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3-Benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones, a new group of antimycobacterial compounds against potentially pathogenic strains

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Abstract

A series of derivatives of 3-benzyl-2*H*-benzoxazine-2,4(3*H*)-dione substituted in positions 6, 7 or 8 on the benzoxazine, and in positions 3 or 4 on the benzyl moiety was synthesized. The compounds were evaluated for in vitro antimycobacterial activity against *Mycobacterium avium* and two strains of *Mycobacterium kansasii*. The disadvantage of the compounds is in their low solubility in water. The antimycobacterial activity of *N*-benzylsalicylamides correlates with that of 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones and depends on the partition coefficients and electronic indexes.

Keywords: Benzoxazines; Tuberculostatics; Antimycobacterial activity; Mycobacterium

1. Introduction

The search for new antimycobacterial compounds is one of the most challenging tasks of current medicinal chemistry. Mycobacterial diseases due to multiresistant strains are not frequent, but mostly fatal in the end. In particular, the study of antimycobacterial properties of salicylanilides is of great interest, as salicylanilides are inhibitors of bacterial two-component systems [1,2] that were also found in mycobacteria. Salicylanilides are broad-spectrum antimycobacterial compounds. However, salicylanilides are unlikely to be effective chemotherapeutic agents themselves due to their effect on mitochondrial respiration [2]. Therefore, we are attempting to find similar compounds not affecting mitochondrial respiration. In our previous study, we assumed that compounds isosteric to salicylanilides would also display antimycobacterial activity [3]. Recently, we have found that 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones are inhibitors of two-component systems as well [4]. The goal of this work was to evaluate structure-activity relationships in the series of 3-benzyl-2*H*-benzoxazin-2,4(3*H*)-diones, substituted on the benzyl moiety in positions 4 (or 3) and in positions 6, 7 or 8 on the benzoxazine, including a more detailed analysis of the relationship.

2. Chemistry

The synthetic pathway leading to 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones is depicted in Fig. 1. Substituted 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones were prepared by the treatment of substituted *N*-benzylsalicylamides with ethyl chloroformate in pyridine. The structural assignment is based on ^{1}H NMR and ^{13}C NMR spectra and IR spectra. In the IR spectra, two absorption maxima of the carbonyl groups were apparent. The synthesis of the starting *N*-benzylsalicylamides has been reported [5]. An overview of the compounds under study is in Fig. 2.

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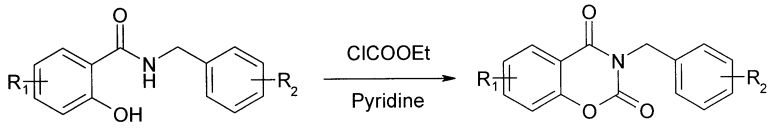
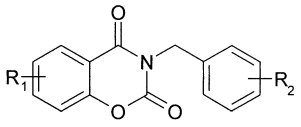


Fig. 1. Preparation of 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones.



	R_1		R_1		R_1		R_2		R_2
a	H	**e**	6-CH_3	**i**	7-Cl	**1**	H	**5**	3,4-Cl_2
b	6-Br	**f**	6,8-Br_2	**k**	8-OCH_3	**2**	4-Cl	**6**	4-OCH_3
c	6-Cl	**g**	7-OCH_3	**l**	6-OCH_3	**3**	4-CH_3		
d	6,8-Cl_2	**h**	6-NO_2			**4**	4-F		

Fig. 2. Overview of the structures of 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones.

3. Experimental

3.1. Chemistry

The melting points were determined on a Kofler apparatus. The samples for analysis and antimycobacterial tests were dried over P_4O_{10} at 61 °C and 66 Pa for 24 h. Elemental analyses (C, H, N) were performed on a CHNS-O CE elemental analyzer (Fisons EA 1110, Milano) 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}. The bonding vibrations of the C=O group [ν(C⋯O)] were found in the region 1686–1707 cm^{-1} and 1742–1778 cm^{-1}, characteristic for 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones. TLC was performed on silica gel plates precoated with a fluorescent indicator Silufol UV 254+366 (Kavalier, Votice Czech Republic), with heptane–ethylacetate (8:3) as the mobile phase, or toluene–acetone (10:1). The ^1H NMR and ^{13}C NMR spectra of new compounds were recorded in DMSO-d_6 or pyridine-d_5 solution at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz. Chemical shifts were recorded as δ values in parts per millions (ppm) and were indirectly referenced to tetramethylsilane *via* the solvent signal (2.49 for ^1H or 39.7 for ^{13}C).

The starting salicylanilides were described in our previous paper [3]. The title compounds were synthesized from the corresponding salicylamides. Ethyl chloroformate (5.2 g, 48 mmol) was added dropwise to a stirred solution of an *N*-benzylsalicylamide (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% potassium hydroxide solution, filtered off again, and crystallized from EtOH (yield 39–70%).

3.1.1. 3-Benzyl-2H-1,3-benzoxazine-2,4(3H)-dione (*1a*)

White crystals. Yield 45%, m.p. 173–175 °C, Refs. [6,7] 133–134 °C. IR (KBr): ν(C=O) 1701, 1757 cm^{-1}, log $P = 3.07$. For $C_{15}H_{11}NO_3$ (253.3) calc.: 71.14% C, 5.53% N, 4.38% H; found: 70.77% C, 5.46% N, 4.40% H. ^1H NMR ($CDCl_3$) δ 8.00 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(5,7) = 1.50$ Hz, H5), 7.82–7.67 (m, 1H. H7), 7.46–7.26 (m, 7H, H6, H8, H2′, H3′, H4′, H5′, H6′), 5.06 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 160.7, 152.6, 148.1, 136.6, 136.3, 128.6, 128.0, 127.9, 127.6, 125.6, 116.6, 114.3, 45.3.

3.1.2. 3-Benzyl-6-bromo-2H-1,3-benzoxazine-2,4(3H)-dione (*1b*)

White crystals. Yield 52%, m.p. 158–160 °C. IR (KBr): ν(C=O) 1701, 1768 cm^{-1}, log $P = 3.90$. For $C_{15}H_{10}BrNO_3$ (332.2) calc.: 54.24% C, 4.22% N, 3.03% H; found: 54.51% C, 4.22% N, 3.20% H. ^1H NMR ($CDCl_3$) δ 8.19 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.54 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.52–7.49 (m, 2H, H2′, H6′), 7.34–7.28 (m, 3H, H3′, H4′, H5′), 7.15 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 5.18 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.3, 151.4, 147.5, 139.0, 135.3, 130.6, 129.3, 129.2, 128.6, 128.2, 118.3, 118.2, 45.9.

3.1.3. 3-Benzyl-6-chloro-2H-1,3-benzoxazine-2,4(3H)-dione (*1c*)

White crystals. Yield 62%, m.p. 144–146 °C. IR (KBr): ν(C=O) 1705, 1767 cm^{-1}, log $P = 3.63$. For $C_{15}H_{10}ClNO_3$ (287.7) calc.: 62.62% C, 4.87% N, 3.50% H; found: 62.34% C, 4.76% N, 3.61% H. ^1H NMR (DMSO-d_6) δ 7.94 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.88 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.70$ Hz, H7), 7.49 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.52–7.49 (m, 5H, H2′, H3′, H4′, H5′, H6′), 5.04 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.9, 151.4, 147.8, 136.2, 136.1, 129.5, 128.6, 127.9, 127.7, 126.5, 118.9, 116.0, 45.5.

*3.1.4. 3-Benzyl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-dione (**1d**)*

White crystals. Yield 58%, m.p. 134–136 °C. IR (KBr): ν(C=O) 1701, 1772 cm^{-1}, log $P = 4.19$. For $C_{15}H_9Cl_2NO_3$ (322.1) calc.: 55.93% C, 4.35% N, 2.82% H; found: 56.28% C, 4.35% N, 3.01% H. ^{1}H NMR (DMSO-d_6) δ 8.19 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.92 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.40–7.28 (m, 5H, H2′, H3′, H4′, H5′, H6′), 5.05 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.4, 147.8, 147.1, 135.8, 135.4, 129.4, 128.5, 127.9, 127.6, 125.6, 121.6, 117.4, 45.7.

*3.1.5. 3-Benzyl-6-methyl-2H-1,3-benzoxazine-2,4(3H)-dione (**1e**)*

White crystals. Yield 45%, m.p. 116–120 °C. IR (KBr): ν(C=O) 1689, 1757 cm^{-1}, log $P = 3.56$. For $C_{16}H_{13}NO_3$ (267.3) calc.: 71.90% C, 5.24% N, 4.90% H; found: 71.84% C, 5.24% N, 4.86% H. ^{1}H NMR (DMSO-d_6) δ 7.78 (d, 1H, $J(5,7) = 2.10$ Hz, H5), 7.60 (dd, 1H, $J(7,8) = 8.10$ Hz, $J(5,7) = 2.10$ Hz, H7), 7.36–7.25 (m, 6H, H8, H2′, H3′, H4′, H5′, H6′), 5.05 (s, 2H, CH_2) 2.38 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 150.7, 137.4, 136.4, 135.2, 128.6, 127.8, 127.6, 127.1, 116.4, 113.9, 45.2, 20.3.

*3.1.6. 3-Benzyl-6,8-dibromo-2H-1,3-benzoxazine-2,4(3H)-dione (**1f**)*

White crystals. Yield 65%, m.p. 169–171 °C. IR (KBr): ν(C=O) 1701, 1770 cm^{-1}, log $P = 4.73$. For $C_{15}H_9Br_2NO_3$ (411.0) calc.: 43.83% C, 3.41% N, 2.21% H; found: 43.61% C, 3.21% N, 2.24% H. ^{1}H NMR (DMSO-d_6) δ 8.38 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 8.06 (d, 1H, $J(5,7) = 2.70$ Hz, H7), 7.39–7.26 (m, 5H, H2′, H3′, H4′, H5′, H6′), 5.04 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.4, 147.2, 140.8, 135.8, 128.1, 128.5, 127.5, 127.9, 127.7, 1176, 117.2, 110.8, 45.7.

*3.1.7. 3-Benzyl-7-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**1g**)*

White crystals. Yield 46%, m.p. 134–136 °C. IR (KBr): ν(C=O) 1693, 1754 cm^{-1}, log $P = 2.95$. For $C_{16}H_{13}NO_4$ (283.3) calc.: 67.84% C, 4.94% N, 4.63% H; found: 67.90% C, 4.83% N, 4.69% H. ^{1}H NMR (DMSO-d_6) δ 7.88 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(5,7) = 0.90$ Hz, H5), 7.37–7.25 (m, 5H, H2′, H3′, H4′, H5′, H6′), 7.02–6.98 (m, 2H, H8, H6), 5.08 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 165.8, 160.2, 154.4, 148.3, 136.4, 129.1, 128.6, 127.8, 127.6, 113.6, 107.1, 100.5, 56.6, 45.0

*3.1.8. 3-Benzyl-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**1h**)*

Yellow crystals. Yield 65%, m.p. 164–165 °C. IR (KBr): ν(C=O) 1705, 1774 cm^{-1}, log $P = 2.46$. For $C_{15}H_{10}N_2O_5$ (298.3) calc.: 60.41% C, 9.39% N, 3.38% H; found: 60.67% C, 9.23% N, 3.47% H. ^{1}H NMR (DMSO-d_6) δ 8.64 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 8.59 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.70$ Hz, H7), 7.70 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.41–7.29 (m, 5H, H2′, H3′, H4′, H5′, H6′), 5.07 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.8, 156.4, 147.4, 144.4, 135.8, 130.9, 128.6, 128.0, 127.7, 123.1, 118.6, 115.5, 45.7.

*3.1.9. 3-Benzyl-7-chloro-2H-1,3-benzoxazine-2,4(3H)-dione (**1i**)*

White crystals. Yield 70%, m.p. 154–155 °C. IR (KBr): ν(C=O) 1688, 1754 cm^{-1}, log $P = 3.63$. For $C_{15}H_{10}ClNO_3$ (287.7) calc.: 62.62% C, 4.87% N, 3.50% H; found: 62.34% C, 4.71% N, 3.48% H. ^{1}H NMR (DMSO-d_6) δ (7.98 d, 1H, $J(5,6) = 8.40$ Hz, H5), 7.69 (d, 1H, $J(6,8) = 1.65$ Hz, H8), 7.50 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(6,8) = 1.65$ Hz, H6), 7.38–7.28 (m, 5H, H2′, H3′, H4′, H5′, H6′), 5.04 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.1, 153.1, 147.8, 140.6, 136.1, 129.2, 128.6, 127.9, 127.7, 125.9, 116.9, 113.6, 45.4.

*3.1.10. 3-Benzyl-8-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**1j**)*

White crystals. Yield 49%, m.p. 144–146 °C. IR (KBr): ν(C=O) 1697, 1756 cm^{-1}, log $P = 2.95$. For $C_{16}H_{13}NO_4$ (283.3) calc.: 67.84% C, 4.94% N, 4.63% H; found: 67.89% C, 4.86% N, 4.30% H. ^{1}H NMR (DMSO-d_6) δ 7.51–7.46 (m, 2H, H5, H7), 7.37–7.25 (m, 6H, H6, H2′, H3′, H4′, H5′, H6′), 5.10 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 147.9, 146.8, 142.2, 136.3, 128.6, 127.8, 127.6, 125.5, 118.3, 117.9, 115.1, 56.6, 45.3.

*3.1.11. 3-Benzyl-6-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**1k**)*

White crystals. Yield 58%, m.p. 151–152 °C. IR (KBr): ν(C=O) 1687, 1754cm^{-1}, log $P = 2.95$. For $C_{16}H_{13}NO_4$ (283.3) calc.: 67.84% C, 4.94% N, 4.63% H; found: 67.95% C, 4.85% N, 4.52% H. ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 8H, H5, H7, H8, H2′, H3′, H4′, H5′, H6′), 5.06 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 160.7, 156.5, 148.1, 146.8, 136.3, 128.6, 127.9, 127.6, 124.4, 118.1, 114.7, 108.8, 56.1, 45.3.

*3.1.12. 3-(4-Chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2a**)*

White crystals. Yield 63%, m.p. 133-135 °C, Ref. [7] 127–130 °C. IR (KBr): ν(C=O) 1693, 1760 cm^{-1}, log $P = 3.63$. For $C_{15}H_{10}ClNO_3$ (287.7) calc.: 62.62% C, 4.87% N, 3.50% H; found: 62.54% C, 4.82% N, 3.55% H. ^{1}H NMR (DMSO-d_6) δ 7.98 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(5,7) = 2.10$ Hz, H5), 7.84–7.79 (m, 1H, H6), 7.46–7.35 (m, 6H, H7, H8, H2′, H3′, H5′, H6′), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.7, 152.6, 148.1, 136.6, 135.3, 132.2, 129.9, 128.5, 127.6, 125.6, 116.6, 114.4, 44.7.

*3.1.13. 6-Bromo-3-(4-chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2b**)*

White crystals. Yield 52%, m.p. 206–208 °C. IR (KBr): ν(C=O) 1694, 1759 cm^{-1}, log $P = 4.46$. For $C_{15}H_9BrClNO_3$ (366.6) calc.: 49.14% C, 3.82% N, 2.43% H; found: 49.19% C, 3.80% N, 2.43% H. ^1H NMR ($CDCl_3$) δ 8.06 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.98 dd, 1H, $J(7,8) = 9.00$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.44 d, 1H, $J(7,8) = 9.00$ Hz, H8), 7.42–7.35 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.8, 151.8, 147.7, 139.0, 135.1, 132.2, 129.9, 129.4, 128.5, 119.2, 117.1, 116.5, 44.9.

*3.1.14. 6-Chloro-3-(4-chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2c**)*

White crystals. Yield 49%, m.p. 198–199 °C. IR (KBr): ν(C=O) 1697, 1765 cm^{-1}, log $P = 4.19$. For $C_{15}H_9Cl_2NO_3$ (322.1) calc.: 55.93% C, 4.35% N, 2.82% H; found: 55.58% C, 4.30% N, 2.77% H. ^1H NMR (DMSO-d_6) δ 7.94 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.88 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.51 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.42–7.35 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.9, 151.4, 147.8, 136.2, 135.1, 132.3, 129.9, 129.5, 128.5, 126.5, 119.0, 116.1, 44.9.

*3.1.15. 6,8-Dichloro-3-(4-chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2d**)*

White crystals. Yield 68%, m.p. 200–202 °C. IR (KBr): ν(C=O) 1691, 1772cm^{-1}, log $P = 4.75$. For $C_{15}H_8Cl_3NO_3$ (356.6) calc.: 50.52% C, 3.93% N, 2.26% H; found: 50.78% C, 3.83% N, 2.25% H. ^1H NMR (DMSO-d_6) δ 8.18 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.91 (d, 1H, $J(5,7) = 2.70$ Hz, H7), 7.42–7.35 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.01 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.5, 147.8, 147.1, 135.5, 134.8, 132.3, 129.9, 129.4, 128.4, 125.5, 121.6, 117.5, 45.2.

*3.1.16. 3-(4-Chlorobenzyl)-6-methyl-2H-1,3-benzoxazine-2,4(3H)-dione (**2e**)*

White crystals. Yield 71%, m.p. 186–188 °C. IR (KBr): ν(C=O) 1693, 1757cm^{-1}, log $P = 4.12$. For $C_{16}H_{12}ClNO_3$ (301.7) calc.: 63.69% C, 4.64% N, 4.01% H; found: 63.64% C, 4.31% N, 3.90% H. ^1H NMR (DMSO-d_6) δ 7.77 (d, 1H, $J(5,7) = 2.10$ Hz, H5), 7.63 (dd, 1H, $J(7,8) = 8.10$ Hz, $J(5,7) = 2.10$ Hz, H7), 7.33–7.15 (m 5H, H8, H2′, H3′, H5′, H6′), 5.03 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 150.7, 148.2, 137.3, 135.4, 135.1, 132.2, 129.8, 128.5, 127.1, 116.4, 114.0, 44.7, 20.3.

*3.1.17. 6,8-Dibromo-3-(4-chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2f**)*

White crystals. Yield 41%, m.p. 245–247 °C. IR (KBr): ν(C=O) 1693, 1752 cm^{-1}, log $P = 5.29$. For $C_{15}H_8Br_2ClNO_3$ (445.5) calc.: 40.44% C, 3.14% N, 1.81% H; found: 40.06% C, 3.15% N, 1.81% H. ^1H NMR ($CDCl_3$) δ 8.38 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 8.05 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.42–7.38 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.4, 149.6, 147.2, 140.8, 134.8, 132.3, 129.9, 129.0, 128.5, 117.7, 117.2, 110.8, 45.1.

*3.1.18. 3-(4-Chlorobenzyl)-7-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**2g**)*

White crystals. Yield 56%, m.p. 154–156 °C. IR (KBr): ν(C=O) 1698, 1778 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.80% C, 4.48% N, 3.85% H. ^1H NMR (DMSO-d_6) δ 7.88 (dd, 1H, $J(5,6) = 9.30$ Hz, $J(5,8) = 0.90$ Hz, H5), 7.41–7.35 (m, 4H, H6, H8, H2′, H6′), 7.00–6.98 (m AA′BB′, 2H, H3′, H5′), 5.01 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 165.8, 160.2, 154.5, 148.3, 135.5, 132.2, 129.9, 129.0, 128.5, 113.5, 107.1, 100.5, 56.6, 44.5.

*3.1.19. 3-(4-Chlorobenzyl)-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**2h**)*

Yellow crystals. Yield 67%, m.p. 186–188 °C. IR (KBr): ν(C=O) 1701, 1771 cm^{-1}, log $P = 3.08$. For $C_{15}H_9ClN_2O_5$ (332.7) calc.: 54.15% C, 8.42% N, 2.73% H; found: 54.26% C, 8.53% N, 2.72% H. ^1H NMR (DMSO-d_6) δ 8.62 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 8.59 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.72 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.40–7.37 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.05 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.8, 156.3, 147.4, 144.3, 134.8, 132.4, 130.9, 130.0, 128.5, 123.0, 118.6, 115.5, 45.1.

*3.1.20. 7-Chloro-3-(4-chlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**2i**)*

White crystals. Yield 49%, m.p. 174–175 °C. IR (KBr): ν(C=O) 1686, 1752 cm^{-1}, log $P = 4.19$. For $C_{15}H_9Cl_2NO_3$ (322.1) calc.: 55.93% C, 4.35% N, 2.82% H; found: 56.32% C, 4.44% N, 2.80% H. ^1H NMR (DMSO-d_6) δ 7.98 (d, 1H, $J(5,6) = 8.40$ Hz, H5), 7.70 (d, 1H, $J(6,8) = 2.40$ Hz, H8), 7.50 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(5,6) = 2.40$ Hz, H6), 7.42–7.36 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.2, 153.2, 147.8, 140.6, 135.1, 132.3, 129.9, 129.2, 128.5, 125.9, 116.8, 113.6, 44.8.

*3.1.21. 3-(4-Chlorobenzyl)-8-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**2j**)*

White crystals. Yield 68%, m.p. 172–174 °C. IR (KBr): ν(C=O) 1687, 1754 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.35% C, 4.25% N, 3.89% H. ^1H NMR (DMSO-d_6) δ 7.51–7.47 (m, 2H, H5, H7), 7.41–7.32 (m, 5H, H6, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 147.9,

146.8, 142.3, 135.3, 132.2, 129.8, 128.5, 125.5, 118.3, 117.9, 115.2, 56.6, 44.7.

3.1.22. 3-(4-Chlorobenzyl)-6-methoxy 2H-1,3-benzoxazine-2,4(3H)-dione (**2k**)

White crystals. Yield 54%, m.p. 192–194 °C. IR (KBr): ν(C=O) 1691, 1757 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.52% C, 4.45% N, 4.00% H. ^{1}H NMR (DMSO-d_6) δ 7.78 (d, 1H, $J(5,7) = 3.00$ Hz, H5), 7.62 (dd, 1H, $J(7,8) = 9.00$ Hz, $J(5,7) = 3.00$ Hz, H7), 7.42–7.32 (m, 5H, H8, H2′, H3′, H5′, H6′), 4.51 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 156.5, 150.7, 148.2, 137.4, 135.4, 135.2, 132.2, 129.8, 128.5, 118.1, 116.4, 56.8, 44.7.

3.1.23. 3-(4-Methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3a**)

White crystals. Yield 68%, m.p. 132–133 °C, Ref. [7] 134–136°C. IR (KBr): ν(C=O) 1701, 1752 cm^{-1}, log $P = 3.56$. For $C_{16}H_{13}NO_3$ (267.3) calc.: 71.90% C, 5.24% N, 4.90% H; found: 71.61% C, 5.18% N, 5.00% H. ^{1}H NMR (DMSO-d_6) δ 8.00–7.96 (m, 1H, H5), 7.81–7.78 (m, 1H, H7), 7.46–7.41 (m, 2H, H6, H8), 7.26–7.10 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.01 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 152.6, 149.0, 136.8, 136.6, 133.3, 129.1, 127.8, 127.6, 125.6, 116.6, 114.3, 45.0, 20.9.

3.1.24. 6-Bromo-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3b**)

White crystals. Yield 62%, m.p. 195–197 °C. IR (KBr): ν(C=O) 1697, 1765 cm^{-1}, log $P = 4.39$. For $C_{16}H_{12}BrNO_3$ (346.2) calc.: 55.51% C, 4.05% N, 3.49% H; found: 55.78% C, 3.95% N, 3.42% H. ^{1}H NMR (DMSO-d_6) δ 8.06 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.97 (dd, 1H, $J(7,8) = 9.00$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.44 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.26–7.23 (m AA′BB′, 2H, H2′, H6′), 7.13–7.09 (m AA′BB′, 2H, H3′, H5′), 4.99 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 159.7, 151.8, 147.7, 138.9, 136.9, 133.1, 129.5, 129.1, 128.0, 126.5, 119.2, 116.4, 45.3, 20.9.

3.1.25. 6-Chloro-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3c**)

White crystals. Yield 53%, m.p. 171–172 °C. IR (KBr): ν(C=O) 1690, 1781 cm^{-1}, log $P = 4.12$. For $C_{16}H_{12}ClNO_3$ (301.7) calc.: 63.69% C, 4.64% N, 4.01% H; found: 63.80% C, 4.38% N, 4.15% H. ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 1H $J(5,7) = 2.40$ Hz, H5), 7.86 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.51 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.27–7.23 (m AA′BB′, 2H, H2′, H6′), 7.13–7.09 (m AA′BB′, 2H, H3′, H5′), 4.99 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 159.8, 151.4, 147.7, 136.9, 136.1, 133.1, 129.5, 129.1, 128.0, 126.5, 118.9, 116.1, 45.3, 20.9.

3.1.26. 6,8-Dichloro-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3d**)

White crystals. Yield 58%, m.p. 171–173 °C. IR (KBr): ν(C=O) 1693, 1757cm^{-1}, log $P = 4.68$. For $C_{16}H_{11}Cl_2NO_3$ (336.2) calc.: 57.17% C, 4.17% N, 3.30% H; found: 57.38% C, 4.13% N, 2.92% H. ^{1}H NMR (DMSO-d_6) δ 8.18 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.91 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.28–7.10 (m AA′BB′, 4H, H2, H3′, H5′, H6′), 5.00 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 159.4, 147.6, 147.0, 136.9, 135.4, 132.8, 129.3, 129.1, 128.0, 125.6, 121.6, 117.4, 45.5, 20.9.

3.1.27. 6-Methyl-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3e**)

White crystals. Yield 47%, m.p. 145–147 °C. IR (KBr): ν(C=O) 1693, 1772 cm^{-1}, log $P = 4.05$. For $C_{17}H_{15}NO_3$ (281.3) calc.: 72.58% C, 4.98% N, 5.37% H; found: 72.65% C, 5.02% N, 5.61% H. ^{1}H NMR (DMSO-d_6) δ 7.77 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.62 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.31 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.25–7.17 (m AA′BB′, 2H, H2′, H6′), 7.13–7.09 (m AA′BB′, 2H, H3′, H5′), 5.00 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 150.6, 148.1, 137.3, 136.8, 135.2, 133.4, 129.1, 127.9, 127.1, 116.4, 113.9, 44.9, 20.8, 20.3.

3.1.28. 6,8-Dibromo-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3f**)

White crystals. Yield 65%, m.p. 217–219 °C. IR (KBr): ν(C=O) 1691, 1759 cm^{-1}, log $P = 5.22$. For $C_{16}H_{11}Br_2NO_3$ (425.1) calc.: 45.21% C, 3.30% N, 2.61% H; found: 45.51% C, 3.28% N, 2.31% H. ^{1}H NMR ($CDCl_3$) δ 8.38 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 8.04 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.27–7.10 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 4.99 (s, 2H, CH_2), 2.26 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.3, 149.2, 147.1, 140.8, 136.9, 132.8, 129.1, 129.0, 128.0, 117.6, 117.2, 110.9, 45.5, 20.9.

3.1.29. 7-Methoxy-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3g**)

White crystals. Yield 45%, m.p. 126–128 °C. IR (KBr): ν(C=O) 1700, 1773 cm^{-1}, log $P = 3.43$. For $C_{17}H_{15}NO_4$ (297.3) calc.: 68.68% C, 4.71% N, 5.26% H; found: 68.80% C, 4.56% N, 5.26% H. ^{1}H NMR (DMSO-d_6) δ 7.87 (dd, 1H, $J(5,6) = 9.00$ Hz, $J(5,8) = 0.60$ Hz, H5), 7.13–7.08 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 7.01–6.96 (m, 2H, H6, H8), 4.97 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 152.6, 149.0, 136.8, 136.6, 133.3, 129.1, 127.8, 127.6, 125.6, 116.6, 114.3, 56.6, 45.0, 20.9.

*3.1.30. 3-(4-Methylbenzyl)-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**3h**)*

Yellow crystals. Yield 68%, m.p. 168–170 °C. IR (KBr): ν(C=O) 1692, 1771 cm^{-1}, log $P = 2.88$. For $C_{16}H_{12}N_2O_5$ (312.3) calc.: 61.54% C, 8.97% N, 3.87% H; found: 61.51% C, 8.62% N, 3.88% H. ^{1}H NMR (DMSO-d_6) δ 8.62 (dd, 1H, $J(7,8) = 8.40$ Hz, $J(5,7) = 3.00$ Hz, H7), 8.58 (d, 1H, $J(5,7) = 3.00$ Hz, H5), 7.70 (d, 1H, $J(7,8) = 8.40$ Hz, H8), 7.21–7.14 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.02 (s, 2H, CH_2), 2.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 159.7, 156.3, 147.3, 144.3, 136.9, 132.8, 130.9, 129.0, 128.1, 123.1, 118.6, 115.4, 45.5, 20.9.

*3.1.31. 7-Chloro-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3i**)*

White crystals. Yield 47%, m.p. 163–164 °C. IR (KBr): ν(C=O) 1694, 1742 cm^{-1}, log $P = 4.12$. For $C_{16}H_{12}ClNO_3$ (301.7) calc.: 63.69% C, 4.64% N, 4.01% H; found: 63.71% C, 4.56% N, 3.76% H. ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 1H, $J(5,6) = 8.10$ Hz, H5), 7.69 (d, 1H, $J(6,8) = 2.10$ Hz, H8), 7.50 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(6,8) = 2.10$ Hz, H6), 7.26–7.01 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 4.99 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.1, 153.1, 147.8, 140.5, 136.9, 133.1, 129.1, 129.1, 128.0, 125.9, 116.8, 113.5, 45.1, 20.9.

*3.1.32. 8-Methoxy-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3j**)*

Yield 62%, m.p. 132–133 °C. IR (KBr): ν(C=O) 1694, 1755 cm^{-1}, log $P = 3.43$. For $C_{17}H_{15}NO_4$ (297.3) calc.: 68.68% C, 4.71% N, 5.26% H; found: 68.58% C, 4.77% N, 5.04% H. ^{1}H NMR (DMSO-d_6) δ 7.52–7.46 (m, 2H, H5, H7), 7.35 (t, 1H, $J(5,6) = 7.80$ Hz, H6), 7.25–7.10 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 5.00 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 147.8, 146.8, 142.2, 136.8, 133.3, 129.1, 127.9, 125.5, 118.3, 117.9, 115.1, 56.6, 45.0, 20.9.

*3.1.33. 6-Methoxy-3-(4-methylbenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**3k**)*

White crystals. Yield 56%, m.p. 163–165 °C. IR (KBr): ν(C=O) 1686, 1750 cm^{-1}, log $P = 3.43$. For $C_{17}H_{15}NO_4$ (297.3) calc.: 68.68% C, 4.71% N, 5.26% H; found: 68.45% C, 4.87% N, 5.15% H. ^{1}H NMR (DMSO-d_6) δ 7.40–7.30 (m, 3H, H5, H7, H8), 7.25–7.22 (m AA′BB′, 2H, H2′, H6′), 7.13–7.09 (m AA′BB′, 2H, H3′, H5′), 5.00 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.6, 156.5, 148.1, 146.8, 136.8, 133.4, 129.1, 127.9, 124.3, 118.1, 114.7, 108.8, 56.1, 45.1, 20.9.

*3.1.34. 3-(4-Fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4a**)*

White crystals. Yield 45%, m.p. 152–153 °C, Ref. [7] 138–141 °C. IR (KBr): ν(C=O) 1698, 1755 cm^{-1}, log $P = 3.23$. For $C_{15}H_{10}FNO_3$ (271.2) calc.: 66.42% C, 5.16% N, 3.72% H; found: 66.36% C, 5.17% N, 3.58% H. ^{1}H NMR (DMSO-d_6) δ 8.00 (d, 1H, $J(5,6) = 1.80$ Hz, H5), 7.80–7.73 (m, 1H, H7), 7.46–7.40 (m AA′BB′, 4H, H2′, H3′, H5′, H6′), 7.16–7.10 (m, 2H, H6, H8), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.3, 160.4 (d, $J = 197.1$ Hz), 152.6, 148.1, 136.6, 132.5 (d, $J = 11.4$ Hz), 130.2 (d, $J = 33.0$ Hz), 127.5, 125.6, 116.6, 115.3 (d, $J = 85.2$ Hz), 114.4, 44.6.

*3.1.35. 6-Bromo-3-(4-fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4b**)*

White crystals. Yield 58%, m.p. 176–179 °C. IR (KBr): ν(C=O) 1698, 1764 cm^{-1}, log $P = 4.06$. For $C_{15}H_9BrFNO_3$ (350.1) calc.: 51.45% C, 4.00% N, 2.59% H; found: 51.21% C, 3.89% N, 2.67% H. ^{1}H NMR (DMSO-d_6) δ 8.06 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.98 (dd, 1H, $J(5,7) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.45–7.40 (m, 3H, H8, H2′, H6′), 7.16–7.11 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.3, 150.8 (d, $J = 195.2$ Hz), 151.8, 147.8, 138.9, 132.3 (d, $J = 11.4$ Hz), 130.3 (d, $J = 31.4$ Hz), 129.4, 119.2, 117.1, 116.5, 115.3 (d, $J = 85.5$ Hz), 44.8.

*3.1.36. 6-Chloro-3-(4-fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4c**)*

White crystals. Yield 65%, m.p. 163–165 °C. IR (KBr): ν(C=O) 1764, 1701 cm^{-1}, log $P = 3.79$. For $C_{15}H_9ClFNO_3$ (305.7) calc.: 58.94% C, 4.58% N, 2.97% H; found: 59.29% C, 4.52% N, 2.97% H. ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.86 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), δ 7.49 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.46–7.41 (m AA′BB′, 2H, H2′, H6′), 7.17–7.11 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 161.8, 160.0 (d, $J = 190.2$ Hz), 151.4, 147.8, 136.2, 132.3 (d, $J = 12.3$ Hz), 130.3 (d, $J = 33.0$ Hz), 129.5, 126.5, 118.9, 116.1, 115.3 (d, $J = 85.5$ Hz), 44.9.

*3.1.37. 6,8-Dichloro-3-(4-fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4d**)*

White crystals. Yield 43%, m.p. 160–161 °C. IR (KBr): ν(C=O) 1700, 1770 cm^{-1}, log $P = 4.35$. For $C_{15}H_8Cl_2FNO_3$ (340.1) calc.: 52.97% C, 4.12% N, 2.37% H; found: 52.66% C, 3.96% N, 2.32% H. ^{1}H NMR (DMSO-d_6) δ 8.19 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.91 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.47–7.41 (m AA′BB′, 2H, H2′, H6′), 7.17–7.11 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.4, 159.8 (d, $J = 212.7$ Hz), 147.8, 147.1, 135.4, 132.0 (d, $J = 11.4$ Hz), 130.3 (d, $J = 33.0$ Hz), 129.3, 125.6, 121.6, 117.4, 115.3 (d, $J = 85.2$ Hz), 45.1.

*3.1.38. 3-(4-Fluorobenzyl)-6-methyl-2H-1,3-benzoxazine-2,4(3H)-dione (**4e**)*

White crystals. Yield 57%, m.p. 167–169 °C. IR (KBr): ν(C=O) 1695, 1757 cm^{-1}, log $P = 3.72$. For $C_{16}H_{12}FNO_3$ (285.3) calc.: 67.36% C, 4.91% N, 4.24% H; found: 67.64% C, 4.77% N, 4.45% H. ^1H NMR (DMSO-d_6) δ 7.74 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.60 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.43–7.39 (m AA′BB′, 2H, H2′, H6′), 7.33 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.18–7.12 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 163.3, 160.7 (d, $J = 210.5$ Hz), 150.7, 148.2, 137.3, 135.2, 132.6 (d, $J = 12.6$ Hz), 130.2 (d, $J = 33.0$ Hz), 127.0, 116.4, 115.3 (d, $J = 85.5$ Hz), 113.9, 44.6.

*3.1.39. 6,8-Dibromo-3-(4-fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4f**)*

White crystals. Yield 49%, m.p. 196–197 °C. IR (KBr): ν(C=O) 1697, 1772 cm^{-1}, log $P = 4.89$. For $C_{15}H_8Br_2FNO_3$ (429.0) calc.: 41.99% C, 3.26% N, 1.88% H; found: 41.98% C, 3.19% N, 1.92% H. ^1H NMR (DMSO-d_6) δ 8.37 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 8.05 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.47–7.41 (m AA′BB′, 2H, H2′, H6′), 7.16–7.11 (m AA′BB′, 2H, H3′, H5′), 5.02 (s 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.4, 159.8 (d, $J = 229.8$ Hz), 149.3, 147.2, 140.8, 132.0 (d, $J = 12.6$ Hz), 130.2 (d, $J = 33.3$ Hz), 129.0, 117.7, 117.2, 115.3 (d, $J = 85.2$ Hz), 110.8, 45.1.

*3.1.40. 3-(4-Fluorobenzyl)-7-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**4g**)*

White crystals. Yield 56%, m.p. 166–168 °C. IR (KBr): ν(C=O) 1692, 1751 cm^{-1}, log $P = 3.10$. For $C_{16}H_{12}FNO_4$ (301.3) calc.: 63.79% C, 4.65% N, 4.01% H; found: 63.89% C, 4.55% N, 4.24% H. ^1H NMR (DMSO-d_6) δ 7.88 (d, 1H, $J(5,6) = 9.00$ Hz, H5), 7.41–7.38 (m AA′BB′, 2H, H2′, H6′), 7.16–7.10 (m AA′BB′, 2H, H3′, H5′), 7.01–6.99 (m, 2H, H6, H8), 5.01 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 165.8, 161.7, 160.2 (d, $J = 200.75$ Hz), 154.5, 148.3, 132.7 (d, $J = 2.85$ Hz), 130.2 (d, $J = 7.95$ Hz), 129.0, 115.4 (d, $J = 21.08$ Hz), 113.5, 107.1, 100.5, 56.6, 44.4.

*3.1.41. 3-(4-Fluorobenzyl)-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**4h**)*

Yellow crystals. Yield 39%, m.p. 188–191 °C. IR (KBr): ν(C=O) 1701, 1771 cm^{-1}, log $P = 2.60$. For $C_{15}H_9FN_2O_5$ (316.2) calc.: 56.97% C, 8.86% N, 2.87% H; found: 57.18% C, 8.93% N, 2.55% H. ^1H NMR (DMSO-d_6) δ 8.63 (dd, 1H, $J(7,8) = 9.00$ Hz, $J(5,7) = 2.40$ Hz, H7), 8.58 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.70 (d, 1H, $J(7,8) = 9.00$ Hz, H8), 7.49–7.44 (m AA′BB′, 2H, H2′, H6′), 7.18–7.12 (m AA′BB′, 2H, H3′, H5′), 5.05 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.4, 160.2, 158.1 (d, $J = 258.2$ Hz), 147.4, 144.3, 132.0 (d, $J = 12.3$ Hz), 130.9, 130.4 (d, $J = 32.1$ Hz), 123.0, 118.6, 115.5, 115.3 (d, $J = 85.5$ Hz), 45.1.

*3.1.42. 7-Chloro-3-(4-fluorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**4i**)*

White crystals. Yield 58%, m.p. 144–146 °C. IR (KBr): ν(C=O) 1756, 1693 cm^{-1}, log $P = 3.79$. For $C_{15}H_9ClFNO_3$ (305.7) calc.: 58.94% C, 4.58% N, 2.97% H; found: 58.64% C, 4.46% N, 2.87% H. ^1H NMR (DMSO-d_6) δ 7.98 (d, 1H, $J(5,6) = 8.40$ Hz, H5), 7.69 (d, 1H, $J(6,8) = 1.80$ Hz, H8), 7.50 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(6,8) = 1.80$ Hz, H6), 7.45–7.41 (m AA′BB′, 2H, H2′, H6′), 7.17–7.10 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 161.8 (d, $J = 238.4$ Hz), 160.1, 153.1, 147.8, 140.5, 132.3 (d, $J = 12.6$ Hz), 130.3 (d, $J = 33.0$ Hz), 129.1, 125.9, 116.8, 115.3 (d, $J = 84.3$ Hz), 113.6, 44.8.

*3.1.43. 3-(4-Fluorobenzyl)-8-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**4j**)*

White crystals. Yield 56%, m.p. 179–181 °C. IR (KBr): ν(C=O) 1688, 1755 cm^{-1}, log $P = 3.10$. For $C_{16}H_{12}FNO_4$ (301.3) calc.: 63.79% C, 4.65% N, 4.01% H; found: 63.45% C, 4.60% N, 4.07% H. ^1H NMR (DMSO-d_6) δ 7.52–7.32 (m 5H, H5, H6, H7, H2′, H6′), 7.16–7.11 (m AA′BB′, 2H, H3′, H5′), 5.02 (s, 2H, CH_2), 3.91 s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 163.3, 160.5 (d, $J = 202.50$ Hz), 147.9, 146.8, 142.3, 132.5 (d, $J = 12.60$ Hz), 130.2 (d, $J = 31.80$ Hz), 125.5, 118.3, 117.9, 115.4, 115.2 (d, $J = 6.60$ Hz), 56.6, 44.7.

*3.1.44. 3-(4-Fluorobenzyl)-6-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**4k**)*

White crystals. Yield 47%, m.p. 160–161 °C. IR (KBr): ν(C=O) 1689, 1750 cm^{-1}, log $P = 3.10$. For $C_{16}H_{12}FNO_4$ (301.3) calc.: 63.79% C, 4.65% N, 4.01% H; found: 63.86% C, 4.65% N, 4.13% H. ^1H NMR (DMSO-d_6) δ 7.46–7.34 (m, 5H, H5, H6, H7, H2′, H6′), 7.19–7.10 (m AA′BB′, 2H, H3′, H5′), 5.03 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 163.3, 160.3 (d, $J = 169.80$ Hz), 156.5, 148.1, 146.8, 132.6 (d, $J = 12.3$ Hz), 130.2 (d, $J = 32.10$ Hz), 124.4, 118.1, 115.3 (d, $J = 85.50$ Hz), 114.8, 108.9, 56.1, 44.7.

*3.1.45. 3-(3,4-Dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5a**)*

White crystals. Yield 51%, m.p. 154–156 °C, Ref. [7] 153–156 °C. IR: ν(C=O) 1687, 1761 cm^{-1}, log $P = 4.19$. For $C_{15}H_9Cl_2NO_3$ (322.1) calc.: 55.93% C, 4.35% N, 2.82% H; found: 55.86% C, 4.20% N, 2.84% H. ^1H NMR (DMSO-d_6) δ 7.98 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(5,7) = 2.10$ Hz, H5), 7.83–7.79 (m, 1H, H7), 7.68 (d, 1H, $J(2',6') = 2.10$ Hz, H2′), 7.56 (d, 1H, $J(5',6') = 8.10$ Hz, H5′), 7.47–7.36 (m, 3H, H6, H8, H6′), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.9, 152.7, 148.2,

137.5, 136.5, 131.2, 130.6, 130.1, 129.9, 128.3, 127.5, 125.5, 116.6, 114.6, 44.4.

3.1.46. 6-Bromo-3-(3,4-dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5b**)

White crystals. Yield 65%, m.p. 175–177 °C. IR (KBr): ν(C=O) 1701, 1770 cm^{-1}, log $P = 5.02$. For $C_{15}H_8BrCl_2NO_3$ (401.0) calc.: 44.92% C, 3.49% N, 2.01% H; found: 45.06% C, 3.16% N, 2.20% H. ^{1}H NMR (DMSO-d_6) δ 8.05 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.99 (dd, 1H, $J(5,7) = 8.70$ Hz, $J(7,8) = 2.40$ Hz, H7), 7.68 (d, 1H, $J(2',6') = 2.40$ Hz, H2′), 7.58 (d, 1H, $J(5',6') = 8.70$ Hz, H5′), 7.43 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.38 (dd, 1H, $J(5',6') = 8.70$ Hz, $J(2',6') = 2.40$ Hz, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.9, 151.9, 147.8, 138.9, 137.2, 131.2, 130.6, 130.2, 129.9, 129.4, 128.3, 119.1, 117.1, 116.6, 44.6.

3.1.47. 6-Chloro-3-(3,4-dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5c**)

White crystals. Yield 57%, m.p. 171–173 °C. IR (KBr): ν(C=O) 1695, 1757 cm^{-1}, log $P = 4.75$. For $C_{15}H_8Cl_3NO_3$ (356.6) calc.: 50.52% C, 3.93% N, 2.26% H; found: 50.45% C, 3.83% N, 2.18% H. ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.88 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.40$ Hz, H7), 7.69 (d, 1H, $J(2',6') = 2.10$ Hz, H2′), 7.57 (d, 1H, $J(5',6') = 8.10$ Hz, H5′), 7.51 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.38 (dd, 1H, $J(5',6') = 8.10$ Hz, $J(2',6') = 2.10$ Hz, H6′), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.0, 151.5, 147.9, 137.2, 136.1, 131.2, 130.6, 130.2, 129.9, 129.4, 128.4, 126.5, 118.9, 116.3, 44.6.

3.1.48. 6,8-Dichloro-3-(3,4-dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5d**)

White crystals. Yield 49%, m.p. 184–186 °C. IR (KBr): ν(C=O) 1699, 1772 cm^{-1}, log $P = 5.30$. For $C_{15}H_7Cl_4NO_3$ (391.0) calc.: 46.07% C, 3.58% N, 1.80% H; found: 46.05% C, 3.47% N, 1.87% H. ^{1}H NMR (DMSO-d_6) δ 8.20 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.93 (d, 1H, $J(5,7) = 2.70$ Hz, H7), 7.69 d, 1H, $J(2',6') = 2.10$ Hz, H2′), 7.58 (d, 1H, $J(5',6') = 8.10$ Hz, H5′), 7.40 (dd, 1H, $J(5',6') = 8.10$ Hz, $J(2',6') = 2.10$ Hz, H6′), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.5, 147.8, 147.1, 136.9, 135.4, 131.2, 130.6, 130.2, 129.7, 129.3, 128.4, 125.6, 121.5, 117.6, 44.8.

3.1.49. 3-(3,4-Dichlorobenzyl)-6-methyl-2H-1,3-benzoxazine-2,4(3H)-dione (**5f**)

White crystals. Yield 67%, m.p. 130–132 °C. IR (KBr): ν(C=O) 1689, 1753 cm^{-1}, log $P = 4.68$. For $C_{16}H_{11}Cl_2NO_3$ (336.2) calc.: 57.17% C, 4.17% N, 3.30% H; found: 56.78% C, 4.31% N, 3.03% H. ^{1}H NMR (DMSO-d_6) δ 7.77 (d, 1H, $J(5,7) = 1.80$ Hz, H5), 7.67 (d, 1H, $J(2',6') = 1.80$ Hz, H2′), 7.62 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 1.80$ Hz, H7), 7.56 (d, 1H, $J(5',6') = 8.40$ Hz, H5′), 7.36 (dd, 1H, $J(5',6') = 8.40$ Hz, $J(2',6') = 1.80$ Hz, H6′), 7.33 d, 1H, $J(7,8) = 8.70$ Hz, H8), 5.03 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 150.8, 148.3, 137.5, 137.3, 135.1, 131.2, 130.7, 130.1, 129.9, 128.3, 127.0, 116.4, 114.1, 44.4, 20.3.

3.1.50. 6,8-Dibromo-3-(3,4-dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5f**)

White crystals. Yield 59%, m.p. 217–219 °C. IR (KBr): ν(C=O) 1699, 1769 cm^{-1}, log $P = 5.85$. For $C_{15}H_7Br_2Cl_2NO_3$ (479.9) calc.: 37.54% C, 2.92% N, 1.47% H; found: 37.71% C, 2.82% N, 1.60% H. ^{1}H NMR (DMSO-d_6) δ 8.38 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 8.05 (d, 1H, $J(5,7) = 2.70$ Hz, H7), 7.69 (d, 1H, $J(2',6') = 1.80$ Hz, H2′), 7.58 (d, 1H, $J(5',6') = 8.10$ Hz, H5′), 7.40 (dd, 1H, $J(5',6') = 8.10$ Hz, $J(2',6') = 1.80$ Hz, H6′), 5.03 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.5, 149.3, 147.3, 140.8, 136.9, 131.1, 130.6, 130.2, 129.7, 129.0, 128.3, 117.8, 117.2, 110.7, 44.8.

3.1.51. 3-(3,4-Dichlorobenzyl)-7-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**5g**)

White crystals. Yield 53%, m.p. 132–135 °C. IR (KBr): ν(C=O) 1693, 1755 cm^{-1}, log $P = 4.06$. For $C_{16}H_{11}Cl_2NO_4$ (352.2) calc.: 54.57% C, 3.98% N, 3.15% H; found: 54.25% C, 3.86% N, 3.16% H. ^{1}H NMR (DMSO-d_6) δ 7.87 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(5,8) = 0.60$ Hz, H5), 7.66 (d, 1H, $J(2',6') = 1.80$ Hz, H2′), 7.56 (d, 1H, $J(5',6') = 8.40$ Hz, H5′), 7.46 (dd, 1H, $J(5',6') = 8.40$ Hz, $J(2',6') = 1.80$ Hz, H6′), 7.02–6.99 (m, 2H, H6, H8), 5.01 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 165.8, 160.3, 154.6, 148.4, 137.6, 131.1, 130.7, 130.2, 129.9, 128.9, 128.3, 113.4, 107.3, 100.5, 56.6, 44.2.

3.1.52. 3-(3,4-Dichlorobenzyl)-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**5h**)

Yellow crystals. Yield 46%, m.p. 170–172 °C. IR (KBr): ν(C=O) 1707, 1771 cm^{-1}, log $P = 3.70$. For $C_{15}H_8Cl_2N_2O_5$ (367.1) calc.: 49.07% C, 7.63% N, 2.20% H; found: 49.39% C, 7.51% N, 1.89% H. ^{1}H NMR (DMSO-d_6) δ 8.64–8.59 (m, 2H, H5, H7), 7.73–7.70 (m, 2H, H2′, H8), 7.59 (d, 1H, $J(5',6') = 8.40$ Hz, H5′), 7.43 (dd, 1H, $J(5',6') = 8.40$ Hz, $J(2',6') = 2.40$ Hz, H6′), 5.06 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 159.9, 156.4, 147.4, 144.3, 136.9, 131.1, 130.9, 130.6, 130.3, 129.9, 128.4, 123.0, 118.5, 115.7, 44.8.

3.1.53. 7-Chloro-3-(3,4-dichlorobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**5i**)

White crystals. Yield 57%, m.p. 172–174 °C. IR (KBr): ν(C=O) 1698, 1758 cm^{-1}, log $P = 4.75$. For $C_{15}H_8Cl_3NO_3$ (356.6) calc.: 50.52% C, 3.93% N, 2.26% H; found: 50.24% C, 3.83% N, 2.33% H. ^{1}H NMR (DMSO-d_6) δ 7.97 (d, 1H, $J(5,6) = 8.40$ Hz, H5), 7.71–

7.68 (m, 2H, H2′, H8), 7.58 (d, 1H, $J(5',6') = 8.40$ Hz, H5′), 7.50 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(6,8) = 2.10$ Hz, H6), 7.38 (dd, 1H, $J(5',6') = 8.40$ Hz, $J(2',6') = 2.10$ Hz, H6′), 5.02 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 160.3, 153.2, 147.9, 140.5, 137.3, 131.2, 130.6, 130.2, 129.9, 129.1, 128.3, 125.8, 116.8, 113.8, 44.5

*3.1.54. 3-(3,4-Dichlorobenzyl)-8-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**5j**)*

White crystals. Yield 56%, m.p. 149–151 °C. IR (KBr): ν(C=O) 1696, 1758 cm^{-1}, log $P = 4.06$. For $C_{16}H_{11}Cl_2NO_4$ (352.2) calc.: 54.57% C, 3.98% N, 3.15% H; found: 54.80% C, 3.90% N, 3.18% H. ^1H NMR (DMSO-d_6) δ 7.67 (d, 1H, $J(2',6') = 1.80$ Hz, H2′), 7.56 (d, 1H, $J(5',6') = 8.10$ Hz, H5′), 7.49–7.46 (m, 2H, H5, H7), 7.41–7.35 (m, 2H, H6, H6′), 5.04 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 156.5, 148.2, 146.9, 138.8, 133.2, 130.4, 127.7, 127.6, 126.5, 124.3, 118.1, 114.8, 108.8, 56.1, 44.9.

*3.1.55. 3-(3-Chlorobenzyl)-6-methoxy-2H-1,3-benzoxazine-2,4(3H)-dione (**5k**)*

White crystals. Yield 66%, m.p. 139–140 °C. IR (KBr): ν(C=O) 1693, 1752 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.35% C, 4.36% N, 3.95% H. ^1H NMR (DMSO-d_6) δ 7.45 (bs, 1H, H5), 7.40–7.37 (m, 3H, H7, H2′, H4′), 7.34–7.31 (m, 3H, H8, H5′, H6′), 5.04 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.8, 156.4, 148.2, 146.9, 138.9, 133.3, 130.5, 127.7, 127.6, 126.6, 124.3, 118.2, 114.9, 108.8, 56.2, 45.0.

*3.1.56. 3-(4-Methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6a**)*

White crystals. Yield 49%, m.p. 110–112 °C, Ref. [7] 104–106 °C. IR (KBr): ν(C=O) 1698, 1753 cm^{-1}, log $P = 2.95$. For $C_{16}H_{13}NO_4$ (283.3) calc.: 67.84% C, 4.94% N, 4.63% H; found: 67.55% C, 4.77% N, 4.69% H. ^1H NMR (DMSO-d_6) δ 7.99 (dd, 1H, $J(5,6) = 8.40$ Hz, $J(5,7) = 1.80$ Hz, H5), 7.85–7.78 (m, 1H, H7), 7.45–7.40 (m, 2H, H6, H8), 7.32–7.29 (m AA′BB′, 2H H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.98 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 158.9, 152.5, 148.1, 136.6, 129.7, 128.3, 127.6, 125.6, 116.6, 114.4, 113.9, 55.3, 44.8.

*3.1.57. 6-Bromo-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6b**)*

White crystals. Yield 56%, m.p. 163–169 °C. IR (KBr): ν(C=O) 1693, 1768 cm^{-1}, log $P = 3.77$. For $C_{16}H_{12}BrNO_4$ (362.2) calc.: 53.06% C, 3.87% N, 3.34% H; found: 53.44% C, 3.50% N, 3.63% H. ^1H NMR (DMSO-d_6) δ 8.06 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.96 (dd, 1H, $J(7,8) = 8.70$ Hz, $J(5,7) = 2.70$ Hz, H7), 7.42 (d, 1H, $J(7,8) = 8.70$ Hz, H8), 7.32–7.29 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.97 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 159.7, 158.9, 151.8, 147.7, 138.9, 129.8, 129.4, 128.0, 119.2, 117.1, 116.4, 113.9, 55.2, 44.9.

*3.1.58. 6-Chloro-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6c**)*

White crystals. Yield 55%, m.p. 155–161 °C. IR (KBr): ν(C=O) 1696, 1769 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.26% C, 4.31% N, 3.74% H. ^1H NMR (DMSO-d_6) δ 7.93 (d, 1H, $J(5,7) = 2.70$ Hz, H5), 7.85 (dd, 1H, $J(7,8) = 9.00$ Hz, $J(5,7) = 2.70$ Hz, H7), 7.49 (d, 1H, $J(7,8) = 9.00$ Hz, H8), 7.33–7.30 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.97 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 159.8, 158.9, 151.3, 147.7, 136.1, 129.8, 129.5, 128.1, 126.5, 118.9, 116.0, 113.9, 55.3, 45.0.

*3.1.59. 6,8-Dichloro-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6d**)*

White crystals. Yield 58%, m.p. 155–157 °C. IR (KBr): ν(C=O) 1707, 1772 cm^{-1}, log $P = 4.06$. For $C_{16}H_{11}Cl_2NO_4$ (352.2) calc.: 54.57% C, 3.98% N, 3.15% H; found: 54.87% C, 3.90% N, 3.07% H. ^1H NMR (DMSO-d_6) δ 8.18 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 7.91 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.33–7.30 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.97 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 159.4, 158.9, 147.7, 147.0, 135.4, 129.8, 129.3, 127.7, 127.6, 121.6, 117.4, 113.9, 55.3, 45.2.

*3.1.60. 3-(4-Methoxybenzyl)-6-methyl-2H-1,3-benzoxazine-2,4(3H)-dione (**6e**)*

White crystals. Yield 64%, m.p. 135–137 °C. IR (KBr): ν(C=O) 1693, 1757 cm^{-1}, log $P = 3.43$. For $C_{17}H_{15}NO_4$ (297.3) calc.: 68.68% C, 4.71% N, 5.09% H; found: 68.61% C, 4.68% N, 5.04% H. ^1H NMR (DMSO-d_6) δ 7.77 (d, 1H, $J(5,7) = 1.80$ Hz, H5), 7.60 (dd, 1H, $J(7,8) = 8.10$ Hz, $J(5,7) = 1.80$ Hz, H7), 7.32 (d, 1H, $J(7,8) = 8.10$ Hz, H8), 7.30–7.28 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.97 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.7, 158.9, 150.6, 148.1, 137.3, 135.1, 129.7, 128.4, 127.0, 116.4, 114.0, 55.3, 44.7, 20.3.

*3.1.61. 6,8-Dibromo-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6f**)*

White crystals. Yield 68%, m.p. 168–170 °C. IR (KBr): ν(C=O) 1701, 1772 cm^{-1}, log $P = 4.60$. For $C_{16}H_{11}Br_2NO_4$ (441.1) calc.: 43.57% C, 3.18% N, 2.51% H; found: 43.62% C, 3.01% N, 2.52% H. ^1H NMR (DMSO-d_6) δ 8.36 (d, 1H, $J(5,7) = 2.40$ Hz, H5), 8.04 (d, 1H, $J(5,7) = 2.40$ Hz, H7), 7.33–7.30 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.96 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3). ^{13}C

NMR (DMSO-d_6) δ 159.3, 158.9, 149.2, 147.1, 140.8, 129.8, 129.0, 127.8, 117.6, 117.2, 113.9, 110.8, 55.3, 45.2.

3.1.62. 3-(4-Methoxybenzyl)-6-nitro-2H-1,3-benzoxazine-2,4(3H)-dione (**6h**)

Yellow crystals. Yield 56%, m.p. 143–151 °C. IR (KBr): ν(C=O) 1704, 1771 cm^{-1}, log $P = 2.59$. For $C_{16}H_{12}N_2O_6$ (328.3) calc.: 58.54% C, 8.53% N, 3.68% H; found: 58.63% C, 8.36% N, 3.69% H. ^{1}H NMR (DMSO-d_6) δ 8.63–8.57 (m, 2H, H5, H7), 8.69 (d, 1H, $J(7,8) = 9.00$ Hz, H8), 7.35–7.32 (m AA′BB′, 2H, H2′, H6′), 6.88–6.86 (m AA′BB′, 2H, H3′, H5′), 4.99 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 159.7, 158.9, 156.3, 147.3, 144.3, 130.9, 129.9, 127.8, 123.1, 118.6, 115.4, 113.9, 55.3, 45.2.

3.1.63. 7-Chloro-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6i**)

White crystals. Yield 64%, m.p. 153–156 °C. IR (KBr): ν(C=O) 1690, 1768 cm^{-1}, log $P = 3.50$. For $C_{16}H_{12}ClNO_4$ (317.7) calc.: 60.48% C, 4.41% N, 3.81% H; found: 60.87% C, 4.15% N, 3.92% H. ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 1H, $J(5,6) = 8.10$ Hz, H5), 7.68 (d, 1H, $J(6,8) = 1.80$ Hz, H8), 7.50 (dd, 1H, $J(5,6) = 8.10$ Hz, $J(6,8) = 1.80$ Hz, H6), 7.32–7.29 (m AA′BB′, 2H, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.96 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 160.0, 158.9, 153.0, 147.8, 140.5, 129.7, 129.2, 128.1, 125.9, 116.8, 113.9, 113.6, 55.3, 44.9.

3.1.64. 8-Methoxy-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6j**)

White crystals. Yield 45%, m.p. 165–167 °C. IR (KBr): ν(C=O) 1684, 1756 cm^{-1}, log $P = 2.82$. For $C_{17}H_{15}NO_5$ (313.3) calc.: 65.17% C, 4.47% N, 4.83% H; found: 64.82% C, 4.33% N, 4.94% H. ^{1}H NMR ($CDCl_3$) δ 7.49–7.46 (m, 2H, H5, H7), 7.37–7.28 (m, 3H, H6, H2′, H6′), 6.88–6.85 (m AA′BB′, 2H, H3′, H5′), 4.97 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 160.7, 158.9, 147.8, 146.8, 142.2, 129.7, 128.3, 125.5, 118.7, 117.9, 11.1, 113.9, 56.6, 55.3, 44.8.

3.1.65. 6-Methoxy-3-(4-methoxybenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (**6k**)

White crystals. Yield 63%, m.p. 158–159 °C. IR (KBr): ν(C=O) 1685, 1751 cm^{-1}, log $P = 2.82$. For $C_{17}H_{15}NO_5$ (313.3) calc.: 65.17% C, 4.47% N, 4.83% H; found: 65.22% C, 4.11% N, 4.80% H. ^{1}H NMR ($CDCl_3$) δ 7.40–7.36 (m, 3H, H5, H7, H8), 7.31–7.29 (m AA′BB′, 2H, H2′, H6′), 6.88–6.84 (m AA′BB′, 2H, H3′, H5′), 4.98 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 160.6, 158.9, 156.5, 148.1, 146.8, 129.7, 128.3, 124.4, 118.1, 114.7, 113.9, 108.8, 56.1, 55.3, 44.8.

3.2. Microbiology

The following strains, obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague, were used for the evaluation of in vitro antimycobacterial activity: *M. kansasii* CNCTC My 235/80, and *M. avium* CNCTC My 330/88, and a clinical isolate of *Mycobacterium kansasii* 6 509/ 96. Antimycobacterial activity of the compounds against these strains was determined in the Šula semisynthetic medium (SEVAC, Prague). The Šula liquid medium (with bovine serum) is routinely used in the Czech Republic. Each strain was simultaneously inoculated into a Petri dish containing the Löwenstein–Jensen medium for the control of the 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 μmol/l. The minimum inhibitory concentrations were determined after incubation at 37 °C for 21 days (see Table 1). MIC was the lowest concentration of an antimycobacterially effective substance (on the above-stated concentration scale), at which inhibition of the growth of the mycobacteria occurred.

3.3. Calculations

Logarithms of the partition coefficients were calculated using ChemOffice 6 software (Table 2). All regression equations were set up using the Linreg and Multireg H programmes (Klemera) for Microsoft Excel. The values of the Hammett constants (Table 3) were taken from Ref. [8].

4. Results and discussion

To set up the regression equations, we employed the "Linreg" programme developed by Klemera for Microsoft Excel. The values of antimycobacterial activity of *N*-benzylsalicylamides were taken from the literature [5]. The antimycobacterial activities of *N*-benzylsalicylamines correlate (see Eqs. (1)–(6)) with those of 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones. Thus, it appears that the mechanisms of antimycobacterial activity are identical. Recently, we have found similar correlations for salicylanilides and 3-aryl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones [4].

4.1. M. avium My 330/88

$$\log \mathrm{MIC_{BO}} = 0.949(\pm 0.111) \log \mathrm{MIC_{SA}} + 0.131(\pm 0.219) \quad (1)$$

$$r = 0.90 \qquad s = 0.20 \qquad n = 19 \qquad F = 73$$

Table 1
In vitro antimycobacterial activity of 3-benzyl-2*H*-1,3-benzoxazin-2,4(3*H*)-diones

Comp.	Minimum inhibitory concentrations (MICs) μmol l^{-1} Incubation 21 days				
	R_1	R_2	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
1a	H	H	**62.5**	62.5	62.5
1b	6-Br	H	62.5	125	125
1c	6-Cl	H	62.5	62.5	125
1d	6,8-Cl_2	H	250	250	125
1e	6-CH_3	H	62.5	62.5	125
1f	6,8-Br_2	H	[a]	[a]	[a]
1g	7-CH_3O	H	[a]	[a]	[a]
1h	6-NO_2	H	[a]	250	250
1i	7-Cl	H	62.5	[a]	[a]
1k	8-CH_3O	H	[a]	[a]	[a]
1l	6-CH_3O	H	[a]	[a]	[a]
2a	H	4-Cl	32	[a]	125
2b	6-Br	4-Cl	[a]	[a]	[a]
2c	6-Cl	4-Cl	32	[a]	[a]
2d	6,8-Cl_2	4-Cl	[a]	[a]	[a]
2e	6-CH_3	4-Cl	[a]	[a]	[a]
2f	6,8-Br_2	4-Cl	[a]	[a]	[a]
2g	7-CH_3O	4-Cl	[a]	[a]	[a]
2h	6-NO_2	4-Cl	[a]	250	125
2i	7-Cl	4-Cl	[a]	[a]	[a]
2k	8-CH_3O	4-Cl	[a]	[a]	[a]
2l	6-CH_3O	4-Cl	[a]	[a]	[a]
3a	H	4-CH_3	62.5	[a]	[a]
3b	6-Br	4-CH_3	[a]	[a]	[a]
3c	6-Cl	4-CH_3	[a]	[a]	[a]
3d	6,8-Cl_2	4-CH_3	[a]	[a]	[a]
3e	6-CH_3	4-CH_3	[a]	[a]	[a]
3f	6,8-Br_2	4-CH_3	[a]	[a]	[a]
3g	7-CH_3O	4-CH_3	[a]	[a]	[a]
3h	6-NO_2	4-CH_3	500	500	250
3i	7-Cl	4-CH_3	[a]	[a]	[a]
3k	8-CH_3O	4-CH_3	[a]	[a]	[a]
3l	6-CH_3O	4-CH_3	[a]	[a]	[a]
4a	H	4-F	125	250	250
4b	6-Br	4-F	62.5	[a]	[a]
4c	6-Cl	4-F	32	62.5	125
4d	6,8-Cl_2	4-F	[a]	[a]	[a]
4e	6-CH_3	4-F	[a]	[a]	[a]
4f	6,8-Br_2	4-F	[a]	[a]	[a]
4g	7-CH_3O	4-F	[a]	[a]	[a]
4h	6-NO_2	4-F	[a]	[a]	[a]
4i	7-Cl	4-F	62.5	125	125
4k	8-CH_3O	4-F	[a]	[a]	[a]
4l	6-CH_3O	4-F	[a]	[a]	[a]
5a	H	3,4-Cl_2	32	62.5	62.5
5b	6-Br	3,4-Cl_2	32	62.5	62.5
5c	6-Cl	3,4-Cl_2	32	62.5	62.5
5d	6,8-Cl_2	3,4-Cl_2	125	125	125
5e	6-CH_3	3,4-Cl_2	[a]	[a]	[a]
5f	6,8-Br_2	3,4-Cl_2	[a]	[a]	[a]
5g	7-CH_3O	3,4-Cl_2	[a]	[a]	[a]
5h	6-NO_2	3,4-Cl_2	250	125	125
5i	7-Cl	3,4-Cl_2	[a]	[a]	[a]
5k	8-CH_3O	3,4-Cl_2	[a]	[a]	[a]
5l	6-CH_3O	3-Cl	[a]	[a]	[a]
6a	H	4-CH_3O	[a]	[a]	250
6b	6-Br	4-CH_3O	[a]	[a]	[a]
6c	6-Cl	4-CH_3O	[a]	[a]	[a]
6d	6,8-Cl_2	4-CH_3O	[a]	[a]	[a]

Table 1 (*Continued*)

Comp.	Minimum inhibitory concentrations (MICs) μmol l^{-1} Incubation 21 days				
	R_1	R_2	*M. avium* My 330/88	*M. kansasii* My 235/80	*M. kansasii* 6509/96
6e	6-CH_3	4-CH_3O	[a]	[a]	[a]
6f	6,8-Br_2	4-CH_3O	[a]	[a]	[a]
6h	6-NO_2	4-CH_3O	1000	500	250
6i	7-Cl	4-CH_3O	125	[a]	[a]
6k	8-CH_3O	4-CH_3O	[a]	[a]	[a]
6l	6-CH_3O	4-CH_3O	[a]	[a]	[a]
INH			250	250	4

[a] log MIC could not be determined due to a low solubility.

Table 2
Lipophilicity (log *P*) of compounds **1a-6l**

Comp.	log *P*	Comp.	log *P*	Comp.	log *P*
1a	3.07	**3a**	3.56	**5a**	4.19
1b	3.90	**3b**	4.39	**5b**	5.02
1c	3.63	**3c**	4.12	**5c**	4.75
1d	4.19	**3d**	4.68	**5d**	5.30
1e	3.56	**3e**	4.05	**5e**	4.68
1f	4.73	**3f**	5.22	**5f**	5.85
1g	2.95	**3g**	3.43	**5g**	4.06
1h	2.46	**3h**	2.88	**5h**	3.70
1i	3.63	**3i**	4.12	**5i**	4.75
1k	2.95	**3k**	3.43	**5k**	4.06
1l	2.95	**3l**	3.43	**5l**	3.50
2a	3.63	**4a**	3.23	**6a**	2.95
2b	4.46	**4b**	4.06	**6b**	3.77
2c	4.19	**4c**	3.79	**6c**	3.50
2d	4.75	**4d**	4.35	**6d**	4.06
2e	4.12	**4e**	3.72	**6e**	3.43
2f	5.29	**4f**	4.89	**6f**	4.60
2g	3.50	**4g**	3.10	**6h**	2.59
2h	3.08	**4h**	2.60	**6i**	3.50
2i	4.19	**4i**	3.79	**6k**	2.82
2k	3.50	**4k**	3.10	**6l**	2.82
2l	3.50	**4l**	3.10		

Table 3
Values of substituent constants

Substituent	σ_m	σ_p
H	0	0
Br	0.39	0.23
Cl	0.37	0.23
NO_2	0.71	0.78
CH_3	−0.07	−0.17
OCH_3	0.12	−0.27
F	0.34	0.06

The values of the substituent constants were taken from Ref. [6]

4.2. M. kansasii My 235/80

$$\log \mathrm{MIC_{BO}} = 0.848(\pm 0.200)\log \mathrm{MIC_{SA}} + 0.487(\pm 0.414) \quad (2)$$

$$r = 0.80 \quad s = 0.20 \quad n = 12 \quad F = 18$$

4.3. M. kansasii 6509/96

$$\log \mathrm{MIC_{BO}} = 0.524(\pm 0.100)\log \mathrm{MIC_{SA}} + 1.062(\pm 0.210) \quad (3)$$

$$r = 0.83 \quad s = 0.13 \quad n = 14 \quad F = 27$$

The QSAR study of the antimycobacterial activity of 3-benzyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones includes the results obtained after 21 days of incubation. The structure–activity relationships of the activity against *M. avium* were expressed by the classical Hansch equations (optimum of log *P* is 5.13). Indicator parameter I was used for disubstituted benzoxazines (3-benzyl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones).The influence of the electronic effects of the substituents on the benzoxazine moiety was expressed by the Hammett constants, with regard to their orientation to the hydroxy group in position 1 $(\sigma)_O$ and to the carbonyl group in position 4 $(\sigma)_{CO}$. The influence of the substituents on the benzyl ring was not important. According to equations 5 and 6, we did not obtain the optimum of log *P* for the activity against both strains of *M. kansasii.* More lipophilic compounds have probably more favourable log *P* for antimycobacterial activity against this species. The compounds under study are more active than INH against standard strains of *M. avium* and *M. kansasii*.

$$\log \mathrm{MIC}_{M.avium21d} = -1.878(\pm 0.510)\log P + 0.183(\pm 0.065)(\log P)^2 + 0.670(\pm 0.141)(\sigma)_O + 0.718(\pm 0.140)I + 6.117(\pm 1.000) \quad (4)$$

$$r = 0.94 \quad s = 0.16 \quad n = 22 \quad F = 32$$

$$\log \mathrm{MIC}_{M.kansasii21d} = -0.232(\pm 0.076)\log P + 0.489(\pm 0.168)(\sigma)_O + 0.481(\pm 0.166)I + 2.756(\pm 0.308) \quad (5)$$

$$r = 0.85 \quad s = 0.19 \quad n = 17 \quad F = 11$$

$$\log \mathrm{MIC}_{M.kansasiiklin.21d} = -0.183(\pm 0.047)\log P + 0.181(\pm 0.047)(\sigma)_{CO} + 2.714(\pm 0.182) \quad (6)$$

$$r = 0.71 \quad s = 0.16 \quad n = 19 \quad F = 9$$

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