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Tetrahedron 59 (2003) 8163–8170

TETRAHEDRON

Synthesis of 4-alkoxy-4-methyl- and 4-alkoxy-4-fluoromethyl-1,3-benzoxazinones

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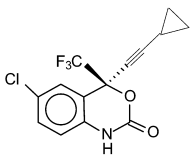
Received 2 May 2003; revised 25 July 2003; accepted 21 August 2003

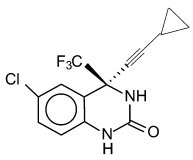
Abstract—Cyclization of 2-hydroxyacetophenone hydrazones with triphosgene resulted in the formation of 4-methylene-1,3-benzoxazinones. These compounds were converted to 4-alkoxy-4-methyl-1,3-benzoxazinones and 4-fluoromethyl-4-methoxy-1,3-benzoxazinones upon treatment with alcohols under refluxing conditions and F-TEDA-BF_4 in acetonitrile and methanol, respectively.

1. Introduction

Bezoxazines are a very important class of heterocyclic compounds and many derivatives of this heterocyclic system exhibit biological activities. One of the most recent and most important examples is the 3,1-benzoxazine derivative *Efavirenz*, which has recently been approved as an anti-HIV drug.[1,2] It has also been reported that analogs of *Efavirenz* where the alkynyl group has been replaced by an alkoxy group show similar activities.[3] Analogs of this ring system such as the quinazoline derivative DPC 961 have also been reported to be HIV-inhibitors.[4]



Efavirenz



DPC 961

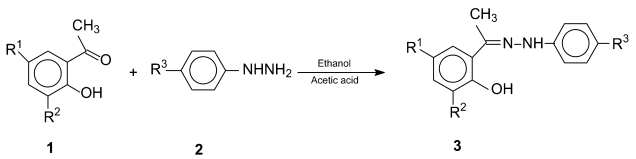
1,3-Benzoxazines, on the other hand, have also been known to exhibit a wide range of biological activities. They have been used as antimycobacterial agents,[5,6]

CNS agents[7] and K^+ channel openers.[8] 1,3-Benzoxazines have been reported to convert to the 3,1-isomer.[9]

In this paper, we report the synthesis of a number of 4,4-disubstituted-1,3-benzoxazinones. Our approach for the synthesis of these compounds is based upon three steps: synthesis of hydrazones of 2-hydroxyacetophenone derivatives followed by their cyclization with triphosgene (bis(trichloromethyl)carbonate) and then treatment of the resulting 4-methylene-1,3-benzoxazinones with alcohols or F-TEDA-BF_4.

2. Results and discussion

A series of hydrazones **3** was prepared from the reaction of substituted 2-hydroxyacetophenone **1** with aromatic hydrazines **2** in ethanol with a few drops of acetic acid (Scheme 1).



Scheme 1.

Compounds **3a–l** (Table 1) show in their IR spectra absorbances for the hydroxyl group at about 3350 cm^{-1} and C=N at 1600 cm^{-1}, while in the ^1H NMR spectra the methyl group appears as a singlet at about δ=2.30 ppm and the hydroxyl group as a broad singlet at δ=12.50 ppm. The ^{13}C NMR and MS spectra of these compounds is in agreement with the proposed structures.

Although **3** could exist as *E* or *Z* isomers, it was used in the next step without investigating its stereochemistry. Previous work on the cyclization of similar hydrazones to give the benzotriazepine ring system did not investigate the stereochemistry of the hydrazones.[10,11] Nevertheless, in our case, if the cyclization proceeds via the enamine form as shown in Scheme 3, the C=N will be broken and its stereochemistry will be lost.

Keywords: 2-hydroxyacetophenone; hydrazones; triphosgene; 1,3-benzoxazinones.

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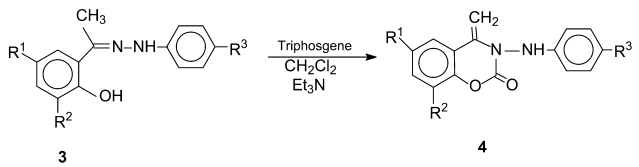
0040–4020/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tet.2003.08.044

Table 1. Hydrazone **3** derivatives

R^1	R^2	R^3	Product	Yield (%)
Br	H	H	**3a**	71
Br	H	Br	**3b**	78
Br	H	Cl	**3c**	75
Br	H	CH_3	**3d**	68
Cl	H	H	**3e**	82
Cl	H	Br	**3f**	63
Cl	H	Cl	**3g**	78
Cl	H	CH_3	**3h**	79
Cl	Cl	H	**3i**	75
Cl	Cl	Cl	**3j**	81
Cl	Cl	CH_3	**3k**	80
Cl	Cl	Br	**3l**	89

Treatment of selected examples from the above hydrazones with triphosgene in dichloromethane in the presence of triethylamine resulted in the formation of the 4-methylene-1,3-benzoxazinones **4a**,**b**,**e**,**i**,**j**,**l** (Scheme 2, Table 2).

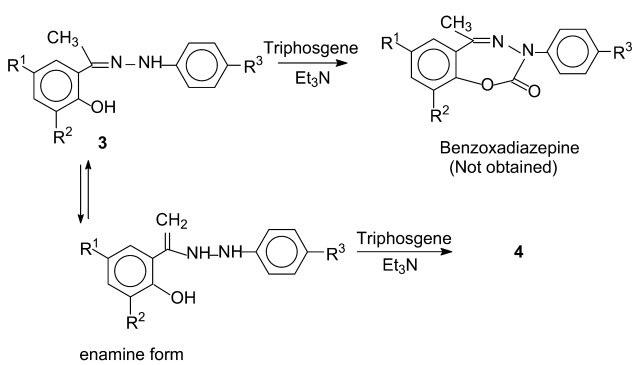


Scheme 2.

Table 2. 4-Methylene-1,3-benzoxazinone derivatives **4**

R^1	R^2	R^3	Product	Yield (%)
Br	H	H	**4a**	65
Br	H	Br	**4b**	77
Cl	H	H	**4e**	58
Cl	Cl	H	**4i**	87
Cl	Cl	Cl	**4j**	56
Cl	Cl	Br	**4l**	67

The cyclization of **3** to **4** did not proceed to form a seven membered ring (benzoxadiazepine) in a similar manner to that previously reported for the cyclization of hydrazones of 2-aminobenzophenone into benzotriazepines with phosgene and paraformaldehyde.[10,11] The methyl group in **3** is involved in the cyclization step via the formation of the enamine form of **3** which reacts with triphosgene to give the six membered ring product (**4**) rather than the seven membered ring benzoxadiazepine (Scheme 3). A similar cyclization across the enol form of acetophenone has previously been reported.[12] To the best of our knowledge, there has been one previous example in the literature were only two similar compounds were prepared using phosgene rather than the more advantageous and easy to handle triphosgene.[13]

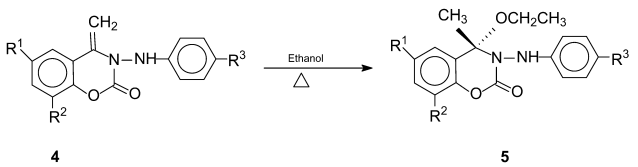


Scheme 3.

Compounds of type **4** show in their IR spectra absorbance for the carbonyl group at 1735 cm^{-1} while the exocylic double bond absorbs at 1600 cm^{-1}. The protons of the latter group appear as two doublets at δ=4.95 and 5.15 ppm with coupling constants of about 2.5–3.0 Hz in the ^1H NMR spectra. Furthermore, the ^{13}C NMR spectra show a distinct absorbance for the exocylic methylene group at about δ=90 ppm, which is in agreement with previous studies on related compounds.[12]

Finally, the structure of compounds of type **4** was confirmed using X-ray crystallography. Figure 1 shows the crystal structure of compound **4a** as a representative example.

Benzoxazinones of type **4** were found to be susceptible to additions across the exocyclic double bond. Reflux of these compounds in ethanol resulted in the addition of ethanol to the exocyclic double bond and the formation of the 4-ethoxy-4-methyl-1,3-benzoxazinones **5a**,**b**,**e**,**i**,**j** (Scheme 4, Table 3).



Scheme 4.

Table 3. 4,4-Disubstituted 1,3-benzoxazinone derivatives **5**

R^1	R^2	R^3	Product	Yield (%)
Br	H	H	**5a**	48
Br	H	Br	**5b**	68
Cl	H	H	**5e**	53
Cl	Cl	H	**5i**	72
Cl	Cl	Cl	**5j**	50

Compounds **5a**,**b**,**e**,**i**,**j** show in their IR spectra no absorbance for the exocyclic methylene group, while their ^1H NMR spectra show absorbance for the newly created methyl group at about δ=2.0 ppm.

Another assembly of compounds of type **5** was prepared in one step from the hydrazone **3**. In this case treatment of **3** with triphosgene followed by refluxing the resulting solid in ethanol gave **5c**,**d**,**f**,**g**,**h**,**k** (Scheme 5, Table 4).

This group of 4,4-disubstituted-1,3-benzoxazinones show similar spectroscopic characteristics to the previous group **5a**,**b**,**e**,**i**,**j**. The structure of compounds of type **5** was confirmed using X-ray crystallography. Figure 2 shows the crystal structure of compound **5j** as a representative product.

In order to test the generality of this reaction process, a series of alcohols with increasing hydrocarbon chain length were used. Methanol, ethanol, propanol and butanol were all

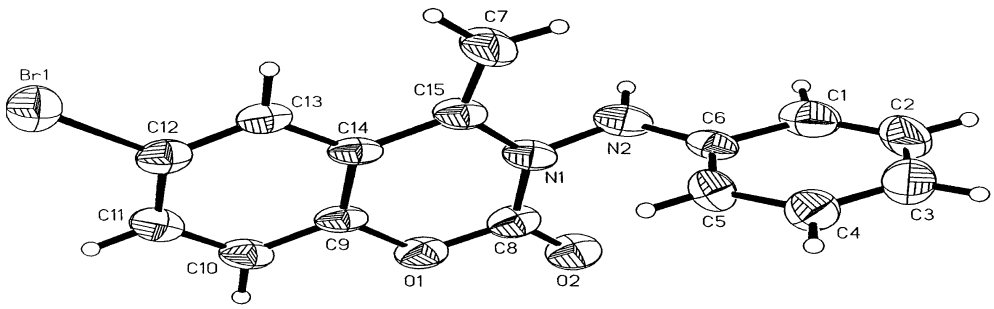
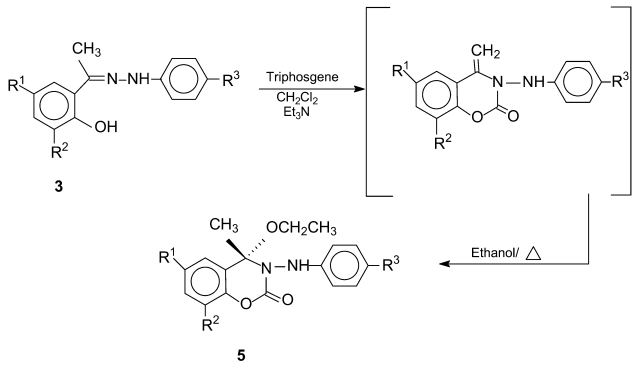


Figure 1. X-Ray crystal structure of **4a**.

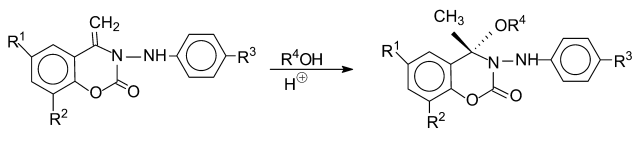


Scheme 5.

Table 4. 4,4-Disubstituted 1,3-benzoxazinone derivatives **5**

R^1	R^2	R^3	Product	Yield (%)
Br	H	Cl	**5c**	84
Br	H	CH_3	**5d**	92
Cl	H	Br	**5f**	82
Cl	H	Cl	**5g**	88
Cl	H	CH_3	**5h**	91
Cl	Cl	CH_3	**5k**	80

reacted with compounds **4j** or **4b** under acidic conditions (Scheme 6, Table 5).



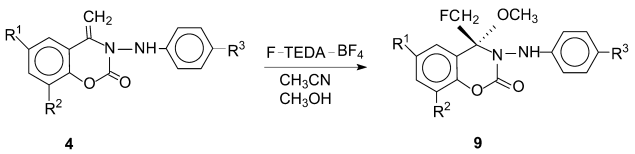
Scheme 6.

Table 5. 4,4-Disubstituted 1,3-benzoxazinones **5**–**8**

R^1	R^2	R^3	R^4	Product	Yield (%)
Cl	Cl	Cl	CH_3	**6j**	73
Cl	Cl	Cl	CH_2CH_3	**5j**	67
Br	H	Br	$(CH_2)_2CH_3$	**7b**	53
Br	H	Br	$(CH_2)_3CH_3$	**8b**	47

It turned out that in all cases the alcohol was added across the exocyclic double bond following Markovnikov's rule to give **5j**, **6j**, **7b** and **8b** in very good yields. These compounds show similar spectroscopic characteristics to those of the previous two groups of type **5**, except for the alkoxy side chain at position 4.

Next, the introduction of a fluorine substituent into the C_4-methyl group of compounds of type **5** was investigated. Compounds **4b** and **4e** (as representative examples) were treated with 1-chloromethyl-4-fluoro-1,4-diazabicyclo [2.2.2]-octane bis(tetrafluoroborate) (F-TEDA-BF_4) in acetonitrile in the presence of methanol (Scheme 7, Table 6).



Scheme 7.

Table 6. 4-Fluoromethyl-4-methoxy-1,3-benzoxazinones **9**

R^1	R^2	R^3	Product	Yield (%)
Br	H	Br	**9b**	49
Cl	H	H	**9e**	42

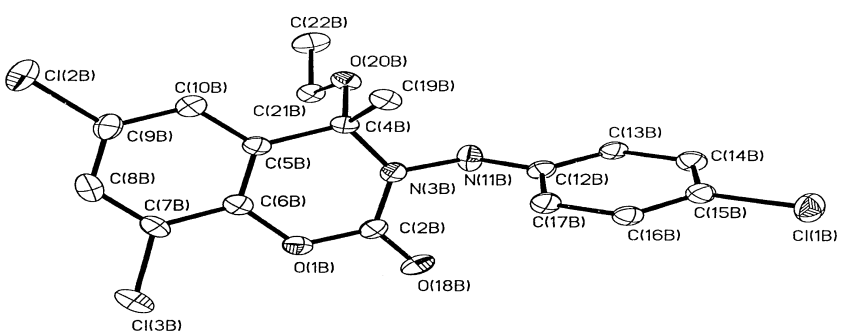


Figure 2. X-Ray crystal structure of **5j**.

F-TEDA-BF_4 is a known electrophilic fluorinating reagent which has previously been used for the fluorination of styrene and other similar alkenes.[14,15] Reaction of **4b** and **4e** with this reagent gave the addition products **9b** and **9e**, respectively. The absorbance for the exocyclic double bond of **4b** and **4e** is no longer present in the IR and NMR spectra of **9b** and **9e**. The ^{1}H NMR spectra of these compounds show signals for the methoxy and CH_2F groups at δ=3.04 and 4.80 ppm for **9b** and δ=3.03 and 4.78 ppm for **9e**. The ^{19}F NMR spectra of **9b** and **9e**, on the other hand, show signals at δ=−118.59 and δ=−117.43 ppm, respectively. Finally, the MS spectra of these two compounds show molecular ions at *m/z*=458 for **9b** and *m/z*=336 for **9e** which is in agreement with the proposed structures.

In conclusion, 4-methylene-1,3-benzoxazinones were obtained from the reaction of hydrazones of 2-hydroxyacetophenone with triphosgene. Addition of alcohols and F-TEDA-BF_4 to the exocyclic double bond of these 1,3-benzoxazinones gave 4-alkoxy-4-methyl- and 4-alkoxy-4-fluoromethyl-1,3-benzoxazinones, respectively.

3. Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 883 spectrophotometer as KBr pellets and expressed as ν in cm^{-1}. NMR spectra were recorded on Jeol FX-100 (100 MHz) and Jeol ECP 400 (400 MHz) in $CDCl_3$ and expressed as δ in ppm. Mass spectra were recorded on Shimadzu QP-5050A GC/MS system. Microanalysis was performed at KACST research laboratories.

3.1. General procedure 1: preparation of hydrazones 3a–l

A solution of the appropriate 2-hydroxyacetophenone derivative (18 mmol), phenylhydrazine derivative (18 mmol), 1 mL of acetic acid in 50 mL of ethanol was refluxed for two hours. The solvent was evaporated and the resulting solid was filtered and washed several times with water. Recrystallization from a mixture of ethanol and water (8:2) afforded the required hydrazones.

3.1.1. 5-Bromo-2-hydroxyacetophenone phenylhydrazone 3a. This compound was prepared from 5-bromo-2-hydroxyacetophenone **9** and phenylhydrazine **10**. Yield=3.9 g, 71%, yellow needles, mp 164°C. [Found: C, 55.16; H, 4.28. $C_{14}H_{13}BrN_2O$ requires: C, 55.10; H, 4.29]. IR: 3307 (OH), 1600 (C=N); ^{1}H NMR: 2.28 (s, 3H), 6.81 (d, 2H, *J*=8.6 Hz), 6.95 (t, 2H, *J*=8.6 Hz), 7.24 (m, 3 H), 7.47 (d, 1H, *J*=1.8 Hz), 12.51 (bs, 1H); MS: *m/z* (%) 306 (M+2, 63), 304 (M$^+$, 60), 287, 256, 224, 200, 171, 153, 133, 106, 92 (100), 91, 77, 65.

3.1.2. 5-Bromo-2-hydroxyacetophenone 4-bromophenylhydrazone 3b. This compound was prepared from **9** and 4-bromophenylhydrazine **11**. Yield=5.3 g, 78%, yellow crystals, mp 201°C. [Found: C, 43.53; H, 3.27. $C_{14}H_{12}Br_2N_2O$ requires: C, 43.78; H, 3.14]. IR: 3372 (OH), 1588 (C=N); ^{1}H NMR: 2.35 (s, 3H), 6.79 (d, 2H, *J*=9.0 Hz), 6.93 (d, 2H, *J*=9.0 Hz), 7.28–7.40 (m, 2H), 7.52 (d, 1H, *J*=1.8 Hz), 12.07 (bs, 1H); MS: *m/z* (%) 386 (M+4, 40), 384 (M+2, 81), 382 (M$^+$, 43), 369, 367, 288, 286, 224, 214, 199, 186, 171 (100), 155, 145, 133, 91, 75, 65, 63.

3.1.3. 5-Bromo-2-hydroxyacetophenone 4-chlorophenylhydrazone 3c. This compound was prepared from **9** and 4-chlorophenylhydrazine **12**. Yield=4.6 g, 75%, pale yellow powder, mp 172°C. [Found: C, 49.73; H, 3.41. $C_{14}H_{12}BrClN_2O$ requires: C, 49.51; H, 3.56]. IR: 3337 (OH), 1592 (C=N); ^{1}H NMR: 2.31 (s, 3H), 6.82 (d, 2H, *J*=8.1 Hz), 6.91 (d, 1H, *J*=7.5 Hz), 7.18–7.31 (m, 3H), 7.49 (d, 1H, *J*=2.0 Hz); 12.32 (bs, 1H); MS: *m/z* (%) 342 (M+4, 23), 340 (M+2, 83), 338 (M$^+$, 68), 323, 174, 163, 161, 127 (100), 91, 65, 63.

3.1.4. 5-Bromo-2-hydroxyacetophenone 4-methylphenylhydrazone 3d. This compound was prepared from **9** and 4-methylphenylhydrazine **13**. Yield=3.9 g, 68%, yellow powder, mp 156°C. [Found: C, 56.19; H, 4.69. $C_{15}H_{15}BrN_2O$ requires: C, 56.44; H, 4.73]. IR: 3345 (OH), 1604 (C=N); ^{1}H NMR: 2.29 (s, 3H); 2.34 (s, 3H), 6.78 (d, 2H, *J*=8.2 Hz), 7.01–7.34 (m, 4H), 7.48 (d, 1H, *J*=2.1 Hz), 12.99 (bs, 1H); MS: *m/z* (%) 320 (M+2, 71), 318 (M$^+$, 78), 303, 301, 238, 222, 200, 183, 145, 107 (100), 91, 75, 63.

3.1.5. 5-Chloro-2-hydroxyacetophenone phenylhydrazone 3e. This compound was prepared from 5-chloro-2-hydroxyacetophenone **14** and **10**. Yield=3.9 g, 82%, yellow needles, mp 170°C. [Found: C, 64.57; H, 4.98. $C_{14}H_{13}ClN_2O$ requires: C, 64.49; H, 5.02]. IR: 3303 (OH), 1600 (C=N); ^{1}H NMR: 2.29 (s, 3H), 6.86 (d, 2H, *J*=8.7 Hz), 7.14–7.34 (m, 6H), 12.48 (bs, 1H); MS: *m/z* (%) 262 (M+2, 26), 260 (M$^+$, 88), 245, 243, 208, 180, 155, 133, 93 (100), 91, 77, 65.

3.1.6. 5-Chloro-2-hydroxyacetophenone 4-bromophenylhydrazone 3f. This compound was prepared from **14** and **11**. Yield=3.9 g, 63%, yellow crystals, mp 190°C. [Found: C, 49.37; H, 3.47. $C_{14}H_{12}BrClN_2O$ requires: C, 49.51; H, 3.56]. IR: 3372 (OH), 1590 (C=N); ^{1}H NMR: 2.33 (s, 3H), 6.84–6.99 (m, 3H), 7.10–7.22 (m, 2H), 7.33–7.49 (m, 2H), 8.30 (bs, 1H), 12.55 (bs, 1H); MS: *m/z* (%) 342 (M+4, 23), 340 (M+2, 94), 338 (M$^+$, 82), 325, 323, 259, 242, 207, 171 (100), 155, 127, 99, 91, 75, 63.

3.1.7. 5-Chloro-2-hydroxyacetophenone 4-chlorophenylhydrazone 3g. This compound was prepared from **14** and **12**. Yield=4.2 g, 78%, pale yellow powder, mp 160°C. [Found: C, 57.11; H, 4.17. $C_{14}H_{12}Cl_2N_2O$ requires: C, 56.96; H, 4.09]. IR: 3359 (OH), 1599 (C=N); ^{1}H NMR: 2.35 (s, 3H), 6.85–7.05 (m, 3H), 7.20–7.38 (m, 4H), 8.32 (s, 1H), 12.58 (bs, 1H); MS: *m/z* (%) 298 (M+4, 7), 296 (M+2, 58), 294 (M$^+$, 89), 281, 279, 259, 242, 169, 141, 127 (100), 111, 99, 91, 75, 65, 63.

3.1.8. 5-Chloro-2-hydroxyacetophenone 4-methylphenylhydrazone 3h. This compound was prepared from **14** and **13**. Yield=3.9 g, 79%, yellow powder, mp 130°C. [Found: C, 65.46; H, 5.39. $C_{15}H_{15}ClN_2O$ requires: C, 65.57; H, 5.50]. IR: 3324 (OH), 1593 (C=N); ^{1}H NMR: 2.30 (s, 3H), 2.35 (s, 3H), 6.92 (d, 2H, *J*=8.2 Hz), 7.06–7.25 (m, 4H), 7.34 (d, 1H, *J*=2.2 Hz), 8.04 (s, 1H), 12.76 (bs, 1H); MS: *m/z* (%) 276 (M+2, 24), 274 (M$^+$, 77), 257, 238, 222, 169, 154, 137, 120, 107 (100), 99, 91, 75, 65, 63.

3.1.9. 3,5-Dichloro-2-hydroxyacetophenone phenylhydrazone 3i. This compund was prepared from 3,5-dichloro-2-hydroxyacetophenone **15** and **10**. Yield=4.0 g, 75%, yellow needles, mp 133°C. [Found: C, 57.25; H, 4.11. $C_{14}H_{12}Cl_2N_2O$ requires: C, 56.96; H, 4.09]. IR: 3338 (OH), 1595 (C=N); ^{1}H NMR: 2.29 (s, 3H), 6.98 (d, 2H, J=8.3 Hz), 7.18–7.28 (m, 5H), 13.26 (bs, 1H); MS: m/z (%) 296 (M+2, 28), 294 (M^+, 52), 279, 277, 202, 166, 133, 106, 93 (100), 91, 77, 65, 63.

3.1.10. 3,5-Dichloro-2-hydroxyacetophenone 4-chlorophenylhydrazone 3j. This compound was prepared from **15** and **12**. Yield=4.8 g, 81%, pale yellow powder, mp 220°C. [Found: C, 51.16; H, 3.29. $C_{14}H_{11}Cl_3N_2O$ requires: C, 51.00; H, 3.36]. IR: 3371 (OH), 1585 (C=N); ^{1}H NMR: 2.33 (s, 3H), 6.92 (d, 2H, J=8.5 Hz), 7.21–7.48 (m, 4H), 13.09 (bs, 1H); MS: m/z (%) 332 (M+4, 11), 330 (M+2, 39), 328 (M^+, 43), 313, 311, 293, 276, 202, 188, 167, 133, 127 (100), 111, 99, 75, 63.

3.1.11. 3,5-Dichloro-2-hydroxyacetophenone 4-methylphenylhydrazone 3k. This compound was prepared from **15** and **13**. Yield=4.5 g, 80%, yellow powder, mp 145°C. [Found: C, 58.42; H, 4.60. $C_{15}H_{14}Cl_2N_2O$ requires: C, 58.26; H, 4.56]. IR: 3362 (OH), 1608 (C=N); ^{1}H NMR: 2.30 (s, 3H), 2.32 (s, 3H), 6.83–7.24 (m, 5H), 7.29 (d, 1H, J=1.8 Hz), 12.76 (bs, 1H); MS: m/z (%) 310 (M+2, 51), 308 (M^+, 78), 254, 230, 188, 147, 107 (100), 91, 65, 63.

3.1.12. 3,5-Dichloro-2-hydroxyacetophenone 4-bromophenylhydrazone 3l. This compound was prepared from **15** and **11**. Yield=6.0 g, 89%, yellow crystals, mp 207°C. [Found: C, 44.79; H, 2.89. $C_{14}H_{11}BrCl_2N_2O$ requires: C, 44.95; H, 2.96]. IR: 3355 (OH), 1604 (C=N); ^{1}H NMR: 2.38 (s, 3H), 6.97 (d, 2H, J=9.0 Hz), 7.32–7.47 (m, 4H), 9.20 (s, 1H), 12.59 (bs, 1H); MS: m/z (%) 376 (M+4, 38), 374 (M+2, 84), 372 (M^+, 52), 359, 357, 295, 276, 222, 191, 173 (100), 157, 133, 106, 91, 63.

3.2. General procedure 2: preparation of 1,3-benzoxazinones 4a,b,e,i,j,l

A solution of the appropriate hydrazone **3** (3 mmol) and 1 mL of triethylamine in 30 mL of dichloromethane was stirred under nitrogen atmosphere. Triphosgene (1.5 mmol) in 10 mL of dichloromethane was added dropwise over a period of 20 min. The mixture was stirred at room temperature for 1 h and then refluxed for 2 h. Water was added, the organic layer was separated followed by extraction of the aqueous layer with dichloromethane (2×30 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting solid was crystallized from ethyl ether.

3.2.1. 6-Bromo-4-methylene-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4a. This compound was prepared from **3a**. Yield=0.64 g, 65%, colorless crystals, mp 155°C. [Found: C, 54.51; H, 3.34. $C_{15}H_{11}BrN_2O_2$ requires: C, 54.40; H, 3.34]. IR: 3330 (NH), 1735 (CO), 1602 (=CH_2); ^{1}H NMR: 4.97 (d, 1H, J=3.0 Hz), 5.13 (d, 1H, J=3.0 Hz), 6.46 (s, 1H, D_2O exchangeable), 6.78–7.03 (m, 3H), 7.28–7.48 (m, 3H), 7.61 (dd, 1H, J_1=8.6 Hz, J_2=2.3 Hz), 7.75 (d, 1H, J=2.3 Hz); ^{13}C NMR: 89.63 (CH_2), 114.0 (CH), 118.11 (C), 119.64 (CH), 121.64 (CH), 127.86 (CH), 129.98 (CH), 134.74 (CH), 138.49 (C), 147.01 (C), 148.30 (C=O); MS: m/z (%) 332 (M+2, 36), 330 (M^+, 38), 287, 285, 251, 223, 198, 180, 168, 103, 92 (100), 77, 65, 63.

3.2.2. X-Ray crystallographic analysis of 6-bromo-4-methylene-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4a. Crystal data. Orthorhombic, Space group *Pccn*, a=20.7767(2), b=18.7789(4), c=6.9452(1) Å, α=90.00, β=90.00, γ=90.00°, V=2709.76(7) Å^3, Z=8. Data collection. A crystal (0.20×0.20×0.10 mm^3) was used to record 14828 reflections on a Siemens SMART diffractometer (Mo–Kα, $\omega-2\theta$). Structure refinement. The structure was refined anisotropically on F^2 (program SHELXLT97, Sheldrick, G. M., University of Gottingen, Germany) to $wR2$=0.174, $R1$=0.061 for 194 parameters and 3521 unique reflections. Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 212482. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.2.3. 6-Bromo-4-methylene-3-[*N*-(4-bromophenyl) amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4b. This compound was prepared from **3b**. Yield=0.94 g, 77%, colorless crystals, mp 166°C. [Found: C, 43.75; H, 2.38. $C_{15}H_{10}Br_2N_2O_2$ requires: C, 43.93; H, 2.45]. IR: 3328 (NH), 1738 (CO), 1604 (=CH_2); ^{1}H NMR: 4.98 (d, 1H, J=2.7 Hz), 5.09 (d, 1H, J=2.7 Hz), 6.43 (s, 1H), 6.67 (d, 2H, J=8.3 Hz), 6.97 (d, 2H, J=8.3 Hz), 7.31 (d, 1H, J=10.0 Hz), 7.46 (dd, 1H, J_1=10.0 Hz, J_2=2.1 Hz), 7.73 (d, 1H, J=2.1 Hz); MS: m/z (%) 412 (M+4, 5), 410 (M+2, 12), 408 (M^+, 6), 367, 314, 287, 243 (100), 217, 199, 170, 103, 91, 77, 63.

3.2.4. 6-Chloro-4-methylene-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4e. This compound was prepared from **3e**. Yield=0.5 g, 58%, colorless powder, mp 135°C. [Found: C, 62.71; H, 3.81. $C_{15}H_{11}ClN_2O_2$ requires: C, 62.83; H, 3.87]. IR: 3323 (NH), 1728 (CO), 1600 (=CH_2); ^{1}H NMR: 4.98 (d, 1H, J=2.6 Hz), 5.14 (d, 1H, J=2.6 Hz), 6.45 (s, 1H), 6.78 (d, 2H, J=8.1 Hz), 7.02–7.28 (m, 5H), 7.60 (d, 1H, J=2.0 Hz); MS: m/z (%) 288 (M+2, 16), 286 (M^+, 51), 271, 243, 209, 180, 166, 125, 111, 92 (100), 77, 65.

3.2.5. 6,8-Dichloro-4-methylene-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4i. This compound was prepared from **3i**. Yield=0.84 g, 87%, colorless powder, mp 153°C. [Found: C, 55.92; H, 3.11. $C_{15}H_{10}Cl_2N_2O_2$ requires: C, 56.09; H, 3.13]. IR: 3328 (NH), 1732 (CO), 1607 (=CH_2); ^{1}H NMR: 5.01 (d, 1H, J=2.5 Hz), 5.19 (d, 1H, J=2.5 Hz), 6.10 (s, 1H), 6.72–6.93 (m, 3H), 7.17–7.25 (m, 2H), 7.32 (d, 1H, J=2.2 Hz), 7.51 (d, 1H, J=2.2 Hz); MS: m/z (%) 322 (M+2, 7), 320 (M^+, 12), 277, 275, 233 (100), 207, 189, 123, 91, 77, 65, 63.

3.2.6. 6,8-Dichloro-4-methylene-3-[*N*-(4-chlorophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4j. This compound was prepared from **3j**. Yield=0.6 g, 56%,

colorless powder, mp 142°C. [Found: C, 50.50; H, 2.48. $C_{15}H_9Cl_3N_2O_2$ requires: C, 50.66; H, 2.55]. IR: 3318 (NH), 1726 (CO), 1601 (=CH_2); ^{1}H NMR: 5.01 (d, 1H, *J*=2.6 Hz), 5.15 (d, 1H, *J*=2.6 Hz), 6.40 (s, 1H), 6.70 (d, 2H, *J*=8.4 Hz), 7.16 (d, 2H, *J*=8.4 Hz), 7.43 (d, 1H, *J*=1.7 Hz), 7.51 (d, 1H, *J*=1.7 Hz); MS: *m/z* (%) 358 (M+4, 7), 356 (M+2, 21), 354 (M^+, 22), 320, 311, 276, 256, 241, 186, 138, 126 (100), 111, 99, 75, 63.

3.2.7. 6,8-Dichloro-4-methylene-3-[*N*-(bromophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 4l. This compound was prepared from **3 l**. Yield=0.8 g, 67%, colorless powder, mp 152°C. [Found: C, 45.15; H, 2.19. $C_{15}H_9BrCl_2N_2O_2$ requires: C, 45.03; H, 2.26]. IR: 3325 (NH), 1736 (CO), 1598 (=CH_2); ^{1}H NMR: 5.01 (d, 1H, *J*=3.0 Hz), 5.14 (d, 1H, *J*=3.0 Hz), 6.47 (s, 1H), 6.66 (d, 2H, *J*=8.8 Hz), 7.31–7.40 (m, 3H), 7.46 (d, 1H, *J*=2.1 Hz); MS: *m/z* (%) 402 (M+4, 30), 400 (M+2, 70), 398 (M^+, 43), 357, 319, 276, 233, 189, 170 (100), 155, 123, 91, 77, 63.

3.3. General procedure 3: preparation of 4,4-disubstituted 1,3-benzoxazinones 5a,b,e,i,j

A solution of the appropriate 4-methylene-1,3-benzoxazine (3 mmol) in 50 mL of ethanol was refluxed for 3 h. After cooling the resulting solid was collected by suction and dried.

3.3.1. 6-Bromo-4-ethoxy-4-methyl-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5a. This compound was prepared from **4a**. Yield=0.54 g, 48%, colorless powder, mp 125°C. [Found: C, 54.52; H, 4.29. $C_{17}H_{17}BrN_2O_3$ requires: C, 54.12; H, 4.54]. IR: 3315 (NH), 1727 (CO); ^{1}H NMR: 0.90 (t, 3H, *J*=7.2 Hz), 1.62 (s, 3H), 3.10 (q, 2H, *J*=7.2 Hz), 6.51–6.82 (m, 3H), 6.98–7.17 (m, 2H), 7.26–7.35 (m, 2H), 7.47 (d, 1H, *J*=2.0 Hz); ^{13}C NMR: 14.79 (CH_3), 25.68 (CH_3), 58.14 (CH_2), 90.34 (C), 112.78 (CH), 117.61 (C), 120.35 (CH), 126.29 (CH), 128.94 (C), 129.05 (CH), 130.01 (CH), 130.77 (CH), 146.83 (C), 147.16 (C), 149.87 (C=O); MS: *m/z* (%) 378 (M+2, 2), 376 (M^+, 2), 330, 287, 223, 198, 168, 103, 92 (100), 77, 65.

3.3.2. 6-Bromo-4-ethoxy-4-methyl-3-[*N*-(bromophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5b. This compound was prepared from **4b**. Yield=0.9 g, 68%, colorless crystals, mp 170°C. [Found: C, 44.52; H, 3.39. $C_{17}H_{16}Br_2N_2O_3$ requires: C, 44.76; H, 3.53]. IR: 3310 (NH), 1726 (CO); ^{1}H NMR: 1.14 (t, 3H, *J*=7.0 Hz), 1.88 (s, 3H), 3.29 (q, 2H, *J*=7.0 Hz), 6.66 (d, 2H, *J*=8.5 Hz), 7.04 (d, 1H, *J*=1.8 Hz), 7.26–7.51 (m, 4H); ^{13}C NMR: 14.94 (CH_3), 18.52 (CH_3), 58.56 (CH_2), 90.62 (C), 114.59 (C), 115.62 (CH), 118.24 (CH), 127.01 (CH), 129.46 CH), 132.21 (CH), 132.34 (C), 134.16 (C), 146.88 (C), 147.41 (C), 150.35 (C=O); MS: *m/z* (%) 456 (M+2, 2), 454 (M^+, 1), 410, 367, 287, 243 (100), 217, 199, 170, 103, 91, 77, 63.

3.3.3. 6-Chloro-4-ethoxy-4-methyl-3-[*N*-phenylamino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5e. This compound was prepared from **4e**. Yield=0.52 g, 53%, colorless powder, mp 147°C. [Found: C, 61.21; H, 5.07. $C_{17}H_{17}ClN_2O_3$ requires: C, 61.35; H, 5.14]. IR: 3297 (NH), 1721 (CO); ^{1}H NMR: 1.10 (t, 3H, *J*=7.2 Hz), 1.51 (s, 3H), 3.16 (q, 2H, *J*=7.2 Hz), 6.65 (d, 2H, *J*=7.8 Hz), 6.91–7.10 (m, 2H), 7.19–7.35 (m, 3H), 7.54 (d, 1H, *J*=2.0 Hz); ^{13}C NMR: 15.01 (CH_3), 23.47 (CH_3), 59.11 (CH_2), 89.98 (C), 113.27 (C), 118.15 (CH), 122.73 (CH), 126.83 (CH), 129.10 (CH), 130.19 (CH), 131.22 (CH), 132.11 (C), 146.67 (C), 147.25 (C), 150.33 (C=O); MS: *m/z* (%) 334 (M+2, 3), 332 (M^+, 1), 288, 286 (100), 271, 209, 165, 103, 91, 77, 65.

3.3.4. 6,8-Dichloro-4-ethoxy-4-methyl-3-[*N*-phenyl-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5i. This compound was prepared from **4i**. Yield=0.79 g, 72%, colorless crystals, mp 167°C. [Found: C, 55.47; H, 4.44. $C_{17}H_{16}Cl_2N_2O_3$ requires: C, 55.60; H, 4.39]. IR: 3333 (NH), 1735 (CO); ^{1}H NMR: 1.12 (t, 3H, *J*=7.2 Hz), 1.91 (s, 3H), 3.14 (q, 2H, *J*=7.2 Hz), 6.65 (s, 1H), 6.83–6.97 (m, 3H), 7.16–7.28 (m, 2H), 7.33 (d, 1H, *J*=1.9 Hz), 7.49 (d, 1H, *J*=1.9 Hz); ^{13}C NMR: 14.81 (CH_3), 18.37 (CH_3), 57.49 CH_2), 91.14 (C), 113.15 (C), 119.02 (CH), 122.46 (C), 124.89 (CH), 129.06 (CH), 129.21 (CH), 130.84 (CH), 136.47 (C), 143.31 (C), 145.16 (C), 149.87 C=O); MS: *m/z* (%) 368 (M+2, 2), 366 (M^+, 4), 322, 320 (100), 277, 275, 235, 207, 189, 123, 91, 77, 65, 63.

3.3.5. 6,8-Dichloro-4-ethoxy-4-methyl-3-[*N*-(4-chloro-phenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5j. This compound was prepared from **4j**. Yield=0.6 g, 50%, colorless crystals, mp 166°C. [Found: C, 50.66; H, 3.69. $C_{17}H_{15}Cl_3N_2O_3$ requires: C, 50.83; H, 3.76]. IR: 3325 (NH), 1730 (CO); ^{1}H NMR: 1.14 (t, 3H, *J*=6.9 Hz), 1.88 (s, 3H), 3.10 (q, 2H, *J*=6.9 Hz), 6.04 (s, 1H), 6.70 (d, 2H, *J*=9.0 Hz), 7.16 (d, 2H, *J*=9.0 Hz), 7.34 (d, 1H, *J*=2.2 Hz), 7.50 (d, 1H, *J*=2.2 Hz); ^{13}C NMR: 14.86 (CH_3), 18.53 (CH_3), 58.97 (CH_2), 90.74 (C), 115.28 (CH), 122.67 (C), 124.87 (CH), 126.57 (C), 129.27 (CH), 130.39 (C), 131.33 (CH), 136.37 (C), 143.41 (C), 145.07 (C), 149.42 (C=O); MS: *m/z* (%) 402 (M+2, 3), 400 (M^+, 3), 356, 354, 313, 276, 235, 233 (100), 205, 189, 126, 111, 99, 75, 63.

3.3.6. X-Ray crystallographic analysis of 6,8-dichloro-4-ethoxy-4-methyl-3-[*N*-(4-chlorophenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5j. Crystal data. Monoclinic, Space group *P2(1)/c*, *a*=26.1426(11), *b*=8.4051(6), *c*=16.1619(11) Å, α=90.00, β=94.971(4), γ=90.00°, *V*=3537.9(4) Å^3, *Z*=8. Data collection. A crystal (0.35×0.32×0.30 mm^3) was used to record 21338 reflections on a Siemens SMART diffractometer (Mo–Kα, $\omega-2\theta$). Structure refinement. The structure was refined anisotropically on F^2 (program SHELXLT97, Sheldrick, G. M., University of Gottingen, Germany) to *wR*2=0.1643, *R*1=0.0678 for 456 parameters and 5986 unique reflections. Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 212483. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.4. General procedure 4: preparation of 4,4-disubstituted 1,3-benzoxazinones 5c,d,f,g,h,k

These compounds were prepared from the corresponding hydrazones and triphosgene using conditions similar to those described in general procedure 2, except that the

resulting solid was refluxed in ethanol for two hours and then cooled to obtain the products.

3.4.1. 6-Bromo-4-ethoxy-4-methyl-3-[*N*-(4-chlorophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5c. This compound was prepared from **3c**. Yield=1.0 g, 81%, colorless crystals, mp 153°C. [Found: C, 49.63; H, 3.87. $C_{17}H_{16}BrClN_2O_3$ requires: C, 49.59; H, 3.91]. IR: 3319 (NH), 1728 (CO); ^{1}H NMR: 1.16 (t, 3H, *J*=7.1 Hz), 1.88 (s, 3H), 3.18 (q, 2H, *J*=7.1 Hz), 6.03 (s, 1H), 6.70 (d, 2H, *J*=9.0 Hz), 7.07–7.25 (m, 4H), 7.58 (d, 1H, *J*=2.1 Hz); ^{13}C NMR: 14.94 (CH_3), 18.52 (CH_3), 58.55 (CH_2), 90.62 (C), 115.22 (CH), 118.84 (CH), 127.01 (CH), 129.30 (CH), 129.43 (CH), 134.10 (C), 134.14 (C), 136.72 (C), 143.71 (C), 147.44 (C), 150.40 (C=O); MS: *m/z* (%) 414 (M+4, 2), 412 (M+2, 6), 410 (M^+, 4), 366, 364, 331, 323, 285, 245, 243 (100), 217, 215, 201, 199, 168, 128, 111, 90, 75, 63.

3.4.2. 6-Bromo-4-ethoxy-4-methyl-3-[*N*-(4-methylphenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5d. This compound was prepared from **3d**. Yield=1.1 g, 94%, colorless powder, mp 135°C. [Found: C, 55.39; H, 4.74. $C_{18}H_{19}BrN_2O_3$ requires: C, 55.25; H, 4.89]. IR: 3316 (NH), 1730 (CO); ^{1}H NMR: 1.12 (t, 3H, *J*=7.0 Hz), 1.92 (s, 3H), 2.26 (s, 3H), 3.09 (q, 2H, *J*=7.0 Hz), 5.96 (s, 1H), 6.67 (d, 2H, *J*=8.6 Hz), 7.01–7.23 (m, 3H), 7.38–7.56 (m, 2H); ^{13}C NMR: 14.97 (CH_3), 18.52 (CH_3), 20.70 (CH_3), 58.54 (CH_2), 89.77 (C), 114.05 (CH), 118.29 (CH), 118.82 (C), 126.98 (CH), 129.87 (CH), 129.96 (CH), 131.84 (C), 136.92 (C), 146.99 (C), 147.51 (C), 150.48 (C=O); MS: *m/z* (%) 392 (M+2, 16), 390 (M^+, 17), 346, 344, 301, 303, 245, 243 (100), 216, 218, 201, 199, 164, 148, 105, 91, 77, 63.

3.4.3. 6-Chloro-4-ethoxy-4-methyl-3-[*N*-(4-bromophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5f. This compound was prepared from **3f**. Yield=1.0 g, 81%, colorless crystal, mp 152°C. [Found: C, 49.41; H, 3.97. $C_{17}H_{16}BrClN_2O_3$ requires: C, 49.59; H, 3.91]. IR: 3307 (NH), 1726 (CO); ^{1}H NMR: 1.13 (t, 3H, *J*=7.0 Hz,), 1.88 (s, 3H), 3.14 (q, 2H, *J*=7.0 Hz,), 6.01 (s, 1H), 6.66 (d, 2H, *J*=8.7 Hz), 7.13–7.43 (m, 5H); ^{13}C NMR: 14.88 (CH_3), 25.90 (CH_3), 58.56 (CH_2), 90.57 (C), 113.0 (C), 114.94 (C), 117.82 (CH), 122.52 (CH), 126.52 (C), 130.45 (CH), 131.03 (CH), 131.97 (CH), 146.13 (C), 146.84 (C), 150.12 (C=O); MS: *m/z* (%) 412 (M+2, 14), 410 (M^+, 11), 366, 364, 351, 273, 271, 242, 199 (100), 183, 155, 125, 91, 77, 63.

3.4.4. 6-Chloro-4-ethoxy-4-methyl-3-[*N*-(4-chlorophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5g. This compound was prepared from **3g**. Yield=1.0 g, 88%, colorless crystals, mp 162°C. [Found: C, 55.38; H, 4.29. $C_{17}H_{16}Cl_2N_2O_3$ requires: C, 55.60; H, 4.39]. IR: 3312 (NH), 1727 (CO); ^{1}H NMR: 1.14 (t, 3H, *J*=7.0 Hz), 1.89 (s, 3H), 3.31 (q, 2H, *J*=7.0 Hz), 5.94 (s, 1H), 6.71 (d, 2H, *J*=9.1 Hz), 7.02–7.23 (m, 3H), 7.38–7.45 (m, 2H); ^{13}C NMR: 14.89 (CH_3), 18.46 (CH_3), 57.91 (CH_2), 90.57 (C), 114.74 (C), 117.83 (CH), 123.95 (CH), 126.42 (CH), 129.09 (C), 129.22 (CH), 131.08 (CH), 136.88 (C), 144.10 (C), 147.25 (C), 150.14 (C=O); MS: *m/z* (%) 368 (M+2, 5), 366 (M^+, 8), 322, 320, 303, 285, 243, 201, 201, 199 (100), 171, 155, 111, 99, 75, 63.

3.4.5. 6-Chloro-4-ethoxy-4-methyl-3-[*N*-(4-methylphenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5h. This compound was prepared from **3 h**. Yield=0.94 g, 91%, colorless crystals, mp 112°C. [Found: C, 62.15; H, 5.64. $C_{18}H_{19}ClN_2O_3$ requires: C, 62.33; H, 5.52]. IR: 3320 (NH), 1722 (CO); ^{1}H NMR: 1.13 (t, 3H, *J*=7.1 Hz), 1.92 (s, 3H), 2.26 (s, 3H), 3.17 (q, 2H, *J*=7.1 Hz), 5.90 (s, 1H), 6.66 (d, 2H, *J*=9.5 Hz), 7.01–7.11 (m, 3H), 7.27–7.43 (m, 2H); ^{13}C NMR: 14.85 (CH_3), 20.56 (CH_3), 20.68 (CH_3), 58.73 (CH_2), 85.10 (C), 112.96 (C), 117.59 (CH), 120.20 (CH), 127.25 (CH), 129.72 (C), 130.04 (CH), 131.50 (CH), 139.82 (C), 145.90 (C), 148.48 (C), 149.03 (C=O); MS: *m/z* (%) 348 (M+2, 14), 346 (M^+, 43), 302, 300, 285, 257, 225, 201, 199 (100), 155, 106, 91, 77, 63.

3.4.6. 6,8-Dichloro-4-ethoxy-4-methyl-3-[*N*-(4-methylphenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5k. This compound was prepared from **3k**. Yield=0.91 g, 80%, colorless powder, mp 148°C. [Found: C, 56.51; H, 4.84. $C_{18}H_{18}Cl_2N_2O_3$ requires: C, 56.70; H, 4.75]. IR: 3333 (NH), 1738 (CO); ^{1}H NMR: 1.15 (t, 3H, *J*=7.0 Hz), 1.91 (s, 3H), 2.30 (s, 3H), 3.30 (q, 2H, *J*=7.0 Hz), 6.37 (s, 1H), 6.67 (d, 2H, *J*=8.8 Hz), 7.00 (d, 2H, *J*=8.8 Hz), 7.32 (d, 1H, *J*=2.1 Hz), 7.49 (d, 1H, *J*=2.1 Hz); ^{13}C NMR: 14.93 (CH_3), 18.52 (CH_3), 20.71 (CH_3), 58.56 (CH_2), 91.13 (C), 114.14 (C), 119.01 (CH), 122.45 (C), 129.87 (CH), 129.97 (CH), 130.49 (C), 131.17 (CH), 136.55 (C), 144.06 (C), 146.63 (C), 149.59 (C=O); MS: *m/z* (%) 382 (M+2, 29), 380 (M^+, 48), 336, 334, 294, 292, 235, 233 (100), 189, 148, 120, 91, 77, 63.

3.5. General procedure 5: preparation of 4,4-disubtituted 1,3-benzoxazinones 5j, 6j, 7b and 8b under acidic conditions

A solution of **4b** or **4j** (3 mmol) in the appropriate alcohol (20 mL) and drops of hydrochloric acid was refluxed for 2 hs. The excess of the alcohol was evaporated under vacuum and ethyl ether was added to precipitate the product which needed no further purification.

3.5.1. 6,8-Dichloro-4-ethoxy-4-methyl-3-[*N*-(4-chlorophenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 5j. Compound **5j** obtained from this method (Yield=0.8 g, 67%) was found to have similar physical and spectroscopic characteristics to that obtained above using general procedure 3.

3.5.2. 6,8-Dichloro-4-methoxy-4-methyl-3-[*N*-(4-chlorophenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 6j. This compound was prepared from **4j** and methanol. Yield=0.85 g, 73%, colorless crystals, mp 160°C. [Found: C, 49.79; H, 3.47. $C_{16}H_{13}Cl_3N_2O_3$ requires: C, 49.57; H, 3.38]. IR: 3295 (NH), 1734 (CO); ^{1}H NMR: 1.89 (s, 3H), 3.10 (s, 3H), 6.12 (s, 1H), 6.70 (d, 2H, *J*=8.8 Hz), 7.16 (d, 2H, *J*=8.8 Hz), 7.31 (d, 1H, *J*=2.1 Hz), 7.51 (d, 1H, *J*=2.1 Hz); ^{13}C NMR: 25.55 (CH_3), 50.45 (CH_3), 91.04 (C), 114.35 (CH), 122.17 (C), 123.28 (C), 124.87 (CH), 125.22 (C), 128.86 (CH), 130.09 (C), 131.09 (CH), 143.31 (C), 145.54 (C), 149.86 (C=O); MS: *m/z* (%) 388 (M+2, 3), 386 (M^+, 2), 356, 354, 313, 311, 276, 221, 219 (100), 187, 159, 126, 111, 99, 77, 63.

3.5.3. 6-Bromo-4-methyl-4-propoxy-3-[*N*-(4-bromophenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one

7b. This compound was prepared from **4b** and propanol. Yield=0.74 g, 53%, colorless powder, mp 142°C. [Found: C, 45.72; H, 3.72. $C_{18}H_{18}Br_2N_2O_3$ requires: C, 45.98; H, 3.85]. IR: 3308 (NH), 1739 (CO); ^{1}H NMR: 0.85 (t, 3H, *J*=7.0 Hz); 1.52 (m, 2H), 1.91 (s, 3H), 3.50 (t, 2H, *J*=6.5 Hz), 6.01 (s, 1H), 6.65 (d, 2H, *J*=9.0 Hz), 6.98 (d, 2H, *J*=9.0 Hz), 7.26–7.38 (m, 2H), 7.54 (d, 1H, *J*=1.9 Hz); ^{13}C NMR: 10.24 (CH_3), 22.68 (CH_3), 25.98 (CH_2), 64.80 (CH_2), 89.97 (C), 114.68 (C), 115.67 (CH), 118.87 (CH), 127.01 (CH), 129.31 (C), 132.23 (CH), 132.37 (CH), 134.17 (C), 144.20 (C), 146.89 (C), 147.38 (C=O); MS: *m/z* (%) 470 (M+2, 4), 468 (M^+, 2), 410, 408, 369, 367, 331, 329, 259, 257, 217, 215 (100), 201, 199, 172, 170, 157, 155, 143, 91, 75, 63.

3.5.4. 6-Bromo-4-butoxy-4-methyl-3-[*N*-(4-bromophenyl)-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 8b. This compound was prepared from **4b** and butanol. Yield=0.73 g, 47%, colorless powder, mp 175°C. [Found: C, 43.53; H, 3.86. $C_{19}H_{20}Br_2N_2O_3$.HCl requires: C, 43.83; H, 4.06]. IR: 3317 (NH), 1729 (CO); ^{1}H NMR: 0.82 (t, 3H, *J*=6.9 Hz), 1.31–1.51 (m, 4H); 1.95 (s, 3H), 3.42 (t, 2H, *J*=6.8 Hz), 6.15 (s, 1H), 6.73 (d, 2H, *J*=8.7 Hz), 7.02 (d, 2H, *J*=8.7 Hz), 7.30–7.45 (m, 2H), 7.51 (d, 1H, *J*=2.1 Hz); ^{13}C NMR: 11.14 (CH_3), 18.98 (CH_3), 22.31 (CH_2), 26.42 (CH_2), 61.78 (CH_2), 89.38 (C), 113.88 (C), 116.21 (CH), 119.11 (CH), 126.89 (CH), 130.36 (C), 132.66 (CH), 133.68 (CH), 135.53 (C), 144.56 (C), 147.41 (C), 148.76 (C=O); MS: *m/z* (%) 520 (M.HCl+2, 3), 518 (M^+.HCl, 2), 446, 444, 410, 408, 365, 307, 305, 251 (100), 249, 214, 212, 172, 170, 145, 143, 91, 77, 63.

3.6. General procedure 6: preparation of 4-fluoromethyl-4-methoxy-1,3-benzoxazinones 9b,e

The appropriate 4-methylene-1,3-benzoxazinone (0.5 mmol) was dissolved in a mixture of 20 mL of acetonitrile and 2 mL of methanol under nitrogen atmosphere. F-TEDA-BF_4 (0.5 mmol) in 10 mL of acetonitrile was added and the reaction mixture was stirred at room temperature for one hour. After addition of dichloromethane (40 mL), the mixture was washed once with 10% aqueous solution of sodium bicarbonate and twice with water. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The resulting solid was crystallized from ethyl ether and further purified using TLC.

3.6.1. 6-Bromo-4-fluoromethyl-4-methoxy-3-[*N*-(4-bromophenyl)amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 9b. This compound was prepared from **4b**. Yield=0.11 g, 48%, colorless powder, mp 178°C. [Found: C, 41.47; H, 2.61. $C_{16}H_{13}Br_2FN_2O_3$ requires: C, 41.76; H, 2.84]. IR: 3325 (NH), 1716 (CO); ^{1}H NMR: 3.04 (s, 3H), 4.80 (m, 2H), 6.10 (s, 1H), 6.81 (d, 2H, *J*=8.0 Hz), 7.05 (d, 1H, *J*=8.8 Hz), 7.35 (d, 2H, *J*=8.0 Hz), 7.54–7.60 (m, 2H); ^{13}C NMR: 50.16 (CH_3), 80.58 (CH_2), 91.94 (C), 115.55 (C), 117.99 (C), 118.20 (CH), 118.60 (CH), 129.35 (CH), 132.21 (CH), 134.95 (CH), 145.27 (C), 148.98 (C), 150.11 (C=O); ^{19}F NMR: −118.59; MS: *m/z* (%) 460 (M+2, 10), 458 (M^+, 5), 428, 426, 387, 385, 249, 247 (100), 215, 170, 136, 107, 81, 76, 63.

3.6.2. 6-Chloro-4-fluoromethyl-4-methoxy-3-[*N*-phenyl-amino]-3,4-dihydro-2*H*-1,3-benzoxazine-2-one 9e. This compound was prepared from **4e**. Yield=0.07 g, 42%, colorless powder, mp 138°C. [Found: C, 56.81; H, 4.05. $C_{16}H_{14}ClFN_2O_3$ requires: C, 57.06; H, 4.19]. IR: 3305 (NH), 1708 (CO); ^{1}H NMR: 3.03 (s, 3H), 4.78 (m, 2H), 6.17 (s, 1H), 6.93 (m, 3H), 7.11 (d, 1H, *J*=8.8 Hz), 7.24–7.35 (m, 2H), 7.42–7.51 (m, 2H); ^{13}C NMR: 50.87 (CH_3), 81.72 (CH_2), 91.78 (C), 113.78 (C), 118.26 (CH), 122.22 (CH), 126.43 (CH), 129.36 (CH), 130.81 (CH), 131.95 (CH), 146.08 (C), 148.55 (C), 150.32 (C=O); ^{19}F NMR: −117.43; MS: *m/z* (%) 338 (M+2, 3), 336 (M^+, 8), 306, 304, 261, 205, 203 (100), 171, 143, 106, 92, 77, 65.

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