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Synthesis of Heteroaryl *ortho*-phenoxyethyl amines via Suzuki cross-coupling: Easy Access to new Potential Scaffolds in Medicinal Chemistry.

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Abstract: Heteroaryl *ortho*-phenoxyethyl amines have been extensively employed in medicinal chemistry as privileged scaffolds for the design of highly potent and selective ligands. Herein we report an efficient, fast and general method for the synthesis of heteroaryl phenoxyethyl amines via Suzuki cross-coupling. 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*-phenoxyethyl amines 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, a potent inhibitor of arachidonate-induced platelets aggregation (**6**),⁷ moPhpC, a fluorescent pyrrolocytosine nucleobase designed for tight binding to guanine (**7**)⁸ and some 2,3- and 3,4-diarylfurans (**8**)⁹ with anti-implantation activity, belong to this versatile class of heteroaryl *ortho*-phenoxyethyl amines.

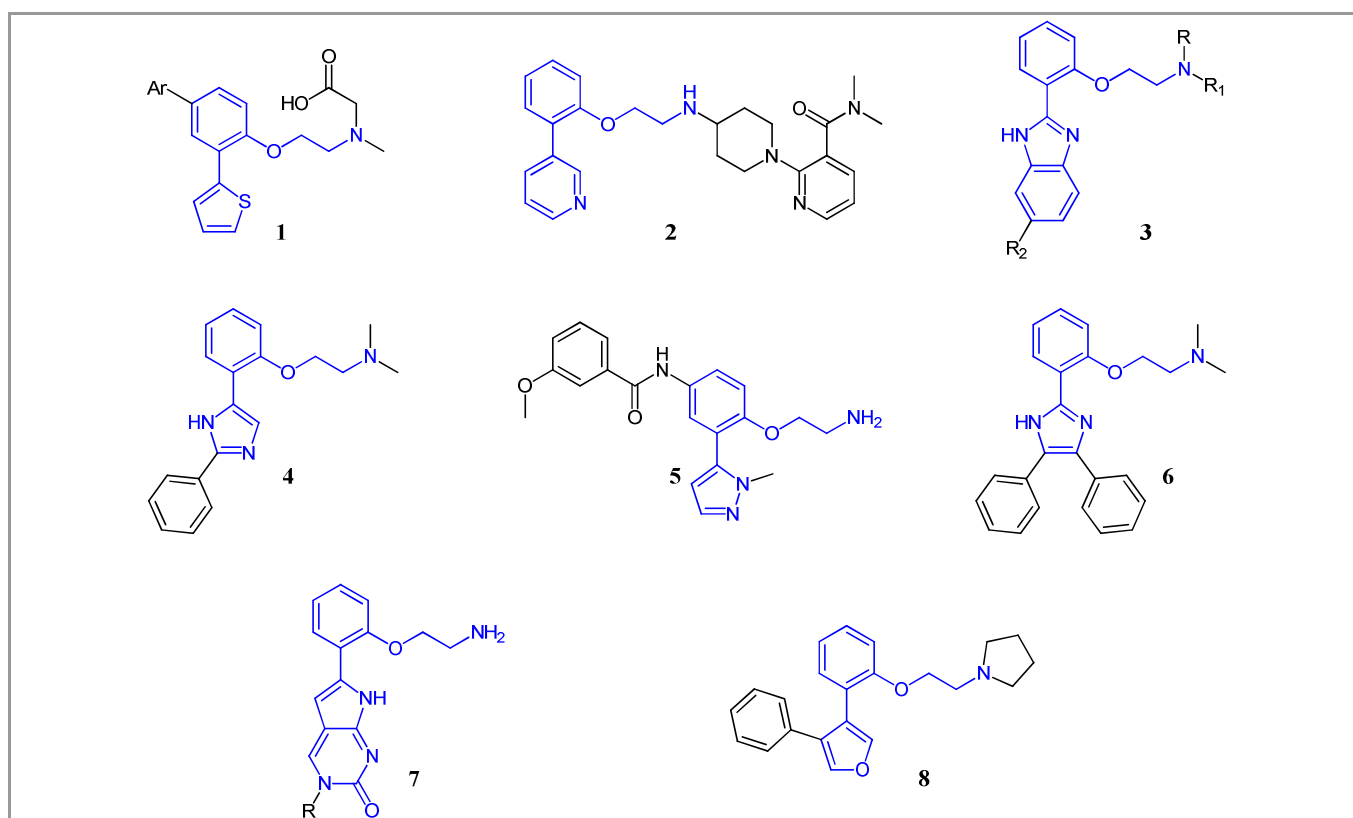


Figure 1. Structures of heteroaryl *ortho*-phenoxyethyl amines based compounds.

Despite the important role of these chemical entities in several fields of medicinal chemistry, a general method for heteroaryl *ortho*-phenoxyethyl amine 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,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 heteroaryl *ortho*-phenoxyethyl amines 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*-

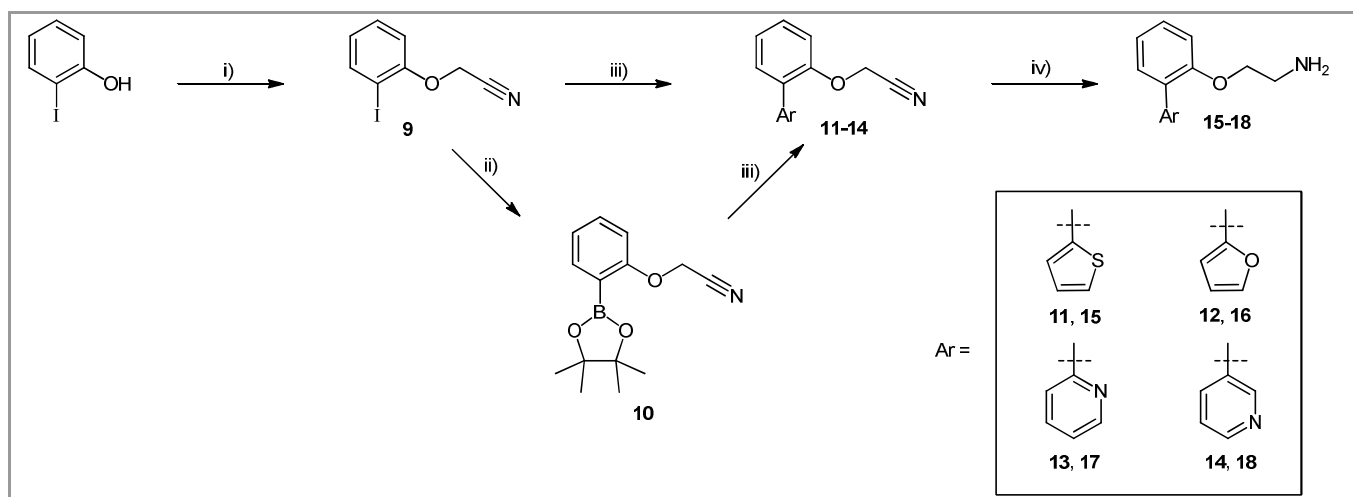
substituted substrates;

iii) the presence of LiAlH₄-sensitive heterocycles such as pyrimidine;

iv) the presence of heteroatoms such as sulphur or nitrogen that may drastically reduce the yields of some steps (i.e. reduction) due to the poisoning of the catalyst;

iv) 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 arylhalide 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 (**10**) and then coupled with the electron-poor aryl halide, as described in Scheme 1.



Scheme 1. Reagents and conditions: i) Bromoacetonitrile, K₂CO₃, 18-crown-6 ether, acetone, 55 °C, 150 W, 1 h, 89%; ii) see Table 1, entry 8, 95%; iii) ArB(OH)₂ (**11**, **12**) or ArBr (**13**, **14**), Na₂CO₃, Pd(PPh₃)₄, toluene/ethanol (3/1 v/v), 90 °C, 8 h, 70% (**11**), 93% (**12**), 68% (**13**), 40% (**14**); iv) LiAlH₄, diethyl ether, 0 °C to 25 °C, 1 h, 92% (**15**), 60% (**16**), 79% (**17**), 79% (**18**).

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

Suzuki coupling of 2-(2-iodophenoxy)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.

In this paper we describe the synthesis of exemplary 2-aryl furan 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.¹⁵ 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.

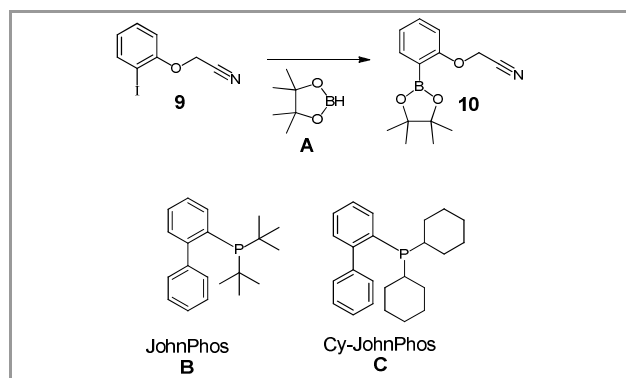
These coupling conditions allow a variety of heterobiaryls to be obtained with good/high yields, starting from the corresponding electron-rich boronic acids, even in the presence of a base sensitive group. Conversely, since it is known that Suzuki reactions of electron-deficient 2-heterocyclic boronates, 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 chromatographic-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**) with high yields we investigated the results published by several groups concerning the Suzuki coupling of sterically hindered substrates.^{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 [Pd(PPh₃)₄] palladium(0), 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)dicyclohexyl-phosphine], 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).

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 bromo-pyrimidine (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 employment of highly reactive reducing agents, such as LiAlH₄, resulted in the degradation of the pyrimidine moiety.

Table 1 Optimization of the borylation reaction of 2-(2-iodophenoxy)acetonitrile **9**.



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

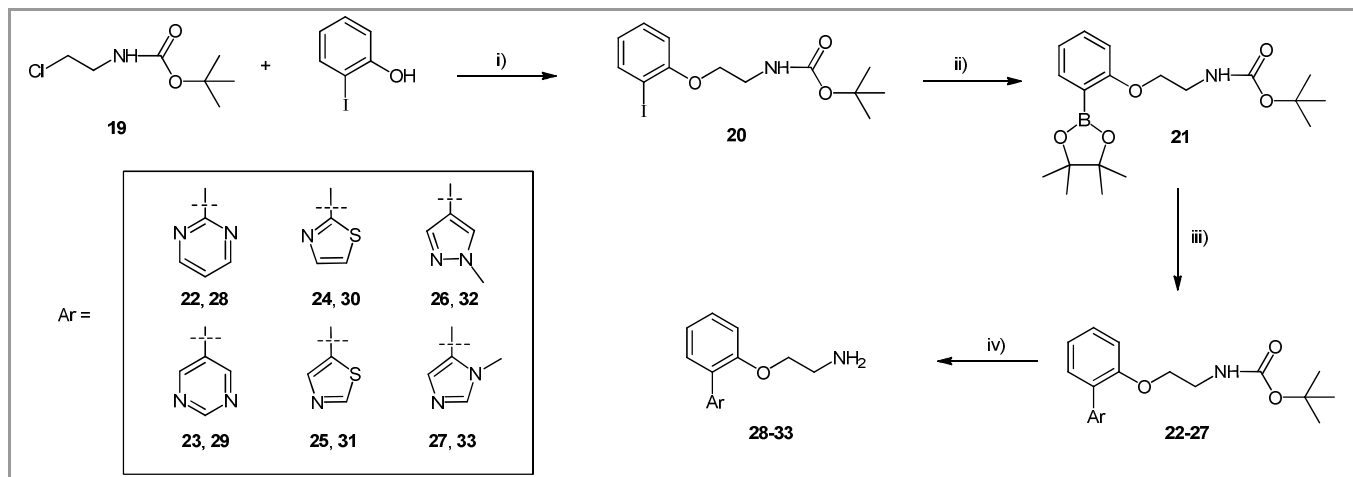
Reagents and conditions: Et₃N (4eq), **A** (3eq), ^a Isolated yields after flash chromatography.

Investigation with thiazole analogs 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. The 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, we designed a second version of the synthetic pathway 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**. In summary, a versatile and efficient method for the

synthesis of heteroaryl *ortho*-phenoxyethyl amines 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 arylhalide 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.



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/ethanol (3/1 v/v), 90 °C, 8 h, 34% (**22**), 42% (**23**), 88% (**24**), 33% (**25**), 54% (**25**), 76% (**27**); iv) HCl, EtOH, 0 °C to 70 °C, 2 h, 82% (**28**), 72% (**29**), 77% (**30**), 78% (**31**), 83% (**32**), 99% (**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 nitrogen 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 Nuclear magnetic resonance (NMR) 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 tetramethylsilane (TMS) as an internal standard. ^{13}C NMR chemical shifts are relative to internal TMS at δ 0.0 or to the ^{13}C signal of solvent: $CDCl_3$ δ 77.04, CD_3OD δ 49.8, $DMSO-d_6$ δ 39.5. NMR data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened), number of protons/carbons, coupling constants 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 bottom 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 was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography to provide the title compound (2.114 g, 8.16 mmol, 89% yield) as a colourless oil.

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

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

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

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 triethylamine (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 nitrogen. The mixture was degassed, purged with nitrogen for 10 minutes and $Pd(OAc)_2$ (0.146 g, 0.65 mmol, 5 mol%) and (2-biphenyl)dicyclohexyl-phosphine (0.92 g, 2.62 mmol, 20 mol%) was added. The mixture was vigorously stirred at 100°C, under nitrogen, for 90 minutes. Then

the reaction was allowed to cool to room temperature and carefully quenched, at 0 °C, with saturated ammonium chloride solution. Then the reaction mixture was extracted with dichloromethane and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated. The crude product was purified using flash column chromatography to give the title compound (3.22 g, 12.4 mmol, 95% yield) as a colourless oil.

IR (neat): 3290 (br), 1774, 1511, 1438, 1366, 1309, 1108 cm⁻¹

¹H-NMR (400MHz, CDCl₃) δ: 1.37 (s, 12H, 4 CH₃), 4.79 (s, 2H, CH₂), 7.01 (d, 1H, J= 7.5 Hz, CH-6 Phe), 7.13 (t, 1H, J= 7.5 Hz, CH-4 Phe), 7.46 (t, 1H, J=, 7.5 Hz, CH-5 Phe), 7.79 (d, 1H, J= 7.5 Hz, CH-3 Phe).

¹³C-NMR (100MHz, CDCl₃) δ: 24.8 (4 CH₃), 56.0 (CH₂), 83.8 (2 C(CH₃)₂), 114.9 (CN), 115.3 (C-6 Phe), 115.6 (C-2 Phe), 123.9 (C-4 Phe), 132.8 (C-5 Phe), 137.3 (C-3 Phe), 161.6 (C-1 Phe).

Anal. Calcd for C₁₄H₁₈BN₃O₃: C, 64.90; H, 7.00; N, 5.41. Found: C, 65.11; H, 7.06; N, 5.38.

General procedure A

A 100 ml round bottom flask, equipped with a condenser and a magnetic stir bar, was charged with *o*-iodophenoxyacetonitrile **9** (1 eq.), Na₂CO₃ (2 eq.) and 20 ml of toluene/ethanol (3/1 v/v). Thereafter the corresponding commercially available arylboronic acid (1.2 eq.) was added to the resulting suspension. The mixture was degassed, purged with nitrogen for 15-20 minutes and then Pd(PPh₃)₄ (10 mol%) was added. The reaction was heated at 90 °C for 8 h under stirring. Then the reaction mixture was allowed to cool to room temperature, brine (20 mL) was added and it was stirred for 30 minutes. The organic layer was then diluted with ethyl acetate, transferred to a separator funnel, washed with water and brine, dried over anhydrous 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-(Thiophen-2-yl)phenoxy]acetonitrile (11)

The title compound was obtained by following the 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 (0.233 g, 1.08 mmol, 70% yield).

IR (neat): 3392, 1662, 1554, 1401, 1368, 1345, 1121, 892, 840 cm⁻¹

¹H-NMR (400MHz, CDCl₃) δ: 4.72 (s, 2H, CH₂), 6.98-7.06 (m, 2H, CH-6 Phe, CH-4 Thio), 7.09 (dt, 1H, J=, 1.2, 7.6 Hz, CH-4 Phe), 7.24 (dt, 1H, J = 1.6, 7.6 Hz, CH-5 Phe), 7.29 (dd, 1H, J= 1.1, 5.1 Hz, CH-3 Thio), 7.37 (dd, 1H, J= 1.1, 3.7 Hz, CH-5 Thio), 7.58 (dd, 1H, J= 1.6, 7.6 Hz, CH-3 Phe).

¹³C-NMR (100MHz, CDCl₃) δ: 54.8 (CH₂), 114.4 (C-6 Phe), 114.9 (CN), 123.9 (C-4 Phe), 124.9 (C-2 Phe), 126.1 (C-3 Thio), 126.3 (C-5 Thio), 127.1 (C-4 Thio), 128.6 (C-5 Phe), 129.7 (C-3 Phe), 138.1 (C-1 Thio), 152.7 (C-1 Phe).

Anal. Calcd for C₁₂H₉NOS: 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 the 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 (0.177g, 0.89mmol, 93% yield).

IR (neat): 3396, 3100, 1666, 1554, 1352, 1107, 950, 811 cm⁻¹

¹H-NMR (400MHz, CDCl₃) δ: 4.85 (s, 2H, CH₂), 6.52 (dd, 1H, J= 1.7, 3.4 Hz, CH-4 Fur), 6.90 (dd, 1H, J =0.7, 3.4 Hz, CH-3 Fur), 7.04 (dd, 1H, J = 1.3, 7.7 Hz, CH-6 Phe), 7.18 (dt, 1H, J = 1.3, 7.7 Hz, CH-4 Phe), 7.29 (dt, 1H, J = 1.7, 7.7 Hz, CH-5 Phe), 7.50 (dd, 1H, J =0.7, 1.7 Hz, CH-5 Fur), 7.90 (dd, 1H, J = 1.7, 7.7 Hz, CH-3 Phe).

¹³C-NMR (100MHz, CDCl₃) δ: 54.9 (CH₂), 109.8 (C-5 Fur), 111.8 (C-4 Fur), 114.5 (C-6 Phe), 114.8 (CN), 123.7 (C-4 Phe), 125.3 (C-2 Phe), 128.6 (C-5 Phe), 129.7 (C-3 Phe), 141.1 (C-3 Fur), 150.3 (C-1 Fur), 152.8 (C-1 Phe).

Anal. Calcd for C₁₂H₉NO₂: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.43; H, 4.72; N, 7.15.

General procedure B

A 100 ml round bottom flask, equipped with a condenser and a magnetic stir bar, was charged with the corresponding bromoheteroaryl (1 eq), Na₂CO₃ (2eq) and 20 ml of toluene/ethanol (3/1 v/v). Thereafter compound **10** or **21** (2.0 eq) was added to the resulting suspension. The mixture obtained was degassed, purged with nitrogen for 15-20 min, and then Pd(PPh₃)₄ (10 mol%) was added. The reaction was stirred and heated at 90°C for 8 h. Then the reaction mixture was allowed to cool to room temperature, brine (20 mL) was added and it was stirred for 30 min. The organic layer was then diluted with ethyl acetate, transferred to a separator funnel, washed with water and brine, dried over anhydrous 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 the general procedure B from 2-bromopyridine (0.157 g, 0.99 mmol) and **10** (0.309 g, 1.98 mmol) as a colorless oil (0.141 g, 0.67 mmol, 68% yield).

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

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

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ : 54.9 (CH_2), 114.5 (C-6 Phe), 114.8 (CN), 121.5 (C-4 Pyr), 123.7 (C-4 Phe), 124.8 (C-6 Pyr), 125.3 (C-2 Phe), 128.6 (C-5 Phe), 129.7 (C-3 Phe), 135.3 (C-5 Pyr) 149.6 (C-3 Pyr), 152.6 (C-1 Phe) 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]acetonitrile (14)

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

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

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

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

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.

General procedure C

The selected nitrile derivative (1 eq.) was dissolved in 1-9 mL of anhydrous diethyl ether and added dropwise to a suspension of LiAlH_4 (3 eq.) in anhydrous diethyl ether (2 mL) at 0 °C. The excess of the reducing agent was immediately and carefully quenched with H_2O and 5% NaOH solution. The reaction mixture was stirred for 15 minutes and then ethyl acetate was added. The resulting organic phase was washed with brine, dried over anhydrous 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 the general procedure C from **11** (0.223 g, 1.03 mmol) as a colorless oil (0.208 g, 0.94 mmol, 92% yield).

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

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

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ : 47.4 (CH_2NH_2), 70.6 (OCH_2), 112.5 (C-6 Phe), 121.3 (C-4 Phe), 123.2 (C-2 Phe), 124.9 (C-3 Thio), 125.5 (C-5 Thio), 126.7 (C-4 Thio), 128.4 (C-5 Phe), 128.7 (C-3 Phe), 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 the general procedure C from **12** (0.170 g, 0.85 mmol) as a yellow oil (0.103 g, 0.50 mmol, 60 % yield).

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

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

$^{13}\text{C-NMR}$ (100MHz, 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 Phe), 120.3 (C-2 Phe), 121.2 (C-4 Phe), 128.4 (C-5 Phe), 128.6 (C-3 Phe), 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 the general procedure C from **13** (0.215 g, 1.02 mmol) as a yellow oil (0.195 g, 0.91 mmol, 79% yield).

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

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ : 1.60 (br s, 2H, NH_2), 3.03 (t, 2H, $J = 5.2$ Hz, CH_2NH_2), 4.05 (t, 2H, $J = 5.2$ Hz, OCH_2), 7.02 (dd, 1H, $J = 1.0, 8.4$ Hz, CH-6 Phe), 7.10 (dt, 1H, $J = 1.0, 7.6$ Hz, CH-4 Phe), 7.16-7.25 (m, 1H, CH-5 Pyr), 7.31-7.40 (m, 1H, CH-5 Phe), 7.62-7.83 (m, 3H, CH-3 Phe, CH-3, CH4 Pyr), 8.63 (d, 1H, $J = 4.6$ Hz, CH-6 Pyr).

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ : 52.2 (CH_2NH_2), 68.9 (OCH_2), 113.1 (C-6 Phe), 121.6 (C-4 Pyr), 121.9 (C-4

Phe), 124.9 (C-6 Pyr), 128.1 (C-2 Phe), 128.7 (C-5 Phe), 129.7 (C-3 Phe), 135.3 (C-5 Pyr) 149.3 (C-3 Pyr), 152.6 (C-1 Phe) 155.9 (C-1 Pyr).

Anal. Calcd for C₁₃H₁₄N₂O: 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 the general procedure C from **14** (0.199 g, 0.95 mmol) as a yellow oil (0.180 g, 0.84 mmol, 79% yield).

IR (neat): 3372 (br), 3247, 3150, 1857, 1663, 1396, 1356, 1129, 711 cm⁻¹

¹H-NMR (400MHz, CDCl₃) δ: 1.79 (br s, 2H, NH₂), 2.95 (t, 2H, J = 5.2 Hz, CH₂NH₂), 3.93 (t, 2H, J = 5.2 Hz, OCH₂), 6.93-7.06 (m, 2H, CH-4, CH-6 Phe), 7.19-7.32 (m, 3H; CH-5 Pyr, CH-3, CH-5 Phe), 7.81 (dt, 1H, J = 1.8, 7.9 Hz, CH-4 Pyr), 8.51 (dd, 1H, J = 1.8, 4.9 Hz, CH-6 Pyr), 8.75 (dd, 1H, J = 0.9, 2.4 Hz, CH-2 Pyr).

¹³C-NMR (100MHz, CDCl₃) δ: 52.3 (CH₂NH₂), 68.7 (OCH₂), 113.3 (C-6 Phe), 121.9 (C-4 Phe), 122.6 (C-5 Pyr), 128.1 (C-2 Phe), 128.7 (C-5 Phe), 129.7 (C-3 Phe), 134.3 (C-1 Pyr), 136.8 (C-6 Pyr) 148.1 (C-4 Pyr), 150.1 (C-2 Pyr), 152.6 (C-1 Phe).

Anal. Calcd for C₁₃H₁₄N₂O: 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 bottom flask 2-chloroethylamine hydrochloride (2 g, 17.0 mmol), triethylamine (2.37 mL, 11.0 mmol) were solubilized in anhydrous dichloromethane (24 mL). Boc₂O (3.6 mL, 15.3 mmol) was added to the resulting solution, under nitrogen at 0°C. The reaction was stirred at room temperature for 4 h. Then the reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title product as a dark liquid (2.91 g, 16.21 mmol, 99% yield) which was used directly in the next synthetic step.

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

¹H-NMR (400MHz, CDCl₃) δ: (s, 9H, CH₃), 3.36-3.48 (m, 2H, CH₂NH), 3.49-3.63 (m, 2H, ClCH₂), 4.93 (br s, 1H, NHCO).

¹³C-NMR (100MHz, CDCl₃) δ: 28.2 (3 CH₃), 32.8 (CH₂NH), 45.7 (CH₂Cl), 79.8 (C(CH₃)₃), 155.8 (CO)

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 (7.55g, 45.46 mmol) were added to a solution of *o*-iodophenol (5.0 g, 22.73 mmol) in dry 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 was cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was taken up with ethyl acetate, washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound as dark oil (8.34 g, 22.97 mmol, 98% yield).

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

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

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

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-dioxaborlan-2-yl)phenoxy]ethyl}carbamate (21)

Pinacolborane (0.387 mL, 2.66 mmol) and triethylamine (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 nitrogen. The mixture was degassed, purged with nitrogen for 10 minutes and Pd(OAc)₂ (0.015 g, 0.05 mmol, 5 mol%) and (2-biphenyl)dicyclohexyl-phosphine (0.098 g, 0.2 mmol, 20 mol%) were added. The mixture was vigorously stirred at 100 °C, under nitrogen, for 2 h. Then the reaction was allowed to cool to room temperature and carefully quenched, at 0 °C, with saturated ammonium chloride solution. Then the reaction mixture was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was purified by using flash column chromatography to give the title compound as a yellow oil (0.216 g, 0.59 mmol, 99 % yield).

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

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

¹³C-NMR (100MHz, CDCl₃) δ: 24.9 (4 CH₃), 28.4 (3 CH₃), 39.9 (CH₂NH), 68.3 (OCH₂), 79.4 (C(CH₃)₃), 83.6 (2 C(CH₃)₂), 114.9 (C-6 Phe), 115.7 (C-2 Phe),

123.2 (C-4 Phe), 131.8 (C-5 Phe), 138.2 (C-3 Phe), 156.7 (NHCOO), 160.9 (C-1 Phe).

Anal. Calcd for $C_{19}H_{30}BNO_5$: 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 the general procedure B from 2-bromopyrimidine (0.238 g, 1.5 mmol) and **21** (0.694 g, 1.90 mmol) as a dark oil (0.171 g, 0.54 mmol, 34% yield).

IR (neat): 3279, 1854, 1740, 1520, 1441, 1375, 1024 cm^{-1}

1H -NMR (400MHz, $CDCl_3$) δ : 1.36 (s, 9H, $C(CH_3)_3$), 3.51 (t, $J = 4.9$ Hz, 2H, CH_2NH), 4.25 (t, $J = 4.9$ Hz, 2H, CH_2O), 5.29 (br s, 1H, NH), 7.06 (d, $J = 8.3$ Hz, 1H, CH-6 Phe), 7.08-7.13 (m, 1H, CH-4 Phe), 7.25 (t, $J = 4.9$ Hz, 1H, CH-5 Pyrim), 7.39-7.48 (m, 1H, CH-5 Phe), 7.82-7.91 (m, 1H, CH-3 Phe), 8.92 (d, $J = 4.9$ Hz, 2H, CH-4, CH-6 Pyrim).

^{13}C -NMR (100MHz, $CDCl_3$) δ : 28.3 (3 CH_3), 40.2 (CH_2NH), 68.1 (OCH_2), 79.7 ($C(CH_3)_3$), 112.3 (C-6 Phe), 118.7 (C-5 Pyrim), 121.5 (C-4 Phe), 128.1 (C-2 Phe), 129.6 (C-5 Phe), 131.3 (C-3 Phe), 154.4 (C-1 Phe), 156.9 (C-4, C-6 Pyrim), 155.9 (CO), 165.96 (C-2 Pyrim).

Anal. Calcd for $C_{17}H_{21}N_3O_3$: 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 the general procedure B from 5-bromopyrimidine (0.238 g, 1.5 mmol) and **21** (0.694 g, 1.90 mmol) as a dark oil (0.206 g, 0.65 mmol, 42% yield).

IR (neat): 3277 (broad), 1847, 1670, 1552. 1343, 883, 686 cm^{-1}

1H -NMR (400MHz, $CDCl_3$) δ : 1.42 (s, 9H, $C(CH_3)_3$), 3.46 (t, $J = 5.4$ Hz, 2H, CH_2NH), 4.09 (t, $J = 5.2$ Hz, 2H, OCH_2), 4.72 (br s, 1H, NH), 7.04 (dd, $J = 1.2, 8.3$ Hz, CH-6 Phe), 7.12 (td, $J = 1.2, 7.4$ Hz, 1H, CH-4 Phe), 7.35 (dd, $J = 1.8, 7.4$ Hz, 1H, CH-3 Phe), 7.42 (ddd, $J = 1.8, 7.4, 8.3$ Hz, 1H, CH-5 Phe), 8.89 (s, 2H, CH-4, CH-6 Pyrim), 9.17 (s, 1H, CH-2 Pyrim).

^{13}C -NMR (100MHz, $CDCl_3$) δ : 28.3 (3 CH_3), 40.2 (CH_2NH), 68.3 (OCH_2), 79.9 ($C(CH_3)_3$), 112.3 (C-6 Phe), 121.5 (C-4 Phe), 124.4 (C-3 Phe), 130.2 (C-2 Phe), 130.6 (C-5 Phe), 132.2 (C-5 Pyrim), 154.4 (C-1 Phe), 155.9 (CO), 156.5 (C-4, C-6 Pyrim), 156.8 (C-2 Pyrim).

Anal. Calcd for $C_{17}H_{21}N_3O_3$: 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 the general procedure B from 2-bromothiazole (0.060 g, 0.34 mmol) and **21** (0.174 g, 0.48 mmol) as a dark oil (0.095 g, 0.30 mmol, 88% yield).

IR (neat): 3291, 3200, 1830, 1716, 1438, 1352, 1052, 876 cm^{-1}

1H -NMR (400MHz, $CDCl_3$) δ : 1.43 (s, 9H, $C(CH_3)_3$), 3.73 (t, 2H, $J = 5.2$ Hz, CH_2N), 4.27 (t, 2H, $J = 5.2$ Hz, OCH_2), 5.25 (br s, 1H, NH), 7.02 (dd, 1H, $J = 1.0, 8.3$ Hz, CH-6 Phe), 7.12 (dt, 1H, $J = 1.0, 7.9$ Hz, CH-4 Phe), 7.40 (ddd, 1H, $J = 1.8, 7.9, 8.3$ Hz, CH-5 Phe), 7.42 (d, 1H, $J = 3.4$ Hz, CH-5 Thia), 7.94 (d, 1H, $J = 3.4$ Hz, CH-4 Thia), 8.40 (dd, 1H, $J = 1.8, 7.9$ Hz, CH-3 Phe).

^{13}C -NMR (100MHz, $CDCl_3$) δ : 28.6 (3 CH_3), 40.3 (CH_2NH), 68.2 (OCH_2), 79.7 ($C(CH_3)_3$), 112.1 (C-6 Phe), 119.5 (C-5 Thia), 121.4 (C-4 Phe), 122.1 (C-2 Phe), 128.7 (C-3 Phe), 130.9 (C-5 Phe), 142.1 (C-4 Thia), 155.5 (C-1 Phe), 155.9 (CO), 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 (0.057 g, 0.18 mmol, 33% yield).

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

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

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

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-1H-pyrazol-4-yl)phenoxy]ethyl}carbamate (26)

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

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

1H -NMR (400MHz, $CDCl_3$) δ : 1.49 (s, 9H, $C(CH_3)_3$), 3.60-3.75 (m, 2H, CH_2NH), 4.00 (s, 3H, NCH_3), 4.16 (t, 2H, $J = 5.2$ Hz, OCH_2), 4.90 (br s, 1H, NH), 6.96

(d, 1H, J = 7.6 Hz, CH-6 Phe), 7.04 (dt, 1H, J = 0.9, 7.5 Hz, CH-4 Phe), 7.17-7.26 (m, 1H, CH-5 Phe), 7.56 (dd, 1H, J = 1.6, 7.6 Hz, CH-3 Phe), 7.89 (s, 1H, CH-5 Pyra), 7.90 (s, 1H, CH-3 Pyra).

¹³C-NMR (100 MHz, CDCl₃) δ: 28.4 (3 CH₃), 39.0 (N-CH₃), 40.3 (CH₂NH), 67.6 (OCH₂), 79.6 (C(CH₃)₃), 112.4 (C-6 Phe), 118.5 (C-4 Pyra), 121.4 (C-4 Phe), 121.8 (C-2 Phe), 127.3 (C-5 Phe), 127.9 (C-3 Phe), 129.4 (C-5 Pyra), 138.1 (C-3 Pyra), 154.7 (C-1 Phe), 155.9 (CO).

Anal. Calcd for C₁₇H₂₃N₃O₃: 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-1H-imidazol-5-yl)phenoxy]ethyl}carbamate (27)

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

IR (neat): 3215 (br), 1833, 1707, 1445, 1338, 1123 cm⁻¹

¹H-NMR (400 MHz, CDCl₃) δ: 1.42 (s, 9H, C(CH₃)₃), 3.40 (m, 2H, CH₂NH), 3.51 (s, 3H, NCH₃), 4.03 (t, 2H, J = 5.2 Hz, OCH₂), 4.84 (br s, 1H, NH), 6.90-7.06 (m, 3H, CH-4, CH-6 Phe, CH-4 Imi); 7.21-7.31 (m, 1H, CH-5 Phe), 7.33-7.42 (m, 1H, CH-3 Phe), 7.50 (s, 1H, CH-2 Imi).

¹³C-NMR (100 MHz, CDCl₃) δ: 28.5 (3 CH₃), 32.4 (N-CH₃), 40.4 (CH₂NH), 67.8 (OCH₂), 79.7 (C(CH₃)₃), 112.3 (C-6 Phe), 121.5 (C-4 Phe), 121.7 (C-2 Phe); 127.3 (C-5 Phe), 127.9 (C-3 Phe), 128.6 (C-4 Imi), 129.9 (C-5 Imi), 138.5 (C-2 Imi), 154.7 (C-1 Phe), 155.9 (CO).

Anal. Calcd for C₁₇H₂₃N₃O₃: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.45; H, 7.51; N, 13.46.

General procedure D

A 25 mL round bottom flask was charged with the selected NHBoc derivative (1 eq.) and 5 mL of EtOH. The solution was cooled to 0°C in an ice water bath and HCl/EtOH 1.25 M (15 eq.) solution was added dropwise. The reaction was allowed to warm to room temperature and refluxed for 2h. The reaction was monitored by TLC. The resulting suspension was cooled to room temperature and the solvent was removed under reduced pressure. The crude solid product was dissolved in H₂O and then was added 5% NaOH until pH = 12. Then the resulting solution was extracted with dichloromethane. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title pure product.

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

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

IR (neat): 3380, 1733, 1709, 1596, 1401, 1397, 985, 907, 715 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ: 1.79 (br s, 2H), 3.00 (t, J = 4.8 Hz, 2H, CH₂NH₂), 4.07 (t, J = 4.8 Hz, 2H, OCH₂), 7.04 (d, J = 8.3 Hz, 1H, CH-6 Phe), 7.09 (td, J = 0.9, 7.5 Hz, 1H, CH-4 Phe), 7.22 (t, J = 4.9 Hz, 1H, CH-5 Pyrim), 7.42 (ddd, J = 1.8, 7.5, 8.3 Hz, 1H, CH-5 Phe), 7.79 (dd, J = 1.8, 7.5 Hz, 1H, CH-3 Phe), 8.85 (d, J = 4.9 Hz, 2H, CH-4, CH-6 Pyrim).

¹³C NMR (100 MHz, CDCl₃) δ: 41.6 (CH₂NH₂), 71.3 (OCH₂), 113.7 (C-6 Phe), 118.7 (C-5 Pyrim), 121.1 (C-4 Phe), 128.6 (C-2 Phe), 131.1 (C-5 Phe), 131.7 (C-3 Phe), 156.9 (C-4, C-6 Pyrim), 157.1 (C-1 Phe), 165.96 (C-2 Pyrim).

Anal. Calcd for C₁₂H₁₃N₃O: 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 the general procedure D from **23** (0.181 g, 0.57 mmol) as a dark oil (0.089 g, 0.41 mmol, 72% yield).

IR (neat): 3248, 3166, 1677, 1563, 1405, 1387, 899, 818 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ: 1.50 (br s, 2H, NH₂), 3.05 (t, J = 5.3 Hz, 2H, CH₂NH₂), 4.04 (t, J = 5.3 Hz, 2H, OCH₂), 7.05 (dd, J = 0.9, 8.3 Hz, 1H, CH-6 Phe), 7.11 (td, J = 0.9, 7.5 Hz, 1H, CH-4 Phe), 7.35 (dd, J = 1.8, 7.5 Hz, 1H, CH-3 Phe), 7.42 (ddd, J = 1.8, 7.5, 8.3 Hz, 1H, CH-5 Phe), 8.93 (s, 2H, CH-4, CH-6 Pyrim), 9.17 (s, 1H, CH-2 Pyrim).

¹³C-NMR (100 MHz, CDCl₃) δ: 41.4 (CH₂NH₂), 70.8 (OCH₂), 112.5 (C-6 Phe), 121.6 (C-4 Phe), 123.6 (C-3 Phe), 130.4 (C-3 Phe), 130.6 (C-5 Phe), 132.2 (C-5 Pyrim.), 155.9 (C-1 Phe), 156.8 (C-4, C-6 Pyrim), 156.9 (C-2 Pyrim).

Anal. Calcd for C₁₂H₁₃N₃O: 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 the general procedure D from **24** (0.135 g, 0.42 mmol) as a dark oil (0.072 g, 0.33 mmol, 77% yield).

IR (neat): 3399 (broad), 3233, 1665, 1397, 1099, 1063, 886, 629 cm⁻¹

¹H-NMR (400 MHz, CDCl₃) δ: 1.73 (br s, 2H, NH₂), 3.32 (t, 2H, J = 5.1 Hz, CH₂NH₂), 4.28 (t, 2H, J = 5.1 Hz, OCH₂), 7.07 (d, 1H, J = 7.9 Hz, CH-6 Phe), 7.14 (dt, 1H, J = 1.0, 7.8 Hz, CH-4 Phe), 7.38-7.50 (m, 2H, CH-5 Thia, CH-5 Phe), 7.97 (d, 1H, J = 3.6 Hz, CH-4 Thia), 8.45 (dd, 1H, J = 1.6, 7.8 Hz, CH-3 Phe).

¹³C-NMR (100 MHz, CDCl₃) δ: 41.7 (CH₂NH₂), 71.5 (OCH₂), 112.0 (C-6 Phe), 119.5 (C-5 Thia), 121.2 (C-

4 Phe), 122.2 (C-2 Phe), 128.6 (C-3 Phe), 130.7 (C-5 Phe), 141.9 (C-4 Thia), 155.4 (C-1 Phe), 162.3 (C-2 Thia).

Anal. Calcd for $C_{11}H_{12}N_2OS$: 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 the general procedure D from **25** (0.056 g, 0.17 mmol) as a dark oil (0.030 g, 0.14 mmol, 78 % yield).

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

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

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

Anal. Calcd for $C_{11}H_{12}N_2OS$: 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 the general procedure D from **26** (0.117 g, 0.34 mmol) as a dark oil (0.067 g, 0.31 mmol, 83 % yield).

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

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

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

Anal. Calcd for $C_{12}H_{15}N_3O$: 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 the general procedure D from **27** (0.294 g, 0.93 mmol) as a dark oil (0.202 g, 0.92 mmol, 99 % yield).

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

1H -NMR (400MHz, $CDCl_3$) δ : 1.37 (br s, 2H, NH_2), 2.98 (t, 2H, $J = 5.3$ Hz, CH_2NH), 3.55 (s, 3H, NCH_3), 4.00 (t, 2H, $J = 5.3$ Hz, OCH_2), 6.95-7.18 (m, 3H, CH-4, CH-6 Phe, CH-4 Imi), 7.21-7.32 (m, 1H, CH-5 Phe), 7.37-7.47 (m, 1H, CH-3 Phe), 7.53 (s, 1H, CH-2 Imi).

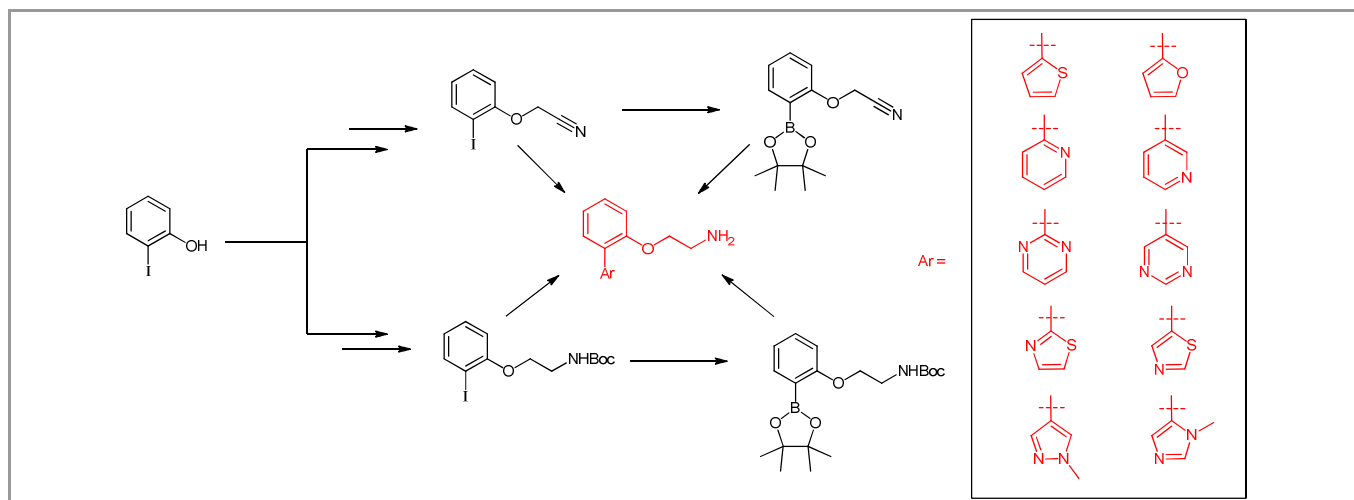
^{13}C -NMR (100MHz, $CDCl_3$) δ : 32.2 (NCH_3), 41.4 (NH_2CH_2), 70.9 (CH_2O), 112.7 (C-6 Phe), 119.4 (C-2 Phe), 121.1 (C-4 Phe), 128.7 (C-4 Imi), 129.7 (C-5 Imi), 130.2 (C-5 Phe), 132.2 (C-3 Phe), 138.3 (C-2 Imi), 156.7 (C-1 Phe).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.31; H, 7.04; N, 19.51.

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