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Rapid access to 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones using palladium-catalyzed C–N bond coupling reaction

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Abstract—A series of 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones have been synthesized by the palladium-catalyzed C–N coupling reaction starting from 3-bromoquinolin-2-(1*H*)-ones. Various nucleophiles including amines, amides, sulfonamides, carbamates and ureas have been used successfully. In all the cases, the reactions take place rapidly in 1,4-dioxane and proceed in good to excellent yield using palladium acetate as a catalyst, Xantphos as a ligand and Cs_2CO_3 as a base.

1. Introduction

Quinolin-2(1*H*)-ones are an important class of heteroaromatic compounds.[1] As isosteres of coumarin, quinolinones display a broad range of biological activities (e.g., antiviral,[2] antitumoral[3]) and a number of analogues of this class of heterocyclic structure have been reported as lead compounds or are currently undergoing clinical trials.[4] The growing importance of these pharmaceutical compounds has led to the development of new methods for their synthesis.[5]

Although quinolin-2(1*H*)-ones exhibit a wide range of biological activities, to date there have been a limited number of methods to prepare 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones. The main routes to these heterocyclic structures are reduction of 3-nitroquinolinones into 3-aminoquinolinones,[6] or Hofmann rearrangement of quinolinone-3-carboxylic acid derivatives followed by further N-functionalization.[7] An alternative route consists of cyclization of a suitable *N*-chloroacetyl-*o*-aminobenzophenone precursor to form α-pyridinium salt followed by hydrazinolysis.[4d] All these multi-step procedures, however, are often moderate to low yielding, and the variety of substrates is very limited.

In an ongoing medicinal chemistry programme, we required the synthesis of 3-(*N*-acyl)-, 3-(*N*-sulfonamyl)- and 3-(*N*-aryl)-aminoquinolin-2(1*H*)-ones as analogues of novobiocin that target the hsp90, an exciting new target in cancer drug discovery.[8] As these compounds are not easily accessible by current methodology, our goal was to explore the palladium-catalyzed C–N bond coupling reaction starting from 3-haloquinolin-2(1*H*)-ones. The latter are of particular interest, in that the coupling would offer a convergent and straightforward approach to various 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones.

Although significant advances have occurred in the metal-catalyzed[9] amination or amidation of aryl halides during the last decade, application of this coupling to various heterocyclic structures is still a relatively unexplored process.[10] To our knowledge, palladium-catalyzed C–N bond-forming reactions between 3-haloquinolin-2(1*H*)-ones[11] and nucleophiles including amines, amides, sulfonamides and carbamates are unknown. Herein we report our studies on these useful reactions.

2. Results and discussion

To optimize conditions for the preparation of aminoquinolin-2(1*H*)-one **3a**, the coupling of 3-bromoquinolin-2(1*H*)-one **1a** with 4-methoxybenzamide **2a** was initially selected as a model reaction for investigating the effects of various ligands (Fig. 1), palladium sources and bases. The results are summarized in Table 1.

As can seen from Table 1, the reaction of **1a** with **2a** was initially examined under the procedure developed by Buchwald[12] for the amidation of aryl halides ($Pd(OAc)_2$, Xantphos,[13] Cs_2CO_3 in 1,4-dioxane at 100 °C). We were

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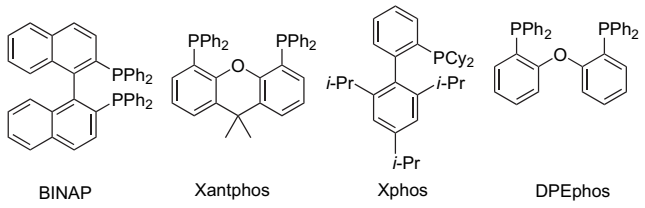
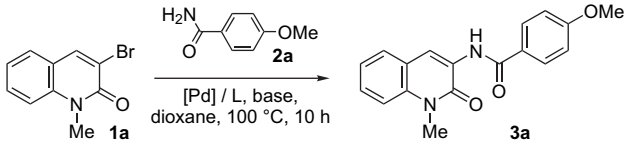


Figure 1. Supporting ligands used in this study.

Table 1. Optimization coupling reaction of **1a** with 4-methoxybenzamide **2a** under various conditions[a]



Entry	[Pd]	Ligand	Base	Conversion[b] (%)	Yield[c] (%)
1	$Pd(OAc)_2$[e]	Xantphos	Cs_2CO_3	100	95[d]
2	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	50	nd[f]
3	$Pd(OAc)_2$	Xphos	Cs_2CO_3	100	85
4	$Pd(OAc)_2$	DPEphos	Cs_2CO_3	64	nd[f]
5	$Pd(OAc)_2$	BINAP	Cs_2CO_3	77	nd[f]
6	$Pd(OAc)_2$	Dppf[g]	Cs_2CO_3	60	nd[f]
7	$Pd(OAc)_2$	Xantphos	Na_2CO_3	0	0[h]
8	$Pd(OAc)_2$	Xantphos	K_3PO_4	100	82
9	$Pd(OAc)_2$	Xantphos	K_2CO_3	100	86

[a] Reactions of **1a** (1.0 mmol) with 4-methoxybenzamide **2a** (1.5 mmol) were performed in a sealed Schlenk tube at 100 °C for 10 h in dioxane (2 mL) by using [Pd] (5 mol %), ligand (5 mol %) and base (2 mmol).
[b] Conversion was determined by ^{1}H NMR in the crude reaction mixture and was based on remaining **1a**.
[c] Isolated yields.
[d] No reaction occurred at room temperature.
[e] No reaction occurred without palladium catalyst.
[f] Yield not determined.
[g] dppf: diphenylphosphino-ferrocene.
[h] Reproducible result after three runs and starting material was recovered unchanged.

pleased to find that these conditions provided the most generally successful results. Complete conversion of **1a** was observed after 10 h using only a 1:1 ratio of Pd/L and the expected coupling product was formed in 95% yield (Table 1, entry 1). It should be noted that no reaction occurred without palladium catalyst. Changing the bidentate ligand phosphine to the sterically hindered monodentate ligand Xphos[14] also led to total conversion although the yield of **3a** was slightly lower (entry 3). The use of other bidentate phosphine ligands such as DPEphos, BINAP or dppf, however, induced a lowering of the conversion rate (entries 4–6). It is interesting to note that in the coupling of **1a** with **2a**, the source of palladium used has an important influence on the reaction rate. Thus, a slow rate was observed when running the reaction with $Pd_2(dba)_3$ instead of $Pd(OAc)_2$ in combination with Xantphos ligand (entry 2). This result clearly indicated that in the present reaction, the catalytic activity of $Pd(OAc)_2$ proved to be superior to $Pd_2(dba)_3$. Finally, use of bases such as K_3PO_4 and K_2CO_3 was found to be highly effective (entries 8 and 9), whereas Na_2CO_3 did not promote the coupling reaction (entry 7).

With a viable coupling procedure in hand, attention was turned to the generality of the process, and the couplings

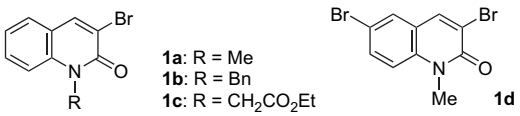


Figure 2. 3-Bromoquinolin-2(1*H*)-ones **1** used in this study.

of structurally diverse nucleophiles with some 3-bromoquinolin-2(1*H*)-ones **1** were studied (Fig. 2).

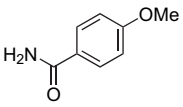
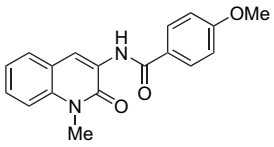
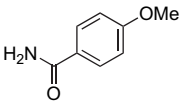
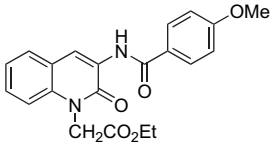
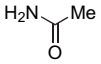
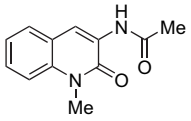
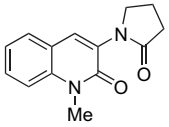
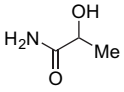
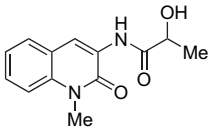
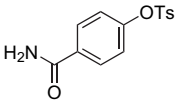
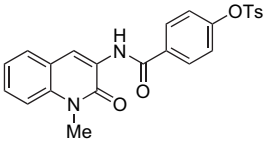
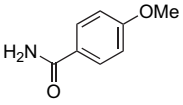
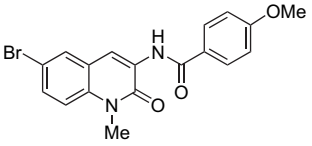
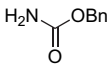
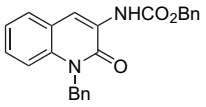
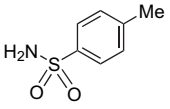
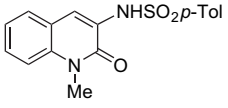
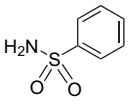
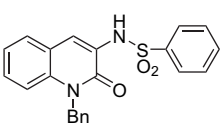
Results summarized in Table 2 show that the optimized conditions described above proved to be general for the coupling with a large variety of nucleophiles. The coupling was found to be compatible with primary aromatic and aliphatic amides (entries 1–3) providing in excellent yields the corresponding coupling products **3a–c**.

The reaction was also effective with cyclic amides (entry 4) as well as with functionalized primary amides (entries 5 and 6), although the yields were slightly lower.

Under our optimal conditions, the reaction selectivity was investigated with substrate **1d** containing two carbon–bromine atoms. The coupling proceeded at the more activated C-3 position and yielded the mono-substitution product **3g** (44%, entry 7) together with the bis-coupling one bis-**3g** (27%). C–N bond-forming reaction was also studied with benzyl carbamate (entry 8) as well as with the less nucleophilic alkyl- or arylsulfonamides (entries 9–12). These substrates also proved to be viable nucleophiles for the coupling reaction and in most cases, good yields of coupling products **3h–l** were obtained. Finally, the C–N bond-forming reactions were examined using acyclic urea and we found that this amide analogue was doubly heteroarylated in good yields (entry 13).

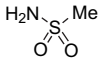
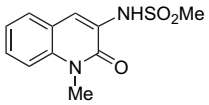
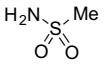
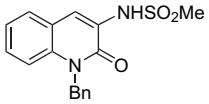
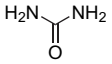
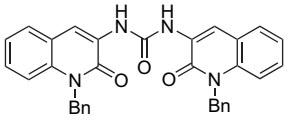
The reaction was next carried out with a series of primary and secondary amines. As shown in Table 3, various 3-(*N*-alkyl)- and 3-(*N*-aryl)-aminoquinolin-2(1*H*)-one derivatives **4** were obtained in good yields by using $Pd(OAc)_2$ as the palladium source, Xantphos as the ligand, Cs_2CO_3 as the base and 1,4-dioxane as the solvent. Under these conditions, anilines proved to be suitable substrates for this C–N bond-forming reaction affording the coupling products in good yields (entries 1 and 2). We were pleased to observe that the ethoxycarbonyl group was tolerated in the presence of our catalyst system (entry 2). Similarly, primary alkyl- and benzylamines worked well in this coupling, although the amines containing a secondary carbon atom in the α-position gave slightly lower reaction yields (entries 4 and 5). Finally, secondary cyclic amines showed similar reaction activity relative to the other primary aliphatic and aromatic amines (entry 7). For substrate **1d** containing two C–Br substituents, the reaction selectivity was examined with morpholine. A 1:1 ratio of **1d**/morpholine gave selectively the monocoupling product **4h** (39%, not shown in table), clearly indicating that the C-3 position is more electrophilic than the C-7 position. Increasing the ratio to 1:1.5 enhanced the reaction yield (48%, entry 8), although a notable amount of bis-coupling product bis-**4h** was obtained (15%). Finally, carrying out the reaction in the presence of an excess of morpholine (5 equiv) had no significant change on the mono- (41%) and bis-coupling (21%) products' yields.

Table 2. Palladium-catalyzed amidation of 3-bromoquinolin-2(1*H*)-ones **1**: synthesis of functionalized 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones **3**[a]

Entry	ArBr	Amide	Product **3**		Yields[b] (%)
1	**1a**			**3a**	95
2	**1c**			**3b**	87
3	**1a**			**3c**	92
4	**1a**			**3d**	69
5	**1a**			**3e**	60
6	**1a**			**3f**	46[c]
7	**1d**			**3g**	44[d]
8	**1b**			**3h**	57
9	**1a**			**3i**	85
10	**1b**			**3j**	74

(*continued*)

Table 2. (*continued*)

Entry	ArBr	Amide	Product **3**		Yields[b] (%)
11	**1a**			**3k**	66
12	**1b**			**3l**	68
13	**1a**			**3m**	61

[a] Reactions of **1** (1.0 mmol) with amide/sulfonamide/carbamate/urea (1.5 mmol) were performed in a sealed Schlenk tube at 100 °C for 10 h in dioxane (2 mL) by using $Pd(OAc)_2$ (5 mol %), Xantphos (5 mol %) and Cs_2CO_3 (2 mmol).
[b] Isolated yields.
[c] No product resulting from the coupling of the C-OTs bond with 4-tosylbenzamide was detected.
[d] A 27% yield of the corresponding bis-coupling compound was obtained.

3. Conclusion

We have demonstrated that the catalytic system used allows the first general C–N bond-forming reaction between 3-bromoquinolin-2(1*H*)-ones and various nucleophiles including amines, amides, sulfonamides, carbamates and ureas. Consequently, various 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones were prepared in good to excellent yields. Investigations on further expanding the scope of the method to other related heterocycles are in progress in our laboratory.

4. Experimental

4.1. Materials

All reactions were conducted under an argon atmosphere. Solvents: cyclohexane, ethyl acetate (EtOAc), methylene chloride (CH_2Cl_2) and methanol (MeOH) for extraction and chromatography were of technical grade. Diethylether (Et_2O) and tetrahydrofuran (THF) were distilled under argon from sodium–benzophenone ketyl, and piperidine, *n*-butylamine, aniline and morpholine from potassium hydroxide.

4.2. Instrumentation

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR, elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a 300 MHz spectrometer. ^{1}H chemical shifts are reported in parts per million from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet), td (triplet of doublet), q (quadruplet), quint (quintuplet). ^{13}C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were acquired on a FTIR and are reported in wave numbers (cm^{-1}). Elemental analyzes were performed with a Perkin–Elmer 240 analyzer. R_f values refer to TLC on 0.25 mm silica gel plates (60-F_{254}). Flash chromatography was performed on silica gel 60 (0.040–0.063 mm). Melting points (mp) were determined on a capillary melting point apparatus and were uncorrected. Amides, sulfonamides, amines, carbamates and ureas are commercially available compounds except *p*-tosylbenzamide that was synthesized as described. 3-Bromoquinolin-2-(1*H*)-one **1a** was synthesized as described.

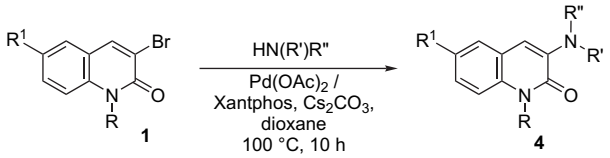
4.3. Synthetic details for 3-bromoquinolin-2(1*H*)-one compounds 1b–d

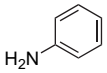
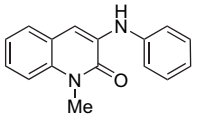
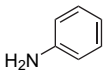
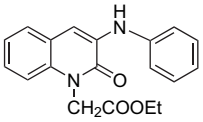
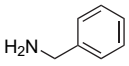
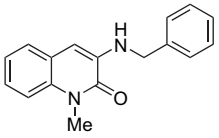
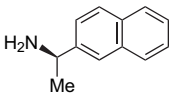
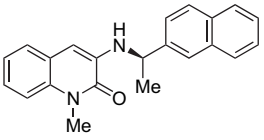
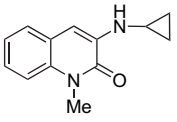
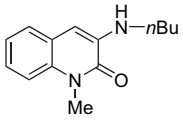
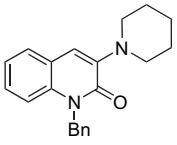
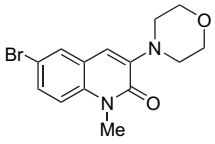
4.3.1. Compound 1b. To a solution of 3-bromo-1-quinolin-2-one (0.5 g, 2.23 mmol) in DMF (2 mL) were added NaH (275 mg of a 65% oil dispersion, 7.44 mmol) and benzyl bromide (533 μL, 4.46 mmol). The reaction mixture was stirred for 3 h at room temperature before being diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/*c*-hexane: 6/4) yielded 644 mg of the desired product **1b**.

Yield: 92%; mp: 150–151 °C; TLC: R_f 0.5 (CH_2Cl_2/*c*-hexane: 9/1); IR (neat): 1646, 1591, 1557, 1494, 1436, 1363, 1289, 1214, 1149, 1069, 1028, 958, 932, 911, 799, 761, 726, 692, 622, 579 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (s, 1H), 7.53 (dd, 1H, J_1=7.8, J_2=1.5 Hz), 7.47 (td, 1H, J_1=8.7, J_2=1.5 Hz), 7.4–7.1 (m, 7H), 5.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7 (CO), 141.1, 138.8, 135.8, 130.9, 128.9 (2CH), 128.2, 127.5, 126.8 (2CH), 122.8, 120.8, 117.4, 115.2, 47.6 (CH_2); *m*/*z* MS (ES^+) 336.0 (M+Na^+, ^{79}Br), 338.0 (M+Na^+, ^{81}Br); Anal. Calcd for $C_{16}H_{12}BrNO$ (313.01): C 61.17, H 3.85, N 4.46; found: C 61.01, H 3.73, N 4.34.

4.3.2. Compound 1c. A 100 mL round bottom flask was sequentially charged with NaH (65% oil dispersion, 447 mg,

Table 3. Pd-catalyzed amination of 3-bromoquinolin-2(1*H*)-ones **1**: synthesis of functionalized 3-(*N*-substituted)-aminoquinolin-2(1*H*)-ones **4**[a]



Entry	ArBr	Amine	Product **4**		Yields[b] (%)
1	**1a**			**4a**	93
2	**1c**			**4b**	89
3	**1a**			**4c**	88
4	**1a**			**4d**	74
5	**1a**			**4e**	60
6	**1a**	H_2NBu		**4f**	83
7	**1b**			**4g**	76
8	**1d**			**4h**	48[c]

[a] Reactions of **1** (1.0 mmol) with amine (1.5 mmol) were performed in a sealed Schlenk tube at 100 °C for 10 h in dioxane (2 mL) by using $Pd(OAc)_2$ (5 mol %), Xantphos (5 mol %) and Cs_2CO_3 (2 mmol).
[b] Isolated yield.
[c] A 15% yield of the corresponding bis-coupling compound was obtained.

12.1 mmol) and dry DMF (5 mL). The resulting suspension was cooled to 0 °C with an ice/water bath and a solution of 3-bromo-1-quinolin-2-one (1.0 g, 4.46 mmol) in dry DMF (25 mL) was slowly added over 10 min. The reaction mixture was allowed to stir for 30 min at 0 °C. Next, a solution of ethyl bromoacetate (1.49 g, 8.92 mmol) in dry DMF (5 mL) was added over 5 min. After 4 h of stirring at room temperature, the reaction mixture was poured into a solution of brine (150 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were then washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (CH_2Cl_2) yielded 3.12 mmol of the desired product **1c**.

Yield: 70%; mp: 151–152 °C; TLC: R_f 0.5 (CH_2Cl_2); IR (neat): 2964, 1736, 1645, 1593, 1558, 1497, 1448, 1417, 1373, 1348, 1298, 1210, 1192, 1084, 1053, 1023, 939, 927, 906, 861, 802, 767, 753, 732, 632, 574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.52–7.42 (m, 2H), 7.18 (td, 1H, J_1=8.0, J_2=0.7 Hz), 7.00 (d, 1H, J=9.4 Hz), 5.05 (s, 2H), 4.15 (m, 2H), 1.19 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.6 (CO), 158.2 (CO), 141.4, 138.7, 131.1, 128.4, 123.0, 120.6, 116.9, 113.8, 61.9, 45.2, 14.1 (CH_2CH_3); *m/z* MS (ES^+) 332.0 ($M+Na^+$, ^{79}Br), 334.0 ($M+Na^+$, ^{81}Br); Anal. Calcd for $C_{13}H_{12}BrNO_3$ (309.00): C 50.34, H 3.90, N 4.52; found: C 49.90, H 3.70, N 4.37.

4.3.3. Compound 1d. To a solution of **1a** (0.5 g, 2.1 mmol) in acetic acid (6 mL) was added a solution of bromine (1.27 g, 8.2 mmol, 4 equiv) in acetic acid (30 mL) and the resulting solution was stirred at room temperature for 20 h. A white precipitate was filtered off, and the filtrate was concentrated. Purification of the residue by silica gel column chromatography (Et_2O) yielded 480 mg of compound **1d** as a white solid.

Yield: 72%; mp: 186–188 °C; TLC: R_f 0.42 (Et_2O); IR (neat): 3050, 1641, 1587, 1553, 1514, 1486, 1454, 1412, 1356, 1315, 1290, 1260, 1213, 1159, 1124, 1091, 1059, 1002, 946, 910, 896, 810, 796, 755, 742, 647, 619, 592, 561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.78 (d, 1H, J=2.4 Hz), 7.65 (dd, 1H, J_1=9.0, J_2=2.4 Hz), 7.4 (d, 1H, J=9.0 Hz), 3.63 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.0 (CO), 139.6, 138.1, 133.3, 129.9, 121.5, 117.8, 117.3, 114.3, 31.0; *m/z* MS (ES^+) 338.0 ($M+Na^+$, ^{79}Br), 340.0 ($M+Na^+$, ^{81}Br); Anal. Calcd for $C_{10}H_7Br_2NO$ (314.88): C 37.89, H 2.23, N 4.42; found: C 37.03, H 2.09, N 4.10.

4.4. General procedure for Pd-catalyzed couplings of 3-bromoquinolin-2(1*H*)-ones with various nucleophiles: amines, amides, sulfonamides, carbamates and ureas

A flame-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ (7.5 mg, 0.05 mmol, 5 mol %), Xantphos (29 mg, 0.05 mmol, 5 mol %), the solid reactant(s) (1.0 mmol of the bromoquinolin-2(1*H*)-one, 1.5 mmol of the amide/amines/carbamate/sulfonamide/urea) and Cs_2CO_3 (651 mg, 2 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and 1,4-dioxane (2 mL) were added through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 100 °C for 10 h. The resulting suspension was cooled to room temperature and filtred through Celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

4.4.1. Compound 3a. Yield: 95%; mp: 181–183 °C; TLC: R_f 0.74 (CH_2Cl_2/EtOAc: 8/2); IR (neat): 3375, 1669, 1638, 1619, 1598, 1576, 1527, 1494, 1465, 1421, 1377, 1327, 1296, 1255, 1217, 1177, 1115, 1023, 965, 947, 907, 858, 838, 800, 777, 752, 739, 716, 692, 621, 598, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.78 (s, 1H), 7.85 (d, 2H, J=9.0 Hz), 7.55 (dd, 1H, J_1=7.8, J_2=1.5 Hz), 7.40 (td, 1H, J_1=8.7, J_2=1.5 Hz), 7.27 (d, 1H, J=8.4 Hz), 7.19 (td, 1H, J_1=8.1, J_2=1.2 Hz), 6.69 (d, 2H, J=9.0 Hz), 3.79 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3 (CO), 162.7, 158.2 (CO), 135.5, 129.1 (2CH), 128.9, 128.8, 127.9, 126.5, 123.1, 121.2, 120.1, 114.5 (2CH), 114.0, 55.5 (OCH_3), 30.3 (CH_3); *m/z* MS (ES^+) 331.0 ($M+Na^+$); Anal. Calcd for $C_{18}H_{16}N_2O_3$ (308.12): C 70.12, H 5.23, N 9.09; found: C 69.98, H 5.02, N 8.97.

4.4.2. Compound 3b. Yield: 87%; mp: 153–155 °C; TLC: R_f 0.39 (CH_2Cl_2); IR (neat): 3390, 1736, 1676, 1636, 1600, 1530, 1507, 1489, 1377, 1247, 1206, 1033, 843, 758, 759, 637, 624, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.86 (s, 1H), 7.85 (d, 2H, J=8.8 Hz), 7.59 (dd, 1H, J_1=7.7, J_2=1.1 Hz), 7.39 (td, 1H, J_1=8.5, J_2=1.4 Hz), 7.23 (d, 1H, J=7.3 Hz), 7.06 (d, 1H, J=8.4 Hz), 6.91 (d, 2H, J=8.8 Hz), 5.03 (s, 2H), 4.18 (q, 2H, J=7.1 Hz), 3.80 (s, 3H), 1.2 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (CO), 165.4 (CO), 162.8, 158.2, 134.9, 129.1 (2CH), 128.9, 128.8, 127.6, 126.3, 123.5, 121.3, 121.1, 114.0 (2CH), 113.3, 61.9, 55.5, 44.7, 14.4; *m/z* MS (ES^+) 404.0 ($M+H^++Na^+$); Anal. Calcd for $C_{21}H_{20}N_2O_5$ (380.14): C 66.31, H 5.30, N 7.36; found: C 65.89, 5.19, N 7.28.

4.4.3. Compound 3c. Yield: 92%; mp: 177–179 °C; TLC: R_f 0.28 (CH_2Cl_2/EtOAc: 9/1); IR (neat): 3300, 1679, 1676, 1628, 1613, 1590, 1521, 1494, 1457, 1419, 1374, 1285, 1229, 1178, 1115, 1039, 1013, 943, 903, 847, 774, 751, 713, 641, 602, 581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.50 (s, 1H), 7.51 (dd, 1H, J_1=7.7, J_2=1.3 Hz), 7.40 (td, 1H, J_1=8.6, J_2=1.5 Hz), 7.25 (d, 1H, J=8.3 Hz), 7.18 (td, 1H, J_1=8.1, J_2=1.0 Hz), 3.70 (s, 3H, CH_3),), 2.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (CO), 157.8 (CO), 135.5, 128.6, 128.5, 127.6, 123.1, 121.0, 120.3, 113.9, 30.3 (CH_3), 24.8 (CH_3); *m/z* MS (ES^+) 239 ($M+Na^+$); Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.08): C 66.65, H 5.59, N 12.96; found: C 66.31, H 5.21, N 12.14.

4.4.4. Compound 3d. Yield: 69%; mp: 100–102 °C; TLC: R_f 0.21 (CH_2Cl_2/EtOAc: 7/3); IR (neat): 3524, 3423, 1674, 1624, 1592, 1461, 1411, 1303, 1267, 1225, 1200, 1147, 1128, 905, 858, 838, 793, 762, 739, 716, 692, 621, 598, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.52–7.45 (m, 2H), 7.27 (d, 1H, J_1=8.4 Hz), 7.18 (dt, 1H, J_1=8.4, J_2=1.0 Hz), 3.91 (t, 2H, J=7.2 Hz), 3.67 (s, 3H, CH_3), 2.50 (t, 2H, J=8.2 Hz), 2.15–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7 (CO), 159.1 (CO), 138.7, 135.2, 130.4, 129.0, 128.5, 122.5, 119.8, 114, 48.9, 31.3, 29.9, 18.9; *m/z* MS (ES^+) 243.0 ($M+H^+$), 265.0 ($M+Na^+$), 507.0 ($2M+Na^+$); Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.10): C 69.41, H 5.82, N 11.56; found: C 68.87, H 5.17, N 11.19.

4.4.5. Compound 3e. Yield: 60%; mp: 188–189 °C; TLC: R_f 0.4 (CH_2Cl_2/EtOAc: 7/3); IR (neat): 3386, 3348, 1679, 1633, 1614, 1592, 1527, 1499, 1463, 1423, 1375, 1321, 1275, 1231, 1209, 1181, 1122, 1041, 1018, 945, 902, 853, 777, 743, 720, 703, 638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.5 (s, 1H), 8.6 (s, 1H), 7.49–7.36 (m, 2H), 7.25 (d, 1H, J=8.3 Hz), 7.18 (td, 1H, J_1=7.6, J_2=0.9 Hz), 4.37 (m,

1H), 3.66 (s, 3H, CH_3), 3.57 (d, 1H, J=4.2 Hz), 1.41 (d, 3H, J=6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (CO), 157.9 (CO), 135.7, 128.8, 128.7, 127.0, 123.1, 120.9, 120.8, 113.9, 69.0, 30.2 (CH_3), 21.0 (CH_3); *m/z* MS (ES^+) 269 ($M+Na^+$); Anal. Calcd for $C_{13}H_{14}N_2O_3$ (246.10): C 63.40, H 5.73, N 11.38, found: C 62.89, H 5.32, N 11.08.

4.4.6. Compound 3f. Yield: 46%; mp: 144–146 °C; TLC: R_f 0.71 (CH_2Cl_2/EtOAc: 9/1); IR (neat): 3371, 1669, 1636, 1619, 1596, 1489, 1365, 1202, 1178, 1151, 1091, 1013, 905, 866, 766, 747, 680, 570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.77 (s, 1H), 7.81 (d, 2H, J= 8.7 Hz), 7.64 (d, 2H, J=8.3 Hz), 7.57 (dd, 1H, J_1=8.7, J_2=1.0 Hz), 7.44 (td, 1H, J_1=8.4, J_2=1.3 Hz), 7.33–7.18 (m, 4H), 7.04 (d, 2H, J=8.7 Hz), 3.57 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6 (CO), 158.1, 152.3, 145.8, 135.7, 132.9, 131.9, 129.9 (2C), 128.9 (3C), 128.8, 128.5 (2C), 127.5, 123.3, 122.8 (2C), 120.9, 120.8, 114.0, 30.4 (OCH_3), 21.8 (CH_3); *m/z* MS (ES^+) 449.0 ($M+H^+$), 471 ($M+Na^+$); Anal. Calcd for $C_{24}H_{20}N_2O_5S$ (448.10): C 64.27, H 4.49, N 6.25; found: C 63.98, H 4.01, N 5.87.

4.4.7. Compound 3g. Yield: 44%; mp: 191–193 °C; TLC: R_f 0.6 (CH_2Cl_2); IR (neat): 3343, 1631, 1619, 1526, 1505, 1461, 1425, 1359, 1334, 1250, 1218, 1173, 1029, 874, 838, 800, 596, 564 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.77 (s, 1H), 7.91 (d, 2H, J=8.8 Hz), 7. 47 (d, 1H, J=2.2 Hz), 7.55 (dd, 1H, J_1=8.9, J_2=2.2 Hz), 7.22 (d, 1H, J=8.9 Hz), 6.98 (d, 2H, J=8.8 Hz), 3.88 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4 (CO), 162.9, 157.9 (CO), 134.4, 131.1, 130.6, 129.2 (2CH), 128.8, 126.2, 122.9, 118.6, 116.1, 115.6, 114.1 (2CH), 55.5 (OCH_3), 30.5 (CH_3); *m/z* MS (ES^+) 409.0 ($M+Na^+$, ^{79}Br), 411.0 ($M+Na^+$, ^{81}Br); Anal. Calcd for $C_{18}H_{15}BrN_2O_3$ (386.02): C 55.83, H 3.90, N 7.23; found: C 55.28, H 3.66, N 7.08.

4.4.8. Compound bis-3g. Yield: 27%; mp: 256–258 °C; TLC: R_f 0.15 (Et_2O); IR (neat): 3387, 3274, 2924, 1734, 1672, 1638, 1603, 1578, 1524, 1490, 1364, 1251, 1180, 1052, 858, 841, 804, 756, 732, 677, 610, 596, 559 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.24 (s, 1H), 9.41 (s, 1H), 8.64 (s, 1H), 8.14 (d, 1H, J=2.2 Hz), 7.99 (d, 2H, J= 8.7 Hz), 7.93–7.89 (m, 3H), 7.56 (d, 1H, J=8.2 Hz), 7.11–7.06 (m, 4H), 3.85 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8 (CO), 164.4 (CO), 162.3, 161.9, 156.9 (CO), 134.6, 131.7, 129.5 (2CH), 129.1 (2CH), 127.8, 126.7, 125.8, 121.8, 120.1, 119.7, 118.4, 114.9, 114.1 (2CH), 113.6 (2CH), 55.5 (OCH_3), 55.4 (OCH_3), 30.1 (CH_3); *m/z* MS (ES^+) 480.0 ($M+Na^+$); Anal. Calcd for $C_{26}H_{23}N_3O_5$ (457.16): C 68.26, H 5.07, N 9.19; found: C 67.79, H 4.88, N 8.88.

4.4.9. Compound 3h. Yield: 57%; mp: 136–138 °C; TLC: R_f 0.71 (CH_2Cl_2); IR (neat): 3266, 1717, 1633, 1622, 1601, 1532, 1490, 1455, 1388, 1364, 1342, 1316, 1256, 1217, 1197, 1129, 1086, 1052, 1027, 993, 974, 940, 926, 906, 887, 847, 772, 744, 730, 637, 563 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.16 (s, 1H), 7.61 (dd, 1H, J_1=7.7, J_2=0.9 Hz), 7.48–7.18 (m, 13H), 5.63 (s, 2H, CH_2Bn), 5.28 (s, 2H, CH_2Bn); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9 (CO), 153.4 (CO), 135.9, 135.8, 134.8, 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2, 127.7, 127.5 (2C), 126.5, 123.1, 121.3, 118.9, 114.7, 67.2 (*C*H_2Bn), 46.8 (*C*H_2Bn); *m/z* MS (ES^+) 407.0 ($M+Na^+$); Anal. Calcd for $C_{24}H_{20}N_2O_3$ (384.14): C 74.98, H 5.24, N 7.29; found: C 74.09, H 5.07, N 7.11.

4.4.10. Compound 3i. Yield: 85%; mp: 167–169 °C; TLC: R_f 0.56 (CH_2Cl_2/EtOAc: 7/3); IR (neat): 3167, 1640, 1618, 1595, 1541, 1507, 1465, 1435, 1418, 1366, 1338, 1308, 1275, 1231, 1189, 1157, 1112, 1090, 1036, 909, 947, 888, 866, 816, 772, 749, 735, 724, 663, 638, 556 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.74–7.70 (m, 3H), 7.47 (d, 1H, J_1=7.8, J_2=1.2 Hz), 7.39 (td, 1H, J_1= 8.4, J_2=1.2 Hz), 7.38–7.13 (m, 3H), 4.94 (s, 1H), 3.62 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (CO), 144.2, 136.0, 135.9, 129.8 (2CH), 128.9, 128.3, 127.2 (2C), 126.9, 123.2, 120.3, 118.9, 114.0, 30.4 (CH_3), 21.5 (CH_3); *m/z* MS (ES^+) 329.0 ($M+H^+$), 351 ($M+Na^+$); Anal. Calcd for $C_{17}H_{16}N_2O_3S$ (328.08): C 62.18, H 4.91, N 8.53; found: C 61.83, H 4.59, N 8.27.

4.4.11. Compound 3j. Yield: 74%; mp: 216–218 °C; TLC: R_f 0.64 (CH_2Cl_2); IR (neat): 3174, 2923, 2854, 1630, 1616, 1597, 1502, 1448, 1432, 1371, 1341, 1319, 1279, 1261, 1216, 1185, 1163, 1119, 1090, 1015, 941, 917, 865, 804, 773, 752, 729, 719, 690, 648, 627 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.88 (s, 1H), 7.95–7.90 (m, 3H), 7.78 (d, 1H, J=7.7 Hz), 7.66 (t, 1H, J=7.4 Hz), 7.59–7.52 (m, 2H), 7.41 (t, 1H, J=7.3 Hz), 7.32 (d, 1H, J=8.5 Hz), 7.28–7.19 (m, 4H), 6.97 (d, 2H, J=6.8 Hz), 5.47 (s, 2H, CH_2Bn); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.5 (CO), 139.4, 136.2, 135.6, 133.1, 129.4, 129.1 (2C), 128.6 (3C), 127.1, 126.9 (2C), 126.7 (2C), 126.4, 124.2, 122.8, 119.7, 114.9, 45.4 (*C*H_2Bn); *m/z* MS (ES^+) 413.0 ($M+Na^+$); Anal. Calcd for $C_{22}H_{18}N_2O_3S$ (390.10): C 67.67, H 4.65, N 7.17; found: C 67.39, H 4.16, N 6.92.

4.4.12. Compound 3k. Yield: 66%; mp: 198–199 °C; TLC: R_f 0.24 (*c*-hexane/EtOAc: 6/4); IR (neat): 3156, 2926, 2854, 1729, 1642, 1621, 1598, 1507, 1447, 1417, 1419, 1361, 1335, 1317, 1280, 1219, 1184, 1146, 1110, 1073, 1040, 981, 968, 921, 894, 869, 858, 780, 755, 712, 658, 634, 556 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.72 (s, 1H), 7.53 (dd, 1H, J_1=7.8, J_2=1.1 Hz), 7.47 (td, 1H, J_1=8.6, J_2=1.4 Hz), 7.31 (d, 1H, J=8.4 Hz), 7.24 (td, 1H, J_1=7.8, J_2=0.6 Hz), 3.75 (s, 3H, CH_3), 2.99 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8 (CO), 136.1, 129.2, 128.5, 127.2, 123.4, 120.3, 119.5, 114.2, 39.4, 30.5. *m/z* MS (ES^+) 275.0 ($M+Na^+$); Anal. Calcd for $C_{11}H_{12}N_2O_3S$ (252.05): C 52.37, H 4.79, N 11.10; found: C 51.82, H 4.33, N 10.86.

4.4.13. Compound 3l. Yield: 68%; mp: 180–182 °C; TLC: R_f 0.50 (CH_2Cl_2); IR (neat): 3179, 1615, 1599, 1583, 1499, 1441, 1367, 1353, 1315, 1278, 1223, 1148, 1119, 1041, 1015, 974, 943, 899, 870, 776, 749, 724, 692, 661, 628 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.71 (br s, 1H), 7.54 (dd, 1H, J_1=7.8, J_2=1.1 Hz), 7.33 (td, 1H, J_1=8.4, J_2=1.3 Hz), 7.27–7.11 (m, 7H), 5.55 (s, 2H), 3.04 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (CO), 135.5 (2C), 129.2, 128.9 (2C), 128.6, 127.6, 127.2, 126.5 (2C), 123.4, 120.5, 119.7, 115.0, 47.1, 39.5; *m/z* MS (ES^+) 351.0 ($M+Na^+$); Anal. Calcd for

$C_{17}H_{16}N_2O_3S$ (328.08): C 62.18, H 4.91, N 8.53; found: C 61.83, H 4.67, N 8.10.

4.4.14. Compound 3m. Yield: 61%; mp: 164–165 °C; TLC: R_f 0.4 (Et_2O/*c*-hexane: 1/1); IR (neat): 3465, 3225, 1702, 1633, 1616, 1525, 1492, 1386, 1237, 1207, 902, 755, 747, 725, 695, 570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 2H, NH), 8.67(s, 2H), 7.72 (d, 2H, J=2.2 Hz), 7.40–7.22 (m, 16H), 5.65 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (2CO), 152.9 (CO), 136.5 (2C), 134.1 (2C), 128.9 (2C), 128.7 (4CH), 127.9 (2C), 127.8 (2C), 121.1 (2C), 126.5 (4CH), 122.8 (2C), 120.9 (2C), 118.2 (2C), 114.8 (2C), 45.6 (2×*C*H_2Bn); *m/z* MS (ES^+) 549.0 ($M+Na^+$); Anal. Calcd for $C_{33}H_{26}N_4O_3$ (526.20): C 75.27, H 4.98, N 10.64; found: C 74.89, H 4.69, N 10.44.

4.4.15. Compound 4a. Yield: 93%; mp: 95–97 °C; TLC: R_f 0.79 (CH_2Cl_2); IR (neat): 3304, 2925, 1599, 1581, 1521, 1490, 1462, 1444, 1415, 1369, 1110, 931, 902, 774, 734, 705, 623, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.09 (m, 10H), 6.97 (t, 1H, J=7.3 Hz), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 140.7, 133.9, 132.7, 129.5 (2CH), 126.4, 125.9, 122.8, 122.6, 122.1, 120.1 (2CH), 113.8, 106.9, 30.4; *m/z* MS (ES^+) 273.0 ($M+Na^+$), 289.0 ($M+K^+$); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.11): C 76.78, H 5.64, N 11.19; found: C 76.49, H 5.47, N 11.09.

4.4.16. Compound 4b. Yield: 89%; mp: 153–154 °C; TLC: R_f 0.45 (CH_2Cl_2); IR (neat): 3291, 1733, 1617, 1587, 1531, 1504, 1464, 1447, 1424, 1377, 1348, 1211, 1123, 1016, 865, 803, 740, 690, 594, 570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–6.96 (m, 11H), 5.10 (s, 2H), 4.18 (q, 2H, J=7.1 Hz), 1.20 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 158.7, 140.5, 133.2, 132.5, 129.5 (2CH), 126.7, 126.1, 123.2, 122.8, 122.2, 120.3 (2CH), 113.2, 107.7, 61.8, 44.8, 14.2; *m/z* MS (ES^+) 345.0 ($M+Na^+$); Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.13): C 70.79, H 5.63, N 8.69; found: C 70.47, H 5.49, N 8.47.

4.4.17. Compound 4c. Yield: 88%; mp: 133–135 °C; TLC: R_f 0.68 (CH_2Cl_2); IR (neat): 3355, 2928, 1615, 1598, 1509, 1488, 1453, 1418, 1377, 1355, 1324, 1295, 1025, 986, 822, 777, 745, 735, 720, 691, 620, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.17 (m, 8H), 7.05 (m, 1H), 6.34 (s, 1H), 5.60 (t, 1H, J=5.2 Hz), 4.34 (d, 2H, J=5.8 Hz), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 138.2, 136.7, 133.2, 128.7 (2CH), 127.3, 127.2 (2CH), 125.8, 124.8, 122.8, 122.6, 113.6, 104.1, 47.3, 30.1; *m/z* MS (ES^+) 287.0 ($M+Na^+$), 303.0 ($M+K^+$); Anal. Calcd for $C_{17}H_{16}N_2O$ (264.12): C 77.25, H 6.10, N 10.60; found: C 77.08, H 6.01, N 10.23.

4.4.18. Compound 4d. Yield: 74%; mp: 163–164 °C; TLC: R_f 0.6 (CH_2Cl_2); IR (neat): 3408, 2973, 1615, 1594, 1509, 1476, 1413, 1365, 1326, 1242, 1204, 1117, 1090, 1040, 852, 827, 804, 779, 754, 742, 647, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J=8.4 Hz), 7.83 (dd, 1H, J_1=7.9, J_2=1.4 Hz), 7.66 (d, 1H, J=8.2 Hz), 7.53–7.41 (m, 3H), 7.30 (t, 1H, J=7.7 Hz), 7.16–7.08 (m, 2H), 6.99–6.89 (m, 2H), 5.96 (s, 1H), 5.70 (d, 1H, J=5.3 Hz), 5.21 (m, 1H), 3.72 (s, 3H), 1.65 (d, 3H, J=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (CO), 138.7, 135.5, 134.1, 133.1, 130.7, 129.2, 127.7, 126.2 125.9, 125.8, 125.5, 124.7, 122.7, 122.5 (2C), 122.2, 113.7, 105.0, 49.3, 30.1, 23.5; *m/z* MS (ES^+) 351.0 ($M+Na^+$); Anal. Calcd for $C_{22}H_{20}N_2O$ (328.15): C 80.46, H 6.14, N 8.53; found: C 89.88, H 6.09, N 8.33.

4.4.19. Compound 4e. Yield: 60%; mp: 98–99 °C; TLC: R_f 0.48 (CH_2Cl_2); IR (neat): 3334, 2941, 1633, 1597, 1510, 1485, 1460, 1414, 1370, 1336, 1252, 1193, 1040, 1022, 979, 863, 824, 779, 741, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, 1H, J=7.5 Hz), 7.24–7.09 (m, 3H), 6.77 (s, 1H), 5.36 (s, 1H), 3.71 (s, 3H), 2.40 (m, 1H), 0.75–0.72 (m, 2H), 0.54–0.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5 (CO), 137.6, 133.4, 128.8, 125.8, 122.9, 122.6, 113.8, 105.1, 30.0, 24.3, 6.9 (2C); *m/z* MS (ES^+) 215 ($M+H^+$) 237.0 ($M+Na^+$), 451.0 ($2M+Na^+$); Anal. Calcd for $C_{13}H_{14}N_2O$ (214.11): C 72.87, H 6.59, N 13.07; found: C 72.02, H 6.34, N 12.79.

4.4.20. Compound 4f. Yield: 83%; mp: 89–90 °C; TLC: R_f 0.45 (CH_2Cl_2); IR (neat): 3334, 2955, 2865, 1632, 1607, 1594, 1509, 1489, 1461, 1417, 1388, 1366, 1319, 1263, 1236, 1205, 1142, 1080, 1042, 918, 847, 824, 805, 778, 729, 645, 576 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (dd, 1H, J_1=8.3, J_2=1.1 Hz), 7.20–7.07 (m, 3H), 6.35 (s, 1H), 5.1 (br s, 1H, NH), 3.71 (s, 3H), 3.09 (q, 2H, J=6.8 Hz), 1.64–1.56 (m, 2H), 145–1.33 (m, 2H), 0.90 (t, 3H, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 137.1, 132.9, 125.5, 124.4, 123.1, 122.6, 113.7, 102.9, 42.8, 30.8, 30.1, 20.4, 13.9; *m/z* MS (ES^+) 231.0 ($M+H^+$), 253.0 ($M+Na^+$); Anal. Calcd for $C_{14}H_{18}N_2O$ (230.14): C 73.01, H 7.88, N 12.16; found: C 72.87, H 7.67, N 12.01.

4.4.21. Compound 4g. Yield: 76%; mp: 125–127 °C; TLC: R_f 0.29 (CH_2Cl_2); IR (neat): 2941, 1630, 1593, 1495, 1455, 1382, 1338, 1301, 1279, 1238, 1185, 1120, 1029, 995, 1034, 885, 858, 736, 718, 696, 670, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, 1H, J_1=7.5, J_2=1.2 Hz), 7.22–7.10 (m, 7H), 7.05 (td, 1H, J_1=8.1, J_2=1.6 Hz), 6.93 (s, 1H), 5.50 (s, 2H), 3.13–3.08 (m, 4H), 1.75–1.68 (m, 4H), 158–1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 143.0, 136.6, 135.6, 128.7 (2C), 127.2 (2C), 127.1, 126.7 (2C), 122.3, 121.7, 119.0, 114.5, 51.1 (2C), 46.6, 25.9 (2C), 24.5; *m/z* MS (ES^+) 341.0 ($M+Na^+$), 357.0 ($M+K^+$); Anal. Calcd for $C_{21}H_{22}N_2O$ (318.17): C 79.21, H 6.96, N 8.80; found: C 78.88, H 6.77, N 8.69.

4.4.22. Compound 4h. Yield: 48%; mp: 141–143 °C; TLC: R_f 0.1 (CH_2Cl_2); IR (neat): 2812, 1634, 1612, 1588, 1493, 1447, 1421, 1377, 1305, 1263, 1226, 1204, 1118, 1059, 1011, 910, 895, 803, 778, 759, 686, 665, 570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, 1H, J=2.2 Hz), 7.48 (dd, 1H, J_1=8.9, J_2=2.2 Hz), 7.18 (d, 1H, J=8.9 Hz), 6.82 (s, 1H), 3.94–3.90 (m, 4H), 3.72 (s, 3H), 3.27–3.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 142.4, 135.0, 130.0, 129.2, 122.8, 116.8, 115.4, 115.2, 66.8 (2C), 49.8 (2C), 30.1; *m/z* MS (ES^+) 345.0 ($M+Na^+$, ^{79}Br), 347.0 ($M+Na^+$, ^{81}Br); Anal. Calcd for $C_{14}H_{15}BrN_2O_2$ (322.03): C 52.03, H 4.68, N 8.67; found: C 51.97, H 4.31, N 8.36.

4.4.23. Compound bis-4h. The compound is not sufficiently stable to be fully characterized. Yield: 15%; TLC: R_f 0.13 (CH_2Cl_2); IR (neat): 2922, 2853, 1637, 1618, 1597, 1568, 1436, 1372, 1321, 1260, 1236, 1203, 1113, 1064, 1009,

931, 898, 801, 781, 704, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, 1H, J=9.1 Hz), 7.02 (dd, 1H, J_1=9.1, J_2=2.6 Hz), 6.88 (d, 1H, J=2.6 Hz), 6.82 (s, 1H), 3.85–3.80 (m, 8H), 3.66 (s, 3H), 3.19–3.14 (m, 4H), 3.13–3.06 (m, 4H); m/z MS (ES^+) 352.0 ($M+Na^+$).

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