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ARTICLE TYPE

Expedient Synthesis of Novel 1,4-Benzoxazine and Butenolide Derivatives

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Highly efficient and rapid method for the synthesis of 2-hydroxy-1,4-benzoxazine and butenolide derivatives has been developed. The key step in this protocol involves the reduction of benzoxazinone derivatives. On further reaction of 2-hydroxy-1,4-benzoxazine with secondary amines and sodium methoxide affords the corresponding 2-amino-1,4-benzoxazines and butenolide derivatives, respectively, in good yields.

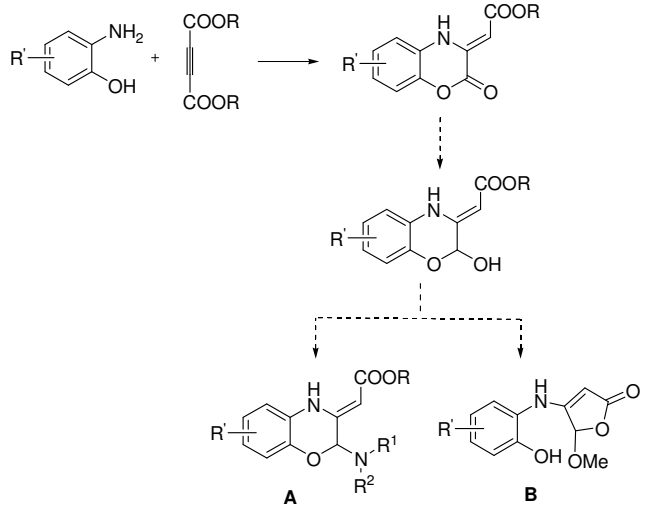
Introduction

Among the various heterocyclic compounds, those containing benzoxazine and butenolide units have gained a considerable importance due to their occurrence in various natural products.[1] The benzoxazine derivatives found to demonstrate a wide range of biological activities like dopamine agonist activity, neuroprotective agents,[2] intracellular calcium antagonist,[3] antitumour[4] and antiangiogenic therapeutic agents.[5] Some of them are used as powerful drugs in treating cardiovascular, cancer and diabetic disorders.[6] Benzoxazine derivatives are also used in agricultural sector as herbicides.[7]

Butenolide unit is an important structural moiety found in many biologically active compounds.[8-13] For example, the vitamin C (ascorbic acid) and penicillic acid are the best known 4-hydroxy-2(5*H*)-furanones having butenolide unit in their structures,[8] butenolides having substituted *o*-chlorobenzylamine have been recognized as antibiotic agents against the multiresistant *Staphillococcus aurus* and also act as intermediates in the synthesis of basidalin which has a marked activity against colon tumors.[9] Moreover anti-inflammatory agent manoalide holds butenolide moiety in substructure of the pyranofuranone.[10] In addition, several have been patented as prodrugs or herbicides and insecticides.[11] Ramariolide A, a spiro oxiranebutenolide, isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora*, exhibits *in vitro* antimicrobial activity against *Mycobacterium smegmatis* and *Mycobacterium* tuberculosis.[12] The metabolites possessing butenolide sub-unit, isolated from the tunicate *Pseudodistoma antinboja*, displays antibacterial activity against Gram-positive strains.[13] As a part of our ongoing research on the development of new synthetic technology in heterocyclic compounds,[14] herein we report an efficient synthesis of functionalized 1,4-benzoxazine and butenolide derivatives starting from the commercially available *o*-aminophenols and dialkyl acetylenedicarboxylates (Scheme 1).

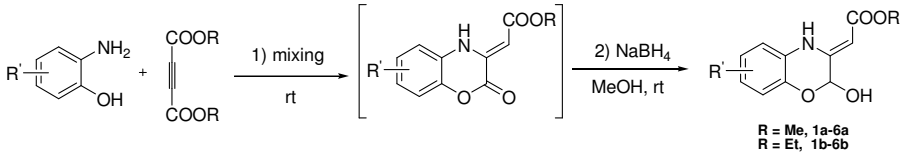
Results and Discussion

Earlier we have reported the synthesis of a series of benzoxazinone derivatives starting from *o*-aminophenols and dialkyl acetylenedicarboxylates by simple mixing of the reactants under solvent-free and catalyst-free conditions.[14a] Since the hemiacetal linkage is found in some of the naturally occurring benzoxazine derivatives,[15] in further investigation it occurred to us that these benzoxazinones would be valuable intermediates for the



Scheme 1. Proposed route for the synthesis of 2-hydroxy-1,4-benzoxazine, 2-aminobenzoxazine and butenolide derivatives.

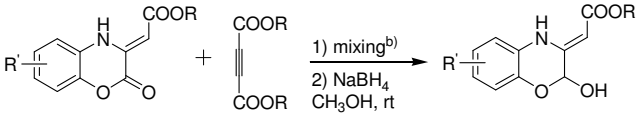
synthesis of corresponding 2-hydroxy-benzoxazine derivatives. These 2-hydroxybenzoxazines could be precursors for several target molecules such as 2-aminobenzoxazine derivatives **A** and butenolide derivatives **B** (Scheme 1). Thus we were interested to synthesize 2-hydroxybenzoxazine derivatives from the corresponding benzoxazinone derivatives. As a prelude to our objective,



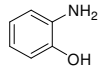
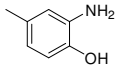
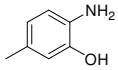
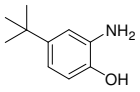
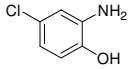
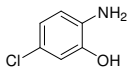
Scheme 2. One pot synthesis and reduction of benzoxazinone derivatives.

the first step was initiated with the reduction of benzoxazinone, derived from the mixing of 2-aminophenol with dimethyl acetylenedicarboxylate, using sodium borohydride in methanol (Scheme 2). In a typical reaction procedure, 2-aminophenol (2 mmol) was mixed with dimethyl acetylenedicarboxylate (2 mmol) for four min at room temperature to afford (*Z*)-3-methoxycarbonylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one in 100% conversion which was further stirred with $NaBH_4$ (2.2 mmol) in methanol for 15 min. Initially the benzoxazinone was having very less solubility in methanol and with the progress of the reaction, it formed a clear solution. After completion of the reaction, the methanol was removed completely with the help of rotary evaporator to give a semi-solid. Upon adding water to the reaction mixture and by scratching with the help of spatula, a brown solid product separated out immediately from the reaction mixture. The solid was filtered and washed with water and dried to furnish methyl (*Z*)-2-(2-hydroxy 2*H*-benzo-1,4-oxazin-3(4*H*)-ylidene)acetate (**1a**) as brown solid with excellent purity in 93% yield (Table 1, Entry 1), which was pure enough for spectroscopic analysis.

Table 1. Reduction of benzoxazinone derivatives.[a]



R' = H, Me, ^{t}butyl, Cl R = CH_3, C_2H_5

Entry	*o*-Aminophenols	R	Time[c] (min)	Product	Yield[d] (%)
1		Me	4 + 15	**1a**	93
2		Et	5 + 15	**1b**	95
3		Me	2 + 10	**2a**	97
4		Et	3 + 10	**2b**	98
5		Me	2 + 10	**3a**	97
6		Et	3 + 10	**3b**	96
7		Me	2 + 15	**4a**	93
8		Et	3 + 15	**4b**	92
9		Me	4 + 10	**5a**	97
10		Et	5 + 10	**5b**	95
11		Me	4 + 10	**6a**	95
12		Et	5 + 10	**6b**	96

[a] All the reactions were carried out with (2 mmol) of each 2-aminophenol and dialkyl acetylenedicarboxylates using 2.2 mmol of $NaBH_4$ in methanol. [b]Mixing of reactants with spatula (in a Petri dish or in an RB flask) for 2-5 min. [c] Total time of reaction (mixing + stirring). [d] Yields of isolated pure products.

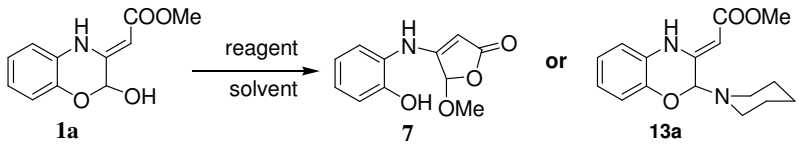
Similarly other derivatives **2a**-**6a**, **1b**-**6b** were also synthesized by above mentioned process in excellent to near to quantitative yields (92-98%) (Table 1). It is noteworthy to mention here that this methodology obviates the use of solvents in purification steps such as column chromatography and extraction.

A number of methods have been developed for the synthesis of 4-aminofuran-2(5*H*)-ones. These processes include the use of Pd–bis(isoxazoline) catalyzed 5-*endo*-*trig*-type cyclization β,γ-unsaturated carbonyl compounds,[16] etherification and amination of mucohalic acid[17] and [2,3]-Wittig rearrangement of dienolates.[18] TFA mediated synthesis of 3-substituted 4-aminofuran-2(5*H*)-ones from 4-hydroxycyclobutenone[19] and the synthesis of 3-unsubstituted 4-aminofuran-2(5*H*)-ones by amine addition on acetylenecarboxylates followed by intramolecular cyclizations[20] are also reported. Herein, we disclose a practical two-step route for the synthesis of novel 4-substituted-5-methoxyfuran-2(5*H*)-one derivatives.

Having various 2-hydroxy-1,4-benzoxazines **1a**-**6a, 1b-6b** in hand, we employed them as reactants for the synthesis of butenolides **7-12**. In the exploration of the reagents for synthesizing butenolides, we selected benzoxazine **1a** as our model substrate. Several reagents were screened for the reaction at room temperature and at reflux conditions and the results are summarized in Table 2. The performance of the reaction using various reagents such as pyridine, DABCO, triethylamine, triphenylphosphine, acetic anhydride (Table 2, entries 1-10) was not encouraging. However, when the reaction was carried out in the presence of 0.5 equiv. of NaOMe in dry methanol at room temperature, 25% of the desired product **7** was achieved in 8 h (Table 2, entry 11). At this juncture, equimolar quantity of sodium methoxide was used in the reaction and it was found that the yield was improved from 25% to 49% at room temperature (Table 2, entry 12). Gratifyingly, the further enhancement in the yield was achieved by performing the reaction with 1 equiv. of NaOMe in dry methanol at reflux temperature (Table 2, entry 13). Thus screening of the reagents in various solvents and at different temperatures identified sodium methoxide as a suitable reagent for the transformation of 2-hydroxybenzoxazine **1a** into butenolide **7**. Accordingly, the reaction of benzoxazine **1a** (1 mmol) was performed with 1 equiv. of sodium methoxide in dry methanol at reflux temperature for four hours. After completion of the reaction, the contents were concentrated and subjected to silica gel (pre-treated with triethyl amine) column chromatography using ethyl acetate and hexanes as eluent to obtain the desired butenolide **7** in 78% yield (Table 3, Entry 1).

The structure of the products was elucidated on the basis of collective information that obtained from IR, ^{1}H and ^{13}C NMR and HRMS spectral data of pure and isolated products. For instance, the carbonyl stretch at 1744 cm^{-1} along with an olefinic

Table 2. Optimization of reaction conditions.[a]



Entry	Reagent	Equiv.	Solvent	Temperature	Time (h)	Product/ Yield (%)[b]
1	Pyridine	1	MeOH	Reflux	12	-
2	DABCO	0.5	MeOH	Reflux	12	-
3	Et_3N	1	MeOH	Reflux	12	-
4	Ph_3P	0.5	THF	Reflux	12	-
5	$(CH_3CO)_2O$	5	Neat	Reflux	12	-
6	$POCl_3$, P_2O_5	5	Neat	Reflux	12	-
7	DMAP	0.5	Toluene	Reflux	12	-
8	NaH, under N_2	1	THF	rt	16	-
9	Pyridiniumtoluene-4-sulphonate	0.5	Toluene	Reflux	12	-
10	I_2	0.5	DCM	rt	16	-
11	NaOMe	0.5	MeOH	rt	8	**7/** 25
12	NaOMe	1	MeOH	rt	8	**7/** 49
13	NaOMe	1	MeOH	Reflux	4	**7/** 78
14	Piperidine	0.5	MeOH	rt	16	**13a/**trace
15	Piperidine	1.5	MeOH	rt	16	**13a/** 21
16	Piperidine	1.5	MeOH	Reflux	6	**13a** /71

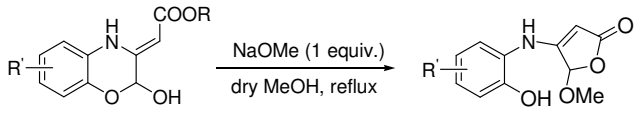
[a] Reactions were performed with **1a** (0.5 mmol) using different reagents in the presence of 2 mL of solvent.
[b] Yields of pure and isolated products

stretch at 1644 cm^{-1} in IR spectrum of **11** is a characteristic band for butenolide systems. The olefinic proton of the lactone ring resonates at δ 5.90 ppm. The proton attached to methoxy group resonates at δ 5.09 ppm in ^1H NMR and the lactone carbonyl carbon resonates at δ 171.8 ppm in ^{13}C NMR.

While optimizing the reaction for the conversion of benzoxazine derivatives **1a** into butenolide **7** (Table 2) using piperidine in methanol, unexpected formation of product **13a** was observed. The spectroscopic analysis confirmed the product as aminobenzo-xazine derivative **13a**. After confirming the structure we then turned our attention towards the optimization of reaction conditions, it was observed that at room temperature the formation of the product was not observed even after 16 h (Table 2, Entry 14) with 50 mol% of the piperidine. When the piperidine loading was further increased to 1.5 equivalents the product was obtained in 21% yield after 16 h of stirring at rt (Table 2, Entry 15). For further improvement, the influence of temperature on the reaction was also investigated (Table 2, Entries 14 and 16) and to our delight, the yield of the reaction improved drastically to 71% yield of **13a** at reflux temperature (Table 2, Entry 16). In a typical reaction procedure, piperidine (1.5 mmol) was added to a solution of **2** (1 mmol) in methanol (4 mL) and the resulting mixture was stirred at the reflux temperature for a period of time as mentioned in Table 4. Then the reaction contents were concentrated and the residue was subjected to silica gel (pre-treated with triethyl amine) chromatography to obtain pure products. As shown in Table 4, regardless of the electronic nature of the aromatic substitution, good to excellent yields (54-86%) were realized in the reactions except in the case of compounds bearing *tert*-butyl

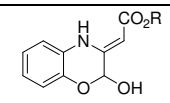
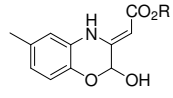
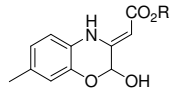
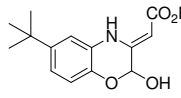
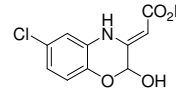
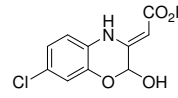
group (Table 4, Entries 7, 8). When the reaction of **4a** was

Table 3. Synthesis of butenolide derivatives.[a]



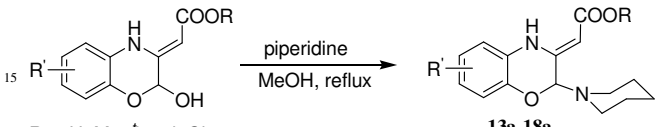
R' = H, Me, ^{t}butyl, Cl

1a-6a,**1b-6b** **7-12**

Entry	Substrate		R	Time (h)	Product	Yield[b] (%)
1		**1a**	Me	5	**7**	78
2		**1b**	Et	6	**7**	76
3		**2a**	Me	4	**8**	84
4		**2b**	Et	6	**8**	81
5		**3a**	Me	4	**9**	82
6		**3b**	Et	6	**9**	83
7		**4a**	Me	8	**10**	61
8		**4b**	Et	10	**10**	58
9		**5a**	Me	4	**11**	89
10		**5b**	Et	6	**11**	91
11		**6a**	Me	4	**12**	90
12		**6b**	Et	6	**12**	87

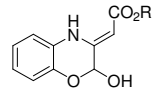
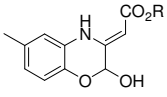
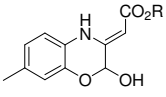
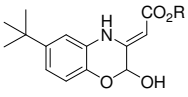
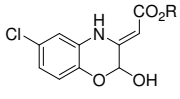
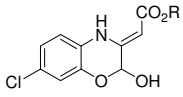
[a] All Reactions were performed with benzoxazine derivative (0.5 mmol) in 4 mL of methanol with sodium methoxide (0.5 mmol) at reflux temperature. [b] Yields of pure and isolated products.

Table 4. Scope of substrates with piperidine.[a]



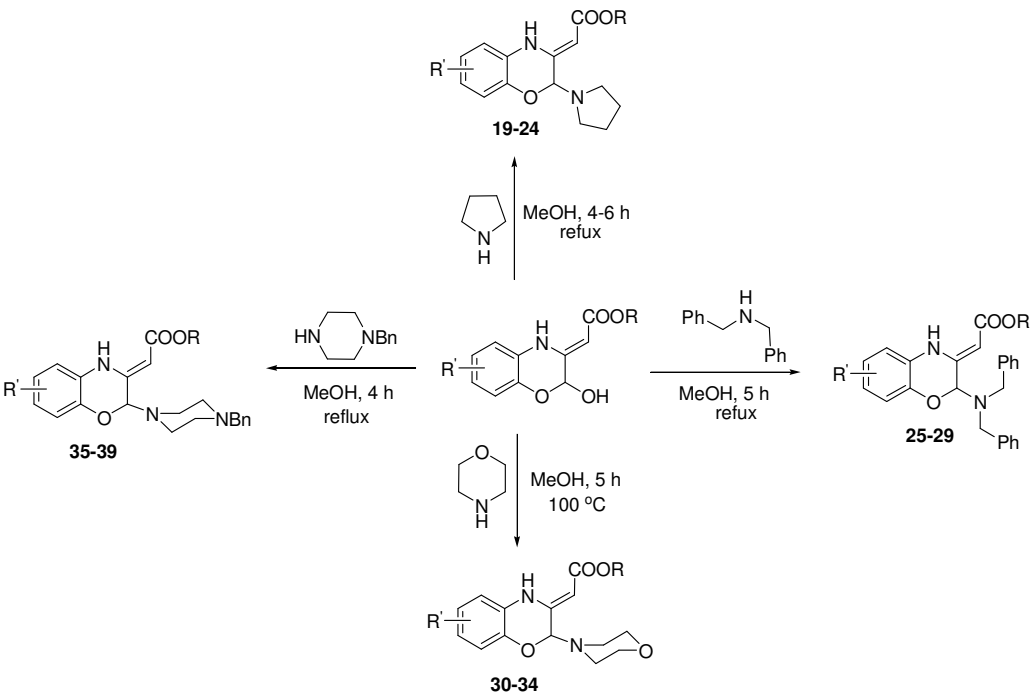
R' = H, Me, ^{t}butyl, Cl

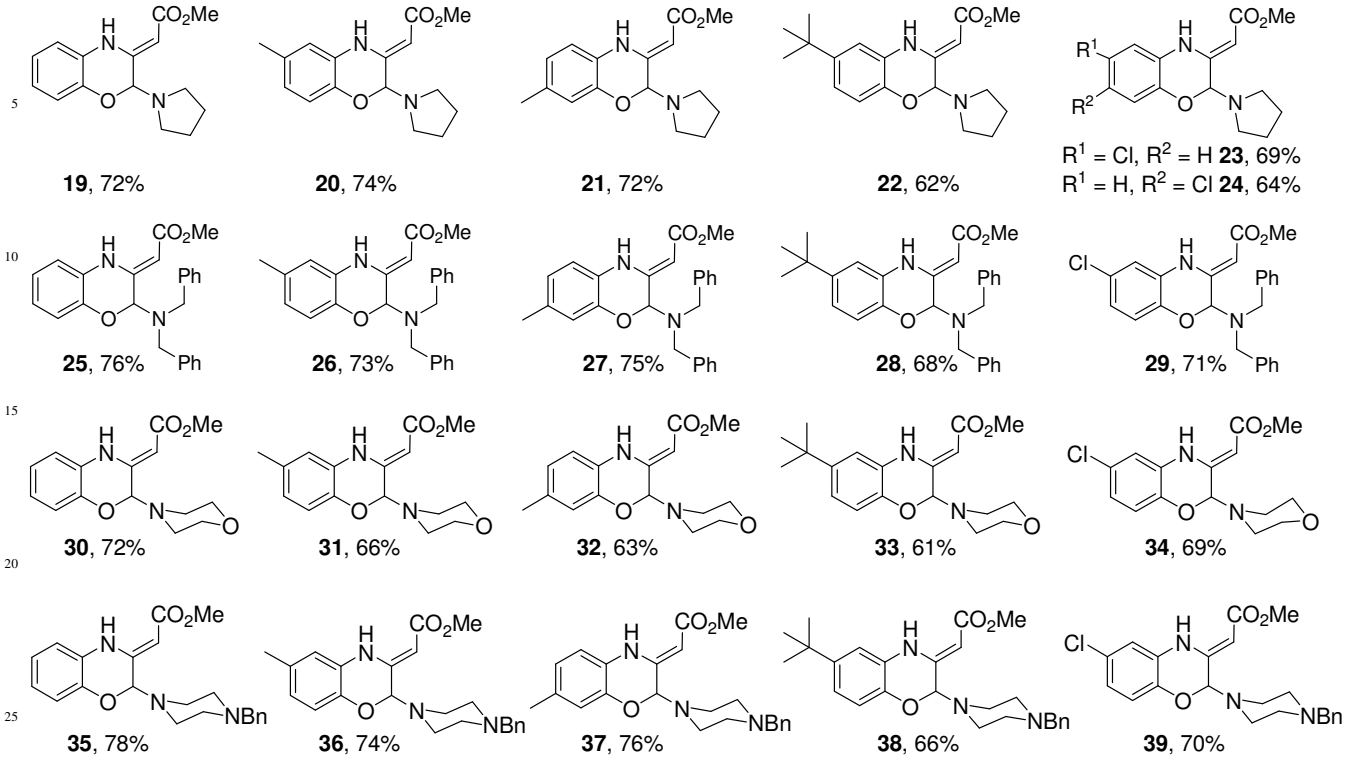
1a-6a, **1b-6b** **13a-18a** **13b-18b**

Entry	Substrate		R	Time (h)	Product	Yield[b] (%)
1		**1a**	Me	5	**13a**	71
2		**1b**	Et	5	**13b**	74
3		**2a**	Me	4	**14a**	75
4		**2b**	Et	4	**14b**	76
5		**3a**	Me	4	**15a**	75
6		**3b**	Et	4	**15b**	77
7		**4a**	Me	8	**16a**	56
8		**4b**	Et	8	**16b**	54
9		**5a**	Me	4	**17a**	79
10		**5b**	Et	4	**17b**	81
11		**6a**	Me	4	**18a**	86
12		**6b**	Et	4	**18b**	81

[a] All Reactions were performed with benzoxazine derivative (0.5 mmol) in 4 mL of methanol with piperidine (0.75 mmol) at reflux temperature. [b] Yields of pure and isolated products.

Scheme 3. Reactions of 2-hydroxy 1,4-benzoxazine derivatives with secondary amines.





performed in methanol with 1.5 equiv. of piperidine, the reaction times are significantly increased and the product **16a** was obtained in 56% yield. The reaction of **4b** proceeded in a similar manner to provide **16b** in 54% yield. All reactions are proceeded smoothly to provide the desired products **13a-18a, 13b-18b** in good to excellent yields. To expand the scope of this novel protocol, the reactions of **1a-6a** with pyrrolidine are carried out to give the corresponding products **19-24** in good yields. Similarly, treatment of the vinylogous carbamates **1a-5a** with *N*,*N*-dibenzylamine resulted in the formation of hemiaminals **25**-**29** (Scheme 3). The reaction of benzoxazinol **1a** with morpholine in methanol did not proceed under reflux conditions. Consequently, the reaction of **1a** and morpholine was performed in a sealed tube at 100 ^{o}C and the the required product **30** was obtained in 72% yield. The other aminobenzoxazines **31**-**34** were achieved using this procedure in acceptable yields. The reaction of benzoxazinols **1a**-**5a** with *N*-benzylpiperazine afforded hemiaminals **35**-**39** in good yields (Scheme 3). The structures of all the products are assigned on the basis of data collected from modern analytical tools.

Conclusions

In summary, we have demonstrated a novel procedure for the reduction of benzoxazinone derivatives into 2-hydroxy-1,4-benzoxazines. Our methodology provides an easy access to a series of butenolide derivatives and 2-amino-1,4-benzoxazine derivatives. In light of simplicity of the procedure, mild conditions and considerable generality, these reactions are certainly noteworthy.

Experimental

1 General Methods:

Unless otherwise noted, chemicals were purchased from Sigma-Aldrich at the highest purity grade available and were used without further purification. IR spectra of the compounds were recorded on a Thermo Nicolet FT-IR Nexus^{TM} and are expressed as wave numbers (cm^{-1}). NMR Spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as internal standard on Brüker AMX-500 instrument. Chemical shifts of ^{1}H NMR spectra were given in parts per million with respect to TMS and the coupling constant *J* was measured in Hz. The signals from solvent $CDCl_3$, 7.26 and 77.0 ppm and DMSO-d_6 2.50 and 39.5 ppm are set as the reference peaks in ^{1}H NMR and ^{13}C NMR spectra, respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = double doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were obtained on a Brüker micrOTOF™-Q II mass spectrometer (ESI-MS).

2 General Procedures:

Procedure for the synthesis of benzoxazine derivative 1a: In a typical reaction procedure 2-aminophenol (2 mmol) was mixed with dimethyl acetylenedicarboxylate (2 mmol) for four minutes at room temperature. Followed by addition of $NaBH_4$ (2.2 mmol) and the reaction mixture was stirred for 15 minutes in methanol. After completion of the reaction, methanol was removed

completely with the help of rotary evaporator which gave a semi solid.

After adding water to the reaction mixture and scratching with the help of spatula, a brown solid product separated out immediately from the reaction mixture. It was filtered and washed with water and dried to afford (*Z*)-methyl 2-(2-hydroxy-2*H*-benzo-1,4-oxazin-3(4*H*)-ylidene)acetate (**1a**) in 93% yield. The other derivatives **2a**-**6a** and **1b**-**6b** were prepared in 92-98% yield following the same procedure.

Procedure for the synthesis of 2-aminobenzoxazine derivative 13a: In a typical reaction procedure, a secondary amine (piperidine/ pyrrolidine/ dibenzylamine/ *N*-benzyl piperazine, 0.75 mmol) was added to a solution of **1a** (0.5 mmol) in methanol (4 mL) and the resulting mixture was stirred at the reflux temperature for a period of time as mentioned in (Table 4 and Scheme 3). After concentrating reaction contents, the crude reaction mixture was subjected to column chromatography on silica gel (pre-treated with triethylamine) and purified by using ethyl acetate and hexanes (90:10 hexanes/EtOAc) as eluent to obtain pure product **13a** in 71% yield. The other derivatives **14a**-**18a**, **13b**-**18b**, **19-29** and **35-39** were prepared in 54-86% yield using the same procedure.

Procedure for the reactions of 2-hydroxy 1,4-benzoxazine derivatives 1a-5a with morpholine: To a mixture of methanol (4 mL) and 2-hydroxy 1,4-benzoxazine derivative **1a** (0.5 mmol) in a dry sealed tube was added morpholine (2 mmol) and the reaction mixture was allowed to heat at 100 ^{o}C for 5 h. After completion of the reaction as shown by the TLC, the crude reaction mixture was subjected to column chromatography on silica gel (pre-treated with triethylamine) and eluted with ethyl acetate and hexanes (90:10 hexanes/EtOAc) to obtain desired products **30**-**34**.

Procedure for the synthesis of butenolide derivative 7: To a solution of **1a/1b** (0.5 mmol) in 4 ml of dry methanol, sodium methoxide (0.5 mmol) was added and stirred at reflux temperature for four hours. The reaction was monitored by TLC at regular intervals. Upon completion of the reaction, crude reaction mixture was purified by silica gel column chromatography using ethyl acetate and hexanes (85:15 of hexanes/EtOAc) as eluting solvent system to obtain the desired pure product **7** in 78% yield The other derivatives **8-12** were prepared in 58-91% yield using the same procedure.

3 Spectroscopic data:

(Z)-Methyl 2-(2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (1a): Brown solid, mp:174-175 °C. IR (KBr): ν_{max} 3286, 1738, 1667, 1597, 1275 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ10.03 (br s, 1H), 6.98-6.91 (m, 3H), 6.86 (d, *J* = 7.5 Hz, 1H), 5.70 (s, 1H), 4.90 (s, 1H), 3.67 (s, 3H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 149.2, 141.2, 126.4, 122.3, 122.2, 117.3, 115.0, 90.3, 83.4, 50.4 ppm. HRMS (ES+): *m/z* calcd for $[C_{11}H_{11}NO_4+Na]^+$: 244.0580, found: 244.0567.

(Z)-Ethyl 2-(2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)ylidene)acetate (1b): Brown solid, mp: 145-146 °C. IR (KBr): ν_{max} 3330, 3269, 2986, 1657, 1621, 1500, 1413, 1364, 1305, 1232, 1166 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 6.97 (t, *J* = 7.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 5.70 (s, 1H), 4.89 (s, 1H), 4.17-4.09 (m, 2H), 3.60 (br s, 1H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 148.3, 140.7, 126.2, 123.2, 122.9, 117.9, 115.5, 90.7, 84.7, 59.7, 14.3 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{13}NO_4+Na]^+$: 258.0737, found: 258.0729.

(Z)-Methyl 2-(2-hydroxy-6-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (2a): Brown solid, mp: 158-159 °C. IR (KBr): ν_{max} 3336, 3270, 2925, 1659, 1623, 1514, 1408, 1351, 1290 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ 9.97 (br s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.68 (s, 1H), 5.67 (s, 1H), 4.88 (s, 1H), 3.67 (s, 3H), 3.49 (br s, 1H), 2.28 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 149.4, 139.5, 132.2, 126.2, 123.0, 117.3, 115.7, 90.6, 83.5, 50.6, 20.7 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{13}NO_4+Na]^+$: 258.0737, found: 258.0736.

(Z)-Ethyl 2-(2-hydroxy-6-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (2b): Brown solid, mp: 148-149 °C. IR (KBr): ν_{max} 3328, 3264, 1654, 1621, 1489, 1415, 1353, 1288 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (br s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 1H), 5.67 (s, 1H), 4.87 (s, 1H), 4.16-4.06 (m, 2H), 3.56 (br s, 1H), 2.28 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 148.5, 138.5, 133.1, 126.2, 123.5, 117.8, 116.2, 91.0, 84.9, 59.7, 21.0, 14.6 ppm. HRMS (ES+): *m/z* calcd for $[C_{13}H_{15}NO_4+Na]^+$: 272.0893, found: 272.0876.

(Z)-Methyl 2-(2-hydroxy-7-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4H)-ylidene)acetate (3a): Brown solid, mp: 113-114 °C. IR (KBr): ν_{max} 3324, 3270, 2980, 2917, 2859, 1652, 1621, 1513, 1412, 1367, 1287, 1230, 1164 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.09 (br s, 1H), 6.95-6.93 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.71 (s, 1H), 4.91(s, 1H), 3.70 (s, 3H), 2.33 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 156.1, 139.8, 138.2, 133.1, 126.3, 121.6, 117.3, 114.5, 89.9, 83.5, 51.4, 20.8 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{13}NO_4+Na]^+$: 258.0737, found: 258.0731.

(Z)-Ethyl 2-(2-hydroxy-7-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (3b): Brown solid, mp: 141-142 °C. IR (KBr): ν_{max} 3323, 3270, 2980, 2917, 2859, 1652, 1621, 1513, 1412, 1367, 1287, 1230, 1164 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 6.79-6.74 (m, 3H), 5.67 (s, 1H), 4.86 (s, 1H), 4.18-4.13 (m, 2H), 2.28 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 156.2, 138.9, 139.1, 133.0, 126.3, 121.8, 117.3, 114.5, 90.4, 84.9, 60.2, 20.8, 14.3 ppm. HRMS (ES+): *m/z* calcd for $[C_{13}H_{15}NO_4+Na]^+$: 272.0893, found: 272.0898.

(Z)-Methyl 2-(6-*tert*-butyl-2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (4a): Brown solid, mp: 135-136 °C. IR (KBr): ν_{max} 3377, 3310, 2957, 2871, 1656, 1613, 1506, 1437, 1370, 1294, 1220, 1070, 1003 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ10.06 (br s, 1H), 6.95 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.91 (s, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 5.69 (s, 1H), 4.89 (s, 1H), 3.67 (s, 3H),

1.29 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 149.4, 145.5, 138.9, 125.6, 119.1, 116.6, 112.2, 90.3, 83.0, 50.3, 33.9, 31.1 ppm. HRMS (ES+): *m/z* calcd for $[C_{15}H_{19}NO_4+Na]^+$: 300.1206, found: 300.1208.

(Z)-ethyl 2-(6-tert-butyl-2-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate (4b): Brown solid, mp: 121-122 °C. IR (KBr): ν_{max} 3426, 3311, 2973, 1664, 1625, 1507, 1422, 1366, 1287, 1225, 1164 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.10 (br s, 1H), 6.94 (dd, *J* = 2.5 Hz, 8.5, 1H), 6.90 (s, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 5.68 (d, *J* = 4.5 Hz, 1H), 4.88 (s, 1H), 4.21-4.11 (m, 2H), 3.43 (br d, *J* = 7.0 Hz, 1H), 1.28 (s, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.5, 146.4, 138.3, 125.5, 119.9, 117.4, 113.1, 91.2, 84.5, 59.5, 34.0, 31.3, 14.6 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{21}NO_4+Na]^+$: 314.1363, found: 314.1343.

(Z)-Methyl 2-(6-chloro-2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (5a): Brown solid, mp: 175-176 °C. IR (KBr): ν_{max} 3321, 3270, 2982, 2912, 1653, 1624, 1515, 1413, 1364, 1289, 1234, 1170 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.04 (br s, 1H), 6.90-6.866 (m, 3H), 5.71 (s, 1H), 4.94 (s, 1H), 3.71 (s, 3H), 3.40 (br s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.2, 148.0, 140.1, 128.9, 125.9, 121.4, 119.0, 115.8, 90.0, 84.7, 50.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{11}H_{10}ClNO_4+Na]^+$: 278.0191, found: 278.0192.

(Z)-Ethyl 2-(6-chloro-2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (5b): Brown solid, mp: 144-145 °C. IR (KBr): ν_{max} 3329, 3267, 2986, 1657, 1608, 1495, 1414, 1341, 1303, 1228, 1169 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 6.89-6.87 (m, 3H), 5.70 (d, *J* = 5.5 Hz, 1H), 4.94 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.24 (d, *J* = 6.0 Hz, 1H), 1.30 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 147.8, 139.7, 127.5, 126.4, 121.2, 117.6, 114.4, 89.7, 84.5, 58.1, 13.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{12}ClNO_4+Na]^+$: 292.0347, found: 292.0321.

(Z)-Methyl 2-(7-chloro-2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (6a): Brown solid, mp: 179-180 °C. IR (KBr): ν_{max} 3336, 3285, 1658, 1627, 1493, 1423, 1284, 1224, 1017 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 7.36 (br d, *J* = 5.0 Hz, 1H), 6.78-6.74 (m, 2H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.50 (br d, *J* = 4.0 Hz, 1H), 4.73 (s, 1H), 3.54 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 148.0, 141.3, 126.2, 124.8, 121.9, 116.9, 115.3, 90.1, 83.6, 50.0 ppm. HRMS (ES+): *m/z* calcd for $[C_{11}H_{10}ClNO_4+Na]^+$: 278.0191, found: 278.0181.

(Z)-Ethyl 2-(7-chloro-2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (6b): Brown solid, mp: 138-139 °C. IR (KBr): ν_{max} 3271, 2988, 1656, 1622, 1497, 1412, 1291, 1224, 1169, 1021 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 5.70 (s, 1H), 4.91 (s, 1H), 4.19-4.11 (m, 2H), 3.49 (br s, 1H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 148.2, 141.5, 126.4, 125.3, 122.1, 117.4, 115.6, 90.1, 84.0, 59.0, 13.7 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{12}ClNO_4+Na]^+$: 292.0347, found: 292.0355.

4-(2-Hydroxyphenylamino)-5-methoxyfuran-2(5*H*)-one (7): viscous liquid. IR (KBr): ν_{max} 3299, 2936, 1717, 1615, 1580, 1533, 1436, 1367, 1157, 1121 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.18 (br s, 1H), 7.03 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.17-7.13 (m, 3H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.80 (s, 1H), 5.34 (s, 1H), 3.72 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 155.9, 140.0, 138.1, 125.7, 122.8, 117.0, 114.8, 100.2, 84.9, 51.6 ppm. HRMS (ES+): *m/z* calcd for $[C_{11}H_{11}NO_4+Na]^+$: 244.0580, found: 244.0573.

4-(2-Hydroxy-5-methylphenylamino)-5-methoxyfuran-2(5*H*)-one (8): viscous liquid. IR (KBr): ν_{max} 3345, 3277, 2931, 1653, 1605, 1527, 1438, 1323, 1167, 1130 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 5.79 (s, 1H), 3.53 (s, 3H) 2.26 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 156.1, 138.2, 135.7, 123.7, 123.4, 117.6, 116.7, 100.2, 84.9, 51.4, 20.9 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{13}NO_4+Na]^+$: 258.0737, found: 258.0738.

4-(2-Hydroxy-4-methylphenylamino)-5-methoxyfuran-2(5*H*)-one (9): viscous liquid, IR (KBr): ν_{max} 3288, 2927, 1725, 1629, 1586, 1528, 1432, 1366, 1169, 1117 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 7.09-7.03 (m, 1H), 6.94 (br s, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 5.78 (s, 1H), 5.23 (s, 1H), 3.54 (s, 3H), 2.26 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 159.7, 146.7, 135.6, 121.4, 119.4, 116.6, 100.1, 85.7, 55.1, 20.9 ppm. HRMS (ES+): *m/z* calcd for $[C_{12}H_{13}NO_4+Na]^+$: 258.0737, found: 258.0741.

4-(5-*tert*-Butyl-2-hydroxyphenylamino)-5-methoxyfuran-2(5*H*)-one (10): viscous liquid, IR (KBr): ν_{max} 3295, 2953, 1716, 1621, 1578, 1532, 1441, 1372, 1168, 1122 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.11 (br s, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 2.0, 9.0 Hz, 2H), 6.97 (d, *J* = 2.0 Hz, 1H), 5.77 (s, 1H), 5.27 (s, 1H), 3.54 (s, 3H) 1.14 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 156.1, 147.6, 138.4, 123.7, 120.0, 116.4, 112.4, 99.9, 85.0, 61.3, 36.0, 31.2 ppm. HRMS (ES+): *m/z* calcd for $[C_{15}H_{19}NO_4+Na]^+$: 300.1206, found: 300.1208.

4-(5-Chloro-2-hydroxyphenylamino)-5-methoxyfuran-2(5*H*)-one (11): viscous liquid, IR (KBr): 3393, 3289, 2929, 1744, 1644, 1590, 1538, 1433, 1312, 1178, 1124 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.34 (br s, 1H), 8.96 (s, 1H), 7.18 (d *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.90 (s, 1H), 5.09 (s, 1H), 3.45 (s, 3H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.8, 160.2, 147.7, 128.5, 124.7, 122.7, 120.3, 116.9, 99.6, 85.1, 55.1 ppm. HRMS (ES+): *m/z* calcd for $[C_{11}H_{10}ClNO_4+Na]^+$: 278.0191, found: 278.0192.

4-(4-Chloro-2-hydroxyphenylamino)-5-methoxyfuran-2(5*H*)-one (12): viscous liquid, IR (KBr): ν_{max} 3278, 2932, 1711, 1621, 1576, 1531, 1428, 1361, 1168, 1111 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 7.05 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 6.81 (q, *J* = 8.0, 15.0 Hz, 2H), 5.80 (s, 1H), 5.34 (s, 1H), 3.56 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 156.4, 138.5, 130.9, 125.1, 122.6, 118.1, 116.6, 99.2, 85.0, 51.7 ppm. HRMS

(ES+): *m/z* calcd for $[C_{11}H_{10}ClNO_4+Na]^+$: 278.0191, found: 278.0199.

(Z)-Methyl 2-(2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (13a): pale yellow viscous liquid. IR (KBr): ν_{max} 3289, 1655, 1623, 1504, 1426, 1377, 1295, 1134 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.36 (br s, 1H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.03 (dt, *J* = 1.5, 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.16 (s, 2H), 3.87 (s, 3H), 2.98 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 1.61-1.54 (m, 4H), 1.51-1.44 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 155.9, 140.0, 138.1, 125.7, 124.1, 122.8, 117.0, 114.8, 90.7, 85.2, 51.5, 49.1, 28.1, 24.1 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{20}N_2O_3+Na]^+$: 311.1366, found: 311.1359.

(Z)-Ethyl 2-(2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (13b): pale yellow viscous liquid. IR (KBr): ν_{max} 3278, 1647, 1594, 1426, 1368, 1279, 1134 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.43 (s, 1H), 6.93-6.87 (m, 3H), 6.82-6.80 (m, 1H), 5.18 (s, 1H), 5.11 (d, *J* = 0.5 Hz, 1H), 4.25-4.17 (m, 2H), 3.06-3.01 (m, 2H), 2.72-2.68 (m, 2H), 1.63-1.58 (m, 4H), 1.53-1.50 (m, 2H), 1.33 (t, *J* = 7.5 Hz, 3H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 150.5, 144.4, 126.6, 122.5, 122.0, 116.6, 115.0, 90.8, 83.6, 59.4, 49.1, 26.2, 24.3, 14.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{17}H_{22}N_2O_3+Na]^+$: 325.1523, found: 325.1522.

(Z)-Methyl 2-(6-methyl-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (14a): pale yellow viscous liquid. IR (KBr): ν_{max} 3278, 1666, 1622, 1504, 1442, 1381, 1281, 1153 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.31 (br s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.66 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 5.11 (s, 1H), 5.08 (s, 1H), 3.72 (s, 3H), 3.00 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 2.54 (s, 3H), 1.60-1.53 (m, 4H), 1.50-1.43 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 156.0, 138.2, 135.7, 123.7, 123.5, 117.6, 116.7, 115.1, 90.4, 85.6, 51.4, 48.0, 29.6, 24.2, 20.9 ppm. HRMS (ES+): *m/z* calcd for $[C_{17}H_{22}N_2O_3+Na]^+$: 325.1523, found: 325.1519.

(Z)-Ethyl 2-(6-methyl-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (14b): pale yellow viscous liquid. IR (KBr): ν_{max} 3308, 1661, 1618, 1507, 1439, 1379, 1285, 1147 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.31 (br s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 5.11 (s, 1H), 5.08 (s, 1H), 4.22-4.11 (m, 2H), 3.00 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 2.25 (s, 3H), 1.61-1.53 (m, 4H), 1.52-1.42 (m, 2H), 1.31 (t, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 156.1, 138.1, 138.0, 135.7, 124.0, 123.4, 116.6, 115.0, 90.9, 82.9, 60.3, 49.0, 25.7, 20.9, 14.3 ppm. HRMS (ES+): *m/z* calcd for $[C_{18}H_{24}N_2O_3+Na]^+$: 339.1679, found: 339.1667.

(Z)-Methyl 2-(7-methyl-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (15a): pale yellow viscous liquid. IR (KBr): ν_{max} 3268, 1648, 1524, 1430, 1374, 1271, 1134 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.34 (br s, 1H), 6.72 (s, 1H), 6.68-6.67 (m, 2H), 5.13 (s, 1H), 5.06 (d, *J* = 0.5 Hz, 1H), 3.71 (s, 3H), 3.02-2.97 (m, 2H), 2.68-2.64 (m, 2H), 2.25 (s, 3H), 1.60-1.54 (m, 4H), 1.51-1.47 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 150.6, 144.1, 132.4, 124.0, 122.3, 117.0, 114.6, 90.7, 82.4, 50.5, 49.0, 26.1, 24.2, 20.8 ppm. HRMS (ES+): *m/z* calcd for $[C_{17}H_{22}N_2O_3+Na]^+$: 325.1523, found: 325.1533.

(Z)-Ethyl 2-(7-methyl-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (15b): pale yellow viscous liquid. IR (KBr): ν_{max} 3278, 1660, 1515, 1453, 1382, 1274, 1147 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.36 (br s, 1H), 6.72 (s, 1H), 6.67 (s, 2H), 5.13 (s, 1H), 5.05 (s, 1H), 4.22-4.12 (m, 2H), 3.00 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 2.26 (s, 3H), 1.60-1.55 (m, 4H), 1.50-1.45 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 150.5, 144.2, 132.3, 124.1, 122.3, 117.0, 114.7, 90.8, 82.9, 59.2, 49.0, 25.9, 20.8, 14.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{18}H_{24}N_2O_3+Na]^+$: 339.1679, found: 339.1665.

(Z)-Methyl 2-(6-*tert*-butyl-2-(piperidin-1-yl)-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-ylidene)acetate (16a): pale yellow solid, mp: 100-101 °C. IR (KBr): ν_{max} 3261, 1661, 1619, 1503, 1435, 1381, 1265, 1139 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.39 (br s, 1H), 6.88 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.83-6.81 (m, 2H), 5.15 (s, 1H), 5.11 (s, 1H), 3.73 (s, 3H), 3.01 (quintet, *J* = 5.0 Hz, 2H), 2.68 (quintet, *J* = 5.0 Hz, 2H), 1.61-1.56 (m, 4H), 1.51-1.45 (m, 2H), 1.27 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 151.0, 145.2, 142.0, 125.8, 119.3, 115.9, 112.2, 90.8, 82.7, 50.6, 49.1, 34.2, 31.3, 26.0, 24.3 ppm. HRMS (ES+): *m/z* calcd for $[C_{20}H_{28}N_2O_3+Na]^+$: 367.1992, found: 367.1986.

(Z)-Ethyl 2-(6-*tert*-butyl-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (16b): pale yellow viscous liquid. IR (KBr): ν_{max} 3253, 1652, 1616, 1503, 1385, 1310, 1217, 1138 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 6.89-6.87 (m, 1H), 6.81-6.80 (m, 2H), 5.14 (s, 1H), 5.09 (s, 1H), 4.25-4.12 (m, 2H), 3.01 (quintet, *J* = 5.5 Hz, 2H), 2.68 (quintet, *J* = 5.5 Hz, 2H), 1.61-1.53 (m, 4H), 1.52-1.44 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.27 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 156.2, 149.3, 138.3, 123.6, 119.9, 116.4, 111.7, 90.7, 84.8, 60.3, 50.0, 34.6, 31.3, 26.8, 25.2, 14.3 ppm. HRMS (ES+): *m/z* calcd for $[C_{21}H_{30}N_2O_3+Na]^+$: 381.2149, found: 381.2132.

(Z)-Methyl 2-(6-chloro-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (17a): pale yellow solid, mp: 76-78 °C. IR (KBr): ν_{max} 3245, 1663, 1608, 1498, 1442, 1333, 1267, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.36 (br s, 1H), 6.82-6.77 (m, 3H), 5.13 (s, 2H), 3.73 (s, 3H), 2.98 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.0 Hz, 2H), 1.59-1.55 (m, 4H), 1.51-1.46 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 149.7, 142.9, 127.5, 126.6, 122.0, 117.5, 114.8, 90.9, 84.5, 50.7, 49.0, 29.7, 24.2 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{19}ClN_2O_3+Na]^+$: 345.0976, found: 345.0988.

(Z)-Ethyl 2-(6-chloro-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (17b): pale yellow viscous liquid. IR (KBr): ν_{max} 3243, 1655, 1621, 1507, 1379, 1311, 1222, 1140 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ10.39 (br s, 1H), 6.80-6.78 (m, 3H), 5.11 (s, 2H), 4.22-4.12 (m, 2H) 2.99 (quintet, *J* = 5.5 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 1.62-1.54 (m, 4H), 1.51-1.43 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ 169.7, 155.4, 138.5, 130.8, 125.2, 122.5, 118.1, 114.7, 92.7, 84.4, 60.6, 49.1, 26.7, 23.2, 14.2 ppm. HRMS (ES+): *m/z* calcd for $[C_{17}H_{21}ClN_2O_3+Na]^+$: 359.1133, found: 359.1123.

(Z)-Methyl 2-(7-chloro-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (18a): pale yellow viscous liquid. IR (KBr): ν_{max} 3321, 1657, 1619, 1511, 1433, 1373, 1289, 1131 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.42 (br s, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 5.12 (s, 1H), 5.08 (s, 1H), 3.82 (s, 3H), 3.00 (quintet, *J* = 5.0 Hz, 2H), 2.67 (quintet, *J* = 5.5 Hz, 2H), 1.53-1.42 (m, 4H), 1.41-1.34 (m, 2H) ppm. .^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 149.6, 144.9, 126.8, 125.2, 121.7, 116.9, 115.4, 91.1, 86.3, 50.7, 49.4, 29.6, 25.2 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{19}ClN_2O_3+Na]^+$: 345.0976, found: 345.0977.

(Z)-Ethyl 2-(7-chloro-2-(piperidin-1-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (18b): pale yellow viscous liquid. IR (KBr): ν_{max} 3266, 1659, 1604, 1486, 1436, 1328, 1266, 1148 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.42 (br s, 1H), 6.85-6.83 (m, 2H), 6.71-6.68 (m, 1H), 5.19 (s, 1H), 5.11 (s, 1H), 4.25-4.13 (m, 2H), 2.99 (quintet, *J* = 5.0 Hz, 2H), 2.67 (quintet, *J* = 5.0 Hz, 2H), 1.53-1.41 (m, 6H), 1.34 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 149.6, 145.0, 126.7, 125.2, 121.7, 116.9, 115.4, 91.0, 84.3, 59.4, 49.0, 26.1, 24.2, 14.4 ppm. HRMS (ES+): *m/z* calcd for $C_{17}H_{21}ClN_2O_3+Na]^+$: 359.1133, found: 359.1143.

(Z)-Methyl 2-(2-(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (19): Thick brown liquid. IR (KBr): ν_{max} 3300, 1667, 1622, 1501, 1429, 1269, 1145 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.26 (br s, 1H), 6.90-6.85 (m, 3H), 6.81-6.78 (m, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 3.05-3.00 (m, 2H), 2.90-2.85 (m, 2H), 3.72 (s, 3H), 1.81-1.75 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 150.4, 144.1, 126.8, 122.5, 122.1, 116.7, 115.1, 87.5, 83.9, 50.7, 40.8, 24.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{15}H_{18}N_2O_3+Na]^+$: 297.1209, found: 297.1214.

(Z)-Methyl 2-(6-methyl-2-(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (20): Thick brown liquid. IR (KBr): ν_{max} 3278, 1667, 1623, 1502, 1434, 1275, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.20 (br s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.69-6.61 (m, 2H), 5.23 (s, 1H), 5.01 (s, 1H), 3.72 (s, 3H), 3.04-2.98 (m, 2H), 2.87-2.84 (m, 2H), 2.26 (s, 3H) 1.81-1.74 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 149.5, 140.9, 130.6, 125.5, 121.9, 115.3, 114.6, 86.5, 82.7, 49.6, 46.9, 23.4, 19.8 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{20}N_2O_3+Na]^+$: 311.1366, found: 311.1356.

(Z)-Methyl 2-(7-methyl-2-(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (21): Thick brown liquid. IR (KBr): ν_{max} 3287, 1663, 1614, 1516, 1430, 1387, 1271, 1145 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.23 (br s, 1H), 6.72 (s, 1H), 6.69-6.68 (m, 2H), 5.26 (s, 1H), 4.99 (s, 1H), 3.71 (s, 3H), 3.03-2.98 (m, 2H), 2.88-2.83 (m, 2H), 2.26 (s, 3H), 1.80-1.74 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 150.3, 143.8, 132.3, 124.2, 122.4, 117.1, 114.6, 87.4, 83.1, 50.5, 47.7, 24.4, 20.7 ppm. HRMS (ES+): *m/z* calcd for $[C_{16}H_{20}N_2O_3+Na]^+$: 311.1366, found: 311.1369.

(Z)-Methyl 2-(6-*tert*-butyl-2-(pyrrolidin-1-yl)-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-ylidene)acetate (22): Thick brown liquid. IR (KBr): ν_{max} 3451, 1664, 1620, 1513, 1458, 1383, 1255, 1174 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.29 (br s, 1H), 6.88 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.80 (s, 1H), 5.28 (s, 1H), 5.03 (d, *J* = 1.0 Hz, 1H), 3.72 (s, 3H), 3.05-3.00 (m, 2H), 2.90-2.85 (m, 2H), 1.81-1.76 (m, 4H), 1.27 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 150.7, 145.3, 141.8, 126.0, 119.4, 116.0, 112.4, 87.5, 83.4, 50.6, 47.8, 34.2, 31.4, 24.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{19}H_{26}N_2O_3+Na]^+$: 353.1836, found: 353.1839.

(Z)-Methyl 2-(6-chloro-2-(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (23): Thick brown liquid. IR (KBr): ν_{max} 3280, 1669, 1629, 1498, 1435, 1379, 1265, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.24 (br s, 1H), 6.80-6.79 (m, 2H), 6.78-6.77 (m, 1H), 5.25 (s, 1H), 5.06 (s, 1H), 3.01-2.97 (m, 2H), 2.87-2.83 (m, 2H), 3.71 (s, 3H) 1.80-1.74 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 149.5, 142.7, 127.8, 126.6, 122.0, 117.6, 114.8, 87.7, 85.1, 50.7, 47.8, 24.4 ppm. HRMS (ES+): m/z calcd for $[C_{15}H_{17}ClN_2O_3+Na]^+$: 331.0820, found: 331.0816.

(Z)-Methyl 2-(7-chloro-2-(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-ylidene)acetate (24): Thick brown liquid. IR (KBr): ν_{max} 3282, 1668, 1623, 1508, 1437, 1382, 1278, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.20 (br s, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 5.22 (s, 1H), 4.97 (s, 1H), 3.64 (s, 3H), 2.96-2.91 (m, 2H), 2.81-2.77 (m, 2H), 1.74-1.61 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 148.6, 143.7, 125.9, 124.6, 120.9, 116.1, 114.5, 86.8, 83.6, 49.8, 46.8, 23.5 ppm. HRMS (ES+): *m/z* calcd for $[C_{15}H_{17}ClN_2O_3+Na]^+$: 331.0820, found: 331.0829.

(Z)-Methyl 2-(2-(dibenzylamino)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (25)

pale yellow solid, mp: 72-73 °C. IR (KBr):ν_{max} 3271, 1659, 1612, 1514, 1456, 1374, 1247 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.51 (br s, 1H), 7.46 (d, *J* = 7.5 Hz, 4H), 7.38 (t, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.0 Hz, 2H), 7.05-7.02 (m, 1H), 6.97-6.91 (m, 2H), 6.85-6.81 (m, 1H), 5.39 (s, 1H), 5.32 (s, 1H), 4.14 (d, *J* = 14.0 Hz, 2H), 3.92 (d, *J* = 14.0 Hz, 2H), 3.77 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 151.4, 144.0, 138.3, 128.6, 128.5, 127.3, 126.4, 122.6, 122.2, 116.6, 115.0, 85.7, 83.0, 52.9, 50.7 ppm.

(Z)-Methyl 2-(2-(dibenzylamino)-6-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (26)

Orange solid, mp: 80-81 °C. IR (KBr): ν_{max} 3269, 1663, 1624, 1525, 1491, 1377, 1279 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 7.44 (d, *J* = 7.0 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.30-7.27 (m, 2H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.63 (d, *J* = 1.5 Hz, 1H), 5.40 (s, 1H), 5.25 (s, 1H), 4.11 (d, *J* = 14.0 Hz, 2H), 3.89 (d, *J* = 14.0 Hz, 2H), 3.75 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0,

151.5, 141.8, 138.3, 131.8, 128.6, 128.5, 127.2, 126.1, 123.1, 116.3, 115.5, 85.7, 82.8, 52.8, 50.7, 20.8 ppm.

(*Z*)-Methyl 2-(2-(dibenzylamino)-7-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (27)

yellow solid. mp: 78-89 ^{o}C, IR (KBr): ν_{max} 3261, 1665, 1619, 1517, 1452, 1383, 1277 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 7.50 (d, *J* = 7.5 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 4H), 7.33 (t, *J* = 7.5 Hz, 2H), 6.89 (s, 1H), 6.77-6.73 (m, 2H), 5.40 (s, 1H), 5.33 (s, 1H), 4.17 (d, *J* = 14.0 Hz, 2H), 3.95 (d, *J* = 14.0 Hz, 2H), 3.79 (s, 3H), 2.36 (s, 3H)ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 151.3, 143.7, 138.2, 132.5, 128.5, 128.4, 127.2, 123.8, 122.6, 117.1, 114.7, 85.6, 82.3, 52.7, 50.5, 20.8 ppm.

(*Z*)-Methyl 2-(6-*tert*-butyl-2-(dibenzylamino)-2*H*-enzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (28)

Yellow solid, mp: 98-99 ^{o}C. IR (KBr): ν_{max} 3272, 1665, 1618, 1521, 1492, 1383, 1259 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.49 (br s, 1H), 7.44 (d, *J* = 7.5 Hz, 4H), 7.36 (t, *J* = 7.5 Hz, 4H), 7.28 (t, *J* = 7.0 Hz, 2H), 6.97-6.92 (m, 2H), 6.84 (d, *J* = 1.5 Hz, 1H), 5.37 (s, 1H), 5.26 (s, 1H), 4.11 (d, *J* = 14.0 Hz, 2H), 3.90 (d, *J* = 14.0 Hz, 2H), 3.75 (s, 3H), 1.30 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ171.2, 151.7, 145.5, 141.6, 138.3, 128.6, 128.5, 127.3, 125.7, 119.5, 116.0, 112.3, 85.7, 82.5, 52.8, 50.7, 34.3, 31.4 ppm.

(*Z*)-Methyl 2-(6-chloro-2-(dibenzylamino)-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (29)

Pale yellow solid, mp: 108-109 ^{o}C. IR (KBr): ν_{max} 3257, 1662, 1617, 1518, 1454, 1363, 1232 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (br s, 1H), 7.42-7.41 (m, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 6.92-6.90 (m, 1H), 6.87 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 5.39 (s, 1H), 5.27 (s, 1H), 4.10 (d, *J* = 13.5 Hz, 2H), 3.87 (d, *J* = 14.0 Hz, 2H), 3.75 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 150.4, 142.5, 138.0, 128.5, 128.5, 127.3, 126.9, 122.1, 117.5, 114.8, 85.9, 84.2, 52.8, 50.8 ppm.

(*Z*)-Methyl 2-(2-morpholino-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (30)

Yellow solid, mp: 78-79 ^{o}C. IR (KBr): ν_{max} 3261, 1671, 1630, 1518, 1462, 1362, 1271cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.35 (br s, 1H), 6.92-6.87 (m, 3H), 6.81-6.79 (m, 1H), 5.12 (s, 1H), 5.08 (s, 1H), 3.73 (s, 3H), 3.70 (t, *J* = 5.0 Hz, 4H), 3.04 (td, *J* = 4.5, 11.5 Hz, 2H), 2.74 (td, *J* = 4.5, 11.0 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 149.3, 143.8, 126.4, 122.7, 122.3, 116.7, 115.1, 89.6, 83.7, 67.0, 50.8, 48.1 ppm.

(*Z*)-Methyl 2-(6-methyl-2-morpholino-2*H*- enzo[*b*][1,4]oxazin -3(4*H*)-ylidene)acetate (31)

Yellow solid, mp:72-73 ^{o}C. IR (KBr): ν_{max} 3265, 1674, 1632, 1512, 1434, 1378, 1246 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.28 (br s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 5.05 (s, 1H), 5.04 (s, 1H), 3.71 (s, 3H), 3.69 (t, *J* = 4.5 Hz, 4H), 3.02 (td, *J* = 4.0, 10.5 Hz, 2H), 2.72 (td, *J* = 4.5, 10.0 Hz, 2H), 2.25 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 149.4, 141.5, 131.9, 126.0, 123.1, 116.3, 115.6, 89.6, 83.6, 67.0, 50.7, 48.0, 20.7 ppm.

(*Z*)-Methyl 2-(7-methyl-2-morpholino-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (32)

Yellow solid, mp: 95-96 ^{o}C. IR (KBr): ν_{max} 3261, 1671, 1630, 1507, 1443, 1367, 1271 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.30 (br s, 1H), 6.70 (s, 1H), 6.65 (s, 2H), 5.04 (s, 1H), 5.00 (s, 1H), 3.68 (s, 3H), 3.65 (t, *J* = 4.5 Hz, 4H), 2.99 (td, *J* = 4.5, 11.5 Hz, 2H), 2.68 (td, *J* = 4.5, 9.5 Hz, 2H), 2.23 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 149.1, 143.4, 132.4, 123.7, 122.5, 116.9, 114.6, 89.4, 82.9, 66.7, 50.4, 47.8, 20.6 ppm.

(*Z*)-Methyl 2-(6-*tert*-butyl-2-morpholino-2*H*-benzo[*b*][1,4] oxazin -3(4*H*)-ylidene)acetate (33)

Pale yellow solid, mp: 114-115 ^{o}C. IR (KBr): ν_{max} 3249, 1668, 1615, 1518, 1436, 1371, 1250 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 6.93 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.86 (s, 1H), 6.84 (s, 1H), 5.13 (s, 1H), 5.10 (s, 1H), 3.75 (s, 3H), 3.73 (t, *J* = 4.5 HZ, 4H), 3.07 (td, *J* = 4.5, 10.0 Hz, 2H), 2.77 (td, *J* = 5.0, 10.0 Hz, 2H), 1.29 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 149.7, 145.6, 141.4, 125.6, 119.6, 116.0, 112.3, 89.6, 83.2, 66.9, 50.7, 48.1, 34.3, 31.4 ppm.

(*Z*)-Methyl 2-(6-chloro-2-morpholino-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (34)

Yellow solid. mp: 100-101 ^{o}C. IR (KBr): ν_{max} 3243, 1668, 1630, 1520, 1465, 1389, 1265 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.32 (br s, 1H), 6.80 (s, 2H), 6.78 (d, *J* = 0.5 Hz, 1H), 5.09 (s, 1H), 5.06 (s, 1H), 3.71 (s, 3H), 3.68 (t, *J* = 5.0 Hz, 4H), 2.99 (td, *J* = 4.5, 11.5 Hz, 2H), 2.71 (td, *J* = 5.0, 10.0 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 148.3, 142.3, 127.3, 126.9, 122.1, 117.6, 114.8, 89.6, 85.0, 66.8, 50.8, 48.0 ppm.

(*Z*)-methyl 2-(2-(4-benzylpiperazin-1-yl)-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ylidene)acetate (35)

Pale yellow solid, mp: 80-81 ^{o}C. IR (KBr):ν_{max} 3264, 1674, 1624, 1506, 1450, 1376, 1268 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 7.37-7.35 (m, 4H), 7.31-7.27 (m, 1H), 6.94-6.90 (m, 3H), 6.84-6.81 (m, 1H), 5.19 (s, 1H), 5.13 (s, 1H), 3.77 (s, 3H), 3.55 (s, 2H), 3.15-3.10 (m, 2H), 2.80 (td, *J* = 4.5, 10.0 Hz, 2H), 2.60-2.41 (br s, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 149.6, 143.9, 137.8, 129.0, 128.0, 126.9, 126.2, 122.5, 121.9, 116.5, 114.8, 89.4, 83.3, 62.8, 53.0, 50.5 ppm.

(*Z*)-Methyl 2-(2-(4-benzylpiperazin-1-yl)-6-methyl-2*H*-benzo [*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (36)

Orange thick liquid. IR (KBr): ν_{max} 3274, 1657, 1621, 1513, 1434, 1382, 1254 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.33 (br s, 1H), 7.34 (d, *J* = 4.0 Hz, 4H), 7.31-7.27 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.63 (s, 1H), 5.14 (s, 1H), 5.08 (s, 1H), 3.75 (s, 3H), 3.53 (s, 2H), 3.13-3.07 (m, 2H), 2.78 (td, *J* = 4.5, 10.0 Hz, 2H), 2.60-2.49 (s, 4H), 2.83 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 149.9, 141.8, 138.0, 131.6, 129.1, 128.1, 127.0, 126.0, 123.0, 116.3, 115.5, 89.5, 83.3, 62.9, 53.1, 50.6, 20.7 ppm.

(*Z*)-Methyl 2-(2-(4-benzylpiperazin-1-yl)-7-methyl-2*H*-benzo [*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (37)

Thick brown liquid. IR (KBr): ν_{max} 3264, 1656, 1614, 1513, 1462, 1371, 1264cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.32 (br s, 1H), 7.33-7.31 (m, 4H), 7.26-7.27 (m, 1H), 6.71 (s, 1H), 6.80 (s, 2H), 5.15 (s, 1H), 5.02 (s, 1H), 3.72 (s, 3H), 3.53 (s, 2H), 3.11-3.06 (m, 2H), 2.80-2.75 (m, 2H), 2.55-2.44 (br s, 4H), 2.26 (s, 3H) ppm, ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 149.8, 143.8, 132.6, 129.2, 128.2, 127.0, 123.8, 122.5, 117.1, 114.7, 89.5, 82.8, 62.9, 53.0, 50.6, 20.8 ppm.

(*Z*)-methyl 2-(2-(4-benzylpiperazin-1-yl)-6-*tert*-butyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (38)

Thick brown liquid. IR (KBr): ν_{max} 3226, 1665, 1615, 1509, 1450, 1365, 1256 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.38 (br s, 1H), 7.32-7.31 (m, 5H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.82-6.79 (m, 2H), 5.16 (s, 1H), 5.07 (s, 1H), 3.73 (s, 3H), 3.51 (s, 2H), 3.11-3.04 (m, 2H), 2.81-2.74 (m, 2H), 2.53-2.44 (m, 4H), 1.26 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 150.2, 145.4, 141.7, 129.2, 128.2, 127.0, 125.6, 119.5, 116.0, 112.3, 89.6, 83.0, 63.0, 53.2, 50.7, 34.3, 31.4 ppm.

(*Z*)-Methyl 2-(2-(4-benzylpiperazin-1-yl)-6-chloro-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (39)

Orange solid, mp: 84-85 °C. IR (KBr): ν_{max} 3248, 1668, 1615, 1518, 1438, 1374, 1249 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.37 (br s, 1H), 7.34 (d, *J* = 4.5 Hz, 4H), 7.31-7.26 (m, 1H), 6.84-6.82 (m, 2H), 6.80 (s, 1H), 5.16 (s, 1H), 5.12 (s, 1H), 3.75 (s, 3H), 3.54 (s, 2H), 3.10-3.07 (m, 2H), 2.78 (td, *J* = 4.5, 10.5 Hz, 2H), 2.56-2.45 (br s, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 148.9, 142.6, 129.2, 128.2, 127.3, 127.1, 126.7, 122.1, 117.6, 114.8, 89.6, 84.8, 62.9, 53.0, 50.8 ppm.

Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C spectra of all new compounds. See DOI: 10.1039/b000000x/

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Expedient Synthesis of Novel 1,4-Benzoxazine and Butenolide Derivatives

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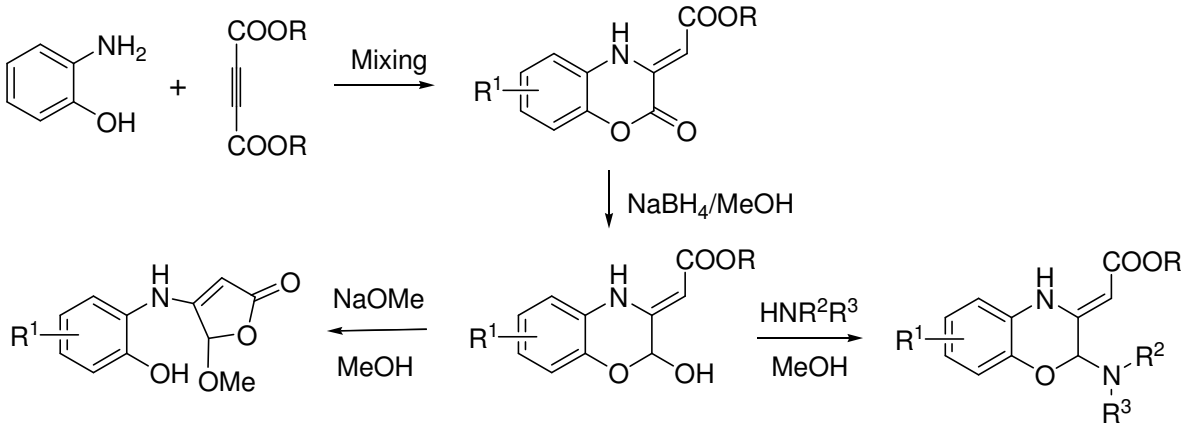

Abstract:

Rapid and efficient protocol for the synthesis of 2-hydroxy-1,4-benzoxazine derivatives has been developed. These intermediates served as precursors for the synthesis of a series of novel butenolide derivatives and 2-amino-1,4-benzoxazine derivatives.