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ORIGINAL PAPER

Antimycobacterial 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones substituted on phenyl and benzoxazine moiety in position 6

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A series of forty-five derivatives of 3-phenyl-4-thioxo-*2H*-1,3-benzoxazine-2(*3H*)-ones and forty-five derivatives of 3-phenyl-*2H*-1,3-benzoxazine-2,4(*3H*)-dithiones was synthesised. The compounds exhibited in-vitro activity against *Mycobacterium tuberculosis*, *M. kansasii* (two strains), and *M. avium*. The most active derivatives were more active than isonicotinhydrazide (INH). The quantitative relationships between the structure and antimycobacterial activity were calculated. The activity against *M. tuberculosis* increased with the lipophilicity of the substituents.

Keywords: benzoxazine, thioxo group, tuberculostatics, QSAR, antimycobacterial activity

Introduction

The prognosis that, following the millennium, tuberculosis would no longer occur in the developed world was wrong (O'Brien & Nunn, 2001). The emergence of multi-drug resistant (MDR-TB) and extensively-drug resistant (XDR-TB) strains of *Mycobacterium tuberculosis* is a serious problem and tuberculosis remains one of the leading infectious diseases worldwide (Dye, 2009). This unfavourable state is also being influenced by an increase in AIDS, which is often accompanied by the mycobacterial diseases and with the low standard of living of displaced persons (Aaron et al., 2004; Naidoo et al., 2011). New mycobacterial diseases are occurring which, until recently, were considered non-transferable to humans (Tortoli, 2009).

From the perspective of pharmaceutical treatment, *N*-benzylsalicylamides, salicylanilides, and their cyclic derivatives, benzoxazinediones, are promising classes of compounds (Matyk et al., 2005; Nemeček et al., 2009; Petrlíková et al., 2011, 2010; Waisser et al., 2006). This study is oriented towards 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, they can be expected to serve as bacterial two-component system inhibitors (Hlasta et al., 1998; Macielag et al., 1998). Benzoxazine derivatives could also target the biosynthesis of menaquinone, a polyisoprenylated naphtoquinone, that plays an important role in the mycobacterial electron transport chain (Li et al., 2010). Both types of mechanism of action are very promising since the consequent antibacterial effects

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are probably different from the effects of other antibacterial drugs (Schroeder et al., 2002; van den Boogaard et al., 2009).

Theoretical

Regressions were calculated using Microsoft Excel Multireg programs. The values of the substituent π and σ constants were taken from the literature (Hansch & Leo, 1979). The stability of the QSAR models was evaluated by cross-validation (leave-one-out procedure) (Gupta et al., 2009; Golbraikh & Tropsha, 2002) in Matlab 7.0 program. The Free–Wilson method (Free & Wilson, 1964) modified by Fujita–Ban (Fujita & Ban, 1971) was used to investigate the activity contribution in the case of sulphur derivatives. 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.

Experimental

Materials and methods

The melting points were determined using the Kofler apparatus (C. Reichert, Vienna, Austria) and the temperature data were corrected. The samples for analyses and antimycobacterial tests were dried over P_2O_5 at 61 ℃ and 66 Pa for 24 h. The elemental analyses (C, H, N, S) were performed on a CHNS-O CE elemental analyzer (Fisions EA 1110, Milan, Italy) and were within ±0.4 % of the theoretical values. The IR spectra of KBr pellets were measured on a Nicolet Impact 400 apparatus (Nicolet, Madison, WI, USA); the wavenumbers are given in cm^{-1}. The purity of the compounds was verified by TLC on silica gel plates pre-coated with a fluorescent indicator Silufol UV 254 + 366 (Kavalier Votice, Czech Republic) and hexane–acetone mixture ($\varphi_r = 3 : 1$) as the mobile phase. The ^{1}H 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 (Varian Inc., Palo Alto, CA, USA) operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts were recorded as δ values and indirectly referenced to tetramethylsilane via the solvent signal (DMSO) (2.5 for ^{1}H or 39.5 for ^{13}C).

General procedure for the preparation of 3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones (I–V) and 3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dithiones (VI–X)

The derivatives of 3-phenyl-*2H*-1,3-benzoxazine-2,4(3*H*)-diones (4 mmol) underwent fusion with P_4S_{10} (10 mmol) for 45 min (180–210 ℃). After cooling to room temperature, a 10 % potassium carbonate solution was poured into the reaction mixture; the crude product was removed by filtration, and dissolved in toluene (p.a., a maximum of 40 mL). Column chromatography using silica gel provided substituted derivatives of 3-phenyl-4-thioxo-*2H*-1,3-benzoxazine-2(3*H*)-one (*I–V*) and substituted derivatives of 3-phenyl-*2H*-1,3-benzoxazine-2,4(3*H*)-dithione (*VI–X*) as orange-yellow and red solids, respectively. Recrystallisation from ethanol was necessary.

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 12 478), *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). In order to control the sterility of the inoculum and its growth, a Petri dish containing the Löwenstein–Jensen medium was inoculated with each strain. The compounds were added to the medium dissolved in DMSO. The final concentrations were 1000 μmol L^{-1}, 500 μmol L^{-1},

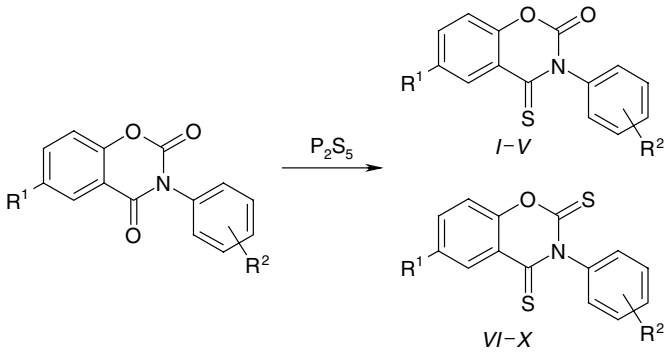

Fig. 1. Synthesis of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones.

Table 1. Overview and characteristics of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones

Comp.	R^1	R^2	Formula	M_r	w_i(calc.)/mass % / w_i(found)/mass %				Yield	M.p.	$\tilde{\nu}$ (CO)
					C	H	N	S	%	°C	cm^{-1}
Ia	Br	4-H	$C_{14}H_8BrNO_2S$	334.2	50.32	2.41	4.19	9.59	38	240–242	1764
					50.30	2.45	4.12	9.32			
Ib	Br	4-CH_3	$C_{15}H_{10}BrNO_2S$	348.2	51.74	2.89	4.02	9.21	36	259–260.5	1759
					51.22	2.62	3.98	9.11			
Ic	Br	4-Cl	$C_{14}H_7BrClNO_2S$	368.6	45.61	1.91	3.80	8.70	31	283–284[a]	1759
					45.31	1.99	3.53	8.52			
Id	Br	3-Cl	$C_{14}H_7BrClNO_2S$	368.6	45.61	1.91	3.80	8.70	33	199–200	1759
					45.29	2.01	3.62	8.35			
Ie	Br	3,4-Cl_2	$C_{14}H_6BrCl_2NO_2S$	403.1	41.72	1.50	3.47	7.96	30	220–222	1961
					41.42	1.85	3.32	7.57			
If	Br	4-Br	$C_{14}H_7Br_2NO_2S$	413.1	40.71	1.71	3.39	7.76	37	260–262[b]	1771
					40.43	1.65	3.15	7.51			
Ig	Br	4-F	$C_{14}H_7BrFNO_2S$	352.2	47.75	2.00	3.98	9.10	30	290–291	1763
					47.56	2.32	3.63	8.83			
Ih	Br	3-F	$C_{14}H_7BrFNO_2S$	352.2	47.75	2.00	3.98	9.10	39	227–228	1764
					47.67	1.88	3.68	8.79			
Ii	Br	4-CF_3	$C_{15}H_7BrF_3NO_2S$	402.2	44.80	1.75	3.48	7.97	35	247–248	1751
					44.63	2.01	3.16	7.68			
IIa	CH_3	4-H	$C_{15}H_{11}NO_2S$	269.3	66.89	4.12	5.20	11.91	34	217–219	1756
					66.51	4,44	4.98	11.63			
IIb	CH_3	4-CH_3	$C_{16}H_{13}NO_2S$	283.3	67.82	4.62	4.94	11.32	30	218–219.5	1755
					67.53	4.84	4.75	11.21			
IIc	CH_3	4-Cl	$C_{15}H_{10}ClNO_2S$	303.8	59.31	3.32	4.61	10.56	32	201–203	1755
					58.95	3.65	4.43	10.37			
IId	CH_3	3-Cl	$C_{15}H_{10}ClNO_2S$	303.8	59.31	3.32	4.61	10.56	31	175–177	1756
					59.63	3.70	4.68	10.25			
IIe	CH_3	3,4-Cl_2	$C_{15}H_9Cl_2NO_2S$	338.2	53.27	2.68	4.14	9.48	37	185–188	1754
					53.52	2,87	4.53	9.21			
IIf	CH_3	4-Br	$C_{15}H_{10}BrNO_2S$	348.2	51.74	2.89	4.02	9.21	36	207–209	1759
					51.52	2.68	5.21	8.94			
IIg	CH_3	4-F	$C_{15}H_{10}FNO_2S$	287.3	62.71	3.51	4.88	11.16	31	206–207	1757
					62.43	3.79	4.52	10.83			
IIh	CH_3	3-F	$C_{15}H_{10}FNO_2S$	287.3	62.71	3.51	4.88	11.16	38	189–199	1758
					62.64	3.32	4.65	11.45			
IIi	CH_3	4-CF_3	$C_{16}H_{10}F_3NO_2S$	337.3	56.97	2.99	4.15	9.51	35	237–238	1760
					56.64	3.26	3.95	9.28			
IIIa	CH_3O	4-H	$C_{15}H_{11}NO_3S$	285.3	63.14	3.89	4.91	11.24	32	233–235	1754
					62.85	4.01	4.73	11,55			
IIIb	CH_3O	4-CH_3	$C_{16}H_{13}NO_3S$	299.3	64.20	4.38	4.68	10.71	31	194–195.5	1757
					63.98	4.56	4.52	10.49			
IIIc	CH_3O	4-Cl	$C_{15}H_{10}ClNO_3S$	319.8	56.34	3.15	4.38	10.03	35	227–228	1755
					56.01	3.36	3.99	9.85			
IIId	CH_3O	3-Cl	$C_{15}H_{10}ClNO_3S$	319.8	56.34	3.15	4.38	10.03	31	234–235	1755
					56.22	2.99	4.10	9.99			
IIIe	CH_3O	3,4-Cl_2	$C_{15}H_9Cl_2NO_3S$	354.2	50.86	2.56	3.95	9.05	38	211–213	1754
					51.08	2.83	3.74	8.87			
IIIf	CH_3O	4-Br	$C_{15}H_{10}BrNO_3S$	364.2	49.47	2.77	3.85	8.80	36	219–220	1750
					49.76	3.05	3.68	8.45			
IIIg	CH_3O	4-F	$C_{15}H_{10}FNO_3S$	303.3	59.40	3.32	4.62	10.57	32	223–224	1759
					59.21	3.64	4.28	10.26			
IIIh	CH_3O	3-F	$C_{15}H_{10}FNO_3S$	303.3	59.40	3.32	4.62	10.57	36	245–246	1763
					59.01	3.72	4.39	10.39			
IIIi	CH_3O	4-CF_3	$C_{16}H_{10}F_3NO_3S$	353.3	54.39	2.85	3.96	9.08	34	202	1751
					54.22	3.24	4.01	8.86			
IVa	F	H	$C_{14}H_8FNO_2S$	273.3	61.53	2.95	5.13	11.73	30	228–229	1762
					61.34	3.28	4.78	11.93			
IVb	F	4-CH_3	$C_{15}H_{10}NO_2S$	287.3	62.71	3.51	4.88	11.16	32	211–213	1756
					62.59	3.83	4.64	10.98			

Table 1. (continued)

Comp.	R^1	R^2	Formula	M_r	w_i(calc.)/mass % / w_i(found)/mass %				Yield	M.p.	$\tilde{\nu}$ (CO)
					C	H	N	S	%	°C	cm^{-1}
IVc	F	4-Cl	$C_{14}H_7ClFNO_2S$	307.7	54.64	2.29	4.55	10.42	33	211–213	1756
					54.37	2.48	4.37	10.17			
IVd	F	3-Cl	$C_{14}H_7ClFNO_2S$	307.7	54.64	2.29	4.55	10.42	34	184–185	1756
					54.24	2.52	4.43	10.36			
IVe	F	3,4-Cl_2	$C_{14}H_6Cl_2FNO_2S$	347.2	49.14	1.77	4.09	9.37	30	203–205	1756
					48.86	2.01	3.98	8.09			
IVf	F	4-Br	$C_{14}H_7BrFNO_2S$	352.2	47.75	2.00	3.98	9.10	31	230–231	1755
					42.56	2.26	3.69	8.85			
IVg	F	4-F	$C_{14}H_7F_2NO_2S$	291.3	57.73	2.42	4.81	11.01	32	175–178	1768
					58.01	2.73	4.32	10.83			
IVh	F	3-F	$C_{14}H_7F_2NO_2S$	291.3	57.73	2.42	4.81	11.01	31	172–174	1755
					57.56	2.68	4.46	10.69			
IVi	F	4-CF_3	$C_{15}H_7F_4NO_2S$	341.3	52.79	2.07	4.10	9.40	33	207–208	1765
					53.05	2.38	3.85	9.73			
Vg	Cl	4-F	$C_{14}H_7ClFNO_2S$	307.7	54.64	2.29	4.55	10.42	34	276–277	1764
					54.48	2.56	4.24	10.27			
Vh	Cl	3-F	$C_{14}H_7ClFNO_2S$	307.7	54.64	2.29	4.55	10.42	30	209–210	1766
					54.28	2.63	4.19	10.18			
Vi	Cl	4-CF_3	$C_{15}H_7ClF_3NO_2S$	352.7	50.36	1.97	3.92	8.96	32	235–236	1754
					50.16	2.35	3.66	8.68			

a) 280–281 °C (Wagner et al., 1966); *b*) 256–258 °C (Wagner et al., 1966).

Table 2. Overview and characteristics of 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones

Comp.	R^1	R^2	Formula	M_r	w_i(calc.)/mass % / w_i(found)/mass %				Yield	M.p.
					C	H	N	S	%	°C
VIa	Br	4-H	$C_{14}H_8BrNOS_2$	350.3	48.01	2.30	4.00	18.31	32	244–245
					47.86	2.45	3.82	18.26		
VIb	Br	4-CH_3	$C_{15}H_{10}BrNOS_2$	364.3	49.46	2.77	3.85	17.60	31	246–248
					49.23	2.96	3.62	17.32		
VIc	Br	4-Cl	$C_{15}H_7BrClNOS_2$	384.7	43.71	1.83	3.64	16.67	33	256–258
					43.48	2.03	3.23	16.29		
VId	Br	3-Cl	$C_{15}H_7BrClNOS_2$	384.7	43.71	1.83	3.64	16.67	31	190–192
					43.51	1.99	3.46	16.55		
VIe	Br	3,4-Cl_2	$C_{14}H_6BrCl_2NOS_2$	419.1	40.12	1.44	3.34	15.30	30	203–205
					39.87	1.79	2.98	14.98		
VIf	Br	4-Br	$C_{14}H_7Br_2NOS_2$	429.2	39.18	1.64	3.26	14.94	33	248–251
					38.96	1.91	3.01	15.02		
VIg	Br	4-F	$C_{15}H_7BrFNOS_2$	368.2	45.66	1.92	3.80	17.42	32	224–226
					45.83	2.30	3.64	17.67		
VIh	Br	3-F	$C_{14}H_7BrFNOS_2$	368.2	45.66	1.92	3.80	17.42	35	231–232
					45.24	2.14	3.51	17.23		
VIi	Br	4-CF_3	$C_{15}H_7BrF_3NOS_2$	418.3	43.07	1.69	3.35	15.33	32	182–184
					42.89	201	3.71	15.58		
VIIa	CH_3	4-H	$C_{16}H_{13}NOS_2$	285.4	63.13	3.89	4.91	22.47	30	198–199
					62.84	3.73	5.21	22.28		
VIIb	CH_3	4-CH_3	$C_{16}H_{13}NOS_2$	299.4	64.18	4.38	4.68	21.42	32	225–227
					63.82	4.32	5.01	21.26		
VIIc	CH_3	4-Cl	$C_{15}H_{10}ClNOS_2$	319.8	56.33	3.15	4.38	20.05	33	192–193
					55.99	2.87	4.01	19.76		
VIId	CH_3	3-Cl	$C_{15}H_{10}ClNOS_2$	319.8	56.33	3.15	4.38	20.05	31	185–186
					56.20	3.38	4.25	20.36		
VIIe	CH_3	3,4-Cl_2	$C_{15}H_9Cl_2NOS_2$	354.3	50.85	2.56	3.95	18.10	32	175–176
					51.17	2.83	3.95	17.79		

Table 2. (continued)

Comp.	R^1	R^2	Formula	M_r	w_i(calc.)/mass % w_i(found)/mass %				Yield	M.p.
					C	H	N	S	%	°C
VIIf	CH_3	4-Br	$C_{15}H_{10}CBrNOS_2$	364.3	49.46	2.77	3.85	17.60	30	218–219
					49.17	3.01	3.63	17.43		
VIIg	CH_3	4-F	$C_{15}H_{10}FNOS_2$	303.4	59.39	3.32	4.62	21.14	33	184–185
					59.18	3.17	4.24	20.89		
VIIh	CH_3	3-F	$C_{15}H_{10}FNOS_2$	303.4	59.39	3.32	4.62	21.14	31	193–194
					59.17	3.63	4.27	20.78		
VIIi	CH_3	4-CF_3	$C_{16}H_{10}F_3NOS_2$	353.3	54.38	2.85	3.96	18.15	31	194–195
					54.23	3.12	3.73	17.96		
VIIIa	CH_3O	4-H	$C_{15}H_{11}NO_2S_3$	301.4	59.78	3.68	4.65	21.28	32	259–260
					59.66	3.97	4.27	20.12		
VIIIb	CH_3O	4-CH_3	$C_{16}H_{13}NO_2S_2$	315.4	60.93	4.15	4.44	20.33	30	190–191
					60.68	4.48	4.23	20.17		
VIIIc	CH_3O	4-Cl	$C_{15}H_{10}ClNO_2S_2$	335.8	53.65	3.00	4.17	19.10	32	181–183
					53.28	3.38	3.82	18.78		
VIIId	CH_3O	3-Cl	$C_{15}H_{10}ClNO_2S_2$	335.8	53.65	3.00	4.17	19.10	33	219–220
					53.36	3.27	3.96	18.84		
VIIIe	CH_3O	3,4-Cl_2	$C_{15}H_9Cl_2NO_2S_2$	370.3	48.66	2.45	3.78	17.32	30	170–172
					48.24	2.63	3.63	17.12		
VIIIf	CH_3O	4-Br	$C_{15}H_{10}BrNO_2S_2$	380.3	47.38	2.65	3.68	16.86	31	171–173
					47.16	2.87	3.37	16.73		
VIIIg	CH_3O	4-F	$C_{15}H_{10}FNO_2S_2$	319.4	56.41	3.16	4.39	20.08	32	211–212
					56.23	3.24	4.16	19.89		
VIIIh	CH_3O	3-F	$C_{15}H_{10}FNO_2S_2$	319.4	56.41	3.16	4.39	20.08	30	278–279
					56.28	3.36	4.23	20.15		
VIIIi	CH_3O	4-CF_3	$C_{16}H_{10}F_3NO_1S_2$	369.4	52.03	2.73	3.79	17.36	33	195–196
					51.96	2.98	3.56	17.15		
IXa	F	H	$C_{14}H_8FNO_2S_2$	289.4	58.11	2.79	4.84	22.16	30	166–167
					57.86	2.93	4.53	21.96		
IXb	F	4-CH_3	$C_{15}H_{10}NOS_2$	303.4	59.39	3.32	4.62	21.14	32	187–189
					59.19	3.54	4.36	20.83		
IXc	F	4-Cl	$C_{14}H_7ClFNOS_2$	323.8	51.93	2.18	4.33	19.81	31	166–168
					51.77	2.34	4.14	19.76		
IXd	F	3-Cl	$C_{14}H_7ClFNOS_2$	323.8	51.93	2.18	4.33	19.81	33	166–168
					51.68	2.42	4.57	19.53		
IXe	F	3,4-Cl_2	$C_{14}H_6Cl_2FNOS_2$	358.2	46.94	1.69	3.91	17.90	32	162–164
					46.62	2.01	3.58	17.65		
IXf	F	4-Br	$C_{14}H_7BrFNOS_2$	368.2	45.66	1.92	3.80	17.42	32	177–178
					46.38	2.37	3.52	17.27		
IXg	F	4-F	$C_{14}H_7F_2NOS_2$	307.3	54.71	2.30	4.56	20.87	30	180–182
					54.83	2.44	4.16	20.93		
IXh	F	3-F	$C_{14}H_7F_2NOS_2$	307.3	54.71	2.30	4.56	20.87	33	189–191
					54.64	2.63	4.27	20.74		
IXi	F	4-CF_3	$C_{15}H_7F_4NOS_2$	357.4	50.42	1.97	3.92	17.95	31	178–179
					50.77	2.23	3.68	17.86		
Xg	Cl	4-F	$C_{14}H_7ClFNOS_2$	323.8	51.93	2.18	4.33	19.81	32	203–204
					51.58	2.14	4.22	19.99		
Xh	Cl	3-F	$C_{14}H_7ClFNOS_2$	323.8	51.93	2.18	4.33	19.81	31	213
					51.88	1.96	4.61	20.02		
Xi	Cl	4-CF_3	$C_{15}H_7ClF_3NOS_2$	373.8	48.20	1.89	4.28	17.16	30	175–176
					47.85	2.17	3.91	17.38		

250 μmol L^{-1}, 125 μmol L^{-1}, 62.5 μmol L^{-1}, 32 μmol L^{-1}, 16 μmol L^{-1}, 8 μmol L^{-1}, 4 μmol L^{-1}, 2 μmol L^{-1}, 1 μmol L^{-1}, and 0.5 μmol L^{-1}. The minimum inhibitory concentrations (MIC) were determined after incubation at 37°C for 14 days and 21 days, respectively. The tests were repeated three times.

Results and discussion

3-Phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones

Table 3. NMR spectral data of newly prepared compounds

Comp.	NMR spectral data[a]
Ia	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.54 (d, 1H, J = 2.35 Hz, H-5), 7.80 (dd, 1H, J = 8.66 Hz, J = 2.35 Hz, H-7), 7.61–7.50 (m, 3H, H-3′, H-4′, H-5′), 7.28–7.19 (m, 3-H, H-8, H-2′, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.9, 148.3, 144.5, 138.8, 138.4, 134.3, 129.9, 129.3, 127.7, 122.0, 118.8, 118.4
Ib	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.54 (d, 1H, J = 2.45 Hz, H-5), 7.80 (dd, 1H, J = 8.52 Hz, J = 2.45 Hz, H-7), 7.40–7.34 (m, AA′, BB′, 2-H, H-2′, H-6′), 7.20 (d, 1H, J = 8.52 Hz, H-8), 7.16–7.11 (m, AA′, BB′, 2-H, H-3′, H-5′), 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
Ic	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.53 (d, 1H, J = 2.40 Hz, H-5), 7.81 (dd, 1H, J = 8.82 Hz, J = 2.40 Hz, H-7), 7.56–7.49 (m, AA′, BB′, 2-H, H-2′, H-6′), 7.21 (d, overlapped, 1H, J = 8.82 Hz, H-8), 7.24–7.16 (m, AA′, BB′, 2-H, H-3′, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.7, 148.2, 144.4, 138.6, 137.1, 135.4, 134.3, 130.2, 129.2, 121.9, 119.0, 118.5
Id	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.51 (d, 1H, J = 2.41 Hz, H-5), 7.81 (dd, 1H, J = 8.83 Hz, J = 2.41 Hz, H-7), 7.51–7.47 (m, 2-H, H-2′, H-4′), 7.28–7.25 (m, 1-H, H-6′), 7.21 (d, 1H, J = 8.83 Hz, H-8), 7.18–7.12 (m, 1-H, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.5, 148.2, 144.2, 139.5, 138.6, 135.3, 134.2, 130.8, 129.7, 128.3, 126.2, 121.9, 119.0, 118.4
Ie	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.51 (d, 1H, J = 2.48 Hz, H-5), 7.82 (dd, 1H, J = 8.71 Hz, J = 2.48 Hz, H-7), 7.63 (d, 1H, J = 8.51 Hz, H-5′), 7.37 (d, 1H, J = 2.42 Hz, H-2′), 7.21 (d, 1H, J = 8.71 Hz, H-8), 7.11 (dd, 1H, J = 8.51 Hz, J = 2.42 Hz, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.4, 148.1, 144.2, 138.8, 137.5, 134.2, 133.9, 133.9, 131.5, 130.1, 127.4, 121.8, 119.1, 118.5
If	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (d, 1H, J = 2.42 Hz, H-5), 7.81 (dd, 1H, J = 8.80 Hz, J = 2.42 Hz, H-7), 7.71–7.65 (m, AA′, BB′, 2-H, H-2′, H-6′), 7.21 (d, 1H, J = 8.80 Hz, H-8), 7.16–7.09 (m, AA′, BB′, 2-H, H-3′, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.6, 148.2, 144.3, 138.6, 137.6, 134.2, 133.2, 129.5, 123.5, 121.9, 119.0, 118.5
Ig	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.53 (d, 1H, J = 2.47 Hz, H-5), 7.81 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.25–7.19 (m, 4-H, H-2′, H-3′, H-5′, H-6′), 7.21 (d, overlapped, 1H, J = 8.79 Hz, H-8) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 190.2, 162.7 (d, J = 249.9 Hz), 148.4, 144.7, 138.7, 134.7 (d, J = 3.4 Hz), 134.4, 129.8 (d, J = 8.9 Hz), 122.1, 119.0, 118.5, 117.1 (d, J = 23.2 Hz)
Ih	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (d, 1H, J = 2.47 Hz, H-5), 7.81 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.58–7.49 (m, 1H, H-6′), 7.27–7.21 (m, 1H, H-2′), 7.21 (d, overlapped, 1H, J = 8.79 Hz, H-8), 7.09–7.03 (m, 1H, H-5′), 7.00 (dt, 1H, J = 8.79 Hz, J = 2.20 Hz, H-4′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 189.7, 163.3 (d, J = 248.8 Hz), 148.3, 144.4, 139.8 (d, J = 10.0 Hz), 138.7, 134.3, 131.1 (J = 8.9 Hz), 123.8 (d, J = 3.47 Hz), 122.0, 119.1, 118.5, 116.7 (d, J = 20.9 Hz), 115.9 (d, J = 23.8 Hz)
Ii	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.36 (d, 1H, J = 2.47 Hz, H-5), 8.06 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.96–7.90 (m, AA′, BB′, 2-H, H-3′, H-5′), 7.69–7.62 (m, AA′, BB′, 2-H, H-2′, H-6′), 7.52 (d, 1H, J = 8.79 Hz, H-8) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.2, 149.2, 144.3, 143.5, 138.9, 132.8, 129.7, 129.5 (q, J = 32.1 Hz), 127.0 (q, J = 3.7 Hz), 124.2 (q, J = 272.6 Hz), 122.5, 119.5, 117.6
IIa	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.22 (d, 1H, J = 1.78 Hz, H-5), 7.60–7.47 (m, 4H, H-7, H-3′, H-4′, H-5′), 7.29–7.24 (m, 2H, H-2′, H-6′), 7.20 (d, 1H, J = 8.24 Hz, H-8), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 192.1, 147.6, 145.3, 139.2, 137.1, 135.9, 131.8, 129.8, 129.2, 127.9, 120.5, 116.3, 20.8
IIb	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.22 (d, 1H, J = 1.92 Hz, H-5), 7.52 (dd, 1H, J = 8.24 Hz, J = 1.92 Hz, H-7), 7.40–7.33 (m, AA′, BB′, 2H, H-2′, H-6′), 7.20 (d, 1H, J = 8.24 Hz, H-8), 7.17–7.12 (m, AA′, BB′, 2H, H-3′, H-5′), 2.45 (bs, 6H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 192.2, 147.6, 145.4, 139.3, 137.0, 136.6, 135.9, 131.8, 130.6, 127.5, 120.5, 116.3, 21.4, 20.8
IIc	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.20 (d, 1H, J = 1.62 Hz, H-5), 7.57–7.49 (m, 3H, H-7, H-2′, H-6′), 7.24–7.16 (m, 3H, H-8, H-3′, H-5′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 191.9, 147.5, 145.1, 137.5, 137.2, 136.1, 135.2, 131.7, 130.1, 129.4, 120.4, 116.3, 20.8
IId	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.21–8.18 (m, 1H, H-5), 7.54 (ddd, 1H, J = 8.24 Hz, J = 2.20 Hz, J = 0.57 Hz, H-7), 7.50–7.45 (m, 2H, H-2′, H-6′), 7.29–7.27 (m, 1H, H-5′), 7.20 (d, overlapped, 1H, J = 8.24 Hz, H-8), 7.20–7.14 (m, 1H, H-4′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 191.7, 147.5, 145.0, 140.0, 137.3, 136.1, 135.3, 131.7, 130.7, 129.6, 128.5, 126.4, 120.3, 116.3, 20.8
IIe	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.20–8.17 (m, 1H, H-5), 7.62 (d, 1H, J = 8.52 Hz, H-5′), 7.54 (dd, 1H, J = 8.52 Hz, J = 2.20 Hz, H-7), 7.38 (d, 1H, J = 2.47 Hz, H-2′), 7.20 (d, 1H, J = 8.52 Hz, H-8), 7.12 (dd, 1H, J = 8.52 Hz, J = 2.47 Hz, H-6′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 191.6, 147.5, 145.0, 138.0, 137.4, 136.2, 133.8, 133.8, 131.7, 131.5, 130.3, 127.6, 120.3, 116.4, 20.8

Table 3. (continued)

Comp.	NMR spectral data[a]
IIf	^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ: 8.21–8.19 (m, 1H, H-5), 7.71–7.64 (m, AA′, BB′, 2H, H-2′, H-6′), 7.54 (m, 1H, H-7), 7.20 (d, 1H, J = 8.24 Hz, H-8), 7.17–7.11 (m, AA′, BB′, 2H, H3′, H5′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ: 191.8, 147.5, 145.1, 138.1, 137.3, 136.1, 133.1, 131.7, 129.7, 123.3, 120.4, 116.3, 20.8
IIg	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.20 (d, 1H, J = 2.20 Hz, H-5), 7.53 (dd, 1H, J = 8.24 Hz, J = 2.20 Hz, H-7), 7.25–7.22 (m, 4H, H-2′ H-3′, H-5′, H-6′), 7.20 (d, 1H, J = 8.24 Hz, H-8), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 192.1, 162.6 (d, J = 249.4 Hz), 147.5, 145.3, 137.2, 136.0, 135.0 (d, J = 3.5 Hz), 131.8, 129.9 (d, J = 8.8 Hz), 120.4, 117.0 (d, J = 23.2 Hz), 116.3, 20.8
IIh	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.22–8.19 (m, 1H, H-5), 7.57–7.48 (m, 2H, H-7, H-6′), 7.25–7.17 (m, 1H, H-2′), 7.20 (d, overlapped, 1H, J = 8.52 Hz, H-8), 7.09–7.04 (m, 1H, H-5′), 7.01 (dd, 1H, J = 8.79 Hz, J = 2.19 Hz, H-4′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.7, 163.2 (d, J = 248.8 Hz), 147.5, 145.0, 140.2 (d, J = 10.3 Hz), 137.2, 136.1, 131.7, 131.0 (d, J = 8.9 Hz), 123.9 (d, J = 3.4 Hz), 120.4, 116.5 (d, J = 20.9 Hz), 115.9 (d, J = 23.8 Hz), 20.8
IIi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.13–8.08 (m, 1H, H-5), 7.96–7.88 (m, AA′, BB′, 2H, H-3′, H-5′), 7.70–7.62 (m, AA′, BB′ overlapped, 2H, H-2′, H-6′), 7.70 (dd, overlapped, 1H, J = 8.52 Hz, J = 2.20 Hz, H-7), 7.40 (d, 1H, J = 8.51 Hz, H-8), 2.41 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.7, 148.1, 144.8, 143.8, 137.6, 135.5, 130.8, 129.8, 129.3 (q, J = 31.8 Hz), 126.8 (q, J = 3.8 Hz), 124.2 (q, J = 272.6 Hz), 120.6, 116.7, 20.5
IIIa	^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.83 (d, 1H, J = 2.74 Hz, H-5), 7.64–7.45 (m, 3H, H-7, H-2′, H-6′), 7.37–7.19 (m, 4H, H-8, H-3′, H-4′, H-5′), 3.90 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.7, 157.1, 143.9, 139.3, 130.0, 129.9, 129.3, 127.9, 125.3, 125.0, 117.9, 112.5, 56.0
IIIb	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.74–7.70 (m, 1H, H-5), 7.56–7.35 (m, 3H, H-7, H-2′, H-6′), 7.33–7.20 (m, 3H, H-8, H-3′, H-5′), 3.83 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.5, 156.5, 144.3, 138.2, 137.8, 130.0, 129.5, 128.1, 124.4, 121.3, 118.3, 112.6, 56.1, 21.0
IIIc	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.72–7.70 (m, 1H, H5), 7.64–7.55 (m, AA′, BB′, 2H, H-2′, H-6′), 7.49–7.39 (m, 4H, H-7, H-8, H-3′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.4, 156.5, 144.8, 144.3, 139.2, 133.5, 130.5, 129.7, 124.6, 121.9, 118.3, 112.5, 56.1
IIId	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.73–7.69 (m, 1H, H5), 7.59–7.50 (m, 3H, H-7, H-2′, H-6′), 7.48–7.38 (m, 3H, H-8, H-4′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.3, 156.6, 144.8, 144.2, 141.5, 133.5, 131.2, 129.0, 128.6, 127.6, 124.6, 121.3, 118.3, 112.5, 56.1
IIIe	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.83 (d, 1H, J = 8.52 Hz, H-5′), 7.79 (d, 1H, J = 2.20 Hz, H-5), 7.72–7.70 (m, 1H, H-2′), 7.50–7.43 (m, 3H, H-7, H-8, H-6′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.3, 156.6, 144.7, 144.2, 140.0, 131.8, 131.8, 131.7, 130.8, 129.4, 124.7, 121.2, 118.4, 112.4, 56.1
IIIf	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.75–7.69 (m, 3H, H-5, H-2′, H-6′), 7.47–7.44 (m, 2H, H-7, H-8), 7.40–7.34 (m, 2H, H-3′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.4, 156.5, 144.8, 144.3, 139.6, 132.7, 130.8, 124.6, 122.1, 121.3, 118.3, 112.5, 56.1
IIIg	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.71 (dd, 1H, J = 2.47 Hz, J = 0.82 Hz, H-5), 7.50–7.41 (m, 4H, H-7, H-8, H-2′, H-6′), 7.40–7.31 (m, 2H, H-3′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 193.1, 162.4 (d, J = 245.1 Hz), 157.0, 145.4, 144.7, 137.0 (d, J = 3.2 Hz), 131.2 (d, J = 8.9 Hz), 125.0, 121.8, 118.9, 117.0 (d, J = 23.2 Hz), 113.1, 56.6
IIIh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.73–7.70 (m, 1H, H-5), 7.62–7.42 (m, 3H, H-7, H-2′, H-6′), 7.38–7.24 (m, 3H, H-8, H-4′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.3, 162.6 (d, J = 244.0 Hz), 156.6, 144.7, 144.2, 141.5 (d, J = 10.9 Hz), 131.2 (d, J = 8.9 Hz), 125.0, 124.6, 121.3, 118.3, 116.0 (d, J = 22.3 Hz), 112.5, 56.1
IIIi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.98–7.88 (m, AA′, BB′, 2H, H-3′, H-5′), 7.74–7.70 (m, 1H, H-5), 7.70–7.64 (m, AA′, BB′, 2H, H-2′, H-6′), 7.49–7.46 (m, 2H, H-7, H-8), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 192.3, 156.6, 144.8, 144.3, 143.9, 129.8, 129.3 (q, J = 32.1 Hz), 126.8 (q, J = 3.8 Hz), 124.7, 124.2 (q, J = 272.3 Hz), 121.3, 118.4, 112.4, 56.1
IVa	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.97 (dd, 1H, J = 9.1 Hz, J = 3.0 Hz, H-5), 7.80–7.71 (m, 1H, H-7), 7.60–7.53 (m, 1H, H-8), 7.53–7.47 (m, 2H, H-2′, H-6′), 7.47–7.40 (m, 1H, H-4′), 7.40–7.34 (m, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.5 (d, J = 3.2 Hz), 158.8 (d, J = 241.6 Hz), 146.3 (d, J = 1.7 Hz), 144.6, 140.0, 129.6, 129.0, 128.3, 123.8 (d, J = 24.9 Hz), 122.0 (d, J = 8.9 Hz), 119.4 (d, J = 8.6 Hz), 116.2 (d, J = 26.6 Hz)

Table 3. (continued)

Comp.	NMR spectral data[a]
IVb	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.96 (dd, 1H, J = 9.2 Hz, J = 3.0 Hz, H-5), 7.78–7.69 (m, 1H, H-7), 7.54 (dd, 1H, J = 9.2 Hz, J = 4.4 Hz, H-8), 7.33–7.27 (m, AA′, BB′, 2H, H-2′, H-6′), 7.26–7.21 (m, AA′, BB′, 2H, H-3′, H-5′), 2.36 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.5 (d, J = 2.9 Hz), 158.7 (d, J = 241.9 Hz), 146.2 (d, J = 1.7 Hz), 144.7, 138.4, 137.5, 130.1, 127.9, 123.8 (d, J = 24.9 Hz), 122.0 (d, J = 8.9 Hz), 119.3 (d, J = 8.3 Hz), 116.2 (d, J = 26.6 Hz), 21.2
IVc	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.97 (dd, 1H, J = 9.1 Hz, J = 3.0 Hz, H-5), 7.80–7.71 (m, 1H, H-7), 7.62–7.53 (m, 3H, H-8, H-2′, H-6′), 7.46–7.39 (m, 2H, AA′, BB′, H3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.5 (d, J = 3.1 Hz), 158.8 (d, J = 242.2 Hz), 146.2 (d, J = 1.4 Hz), 144.5, 138.9, 133.6, 130.3, 129.8, 123.9 (d, J = 24.6 Hz), 121.9 (d, J = 8.8 Hz), 119.4 (d, J = 8.3 Hz), 116.2 (d, J = 26.6 Hz)
IVd	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.97 (dd, 1H, J = 9.1 Hz, J = 3.0 Hz, H-5), 7.81–7.72 (m, 1H, H-7), 7.62–7.50 (m, 4H, H-8, H-2′, H-5′, H-6′), 7.42–7.36 (m, 1H, H-4′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.4 (d, J = 2.9 Hz), 158.8 (d, J = 242.2 Hz), 146.2 (d, J = 1.7 Hz), 144.5, 141.2, 133.5, 131.3, 129.2, 128.4, 127.4, 124.0 (d, J = 24.7 Hz), 121.9 (d, J = 8.9 Hz), 119.4 (d, J = 8.3 Hz), 116.2 (d, J = 26.6 Hz)
IVe	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.98 (dd, 1H, J = 9.1 Hz, J = 3.0 Hz, H-5), 7.82 (d, 1H, J = 8.7 Hz, H-5′), 7.81–7.73 (m, 2H, H-7, H-2′), 7.59 (dd, 1H, J = 9.1 Hz, J = 4.4 Hz, H8), 7.44 (dd, 1H, J = 8.7 Hz, J = 2.2 Hz, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.4 (d, J = 3.1 Hz), 158.8 (d, J = 242.5 Hz), 146.2 (d, J = 1.4 Hz), 144.4, 139.7, 132.0, 131.8, 131.7, 130.6, 129.2, 124.2 (d, J = 24.9 Hz), 121.9 (d, J = 8.9 Hz), 119.5 (d, J = 8.3 Hz), 116.1 (d, J = 26.6 Hz)
IVf	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.97 (dd, 1H, J = 9.1 Hz, J = 3.3 Hz, H-5), 7.81–7.68 (m, 3H, H-7, H-2′, H-6′), 7.57 (dd, 1H, J = 9.1 Hz, J = 4.4 Hz, H-8), 7.39–7.33 (m, AA′, BB′, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.4 (d, J = 3.2 Hz), 158.8 (d, J = 241.9 Hz), 146.2 (d, J = 1.7 Hz), 144.5, 139.3, 132.7, 130.6, 124.0 (d, J = 24.6 Hz), 122.2, 121.9 (d, J = 8.8 Hz), 119.4 (d, J = 8.6 Hz), 116.2 (d, J = 26.6 Hz)
IVg	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.98 (dd, 1H, J = 9.07 Hz, J = 3.02 Hz, H-5), 7.82–7.73 (m, 1H, H-7), 7.59 (dd, 1H, J = 9.06 Hz, J = 4.39 Hz, H-8), 7.50–740 (m, 2H, H-2′, H-6′), 7.40–7.30 (m, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.9, 162.0 (d, J = 245.1 Hz), 158.8 (d, J = 242.2 Hz), 146.3 (d, J = 3.2 Hz), 144.7 (d, J = 2.0 Hz), 136.3 (d, J = 3.2 Hz), 130.6 (d, J = 9.2 Hz), 123.9 (d, J = 24.6 Hz), 122.0 (d, J = 8.9 Hz), 119.4 (d, J = 8.6 Hz), 116.6 (d, J = 23.2 Hz), 116.2 (d, J = 26.3 Hz)
IVh	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00 (dd, 1H, J = 8.52 Hz, J = 3.02 Hz, H-5), 7.58–7.40 (m, 2H, H-7, H-6′), 7.31 (dd, 1H, J = 9.07 Hz, J = 4.12 Hz, H-8), 7.22 (ddd, 1H, J = 8.52 Hz, J = 2.47 Hz, J = 0.82 Hz, H-2′), 7.09–7.04 (m, 1H, H-5′), 7.01 (dt, 1H, J = 8.51 Hz, J = 2.20 Hz, H-4′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 190.1, 163.3 (d, J = 248.9 Hz), 159.7 (d, J = 246.8 Hz), 145.5 (d, J = 2.0 Hz), 144.6, 140.0 (d, J = 10.0 Hz), 131.1 (d, J = 8.8 Hz), 123.8 (d, J = 1.7 Hz), 123.7 (d, J = 23.5 Hz), 121.7 (d, J = 8.9 Hz), 118.7 (d, J = 8.3 Hz), 117.4 (d, J = 26.6 Hz), 116.7 (d, J = 20.9 Hz), 115.9 (d, J = 23.7 Hz)
IVi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.99 (dd, 1H, J = 9.07 Hz, J = 3.30 Hz, H-5), 7.96–7.90 (m, AA′, BB′, 2H, H-3′, H-5′), 7.84–7.75 (m, 1H, H-7), 7.70–7.64 (m, AA′, BB′, 2H, H-2′, H-6′), 7.62 (dd, 1H, J = 9.06 Hz, J = 4.39 Hz, H-8) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.6 (d, J = 3.1 Hz), 158.9 (d, J = 242.5 Hz), 146.4 (d, J = 1.7 Hz), 144.5, 143.7, 129.7, 129.4 (q, J = 32.1 Hz), 126.9 (d, J = 4.0 Hz), 124.2 (q, J = 272.6 Hz), 124.1 (d, J = 24.9 Hz), 122.0 (d, J = 8.9 Hz), 119.5 (d, J = 8.6 Hz), 116.1 (d, J = 26.6 Hz)
Vg	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.24–8.21 (m, 1H, H-5), 7.97–7.91 (m, 1H, H-7), 7.64–7.52 (m, 1H, H-8), 7.38–7.23 (m, 4H, H-2′, H-3′, H-5′, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.6, 162.0 (d, J = 245.1 Hz), 148.7, 144.5, 136.2 (d, J = 3.1 Hz), 136.0, 130.6 (d, J = 8.9 Hz), 130.0, 129.8, 122.2, 119.3, 116.6 (d, J = 23.2 Hz)
Vh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.24 (m, 1H, H5), 7.96–7.91 (m, 1H, H-7), 7.65–7.53 (m, 2H, H-2′, H-6′), 7.39–7.23 (m, 3H, H-8, H-4′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.2, 162 (d, J = 244.2 Hz), 148.6, 144.3, 141.2 (d, J = 10.9 Hz), 136.1, 131.3 (d, J = 8.8 Hz), 129.9, 124.8 (d, J = 3.2 Hz), 122.1, 119.3, 116.2 (d, J = 20.7 Hz), 115.8 (d, J = 23.8 Hz)
Vi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.24–8.22 (m, 1H, H-5), 7.97–7.91 (m, 3H, H-7, H-3′, H-5′), 7.70–7.62 (m, 2H, H-2′, H-6′), 7.59 (d, 1H, J = 8.79 Hz, H-8) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 191.3, 148.7, 144.3, 143.5, 136.1, 129.9, 129.8, 129.7, 129.5 (q, J = 32.1 Hz), 126.9 (d, J = 3.8 Hz), 124.2 (q, J = 272.3 Hz), 122.1, 119.3
VIa	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.45 (d, 1H, J = 2.51 Hz, H-5), 7.81 (dd, 1H, J = 8.82 Hz, J = 2.51 Hz, H-7), 7.61–7.48 (m, 3H, H-3′, H-4′, H-5′), 7.29–7.18 (m, 3H, H-8, H-2′, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.4, 176.9, 148.5, 143.0, 138.6, 134.2, 130.0, 129.1, 127.6, 123.3, 119.5, 118.0
VIb	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.45 (d, 1H, J = 2.40 Hz, H-5), 7.81 (dd, 1H, J = 8.77 Hz, J = 2.40 Hz, H-7), 7.39–7.34 (m, AA′, BB′, 2H, H-2′, H-6′), 7.25 (d, 1H, J = 8.77 Hz, H-8), 7.12–7.06 (m, AA′, BB′, 2H, H-3′, H-5′), 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

Table 3. (continued)

Comp.	NMR spectral data[a]
VIc	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.44 (d, 1H, J = 2.43 Hz, H-5), 7.82 (dd, 1H, J = 8.77 Hz, J = 2.43 Hz, H-7), 7.55–7.49 (m, 2H, H-2′, H-6′), 7.26 (d, 1H, J = 8.77 Hz, H-8), 7.17–7.11 (m, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.3, 176.7, 148.5, 141.3, 138.8, 135.1, 134.2, 130.4, 129.1, 123.2, 119.6, 118.1
VId	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.43 (d, 1H, J = 2.43 Hz, H-5), 7.82 (dd, 1H, J = 8.80 Hz, J = 2.43 Hz, H-7), 7.51–7.45 (m, 2H, H-2′, H-4′), 7.25 (d, 1H, J = 8.80 Hz, H-8), 7.23–7.21 (m, 1H, H-6′), 7.14–7.08 (m, 1H, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.1, 176.5, 148.4, 143.6, 138.8, 135.4, 134.1, 130.9, 129.4, 128.2, 126.1, 123.1, 119.6, 118.1
VIe	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.43 (d, 1H, J = 2.46 Hz, H-5), 7.83 (dd, 1H, J = 8.76 Hz, J = 2.46 Hz, H-7), 7.62 (d, 1H, J = 8.70 Hz, H-5′), 7.32 (d, 1H, J = 2.45 Hz, H-2′), 7.25 (d, 1H, J = 8.76 Hz, H-8), 7.06 (dd, 1H, J = 8.70 Hz, J = 2.45 Hz, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.1, 176.4, 148.4, 141.6, 138.9, 134.1, 134.0, 133.6, 131.7, 130.0, 127.4, 123.0, 119.7, 118.1
VIf	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.44 (d, 1H, J = 2.38 Hz, H-5), 7.82 (dd, 1H, J = 8.80 Hz, J = 2.38 Hz, H-7), 7.70–7.66 (m, AA′, BB′, 2H, H-2′, H-6′), 7.25 (d, 1H, J = 8.80 Hz, H-8), 7.10–7.06 (m, AA′, BB′, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.3, 176.6, 148.5, 141.8, 138.8, 134.2, 133.4, 130.0, 129.5, 123.2, 119.6, 118.1
VIg	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.44 (d, 1H, J = 2.47 Hz, H-5), 7.82 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.29–7.13 (m, 5H, H-8, H-2′ H-3′, H-5′, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.7, 177.1, 162.5 (d, J = 249.9 Hz), 148.6, 138.9, 138.9, 134.3, 129.7 (d, J = 8.9 Hz), 123.3, 119.7, 118.1, 117.3 (d, J = 23.5 Hz)
VIh	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.43 (d, 1H, J = 2.47 Hz, H-5), 7.82 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.57–7.48 (m, 1H, H-6′), 7.26 (d, overlapped, 1H, J = 8.79 Hz, H-8), 7.25–7.17 (m, 1H, H-2′), 7.04–6.99 (m, 1H, H-5′), 6.96 (dt, 1H, J = 8.52 Hz, J = 2.20 Hz, H-4′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.4, 176.7, 163.5 (d, J = 248.8 Hz), 148.6, 144.1 (d, J = 10.3 Hz), 138.9, 134.2, 131.3 (d, J = 8.9 Hz), 123.8 (d, J = 3.4 Hz), 123.3, 119.7, 118.2, 116.5 (d, J = 20.9 Hz), 115.8 (d, J = 24.1 Hz)
VIi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.28 (d, 1H, J = 2.47 Hz, H-5), 8.09 (dd, 1H, J = 8.79 Hz, J = 2.48 Hz, H-7), 7.96–7.89 (m, AA′, BB′, 2H, H-3′, H-5′), 7.65–7.59 (m, AA′, BB′ overlapped, 2H, H-2′, H-6′), 7.60 (d, overlapped, 1H, J = 8.79 Hz, H-8) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 186.9, 177.6, 149.2, 147.1, 139.2, 132.2, 129.5, 129.3 (q, J = 32.1 Hz), 127.2 (q, J = 3.7 Hz), 124.2 (q, J = 278.6 Hz), 124.0, 119.1, 118.7
VIIa	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.16–8.13 (m, 1H, H-5), 7.62–7.46 (m, 4H, H-7, H-3′, H-4′, H-5′), 7.29–7.19 (m, 3H, H-8, H-2′, H-6′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.6, 178.0, 148.0, 143.4, 137.2, 136.8, 131.6, 129.9, 129.0, 127.9, 121.9, 116.0, 20.9
VIIb	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.15–8.13 (m, 1H, H-5), 7.57–7.52 (m, 1H, H-7), 7.40–7.32 (m, AA′, BB′, 2H, H-2′, H-6′), 7.26 (d, 1H, J = 8.52 Hz, H-8), 7.14–7.07 (m, AA′, BB′, 2H, H-3′, H-5′), 2.46 (s, 3H, CH_3), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.7, 178.1, 148.0, 140.9, 139.1, 137.2, 136.7, 131.7, 130.7, 127.5, 121.9, 116.0, 21.4, 20.9
VIIc	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.14–8.11 (m, 1H, H-5), 7.55 (dd, 1H, J = 8.52 Hz, J = 2.20 Hz, H-7), 7.54–7.49 (m, AA′, BB′, 2H, H-2′, H-6′), 7.26 (d, 1H, J = 7.51 Hz, H-8), 7.18–7.12 (m, AA′, BB′, 2H, H-3′, H-5′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.5, 177.8, 148.0, 141.7, 137.4, 136.9, 134.9, 131.6, 130.3, 129.4, 121.7, 116.0, 20.9
VIId	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.14–8.11 (m, 1H, H-5), 7.58–7.53 (m, 1H, H-7), 7.51–7.43 (m, 2H, H-2′, H-6′), 7.26 (d, 1H, J = 8.51 Hz, H-8), 7.25–7.22 (m, 1H, H-5′), 7.15–7.10 (m, 1H, H-4′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.3, 177.6, 148.0, 144.0, 137.4, 136.9, 135.4, 131.6, 130.9, 129.3, 128.5, 126.4, 121.7, 116.1, 20.9
VIIe	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.12–8.10 (m, 1H, H-5), 7.61 (d, 1H, J = 8.52 Hz, H-5′), 7.59–7.54 (m, 1H, H-7), 7.33 (d, 1H, J = 2.47 Hz, H-2′), 7.26 (d, 1H, J = 8.24 Hz, H-8), 7.08 (dd, 1H, J = 8.52 Hz, J = 2.47 Hz, H-6′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.3, 177.5, 148.0, 142.1, 137.6, 137.1, 134.0, 133.5, 131.7, 131.6, 130.3, 127.7, 121.6, 116.1, 21.0
VIIf	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.14–8.11 (m, 1H, H-5), 7.71–7.64 (m, AA′, BB′, 2H, H-2′, H-6′), 7.55 (ddd, 1H, J = 8.38 Hz, J = 2.19 Hz, J = 0.55 Hz, H-7), 7.26 (d, 1H, J = 8.38 Hz, H-8), 7.12–7.06 (m, AA′, BB′, 2H, H-3′, H-5′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.4, 177.7, 148.0, 142.2, 137.4, 136.9, 133.3, 131.6, 129.7, 123.1, 121.8, 116.1, 21.0
VIIg	^{1}H NMR (300 MHz, ($CDCl_3$), δ: 8.14–8.11 (m, 1H, H5), 7.55 (ddd, 1H, J = 8.52 Hz, J = 2.20 Hz, J = 0.50 Hz, H-7), 7.27–7.15 (m, 4H, H-2′ H-3′, H-5′, H-6′), 7.25 (d, overlapped, 1H, J = 8.52 Hz, H-8), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 187.7, 178.0, 162.4 (d, J = 249.6 Hz), 148.0, 139.2 (d, J = 3.5 Hz), 137.3, 136.9, 131.7, 129.8 (d, J = 8.6 Hz), 121.8, 117.1 (d, J = 23.2 Hz), 116.0, 20.9
VIIh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.14–8.11 (m, 1H, H-5), 7.58–7.47 (m, 2H, H-2′, H-6′), 7.25 (d, 1H, J = 8.24 Hz, H-8), 7.20 (tdd, 1H, J = 8.24 Hz, J = 2.47 Hz, J = 0.82 Hz, H-5′), 7.05–7.00 (m, 1H, H-7), 6.97 (dt, 1H, J = 8.79 Hz, J = 2.20 Hz, H-4′), 2.45 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.3, 177.5, 163.5 (d, J = 248.6 Hz), 148.0, 144.2 (d, J = 10.3 Hz), 137.4, 136.9, 131.5, 131.1 (d, J = 8.9 Hz), 123.9 (d, J = 3.1 Hz), 121.7, 116.2 (d, J = 26.0 Hz), 116.1 (d, J = 23.8 Hz), 20.9

Table 3. (continued)

Comp.	NMR spectral data[a]
VIIi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.05–8.02 (m, 1H, H-5), 7.95–7.87 (m, AA′, BB′, 2H, H-3′, H-5′), 7.74 (dd, 1H, J = 8.38 Hz, J = 2.20 Hz, H-7), 7.66–7.59 (m, AA′, BB′, 2H, H-2′, H-6′), 7.49 (d, 1H, J = 8.38 Hz, H-8), 2.42 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 188.3, 178.1, 148.3, 147.3, 137.9, 136.7, 130.7, 129.7, 129.1 (q, J = 32.1 Hz), 127.1 (q, J = 3.8 Hz), 124.2 (q, J = 272.3 Hz), 122.1, 116.3, 20.6
VIIIa	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.63 (d, 1H, J = 2.74 Hz, H-5), 7.57–7.46 (m, 4H, H-7, H-8, H-2′, H-6′), 7.45–7.30 (m, 3H, H-3′, H-4′, H-5′), 3.84 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.9, 178.0, 157.3, 144.8, 144.1, 129.8, 128.8, 128.2, 124.9, 122.9, 118.2, 112.2, 56.2
VIIIb	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.61 (d, 1H, J = 2.75 Hz, H-5), 7.56–7.44 (m, 2H, H-7, H-8), 7.33–7.25 (m, AA′, BB′, 2H, H-2′, H-6′), 7.23–7.15 (m, AA′, BB′, 2H, H-3′, H-5′), 3.84 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.9, 178.0, 157.3, 144.7, 141.6, 138.1, 130.4, 127.9, 124.9, 122.9, 118.1, 112.3, 56.1, 21.1
VIIIc	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.64–7.47 (m, 5H, H-5, H-7, H-8, H-2′, H-6′), 7.42–7.36 (m, AA′, BB′, 2H, H-3′, H-5′), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 188.0, 177.9, 157.3, 144.8, 142.9, 133.3, 130.4, 130.0, 125.0, 122.9, 118.2, 112.1, 56.2
VIIId	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.62 (d, 1H, J = 2.75 Hz, H5), 7.59–7.46 (m, 5H, H-7, H-8, H-2′, H-5′, H-6′), 7.39–7.33 (m, 1H, H-4′), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.9, 177.9, 157.3, 145.1, 144.7, 133.7, 131.5, 128.9, 128.5, 127.4, 125.0, 122.9, 118.2, 112.1, 56.2
VIIIe	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.82 (d, 1H, J = 8.79 Hz, H-5′), 7.77 (d, 1H, J = 2.19 Hz, H-5), 7.62 (d, 1H, J = 3.03 Hz, H-2′), 7.58 (d, 1H, J = 8.52 Hz, H-8), 7.52 (dd, 1H, J = 8.79 Hz, J = 3.02 Hz, H-6′), 7.43 (dd, 1H, J = 8.52 Hz, J = 2.20 Hz, H-7), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.9, 177.8, 157.4, 144.7, 143.6, 132.0, 131.9, 131.6, 130.7, 129.2, 125.1, 122.9, 118.2, 112.1, 56.2
VIIIf	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.75–7.69 (m, AA′, BB, 2H, H-2′, H-6′), 7.62 (d, 1H, J = 2.75 Hz, H-5), 7.56 (dd, 1H, J = 9.07 Hz, J = 0.55 Hz, H-8), 7.50 (dd, 1H, J = 9.06 Hz, J = 2.75 Hz, H-7), 7.36–7.30 (m, AA′, BB′, 2H, H-3′, H-5′), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.9, 177.9, 157.3, 144.8, 143.4, 133.0, 130.7, 125.0, 122.9, 121.9, 118.2, 112.1, 56.2
VIIIg	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.62 (d, 1H, J = 3.02 Hz, H5), 7.58–7.47 (m, 2H, H-2′, H-6′), 7.44–7.32 (m, 4H, H-7, H-8, H-3′, H-5′), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 188.1, 178.1, 161.9 (d, J = 245.3 Hz), 157.3, 144.7, 140.4 (d, J = 3.1 Hz), 130.5 (d, J = 8.9 Hz), 125.0, 122.9, 118.2, 116.8 (d, J = 23.2 Hz), 112.2, 56.2
VIIIh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.63 (d, 1H, J = 3.03 Hz, H-5), 7.61–7.54 (m, 2H, H-2′, H-6′), 7.51 (dd, overlapped, 1H, J = 9.07 Hz, J = 3.03 Hz, H7), 7.36–7.20 (m, 3H, H-8, H-4′, H-5′), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.8, 177.8, 162.9 (d, J = 243.9 Hz), 157.3, 145.2 (d, J = 11.2 Hz), 144.7, 131.5 (d, J = 8.8 Hz), 124.9 (d, J = 16.1 Hz), 124.9, 122.9, 118.2, 116.0 (d, J = 22.6 Hz), 112.1, 56.2
VIIIi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.95–7.88 (m, AA′, BB′, 2H, H-3′, H-5′), 7.67–7.60 (m, AA′, BB′ overlapped, 2H, H-2′, H-6′), 7.61 (d, overlapped, 1H, J = 9.48 Hz, H-8), 7.56 (bs, 1H, H-5), 7.52 (dd, 1H, J = 9.48 Hz, J = 3.02 Hz, H-7), 3.85 (s, 3H, OCH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 188.0, 177.8, 157.4, 147.4, 144.8, 129.7, 129.1 (q, J = 31.8 Hz), 127.1 (q, J = 3.8 Hz), 125.1, 124.2 (q, J = 272.3 Hz), 123.0, 118.2, 112.0, 56.2
IXa	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.97 (dd, 1H, J = 8.8 Hz, J = 3.0 Hz, H-5), 7.83–7.74 (m, 1H, H-7), 7.68–7.62 (m, 1H, H-8), 7.55–7.46 (m, 2H, H-2′, H-6′), 7.45–7.37 (m, 1H, H-4′), 7.36–7.29 (m, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.1 (d, J = 3.1 Hz), 177.8, 159.3 (d, J = 243.4 Hz), 146.5 (d, J = 1.4 Hz), 143.8, 129.9, 128.9, 128.1, 124.2 (d, J = 24.9 Hz), 123.6 (d, J = 9.1 Hz), 119.2 (d, J = 8.5 Hz), 116.2 (d, J = 26.6 Hz)
IXb	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.87 (dd, 1H, J = 8.9 Hz, J = 3.0 Hz, H-5), 7.81–7.72 (m, 1H, H-7), 7.63 (dd, 1H, J = 8.9 Hz, J = 4.4 Hz, H-8), 7.33–7.26 (m, AA′, BB′, 2H, H-2′, H-6′), 7.21–7.15 (m, AA′, BB′, 2H, H-3′, H-5′), 2.35 (s, 3H, CH_3) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.0 (d, J = 3.2 Hz), 177.8, 159.3 (d, J = 243.4 Hz), 146.4 (d, J = 1.4 Hz), 141.3, 138.3, 130.4, 127.7, 124.2 (d, J = 24.9 Hz), 123.5 (d, J = 9.2 Hz), 119.2 (d, J = 8.3 Hz), 116.3 (d, J = 26.6 Hz), 21.2
IXc	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.89 (dd, 1H, J = 8.9 Hz, J = 3.0 Hz, H-5), 7.83–7.75 (m, 1H, H-7), 7.66 (dd, 1H, J = 8.9 Hz, J = 4.4 Hz, H-8), 7.62–7.54 (m, AA′, BB′, 2H, H-2′, H-6′), 7.42–7.33 (m, AA′, BB′, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.1 (d, J = 3.2 Hz), 177.7, 159.3 (d, J = 243.6 Hz), 146.5 (d, J = 1.4 Hz), 142.6, 133.4, 130.2, 130.1, 124.3 (d, J = 24.9 Hz), 123.5 (d, J = 9.1 Hz), 119.2 (d, J = 8.6 Hz), 116.2 (d, J = 26.6 Hz)

Table 3. (continued)

Comp.	NMR spectral data[a]
IXd	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.90 (dd, 1H, J = 9.0 Hz, J = 3.0 Hz, H-5), 7.84–7.75 (m, 1H, H-7), 7.67 (dd, 1H, J = 9.0 Hz, J = 4.4 Hz, H-8), 7.60–7.46 (m, 3H, H-2′, H-5′, H-6′), 7.38–7.32 (1H, m, H-4′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.1 (d, J = 3.2 Hz), 177.7, 159.4 (d, J = 243.6 Hz), 146.5 (d, J = 1.7 Hz), 144.8, 133.8, 131.6, 129.1, 128.3, 127.3, 124.4 (d, J = 25.2 Hz), 123.5 (d, J = 9.2 Hz), 119.3 (d, J = 8.6 Hz), 116.2 (d, J = 26.6 Hz)
IXe	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.91 (dd, 1H, J = 9.1 Hz, J = 2.8 Hz, H-5), 7.86–7.77 (m, 2H, H-7, H-5′), 7.74 (d, 1H, J = 2.3 Hz, H-2′), 7.68 (dd, 1H, J = 9.1 Hz, J = 4.4 Hz, H-8), 7.41 (dd, 1H, J = 8.5 Hz, J = 2.3 Hz, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.1 (d, J = 3.2 Hz), 177.7, 159.4 (d, J = 244.0 Hz), 146.4 (d, J = 1.4 Hz), 143.3, 132.1, 132.0, 131.8, 130.5, 129.1, 124.5 (d, J = 24.9 Hz), 123.5 (d, J = 9.1 Hz), 119.3 (d, J = 8.3 Hz), 116.2 (d, J = 26.6 Hz)
IXf	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.89 (dd, 1H, J = 8.9 Hz, J = 3.3 Hz, H-5), 7.83–7.75 (m, 1H, H-7), 7.75–7.69 (m, AA′, BB′, 2H, H-2′, H-6′), 7.66 (dd, 1H, J = 8.9 Hz, J = 4.1 Hz, H-8), 7.36–7.27 (m, AA′, BB′, 2H, H-3′, H-5′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.0 (d, J = 3.1 Hz), 177.6, 159.3 (d, J = 243.7 Hz), 146.5 (d, J = 1.4 Hz), 143.1, 133.0, 130.5, 124.3 (d, J = 24.9 Hz), 123.5 (d, J = 9.1 Hz), 122.0, 119.2 (d, J = 8.3 Hz), 116.2 (d, J = 26.6 Hz)
IXg	^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00 (dd, 1H, J = 8.52 Hz, J = 3.02 Hz, H-5), 7.50–7.42 (m, 1H, H-7), 7.37 (dd, 1H, J = 9.07 Hz, J = 4.40 Hz, H-8), 7.28–7.14 (m, 4H, H-2′, H-3′, H-5′, H-6′) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 186.2 (d, J = 3.2 Hz), 177.3, 162.5 (d, J = 249.9 Hz), 160.0 (d, J = 247.9 Hz), 146.0, 139.0 (d, J = 3.4 Hz), 129.7 (d, J = 8.8 Hz), 123.8 (d, J = 24.9 Hz), 123.2 (d, J = 8.8 Hz), 118.5 (d, J = 8.3 Hz), 117.4 (d, J = 26.6 Hz), 117.3 (d, J = 23.2 Hz)
IXh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.00 (dd, 1H, J = 8.52 Hz, J = 3.02 Hz, H-5), 7.57–7.42 (m, 2H, H-2′, H-6′), 7.37 (dd, 1H, J = 9.06 Hz, J = 4.40 Hz, H-8), 7.21 (tdd, 1H, J = 8.24 Hz, J = 2.47 Hz, J = 0.83 Hz, H-5′), 7.04–6.99 (m, 1H, H-7), 6.96 (dt, 1H, J = 8.24 Hz, J = 2.47 Hz, H-4′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 185.8, 176.9, 163.6 (d, J = 248.9 Hz), 160.0 (d, J = 247.7 Hz), 146.0, 144.0 (d, J = 10.3 Hz), 131.3 (d, J = 8.9 Hz), 123.9 (d, J = 20.1, Hz), 123.7 (d, J = 7.8 Hz), 123.2 (d, J = 9.1 Hz), 118.5 (d, J = 8.3 Hz), 117.3 (d, J = 26.6 Hz), 116.5 (d, J = 20.9 Hz), 115.9 (d, J = 24.1 Hz)
IXi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.96–7.89 (m, AA′, BB′ overlapped, 3H, H-5, H-3′, H-5′), 7.88–7.79 (m, 1H, H-7), 7.72 (dd, 1H, J = 9.07 Hz, J = 4.40 Hz, H-8), 7.66–7.60 (m, AA′, BB′, 2H, H-2′, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.3 (d, J = 3.2 Hz), 177.8, 159.4 (d, J = 244.2 Hz), 147.3, 146.6 (d, J = 1.7 Hz), 129.6, 129.2 (q, J = 31.8 Hz), 127.2 (d, J = 3.7 Hz), 124.4 (d, J = 25.2 Hz), 124.2 (q, J = 270.9 Hz), 123.6 (d, J = 9.2 Hz), 119.3 (d, J = 8.6 Hz), 116.1 (d, J = 26.6 Hz)
Xg	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.10 (d, 1H, J = 2.47 Hz), 7.92 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H-7), 7.62 (d, 1H, J = 8.79 Hz), 7.40–7.27 (m, 4H, H-2′, H-3′, H-5′, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.2, 178.0, 161.9 (d, J = 245.1 Hz), 148.8, 140.1 (d, J = 3.5 Hz), 136.3, 130.8, 130.5 (d, J = 8.9 Hz), 130.0, 123.6, 119.0, 116.9 (d, J = 23.2 Hz)
Xh	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.14 (d, 1H, J = 2.75 Hz, H-5), 7.97 (dd, 1H, J = 8.79 Hz, J = 2.74 Hz, H-7), 7.66 (d, 1H, J = 8.79 Hz, H-8), 7.62–7.52 (m, 1H, H-6′), 7.34–7.25 (m, 2H, H-2′, H-5′), 7.25–7.20 (m, 1H, H-4′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 186.8, 177.6, 162.9 (d, J = 244.0 Hz), 148.7, 144.8 (d, J = 10.9 Hz), 136.4, 131.6 (d, J = 8.8 Hz), 130.8, 129.9, 124.7 (d, J = 2.9 Hz), 123.5, 119.0, 116.1 (d, J = 20.7 Hz), 115.7 (d, J = 24.1 Hz)
Xi	^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.16–8.14 (m, 1H, H-5), 8.01–7.89 (m, 3H, H-7, H-3′, H-5′), 7.68 (d, 1H, J = 8.79 Hz, H-8), 7.65–7.59 (m, 2H, H-2′, H-6′) ^{13}C NMR (75 MHz, DMSO-d_6), δ: 187.0, 177.6, 148.8, 147.2, 136.4, 130.9, 129.8, 129.5, 129.2 (q, J = 32.1 Hz), 127.2 (q, J = 3.7 Hz), 124.2 (q, J = 272.3 Hz), 123.6, 119.0

a) Atom numbering corresponds to the numbering in Fig. 1.

and 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones were synthesised by treating 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones with phosphorous pentasulphide (Fig. 1). The published methods include thionation using P_2S_5 and Lawesson's reagent (Wagner et al., 1966; Saeed & Ashraf, 2008). The starting 3-phenyl-2*H*-1,3-benzoxazine-2(3*H*)-diones are described in the literature (Waisser et al., 2001a, 2001b). An overview, characterisation, and spectral data of the compounds as prepared are summarised in Tables 1–3. The structural evidence and the physical properties of compounds *Va–Vf* and *Xa–Xf* can be found in the literature (Waisser et al., 2000).

The in-vitro antimycobacterial activity of the compounds was investigated against *M. tuberculosis* CNCTC My 331/88 (identical with H37RV and ATCC 27294), *M. kansasii* CNCTC My 235/80 (identical with ATCC 12 478, resistant to INH), *M. avium* CNCTC My 330/88 (identical with ATCC 25291, resistant to INH) and *M. kansasii* 6509/96. All the strains were obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague. The only exception was *M. kansasii* 6509/96, which was clinically isolated. The dilution micromethod was used for determination of the minimum inhibitory concentrations (MIC) and the MIC values for standard INH were included for comparison. An overview of the biological activity along

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

Comp.	MIC/(μmol L^{-1})[a]			
	M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
Ia	0.5/1	8/16	2/4	2/2
Ib	0.5/1	32/nd[b]	2/4	2/4
Ic	0.5/1	16/32	4/8	4/4
Id	0.5/1	16/32	2/4	2/4
Ie	1/4	32/62.5	4/8	4/8
If	1/2	32/32	4/4	4/4
Ig	0.5/2	nd[b]	8/16	8/16
Ih	2/2	16/32	8/8	8/8
Ii	2/4	32/62.5	8/16	8/16
IIa	1/2	4/4	2/4	2/4
IIb	0.5/1	1/1	2/4	2/2
IIc	0.5/0.5	2/2	2/4	2/4
IId	0.5/0.5	4/4	2/4	2/4
IIe	0.5/0.5	8/16	4/8	8/8
IIf	0.5/0.5	4/4	2/4	4/4
IIg	4/8	4/4	8/16	8/8
IIh	4/8	8/16	16/32	16/16
IIi	4/8	32/32	16/32	16/32
IIIa	16/32	32/32	16/32	8/16
IIIb	16/32	32/32	16/16	8/8
IIIc	8/16	32/nd[b]	16/16	16/16
IIId	16/32	62.5/62.5	16/32	16/32
IIIe	16/32	62.5/nd[b]	62.5/62.5	62.5/62.5
IIIf	32/32	62.5/62.5	32/32	32/32
IIIg	16/16	32/62.5	16/32	16/16
IIIh	16/32	62,5/125	32/32	32/32
IIIi	32/32	125/125	32/62.5	32/62.5
IVa	2/4	16/nt[c]	0.5/nt[c]	0.5/1
IVb	1/2	8/nt[c]	1/nt[c]	1/2
IVc	1/1	4/8	2/nt[c]	1/2
IVd	2/2	4/8	1/nt[c]	0.5/1
IVe	0.5/1	8/8	2/nt[c]	2/2
IVf	1/2	4/8	2/nt[c]	1/4
IVg	1/2	8/16	8/16	8/8
IVh	8/16	16/16	16/16	16/16
IVj	2/4	32/32	8/8	8/8
Va[d]	1/1	8/32	2/4	0.5/1
Vb[d]	0.5/1	16/32	4/8	1/1
Vc[d]	0.5/0.5	16/16	2/4	1/1
Vd[d]	0.5/1	16/32	2/4	1/1
Ve[d]	0.5/1	8/16	2/4	1/1
Vf[b]	0.5/1	8/32	2/4	1/2
Vg	2/4	62.5/62.5	16/16	16/16
Vh	2/4	32/32	16/16	8/8
Vi	4/4	32/32	16/16	16/16
INH[e]	0.5/1	>250/>250	>250/>250	4/4

a) Values given for 14 days/21 days of incubation; *b*) nd – not determined due to low solubility of the compound; *c*) nt – not tested; *d*) the MIC values taken from Waisser et al. (2000); *e*) isoniazid (isonicotinhydrazide) used as a reference drug.

Table 5. In-vitro antimycobacterial activity of 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones

Comp.	MIC/(μmol L^{-1})[a]			
	M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
VIa	2/2	8/16	2/2	2/4
VIb	0.5/1	16/32	4/4	4/4
VIc	1/2	32/32	4/4	4/4
VId	1/1	16/32	2/4	2/4
VIe	2/2	32/62.5	4/8	2/4
VIf	1/2	32/32	4/4	4/4
VIg	1/2	16/16	8/16	8/16
VIh	2/4	16/32	16/16	8/8
VIi	4/4	62.5/125	16/nd[b]	32/32
VIIa	0.5/1	4/4	2/4	2/4
VIIb	0.5/1	2/2	2/4	2/2
VIIc	0.5/1	4/4	4/4	4/8
VIId	0.5/0.5	2/4	2/2	2/4
VIIe	0.5/0.5	8/16	8/8	8/8
VIIf	0,5/0,5	4/4	4/4	4/4
VIIg	2/8	4/4	8/16	4/8
VIIh	4/8	8/8	16/16	8/16
VIIi	4/8	32/32	16/16	16/16
VIIIa	nd[b]	nd[b]	nd[b]	nd[b]
VIIIb	8/16	16/32	16/16	8/16
VIIIc	8/16	62.5/62.5	32/32	16/32
VIIId	16/32	nd[b]	16/32	8/8
VIIIe	16/32	62.5/nd[b]	32/32	32/32
VIIIf	8/16	62.5/62.5	32/32	32/32
VIIIg	16/32	32/nd[b]	16/16	16/16
VIIIh	62.5/nd[b]	nd[b]	nd[b]	nd[b]
VIIIi	16/32	62.5/125	32/32	32/32
IXa	4/4	8/nt[c]	4/nt[c]	1/2
IXb	1/2	16/nt[c]	8/8	2/4
IXc	2/2	16/nt[c]	2/4	4/4
IXd	2/4	8/nt[c]	4/nt[c]	2/2
IXe	1/2	16/nt[c]	4/4	1/2
IXf	1/2	16/nt[c]	4/nt[c]	2/4
IXg	1/2	16/16	8/16	8/8
IXh	16/16	16/16	16/16	16/16
IXj	2/4	32/32	8/8	8/8
Xa[d]	1/1	8/16	2/4	1/1
Xb[d]	0.5/0.5	16/nt[c]	2/4	0.5/1
Xc[d]	0.5/1	16/16	2/8	1/2
Xd[d]	0.5/1	1/2	16/32	2/4
Xe[d]	1/2	16/16	2/4	1/1
Xf[d]	0.5/0.5	16/16	2/8	1/2
Xg	1/2	16/16	8/16	8/8
Xh	2/4	62.5/62.5	8/16	8/8
Xi	4/4	62.5/62.5	16/16	16/16
INH[e]	0.5/1	>250/>250	>250/>250	4/4

a) Values given for 14 days/21 days of incubation; *b*) nd – not determined due to low solubility of the compound, *c)* nt – not tested; *d*) the MIC values taken from Waisser et al. (2000); *e*) isoniazid (isonicotinhydrazide) used as a reference drug.

with the activity of INH is shown in Tables 4 and 5.

The antimycobacterial activities of the starting 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones were in the range of 4–16 μmol L^{-1}. The replacement of one oxo group with a thioxo group significantly increased the antimycobacterial activity. The further replacement had a small effect on the activity. Also the introduction of the third sulphur atom by substituting the phenyl ring with ethoxythiocarbonyl strongly decreased the antimycobacterial activity (Waisser et al., 2009). The MIC values of the sulphur compounds were generally in the range of 0.5–32 μmol L^{-1} but the ma-

Table 6. Activity contribution of the Free–Wilson analyses of of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones and statistical significance of correlation

Parameter	$\Delta\log(\mathrm{MIC}/(\mu\mathrm{mol\ L^{-1}}))$			
	M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
bR^1: Br	–1.333 (± 0.109)	–0.379 (± 0.125)	–0.733 (± 0.102)	–0.700 (± 0.118)
CH_3	–1.200 (± 0.109)	–0.103 (± 0.121)	–0.733 (± 0.102)	–0.633 (± 0.118)
F	–1.067 (± 0.109)	–0.767 (± 0.121)	–0.933 (± 0.102)	–1.000 (± 0.118)
Cl	–1.267 (± 0.109)	–0.467 (± 0.121)	–0.700 (± 0.102)	–0.967 (± 0.118)
OCH_3	0	0	0	0
R^2: 4-CH_3	–0.180 (± 0.146)	0.00 (± 0.162)	0.120 (± 0.137)	0.120 (± 0.159)
4-Cl	–0.240 (± 0.146)	–0.060 (± 0.162)	0.180 (± 0.137)	0.240 (± 0.159)
3-Cl	–0.120 (± 0.146)	0.060 (± 0.162)	0.060 (± 0.137)	0.120 (± 0.159)
3,4-Cl_2	–0.180 (± 0.146)	0.180 (± 0.162)	0.360 (± 0.137)	0.540 (± 0.159)
4-Br	–0.060 (± 0.146)	0.060 (± 0.162)	0.180 (± 0.137)	0.360 (± 0.159)
4-F	0.120 (± 0.146)	0.218 (± 0.176)	0.660 (± 0.137)	0.840 (± 0.159)
3-F	0.420 (± 0.146)	0.300 (± 0.162).	0.840 (± 0.137)	0.960 (± 0.159)
3-CF_3	0.420 (± 0.149)	0.600 (± 0.162)	0.780 (± 0.170)	0.960 (± 0.159)
4-H	0	0	0	0
μ_o	1.213 (± 0.124)	1.549 (± 0.138)	0.98 (± 0.116)	0.803 (± 0.134)
R	0.943	0.883	0.926	0.923
s	0.230	0.256	0.216	0.251
F	21.22	9.12	15.81	15.30
n	45	44	45	45

jority of MICs was in the range of 0.5–4 μmol L^{-1}. The activities against *M. tuberculosis* of most of the compounds tested were comparable with the activity of INH but the activities against *M. kansasii* 6509/96 are higher.

The Hansch approach was carried out to study the relationship between the structure of the compounds and their activity against *M. tuberculosis*. The correlation of the logarithm of the minimum inhibitory concentration for 14 d and 21 d is statistically significant so the QSAR study included only the results obtained after 14 d of incubation. The reliability of the calculation is confirmed by the leave-one-out (LOO) method.

Equation 1 illustrates the structure–activity relationship of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones (*I*–*V*):

$$\log(\mathrm{MIC_{M.tub.14d}}) = -(1.202 \pm 0.176)\pi_1 + \\ + (0.886 \pm 0.327)\sigma_2 - (0.522 \pm 0.182)\pi_2 + \\ + (0.898 \pm 0.130) \quad (1)$$

($r = 0.760$, $Q^2 = 0.486$, $s = 0.396$, $n = 45$, $F = 18.69$, $F^{\alpha=0.05} = 2.83$)

where r is the correlation coefficient, Q^2 is the cross-validation value, s is the standard deviation, n is the number of compounds used for calculation, F is the Fischer–Snedecor distribution, F-test, symbol π_1 represents Hansch constants of R^1 substituents, π_2 Hansch constants of R^2 substituents, and σ_2 Hammett constants of R^2 substituents on the phenyl ring.

The following equation illustrates the structure–activity relationship of 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (*VI*–*X*):

$$\log(\mathrm{MIC_{M.tub.14d}}) = -(1.028 \pm 0.166)\pi_1 + \\ + (1.206 \pm 0.302)\sigma_2 - (0.604 \pm 0.170)\pi_2 + \\ + (0.830 \pm 0.127) \quad (2)$$

($r = 0.762$, $Q^2 = 0.485$, $s = 0.366$, $n = 44$, $F = 18.52$, $F^{\alpha=0.05} = 2.84$)

Eq. (3) illustrates the structure–activity relationship of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-ones (*I*–*V*) and 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (*VI*–*X*) combined:

$$\log(\mathrm{MIC_{M.tub.14d}}) = -(1.116 \pm 0.089)\pi_1 + \\ + (1.046 \pm 0.219)\sigma_2 - (0.564 \pm 0.123)\pi_2 + \\ + (0.866 \pm 0.089) \quad (3)$$

($r = 0.757$, $Q^2 = 0.529$, $s = 0.375$, $n = 89$, $F = 37.99$, $F^{\alpha=0.05} = 2.71$)

Index 1 represents the parameters of R^1 substituents (in position 6 of the benzoxazine ring) and index 2 the parameters of R^2 substituents on the phenyl ring. Both the equations have a significance level lower than 0.05. Both regression equations satisfy the statistical criteria for rejecting the null hypothesis at a significance level lower than 0.05. Cross-validation (Q^2) proved the acceptable stability of these QSAR models. The equations show that activity increases with the lipophilicity of the substituents. The Free–Wilson

Table 7. Activity contribution of the Free–Wilson analyses of 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones and statistical significance of correlation

Parameter	$\Delta\log(\mathrm{MIC}/(\mu\mathrm{mol\ L^{-1}}))$			
	M. tuberculosis My 331/88	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
R^1: Br	–1.037 (± 0.106)	–0.126 (± 0.148)	–0.688 (± 0.119)	–0.587 (± 0.126)
CH_3	–1.203 (± 0.106)	–0.762 (± 0.148)	–0.721 (± 0.119)	–0.620 (± 0.126)
F	–0.870 (± 0.106)	–0.291 (± 0.148)	–0.621 (± 0.119)	–0.787 (± 0.126)
Cl	–1.203 (± 0.106)	–0.292 (± 0.148)	–0.755 (± 0.119)	–0.920 (± 0.126)
OCH_3	0	0	0	0
R^2: 4-CH_3	–0.366 (± 0.147)	0.120 (± 0.186)	0.145 (± 0.157)	0.004 (± 0.167)
4-Cl	–0.246 (± 0.144)	0.360 (± 0.186)	0.206 (± 0.157)	0.304 (± 0.167)
3-Cl	–0.187 (± 0.147)	–0.225 (± 0.194)	0.206 (± 0.157)	0.124 (± 0.167)
3.4-Cl_2	–0.126 (± 0.147)	0.360 (± 0.186)	0.266 (± 0.157)	0.244 (± 0.167)
4-Br	–0.306 (± 0.147)	0.360 (± 0.186)	0.206 (± 0.157)	0.304 (± 0.167)
4-F	0.066 (± 0.147)	0.240 (± 0.186)	0.387 (± 0.157)	0.604 (± 0.167)
3-F	0.474 (± 0.147)	0.450 (± 0.194).	0.750 (± 0.164)	0.825 (± 0.175)
3-CF_3	0.294 (± 0.147)	0.660 (± 0.186)	0.686 (± 0.157)	0.964 (± 0.167)
4-H	0	0	0	0
μ_o	1.228 (± 0.124)	1.200 (± 0.186)	1.071 (± 0.152)	0.879 (± 0.162)
R	0.940	0.852	0.869	0.904
s	0.218	0.275	0.232	0.247
F	19.90	6.35	7.73	11.17
n	44	42	43	43

method modified by Fujita–Ban was used to investigate the activity contribution (Tables 6 and 7). The alkyl derivatives are proposed for future screening because of the decrease in the activity with an increasing value of σ_2 constants and the Free–Wilson analysis results.

Conclusions

The derivatives of 3-phenyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (*I*–*V*) and 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (*VI*–*X*) possess a biological activity similar to INH, the standard used for comparison. The replacement of one oxo group with a thioxo group strongly increased the antimycobacterial activity. The replacement of a further oxo group had a small effect on the activity. 3-(4-Chlorophenyl)-6-methyl-4-thioxo-2*H*-1,3-benzoxazine-2(3*H*)-one (*IIc*) is the most promising compound, as it shows the best activity against all the mycobacterial strains under examination. This compound has been selected for future investigation.

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