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# Oxidative Recyclization of 1*H*-Indoles for Synthesis of 2-Indolylbenzoxazinones via Cleavage of the C2−C3 Bond with AIBN under Air

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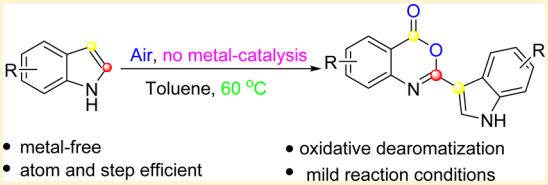
Supporting Information

**ABSTRACT:** A novel and concise method for the oxidation of unprotected indole derivatives to synthesize 2-indolylbenzoxazinones in the presence of AIBN under open air has been successfully demonstrated. This metal-free reaction is both atom- and step-efficient and is applicable to a broad scope of substrates. This new methodology provides a facile pathway for oxidative C2−C3 bond cleavage and recyclization of 1*H*-indoles.




## INTRODUCTION

4*H*-3,1-Benzoxazin-4-ones have been known for more than a century. Compounds possessing this skeleton system are found in a number of physiologically and pharmaceutically bioactive natural products with diverse bioactivities, such as HSV-1 protease inhibition, chymotrypsin inactivation, antifungal, and others.[1] A few representative compounds are outlined in Figure 1.[2] Benzoxazinones are useful synthetic intermediates for some pharmaceutically active compounds,[3] and they also serve as useful building blocks in organic synthesis.[4] Therefore, benzoxazinones represent a class of annulated nitrogen heterocycles that have attracted much interest from both organic and pharmaceutical chemists. In the past decade, great efforts have been devoted to these moieties, and a number of synthetic methods have been reported.[5−7] Among the different methodologies developed for their preparation,[5] the most popular synthetic pathways involve the use of anthranilic acid or its derivatives, *N*-acylanthranilic acids, or isatonic anhydride.[6] Other synthetic methods such as oxidation of 2-substituted indoles and 2-phenylindolenin-3-ones, [4 + 2] cycloaddition of 1,2,3-benzotriazin4-ones with benzaldehydes, electrochemical cyclization of *o*-trichloroacetylanilides, and solid-phase synthesis were described.[7] Although alternative methodologies are known, some of them still suffer from hazardous materials or harsh reaction conditions. Hence, it is still desirable to extend known protocols for benzoxazinone synthesis.

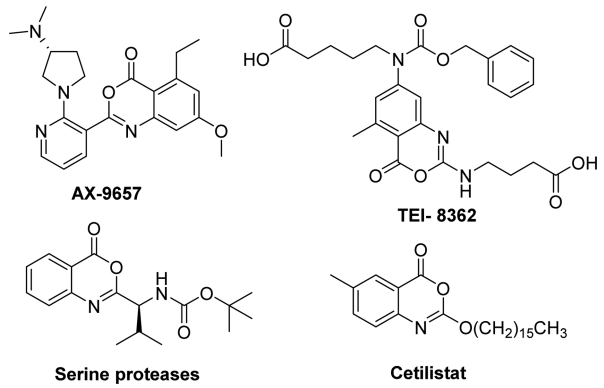



**Figure 1.** Structures of some bioactive 4*H*-3,1-benzoxazin-4-ones.

As we all know, indoles are structural motifs prevalent in bioactive synthetic and natural products.[8] They are employed widely in medicinal chemistry, pharmacological research, and material applications.[9] Consequently, the development of efficient methodologies for the preparation and functionalization of various indole derivatives has been a subject of intense research efforts. Notably, to our knowledge, there is no report for direct functionalization of 1*H*-indoles to afford 2-indolylbenzoxazinones. Herein, we present a facile route for the construction of the benzoxazinone skeleton through the oxidative cleavage of the 1*H*-indole C2−C3 bond along with recyclization in the presence of AIBN and air.

## RESULTS AND DISCUSSION

Initially, we proposed that indole could react with the toluene through the oxidative cross-coupling reaction. We chose 1*H*-indole **1a** as the model to optimize the conditions. By treating the substrate **1a** with AIBN (2.0 equiv) at 60 °C for 6 h in toluene under air, surprisingly, an unexpected product, 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one **2a**, was

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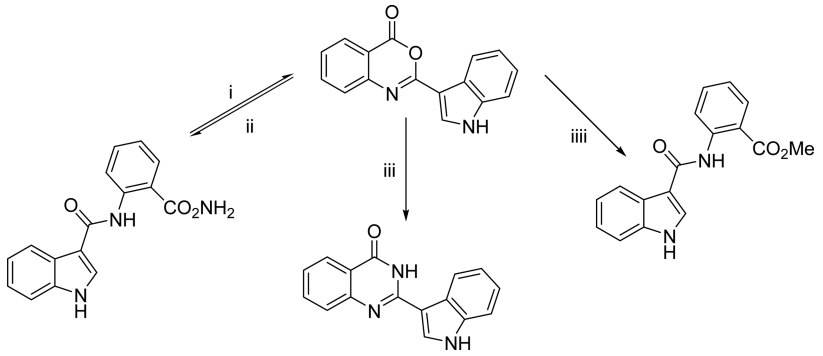
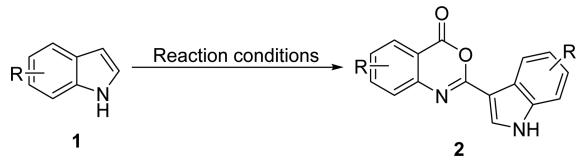


**Figure 2.** Applications of **2a**: (i) $NH_4OAc$, DMF, 70 °C, 2 h; (ii) xylenes, *p*-TsOH (cat.), reflux, (Dean−Stark trap), 24 h; (iii) formamide (neat), 200 °C, 10 min, MW; (iiii) MeOH, reflux, 4 h, 99%.

obtained in 30% yield, and the structure of **2a** was confirmed unambiguously through X-ray crystal analysis (SI, CCDC 1496619). 2-(1*H*-Indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one, a natural product as known as cephalandole A, showed significant cytotoxicity against human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines.[10] Moreover, 2-(1*H*-indol-3-yl)-4*H*-benzo-[*d*][1,3]oxazin-4-one was also the intermediate for some other natural alkaloids (Figure 2). This discovery attracted our interest.[11] Encouraged by this result, a variety of oxidants such as $O_2$, Oxone, DTBP, $PhI(OAc)_2$, and $H_2O_2$ were screened, but all failed to give the desired product in better results than air (entries 1−6; Table 1). Subsequently, a series of additives, including $Et_3N$, HOAc, PivOH, $CF_3COOH$, and TsOH, were examined. PivOH was clearly the most effective, giving **2a** in 76% yield (entries 7−11; Table 1). However, increasing or decreasing the amount of PivOH led to no better yields (entries 12 and 13; Table 1). Optimization of different solvents revealed that DMF, DMSO, PhCl, and DMC were inferior to toluene in the reaction (entries 14−17; Table 1). It should be noted that lower yields of product 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (**2a**) were obtained when we changed the amount of AIBN (entry 18; Table 1). The reaction temperature and time were also varied; 60 °C and 6 h gave the best results (entries 19−21; Table 1). Moreover, when we used TBHP, $I_2$, $Na_2S_2O_8$, and $H_2O_2$ to replace AIBN, we failed to detect the desired product (entry 22; Table 1). Finally, the best result was obtained by using AIBN (2.0 equiv) in the presence of PivOH (1.0 equiv) in toluene at 60 °C under air for 6 h (entry 9; Table 1).

With the optimized reaction conditions established, the scope and generality of the reaction were investigated (Table 2). Delightly, a relatively broad range of indole derivatives with a substituent at the C4, C5, C6, or C7 position of the indole ring were mostly successfully transformed to the desired products in moderate yields. For example, indoles with a methyl at the 4-, 5-, 6-, or 7-positions were examined, affording the desired products in 54%, 62%, 43%, and 68% yield, respectively (Table 2, entries **2b**, **2f**, **2l**, **2o**). Unfortunately, we did not detect the product when a methoxy at C4 of 1*H*-indole (Table 2, entry **2c**), but the indoles with methoxy at the C5, C6, and C7 positions could afford the products **2g**, **2m**, and **2p** in 50%, 44%, and 28% yield (Table 2, entries **2g**, **2m**, and **2p**). In addition, some halogen substituents (F, Cl, or Br) were tested under the optimal conditions, except the bromo group (Table 2, entry **2k**), the others could be smoothly transformed into the desired products (Table 2, entries **2e**, **2i**, **2j**, **2n**, **2q**).

**Table 1. Optimization Studies**[a]




| entry | oxidant (equiv) | additive (equiv) | solvent | temp (°C) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | air | | tol | 60 | 30 |
| 2 | $O_2$ | | tol | 60 | 15 |
| 3 | Oxone | | tol | 60 | 16 |
| 4 | DTBP | | tol | 60 | 20 |
| 5 | PIDA | | tol | 60 | 24 |
| 6 | $H_2O_2$ | | tol | 60 | 8 |
| 7 | air | $Et_3N$ | tol | 60 | 35 |
| 8 | air | HOAc (1.0) | tol | 60 | 58 |
| 9 | air | PivOH (1.0) | tol | 60 | 76 |
| 10 | air | TFA (1.0) | tol | 60 | ND |
| 11 | air | TsOH (1.0) | tol | 60 | ND |
| 12 | air | PivOH (0.5) | tol | 60 | 45 |
| 13 | air | PivOH (2.0) | tol | 60 | 68 |
| 14 | air | PivOH (1.0) | DMF | 60 | trace |
| 15 | air | PivOH (1.0) | DMSO | 60 | ND |
| 16 | air | PivOH (1.0) | PhCl | 60 | 66 |
| 17 | air | PivOH (1.0) | DMC | 60 | 45 |
| 18 | air | PivOH (1.0) | tol | 60 | 45,[c] 46[d] |
| 19 | air | PivOH (1.0) | tol | 60 | 46,[e] 64[f] |
| 20 | air | PivOH (1.0) | tol | 40 | 30[g] |
| 21 | air | PivOH (1.0) | tol | 80 | 55 |
| 22 | air | PivOH (1.0) | tol | 60 | ND[h] |

[a]Indole **1a** (0.5 mmol), AIBN (1.0 mmol, 2.0 equiv), oxidant, additive, and solvent (2 mL) at 60 °C for 6 h. [b]Yield of isolated product. [c]AIBN (0.5 mmol, 1.0 equiv). [d]AIBN (1.5 mmol, 3.0 equiv). [e]4 h. [f]8 h. [g]The reaction was prolonged to 8 h. [h]THBP (2.0 equiv), $I_2$ (2.0 equiv), $Na_2S_2O_8$ (2.0 equiv), $H_2O_2$ (2.0 equiv) instead of AIBN. AIBN = azobis(isobutyronitrile), DTBP = *tert*-butyl peroxide, PIDA = iodobenzene diacetate, TFA = trifluoroacetic acid, tol = toluene, TBHP = *tert*-butyl hydroperoxide, HOAc = acetic acid, PivOH = trimethylacetic acid, TsOH = 4-methylbenzenesulfonic acid, DMF = dimethylformamide, DMSO = dimethyl sulfoxide, DMC = dimethyl phosphate, ND = no detection.

However, 7-azaindole (**1r**) failed to produce the desired product under the optimal conditions (**2r**).

In order to explore the reaction mechanism, some control experiments were conducted (Scheme 1). According to the results of the transformations, we proposed that the 3*H*-indol-3-ones may



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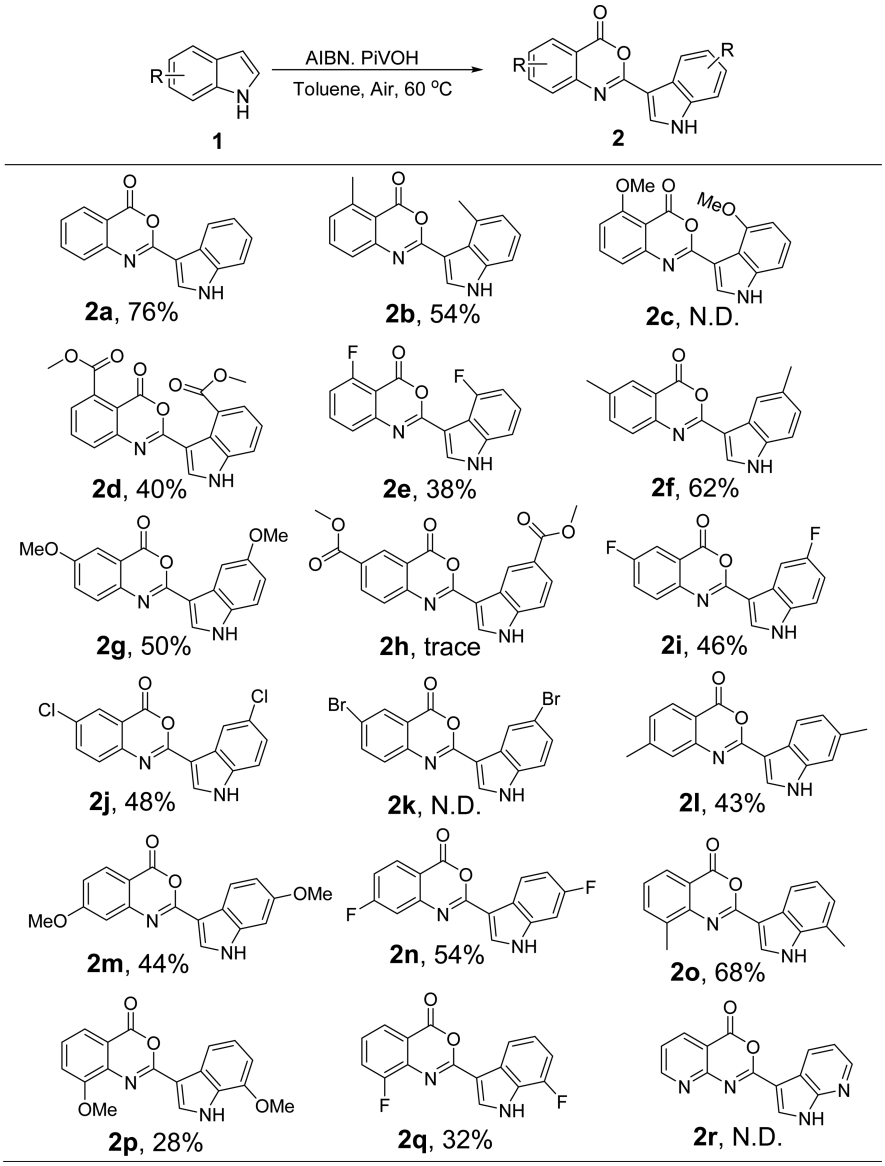
Table 2. Oxidation of 1*H*-Indoles for the Synthesis of 2-Indolylbenzoxazinones with AIBN[a,b]




[a]Reaction conditions: **1a** (0.5 mmol), AIBN (1.0 mmol, 2.0 equiv) in toluene (2 mL) at 60 °C under air for 6 h. [b]Isolated yield. ND = not detection.

in fact be the crucial intermediates in the reaction. Unfortunately, under the optimized conditions, none of the intermediates formed in isolable quantities. Therefore, we performed a control experiment in the absence of PivOH, the high resolution mass spectrum of crude mixtures (see the Supporting Information) withdrawn at 2 h indicated the formation of 3*H*-indol-3-one **3**, 1′*H*,3*H*-[2,3′-biindol]-3-one **4** (Scheme 1, eq 1). As shown in eqs 2 and 3, we conducted the reaction in the absence of AIBN and air, respectively (Scheme 1). The reactions both failed to afford the product **2a**. The results indicated that AIBN and air were important factors in the conversion of **1a** to **2a**. Moreover, we added 2.0 equiv of radical-trapping reagents TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-*tert*-butyl-*p*-cresol) into the reaction system, respectively, resulting in no formation of desired products (Scheme 1, eq 4). The results implied that the radical mechanism might be responsible for the reaction. Then, we used the substrates 2-methyl-1*H*-lindole **1s** and 3-methyl-1*H*-lindole **1t** to perform the reactions (Scheme 1, eqs 5 and 6). Under the standard conditions, 2-methyl-1*H*-lindole could generate 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one **2s** in 30% and 2-methyl-2-(2-methyl-1*H*-indol-3-yl)indolin-3-one **4s** in 48%; however, the transformation of 3-methyl-1*H*-lindole was not very positive, and we detected only a trace amount of 3-methylindolin-2-one **3t**. Consequently, the results of eqs 5 and 6 could also provide evidence for the intermediate of **4**.

On the basis of the above results and literature reports,[12−26] the proposed mechanism is outlined in Scheme 2. First, an initial hydrogen abstraction from the nitrogen atom of the indole ring by AIBN leads to the formation of an indolyl radical **7**. Then, in the presence of dioxygen, the formation of a C3-located indole hydroperoxide **8** is followed by its fractionation to the intermediate 3*H*-indol-3-one **3**. Subsequently, the 1*H*-indole **1a** undergoes nucleophilic attack to **3** mediated by acid to produce another crucial intermediate **4**. Shortly afterward, Baeyer−Villiger oxidation of **4** by **5** or **9** occurs, leading to generationof the product **2a** through C2−C3 bond cleavage.



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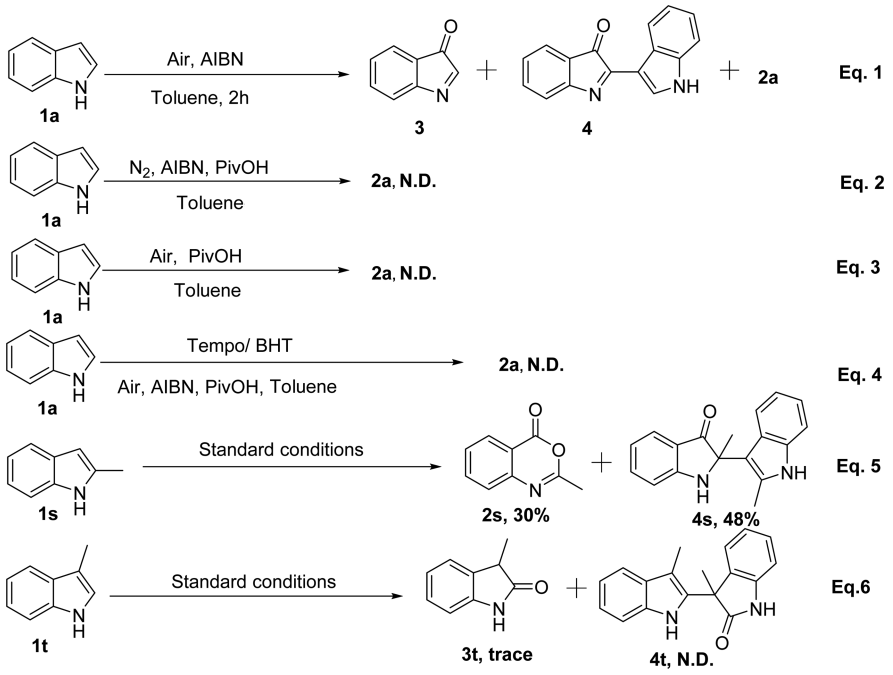
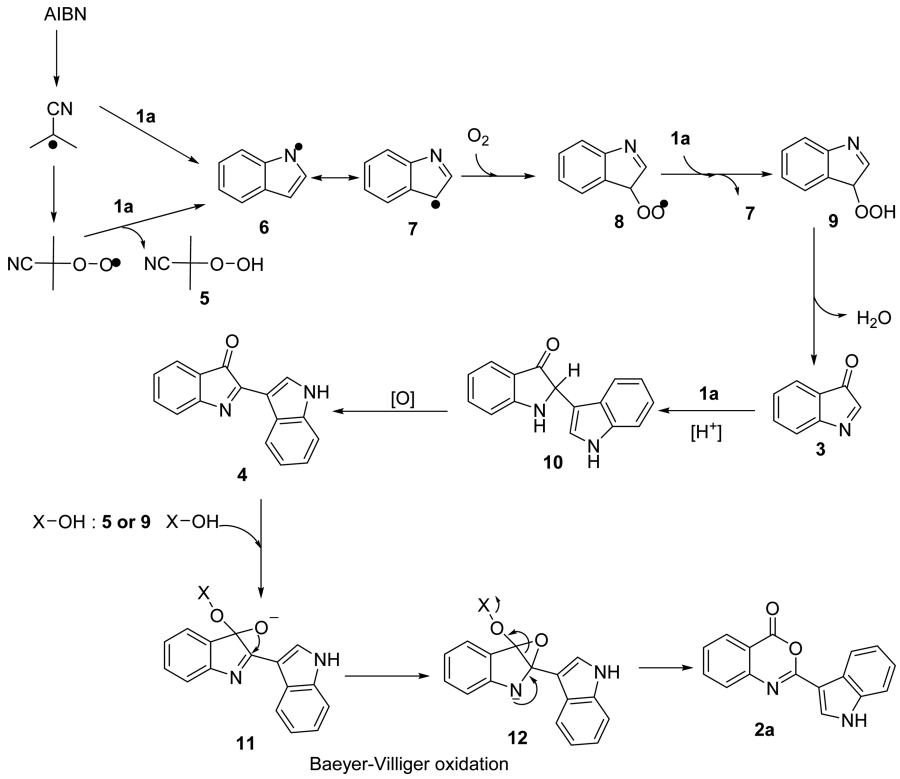
**Scheme 1. Different Control Experiments**




**Scheme 2. Plausible Mechanism**




## CONCLUSIONS

In summary, we have developed a new, simple, and practical method for the oxidative recyclization of 1*H*-indoles through the cleavage of a C2−C3 bond to synthesize 2-indolylbenzoxazinones in the presence of AIBN under open air. This strategy features tolerance of a relatively wide range of functional groups, easily available starting materials, simple operation, and mild reaction conditions. To the best of our knowledge, this is the first example of constructing benzoxazinones from easily available unprotected indole derivatives through a one-pot method.

## EXPERIMENTAL SECTION

**General Information.** All of the reactions were carried out in oven-dried flask. Products were purified by flash chromatography on 200−300 mesh silica gels. Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by



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UV detection. Unless otherwise noted, chemical shifts ($\delta$) are reported in ppm using TMS as internal standard; $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectras were recorded in $CDCl_3$ ($\delta$ = 77.00 ppm) and DMSO-*d* ($\delta$ = 39.50 ppm). The high-resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Melting points were determined on a microscopic apparatus. Copies of $^1$H NMR and $^{13}$C NMR spectra are provided in the Supporting Information. Commercially available reagents were used without further purification.

**Typical Experimental Procedure for the Synthesis of 2-Indolylbenzoxazinones (2).** An oven-dried tube with a magnetic stir bar was charged with the 1*H*-indole compound **1** (0.5 mmol, 1.0 equiv), AIBN (1.0 mmol, 2.0 equiv), PivOH (0.5 mmol, 1.0 equiv), and toluene (2 mL). Then the reaction mixture was stirred at 60 °C under air until complete consumption of starting material as monitored by TLC. After the reaction was finished, the mixture was concentrated in vacuo, and the residues were purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford the desired product **2**.

*2-Methyl-4H-benzo[d][1,3]oxazin-4-one* (***2s***)*:*[27] yield 30%, 24.2 mg; brown solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.12 (dd, $J_1$ = 7.9 Hz, $J_2$ = 1.1 Hz, 1H), 7.77−7.73 (m, 1H), 7.50−7.43 (m, 2H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.0, 159.5, 146.3, 136.4, 128.3, 128.0, 126.2, 116.5, 21.2.

*2-Methyl-2-(2-methyl-1H-indol-3-yl)indolin-3-one* (***4s***)*:*[20] yield 48%, 33.1 mg; yellow solid; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 10.90 (s, 1H), 7.74 (s, 1H), 7.52−7.45 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 6.94 (dt, $J_1$ = 7.1 Hz, $J_2$ = 0.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.81−6.77 (m, 1H), 6.74−6.70 (m, 1H), 2.40 (s, 3H), 1.74 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 203.9, 159.9, 137.5, 134.7, 133.0, 127.2, 124.4, 120.0, 119.4, 118.4, 117.7, 117.0, 111.8, 110.5, 108.5, 66.3, 24.4, 14.0.

*2-(1H-Indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2a***)*:* yield 76%, 49.8 mg; yellow solid; mp 224−226 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.12 (s, 1H), 8.43 (dd, $J_1$ = 6.0 Hz, $J_2$ = 3.2 Hz, 1H), 8.29 (d, *J* = 2.8 Hz, 1H), 8.10 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.2 Hz, 1H), 7.90−7.86 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.54−7.47 (m, 2H), 7.29−7.25 (m, 2H) ; $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.2, 155.6, 147.6, 137.0, 136.7, 131.6, 128.0, 126.8, 126.2, 124.9, 122.9, 121.4, 121.3, 116.2, 112.5, 106.4; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{16}H_{10}N_2O_2H^+$ 263.0815, found 263.0819.

*5-Methyl-2-(4-methyl-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2b***)*:* yield 54%, 39.1 mg; yellow solid; mp 222−224 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$:12.05 (s, 1H), 8.18 (d, *J* = 3.1 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.28(d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 2.89 (s, 3H), 2.71 (s, 3H) ; $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 158.9, 155.5, 148.8, 141.7, 137.6, 135.7, 132.4, 131.3, 129.3, 124.1, 123.54, 123.49, 122.9, 114.4, 110.3, 108.3, 23.1, 22.2; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}N_2O_2H^+$ 291.1128, found 291.1132.

*Methyl 2-(4-(methoxycarbonyl)-1H-indol-3-yl)-4-oxo-4H-benzo-[d][1,3]oxazine-5-carboxylate* (***2d***)*:* yield 40%, 37.8 mg; yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.12 (s, 1H), 7.94 (d, *J* = 3.0 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.53−7.50 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 4.00 (s, 3H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 169.0, 158.1, 155.9, 148.2, 137.4, 136.0, 134.9, 132.4, 128.0, 126.1, 125.5, 123.0, 122.9, 121.2, 115.4, 112.9, 108.2, 53.2, 52.3; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{20}H_{14}N_2O_6H^+$ 379.0925, found 379.0931.

*5-Fluoro-2-(4-fluoro-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2e***)*:* yield 38%, 28.31 mg; yellow solid; mp 258−260 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$:12.46 (s, 1H), 8.36 (s, 1H), 7.89−7.84 (m, 1H), 7.37 (t, *J* = 8.5 Hz, 2H), 7.32−7.22 (m, 2H), 7.01−6.97 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 161.0 (d, *J* = 262.6 Hz), 155.7, 155.4 (d, *J* = 249.6 Hz), 154.9 (d, *J* = 4.8 Hz), 149.4, 139.9 (d, *J* = 10.0 Hz), 137.5 (d, *J* = 10.8 Hz), 133.3, 123.8 (d, *J* = 7.6 Hz), 122.2 (d, *J* = 3.6 Hz), 113.6 (d, *J* = 20.3 Hz), 112.6 (d, *J* = 19.2 Hz), 109.0 (d, *J* = 3.7 Hz), 107.4 (d, *J* = 20.6 Hz), 105.9 (d, *J* = 3.1 Hz), 105.5 (d, *J* = 7.1 Hz); HRMS $[M + H]^+$ *m*/*z* calcd for $C_{16}H_8F_2N_2O_2H^+$ 299.0627, found 299.0622.

*6-Methyl-2-(5-methyl-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2f***)*:* yield 62%, 44.7 mg; yellow solid; mp 252−254 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 11.97 (s, 1H), 8.19 (d, *J* = 2.8 Hz, 2H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.70 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, $J_1$ = 8.2 Hz, $J_2$ = 1.6 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.3, 155.1, 145.5, 137.8, 136.6, 135.3, 131.2, 130.2, 127.4, 126.0, 125.1, 124.3, 120.9, 115.8, 112.1, 106.0, 21.4, 20.6; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}N_2O_2H^+$ 291.1128, found 291.1133.

*6-Methoxy-2-(5-methoxy-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2g***)*:* yield 50%, 40.2 mg; yellow solid; mp 243−246 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 11.92 (d, *J* = 1.6 Hz, 1H), 8.16 (d, *J* = 3.2 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.50−7.47 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.3, 157.7, 155.0, 153.9, 141.7, 131.8, 130.9, 127.9, 125.6, 125.4, 116.7, 113.137, 112.5, 108.7, 106.1, 103.4, 55.8, 55.3; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}N_2O_4H^+$ 323.1026, found 323.1029.

*6-Fluoro-2-(5-fluoro-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2i***)*:* yield 46%, 34.3 mg; yellow solid; mp 265−268 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$::12.21 (s, 1H), 8.30 (d, *J* = 8.7 Hz,1H), 8.05 (dd, *J* = 10.0 Hz, 2.6 Hz, 1H), 7.78 (dt, $J_1$ = 8.4 Hz, $J_2$ = 1.7 Hz, 1H), 7.74 (dd, $J_1$ = 6.5 Hz, $J_2$ = 1.7 Hz, 2H), 7.51 (dd, $J_1$ = 8.9 Hz, $J_2$ = 4.6 Hz, 1H), 7.11(td, $J_1$ = 9.2 Hz, $J_2$ = 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.8 (d, *J* = 246.6 Hz), 158.5 (d, *J* = 3.2 Hz), 158.3 (d, *J* = 235.1 Hz), 154.7, 144.3, 133.6, 132.9, 128.9 (d, *J* = 8.4 Hz), 125.4 (d, *J* = 11.2 Hz), 124.6 (d, *J* = 23.9 Hz), 117.4 (d, *J* = 8.8 Hz), 113.8 (d, *J* = 10.0 Hz), 113.0 (d, *J* = 24.10 Hz), 111.1 (d, *J* = 26.2 Hz), 106.3 (d, *J* = 4.4 Hz), 106.1 (d, *J* = 25.0 Hz); HRMS $[M + H]^+$ *m*/*z* calcd for $C_{16}H_8F_2N_2O_2H^+$ 299.0627, found 299.0632.

*6-Chloro-2-(5-chloro-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2j***)*:* yield 48%, 39.6 mg; yellow solid; mp 248−251 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.33 (s, 1H), 8.36−8.35 (m, 2H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.91−7.88 (m, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.30−7.27 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 158.1, 155.4, 146.2, 136.5, 135.5, 133.2, 130.7, 128.3, 126.8, 126.3, 125.9, 123.0, 120.3, 117.7, 114.2, 106.0; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{16}H_8Cl_2N_2O_2H^+$ 331.0036, found 331.0043.

*7-Methyl-2-(6-methyl-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2l***)*:* yield 43%, 37.2 mg; yellow solid; mp 246−248 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 11.97 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 3.2 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.30 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 2H), 7.09 (dd, $J_1$ = 8.2 Hz, $J_2$ = 1.2 Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.2, 155.8, 147.7, 147.7, 137.4, 132.2, 130.9, 128.1, 127.8, 126.1, 123.12, 122.8, 121.0, 113.5, 112.2, 106.4, 21.5, 21.3; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}N_2O_2H^+$ 291.1128, found 291.1133.

*7-Methoxy-2-(6-methoxy-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2m***)*:* yield 44%, 35.4 mg; yellow solid; mp 250−251 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 11.91 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.14 (d, *J* = 2.5 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.05−7.00 (m, 2H), 6.91−6.89 (m, 1H), 3.94 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 165.9, 158.8, 156.5, 156.4, 150.1, 137.8, 130.5, 129.7, 122.0, 118.8, 115.8, 111.6, 108.8, 108.1, 106.5, 95.2, 39.1,38.9; HRMS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}N_2O_4H^+$ 323.1026, found 323.1029.

*7-Fluoro-2-(6-fluoro-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one* (***2n***)*:* yield 54%, 40.2 mg; yellow solid; mp 278−280 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.17 (s, 1H), 8.34(dd, $J_1$= 8.8 Hz, $J_2$ = 5.6 Hz, 1H), 8.26 (d, *J* = 2.8 Hz, 1H), 8.11 (dd, $J_1$ = 8.7 Hz, $J_2$ = 6.2 Hz, 1H), 7.42−7.39 (m, 1H), 7.32−7.26 (m, 2H), 7.10 (dt, $J_1$ = 9.2 Hz, $J_2$ = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 167.0 (d, *J* = 254.7 Hz), 160.6, 158.2, 156.5, 150.0 (d, *J* = 13.9 Hz), 137.0 (d, *J* = 12.64 Hz), 132.7 (d, *J* = 2.4 Hz), 131.1 (d, *J* = 11.3 Hz), 122.4 (d, *J* = 9.9 Hz), 121.5, 115.0 (d, *J* = 23.6 Hz), 113.2 (d, *J* = 1.8 Hz), 111.8 (d, *J* = 22.7 Hz), 110.0 (d, *J* = 24.1 Hz), 106.3, 98.7 (d, *J* = 26.0 Hz); HRMS $[M + H]^+$ *m*/*z* calcd for $C_{16}H_8F_2N_2O_2H^+$ 299.0627, found 299.0630.



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*8-Methyl-2-(7-methyl-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one (**2o**):* yield 68%, 49.3 mg; yellow solid; mp 266−268 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.14 (s, 1H), 8.26−8.24 (m, 2H), 7.94−7.92 (m, 1H), 7.75 (d, $J$ = 6.9 Hz, 1H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.06 (d, $J$ = 7.1 Hz, 1H), 2.62 (s, 3H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.6, 154.6, 145.9, 137.0, 136.5, 134.3, 130.9, 126.2, 125.5, 124.8, 123.4, 121.8, 121.7, 118.8, 115.9, 107.1, 16.9, 16.7; HRMS $[M + H]^+$ $m/z$ calcd for $C_{18}H_{14}N_2O_2H^+$: 291.1128, found 291.1132.

*8-Methoxy-2-(7-methoxy-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one (**2p**):* yield 28%, 22.5 mg; yellow solid; mp 225−228 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.26 (s, 1H), 8.06−8.03 (m, 2H), 7.66 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.2 Hz, 1H), 7.50−7.48 (m, 1H), 7.43 (t, $J$ = 7.8 Hz, 1H), 7.19 (t, $J$ = 8.0 Hz, 1H), 6.84 (d, $J$ = 7.6 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 159.3, 154.4, 153.6, 146.4, 137.6, 130.1, 127.1, 126.9, 126.5, 122.2, 118.9, 117.9, 116.9, 114.0, 107.4, 103.5, 56.4, 55.3; HRMS $[M + H]^+$ $m/z$ calcd for $C_{18}H_{14}N_2O_4H^+$ 323.1026, found 323.1030.

*8-Fluoro-2-(7-fluoro-1H-indol-3-yl)-4H-benzo[d][1,3]oxazin-4-one (**2q**):* yield 32%, 23.8 mg; yellow solid; mp 276−278 °C; $^1$H NMR (400 MHz, DMSO-*d*) $\delta$ 12.74 (s, 1H), 8.33 (d, $J$ = 2.0 Hz, 1H), 8.20 (d, $J$ = 8.0 Hz, 1H), 7.90 (d, $J$ = 7.7 Hz, 1H), 7.80−7.75 (m, 1H), 7.50−7.45 (m, 1H), 7.28−7.23 (m, 1H), 7.14−7.09 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*) $\delta$ 158.1, 158.0, 155.8, 155.4 (d, $J$ = 251.8 Hz), 149.2 (d, $J$ = 243.3 Hz), 136.4 (d, $J$ = 12.0 Hz), 132.5, 128.5 (d, $J$ = 5.0 Hz), 127.2 (d, $J$ = 7.6 Hz), 124.9 (d, $J$ = 13.9 Hz), 123.7 (d, $J$ = 3.8 Hz), 122.3 (d, $J$ = 13.8 Hz), 122.2, 118.3, 117.3 (d, $J$ = 3.4 Hz), 108.0 (d, $J$ = 15.6 Hz), 107.5; HRMS $[M + H]^+$ $m/z$ calcd for $C_{16}H_8F_2N_2O_2H^+$ 299.0627, found 299.0624.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02893.

Experimental procedures, characterization data, and $^1$H/$^{13}$C NMR spectra of all products (PDF)

X-ray crystallographic data of compound **2a** (CIF)

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### Notes

The authors declare no competing financial interest.

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