Discovery of novel inhibitors to investigate diacylglycerol lipases and α/β hydrolase domain 16A

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CHAPTER 4

α-Keto heterocycles as highly selective and drug-like *sn*-1 diacylglycerol lipase α inhibitors*

Introduction

Sn-1 diacylglycerol lipase (DAGL) inhibitors have been utilized to study the role of the endocannabinoid 2-arachidonoylglycerol (2-AG) in several (patho)physiological processes. Perturbation of 2-AG biosynthesis reduces cannabinoid receptors (CB1R and CB2R) signaling and decreases eicosanoid formation in a tissue dependent manner. As such, disruption of DAGL activity has shown potential therapeutic benefits in the treatment of obesity & metabolic syndrome,[1,2] diabetes,[3] constipation,[4] nicotine addiction,[5] pathological pain,[6] and (neuro)inflammation.[7–9]

The reversible α-ketoheterocycle LEI104 (**1**) has been discovered as a selective inhibitor for DAGLα (Chapter 2).[10] Detailed structure-activity relationship (SAR) studies on LEI104 (**1**) provided highly valuable information for the structural requirements for DAGLα inhibition (Chapter 3).[11] Using this information, a homology model was validated which led to the discovery of LEI105 (**2**), a potent and selective DAGLα and DAGLβ inhibitor (see Table 1).[12] Introduction of the *p*-tolyl substituent of LEI105 (**2**) was crucial for obtaining selectivity over fatty acid amide hydrolase (FAAH) and increased potency 6 fold compared to LEI104.[12] On the other hand, lipophilicity increased almost 250 fold (Table 1). Lipophilicity is reported as one of the most important parameters to control during lead optimization.[13] High lipophilicity is associated with solubility issues, increased aspecific binding (to unwanted off-targets), human ether-a-go-go-related potassium channel protein (hERG) channel affinity,[14,15] toxicity by promoting cellular phospholipidosis[16] and increased cytochrome P450 (CYP) liability.[17] Hence, the sub-optimal drug-like properties of LEI105 hamper its widespread use as a drug candidate.

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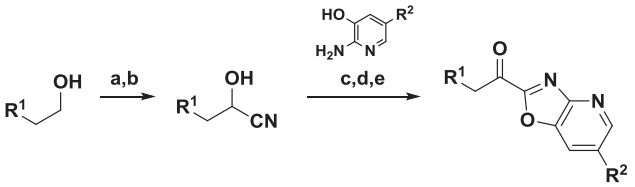
As such, lipophilic efficiency (LipE, which is calculated by pIC_{50} - cLogP) is an important objective in lead generation and optimization programmes.[13] Typically LipE of 5 or greater is required for drug candidates.[13] Here, an optimization of LEI105 is reported, by combined activity-based protein profiling (ABPP) and LipE guided structure-based design. The identification of a highly efficient C2 acyl spacer, followed by careful selection of the most selective and efficient substituted heterocyclic scaffold led to the discovery of LEI107 (**16**), a highly selective DAGLα inhibitor with drug-like properties.

Results

LEI105 (**2**) showed a marked decrease in LipE 2.1, versus 3.4 for LEI104 (Table 1), hence an optimization program on LEI105 was initiated in order to reduce lipophilicity while maintaining potency. The LEI105 derivatives were synthesized according to previously reported procedures.[10–12] In brief, an alcohol precursor (usually commercially available) was oxidized by Swern oxidation (Scheme 1a) to the corresponding aldehyde and treated with potassium cyanide (b) to yield the cyanohydrin as key intermediate. The cyanohydrin was converted to the corresponding Pinner salt using dry acidic conditions in EtOH (c), followed by reflux with a corresponding aminohydroxypyridine, in EtOH with pyridine (d). The obtained alcohol was oxidized to the ketone by Dess-Martin Periodinane (DMP) oxidation (e).



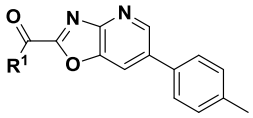
Scheme 1. General synthetic approach towards LEI105 derivatives **3**-**18**. **a)** DMSO, $(COCl)_2$, DCM, Et_3N, -78°C. **b)** KCN, THF/H_2O, rt. **c)** AcCl, EtOH, 0°C to rt. **d)** Corresponding aminohydroxypyridine, EtOH, Pyr., 80°C. **e)** DMP, DCM, rt.

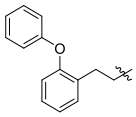
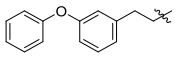
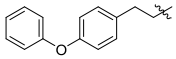
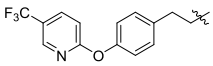
Optimization of the 2-acyl substituent

During the investigation of the SAR of LEI104, longer spacers length increased potency, but not necessarily LipE (Chapter 3).[11] Therefore the effect of LEI105 spacer length was systematically reduced. Compounds **4,** containing a C3 methylene spacer is 2.5 times more efficient than LEI105. To gain activity while reducing lipophilicity, incorporation of an electron withdrawing trifluoromethyl (CF_3) spacer was envisioned. To test this hypothesis, **7** and **8** were synthesized. Water free nitrilation of commercially available 3,3,3-trifluoropropanol followed by the standard synthesis procedures of Scheme 1 yielded **7**. The synthesis of cyanohydrin precursor of **8** was optimized through a TEMPO NaOCl oxidation from commercially available 4,4,4-trifluorobutanol (DMP oxidation was very low yielding, other oxidants were uniformly unsuccessful). Room temperature evaporation of the corresponding aldehyde *in vacuo* followed by direct nitrilation and additional steps (Scheme

1c-e) yielded **8**. Compound **7** appeared unstable, whereas compound **8** showed tremendous improvement in overall LipE and displayed no stability issues upon workup. The lack of stability of **7** could be explained by the CF_3 being positioned too close to the ketone warhead. Conformational restriction was investigated with derivatives **9**-**12**, as such biphenylethers were incorporated to mimic the natural substrate fatty acid chains. The alcohol precursors of **9**-**12** were not commercially available and were synthesized in three steps from the corresponding fluorobenzaldehyde by nucleophilic aromatic substitution with phenol, followed by Wittig-Horner olefination and lithium aluminium hydride (LAH) reduction to the corresponding alcohol (see Experimental). Subsequently, the 5-step general synthesis (Scheme 1) yielded **9**-**12**. Biphenylethers **9**-**11** had significantly decreased LipE, whereas compound **6** showed minor LipE improvement (LipE = 2.42).

Table 1. Optimization of the 2-acyl substituent derivatives **3**-**12**.



Entry	Structure	DAGLα (pIC_{50} ± SEM)	cLogP	LipE
1 (LEI104)[10,12]	-	7.43 ± 0.05	4.07	3.36
2 (LEI105)[12]	-$C_5H_{10}Ph$	8.52 ± 0.06	6.46	2.06
3	-C_4H_8Ph	7.84 ± 0.04	5.93	1.91
4	-C_3H_4Ph	7.86 ± 0.08	5.40	2.46
5	-C_2H_4Ph	7.22 ± 0.11	5.02	2.20
6	-C_1H_2Ph	6.31 ± 0.09	4.69	1.62
7	-$C_1H_2CF_3$	5.76 ± 0.07	3.21	2.55
8	-$C_2H_4CF_3$	7.83 ± 0.07	3.69	4.14
9		8.02 ± 0.08	7.12	0.90
10		8.43 ± 0.08	7.12	1.31
11		8.29 ± 0.08	7.12	1.17
12		9.07 ± 0.06	6.65	2.42

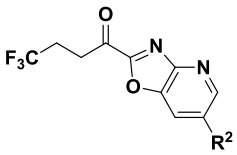
Optimization of the heterocyclic scaffold

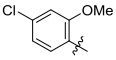
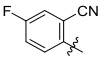
Previously, the oxazolopyridine scaffold was found most optimal (Chapter 3), therefore the effect of the scaffold substituent pattern was investigated. As a starting point, compound **8** was selected due to its highest LipE. Electron donating and withdrawing substituents, methoxy and cyano functionalities were introduced in compounds **13**, **14** and **15** to assess the electronic effects of the phenyl ring and simultaneously decrease inhibitor lipophilicity. Of note, the *p*-chloro substituted aminohydroxypyridine precursor of **13** was obtained through a HBr/AcOH deprotection from its corresponding benzyl protected precursor (standard Pd/H_2 hydrogenation conditions consistently resulted in a loss of the chlorine substituent). Compound **14** showed a thousand-fold increase in LipE compared to LEI105 (**2**). To increase metabolic stability, the *p*-methyl group of **8** was replaced with *p*-fluoro (**16**), *p*-chloro (**17**), *p*,*m*-dioxymethylene (**18**). Assessment of these compounds in the colorimetric activity assay shows that compound **16** is most potent (pIC_{50} = 8.59 ± 0.04) in this study and displays the highest LipE (5.25).

Natural substrate DAGLα activity assay

To assess if the inhibitors were able to block conversion of the natural substrate of DAGLα, all compounds were measured in a previously reported 96-well plate DAGLα natural substrate activity (N = 2, n = 2).[18] In brief, the assay is based on the conversion of 1-stearoyl-2-arachidonoyl-*sn*-glycerol (SAG) by HEK293T cell membrane fractions overexpressing hDAGLα. The formation of 2-AG from SAG is coupled via glycerol formation to a fluorescent readout using an additional 4 enzyme cascade.[18] In this assay, the 2-acyl trifluoromethyl spacer (**8**) was equally potent compared to the original spacer of LEI105 (**2**, Table 2). Compounds **16** and **17** were highly potent and inhibited the conversion of SAG to 2-AG by DAGLα *in vitro* with pIC_{50} values of 7.92 ± 0.10 and 8.11 ± 0.07 respectively (Table 2)

Table 2. Optimization of the heterocyclic scaffold. *LEI105 was measured on ABPP in a 5 point 5 fold dilution array, whereas all other compounds were measured in the general 10 fold dilution used in other biochemical activity assays (colorimetric PNP and SAG). Colorimetric PNP assay N = 2, n = 2. ABPP, N = 3. ****16** is measured N = 1.



Entry	Structure	DAGLα (pIC_{50} ± SEM)			cLogP	LipE
		PNP	SAG	ABPP		
2 (LEI105)	-	8.52 ± 0.06	7.9 ± 0.1	7.5 ± 0.1*	6.46	2.06
8		7.83 ± 0.07	8.01 ± 0.13	7.0 ± 0.1	3.69	4.14
13		8.41 ± 0.05	7.96 ± 0.12	7.1 ± 0.1	3.44	4.97
14		7.79 ± 0.03	7.06 ± 0.15	6.5 ± 0.1	2.63	5.16
15		7.61 ± 0.06	N.D.	N.D.	2.78	4.83
16 (LEI107)		8.59 ± 0.04	7.92 ± 0.10**	7.2 ± 0.1	3.34	5.25
17		8.57 ± 0.07	8.11 ± 0.07	7.1 ± 0.1	3.91	4.66
18		8.16 ± 0.04	7.66 ± 0.14	6.5 ± 0.1	3.23	4.56

Activity-based protein profiling

Introduction of the *p*-tolyl substituent in LEI105 was shown to be crucial for obtaining selectivity over FAAH.[12] To determine if compounds **16** and **17** are selective over FAAH, and other enzymes involved in the endocannabinoid system, **16** and **17** were measured in mouse brain membrane homogenate using two broad-spectrum probes MB064 and TAMRA-FP, as previously reported (N = 3).[10,12,19] Both compounds **16** and **17** displayed a highly selective profile, as no significant reduction of other bands than DAGLα and DAGLα* was observed in this ABPP setting. Of note, compound **16** was screened at a concentration of 100 µM on broad-spectrum probe TAMRA-FP, showing no observable off-target activity. Consequently, compound **16** has a selectivity window of >1000 over off-targets of broad-spectrum serine hydrolase probe TAMRA-FP, including endocannabinoid system related ABHD6, ABHD12, monoacylglycerol lipase (MAGL) and FAAH as assessed by in-gel fluorescence scanning. Chemoproteomics might be applied to further investigate this highly selective profile. Due to combination of high potency, selectivity and LipE, compound **16** was named LEI107.

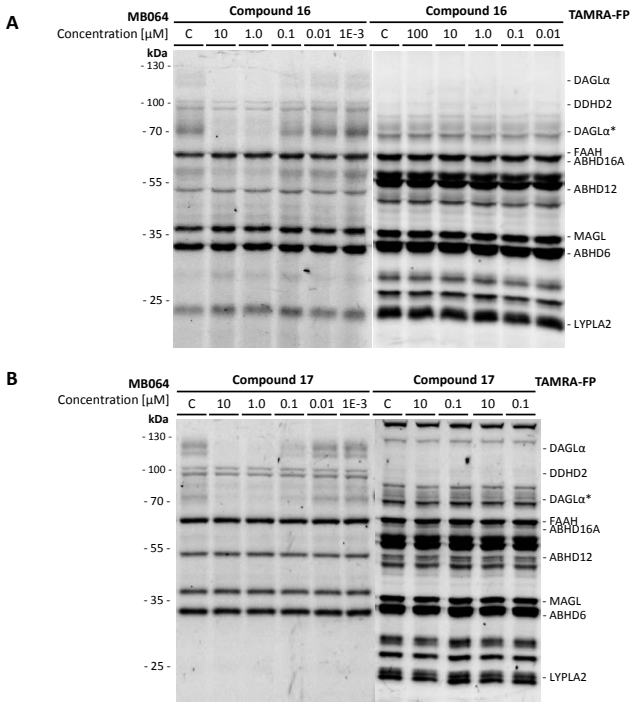


Figure 1. **A)** Characterization of compound **16** on ABPP with probes MB064 (left) and TAMRA-FP (right). pIC_{50} DAGLα* of **16** = 7.2 ± 0.1 (N = 3). Compound **16** shows no reduction of probe labeling on ABHD6 and others at 10 μM inhibitor concentration using MB064, and on FAAH labeling and others at 100 μM inhibitor concentration using TAMRA-FP (N = 3). Of note, left panel DAGLα < DAGLα*, the exact mechanism for DAGLα* formation is unknown to date but absence of DAGLα* is also observed in DAGLα KO mice.[11] **B)** Characterization of compound **17** on ABPP with probes MB064 (left) and TAMRA-FP (right). pIC_{50} DAGLα of **17** = 7.1 ± 0.1 (N = 3). Compound **17** shows no effect on ABHD6 and FAAH (and any other protein tested) at 10 μM concentration (N = 3).

Conclusions

To conclude, the sub-optimal lipophilicity of LEI105 was improved by LipE guided structure-based design in combination with ABPP. First, optimization of the 2-acyl substituent led to a potent trifluorobutanoyl spacer with significantly improved LipE. Second, investigation of the heterocyclic scaffold showed that a *p*-fluorophenyl substituent was optimal, yielding LEI107 (**16**), an α-keto heterocycle with drug-like properties and high potency in a DAGLα natural substrate activity assay. Projecting forward, it is important to test whether LEI107 is a dual inhibitor of DAGLα and DAGLβ.[12] Due to its optimized physicochemical properties, LEI107 can now be fully characterized on early absorption, distribution, metabolism and extraction (ADME) properties. Moreover, both *in vivo* stability and CYP liability are also important. LEI107 can be a highly important inhibitor for studying the role of the 2-AG perturbation in many pathophysiological conditions including (mouse models of) obesity, Alzheimer's and Parkinson's disease.[20] Important to keep in mind, possible hemiacetal formation can occur at

the ketone. Therefore, its consequences with regard to *in vivo* stability need to be investigated. Due to the covalent reversible binding mode of α-keto heterocycles, LEI107 could shed light on whether a therapeutic window for DAGL inhibition can be established, with regard to possible CNS mediated side-effects.

Experimental

Experimental procedures biochemistry

Cloning procedures

Cloning procedures were performed as previously reported.[12] In brief, full-length human hDAGL-α cDNA was purchased from Biosource and cloned into mammalian expression vector pcDNA3.1, containing genes for ampicillin and neomycin resistance. The empty vector was used as a negative control (mock). All plasmids were grown in XL-10 Z-competent cells and prepped (Maxi Prep, Qiagen). The sequences were confirmed by sequence analysis at the Leiden Genome Technology Centre.

Cell culture and membrane preparation

Cell culture and membrane preperations were performed as previously reported.[12] In brief, HEK293T cells were grown in DMEM with stable glutamine and phenol red (PAA) with 10% new born calf serum, penicillin, and streptomycin. Cells were passaged every 2−3 days by resuspension in medium and seeding to the appropriate confluence. Membranes were prepared from transiently transfected HEK293T cells. 24 Hours prior to transfection, 10^7 cells were seeded in a 15 cm Petri dish. Cells were transfected by the addition of a 3:1 mixture of polyethyleneimine (60 μg) and plasmid DNA (20 μg) in 2 mL of serum free medium. The medium was refreshed after 24 h, and after 72 h the cells were harvested by suspending them in 20 mL of medium. The supernatant was removed by centrifuge for 10 min at 1000 rpm. The cell pellet quickly frozen in liquid nitrogen and stored at −80 °C until use. Cell pellets were thawed on ice and suspended in lysis buffer A (20 mM HEPES, pH 7.2, 2 mM DTT, 0.25 M sucrose, 1 mM $MgCl_2$, 1× cocktail (Roche cOmplete EDTA free), 25 U/mL Benzonase). The suspension was homogenized by polytrone (3 × 7 s) and incubated for 30 min on ice. The membrane fraction was separated by ultracentrifuge (100.000g, 30 min, 4 °C, Beckman Coulter, type Ti70 rotor) and the pellet was resuspended in lysis buffer B (20 mM HEPES, pH 7.2, 2 mM DTT, 1× cocktail (Roche cOmplete EDTA free)). The protein concentration was determined with Qubit protein assay (Invitrogen). The total protein concentration was diluted to 1 mg/mL and the samples were quickly frozen in liquid nitrogen and stored in small aliquots at −80 °C until use.

Biochemical hDAGLα activity assay

The biochemical hDAGL-α activity assay was performed as previously reported.[12] In brief, the biochemical hDAGL-α activity assay is based on the hydrolysis of *para*-nitrophenylbutyrate (PNP-butyrate) by membrane preparations from HEK293T cells transiently transfected with hDAGL-α. Reactions (200 μL) were performed in a flat bottom Greiner 96-wells plates, 50 mM HEPES pH 7.2 buffer with 0.05 μg/μL (final protein concentration) hDAGL-α transfected membrane fractions.

Biochemical hDAGLα natural substrate assay

The natural substrate assay for DAGLα was performed as previously reported.[18]

Biochemical ABPP assay

The biochemical ABPP assay on mouse brain proteome was performed as previously reported.[10,12]

Experimental procedures chemistry

General Remarks

All reactions were performed using oven- or flame-dried glassware and dry solvents. Reagents were purchased from Sigma-Aldrich, Acros, and Merck and used without further purification unless noted otherwise. All

moisture sensitive reactions were performed under an argon atmosphere. Traces of water were removed from starting compounds by co-evaporation with toluene. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 MHz spectrometer at 400.2 (^{1}H) and 100.6 (^{13}C) MHz using the reported deuterated solvent. Chemical shift values are reported in ppm with tetramethylsilane or solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C; CD_3OD: δ 3.31 for 1H, δ 49.00 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, quintet = quint, b = broad, m = multiplet), coupling constants J (*Hz*), and integration. High resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap XL. Compound purity (>95% unless stated otherwise) was measured by liquid chromatography on a Finnigan Surveyor LC-MS system, equipped with a C18 column. Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230−400 mesh). TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H_2O (500 mL), and H_2SO_4 (25 mL)) or a $KMnO_4$ stain (K_2CO_3 (40 g), $KMnO_4$ (6 g), and H_2O (600 mL)).

2-Hydroxy-7-phenylheptanenitrile (19)

The title compound was synthesized from commercially available 6-phenylhexan-1-ol (1.70 g, 9.51 mmol) to yield 2-hydroxy-7-phenylheptanenitrile (1.67 g, 8.22 mmol, 86% over 2 steps) using previously reported procedures. Spectroscopic data are in agreement with those previously reported.[10]

1-(6-(*p*-Tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-6-phenylhexan-1-ol (20)

The title compound was synthesized from 2-hydroxy-7-phenylheptanenitrile (**19**) as previously reported. Spectroscopic data are in agreement with those previously reported.[12]

1-(6-(*p*-Tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-6-phenylhexan-1-one (2)

The title compound was synthesized from 1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-6-phenylhexan-1-ol (**20**) by DMP oxidation as previously reported. Spectroscopic data are in agreement with those previously reported.[12]

2-Hydroxy-6-phenylhexanenitrile (21)

The title compound was synthesized from commercially available 5-phenylpentan-1-ol according to the previously reported procedures.[10,11]

5-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)pentan-1-ol (22)

The title compound was synthesized from 2-hydroxy-6-phenylhexanenitrile (**21**, 88 mg, 0.47 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (62 mg, 0.31 mmol) according to procedure described for compound **20**. This yielded 5-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)pentan-1-ol (21 mg, 0.056 mmol, 18 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 1.9 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.33 – 7.28 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.10 (m, 3H), 5.04 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.71 (bs, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.17 – 1.97 (m, 2H), 1.77 – 1.49 (m, 4H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 171.26, 153.96, 145.68, 143.58, 142.40, 138.45, 134.77, 134.63, 130.09(2C), 128.50(2C), 128.41(2C), 127.50(2C), 125.84, 116.87, 68.27, 35.85, 35.46, 31.27, 24.75, 21.29.

5-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)pentan-1-one (3)

The title compound was synthesized from 5-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)pentan-1-ol (**22**, 20 mg, 0.054 mmol) according to procedure described for compound 1. This yielded 5-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)pentan-1-one (19 mg, 0.051 mmol, 95%). HRMS (ESI+) m/z: calculated for $C_{24}H_{23}N_2O_2$ ([M + H]), 371.1754; found, 371.1754. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (s, 1H), 8.09 (s, 1H), 7.56 – 7.51 (m, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.23 – 7.14 (m, 3H), 3.32 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* =

7.5 Hz, 2H), 2.44 (s, 3H), 1.94 – 1.83 (m, 2H), 1.84 – 1.71 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 190.23, 158.72, 153.13, 153.11, 148.22, 148.10, 142.07, 139.15, 134.13, 130.25(2C), 128.55(2C), 128.49(2C), 127.66(2C), 125.96, 117.80, 39.73, 35.75, 30.96, 23.63, 21.36. Purity of 80% as determined by LC-MS.

2-Hydroxy-5-phenylpentanenitrile (23)

The title compound was synthesized as previously reported.[11]

4-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (24)

The title compound was synthesized from 2-hydroxy-5-phenylpentanenitrile (**23**, 108 mg, 0.62 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (87 mg, 0.44 mmol) according to procedure described for compound **20**. This yielded 4-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (20 mg, 0.056 mmol, 13%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.32 – 7.22 (m, 4H), 7.20 – 7.11 (m, 3H), 5.05 (dd, *J* = 7.6, 5.1 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.18 – 1.97 (m, 2H), 1.95 – 1.79 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 171.20, 153.92, 145.66, 143.58, 141.83, 138.46, 134.80, 134.60, 130.09(2C), 128.54(2C), 128.48(2C), 127.51(2C), 126.02, 116.91, 68.20, 35.57, 35.07, 26.77, 21.29.

4-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-one (4)

The title compound was synthesized from 4-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (**24**, 19 mg, 0.053 mmol) according to procedure described for compound **2**. This yielded 4-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-one (6 mg, 0.017 mmol, 32%). HRMS (ESI+) m/z: calculated for $C_{23}H_{21}N_2O_2$ ([M + H]), 357.1598; found, 357.1597. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (d, *J* = 1.3 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.37 – 7.27 (m, 4H), 7.25 – 7.14 (m, 3H), 3.31 (t, *J* = 7.4 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 2.26 – 2.10 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 190.07, 158.70, 153.11, 148.30, 144.21, 141.25, 139.16, 137.68, 134.10, 130.26(2C), 128.67(2C), 128.61(2C), 127.66(2C), 126.26, 117.85, 39.24, 35.17, 25.51, 21.35. Purity of 95% as determined by LC-MS.

2-Hydroxy-4-phenylbutanenitrile (25)

The title compound was synthesized as previously reported.[11]

3-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (26)

The title compound was synthesized from 2-hydroxy-4-phenylbutanenitrile (**25**, 114 mg, 0.71 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (84 mg, 0.42 mmol) according to procedure described for compound **20**. This yielded 3-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (24 mg, 0.071 mmol, 17%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.32 – 7.28 (m, 2H), 7.27 – 7.21 (m, 4H), 7.19 – 7.13 (m, 1H), 5.04 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.75 (bs, 1H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.42 (s, 3H), 2.40 – 2.28 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 171.12, 153.90, 145.67, 143.60, 140.86, 138.48, 134.83, 134.60, 130.10(2C), 128.71(2C), 128.59(2C), 127.51(2C), 126.22, 116.88, 67.46, 36.96, 31.16, 21.29.

3-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (5)

The title compound was synthesized from 3-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (**26**, 23 mg, 0.067 mmol) according to procedure described for compound **2**. This yielded 3-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (15 mg, 0.044 mmol, 65%). HRMS (ESI+) m/z: calculated for $C_{22}H_{19}N_2O_2$ ([M + H]), 343.1441; found, 343.1441. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.36 – 7.27 (m, 4H), 7.27 – 7.17 (m, 1H), 3.64 (t, *J* = 7.4 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.44 (s, 3H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 189.30, 158.63, 153.06, 148.33, 144.26, 140.16, 139.18, 137.74, 134.06, 130.26(2C), 128.74(2C), 128.60(2C), 127.65(2C), 126.54, 117.88, 41.40, 29.77, 21.35. Purity of 92% as determined by LC-MS.

2-Hydroxy-3-phenylpropanenitrile (27)

The title compound was synthesized from commercially available 2-phenylacetaldehyde (1.27 g, 10.53 mmol) according to the previously reported procedure.[1] This yielded 2-hydroxy-3-phenylpropanenitrile (610 mg, 4.14 mmol, 39%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.24 (m, 5H), 4.62 (t, *J* = 6.5 Hz, 1H), 3.10 (d, *J* = 6.5 Hz, 2H), 2.88 (bs, 1H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): 133.92, 129.82(2C), 129.05(2C), 127.97, 119.44, 62.27, 41.45.

2-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)ethan-1-ol (28)

The title compound was synthesized from 2-hydroxy-3-phenylpropanenitrile (**27**, 112 mg, 0.76 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (93 mg, 0.46 mmol) according to procedure described for compound **20**. This yielded 2-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)ethan-1-ol (29 mg, 0.087 mmol, 19%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.36 – 7.19 (m, 7H), 5.26 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.42 (dd, J = 13.9, 5.0 Hz, 1H), 3.30 (dd, J = 13.9, 7.8 Hz, 1H), 2.43 (s, 3H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 170.24, 153.92, 145.76, 143.52, 138.47, 136.07, 134.85, 134.58, 130.09(2C), 129.65(2C), 128.76(2C), 127.51(2C), 127.22, 116.89, 69.28, 41.90, 29.82.

2-Phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)ethan-1-one (6)

The title compound was synthesized from 2-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)ethan-1-ol (**28**, 20 mg, 0.061 mmol) according to procedure described for compound **2**. This yielded 2-phenyl-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)ethan-1-one (12 mg, 0.037 mmol, 60%). HRMS (ESI+) m/z: calculated for $C_{21}H_{17}N_2O_2$ ([M + H]), 329.1285; found, 329.1283. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 7.40 – 7.27 (m, 5H), 4.57 (s, 2H), 2.44 (s, 4H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 187.23, 158.63, 153.11, 148.41, 144.51, 139.20, 137.82, 134.07, 132.47, 130.26(2C), 130.15(2C), 129.37, 128.97(2C), 127.66(2C), 117.88, 46.19, 21.35. Purity of >95% as determined by LC-MS (44:56 enol/ketone).

4,4,4-Trifluoro-2-hydroxybutanenitrile (29)

The title compound was synthesized from commercially available 3,3,3-trifluoropropanol (1 g, 8.92 mmol) according to previously reported nitrilation procedures with only THF as solvent.[1] This yielded 4,4,4-trifluoro-2-hydroxybutanenitrile (137 mg, 0.99 mmol, 10%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.14 (bs, 1H), 4.82 (t, *J* = 6.6 Hz, 1H), 2.77 – 2.65 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 124.47 (q, *J* = 277.0 Hz), 120.34, 39.15 (q, *J* = 29.3 Hz), 36.57 (q, *J* = 3.0 Hz).

3,3,3-Trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (30)

The title compound was synthesized from 4,4,4-trifluoro-2-hydroxybutanenitrile (**29**, 130 mg, 0.94 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (120 mg, 0.60 mmol) according to procedure described for compound **20**. This yielded 3,3,3-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (7 mg, 0.022 mmol, 4%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.31 (dd, *J* = 8.7, 4.3 Hz, 1H), 2.41 (s, 3H), 2.36 – 2.15 (m, 2H). ^{13}C BBDEC NMR (MeOD, 101 MHz): δ 161.67, 146.19, 145.29, 139.73, 136.79, 135.50, 131.00(2C), 128.48(2C), 124.17 (q, *J* = 269.7 Hz), 118.76, 61.54, 39.55 (q, *J* = 30.3 Hz), 37.53 (q, *J* = 4.04 Hz), 21.16.

3,3,3-Trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (7)

The title compound was synthesized from 3,3,3-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (**30**, 7 mg, 0.022 mmol) according to procedure described for compound **2**. This yielded 3,3,3-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (3 mg, 9.4 µmol, 43%). HRMS (ESI+) m/z: calculated for $C_{16}H_{14}F_3N_2O_3$ ([M + H_3O]), 339.0951; found, 339.0949. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.06 (bs, 1H), 8.15 (bs, 1H), 7.59 – 7.51 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 4.19 (q, *J* = 9.8 Hz, 2H), 2.45 (s, 3H).^{13}C BBDEC NMR ($CDCl_3$, 101

MHz): δ 179.36 (q, *J* = 2.7 Hz), 173.18, 157.74, 157.73, 139.41, 133.75, 130.26(2C), 127.62(2C), 127.43, 123.31 (q, *J* = 277.8 Hz), 117.84, 117.82, 42.89 (q, *J* = 29.9 Hz), 21.30. **Final compound not stable.**

5,5,5-Trifluoro-2-hydroxypentanenitrile (31)

To a vigorously stirred solution of commercially available 4,4,4-trifluorobutanol (5.0 g, 39 mmol) in CH_2Cl_2 (100 mL) was added KBr (485 mg, 4.08 mmol), TEMPO (30 mg, 0.005 mmol) and a solution of NaOCl (59 mmol) in 10% sat. $NaHCO_3$ (aq). After complete conversion (2 h), the organic layer was separated and the aquous layer was extracted 2x with 50 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, after which THF (100 mL) was added. CH_2Cl_2 was evaporated at rt, 300 mbar, whereafter nitrilation was performed as previously reported.[1] The product was purified by flash chromatography (Et_2O/ pentane) and evaporated at rt to obtain 5,5,5-trifluoro-2-hydroxypentanenitrile (3.53 g, 23.1 mmol, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.62 (t, *J* = 6.1 Hz, 1H), 2.93 (bs, 1H), 2.46 – 2.28 (m, 2H), 2.17 – 2.09 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 126.57 (q, *J* = 275.9 Hz), 118.93, 59.63, 29.20 (q, *J* = 30.1 Hz), 27.91 (q, *J* = 3.1 Hz).

4,4,4-Trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (32)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 117 mg, 0,76 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (85 mg, 0.42 mmol) according to procedure described for compound **20**. This yielded 4,4,4-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (6 mg, 0.017 mmol, 4%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 1.9 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.36 – 7.29 (m, 2H), 5.13 (dd, *J* = 8.0, 3.8 Hz, 1H), 3.79 (bs, 1H), 2.43 (s, 3H), 2.41 – 2.23 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 169.81, 153.65, 146.04, 143.74, 138.63, 135.20, 134.48, 130.15(2C), 127.54(2C), 127.1 (q, *J* = 276.7 Hz), 117.04, 66.67, 29.66 (q, *J* = 30.3 Hz), 27.82 (q, *J* = 3.0 Hz), 21.30.

4,4,4-Trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-one (8)

The title compound was synthesized from 4,4,4-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (**32,** 6 mg, 0.017 mmol) according to procedure described for compound **2**. This yielded 4,4,4-trifluoro-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-one (4 mg, 0.012 mmol, 70%). HRMS (ESI+) m/z: calculated for $C_{17}H_{14}F_3N_2O_2$ ([M + H]), 335.1002; found, 335.1003. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.01 (d, *J* = 2.1 Hz, 1H), 8.12 (d, *J* = 2.1 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.60 (t, *J* = 7.6 Hz, 2H), 2.76 – 2.61 (m, 2H), 2.45 (s, 3H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 186.61, 158.08, 152.80, 148.68, 141.98, 139.34, 138.11, 131.98, 130.31(2C), 127.68(2C), 126.69 (q, *J* = 277.8 Hz), 117.95, 32.76 (q, *J* = 3.0 Hz), 28.03 (q, *J* = 30.5 Hz), 21.36. Purity of >95% as determined by LC-MS.

2-Phenoxybenzaldehyde (33)

K_2CO_3 (22 g, 159 mmol) was added to a stirred solution of phenol (7.60 g, 81 mmol) in THF (100 mL) at reflux. After 1 h 2-fluorobenzaldehyde (8.49 mL, 101 mmol) was added and the reaction mixture was refluxed for an additional 24 h. Upon completion the mixture was cooled to rt and concentrated *in vacuo*. Saturated $NaHCO_3$ (100 mL) was added and product was extracted using EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried, *concentrated in vacuo* and purified by flash chromatography to yield 2-phenoxybenzaldehyde (8.05 g, 40,6 mmol, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.52 (s, 1H), 7.94 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.43 – 7.36 (m, 2H), 7.22 – 7.15 (m, 2H), 7.10 – 7.04 (m, 2H), 6.90 (d, *J* = 8.4, 1H).

Methyl 3-(2-phenoxyphenyl)acrylate (34)

n-BuLi (30.6 ml, 76 mmol) was added dropwise over 10 minutes to a cooled solution (-80 °C) of methyl 2-(dimethoxyphosphoryl)acetate (11.04 mL, 76 mmol) in THF (100 mL) and the resulting mixture was stirred for 1 h. 2-Phenoxybenzaldehyde (**33**, 7.57 g, 38.2 mmol) was added and the reaction mixture was slowly warmed to rt and stirred overnight. Upon completion the mixture was concentrated *in vacuo*, saturated $NaHCO_3$ (80 mL)

was added and product was extracted using EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* and purified by flash chromatography to yield methyl 3-(2-phenoxyphenyl)acrylate (6.6 g, 26.0 mmol, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 16.2 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.39 –6.81 (m, 8H), 6.57 (d, *J* = 16.2, 1H), 3.79 (s, 3H).

3-(2-Phenoxyphenyl)propan-1-ol (35)

Lithium aluminum hydride (22,71 ml, 54,5 mmol) was added to a stirred and cooled solution (0 °C) of methyl 3-(2-phenoxyphenyl)acrylate (**34**, 6.6 g, 26,0 mmol) in THF (100 mL) over 10 minutes. The reaction mixture was stirred for 2 hours and upon completion the mixture was concentrated *in vacuo*, saturated $NaHCO_3$ (80 mL) was added and product was extracted using EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* and purified by flash chromatography to yield 3-(2-phenoxyphenyl)propan-1-ol (1.3 g, 5.69 mmol, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.26 (m, 3H), 7.17 (td, *J* = 7.7, 1.8 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.96 – 6.91 (m, 2H), 6.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.94 – 1.82 (m, 2H), 1.76 (bs, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.82, 154.69, 133.25, 130.87, 129.87(2C), 127.56, 124.13, 122.89, 119.56, 117.89(2C), 62.21, 33.20, 26.31.

2-Hydroxy-4-(2-phenoxyphenyl)butanenitrile (36)

The title compound was synthesized from 3-(2-phenoxyphenyl)propan-1-ol (**35**, 1.3 g, 5.69 mmol) according to the previously reported 2 step procedure.[1] This yielded 2-hydroxy-4-(2-phenoxyphenyl)butanenitrile (727.9 mg, 2.87 mmol, 50%, 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.30 (m, 2H), 7.27 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.21 (td, *J* = 7.8, 1.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.96 – 6.93 (m, 2H), 6.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.42 (q, *J* = 6.3 Hz, 1H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.28 – 2.07 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.32, 154.88, 131.03, 130.89, 130.00(2C), 128.35, 124.22, 123.32, 119.84, 119.41, 118.13(2C), 60.67, 35.67, 25.61.

3-(2-Phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (37)

The title compound was synthesized from 2-hydroxy-4-(2-phenoxyphenyl)butanenitrile (**36**, 144.6 mg, 0.571 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (84.6 mg, 0.422 mmol) according to the procedure described for compound **20**. This yielded 3-(2-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (35.9 mg, 0.082 mmol, 19%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.33 – 7.27 (m, 5H), 7.17 – 7.11 (m, 1H), 7.07 – 7.01 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.02 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.49 (bs, 1H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H), 2.40 – 2.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.93, 170.90, 157.63, 154.80, 153.94, 145.65, 143.55, 138.42, 134.67, 132.18, 131.12, 130.08(2C), 129.85(2C), 127.84, 127.50(2C), 124.06, 122.94, 119.44, 118.00(2C), 116.79, 67.61, 35.70, 25.81, 21.30.

3-(2-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (9)

The title compound was synthesized from 3-(2-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (**37**, 24.1 mg, 0.055 mmol) according to the procedure described for compound **2**. This yielded 3-(2-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (13.7 mg, 0.032 mmol, 57%). HRMS (ESI+) m/z: calculated for $C_{28}H_{23}N_2O_3$ ([M + H]), 435.1703; found, 435.1699. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.96 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.38 – 7.27 (m, 5H), 7.21 – 7.14 (m, 1H), 7.10 – 7.02 (m, 2H), 6.99 – 6.93 (m, 2H), 6.89 – 6.83 (m, 1H), 3.65 (t, *J* = 7.4 Hz, 2H), 3.20 (t, *J* = 7.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 189.42, 158.62, 157.38, 155.05, 153.11, 148.24, 144.14, 139.12, 137.57, 134.10, 131.31, 130.92(2C), 130.24(2C), 129.87, 128.11, 127.64(2C), 123.89, 123.10, 119.03, 118.34(2C), 117.79, 40.23, 24.89, 21.35. Purity of >95% as determined by LC-MS.

Methyl 3-(3-phenoxyphenyl)acrylate (38)

The title compound was synthesized from commercially available 3-phenoxybenzaldehyde (3.0 ml, 17,36 mmol) according to the procedure described for compound **34**. This yielded methyl 3-(3-phenoxyphenyl)acrylate (4,53 g, 17,81 mmol, 103%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, *J* = 16.0 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.08 – 7.01 (m, 1H), 6.99 – 6.90 (m, 3H), 6.36 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.34, 157.37, 156.33, 143.48, 135.83, 129.72, 129.47(2C), 123.21, 122.53, 119.95, 118.65(2C), 118.21, 117.51, 51.01.

3-(3-Phenoxyphenyl)propan-1-ol (39)

The title compound was synthesized from methyl 3-(3-phenoxyphenyl)acrylate (**38**, 4.50 g, 17.70 mmol) according to the procedure described for compound **35**. This yielded 3-(3-phenoxyphenyl)propan-1-ol (3.15 g, 13.80 mmol, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.28 (m, 2H), 7.28 – 7.21 (m, 1H), 7.12 – 7.06 (m, 1H), 7.03 – 6.97 (m, 2H), 6.96 – 6.92 (m, 1H), 6.89 – 6.80 (m, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.56 (bs, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.43, 157.40, 144.06, 129.85(2C), 129.75, 123.51, 123.28, 119.04, 118.96(2C), 116.47, 62.33, 34.17, 32.09.

2-Hydroxy-4-(3-phenoxyphenyl)butanenitrile (40)

The title compound was synthesized from 3-(3-phenoxyphenyl)propan-1-ol (**39**, 3.1 g, 13.58 mmol) according to the procedure described for compound **19**. This yielded 2-hydroxy-4-(3-phenoxyphenyl)butanenitrile (2.10 g, 8.29 mmol, 61% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.14 – 7.09 (m, 1H), 7.02 – 6.98 (m, 2H), 6.94 (dt, *J* = 7.6, 1.3 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.43 (t, J = 6.3 Hz, 1H), 3.03 (bs, 1H), 2.88 – 2.72 (m, 2H), 2.24 – 2.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.72, 157.09, 141.78, 130.11, 129.92(2C), 123.53, 123.40, 119.87, 119.08(2C), 118.90, 116.96, 60.42, 36.54, 30.63.

3-(3-Phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (41)

The title compound was synthesized from 2-hydroxy-4-(3-phenoxyphenyl)butanenitrile (**40**, 184.1 mg, 0.727 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (91.3 mg, 0.456 mmol) according to the procedure described for compound **20**. This yielded 3-(3-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (41.9 mg, 0.096 mmol, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (d, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 1.9 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.24 (m, 4H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 – 6.90 (m, 4H), 6.79 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.07 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.36 (bs, 1H), 2.90 – 2.81 (m, 2H), 2.41 (s, 3H), 2.38 – 2.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.27, 157.38, 157.26, 153.75, 145.55, 143.53, 143.05, 138.44, 134.79, 134.49, 130.06(2C), 129.82(2C), 129.78, 127.48(2C), 123.65, 123.26, 119.16, 118.92(2C), 116.91, 116.58, 67.34, 36.74, 31.09, 21.28.

3-(3-Phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (10)

The title compound was synthesized from 3-(3-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (**41**, 24.1 mg, 0.055 mmol) according to the procedure described for compound **2**. This yielded 3-(3-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (13.7 mg, 0.032 mmol, 57%). HRMS (ESI+) m/z: calculated for $C_{28}H_{23}N_2O_3$ ([M + H]), 435.1703; found, 435.1701. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.38 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 7.13 – 7.06 (m, 1H), 7.05 – 6.98 (m, 3H), 6.94 (t, *J* = 2.0 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): 189.11, 158.54, 157.58, 157.19, 153.03, 148.39, 144.24, 142.17, 139.18, 137.74, 134.04, 130.26(2C), 130.00, 129.87(2C), 127.65(2C), 123.41, 123.38, 119.07(2C), 118.98, 117.85, 116.91, 41.17, 29.58, 21.36. Purity of >95% as determined by LC-MS.

Methyl 3-(4-phenoxyphenyl)acrylate (42)

The title compound was synthesized from commercially available 4-phenoxybenzaldehyde (0.88 mL, 5.05 mmol) according to the procedure described for compound **34**. This yielded methyl 3-(4-phenoxyphenyl)acrylate (1.14 g, 4.50 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.37 – 7.31 (m, 2H), 7.17 – 7.10 (m, 1H), 7.05 – 6.99 (m, 2H), 6.98 – 6.91 (m, 2H), 6.33 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.45, 159.46, 156.06, 144.05, 129.90(2C), 129.73(2C), 129.08, 124.08, 119.64(2C), 118.33(2C), 116.39, 51.56.

3-(4-Phenoxyphenyl)propan-1-ol (43)

Catalytic Pd/C was added to a solution of methyl 3-(4-phenoxyphenyl)acrylate (**42**, 1.14 g, 4.48 mmol) in MeOH (50 mL) and the mixture was stirred under H_2 (g) for 6 days. Upon completion the mixture was concentrated *in vacuo* and purified by flash chromatography to yield methyl 3-(4-phenoxyphenyl)propanoate. This was directly converted to the title compound according to the procedure described for compound **35.** This yielded 3-(4-phenoxyphenyl)propan-1-ol (0.545 g, 2.39 mmol, 53% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 – 7.23 (m, 2H), 7.14 – 7.09 (m, 2H), 7.03 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.93 – 6.87 (m, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.84 (bs, 1H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.54, 155.09, 136.84, 129.67(2C), 129.61(2C), 122.94, 119.02(2C), 118.48(2C), 61.87, 34.24, 31.29.

2-Hydroxy-4-(4-phenoxyphenyl)butanenitrile (44)

The title compound was synthesized from 3-(4-phenoxyphenyl)propan-1-ol (**43**, 0.544 g, 2.39 mmol) according to the procedure described for compound **19**. This yielded 2-hydroxy-4-(4-phenoxyphenyl)butanenitrile (0.563 g, 2.22 mmol, 93% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.25 (m, 2H), 7.16 – 7.10 (m, 2H), 7.09 – 7.04 (m, 1H), 7.00 – 6.95 (m, 2H), 6.95 – 6.89 (m, 2H), 4.40 (t, *J* = 6.8 Hz, 1H), 3.82 (bs, 1H), 2.86 – 2.71 (m, 2H), 2.22 – 2.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.26, 155.73, 134.52, 129.78(2C), 129.75(2C), 123.25, 120.07, 119.18(2C), 118.71(2C), 60.20, 36.59, 29.91.

3-(4-Phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (45)

The title compound was synthesized from 2-hydroxy-4-(4-phenoxyphenyl)butanenitrile (**44**, 126.9 mg, 0.501 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (83.0 mg, 0.415 mmol) according to the procedure described for compound **20**. This yielded 3-(4-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (28.4 mg, 0.065 mmol, 16%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, *J* = 1.9 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.34 – 7.27 (m, 4H), 7.22 – 7.16 (m, 2H), 7.11 – 7.03 (m, 1H), 6.99 – 6.93 (m, 2H), 6.93 – 6.87 (m, 2H), 5.08 (dd, J = 7.8, 5.0 Hz, 1H), 4.14 (bs, 1H), 2.88 (t, *J* = 7.7 Hz, 2H), 2.42 (s, 3H), 2.40 – 2.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.19, 157.53, 155.49, 153.85, 145.65, 143.55, 138.46, 135.81, 134.79, 134.54, 130.08(2C), 129.94(2C), 129.79(2C), 127.50(2C), 123.12, 119.13(2C), 118.70(2C), 116.85, 67.35, 37.03, 30.45, 21.29.

3-(4-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (11)

The title compound was synthesized from 3-(4-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-ol (**45**, 21.3 mg, 0.049 mmol) according to the procedure described for compound **2**. This yielded 3-(4-phenoxyphenyl)-1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)propan-1-one (12.9 mg, 0.030 mmol, 61%). HRMS (ESI+) m/z: calculated for $C_{28}H_{23}N_2O_3$ ([M + H]), 435.1703; found, 435.1700. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.00 – 8.95 (m, 1H), 8.11 – 8.06 (m, 1H), 7.57 – 7.51 (m, 2H), 7.36 – 7.28 (m, 4H), 7.28 – 7.22 (m, 2H), 7.11 – 7.05 (m, 1H), 7.01 – 6.92 (m, 4H), 3.63 (t, *J* = 7.5 Hz, 2H), 3.15 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 189.30, 158.58, 157.50, 155.76, 153.05, 148.38, 144.24, 139.17, 137.74, 135.05, 134.04, 130.25(2C), 129.88(2C), 129.82(2C), 127.64(2C), 123.19, 119.26(2C), 118.77(2C), 117.85, 41.52, 29.07, 21.36. Purity of >95% as determined by LC-MS.

3-(4-((5-(Trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (46)

The title compound was synthesized from 4-(3-hydroxypropyl)phenol (1.311 g, 8.61 mmol), 2-fluoro-5-(trifluoromethyl)pyridine (1.49 g, 9,03 mmol) and K_2CO_3 (1.2 g, 8.68 mmol) according to the procedure described for compound **35**. This yielded 3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (2.15 g, 7.24 mmol, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 – 8.41 (m, 1H), 7.89 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.09 – 7.04 (m, 2H), 7.02 – 6.96 (m, 1H), 3.71 (t, *J* = 6.4 Hz, 2H), 2.78 – 2.70 (m, 2H), 1.96 – 1.86 (m, 2H), 1.58 (bs, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.09, 151.30, 145.61 (q, *J* = 4.3 Hz), 139.19, 136.77 (q, *J* = 3.1 Hz), 129.89(2C), 123.82 (q, *J* = 272.4 Hz), 121.48 (q, *J* = 33.3 Hz), 121.46(2C), 111.36, 62.30, 34.25, 31.61.

2-Hydroxy-4-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)butanenitrile (47)

The title compound was synthesized from 3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (**46**, 1.38 g, 4.64 mmol) according to the previously described general synthesis scheme. This yielded 2-hydroxy-4-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)butanenitrile (1.20 g, 3.72 mmol, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 – 8.40 (m, 1H), 7.91 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.27 (dd, *J* = 6.7, 1.8 Hz, 2H), 7.13 – 7.05 (m, 2H), 7.03 – 6.98 (m, 1H), 4.45 (t, *J* = 6.7 Hz, 1H), 2.95 – 2.79 (m, 2H), 2.27 – 2.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.91, 154.50, 151.77, 145.51 (q, *J* = 4.3 Hz), 136.99 (q, *J* = 3.4 Hz), 130.02(2C), 123.74 (q, *J* = 272.6 Hz), 121.91(2C), 121.74 (q, *J* = 33.5 Hz), 119.93, 111.47, 60.38, 36.62, 30.18.

1-(6-(*p*-Tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (48)

The title compound was synthesized from 2-hydroxy-4-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)butanenitrile (**47**, 0.167 g, 0.518 mmol) and 2-amino-5-(*p*-tolyl)pyridin-3-ol (214 mg, 1.069 mmol) according to the procedure described for compound **20**. This yielded 1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (57.3 mg, 0.113 mmol, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 – 8.66 (m, 1H), 8.50 – 8.36 (m, 1H), 7.94 – 7.90 (m, 1H), 7.86 (dd, J = 8.7, 2.6 Hz, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.36 – 7.23 (m, 4H), 7.11 – 7.00 (m, 2H), 6.96 (d, J = 8.6 Hz, 1H), 5.16 – 5.08 (m, 1H), 4.41 (bs, 1H), 2.92 (t, J = 7.6 Hz, 2H), 2.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.16, 165.98, 153.87, 151.47, 145.63, 145.56 (q, *J* = 4.0 Hz), 143.57, 138.46, 138.19, 136.75 (q, *J* = 3.0 Hz), 134.81, 134.54, 130.06(4C), 127.48(2C), 123.80 (q, *J* = 272.7 Hz), 121.50 (q, *J* = 34.3 Hz), 121.49(2C), 116.86, 111.34, 67.35, 36.83, 30.62, 21.26.

1-(6-(*p*-Tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-one (12)

The title compound was synthesized from 1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-ol (**48**, 38.5 mg, 0.076 mmol) according to the procedure described for compound **2**. This yielded 1-(6-(*p*-tolyl)oxazolo[4,5-*b*]pyridin-2-yl)-3-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)propan-1-one (30 mg, 0.060 mmol, 78%). HRMS (ESI+) m/z: calculated for $C_{28}H_{21}F_3N_3O_3$ ([M + H]), 504.1530; found, 504.1527. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (d, *J* = 2.0 Hz, 1H), 8.46 – 8.41 (m, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.35 (t, *J* = 8.5 Hz, 4H), 7.12 – 7.07 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 3.67 (t, *J* = 7.5 Hz, 2H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 189.16, 166.00, 158.59, 153.07, 151.76, 148.43, 145.63 (q, *J* = 4.3 Hz), 144.28, 139.20, 137.79, 137.40, 136,78 (q, *J* = 3.1 Hz), 134.06, 130.27(2C), 130.03(2C), 127.66(2C), 121.73(2C), 117.85, 111.41, 41.31, 29.16, 21.35. Two carbon signals (quatonary quartets of -**C**F_3 and -**C**-CF_3) not observed. Purity of >95% as determined by LC-MS.

2-Amino-5-(4-chloro-2-methoxyphenyl)pyridin-3-ol (49)

The title compound was synthesized from 3-(benzyloxy)-5-bromopyridin-2-amine (341 mg, 1.22 mmol) according to the previously reported procedure. Next the crude product (385 mg) was refluxed in HBr (0.35 mL, 48%, 2.7 eq.)/ Acetic acid (2.0 mL, 30 eq.). After complete conversion (24 h) the reaction mixture was slowly poured into excess sat. $NaHCO_3$ (aq), extracted with EtOAc, washed with brine, dried, filtered, concentrated *in*

vacuo and purified by flash chromatography to obtain 2-amino-5-(4-chloro-2-methoxyphenyl)pyridin-3-ol (128 mg, 0.51 mmol, 42%, 2 steps). ^{1}H NMR (MeOD, 400 MHz): δ 7.49 (d, *J* = 1.9 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 158.62, 150.46, 141.46, 135.51, 134.85, 131.83, 127.20, 124.82, 124.79, 121.89, 113.05, 56.37.

1-(6-(4-Chloro-2-methoxyphenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (50)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 92 mg, 0.60 mmol) and 2-amino-5-(4-chloro-2-methoxyphenyl)pyridin-3-ol (**49**, 80 mg, 0.32 mmol) according to procedure described for compound **20**. This yielded 1-(6-(4-chloro-2-methoxyphenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (27 mg, 0.07 mmol, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, *J* = 1.9 Hz, 1H), 8.00 (d, *J* = 1.9 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.07 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 5.18 (dd, *J* = 8.0, 4.3 Hz, 1H), 3.83 (s, 3H), 2.50 – 2.22 (m, 4H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 157.09, 153.41, 147.48, 143.02, 135.61, 131.67, 131.16, 127.13 (q, *J* = 276.0 Hz), 124.76, 121.42, 119.93, 112.24, 55.97, 29.78 (q, *J* = 30.3 Hz), 27.79 (q, *J* = 3.03 Hz).

1-(6-(4-Chloro-2-methoxyphenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (13)

The title compound was synthesized from 1-(6-(4-chloro-2-methoxyphenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (**50**, 27 mg, 0.07 mmol) according to procedure described for compound **2**. This yielded 1-(6-(4-chloro-2-methoxyphenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (22 mg, 0.06 mmol, 82%). LCQ (ESI+) m/z: calculated for $C_{17}H_{13}ClF_3N_2O_3$ ([M + H]), 385.06; found, 385.00. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, J = 1.9 Hz, 1H), 8.16 (d, *J* = 1.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 3.86 (s, 3H), 3.61 (t, *J* = 7.6 Hz, 2H), 2.79 – 2.59 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 186.66, 158.11, 157.16, 152.63, 150.29, 143.75, 136.17, 134.18, 131.70, 126.67 (q, *J* = 276.0 Hz), 124.34, 121.56, 120.89, 112.37, 56.04, 32.75 (q, *J* = 2.7 Hz), 27.99 (q, *J* = 30.5 Hz). Purity of 95% as determined by LC-MS.

2-(6-Amino-5-hydroxypyridin-3-yl)benzonitrile (51):

The title compound was synthesized from 2-amino-5-bromopyridin-3-ol (380 mg, 1.4 mmol) and 2-cyanophenylboronic acid (300 mg, 2.0 mmol) according to the previously reported procedures.[12] This yielded 2-(6-amino-5-hydroxypyridin-3-yl)benzonitrile (90 mg, 0.42 mmol, 30%). ^{1}H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.02 – 7.82 (m, 1H), 7.74 (td, *J* = 7.7, 1.4 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.1 Hz, 1H), 7.09 (t, *J* = 4.6 Hz, 1H), 5.90 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 151.38, 142.88, 139.22, 137.62, 134.38, 133.98, 129.97, 127.75, 122.78, 119.35, 118.53, 109.99.

2-(2-(4,4,4-Trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (52)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 83 mg, 0.54 mmol) and 2-(6-amino-5-hydroxypyridin-3-yl)benzonitrile (**51**, 127 mg, 0.60 mmol) according to procedure described for compound **19**. This yielded 2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (48 mg, 0.138 mmol, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.68 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.78 – 7.71 (m, 1H), 7.60 – 7.56 (m, 2H), 5.21 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.56 (bs, 1H), 2.54 – 2.08 (m, 4H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 175.24, 155.42, 146.75, 143.00, 141.38, 134.16, 133.45, 131.30, 130.60, 128.85, 127.10 (q, J = 276.7 Hz), 119.03, 118.19, 111.93, 70.22. 29.68 (q, J = 29.3 Hz). 27.78 (q, J = 3.0 Hz).

2-(2-(4,4,4-Trifluorobutanoyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (14)

The title compound was synthesized from 2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (**52**, 40 mg, 0.115 mmol) according to procedure described for compound **2** This yielded 2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (17 mg, 0.049 mmol, 43%). HRMS (ESI+) m/z: calculated for $C_{17}H_{11}F_3N_3O_2$ ([M + H]), 346.0798; found, 346.0799. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.92 (d, *J* =

2.1 Hz, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.89 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.79 (td, *J* = 7.7, 1.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 3.63 (t, *J* = 7.5 Hz, 2H), 2.77 – 2.62 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 186.48, 158.79, 154.10, 149.37, 143.51, 140.55, 134.49, 134.28, 133.56, 130.58, 129.41, 126.63 (q, *J* = 2717.1 Hz), 120.62, 117.87, 112.09, 32.87 (q, *J* = 2.9 Hz), 27.94 (q, *J* = 30.4 Hz). Purity of 95% as determined by LC-MS.

2-(6-Amino-5-hydroxypyridin-3-yl)-5-fluorobenzonitrile (53)

The title compound was synthesized from 2-amino-5-bromopyridin-3-ol and 2-cyano-4-fluorophenylboronic acid according to the previously reported procedures.[12]

5-Fluoro-2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-b]pyridin-6-yl)benzonitrile (**54**)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 222 mg, 1.448mmol) and 2-(6-amino-5-hydroxypyridin-3-yl)-5-fluorobenzonitrile (**53**, 83 mg, 0.362mmol) according to procedure described for compound **19**. This yielded 5-fluoro-2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (16 mg, 0.044 mmol, 12%).^{1}H NMR (MeOD, 400 MHz) δ 8.69 (d, *J* = 1.9 Hz, 1H), 8.37 (d, *J* = 1.9 Hz, 1H), 7.75 (td, *J* = 6.8, 5.1, 2.5 Hz, 2H), 7.65 – 7.56 (m, 1H), 5.10 – 5.04 (m, 1H), 2.54 – 2.41 (m, 2H), 2.40 – 2.18 (m, 2H).^{13}C NMR (MeOD, 101 MHz) δ 173.19, 164.73 (d, *J* = 249.6 Hz), 156.31, 147.50, 144.36, 138.97 (d, *J* = 3.7 Hz), 134.26 (d, *J* = 8.6 Hz), 132.53, 130.14 (q, *J* = 275.7 Hz), 122.21 (d, *J* = 21.2 Hz), 121.74 (d, *J* = 25.9 Hz), 121.14, 118.01 (2.4 Hz), 114.67(d, *J* = 9.6Hz), 67.14, 30.60(q, *J* = 29.3 Hz), 28.55(q, *J* = 3.0 Hz)

5-Fluoro-2-(2-(4,4,4-trifluorobutanoyl)oxazolo[4,5-b]pyridin-6-yl)benzonitrile (**15**)

The title compound was synthesized from 5-fluoro-2-(2-(4,4,4-trifluoro-1-hydroxybutyl)oxazolo[4,5-*b*]pyridin-6-yl)benzonitrile (**54**, 28 mg, 0.077 mmol) according to procedure described for compound **2**. This yielded 5-fluoro-2-(2-(4,4,4-trifluorobutanoyl)oxazolo[4,5-b]pyridin-6-yl)benzonitrile (2 mg, 0.005mmol, 7%). LCQ (ESI+) m/z: calculated for $C_{16}H_{10}F_2N_2O_2$ ([M + H]), 363.27; found, 364.20. ^{1}H NMR (CDCl3, 400 MHz) δ 8.88 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.54 – 7.45 (m, 1H), 3.62 (t, *J* = 7.5 Hz, 2H), 2.70 (qt, *J* = 10.6, 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 186.50, 163.13 (d, *J* = 249.53 Hz), 158.81, 154.20, 149.31, 143.43, 136.95(d, *J* = 4.08 Hz), 133.46, 132.68 (d, *J* = 8.46 Hz), 127.51 (q, *J* = 275.48 Hz), 121.47 (d, *J* = 21.47 Hz), 121.24 (d, *J* = 24.90 Hz), 120.64, 116.75 (d, *J* = 2.6 Hz), 113.60 (d, *J* = 9.34 Hz), 32.90 (q, *J* = 2.99 Hz), 27.98 (q, *J* = 30.8 Hz). Purity of 93% as determined by LC-MS. **Final compound not stable upon storage.**

2-Amino-5-(4-fluorophenyl)pyridin-3-ol (**55**)

The title compound was synthesized from 3-(benzyloxy)-5-bromopyridin-2-amine (300 mg, 1.07 mmol) according to the previously reported procedures.[12] This yielded 2-amino-5-(4-fluorophenyl)pyridin-3-ol (143 mg, 0.71 mmol, 66%, 2 steps). ^{1}H NMR (MeOD, 400 MHz) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.19 – 7.08 (m, 3H), 3.35 (s, 1H). ^{13}C NMR (MeOD, 101 MHz) δ 164.77(d, *J* = 246.3 Hz), 151.12, 135.99, 134.26, 128.97(2C, d, *J* = 8.0 Hz) 127.75, 118.91, 116.67(2C, d, *J* = 21.6 Hz).

4,4,4-Trifluoro-1-(6-(4-fluorophenyl)oxazolo[4,5-b]pyridin-2-yl)butan-1-ol (56)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 270 mg, 1.76 mmol) and 2-amino-5-(4-fluorophenyl)pyridin-3-ol (**55**, 90 mg, 0.44 mmol) according to procedure described for compound **20**. This yielded 4,4,4-trifluoro-1-(6-(4-fluorophenyl)oxazolo[4,5-b]pyridin-2-yl)butan-1-ol (16 mg, 0.5 mmol, 11%). ^{1}H NMR (MeOD, 400 MHz) δ 8.75 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.31 – 7.18 (m, 2H), 5.04 (dd, *J* = 8.2, 4.8 Hz, 1H), 2.52 – 2.38 (m, 2H), 2.36 – 2.17 (m, 2H). ^{13}C NMR (MeOD, 101 MHz) δ 172.29, 165.75(d, 247.3Hz), 155.22, 146.09, 145.07, 135.54, 134.85(d, 3.4 Hz), 130.72(2C, d, 8.2 Hz), 130.15(q, 276.1 Hz), 118.93, 117.22(2C, d, 22.0 Hz), 67.11, 30.77(q, 29.3 Hz), 28.57(q, 2.8 Hz).

4,4,4-Trifluoro-1-(6-(4-fluorophenyl)oxazolo[4,5-b]pyridin-2-yl)butan-1-one (**16, LEI107**)

The title compound was synthesized from 4,4,4-trifluoro-1-(6-(4-fluorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol (**56**, 10 mg, 0.029 mmol) according to procedure described for compound **2**. This yielded 4,4,4-trifluoro-1-(6-(4-fluorophenyl)oxazolo[4,5-b]pyridin-2-yl)butan-1-one (3 mg, 0.01mmol, 30%). LCQ (ESI+) m/z: calculated for $C_{16}H_{11}F_2N_2O_2$ ([M + H]), 339.07; found, 339.07. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.25 – 7.21 (m, 2H), 3.66 – 3.57 (m, 2H), 2.74 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.46, 164.64(d, 249.53 Hz), 158.24, 153.10, 148.61, 144.26, 137.01, 133.01, 129.56(2C, d, 8.4 Hz), 127.76(q, 276.75 Hz), 118.01, 116.68(2C, d, 21.9 Hz), 32.67(q, 2.7 Hz), 28.03(q, 30.2 Hz). Purity of 95% as determined by LC-MS.

2-Amino-5-(4-chlorophenyl)pyridin-3-ol (57)

The title compound was synthesized from 3-(benzyloxy)-5-bromopyridin-2-amine (303 mg, 1.09 mmol) according to the previously reported procedures.[12] This yielded 2-amino-5-(4-chlorophenyl)pyridin-3-ol (60 mg, 0.27 mmol, 25%, 2 steps). ^{1}H NMR (MeOD, 400 MHz): δ 7.67 – 7.61 (m, 1H), 7.48 – 7.44 (m, 2H), 7.39 – 7.35 (m, 2H), 7.16 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 151.24, 138.10, 133.75, 133.70, 130.17, 129.96(2C), 128.50(2C), 127.14, 118.65.

1-(6-(4-Chlorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (58)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 62 mg, 0.41 mmol) and 2-amino-5-(4-chlorophenyl)pyridin-3-ol (**57**, 60 mg, 0.27 mmol) according to procedure described for compound **20**. This yielded 1-(6-(4-chlorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (15 mg, 0.04 mmol, 15%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.54 – 7.46 (m, 4H), 5.17 (dd, *J* = 8.1, 4.1 Hz, 1H), 2.52 – 2.20 (m, 4H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 170.67, 153.98, 145.78, 143.61, 135.68, 135.01, 134.04, 131.19, 129.67, 128.91, 127.08 (q, *J* = 276.7 Hz), 117.30, 66.60, 29.66 (q, *J* = 30.3 Hz), 27.77 (q, *J* = 3.0 Hz)

1-(6-(4-Chlorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (17)

The title compound was synthesized from 1-(6-(4-chlorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (**58**, 15 mg, 0.04 mmol) according to procedure described for compound **2**. This yielded 1-(6-(4-chlorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (5.2 mg, 0.02 mmol, 35%). LCQ (ESI+) m/z: calculated for $C_{16}H_{11}ClF_3N_2O_2$ ([M + H]), 355.05; found, 355.07. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (bs, 1H), 8.12 (d, *J* = 1.8 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.55 – 7.48 (m, 2H), 3.61 (t, *J* = 7.6 Hz, 2H), 2.78 – 2.60 (m, 2H). ^{13}C BBDEC NMR ($CDCl_3$, 101 MHz): δ 186.38, 158.28, 153.15, 148.18, 144.08, 141.44, 136.53, 135.21, 135.16, 129.58, 129.06, 126.69 (q, *J* = 276.0 Hz), 118.24, 32.55 (q, *J* = 3.0 Hz), 27.68 (q, *J* = 30.4 Hz). Purity of 95% as determined by LC-MS.

2-Amino-5-(benzo[*d*][1,3]dioxol-5-yl)pyridin-3-ol (59)

The title compound was synthesized from 3-(benzyloxy)-5-bromopyridin-2-amine (279 mg, 1.00 mmol) according to the previously reported procedures.[12] This yielded 2-amino-5-(benzo[*d*][1,3]dioxol-5-yl)pyridin-3-ol (202 mg, 0.88 mmol, 88%, 2 steps). ^{1}H NMR (MeOD, 400 MHz) δ 7.57 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 7.00 – 6.92 (m, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.96(s, 2H). ^{13}C NMR (MeOD , 101 MHz) δ 150.40, 149.75, 148.45, 142.73, 133.42, 131.99, 128.65, 120.70, 119.38, 109.58, 107.64, 102.54.

1-(6-(Benzo[*d*][1,3]dioxol-5-yl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (60)

The title compound was synthesized from 5,5,5-trifluoro-2-hydroxypentanenitrile (**31**, 239 mg, 1.56 mmol) and 2-amino-5-(4-fluorophenyl)pyridin-3-ol (**59**, 90 mg, 0.39 mmol) according to procedure described for compound **20**. This yielded 1-(6-(benzo[*d*][1,3]dioxol-5-yl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol

(10 mg, 0.027 mmol, 7%). ^{1}H NMR (MeOD, 400 MHz) δ 8.70 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 7.24 – 7.16 (m, 2H), 6.98 – 6.93 (m, 1H), 6.02 (s, 2H), 5.07 – 4.96 (m, 1H), 2.48-2.27 (m, 4H).

1-(6-(Benzo[*d*][1,3]dioxol-5-yl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (18)

The title compound was synthesized from 1-(6-(benzo[*d*][1,3]dioxol-5-yl)oxazolo[4,5-b]pyridin-2-yl)-4,4,4-trifluorobutan-1-ol (**60**, 14 mg, 0.038 mmol) according to procedure described for compound **2**. This yielded 1-(6-(benzo[*d*][1,3]dioxol-5-yl)oxazolo[4,5-*b*]pyridin-2-yl)-4,4,4-trifluorobutan-1-one (4 mg, 0.01mmol, 29%). LCQ (ESI+) m/z: calculated for $C_{17}H_{12}F_3N_2O_4$ ([M + H]), 365.07; found, 365.13. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.01 – 6.94 (m, 1H), 6.08 (s, 2H), 3.61 (t, *J* = 7.6 Hz, 2H), 2.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 186.60, 158.06, 152.75, 148.91, 148.71, 148.60, 144.35, 137.87, 130.90, 127.59(d, 276.1 Hz), 121.91, 117.77, 109.34, 108.04, 101.82, 32.76(q, 2.9 Hz), 28.31(q, 30.3 Hz). Purity of 95% as determined by LC-MS.

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