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An Efficient Continuous Flow Approach to Furnish Furan-Based Biaryls

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Suzuki cross-couplings of 5-formyl-2-furanylboronic acid with activated or neutral aryl bromides were performed under continuous flow conditions in the presence of $(Bu)_4N^+F^-$ and the immobilised *t*-butyl based palladium catalyst CatCart™ FC1032™. Deactivated aryl bromides and activated aryl chlorides were cross-coupled with 5-formyl-2-furanylboronic in the presence of $(Bu)_4N^+OAc^-$ using the bis-triphenylphosphine CatCart™ $PdCl_2(PPh_3)_2$-DVB. Initial evidence indicates the latter method may serve as a universal approach to conduct Suzuki cross-couplings with the protocol successfully employed in the synthesis of the current gold standard ~~h~~Hedgehog pathway inhibitor LDE225.

Introduction

The furan-based biaryl motif is an intriguing molecular framework which serves as a pivotal core for a range of bioactive molecules. The furan biaryl motif is an integral feature of a number of kinase inhibitors including pan-Pim (**1**)[1] and class I phosphoinositide 3-kinase[2] inhibitors (**2**), a family of Bcl-xL inhibitors (**3**),[3] HIV-1 fusion inhibitors (**4**),[4] in addition to a class of antibacterial agents (**5**)[5] (Figure 1). However, of particular interest to our research, the furan-based biaryl motif forms the core of a number of small molecules possessing inhibitory activity within the hedgehog signalling pathway such as **6**.[6-8]

It is unknown if the diverse bioactivities of furan-biaryl based molecules are related to unique molecular recognitions or is simply a reflection of the scaffold being overrepresented in high-throughput-screening libraries. Nevertheless, a noteworthy feature of the furanyl-biaryl scaffold is that in contrast to the majority of biaryl molecular frameworks, modelling[9] and crystallographic data[10] demonstrate that this system preferentially adopts a planar conformation.

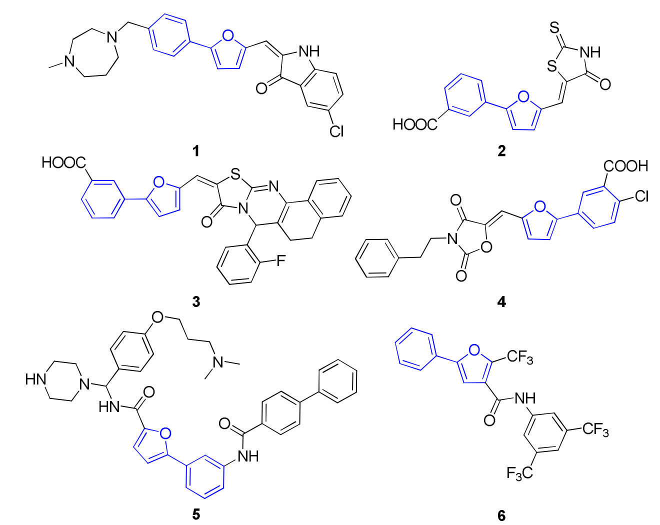


Figure 1: Illustrative examples of bioactive compounds constructed around the furanyl-biaryl core. Structure of the pan-Pim (**1**)[1] and class I phosphoinositide 3-kinase (**2**)[2] inhibitors, along with the Bcl-xL inhibitor (**3**),[3] the HIV-1 fusion inhibitors (**4**),[4] the gram-negative antibacterial agent (**5**), and the hedgehog signalling pathway inhibitor (**6**).[6, 7]

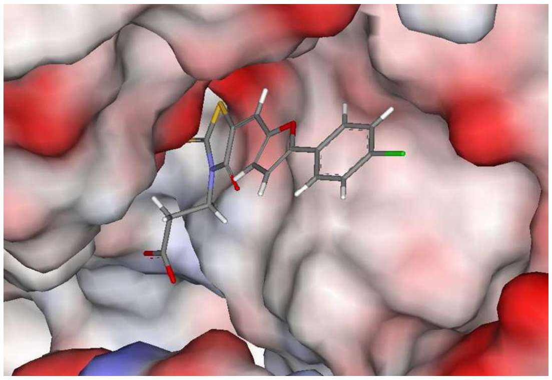


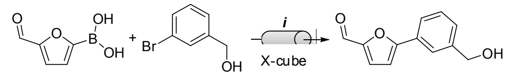
Figure 2: Co-crystallised structure of 3-{5-[5-(4-chloro-phenyl)-furan-2-ylmethylene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid with the *Bacillus anthracis* lethal factor metalloproteinase. This structure indicates that in contrast to the majority of biaryl systems the furanyl-biaryl motif adopts a planar conformation. (*PDB accession code 1ZXV.pdb*).[10]

Given the abundance of furanyl-biaryl analogues in the literature it is unsurprising that synthetic methodologies to access the scaffold have been extensively reported. Typical approaches involve the use of a furanylboronic acid or furanylbromide in Suzuki cross-coupling conditions with a range of Pd-based catalysts including $Pd(OAc)_2$,[2, 11-17] $PdCl_2(PPh_3)_2$,[18-20] $Pd(PPh_3)_4$,[18-26] $Pd_2(dba)_3$,[27] and $Pd(OH)_2$.[28]

Whilst these methodologies typically afford the furanyl-biaryl scaffold in good to excellent yields a common problem faced, particularly by the pharmaceutical industry, in using homogeneous catalysts is the–removal of residual Pd from catalyst leaching.[29-33] This has in part been negated by the use of immobilised solid supported catalysts that can be simply partitioned from reaction mixtures. To this end, a suite of solid supported precursors to $L_2Pd(0)$ catalysts, known as FibreCats® are now commercially available.[29-33] A number of these FibreCats® systems are available in pre-packed cartridges which are compatible with a number of flow reactors including the ThalesNano X-Cube™. Further various flow systems utilising a range of immobilised catalysts have previously been successfully utilised to conduct a number of cross-coupling reactions.[34-37] Herein we report the development of a FibreCats® compatible flow chemistry methodology that provides a robust and expedient means of accessing furanyl-biaryl based analogues as building blocks for drug development programs.

Results and Discussion

Our primary interest in the furan-based biaryl motif relates to our current interest in developing a series of ~~h~~Hedgehog signalling pathway inhibitors. To this end our primary aim was to develop a series of furfural-based analogues, e.g. **7** (Scheme 1), as the aldehyde moiety readily permits further synthetic manipulations. To this end, our investigations commenced with flowing a methanolic solution of 5-formyl-2-furanylboronic acid (**8**), 3-bromobenzyl alcohol (**9**), and three equivalents of $(Bu)_4N^+F^-$ through an X-cube™ charged with an FC1001 FibreCat® at 0.5 mL.min^{-1} at a temperature of 80 °C (Scheme 1). This equated to a 2.2 min catalyst residence time. The effect of recycling through the catalyst was evaluated by HPLC-MS analysis.



8 9 7

Scheme 1. *Reagents and Conditions*: (*i*) 5-formyl-2-furanylboronic acid (**8**) (1 mmol), 3-bromobenzyl alcohol (**9**) (1 mmol), $(Bu)_4N^+F^-$ (3 mmol), MeOH (30 mL), FibreCat® 1001, X-Cube™, 0.5 mL.min^{-1}, and 80 °C.

Table 1. Ratio of **7** and **9** peak areas obtained after subsequent cycles through various FibreCat® catalysts. Reagents and conditions are as per Scheme 1.

Entry	Pd-Ligand	FibreCat®	Number of catalyst cycles Ratio of 7 : 9[a]			
			1	2	3	4
1		FC1001™	1:1.2	1:0.7	1:0.5	1:0.4
2		FC1007™	1:1.3	1:0.7	1:0.4	1:0.2
3		FC1032™	1:0.7	1:0.4	1:0.3	1:0.2
4		Pd-Tetrakis	1:0.4	1:0.3	1:0.3	1:0.2

[a] Ratio of peak areas determined by HPLC analysis at 220 nm.

The initial reaction conditions gave a 1:1.2 ratio of **7** to **9** obtained after a single cycle (Table 1), increasing to 2:1 after 4 cycles using FibreCat® 1001. However, given that the Suzuki reaction coupling efficiencies can be significantly affected by the ligand utilised, we investigated a number of alternative FibreCat® columns (Table 1, entries 2-4). Each FibreCat® catalyst furnished the desired Suzuki reaction with relatively high efficiencies with Pd-Tetrakis providing the most efficient coupling with a near 4:1 ratio of **7** to **9** afforded within two catalyst cycles (Table 1, entry 4).

Further improvements in the Pd-Tetrakis coupling efficiency were noted on increasing reaction temperature to 120 ºC with a 1 : 0.08 ratio of **7** : **9** observed at a 0.5 mL.min^{-1} flow rate (a 1.3 min catalyst residence time) (Figure 3b). However, at T > 100 ºC increased aryl-bromide homocoupling with the excessive formation of **10** observed at 140 ºC (Figure 3b). Increased reaction pressures at 80 °C afforded similar results, with pressures above 60 bar enhancing the formation of both **7** and **10** (Figure 3c). At elevated pressure the aryl-bromide homocoupled product **10** was the major product.

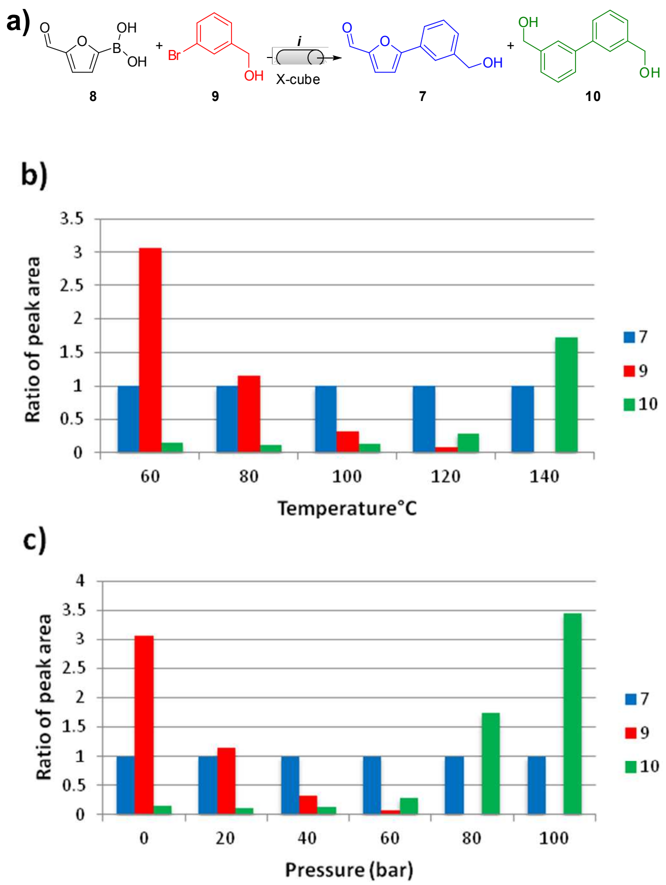


Figure 3: a) *Reagents and conditions*: (*i*) 5-formyl-2-furanylboronic acid (**8**) (1 mmol), 3-bromobenzyl alcohol (**9**) (1 mmol), $(Bu)_4N^+F^-$ (3 mmol), and MeOH (30 mL) at 0.5 $mL.min^{-1}$, Pd-tetrakis; **b)** Comparison of the relative quantities of aryl bromide (**9**), desired product (**7**), and aryl bromide homocoupled (**10**) product returned at temperatures of 60 to 140 °C with 0 bar pressure; **c)** Comparison of the relative quantities of aryl bromide (**9**), desired product (**7**), and aryl bromide homocoupled product returned at pressures of 0 to 100 bar at 80 °C. HPLC analysis conducted at 220 nm. Maximum total recoverable Pd content by ICP MS analysis 5.2 ppm.

Given the undesired production of **10**, we re-examined FibreCat® 1032 (Table 1, entry 3), while not as effective as Pd-Tetrakis, it did produce a higher level of coupling selectivity with only trace levels of homocoupled product after 4 catalyst cycles. Consequently FibreCat® 1032 was subjected to a temperature screen as with Pd-Terrakis (Scheme 1 & Table 2). Optimisation of the reaction temperature and flow rate revealed near quantitative conversion to **7** at 120 ºC and 0.5 $mL.min^{-1}$. After two catalyst cycles (2.6 min retention time). Only trace levels of starting material (**9**) and homocoupled (**10**) were evident (Table 2). Workup furnished the desired product **7** in a 93% isolated yield, which compares favourably with the reported batch yield of 88%.[38] Further, constant with the previous studies which examined palladium leaching,[29, 30] ICP MS analysis demonstrated negligible levels of palladium leaching with a maximum total recoverable palladium content of 5.2 ppm observed for a crude sample of compound **7**. As context the European Agency for the Evaluation of Medicines states that for oral administration the permitted daily exposure of class A1 metals such as palladium should not exceed 10 mg kg^{-1} and thus the Pd content of **7** is within this guideline.[39, 40]

Table 2: Temperature screen using FibreCat® 1032 at 0 bar pressure. Reagents and conditions are as per Figure 3**.**

Temperature °C	Ratio of Peak Area After Two Cycles[a]		
	7	9	10
60	1	7.8	0
80	1	1.1	0
100	1	0.37	0
120	1	0.05	0

[a] Ratio of peak areas determined HPLC analysis at 220 nm.. Maximum total recoverable Pd content by ICP MS analysis 5.2 ppm.

While the optimised protocol efficiently furnished **7**, the practicality of this continuous flow approach could only be judged by amenability to aryl bromide variations. Thus, the coupling of a small library of aryl bromides, sulfonamide based aryl bromides, and an amide based aryl bromide was investigated. The data presented in Table 3 illustrates the utility of FibreCat® 1032, $(Bu)_4N^+F^-$, at a flow rate of 0.5 mL/min, over two catalyst cycles and temperature of 120 °C in furnishing a small library in excellent isolated yields (82-92 %).

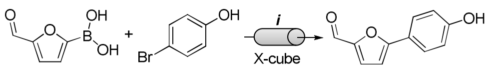
Table 3. Suzuki cross-couplings using a series of aryl bromides (**9a-f**) with FibreCat® 1032.

Reagents and conditions: 5-formyl-2-furanylboronic acid (**8**) (1 mmol), aryl bromides (**9a - 9f**) (1 mmol), $(Bu)_4N^+F^-3H_2O$ (3 mmol), MeOH, FibreCat® 1032, X-Cube™, and 0.5 $mL.min^{-1}$ over two catalyst cycles.

Compound	R	Conversion (%)	Isolated Yield (%)
12a		96	87
12b		95	82
12c		90	91
12d		95	85
12e		91	87
12f		98	92

Given our success with FibreCat® 1032 we next turned our attention to the Suzuki cross-coupling of deactivated aryl bromides such as 4-bromophenol (**13**, Scheme 2). The synthesis of the desired analogue **14** had been previously reported *via* coupling of 4-iodophenol and **8** using Pd-Tetrakis to afford **14** in an 87 % yield,[19] however, equivalent Pd-Tetrakis coupling with 4-bromophenol (13) gave **14** in only 10 %.[2] Using our flow protocol resulted in an improvement on the batch synthesis with an approximate 30 % conversion (and 23%

isolated yield) of **14** after three catalyst cycles (Table 3, entry 1). This however, was not the near quantitative yields obtained with the more activated aryl bromides (**9a-f**). Given that our prior studies with Pd-Tetrakis highlighted increasing homocoupled product with increased temperature and pressures, our initial reaction optimisation examined the effect of varying the tetrabutylammonium salt which has previously been observed impart subtle variations on cross-coupling yields.[41]



8 13 14
Isolated yield 23%

Scheme 2: ***Reagents and Conditions***: (*i*) 5-formyl-2-furanylboronic acid (**8**) (1 mmol), 4-bromophenol benzyl alcohol (**13**) (1 mmol), $(Bu)_4N^+F^-3H_2O$ (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL.min^{-1}, and 120 °C.

Varying the halogen counterion from –F to –Cl, -Br and –I resulted in reduced coupling efficiencies (Table 4, entries 2-5), as with the BF_4^- (Table 4, entry 5), and HSO_4^- salts (Table 4, entry 6). However, the use of $(Bu)_4N^+OAc^-$ (Table 4, entry 7) resulted in improved coupling efficiency with a near to 80 % conversion after a single catalyst cycle. Presumably the excess acetate ions activate the boronic acid (as is the case with K_2CO_3), and halogen abstraction from the first organopalladium intermediate in the Suzuki cycle.

Binary mixtures of $(Bu)_4N^+F^-$ and Cs_2CO_3 improved the efficiency of the cross coupling from 0.46 : 1 with $(Bu)_4N^+F^-$ alone (Table 4, entry 1) to 0.2 : 1 (Table 4, entry 8). The binary combination of $(Bu)_4N^+OAc^-$ and Cs_2CO_3 gave a coupling efficiency ratio of 0.24 : 1, essentially identical to that of $(Bu)_4N^+OAc^-$ alone (Table 4, entry 9 and 7 respectively), supporting the hypothesized additional role of the $^-$OAc. Performing the cross-coupling reaction with only Cs_2CO_3 the yield of **14** was reduced to ~ 20 % whilst the aryl bromide homocoupled product was obtained in a 52 % yield confirming the crucial nature of the tetrabutylammonium salt.

Table 4: Tetrabutylammonium salt screen using FibreCat® 1032.

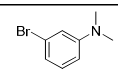
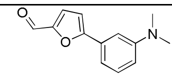
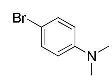
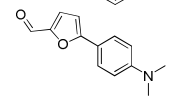
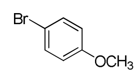
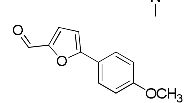
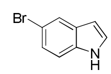
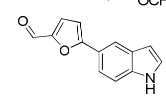
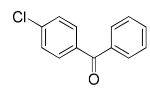
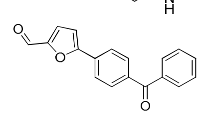
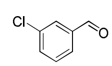
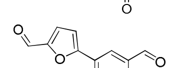
Entry	Tetrabutylammonium salt	Ratio of Peak Area [a]	
		13	14
1	$(Bu)_4N^+F^-$	0.46	1
2	$(Bu)_4N^+Cl^-$	0.65	1
3	$(Bu)_4N^+Br^-$	21.82	1
4	$(Bu)_4N^+I^-$	30.11	1
5	$(Bu)_4N^+BF_4^-$	2.47	1
6	$(Bu)_4N^+HSO_4^-$	1.51	1
7	$(Bu)_4N^+OAc^-$	0.22	1
8	$(Bu)_4N^+F^- + Cs_2CO_3$	0.20	1
9	$(Bu)_4N^+OAc^- + Cs_2CO_3$	0.24	1

[a]Ratio of peak areas determined by HPLC analysis at 220 nm.

Using $(Bu)_4N^+OAc^-$ in conjunction with FibreCat® 1032 gave **14** in a 72 % isolated yield of **14**, from **13**. However other deactivated aryl bromides such as the dimethylamino analogues **15a** and **15b**, the methoxy analogue **15c**, and the indole **15d**, aryl chlorides **15e** and **15f** gave unacceptably low levels of the desired cross coupled products (Table 5).

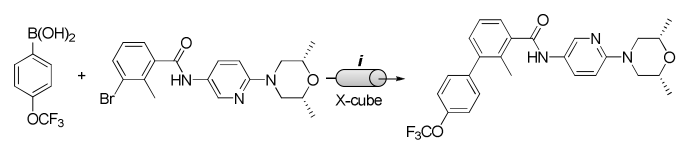
We consequently investigated the more activated CatCart™ $PdCl_2(PPh_3)_2$-DVB catalysts which has been shown to be highly effective in Sonogashira couplings.[42] The flow coupling steps were optimised as before with the CatCart™ $PdCl_2(PPh_3)_2$-DVB catalyst and we noted that clean coupling, with near quantitative conversions was accomplished at 120 ºC, after three catalyst cycles at 0.3 mL.min^{-1} (Table 5).

Table 5: Suzuki couplings with deactivated aryl bromides and aryl chlorides.

	Aryl Halide	Product [a]	Percent Conversion [b]	
			FC1032 ™	$PdCl_2(PPh_3)_2$-DVB
15a			28	96
15b			12	87
15c			16	92
15d			16	92
15e			< 5	83
15f			< 5	87

[a] Reagents and Conditions: (i) 5-formyl-2-furanylboronic acid (1 mmol), aryl halide (1 mmol), $(Bu)_4N^+OAc^-$ (3 mmol), MeOH (30 mL), X-Cube™, 0.3 mL.min^{-1}, and 120 °C, three catalyst cycles. B Percentage conversion determined by HPLC analysis at 220 nm.

We subsequently used this protocol to effect the cross-coupling of **16** and **17** and gained expedient access to the potent smoothened inhibitor LDE225 (**18**) which is a crucial component of our Hedgehog pathway inhibitor development program.

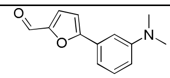
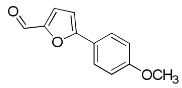
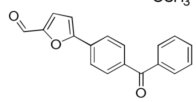
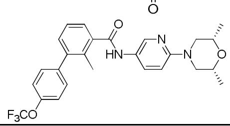


16 17 18

Scheme 3: *Reagents and Conditions*: (*i*) 4-(trifluoromethoxy)phenylboronic acid (**16**), 3-bromo-*N*-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methylbenzamide (**17**), $(Bu)_4N^+OAc^-$, MeOH (30 mL), $PdCl_2(PPh_3)_2$-DVB, 0.3 mL/min, and 120 °C.

Thus whilst increasing catalyst retention time and catalysts cycles significantly enhanced coupling efficiencies of deactivated aryl-bromides and aryl-chlorides, we were cognisant that these conditions may promote increased levels of palladium leaching. However as outlined in table 6, negligible levels of palladium leaching were observed with a maximum total recoverable Pd content by ICP MS analysis of 52 ppm for **15d**, 5.2 ppm for **15e,** whilst the remainder of samples analysed contenting less than 1 ppm palladium content.

Table 6: Total recoverable trace palladium by ICP MS of selected samples.

	Product [a]	$PdCl_2(PPh_3)_2$-DVB (yield %)	Palladium Content[a]
15a		96	0.65 ppm
15c		92	0.48 ppm
15e		83	0.72 ppm
18		87	5.2 ppm

[a] ICP MS analysis was conducted by the Australian National Measurement Institute.

Conclusion

A combination of un-distilled methanol, $(Bu)_4{}^+OAc^-$, 5-formyl-2-furanylboronic acid, an activated or neutral aryl bromide, along with the X-cube™ continuous flow reactor charged with the *t*-butyl based palladium catalyst FC1032™ efficiently afforded Suzuki cross-coupled products in excellent yield (>80%) with negligible homocoupling observed. In relation to deactivated aryl bromides or aryl chlorides the use of a more active Pd-based catalyst such as $PdCl_2(PPh_3)_2$-DVB, provided efficient coupling to the desired products. This optimised continuous flow Suzuki cross-coupling methodology~~ies~~ appears amenable with a range of boronic acids. However, we note that when CatCart™ $PdCl_2(PPh_3)_2$-DVB was employed to perform the initial cross-coupling investigation (i.e. Scheme 1), as was the case with Pd-Tetrakis, a significant (~ 30 %) amount of aryl bromide homocoupling product was observed. Consequently we propose that FC1032™ serves as a more effective catalyst for the cross-coupling of activated or neutral aryl bromides. We have used this protocol to provide expedient access to the potent smoothened inhibitor LDE225 (**18**). Significantly, negligible palladium leaching was observed with the immobilised catalysts[29, 31] and thus this continuous flow Suzuki cross-coupling protocol is ideally suited to medicinal chemistry research programs. We are currently investigating the versatility of these conditions with other palladium catalysed cross-coupling reactions and the outcomes of these investigations will be reported in due course.

Experimental Section

All reagents were purchased from Sigma Aldrich and were used without purification, with the exception of furfural, which was distilled through glass prior to use. Solvents were bulk, and distilled through glass prior to use.

^1H and ^{13}C NMR spectra were recorded on a Bruker Advance™ AMX 400 MHz spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured to relative the internal standards. Coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV using a mobile phase of 1:1 acetonitirle:H2O with 0.1 % formic acid. Gas chromatography-mass spectrometry (GC-MS) was performed on a Shimadzu GC-MS QF2010 EI/NCI System equipped with a ZB-5MS capillary column of 5% phenyl-arylene stationary phase. High-resolution mass spectra (HRMS) were determined on a Micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as lockmass. Monoisotopic molecular masses were calculated utilising ChemDraw Ultra 8.0.

Analytical HPLC traces were obtained using a Shimadzu system possessing a SIL-20A auto-sampler, dual LC-20AP pumps, CBM-20A bus module, CTO-20A column heater, and a SPD-20A UV/vis detector. This system was fitted with an Alltima™ C18 5u 150 mm x 4.6 mm column with solvent A: 0.06% TFA in water and solvent B: 0.06% TFA in CH_3CN:H_2O (90:10). In each case HPLC traces were acquired at a flow rate of 2.0 mL/min, gradient 10-100 (%B), curve = 6, over 15.0 mins, with detection at 220 nm and 265 nm.

Where applicable, melting points were recorded on a BUCHI Melting Point M-565. IR spectra were recorded on a PerkinElmer Spectrum Two™ FTIR Spectrometer. Thin layer chromatography (TLC) was performed on Merck 60 F254 pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230-400 mesh).

ICP MS analysis was conducted by the Australian National Measurement Institute 105 Delhi Road, North Ryde NSW 2113 (www.measurement.gov.au)

Biphenyl-3,3'-diyldimethanol (10) and 5-(3-(hydroxymethyl)phenyl)furan-2-carbaldehyde (7)

A solution of (3-bromophenyl)methanol (0.28 mL, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAF (2.16 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through an X-Cube™ fitted with a Fibrecat®1001 catalyst at flow rate of 0.5 mL/min, at a temperature of 80 °C, and 0 bar pressure for 2 h (i.e. total of two catalyst cycles). The eluent was concentrated *in vacuo*, diluted with DCM (30 mL), washed with 1 M HCl (2 x 30 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the crude was subjected to flash silica gel chromatography (1:1 EtOAc:Hexanes) to afford biphenyl-3,3'-diyldimethanol (**10**) as a colourless oil (0.01 g, 3 %). LRMS (ESI+) m/z 215(M+1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 141.3, 129.0, 129.0, 126.5, 126.0, 125.8, 65.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 10.39 min. Continued elution (1:1 EtOAc:Hexanes) afforded 5-(3-(hydroxymethyl)phenyl)furan-2-carbaldehyde (**7**) as an orange oil (0.37 g, 82 %). LRMS (ESI+) m/z 203 (M+1); HRMS (ES+) for $C_{12}H_{11}O_3$; calculated 201.0630, found 202.0681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.74 (s, 1H), 7.67 – 7.57 (m, 1H), 7.32 (m, 2H), 7.25 (d, J = 3.7 Hz, 1H), 6.76 (d, J = 3.7 Hz, 1H), 4.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.34, 159.5, 151.8, 142.1, 129.0 (C x 2), 128.9, 128.2, 124.3, 123.6, 107.9, 77.5, 77.2, 76.9, 64.4. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 9.10 min.

5-(4-acetylphenyl)-2-furancarboxaldehyde (12a)

General procedure 1: A solution of 4-bromoanisole (0.40 g, 2.1 mmol), 5-formyl-2-furanylboronic acid (0.30 g, 2.1 mmol) and TBAF (2.16 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through an X-Cube™ fitted with a Fibrecat®1032 catalyst at flow rate of 0.5 mL/min, at a temperature of 120 °C, and 0 bar pressure for 2 h (i.e. total of two catalyst cycles). The eluent was concentrated *in vacuo*, diluted with DCM (30 mL), washed with 1 M HCl (2 x 30 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the crude was subjected to flash silica gel chromatography (1:1 EtOAc:Hexanes) to afford 5-(4-acetylphenyl)-2-furancarboxaldehyde (**12a**) as a yellow oil (0.36 g, 87 %). LRMS (ESI+) m/z 215 (M+1); HRMS (ES+) for $C_{13}H_{11}O_3$; calculated 215.0630, found 214.0637; ^{1}H NMR ($CDCl_3$, 400 MHz); δ 9.60 (s, 1H), 7.77 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 3.7 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 3.7 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (CDCl3, 101 MHz): δ 176.9, 160.91, 159.8, 151.6, 129.0, 127.0, 121.8, 114.4, 106.3, 55.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 14.26 min.

2-(4-(5-formylfuran-2-yl)phenyl)acetonitrile (12b)

Compound (12b) was ~~S~~synthesised as described in general procedure 1 from 4-bromoacetonitrile (0.44 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAF (2.04 g, 6.7 mmol). The crude reaction mixture was subjected to flash silica chromatography (4:1 Hex:EtOAc) to afford **12b** as an orange solid (0.38 g, 82 %). LRMS (ESI+) m/z 212 (M+1); HRMS (ES+) for $C_{13}H_{10}NO_2$; calculated 216.0630, found 216.0637; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.67 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 3.7 Hz, 1H), 6.87 (d, J = 3.7 Hz, 1H), 3.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.3, 158.37, 152.2, 131.3, 128.9, 128.6, 126.0, 108.2, 23.6. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 14.27 min.

5-(4-Methylphenyl)-2-furancarboxaldehyde (12c)

Compound **12c** was prepared utilising general procedure 1, 4-bromotoluene (0.28 mL, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol), TBAF (2.16 g, 6.86 mmol), and MeOH (30 mL). The eluent was concentrated *in vacuo* and the crude material was diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL). The organic layer was dried (MgSO4), and concentrated *in vacuo* to yield an oil which was further purified using flash chromatography (1:9 EtOAc:Hexanes) to afford 5-(4-Methylphenyl)-2-furancarboxaldehyde as an orange oil/solid (0.39 g, 91 %) m.p 50-56 °C. LRMS (ESI+) m/z 187 (M+1); HRMS (ES+) for $C_{12}H_{11}O_2$; calculated 187.0681, found 186.0678; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.63 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 3.7 Hz, 1H), 7.25 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 3.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.1, 159.8, 151.8, 140.0, 129.7, 126.3, 125.3, 107.1, 21.5; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 17.41 min.

5-(dimethylamino)-N-(4-(5-formylfuran-2-yl)phenyl)naphthalene-1-sulfonamide (12d)

Compound **12d** was prepared utilising general procedure 1, and *N*-(4-bromophenyl)-5-(dimethylamino)naphthalene-1-sulfonamide (0.92 g, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol), TBAF (2.16 g, 6.86 mmol), and MeOH (30 mL). The eluent was concentrated *in vacuo*, the crude material was diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to yield an oil which was further purified using flash chromatography (5:1 EtOAc:Hexanes) to afford 5-(4-Methylphenyl)-2-furancarboxaldehyde as an yellow oil/solid (0.82 g, 87 %). LRMS (ESI+) m/z 421 (M+1); HRMS (ES+) for $C_{23}H_{21}N_2O_4S$; calculated 421.1144, found 421.1144; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.46 – 8.25 (m, 2H), 8.13 (s, 1H), 7.56 – 7.51 (m, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.47 – 7.42 (m, 1H), 7.23 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 3.7 Hz, 1H), 2.85 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.2, 158.9, 151.7, 138.2, 134.1, 132.1, 131.0, 130.4, 129.7, 129.6, 128.7, 126.3, 125.0, 123.2, 122.7, 120.3, 115.5, 111.1, 107.3, 45.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 9.60 min.

***N*-(4-(5-formylfuran-2-yl)phenyl)benzenesulfonamide (12e)**

Compound **12e** was prepared utilising general procedure 1, and *N*-(4-bromophenyl)benzenesulfonamide (0.77 g, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol), TBAF (2.16 g, 6.86 mmol), and MeOH (30 mL). The eluent was concentrated *in vacuo*, the crude material was diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to yield an oil which was further purified using flash chromatography (4:1 EtOAc:Hexanes) to afford *N*-(4-(5-formylfuran-2-yl)phenyl)benzenesulfonamide as an yellow oil/solid (0.65 g, 87 %). LRMS (ESI+) m/z 328 (M+1); HRMS (ES+) for $C_{17}H_{14}NO_4S$; calculated 328.0565, found 327.0556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.85 – 7.78 (m, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.46 (*t*, J = 7.7 Hz, 2H), 7.30 (d, J = 3.7 Hz, 1H), 7.26 (s, 1H), 7.18 (d, J = 8.7 Hz, 3H), 6.76 (d, J = 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 158.6, 151.89, 138.8, 137.8, 129.2, 127.2, 126.6, 125.8, 121.1 (Cx2), 107.6. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 15.58 min.

_N_-(2,4-dimethoxyphenyl)-4-(5-formylfuran-2-yl)benzamide (12f)

Compound **12f** was synthesised utilising general procedure 1, 4-bromo-*N*-(2,4-dimethoxyphenyl)benzamide (0.73 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAF (2.14 g, 6.6 mmol) to afford N-(2,4-dimethoxyphenyl)-4-(5-formylfuran-2-yl)benzamide as a light brown solid (0.71. g, 92 %). LRMS (ESI-) m/z 352 (M-1); HRMS (ES-) for $C_{20}H_{18}NO_5$; calculated 352.1107, found 352.1113; ^{1}H NMR (400 MHz, DMSO-d6): δ 9.66 (s, 1H), 9.54 (s, NH), 8.09 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 3.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 6.55 (dd, J = 8.7, 2.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (400MHz, DMSO-d6): δ 178.6, 164.8, 158.5, 157.6, 154.1, 152.6, 135.55, 131.6, 128.9, 127.1, 125.3, 120.0, 110.7, 104.7, 99.4, 56.2, 55.8; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 18.12 min.

5-(4-hydroxyphenyl)-2-furancarboxaldehyde (14)

Compound **14** was synthesised utilising general procedure 1, 4-bromophenol (0.38 g, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAF (2.10 g, 6.9 mmol). The crude was subjected to silica gel chromatography (4:1 EtOAc:Hex) to afford 5-(4-hydroxyphenyl)-2-furancarboxaldehyde as an orange oil/solid (0.09 g, 30 %). LRMS (ESI-) m/z 187 (M-1); HRMS (ES-) for $C_{11}H_7O_3$; calculated 187.0473, found 187.0468; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.60 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 3.7 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.9, 157.1, 128.0, 127.3, 122.0, 116.0, 115.6, 106.3. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 10.68 min.

5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde (15a)

General Procedure 2: A solution of 3-bromo-*N*,*N*-dimethylaniline (0.28 mL, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAA (2.08 g, 6.86 mmol) was diluted with MeOH (30 mL) to afford a 0.05 M. This solution was flowed through an X-Cube™ fitted with a CatCart® $PdCl_2(PPh_3)_2$-DVB catalyst at flow rate of 0.3 mL/min, at a temperature of 120 °C, and 0 bar pressure for 3 h (i.e. total of three catalyst cycles). The eluent was concentrated *in vacuo*, diluted with DCM (30 mL) and washed with 1 M HCl (2 x 30 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the crude was subjected to flash silica gel chromatography (7:1 EtOAc:Hexanes) to afford 5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde as a colourless oil (0.43 g, 87 %). LRMS (ESI+) m/z 216 (M+1); HRMS (ES+) for $C_{13}H_{14}NO_2$; calculated 216.0946, found 216.0942; ^{1}H NMR (DMSO-d6, 400 MHz): δ 9.59 (s, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.81 (dd, J = 8.3, 2.4 Hz, 1H), 2.97 (s, 6H). ^{13}C NMR (DMSO-d6, 101 MHz): δ 178.1, 159.7, 151.9, 151.2, 130.2, 129.7, 114.3, 113.5, 109.0, 108.5, 40.5. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 9.60 min.

5-(4-(dimethylamino)phenyl)-2-furancarboxaldehyde (15b)

Compound **15b** was synthesised utilising general procedure 2 and 4-bromo-*N*,*N*-dimethylaniline (0.46 g, 2.3 mmol), 5-formyl-2-furanylboronic acid (0.32 g, 2.3 mmol) and TBAA (2.08 g, 6.90 mmol). The crude was subject to flash silica gel chromatography (7:1 EtOAc:Hex) to afford 5-(4-(dimethylamino)phenyl)-2-furancarboxaldehyde as a yellow solid (0.43 g, 87 %). M.p. 96-98 °C (Lit mp: 95-98 °C). LRMS (ESI^-) m/z 216 (M+1); HRMS (ES+) for $C_{13}H_{14}NO_2$; calculated 216.0946, found 216.0950; ^{1}H NMR (DMSO-d6, 400 MHz): δ 9.48 (d, J = 3.2 Hz, 1H), 7.69 (dd, J = 8.2, 3.6 Hz, 2H), 7.59 (t, J = 3.8 Hz, 1H), 7.00 (t, J = 3.9 Hz, 1H), 6.81 (dd, J = 8.3, 3.4 Hz, 2H), 3.00 (d, J = 3.2 Hz, 6H); ^{13}C NMR (DMSO-d6, 101 MHz): δ 176.9, 160.6, 151.6, 151.1, 126.9, 116.4, 112.5, 106.0; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 10.68 min.

5-(4-methoxyphenyl)-2-furancarboxaldehyde (15c)

Compound **15c** was synthesised utilised general procedure 2, 4-bromoanisole (0.41 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAA (1.99 g, 6.6 mmol). The crude was subjected to flash silica gel chromatography (5:1 Hex:EtOAc) to afford 5-(4-methoxyphenyl)-2 furancarboxaldehyde as a pale yellow oil (0.42 g, 92 %). LRMS (ESI^-) m/z 201 (M-1); HRMS (ES-) for $C_{12}H_9O_3$; calculated 201.0630, found 201.0637; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.60 (s, 1H), 7.77 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 3.7 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 3.7 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.9, 160.91, 159.8, 151.6, 129.0, 127.0, 121.8, 114.4, 106.3, 55.4; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 18.92 min.

5-(1*H*-indol-6-yl)-2-furancarboxaldehyde (15d)

Compound **15d** was synthesised utilising general procedure 2, 6-bromo-1*H*-indole (0.41 g, 2.1 mmol), 5-formyl-2-furanylboronic acid (0.29 g, 2.1 mmol) and TBAA (1.90 g, 6.3 mmol). The crude was subjected to flash silica gel chromatography (3:1 EtOAc:Hex) to afford 5-(1*H*-indol-6-yl)-2-furancarboxaldehyde as an off-white solid (0.48. g, 83 %). LRMS (ESI^+) m/z 212 (M+1); HRMS (ES+) for $C_{13}H_{10}NO_2$; calculated 212.0633, found 212.0635; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.61 (s, 1H), 8.43 (s, NH), 7.95 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 8.3, 1.4 Hz, 1H), 7.34 (d, J = 3.7 Hz, 1H), 7.33 – 7.31 (m, 1H), 6.83 (d, J = 3.7 Hz, 1H), 6.60 – 6.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.8, 161.3, 151.6, 135.9, 129.2, 126.5, 122.9, 121.2, 117.7, 108.4, 106.8, 103.1; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 15.58 min.

5-(4-benzoylphenyl)-2-furancarboxaldehyde (15e)

Compound **15e** was synthesised using general procedure 2, (4-chlorophenyl)(phenyl)methanone,(0.41 g, 2.2 mmol), 5-formyl-2-furanylboronic acid (0.31 g, 2.2 mmol) and TBAF (1.99 g, 6.60 mmol). The crude was subjected to flash silica gel chromatography (4:1 Hex:EtOAc) to afford 5-(4-benzoylphenyl)-2-furancarboxaldehyde as a of white solid (0.38. g, 87 %). LRMS (ESI^+) m/z 277 (M+1); HRMS (ES+) for $C_{18}H_{13}O_3$; calculated 277.0786, found 277.0791; ^{1}H NMR (DMSO-d6, 100 MHz): δ 9.67 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.78 – 7.75 (m, 2H), 7.73 – 7.69 (m, 2H), 7.59 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.5, 178.7, 157.3, 152.8, 137.7, 137.3, 133.3, 132.6, 131.0, 130.1, 129.1, 125.4, 111.3; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 18.21 min.

5-(3-formylphenyl)furan-2-carbaldehyde (15f)

Compound **15f** was synthesised using general procedure, 3-chlorobenzaldehyde (0.28 g, 2.0 mmol), 5-formyl-2-furanylboronic acid (0.28 g, 2.0 mmol) and TBAF (1.81 g, 6.0 mmol). The crude was subjected to flash silica gel chromatography (9:1 Hex:EtOAc) to afford 5-(4-benzoylphenyl)-2-furancarboxaldehyde as a of white solid (0.34. g, 85 %). LRMS (ESI^-) m/z 199 (M-1); HRMS (ES-) for $C_{12}H_7O_3$; calculated 199.0473, found 199.0482; ^{1}H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 9.66 (s, 1H), 8.38 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.46 (d, J = 3.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 193.33, 178.61, 157.24, 152.51, 137.38, 131.03, 130.65, 130.63, 129.99, 126.09, 125.91, 125.67, 110.34; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 10.68 min.

***N*-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide (LDE225) (18)**

Compound **18** was synthesised using general procedure 2, 3-bromo-*N*-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methylbenzamide (0.48 g, 1.2 mmol), 4-(trifluoromethoxy)phenylboronic acid (0.25 g, 1.2 mmol), and TBAF (1.08 g, 3.6 mmol). The crude was subjected to flash silica gel chromatography (9:1 DCM:MeOH) to afford LDE225 as a of white solid (0.55 g, 94 %). LRMS (ESI^+) m/z 486 (M+1); ^{1}H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 9.1, 2.5 Hz, 1H), 7.47 (s, 4H), 7.42 – 7.25 (m, 2H), 6.86 (d, J = 9.1 Hz, 1H), 4.06 (d, J = 12.0 Hz, 2H), 3.67 – 3.54 (m, 2H), 2.41 – 2.27 (m, 2H), 2.22 (s, 3H), 1.16 (d, J = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d6) δ .19, 156.18, 148.00, 141.40, 140.63, 139.87, 139.05, 132.53, 131.52, 131.14, 130.66, 127.49, 127.05, 126.26, 121.85, 121.38, 119.31, 107.32, 71.32, 51.25, 19.30, 17.71;193.33, 178.61, 157.24, 152.51, 137.38, 131.03, 130.65, 130.63, 129.99, 126.09, 125.91, 125.67, 110.34; RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min, t_R 17.41 min.

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