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Meglumine: A Novel and Efficient Catalyst for One-Pot, Three-Component Combinatorial Synthesis of Functionalized 2-Amino-4*H*-pyrans

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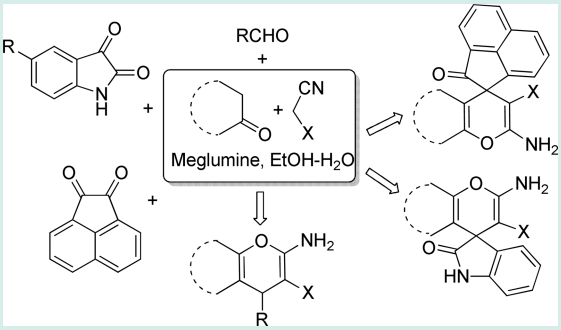
Supporting Information

ABSTRACT: An efficient one-pot synthesis of functionalized 2-amino-4*H*-pyrans by a meglumine-catalyzed three-component reaction has been developed. A broad range of substrates including aromatic and heteroaromatic aldehydes, isatin derivatives, and acenaphthenequinone are condensed with enolizable C−H activated compounds and alkylmalonates to give the desired products in high to excellent yields. This methodology provides an alternative approach for rapid access to construct a diversity-oriented library of 4*H*-pyrans.



KEYWORDS: *one-pot synthesis, three-component reaction, functionalized 2-amino-4H-pyrans, meglumine*

Pyran and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products[1] as well as photochromic materials.[2] They exhibit a wide range of biological activities such as anticancer,[3] antimicrobial,[4] antioxidant,[5] and antiproliferative properties.[6] 4*H*-Pyran derivatives are also potential calcium channel antagonists, which are structurally similar to biologically active 1,4-dihydropyridines.[7] In addition, amino-4*H*-pyrans are often used in cosmetics and pigments, or are utilized as potentially biodegradable agrochemicals. The 4*H*-pyran derivatives bearing a nitrile functionality are also useful intermediates for the synthesis of various compounds such as pyridones, 1,4-dihydropyridines, lactones, pyranopyrazoles, imidoesters, and aminopyrimidines.[8] Because of the important aforementioned properties of pyran derivatives, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.[9] The most straightforward synthesis of this heterocyclic system involves a three-component coupling of an aldehyde with alkylmalonates and diverse enolizable C−H activated acidic compounds in the presence of homogeneous or heterogeneous catalysts such as diammonium hydrogen phosphate,[10] *N*-methylimidazole,[11] 4-(dimethylamino)pyridine (DMAP),[12] lithium bromide,[13] hexamethylenetetramine,[14] 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[15] potassium phthalimide-*N*-oxyl,[16] lipase,[17] $Ce(SO_4)_2{\cdot}4H_2O$,[18] cerium(III) chloride,[19] tetrabutylammonium fluoride (TBAF),[20] or a basic ionic liquid.[21] This reaction proceeds in glycerol[22] or choline chloride-urea.[23] With widespread applications and bioactivity, the development of efficient, economically and environmentally benign synthetic methodology for the preparation of these heterocyclic compounds is highly desirable.

Following the increasing environmental and economic considerations, the search for enviro-economic synthetic methods for organic reactions has received overwhelming attention. In this regard, efforts are being made to replace the expensive and hazardous catalysts with biodegradable materials, which are safe, inexpensive, harmless, and environmentally benign. Recently, Gu et al. introduced meglumine and gluconic acid aqueous solution as a promoting medium and catalyst for the multicomponent reaction of β-ketosulfones and formaldehyde.[24] Meglumine is an amino sugar derived from sorbitol with molecular formula $C_7H_{17}NO_5$ (Figure 1). In particular, the

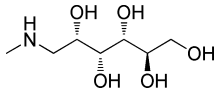


Figure 1. Structure of meglumine.

low toxicity of meglumine allows its use in the formulation of pharmaceuticals as an excipient and in conjunction with iodinated compounds in contrast media such as diatrizoate meglumine and iodipamide meglumine.[25] Meglumine possesses environmentally benign properties such as biodegradability and physiological inertness. Additionally, meglumine is inexpensive,

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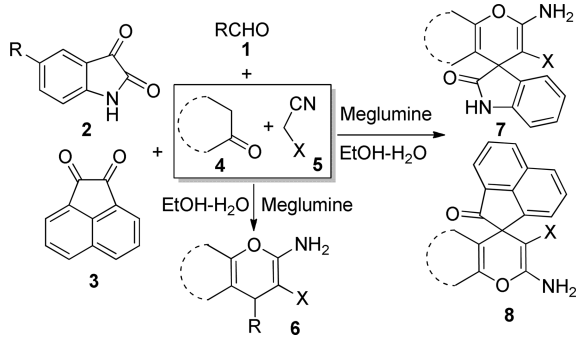
noncorrosive, stable to air and moisture, and readily available in the market. It contains an amino group, primary and secondary hydroxyl groups that can activate the nucleophilic as well as electrophilic components of the reactions by hydrogen bonding and donation of a lone pair of electrons, respectively. Multicomponent coupling reactions (MCRs) have been acknowledged as powerful and bond-forming efficient tools for the construction of novel and structurally complex molecules with a minimum of reaction steps and simple workup procedures. Thus, the combination of MCRs, a biodegradable catalyst, and a green solvent will make the chemical reaction more environmentally as well as economically viable.[26]

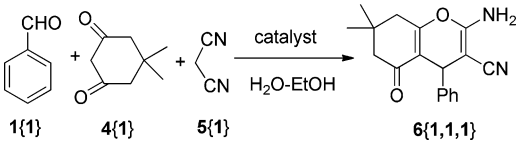
Considering the above subjects and continuing our efforts on the development of new MCRs and environmental benign synthetic methodologies,[27] we wish to report a facile, one-pot, three-component process for the synthesis of functionalized 2-amino-4*H*-pyrans from the reaction of aldehydes, isatin derivatives, or acenaphthenequinone with enolizable C−H activated compounds and alkylmalonates in the presence of meglumine at room temperature (Scheme 1).

Scheme 1. Synthesis of Functionalized 2-amino-4*H*-pyrans Catalyzed by Meglumine



To explore the generality and feasibility of meglumine catalyzed MCRs, we investigated the optimization of the reaction conditions using benzaldehyde, 5,5-dimethylcyclohexane-1,3-dione, and malononitrile as model reactants. Various catalysts were examined, and the results are summarized in Table 1. To justify the significance of catalyst in this three-component process, the reaction was first performed in the absence of the catalyst wherein only 40% yield of the target product was observed even at prolonged reaction time (Table 1, entry 1). In the presence of potassium carbonate, sodium acetate, or ammonium acetate, the reaction gave 55%, 45%, and 50% isolated yield of product after 1 h, respectively. In addition, sodium dodecylbenzenesulfonate, triethylamine, tetrabutylammonium bromide, and *L*-proline could also catalyze this transformation, but no improvement was observed (Table 1, entries 5−8). The reaction was then performed in the presence of metal oxides such as CuO, CeO_2, ZnO, and MgO (Table 1, entries 9−12). However, these catalysts were less effective. We then tested the reaction in the presence of meglumine. Meglumine was found to be the best catalyst for this process, and the desired product **6**{*1,1,1*}was formed in 97% yield in just 5 min (Table 1, entry 13). We think that in addition to the amino group, the presence of multiple hydroxyl groups in the structure of meglumine plays an important role for the formation of product because of the stabilization of the corresponding intermediates and transition states by hydrogen bonding.

Table 1. Influence of Different Catalysts on the Reaction of Benzaldehyde, 5,5-Dimethylcyclohexane-1,3-dione, and Malononitrile[a]



entry	catalyst	time (min)	yield (%)[b]
1	no	60	40
2	K_2CO_3	60	55
3	CH_3COONa	60	45
4	CH_3COONH_4	60	50
5	sodium dodecylbenzenesulfonate	60	65
6	triethylamine	60	60
7	tetrabutylammonium bromide	60	50
8	L-proline	60	50
9	CuO	60	45
10	CeO_2	60	40
11	nano ZnO	60	45
12	nano MgO	60	40
13	meglumine	5	97

[a]Experimental conditions: benzaldehyde (1 mmol), 5,5-dimethylcyclohexane-1,3-dione, (1 mmol), malononitrile (1 mmol), catalyst (5 mol %), EtOH-H_2O (1:1, 2 mL), room temperature. [b]Isolated yields.

Table 2. Optimization of Reaction Conditions[a]

entry	catalyst loading (mol %)	solvent	time (min)	yield (%)[b]
1	5	no	10	93
2	5	MeOH	20	80
3	5	EtOH	10	95
4	5	PEG 400	60	70
5	5	H_2O	60	30
6	5	EtOH-H_2O (1:1)	5	97
7	5	EtOH-H_2O (2:1)	10	95
8	5	EtOH-H_2O (1:2)	10	93
9	1	EtOH-H_2O (1:1)	5	88
10	3	EtOH-H_2O (1:1)	5	92
11[c]	5	EtOH-H_2O (1:1)	5	96
12[d]	5	EtOH-H_2O (1:1)	5	96, 95, 93

[a]Experimental conditions: benzaldehyde (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), malononitrile (1 mmol), solvent (2 mL), room temperature. [b]Isolated yields. [c]The reaction was carried out in 50 mmol scale. [d]Catalyst was reused three times.

Next, we screened the effect of the solvent and catalyst loading (Table 2). The reaction was not satisfactory in water, possibly because of incomplete homogeneity of the reaction mixture. Further studies showed that aqueous-ethanol (1:1 v/v) was the best choice of solvent for this transformation. The reaction was also carried out using different amounts of the catalyst, and the results showed that 5 mol % of catalyst was the best choice for completing the reaction in aqueous-ethanol. By decreasing the amount of catalyst to 3 mol % relative to substrate, the yield of product decreased (Table 2, entry 10). Consequently, the best result was obtained by using 5 mol % of meglumine as the catalyst and aqueous-ethanol (1:1 v/v) as the solvent (Table 2, entry 6).

Furthermore, when the reaction was scaled up to 50 mmol, an excellent result was obtained in the same time (Table 2, entry 11). For utility in large scale syntheses we demonstrated

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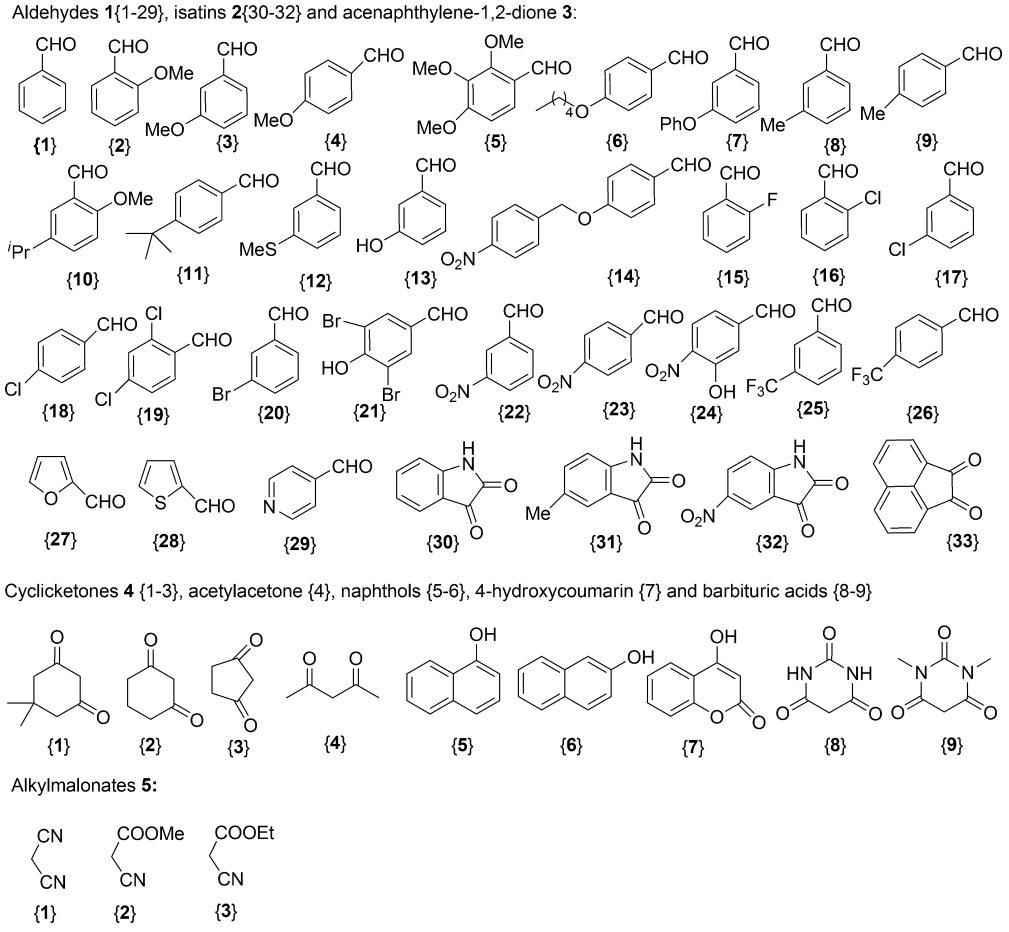

Figure 2. Diversity of reagents.

the recyclability of meglumine for three consecutive cycles with almost the same catalytic activity (Table 2, entry 12). After completion of each reaction, the precipitated product was filtered and washed with aqueous ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product. To recover the catalyst, the filtrate was dried under reduced pressure and the recovered catalyst was washed with diethyl ether and reused after drying.

To investigate the scope and limitation of this catalytic process, 29 aldehydes **1**{1−29}, 3 isatins **2**{30−32}, acenaphthenequinone **3**{33}, 3 cyclic ketones **4**{1−3}, 1 acyclic 1,3-dicarbonyl compounds **4**{4}, 2 naphthols **4**{5−6}, 4-hydroxycoumarin **4**{7}, 2 barbituric acids **4**{8−9}, and 3 acetonitrile derivatives **5**{1−3} were chosen for library validation (Figure 2). We first examined the reaction of 5,5-dimethylcyclohexane-1,3-dione **4**{1} and malononitrile **5**{1} with a diverse array of aldehydes. As evident from Table 3, this multicomponent reaction proceeded efficiently, and the desired products were obtained in high to excellent yields in relatively short times. The nature of the functional group on the aromatic ring of the aldehyde exerted a slight influence on the product yield and reaction time. It was observed that arylaldehydes carrying an electron-withdrawing group reacted faster with better yield than those having an electron-donating group. The reaction was also sensitive to the steric environment of the aromatic aldehyde with longer reaction times being required for benzaldehydes containing substituents at the 2-position. Heteroaromatic aldehydes, such as furan-2-carbaldehyde, thiophene-2-carbaldehyde, and pyridine-4-carbaldehyde, readily participated in this transformation, affording the potentially biologically important 2-amino-4*H*-pyrans in high yields (Table 3, entries 27−29). To further demonstrate the scope of the substrates subject to meglumine catalysis, isatins were used as reactants with 5,5-dimethylcyclohexane-1,3-dione and malononitrile. Gratifyingly, it was found that the expected products were obtained in excellent yields, regardless of the effect of substitution on the isatins (Table 3, entries 30−32). In the case of acenaphthenequinone **3**{33}, the desired spiro-4*H*-pyrans **8**{*33,1,1*} was also produced in 93% yield (Table 3, entry 33). It should be noted that the reaction with methyl cyanoacetate or ethyl cyanoacetate required longer reaction times than those with malononitrile, which was probably due to their lower reactivity (Table 3, entries 34−37).

Subsequently, a variety of enolizable C−H activated compounds such as carbonyl compounds possessing a reactive α-methylene group cyclohexane-1,3-dione and cyclopentane-1,3-dione, α-naphthol and β-naphthol, 4-hydroxycoumarin, and barbituric acids were evaluated in this three-component reaction. In all cases, the corresponding functionalized 2-amino-4*H*-pyrans were formed in high to excellent yields. Furthermore, the reaction may also be extended to acyclic 1,3-dicarbonyl compounds such as acetylacetone, although longer reaction times were required (Table 3, entries 44−46). The above results clearly indicate the present catalytic procedure is extendable to a wide variety of substrates to construct a diversity-oriented library of 4*H*-pyrans.

In summary, we have developed a simple and efficient one-pot, three-component, meglumine catalyzed synthesis of functionalized

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Table 3. One-Pot Synthesis of 2-Amino-4*H*-pyran Derivatives

entry	product	time (min)	yield (%)[a]	mp (°C) found	mp (°C) reported
1	**6**{*1,1,1*}	5	97	225–226	224–226[22]
2	**6**{*2,1,1*}	15	92	200–201	203–205[17]
3	**6**{*3,1,1*}	13	94	190–191	188–190[18]
4	**6**{*4,1,1*}	13	95	200–201	201–203[16]
5	**6**{*5,1,1*}	25	92	209–210	209–210[13]
6	**6**{*6,1,1*}	20	91	177–178	
7	**6**{*7,1,1*}	20	93	194–195	195–196[20]
8	**6**{*8,1,1*}	12	95	224–225	223–225[17]
9	**6**{*9,1,1*}	12	93	211–212	219–222[10]
10	**6**{*10,1,1*}	17	93	227–228	226–228[19]
11	**6**{*11,1,1*}	18	93	241–242	240–242[19]
12	**6**{*12,1,1*}	14	93	209–210	208–209[21]
13	**6**{*13,1,1*}	13	93	205–206	204–205[10]
16	**6**{*14,1,1*}	20	93	215–216	
15	**6**{*15,1,1*}	7	96	233–234	232–233[20]
16	**6**{*16,1,1*}	8	95	216–217	215–216[11]
17	**6**{*17,1,1*}	5	96	235–236	236–237[10]
18	**6**{*18,1,1*}	5	96	215–216	213-215[22]
19	**6**{*19,1,1*}	10	94	193–195	192–195[10]
20	**6**{*20,1,1*}	5	93	229–230	228–230[28]
21	**6**{*21,1,1*}	10	95	241–242	
22	**6**{*22,1,1*}	5	96	215–216	213-217[10]
23	**6**{*23,1,1*}	5	96	185–186	181–184[10]
24	**6**{*24,1,1*}	10	93	227–228	226–228[13]
25	**6**{*25,1,1*}	5	96	224–226	
26	**6**{*26,1,1*}	5	95	218–219	217–218[29]
27	**6**{*27,1,1*}	15	95	226–227	225–226[13]
28	**6**{*28,1,1*}	15	92	221–222	222–223[22]
29	**6**{*29,1,1*}	14	96	153	
30	**7**{*30,1,1*}	18	96	290–292	291–293[22]
31	**7**{*31,1,1*}	18	93	278–279	277–278[22]
32	**7**{*32,1,1*}	10	95	303–304	302–304[30]
33	**8**{*33,1,1*}	20	93	269–270	268–270[31]
34	**6**{*18,1,2*}	20	91	170–171	171[10]
35	**6**{*23,1,2*}	18	92	187–188	186–188[10]
36	**6**{*18,1,3*}	22	90	150–151	150[10]
37	**6**{*23,1,3*}	20	91	180–181	179–181[10]
38	**6**{*9,2,1*}	10	95	232–233	233–235[22]
39	**6**{*18,2,1*}	7	96	242–243	241–243[12]
40	**6**{*22,2,1*}	6	93	202–203	201–202[17]
41	**6**{*23,2,1*}	5	96	235–236	235–236[13]
42	**6**{*18,3,1*}	5	95	218–219	216–218[12]
43	**6**{*26,3,1*}	5	96	178–180	
44	**6**{*1,4,1*}	150	92	165–166	164[32]
45	**6**{*18,4,1*}	120	93	155–156	154[32]
46	**6**{*23,4,1*}	90	94	169–170	170[32]
47	**6**{*2,5,1*}	15	94	207–208	
48	**6**{*9,5,1*}	15	94	206–207	205–206[15]
49	**6**{*18,5,1*}	15	95	245–246	243–244[12]
50	**6**{*23,5,1*}	10	97	235–236	236[35]
51	**6**{*25,5,1*}	15	95	218–220	
52	**6**{*9,6,1*}	140	90	255–256	255[35]
53	**6**{*16,6,1*}	120	92	259–60	260[35]
54	**6**{*23,6,1*}	110	93	187–188	187[35]
55	**6**{*9,7,1*}	20	93	254–255	255–256[22]
56	**6**{*15,7,1*}	15	96	248–249	247–249[14]
57	**6**{*18,7,1*}	17	93	265–266	264–266[12]
58	**6**{*26,7,1*}	13	96	208–210	
59	**6**{*2,8,1*}	30	95	232–233	231–232[22]
60	**6**{*18,8,1*}	19	95	264–265	263–264[22]
61	**6**{*23,8,1*}	15	96	263–264	262–263[22]
62	**6**{*9,9,1*}	20	93	203–204	203[33]
63	**6**{*18,9,1*}	18	95	239–240	238–240[33]
64	**6**{*26,9,1*}	15	97	>300	
65	**7**{*30,2,1*}	15	94	298–299	297–298[22]
66	**7**{*30,3,1*}	25	97	>300	>300[34]
67	**7**{*30,5,1*}	30	95	221–222	220–222[22]
68	**7**{*30,6,1*}	35	93	235–236	233–235[22]
69	**7**{*30,7,1*}	20	95	>300	>300[22]
70	**7**{*30,8,1*}	30	95	298–299	296–298[22]
71	**7**{*30,9,1*}	25	97	229–230	228–229[36]
72	**7**{*31,5,1*}	40	93	>300	
73	**7**{*32,5,1*}	15	95	>300	
74	**7**{*32,9,1*}	20	95	225–227	
75	**8**{*33,2,1*}	25	94	>300	>300[37]
76	**8**{*33,3,1*}	25	95	276–277	
77	**8**{*33,7,1*}	30	80	>300	>300[31]
78	**8**{*33,8,1*}	35	90	>300	>300[31]
79	**8**{*33,9,1*}	40	92	>300	>300[37]

[a]Isolated yield.

2-amino-4*H*-pyrans using readily available starting materials. The salient features of this new methodology are broad substrate scope, room temperature reaction conditions, short reaction times, high yields of the products, operational simplicity, reusability of catalyst and the absence of hazardous organic solvents, which make it an applicable method for constructing diverse libraries of 4*H*-pyrans.

EXPERIMENTAL PROCEDURES

General Information. All solvents and chemicals used in this work were obtained commercially and were used as received. Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were obtained as potassium bromide pellets with a Bruker-TENSOR 27 spectrometer. NMR spectra were recorded with a Bruker DRX-500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) using DMSO-d_6 or $CDCl_3$ as the solvent with TMS as internal standard. Elemental analysis was performed by using a Vario EL III CHNOS elemental analyzer.

Typical Procedure for Synthesis of 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 6 {*1,1,1*}. A mixture of benzaldehyde **1**{*1*} (0.11 g, 1 mmol)), 5,5-dimethylcyclohexane-1,3-dione **2**{*1*} (0.14 g, 1 mmol), malononitrile **3**{*1*} (0.07 g, 1 mmol), and meglumine (5 mol %, 0.01g) in EtOH-H_2O (1:1, 2 mL) was stirred at room temperature for 5 min. The progress of the reaction was monitored by TLC (hexane-EtOAc, 5:1). After completion of the reaction, the precipitated product was filtered and washed with aqueous ethanol (5 mL). The crude product was purified by recrystallization from ethanol to afford the desired product. To recover the catalyst, the filtrate was dried under reduced pressure, and recovered catalyst was washed with diethyl ether (2 mL) twice and reused after drying.

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Compound ***6****{6,1,1}*. White solid; IR (KBr): 3545, 3327, 3215, 2937, 2193, 1683, 1653, 1606, 1508, 1367, 1251, 1211, 1174, 1035, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.33−1.44 (m, 4H, 2 × CH_2), 1.75 (quin, J = 7.0 Hz, 2H, CH_2), 2.19 and 2.24 (AB system, J = 16.5 Hz, 2H, CH_2), 2.44 (s, 2H, CH_2), 3.90 (t, J = 7.0 Hz, 2H, OCH_2), 4.35 (s, 1H, CH), 4.49 (s, 2H, NH_2), 6.80 (d, J = 8.5 Hz, 2H, HAr), 7.13 (d, J = 8.5 Hz, 2H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 27.6, 28.2, 28.9, 29.0, 32.2, 34.8, 40.7, 50.7, 63.1, 67.9, 114.2, 114.5, 115.6, 119.0, 128.6, 133.6, 135.4, 157.7, 158.2, 161.4, 196.2 ppm; Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.42; H, 7.26; N, 7.55.

Compound ***6****{14,1,1}*. White solid; IR (KBr): 3433, 3331, 3219, 2955, 2185, 1687, 1672, 1602, 1518, 1425, 1369, 1344, 1253, 1138, 1039, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.11(s, 3H, CH_3), 2.19 and 2.24 (AB system, J = 16.5 Hz, 2H, CH_2), 2.44 (s, 2H, CH_2), 4.37(s, 1H, CH), 4.50 (s, 2H, NH_2), 5.13 (s, 2H, CH_2), 6.87 (d, J = 8.5 Hz, 2H, HAr), 7.17 (d, J = 8.5 Hz, 2H, HAr), 7.59 (d, J = 8.5 Hz, 2H, HAr), 8.24 (d, J = 8.5 Hz, 2H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.8, 31.3, 32.2, 34.4, 34.9, 40.7, 50.7, 63.9, 114.2, 118.8, 125.5, 127.0, 140.1, 149.7, 157.5, 161.5, 196.0 ppm; Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43. Found: C, 67.22; H, 5.38; N, 9.62.

Compound ***6****{21,1,1}*. White solid; IR (KBr): 3421, 3336, 3217, 2960, 2191, 1700, 1660, 1480, 1430, 1365, 1251, 1211, 1138, 1039, 875 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.24 (s, CH_2), 2.43 and 2.50 (AB system, J = 18.0 Hz, 2H, CH_2), 4.31 (s, 1H, OH), 4.59 (s, 2H, NH_2), 5.81 (s, 1H, CH), 7.31 (s, 2H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.8, 31.3, 32.2, 34.4, 34.9, 40.7, 50.7, 63.9, 114.2, 118.8, 125.5, 127.0, 140.1, 149.7, 157.5, 161.5, 196.0 ppm; Anal. Calcd for $C_{18}H_{16}Br_2N_2O_3$: C, 46.18; H, 3.44; N, 5.98. Found: C, 45.99; H, 3.60; N, 6.16.

Compound ***6****{25,1,1}*. White solid; IR (KBr): 3350, 3259, 3176, 2966, 2191, 1683, 1658, 1606, 1469, 1417, 1371, 1330, 1219, 1124, 1039, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.19 and 2.24 (AB system, J = 16.5 Hz, 2H, CH_2), 2.48 (s, 2H, CH_2), 4.47 (s, 1H, CH), 4.60 (s, 2H, NH_2), 7.42 (t, J = 7.5 Hz, 1H, HAr), 7.42 (s, 1H), 7.47 (d, J = 7.5 Hz, 1H, HAr), 7.48 (d, J = 7.5 Hz, 1H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 29.0, 32.2, 35.6, 40.7, 50.6, 62.9, 113.5, 118.2, 124.1 (q, $^3J_{FC}$ = 3.75 Hz), 125.2 (q, $^1J_{FC}$ = 271.0 Hz), 129.0, 131.1 (q, $^2J_{FC}$ = 32.0 Hz), 131.4, 144.2, 157.6, 161.9, 195.7 ppm; Anal. Calcd for $C_{19}H_{17}F_3N_2O_2$: C, 62.98; H, 4.73; N, 7.73. Found: C, 63.12; H, 4.90; N, 7.55.

Compound ***6****{29,1,1}*. White solid; IR (KBr): 3419, 3394, 3216, 2956, 2187, 1683, 1672, 1600, 1421, 1373, 1251, 1205, 1138, 1037, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.21 and 2.27 (AB system, J = 16.5 Hz, 2H, CH_2), 2.48 (s, 2H, CH_2), 4.40 (s, 1H, CH), 4.69 (s, 2H, NH_2), 7.18 (d, J = 6.0 Hz, 2H, HAr), 8.54 (d, J = 6.0 Hz, 2H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 28.9, 32.3, 35.1, 40.7, 50.5, 61.8, 112.9, 118.1, 122.8, 150.1, 151.6, 157.9, 162.3, 195.6 ppm; Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.98; H, 5.96; N, 14.05.

Compound ***6****{26,3,1}*. White solid; IR (KBr): 3404, 3333, 3211, 2937, 2193, 1670, 1643, 1597, 1442, 1375, 1329, 1234, 1166, 1111, 1066, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.49−2.52 (m, 2H, CH_2), 2.74−2.77 (m, 2H, CH_2), 4.44 (s, 1H, CH), 4.79 (s, 2H, NH_2), 7.40 (d, J = 8.0 Hz, 2H, HAr), 7.59 (d, J = 8.0 Hz, 2H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 33.6, 35.7, 61.4, 117.9, 118.3, 125.7 (q, $^3J_{FC}$ = 3.5 Hz), 126.2 (q, $^1J_{FC}$ = 270.6 Hz), 129.9 (q, $^2J_{FC}$ = 32.1 Hz), 144.6, 159.0, 175.3, 200.8 ppm; Anal. Calcd for $C_{16}H_{11}F_3N_2O_2$: C, 60.00; H, 3.46; N, 8.75. Found: C, 58.91; H, 3.52; N, 8.93.

Compound ***6****{2,5,1}*. White solid; IR (KBr): 3471, 3396, 3198, 2933, 2185, 1662, 1614, 1573, 1489, 1458, 1377, 1261, 1192, 1105, 1022, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H, OCH_3), 4.70 (s, 2H, NH_2), 5.42 (s, 1H, CH), 6.86 (t, J = 7.5 Hz, 1H, HAr), 6.91 (d, J = 8.0 Hz, 1H, HAr), 7.02 (dd, J = 7.5, 1.5 Hz, 1H, HAr), 7.12 (d, J = 8.5 Hz, 1H, HAr), 7.20 (td, J = 7.5, 1.5 Hz, 1H, HAr), 7.48 (d, J = 8.5 Hz, 1H, HAr), 7.51 (d, J = 8.5 Hz, 1H, HAr), 7.56 (t, J = 7.5 Hz, 1H, HAr), 7.78 (d, J = 8.0 Hz, 1H, HAr), 8.16 (d, J = 8.0 Hz, 1H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2, 55.7, 60.7, 111.1, 117.9, 120.0, 120.7, 121.1, 123.2, 124.5, 126.2, 126.5, 127.7, 128.4, 129.6, 132.8, 133.2, 143.6, 156.8, 159.8 ppm; Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.66; H, 5.10; N, 8.38.

Compound ***6****{25,5,1}*. White solid; IR (KBr): 3473, 3338, 3198, 2935, 2195, 1670, 1602, 1572, 1460, 1408, 1379, 1261, 1188, 1114, 1050, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 2H, NH_2), 4.97 (s, 1H, CH), 6.98 (d, J = 8.0 Hz, 1H, HAr), 7.45−7.54 (m, 5H, HAr), 7.56 (d, J = 8.0 Hz, 1H, HAr), 7.60 (t, J = 8.0 Hz, 1H, HAr), 7.81 (d, J = 8.0 Hz, 1H, HAr), 8.19 (d, J = 8.0 Hz, 1H, HAr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.4, 60.4, 116.3, 119.5, 120.9, 123.2, 124.0 (q, $^1J_{FC}$ = 271.0 Hz),124.4 (q, $^3J_{FC}$ = 3.8 Hz), 124.8 (q, $^3J_{FC}$ = 3.8 Hz), 125.0, 125.8, 126.9, 127.1, 127.8, 129.4, 131.3 (q, $^2J_{FC}$ = 32.1 Hz), 131.7, 133.5, 143.4, 145.4, 159.3 ppm; Anal. Calcd for $C_{21}H_{13}F_3N_2O$: C, 68.85; H, 3.58; N, 7.65. Found: C, 69.02; H, 3.75; N, 7.48.

Compound ***6****{26,7,1}*. White solid; IR (KBr): 3325, 3194, 3072, 2877, 2198, 1716, 1602, 1377, 1112, 765 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.60 (s, 1H, CH), 7.47−7.53 (m, 6H, HAr and NH_2), 7.68 (d, J = 8.5 Hz, 2H, HAr), 7.73 (t, J = 7.0 Hz, 1H, HAr), 7.91(d, J = 7.5 Hz, 1H, HAr) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 37.3, 57.6, 103.6, 113.4, 117.1, 119.5, 123.0, 125.2, 125.8 (q, $^1J_{FC}$ = 270.4 Hz), 125.9 (q, $^3J_{FC}$ = 3.8 Hz), 128.3 (q, $^2J_{FC}$ = 31.2 Hz), 129.1, 133.6, 148.4, 152.7, 154.3, 158.5, 160.6 ppm; Anal. Calcd for $C_{20}H_{13}F_3N_2O_3$: C, 62.18; H, 3.39; N, 7.25. Found: C, 61.99; H, 3.58; N, 7.43.

Compound ***6****{26,9,1}*. White solid; IR (KBr): 3441, 3304, 3183, 2193, 1705, 1608, 1323, 1126, 839 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.07 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.45 (s, 1H, CH), 7.44 (s, 2H, NH_2), 7.49 (d, J = 8.0 Hz, 2H, HAr), 7.66 (d, J = 8.0 Hz, 2H, HAr) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.1, 29.6, 36.9, 58.2, 88.4, 119.3, 125.2 (q, $^1J_{FC}$ = 270.2 Hz), 125.7 (q, $^3J_{FC}$ = 3.8 Hz), 127.9 (q, $^2J_{FC}$ = 31.2 Hz), 128.0, 149.3, 150.5, 151.8, 158.2, 160.9 ppm; Anal. Calcd for $C_{17}H_{13}F_3N_4O_3$: C, 53.97; H, 3.46; N, 14.81. Found: C, 54.15; H, 3.62; N, 15.00.

Compound ***7****{31,5,1}*. White solid; IR (KBr): 3483, 3300, 3066, 2966, 2195, 1651, 1597, 1107, 692 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.20 (s, 3H, CH_3), 6.57 (d, J = 9.0 Hz, 1H, HAr), 6.88 (d, J = 7.5 Hz, 1H, HAr), 6.90 (s, 1H, HAr), 7.09 (d, J = 7.5 Hz, 1H, HAr), 7.43 (s, 2H, NH_2), 7.57 (d, J = 9.0 Hz, 1H, HAr), 7.60 (t, J = 7.5 Hz, 1H, HAr), 7.69 (t, J = 7.5 Hz, 1H, HAr), 7.90 (d, J = 8.5 Hz,1H, HAr), 8.27 (d, J = 8.5 Hz, 1H, HAr), 10.6 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.0, 51.4, 55.0, 110.3, 115.4, 119.1, 121.2, 123.3, 123.7, 125.0, 125.9, 127.5, 127.8, 128.2, 130.0, 132.2, 133.5, 135.5, 139.8,

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144.0, 161.5, 179.3 ppm; Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.60; H, 4.45; N, 12.03.

Compound 7{32,5,1}. White solid; IR (KBr): 3481, 3298, 3196, 2860, 2189, 1627, 1527, 1338, 1107, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.64 (d, J = 9.0 Hz, 1H, HAr), 7.22 (d, J = 9.0 Hz, 1H, HAr), 7.59−7.65 (m, 4H, NH_2 and HAr), 7.71 (t, J = 8.0 Hz, 1H, HAr), 7.93 (d, J = 8.0 Hz, 1H, HAr), 8.02 (s, 1H, HAr), 8.29 (t, J = 7.0 Hz, 2H, HAr), 11.4 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 51.6, 53.6, 111.1, 113.7, 118.8, 121.3, 121.4, 123.3, 123.4, 125.3, 127.1, 127.6, 128.0, 128.2, 133.8, 136.1, 143.6, 144.3, 148.8, 161.6, 179.7 ppm; Anal. Calcd for $C_{21}H_{12}N_4O_4$: C, 65.62; H, 3.15; N, 14.58. Found: C, 65.80; H, 2.96; N, 14.66.

Compound 7{32,9,1}. White solid; IR (KBr): 3396, 3186, 2968, 2362, 2202, 1743, 1506, 1390, 754 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.02 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 7.03 (d, J = 8.5 Hz, 1H, HAr), 7.77 (s, 2H, NH_2), 8.17 (d, J = 8.5 Hz, 1H, HAr), 8.19 (s, 1H, HAr), 11.3 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.1, 29.8, 48.0, 56.6, 86.5, 109.9, 117.1, 120.3, 126.5, 135.2, 143.0, 149.1, 150.1, 153.0, 158.9, 160.1, 178.7 ppm; Anal. Calcd for $C_{17}H_{12}N_6O_6$: C, 51.52; H, 3.05; N, 21.21. Found: C, 51.70; H, 2.91; N, 21.39.

Compound 8{33,3,1}. Light yellow solid; IR (KBr): 3471, 3362, 3194, 2929, 2193, 1712, 1589, 1361, 1026, 781 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.34 (t, J = 4.5 Hz, 2H, CH_2), 2.88 (t, J = 4.5 Hz, 2H, CH_2), 7.48 (d, J = 7.0 Hz, 1H, HAr), 7.62 (s, 2H, NH_2), 7.71 (t, J = 7.5 Hz, 1H, HAr), 7.87 (t, J = 8.0 Hz, 1H, HAr), 8.00 (t, J = 9.0 Hz, 2H, HAr), 8.35 (d, J = 8.0 Hz, 1H, HAr) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.5, 33.6, 51.4, 57.6, 116.3, 118.1, 121.5, 122.5, 125.5, 129.2, 129.5, 130.4, 131.8, 132.8, 141.2, 141.8, 161.1, 178.3, 200.6, 203.6 ppm; Anal. Calcd for $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 72.98; H, 3.85; N, 8.66.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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