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Graphical Abstract

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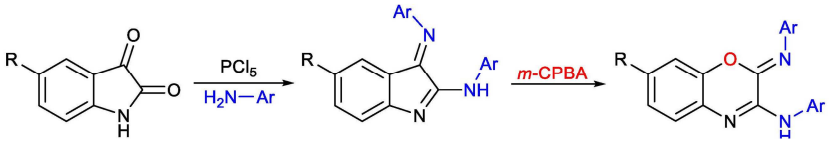

A simple route for the synthesis of novel 1,4-benzoxazine derivatives by Baeyer-Villiger oxidation reaction

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ABSTRACT

Novel 1,4-benzoxazine derivatives were synthesized by an efficient and simple method in high yields. Readily available starting materials, operational simplicity, mild reaction conditions and novelty are the key advantages of this method. The synthetically attractive feature of the procedure is reflected by its applicability to a wide range of isatin and aniline derivatives. Besides their novel structures, these compounds may have important biological activities and industrial applications. Furthermore, we demonstrated that in Baeyer-Villiger oxidation reaction, the phenyl group migrate better than amidine groups but not as good as amide group. The migratory ability for these groups in Baeye-Villiger oxidation reaction is ranked amide > phenyl > amidine.

Keywords:
1,4-Benzoxazine
Baeyer-Villiger oxidation
N-oxide
Isatin
Heterocyclic

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1. Introduction

Heterocyclic rings having heteroatoms at 1,4-positions and fused to a benzene ring are fundamental components in medicinal chemistry due to their wide range of therapeutic and biological properties. Among them, 1,4-benzoxazines have been an integral part of molecular skeletons for design of a variety of biologically active compounds.[1-9] According to their substituents, these compounds are potential drugs for treating infections,[10] diabetes,[11] heart disease, inflammatory, neurodegenerative, autoimmune and cardiovascular disorders.[12,13] For example, 1,4-benzoxazines **1** and **2** has been shown as inhibitors of nitric oxide synthase which are potential drugs for treating neurodegenerative, autoimmune, inflammatory and cardiovascular disorders.[12]

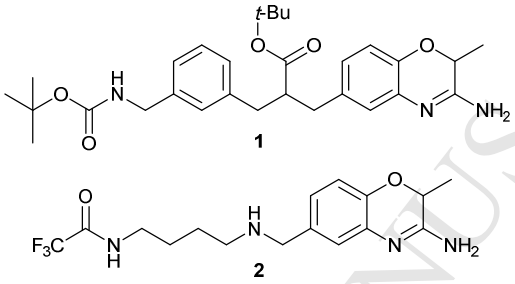
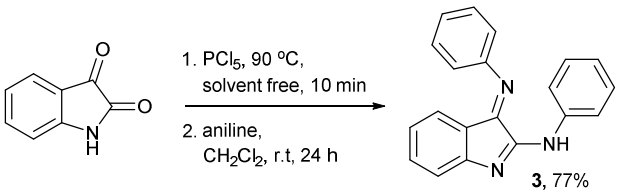


Fig. 1. Structures of some bioactive compounds with a 1,4-benzoxazine core structure.

Due to the importance of 1,4-benzoxazines, their synthesis has attracted much attention in recent years and many efforts have been made to develop methodologies for the synthesis of 1,4-benzoxazines derivatives.[14-22] 1,4-benzoxazin derivatives are often achieved from 2-aminophenols or 2-nitrophenols derivatives. However, most of the these methods suffer from one or more drawbacks such as lengthy sequences, higher reaction temperature, longer reaction time, toxic catalysts used, low overall yields, and limited ability to vary substituents. Moreover, the starting materials were often not readily available. Thus, the development of new and simple synthetic methods for the efficient preparation of the heterocycles containing of 1,4-benzoxazines ring fragments will be a beneficial and interesting challenge. As part of our ongoing research program on the development of efficient methods for the preparation of heterocyclic compounds,[23-30] herein we report a new procedure for the synthesis of novel 1,4-benzoxazines derivatives with different substituents at 2 and 3 positions. The notable advantages offered by this method are simple operation, readily available starting materials, and good yields of the products.

2. Results and discussion

At the outset of our study, we prepared the *N*-phenyl-3-(phenylimino)-3*H*-indol-2-amine **3a** from commercially available isatin, PCl_5 and aniline, using the modified procedure as previously reported (Scheme 1).[31]



Scheme 1. Synthesis of *N*-phenyl-3-(phenylimino)-3*H*-indol-2-amine **3a**

To further test this approach, particularly with regard to construction of a library of compounds, this methodology was evaluated by using different derivatives of isatin and aniline. The corresponding *N*-aryl-3-(arylimino)-3*H*-indol-2-amine derivatives **3** were synthesized under solvent-free condition. The results are summarized in Figure 2.

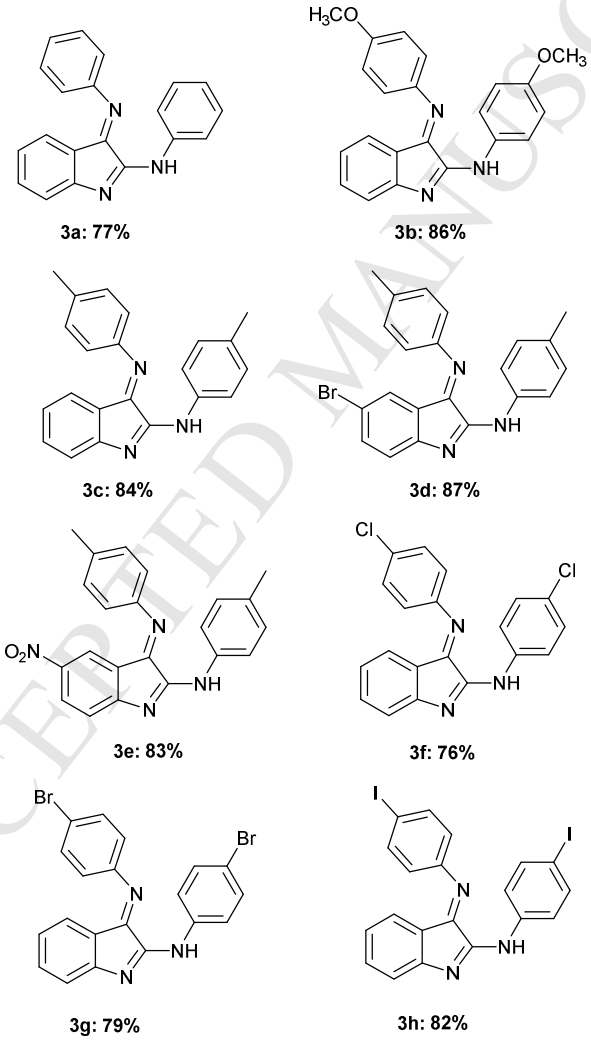
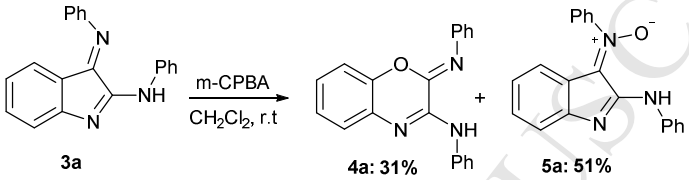


Fig. 2. Synthesis of *N*-aryl-3-(arylimino)-3*H*-indol-2-amine derivatives **3a-h**. Yields are given for the isolated products.

After the preparation of various derivatives of *N*-aryl-3-(arylimino)-3*H*-indol-2-amine **3**, we turned our focus on the evaluation of the Baeyer–Villiger oxidation reaction of these compounds. For this

approach, we investigated the reaction of *N*-phenyl-3-(phenylimino)-3*H*-indol-2-amine **3a**, as model substrates, with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane as solvent at room temperature. It was found that Baeyer-Villiger oxidation reaction proceeded with formation of *N*-oxide product **5a**. The products were easily purified by column chromatography, and pure products **4a** and **5a** were characterized by spectroscopic analysis. At room temperature, the major product is *N*-oxide (51%) (Scheme 2). To achieve suitable conditions for the selective synthesis of 1,4-benzoxazine **4a**, we investigated the reaction conditions. It was found that the temperature played a key role in the formation of 1,4-benzoxazines **4a**. For example, only 31% of 1,4-benzoxazines **4a** was detected when the reaction was performed at room temperature, but the yield of the 1,4-benzoxazines product **4a** increased to 78% at −20 ˚C.



Scheme 2. Model reaction for the synthesis of 1,4-benzoxazines

Under the optimized conditions, the substrate scope of this reaction was investigated, and the results are summarized in Figure 3. To the best of our knowledge, this new procedure provides the first example of an efficient method for the synthesis of this 1,4-benzoxazines class. Given the large number of commercially available aniline and isatin, the present method should be amenable for the synthesis of libraries with high diversity. We expect this method to find extensive application in the field of diversity oriented synthesis and drug discovery.

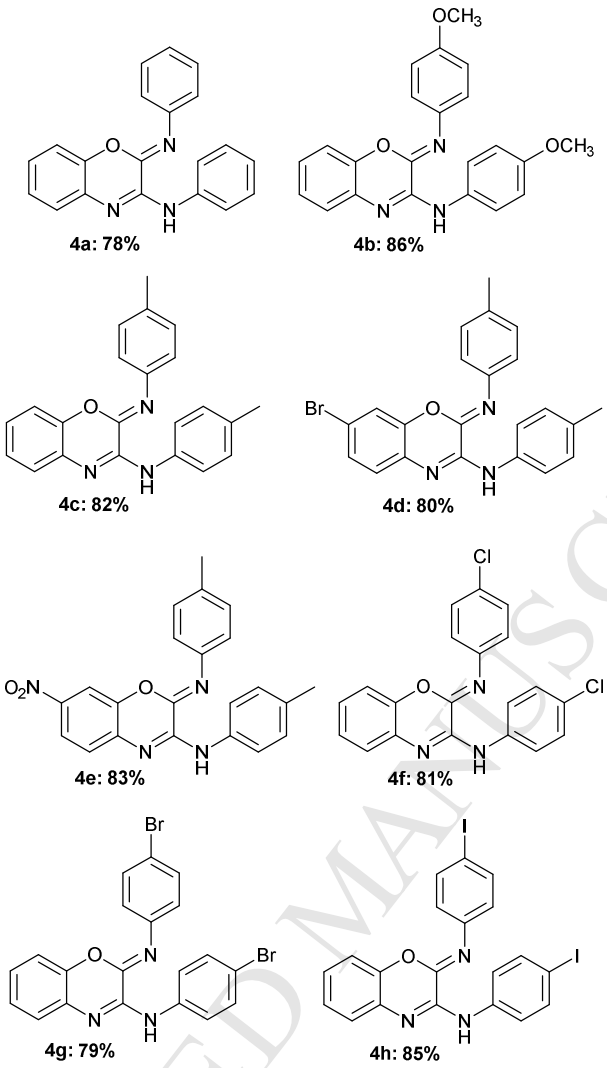


Fig. 3. Synthesis of 1,4-benzoxazines derivatives **4a-h**. Yields are given for the isolated products.

The structures of the products were characterized by spectroscopic analysis and further confirmed by an X-ray diffraction study of **4b** as a representative example (Fig. 4).[32,33]

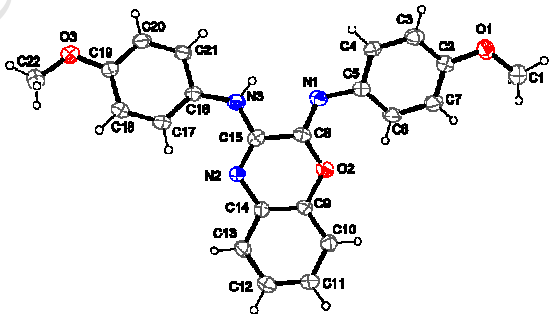


Fig. 4. Solid-state molecular structure of **4b**.

As mentioned earlier, the reaction produces *N*-oxide **5a** as major product at room temperature. To evaluate the potential of this methodology for the synthesis of *N*-oxide derivatives, we investigated the reaction with a series of *N*-aryl-3-(arylimino)-3H-indol-2-amine derivatives **3**, and the corresponding *N*-oxide derivatives **5** were obtained in good yields at room temperature (Fig. 5).

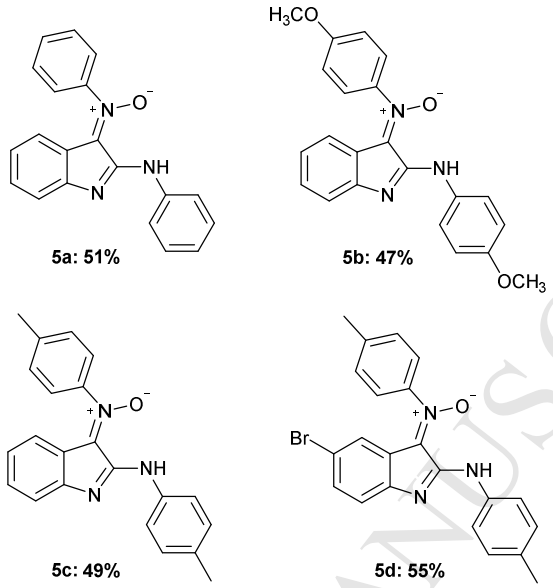


Fig. 5. Synthesis of *N*-oxide derivatives **5a-d**. Yields are given for the isolated products.

The structures of the products were characterized by spectroscopic analysis and further confirmed by an X-ray diffraction study of **5d** as a representative example (Fig. 6).[34,35]

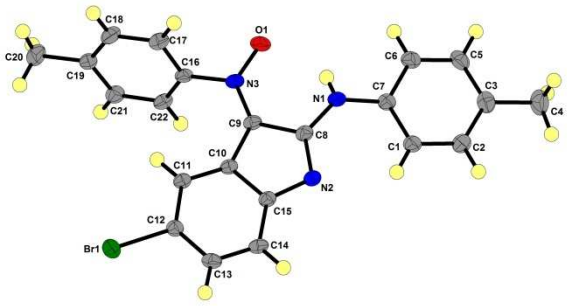
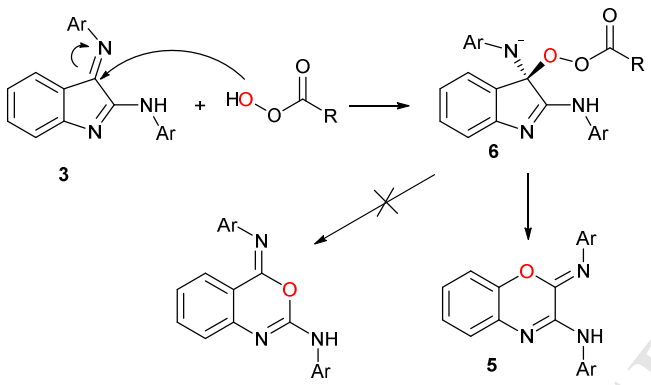


Fig. 6: Solid-state molecular structure of **5d**

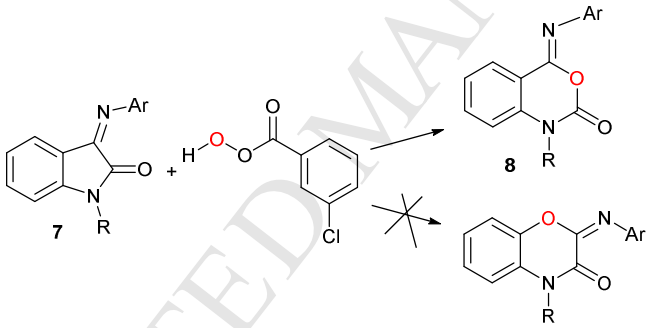
On the basis of previous chemistry and the results of our study, a plausible mechanism for the syntheses of the products is shown in Scheme 3.[36,37] In the first step, the peroxy acid attacks the carbon of the imine group forming intermediate **6**. In the next step of the reaction mechanism, through a concerted mechanism, one of the substituents on the carbon of the imine migrates to the oxygen of the peroxide group while a carboxylic acid leaves. In this step, there are two substituents attached to the carbon of the imine group for migration, phenyl and amidine group. The regiospecificity of the reaction depends on the relative migratory ability of the substituents. According to the product of

reaction, it was found that the phenyl group migrate better than amidine group and deliver only 1,4-benzoxazine **5** as product.



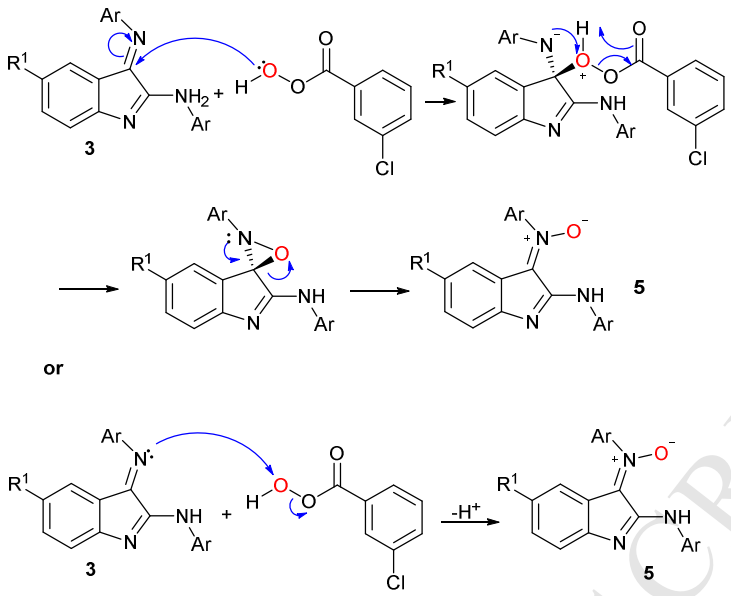
Scheme 3. Possible reaction mechanism.

In 2000, we reported Baeyer–Villiger oxidation of 1-alkyl-3-(arylimino)indolin-2-one **7** and we showed that the amide group migrated better than phenyl group and 1-alkyl-4-(arylimino)-1*H*-benzo[d][1,3]oxazin-2(4*H*)-one **8** formed in good yield (Scheme 4).[38,39]



Scheme 4. Synthesis of 1-alkyl-4-(arylimino)-1H-benzo[d][1,3]oxazin-2(4*H*)-one **8**

Therefore, due to higher migratory aptitude of amid group and lower migratory aptitude of amidine group relative to phenyl group, the migratory ability for these groups in Baeyer-Villiger oxidation reaction is ranked amide > phenyl > amidine. Although the mechanism for the formation of *N*-oxide **5** has not been established experimentally, however, based on previous studies plausible mechanisms are shown in the Scheme **5**.[40-43]



Scheme 5. Proposed mechanisms for the formation of the *N*-oxide **5**

3. Conclusions

In conclusion, we have demonstrated an simple and efficient method for the preparation of 1,4-benzoxazine derivatives by using readily available starting materials. Novelty, operational simplicity, and good yields are the key advantages of this method. The methodology with substrate diversity enables us to synthesize various derivatives of 1,4-benzoxazine. The reaction can be applied for the synthesis of a variety of 1,4-benzoxazine with different functional groups by using other isatin and aniline derivatives. With the results obtained in this paper and the previous our work, we demonstrated that in Baeyer-Villiger oxidation reaction, the phenyl group migrate better than amidine groups but not as good as amide group. Therefore, the migratory ability for these groups in Baeyer-Villiger oxidation reaction is ranked amide > phenyl > amidine. Further reactivity studies and synthetic applications of this methodology are in progress in our laboratory.

4. Experimental section

4.1. General

Solvents were distilled before use. CH_2Cl_2 was distilled under nitrogen from CaH_2. All other commercially available reagents were utilized as received without purification. PCl_5, Isatin and aniline derivatives were purchased from Alfa Aesar, Acros and Merck. Thin layer chromatography (TLC) analysis was performed using Silicycle precoated TLC plates (silica gel 60 F_{254}). The products were purified by preparative column chromatography on silica gel (0.063-0.200 mm; Merck). IR Spectra: Shimadzu FT-IR-4300 spectrometer; in cm^{-1}. ^{1}H and ^{13}C-NMR Spectra: were recorded on Bruker DRX-300-Advance instrument; in $CDCl_3$ at 300.1, and 75.4 MHz, resp; δ in ppm, J in Hz. EI-MS (70

eV): HP 5973 GC-MS instrument; in m/z. Melting points: Electrothermal 9200 apparatus. Elemental analyses were performed with a Thermo Finnigan Flash-1112EA microanalyzer.

4.1.1 General procedure for the synthesis of N-aryl-3-(arylimino)-3H-indol-2-amine derivatives **3***:*

A mixture of isatin (0.29 g, 2 mmol) and PCl_5 (0.50 g, 2.4 mmol) was stirred at 90°C under nitrogen for 10 min. Allowed to cold up to r.t. and then, the solution of aniline (6 mmol) in dry CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred under nitrogen for 24 h at r.t. After this time, concentration of the solution by rotary evaporation under reduced pressure gave a residue that was purified by column chromatography using 20% ethyl acetate/hexane as eluent.

*4.1.1.1 N-Phenyl-3-(phenylimino)-3H-indol-2-amine (***3a***):*

Red solid (77%), m.p. 212-214 ºC; [Found: C, 80.61; H, 4.95; N, 14.01. $C_{20}H_{15}N_3$ requires C, 80.78; H, 5.08; N, 14.13%]; ν_{max}(KBr) 3336, 1574, 1546, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.69-6.71 (2H, m), 7.10 (2H, d, *J* 7.5 Hz), 7.16 (1H, t, *J* 7.5 Hz), 7.30-7.33 (3H, m), 7.42-7.51 (4H, m), 7.88 (2H, d, *J* 7.7 Hz); δ_C (75.46 MHz, $CDCl_3$) 120.7, 120.7, 121.3, 122.3, 124.8, 125.7, 127.6, 131.3, 131.3, 131.4, 131.4, 136.6, 140.3, 150.7, 159.5, 161.7; *m/z* (CI) 297 (M^+, 100), 220 (65), 77 (95), 51 (68%).

*4.1.1.2. N-(4-Methoxyphenyl)-3-((4-methoxyphenyl)imino)-3H-indol-2-amine (**3b**):*

Yellow solid (86%), m.p. 228-232 ºC; [Found: C, 73.78; H, 5.27; N, 11.57. $C_{22}H_{19}N_3O_2$ requires C, 73.93; H, 5.36; N, 11.76%]; ν_{max}(KBr) 3343, 1572, 1533, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.93-7.03 (2H, m), 7.11-7.26 (2H, m), 7.45-7.56 (4H, m), 7.87 (1H, d, *J* 8.5 Hz), 7.94 (1H, d, *J* 8.6 Hz), 8.03-8.09 (2H, m); δ_C (75.46 MHz, $CDCl_3$) 55.5, 55.6, 114.0, 114.2, 115.0, 121.3, 124.5, 124.7, 125.9, 132.1, 132.2, 136.4, 138.4, 143.3, 144.7, 155.7, 157.5; *m/z* (CI) 357 (M^+, 100), 235 (55), 122 (45), 77 (90%).

4.1.1.3. N-(p-Tolyl)-3-(p-tolylimino)-3H-indol-2-amine (**3c**):

Light yellow solid (84%), m.p. 214-218 ºC; [Found: C, 81.36; H, 5.98; N, 13.07. $C_{22}H_{19}N_3$ requires C, 81.20; H, 5.89; N, 12.91%]; ν_{max}(KBr) 3333, 1654, 1611, 1572 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 2.42 (3H, s, CH_3), 7.09-7.12 (2H, m), 7.16-7.28 (5H, m), 7.35 (2H, d, *J* 8.3 Hz), 7.48 (1H, d, *J* 7.4 Hz), 7.82 (2H, d, *J* 8.4 Hz); δ_C (75.46 MHz, $CDCl_3$) 20.9, 22.4, 116.7, 118.2, 119.9, 123.7, 127.1, 127.8, 129.5, 130.5, 131.4, 133.3, 135.6, 135.9, 139.4, 140.5, 143.5, 144.6; *m/z* (CI) 325 (M^+, 70), 219 (55), 105 (100), 91 (90%).

4.1.1.4. 5-Bromo-N-(p-tolyl)-3-(p-tolylimino)-3H-indol-2-amine (**3d**):

Light brown solid (87%), m.p. 203-206 ºC; [Found: C, 65.22; H, 4.37; N, 10.25. $C_{22}H_{18}BrN_3$ requires C, 65.36; H, 4.49; N, 10.39%]; ν_{max}(KBr) 3280, 1670, 1625, 1560 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.37

(3H, CH_3), 2.46 (3H, CH_3), 6.98-7.02 (3H, m), 7.08 (1H, d, *J* 8.2 Hz), 7.21 (2H, d, *J* 8.2 Hz), 7.29 (2H, d, *J* 8.0 Hz), 7.37 (1H, dd, *J* 2.0, 8.2 Hz), 7.73 (2H, d, *J* 8.2 Hz); δ_C (75.46 MHz, $CDCl_3$) 18.5, 18.7, 112.2, 116.7, 116.8, 117.7, 118.6, 125.5, 127.3, 127.5, 130.9, 133.2, 133.6, 113.7, 134.2, 142.9, 155.2, 155.7; *m/z* (CI) 404 (M^+, 60), 285 (80), 167 (30), 91 (100%).

4.1.1.5. 5-Nitro-N-(p-tolyl)-3-(p-tolylimino)-3H-indol-2-amine (**3e**):

Red solid (83%), m.p. 242-245 ºC; [Found: C, 71.45; H, 5.02; N, 15.24. $C_{22}H_{18}N_4O_2$ requires C, 71.34; H, 4.90; N, 15.13%]; ν_{max}(KBr) 3314, 1636, 1597, 1565, 1318 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.31 (3H, CH_3), 2.44 (3H, CH_3), 7.06-7.13 (2H, m), 7.20 (2H, d, *J* 8.2 Hz), 7.32-7.36 (3H, m), 7.54 (2H, d, *J* 8.2 Hz), 8.08 (1H, d, *J* 2.0 Hz), 8.19-8.22 (1H, m); δ_C (75.46 MHz, $CDCl_3$) 21.06, 21.34, 116.4, 117.5, 118.5, 120.0, 120.1, 122.2, 122.8, 130.2, 130.4, 131.8, 138.4, 139.2, 144.1, 151.5, 156.7, 157.7; *m/z* (CI) 370 (M^+, 30), 355 (100), 309 (25), 91 (75%).

4.1.1.6. N-(4-Chlorophenyl)-3-((4-chlorophenyl)imino)-3H-indol-2-amine (**3f**):

Light yellow solid (76%), m.p. 226-230 ºC; [Found: C, 65.43; H, 3.47; N, 11.33. $C_{20}H_{13}Cl_2N_3$ requires C, 65.59; H, 3.58; N, 11.47%]; ν_{max}(KBr) 3376, 1654, 1562, 1543, 777 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.91-7.03 (4H, m), 7.17-7.22 (4H, m), 7.52 (2H, d, *J* 8.7 Hz), 7.84 (2H, d, *J* 7.5 Hz). δ_C (75.46 MHz, $CDCl_3$) 114.3, 114.9, 115.1, 121.5, 125.1, 125.5, 125.7, 126.4, 131.6, 137.8, 137.9, 138.4, 139.6, 143.0, 143.1, 144.0; *m/z* (CI) 366 (M^+, 100), 254 (70), 239 (75), 126 (55), 111 (40%).

4.1.1.7. N-(4-Bromophenyl)-3-((4-bromophenyl)imino)-3H-indol-2-amine (**3g**):

Light red solid (79%), m.p. 222-225 ºC; [Found: C, 52.64; H, 2.75; N, 9.09. $C_{20}H_{13}Br_2N_3$ requires C, 52.78; H, 2.88; N, 9.23%]; ν_{max}(KBr) 3445, 1713, 1562, 1442, 811 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.77 (2H, d, *J* 7.6 Hz), 6.86 (2H, d, *J* 7.7 Hz), 7.22-7.33 (3H, m), 7.62 -7.70 (3H, m), 7.81 (2H, d, *J* 8.5 Hz); δ_C (75.46 MHz, $CDCl_3$) 112.4, 116.1, 120.0, 120.7, 122.9, 123.5, 124.4, 126.1, 132.7, 133.3, 135.5, 146.2, 148.0, 149.0, 153.4, 155.6; *m/z* (CI) 454 (M^+, 50), 374 (100), 294 (55), 219 (15), 155 (20%).

4.1.1.8. N-(4-Iodophenyl)-3-((4-iodophenyl)imino)-3H-indol-2-amine (**3h**):

Red solid (82%), m.p. 195-197 ºC; [Found: C, 43.88; H, 2.53; N, 7.81. $C_{20}H_{13}I_2N_3$ requires C, 43.74; H, 2.39; N, 7.65%]; ν_{max}(KBr) 3427, 1621, 1592, 1561, 808 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.70-6.78 (2H, m), 6.85 (2H, d, *J* 8.5 Hz), 7.21 (1H, d, *J* 7.6 Hz), 7.28 -7.33 (1H, m), 7.62 (2H, d, *J* 8.4 Hz), 7.69 (2H, d, *J* 8.7 Hz), 7.78 (2H, d, *J* 8.4 Hz); δ_C (75.46 MHz, $CDCl_3$) 86.9, 87.0, 119.0, 121.1, 121.1, 121.3, 123.2, 125.8, 135.1, 138.2, 138.2, 138.5, 138.5, 148.2, 157.1, 159.8; *m/z* (CI) 549 (M^+, 40), 422 (100), 294 (35), 219 (20), 97 (30%).

4.1.2. General procedure for the synthesis of 1,4-benzoxazines derivatives (**4**):

The solution of *N*-aryl-3-(arylimino)-3*H*-indol-2-amine **3** (0.30 g, 1.0 mmol) in 25 mL CH_2Cl_2 was cooled to −20 ºC. Then, *m*-CPBA (0.26 g, 1.5 mmol) dissolved in 25 mL CH_2Cl_2 was added dropwise to the stirred solution of **3**. After stirring for 6 h at −20 °C, 1,4-benzoxazine **4** was formed (monitoring by TLC). The crude product was poured into water and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over Na_2SO_4, and evaporation of the solvent afforded crude product **4**. The crude product **4** was purified on silica gel by column chromatography using 20% ethyl acetate/hexane as eluent.

*4.1.2.1. N-Phenyl-2-(phenylimino)-2H-benzo[b][1,4]oxazin-3-amine (**4a**):*

Light yellow solid (78%), m.p. 118-120 ºC; [Found: C, 76.85; H, 4.98; N, 13.56. $C_{20}H_{15}N_3O$ requires C, 76.66; H, 4.83; N, 13.41%]; ν_{max}(KBr) 3426, 1650, 1592, 1444, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07-7.26 (5H, m), 7.41-7.52 (7H, m), 7.96 (2H, d, *J* 7.6 Hz), 8.74 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 115.2, 119.7, 123.4, 123.6, 124.8, 125.1, 125.5, 126.3, 128.9, 129.0, 131.0, 138.8, 139.4, 143.6, 143.7, 144.5; *m/z* (CI) 313 (M^+, 97), 210 (100), 181(30), 77 (68%).

*4.1.2.2. N-(4-Methoxyphenyl)-2-((4-methoxyphenyl)imino)-2H-benzo[b][1,4]oxazin-3-amine (**4b**):*

Yellow solid (86%), m.p. 169-171 ºC; [Found: C, 70.92; H, 5.27; N, 11.41. $C_{22}H_{19}N_3O_3$ requires C, 70.76; H, 5.13; N, 11.25%]; ν_{max}(KBr) 3441, 1651, 1538, 1243 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.95-7.00 (4H, m), 7.12 (2H, d, *J* 3.8 Hz), 7.16-7,21 (1H, m), 7.46 (1H, d, *J* 7.6 Hz), 7.52 (2H, d, *J* 8.9 Hz), 7.85 (2H, d, *J* 8.9 Hz), 8.65 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 55.5, 55.6, 114.1, 114.2, 115.0, 121.3, 121.4, 124.6, 124.7, 125.9, 132.1, 132.2, 136.4, 138.4, 143.3, 144.7, 155.8, 157.6; *m/z* (CI) 373 (M^+, 60), 260 (50), 225 (100), 197 (20), 90 (30%).

*4.1.2.3. N-(p-Tolyl)-2-(p-tolylimino)-2H-benzo[b][1,4]oxazin-3-amine (**4c**):*

Light yellow solid (82%), m.p. 160-162 ºC; [Found: C, 77.22; H, 5.40; N, 12.14. $C_{22}H_{19}N_3O$ requires C, 77.40; H, 5.61; N, 12.31%]; ν_{max}(KBr) 3328, 1656, 1596, 1536, 1203 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 2.42 (3H, s, CH_3), 7.10-7.17 (2H, m), 7.21-7.27 (5H, m), 7.35 (2H, d, *J* 7.6 Hz), 7.49 (1H, d, *J* 7.5 Hz), 7.82 (2H, d, *J* 7.2 Hz), 8.70 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 20.9, 21.2, 115.1, 119.8, 123.8, 124.7, 124.8, 126.1, 129.5, 129.5, 132.1, 133.0, 135.3, 136.2, 139.1, 140.9, 143.3, 144.6; *m/z* (CI) 341 (M^+, 100), 224 (95), 116 (20), 91 (55), 77 (20%).

*4.1.2.4. 2-(p-Tolylimino)-7-bromo-N-p-tolyl-2H-benzo[b][1,4]oxazin-3-amine (**4d**):*

Light green (80%), m.p. 206-208 ºC; [Found: C, 63.05; H, 4.47; N, 10.17. $C_{22}H_{18}BrN_3O$ requires C, 62.87; H, 4.32; N, 10.00%]; ν_{max}(KBr) 3447, 1655, 1602, 1563, 1472 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 2.42 (3H, s, CH_3), 7.21-7.26 (5H, m), 7.31-7.37 (4H, m), 7.79 (2H, d, *J* 8.3 Hz), 8.74 (1H, br, NH); δ_C (75.46 MHz, $CDCl_3$) 20.2, 20.4, 116.0, 117.5, 119.1, 123.1, 126.3, 127.1, 128.8,

128.8, 130.6, 132.5, 135.0, 135.2, 137.4, 139.7, 142.7, 143.7; *m/z* (CI) 420 (M^+, 60), 302 (100), 224 (20), 116 (25), 91 (90%).

*4.1.2.5. 7-Nitro-N-(p-tolyl)-2-(p-tolylimino)-2H-benzo[b][1,4]oxazin-3-amine (**4e**):*

Yellow solid (83%), m.p. 224-227 ºC; [Found: C, 68.58; H, 4.86; N, 14.67. $C_{22}H_{18}N_4O_3$ requires C, 68.38; H, 4.70; N, 14.50%]; ν_{max}(KBr) 3417, 1665, 1617, 1549, 1507, 1331, 818 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 2.44 (3H, s, CH_3), 7.24-7.26 (3H, m), 7.27-7.29 (1H, m), 7.37 (2H, d, *J* 8.2 Hz), 7.53 (1H, d, *J* 8.5 Hz), 7.81 (2H, d, *J* 7.6 Hz), 7.99 (1H, d, *J* 2.0 Hz), 8.08 (1H, d, *J* 8.2 Hz), 8.93 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 21.1, 21.2, 111.2, 120.5, 120.6, 124.1, 125.9, 129.7, 129.7, 134.5, 135.2, 136.5, 137.4, 138.4, 139.9, 142.5, 143.5, 146.1; *m/z* (CI) 386 (M^+,100), 370 (20), 269 (90), 239 (20), 195 (15), 118 (20), 91 (35%).

*4.1.2.6. N-(4-Chlorophenyl)-2-((4-chlorophenyl)imino)-2H-benzo[b][1,4]oxazin-3-amine (**4f**):*

Light yellow solid (81%), m.p. 217-220 ºC; [Found: C, 62.66; H, 3.23; N, 10.81. $C_{20}H_{13}Cl_2N_3O$ requires C, 62.84; H, 3.43; N, 10.99%]; ν_{max}(KBr) 3403, 1728, 1645, 1527, 1263, 1088 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07-7.25 (5H, m), 7.50 (1H, d, *J* 7.4 Hz), 7.71-7.76 (6H, m), 8.65 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 116.5, 119.6, 121.8, 124.4, 126.6, 126.8, 127.3, 128.4, 129.4, 130.4, 130.8, 134.2, 136.5, 136.4, 141.3, 145.7; *m/z* (CI) 382 (M^+, 30), 244 (70), 149 (100), 131 (30), 92 (20%).

*4.1.2.7. N-(4-Bromophenyl)-2-((4-bromophenyl)imino)-2H-benzo[b][1,4]oxazin-3-amine (**4g**):*

Light yellow solid (79%), m.p. decomposed at 228 ºC; [Found: C, 50.77; H, 2.58; N, 8.71. $C_{20}H_{13}Br_2N_3O$ requires C, 50.99; H, 2.78; N, 8.92%]; ν_{max}(KBr) 3437, 1649, 1611, 1535, 1073, 826 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.10-7.27 (5H, m), 7.52-7.54 (5H, m), 7.84-7.86 (2H, m), 8.66 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 108.5, 112.3, 116.1, 116.7, 118.8, 119.9, 122.8, 125.8, 126.7, 126.8, 127.8, 128.9, 132.6, 134.2, 142.9, 144.6; *m/z* (CI) 471 (M^+, 60), 290 (100), 209 (30), 155 (30), 102 (50), 75 (40%).

*4.1.2.8. N-(4-Iodophenyl)-2-((4-iodophenyl)imino)-2H-benzo[b][1,4]oxazin-3-amine (**4h**):*

Yellow solid (85%), m.p. 206-210 ºC; [Found: C, 42.29; H, 2.11; N, 7.23. $C_{20}H_{13}I_2N_3O$ requires C, 42.51; H, 2.32; N, 7.44%]; ν_{max}(KBr) 3430, 1645, 1579, 1262, 806 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07-7.24 (5H, m), 7.49 (1H, d, *J* 7.5 Hz), 7.68-7.76 (6H, m), 8.65 (1H, s, NH); δ_C (75.46 MHz, $CDCl_3$) 86.4, 89.8, 115.2, 121.5, 125.2, 125.6, 125.7, 126.4, 131.6, 137.9, 138.0, 138.4, 139.6, 143.0, 143.2, 144.0; *m/z* (CI) 565 (M^+, 65), 336 (70), 209 (50), 167 (40), 102 (60), 76 (100%).

*4.1.3. General procedure for the synthesis of N-oxides (**5**):*

The solution of *m*-CPBA (0.26 g, 1.5 mmol) dissolved in 25 mL CH_2Cl_2 was added dropwise to the stirred solution of *N*-aryl-3-(arylimino)-3*H*-indol-2-amine **3** (1.0 mmol) in 25 mL CH_2Cl_2 at room temperature. After stirring for 6 h, *N*-oxide **5** was formed (monitoring by TLC). The crude product was poured into water and extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over Na_2SO_4, and evaporation of the solvent afforded crude product **5**. The crude product **5** was purified on silica gel by column chromatography using 30% ethyl acetate/hexane as eluent.

*4.1.3.1. (Z)-N-Phenyl-2-(phenylamino)-3H-indol-3-imine oxide (**5a**):*

Violet solid (51%) yield, m.p. 183-184 ºC; [Found: C, 76.51; H, 4.66; N, 13.25. $C_{20}H_{15}N_3O$ requires C, 76.66; H, 4.83; N, 13.41%]; ν_{max}(KBr) 3421, 1617, 1565, 1442, 1195, 754 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.89 (1H, d, *J* 7.8 Hz), 6.63 (1H, t, *J* 7.5 Hz), 7.16 (1H, t, *J* 7.4 Hz), 7.22-7.33 (1H, m), 7.44 (3H, t, *J* 7.6 Hz), 7.55-7.58 (2H, m), 7.64-7.70 (3H, m), 7.99 (2H, d, *J* 8.0 Hz), 11.45 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 118.6, 119.3, 120.8, 121.6, 122.7, 123.3, 124.2, 129.1, 129.3, 130.4, 131.4, 132.4, 138.4, 142.6, 145.7, 155.5; *m/z* (CI) 313 (M^+, 72), 296 (75), 221 (50), 119 (45), 77 (100%).

*4.1.3.2. (Z)-N-(4-Methoxyphenyl)-2-((4-methoxyphenyl)amino)-3H-indol-3-imine oxide (**5b**):*

Red solid (47%), m.p. 188-192 ºC; [Found: C, 70.51; H, 4.90; N, 11.02. $C_{22}H_{19}N_3O_3$ requires C, 70.76; H, 5.13; N, 11.25%]; ν_{max}(KBr) 3400, 1652, 1609, 1560 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.11 (1H, d, *J* 7.8 Hz), 6.67 (1H, t, *J* 7.5 Hz), 6.99 (2H, d, *J* 8.7 Hz), 7.11 (2H, d, *J* 8.6 Hz), 7.25-7.33 (2H, m), 7.51 (2H, d, *J* 8.6 Hz), 7.91 (2H, d, *J* 8.7 Hz), 11.58 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 55.5, 55.8, 114.6, 115.1, 118.2, 119.2, 121.4, 122.3, 122.7, 124.9, 124.9, 129.5, 131.4, 132.3, 138.9, 143.2, 156.5, 161.5; *m/z* (CI) 373 (M^+, 50), 357 (55), 250 (40), 167 (20), 93 (30), 77 (100%).

*4.1.3.3. (Z)-N-(p-Tolyl)-2-(p-tolylamino)-3H-indol-3-imine oxide (**5c**):*

Violet solid (49%), m.p. 215-218 ºC; [Found: C, 77.61; H, 5.79; N, 12.50. $C_{22}H_{19}N_3O$ requires C, 77.40; H, 5.61; N, 12.31%]; ν_{max}(KBr) 3410, 1715, 1619, 1565, 1439, 1101, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 2.54 (3H, s, CH_3), 5.98 (1H, d, *J* 7.6 Hz), 6.61-6.67 (1H, m), 7.23-7.26 (4H, m), 7.42-7.46 (4H, m), 7.87 (2H, d, *J* 8.3 Hz), 11.45 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 21.1, 21.5, 103.1, 118.4, 119.5, 120.7, 121.3, 122.7, 123.1, 129.8, 130.8, 132.2, 133.8, 135.9, 141.8, 142.5, 143.5, 155.6; *m/z* (CI) 341 (M^+, 80), 324 (100), 235 (20), 91 (50%).

*4.1.3.4. (Z)-5-Bromo-N-(p-tolyl)-2-(p-tolylamino)-3H-indol-3-imine oxide (**5d**):*

Grey solid (55%), m.p. 218-222 ºC; [Found: C, 62.68; H, 4.17; N, 9.81. $C_{22}H_{18}BrN_3O$ requires C, 62.87; H, 4.32; N, 10.00%]; ν_{max}(KBr) 3453, 1622, 1560, 1211, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 2.55 (3H, s, CH_3), 6.06 (1H, s), 7.14-7.26 (4H, m), 7.31-7.48 (5H, m), 7.84 (2H, d, *J* 8.2

Hz), 11.38 (1H, NH); δ_C (75.46 MHz, $CDCl_3$) 21.1, 21.6, 113.7, 119.6, 121.0, 123.0, 125.4, 127.7, 129.6, 129.9, 130.9, 131.2, 134.2, 134.6, 142.3, 143.2, 151.8, 155.4; *m/z* (CI) 420 (M^+, 100), 404 (70), 388 (80), 314 (20), 107 (20), 91 (70), 81 (10%).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/.

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