Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Electronic Supplementary Information

Enabling organometallic libraries by flow:

A tale of two metals

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S1 – General Considerations

S1.1 – General Experimental

Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. For the following reagents, the grade used was of importance: THF (Merck, 186562-2L, anhydrous contains 250 ppm BHT as inhibitor), LiCl (ThermoScientific, A10531.36, anhydrous), Zinc (Merck, 243469, granular, 20-30 mesh, ACS reagent, ≥99.8%), Magnesium (Merck, 254126, 20-230 mesh, reagent grade, 98%). Molecular sieves 4 Å (ThermoScientific, 197265000, 4-8 mesh) were stored in an oven at 150°C and then further dried under vacuum whilst being heated with a heat gun immediately before use.

LCMS analysis was performed using an Agilent 1290 Infinity II UHPLC series connected to a TOF 6230 with an ES ionisation source (positive or negative mode ionisation). The LCMS was configured with a buffered mobile phase - polar: Water /10 mM ammonium formate / 0.08% (v/v) formic acid pH = 3.3; apolar: Acetonitrile / 5.3 % (v/v) ammonium formate / 0.08% (v/v) formic acid. The mobile phase passed through a Phenomenex Kinetex C18 column, 2.6 microns, 50 x 2 mm, temperature: 55°C at a flow rate of 1.3 mL/min. A 1 µL sample was injected and purified using a 5 to 95% gradient in 1.18 minutes, total run time 1.95 minutes.

Compounds were purified using either a Teledyne Isco CombiFlash NextGen 300+, Teledyne Isco ACCQPrep HP125 or Waters prep HPLC system. The Waters prep HPLC consisted of the following components: 3767 Sample Manager, 2545 Binary Gradient Module, 515 HPLC Pump, SFO (System Fluidics Organiser), 2998 PDA (Photodiode Array) and Acquity QDa Mass Detector. All reverse phase purification was carried out using a Gemini 5 µm NX-C18 110 Å column, 250 x 30 mm, AXIA packed with a flow rate of 40 mL/min.

NMR spectra were acquired on either a Bruker AVANCE NEO 400 MHz UltraShield spectrometer coupled to a SampleCase Plus automatic sample changer, or a Bruker AVANCE III HD 600 MHz UltraShield spectrometer with a QCI-F cryoprobe coupled to a SampleJet automatic sample changer. For ^{13}C multiplets showing a ^{19}F coupling, the chemical shift of the middle of the multiplet was reported. Where compounds are a mixture (e.g., diastereoisomers) then the two shifts are separated by a "/".

S1.2 - Fluidic System Components

A commercially available flow reactor (Syrris Asia) was used for all experiments. The system comprising of the following components:

- Asia Pump (Part no. 2200292) fitted with pairs of 2.5 mL & 5 mL (red) syringes
- Asia Pressurised Input Store (Part no. 2200400)
- Asia Automated Reagent Injector (Part no. 2201126) fitted with 5 mL injection loops and with accompanying 2, 8 and 40 mL racks
- Two Asia Heaters (Part no. 2200527)
    - One fitted with Solid Phase Reactor Adaptor (Part no. 2200528)
    - One fitted with Tube Reactor Adaptor (Part no. 2200530)
- Diba Omnifit EZ Solventplus column reactor with two fixed endpieces, 10 mm internal diameter (Part no. 006EZS-10-10-FF), fitted with 30 µm PTFE frits (Part no. 006FR-10-30)
- Idex Low-Pressure Union, Male Straight, Natural PCTFE, 0.062" Bore, 1/4-28 Flat Bottom, (Part no. P-645), joining the column reactor directly into the T-mixer
- T-Mixer - Idex Low-Pressure Tee Body, Natural PEEK, 0.040" Bore, 1/16" OD Tubing, 1/4-28 Flat Bottom, (Part no. P-714)
- 16 mL Tube Reactor PTFE (Part no. 2200542)
- Asia Pressure Controller (Part no. 2200532) back pressure regulator
- Asia Automated Collector (Mini) (Part no. 2200535) with accompanying racks
    - 2 mL vials – Gilson code 0 (Part no. 270430)
    - 13 mL test tubes – Gilson code 22 (Part no. 150498)
    - 30 mL glass vials – 3D printed, see S13 – 3D Printed Custom Collection Racks
- Asia Automator (Part no. 2200536)
- PC with Asia Manager software installed
- Flexible LED strip light (purchased from Amazon, ASIN B07B7LQ2J4), DC 12 V, actinic blue (440 – 450 nm), 60 LEDs per metre, 4.35 m of 5 m reel used
- Aurora constant voltage LED driver (Part no. AU-LED2512CV), 25 W non-dimmable 12 V DC output

S1.3 – Negishi Reaction Fluidic Setup

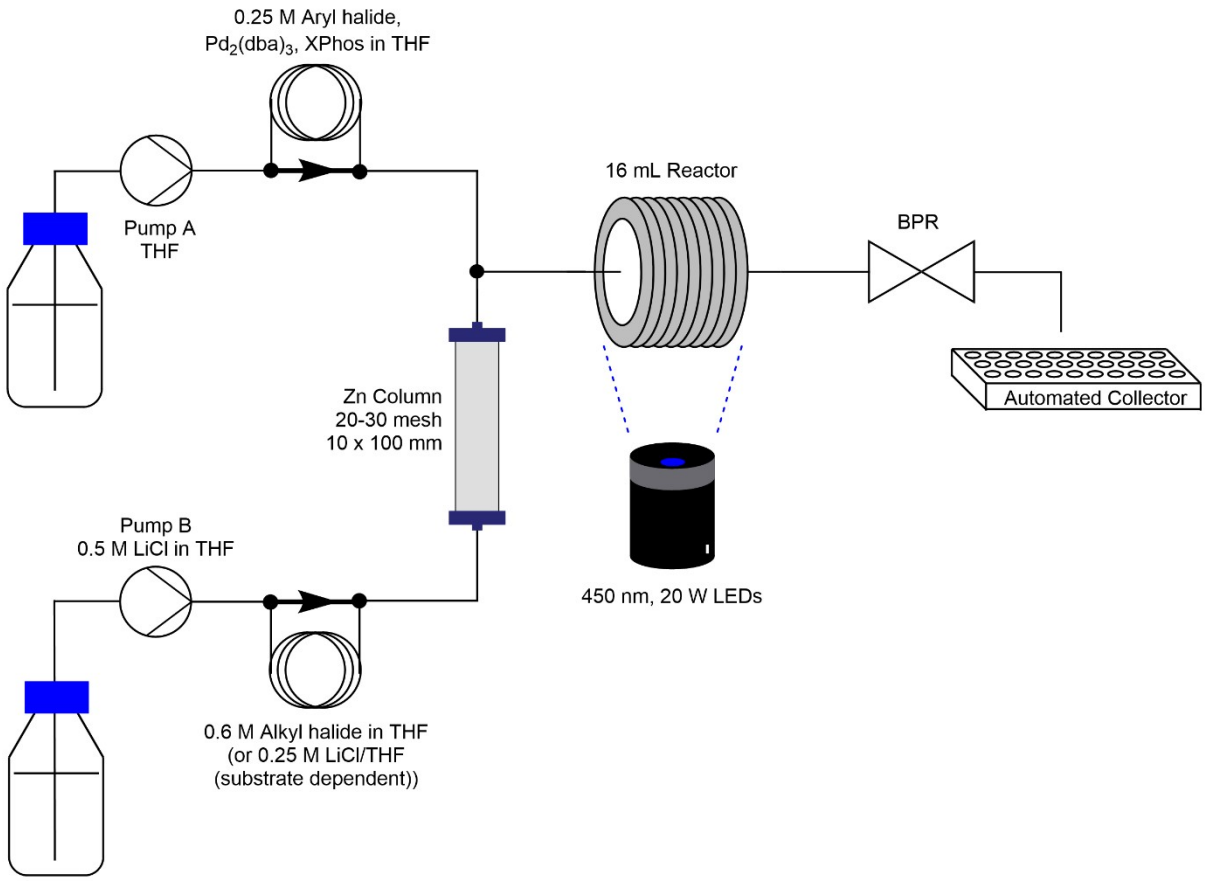


Figure 1 - Negishi generic fluidic scheme

Pump A and the two pump channels washing the Automated Injector loops were fed from a bottle containing THF and freshly dried 4 Å molecular sieves.

Pump B was fed from a bottle containing 0.5 M LiCl in THF solution (see S2.3 – 0.5 M LiCl in THF Preparation) and freshly dried 4 Å molecular sieves.

To ensure the organometallic species was generated and then subsequently mixed with its coupling partner in as brief a window as possible, a male 1/4-28 union was used to connect the output of the column directly to the T-mixer (swept volume 61.3 µL).

The 16 mL reactor was wrapped in a flexible strip of 450 nm LEDs (cut to approximately 4.35 m in length), powered by a 25 W 12 V LED driver. This results in the reactor being irradiated with approximately 20 W of light.

S1.4 – Grignard Reaction Fluidic Setup

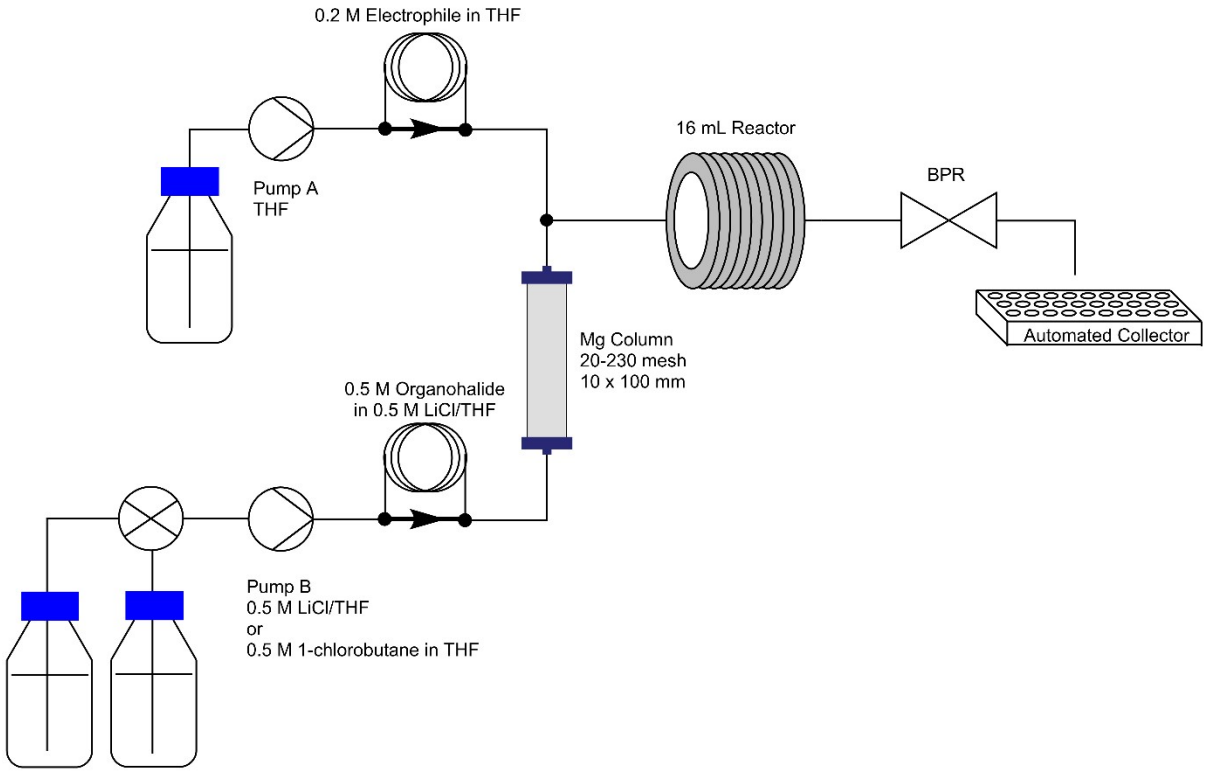


Figure 2 - Grignard generic fluidic scheme

Pump A and the two pump channels washing the Automated Injector loops were fed from a bottle containing THF and freshly dried 4 Å molecular sieves.

Pump B was equipped with two feed bottles that could be selected using a rotary valve. One bottle contained 0.5 M LiCl in THF solution (see S2.3 – 0.5 M LiCl in THF Preparation) and freshly dried 4 Å molecular sieves. The other bottle contained a 0.5 M solution of 1-chlorobutane (10.4 mL, 100 mmol) in THF (200 mL) and freshly dried 4 Å molecular sieves. Pump B valve selection position is detailed within each experimental section.

To ensure the organometallic species was generated and then subsequently mixed with its coupling partner in as brief a window as possible a male 1/4-28 union was used to connect the output of the column directly to the T-mixer (swept volume 61.3 µL).

S2 – General Methods

S2.1 – Zinc Column Preparation

To a 10 mm internal diameter, 100 mm length Omnifit EZ Solventplus column was added granular zinc (approximately 13.4 g, 20-30 mesh), with a small cotton wool wad at each end. The column was then primed with THF by syringe until solvent was observed exiting the other end (approximately 3.5 mL). In one example, the column volume was determined accurately by weighing before and after priming, the 3.09 g gain in mass after priming with THF corresponded to a volume of 3475 µL (solvent density 0.8892 g/mol).

Note: Unlike magnesium, there is no need to grind the metal before packing.

The zinc column was packed in the same manner as the previously published literature, the authors recommend consulting this publication for detailed step-by-step photographs if required.[1]

S2.2 – Magnesium Column Preparation

In a round bottomed flask under nitrogen magnesium powder (20-230 mesh) was ground with a large, slowly turning, magnetic stirrer overnight during which time the metal surface is observed to darken. It was found that a freshly ground surface was essential to successful column activation.

To a 10 mm internal diameter, 100 mm length Omnifit EZ Solventplus column was added the freshly ground magnesium powder (approximately 4.7 g), with a small cotton wool wad at each end. The column was then primed with THF by syringe until solvent was observed exiting the other end (column volume approximately 3 mL).

If required, the authors recommend consulting this analogous publication detailing zinc column preparation from Berton *et al.* for detailed step-by-step photographs of the process.[1]

S2.3 – 0.5 M LiCl in THF Preparation

Lithium chloride is highly hygroscopic therefore care must be taken to avoid any opportunity for water to be absorbed by the solid or solution. In our experience, it is best to make a THF solution of lithium chloride using dry, free-flowing powder directly ‘off the shelf’ and removing any residual trace of water with 4 Å molecular sieves once in solution. If rigorously dried powder is used it can be challenging to achieve a homogenous solution where all lithium chloride has been fully dissolved.

Into a round bottomed flask equipped with a stopper was added lithium chloride powder (9.70 g, 228.8 mmol), the flask was then immediately placed under nitrogen before THF (458 mL) was swiftly added. The flask was then equipped with a condenser and placed in an ultrasonic bath and sonicated until solid had fully dissolved (typically 2-4 hours). Note – prolonged usage leads to an increase in bath temperature, the water was therefore replaced once the temperature reached approximately 40-45°C to prevent solvent loss. Anecdotally, we have noticed solubility also tends to improve when the water bath temperature is lowered back down to room temperature.

Once a totally clear, homogenous 0.5 M solution of lithium chloride in THF was achieved, 10% w/v of freshly dried 4 Å molecular sieves were added and the condenser was removed. The solution was then left to stand overnight before use.

The solution is then ok to store under nitrogen and use for approximately one to two weeks without risk of lithium chloride precipitation or uptake of water. When large quantities were transferred (such as to a pump solvent feed bottle) further freshly dried 4 Å molecular sieves were then added to both the source and destination vessels to ensure no moisture ingress arising from this process.

S2.4 – General Method A: Zinc Column Activation

The zinc column was activated using the previously published method with minor modifications.[1]

Pump A and B flow rates were both set to 1 mL/min, with the back pressure regulator set to 2 bar, the column reactor heated to 40°C, and the 16 mL reactor at room temperature.

Two activation solutions were prepared for injection:

To create a 2 M trimethylchlorosilane (TMSCl) in THF solution, to a 40 mL vial containing 14 mL of THF was added trimethylchlorosilane (3.36 mL, 26.47 mmol).

To create a 1 M 1,2-dibromoethane in DMF solution, to a 40 mL vial containing 14 mL of DMF was added 1,2-dibromoethane (1.17 mL, 13.53 mmol).

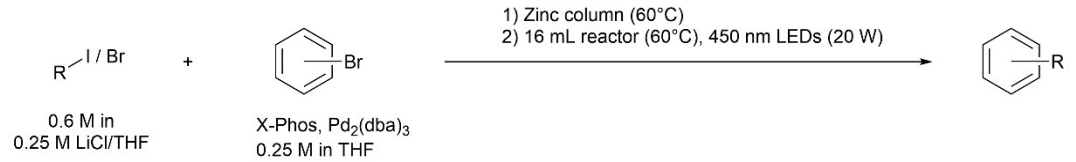
A 5 mL slug of 2 M TMSCl/THF solution was injected into the system and through the column reactor. At the end of the slug injection pumping was stopped immediately (TMSCl slug sat on the column). The injection loop was then refilled and a second 5 mL TMSCl slug was pumped through the column, thus creating effectively a 10 mL 2 M TMSCl/THF slug. The pumps were again stopped immediately after the end of the second slug injection.

The injection loop was then filled with 5 mL of 1 M dibromoethane/DMF solution and pumped through the column. Bubbling and a ~0.5 bar pressure increase was observed as the slug passed through the reactor. At the end of the slug injection, pumping was stopped immediately and a second 5 mL dibromoethane slug was loaded into the loop. Pumping was resumed resulting in effectively a 10 mL 1 M dibromoethane/DMF slug passing through the zinc column.

Once the second dibromoethane injection had finished pump A (THF) flowrate was increased to 2 mL/min (pump B remained unchanged at 1 mL/min). Pumping was continued for approximately six minutes – until all bubbles had been removed from the 16 mL reactor.

The zinc column is now ready for organozinc generation or timing experiment. Note: the column should be used immediately at this point to prevent deactivation of the metal surface.

S2.5 – General Method B: Flow Negishi Library Synthesis



Reactions were performed under automation using Asia Manager software, with the zinc column having been brought to an active state beforehand using General Method A. Effective zinc column volume was determined using the iodine timing experiment (see S3 – Zinc Column Iodine Timing Experiment).

The rack for Automated Reagent Injector A was loaded with 0.25 M solutions of aryl halide in THF. Reagent vials were prepared as follows: To an 8 mL vial was added aryl halide (0.75 mmol, 1 eq), X-Phos (36 mg, 0.08 mmol, 0.1 eq) and $Pd_2(dba)_3$ (34 mg, 0.04 mmol, 0.05 eq). The vial was sealed and purged with nitrogen for 5 minutes before THF (3 mL) was added. The vial was then sonicated to ensure a homogenous solution. Where aryl halide solubility was poor, DMF could be used in place of THF.

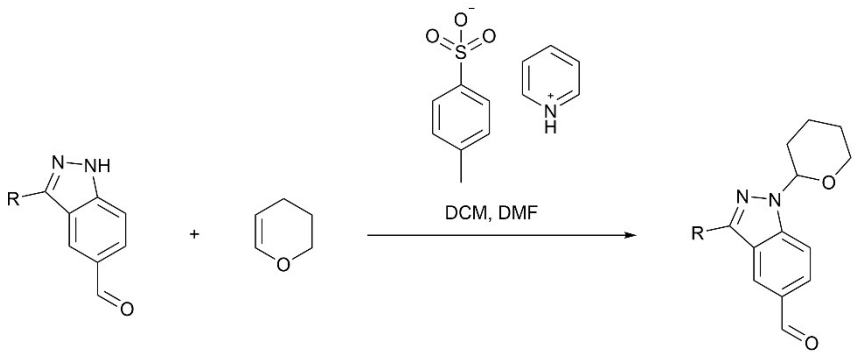
The rack for Automated Reagent Injector B was loaded with 0.6 M solutions of alkyl halide in 0.25 M LiCl/THF. Reagent vials were prepared as follows: To an 8 mL vial was added alkyl halide (1.5 mmol). The vial was sealed and purged with nitrogen for 5 minutes before THF (1.25 mL) and 0.5 M LiCl/THF (1.25 mL) were added. The vial was shaken to ensure a homogenous solution.

Reactions were performed with an approximately 40-minute residence time on the 16 mL reactor – this resulted in flow rates of pump A (THF) 178 µL/min and pump B (0.5 M LiCl in THF) 222 µL/min.

Reactions were performed on a 0.06 mmol (240 µL slug, approximately 13 mg) scale, with 3 equivalents of alkyl zinc (299 µL slug, 0.18 mmol). The zinc column and 16 mL reactor heaters were both set to 60°C and the back pressure was set to 2 bar. The 16 mL reactor was irradiated with flexible 450 nm LEDs (approx. 20 W) wrapped around the reactor. Each reaction slug was collected into an 8 mL vial. Slugs were collected with a 125 µL pre-slug and 375 µL post-slug to ensure all material was collected.

Reaction slugs were scheduled using ‘efficient’ parallel scheduling, enabling multiple slugs to be within the system at the same time – resulting in a new product being collected every 23 minutes. Crude mixtures were analysed by LCMS to check the outcome of the Negishi reactions. A mass ion peak corresponding to product was observed in 20 out of 21 reactions.

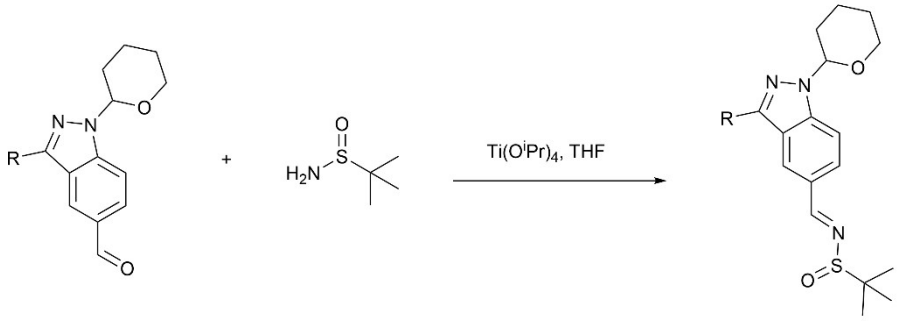
S2.6 – General Method C: THP Protection



To a solution of 1H-indazole (1 eq) in DCM (3 mL/mmol) and DMF (0.6 mL/mmol) was added Pyridinium p-Toluenesulfonate (0.1 eq) and 3,4-Dihydro-2H-pyran (3 eq). The reaction was stirred overnight at room temperature.

The reaction was partitioned between DCM and sat. $NaHCO_3$. The layers were separated, the organics were washed with brine 3 times before being dried through a phase separator and evaporated. The crude was loaded onto Isolute HM-N and purified by automated flash chromatography to yield THP-protected indazole.

S2.7 – General Method D: Sulfinyl Imines Formation



To a solution of aldehyde (1 eq) and 2-methyl-2-propanesulfinamide (1.05 eq) in THF (0.7 mL/mmol) was added under a nitrogen atmosphere Titanium(IV) isopropoxide (2 eq). The reaction was stirred at 70°C overnight.

The reaction mixture was cooled to room temperature and then further down to 0°C in an ice bath. To the reaction was then added brine (2.3 mL/mmol), heptane (6.9 mL/mmol) and ethyl acetate (6.9 mL/mmol), the mixture was then stirred vigorously for 10 minutes.

The reaction was filtered through a Celite 545 cartridge, washing with further ethyl acetate until no more elution observed by TLC spot. The organics were washed with brine, dried with $MgSO_4$, filtered, and evaporated to give the crude product.

Crude product was loaded onto Isolute HM-N and purified by automated flash chromatography to yield sulfinyl imine product.

S2.8 – General Method E: Magnesium Column Initial Activation

The magnesium column was activated using the previously published method with minor modifications.[2]

If a column timing experiment was to be performed immediately after activation, then Pump B selection valve position was set to 0.5 M LiCl/THF, otherwise the 0.5 M 1-chlorobutane (BuCl) feed can be used instead.

Pump A and B flow rates were both set to 1 mL/min, the back pressure regulator set to 1 bar, the column reactor heated to 40°C and the16 mL reactor at room temperature.

A 4.8 mL slug of 0.5 M DIBAL in toluene solution was injected into the system and through the column reactor (small bubbles were observed leaving the Mg column). At the end of the slug injection pumping was stopped immediately (DIBAL slug sat on the column).

The injection loop was then filled with a 5 mL slug of a mixed solution of 2 M TMSCl (3.1 mL, 24 mmol) and 0.24 M 1,2-dibromoethane (0.25 mL, 2.88 mmol) in 1:1 THF (6 mL): Toluene (6 mL). Pumping was resumed (small bubbles observed leaving the Mg column) and again immediately stopped at the end of the slug. The injection loop was filled with a second 5 mL slug of this activation mixture which was then also pumped through the column.

Once the second injection of activation solution had finished pump A (THF) flow rate was increased to 2.5 mL/min (pump B remained unchanged at 1 mL/min). Pumping was continued for 5 minutes to ensure removal of the activation solution from the system.

The magnesium column is now ready for organomagnesium generation or timing experiment (timing experiment must be initiated immediately to prevent the column losing activity).

If the column is filled with 0.5 M BuCl/THF, the column can be cooled to room temperature and re-activated using shorter General Method F at a later point in time.

S2.9 – General Method F: Magnesium Column Rapid Re-activation

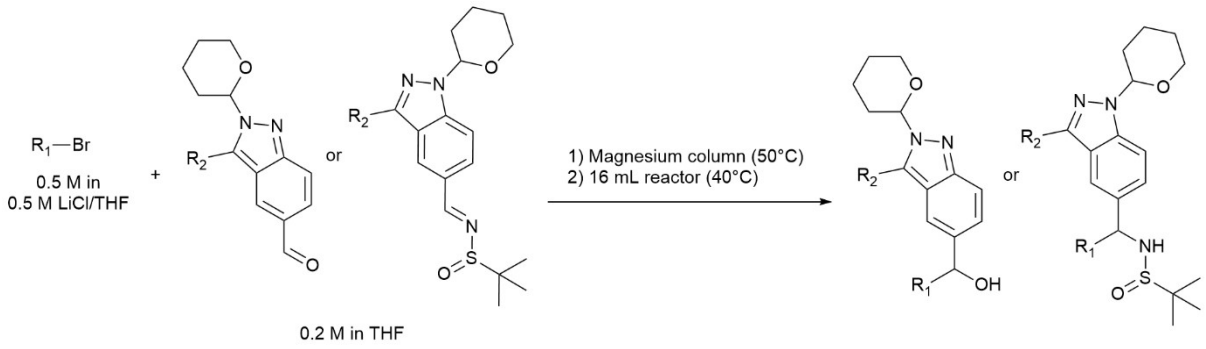
If not already, Pump B selection valve position was set to 0.5 M 1-chlorobutane (BuCl) in THF and the magnesium column was filled with 0.5 M BuCl/THF solution.

System pumps were stopped, back pressure regulator set to 2 bar and column heater set to 80°C. Once the magnesium column had been held at 80°C for 30 minutes system pumps were started – Pump A (THF) at 250 µL/min, Pump B (0.5 M BuCl/THF) at 500 µL/min.

After 10 minutes a 500 µL slug of 0.2 M iodine (305 mg, 1.2 mmol) in 0.5 M LiCl/THF (6 mL) was injected through RIM channel A. Decolourisation of the slug after mixing with the output stream from the magnesium column indicated successful reactivation of the magnesium column – and that organomagnesium is being formed.

If the subsequent experiment to be performed is a timing experiment (i.e. the carrier solvent needs to be 0.5 M LiCl/THF) then the column heater is set to 50°C, the Pump B selection valve set to 0.5 M LiCl/THF and pumping commenced with flow rates Pump A (THF) at 250 µL/min, Pump B (0.5 M LiCl/THF) at 500 µL/min. After pumping for 10 minutes all residual 1-chlorobutane has been flushed from the column – timing experiments can now be performed.

S2.10 – General Method G: Flow Grignard Library Synthesis



Reactions were performed under automation using Asia Manager software, with the magnesium column having been brought to an active state beforehand using General Method F. Effective magnesium column volume had been determined beforehand using an iodine timing experiment (see S7 – Magnesium Column Iodine Timing Experiment).

The rack for Automated Reagent Injector A was loaded with 0.2 M solutions of electrophiles (aldehyde or sulfinyl imine substrates) in THF.

The rack for Automated Reagent Injector B was loaded with 0.5 M solutions of aryl bromides in 0.5 M LiCl/THF.

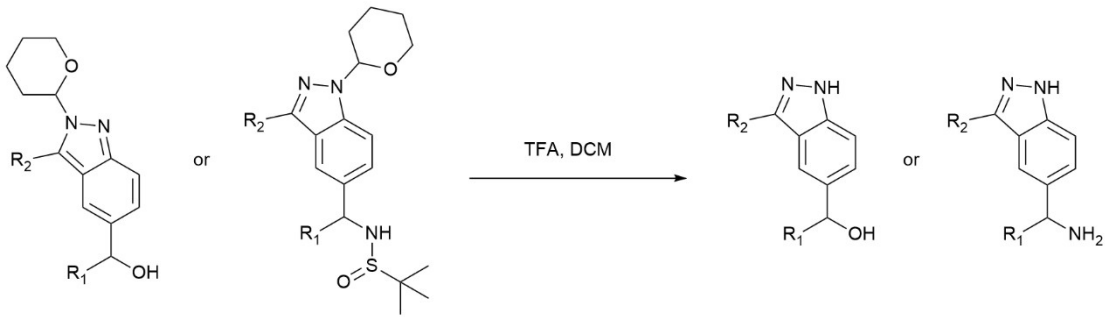
Reactions were performed with a 20-minute residence time on the 16 mL reactor – this resulted in flow rates of pump A (THF) 444.5 µL/min and pump B (0.5 M BuCl/THF) 355.5 µL/min. For clarity: Pump B selection valve was set to the 0.5 M BuCl/THF position.

Reactions were performed on a 0.25 mmol scale, with 2 equivalents of aryl bromide (0.5 mmol). The magnesium column reactor was set to 50°C, the 16 mL reactor set to 40°C, the back pressure set to 2 bar. Each reaction slug was collected into a 30 mL vial using a 3D printed rack (see S13 – 3D Printed Custom Collection Racks). Slugs were collected with a 1 mL pre-slug and 3 mL post-slug to ensure all material was collected.

Reaction slugs were scheduled using ‘efficient’ parallel scheduling, this resulted in multiple slugs within the system at the same time – resulting in a new product being collected every 16 minutes.

Collected reaction slugs were concentrated under reduced pressure by Biotage V10 (mixed volatiles method). DCM (2 mL) was then added, salts were allowed to settle. Crude mixtures were then analysed by LCMS to check the outcome of the Grignard reactions. A mass ion peak corresponding to product was observed in 70 out of 76 reactions.

S2.11 – General Method H: Batch Parallel Deprotection



Crude Grignard reaction mixtures (from General Method G, 0.25 mmol) were suspended in DCM (3 mL), trifluoroacetic acid (0.38 mL, 4.9 mmol) was then added and the vial sealed.

For OH (aldehyde substrates) targets the vials were shaken at 20°C for 1.5 hours. For NH_2 (sulfinyl imine substrates) targets the vials were shaken at 40°C for 2 hours.

Crude reaction mixtures were concentrated to dryness by Biotage V10 (mixed volatiles method). To the residue was added DCM (2 mL) followed by saturated aqueous sodium bicarbonate solution (0.5 mL). Vials were shaken until effervescence ceased and then concentrated again by Biotage V10 (mixed volatiles and high boiling point method).

Residual water (approximately 250-300 µL) remained, DMSO (2.3 mL) was therefore added to form a 9:1 DMSO:Water 100 mM solution after sonication and warming. This stock solution could then be diluted to make an LCMS analysis plate along with plates suitable for Crude Reaction Screening (CRS) assays as required. The bulk crude reaction mixture was stored to allow purification once compounds of interest had been identified, some of which were successfully purified after 18 months of storage at room temperature in the dark.

S3 – Zinc Column Iodine Timing Experiment

With the zinc column in an active state (using General Method A), the back pressure regulator set to 2 bar, and both the column heater and 16 mL reactor set to 60°C, pumping was commenced with Pump A (THF) at 261 µL/min, Pump B (0.5 M LiCl/THF) at 544 µL/min.

At timepoint t_0 a 2 mL slug of 0.6 M 1-Boc-4-iodomethylpiperidine (585 mg, 1.8 mmol) in 0.25 M LiCl/THF (3 mL, a 1:1 ratio of THF and 0.5 M LiCl/THF stock solution) was injected into channel B, through the Zn column. **Note:** once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At timepoint t_0 + 2 minutes a 4 mL slug of 0.2 M iodine (406 mg, 1.6 mmol) in THF (8 mL) was injected into channel A. Iodine colour was observed at the T-mixer approximately 30-45 seconds later. During the injection period of the iodine slug, the organozinc slug is expected to elute from the column, resulting in decolourisation of the iodine (Figure 3).

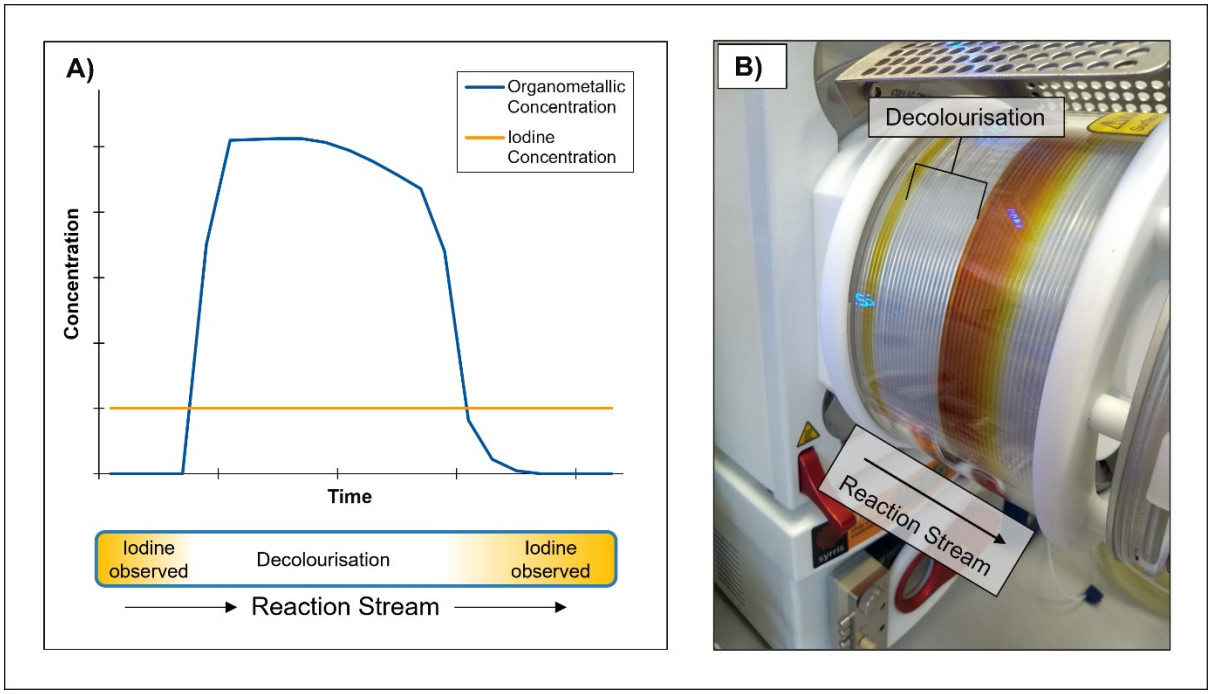


Figure 3 - A) A graphical representation of the iodine timing experiment concept. When organometallic concentration is greater than the iodine concentration decolourisation is observed. B) A band of decolourisation passing through the 16mL reactor

From timepoint t_0 + 21 minutes the reactor output stream was collected into 2 mL vials, changing vial position every 20 seconds, allowing accurate back-calculation of the time the two slugs met at the T-mixer.

Once the iodine slug has been collected the pumps can be stopped and the reactors cooled. The vial where full decolourisation is observed for the first and last time should be noted and the collection time point for those vials determined (Figure 4). The decolourisation window is typically 3-4 minutes long (some streaking is observed when alkyl halides are made up in just THF and is dependent of the nature of the alkyl halide itself), an example from our system gave decolourisation between 31 minutes 20 seconds to 34 minutes 20 seconds.

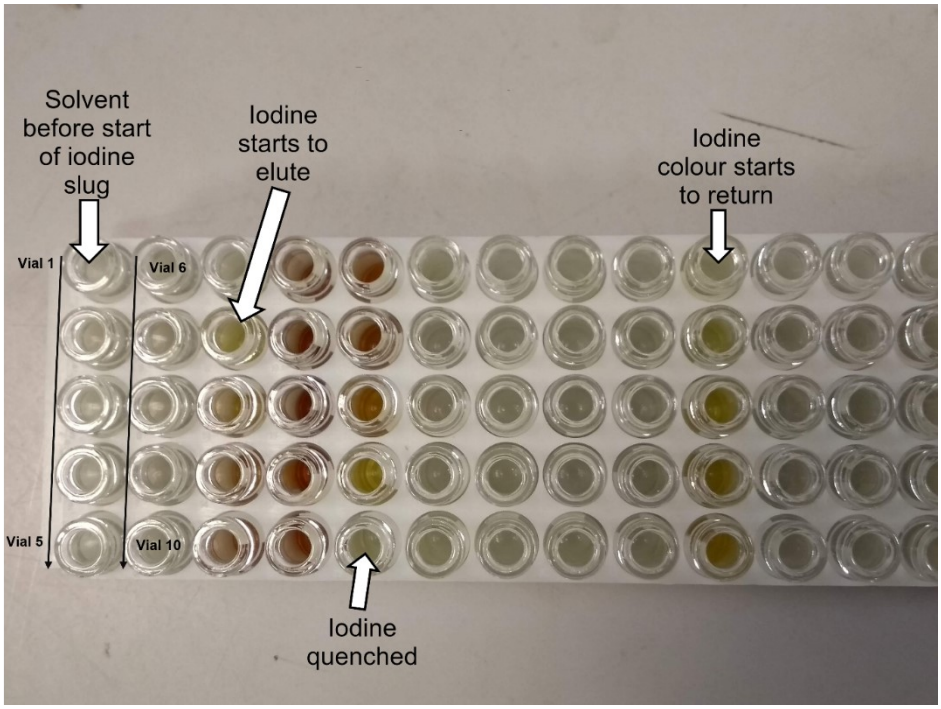


Figure 4 - A typical example of the vials collected from an iodine timing experiment (note – picture was not taken during the experiment reported here)

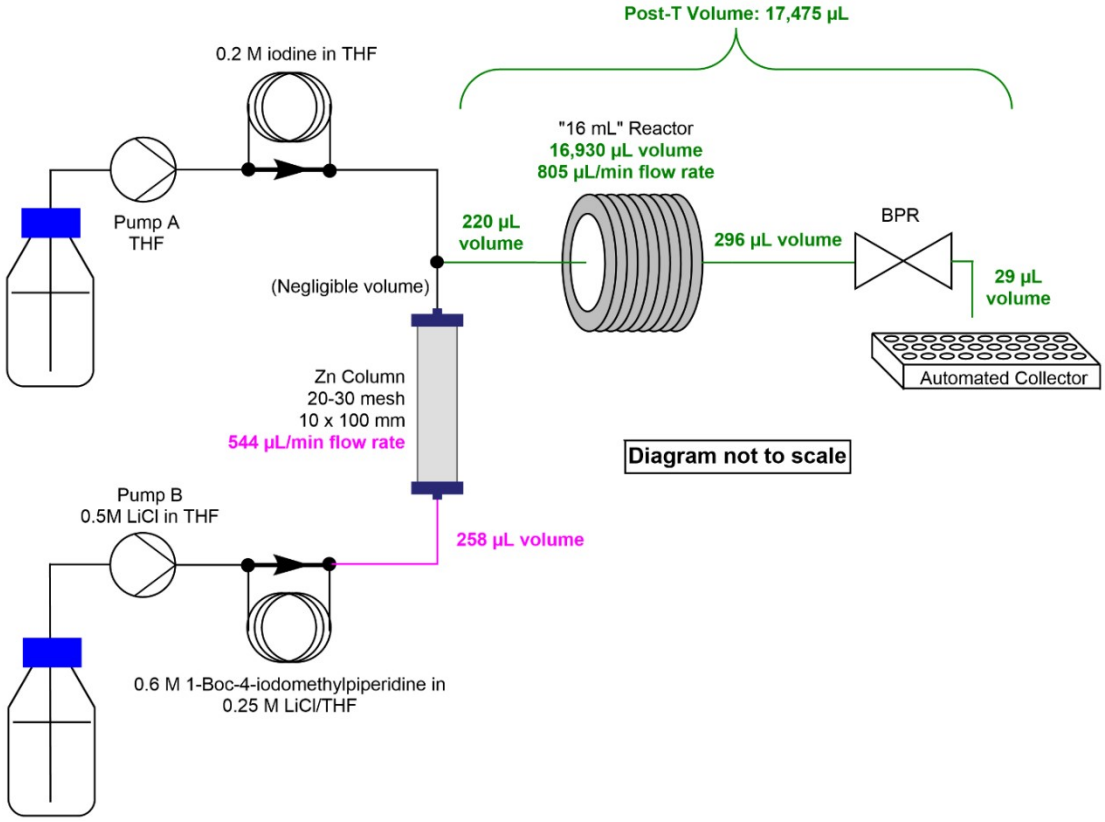


Figure 5 - Fluidic diagram with key volumes and flow rates required for organometallic column volume determination labelled

The volume of the fluidic system after the T-mixer is determined by combining the known volumes of each pipe and the 16 mL reactor. For our system that value was 17475 µL (Figure 5). To determine the time it takes for a slug to get from the T-mixer to the collector, the volume after the T-mixer was divided by the flow rate through that section (805 µL/min). For our system, approximately 21 minutes and 40 seconds.

The time at which the Negishi slug was at the T-mixer was therefore determined by subtracting the timing of T-mixer to collector (just calculated) from the time at which decolourisation was first collected in a vial (Equation 1). In this example the calculation is 31 minutes 20 seconds minus 21 minutes 40 seconds, resulting in 9 minutes 40 seconds. This Indicates that the start of the Negishi slug was at the T-mixer at 9 minutes 40 seconds.

$$Time\ slug\ at\ Tmix\ = Time\ of\ decolourisation - \left(\frac{Post\ T\ volume}{Post\ T\ flow\ rate}\right)$$

Equation 1 - Formula used to back-calculate the time at which the organozinc slug was first present at the T-mixer

The flow rate through the zinc column (544 µL/min) was multiplied by the time taken to get to the T-mixer to determine the apparent volume of the system up to this point (5259 µL in this example). From this, the volume of pipe between the injection loop and the zinc column (258 µL) was subtracted (Equation 2). The remaining volume is the effective volume of the zinc column, accounting for any delay caused by interaction with the metal surface. In this example, the volume was therefore determined to be 5001 µL.

$$Effective\ Zn\ Volume = (Time\ slug\ at\ Tmix\ \times Column\ flow\ rate) - Pipe\ volume\ to\ Zn$$

Equation 2 - Formula used to determine the effective volume of the zinc column, to account for the chromatographic effect of the metal surface

The effective volume is significantly greater than the actual column volume of 3475 µL determined during column preparation, by measuring the change in column mass before and after wetting the column with solvent.

S4 – Studies of Zinc Column Activity Durability

To determine the quantity of solvent than can be pumped through the zinc column before activity begins to fall, a series of experiments were performed where slugs of aryl halide were injected with increasing solvent gaps between each slug.

Slugs were timed to meet an iodine solution; decolourisation would be expected to be observed when Negishi reagent has been successfully formed. The degree of quenching of iodine colour was monitored 120 µL after the T-mixer (at the point of entry to the 16 mL reactor), a decrease in apparent slug duration or no decolourisation at all would indicate a loss of zinc activity.

Preparation for durability experiments is the same procedure each time:

Two stock solutions were prepared, for repeated injection during the experiment: 0.6 M ethyl bromoacetate (3.01 g, 2 mL, 18 mmol) in THF (30 mL), and 0.2 M iodine (1.02 g, 4 mmol) in THF (20 mL).

Experiments could begin once the zinc column was in an active state (using General Method A), the back pressure regulator set to 2 bar, and both the column heater and 16 mL reactor set to 60°C, pumping was commenced with Pump A (THF) at 261 µL/min, Pump B (0.5 M LiCl/THF) at 544 µL/min.

S4.1 – 2 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent

At t_0 the first 2 mL slug of alkyl halide was injected through channel B, passing through the zinc column at a flow rate of 544 µL/min. Note: once the slug is injected, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 4 minutes a 2.5 mL slug of 0.2 M iodine in 0.5 M LiCl/THF was injected through channel A. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organozinc reagent would elute (at approximately t_0 + 8 minutes) and would still be passing through the mixer after the organozinc slug had finished.

This procedure was repeated multiple times with increasing solvent gaps between each alkyl halide injection. Table 1 summarises all the key injection timings, the volume of solvent spacer between each organohalide slug and observations regarding decolourisation of the iodine slugs.

Volume of 0.5 M LiCl/THF spacer ahead of organohalide slug (mL)	0.6 M ethyl bromoacetate 2 mL injection timepoint (t_0 + x minutes)	0.2 M iodine 2.5 mL injection timepoint (t_0 + x minutes)	Anticipated decolourisation timepoint (t_0 + x minutes)	Observations
N/A	0	4	7mins 40s	Decolourisation slug seen at 8min20s, >6min long
6	15	19	22mins 40s	Decolourisation slug seen at 23min, >6min long
8.7	35	39	42mins 40s	Decolourisation slug seen at 43min45s, >6min long
14.2	65	69	72mins 40s	Decolourisation slug seen at 74min30s, >5min long
14.2	95	99	102mins 40s	Decolourisation slug seen at 104min20s, >5min long
22.3	140	147	151mins 40s	No decolourisation observed

Table 1 - Summary of zinc 2 mL slug durability experiment with 0.5 M LiCl/THF flowing through the column between slugs

The results show that zinc activity can be maintained when the solvent spacer between 2 mL slugs is approximately 14 mL; when the solvent spacer is increased to 22 mL, however, activity is lost. This demonstrates that zinc columns are much more durable to washing with 0.5 M LiCl/THF than magnesium (see S8 – Studies of Magnesium Column Activity Durability), which on this scale slug the magnesium column lost activity when washing with between 8 and 13 mL of 0.5M LiCl/THF between slugs. In this example, a significant broadening of the slug is observed: decolourisation lasts for more than 6 minutes, when the initial injection is below 4 minutes.

On sporadic occasions we have observed either a streaking or catch/release type behaviour by some alkyl halides. See Section 6 for further discussion, however in summary injecting a slug of dilute activation solution (0.5 M TMSCl & 0.2 M 1,2-dibromoethane in THF) after the problematic alkyl halide helps to clear the zinc surface. This observation is further supported by investigations by Hanada *et al.*, demonstrating by Fluorescence Lifetime Imaging Microscopy (FLIM) the ability for TMSCl to solubilise organozinc reagents from the metal surface.[3] An alternative to injecting an activation injection to 'wash' the column would be to use a dilute activation solution as the system solvent flowing through the zinc column, such as described in this recent publication from Abdiaj *et al.*.[4]

S4.2 – 0.5 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent

At t_0 the first 0.5 mL slug of alkyl halide was injected through channel B, passing through the zinc column at a flow rate of 544 µL/min. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 4 minutes a 2.5 mL slug of 0.2 M iodine in 0.5 M LiCl/THF was injected through channel A. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organozinc reagent would elute (at approximately t_0 + 8 minutes) and would still be passing through the mixer after the organozinc slug had finished.

In the same manner as the other durability tests, it was intended to repeat the procedure multiple times with increasing solvent gaps between each alkyl halide injection. However, despite numerous attempts with several alkyl halides, iodine decolourisation with a 0.5 mL slug could not be observed, even for the first injection.

This result is confusing, the Negishi library generation experiment (General Method B) clearly demonstrates that the column is competent and maintains activity even with slugs smaller than the 0.5 mL used here – yielding cross-coupled products reliably. Yet, despite our efforts, visualisation by iodine quenching was not possible. It is therefore postulated that the slight slug broadening that occurs whilst passing through the column results in a concentration below the threshold to fully quench the iodine colour when very small slugs are processed (see 2 mL durability experiment above: approximately 4-minute injections result in a 5-6 minute long period of decolourisation).

S4.3 – 2 mL Slug Durability with THF Carrier Solvent

At t_0 the first 2 mL slug of alkyl halide was injected through channel B, passing through the zinc column at a flow rate of 544 µL/min. Note: instead of switching the injection loop back to fill mode, the loop was left open – meaning 3 mL of pure THF followed the first slug through the zinc column.

At t_0 + 4 minutes a 2.5 mL slug of 0.2 M iodine in 0.5 M LiCl/THF was injected through channel A. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organozinc reagent would elute (at approximately t_0 + 8 minutes) and would still be passing through the mixer after the organozinc slug had finished.

Like the first two experiments in the 2 mL slug durability experiment, a second injection was performed 15 minutes later. As Table 2 summarises, all column activity had been lost – demonstrating the high sensitivity of the Zinc column activity to pure THF.

Volume of solvent spacer ahead of organohalide slug (mL)	**0.6 M ethyl bromoacetate 2 mL injection timepoint (t_0 + x minutes)**	**0.2 M iodine 2.5 mL injection timepoint (t_0 + x minutes)**	**Anticipated decolourisation timepoint (t_0 + x minutes)**	**Observations**
N/A	0	4	7mins 40s	Decolourisation slug seen at 8min20s, >6min long
6 (3 mL THF and then 3 mL 0.5 M LiCl/THF)	15	19	22mins 40s	No decolourisation

Table 2 - Summary of zinc 2 mL slug durability experiment with with pure THF flowing through the column between slugs

S5 – Negishi Flow Library Synthesis

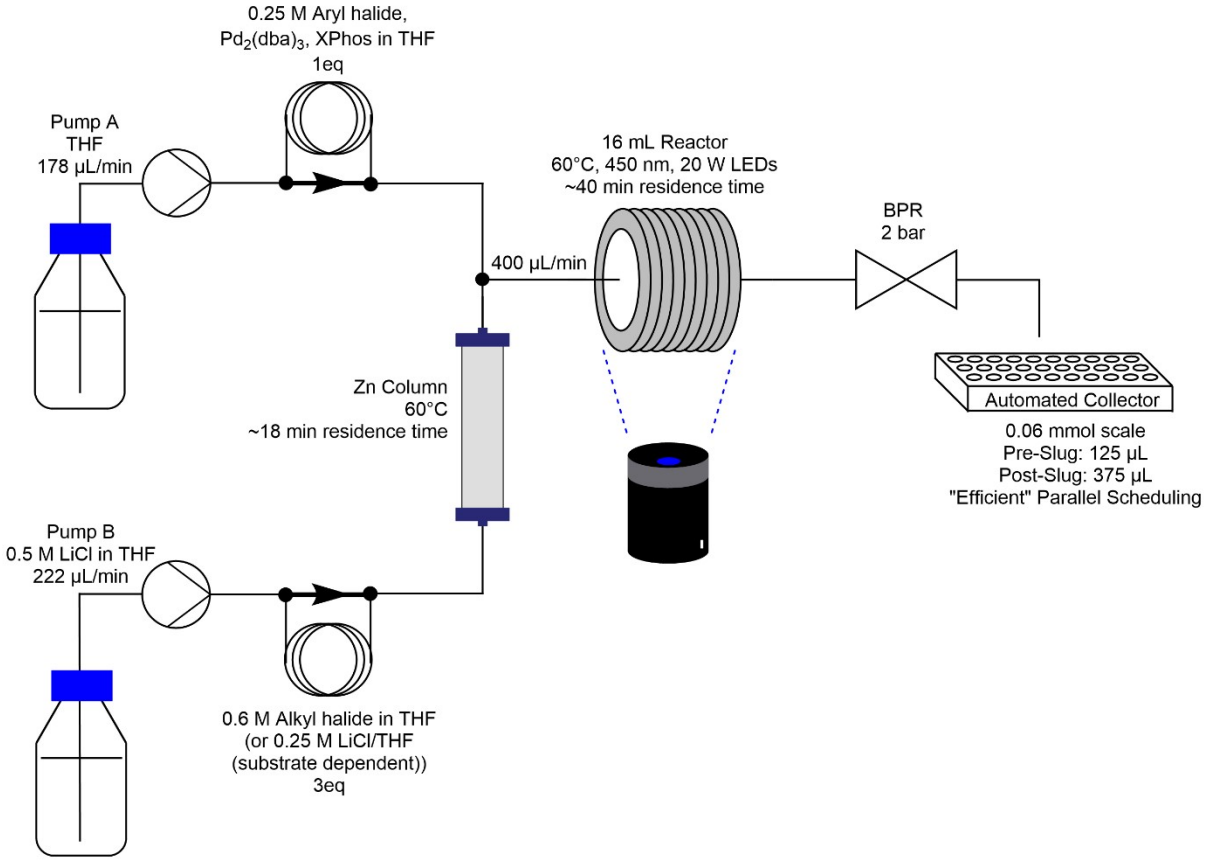
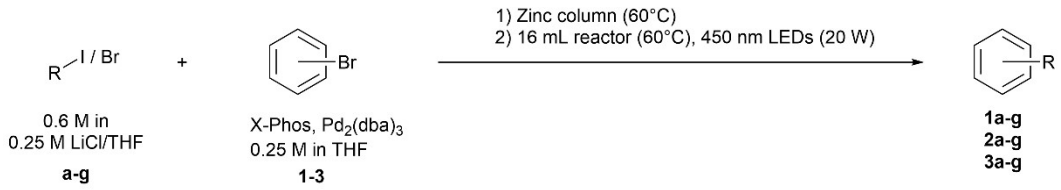


Figure 6 - Negishi library synthesis fluidic scheme



Negishi library synthesis was performed according to General Method B, to give the crude title compounds suitable for aliquoting and activity assessment by crude reaction screening (CRS). Compounds of interest could be re-synthesised on a larger scale, enabling isolation of the purified product.

To enable a rapid synthesis and screening cycle, by design the library consists of crude reaction mixtures. As a result, analysis is limited to HRMS for all compounds that were not deemed to be of interest and thus not re-synthesised on a scale suitable for purification and isolation.

For the analytical data generated for the library, see Appendix 1 – HRMS Data for Negishi CRS Library.

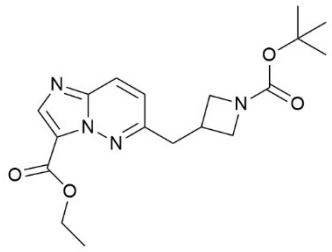
S5.1 – Resynthesis and Purification of Compounds of Interest

Compounds of interest were re-synthesised according to General Method B, however the reaction scale was increased to 0.5 mmol (2 mL injection of aryl halide, 2.5 mL injection of alkyl halide).

Crude reaction mixtures were diluted with ethyl acetate and then dilute aqueous ammonium chloride solution was added. The layers were separated and the aqueous back-extracted with ethyl acetate once. The organics were combined and dried over $MgSO_4$, filtered and then concentrated under reduced pressure.

Crude material was loaded onto Isolute HM-N (DCM/methanol), dried and then purified by automated flash chromatography (Combiflash 300+, Silica 24 g RediSep column) eluting with 0 to 100% Ethyl Acetate in Heptane. Product fractions were combined and concentrated to give product.

S5.1.1 – tert-butyl 3-{[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]methyl}azetidine-1-carboxylate, 1a



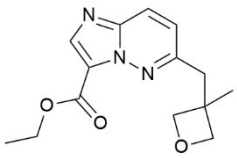
Product was retained on the column after heptane/ethyl acetate gradient, therefore a gradient of DCM to 15% methanol in DCM was then also applied, yielding tert-butyl 3-{[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]methyl}azetidine-1-carboxylate (52 mg, 0.14 mmol, 28%) as a yellow solid.

^{1}H NMR (600 MHz, DMSO) δ 8.33 (s, 1H), 8.22 (d, J = 9.4 Hz, 1H), 7.41 (d, J = 9.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 4.09 – 3.95 (br m, 2H), 3.76 – 3.61 (br m, 2H), 3.22 (d, J = 7.8 Hz, 2H), 3.07 – 2.99 (m, 1H), 1.37 (s, 9H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO) δ 158.6, 156.0, 155.5, 141.7, 140.7, 126.4, 122.2, 119.6, 78.8, 60.7, 55.1(b), 53.9(b), 38.8, 28.6, 27.6, 14.8.

HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{24}N_4O_4$): 360.1798, Mass found: 360.1802.

S5.1.2 – ethyl 6-[(3-methyloxetan-3-yl)methyl]imidazo[1,2-b]pyridazine-3-carboxylate, 1b



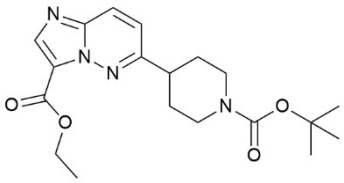
A Silica 4 g RediSep column was used instead, yielding ethyl 6-[(3-methyloxetan-3-yl)methyl]imidazo[1,2-b]pyridazine-3-carboxylate (37.5 mg, 27.24%) as an orange oil.

^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 8.22 (d, J = 9.4 Hz, 1H), 7.40 (d, J = 9.4 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.32 (d, J = 5.8 Hz, 2H), 3.25 (s, 2H), 1.34 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO) δ 158.6, 154.8, 141.6, 140.8, 126.2, 122.9, 119.6, 81.7, 60.7, 43.0, 39.4, 23.7, 14.8.

HRMS (ESI^{+}) Mass required for exact match ($C_{14}H_{17}N_3O_3$): 275.1270, Mass found: 275.1278.

S5.1.3 – tert-butyl 4-[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]piperidine-1-carboxylate, 1d



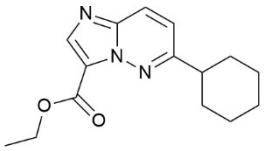
Product was not purified by normal phase chromatography. Instead of loading onto Isolute HM-N, crude material was dissolved in 4 mL of 10% MeOH/DMSO and then over two injections purified by preparative HPLC automated chromatography (ISCO ACCQ HP125, Gemini-NX C18 Dimensions: 30 mm x 250 mm 5 µm) eluting with 5 to 95% acetonitrile/0.1% formic acid in Water/0.1% formic acid. Product containing fractions were combined, acetonitrile was removed under reduced pressure and then the residual aqueous was freeze dried to yield tert-butyl 4-[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]piperidine-1-carboxylate (10.3 mg, 0.03 mmol, 6%) as an orange gum.

^{1}H NMR (600 MHz, DMSO) δ 8.33 (s, 1H), 8.23 (d, J = 9.4 Hz, 1H), 7.52 (d, J = 9.4 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.14 – 4.01 (br m, 2H), 3.14 – 3.07 (m, 1H), 3.05 – 2.79 (br m, 2H), 1.98 – 1.91 (m, 2H), 1.73 – 1.62 (m, 2H), 1.43 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO) δ 159.7, 158.5, 154.3, 141.9, 140.8, 126.6, 121.0, 119.6, 79.1, 60.6, 44.1(b), 43.3(b), 41.6, 30.8, 28.6, 14.7.

HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{26}N_4O_4$): 374.1954, Mass found: 374.1957.

S5.1.4 – ethyl 6-cyclohexylimidazo[1,2-b]pyridazine-3-carboxylate, 1e



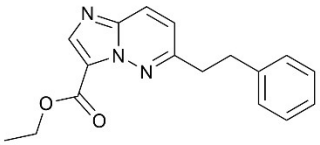
A Silica 12 g Gold RediSep column was used instead, yielding ethyl 6-cyclohexylimidazo[1,2-b]pyridazine-3-carboxylate (8.9 mg, 7.57%) as a white film.

^{1}H NMR (600 MHz, DMSO) δ 8.31 (s, 1H), 8.20 (d, J = 9.4 Hz, 1H), 7.48 (d, J = 9.4 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.91- 2.84 (m, 1H), 1.98 – 1.92 (m, 2H), 1.87 – 1.80 (m, 2H), 1.76 – 1.69 (m, 1H), 1.63 – 1.54 (m, 2H), 1.47 – 1.37 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.32 – 1.23 (m, 1H).

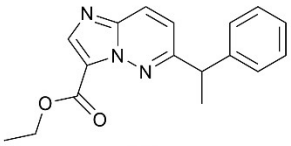
^{13}C NMR (150 MHz, DMSO) δ 161.1, 158.5, 141.9, 140.6, 126.4, 121.0, 119.6, 60.6, 43.9, 31.9, 26.1, 25.9, 14.7.

HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{19}N_3O_2$): 273.1477, Mass found: 273.1479.

S5.1.5 – ethyl 6-(2-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, 1f & ethyl 6-(1-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, S-1



1f



S-1

Two peaks with product mass were identified by crude LCMS when using (2-iodoethyl)benzene. It appears that the iodo(2-phenylethyl)zinc species formed in the first step can undergo rearrangement/isomerisation leading to a mix of the desired 2-phenylethyl product alongside the 1-phenylethyl isomer.

The two isomers were successfully separated using the standard purification conditions, with only one mixed fraction being discarded. Purification gave ethyl 6-(2-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, compound 1f, (41 mg, 0.14 mmol, 27.76%) as a yellow oil and ethyl 6-(1-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, compound S-1, (37 mg, 0.13 mmol, 25.06%) as a yellow oil. Combined yield of approximately 53%.

ethyl 6-(2-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, 1f:

^{1}H NMR (400 MHz, DMSO) δ 8.32 (s, 1H), 8.21 (d, J = 9.4 Hz, 1H), 7.46 (d, J = 9.4 Hz, 1H), 7.35 – 7.26 (m, 4H), 7.22 – 7.16 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.25 – 3.19 (m, 2H), 3.14 – 3.07 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO) δ 158.5, 156.8, 141.8, 141.2, 140.6, 128.9, 128.8, 126.6, 126.2, 122.2, 119.5, 60.6, 36.9, 34.0, 14.7.

HRMS (ESI^{+}) Mass required for exact match ($C_{17}H_{17}N_3O_2$): 295.1321, Mass found: 295.1324.

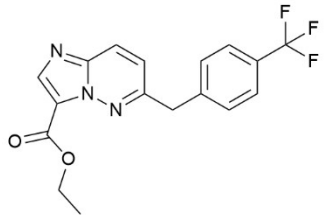
ethyl 6-(1-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate, S-1:

^{1}H NMR (400 MHz, DMSO) δ 8.34 (s, 1H), 8.17 (d, J = 9.4 Hz, 1H), 7.39 – 7.30 (m, 5H), 7.27 – 7.21 (m, 1H), 4.48 (q, J = 7.1 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.70 (d, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO) δ 159.6, 158.6, 143.9, 141.7, 140.8, 129.2, 128.1, 127.3, 126.5, 121.6, 119.9, 60.7, 44.9, 20.2, 14.7.

HRMS (ESI^{+}) Mass required for exact match ($C_{17}H_{17}N_3O_2$): 295.1321, Mass found: 295.1323.

S5.1.6 – ethyl 6-{[4-(trifluoromethyl)phenyl]methyl}imidazo[1,2-b]pyridazine-3-carboxylate, 1g



Reaction was performed on a 1.5 mmol scale (3 x 0.5 mmol scale injections), yielding ethyl 6-{[4-(trifluoromethyl)phenyl]methyl}imidazo[1,2-b]pyridazine-3-carboxylate (376.6 mg, 1.08 mmol, 71.88%) as a beige solid.

^{1}H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 8.24 (d, J = 9.4 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.62 – 7.57 (m, 2H), 7.43 (d, J = 9.4 Hz, 1H), 4.38 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO) δ 158.5, 155.8, 143.1, 141.7, 140.9, 130.4, 128.0, 126.9, 126.0, 124.8, 122.1, 119.7, 60.7, 40.9, 14.7.

^{19}F NMR (376 MHz, DMSO) δ -60.9.

HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{14}N_3O_2F_3$): 349.1038, Mass found: 349.1043.

S6 – Studies of Cross Contamination During Resynthesis of Compounds of Interest (Negishi Couplings)

When the compounds of interest were 'scaled up' (0.5 mmol scale), we noticed some cross contamination (<10%) occurred with 1-Boc-3-(iodomethyl)azetidine **a** (cross contamination was only seen with alkyl iodide **a** during our experiments). As discussed in S4.1, in our studies we found that TMSCl appeared to help release 'sticky' alkyl halides from the metal surface. To investigate this phenomenon further we modified our Negishi coupling set-up by adding an inline detector[5] just after the Zn column (Figure 7). We then performed sequential couplings with alkyl iodides **a** and **f**, looking for cross-contamination by LCMS.

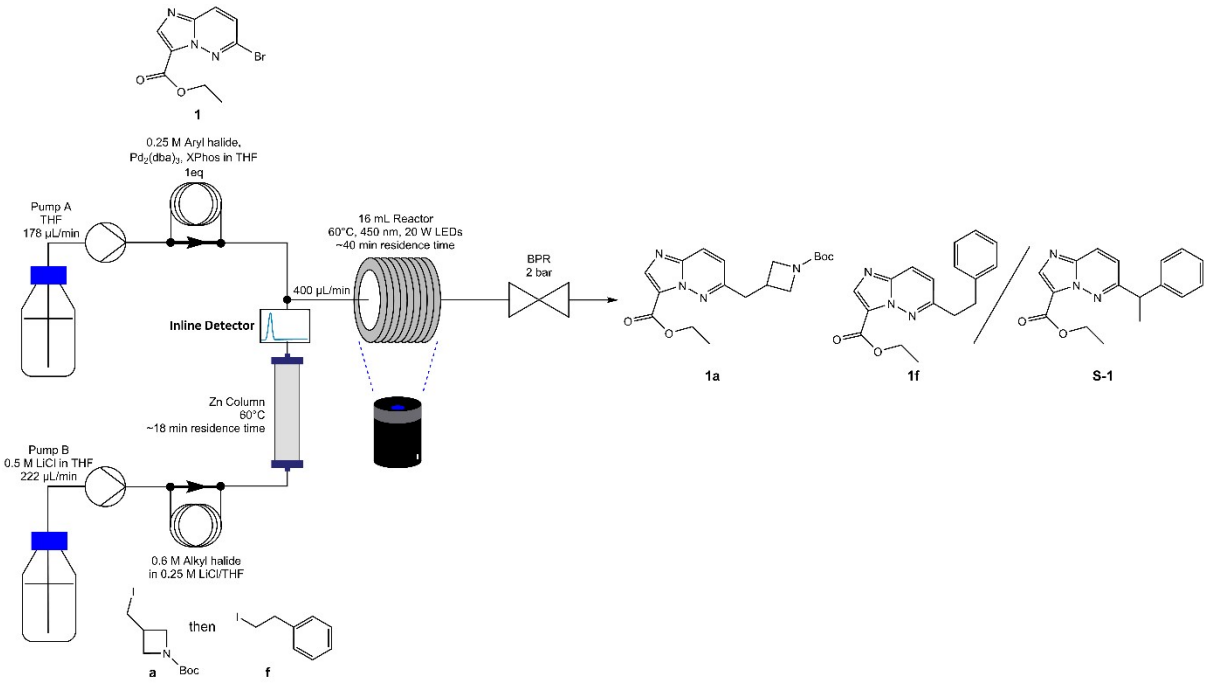


Figure 7 - Negishi coupling set-up coupled with inline detection for cross contamination experiments

The results are presented in the table and graph below.

Experiment number	Injection from loop B	Product (conversion %)	Product from cross contamination (conversion %)
1	Alkyl iodide **a**	**1a** (60%)	n/a
2	Alkyl iodide **f**	**1f/S-1** (79%)	**1a** (9%)
3	Alkyl iodide **a**	**1a** (33%)	n/a
4	'One shot' activation solution	n/a	n/a
5	Alkyl iodide **f**	**1f/S-1** (70%)	**1a** (0%)

Table 3 - LCMS conversion during cross contamination experiments

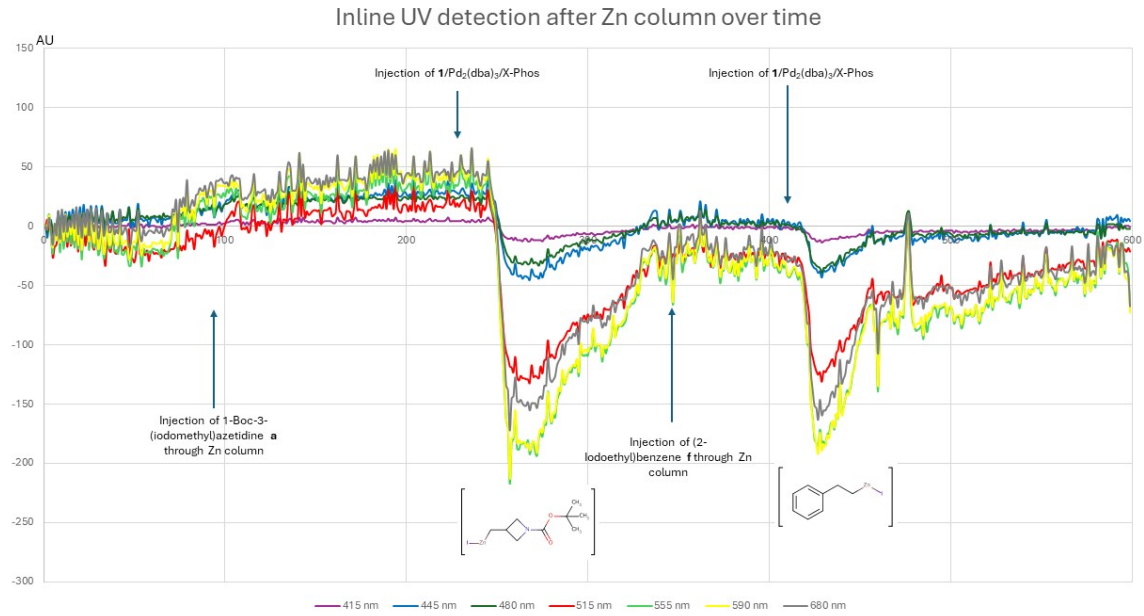


Figure 8 - Inline light absorption detection during experiments 1 and 2

When performing 2 sequential injections (0.5 mmol scale of **1**) in automated mode (injection 1: alkyl iodide **a** – injection 2: alkyl iodide **f**), 9% of product **1a** was found in experiment 2. The inline detector trace however showed that the cross contamination did not occur due to slug broadening of the organozinc reagent made from **a** (the absorbance goes back to baseline before the second injection of **1**/$Pd_2(dba)_3$/X-Phos). The likely hypothesis is that **a** 'stuck' to the Zn column and was then released during the injection of **f** through the Zn column. To test the ability of TMSCl to clean the column, the two injections were repeated with the injection of a 'one shot' activation solution in between (0.5 M TMSCl / 0.2 M 1,2-dibromoethane in THF, similar to the carrier solvent used by Alcazar's group[4]). No cross contamination was observed this time (see experiment 5 in Table 3).

S7 – Magnesium Column Iodine Timing Experiment

The general experiment concept and approach matches the zinc column timing experiment (see S3 – Zinc Column Iodine Timing Experiment). Minor differences between procedures are present to ensure both tests accurately represent the standard conditions (e.g., flow rate) used for organometallic production.

With the magnesium column in an active state (using General Method E or F), the pump B selection valve set to 0.5 M LiCl/THF, the back pressure regulator set to 2 bar, the column heater set to 40°C, and the 16 mL reactor left at room temperature, pumping was commenced with Pump A (THF) at 250 µL/min, Pump B (0.5 M LiCl/THF) at 500 µL/min.

At timepoint t_0 a 2 mL slug of 0.5 M 4-bromotoluene (310 mg, 1.81 mmol) in 0.5 M LiCl/THF (3.6 mL) was injected into channel B, through the Mg column. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At timepoint t_0 + 4 minutes a 4 mL slug of 0.2 M iodine (305 mg, 1.2 mmol) in 0.5 M LiCl/THF (6 mL) was injected into channel A. Iodine colour was observed at the T-mixer approximately 30-45 seconds later. During the injection period of the iodine slug, the organomagnesium slug is expected to elute from the column, resulting in decolourisation of the iodine.

Once iodine slug colour has returned (indicating slug has finished eluting from the magnesium column) the feed selection valve to pump B was changed from 0.5 M LiCl/THF to 0.5 M BuCl/THF. This maintains column activity and enables easy re-activation (see S2.9 – General Method F: Magnesium Column Rapid Re-activation).

From timepoint t_0 + 25 minutes the reactor output stream was collected into 2 mL vials, changing vial position every 20 seconds, allowing accurate back-calculation of the time the two slugs met at the T-mixer.

Once the iodine slug has been collected pumps can be stopped and the reactors cooled. The vial where full decolourisation is observed for the first and last time should be noted and the collection time point for those vials determined. The decolourisation window is typically 4 minutes long, an example from our system is decolourisation between 30 minutes 40 seconds to 35 minutes.

Using equations 1 and 2 (see S3 – Zinc Column Iodine Timing Experiment), Grignard reagent was determined to be at the T-mixer at 6 minutes and 35 seconds – corresponding to an effective column volume of 3182 µL.

S8 – Studies of Magnesium Column Activity Durability

In a similar manner to the durability experiments carried out on the zinc column, we sought to determine the quantity of solvent than can be pumped through the magnesium column before activity begins to fall.

Slugs were timed to meet an iodine solution; decolourisation would be expected to be observed when Grignard reagent has been successfully formed. The degree of quenching of iodine colour was monitored 120 µL after the T-mixer (at the point of entry to the 16 mL reactor), a decrease in apparent slug duration or no decolourisation at all would indicate a loss of magnesium activity.

Preparation for durability experiments is the same procedure each time:

Two stock solutions were prepared, for repeated injection during the experiment: 0.5 M 4-bromotoluene (1.71g, 10 mmol) in 0.5 M LiCl/THF (20 mL), and 0.2 M iodine (1.27g, 5 mmol) in 0.5 M LiCl/THF (25 mL).

Once the magnesium column was activated (using General Method E or F), the feed selection valve to pump B was changed from 0.5 M BuCl/THF to 0.5 M LiCl/THF if required. The column was cleared of 1-chlorobutane by running pump B at 500 µL/min with 0.5 M LiCl/THF for 10 minutes, the back pressure regulator was set to 2 bar, the column heater set to 50°C and the 16 mL reactor left at room temperature. The durability experiment can now begin.

S8.1 – 2 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent

At time t_0 the first 2 mL slug of 0.5 M 4-bromotoluene solution was injected, passing through the magnesium column at a flow rate of 500 µL/min. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 4 minutes a 2.5 mL slug of 0.2 M iodine solution was injected into the system at a flow rate of 250 µL/min. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organomagnesium reagent would elute (at approximately t_0 + 7 minutes) and would still be passing through the mixer after the organomagnesium slug had finished.

This procedure was repeated multiple times with increasing solvent gaps between each aryl halide injection. Table 4 summarises all the key injection timings, the volume of solvent spacer between each organohalide slug and observations regarding decolourisation of the iodine slugs.

Volume of 0.5 M LiCl/THF spacer ahead of organohalide slug (mL)	0.5 M 4-bromotoluene 2 mL injection timepoint (t_0 + x minutes)	0.2 M iodine 2.5 mL injection timepoint (t_0 + x minutes)	Anticipated decolourisation timepoint (t_0 + x minutes)	Observations
N/A	0	4	7	Decolourisation slug seen, ~4.5mins long
5.5	15	21 [a]	22	Decolourisation slug seen, unable to accurately quantify length as no I_2 seen before slug, but at least 4 mins
8	35	39	42	Decolourisation slug seen, ~4.5mins long
13	65	69	72	Decolourisation slug seen, ~1.5mins long (and appeared later than anticipated)
13	95	99	102	No decolourisation observed

Table 4 – Summary of results for 2 mL slug experiment, using 0.5 M LiCl/THF as the solvent spacer passing through the column. a - injected at 21 minutes instead of 19 minutes due to lack of time for injection loop to refill

The results show that magnesium activity can be maintained when the solvent spacer between 2 mL slugs is 8 mL; when the solvent spacer is increased to 13 mL, however, activity rapidly drops off. For reference, one column volume is approximately 3 mL.

S8.2 – 0.5 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent

At time t_0 the first 0.5 mL slug of 0.5 M 4-bromotoluene solution was injected, passing through the magnesium column at a flow rate of 500 µL/min. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 5 minutes a 1.5 mL slug of 0.2 M iodine solution was injected into the system at a flow rate of 250 µL/min. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organomagnesium reagent would elute (at approximately t_0 + 7 minutes) and would still be passing through the mixer after the organomagnesium slug had finished.

This procedure was repeated multiple times with increasing solvent gaps between each aryl halide injection. Table 5 summarises all the key injection timings, the volume of solvent spacer between each organohalide slug and observations regarding decolourisation of the iodine slugs.

Volume of 0.5 M LiCl/THF spacer ahead of organohalide slug (mL)	**0.5 M 4-bromotoluene 0.5 mL injection timepoint (t_0 + x minutes)**	**0.2 M iodine 1.5 mL injection timepoint (t_0 + x minutes)**	**Anticipated decolourisation timepoint (t_0 + x minutes)**	**Observations**
N/A	0	5	7	Decolourisation slug seen, ~1.5mins long
6	13	18	20	Decolourisation slug seen, ~1.5mins long
6	26	31	33	Decolourisation slug seen, ~1.5mins long
8	43	48	50	Decolourisation slug seen, ~1 min long
8	60	65	67	No decolourisation observed

Table 5 - Summary of results for 0.5 mL slug experiment, using 0.5 M LiCl/THF as the solvent spacer passing through the column

The results show that magnesium activity can be maintained when the solvent spacer between 0.5 mL slugs is 6 mL; when the solvent spacer is increased to 8 mL, however, activity rapidly drops off.

When this experiment was repeated on a partially used magnesium column (1/3 of the column was black in colour) complete decolourisation of the iodine slug with a 0.5 mL organohalide injection was no longer observed, even after a full re-activation of the magnesium column (General Method E). To demonstrate that the magnesium was active a 0.5 mL injection was sequenced between two 2 mL injections see Table 6.

Volume of 0.5 M LiCl/THF spacer ahead of organohalide slug (mL)	0.5 M 4-bromotoluene injection timepoint (t_0 + x minutes)	0.2 M iodine 2.5 mL injection timepoint (t_0 + x minutes)	Anticipated decolourisation timepoint (t_0 + x minutes)	Observations
N/A	0 (2 mL slug)	4	7	Decolourisation slug seen, ~5mins long. Although nearly 2 minutes later than anticipated
6	16 (0.5 mL slug)	20	23	No decolourisation observed
8.5	34 mins 15s [a] (2 mL slug)	38	41 mins 15s	Decolourisation slug seen, ~5mins long. Although nearly 2 minutes later than anticipated

Table 6 – Summary of results for repeat 0.5 mL slug experiment with 0.5 M LiCl/THF as the solvent spacer passing through the column, after the column had been partially used (~1/3 black in colour). a – 0.5 M 1-chlorobutane solution was used instead

In this experiment organomagnesium slugs eluted approximately 2 minutes later than anticipated, however still showed a similar duration – this change in column retention time is due to degradation of the magnesium material (observed as a black band). See S10 – Change in Magnesium Column Effective Volume During Consumption for a more detailed investigation of column degradation.

It also shows that as the magnesium metal in the column is consumed, the 0.5 mL slug is no longer able to quench the 0.2M Iodine solution, even though the magnesium column was still active (as demonstrated by the third injection in Table 6). This is similar to the phenomena observed with 0.5 mL slugs in a zinc column (see section S4.2 – 0.5 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent) where 0.5 mL slugs were unable to quench the colour of iodine but were able to perform Negishi couplings. We are unable to determine the underlying reason behind this phenomenon but believe the most likely explanation to be due to slight broadening of the slug, resulting in a peak slug concentration below the threshold to quench the iodine colour completely.

S8.3 – 2 mL Slug Durability with THF Carrier Solvent

This section tests the critical need for 0.5 M LiCl/THF as the carrier solvent flowing through the magnesium column when operating in slug flow regime. On a freshly packed and activated magnesium column 2 mL slugs were flowed through the system using an 8 mL THF spacer, this volume having been shown to be a reliable system when 0.5 M LiCl/THF was used as the carrier solvent (See section S8.1 – 2 mL Slug Durability with 0.5M LiCl/THF Carrier Solvent).

To achieve this, only minor modification of the standard durability experiment method was required: an additional selection valve was added to the pump B inlet feed, thus allowing the pump to be fed by either 0.5 M BuCl/THF, 0.5 M LiCl/THF or just THF depending on the valve configuration.

As with the other column durability experiments, once the column had been activated (General Method E or F) the column was washed for 10 minutes at 500 µL/min with 0.5 M LiCl/THF to remove all 1-chlorobutane from the system. The solvent feed to pump B was then changed at this point to THF only, so that the carrier solvent after the first injection would be THF.

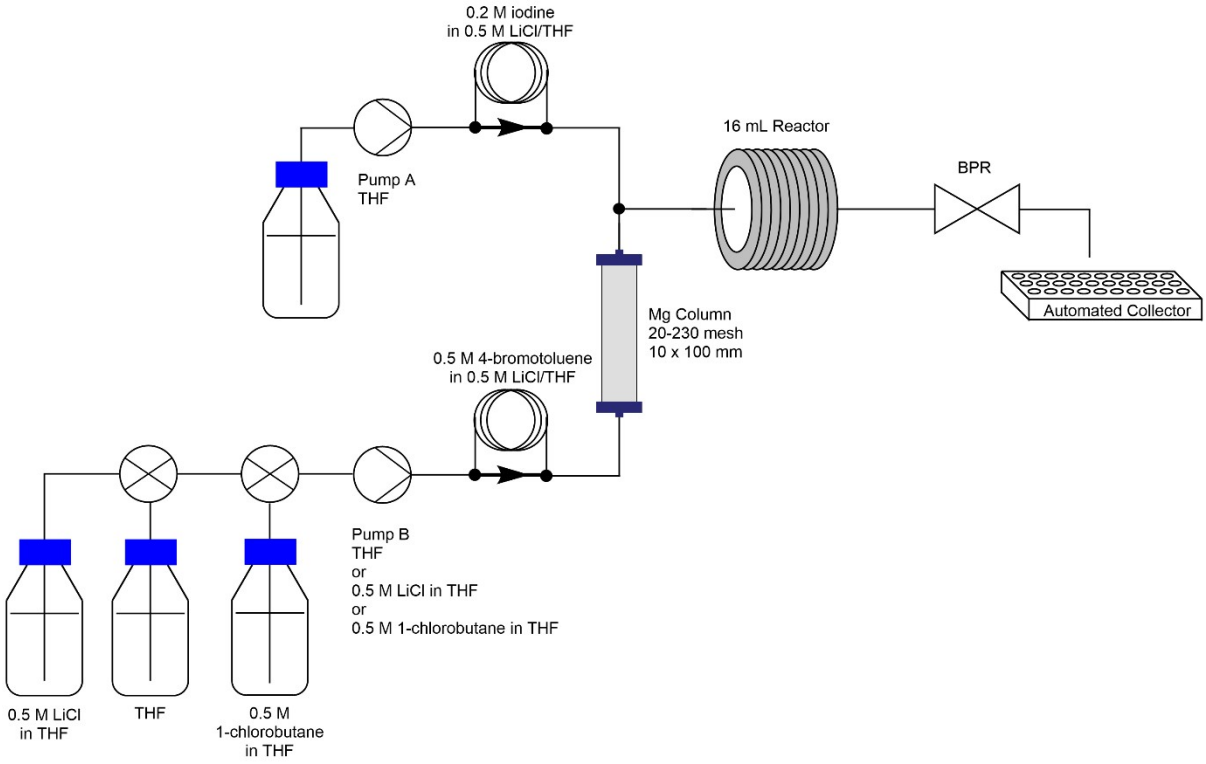


Figure 9 - Two valves on pump B inlet allow for the selection of one of three solvents

At time t_0 the first 2 mL slug of 0.5 M 4-bromotoluene solution was injected, passing through the magnesium column at a flow rate of 500 µL/min. At t_0 + 4 minutes a 2.5 mL slug of 0.2 M iodine solution was injected into the system at a flow rate of 250 µL/min. Table 7 summarises the injection timings and results.

Volume THF spacer ahead of organohalide slug (mL)	0.5 M 4-bromotoluene 2 mL injection timepoint (t_0 + x minutes)	0.2 M iodine 2.5 mL injection timepoint (t_0 + x minutes)	Anticipated decolourisation timepoint (t_0 + x minutes)	Observations
N/A	0	5	7	Decolourisation slug seen, ~4.5mins long
8	20	24	27	Decolourisation slug seen, however delayed by 2 minutes and only ~2mins long
8	40	44	47	No decolourisation observed

Table 7 - Summary of results for 2 mL slug experiment, using THF as the solvent spacer passing through the column. Activity rapidly degrades.

The results show, like our experience with zinc, that magnesium activity is rapidly lost when THF is used as the carrier solvent instead of 0.5 M LiCl/THF. Anecdotally, a yellow colour could be seen streaking through the 16 mL reactor – this could be an indication salts leach from the column when THF is used. This behaviour has not been seen in other durability experiments, but some 'salt' build-up can be seen towards the end of a library campaign.

'Revival' of the now inactive column was attempted. The column was refilled with 0.5 M 1-chlorobutane in THF solution, and the rapid restart procedure General Method F was performed. To our surprise, the column activity was restored - when an iodine slug was injected following the same procedure as above, decolourisation was observed. This result indicates that perhaps a deactivated column does not always require a "full" reactivation (i.e. treatment with DIBAL, TMSCl etc.) once the surface has been activated.

S9 – Comparison of Grignard Elution Time for Various Substrates

Timing experiments were performed for a range of aryl halides used in the Grignard library synthesis campaign that gave varying degrees of desired product to butyl by-product ratio, to understand if the variation in conversion was due to slug mistiming.

A 0.2 M iodine (1.52g, 6 mmol) in 0.5 M LiCl/THF (30 mL) stock solution was prepared for injection for all timing experiments. 0.5 M solutions of aryl halides (1.5 mmol) in 0.5 M LiCl/THF (3 mL) were also prepared for injection.

Once the magnesium column was activated (using General Method E or F) and subsequently cleared of 1-chlorobutane with 0.5 M LiCl/THF, the back pressure regulator was set to 2 bar, the column heater was set to 50°C and the 16 mL reactor left at room temperature. Pump B selection valve had been set to 0.5 M LiCl/THF, therefore pumping was then commenced with Pump A (THF) at 250 µL/min and Pump B (0.5 M LiCl/THF) at 500 µL/min. Timing experiments can now begin.

At time t_0 the first 2 mL slug of 0.5 M aryl halide solution was injected, passing through the magnesium column at a flow rate of 500 µL/min. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 4 minutes a 3.5 mL slug of 0.2 M iodine solution was injected into the system at a flow rate of 250 µL/min. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organomagnesium reagent would elute (at approximately t_0 + 7 minutes) and would still be passing through the mixer after the organomagnesium slug had finished. Decolourisation timing was monitored at the point of entry to the 16 mL reactor, 120 µL after the T-mixer. This procedure was repeated for each selected aryl halide, Table 8 summarises the results.

ID	Aryl Halide	Library LCMS Purity (%)	Decolourisation Started (Time after slug injection)	Decolourisation Ended (Time after slug injection)	Colourless Duration	Observations
S-2	4-bromotoluene	88	7mins 20s	11mins 40s	4mins 20s	Total decolourisation
S-3	3-bromopyridine	6	6mins 20s [a]	13mins [a]	6mins 40s [a]	Two fully decolourised bands, with orange between – organometallic appears to be coloured at higher concentrations.
S-4	2-bromo-1,3,5-trimethylbenzene	8	7mins 40s	12mins 20s	4mins 40s	Initial decolourisation then pale brown gradient back to colourless – organometallic appears to be coloured at higher concentrations.
S-5	1-bromo-3,5-dimethoxybenzene	18	7mins 30s	11mins 30s	4 mins	Total decolourisation
S-6 [b]	2-bromo-1,4-difluorobenzene	14	7mins 35s	12mins 50s	5mins 15s	Total decolourisation
S-7 [b]	4-bromo-N,N-dimethylaniline	57	7mins 40s	11mins 50s	4mins 10s	Total decolourisation
S-2	4-bromotoluene	88	7mins 50s	11mins 45s	3mins 55s	Total decolourisation (repeat control experiment)

Table 8. Summary of elution times of various organomagnesium compounds – all show very similar elution time. a – timings back calculated from collection point due to decolourisation being unclear until on the 16 mL reactor, b – the first time this experiment was performed no decolourisation was observed, unclear why magnesium had become inactive

The results show that all aryl halides have a similar elution time from the magnesium column, therefore the variation in desired product: butyl by-product is not due to the varying affinities of each aryl halide to the magnesium surface.

Compounds S-3 and S-4 showed an unusual profile – the slugs showed full decolourisation at the start and end of their elution, however in the middle had an orange/brown colour. It is believed the only explanation for this is that the organomagnesium reagent itself is coloured, therefore at higher concentrations (in the middle of the slug) colourisation is observed due to the organomagnesium species, not from iodine.

S10 – Change in Magnesium Column Effective Volume During Consumption

During our studies it was observed that the magnesium column turned black progressively upwards during usage. This same observation has also been made by others, reporting that XPS analysis showed the presence of magnesium, oxygen, carbon, and chlorine in the isolated residue.[6]

Anecdotally, we noticed that as the amount of black material increased, organometallic slugs appeared to elute later – this would result in slug mistiming leading to a reduction in conversion to desired product.

To study this in detail, 0.5 M 1-chlorobutane (BuCl) was pumped through a magnesium column to deliberately consume the metal and form the resulting black residue. Timing experiments were then performed at points through the degradation process, noting any change in slug elution time or duration. A n=2 baseline elution time had been determined for the column in the experiment that generated the results shown in Table 8.

Due to the long duration of this experiment pumps were paused and solvent feeds topped up (including additional molecular sieves) as required.

Two stock solutions were prepared: a 0.2 M iodine (1.02 g, 4 mmol) in 0.5 M LiCl/THF (20 mL) and a 0.5 M 4-bromotoluene (0.43 mL, 3.5 mmol) in 0.5 M LiCl/THF (7 mL) solution.

At specified timepoints in the study, Grignard production would be changed from continuous flow to slug flow regime. Whilst in slug flow regime the elution time could be determined. Once the timing experiment was complete Grignard production would return to continuous flow mode until the next timepoint.

Once the magnesium column was activated (using General Method E or F), the back pressure regulator was set to 2 bar, the column heater was set to 50°C and the 16 mL reactor was left at room temperature. Pumping was then commenced with Pump A (THF) at 250 µL/min, Pump B (0.5 M BuCl/THF) at 500 µL/min.

After approximately 3 hours, 45 mmol of 1-chlorobutane had been processed, resulting in approximately 2 cm growth of the black region. Pump B selection valve was changed to 0.5 M LiCl/THF, and the column was flushed with 0.5 M LiCl/THF for 10 minutes at the same flow rate (500 µL/min) to remove all 1-chlorobutane from the column.

A timing experiment was then performed: at t_0 a 2 mL slug of 0.5 M 4-bromotoluene solution was injected through channel B onto the magnesium column at a flow rate of 500 µL/min. Note: once the slug has completed injection, immediately switch the injection valve back to fill mode to prevent pure THF in the loop being injected onto the column.

At t_0 + 4 minutes a 3.5 mL slug of 0.2 M iodine solution was injected into the system at a flow rate of 250 µL/min. The iodine slug has a longer duration than the organohalide slug – this is so that it would pass through the T-mixer before the anticipated time that organomagnesium reagent would elute (at approximately t_0 + 7 minutes) and would still be passing through the mixer after the organomagnesium slug had finished. Decolourisation timing was monitored at the point of entry to

the 16 mL reactor, 120 µL after the T-mixer. Once iodine colour returned, Pump B selection valve was changed back to 0.5 M BuCl/THF solution.

A further timing experiment was performed 3.5 hours later (a further 52.5 mmol of 1-chlorobutane processed, 97.5 mmol in total at this point) when the black band had reached the 5 cm mark.

4 hours later (a further 60 mmol 1-chlorobutane processed, 157.5 mmol in total) the entire column was black; no quenching of iodine was observed – confirming the belief that the black material is not able to generate organometallic product.

Results of the timing experiments are summarised below in Table 9 and plotted as a graph in Figure 10. See Figure 11 for images of the column throughout the experiment showing the increase in the black region.

Height to top of black region (cm)	**Length of black region (cm)**	**Decolourisation Started (Time after slug injection)**	**Decolourisation Ended (Time after slug injection)**	**Duration**	**Comments**
1	0.5	7mins 35s	11mins 45s	4mins 10s	An average of 2 results
3	2.5	9mins	14mins	5mins	
5	4.5	10mins 40s	15mins 20s	4mins 40s	Solid dark to 5cm, some darkening throughout whole length

Table 9 - Summary of the change in organomagnesium elution time as the black region in the column grows

The results show a linear relationship between the size of the black region and the elution time. For every 1 cm of black region growth, the elution time was delayed by approximately 45 seconds corresponding to a volume of 375 µL. We therefore propose that once a magnesium column is commissioned and the initial timing experiment performed, the effective volume of the column can be increased by 375 µL per centimetre of growth. This will improve slug timing without the requirement to perform a further timing experiment.

This experiment proceeded without increase in back pressure (or blocking) in the magnesium column reactor. There was however some magnesium salt build up in the 16 mL reactor, this is because the Grignard reagent being generated in this experiment was not being consumed to form a product. In this experiment over 150 mmol of organohalide was processed – a cumulative run time of 10 hours.

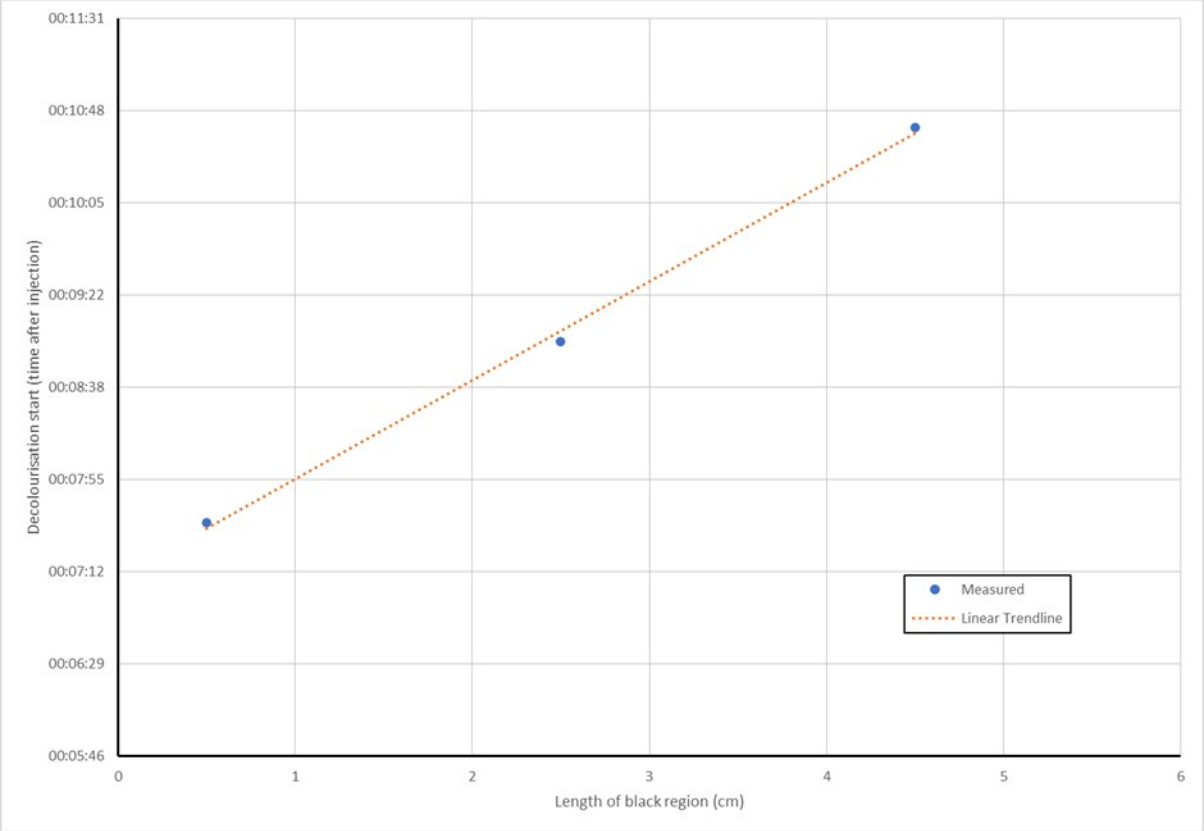


Figure 10 - A graph showing the change in decolourisation start time versus the length of black region on the column

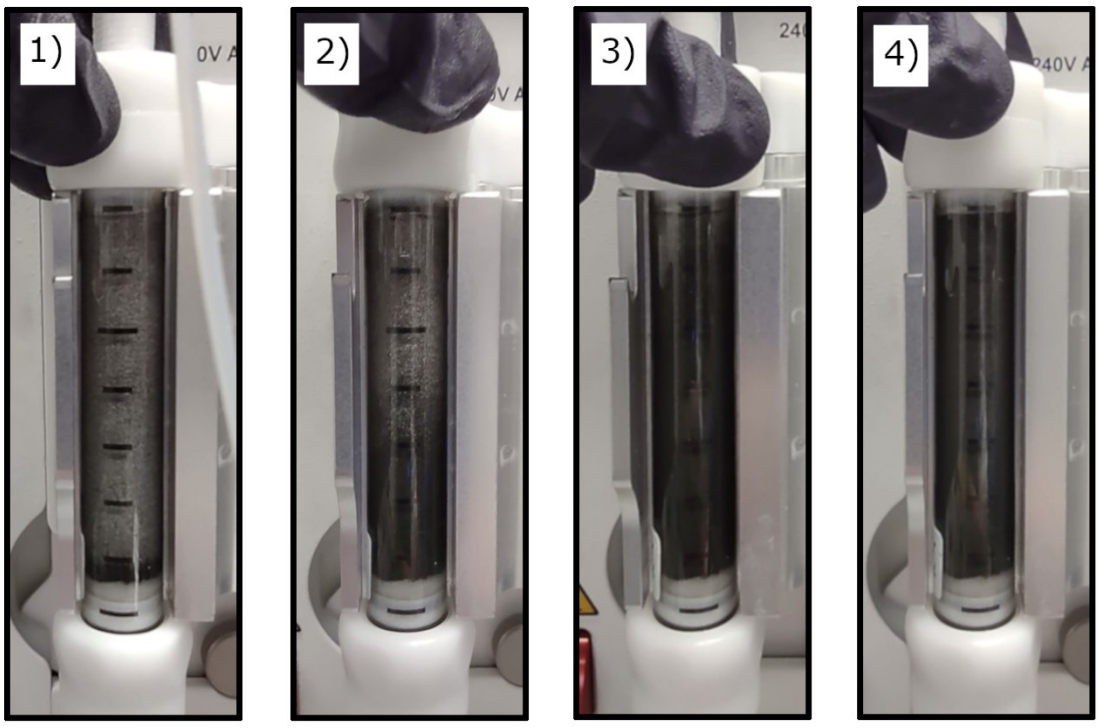
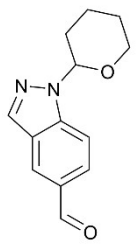


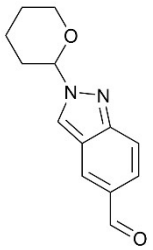
Figure 11 - Images of the magnesium column during use, the black band can be seen increasing up the column. 1) black band at 1 cm point, 2) black band at 3 cm point, 3) black band at 5 cm point, 4) column no longer active – entirely black.

S11 – Synthesis of Grignard Library Intermediates

S11.1 – 1-(oxan-2-yl)indazole-5-carbaldehyde, S-8 & 2-(oxan-2-yl)indazole-5-carbaldehyde, 6



S-8



6

1H-Indazole-5-carboxaldehyde (5 g, 34.21 mmol, 1 eq) was reacted following General Method C, LCMS showed a mixture of N-1 and N-2 THP isomers.

The mixture was purified by automated flash chromatography (Combiflash 300+, Silica 80 g Gold RediSep column) eluting with 0 to 44% Ethyl Acetate in Heptane.

Two major peaks eluted: the first peak gave 1-(oxan-2-yl)indazole-5-carbaldehyde, compound S-8, (4.18 g, 18.15 mmol, 53.06%) as a yellow oil (Purity:>95%) (ethyl acetate, 0.05 eq), the second peak gave 2-(oxan-2-yl)indazole-5-carbaldehyde, compound 6, (2.7 g, 11.73 mmol, 34.27%) as a white solid (Purity:>95%).

1-(oxan-2-yl)indazole-5-carbaldehyde, S-8:

^{1}H NMR (400 MHz, DMSO) δ 10.05 (s, 1H), 8.45 (t, J = 1.2 Hz, 1H), 8.38 (s, 1H), 7.94 – 7.88 (m, 2H), 5.94 (dd, J = 9.6, 2.4 Hz, 1H), 3.94 – 3.86 (m, 1H), 3.83 – 3.71 (m, 1H), 2.48 – 2.35 (m, 1H), 2.09 – 1.96 (m, 2H), 1.84 – 1.69 (m, 1H), 1.67 – 1.53 (m, 2H).

^{13}C NMR (100 MHz, DMSO) δ 192.8, 142.1, 136.2, 131.2, 127.9, 125.4, 124.4, 111.8, 84.7, 67.1, 29.3, 25.2, 22.5.

HRMS (ESI^{+}) Mass required for exact match ($C_{13}H_{14}N_2O_2$): 230.1055, Mass required for -THP fragment ion ($C_8H_6N_2O$): 146.0480, Mass found: 146.0477.

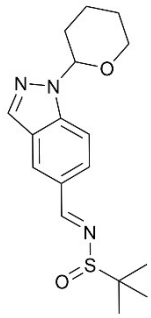
2-(oxan-2-yl)indazole-5-carbaldehyde, 6:

^{1}H NMR (400 MHz, DMSO) δ 9.99 (d, J = 0.6 Hz 1H), 8.87 (d, J = 0.9 Hz, 1H), 8.49 – 8.47 (m, 1H), 7.77 – 7.73 (m, 1H), 7.69 (dd, J = 9.1, 1.5 Hz, 1H), 5.82 (dd, J = 9.4, 2.9 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.81 – 3.70 (m, 1H), 2.25 – 2.06 (m, 2H), 2.01 – 1.91 (m, 1H), 1.83 – 1.54 (m, 3H).

^{13}C NMR (100 MHz, DMSO) δ 192.8, 149.7, 131.5, 131.5, 127.0, 122.9, 121.0, 118.9, 88.6, 67.6, 30.9, 25.0, 22.0.

HRMS (ESI$^+$) Mass required for exact match ($C_{13}H_{14}N_2O_2$): 230.1055, Mass required for -THP fragment ion ($C_8H_6N_2O$): 146.0480, Mass found: 146.0474.

S11.2 – 2-methyl-N-[(1E)-[1-(oxan-2-yl)indazol-5-yl]methylidene]propane-2-sulfinamide, 4



1-(oxan-2-yl)indazole-5-carbaldehyde (2 g, 8.69 mmol, 1 eq) was reacted following General Method D and purified by automated flash chromatography (Combiflash 300+, Silica 40 g Gold RediSep column) eluting with 0 to 50% Ethyl Acetate in Heptane.

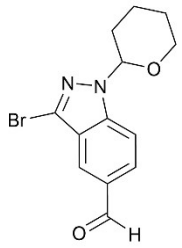
Product fractions were combined to afford 2-methyl-N-[(1E)-[1-(oxan-2-yl)indazol-5-yl]methylidene]propane-2-sulfinamide (1.85 g, 5.55 mmol, 63.88%) as a colourless oil (Purity:>95%, ethyl acetate 0.01 eq). NMR showed a mix of diastereoisomers.

^{1}H NMR (400 MHz, DMSO) δ 8.64 (s, 1H), 8.41 – 8.38 (m, 1H), 8.30 (s, 1H), 8.05 – 7.99 (m, 1H), 7.90 – 7.84 (m, 1H), 5.96 – 5.89 (m, 1H), 3.94 – 3.85 (m, 1H), 3.83 – 3.71 (m, 1H), 2.47 – 2.34 (m, 1H), 2.11 – 1.95 (m, 2H), 1.85 – 1.68 (m, 1H), 1.68 – 1.51 (m, 2H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, DMSO) δ 163.1/163.1, 141.4/141.3, 135.7/135.7, 128.2, 126.2/126.1, 126.0/125.9, 124.7/124.6, 111.8/111.8, 84.7/84.6, 67.0/67.0, 57.6/57.6, 29.4/29.3, 25.2, 22.5, 22.5.

HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{23}N_3O_2S$): 333.1511, Mass found: 333.1512.

S11.3 – 3-bromo-1-(oxan-2-yl)indazole-5-carbaldehyde, S-9



3-Bromo-1H-indazole-5-carbaldehyde (4 g, 17.77 mmol, 1 eq) was reacted following General Method C. Incomplete conversion was observed after overnight reaction, therefore stronger p-toluenesulfonic acid monohydrate (676.2 mg, 3.55 mmol, 0.2 eq) and further 3,4-Dihydro-2H-pyran (8.11 mL, 0.92 g/mL, 88.87 mmol, 5 eq) were added and the reaction left to stir over the weekend.

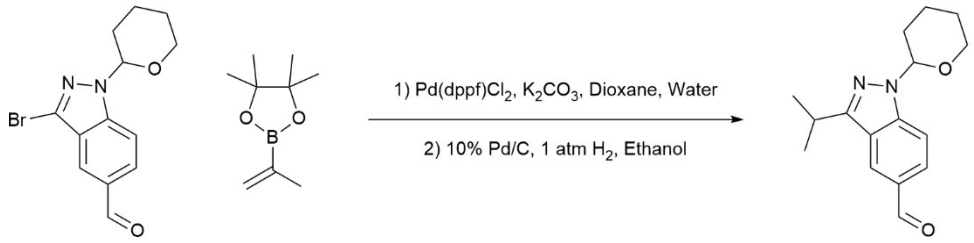
Purification by automated flash chromatography (Combiflash 300+, Silica 330 g RediSep column) eluting with 10 to 44% Ethyl Acetate in Heptane gave 3-bromo-1-(oxan-2-yl)indazole-5-carbaldehyde (3.45 g, 11.15 mmol, 62.75%) as a pale yellow oil.

^{1}H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 8.32 – 8.29 (m, 1H), 8.02 – 7.96 (m, 2H), 5.96 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.94 – 3.86 (m, 1H), 3.82 – 3.71 (m, 1H), 2.41 – 2.27 (m, 1H), 2.09 – 1.96 (m, 1H), 1.82 – 1.55 (m, 4H).

^{13}C NMR (100 MHz, DMSO) δ 192.6, 143.2, 132.0, 126.5, 126.5, 123.9, 123.7, 112.5, 84.8, 67.2, 29.2, 25.0, 22.4.

HRMS (ESI^{+}) Mass required for exact match ($C_{13}H_{13}N_2O_2Br$): 308.0160, Mass found: 386.2899. We are unable to rationalise this higher mass, however product structure was confirmed by NMR and behaved as anticipated at the next step (giving the anticipated product mass ion).

S11.4 – 3-isopropyl-1-(oxan-2-yl)indazole-5-carbaldehyde, 7



To a 250 mL round bottomed flask suitable for sealing and heating as a bomb was added a solution of 3-bromo-1-(oxan-2-yl)indazole-5-carbaldehyde (3.45 g, 11.16 mmol, 1 eq) in 1,4-Dioxane (57 mL) , to this was then added Water (17 mL) , 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.15

mL, 0.89 g/mL, 16.74 mmol, 1.5 eq) , potassium carbonate (4.63 g, 33.48 mmol, 3 eq) and finally Pd(dppf)Cl_2 (816.54 mg, 1.12 mmol, 0.1 eq) . The mixture was sparged with nitrogen for 5 minutes before the flask was sealed, placed behind a blast shield, and heated to 120°C for 4 hours.

LCMS showed peak to peak conversion to alkene intermediate. The reaction was left to stir at room temperature overnight before water and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous back extracted with ethyl acetate once. Combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield 5 g of brown oil.

Oil was dissolved in ethanol (60 mL) and transferred to a hydrogenation flask. Under an atmosphere of nitrogen Palladium on carbon (600 mg) slurried in minimal IPA was added. The vessel was sealed, evacuated and back filled with nitrogen three times before finally evacuating and filling with hydrogen. The flask was then left to shake at room temperature overnight under 1 atmosphere of hydrogen, supplied by burette.

LCMS showed some conversion, hydrogen uptake seemed to slow overnight. Additional catalyst was added (600 mg) and the reaction was shaken at room temperature during the day and then stirred at 22°C overnight. LCMS showed much better conversion, but still 0.3eq of starting material by NMR. The reaction was filtered through a Celite 545 cartridge (10 g) washing with ethyl acetate. The filtrate was concentrated to yield 4.3 g of brown oil.

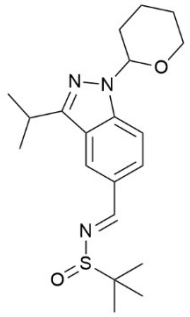
Material was loaded onto Isolute HM-N (DCM/MeOH), dried and then purified by automated flash chromatography (Combiflash 300+, Silica 80 g RediSep column) eluting with 0 to 16% Ethyl Acetate in Heptane to give a mix of N-1 and N-2 THP protected isomers, 3-isopropyl-1-(oxan-2-yl)indazole-5-carbaldehyde & 2-(oxan-2-yl)-3-(propan-2-yl)-2H-indazole-5-carbaldehyde (906 mg, 3.33 mmol, 29.81%) as an orange oil.

^{1}H NMR (400 MHz, DMSO) δ 10.05 (s, 1H), 8.52 – 8.49 (m, 1H), 7.90 – 7.86 (m, 1H), 7.85 – 7.81 (m, 1H), 5.85 (dd, *J* = 9.9, 2.5 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.81 – 3.69 (m, 1H), 3.51 – 3.39 (m, 1H), 2.47 – 2.33 (m, 1H), 2.09 – 1.90 (m, 2H), 1.83 – 1.53 (m, 3H), 1.41 (d, J = 7.0 Hz, 3H), 1.41 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, DMSO) δ 192.7, 153.0, 143.2, 130.5, 127.7, 125.2, 122.2, 111.7, 84.6, 67.2, 29.4, 27.6, 25.2, 22.7, 22.5.

HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{20}N_2O_2$): 272.1525, Mass found: 272.1524.

S11.5 – N-[(1E)-[3-isopropyl-1-(oxan-2-yl)indazol-5-yl]methylidene]-2-methylpropane-2-sulfinamide, 5



3-isopropyl-1-(oxan-2-yl)indazole-5-carbaldehyde, 3534-DM-071-001 (817 mg, 3 mmol, 1 eq) was reacted following General Method D.

Crude material was purified by automated flash chromatography (Combiflash 300+, Silica 40 g Gold RediSep column) eluting with 0 to 28% Ethyl Acetate in Heptane to yield N-[(1E)-[3-isopropyl-1-(oxan-2-yl)indazol-5-yl]methylidene]-2-methylpropane-2-sulfinamide (585 mg, 1.56 mmol, 51.93%) as a white solid. NMR showed 0.13 eq isopropenyl impurity co-eluted (impurity from earlier in the route). Observed as a mix of diastereoisomers.

^{1}H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 8.48 – 8.44 (m, 1H), 8.03 – 7.98 (m, 1H), 7.82 – 7.77 (m, 1H), 5.86 – 5.79 (m, 1H), 3.95 – 3.86 (m, 1H), 3.80 – 3.69 (m, 1H), 3.47 – 3.35 (m, 1H), 2.47 – 2.32 (m, 1H), 2.10 – 1.90 (m, 2H), 1.84 – 1.68 (m, 1H), 1.68 – 1.53 (m, 2H), 1.44 – 1.37 (m, 6H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, DMSO) δ 163.2/163.2, 152.5/152.5, 142.5/142.4, 127.5, 126.3/126.3, 125.6/125.6, 122.4/122.4, 111.9/111.8, 84.6/84.5, 67.2, 57.6/57.6, 29.4, 27.6, 25.2, 22.7, 22.5, 22.5, 22.4.

HRMS (ESI^{+}) Mass required for exact match ($C_{20}H_{29}N_3O_2S$): 375.1980, Mass found: 375.1980.

S12 – Mechanism of Organomagnesium Formation: Direct Mg Insertion or Mg/Halogen Exchange?

It was suggested during the review process of this publication to explore the mechanism of formation or the organomagnesium species, and especially the possibility of an Mg/halogen exchange between the 'sacrificial BuMgCl' and an arylbromide.

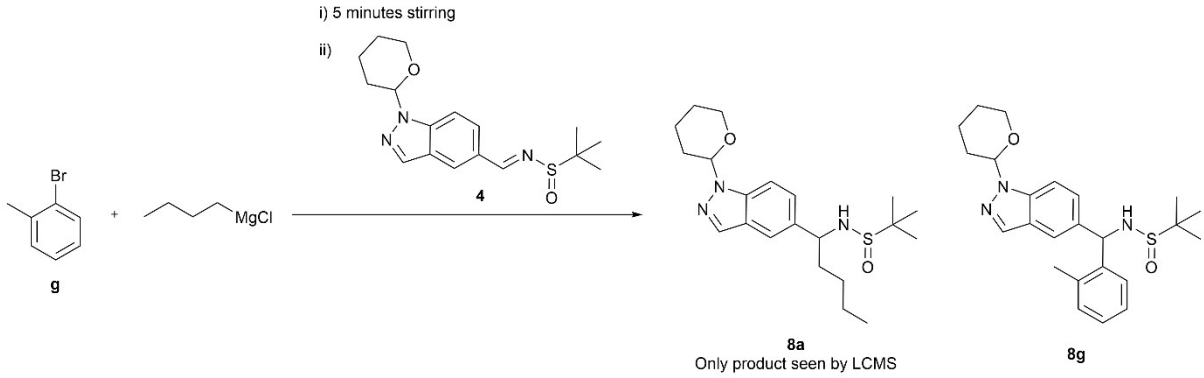


Figure 12 - Mg/halogen exchange experiment

To this end, a solution of ortho-tolylbromide, aryl g (0.12 mL, 1 mmol, 3 eq) and BuMgCl (2 mL, 0.5 M in THF – made using standard flow conditions described before and titrated before use, 3 eq) was stirred under nitrogen for 5 minutes to replicate potential Mg/halogen exchange whilst passing through the magnesium column. A solution of 2-methyl-N-[(1E)-[1-(oxan-2-yl)indazol-5-yl]methylidene]propane-2-sulfinamide, intermediate 4 (100 mg, 0.33 mmol, 1 eq) in 1 mL THF was then added. The reaction was stirred at 40°C for 16 hours. Only product 8a was present by LCMS.

This result suggests that the organomagnesium species formation does not proceed via Mg/halogen exchange, but rather by direct Mg insertion. This is further supported by the slug durability experiments in sections S8.1, S8.2 and the substrate timing experiments in S9. Organomagnesium species were effectively produced and no sacrificial BuMgCl was used in between slug injections (0.5M LiCl in THF was the carrier solvent).

S13 – 3D Printed Custom Collection Racks

To streamline the flow to batch library synthesis workflow, 3D printed racks were designed to allow flow Grignard reaction slugs to be collected in a screw neck vial suitable for use in the subsequent batch deprotection step (via a concentration step using a Biotage V10 evaporator) – see General Methods G and H for further information on the experimental procedure.

Designs were made to hold 40 x 8 mL vials with a 15-425 screw neck, dimensions 17 mm × 60 mm (e.g. Supelco 27072-U) or 21 x 30 mL vials with a 24-400 screw neck, dimensions 72.5 x 27.5mm (e.g. BGB EPA30). For the library synthesis performed in this paper, 30 mL vials were used.

The racks were designed to fit the keyway responsible for holding accessory racks in a fixed position on the Asia Automated Collector (Mini) catalogue number 2200535 (more widely known as a Gilson FC203B). The racks are a modular construction (see Figure 13) with all parts printed in PLA and glued together.

Full assembly instructions, .stl files and Asia Manager rack geometry files can be found on GitHub:

https://github.com/vernalis/3Dprint_files/tree/master/Syrris%20Asia%20Collector%20Racks

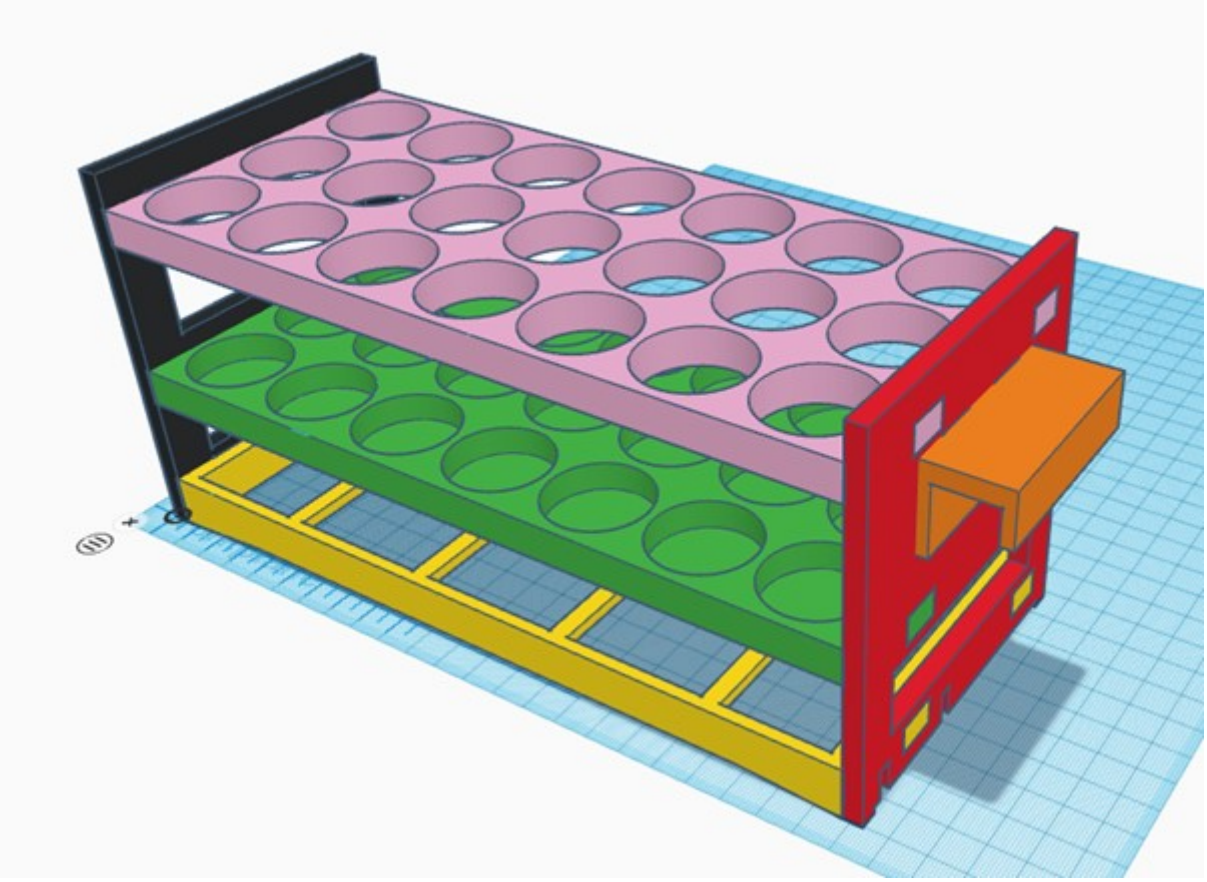


Figure 13 - CAD rendering of 30mL vial rack, to highlight modular construction each component has been uniquely coloured.

S14 – Grignard Flow Library Synthesis

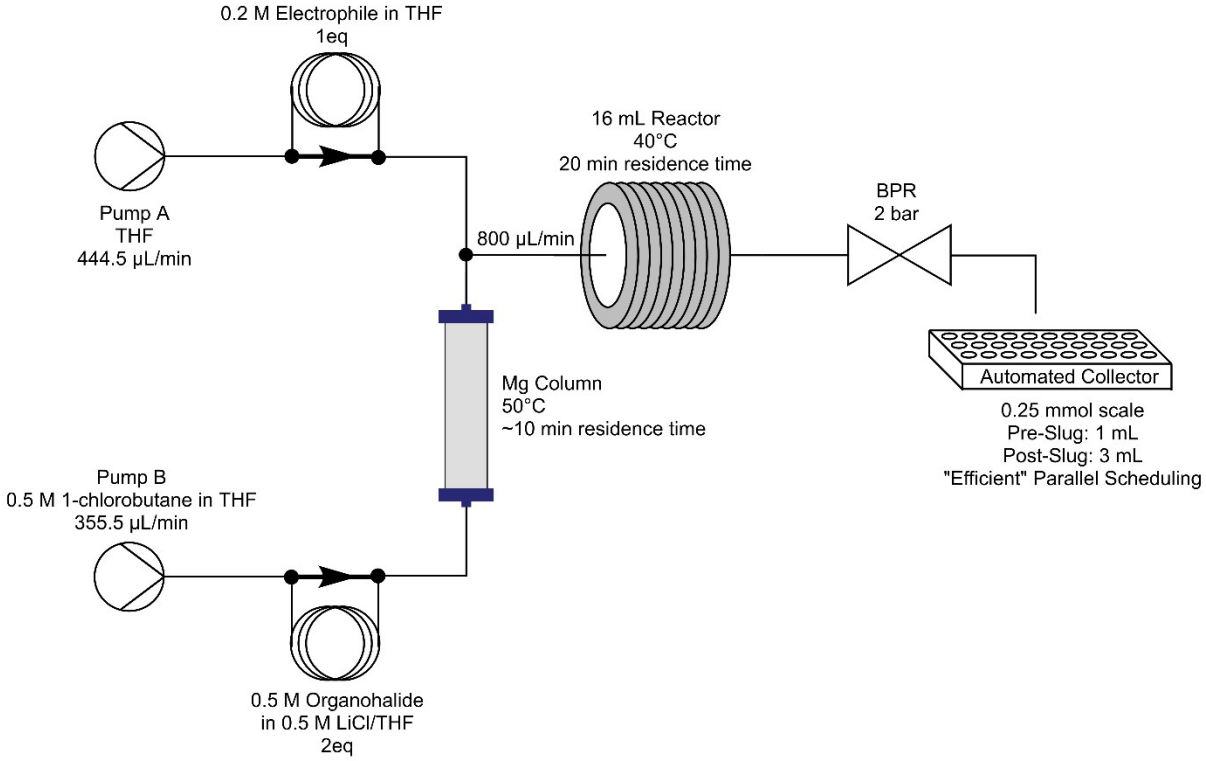
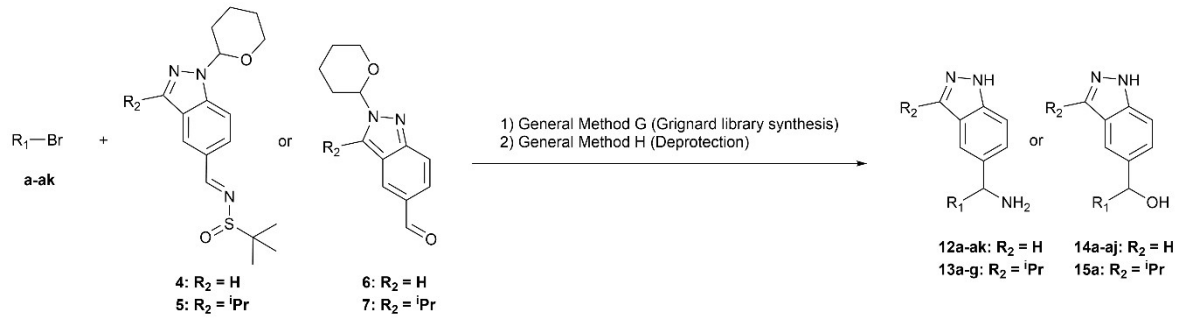


Figure 14 - Grignard library synthesis fluidic scheme

Grignard library compounds were synthesised using a flow to batch process: organomagnesium generation and subsequent reaction were performed in flow using General Method G. Crude products were then deprotected using General Method H to give the crude title compounds suitable for aliquoting and activity assessment by crude reaction screening (CRS). Once compounds of interest had been identified bulk crude material was then purified to yield the pure compound, allowing validation of the CRS hit.

To enable a rapid synthesis and screening cycle, by design the library consists of crude reaction mixtures. As a result, analysis is limited to HRMS for all compounds that were not deemed to be of biological interest and thus not purified for follow up assessment. HRMS is however reported for the compounds at both the protected intermediate stage as well as the final deprotected compound.



Note: products with an NH_2 group were typically observed as the -NH_3 fragment ion by the LCMS. (Further analysis of the purified NH_2 containing compounds by negative ionisation HRMS and NMR, confirmed the fragmentation to be an LCMS artefact)

For the analytical data generated for the library, see Appendix 2 – HRMS Data for Grignard CRS Library.

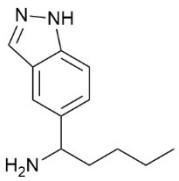
S14.1 – Purification of Compounds of Interest

As described in General Method H, the entirety of the crude reaction mixture was made up into a 100 mM DMSO/water stock solution. Aliquots were taken for analysis and crude reaction screening, leaving approximately 2 mL of bulk solution available for purification if the compound was deemed of interest.

Stock solutions were filtered through cotton wool before purifying by prep HPLC as a single 2 mL injection. Purification was performed using either: a Waters prep HPLC, using the Gemini-NX C18 column Dimensions: 30 mm x 250 mm 5 µm at pH4, with a 10 mM ammonium acetate/acetic acid buffer; or a ISCO ACCQPrep HP125 using the same column at pH4 however the mobile phase was unbuffered (0.1% formic acid solution). A 5 to 50% gradient was used unless stated otherwise below. Product fractions were combined and concentrated on a Biotage V10 or on a freeze drier.

Note: products with an NH_2 group were typically observed as the -NH_3 fragment ion by the LCMS under positive ionisation conditions. In some cases, negative ionisation did not result in fragmentation and so the full anticipated mass was observed (and is reported). NMR also confirmed the presence of the NH_2 group in the molecule in all cases.

S14.1.1 – 1-(1H-indazol-5-yl)pentan-1-amine, 12a



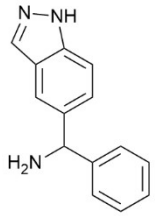
Waters prep HPLC purification gave 1-(1H-indazol-5-yl)pentan-1-amine (48.6 mg, 46.73%) as a colourless gum.

^{1}H NMR (600 MHz, DMSO) δ 12.96 (br s, 1H), 8.01 (s, 1H), 7.67 – 7.64 (m, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.36 (dd, J = 8.7, 1.5 Hz, 1H), 3.91 (t, J = 6.9 Hz, 1H), 1.71 – 1.54 (m, 2H), 1.32 – 1.18 (m, 3H), 1.14 – 1.03 (m, 1H), 0.81 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO) δ 139.7, 138.8, 133.6, 125.8, 123.2, 118.0, 110.3, 56.0, 39.2, 28.7, 22.6, 14.4.

HRMS (ESI$^+$) Mass required for exact match ($C_{12}H_{17}N_3$): 203.1422, mass required for -NH_3 fragment ion ($C_{12}H_{14}N_2$): 186.1157, Mass found: 186.1157.

S14.1.2 – 1H-indazol-5-yl(phenyl)methanamine, 12b



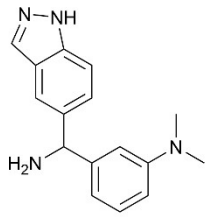
Waters prep HPLC purification gave 1H-indazol-5-yl(phenyl)methanamine (18.4 mg, 19.5%) as a white solid.

^{1}H NMR (600 MHz, DMSO) δ 12.94 (br s, 1H), 8.01 (s, 1H), 7.78 – 7.76 (m, 1H), 7.44 – 7.40 (m, 3H), 7.34 (dd, J = 8.7, 1.6 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.19 – 7.14 (m, 1H), 5.20 (s, 1H).

^{13}C NMR (150 MHz, DMSO) δ 147.6, 139.5, 139.4, 133.7, 128.5, 127.2, 126.7, 126.4, 123.1, 117.9, 110.3, 59.6.

HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{13}N_3$): 223.1109, mass required for -NH_3 fragment ion ($C_{14}H_{10}N_2$): 206.0844, Mass found: 206.0845.

S14.1.3 – 3-[amino(1H-indazol-5-yl)methyl]-N,N-dimethylaniline, 12z



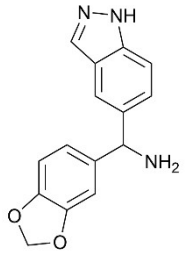
Teledyne ISCO ACCQPrep HP125 purification, using a focussed 5-45% gradient gave 3-[amino(1H-indazol-5-yl)methyl]-N,N-dimethylaniline (22.3 mg, 33.5%) as a white solid. NMR showed this to be the TFA salt.

^{1}H NMR (600 MHz, DMSO) δ 13.19 (s, 1H), 8.71 (br s, 3H), 8.14 (s, 1H), 7.88 – 7.84 (m, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.43 (dd, J = 8.7, 1.6 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.74 – 6.71 (m, 1H), 6.71 – 6.67 (m, 1H), 5.62 (s, 1H), 2.90 (s, 6H).

^{13}C NMR (150 MHz, DMSO) δ 151.1, 140.1, 139.8(b), 134.3(b), 131.4, 129.8, 126.0, 123.0, 119.6, 115.0, 112.4, 111.3, 111.0(b), 58.2, 40.5.

HRMS (ESI^{+}) Mass required for exact match ($C_{16}H_{18}N_4$): 266.1531, mass required for -NH_3 fragment ion ($C_{16}H_{15}N_3$): 249.1266, Mass found: 249.1270. HRMS (ESI^{-}) Mass required for exact match ($C_{16}H_{18}N_4$): 266.1531, Mass found: 266.1548.

S14.1.4 – 2H-1,3-benzodioxol-5-yl(1H-indazol-5-yl)methanamine, 12aa



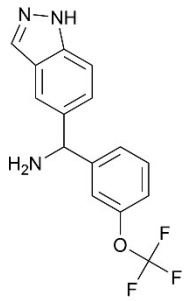
Teledyne ISCO ACCQPrep HP125 purification, using a focussed 5-30% gradient gave 2H-1,3-benzodioxol-5-yl(1H-indazol-5-yl)methanamine (18.1 mg, 27.1%) as a white solid. NMR showed this to be the formate salt (0.5eq).

^{1}H NMR (600 MHz, DMSO) δ 13.10 (br s, 1H), 8.09 (s, 1H), 7.82 – 7.80 (m, 1H), 7.54 – 7.50 (m, 1H), 7.39 – 7.35 (m, 1H), 7.05 – 7.02 (m, 1H), 6.94 – 6.91 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.02 – 5.96 (m, 2H), 5.44 (s, 1H).

^{13}C NMR (150 MHz, DMSO) δ147.8, 146.9, 139.7, 136.8, 134.6, 134.0, 126.1, 123.1, 120.9, 118.7, 110.8, 108.6, 107.9, 101.5, 58.1.

HRMS (ESI^{+}) Mass required for exact match ($C_{15}H_{13}N_3O_2$): 267.1008, mass required for -NH_3 fragment ion ($C_{15}H_{10}N_2O_2$): 250.0742, Mass found: 250.0746. HRMS (ESI^{-}) Mass required for exact match ($C_{15}H_{13}N_3O_2$): 267.1008, Mass found: 267.1007.

S14.1.5 – 1H-indazol-5-yl[3-(trifluoromethoxy)phenyl]methanamine, 12ai



Teledyne ISCO ACCQPrep HP125 purification, using a focussed 10-65% gradient gave 1H-indazol-5-yl[3-(trifluoromethoxy)phenyl]methanamine (14.2 mg, 18.5%) as an off-white solid. NMR showed this to be the formate salt (0.5eq).

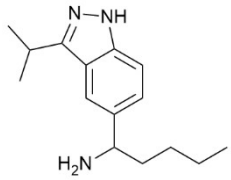
^{1}H NMR (600 MHz, DMSO) δ 13.03 (br s, 1H), 8.05 (s, 1H), 7.82 – 7.79 (m, 1H), 7.50 – 7.41 (m, 4H), 7.38 – 7.34 (m, 1H), 7.22 – 7.18 (m, 1H), 5.38 (s, 1H).

^{13}C NMR (150 MHz, DMSO) δ 149.1, 148.9, 139.7, 137.2, 133.9, 130.6, 126.5, 126.1, 123.2, 120.5, 119.6, 119.4, 118.5, 110.7, 58.6.

^{19}F NMR (564 MHz, DMSO) δ -55.6.

HRMS (ESI^{+}) Mass required for exact match ($C_{15}H_{12}N_3OF_3$): 307.0932, mass required for -NH_3 fragment ion ($C_{15}H_9N_2OF_3$): 290.0667, Mass found: 290.0666. HRMS (ESI^{-}) Mass required for exact match ($C_{15}H_{12}N_3OF_3$): 307.0932, Mass found: 307.0964.

S14.1.6 – 1-(3-isopropyl-1H-indazol-5-yl)pentan-1-amine, 13a



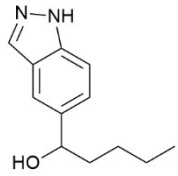
Waters prep HPLC purification gave 1-(3-isopropyl-1H-indazol-5-yl)pentan-1-amine (44.3 mg, 30.04%) as a colourless gum.

^{1}H NMR (600 MHz, DMSO) δ 12.49 (br s, 1H), 7.69 – 7.67 (m, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 8.6, 1.5 Hz, 1H), 3.92 (t, J = 6.9 Hz, 1H), 3.38 – 3.30 (m, 1H), 1.72 – 1.55 (m, 2H), 1.37 (d, J = 7.0, 3H), 1.37 (d, J = 7.0, 3H), 1.31 – 1.20 (m, 3H), 1.14 – 1.04 (m, 1H), 0.82 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO) δ 150.4, 141.0, 137.5, 125.5, 120.8, 117.8, 110.3, 56.0, 39.1, 28.6, 27.5, 22.7, 22.7, 22.6, 14.4.

HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{23}N_3$): 245.1892, mass required for -NH_3 fragment ion ($C_{15}H_{20}N_2$): 228.1626, Mass found: 228.1627.

S14.1.7 – 1-(1H-indazol-5-yl)pentan-1-ol, 14a



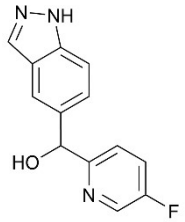
Waters prep HPLC purification gave 1-(1H-indazol-5-yl)pentan-1-ol (8.8 mg, 17.23%) as a colourless gum.

^{1}H NMR (600 MHz, DMSO) δ 12.94 (s, 1H), 8.01 (s, 1H), 7.65 – 7.62 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 8.6, 1.5 Hz, 1H), 5.08 (d, J = 4.2 Hz, 1H), 4.62 – 4.56 (m, 1H), 1.71 – 1.64 (m, 1H), 1.64 – 1.56 (m, 1H), 1.35 – 1.13 (m, 4H), 0.83 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO) δ 139.7, 138.9, 133.8, 125.3, 123.1, 117.4, 110.1, 73.0, 39.7, 28.1, 22.6, 14.5.

HRMS (ESI$^+$) Mass required for exact match ($C_{12}H_{16}N_2O$): 204.1263, Mass found: 204.1259.

S14.1.8 – (5-fluoropyridin-2-yl)(1H-indazol-5-yl)methanol, 14l



Teledyne ISCO ACCQPrep HP125 purification, using a focussed 5-50% gradient gave (5-fluoropyridin-2-yl)(1H-indazol-5-yl)methanol (9.6 mg, 15.8%) as an off-white solid.

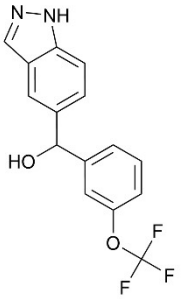
^{1}H NMR (600 MHz, DMSO) δ 13.00 (s, 1H), 8.44 (d, J = 2.7 Hz, 1H), 8.05 – 8.01 (m, 1H), 7.76 – 7.73 (m, 1H), 7.73 – 7.69 (m, 1H), 7.69 – 7.65 (m, 1H), 7.47 – 7.43 (m, 1H), 7.36 – 7.33 (m, 1H), 6.17 (br s, 1H), 5.83 (s, 1H).

^{13}C NMR (150 MHz, DMSO) δ 161.3, 158.4, 139.7, 136.8, 136.6, 134.0, 125.7, 124.1, 123.0, 121.8, 118.3, 110.3, 75.8.

^{19}F NMR (564 MHz, DMSO) δ -130.5.

HRMS (ESI$^+$) Mass required for exact match ($C_{13}H_{10}N_3OF$): 243.0808, mass required for -OH fragment ion ($C_{13}H_8N_3F$): 225.0702, Mass found: 225.0707. HRMS (ESI$^-$) Mass required for exact match ($C_{13}H_{10}N_3OF$): 243.0808, Mass found: 243.0836.

S14.1.9 – 1H-indazol-5-yl[3-(trifluoromethoxy)phenyl]methanol, 14ai



Teledyne ISCO ACCQPrep HP125 purification, using a 10-95% gradient gave 1H-indazol-5-yl[3-(trifluoromethoxy)phenyl]methanol (12.8 mg, 16.6%) as a white solid.

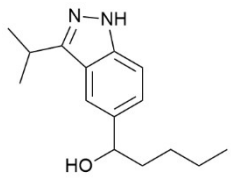
^{1}H NMR (600 MHz, DMSO) δ 13.01 (s, 1H), 8.05 (s, 1H), 7.78 – 7.76 (m, 1H), 7.49 – 7.45 (m, 1H), 7.45 – 7.41 (m, 1H), 7.41 – 7.38 (m, 2H), 7.34- 7.30 (m, 1H), 7.21 – 7.17 (m, 1H), 6.10 (d, J = 3.9 Hz, 1H), 5.89 – 5.86 (m, 1H).

^{13}C NMR (150 MHz, DMSO) δ 149.5, 148.8, 139.7, 137.6, 134.0, 130.5, 125.8, 125.6, 123.0, 120.6, 119.4, 118.7, 118.1, 110.5, 74.0.

^{19}F NMR (564 MHz, DMSO) δ -56.6.

HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{11}N_2O_2F_3$): 308.0773, Mass found: 308.0776.

S14.1.10 – 1-(3-isopropyl-1H-indazol-5-yl)pentan-1-ol, 15a



Waters prep HPLC purification, using a 5-95% gradient gave 1-(3-isopropyl-1H-indazol-5-yl)pentan-1-ol (6.4 mg, 10.39%) as a colourless glass.

^{1}H NMR (600 MHz, DMSO) δ 12.46 (s, 1H), 7.65 – 7.62 (m, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.28 (dd, J = 8.6, 1.5 Hz, 1H), 5.06 (d, J = 4.3 Hz, 1H), 4.61 – 4.57 (m, 1H), 3.38 – 3.29 (m, 1H), 1.72 – 1.63 (m, 1H), 1.63 – 1.55 (m, 1H), 1.37 (d, J = 6.9 Hz, 6H), 1.36 – 1.15 (m, 4H), 0.84 (t, J = 7.1 Hz, 3H). One CH proton is obscured by the water peak.

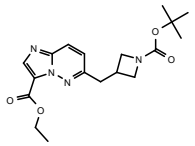
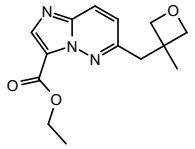
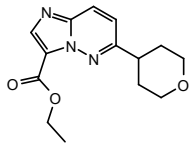
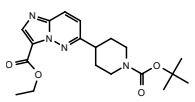
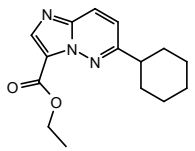
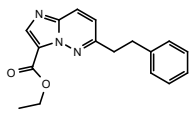
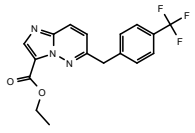
^{13}C NMR (150 MHz, DMSO) δ 150.5, 141.0, 138.0, 125.0, 120.6, 117.1, 110.1, 73.1, 39.8, 28.2, 27.5, 22.7, 22.7, 22.6, 14.5.

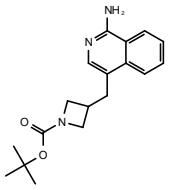
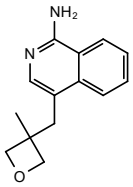
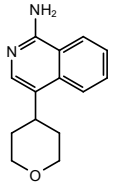
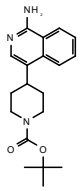
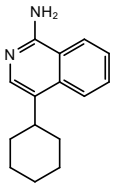
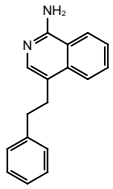
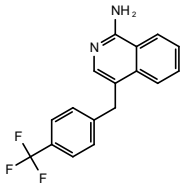
HRMS (ESI^{+}) Mass required for exact match ($C_{15}H_{22}N_2O$): 246.1732, Mass found: 246.1732.

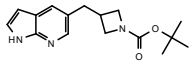
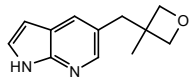
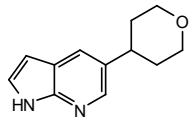
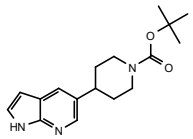
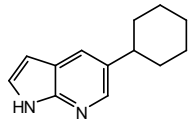
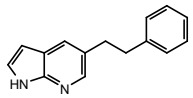
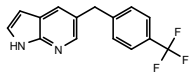
S15 – References

1. M. Berton *et al.*, On-demand synthesis of organozinc halides under continuous flow conditions, *Nat. Protoc.*, 2018, **13**, 324.
2. L. Huck *et al.*, Grignard Reagents on a Tab: Direct Magnesium Insertion under Flow Conditions, *Org. Lett.*, 2017, **19**, 3747.
3. E. M. Hanada *et al.*, Trimethylsilyl Chloride Aids in Solubilization of Oxidative Addition Intermediates from Zinc Metal, *Angew. Chem., Int. Ed.*, 2023, DOI: 10.1002/anie.202307787
4. I. Abdiaj *et al.*, End-to-End Automated Synthesis of C(sp^3)-Enriched Drug-like Molecules via Negishi Coupling and Novel, Automated Liquid–Liquid Extraction, *J. Med. Chem.*, 2023, **66**, 716.
5. D. Maddox *et al.*, Development of a Low-Cost Multi-Wavelength Inline Detector for Slug Detection in Continuous Flow, *ChemRxiv*, 2023, preprint, DOI: 10.26434/chemrxiv-2023-r52zg
6. M. Berton *et al.*, Disposable cartridge concept for the on-demand synthesis of turbo Grignards, Knochel–Hauser amides, and magnesium alkoxides, *Beilstein J. Org. Chem.*, 2020, **16**, 1343.

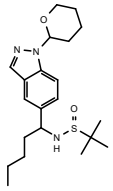
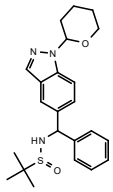
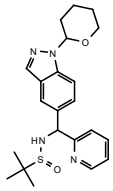
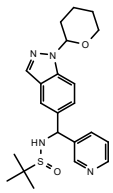
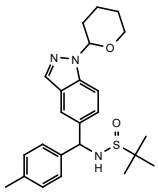
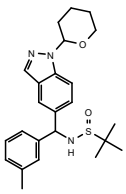
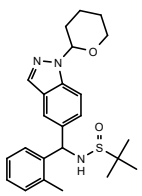
Appendix 1 – HRMS Data for Negishi CRS Library

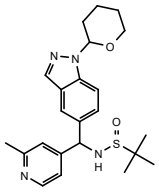
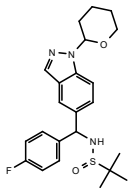
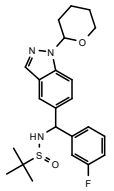
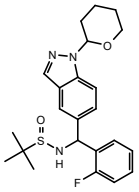
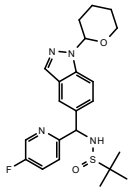
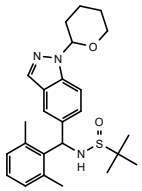
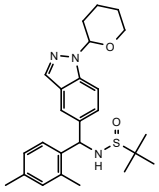
ID	Structure	Outcome	HRMS Result
1a		Fragment match	tert-butyl 3-{[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]methyl}azetidine-1-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{24}N_4O_4$): 360.1798, mass required for -NH_3 fragment ion ($C_{14}H_{16}N_4O_4$): 304.1172, Mass found: 304.1171.
1b		Exact match	ethyl 6-[(3-methyloxetan-3-yl)methyl]imidazo[1,2-b]pyridazine-3-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{17}N_3O_3$): 275.1270, Mass found: 275.1266.
1c		Exact match	ethyl 6-(oxan-4-yl)imidazo[1,2-b]pyridazine-3-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{17}N_3O_3$): 275.1270, Mass found: 275.1270.
1d		Exact match	tert-butyl 4-[3-(ethoxycarbonyl)imidazo[1,2-b]pyridazin-6-yl]piperidine-1-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{26}N_4O_4$): 374.1954, Mass found: 374.1951.
1e		Exact match	ethyl 6-cyclohexylimidazo[1,2-b]pyridazine-3-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{19}N_3O_2$): 273.1477, Mass found: 273.1475.
1f		Exact match	ethyl 6-(2-phenylethyl)imidazo[1,2-b]pyridazine-3-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{17}N_3O_2$): 295.1321, Mass found: 295.1321.
1g		Exact match	ethyl 6-{[4-(trifluoromethyl)phenyl]methyl}imidazo[1,2-b]pyridazine-3-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{14}F_3N_3O_2$): 349.1038, Mass found: 349.1037.

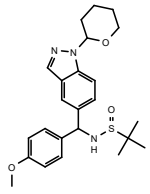
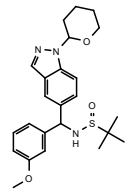
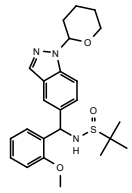
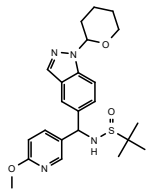
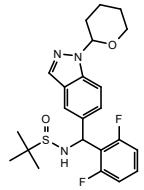
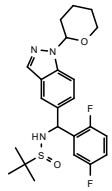
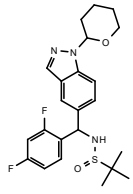
2a		Exact match	tert-butyl 3-[(1-aminoisoquinolin-4-yl)methyl]azetidine-1-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{23}N_3O_2$): 313.1790, Mass found: 313.1792.
2b		Exact match	4-[(3-methyloxetan-3-yl)methyl]isoquinolin-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{16}N_2O$): 228.1263, Mass found: 228.1265.
2c		Exact match	4-(oxan-4-yl)isoquinolin-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{16}N_2O$): 228.1263, Mass found: 228.1264.
2d		Exact match	tert-butyl 4-(1-aminoisoquinolin-4-yl)piperidine-1-carboxylate. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{25}N_3O_2$): 327.1947, Mass found: 327.1944.
2e		Exact match	4-cyclohexylisoquinolin-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{18}N_2$): 226.1470, Mass found: 226.1471.
2f		Exact match	4-(2-phenylethyl)isoquinolin-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{16}N_2$): 248.1313, Mass found: 248.1315.
2g		Exact match	4-{[4-(trifluoromethyl)phenyl]methyl}isoquinolin-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{13}F_3N_2$): 302.1031, Mass found: 302.1030.

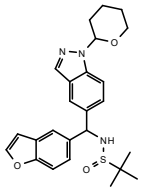
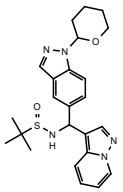
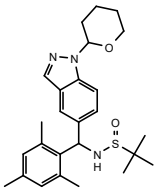
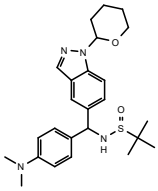
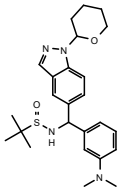
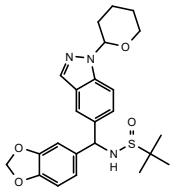
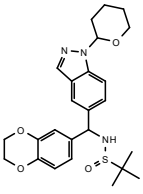
3a		Fragment match	tert-butyl 3-({1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)azetidine-1-carboxylate. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{21}N_3O_2$): 287.1634, mass required for -NH_3 fragment ion ($C_{12}H_{13}N_3O_2$): 231.1008, Mass found: 231.1009.
3b		Exact match	5-[(3-methyloxetan-3-yl)methyl]-1H-pyrrolo[2,3-b]pyridine. HRMS (ESI^+) Mass required for exact match ($C_{12}H_{14}N_2O$): 202.1106, Mass found: 202.1107.
3c		Exact match	5-(oxan-4-yl)-1H-pyrrolo[2,3-b]pyridine. HRMS (ESI^+) Mass required for exact match ($C_{12}H_{14}N_2O$): 202.1106, Mass found: 202.1107.
3d		Exact match	tert-butyl 4-{1H-pyrrolo[2,3-b]pyridin-5-yl}piperidine-1-carboxylate. HRMS (ESI^+) Mass required for exact match ($C_{17}H_{23}N_3O_2$): 301.1790, Mass found: 301.1793.
3e		Exact match	5-cyclohexyl-1H-pyrrolo[2,3-b]pyridine. HRMS (ESI^+) Mass required for exact match ($C_{13}H_{16}N_2$): 200.1313, Mass found: 200.1315.
3f		Exact match	5-(2-phenylethyl)-1H-pyrrolo[2,3-b]pyridine. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{14}N_2$): 222.1157, Mass found: 222.1159.
3g		Failed reaction	5-{[4-(trifluoromethyl)phenyl]methyl}-1H-pyrrolo[2,3-b]pyridine. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{11}F_3N_2$): 276.0874, no target mass found - reaction failed.

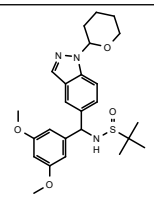
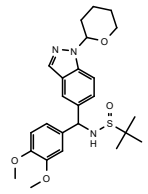
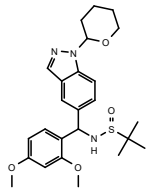
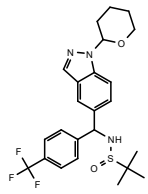
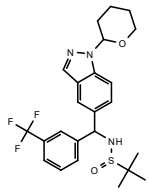
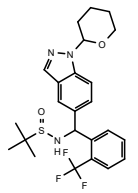
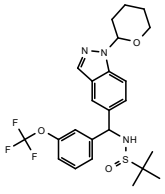
Appendix 2 – HRMS Data for Grignard CRS Library: Flow Grignard Step

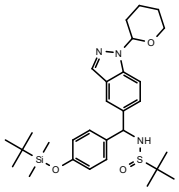
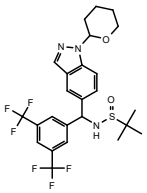
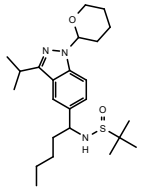
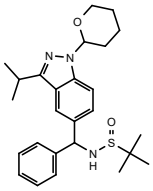
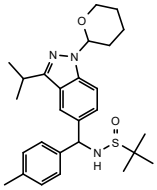
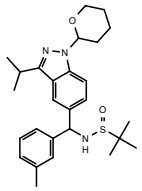
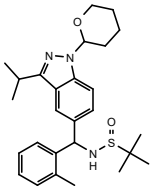
ID	Structure	Outcome	HRMS Result
8a		Exact match	2-methyl-N-{1-[1-(oxan-2-yl)-1H-indazol-5-yl]pentyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{21}H_{33}N_3O_2S$): 391.2293, Mass found: 391.2296.
8b		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl](phenyl)methyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{29}N_3O_2S$): 411.1980, Mass found: 411.1983.
8c		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl](pyridin-2-yl)methyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{22}H_{28}N_4O_2S$): 412.1933, Mass found: 412.1948.
8d		Failed reaction	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl](pyridin-3-yl)methyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{22}H_{28}N_4O_2S$): 412.1933, Mass found: 412.1930. No product UV peak identified, marked as failed.
8e		Exact match	2-methyl-N-[(4-methylphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_2S$): 425.2137, Mass found: 425.2140.
8f		Exact match	2-methyl-N-[(3-methylphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_2S$): 425.2137, Mass found: 425.2138.
8g		Exact match	2-methyl-N-[(2-methylphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_2S$): 425.2137, Mass found: 425.2137.

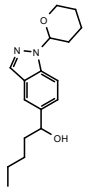
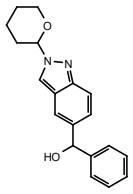
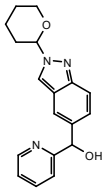
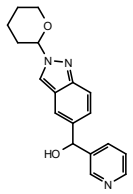
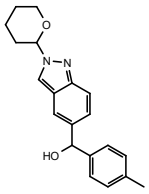
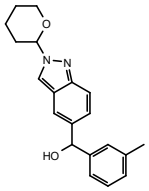
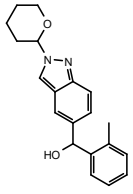
8h		Failed reaction	2-methyl-N-[(2-methylpyridin-4-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{30}N_4O_2S$): 426.2089, Mass found: 426.2086. No product UV peak identified, marked as failed.
8i		Exact match	N-[(4-fluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{28}FN_3O_2S$): 429.1886, Mass found: 429.1887.
8j		Exact match	N-[(3-fluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{28}FN_3O_2S$): 429.1886, Mass found: 429.1885.
8k		Failed reaction	N-[(2-fluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{28}FN_3O_2S$): 429.1886, no target mass found - reaction failed.
8l		Exact match	N-[(5-fluoropyridin-2-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{22}H_{27}FN_4O_2S$): 430.1839, Mass found: 430.1842.
8m		Exact match	N-[(2,6-dimethylphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{33}N_3O_2S$): 439.2293, Mass found: 439.2290.
8n		Exact match	N-[(2,4-dimethylphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{33}N_3O_2S$): 439.2293, Mass found: 439.2293.

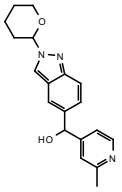
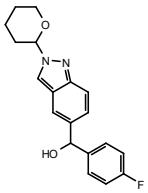
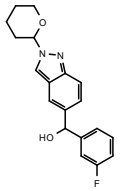
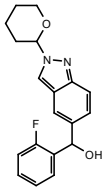
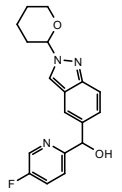
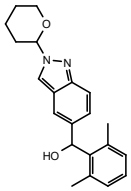
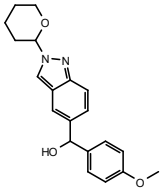
8o		Exact match	N-[(4-methoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_3S$): 441.2086, Mass found: 441.2079.
8p		Exact match	N-[(3-methoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_3S$): 441.2086, Mass found: 441.2087.
8q		Exact match	N-[(2-methoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{31}N_3O_3S$): 441.2086, Mass found: 441.2079.
8r		Failed reaction	N-[(6-methoxypyridin-3-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{30}N_4O_3S$): 442.2039, Mass found: 442.2035. No product UV peak identified, marked as failed.
8s		Failed reaction	N-[(2,6-difluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{27}F_2N_3O_2S$): 447.1792, Mass found: 447.1809. No product UV peak identified, marked as failed.
8t		Exact match	N-[(2,5-difluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{27}F_2N_3O_2S$): 447.1792, Mass found: 447.1792.
8u		Failed reaction	N-[(2,4-difluorophenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{23}H_{27}F_2N_3O_2S$): 447.1792, Mass found: 447.1791. No product UV peak identified, marked as failed.

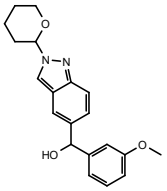
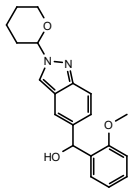
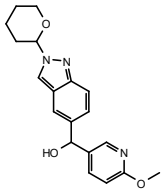
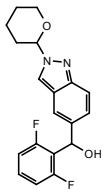
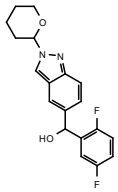
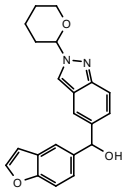
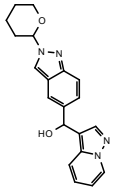
8v		Exact match	N-[(1-benzofuran-5-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{29}N_3O_3S$): 451.1930, Mass found: 451.1931.
8w		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl]({pyrazolo[1,5-a]pyridin-3-yl})methyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{29}N_5O_2S$): 451.2042, Mass found: 451.2036.
8x		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl](2,4,6-trimethylphenyl)methyl}propane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{26}H_{35}N_3O_2S$): 453.2450, Mass found: 453.2452.
8y		Exact match	N-{[4-(dimethylamino)phenyl][1-(oxan-2-yl)-1H-indazol-5-yl]methyl}-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{34}N_4O_2S$): 454.2402, Mass found: 454.2393.
8z		Exact match	N-{[3-(dimethylamino)phenyl][1-(oxan-2-yl)-1H-indazol-5-yl]methyl}-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{34}N_4O_2S$): 454.2402, Mass found: 454.2403.
8aa		Exact match	N-[(2H-1,3-benzodioxol-5-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{24}H_{29}N_3O_4S$): 455.1879, Mass found: 455.1877.
8ab		Exact match	N-[(2,3-dihydro-1,4-benzodioxin-6-yl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI^+) Mass required for exact match ($C_{25}H_{31}N_3O_4S$): 469.2035, Mass found: 469.2035.

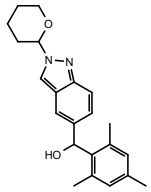
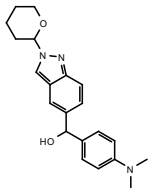
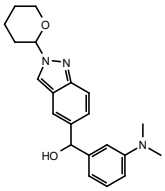
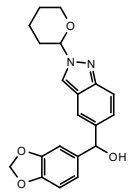
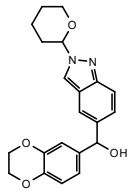
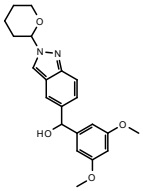
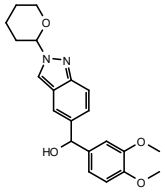
8ac		Exact match	N-[(3,5-dimethoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{25}H_{33}N_3O_4S$): 471.2192, Mass found: 471.2195.
8ad		Exact match	N-[(3,4-dimethoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{25}H_{33}N_3O_4S$): 471.2192, Mass found: 471.2188.
8ae		Exact match	N-[(2,4-dimethoxyphenyl)[1-(oxan-2-yl)-1H-indazol-5-yl]methyl]-2-methylpropane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{25}H_{33}N_3O_4S$): 471.2192, Mass found: 471.2190.
8af		Failed reaction	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl][4-(trifluoromethyl)phenyl]methyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{24}H_{28}F_3N_3O_2S$): 479.1854, Mass found: 479.1855. No product UV peak identified, marked as failed.
8ag		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl][3-(trifluoromethyl)phenyl]methyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{24}H_{28}F_3N_3O_2S$): 479.1854, Mass found: 479.1856.
8ah		Failed reaction	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl][2-(trifluoromethyl)phenyl]methyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{24}H_{28}F_3N_3O_2S$): 479.1854, Mass found: 479.1861. No product UV peak identified, marked as failed.
8ai		Exact match	2-methyl-N-{[1-(oxan-2-yl)-1H-indazol-5-yl][3-(trifluoromethoxy)phenyl]methyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{24}H_{28}F_3N_3O_3S$): 495.1803, Mass found: 495.1806.

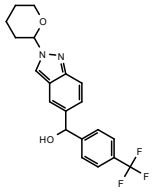
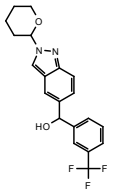
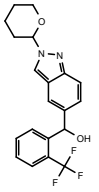
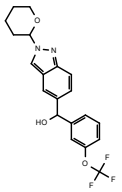
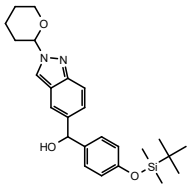
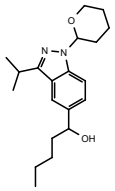
8aj		Exact match	N-({4-[(tert-butyldimethylsilyl)oxy]phenyl}[1-(oxan-2-yl)-1H-indazol-5-yl]methyl)-2-methylpropane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{29}H_{43}N_3O_3SSi$): 541.2794, Mass found: 541.2791.
8ak		Exact match	N-{[3,5-bis(trifluoromethyl)phenyl][1-(oxan-2-yl)-1H-indazol-5-yl]methyl}-2-methylpropane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{25}H_{27}F_6N_3O_2S$): 547.1728, Mass found: 547.1725.
9a		Exact match	2-methyl-N-{1-[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl]pentyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{24}H_{39}N_3O_2S$): 433.2763, Mass found: 433.2758.
9b		Exact match	2-methyl-N-{[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl](phenyl)methyl}propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{26}H_{35}N_3O_2S$): 453.2450, Mass found: 453.2445.
9e		Exact match	2-methyl-N-[(4-methylphenyl)[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{27}H_{37}N_3O_2S$): 467.2606, Mass found: 467.2599.
9f		Exact match	2-methyl-N-[(3-methylphenyl)[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{27}H_{37}N_3O_2S$): 467.2606, Mass found: 467.2602.
9g		Exact match	2-methyl-N-[(2-methylphenyl)[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl]methyl]propane-2-sulfinamide. HRMS (ESI$^+$) Mass required for exact match ($C_{27}H_{37}N_3O_2S$): 467.2606, Mass found: 467.2600.

10a		Exact match	1-[1-(oxan-2-yl)-1H-indazol-5-yl]pentan-1-ol. HRMS (ESI^+) Mass required for exact match ($C_{17}H_{24}N_2O_2$): 288.1838, Mass found: 288.1838.
10b		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl](phenyl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{19}H_{20}N_2O_2$): 308.1525, Mass found: 308.1529.
10c		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl](pyridin-2-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{18}H_{19}N_3O_2$): 309.1477, Mass found: 309.1479.
10d		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl](pyridin-3-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{18}H_{19}N_3O_2$): 309.1477, Mass found: 309.1480.
10e		Exact match	(4-methylphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI^+) Mass required for exact match ($C_{20}H_{22}N_2O_2$): 322.1681, Mass found: 322.1670.
10f		Exact match	(3-methylphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI^+) Mass required for exact match ($C_{20}H_{22}N_2O_2$): 322.1681, Mass found: 322.1676.
10g		Exact match	(2-methylphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI^+) Mass required for exact match ($C_{20}H_{22}N_2O_2$): 322.1681, Mass found: 322.1673.

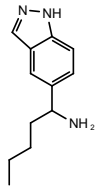
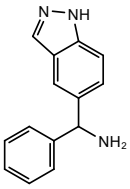
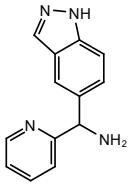
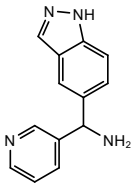
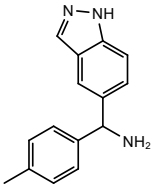
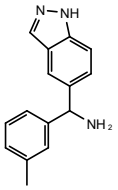
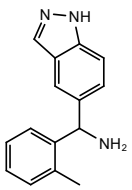
10h		Exact match	(2-methylpyridin-4-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{21}N_3O_2$): 323.1634, Mass found: 323.1629.
10i		Exact match	(4-fluorophenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{19}FN_2O_2$): 326.1431, Mass found: 326.1428.
10j		Exact match	(3-fluorophenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{19}FN_2O_2$): 326.1431, Mass found: 326.1427.
10k		Exact match	(2-fluorophenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{19}FN_2O_2$): 326.1431, Mass found: 326.1431.
10l		Exact match	(5-fluoropyridin-2-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{18}FN_3O_2$): 327.1383, Mass found: 327.1387.
10m		Exact match	(2,6-dimethylphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{24}N_2O_2$): 336.1838, Mass found: 336.1834.
10o		Exact match	(4-methoxyphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{22}N_2O_3$): 338.1630, Mass found: 338.1614.

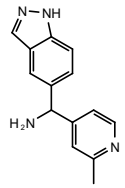
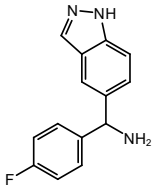
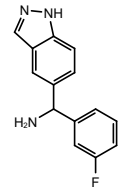
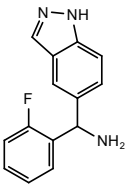
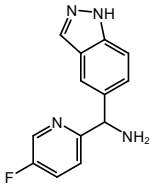
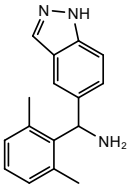
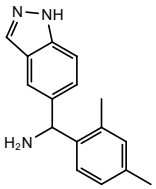
10p		Exact match	(3-methoxyphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{22}N_2O_3$): 338.1630, Mass found: 338.1625.
10q		Exact match	(2-methoxyphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{22}N_2O_3$): 338.1630, Mass found: 338.1605.
10r		Exact match	(6-methoxypyridin-3-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{21}N_3O_3$): 339.1583, Mass found: 339.1585.
10s		Exact match	(2,6-difluorophenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{18}F_2N_2O_2$): 344.1336, Mass found: 344.1336.
10t		Exact match	(2,5-difluorophenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{19}H_{18}F_2N_2O_2$): 344.1336, Mass found: 344.1338.
10v		Exact match	(1-benzofuran-5-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{20}N_2O_3$): 348.1474, Mass found: 348.1470.
10w		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl]({pyrazolo[1,5-a]pyridin-3-yl})methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{20}N_4O_2$): 348.1586, Mass found: 348.1589.

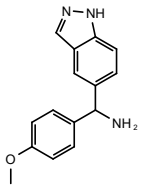
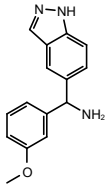
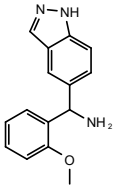
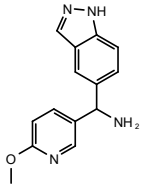
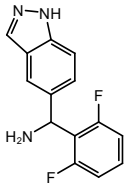
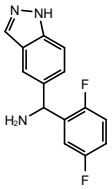
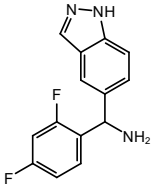
10x		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl](2,4,6-trimethylphenyl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{22}H_{26}N_2O_2$): 350.1994, Mass found: 350.1996.
10y		Exact match	[4-(dimethylamino)phenyl][2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{25}N_3O_2$): 351.1947, Mass found: 351.1944.
10z		Exact match	[3-(dimethylamino)phenyl][2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{25}N_3O_2$): 351.1947, Mass found: 351.1949.
10aa		Exact match	(2H-1,3-benzodioxol-5-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{20}N_2O_4$): 352.1423, Mass found: 352.1426.
10ab		Exact match	(2,3-dihydro-1,4-benzodioxin-6-yl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{22}N_2O_4$): 366.1580, Mass found: 366.1581.
10ac		Exact match	(3,5-dimethoxyphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{24}N_2O_4$): 368.1736, Mass found: 368.1737.
10ad		Exact match	(3,4-dimethoxyphenyl)[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{21}H_{24}N_2O_4$): 368.1736, Mass found: 368.1735.

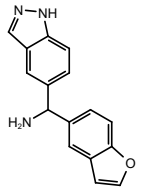
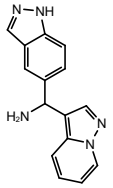
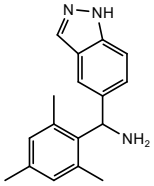
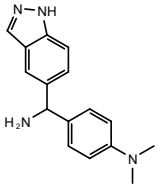
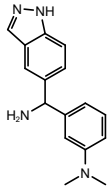
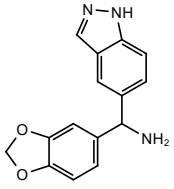
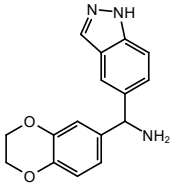
10af		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl][4-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{19}F_3N_2O_2$): 376.1399, Mass found: 376.1398.
10ag		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl][3-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{19}F_3N_2O_2$): 376.1399, Mass found: 376.1397.
10ah		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl][2-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{19}F_3N_2O_2$): 376.1399, Mass found: 376.1395.
10ai		Exact match	[2-(oxan-2-yl)-2H-indazol-5-yl][3-(trifluoromethoxy)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{19}F_3N_2O_3$): 392.1348, Mass found: 392.1347.
10aj		Exact match	{4-[(tert-butyldimethylsilyl)oxy]phenyl}[2-(oxan-2-yl)-2H-indazol-5-yl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{25}H_{34}N_2O_3Si$): 438.2339, Mass found: 438.2342.
11a		Exact match	1-[1-(oxan-2-yl)-3-(propan-2-yl)-1H-indazol-5-yl]pentan-1-ol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{30}N_2O_2$): 330.2307, Mass found: 330.2308.

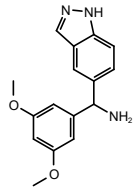
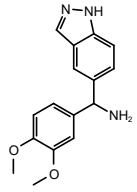
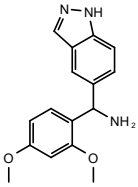
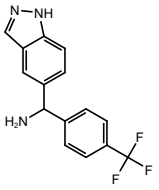
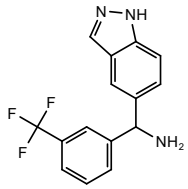
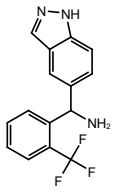
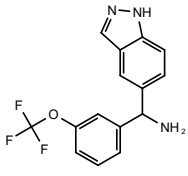
Appendix 3 – HRMS Data for Grignard CRS Library: Batch Deprotection Step

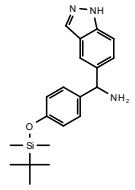
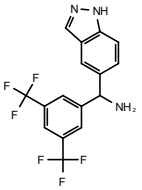
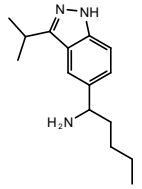
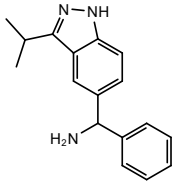
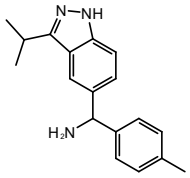
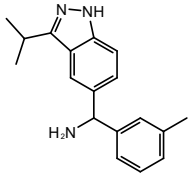
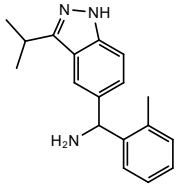
ID	Structure	Outcome	HRMS Result
12a		Exact match	1-(1H-indazol-5-yl)pentan-1-amine. HRMS (ESI^+) Mass required for exact match ($C_{12}H_{17}N_3$): 203.1422, Mass found: 203.1421.
12b		Exact match	1-(1H-indazol-5-yl)-1-phenylmethanamine. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{13}N_3$): 223.1109, Mass found: 223.1094.
12c		Exact match	1-(1H-indazol-5-yl)-1-(pyridin-2-yl)methanamine. HRMS (ESI^+) Mass required for exact match ($C_{13}H_{12}N_4$): 224.1062, Mass found: 224.1061.
12d		Failed reaction	1-(1H-indazol-5-yl)-1-(pyridin-3-yl)methanamine. HRMS (ESI^+) Mass required for exact match ($C_{13}H_{12}N_4$): 224.1062, Mass found: 224.1063. No product UV peak identified, marked as failed.
12e		Exact match	1-(1H-indazol-5-yl)-1-(4-methylphenyl)methanamine. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{15}N_3$): 237.1266, Mass found: 237.1260.
12f		Exact match	1-(1H-indazol-5-yl)-1-(3-methylphenyl)methanamine. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{15}N_3$): 237.1266, Mass found: 237.1261.
12g		Exact match	1-(1H-indazol-5-yl)-1-(2-methylphenyl)methanamine. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{15}N_3$): 237.1266, Mass found: 237.1267.

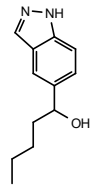
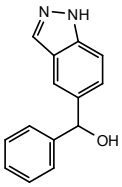
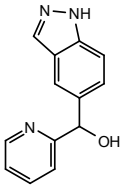
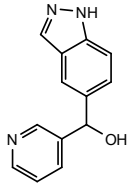
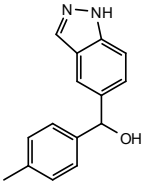
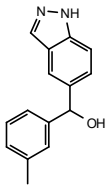
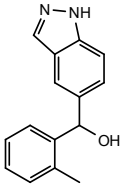
12h		Exact match	1-(1H-indazol-5-yl)-1-(2-methylpyridin-4-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{14}N_4$): 238.1218, Mass found: 238.1220.
12i		Exact match	1-(4-fluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{12}FN_3$): 241.1015, Mass found: 241.1009.
12j		Fragment match	1-(3-fluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{12}FN_3$): 241.1015, mass required for -NH_3 fragment ion ($C_{14}H_9FN_2$): 224.0750, Mass found: 224.0753.
12k		Fragment match	1-(2-fluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{12}FN_3$): 241.1015, mass required for -NH_3 fragment ion ($C_{14}H_9FN_2$): 224.0750, Mass found: 224.0761.
12l		Fragment match	1-(5-fluoropyridin-2-yl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{13}H_{11}FN_4$): 242.0968, mass required for -NH_3 fragment ion ($C_{13}H_8FN_3$): 225.0702, Mass found: 225.0707.
12m		Exact match	1-(2,6-dimethylphenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{17}N_3$): 251.1422, Mass found: 251.1420.
12n		Fragment match	1-(2,4-dimethylphenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{17}N_3$): 251.1422, mass required for -NH_3 fragment ion ($C_{16}H_{14}N_2$): 234.1157, Mass found: 234.1160.

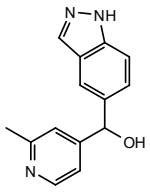
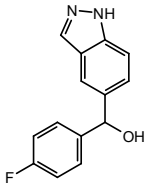
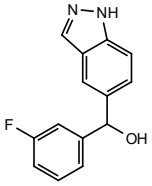
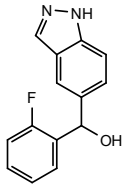
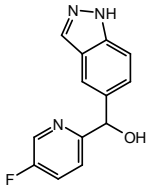
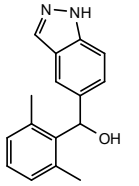
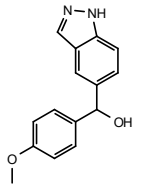
12o		Exact match	1-(1H-indazol-5-yl)-1-(4-methoxyphenyl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{15}N_3O$): 253.1215, Mass found: 253.1218.
12p		Exact match	1-(1H-indazol-5-yl)-1-(3-methoxyphenyl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{15}N_3O$): 253.1215, Mass found: 253.1209.
12q		Exact match	1-(1H-indazol-5-yl)-1-(2-methoxyphenyl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{15}N_3O$): 253.1215, Mass found: 253.1216.
12r		Failed reaction	1-(1H-indazol-5-yl)-1-(6-methoxypyridin-3-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{14}N_4O$): 254.1168, Mass found: 254.1170. No product UV peak identified, marked as failed.
12s		Failed reaction	1-(2,6-difluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{11}F_2N_3$): 259.0921, mass required for -NH_3 fragment ion ($C_{14}H_8F_2N_2$): 242.0656, no target mass found - reaction failed.
12t		Exact match	1-(2,5-difluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{11}F_2N_3$): 259.0921, Mass found: 259.0920.
12u		Failed reaction	1-(2,4-difluorophenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{11}F_2N_3$): 259.0921, mass required for -NH_3 fragment ion ($C_{14}H_8F_2N_2$): 242.0656, no target mass found - reaction failed.

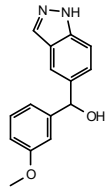
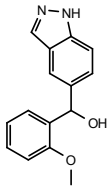
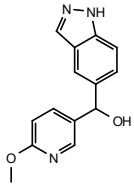
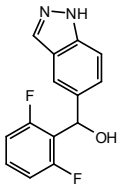
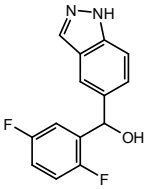
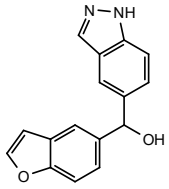
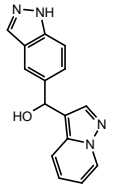
12v		Fragment match	1-(1-benzofuran-5-yl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{13}N_3O$): 263.1059, mass required for -NH_3 fragment ion ($C_{16}H_{10}N_2O$): 246.0793, Mass found: 246.0795.
12w		Failed reaction	1-(1H-indazol-5-yl)-1-{pyrazolo[1,5-a]pyridin-3-yl}methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{13}N_5$): 263.1171, mass required for -NH_3 fragment ion ($C_{15}H_{10}N_4$): 246.0905, no target mass found - reaction failed.
12x		Exact match	1-(1H-indazol-5-yl)-1-(2,4,6-trimethylphenyl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{19}N_3$): 265.1579, Mass found: 265.1570.
12y		Exact match	4-[amino(1H-indazol-5-yl)methyl]-N,N-dimethylaniline. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{18}N_4$): 266.1531, Mass found: 266.1532.
12z		Fragment match	3-[amino(1H-indazol-5-yl)methyl]-N,N-dimethylaniline. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{18}N_4$): 266.1531, mass required for -NH_3 fragment ion ($C_{16}H_{15}N_3$): 249.1266, Mass found: 249.1269.
12aa		Exact match	1-(2H-1,3-benzodioxol-5-yl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{13}N_3O_2$): 267.1008, Mass found: 267.1005.
12ab		Exact match	1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{15}N_3O_2$): 281.1164, Mass found: 281.1169.

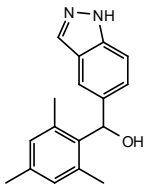
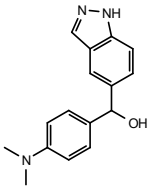
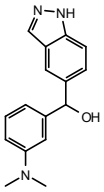
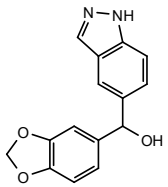
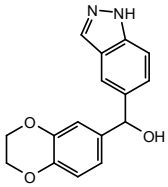
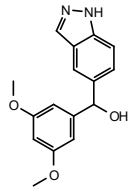
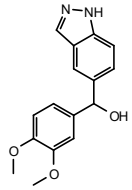
12ac		Exact match	1-(3,5-dimethoxyphenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{17}N_3O_2$): 283.1321, Mass found: 283.1311.
12ad		Exact match	1-(3,4-dimethoxyphenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{17}N_3O_2$): 283.1321, Mass found: 283.1317.
12ae		Failed reaction	1-(2,4-dimethoxyphenyl)-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{17}N_3O_2$): 283.1321, mass required for -NH_3 fragment ion ($C_{16}H_{14}N_2O_2$): 266.1055, no target mass found - reaction failed.
12af		Exact match	1-(1H-indazol-5-yl)-1-[4-(trifluoromethyl)phenyl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{12}F_3N_3$): 291.0983, Mass found: 291.0980.
12ag		Exact match	1-(1H-indazol-5-yl)-1-[3-(trifluoromethyl)phenyl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{12}F_3N_3$): 291.0983, Mass found: 291.0982.
12ah		Fragment match	1-(1H-indazol-5-yl)-1-[2-(trifluoromethyl)phenyl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{12}F_3N_3$): 291.0983, mass required for -NH_3 fragment ion ($C_{15}H_9F_3N_2$): 274.0718, Mass found: 274.0716.
12ai		Exact match	1-(1H-indazol-5-yl)-1-[3-(trifluoromethoxy)phenyl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{12}F_3N_3O$): 307.0932, Mass found: 307.0936.

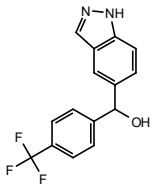
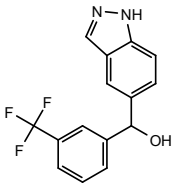
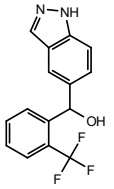
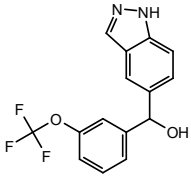
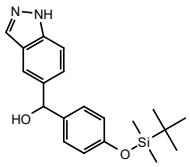
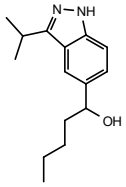
12aj		Fragment match	1-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{27}N_3OSi$): 353.1923, mass required for -NH_3 fragment ion ($C_{20}H_{24}N_2OSi$): 336.1658, Mass found: 336.1659.
12ak		Fragment match	1-[3,5-bis(trifluoromethyl)phenyl]-1-(1H-indazol-5-yl)methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{16}H_{11}F_6N_3$): 359.0857, mass required for -NH_3 fragment ion ($C_{16}H_8F_6N_2$): 342.0592, Mass found: 342.0591.
13a		Exact match	1-[3-(propan-2-yl)-1H-indazol-5-yl]pentan-1-amine. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{23}N_3$): 245.1892, Mass found: 245.1892.
13b		Exact match	1-phenyl-1-[3-(propan-2-yl)-1H-indazol-5-yl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{17}H_{19}N_3$): 265.1579, Mass found: 265.1579.
13e		Fragment match	1-(4-methylphenyl)-1-[3-(propan-2-yl)-1H-indazol-5-yl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{21}N_3$): 279.1735, mass required for -NH_3 fragment ion ($C_{18}H_{18}N_2$): 262.1470, Mass found: 262.1469.
13f		Fragment match	1-(3-methylphenyl)-1-[3-(propan-2-yl)-1H-indazol-5-yl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{21}N_3$): 279.1735, mass required for -NH_3 fragment ion ($C_{18}H_{18}N_2$): 262.1470, Mass found: 262.1467.
13g		Fragment match	1-(2-methylphenyl)-1-[3-(propan-2-yl)-1H-indazol-5-yl]methanamine. HRMS (ESI$^+$) Mass required for exact match ($C_{18}H_{21}N_3$): 279.1735, mass required for -NH_3 fragment ion ($C_{18}H_{18}N_2$): 262.1470, Mass found: 262.1474.

14a		Exact match	1-(1H-indazol-5-yl)pentan-1-ol. HRMS (ESI$^+$) Mass required for exact match ($C_{12}H_{16}N_2O$): 204.1263, Mass found: 204.1256.
14b		Failed reaction	(1H-indazol-5-yl)(phenyl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{14}H_{12}N_2O$): 224.0950, Mass found: 224.0952. No product UV peak identified, marked as failed.
14c		Exact match	(1H-indazol-5-yl)(pyridin-2-yl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{13}H_{11}N_3O$): 225.0902, Mass found: 225.0905.
14d		Exact match	(1H-indazol-5-yl)(pyridin-3-yl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{13}H_{11}N_3O$): 225.0902, Mass found: 225.0906.
14e		Failed reaction	(1H-indazol-5-yl)(4-methylphenyl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{14}N_2O$): 238.1106, Mass found: 238.1120. No product UV peak identified, marked as failed.
14f		Exact match	(1H-indazol-5-yl)(3-methylphenyl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{14}N_2O$): 238.1106, Mass found: 238.1096.
14g		Exact match	(1H-indazol-5-yl)(2-methylphenyl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{14}N_2O$): 238.1106, Mass found: 238.1095.

14h		Exact match	(1H-indazol-5-yl)(2-methylpyridin-4-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{13}N_3O$): 239.1059, Mass found: 239.1061.
14i		Failed reaction	(4-fluorophenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{11}FN_2O$): 242.0855, Mass found: 242.0854. No product UV peak identified, marked as failed.
14j		Exact match	(3-fluorophenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{11}FN_2O$): 242.0855, Mass found: 242.0857.
14k		Exact match	(2-fluorophenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{11}FN_2O$): 242.0855, Mass found: 242.0855.
14l		Exact match	(5-fluoropyridin-2-yl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{13}H_{10}FN_3O$): 243.0808, Mass found: 243.0813.
14m		Failed reaction	(2,6-dimethylphenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{16}N_2O$): 252.1263, Mass found: 252.1267. No product UV peak identified, marked as failed.
14o		Failed reaction	(1H-indazol-5-yl)(4-methoxyphenyl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{14}N_2O_2$): 254.1055, no target mass found - reaction failed.

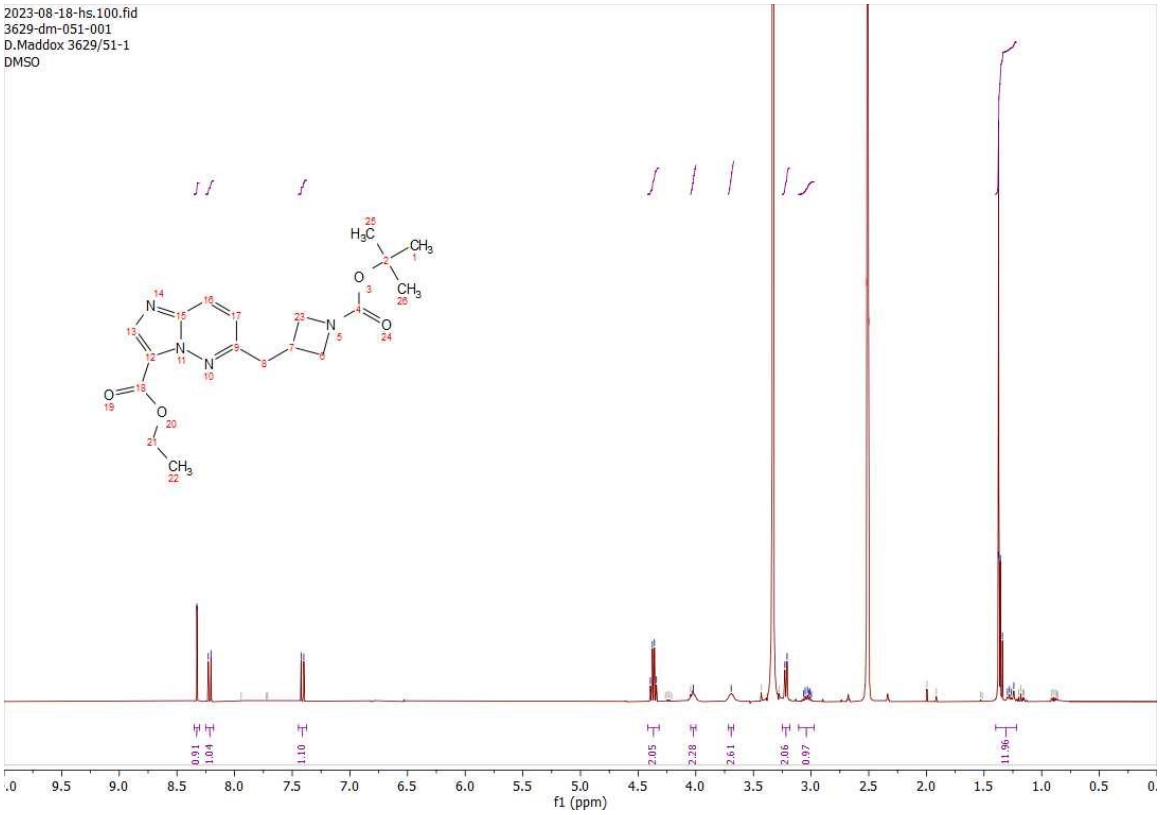
14p		Failed reaction	(1H-indazol-5-yl)(3-methoxyphenyl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{14}N_2O_2$): 254.1055, Mass found: 254.1057. No product UV peak identified, marked as failed.
14q		Failed reaction	(1H-indazol-5-yl)(2-methoxyphenyl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{14}N_2O_2$): 254.1055, no target mass found - reaction failed.
14r		Exact match	(1H-indazol-5-yl)(6-methoxypyridin-3-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{13}N_3O_2$): 255.1008, Mass found: 255.1010.
14s		Failed reaction	(2,6-difluorophenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{10}F_2N_2O$): 260.0761, Mass found: 260.0764. No product UV peak identified, marked as failed.
14t		Exact match	(2,5-difluorophenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{14}H_{10}F_2N_2O$): 260.0761, Mass found: 260.0756.
14v		Failed reaction	(1-benzofuran-5-yl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{12}N_2O_2$): 264.0899, Mass found: 264.0908. No product UV peak identified, marked as failed.
14w		Failed reaction	(1H-indazol-5-yl)({pyrazolo[1,5-a]pyridin-3-yl})methanol. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{12}N_4O$): 264.1011, no target mass found - reaction failed.

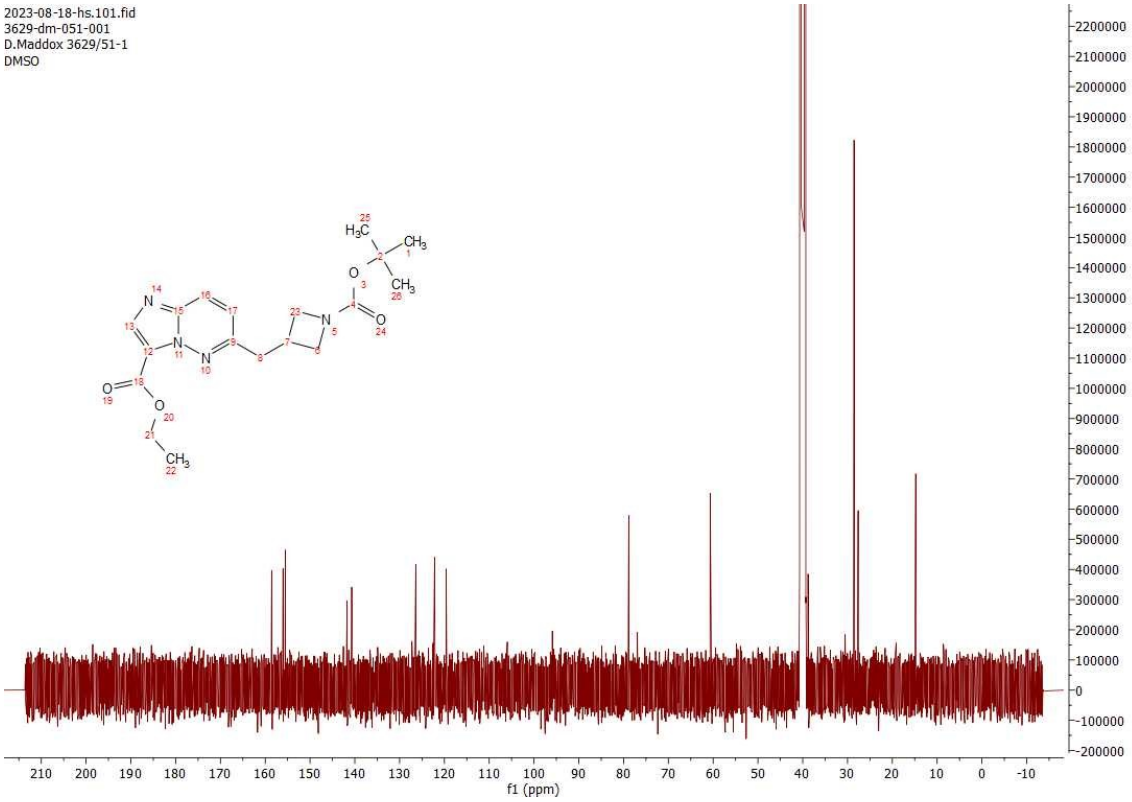
14x		Failed reaction	(1H-indazol-5-yl)(2,4,6-trimethylphenyl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{17}H_{18}N_2O$): 266.1419, Mass found: 266.1421. No product UV peak identified, marked as failed.
14y		Failed reaction	[4-(dimethylamino)phenyl](1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{17}N_3O$): 267.1372, Mass found: 267.1373. No product UV peak identified, marked as failed.
14z		Exact match	[3-(dimethylamino)phenyl](1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{17}N_3O$): 267.1372, Mass found: 267.1376.
14aa		Failed reaction	(2H-1,3-benzodioxol-5-yl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{15}H_{12}N_2O_3$): 268.0848, Mass found: 268.0847. No product UV peak identified, marked as failed.
14ab		Failed reaction	(2,3-dihydro-1,4-benzodioxin-6-yl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{14}N_2O_3$): 282.1004, no target mass found - reaction failed.
14ac		Failed reaction	(3,5-dimethoxyphenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{16}N_2O_3$): 284.1161, no target mass found - reaction failed.
14ad		Failed reaction	(3,4-dimethoxyphenyl)(1H-indazol-5-yl)methanol. HRMS (ESI^+) Mass required for exact match ($C_{16}H_{16}N_2O_3$): 284.1161, no target mass found - reaction failed.

14af		Exact match	(1H-indazol-5-yl)[4-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{11}F_3N_2O$): 292.0823, Mass found: 292.0825.
14ag		Exact match	(1H-indazol-5-yl)[3-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{11}F_3N_2O$): 292.0823, Mass found: 292.0824.
14ah		Exact match	(1H-indazol-5-yl)[2-(trifluoromethyl)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{11}F_3N_2O$): 292.0823, Mass found: 292.0825.
14ai		Exact match	(1H-indazol-5-yl)[3-(trifluoromethoxy)phenyl]methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{11}F_3N_2O_2$): 308.0773, Mass found: 308.0774.
14aj		Failed reaction	{4-[(tert-butyldimethylsilyl)oxy]phenyl}(1H-indazol-5-yl)methanol. HRMS (ESI$^+$) Mass required for exact match ($C_{20}H_{26}N_2O_2Si$): 354.1764, no target mass found - reaction failed.
15a		Exact match	1-[3-(propan-2-yl)-1H-indazol-5-yl]pentan-1-ol. HRMS (ESI$^+$) Mass required for exact match ($C_{15}H_{22}N_2O$): 246.1732, Mass found: 246.1734.

Appendix 4 – NMR Spectra

1a





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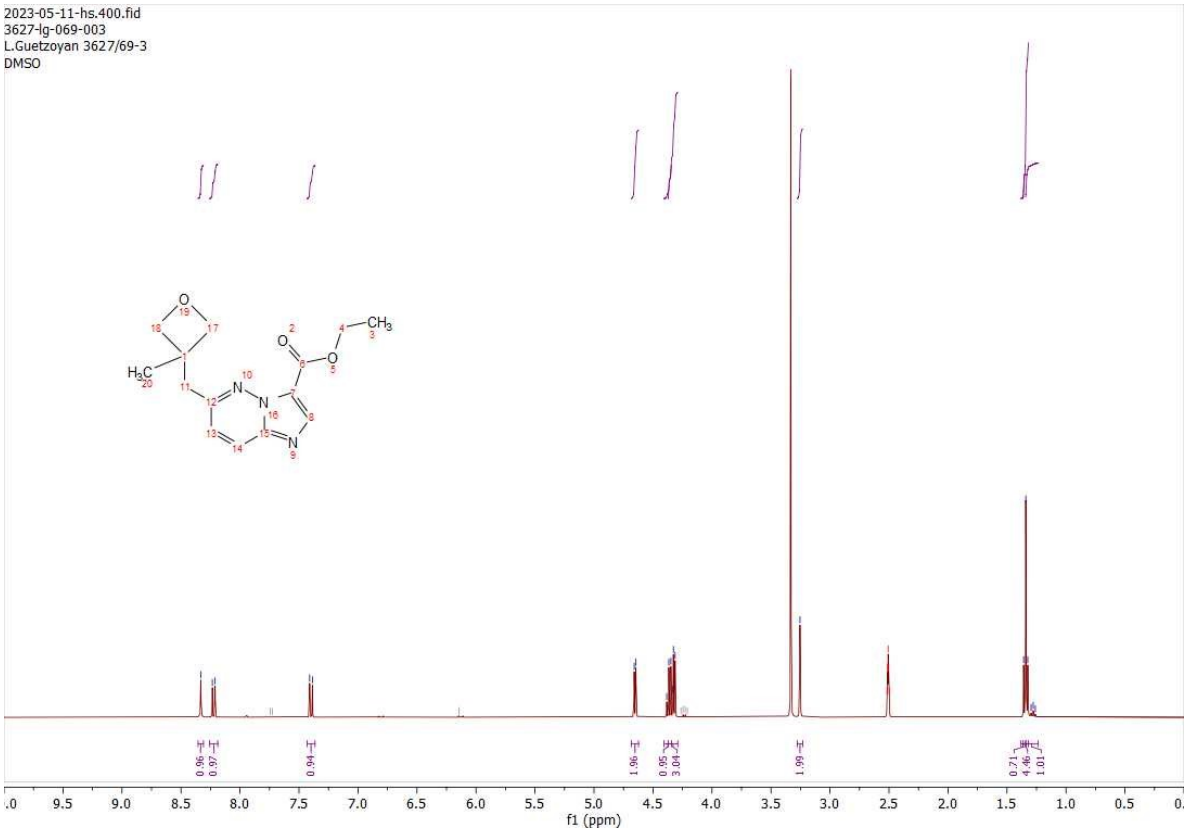
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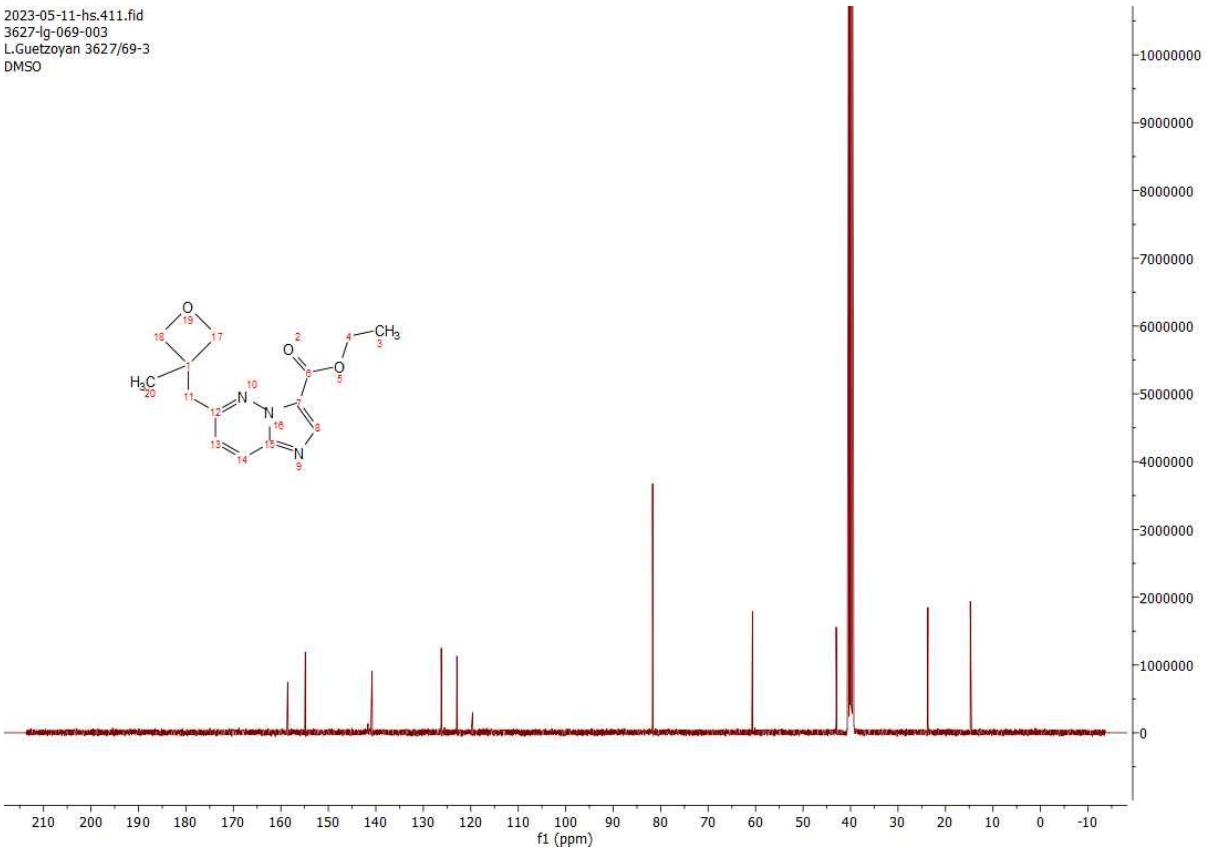
3627-lg-069-003
L.Guetzoyan 3627/69-3
DMSO
f1 (ppm)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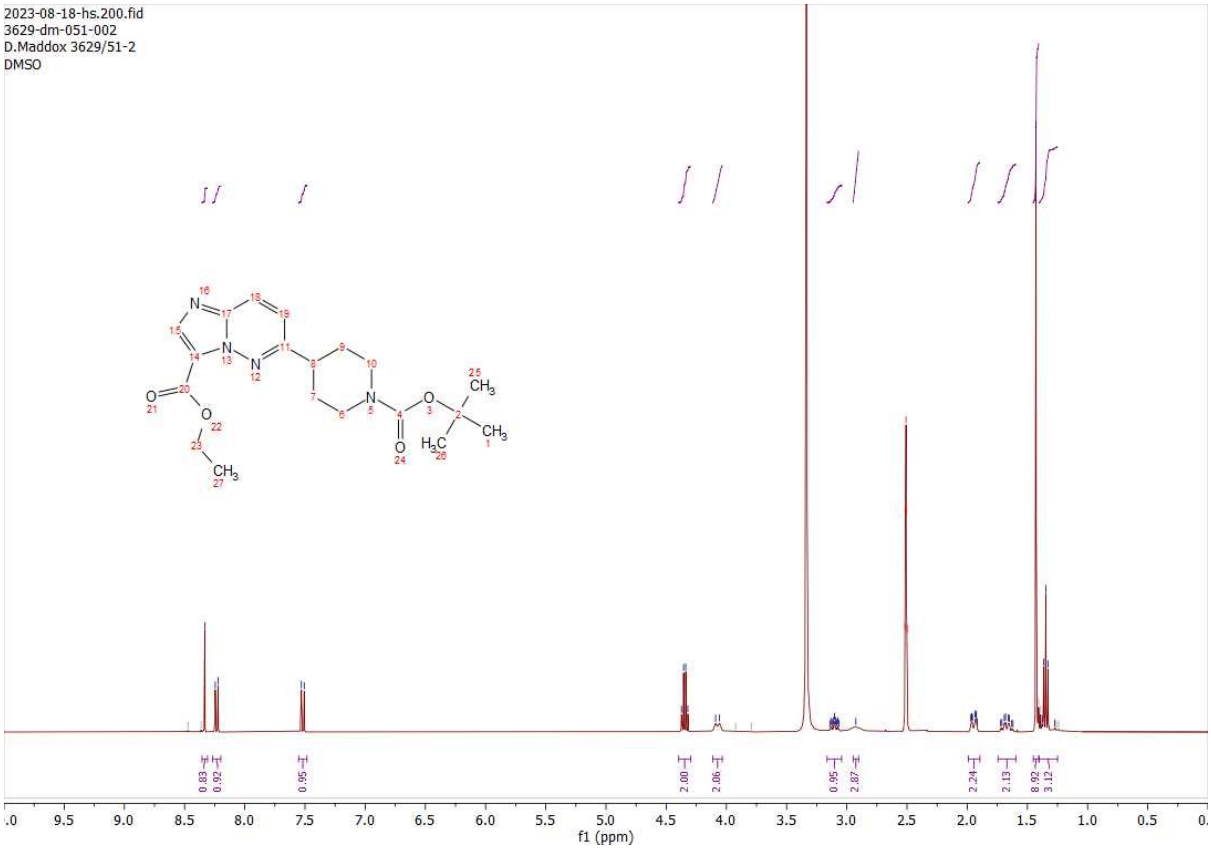
3627-lg-069-003
L.Guetzoyan 3627/69-3
DMSO
f1 (ppm)

1d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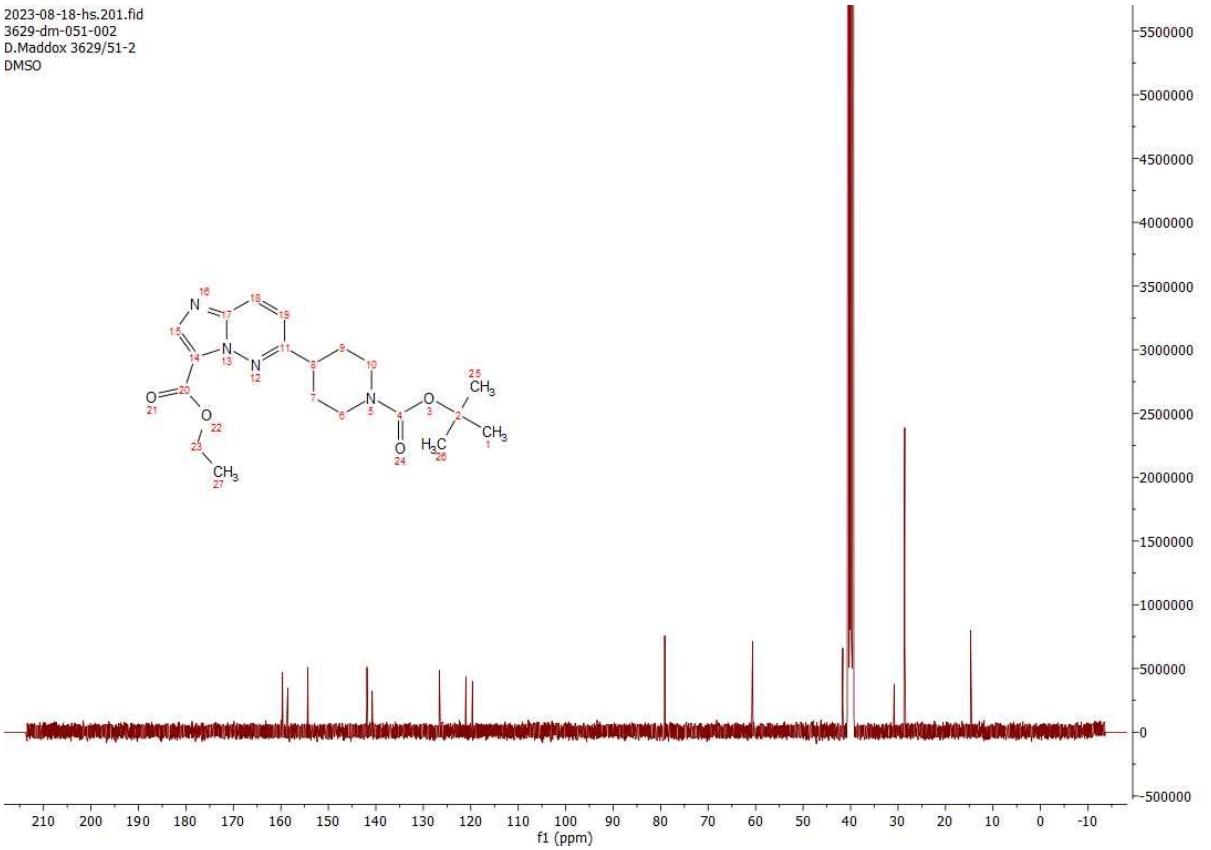
3629-dm-051-002
D.Maddox 3629/51-2
DMSO
f1 (ppm)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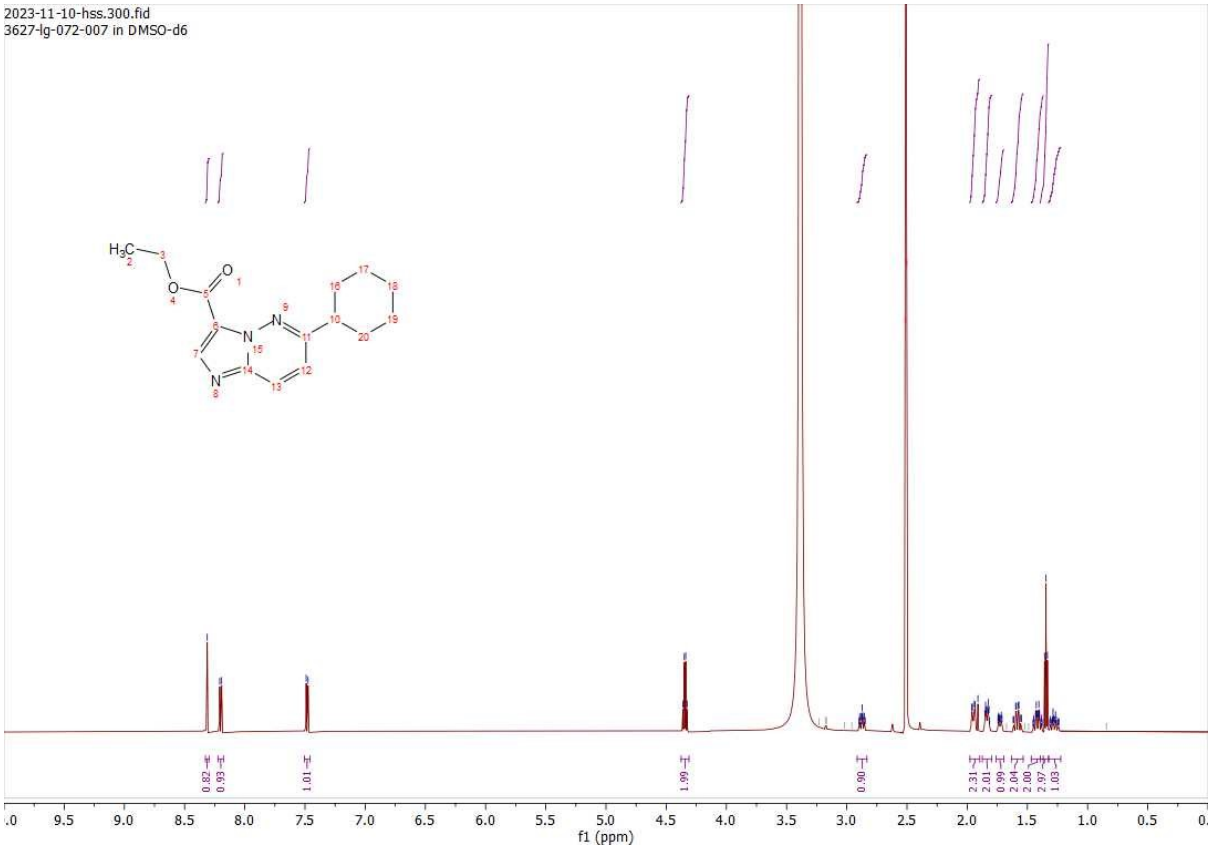
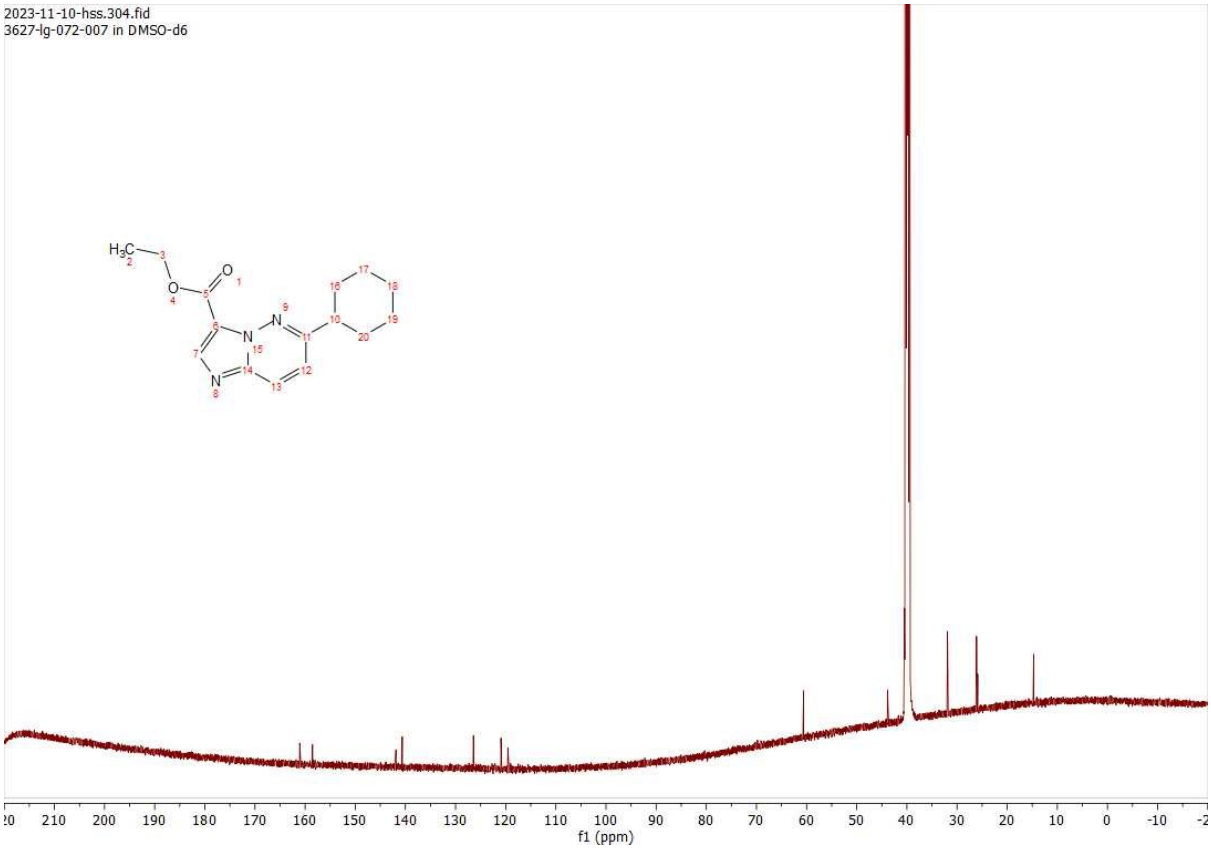
D.Maddox 3629/51-2
DMSO
f1 (ppm)

1e


2023-11-10-hss.300.fid
3627-lg-072-007 in DMSO-d6
0.82
0.93
1.01
1.99
0.90
2.31
2.01
0.99
2.04
2.00
2.97
1.03
f1 (ppm)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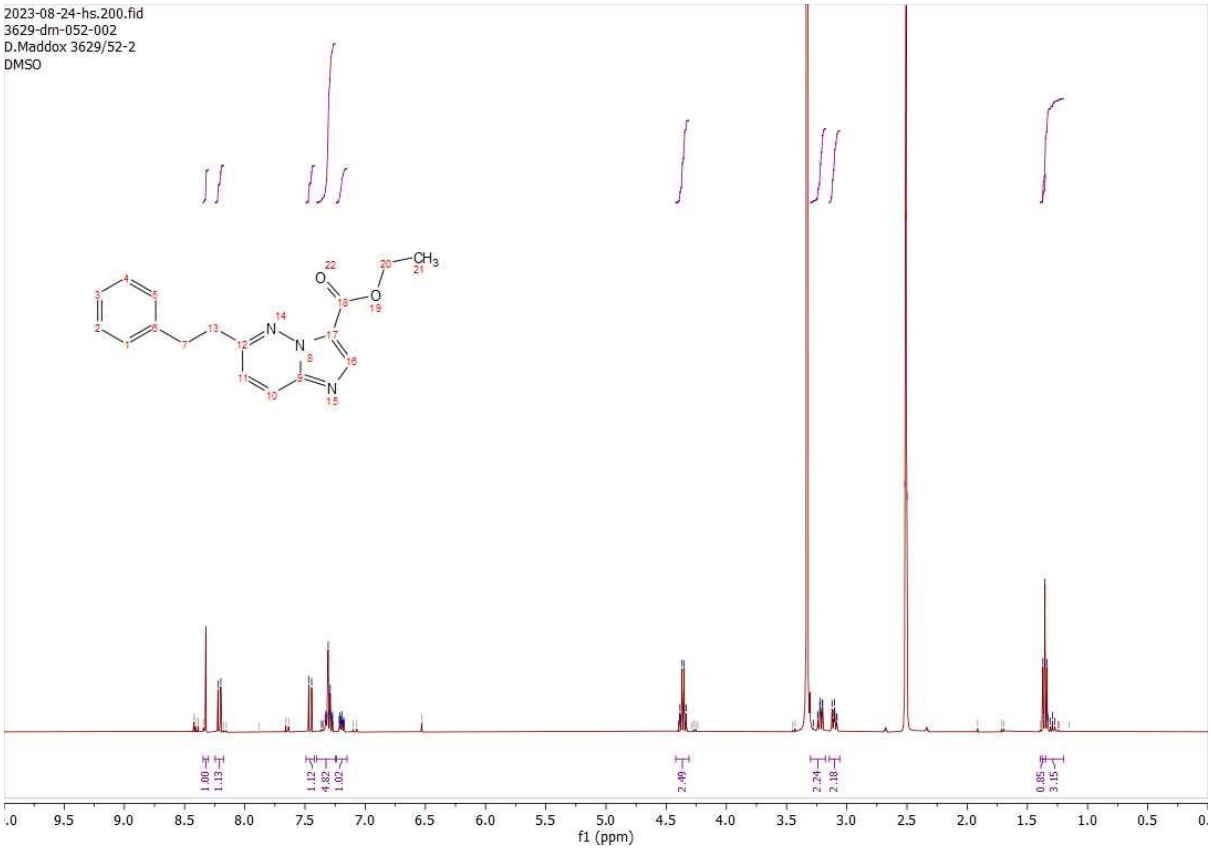
3627-lg-072-007 in DMSO-d6
f1 (ppm)

1f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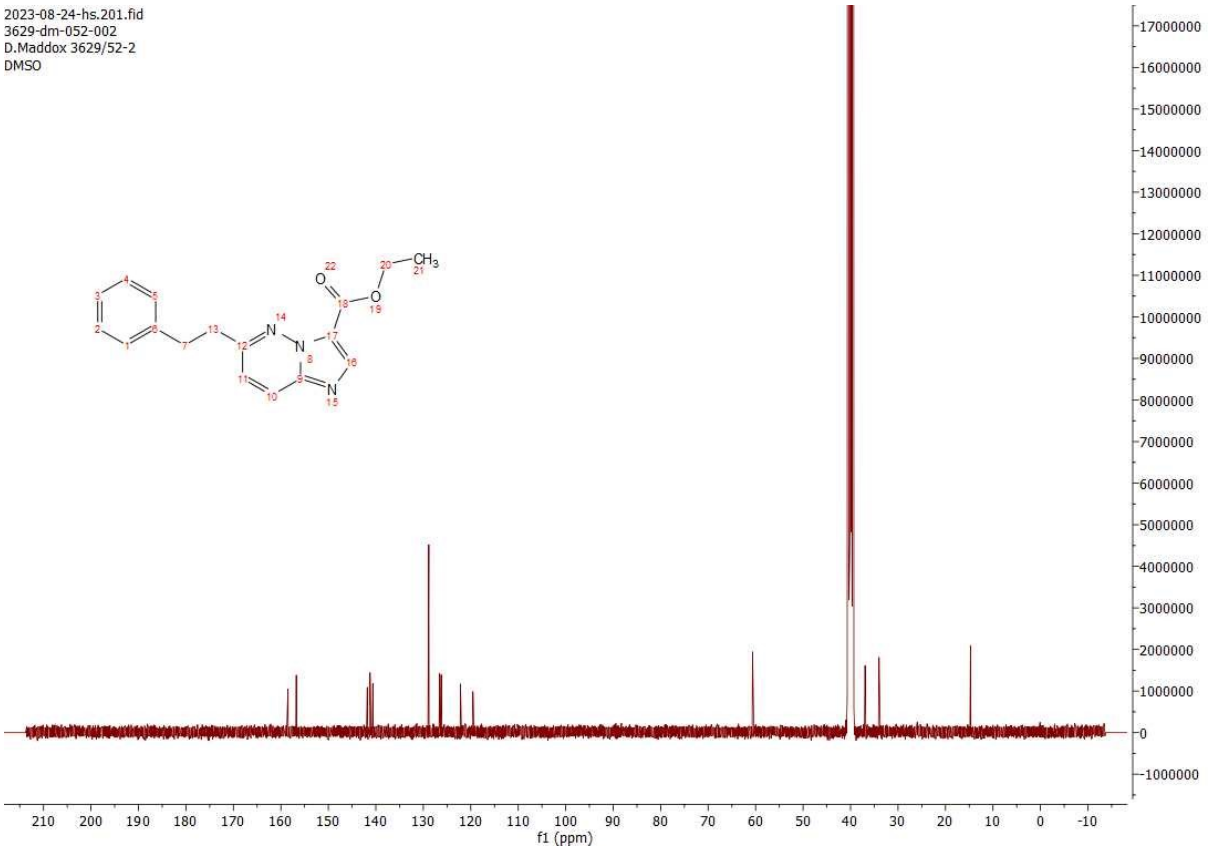
3629-dm-052-002
D.Maddox 3629/52-2
DMSO
f1 (ppm)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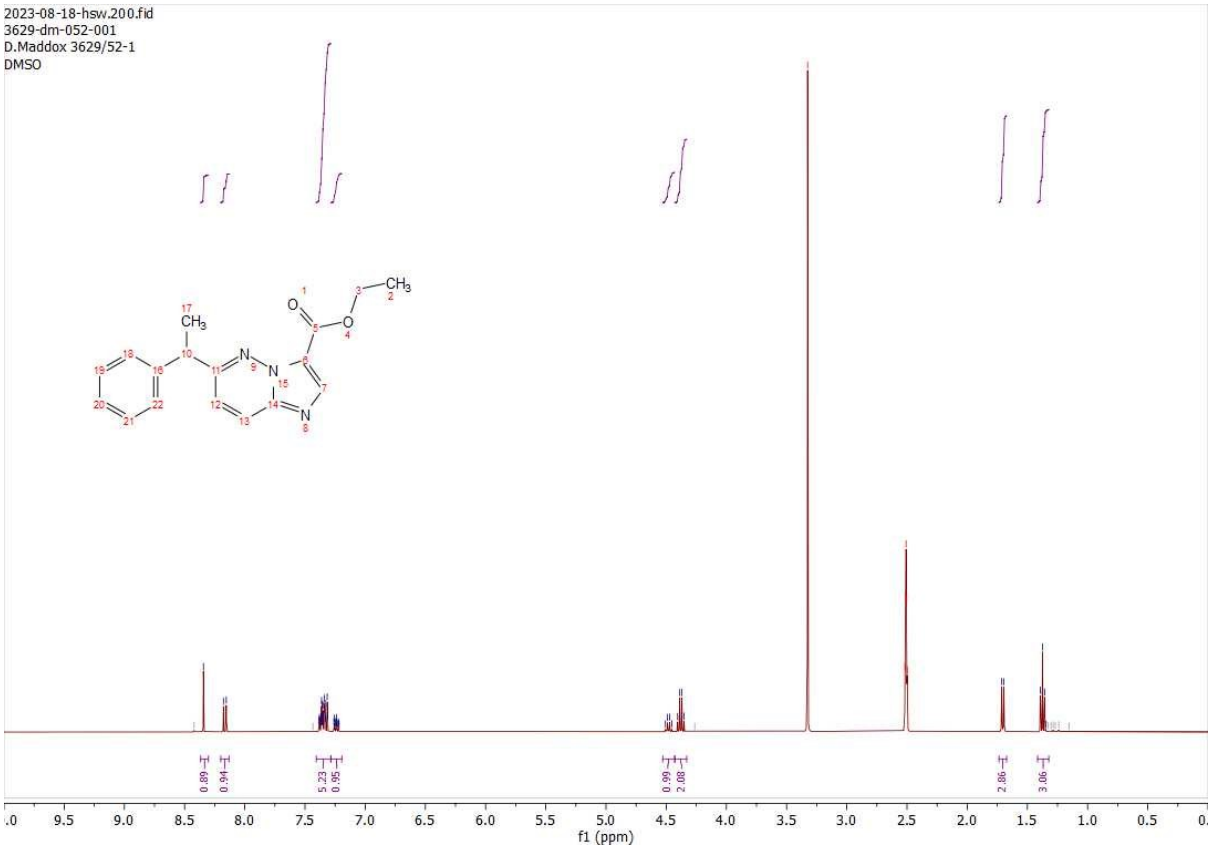
D.Maddox 3629/52-2
DMSO
f1 (ppm)

S-1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D.Maddox 3629/52-1
DMSO
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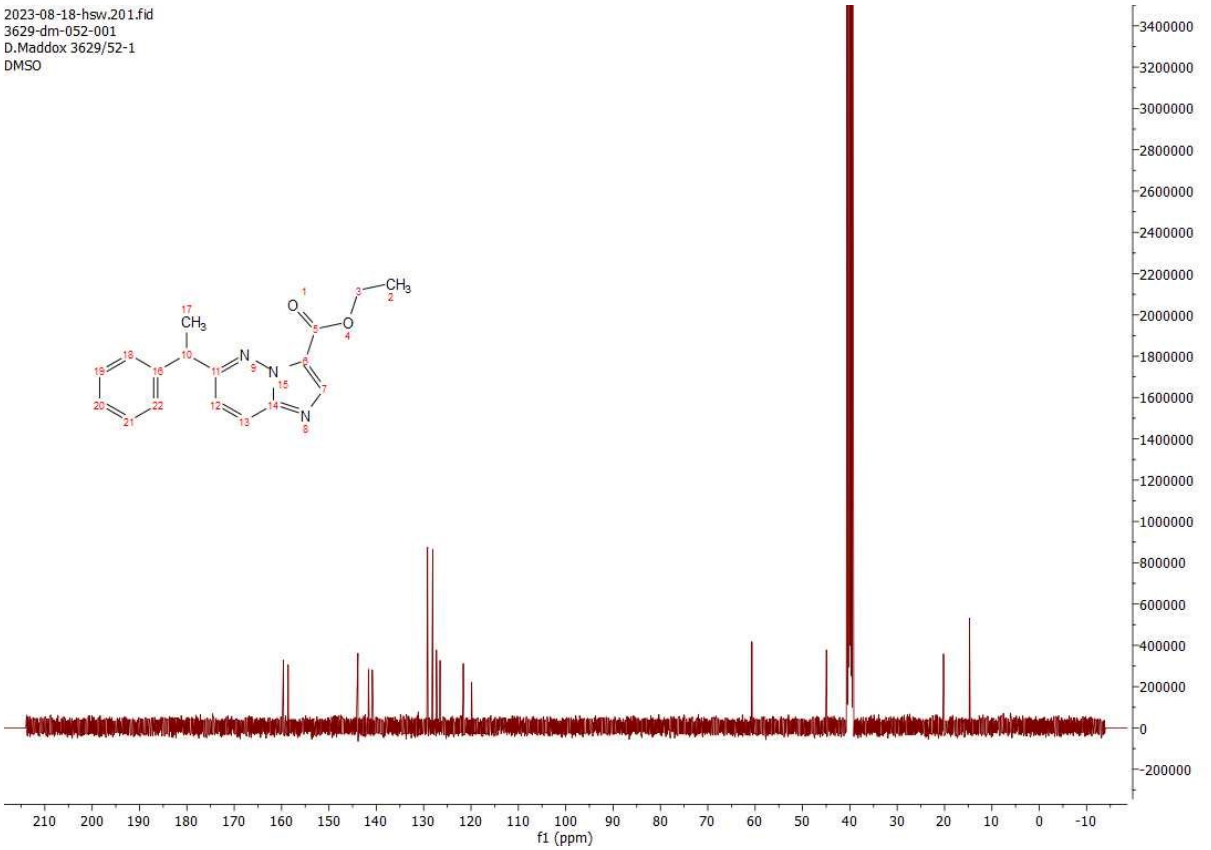
0.94
5.23
0.95
0.99
2.08
2.86
3.06
f1 (ppm)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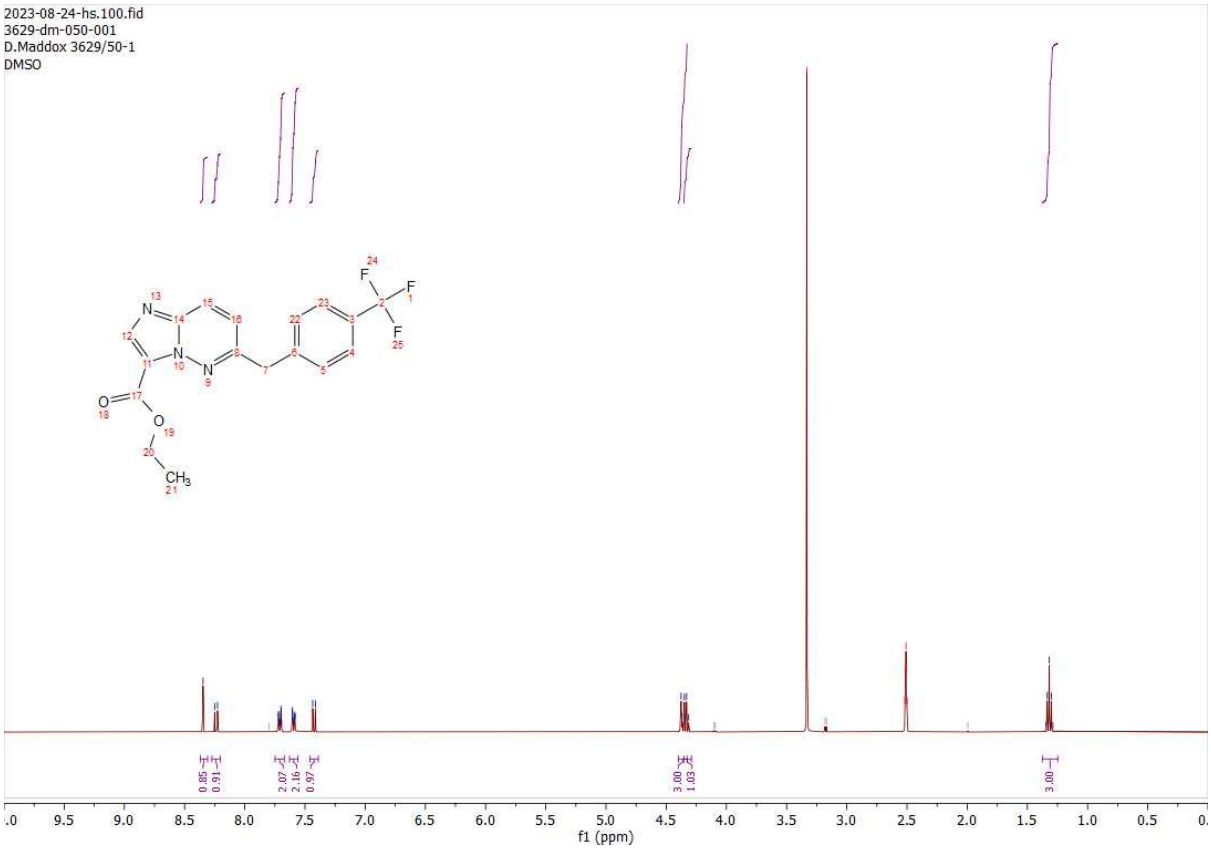
D.Maddox 3629/52-1
DMSO
f1 (ppm)

1g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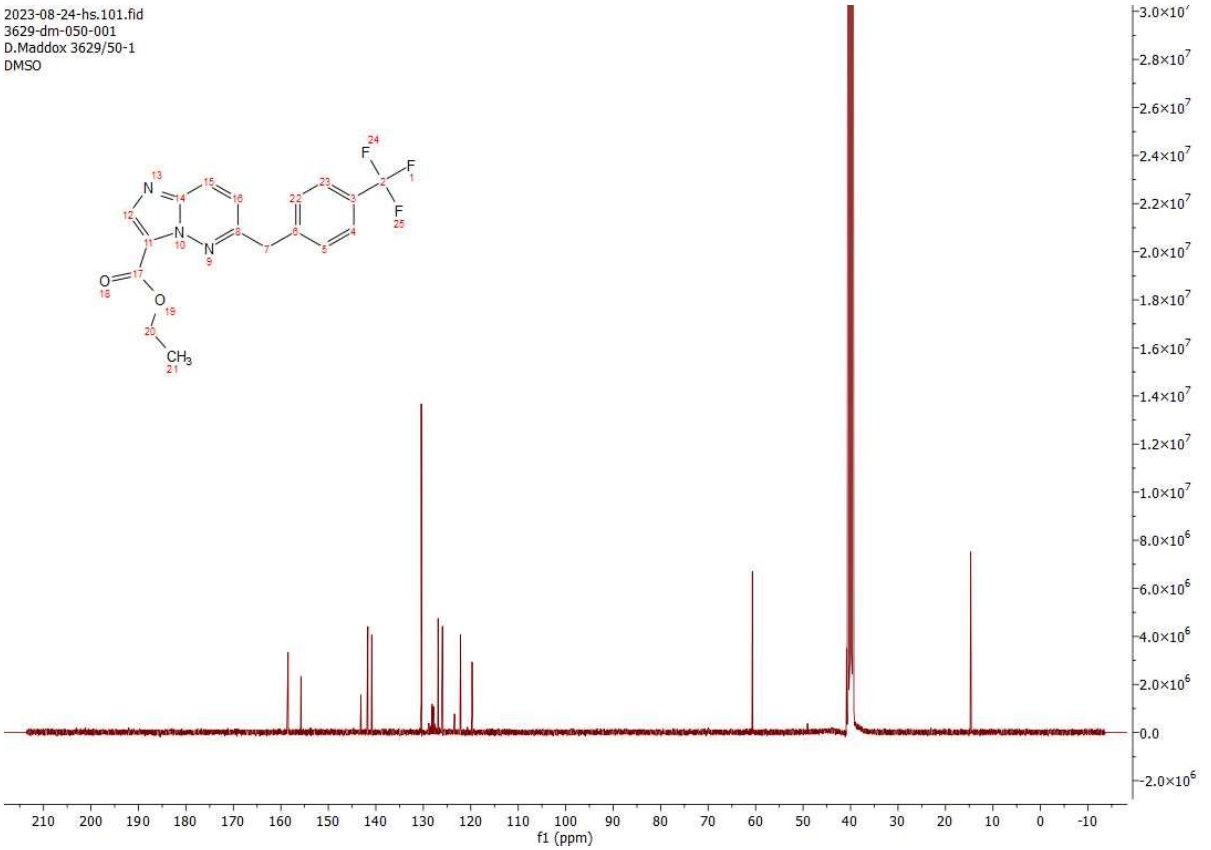
3629-dm-050-001
D.Maddox 3629/50-1
DMSO
f1 (ppm)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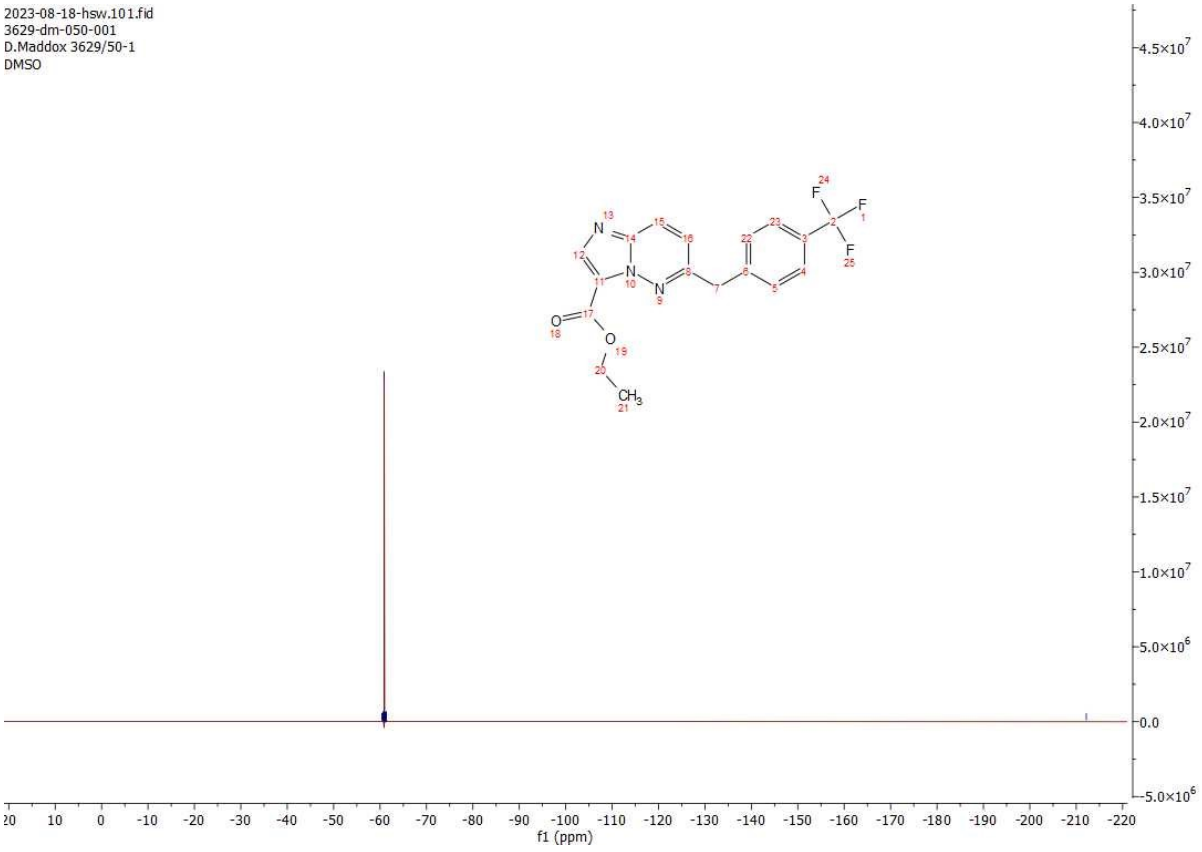
D.Maddox 3629/50-1
DMSO
f1 (ppm)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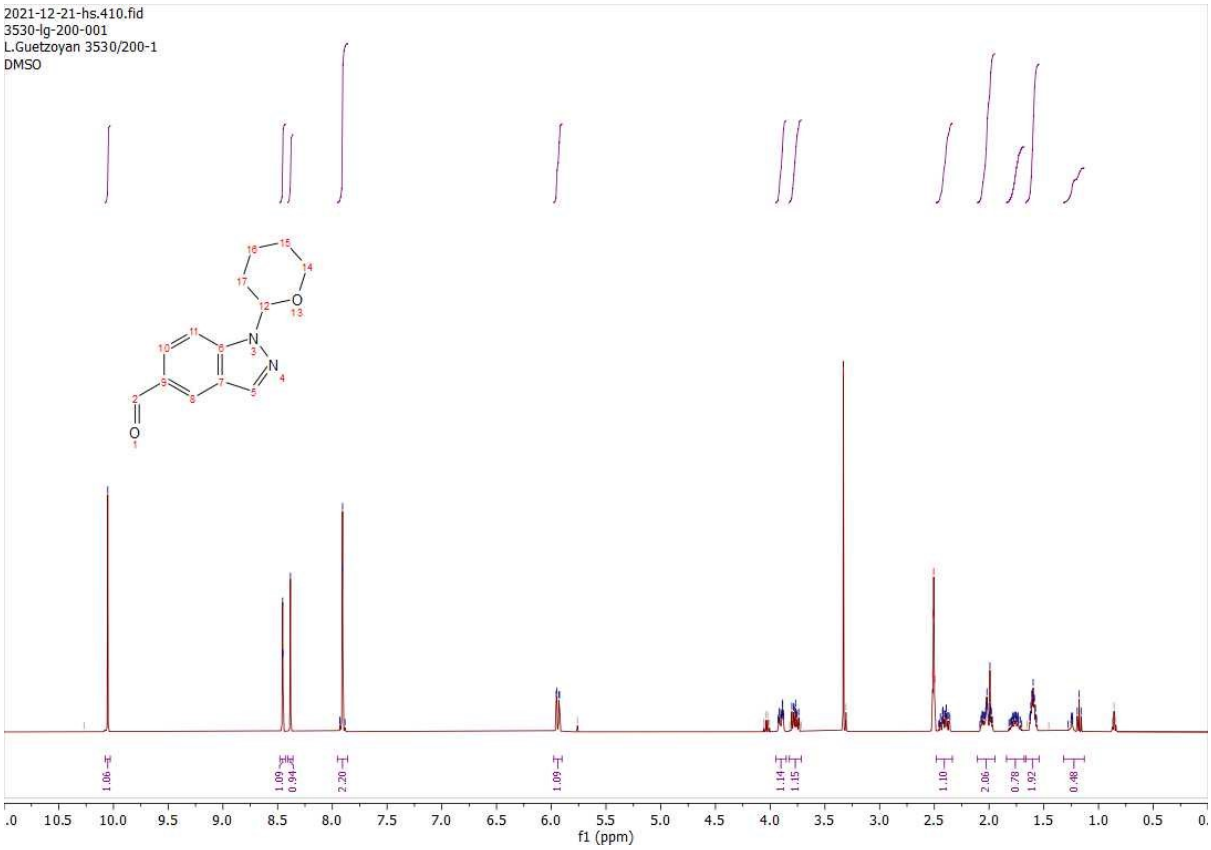
3629-dm-050-001
D.Maddox 3629/50-1
DMSO
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6
f1 (ppm)

S-8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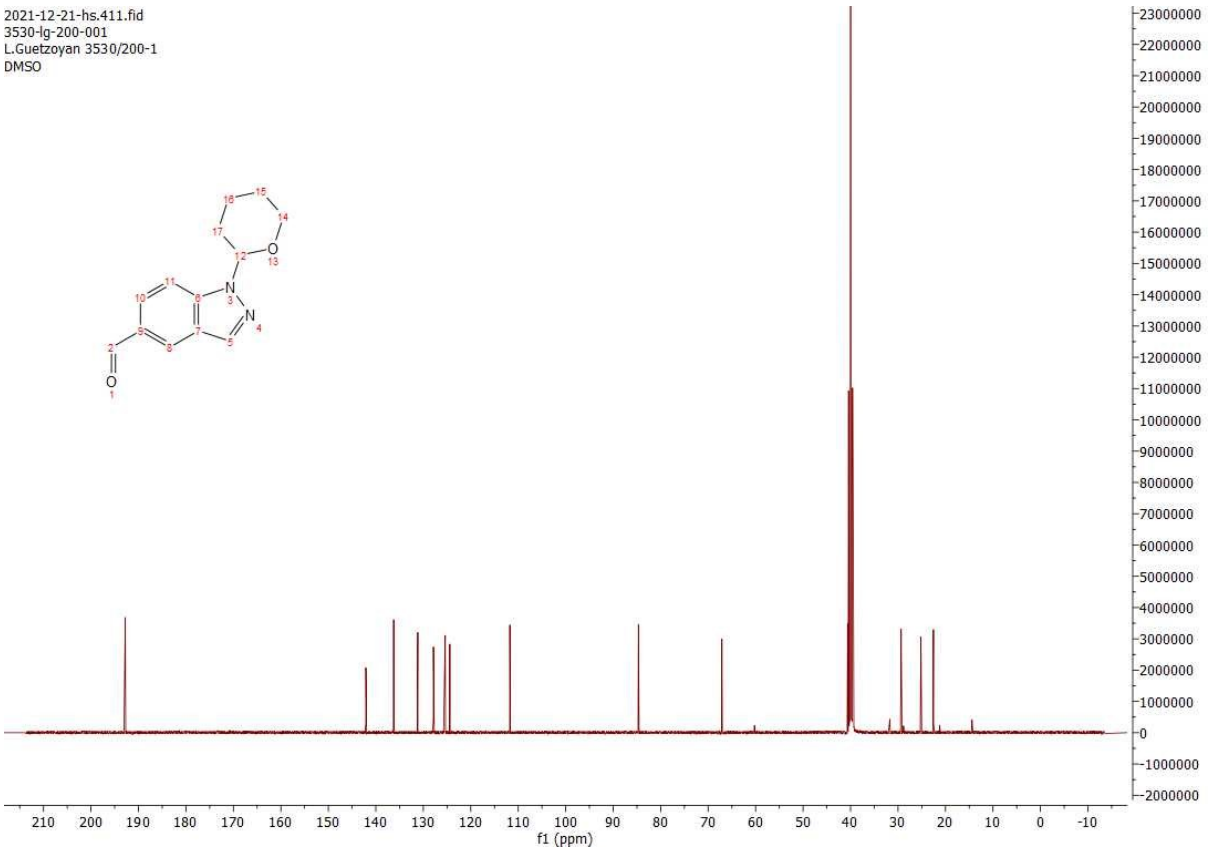
3530-lg-200-001
L.Guetzoyan 3530/200-1
DMSO
1.06
1.09
0.94
2.20
1.09
1.14
1.15
1.10
2.06
0.78
1.92
0.48
f1 (ppm)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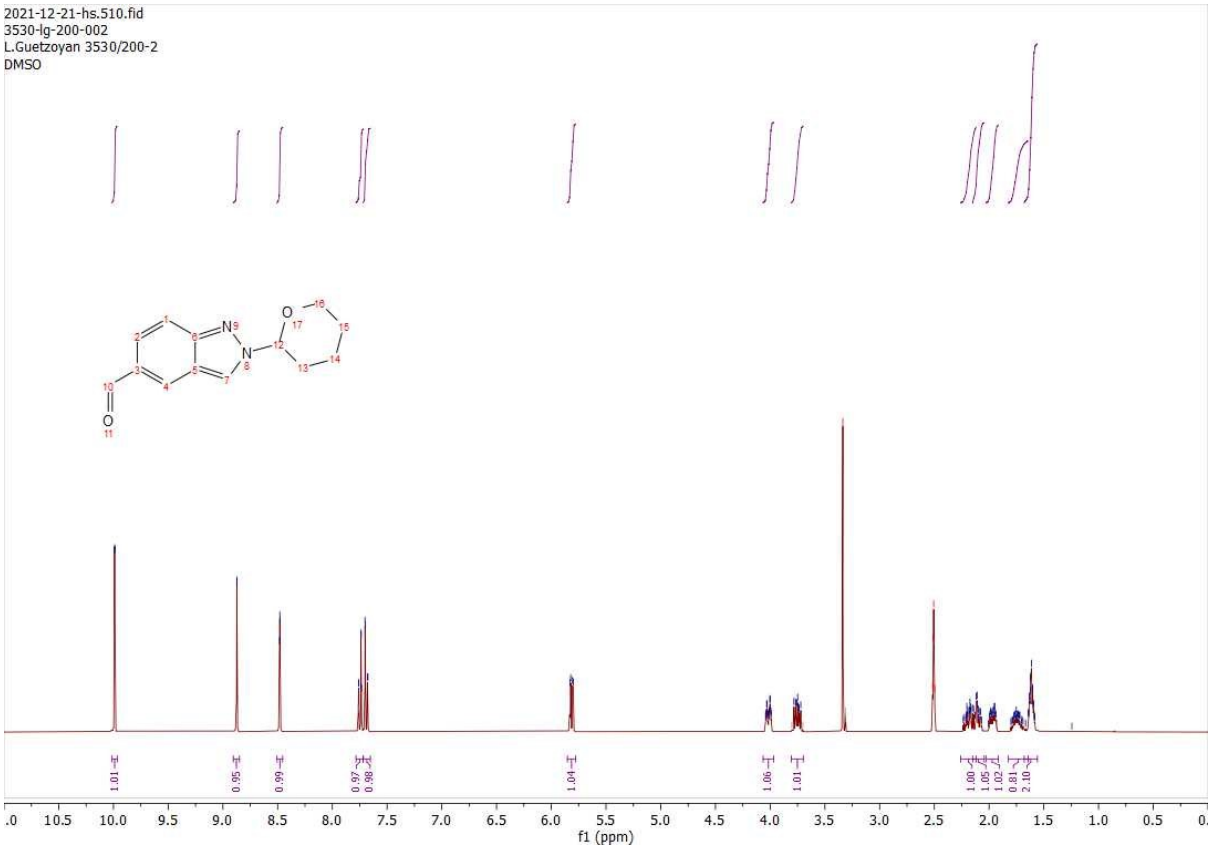
L.Guetzoyan 3530/200-1
DMSO
f1 (ppm)

6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L.Guetzoyan 3530/200-2
DMSO
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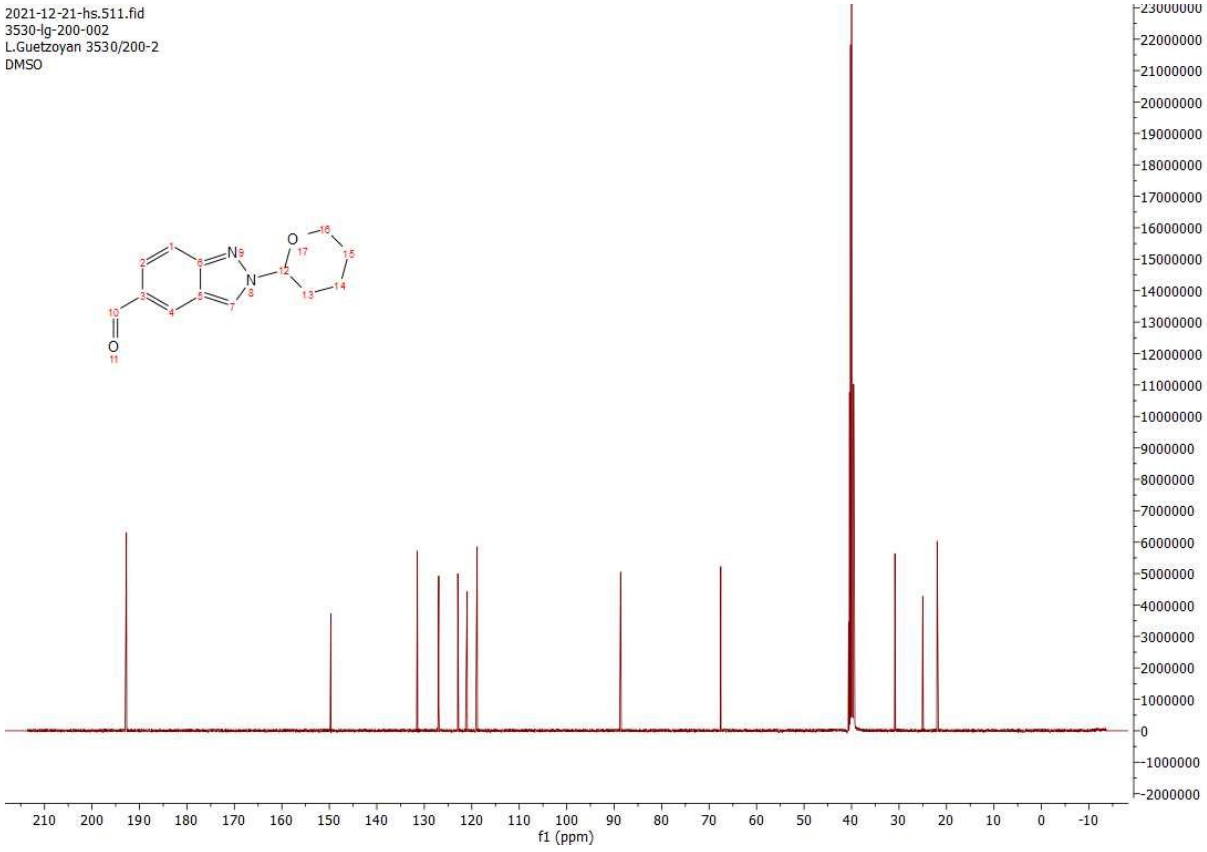
0.95
0.99
0.97
0.98
1.04
1.06
1.01
1.00
1.05
1.02
0.81
2.10
f1 (ppm)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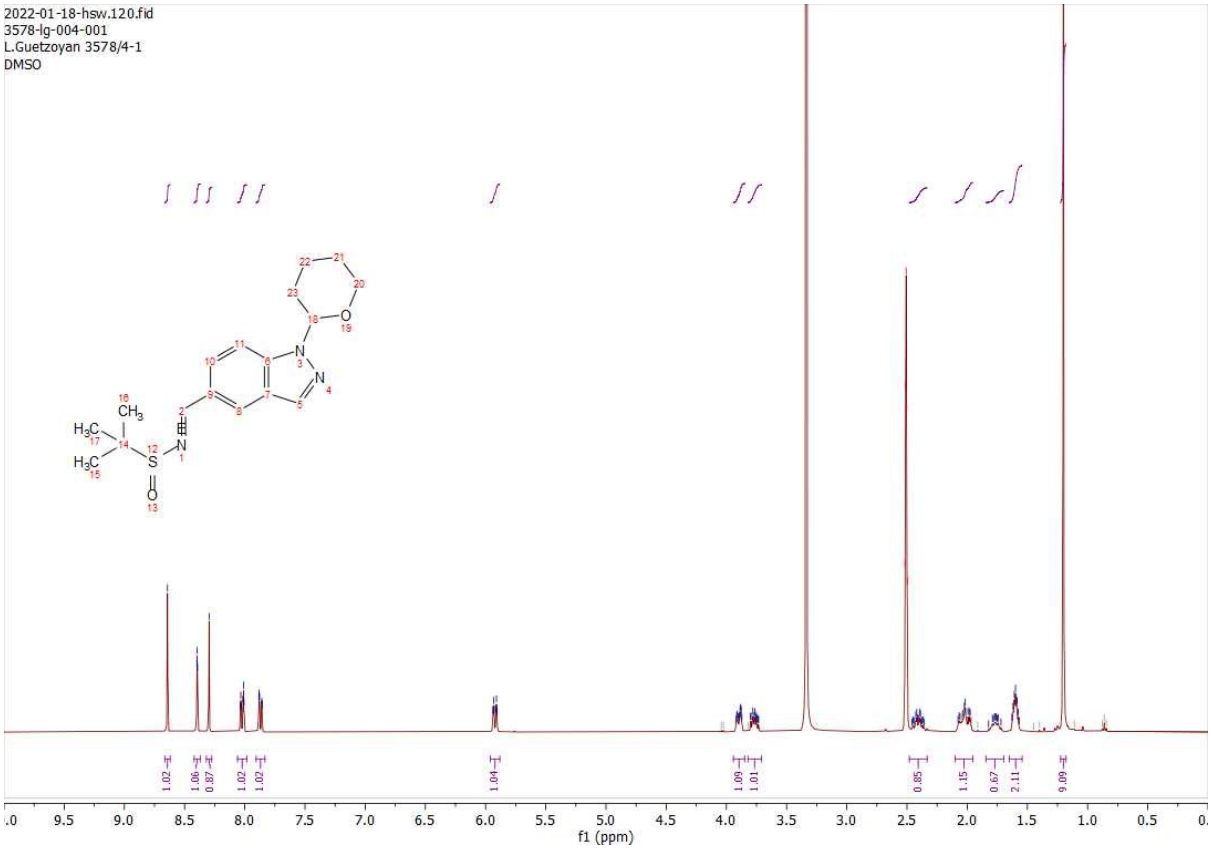
L.Guetzoyan 3530/200-2
DMSO
f1 (ppm)

4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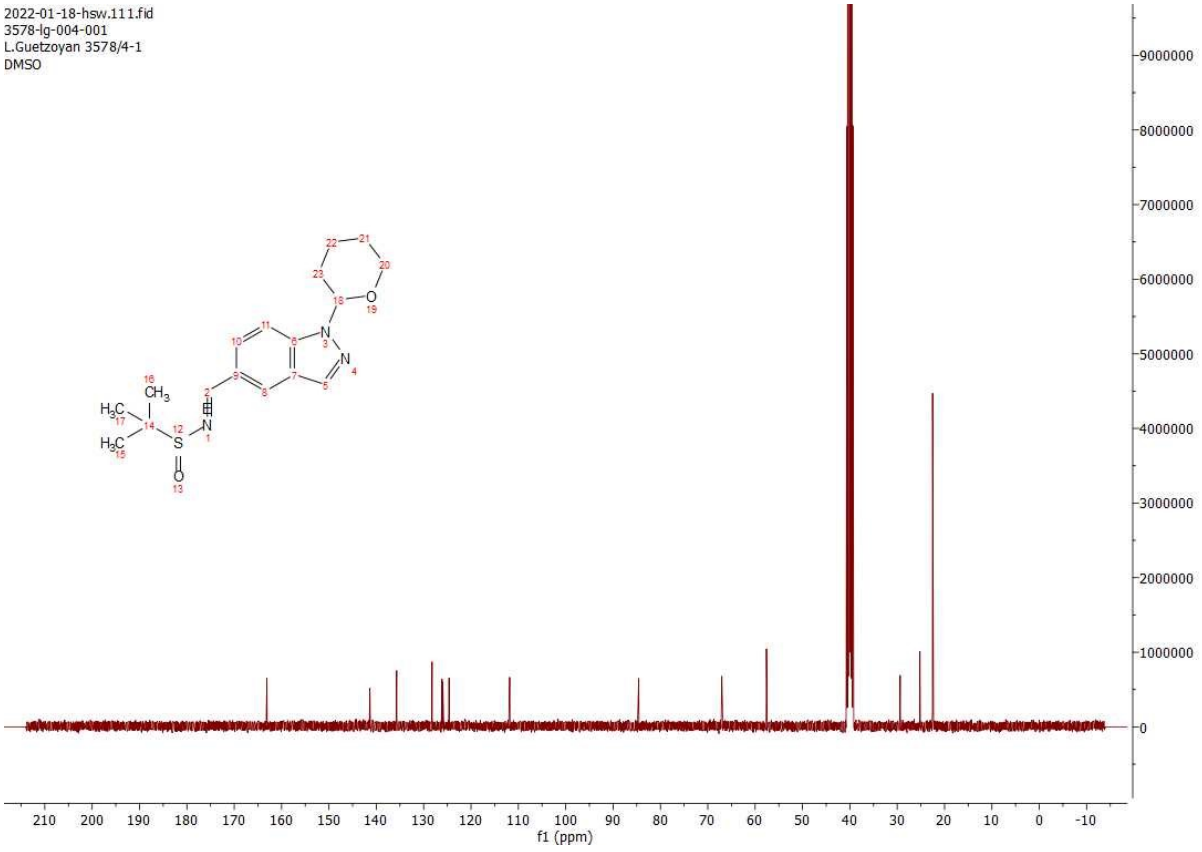
L.Guetzoyan 3578/4-1
DMSO
1.02
1.06
0.87
1.02
1.02
1.04
1.09
1.01
0.85
1.15
0.67
2.11
9.09
f1 (ppm)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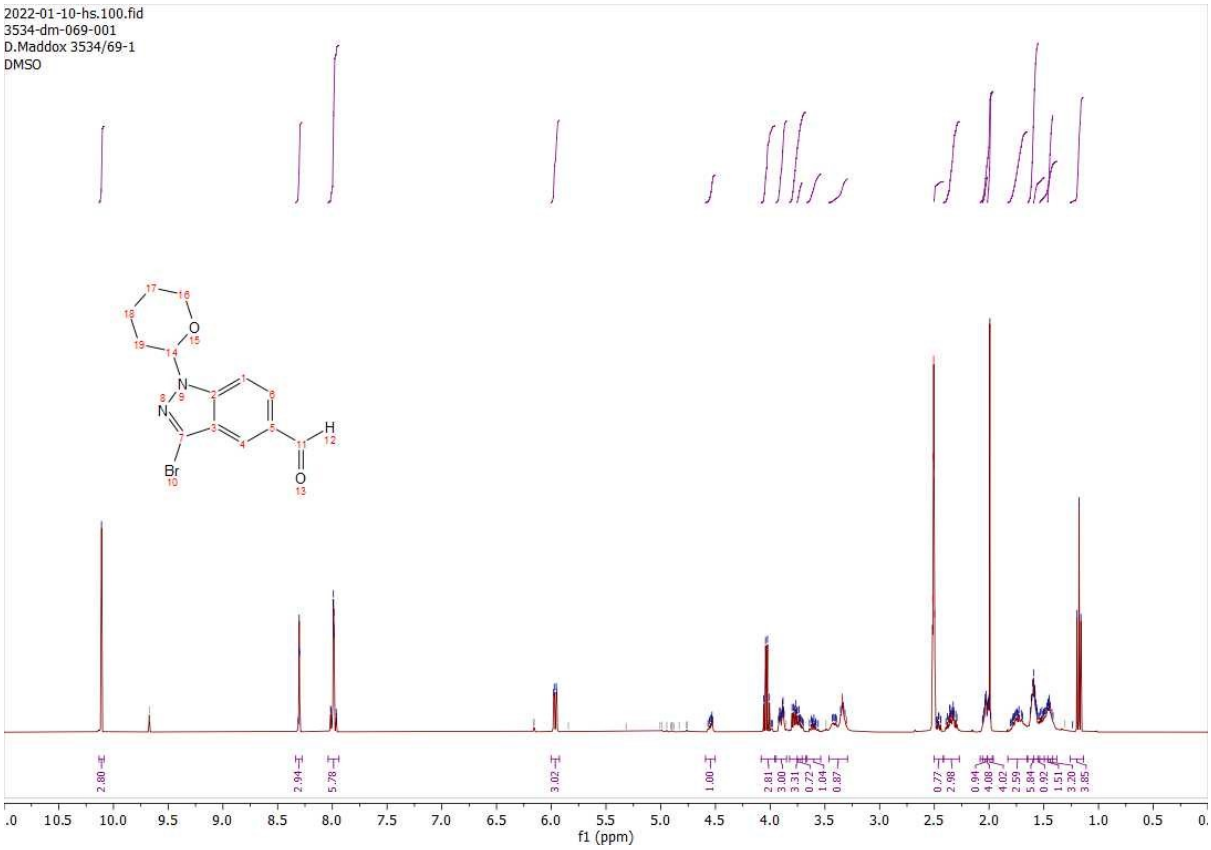
L.Guetzoyan 3578/4-1
DMSO
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

S9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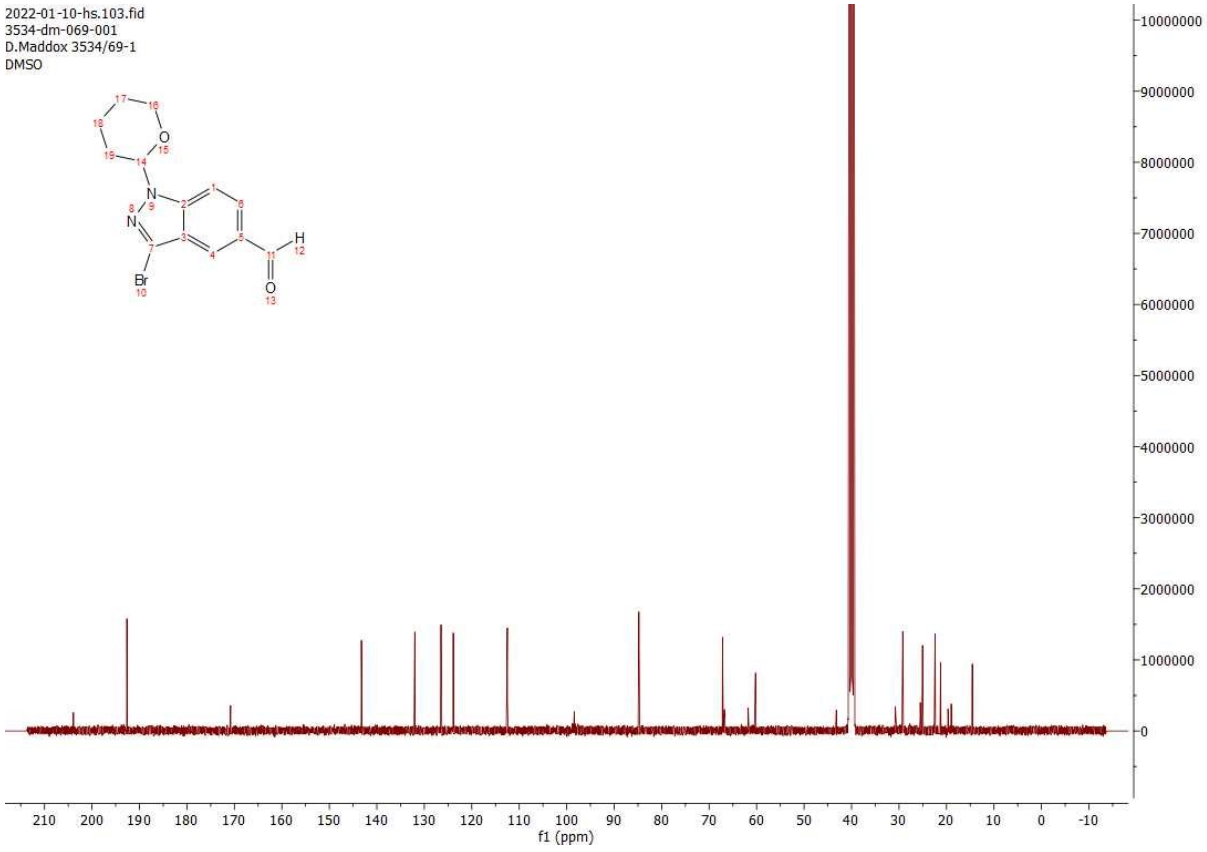
D.Maddox 3534/69-1
DMSO
f1 (ppm)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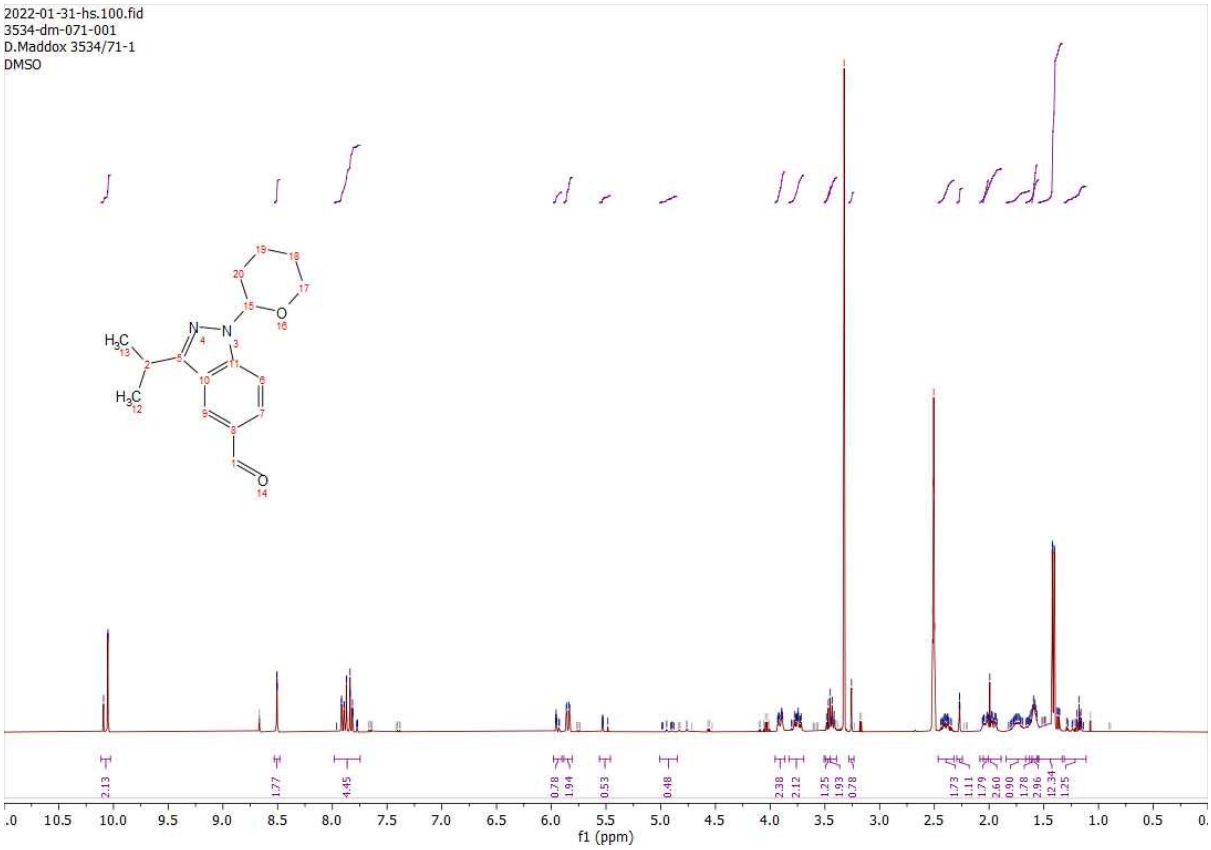
D.Maddox 3534/69-1
DMSO
f1 (ppm)

7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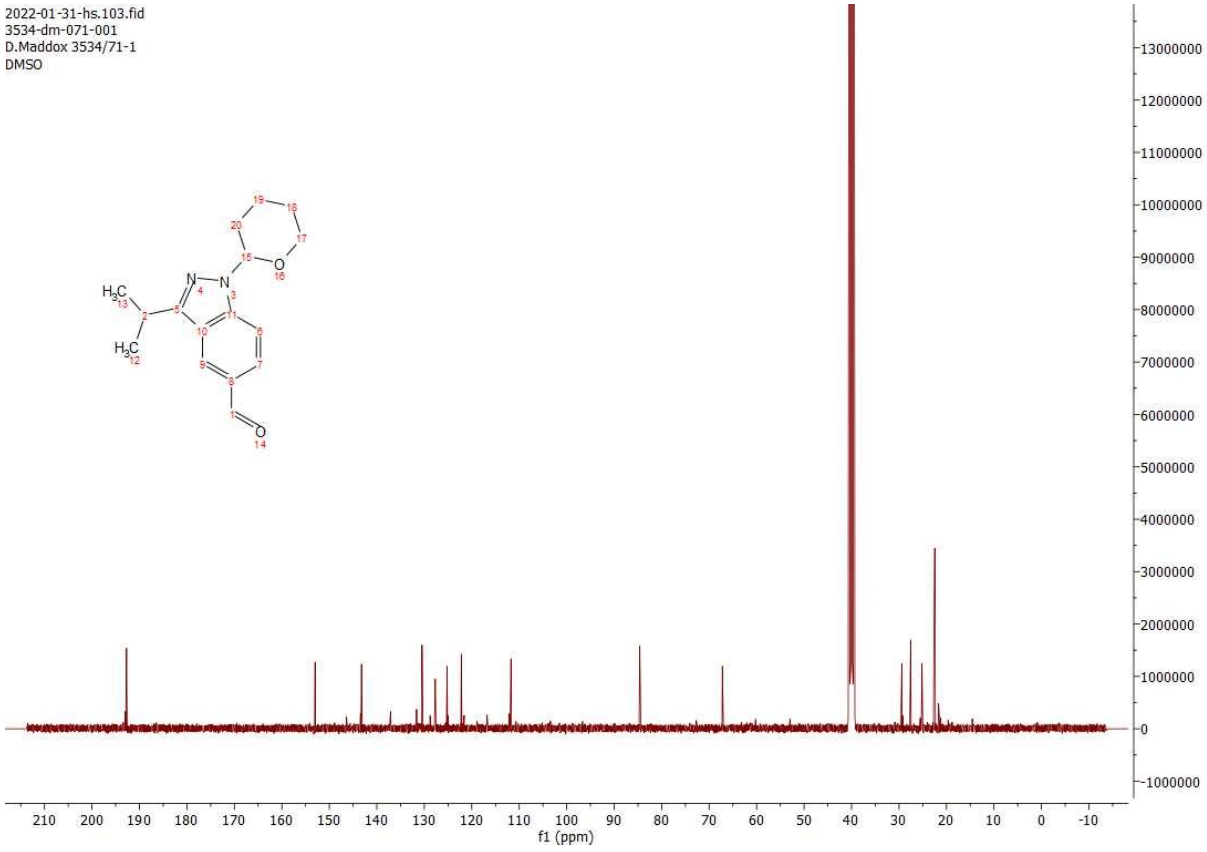
D.Maddox 3534/71-1
DMSO
f1 (ppm)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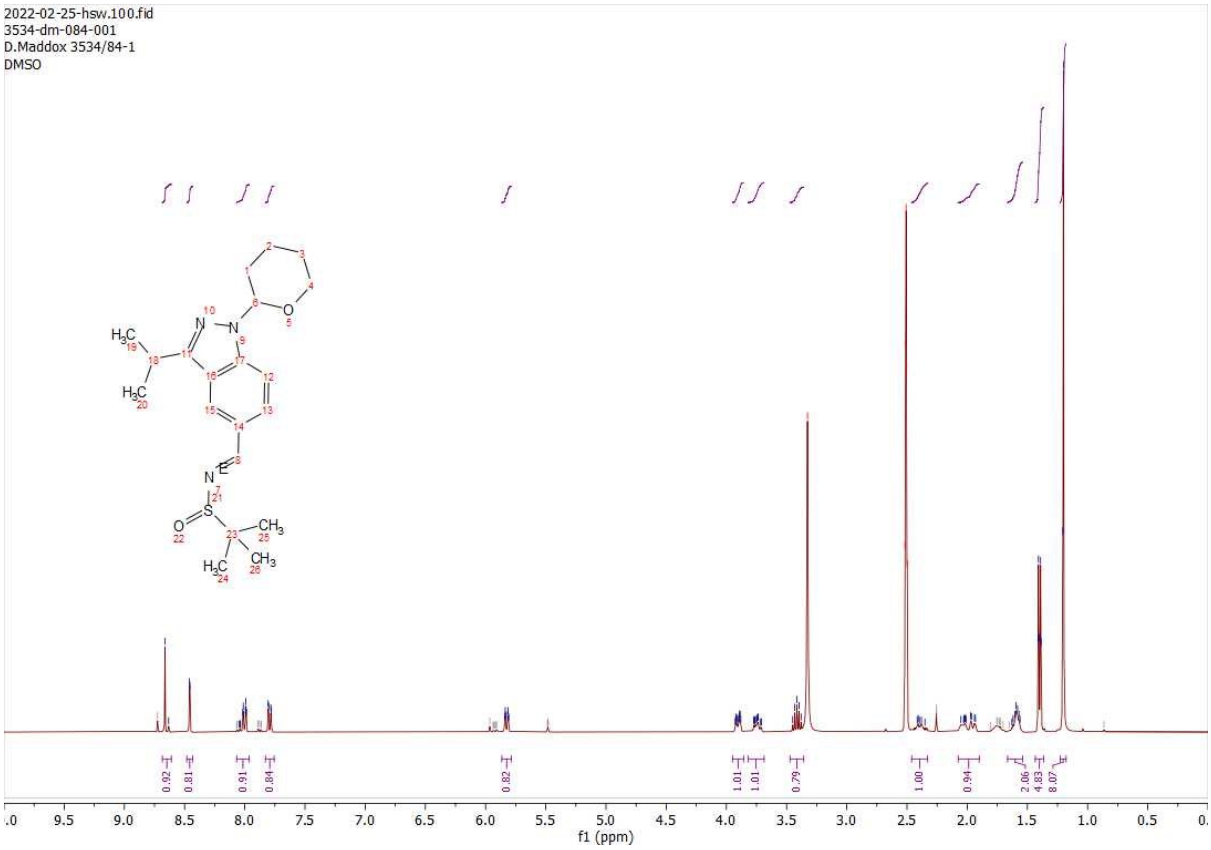
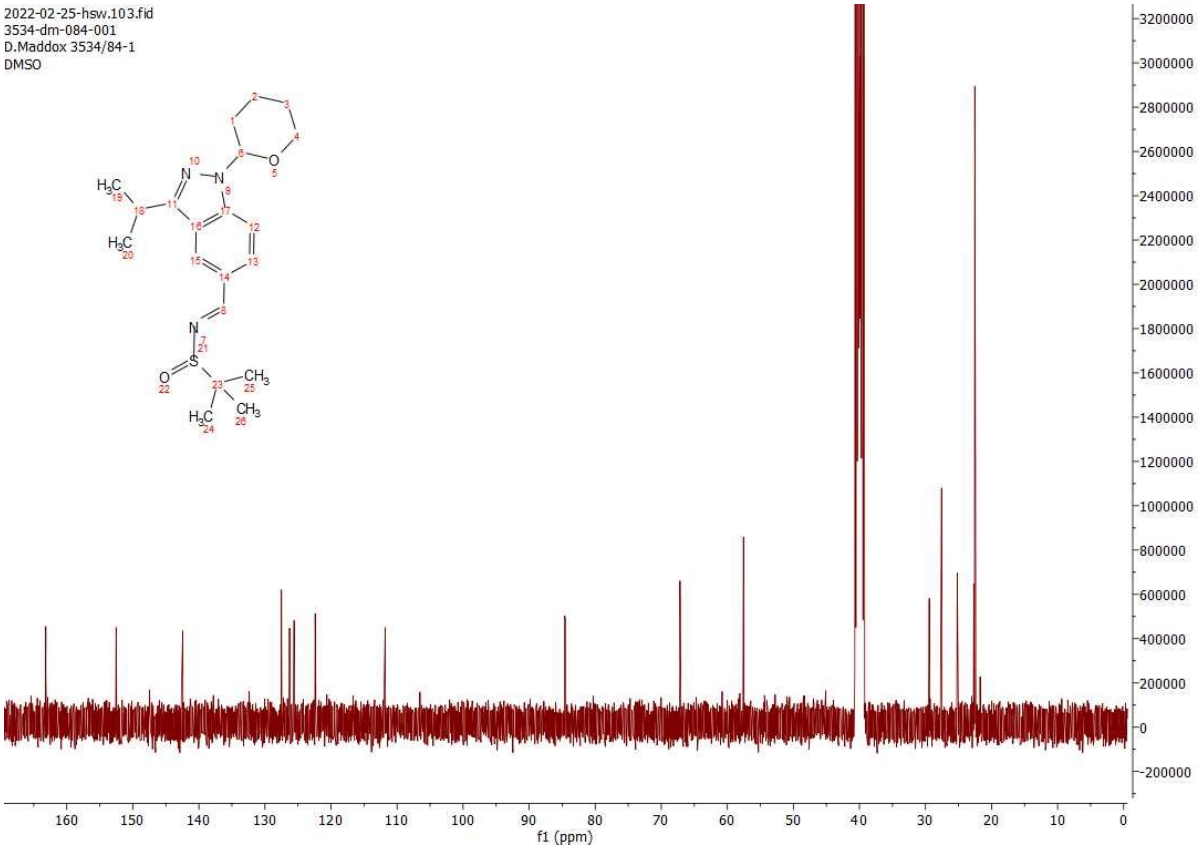
3534-dm-071-001
D.Maddox 3534/71-1
DMSO
f1 (ppm)

5


2022-02-25-hsw.100.fid
3534-dm-084-001
D.Maddox 3534/84-1
DMSO
0.92
0.81
0.91
0.84
0.82
1.01
1.01
0.79
1.00
0.94
2.06
4.83
8.07
f1 (ppm)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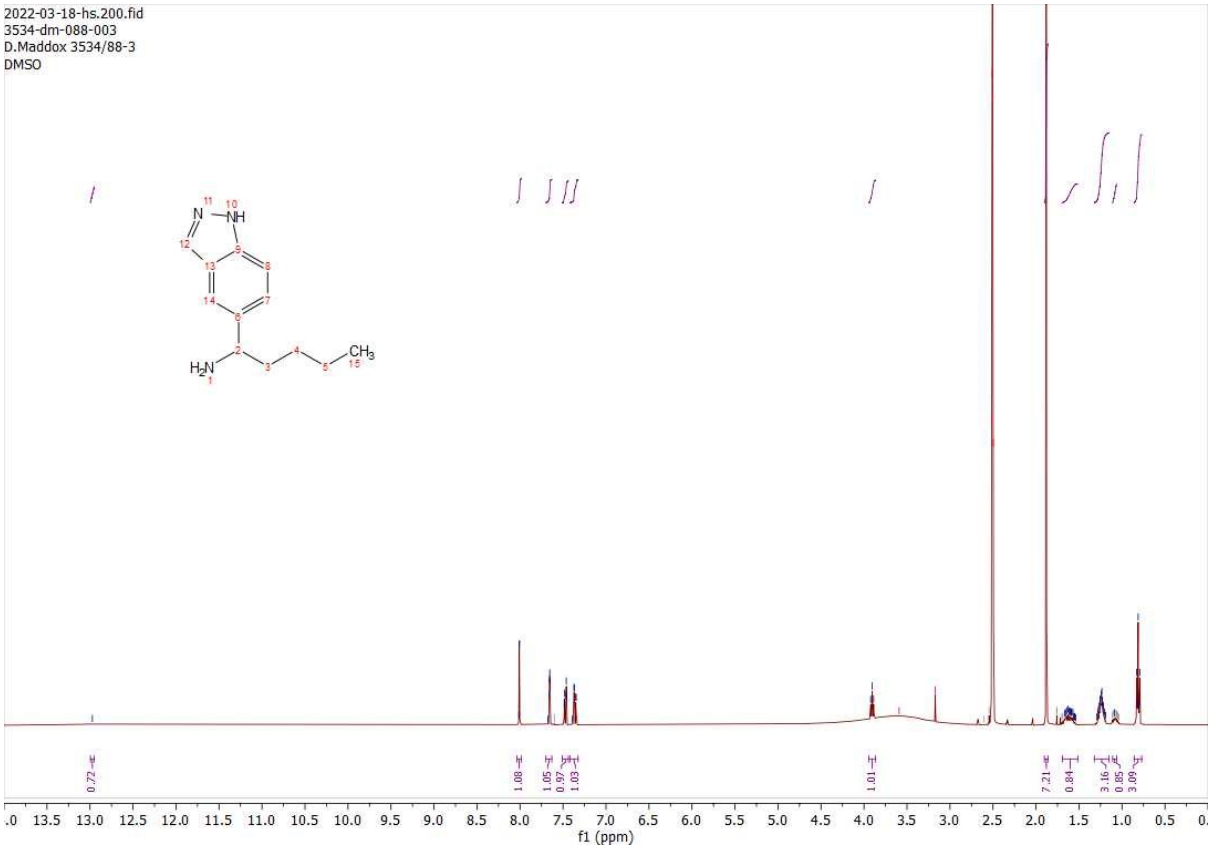
D.Maddox 3534/84-1
DMSO
f1 (ppm)

12a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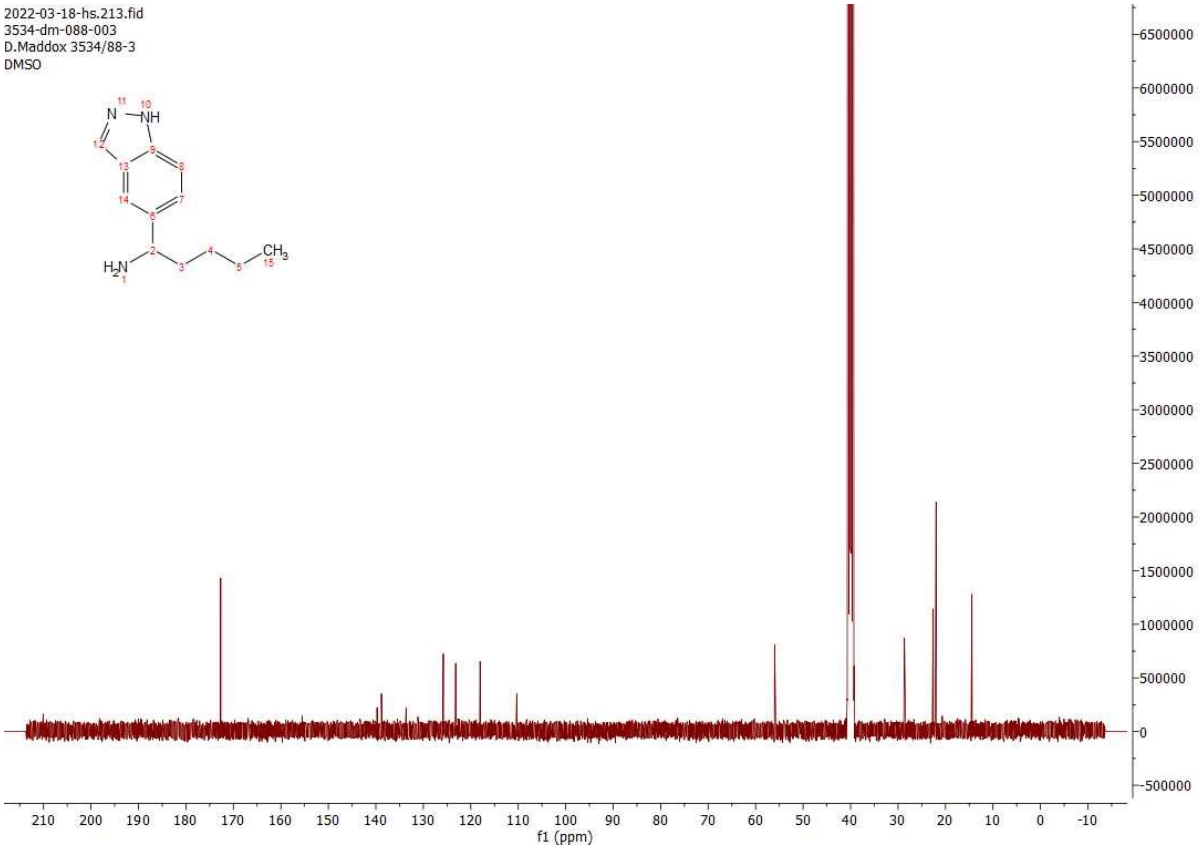
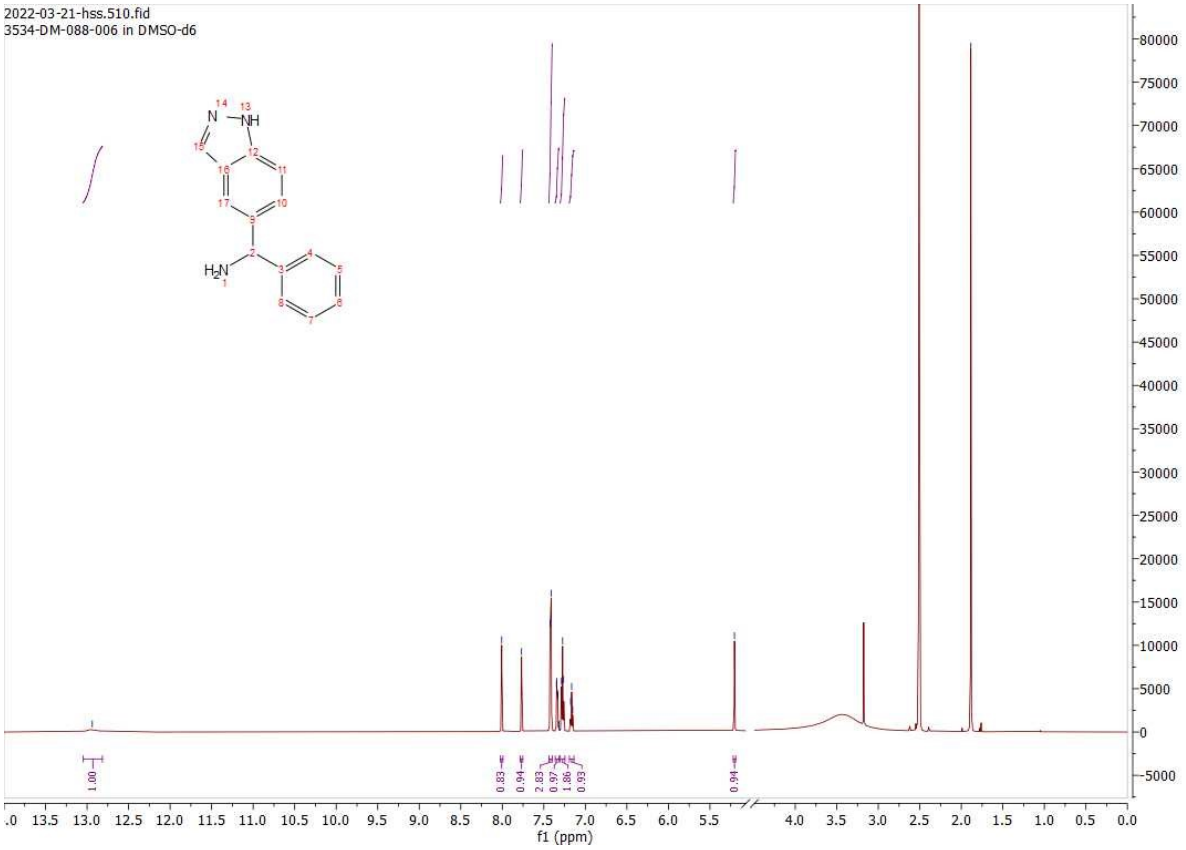
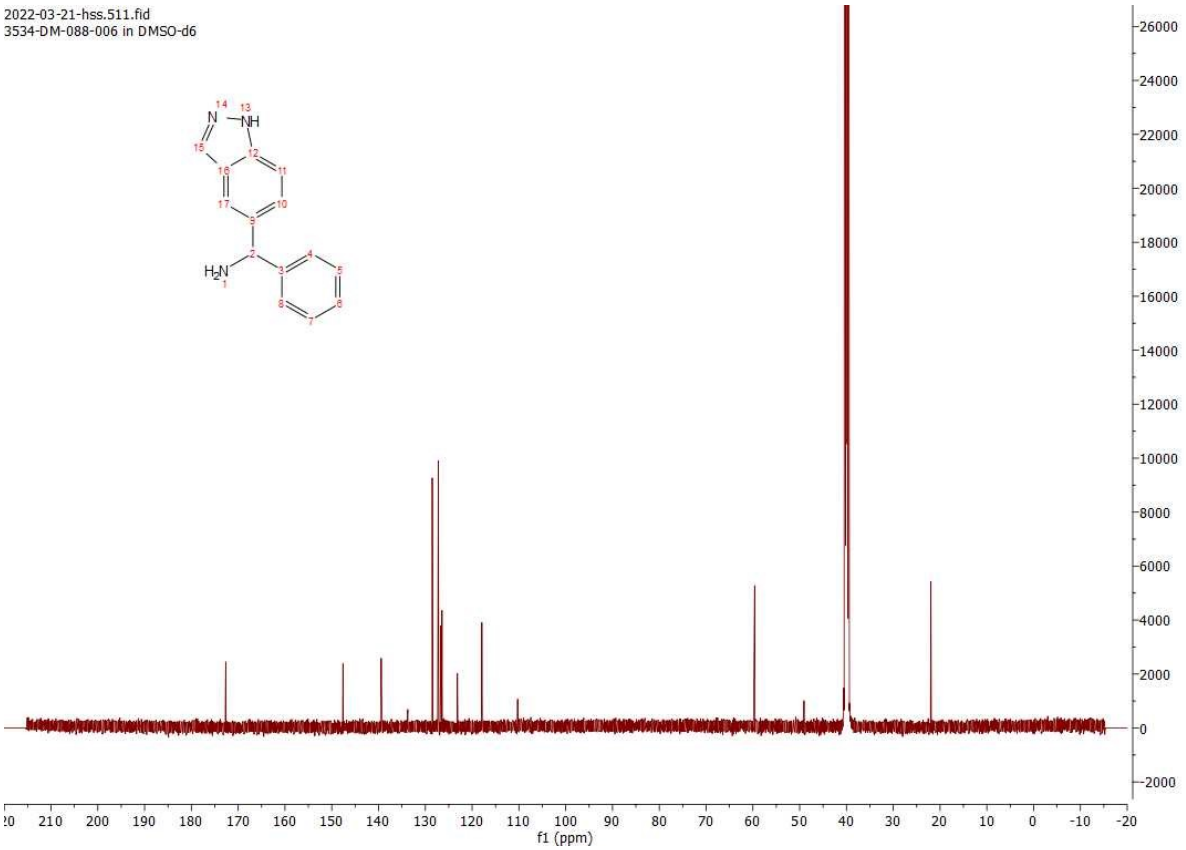
3534-dm-088-003
D.Maddox 3534/88-3
DMSO
f1 (ppm)

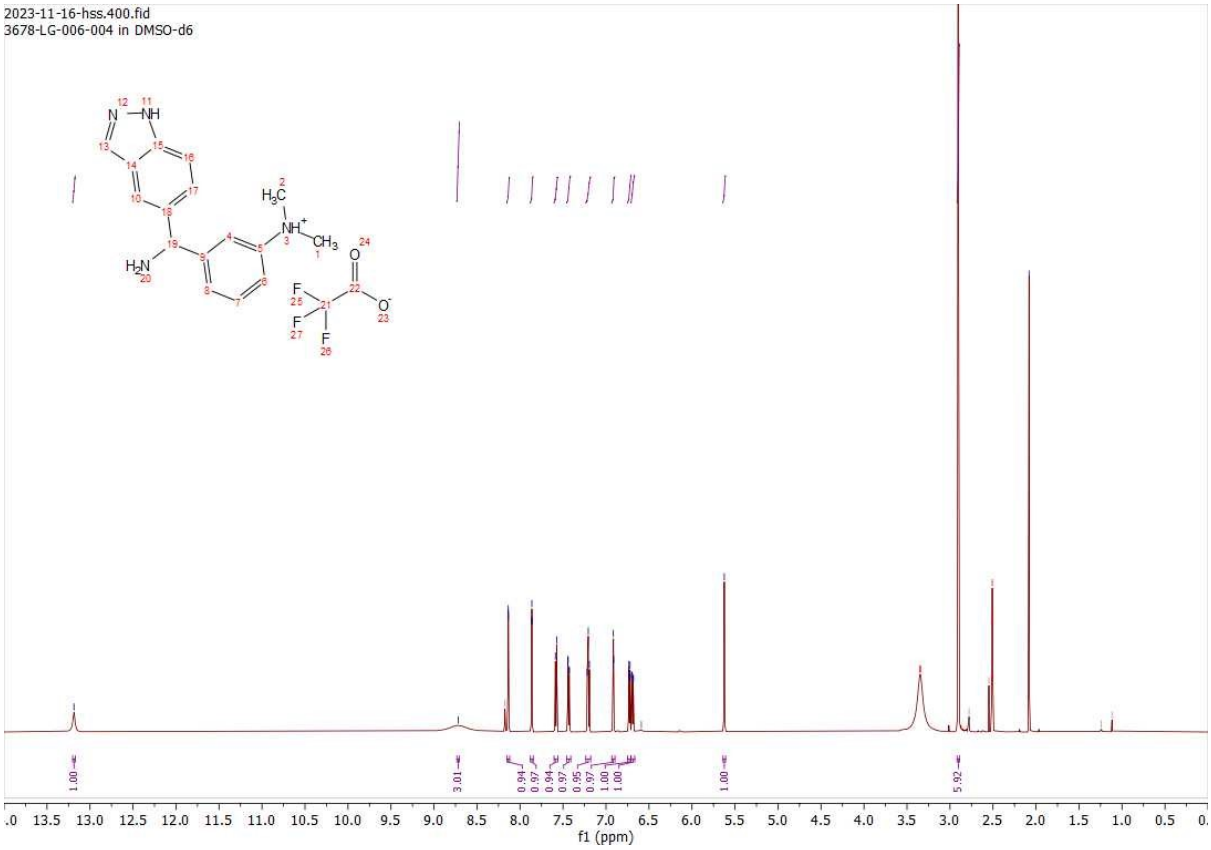

2022-03-18-hs.213.fid
3534-dm-088-003
D.Maddox 3534/88-3
DMSO
N
NH
H_2N
CH_3
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

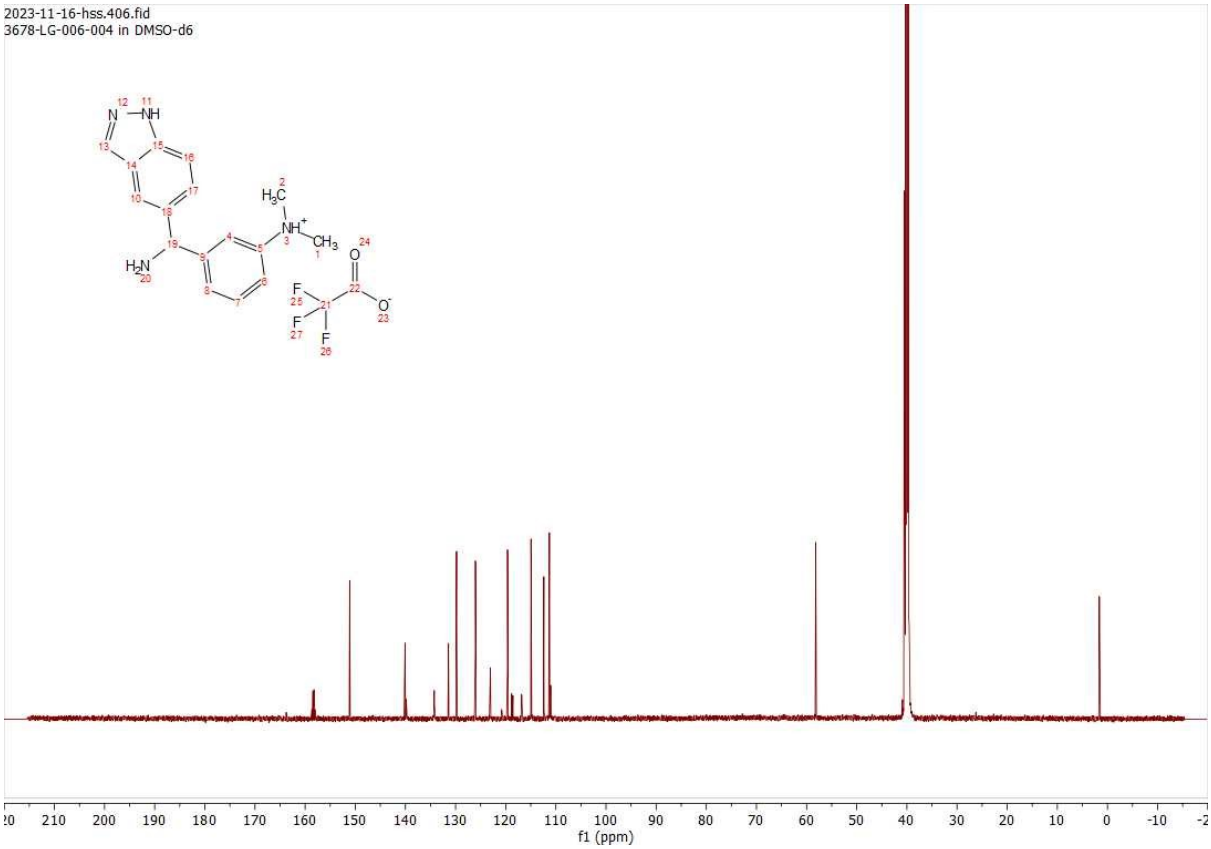
12b

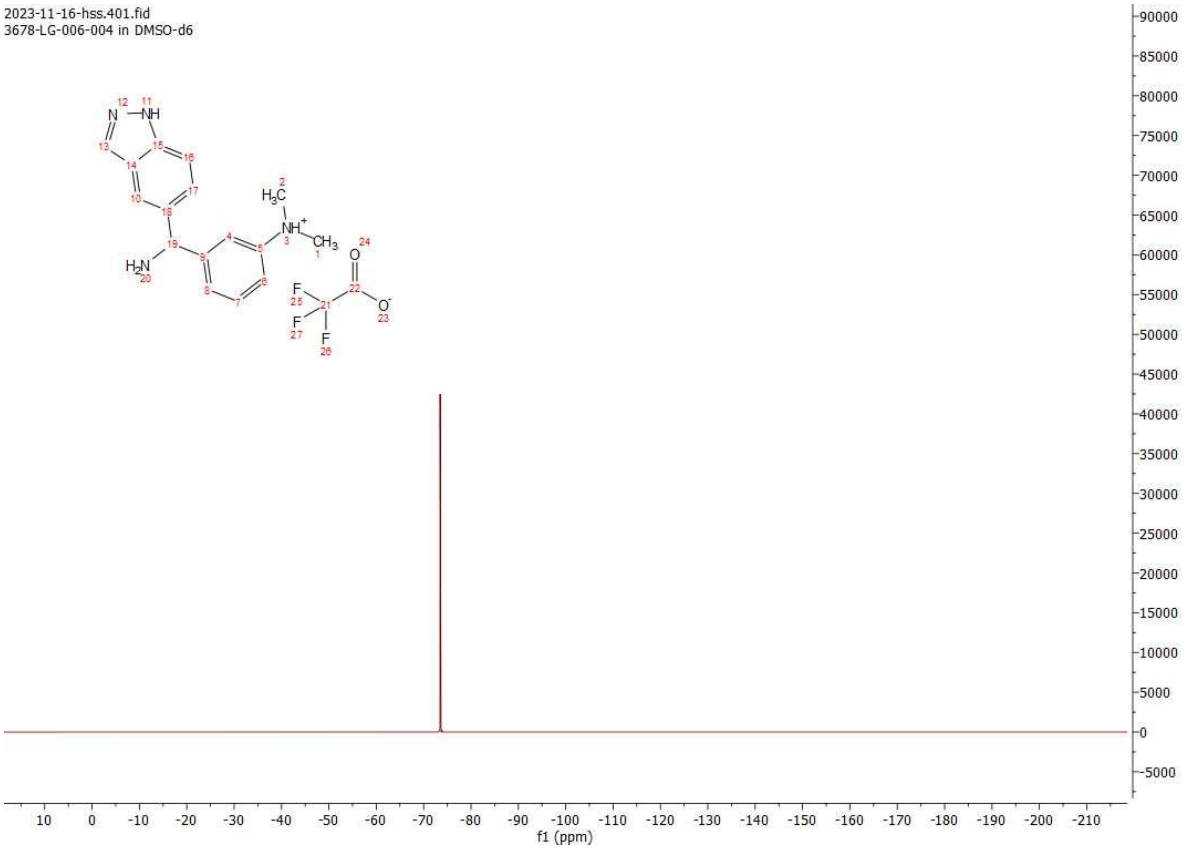

2022-03-21-hss.510.fid
3534-DM-088-006 in DMSO-d6
f1 (ppm)


2022-03-21-hss.511.fid
3534-DM-088-006 in DMSO-d6
f1 (ppm)

12z


2023-11-16-hss.400.fid
3678-LG-006-004 in DMSO-d6
f1 (ppm)


2023-11-16-hss.406.fid
3678-LG-006-004 in DMSO-d6
f1 (ppm)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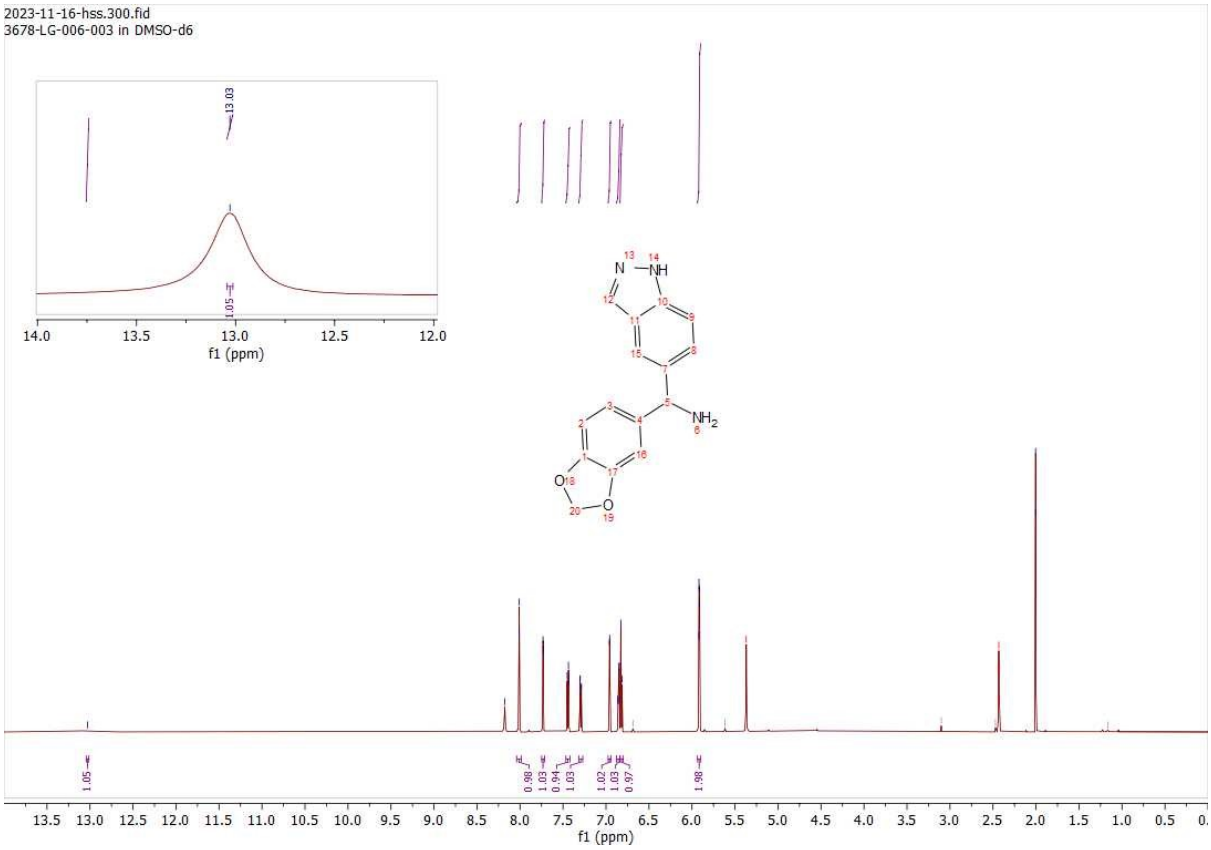
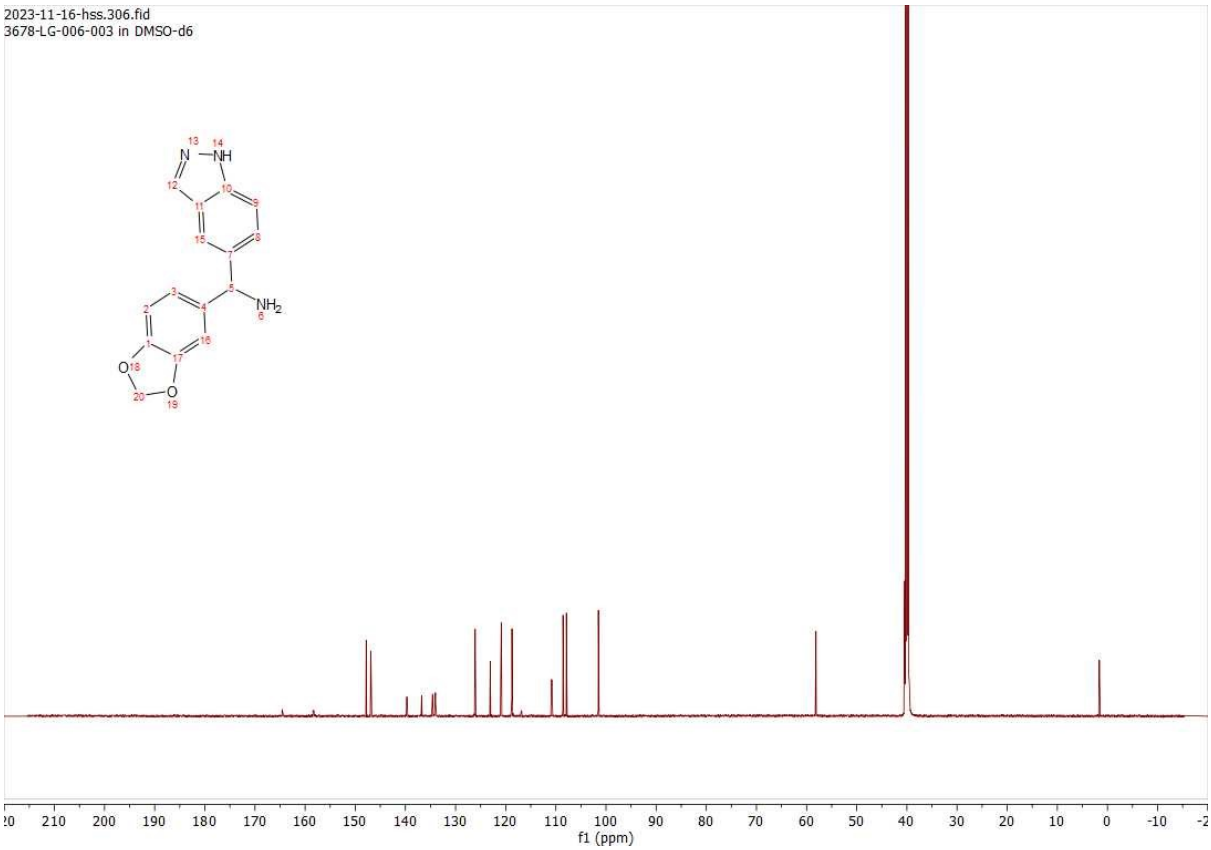
3678-LG-006-004 in DMSO-d6
f1 (ppm)

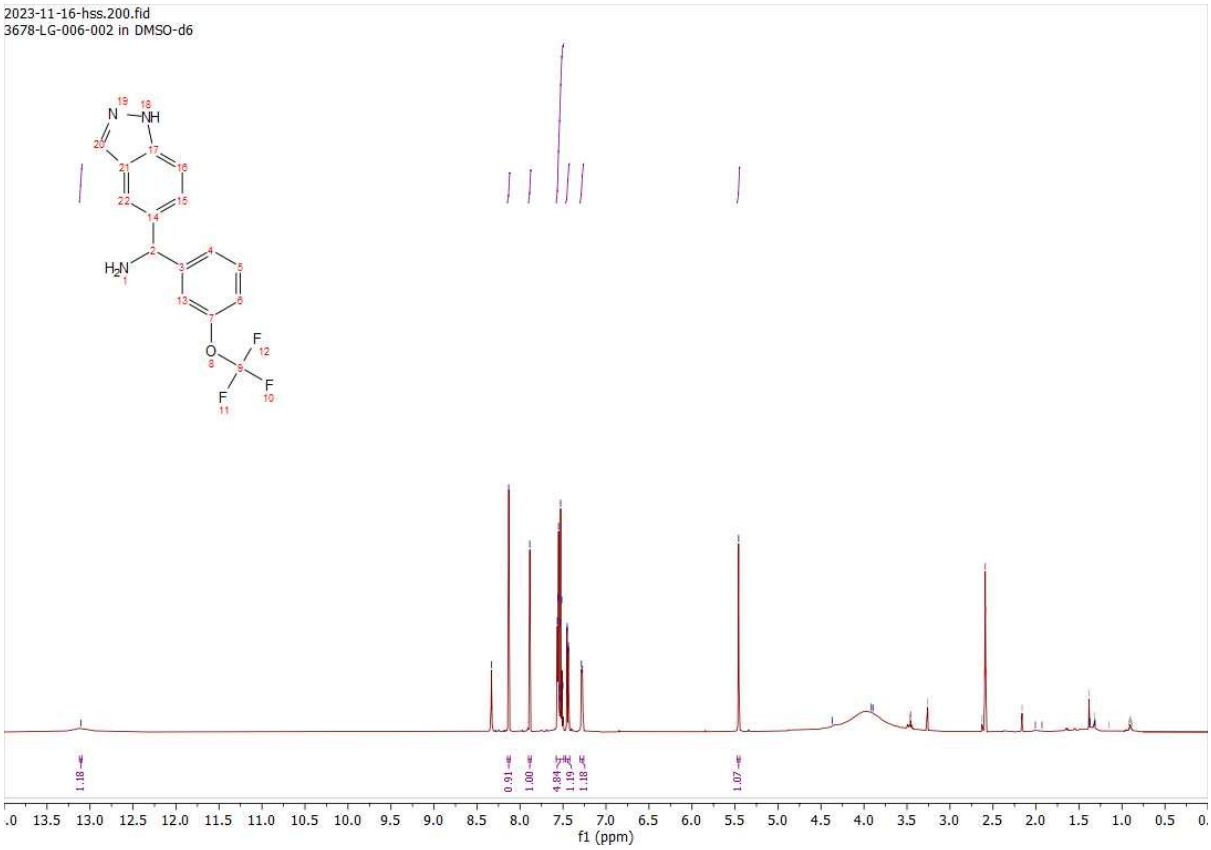
12aa

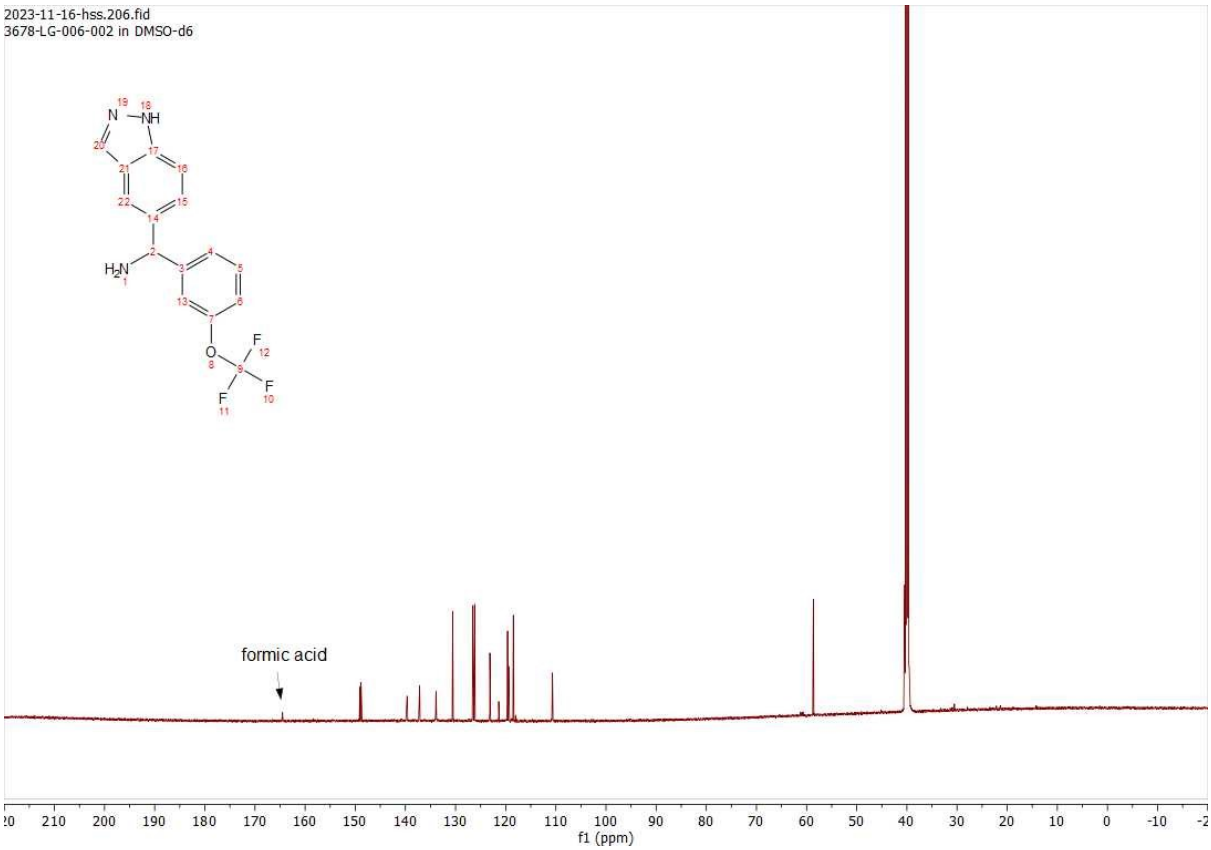

2023-11-16-hss.300.fid
3678-LG-006-003 in DMSO-d6
13.03
1.05
14.0
13.5
13.0
12.5
12.0
f1 (ppm)
N
NH
NH2
O
O
1.05
0.98
1.03
0.94
1.03
1.02
1.03
0.97
1.98
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

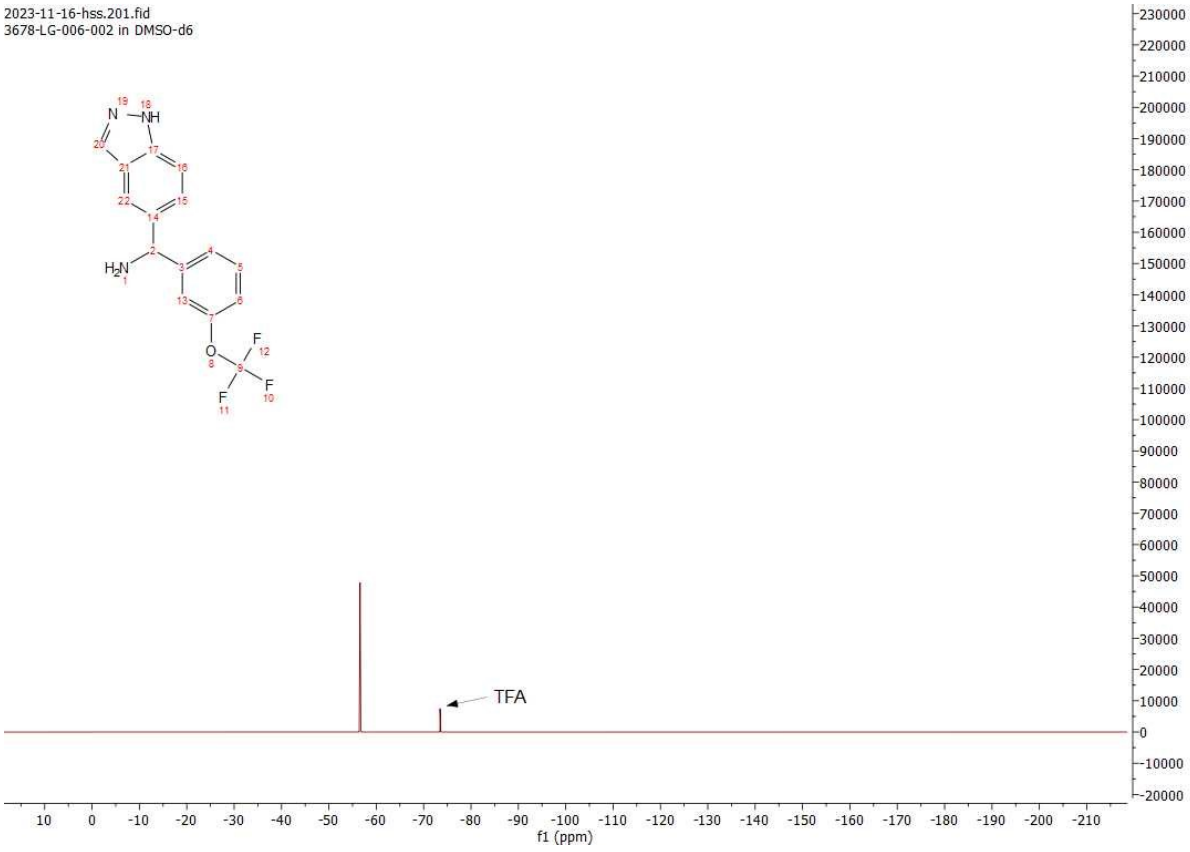

2023-11-16-hss.306.fid
3678-LG-006-003 in DMSO-d6
N
NH
NH2
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


2023-11-16-hss.301.fid
3678-LG-006-003 in DMSO-d6
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

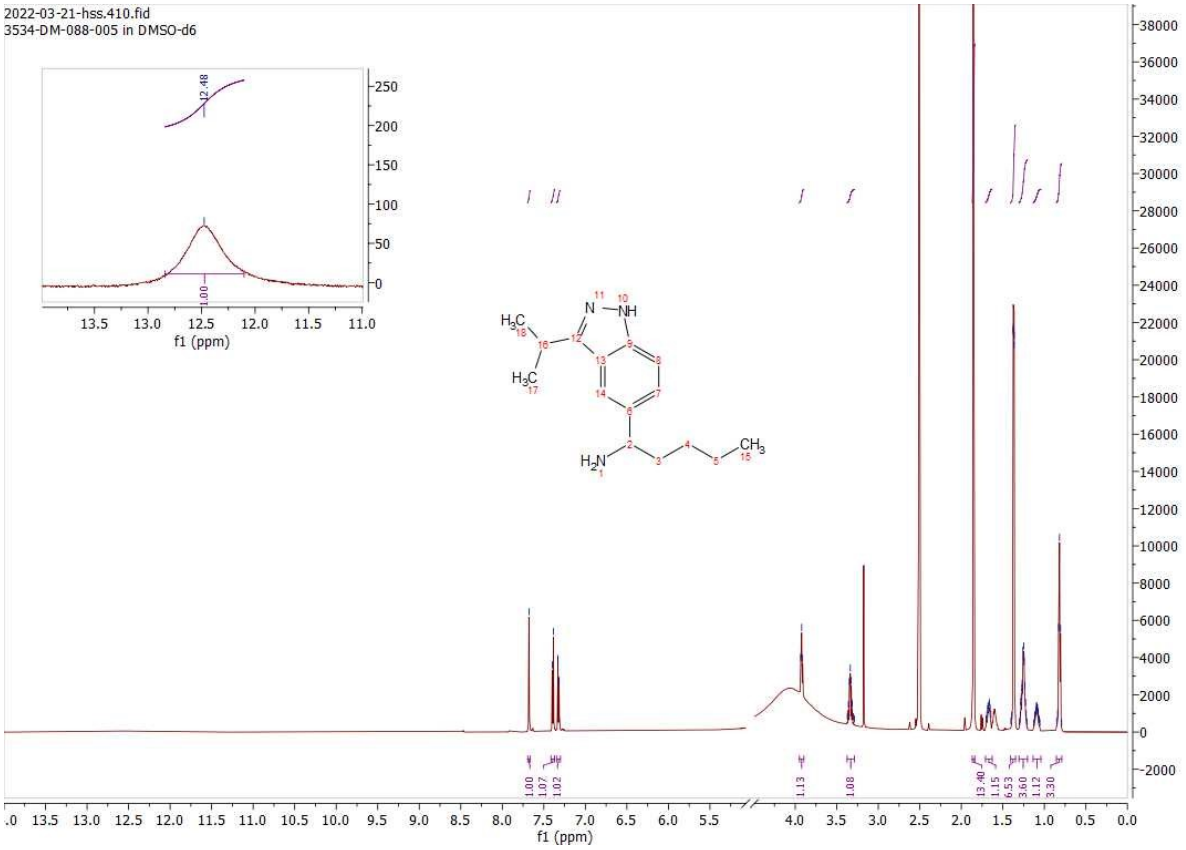
12ai

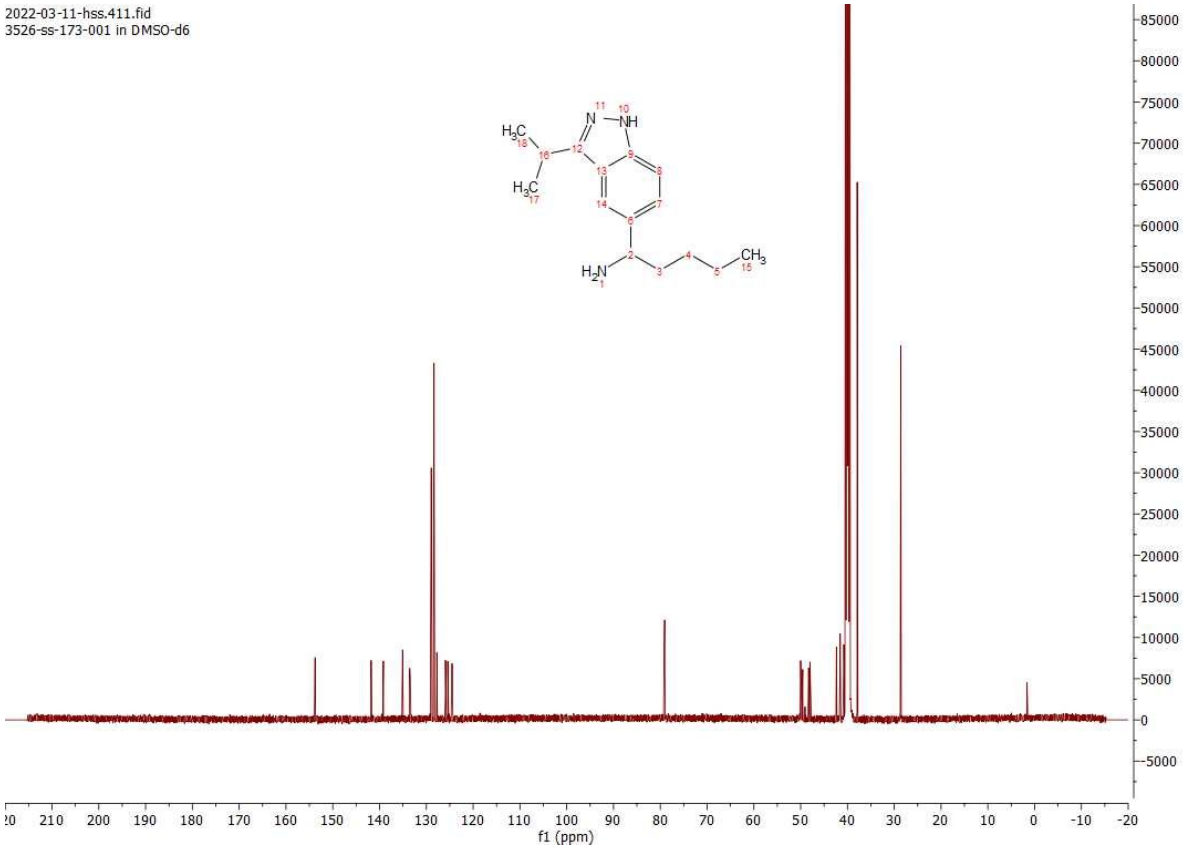

2023-11-16-hss.200.fid
3678-LG-006-002 in DMSO-d6
1.18
0.91
1.00
4.84
1.19
1.18
1.07
f1 (ppm)


2023-11-16-hss.206.fid
3678-LG-006-002 in DMSO-d6
formic acid
f1 (ppm)

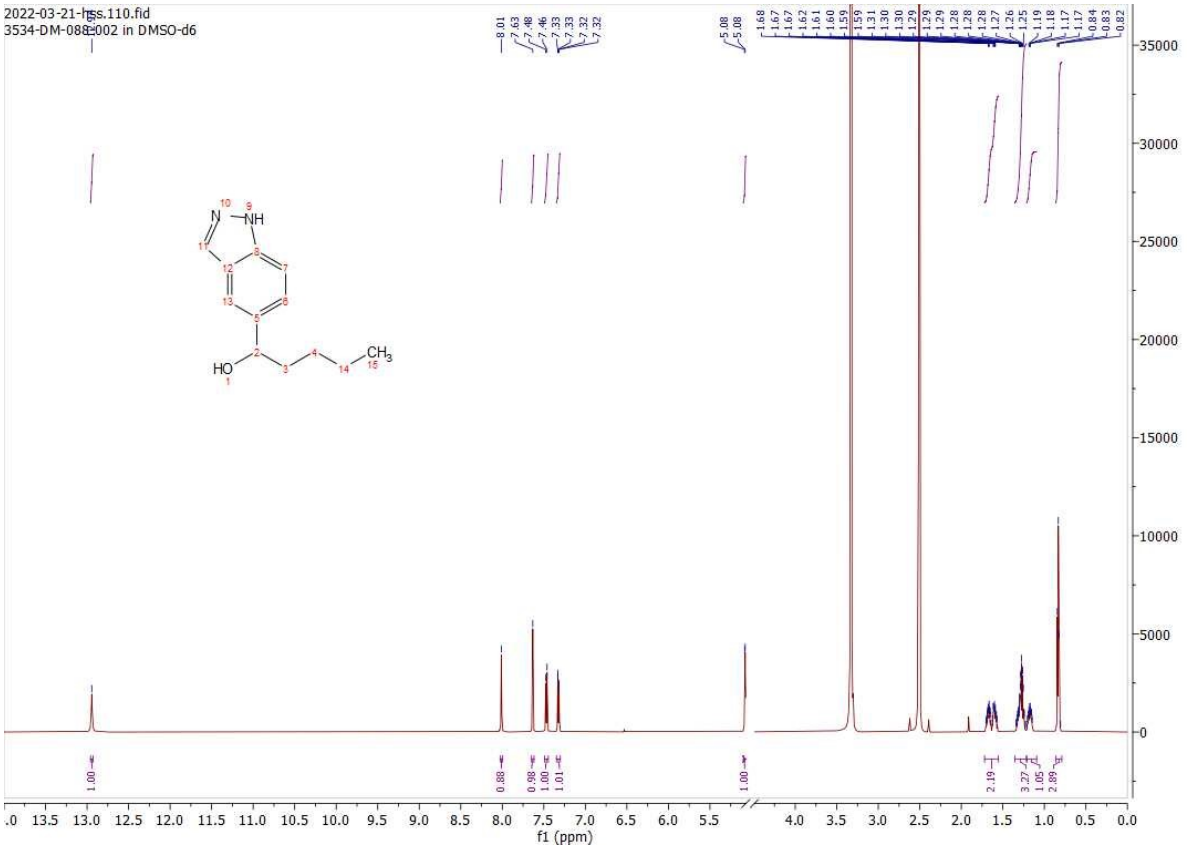

2023-11-16-hss.201.fid
3678-LG-006-002 in DMSO-d6
TFA
f1 (ppm)

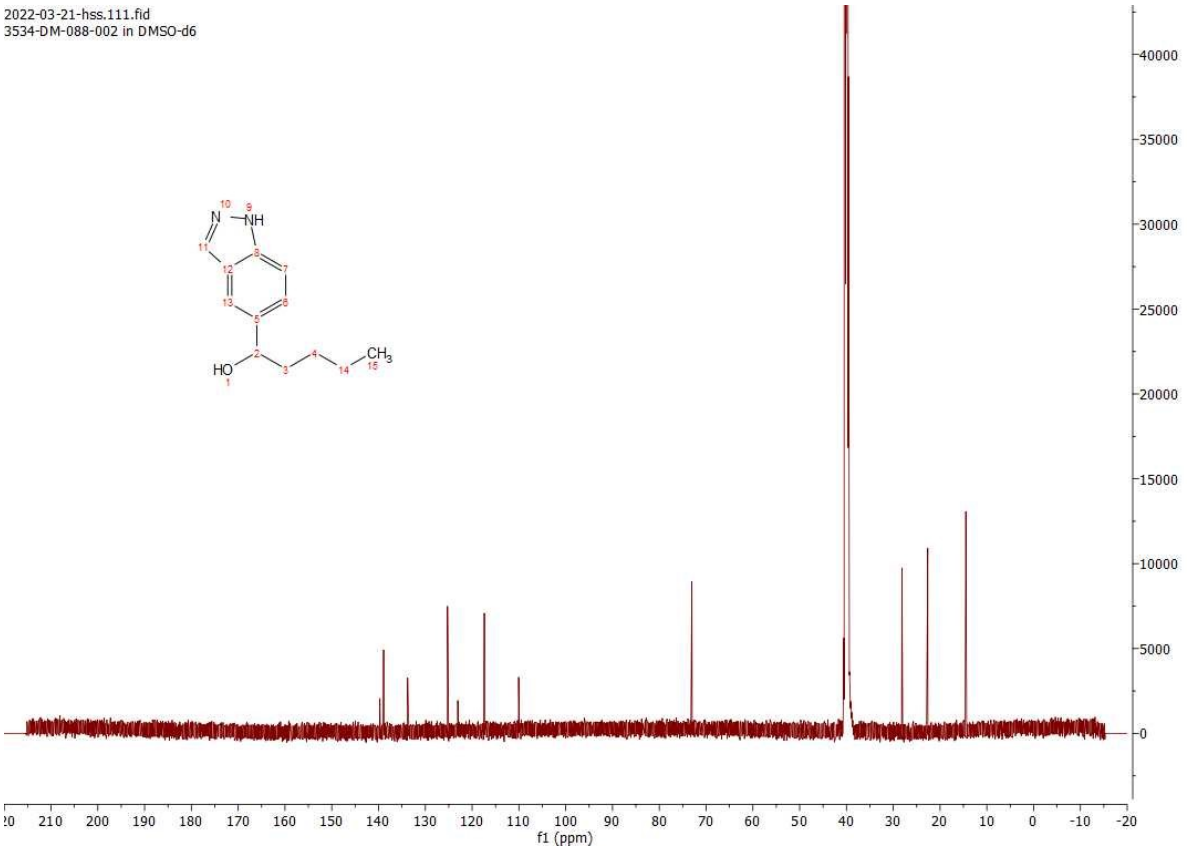
13a


2022-03-21-hss.410.fid
3534-DM-088-005 in DMSO-d6
12.48
1.00
f1 (ppm)
f1 (ppm)

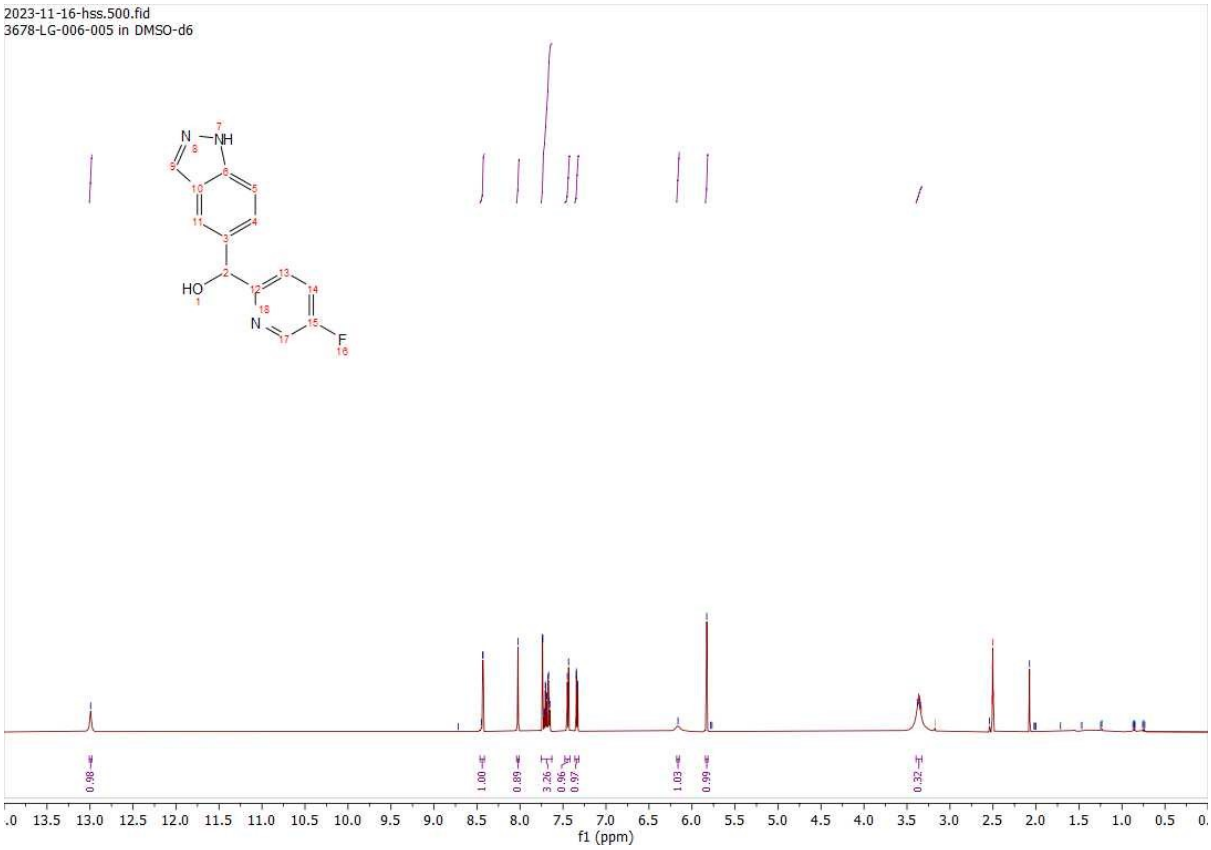

2022-03-11-hss.411.fid
3526-ss-173-001 in DMSO-d6
f1 (ppm)

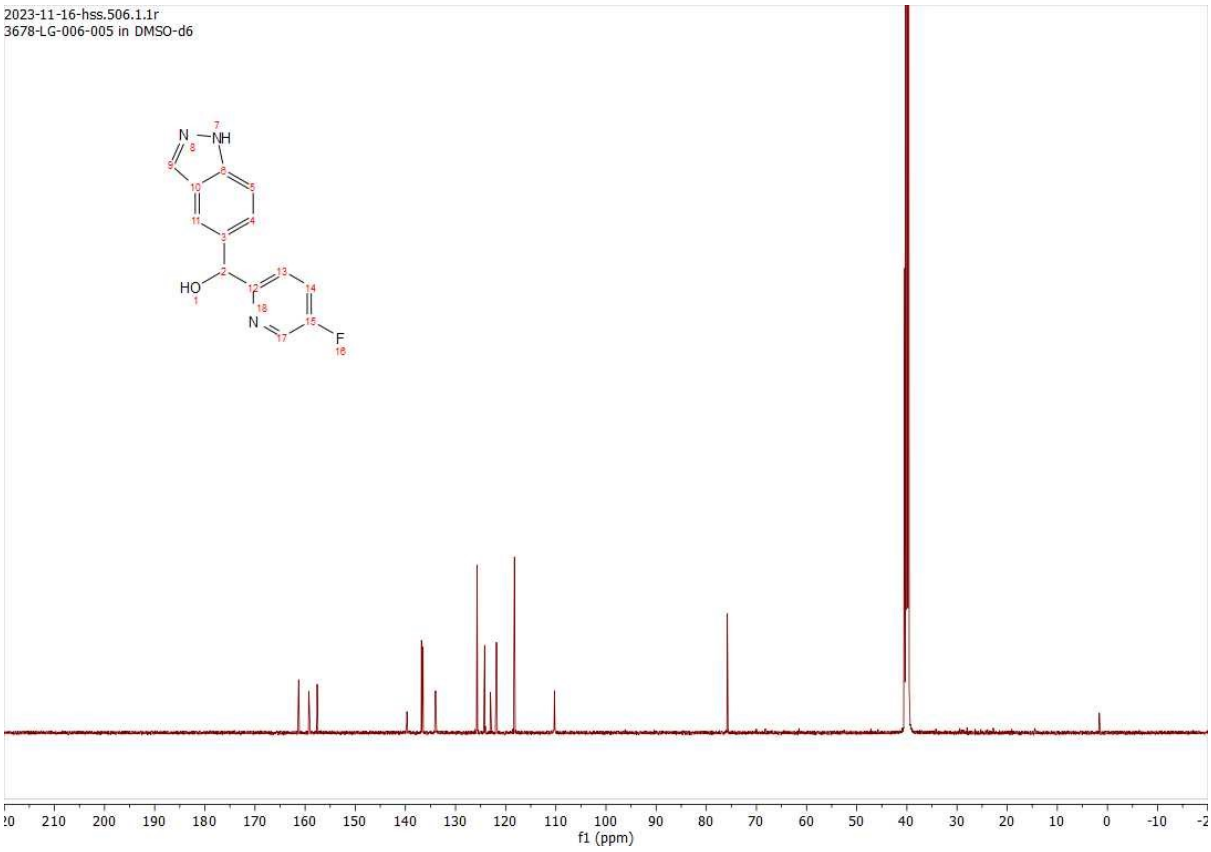
14a

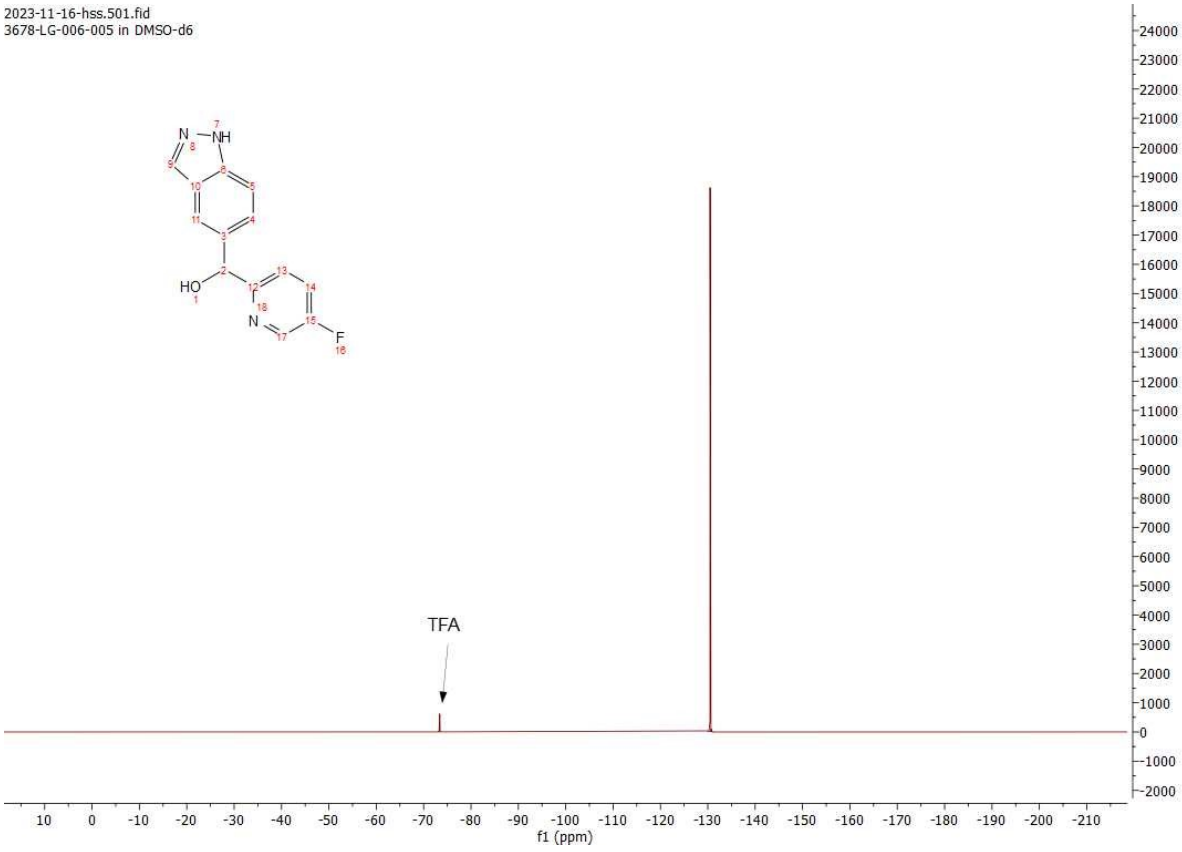

2022-03-21-hss.110.fid
3534-DM-088-002 in DMSO-d6
f1 (ppm)


2022-03-21-hss.111.fid
3534-DM-088-002 in DMSO-d6
f1 (ppm)

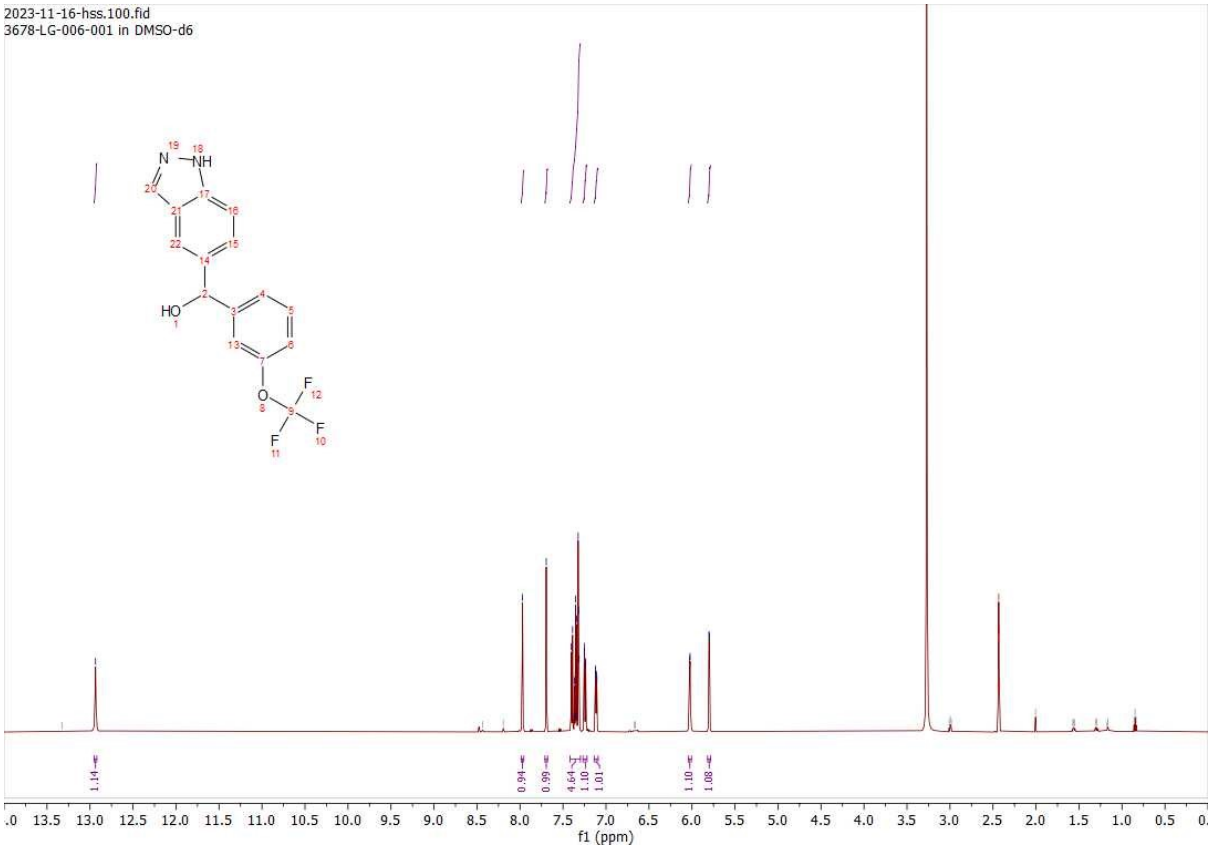
14l

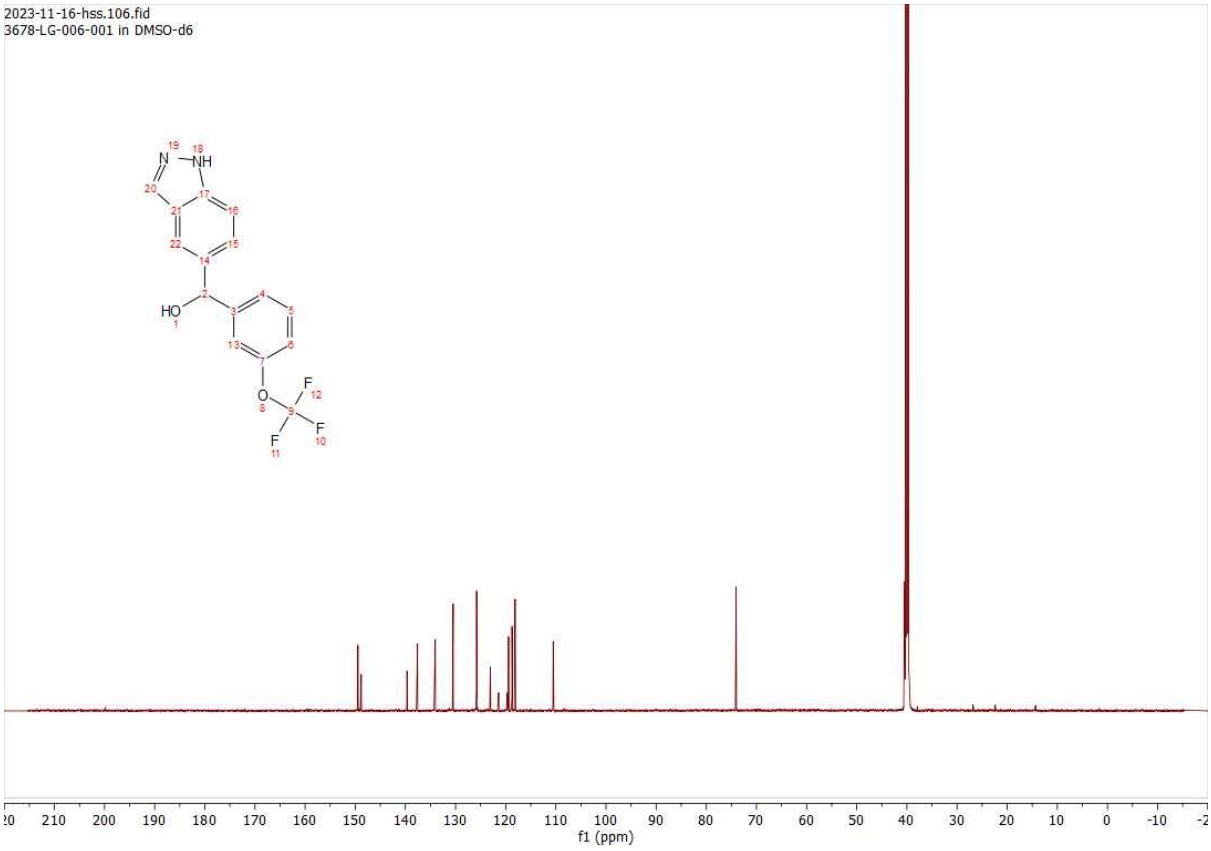

2023-11-16-hss.500.fid
3678-LG-006-005 in DMSO-d6
0.68
1.00
0.89
3.26
0.96
0.97
1.03
0.99
0.32
f1 (ppm)


2023-11-16-hss.506.1.1r
3678-LG-006-005 in DMSO-d6
f1 (ppm)


2023-11-16-hss.501.fid
3678-LG-006-005 in DMSO-d6
TFA
f1 (ppm)

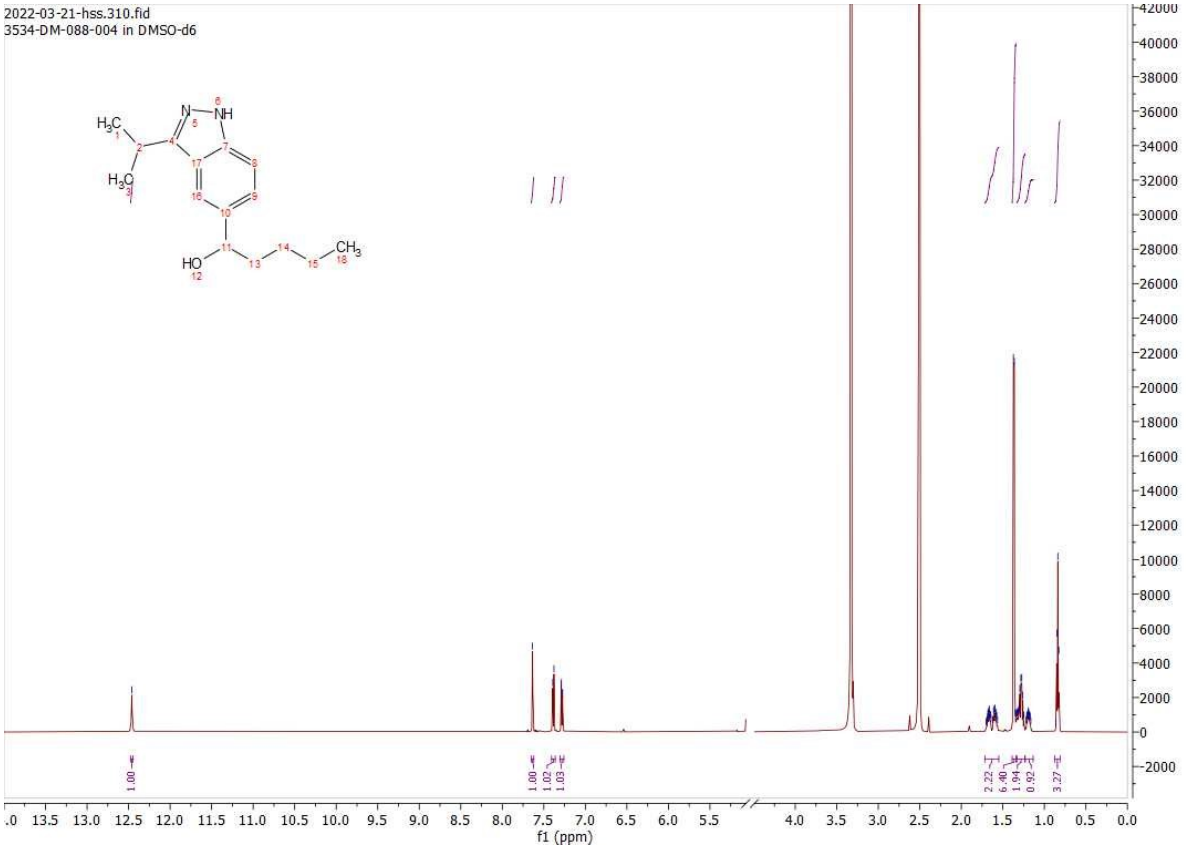
14ai

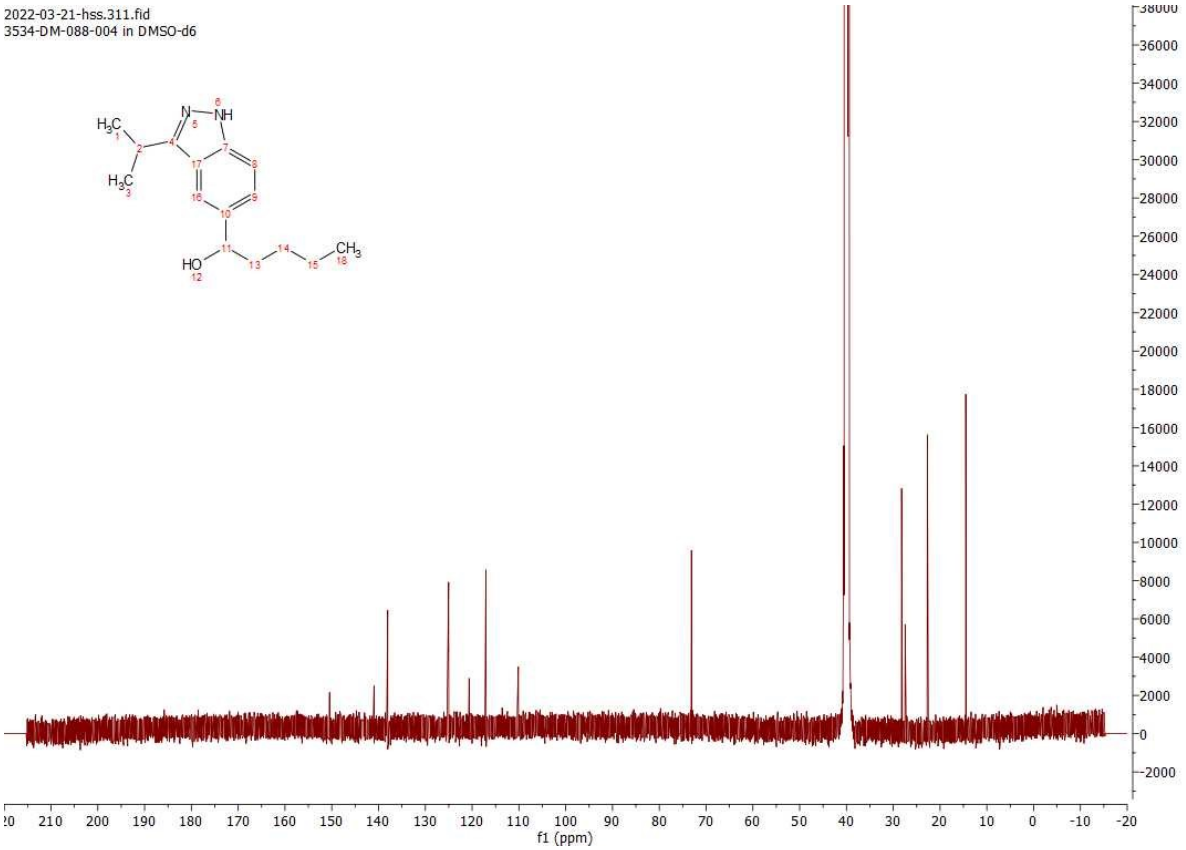

2023-11-16-hss.100.fid
3678-LG-006-001 in DMSO-d6
1.14
0.94
0.99
4.64
1.10
1.01
1.10
1.08
f1 (ppm)


2023-11-16-hss.106.fid
3678-LG-006-001 in DMSO-d6
f1 (ppm)


2023-11-16-hss.101.fid
3678-LG-006-001 in DMSO-d6
HO
1
2
3
4
5
6
7
O
8
9
F
10
F
11
F
12
13
14
15
16
17
NH
18
19
N
20
21
22
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

15a


2022-03-21-hss.310.fid
3534-DM-088-004 in DMSO-d6
f1 (ppm)


2022-03-21-hss.311.fid
3534-DM-088-004 in DMSO-d6
f1 (ppm)