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Supporting Data for An Efficient Continuous Flow Approach to Furnish Furan-Based Biaryls

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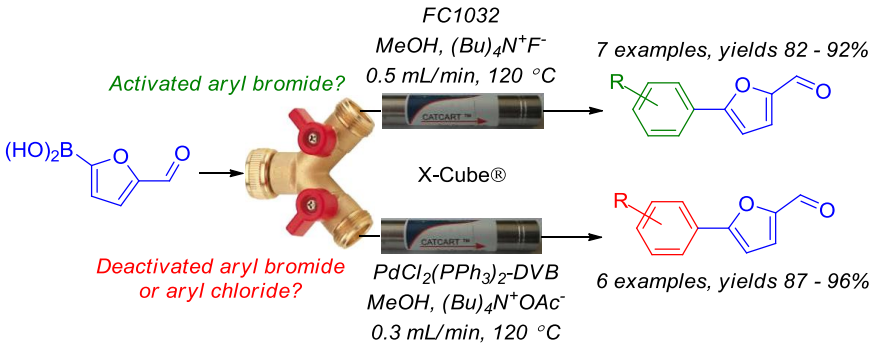
Abstract

Suzuki cross-couplings of 5-formyl-2-furanylboroic acid with activated or neutral aryl bromides were performed under continuous flow conditions in the presence of tetrabutylammonium fluoride and immobilised *t*-butyl based palladium catalyst CatCart™ FC1032. Deactivated aryl bromides and aryl chlorides were cross-coupled with 5-formyl-2-furanylboroic in the presence of tetrabutylammonium acetate using the bis-tripehnylphosphine CatCart™ $PdCl_2(PPh_3)_2$-DVB which efficiently furnished a series of decorated aldehyde based building blocks. Initial evidence indicates the latter method my serve as a universal approach to conduct Suzuki cross-couplings as it was employed in the successful synthesis of the current gold standard hedgehog pathway inhibitor LDE225.

Graphical Abstract



Supporting Information

S1. General Chemistry

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.

^{1}H 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 analysis was conducted by the Australian National Measurement Institute 105 Delhi Road, North Ryde NSW 2113 (www.measurement.gov.au)

S2. Initial Synthesis of Compound 10

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

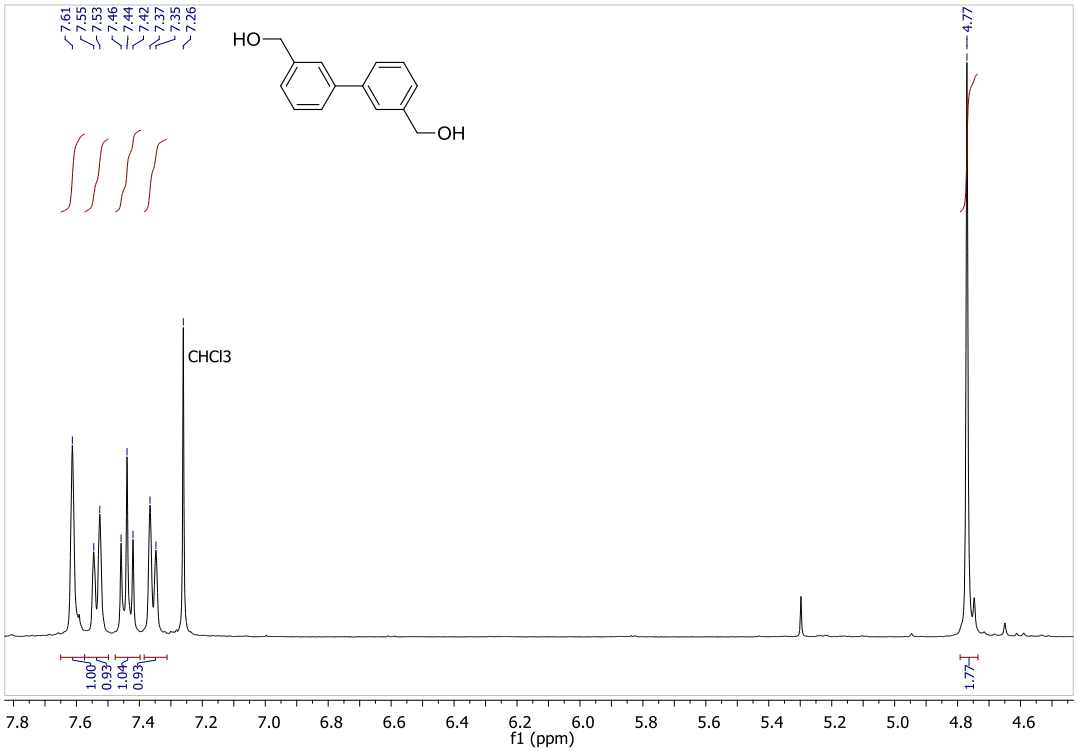


Figure S1: ^{1}H NMR spectrum of compound **10**, solvent $CDCl_3$.

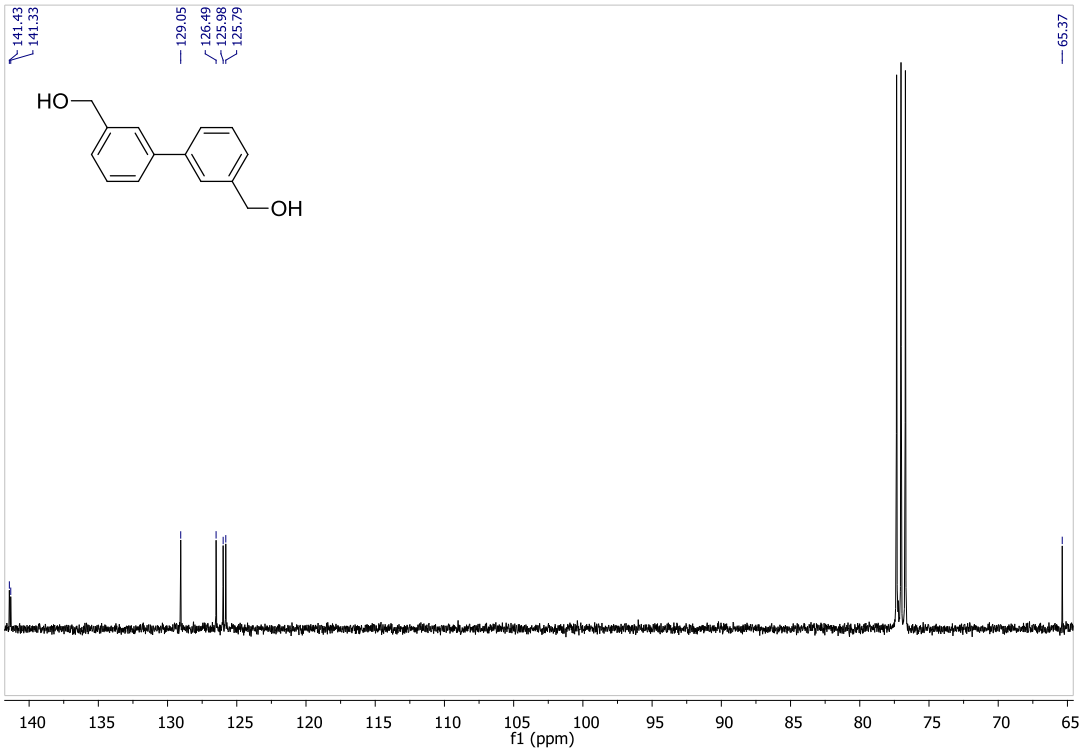


Figure S2: ^{13}C NMR spectrum of compound **10**, solvent $CDCl_3$.

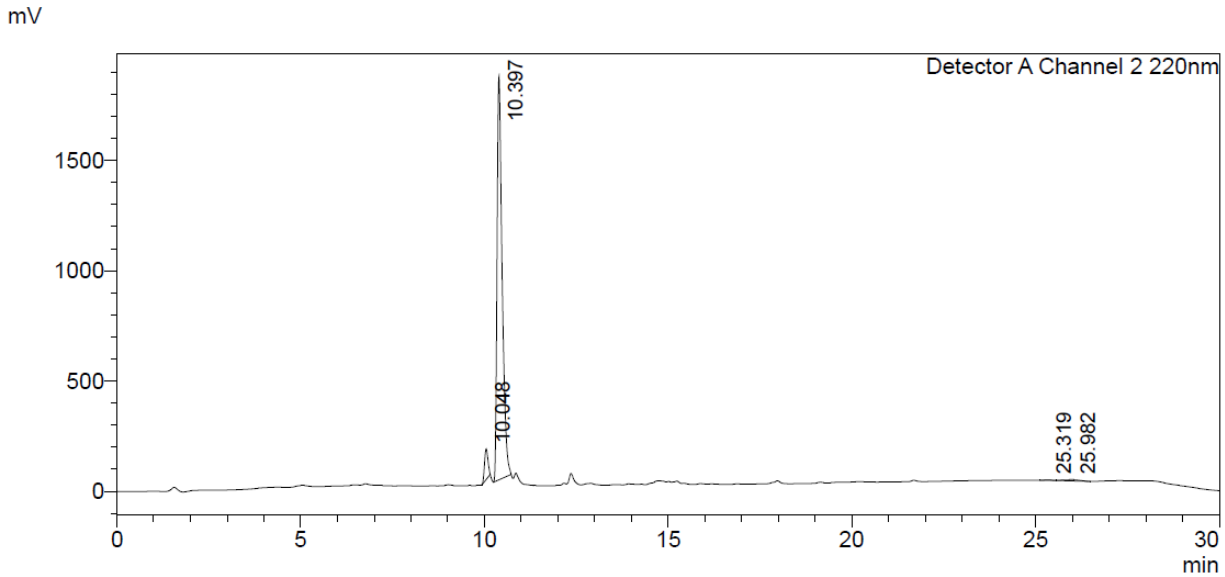


Figure S3: HPLC chromatogram of compound **10**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

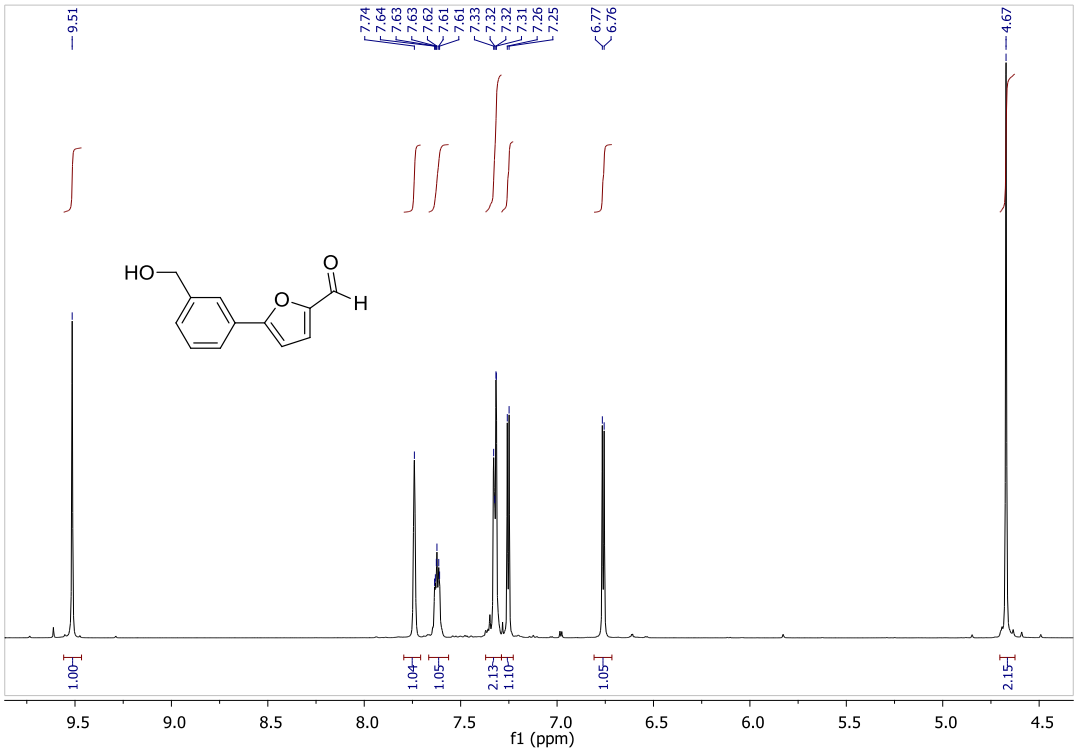


Figure S4: ^{1}H NMR spectrum of compound **7**, solvent $CDCl_3$.

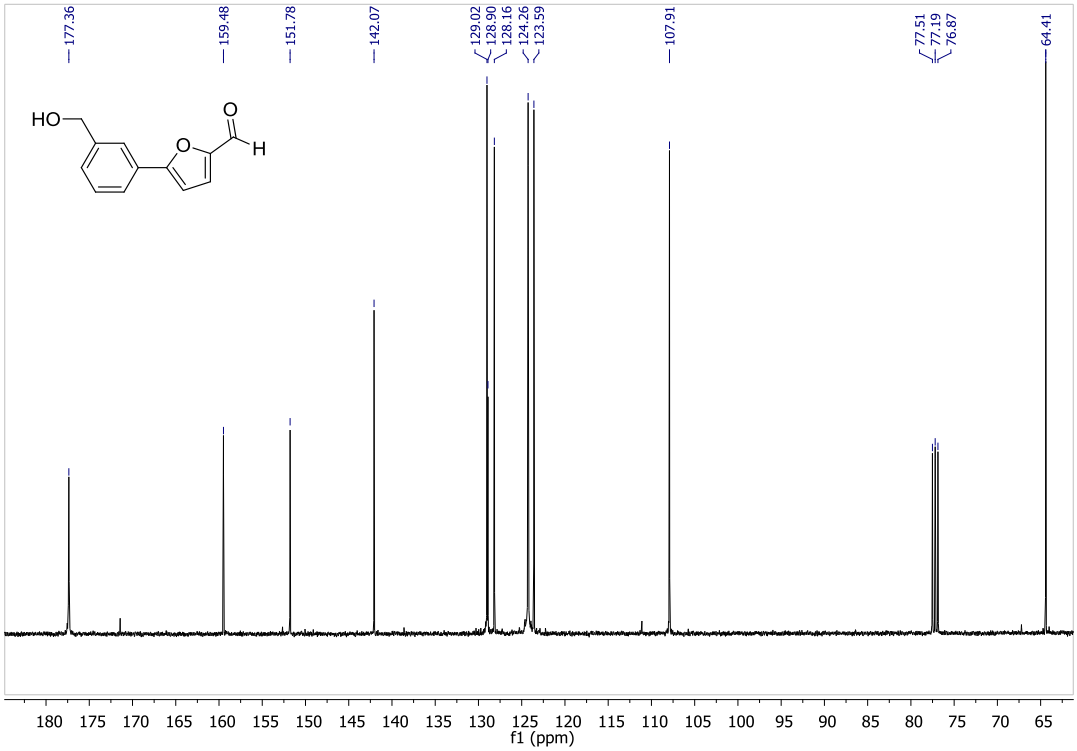


Figure S5: ^{13}C NMR spectrum of compound **7**, solvent $CDCl_3$.

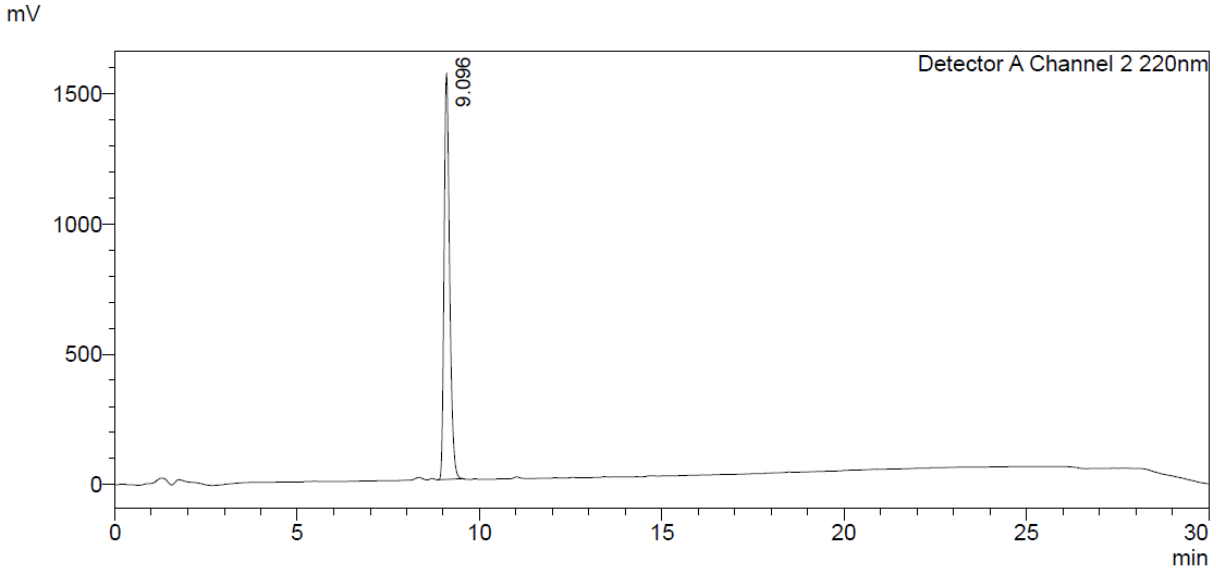
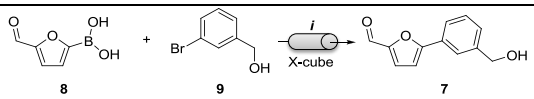


Figure S6: HPLC chromatogram of compound **7**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min

S3. Initial Catalyst Screening Optimisation Investigations

The optimisation investigations were performed in accordance with the protocol outlined for the initial synthesis of compound **9** (i.e. section S2) with the only variation being the catalyst employed.

Table S1: Ratio of **7** and **9** peak areas obtained after subsequent cycles FibreCat® 1001. ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, and 80 °C.



8 9 7

Entry	Pd-Ligand	FibreCat®	Number of catalyst cycles Ratio of 7 : 9[a]			
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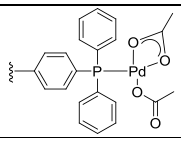
1		FC1001	1:1.2	1:0.7	1:0.5	1:0.4

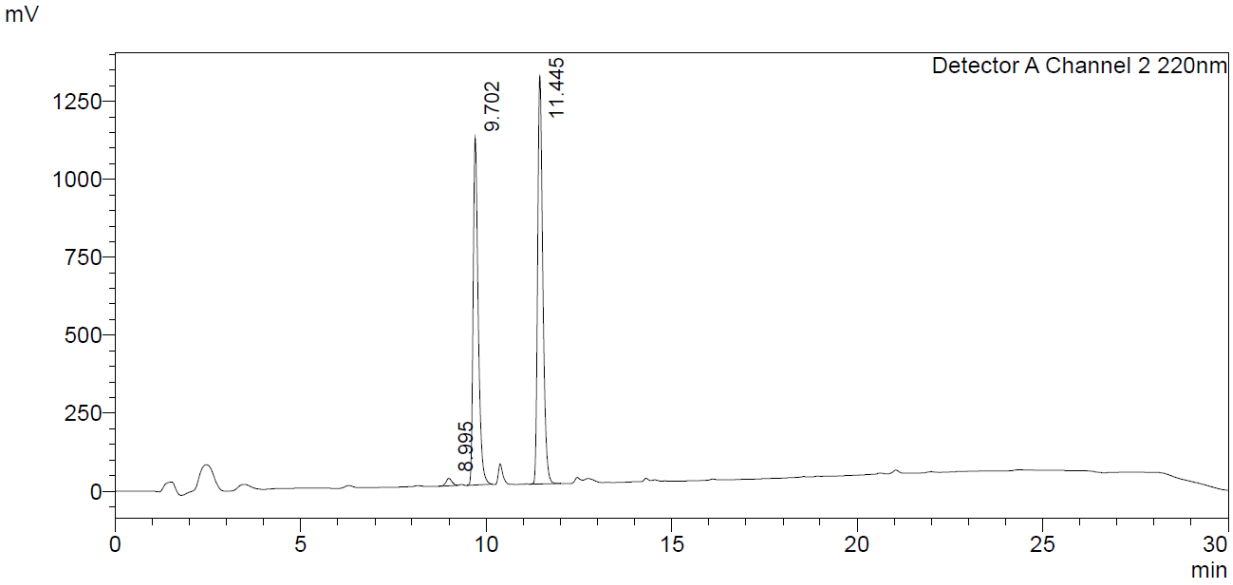


Figure S7: HPLC chromatogram of the reaction mixture outlined in table S1 after a single catalyst cycle. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

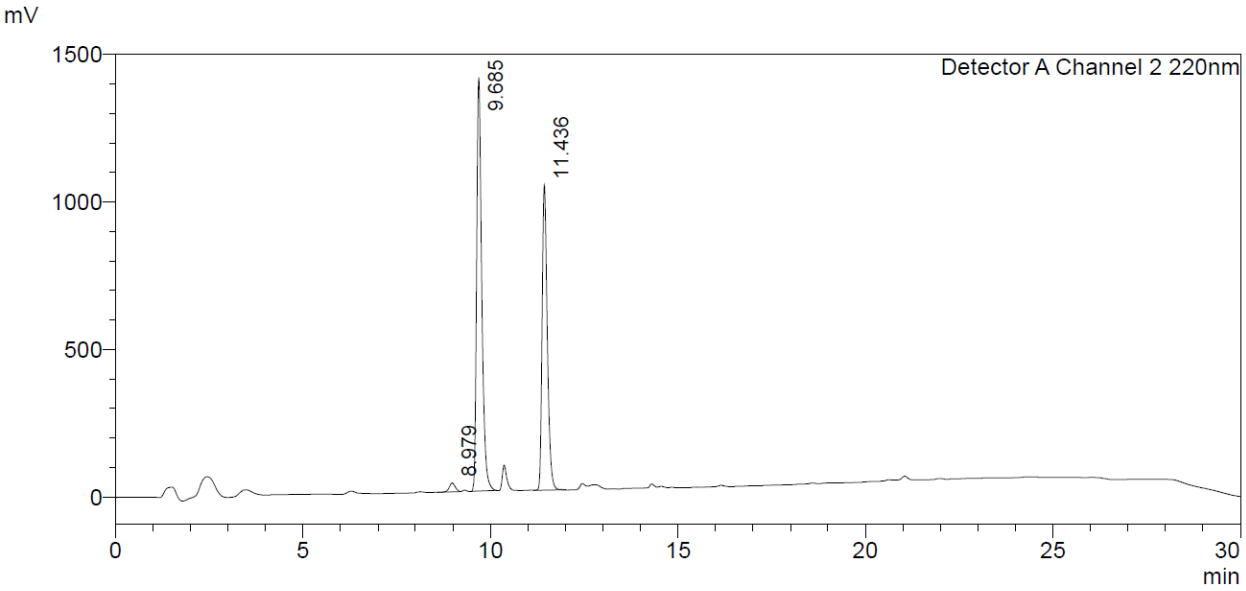


Figure S8: HPLC chromatogram of the reaction mixture outlined in table S1 after two catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

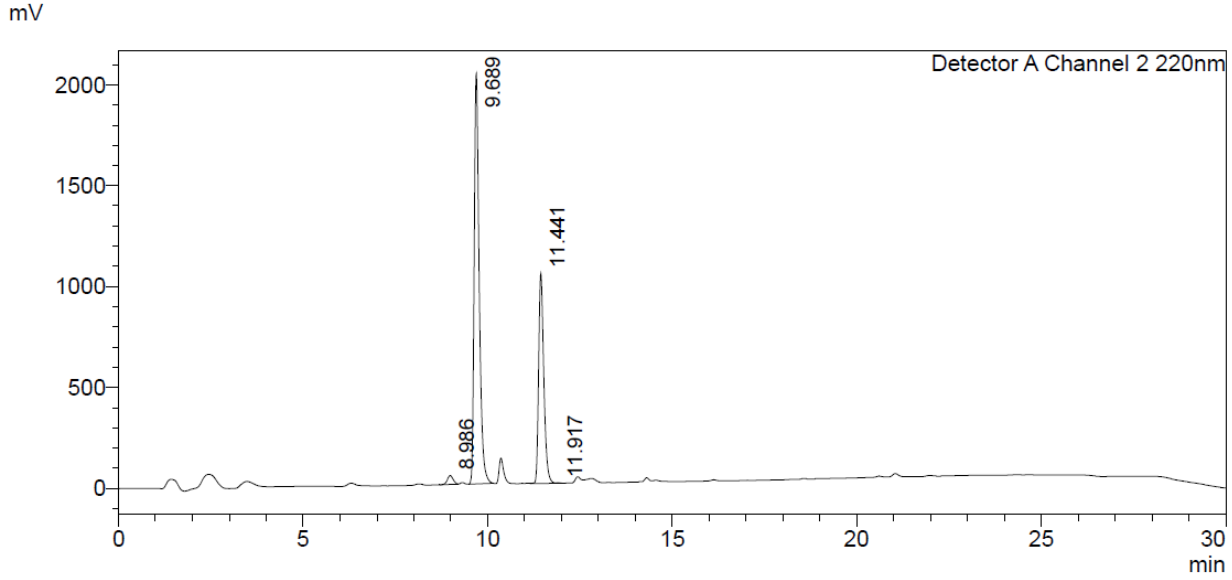


Figure S8: HPLC chromatogram of the reaction mixture outlined in table S1 after three catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

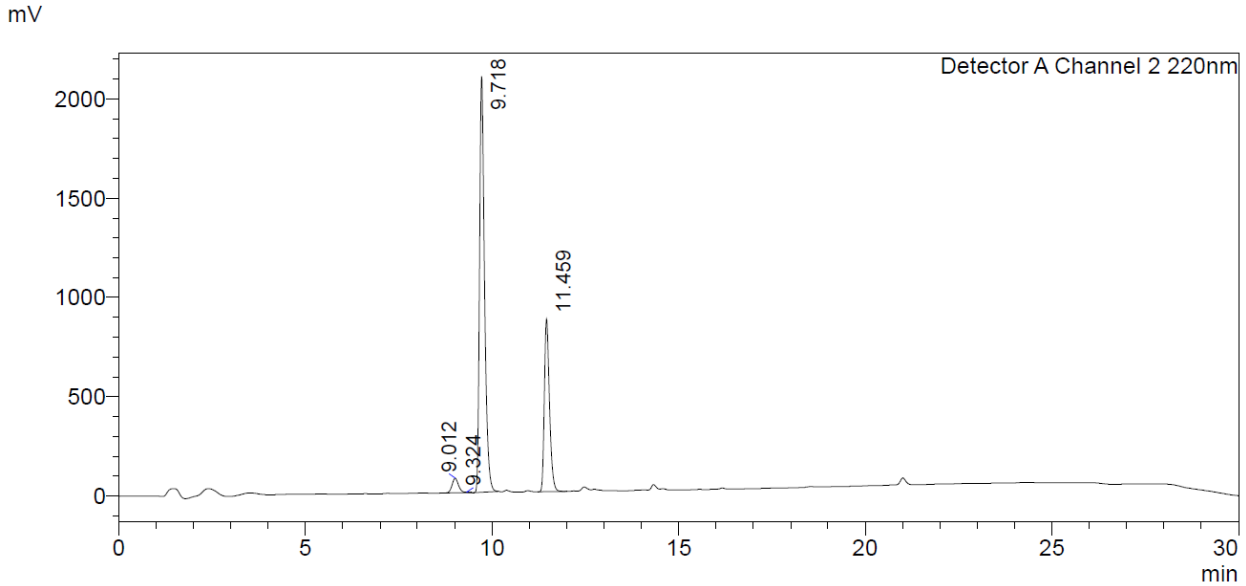
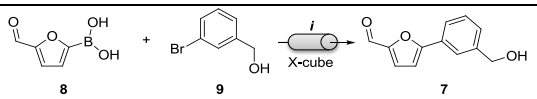
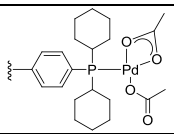


Figure S9: HPLC chromatogram of the reaction mixture outlined in table S1 after four catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S2: Ratio of **7** and **9** peak areas obtained after subsequent cycles FibreCat® 1007. ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, and 80 °C.



8 9 7

Entry	Pd-Ligand	FibreCat®	Number of catalyst cycles Ratio of 7 : 9[a] 1	2	3	4
2		FC1007	1:1.3	1:0.7	1:0.4	1:0.2

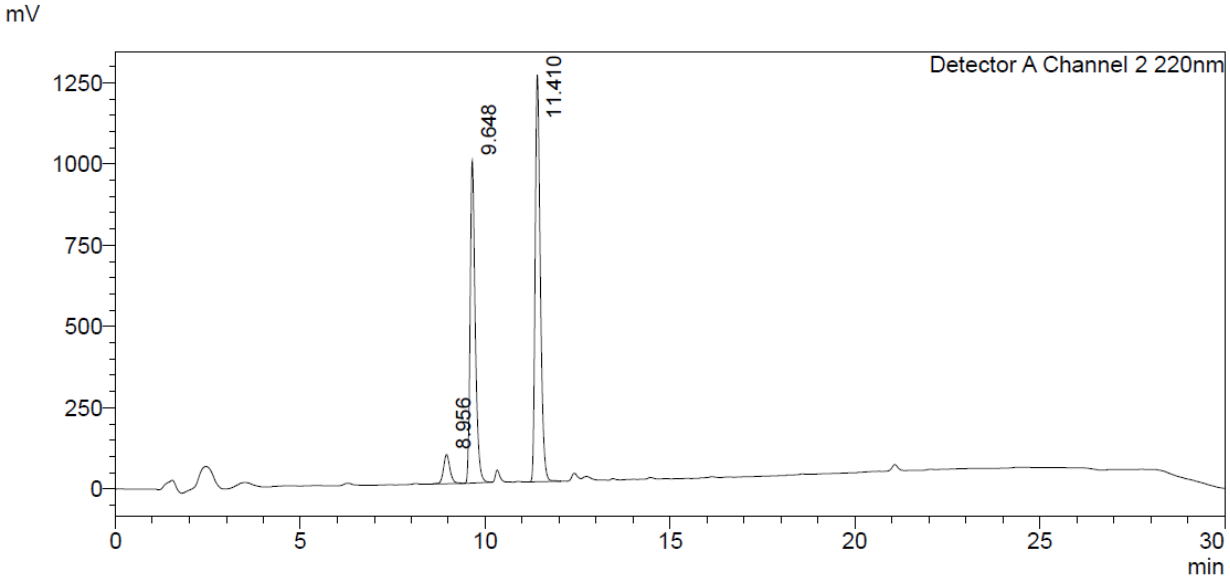


Figure S10: HPLC chromatogram of the reaction mixture outlined in table S2 after a single catalyst cycle. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

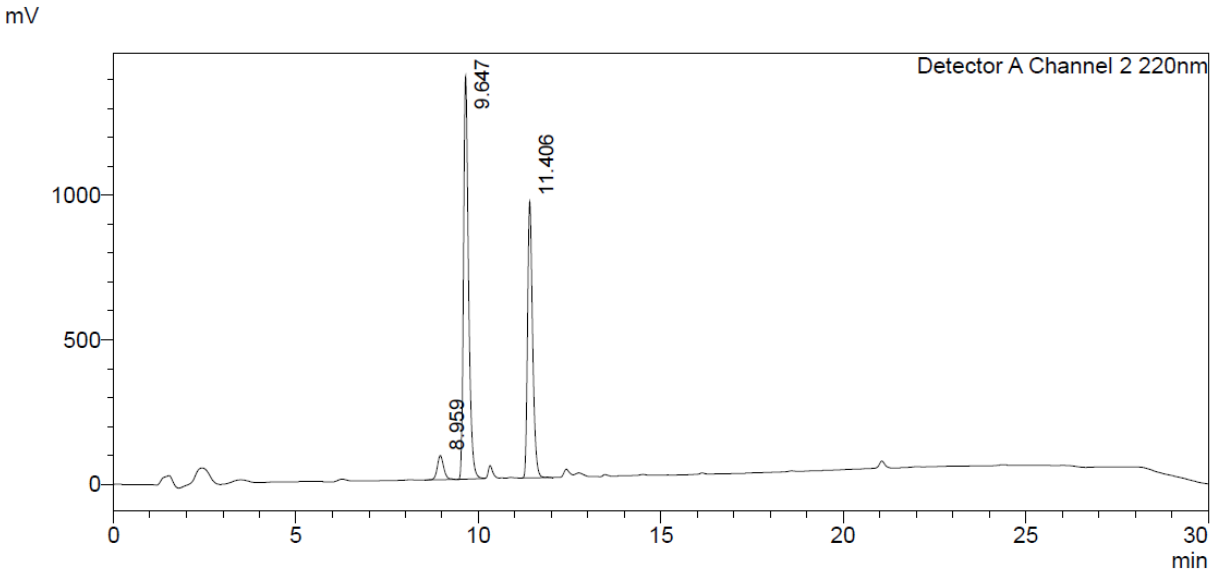


Figure S11: HPLC chromatogram of the reaction mixture outlined in table S2 after two catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

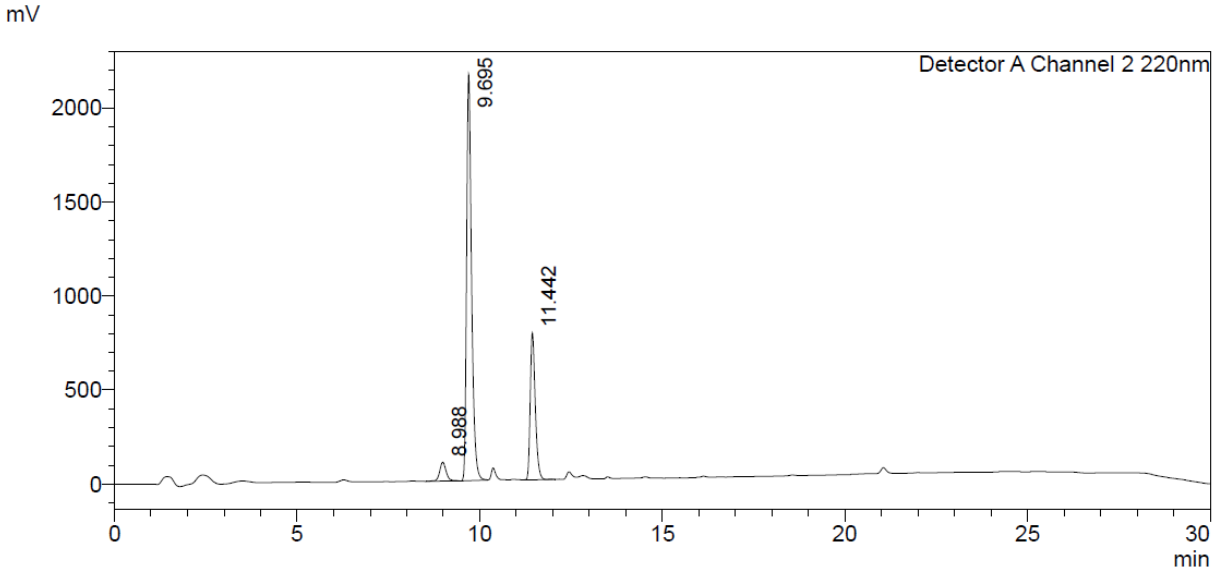


Figure S12: HPLC chromatogram of the reaction mixture outlined in table S2 after three catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

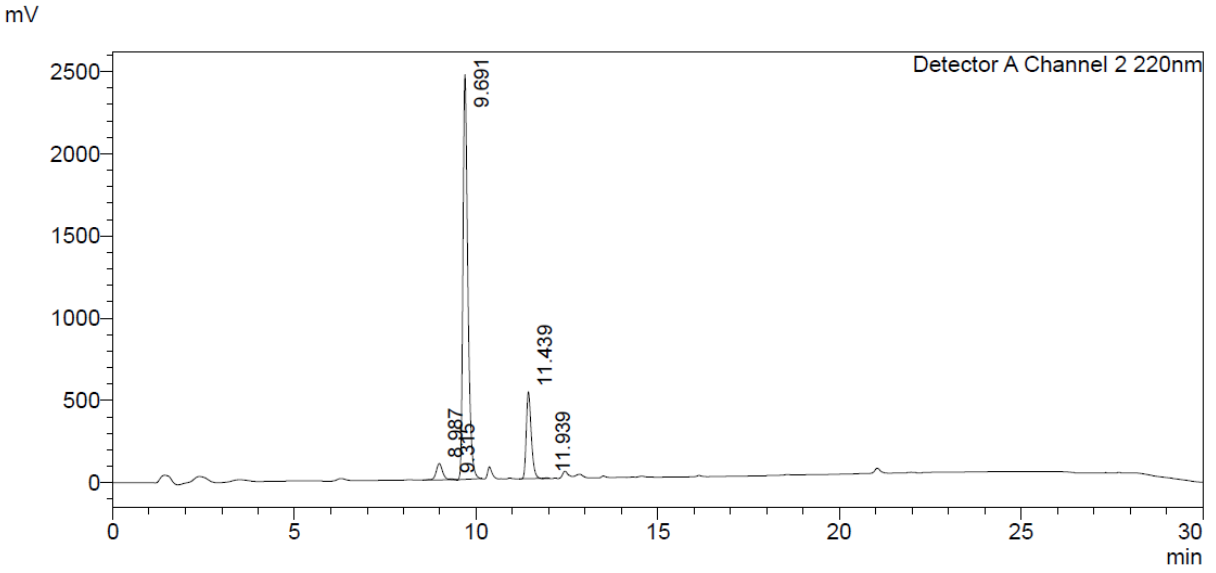
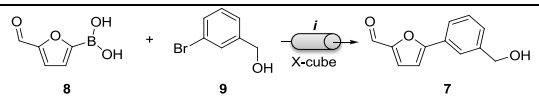


Figure S13: HPLC chromatogram of the reaction mixture outlined in table S2 after four catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S3: Ratio of **7** and **9** peak areas obtained after subsequent cycles FibreCat® 1032. ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, and 80 °C.



8 9 7

Entry	Pd-Ligand	FibreCat®	Number of catalyst cycles Ratio of 7 : 9[a]			
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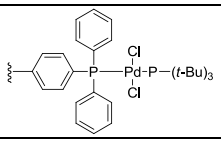
3		FC1032	1:0.7	1:0.4	1:0.3	1:0.2

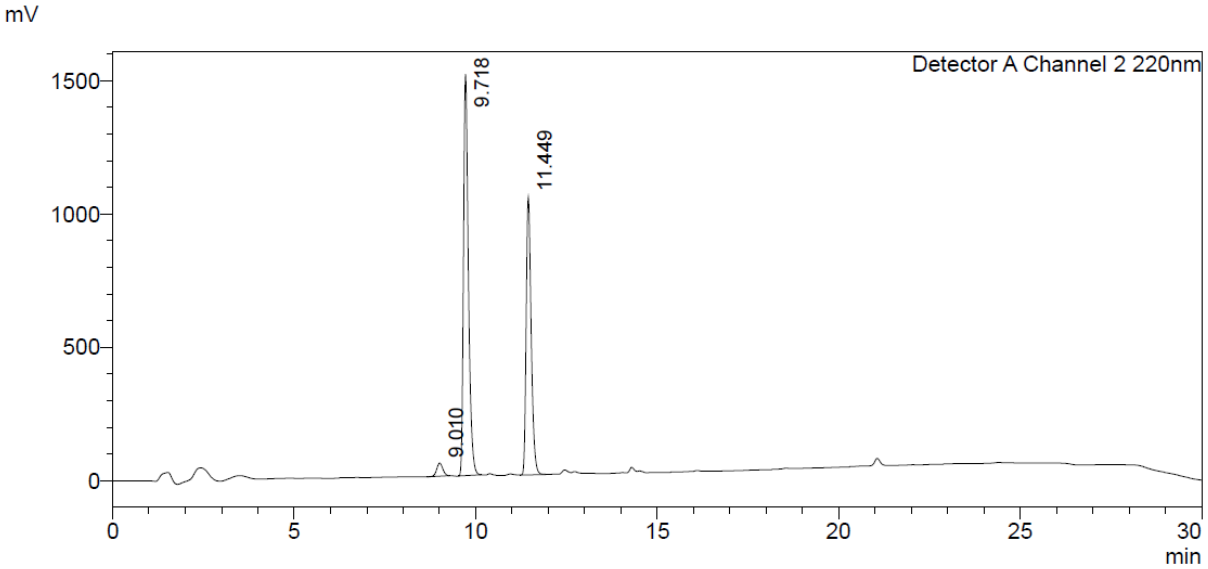


Figure S14: HPLC chromatogram of the reaction mixture outlined in table S3 after a single catalyst cycle. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

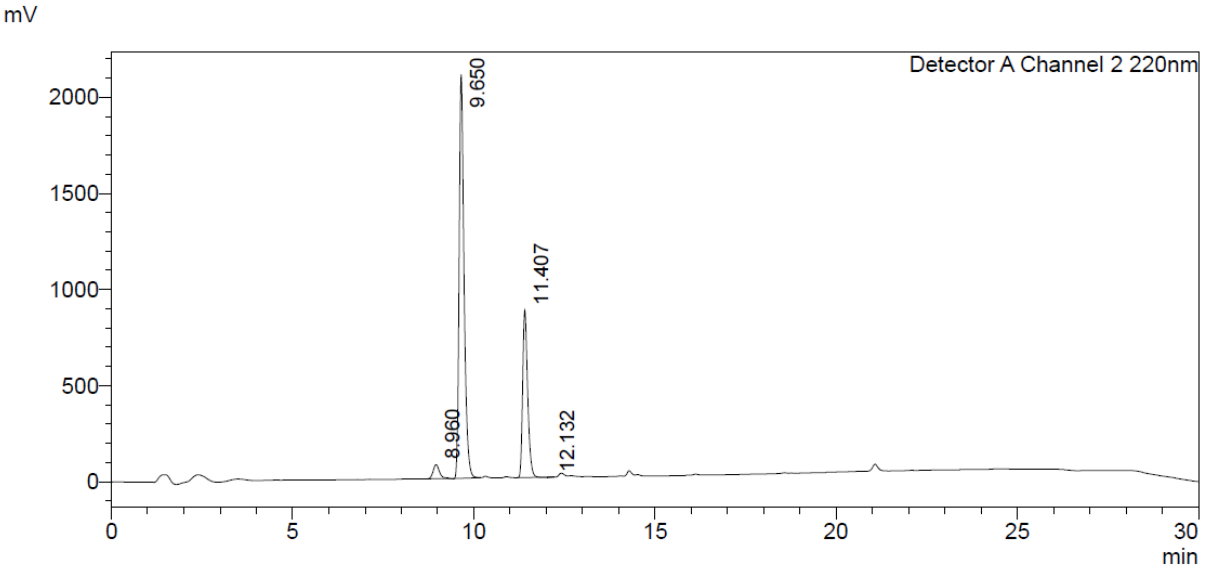


Figure S15: HPLC chromatogram of the reaction mixture outlined in table S3 after two catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

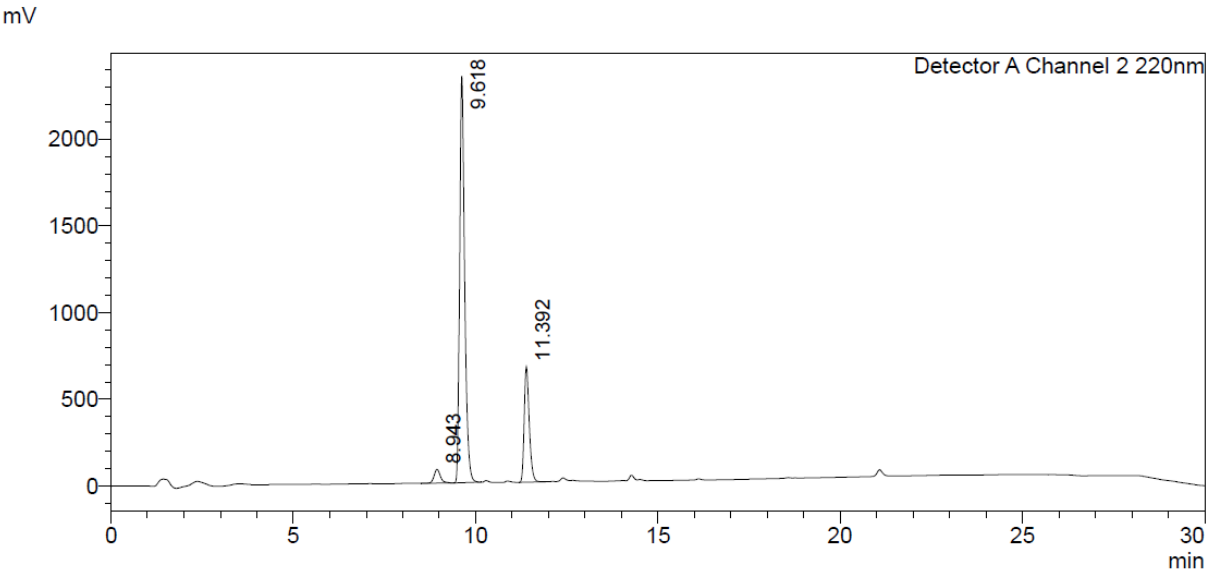


Figure S16: HPLC chromatogram of the reaction mixture outlined in table S3 after three catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

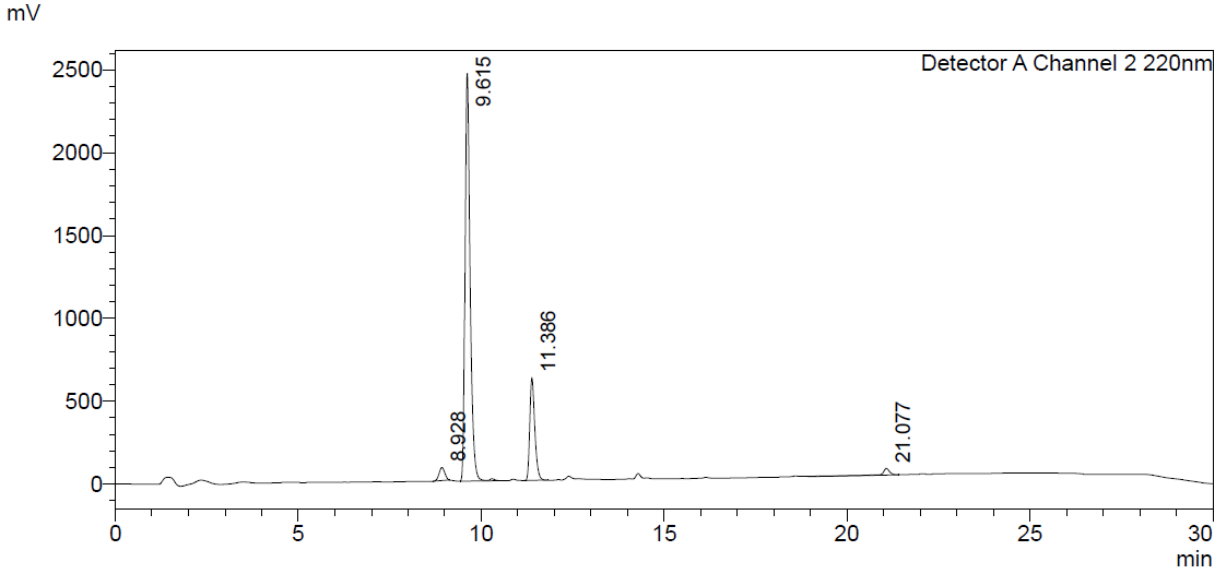
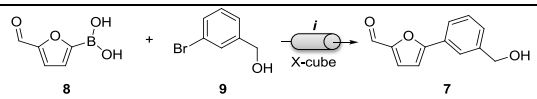
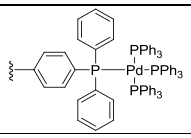


Figure S17: HPLC chromatogram of the reaction mixture outlined in table S3 after four catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S4: Ratio of **7** and **9** peak areas obtained after subsequent cycles FibreCat® Pd-tetrakis. ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, and 80 °C.



Entry	Pd-Ligand	FibreCat®	Number of catalyst cycles Ratio of 7 : 9[a]			
			1	2	3	4
4		Pd-Tetrakis	1:0.4	1:0.3	1:0.3	1:0.2

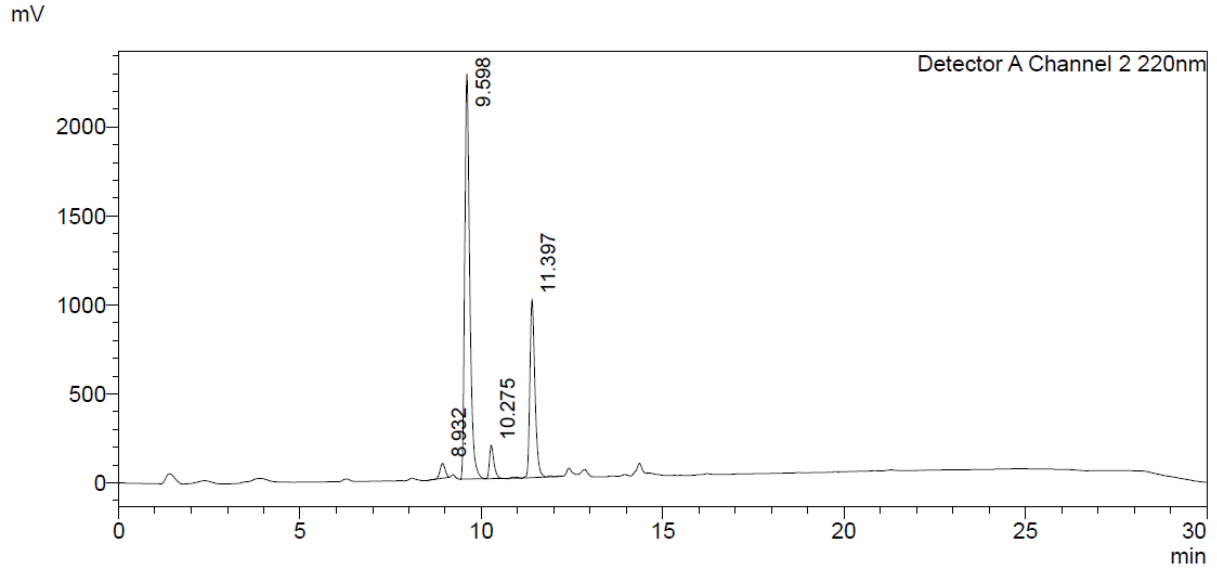


Figure S18: HPLC chromatogram of the reaction mixture outlined in table S4 after a single catalyst cycle. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

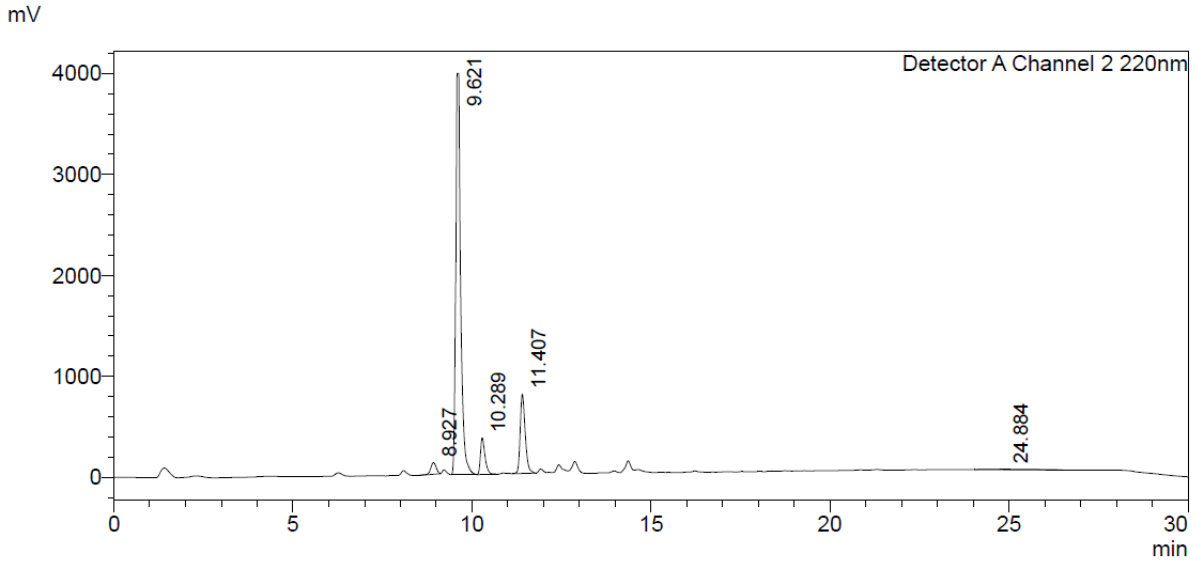


Figure S19: HPLC chromatogram of the reaction mixture outlined in table S4 after two catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

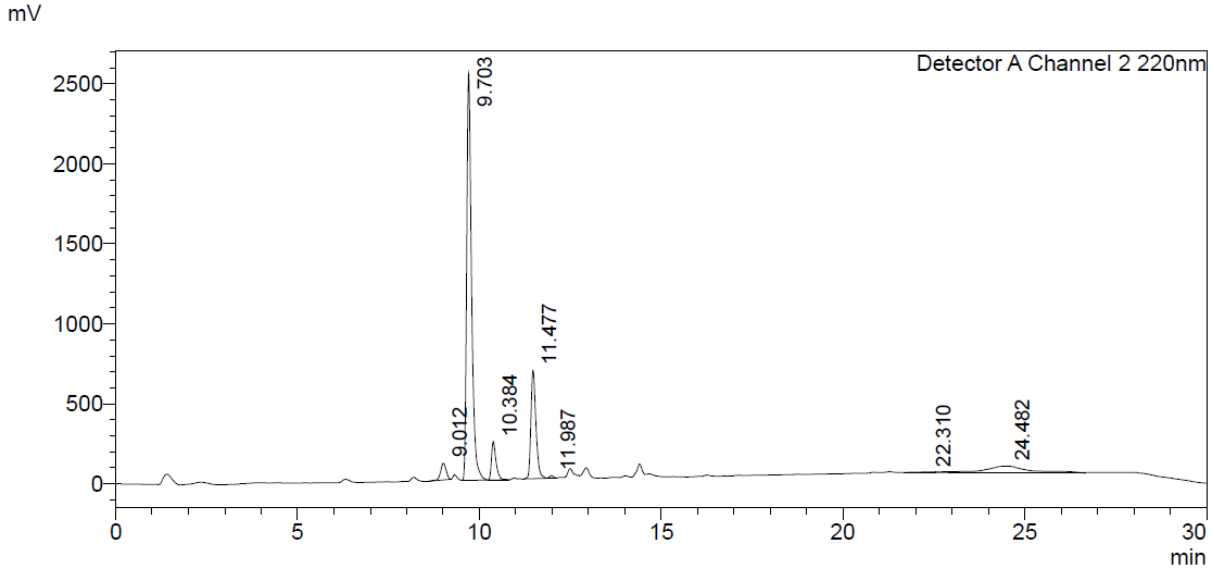


Figure S19: HPLC chromatogram of the reaction mixture outlined in table S4 after three catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

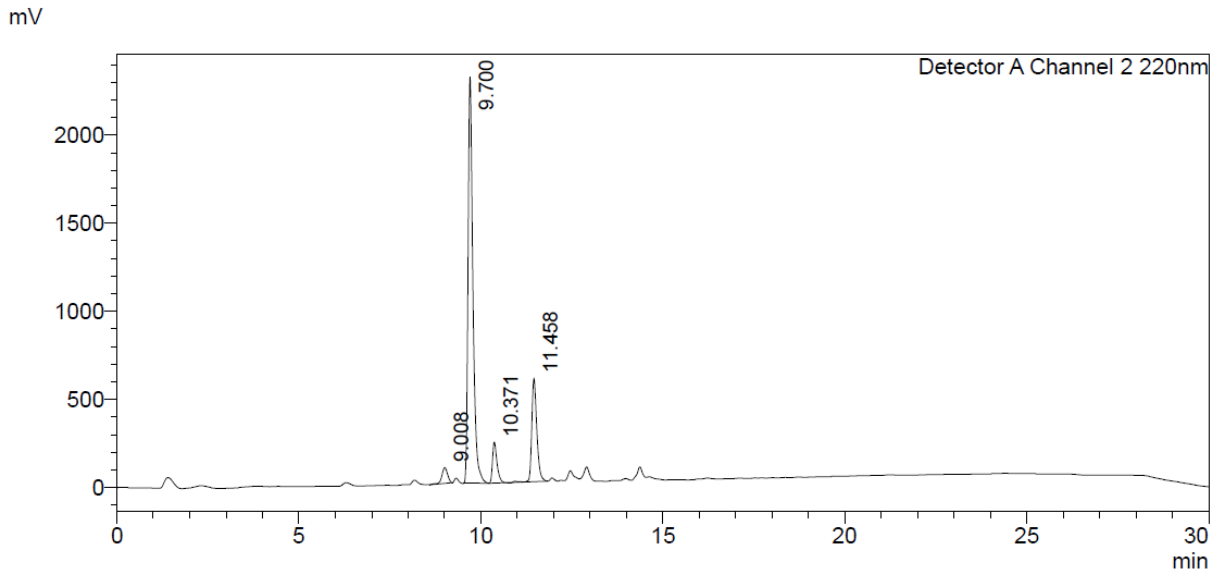


Figure S20: HPLC chromatogram of the reaction mixture outlined in table S4 after four catalyst cycles. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

S4. Investigation of Temperature Variations Using Pd-Tetrakis

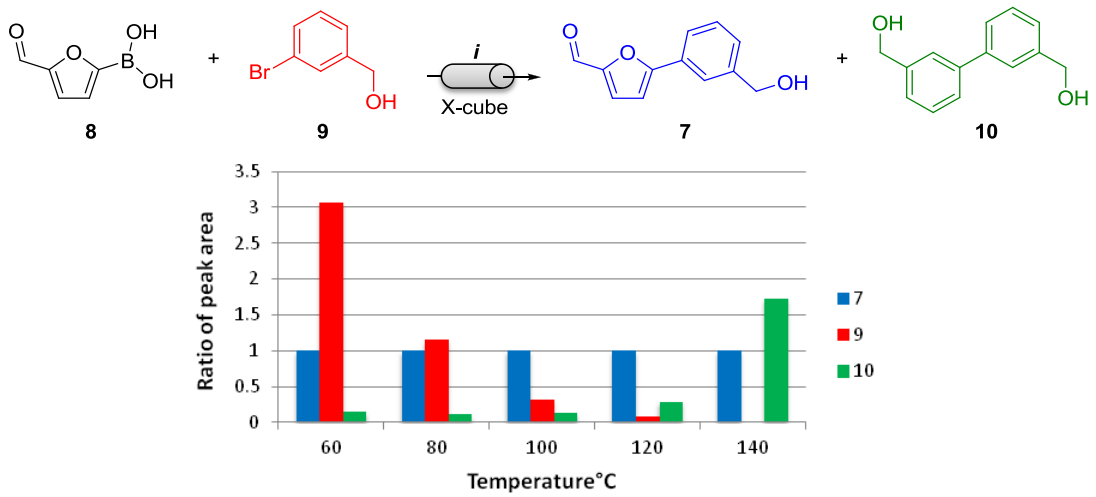


Figure S21: ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, Pd-tetrakis; **b**) Comparison of the relative quantities of aryl bromide (**9**), desired product (7), and aryl bromide homocoupled product retuned at temperatures of 60 to 140 °C with 0 bar pressure (*Note: ratio of peak areas determined at 220 nm*).

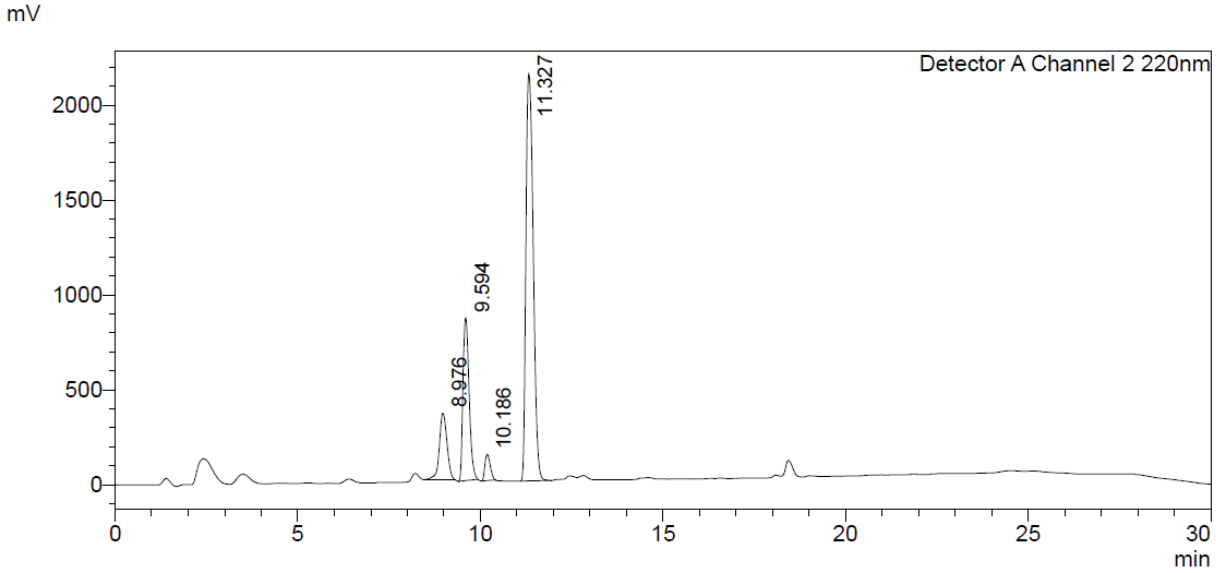


Figure S22: HPLC chromatogram of the reaction mixture outlined in figure S21at 60 °C. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

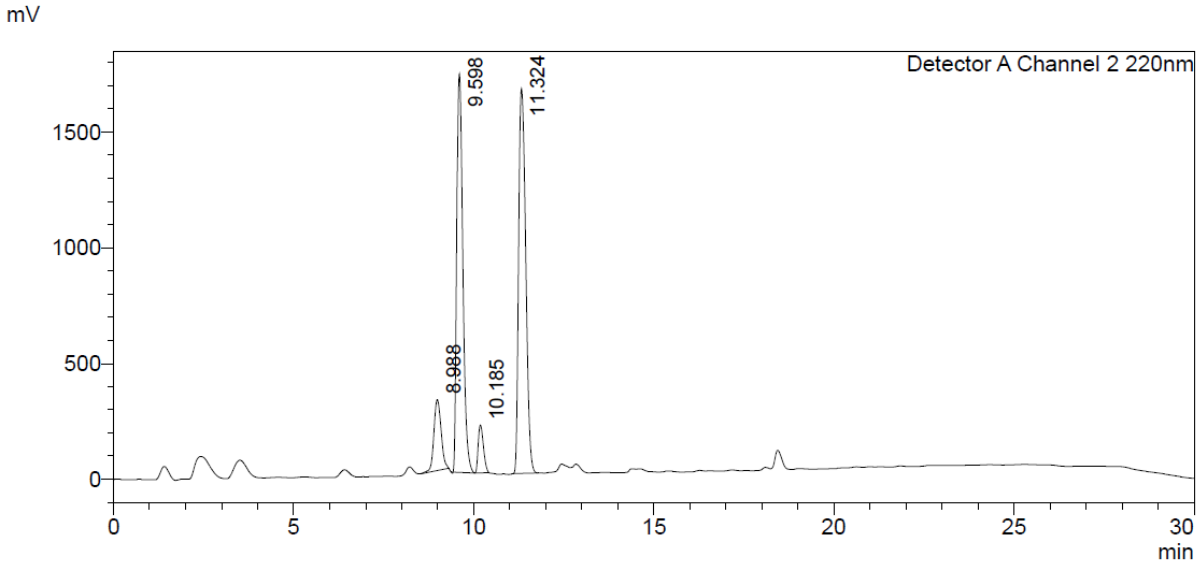


Figure S23: HPLC chromatogram of the reaction mixture outlined in figure S21at 80 °C. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

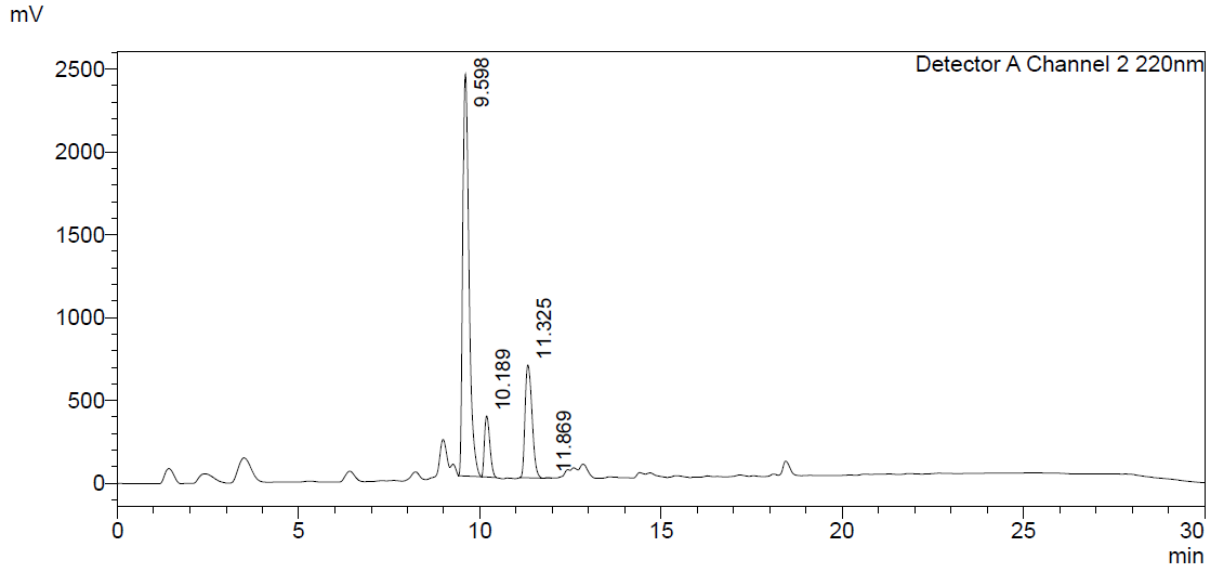


Figure S24: HPLC chromatogram of the reaction mixture outlined in figure S21at 100 °C. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

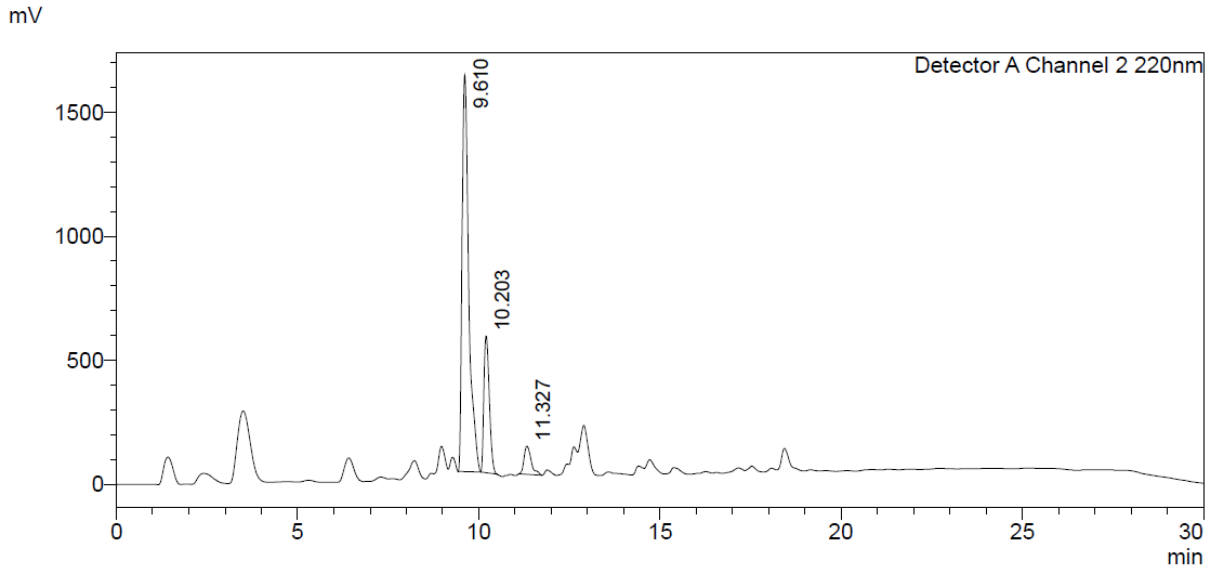


Figure S25: HPLC chromatogram of the reaction mixture outlined in figure S21at 120 °C. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

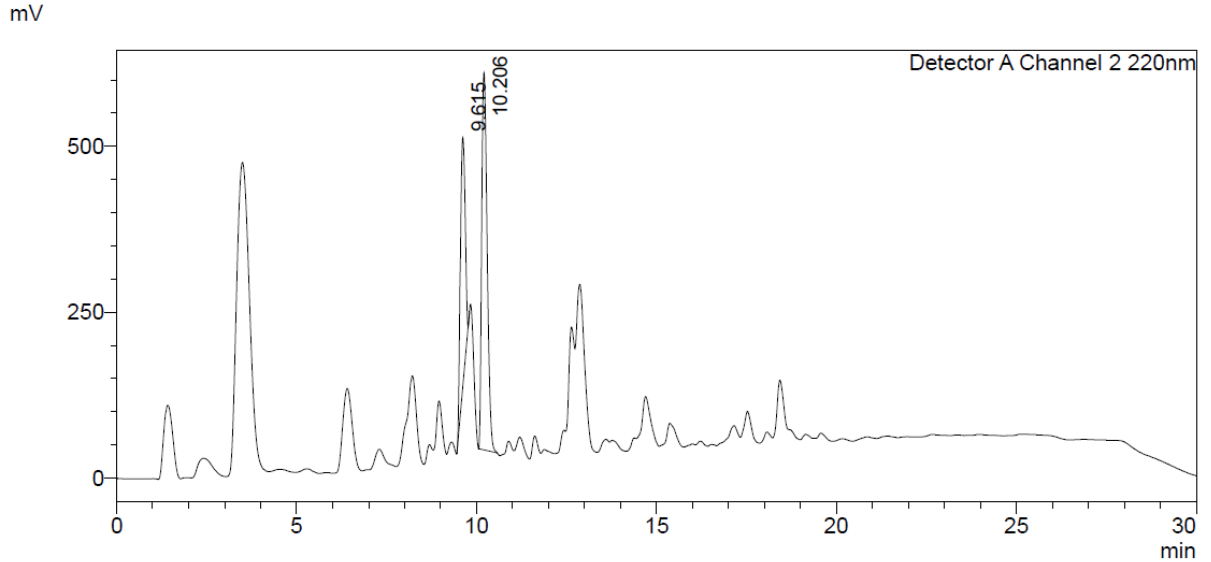


Figure S26: HPLC chromatogram of the reaction mixture outlined in figure S21at 140 °C. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

S5. Investigation of Pressure Variations Using Pd-Tetrakis

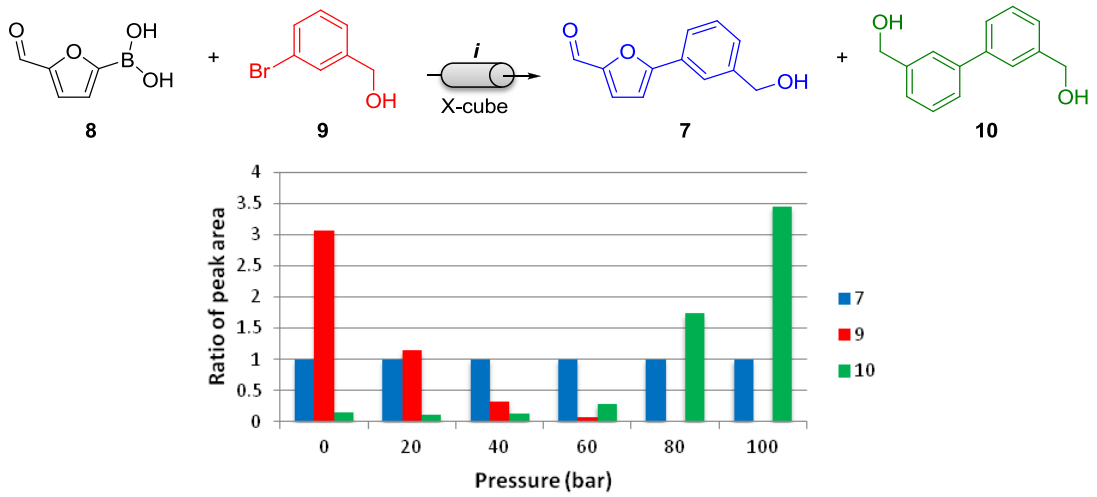


Figure S27: **a**) ***Reagents and conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 3-bromobenzyl alcohol (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), and MeOH (30 mL) at 0.5 mL/min, Pd-tetrakis; **b**) Comparison of the relative quantities of aryl bromide (**9**), desired product (**7**), and aryl bromide homocoupled product retuned at pressures of 0 to 100 bar at 80 °C (*Note: ratio of peak areas determined at 220 nm*).

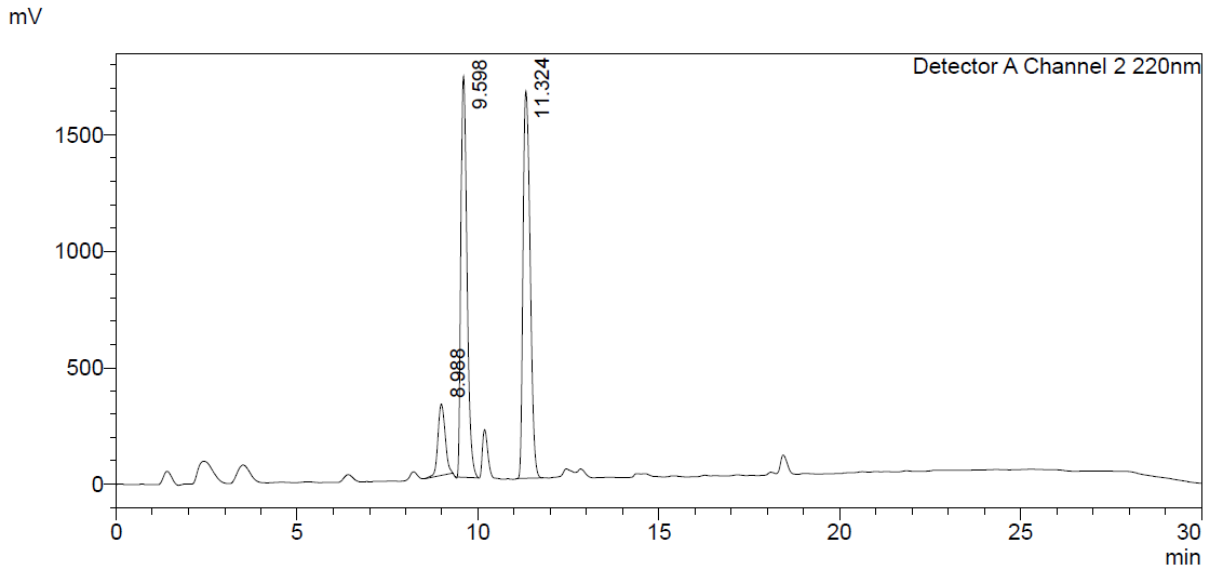


Figure S28: HPLC chromatogram of the reaction mixture outlined in figure S27 at 80 °C and 20 bar pressure. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

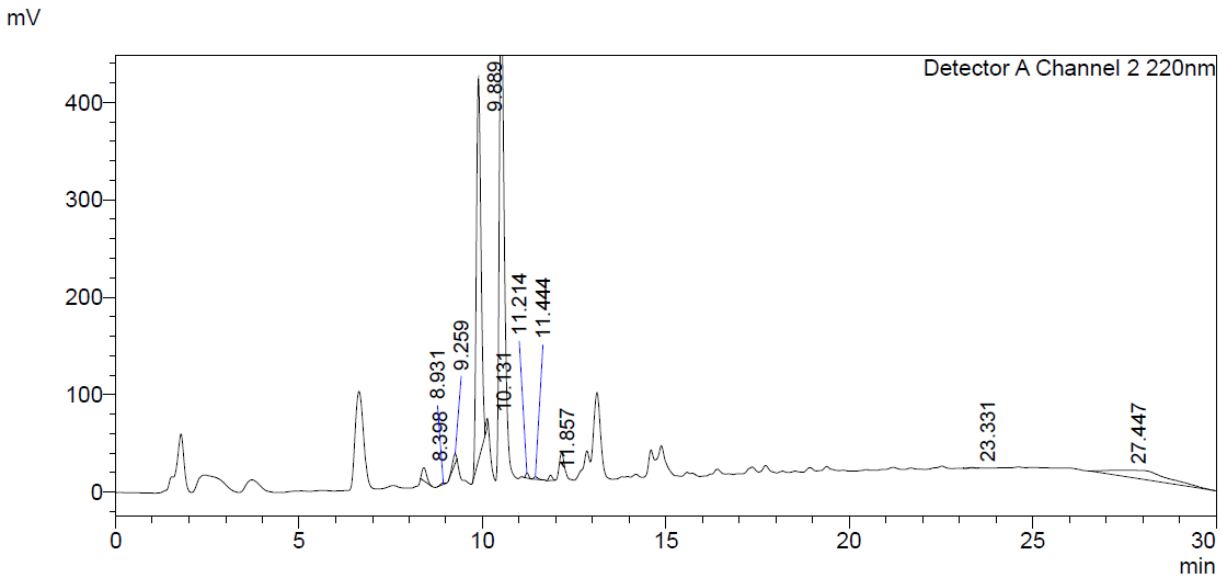


Figure S29: HPLC chromatogram of the reaction mixture outlined in figure S27 at 80 °C and 40 bar pressure. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

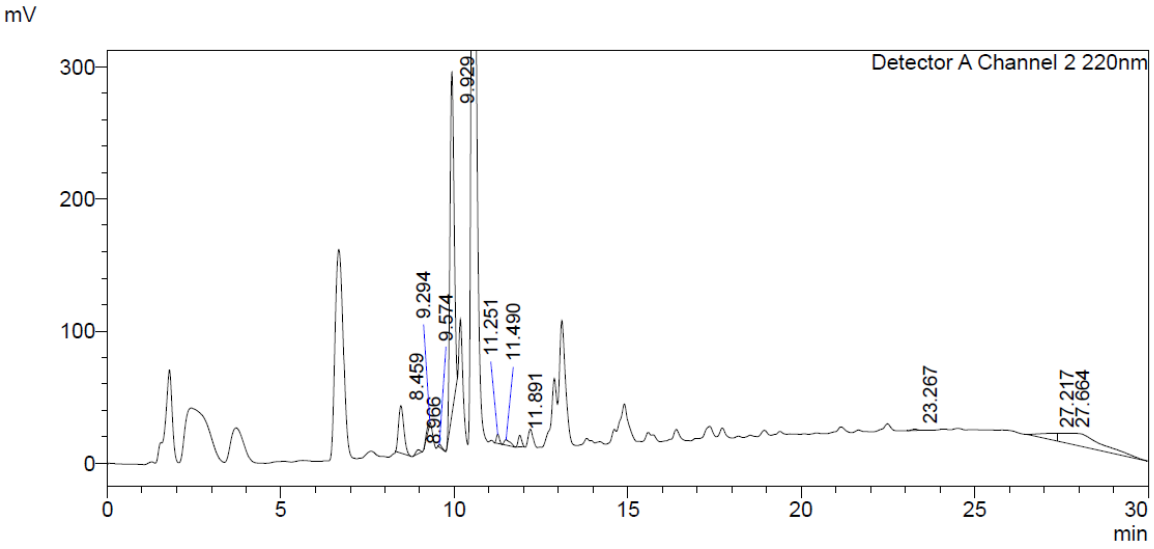


Figure S30: HPLC chromatogram of the reaction mixture outlined in figure S27 at 80 °C and 60 bar pressure. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

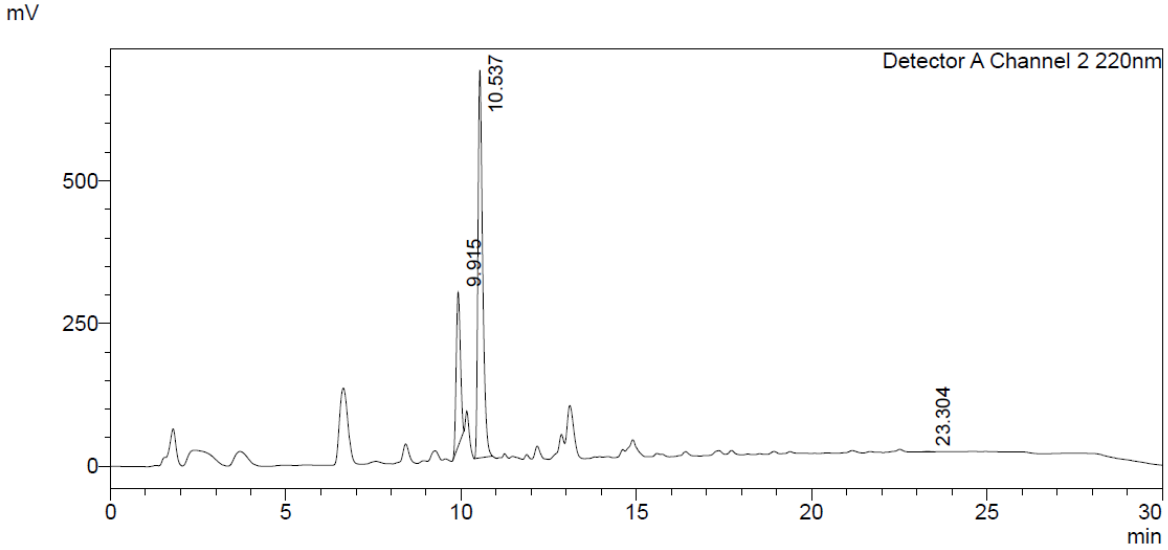


Figure S31: HPLC chromatogram of the reaction mixture outlined in figure S27 at 80 °C and 80 bar pressure. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

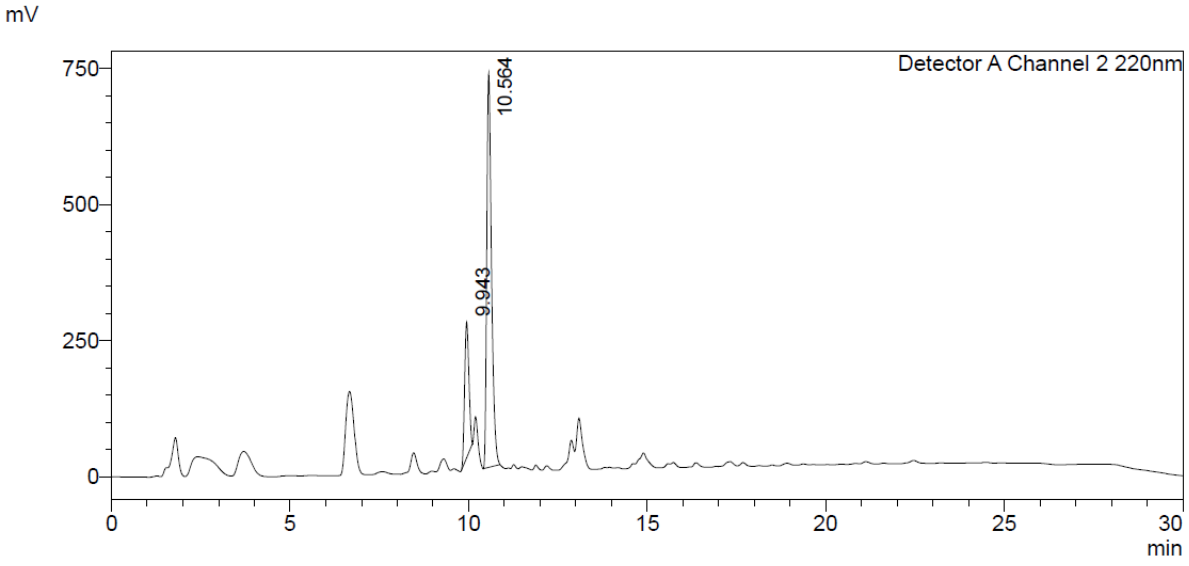


Figure S32: HPLC chromatogram of the reaction mixture outlined in figure S27 at 80 °C and 100 bar pressure. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

S6. General Procedure 1 using $(Bu)_4N^+F^-$ and FC1032™

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

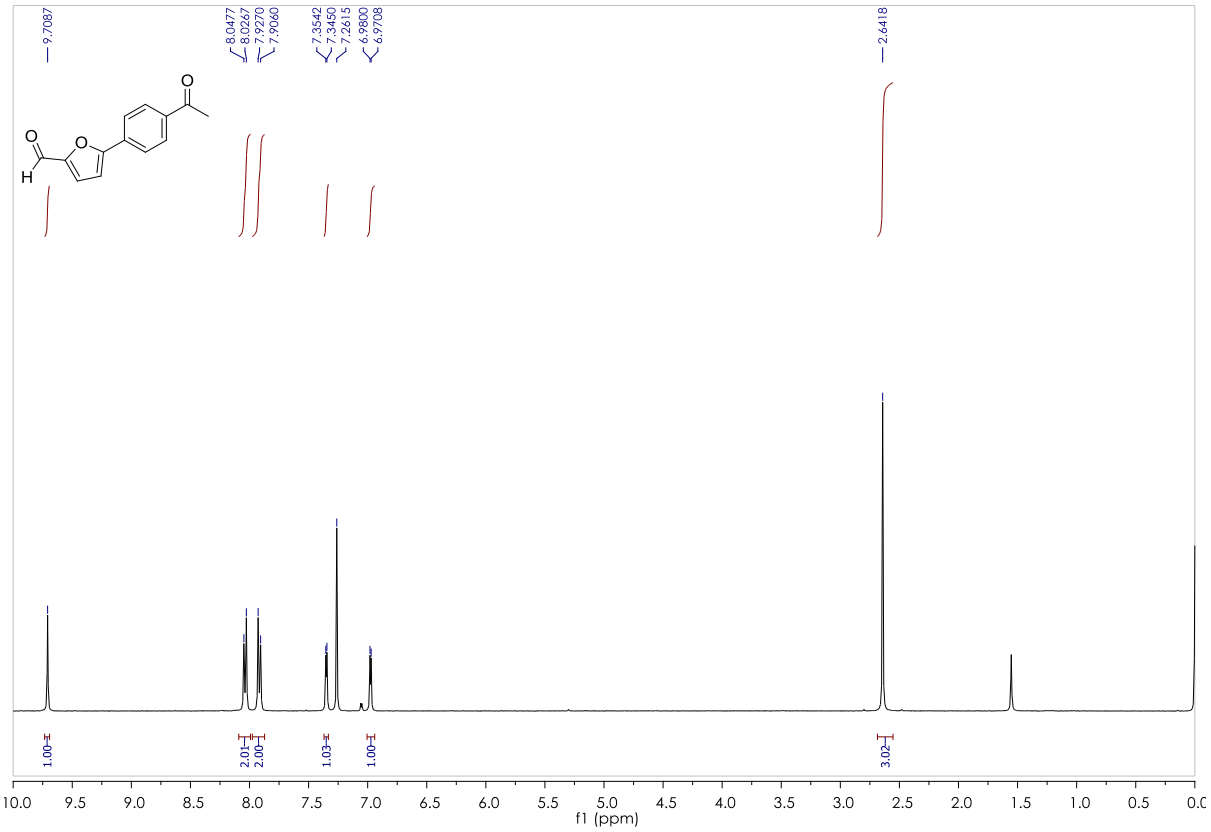


Fig S33: ^1H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(4-acetylphenyl)-2-furancarboxaldehyde (**12a**)

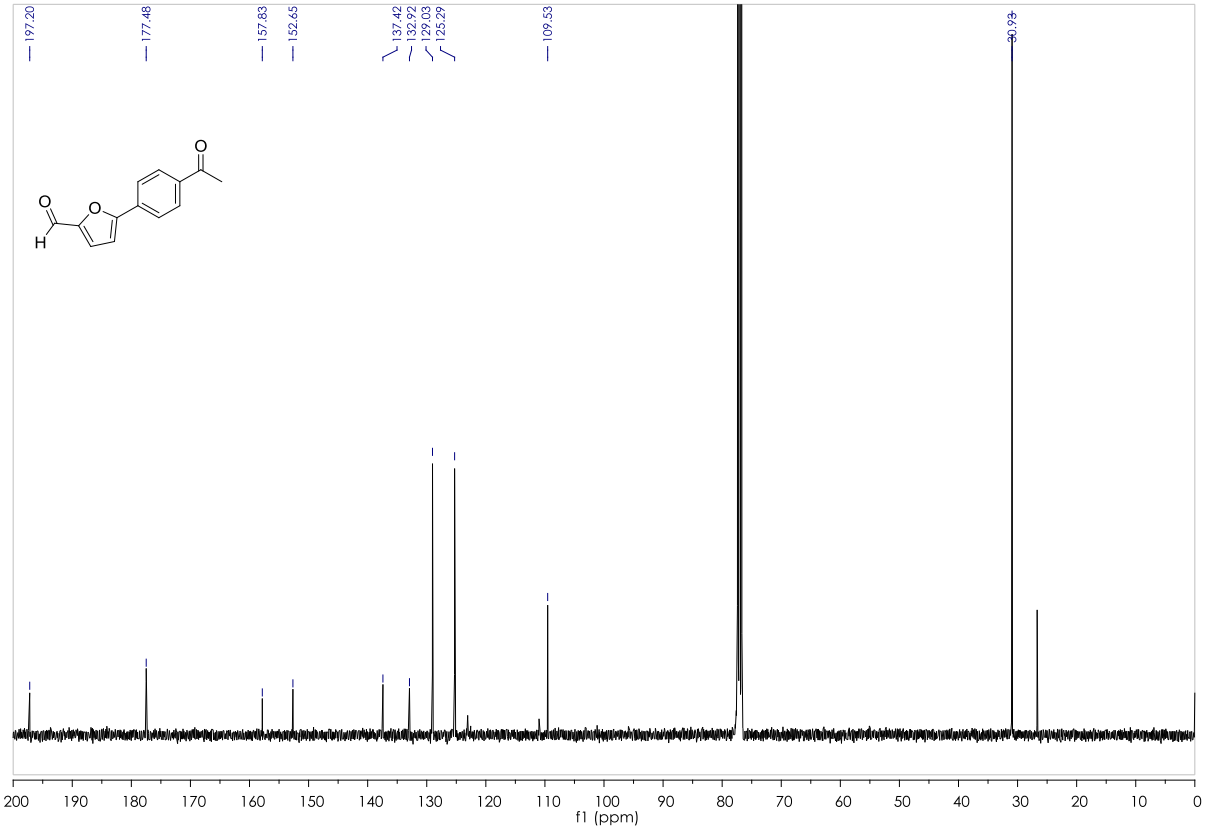


Fig S34: ^{13}C NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(4-acetylphenyl)-2-furancarboxaldehyde (**12a**).

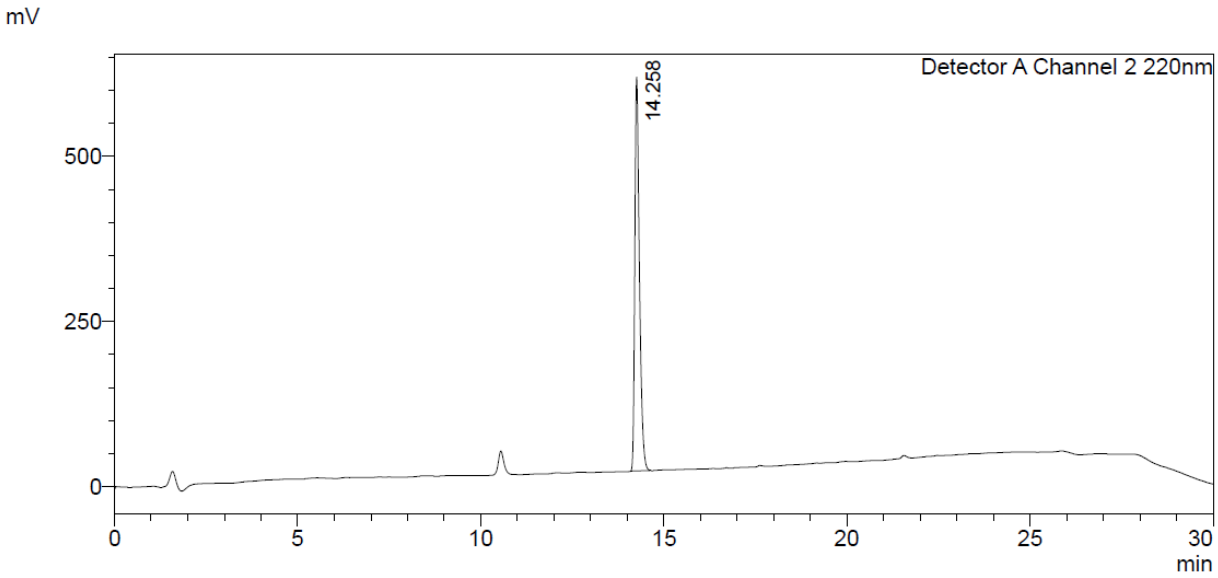


Figure S35: HPLC chromatogram of compound **12a**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

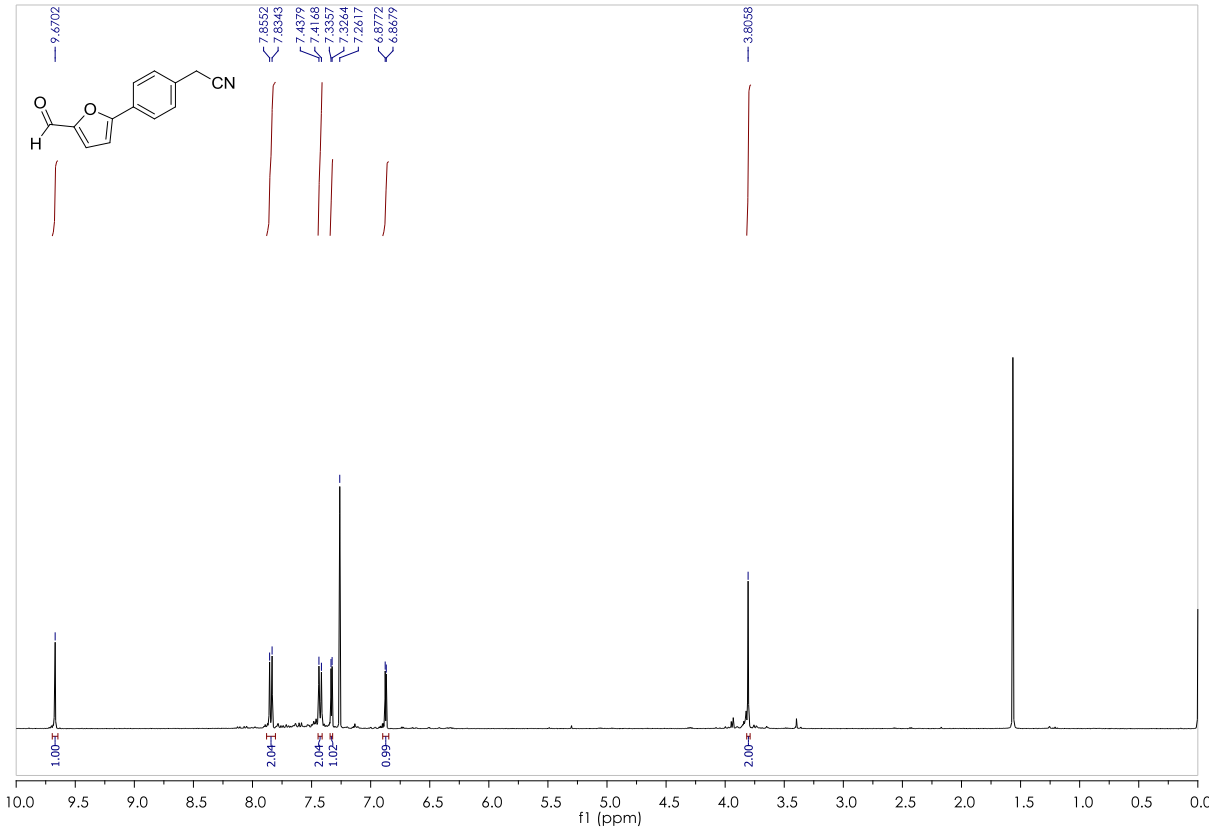


Fig S36: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 2-(4-(5-formylfuran-2-yl)phenyl)acetonitrile (**12b**)

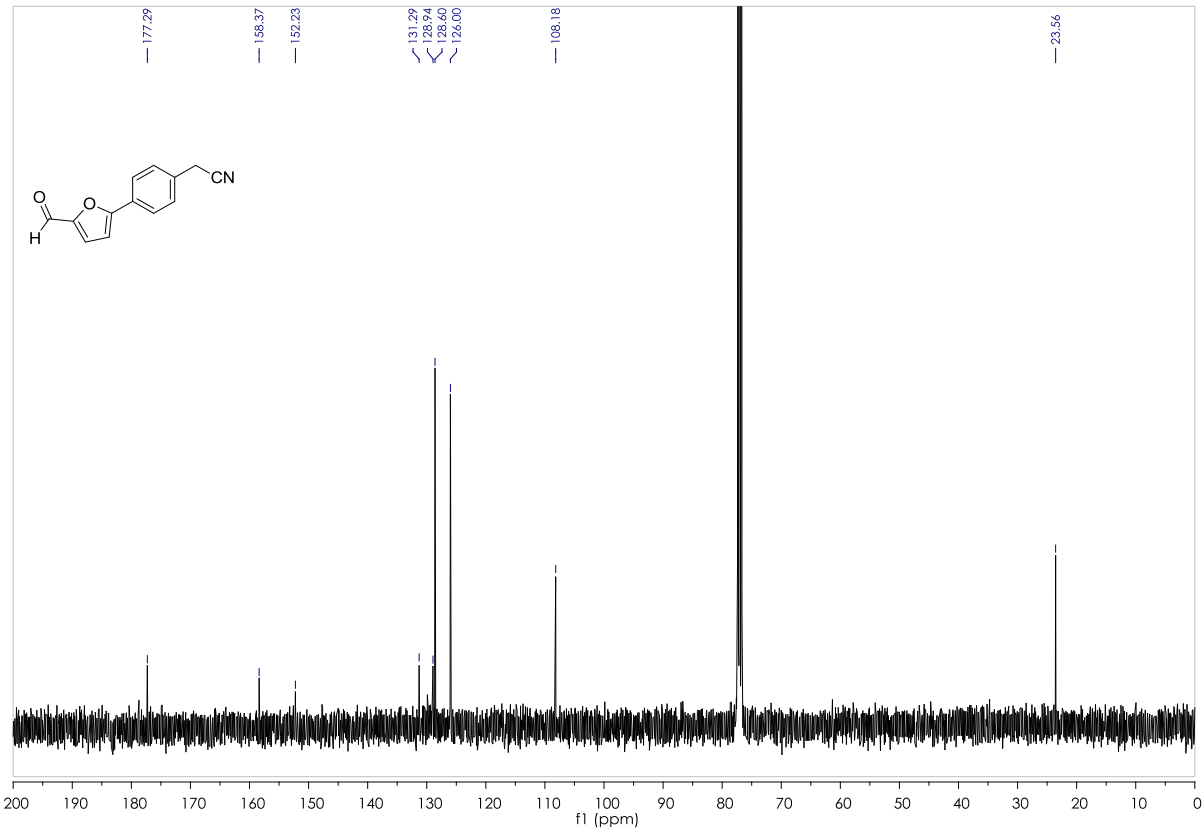


Fig S37: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 2-(4-(5-formylfuran-2-yl)phenyl)acetonitrile (**12b**)

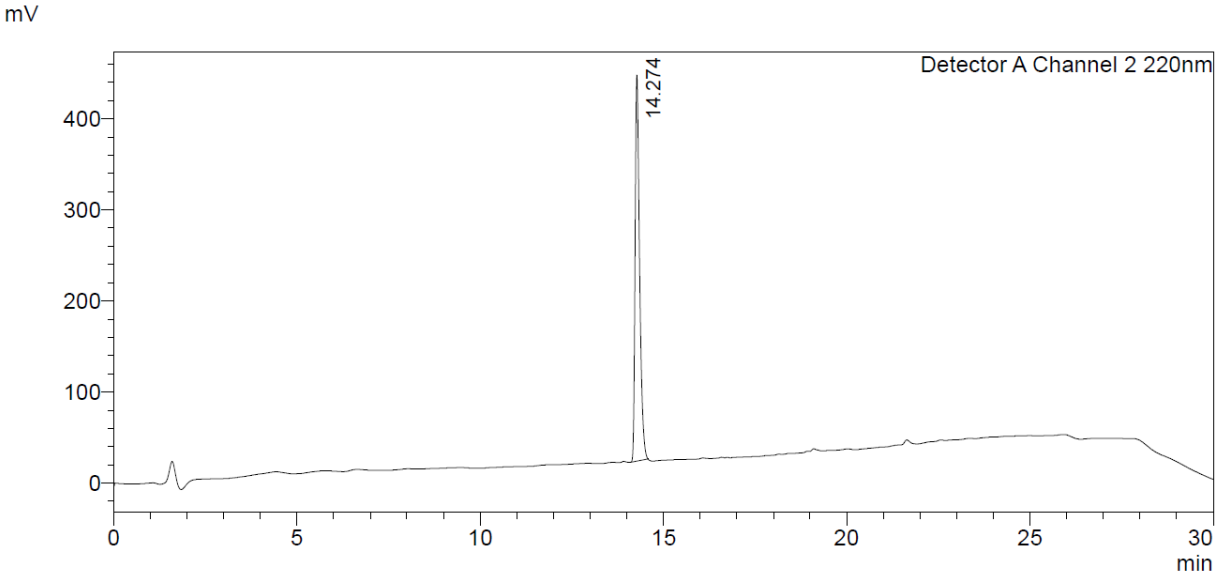


Figure S38: HPLC chromatogram of compound **12b**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

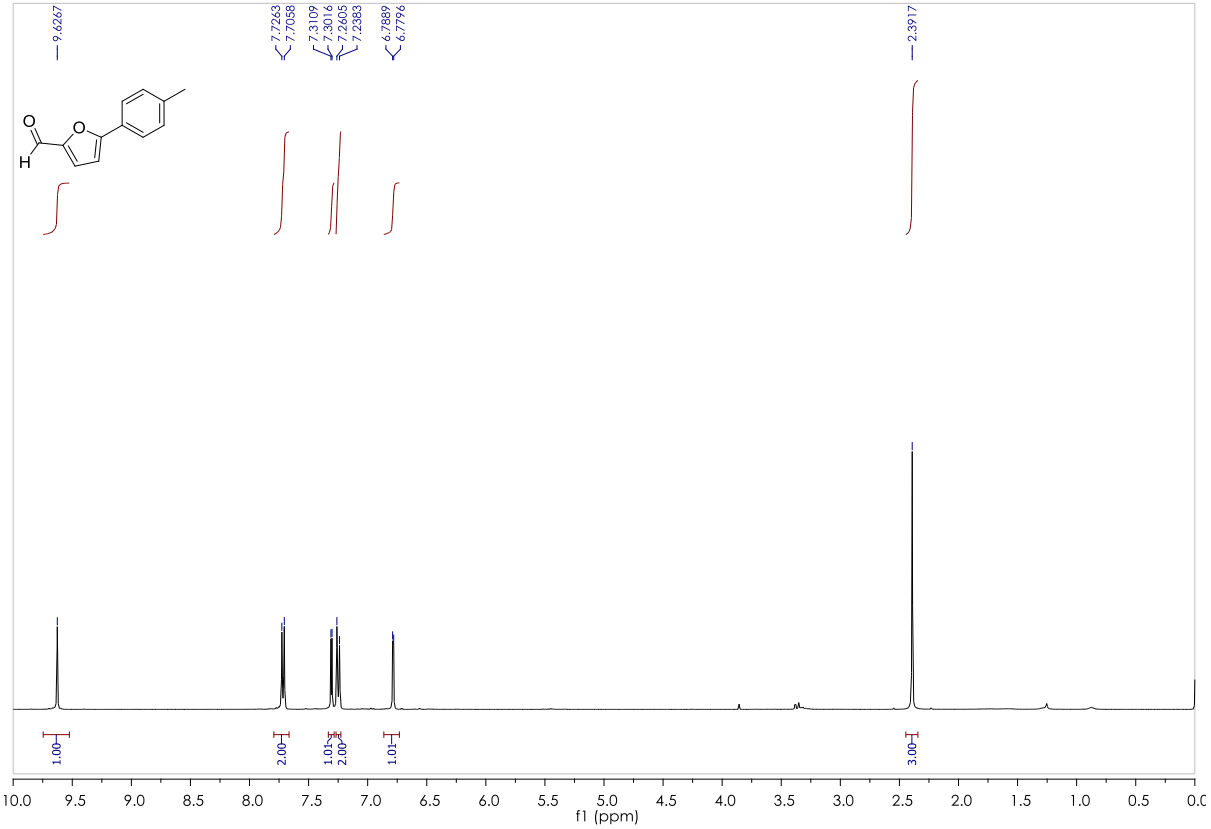


Fig S39: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(4-Methylphenyl)-2-furancarboxaldehyde (**12c**)

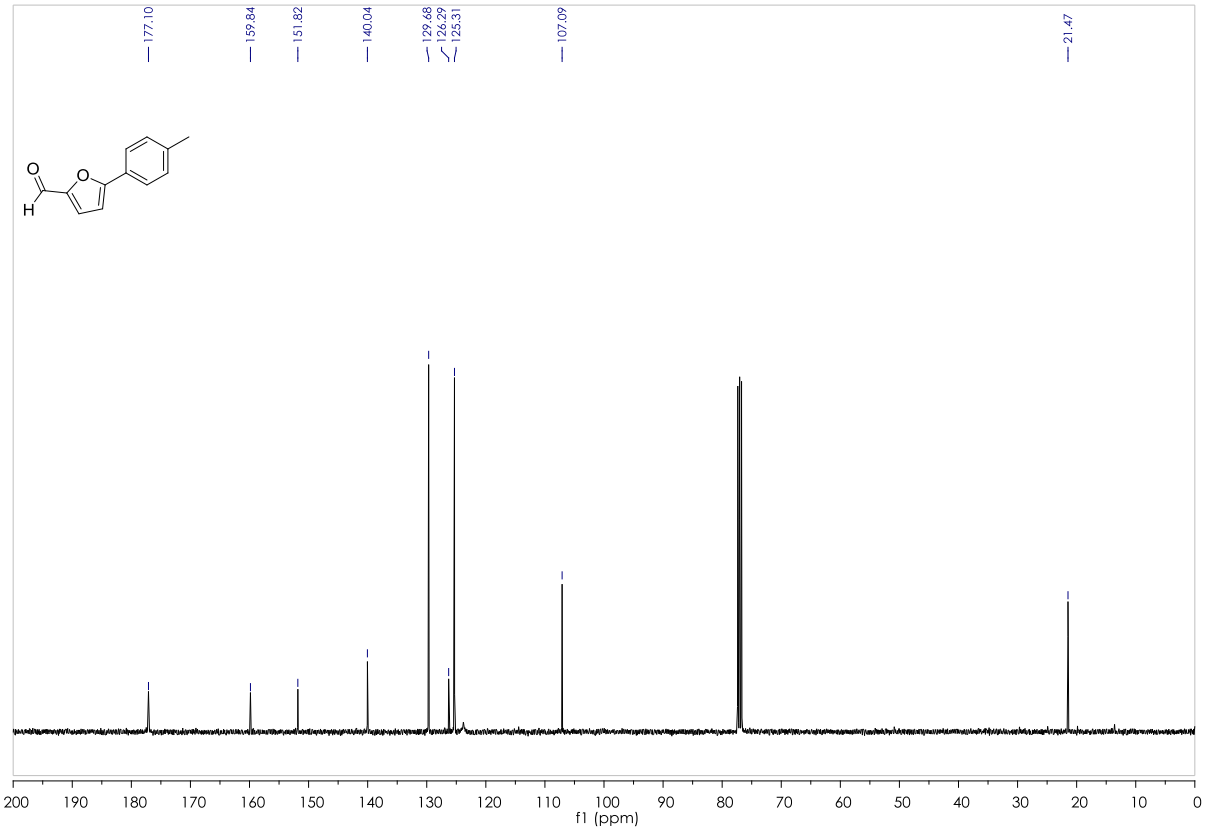


Fig S40: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 5-(4-Methylphenyl)-2-furancarboxaldehyde (**12c**)

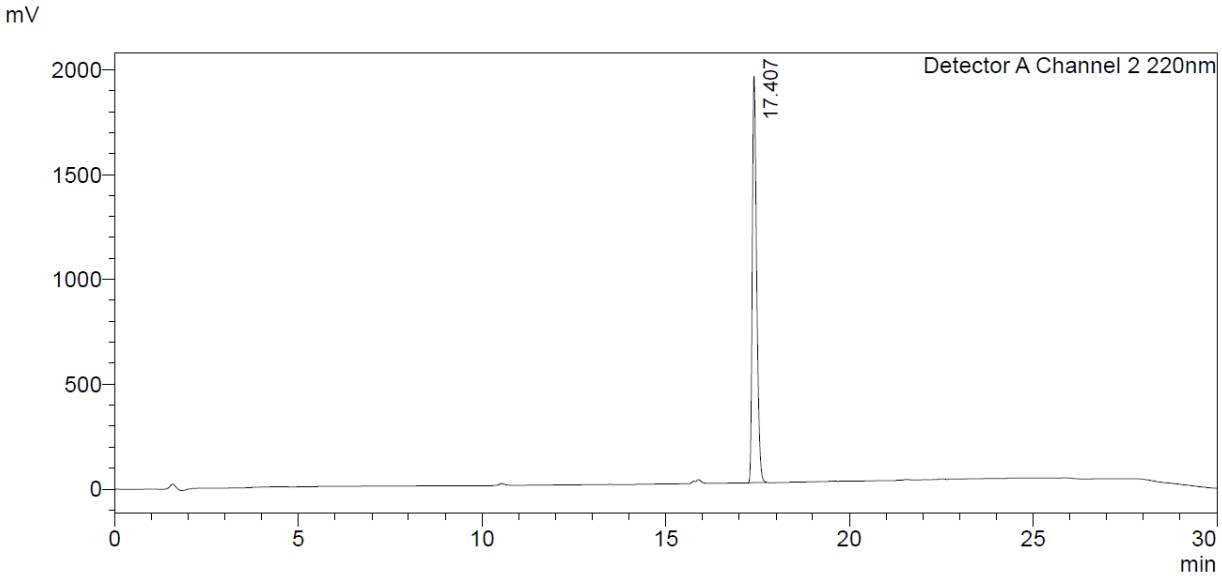


Figure S41: HPLC chromatogram of compound **12c**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

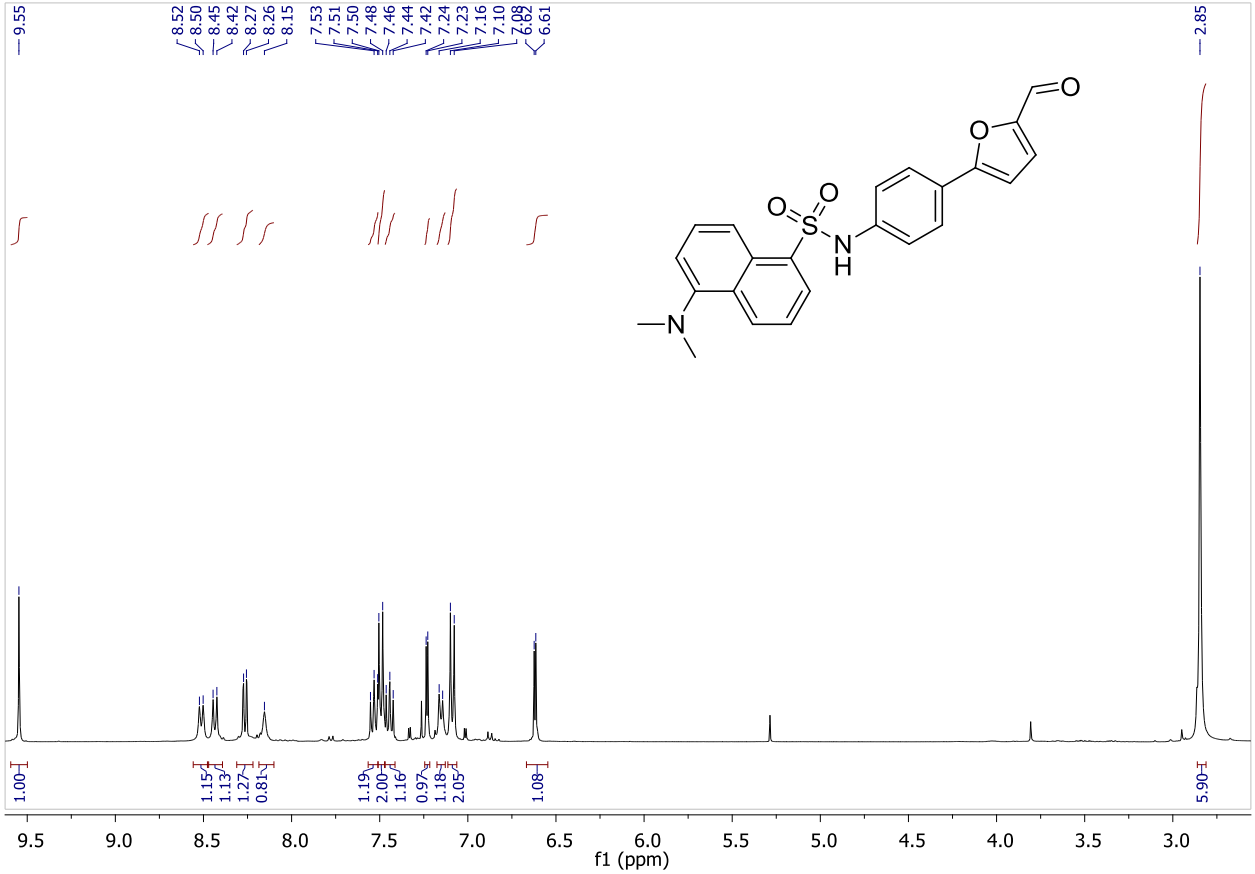


Figure S42: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(dimethylamino)-N-(4-(5-formylfuran-2-yl)phenyl)naphthalene-1-sulfonamide (**12d**).

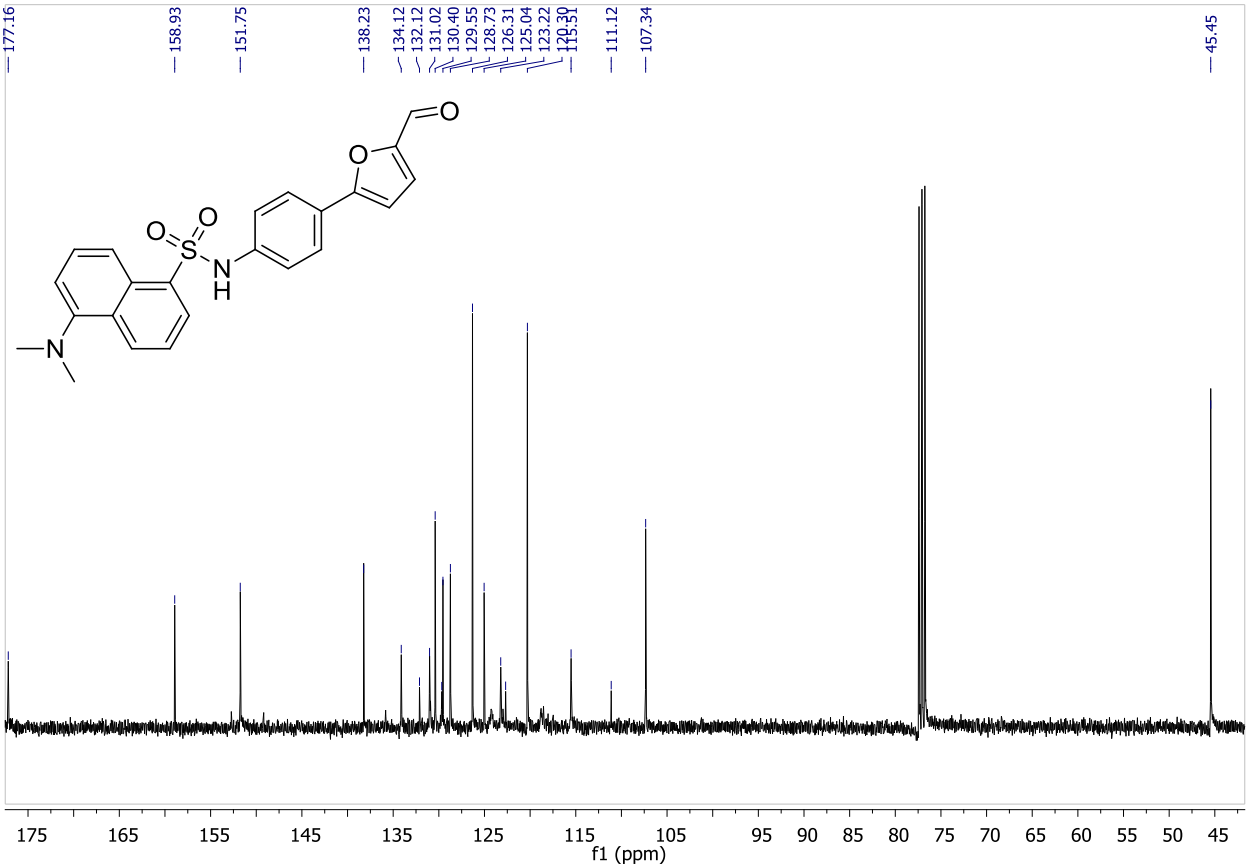


Figure S43: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 5-(dimethylamino)-N-(4-(5-formylfuran-2-yl)phenyl)naphthalene-1-sulfonamide (**12d**).

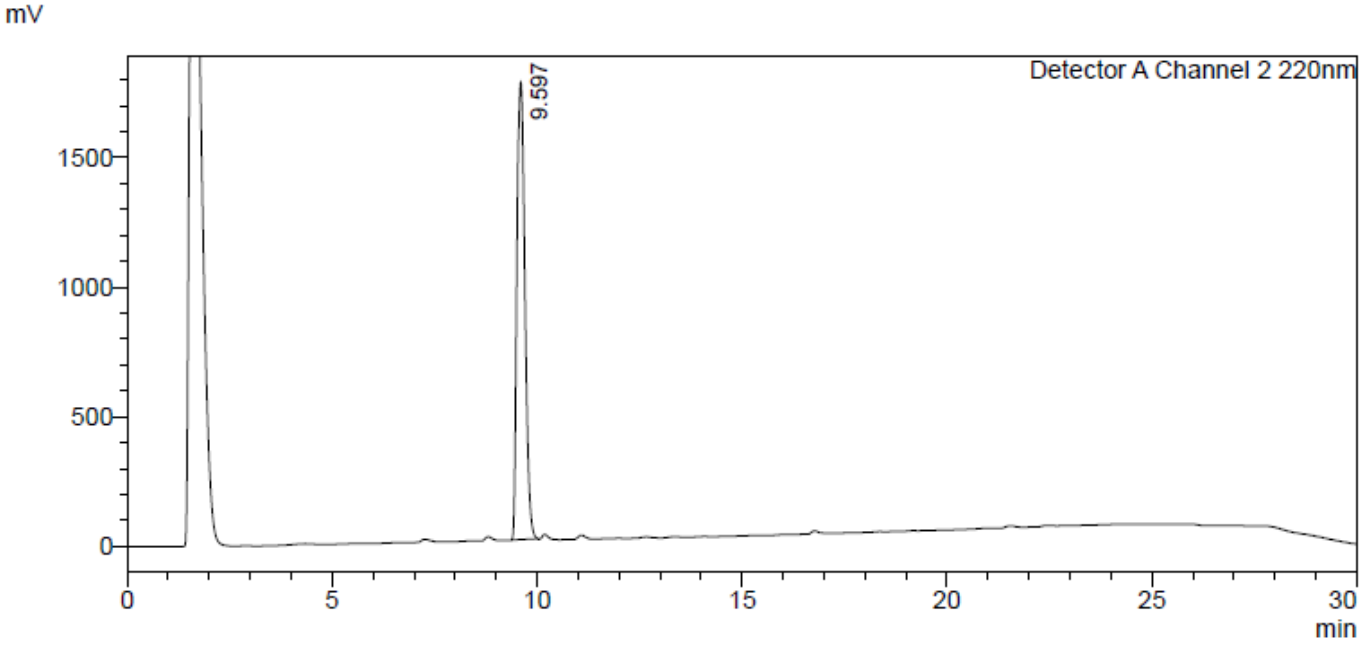


Figure S44: HPLC chromatogram of compound **12d**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

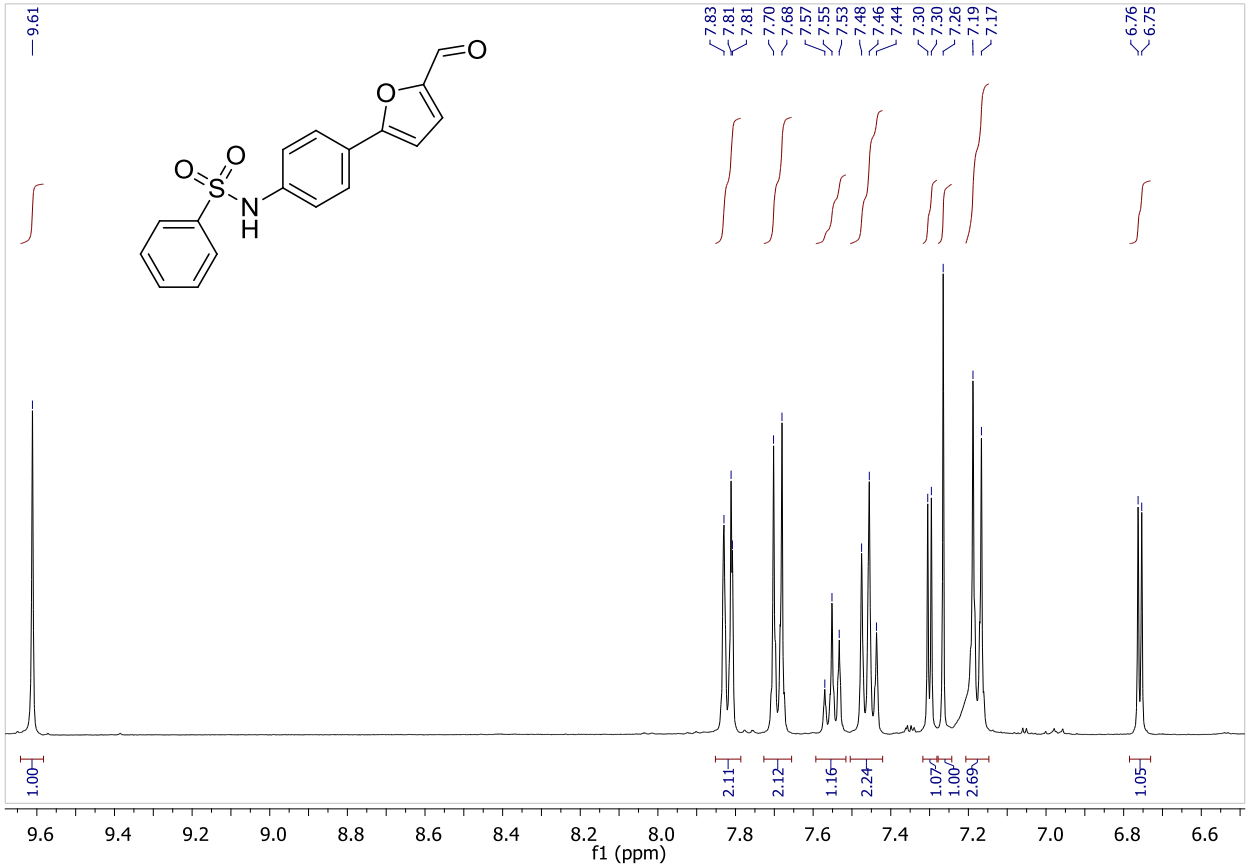


Figure S45: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *N*-(4-(5-formylfuran-2-yl)phenyl)benzenesulfonamide (**12e**).

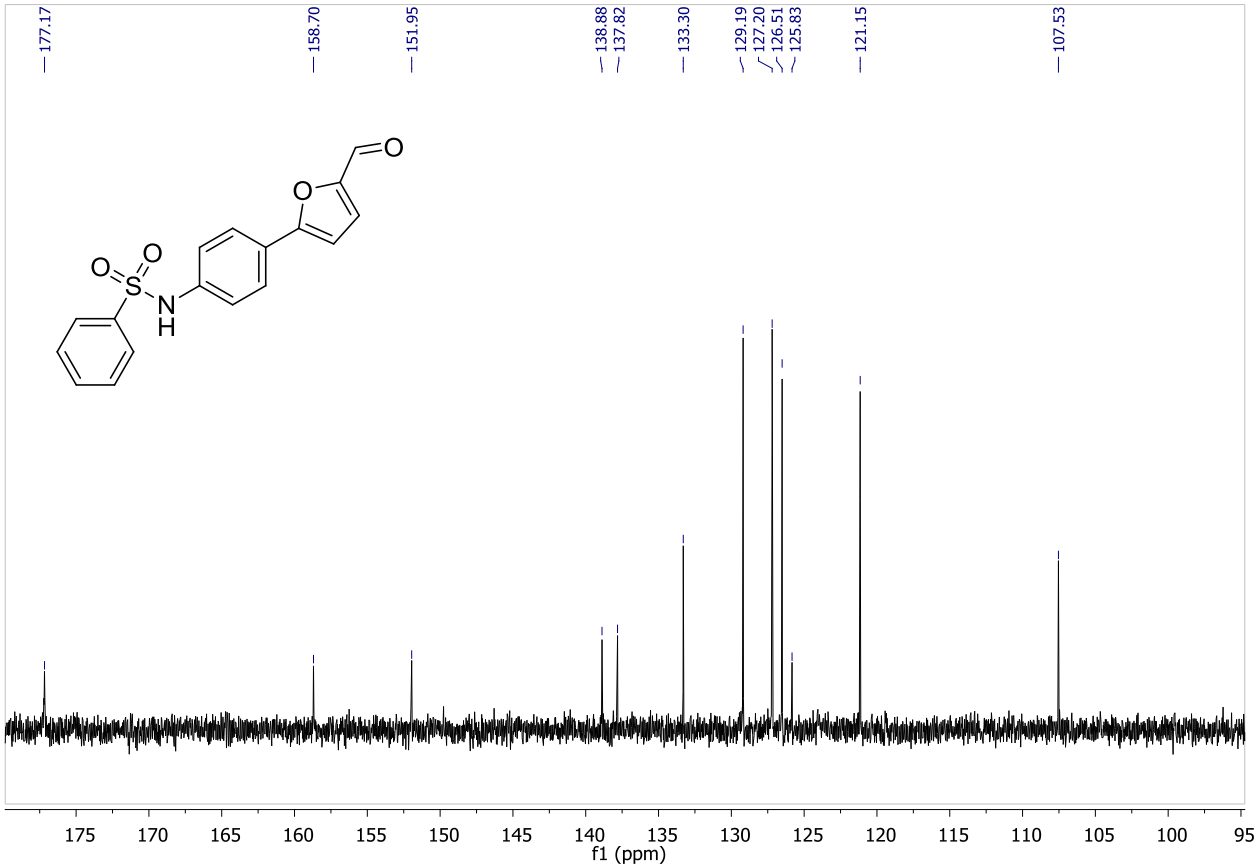


Figure S46: ^{1}C NMR Spectrum ($CDCl_3$, 101 MHz) of *N*-(4-(5-formylfuran-2-yl)phenyl)benzenesulfonamide (**12e**).

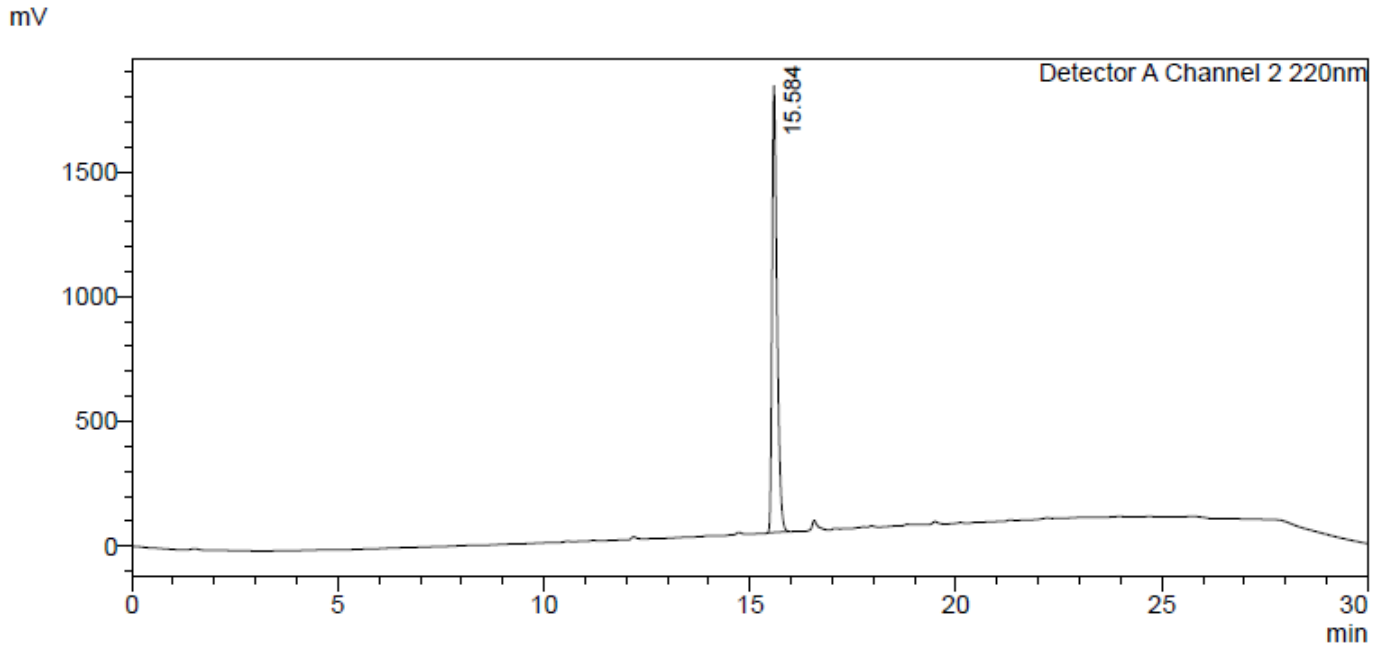


Figure S47: HPLC chromatogram of compound **12e**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

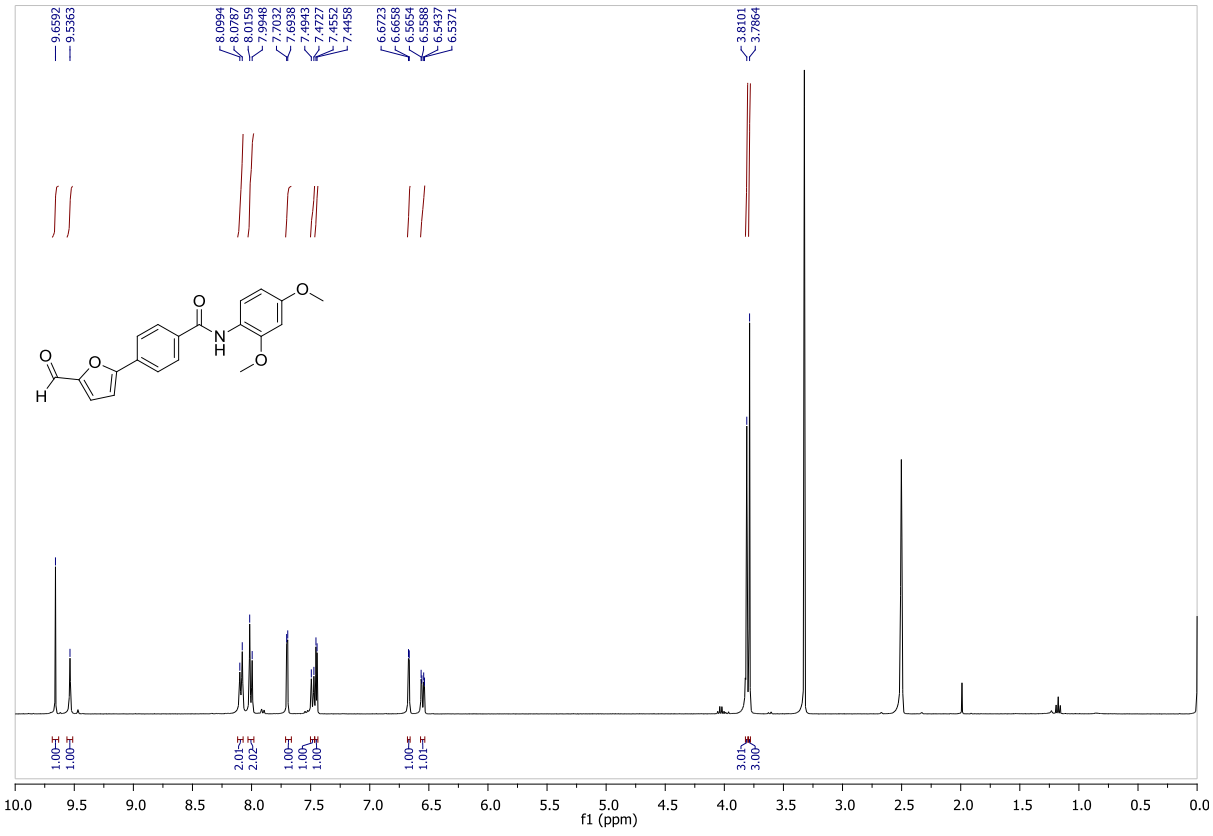


Figure S48: ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of *N*-(2,4-dimethoxyphenyl)-4-(5-formylfuran-2-yl)benzamide (**12f**).

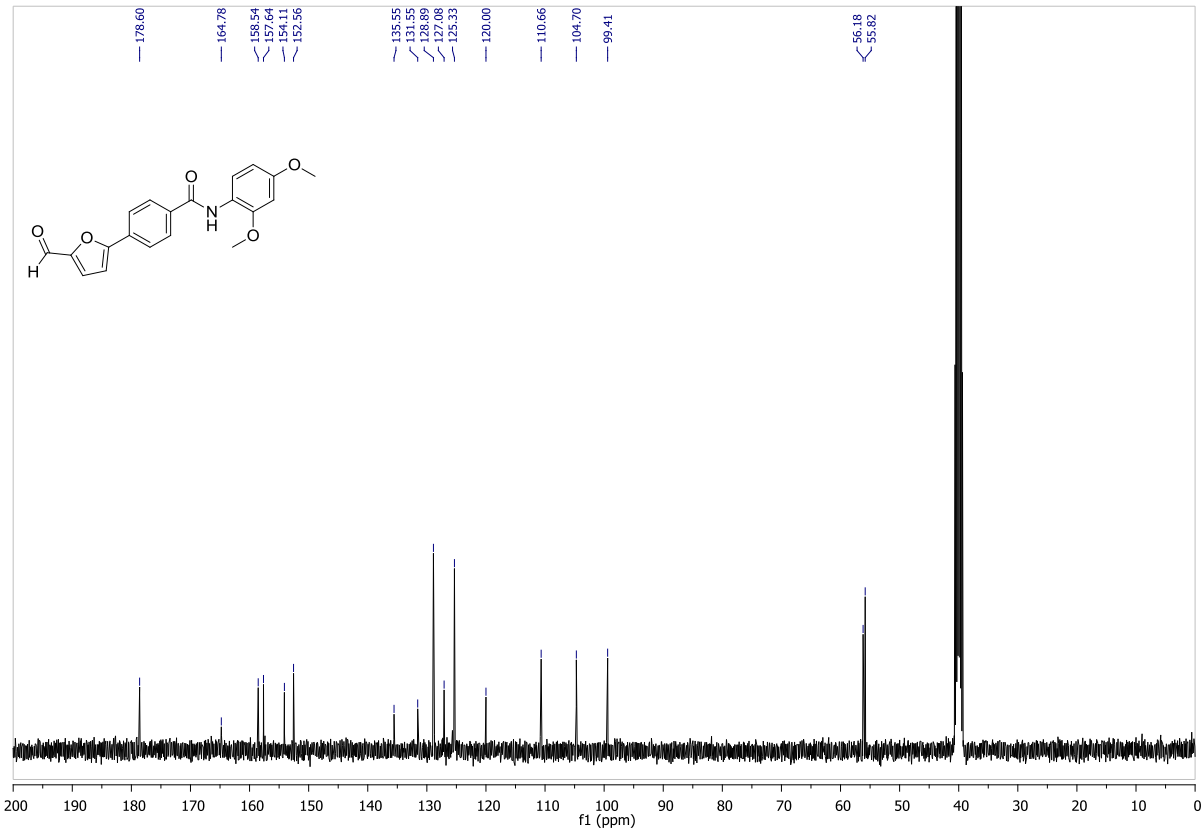


Figure S49: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5-(4-benzoylphenyl)-2-furancarboxaldehyde (**12f**)

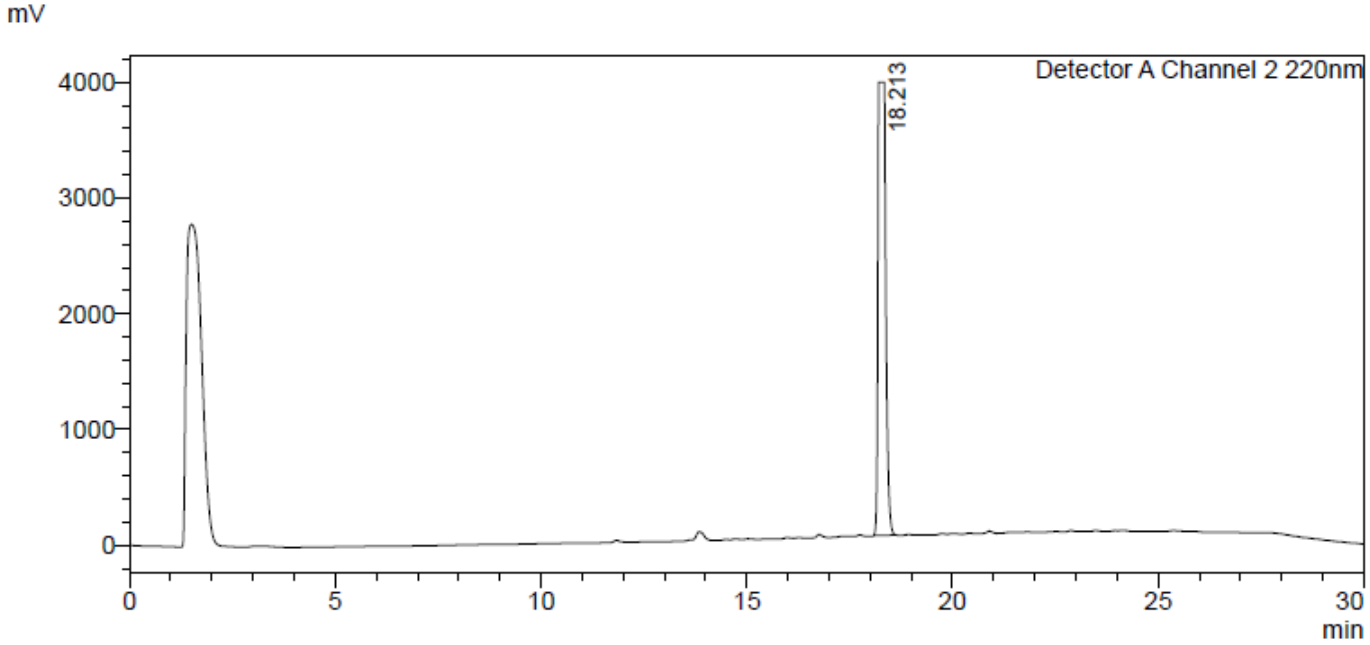


Figure S50: HPLC chromatogram of compound **12f**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

S7. Tetrabutylammonium Salt Counterion Variations with FC1032™

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

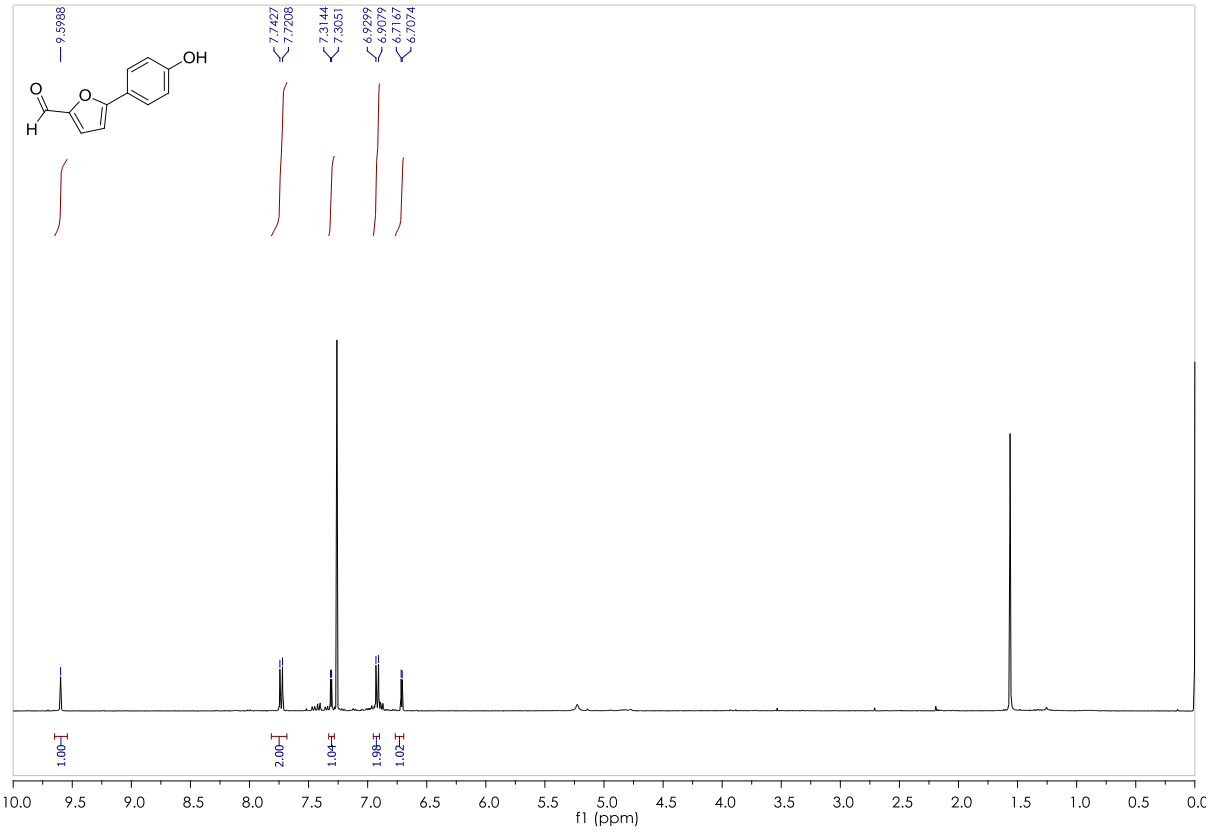


Figure S51: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(4-hydroxyphenyl)-2-furancarboxaldehyde (**14**).

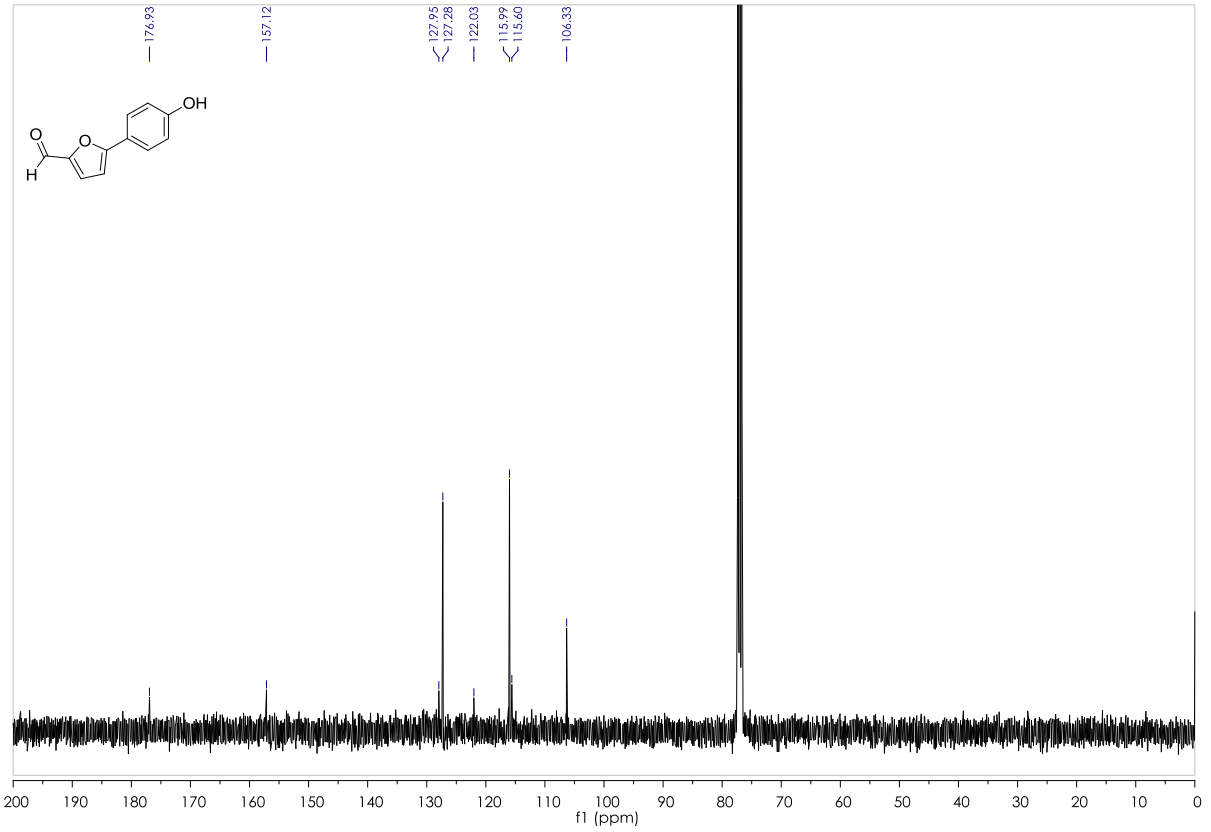
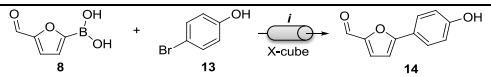


Figure S52: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 5-(4-hydroxyphenyl)-2-furancarboxaldehyde (**14**).

Table S5: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
1	$(Bu)_4N^+F^-$	0.46	1

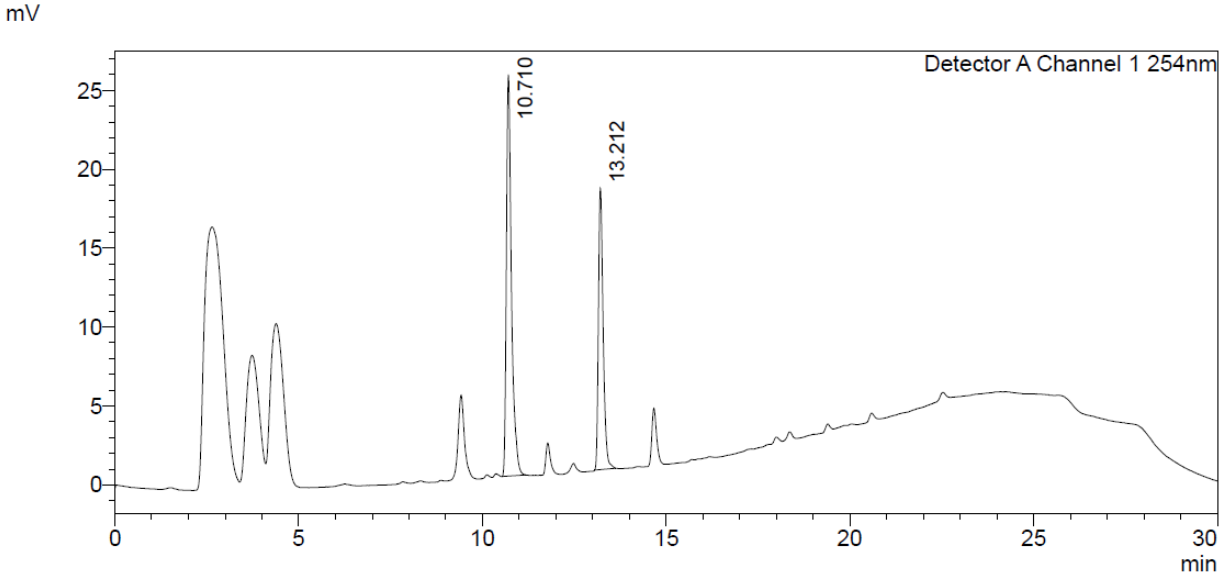
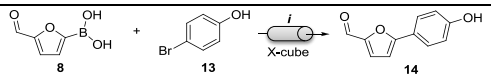


Figure S53: HPLC chromatogram of the crude material obtained from the reaction outlined in table S5 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S6: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
2	$(Bu)_4N^+Cl^-$	0.65	1

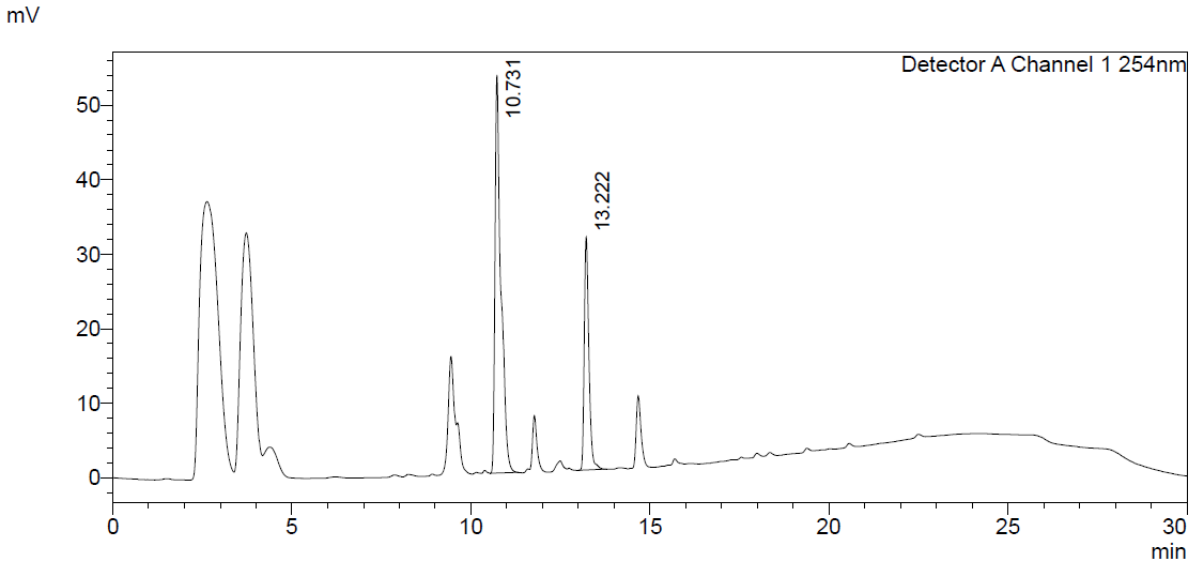
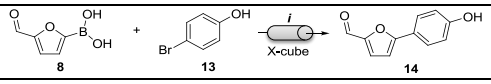


Figure S54: HPLC chromatogram of the crude material obtained from the reaction outlined in table S6 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S7: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
3	$(Bu)_4N^+Br^-$	21.82	1

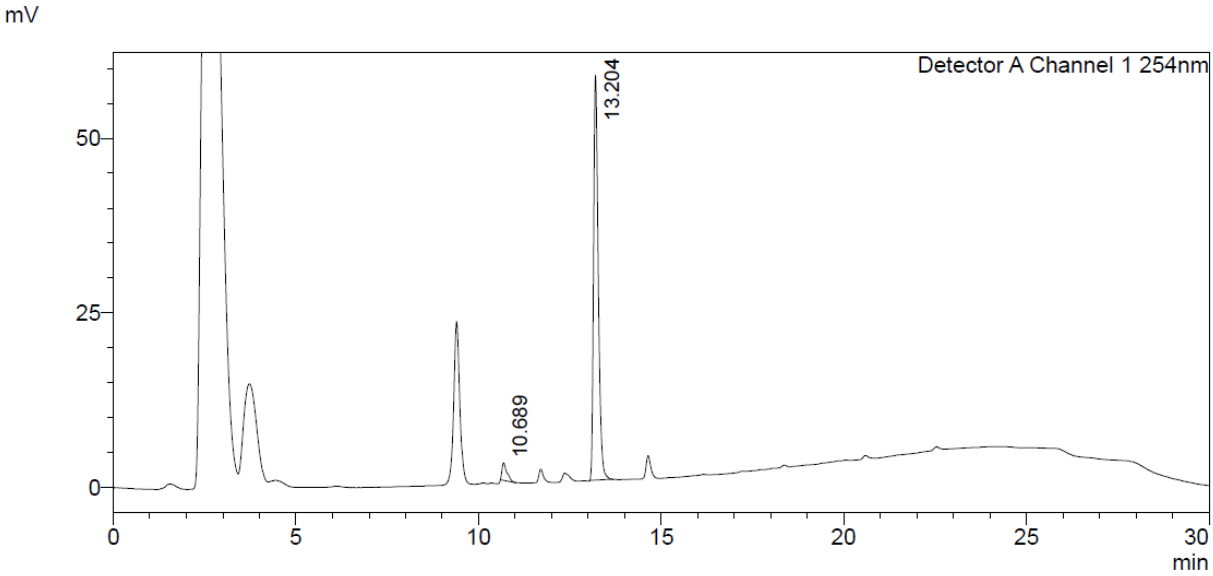
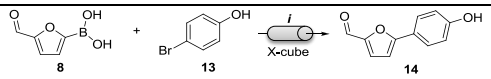


Figure S55: HPLC chromatogram of the crude material obtained from the reaction outlined in table S7 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S8: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
4	$(Bu)_4N^+I^-$	30.11	1

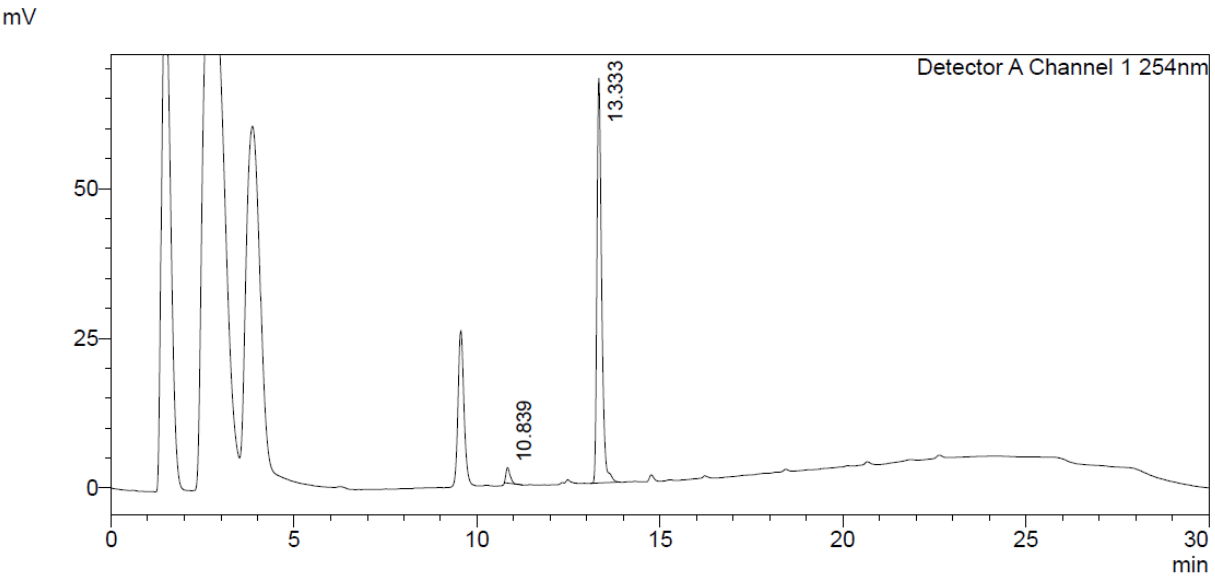
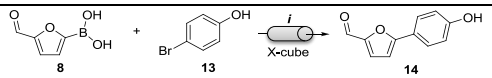


Figure S56: HPLC chromatogram of the crude material obtained from the reaction outlined in table S8 with the peak at 10.8 mins corresponding to the desired product **14** whilst the peak at 13.3 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S9: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
5	$(Bu)_4N^+BF_4^-$	2.47	1

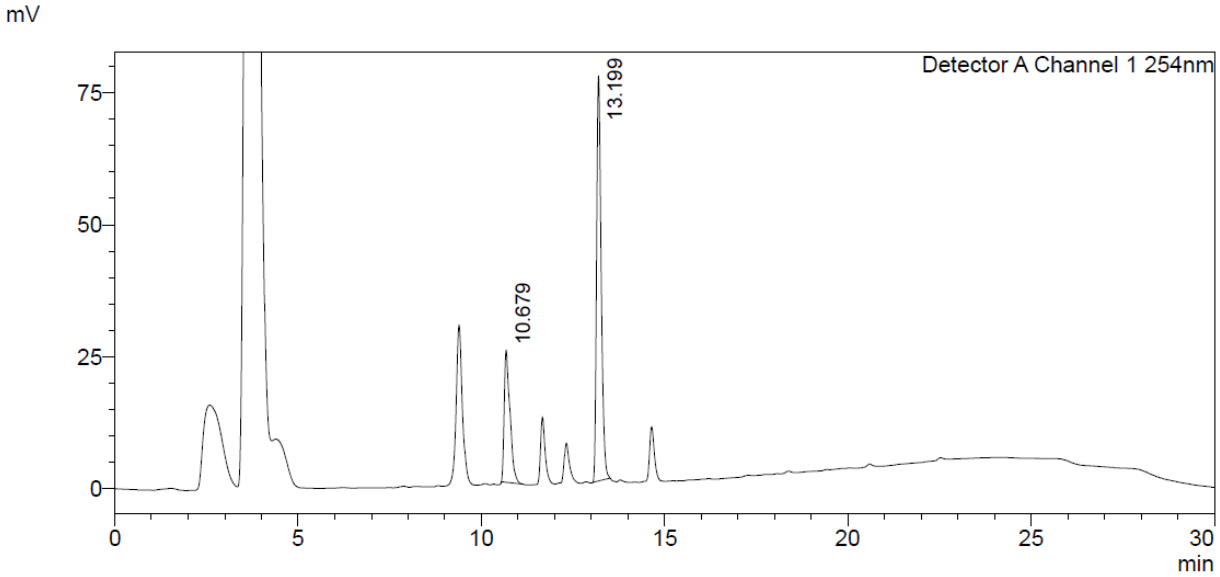
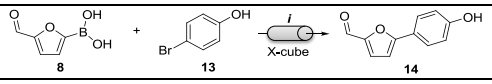


Figure S57: HPLC chromatogram of the crude material obtained from the reaction outlined in table S9 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S10: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	**14**
6	$(Bu)_4N^+HSO_4^-$	1.51	1

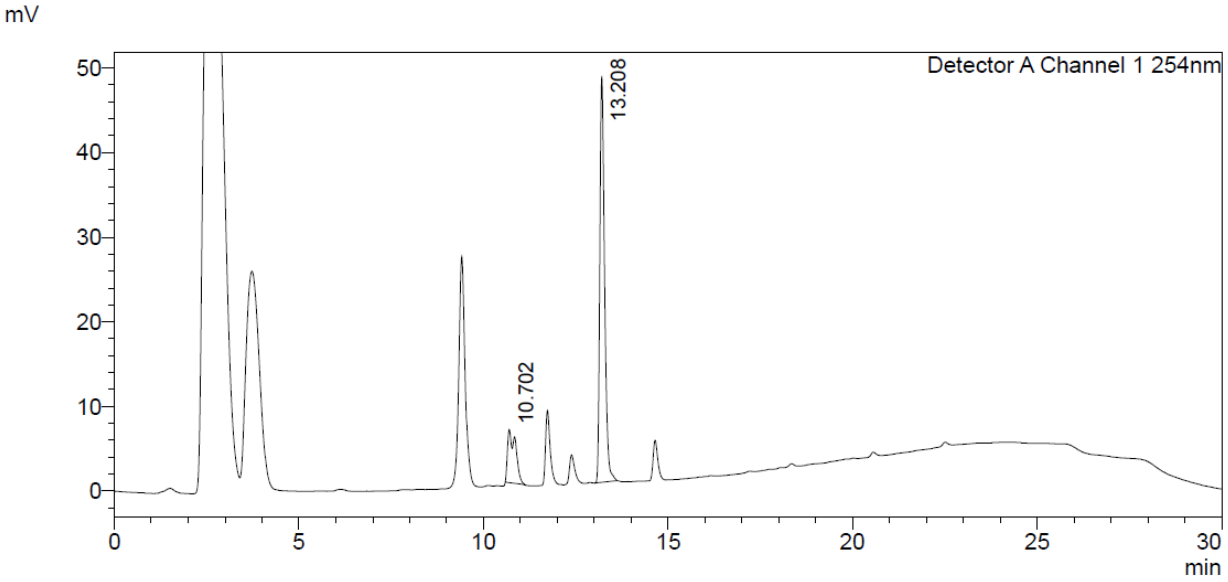
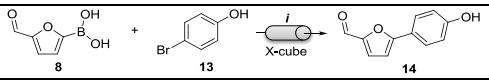


Figure S58: HPLC chromatogram of the crude material obtained from the reaction outlined in table S10 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S11: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	14
7	$(Bu)_4N^+OAc^-$	0.22	1

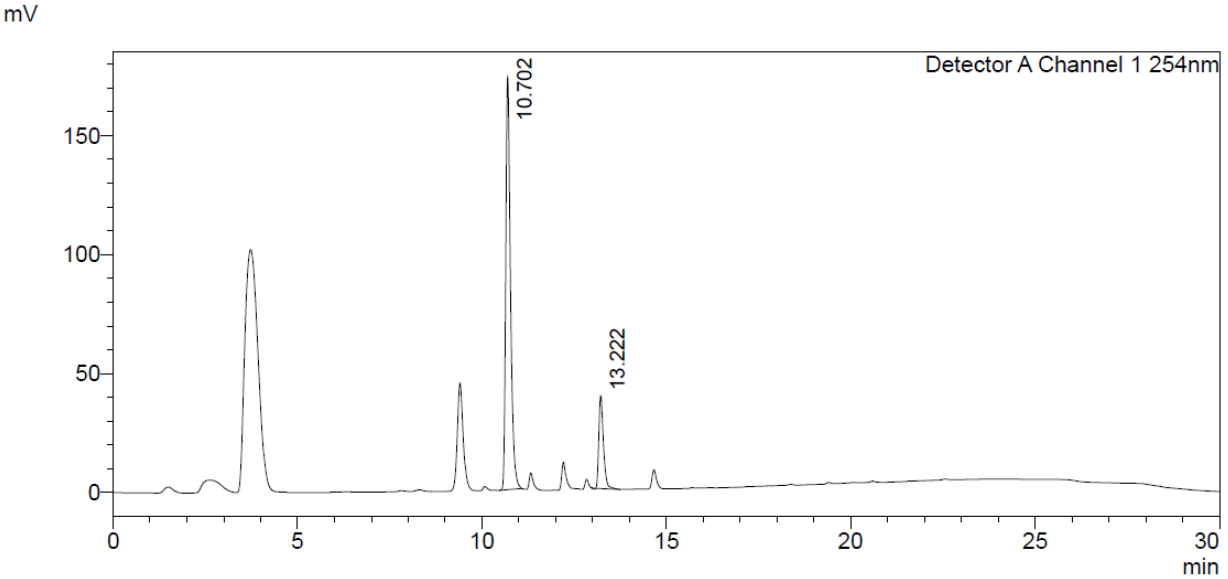
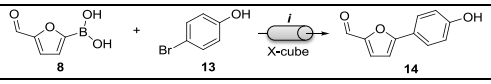


Figure S59: HPLC chromatogram of the crude material obtained from the reaction outlined in table S11 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S12: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**13**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	14
8	$(Bu)_4N^+F^- + Cs_2CO_3$	0.20	1

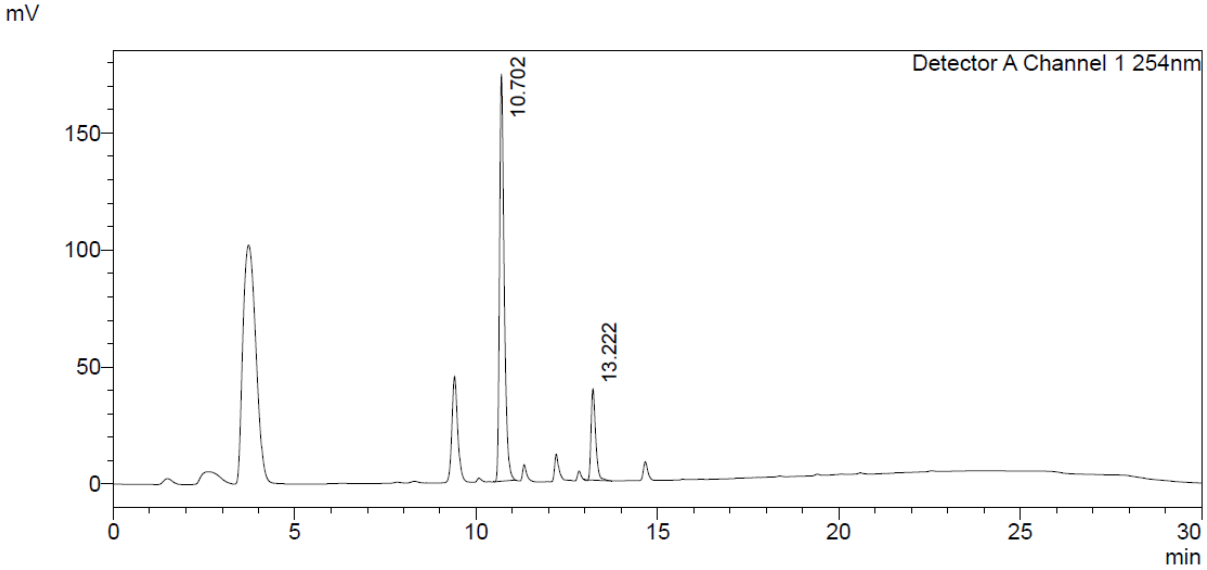
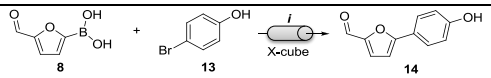


Figure S60: HPLC chromatogram of the crude material obtained from the reaction outlined in table S12 with the peak at 10.7 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Table S13: Tetrabutylammonium salt screen using FibreCat® 1032. ***Reagents and Conditions***: (***i***) 5-formyl-2-furanylboroic acid (1 mmol), 4-bromophenol benzyl (**10**) (1 mmol), tetrabutylammonium fluoride trihydrate (3 mmol), MeOH (30 mL), FibreCat® 1032, X-Cube™, 0.5 mL/min, and 120 °C.



Entry	Tetrabutylammonium salt	Ratio of Peak Area[a]	
		13	14
9	$(Bu)_4N^+OAc^- + Cs_2CO_3$	0.24	1

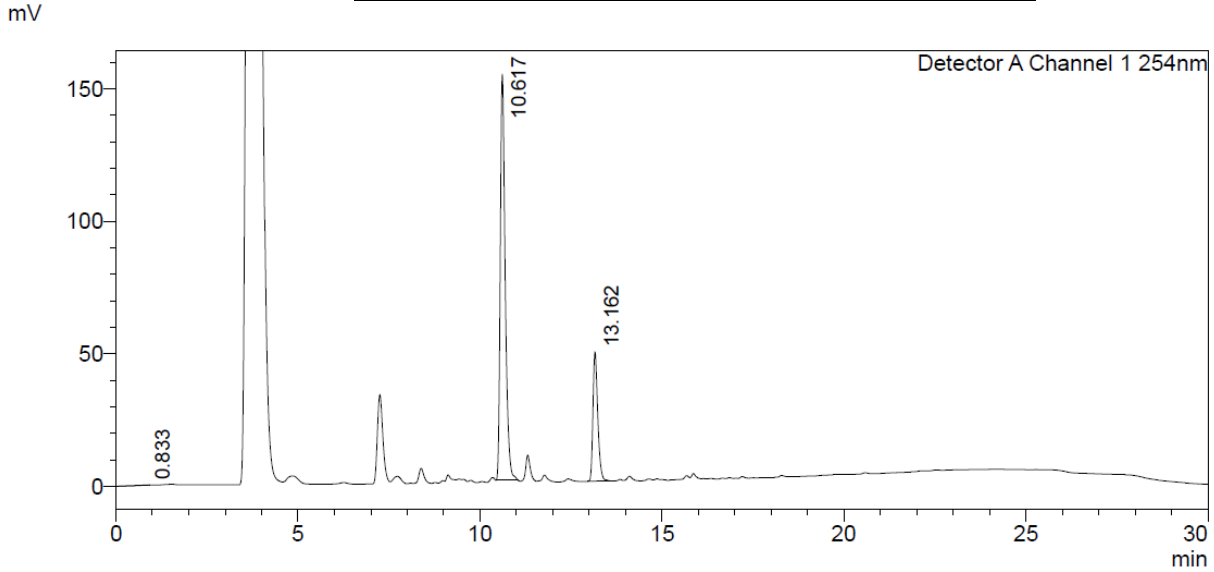


Figure S61: HPLC chromatogram of the crude material obtained from the reaction outlined in table S13 with the peak at 10.6 mins corresponding to the desired product **14** whilst the peak at 13.2 mins corresponds to the aryl bromide starting material **13**. RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

S8. General Procedure 2 using $(Bu)_4N^+OAc^-$ with CatCart™ $PdCl_2(PPh_3)_2$-DVB

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

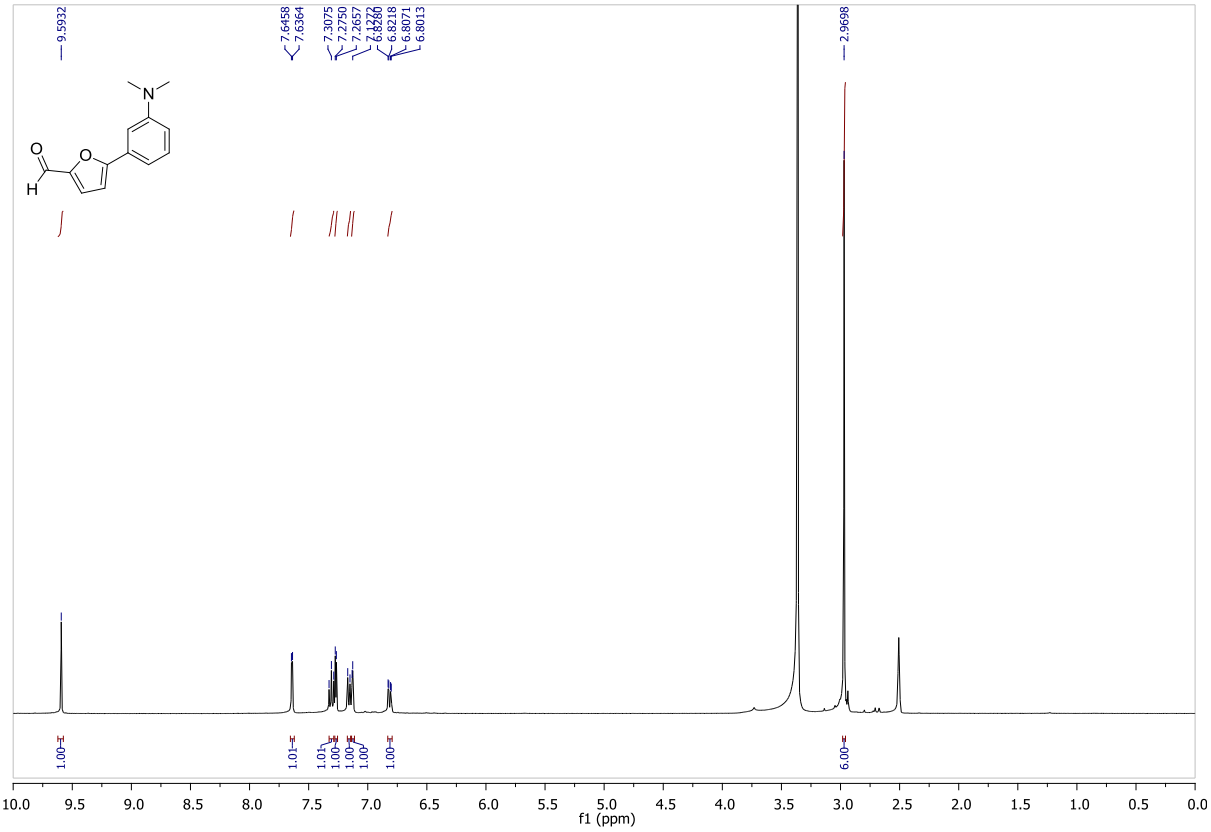


Figure S62: ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of 5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde (**15a**)

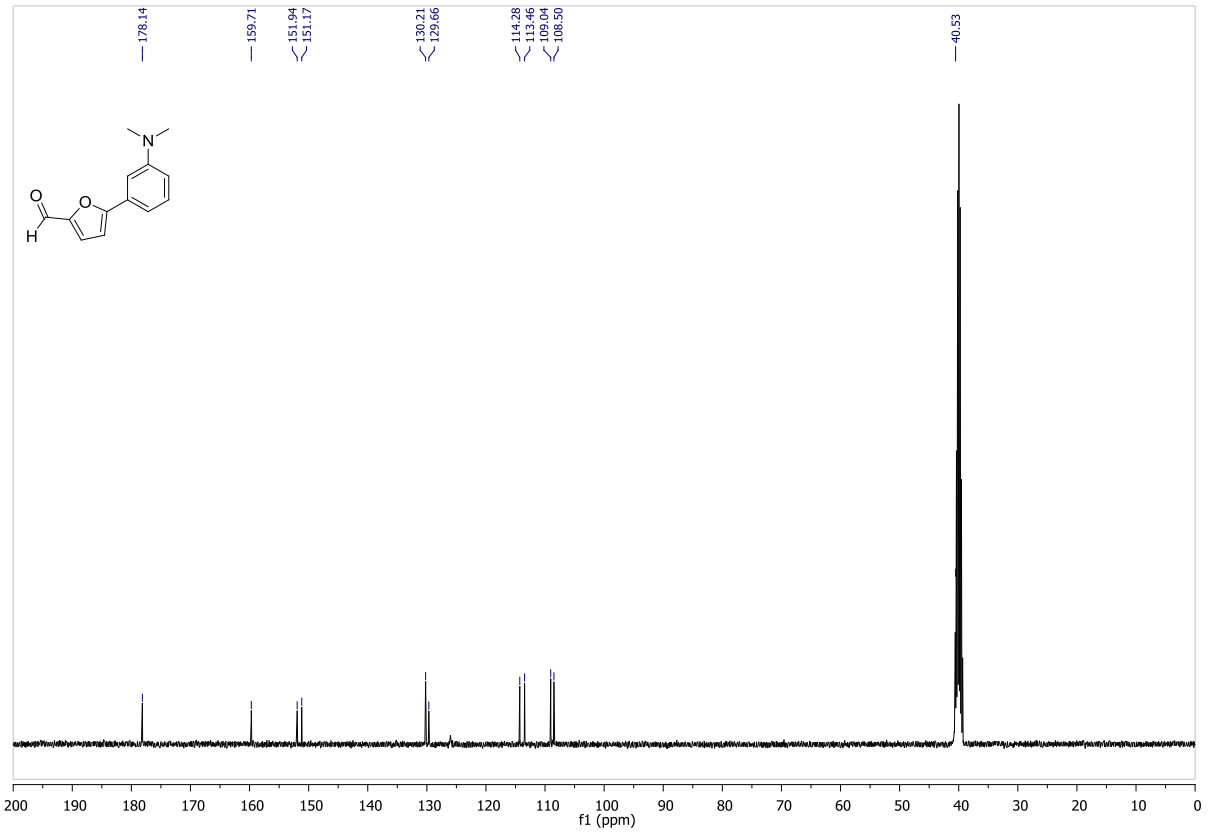


Figure S63: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5-(3-(dimethylamino)phenyl)-2-furancarboxaldehyde (**15a**).

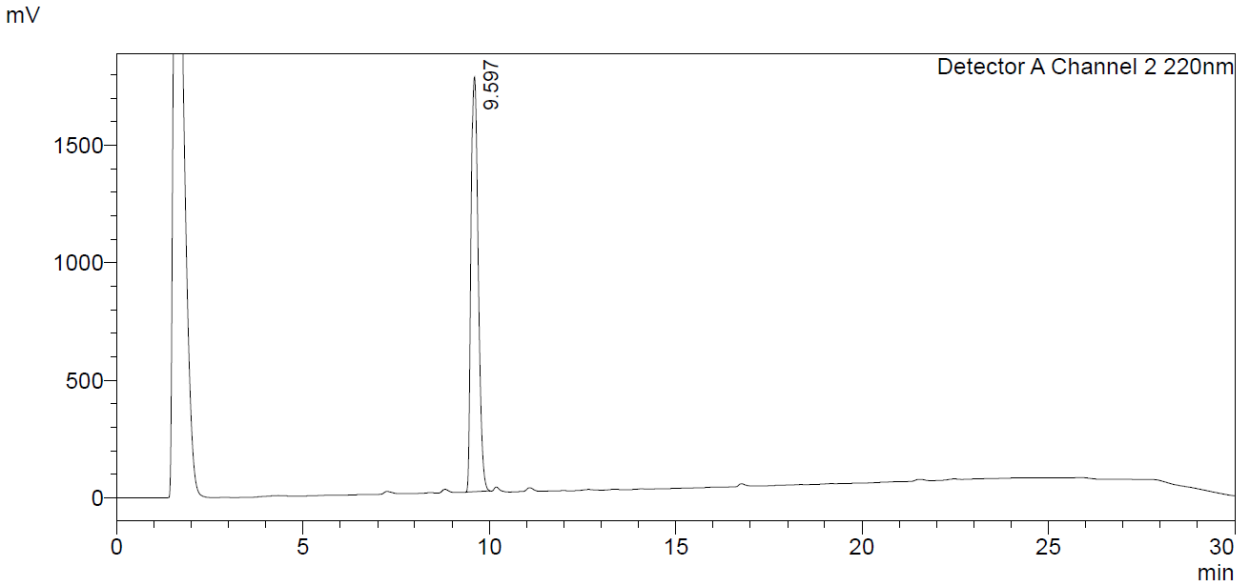


Figure S64: HPLC chromatogram of compound **15a**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

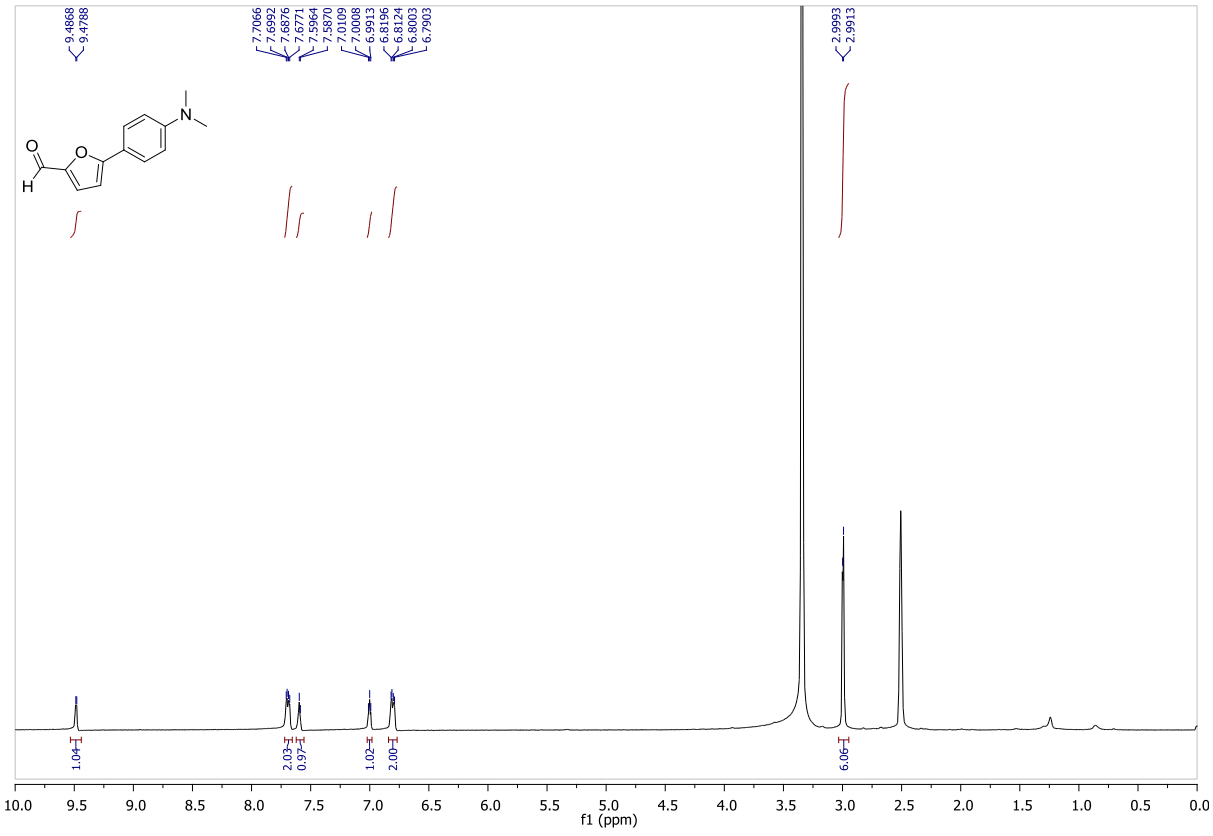


Figure S65: ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of 5-(4-(dimethylamino)phenyl)-2-furancarboxaldehyde (**15b**)

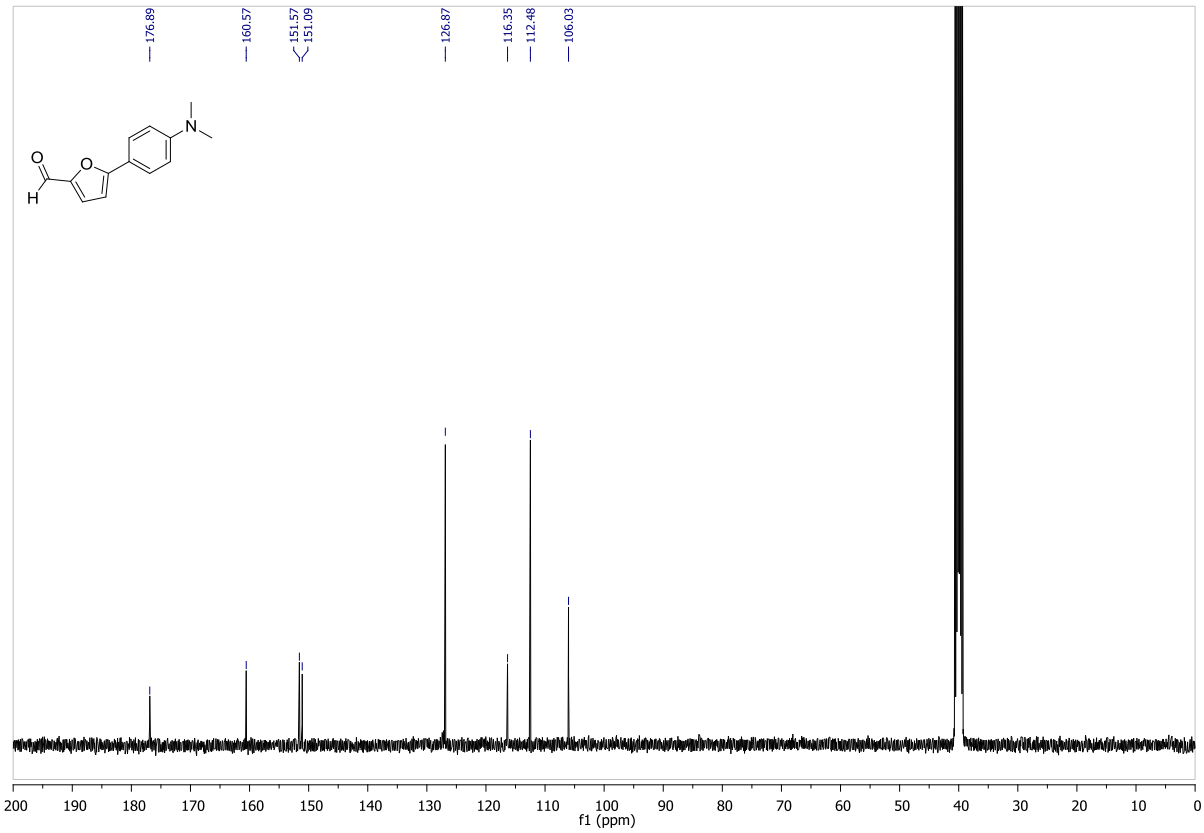


Figure S66: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5-(4-(dimethylamino)phenyl)-2-furancarboxaldehyde (**15b**).

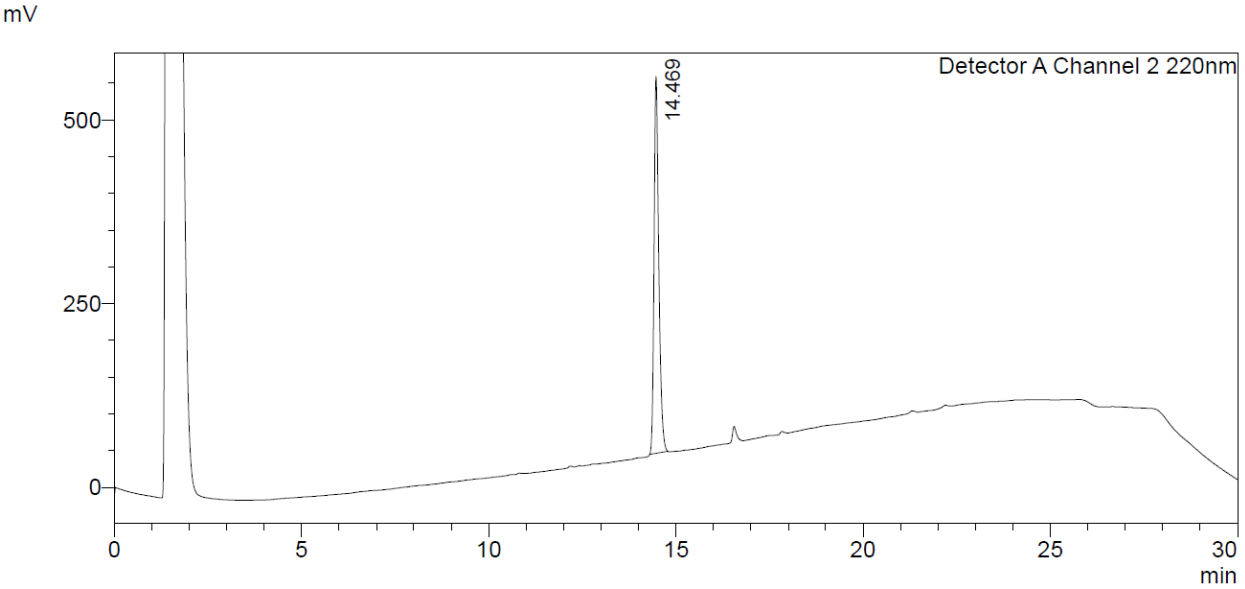


Figure S67: HPLC chromatogram of compound **15b**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

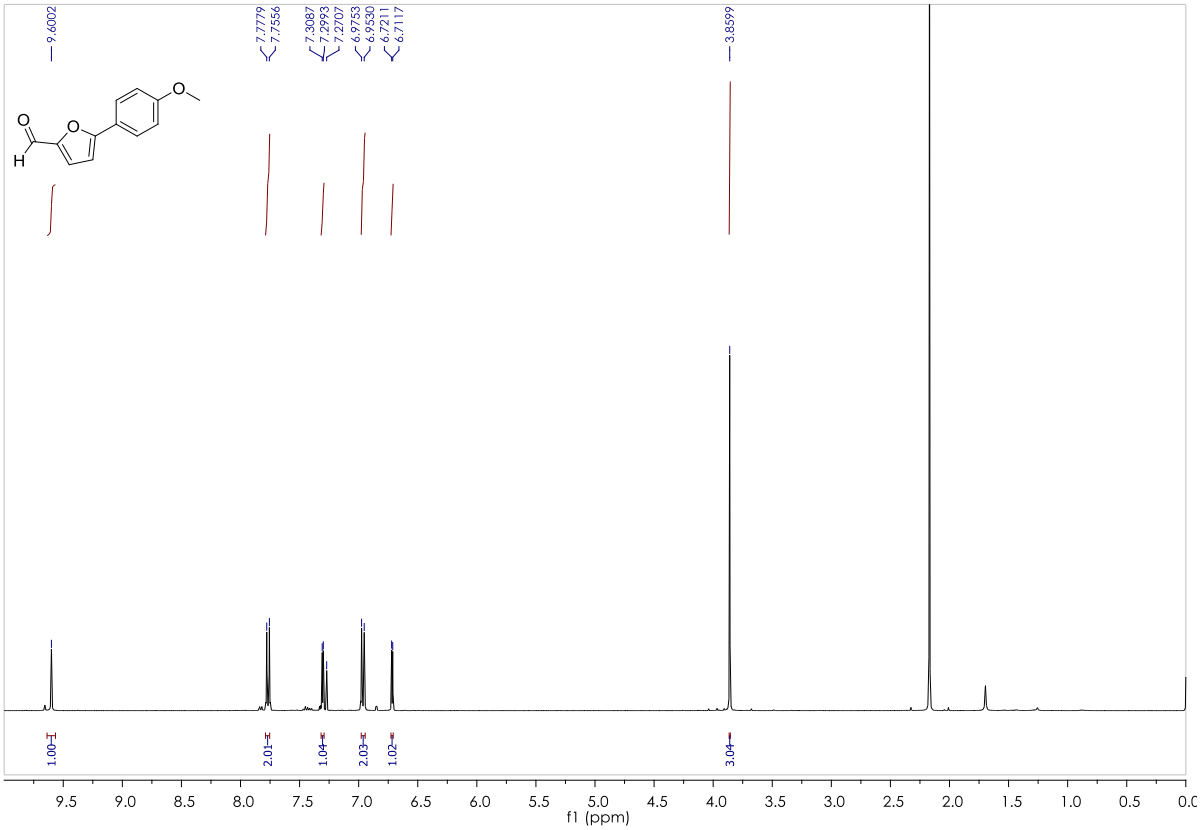


Fig S68: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(4-methoxyphenyl)-2-furancarboxaldehyde (**15c**).

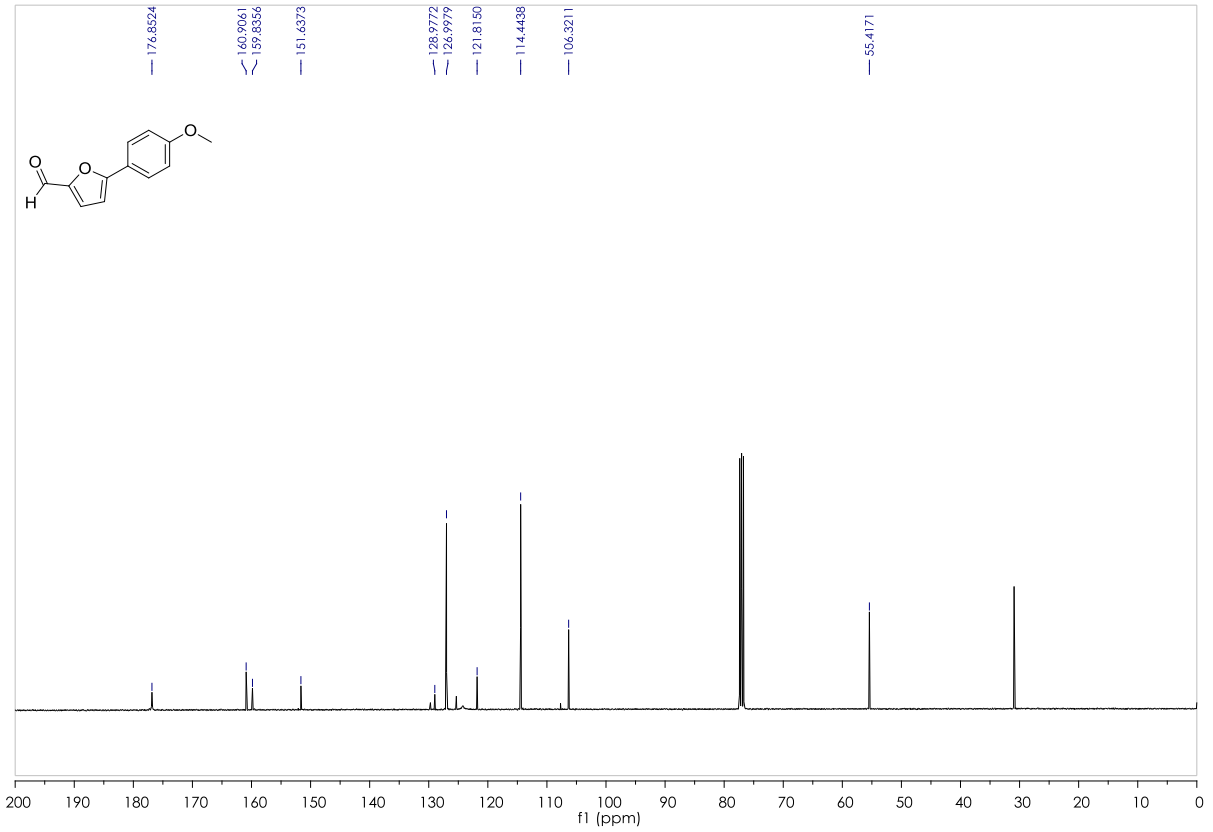


Figure S69: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 5-(4-methoxyphenyl)-2-furancarboxaldehyde (**15c**).

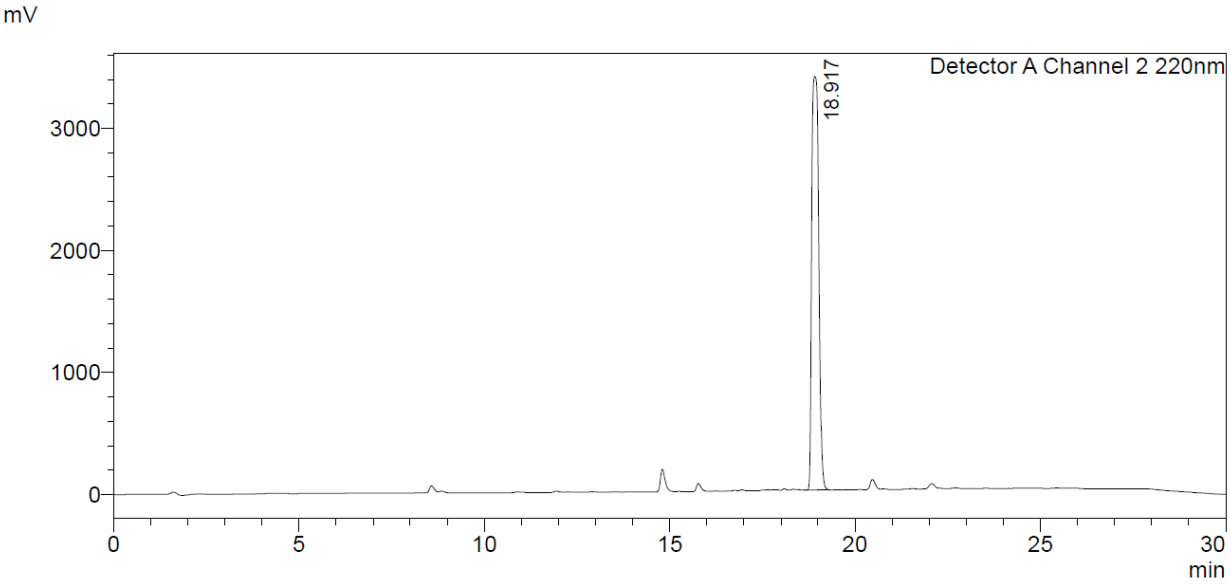


Figure S70: HPLC chromatogram of compound **15c**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

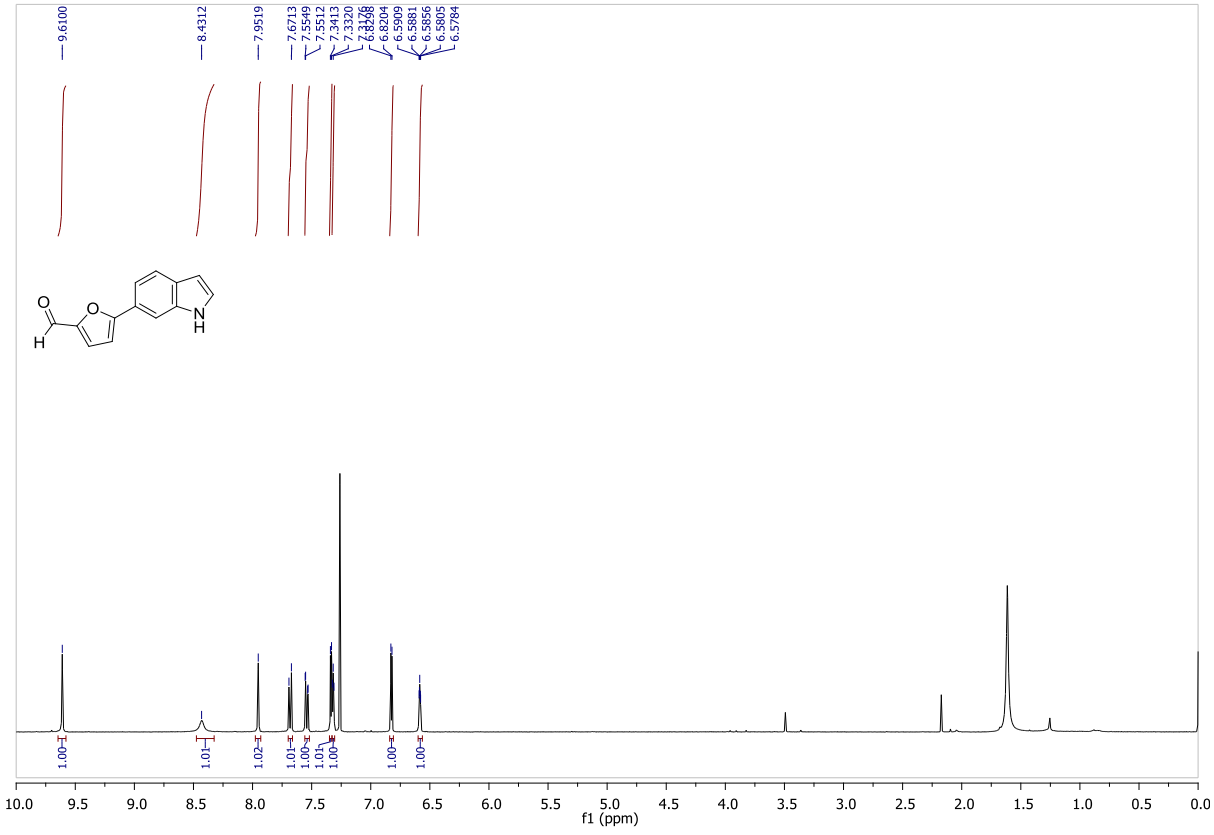


Figure S71: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 5-(1*H*-indol-6-yl)-2-furancarboxaldehyde (**15d**).

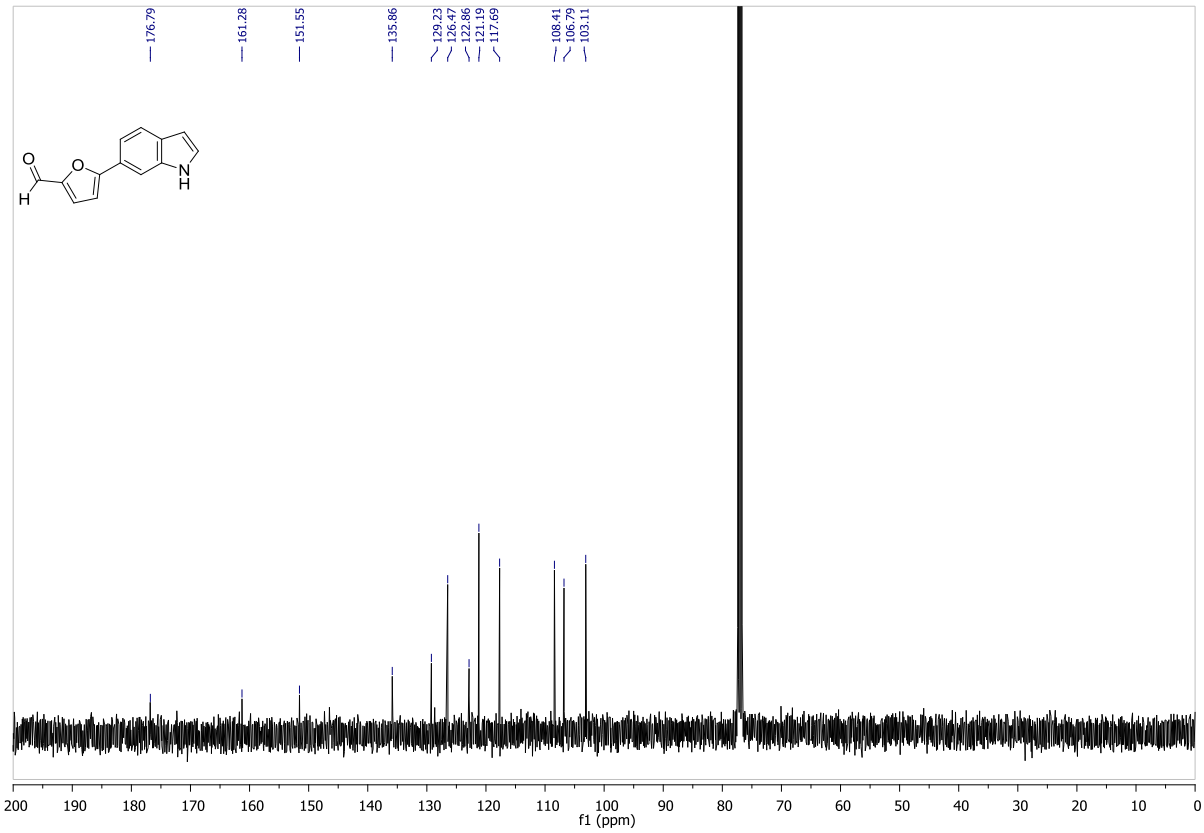


Figure S72: ^{13}C NMR Spectrum ($CDCl_3$, 101 MHz) of 5-(1*H*-indol-6-yl)-2-furancarboxaldehyde (**15d**).

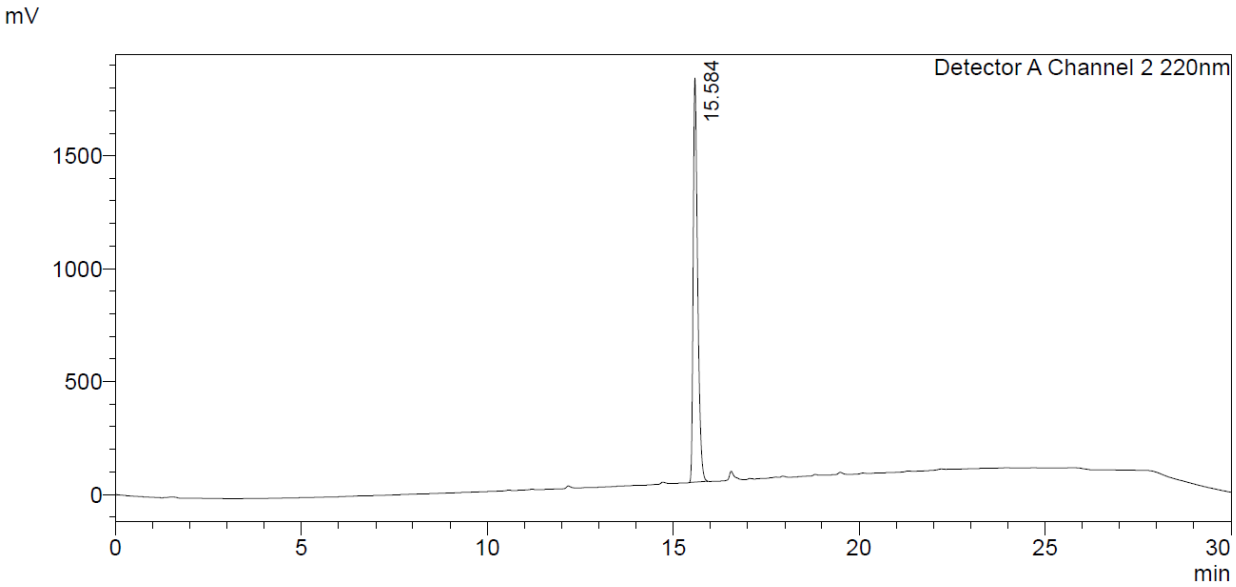


Figure S73: HPLC chromatogram of compound **15d**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

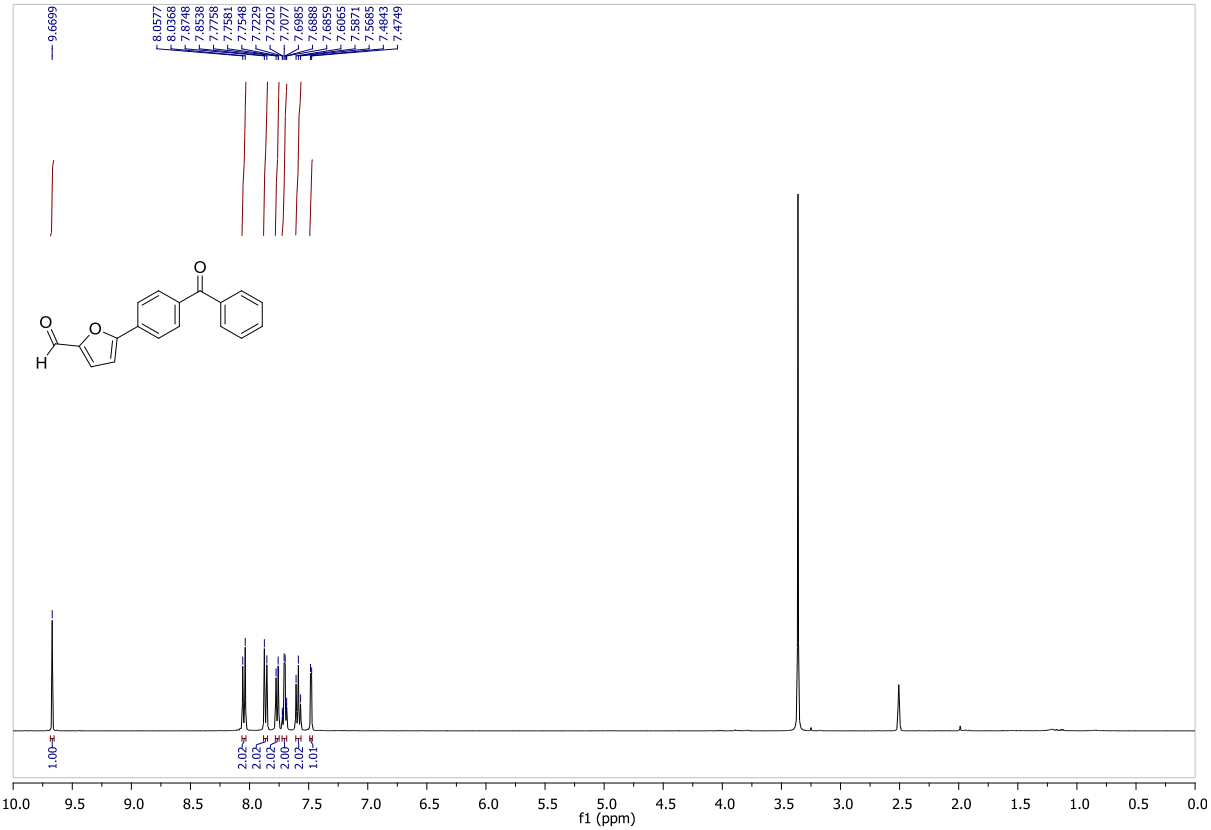


Figure S74 : ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of 5-(4-benzoylphenyl)-2-furancarboxaldehyde (**15e**).

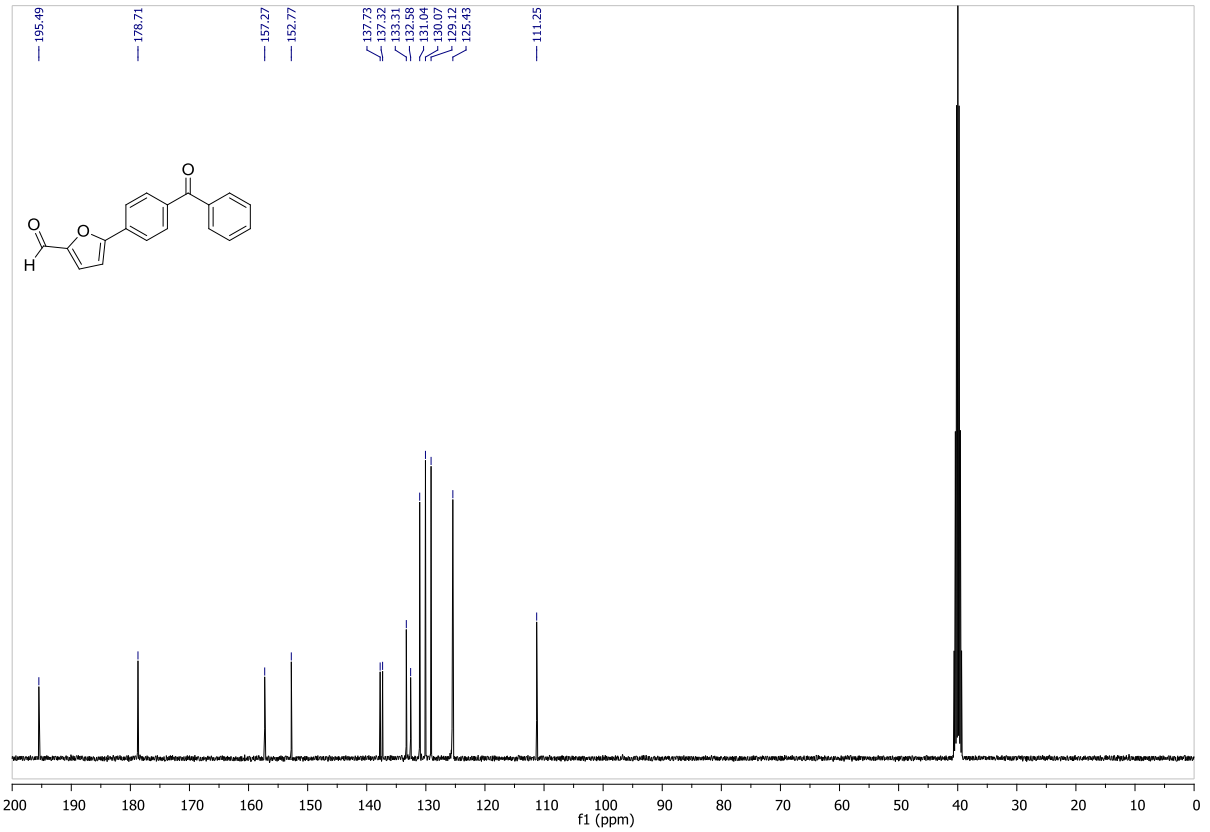


Figure S75: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5-(4-benzoylphenyl)-2-furancarboxaldehyde (**15e**).

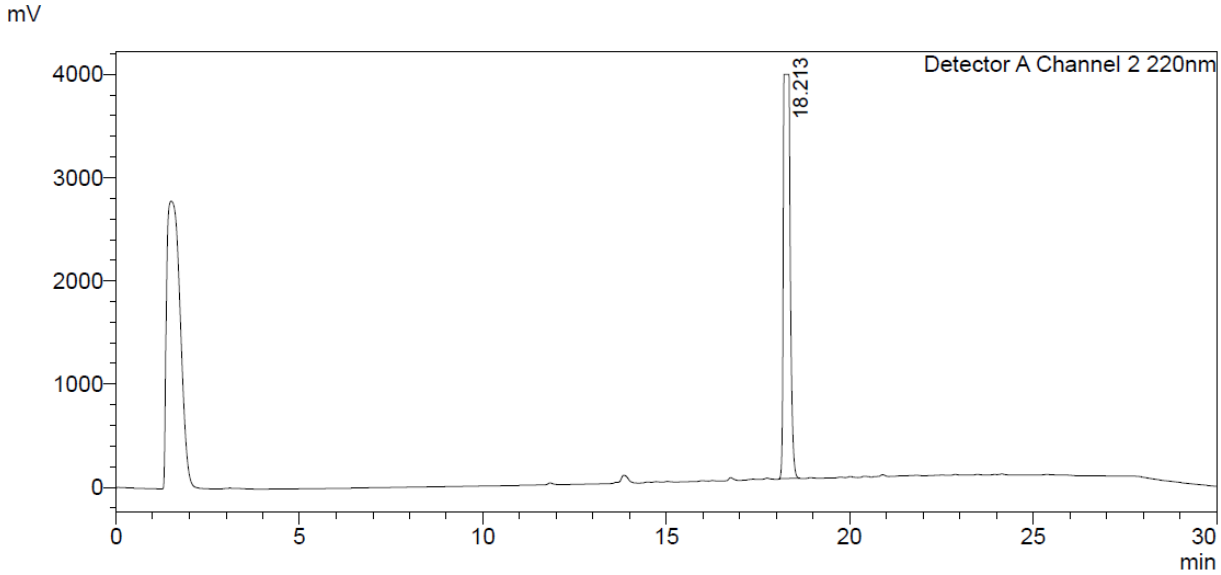


Figure S76: HPLC chromatogram of compound **15d**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

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

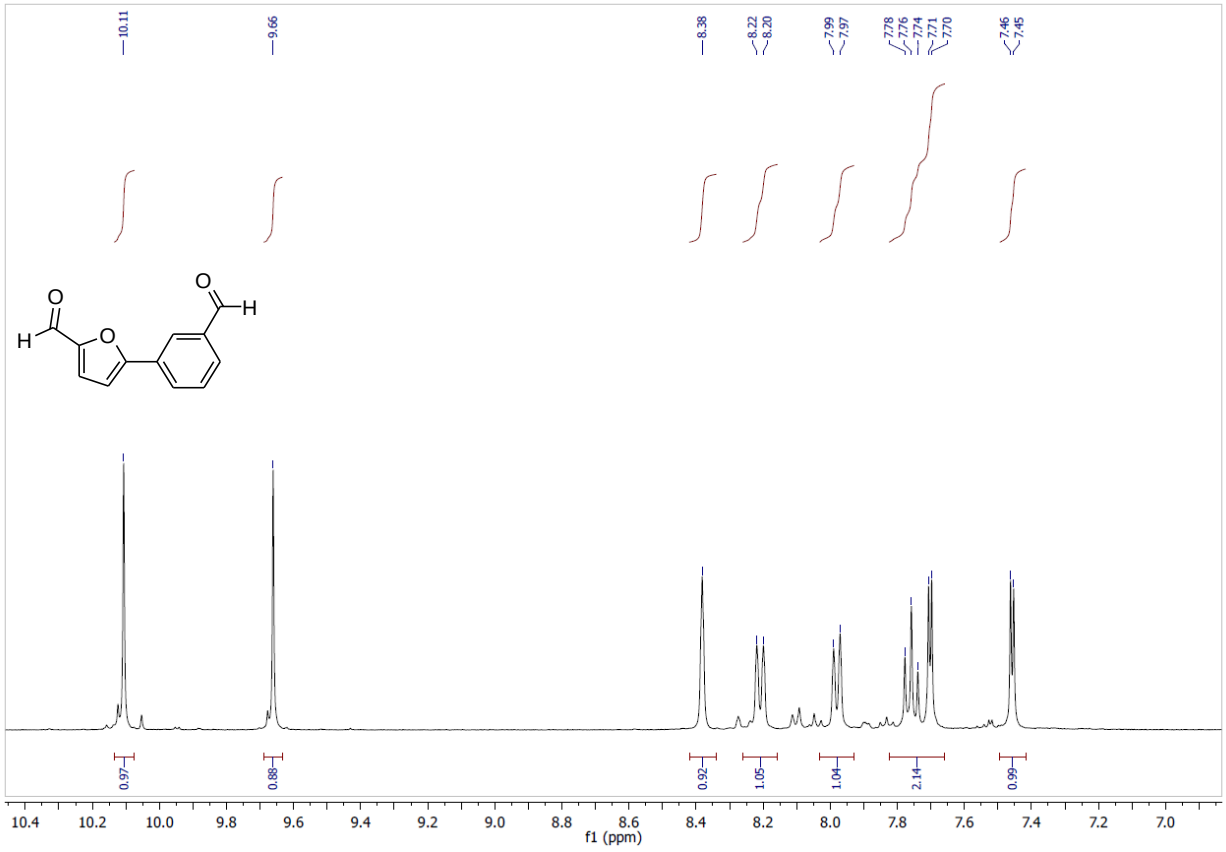


Figure S77 : ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of 5-(3-formylphenyl)furan-2-carbaldehyde (**15f**).

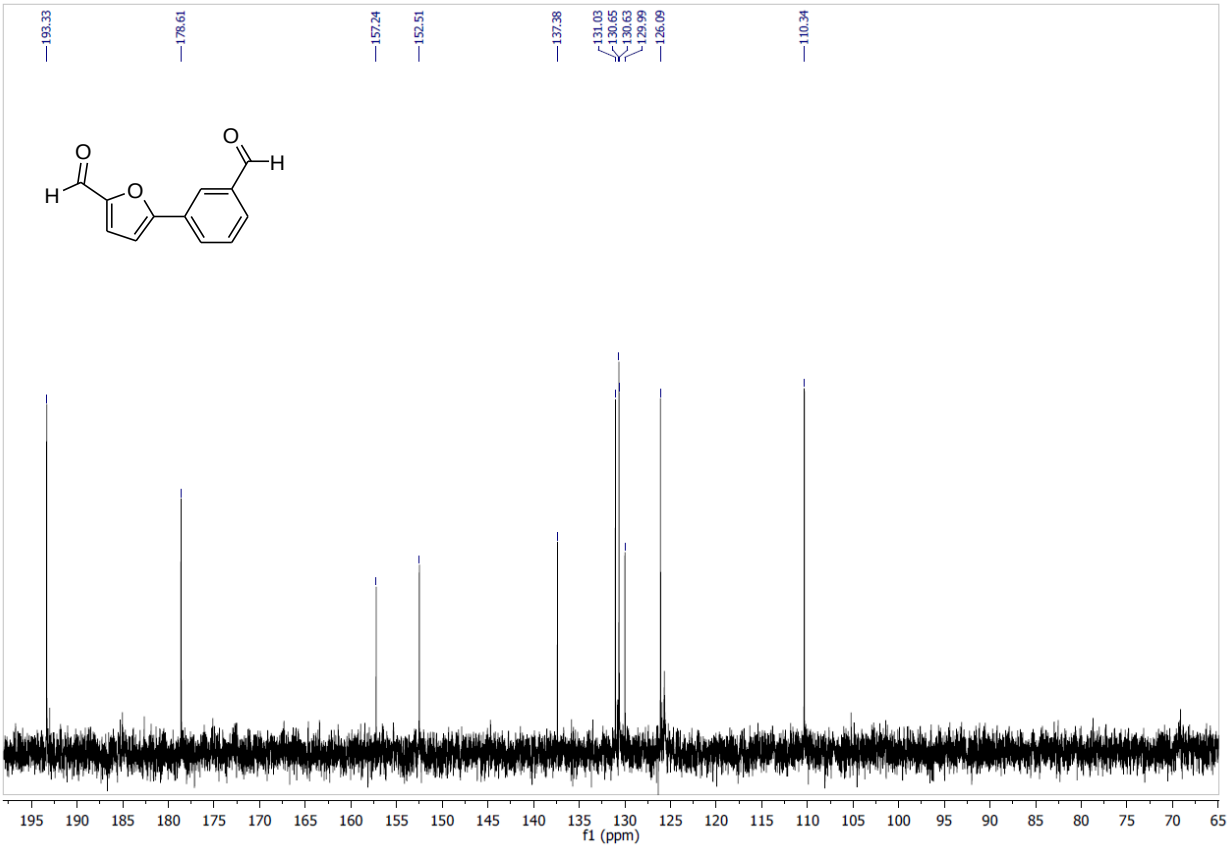


Figure S78: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5-(3-formylphenyl)furan-2-carbaldehyde (**15f**).

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

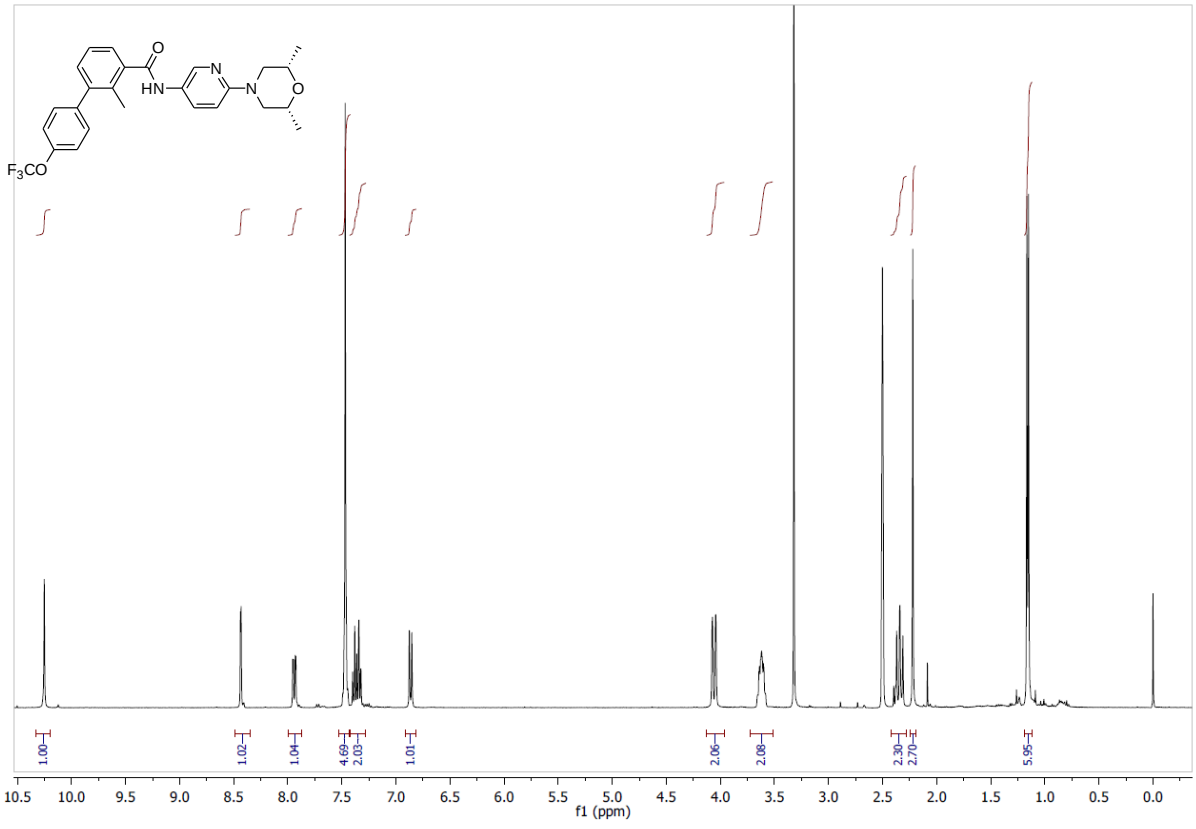


Figure S80: ^{1}H NMR Spectrum (DMSO-d6, 400 MHz) of *N*-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide (**18**).

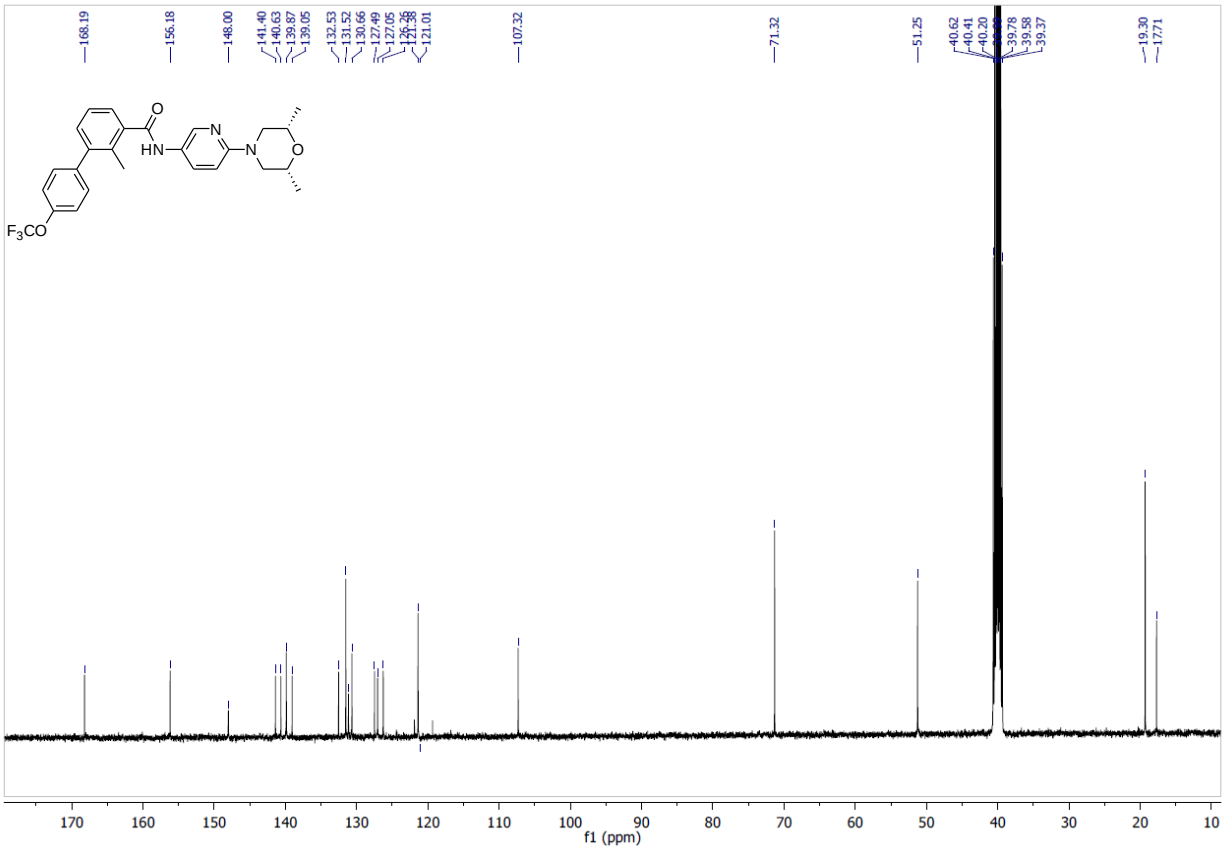


Figure S81: ^{13}C NMR Spectrum (DMSO-d6, 101 MHz) of 5 *N*-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide (**18**).

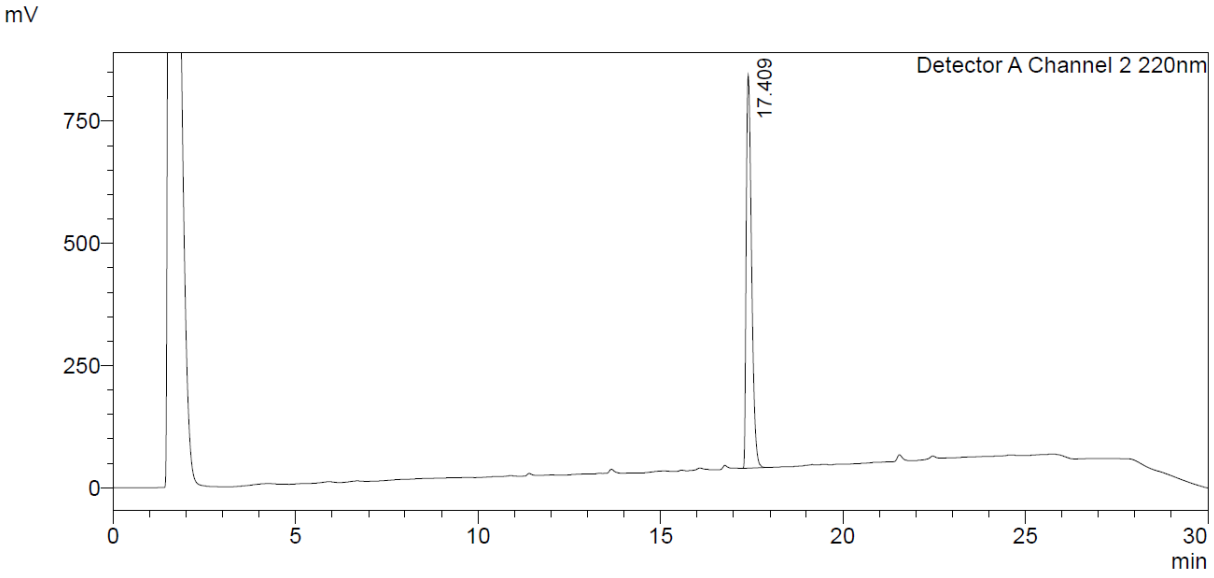


Figure S82: HPLC chromatogram of compound **18**, RP-HPLC Alltima™ C18 5u 150mm x 4.6 mm, 10-100 % B in 15 min.

Australian Government
National Measurement Institute

QUALITY ASSURANCE REPORT

Client: **UNIVERSITY OF WESTERN SYDNEY**

NMI QA Report No: **UNIW32/140910T1** **Sample Matrix:** Liquid
Solid

Analyte	Method	LOR	Blank	Duplicates			Recoveries	
				Sample	Duplicate	RPD	LCS	Matrix Spike
		ug/L	ug/L	ug/L	ug/L	%	%	
Inorganics Section				**N14/022318**				**N14/022318**
Palladium	NT2.49	1	<1	42	43	2	104	100
		mg/kg	**mg/kg**	**mg/kg**	**mg/kg**			
Palladium	NT2.49	0.5	<0.5	ND	ND	ND	104	ND

Filename = K:\Inorganics\Quality System\QA Reports\TE\QAR2014\Food & Mis\

Legend:
Acceptable recovery is 75-120%.
Acceptable RPDs on duplicates is 44% at concentrations >5 times LOR. Greater RPD may be expected at <5 times LOR.
LOR = Limit Of Reporting
RPD = Relative Percent Difference
LCS = Laboratory Control Sample.
ND = Not Determined
NA = Not Applicable
#: Spike level is less than 50% of the sample's concentration, hence the recovery data is not reliable.
**: reference value not available

Comments:
Results greater than ten times LOR have been rounded to two significant figures.
This report shall not be reproduced except in full.

Signed:

Dr Michael Wu
Inorganics Manager, NMI-North Ryde
Date: **26/09/2014**

REPORT OF ANALYSIS

Report No. RN1038128

Client	: UNIVERSITY OF WESTERN SYDNEY	**Job No.**	: UNIW32/140910
	SCHOOL OF MEDICINE - BUILDING 30	**Quote No.**	: QT-02021
	CAMPBELLTOWN CAMPUS	**Order No.**	:
	CAMPBELLTOWN NSW 2560	**Date Sampled**	:
		Date Received	: 10-SEP-2014
Attention	DAVID HARMAN	**Sampled By**	: CLIENT
Project Name	:		
Your Client Services Manager	: RICHARD COGHLAN	**Phone**	: (02) 94490161

Lab Reg No.	Sample Ref	Sample Description
N14/022316	TP8B4	LIQUID
N14/022317	TP174B3	LIQUID
N14/022318	TP188B3	LIQUID

Lab Reg No.		N14/022316	N14/022317	N14/022318		
Sample Reference	Units	TP8B4	TP174B3	TP188B3		
Filtered Trace Elements by ICP						
Palladium	ug/L	39	29	43		

N14/022316
- N14/022318
Method Used: NMI NT 2.49.

Ling Shuang Lu, Analyst
Inorganics - NSW
Accreditation No. 198

26-SEP-2014

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This Report supersedes reports: *RN1038125*

Australian Government

National Measurement Institute

REPORT OF ANALYSIS

Report No. RN1038127

Client	: UNIVERSITY OF WESTERN SYDNEY	**Job No.**	: UNIW32/140910
	SCHOOL OF MEDICINE - BUILDING 30	**Quote No.**	: QT-02021
	CAMPBELLTOWN CAMPUS	**Order No.**	:
	CAMPBELLTOWN NSW 2560	**Date Sampled**	:
		Date Received	: 10-SEP-2014
Attention	DAVID HARMAN	**Sampled By**	: CLIENT
Project Name	:		
Your Client Services Manager	: RICHARD COGHLAN	**Phone**	: (02) 94490161

Lab Reg No.	Sample Ref	Sample Description
N14/022313	TP15B4	SOLID
N14/022314	TP176B3	SOLID
N14/022315	TP188B3	SOLID

Lab Reg No.		N14/022313	N14/022314	N14/022315		
Sample Reference	Units	TP15B4	TP176B3	TP188B3		Method
Total Recoverable Trace Elements by ICP						
Palladium	mg/kg	5.2	340	52		NT2_49

Ling Shuang Lu, Analyst
Inorganics - NSW
Accreditation No. 198

26-SEP-2014

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National Measurement Institute

REPORT OF ANALYSIS

Report No. RN1038127

Client	: UNIVERSITY OF WESTERN SYDNEY	**Job No.**	: UNIW32/140910
	SCHOOL OF MEDICINE - BUILDING 30	**Quote No.**	: QT-02021
	CAMPBELLTOWN CAMPUS	**Order No.**	:
	CAMPBELLTOWN NSW 2560	**Date Sampled**	:
		Date Received	: 10-SEP-2014
Attention	DAVID HARMAN	**Sampled By**	: CLIENT
Project Name	:		
Your Client Services Manager	: RICHARD COGHLAN	**Phone**	: (02) 94490161

Lab Reg No.	Sample Ref	Sample Description
N14/022313	TP15B4	SOLID
N14/022314	TP176B3	SOLID
N14/022315	TP188B3	SOLID

Lab Reg No.		N14/022313	N14/022314	N14/022315		
Sample Reference	Units	TP15B4	TP176B3	TP188B3		Method
Total Recoverable Trace Elements by ICP						
Palladium	mg/kg	5.2	340	52		NT2_49

Ling Shuang Lu, Analyst
Inorganics - NSW
Accreditation No. 198

26-SEP-2014

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