Bioorganic & Medicinal Chemistry 18 (2010) 8178–8187

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Highly active antimycobacterial derivatives of benzoxazine

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ARTICLE INFO

Article history:
Received 27 June 2010
Revised 28 September 2010
Accepted 6 October 2010
Available online 19 October 2010

Keywords:
Benzoxazine
Thioxo group
Antimycobacterial activity
Tuberculosis

ABSTRACT

New 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones were synthesized. The compounds were tested for in vitro antimycobacterial activity against *Mycobacterium tuberculosis*, *Mycobacterium avium* and two strains of *Mycobacterium kansasii*. The antimycobacterial activity increased with the replacement of the carbonyl group by the thiocarbonyl group in the starting 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones. The most active derivatives were more active than isonicotinhydrazide (INH). Free-Wilson analysis was also carried out and the activity contribution was examined.

1. Introduction

Tuberculosis is an infectious bacterial disease that can be transmitted from person to person because of the droplets from the throat and lungs of people suffering from the active respiratory disease. Tuberculosis was always a serious problem in developing countries and the multidrug resistant strains of *Mycobacterium tuberculosis* are transferred by the migration of a population to Europe and North America. More than two billion people (one third of the world's population) are, according to WHO, infected with TB bacilli, the microbes that cause tuberculosis.[1] WHO also estimated that 9.37 million incident cases of TB and 11.09 million prevalent cases of TB occurred in the year 2008. There were 1.32 million deaths from TB in the same year.[2] Hence, there is a great need to develop new drugs and found new strategies to control this outbreak of tuberculosis.[3]

Many antituberculosis agents containing a thioxo group were important in the history of antituberculosis drugs. For example, *p*-acetamidobenzaldehyde thiosemicarbazone (Thiacetazone), 4,4′-bis(isopentoxy)thiocarbanilide (Isoxyl), or 2-ethylpyridine-4-carbotioamide (Ethionamide) are known to inhibit the mycolic acids biosynthesis.[4–6]

This study is oriented on the derivatives of benzoxazinediones in which one or both oxo groups were replaced by the thioxo group. Since the compounds are cyclic derivatives of salicylanilides it can be supposed that they can serve as bacterial two-component system inhibitors.[7,8] This type of mechanism of action is very promising while such a type of the antibacterial effect is probably different from the effect of other antibacterial drugs.[6,9,10]

2. Chemistry

The starting 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones were prepared by the reaction of *N*-(4-alkylphenyl)salicylamides with methyl chloroformate in dry pyridine and purified by crystallization from ethanol. Several methods have been reported for the preparation of these heterocycles.[11–14] 3-(4-Alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones were synthesized by the treatment of 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones with phosphorus pentasulfide. The published methods include thionation using P_2S_5 and Lawesson's reagent.[15,16] The structural assignment is based on ^{1}H NMR, ^{13}C NMR, and IR spectra. The purity of the compounds was confirmed by means of elemental analysis. An overview of the synthesis is in Scheme 1. The structures of the prepared compounds are summarized in Tables 1–3.

3. Antimycobacterial activity

The in vitro antimycobacterial activity of the compounds was investigated against *M. tuberculosis* CNCTC My 331/88 (identical with H37RV and ATCC 27294), *Mycobacterium kansasii* CNCTC My 235/80 (identical with ATCC 12478, resistant to INH), *Mycobacterium avium* CNCTC My 330/88 (identical with ATCC 25291, resistant to INH), and *M. kansasii* 6509/96. All the strains were

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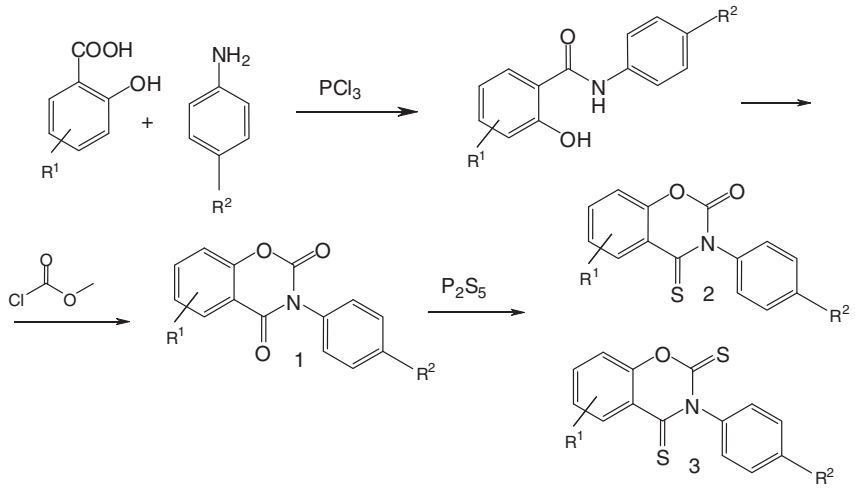
doi:10.1016/j.bmc.2010.10.017



Scheme 1. Synthesis of 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (**1**), 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones (**2**), and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (**3**).

Table 1
In vitro antimycobacterial activity of 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones.

	Compound		MIC (μmol/L) Incubation time 14 d/21 d			
	R^1	R^2	*M. tuberculosis* My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
1a	6-Br	Methyl	16/16[a]	31/31[a]	–62/62[a]	–[d]
1b	6-Br	Ethyl	8/8	32/32	8/16	16/16
1c	6-Cl	Ethyl	8/16[c]	16/32[c]	16/16[c]	16/16[c]
1d	7-Cl	Ethyl	8/8	8/16	16/16	16/16
1e	6-Br	Isopropyl	2/4	8/16	8/8	4/8
1f	6-Cl	Isopropyl	4/8[c]	32/32[c]	8/16[c]	8/16[c]
1g	7-Cl	Isopropyl	4/4	8/16	8/16	8/8
1h	6-F	Isopropyl	8/8	8/16	8/8	8/16
1i	7-CH_3	Isopropyl	n/n	n/n	n/n	32/n
1j	6-Br	*sec*-Butyl	4/8	16/32	8/8	8/16
1k	6-Cl	*sec*-Butyl	4/8[c]	32/32[c]	16/16[c]	16/16[c]
1l	7-Cl	*sec*-Butyl	4/4	8/8	8/8	8/8
1m	6-F	*sec*-Butyl	8/8	8/8	8/8	4/8
1n	7-CH_3	*sec*-Butyl	n/n	n/n	n/n	32/n
1o	6-Cl	Butyl	16/16[b]	16/16[b]	8/8[b]	8/16[b]
1p	6-Cl	*tert*-Butyl	8/16[b]	16/32[b]	8/16[b]	8/8[b]
1q	7-Cl	*tert*-Butyl	4/4[b]	4/8[b]	8/16[b]	8/8[b]
1r	6-F	*tert*-Butyl	16/16	16/16	16/16	8/16
1s	7-CH_3	*tert*-Butyl	n/n	n/n	n/n	n/n
INH			0.5/0.5	>250/>250	>250/>250	8/8

[a] Waisser, Hladůvková (19).
[b] Waisser, Matyk (17).
[c] Kubicová (18).
[d] Not tested, n: the MIC value could not be determined due to the limited solubility of the compound in the test medium.

obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague. The only exception is *M. kansasii* 6509/96 that was clinically isolated and, that is, in contrast to the standard strain not resistant to isoniazid (INH). The dilution micromethod was used for the determination of minimum inhibitory concentrations (MIC) and the MIC values for the standard INH were included for the sake of comparison. The overview of the biological activity together with the activity of INH is shown in Tables 1–3. The MIC values of compounds **1a**, **1c**, **1f**, **1k**, **1o**, 1p, and **1q** were taken from our previous papers[17–19] to complete the evaluation and to compare with the biological activity.

The antimycobacterial activity of the starting 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones is in the range of 4–16 μmol/L. The replacement of one oxo group with a thioxo group strongly increases the antimycobacterial activity. The additional replacement has a small effect on the activity. Figure 1 shows such an increase in the activity in the case of *M. tuberculosis*. The MIC values of the sulfur compounds are generally within the range of 0.25–125 μmol/L but the majority of MICs is in the range of 0.25–8 μmol/L. All the sulfur derivatives are more active than INH.

4. Free-Wilson analysis

The Free-Wilson method[20] with the Fujita–Ban modification[21] was used to investigate the activity contribution in the case of sulfur derivatives (Tables 4 and 5). All the calculations were carried out using the MULTIREG program for Microsoft Excel. Since the MIC values after 14 d and 21 d incubation correlated with each other, only the MICs after 14 d evaluation were taken for the calculations. The MICs of sulfur derivatives of 6-bromo-3-(4-propylphenyl)-1, 3-benzoxazine-2,4(3*H*)-dione, 6-bromo-3-(4-butylphenyl)-1,

Table 2
In vitro antimycobacterial activity of 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones

	Compound		MIC (μmol/L) Incubation time 14 d/21 d			
	R^1	R^2	*M. tuberculosis* My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
2a	6-Br	Methyl	0.5/1	32/32	2/4	2/4
2b	6-Br	Ethyl	0.5/0.5	32/32	8/16	4/8
2c	6-Cl	Ethyl	0.5/0.5	16/16	8/8	4/4
2d	7-Cl	Ethyl	0.5/0.5	8/8	8/8	8/8
2e	6-Br	Isopropyl	0.25/0.5	4/8	32/62.5	4/8
2f	6-Cl	Isopropyl	0.5/1	32/125	8/16	1/2
2g	7-Cl	Isopropyl	0.5/1	8/8	8/8	4/8
2h	6-F	Isopropyl	0.25/0.5	0.5/1	2/4	4/4
2i	7-CH_3	Isopropyl	0.25/0.5	0.5/1	2/4	1/2
2j	6-Br	*sec*-Butyl	0.25/0.5	16/32	4/8	2/4
2k	6-Cl	*sec*-Butyl	0.5/1	32/32	8/8	4/8
2l	7-Cl	*sec*-Butyl	1/2	8/8	4/8	1/2
2m	6-F	*sec*-Butyl	0.25/0.5	1/1	4/4	2/4
2n	7-CH_3	*sec*-Butyl	0.25/0.5	0.5/0.5	1/2	0.5/1
2o	6-Cl	Butyl	1/2	8/16	8/16	4/4
2p	6-Cl	*tert*-Butyl	0.25/0.5	1/2	8/8	4/8
2q	7-Cl	*tert*-Butyl	2/2	4/8	4/8	2/4
2r	6-F	*tert*-Butyl	0.25/0.5	0.5/1	4/8	8/8
2s	7-CH_3	*tert*-Butyl	0.25/0.5	0.25/0.5	2/2	1/1
INH			1/1	>250/>250	>250/>250	8/8

Table 3
In vitro antimycobacterial activity of 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones

	Compound		MIC (μmol/L) Incubation time 14 d/21 d			
	R^1	R^2	*M. tuberculosis* My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
3a	6-Br	Methyl	0.5/1	15/30	4/4	4/4
3b	6-Br	Ethyl	1/2	62.5/62.5	8/16	4/8
3c	6-Cl	Ethyl	0.5/0.5	8/16	8/8	4/6
3d	7-Cl	Ethyl	0.5/0.5	4/8	8/16	8/16
3e	6-Br	Isopropyl	0.5/1	8/16	32/62.5	4/8
3f	6-Cl	Isopropyl	0.5/1	32/125	8/16	1/2
3g	7-Cl	Isopropyl	0.5/1	8/8	4/8	4/4
3h	6-F	Isopropyl	0.25/0.5	0.5/1	4/8	2/4
3i	7-CH_3	Isopropyl	0.5/1	0.5/0.5	2/4	1/2
3j	6-Br	*sec*-Butyl	1/2	32/32	4/8	2/4
3k	6-Cl	*sec*-Butyl	1/2	16/32	8/16	4/8
3l	7-Cl	*sec*-Butyl	1/1	4/8	4/8	1/2
3m	6-F	*sec*-Butyl	0.25/0.25	0.5/1	2/4	2/4
3n	7-CH_3	*sec*-Butyl	0.25/0.5	0.25/0.5	2/2	0.5/1
3o	6-Cl	Butyl	2/4	8/16	8/8	8/8
3p	6-Cl	*tert*-Butyl	0.25/0.5	1/2	8/8	8/8
3q	7-Cl	*tert*-Butyl	0.5/0.5	2/4	2/4	2/4
3r	6-F	*tert*-Butyl	0.5/0.5	0.5/1	8/8	4/8
3s	7-CH_3	*tert*-Butyl	0.25/0.5	0.5/1	2/2	1/2
INH			1/1	>250/>250	>250/>250	8/8

3-benzoxazine-2,4(3*H*)-dione, and 7-chloro-3-(4-butylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione were taken from the literature[22] and used for the calculation. Chlorine as the R^1 substituent at the position 7 on the benzoxazine ring and propyl as the R^2 substituent were used as the standards. The results show that the biological activity increases with the fluorine or methyl moiety as the R^1 substituents. The increase in activity is also connected with the branched R^2 substituents.

5. Conclusion

The replacement of the carbonyl group by the thiocarbonyl group in 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones increases the antimycobacterial activity. The derivatives of 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones (**2a–2s**) and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (**3a**–**3s**) possess a better biological activity than INH, the standard used for the sake of comparison. An advantage is the presumption that these compounds can be of different mechanisms of action from the antituberculosis drugs already in use. (4-*sec*-Butylphenyl)-7-methyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (**2n**) seems to be the most prospective compound as it shows the best activity against all mycobacterial strains under tests. This compound has been selected for future investigation.

6. Experimental protocols

6.1. Chemistry, general information

The melting points were determined on a Kofler apparatus. The samples for the analyzes and antimycobacterial tests were dried over P_2O_5 at 61 °C and 66 Pa for 24 h. Elemental analyzes (C, H,

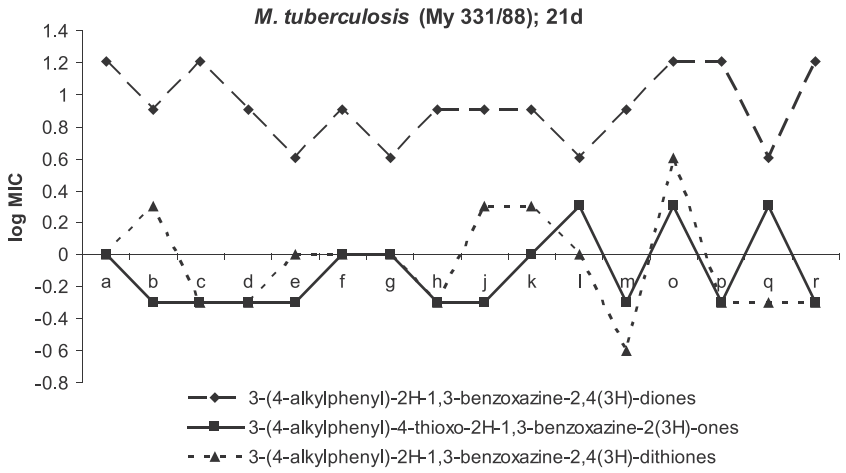


Figure 1. Increase in the biological activity after the replacement of the oxo group with the thioxo group.

Table 4
Activity contribution of the free-Wilson analyzes of 3-(4-alkylphenyl)-4-thioxo-*2H*-1,3-benzoxazine-2(*3H*)-ones and statistical significances of correlation

	Parameter	Δlog MIC (μmol/L) 14 d			
		M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
R^1	7-Cl	0	0	0	0
	6-Cl	−0.482 (±0.197)	0.180 (±0.208)	0.060 (±0.144)	−0.060 (±0.161)
	6-Br	−0.295 (±0.212)	0.176 (±0.224)	0.202 (±0.155)	0.133 (±0.173)
	6-F	−0.563 (±0.237)	−0.949 (±0.251)	−0.292 (±0.173)	0.218 (±0.194)
	7-CH_3	−0.563 (±0.237)	−1.150 (±0.251)	−0.594 (±0.173)	−0.485 (±0.194)
R^2	Methyl	−0.301 (±0.440)	−0.028 (±0.466)	−0.602 (±0.322)	−0.602 (±0.359)
	Ethyl	−0.337 (±0.380)	−0.244 (±0.403)	0.115 (±0.278)	−0.092 (±0.311)
	i-Propyl	−0.396 (±0.371)	−0.499 (±0.393)	0.206 (±0.272)	−0.370 (±0.304)
	sec-Butyl	−0.335 (±0.371)	−0.318 (±0.393)	−0.034 (±0.272)	−0.551 (±0.304)
	tert-Butyl	−0.269 (±0.394)	−0.925 (±0.417)	0.108 (±0.288)	−0.237 (±0.322)
	Propyl	0	0	0	0
	Butyl	0.767 (±0.380)	−0.444 (±0.403)	0.315 (±0.278)	0.109 (±0.311)
	μ_0	0.295 (±0.376)	1.329 (±0.398)	0.701 (±0.275)	0.770 (±0.308)
	r	0.90	0.94	0.89	0.88
	s	0.311	0.329	0.227	0.254
	F	4.94	8.92	4.06	3.58
	n	22	22	22	22

Table 5
Activity contribution of the Free-Wilson analyzes of 3-(4-alkylphenyl)-*2H*-1,3-benzoxazine-2,4(*3H*)-dithiones and statistical significances of correlation

	Parameter	Δlog MIC (μmol/L) 14 d			
		M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
R^1	7-Cl	0	0	0	0
	6-Cl	−0.180 (±0.168)	0.301 (±0.200)	0.241 (±0.135)	0.120 (±0.150)
	6-Br	−0.234 (±0.181)	0.830 (±0.216)	0.299 (±0.146)	0.200 (±0.162)
	6-F	−0.280 (±0.202)	−0.888 (±0.241)	0.047 (±0.163)	0.096 (±0.181)
	7-CH_3	−0.280 (±0.202)	−0.988 (±0.241)	−0.254 (±0.163)	−0.406 (±0.181)
R^2	Methyl	−0.301 (±0.375)	−0.329 (±0.447)	−0.301 (±0.303)	−0.301 (±0.336)
	Ethyl	−0.016 (±0.324)	0.048 (±0.387)	0.119 (±0.262)	−0.108 (±0.291)
	i-Propyl	−0.026 (±0.317)	0.136 (±0.378)	−0.009 (±0.256)	−0.464 (±0.284)
	sec-Butyl	0.095 (±0.317)	−0.045 (±0.378)	−0.129 (±0.256)	−0.525 (±0.284)
	tert-Butyl	−0.323 (±0.336)	−0.357 (±0.401)	−0.011 (±0.271)	−0.204 (±0.302)
	Propyl	0	0	0	0
	Butyl	1.120 (±0.324)	−0.149 (±0.387)	0.320 (±0.262)	0.194 (±0.291)
	μ_0	−0.234 (±0.321)	0.676 (±0.383)	0.604 (±0.259)	0.703 (±0.288)
	r	0.93	0.95	0.86	0.90
	s	0.265	0.316	0.214	0.238
	F	6.57	10.85	3.12	4.56
	n	22	22	22	22

N) were performed on a CHNS-O CE elemental analyzer (Fisions EA 1110, Milan) and were within ±0.4% of the theoretical values. The IR spectra were measured in KBr pellets on a Nicolet Impact 400 apparatus; the wavenumbers are given in cm^{-1}. TLC was performed on silica gel plates precoated with the fluorescent indicator Silufol UV 254 + 366 (Kavalier Votice, Czech Republic), hexane/acetone (3:1) was used as the mobile phase. Crystallization of products was carried out from ethanol. The ^1H NMR and ^{13}C NMR spectra of new compounds were recorded in DMSO-d_6 solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Chemical shifts were recorded as δ values in parts per million (ppm) and were indirectly referenced to tetramethylsilane via the solvent signal (2.49 for ^1H or 39.7 for ^{13}C).

6.2. Chemistry, synthetic procedures to preparation of 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (1b, 1d, 1e, 1g, 1h–1j, 1l–1n, 1r, 1s)

Methyl chloroformate (5.2 g, 48 mmol) was added dropwise to a stirred solution of the corresponding salicylanilide (40 mmol) in dry pyridine (20 mL) under ice cooling. The mixture was heated on a steam bath for 1 h and then poured into 5% hydrochloric acid (140 mL). After 24 h the product was filtered off, suspended in 5% natrium carbonate solution and the solid was filtered off. The crude product was purified by crystallization from ethanol.

6.2.1. 6-Bromo-3-(4-ethylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1b)

White solid, yield 59%, mp 219–222 °C, IR (ν CO) 1772, 1703 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.07–7.97 (2H, m, H5, H7), 7.49 (1H, d, J = 8.5 Hz, H8), 7.37–7.27 (4H, m, H2′, H3′, H5′, H6′), 2.67 (2H, q, J = 7.6 Hz, CH_2), 1.22 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 159.9, 151.9, 147.5, 144.7, 138.9, 132.8, 129.5, 128.6, 128.4, 119.2, 117.1, 117.0, 28.1, 15.7. Anal. Calcd for $C_{16}H_{12}BrNO_3$ (346.18): C, 55.51; H, 3.49; N, 4.05. Found: C, 55.67; H, 3.55; N, 3.80.

6.2.2. 7-Chloro-3-(4-ethylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1d)

White solid, yield 58%, mp 185–189 °C, IR (ν CO) 1776, 1708 cm $^{-1}$; ^1H NMR (300 MHz, DMSO) δ 7.98 (1H, d, J = 8.4 Hz, H5), 7.75 (1H, d, J = 1.8 Hz, H8), 7.51 (1H, dd, J = 8.4 Hz, J = 1.8 Hz, H6), 7.37–7.27 (4H, m, H2′, H3′, H5′, H6′), 2.67 (2H, q, J = 7.6 Hz, CH_2), 1.22 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.3, 153.3, 147.6, 144.6, 140.5, 132.8, 129.2, 128.6, 128.5, 125.8, 116.8, 114.2, 28.1, 15.7. Anal. Calcd for $C_{16}H_{12}ClNO_3$ (301.73): C, 63.69; H, 4.01; N, 4.46. Found: C, 63.59; H, 3.95; N, 4.36.

6.2.3. 6-Bromo-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1e)

White solid, yield 72%, mp 174–177 °C, IR (ν CO) 1763, 1703 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.08–7.97 (2H, m, H5, H7), 7.49 (1H, d, J = 8.5 Hz, H8), 7.41–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.34–7.26 (2H, m, AA′, BB′, H3′, H5′), 3.05–2.85 (1H, CH), 1.24 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 159.9, 151.9, 149.2, 147.5, 138.9, 132.8, 129.5, 128.4, 127.1, 119.2, 117.1, 117.0, 33.4, 24.0. Anal. Calcd for $C_{17}H_{14}BrNO_3$ (360.2): C, 56.69; H, 3.92; N, 3.89. Found: C, 56.47; H, 3.97; N, 3.80.

6.2.4. 7-Chloro-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1g)

White solid, yield 61%, mp 180–183 °C, IR (ν CO) 1770, 1704 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.98 (1H, d, J = 8.5 Hz, H5), 7.74 (1H, d, J = 1.8 Hz, H8), 7.51 (1H, dd, J = 8.5 Hz, J = 1.8 Hz, H6), 7.41–7.27 (4H, m, H2′, H3′, H5′, H6′), 3.04–2.88 (1H, m, CH), 1.25 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.3, 153.3, 149.2, 147.6, 140.5, 132.8, 129.3, 128.5, 127.1, 125.8, 116.8, 114.2, 33.4, 24.0. Anal. Calcd for $C_{17}H_{14}ClNO_3$ (315.76): C, 64.67; H, 4.47; N, 4.44. Found: C, 64.62; H, 4.43; N, 4.20.

6.2.5. 6-Fluoro-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1h)

White solid, yield 60%, mp 193–194 °C, IR (ν CO) 1770, 1700 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.79–7.69 (2H, m, H5, H7), 7.62–7.54 (1H, m, H8), 7.41–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.34–7.28 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.87 (1H, m, CH), 1.25 (6H, d, J = 6.9 Hz, CH_3). Anal. Calcd for $C_{17}H_{14}FNO_3$ (299.3): C, 68.22; H, 4.71; N, 4.68. Found: C, 68.03; H, 4.71; N, 4.55.

6.2.6. 3-(4-Isopropylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dione (1i)

White solid, yield 67%, mp 212–213 °C, IR (ν CO) 1764, 1689 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.86 (1H, d, J = 8.0 Hz, H5), 7.41–7.24 (6H, m, H6, H8, H2′, H3′, H5′, H6′), 3.05–2.87 (1H, m, CH), 2.46 (3H, s, CH_3), 1.25 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.8, 152.7, 149.0, 148.0, 147.8, 133.0, 128.6, 127.4, 127.0, 126.5, 116.4, 112.4, 33.4, 24.0, 21.5. Anal. Calcd for $C_{18}H_{17}NO_3$ (295.34): C, 73.20; H, 5.80; N, 4.74. Found: C, 72.81; H, 5.80; N, 4.57.

6.2.7. 6-Bromo-3-(4-*sec*-butylphenyl)-1,3-benzoxazine-2,4(3*H*)-dione (1j)

White solid, yield 64%, mp 208–209 °C, IR (ν CO) 1770, 1703 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.07–7.98 (2H, m, H5, H7), 7.49 (1H, d, J = 8.5 Hz, H8), 7.37–7.26 (4H, m, H2′, H3′, H5′, H6′), 2.75–2.59 (1H, m, CH), 1.66–1.52 (2H, m, CH_2), 1.22 (3H, d, J = 7.1 Hz, CH_3), 0.81 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 159.9, 151.9, 148.0, 147.5, 138.9, 132.8, 129.4, 128.4, 127.7, 119.2, 117.1, 117.0, 40.8, 30.7, 21.8, 12.3. Anal. Calcd for $C_{18}H_{16}BrNO_3$ (374.24): C, 57.77; H, 4.31; N, 3.74. Found: C, 57.54; H, 4.27; N, 3.50.

6.2.8. 3-(4-*sec*-Butylphenyl)-7-chloro-1,3-benzoxazine-2,4(3*H*)-dione (1l)

White solid, yield 70%, mp 136–137 °C, IR (ν CO) 1776, 1696 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.98 (1H, d, J = 8.2 Hz, H5), 7.75 (1H, d, J = 1.9 Hz, H8), 7.52 (1H, dd, J = 8.2 Hz, J = 1.9 Hz, H6), 7.37–7.24 (4H, m, H2′, H3′, H5′, H6′), 2.74–2.59 (1H, m, CH), 1.66–1.51 (2H, m, CH_2), 1.22 (3H, d, J = 7.1 Hz, CH_3), 0.81 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.3, 153.3, 148.0, 147.6, 140.5, 132.8, 129.2, 128.4, 127.7, 125.8, 116.8, 114.2, 40.8, 30.7, 21.8, 12.3. Anal. Calcd for $C_{18}H_{16}ClNO_3$ (329.79): C, 65.56; H, 4.89; N, 4.25. Found: C, 65.27; H, 4.90; N, 4.07.

6.2.9. 3-(4-*sec*-Butylphenyl)-6-fluoro-1,3-benzoxazine-2,4(3*H*)-dione (1m)

White solid, yield 63%, mp 114–116 °C, IR (ν CO) 1767, 1734 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.82–7.68 (2H, m, H5, H7), 7.64–7.54 (1H, m, H8), 7.37–7.27 (4H, m, H2′, H3′, H5′, H6′), 2.74–2.58 (1H, m, CH), 1.67–1.50 (2H, m, CH_2), 1.22 (3H, d, J = 7.2 Hz, CH_3), 0.81 (3H, d, J = 7.2 Hz, CH_3). Anal. Calcd for $C_{18}H_{16}FNO_3$ (313.3): C, 69.00; H, 5.15; N, 4.47. Found: C, 68.93; H, 5.25; N, 4.37.

6.2.10. 3-(4-*sec*-Butylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dione (1n)

White solid, yield 71%, mp 137–140 °C, IR (ν CO) 1761, 1694 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.86 (1H, d, J = 8.0 Hz, H5), 7.36–7.24 (6H, m, H6, H8, H2′, H3′, H5′, H6′), 2.74–2.58 (1H, m, CH), 2.46 (3H, s, CH_3), 1.66–1.49 (2H, m, CH_2), 1.22 (3H, d, J = 7.1 Hz, CH_3), 1.81 (3H, d, J = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.8, 152.8, 148.0, 147.8, 133.1, 128.6, 127.4, 127.2, 126.5, 116.5, 112.4, 40.8, 30.8, 22.0, 12.3. Anal. Calcd for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.96; H, 6.28; N, 4.45.

6.2.11. 3-(4-*tert*-Butylphenyl)-6-fluoro-1,3-benzoxazine-2,4(3*H*)-dione (1r)

White solid, yield 58%, mp 145–147 °C, IR (ν CO) 1770, 1733 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.80–7.68 (1H, m, H5), 7.64–7.53 (1H, m, H7), 7.55–7.48 (2H, m, AA′, BB′, H2′, H6′), 7.42–7.35 (1H, m, H8), 7.35–7.28 (2H, m, AA′, BB′, H3′, H5′), 1.32 (9H, s, CH_3). Anal. Calcd for $C_{18}H_{16}FNO_3$ (313.3): C, 69.00; H, 5.15; N, 4.47. Found: C, 68.90; H, 5.21; N, 4.39.

6.2.12. 3-(4-*tert*-Butylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dione (1s)

White solid, yield 70%, mp 170–172 °C, IR (ν CO) 1753, 1707 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.86 (1H, d, *J* = 8.0 Hz, H5), 7.55–7.47 (2H, m, H2′, H6′), 7.35–7.24 (4H, m, H6, H8, H3′, H5′), 2.46 (3H, s, CH_3), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 160.9, 152.8, 151.2, 148.1, 147.8, 132.8, 128.3, 127.5, 126.5, 126.0, 116.5, 112.4, 34.7, 31.3, 21.6. Anal. Calcd for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.49; H, 6.17; N, 4.36.

6.3. Chemistry, synthetic procedures for the preparation of 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones (2a–2s) and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (3a–3s)

3-(4-Alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (3.8 mmol) were melted with P_4S_{10} (7.6 mmol) for 20 min (175–200 °C). After cooling to the room temperature, a 10% potassium carbonate solution (60 mL) was poured into the reaction mixture; the crude product was filtered off, and dissolved in toluene (p.a., 40 mL). Column chromatography on silica gel yielded 3-(4-alkylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones. The products were crystallized from ethanol.

6.3.1. 6-Bromo-3-(4-methylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2a)

Yellow solid, yield 36%, mp 259–261 °C, IR (ν CO) 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1H, *J* = 2.45 Hz, H5), 7.80 (dd, 1H, *J* = 8.52 Hz, *J* = 2.45 Hz, H7), 7.40–7.34 (m, AA′, BB′, 2H, H2′, H6′), 7.20 (d, 1H, *J* = 8.52 Hz, H8), 7.16–7.11 (m, AA′, BB′, 2H, H3′, H5′), 2.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 148.2, 144.6, 139.5, 138.4, 136.2, 134.3, 130.6, 127.3, 122.0, 118.8, 118.4, 21.5. Anal. Calcd for $C_{15}H_{10}BrNO_2S$ (348.2): C, 51.74; H, 2.89; N, 4.02; S, 9.21. Found: C, 51.22; H, 2.62; N, 3.98; S, 9.11.

6.3.2. 6-Bromo-3-(4-ethylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2b)

Yellow solid, yield 42%, mp 227–229 °C, IR (ν CO) 1759 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.35 (1H, d, *J* = 2.3 Hz, H5), 8.02 (1H, dd, *J* = 8.8 Hz, *J* = 2.3 Hz, H7), 7.47 (1H, d, *J* = 8.8 Hz, H8), 7.38–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.23 (2H, m, AA′, BB′, H3′, H5′), 2.66 (2H, q, *J* = 7.6 Hz, CH_2), 1.22 (3H, t, *J* = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.4, 149.1, 144.5, 138.6, 137.6, 133.0, 128.9, 128.0, 122.5, 119.4, 117.4, 28.1, 15.6. Anal. Calcd for $C_{16}H_{12}BrNO_2S$ (361.0): C, 52.05; H, 3.34; N, 3.87; S, 8.85. Found: C, 52.80; H, 3.33; N, 3.56; 8.73.

6.3.3. 6-Chloro-3-(4-ethylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2c)

Yellow solid, yield 33%, mp 199–202 °C, IR (ν CO) 1761 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.22 (1H, d, *J* = 2.6 Hz, H5), 7.91 (1H, dd, *J* = 8.8 Hz, *J* = 2.6 Hz, H7), 7.55 (1H, d, *J* = 8.8 Hz, H8), 7.38–7.31 (2H, m, AA′, BB′, H2′, H6′), 7.31–7.24 (2H, m, AA′, BB′, H3′, H5′), 2.67 (2H, q, *J* = 7.6 Hz, CH_2), 1.22 (3H, t, *J* = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.5, 148.7, 144.6, 144.5, 137.7, 135.8, 130.0, 129.7, 128.9, 128.0, 122.2, 119.2, 28.1, 15.6. Anal. Calcd for $C_{16}H_{12}ClNO_2S$ (317.0): C, 60.47; H, 3.81; N, 4.41; S, 10.99. Found: C, 60.39; H, 3.84; N, 4.31; S, 11.28.

6.3.4. 7-Chloro-3-(4-ethylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2d)

Yellow solid, yield 39%, mp 188–190 °C, IR (ν CO) 1761 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.28 (1H, d, *J* = 8.8 Hz, H5), 7.74 (1H, d, *J* = 2.2 Hz, H8), 7.50 (1H, dd, *J* = 8.8 Hz, *J* = 2.2 Hz, H6), 7.38–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.29–7.23 (2H, m, AA′, BB′, H3′, H5′), 2.67 (2H, q, *J* = 7.6 Hz, CH_2), 1.53 (3H, t, *J* = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.9, 150.2, 144.5, 144.5, 140.7, 137.6, 133.0, 128.9, 128.1, 126.2, 120.1, 116.8, 28.1, 15.6. Anal. Calcd for $C_{16}H_{12}ClNO_2S$ (317.0): C, 60.47; H, 3.81; N, 4.41; S, 10.99. Found: C, 60.33; H, 3.79; N, 4.22; S, 10.22.

6.3.5. 6-Bromo-3-(4-isopropylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2e)

Yellow solid, yield 26%, mp 199–201 °C, IR (ν CO) 1759 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.35 (1H, d, *J* = 2.5 Hz, H5), 8.01 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz, H7), 7.47 (1H, d, *J* = 8.8 Hz, H8), 7.42–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.32–7.24 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.87 (1H, m, CH), 1.24 (6H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.3, 149.1, 149.0, 144.5, 138.6, 137.7, 133.0, 128.0, 127.4, 122.5, 119.4, 117.4, 33.4, 24.0. Anal. Calcd for $C_{17}H_{14}BrNO_2S$ (376.27): C, 54.27; H, 3.75; N, 3.72; S, 8.52. Found: C, 54.04; H, 3.62; N, 3.62; S, 8.51.

6.3.6. 6-Chloro-3-(4-isopropyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2f)

Yellow solid, yield 14%, mp 163–165 °C, IR (ν CO) 1751 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.22 (1H, d, *J* = 2.6 Hz, H5), 7.91 (1H, dd, *J* = 8.8 Hz, *J* = 2.6 Hz, H7), 7.54 (1H, d, *J* = 8.8 Hz, H8), 7.41–7.35 (2H, m, AA′, BB′, H2′, H6′), 7.31–7.25 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.86 (1H, CH), 1.24 (6H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.4, 149.0, 148.7, 144.6, 137.7, 135.8, 130.1, 129.7, 128.0, 127.4, 122.2, 119.2, 33.4, 24.0. Anal. Calcd for $C_{17}H_{14}ClNO_2S$ (331.8): C, 61.53; H, 4.25; N, 4.22; S, 9.66. Found: C, 61.18; H, 4.27; N, 3.77; S, 10.05.

6.3.7. 7-Chloro-3-(4-isopropylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2g)

Yellow solid, yield 31%, mp 198–199 °C, IR (ν CO) 1761 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.28 (1H, d, *J* = 8.8 Hz, H5), 7.73 (1H, d, *J* = 2.1 Hz, H8), 7.50 (1H, dd, *J* = 8.8 Hz, *J* = 2.1 Hz, H6), 7.46–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.24 (2H, m, AA′, BB′, H3′, H5′), 3.03–2.87 (1H, m, CH), 1.24 (6H, t, *J* = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 192.3, 150.7, 149.5, 145.0, 141.2, 138.1, 133.5, 128.6, 127.9, 126.6, 120.6, 117.3, 33.9, 24.5. Anal. Calcd for $C_{17}H_{14}ClNO_2S$ (331.8): C, 61.54; H, 4.25; N, 4.22; S, 9.66. Found: C, 61.55; H, 4.07; N, 3.99; S, 9.91.

6.3.8. 6-Fluoro-3-(4-isopropylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2h)

Yellow solid, yield 58%, mp 197–200 °C, IR (ν CO) 1749 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.97 (1H, dd, *J* = 9.1 Hz, *J* = 2.9 Hz, H5), 7.76 (1H, dt, *J* = 9.1 Hz, *J* = 2.9 Hz, H7), 7.57 (1H, dd, *J* = 9.1 Hz, *J* = 4.7 Hz, H8), 7.41–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.32–7.25 (2H, m, AA′, BB′, H3′, H5′), 3.06–2.87 (1H, m, CH), 1.24 (6H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 191.7 (d, *J* = 2.9 Hz), 158.8 (d, *J* = 242.5 Hz), 149.0, 146.3 (d, *J* = 1.7 Hz), 144.7, 137.8, 128.0, 127.4, 123.8 (d, *J* = 25.4 Hz), 122.0 (d, *J* = −9.2 Hz), 119.3 (d, *J* = 8.0 Hz), 116.2 (d, *J* = 26.5 Hz), 33.4, 24.0. Anal. Calcd for $C_{17}H_{14}FNO_2S$ (315.4): C, 64.75; H, 4.47; N, 4.44; S, 10.17. Found: C, 64.74; H, 4.66; N, 4.27; S, 9.78.

6.3.9. 3-(4-Isopropylphenyl)-7-methyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2i)

Yellow solid, yield 20%, mp 203–207 °C, IR (*ν* CO) 1746 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.17 (1H, d, *J* = 8.0 Hz, H5), 7.41–7.22 (6H, m, H6, H8, H2′, H3′, H5′, H6′), 3.03–2.87 (1H, m, CH), 2.44 (3H, s, CH_3), 1.24 (6H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 192.6, 149.8, 148.8, 148.1, 145.0, 137.8, 131.4, 128.2, 127.3, 127.0, 118.9, 116.4, 33.4, 24.0, 21.5. Anal. Calcd for $C_{18}H_{17}NO_2S$ (311.4): C, 69.43; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.06; H, 5.41; N, 4.54; S, 10.50.

6.3.10. 6-Bromo-3-(4-*sec*-butylphenyl)-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2j)

Yellow solid, yield 24%, mp 189–190 °C, IR (*ν* CO) 1756 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.35 (1H, d, *J* = 2.5 Hz, H5), 8.02 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz, H7), 7.47 (1H, d, *J* = 8.8 Hz, H8), 7.37–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.24 (2H, m, AA′, BB′, H3′, H5′), 2.73–2.59 (1H, m, CH), 1.65–1.51 (2H, m, CH_2), 1.23 (3H, d, *J* = 7.2 Hz, CH_2), 0.80 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.4, 149.1, 147.9, 144.5, 138.6, 137.7, 133.0, 128.0, 122.5, 119.4, 117.4, 40.8, 30.7, 21.7, 12.3. Anal. Calcd for $C_{18}H_{16}BrNO_2S$ (390.30): C, 55.39; H, 4.13; N, 3.59; S, 8.22. Found: C, 55.08; H, 4.15; N, 3.44; S, 8.43.

6.3.11. 3-(4-*sec*-Butylphenyl)-6-chloro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2k)

Yellow solid, yield 32%, mp 154–155 °C, IR (*ν* CO) 1759 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.22 (1H, d, *J* = 2.5 Hz, H5), 7.91 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz, H7), 7.54 (1H, d, *J* = 8.8 Hz, H8), 7.37–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.25 (2H, m, AA′, BB′, H3′, H5′), 2.74–2.59 (1H, m, CH), 1.66–1.51 (2H, m, CH_2), 1.23 (3H, d, *J* = 7.2 Hz, CH_2), 0.80 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.5, 148.7, 147.9, 144.6, 137.7, 135.8, 130.0, 129.7, 128.0, 122.2, 119.2, 40.8, 30.8, 21.7, 12.3. Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.85): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.29; H, 4.64; N, 3.92; S, 9.47.

6.3.12. 3-(4-*sec*-Butylphenyl)-7-chloro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2l)

Yellow solid, yield 18%, mp 114–116 °C, IR (*ν* CO) 1751 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.28 (1H, d, *J* = 8.8 Hz, H5), 7.74 (1H, d, *J* = 2.3 Hz, H8), 7.51 (1H, dd, *J* = 8.8 Hz, *J* = 2.3 Hz, H6), 7.36–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.24 (2H, m, AA′, BB′, H3′, H5′), 2.74–2.58 (1H, m, CH), 1.69–1.49 (2H, m, CH_2), 1.23 (3H, d, *J* = 6.9 Hz, CH_3), 0.80 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.8, 150.2, 147.8, 144.5, 140.7, 137.7, 133.0, 128.0, 127.9, 126.1, 120.1, 116.8, 40.8, 30.7, 21.7, 12.3. Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.8): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.12; H, 4.92; N, 3.82; S, 9.25.

6.3.13. 3-(4-*sec*-Butylphenyl)-6-fluoro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2m)

Yellow solid, yield 42%, mp 141–142 °C, IR (*ν* CO) 1753 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 7.97 (1H, dd, *J* = 9.4 Hz, *J* = 2.9 Hz, H5), 7.80–7.72 (1H, m, H7), 7.57 (1H, dd, *J* = 9.4 Hz, *J* = 4.7 Hz, H8), 7.37–7.31 (2H, m, AA′, BB′, H2′, H6′), 7.31–7.25 (2H, m, AA′, BB′, H3′, H5′), 2.75–2.58 (1H, m, CH), 1.68–1.50 (2H, m, CH_2), 1.23 (3H, d, *J* = 6.8 Hz, CH_3), 0.80 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.7 (d, *J* = 3.5 Hz), 158.8 (d, *J* = 242.5 Hz), 147.8, 146.3, 146.3, 144.7, 137.8, 128.0, 123.7 (d, *J* = 25.3 Hz), 122.0 (d, *J* = 8.6 Hz), 119.3 (d, *J* = 8.0 Hz), 116.2 (d, *J* = 26.5 Hz), 40.7, 30.7, 21.6, 12.3. Anal. Calcd for $C_{18}H_{16}FNO_2S$ (329.4): C, 65.63; H, 4.90; N, 4.25; S, 9.73. Found: C, 65.42; H, 4.91; N, 4.07; S, 9.43.

6.3.14. 3-(4-*sec*-Butylphenyl)-7-methyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2n)

Yellow solid, yield 9%, mp 179–182 °C, IR (*ν* CO) 1749 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.18 (1H, d, *J* = 8.2 Hz, H5), 7.35–7.22 (6H, m, H6, H8, H2′, H3′, H5′, H6′), 2.72–2.59 (1H, m, CH), 2.44 (3H, s, CH_3), 1.66–1.49 (2H, m, CH_2), 1.23 (3H, d, *J* = 7.2 Hz, CH_3), 0.81 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 192.6, 149.8, 148.1, 147.6, 145.0, 137.8, 131.4, 128.2, 127.8, 127.0, 118.9, 116.4, 40.7, 30.7, 21.7, 21.4, 12.3. Anal. Calcd for $C_{19}H_{19}NO_2S$ (325.43): C, 70.13; H, 5.88; N, 4.30; S, 9.85. Found: C, 69.79; H, 5.96; N, 4.22; S, 9.50.

6.3.15. 3-(4-Butylphenyl)-6-chloro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2o)

Yellow solid, yield 29%, mp 149–152 °C, IR (*ν* CO) 1771 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.22 (1H, d, *J* = 2.6 Hz, H5), 7.91 (1H, dd, *J* = 8.8 Hz, *J* = 2.6 Hz, H7), 7.55 (1H, d, *J* = 8.8 Hz, H8), 7.36–7.29 (2H, m, AA′, BB′, H2′, H6′), 7.29–7.22 (2H, m, AA′, BB′, H3′, H5′), 2.63 (2H, t, *J* = 7.5 Hz, CH_2), 1.67–1.52 (2H, m, CH_2), 1.42–1.26 (2H, m, CH_2), 0.92 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.5, 148.7, 144.5, 143.2, 137.6, 135.8, 13.0, 129.7, 129.4, 127.9, 122.2, 119.2, 34.7, 33.2, 22.0, 14.0. Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.8): C, 62.51; H, 4.66; N, 4.05. Found: C, 62.38; H, 4.73; N, 3.91.

6.3.16. 3-(4-*tert*-Butylphenyl)-6-chloro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2p)

Yellow solid, yield 25%, mp 226–229 °C, IR (*ν* CO) 1753 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.22 (1H, d, *J* = 2.9 Hz, H5), 7.91 (1H, dd, *J* = 8.8 Hz, *J* = 2.9 Hz, H7), 7.58–7.48 (3H, m, H8, H2′, H6′), 7.33–7.24 (2H, m, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.4, 151.2, 148.7, 144.5, 137.4, 135.8, 130.0, 129.7, 127.7, 126.4, 122.1, 119.2, 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.8): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.81; H, 4.74; N, 3.82; S, 9.43.

6.3.17. 3-(4-*tert*-Butylphenyl)-7-chloro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2q)

Yellow solid, yield 33%, mp 147–148 °C, IR (*ν* CO) 1745 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.28 (1H, d, *J* = 8.5 Hz, H5), 7.73 (1H, d, *J* = 1.9 Hz, H8), 7.56–7.47 (3H, m, H6, H2′, H6′), 7.31–7.25 (2H, m, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.8, 151.2, 150.2, 144.5, 140.7, 137.4, 133.0, 128.4, 127.8, 126.3, 120.1, 116.8, 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.8): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.30; H, 4.63; N, 4.10; S, 9.61.

6.3.18. 3-(4-*tert*-Butylphenyl)-6-fluoro-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2r)

Yellow solid, yield 29%, mp 161–163 °C, IR (*ν* CO) 1754 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 7.98 (1H, dd, *J* = 9.4 Hz, *J* = 3.5 Hz, H5), 7.81–7.71 (1H, m, H7), 7.57 (1H, dd overlapped, *J* = 9.4 Hz, *J* = 4.7 Hz, H8), 7.56–7.49 (2H, m, AA′, BB′, H2′, H6′), 7.33–7.25 (2H, m, AA′, BB′, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 191.7 (d, *J* = 2.9 Hz), 158.8 (d, *J* = 242.5 Hz), 151.2, 146.3, 144.7, 137.5, 127.7, 126.4, 123.7 (d, *J* = 24.8 Hz), 120.0 (d, *J* = 8.7 Hz), 119.3 (d, *J* = 8.1 Hz), 116.2 (d, *J* = 26.5 Hz), 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}FNO_2S$ (329.4): C, 65.63; H, 4.90; N, 4.25; S, 9.73. Found: C, 65.49; H, 4.96; N, 4.15; S, 9.39.

6.3.19. 3-(4-*tert*-Butylphenyl)-7-methyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (2s)

Yellow solid, yield 31%, mp 156–159 °C, IR (*ν* CO) 1746 cm^{-1}; ^1H NMR (300 MHz, DMSO) *δ* 8.18 (1H, d, *J* = 8.0 Hz, H5), 7.55–7.47 (2H, m, H2′, H6′), 7.32–7.23 (4H, m, H6, H8, H3′, H5′), 2.44 (3H, s, CH_3), 1.33 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) *δ* 192.5, 151.0, 149.7, 148.1, 145.0, 137.5, 131.4, 127.9, 127.0, 126.2, 118.9, 116.4, 34.6,

31.3, 21.4. Anal. Calcd for $C_{19}H_{19}NO_2S$ (325.43): C, 70.13; H, 5.88; N, 4.30; S, 9.85. Found: C, 70.18; H, 5.98; N, 4.20; S, 9.50.

6.3.20. 6-Bromo-3-(4-methylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3a)

Red solid, yield 31%, mp 246–248 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 2.40 Hz, H5), 7.81 (dd, 1H, J = 8.77 Hz, J = 2.40 Hz, H7), 7.39–7.34 (m, AA′, BB′, 2H, H2′, H6′), 7.25 (d, 1H, J = 8.77 Hz, H8), 7.12–7.06 (m, AA′, BB′, 2H, H3′, H5′), 2.46 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 177.0, 148.5, 140.5, 139.2, 138.6, 134.2, 130.7, 127.2, 123.3, 119.5, 118.0, 21.6. Anal. Calcd for $C_{15}H_{10}BrNOS_2$ (364.3): C, 49.46; H, 2.77; N, 3.85; S, 17.60. Found: C, 49.23; H, 2.96; N, 3.62; S, 17.32.

6.3.21. 6-Bromo-3-(4-ethylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3b)

Red solid, yield 17%, mp 195 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.26 (1H, d, J = 2.3 Hz, H5), 8.05 (1H, dd, J = 8.8 Hz, J = 2.3 Hz, H7), 7.55 (1H, d, J = 8.8 Hz, H8), 7.37–7.29 (2H, m, AA′, BB′, H2′, H6′), 7.25–7.17 (2H, m, AA′, BB′, H3′, H5′), 2.66 (2H, q, J = 7.6 Hz, CH_2), 1.22 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.8, 177.8, 149.1, 144.3, 141.5, 138.9, 133.1, 129.2, 127.8, 123.9, 119.0, 118.5, 28.0, 15.5. Anal. Calcd for $C_{16}H_{12}BrNOS_2$ (378.3): C, 50.80; H, 3.20; N, 3.70; S, 16.95. Found: C, 50.64; H, 3.25; N, 3.44; S, 16.78.

6.3.22. 6-Chloro-3-(4-ethylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3c)

Red solid, yield 21%, mp 173–174 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.12 (1H, d, J = 2.3 Hz, H5), 7.93 (1H, dd, J = 8.8 Hz, J = 2.3 Hz, H7), 7.63 (1H, d, J = 8.8 Hz, H8), 7.38–7.29 (2H, m, AA′, BB′, H2′, H6′), 7.25–7.17 (2H, m, AA′, BB′, H3′, H5′), 2.66 (2H, q, J = 7.6 Hz, CH_2), 1.22 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.9, 177.8, 148.7, 144.3, 141.5, 136.2, 130.7, 130.0, 129.1, 127.8, 123.6, 118.9, 28.0, 15.4. Anal. Calcd for $C_{16}H_{12}ClNOS_2$ (333.9): C, 57.56; H, 3.62; N, 4.20; S, 19.21. Found: C, 57.45; H, 3.53; N, 4.04; S, 18.82.

6.3.23. 7-Chloro-3-(4-ethylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3d)

Red solid, yield 50%, mp 205–208 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.20 (1H, d, J = 8.8 Hz, H5), 7.84 (1H, d, J = 1.8 Hz, H8), 7.53 (1H, dd, J = 8.8 Hz, J = 1.8 Hz, H6), 7.37–7.28 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.17 (2H, m, AA′, BB′, H3′, H5′), 2.66 (2H, q, J = 7.6 Hz, CH_2), 1.22 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.4, 177.9, 150.2, 144.3, 141.5, 141.2, 133.1, 129.1, 127.9, 127.1, 121.5, 116.5, 28.0, 15.4. Anal. Calcd for $C_{16}H_{12}ClNOS_2$ (333.9): C, 57.56; H, 3.62; N, 4.20; 19.21. Found: C, 57.27; H, 3.53; N, 3.99; S, 19.03.

6.3.24. 6-Bromo-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3e)

Red solid, yield 32%, mp 181–182 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.26 (1H, d, J = 2.5 Hz, H5), 8.04 (1H, dd, J = 8.8 Hz, J = 2.5 Hz, H7), 7.55 (1H, d, J = 8.8 Hz, H8), 7.41–7.33 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.18 (2H, m, AA′, BB′, H3′, H5′), 3.03–2.86 (1H, m, CH), 1.24 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.8, 177.8, 149.1, 148.9, 141.5, 138.9, 133.0, 127.8, 127.7, 123.9, 119.0, 118.5, 33.3, 24.0. Anal. Calcd for $C_{17}H_{14}BrNOS_2$ (392.34): C, 52.04; H, 3.60; N, 3.57; S, 16.35. Found: C, 51.78; H, 3.48; N, 3.47; S, 16.20.

6.3.25. 6-Chloro-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3f)

Red solid, yield 28%, mp 163–166 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.13 (1H, d, J = 2.6 Hz, H5), 7.94 (1H, dd, J = 8.8 Hz, J = 2.6 Hz, H7), 7.63 (1H, d, J = 8.8 Hz, H8), 7.41–7.34 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.19 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.85 (1H, CH), 1.24 (6H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.0, 177.8, 148.9, 148.7, 141.6, 136.1, 130.7, 130.0, 127.8, 127.7, 123.6, 118.9, 33.3, 24.0. Anal. Calcd for $C_{17}H_{14}ClNOS_2$ (347.89): C, 58.69; H, 4.06; N, 4.03; S, 18.43. Found: C, 58.27; H, 3.90; N, 4.07; S, 18.75.

6.3.26. 7-Chloro-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3g)

Red solid, yield 24%, mp 200–202 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.19 (1H, d, J = 8.2 Hz, H5), 7.83 (1H, d, J = 2.3 Hz, H8), 7.53 (1H, dd, J = 8.2 Hz, J = 2.3 Hz, H6), 7.41–7.33 (2H, m, AA′, BB′, H2′, H6′), 7.25–7.19 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.86 (1H, m, CH), 1.24 (6H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.4, 177.9, 150.1, 148.8, 141.5, 141.2, 133.1, 127.9, 127.7, 127.1, 121.5, 116.5, 33.3, 24.0. Anal. Calcd for $C_{17}H_{14}ClNOS_2$ (347.89): C, 57.69; H, 4.06; N, 4.03; S, 18.43. Found: C, 57.45; H, 3.89; N, 3.86; S, 18.56.

6.3.27. 6-Fluoro-3-(4-isopropylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3h)

Red solid, yield 17%, mp 141–143 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.90 (1H, dd, J = 9.4 Hz, J = 2.9 Hz, H5), 7.84–7.76 (1H, m, H7), 7.67 (1H, dd, J = 9.4 Hz, J = 4.1 Hz, H8), 7.41–7.33 (2H, m, AA′, BB′, H2′, H6′), 7.27–7.20 (2H, m, AA′, BB′, H3′, H5′), 3.04–2.85 (1H, m, CH), 1.24 (6H, d, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.2 (d, J = 3.5 Hz), 177.9, 159.4 (d, J = 244.1 Hz), 148.8, 146.5 (d, J = 1.7 Hz), 141.6, 127.8, 127.7, 124.1 (d, J = 25.3 Hz), 123.6 (d, J = −9.2 Hz), 119.2 (d, J = 8.7 Hz), 116.2 (d, J = 27.0 Hz), 33.3, 24.0. Anal. Calcd for $C_{17}H_{14}FNO_2S$ (331.4): C, 61.61; H, 4.26; N, 4.23; S, 19.35. Found: C, 61.74; H, 4.37; N, 3.96; S, 19.43.

6.3.28. 3-(4-Isopropylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dithione (3i)

Red solid, yield 29%, mp 195–197 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.10 (1H, d, J = 8.2 Hz, H5), 7.40–7.26 (4H, m, H6, H8, H2′, H6′), 7.25–7.18 (2H, m, H3′, H5′), 3.01–2.86 (1H, m, CH), 2.44 (3H, s, CH_3), 1.24 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 188.0, 178.4, 149.8, 148.7, 148.6, 141.6, 131.4, 128.1, 128.0, 127.6, 120.4, 116.0, 33.3, 24.0, 21.5. Anal. Calcd for $C_{18}H_{17}NOS_2$ (327.47): C, 66.02; H, 5.23; N, 4.28; S, 19.58. Found: C, 66.00; H, 5.34; N, 4.18; S, 19.19.

6.3.29. 6-Bromo-3-(4-*sec*-butylphenyl)-1,3-benzoxazine-2,4(3*H*)-dithione (3j)

Red solid, yield 38%, mp 161–162 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.26 (1H, d, J = 2.5 Hz, H5), 8.04 (1H, dd, J = 8.8 Hz, J = 2.5 Hz, H7), 7.55 (1H, d, J = 8.8 Hz, H8), 7.36–7.28 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.18 (2H, m, AA′, BB′, H3′, H5′), 2.73–2.58 (1H, m, CH), 1.67–1.47 (2H, m, CH_2), 1.23 (3H, d, J = 7.2 Hz, CH_2), 0.78 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.8, 177.7, 149.1, 147.7, 141.6, 138.9, 133.0, 128.3, 127.7, 123.9, 119.0, 118.5, 40.7, 30.8, 21.6, 12.2. Anal. Calcd for $C_{18}H_{16}BrNOS_2$ (406.37): C, 53.20; H, 3.97; N, 3.45; S, 15.78. Found: C, 52.90; H, 3.95; N, 3.31; S, 15.80.

6.3.30. 3-(4-*sec*-Butylphenyl)-6-chloro-1,3-benzoxazine-2,4(3*H*)-dithione (3k)

Red solid, yield 27%, mp 153–154 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.22 (1H, d, J = 2.5 Hz, H5), 7.91 (1H, dd, J = 8.8 Hz, J = 2.5 Hz, H7), 7.54 (1H, d, J = 8.8 Hz, H8), 7.37–7.30 (2H, m, AA′, BB′, H2′, H6′), 7.30–7.24 (2H, m, AA′, BB′, H3′, H5′), 2.73–2.57 (1H, m, CH), 1.66–1.50 (2H, m, CH_2), 1.23 (3H, d, J = 7.2 Hz, CH_2), 0.80 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.9, 177.8, 148.7, 147.7, 141.6, 136.2, 130.7, 130.0, 128.3, 127.8, 123.6, 118.9, 40.7, 30.8, 21.6, 12.2. Anal. Calcd for $C_{18}H_{16}ClNOS_2$ (361.92): C, 59.74; H, 4.46; N, 3.87; S, 17.72. Found: C, 59.48; H, 4.36; N, 3.80; S, 17.95.

6.3.31. 3-(4-*sec*-Butylphenyl)-7-chloro-1,3-benzoxazine-2,4(3*H*)-dithione (3l)

Red solid, yield 32%, mp 169–170 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.20 (1H, d, J = 8.8 Hz, H5), 7.83 (1H, d, J = 1.8 Hz, H8), 7.53 (1H, dd, J = 8.8 Hz, J = 1.8 Hz, H6), 7.35–7.28 (2H, m, AA′, BB′, H2′, H6′), 7.25–7.18 (2H, m, AA′, BB′, H3′, H5′), 2.75–2.56 (1H, m, CH), 1.68–1.47 (2H, m, CH_2), 1.22 (3H, d, J = 6.9 Hz, CH_3), 0.78 (3H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.4, 177.9, 150.2, 147.6, 141.6, 141.2, 133.1, 128.2, 127.8, 127.1, 121.5, 116.5, 40.7, 30.8, 21.6, 12.2. Anal. Calcd for $C_{18}H_{16}ClNOS_2$ (361.9): C, 59.74; H, 4.46; N, 3.87; S, 17.72. Found: C, 59.76; H, 4.60; N, 3.64; S, 17.36.

6.3.32. 3-(4-*sec*-Butylphenyl)-6-fluoro-1,3-benzoxazine-2,4(3*H*)-dithione (3m)

Red solid, yield 25%, mp 107–109 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.90 (1H, dd, J = 8.8 Hz, J = 2.9 Hz, H5), 7.85–7.75 (1H, m, H7), 7.66 (1H, dd, J = 8.8 Hz, J = 4.7 Hz, H8), 7.36–7.28 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.18 (2H, m, AA′, BB′, H3′, H5′), 2.73–2.57 (1H, m, CH), 1.67–1.47 (2H, m, CH_2), 1.23 (3H, d, J = 7.3 Hz, CH_3), 0.78 (3H, d, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.2 (d, J = 3.5 Hz), 177.9, 159.4 (d, J = 244.1 Hz), 147.7, 146.5, 141.7, 128.2, 127.8, 124.1 (d, J = 24.8 Hz), 123.6 (d, J = 8.7 Hz), 119.2 (d, J = 8.7 Hz), 116.2 (d, J = 26.5 Hz), 40.7, 30.8, 21.6, 12.2. Anal. Calcd for $C_{18}H_{16}FNOS_2$ (345.5): C, 62.58; H, 4.67; N, 4.05; S, 18.56. Found: C, 62.48; H, 4.38; N, 4.18; S, 18.24.

6.3.33. 3-(4-*sec*-Butylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dithione (3n)

Red solid, yield 40%, mp 169–170 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.11 (1H, d, J = 8.3 Hz, H5), 7.39–7.27 (4H, m, H6, H8, H2′, H6′), 7.25–7.17 (2H, m, H3′, H5′), 2.73–2.59 (1H, m, CH), 2.45 (3H, s, CH_3), 1.65–1.48 (2H, m, CH_2), 1.23 (3H, d, J = 7.1 Hz, CH_3), 0.79 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 188.0, 178.3, 149.8, 148.6, 147.5, 141.6, 131.4, 128.1, 128.0, 120.3, 116.0, 40.7, 30.8, 21.6, 21.5, 12.2. Anal. Calcd for $C_{19}H_{19}NOS_2$ (341.50): C, 66.83; H, 5.61; N, 4.10; S, 18.78. Found: C, 66.77; H, 5.52; N, 4.27; S, 18.49.

6.3.34. 3-(4-Butylphenyl)-6-chloro-1,3-benzoxazine-2,4(3*H*)-dithione (3o)

Red solid, yield 26%, mp 125–127 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.13 (1H, d, J = 2.6 Hz, H5), 7.94 (1H, dd, J = 8.8 Hz, J = 2.6 Hz, H7), 7.63 (1H, d, J = 8.8 Hz, H8), 7.35–7.27 (2H, m, AA′, BB′, H2′, H6′), 7.24–7.16 (2H, m, AA′, BB′, H3′, H5′), 2.63 (2H, t, J = 7.5 Hz, CH_2), 1.67–1.51 (2H, m, CH_2), 1.41–1.24 (2H, m, CH_2), 0.91 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.9, 177.8, 148.7, 143.0, 141.5, 136.2, 130.7, 130.0, 129.6, 127.8, 123.6, 118.9, 34.7, 33.1, 22.0, 14.0. Anal. Calcd for $C_{18}H_{16}ClNOS_2$ (361.9): C, 59.74; H, 4.46; N, 3.87. Found: C, 59.56; H, 4.44; N, 3.55.

6.3.35. 3-(4-*tert*-Butylphenyl)-6-chloro-1,3-benzoxazine-2,4(3*H*)-dithione (3p)

Red solid, yield 22%, mp 219–222 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.13 (1H, d, J = 2.9 Hz, H5), 7.94 (1H, dd, J = 8.8 Hz, J = 2.9 Hz, H7), 7.63 (d, 1H, J = 8.8 Hz, H8), 7.56–7.48 (2H, m, AA′, BB′, H2′, H6′), 7.26–7.20 (2H, m, AA′, BB′, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 186.9, 177.8, 151.2, 148.7, 141.3, 136.1, 130.7, 130.0, 127.5, 126.6, 123.5, 118.9, 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}ClNOS_2$ (361.9): C, 59.74; H, 4.46; N, 3.87; S, 17.72. Found: C, 59.60; H, 4.45; N, 3.71; S, 17.48.

6.3.36. 3-(4-*tert*-Butylphenyl)-7-chloro-1,3-benzoxazine-2,4(3*H*)-dithione (3q)

Red solid, yield 29%, mp 255–256 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.20 (1H, d, J = 8.8 Hz, H5), 7.82 (1H, d, J = 1.9 Hz, H8), 7.56–7.48 (3H, m, H6, H2′, H6′), 7.27–7.19 (2H, m, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.4, 177.8, 151.1, 150.1, 141.2, 141.2, 133.1, 127.5, 127.1, 126.6, 121.5, 116.5, 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}ClNOS_2$ (361.9): C, 59.74; H, 4.46; N, 3.87; S, 17.72. Found: C, 59.83; H, 4.38; N, 3.99; S, 18.15.

6.3.37. 3-(4-*tert*-Butylphenyl)-6-fluoro-1,3-benzoxazine-2,4(3*H*)-dithione (3r)

Red solid, yield 40%, mp 168–169 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.90 (1H, dd, J = 8.9 Hz, J = 2.9 Hz, H5), 7.80 (1H, dt, J = 8.9 Hz, J = 2.9 Hz, H7), 7.66 (1H, dd, J = 8.9 Hz, J = 4.7 Hz, H8), 7.56–7.48 (2H, m, AA′, BB′, H2′, H6′), 7.27–7.20 (2H, m, AA′, BB′, H3′, H5′), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 187.2 (d, J = 3.5 Hz), 177.9, 159.4 (d, J = 24.4 Hz), 151.1, 146.5, 141.4, 127.5, 126.6, 124.1 (d, J = 24.8 Hz), 123.5 (d, J = 9.2 Hz), 119.2 (d, J = 8.7 Hz), 116.2 (d, J = 26.5 Hz), 34.7, 31.3. Anal. Calcd for $C_{18}H_{16}FNOS_2$ (345.5): C, 62.58; H, 4.67; N, 4.05; S, 18.56. Found: C, 62.50; H, 4.60; N, 3.88; S, 18.21.

6.3.38. 3-(4-*tert*-Butylphenyl)-7-methyl-1,3-benzoxazine-2,4(3*H*)-dithione (3s)

Red solid, yield 16%, mp 260–262 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.11 (1H, d, J = 8.3 Hz, H5), 7.55–7.47 (2H, m, AA′, BB′, H2′, H6′), 7.39 (1H, s, H8), 7.34–7.26 (1H, m, H6), 7.26–7.18 (2H, m, AA′, BB′, H3′, H5′), 2.45 (3H, s, CH_3), 1.32 (9H, s, CH_3); ^{13}C NMR (75 MHz, DMSO) δ 188.0, 178.3, 151.0, 149.8, 148.6, 141.3, 131.4, 128.1, 127.7, 126.5, 120.3, 116.0, 34.7, 31.4, 21.5. Anal. Calcd for $C_{19}H_{19}NOS_2$ (341.50): C, 66.83; H, 5.61; N, 4.10; S, 18.78. Found: C, 67.13; H, 5.59; N, 4.26; S, 18.53.

6.4. Antimycobacterial susceptibility testing

For the in vitro evaluation of the antimycobacterial activity of the substances, the following strains were used: *M. tuberculosis* CNCTC My 331/88 (identical with H37RV and ATCC 27294), *M. kansasii* CNCTC My 235/80 (identical with ATCC 12478), *M. avium* CNCTC My 330/88 (identical with ATCC 25291), obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague, and a clinical isolate of *M. kansasii* 6509/96. The antimycobacterial activity of the compounds was determined in the Šula semisynthetic medium (SEVAC, Prague). Each strain was simultaneously inoculated into a Petri dish containing the Löwenstein-Jensen medium for the control of sterility of the inoculum and its growth. The compounds were added to the medium in DMSO solutions. The final concentrations were 1000, 500, 250, 125, 62.5, 32, 16, 8, 4, 2, 1, 0.5, and 0.25 μmol/L. The MICs were determined after incubation at 37 °C for 14 days and 21 days. The MIC was the lowest concentration of the antimycobacterially effective substance (on the above concentration scale), at which the inhibition of the growth of mycobacteria occurred. The evaluation was repeated three times and the values of the MIC were the same.

Acknowledgments

This work is financially supported by project no. MSM 0021620822 of the Ministry of Education of the Czech Republic, by grant no. SVV-2010-261-001 and Grant Agency of Charles University (GAUK 11809/2009/B-CH/FAF).

The authors have declared no conflict of interest.

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