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A simple and facile route for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones via reductive cyclization of 2-(2-nitrophenoxy)acetonitrile adducts in the presence of Fe/acetic acid

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ABSTRACT

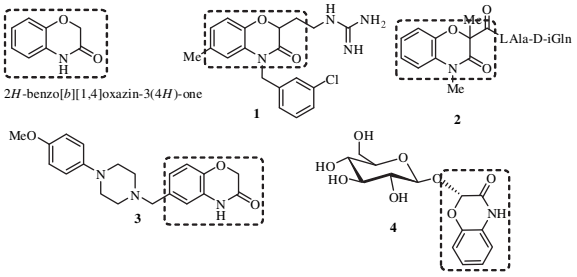
A simple route for the synthesis of 1,4-benzoxazin-3-(4*H*)-ones is described herein. This method involves the reductive cyclization of 2-(2-nitrophenoxy)acetonitrile adducts in the presence of Fe/acetic acid in good to excellent yields. This system was compatible with various other functional groups.

1. Introduction

The synthesis of *N*-heterocycles is an important area of research in the present days due to their diverse therapeutic applications.[1] Among them, 1,4-benzoxazines are the important scaffolds present in various agrochemicals.[2] In particular, 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives are the interesting group of compounds known to possess useful biological and medicinal properties (Scheme 1). The compound **1** is a potential antibacterial agent and also acts as an inhibitor of bacterial histidine protein kinase.[3] Similarly, the 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid **2** was found to be potent immunostimulant.[4] The compound **3** possess D2 receptor antagonistic activity and is a potential antipsychotic agent.[5] Blepharin **4**, the 1,4-benzoxazine glycoside was isolated from rye and corn seeds of Blepharis edulispers, which is used to cure the anxiety, nervous tension, and over-sensitive stress disorders.[6]

Moreover, the molecules containing 2*H*-1,4-benzoxazin-3(4*H*)-one moieties are also known to exhibit other activities, such as anti-inflammatory,[7] antiulcer,[8] antipyretic,[9] antihypertensive,[10] antifungal,[11] potassium channel modulators,[12] antirheumatic agents,[13] and plant resistance factors against microbial diseases and insects.[14] Some of the other important 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives have been described in the recent review.[15]

Owing to the diverse biological activities of the compounds containing 2*H*-1,4-benzoxazin-3-(4*H*)-one moieties, several methods were developed towards the synthesis of these scaffolds. In this context, 2-halophenols,[16] 2-aminophenols or substituted 2-nitrophenols[17] were most commonly used as the starting materials



Scheme 1. 2*H*-1,4-benzoxazin-3-(4*H*)-one scaffolds in some biologically significant molecules.

for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones. With 2-aminophenols as the starting substrate, various protection and deprotection steps are required.[18] Whereas, with 2-nitrophenols involves only two steps. The first step is the O-alkylation with an appropriate base and the second step involves the reductive cyclization. The reductive cyclization reaction was reported with various reagents, such as Pd/C and $NaBH_4$ in aqueous dioxane,[19] $Sm/TiCl_4$ in THF,[20] Zn/NH_4Cl,[21] and Pd/C, H_2 in $CHCl_3$.[22] In addition to the above developments, reports emerged in the literature for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives using microwave irradiations[17f,23] and solid phase combinatorial synthesis.[24] However, most of the reported methods suffer from many short comings, such as long reaction times, low yields of the desired products, the use of expensive and explosive reagents.

The use of Fe/acetic acid in organic synthesis has been known for a long time. In the recent years, it has received considerable attention as an effective reagent for the reductive cyclization due to its availability, environmental safety, low cost, and functional group tolerance. The Fe/acetic acid was used for the synthesis of quinolines and its analouges,[25] double reductive cyclization reactions,[26]

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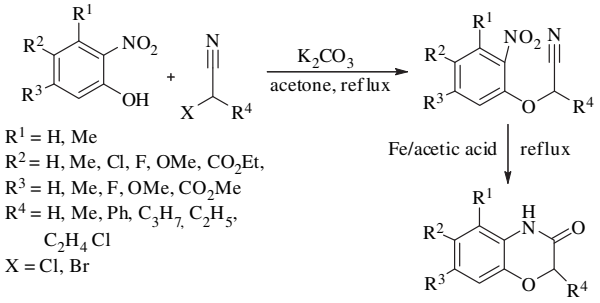
disubstituted α-methylene-γ-butyrolactams[27] and synthesis of tri and tetracyclic frame works containing [1,8]naphthyridin-2-one derivatives.[28] Recently, we reported the synthesis of indolylquinolines, 3,3′-biindoles and synthesis of quinoline derivatives via reductive cyclization in the presence of Fe/acetic acid.[29] Therefore, in continuation of our research work on Fe/acetic acid, we herein report a simple and facile procedure for one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives upon treatment of 2-(2-nitrophenoxy)acetonitrile adducts with Fe/acetic acid (Scheme 2).



Scheme 2. Route to the synthesis of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives.

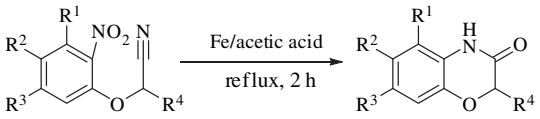
2. Results and discussion

Initially, we carried out the O-alkylation reaction of nitrophenols with chloroacetonitrile or bromoacetonitrile in the presence of K_2CO_3 in dry acetone under refluxing conditions. The *O*-alkylated adducts were obtained in 71–93% yields. However, **2p** and **2s** were prepared in the presence of K_2CO_3 in DMF at room temperature and **2t** was prepared in the presence of K_2CO_3 in acetonitrile under reflux conditions. In the second step, we were mainly interested for the search of a suitable reagent for the reduction of the nitro functionality and followed by cylization to afford the corresponding 2*H*-1,4-benzoxazin-3(4*H*)-ones. Inspired by our earlier results with Fe/acetic acid system,[29] we first examined the reaction of 2-(2-nitrophenoxy)acetonitrile **2a** adduct in the presence of Fe/acetic acid under refluxing conditions. We were pleased to obtain 2*H*-1,4-benzoxazin-3(4*H*)-one **3a** in quantitative yield. With this encouraging result in hand, we became interested to study some more derivatives of 2-(2-nitrophenoxy)acetonitrile adducts (**2a**–**u**) with Fe/acetic acid under the same reaction conditions.

We further probed the scope and limitations of this protocol by reacting various substituted 2-(2-nitrophenoxy)acetonitrile adducts (**2a**–**u**) with Fe/acetic acid under the same reaction conditions. The results are summarized in Table 1. It was observed that the reductive cyclization was not affected by any of the substituent present on the benzene ring of the 2-(2-nitrophenoxy)acetonitrile adducts. The substrates containing electron-donating groups (Table 1, entries 2, 5, 7, 9, and 11) as well as electron-withdrawing groups (entries 3, 4, and 8) reacted smoothly, giving good yields of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives. It is important to note that the reaction of 2-(2-nitrophenoxy)acetonitrile containing ester functionality furnished moderate yield of products (entries 6 and 10). The substrates containing methyl group at second position of the 2-(2-nitrophenoxy)acetonitrile adducts were afforded excellent product yields (entries 13–15). However, the presence of phenyl group at second position of the 2-(2-nitrophenoxy)acetonitrile adduct was produced moderate product yield (entry 16).

The substrates containing propyl and ethyl groups at second position of the 2-(2-nitrophenoxy)acetonitrile adducts reacted smoothly to its corresponding products in good yields (entries 17 and 21). In case of 4-(2-nitrophenoxy)butanenitrile we were not able to observe the expected product under the same reaction conditions. Moreover, *N*-acylated product was obtained (entry 18). A moderate

Table 1
Reductive cyclization of 2-(2-nitrophenoxy)acetonitrile adducts in the presence of Fe/acetic acid



2a-u **3a-u**

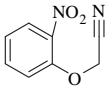
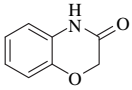
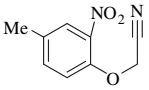
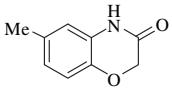
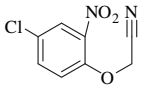
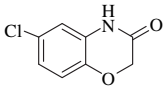
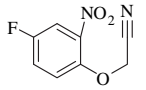
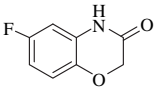
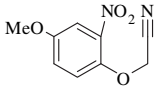
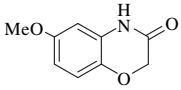
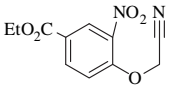
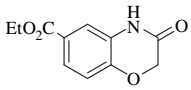
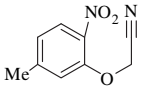
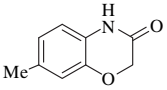
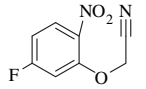
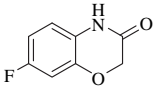
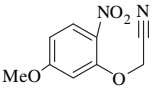
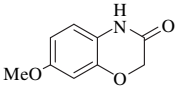
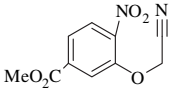
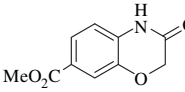
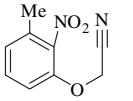
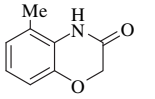
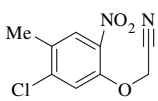
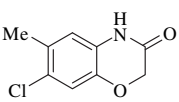
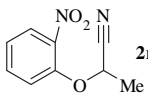
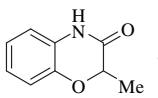
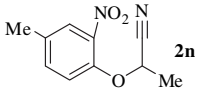
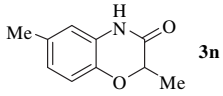
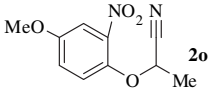
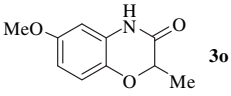
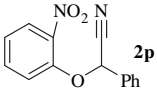
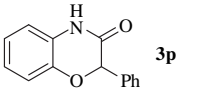
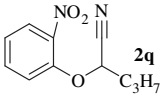
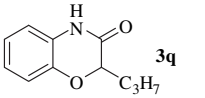
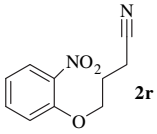
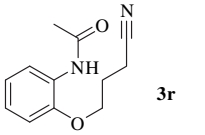
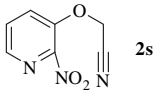
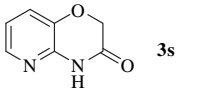
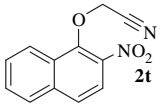
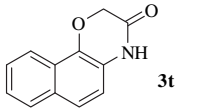
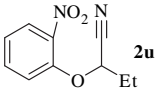
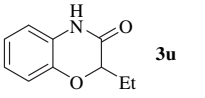
Entry	Substrate (2)	Product (3)	Yield[a,b]
1	 **2a**	 **3a**	93
2	 **2b**	 **3b**	90
3	 **2c**	 **3c**	91
4	 **2d**	 **3d**	93
5	 **2e**	 **3e**	91
6	 **2f**	 **3f**	54
7	 **2g**	 **3g**	90
8	 **2h**	 **3h**	93
9	 **2i**	 **3i**	90
10	 **2j**	 **3j**	55
11	 **2k**	 **3k**	91
12	 **2l**	 **3l**	90
13	 **2m**	 **3m**	94

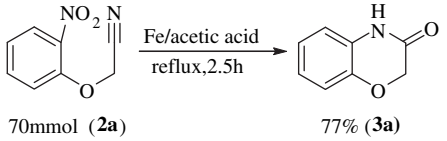
Table 1 (*continued*)

Entry	Substrate (2)	Product (3)	Yield[a,b]
14	 **2n**	 **3n**	95
15	 **2o**	 **3o**	93
16	 **2p**	 **3p**	81
17	 **2q**	 **3q**	84
18	 **2r**	 **3r**	71
19	 **2s**	 **3s**	77
20	 **2t**	 **3t**	79
21	 **2u**	 **3u**	81

[a] Isolated yields.
[b] All the reactions were carried out on 2 mmol scale under reflux for 2 h.

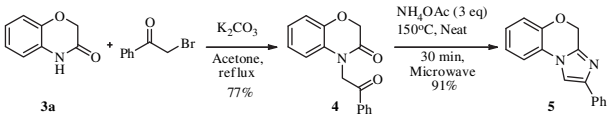
product yield was observed with 2-(2-nitropyridin-3-yloxy)acetonitrile adduct under same reaction condition (entry 19). It is note worthy that the reaction of 2-(2-nitronaphthalen-1-yloxy)acetonitrile underwent smoothly to produce its corresponding product in good yield (entry 20). The formation of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives can be explained by one-pot reductive cyclization of the substrates **2a**–**u** followed by in situ hydrolysis of its corresponding intermediates leading to the formation of the products (entries 1–21). All the 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives (**3a**–**u**) obtained were fully characterized by the spectral techniques IR, ^{1}H, ^{13}C NMR, and HRMS. To illustrate the scalability of our protocol, we performed the cyclization reaction with substrate 2-(2-nitrophenoxy)acetonitrile **2a** (70 mmol) in the presence of iron powder (418 mmol, 6 equiv) and acetic acid (50 ml). The desired product 2*H*-1,4-benzoxazin-3(4*H*)-one (**3a**) was obtained in 77% yield. Therefore, the multigram scale reaction resulted in decrease of the product yield and increase in the reaction time by 0.5 h in comparison with the reaction of milligram scale (Scheme 3).

The present methodology was applied for the synthesis of the 2-phenyl-4*H*-benzo[*b*]imidazo[1,2-*d*][1,4]oxazine fused tricyclic molecule (**5**). The benzoxazinone (**3a**) was treated with 2-bromo-1-phenylethanone in the presence of K_2CO_3 in acetone at reflux for 3 h to afford the compound **4** in good yield. This 4-(2-oxo-2-phenylethyl)-2*H*-benzo[*b*][1,4]oxazin-(4*H*)-one (**4**) was further treated



Scheme 3. Large-scale reaction of 2-(2-nitrophenoxy)acetonitrile (**2a**) to 2*H*-1,4-benzoxazin-3(4*H*)-one (**3a**).

with NH_4OAc (3 equiv) at 150 °C under neat reaction condition (solid phase) in microwave for 30 min to obtain **5** in high yield (Scheme 4). The structural elucidation was confirmed from the spectral analysis (IR, ^{1}H and ^{13}C NMR, and MS) also in comparison with the previous literature report by Sundaramurthy et al.[30] Although we noticed a marginal improvement in terms of yield, the main advantage associated with our procedure is solvent free conditions and lesser reaction time. Hence, we setup an improved procedure towards the synthesis of compound **5** over the existing method.



Scheme 4. Microwave assisted synthesis of 2-phenyl-4*H*-benzo[ ]imidazo[1,2-d][1,4] oxazine.

3. Conclusion

In conclusion, we developed an easy and convenient one-pot method for the synthesis of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives from 2-(2-nitrophenoxy)acetonitrile adducts under a conventional reducing reagent (Fe/acetic acid) afforded excellent yields. The desired products (**3a**–**u**) possessing alkyl, ester, halogen group(s) were well tolerated in this method. The present protocol has been applied for the synthesis of the 2-phenyl-4*H*-benzo[*b*] imidazo[1,2-*d*][1,4]oxazine fused tricyclic molecule (**5**).

4. Experimental

4.1. General

All the reactions were performed in oven (130 °C) dried glassware under an inert atmosphere of argon unless otherwise specified. Solvents for extraction and chromatography were distilled before use. All the chemicals used in this study were of commercial grade and used after distillation. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F_{254} aluminum plates. All purifications were carried out by flash chromatography using 230–400 mesh silica gel. ^{1}H and ^{13}C NMR were recorded with Bruker Avance EX 400 FT NMR. Chemical shifts were reported in parts per million (δ) using TMS as internal standard and coupling constants were expressed in hertz. Mass spectra were obtained on a JOEL SX-102A spectrometer at an ionization potential of 70 eV and data are reported as mass/charge (m/z) with the percent relative abundance. High-resolution mass spectra (HRMS) were acquired with a FINNIGAN MAT-95XL spectrometer. Microwave reactions were carried out in a commercially available monomode system (CEM Discover). The reactor has a variable power output from 0 to 300 W.

4.2. General procedure for the reductive cyclization (3a–u)

To a stirred solution of **2a** (2 mmol) in acetic acid (10 mL), powdered Fe (12 mmol) was added and the reaction mixture was then refluxed for 2 h. The progress of the reaction was monitored by

TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the acetic acid was removed under reduced pressure, EtOAc (20 mL) was added and was stirred for 2 min and then filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (20 mL). The filtrate and washings were combined and dried over anhydrous MgSO4. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography to obtain the pure product **3a**.

4.3. Procedure for the large-scale synthesis of 2*H*-1,4-benzoxazin-3(4*H*)-one (3a)

To a stirred solution of **2a** (70 mmol) in acetic acid (50 mL), powdered Fe (418 mmol, 6 equiv) was added and the reaction mixture was stirred for 2–5 min at room temperature and immediately the reaction mixture was cooled to 0 °C and stirred for 2 min in ice cold water bath (slightly exothermic) and the reaction mixture was then refluxed for 2.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the acetic acid was removed under reduced pressure, EtOAc (150 mL) was added and was stirred for 2 min, and then filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (100 mL). The filtrate and washings were combined and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography to obtain the pure product **3a**.

*4.3.1. 2H-benzo[b][1,4]oxazin-3(4H)-one (**3a**).* White solid; mp: 171–173 °C (Chloroform–DCM); IR(KBr)ν/cm^{-1}: 1707, 1660, 1606, 1501. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 6.97–6.85 (m, 4H), 4.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 143.8, 126.2, 124.4, 122.9, 116.9, 116.4, 67.3. MS (EI) (*m*/*z*) (relative intensity) 149 (M^+, 100), 120 (24). HRMS calcd for $C_8H_7NO_2$ (M^+) 149.0471 found 149.0478.

*4.3.2. 6-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3b**).* White solid; mp: 202–204 °C (Chloroform–DCM); IR(KBr) ν/cm^{-1}: 1702, 1651, 1606, 1521. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 6.85 (d, *J*=8.0 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 6.66 (s, 1H), 4.59 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 141.7, 132.7, 126.0, 124.9, 116.7, 116.6, 67.4, 20.8. MS (EI) (*m*/*z*) (relative intensity) 163 (M^+, 100), 134 (93). HRMS calcd for $C_9H_9NO_2$ (M^+) 163.0628 found 163.0633.

*4.3.3. 6-Chloro-2H-benzo[b][1,4]oxazin-3(4H)-one (**3c**).* White solid; mp: 209–211 °C (Chloroform–DCM); IR (KBr)ν/cm^{-1}: 1703, 1645, 1604, 1496. ^{1}H NMR (400 MHz, CDCl3) δ 8.46 (br s, 1H), 6.95–6.82 (m, 3H), 4.61 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 164.5, 141.6, 127.7, 126.5, 122.3, 116.8, 115.5, 66.5. MS (EI) (*m*/*z*) (relative intensity) 183 (M^+, 100), 153 (31). HRMS calcd for $C_8H_6{}^{35}ClNO_2$ (M^+) 183.0082 found 183.0090. $C_8H_6{}^{37}ClNO_2$ (M^+) 185.0052 found 183.0063.

*4.3.4. 6-Fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one (**3d**).* White solid; mp: 203–205 °C (Chloroform–DCM); IR(KBr) ν/cm^{-1}: 1704, 1651, 1624, 1514. ^{1}H NMR (400 MHz, $CDCl_3$, and DMSO-d_6) δ 10.46 (br s, 1H), 6.77–6.47 (m, 3H), 4.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 164.7, 157.3 (d, *J*=238.0 Hz), 139.1, 127.6 (d, *J*=11.0 Hz), 116.3 (d, *J*=9.0 Hz), 108.4 (d, *J*=24.0 Hz), 102.9 (d, *J*=27.0 Hz), 66.6. MS (EI) (*m*/*z*) (relative intensity) 167 (M^+, 100), 138 (63). HRMS calcd for $C_8H_6FNO_2$ (M^+) 167.0377 found 167.0385.

*4.3.5. 6-Methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one (**3e**).* Pale white solid; mp: 162–164 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1695, 1608, 1519, 1500. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 6.89–6.41 (m, 3H) 4.56 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 165.3, 154.6, 137.0, 127.4, 116.2, 107.4, 101.8, 66.8, 55.1. MS (EI) (*m*/*z*) (relative intensity) 179 (M^+, 100), 150 (30). HRMS calcd for $C_9H_9NO_3$ (M^+) 179.0577 found 179.0586.

*4.3.6. Ethyl 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylate (**3f**).* Yellow solid; mp: 130–132 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1715, 1699, 1616, 1493. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.60 (s, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 4.69 (s, 2H), 4.36 (q, *J*=7.0 Hz, 2H), 1.38 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.4, 147.4, 126.2, 126.1, 125.0, 117.8, 116.5, 67.2, 61.4, 14.4. MS (EI) (*m*/*z*) (relative intensity) 221 (M^+, 90), 193 (29), 176 (100), 164 (37). HRMS calcd for $C_{11}H_{11}NO_4$ (M^+) 221.0683 found 221.0687.

*4.3.7. 7-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3g**).* White solid; mp: 189–191 °C (Chloroform–DCM); IR(KBr) ν/cm^{-1}: 1686, 1522, 1443, 1402. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (br s, 1H), 6.78–6.74 (m, 3H), 4.59 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.7, 134.5, 123.7, 123.4, 117.4, 116.0, 67.4, 21.1. MS (EI) (*m*/*z*) (relative intensity) 163 (M^+, 100), 134 (45). HRMS calcd for $C_9H_9NO_2$ (M^+) 163.0628 found 163.0632.

*4.3.8. 7-Fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one (**3h**).* Pale white solid; mp: 204–206 °C (Chloroform–DCM); IR(KBr)ν/cm^{-1}: 1686, 1522, 1402. ^{1}H NMR (400 MHz, $CDCl_3$, and DMSO-d_6) δ 10.48 (br s, 1H), 6.80–6.52 (m, 3H), 4.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 164.0, 157.9 (d, *J*=239.0 Hz), 143.6 (d, *J*=12.0 Hz), 122.9, 116.0 (d, *J*=10.0 Hz), 108.2 (d, *J*=23.0 Hz), 103.7 (d, *J*=26.0 Hz), 66.5. MS (EI) (*m*/*z*) (relative intensity) 167 (M^+, 100), 138 (31). HRMS calcd for $C_8H_6FNO_2$ (M^+) 167.0377 found 167.0383.

*4.3.9. 7-Methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one (**3i**).* Pink solid; mp: 158–160 °C (EtOAc–hexane); IR(KBr) ν/cm^{-1}: 1678, 1515, 1438. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 6.77–6.49 (m, 3H), 4.59 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 156.8, 144.7, 119.7, 116.7, 108.2, 103.1, 67.3, 55.8. MS (EI) (*m*/*z*) (relative intensity) 179 (M^+, 100), 150 (40). HRMS calcd for $C_9H_9NO_3$ (M^+) 179.0577 found 179.0585.

*4.3.10. Methyl 3-oxo-3,4-dihydro-2H-benzo[b][1,4] oxazine-7-carboxylate (**3j**).* Pale yellow solid; mp: 245–247 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1723, 1706, 1612. ^{1}H NMR (400 MHz, $CDCl_3$, and DMSO-d_6) δ 10.75 (br s, 1H), 7.50 (d, *J*=8.2, 1H), 7.45 (s, 1H), 6.87 (d, *J*=8.2 Hz, 1H), 4.48 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 165.3, 164.3, 142.4, 131.1, 124.2, 123.6, 116.7, 115.2, 66.4, 51.3. MS (EI) (*m*/*z*) (relative intensity) 207 (M^+, 96), 176 (100). HRMS calcd for $C_{10}H_9NO_4$ (M^+) 207.0526 found 207.0534.

*4.3.11. 5-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3k**).* White solid; mp: 188–190 °C (Chloroform–DCM); IR(KBr)ν/cm^{-1}: 1679, 1498, 1401. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 6.88–6.81 (m, 3H), 4.58 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 144.0, 125.0, 124.8, 124.5, 123.6, 114.7, 67.2, 16.6. MS (EI) (*m*/*z*) (relative intensity) 163 (M^+, 100), 134 (80). HRMS calcd for $C_9H_9NO_2$ (M^+) 163.0628 found 163.0636.

*4.3.12. 7-Chloro-6-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3l**).* White solid; mp: 236–238 °C (Chloroform–DCM); IR(KBr)ν/cm^{-1}: 1701, 1644, 1647, 1505, 1405. ^{1}H NMR (400 MHz, $CDCl_3$, and DMSO-d_6) δ 10.46 (br s, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 4.40 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 164.1, 141.5, 129.4, 126.0, 125.7, 117.8, 115.5, 66.5, 18.8. MS (EI) (*m*/*z*) (relative intensity) 197 (M^+, 100), 168 (66). HRMS calcd for $C_9H_8{}^{35}ClNO_2$

(M^+) 197.0238 found 197.0247. $C_9H_8{}^{37}ClNO_2$ (M^+) 199.0209 found 199.0218.

*4.3.13. 2-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3m**).* White solid; mp: 140–142 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1679, 1609, 1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 6.97–6.86 (m, 4H), 4.67 (q, *J*=6.8 Hz, 1H), 1.59 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 143.3, 126.7, 124.2, 122.7, 117.1, 116.1, 73.4, 16.3. MS (EI) (*m*/*z*) (relative intensity) 163 (M^+, 100), 120 (36). HRMS calcd for $C_9H_9NO_2$ (M^+) 163.0628 found 163.0636.

*4.3.14. 2,6-Dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3n**).* White solid; mp: 144–145 °C (EtOAc–hexane); IR (KBr)ν/cm^{-1}: 1682, 1607, 1520. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (br s, 1H), 6.86–6.65 (m, 3H), 4.63 (q, *J*=6.8 Hz, 1H), 2.28 (s, 3H), 1.57 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 141.0, 132.4, 126.3, 124.7, 116.7, 116.5, 73.3, 20.7, 16.3. MS (EI) (*m*/*z*) (relative intensity) 177 (M^+, 100), 134 (50). HRMS calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0784 found 177.0793.

*4.3.15. 6-Methoxy-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3o**).* White solid; mp: 139–141 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1683, 1608, 1503. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 6.89–6.87 (m, 1H), 6.52–6.41 (m, 2H), 4.59 (q, *J*=6.8 Hz, 1H), 3.76 (s, 3H), 1.56 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 155.3, 137.3, 127.4, 117.5, 108.8, 102.2, 73.4, 55.9, 16.2. MS (EI) (*m*/*z*) (relative intensity) 193 (M^+, 100), 150 (35). HRMS calcd for $C_{10}H_{11}NO_3$ (M^+) 193.0733 found 193.0745.

*4.3.16. 2-Phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3p**).* White solid; mp: 160–162 °C (EtOAc–hexane); IR(KBr) ν/cm^{-1}: 1694, 1608, 1502, 1387. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 7.50–7.45 (m, 2H), 7.40–7.33 (m, 3H), 7.04–6.91 (m, 3H), 6.82–6.80 (m, 1H), 5.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 143.0, 135.3, 129.0, 128.8, 127.2, 126.0, 124.5, 122.8, 117.3, 116.3, 78.6. MS (EI) (*m*/*z*) (relative intensity) 225 (M^+, 100), 118 (20). HRMS calcd for $C_{14}H_{11}NO_2$ (M^+) 225.0784 found 225.0793.

*4.3.17. 2-Propyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3q**).* White solid; mp: 108–110 °C (EtOAc–hexane); IR(KBr) ν/cm^{-1}: 1682, 1609, 1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30(br s, 1H), 6.97–6.92 (m, 3H), 6.85–6.83 (m, 1H), 4.58 (dd, *J*=8.0, 4.8 Hz, 1H), 1.89–1.84 (m, 2H), 1.62–1.51 (m, 2H), 0.97 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 142.9, 127.5, 124.4, 123.3, 117.3, 116.4, 76.6, 32.5, 18.3, 14.1. MS (EI) (*m*/*z*) (relative intensity) 191 (M^+, 100), 149 (69). HRMS calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0941 found 191.0949.

*4.3.18. N-(2-(3-cyanopropoxy)phenyl)acetamide (**3r**).* White solid; mp: 92–94 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 2243, 1681, 1599, 1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.36 (m, 1H), 8.01 (br s, 1H), 7.01–6.95 (m, 2H), 6.84–6.8 (m, 1H), 4.15 (t, *J*=5.5 Hz, 2H), 2.57 (t, *J*=6.3 Hz, 2H), 2.24–2.19 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 148.4, 127.5, 124.2, 121.9, 121.0, 120.4, 111.8, 66.6, 24.7, 23.9, 13.5. MS (EI) (*m*/*z*) (relative intensity) 218 (M^+, 100), 176 (80), 108 (20). HRMS calcd for $C_{12}H_{14}N_2O_2$ (M^+) 218.1050 found 218.1057.

*4.3.19. 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (**3s**).* White solid; mp: 190–192 °C (EtOAc–hexane); IR(KBr) ν/cm^{-1}: 1707, 1609, 1513, 1468. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1H), 8.06 (d, *J*=4.4 Hz, 1H), 7.27 (d, *J*=7.2 Hz, 1H), 6.97 (dd, *J*=7.8, 5.0 Hz, 1H), 4.68 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 141.5, 141.0, 139.6, 124.0, 119.6, 67.3. MS (EI) (*m*/*z*) (relative intensity) 150 (M^+, 100), 95 (15). HRMS calcd for $C_7H_6N_2O_2$ (M^+) 150.0424 found 150.0432.

*4.3.20. 2H-naphtho[1,2-b][1,4]oxazin-3(4H)-one (**3t**).* Dark red solid; mp: 247–249 °C (EtOAc–hexane); IR(KBr) ν/cm^{-1}: 1683, 1414. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 8.08 (d, *J*=8.4 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.52–7.48 (m, 2H), 7.41 (t, *J*=7.5 Hz, 1H), 7.02 (d, *J*=8.6 Hz, 1H), 4.81 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, and DMSO-d_6) δ 164.4, 136.4, 129.8, 127.1, 125.6, 124.2, 123.9, 121.7, 121.5, 120.0, 116.1, 67.0. MS (EI) (*m*/*z*) (relative intensity) 199 (M^+, 100). HRMS calcd for $C_{12}H_9NO_2$ (M^+) 199.0628 found 199.0635.

*4.3.21. 2-Ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3u**).* White solid; mp: 80–82 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1676, 1609, 1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 6.98–6.92 (m, 3H), 6.81–6.79 (m, 1H), 4.51 (dd, *J*=8.1, 4.5 Hz, 1H), 1.98–1.88 (m, 2H), 1.09 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 143.1, 126.5, 124.3, 122.6, 117.1, 116.0, 78.2, 24.0, 9.5. MS (EI) (*m*/*z*) (relative intensity) 177 (M^+, 100), 149 (19), 120(23). HRMS calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0784 found 177.0794.

*4.3.22. 4-(2-Oxo-2-phenylethyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (**4**).* White solid; mp: 131–132 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1704, 1682, 1596, 1503. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.67–7.63 (m, 1H), 7.55–7.51 (m, 2H), 7.03–6.91 (m, 3H), 6.63–6.60 (m, 1H), 5.35 (s, 2H), 4.73 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 165.2, 145.3, 134.7, 134.2, 129.1, 128.9, 128.2, 124.2, 123.0, 117.2, 114.8, 67.6, 48.1. MS (EI) (*m*/*z*) (relative intensity) 267 (M^+, 100), 162 (20), 105 (28). HRMS calcd for $C_{16}H_{13}NO_3$ (M^+) 267.0890 found 267.0900.

4.4. Procedure for the preparation of starting material (4)

In an oven dried round-bottom flask, under a nitrogen atmosphere, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **3a** (2.0 mmol, 1 equiv) was dissolved in dry acetone (5 mL) and stirred with anhydrous K_2CO_3 (2.6 mmol, 1.3 equiv). 2-bromo-1-phenylethanone (2.4 mmol, 1.2 equiv) was added to the reaction mixture and refluxed fluxed for 3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (25 mL), washed with water (3×10 mL), brine (2×10 mL), and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (Yield 77%).

4.5. Procedure for the synthesis of 2-phenyl-4*H*-benzo[*b*] imidazo[1,2-d][1,4]oxazine (5)

4-(2-oxo-2-phenylethyl)-2*H*-benzo[*b*][1,4]oxazin-(4*H*)-one (4, 1mmol) was weighed in a 10 mL Emrys reaction vial, and NH_4OAc (3 equiv) was then added. Subsequently, the reaction vial was capped and then stirred for 15 s. The reaction mixture was irradiated at 150 °C (100 W) under neat reaction condition (solid phase) until TLC (petroleum ether/ethyl acetate) showed the disappearance of the starting material (30 min). The reaction mixture was then cooled to room temperature and then diluted with water, extracted with ethyl acetate followed by brine solution, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to obtain the crude product. The crude product was purified by column chromatography to furnish the pure product **5** as a white solid in 91% yield.

*4.5.1. 2-Phenyl-4H-benzo[b]imidazo[1,2-d][1,4]oxazine (**5**).* White solid; mp: 117–119 °C (EtOAc–hexane); IR(KBr)ν/cm^{-1}: 1602, 1537, 1507, 1427, 1242. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H), 7.63 (s, 1H), 7.43–7.39 (m, 2H), 7.34–7.29 (m, 2H), 7.16–7.09 (m, 3H), 5.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 143.1, 140.1, 133.5, 128.8, 127.5, 126.7, 125.1, 124.8, 122.9, 118.2, 115.6, 108.4, 64.3.

MS (EI) (*m*/*z*) (relative intensity) 248 (M^+, 100), 145 (10). HRMS calcd for $C_{16}H_{12}N_2O$ (M^+) 248.0944 found 248.0955.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.11.095.

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