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Microwave-assisted synthesis of novel [1,4] oxazine derivatives as potent anti-bacterial and antioxidant agents

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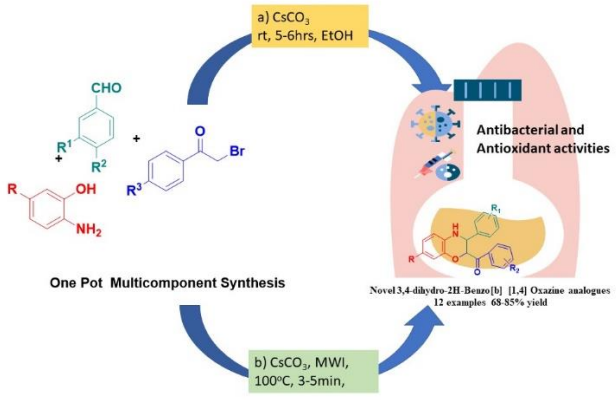
Abstract

A library of 12 members of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines has been synthesized from substituted 2-aminophenols, benzaldehydes and phenacyl bromides via one-pot multicomponent reactions using Cs_2CO_3 as a base catalyst, by both conventional and microwave-assisted heating. Microwave assistance reduced the reaction time and solvent, improved the yield, purity, and made the work-up easier. The results suggested that the products possess moderate to good antibacterial activity. These findings imply that the synthesized compounds may make excellent candidates for further studies aimed at discovering novel antibacterial agents. In vitro antioxidant qualities of the synthesized oxazines are evaluated. In the tests for reducing power and radical scavenging, all the compounds demonstrated strong antioxidant activity—even surpassing that of the positive control, Trolox.



Keywords: Oxazine; microwave; multicomponent reaction; antibacterial; antioxidant

Introduction

Oxazines are an important class of heterocycles and are a recognizable element in a number of natural products known for their biological activity and pharmacological significance.[1–3] They exhibit encouraging outcomes in differing degrees and function as anticancer, antimicrobial, anti-mycobacterial tuberculosis, platelet aggregation inhibition, anti-stress oxidative etc. These heterocycles have the potential to contribute to the production of better materials that will further improve the environment and humanity as a whole.[4–14]

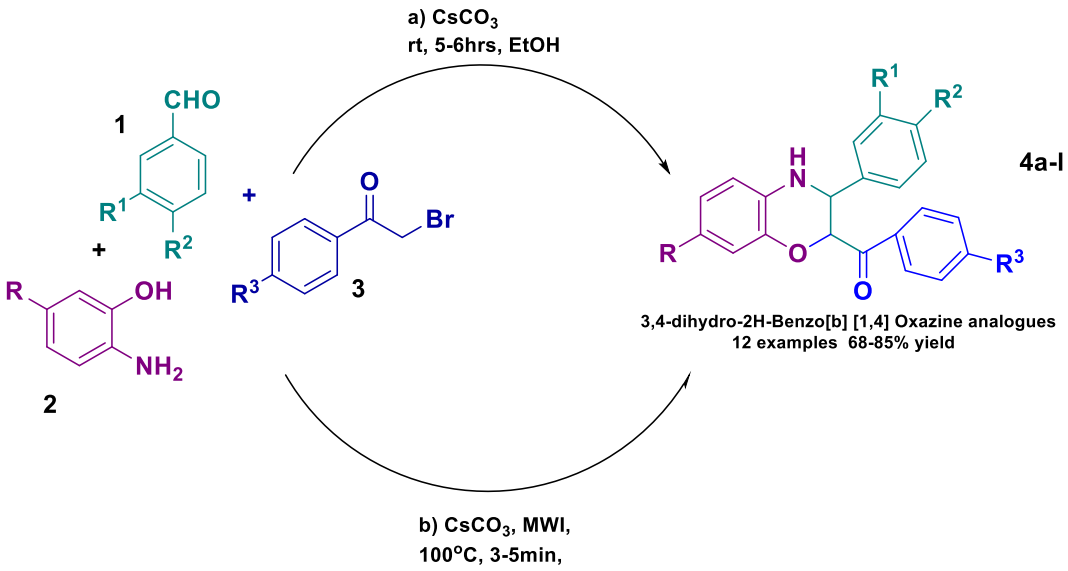
Many 1,4 Oxazines are already either approved as drugs or are currently undergoing clinical trials approaching the late developmental stages.[15–18] The importance of 1,4-benzoxazines has led to various approaches to synthesize of their derivatives. Substituted 2-aminophenols or substituted 2-nitrophenols are commonly used. [19–22] Oxazine syntheses which involve the creation of oxazine rings, can present several challenges and problems. Some common issues encountered during the synthesis of oxazine compounds require precise control of reactivity to prevent unwanted side reactions. For example, intermediates or reagents might be highly reactive, leading to multiple by-products. Achieving selective formation of the desired oxazine isomers can be difficult due to the presence of multiple reactive sites in the starting materials or intermediates. The synthesis of oxazines can sometimes result in low yields due to the formation of side products or incomplete reactions. Purifying the final oxazine product from reaction mixtures can be challenging, particularly if the by-products have similar physical and chemical properties. Some oxazine syntheses require harsh conditions such as high temperatures, strong acids or bases, or specific catalysts, which can limit the choice of substrates and make the process less environmentally friendly. Certain intermediates or reagents used in oxazine synthesis may be sensitive to moisture or air, requiring an inert atmosphere and specialized handling.

Sharma *et al.* reported several synthetic benzoxazines as potential antioxidant agents.[23] This led us to synthesize more non-naturally occurring benzo[1,4]oxazines analogs. We have recently reported the synthesis of fifteen 2*H*-benzo[*b*][1,4]oxazines using microwave irradiation. All the synthesized compounds were screened for their efficacy as antibacterial and antioxidants and showed good results. Drawing on each of the preceding considerations and as an extension of our studies on the establishment of new strategies for the synthesis of oxazines,[24–27] we report a facile method for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines (Scheme 1). Cesium carbonate is used as a base catalyst because of its high solubility and cesium cation is known for its softness. Cesium carbonate is highly soluble in organic solvents such as alcohol, DMF, and diethyl ether. It promotes successful amine carbonation due to its high solubility in polar solvents only and additionally suppresses common side effects associated with other protocols. Multicomponent reactions are used as promising one-pot techniques for creating and modifying compound libraries using combinatorial chemistry. Comparison research was also reported, demonstrating the advantages of the microwave method over a more conventional method in terms of reaction time. Under microwave irradiation, the reactions that had taken hours under ambient conditions were completed in a matter of minutes, with increase in yields and less byproducts.

Results and Discussion

Synthesis. Our investigation started initially with the reaction of as 2-aminophenol (1.0 mmol), 4-nitro benzaldehyde (1.0 mmol) and 4-bromophenacyl bromide (1.0 mmol), and in the presence of Cs_2CO_3 (1.5 mmol) in ethanol (10 mL). (Entry 1, Table 1) As is to be expected, when the domino reaction is conducted at room temperature in the presence of Cs_2CO_3, it proceeded to produce the desired product **4a** in good yield. Following an extractive work-up, separation was carried out via silica gel chromatography to afford a pure product of yield

40-85%. We also noticed that yields are higher and that using Cs_2CO_3 as the base is generally easier to work up with higher yields. The reaction did not proceed without base. An identical outcome was achieved when the same reaction when carried out in a microwave digester, but in less time. Reactions under conventional method were observed to have taken longer time to complete with comparatively lower yields (Table 1). The same reactions assisted by microwave at 150 W power output and at 100 °C temperature gives high purity of products in shorter time.



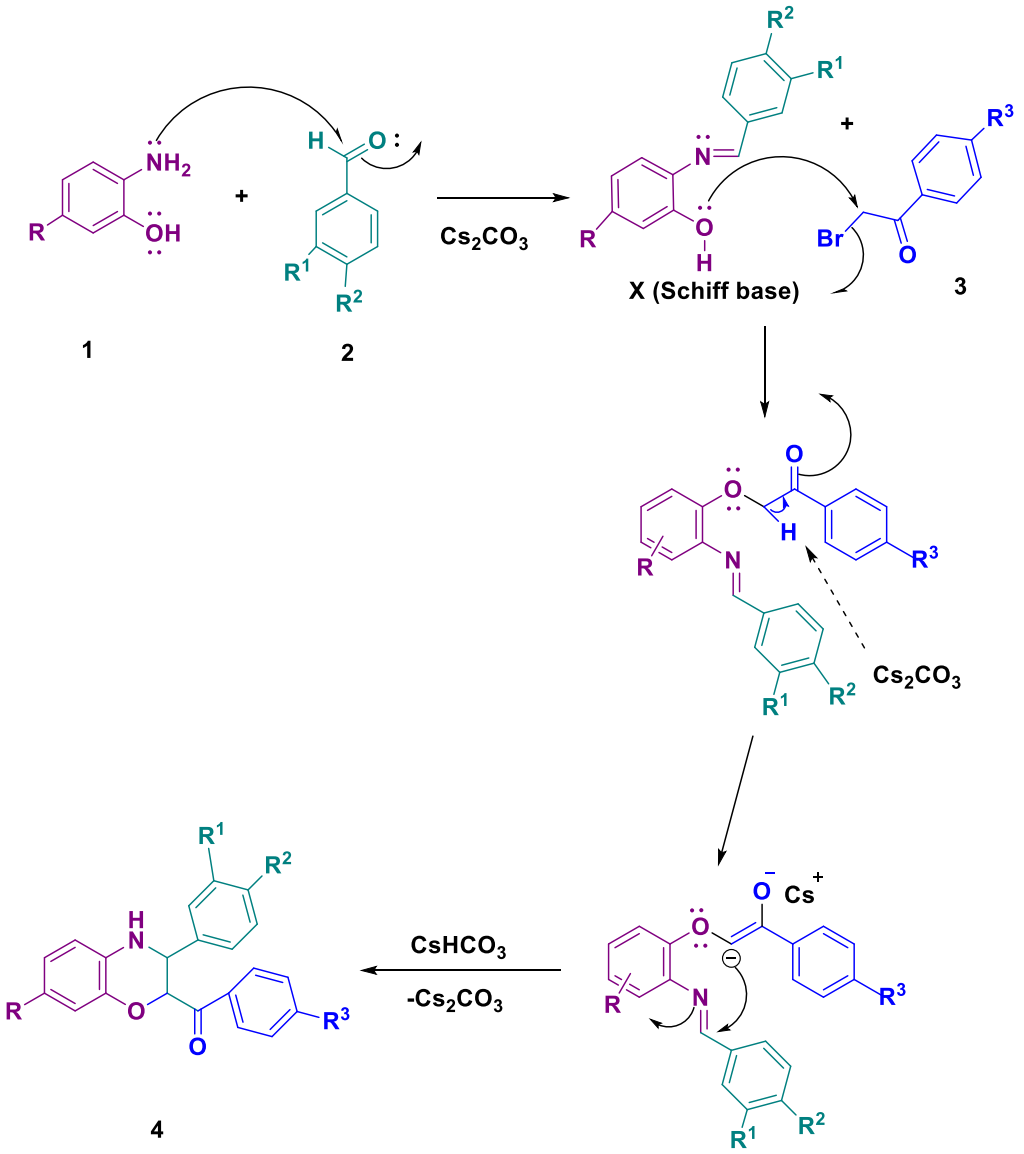
Scheme 1. Synthesis of 3,4-dihydro-2*H*-Benzo[b] [1,4] Oxazines.

Table 1. List of synthesised compounds

Product	R	R^1	R^2	R^3	Reflux [a]		Microwave irradiation [b]	
					Time taken (hours)	Yield (%)	Time taken (minutes)	Yield (%)
4a	H	H	NO_2	Br	6	50	5	80
4b	CH_3	H	NO_2	Cl	8	67	3	75
4c	CH_3	H	Cl	CH_3	9	65	3	79
4d	H	H	Br	CH_3	7	48	3	82
4e	H	H	OCH_3	NO_2	9	40	5	85
4f	CH_3	H	CH_3	Cl	6	50	4	68
4g	H	H	OH	CH_3	5	70	5	76
4h	H	H	CH_3	Br	7	85	4	75
4i	CH_3	H	Cl	OCH_3	9	65	4	82
4j	H	CH_3	CH_3	OCH_3	6	44	3	80
4k	H	H	CH_3	OCH_3	7	63	3	77
4l	CH_3	H	NO_2	H	8	56	4	83

Reaction Conditions: a) room temperature, ethanol 10 ml, DMAP, $CsCO_3$ b) MW, 100 ^oC, Cs_2CO_3

Based on the experimental findings and previously published literature, [28,29] a tenable mechanism is postulated, as outlined in Scheme 2. The reaction proceeds by means of the amine of **1** (amino phenol) adding to the aldehyde carbonyl carbon, which then proceed via a proton shift and dehydration, forms the imine/Schiff-base intermediate **X**. 2. The phenolic hydroxyl the α-carbon of the phenacyl bromide **3**, proceeding though with base-mediated intramolecular cyclization, to the corresponding 1,4-benzoxazines **4**. To support this mechanism, the intermediate **Xa** (R=H, R^1=H, R^2= NO_2) of the first entry as an example reaction, was isolated and characterized by mass spectrometry, carbon and proton NMR.



Scheme 2. Plausible reaction pathway via formation of imine/ Schiff-base (X) as intermediate.

Antibacterial activity

Antimicrobial activity was tested against two strains of gram-positive bacteria and two strains of gram-negative bacteria and compared to streptomycin which was used as the standard. Compounds **4j** and **4g** showed the most inhibition against two out of four bacteria strains with inhibition zone of 19mm for *Escherichia coli* (EC) and *Bacillus subtilis* (BS). Compound **4f** also showed good inhibition against all the bacteria strains with inhibition

zone of 18mm for *Klebsiella pneumonia* (KP), and 17mm for *Bacillus subtilis* (BS). Compound **4k** showed the most negligible inhibition to almost no inhibition.

Further, to quantify its anti-bacterial activity Minimum Inhibitory Concentration (MIC) of all the compounds was determined. Compound **4j** exhibited the minimum inhibition concentration for most bacterial strains with MIC (mg/l) value of 0.005 for Klebsiella *pneumonia* (KP) and *Bacillus subtilis* (BS) and 0.187 for *Staphylococcus aureus* (SA). Overall, all the compounds are observed to be promising antibacterial agents.

Antioxidant Activities

2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity: The radical scavenging activities of the synthesized oxazines at different concentrations (20, 40, 60, 80 and 100 µg/ml) were studied with 2,2-diphenyl-1-picrylhydrazyl (DPPH) using Trolox as the positive control**.** The concentration of each compound required to scavenge 50% of the DPPH radical present in the assay medium was established and referred to as IC_{50}. IC_{50} is thus defined as the amount of the antioxidant needed to halve the concentration of DPPH present in the test solution. The lower the value of IC_{50} value the better the DPPH radical scavenging activity. The reduction in absorbance of DPPH radicals at 517nm caused by antioxidants was used to assess their capacity for reduction. All the compounds showed higher antioxidant activity than Trolox whose IC_{50} was 79.86 µg/ml.

Ferric reducing antioxidant power (FRAP) assay: Another popular nonradical method for measuring the antioxidant capacity is the FRAP assay. It depends on reducing ferric ion (Fe^{3+}) into ferrous ion (Fe^{2+}). This assay primarily assesses the reducing capacity of an antioxidant when it reacts with Fe^{3+} ($K_3Fe(CN)_6$) to produce a colored Fe^{2+} ($K_3Fe(CN)_6$) complex. Potassium ferricyanide is employed as a ferric-binding reagent, resulting in a blue-colored ferrous complex that was spectrophotometrically evaluated, demonstrating reducing power of the the antioxidant. Increased absorbance at 700 nm suggests antioxidant activity. The ability of any compound to donate an electron or hydrogen atom to a metal atom is accountable for its reducing power. The synthesized compounds were assayed over a range of dilutions (20, 40, 60, 80 and 100 µg/ml) and the results in the form of absorbance.

While all the compounds showed antioxidant activity, the compound 3-(4-ethoxyphenyl)-6-methyl-2*H*-benzo[*b*] [1,4] oxazine **(4d)** was observed to act as a better antioxidant in both radical scavenging and reducing power assay.

Structure activity relationship

The results of antimicrobial activity are significantly impacted by the different substituents on the aromatic ring of compounds (**4a–l**). Electron-donating and -withdrawing groups when introduced at *para* position of the aromatic benzene rings increased antibacterial potency of the compounds. Compound **4j** containing methoxy groups at *meta* and *para* positions (R^1, R^2, R^3) showed maximum effect against E. *coli*, and B. *subtilis* i.e., inhibition at MIC 0.005 mg/L^{-1} for both. Compounds **4d** and **4g** containing methyl at para positions (R^3) showed significant inhibition against *B. aureus* at MIC 0.023 mg/L^{-1} for both. The inhibition activity was reduced with the introduction of electron-withdrawing chloro and nitro groups at R^2 position as shown by compounds **4c** and **4l.** The presence of an electron-withdrawing group (**4a, 4b)** along with a nitro group at *para* position of the substituted benzene ring (R^2) added to the results with good activity shown against all the gram positive and gram-negative bacteria bus lesser in comparison to the methyl and methoxy containing compounds. Compound **4d**, with bromo group at R^2 showed significant potency against *S. aureus* at MIC 0.023 mg/L^{-1}. In case of antibacterial activity against K.P, compound **4f** having electron withdrawing chloro group on R^2 and methyl groups at R and R^3 was found to be the most active. The strain S. *aureus* was observed to be resistant toward

synthesized compounds **4c** and **4i**, while compound **4k** showed no inhibition against *E. coli* and *B. subtilis* MIC results displayed that substitution of electron-withdrawing groups on the benzene ring showed lesser potency than electron donating group. The good potencies against both Gram-positive and Gram-negative bacteria make these derivatives promising leads for further investigations.

Data of antioxidant activity revealed that compounds **4d, 4i, 4l** with methyl group on R^3 substitution of benzene ring showed excellent activity with IC_{50} values of 43.98, 49.96 and 48.35 μg/L^{-1}, which is significantly lower than the value of the positive control Trolox. Compounds **4a, 4b,** and **4e** with presence of nitro group at R^2 or R^3 also showed to have good antioxidant activity with IC_{50} values of 54.29, 54.29 and 51.69 μg/L^{-1} respectively. The introduction of methyl group at R^3 position along with the nitro group at R^2 seemed to have increased the activity as shown by compound **4l**.

Conclusions

In summary, a simple domino reaction was devised to produce variously substituted 1,4-benzoxazines from readily available starting materials. This is the first report on the antibacterial and antioxidant activities of the 3,4-dihydro-2*H*-benzo[b][1,4]oxazine analogues. This method allows for easy access to novel bioactive heterocyclic compounds 1,4-benzoxazines. The established protocol has a broad substrate scope, high functional group tolerance, and high atom and step efficiency. The reaction proved to be cost-effective and timesaving because it took only a few minutes to complete. This method is being actively pursued for the synthesis of other pharmaceutically promising compounds, and the results will be available soon. The halogen atoms in synthesized products provide additional opportunities for post-functionalization. The screening tests were performed for four bacterial strains *Bacillus subtilis* (BS), *Staphylococcus aureus* (SA), *Escherichia coli* (EC) and *Klebsiella pneumonia* (KP) to study the potential antibacterial properties of the synthesized compounds. Evaluations of the compounds **4a–l** revealed that they presented notable activities against all the strains. These results suggest that the synthesized compounds can be good nominees for future investigations to find new antibacterial agents. The in vitro antioxidant properties of the synthesized oxazines were assessed using 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and Ferric reducing antioxidant power (FRAP) assay. All of the compounds showed good antioxidant activity, even higher than the positive control Trolox in both radical scavenging and reducing power assay.

Experimental Section

General. All reagents were purchased from Merck and used without purification. Reactions were carried out in Microwave Digester (Anton Paar Monowave 400). Melting points were measured on an Ikon melting point apparatus and compared with reported values of known compounds. IR spectra were recorded on an FTIR spectrometer (Perkin Elmer 1725X, Model: Spectrum Two FT-IR). Mass spectra were recorded on mass spectrophotometer (Advion expressions). NMR spectra were recorded with a Bruker spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) in $CDCl_3$ as solvent and with TMS as internal standard, and chemical shifts are expressed as d/ppm.

General procedure for preparation of *2H*-benzo[*b*][1,4]oxazines under reflux conditions. Aminophenol **1** (1 mmol), benzaldehyde **2** (1 mmol), phenacyl bromide **3** (1mmol) along with base Cs_2CO_3(1.50mmol), ethanol (10

ml) were taken in a round bottom flask and stirred at rt for 5-8 h. The reaction progress was monitored by thin layer chromatography (TLC) using Silica coated aluminium plates in 20% ethyl acetate/hexane. The crude product was purified using silical gel column chromatography (Silica gel, Merck, 100-200 mesh) or by repeated recrystallization in warm ethanol.

General procedure for preparation of 2*H*-Benzo[*b*][1,4]oxazines under microwave irradiation. Aminophenol **1** (1 mmol), benzaldehyde **2** (1 mmol), phenacyl bromide **3** (1mmol) along with base Cs_2CO_3(1.50mmol), and a few drops of aqueous ethanol were taken in a Pyrex test-tube (Glass vial G10ml) and irradiated for 3-5 minutes at 100 ^oC. The reaction progress was monitored by thin layer chromatography (TLC) using Silica coated Aluminium plates in 20% ethyl acetate/hexane. The crude product was purified using silica gel column chromatography (Silica gel, Merck, 100-200 mesh) or by repeated recrystallization in warm ethanol.

The structures of all the synthesized molecules were established by spectral analyses (IR, ^{1}H NMR, ^{13}CNMR, and mass) data. All the synthesized compounds showed appropriate characteristic signals, which confirm their structures. The data are given below.

Intermediate Xa. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.32 (d, 2H), 8.09 (d, 2H), 7.34 (m, 2H), 7.06 (s, 1H), 6.94 (s, 1H) ppm, ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.83, 152.88, 149.30, 141.14, 134.45, 130.46, 129.32, 124.16, 120.37, 115.90, 115.62 ppm, MS: *m/z* 224 (M^+).

4-Bromophenyl)(3-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (4a). Yield: 80%, m.p. 141°C, IR (KBr) ϑ: 3366, 3025, 2891, 1679, 1428, 1438, 1429, 1357, 1322, 1252, 1198, 1126, 975, 729, 677, 615 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.76 (s, 2H), 8.33-8.32, (d, 2H), 8.30-8.29 (d, 2H), 8.07-8.06 (d, 2H), 7.35-7.32 (m, 1H), 7.33 (s, 1H), 6.93 (m, 2H), 6.25, (s, 1H), 5.25 (s, 1H), 5.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.12, 153.84, 152.87, 149.31, 141.14, 134.48, 130.60, 129.29, 129.05, 124.30, 124.13, 123.92, 120.36, 115.91, 115.62, 78.94, 54.38.ppm. MS: *m/z* 436 (M^+).

4-Chlorophenyl)(7-methyl-3-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (**4b).** Yield: 75%. m.p. 89 °C, IR (KBr) ϑ: 3361, 3026, 2878, 1656, 1494, 1468, 1435, 1356, 1318, 1268, 1132, 1137, 988, 731, 669, 626 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.39 (m, 3H), 8.33 (d, J=8.1 Hz, 2H), 8.11 – 8.08 (m, 2H), 7.29 – 7.00 (m, 4H), 4.21(d, J = 9.5 Hz, 3H), 1.28 (d, J=8.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.35, 153.90, 152.88, 151.13, 149.65, 141.14, 140.06, 134.50, 130.50, 129.32, 129.25, 128.83, 124.63, 120.35, 115.91, 78.43, 61.32, 22.98 ppm. MS: *m/z* 408 (M^+).

3-(4-Chlorophenyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)(*p*-tolyl)methanone (4c). Yield: 97%. m.p. 162 °C, IR (KBr) ϑ: 3356, 3024, 2894, 1663, 1424, 1416, 1401, 1352, 1335, 1257, 1208, 1178, 975, 732, 689, 613 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J= 8.3 Hz, 2H), 7.27 – 7.05 (m, 6H), 6.96 – 6.94 (s, 1H), 6.29 (d, J= 7.0 Hz, 1H), 5.58– 5.50(d, J=6.7 Hz, 1H), 5.30– 5.24 (d, J=7.1 Hz, 1H), (s, 1H), 5.11 (s,1H), 2.48 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.33, 141.15, 140.04, 134.48, 130.49, 129.30, 124.42, 124.31, 124.14, 123.69, 123.42, 120.38, 115.90, 114.21, 78.81, 68.17, 55.45, 23.74, 22.99 ppm MS: *m/z* 379 (M^+).

(3-(4-Bromophenyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-2-yl)(*p*-tolyl)methanone (4d). Yield: 112%. m.p. 162 °C, IR (KBr) ϑ: 3376, 3054, 2868, 1673, 1528, 1448, 1414, 1370, 1362, 1253, 1134, 1123, 981, 737, 667, 608 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.76– 7.47 (m, 4H), 7.29– 7.21(m, 2H), 7.15 – 7.00, (d, J=6.1 Hz, 1H), 6.94 – 6.92(d, J=6.7 Hz, 1H), 6.75– 6.64 (d, J=7.6 Hz,1H), 6.57– 6.52 (d, J=6.9 Hz, 1H), 6.28– 6.30 (d, J=8.0 Hz, 1H), 5.28 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.15, 152.65, 151.85, 139.98, 134.64, 131.90, 130.97, 130.25, 128.47, 127.74, 123.31, 122.59, 118.90, 118.76, 117.90, 78.28, 60.58, 21.07, 14.18 ppm. MS: *m/z* 407 (M^+).

4-Methoxyphenyl)(3-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (4e). Yield: 85%. m.p. 82 °C, IR (KBr) ϑ: 3378, 2964, 2913, 2875 1554, 1511, 1276, 1420, 1031, 813, 723, 678, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23(d, 2H), 7.77 – 7.62 (d, J=.6.3 Hz, 2H), 7.59– 7.57 (d, J=7.5 Hz, 2H), 7.35 – 7.23, (d, J=7.7 Hz,

2H), 7.04 – 6.56 (m , 5H), 5.35 (s, 1H), 5.21 (s, 1H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 164.19, 148.25, 147.64, 147.00, 142.51, 131.57, 128.68, 127.87, 124.00, 123.85, 119.29, 115.53, 114.60, 113.92, 78.53, 77.39, 77.07, 76.75, 57.77, 55.81 ppm. MS: *m/z* 391 (M^+).

4-Chlorophenyl)(7-methyl-3-(p-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (4). Yield: 109%. m.p. 162 °C, IR (KBr) ϑ: 3392, 3037, 2975, 2913, 1679, 1617, 1487, 1431, 1256, 1208, 1083, 1013, 811, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (d, J=7.5 Hz, 2H), 7.46 – 7.40 (d, J=8.0 Hz, 2H), 7.34– 7.24 (d, J=8.5 Hz, 2H), 7.13 – 6.95 (d, J=8.3 Hz, 2H), 7.88 – 6.71(d, J=7.1, 2H), 6.67 – 6.31 (m, 2H), 5.33 (s, 1H), 5.22 (s, 1H), 2.31 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.18, 156.98, 156.84, 152.21, 149.68, 149.41, 135.68, 129.34, 129.15, 128.95, 128.86, 124.56, 116.67, 114.62, 110.54, 108.84, 78.20, 55.59, 20.93, 20.83 ppm. MS: *m/z* 378 (M^+).

3-(4-Hydroxyphenyl)-3,4-dihydro-2*H*-benzo*[b]*[1,4]oxazin-2-yl)(*p*-tolyl)methanone (4g). Yield: 76%. m.p. 122 °C, IR (KBr) ϑ: 3381, 2370, 2240, 1674, 1491, 1465, 1409, 1347, 1321, 1249, 1173, 1118, 983, 773, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.95 (d, J=8.5 Hz 2H), 7.81 – 7.56 (m, 2H), 7.34– 7.17 (m, 2H), 7.09 – 7.00 (m, 2H), 6.59 (s, 1H), 6.59– 6.40 (d, J=8.0, 1H), 5.39 (s, 1H), 5.23 (s, 1H), 2.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.35, 155.20, 151.43, 149.58, 140.65, 135.14, 130.52, 129.99, 129.87, 129.56, 125.33, 124.23, 116.74, 116.28, 115.91, 78.12, 59.11, 29.72 ppm. MS: *m/z* 345 (M^+).

4-**Bromophenyl)(3-(*p*-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (4h).** Yield: 75%. m.p. 95 °C, IR (KBr) ϑ: 3387, 2952, 2914, 2357, 2334, 1689, 1615, 1579, 1505, 1323, 1289, 1117, 1028, 913, 845, 810, 748, 517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.85 (d, J=8.7 Hz, 2H), 7.65 – 7.53 (m, 2H), 7.30– 7.03 (m, 4H), 6.93– 6.80 (m, 2H), 6.77 – 6.66 (m, 2H), 6.35 (s, 1H), 5.39 (s, 1H), 5.22 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.91, 153.97, 153.79, 152.64, 148.69, 137.42, 134.44, 134.12, 130.12, 128.85, 125.79, 123.26, 120.35, 115.99, 115.57, 78.66, 52.24, 29.74 ppm. MS: *m/z* 407 (M^+).

3-(4-Chlorophenyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)(4-methoxyphenyl)methanone (4i). Yield: 82%. m.p. 98 °C, IR (KBr) ϑ: 3391, 2963, 2919, 2865, 1590, 1512, 1267, 1422, 1032, 811, 747, 682cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 2H), 7.49 (s, 2H), 7.25– 7.24 (m, 2H), 7.13 – 6.67 (m, 2H), 6.60 – 6.54 (d, J=7.8 Hz, 1H), 6.40 – 6.28 (m , 1H), 6.19 – 6.08 (m, 1H), 6.19 – 6.08 (m, 2H), 5.38 (s, 1H), 5.21 (s, 1H), 3.95 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.04, 158.38, 152.70, 150.50, 149.50, 143.21, 130.06, 128.67, 127.76, 127.01, 117.97, 117.94, 116.41, 109.47, 108.82, 78.45, 56.21, 55.60, 29.64 ppm. MS: *m/z* 396 (M^+).

(3-(3,4-Dimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)(*p*-tolyl)methanone (4j). Yield: 80%. m.p. 100 °C, IR (KBr) ϑ: 3380, 2959, 2926, 2858, 1589, 1513, 1209, 1405, 1023, 812, 751, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.58 (s, 2H), 7.49– 7.30 (d, J=8.1 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.01 – 6.95 (d, J=8.7 Hz, 2H), 6.68 – 6.56 (d, J=8.1 Hz, 2H), 5.39 (s, 1H), 5.25 (s, 1H), 3.95 – 3.99 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.63, 163.52, 153.66, 150.69, 148.56, 137.32, 130.58, 130.52, 128.74, 127.47, 125.19, 122.94, 119.57, 118.50, 117.10, 114.92, 113.14, 78.25, 56.24, 55.88, 55.56 ppm. MS: *m/z* 469 (M^+).

4-Methoxyphenyl)(3-(*p*-tolyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanone (4k). Yield: 77%. m.p. 107 °C, IR (KBr) ϑ: 3371, 2932, 1679, 1612, 1508, 1318, 1247, 1100, 1012, 817, 732 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 8.26 (s, 2H), 7.88 – 7.73 (m, 2H), 7.70– 7.45 (m, 2H), 7.43– 7.40 (m, 2H), 7.31 – 7.04 (m, 2H), 6.92 – 6.90 (d, J=8.1, 1H), 6.78 – 6.76 (d, J=7.8 Hz, 2H), 6.65 – 6.26 (d, J=8.7 Hz, 2H), 5.42 (s, 1H), 5.23 (s, 1H), 3.93 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.49, 153.29, 147.82, 144.96, 134.71, 134.61, 129.09, 128.84, 126.20, 124.36, 122.52, 121.14, 119.46, 115.33, 113.49, 78.79, 56.52, 56.04, 19.03 ppm. MS: *m/z* 360(M^+).

(7-Methyl-3-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)(phenyl) methanone (4l). Yield: 83%. m.p. 98 °C, IR (KBr) ϑ: 3378, 2358, 2341, 1676, 1613, 1529, 1488, 1469, 1415, 1347, 1321, 1247, 1197, 1098, 983, 757, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.55 (d, J=8.1 Hz, 2H), 7.90– 7.70 (m, 4H), 7.49– 7.33 (m, 2H), 7.25 – 7.23 (m, 1H), 7.04 – 7.02 (m, 2H), 6.93 – 6.91 (m, 2H), 6.81 – 6.62 (m, 1H), 5.35 (s, 1H), 5.22 (s, 1H),

2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.31, 149.64, 147.94, 142.23, 133.09, 130.89, 129.43, 128.35, 127.92, 125.62, 123.50, 123.43, 118.88, 117.36, 114.03, 78.56, 60.65, 27.33 ppm. MS: *m/z* 374 (M^+).

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Supplementary Material

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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