol-6-yl methanesulfonate (**5j**): The title compound (yellow crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and methanesulfonyl chloride. Yield: 501 mg (41%), mp: 119–121 °C. ^{1}H NMR (600 MHz, DMSO) δ 7.89 (d, $J = 8.6$ Hz, 1H, H-4), 7.64 (d, $J = 2.3$ Hz, 1H, H-7), 7.36 (dd, $J = 8.6$, 2.4 Hz, 1H, H-5), 3.45 (s, 3H, H-2'). ^{13}C NMR (151 MHz, DMSO) δ 169.60 (C-2), 148.57 (C-6), 148.39 (C-7a), 124.96 (C-4), 122.24 (C-3a), 120.09 (C-5), 107.64 (C-7), 37.94 (C-2'). Purity: 94%. HRMS-ESI *m/z* $[M]^+$ 245.9647 (Calc. for $C_8H_6O_5S_2$: 245.9651).

4-[({4-[(4-Cyanobenzyl)oxy]-2-hydroxyphenyl}thio) methyl]benzonitrile (**6a**): The title compound (off-white granules) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 4-(bromomethyl)benzonitrile. Yield: 69 mg (5%), mp: 125–128 °C. ^{1}H NMR (600 MHz, DMSO) δ 10.04 (d, $J = 71.8$ Hz, 1H, H-1), 7.86 (d, $J = 8.3$ Hz, 2H, H-4', H-6'), 7.69 (d, $J = 8.3$ Hz, 2H, H-3', H-7'), 7.60 (d, $J = 8.3$ Hz, 2H, H-4", H-6"), 7.36 (d, $J = 8.2$ Hz, 2H, H-3", H-7"), 6.99 (d, $J = 8.5$ Hz, 1H, H-4), 6.51 (d, $J = 2.6$ Hz, 1H, H-7), 6.37 (dd, $J = 8.6$, 2.6 Hz, 1H, H-5), 5.13 (s, 2H, H-1'), 4.05 (s, 2H, H-1"). ^{13}C NMR (151 MHz, DMSO) δ 159.45 (C-6), 158.74 (C-2), 145.08 (C-2"), 143.25 (C-2'), 134.89 (C-4), 132.86 (C-4', C-6'), 132.52 (C-4", C-6"), 130.16 (C-3", C-7"), 128.46 (C-3', C-7'), 119.31 (C-8',), 119.21 (C-8"), 111.58 (C-3), 110.92 (C-5), 109.82 (C-5'), 106.38 (C-5"), 102.89 (C-7), 68.67 (C-1'), 37.18 (C-1"). Purity: 97%. HRMS-ESI *m/z* $[M]^+$ 372.0935 (Calc. for $C_{22}H_{16}N_2O_2S$: 372.0927).

5-[(4-Bromobenzyl)oxy]-2-[(4-bromobenzyl)thio]phenol (**6b**): The title compound (off-white powder) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-bromo-4-(bromomethyl)benzene. Yield: 670 mg (37%), mp: 130–134 °C. ^{1}H NMR (600 MHz, DMSO) δ 9.88 (s, 1H, H-1), 7.59 (d, $J = 8.4$ Hz, 2H, H-4', H-6'), 7.43 (d, $J = 8.4$ Hz, 2H, H-3', H-7'), 7.38 (d, $J = 8.4$ Hz, 2H, H-4", H-6"), 7.15 (d, $J = 8.4$ Hz, 2H, H-3", H-7"), 7.01 (d, $J = 8.5$ Hz, 1H, H-4), 6.50 (d, $J = 2.6$ Hz, 1H, H-7), 6.37 (dd, $J = 8.5$, 2.6 Hz, 1H, H-5), 5.01 (s, 2H, H-1'), 3.96 (s, 2H, H-1"). ^{13}C NMR (151 MHz, DMSO) δ 159.48 (C-6), 158.56 (C-2), 138.45 (C-2"), 136.93 (C-2'), 134.60 (C-4), 131.80 (C-4', C-6'), 131.49 (C-4", C-6"), 131.38 (C-3", C-7"), 130.19 (C-3', C-7'), 121.37 (C-5'), 120.21 (C-5"), 111.92 (C-3), 106.41 (C-5), 102.87 (C-7), 68.80 (C-1'), 36.85 (C-1"). Purity: 99%. HRMS-ESI *m/z* $[M]^+$ 477.9234 (Calc. for $C_{20}H_{16}Br_2O_2S$: 477.9232).

5-[(4-Fluorobenzyl)oxy]-2-[(4-fluorobenzyl)thio]phenol (**6c**): The title compound (light yellow crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 1-(bromomethyl)-4-fluorobenzene. Yield: 496 mg (37%), mp: 110–112 °C. ^{1}H NMR (600 MHz, DMSO) δ 9.84 (s, 1H, H-1), 7.47 (m, 2H, H-4', H-6'), 7.25 – 7.19 (m, 4H, H-3', H-7', H-4", H-6"), 7.06 (t, $J = 8.9$ Hz, 2H, H-3", H-7"), 7.03 (d, $J = 8.5$ Hz, 1H, H-4), 6.51 (d, $J = 2.6$ Hz, 1H, H-7), 6.39 (dd, $J = 8.5$, 2.6 Hz, 1H, H-5), 5.00 (s, 2H, H-1'), 3.98

(s, 2H, H-1"). ^{13}C NMR (151 MHz, DMSO) δ 163.03 / 162.32 (C-5'), 161.41 / 160.71 (C-5"), 159.56 (C-6), 158.49 (C-2), 135.06 / 135.04 (C-2"), 134.55 (C-4), 133.66 / 133.64 (C-2'), 131.09 / 131.04 (C-3', C-7'), 130.39 / 130.34 (C-3", C-7"), 115.75 / 115.61 (C-4', C-6'), 115.44 / 115.30 (C-4", C-6"), 112.08 (C-3), 106.42 (C-5), 102.81 (C-7), 68.91 (C-1'), 36.82 (C-1"). Purity: 99%. HRMS-ESI *m/z* $[M]^+$ 358.0844 (Calc. for $C_{20}H_{16}F_2O_2S$: 358.0834).

[2,4-Bis(naphthalen-2-ylmethoxy)phenyl](naphthalen-2-ylmethyl)sulfane (**7**): The title compound (off-white crystals) was afforded from 6-hydroxy-1,3-benzoxathiol-2-one (5 mmol) and 2-(bromomethyl)naphthalene. Yield: 259 mg (18%), mp: 107–109 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.03 (s, 1H, H-7'), 7.96 – 7.88 (m, 7H, H-4", H-8', H-8", H-8"', H-11', H-11", H-11"'), 7.85 – 7.81 (m, 1H, H-4"'), 7.76 (d, $J = 8.4$ Hz, 1H, H-4'), 7.69 – 7.65 (m, 1H, H-7"), 7.66 – 7.61 (m, 2H, H-7"', H-10'), 7.56 – 7.52 (m, 5H, H-10", H-10"', H-9', H-9", H-9"'), 7.47 – 7.43 (m, 2H, H-3', H-3"), 7.41 (dd, $J = 8.4$, 1.7 Hz, 1H, H-3"'), 7.22 (d, $J = 8.5$ Hz, 1H, H-4), 6.93 (d, $J = 2.5$ Hz, 1H, H-7), 6.59 (dd, $J = 8.5$, 2.5 Hz, 1H, H-5), 5.37 (s, 2H, H-1'), 5.25 (s, 2H, H-1"), 4.22 (s, 2H, H-1"'). ^{13}C NMR (151 MHz, DMSO) δ 159.59 (C-6), 158.56 (C-2), 136.06 (C-7), 135.00 (C-2'), 134.95 (C-2"), 133.43 – 133.02 (C-5', C-5", C-5"', C-6', C-6", C-6"'), 132.42 (C-2"'), 128.61 – 126.12 (C-3', C-3", C-3"', C-4', C-4", C-4"', C-7', C-7", C-7"', C-8', C-8", C-8"', C-9', C-9", C-9"', C-10', C-10", C-10"', C-11', C-11", C-11"'), 115.10 (C-4), 107.21 (C-3), 101.89 (C-5), 70.50 (C-1'), 70.05 (C-1"), 37.67 (C-1"'). Purity: 99%. HRMS-ESI *m/z* $[MH]^+$ 563.2012 (Calc. for $C_{39}H_{31}O_2S$: 563.2039).

The measurement of MAO activity

Recombinant human MAO-A and MAO-B were obtained from Sigma-Aldrich and IC_{50} values were measured according to the reported protocol [23, 24]. All incubations and measurements were carried out in white 96-well microtiter plates. Kynuramine served as substrate for both MAO isoforms and is oxidised to yield 4-hydroxyquinoline. 4-Hydroxyquinoline fluoresces at a basic pH which allows measurement by fluorescence spectrophotometry. The MAO enzymes and substrate were incubated for 20 min in the presence of a range of inhibitor concentrations (0.003–100 µM). At the endpoint, NaOH (2 N) was added to terminate the reactions and the concentration of 4-hydroxyquinoline was quantified. The enzyme activities were determined from the concentration data, and sigmoidal plots of activity versus inhibitor concentration (log [I]) were constructed. The IC_{50} values were calculated from these plots and are given as the mean ± SD of triplicate measurements.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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