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Synthesis of alkyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates as peptidomimetic building blocks

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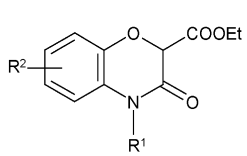
Abstract—A general synthesis of new alkyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate peptidomimetic building blocks from the corresponding alkyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates through carbanion oxidation is described.

1. Introduction

In a previous communication we reported an unexpected synthesis of the hitherto unknown ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2** on treatment of 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **1** with sodium hydride in an inert polar solvent.[1] Compounds **1** and **2** are useful peptidomimetic building blocks which have been used, inter alia, for the synthesis of fibrinogen receptor antagonists and Factor Xa inhibitors.[2,3] The structure of hydroxy compounds **2** was established unambiguously by NMR studies and X-ray crystallography,[1] but the proposed reaction mechanism of the conversion of **1** to **2**, by oxidizing the carbanion of **1**, remained to be clarified. In this paper we present further experiments that illustrate both the reactivity of compounds **1** for hydroxylation in position 2 and the scope of the reaction, in order to elucidate the potential of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives **1** and **2** as synthons for the construction of peptidomimetics.



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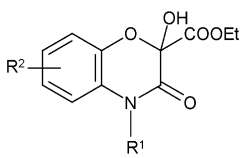

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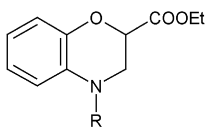
2. Results and discussion

The synthesis of 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **1** by phase-transfer alkylation of 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-carboxylates **3** has been described.[4] Using this method, compounds **1a**–**1k** were synthesized, among which **1c** and **1e**–**1k** have not been described so far.

Initially, the conversion of compounds **1** into the corresponding ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2** was performed by stirring **1** with an equimolar quantity of sodium hydride in dioxane under argon for 2–3 h. In order to study the reactivity of 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **1** for hydroxylation in position 2, and to expand the pool of peptidomimetic templates, the same reaction was attempted using ethyl 4-alkyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **4** (R=Me, Bn) and 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**5**) as substrates. Compounds **4** and **5** were prepared by a combination of published procedures.[5–7] Neither **4** nor **5** reacted under the standard reaction conditions[1] to give the corresponding 2-hydroxy derivatives, indicating that the 2-ethoxycarbonyl and 3-oxo groups of **1** are both required for the hydroxylation reaction to proceed.



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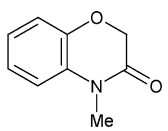

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The presence of two carbonyl groups at positions α to carbon atom 2 at which hydroxylation takes place, is obviously necessary to ensure the appropriate acidity of the proton at position 2. According to the literature,[8,9] the formation of a carbanion and its subsequent attack on the molecule of oxygen is crucial for oxidation of carbanions.

Keywords: carbanion oxidation; 1,4-benzoxazine-2-carboxylates; peptidomimetic building blocks.
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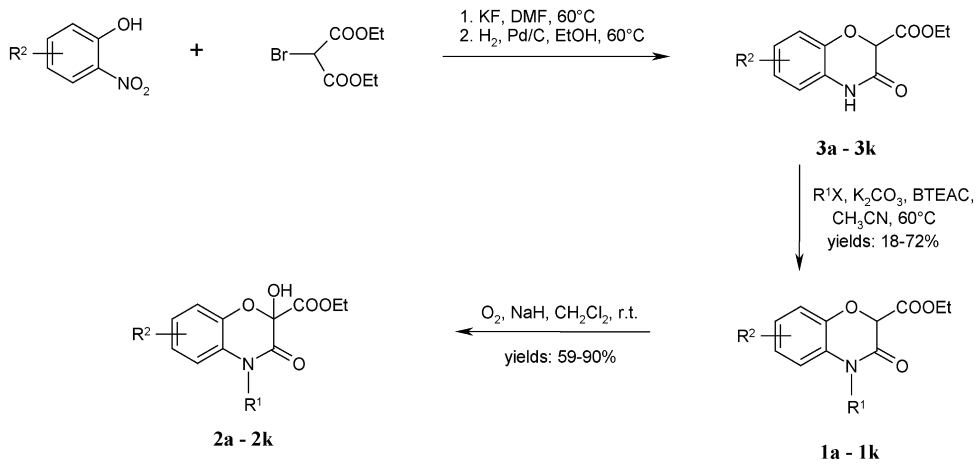

Scheme 1. The synthesis of ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2a**–**2k**.

Efforts were made to improve the reaction yields of the oxidation step. For this purpose, *m*-chloroperoxybenzoic acid was used as an oxidizing agent, leading to the formation of the desired products **2**, but without any improvement in yield. Since the initial experiments for converting **1** into **2** were carried out under an argon atmosphere and, given the low yields of **2a**–**f**,[1] self-oxidation of **1** (i.e. compound **1** acting both as a substrate and an oxidizing agent) could not be excluded as a plausible mechanism. However, it also seemed possible, that traces of oxygen present in the reaction mixture might cause oxidation of **1**. The reaction of **1a** (R^1=Me, R^2=H) and **1d** (R^1=Bn, R^2=H) were repeated in dichloromethane, with the only modification that oxygen was bubbled continuously through the reaction mixture. Dioxane was replaced by dichloromethane, due to the possibility of peroxide formation from dioxane in the presence of oxygen. It was previously established that there was no difference in the reaction course and in the yields of **2a** and **2d** in the two solvents. Interestingly, neither compound **1a** nor **1d** was found in the reaction mixture when the reaction took place in the presence of oxygen. In all cases, polar by-products were formed which could not be eluted from the baseline on TLC (silica gel; dichloromethane/methanol=50:1). In the case of substrate **1a**, the polar by-product was identified as 4-methyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid. This indicated that compounds **1a**–**k** were quantitatively oxidized under the modified reaction conditions in the presence of oxygen (Scheme 1). However, the hydroxy compounds **2a**–**k** were partially hydrolyzed to give the corresponding carboxylic acids.

In order to restrict the extent of hydrolysis and to produce the desired ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2a**–**2k** in higher yields, triethylamine was used as a base instead of sodium hydride. Again, no formation of products **2** was observed. The undesirable presence of traces of water leading to hydrolysis of **2a**–**2k** was finally solved by adding molecular sieves to the reaction mixture. The yields of **2a**–**2k** were additionally improved using an excess of sodium hydride, prolonged introduction of oxygen and by stirring the reaction mixture overnight. In this way very high yields of **2a**–**2k** were achieved.

We were also able to simplify the isolation process. Instead of column chromatography, which was initially needed to separate the oxidized products **2a**–**2f** from the starting compounds **1a**–**1f** and from the hydrolyzed products **6a**–**6f**, we now isolate the products **2a**–**2k** simply by extraction. We found that in the previous procedure the addition of aqueous hydrogen chloride to the reaction mixture to neutralize the strongly basic medium resulted in considerable additional product hydrolysis. Therefore, we decided to carry out the neutralization by adding solid citric acid followed by extraction of the weakly acidic organic phase. In this way the extent of undesirable hydrolysis of **2a**–**2k** was further suppressed.

Subsequently, we concentrated on extending the pool of 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate peptidomimetic building blocks **2**. Thus, we describe the synthesis of novel peptidomimetic scaffolds, 4-ethoxylcarbonylpropyl-, 4-*tert*-butyloxycarbonylmethyl- and 4-benzyloxycarbonylmethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2g**–**2i** (Table 1) which allow easy derivatization at position 4. As an extension of this work, the 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate analogues with substituted benzene core **2j**–**2k** were also prepared as peptidomimetic building blocks that enable additional functionalization of the aromatic ring.

Table 1. Ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2a**–**2k** prepared

	R^1	R^2	Yield (%)
2a	Me	H	82
2b	Et	H	75
2c	Pr	H	76
2d	CH_2Ph	H	90
2e	CH_2–(4-CN)–C_6H_4	H	85
2f	CH_2COOEt	H	86
2g	$(CH_2)_3COOEt$	H	56
2h	CH_2COO^tBu	H	71
2i	CH_2COOCH_2Ph	H	59
2j	Me	6-COOEt	85
2k	Me	7-COOEt	79

3. Conclusion

In conclusion, we have established a general synthetic method for synthesizing of alkyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates, which are interesting peptidomimetic building blocks for the synthesis of integrin receptor antagonists and serine protease inhibitors.

4. Experimental

4.1. Materials

Chemicals from Aldrich Chemical Co. and Fluka were used without further purification. Anhydrous 1,4-dioxane, dichloromethane and triethylamine were prepared according to described procedures.[10] Analytical TLC was performed on Merck silica gel (60 F 254) plates (0.25 mm) and components visualized with ultraviolet light. Column chromatography was carried out on silica gel 60 (particle size 240–400 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX$_{300}$ spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as the internal standard. IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. Microanalyses were performed on a Perkin–Elmer C, H, N analyzer 240 C. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer. All reported yields are yields of purified products.

4.2. General procedure for preparing ethyl 4-alkyl-3-oxo-3,4-dihydro-2*H*-1, 4-benzoxazine-2-carboxylates 1a–1k by alkylation of ethyl 3-oxo-3,4-dihydro-2*H*-1, 4-benzoxazine-2-carboxylates 3a–3k

A suspension of ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate **3** (10 mmol),[11] the corresponding alkyl halide (10 mmol), potassium carbonate (2.07 g, 25 mmol) and benzyltriethylammonium chloride (2.28 g, 10 mmol) in acetonitrile (50 mL) was heated at 60°C overnight. The reaction mixture was filtered and the solution evaporated under vacuum. The oily residue was dissolved in dichloromethane (150 mL) and washed with 10% citric acid (2×40 mL), saturated aqueous $NaHCO_3$ (2×40 mL) and dried over Na_2SO_4. The solvent was evaporated to dryness under reduced pressure and the reaction mixture purified by column chromatography on silica gel.

4.2.1. Ethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1a). The crude product was purified by column chromatography using dichloromethane/methanol (50:1) as eluent to give white crystals (0.67 g, 71%); mp 56–59°C (lit.[4] 55–59°C). Spectroscopic data identical to that reported previously.[4]

4.2.2. Ethyl 4-ethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1b). The crude product was purified by column chromatography using dichloromethane/methanol (100:1) as eluent to give a viscous oil (0.36 g, 72%). Spectroscopic data identical to that reported previously.[4]

4.2.3. Ethyl 3-oxo-4-propyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1c). The crude product was purified by column chromatography using dichloromethane/methanol (100:1) as eluent to give a viscous oil (0.80 g, 31%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H, J=7.2 Hz, $-CH_2CH_2\mathit{CH_3}$), 1.21 (t, 3H, J=7.2 Hz, $-CH_2\mathit{CH_3}$), 1.54–1.61 (m, 2H, $-CH_2\mathit{CH_2}CH_3$), 3.83–3.94 (m, 2H, $-\mathit{CH_2}CH_2CH_3$), 4.13 (q, 2H, J=7.2 Hz, $\mathit{CH_2}CH_3$), 5.53 (s, 1H, 2-H), 7.01–7.12 (m, 3H, Ar-H), 7.22–7.26 (m, 1H, Ar-H) ppm. IR (NaCl-film): 2967, 1750, 1686, 1610, 1502, 1401, 1246, 1195, 1095, 1021, 752 cm^{-1}. MS (EI): 263 (M^+, 93), 249 (22), 221 (20), 190 (61), 162 (92), 148 (100), 135 (37), 120 (80). Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.74; H, 6.40; N, 5.59.

4.2.4. Ethyl 4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1d). The crude product was purified by column chromatography using chloroform as eluent to give white crystals (0.62 g, 20%); mp 78–79°C (lit.[4] 76–79°C). Spectroscopic data identical to that reported previously.[4]

4.2.5. Ethyl 4-(4-cyanobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1e). The crude product was purified by column chromatography using dichloromethane as eluent to give a viscous oil (0.60 g, 18%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (t, 3H, J=7.2 Hz, $-CH_2\mathit{CH_3}$), 4.19 (q, 2H, J=7.2 Hz, $\mathit{CH_2}CH_3$), 5.17 (d, 1H, $J_{A,B}$=17.0 Hz, $-\mathit{CH_2}$-4-CN–C_6H_4), 5.35 (d, 1H, $J_{A,B}$=17.0 Hz, $-\mathit{CH_2}$-4-CN–C_6H_4), 5.75 (s, 1H, 2-H), 6.97–7.07 (m, 3H, Ar-H), 7.11–7.15 (m, 1H, Ar-H), 7.45 (d, 2H, J=8.5 Hz, Ar-H), 7.84 (d, 2H, J=8.5 Hz, Ar-H) ppm. IR (KBr): 2980, 2228, 1748, 1694, 1608, 1504, 1466, 1430, 1398, 1333, 1249, 1224, 1189, 1096, 1017, 907, 828, 748, 550, 509 cm^{-1}. MS (EI): 336 (M^+, 50), 263 (19), 235 (23), 176 (9), 148 (34), 116 (100), 89 (24). Anal. calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.75; H, 4.88; N, 8.09.

4.2.6. Ethyl 4-(ethoxycarbonylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-carboxylate (1f). The crude product was purified by column chromatography using chloroform/methanol (100:1) as eluent to give a viscous oil (1.76 g, 57%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H, J=7.2 Hz, $-CH_2\mathit{CH_3}$), 1.19 (t, 3H, J=7.2 Hz, $-CH_2$-$COOCH_2\mathit{CH_3}$), 4.11–4.18 (m, 4H, $-\mathit{CH_2}CH_3$), 4.70 (d, 1H, $J_{A,B}$=17.7 Hz, $-\mathit{CH_2}COOCH_2CH_3$), 4.81 (d, 1H, $J_{A,B}$=17.7 Hz, $-\mathit{CH_2}COOCH_2CH_3$), 5.66 (s, 1H, 2-H), 7.05–7.15 (m, 4H, Ar-H) ppm. IR (KBr): 2985, 1748, 1694, 1611, 1503, 1393, 1207, 1100, 1025, 754 cm^{-1}. MS (EI): 307 (M^+, 100), 234 (64), 206 (99), 189 (23), 178 (61), 161 (55), 133 (68). Anal. calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.57; H, 5.66; N, 4.62.

4.2.7. Ethyl 4-(3-ethoxycarbonylpropyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1g). The crude product was purified by column chromatography using dichloromethane as eluent to give white crystals (1.12 g, 33%); mp 59–63°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (t, 3H, J=7.2 Hz, $-CH_2\mathit{CH_3}$), 1.18 (t, 3H, J=7.2 Hz, $-CH_2\mathit{CH_3}$), 1.76–1.86 (m, 2H, $-CH_2\mathit{CH_2}CH_2-$COOEt), 2.38 (t, 2H, J=7.4 Hz, $-NCH_2CH_2\mathit{CH_2}COOEt$), 3.88–4.00 (m, 2H, $-N\mathit{CH_2}CH_2CH_2COOEt$), 4.06 (q, 2H,

J=7.0 Hz, $-CH_2CH_3$), 4.14 (q, 2H, J=7.0 Hz, $-CH_2CH_3$), 5.75 (s, 1H, 2-H), 7.02–7.16 (m, 3H, Ar-H), 7.26–7.32 (m, 1H, Ar-H) ppm. IR (NaCl-film): 1737, 1691, 1606, 1500, 1402, 1193, 1095, 753 cm^{-1}. MS (FAB): 335 (M^+, 100), 290 (48), 262 (36), 204 (19), 115 (43). Anal. calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.72; H, 6.51; N, 4.46.

4.2.8. Ethyl 4-[(*tert*-butoxycarbonyl)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1h). The crude product was purified by column chromatography using dichloromethane as eluent to give white crystals (1.06 g, 32%); mp 62–66°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.39 (s, 9H, $-COO^tBu$), 4.10–4.18 (m, 2H, $-CH_2CH_3$), 4.59 (d, 1H, $J_{A,B}$=17.5 Hz, $-CH_2COO^tBu$), 4.69 (d, 1H, $J_{A,B}$=17.5 Hz, $-CH_2COO^tBu$), 5.75 (s, 1H, 2-H), 7.05–7.14 (m, 4H, Ar-H) ppm. IR (NaCl-film): 2980, 1747, 1697, 1504, 1394, 1369, 1231, 1155, 1097, 844, 753 cm^{-1}. MS (FAB): 335 (M^+, 35), 280 (77), 234 (68), 206 (52), 178 (37), 120 (27), 57 (100). Anal. calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.86; H, 6.56; N, 4.36.

4.2.9. Ethyl 4-[(benzyloxycarbonyl)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (1i). The crude product was purified by column chromatography using dichloromethane as eluent to give a viscous oil (0.84 g, 32%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 4.06–4.16 (m, 2H, $-CH_2CH_3$), 4.80 (d, 1H, $J_{A,B}$=17.7 Hz, $-CH_2COOCH_2Ph$), 4.90 (d, 1H, $J_{A,B}$=17.7 Hz, $-CH_2COOCH_2Ph$), 5.18 (s, 2H, $-COOCH_2Ph$), 5.67 (s, 1H, 2-H), 7.02–7.15 (m, 4H, Ar-H), 7.31–7.41 (m, 5H, $-CH_2Ph$) ppm. IR (KBr): 2983, 1748, 1697, 1503, 1395, 1193, 1100, 1026, 752, 699 cm^{-1}. MS (EI): 369 (M^+, 55), 234 (35), 206 (25), 178 (13), 133 (25), 91 (100). Anal. calcd for $C_{20}H_{19}NO_6 \times H_2O$: C, 63.49; H, 5.33; N, 3.70. Found: C, 63.11; H, 5.37; N, 3.51.

4.2.10. Diethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,6-dicarboxylate (1j). The crude product was purified by column chromatography using dichloromethane as eluent to give white crystals (0.76 g, 25%); mp 101–103°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.32 (t, 3H, J=7.2 Hz, $ArCOOCH_2CH_3$), 3.36 (s, 3H, N–*Me*), 4.10–4.21 (m, 2H, $-CH_2CH_3$), 4.32 (q, 2H, J=7.2 Hz, $ArCOOCH_2CH_3$), 5.69 (s, 1H, 2-H), 7.21 (d, 1H, J=8.3 Hz, Ar-H), 7.65 (d, 1H, J=1.9 Hz, Ar-H), 7.69 (dd, 1H, J_1=8.3 Hz, J_2=1.9 Hz, Ar-H) ppm. IR (KBr): 2988, 1743, 1692, 1611, 1511, 1478, 1368, 1244, 1090, 1016, 970, 766, 536 cm^{-1}. MS (FAB): 308 (M^+, 100), 264 (13), 234 (22), 206 (15), 154 (30), 136 (32), 73 (35), 55 (43). Anal. calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.40; H, 5.68; N, 4.55.

4.2.11. Diethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,7-dicarboxylate (1k). The crude product was purified by column chromatography using dichloromethane as eluent to give a viscous oil (1.60 g, 52%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.32 (t, 3H, J=7.2 Hz, $ArCOOCH_2CH_3$), 3.35 (s, 3H, N–*Me*), 4.10–4.20 (m, 2H, $-CH_2CH_3$), 4.24–4.35 (m, 2H, $ArCOOCH_2CH_3$), 5.66 (s, 1H, 2-H), 7.32 (d, 1H, J=8.3 Hz, Ar-H), 7.56 (d, 1H, J=1.9 Hz, Ar-H), 7.70 (dd, 1H, J_1=8.3 Hz, J_2=1.9 Hz, Ar-H) ppm. IR (KBr): 3734, 2983, 1752, 1698, 1615, 1514, 1382, 1288, 1102, 1020, 763 cm^{-1}. MS (EI): 307 (M^+, 100), 262 (33), 234 (64), 221 (23), 206 (90), 178 (63), 162 (24), 133 (25), 92 (25). Anal. calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.33; H, 5.63; N, 4.85.

4.3. General procedure for preparing ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates 2a–2k

The corresponding ethyl 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate **1** (1 mmol) was dissolved in anhydrous dichloromethane (10 mL). Activated molecular sieves (4 Å) and sodium hydride (1 mmol) were added and the reaction mixture stirred for 10–15 min. Oxygen was bubbled into the reaction mixture at room temperature for 2–3 h and the reaction mixture then left stirring overnight. Addition of molecular sieves and sodium hydride was repeated two to three times until quantitative transformation of **1a–1k** was obtained. Citric acid (0.29 g, 1.5 mmol) was added to the reaction mixture and the suspension washed with saturated $NaHCO_3$ solution (20+10 mL), dried with Na_2SO_4 and the solvent evaporated under vacuum to produce an oily product.

4.3.1. Ethyl 2-hydroxy-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2a). The procedure described yielded 0.20 g (82%) of **2a** as white crystals; mp 98–101°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 3.31 (s, 3H, N–CH_3), 4.25 (q, 2H, J=7.3 Hz, $-CH_2CH_3$), 7.05–7.18 (m, 3H, Ar-H), 7.23–7.26 (m, 1H, Ar-H), 8.55 (s, 1H, –OH) ppm. IR (KBr): 3376, 2991, 1750, 1675, 1609, 1502, 1394, 1229, 1140, 1048, 979, 860, 753, 632 cm^{-1}. MS (EI): 251 (M^+, 28), 235 (26), 221 (45), 189 (6), 178 (62), 150 (23), 94 (33), 77 (100), 65 (80). Anal. calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.00; H, 5.14; N, 5.40.

4.3.2. Ethyl 4-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2b). The procedure described yielded 0.20 g (75%) of **2b** as white crystals; mp 77–81°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, 3H, J=7.16 Hz, $-CH_2CH_3$), 1.22 (t, 3H, J=7.16 Hz, $-CH_2CH_3$), 3.87–4.04 (m, 2H, $-CH_2CH_3$), 4.24 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 7.06–7.08 (m, 2H, Ar-H), 7.10–7.17 (m, 1H, Ar-H), 7.28 (d, 1H, J=7.5 Hz, Ar-H), 8.53 (s, 1H, –OH) ppm. IR (NaCl-film): 3378, 2982, 1756, 1682, 1501, 1424, 1268, 1141, 1076, 861, 756 cm^{-1}. MS (FAB): 266 (MH^+, 100), 248 (64), 220 (10), 192 (29), 185 (25), 164 (16), 93 (47). Anal. calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 5.57; N, 5.39.

4.3.3. Ethyl 2-hydroxy-3-oxo-4-propyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2c). The procedure described yielded 0.21 g (76%) of **2c** as a viscous oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.89 (t, 3H, J=7.2 Hz, $-CH_2CH_2CH_3$), 1.21 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.55–1.62 (m, 2H, $-CH_2CH_2CH_3$), 3.87–3.92 (m, 2H, $-CH_2CH_2CH_3$), 4.23 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 7.06–7.16 (m, 3H, Ar-H), 7.27–7.29 (m, 1H, Ar-H), 8.53 (bs, 1H, –OH) ppm. IR (KBr): 3370, 2968, 1759, 1686, 1500, 1422, 1247, 1142, 1078, 758 cm^{-1}. MS (FAB): 280

(MH$^+$, 12), 262 (50), 234 (14), 206 (50), 178 (13), 164 (26), 147, (24), 73 (100). Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.36; H, 6.10; N, 5.09.

4.3.4. Ethyl 4-benzyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2d). The procedure described yielded 0.29 g (90%) of **2d** as white crystals; mp 98–103°C. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.24 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 4.28 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 5.12 (d, 1H, $J_{A,B}$=16.2 Hz, $-CH_2Ph$), 5.27 (d, 1H, $J_{A,B}$=16.2 Hz, $-CH_2Ph$), 6.99–7.10 (m, 4H, Ar-H), 7.26–7.37 (m, 5H, $-CH_2Ph$), 8.74 (s, 1H, –OH) ppm. IR (KBr): 3446, 2982, 1755, 1686, 1500, 1431, 1291, 1130, 1080, 861, 754, 695 cm^{-1}. MS (EI): 327 (M$^+$, 9), 254 (30), 226 (13), 91 (100), 65 (15). Anal. calcd for $C_{18}H_{17}NO_5\times1/2H_2O$: C, 64.28; H, 5.39; N, 4.16. Found: C, 64.09; H, 5.02; N, 3.85.

4.3.5. Ethyl 4-(4-cyanobenzyl)-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2e). The procedure described yielded 0.30 g (85%) of **2e** as yellow crystals; mp 54–56°C. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.24 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 4.28 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 5.20 (d, 1H, $J_{A,B}$=17.0 Hz, CH_2-4-CN–C_6H_4), 5.38 (d, 1H, $J_{A,B}$=17.0 Hz, CH_2-4-CN–C_6H_4), 7.03–7.12 (m, 4H, Ar-H), 7.44 (d, 2H, J=8.3 Hz, Ar-H), 7.85 (d, 2H, J=8.3 Hz, Ar-H), 8.83 (bs, 1H, –OH) ppm. IR (KBr): 3355, 2999, 2235, 1759, 1610, 1499, 1428, 1332, 1264, 1137, 1070, 1015, 859, 743, 601 cm^{-1}. MS (FAB): 353 (MH$^+$, 62), 335 (36), 312 (13), 279 (12), 251 (8), 220 (9), 164 (8), 116 (49), 75 (25). Anal. calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 65.04; H, 4.57; N, 7.65.

4.3.6. Ethyl 4-(ethoxycarbonylmethyl)-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2f). The procedure described yielded 0.28 g (86%) of **2f** as a viscous oil. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.21 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.20 (t, 3H, J=6.9 Hz, $-CH_2CH_3$), 4.15 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 4.26 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 4.62 (d, 1H, $J_{A,B}$=17.7 Hz, $-CH_2COOCH_2CH_3$), 4.84 (d, 1H, $J_{A,B}$=17.7 Hz, $-CH_2COOCH_2CH_3$), 7.09–7.17 (m, 4H, Ar-H), 8.65 (bs, 1H, 2-OH) ppm. IR (KBr): 3392, 2982, 1752, 1692, 1502, 1414, 1245, 1207, 1141, 1020, 858, 751 cm^{-1}. MS (EI): 323 (M$^+$, 20), 278 (6), 250 (87), 222 (35), 204 (58), 176 (82), 148 (100), 120 (38). Anal. calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C, 55.97; H, 5.37; N, 4.24.

4.3.7. Ethyl 4-(ethoxycarbonylpropyl)-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2g). The procedure described yielded 0.188 g (56%) of **2g** as a viscous oil. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.18 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.22 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.77–1.86 (m, 2H, $-CH_2CH_2CH_2COOEt$), 2.38 (t, 2H, J=7.2 Hz, $-NCH_2CH_2CH_2COOEt$), 3.90–4.00 (m, 2H, $-NCH_2$ CH_2CH_2COOEt), 4.07 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 4.24 (q, 2H, J=7.0 Hz, $-CH_2CH_3$), 7.07–7.09 (m, 2H, Ar-H), 7.12–7.18 (m, 1H, Ar-H), 7.33–7.35 (m, 1H, Ar-H), 8.58 (bs, 1H, 2-OH) ppm. IR (KBr): 3355, 2983, 1760, 1689, 1610, 1502, 1420, 1145, 1078, 860, 759 cm^{-1}. MS (FAB): 352 (MH$^+$, 31), 339 (6), 334 (15), 123 (17), 107 (29), 71 (87), 55 (94). Anal. calcd for $C_{17}H_{21}NO_7\times1/3H_2O$: C, 57.14; H, 6.11; N, 3.92. Found: C, 57.12; H, 5.63; N, 4.05.

4.3.8. Ethyl 4-[(*tert*-butoxycarbonyl)methyl]-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2h). The procedure described yielded 0.25 g (72%) of **2h** as white crystals; mp 147–151°C. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.22 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.39 (s, 9H, $-COO^tBu$), 4.25 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 4.61 (d, 1H, $J_{A,B}$=17.5 Hz, $-CH_2COO^tBu$), 4.71 (d, 1H, $J_{A,B}$=17.5 Hz, $-CH_2COO^tBu$), 7.08–7.12 (m, 4H, Ar-H), 8.61 (s, 1H, 2-OH) ppm. IR (KBr): 3431, 2985, 1746, 1693, 1504, 1367, 1238, 1158, 1047, 857, 766, 550 cm^{-1}. MS (EI): 351 (M$^+$, 18), 278 (20), 222 (100), 194 (22), 176 (26), 148 (37), 120 (26), 77 (34), 57 (85). Anal. calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.23; H, 5.93; N, 3.74.

4.3.9. Ethyl 4-[(benzyloxycarbonyl)methyl]-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-bezoxazine-2-carboxylate (2i). The procedure described yielded 0.23 g (59%) of **2i** as a viscous oil. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.20 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 4.22 (q, J=7.0 Hz, 2H, $-CH_2CH_3$), 4.76 (d, 1H, $J_{A,B}$=17.0 Hz, $-CH_2COOCH_2Ph$), 4.89 (d, 1H, $J_{A,B}$=17.0 Hz, $-CH_2COOCH_2Ph$), 5.19 (s, 2H, $-COO-CH_2Ph$), 7.06–7.11 (m, 4H, Ar-H), 7.24–7.36 (m, 5H, $-CH_2Ph$) ppm. IR (NaCl-film): 3412, 1754, 1693, 1502, 1391, 1245, 1191, 1026, 750 cm^{-1}. MS (EI): 385 (M$^+$, 20), 368 (24), 312 (25), 278 (9), 222 (10), 181 (14), 120 (22), 91 (100). Anal. calcd for $C_{20}H_{19}NO_7\times H_2O$: C, 59.55; H, 5.25; N, 3.47. Found: C, 59.33; H, 5.15; N, 3.36.

4.3.10. Diethyl 2-hydroxy-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,6-dicarboxylate (2j). The procedure described yielded 0.28 (85%) of **2j** as white crystals; mp 159–163°C. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.23 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.33 (t, 3H, J=7.2 Hz, $ArCOOCH_2CH_3$), 3.40 (s, 3H, N–*Me*), 4.27 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 4.33 (q, 2H, J=7.2 Hz, $-CH_2CH_3$), 7.21 (d, 1H, J=8.7 Hz, Ar-H), 7.70–7.73 (m, 2H, Ar-H) ppm. IR (KBr): 3352, 2991, 1760, 1699, 1611, 1443, 1264, 1149, 1078, 1016, 766 cm^{-1}. MS (EI): 323 (M$^+$, 15), 278 (9), 264 (23), 250 (100), 222 (57), 194 (22), 174 (15). Anal. calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C, 55.97; H, 5.37; N, 4.24.

4.3.11. Diethyl 2-hydroxy-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,7-dicarboxylate (2k). The procedure described yielded 0.26 g (79%) of **2k** as a viscous oil. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.23 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.32 (t, 3H, J=7.2 Hz, $ArCOO-CH_2CH_3$), 3.38 (s, 3H, N–*Me*), 4.21–4.34 (m, 4H, $-CH_2CH_3$+ $ArCOOCH_2CH_3$), 7.37 (d, 1H, J=8.3 Hz, Ar-H), 7.54 (d, 1H, J=1.9 Hz, Ar-H), 7.75 (dd, 1H, J_1=8.3 Hz, J_2=1.9 Hz, Ar-H), 8.81 (s, 1H, 2-OH) ppm. IR (KBr): 3402, 2984, 1763, 1702, 1616, 1514, 1371, 1294, 1101, 1018, 762 cm^{-1}. MS (FAB): 324 (33), 306 (40), 278 (13), 250 (33), 222 (18), 192 (30), 176 (15), 154 (49), 136 (45), 83 (49), 69 (77), 57 (100). Anal. calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C, 55.97; H, 5.34; N, 4.52.

4.4. Procedure for preparing new diethyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,6- and 2,7-dicarboxylates (3j and 3k)

4.4.1. Diethyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,6-dicarboxylate (3j). A suspension of ethyl 4-hydroxy-3-nitrobenzoate (4.22 g, 20 mmol), potassium fluoride

(2.91 g, 50 mmol) and diethyl bromomalonate (4.78 g, 20 mmol) in *N*,*N*-dimethyl-formamide (40 mL) was heated at 60°C overnight. The reaction mixture was cooled and poured onto crushed ice (80 g) and extracted with diethyl ether (3×50 mL). The combined organic fractions were washed with 0.1 M NaOH (3×50 mL), dried over Na_2SO_4 and the solvent evaporated under vacuum. The crude product was dissolved in anhydrous ethanol (100 mL) and hydrogenated over palladium on charcoal (10 wt%) at 60°C and 10 atm pressure. The solvent was evaporated under vacuum to half volume and left in refrigerator overnight. The precipitated product was filtered off to give 1.77 g (30%) of white crystals; mp 138–141°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, 3H, J=7.0 Hz, $-CH_2CH_3$), 1.30 (t, 3H, J=7.2 Hz, $ArCOOCH_2CH_3$), 4.14–4.21 (m, 2H, $-CH_2CH_3$), 4.25–4.34 (m, 2H, $ArCOOCH_2CH_3$), 5.57 (s, 1H, 2-H), 7.15 (d, 1H, J=8.3 Hz, Ar-H), 7.52–7.53 (m, 1H, Ar-H), 7.57–7.61 (m, 1H, Ar-H), 11.16 (s, 1H, –NHCO–) ppm. IR (KBr): 3131, 2990, 1746, 1693, 1491, 1391, 1294, 1207, 1079, 1027, 764 cm^{-1}. MS (EI): 293 (M^+, 100), 248 (33), 220 (84), 192 (73), 164 (66), 148 (19), 119 (20). Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 56.99; H, 5.15; N, 4.95.

4.4.2. Diethyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2,7-dicarboxylate (3k). Compound **3k** was prepared from ethyl 3-hydroxy-4-nitrobenzoate using the procedure described for the synthesis of **3j**; yield: 1.52 g (26%); white crystals; mp 153–154°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, 3H, J=7.2 Hz, $-CH_2CH_3$), 1.31 (t, 3H, J=7.2 Hz, $ArCOOCH_2CH_3$), 4.13–4.21 (m, 2H, $-CH_2CH_3$), 4.29 (q, 2H, J=7.2 Hz, $ArCOOCH_2CH_3$), 5.54 (s, 1H, 2-H), 7.01 (d, 1H, J=8.3 Hz, Ar-H), 7.52 (d, 1H, J=1.9 Hz, Ar-H), 7.62 (dd, 1H, J_1=8.3 Hz, J_2=1.9 Hz, Ar-H), 11.34 (s, 1H, –NHCO–) ppm. IR (KBr): 3201, 2978, 1751, 1691, 1618, 1517, 1386, 1295, 1233, 1100, 1025, 760 cm^{-1}. MS (EI): 293 (M^+, 93), 248 (41), 220 (100), 192 (75), 164 (67), 148 (27), 119 (24). Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.01; H, 5.17; N, 4.56.

4.5. Procedure for preparing ethyl 4-alkyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates 4

4.5.1. Ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (4; R=H). A suspension of 2-aminophenol (1.09 g, 10 mmol) and potassium carbonate (0.92 g, 6.67 mmol) in anhydrous acetone (20 mL) was heated to 40°C. Subsequently potassium carbonate (1.08 g, 23.3 mmol) and ethyl 2,3-dibromopropionate (0.87 g, 9.9 mmol) were added in three portions and the reaction mixture heated for 18 h. After the reaction was complete the potassium carbonate was filtered off and the solvent evaporated under reduced pressure. The oily residue was suspended in water, extracted with ethyl acetate (3×50 mL), and the combined organic fractions dried over Na_2SO_4. The solution was evaporated to dryness under vacuum and the product purified by column chromatography using petroleum ether/ethyl acetate (5:1) as eluent to produce a viscous oil (0.714 g, 35%). Spectroscopic data identical to that reported previously.[7b]

4.5.2. Ethyl 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (4, R=Me). A suspension of ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (0.300 g, 1.44 mmol), potassium carbonate (0.39 g, 2.82 mmol) and dimethyl sulphate (0.24 g, 1.9 mmol) in anhydrous acetone (15 mL) was prepared and refluxed for 48 h. Potassium carbonate was filtered off and the solvent evaporated under vacuum. The oily residue was purified by column chromatography using petroleum ether/ethyl acetate (3:1) as eluent to produce a viscous oil (0.143 g, 52%). Spectroscopic data identical to that reported previously.[7c]

4.5.3. Ethyl 4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (4, R=Bn). A suspension of ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (0.22 g, 1.05 mmol), potassium carbonate (0.61 g, 4.12 mmol) and benzyl bromide (0.36 g, 2.10 mmol) in anhydrous acetone (10 mL) was prepared and refluxed for 48 h. Potassium carbonate was filtered off and the solvent evaporated under vacuum. The oily residue was purified by column chromatography using petroleum ether/ethyl acetate (5:1) as a eluent to produce a viscous oil (0.184 g, 59%). Spectroscopic data identical to that reported previously.[7c]

4.6. Procedure for preparing 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one

4-Methyl-2*H*-1,4-benzoxazin-3(4*H*)-one was prepared from 2*H*-1,4-benzoxazin-3(4*H*)-one according to the general procedure for preparing ethyl 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates (Section 4.2). The crude product was purified by column chromatography using chloroform/methanol (100:1) as eluent to produce a viscous oil (1.53 g, 94%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.28 (s, 3H, N–CH_3), 4.64 (s, 2H, $-CH_2CO-$), 6.98–7.03 (m, 2H, Ar-H), 7.04–7.10 (m, 1H, Ar-H), 7.15–7.18 (m, 1H, Ar-H) ppm. IR (NaCl-film): 1681, 1504, 1386, 1282, 1228, 1124, 1048, 819, 764 cm^{-1}. MS (EI): 163 (M^+, 100), 134 (87), 120 (41). Anal. calcd for $C_9H_9NO_2$×1/2H_2O: C, 64.47; H, 5.71; N, 8.35. Found: C, 64.39; H, 5.62; N, 8.46.

4.6.1. 2*H*-1,4-Benzoxazin-3(4*H*)-one. A suspension of 2-aminophenol (2.78 g, 20 mmol), potassium fluoride (2.91 g, 50 mmol) and ethyl bromoacetate (3.34 g, 20 mmol) in *N*,*N*-dimethylformamide (40 mL) was heated at 60°C overnight. The reaction mixture was poured into ice-cooled water (100 mL) and the precipitated product filtered off. The crude product was dissolved in absolute ethanol (60 mL) and hydrogenated over palladium on charcoal (10 wt%) at 60°C and 10 atm pressure. The solvent was evaporated under vacuum and the obtained product recrystallized from ethanol to produce 1.91 g (64%) of white crystals; mp 168–172°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.55 (s, 2H, $-CH_2CO-$), 6.87–6.97 (m, 4H, Ar-H), 10.67 (s, 1H, –NHCO–) ppm. IR (KBr): 3056, 2896, 1710, 1606, 1501, 1401, 1217, 1114, 1046, 926, 812, 743, 685, 524, 469 cm^{-1}. MS (EI): 149 (M^+, 93), 120 (100), 108 (12), 93 (16), 79 (23), 65 (17), 52 (38). Anal. calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.44; H, 4.77; N, 9.18.

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