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One-pot regioselective annulation toward 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds under controlled microwave heating☆

Gaofeng Feng,[a] Jinlong Wu[a] and Wei-Min Dai[a,b,*]

[a]*Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, China*
[b]*Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*

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Abstract—An efficient and general synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines under controlled microwave heating has been established. It consists of a microwave-assisted reductive N-arylmethylation of substituted 2-aminophenols with aromatic aldehydes followed by a one-pot base-mediated regioselective O-alkylation of the *N*-arylmethyl-2-aminophenols with 2-bromoalkanoates to give the acyclic intermediates, which cyclize spontaneously to furnish the benzoxazine scaffolds in good to excellent yields. It was found that microwave heating over 180 °C was necessary for ring closure of the acyclic intermediates possessing an electron-withdrawing group.

1. Introduction

A variety of naturally occurring and synthetic bioactive compounds are known to possess the 2*H*-1,4-benzoxazine scalffold.[1] For instance, the enediyne antitumor antibiotic, C-1027,[2] consists of a 2-methylene-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine moiety in the chromophore subunit. Many derivatives of 2*H*-1,4-benzoxazine have been reported as plant resistance factors against microbial disease and insects,[3] serotonin-3 (5-HT_3) receptor antagonists,[4] potassium channel modulators,[5] antirheumatic agents,[6] antihypertensive agents,[7] inotropic vasodilator agents,[8] cannabinoid receptor agonists,[9] intracellular calcium antagonists,[10] neuroprotective antioxidants,[11] and others.[12a,b] 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine skeleton is also considered as the bioisoster of 2(3*H*)-benzoxazolone[12c] and can be used as the privileged scaffold in drug design. From the synthetic point of view, 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine **1** presents a heterocycle system with three points of structural diversity (X, Y, and Z) on the aromatic ring, the nitrogen, and the C2 carbon (Fig. 1). 2-Aminophenols **2** and 2-nitrophenols **3** are the common building blocks for the synthesis of **1**.[1b] Normally, stepwise synthetic sequences were adopted, for example, 2-nitrophenols underwent an O-alkylation followed by nitro reduction and subsequent intramolecular *N*-substitution.[6,9,13] In the case of 2-aminophenols, protection and deprotection manipulations were used to achieve the desired regioselectivity.[14] When treating 2-aminophenols with 2-haloalkanoyl chlorides or bromides N-acylation took place to give 2-(*N*-2′-haloacylamino)phenols, which underwent an intramolecular O-alkylation on heating at ca. 70 °C in the presence of a base to afford 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines.[4c,5a–c,8,13a] Microwave heating up to 80 °C was used in a recent synthesis.[5c] However, for the electron-deficient 2-(*N*-2′-haloacylamino)phenols, higher temperatures were required for complete cyclization.[15] Moreover, various annulation methods including Pd-catalyzed reactions have been reported for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines.[7,10,14a,16] In connection with our previous studies on synthesis of indoles,[17,18] benzofurans,[19a] and benzoxazines[19b] from substituted 2-aminophenols, we report here a regioselective annulation approach

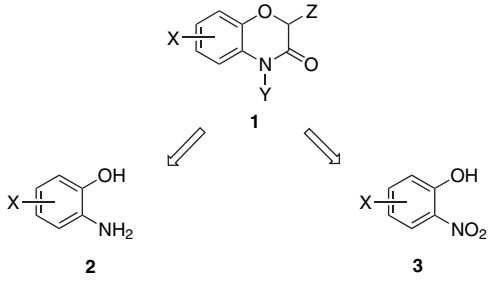

Figure 1. Common building blocks for 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1**.

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* Corresponding author at present address: Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China. Tel.: +852 23587365; fax: +852 23581594; e-mail addresses: chdai@ust.hk; chdai@zju.edu.cn

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for rapidly accessing 4-arylmethyl-3,4-dihydro-2-alkyl-3-oxo-2*H*-1,4-benzoxazines in aqueous DMF under controlled microwave heating.[20]

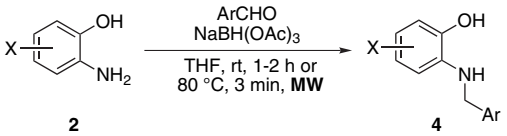
2. Results and discussion

In order to avoid the nitro reduction step in the synthesis starting from 2-nitrophenols **3**, we selected 2-aminophenols **2** as the building blocks in the current work. Although 2-haloalkanoyl halides were found to give an excellent regioselectivity in reactions with **2**,[4c,5a–c,8,13a,15] a recent study reported that reactions of 2-aminophenols with acyl chlorides at 210 °C under microwave irradiation for 15 min afforded benzoxazoles.[21] We preferred to use mild and easily handling 2-bromoalkanoates[4d] as the annulation agents, which are also suitable for running reactions in aqueous media. In our previous study,[19b] we found that heating a mixture of 2-aminophenol **2** (X=H) with ethyl 2-bromopropionate in NMP at 180 °C in the absence of a base resulted in almost exclusive formation of 3-methyl-3,4-dihydro-2-oxo-2*H*-1,4-benzoxazine along with some N,O-bisalkylation byproduct. It was found that a base such as DBU could preferentially remove the phenolic proton and promote O-alkylation of 2-aminophenols with 2-bromoalkanoates, leading to the formation of acyclic intermediates, which then underwent in situ intramolecular amidation at high temperatures under controlled microwave heating to furnish the scaffolds **1** (Y=H). By heating a mixture of 2-aminophenols **2**, ethyl 2-bromopropionate, and DBU in NMP at 180 °C for 3 min, we prepared a number of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazines in 44–82% yields. However, with bulky 2-bromoalkanoates, significantly reduced yields were obtained for the desired benzoxazine products.[19b] Moreover, the reactions of *N*-substituted 2-aminophenols have not been generally investigated for the one-pot synthesis except for one report where ethyl bromoacetate was reacted with *N*-methyl 2-aminophenols in refluxing MeOH in the presence of 10% aqueous NaOH.[4d] It is the purpose of our current study to establish a reliable, general, and efficient procedure for synthesis of the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1** with three points of diversity at X, Y, and Z.

We prepared a variety of *N*-arylmethylated 2-aminophenols **4a–i**[22] from **2** and four representative electron-rich and electron-deficient aromatic aldehydes (Table 1) under microwave heating (80 °C, 3 min).[23] The yields of **4a–i** were comparable to those obtained from the reactions at room temperature (1–2 h), despite that direct reduction of aldehydes by $NaBH(OAc)_3$ is a known competitive side-reaction, especially for strongly electron-deficient aldehydes.[24] An improved yield for the microwave-assisted reaction was achieved for compound **4d** (58%), which was accompanied by bis-arylmethylation byproduct (20%) at room temperature. The high-throughput rate is a unique strength of the microwave-assisted reactions.

The annulation of **4a–c** with ethyl 2-bromoalkanoates was examined using microwave heating in a mixture of DMF–H_2O (2:1) with dissolved K_2CO_3 as the base for avoiding generation of 'hot spots', which may damage the reaction vial (Table 2). On the basis of the results we can conclude

Table 1. Reductive N-alkylation of **2** at room temperature and under controlled microwave heating[a]



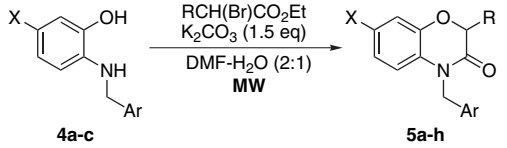
2 **4**

Entry	**2**: X	**4**	Yield (%)[b]
1	H	**4a**: X=H, Ar=2-furyl	73 (95)
2	5-Me	**4b**: X=5-Me, Ar=Ph	79 (97)
3	5-Me	**4c**: X=5-Me, Ar=2-furyl	75 (90)
4	4,5-$(CH_2)_4$–	**4d**: X=4,5-$(CH_2)_4$–, Ar=2-furyl	58 (48)[c]
5	4-NO_2	**4e**: X=4-NO_2, Ar=2-furyl	81 (98)
6	4-Cl	**4f**: X=4-Cl, Ar=2-furyl	86 (99)
7	4-Cl	**4g**: X=4-Cl, Ar=Ph	91 (99)
8	4-Cl	**4h**: X=4-Cl, Ar=4-$MeOC_6H_4$	80
9	4-Cl	**4i**: X=4-Cl, Ar=3-pyridinyl	87

[a] Compound **2** (1 equiv), 1.1 equiv of ArCHO, and 3 equiv of $NaBH(OAc)_3$ were used. All reactions with microwave heating were carried out on a commercial technical microwave reactor with temperature and pressure controlling capacity.
[b] Isolated yields of **4**. The numbers given in the parentheses are the yields for the room temperature reactions.
[c] The bisalkylation byproduct was isolated in 20% yield.

the following points: (a) use of 2 equiv of 2-bromoalkanoates gave slightly higher yields (Table 2, entry 2 vs entry 1); (b) N,O-bisalkylation byproducts were not observed even using excess 2-bromoalkanoates with R≠H; (c) annulations using 2-bromoacetate (R=H) always formed N,O-bisalkylation byproducts and lower temperatures afforded higher yields of the desired products (Table 2, entry 6 vs entry 5 and entry 7 vs entry 10); and (d) for the reactions of bulky 2-bromoalkanoates, excellent yields were obtained at high reaction temperatures (Table 2, entries 11–13 vs entries 8 and 9). Moreover, we found that the microwave-assisted annulation reactions of bulky bromo esters at 180 °C gave comparable chemical yields as to those obtained from

Table 2. One-pot annulation of **4a–c** under microwave heating[a]

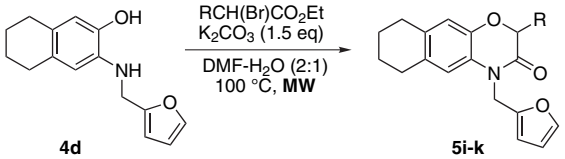


4a-c **5a-h**

Entry	*T* (°C), *t* (min)	**5**	Yield (%)[c]
1	100, 20[b]	**5a**: X=R=H, Ar=2-furyl	64[d]
2	100, 20	**5a**: X=R=H, Ar=2-furyl	68[d]
3	100, 20	**5b**: X=H, R=Et, Ar=2-furyl	75
4	100, 25	**5c**: X=H, R=*n*-Pr, Ar=2-furyl	74
5	120, 15[b]	**5d**: X=Me, R=H, Ar=Ph	51[d]
6	100, 20[b]	**5d**: X=Me, R=H, Ar=Ph	60[d]
7	80, 15[b]	**5e**: X=Me, R=H, Ar=2-furyl	74[d] (80)
8	100, 20[b]	**5g**: X=Me, R=Et, Ar=2-furyl	68
9	100, 20[b]	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	67
10	180, 20	**5e**: X=Me, R=H, Ar=2-furyl	62[d]
11	180, 20	**5f**: X=Me, R=Me, Ar=2-furyl	85
12	180, 20	**5g**: X=Me, R=Et, Ar=2-furyl	81 (92)
13	180, 20	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	80 (74)

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] $RCH(Br)CO_2Et$ (1.5 equiv) was used.
[c] Isolated yields of **5**. The numbers given in the parentheses are the yields for the room temperature reactions (DMF, 3–4.5 h).
[d] Various amounts of N,O-bisalkylation byproducts were detected.

Table 3. One-pot annulation of **4d** under microwave heating[a]



4d **5i-k**

Entry	*t* (min)	**5**	Yield (%)[b]
1	25	**5i**: R=H	67[c]
2	35	**5j**: R=Et	75
3	35	**5k**: R=*n*-Pr	75

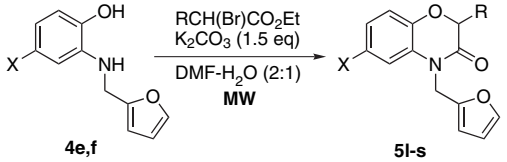
[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.
[c] The N,O-bisalkylation byproduct was detected.

reactions of **4a–c** at room temperature but with greatly shortened reaction times (Table 2, entries 12 and 13 vs entries 8 and 9).

Table 3 shows the reactions of the bicyclic 2-aminophenol **4d** at 100 °C under microwave irradiation. Good yields were obtained for **5i–k** and the N,O-bisalkylation byproduct was also detected in the reaction of 2-bromoacetate (Table 3, entry 1).

The reactions of 2-aminophenols **4e**,**f** possessing an electron-withdrawing group are very different from those described in Tables 2 and 3. When **4e** was treated with ethyl 2-bromoacetate and K_2CO_3 in DMF at room temperature, the O-alkylation intermediate[25] was isolated in 99% yield without formation of the expected **5l**, which was formed in 56% yield by heating at 200 °C for 40 min (Table 4, entry 1). Also, the annulation of **4f** with ethyl 2-bromovalerate at 100 °C for 30 min produced a mixture of the acyclic O-alkylation intermediate and **5s** in 20% and 68% yields, respectively (Table 4, entry 8). The one-pot reactions of **4f** with 2-bromoalkanoates at 180 °C furnished the products **5q–s** in 81–96% yields (Table 4, entries 5–7 and 9). On the other hand, annulation reactions of **4e** with 2-bromoalkanoates required heating at 190 °C for 40–45 min to give

Table 4. One-pot annulation of **4e**,**f** under microwave heating[a]

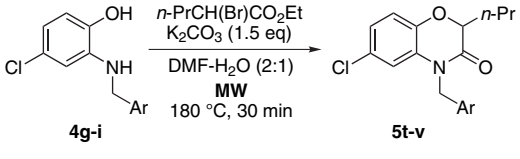


4e,f **5l-s**

Entry	*T* (°C), *t* (min)	**5**	Yield (%)[b]
1	200, 40	**5l**: X=NO_2, R=H	56
2	190, 40	**5m**: X=NO_2, R=Me	74
3	190, 45	**5n**: X=NO_2, R=Et	71
4	190, 40	**5o**: X=NO_2, R=*n*-Pr	85
5	180, 30	**5p**: X=Cl, R=H	81
6	180, 30	**5q**: X=Cl, R=Me	88
7	180, 30	**5r**: X=Cl, R=Et	90
8	100, 30	**5s**: X=Cl, R=*n*-Pr	68[c]
9	180, 30	**5s**: X=Cl, R=*n*-Pr	96

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.
[c] The O-alkylation intermediate was obtained in 20% yield.

Table 5. One-pot annulation of **4g–i** under microwave heating[a]



4g-i **5t-v**

Entry	**5**	Yield (%)[b]
1	**5t**: Ar=Ph	91
2	**5u**: Ar=4-$MeOC_6H_4$	98
3	**5v**: Ar=3-pyridinyl	70

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.

2-alkyl-3,4-dihydro-6-nitro-3-oxo-2*H*-1,4-benzoxazines **5m–o** in 71–85% yields (Table 4, entries 2–4).

Finally, we evaluated the one-pot annulation of **4g–i** bearing different arylmethyl groups on the nitrogen atom (Table 5). By heating at 180 °C for 30 min, the products **5t** and **5u** possessing *N*-benzyl and *N*-4-methoxybenzyl (PMB) groups were formed in 91% and 98% yields, respectively. The 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine **5v** was isolated in 70% yield presumably due to the influence of the 3-pyridinylmethyl group.

3. Conclusion

In summary, we have established a high-throughput synthesis for access to a variety of 2-alkyl-4-arylmethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds starting from readily available substituted 2-aminophenols. The synthesis takes advantage of microwave-assisted fast reductive N-arylmethylation (80 °C, 3 min) of 2-aminophenols, followed by microwave-assisted one-pot regioselective annulation with 2-bromoalkanoates in aqueous DMF in the presence of K_2CO_3 (100–200 °C, 20–45 min). In particular, microwave heating at 180 °C or above is necessary for high yielding of the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines possessing an electron-withdrawing NO_2 or Cl group at the C6 position.

4. Experimental

4.1. General information and the microwave reactor

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, or DMSO-d_6 (500 or 400 MHz for ^1H and 125 or 100 MHz for ^{13}C, respectively) with $CHCl_3$, acetone, or DMSO as the internal reference. IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the ESI method. Elemental analyses were performed at Zhejiang University. All reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. The reaction mixture was checked by thin-layer chromatography on silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Flash column chromatography over silica gel was used for

purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.2. General procedure for reductive N-alkylation of 2-aminophenols under microwave irradiation

A 10 mL pressurized process vial was charged with a mixture of an aldehyde (0.74 mmol), 2-aminophenol **2** (0.66 mmol), and $NaBH(OAc)_3$ (424.0 mg, 2 mmol) in THF (5 mL) and was tightly sealed with a cap containing a silicon septum. The loaded vial was then placed into the microwave reactor cavity and heated at the final temperature of 80 °C for 3 min. After cooling to room temperature the reaction mixture was diluted with water and the resultant mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel to provide the product **4**. The yields are listed in Table 1.

4.2.1. 2-(2′-Furylmethyl)aminophenol (4a). Prepared in 73% yield. *Compound* **4a**. A pale yellow gum; R_f=0.40 (20% EtOAc in hexane); IR (film) 3406, 3327, 3120, 1609, 1509, 1449, 1265, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.89–6.67 (m, 4H), 6.33 (br s, 1H), 6.25 (br s, 1H), 5.50–4.50 (br s, 2H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 144.2, 141.9, 136.2, 121.4, 118.9, 114.7, 113.4, 110.3, 107.1, 41.9; MS (−ESI) *m*/*z* 188 (M−H$^+$, 100). HRMS (+ESI) calcd for $C_{11}H_{11}NO_2Na$ 212.0683 (M+Na$^+$), found 212.0680.

4.2.2. 2-Benzylamino-5-methylphenol (4b). Prepared in 79% yield. *Compound* **4b**. A white crystalline solid; mp 98–102 °C (EtOAc–hexane); R_f=0.46 (20% EtOAc in hexane); IR (KBr) 3422 (br), 3314, 3033, 2918, 1527, 1474, 1451, 1420, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H), 6.59 (s, 2H), 6.44 (s, 1H), 4.71 (br s, 2H), 4.25 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.4, 134.1, 128.6 (×2), 128.5, 127.7 (×2), 127.2, 121.6, 115.6, 113.6, 49.3, 20.6; MS (+ESI) *m*/*z* 235 (M+Na$^+$, 81), 213 (M$^+$, 100). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.92; H, 7.16; N, 6.65%.

4.2.3. 2-(2′-Furylmethyl)amino-5-methylphenol (4c). Prepared in 75% yield. *Compound* **4c**. A white crystalline solid; mp 80–82 °C (EtOAc–hexane); R_f=0.42 (20% EtOAc in hexane); IR (KBr) 3429 (br), 3350, 3339, 2919, 1529, 1451, 1419, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.6 Hz, 1H), 6.71 (d, *J*=8.0 Hz, 1H), 6.67 (d, *J*=8.4 Hz, 1H), 6.46 (s, 1H), 6.33 (dd, *J*=1.6, 3.2 Hz, 1H), 6.23 (d, *J*=3.2 Hz, 1H), 5.16 (br s, 2H), 4.29 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 145.0, 141.9, 133.3, 129.5, 121.4, 115.8, 114.5, 110.3, 107.2, 42.5, 20.6; MS (−ESI) *m*/*z* 202 (M−H$^+$, 100). Anal. Calcd for $C_{12}H_{13}NO_2 \cdot 1/8\ H_2O$: C, 70.14; H, 6.50; N, 6.82. Found: C, 70.31; H, 6.67; N, 5.62%.

4.2.4. 3-(2′-Furylmethyl)amino-5,6,7,8-tetrahydro-2-naphthol (4d). Prepared in 58% yield. *Compound* **4d**. A white crystalline solid; mp 76–78 °C (CH_2Cl_2–hexane); R_f=0.44 (20% EtOAc in hexane); IR (KBr) 3456 (br), 3339, 2921, 1527, 1448, 1258, 1188, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.48 (s, 1H), 6.40 (s, 1H), 6.33 (dd, *J*=1.2, 3.2 Hz, 1H), 6.24 (d, *J*=3.2 Hz, 1H), 4.63 (br s, 2H), 4.27 (s, 2H), 2.66–2.60 (m, 4H), 1.75 (br s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6, recorded at 80 °C) δ 154.0, 142.6, 141.7, 135.0, 127.1, 124.4, 114.4, 111.2, 110.3, 106.5, 40.9, 28.6, 28.2, 23.3, 23.3; MS (−ESI) *m*/*z* 242 (M−H$^+$, 100). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.73; H, 6.94; N, 4.88%.

4.2.5. 2-(2′-Furylmethyl)amino-4-nitrophenol (4e). Prepared in 81% yield. *Compound* **4e**. A red crystalline solid; mp 118–120 °C (EtOAc–hexane); R_f=0.17 (20% EtOAc in hexane); IR (KBr) 3407, 1527, 1468, 1335, 1275, 1245, 1101 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 7.58 (d, *J*=1.6 Hz, 1H), 7.46 (dd, *J*=2.8, 8.4 Hz, 1H), 7.34 (d, *J*=2.8 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.39 (dd, *J*=1.6, 3.2 Hz, 1H), 6.29 (d, *J*=3.2 Hz, 1H), 5.81 (br s, 1H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0, 151.4, 142.5, 140.7, 137.6, 113.8, 112.6, 110.8, 107.4, 104.0, 31.1; MS (−ESI) *m*/*z* 233 (M−H$^+$, 100). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.29; H, 4.37; N, 12.31%.

4.2.6. 4-Chloro-2-(2′-furylmethyl)aminophenol (4f). Prepared in 86% yield. *Compound* **4f**. A white crystalline solid; mp 84–87 °C (CH_2Cl_2–hexane); R_f=0.31 (20% EtOAc in hexane); IR (KBr) 3407, 1611, 1512, 1445, 1419, 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.69 (s, 1H), 6.60–6.55 (m, 2H), 6.34 (dd, *J*=1.6, 3.2 Hz, 1H), 6.25 (d, *J*=3.2 Hz, 1H), 4.76 (br s, 2H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.1, 142.0, 137.4, 126.5, 117.4, 115.1, 112.3, 110.4, 107.4, 41.3; MS (−ESI) *m*/*z* 222 (M−H$^+$, 61.5), 224 (M+2−H$^+$, 19.7), 445 (2M−H$^+$, 100). Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.82; H, 4.64; N, 5.95%.

4.2.7. 2-Benzylamino-4-chlorophenol (4g). Prepared in 91% yield. *Compound* **4g**. A pale yellow crystalline solid; mp 118–120 °C (EtOAc–hexane); R_f=0.36 (20% EtOAc in hexane); IR (KBr) 3505, 3403, 1609, 1514, 1154, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 6.63 (d, *J*=8.0 Hz, 1H), 6.62 (d, *J*=2.0 Hz, 1H), 6.56 (dd, *J*=2.0, 8.0 Hz, 1H), 4.32 (s, 2H) (signals for OH and NH were not found); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.4, 137.9, 128.7 (×2), 127.6 (×2), 127.5, 126.6, 116.8, 114.9, 111.8, 48.2; MS (−ESI) *m*/*z* 232 (M−H$^+$, 100), 234 (M+2−H$^+$, 31). Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.87; H, 5.19; N, 6.00%.

4.2.8. 4-Chloro-2-((4′-methoxyphenyl)methyl)aminophenol (4h). Prepared in 80% yield. *Compound* **4h**. A white crystalline solid; mp 148–151 °C (EtOAc–hexane); R_f=0.34 (20% EtOAc in hexane); IR (KBr) 3497, 3409, 1608, 1513, 1415, 1253, 1116 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.59 (s, 1H), 7.33 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.4 Hz, 2H), 6.70 (d, *J*=8.4 Hz, 1H), 6.48 (d, *J*=2.4 Hz, 1H), 6.42 (dd, *J*=2.4, 8.4 Hz, 1H), 5.11 (br s, 1H), 4.34 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.8, 142.7, 138.8, 131.5, 128.3 (×2), 124.6, 114.9, 113.9, 113.7 (×2), 109.8, 54.5, 46.3; MS (−ESI) *m*/*z* 262 (M−H$^+$, 72), 264 (M+2−H$^+$, 23), 525.3 (2M−H$^+$, 100). Anal. Calcd for

$C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.52; H, 5.52; N, 3.51%.

4.2.9. 4-Chloro-2-(3′-pyridinylmethyl)aminophenol (4i). Prepared in 87% yield. *Compound* **4i**. A pale green crystalline solid; mp 168–174 °C (MeOH); R_f=0.19 (67% EtOAc in hexane); IR (KBr) 3435, 2931, 1609, 1582, 1519, 1428, 1251, 1206 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.56 (s, 1H), 8.43 (d, J=4.8 Hz, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.33 (dd, J=4.8, 7.6 Hz, 1H), 6.63 (d, J=8.4 Hz, 1H), 6.39 (dd, J=2.0, 8.4 Hz, 1H), 6.35 (d, J=2.0 Hz, 1H), 5.77 (br s, 1H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 148.3, 143.5, 138.6, 135.8, 135.3, 123.9, 123.6, 115.3, 114.5, 109.7, 43.9; MS (−ESI) m/z 233 (M−H$^+$, 100), 235 (M+2−H$^+$, 32). Anal. Calcd for $C_{12}H_{11}ClN_2O\cdot 1/8\ H_2O$: C, 60.83; H, 4.79; N, 11.82. Found: C, 60.74; H, 4.96; N, 11.08%.

4.3. General procedure for microwave-assisted one-pot synthesis of 5

A 10 mL pressurized process vial was charged with a mixture of the aminophenol **4** (0.30 mmol), ethyl 2-bromo ester (0.60 mmol), and K_2CO_3 (62.8 mg, 0.45 mmol) in water (1 mL) and DMF (2 mL) and was tightly sealed with a cap containing a silicon septum. The loaded vial was then placed into the microwave reactor cavity and was heated at the final temperature for the specified time (see Tables 2–5 for details). After cooling to room temperature the reaction mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to furnish the product **5**. The yields are listed in Tables 2–5.

4.3.1. 3,4-Dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5a). Prepared in 68% yield. *Compound* **5a**. A yellow oil; R_f=0.41 (11% EtOAc in hexane); IR (film) 3120, 2890, 1690, 1502, 1400, 1281, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=1.6, 1.2 Hz, 1H), 7.24–7.21 (m, 1H), 7.03–6.97 (m, 3H), 6.33–6.31 (m, 2H), 5.08 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 149.6, 145.3, 142.2, 128.7, 124.1, 122.8, 117.0, 115.5, 110.6, 108.8, 67.7, 38.3; MS (+ESI) m/z 481 (2M+Na$^+$, 100), 252 (M+Na$^+$, 98). HRMS (+ESI) calcd for $C_{13}H_{11}NO_3Na$ 252.0631 (M+Na$^+$), found 252.0629.

4.3.2. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5b). Prepared in 75% yield. *Compound* **5b**. A yellowish crystalline solid; mp 54–55 °C (EtOAc–hexane); R_f=0.53 (11% EtOAc in hexane); IR (KBr) 2972, 1687, 1502, 1401, 1278, 1141, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=2.0, 0.8 Hz, 1H), 7.19–7.15 (m, 1H), 7.01–6.98 (m, 3H), 6.31 (dd, J=3.2, 2.0 Hz, 1H), 6.29 (dd, J=3.2, 0.8 Hz, 1H), 5.10 and 5.04 (ABq, J=16.2 Hz, 2H), 4.50 (dd, J=8.8, 4.8 Hz, 1H), 1.99–1.83 (m, 2H), 1.08 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.9, 144.2, 142.1, 128.9, 124.0, 122.5, 117.3, 115.1, 110.6, 108.4, 78.2, 38.6, 23.7, 9.4; MS (+ESI) m/z 537 (2M+Na$^+$, 100), 280 (M+Na$^+$, 41). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.05; H, 6.07; N, 5.48%.

4.3.3. 3,4-Dihydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5c). Prepared in 74% yield. *Compound* **5c**. A white amorphous solid; R_f=0.65 (11% EtOAc in hexane); IR (KBr) 2962, 1688, 1502, 1401, 1279, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=1.6, 0.8 Hz, 1H), 7.18–7.16 (m, 1H), 7.01–6.97 (m, 3H), 6.31 (dd, J=2.8, 1.6 Hz, 1H), 6.28 (dd, J=2.8, 0.8 Hz, 1H), 5.11 and 5.03 (ABq, J=16.2 Hz, 2H), 4.59 (dd, J=8.4, 5.2 Hz, 1H), 1.88–1.81 (m, 2H), 1.64–1.49 (m, 2H), 0.96 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 149.9, 144.1, 142.1, 128.9, 124.0, 122.5, 117.4, 115.1, 110.6, 108.4, 76.9, 38.6, 32.2, 18.3, 13.7; MS (+ESI) m/z 565 (2M+Na$^+$, 100), 294 (M+Na$^+$, 29). HRMS (+ESI) calcd for $C_{16}H_{17}NO_3Na$ 294.1101 (M+Na$^+$), found 294.1108.

4.3.4. 4-Benzyl-3,4-dihydro-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5d). Prepared in 60% yield. *Compound* **5d**. A white crystalline solid; mp 87–89 °C (EtOAc–hexane); R_f=0.53 (20% EtOAc in hexane); IR (KBr) 1683, 1513, 1405, 1296, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 6.82 (s, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 5.15 (s, 2H), 4.71 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 145.2, 136.1, 134.1, 128.9 (×2), 127.5, 126.7 (×2), 126.3, 123.3, 117.6, 115.5, 67.8, 45.0, 20.7; MS (+ESI) m/z 529 (2M+Na$^+$, 100), 276 (M+Na$^+$, 85). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.75; H, 5.94; N, 5.52%.

4.3.5. 3,4-Dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5e). Prepared in 74% yield. *Compound* **5e**. A yellowish crystalline solid; mp 75–76 °C (EtOAc–hexane); R_f=0.38 (11% EtOAc in hexane); IR (KBr) 1679, 1514, 1407, 1152, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.08 (d, J=8.0 Hz, 1H), 6.81 (d, J=8.0 Hz, 1H), 6.81 (s, 1H), 6.31 (s, 1H), 6.30 (s, 1H), 5.06 (s, 2H), 4.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.6, 145.0, 142.1, 134.1, 126.2, 123.2, 117.5, 115.1, 110.5, 108.6, 67.7, 38.2, 20.7; MS (+ESI) m/z 509 (2M+Na$^+$, 100), 266 (M+Na$^+$, 46). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.46; N, 5.68%.

4.3.6. 3,4-Dihydro-4-(2′-furylmethyl)-2,7-dimethyl-3-oxo-2*H*-1,4-benzoxazine (5f). Prepared in 85% yield. *Compound* **5f**. A yellowish crystalline solid; mp 67–68 °C (EtOAc–hexane); R_f=0.48 (11% EtOAc in hexane); IR (KBr) 2981, 1513, 1399, 1158, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.06 (d, J=8.4 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 6.80 (s, 1H), 6.30 (dd, J=3.2, 2.0 Hz, 1H), 6.28 (d, J=3.2 Hz, 1H), 5.12 and 4.97 (ABq, J=15.8 Hz, 2H), 4.62 (q, J=6.8 Hz, 1H), 2.28 (s, 3H), 1.56 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 149.9, 144.3, 142.1, 134.0, 126.5, 123.1, 117.8, 114.9, 110.5, 108.4, 73.5, 38.7, 20.7, 16.2; MS (+ESI) m/z 537 (2M+Na$^+$, 100), 280 (M+Na$^+$, 44). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 6.10; N, 5.46%.

4.3.7. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5g). Prepared in 81% yield. *Compound* **5g**. A yellowish oil; R_f=0.56 (11% EtOAc in hexane); IR (film) 2971, 1686, 1514, 1403, 1149 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=2.0 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.81 (s, 1H), 6.79 (d, J=8.0 Hz, 1H), 6.30 (dd, J=3.2, 2.0 Hz, 1H), 6.27 (d, J=3.2 Hz, 1H), 5.09 and 5.02 (ABq, J=16.0 Hz, 2H), 4.48 (dd, J=8.4, 4.4 Hz, 1H), 2.28 (s, 3H), 1.95–1.82 (m, 2H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.9, 143.9, 142.0, 134.0, 126.3, 122.9, 117.8, 114.8, 110.5, 108.2, 78.2, 38.5, 23.6, 20.7, 9.4; MS (+ESI) m/z 565 (2M+Na$^+$, 100), 294 (M+Na$^+$, 41). HRMS (+ESI) calcd for $C_{16}H_{17}NO_3Na$ 294.1101 (M+Na$^+$), found 294.1102.

4.3.8. 3,4-Dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5h). Prepared in 80% yield. *Compound* **5h**. A yellow amorphous solid; R_f=0.62 (11% EtOAc in hexane); IR (KBr) 2961, 1686, 1514, 1401, 1292, 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=1.2 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.80 (s, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.30 (dd, J=2.8, 1.2 Hz, 1H), 6.26 (d, J=2.8 Hz, 1H), 5.09 and 5.00 (ABq, J=15.8 Hz, 2H), 4.56 (dd, J=8.0, 4.8 Hz, 1H), 2.28 (s, 3H), 1.86–1.80 (m, 2H), 1.61–1.48 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 149.9, 143.8, 142.0, 134.0, 126.3, 122.9, 117.9, 114.8, 110.5, 108.2, 76.9, 38.5, 32.1, 20.7, 18.3, 13.6; MS (+ESI) m/z 593 (2M+Na$^+$, 100), 308 (M+Na$^+$, 32). HRMS (+ESI) calcd for $C_{17}H_{19}NO_3Na$ 308.1257 (M+Na$^+$), found 308.1256.

4.3.9. 6,7,8,9-Tetrahydro-4-(2′-furylmethyl)-3-oxo-2*H*-naphtho[2,3,*b*][1,4]oxazine (5i). Prepared in 67% yield. *Compound* **5i**. A white crystalline solid; mp 104–106 °C (EtOAc–hexane); R_f=0.39 (11% EtOAc in hexane); IR (KBr) 2926, 1701, 1679, 1515, 1389, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J=1.6, 0.8 Hz, 1H), 6.88 (s, 1H), 6.69 (s, 1H), 6.32 (dd, J=3.2, 1.6 Hz, 1H), 6.30 (dd, J=3.2, 0.8 Hz, 1H), 5.06 (s, 2H), 4.58 (s, 2H), 2.71–2.68 (m, 4H), 1.79–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 149.8, 143.2, 142.1, 133.0, 131.4, 126.4, 116.9, 115.6, 110.6, 108.6, 67.8, 38.3, 29.1, 28.8, 23.1, 23.0; MS (+ESI) m/z 589 (2M+Na$^+$, 100), 306 (M+Na$^+$, 34). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.30; N, 5.15%.

4.3.10. 2-Ethyl-6,7,8,9-tetrahydro-4-(2′-furylmethyl)-3-oxo-2*H*-naphtho[2,3,*b*][1,4]oxazine (5j). Prepared in 75% yield. *Compound* **5j**. A white crystalline solid; mp 79–80 °C (EtOAc–hexane); R_f=0.53 (11% EtOAc in hexane); IR (KBr) 2936, 1680, 1514, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=2.0, 0.4 Hz, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.31 (dd, J=2.8, 2.0 Hz, 1H), 6.30 (dd, J=2.8, 0.4 Hz, 1H), 5.08 and 5.00 (ABq, J=15.8 Hz, 2H), 4.45 (dd, J=8.4, 4.4 Hz, 1H), 2.71–2.67 (m, 4H), 1.94–1.82 (m, 2H), 1.78–1.73 (m, 4H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.0, 142.0, 141.7, 132.9, 131.0, 126.4, 117.2, 115.2, 110.5, 108.2, 78.3, 38.5, 29.1, 28.8, 23.6, 23.2, 23.0, 9.5; MS (+ESI) m/z 645 (2M+Na$^+$, 100), 334 (M+Na$^+$, 86). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.31; H, 7.36; N, 4.74%.

4.3.11. 6,7,8,9-Tetrahydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-naphtho[2,3,*b*][1,4]oxazine (5k). Prepared in 75% yield. *Compound* **5k**. A white crystalline solid; mp 96–97 °C (EtOAc–hexane); R_f=0.58 (11% EtOAc in hexane); IR (KBr) 2958, 1682, 1509, 1395, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J=2.0 Hz, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 6.31 (dd, J=3.2, 2.0 Hz, 1H), 6.27 (d, J=3.2 Hz, 1H), 5.09 and 4.99 (ABq, J=16.0 Hz, 2H), 4.54 (dd, J=7.2, 6.0 Hz, 1H), 2.71–2.68 (m, 4H), 1.85–1.78 (m, 2H), 1.77–1.75 (m, 4H), 1.61–1.47 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.0, 142.0, 141.7, 132.9, 131.0, 126.4, 117.2, 115.2, 110.5, 108.2, 76.9, 38.5, 32.1, 29.1, 28.8, 23.2, 23.0, 18.3, 13.6; MS (+ESI) m/z 673 (2M+Na$^+$, 100), 348 (M+Na$^+$, 45). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.79; H, 7.67; N, 4.41%.

4.3.12. 3,4-Dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5l). Prepared in 56% yield. *Compound* **5l**. A yellow crystalline solid; mp 125–126 °C (CH_2Cl_2–hexane); R_f=0.14 (11% EtOAc in hexane); IR (KBr) 1705, 1519, 1341, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J=2.4 Hz, 1H), 7.93 (dd, J=8.8, 2.4 Hz, 1H), 7.38 (dd, J=2.0, 0.8 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.43 (dd, J=3.6, 0.8 Hz, 1H), 6.34 (dd, J=3.6, 2.0 Hz, 1H), 5.16 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.0, 148.3, 143.0, 142.8, 128.7, 120.0, 117.1, 111.3, 110.7, 109.8, 67.3, 38.2; MS (+ESI) m/z 571 (2M+Na$^+$, 43), 297 (M+Na$^+$, 100). Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.84; H, 3.66; N, 10.25%.

4.3.13. 3,4-Dihydro-4-(2′-furylmethyl)-2-methyl-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5m). Prepared in 74% yield. *Compound* **5m**. A yellow crystalline solid; mp 146–147 °C (CH_2Cl_2–hexane); R_f=0.24 (11% EtOAc in hexane); IR (KBr) 1685, 1522, 1341, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=2.4 Hz, 1H), 7.93 (dd, J=8.8, 2.4 Hz, 1H), 7.37 (d, J=1.6 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.40 (d, J=3.2 Hz, 1H), 6.33 (dd, J=3.2, 1.6 Hz, 1H), 5.20 and 5.07 (ABq, J=16.2 Hz, 2H), 4.78 (q, J=6.8 Hz, 1H), 1.61 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.6, 148.5, 143.0, 142.8, 129.0, 120.0, 117.4, 111.1, 110.6, 109.5, 73.9, 38.6, 16.9; MS (+ESI) m/z 311 (M+Na$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.32; H, 4.36; N, 9.88%.

4.3.14. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5n). Prepared in 71% yield. *Compound* **5n**. A yellow crystalline solid; mp 77–78 °C (CH_2Cl_2–hexane); R_f=0.32 (11% EtOAc in hexane); IR (KBr) 2976, 1689, 1523, 1243, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=2.4 Hz, 1H), 7.91 (dd, J=2.4, 2.8 Hz, 1H), 7.35 (d, J=2.0 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.39 (d, J=3.2 Hz, 1H), 6.32 (dd, J=3.2, 2.0 Hz, 1H), 5.17 and 5.09 (ABq, J=15.8 Hz, 2H), 4.72 (dd, J=8.8, 4.8 Hz, 1H), 1.91–1.82 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.4, 148.5, 142.8, 142.7, 128.8, 120.0, 117.3, 110.9, 110.6, 109.4, 78.5, 38.4, 24.3, 9.1; MS (+ESI) m/z 325 (M+Na$^+$, 100). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.65; H, 4.81; N, 9.47%.

4.3.15. 3,4-Dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5o). Prepared in 85% yield.

Compound **5o**. A yellow crystalline solid; mp 62–64 °C (EtOAc–hexane); R_f=0.40 (11% EtOAc in hexane); IR (KBr) 2966, 1692, 1525, 1340, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=2.4 Hz, 1H), 7.91 (dd, J=8.8, 2.8 Hz, 1H), 7.35 (d, J=1.6 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.38 (d, J=3.2 Hz, 1H), 6.32 (dd, J=3.2, 1.6 Hz, 1H), 5.17 and 5.09 (ABq, J=15.8 Hz, 2H), 4.72 (dd, J=8.8, 4.8 Hz, 1H), 1.91–1.82 (m, 2H), 1.58–1.48 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 149.3, 148.5, 142.8, 142.7, 128.8, 120.0, 117.4, 110.1, 110.6, 109.4, 77.3, 38.4, 32.8, 18.0, 13.5; MS (+ESI) m/z 339 (M+Na^+, 100). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.80; H, 5.21; N, 8.87%.

4.3.16. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5p). Prepared in 81% yield. *Compound* **5p**. A white crystalline solid; mp 88–90 °C (CH_2Cl_2–hexane); R_f=0.39 (11% EtOAc in hexane); IR (KBr) 1687, 1498, 1373, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J=0.8 Hz, 1H), 7.23 (d, J=2.0 Hz, 1H), 6.96 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.35–6.32 (m, 2H), 5.05 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.0, 143.8, 142.4, 129.7, 127.8, 123.7, 117.9, 115.6, 110.6, 109.1, 67.5, 38.3; MS (+ESI) m/z 286 (M+Na^+, 100), 288 (M+2+Na^+, 32). Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.12; H, 3.80; N, 5.22%.

4.3.17. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-2-methyl-3-oxo-2*H*-1,4-benzoxazine (5q). Prepared in 88% yield. *Compound* **5q**. A white crystalline solid; mp 96–97 °C (CH_2Cl_2–hexane); R_f=0.50 (11% EtOAc in hexane); IR (KBr) 2938, 1672, 1499, 1374, 1264, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.21 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.33 (s, 2H), 5.11 and 4.94 (ABq, J=15.8 Hz, 2H), 4.62 (q, J=6.4 Hz, 1H), 1.56 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.2, 143.1, 142.4, 130.1, 127.6, 123.6, 118.2, 115.4, 110.6, 108.9, 73.5, 38.8, 16.1; MS (+ESI) m/z 300 (M+Na^+, 100), 302 (M+2+Na^+, 32). Anal. Calcd for $C_{14}H_{12}ClNO_3$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.53; H, 4.46; N, 5.19%.

4.3.18. 6-Chloro-2-ethyl-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5r). Prepared in 90% yield. *Compound* **5r**. A white crystalline solid; mp 98–100 °C (EtOAc–hexane); R_f=0.56 (11% EtOAc in hexane); IR (KBr) 2975, 1667, 1499, 1375, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J=0.8 Hz, 1H), 7.18 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.33–6.30 (m, 2H), 5.06 and 5.00 (ABq, J=16.0 Hz, 2H), 4.48 (dd, J=8.4, 4.4 Hz, 1H), 1.96–1.81 (m, 2H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 149.2, 142.7, 142.3, 129.8, 127.5, 123.6, 118.2, 115.3, 110.6, 108.8, 78.2, 38.6, 23.6, 9.3; MS (+ESI) m/z 314 (M+Na^+, 100), 316 (M+2+Na^+, 31). Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.86; H, 5.10; N, 5.05%.

4.3.19. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5s). Prepared in 96% yield. *Compound* **5s**. A white crystalline solid; mp 46–47 °C (EtOAc–hexane); R_f=0.63 (11% EtOAc in hexane); IR (KBr) 2964, 1679, 1500, 1437, 1366, 1273, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J=2.0, 0.8 Hz, 1H), 7.18 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.89 (d, J=8.4 Hz, 1H), 6.32 (dd, J=3.2, 2.0 Hz, 1H), 6.31 (dd, J=3.2, 0.8 Hz, 1H), 5.07 and 4.98 (ABq, J=16.0 Hz, 2H), 4.56 (dd, J=8.8, 4.8 Hz, 1H), 1.86–1.78 (m, 2H), 1.58–1.49 (m, 2H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 149.2, 142.7, 142.3, 129.9, 127.5, 123.6, 118.2, 115.3, 110.6, 108.8, 76.9, 38.6, 32.1, 18.2, 13.6; MS (+ESI) m/z 328 (M+Na^+, 100), 331 (M+2+Na^+, 32). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.01; H, 5.64; N, 4.82%.

4.3.20. 4-Benzyl-6-chloro-3,4-dihydro-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5t). Prepared in 91% yield. *Compound* **5t**. A white crystalline solid; mp 70–73 °C (EtOAc–hexane); R_f=0.71 (20% EtOAc in hexane); IR (KBr) 2962, 1688, 1497, 1439, 1377, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 6.87 (s, 2H), 6.80 (s, 1H), 5.15 and 4.96 (ABq, J=16.4 Hz, 2H), 4.63 (dd, J=8.4, 5.6 Hz, 1H), 1.89–1.82 (m, 2H), 1.62–1.47 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 142.5, 135.5, 129.9, 128.9 (×2), 127.6, 127.4, 126.4 (×2), 123.6, 118.3, 115.4, 76.9, 45.1, 32.2, 18.2, 13.6; MS (+ESI) m/z 338 (M+Na^+, 100), 340 (M+2+Na^+, 31). HRMS (+ESI) calcd for $C_{18}H_{20}ClNO_2Na$ 338.0919 (M+Na^+), found 338.0920.

4.3.21. 6-Chloro-3,4-dihydro-4-(4′-methoxybenzyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5u). Prepared in 98% yield. *Compound* **5u**. A white crystalline solid; mp 74–75 °C (EtOAc–hexane); R_f=0.63 (20% EtOAc in hexane); IR (KBr) 2963, 1685, 1513, 1498, 1439, 1382, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J=8.8 Hz, 2H), 6.90–6.85 (m, 5H), 5.12 and 4.94 (ABq, J=16.0 Hz, 2H), 4.65 (dd, J=8.4, 5.2 Hz, 1H), 3.78 (s, 3H), 1.91–1.84 (m, 2H), 1.63–1.52 (m, 2H), 0.98 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.0, 142.6, 129.9, 127.9 (×2), 127.6, 127.3, 123.5, 118.2, 115.4, 114.3 (×2), 76.9, 55.2, 44.6, 32.2, 18.2, 13.6; MS (+ESI) m/z 368 (M+Na^+, 100), 370 (M+2+Na^+, 32). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.72; H, 6.01; N, 3.35.

4.3.22. 6-Chloro-3,4-dihydro-3-oxo-2-propyl-4-(3′-pyridinylmethyl)-2*H*-1,4-benzoxazine (5v). Prepared in 70% yield. *Compound* **5v**. A white crystalline solid; mp 80–81 °C (EtOAc–hexane); R_f=0.11 (20% EtOAc in hexane); IR (KBr) 2963, 1685, 1498, 1437, 1382, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.51 (d, J=4.8 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.25 (dd, J=8.0, 4.8 Hz, 1H), 6.93–6.88 (m, 2H), 6.78 (s, 1H), 5.17 and 5.01 (ABq, J=16.4 Hz, 2H), 4.63 (dd, J=8.0, 5.2 Hz, 1H), 1.88–1.82 (m, 2H), 1.58–1.49 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 149.1, 148.3, 142.6, 134.4, 131.3, 129.4, 127.5, 123.9, 123.8, 118.5, 114.9, 76.9, 42.8, 32.1, 18.2, 13.6; MS (+ESI) m/z 339 (M+Na^+, 100), 341 (M+2+Na^+, 31). Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.51; H, 5.47; N, 8.83.

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