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Short Communication

Influence of the replacement of the oxo function with the thioxo group on the antimycobacterial activity of 3-aryl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and 3-arylquinazoline-2,4(1*H*,3*H*)-diones

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Abstract

Series of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones, 3-arylquinazoline-2,4(1*H*,3*H*)-diones and 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones were synthesized, and the antimycobacterial activities of the derivatives evaluated in vitro. The compounds were active against *Mycobacterium tuberculosis* and conditionally pathogenic mycobacteria (*Mycobacterium kansasii* and *Mycobacterium avium*). The replacement of oxygen by sulfur in 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and 3-arylquinazoline-2,4(1*H*,3*H*)-diones gave rise to an increase of antimycobacterial activity. The most active compound was 3-(3-chlorophenyl)-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione.

Keywords: Benzoxazines; Quinazolines; Tubeculostatics; Antimycobacterial activity; Mycobacteria

1. Introduction

In conjunction with the main goal of our group being the development of new antituberculotic agents, we have recently studied a number of structurally different compounds, such as the derivatives of pyridine [1,2], benzoxazine [3], quinazoline [4,5] and related compounds [6,7]. Some time ago, when exploring the properties of antimycobacterial thiolactams [8,9], we found that 3-(4-cyclohexylphenyl)-2*H*-1,3-benzoxazine-2,4-(3*H*)-dithione, 3-(4-cyclohexylphenyl)-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one, 6-chloro-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones and 6-chloro-3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones are broad-spectrum antimycobacterial compounds, the activity of which is equal to that of INH against *Mycobacterium tuberculosis*, and is superior to the drug against *Mycobacterium kansasii* and *Mycobacterium avium*. Thus, these compounds can be considered as new potential antituberculotics. The aim of this work was to prepare a series of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and 3-phenylquinazoline-2,4(1*H*,3*H*)-diones, and to evaluate the derivatives for antimy-

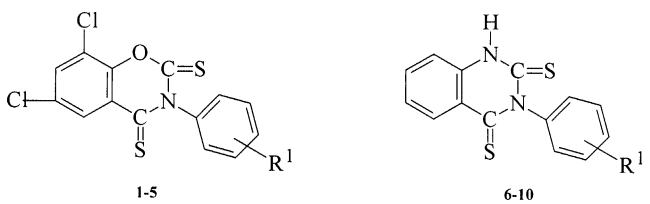

Fig. 1. General structure of the derivatives of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (**1–5**) and 3-phenylquinazoline-2,4(1*H*,3*H*)-dithione (**6–10**).

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cobacterial activity against *M. tuberculosis*, *M. kansasii* and *M. avium*. Next we assumed that the replacement of the oxo group with the isosteric thioxo moiety would lead to an enhancement of the antimycobacterial activity of the compounds. As the electron-accepting properties of the substituents generally boost the antimycobacterial effect, we presumed that 3-phenyl-6,8 - dichloro - 2*H* - 1,3 - benzoxazine - 2,4(3*H*) - dithiones would turn out to be important antimycobacterial compounds. Structural modifications were carried out by varying substituents on the phenyl ring at C(3). Simultaneously we intended to study the antimycobacterial activity of the isosteric 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones. The general structures of **1**–**10** are shown in Fig. 1.

2. Chemistry

The preparation of the starting 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones was described in our previous communication [3]. 3-Phenylquinazoline-2,4(1*H*,3*H*)-diones were also synthesized as previously reported by us [4]. To convert the oxo group into the thioxo moiety, the starting compounds were heated with phosphorus pentasulfide. The products had no absorption bands in the carbonyl region of the IR spectra (1650–1750 cm^{-1}), while the bands of the thioxo group were apparent at about 1450 cm^{-1}. The identity of the compounds was confirmed by NMR spectra and their purity by elemental analysis (Table 2). As regards the synthesis, the method is not suitable for the preparation of nitro- and methoxy derivatives.

3. Experimental

3.1. Chemistry

The melting points were determined on a Kofler apparatus and are uncorrected. Analytical samples were dried over P_4O_{10} at 60 °C and 30 Pa for 8–10 h. Elemental analyses were performed on a CHNS-O CE instrument (FISONS EA 1110). The results were within $\pm 0.4\%$ of the calculated values. IR spectra were obtained on a Nicolet Impact 400 spectrometer in KBr pellets. The ^1H NMR and ^{13}C NMR spectra were recorded for $CDCl_3$ or DMSO-d_6 solutions at room temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts were recorded as δ values in parts per million (ppm), and were indirectly referenced to tetramethylsilane via the solvent signal (7.26 for ^1H). Multiplicities are given together with the coupling constant(s) (in Hz). The signals were assigned to the corresponding protons only if an unequivocal assignment could be made (1D decoupling experiments were done when necessary). The reactions were monitored and the purity of the compounds checked by TLC (Silufol UV254, Kavalier, Votice, Czech Republic) in a mixture of ethyl acetate:petroleum ether (2:3) using UV detection.

3.1.1. General procedure for the replacement of the carbonyl oxygen by sulfur for obtaining thioxo derivatives

The starting dione (3.8 mmol) was melted with P_2S_5 (7.6 mmol) at 175–200 °C for 20 min. A 10% aqueous solution of potassium carbonate (60 ml) was poured into the reaction mixture after cooling and the crude product was filtered off.

The resultant material was dissolved in a maximum of 40 ml of toluene. Red and orange–yellow products were separated by column chromatography on silica gel. Recrystallization from ethanol was necessary.

3.1.2. 3-Phenyl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dithione (**1**)

Red crystals 39% yield, m.p. 189–191 °C; IR (KBr, cm^{-1}) 1449 (C=S),^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 1H, $J = 2.48$ (H5)), 7.75 (d, 1H, $J = 2.48$ (H7)), 7.62–7.47 (m, 3H (H3′, H4′, H5′)), 7.24–7.18 (m, 2H (H2′, H6′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 184.8$, 175.6, 144.8, 143.0, 135.4, 131.7, 130.2, 129.9, 129.3, 127.6, 123.7, 122.4. *Anal.* (C, H, N, S).

3.1.3. 3-(4-Bromopheny)l-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dithione (**2**)

Red crystals 38% yield, m.p. 182–184 °C; IR (KBr, cm^{-1}) 1454 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 1H, $J = 2.47$ (H5)), 7.75 (d, 1H, $J = 2.47$ (H7)), 7.40–7.34 (m, 2H, AA′, BB′ (H2′, H6′)), 7.12–7.05 (m, 2H, AA′, BB′ (H3′, H5′)), 2.45 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 184.9$, 175.8, 144.8, 140.6, 139.5, 135.4, 131.7, 130.9, 130.0, 127.2, 123.7, 122.4, 21.5. *Anal.* (C, H, N, S).

3.1.4. 3-(4-Methylpheny)l-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dithione (**3**)

Red crystals 39% yield, m.p. 210–212 °C; IR (KBr, cm^{-1}) 1452 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, 1H, $J = 2.47$ (H5)), 7.76 (d, 1H, $J = 2.47$ (H7)), 7.72–7.65 (m, 2H, AA′, BB′ (H3′, H5′)), 7.11–7.04 (m, 2H, AA′, BB′ (H2′, H6′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 184.6$, 175.3, 144.8, 141.8, 135.5, 133.5, 131.8, 129.8, 129.5, 129.4, 123.4, 122.5. *Anal.* (C, H, N, S).

*3.1.5. 3-(4-Chlorophenyl)-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dithione (**4**)*

Red crystals 36% yield, m.p. 192–194 °C; IR (KBr, cm^{-1}) 1453 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, 1H, $J = 2.47$ (H5)), 7.76 (d, 1H, $J = 2.47$ (H7)), 7.56–7.50 (m, 2H, AA′, BB′ (H2′, H6′)), 7.16–7.10 (m, 2H, AA′, BB′ (H3′, H5′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 184.7$, 175.5, 144.8, 141.3, 135.8, 135.3, 131.9, 130.6, 129.9, 129.1, 123.6, 122.5. *Anal.* (C, H, N, S).

*3.1.6. 3-(3-Chlorophenyl)-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dithione (**5**)*

Red crystals 35% yield, m.p. 192–194 °C; IR (KBr, cm^{-1}) 1453 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 1H, $J = 2.47$ (H5)), 7.76 (d, 1H, $J = 2.47$ (H7)), 7.52–7.45 (m, 2H (H2′, H6′)), 7.23–7.19 (m, 1H (H5′)), 7.13–7.07 (m, 1H (H4′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 184.6$, 175.3, 144.8, 143.7, 135.7, 135.6, 131.9, 131.1, 129.8, 129.6, 128.2, 126.1, 123.6, 122.5. *Anal.* (C, H, N, S).

*3.1.7. 3-Phenylquinazoline-2,4(1H,3H)-dithione (**6**)*

Orange crystals 39% yield, m.p. 258–261 °C; lit. [10] m.p. 252–254 °C. IR (KBr, cm^{-1}) 1442 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 11.56 (bs, 1H (NH)), 8.49 (dd, 1H, $J = 8.24$, $J = 1.1$ (H5)), 7.67–7.48 (m, 4H (H7, H3′, H4′, H5′)), 7.30 (dt, 1H, $J = 8.24$, $J = 1.1$, (H6)), 7.27–7.17 (m, 3H (H8, H2′, H6′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 190.1$, 173.4, 144.0, 135.7, 134.3, 133.1, 130.0, 129.1, 128.5, 126.3, 124.9, 115.4. *Anal.* (C, H, N, S).

*3.1.8. 3-(4-Bromophenyl)quinazoline-2,4(1H,3H)-dithione (**7**)*

Orange crystals 32% yield, m.p. 287–289 °C; IR (KBr, cm^{-1}) 1442 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 10.86 (bs, 1H (NH)), 8.48 (dd, 1H, $J = 8.24$, $J = 1.1$ (H5)), 7.71–7.74 (m, 3H (H7, H3′, H5′)), 7.32 (dt, 1H, $J = 8.24$, $J = 1.1$, (H6)), 7.14 (dm, 1H (H8)), 7.12–7.07 (m, 2H, AA′,BB′(H2′, H6′). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 189.6$ 172.9, 142.5, 135.6, 133.9, 133.1, 133.0, 129.9, 126.0, 124.4, 122.8, 114.8. *Anal.* (C, H, N, S).

*3.1.9. 3-(4-Methylphenyl)quinazoline-2,4(1H,3H)-dithione (**8**)*

Orange crystals 38% yield, m.p. 296–303 °C; lit. [10] m.p. 286–287 °C. IR (KBr, cm^{-1}) 1441 (C=S). *Anal.* (C, H, N, S).

*3.1.10. 3-(4-Chlorophenyl)quinazoline-2,4(1H,3H)-dithione (**9**) (T2299)*

Orange crystals 29% yield, m.p.273–278 °C; IR (KBr, cm^{-1}) 1442 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 10.82 (bs, 1H (NH)), 8.48 (dd, 1H, $J = 8.24$, $J = 1.37$ (H5)), 7.67 (dt, 1H, $J = 8.24$, $J = 1.37$ (H7)), 7.54–7.45 (m, 2H (H2′, H6′)), 7.32 (dt, 1H, $J = 8.24$, $J = 1.37$, (H6)), 7.25–7.22 (m, 1H (H5′)), 7.17–7.11 (m, 2H (H8, H4′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 189.5$, 172.9, 144.3, 135.6, 135.2, 133.9, 132.9, 130.6, 129.1, 128.8, 126.7, 126.0, 124.4, 114.9. *Anal.* (C, H, N, S).

*3.1.11. 3-(3,4-Dichlorophenyl)quinazoline-2,4(1H,3H)-dithione (**10**)*

Orange crystals 31% yield, m.p. 291–294 °C; IR (KBr, cm^{-1}) 1442 (C=S). ^1H NMR (300 MHz, $CDCl_3$) δ 11.00 (bs, 1H (NH)), 8.47 (dd, 1H, $J = 8.24$, $J = 1.1$ (H5)), 7.68 (dt, 1H, $J = 8.24$, $J = 1.1$, (H7)), 7.63 (d, 1H, $J = 8.52$ (H5′)), 7.33 (dt, overlapped 1H, $J = 8.24$, $J = 1.1$, (H6)), 7.33 (d, overlapped 1H, $J = 2.47$ (H2′)), 7.15 (ddd, 1H, $J = 8.24$, $J = 1.1$, $J = 0.55$ (H8)), 7.09 (dd, 1H, $J = 8.52$, $J = 2.47$ (H6′)). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 189.4$, 172.8, 142.3, 135.8, 133.8, 133.7, 133.2, 132.9, 131.4, 130.5, 127.9, 126.2, 124.3, 114.9. *Anal.* (C, H, N, S).

3.2. Microbiology

For the evaluation of the antimycobacterial activity of the substances in vitro, the following strains were used: *M. tuberculosis* CNCTC My 331/ 88, *M. kansasii* CNCTC My 235/ 80, *M. avium* CNCTC My 330/ 88, obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague, and a clinical isolate of *M. kansasii* 6 509/ 96. The antimycobacterial activities of the compounds against these strains were determined in the Šula semisynthetic medium (SEVAC, Prague). The compounds were added to the medium in dimethyl sulfoxide solutions. The following concentrations were used: 125, 64, 32, 16, 8, and 4 μmol/l. The minimum inhibitory concentrations were determined after incubation at 37 °C for 14 and 21 days. MIC was the lowest concentration of a substance, at which the inhibition of the growth of mycobacteria occurred.

4. Results and discussion

The antimycobacterial activities of the compounds together with that of isoniazide (INH) are shown in Tables 1 and 3. It can be concluded that the conditionally pathogenic strains of *M. kansasii* CNCTC My 235/ 80 and *M. avium* CNCTC My 330/ 88 are not susceptible against INH. The clinical isolate of *M. kansasii* 6 509/ 96 is susceptible against INH, but the most active of the new substances match the activity of the drug. They are, however, more efficient than this standard against the other two strains. In general, the replacement of the oxo function with the thioxo moiety gives rise to an increase of antimycobacterial activity. In the

Table 1
Antimycobacterial activity in vitro expressed as MIC (μmol/l)

Comp.	R^1	*M. tuberculosis* 331/81		*M. kansasii* 235/80		*M. kansasii* 6509/96		*M. avium* 330/88	
		14 d	21 d	14 d	21 d	14 d	21 d	14 d	21 d
1	H	8	8	16	16	16	16	62	62
2	4-Br	16	16	32	16	32	32	62	62
3	4-CH_3	4	8	16	32	16	16	125	125
4	4-Cl	8	16	16	32	32	32	64	64
5	3-Cl	4	8	8	16	16	16	32	32
6	H	32	64	64	64	125	125	64	>64
7	4-Br	16	32	64	64	32	64	32	>64
8	4-CH_3	16	16	64	64	64	>64	32	32
9	4-Cl	32	64	32	>64	64	>125	64	>64
10	3,4-Cl_2	16	32	32	64	32	>64	32	32
INH		4	4	500	500	16	16	500	500

Table 2
Elemental analyses of compounds **1–10**

Comp.	Analyses calculated/found%			
	C	H	N	S
1	49.42/49.37	2.07/2.45	4.12/4.07	18.85/18.61
2	40.12/39.93	1.44/1.81	3.34/3.26	15.30/14.90
3	50.85/50.85	2.56/2.84	3.95/3.80	18.10/18.15
4	44.88/45.24	1.61/2.01	3.74/3.65	17.11/16.76
5	44.88/44.84	1.61/1.27	3.74/3.56	17.11/16.99
6	62.19/62.28	3.73/3.50	10.36/10.35	23.72/23.81
7	48.15/48.08	2.60/2.59	8.02/7.97	18.36/18.67
8	63.35/63.29	4.25/4.29	9.85/9.79	22.55/22.39
9	55.17/55.29	2.98/2.83	9.19/8.92	21.04/20.96
10	49.97/49.63	2.38/2.31	8.26/8.18	18.90/18.94

case of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dione derivatives, there is an observable rise in activity, which acquires the highest value against *M. tuberculosis*. MIC values against *M. tuberculosis* are within 4–32 μmol/l and the most active compounds are comparable to INH. Even though the activity against *M. kansasii* and *M. avium* is somewhat lower than that against *M. tuberculosis*, the most efficient of the newly prepared compounds can be considered as important substances with potential use against conditionally pathogenic mycobacteria. MIC values obtained after 14 days of incubation correlate well with those obtained after 21 days. The increase of antimycobacterial activity upon replacement of the carbonyl group with the thioxo moiety is most significant in the group of 3-

Table 3
Results of the Free–Wilson analysis of the antimycobacterial activity of the derivatives of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dione and 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione

Fragment	Δlog MIC		
	M. tuberculosis 331/88	*M. kansasii* 330/88	*M. avium* 235/80
$C_{(2)}$=O, $C_{(4)}$=O	0.210	0.210	0.088
$C_{(2)}$=S $C_{(4)}$=S	−0.210	−0.210	−0.088
H	0.301	0.297	0.059
4′-Br	0.151	−0.150	0.059
4′-CH_3	−0.151	0.152	0.205
4′-Cl	0	0.001	−0.086
3′-Cl	−0.301	−0.300	−0.237
Statistical parameter	$R = 0.890$ $s = 0.24$ $F = 3.05$ $n = 10$	$R = 0.891$ $s = 0.24$ $F = 3.07$ $n = 10$	$R = 0.924$ $s = 0.114$ $F = 4.66$ $n = 10$

phenylquinazoline-2,4(1*H*,3*H*)-dithiones, where the parent carbonyl compounds were largely inactive [4]. To be able to draw similar conclusions in the series of 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-thiones, we separated the influence of structure modifications at two centers, one center being the groups in 1 and 3 positions (replacement of C=O with C=S), and the other being the substituents at the phenyl moiety at C(3) of the benzoxazine skeleton. The analysis of antimycobacterial activity was carried out only for values obtained after 14 days of incubation; the values of antimycobacterial activities for the parent 3-phenyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones were published in our previous paper [3]. The analysis shows that the conversion of the oxo group into the thioxo function enhances antimycobacterial activity of the compounds, which is more significant against *M. tuberculosis* and *M. kansasii* than *M. avium*. Of all the compounds, 3-(3-chlorophenyl)-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (**5**) possessed the highest activity.

In conclusion, both series can be viewed as new groups of potential antituberculotics.

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