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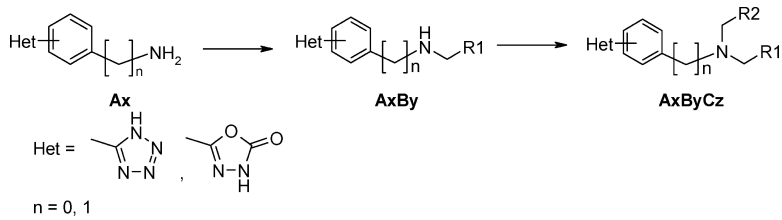

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An Efficient and Expeditious Synthesis of Di- and Trisubstituted Amino-phenyl and -benzyl Derivatives of Tetrazole and [1,3,4]Oxadiazol-2-one

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A practical protocol for the parallel synthesis and purification of amino tetrazole and [1,3,4]oxadiazol-2-one derivatives as carboxylic acid bioisosteres is described. Phenyl- and benzyl-amines, substituted with tetrazole or [1,3,4]oxadiazol-2-one, were transformed into functionally diverse and novel compounds, with pK_a values ranging from 4.9 to 8.4, by two sequential reductive alkylation reactions. These series of di- and trisubstituted amino-phenyl and -benzyl derivatives were produced in solution using solid-supported reagents and were purified by solid-phase extraction (SPE) techniques.

Introduction

Bioisostere replacement is a powerful strategy that medicinal chemists use when their lead molecules contain structural features that are important for activity but that, at the same time, adversely influence absorption, metabolism, excretion, or toxicity.[1] While tetrazoles are commonly used as carboxylic acid bioisosteres in drug discovery,[2] oxadiazolones have been reported more recently as tetrazole and carboxylic acid replacements.[3,4]

Historically, bioisosteric replacements are attempted later in the lead-optimization phase of the drug-discovery process. In our continued effort to design lead-like hits, we decided to include the carboxylic acid bioisosteres, tetrazoles and oxadiazolones, into our hit-finding libraries. This effort requires a careful selection of building blocks, combined with the development of a process to get pure final compounds to be screened. Tetrazole libraries have been reported in solution and on the solid phase.[5] In these reports, the tetrazole ring was introduced in the last step or was used in the N-protected form, which requires an additional deprotection step. To our knowledge, oxadiazolones as bioisosteres were used in specific lead optimization programs,[4] but not in library production. Our approach involved the elaboration of tetrazole and [1,3,4]oxadiazol-2-one phenyl- and benzyl-amines (**Ax**) with two successive reductive alkylation reactions to provide two libraries, **AxBy** and **AxByCz**, respectively (Scheme 1). The two libraries were designed to incorporate a wide range of pK_a values and introduce groups R1 and R2, which possess drug-like properties.[6]

To study the scope of this approach, we selected ten main building blocks (**Ax**), six phenylamines and four benzylamines, which were substituted with either a tetrazole or an [1,3,4]oxadiazol-2-one (Figure 1). These compounds are seldom used as building blocks, although **A1**−**A3** are commercially available, and the synthesis of **A4**,[7a,b] **A5**,[7c,d] **A6**,[7c,d] and **A10**[7e,f] has been reported. Reactions were carried out in solution, using solid-supported reagents. Solid-phase extraction (SPE) was selected for the parallel purification of the final products, which can take advantage of their acidic and basic properties. The demonstration of this approach in parallel synthesis is documented here through the synthesis of a set of 73 compounds.

Building-Block Access

The three (1*H*-tetrazol-5-yl) phenylamine isomers, **A1**−**A3,** are commercially available. The remaining building blocks had to be synthesized. The synthesis of three 1,3,4-oxadiazol-2-one phenylamine derivatives, **A4**−**A6,** was initiated with the addition of 1,1′-carbodiimidazole to the

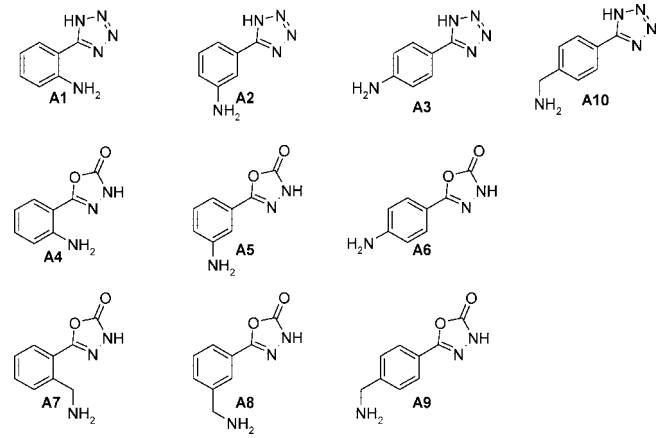

Figure 1. Selected phenyl- and benzyl-amines substituted with tetrazole or [1,3,4]oxadiazol-2-one as carboxylic acid bioisosteres.

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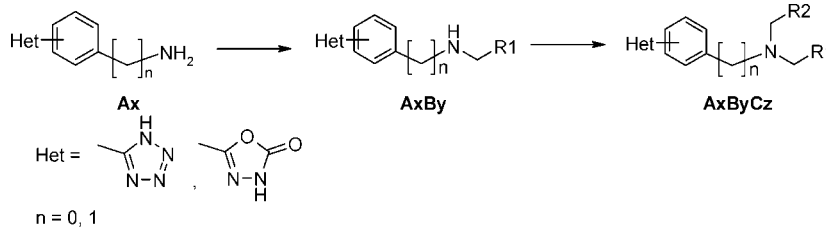
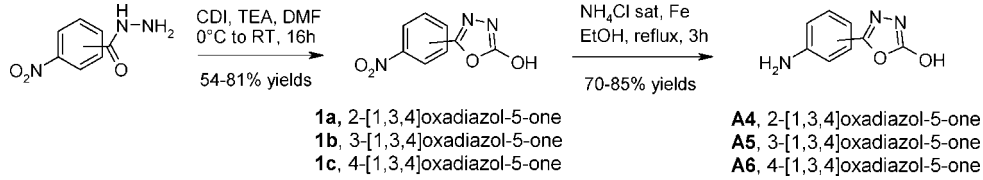
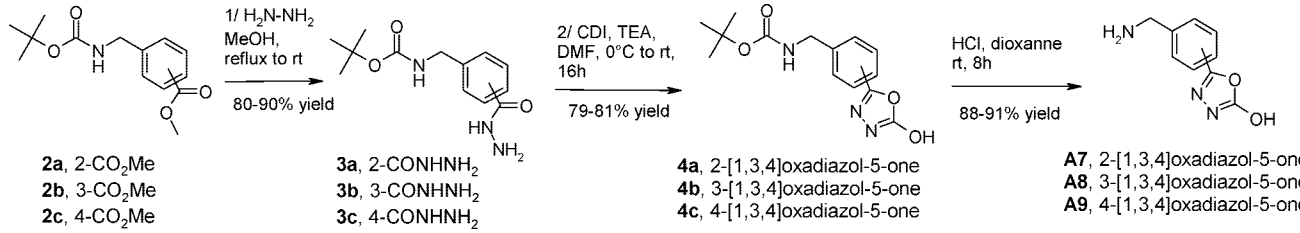
Scheme 1. General Scheme of the Library



Scheme 2. Synthesis of Building Blocks **A4**−**A6**



Scheme 3. Synthesis of Building Blocks **A7**−**A9**



appropriate commercially available nitro-benzoic acid hydrazide to afford intermediates **1a**−**c**. Reduction of the nitro group with iron and ammonium chloride, provided derivatives **A4**−**A6** in gram scale and in good yields (Scheme 2).

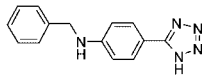
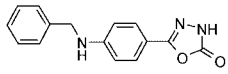
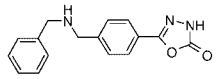
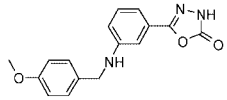
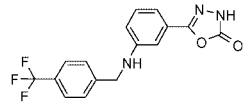
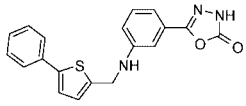
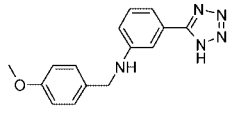
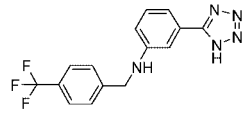
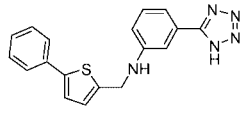
The corresponding [1,3,4]oxadiazol-2-one benzylamine derivatives, **A7**−**A9,**[8] were obtained through a similar synthetic pathway, starting with the *N*-boc protected aminomethyl benzoate **2a-c**[9] (Scheme 2). Hydrazine addition in MeOH afforded intermediates **3a**−**c** in good yields (80−90%). Cyclization with 1,1′-carbodiimidazole afforded the *N*-boc-protected benzylamine intermediates **4a**−**c**. The final *N*-boc deprotection afforded the [1,3,4]oxadiazol-2-one benzylamine building blocks, **A7**−**A9**, in 88−91% yields (Scheme 3). To our knowledge, this is the first synthesis of these three building blocks. The tetrazole benzylamine building block, **A10**, was synthesized according to reported procedures.[7e,f]

Synthesis and Purification Optimization

The initial diversification step of the ten building blocks **A1**−**A10** consisted of a reductive alkylation reaction. Parallel reductive alkylation in solution phase has been facilitated by the development of polymer-supported reducing agents.[10] Optimized conditions for the reductive alkylation of building blocks **A1**−**A6** resulted in the use of 1.1 equiv of aldehyde and 2.5 equiv of polymer-supported cyanoborohydride in a mixture of THF and DMF containing AcOH (25% vol) at room temperature for 24 h. With building blocks **A7**−**A9**, the reaction was performed at 0 °C, to minimize double-reductive alkylation. With tetrazole benzylamine, **A10**, double reductive alkylation could not be avoided under these conditions. For this reason, this building block was not used in the library production. The excess of polymer-supported reducing agent was easily removed by filtration. Solid-phase extraction (SPE) was explored to purify the products, taking advantage of their acidic and basic properties. Although such workup techniques are widely used in parallel synthesis,[11] their use has not been reported with acidic heterocycles such as tetrazoles and 1,3,4-oxadiazol-2-ones. To select the most suitable column for solid-phase ion-exchange extraction, the pK_a values of a representative number of compounds were calculated (Table 1).[12] Benzyl-phenyl secondary amines **A3B1** and **A6B1** have a pK_a of 2.8−2.9, whereas a pK_a of 9.1 was calculated for bis-benzyl amine **A9B1.** The pK_a of the acid heterocycles was also determined, and an average value of 5.0 was obtained for the tetrazolyl moiety and 7.3 for the [1,3,4]oxadiazol-2-yl moiety. Compounds with a substituted benzyl amine, **A5B2**, **A5B3**, **A2B2**, and **A2B3**, gave similar secondary amine and acid heterocycle pK_a values compared to the ones calculated for the compounds with unsubstituted benzyl amines, **A3B1** and **A6B1**.

Because compounds **AxBy** contain an acidic bioisostere and an amino group, either strong anion or cation solid-phase exchange sorbents can be used to purify them. While anion-exchange sorbent Isolute NH_2 SPE, an aminopropyl phase, was able to retain the tetrazole derivatives, it was not basic enough to retain the [1,3,4]oxadiazol-2-one derivatives. On the other hand, the strong anion-exchange sorbent Isolute SAX SPE, a quaternary amine phase with a hydroxyl counterion, was able to retain both series of compounds. The hydroxyl counterion on this sorbent could be easily obtained from the corresponding commercially available chlorine counterion by treatment with either a sodium or potassium hydroxide solution. A typical purification procedure with the strong anion-exchange sorbent Isolute SAX SPE consisted of the evaporation of the reaction mixture (to avoid saturating

Table 1. Purification by Isolute SAX SPE and Isolute SCX SPE

Compound	PKa sec amines	PKa acid heterocycle	HPLC Purity % (Yield %)		
			Before SPE	After SPE SAX	After SPE SCX
 *A3B1*	2.9	5.1	80	82 (78)	86 (76)
 *A6B1*	2.8	8.4	96	100 (84)	98 (85)
 *A9B1*	9.1	8.2	91	95 (89)	98 (91)
 *A5B2*	3.1	6.7	82	91 (80)	95 (43)
 *A5B3*	3.1	6.7	94	98 (80)	100 (65)
 *A5B5*	2.8	6.7	77	77 (85)	96 (85)
 *A2B2*	3.2	5.0	73	97 (77)	97 (49)
 *A2B3*	3.2	5.0	89	92 (62)	95 (42)
 *A2B5*	2.9	5.0	82	96 (85)	89 (67)

the sorbent with acetic acid), dissolution in THF/DMF mixture, and loading of the resulting solution onto the conditioned Isolute SAX SPE sorbent. Excess aldehyde was removed by washing the column with CH_3CN, and the desired product was released with a HCl solution (0.1−1 N) in CH_3CN/MeOH mixture. Alternatively, by taking advantage of the basic amine, a strong cation-exchange sorbent ISOLUTE SCX SPE, a benzenesulfonic acid phase, could be used to purify the final products. A similar protocol was followed, except the release step that was performed with a NH_3 solution (0.1−0.5 N) in methanol. Yields and purities were compared with both the Isolute SAX SPE and

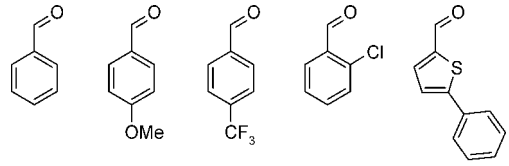


Figure 2. Aldehydes selected for the first reductive alkylation reaction.

the Isolute SCX SPE sorbents (Table 1). Similar results were obtained with both the strong anionic and the cationic exchange sorbents. However, when the strong cationic exchange sorbent, ISOLUTE SCX SPE, was used, the reaction mixtures could be directly loaded onto the column because acetic acid is not retained on this sulfonic acid phase. Thus Isolute SCX SPE sorbent use was found to be more expeditious.

Libraries Production

The first step in the library production was to react the nine phenylamino and benzylamino acid derivatives, **A1**−**A9**, with five commercially available aromatic aldehydes, **B1**−**B5**, that possess diverse functionality and electronic properties (Figure 2).[13] The reactions were performed on a 0.18 mmol scale, with a reaction mixture concentration of 0.08 M, in 4 mL vials placed in a orbital shakers. The resulting secondary amines, **AxBy**, were purified by SPE using Isolute SCX SPE columns on a VacMaster−20 manifold (Table 2).

The yields were dramatically influenced by the mode of purification and were improved with the use of a more concentrated ammonia solution for the releasing step from Isolute SCX SPE (0.5 vs 0.1 N, Table 2, note [b]). Interestingly, the electronic density of the secondary amines, **AxBy**, had no influence on the overall yields or purity of the final products (Table 2, column 4). In some cases, the desired product was precipitated after ISOLUTE SCX SPE purification (Table 2, note [c]), which resulted in higher purity but

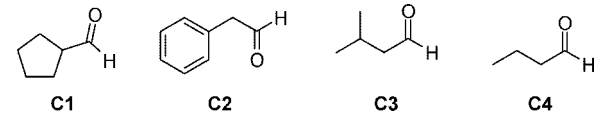


Figure 3. Aldehydes selected for the second reductive alkylation reaction.

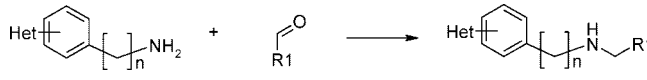
lower yields (24−34% yields). With the building blocks **A7**−**A9**, the resulting bis-benzyl amines were purified following the same protocol as the benzyl-phenyl amines, even though the pK_a of the resulting secondary amines are very different (around 9 vs 3). This illustrates the generality of the procedure. In summary, under these conditions, compounds **AxBy** could be isolated with high purity (>80% in most cases) and with moderate to excellent yields. In addition, this practical reaction procedure allowed the use of classical instruments.

Based on these promising results, the secondary amines, **AxBy**, were subjected to a second reductive alkylation step. Low molecular weight aldehydes were selected to provide final compounds, **AxByCz**, with molecular weights below 350 g mol^{-1} (Figure 3). An excess of the aldehyde (5 equiv) and a reaction mixture concentration of 0.08 M were found to be crucial for complete conversion to the final products, **AxByCz**. After 24 h at 50 °C and similar to the first reaction, the reaction mixtures were purified in parallel using the Isolute SCX SPE column. Under these conditions, the final tertiary amine products, **AxByCz**, were isolated in high purity (>80% in most of the cases) and modest to excellent isolated yields (27 to 98%) (Table 3). However, steric hindrance of benzyl-phenylamines bearing an ortho acidic heterocycle, such as **A1B1** and **A4B1**, prevented from the second reductive amination. These two secondary amines were removed in the final library production.

Analysis of the Library

The two libraries of tetrazole and [1,3,4]oxadiazol-2-one derivatives, **AxBy** and **AxByCz**, were evaluated in silico for

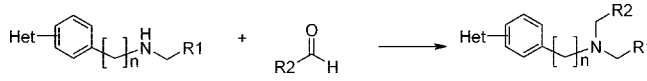
Table 2. First Reductive Alkylation Reaction



purity % (yield %)	A1	A2	A3	A4	A5	A6	A7[d]	A8[d]	A9[d]
B1	91 (80)[b]	90 (92)[b]	81 (98)[a]	89 (97)[b]	97 (84)[b]	94 (52)[b]	98 (70)[b]	97 (32)[c]	81 (76)[b]
B2	78 (90)[b]	98 (68)[b]	83 (98)[b]	87 (85)[b]	85 (98)[b]	88 (55)[b]	85 (40)[a]	93 (24)[c]	99 (28)[c]
B3	92 (78)[b]	95 (42)[a]	84 (20)[a]	95 (72)[b]	99 (25)[a]	96 (17)[a]	68 (32)[a]	85 (64)[b]	99 (34)[c]
B4	93 (82)[b]	96 (72)[b]	92 (87)[b]	25 (60)[b]	95 (63)[b]	92 (50)[b]	67 (59)[b]	83 (62)[b]	60 (80)[b]
B5	55 (31)[a]	83 (44)[a]	77 (30)[a]	91 (74)[b]	99 (44)[a]	99 (40)[a]	86 (73)[b]	91 (31)[c]	97 (33)[c]

[a] NH_3 solution (2 × 0.1 N) in MeOH used for the release step. [b] NH_3 solution (0.1 N + 0.5 N) in MeOH used for the release step. [c] Purification by Isolute SCX SPE, followed by filtration of the resulting precipitate. [d] Reactions performed at 0 °C to avoid double reductive alkylation.

Table 3. Second Reductive Alkylation Reaction



purity % (yield %)	A2B1	A3B1	A5B1	A6B1	A7B1	A8B1	A9B1
C1	87 (98)	88 (50)	92 (97)	63 (98)	93 (85)	97 (34)	84 (98)
C2	85 (98)	80 (98)	92 (98)	76 (98)	92 (83)	81 (84)	86 (98)
C3	92 (96)	90 (67)	95 (61)	83 (98)	96 (83)	95 (27)	83 (91)
C4	87 (91)	91 (54)	92 (97)	98 (98)	96 (69)	93 (33)	84 (81)

Table 4. Molecular Properties of the Library Members (Average Values)

compound	MW	AlogP98	HBAs	HBDs	rotlbonds	tPSA
AxBy	309.23	3.3	5	2	5	71.5
AxByCz	346.11	4.7	5	1	8	61.1

their drug-like properties[6] (molecular weight (MW), AlogP98, number of hydrogen bond donors (HBDs) and acceptors (HBAs), rotating bonds and polar surface area (tPSA), Table 4).[14] Overall, 97% of the library had no "Rule of 5" violation. The majority of the tertiary amines showed AlogP98 value below 5, with an average value of 4.7. As a general observation, all parameters remained in an acceptable range for a lead-like collection of compounds, especially with potential as orally bioavailable agents.

Conclusion

We have developed an efficient and expeditious method to synthesize and purify drug-like amino tetrazole and [1,3,4]oxadiazol-2-one derivatives with good purities. Phenyl- and benzyl-amines, substituted with tetrazole or [1,3,4]oxadiazol-2-one carboxylic acid bioisosteres, were transformed into functionally diverse and novel compounds, with pK_a values ranging from 4.9 to 8.4, by two sequential reductive alkylation reactions. Since tetrazole and [1,3,4]oxadiazol-2-one derivatives have charge distribution over a greater molecular surface compared with the corresponding carboxylic acids, these compounds may offer different interactions with receptors or enzymes. Biological evaluation of these compounds, as well as a larger production of the library, is currently under way. Such primary library-bearing acid bioisosteres can be useful for several important therapeutic classes like NSAIDs (non-steroidal anti-inflammatory drugs), sartans, and glitazones. Such drugs target very different protein classes, enzymes, GPCRs (G-protein coupled receptors), and nuclear hormone receptors.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX-300 spectrometer (300 and 75.47 MHz, respectively). HPLC analyses were performed on a Waters 2695 instrument, equipped with a Waters 996 Photodiode Array Detector and an XTerra MSC8 3.5 μm 4.6 × 50 mm column. Chromatographic conditions consisted of a gradient from 95% H_2O (0.1% TFA)/5% CH_3CN (0.1% TFA) to 5% H_2O (0.1% TFA)/95% CH_3CN (0.1% TFA) over 8 min with a flow of 2 mL/min. Mass spectra were determined on a Micromass ZMD (electrospray, positive or negative ionization). Elemental analyses were performed on an Erba Science 11108 CHN analyzer. Macroporous cyanoborohydride resin (macroporous triethylammonium methylpolystyrene cyanoborohydride, 0.5% inorganic antistatic agent, 655 μm, loading 2.32 mmol/g, Part no. 800406) was purchased from Argonaut. All SPE columns were purchased from Separtis. The sulfonic acid-functionalized SPE columns were Isolute SCX SPE columns (1 g: Part no. 530−0100-C, ion-exchange capacity 0.29 mequiv/g; 100 mg: Part no. 530−0010-B, ion-exchange capacity 0.29 mequiv/g). The aminopropyl-functionalized SPE columns were Isolute NH2 SPE column (500 mg: Part no. 470−0050-B, ion-exchange capacity 0.56 mequiv/g), and the quaternary amine (chloride counterion) functionalized SPE columns were Isolute SAX SPE columns (500 mg: Part no. 500−0050-B, ion-exchange capacity 0.55 mequiv/g). 4-(1*H*-Tetrazol-5-yl)-phenylamine and 2-(5-tetrazolyl)-aniline were bought from Dynamit and 3-(1*H*-tetrazol-5-yl)-phenylamine was purchased from Avocado. 4-Nitro-benzoic acid hydrazide, 3-nitro-benzoic acid hydrazide, and 2-nitro-benzoic acid hydrazide were bought from Aldrich. All other reagents were bought from Aldrich or Avocado and used without purification. Anhydrous solvents were purchased, stored on activated molecular sieves, and used without prior distillation.

Starting Material Synthesis. 2-(2-Aminophenyl)-1,3,4-oxadiazol-2-one (A4). To a solution of 2-nitro-benzoic acid hydrazide (20 g, 0.11 mol) in dimethylformamide (200 mL), triethylamine (19 mL, 0.33 mol) was added. The reaction mixture was cooled to 0 °C for 10 min under nitrogen atmosphere. Then 1,1-carbonyl diimidazole (26 g, 0.16 mol) was added portionwise. The reaction mixture was stirred at room temperature for 10 h. Completion of the reaction was confirmed by TLC. The solvents were evaporated, and the residue was triturated in water (150 mL). The solid obtained was filtered and washed with water to afford 12 g of **1a** (54%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.82−7.95 (m, 3H), 8.09−8.12 (m, 1H), 12.87 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 117.2, 124.5, 130.3, 133.0, 133.4, 147.5, 150.5, 154.1. HPLC: t_R = 2.43 min. ES-MS: m/z 205.9 $(M + H)^+$. To a mixture of 5-(2-nitrophenyl)-1,3,4-oxadiazol-2-one (10 g, 0.05. mmol) and iron powder (13.28 g, 0.24 mol) in ethanol (120 mL) heated at reflux was added dropwise a saturated aqueous solution of ammonium chloride (100 mL). The reaction mixture was heated to 80 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to afford 6 g of **A4** (70%) as a white solid.[7a,b] ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.30 (s, 2 H), 6.64 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 12.50 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 104.5, 115.5, 115.8, 126.7, 131.8, 146.9, 153.6, 154.6. HPLC: t_R = 2.19 min. ES-MS: m/z 177.9 $(M + H)^+$.

2-(3-Aminophenyl)-1,3,4-oxadiazol-2-one (A5). To a solution of 3-nitro-benzoic acid hydrazide (19 g, 0.10 mol, 1 equiv) in dry DMF (200 mL) at 0 °C was added TEA (29 mL, 0.21 mol, 2 equiv) and CDI (25.5 g, 0.16 mol, 1.5 equiv). The reaction mixture was stirred at room temperature under nitrogen for 18 h and concentrated under reduced pressure. The residue was taken up in water (200 mL), and the precipitate was filtered and dried under suction to afford 15 g of **1b** (71%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.84 (d, J = 8 Hz, 1H), 8.18−8.20 (m, 1H), 8.37−8.42 (m, 2H), 12.83 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 119.6, 125.5, 125.7, 131.1, 131.2, 148.1, 152.1, 154.1. HPLC: t_R = 2.53 min. ES-MS: m/z 205.9 $(M + H)^+$. mp: 190−192 °C. To a solution of 5-(3-nitrophenyl)-1,3,4-oxadiazol-2-one (15 g, 0.07 mol, 1 equiv) in ethanol

(400 mL) was added a saturated solution of ammonium chloride (300 mL) followed by iron powder (20 g, 0.35 mol, 5 equiv). The reaction mixture was refluxed for 3 h, cooled down to room temperature, and filtered. The filtrate was concentrated, and the residue was diluted with ethyl acetate (200 mL), washed with water and brine, and dried. Solvents were removed under reduced pressure to afford 10 g (77%) of **A5** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.45 (s, 2H), 6.70−6.72 (m, 1H), 6.89−6.91 (m, 1H), 6.98 (s, 1H), 7.15 (t, J = 8 Hz, 1H), 12.45 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 110.2, 112.8, 117.1, 124.7, 130.0, 149.6, 154.7, 154.9. HPLC: t_R = 4.06 min. ES-MS: m/z 177.9 $(M + H)^+$. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.46; H, 4.11; N, 23.04. mp: 183−185 °C.

2-(4-Aminophenyl)-1,3,4-oxadiazol-2-one (A6). To a solution of 4-nitro-benzoic acid hydrazide (19 g, 0.10 mol, 1 equiv) in dry DMF (200 mL) at 0 °C was added TEA (29 mL, 0.21 mol, 2 equiv) and CDI (25.6 g, 0.16 mol, 1.5 equiv). The reaction mixture was stirred at room temperature under nitrogen for 18 h and concentrated under reduced pressure. The residue was taken up in water (200 mL), and the resulting solid was filtered and dried under suction to afford 17 g of **1c** (81%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 8.02 (d, J = 9 Hz, 2H), 8.34 (d, J = 9 Hz, 2H), 12.90 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 124.4, 126.5, 129.6, 148.7, 152.3, 154.2. HPLC: t_R = 2.60 min. ES-MS: m/z 205.9 $(M - H)^-$. mp: 192 °C (decomposition). To a solution of 5-(4-nitrophenyl)-1,3,4-oxadiazol-2-one (15 g, 0.07 mol, 1 equiv) in ethanol (400 mL) was added a saturated aqueous solution of ammonium chloride (300 mL), followed by iron powder (20 g, 0.35 mol, 5 equiv). The reaction mixture was refluxed for 3 h, cooled, and filtered. The filtrate was concentrated under reduced pressure, and the residue was diluted with ethyl acetate (200 mL), washed with water, brine and dried. The solvent was evaporated under reduced pressure to afford 11 g (85%) of **A6** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.84 (s, 2H), 6.60−6.63 (d, J = 8.6 Hz, 2H), 7.41−7.44 (d, J = 8.3 Hz, 2H), 12.14 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 110.7, 113.8, 127.0, 152.2, 155.0, 155.2. HPLC: t_R = 4.08 min. ES-MS: m/z 177.9 $(M + H)^+$. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 53.91; H, 4.13; N, 23.39. mp: 163−165 °C.

2-[2-(Aminomethyl)Phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (A7). To a solution of methyl 2-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **2a**[9] (5 g, 18.00 mmol) in methanol (70 mL) was added hydrazine hydrate (1.88 g, 0.04 mol), and the mixture was refluxed for 12 h. The solvent was removed under vacuum, and the residue was triturated in water. The resulting solid was filtered and dried under suction to afford 4.2 g (84%) of **3a** as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (s, 9H), 4.24 (d, J = 6 Hz, 2H), 4.46 (s, 2H), 7.18 8t, J = 7.2 Hz, 1H), 7.25−7.45 (m, 4H), 9.52 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.2, 41.2, 77.9, 126.4, 127.1, 127.3, 129.7, 134.1, 138.1, 155.7, 167.9. HPLC: t_R = 2.21 min. ES-MS: m/z 265.9 $(M + H)^+$. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.57; H, 7.22; N, 15.75. To a solution of *tert*-butyl [2-(hydrazinocarbonyl)benzyl]carbamate **3a** (4.0 g, 15.00 mmol) in dry DMF (100 mL) at 0 °C was added TEA (3.04 g, 0.03 mol) followed by CDI (3.6 g, 0.02 mol). The reaction mixture was stirred at room temperature under nitrogen for 10 h and concentrated under reduced pressure. The residue was triturated in water (100 mL), and the resulting solid was filtered and dried under suction to afford 3.4 g (79%) of derivative **4a** as an off white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.40 (s, 9H), 4.44 (d, J = 5 Hz, 2H), 7.33−7.74 (m, 5H), 12.59 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.2, 41.9, 78.0, 121.6, 127.1, 127.4, 127.9, 131.1, 138.9, 153.6, 154.2, 155.8. HPLC: t_R = 3.52 min. ES-MS: m/z 290.0 $(M - H)^-$. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.55; H, 5.83; N, 14.40. To a solution of *tert*-butyl [2-(5-hydroxy-1,3,4-oxadiazol-2-yl)benzyl]carbamate **4a** (4.5 g, 15.00 mmol) in dioxane (20 mL) was added a solution of HCl (4M) in dioxane (50 mL), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was evaporated under reduced pressure to afford 3.1 g (88%) of **A7** as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.37 (br s, 2H), 7.55−7.70 (m, 3H), 7.81−7.84 (m, 1H), 8.54 (br s, 3H), 12.91 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 40.4, 123.0, 127.9, 129.3, 131.2, 131.6, 131.9, 152.9, 154.0. HPLC: t_R = 1.12 min. Anal. Calcd for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46, Cl, 15.57. Found: C, 47.36; H, 4.32; N, 18.40, Cl, 15.35.

2-[3-(Aminomethyl)Phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (A8). To a solution of methyl 3-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **2b**[9] (5.0 g, 0.02 mol, 1 equiv) in methanol (70 mL) was added hydrazine hydrate (2.0 g, 0.04 mol, 2 equiv), and the mixture was refluxed for 12 h. The solvent was removed under vacuum, and the residue was triturated in water. The resulting solid was filtered and dried under suction to afford 4 g (80%) of **3b** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.39 (s, 9H), 4.16 (d, J = 7 Hz, 2H), 4.48 (s, 2H), 7.36−7.42 (m, 3H), 7.65−7.72 (m, 2H), 9.73 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.2, 43.2, 77.8, 124.9, 125.9, 128.1, 129.5, 133.3, 140.3, 155.8, 165.9. HPLC: t_R = 2.18 min. ES-MS: m/z 263.9 $(M - H)^-$. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.53; H, 7.12; N, 15.78. mp: 99.2−100.9 °C. To a solution of **3b** (8.0 g, 0.03 mol, 1 equiv) in dry DMF (150 mL) at 0 °C was added TEA (8.3 mL, 0.06 mol, 2 equiv) and CDI (4.9 g, 0.03 mol, 2 equiv). The reaction mixture was stirred at room temperature under nitrogen for 10 h and concentrated under reduced pressure. The residue was triturated in water (100 mL), and the resulting solid was filtered and dried under suction to afford 7 g (79%) of **4b** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.39 (s, 9H), 4.20 (d, J = 6 Hz, 2H), 7.41−7.49 (m, 3H), 7.64−7.67 (m, 2H), 12.57 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.2, 43.0, 78.0, 123.5, 123.6, 123.9, 129.2, 130.0, 141.4, 1538, 154.4, 155.8. HPLC: t_R = 3.35 min. ES-MS: m/z 289.9 $(M - H)^-$. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.89; H, 5.75; N, 14.58. mp: 122−124 °C. To a solution of **4b** (7.0 g, 24.00 mmol, 1 equiv) in dioxane (50 mL) was added a solution of HCl (4M) in dioxane (50 mL), and

reaction mixture was stirred at room temperature for 8 h. The reaction mixture was evaporated under reduced pressure to afford 4.8 g (88%) of 5-(3-aminomethyl-phenyl)-[1,3,4]oxadiazol-2-one **A8** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.09 (s, 2H), 7.56−7.60 (m, 1H), 7.69−7.71 (m, 1H), 7.77−7.79 (m, 1H), 7.96 (s, 1H), 8.57 (s, 3H), 12.76 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 42.0, 124.5, 125.4, 126.8, 129.8, 132.4, 135.7, 153.7, 154.7. HPLC: t_R = 3.89 min. ES-MS: *m/z* 191.9 $(M + H)^+$. Anal. Calcd. for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46, Cl, 15.57. Found: C, 47.16; H, 4.33; N, 18.12, Cl, 15.29. mp: 253 °C (decomposition).

2-[4-(Aminomethyl)Phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (A9). To a solution of methyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **2c**[9] (5 g, 0.02 mol, 1 equiv) in methanol (70 mL) was added hydrazine hydrate (2 g, 0.04 mol, 2 equiv), and the mixture was refluxed for 12 h. The solvent was removed under vacuum, and the residue was triturated in water. The resulting solid was filtered and dried under suction to afford 4.5 g (90%) of derivative **3c** as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.40 (s, 9H), 4.15 (d, J = 7 Hz, 2H), 4.47 (s, 2H), 7.28 (d, J = 8 Hz, 2H), 7.43 (t, J = 6 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 9.71 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.3, 43.1, 77.9, 126.7, 126.9, 131.8, 143.3, 155.8, 165.7. HPLC: t_R = 2.10 min. ES-MS: *m/z* 265.9 $(M + H)^+$. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.89; H, 6.87; N, 15.83. mp: 128.8−129.9 °C. To a solution of **3c** (4.5 g, 0.02 mol, 1 equiv) in dry DMF (100 mL) at 0 °C was added TEA (3.5 mL, 0.03 mol, 1.5 equiv), followed by CDI (2.7 g, 0.02 mol, 1 equiv). The reaction mixture was stirred at room temperature under nitrogen for 10 h and concentrated under reduced pressure. The residue was triturated in water (100 mL), and the resulting solid was filtered, dried under suction to afford 4 g (81%) of **4c** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.39 (s, 9H), 4.18 (d, J = 6 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.46 (t, J = 6 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 12.54 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 28.2, 43.2, 77.9, 122.3, 125.2, 127.6, 143.8, 153.8, 154.4, 155.8. HPLC: t_R = 3.28 min. ES-MS *m/z* 289.9 $(M - H)^-$. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.75; H, 5.92; N, 14.20. mp: 157−158 °C. To a solution of **4c** (4 g, 0.01 mol, 1 equiv) in dioxane (20 mL) was added a solution of HCl (4M) in dioxane (30 mL), and reaction mixture was stirred at room temperature for 8 h. The reaction mixture was evaporated under reduced pressure to afford 3 g (91%) of 5-(4-aminomethyl-phenyl)-[1,3,4]oxadiazol-2-one **A9** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.09 (br s, 2H), 7.67 (d, J = 8 Hz, 2H), 7.82 (d, J = 8 Hz, 2H), 8.64 (br s, 3H), 12.71 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 42.1, 67.0, 124.2, 125.7, 130.1, 137.8, 153.7, 154.7. HPLC: t_R = 3.83 min. ES-MS: *m/z* 191.9 $(M + H)^+$. Anal. Calcd for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46; Cl, 15.57. Found: C, 47.83; H, 4.42; N, 18.29; Cl, 16.03. mp 274 °C (decomposition).

General Procedure for First Reductive Amination with Aniline Derivatives. In a 8 mL vial, a solution of R_1-CHO (0.27 mmol, 1.50 equiv) in DMF (1 mL) was mixed with R_3-NH_2 (0.18 mmol, 1 equiv) in THF (1 mL) and acetic acid (8.80 mmol; 500 μL; 44.00 equiv). MP-cyanoborohydride was added, and the reaction mixture was stirred at rt for 24 h. After 24 h, the resin was filtered off in 8 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on Isolute SCX SPE 1 g (Pol-SO_3H) using the following conditions:

(1) SPE column was washed with 1 × 6 mL of MeOH.
(2) SPE column was washed with 1 × 6 mL of MeOH/DCM (1/1).
(3) The reaction mixture was deposited as a solution.
(4) SPE column was washed with 1 × 1.5 mL of CH_3CN.
(5) The desired product was eluted with 1 × 3 mL of NH_3 0.1 M solution in MeOH.
(6) The desired product was further eluted 1 × 4 mL of NH_3 0.5 M solution in MeOH. Fractions 5 and 6 are combined in a 8 mL vial, and the solvents are evaporated with Genevac until dryness.

Compound A1B1. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.56 (s, 2H), 6.71−6.76 (m, 2H), 7.23−7.50 (m, 6H), 7.81−7.85 (m, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 46.3, 106.2, 111.8, 115.5, 126.9, 127.1, 128.0, 128.3, 128.5, 129.2, 131.9, 139.3, 146.4, 155.1. HPLC: t_R = 4.00 min. ES-MS: *m/z* 251.85 $(M + H)^+$. Yield: 80%.

Compound A1B3. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.70 (br s, 2H), 6.72−6.79 (m, 2H), 7.26−7.32 (m, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.81−7.84 (m, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 45.6, 105.7, 111.9, 115.8, 124.3 (q, J = 271.7 Hz), 125.4 (q, J = 3.8 Hz), 127.5 (q, J = 31.6 Hz), 127.6, 128.5, 131.6, 132.3, 144.6, 146.2. HPLC: t_R = 4.52 min. ES-MS: *m/z* 319.86 $(M + H)^+$. Yield: 78%.

Compound A1B4. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.63 (s, 2H), 6.71−6.78 (m, 2H), 7.28−7.34 (m, 3H), 7.39−7.42 (m, 1H), 7.47−7.50 (m, 1H), 7.82−7.85 (m, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 44.1, 105.7, 111.7, 115.9, 127.3, 128.5, 128.8, 128.9, 129.4, 132.3, 132.4, 136.1, 146.1, 154.6. HPLC: t_R = 4.27 min. ES-MS: *m/z* 285.86 $(M + H)^+$. Yield: 82%.

Compound A2B1. HPLC: t_R = 4.03 min. ES-MS: *m/z* 320.21 $(M + H)^+$. Yield: 92%.

Compound A2B2. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.71 (s, 3H), 4.22 (s, 2H), 6.17 (br s, 1H), 6.46−6.50 (m, 1H), 6.86−6.90 (m, 2H), 7.01−7.07 (m, 1H), 7.10−7.16 (m, 1H), 7.24−7.37 (m, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 45.9, 55.0, 110.1, 111.3, 113.6, 113.7, 114.0, 128.3, 128.7, 132.1, 132.3, 148.6, 158.0, 160.6. HPLC: t_R = 2.81 min. ES-MS: *m/z* 281.88 $(M + H)^+$. Yield: 68%.

Compound A2B3. HPLC: t_R = 4.03 min. ES-MS: *m/z* 320.21 $(M + H)^+$. Yield: 42%.

Compound A2B4. HPLC: t_R = 3.73 min. ES-MS: *m/z* 286.18 $(M + H)^+$. Yield: 72%.

Compound A2B5. HPLC: t_R = 3.73 min. ES-MS: *m/z* 286.18 $(M + H)^+$. Yield: 44%.

Compound A3B1. HPLC: t_R = 3.18 min. ES-MS: *m/z* 252.18 $(M + H)^+$. Yield: 98%.

Compound A3B2. HPLC: t_R = 3.07 min. ES-MS: *m/z* 239.18 $(M + H)^+$. Yield: 98%.

Compound A3B3. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.48 (s, 2H), 6.71−6.74 (m, 2H), 7.08−7.10 (t, J = 6 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 7.69−7.74 (m, 4H), 16.22 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 45.4, 110.9, 112.3, 124.3 (q, J = 271.1 Hz), 125.2 (q, J = 3.8 Hz), 127.8, 128.2, 131.1 (q, J = 33.7 Hz), 144.7, 150.8. HPLC: t_R = 3.93 min. ES-MS: m/z 319.84 $(M + H)^+$. Yield: 20%.

Compound A3B4. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.41 (d, J = 5 Hz, 2H), 6.71 (d, J = 9 Hz, 2H), 6.93 (t, J = 6 Hz, 1H), 6.27−7.33 (m, 2H), 7.37−7.40 (m, 1H), 7.45−7.49 (m, 1H), 7.73 (d, J = 9 Hz, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 43.8, 111.2, 112.1, 127.2, 128.2, 128.6, 128.8, 129.3, 132.3, 136.3, 150.6, 155.1. HPLC: t_R = 3.61 min. ES-MS: m/z 286.18 $(M + H)^+$. Yield: 87%.

Compound A4B1. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.49 (d, J = 5.6 Hz, 2H), 6.68−6.78 (m, 2H), 7.11 (t, J = 5.6 Hz, 1H), 7.22−7.39 (m, 6H), 7.47−7.61 (m, 1H), 12.58 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 46.2, 105.4, 111.4, 115.6, 127.0, 127.1, 127.2, 128.5, 132.2, 138.9, 146.0, 153.4, 154.5. HPLC: t_R = 4.28 min. ES-MS: m/z 267.89 $(M + H)^+$. Yield: 97%.

Compound A4B2. HPLC: t_R = 3.95 min. ES-MS: m/z 297.91 $(M + H)^+$. Yield: 85%.

Compound A4B3. HPLC: t_R = 4.67 min. ES-MS: m/z 335.91 $(M + H)^+$. Yield: 72%.

Compound A4B5. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.72 (d, J = 5.5 Hz, 2H), 6.73−6.77 (m, 1H), 6.93−6.95 (m, 1H), 7.10−7.11 (m, 1H), 7.16 (t, J = 5.5 Hz, 1H), 7.25−7.41 (m, 5H), 7.55−7.60 (m, 3H), 12.60 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 41.8, 105.7, 111.6, 116.1, 123.3, 125.1, 126.6, 127.3, 127.5, 129.1, 132.3, 133.6, 142.2, 142.5, 145.6, 153.4, 154.4. HPLC: t_R = 4.96 min. ES-MS: m/z 348.3 $(M - H)^-$. Yield: 74%.

Compound A5B1. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.31 (d, J = 5.8 Hz, 2H), 6.67 (t, J = 5.8 Hz, 1H), 6.74−6.77 (m, 1H), 6.93−6.99 (m, 2H), 7.16−7.25 (m, 2H), 7.30−7.38 (m, 5H), 12.46 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 46.2, 108.3, 112.6, 115.1, 124.4, 126.7, 127.1, 128.3, 129.7, 139.7, 149.0, 154.3, 154.5. HPLC: t_R = 3.54 min. ES-MS: m/z 268.13 $(M + H)^+$. Yield: 84%.

Compound A5B2. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.71 (s, 3H), 4.23 (d, J = 6 Hz, 2H), 6.57 (t, J = 6 Hz, 1H), 6.73−6.76 (m, 1H), 6.84−7.01 (m, 4H), 7.16−7.21 (m, 1H), 7.25−7.29 (m, 2H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 46.0, 55.3, 108.7, 112.9, 114.1, 115.5, 124.8, 128.7, 130.0, 131.7, 149.4, 154.7, 154.9, 158.5, 162.6. HPLC: t_R = 3.29 min. ES-MS: m/z 296.19 (M − H). Yield: 98%.

Compound A5B3. HPLC: t_R = 4.35 min. ES-MS: m/z 336.13 $(M + H)^+$. Yield: 25%.

Compound A5B4. HPLC: t_R = 4.11 min. ES-MS: m/z 302.16 $(M + H)^+$. Yield: 63%.

Compound A5B5. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.41 (s, 1H), 4.51 (s, 2H), 6.83−6.86 (m, 1H), 6.97−7.00 (m, 1H), 7.06−7.07 (m, 2H), 7.21−7.29 (m, 2H), 7.35−7.40 (m, 3H), 7.57−7.59 (m, 2H), 12.47 (s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 42.3, 109.0, 113.5, 115.7, 123.6, 124.9, 125.4, 126.4, 127.8, 129.4, 134.2, 139.6, 142.2, 144.2, 149.1, 154.6, 155.0, 162.6, 184.4. HPLC: t_R = 4.47 min. ES-MS: m/z 348.15 $(M + H)^+$. Yield: 44%.

Compound A6B1. HPLC: t_R = 3.61 min. ES-MS: m/z 267.83 $(M + H)^+$. Yield: 52%.

Compound A6B2. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.72 (s, 3H), 4.25 (d, J = 5.8 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.93 (t, J = 6.3 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 9.1 Hz, 2H), 7.68 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 45.3, 55.0, 110.5, 112.0, 123.8, 121.6, 126.6, 128.4, 131.1, 135.1, 151.2, 154.6, 154.7, 158.2. HPLC: t_R = 3.51 min. ES-MS: m/z 297.87 $(M + H)^+$. Yield: 55%.

Compound A6B3. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.45 (d, J = 7 Hz, 2H), 6.66 (d, J = 9 Hz, 2H), 7.13 (t, J = 6 Hz, 1H), 7.47 (d, J = 9 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H)12.19 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 45.4, 111.0, 112.1, 124.3 (q, J = 271.7 Hz), 125.2 (q, J = 4.1 Hz), 126.7, 127.7, 131.0 (q, J = 32.2 Hz), 144.6 (q, J = 1.4 Hz), 150.9, 154.6. HPLC: t_R = 4.23 min. ES-MS: m/z 336.19 $(M + H)^+$. Yield: 17%.

Compound A6B4. HPLC: t_R = 4.01 min. ES-MS: m/z 302.14 $(M + H)^+$. Yield: 50%.

Compound A6B5. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.53 (d, J = 5.9 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 7.06−7.10 (m, 2H), 7.24−7.29 (m, 1H), 7.36−7.41 (m, 3H), 7.49−7.52 (m, 2H), 7.57−7.60 (m, 2H), 12.20 (br s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 41.5, 111.1, 112.3, 123.2, 125.0, 126.4, 126.6, 127.4, 129.0, 133.8, 141.9, 143.2, 150.7, 154.6. HPLC: t_R = 4.46 min. ES-MS: m/z 347.95 $(M - H)^-$. Yield: 40%.

General Procedure for First Reductive Amination with Benzylamine Derivatives. In a 8 mL vial, a solution of R_1-CHO (0.19 mmol, 1.10 equiv) in DMF (1 mL) was mixed with R_3-NH_2 (0.18 mmol, 1 equiv) in THF (1 mL) and acetic acid (8.80 mmol; 500 μL; 44.00 equiv). MP-cyanoborohydride was added, and the reaction mixture was stirred at 0 °C for 5 h. After 5 h, the resin was filtered off in 8 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on Isolute SCX SPE 1 g (Pol-SO_3H) using the following conditions:

(1) SPE column was washed with 1 × 6 mL of MeOH.
(2) SPE column was washed with 1 × 6 mL of MeOH/DCM (1/1).
(3) The reaction mixture was deposit as solution.
(4) SPE column was washed with 1 × 1.5 mL of CH_3CN.
(5) The desired product was eluted with 1 × 3 mL of NH_3 0.1 M solution in MeOH.
(6) The desired product was further eluted 1 × 4 mL of NH_3 0.5 M solution in MeOH. Fractions 5 and 6 are combined in a 8 mL vial, and solvents are evaporated with Genevac until dryness.

Compound A7B1. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.19 (br s, 2H), 4.46 (br s, 2H), 7.30−7.46 (m, 4H), 7.58−7.64 (m, 3H), 7.74−7.76 (m, 1H), 7.79−7.84 (m, 1H), 10.21 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 48.1, 50.6, 123.7, 127.8, 128.5, 128.9, 129.7, 130.1, 130.2, 131.1, 131.8, 132.9, 153.0, 154.0. HPLC: t_R = 2.05 min. ES-MS: m/z 280.30 $(M - H)^-$. Yield: 70%.

Compound A7B2. HPLC: t_R = 2.46 min. ES-MS: m/z 282.2 $(M + H)^+$. Yield: 40%.

Compound A7B5. HPLC: t_R = 3.12 min. ES-MS: *m/z* 363.87 $(M + H)^+$. Yield: 73%.

Compound A8B1. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.18 (s, 2H), 4.26 (s, 2H), 7.42−7.44 (m, 3H), 7.51−7.57 (m, 2H), 7.58−7.63 (m, 1H), 7.70−7.73 (m, 1H), 7.82−7.84 (m, 1H), 8.01 (m, 1H), 9.53 (br s, 1H), 12.26 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 49.9, 50.5, 124.5, 124.6, 125.9, 126.0, 127.3, 129.0, 129.3, 129.9, 130.4, 132.2, 132.3, 133.4, 153.8, 154.7. HPLC: t_R = 1.62 min. ES-MS: *m/z* 282.23 $(M + H)^+$. Yield: 32%.

Compound A8B2. HPLC: t_R = 1.79 min. ES-MS: *m/z* 312.28 $(M + H)^+$. Yield: 24%.

Compound A8B3. HPLC: t_R = 2.74 min. ES-MS: *m/z* 350.25 (M + H)+. Yield: 64%.

Compound A8B4. HPLC: t_R = 2.19 min. ES-MS: *m/z* 316.21 $(M + H)^+$. Yield: 62%.

Compound A8B5. HPLC: t_R = 2.68 min. ES-MS: *m/z* 364.25 $(M + H)^+$. Yield: 31%.

Compound A9B1. HPLC: t_R = 1.94 min. ES-MS: *m/z* 282.22 $(M + H)^+$. Yield: 76%.

Compound A9B2. HPLC: t_R = 1.77 min. ES-MS: *m/z* 310.24 $(M - H)^+$. Yield: 28%.

Compound A9B3. HPLC: t_R = 2.25 min. ES-MS: *m/z* 350.23 $(M + H)^+$. Yield: 34%.

Compound A9B5. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.25 (s, 2H), 4.41 (s, 2H), 7.31−7.49 (m, 5H), 7.64−7.66 (d, J = 7 Hz, 2H), 7.72−7.77 (d, J = 7 Hz, 2H), 7.83−7.86 (d, J = 9 Hz, 2H), 9.90 (br s, 1H), 12.74 (br s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 44.6, 49.4, 124.0, 124.7, 125.7, 125.8, 128.4, 129.6, 129.6, 131.3, 131.4, 132.5, 132.6, 133.6, 133.6, 135.5, 145.6, 153.8, 154.8, 162.7. HPLC: t_R = 2.68 min. ES-MS: *m/z* 364.23 $(M + H)^+$. Yield: 33%.

General Procedure for Second Reductive Amination. To one of the five solutions obtained in the previous step, containing R_3-NH(R_1) (0.02 mmol, 1 equiv), was added a solution of R_2-CHO (0.06 mmol, 3 equiv) in THF (total volume of R_2CHO + THF = 73 μL) and acetic acid (4.40 mmol; 63 μL; 25% vol). Mp-cyanoborohydride was added, and the reaction mixture was stirred at rt for 24 h. After 24 h, when the reaction was not complete, 3 equiv of aldehyde R_2-CHO (0.06 mmol, 3 equiv) was added, and the reaction mixture was stirred for one more night at rt. On the next morning, if the reaction was still not complete, 6 equiv of aldehyde R_2-CHO (0.12 mmol, 6 equiv) was added, and the reaction mixture was stirred at 50 °C for 2 days. When reaction was completed, the resin was filtered off in 4 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on Isolute SCX SPE 100 mg (Pol-SO_3H) using the following conditions:

(1) SPE column was washed with 1 × 3 mL of MeOH.
(2) SPE column was washed with 1 × 3 mL of MeOH/DCM (1/1).
(3) The reaction mixture was deposit as solution.
(4) SPE column was washed with 1 × 750 μL of CH_3CN.
(5) The desired product was eluted with 1 × 2 mL of NH_3 0.1 M solution in MeOH.
(6) The desired product was further eluted 1 × 2 mL of NH_3 0.5 M solution in MeOH. Fractions 5 and 6 are combined in a 8 mL vial and solvents are evaporated with Genevac until dryness.

Compound A2B1C1. HPLC: t_R = 4.83 min. ES-MS: *m/z* 334.27 $(M + H)^+$. Yield: 98%.

Compound A3B1C1. HPLC: t_R = 4.86 min. ES-MS: *m/z* 334.26 $(M + H)^+$. Yield: 50%.

Compound A5B1C1. HPLC: t_R = 5.23 min. ES-MS: *m/z* 350.26 $(M + H)^+$. Yield: 97%.

Compound A2B1C2. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.91−2.94 (m, 2H), 3.64−3.70 (m, 2H), 4.58 (s, 2H), 6.78−6.79 (m, 1H), 7.19−7.34 (m, 13H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 32.7, 52.6, 53.4, 109.6, 113.0, 114.1, 126.1, 126.5, 126.7, 128.4, 128.5, 128.8, 129.7, 138.8, 139.3, 148.0, 157.9. HPLC: t_R = 4.81 min. ES-MS: *m/z* 356.29 $(M + H)^+$. Yield: 98%.

Compound A3B1C2. HPLC: t_R = 4.72 min. ES-MS: *m/z* 356.25 $(M + H)^+$. Yield: 98%.

Compound A5B1C2. HPLC: t_R = 5.11 min. ES-MS: *m/z* 372.29 $(M + H)^+$. Yield: 98%.

Compound A2B1C3. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.91 (s, 3H), 0.94 (s, 3H), 1.47−1.54 (m, 2H), 1.57−1.68 (m, 1H), 3.45−3.50 (m, 2H), 4.62 (s, 2H), 6.379−6.82 (m, 1H), 7.23−7.25 (m, 4H), 7.28−7.35 (m, 5H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 22.5, 25.6, 35.2, 49.0, 53.3, 109.6, 113.8, 114.3, 125.1, 126.5, 126.7, 128.5, 130.0, 138.7, 148.2, 155.9. HPLC: t_R = 4.97 min. ES-MS: *m/z* 338.31 $(M + H)^+$. Yield: 96%.

Compound A3B1C3. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.89 (d, J = 5.9 Hz, 6H), 1.5 (br s, 2H), 1.56−1.62 (m, 1H), 3.47 (br s, 2H), 4.62 (s, 2H), 6.78 (d, J = 8.9 Hz, 2H), 7.19−7.31 (m, 6H), 7.79 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 22.4, 25.6, 35.2, 49.0, 53.2, 110.2, 111.8, 126.4, 126.5, 126.7, 128.2, 128.5, 128.6, 138.4, 149.9, 154.8. HPLC: t_R = 4.79 min. ES-MS: *m/z* 322.26 $(M + H)^+$. Yield: 67%.

Compound A5B1C3. HPLC: t_R = 4.55 min. ES-MS: *m/z* 322.25 $(M + H)^+$. Yield: 61%.

Compound A6B1C3. HPLC: t_R = 5.18 min. ES-MS: *m/z* 338.24 $(M + H)^+$. Yield: 98%.

Compound A2B1C4. HPLC: t_R = 3.58 min. ES-MS: *m/z* 308.29 $(M + H)^+$. Yield: 91%.

Compound A3B1C4. HPLC: t_R = 4.52 min. ES-MS: *m/z* 308.24 $(M + H)^+$. Yield: 54%.

Compound A5B1C4. HPLC: t_R = 3.97 min. ES-MS: *m/z* 324.28 $(M + H)^+$. Yield: 97%.

Compound A6B1C4. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.91 (t, J = 7.3 Hz, 3H), 1.30−1.38 (m, 2H), 1.56−1.61 (m, 2H), 3.47 (t, J = 7.6 Hz, 2H), 4.64 (s, 2H), 6.74 (d, J = 9.6 Hz, 2H), 7.18−7.25 (m, 3H), 7.30−7.35 (m, 2H), 7.52 (d, J = 8.9 Hz, 2H), 12.20 (br s, 1H). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C 13.8, 19.6, 28.7, 50.5, 53.2, 110.3, 111.6, 126.3, 126.6, 126.7, 128.5, 138.3, 150.1, 154.5, 154.6. HPLC: t_R = 4.92 min. ES-MS: *m/z* 324.23 $(M + H)^+$. Yield: 98%.

Compound A7B1C1. HPLC: t_R = 2.95 min. ES-MS: *m/z* 364.40 $(M + H)^+$. Yield: 85%.

Compound A8B1C1. HPLC: t_R = 3.07 min. ES-MS: *m/z* 364.30 $(M + H)^+$. Yield: 34%.

Compound A9B1C1. HPLC: t_R = 3.04 min. ES-MS: *m/z* 364.28 $(M + H)^+$. Yield: 98%.

Compound A7B1C2. HPLC: $t_R = 2.89$ min. ES-MS: *m/z* 386.40 $(M + H)^+$. Yield: 83%.

Compound A8B1C2. HPLC: $t_R = 3.15$ min. ES-MS: *m/z* 386.37 $(M + H)^+$. Yield: 84%.

Compound A9B1C2. HPLC: $t_R = 3.15$ min. ES-MS: *m/z* 386.32 $(M + H)^+$. Yield: 98%.

Compound A7B1C3. HPLC: $t_R = 3.01$ min. ES-MS: *m/z* 352.30 $(M + H)^+$. Yield: 83%.

Compound A8B1C3. HPLC: $t_R = 3.03$ min. ES-MS: *m/z* 352.29 $(M + H)^+$. Yield: 27%.

Compound A9B1C3. HPLC: $t_R = 3.02$ min. ES-MS: *m/z* 352.28 $(M + H)^+$. Yield: 91%.

Compound A7B1C4. HPLC: $t_R = 2.72$ min. ES-MS: *m/z* 338.30 $(M + H)^+$. Yield: 69%.

Compound A8B1C4. HPLC: $t_R = 2.74$ min. ES-MS: *m/z* 338.27 $(M + H)^+$. Yield: 33%.

Compound A9B1C4. HPLC: $t_R = 2.72$ min. ES-MS: *m/z* 338.26 $(M + H)^+$. Yield: 81%.

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

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