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Solid Support Synthesis of 2-Substituted Dibenz[b,f]oxazepin- 11(10*H*)-ones *via* S_NAr Methodology on AMEBA Resin.

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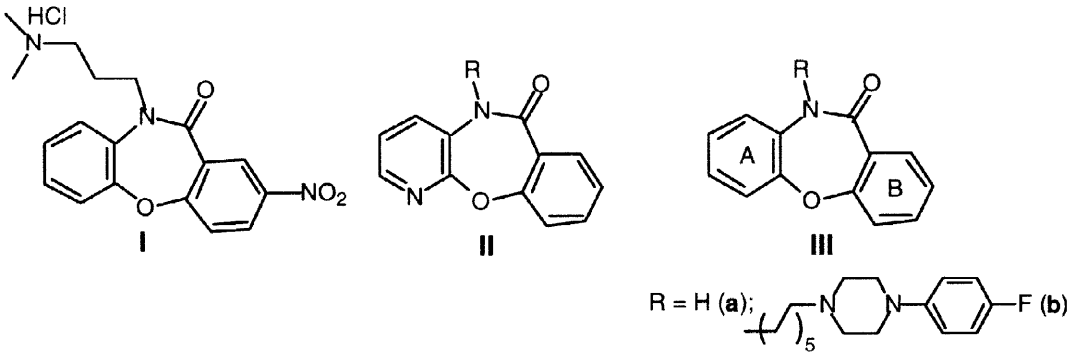
Abstract: Efficient assembly of dibenz[b,f]oxazepin-11(10H)-ones utilizing the S_NAr of fluorine in 2-fluoro-5-nitrobenzoic acid with the OH of various 2-aminophenols on solid support is reported. The flexibility of this synthesis, as well as the excellent purity (>90%) of the final products are the distinctive characteristics of the resulting library.

Keywords: oxazepines; supported reagents/reactions; solid-phase synthesis

The application of combinatorial chemistry as both a lead generation, and a lead optimization tool for drug research and development is well documented.[1] Numerous solid-phase, and solution-phase techniques have been developed to generate a diverse array of compounds based upon a wide range of reaction types, and scaffolds.[2] In our continuing effort toward the identification of new reaction templates to investigate by solid support methods,[3] we were interested in the versatile synthesis of dibenz[b,f]oxazepin-11(10*H*)-ones. Numerous physiologically active compounds contain the benz[b,f][1,4]oxazepin ring system (examples, **I-III**). Nitroxazepine (**I**) (Sintamil^R), and related compounds represent pronounced antidepressant activity.[4] Various derivatives of **II** and **III** were reported to selectively inhibit HIV type 1 reverse transcriptase with IC values as low as 19 nM.[5] Substitution of the A-ring in **IIIa** (R = H) was reported to affect the anti-HIV activity of the compound. Substituents *ortho-*, and *para-* to the *N*-atom of the lactam enhanced potency.[5] Calcium antagonist activity was reported for **IIIb**.[6] Analgetic, antipyretic, and sedative activities have also been reported for this class of compounds.[7]



Several synthetic strategies toward the dibenz[b,f]oxazepin-11(10*H*)-one framework have been reported. The nucleophilic aromatic substitution (S_NAr) of a halogen atom with the phenolic oxygen in 2-X-5-nitrobenzamides of *o*-aminophenols is the most widely used protocol.[8] Beckmann

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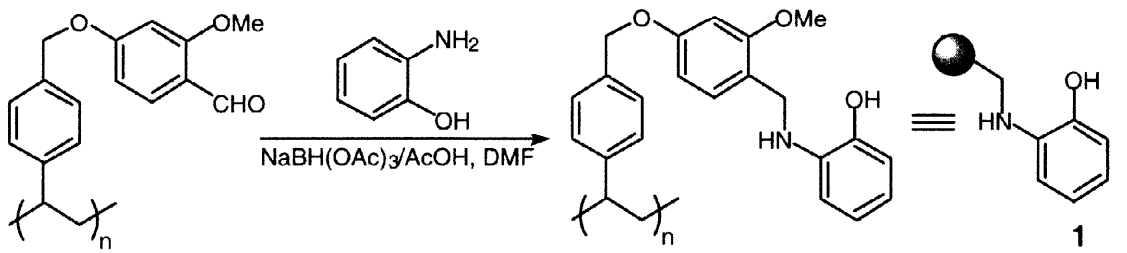
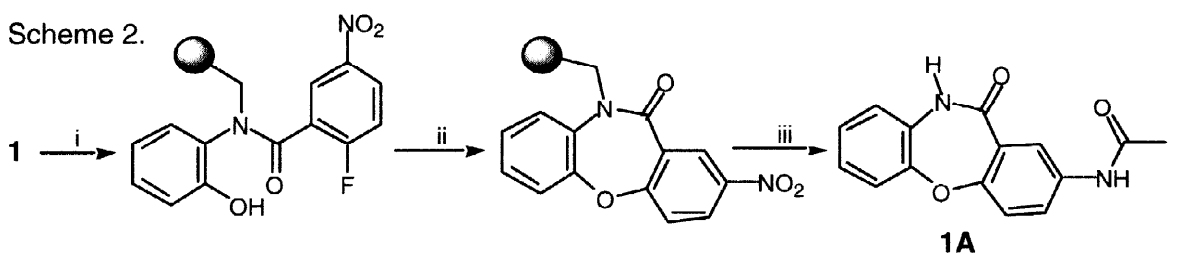
rearrangement of xanthone oximes was reported to yield the desired oxazepinone ring system, albeit in lower yields.[9] Lactamization of the properly substituted biaryl phenols to afford the desired seven-membered ring was reported to afford compounds **III** in high yield.[10] Exceptionally mild coupling conditions, the ready availability of starting materials, as well as the possibility to expand the diversity of the substituents in the final dibenzoxazepinones *via* postmodification reactions of nitro group make the S_NAr strategy more amenable for solid phase. In our approach, we decided to use commercially available 2-fluoro-5-nitrobenzoic acid and various aminophenols as components for the S_NAr coupling.[11] In the initial experiment, we prepared resin **1** by the reductive amination of *o*-aminophenol on the recently reported **A**cid sensitive **ME**thoxy **B**enz**A**ldehyde (**AMEBA**) polystyrene resin (Scheme 1).[12]

Scheme 1.



Resin **1** was further modified with the commercially available 2-fluoro-5-nitrobenzoic acid (Scheme 2) using the HOAt/DIC strategy[13] to afford the immobilized substrate, which was ready for the assembly of the desired dibenz[b,f]oxazepin-11(10*H*)-one derivatives. The key cyclization step (S_NAr) was performed using a 5% solution of DBU in DMF. Treatment of the resulting resin with 15% TFA in CH_2Cl_2 afforded the intermediate 2-nitro-dibenz[b,f]oxazepin-11(10*H*)-one in a quantitative yield.

Scheme 2.



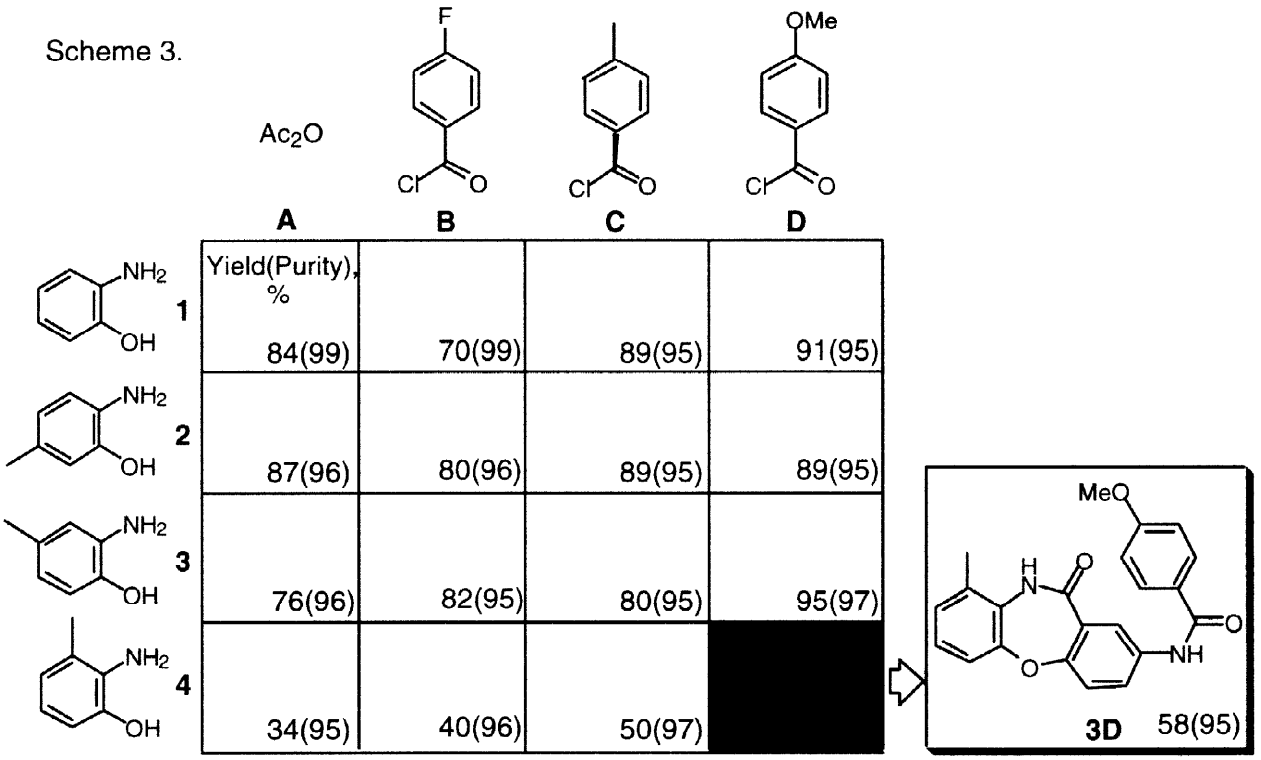
Reagents and Conditions: i) **2**, HOAt, DIC, DMF, 12 h., RT; ii) 5% DBU, DMF, 12 h., RT; iii) $SnCl_2$ $2H_2O$, DMF, 24 h., RT; Ac_2O, DMF, 12 h., RT; 20% TFA/ CH_2Cl_2

N-Methylmorpholine, and 1,1,3,3-tetramethylguanidine were also used for the S_NAr step. However, the yield and the purity of the intermediate 2-nitro-dibenz[b,f]oxazepin-11(10*H*)-one were somewhat lower (36% and 45% respectively). Cyclization was not observed with K_2CO_3/18-crown-6 system in DMF.[14,15] The reduction of the nitro group in the resulting 2-nitro-dibenz[b,f]oxazepin-11(10*H*)-one resin was successfully accomplished with a 1.5M solution of $SnCl_2$•$2H_2O$ in DMF to afford the corresponding immobilized 2-amino derivative in quantitative yield.[16] Further treatment of the resin with acetic anhydride followed by the TFA cleavage afforded the desired dibenz[b,f]oxazepin-11(10*H*)-one **1A** in 84% yield and 99% purity (HPLC).

The elaboration of the reaction conditions allowed us to synthesize a library of 16 members (Scheme 3). Aminophenols (**1-4**, Scheme 3) containing electron-donating functions were easily immobilized on the **AMEBA** resin, and converted into the desired compounds **1A-4D**. The yields of dibenz[b,f]oxazepin-11(10*H*)-ones varied from 34% (**4A**), to 95% (**3D**), depending upon the

substitution pattern in the starting *o*-aminophenols. The purity of the synthesized library was estimated to be 95-99% by HPLC. The lowest yields (34-58%) were obtained with **4**. The nature of the acylating agent affected neither the yield nor the purity of the desired heterocycles.

Scheme 3.



Attempts to prepare dibenz[b,f]oxazepin-11(10*H*)-ones containing electron-withdrawing groups in the A ring using similar strategy were unsuccessful. For example, several *o*-aminophenols containing Cl, Br, or NO_2 substituents were immobilized on **AMEBA** resin using the reductive amination protocol described above. The subsequent acylation of the resultant resins (500 mg) with 4-nitrobenzoyl chloride followed by their treatment with 30% solution of TFA in CH_2Cl_2 afforded the desired amides in less than 10% yields (4.5-5.0 mg). This result was attributed to the low loading levels of the corresponding *o*-aminophenol resins.

In summary, we developed an efficient route to the 2-substituted dibenz[b,f]oxazepin-11(10H)-ones utilizing the S_NAr of fluorine in 2-fluoro-5-nitrobenzoic acid with the OH of various 2-aminophenols on solid support. The flexibility of this synthesis as well as the excellent purity (>90%) of the final products are the distinctive characteristics of the resulting library.

Experimental Section

Materials and Methods. All reactions were carried out in peptide synthesis vessels, and agitated on an orbit shaker at room temperature. Reagents were purchased from Aldrich, and used without further purification. 4-Formyl-3-methoxyphenoxymethyl resin (**AMEBA** resin, 100-180 mesh) was purchased from Colorado Biotech Inc. with a loading of 1.25 mmol/g, and was washed with DMF, MeOH, and DCM before use. Concentration of the solutions after workup was performed by reduced pressure rotary evaporation on Büchi 535 apparatus. Melting points are uncorrected and measure in open capillary tubes. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker 400 instrument. MS analyses (ES, and CI modes) were performed on a Perkin Elmer API 165 instrument. HPLC analysis

was performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm, and 254 nm. The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. The solvent system was MeCN/H_2O (start: 5:95 ratio; finish: 10:90; 8 min runs; .1% TFA added), with a flow rate of 1 mL/min.

General Procedure for Reductive Amination of Aminophenols on 4-Formyl-3-methoxyphenoxymethyl (AMEBA) Resin. In a typical experimental procedure, 4-Formyl-3-methoxy-phenoxymethyl resin (5 g; loading 1.25 mmol/g) was added to a 1 L flask. After the addition of trimethyl orthoformate (50 mL) and anhydrous DMF (50 mL), 2-aminophenol (2 g, 18.75 mmol) was added to the reaction mixture followed by 0.5 mL of glacial AcOH. The mixture was stirred under nitrogen for 8 h. $NaBH(OAc)_3$ (5.3 g, 25 mmol) was added, and the slurry was slowly stirred under nitrogen for another 12 h. 200 mL of MeOH was added to the mixture, and the resulting mixture was stirred in open air for 5 min. The resin was filtered, washed twice with MeOH, DCM, DMF, dioxane and Et_2O, dried *in vacuo*, and stored at 0°C. The loading of the resin (as determined by its acylation with 4-nitrobenzoyl chloride followed by cleavage of the product with 30% solution of TFA in CH_2Cl_2) was 0.75 mmol/g.

General Procedure for the Synthesis of 2-Nitro-dibenz[b,f]oxazepin-11(10*H*)-ones on Solid Support. This procedure was run using the following reaction conditions: 200 mL of a mixture of 3-fluoro-4-nitrobenzoic acid (3.7 g, 20 mM), HOAt (2.72 g, 20 mM), and DIC (2.77 g, 22 mM) (clear solution in 100 mL of DMF) was added to a corresponding*o*-aminophenol resin (5 g, 1.25 mmol/g loading). The resultant slurry was stirred for 8 h., filtered, washed with DMF, MeOH, CH_2Cl_2, and treated with 100 mL of a 5% solution of DBU in DMF at room temperature for 24 h., filtered, washed with a 10% AcOH in DMF, DMF, MeOH, CH_2Cl_2, and dried *in vacuo*. The loading of the resultant resin (as determined by cleavage of the product with 30% solution of TFA in CH_2Cl_2) was 0.7 mmol/g.

General Procedure for the Synthesis of 2-Substituted-dibenz[b,f]oxazepin-11(10*H*)-ones (1A-4D) on Solid Support. The 2-Nitro-dibenz[b,f]oxazepin-11(10*H*)-one resin (**1-4**, 5g, 0.7 mmol/g loading) was treated with a 1.5M solution of $SnCl_2 \cdot 2H_2O$ (100 mL) in DMF for 24 h., and filtered. The resin was then washed with MeOH, CH_2Cl_2, DMF, dioxane, Et_2O, and dried *in vacuo*. The resultant immobilized 2-amino-dibenz[b,f]-oxazepin-11(10H)-one (100 mg) was treated with a 0.6 M solution of N,N-diisopropylethylamine in CH_2Cl_2 (20 mL), followed by a 0.4 M solution of acetic anhydride (**A**), or benzoyl chlorides (**B-D**) (25 mL) in the same solvent. The reaction mixture was shaken for 12 h., the resin was filtered, washed with DMF, MeOH, CH_2Cl_2 and dried *in vacuo*. The resultant resin was treated with 100 mL of a 40% TFA solution in CH_2Cl_2 for 30 min., and filtered. This procedure was repeated twice to assure the complete cleavage of the desired 2-substituted-dibenz[b,f]oxazepin-11(10*H*)-ones (**1A-4D**) off the solid support (additional 10-15% of the material were cleaved). The filtrates were combined, and concentrated to afford an oily residue. The residue was co-evaporated twice with MeOH to afford the desired products as yellow solids.

Analytical Data:

2-nitro-10*H*-dibenzo[b,f]1,4-oxazepin-11-one. m.p. 259-260 °C (lit.[8a] 258-260 °C).
7-methyl-2-nitro-10*H*-dibenzo[b,f]1,4-oxazepin-11-one. m.p. 277-278 °C (lit.[5a] 274-277 °C).
8-methyl-2-nitro-10*H*-dibenzo[b,f]1,4-oxazepin-11-one. m.p. >300 °C (lit.[8a] 274-277 °C).
IR (KBr) ν: 3095m, 1682s, 1619s, 1350s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.81 (s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.44 (dd, J_1 = 8.9 Hz, J_2 = 2.7 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.28 (d, 8.2 Hz, 1H), 6.98

(d, J = 7.5 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO- d_6) 163.2, 147.2, 144.5, 136.1, 129.8, 129.4, 127.2, 126.5, 126.1, 122.6, 122.1, 122.0, 121.3, 20.3; HRMS (FAB) calcd for $C_{14}H_{10}N_2O_4$: m/z = 271.0719 (MH^+), found: 271.0713 .

9-methyl-2-nitro-10*H*-dibenzo[b,f]1,4-oxazepin-11-one. m.p. 270-272°C; IR (KBr) ν 3449m, 1676s, 1350s cm^{-1}; ^1H NMR (DMF-d_6) δ 10.22 (s, 1H), 8.58 (d, J = 2.8 Hz, 1H), 8.51 (dd, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.33 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.21-7.15 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (DMSO- d_6) 164.1, 163.7, 151.6, 144.7, 132.1, 129.1, 128.9, 128.3, 127.2, 126.9, 125.9, 122.4, 119.0, 17.8; HRMS (FAB) calcd for $C_{14}H_{10}N_2O_4$: m/z = 271.0719 (MH^+), found: 271.0717.

***N*-(11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)ethanamide (1A).** Yield: 15.8 mg (84%); m.p. 222-223°C; HPLC: t_R=5.18; IR (KBr) ν: 3200m, 1671s, 1491s, 1431s, 1369s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.48 (s, 1H), 10.09 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.77 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1H), 7.30-7.26 (m, 2H), 7.16 (bs, 2H), 7.14-7.12 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (DMSO- d_6) 168.4, 165.7, 154.2, 150.6, 136.6, 131.2, 125.9, 125.7, 125.3, 124.7, 121.7, 121.2, 121.0, 120.9, 23.9; HRMS (FAB) calcd for $C_{15}H_{12}N_2O_3$: m/z = 269.0926 (MH^+), found: 269.0922.

(4-fluorophenyl)-*N*-(11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (1B). Yield: 17.1 mg (70%); m.p. 285-286°C; HPLC: t_R=6.78; IR (KBr) ν: 3221s, 1674s, 1605m, 1493s, 1354s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.52 (s, 1H), 10.42 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 8.06-8.03 (m, 2H), 7.98 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 7.36 (q , J = 8.5 Hz, 3H), 7.32 (d, J = 8.6 Hz, 1H), 7.19-7.7.18 (m, 2H), 7.15-7.13 (m, 1H); ^{13}C NMR (DMSO-d_6) 165.6, 165.4, 164.4, 163.0, 154.7, 150.6, 136.3, 131.1, 130.5, 130.4, 126.0, 125.9, 125.7, 125.3, 122.7, 121.7, 121.2, 120.9, 115.5, 115.3; HRMS (FAB) calcd for $C_{20}H_{13}FN_2O_3$: m/z = 349.0988 (MH^+), found: 349.0978.

(4-methylphenyl)-*N*-(11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (1C). Yield: 21.5 mg (89%); m.p. 278-279°C; HPLC: t_R=7.00; IR (KBr) ν: 3210m, 1763w, 1671s, 1546s, 1492s, 1364m cm^{-1};^1H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.34 (s, 1H), 8.20 (d, J = 2.4 Hz, 1H), 8.01 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 7.88 (bd, J = 7.9 Hz, 2H), 7.35-7.33 (m, 4H), 7.18-7.17 (m, 2H), 7.15-7.14 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6) 165.7, 165.3, 154.6, 150.6, 141.8, 136.6, 136.5, 131.6, 131.2, 131.1, 129.0, 127.8, 126.0, 125.9, 125.6, 125.3, 122.7, 121.7, 121.2, 120.8, 21.0; HRMS (FAB) calcd for $C_{21}H_{16}N_2O_3$: m/z = 345.1239 (MH^+), found: 345.1226.

(4-methoxyphenyl)-*N*-(11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (1D). Yield: 23.0 mg (91%); m.p. 255-256°C; HPLC: t_R=6.65; IR (KBr) ν: 3210m, 1671s, 1608m, 1492 s, 1255s, 1178m cm^{-1};^1H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.34 (s, 1H), 8.20 (d, J = 2.5 Hz, 1H), 8.02 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1H), 7.97 (bd, J = 8.7 Hz, 2H), 7.34 (d, J = 3.9 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 7.19-7.17 (m, 2H), 7.16-7.7.13 (m, 1H), 7.08 (bs, 1H), 7.06 (bs,1H), 3.84 (s, 3H); ^{13}C NMR (DMSO-d_6) 145.2, 142.6, 139.4, 137.4, 135.4, 129.5, 129.3, 129.0, 128.1, 127.8, 127.3, 126.8, 124.0, 121.4, 121.2, 120.1, 109.8, 43.5; HRMS (FAB) calcd for $C_{21}H_{16}N_2O_4$: m/z = 361.1188 (MH^+), found: 361.1199.

***N*-(7-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)ethanamide (2A)** Yield: 17.2 mg (87%); m.p. 208-209°C; HPLC: t_R=5.63; IR (KBr) ν: 3191m, 1676s, 1490s, 1438s, 1369s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.42 (s, 1H), 10.11 (s, 1H), 7.98 (bs, 1H), 7.77 (bd, J = 8.4 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.12 (bs, 1H), 7.04-6.97 (m, 2H), 2.26 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6) 168.4, 165.6, 154.1, 150.5, 136.5, 135.0, 128.4, 126.3, 125.8, 124.5, 121.4, 121.3, 121.1, 120.9, 23.9, 20.2; HRMS (FAB) calcd for $C_{16}H_{14}N_2O_3$: m/z = 283.1083 (MH^+), found: 283.1081.

(4-fluorophenyl)-*N*-(7-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (2B). Yield: 20.3 mg (80%); m.p. 305-307°C; HPLC: t_R=7.22; IR (KBr) ν: 3217m, 1672s, 1551m,

1364s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.45 (s, 1H), 10.43 (s, 1H), 8.17 (bs, 1H), 8.06-8.04 (m, 2H), 8.00-7.98 (m, 1H), 7.37 (tt, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 2H), 7.32 (dt, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 1H), 7.14 (bs, 1H), 7.05 (bd, J = 7.6 Hz, 1H), 6.99 (bd, J = 7.6 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (DMSO- d_6) 165.6, 164.4, 162.9, 154.7, 150.5, 136.3, 135.0, 130.9, 130.5, 130.4, 128.4, 126.3, 125.9, 125.7, 122.7, 121.5, 121.4, 120.9, 115.5, 115.3, 20.2; HRMS (FAB) calcd for $C_{21}H_{15}FN_2O_3$: m/z = 363.1145 (MH^+), found: 363.1140.

(4-methylphenyl)-*N*-(7-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (2C). Yield: 22.4 mg (89%); m.p. 277-279°C; HPLC: t_R=7.40; IR (KBr) ν: 3205m, 1659s, 1491s, 1358s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.42 (s, 1H), 10.31 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 8.00 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1 H), 7.88 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 2.38 (s, 3H), 2.27 (s, 3 H); ^{13}C NMR (DMSO- d_6) 165.9, 165.6, 154.9, 150.8, 142.1, 136.8, 135.3, 131.9, 129.3, 128.8, 128.1, 126.7, 126.2, 126.0, 123.0, 122.9, 121.8, 121.7, 121.6, 121.1, 21.4, 20.5; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_3$: m/z = 359.1396 (MH^+), found: 359.1405.

(4-methoxyphenyl)-*N*-(7-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (2D). Yield: 23.4 mg (89%); m.p. 238-239°C; HPLC: t_R=7.07; IR (KBr) ν: 3399m, 1670s, 1509s, 1363m, 1253s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.41 (s, 1H), 10.24 (s, 1H), 8.17 (d, J = 2.6 Hz, 1H), 8.00 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.7 Hz, 1H), 7.14 (s, 1H), 7.07-7.04 (m, 3H), 6.98 (d, J = 8.2 Hz, 1H), 3.84 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (DMSO- d_6) 165.7, 164.9, 162.1, 154.5, 150.5, 136.6, 135.0, 129.7, 128.4, 128.3, 126.5, 126.3, 125.8, 125.7, 122.6, 121.5, 121.4, 120.8, 113.8, 113.7, 55.4, 20.2; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_4$: m/z = 375.1345 (MH^+), found: 375.1336.

***N*-(8-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)ethanamide (3A)** Yield: 15.1 mg (76%); m.p. 264-265°C; HPLC: t_R=5.65; IR (KBr) ν: 3236m, 1676s, 1489m,1364m cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.45 (s, 1H), 10.10 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.76 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.94 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 2.23 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO- d_6) 168.3, 165.7, 154.2, 148.5, 136.5, 135.1, 130.7, 125.7, 124.5, 121.8, 121.7, 121.1,121.0, 120.8, 23.9, 20.3; HRMS (FAB) calcd for $C_{16}H_{14}N_2O_3$: m/z = 283.1083 (MH^+), found: 283.1081

(4-fluorophenyl)-*N*-(8-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (3B). Yield: 20.8 mg (82%); m.p. 255-256°C; HPLC: t_R=7.23; IR (KBr) ν: 3449m, 1671s, 1491s,1357s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.43 (s, 1H), 8.18 (d, J = 2.6 Hz, 1H), 8.07-8.04 (m, 2H), 7.99 (dd, J_1= 8.7 Hz, J_2 = 2.6 Hz, 1H), 7.38 (t, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.97 (bs, 1H), 6.93 (bd, J = 8.2 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (DMSO- d_6) 165.7, 165.4, 163.0, 154.8, 148.5, 136.2, 135.2, 130.9, 130.7, 130.5, 130.4, 126.0, 125.7, 122.7, 122.6, 121.8, 120.9, 120.8, 115.5, 115.3, 20.4; HRMS (FAB) calcd for $C_{21}H_{15}FN_2O_3$: m/z = 363.1145 (MH^+), found: 363.1152.

(4-methylphenyl)-*N*-(8-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (3C). Yield: 20.1 mg (80%); m.p. 217-218°C; HPLC: t_R=7.40; IR (KBr) ν: 3223m, 1671s, 1357s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.48 (s, 1H), 10.33 (s, 1H), 8.19 (d, J = 2.3 Hz, 1H), 8.00 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.96 (s, 1H), 6.93 (d, J = 8.3 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 3 H); ^{13}C NMR (DMSO- d_6) 165.8, 165.3, 154.7, 148.5, 141.8, 136.4, 135.2, 131.6, 130.7, 130.6, 129.4, 129.1, 129.0, 127.7, 125.9, 125.7, 122.7, 121.8, 120.9, 120.7, 21.0, 20.4; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_3$: m/z = 359.1396 (MH^+), found: 359.1404.

(4-methoxyphenyl)-*N*-(8-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (3D). Yield: 24.9 mg (95%); m.p. 282-284°C; HPLC: t_R=7.08; IR (KBr) ν: 3216m, 1671s, 1509m, 1359s, 1253s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.48 (s, 1H), 10.26 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.01 -7.96 (m, 3H), 7.30 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.96 (s, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (DMSO- d_6) 165.8, 164.8, 162.0, 154.6, 148.5, 136.5, 135.2, 130.7, 129.7, 126.5, 125.9, 125.7, 125.6, 122.6, 122.5, 121.8, 121.7, 120.9, 120.7, 113.7, 55.5, 20.4; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_4$: m/z = 375.1345 (MH^+), found: 375.1335.

***N*-(9-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)ethanamide (4A).** Yield: 6.7 mg (34%); m.p. 175-176°C; HPLC: t_R=5.52; IR (KBr) ν: 3235m, 1676s, 1490m, 1438s, 1364m cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.10 (s, 1H), 9.91 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.71 (dd, J_1 = 8.7 Hz, J_2 = 2.5 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.15 (t, J = 5.0 Hz, 1H), 7.05 (d, J = 4.9 Hz, 2H), 2.32 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6) 168.4, 165.9, 154.7, 152.7, 136.6, 131.5, 129.5, 127.4, 126.1, 125.4, 124.3, 120.8, 119.1, 118.7, 23.9, 17.8; HRMS (FAB) calcd for $C_{16}H_{14}N_2O_3$: m/z = 283.1083 (MH^+), found: 283.1080.

(4-fluorophenyl)-*N*-(9-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (4B). Yield: 10.2 mg (40%); m.p. 237-238°C; HPLC: t_R=7.12; IR (KBr) ν: 3399m, 1655s, 1508m cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.41 (s, 1H), 9.92 (s, 1H), 8.15 (d, J = 2.4 Hz, 1H), 8.05-8.02 (m, 2H), 7.95 (dd, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 1H) , 7.37 (t, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 1H), 7.18 (t, J = 4.3 Hz, 1H), 7.07-7.06 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6) 165.9, 165.4, 164.4, 162.9, 155.3, 152.7, 136.4, 131.6, 130.5, 130.4, 129.4, 127.5, 126.2, 125.7, 125.5, 122.4, 120.6, 118.7, 115.5, 115.3, 17.8; HRMS (FAB) calcd for $C_{21}H_{15}FN_2O_3$: m/z = 363.1145 (MH^+), found: 363.1139.

(4-methylphenyl)-*N*-(9-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (4C). Yield: 12.6 mg (50%); m.p. 128-129°C; HPLC: t_R=7.32; IR (KBr) ν: 3299m, 1655s, 1425m, 1204s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.31 (s, 1H), 9.91 (s, 1H), 8.17 (d, J = 2.4 Hz, 1H), 7.96 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 7.88 (d, J = 7.9 Hz, 2H), 7.34-7.31 (m, 3H), 7.18 (t, J = 4.2 Hz, 1H), 7.07-7.06 (m, 2H), 2.38 (s, 3H), 2.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) 165.9, 155.2, 152.5, 141.8, 136.0, 131.6, 129.9, 129.5, 129.0, 127.9, 125.7, 127.7, 127.5, 127.2, 126.0, 125.5, 122.3, 122.2, 120.6, 118.7, 21.0, 17.8; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_3$: m/z = 359.1396 (MH^+), found: 359.1405.

(4-methoxyphenyl)-*N*-(9-methyl-11-oxo-10*H*-benzo[b]-benzo[3,4-f]1,4-oxazepin-2-yl)formamide (4D). Yield: 15.2 mg (58%); m.p. 215-216°C; HPLC: t_R=6.98; IR (KBr) ν: 3387m, 1655s, 1425m, 1251s cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.23 (s, 1H), 9.90 (s, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.97-7.95 (m, 3H), 7.31 (d, J = 8.7 Hz, 1H), 7.18 (t, J = 4.1 Hz, 1H), 7.07-7.05 (m, 4H), 3.83 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (DMSO-d_6) 165.9, 165.8, 162.0, 155.1, 152.7, 136.7, 131.6, 129.6, 129.5, 129.0, 127.5, 126.4, 126.1, 125.6, 125.5, 122.3, 122.2, 120.5, 118.7, 113.7, 55.5, 17.8; HRMS (FAB) calcd for $C_{22}H_{18}N_2O_4$: m/z = 375.1345 (MH^+), found: 375.1337.

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