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Fast and Efficient Synthesis of Substituted Dibenz[b,f]oxazocines on Solid Support

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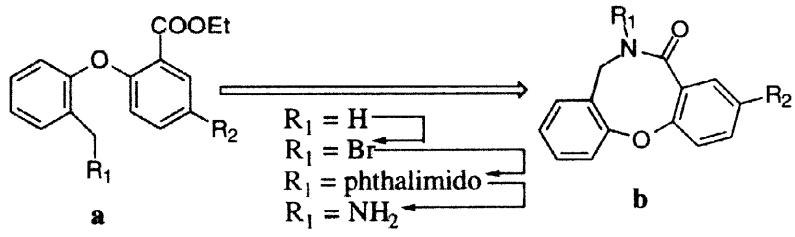
Summary: An efficient synthesis of substituted dibenzazocines on solid support is described. The targeted heterocycles are assembled *via* the nucleophilic aromatic substitution of fluorine in 2-fluoro-5-nitrobenzoic acid with the OH function of the immobilized polysubstituted phenols. High yields and excellent purities of the final products are the distinct characteristics of the resultant 15-member library.

Keywords: azocines; supported reagents/reactions; substitution

Nucleophilic aromatic substitution (S_NAr) is a powerful technique for the synthesis of polysubstituted aromatic compounds.[1] Both the theoretical, and the practical aspects of this reaction have been under investigation for a long time. As a result, a wide array of nucleophiles and leaving groups have been identified for the assembly of the desired aromatic molecules using S_NAr.[2] The unique features of fluorine as a leaving group are: i) low enthalpy of formation of the fluoride anion, and ii) easy availability of the fluorinated substrates for the S_NAr.[2] Formation of the cyclic systems *via* S_NAr of fluorine deserves special attention. Several research groups reported the successful application of this method as a key step in the preparation of dibenz[b,f]oxazepinones.[3] Research groups of Evans, Boger, Zhou, and others[1,4] clearly demonstrated the power of this strategy in the synthesis of macrocycles related to the vancomycin family of antibiotics. However, synthesis of eight-membered rings using this strategy is currently unknown.

In our effort toward the development of strategies for the fast and efficient assemblies of heterocycles,[6] we attempted the synthesis of the disubstituted dibenz[b,f]azocines. One of the reported approaches toward this heterocyclic system involved bromination of the biphenyl ether **a** followed by its treatment with potassium phthalimide. Hydrazinolysis of the resultant intermediate, and subsequent intramolecular cyclization of the amine



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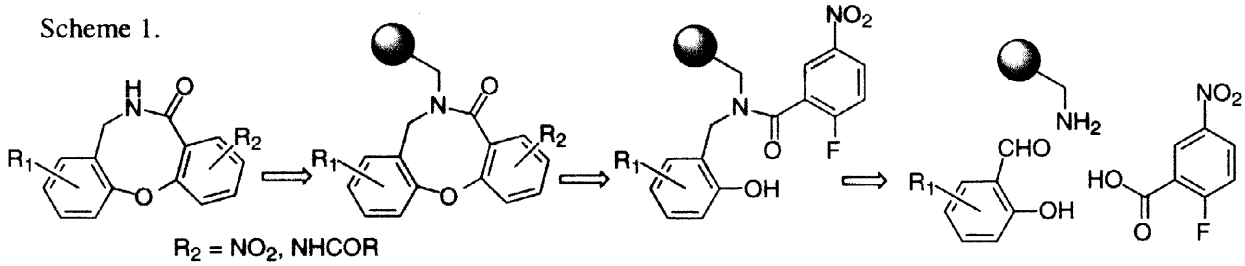
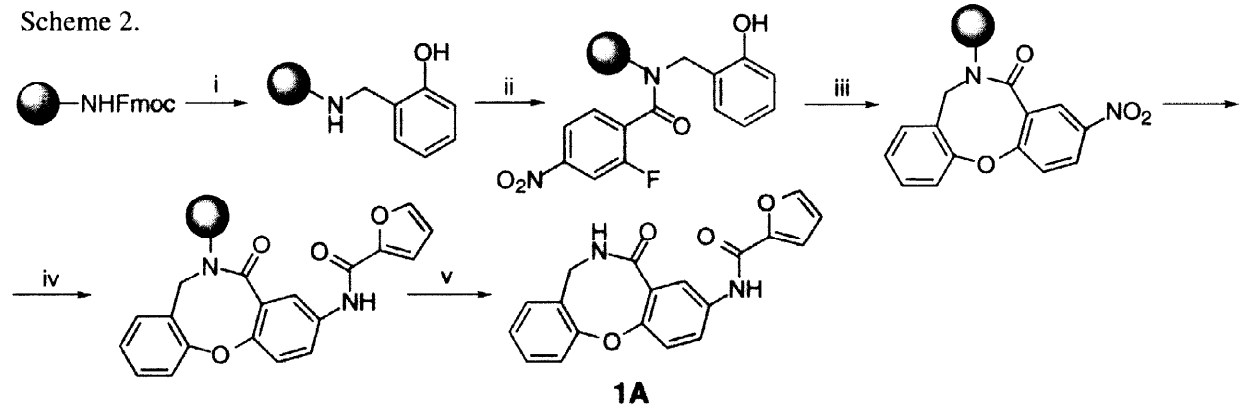
afforded the targeted eight-membered lactam **b**.[5] The disadvantages of the reported procedure were: i) multi-step synthesis, and ii) formation of side products. Retrosynthetic analysis of these 8-membered heterocycles suggested the S_NAr of fluorine in 2-fluoro-5-nitrobenzoic acid with the OH functionality of the *ortho*-substituted phenols. In order to accelerate the synthesis and to minimize the purification, we decided to conduct our synthesis on solid support (Scheme 1).

Scheme 1.



In our initial effort, we successfully modified the commercially available Rink Amide resin with salicylaldehyde using a standard reductive amination protocol with $NaBH(OAc)_3$.[3a] The subsequent attachment of the commercially available 2-fluoro-5-nitrobenzoic acid to the resulting resin *via* the reported HOAt/DIC protocol[7] afforded the intermediate which was suited for the S_NAr step. The subsequent smooth cyclization of the intermediate was achieved using 5% DBU in DMF. Progress of this step was monitored by the previously reported ^{19}F NMR technique.[8] The reaction was completed in 12 h. The resultant immobilized nitrodibenz[b,f]oxazocine was treated with 1.5M solution of $SnCl_2 \cdot 2H_2O$ in DMF[9] to afford the corresponding amino derivative, which was then successfully acylated with furoyl chloride, and cleaved with 20% TFA in CH_2Cl_2 to provide the desired heterocycle **1A** in a 77% yield (Scheme 2).

Scheme 2.



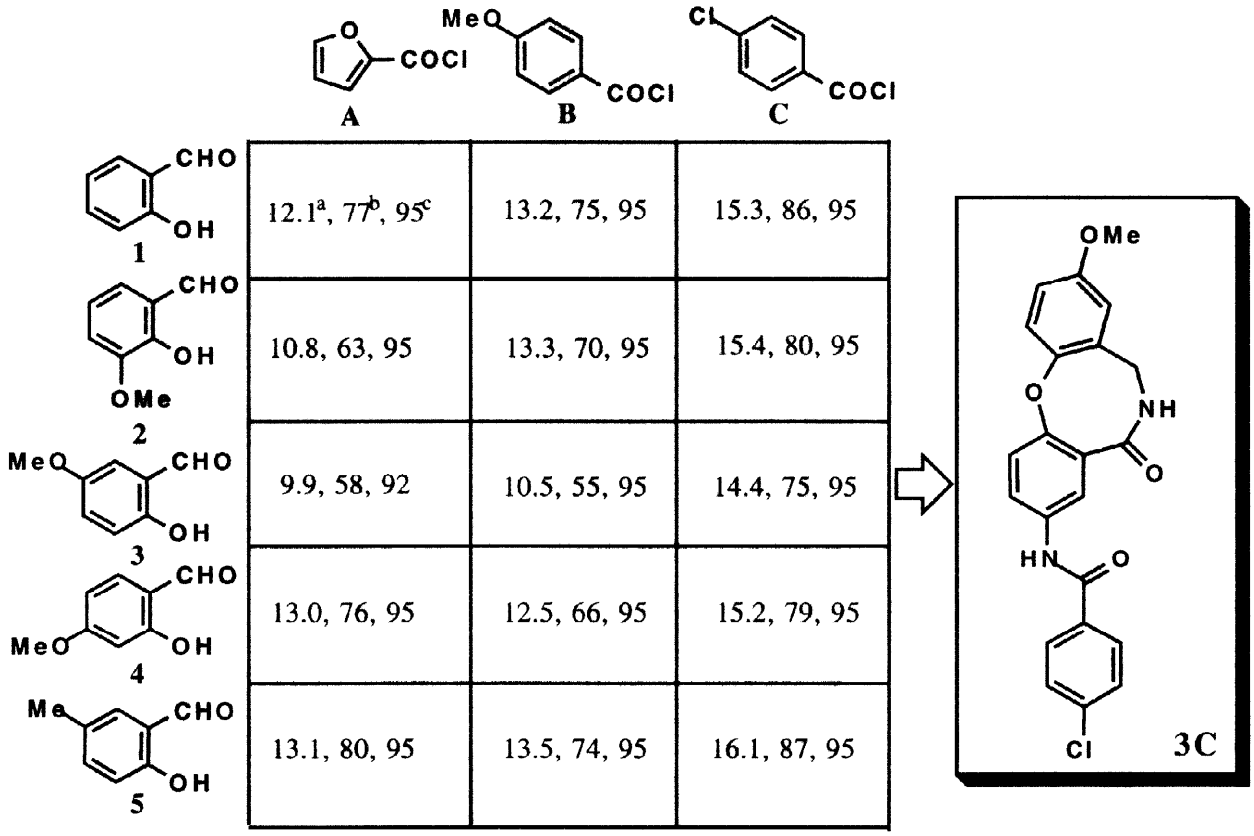
Reagents and Conditions: i) 20% piperidine, DMF, 20 min, RT; salicylaldehyde (**1**), $HC(OMe)_3$; $NaBH(OAc)_3$, DMF,12 h, RT; ii) 2-fluoro-5-nitrobenzoic acid, HOAt, DIC, DMF, 24 h, RT; iii) 5% DBU, DMF, 24 h, RT; iv) $SnCl_2$ $2H_2O$, DMF, 12 h, RT; furoyl chloride (**A**), Hunig's base, DMF, 8 h, RT; v) 20% TFA , CH_2Cl_2, 40 min

Several other cyclization strategies, including S_NAr reactions promoted by a 5% solution of tetramethylguanidine in DMF, or 1M solution of Bu_4NF in THF afforded similar results. Application of Cs_2CO_3 as a base for the cyclization afforded the desired dibenz[b,f]oxazocine in only a 10% yield. In this case, the major component of

the reaction mixture after TFA cleavage was identified to be the noncyclized material (LC MS). *Protection of the phenolic OH functionality was not required throughout the synthesis.*

Development of the optimal reaction conditions (see Experimental Section) allowed us to synthesize a 15-member library of dibenz[b,f]oxazocines (Scheme 3).[10] It is worth noting that the experimental protocol allows for the synthesis of much larger libraries of the desired eight-membered heterocycles.

Scheme 3. Yields and purities [11] of the dibenz[b,f]oxazocine library.



	A	B	C
1	12.1[a], 77[b], 95[c]	13.2, 75, 95	15.3, 86, 95
2	10.8, 63, 95	13.3, 70, 95	15.4, 80, 95
3	9.9, 58, 92	10.5, 55, 95	14.4, 75, 95
4	13.0, 76, 95	12.5, 66, 95	15.2, 79, 95
5	13.1, 80, 95	13.5, 74, 95	16.1, 87, 95

a. yield (mg) from 100 mg of resin; b. yield (%) based on initial loading; c. HPLC purity (%).

The nature of the acylating agents **A-C** did not affect the yield or purity of the products. The parent salicylic aldehyde as well as its derivatives containing electron-donating substituents afforded oxazocines **1A-5C** in good to excellent yields (55-87%), and purity acceptable for immediate biological testing.11 However, the desired dibenz[b,f]oxazocines were not isolated when the salicylic aldehydes containing electron withdrawing substituents (COOMe, or halogen) were used. We believe the poor loading of the Rink Amide resin with these aldehydes after the reductive amination step is at least partially responsible for this result.[10]

Overall, the solid support synthesis of dibenz[b,f]oxazocines described in this paper yields the target heterocycles in good yield, and excellent purity. The approach presented in this paper is the first example of the application of the nucleophilic aromatic substitution protocol towards the synthesis of the dibenz[b,f]oxazocine core. The flexibility, and robustness of this procedure makes the overall strategy easily adaptable for the parallel synthesis of the targeted structures on solid support.

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. The rink amide resin (100-200 mesh) purchased from Novabiochem with a loading of 0.47 mmol/g was deprotected by 40 % piperidine in DMF followed by washing with DMF, MeOH, and DCM before use. Concentration of the solutions after workup was performed by reduced pressure rotary evaporation on a Büchi 535 apparatus. ^1H NMR spectra were obtained on a Bruker 500 instrument with DMSO-d_6 as the solvent. MS analyses (ES, and CI modes) were performed on a Perkin Elmer API 165 instrument. Melting points were measured by a Büchi 535 melting point apparatus. 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. For method one, 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. For method two, the column employed was a Waters C18 cartridge 50mm x 4.6 mm. The solvent system was MeCN/H_2O (start: 20:100 ratio; finish: 10:90; 3 min runs; .1% TFA added), with a flow rate of 3 mL/min.

General Procedure for Reductive Amination of Salicylaldehydes on Rink Amide Resin. In a typical experimental procedure, Rink amide resin (1 g; loading 0.47 mmol/g) was added to a 100 mL peptide vessel. After the addition of trimethyl orthoformate (20 mL), salicylaldehyde (4.88 g, 40 mmol) was added to the vessel. The mixture was shaken for 8 h, filtered, and the resin was washed with anhydrous DCM and DMF three times. $NaBH(OAc)_3$ (10.6 g, 50 mmol) in 30 mL of anhydrous DMF was added, and the slurry was slowly shaken for another 12 h. 40 mL of MeOH was added to the mixture, and the resulting mixture was left 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.

General Procedure for the Synthesis of 3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-ones Solid Support. This procedure was run using the following reaction conditions: 20 mL of a mixture of 3-fluoro-4-nitrobenzoic acid (0.37 g, 2 mM), HOAt (0.272 g, 2 mM), and DIC (0.277 g, 2.2 mM) was added to a corresponding 1 g of reductive aminated salicylaldehyde resin. The resultant slurry was shaken for 8 h., filtered, washed with DMF, MeOH, CH_2Cl_2, and treated with 50 mL of a 5% solution of DBU in DMF at room temperature for 24 h., filtered, washed with 10% AcOH in DMF, MeOH, CH_2Cl_2, and dried *in vacuo*. Portions of the resins (100 mg quantity) were cleaved by 40% TFA to yield fresh bright yellow solids.

General Procedure for the Synthesis of 3-substituted-6H,7H-dibenzo[b,g]1,5-oxazocin-5-ones (1A-5D) on Solid Support. The 3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-ones (**1-5**, 1 g) were treated with a 1.5 M solution of $SnCl_2 \cdot 2H_2O$ (20 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 3-amino-6H,7H-dibenzo[b,g]1,5-oxazocin-5-ones (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 furfuryl chloride or benzoyl chlorides (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 3-substituted-

6H,7H-dibenzo[b,g]1,5-oxazocin-5-ones (**1A-5C**) off the solid support (an 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, extracted with EtOAc, washed with saturated NaHCO3, dried over Na2SO4, concentrated, and purified by radial chromatography (Chromatotron, Silicagel, eluent: $CHCl_3$/MeOH, 97:3) to afford analytically pure dibenzo[b,g]1,5-oxazocin-5-ones.

Selected Analytical Data:

3-Nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-one. Yield: 6.3 mg (50%). m.p. >280 °C. HPLC (method 1): t_R=5.63;^{1}H NMR (DMSO-d_6) δ 8.61 (s, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.27 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.41 (m, 2H), 7.17 (m, 2H), 4.11 (d, J= 6.3 Hz); HRMS (FAB) calcd for $C_{14}H_{10}N_2O_4$: m/z = 271.0719 (MH^+), found: 271.0718. Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.03; H, 3.56; N, 10.18.

8-Methoxy-3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-one. Yield: 6.8 mg (48%). m.p. >280 °C. HPLC (method 1): t_R=5.50;^{1}H NMR (DMSO-d_6) δ 8.59 (t, J=6.3 Hz), 8.37 (dd, J_1 = 8.9 Hz, J_2 = 2.7 Hz, 1H), 8.27 (d, J = 2.64 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.11 (m, 2H), 6.74 (d, J = 7.4 Hz, 1H), 4.10 (d, J= 6.5 Hz, 2H), 3.91 (s, 3H); HRMS (FAB) calcd for $C_{15}H_{12}N_2O_5$: m/z = 301.0824 (MH^+), found: 301.0821. Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.72; H, 3.91; N, 9.24.

9-Methoxy-3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-one. Yield: 4.4 mg (31%). m.p. >280 °C. HPLC (method 1): t_R=5.75;^{1}H NMR (DMSO-d_6) δ 8.57 (t, J=6.55 Hz, 1H), 8.37 (dd, J_1 = 9.9 Hz, J_2 = 2.8 Hz, 1H), 8.26 (d, J = 2.8 Hz, 1H), 7.5 (d, J = 8.9 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 6.92 (dd, J_1 = 8.8 Hz, J_2 = 3.1 Hz, 1H), 6.78 (d, J=3 Hz, 1H), 4.07 (d, J = 6.6 Hz, 2H), 3.72 (s, 3H); HRMS (FAB) calcd for $C_{15}H_{12}N_2O_5$: m/z = 301.0824 (MH^+), found: 301.0821.

9-Methyl-3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-one. Yield: 5.1 mg (38%). m.p. >280 °C. HPLC (method 1): t_R=6.16;^{1}H NMR (DMSO-d_6) δ 8.56 (d, J=6.96 Hz, 1H), 8.37 (t, J=8.27 Hz, 1H), 8.26 (d, J = 4.8 Hz, 1H), 7.5 (t, J = 8.5 Hz, 1H), 7.30 (t, J=7.7 Hz, 1H), 7.18 (d, J_1 = 6.7 Hz, 1H), 6.98 (d, J=6 Hz, 1H), 4.05 (d, J = 6.5 Hz, 2H), 2.25 (d, J=7.3 Hz, 3H); HRMS (FAB) calcd for $C_{15}H_{12}N_2O_4$: m/z = 285.0875 (MH^+), found: 285.0872.

10-Methoxy-3-nitro-6H,7H-dibenzo[b,g]1,5-oxazocin-5-one. Yield: 5.9 mg (42%). m.p. 222-224 °C. HPLC (method 2): t_R=1.58;^{1}H NMR (DMSO-d_6) δ 8.57 (t, J=6.67 Hz, 1H), 8.38 (dd, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1H), 8.26 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 4.02 (d, J = 6.14 Hz, 2H), 3.80 (s, 3H); HRMS (FAB) calcd for $C_{15}H_{12}N_2O_5$: m/z = 301.0824 (MH^+), found: 301.0820. Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.87; H, 3.97; N, 9.11.

(4-Methoxyphenyl)-N-(5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (1B). Yield: 11.9 mg (68%); m.p. 252-256°C; HPLC (method 1): t_R=6.08;^{1}H NMR (DMSO-d_6) δ 10.24 (s, 1H), 8.32 (t, J=2.26 Hz, 1H), 7.97 (dd, J_1 = 8.0 Hz, J_2 = 2.6 Hz, 2H), 7.91 (m, 2H), 7.33 (m, 2H), 7.20 (dd, J_1 = 6.2 Hz, J_2 = 3 Hz, 1H),7.10 (s, 1H), 7.06 (dd, J_1 = 8.3 Hz, J_2 = 3 Hz, 2H), 4.08 (b, 2H), 3.84 (d, J= 3 Hz, 3H); HRMS (FAB) calcd for $C_{22}H_{18}N_2O_4$: m/z = 397.1164 (MNa^+), found: 397.1156. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.28; H, 4.63; N, 7.22.

(4-Chlorophenyl)-N-(5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (1C). Yield: 13.5 mg (76%); m.p. >280°C; HPLC (method 1): t_R=6.67;^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 8.34 (t, J=5.99 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.90 (m, 2H), 7.62 (d, J= 8.3 Hz, 2H), 7.33 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H),7.15 (d, J=6.86 Hz, 1H), 7.10(m, 1H), 4.08 (d, J=6.27 Hz, 2H); HRMS (FAB) calcd for $C_{21}H_{15}ClN_2O_3$: m/z = 401.0669 (MNa^+), found: 401.0660. Anal. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.36; H, 3.78; N, 7.25.

2-Furyl-N-(8-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (2A). Yield: 8.9 mg (52%); m.p. 259-262°C; HPLC (method 1): t_R=5.18;^{1}H NMR (DMSO-d_6) δ 10.32 (s, 1H), 8.29 (t, J=6.32 Hz, 1H), 7.94 (s, 1H), 7.88 (d, J= 2.27 Hz, 1H), 7.86 (dd, J_1 = 8.75 Hz, J_2 = 2.37 Hz, 1H),7.35 (m, 1H), 7.09 (m, 1H), 7.02 (t, J=7.74 Hz, 1H), 6.69 (m, 2H), 4.06 (d, J=6.38 Hz, 2H), 3.89 (s, 3H); HRMS (FAB) calcd for $C_{20}H_{16}N_2O_5$: m/z = 365.1137 (MH^+), found: 365.1131. Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.71; H, 4.67; N, 7.46.

N-(8-Methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))(4-methoxyphenyl)formamide (2B). Yield: 11.3 mg (59%); m.p. >280°C; HPLC (method 1): t_R=5.87;^{1}H NMR (DMSO-d_6) δ 10.24 (s, 1H), 8.29 (t, J=6.74 Hz, 1H), 7.96 (d, J=8.4 Hz, 2H), 7.88 (m, 2H), 7.05 (m, 6H), 6.69 (d, J=7.04 Hz, 1H), 4.06 (d, J=6.2 Hz, 2H), 3.89 (s, 3H), 3.84, (s, 1H); HRMS (FAB) calcd for $C_{23}H_{20}N_2O_5$: m/z = 405.1450 (MH^+), found: 405.1455. Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.30; H, 4.99; N, 6.93. Found: C, 68.07; H, 5.10; N, 6.82.

(4-Chlorophenyl)-N-(8-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (2C). Yield: 13.6 mg (71%); m.p. 250-252°C; HPLC (method 1): t_R=6.47;^{1}H NMR (DMSO-d_6) δ 10.46 (s, 1H), 8.32 (t, J=6.43 Hz, 1H), 7.98 (d, J= 8.43 Hz, 2H), 7.90 (m, 2H), 7.61 (d, J=8.43 Hz, 2H), 7.09 (m, 2H), 7.03 (t, J=7.6 Hz, 1H), 6.69 (d, J=7.4 Hz, 1H), 4.06 (d, J=6.22 Hz, 2H), 3.90 (s, 3H); HRMS (FAB) calcd for $C_{22}H_{17}ClN_2O_4$: m/z = 409.0955 (MH^+), found: 409.0970.

2-Furyl-N-(9-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (3A). Yield: 8.1 mg (47%); m.p. 199-202°C; HPLC (method 1): t_R=5.45;^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.32 (t, J=6.32 Hz, 1H), 7.94 (s, 1H), 7.88 (d, J= 2.27 Hz, 1H), 7.85 (m, 2H),7.35 (d, J=3.4 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 7.19 (d, J=9.3 Hz, 1H), 6.88 (dd, J_1 = 8.7 Hz, J_2 = 3 Hz, 1H), 6.73 (d, J= 2.9 Hz, 1H), 6.70 (m, 1H) 4.04 (d, J=5.66 Hz, 2H), 3.71 (s, 3H); HRMS (FAB) calcd for $C_{20}H_{16}N_2O_5$: m/z = 365.1137 (MH^+), found: 365.1127. Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.68; H, 4.66; N, 7.48.

(4-Chlorophenyl)-N-(9-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (3C). Yield: 12.7 mg (66%); m.p. 266-268°C; HPLC (method 1): t_R=6.65;^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.32 (t, J=6.32 Hz, 1H), 7.94 (s, 1H), 7.88 (d, J= 2.27 Hz, 1H), 7.85 (m, 2H),7.35 (d, J=3.4 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 7.19 (d, J=9.3 Hz, 1H), 6.88 (dd, J_1 = 8.7 Hz, J_2 = 3 Hz, 1H), 6.73 (d, J= 2.9 Hz, 1H), 6.70 (m, 1H) 4.04 (d, J=5.66 Hz, 2H), 3.71 (s, 3H); HRMS (FAB) calcd for $C_{22}H_{17}ClN_2O_4$: m/z = 409.0955 (MH^+), found: 409.0968. Anal. Calcd for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.37; H, 4.11; N, 6.78.

2-Furyl-N-(10-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (4A). Yield: 10.5 mg (61%); m.p. >280°C; HPLC (method 2): t_R=1.45;^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 8.32 (t, J=6.5 Hz, 1H), 7.95 (s, 1H), 7.87 (m, 2H), 7.35 (m, 1H), 7.24 (m, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.91 (d,

J=2.4 Hz, 1H), 6.71 (m, 1H), 6.67 (dd, J_1 = 8.3Hz, J_2 = 2.5 Hz, 1H), 3.98 (d, J=6.5 Hz, 2H), 3.79 (s, 3H); HRMS (FAB) calcd for $C_{20}H_{16}N_2O_5$: m/z = 365.1137 (MH^+), found: 365.1133. Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.65; H, 4.19; N, 7.41.

N-(10-Methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))(4-methoxyphenyl)formamide (4B). Yield: 10.4 mg (55%); m.p. 282-284°C; HPLC (method 2): t_R=1.73; ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 8.31 (t, J=6.7 Hz, 1H), 7.96 (d, J=8.5 Hz, 2H), 7.89 (m, 2H), 7.23 (d, J=8.2 Hz, 1H), 7.05 (m, 3H), 6.91 (d, J=1.5 Hz, 1H), 6.67 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 3.99 (d, J=6 Hz, 2H), 3.84 (s, 3H), 3.79, (s, 3H); HRMS (FAB) calcd for $C_{23}H_{20}N_2O_5$: m/z = 405.1450 (MH^+), found: 405.1438. Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.3; H, 4.99; N, 6.93. Found: C, 68.18; H, 4.90; N, 6.77.

(4-Chlorophenyl)-N-(8-methoxy-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (4C). Yield: 13.7 mg (71%); m.p. >280°C; HPLC (method 2): t_R=1.65;^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 8.33 (t, J=6.45 Hz, 1H), 7.98 (d, J= 8.57 Hz, 2H), 7.90 (m, 2H), 7.62 (d, J=8.53 Hz, 2H), 7.26 (d, J=9.47 Hz, 1H), 7.05 (d, J=8.4 Hz, 1H), 6.92 (d, J=2.5 Hz, 1H), 6.67 (dd, J_1 = 8.48 Hz, J_2 = 2.6 Hz, 1H), 3.99 (d, J=6.6 Hz, 2H), 3.79 (s, 3H); HRMS (FAB) calcd for $C_{22}H_{17}ClN_2O_4$: m/z = 409.0955 (MH^+), found: 409.0946.

2-Furyl-N-(9-methyl-5-oxo(6H,7H-dibenzo[b,g]1,5-oxazocin-3-yl))formamide (5A). Yield: 11.5 mg (70%); m.p. >280°C; HPLC (method 2): t_R=1.73;^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.31 (t, J=6.3 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J= 8.78 Hz, 2H), 7.35 (m, 1H), 7.18 (t, J=7.27 Hz, 2H), 7.13 (d, J=7.88 Hz, 1H), 6.93 (s, 1H), 6.71 (s, 1H), 4.02 (d, J=5.86 Hz, 2H), 2.24 (s, 3H); HRMS (FAB) calcd for $C_{20}H_{16}N_2O_4$: m/z = 371.1008 (MNa^+), found: 371.1016. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.95; H, 4.63; N, 8.04. Found: C, 68.67; H, 4.46; N, 7.92.

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10. The resin obtained from the reductive amination step with 5-bromosalicylic aldehyde was treated with the acylating agent (*p*-nitrobenzoyl chloride), and TFA. The yield of the expected amide was only 2%. Our attempts to modify the reductive amination conditions to overcome this problem, for example to use $NaBH_3CN$ or $NaBH_4$ as reducing agents, were not successful.
11. Analytically pure compounds were obtained by radial chromatography as described in the Experimental Section. All desired dibenz[b,f]oxazocines were fully characterized by ^1H NMR, HPLC, ESI MS, HRESI MS, and afforded satisfactory combustion analysis.