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One-pot synthesis of substituted dibenzoxazepinones and pyridobenzoxazepinones using octacarbonyldicobalt as an effective CO source

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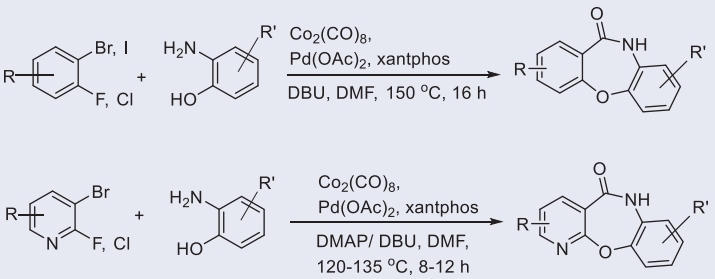
ABSTRACT

A facile one-pot protocol for the synthesis of substituted dibenzoxazepinones and pyridobenzoxazepinones from commercially available aryl/heteroaryl halides and amino phenols using octacarbonyldicobalt ($Co_2(CO)_8$) as an effective metal carbonyl source has been demonstrated. This method proceeds via the sequential coupling of aryl/heteroaryl halides with aminophenol by amidation and intramolecular cyclization to give dibenzoxazepinones/pyridobenzoxazepinones.

GRAPHICAL ABSTRACT



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KEYWORDS
Amidation; $Co_2(CO)8$; dibenzoxazepinones; intramolecular cyclization; pyridobenzoxazepinones

Introduction

The 6/7/6 fused tricyclic heterocycles, especially pyridobenzoxazepinones, dibenzoxazepinones and its derivatives, constitute a key building block for number of biologically active molecules.[1,2] Dibenzoxazepinones were isolated as natural products from the leaves of Carex distachya (a and b, **I**) and mycemycins A–E (a–e, **II**) from the ethanolic extracts of mycelia of two different streptomycetes (Fig. 1).[3]

The derivatives of pyridobenzoxazepinones and dibenzoxazepinone have been found to show many biological activities such as anti-tumor,[4] H_4R agonist,[5] anti-inflammatory activities,[6] and non-nucleoside inhibitors of HIV-1 reverse

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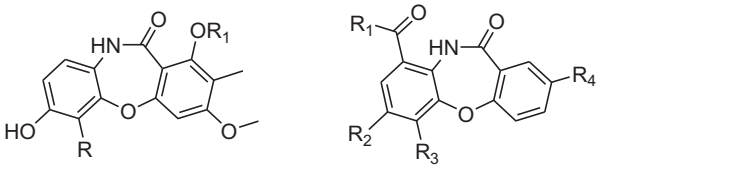


I

a) R = R_1 = CH_3
b) R = R_1 = H

II

a) R_1 = OMe, R_2 = R_3 = R_4 = H
b) R_1 = OMe, R_2 = R_3 = H, R_4 = Cl
c) R_1 = OMe, R_2 = Cl, R_3 = CH_3, R_4 = Cl
d) R_1 = NH_2, R_2 = Cl, R_3 = CH_3, R_4 = H
e) R_1 = NH_2, R_2 = Cl, R_3 = CH_3, R_4 = Cl

Figure 1. Chemical structures of dibenzoxazepinones from Carex distachya (a and b, **I**) and mycemycins A–E (a–e, **II**).

transcriptase.[7] Furthermore, the dibenzoxazepinone and pyridobenzoxazepinone compounds are precursor for the synthesis of numerous pharmaceutical agents with various biological activities. For example, nitroxazepine brand name Sintamil (**III**) bearing dibenzoxazepinone skeleton is used as an antidepressant agent.[8] Amoxapine (**IV**),[9] a derived skeleton of dibenzoxazepinone is a marketed antidepressant drug. Loxapine (**V**),[10] is a typical antipsychotic medication used in the treatment of schizophrenia (Fig. 2). 5-(4-Methylpiperazin-1-yl)-8-chloro-pyrido[2,3-b][1,5]-benzoxazepine, **JL 13** with potential atypical antipsychotic activity[11] (Fig. 3) is derived from pyridobenzoxazepinone derivative.

Conventional methods to prepare dibenzoxazepinones and their derivatives involve traditional intermolecular cyclization of ortho-amino phenols with ortho halo benzoic acids [5,12]/or ortho-nitro benzoic acids,[13] or through a reduction – lactamization route.[14] Pyridobenzoxazepinones and their derivatives can be prepared either by condensation/S_NAr sequence of ortho-halo nicotinoyl chloride/ortho-halo nicotinic acid with ortho-amino phenols or by Smiles rearrangement of ortho halo nicotinamide with ortho-halo phenols.[15] Alper and coworkers reported an intramolecular carbonylation for the synthesis of dibenzoxazepinones by employing a palladium-complexed dendrimers.[16] Yunfei and coworkers reported a synthesis of dibenzoxazepinone compounds from 2-(aryloxy)benzamides through hypervalent iodine(III)-mediated oxidative cyclization.[17] Recently, phenyliodine(III) diacetate-mediated synthesis of diaryl ethers with an o-CHO and secondary amine substituents upon subsequent treatment with $NaBH(OAc)_3$ and PCC provided dibenzoxazepines and dibenzoxazepinones, respectively was reported.[18] All these routes usually involve multistep synthesis, the isolation of intermediates, severe conditions and low yields of products are obtained in some cases. Thus, developing an innovative, general and highly efficient route to synthesize the skeleton of dibenzoxazepinones and pyridobenzoxazepinones from commercially available reagents is an interesting and challenging topic for organic chemists. The transition metal-catalyzed carbonylation has become an important tool in organic synthesis.[19] Wu and coworkers have reported (Scheme 1) the one- pot fusion of palladium-catalyzed carbonylative S_NAr approach for the synthesis of dibenzoxazepinones,[20a]

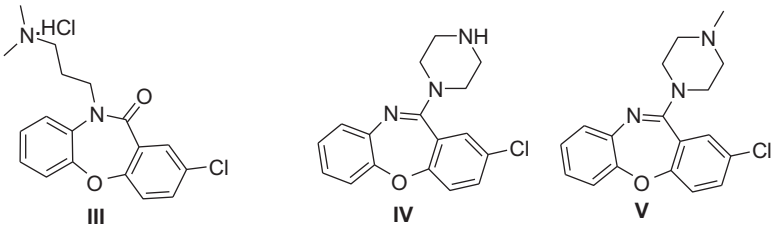


Figure 2. Representative biologically active dibenzoxazepinones and their derivatives.

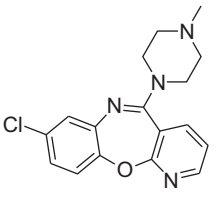
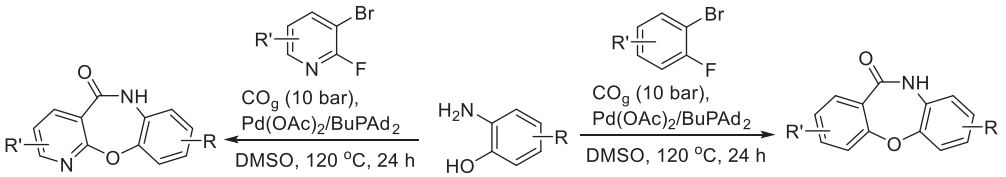


Figure 3. Potential atypical antipsychotic **JL 13 (AAP)**.



Scheme 1. Benzoxazepinone synthesis by using CO gas.

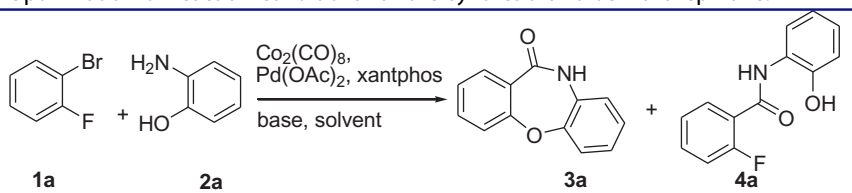
pyridobenzoxazepinones,[20b] chromones,[20c] thiochromenones,[20d] using CO gas as a carbonylation source. These reactions involve initial evacuation of toxic CO gas and high pressure of CO gas (10 bar). Although the methodology is useful in the industry on a large scale, the toxicity of CO gas as well as the requirement of special pressure reaction set-ups make it inconvenient in small-scale laboratory and library (analogous) synthesis.

In our previous work, we have described the synthesis of benzamides, phthalazinones and β-ketoesters using $CO_2(CO)_8$ as a successful *in situ* CO source.[21] Based on that, in our present work, we have focused on developing an one-pot protocol for the rapid ring construction of dibenzoxazepinones, pyridobenzoxazepinones and their derivatives using $CO_2(CO)_8$ as an effective *in situ*-generated, stoichiometric CO source starting from readily available raw materials. Moreover, reactions were carried out using a commercially available sealed tubes or Microwave vials.

Results and discussion

Initially, 1-bromo-2-fluorobenzene (**1a**) and 2-amino phenol (**2a**) (Table 1) were selected as the model substrate to optimize the reaction conditions including

Table 1. Optimization of reaction conditions for the synthesis of dibenzoxazepinone.



1a **2a** **3a** **4a**

Entry	Solvent	Temp (°C)	Base	Time (h)	Yield (%)[a] **3a**
1	1,4-Dioxane	90	DMAP	2	7
2	Toluene	90	DMAP	2	5
3	THF	90	DMAP	2	12
4	1,4-Dioxane	120	DMAP	2	16
5	DMF	120	DMAP	2	22
6	DMSO	120	DMAP	2	18
7	NMP	120	DMAP	2	17
8	DMA	120	DMAP	2	20
9	DMF	150	DMAP	2	22
10	DMF	150	DMAP	5	35
11	DMSO	150	DBU	5	45
12	DMF	150	DABCO	5	42
13	DMF	150	DBU	8	62
14	DMF	150	DBU	12	84
15	DMF	150	DBU	16	89
16	DMF	90	DBU	2	35[b]
17	DMF	90	DBU	8	62[b]

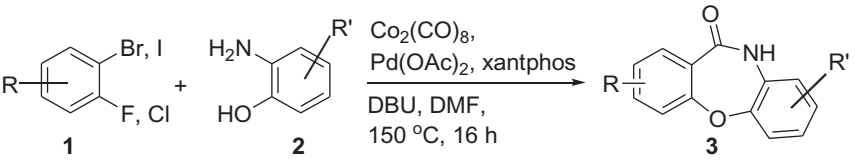
Notes. All the reactions were executed with 1-bromo-2-fluorobenzene **1a** (1 mmol), 2-amino phenol **2a** (1 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (5 mol%), base (2.5 mmol), solvent (10 V) and $Co_2(CO)_8$ (0.25 mmol).
[a]Yield of isolated products. [b]isolated yields of Un-cyclised **4a** was isolated.

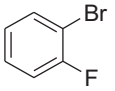
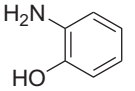
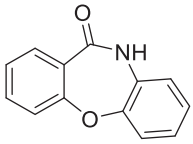
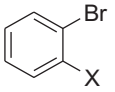
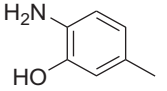
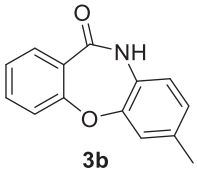
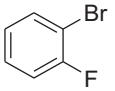
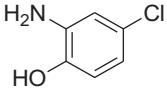
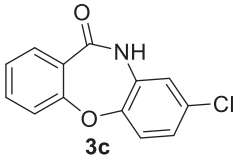
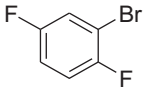
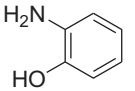
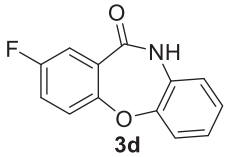
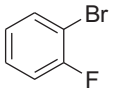
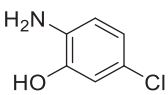
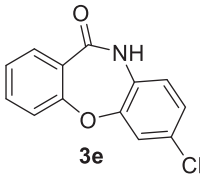
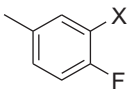
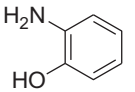
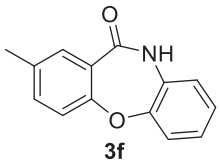
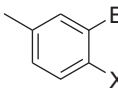
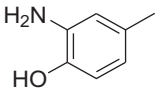
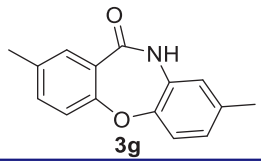
optimization of the catalysts, ligands, bases, and solvents. Guided by the literature and our own results, a preliminary study was carried out on a 1 mmol of **1a**, 1 mmol of **2a** using DMAP, $Pd(OAc)_2$, xantphos and $CO_2(CO)_8$ in DMSO at 150 °C for 5 h in a sealed tube. We obtained a mixture of dibenzoxazepinone **3a** and uncyclized product **4a** in low yields. Further investigation on bases, solvents and temperature systems were conducted. Among the tested solvents, we found that DMF was the best solvent (Table 1, entry 5). Investigations on the tested bases revealed that the highest yield was achieved when DBU was used (Table 1, entry 15) at 150 °C for 16 h.

All the reactions were carried out by the conventional heating method and the yields were concluded by an average isolated yield of reactions performed twice. By the controlled experiment conditions (Table 1 entry 16 and 17), we found that the reaction proceeds via the aminocarbonylation followed by cyclization. The optimization of the catalytic system employed in the study has been carried out and the result indicated that $Pd(OAc)_2$/xantphos was found to be the best system. Further, the scope and generality of the method was next explored under the optimized reaction conditions (Table 1, entry 15). A variety of dibenzoxazepinones (**3a–3k**) were synthesized in good to excellent yields. Several useful functional groups of both the aryl halides (I, Br) and amino phenols were tolerated in the reaction condition (Table 2).

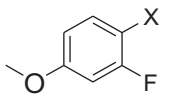
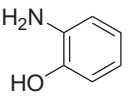
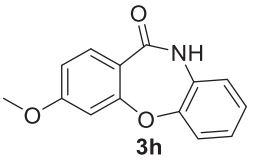
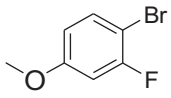
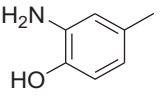
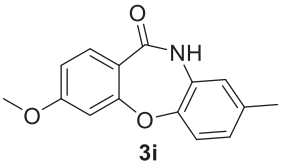
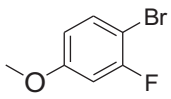
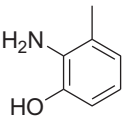
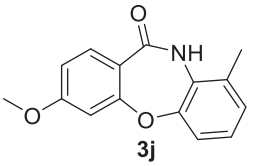
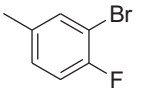
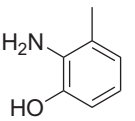
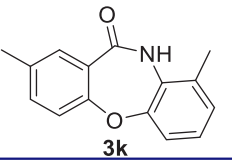
The accessibility of this method was further explored by the synthesis of pyridobenzoxazepinones. Initially, we have attempted with our optimized reaction condition as that of dibenzoxazepinones (Table 1, entry 15) starting from 3-bromo-2-chloro pyridine

Table 2. Synthesis of substituted dibenzoxazepinones.



Entry	Substrate (**1**)	Substrate (**2**)	Product (**3**)	Yield (%)[a]
1			 **3a**	89
2			 **3b**	X = F, 91, X = Cl, 79
3			 **3c**	88
4			 **3d**	72
5			 **3e**	85
6			 **3f**	X= Br, 92, X =I, 90
7			 **3g**	X = F, 90, X = Cl, 74

(*continued*)

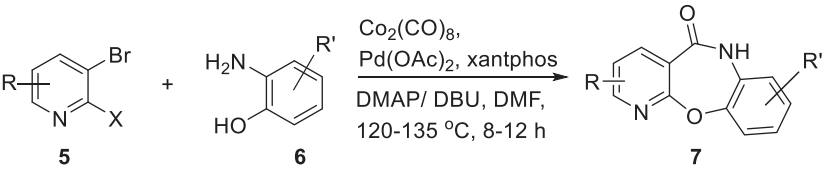
8			 **3h**	X=Br, 72, X=I, 75
9			 **3i**	76
10			 **3j**	80
11			 **3k**	77

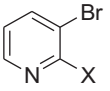
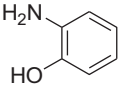
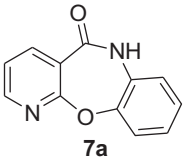
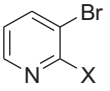
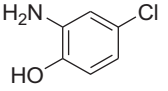
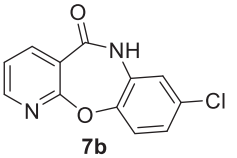
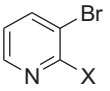
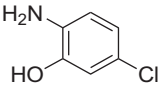
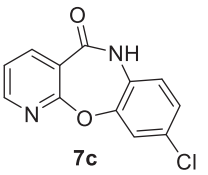
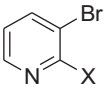
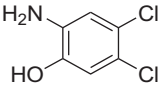
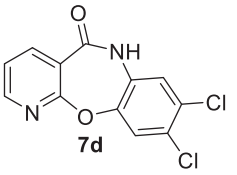
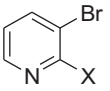
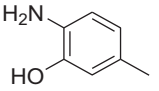
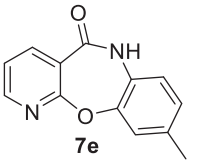
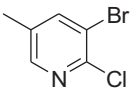
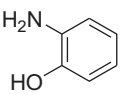
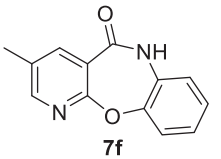
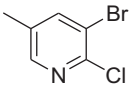
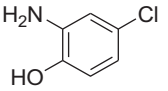
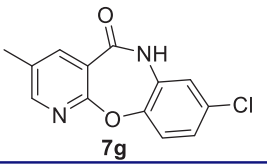
Notes. All the reactions were executed with **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (5 mol%), $Co_2(CO)_8$ (0.25 mmol), DBU (2.5 mmol), DMF (10 V), 150 °C and 16 h. [a] Yields quoted are isolated yields.

and 2-amino phenol. As anticipated, the reaction got completed but the isolated yield was poor (27%). Then, we studied the reaction by reducing the reaction temperature and isolated 82% of the desired product 7**a** at 135 °C for 12 h (Table 3, entry 1). Further reducing the temperature did not improve the yield. Next, we tried the same reaction condition with 3-bromo-2-fluoro pyridine and 2-amino phenol, and surprisingly ended up with a very low yield (<5%). Further, we optimized the temp and base in the reaction and identified the optimum reaction condition is DMAP as base at 120 °C for fluoro substituted aryl halides. Finally, we explored a variety of heteroaryl halides (**5a–5j**) with various amino phenols and isolated corresponding pyridobenzoxazepinones (**7a–7j**) in moderate yields by appropriate reaction conditions.

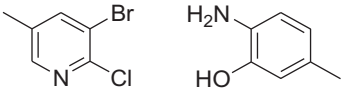
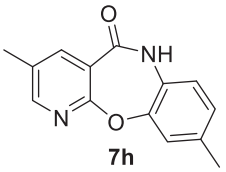
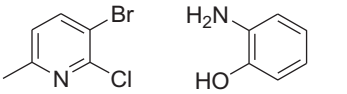
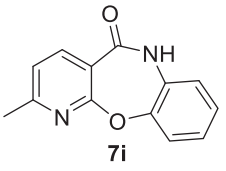
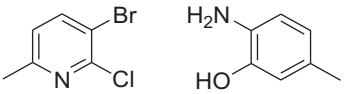
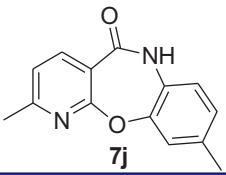
To conclude, we have demonstrated this method to be a parallel synthesis technique (20 reactions sequence). All the above-synthesized benzoxazepinone (**3a–3k** and **7a–7j**) compounds were experimented on 100 mg scale of corresponding aryl/heteroaryl halide and the isolated yields were similar to the previously reported yields. Then, we explored in gram scale (1 g and 5 g scale) and isolated a moderate yield (Scheme 2). The consistency of yields obtained encouraged us to synthesize a potential atypical antipsychotic molecule **JL 13 (AAP)** by carbonylation synthetic sequence (Scheme 2, Steps – 1, 2 and 3).[1]

Table 3. Synthesis of substituted pyridobenzoxazepinones.



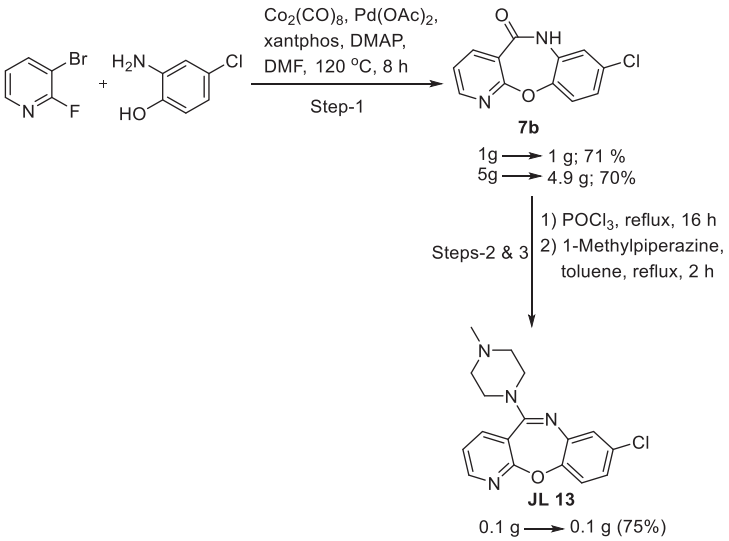
Entry	Substrate (**5**)	Substrate (**6**)	Product (**7**)	Yield (%)[a]
1			 **7a**	X= F, 76, X= Cl, 82
2			 **7b**	X= F, 70, X= Cl, 65
3			 **7c**	X= F, 78, X= Cl, 72
4			 **7d**	X= F, 68, X= Cl, 56
5			 **7e**	X= F, 88, X= Cl, 81
6			 **7f**	67
7			 **7g**	73

(*continued*)

8			 **7h**	71
9			 **7i**	70
10			 **7j**	73

Notes. All the reactions were executed with **5** (1 mmol), **6** (1 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (5 mol%), DMF (10 V) and $Co_2(CO)_8$ (0.25 mmol).

[a]Yields quoted are isolated yields. When X = F, reaction was executed with DMAP (2.5 mmol) as a base at 120 °C for 8 h. When X = Cl, reaction was executed with DBU (2.5 mmol) as a base at 135 °C for 12 h.



Scheme 2. Synthesis of 7b and 5-(4-Methylpiperazin-1-yl)-8-chloro-pyrido[2,3-b][1,5]-benzoxazepine (**JL 13, AAP**).

Conclusion

We have successfully developed an effective method for the synthesis of dibenzoxazepinones and pyridobenzoxazepinones by employing one-pot amino carbonylation followed by etherification using $CO_2(CO)_8$ as an effective *in situ* CO source. The aryl halides and heteroaryl halides were separately optimized and isolated good to moderate yields. These reactions were performed in regular laboratory fume hood without the

requirement of much precautions, such as handling the carbon monoxide cylinders, initial CO evacuation of the reaction vessels and special fume hood. We believe the methodology can be significant in the synthesis of various new bio-significant molecules constituted of dibenzoxazepinones and pyridobenzoxazepinones core. These reactions can be performed using common sealed tubes/glass pressure tubes. This method is very convenient in academic and laboratory small scale studies as well as library (analogous) synthesis as the special pressure reaction equipments are not involved.

Experimental

Commercially available reagents were used as received in this work. Purification of products was performed by silica-gel column chromatography. ^{1}H NMR spectra were obtained using a 300-MHz or 400-MHz spectrometer. ^{13}C NMR spectra were obtained from a 75-MHz or 100-MHz spectrometer. All ^{1}H and ^{13}C NMR experiments are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and were measured relative to the signals for residual chloroform in the deuterated solvents. The mass spectra were recorded on liquid chromatography–mass spectrometry (LCMS). All the spectral data matched well with the literature descriptions. For the unknown compounds were further characterized by elemental analysis (CHN).

General experimental procedure

General procedure for the synthesis of substituted dibenzoxazepinones

A sealed tube equipped with a magnetic stir bar was charged with the corresponding 1-bromo-2-fluoro (or chloro) benzene/1-fluoro-2-iodobenzene (1 mmol), amino phenol (1 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (5 mol%) and DBU (2.5 mmol). The tube was purged with argon. Then DMF (10 V) was added followed by the addition of $CO_2(CO)_8$ (0.25 mmol). The tube was closed with seal plug instantly. The reaction tube was placed in a preheated oil bath at 150 °C for 16 h. On completion, the reaction mixture was cooled to room temperature, added water and ethyl acetate (1:1). Precipitated solid was filtered through a celite bed. The bed was washed thoroughly with ethyl acetate. Organic layer was separated. Aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate. Organic layer was concentrated under reduced pressure and purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate and petroleum ether as eluent to afford the corresponding dibenzoxazepinone.

General procedure for the synthesis of substituted pyridobenzoxazepinones

A sealed tube equipped with a magnetic stir bar was charged with the corresponding 3-bromo-2-fluoropyridine (1 mmol), amino phenol (1 mmol), $Pd(OAc)_2$ (5 mol%), xantphos (5 mol%) and DMAP (2.5 mmol). The tube was purged with argon. Then DMF (10 V) was added followed by the addition of $CO_2(CO)_8$ (0.25 mmol). The tube was closed with seal plug instantly. The reaction tube was placed in a preheated oil bath at 120 °C to 135 °C for 8–12 h. On completion, the reaction mixture was cooled to room

temperature, added water and ethyl acetate (1:1). Precipitated solid was filtered through a celite bed. The bed was washed thoroughly with ethyl acetate. Organic layer was separated. Aqueous layer extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate. Organic layer was concentrated under reduced pressure and purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate and petroleum ether as eluent to afford the corresponding pyridobenzoxazepinone.

Selected spectroscopic data

Dibenzo[b,f][1,4]oxazepin-11(10H)-one (3a)[16,19a]

Following the general procedure using 1-bromo-2-fluorobenzene (175 mg, 1 mmol) and 2-aminophenol (110 mg, 1 mmol) provided 188 mg (89% yield) of **3a** as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H), 7.77 (dd, $J = 1.60$, 7.80 Hz, 1H), 7.64–7.59 (m, 1H), 7.36–7.30 (m, 3H), 7.19–7.11 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 159.7, 150.9, 134.5, 132.0, 130.6, 125.9, 125.8, 125.2, 125.1, 121.7, 121.3, 120.8; LCMS (APCI-MS) Calcd. for $C_{13}H_9NO_2$: 211.06, found $[M + H]^+ = 212.4$.

Benzo[b]pyrido[3,2-f][1,4]oxazepin-5(6H)-one (7a)[19b]

Following the general procedure using 3-bromo-2-fluoropyridine (175 mg, 1 mmol) and 2-aminophenol (109 mg, 1 mmol) provided 161 mg (76% yield) of **7a** as a white solid. Following the general procedure using 3-bromo-2-chloropyridine (190 mg, 1 mmol) and 2-aminophenol (109 mg, 1 mmol) provided 174 mg (82% yield) of **7a** as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.51 (dd, $J = 1.96$, 4.74Hz, 1H), 8.28 (dd, $J = 1.92$, 7.58Hz, 1H), 7.47 (dd, $J = 4.80$, 7.56 Hz, 1H), 7.36–7.34 (m, 1H), 7.26–7.16 (m, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 164.4, 162.4, 152.5, 148.2, 142.5, 130.6, 126.5, 125.6, 122.6, 121.9, 121.8, 120.1; LCMS (APCI-MS) Calcd. for $C_{12}H_8N_2O_2$: 212.05, found $[M + H]^+ = 213.2$.

5-(4-Methylpiperazin-1-yl)-8-chloro-pyrido[2,3-b][1,5]-benzoxazepine (JL 13)[1]

A solution of 8-chlorobenzo[b]pyrido[3,2-f][1,4]oxazepin-5(6H)-one **7b** (100 mg, 0.41 mmol) in $POCl_3$ (2 mL) was heated to reflux for 16 h. On completion, the reaction mixture was cooled to RT; the excess phosphorus oxychloride was removed under reduced pressure. The residue obtained was co-evaporated with toluene (2 × 10 mL) to afford crude iminochloride as a brown sticky residue which was used without further purification. It was dissolved in toluene (2 mL), and an excess of 1-methylpiperazine (406 mg, 4.1 mmol) was added. The mixture was heated to reflux for 2 h. The solvent was then evaporated under reduced pressure, and the residue was dissolved in chloroform (15 mL) and washed with water (2 × 10 mL), brine (1 × 10 mL), dried over anhydrous sodium sulfate filtered through a cotton plug and concentrated under reduced pressure to afford crude. Crude obtained was purified by flash column chromatography on silica gel (230–400 mesh) with MeOH and dichloromethane as eluent to afford 133 mg (75% yield) of **JL 13** as beige solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.51

(dd, $J = 1.20$, 4.60 Hz, 1H), 7.60 (dd, $J = 1.20$, 8.20 Hz, 1H), 7.43 (dd, $J = 4.40$, 8.20 Hz, 1H), 7.16 (d, $J = 2.80$ Hz, 1H), 7.06 (d, $J = 8.40$ Hz, 1H), 06.91 (dd, $J = 2.40$, 8.60 Hz, 1H), 3.74–3.73 (m, 4H), 2.60–2.50 (m, 4H), 2.38 (s, 3H); LCMS (APCI-MS) Calcd. for $C_{17}H_{17}ClN_4O$: 328.10, found $[M + H]^+ = 329.0$.

Full experimental details, ^1H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article webpage

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Disclosure statement

No potential conflict of interest was reported by the authors.

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