Synthesis of Heteroaryl *ortho*-Phenoxyethylamines via Suzuki Cross-Coupling: Easy Access to New Potential Scaffolds in Medicinal Chemistry

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Abstract Heteroaryl *ortho*-phenoxyethylamines have been extensively employed in medicinal chemistry as privileged scaffolds for the design of highly potent and selective ligands. Herein an efficient, fast, and general method for the synthesis of heteroaryl phenoxyethylamines via Suzuki cross-coupling is reported. This approach offers the opportunity to obtain a large variety of biaryls incorporating five-membered (thiophene, furan, thiazole, pyrazole, imidazole) or six-membered (pyridine, pyrimidine) heteroaromatic rings for appropriate libraries of ligands. All the compounds presented here have never been synthesized before and a full structural characterization is given.

Key words C–C coupling, heterocycles, palladium, Suzuki–Miyaura cross-coupling, building blocks

Heteroaryl *ortho*-phenoxyethylamines have been extensively employed in medicinal chemistry as privileged scaffolds for the design of highly potent and selective ligands (Figure 1) for glycine transporter GlyT1 (**1**),¹ α_1 adrenergic receptor **2**,² DNA topoisomerases **3**,³ AMPA receptor **4**,⁴ and 5-HT_{2A} receptor **5**.^{5,6} Moreover, Trifenagrel (**6**), a potent inhibitor of arachidonate-induced platelets aggregation,⁷ moPhpC **7**, fluorescent pyrrolocytosine nucleobases designed for tight binding to guanine,⁸ and some 2,3- and 3,4-diarylfurans, for example, **8**,⁹ with anti-implantation activity, belong to this versatile class of heteroaryl *ortho*-phenoxyethylamines.

Despite the important role of these chemical entities in several fields of medicinal chemistry, a general method for heteroaryl *ortho*-phenoxyethylamine synthesis has not yet been reported. From a practical point of view, the assembly of these building blocks could be achieved via cross-coupling of two monocyclic units. Among the various method-

ologies available,¹⁰ the Suzuki–Miyaura reaction, one of the most popular and powerful methods for the joining of aryl–aryl and aryl–heteroaryl moieties, was chosen.¹¹ Thanks to its compatibility with a variety of functional groups, the stability, commercial availability, and low toxicity of a wide range of boronic starting materials, along with the ease of working up the reaction mixtures, this reaction has found many applications, in both research laboratories and large-scale industrial processes.¹²

In this work, we describe the synthesis of several heteroaryl *ortho*-phenoxyethylamines via Suzuki cross-coupling. This approach offers the opportunity to obtain a large variety of biaryls incorporating five-membered electron-rich (thiophene, furan), six-membered electron-poor (pyridine, pyrimidine), or five-membered rings with two heteroatoms (thiazole, pyrazole, imidazole) for appropriate libraries of ligands.

In an attempt to find a convenient and versatile strategy to build the *ortho*-substituted biaryl scaffold, we took into account several factors: i) the different nature of the heterocycle to be coupled: electron-rich or electron-poor; ii) the presence of sterically hindered *ortho*-substituted substrates; iii) the presence of LiAlH₄-sensitive heterocycles such as pyrimidine; iv) the presence of heteroatoms such as sulfur or nitrogen that may drastically reduce the yields of some steps (i.e., reduction) due to the poisoning of the catalyst; and v) the opportunity to start from a common precursor (nitrile or masked amine) by inserting the structural diversity in the last step of the synthesis.

It is well known that the optimal conditions for Suzuki coupling is the electron-poor nature of aryl halide and the electron-rich nature of arylboronic acid. Keeping this in mind, we designed a synthetic approach, employing a common key intermediate **9**, which directly underwent Suzuki

Figure 1 Structures of heteroaryl *ortho*-phenoxyethylamine-based compounds

coupling in the case of electron-rich substrates or was converted into the corresponding pinacolboronic ester **10** and then coupled with the electron-poor aryl halide, as described in Scheme 1.

Alkylation of 2-iodophenol in the standard conditions reported for the Williamson reaction provided the aryl iodide **9** in high yield (89%). Suzuki coupling of 2-(2-iodophe-

noxy)acetonitrile (**9**) with an aryl pinacolboronic ester has recently been described.¹³ However, while many references relating to the coupling of the *o*-iodoanisole or higher homologues, such as **9**, with a variety of boronic acids/esters have been reported,^{13,14} to the best of our knowledge, there are no examples of unsubstituted *o*-iodoanisole coupled with 2-thiophenyl- or 2-furanylboronic acids.

Scheme 1 Reagents and conditions: i) bromoacetonitrile, K_2CO_3 , 18-crown-6 ether, acetone, 55 °C, 150 W, 1 h, 89%; ii) see Table 1, entry 8, 95%; iii) $ArB(OH)_2$ (for **11**, **12**) or $ArBr$ (for **13**, **14**), Na_2CO_3 , $Pd(PPh_3)_4$, toluene–EtOH (3:1 v/v), 90 °C, 8 h, 70% (**11**), 93% (**12**), 68% (**13**), 40% (**14**); iv) $LiAlH_4$, Et_2O , 0 to 25 °C, 1 h, 92% (**15**), 60% (**16**), 79% (**17**), 79% (**18**).

In this paper, we describe the synthesis of exemplary 2-arylfuran or -thiophene derivatives, via palladium-catalyzed coupling, starting from the corresponding electronically activated boronic acids. It is known that 2-thiophenyl- or 2-furanylboronic acids easily undergo deboronation under the basic conditions of the Suzuki–Miyaura coupling.¹⁵ Here we have developed an optimized procedure in which the degree of deboronation is negligible or absent, as attested by the good/excellent yields reported for heterobiaryls **11** and **12** (70 and 93%, respectively).

We found that the best reaction conditions were tetrakis(triphenylphosphine)palladium(0) as a catalyst in combination with the cheap base potassium carbonate; a mixture of toluene and ethanol was more effective than DMF as a reaction solvent, as attested by the higher yields, compared to those previously reported.¹³ However, when a mixture of toluene–ethanol (1:1 v/v) was employed, along with the desired product **11** (55% yield), the corresponding ethyl ester (14%) was isolated, due to the alcoholysis of the nitrile. Since the presence of an alcohol may improve water/toluene miscibility and consequently the activation of the boronic acid to boronate by the hydroxyl anion, in order to prevent the formation of the ethyl ester, the amount of ethanol was lowered (toluene–ethanol, 3:1 v/v). Under these conditions the ester was found in trace amounts and **11** was isolated in good yield (70%). By using the same coupling conditions described for **11**, the 2-furanyl derivative **12** was synthesized in excellent yield (93%) without any optimization steps.

These coupling conditions allow a variety of heterobiaryls to be obtained in good/high yields, starting from the corresponding electron-rich boronic acids, even in the presence of a base sensitive group.

Conversely, since it is known that Suzuki reactions of electron-deficient 2-heterocyclic boronates, such as 2-pyridyl, generally give low conversions,¹⁶ **13** was obtained by reacting the corresponding commercially available bromo derivative with the pinacolboronic ester **10**. Pinacol boronates are a very attractive synthon since they are air-, moisture-, temperature-, and chromatography-stable. However, for *ortho*-substituted substrates, as for **9**, the synthesis of the corresponding boronic ester provides very low yields and also requires harsh conditions, due to the steric hindrance created by the *ortho*-substituent.¹⁷ In an attempt to obtain the pinacolboronic intermediate **10** in high yields, the results published by several groups concerning the Suzuki coupling of sterically hindered substrates were investigated.^{17,18} In fact, it has been reported that the employment of a phosphine ligand might improve the borylation of *ortho*-substituted aryl halides under mild conditions.

A series of commercially available palladium-based catalysts such as tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄], tris(dibenzylideneacetone)dipalladium(0) [Pd₂(dba)₃], and palladium(II) acetate [Pd(OAc)₂] alone or in

combination with palladium ligands such as JohnPhos [1,1'-biphenyl]-2-yl-di-*tert*-butylphosphine or Cy-JohnPhos [(2-biphenyl)dicyclohexylphosphine], were considered.

In Table 1, the optimization of the borylation reaction, including solvent (Et₃N or DMF) and reaction time, is shown. The optimal reaction conditions were found to be associated with the employment of Pd(OAc)₂ and a biphenylphosphine ligand. In particular, a molar ratio of 4:1 ligand (Cy-JohnPhos) to catalyst [Pd(OAc)₂] afforded **10** with the highest yield (95%) and the lowest reaction time (2 h) (Table 1, entry 8).

Table 1 Optimization of the Borylation Reaction of 2-(2-Iodophenoxy)acetonitrile (**9**)^a

Entry	Pd catalyst	Temp (°C)	Time (h)	10 Yield (%) ^b
1	5 mol% Pd(PPh ₃) ₄	100	10	0
2	10 mol% Pd(PPh ₃) ₄	100	10	0
3	5 mol% Pd ₂ dba ₃	100	10	0
4	10 mol% Pd ₂ dba ₃	100	10	0
5	5 mol% Pd(OAc) ₂ , 10 mol% B	100	20	33
6	5 mol% Pd(OAc) ₂ , 20 mol% B	100	20	54
7	5 mol% Pd(OAc) ₂ , 10 mol% C	100	5	82
8	5 mol% Pd(OAc) ₂ , 20 mol% C	100	2	95

^a Reagents and conditions: Et₃N (4 equiv), **A** (3 equiv).

^b Isolated yields after flash chromatography.

Thus, the pinacolboronic ester **10** was allowed to react with 2-bromo- or 3-bromopyridine using the same coupling conditions described for **11**, to afford the pyridinyl derivatives **13** and **14** in good (68%) and moderate (40%) yields, respectively. The same conditions were successfully applied for the coupling of highly electronically deactivated aryl halides, such as bromopyrimidine (data not shown).

Scheme 2 Reagents and conditions: i) K_2CO_3 , KI, DMF, 160 °C, 4 h, 95%; ii) Et_3N , pinacolborane, $Pd(OAc)_2$, (2-biphenyl)dicyclohexylphosphine, 1,4-dioxane, 100 °C, 2 h, 99%; iii) $ArBr$, Na_2CO_3 , $Pd(PPh_3)_4$, toluene–EtOH (3:1, v/v), 90 °C, 8 h, 34% (**22**), 42% (**23**), 88% (**24**), 33% (**25**), 54% (**25**), 76% (**27**); iv) HCl, EtOH, 0 to 70 °C, 2 h, 82% (**28**), 72% (**29**), 77% (**30**), 78% (**31**), 83% (**32**), 99% (**33**).

Finally, the desired amines **15–18** were obtained in good/high yields (60–92%) after reduction of the nitriles **11–14** by $LiAlH_4$. Unfortunately, in the case of pyrimidinyl biaryls the use of highly reactive reducing agents, such as $LiAlH_4$, resulted in the degradation of the pyrimidine moiety.

Investigation with thiazole analogues led to similar results. This side-reaction can be explained by the low aromatic stability and/or the electron-poor nature of these rings that easily undergo reduction under the conditions required for the conversion of the nitrile to amine. An attempt to increase the chemoselectivity (i.e., by lowering the temperature to 0 °C) resulted in very low yields of the desired amine.

Thus, for the synthesis of biaryls incorporating $LiAlH_4$ -sensitive heterocycles, such as pyrimidine, thiazole, or pyrazole, a second version of the synthetic pathway was designed that involved the introduction of a masked amino group before the construction of the biaryl scaffold. In particular, the *tert*-butoxycarbonyl group (Boc) was chosen as the protecting group for the primary amine, due to its stability under the basic conditions required for the coupling and to the ease of removal (Scheme 2). Briefly, the Boc-protected amine **19**, synthesized in accordance with the literature,¹⁹ was reacted with 2-iodophenol to obtain the intermediate **20** that was quantitatively converted into the corresponding pinacolboronate derivative **21**, using the optimized conditions reported for **10** (Table 1, entry 8). The pinacolboronic ester **21** was reacted with the selected commercially available bromo derivatives under the same con-

ditions as described for **11** to provide the biaryls **22–27**. Finally, deprotection of **22–27** under acidic conditions afforded the desired amines **28–33**.

In summary, a versatile and efficient method for the synthesis of heteroaryl *ortho*-phenoxyethylamines has been described. This approach offers the opportunity to obtain a large variety of biaryls incorporating five-membered rings with one (thiophene, furan) or two (thiazole, pyrazole, imidazole) heteroatoms and six-membered (pyridine, pyrimidine) heteroaromatic cycles starting from electron-poor aryl halide or electron-rich arylboronic acids. To date, a number of new compounds have been synthesized using this procedure and currently they are under investigation in a field as important as medicinal chemistry.

Reagents, solvents, and other chemicals were used as purchased without further purification, unless otherwise specified. Air- or moisture-sensitive reactants and solvents were employed in reactions carried out under N_2 atmosphere, unless otherwise noted. Flash column chromatography purification (medium-pressure liquid chromatography) was carried out using Merck silica gel 60 (230–400 mesh, ASTM). The structures of all the isolated compounds were ensured by NMR spectra and elemental analysis (C, H, N). NMR data (^1H and ^{13}C , 1D and 2D experiments) were obtained using a DPX 400 Avance spectrometer (Bruker). Chemical shifts are expressed in δ (ppm). ^1H NMR chemical shifts are relative to TMS as an internal standard. ^{13}C NMR chemical shifts are relative to internal TMS at $\delta = 0.0$ or to the ^{13}C signal of solvent: $CDCl_3$ $\delta = 77.04$, CD_3OD $\delta = 49.8$, $DMSO-d_6$ $\delta = 39.5$. ^1H NMR data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constants, number of protons, and assignment. The elemental analysis was performed on a Carlo Erba 1106 Analyzer in the Microanalysis Laboratory of the Life Sciences Department of the Università degli Studi di Modena e Reggio Emilia and the results shown here are within $\pm 0.4\%$ of the theoretical values.

2-(2-Iodophenoxy)acetonitrile (9)

A round-bottomed flask was charged with *o*-iodophenol (2 g, 9.09 mmol), bromoacetonitrile (3.16 g, 26.0 mmol), K_2CO_3 (6.28 g, 45.0 mmol), and a catalytic amount of 18-crown-6. The reaction mixture was suspended in anhydrous acetone (35 mL) and heated in 'open-vessel' conditions under microwave irradiation at 55 °C, 150 W for 1 h. Then, the reaction mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography to provide the title compound as a colorless oil; yield: 2.114 g (8.16 mmol, 89%).

IR (neat): 1493, 1238, 1098, 1031, 780 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 4.75 (s, 2 H, CH_2), 6.80 (dt, J = 1.2, 7.7 Hz, 1 H, CH-4 Ar), 6.92 (dd, J = 1.2, 7.7 Hz, 1 H, CH-6 Ar), 7.30 (dt, J = 1.5, 7.7 Hz, 1 H, CH-5 Ar), 7.75 (dd, J = 1.5, 7.7 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.9 (CH_2), 86.7 (C-2 Ar), 113.7 (C-6 Ar), 114.6 (CN), 125.2 (C-4 Ar), 129.8 (C-5 Ar), 140.2 (C-3 Ar), 155.5 (C-1 Ar).

Anal. Calcd for C_8H_6INO : C, 37.09; H, 2.33; N, 5.41. Found: C, 37.24; H, 2.46; N, 5.56.

2-[2-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)phenoxy]acetonitrile (10)

Pinacolborane (4.93 mL, 34.0 mmol) and Et_3N (7.28 mL, 52.4 mmol) were added to a solution of **9** (3.4 g, 13.1 mmol) in anhydrous 1,4-dioxane (35 mL) under N_2 . The mixture was degassed, purged with N_2 for 10 minutes, and $Pd(OAc)_2$ (0.146 g, 0.65 mmol, 5 mol%) and (2-biphenyl)dicyclohexylphosphine (0.92 g, 2.62 mmol, 20 mol%) were added. The mixture was vigorously stirred at 100 °C under N_2 for 90 min. Then, the reaction mixture was allowed to cool to r.t. and carefully quenched with sat. aq. NH_4Cl at 0 °C. The mixture was then extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified using flash column chromatography to give the title compound as a colorless oil; yield: 3.22 g (12.4 mmol, 95%).

IR (neat): 3290 (br), 1774, 1511, 1438, 1366, 1309, 1108 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 [s, 12 H, $2 \times C(CH_3)_2$], 4.79 (s, 2 H, CH_2), 7.01 (d, J = 7.5 Hz, 1 H, CH-6 Ar), 7.13 (t, J = 7.5 Hz, 1 H, CH-4 Ar), 7.46 (t, J = 7.5 Hz, 1 H, CH-5 Ar), 7.79 (d, J = 7.5 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 [$2 \times C(CH_3)_2$], 56.0 (CH_2), 83.8 [$2 \times C(CH_3)_2$], 114.9 (CN), 115.3 (C-6 Ar), 115.6 (C-2 Ar), 123.9 (C-4 Ar), 132.8 (C-5 Ar), 137.3 (C-3 Ar), 161.6 (C-1 Ar).

Anal. Calcd for $C_{14}H_{18}BNO_3$: C, 64.90; H, 7.00; N, 5.41. Found: C, 65.11; H, 7.06; N, 5.38.

Suzuki-Coupling Reactions of **9**; General Procedure A

A 100 mL round-bottomed flask, equipped with a condenser and a magnetic stir bar, was charged with *o*-iodophenoxyacetonitrile (**9**; 1 equiv), Na_2CO_3 (2 equiv), and toluene-EtOH mixture (20 mL, 3:1 v/v). Thereafter, the corresponding commercially available arylboronic acid (1.2 equiv) was added to the resulting suspension. The mixture was degassed, purged with N_2 for 15–20 min, and then $Pd(PPh_3)_4$ (10 mol%) was added. The reaction mixture was heated at 90 °C for 8 h under stirring. The reaction mixture was allowed to cool to r.t., brine (20 mL) was added, and the mixture stirred for 30 min. The organic layer was then diluted with EtOAc, transferred to a separatory funnel, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified on silica gel to provide the title compound as an oil.

2-[2-(Thiophen-2-yl)phenoxy]acetonitrile (11)

The title compound was obtained by following General Procedure A from **9** (0.400 g, 1.54 mmol) and 2-thiophenylboronic acid (0.237 g, 1.85 mmol) as a dark oil; yield: 0.233 g (1.08 mmol, 70%).

IR (neat): 3392, 1662, 1554, 1401, 1368, 1345, 1121, 892, 840 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 4.72 (s, 2 H, CH_2), 6.98–7.06 (m, 2 H, CH-6 Ar, CH-4 Thio), 7.09 (dt, J = 1.2, 7.6 Hz, 1 H, CH-4 Ar), 7.24 (dt, J = 1.6, 7.6 Hz, 1 H, CH-5 Ar), 7.29 (dd, J = 1.1, 5.1 Hz, 1 H, CH-3 Thio), 7.37 (dd, J = 1.1, 3.7 Hz, 1 H, CH-5 Thio), 7.58 (dd, J = 1.6, 7.6 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.8 (CH_2), 114.4 (C-6 Ar), 114.9 (CN), 123.9 (C-4 Ar), 124.9 (C-2 Ar), 126.1 (C-3 Thio), 126.3 (C-5 Thio), 127.1 (C-4 Thio), 128.6 (C-5 Ar), 129.7 (C-3 Ar), 138.1 (C-1 Thio), 152.7 (C-1 Ar).

Anal. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.99; H, 4.23; N, 6.67.

2-[2-(Furan-2-yl)phenoxy]acetonitrile (12)

The title compound was obtained by following General Procedure A from **9** (0.250 g, 0.97 mmol) and 2-furanylboronic acid (0.431 g, 3.86 mmol) as a yellow oil; yield: 0.177 g (0.89 mmol, 93%).

IR (neat): 3396, 3100, 1666, 1554, 1352, 1107, 950, 811 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (s, 2 H, CH_2), 6.52 (dd, J = 1.7, 3.4 Hz, 1 H, CH-4 Fur), 6.90 (dd, J = 0.7, 3.4 Hz, 1 H, CH-3 Fur), 7.04 (dd, J = 1.3, 7.7 Hz, 1 H, CH-6 Ar), 7.18 (dt, J = 1.3, 7.7 Hz, 1 H, CH-4 Ar), 7.29 (dt, J = 1.7, 7.7 Hz, 1 H, CH-5 Ar), 7.50 (dd, J = 0.7, 1.7 Hz, 1 H, CH-5 Fur), 7.90 (dd, J = 1.7, 7.7 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.9 (CH_2), 109.8 (C-5 Fur), 111.8 (C-4 Fur), 114.5 (C-6 Ar), 114.8 (CN), 123.7 (C-4 Ar), 125.3 (C-2 Ar), 128.6 (C-5 Ar), 129.7 (C-3 Ar), 141.1 (C-3 Fur), 150.3 (C-1 Fur), 152.8 (C-1 Ar).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.43; H, 4.72; N, 7.15.

Suzuki-Coupling Reactions of Pinacolboronate Esters **10** and **21**; General Procedure B

A 100 mL round-bottomed flask, equipped with a condenser and a magnetic stir bar, was charged with the corresponding bromoheteroaryl (1 equiv), Na_2CO_3 (2 equiv) and toluene-EtOH (20 mL, 3:1 v/v). Thereafter, compound **10** or **21** (see below for the preparation of **21**) (2.0 equiv) was added to the resulting suspension. The mixture obtained was degassed, purged with N_2 for 15–20 min, and then $Pd(PPh_3)_4$ (10 mol%) was added. The reaction mixture was stirred and heated at 90 °C for 8 h. The mixture was allowed to cool to r.t., brine (20 mL) was added, and stirred for 30 min. The organic layer was then diluted with EtOAc, transferred to a separatory funnel, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified on silica gel to provide the title compound as an oil.

2-[2-(Pyridin-2-yl)phenoxy]acetonitrile (13)

The title compound was obtained by following General Procedure B from 2-bromopyridine (0.157 g, 0.99 mmol) and **10** (0.309 g, 1.98 mmol) as a colorless oil; yield: 0.141 g (0.67 mmol, 68%).

IR (neat): 3358, 3206, 1774, 1658, 1585, 1359, 1145, 854 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 4.75 (s, 2 H, CH_2), 7.11 (dd, J = 0.9, 8.2 Hz, 1 H, CH-6 Ar), 7.16–7.29 (m, 2 H, CH-4 Ar, CH-5 Pyr), 7.43 (ddd, J = 1.7, 7.4, 8.2 Hz, 1 H, CH-5 Ar), 7.51–7.82 (m, 3 H, CH-3 Ar, CH-3 and CH-4 Pyr), 8.65–8.74 (m, 1 H, CH-6 Pyr).

^{13}C NMR (100 MHz, CDCl_3): δ = 54.9 (CH_2), 114.5 (C-6 Ar), 114.8 (CN), 121.5 (C-4 Pyr), 123.7 (C-4 Ar), 124.8 (C-6 Pyr), 125.3 (C-2 Ar), 128.6 (C-5 Ar), 129.7 (C-3 Ar), 135.3 (C-5 Pyr), 149.6 (C-3 Pyr), 152.6 (C-1 Ar), 157.6 (C-1 Pyr).

Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.31; H, 4.88; N, 13.22.

2-[2-(Pyridin-3-yl)phenoxy]acetoneitrile (14)

The title compound was obtained by following General Procedure B from 3-bromopyridine (0.093 mL, 0.96 mmol) and **10** (0.30 g, 1.16 mmol) as a colorless oil; yield: 0.096 g (0.45 mmol, 40%).

IR (neat): 3375, 1663, 1637, 1559, 1394, 1349, 1127, 876, 808 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 4.71 (s, 2 H, CH_2), 7.12 (dd, J = 0.9, 8.2 Hz, 1 H, CH-6 Ar), 7.21 (dt, J = 0.9, 8.6 Hz, 1 H, CH-4 Ar), 7.30–7.52 (m, 3 H, CH-5 Pyr, CH-3 and CH-5 Ar), 7.81 (dt, J = 1.8, 7.9 Hz, 1 H, CH-4 Ar), 8.59 (d, J = 1.8, 4.9 Hz, 1 H, CH-6 Pyr), 8.72 (dd, J = 0.8, 2.3 Hz, 1 H, CH-2 Pyr).

^{13}C NMR (100 MHz, CDCl_3): δ = 54.9 (CH_2), 114.5 (C-6 Ar), 114.8 (CN), 122.8 (C-5 Pyr), 123.7 (C-4 Ar), 125.3 (C-2 Ar), 128.6 (C-5 Ar), 129.7 (C-3 Ar), 134.6 (C-1 Pyr), 136.9 (C-6 Pyr), 148.2 (C-4 Pyr), 150.2 (C-2 Pyr), 152.6 (C-1 Ar).

Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.43; H, 4.92; N, 13.39.

LiAlH_4 Reduction of Nitriles; General Procedure C

The selected nitrile derivative (1 equiv) was dissolved in of anhydrous Et_2O (1–9 mL) and added dropwise to a suspension of LiAlH_4 (3 equiv) in anhydrous Et_2O (2 mL) at 0 °C. The excess of the reducing agent was immediately and carefully quenched with H_2O and 5% aq NaOH. The reaction mixture was stirred for 15 min and then EtOAc was added. The resulting organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was used in the next synthetic step without any purification.

2-[2-(Thiophen-2-yl)phenoxy]ethanamine (15)

The title compound was obtained by following General Procedure C from **11** (0.223 g, 1.03 mmol) as a colorless oil; yield: 0.208 g (0.94 mmol, 92%).

IR (neat): 3425 (br), 3248, 3085, 1859, 1641, 1388, 1365, 1101, 813, 708 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 2.76 (br s, 2 H, NH_2), 3.16 (t, J = 5.0 Hz, 2 H, CH_2NH_2), 4.08 (t, J = 5.0 Hz, 2 H, OCH_2), 6.95 (dd, J = 1.0, 8.2 Hz, 1 H, CH-6 Ar), 7.02 (dt, J = 1.0, 7.6 Hz, 1 H, CH-4 Ar), 7.11 (dd, J = 3.7, 5.1 Hz, 1 H, CH-4 Thio), 7.23–7.30 (m, 1 H, CH-5 Ar), 7.35 (dd, J = 1.1, 5.1 Hz, 1 H, CH-5 Thio), 7.50 (dd, J = 1.1, 3.7 Hz, 1 H, CH-3 Thio), 7.69 (dd, 1 H, J = 1.7, 7.6 Hz, CH-3 Ar).

^{13}C NMR (100 MHz, CDCl_3): δ = 47.4 (CH_2NH_2), 70.6 (OCH_2), 112.5 (C-6 Ar), 121.3 (C-4 Ar), 123.2 (C-2 Ar), 124.9 (C-3 Thio), 125.5 (C-5 Thio), 126.7 (C-4 Thio), 128.4 (C-5 Ar), 128.7 (C-3 Ar), 139.2 (C-1 Thio), 154.6 (C-1).

Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NOS}$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.83; H, 6.16; N, 6.67.

2-[2-(Furan-2-yl)phenoxy]ethanamine (16)

The title compound was obtained by following General Procedure C from **12** (0.170 g, 0.85 mmol) as a yellow oil; yield: 0.103 g (0.50 mmol, 60%).

IR (neat): 3368 (br), 3251, 3146, 1859, 1667, 1354, 1093, 863, 706 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.40 (br s, 2 H, NH_2), 3.20 (t, J = 5.1 Hz, 2 H, CH_2NH_2), 4.14 (t, J = 5.1 Hz, 2 H, OCH_2), 6.50 (dd, J = 1.7, 3.2 Hz, 1 H, CH-4 Fur), 6.94 (dd, J = 0.7, 3.2 Hz, 1 H, CH-3 Fur), 6.96 (dd, J = 1.2, 8.0 Hz, 1 H, CH-6 Ar), 7.04 (dt, J = 1.2, 7.6 Hz, 1 H, CH-4 Ar), 7.24 (ddd, J = 1.7, 7.6, 8.0 Hz, 1 H, CH-5 Ar), 7.48 (dd, J = 0.7, 1.7 Hz, 1 H, CH-5 Fur), 7.87 (dd, J = 1.7, 7.6 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, CDCl_3): δ = 47.6 (CH_2NH_2), 70.7 (OCH_2), 109.9 (C-5 Fur), 111.8 (C-4 Fur), 112.7 (C-6 Ar), 120.3 (C-2 Ar), 121.2 (C-4 Ar), 128.4 (C-5 Ar), 128.6 (C-3 Ar), 141.3 (C-3 Fur), 150.4 (C-1 Fur), 154.6 (C-1).

Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.96; H, 6.53; N, 6.95.

2-[2-(Pyridin-2-yl)phenoxy]ethanamine (17)

The title compound was obtained by following General Procedure C from **13** (0.215 g, 1.02 mmol) as a yellow oil; yield: 0.195 g (0.91 mmol, 79%).

IR (neat): 3374 (br), 3236, 3171, 3101, 1853, 1781, 1625, 1390, 1153, 652 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.60 (br s, 2 H, NH_2), 3.03 (t, J = 5.2 Hz, 2 H, CH_2NH_2), 4.05 (t, J = 5.2 Hz, 2 H, OCH_2), 7.02 (dd, J = 1.0, 8.4 Hz, 1 H, CH-6 Ar), 7.10 (dt, J = 1.0, 7.6 Hz, 1 H, CH-4 Ar), 7.16–7.25 (m, 1 H, CH-5 Pyr), 7.31–7.40 (m, 1 H, CH-5 Ar), 7.62–7.83 (m, 3 H, CH-3 Ar, CH-3 and CH-4 Pyr), 8.63 (d, J = 4.6 Hz, 1 H, CH-6 Pyr).

^{13}C NMR (100 MHz, CDCl_3): δ = 52.2 (CH_2NH_2), 68.9 (OCH_2), 113.1 (C-6 Ar), 121.6 (C-4 Pyr), 121.9 (C-4 Ar), 124.9 (C-6 Pyr), 128.1 (C-2 Ar), 128.7 (C-5 Ar), 129.7 (C-3 Ar), 135.3 (C-5 Pyr), 149.3 (C-3 Pyr), 152.6 (C-1 Ar), 155.9 (C-1 Pyr).

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.85; H, 6.69; N, 13.21.

2-[2-(Pyridin-3-yl)phenoxy]ethanamine (18)

The title compound was obtained by following General Procedure C from **14** (0.199 g, 0.95 mmol) as a yellow oil; yield: 0.180 g (0.84 mmol, 79%).

IR (neat): 3372 (br), 3247, 3150, 1857, 1663, 1396, 1356, 1129, 711 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.79 (br s, 2 H, NH_2), 2.95 (t, J = 5.2 Hz, 2 H, CH_2NH_2), 3.93 (t, J = 5.2 Hz, 2 H, OCH_2), 6.93–7.06 (m, 2 H, CH-4, CH-6 Ar), 7.19–7.32 (m, 3 H, CH-5 Pyr, CH-3 and CH-5 Ar), 7.81 (dt, J = 1.8, 7.9 Hz, 1 H, CH-4 Pyr), 8.51 (dd, J = 1.8, 4.9 Hz, 1 H, CH-6 Pyr), 8.75 (dd, J = 0.9, 2.4 Hz, 1 H, CH-2 Pyr).

^{13}C NMR (100 MHz, CDCl_3): δ = 52.3 (CH_2NH_2), 68.7 (OCH_2), 113.3 (C-6 Ar), 121.9 (C-4 Ar), 122.6 (C-5 Pyr), 128.1 (C-2 Ar), 128.7 (C-5 Ar), 129.7 (C-3 Ar), 134.3 (C-1 Pyr), 136.8 (C-6 Pyr), 148.1 (C-4 Pyr), 150.1 (C-2 Pyr), 152.6 (C-1 Ar).

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.96; H, 6.74; N, 13.36.

tert-Butyl N-(2-Chloroethyl)carbamate (19)

In a round-bottomed flask, 2-chloroethylamine hydrochloride (2 g, 17.0 mmol) and Et₃N (2.37 mL, 11.0 mmol) were dissolved in anhydrous CH₂Cl₂ (24 mL). Boc₂O (3.6 mL, 15.3 mmol) was added to the resulting solution under N₂ at 0 °C. The reaction mixture was stirred at r.t. for 4 h. The mixture was then washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give the title product as a dark liquid; yield: 2.91 g (16.21 mmol, 99%), which was used directly in the next synthetic step.

IR (neat): 3347, 2924, 2854, 2361, 2342, 1725, 1709, 1503, 1462 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = ?? [s, 9 H, C(CH₃)₃], 3.36–3.48 (m, 2 H, CH₂NH), 3.49–3.63 (m, 2 H, ClCH₂), 4.93 (br s, 1 H, NHCO).

¹³C NMR (100 MHz, CDCl₃): δ = 28.2 [C(CH₃)₃], 32.8 (CH₂NH), 45.7 (CH₂Cl), 79.8 [C(CH₃)₃], 155.8 (C=O).

Anal. Calcd for C₇H₁₄ClNO₂: C, 46.80; H, 7.86; N, 7.80. Found: C, 46.91; H, 7.89; N, 7.74.

tert-Butyl [2-(2-Iodophenoxy)ethyl]carbamate (20)

Compound **19** (4.9 g, 27.27 mmol) and KI (7.55 g, 45.46 mmol) were added to a solution of *o*-iodophenol (5.0 g, 22.73 mmol) in anhydrous DMF (80 mL) in the presence of K₂CO₃ (9.43 g, 68.2 mmol). The reaction mixture was magnetically stirred and refluxed for 4 h. Then the reaction mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in EtOAc, and the EtOAc layer was washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford the title compound as a dark oil; yield: 8.34 g (22.97 mmol, 98%).

IR (neat): 3268, 1858, 1672, 1641, 1385, 1347, 1138, 1075 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.45 [s, 9 H, C(CH₃)₃], 3.59 (q, 2 H, J = 5.3 Hz, CH₂NH), 4.06 (t, J = 4.9 Hz, 2 H, OCH₂), 6.13 (br s, 1 H, NH), 6.73 (dt, J = 1.5, 7.6 Hz, 1 H, CH-4 Ar), 6.81 (dd, J = 1.5, 8.2 Hz, 1 H, CH-6 Ar), 7.29 (ddd, J = 1.5, 7.6, 8.2 Hz, 1 H, CH-5 Ar), 7.77 (dd, J = 1.5, 7.8 Hz, 1 H, CH-3 Ar).

¹³C NMR (100 MHz, CDCl₃): δ = 28.2 [C(CH₃)₃], 39.8 (CH₂NH), 68.4 (OCH₂), 79.2 [C(CH₃)₃], 86.6 (C-2 Ar), 112.3 (C-6 Ar), 122.8 (C-4 Ar), 129.4 (C-5 Ar), 139.1 (C-3 Ar), 155.7 (C-1 Ar), 156.8 (NHCO₂).

Anal. Calcd for C₁₃H₁₈INO₃: C, 42.99; H, 5.00; N, 3.86. Found: C, 43.23; H, 5.18; N, 3.96.

tert-Butyl [2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate (21)

Pinacolborane (0.387 mL, 2.66 mmol) and Et₃N (0.574 mL, 4.12 mmol) were added to a solution of **20** (0.372 g, 1.03 mmol) in anhydrous 1,4-dioxane (10 mL) under N₂. The mixture was degassed, purged with N₂ for 10 min, and Pd(OAc)₂ (0.015 g, 0.05 mmol, 5 mol%) and (2-biphenyl)dicyclohexylphosphine (0.098 g, 0.2 mmol, 20 mol%) were added. The mixture was vigorously stirred at 100 °C under N₂ for 2 h. The reaction mixture was allowed to cool to r.t., carefully quenched with sat. aq. NH₄Cl at 0 °C, and extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give the title compound as a yellow oil; yield: 0.216 g (0.59 mmol, 99%).

IR (neat): 3295 (br), 3200, 1836, 1710, 1503, 1345, 841 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.39 [s, 9 H, C(CH₃)₃], 1.47 [s, 12 H, 2 × C(CH₃)₂], 3.59 (q, J = 5.1 Hz, 2 H, CH₂NH), 4.06 (t, J = 5.1 Hz, 2 H, OCH₂), 6.18 (br s, 1 H, NH), 6.85 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 6.98 (dt, J = 0.9, 7.4 Hz, 1 H, CH-4 Ar), 7.43 (ddd, J = 1.8, 7.4, 8.3 Hz, 1 H, CH-5 Ar), 7.71 (dd, J = 1.8, 7.4 Hz, 1 H, CH-3 Ar).

¹³C NMR (100 MHz, CDCl₃): δ = 24.9 [2 × C(CH₃)₂], 28.4 [C(CH₃)₃], 39.9 (CH₂NH), 68.3 (OCH₂), 79.4 [C(CH₃)₃], 83.6 [2 × C(CH₃)₂], 114.9 (C-6 Ar), 115.7 (C-2 Ar), 123.2 (C-4 Ar), 131.8 (C-5 Ar), 138.2 (C-3 Ar), 156.7 (NHCO₂), 160.9 (C-1 Ar).

Anal. Calcd for C₁₉H₃₀BNO₃: C, 62.82; H, 8.32; N, 3.86. Found: C, 63.02; H, 8.41; N, 3.71.

tert-Butyl N-[2-[2-(Pyrimidin-2-yl)phenoxy]ethyl]carbamate (22)

The title compound was obtained by following General Procedure B from 2-bromopyrimidine (0.238 g, 1.5 mmol) and **21** (0.694 g, 1.90 mmol) as a dark oil; yield: 0.171 g, 0.54 mmol (34%).

IR (neat): 3279, 1854, 1740, 1520, 1441, 1375, 1024 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.36 [s, 9 H, C(CH₃)₃], 3.51 (t, J = 4.9 Hz, 2 H, CH₂NH), 4.25 (t, J = 4.9 Hz, 2 H, CH₂O), 5.29 (br s, 1 H, NH), 7.06 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 7.08–7.13 (m, 1 H, CH-4 Ar), 7.25 (t, J = 4.9 Hz, 1 H, CH-5 Pyrim), 7.39–7.48 (m, 1 H, CH-5 Ar), 7.82–7.91 (m, 1 H, CH-3 Ar), 8.92 (d, J = 4.9 Hz, 2 H, CH-4, CH-6 Pyrim).

¹³C NMR (100 MHz, CDCl₃): δ = 28.3 [C(CH₃)₃], 40.2 (CH₂NH), 68.1 (OCH₂), 79.7 [C(CH₃)₃], 112.3 (C-6 Ar), 118.7 (C-5 Pyrim), 121.5 (C-4 Ar), 128.1 (C-2 Ar), 129.6 (C-5 Ar), 131.3 (C-3 Ar), 154.4 (C-1 Ar), 156.9 (C-4, C-6 Pyrim), 155.9 (C=O), 165.96 (C-2 Pyrim).

Anal. Calcd for C₁₇H₂₁N₃O₃: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.62; H, 6.41; N, 13.61.

tert-Butyl N-[2-[2-(Pyrimidin-5-yl)phenoxy]ethyl]carbamate (23)

The title compound was obtained by following General Procedure B from 5-bromopyrimidine (0.238 g, 1.5 mmol) and **21** (0.694 g, 1.90 mmol) as a dark oil; yield: 0.206 g (0.65 mmol, 42%).

IR (neat): 3277 (br), 1847, 1670, 1552, 1343, 883, 686 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.42 [s, 9 H, C(CH₃)₃], 3.46 (t, J = 5.4 Hz, 2 H, CH₂NH), 4.09 (t, J = 5.2 Hz, 2 H, OCH₂), 4.72 (br s, 1 H, NH), 7.04 (dd, J = 1.2, 8.3 Hz, CH-6 Ar), 7.12 (td, J = 1.2, 7.4 Hz, 1 H, CH-4 Ar), 7.35 (dd, J = 1.8, 7.4 Hz, 1 H, CH-3 Ar), 7.42 (ddd, J = 1.8, 7.4, 8.3 Hz, 1 H, CH-5 Ar), 8.89 (s, 2 H, CH-4, CH-6 Pyrim), 9.17 (s, 1 H, CH-2 Pyrim).

¹³C NMR (100 MHz, CDCl₃): δ = 28.3 [C(CH₃)₃], 40.2 (CH₂NH), 68.3 (OCH₂), 79.9 [C(CH₃)₃], 112.3 (C-6 Ar), 121.5 (C-4 Ar), 124.4 (C-3 Ar), 130.2 (C-2 Ar), 130.6 (C-5 Ar), 132.2 (C-5 Pyrim), 154.4 (C-1 Ar), 155.9 (C=O), 156.5 (C-4, C-6 Pyrim), 156.8 (C-2 Pyrim).

Anal. Calcd for C₁₇H₂₁N₃O₃: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.60; H, 6.49; N, 13.56.

tert-Butyl N-[2-[2-(1,3-Thiazol-2-yl)phenoxy]ethyl]carbamate (24)

The title compound was obtained by following General Procedure B from 2-bromothiazole (0.060 g, 0.34 mmol) and **21** (0.174 g, 0.48 mmol) as a dark oil; yield: 0.095 g (0.30 mmol, 88%).

IR (neat): 3291, 3200, 1830, 1716, 1438, 1352, 1052, 876 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.43 [s, 9 H, C(CH₃)₃], 3.73 (t, J = 5.2 Hz, 2 H, CH₂NH), 4.27 (t, J = 5.2 Hz, 2 H, OCH₂), 5.25 (br s, 1 H, NH), 7.02 (dd, J = 1.0, 8.3 Hz, 1 H, CH-6 Ar), 7.12 (dt, J = 1.0, 7.9 Hz, 1 H, CH-4 Ar), 7.40 (ddd, J = 1.8, 7.9, 8.3 Hz, 1 H, CH-5 Ar), 7.42 (d, J = 3.4 Hz, 1 H, CH-5 Thia), 7.94 (d, J = 3.4 Hz, 1 H, CH-4 Thia), 8.40 (dd, J = 1.8, 7.9 Hz, 1 H, CH-3 Ar).

¹³C NMR (100 MHz, CDCl₃): δ = 28.6 [C(CH₃)₃], 40.3 (CH₂NH), 68.2 (OCH₂), 79.7 [C(CH₃)₃], 112.1 (C-6 Ar), 119.5 (C-5 Thia), 121.4 (C-4 Ar), 122.1 (C-2 Ar), 128.7 (C-3 Ar), 130.9 (C-5 Ar), 142.1 (C-4 Thia), 155.5 (C-1 Ar), 155.9 (C=O), 162.1 (C-2 Thia).

Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 60.12; H, 6.37; N, 8.91.

***tert*-Butyl *N*-{2-[2-(1,3-Thiazol-5-yl)phenoxy]ethyl}carbamate (25)**

The title compound was obtained by following the General Procedure B from 5-bromothiazole (0.087 g, 0.64 mmol) and **21** (0.192 g, 0.53 mmol) as a dark oil; yield: 0.057 g (0.18 mmol, 33%).

IR (neat): 3291, 1832, 1708, 1467, 1395, 1338, 880 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 3.60–3.74 (m, 2 H, CH_2NH), 4.20 (t, J = 5.0 Hz, 2 H, OCH_2), 5.04 (br s, 1 H, NH), 7.02 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 7.09 (dt, J = 1.0, 7.6 Hz, 1 H, CH-4 Ar), 7.36 (ddd, J = 1.5, 7.6, 8.3 Hz, 1 H, CH-5 Ar), 7.71 (dd, J = 1.5, 7.6 Hz, 1 H, CH-3 Ar), 8.29 (s, 1 H, CH-4 Thia), 8.85 (s, 1 H, CH-2 Thia).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 40.1 (CH_2NH), 68.1 (OCH_2), 79.8 [$C(CH_3)_3$], 112.3 (C-6 Ar), 120.2 (C-2 Ar), 121.5 (C-4 Ar), 128.8 (C-3 Ar), 129.6 (C-5 Ar), 133.8 (C-5 Thia), 140.9 (C-4 Thia), 152.9 (C-2 Thia), 154.4 (C-1 Ar), 155.9 (C=O).

Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.82; H, 6.39; N, 8.89.

***tert*-Butyl *N*-{2-[2-(1-Methyl-1*H*-pyrazol-4-yl)phenoxy]ethyl}carbamate (26)**

The title compound was obtained by following the General Procedure B from 4-bromo-1-methyl-1*H*-pyrazole (0.084 g, 0.52 mmol) and **21** (0.190 g, 0.52 mmol) as a dark oil; yield: 0.090 g (0.28 mmol, 54%).

IR (neat): 3291 (br), 1809, 1708, 1442, 1385, 893 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 3.60–3.75 (m, 2 H, CH_2NH), 4.00 (s, 3 H, NCH_3), 4.16 (t, J = 5.2 Hz, 2 H, OCH_2), 4.90 (br s, 1 H, NH), 6.96 (d, J = 7.6 Hz, 1 H, CH-6 Ar), 7.04 (dt, J = 0.9, 7.5 Hz, 1 H, CH-4 Ar), 7.17–7.26 (m, 1 H, CH-5 Ar), 7.56 (dd, J = 1.6, 7.6 Hz, 1 H, CH-3 Ar), 7.89 (s, 1 H, CH-5 Pyra), 7.90 (s, 1 H, CH-3 Pyra).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 39.0 (NCH_3), 40.3 (CH_2NH), 67.6 (OCH_2), 79.6 [$C(CH_3)_3$], 112.4 (C-6 Ar), 118.5 (C-4 Pyra), 121.4 (C-4 Ar), 121.8 (C-2 Ar), 127.3 (C-5 Ar), 127.9 (C-3 Ar), 129.4 (C-5 Pyra), 138.1 (C-3 Pyra), 154.7 (C-1 Ar), 155.9 (C=O).

Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.26; H, 7.21; N, 13.39.

***tert*-Butyl *N*-{2-[2-(1-Methyl-1*H*-imidazol-5-yl)phenoxy]ethyl}carbamate (27)**

The title compound was obtained by following the General Procedure B from 5-bromo-1-methyl-1*H*-imidazole (0.391 g, 2.44 mmol) and **21** (0.444 g, 1.22 mmol) as an oil; yield: 0.294 g (0.93 mmol, 76%).

IR (neat): 3215 (br), 1833, 1707, 1445, 1338, 1123 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 3.40 (m, 2 H, CH_2NH), 3.51 (s, 3 H, NCH_3), 4.03 (t, J = 5.2 Hz, 2 H, OCH_2), 4.84 (br s, 1 H, NH), 6.90–7.06 (m, 3 H, CH-4 and CH-6 Ar, CH-4 Imi), 7.21–7.31 (m, 1 H, CH-5 Ar), 7.33–7.42 (m, 1 H, CH-3 Ar), 7.50 (s, 1 H, CH-2 Imi).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5 [$C(CH_3)_3$], 32.4 (NCH_3), 40.4 (CH_2NH), 67.8 (OCH_2), 79.7 [$C(CH_3)_3$], 112.3 (C-6 Ar), 121.5 (C-4 Ar), 121.7 (C-2 Ar), 127.3 (C-5 Ar), 127.9 (C-3 Ar), 128.6 (C-4 Imi), 129.9 (C-5 Imi), 138.5 (C-2 Imi), 154.7 (C-1 Ar), 155.9 (C=O).

Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.45; H, 7.51; N, 13.46.

Hydrolysis of Boc Esters; General Procedure D

A 25 mL round-bottomed flask was charged with the selected NHBoc derivative (1 equiv) and EtOH (5 mL). The solution was cooled to 0 °C in an ice water bath and 1.25 M HCl in EtOH (15 equiv) solution was added dropwise. The reaction was allowed to warm to r.t. and refluxed for 2 h. The reaction was monitored by TLC (eluent: ????). The resulting suspension was cooled to r.t. and the solvent was removed under reduced pressure. The crude solid product was dissolved in H_2O and then aq 5% NaOH was added until pH 12. The resulting solution was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the corresponding pure product.

2-[2-(Pyrimidin-2-yl)phenoxy]ethanamine (28)

The title compound was obtained by following General Procedure D from **22** (0.171 g, 0.54 mmol) as a dark oil; yield: 0.092 g (0.42 mmol, 82%).

IR (neat): 3380, 1733, 1709, 1596, 1401, 1397, 985, 907, 715 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.79 (br s, 2 H), 3.00 (t, J = 4.8 Hz, 2 H, CH_2NH_2), 4.07 (t, J = 4.8 Hz, 2 H, OCH_2), 7.04 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 7.09 (td, J = 0.9, 7.5 Hz, 1 H, CH-4 Ar), 7.22 (t, J = 4.9 Hz, 1 H, CH-5 Pyrim), 7.42 (ddd, J = 1.8, 7.5, 8.3 Hz, 1 H, CH-5 Ar), 7.79 (dd, J = 1.8, 7.5 Hz, 1 H, CH-3 Ar), 8.85 (d, J = 4.9 Hz, 2 H, CH-4, CH-6 Pyrim).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.6 (CH_2NH_2), 71.3 (OCH_2), 113.7 (C-6 Ar), 118.7 (C-5 Pyrim), 121.1 (C-4 Ar), 128.6 (C-2 Ar), 131.1 (C-5 Ar), 131.7 (C-3 Ar), 156.9 (C-4, C-6 Pyrim), 157.1 (C-1 Ar), 165.96 (C-2 Pyrim).

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.90; H, 6.00; N, 19.66.

2-[2-(Pyrimidin-5-yl)phenoxy]ethanamine (29)

The title compound was obtained by following General Procedure D from **23** (0.181 g, 0.57 mmol) as a dark oil; yield: 0.089 g (0.41 mmol, 72%).

IR (neat): 3248, 3166, 1677, 1563, 1405, 1387, 899, 818 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (br s, 2 H, NH_2), 3.05 (t, J = 5.3 Hz, 2 H, CH_2NH_2), 4.04 (t, J = 5.3 Hz, 2 H, OCH_2), 7.05 (dd, J = 0.9, 8.3 Hz, 1 H, CH-6 Ar), 7.11 (td, J = 0.9, 7.5 Hz, 1 H, CH-4 Ar), 7.35 (dd, J = 1.8, 7.5 Hz, 1 H, CH-3 Ar), 7.42 (ddd, J = 1.8, 7.5, 8.3 Hz, 1 H, CH-5 Ar), 8.93 (s, 2 H, CH-4, CH-6 Pyrim), 9.17 (s, 1 H, CH-2 Pyrim).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.4 (CH_2NH_2), 70.8 (OCH_2), 112.5 (C-6 Ar), 121.6 (C-4 Ar), 123.6 (C-3 Ar), 130.4 (C-3 Ar), 130.6 (C-5 Ar), 132.2 (C-5 Pyrim), 155.9 (C-1 Ar), 156.8 (C-4, C-6 Pyrim), 156.9 (C-2 Pyrim).

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.92; H, 6.07; N, 19.59.

2-[2-(Thiazol-2-yl)phenoxy]ethanamine (30)

The title compound was obtained by following General Procedure D from **24** (0.135 g, 0.42 mmol) as a dark oil; yield: 0.072 g (0.33 mmol, 77%).

IR (neat): 3399 (br), 3233, 1665, 1397, 1099, 1063, 886, 629 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 1.73 (br s, 2 H, NH_2), 3.32 (t, J = 5.1 Hz, 2 H, CH_2NH_2), 4.28 (t, J = 5.1 Hz, 2 H, OCH_2), 7.07 (d, J = 7.9 Hz, 1 H, CH-6 Ar), 7.14 (dt, J = 1.0, 7.8 Hz, 1 H, CH-4 Ar), 7.38–7.50 (m, 2 H, CH-5 Thia, CH-5 Ar), 7.97 (d, J = 3.6 Hz, 1 H, CH-4 Thia), 8.45 (dd, J = 1.6, 7.8 Hz, 1 H, CH-3 Ar).

^{13}C NMR (100 MHz, CDCl_3): δ = 41.7 (CH_2NH_2), 71.5 (OCH_2), 112.0 (C-6 Ar), 119.5 (C-5 Thia), 121.2 (C-4 Ar), 122.2 (C-2 Ar), 128.6 (C-3 Ar), 130.7 (C-5 Ar), 141.9 (C-4 Thia), 155.4 (C-1 Ar), 162.3 (C-2 Thia).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.13; H, 5.66; N, 12.98.

2-[2-(Thiazol-5-yl)phenoxy]ethanamine (31)

The title compound was obtained by following General Procedure D from **25** (0.056 g, 0.17 mmol) as a dark oil; yield: 0.030 g (0.14 mmol, 78%).

IR (neat): 3283, 3208, 1843, 1666, 1395, 1129, 888, 874 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.58 (br s, 2 H, NH_2), 3.20 (t, J = 5.2 Hz, 2 H, CH_2NH_2), 4.14 (t, J = 5.2 Hz, 2 H, CH_2O), 7.00 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 7.04 (dt, J = 1.0, 7.5 Hz, 1 H, CH-4 Ar), 7.27–7.36 (m, 1 H, CH-5 Ar), 7.67 (dd, J = 1.6, 7.5 Hz, 1 H, CH-3 Ar), 8.27 (s, 1 H, CH-4 Thia), 8.79 (s, 1 H, CH-2 Thia).

^{13}C NMR (100 MHz, CDCl_3): δ = 41.7 (CH_2NH_2), 71.5 (OCH_2), 112.0 (C-6 Ar), 121.2 (C-4 Ar), 122.2 (C-2 Ar), 128.6 (C-3 Ar), 130.7 (C-5 Ar), 133.7 (C-5 Thia), 141.1 (C-4 Thia), 153.0 (C-2 Thia), 155.4 (C-1 Ar).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.13; H, 5.66; N, 12.98.

2-[2-(1-Methyl-1H-pyrazol-4-yl)phenoxy]ethanamine (32)

The title compound was obtained by following General Procedure D from **26** (0.117 g, 0.34 mmol) as a dark oil; yield: 0.067 g (0.31 mmol, 83%).

IR (neat): 3302, 3278, 1782, 1691, 1580, 1385, 113, 858 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.55 (br s, 2 H, NH_2), 3.17 (t, J = 4.9 Hz, 2 H, CH_2NH_2), 3.95 (s, 3 H, NCH_3), 4.10 (t, J = 4.9 Hz, 2 H, OCH_2), 6.86 (d, J = 8.1 Hz, 1 H, CH-6 Ar), 6.94 (dt, J = 1.2, 7.6 Hz, 1 H, CH-4 Ar), 7.18–7.27 (m, 1 H, CH-5 Ar), 7.51 (d, J = 7.6 Hz, 1 H, CH-3 Ar), 7.76–7.90 (m, 2 H, CH-4, CH-5 Pyra).

^{13}C NMR (100 MHz, CDCl_3): δ = 39.1 (NCH_3), 39.7 (NH_2CH_2), 67.4 (CH_2O), 112.6 (C-6 Ar), 117.9 (C-4 Pyra), 121.7 (C-2 Ar), 121.7 (C-4 Ar), 127.8 (C-5 Ar), 128.6 (C-3 Ar), 130.1 (C-5 Pyra), 137.0 (C-3 Pyra), 155.2 (C-1 Ar).

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.46; H, 7.17; N, 19.44.

2-[2-(1-Methyl-1H-imidazol-5-yl)phenoxy]ethanamine (33)

The title compound was obtained by following General Procedure D from **27** (0.294 g, 0.93 mmol) as a dark oil; yield: 0.202 g (0.92 mmol, 99%).

IR (neat): 3281, 3225, 3045, 1845, 1684, 1394, 1137, 886, 603 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.37 (br s, 2 H, NH_2), 2.98 (t, J = 5.3 Hz, 2 H, CH_2NH_2), 3.55 (s, 3 H, NCH_3), 4.00 (t, J = 5.3 Hz, 2 H, OCH_2), 6.95–7.18 (m, 3 H, CH-4 and CH-6 Ar, CH-4 Imi), 7.21–7.32 (m, 1 H, CH-5 Ar), 7.37–7.47 (m, 1 H, CH-3 Ar), 7.53 (s, 1 H, CH-2 Imi).

^{13}C NMR (100 MHz, CDCl_3): δ = 32.2 (NCH_3), 41.4 (NH_2CH_2), 70.9 (CH_2O), 112.7 (C-6 Ar), 119.4 (C-2 Ar), 121.1 (C-4 Ar), 128.7 (C-4 Imi), 129.7 (C-5 Imi), 130.2 (C-5 Ar), 132.2 (C-3 Ar), 138.3 (C-2 Imi), 156.7 (C-1 Ar).

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.31; H, 7.04; N, 19.51.

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