Exploiting C-H Borylation for the Multidirectional Elaboration of 2-Halopyridines

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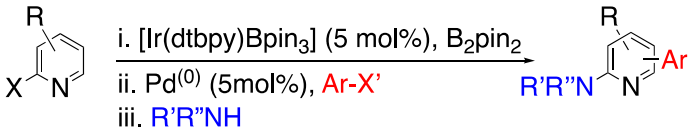
Graphical Abstract



32 examples of regioselective pyridine synthesis (3—51%)
Ar = Aryl and heteroaryl; X = Cl, F; X' = I, Br; R',R" = Alkyl, cycloalkyl, H

Exploiting C-H Borylation for the Multidirectional Elaboration of 2-Halopyridines

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Abstract

Regioselectively polysubstituted pyridines can be efficiently accessed from 2-halopyridines via a sequence involving C-H borylation, Suzuki-Miyaura cross-coupling and nucleophilic aromatic substitution chemistry.

Dedication

Dedicated to Professor Steve Davies in recognition of his outstanding contributions to advancing organic chemistry though both his teaching and his research.

Keywords

Pyridine; C-H Borylation; Suzuki-Miyaura; Multidirectional synthesis

Introduction

The pyridine ring represents an essential structural component of many functional molecules including sensors, pharmaceuticals, agrochemicals, ligands for catalysis etc and is also found in numerous natural products (Fig. 1). [1,2,3,4]

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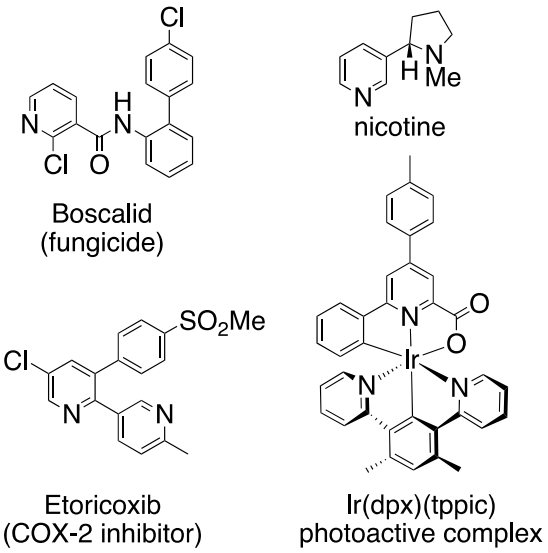


Figure 1. Representative functional pyridines

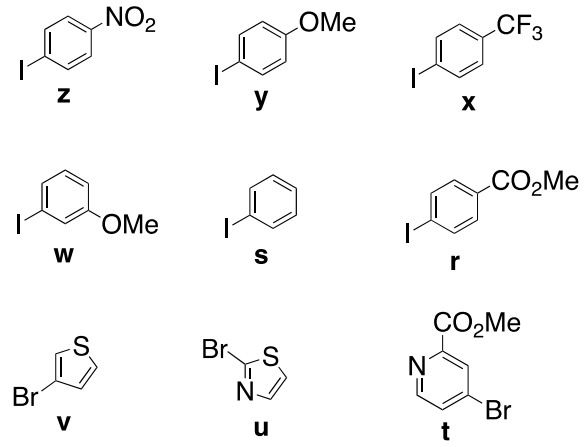
As such, methods to synthesise functionalised pyridines are of great value and much effort has been applied towards this effect.[5-11] Given the low reactivity of the electron deficient azinyl ring towards electrophilic aromatic substitution, most routes to substituted pyridines involve *de novo* synthesis with substituents and substitution patterns determined by the building blocks employed. However, the ability to manipulate a preformed pyridine ring is particularly valuable for late stage diversification. Among the various strategies for preparing polyfunctionalised pyridines in this way are ring metalation with various strong bases,[12,13] radical substitution[14,15] and transition metal mediated C-H activation. [16,11] Whilst each has its merit, the last is particularly attractive providing both high atom and step efficiency and represent the ideal for green sustainable processes. Reflecting the versatility of the resulting arylboronate esters for further downstream transformations and the functional group tolerance of the process, Ir catalysed C-H borylation is a particularly attractive option for elaboration of a preformed pyridine ring.[17,11] First reported by Miyaura and Ishiyama in 2002,[18,19] the borylation of pyridine is challenged by the Lewis basicity of the azinyl nitrogen atom which can coordinate to and inhibit the catalytically active species. Moreover, the azinyl nitrogen also affects both the regiochemistry of pyridine borylation disfavouring substitution at the 2 and 6 positions and also rendering the products unstable with respect to protodeborylation.[20-23] In recent work we have shown this effect can be modulated by the presence of an electron withdrawing 2-halo substituent which, not only sterically protects the catalyst by blocking co-ordination to the iridium centre but also lowers the basicity of the azinyl lone pair enhancing reactivity at the α-positions and increasing stability to protodeborylation.[24] The resultant 2-halopyridine boronate

esters are versatile building blocks for multi-directional elaboration and in this report we demonstrate this concept with the synthesis of a diverse set of trifunctional pyridine scaffolds.

Results & Discussion

Building on our earlier work, initial studies focused on the borylation of simple 2,4-disubstituted pyridines. The borylation of 2-chloro-4-trifluoromethyl- and 2-chloro-4-*tert*butylpyridine **1** and **2** (Table 1), using $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2Pin_2 in THF, occurred as predicted at the sterically uninhibited 6-position. Although adjacent to the azinyl nitrogen atom, the stabilising effect of the 2-chloro substituent allowed the isolation of the boronate ester which could be identified by a characteristic downfield shift of the signal for the adjacent 5-hydrogen in the ^1H NMR spectrum. Whilst sufficiently stable to be analysed as a crude product, attempts to chromatographically purify this compound were complicated by significant protodeborylation and it was more effective to use the crude reaction mixture directly in subsequent steps. Using the Suzuki-Miyuara reaction as a classic exemplar transformation, reaction with 4-iodo-nitrobenzene (1.5 equiv) in the presence of $PdCl_2$(dppf) (5 mol%) as the precatalyst afforded the desired biaryl **5z** in 58% yield over the two steps (Table 1, entry 1). A range of arenes and heteroarenes (Fig. 2a), including those containing both electron withdrawing and donating substituents, proved viable giving moderate to good yields under these standard conditions. Having exploited the ability of the halogen to enable and direct the C-H borylation, it was then of interest to use this as a handle for further functionalisation. Using pyrrolidine as a test substrate, efficient reaction could be achieved by simply heating the halopyridine with an excess of the amine in THF in a sealed microwave vessel for 60 minutes. This proved to be a general observation and was extended to include a range of amines (Fig. 2b), including primary, secondary cyclic and acyclic alkyl amines but not aniline. Attempts to carry out the whole sequence in a single operation were possible (Table 1 entry 6) but generally lead to more complex crude reaction mixtures and slightly lower overall yields.

a. arene electrophiles



b. amine nucleophiles

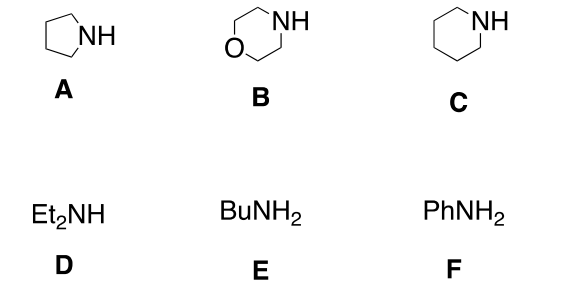
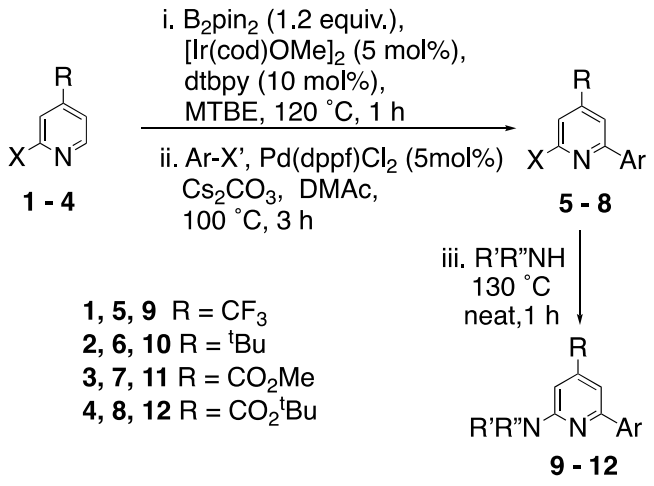


Figure 2. Arenes and amines employed in this study



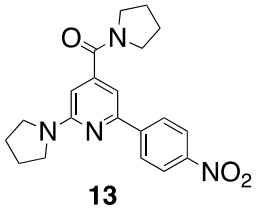
Entry	1 - 4	X	Ar-X'	5-8 (%)[i]	R'R"NH	9-12 (%)[ii]
1	1	Cl	z	**5z** (58)%	A	**9zA** (78)
2	1	Cl	z	**5z**	B	**9zB** (92)
3	1	Cl	z	**5z**	D	**9zD** (61)
4	1	Cl	z	**5z**	E	**9zE** (75)
5	1	Cl	z	**5z**	F	**9zF** (0)
6	1	Cl	y	**5y** (36)	A	**9yA** (20)[iii]
7	1	Cl	w	**5w** (51)	-	-
8	2	Cl	z	**6z** (40)	A	**10zA** (31)
9	2	Cl	y	**6y** (44)	-	-
10	2	Cl	v	**6v** (67)	-	-
11	2	Cl	u	**6u** (66)	-	-
12	2	Cl	t	**6t** (42)	-	-
13	3	Cl	z	**7z** (45)	-	-
14	3	Cl	y	**7y** (48)	-	-
15	3	F	y	**7'y** (55)	A	**11yA** (85)[iv]
16	3	F	x	**7'x** (50)	B	**11xB** (83)[iv]
17	3	F	x	**7'x**	E	**11xE** (64)[iv]
18	4	Cl	z	**8z** (61)	B	**12zB** (78)
19	4	Cl	y	**8y** (57)	A	**12yA** (90)
20	4	Cl	y	**8y**	F	**12yF** (0)
21	4	Cl	x	**8x** (39)	A	**12xA** (91)

i. Yield of isolated purified product from **1-4** in a one-pot two-step process; ii. Yield of isolated purified **9-12** based on **5-8**; iii.yield for a one-pot three-step process from **1**.; iv. Step iii. conditions: R'R"NH (2 equiv), dioxane, reflux, 6 h

Table 1: Sequential borylation cross-coupling amination of 2-halopyridines

Turning to the corresponding isonicotinates (Table 1, entries 13-21) initial attempts were hampered by inefficient borylation of the corresponding esters **2** and **3** under the "standard" conditions (~68% conversion compared with >90% for the other substrates). Attributing this to competitive coordination of the Lewis acidic active catalyst, this could be simply addressed by increasing the catalyst loading to 5 mol% which enabled conversions in excess

of 90% to be routinely achieved. As with the earlier examples, cross-coupling of the resultant pyridyl boronate esters occurred efficiently. However initial attempts to employ methyl ester **7z** in the S_NAr step led to the formation of the corresponding amide **13**. Two strategies to circumvent this problem were developed. Simply replacing the methyl ester by a *tert*-butyl ester enabled the amino esters to be isolated in moderate yields (Table 1 entries 18-21) although aromatic amines were still not tolerated (Table 1, entry 20). Alternatively, using the more reactive 2-fluoropyridine starting material enhanced the facility of the S_NAr reaction enabling lower reaction temperatures to be employed, leading to selective reaction at C-2 even in the presence of the methyl ester (Table 1 entries 13-17).

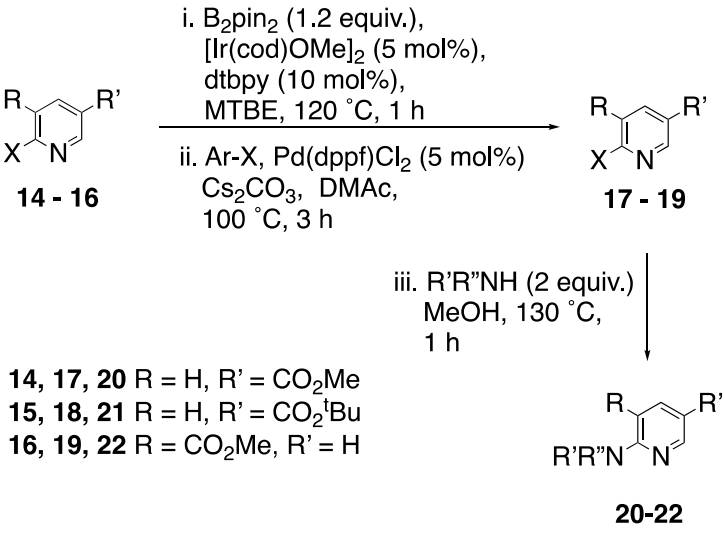


13

Figure 3: Structure of amide 13.

Having demonstrated the possibility for multidirectional approaches around a pyridine template it was of interest to explore other starting pyridine substitution patterns. Retaining a 2-halo substituent, as the borylation enabling (coordination blocking) but labile group, both 2,3- and 2,5-nicotinates were then explored (Table 2). As expected borylation of the 2,5-isomers **14** and **15** occurred preferentially at the sterically unencumbered C-5 site removed from the azinyl nitrogen.[20-24] However small amounts (6-9%) of the α-azinyl (C-6) boronate ester could be observed in the crude reaction mixture but underwent rapid protodeborylation and was not isolable or detectable following the *in situ* cross coupling reaction. With the 2,3-isomer **16**, similar sterically directed borylation led exclusively to the 3-borylated product. For this group of compounds use of the smaller 2-fluoro starting material led to a faster reaction consistent with other observations describing fluorine to act as a C-H activation enhancing group.[25,26,27] In both cases whilst the major boronate esters were isolable, it was more efficient to carry out a 'one-pot' process to afford the corresponding biaryl (**17-19**) in acceptable yields following application of the standard cross coupling conditions. As before S_NAr chemistry with a variety of amines proved facile with anilines again requiring the use of the more reactive fluorine leaving group. With the 2,3 series use of a diamine enabled double substitution to afford the pyridodiazepinone **23** (Scheme 1a). For these substrates, reflecting the higher stability of a non α-azinyl boronate ester, the alternative order of events involving

initial displacement with the amine and then borylation of the corresponding 2-amino-pyridine proved to be equally effective (Scheme 1b).



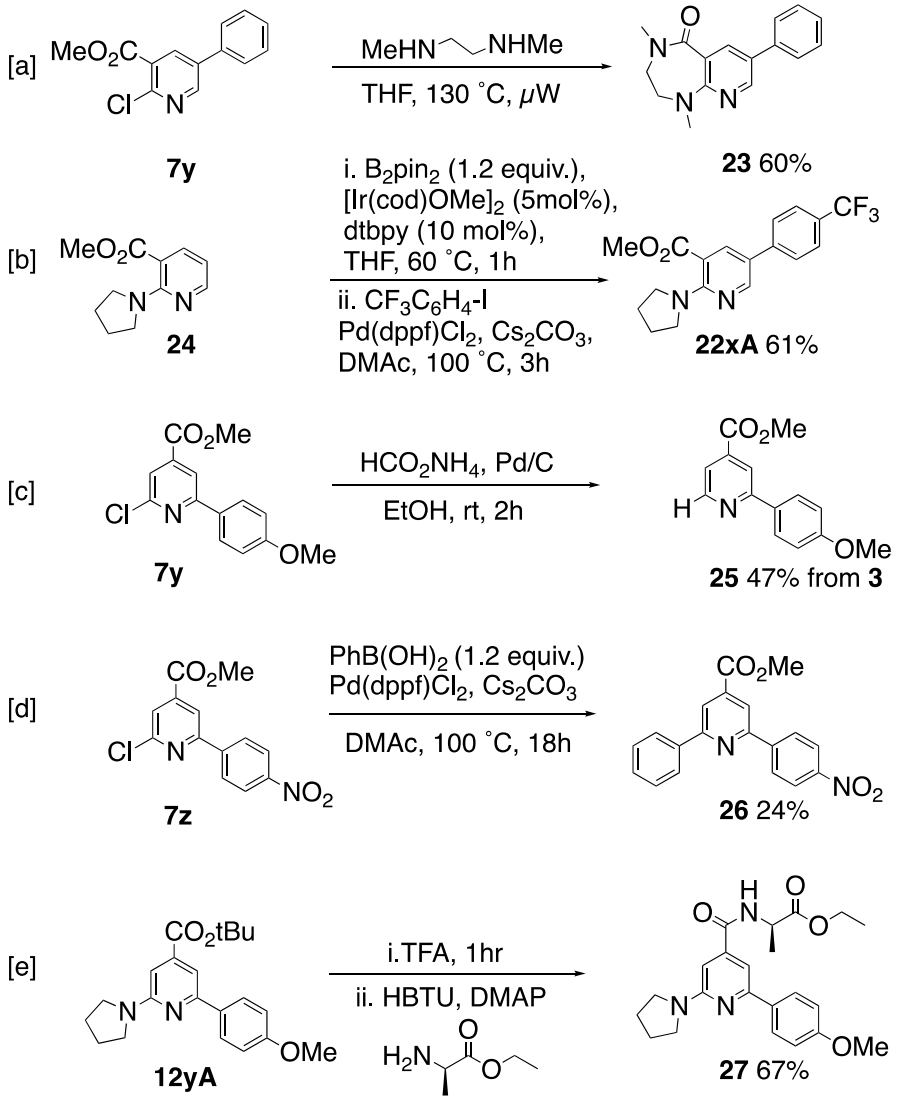
Entry	14-16	X	Ar-X	17-19 (%)[i]	R'R"NH	20-22 (%)[ii]
1	14	Cl	w	17w (32)	-	-
2	14	F	y	17'y (58)	B	20yB (88)[iii]
3	14	Cl	y	17y (61)	A	20yA (71)
4	14	Cl	x	17x (55)	A	20xA (84)
5	15	Cl	y	18y (44)		21yA (75)[iv]
6	15	Cl	y	18y	B	21yB (87)[iv]
7	15	Cl	y	18y	F	21yF (0)[iv]
8	15	Cl	x	18x (32)	B	21xB (82)[iv]
9	16	Cl	z	19z	A	22zA (32)[v]
10	16	Cl	y	19y (20)	B	22yB (93)
11	16	Cl	y	19y	C	22yC (89)
12	16	Cl	y	19y	E	22yE (60)
13	16	F	y	19'y (62)	-	-
14	16	OMe	y	19"y (81)	-	-
15	16	Cl	x	19x (24)	A	22xA (50)
16	16	Cl	x	19x	B	22xB (43)
17	16	Cl	x	19x	C	22xC (13)
18	16	Cl	v	19v (19)	-	-
19	16	Cl	s	19s (38)	-	-
20	16	Cl	r	19r (65)	A	22rA (81)

i. Yield of isolated purified product from **1-4** in a one-pot two-step process; ii. Yield of isolated purified **9-12** based on **5-8**; iii. Step iii conditions: R'R"NH (2 equiv), dioxane, reflux, 6 h; iv. Step iii conditions: R'R"NH (neat), 130 ^{o}C, 1 h; v. yield for a one-pot three -step process from **16.**

Table 2: Sequential borylation cross-coupling amination of 2-halonicotinates

Further extension of the levels of diversity possible can be realised through other standard functional group transformations (Scheme 1). For example, rather than exploit the 2-halo

substituent through S_NAr chemistry other options exist using further metal catalysed transformations, with simple reduction using ammonium formate giving ester **25** (Scheme 1c) or via a second Suzuki-Miyaura reaction, the diarylpyridine **26** (Scheme 1d). Similarly, the ester substituents can easily be converted to the corresponding acid and hence provides a simple handle for the introduction of further variation into the reaction sequence (Scheme 1e).



Scheme 1: Exemplar diversity synthesis of pyridines enabled by C-H borylation

Conclusion

In this report we have demonstrated that the combination of iridium catalysed C-H borylation and S_NAr chemistry provide a very simple method to elaborate a 2-halopyridine ring and provide substitution patterns that would be difficult to achieve using traditional heterocycle synthesis. The functional group tolerant nature of the borylation reaction allows many

alternative diverse elements to be incorporated in this sequence with minimal impact on the chemistry enabled. Given the wide scope for elaboration of the intermediate boronate ester the potential of the approach to generate diversity extends beyond the examples presented. Overall this study provides further testimony for the use of C-H borylation as a powerful means to generating otherwise challenging pyridine, and other heterocycle, substitution patterns.

Experimental

General Procedure A: Tandem C-H Borylation-Suzuki-Miyaura Cross-Coupling Sequence:

A solution of $[Ir(COD)OMe]_2$ (5mol%), dtbpy (5mol%) and B_2pin_2 (1.2mol %) in MTBE (0.4M) was prepared in a sealed vial and an aliquot then added to a thick-walled microwave synthesis vial containing the starting pyridine . The vessel was sealed with a crimp top septum cap and shaken until all of the substrate was dissolved. The reaction mixture was stirred on a magnetic stirring block or irradiated in a microwave reactor for the stated time and temperature. Upon completion, the volatiles were removed *in vacuo* to afford the crude borylated product.

To the crude mixture under N_2, was added palladium catalyst (5 mol%), base (2 eq.), aryl halide (1.1 – 2.0 eq.) and the stated solvent. The reaction was heated at the stated temperature for the stated time. The reaction mixture was diluted with water and extracted into EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. This was dry-loaded onto silica gel and purified by silica gel flash column chromatography using the stated solvent system.

General Method B S_NAr substitution of 2-fluorinated pyridines:

A mixture of the 2-fluorinated pyridine derivatives (1 eq.), K_2CO_3 (2 eq.) and amine (2 eq.) were heated under reflux in dioxane for 6 h. The reaction was cooled to room temperature and filtered through Celite. Purification was achieved by flash column chromatography using EtOAc in hexane.

General method C S_NAr substitution of 2-chlorinated pyridines (-CO_2Me substituted):

To a sealed, evacuated and N_2 backfilled vial containing the 2-chloropyridine derivative, methanol was added. To this solution, the amine was added and the reaction mixture was

irradiated in a microwave reactor at 130 ºC for 30 mins. Following evaporation of volatiles, the resulting mixture was redissolved in DCM and washed with $NaHCO_3$. Purification through column chromatography using EtOAc in hexane yielded the title compound.

General Method D S_NAr substitution of 2-chlorinated pyridines (non -CO_2Me substituted):

2-Chloropyridine derivatives were transferred to microwave vessel which was then sealed, evacuated and backfilled with N_2. The amine (2ml) was then added and the reaction mixture was irradiated in a microwave reactor at 130 ºC for 30 mins. Following the reaction, the resulting mixture was dissolved in DCM and washed with $NaHCO_3$. Purification was achieved by flash column chromatography using EtOAc in Hexane.

(5z) *4-Trifluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine*

Following general procedure A and purification using toluene in hexane (0-50%) yielded the title compound as a white solid (175 mg, 58 %). mp 120-121 ºC. δ_H (700 MHz, $CDCl_3$) 8.36-8.33 (2H, m, 3',5'-H), 8.24-8.20 (2H, m, 2',6'-H), 7.9 (1H, s, 3-H), 7.6 (1H, s, 5- H); δ_C (176 MHz, $CDCl_3$) 156.9 (C-2), 153.0 (C-6), 149.2 (C-4'), 142.3 (q, *J* = 34.7 Hz, C-4), 142.1 (C-1'), 128.2 (C-2',6'), 124.3 (C-3',5'), 122.1 (q, *J* = 274 Hz, CF_3), 120.3 (q, *J* = 3.6 Hz, C-5), 115.4 (q, *J* = 3.4 Hz, C-3). υ_{max} (ATR) 1601, 1564, 1516, 1409, 1350, 1328, 1263, 1173, 1140, 1101, 1071, 860, 873, 818, 760, 707, 696, 675 cm^{-1}. m/z (GC-MS, EI^+) 304 ([M] (^{37}Cl)]$^+$, 31%), 302 ([M] (^{35}Cl)]$^+$, 100%). Accurate mass (ES^+) *m/z* found $[MH]^+$ 303.0138; $C_{12}H_7{}^{35}ClF_3N_2O_2$ requires *M*, 303.0148.

(9zA) *4-Trifluoromethyl-6-(N-pyrrolidin-yl)-2(4'-nitrophenyl)-pyridine*

Following general procedure D and purification using EtOAc in hexane (0-8%) yielded the title compound as a yellow solid (263 mg, 78 %). mp 212-213 ºC. δ_H (700 MHz, $CDCl_3$) 8.31-8.27 (2H, m, 3',5'-*H*), 8.22-8.18 (2H, m, 2',6'-*H*), 7.19 (1H, s, 3-*H*), 6.57 (1H, s, 5-*H*), 3.63-3.59 (4H, m, 2",5"-*H*$_2$), 2.11-2.04 (4H, m, 3", 4"-*H*$_2$); δ_C (176 MHz, $CDCl_3$) 157.16 (*C*6), 154.3 (*C*-2), 148.3 (*C*-4'), 145.1 (*C*-1'), 140.39 (q, *J* = 32.9, *C*-4), 127.7 (*C*-2',6'), 123.9 (*C*-3',5'), 123.43 (q, *J* = 273 Hz, *C*F_3), 103.6 (q, *J* = 3.3 Hz, *C*-3), 102.44 (q, *J* = 4.0 Hz, *C*-5), 47.1 (*C*-2",5"), 25.6 (*C*-3",4"); υ_{max} (ATR) 1616, 1601, 1564, 1519, 1492, 1480, 1443, 1390, 1344, 1322, 1290, 1249, 1159, 1108, 1093, 1010, 972, 849, 826, 756, 722, 694,

671 cm^{-1}. *m/z* (GC-MS, EI^+) 337 ($[M]^+$ 39%), 308 ($[M\text{-}C_2H_5]^+$ 100%), Accurate Mass (ESI) *m/z* found $[M+H]^+$ 338.1105; $C_{16}H_{15}F_3N_3O_2$ requires *M*, 338.1116.

(9zB) *4-Trifluoromethyl-6-(N-morpholin-yl)-2(4'-nitrophenyl)-pyridine*

Following general procedure D and purification using EtOAc in hexane (0-12%) yielded the title compound as a yellow solid (325 mg, 92 %). mp 268-269 ^oC. δ_H (700 MHz, $CDCl_3$) 8.35-8.26 (2H, m, 3',5'-*H*), 8.23-8.12 (2H, m, 2',6'-*H*), 7.33 (1H, s, 3-*H*), 6.85 (1H, s, 5-*H*), 3.9-3.86 (4H, m, 3",5"-H_2), 3.71-3.67 (4H, m, 2",6"-H_2); δ_C (176 MHz, $CDCl_3$) 159.4 (*C*-6), 154.4 (*C*-2), 148.5 (C-4'), 144.6 (C-1'), 141.3 (q, *J* = 33.0 Hz, *C*-4), 127 (*C*-2', 6'), 124.1 *(C*-3', 5'), 123.2 (q, *J* = 273 Hz, *C*F_3), 106.1 (q, *J* = 3.3 Hz, *C*-3), 102.6 (q, *J* = 4.0 Hz, *C*-5), 66.7 (*C*-3",5"), 45.4 (*C*-2",6"). υ_{max} (ATR) 1603, 1567, 1517, 1438, 1324, 1302, 1242, 1161, 1111, 982, 967, 847, 825, 757, 711, 695, 675 cm^{-1}. *m/z* (GC-MS, EI^+) (353 $[M]^+$), 68%, (334 $[M\text{-}F]^+$, 17%), 308 ($[MH\text{-}NO_2]^+$, 24%). Accurate Mass (ESI) *m/z* found $[M+H]^+$ 354.1067; $C_{16}H_{15}F_3N_3O_3$ requires *M*, 354.1066.

(9zD) *Diethyl-[6-(4'-nitrophenyl)-4-trifluoromethylpyridine-2-yl]amine*

Following general procedure D, and purification using EtOAc in hexane (0-8%) yielded the title compound as a yellow solid (207 mg, 61 %). mp 88-89 ^oC. δ_H (700 MHz, $CDCl_3$) 8.32-8.27 (2H, m, 3',5'-*H*), 8.21-8.15 (2H, m, 2',6'-*H*), 7.20 (1H, s, 3-*H*), 6.7 (1H, s, 5-*H*), 3.63-3.59 (4H, q, *J* = 7.1 Hz, 2",4"-H_2), 1.26 (6H, t, *J* = 7.1 Hz, 3",5"-H_3); δ_C (176 MHz, $CDCl_3$) 157.5 (*C*-6), 154.3 (*C*-2), 148.3 (*C*-4'), 145.2 (*C*-1'), 140.7 (q, *J* = 32.7, *C*-4), 127.6 (*C*-2',6'), 124.0 (*C*-3',5'), 123.4 (q, *J* = 273 Hz, *C*F_3), 103.5 (q, *J* = 3.3 Hz, *C*-3), 101.4 (q, *J* = 4.0 Hz, *C*-5), 43.13 (*C*-2",4"), 12.9 (*C*-3",5"). υ_{max} (ATR) 1616, 1601, 1566, 1516, 1503, 1442, 1349, 1344, 1332, 1263, 1249, 1175, 1123, 1110, 979, 853, 829, 758, 710, 695, 676 cm^{-1}. *m/z* (GC-MS, EI^+) 339 ($[M]^+$, 43%), 324 ($[M\text{-}CH_3]^+$, 64%), 310 ($[M\text{-}C_2H_5]^+$, 100%). Accurate Mass (ESI) *m/z* found $[M+H]^+$ 340.1270; $C_{16}H_{17}F_3N_3O_2$ requires *M*, 340.1273.

(9zE) *Butyl-[6-(4'-nitrophenyl)-4-trifluoromethylpyridine-2-yl]amine*

Following general procedure D, and purification using EtOAc in hexane (0-8%) yielded the title compound as a yellow solid (255 mg, 75 %), mp = 163-164 ^oC. δ_H (700 MHz, $CDCl_3$) 8.31-8.26 (2H, m, 3',5'-*H*), 8.18-8.11 (2H, m, 2',6'-*H*), 7.2 (1H, d, *J* = 0.6 Hz, 3-*H*), 6.6 (1H, s, 5-*H*), 4.9 (1H, s broad, *NH*), 3.44-3.39 (2H, m, 1"-H_2), 1.69-1.64 (2H, m, 2"-H_2), 1.51.44 (2H, m, 3"-H_2), 1.0 (3H, t, *J* = 7.4 Hz, 4"-H_3); δ_C (176 MHz, $CDCl_3$)

159.1 (*C*-6), 154.7 (*C*-2'), 148.4 (*C*-4'), 144.7 (*C*-1'), 140.8 (q, *J* = 33.2 Hz, *C*-4), 127.7 (*C*-2',6'), 124.0 *(C*3',5'), 123.2 (q, *J* = 273 Hz, *C*F_3), 105.3 (q, *J* = 3.3 Hz, *C*-3), 102.8 (*C*-5), 42.0 (*C*-2"), 31.6 (*C*-3"), 20.3 (*C*-4"), 14.0 (*C*-5"). υ_{max} (ATR) 3401 (*N*H), 1625, 1604, 1573, 1533, 1459, 1413, 1396, 1331, 1257, 1158, 1117, 1096, 860, 830, 757, 723, 695, 678, 639 cm^{-1}. *m/z* (GC-MS, EI^+) 339 ($[M]^+$, 31%), 310 ($[M-C_2H_5]^+$, 52%), 296 ($[M-C_3H_7]^+$, 100%). Accurate Mass (ESI) *m/z* found $[M+H]^+$ 340.1276; $C_{16}H_{17}F_3N_3O_2$ requires *M*, 340.1273.

(5y) *4-Trifluoromethyl-6-chloro-2-(4'-methoxyphenyl)-pyridine*

Following general procedure A, and purification using Et_2O in hexane (0-5%) yielded the title compound as a yellow oil (105 mg, 36 %). δ_H (700 MHz, $CDCl_3$) 7.99-7.94 (2H, m, 2',6'-H), 7.73 (1H, d, *J* = 0.6 Hz, 3-H), 7.37 (1H, d, *J* = 0.6 Hz, 5-H), 6.99-6.94 (2H, m, 3',5'-H), 3.85 (3H, s, OCH_3); δ_C (176 MHz, $CDCl_3$) 161.7 (C-4'), 159.1 (C-2), 151.2 (C-6), 141.5 (q, *J* = 34.1 Hz, C-4), 129.0 (C-1'), 128.6 (C-2',6'), 122.4 (q, *J* = 273 Hz, CF_3), 117.0 (q, *J* = 3.7 Hz, C-5), 114.4 (C-3',5'), 113.4 (q, *J* = 3.7 Hz, C-3), 55.4 (O-CH_3). υ_{max} (ATR) 1606, 1557, 1518, 1408, 1394, 1331, 1265, 1253, 1175, 1135, 1098, 1072, 1031, 830, 694, 665, 581 cm^{-1}. m/z (GC-MS, EI^+) 289 [M (^{37}Cl)]$^+$, 33%, 287 ([M (^{35}Cl)]$^+$, 100%). Accurate mass (ES^+) *m/z* found $[MH]^+$ 288.0401; $C_{13}H_{10}{}^{35}ClF_3NO$ requires *M*, 288.0403.

(9yA) *4-Trifluoromethyl-6-(N-pyrrolidin-yl)-2-(4'-methoxyphenyl)pyridine*

Following general procedure D, the crude mixture of 4-trifluoromethyl-6-chloro-2-(4'methoxyphenyl)-pyridine in (~1.0 mmol) and pyrrolidine (0.46 ml, 5.5 mmol) were combined at 130 ºC for 30 min. Purification through flash chromatography using EtOAc in hexane (0-5%) yielded the title compound as an off white solid (65 mg, 20 % (over 3 steps)). mp 103-104 ºC. δ_H (700 MHz, $CDCl_3$) 8.06-8.00 (2H, m, 2', 6'-*H*), 7.11 (1H, s, 3*H*), 7.01-6.96 (2H, m, 3',5'-*H*), 6.42 (1H, s, 5-*H*), 3.86 (3H, s, OCH_3), 3.64-3.53 (4H, m, 2",5"-H_2), 2.08-2.00 (4H, m, 3",4"-H_2); δ_C (176 MHz, $CDCl_3$) 160.7 (*C*-4'), 157.0 (*C*-6), 156.6 (*C*-2), 140.0 (q, *J* = 32.4 Hz, *C*-4), 132.0 (*C*-1'), 128.3 (*C*-2',6'), 123.77 (q, *J* = 273 Hz, *C*F_3), 114.0 (*C*-3',5'), 102.1 (q, *J* = 3.4 Hz, *C*-3), 100.0 (q, *J* = 4.0 Hz, *C*-5), 55.4 (O-*C*H_3), 46.9 (*C*-2",5"), 25.6 (*C*-3",4"). υ_{max} (ATR) 1613, 1563, 1497, 1460 1439, 1408, 1389, 1351, 1333, 1304, 1293,1246, 1183, 1157, 1120, 1105, 1097, 1051, 1032, 1014, 1004, 842, 825, 804, 782, 711, 680, 671, 648, 637, 618, 586, 522, 504 cm^{-1}.

m/z (GC-MS, EI^+) 323 $[MH]^+$, 7%, 322 $[M]^+$, 42%, 293 $[MHOCH_3]^+$, 100%; Accurate Mass (ESI) *m/z* found $[M+H]^+$ 323.1364; $C_{17}H_{18}F_3N_2O$ requires *M*, 323.1371.

(5w) *2-Chloro-4-(trifluoromethyl)-6-(3'-methoxyphenyl)pyridine*

Following general procedure A, and purification using Et_2O in heptane (0-3%) yielded the title compound as an off-white amorphous solid (147 mg, 51%). δ_H (700 MHz, $CDCl_3$) 7.83 (1H, s, 5-*H*), 7.59 (1H, t, *J* = 2.3, 2'-*H*), 7.58 (1H, d, *J* = 7.9, 6'-*H*), 7.48 (1H, s, 3-*H*), 7.41 (1H, t, *J* = 7.9, 5'-*H*), 7.03 (1H, dd, *J* = 7.9, 2.3, 4'-*H*), 3.91 (3H, s, OCH_3); δ_C (176 MHz, $CDCl_3$) 160.4 (*C*-3'), 159.4 (*C*-6), 152.4 (*C*-2), 141.8 (q, *J* = 34.3, *C*-4), 138.0 (*C*-1'), 130.2 (*C*-5'), 122.3 (q, *J* = 274.0, CF_3), 119.6 (*C*-6'), 118.7 (q, *J* = 3.7, *C*-3), 116.6 (*C*-4'), 114.8 (q, *J* = 3.5, *C*-5), 112.6 (*C*-2'), 55.6 (OCH_3); δ_F (376 MHz, $CDCl_3$) −64.7 (s); ν_{max} (ATR) 1600, 1561, 1459, 1400, 1333, 1274, 1221, 1177, 1142, 1102 cm^{-1}; Accurate Mass (ASAP) *m/z* found $[M]^+$ 287.0330; $C_{13}H_9{}^{35}ClF_3NO$ requires *M*, 287.0325.

(6z) *4-Tert butyl-6-chloro-2-(4'-nitrophenyl)pyridine*

Following general procedure A and purification using EtOAc in hexane (0-6%) yielded the title compound as an off white solid (117 mg, 40 %). mp 192-193 °C. δ_H (700 MHz, $CDCl_3$) 8.33-8.27 (2H, m, 3',5'-H) 8.19-8.12 (2H, m, 2',6'-H), 7.69 (1H, d, *J* = 1.5 Hz, 3-H), 7.34 (1H, d, *J* = 1.5 Hz, 5-H), 1.38 (9H, s, 4-C(CH_3)$_3$); δ_C (176 MHz, $CDCl_3$) 164.8 (C-4), 155.3 (C-2), 152.3 (C-6), 148.5 (C-4'), 144.3 (C-1'), 128.0 (C-2',6'), 124.1 (C-3',5'), 121.4 (C-5), 117.2 (C-3), 35.5 (4-*C*), 30.6 (CH_3) υ_{max} (ATR), 1588, 1533, 1509, 1410, 1338, 1171, 1104, 856, 813, 762, 731, 698, 644 cm^{-1}. Accurate mass (ES^+) *m/z* found $[MH]^+$ 291.0904; $C_{15}H_{16}{}^{35}ClN_2O_2$ requires *M*, 291.0900.

(10zA) *4-Tert butyl-6-(N-pyrrolidinyl)-2-(4'-nitrophenyl)pyridine*

Following general procedure D and purification using EtOAc in hexane (0-8%) yielded the title compound as a red solid (100 mg, 31 %), mp 180.5-182.5 °C. δ_H (700 MHz, $CDCl_3$) 8.3-8.23 (2H, m, 3',5'-*H*), 8.21-8.17 (2H, m, 2',6'-*H*), 7.09 (1H, d, *J* = 1.3 Hz, 3-*H*), 6.38 (1H, d, *J* = 1.3 Hz, 5-*H*), 3.55-3.60 (4H, m, 2",5"-H_2), 2.06-2.01 (4H, m, 3",4"-H_2), 1.35 (9H, s, CH_3); δ_C (176 MHz, $CDCl_3$) 161.9 (*C*4),157.7 (*C*-6), 152.6 (*C*-2), 147.7 (*C*-4'), 146.9 (*C*-4'), 127.6 (*C*-2',6'), 123.8 (*C*-3',5'), 107.03 (*C*-3), 103.4 (*C*-5), 47.0 (*C*-2",5"), 35.12 (*4-C*), 30.8 (4-C-(CH_3)$_3$)), 25.7 (*C*-3‴, 4‴). υ_{max} (ATR) 1597, 1549, 1501, 1476, 1456, 1323, 1107, 1101, 1011, 865, 850, 842, 832, 760, 698, 659,

631, 495 cm^{-1}; *m/z* (GC-MS, EI^+) 326 ($[MH]^+$, 16%), 325 ($[M]^+$, 78%). Accurate Mass (ESI) *m/z* found $[M+H]^+$ 326.1869; $C_{19}H_{24}N_3O_2$ requires *M*, 326.1869.

(6y) *4-Tert butyl-6-chloro-2-(4'-methoxyphenyl)pyridine*

Following general procedure A and purification using Et_2O in hexane (0-5%) yielded the title compound as a colourless oil (121 mg, 44 %). δ_H (700 MHz, $CDCl_3$) 7.96-7.92 (2H, m, 2', 6'-H), 7.55 (1H, d, *J* = 1.5 Hz, 3-H), 7.18 (1H, d, *J* = 1.5 Hz, 5-H), 7.00-6.95 (2H, m, 3',5'-H), 3.86 (3H, s, OCH_3), 1.35 (9H, s, 4-C(CH_3)$_3$); δ_C (176 MHz, $CDCl_3$) 164.0 (C-4), 160.9 (C-4'), 157.7 (C-2), 151.6 (C-6), 131.0 (C-1'), 128.5 (C-2', 6'), 119.0 (C-5), 115.5 (C3), 114.2 (C-3', 5'), 55.5 (OCH_3), 36.3 (4-*C*), 30.6 (CH_3). υ_{max} (ATR) 1607, 1591, 1535, 1514, 1462, 1410, 1385, 1303, 1247, 1175, 1111, 1074, 1031, 878, 831, 780, 650, 585, 507 cm^{-1}. m/z (GC-MS, EI^+) 277 ($[M (^{37}Cl)]^+$, 31%), 275 ($[M (35Cl)]^+$, 100%). Accurate mass (ES^+) *m/z* found $[MH]^+$ 276.1159; $C_{16}H_{19}{}^{35}ClNO$ requires *M*, 276.1155.

(6v) *4-Tertbutyl-6-chloro-2-(3'-thiophenyl) pyridine*

Following general procedure A and purification using EtOAc in hexane (0-7%) yielded the title compound as a white solid (168 mg, 67%). mp 50-51 ^oC. δ_H (700 MHz, $CDCl_3$) 8.95 (1H, dd, *J* = 3.0, 1.3 Hz, 2'-H), 7.6 (1H, dd, *J* = 5.0, 1.3 Hz, 4'-H), 7.5 (1H, d, *J* = 1.5 Hz, 3-H), 7.3 (1H, dd, *J* = 5.0, 3.0 Hz, 5'-H), 7.18 (1H, d, *J* = 1.5 Hz, 5-H), 1.35 (9H, s, CH_3); δ_C (176 MHz, $CDCl_3$) 164.2 (C-4), 153.9 (C-2), 151.6 (C-6), 141.2 (C-3'), 126.5 (C-5'), 126.3 (C-4'), 124.5 (C-2'), 119.4 (C-5), 116.1 (C-3), 35.3 (4-C), 30.6 (CH_3). υ_{max} (ATR) 1591, 1540, 1477, 1434, 1422, 1362, 1346, 1287, 1200, 1165, 1079, 1062, 861, 831, 794, 774, 731, 671 cm^{-1}. Accurate mass (ES^+) *m/z* found $[MH]^+$ 252.0596; $C_{13}H_{15}{}^{35}ClNS$ requires *M*, 252.0614.

(6u) *4-Tertbutyl-6-chloro-2-(2'-thiazolyl)pyridine*

Following general procedure A and purification using EtOAc in hexane (0-10%) yielded the title compound as an off white solid (106 mg, 42%). mp. 96.5-97.5 ^oC. δ_H (700 MHz, $CDCl_3$) 8.12 (1H, d, *J* = 1.5 Hz, 3-H) 7.9 (1H, d, J = 3.1 Hz, 5'-H), 7.5 (1H, d, *J* = 3.1 Hz, 4'-H), 7.3 (1H, d, *J* = 1.5 Hz, 5-H), 1.36 (9H, s, CH_3); δ_C (176 MHz, $CDCl_3$) 168.2 (C-2'), 165.0 (C-4), 151.6 (C-2), 151.4 (C-6), 144.1 (C-5'), 122.2 (C-5), 122.0 (C-4'), 115.6 (C-3), 35.5 (4-C), 30.6 (CH_3). υ_{max} (ATR) 1591, 1541, 1500, 1478, 1440, 1381, 1242, 1168, 1151, 1048, 874, 863, 794, 770, 745, 723, 620, 583, 515 cm^{-1}. m/z (GC-MS, EI^+) 254 ($[M (^{37}Cl)]^+$, 24%), 252

([M (^{35}Cl)]$^+$, 65%). Accurate mass (ES$^+$) *m/z* found [MH]$^+$ 253.0584; $C_{12}H_{15}{}^{35}ClN_2S$ requires *M*, 253.0566.

(6t) *4-Tertbutyl-6-chloro-2,2'-bipyridinyl-4'-carboxylic acid methyl ester*

Following general procedure A and purification using EtOAc in chloroform (0-5%) yielded the title compound as a white solid (200 mg, 66 %). mp. 103-104 ^{o}C. δ_H (600 MHz, $CDCl_3$) 8.9 (1H, bs, 3'-H) 8.8 (1H, d, *J* = 5.0 Hz, 6'-H), 8.4 (1H, d, J = 1.6 Hz, 3-H), 7.86 (1H, dd, *J* = 5.0, 1.6 Hz, 5'-H), 7.3 (1H, d, J = 1.6 Hz, 5-H), 4.0 (3H, s, OCH_3), 1.38 (9H, s, $C(CH_3)_3$); δ_C (151 MHz, $CDCl_3$) 165.8 (C=O), 164.7 (C-4), 156.3 (C-2'), 155.7 (C-2), 151.5 (C-6), 150.0 (C-6'), 138.7 (C-4'), 123.3 (C-5'), 122.0 (C-5), 121.0 (C-3'), 117.2 (C-3), 52.8 (OCH_3), 35.5 (4-*C*), 30.6 (CCH_3). υ_{max} (ATR), 1726 (C=O), 1585, 1532, 1478, 1438, 1373, 1365, 1356, 1315, 1294, 1268, 1165, 1133, 1100, 966, 891, 859, 769, 751, 694, 674, 650 cm^{-1}. m/z (GC-MS, EI$^+$) 306 ([M(^{37}Cl)]$^+$, 8%), 304 ([M (^{35}Cl)]$^+$, 25%), 291 ([M (^{37}Cl)-CH_3]$^+$, 37%), 289 ([M (^{35}Cl)-CH_3]$^+$, 100%). Accurate mass (ES$^+$) *m/z* found [MH]$^+$ 305.1065; $C_{16}H_{17}{}^{35}ClN_2O_2$ requires *M*, 305.1057.

(7z) *Methyl-6-chloro-2-(4'-nitrophenyl)pyridine-4-carboxylate*

Following general procedure A and purification using DCM in toluene (0-30%) yielded the title compound as a yellow solid (130 mg, 45 %), mp 166-167 ^{o}C. δ_H (700 MHz, $CDCl_3$) 8.36-8.33 (2H, m, 3',5'-*H*), 8.3 (1H, d, *J* = 1.1 Hz, 3-*H*), 8.3-8.23 (2H, m, 2',6'-*H*), 7.9 (1H, d, *J* = 1.1 Hz, 5-*H*), 4.0 (3H, s, OCH_3). δ_C (176 MHz, $CDCl_3$) 164.3 (*C*=O), 156.9 (*C*-2), 152.9 (*C*-6), 149.0 (*C*-4'), 142.8 (*C*1'), 141.5 (*C*-4), 128.1 (*C*-2',6'), 124.3 (*C*-3',5'), 123.8 (*C*-3), 119.0 (*C*-5), 53.4 (OCH_3). υ_{max} (ATR) 1733 (C=O), 1591, 1557, 1514, 1439, 1404, 1340, 1317, 1252, 1244, 1156, 1104, 982, 857, 818, 770, 755, 742, 722, 689 cm^{-1}; *m/z* (GC-MS, EI$^+$) 294 ([M (^{37}Cl)]$^+$, 33%), 292 ([M (^{35}Cl)]$^+$, 100%). Accurate mass (ES$^+$) *m/z* found [MH]$^+$ 293.0344; $C_{13}H_{10}{}^{35}ClN_2O_4$ requires *M*, 293.0329.

(7y) *Methyl-6-chloro-2-(4'-methoxyphenyl)-pyridine-4-carboxylate*

Following general procedure A and purification using EtOAc in hexane (0-10%) yielded the title compound as a white solid (134.5 mg, 48 %). mp. 102-103 ^{o}C. δ_H (700 MHz, $CDCl_3$) 8.11 (1H, d, *J* = 1.2 Hz, 3- H), 8.03-7.96 (2H, m, 2',6'-H), 7.7 (1H, d, *J* = 1.2 Hz, 5-H), 7.01-6.93 (2H, m, 3',5'-H), 4.0 (3H, s, CO_2CH_3), 3.86 (3H, s, 4'-OCH_3); δ_C (176 MHz, $CDCl_3$) 164.8 (C=O), 161.4 (C-4'), 158.7 (C-2), 152.0 (C-6), 140.8 (C-4), 129.6 (C-1'), 128.6 (C-

2',6'), 121.1 (C-5), 117.3 (C3), 114.4 (C-3',5'), 55.5 (4'-O*C*H$_3$), 53.1 (CO$_2$*C*H$_3$) υ_{max} (ATR) 1734 (C=O), 1606, 1597, 1583, 1549, 1519, 1441, 1404, 1390, 1302, 1256, 1180, 1161, 1113, 1071, 1021, 981, 824, 761, 732, 615, 585 cm^{-1}. m/z (GC-MS, EI$^+$) 279 ([M (^{37}Cl)]$^+$, 32%), 277 ([M (^{35}Cl)]$^+$, 100%). Accurate mass (ES$^+$) *m/z* found [MH]$^+$ 278.0600; $C_{14}H_{13}{}^{35}ClNO_3$ requires *M*, 278.0584.

(7'y) *methyl 2-fluoro-6-(4'-methoxyphenyl)pyridine-4-carboxylate*

Following general procedure A and purification using EtOAc in hexanes (0-20%) yielded the title compound as a colourless oil (157 mg, 55%). δ_H (700 MHz, $CDCl_3$) 8.13 (1H, m, 5-*H*), 8.03 (2H, m, 2', 6'-*H*), 7.32 (1H, m, 3-*H*), 7.00 (2H, m, 3', 5'-*H*), 4.00 (3H, s, CO$_2$C*H*$_3$), 3.88 (3H, s, COC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 164.8 (d, *J* = 4.2, *C*O$_2$CH$_3$), 162.3 (d, *J* = 247.0, *C*-2), 161.5 (*C*-4'), 157.2 (d, *J* = 14.0, *C*-6), 143.4 (d, J = 8.0, *C*-4), 129.5 (*C*-1'), 128.6 (*C*-2', 6'), 116.3 (d, J = 5.0, *C*-5), 114.4 (*C*-3', 5'), 106.7 (d, J = 40.0 Hz, *C*-3), 55.6 (CO$_2$*C*H$_3$), 53.1 (O*C*H$_3$); δ_F (376 MHz, $CDCl_3$) -66.2 (s); ν_{max} (ATR) 1733, 1608, 1568, 1520, 1420, 1396, 1352, 1252, 1206 1177 cm^{-1}; GC/MS (EI) *m/z* 261 [M]$^+$, 246 [M−CH$_3$]$^+$, 230 [M−OCH$_3$]. Accurate Mass (ASAP) *m/z* found [M]$^+$ 261.0811; $C_{14}H_{12}FNO_3$ requires *M*, 261.0801.

(11yA) *Methyl 2-(4'-methoxyphenyl)-6-(pyrrolidin-1''-yl)pyridine-4-carboxylate*

Following general procedure B and purification using EtOAc in hexane (0-15%) yielded the title compound as a white amorphous solid (32 mg 85%) δ_H (600 MHz, $CDCl_3$) 8.02 (2H, d, *J* = 8.8 Hz, 2', 6'-H), 7.46 (1H, d, *J* = 1.2 Hz, 3-H), 6.95 (2H, d, *J* = 8.8 Hz, 3', 5'-H), 6.83 (1H. d, *J* = 1.2 Hz, 5-H), 3.93 (3H, s, CO$_2$C*H*$_3$), 3.84 (3H, s, 4'-OC*H*$_3$), 3.54-3.62 (4H, m, 2'',5''-*H*$_2$), 2.11 – 1.92 (4H, m, 3''H, 4''-*H*$_2$). δ_C (151 MHz, $CDCl_3$) 166.86 (C=O), 161.08 (C-4'), 157.22 (C-2), 156.11 (C-2), 155.8 (C-6), 132.1 (C-1'), 139.08 (C-4), 128.1 (C-2', 6'), 113.8 (C-3', 5'), 105.8 (C-3), 104.2 (C-5), 55.31 (4'-OCH$_3$), 52.36 (CO$_2$*C*H$_3$), 46.9 (C-2'', 5''), 25.5 (C-3'', 4''). ν_{max} (ATR) 2949, 2848, 1719, 1611, 1554, 1444, 1243, 1030, 1178, 766 cm^{-1}. GC/MS (EI) *m/z* 313.1 [M+H]$^+$ (100%). Accurate Mass (ES$^+$) *m/z* found [M+H]$^+$ 313.1562, $C_{18}H_{21}N_2O_3$ requires *M*, 313.1552.

(7'x) *Methyl 2-fluoro-6-(4'-trifluoromethylphenyl) pyridine-4-carboxylate*

Following general procedure A and purification using C18 reverse phase chromatography (H$_2$O: MeCN, 0-100%) to yield the title compound as a white amorphous solid (151 mg, 50%). δ_H (700 MHz, $CDCl_3$) 8.22 (1H, dd, *J* = 2.0, 0.8 Hz, 5-H), 8.15 (2H, d, *J* = 8.4, 2',6'-

H), 7.74 (2H, d, *J* = 8.4, 3',5'-H), 7.46 (1H. dd, 0.8, 0.4 Hz, 3-H), 4.01 (3H, s, -OCH_3). δ_C (176 MHz, $CDCl_3$) 164.3 (d, *J* = 4.1 Hz C=O), 163.8 (d, *J* = 241.1 Hz, C-2), 155.5 (d, *J* = 14.0 Hz, C-6) 143.7 (d, *J* = 6.9 Hz, C-4), 139.92 (C-1'), 131.8 (q, *J* = 32.2 Hz, C-6'), 127.3 (C-2', 6'), 125.8 (C-3', 5'), 124.0 (q, *J* = 263.3 Hz, -CF_3), 117.3 (d, *J* = 4.7 Hz C-5), 108.8 (d, *J* = 39.7 Hz, C-3) 53.1 (-OCH_3). δ_F (376 MHz, $CDCl_3$) -62.78 (-CF_3), -65.15 (Ar-F). ν_{max} (ATR) 2957, 2256, 1741, 1578, 1329, 1255, 1136, 905, 731 cm^{-1}. GC/MS (EI) *m/z* found $[M+H]^+$ 300.0, $[M+MeCN+H]^+$ 341.1. Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 300.0670, $C_{14}H_{10}F_4NO_2$ requires *M* 300.0648.

(11xB) *Methyl 2-(morpholin-4''-yl)-6-[4'-(trifluoromethyl)phenyl]pyridine-4-carboxylate*
Following general procedure B and purification using EtOAc in hexane (0-15%) yielded the title compound as an off white solid (28 mg, 83%). mp. 272-273 ^oC (ethanol). δ_H (599 MHz, $CDCl_3$) 8.14 (2H, d, *J* = 8.3 Hz, 3', 5'-H), 7.70 (2H, d, *J* = 8.3 Hz, 2', 6'-H), 7.69 (1H, d, *J* = 1.0 Hz, 3-H), 7.25 (1H, d, *J* = 1.0 Hz, 5-H), 3.97 (3H, s, -OC*H*$_3$), 3.90 – 3.83 (2H, m, 3'', 5''-H_2), 3.71 – 3.64 (1H, m, 2'', 6''-H_2). δ_C (151 MHz, $CDCl_3$) 166.1 (C=O), 159.54 (C-2), 154.6 (C-4), 142.3 (C-6), 140.0 (C-1'), 130.9 (q, *J* = 30.7 Hz, C-4') 127.1 (C-2'', 6''), 125.5 (q, *J* = 4.0 Hz C-3'', 5''), 124.2 (q, *J* = 271.0 Hz -CF_3), 109.42 (C-3), 106.1 (C-5), 66.7 (C-3'', 5''), 52.6 (-OCH_3), 45.5 (C-2'', 6''). δ_F (376 MHz, $CDCl_3$) -62.56. ν_{max} (ATR) 2960, 2860, 2259, 1734, 1604, 1563, 1444, 1237, 1124 cm^{-1}. GC/MS (EI) *m/z* found $[M+H]^+$ 367.1. Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 367.1279, $C_{18}H_{18}F_3N_2O_3$ requires *M* 367.1270.

(11xE) *methyl 2-(butylamino)-6-[4'-(trifluoromethyl)phenyl]pyridine-4-carboxylate*
Following general procedure B and purification using EtOAc in hexane (0-40%) yielded the title compound as a light yellow oil (36 mg, 64%). δ_H (700 MHz, $CDCl_3$) 8.10 (1H, d, *J* = 7.6 Hz, 2', 6'-H), 7.71 (2H, d, *J* = 7.6 Hz, 3', 5'H), 7.55 (1H, d, *J* = 1.1 Hz, 3-H), 6.98 (1H, d, *J* = 1.1 Hz, 5-H), 3.95 (3H, s, -OCH_3), 3.39 (2H, q, *J* = 6.7 Hz, 1''-H_2), 1.70 – 1.62 (2H, m, 2''-H_2), 1.46 (1H, m, 3''-H_2), 0.97 (3H, t, *J* = 7.4 Hz, 4''-C*H*$_3$). δ_C (176 MHz, $CDCl_3$) 166.1 (C=O), 166.0 (C-2), 158.98 (C-6), 154.3 (C-4) 140.0 (C-1'), 130.8 (q, *J* = 30.8 Hz, C-4') 127.1 (C-2', 6') , 125.5 (q, *J* = 3.8 Hz, C-3', 5'), 124.1 (q, *J* = 272.0 Hz -CF_3), 108.6 (C-3), 106.1 (C-5), 52.6 (-OCH_3), 42.0 (C-1''), 31.5 (C-2''), 20.2 (C-3''), 13.8 (C-4''). δ_F (376 MHz, $CDCl_3$) -62.58 (-CF_3). ν_{max} (ATR) 3423, 2960, 2259, 1724, 1571, 1329, 1249, 1124 cm^{-1}. GC/MS (EI) *m/z* found $[M+H]^+$ 353.5. Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 353.1484, $C_{18}H_{20}F_3N_2O_2$ requires *M* 353.1477.

(8z) *Tert butyl 2-chloro-6-(4'-nitrophenyl)pyridine-4-carboxylate*

Following general procedure A and purification using $CHCl_3$ in hexane (0-60%) yielded the title compound as a bright yellow solid (203 mg, 61%). mp 141-142 ^oC (methanol). δ_H (599 MHz, $CDCl_3$) 8.32 (2H, d, *J* = 8.9 Hz, 3',5'-H), 8.23 – 8.19 (3H, m, 2',6', 5-H), 7.81 (1H, d, *J* = 1.1 Hz, 3-H), 1.62 (9H, s, OC(CH_3)$_3$). δ_C (151 MHz, $CDCl_3$) 162.5 (C=O), 156.0 (C-6), 152.5 (C-2), 148.7 (C-4'), 143.32 (C-4), 142.8 (C-1'), 127.9 (C-2', 6'), 124.1 (C-3', 5'), 123.6 (C-3), 118.9 (C-5), 83.7 (O*C*(CH_3)$_3$), 28.0 ((*C*H_3)$_3$). ν_{max} (ATR) 2984, 1719, 1593, 1548, 1524, 1346, 1160, 861 cm^{-1}. GC/MS (EI) *m/z* found 325.3 ([M (^{35}Cl)+H]$^+$ 100%), 327.3 ([M (^{37}Cl)+H]$^+$ 31%). Accurate Mass (ES^+) *m/z* found [M (^{35}Cl)+H]$^+$ 335.0803 , [M-tBu+H]$^+$ 279.0191, $C_{16}H_{16}{}^{35}ClN_2O_4$ requires *M* 335.0799.

(12zB) *Tert butyl 2-(morpholin-4"-yl)-6-(4'-nitrophenyl)pyridine-4-carboxylate*

Following general procedure D and purification using EtOAc in hexane (0-15%) yielded the title compound as a bright yellow solid (27 mg, 78%). mp 216-217 ^oC (ethanol)**.** δ_H (600 MHz, $CDCl_3$) 8.30 (2H, d, *J* = 8.9 Hz, 3', 5'-H), 8.19 (2H, d, *J* = 8.9 Hz, 2', 6'-H), 7.66 (1H, d, *J* = 1.0 Hz, 3-H), 7.24 (1H, d, *J* = 1.0 Hz, 5-H), 3.88 (4H, t, *J* = 4.9 Hz, 3'', 5''-H_2), 3.69 (4H, t, *J* = 4.9 Hz, 2'', 6''-H_2), 1.63 (9H, s, -(CH_3)$_3$). δ_C (151 MHz, $CDCl_3$) 164.4 (C=O) , 159.5 (C-2), 153.3 (C-4'), 148.1 (C-1'), 145.0 (C-6), 142.1 (C-4), 127.6 (C-2', 6'), 123.8 (C-3', 5'), 110.0 (C-3), 106.8 (C-5), 82.6 (-*C*(CH_3)$_3$), 66.6 (C-3'', 5''), 45.6 (C-2'', 6''), 28.1 (-(CH_3)$_3$). ν_{max} (ATR) 2982, 2863, 1717, 1596, 1563, 1516, 1433, 1341, 1251, 998 cm^{-1}. GC/MS (EI) *m/z* found 386.1 ([M+H]$^+$ 100%), 330.1 ([M-tBu+H]$^+$ 62%). Accurate Mass (ES^+) *m/z* found [M+H]$^+$ 386.1726, $C_{20}H_{24}N_3O_5$ requires *M* 386.1716.

(8y) *Tert butyl 2-chloro-6-(4'-methoxyphenyl)pyridine-4-carboxylate*

Following general procedure A and purification using $CHCl_3$ in hexane (0-55%) yielded the title compound as an off white solid (182 mg, 57%). mp, 119-120 ^oC (methanol). δH (600 MHz, $CDCl_3$) 8.07 (1H, d, *J* = 1.2 Hz, 3-H), 8.01 – 7.96 (2H, m, 2', 6'-H), 7.63 (1H, d, *J* = 1.1 Hz, 5-H), 7.01 – 6.95 (2H, m, 3',5'-H), 3.85 (3H, s, -OCH_3), 1.61 (9H, s, -(CH_3)$_3$). δ_C (151 MHz, $CDCl_3$)163.2 (C=O), 161.2 (C-4'), 158.4 (C-6), 151.8 (C-2), 142.7 (C-4), 129.7 (C-1'), 128.5 (C-5), 121.0 (C-2', 6'), 117.3 (C-3), 114.22 (C-3' 5'), 83.01 (-*C*(CH_3)$_3$, 55.37 (-OCH_3), 28.0 (OC(*C*H_3)$_3$). ν_{max} (ATR) 2986, 2874, 1728, 1595, 1548, 1415, 1323, 1238, 1147, 1027 cm^{-1}. GC/MS (EI) *m/z* found 320.6 ([M(^{35}Cl)+H]$^+$ 72%), 322.5 ([M(^{37}Cl)+H]$^+$ 21%).

Accurate Mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 320.1071, $C_{17}H_{19}NO_3{}^{35}Cl$ requires *M* 320.1053.

(12yA) *Tert butyl 2-(4'-methoxyphenyl)-6-(pyrrolidin"-yl)pyridine-4-carboxylate*

Following general procedure D and purification using EtOAC in hexane (0-20%) yielded the title compound as an off white amorphous solid (41 mg, 90%). δ_H (600 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 8.7 Hz, 2', 6'-H), 7.40 (1H, d, *J* = 1.1 Hz, 3-H), 6.98 (2H, d, *J* = 8.7 Hz, 3', 5'-H), 6.82 (1H, d, *J* = 1.1 Hz, 5-H), 3.86 (3H, s, -OCH_3), 3.57-3.63 (4H, m, 3'', 4''-H_2), 2.13 – 1.93 (4H, m, 2'',5''-H_2), 1.61 (9H, s, -$(CH_3)_3$). δ_C (151 MHz, CDC_3) 165.4 (C=O), 160.3 (C-4'), 155.5 (C-2) 141.0 (C-6), 128.2 (C-2',6'), 124.6 (C-1'), 121.6 (C-4), 113.8 (C-3',5'), 106.0 (C-3), 104.2 (C-5), 81.7 (-*C*$(CH_3)_3$), 55.3 (-OCH_3), 47.0 (C-2'',5''), 28.1 (C(CH_3)$_3$), 25.5 (C-3'',4''). ν_{max} (ATR) 2972, 2859, 1714, 1607, 1557, 1459, 1382, 1246, 1030 cm^{-1}. GC/MS (EI) *m/z* found 356.3 ($[M+H]^+$ 100%), Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 355.2022, $C_{21}H_{27}N_2O_3$ requires *M* 355.2022.

(8x) *tert-butyl 2-chloro-6-(4-triflurometh-lphenyl)pyridine-4-carboxylate*
Following general procedure A and purification using C18 reverse phase chromatography (H_2O: MeCN, 0-100%) yielded the title compound as a light brown amorphous solid (140 mg, 39%). δH (700 MHz, $CDCl_3$) 8.19 (1H, d, *J* = 1.1 Hz, 3-H), 8.18 – 8.15 (2H, d, *J* = 1, 2', 6'-H), 7.79 (1H, d, *J* = 1.1 Hz, 5-H), 7.74 (2H, d, *J* = 8.1 Hz m, 3', 5'-H), 1.63 (9H, s, -$(CH_3)_3$). δC (176 MHz, $CDCl_3$) 162.7 (C=O), 157.0 (C-2), 152.3 (C-1'), 143.1 (C-4), 140.4 (C-6), 127.4 (C-2', 6'), 125.8 (q, *J* = 3.9 Hz, C-3', 5'), 123.9 (q, *J* = 272.2 Hz, -CF_3), 123.0 (C-5), 118.5 (C-3), 83.4 (-*C*$(CH_3)_3$), 28.0 (-$(CH_3)_3$). δF (376 MHz, $CDCl_3$) -62.72 (-CF_3). ν_{max} (ATR) 2975, 2887, 1726, 1557, 1471, 1382, 1326, 1261, 1131, 950 cm^{-1}. GC/MS (EI) *m/z* found 358.1 ($[M(^{35}Cl)+H]^+$ 100%), 360.1 ($[M(^{37}Cl)+H]^+$ 39%). Accurate Mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 358.0826, $[M(^{35}Cl)$-tBu+H$]^+$ 302.0210, $C_{17}H_{16}{}^{35}ClF_3NO_2$ requires *M* 358.0822.

(12xA) *tert-butyl 2-(pyrrolidin-1-yl)-6-[4-(trifluoromethyl)phenyl]pyridine-4-carboxylate*
Following general procedure D and purification using EtOAC in hexane (0-10%) yielded the title compound as a white solid (39 mg, 90%). mp 168-169 ^oC (ethanol). δH (600 MHz, $CDCl_3$) 8.19 – 8.15 (2H, d, *J* = 8.2 Hz, 2', 6'-H), 7.69 (2H, d, *J* = 8.2 Hz, 3', 5'-H), 7.48 (1H, d, *J* = 1.1 Hz, 3-H), 6.92 (1H, d, *J* = 1.1 Hz, 5-H), 3.62-3.58 (4H, m, 2'', 5''-H), 2.02-2.07

(4H, m, 3', 4'H), 1.62 (9H, s, -(CH_3)$_3$). δC (151 MHz, $CDCl_3$) 165.1 (C=O), 157.36 (C-2), 154.32 (C-6), 142.81 (C-4), 141.2 (C-1'), 130.4 (q, *J* = 32.6 Hz C-4), 127.1 (C-2',6'), 125.3 (q, *J* = 3.8 Hz C-3', 5'), 124.3 (q, *J* = 273.4 Hz, -CF_3), 107.0 (C-3), 106.0 (C-5), 82.0 (-*C*(CH_3)$_3$), 46.9 (C-2'', 5'', 28.1 (-(CH_3)$_3$), 25.5 (C-3'', 4''). δF (376 MHz, $CDCl_3$) -62.49 (-CF_3). ν_{max} (ATR) 2972, 2839, 2259, 1734, 1604, 1566, 1443, 1326, 1251, 1124 cm^{-1}. GC/MS (EI) *m/z* found 393.5 ($[M+H]^+$ 100%), Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 393.1785, $C_{21}H_{24}F_3N_2O_2$ requires *M* 393.1789.

13 *2-(4'-nitrophenyl)-6-(pyrrolidin-1"-yl)-4-(pyrrolidine-1'''-carbonyl)pyridine*
Following procedure D and purification using EtOAc in hexane (0-50%) yielded the title compound as a yellow solid (275 mg, 75 %). mp 239.5-240.5 °C. δ_H (500 MHz, $CDCl_3$) 8.29-8.21 (2H, m, 3',5'-*H*), 8.21-8.14 (2H, m, 2',6'-*H*), 7.1 (1H, s, 3-*H*), 6.4 (1H, s, 5-*H*), 3.7 (2H, t, *J* = 7.0 Hz, 2"'-H_2), 3.60-3.49 (4H, m, 2",5"-H_2), 3.43 (2H, t, *J* = 6.7 Hz, 5"'-H_2), 2.06-2.01 (4H, m, 3",4"-H_2), 2.0 (2H, p, *J* = 7.0 Hz, 3"'-H_2), 1.9 (2H, p, *J* = 6.7 Hz, 4"'-H_2); δ_C (125 MHz, $CDCl_3$) 168.4 (*C*=O), 157.2 (*C*-6), 153.3 (*C*-2), 148.0 (*C*-4'), 146.9 (*C*-4), 145.8 (*C*-1'), 127.5 (*C*-2',6'), 123.8 (*C*-3',5'), 106.0 (*C*-3), 104.1 (*C*-5), 49.4 (*C*-5"'), 46.9 (C-2",5"), 46.2 (*C*-2"'), 26.4 (*C*-4"'), 25.6 (*C*-3",4"), 24.5 (*C*-3"'); ν_{max} 1618, 1616, 1598, 1541, 1512, 1478, 1456, 1442, 1419, 1344, 1322, 1102, 858, 755, 702, 513 cm^{-1}; *m/z* (LC-MS, ES^+) 1121 ($[M_3Na]^+$, 38%), 755 ($[M_2Na]^+$, 81%), 366 ($[M]^+$, 100%); Accurate mass (ES^+) *m/z* found $[MH]^+$ 367.1781; $C_{20}H_{23}N_4O_3$ requires *M*, 367.1770.

(17w) *Methyl 6-chloro-5-(3-methoxyphenyl)pyridine-3-carboxylate*
Following general procedure and purification using EtOAc in heptane (0-15%) yielded the title compound as a white amorphous solid (229 mg, 76%). δ_H (700 MHz, $CDCl_3$) 8.49 (1H, d, *J* = 2.2, 6-*H*), 8.34 (1H, d, *J* = 2.2, 4-*H*), 7.48 (2H, m, 2', 6'-*H*), 7.00 (2H, m, 3', 5'-*H*), 4.10 (3H, s, 2-COCH_3), 3.93 (3H, s, CO_2CH_3), 3.86 (3H, s, 4'-OCH_3); δ_C (176 MHz, $CDCl_3$) 165.7 (CO_2CH_3), 161.4 (*C*-2), 159.7 (*C*-4'), 148.2 (*C*-6), 139.7 (*C*-4), 129.8 (*C*-5), 129.3 (*C*-1'), 128.0 (*C*-2', 6'), 114.7 (*C*-3', 5'), 113.9 (*C*-3), 55.5 (4'-OCH_3), 54.6 (2-COCH_3), 52.5 (CO_2CH_3); ν_{max} (ATR) 1732, 1606, 1563, 1519, 1474, 1417, 1327, 1285, 1245, 1181, 1087, 1060, 1014 cm^{-1}; Accurate Mass (ASAP) *m/z* found $[M+H]^+$ 274.1075; $C_{15}H_{16}NO_4$ requires *M*, 274.1079.

(17'y) *Methyl 6-fluoro-5-(4'-methoxyphenyl)pyridine-3-carboxylate*

Following general procedure A and purification using EtOAc in hexane (0-50%) yielded the title product as a pale yellow amorphous solid (107 mg, 58%). δ_H (600 MHz, $CDCl_3$) 8.77 (1H, m, 6-*H*), 8.45 (1H, m, 4-*H*), 7.54 (2H, d, *J* = 8.6, 2', 5'-*H*), 7.01 (2H, d, *J* = 8.6, 3', 5'-*H*), 3.96 (3H, s, CO_2CH_3), 3.86 (3H, s, OCH_3); δ_C (151 MHz, $CDCl_3$) 165.0 (CO_2CH_3), 162.6 (d, *J* = 246.2, *C*-6), 160.3 (*C*-4'), 147.8 (dd, *J* = 16.7, 5.1, *C*-6), 141.5 (d, *J* = 6.4, *C*-4), 130.2 (d, *J* = 6.4, *C*-2', 6'), 125.1 (m, *C*-1'), 123.7 (d, *J* = 28.6, *C*-3), 114.5 (*C*-3', 5'), 55.5 (OCH_3), 52.7 (CO_2CH_3); δ_F (376 MHz, $CDCl_3$) −65.4 (s); ν_{max} (ATR) 1725, 1609, 1518, 1434, 1411, 1313, 1250, 1200, 1181, 1120, 1047, 1029 cm^{-1}; Accurate Mass (ASAP) *m/z* found $[M]^+$ 261.0819; $C_{14}H_{12}FNO_3$ requires *M*, 261.0801.

(20yB) *Methyl 5-(4'-methoxyphenyl)-6-(morpholin-4''-yl)pyridine-3-carboxylate*
Following general procedure B and purification using EtOAc in hexane (0-20%) yielded the title compound as a light yellow solid (22 mg, 88%). mp 242-243 °C. δ_H (599 MHz, $CDCl_3$) 8.78 (1H, d, *J* = 2.3 Hz, 6-H), 7.97 (1H, d, *J* = 2.3 Hz, 4-H), 7.44 (2H, d, *J* = 8.3 Hz, 3', 5'-H), 6.95 (2H, d, *J* = 8.3 Hz, 3', 6'-H), 3.88 (3H, s, CO_2CH_3), 3.84 (3H. s, 4'-OCH_3), 3.62 (4H, t, *J* = 4.5 Hz, 3'', 5''-H_2), 3.24 (4H, t, *J* = 4.5 Hz, 2'', 6''-H_2). δ_C (151 MHz, $CDCl_3$) 159.2 (C=O), 147.9 (C-4'), 140.7 (C-2), 131.4 (C-3), 128.7 (C-4), 127.8 (C-2', 6'), 125.8 (C-1') , 124.8 (C-6), 118.5 (C-4), 114.4 (C-3', 5'), 66.6 (-OCH_3), 55.3 (CO_2CH_3), 51.9 (C-2'', 6''), 48.7 (C-3'', 5''). ν_{max} (ATR) 2967, 2854, 1717, 1596, 1509, 1411, 1361, 1249, 1234, 1100 cm^{-1}. *m/z* (LC-MS, ES^+) 329.1 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 329.1511; $C_{18}H_{21}N_2O_4$ requires *M*, 329.1501.

(17y) *Methyl 6-chloro-5-(4'-methoxyphenyl)pyridine-3-carboxylate*
Following general procedure A and purification using $CHCl_3$ in hexane (0-50%) yielded the title compound as an off white solid (169 mg, 61%). mp 171-172 °C. δH (700 MHz, $CDCl_3$) 8.93 (1H, d, *J* = 2.3 Hz, 6-H), 8.24 (1H, d, *J* = 2.3 Hz, 4-H), 7.42 (2H, d, *J* = 8.7 Hz, 2', 6'-H), 6.99 (2H, d, *J* = 8.7 Hz, 3', 5'-H), 3.95 (3H, s, CO_2CH_3), 3.86 (3H, s, -OCH_3). δC (176 MHz, $CDCl_3$) 165.0 (C=O), 159.9 (C-4'), 153.8 (C-2), 148.9 (C-6), 140.2 (C-4), 136.5 (C-3), 130.5 (C-2', 6'), 128.7 (C-1'), 125.2 (C-5), 113.9 (C-3', 5'), 55.3 (4'-OCH_3), 52.6 (CO_2CH_3). ν_{max} (ATR) 2960, 2849, 1726, 1614, 1591, 1523, 1446, 1394, 1317, 1252, 1181 cm^{-1}. *m/z* (LC-MS, ES^+) 279.0 ($[M(^{35}Cl)+H]^+$, 100%), 281.1 ($[M(^{37}Cl)+H]^+$, 28%), Accurate mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 278.0601, $C_{14}H_{13}NO_3{}^{35}Cl$ requires *M* 278.0584.

(20yA) *Methyl 5-(4'-methoxyphenyl)-6-(pyrrolidin-1''-yl)pyridine-3-carboxylate*
Following general procedure B and purification using EtOAC in hexane (0-15%) yielded the title compound as a light yellow amorphous solid (24 mg, 71%). δ_H (599 MHz, $CDCl_3$) 8.03 (2H, *J* = 8.8 Hz, 3', 5'-H), 7.46 (1H, d, *J* = 1.2 Hz, 6-H), 6.97 (2H, d, *J* = 8.8 Hz, 2', 6'-H), 6.86 (1H, , d, *J* = 1.2 Hz, 4-H), 3.95 (3H, s, CO_2CH_3), 3.85 (2H, s, 4'-OCH_3), 3.62 (2H, m, 2'', 5''-H_2), 2.08 – 2.01 (1H, m, 3'', 4''-H_2). δC (151 MHz, $CDCl_3$) 166.7 (C=O), 160.5 (C-4'), 157.0 (C-2), 155.6 (C-3), 139.1 (C-4), 128.3 (C-2', 6'), 113.8 (C-3', 5'), 113.1 (C-1'), 105.9 (C-6), 104.4 (C-4), 55.3 (-OCH_3), 52.4 (CO_2CH_3), 47.0 (C-2'', 5''), 25.5 (C-3'', 4''). ν_{max} (ATR) 2972, 1731, 1607, 1557, 1518, 1477, 1459, 1246, 1216, 1178, 1030 cm^{-1}. *m/z* (LC-MS, ES^+) 313.1 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 313.1571, $C_{18}H_{21}N_2O_3$ requires *M* 313.1552.

(17x) *Methyl 6-chloro-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*
Following General procedure A and purification using C18 reverse phase chromatography (H_2O: MeCN, 0-100%) yielded the title compound as an off white amorphous solid (173 mg, 55%). δ_H (599 MHz, $CDCl_3$) 9.02 (1H, d, *J* = 2.3 Hz, 6-H), 8.27 (1H, d, *J* = 2.3 Hz, 4-H), 7.85 – 7.67 (2H, m, 3', 5'-H), 7.65 – 7.53 (2H, m, 2', 6'-H), 3.98 (3H, s, CO_2CH_3). δ_C (151 MHz, $CDCl_3$) 164.6 (C=O), 153.5 (C-2), 150.0 (C-6), 140.2 (C-4), 140.0 (C-1'), 135.5 (C-2), 131.01 (q, *J* = 32.8 Hz, C-4') 129.7 (C-2', 6'), 127.7 (C-4), 125.5 (q *J* = 3.7 Hz C-3',5'), 123.8 (q, *J* = 269.4 Hz, -CF_3) 52.7 (CO_2CH_3). δ_F (376 MHz, $CDCl_3$) -62.73 (-CF_3). ν_{max} (ATR) 3070, 2964, 1714, 1596, 1397, 1323, 1261, 1169, 1124, 1071 cm^{-1}. *m/z* (LC-MS, ES^+) 316.4 ($[M(^{35}Cl)+H]^+$, 72%), 318.3 ($[M(^{37}Cl)+H]^+$, 22%), Accurate mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 316.0359, $C_{14}H_{10}{}^{35}ClF_3NO_2$ requires *M* 316.0352.

(20xA) *Methyl 6-(pyrrolidin-1''-yl)-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*
Following general procedure C and purification using EtOAc in hexane (0-15%) yielded the title compound as a light yellow amorphous solid (36 mg, 88%). δ_H (599 MHz, $CDCl_3$) 8.16 (2H, d, *J* = 8.1 Hz, 3', 5'-H), 7.68 (2H, d, *J* = 8.1 Hz, 2', 6'-H), 7.53 (1H, d, *J* = 1.2 Hz, 6-H), 6.95 (1H, d, *J* = 1.2 Hz, 4-H), 3.95 (3H, s, CO_2CH_3), 3.59 (4H, d, *J* = 6.4 Hz, C-2'', 5''-H_2), 2.09 – 1.97 (4H, m, C-3'', 4''-H_2). δ_C (151 MHz, $CDCl_3$) 166.44 (C=O), 157.3 (C-2), 154.50 (C-5), 142.6 (C-3), 139.2 (C-1'), 130.7 (q, *J* = 32.6 Hz C-6'), 127.1 (C-3', 5'), 125.35 (C-2', 6'), 124.1 (q, *J* = 263.78 Hz, CF_3), 106.9 (C-6), 106.1 (C-4), 52.5 (-OCH_3), 47.0 (C-2'', 5''), 25.5 (C-3'', 4''). δ_F (376 MHz, $CDCl_3$) δ -62.52. ν_{max} (ATR) 2966, 2863, 1723, 1609, 1560,

1477, 1446, 1323, 1238, 1112 cm^{-1}. *m/z* (LC-MS, ES^+) 351.1 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 351.1308, $C_{18}H_{18}F_3N_2O_2$ requires *M* 351.1320.

(18y) *Tert butyl 6-chloro-5-(4'-methoxyphenyl)pyridine-3-carboxylate*
Following General procedure A and purification using EtOAc in hexane yielded the title compound as an off white solid (140 mg 44%). mp. 177-178 ^oC (methanol). δ_H (599 MHz, $CDCl_3$) 8.86 (1H, d, *J* = 2.5 Hz, 6-H), 8.16 (1H, d, *J* = 2.4 Hz, 4-H), 7.39 (2H, d, *J* = 9.1, 2', 6'-H), 6.99 (2H, d, *J* = 9.1 Hz, 3', 5'-H), 3.86 (3H, s, 4'-OCH_3), 1.59 (9H, s, (C*H*$_3$)$_3$). δ_C (151 MHz, $CDCl_3$) 163.6 (C=O), 159.9 (C-4'), 153.3 (C-2), 148.9 (C-6), 140.1 (C-4), 136.3 (C-3), 130.5 (C-2', 6'), 129.0 (C-1'), 126.9 (C-5), 113.9 (C-3' 5'), 82.5 (-$C(CH_3)_3$), 55.3 (-OCH_3), 28.1 ($C(CH_3)_3$). ν_{max} (ATR) 2987, 2830, 2164, 1726, 1593, 1400, 1258, 1136, 1033 cm^{-1}. *m/z* (LC-MS, ES^+) 320.1 ($[M(^{35}Cl)+H]^+$, 46%), 322.1 ($[M(^{37}Cl)+H]^+$, 18%), 264.0 ($[M(^{35}Cl)$-tBu+H]$^+$, 100%), 266.0 ($[M(^{37}Cl)$-tBu+H]$^+$, 38%) Accurate mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 320.1075, $C_{17}H_{19}{}^{35}ClNO_3$ requires *M* 320.1053.

(21yA) *Tert butyl 5-(4'-methoxyphenyl)-6-(pyrrolidin-1''-yl)pyridine-3-carboxylate*
Following general procedure D and purification using EtOAC in hexane (0-20%) yielded the title compound as a light yellow solid (26 mg, 75%). mp 248-249 ^oC (ethanol). δ_H (700 MHz, CDCl3) 8.73 (1H, d, *J* = 2.2 Hz, 6-H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.24 – 7.20 (2H, m, 2', 6'-H), 6.91 – 6.87 (2H, m, 3', 5'-H), 3.83 (3H, s, 4'-OCH_3), 3.17 – 3.23 (4H, m, 2'', 5''-H_2), 1.79 – 1.75 (4H, m, 3'', 4''-H_2), 1.54 (9H, s, C(*CH*$_3$)$_3$). δ_C (176 MHz, $CDCl_3$) 165.3 (C=O), 158.6 (C-4'), 148.2 (C-6), 140.6 (C-4), 132.4 (C-1') 130.1 (C-2', 6'), 128.3 (C-2), 127.8 (C-3), 116.7 (C-5) 113.4 (C-3', 5'), 80.5 (*C*$(CH_3)_3$), 55.7 (-OCH_3), 50.3 (C-2'', 5''), 28.3 ($C(CH_3)_3$), 25.6 (C-3'', 4''). ν_{max} (ATR) 2985, 2880, 2256, 1699, 1598, 1513, 1459, 1308, 1251, 1166 cm^{-1}. *m/z* (LC-MS, ES^+) 355.2 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 355.2033, $C_{21}H_{27}N_2O_3$ requires *M* 355.2022

(21yB) *Tert butyl 5-(4'-methoxyphenyl)-6-(morpholin-4''-yl)pyridine-3-carboxylate*
Following general procedure D and purification using EtOAC in hexane (0-20%) yielded the title compound as a light yellow amorphous solid (30 mg, 87%). δ_H (700 MHz, $CDCl_3$) 8.74 (1H, d, *J* = 2.3 Hz, 6-H), 7.92 (1H, d, *J* = 2.3 Hz, 4-H), 7.45 (2H, d, *J* = 8.7 Hz, 2', 6'-C), 6.95 (2H, d, *J* = 8.7 Hz, 3', 5--H), 3.84 (3H, s, 4'-OCH_3), 3.61 (4H, t, *J* = 4.7 Hz, 3'', 5''-H_2), 3.21 (4H, t, *J* = 4.7 Hz, 2'', 6''-H_2), 1.56 (9H, s, C(C*H*$_3$)$_3$). δ_C (176 MHz, $CDCl_3$) 164.9

(C=O), 159.1 (C-4'), 147.7 (C-5), 140.5 (C-4), 131.6 (C-1'), 128.8 (C-2'', 6''), 125.7 (C-2), 124.7 (C-3), 120.4 (C-5), 114.3 (C-3'', 5''), 81.1 ($C(CH_3)_3$), 66.6 (C-2'', 6''), 55.3 ($-OCH_3$), 48.8 (C-3'', 5''), 28.3 ($C(CH_3)_3$). ν_{max} (ATR) 2967, 2246, 1731, 1569, 1414, 1320, 1112 cm^{-1}. *m/z* (LC-MS, ES^+) 371.2 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 371.2000, $C_{21}H_{26}N_2O_4$ requires *M* 371.1971.

(18x) *Tert butyl 6-chloro-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*
Following General procedure A and purification using C18 reverse phase chromatography (H_2O: MeCN, 0-100%) yielded the title compound as a white solid (177 mg, 32%). mp 105-106 ^oC. δ_H (700 MHz, $CDCl_3$) 8.95 (1H, d, *J* = 2.3 Hz, 6-H), 8.18 (1H, d, *J* = 2.3 Hz, 3-H), 7.78 – 7.71 (2H, m, 2',6'-H), 7.61 – 7.56 (2H, m, 3'-5'-H), 1.61 (9H, s, $C(CH_3)_3$). δ_C (176 MHz, $CDCl_3$) 163.2 (C=O), 152.9 (C-2), 150.0 (C-6), 140.24 (C-1'), 140.1 (C-4), 135.2 (C-3), 130.8 (q, *J* = 32.7 Hz, C-4') 129.7 (C-2'', 6''), 127.1 (C-5), 125.4 (q, *J* = 3.7 Hz, C-3'', 5'') 123.8 (q, *J* = 272.6 Hz, $-CF_3$) 82.9 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$). δF (376 MHz, $CDCl_3$) -62.70 ($-CF_3$). ν_{max} (ATR) 2983, 2930, 1723, 1623,1598, 1392, 1320, 1261, 1112 cm^{-1}. *m/z* (LC-MS, ES^+) 358.1 ($[M(^{35}Cl)+H]^+$, 42%), 360.1 ($[M(^{37}Cl)+H]^+$, 15%), 302.0 ($[M(^{35}Cl)$-tBu+$H]^+$, 100%), 304.0 ($[M(^{37}Cl)$-tBu+$H]^+$, 38%) Accurate mass (ES^+) *m/z* found $[M(^{35}Cl)+H]^+$ 358.0828, $C_{17}H_{16}{}^{35}ClNO_2F_3$ requires *M* 358.0822.

(21xB) *Tert butyl 6-(morpholin-4"-yl)-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*
Following general procedure D and purification using EtOAC in hexane (0-20%) yielded the title compound as an off white amorphous solid (41 mg, 82%) δ_H (599 MHz, $CDCl_3$) 8.80 (1H, d, *J* = 2.2 Hz, 6-H), 7.95 (1H, d, *J* = 2.2 Hz, 4-H), 7.67 (4H, m, Ar-H), 3.60 (4H, t, *J* = 4.7 Hz, 3'', 5''-H_2), 3.20 (4H, t, *J* = 4.7 Hz, 2'', 6''-H_2), 1.56 (9H, s, $C(CH_3)_3$). δ_C (151 MHz, $CDCl_3$) 164.6 (C=O), 160.8 (C-2), 149.1 (C-6), 143.26 (C-1'), 140.8 (C-4), 129.9 (q, *J* = 33.1 Hz C-4')), 127.9 (C-2', 6'), 125.9 (q, *J* = 3.7 Hz, C-3', 5'), 123.9 (q, *J* = 278.0 Hz, $-CF_3$) 120.47 (C-5), 81.3 ($-C(CH_3)_3$, 66.4 (C-3'', 5''), 49.1 (C-2'', 6''), 28.2 ($C(CH_3)_3$). δ_F (376 MHz, $CDCl_3$) -62.55 ($-CF_3$). ν_{max} (ATR) 2950, 2829, 1729, 1678, 1610, 1497, 1343, 1265, 1184 cm^{-1}. *m/z* (LC-MS, ES^+) 409.1 ($[M+H]^+$, 100%), 353.1 ($[M$-tBu+$H]^+$, 52%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 409.1750, $C_{21}H_{24}F_3N_2O_3$ requires *M* 409.1739.

(22zA) *Methyl 5-(4'-nitrophenyl)-2-(pyrrolidin-1"-yl)pyridine-3-carboxylate*

Following general procedure A gave the crude aryl-nicotinate intermediate which was used without further purification according to general procedure C to yield, upon purification using EtOAc in hexane (0-25%) the title compound as a dark yellow amorphous solid (62 mg, 32%), δ_H (700 MHz, $CDCl_3$) 8.58 (1H, d, *J* = 2.5 Hz, 6-H), 8.27 (2H, d, *J* = 8.8 Hz, 3', 5'-H), 8.17 (1H, d, *J* = 2.5 Hz, 3-H), 7.67 (2H, d, *J* = 8.8 Hz, 2', 6'-H), 3.93 (3H, s, CO_2CH_3), 3.51 (4H, d, *J* = 6.6 Hz, 2'', 5''-H_2), 1.99 (4H, d, *J* = 6.6 Hz, 3'', 4''-H_2). δ_C (176 MHz, $CDCl_3$) 167.2 (C=O), 155.42 (C-2), 152.92 (C-3), 146.6 (C-4'), 130.41 (C-6), 129.00, 126.2, (C-2'', C-6''), 124.4 (C-3', 5'), 121.5 (C-5), 117.48 (C-1'), 52.49 (CO_2CH_3), 50.30 (C-2'', 5''), 25.58 (C-3'', 4''). ν_{max} (ATR) 2925, 2291, 1970, 1757, 1669, 1561, 1533, 1371, 1280, 1168 cm^{-1}. *m/z* (LC-MS, ES^+) 328.1 ($[M+H]^+$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 328.1291, $C_{17}H_{18}N_3O_4$ requires *M* 328.1297.

(19y) *Methyl 2-chloro-5-(4'-methoxyphenyl)pyridine-3-carboxylate*

Following general procedure A and purification using EtOAc in hexane (0-25%) yielded the title compound as a white amorphous solid. Purification using (0-35% EtOAc-hexane,) afforded the title compounds as an amorphous white solid (55 mg, 20%) δ_H (700 MHz, $CDCl_3$) 8.71-8.64 (1H, m, 6-H), 8.30 (1H, d, *J* = 2.5, 4-H), 7.54-7.50 (2H, m, 2-H), 7.04-6.98 (2H, m, 3',5'-H), 3.98 (3H, s, CO_2CH_3), 3.86 (3H, s, 4'-OCH_3); δ_C (176 MHz, $CDCl_3$) 165.1 (C=O), 160.3 (C-2), 149.5 (C-6), 147.8 (C-5), 137.9 (C-4), 135.2 (C-1), 128.2 (C-2'), 127.7 (C-1'), 126.4 (C-3), 114.8 (C-3'), 55.4 (5'-OCH_3), 52.9 (CO_2CH_3); ν_{max} (ATR) 3019, 2961, 2933, 2839, 1737 (s) (C=O), 1608, 1582, 1552, 1515, 1324, 1310, 1293, 1226, 1184, 1064, 1054, 1033, cm^{-1}. *m/z* (LC-MS, ES^+) $[M+H]^+$ 279.8 (100), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 278.0583, $C_{14}H_{13}NO_3Cl$ requires *M* 278.0584.

(22yB) *Methyl 5-(4''-methoxyphenyl)-2-(morpholin-4'-yl)pyridine-3-carboxylate*

Following general method C and purification using EtOAc in heptane (20-30%) yielded the title product as a white amorphous solid (141 mg, 93%). δ_H (700 MHz, $CDCl_3$) 8.51 (1H, s, 6-*H*), 8.20 (1H, s, 4-*H*), 7.47 (2H, d, *J* = 8.0, 2'',6''-*H*), 6.98 (2H, d, *J* = 8.0, 3'', 5''-*H*), 3.91 (3H, s, CO_2CH_3), 3.85 (7H, m, OCH_3, 3', 5'-H_2), 3.44 (4H, m, 2', 6'-H_2); δ_C (176 MHz, $CDCl_3$) 167.5 (CO_2CH_3), 159.3 (*C*-4''), 158.2 (*C*-2), 148.4 (*C*-6), 138.8 (*C*-4), 129.5 (*C*-1''), 127.6 (*C*-5), 127.4 (*C*-2'', 6''), 114.5 (*C*-3'', 5''), 113.6 (*C*-3), 66.9 (*C*-3', 5'), 55.4 (OCH_3), 52.2 (CO_2CH_3), 49.9 (*C*-2'', 6''); ν_{max} (ATR) 1717, 1601, 1472, 1440, 1246, 1212, 1182,

1114, 1087 cm^{-1}; Accurate Mass (ESI) *m/z* found $[M+H]^+$ 329.1510; $C_{18}H_{21}N_2O_4$ requires *M*, 329.1501.

(22yC) *Methyl 5-(4”-methoxyphenyl)-2-(piperidin-1’-yl)pyridine-3-carboxylate*

Following general procedure C and purification using EtOAc in heptane yielded the title compound as a yellow amorphous solid (57 mg, 89%). δ_H (700 MHz, $CDCl_3$) 8.47 (1H, d, *J* = 2.4, 6-*H*), 8.11 (1H, d, *J* = 2.4, 4-*H*), 7.45 (2H, d, *J* = 8.6, 2’’, 6’’-*H*), 6.97 (2H, d, *J* = 8.6, 3’’, 5’’-*H*), 3.91 (3H, s, CO_2CH_3), 3.84 (3H, s, OCH_3), 3.39 (4H, m, 2’, 6’-H_2), 1.68 (6H, m, 3’, 4’, 5’-H_2); δ_C (176 MHz, $CDCl_3$) 168.4 (CO_2CH_3), 159.2 (*C*-4’’), 158.6 (*C*-2), 148.3 (*C*-6), 138.7 (*C*-4), 130.0 (*C*-1’’), 127.5 (*C*-2’’, 6’’), 126.4 (*C*-5) 114.6 (*C*-3’’, 5’’), 113.4 (*C*-3), 55.5 (OCH_3), 52.3 (CO_2CH_3), 50.7 (*C*-2’, 6’), 26.1 (Alk*C*), 24.7 (Alk*C*); υ_{max} (ATR) 1716, 1694, 1608, 1441, 1247, 1180 cm^{-1}; Accurate Mass (ESI) *m/z* found $[M+H]^+$ 327.1701; $C_{19}H_{23}N_2O_3$ requires *M*, 327.1709.

(22yE) *Methyl 2-(butylamino)-5-(4’-methoxyphenyl)pyridine-3-carboxylate*

Following general procedure C and purification using EtOAC in hexane (0-20%) yielded the title compound as a yellow amorphous solid (38 mg, 60%). δ_H (700 MHz, $CDCl_3$) 8.50 (1H, d, *J* = 2.5 Hz, 6-H), 8.32 (1H, d, *J* = 2.5 Hz, 4-H), 7.42 (2H, d, *J* = 8.7 Hz, 2’, 6’-H), 6.96 (2H, d, *J* = 8.7 Hz, 3’, 5’-H), 3.89 (3H, s, CO_2CH_3), 3.83 (3H, s, 4’-OCH_3), 3.60-3.52 (2H, m, 1’’-H_2), 1.71 – 1.63 (2H, m, 2’’-H_2), 1.52 – 1.42 (2H, m, 3’’-H_2), 0.97 (3H, t, *J* = 7.4 Hz, 4’’-H_3). δ_C NMR (176 MHz, $CDCl_3$) 162.6 (C=O), 159.0 (C-4’), 152.9 (C-2), 146.4 (C-6), 138.6 (C-4), 131.0 (C-1’), 127.1 (C-2’, 6’), 123.9 (C-5), 117.8 (C-4), 114.4 (C-3’, 5’), 67.1 (C-1’’), 55.4 (-OCH_3), 52.0 (CO_2CH_3), 31.6 (C-2’’), 20.3 (C-3’’), 13.9 (C-4’’). υ_{max} (ATR) 3381, 2960, 2259, 1693, 1611, 1504, 1243, 1036 cm^{-1}. *m/z* (LC-MS, ES^+) 313.3 ($[M-H]^-$, 100%), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 315.1705, $C_{18}H_{23}N_2O_3$ requires *M* 315.1709.

(19’y) *Methyl 2-fluoro-5-(4-methoxyphenyl)pyridine-3-carboxylate*

Following general procedure A, and purification using EtOAc in heptane (0-20%) yielded the title product as an off-white amorphous solid (715 mg, 62%). δ_H (700 MHz, $CDCl_3$) 8.51 (2H, m, 4, 6-*H*), 7.50 (2H, m, 2’, 6’-*H*), 7.01 (2H, m, 3’, 5’-*H*), 3.98 (3H, s, CO_2CH_3), 3.86 (OCH_3); δ_C (176 MHz, $CDCl_3$) 164.0 (d, *J* = 8.1, CO_2CH_3), 160.5 (d, *J* = 249.8, *C*-2), 160.3

(*C*-4'), 149.1 (d, *J* = 15.4, Ar*C*), 141.7 (d, *J* = 1.6, Ar*C*), 135.0 (*C*-5), 128.3 (*C*-2', 6'), 128.0 (*C*-1'), 114.9 (*C*-3, 5'), 113.4 (d, *J* = 25.6, *C*-3), 55.6 (O*C*H_3), 53.0 ($CO_2C H_3$); δ_F (376 MHz, $CDCl_3$) −66.3 (s); ν_{max} (ATR) 1722, 1603, 1459, 1446, 1327, 1292, 1249, 1179, 1089, 1042, 977 cm^{-1}; Accurate Mass (ASAP) *m/z* found $[M]^+$ 261.0824; $C_{14}H_{12}FNO_3$ requires *M*, 261.0801

(19''y) *Methyl 2-methoxy-5-(4-methoxyphenyl)pyridine-3-carboxylate*

Following general procedure A and purification using EtOAc in heptane (0-15%) yielded the title compound as a white amorphous solid (229 mg, 76%). δ_H (700 MHz, $CDCl_3$) 8.49 (1H, d, *J* = 2.2, 6-*H*), 8.34 (1H, d, *J* = 2.2, 4-*H*), 7.48 (2H, m, 2', 6'-*H*), 7.00 (2H, m, 3', 5'-*H*), 4.10 (3H, s, 2-OCH_3), 3.93 (3H, s, $CO_2C H_3$), 3.86 (3H, s, 4'-OCH_3); δ_C (176 MHz, $CDCl_3$) 165.7 (CO_2CH_3), 161.4 (*C*-2), 159.7 (*C*-4'), 148.2 (*C*-6), 139.7 (*C*-4), 129.8 (*C*-5), 129.3 (*C*-1'), 128.0 (*C*-2', 6'), 114.7 (*C*-3', 5'), 113.9 (*C*-3), 55.5 (4'-CO*C*H_3), 54.6 (2-CO*C*H_3), 52.5 (CO_2CH_3); ν_{max} (ATR) 1732, 1606, 1563, 1519, 1474, 1417, 1327, 1285, 1245, 1181, 1087, 1060, 1014 cm^{-1}. Accurate Mass (ASAP) *m/z* found $[M+H]^+$ 274.1075; $C_{15}H_{16}NO_4$ requires *M*, 274.1079.

(19x) *Methyl 2-chloro-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*
Following general procedure A and purification using EtOAc in hexane (0-15%) to yield the title compound as a white amorphous solid (64 mg, 24%); δ_H (700 MHz, $CDCl_3$) 8.74 (1H, m, 6-H), 8.,37 (1H, d, *J* = 2.1, 4-H), 7.77 (2H, d, *J* = 8.1, C-2', 6'), 7.70 (2H, d, *J* = 8.1, C-3', 5'), 4.00 (3H, s, $CO_2C H_3$). δ_C (176 MHz, $CDCl_3$) δ 164.9 (C=O), 149.9 (C-2), 149.8 (C-6), 139.1 (C-5), 138.9 (C-4), 134.2 (C-1'), 131.2 (q, *J*=33.2 Hz, C-4'), 127.7 (C-2', 6'), 126.5 (q, *J*=3.8 Hz, C-3', 5')), 124.0 (q, *J*=272.0 Hz, -CF_3), 121.5 (C-3), 53.2 (CO_2CH_3), δ_F (376 MHz, $CDCl_3$) δ -62.83 (-CF_3); ν_{max} (ATR) 2174, 1982, 1730 (C=O), 1555, 1520, 1414, 1224, 1111, 1052, 1033, 962, cm^{-1}; *m/z* (LCMS-ESI) 318 ($[M(^{37}Cl)]^+$, 31 %), 316 ($[M(^{35}Cl)+H]^+$), 100), Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 316.0345, $C_{14}H_{20}NO_2F_3{}^{35}CI$ requires *M* 316.0352.

(22xA) *Methyl 2-(pyrrolidin-1''-yl)-5-[4'-trifluoromethylphenyl]pyridine-3-carboxylate*

Following general procedure C and purification using EtOAc in hexane (0-20%) yielded the title compound as an amorphous white solid (23 mg, 50%). δ_H (700 MHz, $CDCl_3$) 8.53 (1H, bs, 6-H), 8.11 (1H, d, *J* = 2.2, 4-H), 7.69-7.61 (4H, m, Ar), 3.92 (3H, s, $CO_2C H_3$), 3.47-3.45 (4H, m, 2", 5"-H_2), 1.97-1.94 (4H, m, 3",4"-H_2); δ_C (176 MHz, $CDCl_3$) 167.7 (C=O), 155.3,

148.7, 141.1, 138.0 128.7, 126.6, 126.1, 124.4, 122.7, 110.8, 52.4, 49.9, 25.8; δ_F (564 MHz, $CDCl_3$) -62.42; ν_{max} (ATR) 2979, 2954, 2876, 1710 (C=O) , 1599, 1546, 1488, 1479, 1321, 1244, 1211, 1160, 1137, 1116, 1100,cm^{-1}; *m/z* (LCMS-ESI) 350 ($[M]^+$, 86 %), 351 ($[M+H]^+$, 100%), Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 351.1300, $C_{18}H_{19}N_2O_2F_3$ requires *M* 351.1320.

(22xB) *Methyl 2-(morpholin-4''-yl)-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*

Following general procedure C and purification using EtOAc in DCM (0-20%) yielded the title compound as a white amorphous solid (16 mg, 43%) ; δ_H, (700 MHz, $CDCl_3$) 8.56-8.54 (1H, m, 6-H), 8.25 (1H, d, J 2.5 Hz, 4-H), 7.71-7.63 (4H, m, Ar), 3.93 (3H, s, CO_2CH_3), 3.85-3.81 (4H, m, 3'', 5''-H_2), 3.52-3.49 (4H, m, 2'', 6''-H_2); δ_C (176 MHz, $CDCl_3$) 167.3 (C=O), 158.6 (C-2), 148.7 (C-6), 140.6 (C-1'), 139.5 (C-4) 129.4 (q, *J* = 32.4 Hz, C-4'), 126.4 (C-2',6'), 126.0 (q, *J* = 33.1 Hz, C-3', 5'), 124.1 (q, *J* = 272.2 Hz, CF_3), 123.1 (C-5) 113.1 (C-3), 66.8 (C-3'', 5''), 52.4 (CO_2CH_3), 49.6 (C-2'', 6''); δ_F (376 MHz, $CDCl_3$) -62.47 (CF_3); ν_{max} 2957, 2925, 2847, 1707 (C=O), 1599, 1537, 1526, 1478, 1452, 1441, 1422, 1324, 1252, 1213, 1162, 1109, 1098, 1073, 1052, 1043, 1016 cm^{-1}, *m/z* (LCMS-ESI) 367 ($[M+H]^+$, 100%). Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 367.1265, $C_{18}H_{18}N_2O_3F_3$ requires *M* 367.1270

(22xC) *Methyl 2-(piperidin-1''-yl)-5-[4'-(trifluoromethyl)phenyl]pyridine-3-carboxylate*

Following general procedure C and purification using EtOAc in DCM (0-20%) yielded the title compound as a white amorphous solid; (5 mg, 13%); δ_H (700 MHz, $CDCl_3$) 8.52 (1H, d, *J* = 2.5, 6-H), 8.17 (1H, d, *J* = 2.5, 4-H), 7.70-7.61 (4H, m, Ar), 3.91 (3H, s, CO_2CH_3), 3.45 (4H, bs, 2'', 6''-H_2), 1.69 (6H, bs, 3'',4'' ,5''-H_2); δ_C (176 MHz, $CDCl_3$) 168.0, 157.3, 148.6, 141.0, 139.3, 129.4, 126.4, 126.0, 125.2, 123.6, 112.9, 52.4, 50.4, 26.0, 24.7; δ_F (376 MHz, $CDCl_3$) -62.42 (-CF_3); ν_{max} 2952, 2876, 2360, 1711 (C=O), 1599, 1541, 1489, 1480, 1461, 1448, 1434, 1322, 1244, 1211, 1160, 1138, 1102, 1086, 1071, 1052, 1014 cm^{-1}; *m/z* (LCMS-ESI) 364 ($[M]^+$, 60%), 365 ($[M+H]^+$, 100%), Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 365.1464, $C_{19}H_{21}N_2O_2F_3$ requires *M* 365.1477.

(19v) *Methyl 2-chloro-5-(thiophen-3'-yl)pyridine-3-carboxylate*

Following general procedure A and purification using EtOAc in hexane (0-35%) yielded the title compound as an off white amorphous solid (55 mg, 19%). δ_H (400 MHz, $CDCl_3$) 8.72

(1H, m, 6-H), 8.32 (1H, d, J = 2.4, 4-H), 7.58 (1H, dd, *J* = 3.0, 1.4, 4'-H), 7.47 (1H, dd, *J* = 5.0, 3.0, 3'-H), 7.38 (1H, dd, *J* = 5.0, 1.4, 2'-H), 3.98 (3H, s, $CO_2C\mathit{H_3}$); δ_C (101 MHz, $CDCl_3$) 168.0 (C=O), 159.6, 157.3, 150.1, 143.2, 140.8, 136.5, 127.8, 125.7, 123.1, 53.0 ($CO_2\mathit{C}H_3$). ν_{max} (ATR) 3091, 2960, 2360, 1738, 1722 (C=O), 1596 , 1562, 1525, 1432, 1418, 1404, 1327, 1296, 1242, 1194, 1134, 1101, 1064, 918, 776 cm^{-1}. *m/z* (GC-MS, ES^+) 222 ($[M\text{-}OMe]^+$), 253 ($[M]^+$); Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 254.0048, $C_{11}H_9NO_2S^{35}CI$ requires *M* 254.0043.

(19s) *Methyl 2-chloro-5-phenylpyridine-3-carboxylate*

Following general procedure A and purification using EtOAc in hexane (0-35%) yielded the title compound as an off white amorphous solid (27 mg, 38%); δ_H, (700 MHz, $CDCl_3$) 8.71 (1H, d, *J* = 2.6, 6-H), 8.35 (d, *J* = 2.6, 1H, 4-H), 7.58 (2H, m, 2',6'-H), 7.50 (2H, m, 3',4'-H), 7.45 (1H, t, *J* = 7.4, 4'-H), 3.99 (3H, s, $CO_2C\mathit{H_3}$); δc (176 MHz, $CDCl_3$) 165.0 (3-CO_2CH_3, 149.9 (C-6), 138.5 (C-4), 135.6, 135.4, 129.3, 129.3 (C- 3'), 128.9 (C-4), 127.0 (C-2'), 126.5, 52.9 (3-CO_2CH_3); ν_{max} (ATR) 2359, 2184, 1731 (C=O), 1425, 1317, 1255, 1129, 1064 cm^{-1}. *m/z* (LCMS-ESI) 247 ($[M]^+$, 67%), 248 ($[M+H]^+$, 100).

(19r) Methyl 2-chloro-5-[4'-(methoxycarbonyl)phenyl]pyridine-3-carboxylate

Following general procedure A and purification using EtOAc in hexane (0-35%) yielded the title compound as a white amorphous solid (57 mg, 65 %); δ_H (700 MHz, $CDCl_3$) 8.76 (1H, bs, 6-H), 8.39 (1H, d, *J* = 2.4, 4-H), 8.17 (2H, d, *J* = 8.3, Ar-H), 7.66 (2H, d, J = 8.3, Ar -H), 4.00 (3H, s, 4'-$CO_2C\mathit{H_3}$), 3.96 (3H, s, 3-$CO_2C\mathit{H_3}$); δc (176 MHz, $CDCl_3$) 166.4 (4'-$CO_2\mathit{C}H_3$), 164.8 (3-$CO_2\mathit{C}H_3$) 149.9 (C-6), 149.5 (C-2), 139.7 (C-4), 138.7 (C-3), 130.5 (C-3',5'), 130.5 (C-4'), 127.0 (C-5), 123.3 (C-2', 6'), 121.8 (C-1'), 53.0 (3-$CO_2\mathit{C}H_3$), 52.3 (4'-$CO_2\mathit{C}H_3$); ν_{max} (ATR) 2364, 1711 (C=O), 1427 , 1275, 1108, 1060, 767, 421 cm^{-1}. *m/z* (LCMS-ESI); 306 ($[M+H]^+$ 100 %), 307 ($[M+2]^+$, 32%), 328 ($[M+Na]^+$, 9%); Accurate Mass (ESI-TOF) *m/z* Found $[M+H]^+$ 306.0540, $C_{15}H_{13}ClNO_4$ requires *M* 306.0533.

(22rA) *Methyl 5-[4'-(methoxycarbonyl)phenyl]-2-(pyrrolidin-1''-yl)pyridine-3-carboxylate*

Following general procedure C and purification using EtOAC in hexane (0-20%) yielded the title compound as an off white amorphous solid (19 mg, 81%). δ_H (700 MHz, $CDCl_3$) 8.56 (1H, d, *J* = 2.5 Hz, 6-H), 8.15 (1H, d, *J* = 2.5 Hz, 4-H), 8.07 (1H d, *J* = 8.4 Hz, 2', 6'-H), 7.59 (2H, d, *J* = 8.4 Hz, 3', 5'-H), 3.89-3.94 (6H, m, CO_2Me), 3.48 (4H, t, *J* = 7.0, 2'', 5''-H_2),

1.97 (4H, t, J = 7.0, 3’’, 4’’-H_2); δ_C (176 MHz, $CDCl_3$) 168.9 (4’-C=O), 166.9 (3-C=O), 144.1, 142.0, 138.3, 138.2, 134.0, 130.3, 128.4, 125.6, 122.8, 52.3, 52.1, 49.9, 25.6. ν_{max} (ATR) 3025, 2957, 1719, 1591, 1536, 1477, 1462, 1438, 1326, 1273, 1089 cm^{-1}. *m/z* (LCMS-ESI); 341.2 ($[M+H]^+$ 100 %), Accurate mass (ES^+) *m/z* found $[M+H]^+$ 341.1509, $C_{19}H_{21}N_2O_4$ requires *M* 341.1501.

(23) *1,4-dimethyl-7-phenyl-1H,2H,3H,4H,5H-pyrido[2,3-e][1,4]diazepin-5-one*

Following general procedure C and purification with EtOAc in DCM (0-10%), yielded the title compound as a white amorphous solid (10 mg, 60 %); δ_H (700 MHz, $CDCl_3$) 8.56 (1H, m, 6-H)), 8.29 (1H, d, J = 2.8, 8-H), 7.56 (2H, dd, J = 8.2, 1.4, 2’-H, 6’-H), 7.43 (2H, td, J = 7.5, 8.2, 3', 5’-H), 7.33 (1H, td, J = 7.5, 1.4 Hz , m , 4'-H), 3.67-3.58 (4H, m, 2-H_2, 3-H_2), 3.22 (3H, s, 4''-H), 3.13 (3H, s, 1''-H); δ_C (176 MHz, $CDCl_3$) 169.3, 153.9, 149.5, 146.0, 139.5, 130.6, 129.3, 127.8, 127.7, 127.6, 126.7, 118.8, 52.6, 48.4, 39.4, 36.0. ν_{max} 2925, 1716, 1632 (C=O) , 1599 , 1513, 1450, 1412, 1379, 1312, 1260, 1054, 1028 cm^{-1}. *m/z* (LC-MS, ES^+) 268 ($[M+H]^+$, 100), Accurate Mass (ESI-TOF) *m/z* found $[M+H]^+$ 268.1456, $C_{16}H_{13}N_3O$ requires [M+H] 268.1450.

(24) *Methyl 2-(pyrrolidin-1’-yl)pyridine-3-carboxylate*

Following general procedure C and purification by 3 successive washes of the organic layer with water, the title compound was isolated as an orange oil (492 mg, 80%); δ_H (700 MHz, $CDCl_3$) 8.21-8.17 (1H, m, 6-H), 7.80 (1H, m, 5-H), 6.53 (1H, m, 4H), 3.82 (3H, s, CO_2CH_3), 3.35 (4H, t, J = 6.3, 2’,5’-H_2), 1.87 (4H, m, 3’,4’-H_2). δ_C (176 MHz, $CDCl_3$) 167.9 (*C*=O), 155.8 (C-2), 150.4 (C-6), 139.5 (C-5), 110.9 (C-4), 110.7 (C-3), 52.0 (O*C*H_3), 49.5 (C-2’,5’), 25.6 (C-3’, 4’); ν_{max} 2948, 2872, 1709 (C=0), 1585, 1549, 1470, 1444, 1284, 1247, 1220, 1114, 1083, 1053, 764, 746 cm^{-1}; *m/z* (LCMS-ESI) 175 ($[M-OMe]^+$, 75%), 206, ($[M]^+$, 65%), 208 ($[M+2H]^+$, 100%), 209 ($[M+3H]^+$, 20%) Accurate Mass (ESI-TOF) *m/z* found $[M+H]^+$ 207.1124, $C_{11}H_{15}N_2O_2$ requires *M*, 207.1134

(25) *Methyl 2-(4’-methoxyphenyl)pyridine-4-carboxylate*

Following general procedure A, the crude cross-coupling reaction product used without further purification and was dissolved in ethanol (20 mL) to which ammonium formate (2.5 g, 40 mmol) was added. The reaction vessel was evacuated and backfilled with nitrogen (3 cycles) before 10% Pd/C (106 mg, 0.1 mmol) was slowly added under a positive pressure of

nitrogen. The reaction was stirred at room temperature for 2 h then filtered through a plug of Celite and absorbed onto silica. Purification using EtOAc in hexane (0-20%) yielded the title compound as a white amorphous solid (230 mg, 47%). δ_H (700 MHz, $CDCl_3$) 8.77 (1H, d, *J* = 5.0 6-*H*), 8.22 (1H, s, 3-*H*), 8.01 (2H, m, 2', 6'-*H*), 7.69 (1H, d, *J* = 5.0, 5-*H*), 7.00 (2H, m, 3', 5'-*H*), 3.97 (3H, s, CO_2CH_3), 3.86 (3H, s, OCH_3); δ_c (176 MHz, $CDCl_3$) 166.0 (CO_2CH_3), 161.0 (*C*-4'), 158.2 (*C*-2), 150.4 (*C*-6), 138.1 (*C*-4), 131.2 (*C*-1'), 128.4 (*C*-2', 6'), 120.4 (*C*-5), 119.0 (*C*-3), 114.3 (*C*-3', 5'), 55.5 (OCH_3), 52.8 (CO_2CH_3); ν_{max} (ATR) 1730, 1607, 1580, 1557, 1516, 1467, 1436, 1421, 1390, 1301, 1274, 1249, 1176, 1111, 1060, 1031 cm^{-1}; Accurate Mass (ASAP) *m/z* found $[M+H]^+$ 244.0957; $C_{14}H_{14}NO_3$ requires *M*, 244.0974.

(26) *methyl 2-(4'-nitrophenyl)-6-phenylpyridine-4-carboxylate*

Methyl 2-chloro-6-(4-nitrophenyl)pyridine-4-carboxylate (**2cz**) (130 mg, 0.45mmol, 1equiv.) was combined with phenyl boronic acid (1.2 equiv)) and $CsCO_3$ (1.5 equiv) and was subjected to 3 N_2 purge/refill cycles. DMAC (0.5M) was added and the vial was subjected to microwave irradiation for 18 hours at 100 ^oC. Purification using C18 reverse phase chromatography yielded the title compound as a yellow oil (36 mg, 24%). δ_H (700 MHz, $CDCl_3$) 8.40 – 8.35 (4H, m), 8.33 (1H, d, *J* = 1.2 Hz), 8.31(1H, d, *J* = 1.2 Hz), 8.21 – 8.18 (2H, m), 7.54 (2H dd, *J* = 8.2, 6.7 Hz), 7.49 (1H, d, *J* = 6.7 Hz,), 4.04 (3H, s, OCH_3). δ_c (176 MHz, $CDCl_3$) 165.5, 158.5, 155.3, 148.4, 144.4, 139.6, 138.0, 129.9, 128.9, 127.9, 127.1, 124.0, 119.3, 118.5, 53.0. ν_{max} (ATR) 2970, 2801, 2299, 1731, 1662, 1572, 1496, 1331, 1271, 1146 cm^{-1}. *m/z* (LCMS-ESI) 335.1 ($[M+H]^+$, 100%), Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 335.1046, $C_{19}H_{15}N_2O_4$ requires *M*, 335.1032.

(27) *Ethyl 2-{[2-(4'-methoxyphenyl)-6-(pyrrolidin-1''-yl)pyridin-4-yl]formamido}propanoate*

Tert butyl 2-(4-methoxyphenyl)-6-(pyrrolidin-1-yl)pyridine-4-carboxylate (**3dyA**) (38 mg, 0.1mmol, 1equiv.) was treated with TFA for 1 hour when the reaction was concentrated in a stream of nitrogen. The crude residue was combined with HBTU (1.1equiv.), DMAP (1.1equiv.) and DCM (0.1M). The mixture was allowed to stir for 16 hours and quenched with water and extracted with DCM. Purification by column chromatography using EtOAc in Hexane (0-70%) afforded the title compound as a light yellow oil (31 mg, 67% (over 2 steps)). δ_H (700 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 8.8 Hz, 2', 6'-H), 7.16-7.20 (1H, m, 3-H), 6.95 (2H, d, *J* = 8.8 Hz, 3', 5'-H), 6.60-6.68 (1H, m, 5-H), 4.76 (1H, q, *J* = 7.2 Hz), 4.25 (2H, q, *J* = 7.1 Hz, OCH_2), 3.84 (3H, s, OCH_3), 3.56-3.60 (4H, m, 2'', 5''-H), 1.99-2.03 (4H, m, 3'', 4''-H_2), 1.54 (3H, d, *J* = 7.2 Hz, $C_\alpha CH_3$), 1.31 (t, *J* = 7.1 Hz, CH_2CH_3). δ_C (176 MHz,

$CDCl_3$) 173.0 (NH*C*=O), 166.5 (O*C*=O), 165.9 (C-4'), 160.5 (C-2), 143.4 (C-6), 131.0 (C-3), 128.4 (C-2', 6'), 128.3 (C-5), 127.8 (C-4), 125.8 (C-1'), 113.8 (C-3', 5'), 61.7 (-OCH_2), 55.3 (O*C*H_3), 48.6 (C_α) 48.2 (C-2'', 5''), 25.5 (C-3'', 4''), 18.2 (C_α*C*H_3), 14.1 (CH_2CH_3). ν_{max} (ATR) 3227, 2975, 2259, 1738, 1655, 1604, 1518, 1456, 1349, 1026 cm^{-1}. *m/z* (LCMS-ESI) 398.7 ($[M+H]^+$, 100%), Accurate Mass (ES^+) *m/z* found $[M+H]^+$ 398.2079, $C_{22}H_{28}N_3O_4$ requires *M*, 398.2080

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