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RESEARCH ARTICLE

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Regioselective Synthesis of Fused Oxazepinone Scaffolds through One-Pot Smiles Rearrangement Tandem Reaction

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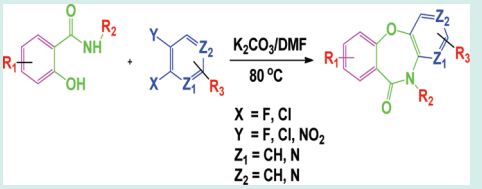
Supporting Information

ABSTRACT: The paper describes a convenient and facile methodology for the regioselective synthesis of fused oxazepinone scaffolds. This process is an efficient construction of the oxazepinone scaffold by a one-pot coupling/Smiles rearrangement/cyclization approach. This transition metal-free process has potential applications in the synthesis of biologically and medicinally relevant compounds.

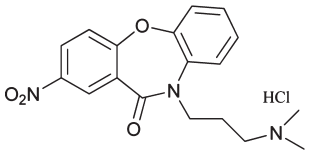


KEYWORDS: one-pot, coupling/Smiles rearrangement/cyclization process, fused oxazepinone scaffolds

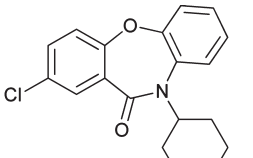
INTRODUCTION

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. Combinatorial chemistry[1] has emerged as a useful tool for the synthesis of biological compounds.

Fused oxazepinone derivatives have attracted considerable attention owing to their promising biological activities, such as anticancer,[2] anti-HIV,[3] antidepressant,[4] and antitumor[5] activities. They also show a wide range of pharmacological and neurochemical activities as potential central nervous system agents,[6] potential atypical antipsychotics,[7] β-secretase inhibitors,[8] histone deacetylase inhibitors,[9] and muscarinic cholinergic receptors.[10] Among them, Sintamil(I)[4] and its derivatives were reported as antidepressants. Ioxapine[7] was reported for its potential clozapine-like properties.



Sintamil I



Ioxapine

As a result, various methods have been developed to synthesize fused oxazepinone scaffolds, including intramolecular aromatic substitution in 2-hydroxyanilines of *ortho* substituted benzoic acids (X = F, Cl, NO_2),[11] the reaction of 2-(2-halophenoxy)-phenylamines and 2-(2-halophenoxy)pyridine-3-amines with carbon monoxide under pressure using palladium catalysts,[12] the heating of xanthen-9-one oximes with phosphorus pentachloride via Beckmann rearrangement,[13] and the intramolecular cyclocarbonylation of substituted 2-(2-iodophenoxy)anilines.[14] However, these methods are not ideal because they either involve multiple steps or use a transition metal catalyst.

A one-step synthetic route, without transition metal catalyst, would be a very useful improvement. The Smiles rearrangement has become a powerful method in pharmaceutical, biomedical, and optical chemistry.[15] Herein, we report an effective regioselective synthesis of fused oxazepinone scaffolds via Smiles rearrangement tandem reaction by the reaction of commercially available *N*-substituted salicylamides with substituted benzenes or pyridines (Scheme 1).

RESULTS AND DISCUSSION

To study the range of the reaction, various *N*-substituted salicylamides were reacted with 1,2-difluoro-4-nitrobenzene, with the results shown in Table 1. Both the *N*-alkyl and *N*-aryl salicylamides produced the corresponding products with good to excellent yields (Table 1, entries 1−12).

A variety of compounds **2** were then studied under the same reaction conditions, with the results in Table 2. When **1b** was reacted with benzenes possessing electron-withdrawing groups, such as nitro, nitrile, halogen, and trifluoromethyl, the desired products **4b**−**i** were generated in good to excellent yields (Table 2, entries 1−8).

Moreover, reactions of **1b** with **2j** under the same conditions produced the corresponding pentacyclic heterocycle product **4j** with 60% yield (entry 9). As **1b** was reacted with an electron-donating group, such as methyl **2l** and acetamide **2m**, and the corresponding products **4l**−**m** were generated with moderate yields (entries 11−12). It is noteworthy that the yield of the reaction with a benzene ring having an electron-withdrawing group is higher than that with an electron-donating group.

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Scheme 1. Synthesis of Fused Oxazepinone Scaffolds

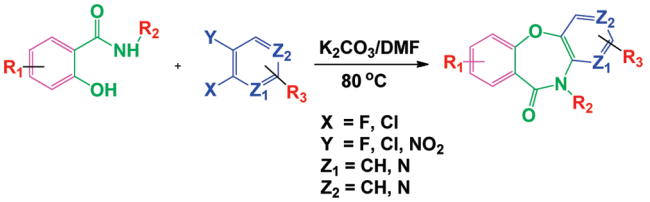
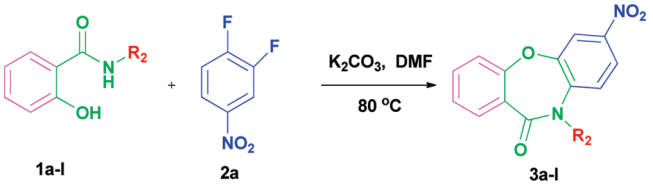


Table 1. Reaction of *N*-Substituted Salicylamides with 1, 2-Difluoro-4-nitrobenzene[a]



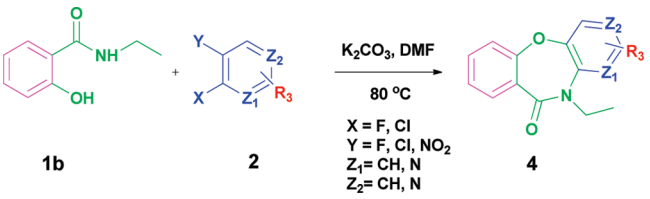
entry	R_2	product	time/h	yield[b] (%)
1	Me (**1a**)	**3a**	1	93
2	Et (**1b**)	**3b**	2	96
3	Pr (**1c**)	**3c**	1	87
4	*i*-Pr (**1d**)	**3d**	1	96
5	*c*-Hex (**1e**)	**3e**	1	87
6	Bn (**1f**)	**3f**	1	88
7	Ph (**1 g**)	**3g**	1	83
8	4-MePh (**1 h**)	**3h**	1	71
9	4-OMePh (**1i**)	**3i**	1	82
10	4-FPh (**1j**)	**3j**	1	80
11	4-ClPh (**1k**)	**3k**	4	79
12	4-BrPh (**1 L**)	**3l**	1	97

[a] Reaction conditions: 1.2 mmol **1a**−**l**, 1 mmol **2a**, 3 mmol K_2CO_3, 10 mL of DMF, 80 °C, 1−4 h. [b] Isolated yield.

Furthermore, the reaction of a variety of functional *N*-benzyl salicylamides with 1,2-difluoro-4-nitrobenzene was then investigated, with the results shown in Table 3. Reactions of *N*-benzyl salicylamide containing an electron-donating substitutent **5a** with **2a** gave the corresponding product **6a** with 88% yield (Table 3, entry 1). *N*-benzyl salicylamide bearing a halogen atom, such as **5b**, was successfully utilized to give rise to the desired product **6b** with 90% yield (entry 2). *N*-benzyl-3-hydroxy-2-naphthamide **5c** and *N*-benzyl-1-hydroxy-2-naphthamide **5d** were converted into the desired products **6c**−**d** with 92% and 50% yield (entries 3−4).

On the basis of reported Smiles rearrangement chemistry and our experimental results, a plausible reaction mechanism is presented in Scheme 2. The reaction of **1a**−**l** with **2a** yielded compound **7a**−**l**. Compound **7a**−**l** could proceed in two paths (I and II). Path I would afford the direct intramolecular nucleophilic substitution product **9a**−**l**. Path II would lead to compound **3a**−**l** via Smiles rearrangement. However, **9a**−**l** was not detected. Therefore, Imido nitrogen in compound **8a**−**l** underwent intramolecular nucleophilic attack on the carbonium (*para* position to the nitro group). Migration of the spiro-oxygen, proceeding through the

Table 2. Reaction of *N*-Ethyl Salicylamide 1b with Various 2[a]



Entry	**2b-m**	Product **4b-m**	Time /h	Yield[b] (%)
1	**2b**	**4b**	2	75
2	**2c**	**4c**	1	89
3	**2d**	**4d**	1	91
4	**2e**	**4e**	2	80
5	**2f**	**4f**	1	70
6	**2g**	**4g**	2	73
7	**2h**	**4h**	5	64
8	**2i**	**4i**	3	65
9	**2j**	**4j**	6	60
10	**2k**	**4k**	5	50
11	**2l**	**4l**	6	56
12	**2m**	**4m**	4	56

[a] Reaction conditions: 1.2 mmol **1b**, 1 mmol **2**, 3 mmol K_2CO_3, 10 mL of DMF, 80 °C, 1−6 h. [b] Isolated yield.

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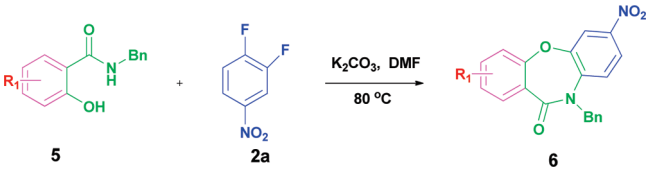
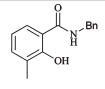
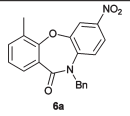
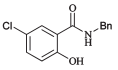
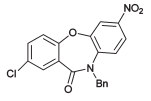
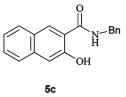
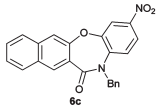
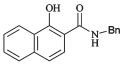
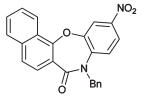
"Meisenheimer Complex" **10a**−**l**, with intramolecular nucleophilic displacement of fluoride anion by an oxygen anion of compound **11a**−**l** yielded the desired cyclization product **3a**−**l**.

Table 3. Reaction of Functional *N*-Benzyl Salicylamide with 1,2-Difluoro-4-nitrobenzene[a]



5 2a 6

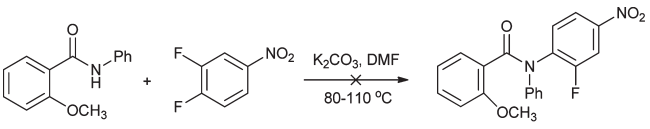
Entry	5	Product	Time /h	Yield[b] (%)
1	 5a	 6a	1	88
2	 5b	 6b	1	90
3	 5c	 6c	4	92
4	 5d	 6d	10	50

[a] Reaction conditions: 1.2 mmol **5**, 1 mmol **2a**, 3 mmol K_2CO_3, 10 mL of DMF, 80 °C, 1−10.5 h. [b] Isolated yield.

In support of the proposed mechanism, compound **12** was reacted with **2a** under the same conditions as above. In this instance, no reaction took place, even when the temperature was up to 110 °C (Scheme 3). This result indicates that the amide group in *N*-substituted salicylamides cannot serve as the nucleophilic reaction center. It is important to note that the reaction was performed via Smiles rearrangement.

Additionally, the result can be unambiguously supported by the molecular structure of **4d** being confirmed by X-ray analysis (Figure 1).

Scheme 3. Reaction of 12 with 2a



12 2a 13

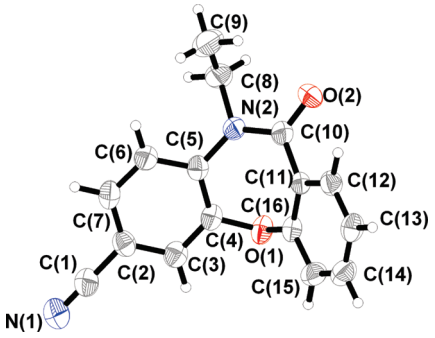
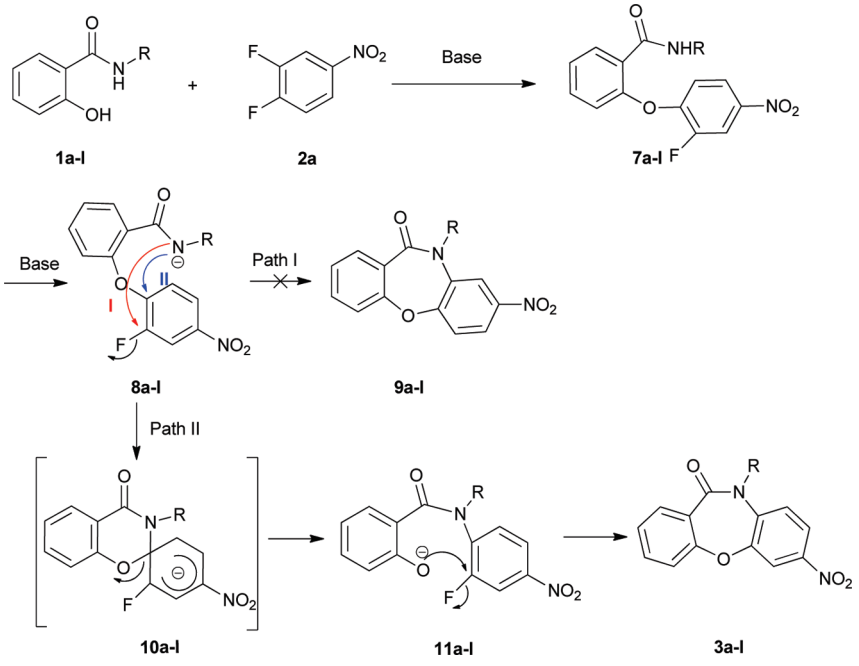


Figure 1. X-ray crystal structure of **4d**.

Scheme 2. Plausible Reaction Mechanism



1a-l 2a 7a-l 8a-l 9a-l 10a-l 11a-l 3a-l

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CONCLUSION

In conclusion, a variety of fused oxazepinone derivatives were systematically obtained in moderate to excellent yields via a Smiles rearrangement tandem reaction. Of particular importance, the described chemistry is a transition metal-catalyst-free process, and therefore a green method for the construction of these important heterocyclic compounds, which exhibits a wide range of applications in medicinal chemistry. Further studies on its application in the synthesis of biologically relevant compounds are currently in progress.

EXPERIMENTAL PROCEDURES

General Experimental Procedure for the Synthesis of (3a−l), (4b−m), (6a−d). *Representative Procedure for the Synthesis of 10-Ethyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3b**).* To a solution of *N*-ethyl salicylamide (150 mg, 0.9 mmol) in dry dimethylformamide (DMF, 10 mL) were added 1,2-difluoro-4-nitrobenzene (120 mg, 0.8 mmol) and K_2CO_3 (310 mg, 2.3 mmol), then the mixture was stirred for 1 h at 80 °C (oil bath), and then H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL) . The combined organic layers were washed with sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (PE/EtOAc = 5:1) to afford the desired product **3b** as a pale yellow oil (207 mg, 96%).

*10-Methyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3a**).* White crystal, mp 158−163 °C ^{1}H NMR (300 MHz, CDCl3) δ 8.15 (d, 1H, J = 2.7 Hz), 8.08−8.12 (dd, 1H, J = 2.7, 9 Hz), 7.89−7.92 (dd, 1H, J = 1.8, 9 Hz), 7.50−7.56 (m, 1H), 7.34−7.37 (d, 1H, J = 9 Hz), 7.26−7.31 (m, 2H), 3.63 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 165.76, 159.57, 152.86, 144.74, 142.26, 134.33, 132.56, 125.98, 125.31, 122.40, 121.27, 119.86, 117.56, 37.02. HRMS calcd for $C_{14}H_{10}N_2O_4$, 270.0641; found, 270.0721.

*10-Ethyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3b**).* Pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 8.14−8.15 (d, 1H, J = 2.7 Hz), 8.07−8.11 (dd, 1H, J = 2.4, 9 Hz), 7.84−7.87 (dd, 1H, J = 1.8, 7.8 Hz), 7.43−7.54 (m, 2H), 7.23−7.30 (m, 2H), 4.09−4.23 (q, 2H, J = 7.2 Hz), 1.39−1.44 (t, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.48, 159.61, 153.71, 144.75, 141.36, 134.03, 132.27, 126.14, 125.98, 122.82, 121.23, 119.66, 117.65, 44.71, 13.75. HRMS calcd for $C_{15}H_{12}N_2O_4$, 284.0797; found, 284.0876.

*7-Nitro-10-propyldibenzo[b,f][1,4]oxazepin-11(10H)-one (**3c**).* Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.14−8.15 (d, 1H, J = 2.7 Hz), 8.07−8.10 (dd, 1H, J = 2.4, 9 Hz), 7.84−7.87 (dd, 1H, J = 1.5, 7.5 Hz), 7.48−7.53 (m, 1H), 7.41−7.44 (d, 1H, J = 9 Hz), 7.24−7.30 (m, 2H), 4.11−4.16 (t, 2H, J = 6.9 Hz), 1.71−1.83 (m, 2H), 0.94−0.99 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.68, 159.76, 154.11, 144.85, 141.28, 133.99, 132.35, 126.11, 125.99, 123.35, 121.16, 119.64, 117.73, 50.58, 21.24, 11.09. HRMS calcd for $C_{16}H_{14}N_2O_4$, 298.0954; found, 298.1031.

*10-Isopropyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3d**).* Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.12 (d, 1H, J = 2.6 Hz), 8.04−8.07 (dd, 1H, J = 2.6, 8.88 Hz), 7.84−7.86 (dd, 1H, J = 1.6, 7.64 Hz), 7.50−7.52 (d, 1H, J = 8.96 Hz), 7.45−7.49 (m, 1H), 7.22−7.31 (m, 2H), 4.70−4.77 (m, 1H), 1.58−1.59 (d, 6H, J = 6.56 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.62, 160.07, 155.09, 145.17, 140.97, 133.82, 132.41, 126.51, 125.92, 124.57, 120.69, 119.49, 117.43, 54.20, 21.37. HRMS calcd for $C_{16}H_{14}N_2O_4$, 298.0954; found, 298.1026.

*10-Cyclohexyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3e**).* Pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 8.10−8.11 (d, 1H, J = 2.7 Hz), 8.02−8.06 (dd, 1H, J = 2.7, 9 Hz), 7.80−7.83 (dd, 1H, J = 1.5, 7.5 Hz), 7.50−7.53 (d, 1H, J = 8.7 Hz), 7.42−7.48 (m, 1H), 7.19−7.26 (m, 2H), 4.26−4.30 (m, 1H), 0.81−2.11 (m, 10H). ^{13}C NMR (75 MHz, CDCl3) δ 165.75, 160.17, 155.46, 145.21, 141.10, 133.71, 132.43, 126.61, 125.92, 125.16, 120.60, 119.42, 117.34, 63.14, 31.54, 26.41, 25.54. HRMS calcd for $C_{19}H_{18}N_2O_4$, 338.1267; found, 338.1338.

*10-Benzyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3f**).* Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.10 (d, 1H, J = 2.56 Hz), 7.90−7.93 (dd, 2H, J = 2.28, 9 Hz), 7.50−7.55 (m, 1H), 7.27−7.33 (m, 8H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 166.02, 159.74, 153.54, 144.92, 141.20, 136.17, 134.36, 132.55, 128.95, 127.62, 126.68, 126.11, 125.76, 123.17, 121.14, 119.86, 117.56, 52.53. HRMS calcd for $C_{20}H_{14}N_2O_4$, 346.0954; found, 346.1023.

*7-Nitro-10-phenyldibenzo[b,f][1,4]oxazepin-11(10H)-one (**3g**).* Pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 8.19−8.20 (d, 1H, J = 2.7 Hz), 7.93−7.96 (dd, 1H, J = 1.8, 5.7 Hz), 7.84−7.88 (dd, 1H, J = 2.4, 9 Hz), 7.49−7.59 (m, 3H), 7.33−7.47 (m, 3H), 7.29−7.31 (m, 2H), 6.87−6.90 (d, 1H, J = 9 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.56, 159.55, 152.90, 144.61, 141.85, 141.15, 134.48, 132.63, 129.87, 129.05, 128.56, 126.16, 126.00, 125.59, 120.82, 119.98, 117.73. HRMS calcd for $C_{19}H_{12}N_2O_4$, 332.0797; found, 332.0885.

*7-Nitro-10-(p-tolyl)dibenzo[b,f][1,4]oxazepin-11(10H)-one (**3h**).* White crystal, mp 185−187 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.18−8.19 (d, 1H, J = 2.44 Hz), 7.92−7.95 (dd, 1H, J = 1.48, 8.04 Hz), 7.84−7.87 (dd, 1H, J = 2.44, 9.04 Hz), 7.54−7.58 (m, 1H), 7.27−7.33 (m, 6H), 6.90−6.92 (d, 1H, J = 9.04 Hz), 2.43 (s, 3H). ^{13}C NMR (400 MHz, CDCl3) δ 165.71, 159.56, 152.85, 144.55, 142.00, 138.64, 138.51, 134.37, 132.66, 130.52, 128.67, 126.13, 126.08, 125.48, 120.75, 119.91, 117.74, 21.23. ^{13}C NMR (75 MHz, CDCl3) δ 165.71, 159.56, 153.85, 144.55, 142.00, 138.64, 138.51, 134.37, 132.66, 130.52, 128.67, 126.13, 126.08, 125.48, 120.75, 119.91, 117.74, 21.23. HRMS calcd for $C_{20}H_{14}N_2O_4$, 346.0954; found, 346.1042.

*10-(4-Methoxyphenyl)-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3i**).* White crystal, mp 128−132 °C. ^{1}H NMR (300 MHz, CDCl3) δ 8.18−8.19 (d, 1H, J = 2.7 Hz), 7.92−7.95 (dd, 1H, J = 1.8, 8.1 Hz), 7.85−7.89 (dd, 1H, J = 2.7, 9 Hz), 7.53−7.59 (m, 1H), 7.27−7.34 (m, 4H), 7.01−7.05 (m, 2H), 6.91−6.94 (d, 1H, J = 9 Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 165.87, 159.57, 159.39, 152.75, 144.52, 142.12, 134.39, 133.76, 132.67, 129.99, 126.12, 126.02, 125.42, 120.76, 119.91, 117.75, 115.08, 55.56. HRMS calcd for $C_{19}H_{14}N_2O_5$, 362.0903; found, 362.0991.

*10-(4-Fluorophenyl)-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3j**).* White crystal, mp 82−85 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.20−8.21 (d, 1H, J = 2.48 Hz), 7.92−7.95 (dd, 1H, J = 1.6, 8.04 Hz), 7.88−7.91 (dd, 1H, J = 2.52, 9.04 Hz), 7.56−7.60 (m, 1H), 7.31−7.40 (m, 4H), 7.19−7.24 (t, 2H, J = 8.32 Hz), 6.88−6.90 (d, 1H, J = 9.04 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.65, 163.35, 160.87, 159.58, 152.97, 144.76, 141.67, 136.96, 134.60, 132.69, 130.86, 126.21, 125.71, 120.87, 120.00, 117.86, 116.75. HRMS calcd for $C_{19}H_{11}FN_2O_4$, 350.0703; found, 350.0704.

*10-(4-Chlorophenyl)-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**3k**).* White crystal, mp 186−189 °C. ^{1}H NMR

(400 MHz, CDCl3) δ 8.20 (d, 1H, *J* = 2.36 Hz), 7.92−7.94 (dd, 1H, *J* = 1.36, 8.04 Hz), 7.87−7.90 (dd, 1H, *J* = 2.44, 9.04 Hz), 7.55−7.60 (m, 1H), 7.49−7.51 (d, 2H, *J* = 8.52 Hz), 7.32−7.35 (m, 4H), 6.87−6.89 (d, 1H, *J* = 9 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.47, 159.58, 153.10, 144.86, 141.47, 139.53, 134.65, 134.47, 132.70, 130.37, 130.08, 126.24, 125.66, 125.45, 120.89, 120.02, 117.89. HRMS calcd for $C_{19}H_{11}ClN_2O_4$, 366.0407; found, 366.0474.

10-(4-Bromophenyl)-7-nitrodibenzo[b,f][1,4]oxazepin-11-(10H)-one (**3l**). White crystal, mp 203−205 °C. ^{1}H NMR (300 MHz, CDCl3) δ 8.20 (d, 1H, *J* = 2.4 Hz), 7.87−7.95 (m, 2H), 7.64−7.67 (d, 2H, *J* = 8.7 Hz), 7.55−7.61 (m, 1H), 7,26−7.35 (m, 4H), 6.87−6.90 (d, 1H, *J* = 9 Hz). ^{13}C NMR (75 MHz, CDCl3) δ 165.41, 159.57, 153.11, 144.86, 141.40, 140.05, 134.66, 132.07, 132.69, 130.68, 126.24, 125.63, 125.47, 122.51, 120.90, 120.02, 117.90. HRMS calcd for $C_{19}H_{11}BrN_2O_4$, 409.9902; found, 409.9973.

10-Ethyl-7-fluorodibenzo[b,f][1,4]oxazepin-11(10H)-one (**4b**). Pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 7.83−7.86 (dd, 1H, *J* = 1.8, 7.8 Hz), 7.41−7.46 (m, 1H), 7.20−7.28 (m, 2H), 7.14−7.17 (dd, 1H, *J* = 0.6, 8.1 Hz), 6.98−7.01 (dd, 1H, *J* = 2.7, 8.4 Hz), 6.88−6.94 (m, 1H), 4.09−4.16 (q, 2H, *J* = 6.9 Hz), 1.32−1.3 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.82, 161.18, 160.35, 158.71, 155.62, 155.51, 133.31, 132.13, 131.83, 131.22, 131.19, 126.83, 125.57, 123.99, 123.89, 119.58, 112.89, 112.67, 109.27, 109.03, 44.38, 13.71. HRMS calcd for $C_{15}H_{12}FNO_4$, 257.0852; found, 257.0937

11-Ethyl-3-(trifluoromethyl)benzo[f]pyrido[3,2-b][1,4]oxazepin-10(11H)-on (**4c**). Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (d, 1H, *J* = 0.96 Hz), 7.79−7.81 (dd, 1H, *J* = 1.64, 7.8 Hz), 7.67 (d, 1H, *J* = 1.96 Hz), 7.38−7.43 (m, 1H), 7.11−7.20 (m, 2H), 4.23−4.29 (q, 2H, *J* = 7 Hz), 1.30−1.33 (t, 3H, *J* = 7 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 164.08, 157.69, 150.32, 146.52, 140.75, 140.71, 140.67, 140.63, 132.96, 131.60, 125.89, 125.86, 125.82, 125.79, 125.12, 124.95, 123.25, 123.18, 122.91, 122.58, 122.24, 120.48, 118.39, 41.60, 12.69. HRMS calcd for $C_{15}H_{11}F_3N_2O_2$, 308.0773; found, 309.0870.

10-Ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-7-carbonitrile (**4d**). White crystal, mp 161−164 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.84−7.86 (dd, 1H, *J* = 1.56, 7.76 Hz), 7.56−7.57 (d, 1H, *J* = 1.8 Hz), 7.47−7.51 (m, 2H), 7.39−7.41 (d, 1H, *J* = 8.44 Hz), 7.19−7.28 (m, 2H), 4.14−4.19 (q, 2H, *J* = 7.08 Hz), 1.38−1.41 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.55, 159.74, 154.03, 139.76, 133.91, 132.29, 129.75, 126.25, 125.89, 125.69, 123.54, 119.57, 117.47, 109.41, 44.50, 13.76. HRMS calcd for $C_{16}H_{12}N_2O_2$, 264.0899; found, 264.1162.

10-Ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-9-carbonitrile (**4e**). White crystal, mp 120−122 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.84−7.87 (dd, 1H, *J* = 1.56, 7.72 Hz), 7.51−7.53 (d, 2H, *J* = 7.92 Hz), 7.42−7.47 (m, 1H), 7.24−7.30 (m, 2H), 7.16−7.18 (d, 1H, *J* = 8.08 Hz), 4.82−4.89 (m, 1H), 3.80−3.89 (m, 1H), 1.23−1.26 (t, 3H, *J* = 7.12 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.97, 160.84, 157.76, 137.72, 133.56, 132.26, 131.32, 127.50, 126.52, 126.35, 126.01, 119.52, 116.25, 109.98, 45.52, 13.59. HRMS calcd for $C_{16}H_{12}N_2O_2$, 264.0899; found, 264.1005.

5-Ethylbenzo[f]pyrido[3,4-b][1,4]oxazepin-6(5H)-one (**4f**). Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.54 (s, 1H), 8.38−8.39 (d, 1H, *J* = 5.44 Hz), 7.84−7.86 (dd, 1H, *J* = 1.76, 8.24 Hz), 7.45−7.50 (m, 1H), 7.20−7.25 (m, 3H), 4.12−4.17 (q, 2H, *J* = 7.08 Hz), 1.39−1.42 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.78, 160.01, 149.69, 147.28, 143.98, 141.99, 133.97, 132.46, 126.21, 125.62, 119.71, 115.87, 43.78, 13.64. HRMS calcd for $C_{14}H_{12}N_2O_2$, 240.0899; found, 240.1005.

10-Ethyl-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**4g**). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 2.56 Hz), 8.07−8.10 (dd, 1H, *J* = 2.56, 9 Hz), 7.84−7.86 (dd, 1H, *J* = 1.32, 7.64 Hz), 7.45−7.51 (m, 2H), 7.24−7.29 (m, 2H), 4.17−4.23 (q, 2H, *J* = 7.08 Hz), 1.41−1.44 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.46, 159.56, 153.64, 144.70, 141.33, 134.03, 132.22, 126.11, 125.95, 122.84, 121.24, 119.66, 117.60, 44.71, 13.73. HRMS calcd for $C_{15}H_{12}N_2O_4$, 284.0797; found, 284.0880.

9-Chloro-10-ethyldibenzo[b,f][1,4]oxazepin-11(10H)-one (**4h**). White crystal, mp 80−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.83 (dd, 1H, *J* = 6.16, 7.68 Hz), 7.36−7.40 (m, 1H), 7.10−7.27 (m, 5H), 4.62−4.71 (m, 1H), 3.60−3.69 (m, 1H), 1.17−1.21 (t, 3H, *J* = 7.12 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 166.75, 161.33, 159.21, 133.16, 132.40, 131.84, 130.69, 127.82, 127.76, 126.99, 125.66, 119.72, 119.66, 44.42, 13.38. HRMS calcd for $C_{15}H_{12}ClNO_2$, 273.0557; found, 273.0629.

10-Ethyl-7-(trifluoromethyl)dibenzo[b,f][1,4]oxazepin-11-(10H)-one (**4i**). White crystal, mp 58−61 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.85−7.87 (dd, 1H, *J* = 1.56, 7.72 Hz), 7.54 (s, 1H), 7.41−7.47 (m, 3H), 7.19−7.25 (m, 2H), 4.15−4.20 (q, 2H, *J* = 7.08 Hz), 1.37−1.40 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.72, 160.10, 154.21, 138.30, 133.66, 132.21, 128.10, 127.77, 127.36, 126.50, 125.65, 124.66, 123.29, 122.82, 122.78, 122.74, 122.71, 121.95, 119.62, 119.24, 119.20, 119.17, 119.13, 44.39, 13.70. HRMS calcd for $C_{16}H_{12}NO_2F_3$, 307.0820; found, 307.0958.

4j: White crystal, mp 210−212 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.82−7.84 (dd, 2H, *J* = 1.24, 7.76 Hz), 7.42−7.46 (m, 2H), 7.15−7.24 (m, 6H), 4.08−4.13 (q, 4H, *J* = 6.88 Hz), 1.35−1.38 (t, 6H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 165.80, 160.23, 152.00, 133.47, 132.62, 132.24, 126.60, 125.58, 119.60, 116.99, 114.38, 44.62, 13.84. HRMS calcd for $C_{24}H_{20}N_2O_4$, 400.1423; found, 400.1495.

10-Ethyldibenzo[b,f][1,4]oxazepin-11(10H)-one (**4k**). White crystal, mp 92−95 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.83−7.85 (dd, 1H, *J* = 1.52, 7.68 Hz), 7.38−7.43 (m, 1H), 7.29−7.31 (dd, 1H, *J* = 1.6, 7.92 Hz), 7.24−7.26 (dd, 1H, *J* = 1.76, 7.64 Hz), 7.10−7.21 (m, 4H), 4.13−4.18 (q, 2H, *J* = 6.92 Hz), 1.36 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 166.13, 160.73, 154.78, 134.85, 133.21, 132.04, 127.07, 126.38, 125.80, 125.22, 123.07, 121.59, 119.64, 44.24, 13.81. HRMS calcd for $C_{15}H_{13}NO_2$, 239.0946; found, 239.1026.

10-Ethyl-9-methyldibenzo[b,f][1,4]oxazepin-11(10H)-one (**4l**). White crystal, mp 70−75 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.79−7.82 (dd, 1H, *J* = 1.68, 7.68 Hz), 7.34−7.38 (m, 1H), 7.06−7.19 (m, 4H), 7.00−7.02 (dd, 1H, *J* = 1.24, 7.08 Hz), 4.64−4.73 (m, 1H), 3.21−3.29 (m, 1H), 2,30 (s, 3H), 1.17−1.27 (t, 3H, *J* = 7.08 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 167.35, 161.75, 158.37, 135.27, 133.24, 132.90, 131.54, 128.37, 127.44, 127.18, 125.27, 119.75, 118.40, 44.72, 19.90, 13.25. HRMS calcd for $C_{16}H_{15}NO_2$, 253.1103; found, 253.1186.

N-(10-Ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-7-yl)acetamide (**4m**). White crystal, mp 170−173 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.81−7.83 (dd, 1H, *J* = 1.56, 7.72 Hz), 7.60−7.61 (d, 1H, *J* = 1.88 Hz), 7.39−7.44 (m, 2H), 7.15−7.24 (m, 4H), 4.10−4.15 (q, 2H, *J* = 6.72 Hz), 2.17 (s, 3H), 1.34 (s, 3H), ^{13}C NMR (100 MHz, CDCl3) δ 168.47, 166.20, 160.52, 155.01, 136.37, 133.27, 131.92, 130.47, 126.94, 125.34, 123.21,

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119.77, 116.84, 112.90, 44.18, 24.50, 13.75. HRMS calcd for $C_{17}H_{16}N_2O_3$, 296.1161; found, 296.1230.

*10-Benzyl-4-methyl-7-nitrodibenzo[b,f][1,4]oxazepin-11-(10H)-one (**6a**).* White crystal, mp 166−168 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.10 (d, 1H, J = 2.56 Hz), 7.93−7.96 (dd, 1H, J = 2.56, 9 Hz), 7.72−7.74 (dd, 1H, J = 1.2, 7.76 Hz), 7.39−7.41 (d, 1H, J = 7.08 Hz), 7.27−7.35 (m, 7H), 7.16−7.20 (t, 3H, J = 7.64 Hz), 5.38 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 166.40, 157.80, 153.48, 144.76, 141.61, 136.16, 135.42, 130.18, 129.14, 128.94, 127.60, 126.66, 125.88, 125.63, 123.06, 121.04, 117.62, 52.45, 16.24. HRMS calcd for $C_{24}H_{20}N_2O_4$, 360.1110; found, 360.1180.

*10-Benzyl-2-chloro-7-nitrodibenzo[b,f][1,4]oxazepin-11(10H)-one (**6b**).* White crystal, mp 155−157 °C. ^{1}H NMR (300 MHz, CDCl3) δ 8.10−8.11 (d, 1H, J = 2.4 Hz), 7.95−7.99 (dd, 1H, J = 2.4, 9 Hz), 7.89−7.90 (d, 1H, J = 2.4 Hz), 7.47−7.51 (dd, 1H, J = 2.7, 8.4 Hz), 7.23−7.37 (m, 7H), 5.36 (s, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 164.79, 158.15, 153.35, 145.06, 140.78, 135.79, 134.14, 132.19, 131.69, 129.01, 127.76, 127.05, 126.65, 123.32, 121.35, 117.52, 52.74. HRMS calcd for $C_{20}H_{13}ClN_2O_4$, 380.0564; found, 380.0638.

*13-Benzyl-3-nitrobenzo[b]naphtho[2,3-f][1,4]oxazepin-12-(13H)-one (**6c**).* White crystal, mp 189−192 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.52 (s, 1H), 8.21 (d, 1H, J = 2.6 Hz), 7.92−7.96 (m, 2H), 7.84−7.86 (d, 1H, J = 8.24 Hz), 7.72 (s, 1H), 7.58−7.62 (m, 1H), 7.49−7.53 (m, 1H), 7.28−7.38 (m, 6H), 5.43 (s, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 166.18, 156.20, 153.23, 145.04, 141.29, 136.17, 136.00, 134.48, 130.90, 129.12, 128.99, 127.65, 127.22, 126.68, 136.50, 125.17, 123.14, 121.13, 117.83, 116.38, 52.81. HRMS calcd for $C_{24}H_{16}N_2O_4$, 396.1110; found, 396.1192.

*8-Benzyl-11-nitrobenzo[b]naphtho[2,1-f][1,4]oxazepin-7(8H)-one (**6d**).* Pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.59−8.61 (d, 1H, J = 8.32 Hz), 8.23 (d, 1H, J = 2.56 Hz), 7.95−7.98 (dd, 1H, J = 2.56, 9 Hz), 7.87−7.91 (t, 3H, J = 7.72 Hz), 7.70−7.75 (t, 2H, J = 8.4 Hz), 7.68−7.70 (t, 1H, J = 6.88 Hz), 7.26−7.38 (m, 6H), 5.45 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 166.47, 156.58, 153.67, 144.81, 141.66, 136.78, 136.16, 129.09, 129.00, 128.03, 127.77, 127.69, 126.80, 125.57, 125.43, 123.09, 122.64, 121.22, 120.67, 117.53, 53.41. HRMS calcd for $C_{24}H_{16}N_2O_4$, 396.1110; found, 396.1191.

■ ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures, spectral data of compounds **3a**−**l**, **4b**−**m**, **6a**−**d** and crystallographic information files (CIF) of **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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