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REGIOSELECTIVE FORMYLATION OF ETHYL 3,4-DIHYDRO-2*H*-1,4-BENZOXAZINE-2-CARBOXYLATE OR 2-ACETATE DERIVATIVES

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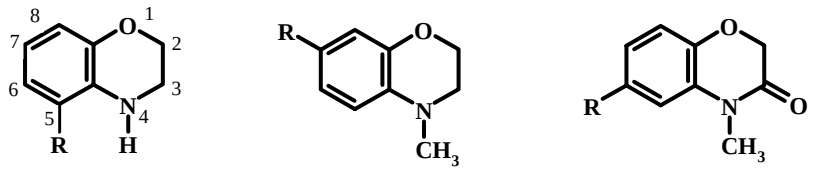
Abstract- Formylation reactions on ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate or 2-acetate derivatives were carried out using either Vilsmeier-Haack's conditions or Rieche's method. 7-Formyl compounds were exclusively obtained from *N*-benzyl-3,4-dihydro-2*H*-1,4-benzoxazines derivatives through Vilsmeier's procedure. A mixture of 6- and 8-formyl compounds, where the isomer in position-6 was predominant, was formed using the Rieche's method.

3,4-Dihydro-2*H*-1,4-benzoxazine system has received an increasing attention due to its pharmacological properties and therefore a large number of related compounds have been synthesized in the past two decades.[1-11] For our own part we have used this scaffold for the synthesis of new calcium antagonists;[12] recently we have described imidazolinic benzoxazines derivatives with potential antihypertensive activity.[13] In the course of our research of antagonists to the glycoproteins GPIIb/IIIa receptor,[14] we have investigated the formylation of ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate or 2-acetate derivatives. There are few studies about this reaction, and more generally on electrophilic substitutions on this heterocyclic system. Benzonitrile in the presence of $AlCl_3$ and BCl_3 reacted on 3,4-dihydro-1,4-benzoxazine (**1**) to give the phenyl ketone (**2**), after hydrolysis.[15] It has also been reported Vilsmeier-



1 R = H
2 R = COC_6H_5

3 R = H
4 R = CHO

5a R = H
5b R = CHO

Figure 1.

Haack reaction on 4-methyl-3,4-dihydro-1,4-*2H*-benzoxazine (**3**) which afforded 7-formyl derivative (**4**) in 78 % yield.[16] Rieche's formylation of 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (**5a**) gave 6-formyl derivative (**5b**) in 40 % yield[17] (Figure 1).

We anticipated that this electrophilic substitution was facilitated due to the presence of two activating groups on the aromatic nucleus. However, these ones turn the electrophilic substitution on different positions without discrimination. The alkoxy moiety directs the substitution towards position-6 and -8, and the amino moiety on position-5 and -7. Thus, it seems difficult to predict on which position the electrophilic substitutions will be directed. Considering the close electronic contribution of the oxygen and nitrogen atoms, we can postulate that, while modulating their chemical environments, we will achieve to develop conditions allowing to formylate position-6 as well as position-7 in a regiospecific way. So we studied the formylation of 3,4-dihydro-1,4-benzoxazines variously substituted on position-4 with benzyl, acetyl or benzyloxycarbonyl group. The chain on position-2 can have 0 or 1 methylene link (respectively ethyl carboxylate series and ethyl acetate series). The position-6 can be occupied by a bromine, a chlorine or a methyl substituent. Among the various methods of formylation, we choose to apply the Vilmseier-Haack's [18] and the Rieche's reactions; this latter method already allowed us the introduction of a formyl group on 1,4-benzodioxine derivative.[19]

The starting benzoxazines derivatives (**6, 7**) were prepared according to the classical way;[8,10,20] thus ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate derivatives (**6a-d)** were obtained from the corresponding

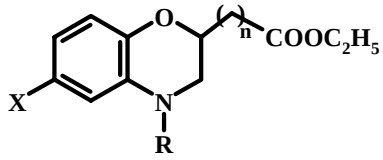


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Figure 2.

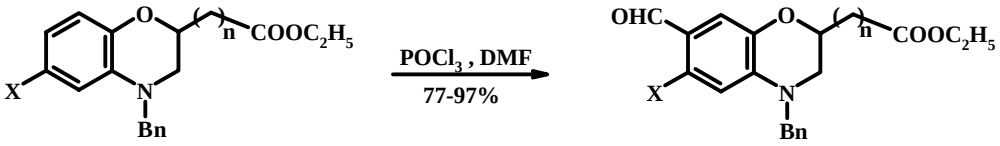
Product	**6a**[8,20]	**6b**[22]	**6c**	**6d**[22]	**6e**[12]	**7a**[12]	**7b**	**7c**	**7d**
X	H	Cl	Br	CH_3	H	H	Cl	Br	CH_3
R	H	H	H	H	H	Bn	Bn	Bn	Bn
n	0	0	0	0	1	0	0	0	0
Yield (%)	81	79	55	64	92	63	88	80	69

Product	**7e**[21,23]	**7f**	**7g**	**8a**[8]	**8b**	**8c**	**8d**	**8e**	**9a**
X	H	Cl	Br	H	Cl	Br	CH_3	H	H
R	Bn	Bn	Bn	Ac	Ac	Ac	Ac	Ac	Cbz
n	1	1	1	0	0	0	0	1	0
Yield (%)	84	89	86	89	78	92	99	96	82

Table 1.

2-aminophenols and ethyl 2,3-dibromopropanoate. Compounds (**7e-h**) (acetate series), were prepared according to the protocol developed by Masuoka[21] starting from the corresponding 2-benzylaminophenols and ethyl bromocrotonate. The hydrogenolysis of compound (**7e**) led to derivative (**6e**) in 92% yield. Dihydro-1,4-benzoxazines derivatives (**6a-d**), in the presence of benzyl bromide and potassium carbonate in acetonitrile at reflux led to benzyl derivatives (**7a-d**) in 63-88 % yield. The acetylation reactions of compounds (**6a-e**) were carried out with triethylamine and acetyl chloride in dichloromethane at room temperature and afforded *N*-acetyl derivatives (**8a-e**) in 78-99 % yield. Reaction of compound (**6a**) with benzyl chloroformate in THF in the presence of sodium hydride gave **9a** in 82 % yield (Figure 2 and Table 1).

For each formylating method, the nature of the substituent on the nitrogen atom in position-4 of the dihydro-1,4-benzoxazine derivatives proved to be a preponderant factor. The Vilsmeier-Haack's conditions (phosphorous oxychloride / DMF at 0°C then at room temperature) gave good results if the nitrogen atom was substituted by a benzyl substituent. So compound (**7a**) afforded 7-formyl derivative (**10a**) in 89 % yield (Scheme 1).



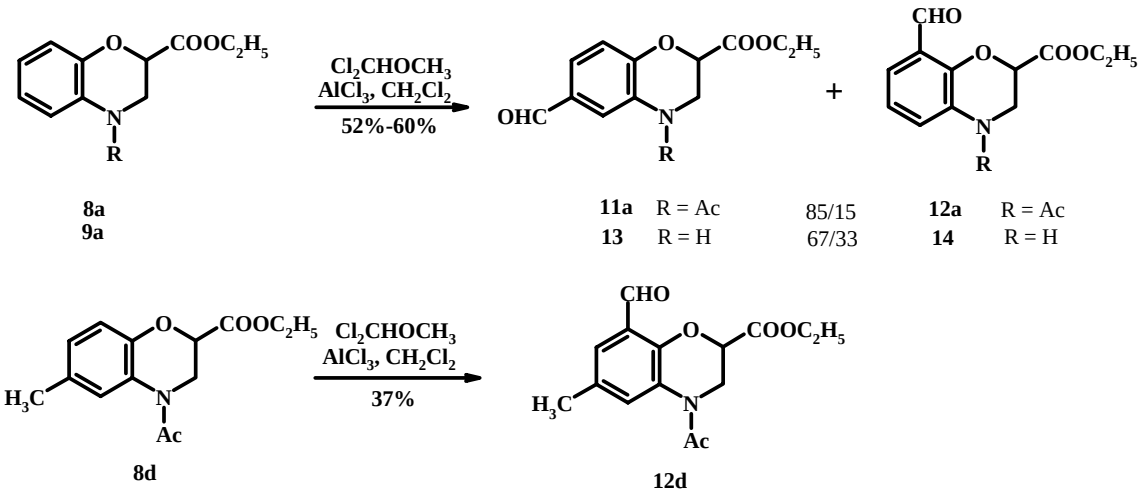
7a-g **10a-g**

Compound	**10a**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**
X	H	Cl	Br	CH_3	H	Cl	Br
n	0	0	0	0	1	1	1
Yield (%)	89	78	79	95	97	85	97

Scheme 1.

If the position-6 was substituted with a methyl group as **7d**, the reaction was always directed on position-7 to give **10d** with a good yield (95%). The formylation reaction time was increased when position-6 was substituted with a chloro or a bromo substituent. Thus, **10b** and **10g** were obtained respectively in 74 and 78% yields at room temperature after 6 days instead of 15 h for **10a**. Nevertheless the reaction yields of **10b** and **10g** have been improved (78% and 97%) by heating at 60°C for 24 h. The chain length in position-2 has no influence on the reaction, **10a** and **10e** were obtained respectively in 89 and 97% yields. This formylation reaction failed for compounds (**6e**) (a degradation reaction of the mixture was observed) and **(8e**) (for this compound a partial desacetylation of the nitrogen atom was observed with formation of compound (**6e**). Only the *N*-benzyl derivatives (**7a-g**) afforded 7-formyl derivatives (**10a-g**) in good yields (Scheme 1). The regiochemistry of the aldehyde group in **10a** was established by its oxidation into an ethyl ester, which was also obtained by an independent synthesis from ethyl 3-hydroxy-4-aminobenzoate.

Contrary to the Vilsmeier-Haack reaction, the Rieche's formylation conditions (2,2-dichloromethyl methyl ether (3.3 equiv) and aluminum trichloride (3.3 equiv) in dichloromethane) applied to the N-benzyl derivative (**7a**) gave no reaction. The same result was observed with the N-H compound (**6a)**. The Rieche's conditions applied on **8a** and **9a**, where the nitrogen atom was protected by an acetyl or a benzyloxycarbonyl group, afforded a non-separable mixture of 6-formyl and 8-formyl derivatives where the 6-formyl derivative was always predominant. Thus formyl compounds (**11a**) and (**12a**) were obtained from **8a** in a global yield of 60% in a ratio 85:15 (Scheme 2). In the case of **9a**, a mixture of ethyl 6-formyl- and 8-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates (**13**) and (**14**) was obtained in 52% yield in a ratio 67:33 with a loss of the Cbz group. For its part, the N-acetyl derivative (**8d**) substituted in position-6 with a methyl group gave the 8-formyl derivative (**12d**) in 37 % yield. The corresponding chloro or bromo derivatives (**8b**,**c**) was inactive. A large excess of 2,2-dichloromethyl methyl ether and aluminum trichloride (12 equiv) was required for the N-acetyl derivative (**8e**). In this case, a mixture of 6-formyl derivative (**11e**) and 8-formyl derivative (**12e**) was isolated in low yield (24%, ratio 88:12) due to the formation of dimer (**15**) in 22% yield (Scheme 3). This results show that the lateral chain length in position-2 has an influence on the reaction course contrary to Vilsmeier's reaction.

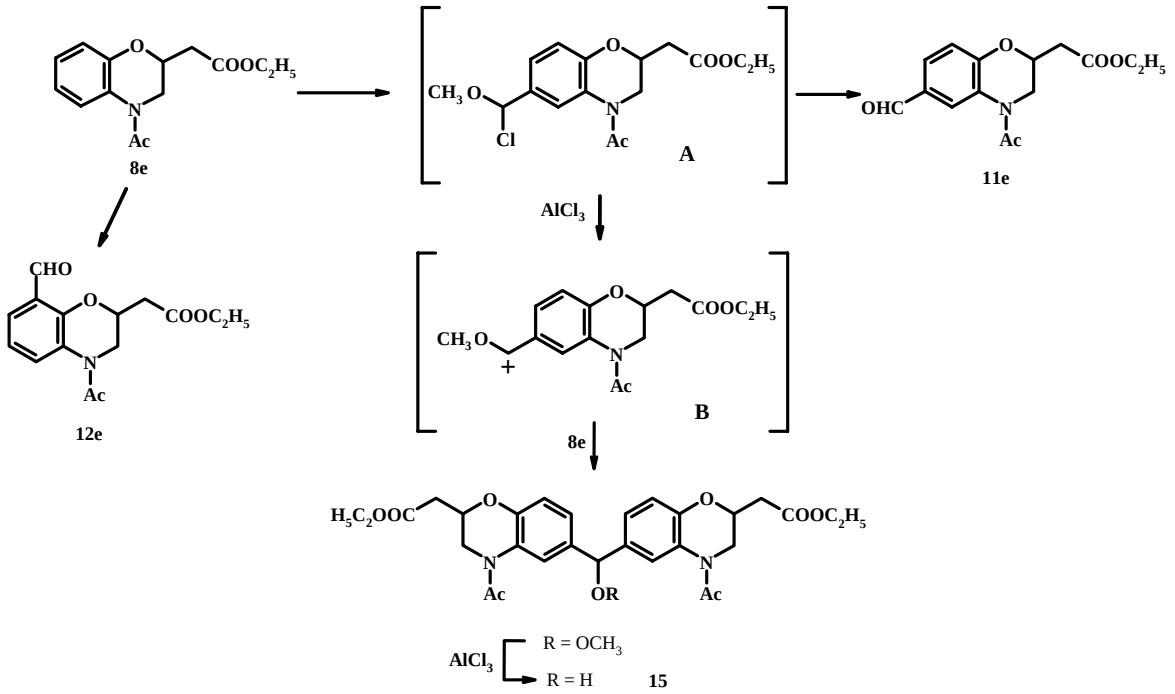


Scheme 2.

Formation of dimer (**15**) may be the result of a condensation of carbonium species (**B**) with a second molecule of **8e**; the intermediate methyl ether so formed reacted with aluminum trichloride to afford alcohol (**15**). Species (**B**) was generated in the medium by loss of chlorine atom, under complexation with aluminum trichloride, from intermediate (**A**) (Scheme 3); **A** which was the result of an electrophilic attack of the Rieche reagent in position-6 gave also **11e** after hydrolysis.

By modifying different parameters, we attempted to increase the selectivity of the Rieche's formylation reaction on **8a**. Replacement of dichloromethane with nitromethane as solvent gave the same ratio of the two aldehydes (**11a/12a**). A very slow formylation reaction was observed with carbon disulfide (12% after

3 days). Varying the temperature from -20°C to room temperature did not greatly influence the reaction. Aluminum trichloride was changed by others Lewis acids; thus if stannic chloride has small influence, titanium tetrachloride gave a quicker reaction but the ratio of the isomers (**11a**/**12a**) was 67:33 instead of 85:15.



Scheme 3.

The exclusive formylation in position-7, using Vilsmeier-Haack's conditions, indicated that the electrophilic substitution was totally governed by the expected more powerful *para* directing ability of the nitrogen atom of the 1,4-oxazino ring. Free NH derivatives did not survive the experimental conditions. Rieche's formylation, essentially in position-6, was upon dependance of the *para* directing ability of the oxygen atom which means that the usual more potent directing nitrogen substituent was not effective. That can be explained by the preferred complexation of a nitrogen atom compared to an oxygen atom with Lewis acids.[24,25] In order to have more explanation on the regioselectivity in position-6 for the Rieche formylation method, we have calculated the energy of formation of cationic intermediates with the Mopac software using the AM1 Hamiltonian.[26] All the calculation has converged but the prediction based on the more stable intermediate was not conclusive due to the complexation of the Lewis acid with the nitrogen and oxygen atoms of the 1,4-oxazino ring.

In conclusion we have demonstrated the complementarity of two methods of formylation. The Vilsmeier-Haack's reaction allows an exclusive formylation on the position-7 of ethyl 4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate or acetate, in high yield. The Rieche's formylation method gave a mixture of 6- and 8-formylated derivatives where the 6-isomer was predominant. This formylation reaction was only

possible if the nitrogen atom was substituted by electrowithdrawing groups. The formyl derivatives (**10**) so obtained will be used for the synthesis of new indolic derivatives according to the Hemetsberger approach.

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and were uncorrected. NMR spectra were recorded on a Bruker instrument Avance DPX250 at 250 MHz (^{1}H) or 62.5 MHz (^{13}C NMR) in $CDCl_3$ or in DMSO-d_6. Chemical shifts (δ values) were reported in ppm and coupling constants (*J* values) in Hz. IR spectra were recorded as a thin film on NaCl plates for the oils and in a KBr pellet for the solids on a Perkin-Elmer spectrophotometer FT Paragon 1000 PC. MS spectra were recorded on a Perkin-Elmer mass spectrometer Sciex API 300 (ionspray IS). Flash chromatography was performed on silica gel (Merk 60, 230-400 msh). TLC was performed on pre-coated silica gel plates (Merk 60, F_{254}, 0.25mm). Organic solvents used were HPLC grade or were purified by standard procedure. All reagents were of commercial quality or were purified before use.

The ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates (**6a,b,d, 7a, 8a**) and ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetates (**6e**,**7e**) were prepared according the literature. [8,12,21,23]

Ethyl 6-Bromo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (6c).

To a solution of *2*-amino-4-bromophenol (**5c**)[27] (849 mg, 4.52 mmol) in dry acetone (10 mL) were added K_2CO_3 (1.44 g, 10.33 mmol) and ethyl 2,3-dibromopropanoate (1.29 g, 4.97 mmol). The mixture was refluxed for 48 h and cool to rt. The salts were filtered and washed with acetone. The filtrate were evaporated, the residue poured into H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with H_2O (100 mL) and dried over $MgSO_4$. The crude product (**6c**) crystallised from diisopropyl ether at 0°C to give **6c** (713 mg, 55 %) as an orange solid; mp 94-96°C. IR (KBr, cm^{-1}) ν 3387 (NH), 1746 (CO). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, CH_3, *J* = 7.1 Hz); 3.57 (d, 2H, CH_2N, *J* = 4.0 Hz); 3.85 (br s, exchangeable D_2O, 1H, NH); 4.20-4.29 (m, 2H, CH_2O); 4.77 (t, 1H, OCH, *J* = 4.0 Hz); 6.72 (s, 1H, Harom); 7.78 (s, 2H, Harom). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 42.4 (CH_2N); 61.9 (CH_2O); 72.7 (OCH); 113.8 (C); 118.1 (CH); 118.5 (CH); 122.2 (CH); 134.2 (C); 142.1 (C); 169.2 (CO). MS (m/z) (IS) : 286 $[M+H]^+$ ^{79}Br, 288 $[M+H]^+$ ^{81}Br. Anal. Calcd for $C_{11}H_{12}NO_3Br$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.42; H, 4.11; N, 5.07.

Ethyl 4-Benzyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (7b).

Similarly obtained as **7a**[12] starting from 3,4-dihydro-1,4-benzoxazine (**6b**) (496 mg, 2.05 mmol). Reaction time 15 h. Yellow solid; 599 mg (88 %); mp 98-100°C (EtOAc). IR (KBr, cm^{-1}) ν 1750 (CO). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, *J* = 7.1 Hz); 3.50 (d, 2H, CH_2N, *J* = 4.1 Hz); 4.13-4.27 (m, 2H, CH_2O); 4.32 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.0 Hz); 4.47 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.0 Hz); 4.80 (t, 1H, OCH, *J* = 4.1 Hz);

6.64 (dd, 1H, H_7, *J* = 2.4 Hz, *J* = 9.3 Hz); 6.65 (d, 1H, H_5, *J* = 2.4 Hz); 6.87 (d, 1H, H_8, *J* = 9.3 Hz); 7.21-7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 48.0 (CH_2N); 54.8 (NCH_2Ph); 61.9 (CH_2O); 72.5 (OCH); 114.4 (C); 115.3 (CH); 118.1 (CH); 121.4 (CH); 127.4 (2 CH Bn); 127.8 (CH Bn); 129.0 (2 CH Bn); 136.2 (C); 137.0 (C); 142.1 (C); 169.1 (CO). MS (m/z) (IS) : 332 $[M+H]^{+\ 35}$Cl, 334 $[M+H]^{+\ 37}$Cl. Anal. Calcd for $C_{18}H_{18}NO_3Cl$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.44; H, 5.39; N, 4.12.

Ethyl 4-Benzyl-6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (7c).

Same procedure as for **7a** starting from 3,4-dihydro-1,4-benzoxazine (**6c**) (451 mg, 1.58 mmol); orange solid; 474 mg (80 %); mp 96-98°C (EtOAc). IR (KBr, cm^{-1}) ν 1755 (CO). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3, *J* = 7.2 Hz); 3.49 (d, 2H, CH_2N, *J* = 3.9 Hz); 4.11-4.26 (m, 2H, CH_2O); 4.31 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.0 Hz) ; 4.47 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.0 Hz); 4.79 (t, 1H, OCH, *J* = 3.9 Hz); 6.80 (s, 3H, H_5, H_7, H_8); 7.21-7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 48.0 (CH_2N); 54.8 (NCH_2Ph); 61.9 (CH_2); 72.5 (OCH); 114.4 (C); 115.3 (CH); 118.1 (CH); 121.4 (CH); 127.4 (2 CH Bn); 127.8 (CH Bn); 129.0 (2 CH Bn); 136.2 (C); 137.0 (C); 142.1 (C); 169.1 (CO). MS (m/z) (IS) : 376 $[M+H]^{+\ 79}$Br, 378 $[M+H]^{+\ 81}$Br. Anal. Calcd for $C_{18}H_{18}NO_3Br$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.70; H, 4.75; N, 3.91.

Ethyl 4-Benzyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine-2-carboxylate (7d).

Same procedure as for **7a**; starting from 3,4-dihydro-1,4-benzoxazine (**6d**) (304 mg, 1.37 mmol). Beige solid; 295 mg (69 %); mp 98-100°C (EtOH). IR (KBr, cm^{-1}) ν 1741 (CO). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, *J* = 7.1 Hz); 2.19 (s, 3H, C_6-CH_3); 3.47 (d, 2H, CH_2N, *J* = 4.1 Hz); 4.14-4.27 (m, 2H, CH_2O); 4.31 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.0 Hz); 4.49 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.0 Hz); 4.79 (t, 1H, OCH, *J* = 4.1 Hz); 6.50 (d, 1H, H_7, *J* = 6.9 Hz); 6.52 (s, 1H, H_5); 6.86 (d, 1H, H_8, *J* = 6.9 Hz); 7.23-7.34 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 21.3 (C_6-CH_3); 48.6 (CH_2N); 55.0 (NCH_2Ph); 61.7 (CH_2O); 72.6 (OCH); 113.6 (CH); 116.5 (CH); 119.4 (CH); 127.4 (2 CH Bn); 127.5 (CH Bn); 128.8 (2 CH Bn); 131.4 (C); 134.7 (C); 138.0 (C); 141.0 (C); 169.6 (CO). MS (m/z) (IS) : 312 $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.62; H, 6.98; N, 4.35.

Ethyl 2-(4-Benzyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (7f).

Similarly obtained as for **7e**[12, 21] starting from 2-benzylamino-4-chlorophenol (6.99 g, 29.90 mmol), ethyl bromocrotonate (6.35 g, 32.9 mmol), and $NaHCO_3$ (3.01 g, 35.9 mmol) in ethanol (60 mL). After 5 d at rt the N-alkylation was complete, the mixture was evaporated and water was added. Extraction with ethyl acetate, drying over magnesium sulfate and evaporation leave an oil; the crude oil was dissolved in ethanol (60 mL) and potassium carbonate (4.15 g, 30 mmol) was added. After stirring at rt for 18 h ethanol was evaporated, followed by addition of water and extraction with ethyl acetate. Drying over magnesium sulfate of the organic layer and evaporation leave a residue which was chromatographed on a

silica gel column (pet. ether/EtOAc 80/20) to afford **7f** (9.21 g, 89 %) as an oil. IR (NaCl, cm^{-1}) ν 1731 (CO). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH_3, *J* = 7.2 Hz); 2.54 (dd, 1H, CHC**H$_a$**H$_b$CO, *J* = 6.4 Hz, *J* = 15.7 Hz); 2.74 (dd, 1H, CHCH$_a$**H$_b$**CO, *J* = 6.9 Hz *J* = 15.7 Hz); 3.14 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.2 Hz, *J* = 11.9 Hz); 3.35 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 2.8 Hz, *J* = 11.9 Hz); 4.15 (q, 2H, CH_2O, *J* = 7.2 Hz); 4.35 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.0 Hz); 4.43 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.0 Hz); 4.53-4.62 (m, 1H, OCH); 6.57 (dd, 1H, H_7, *J* = 2.4 Hz, *J* = 8.5 Hz); 6.64 (d, 1H, H_5, *J* = 2.4 Hz); 6.71 (d, 1H, H_8, *J* = 8.5 Hz); 7.17-7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 38.0 (CH_2CO); 50.6 (CH_2N); 54.7 (NCH_2Ph); 61.0 (CH_2O); 70.0 (OCH) ; 112.0 (CH); 117.5 (2 CH); 126.7 (C); 127.2 (2 CH Bn); 127.6 (CH Bn); 128.9 (2 CH Bn); 135.9 (C); 137.3 (C); 141.8 (C); 170.2 (CO). MS (m/z) (HN) : 346 $[M+H]^+$ ^{35}Cl, 348 $[M+H]^+$ ^{37}Cl. Anal. Calcd for $C_{19}H_{20}NO_3Cl$: C, 65.99; H, 5.83; N, 4.05. Found: C, 70.33; H, 5.95; N, 4.13.

Ethyl 2-(4-Benzyl-6-bromo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (7g).

Similarly obtained as for **7e** starting from 2-benzylamino-4-bromophenol (27.9 mmol); yellow solid; 9.33 g (86 %); mp 58-62°C (EtOAc). IR (KBr, cm^{-1}) ν 1732 (CO). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3, *J* = 7.0 Hz); 2.55 (dd, 1H, CHC**H$_a$**H$_b$CO, *J* = 6.4 Hz, *J* = 16.0 Hz); 2.75 (dd, 1H, CHCH$_a$**H$_b$**CO, *J* = 6.9 Hz *J* = 16.0 Hz); 3.15 (dd, 1H, CHC**H$_a$**H$_b$N, *J* = 7.1 Hz, *J* = 11.8 Hz); 3.36 (dd, 1H, CHCH$_a$**H$_b$**N, *J* = 2.7 Hz, *J* = 11.8 Hz); 4.16 (q, 2H, CH_2O, *J* = 7.0 Hz); 4.37 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.3 Hz); 4.45 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.3 Hz); 4.53-4.63 (m, 1H, OCH); 6.66 (d, 1H, H_8, *J* = 8.4 Hz); 6.73 (dd, 1H, H_7, *J* = 2.0 Hz, *J* = 8.4 Hz); 6.80 (d, 1H, H_5, *J* = 2.0 Hz); 7.24-7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3); 38.1 (CH_2CO); 50.6 (CH_2N); 54.8 (NCH_2Ph); 61.1 (CH_2); 70.0 (OCH); 114.2 (C); 114.9 (C_5H); 118.1 (C_8H); 120.7 (C_7H); 127.3 (2 CH Bn); 127.7 (CH Bn); 129.0 (2 CH Bn); 136.4 (C); 137.3 (C); 142.4 (C); 170.3 (CO). MS (m/z) (IS) : 390 $[M+H]^+$ ^{79}Br, 392 $[M+H]^+$ ^{81}Br. Anal. Calcd for $C_{19}H_{20}NO_3Br$: C, 58.47; H, 5.17; N, 3.59. Found: C, 58.19; H, 5.31; N, 3.44;

Ethyl 4-Acetyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (8a).

To a solution of **6a** (1.00 g, 4.85 mmol) in dichloromethane (15 mL) cooled with an ice-bath, triethylamine (740 µ L, 5.31 mmol) was added, then acetyl chloride (380 µ L, 5.34 mmol) in dichloromethane (5 mL) was dropwise added; after 2 h at rt, dichloromethane was added and the mixture washed sequentially with a saturated solution of sodium hydrogencarbonate, then water; the organic layer was dried over magnesium sulfate and evaporated; purification on a silica gel column (pet. ether/EtOAc 60/40), gave **8a** (1.08 g, 89 %) as a yellow solid; mp 52-54°C (EtOAc). IR (KBr, cm^{-1}) ν 1750 (CO), 1663 (NCO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.19 (t, 3H, CH_3, *J* = 7.1 Hz); 2.20 (s, 3H, $COCH_3$); 3.69 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.4 Hz, *J* = 13.8 Hz); 4.14 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.43 (dd, 1H, OCHCH$_a$H$_b$N, *J* = 3.7 Hz, *J* = 13.8 Hz); 5.10-5.20 (m, 1H, OCH); 6.88-7.12 (m, 3H, H_6, H_7, H_8); 7.57 (d, 1H, H_5, *J* = 7.8 Hz). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 21.7 ($COCH_3$); 41.8 (CH_2N); 60.7

(CH_2O); 72.7 (OCH); 116.2 (CH); 119.7 (CH); 123.6 (CH); 125.2 (CH); 125.9 (C); 145.0 (C); 168.0 and 168.1 (CO, NCO). MS (m/z) (IS) : 250 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.27; H, 6.14; N, 5.74.

Ethyl 4-Acetyl-6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (8b).

Same procedure as for **8a**, starting from **6b** orange solid; 226 mg (78 %); mp 86-88°C (EtOAc). IR (KBr, cm^{-1}) ν 1743 (CO); 1663 (NCO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.18 (t, 3H, CH_3, *J* = 7.0 Hz); 2.23 (s, 3H, $COCH_3$); 3.73 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.3 Hz, *J* = 14.0 Hz); 4.15 (q, 2H, CH_2O, *J* =7.0 Hz); 4.34 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.6 Hz, *J* = 14.0 Hz); 5.21-5.30 (m, 1H, OCH); 6.99 (d, 1H, H_8, *J* = 8.8 Hz); 7.10 (dd, 1H, H_7, *J* = 2.3 Hz, *J* = 8.8 Hz); 7.81 (d, 1H, H_5, *J* = 2.3 Hz).^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 21.8 ($COCH_3$); 42.4 (CH_2N); 60.9 (CH_2O); 72.5 (OCH); 117.6 (CH); 122.8 (CH); 123.4 (C); 124.6 (CH); 126.7 (C); 143.7 (C); 167.7 and 168.3 (CO, NCO). MS (m/z) (IS) : 284 $[M+H]^+$ ^{35}Cl, 286 $[M+H]^+$ ^{37}Cl. Anal. Calcd for $C_{13}H_{14}NO_4Cl$: C, 55.04 H, 4.97; N, 4.94. Found: C, 54.76; H, 4.82; N, 5.10.

Ethyl 4-Acetyl-6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (8c).

Similarly obtained as for **8a** starting from **6c**; yellow solid; 103 mg (92 %); mp 96-98°C (CH_2Cl_2). IR (KBr, cm^{-1}) ν 1743 (CO); 1665 (NCO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.18 (t, 3H, CH_3, *J* = 7.1 Hz); 2.22 (s, 3H, $COCH_3$); 3.73 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.4 Hz, *J* = 13.9 Hz); 4.14 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.38 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.7 Hz, *J* = 13.9 Hz); 5.12-5.20 (m, 1H, OCH); 6.94 (d, 1H, H_8, *J* = 8.8 Hz); 7.23 (dd, 1H, H_7, *J* = 2.4 Hz, *J* = 8.8 Hz); 7.93 (d, 1H, H_5, *J* = 2.4 Hz). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 21.8 ($COCH_3$); 42.4 (CH_2N); 60.9 (CH_2O); 72.5 (OCH); 110.8 (C); 118.1 (CH); 125.6 (CH); 127.1 (C); 127.5 (CH); 144.2 (C); 167.7 and 168.3 (CO, NCO). MS (m/z) (IS) : 328 $[M+H]^+$ ^{79}Br, 330 $[M+H]^+$ ^{81}Br. Anal. Calcd for $C_{13}H_{14}NO_4Br$: C, 47.58; H, 4.30; N, 4.27. Found: C, 47.89; H, 4.44; N, 4.33.

Ethyl 4-Acetyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine-2-carboxylate (8d).

Same procedure as for **8a** starting from **6b**; orange solid; mp 96-98°C (EtOAc). IR (KBr, cm^{-1}) ν 1756 (CO); 1672 ($NCOCH_3$). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.18 (t, 3H, CH_3, *J* = 7.1 Hz); 2.20 and 2.24 (2s, 3H, 3H, C_6-CH_3, $COCH_3$); 3.66 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.6 Hz, *J* = 13.7 Hz); 4.13 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.38 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.6 Hz, *J* = 13.7 Hz); 5.07 (t, 1H, OCH, *J* = 3.6 Hz); 6.84 (d, 1H, H_8, *J* = 8.5 Hz); 6.90 (d, 1H, H_7, *J* = 8.5 Hz); 7.38 (br s, 1H, H_5). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 19.7 (C_6-CH_3); 21.7 ($COCH_3$); 41.9 (CH_2N); 60.6 (CH_2O); 72.6 (OCH); 115.8 (CH); 123.7 (CH); 125.5 (C); 125.7 (CH); 128.7 (C); 142.8 (C); 168.1 (CO, $NCOCH_3$). MS (m/z) (IS) : 264 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64. 22; H, 6.70; N, 5.52.

Ethyl 2-[(4-Acetyl-3,4-dihydro-2*H*-1,4-benzoxazin)-2-yl]acetate (8e).

Similarly obtained as for **8a** starting from **6e**, orange solid; 664 mg (96 %); mp 56-58°C (CH_2Cl_2).

IR (KBr, cm^{-1}) ν 1727 (CO); 1663 (NCO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.22 (t, 3H, CH_3, *J* = 7.1 Hz); 2.25 (s, 3H, $COCH_3$); 2.64 (dd, 1H, CHC**H$_a$**H$_b$CO, *J* = 7.3 Hz, *J* = 15.9 Hz); 2.77 (dd, 1H, CHCH$_a$**H$_b$**CO, *J* = 5.4 Hz *J* = 15.9 Hz); 3.46 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.8 Hz, *J* = 13.5 Hz); 4.14 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.22 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.1 Hz, *J* = 13.5 Hz); 4.54-4.63 (m, 1H, OCH); 6.83-6.90 (m, 2H, Harom); 7.00-7.07 (m, 1H, Harom); 7.66 (d, 1H, H_8, *J* = 7.8 Hz). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.5 (CH_3); 22.2 ($COCH_3$); 36.8 (CH_2CO); 44.4 (CH_2N); 59.7 (CH_2O); 71.7 (OCH); 116.3 (CH); 119.4 (CH); 123.4 (CH); 124.8 (CH); 125.7 (C); 145.5 (C); 168.1, 168.9 (CO, NCO). MS (m/z) (IS) : 264 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.50; H, 6.38; N, 5.43.

Ethyl 4-benzyloxycarbonyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (9a)

Compound (**6a**) (241 mg, 1.16 mmol) in THF (4 mL) was dropwise added to an ice-cooled suspension of 60% NaH (43 mg, 1.80 mmol) in THF (2 mL); after 30 min benzyl chloroformate (0.23 mL, 1.53 mmol) was dropwise added and the mixture was stirred at rt for 20 h. Evaporation of the solvent, addition of water, extraction with dichloromethane leave after drying over magnesium sulfate an oil which was chromatographed on silica gel column (pet. ether/CH_2Cl_2 20/80) to give **9a** (324 mg, 82%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H, CH_3, *J* = 7.1 Hz); 3.96 (dd, 1H, CH_2N, *J* = 3.7 Hz, *J* = 13.6 Hz); 4.12-4.17 (m, 2H, CH_2O); 4.28 (dd, 1H, CH_2N, *J* = 5.0 Hz, *J*= 13.6 Hz); 4.85 (dd, 1H, OCH, *J* = 3.7 Hz, *J* = 5.0 Hz); 5.25 (s, 2H, OCH_2); 6.91-7.05 (m, 3H, Harom); 7.34-7.39 (m, 5H, Harom); 7.76 (br s, 1H, Harom). MS (m/z) (IS) : 342 $[M+H]^+$.

Vilsmeier-Haack's formylation; General Procedure

Phosphorous oxychloride (450 μL, 4.78 mmol) was slowly added to DMF (2 mL) cooled with an ice-bath; after 30 min a solution of 3,4-dihydro-1,4-benzoxazine (**7**) (3.21 mmol) in DMF (3 mL) was dropwise added to the mixture; after stirring at rt for 15 h, ice and 7.5 N NaOH (5 mL) were added; extraction with ethyl acetate and drying over magnesium sulfate leave an oil after evaporation. Purification on silica gel column chromatography (pet. ether/EtOAc 75/25) gave the formyl derivative (**10**).

Ethyl 4-Benzyl-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (10a).

Obtained from 3,4-dihydro-1,4-benzoxazine (**7a**) (7.01 g, 23.58 mmol). Reaction time 15 h; column chromatography (pet. ether/EtOAc 70/30); beige solid; 6.83 g (89 %); mp 76-78°C (EtOAc). IR (KBr, cm^{-1}) ν 1746 (CO); 1668 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3, *J* = 7.2 Hz); 3.68 (d, 2H, CH_2N, *J* = 4.4 Hz); 4.13-4.22 (m, 2H, CH_2O); 4.51 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.3 Hz); 4.61 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.3 Hz); 4.85 (t, 1H, OCH, *J* = 4.4 Hz); 6.73 (d, 1H, H_5, *J* = 8.5 Hz); 7.20-7.37 (m, 6H, H_6 and Ph); 7.47 (d, 1H, H_8, *J* = 1.6 Hz); 9.72 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 48.6 (CH_2N); 54.7 (NCH_2Ph); 62.1 (CH_2O); 71.9 (OCH); 111.6 (CH); 117.3 (CH); 126.1 (CH); 127.0 (2 CH Bn); 127.6 (C); 127.9 (CH Bn); 129.1 (2 CH Bn); 136.4 (C); 140.4 (C); 142.4 (C); 168.9 (CO); 190.4 (CHO).

MS (m/z) (IS) :326 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.79; H, 5.97; N, 4.46.

Ethyl 4-Benzyl-6-chloro-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (10b).

Obtained from 3,4-dihydro-1,4-benzoxazine (**7b**) (155 mg, 0.47 mmol). Reaction time 24 h at 60°C; column chromatography (pet. ether/EtOAc 70/30); white solid; 130 mg (77 %); mp 130-132°C (EtOAc). IR (KBr, cm^{-1}) ν 1743 (CO); 1661 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3, *J* = 7.2 Hz); 3.66 (d, 2H, CH_2N, *J* = 4.1 Hz); 4.12-4.27 (m, 2H, OCH_2); 4.49 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.4 Hz); 4.59 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.4 Hz); 4.83 (t, 1H, OCH, *J* = 4.1 Hz); 6.64 (s, 1H, H_5 or H_8); 7.19-7.37 (m, 5H, Ph); 7.51 (s, 1H, H_5 or H_8); 10.18 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 48.1 (CH_2N); 54.5 (NCH_2Ph); 62.2 (CH_2O); 71.6 (OCH); 111.9 (CH); 116.6 (CH); 122.9 (C); 127.0 (2 CH Bn); 128.2 (CH Bn); 129.3 (2 CH Bn); 133.0 (C); 135.7 (C); 140.8 (C); 141.2 (C); 168.6 (CO); 188.3 (CHO). MS (m/z) (IS) : 360 $[M+H]^{+\,35}$Cl, 362 $[M+H]^{+\,37}$Cl. Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.83; H, 5.09; N, 3.74.

Ethyl 4-Benzyl-6-bromo-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (10c).

Similarly obtained as for (**10e**) starting from 3,4-dihydro-1,4-benzoxazine (**7c**) (299 mg, 0.79 mmol). Reaction time 17 h at 60°C; colum chromatography (pet. ether/EtOAc 75/25); yellow solid; 255 mg (79 %); mp 120-124°C (EtOAc). IR (KBr, cm^{-1}) ν 1743 (CO); 1661 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3, *J* = 7.2 Hz); 3.64 (d, 2H, CH_2N, *J* = 4.1 Hz); 4.11-4.26 (m, 2H, CH_2O); 4.48 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.3 Hz); 4.59 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.3 Hz); 4.82 (t, 1H, OCH, *J* = 4.1 Hz); 6.84 (s, 1H, H_5 or H_8); 7.18-7.22 (m, 2H, Ph); 7.31-7.40 (m, 3H, Ph); 7.51 (s, 1H, H_5 or H_8); 10.05 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 48.0 (CH_2N); 54.5 (NCH_2Ph); 62.2 (CH_2O); 71.6 (OCH); 115.0 (CH); 117.1 (CH); 121.6 (C); 123.9 (C); 127.1 (2 CH Bn); 128.1 (CH Bn); 129.2 (2 CH Bn); 135.6 (C); 141.0 (C); 141.8 (C); 168.5 (CO); 190.3 (CHO). MS (m/z) (IS) : 404 $[M+H]^{+\,79}$Br, 406 $[M+H]^{+\,81}$Br. Anal. Calcd for $C_{19}H_{18}NO_4Br$: C, 56.45; H, 4.49; N, 3.46. Found: C, 56.18; H, 4.31; N, 3.33.

Ethyl 4-Benzyl-7-formyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine-2-carboxylate (10d).

Similarly obtained as for **10e** starting from 3,4-dihydro-1,4-benzoxazine (**7d**) (203 mg, 0.65 mmol). Time reaction 15 h at rt; column chromatography (pet. ether/EtOAc 70/30); orange solid; 210 mg (95 %); mp 116-118°C (EtOAc). IR (KBr, cm^{-1}) ν 1745 (CO); 1655 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3, *J* = 7.1 Hz); 2.49 (s, 3H, C_6-CH_3); 3.64 (d, 2H, CH_2N, *J* = 4.2 Hz); 4.13-4.27 (m, 2H, CH_2O); 4.49 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.3 Hz); 4.61 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.3 Hz); 4.81 (t, 1H, OCH, *J* = 4.2 Hz); 6.47 (s, 1H, H_5 or H_8); 7.20-7.39 (m, 5H, Ph); 7.39 (s, 1H, H_5 or H_8); 9.98 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 19.4 (C_6-CH_3); 48.5 (CH_2N); 54.4 (NCH_2Ph); 62.0 (CH_2O); 71.8 (OCH); 113.9 (CH); 119.7 (CH); 125.0 (C); 127.0 (2 CH Bn); 127.9 (CH Bn); 129.1 (2 CH Bn); 136.4 (C); 136.5 (C); 139.5 (C);

140.3 (C); 168.9 (CO); 190.3 (CHO). MS (m/z) (IS) : 340 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.42; H, 6.30; N, 4.28.

Ethyl 2-(4-Benzyl-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (10e).

Phosphorous oxychloride (450 μL, 4.78 mmol,) was slowly added to DMF (2 mL) cooled with an ice-bath; after 30 mn a solution of 3,4-dihydro-1,4-benzoxazine (**7e**) (1.00 g, 3.21 mmol) in DMF (3 mL) was dropwise added to the mixture; after stirring at rt for 15 h, ice/ water and 7.5 N NaOH (5 mL) were added; extraction with ethyl acetate and drying over magnesium sulfate leave an oil after evaporation. Purification on silica gel column chromatography (PE/EtOAc 75/25) gave **10e** (1.06 g, 97 %) as an oil; IR (NaCl, cm^{-1}) ν 1735 (CO); 1677 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, *J* = 7.1 Hz); 2.56 (dd, 1H, C**H$_a$**H$_b$CO, *J* = 6.3 Hz, *J* = 16.0 Hz); 2.74 (dd, 1H, CH$_a$**H$_b$**CO, *J* = 6.9 Hz, *J* = 16.0 Hz); 3.31 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.5 Hz, *J* = 12.2 Hz); 3.48 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 2.8 Hz, *J* = 12.2 Hz); 4.14 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.47 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.5 Hz); 4.57 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.5 Hz); 4.50-4.60 (m, 1H, OCH); 6.67 (d, 1H, H_5, *J* = 8.2 Hz); 7.18-7.34 (m, 7H, H_6, H_8 and Ph); 9.61 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3); 37.5 (CH_2CO); 50.9 (CH_2N); 54.0 (NCH_2Ph); 60.7 (CH_2); 69.2 (OCH); 110.6 (CH); 116.3 (CH); 126.2 (CH); 126.5 (C); 126.6 (2 CH Bn); 127.4 (CH Bn); 128.7 (2 CH Bn); 136.3 (C); 140.3 (C); 142.4 (C); 169.7 (CO); 189.8 (CHO). MS (m/z) (IS) : 340 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.45; H, 6.42; N, 4.01.

Ethyl 2-(4-Benzyl-6-chloro-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (10f).

Similarly obtained as for **10e** starting from 3,4-dihydro-1,4-benzoxazine (**7f**) (6.20 g, 17.92 mmol). Reaction time 17 h at 60°C; the crude solid obtained after addition of water/NaOH was crystallized in ethanol to give **10f** (5.67 g, 85 %) as an orange solid; mp 98-100°C. IR (KBr, cm^{-1}) ν 1732 (CO); 1663 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, CH_3, *J* = 7.2 Hz); 2.56 (dd, 1H, C**H$_a$**H$_b$CO, *J* = 6.6 Hz, *J* = 16.0 Hz); 2.77 (dd, 1H, CH$_a$**H$_b$**CO, *J* = 6.9 Hz *J* = 16.0 Hz); 3.34 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.5 Hz, *J* = 12.2 Hz); 3.51 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 2.8 Hz, *J* = 12.2 Hz); 4.13-4.21 (m, 2H, CH_2O); 4.51 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.7 Hz); 4.50-4.59 (m, 1H, OCH); 4.60 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.7 Hz); 6.63 (s, 1H, H_5 or H_8); 7.21-7.41 (m, 5H, Ph); 7.37 (s, 1H, H_5 or H_8); 10.15 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3); 37.8 (CH_2CO); 50.9 (CH_2N); 54.5 (NCH_2Ph); 61.3 (CH_2O); 69.5 (OCH) ; 114.4 (CH); 116.4 (CH); 122.4 (C); 126.9 (2 CH Bn); 128.1 (CH Bn); 129.3 (2 CH Bn); 133.1(C); 135.8 (C); 141.1 (C); 141.6 (C); 170.0 (CO); 188.2 (CHO). MS (m/z) (IS) : 374 $[M+H]^+$ ^{35}Cl, 376 $[M+H]^+$ ^{37}Cl. Anal. Calcd for $C_{20}H_{20}NO_4Cl$: C, 64.26; H, 5.39; N, 3.75. Found: C, 63.93; H, 5.27; N, 3.88.

Ethyl 2-(4-Benzyl-6-bromo-7-formyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (10g).

Similarly obtained as for **10e** starting from 3,4-dihydro-1,4-benzoxazine (**7g**) (5.00 g, 12.81 mmol). Reaction time 28 h at 60°C; the crude solid obtained after addition of water/NaOH was crystallized in

ethanol to afford **10g** (5.21 g, 97 %) as a beige solid; mp 118-120°C (EtOH). IR (KBr, cm^{-1}) ν 1735 (CO); 1654 (CHO). ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, CH_3, *J* = 7.1 Hz); 2.56 (dd, 1H, C**H$_a$**H$_b$CO, *J* = 6.5 Hz, *J* = 16.0 Hz); 2.77 (dd, 1H, CH$_a$**H$_b$**CO, *J* = 6.7 Hz *J* = 16.0 Hz); 3.33 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.5 Hz, *J* = 12.2 Hz); 3.50 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 2.8 Hz, *J* = 12.2 Hz); 4.12-4.21 (m, 2H, CH_2O); 4.51 (d, 1H, NC**H$_a$**H$_b$Ph, *J* = 16.5 Hz); 4.60 (d, 1H, NCH$_a$**H$_b$**Ph, *J* = 16.5 Hz); 4.49-4.59 (m, 1H, OCH); 6.83 (s, 1H, H_5 or H_8); 7.21-7.41 (m, 6H, Ph and H_5 or H_8); 10.03 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 37.8 (CH_2CO); 50.8 (CH_2N); 54.4 (NCH_2Ph); 61.3 (CH_2O); 69.5 (OCH); 114.6 (CH); 117.0 (CH); 121.8 (C); 123.4 (C); 127.0 (2 CH Bn); 128.1 (CH Bn); 129.3 (2 CH Bn); 135.8 (C); 141.3 (C); 142.1 (C); 169.9 (CO); 190.3 (CHO). MS (m/z) (IS) : 418 $[M+H]^{+\,79}$Br, 420 $[M+H]^{+\,81}$Br. Anal. Calcd for $C_{20}H_{20}NO_4Br$: C, 57.43; H, 4.82; N, 3.35. Found: C, 57.81; H, 4.69; N, 3.50.

Ethyl 4-Acetyl-6-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (11a).

2,2-Dichloromethyl methyl ether (170 μL, 1.84 mmol) was slowly added to a solution of 3,4-dihydro-1,4-benzoxazine (**8a**) (139 mg, 0.56 mmol) in dichloromethane (3.5 mL). To the ice-cooled mixture aluminum chloride (249 mg, 1.84 mmol) was portionwise added (15 min). The mixture was stirred at rt for 20 h; ice was added and the mixture was extracted with ethyl acetate; the organic extracts were washed with a saturated solution of sodium hydrogencarbonate and water; drying over magnesium sulfate and evaporation leave an oil which was purified on silica gel column (pet. ether/EtOAc 50/50), a mixture of nonseparable aldehydes (**11a**) and (**12a**) (93 mg, 60 %, 85/15) was obtained as an oil. IR (NaCl, cm^{-1}) ν 1750 (CO); 1715-1630 (CHO and $NCOCH_3$). **11a** ^{1}H NMR (DMSO-d_6, 80°C) δ 1.19 (t, 3H, CH_3, *J* = 7.1 Hz); 2.25 (s, 3H, $COCH_3$); 3.78 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.4 Hz, *J* = 14.1 Hz); 4.16 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.47 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.4 Hz, *J* = 14.1 Hz); 5.28 (t, 1H, OCH, *J* = 3.4 Hz); 7.17 (d, 1H, H_8, *J* = 8.6 Hz); 7.65 (dd, 1H, H_7, *J* = 2.0 Hz, *J* = 8.6 Hz); 8.24 (br s, 1H, H_5); 9.87 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 21.7 ($COCH_3$); 42.2 (CH_2N); 61.0 (CH_2O); 73.0 (OCH); 117.1 (CH); 125.3 (CH); 126.2 (C); 126.3 (CH); 129.2 (C); 149.7 (C); 167.6 and 168.3 (CO, NCO); 190.6 (CHO). MS (m/z) (IS) : 278 $[M+H]^+$.

Ethyl 4-Acetyl-8-formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (12a).

Oil obtained as a mixture (**11a/12a**); ^{1}H NMR (DMSO-d_6, 80°C) δ 1.19 (t, 3H, CH_3, *J* = 7.1 Hz); 2.22 (s, 3H, $COCH_3$); 3.83 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.4 Hz, *J* = 14.0 Hz); 4.16 (q, 2H, OCH_2, *J* = 7.1 Hz); 4.48 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.4 Hz, *J* = 14.0 Hz); 5.35 (t, 1H, OCH, *J* = 3.4 Hz); 7.06 (t, 1H, H_6, *J* = 7.8 Hz); 7.53 (dd, 1H, H_7, *J* = 1.6 Hz, *J* = 7.8 Hz); 7.91 (d, 1H, H_5, *J* = 7.8 Hz); 10.38 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 21.6 ($COCH_3$); 41.7 (CH_2N); 61.0 (CH_2O); 73.2 (OCH); 119.7 (CH); 123.5 (CH); 123.9 (C); 127.0 (C); 129.5 (CH); 147.5 (C); 167.6 and 168.3 (CO, NCO); 190.6 (CHO). MS (m/z) (IS) : 278 $[M+H]^+$.

Ethyl 2-(4-Acetyl-6-formyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetate (11e).

Similarly obtained as for **11a** starting from 3,4-dihydro-1,4-benzoxazine (**8e**) (195 mg, 0.74 mmol). After 3 h at rt, 5 h and 10 h, 3 eq of α,α-dichloromethyl methyl ether and aluminum trichloride were sequentially added. Purification by silica gel column (pet. ether/EtOAc 60/40) afforded a mixture of **11e** and **12e**, (88/12) as a pasty solid; 52 mg (24 %) then compound (**15**). **11e** ^{1}H NMR (DMSO-d_6, 80°C) δ 1.22 (t, 3H, CH_3, *J* = 7.1 Hz); 2.29 (s, 3H, $COCH_3$); 2.69 (dd, 1H, CHC**H$_a$**H$_b$CO, *J* = 7.3 Hz, *J* = 16.0 Hz); 2.84 (dd, 1H, CHCH$_a$**H$_b$**CO, *J* = 5.4 Hz *J* = 16.0 Hz); 3.54 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 7.8 Hz, *J* = 13.7 Hz); 4.15 (q, 2H, CH_2O, *J* = 7.1 Hz); 4.27 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 2.9 Hz, *J* = 13.7 Hz); 4.67-4.76 (m, 1H, OCH); 7.03 (d, 1H, H_8, *J* = 8.4 Hz); 7.59 (dd, 1H, H_7, *J* = 2.0 Hz, *J* = 8.4 Hz); 8.33 (br s, 1H, H_5); 9.85 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.5 (CH_3); 22.1 ($COCH_3$); 36.5 (CH_2CO); 44.6 (CH_2N); 59.8 (CH_2O); 72.3 (OCH); 117.1 (CH); 125.2 (CH); 126.0 (C); 126.1 (CH); 128.9 (C); 150.4 (C); 168.4 and 168.8 (CO, NCO); 190.5 (COH). MS (m/z) (IS) : 292 $[M+H]^+$.

Ethyl 4-Acetyl-8-formyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine-2-carboxylate (12d).

Similarly obtained as for **11a** starting from 3,4-dihydro-1,4-benzoxazine (**8d**) (104 mg, 0.39 mmol). After 3 h at rt, 3.3 eq of α,α-dichloromethyl methyl ether (119 µL, 1.29 mmol) and aluminum trichloride (174 mg, 1.29 mmol) were added. Purification by silica gel column chromatography (pet. ether/EtOAc 60/40); white solid; 43 mg (37 %); mp 92-94°C (EtOAc). IR (KBr, cm^{-1}) ν 1745 (CO); 1673 (NCO, CHO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.19 (t, 3H, CH_3, *J* = 7.2 Hz); 2.23 (s, 3H, $COCH_3$); 2.29 (s, 3H, CH_3); 3.80 (dd, 1H, OCHC**H$_a$**H$_b$N, *J* = 3.7 Hz, *J* = 13.9 Hz); 4.16 (q, 2H, CH_2O, *J* = 7.2 Hz); 4.46 (dd, 1H, OCHCH$_a$**H$_b$**N, *J* = 3.7 Hz, *J* = 13.9 Hz); 5.30 (t, 1H, OCH, *J* = 3.7 Hz); 7.33 (d, 1H, H_7, *J* = 1.6 Hz); 7.74 (s, 1H, H_5); 10.35 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.3 (CH_3); 19.6 (C_6CH_3); 21.6 ($COCH_3$); 41.8 (CH_2N); 61.0 (CH_2O); 73.0 (OCH); 123.4 (C); 123.5 (CH); 126.7 (CH); 128.9 (C); 129.9 (CH); 145.5 (C); 167.6 and 168.3 (CO and NCO); 187.9 (CHO). MS (m/z) (IS) : 292 $[M+H]^+$. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.54; H, 5.79; N, 4.63.

Ethyl 6-Formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (13).

Similarly obtained as for **11a** starting from dihydro-1,4-benzoxazine (**9a**) (317 mg, 0.93 mmol). Reaction time 5 h at rt. Purification by silica gel column chromatography (pet. ether/EtOAc 60/40); a mixture (114 mg, 52 %) of **13** and **14** (2/1) was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, CH_3, *J* = 7.1 Hz); 3.52 (d, 2H, OCHC**H$_2$**N, *J* = 3.8 Hz); 4.09-4.25 (m, 2H, CH_2O); 4.80 (t, 1H, OCH, *J* = 3.8 Hz); 6.93 (d, 1H, H_8, *J* = 8.1 Hz); 7.05 (d, 1H, H_5, *J* = 1.8 Hz); 7.14 (dd, 1H, H_7, *J* = 1.8 Hz, *J* = 8.1 Hz); 9.67 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 42.1 (CH_2N); 61.9 (CH_2O); 73.1 (OCH); 115.1 (CH); 117.1 (CH); 123.4 (CH); 133.7 (C); 130.8 (C); 148.4 (C); 168.9 (CO); 191.4 (CHO). MS (m/z) (IS) : 236 $[M+H]^+$.

Ethyl 8-Formyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (14).

^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, CH_3, *J* = 7.1 Hz); 3.83 (d, 2H, OCHC**H$_a$**H$_b$N, *J* = 3.5 Hz); 4.09-4.25 (m, 2H, CH_2O); 4.86 (t, 1H, OCH, *J* = 3.5 Hz); 6.69-6.77 (m, 2H, H_5, H_6 or H_7); 7.12-7.16 (m, 1H, H_5, H_6 or H_7); 10.39 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 42.0 (CH_2N); 61.9 (CH_2O); 72.9 (OCH); 118.0 (CH); 120.9 (CH); 121.3 (CH); 124.6 (C); 133.7 (C); 145.9 (C); 168.9 (CO); 189.8 (CHO).

Diethyl 6,6-hydroxymethylene-bis(4-acetyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl acetate) (15).

Obtained during the synthesis of **11e**; white solid; 91 mg (22 %); mp 68-70°C (EtOAc). IR (KBr, cm^{-1}ν 3432 (OH); 1730 (CO); 1666 (NCO). ^{1}H NMR (DMSO-d_6, 80°C) δ 1.21 (t, 6H, 2 CH_3, *J* = 7.1 Hz); 2.22 (s, 6H, 2 $NCOCH_3$); 2.62 (dd, 2H, 2 CHC**H$_a$**H$_b$CO, *J* = 7.3 Hz, *J* = 15.9 Hz); 2.75 (dd, 2H, 2 CHCH$_a$**H$_b$**CO, *J* = 5.6 Hz, *J* = 15.9 Hz); 3.08 (br s, exchangeable D_2O, 1H, OH); 3.44 (dd, 2H, 2 OCHC**H$_a$**H$_b$N, *J* = 7.7 Hz, *J* = 12.8 Hz); 4.13 (q, 4H, CH_2O, *J* = 7.1 Hz); 4.20 (d, 2H, 2 OCHCH$_a$**H$_b$**N, *J* = 12.8 Hz) ; 4.51-4.60 (m, 2H, 2 OCH); 5.57 (br s, 1H, C**H**OH); 6.78 (d, 2H, 2 H_8, *J* = 8.4 Hz); 7.01 (dd, 2H, 2 H_7, *J* = 2.0 Hz, *J* = 8.4 Hz); 7.63 (br s, 2H, 2 H_5). ^{13}C NMR (DMSO-d_6, 80°C) δ 13.5 (2 CH_3); 22.1 (2 $NCOCH_3$); 36.8 (2 CH_2CO); 44.4 (2 CH_2N); 59.8 (2 CH_2O); 71.7 (2 OCH); 73.1 (C**H**OH); 115.9 (2 CH); 121.4 (2 CH); 123.0 (2 CH); 125.1 (2 C); 137.2 (2 C); 144.3 (2 C); 168.2 and 169.0 (2CO, 2 $NCOCH_3$). MS (m/z) (IS) : 555 $[M+H]^+$. Anal. Calcd for $C_{29}H_{34}N_2O_9$: C, 62.81; H, 6.18; N, 5.05. Found: C, 63.20; H, 6.07; N, 5.23.

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