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 biaryl rings 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), α, adrenergic receptor 2, DNA topoisomerases 3, AMPA receptor 4, and 5-HT2A receptor 5. Moreover, Trifenagrel (6), a potent inhibitor of arachidonate-induced platelets aggregation, moPhePC 7, fluorescent pyrrolocytosine nucleobases designed for tight binding to guanine, and some 2,3- and 3,4-diharylfurans, for example, 8 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 methodologies available, the Suzuki–Miyaura reaction, one of the most popular and powerful methods for the joining of aryl–aryl and aryl–heteroaryl moieties, was chosen. 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.

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 biaryl rings 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
coupling in the case of electron-rich substrates or was converted into the corresponding pinacolboronic ester \( \text{10} \) 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 \( \text{9} \) in high yield (89%). Suzuki coupling of 2-(2-iodophenoxy)acetonitrile (\( \text{9} \)) 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 \( \text{9} \), 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, \( \text{K}_2\text{CO}_3 \), 18-crown-6 ether, acetone, 55 °C, 150 W, 1 h, 89%; ii) see Table 1, entry 8, 95%; iii) \( \text{ArB(OH)}_2 \) (for \( \text{11} \), \( \text{12} \)) or \( \text{ArBr} \) (for \( \text{13} \), \( \text{14} \)), \( \text{Na}_2\text{CO}_3 \), \( \text{Pd(PPh}_3)_4 \), toluene–EtOH (3:1 v/v), 90 °C, 8 h, 70% (11), 93% (12), 68% (13), 40% (14); iv) \( \text{LiAlH}_4 \), \( \text{Et}_2\text{O} \), 0 to 25 °C, 1 h, 92% (15), 66% (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.\textsuperscript{13} 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 combination with the expensive base potassium carbonate; a tetrakis(triphenylphosphine)palladium(0) as a catalyst in general gives low conversions,\textsuperscript{16} electron-deficient 2-heterocyclic boronates, such as 2-pyrindylboronic esters, to be obtained in good/high yields, starting from the optimized steps.

Thus, the pinacolboronic intermediate \( \text{BH} \) was obtained by the reacted 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.\textsuperscript{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.\textsuperscript{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) \( \text{[Pd(PPh\_3)\_4]} \), tris(dibenzylideneacetone)dipalladium(0) \( \text{[Pd(dba)\_2]} \), and palladium(II) acetate \( \text{[Pd(OAc)\_2]} \) alone or in combination with palladium ligands such as \( \text{Cy-JohnPhos} \) to catalyst \( \text{[Pd(OAc)\_2]} \), and a biphosphine ligand. In particular, a molar ratio of 4:1 ligand (Cy-JohnPhos) to catalyst \( \text{[Pd(OAc)\_2]} \) afforded 10 with the highest yield (95%) and the lowest reaction time (2 h) (Table 1, entry 8).

| Entry | Pd catalyst | Temp (°C) | Time (h) | Yield (%)\textsuperscript{b} of 10 |
|-------|-------------|-----------|----------|---------------------------------|
| 1     | 5 mol% Pd(PPh\_3)\_4 | 100       | 10       | 0                               |
| 2     | 10 mol% Pd(PPh\_3)\_4 | 100       | 10       | 0                               |
| 3     | 5 mol% Pd(dba)\_2 | 100       | 10       | 0                               |
| 4     | 10 mol% Pd(dba)\_2 | 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 | 20 | 95                             |

\textsuperscript{a} Reagents and conditions: Et\textsubscript{3}N (4 equiv), A (3 equiv).
\textsuperscript{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).
Finally, the desired amines 15–18 were obtained in good/high yields (60–92%) after reduction of the nitriles 11–14 by LiAlH4. Unfortunately, in the case of pyrimidinyl biaryls the use of highly reactive reducing agents, such as LiAlH4, 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 LiAlH4-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-butyloxycarbonyl 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 conditions as described for 11 to provide the biaryls 22–27. Finally, deprotection of 22–27 under acidic conditions afforded the desired amines 28–33.

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 N2 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 13C, ASTM). The structures of all the isolated compounds were ensured by NMR spectra and elemental analysis (C,H,N). NMR data (1H and 13C, 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. 13C NMR chemical shifts are relative to internal TMS at δ = 0.0 or to the 13C signal of solvent: CDCl3 δ = 77.04, CD3OD δ = 49.8, DMSO-δ6 δ = 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 ± 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), K₂CO₃ (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, CDCl₃): δ = 4.75 (s, 2 H, CH₂), 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).

13C NMR (100 MHz, CDCl₃): δ = 54.9 (CH₂), 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. Calc. for C₁₄H₁₈BNO₃: C, 64.90; H, 7.00; N, 5.41. Found: C, 65.11; H, 7.01; N, 5.43.

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, 1541, 1368, 1345, 1121, 840 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.72 (s, 2 H, CH₂), 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).

13C NMR (100 MHz, CDCl₃): δ = 54.8 (CH₂), 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. Calc. for C₂₉H₂₇NOS: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.99; H, 4.23; N, 6.67.

2-[2-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)phenoxy]acetonitrile (10)
Pinacolborane (4.93 mL, 340 mmol) and Et₃N (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 N₂. The mixture was degassed, purged with N₂ for 10 minutes, and Pd(OAc)₂ (0.146 g, 0.65 mmol, 5 mol%) and (2-biphenyldicyclohexylphosphine (0.92 g, 262 mmol, 20 mol%) were added. The mixture was vigorously stirred at 100 °C under N₂ for 90 min. 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 give the title compound as a colorless oil; yield: 1.322 g (12.4 mmol, 95%).

IR (neat): 3392, 1662, 1554, 1352, 1107, 950, 811 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.85 (s, 2 H, CH₂), 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-3 Fur), 7.90 (dd, J = 1.7, 7.7 Hz, 1 H, CH-3 Ar).

13C NMR (100 MHz, CDCl₃): δ = 54.9 (CH₂), 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. Calc. for C₂₉H₂₇NOS: C, 67.35; H, 4.55; N, 7.03. Found: C, 67.43; 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), Na₂CO₃ (2 equiv), and toluene–EtOH mixture (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 N₂ for 15–20 min, and then Pd[PPh₃]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 H₂O and brine, dried (Na₂SO₄), 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 9 (0.250 g, 0.97 mmol) and 2-furanylbromonic acid (0.431 g, 3.86 mmol) as a yellow oil; yield: 0.177 g (0.89 mmol, 93%).

IR (neat): 3358, 3206, 1774, 1658, 1585, 1359, 1145, 854 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.24 (s, 2 H, CH₂), 6.52 (dt, J = 1.7, 3.4 Hz, 1 H, CH-4 Ar), 6.90 (dd, J = 0.7, 3.4 Hz, 1 H, CH-3 Ar), 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-3 Fur), 7.90 (dd, J = 1.7, 7.7 Hz, 1 H, CH-3 Ar).

13C NMR (100 MHz, CDCl₃): δ = 54.9 (CH₂), 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. Calc. for C₂₉H₂₇NOS: C, 67.35; H, 4.55; N, 7.03. Found: C, 67.43; H, 4.72; N, 7.15.
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, 1456, 1467, 1534, 1093, 863, 706 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 6.40 (s, 2 H, NH₂), 7.03 (d, J = 1.7 Hz, 1 H, CH-3 Ar), 7.21–7.23 (m, 1 H, CH-5 Ar), 7.25 (d, J = 8.0 Hz, 1 H, CH-6 Ar), 7.30 (d, J = 1.7 Hz, 1 H, CH-5 Ar), 7.34 (d, J = 7.6 Hz, 1 H, CH-4 Ar), 7.52 (d, J = 1.7 Hz, 1 H, CH-3 Ar), 7.53 (d, J = 1.5 Hz, 1 H, CH-5 Ar), 8.05 (d, J = 1.5 Hz, 1 H, CH-6 Ar).

13C NMR (100 MHz, CDCl₃): δ = 47.1 (CH₂NH₂), 69.1 (OCH₂), 109.6 (C-5 Ar), 124.8 (C-6 Ar), 128.2 (C-5 Thio), 128.5 (C-3 Thio), 130.7 (C-2 Ar), 133.6 (C-4 Thio), 158.7 (C-3 Ar), 152.8 (C-5 Pyr), 157.6 (C-1 Ar).

Anal. Calcd for C₁₂H₁₄N₂O: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.85; H, 6.59; N, 13.12.

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): 3374 (br), 3236, 3171, 3101, 1853, 1781, 1625, 1390, 1153, 652 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.68 (t, J = 7.9 Hz, 1 H, CH-5 Ar), 7.87 (dd, J = 1.7, 3.2 Hz, 1 H, CH-4 Ar), 7.93 (d, J = 0.8 Hz, 1 H, CH-5 Thio), 8.01 (d, J = 1.7 Hz, 1 H, CH-3 Ar), 8.52 (d, J = 1.7 Hz, 1 H, CH-6 Ar), 8.59 (d, J = 1.7 Hz, 1 H, CH-4 Ar).

13C NMR (100 MHz, CDCl₃): δ = 123.7 (C-3 Thio), 128.4 (C-4 Thio), 129.5 (C-5 Thio), 130.5 (C-3 Ar), 135.1 (C-5 Pyr), 149.6 (C-3 Pyr), 152.5 (C-5 Ar), 156.3 (C-1 Ar).

Anal. Calcd for C₁₃H₁₄N₂O: C, 74.31; H, 4.88; N, 13.22.

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 compound as a dark yellow oil; yield: 2.91 g (16.21 mmol, 99%).

**Compound 19**: 1H NMR (400 MHz, CDCl₃): δ = 1.45 [s, 9 H, (CH₃)₃], 3.59 (q, 2 H, J = 5.2 Hz, 2 H, 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 (dd, 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).

**Compound 20**: 1H NMR (400 MHz, CDCl₃): δ = 28.2 [C(CH₃)₃], 39.8 (CH₂NH), 68.4 (OCH₂), 79.2 [C(CH₃)₂], 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 (NCHO). Anal. Calcd for C₂₁H₂₃N₃O₃: C, 64.74; H, 6.71; N, 13.86. Found: C, 64.62; H, 6.41; N, 13.61.

**tert-Butyl N-[2-(2-Iodophenoxy)ethyl]carbamate (21)**

Pinacolborane (0.387 mL, 2.66 mmol) and Et₃N (0.574 mL, 4.12 mmol) were added to a solution of 19 (3.372 g, 1.03 mmol) in anhydrous DME (80 mL) in the presence of K₂CO₃ (9.43 g, 68.2 mmol). 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 compound as a dark oil; yield: 0.206 g (0.65 mmol, 42%).

**Tert-Butyl N-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxo]ethyl]carbamate (22)**

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%).

**tert-Butyl N-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxo]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%).

**tert-Butyl N-[2-(1,3-Thiazol-2-yl)phenoxo]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%).

**tert-Butyl N-[2-(1,3-Thiazol-2-yl)phenoxo]ethyl]carbamate (25)**

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%).

**tert-Butyl N-[2-(Pyrimidin-2-ylphenoxo)ethyl]carbamate (26)**

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: 0.171 g, 0.54 mmol (34%).

**tert-Butyl N-[2-(Pyrimidin-5-ylphenoxo)ethyl]carbamate (27)**

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

The title compound was obtained by following 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 (18 mmol, 33%).

IR (neat): 3291, 1832, 1708, 1467, 1395, 1338, 880 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.49 [s, 9 H, C(CH₃)₃], 3.60–3.74 (m, 2 H, CH₂CH₃), 4.20 (t, J = 5.0 Hz, 2 H, OCH₂), 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, 1 H, CH-3 Ar), 8.29 (s, 1 H, CH-4 Thia), 8.85 (s, 1 H, CH-2 Thia).

13C NMR (100 MHz, CDCl₃): δ = 28.5 [C(CH₃)₃], 40.1 (CH₂NH₂), 61.8 (OCH₂), 79.8 (CH₂CH₃), 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), 140.9 (C-4 Thia), 152.9 (C-2 Thia), 154.4 (C-4 Thia), 155.9 (C=O).

Anal. Calcd for C₁₇H₂₃N₃O₃: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.55; H, 6.63; 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 re-fluxed for 2 h. The reaction was monitored by TLC (eluent: cyclohexane–EtOAc, 1:1). The resulting suspension was cooled to r.t. and the solvent was removed under reduced pressure. The crude solid product was dissolved in H₂O and thenaq 5% NaOH was added until pH 12. The resulting solution was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), 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, CDCl₃): δ = 1.79 (br s, 2 H), 3.00 (t, J = 4.8 Hz, 2 H, CH₂NH₂), 4.07 (t, J = 4.8 Hz, 2 H, OCH₂), 7.04 (d, J = 8.3 Hz, 1 H, CH-6 Ar), 7.09 (dd, 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).

13C NMR (100 MHz, CDCl₃): δ = 41.6 (CH₂NH₂), 71.3 (OCH₂), 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), 165.9 (C-2 Pyrim).

Anal. Calcd for C₁₂H₁₉N₅O: 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, 3116, 1677, 1563, 1405, 1387, 899, 818 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.50 (br s, 2 H, NH₂), 3.05 (t, J = 5.3 Hz, 2 H, CH₂NH₂), 4.04 (t, J = 5.3 Hz, 2 H, OCH₂), 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 (dd, 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).

13C NMR (100 MHz, CDCl₃): δ = 41.4 (CH₂NH₂), 70.8 (OCH₂), 112.5 (C-6 Ar), 121.6 (C-4 Ar), 123.6 (C-3 Ar), 130.4 (C-5 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 C₁₂H₁₉N₅O: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.92; H, 6.00; 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, 866, 629 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.73 (br s, 2 H, NH₂), 3.32 (t, J = 5.1 Hz, 2 H, CH₂NH₂), 4.28 (t, J = 5.1 Hz, 2 H, OCH₂), 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, CH₂Thia–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).

13C NMR (100 MHz, CDCl₃): δ = 41.7 (CH₂NH₂), 71.5 (OCH₂), 112.0 (C-6 Thia), 119.5 (C-5 Thia), 121.2 (C-4 Thia), 122.2 (C-2 Thia), 128.6 (C-3 Thia), 130.7 (C-5 Thia), 141.9 (C-4 Thia), 155.4 (C-1 Thia), 162.3 (C-2 Thia).

Anal. Calcd for C₁₂H₁₉N₅O:S: 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): 3302, 3278, 1782, 1691, 1580, 1385, 113, 858 cm⁻¹.

83%.

1H NMR (400 MHz, CDCl₃): δ = 1.58 (br s, 2 H, NH₂), 3.17 (t, J = 4.9 Hz, 2 H, CH₂O), 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).

13C NMR (100 MHz, CDCl₃): δ = 41.7 (CH₂NH₂), 71.5 (OCH₂), 112.0 (C-6 Ar), 112.1 (C-4 Ar), 121.2 (C-2 Ar), 128.6 (C-3 Ar), 130.7 (C-5 Ar), 132.2 (C-3 Ar), 138.3 (C-2 Imi), 156.7 (C-1 Ar).

Anal. Calcd for C₁₁H₁₂N₂O₂S: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.13; H, 5.66; N, 12.98.

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