

**Tetramethylolglycoluril Mediated C3 Sulfonylmethylation of
Pyrazolo[1,5-*a*]pyrimidines under Transition Metal-free
Conditions**

M.Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

MAY 2026

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*Submitted in partial fulfillment of the
requirements for the award of the degree*

of

Master of Science

by

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MAY 2026



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CANDIDATE'S DECLARATION

I hereby certify that the work being presented in the thesis entitled “**Tetramethylglycoluril Mediated C3 Sulfonylmethylation of Pyrazolo[1,5-*a*]pyrimidines under Transition Metal-free Conditions**” in the partial fulfilment of the requirements for the award of the degree of MASTER OF SCIENCE and submitted to the Department of Chemistry, Indian Institute of Technology Indore, is an authentic record of my work carried out during the period from July 2025 to May 2026 under the supervision of Dr. Umesh A. Kshirsagar, Associate Professor, Department of Chemistry, IIT Indore.

Mahesh Sasamal
Dt:-22/05/2026

Mahesh Sasamal

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

22/05/2026 

Dr. Umesh A. Kshirsagar

Mahesh Sasamal has successfully given his M.Sc. Oral Examination held on 21/05/2026.

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Lastly, I extend my heartfelt gratitude to my friends and family for standing by me and supporting me in both challenging and successful moments.

Mahesh Sasamal

M.Sc. Second Year

2403131015

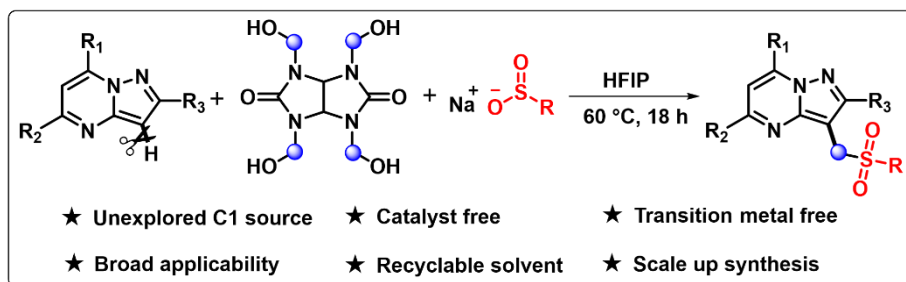
Department of Chemistry, IIT Indore



JAY JAGANNATH

**DEDICATED TO
MY FAMILY.....**

ABSTRACT



HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) promoted transition metal-free protocol for regioselective C3 sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines by using tetramethyloglycoluril as a nontoxic, in situ C1 source and sodium sulfinate salts has been developed. This methodology is operationally simple, cost-effective, and environmentally benign, and affords sulfonylmethylated products in moderate to good yields. Mechanistic studies suggest that the reaction proceeds via an ionic path.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

ACRONYMS

ABBREVIATIONS

Chapter 1 - Introduction.....1-5

1.1. Objective.....1

1.2. Motivation.....1-3

1.3. Literature survey.....3-4

1.4. Research gap and Scope of the Proposed
Work.....5

Chapter 2 - Results and Discussion.....6-12

2.1. Reaction Optimization.....6-7

2.2. Substrate Scope.....7-9

2.3. Scale up reaction.....10

2.4. Control Experiments.....10-11

2.5. Plausible Mechanism.....12

Chapter 3 - Experimental work.....13-20

3.1. Material and instrumentation 13

3.2. Synthesis

3.2.1. General procedure for the synthesis of substituted
pyrazolo[1,5-*a*] pyrimidines 13

3.2.2. General procedure for the synthesis of trisubstituted
pyrazolo[1,5-*a*] pyrimidines.....14-15

3.2.3. General Procedure for Synthesis of Sodium Sulfinate
salts.....16

3.2.4. General Procedure for sulfonylmethylation of pyrazolo[1,5- <i>a</i>]pyrimidine	17
3.2.5. Experimental procedure for the scale-up synthesis of 4l and solvent recycling	17-18
3.2.6. Experimental procedure for the synthesis of compound 7	18
3.2.7. Control experiments for the sulfonylmethylation of pyrazolo[1,5- <i>a</i>]pyrimidine	19
3.2.8. Experimental procedure for radical quenching experiments.....	19-20
3.2.9. Experimental procedure for intermediate detection.....	20
3.2.10. Conclusion.....	20
Chapter 4 - Supporting information.....	21-50
4.1. Characterization data of compounds (4a-4t, 7).....	21-28
4.2. NMR spectra of compounds (4a-4t, 7).....	29-50
Chapter 5 - References	51-54

LIST OF FIGURES

Figure. 1: Bioactive compounds with pyrazolo[1,5-*a*]pyrimidine framework

Figure. 2: Representative clinical drugs consisting of methylene sulfonyl unit

Figure. (3-46): ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR of compounds (**4a-4t, 7**)

LIST OF SCHEMES

- Scheme 1.** Schematic representation of our work.
- Scheme 2.** Sulfonylmethylation of imidazo[1,2-*a*]pyridine under visible light.
- Scheme 3.** Sulfonylmethylation using *p*-toluenesulfonylmethyl isocyanide.
- Scheme 4.** Sulfonylmethylation using ferric chloride.
- Scheme 5.** Sulfonylation of arylacetic acids using copper (II) acetate monohydrate.
- Scheme 6.** Substrate scope for sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines.
- Scheme 7.** Substrate scope for sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines with various sulfinates.
- Scheme 8.** Scale up synthesis and solvent recycling.
- Scheme 9.** Control experiments for elucidation of reaction mechanism.
- Scheme 10.** Plausible reaction pathway.
- Scheme 11.** Synthesis of substituted pyrazolo[1,5-*a*]pyrimidines.
- Scheme 12.** Synthesis of trisubstituted pyrazolo[1,5-*a*]pyrimidines.
- Scheme 13.** Synthesis of sodium sulfinates.
- Scheme 14.** Sulfonylmethylation of substituted pyrazolo[1,5-*a*]pyrimidines.
- Scheme 15.** Scale up synthesis of **4l** and solvent recycling.
- Scheme 16.** Synthetic application of **4a**.
- Scheme 17.** Radical quenching and intermediate detection.

Acronyms

s	Singlet
d	Doublet
q	Quartet
dd	Doublet of doublet
m	Multiplet
J	Coupling constant
CDCl_3	Chloroform-d
EtOAc	Ethyl acetate
Na_2SO_4	Sodium sulphate
NMR	Nuclear magnetic resonance

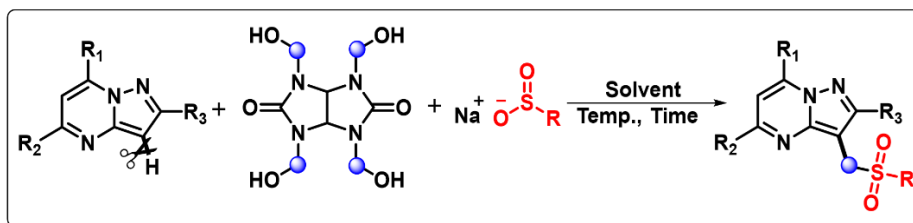
ABBREVIATIONS

°C	Degree Celsius
h	Hour
mg	Milligram
mL	Millilitre
mmol	Millimole
equiv.	equivalent
δ	chemical shift

Chapter 1 – INTRODUCTION

1.1. OBJECTIVE

The development of sustainable synthetic methodologies for C-H functionalization of biologically relevant heterocycles has gained significant attention, particularly through transition metal-free strategies. The use of one carbon synthons for C-H functionalization has provided a novel pathway for constructing complex organic molecules. In this context, our objective is to improve the reaction efficiency while minimizing environmental impact and reducing overall cost. We aim to design a protocol for the regioselective C3 sulfonylmethylation of N-heterocycles via a nucleophilic attack on a methylene containing reagent under mild reaction conditions. This strategy enables efficient construction of C-C and C-S bonds.



Scheme 1. Schematic representation of our work

1.2. MOTIVATION

The pyrazolo[1,5-*a*]pyrimidine scaffold is a privileged heterocyclic framework that has attracted considerable attention owing to its broad spectrum of pharmacological and biological activities [1]. It plays a crucial role in the development of anticancer agents, particularly by inhibiting kinases that regulate cancer cell growth and proliferation. This scaffold is present in several clinically approved anticancer drugs, including dinaciclib, repotrectinib, and larotrectinib, highlighting its significance in oncology [2]. Beyond cancer treatment, pyrazolo[1,5-*a*]pyrimidines also served as the core unit in insomnia medications such as zaleplon, indiplon and lorediplon, underscoring their broad therapeutic relevance and versatility in drug design (**Fig.1**) [3,4].

Furthermore, this heterocyclic framework also finds applications in the field of material chemistry and sensing technologies [5,6].

C–H functionalization has emerged as a powerful strategy in modern synthetic organic chemistry, providing access to innovative retrosynthetic disconnections and efficient C–C bond formation strategies. This strategy has gained remarkable attention in recent years for its ability to introduce functional groups at specific positions within molecules without the need for pre-functionalized precursors. By eliminating the requirement for pre-functionalization, C–H functionalization offers a step economic alternative to classical transformations and cross-coupling reactions, thereby advancing synthetic efficiency and contributing to sustainability in chemical synthesis [7].

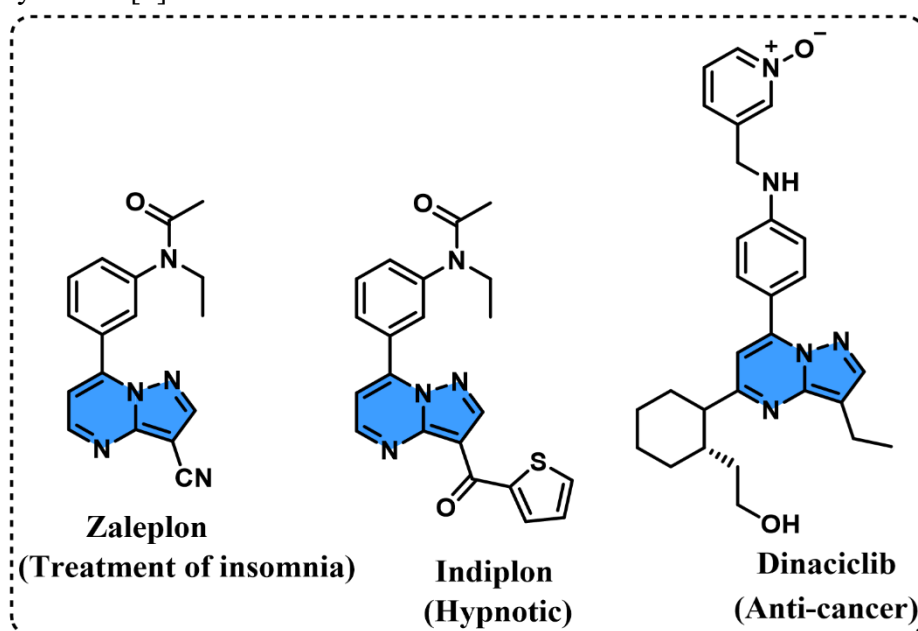


Figure 1. Bioactive compounds with pyrazolo[1,5-*a*]pyrimidine framework.

The synthesis of sulfone containing compounds has attracted significant attention in organic chemistry due to their broad applications in pharmaceuticals, materials science, polymer chemistry, and agrochemicals [8-12]. Apart from their direct utility, sulfones also serve as valuable intermediates and functional motifs in synthetic transformations and organocatalysis [13,14]. Importantly, the sulfonyl functional group serves as a crucial pharmacophoric element and is

present in several clinically approved drugs, including Naratriptan, Tinidazole, and Apremilast, underscoring its therapeutic relevance (Fig.2).

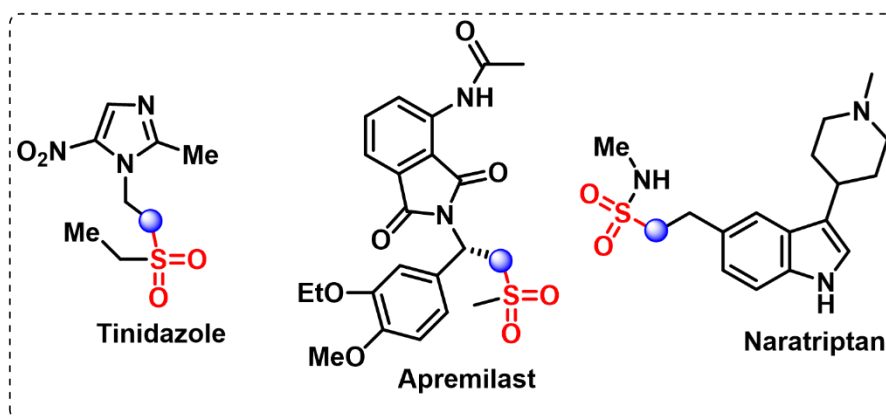


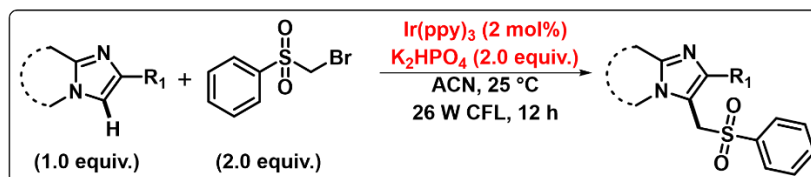
Figure 2. Representative clinical drugs consisting of methylene sulfonyl unit.

C1 homologation is a versatile tool for the selective introduction of a methylene unit in organic skeletons [15,16]. It is recognized as a valuable strategy in medicinal chemistry for generating therapeutic agents. This approach increases molecular diversity and modifies the parent framework, thereby tuning the physiochemical properties such as lipophilicity and chemical reactivity [17,18].

1.3. Literature survey

Previous work

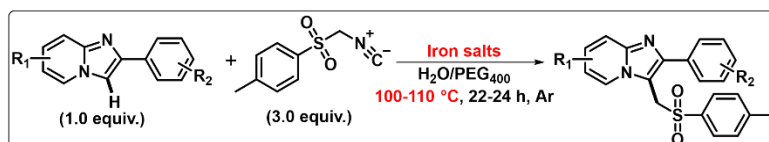
- Zang and co-workers developed a visible light mediated strategy for the sulfonylmethylation of heterocycles by using an iridium-based photocatalyst, along with a stoichiometric amount of base (dipotassium phosphate) [19].



Scheme 2. Sulfonylmethylation of imidazo[1,2-*a*]pyridine under visible light.

Kong *et al. Chin. Chem. Lett.* **2019**, *30*, 2295–2298

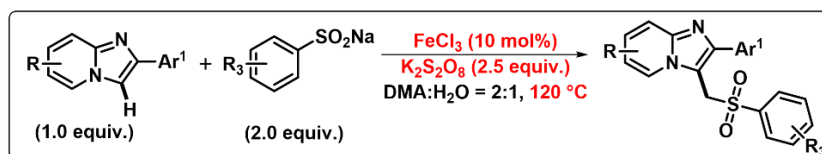
- Wang's group developed a protocol for the tosylmethylation of imidazo[1,2-*a*]pyridine that employs a stoichiometric amount of ferric chloride and requires elevated temperature under an inert atmosphere [20].



Scheme 3. Sulfonylmethylation using *p*-toluenesulfonylmethyl isocyanide.

Wang *et al. J. Org. Chem.* **2016**, *81*, 8370–8377

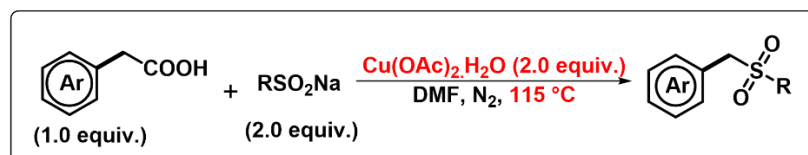
- Sun's group reported a similar strategy for the sulfonylmethylation of the heterocycles via iron catalyzed condition, using *N,N*-Dimethylacetamide serves as a single carbon source, along with stoichiometric amount of oxidant and harsh conditions [21].



Scheme 4. Sulfonylmethylation using ferric chloride.

Sun *et al. Molecules* **2024**, *29* (13), 3196

- Wu's group demonstrated a decarboxylative sulfonylation of arylacetic acids with stoichiometric amount of copper (II) acetate monohydrate under high heating and in an inert condition [22].



Scheme 5. Sulfonylation of arylacetic acids using copper (II) acetate monohydrate.

Chen *et al. Org. Lett.* **2020**, *22* (18), 7164–7168

1.4. Research Gap and Scope of Proposed Work

Previous reports indicate that sulfonylmethylation of N-heterocycles relied on the use of transition metal-based reagents, additives, high temperatures and inert conditions. Therefore, there is a need to develop a more sustainable approach aligned with the principles of green chemistry. We aim to develop a one pot, sustainable and environmentally benign approach for the sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidine using tetramethyloglycoluril as a C1 source and sodium sulfinate salts in HFIP at 60 °C. Tetramethyloglycoluril is well known as a crosslinking agent in polymer industries [23]; however, its use as a single carbon unit has not been explored in synthetic organic chemistry. This work enables the formation of both C-C and C-S bonds simultaneously, with recycling of HFIP highlighting the cost effectiveness of this method.

Chapter -2 RESULTS AND DISCUSSION

To initiate our investigation, 2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**1a**), tetramethylolglycoluril (**2**) and *p*-toluenesulfonate salt (**3a**) were selected as model substrates for the reaction optimisation.

2.1 Optimization of reaction conditions

Table 1. Optimization table^a

Sr. No.	Solvent	Temperature	Yield (%) ^b
1.	MeOH	60 °C	n.r.
2.	TFE	60 °C	20
3	Water	60 °C	17
4.	HFIP	60 °C	85
5. ^c	HFIP	60 °C	86
6. ^d	HFIP	60 °C	88
7. ^e	HFIP	60 °C	60
8.	HFIP	40 °C	54
9.	HFIP	RT	15
10. ^f	HFIP	60 °C	51
11. ^g	HFIP	60 °C	38

^aReaction condition: **1a** (0.2 mmol), **2** (0.12 mmol), **3a** (0.4 mmol), solvent (2.0 mL), 60 °C, 18 h; ^bIsolated yield; ^c0.7 equiv. of **2** was used, ^d 1.0 equiv. of **2** was used, ^e0.5 equiv. of **2** was used, ^f1.5 equiv. of **3** was used, ^g0.6 equiv. of paraformaldehyde was used, (TFE = 2,2,2-Trifluoroethanol), (HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol).

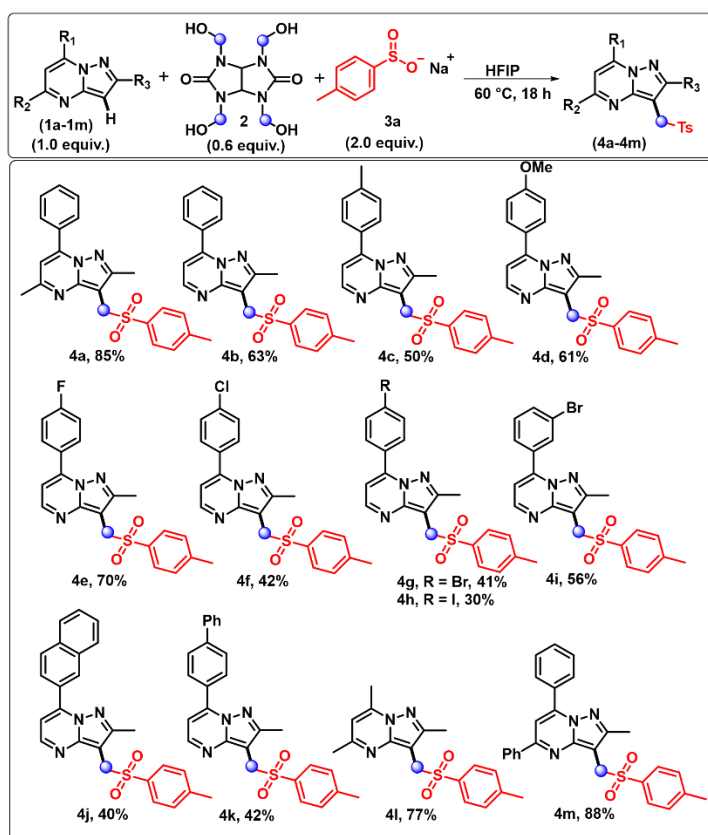
At first, a mixture of 2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**1a**), tetramethyloglycoluril (**2**) and Sodium *p*-toluenesulfinate (**3a**) were subjected to various protic solvents including methanol, TFE (2,2,2-Trifluoroethanol), water and HFIP. The reaction mixture was stirred at 60 °C for 18 h. No product formation was observed in methanol, whereas the desired product **4a** was obtained in 20% and 17% yields when TFE and water were employed as solvents (**Table 1, entries 1-3**). Interestingly, when the reaction was carried out in HFIP, the desired product **4a** was obtained with a yield of 85% and was confirmed with the help of ¹H, ¹³C NMR spectroscopy, high resolution mass spectrometry (HRMS) and single crystal X-ray diffraction analysis. From these results, HFIP was identified as the optimal solvent and subsequent optimization studies were carried out.

Changing the stoichiometry of substrate **2** from 0.6 to 0.7 and 1.0 equivalents resulted in marginally increase in the yields (86% and 88% respectively), while reducing its loading to 0.5 equivalent results in a gradual decrease in yield to 60% (**Table 1, entries 5-7**). The influence of temperature on the reaction condition was examined. Decreasing the temperature of the reaction to 40 °C and room temperature resulted in lower yields of the desired product (54% and 15%, respectively; **Table 1, entries 8 and 9**). After that, when the loading of **3a** was changed from 2.0 equivalent to 1.5 equivalent, the yield of the desired product drastically reduced to 51% (**Table 1, entry 10**). Finally, replacing the substrate **2** with paraformaldehyde (0.6 equivalent) resulted in a lower yield of 38% (**Table 1, entry 11**).

Based on these observations, the optimal reaction condition was determined to be 1.0 equivalent of **1a**, 0.6 equivalent of tetramethyloglycoluril **2**, and 2.0 equivalents of sodium *p*-toluenesulfinate **3a** in HFIP at 60 °C for 18 h, under which the desired product **4a** was obtained in 85% yield.

2.2. Substrate Scope

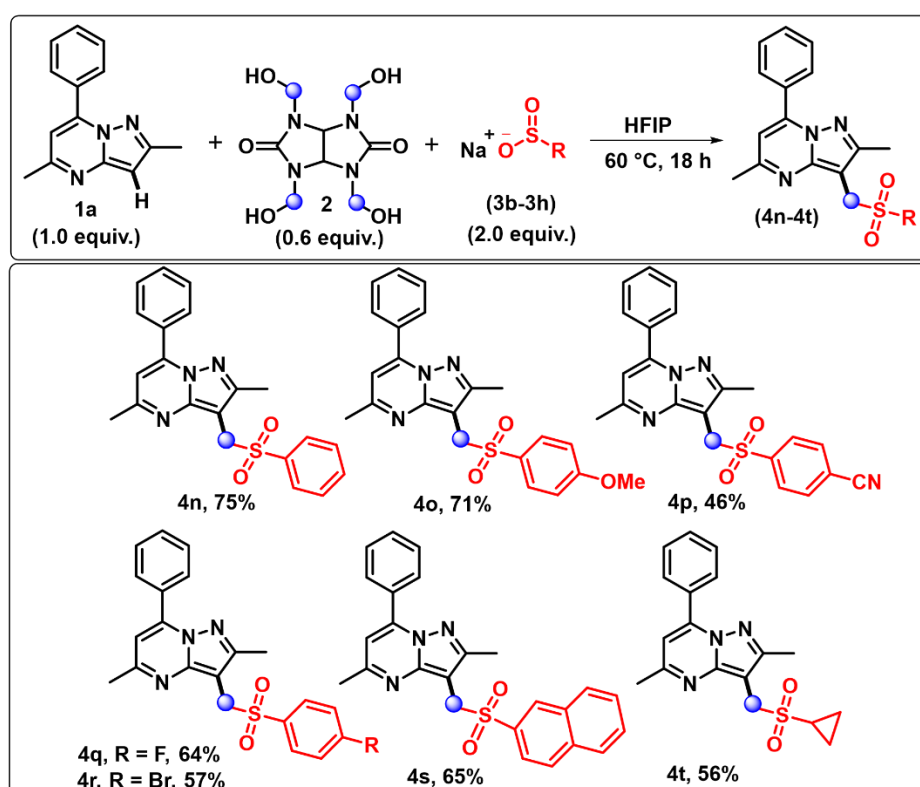
With the optimized conditions, we proceed to examine the substrate scope for the sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines (Scheme 6). The three-component sulfonylmethylation of 2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine afforded product **4b** in 63% yield. A variety of phenyl-substituted pyrazolo[1,5-*a*]pyrimidines bearing electron-donating groups (*p*-Me, *p*-OMe) and halogen substituents (*p*-F, *p*-Cl, *p*-I, *p*-Br, *m*-Br) on the phenyl ring underwent a smooth transformation and resulted in the formation of the corresponding C3 sulfonylmethylated products (**4c-4i**) in moderate to good yields. Moreover, 2-Methyl-7-(naphthalen-2-yl)pyrazolo[1,5-*a*]pyrimidine, 7-([1,1'-Biphenyl]-4-yl) 2-methylpyrazolo[1,5-*a*]pyrimidine reacted well under these optimized conditions to form the products (**4j** and **4k**) in 40% and 42% yields. Furthermore, trisubstituted pyrazolo[1,5-*a*]pyrimidines furnished the corresponding sulfonylmethylated products (**4l** and **4m**) with 77% and 88% yields (Scheme 6).



Scheme 6. Substrate scope for sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines.

Reaction condition: **1a** (0.2 mmol), **2** (0.12 mmol), **3a** (0.4 mmol), HFIP (2.0 mL), 60 °C, 18 h. Isolated yield.

The developed reaction conditions were extended to various substituted sulfonate salts having electron donating, electron withdrawing and halogen substituted groups, which react well under these conditions to form the corresponding products (**4m-4s**) with yields ranging from 46% to 75% (**Scheme 7**).

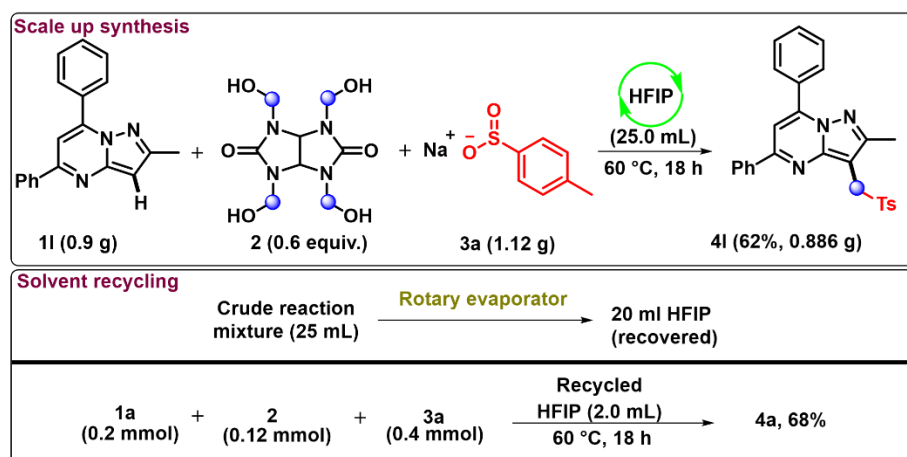


Scheme 7. Substrate scope for sulfonylmethylation with various sodium sulfinate salts.

Reaction condition: **1a** (0.2 mmol), **2** (0.12 mmol), **3a** (0.4 mmol), HFIP (2.0 mL), 60 °C, 18 h. Isolated yield.

2.3. Scale up synthesis and solvent recycling

The scale up reaction was performed using 2-methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**1l**, 3.15 mmol), tetramethylolglycoluril (**2**, 0.6 equiv.) and 2.0 equivalents of **3a** (Scheme 8). The reaction was carried out in 25 ml of HFIP at 60 °C for 18 hours, and results in the formation of the desired product **4l** in 62% yield. After completion of the reaction, the solvent was removed under reduced pressure by using rotary evaporator, and 20 mL of HFIP was recovered (Scheme 8). The recycled HFIP was subsequently used to carry out the tosylmethylation of **1a** (0.2 mmol) under the optimized conditions to afford the desired product **4a** in 68% yield. This solvent recycling and reuse study further demonstrates the practicality and cost effectiveness of the developed protocol.

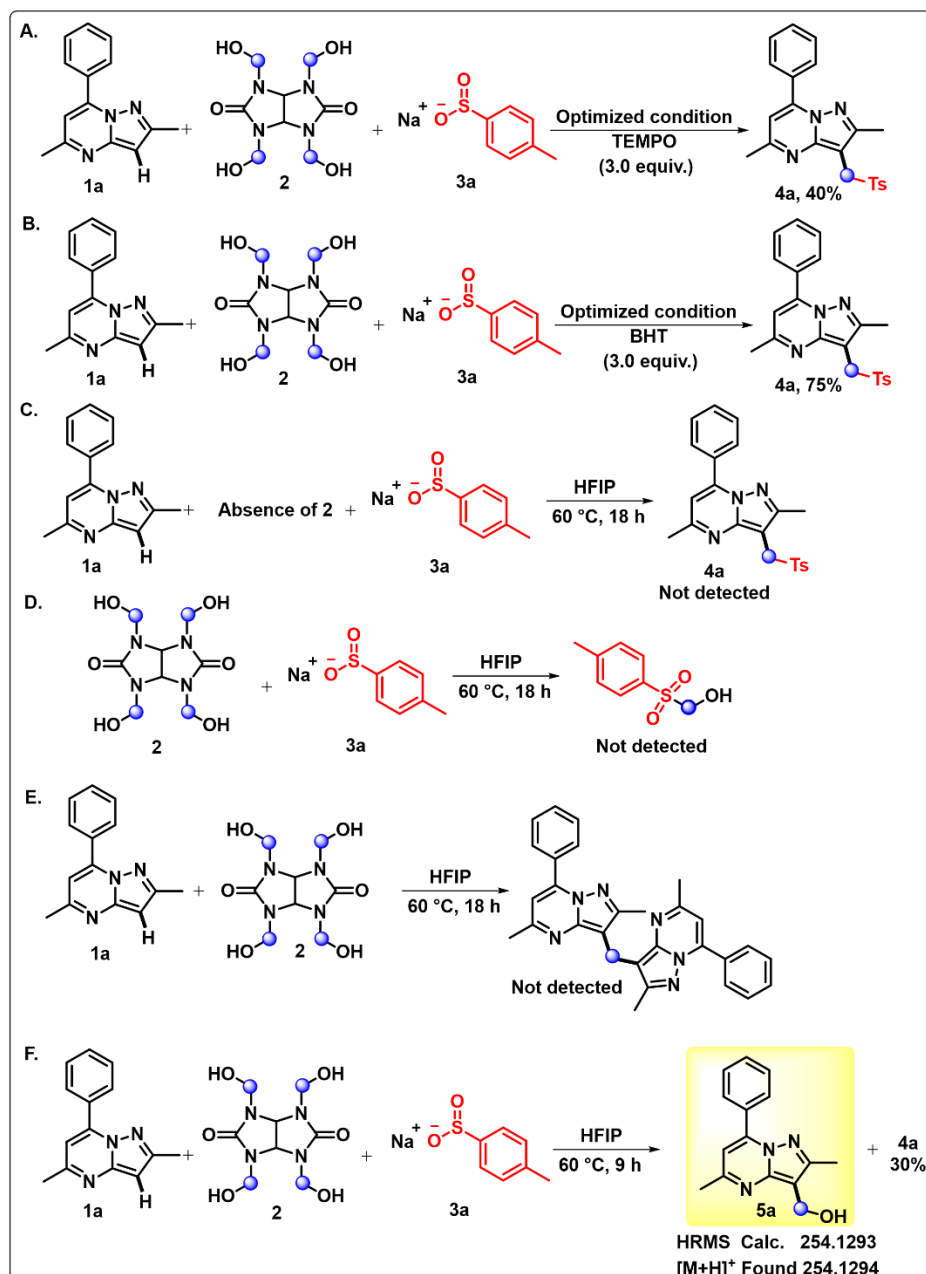


Scheme 8. Scale up synthesis and solvent recycling.

2.4. Control Experiments

For the mechanistic study, few control experiments were carried out (Scheme 9). Initially, the reaction of **1a**, **2** and **3a** was carried out in the presence of 3.0 equivalents of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and BHT (Butylated hydroxytoluene). The desired product **4a** was obtained in yields of 40% and 75% respectively, indicating the involvement of the ionic pathway. When the reaction was conducted involving **1a** and **3a**, in the absence of **2**, the product **4a** was not observed. Subsequently, when the reaction was carried out between **2** and **3a**, tosylmethanol was not observed. In order to detect the

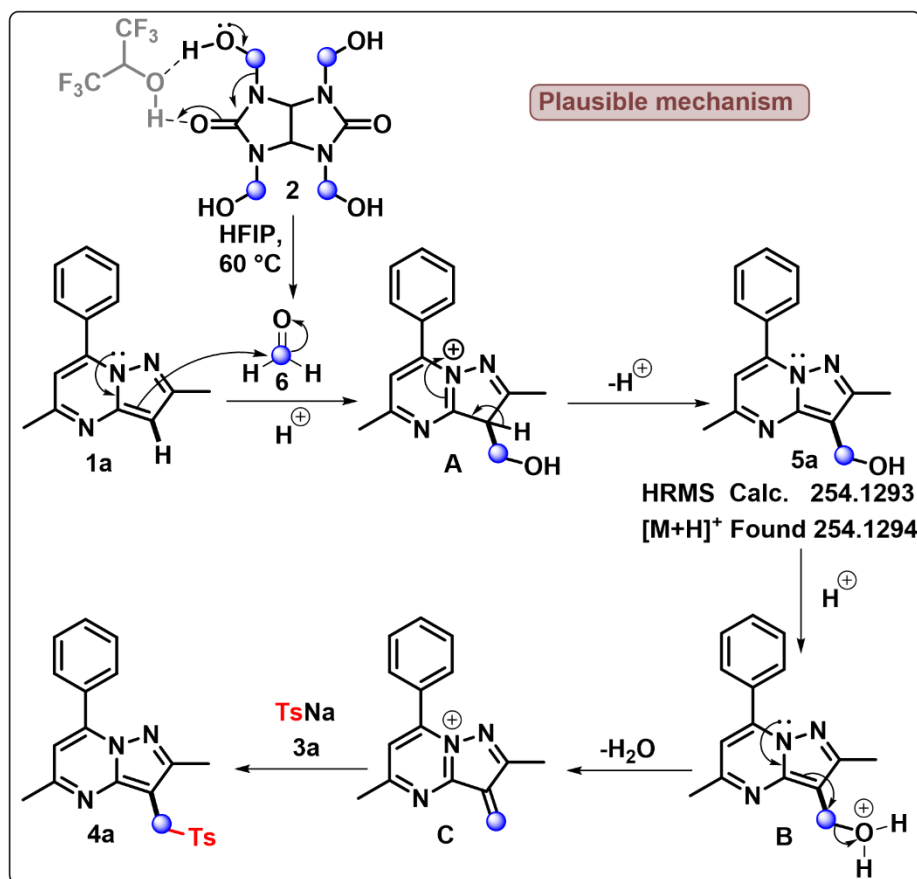
intermediate involved, the reaction was quenched after 9 h, and compound **5a** was successfully trapped, as confirmed by HRMS (High Resolution Mass Spectrometry) analysis of the crude reaction mixture, along with the desired product **4a** in 30% yield, as determined by ^1H NMR analysis of the crude reaction mixture.



Scheme 9. Control experiments for elucidation of reaction mechanism.

2.5. Proposed Mechanism

On the basis of these control experiments and the previous literature reports [19-25], a plausible mechanism for the formation of **4a** is proposed (**Scheme 10**). Here, tetramethylolglycoluril (**2**) acts as a masked source of formaldehyde and releasing it in the presence of HFIP. The liberated formaldehyde (**6**) reacts with substrate **1a** to form the intermediate **A**, which on deprotonation gives intermediate **5a**. The presence of intermediate **5a** was confirmed by HRMS analysis of the crude reaction mixture. Followed by protonation of the hydroxyl group in intermediate **5a**, promoting elimination of a water molecule and formation of intermediate **C**. Finally, the nucleophilic attack of **3a** on the intermediate **C** furnishes the desired product **4a**.



Scheme 10. Plausible reaction pathway.

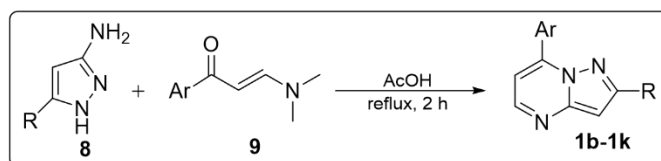
Chapter -3 EXPERIMENTAL WORK

3.1. Material and instrumentation

All chemicals and reagents were purchased from commercial suppliers (TCI, Spectrochem, BLD Pharm and ARL) and were used without further purification. Reactions were carried out in an oven dried borosilicate screw cap test tube. Reaction progress was monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60F₂₅₄ plates (Merck) and visualised under UV light (254 nm). Organic solutions were concentrated under reduced pressure using Heidolph rotary evaporator. Purification of the products was performed through column chromatography on silica gel with a mesh size of 100-200 using hexane /ethyl acetate as eluent. Nuclear magnetic resonance spectra of proton nuclei (¹H NMR, 500 MHz), carbon nuclei (¹³C NMR, 126 MHz), and fluorine nuclei (¹⁹F NMR, 471 MHz) were recorded on a Bruker Avance spectrometer. CDCl₃ was used as the deuterated solvent, and chemical shifts are reported in δ (ppm) relative to tetramethylsilane. High-resolution mass spectrometric analyses (HRMS) were performed using an electrospray ionization time-of-flight mass spectrometer (ESI-TOF-MS), comprising of Xevo G3 QTOF mass spectrometer coupled with the Acquity H-class plus UPLC with mass range 20 to 1500 daltons in ESI+ Ionisation mode. The melting points were determined using electrothermal melting point apparatus and are uncorrected. All the starting materials and substrates were synthesized according to literature reports.

3.2. Preparation of starting materials

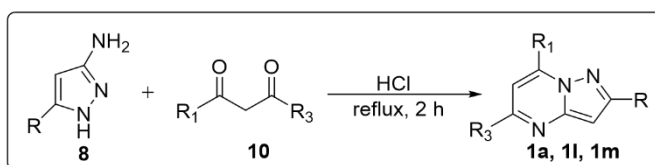
3.2.1. General procedure for the synthesis of substituted pyrazolo[1,5-*a*]pyrimidines [26]:



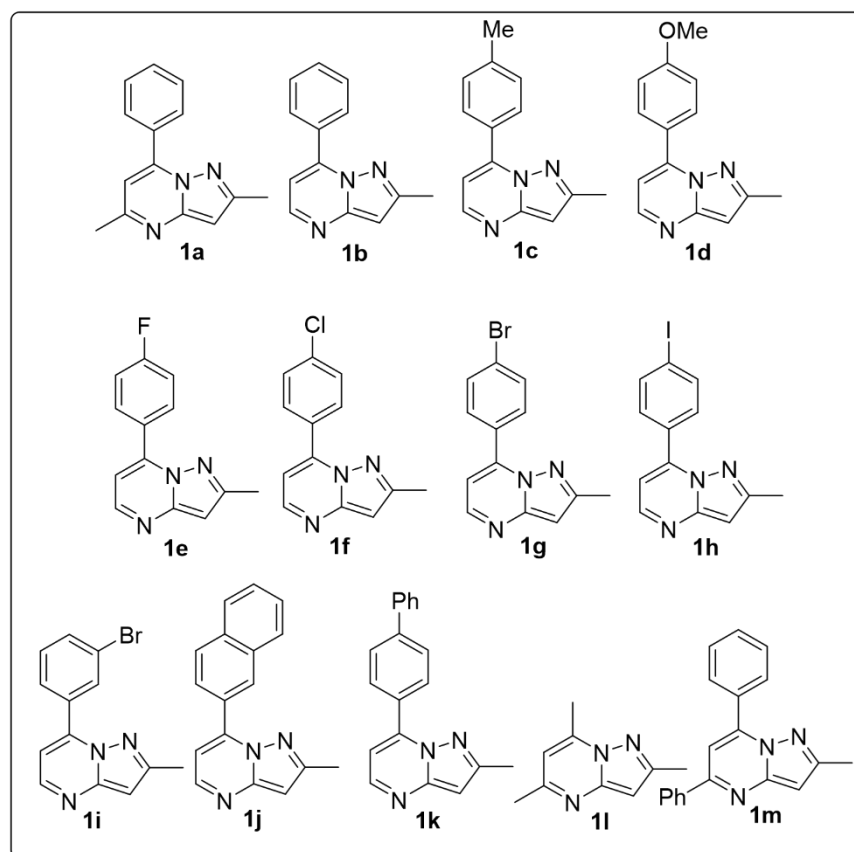
Scheme 11. Synthesis of substituted pyrazolo[1,5-*a*]pyrimidines.

A mixture of substituted amino pyrazoles (**8**) (1.0 equiv., 1.0 mmol) and enones (**9**) (1.0 equiv., 1.0 mmol) in acetic acid (AcOH) (1.0 mL) was refluxed in an oven dried round bottom flask using an oil bath and vigorous stirring. Progress of the reaction was monitored via TLC. Following completion, the mixture was extracted with DCM and water. The organic layer was concentrated to yield crude pyrazolo[1,5-*a*]pyrimidine derivatives. Purification was achieved by column chromatography using 100-200 mesh silica gel and a gradient elution of ethyl acetate-hexane (1:9 to 1:4). The product was confirmed by ^1H and ^{13}C NMR spectroscopy.

3.2.2. General procedure for the synthesis of trisubstituted pyrazolo[1,5-*a*]pyrimidines [27]:

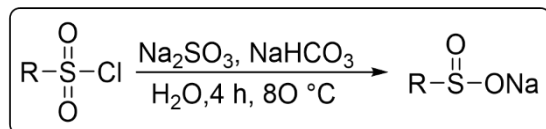


Scheme 12. Synthesis of trisubstituted pyrazolo[1,5-*a*]pyrimidines. Substituted amino pyrazoles (**8**) (1.0 equiv., 1.0 mmol) and diketones (**10**) (1.0 equiv., 1.0 mmol) were taken in an oven dried round bottom flask (RB), 1.0 mL HCl was added to the RB and the reaction mixture was refluxed with vigorous stirring in an oil bath. The reaction progress was checked by TLC analysis. After completion of the reaction, the mixture was extracted with DCM and water. The organic layer was evaporated to get the crude pyrazolo[1,5-*a*]pyrimidine derivatives. The product was confirmed by ^1H and ^{13}C NMR spectroscopy.



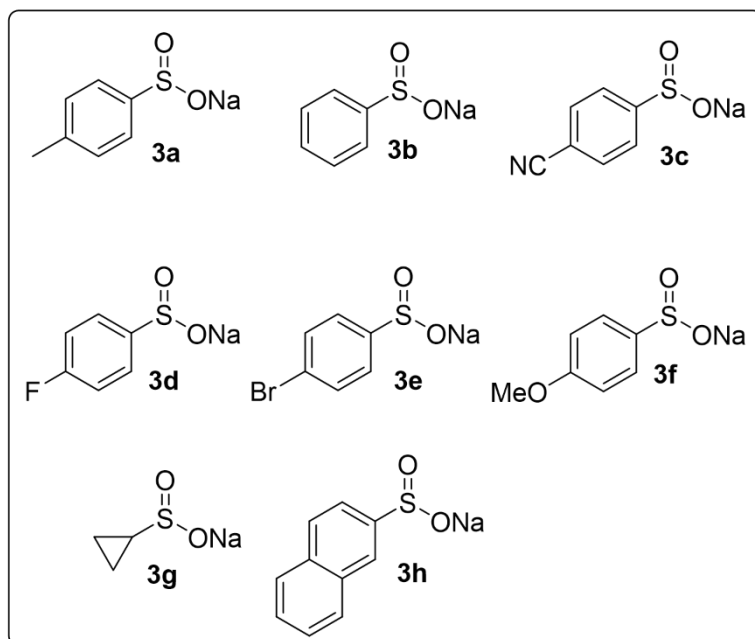
3.2.3. General Procedure for Synthesis of Sodium Sulfinates

[28]:

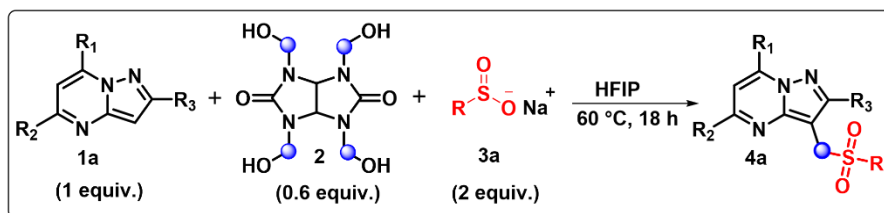


Scheme 13. Synthesis of sodium sulfinates.

To an oven dried 25 mL round bottom flask equipped with a magnetic stir bar was charged with substituted sulfonyl chloride (1.0 mmol, 1.0 equiv.), sodium sulfite (2.0 mmol, 2.0 equiv.) and the corresponding sodium bicarbonate (2.0 mmol, 2.0 equiv.) in distilled water (2 mL). The reaction mixture was stirred for 4 h at 80 °C. After cooling down to room temperature, water was removed in vacuo. The white residue formed was then treated with ethanol (2.5 mL) and the resulting heterogeneous solution was filtered. The filtrate was concentrated under reduced pressure and the desired sodium sulfinates were obtained as white crystalline powders in good yields.



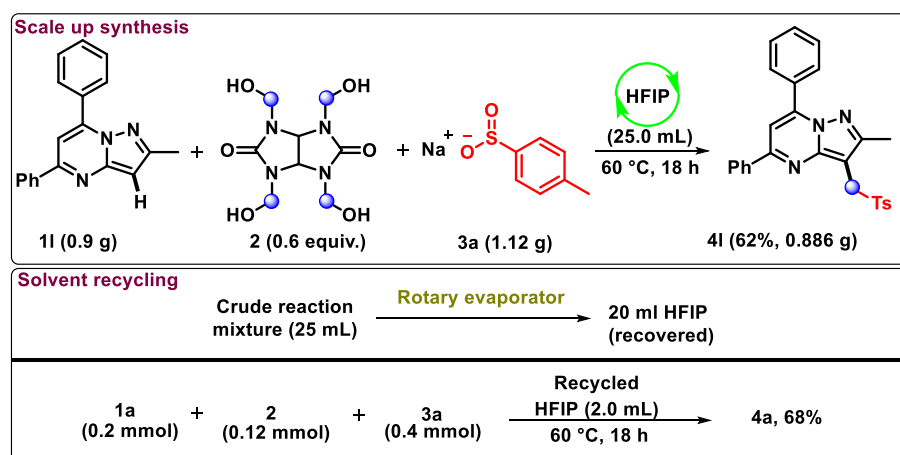
3.2.4. General Procedure for Synthesis of the sulfonylmethylated pyrazolo[1,5-*a*]pyrimidines:



Scheme 14. Sulfonylmethylation of substituted pyrazolo[1,5-*a*]pyrimidine.

Substituted pyrazolo[1,5-*a*]pyrimidine **1a** (0.2 mmol, 1.0 equiv.), tetramethylolglycoluril **2** (0.12 mmol, 0.6 equiv.), and sodium sulfinate salt **3a** (0.4 mmol, 2.0 equiv.) were added to an oven-dried test tube equipped with a magnetic stir bar. After that, hexafluoroisopropanol (HFIP, 2.0 mL) was added, and the resulting reaction mixture was heated at 60 °C in a preheated oil bath for 18 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion of the reaction, HFIP was removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel (100-200 mesh) using a mixture of hexane and ethyl acetate as the eluent.

3.2.5. Experimental procedure for the scale-up synthesis of **4l** and solvent recycling:



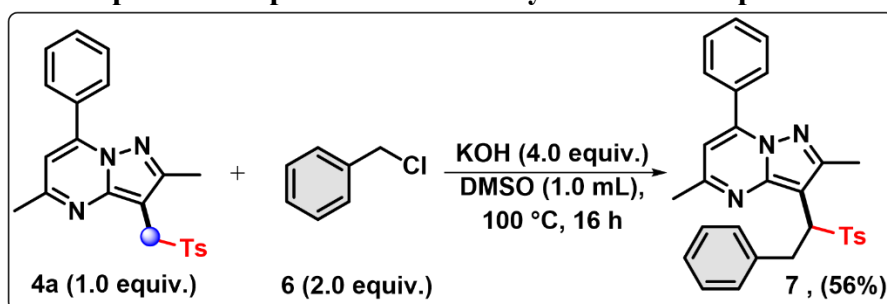
Scheme 15. Scale up synthesis of **4l** and solvent recycling.

2-methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine **1l** (0.9 g, 3.15 mmol), **2** (0.6 equiv.), **3a** (2.0 equiv.) were taken in an oven-dried 50 mL round bottom flask equipped with a magnetic stir bar. Hexafluoroisopropanol (HFIP, 25.0 mL) was added, and the resulting reaction mixture was

heated at 60 °C in a preheated oil bath for 18 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion of the reaction, HFIP from the crude reaction mixture was recovered using rotary evaporator. The crude residue was purified by column chromatography on silica gel (100-200 mesh) using a mixture of hexane and ethyl acetate as the eluent giving the product **4l** in 62% yield.

The recovered HFIP was used for carrying out tosylmethylation of **1a** (0.2 mmol) under the optimized condition where corresponding product **4a** was isolated in 68% yield.

3.2.6. Experimental procedure for the synthesis of compound 7:



Scheme 16. Synthetic application of **4a**.

2,5-Dimethyl-7-phenyl-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine **4a** (1.0 equiv., 0.2 mmol) and benzyl chloride (2.0 equiv., 0.4 mmol) was added to an oven dried test tube along with 1.0 mL of DMSO, 4.0 equivalents of KOH was added to this reaction mixture and the reaction was heated in the 100 °C in the preheated oil bath, with vigorous stirring for 16 hours. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction was quenched with brine solution and extracted using ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate as the eluent (7:3). Product **7** was isolated in 56% yield.

3.2.7. Experimental procedure for control Experiments:

Scheme 17. Radical quenching and intermediate detection.

To an oven-dried test tube equipped with a magnetic stir bar, **1a** (1.0 equiv., 0.2 mmol), tetramethylolglycoluril **2** (0.6 equiv., 0.12 mmol.), and sodium sulfinate salt **3a** (2.0 equiv., 0.4 mmol) were added, followed by hexafluoroisopropanol (HFIP, 2.0 mL) and 3.0 equiv. of radical quenchers (TEMPO/ BHT). The resulting reaction mixture was heated at 60 °C in a preheated oil bath for 18 h. The progress of the reaction was monitored by thin layer chromatography (TLC). Upon completion, HFIP was removed under reduced pressure, and the crude residue was

purified by column chromatography on silica gel (100–200 mesh) using a mixture of hexane and ethyl acetate as the eluent.

Furthermore, control experiments were carried out in the absence of substrate **2** under the optimised conditions, no formation of desired product **4a** was observed. Subsequently, when the reaction was performed with substrate **2** and **3a** under optimised conditions, the corresponding tosylmethanol was not detected. Finally, when the substrate **1a** and **2** were reacted in the absence of substrate **3a** under the developed conditions, the formation of bis(2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methane was not observed.

3.2.9. Experimental procedure for intermediate detection:

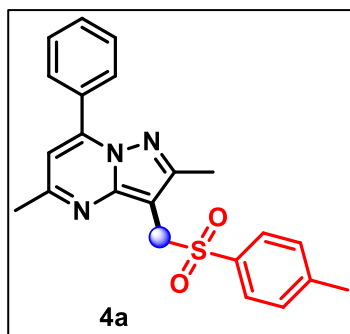
2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine **1a** (0.2 mmol), tetramethylglycoluril **2** (0.6 equiv.), and sodium sulfinic acid salt **3a** (2.0 equiv.) were placed in an oven-dried test tube equipped with a magnetic stir bar. Hexafluoroisopropanol (HFIP, 2.0 mL) was then added, and the resulting reaction mixture was heated at 60 °C in a preheated oil bath for 9 h. After 9 hours an aliquot from the reaction mixture was taken and analysed through HRMS to detect the formation of intermediate **5a**, along with the product **4a** was obtained with 30% yield (¹H NMR analysis of crude reaction mixture).

3.2.10. Conclusion:

In summary, we have developed a sulfonylmethylation of pyrazolo[1,5-*a*]pyrimidines using tetramethylglycoluril as a one carbon synthon. This reaction utilizes HFIP as a recyclable and reusable solvent. The developed protocol shows a broad substrate scope with moderate to good yields. Mechanistic studies revealed that the reaction proceeds through an ionic pathway.

CHAPTER- 4 SUPPORTING INFORMATION

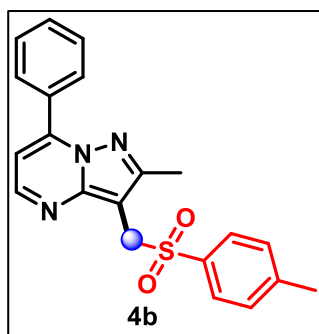
4.1. Characterization data of compounds (4a-4t)



2,5-Dimethyl-7-phenyl-3-(tosylmethyl)pyrazolo[1,5-

a]pyrimidine(4a): Yellow solid; 85% (66.0 mg); m.p. 122-124 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.00 (dd, *J* = 6.9, 2.8 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.18 (d, *J* = 8.2 Hz,

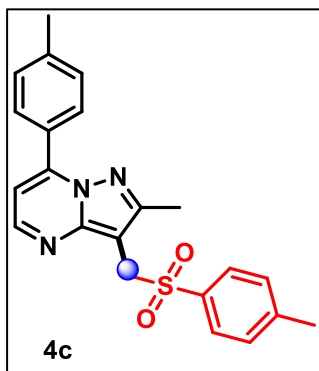
2H), 6.63 (s, 1H), 4.59 (s, 2H), 2.44 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H); ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 158.8, 155.2, 148.5, 145.8, 144.2, 135.6, 131.2, 130.7, 129.3, 129.2, 128.9, 128.7, 108.1, 94.8, 51.8, 24.2, 21.6, 13.0; HRMS (ESI, *m/z*): Calculated for C₂₂H₂₂N₃O₂S [M+H]⁺: 392.1433, found 392.1445.



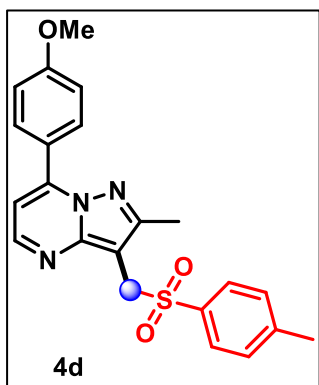
2-Methyl-7-phenyl-3-(tosylmethyl)pyrazolo[1,5-

a]pyrimidine(4b): Off white solid; 63% (47.8 mg); m.p. 130-132 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.36 (d, *J* = 4.4 Hz, 1H), 8.07 – 7.99 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.57 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.23 (d, *J* = 8.1 Hz,

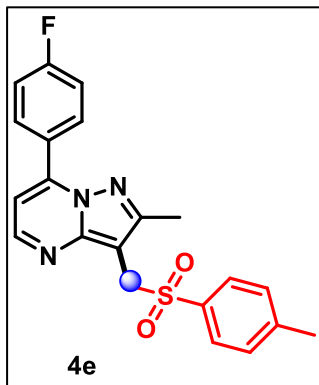
2H), 6.82 (d, *J* = 4.4 Hz, 1H), 4.61 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H); ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 155.5, 149.1 (2C), 146.7, 144.6, 135.8, 131.5, 130.8, 129.7, 129.5, 128.9, 128.8, 107.4, 95.9, 52.0, 21.7, 13.1; HRMS (ESI, *m/z*): Calculated for C₂₁H₂₀N₃O₂S [M+H]⁺: 378.1276, found 378.1282.



2-Methyl-7-(*p*-tolyl)-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4c): Yellow solid; 50% (39.0 mg); m.p. 180-182 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.32 (d, $J = 4.4$ Hz, 1H), 7.94 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.2$ Hz, 2H), 6.79 (s, 1H), 4.58 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 155.3, 149.3, 149.2, 146.6, 144.6, 141.9, 135.8, 129.7, 129.6, 129.4, 128.8, 127.9, 107.1, 95.7, 52.0, 21.7 (2C), 13.1; HRMS (ESI, m/z): Calculated for $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 392.1433, found 392.1434.

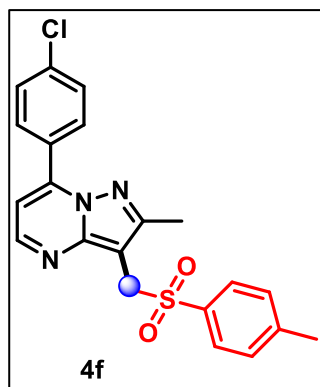


7-(4-Methoxyphenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4d): Off white solid; 61% (50.0 mg); m.p. 182-184 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.31 (d, $J = 4.4$ Hz, 1H), 8.12 – 8.05 (m, 2H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.10 – 7.05 (m, 2H), 6.79 (d, $J = 4.4$ Hz, 1H), 4.60 (s, 2H), 3.90 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 162.2, 155.4, 149.2, 149.0, 146.5, 144.6, 135.8, 131.3, 129.7, 128.8, 122.8, 114.3, 106.5, 95.6, 55.7, 52.0, 21.7, 13.1; HRMS (ESI, m/z): Calculated for $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 408.1382, found 408.1389.

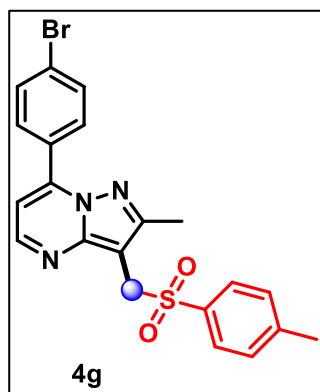


7-(4-Fluorophenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4e): Off white solid; 70% (55.4 mg); m.p. 142-144 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.35 (d, $J = 4.4$ Hz, 1H), 8.13 – 8.03 (m, 2H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.24 (dd, $J = 8.4, 4.0$ Hz, 4H), 6.79 (d, $J = 4.4$ Hz, 1H), 4.59 (s, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C { ^1H } NMR (126 MHz,

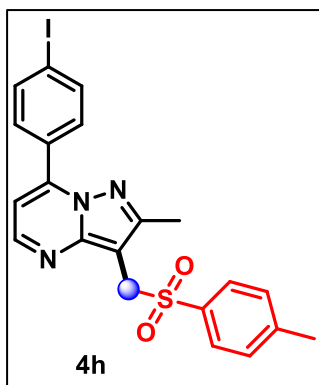
CDCl₃) δ 165.5, 163.5, 155.5, 149.3, 149.2, 145.5, 144.7, 135.8, 131.8, 131.7, 129.7, 128.8, 126.8, 126.7, 116.2, 116.0, 107.2, 96.0, 51.9, 21.7, 13.1; **¹⁹F NMR** (471 MHz, CDCl₃) δ -107.68; **HRMS** (ESI, *m/z*): Calculated for C₂₁H₁₉FN₃O₂S [M+H]⁺: 396.1182, found 396.1190.



7-(4-Chlorophenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-a]pyrimidine(4f): Off white solid; 42% (34.6 mg); m.p. 200-202 °C; **¹H NMR** (500 MHz, CDCl₃) δ 8.36 (d, *J* = 4.4 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 6.80 (d, *J* = 4.4 Hz, 1H), 4.59 (s, 2H), 2.40 (s, 3H), 2.36 (s, 3H); **¹³C {¹H} NMR** (126 MHz, CDCl₃) δ 155.6, 149.3, 149.2, 145.3, 144.7, 137.6, 135.8, 130.8, 129.7, 129.2, 129.1, 128.8, 107.2, 96.1, 51.9, 21.7, 13.1; **HRMS** (ESI, *m/z*): Calculated for C₂₁H₁₉ClN₃O₂S [M+H]⁺: 412.0887, found 412.0893.



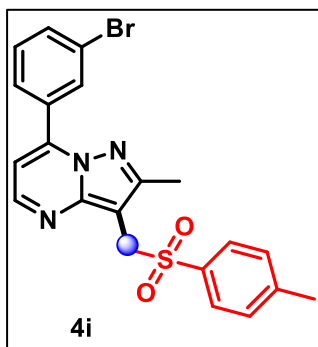
7-(4-Bromophenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-a]pyrimidine(4g): White solid; 41% (37.2 mg); m.p. 236-238 °C; **¹H NMR** (500 MHz, CDCl₃) δ 8.36 (d, *J* = 4.4 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.72 – 7.68 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 4.4 Hz, 1H), 4.59 (s, 2H), 2.40 (s, 3H), 2.36 (s, 3H); **¹³C {¹H} NMR** (126 MHz, CDCl₃) δ 155.6, 149.2, 149.1, 145.4, 144.7, 135.8, 132.2, 131.0, 129.8, 129.6, 128.8, 126.1, 107.2, 96.1, 51.9, 21.7, 13.1; **HRMS** (ESI, *m/z*): Calculated for C₂₁H₁₉BrN₃O₂S [M+H]⁺: 456.0381, found 456.0386.



7-(4-iodophenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4h):

White solid; 30% (26.0 mg); m.p. 240-242 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.35, 8.35, 7.92, 7.90, 7.79, 7.78, 7.66, 7.64, 7.24, 7.23, 6.80, 6.79, 4.58, 2.40, 2.36. ¹³C NMR (126 MHz, CDCl₃) δ 155.51,

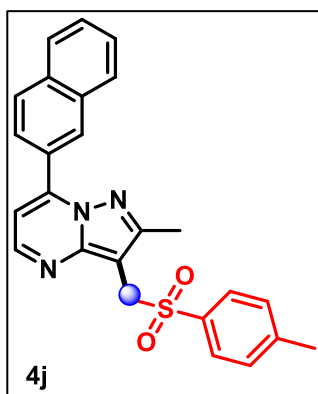
149.37, 149.25, 145.44, 144.67, 138.14, 135.83, 130.90, 130.21, 129.74, 128.78, 107.17, 98.19, 96.12, 51.92, 21.75, 13.06; HRMS (ESI, *m/z*): Calculated for C₂₁H₁₉IN₃O₂S [M+H]⁺: 504.0243, found 504.0254.



7-(3-Bromophenyl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4i):

White solid; 56% (50.0 mg); m.p. 230-232 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, *J* = 4.3 Hz, 1H), 8.16 (t, *J* = 1.9 Hz, 1H), 7.98 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H), 7.64 (d,

J = 8.2 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.79 (s, 1H), 4.58 (s, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 155.6, 149.3, 149.2, 144.7, 144.6, 135.8, 134.3, 132.7, 132.2, 130.4, 129.7, 128.8, 128.0, 122.9, 107.5, 96.2, 51.9, 21.7, 13.1; HRMS (ESI, *m/z*): Calculated for C₂₁H₁₉BrN₃O₂S [M+H]⁺: 456.0381, found 456.0384.

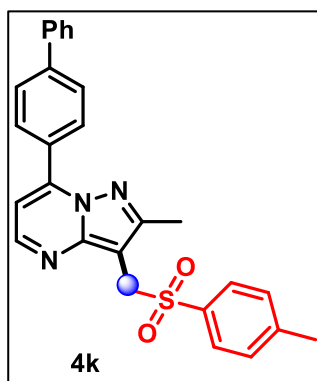


2-Methyl-7-(naphthalen-2-yl)-3-(tosylmethyl)pyrazolo[1,5-*a*]pyrimidine(4j):

Off white solid; 40% (34.0 mg); m.p. 162-164 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.60 (s, 1H), 8.38 (d, *J* = 4.3 Hz, 1H), 8.06 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.63 – 7.56 (m, 2H), 7.24 (d, *J* =

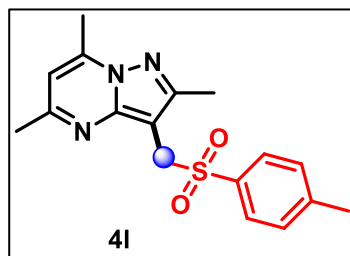
7.9 Hz, 2H), 6.93 (d, *J* = 4.3 Hz, 1H), 4.62 (s, 2H), 2.40 (s, 3H), 2.39 (s,

3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.5, 149.4, 149.3, 146.5, 144.6, 135.8, 134.6, 133.0, 130.1, 129.7, 129.1, 128.8, 128.5, 128.2, 128.1, 127.9, 127.0, 125.6, 107.7, 95.9, 52.0, 21.7, 13.1; **HRMS** (ESI, m/z): Calculated for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 428.1433, found 428.1442.



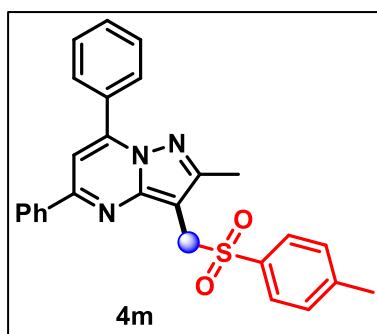
7-([1,1'-Biphenyl]-4-yl)-2-methyl-3-(tosylmethyl)pyrazolo[1,5-a]pyrimidine(4k): Off white solid; 42% (37.7 mg); m.p. 218-220 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.36 (d, J = 4.4 Hz, 1H), 8.15 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.65 (dd, J = 8.2, 2.6 Hz, 4H), 7.49 (t, J = 7.6

Hz, 2H), 7.44 – 7.39 (m, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 4.3 Hz, 1H), 4.61 (s, 2H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.4, 149.4, 149.3, 146.1, 144.6, 144.3, 140.2, 135.8, 129.9, 129.7, 129.5, 129.1, 128.8, 128.2, 127.5, 127.3, 107.2, 95.9, 52.0, 21.7, 13.1; **HRMS** (ESI, m/z): Calculated for $\text{C}_{27}\text{H}_{24}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 454.1589, found 454.1591.



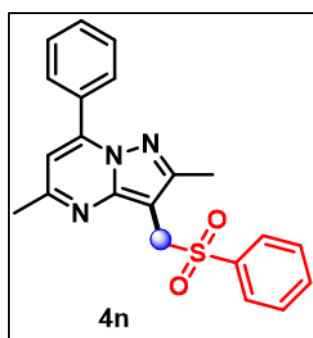
2,5,7-Trimethyl-3-(tosylmethyl)pyrazolo[1,5-a]pyrimidine(4l): Brown solid; 77% (50.4 mg); m.p. 150-152 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, J = 8.4 Hz,

2H), 7.15 (d, J = 8.1 Hz, 2H), 6.40 (s, 1H), 4.52 (s, 2H), 2.66 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 158.6, 154.9, 147.8, 144.9, 144.3, 135.6, 129.4, 129.0, 108.3, 94.9, 51.9, 24.2, 21.6, 17.0, 13.0; **HRMS** (ESI, m/z): Calculated for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 330.1276, found 330.1286.



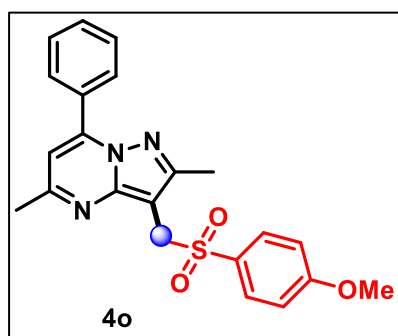
2-Methyl-5,7-diphenyl-3-(tosylmethyl)pyrazolo[1,5-a]pyrimidine(4m): Yellow solid; 88% (80.1 mg); m.p. 224-226 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.11 – 8.04 (m, 2H), 7.93 – 7.86 (m, 2H), 7.62 – 7.53 (m, 5H), 7.48 (dd, J = 5.1, 2.1 Hz, 3H), 7.21

(s, 1H), 7.05 (d, J = 7.9 Hz, 2H), 4.65 (s, 2H), 2.51 (s, 3H), 2.08 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.9, 155.6, 148.9, 146.3, 144.6, 136.8, 135.5, 131.3, 131.2, 130.5, 129.4, 129.3, 128.9, 128.8, 128.7, 127.3, 104.5, 96.4, 52.2, 21.4, 13.3; HRMS (ESI, m/z): Calculated for $\text{C}_{27}\text{H}_{24}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 454.1589, found 454.1601.



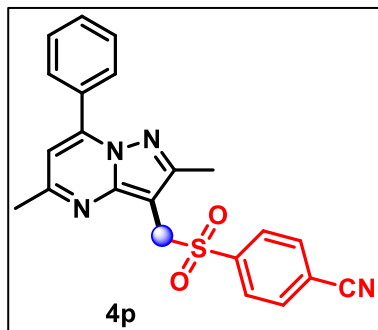
2,5-Dimethyl-7-phenyl-3-((phenylsulfonyl)methyl)pyrazolo[1,5-a]pyrimidine(4n): Off white solid; 75% (56.2 mg); m.p. 160-162 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.02 – 7.96 (m, 2H), 7.73 – 7.67 (m, 2H), 7.56 – 7.49 (m, 4H), 7.37 (t, J = 7.9 Hz, 2H), 6.60 (s, 1H), 4.60 (s, 2H), 2.40

(s, 3H), 2.39 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.0, 155.1, 148.9, 145.6, 138.7, 133.4, 131.2, 130.9, 129.4, 129.0, 128.8, 128.7, 108.3, 94.7, 51.9, 24.6, 13.1; HRMS (ESI, m/z): Calculated for $\text{C}_{21}\text{H}_{20}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 378.1276, found 378.1290.



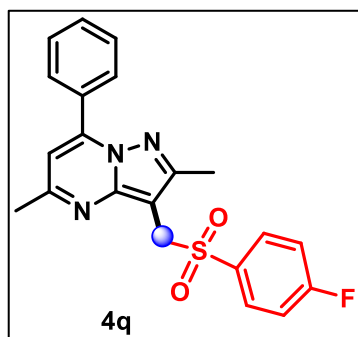
3-(((4-Methoxyphenyl)sulfonyl)methyl)-2,5-dimethyl-7-phenylpyrazolo[1,5-a]pyrimidine(4o): Off white solid; 71% (58.0 mg); m.p. 178-180 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.02 – 7.97 (m, 2H), 7.62 – 7.57 (m, 2H), 7.56 – 7.52 (m, 3H), 6.85 – 6.79 (m, 2H), 6.61 (s, 1H), 4.55 (s, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ

163.7, 158.9, 155.1, 148.9, 145.6, 131.2, 130.9, 130.1, 129.4, 128.8, 113.9, 108.2, 95.2, 55.7, 52.1, 24.5, 13.1; **HRMS** (ESI, m/z): Calculated for $C_{22}H_{22}N_3O_3S$ $[M+H]^+$: 408.1382, found 408.1382.



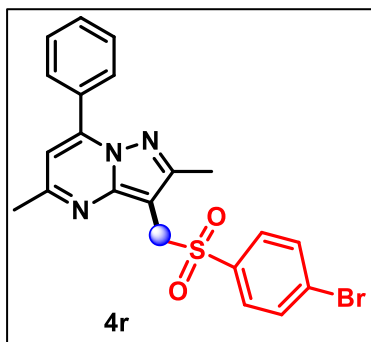
4-(((2,5-Dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)sulfonyl)benzonitrile(4p):

Yellow solid; 46% (37.1 mg); m.p. 196-198 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.55 (dd, J = 5.2, 2.0 Hz, 3H), 6.62 (s, 1H), 4.62 (s, 2H), 2.52 (s, 3H), 2.35 (s, 3H); ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.2, 155.3, 148.6, 145.9, 142.7, 132.2, 131.4, 130.6, 130.0, 129.4, 128.9, 117.4, 117.0, 108.2, 94.0, 51.9, 24.5, 13.3; **HRMS** (ESI, m/z): Calculated for $C_{22}H_{19}N_4O_2S$ $[M+H]^+$: 403.1229, found 403.1234.



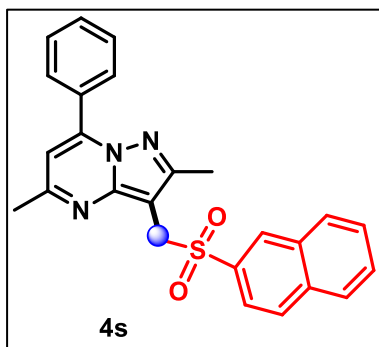
3-(((4-Fluorophenyl)sulfonyl)methyl)-2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine(4q):

Off white solid; 64% (50.0 mg); m.p. 170-172 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.75 – 7.62 (m, 2H), 7.55 (s, 3H), 7.03 (t, J = 7.9 Hz, 2H), 6.62 (s, 1H), 4.58 (s, 2H), 2.47 (s, 3H), 2.39 (s, 3H); ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.0, 164.9, 159.1, 155.2, 148.8, 145.7, 134.4, 132.0, 131.9, 131.3, 130.8, 129.4, 128.8, 116.0, 115.8, 108.2, 94.7, 52.1, 24.4, 13.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -104.68; **HRMS** (ESI, m/z): Calculated for $C_{21}H_{19}FN_3O_2S$ $[M+H]^+$: 396.1182, found 396.1190.



3-(((4-Bromophenyl)sulfonyl)methyl)-2,5-dimethyl-7-phenylpyrazolo[1,5-a]pyrimidine(4r): Off white solid; 57% (52.6 mg); m.p. 190-192 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.05 – 7.94 (m, 2H), 7.59 – 7.42 (m, 7H), 6.62 (s, 1H), 4.57 (s, 2H), 2.48 (s, 3H), 2.39 (s, 3H);

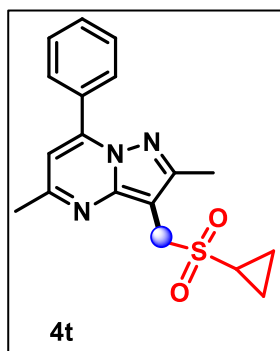
^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.2, 155.2, 148.7, 145.8, 137.2, 131.9, 131.3, 130.7 (2C), 129.4, 128.8, 128.7, 108.2, 94.6, 52.0, 24.4, 13.2; **HRMS** (ESI, m/z): Calculated for $\text{C}_{21}\text{H}_{19}\text{BrN}_3\text{O}_2\text{S}[\text{M}+\text{H}]^+$: 456.0381, found 456.0385.



2,5-Dimethyl-3-((naphthalen-2-ylsulfonyl)methyl)-7-phenylpyrazolo[1,5-a]pyrimidine(4s):

Off white solid; 65% (55.6 mg), m.p. 216-218 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.22 (s, 1H), 7.96 – 7.91 (m, 2H), 7.83 (t, J = 8.9 Hz, 2H), 7.75 (d, J

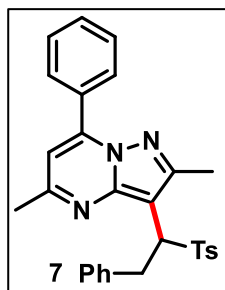
= 8.7 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.53 (dd, J = 5.0, 1.8 Hz, 4H), 6.38 (s, 1H), 4.64 (s, 2H), 2.49 (s, 3H), 1.91 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 158.8, 155.2, 148.8, 145.5, 135.4, 135.3, 132.2, 131.2, 131.0, 130.9, 129.4, 129.3, 129.1, 128.8, 128.5, 127.8, 127.3, 123.9, 107.9, 94.9, 52.1, 23.9, 13.3; **HRMS** (ESI, m/z): Calculated for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_2\text{S} [\text{M}+\text{H}]^+$: 428.1433, found 428.1431.



3-((Cyclopropylsulfonyl)methyl)-2,5-dimethyl-7-phenylpyrazolo[1,5-a]pyrimidine(4t): White solid; 56% (38.1 mg); m.p. 250-252 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.05 – 7.98 (m, 2H), 7.58 – 7.50 (m, 3H), 6.74 (s, 1H), 4.53 (s, 2H), 2.61 (s, 3H), 2.57 (s, 3H), 2.35 (tt, J = 7.9, 4.9 Hz, 1H), 1.22

– 1.15 (m, 2H), 0.94 – 0.86 (m, 2H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

δ 159.3, 155.3, 149.0, 145.9, 131.2, 130.9, 129.4, 128.8, 108.4, 95.0, 49.3, 28.8, 24.9, 13.4, 5.1; **HRMS** (ESI, m/z): Calculated for $C_{18}H_{20}N_3O_2S$ $[M+H]^+$: 342.1276, found 342.128.



2,5-Dimethyl-7-phenyl-3-(2-phenyl-1-tosylethyl)pyrazolo[1,5-a]pyrimidine(8): Yellow solid, 53.8 mg (56%); **^1H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, $J = 9.9$ Hz, 2H), 7.52 (d, $J = 8.1$ Hz, 3H), 7.48 (dd, $J = 5.3, 2.1$ Hz, 3H), 7.25 (s, 1H), 7.16 (d, $J = 7.8$ Hz, 5H), 6.56 (s, 1H), 5.01 (dd, $J = 10.5, 4.9$

Hz, 1H), 3.82 (dd, $J = 14.6, 4.9$ Hz, 1H), 3.56 (dd, $J = 14.6, 10.5$ Hz, 1H), 2.56 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H); **^{13}C { ^1H } NMR** (126 MHz, $CDCl_3$) δ 157.4, 153.4, 147.5, 145.3, 144.2, 135.3, 132.6, 131.2, 131.0, 130.4, 129.3, 129.3, 129.0, 128.7, 128.6, 128.2, 107.5, 101.6, 69.8, 24.7, 23.1, 21.7, 13.1; **HRMS** (ESI, m/z): Calculated for $C_{29}H_{28}N_3O_2S$ $[M+H]^+$: 482.1902, found 482.1914.

4.2. NMR spectra of compounds (4a-4t)

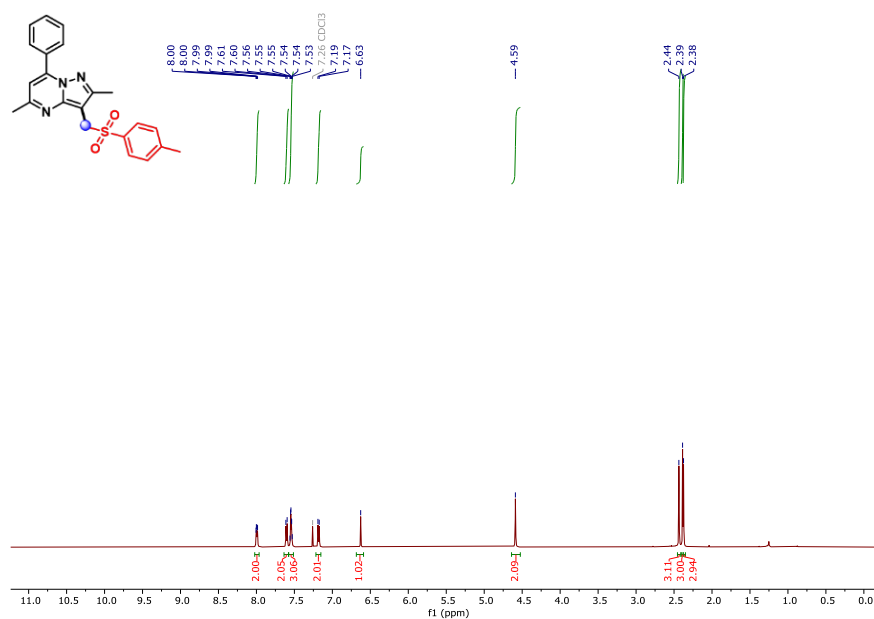


Figure 3: ¹H NMR (500MHz, CDCl₃) of 4a

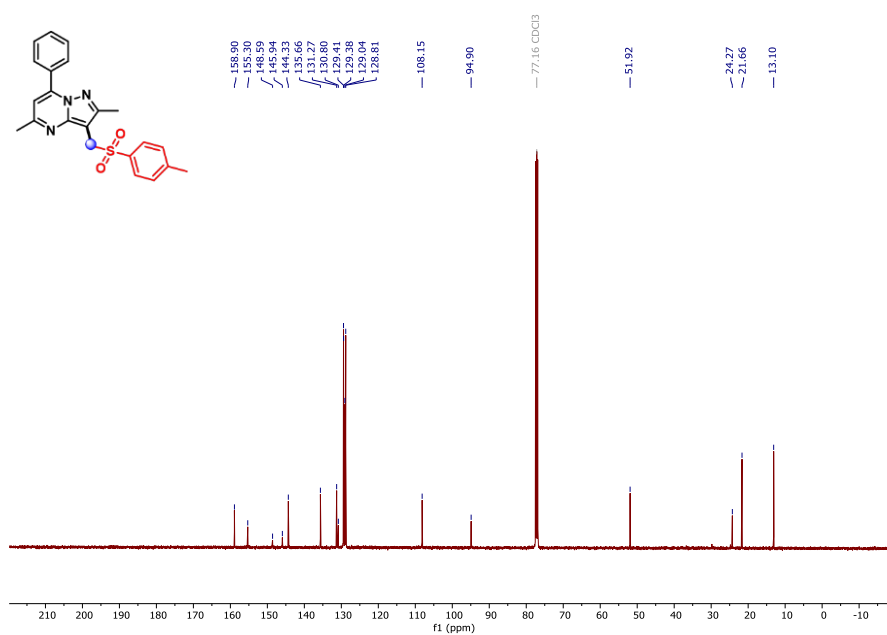


Figure 4: ¹³C NMR (126MHz, CDCl₃) of 4a

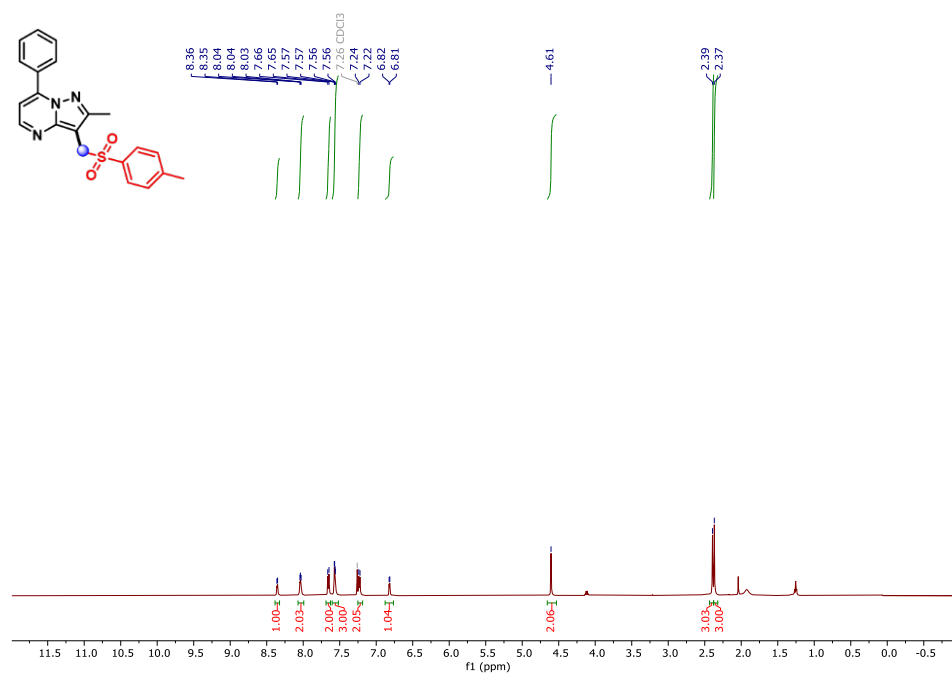


Figure 5: ¹H NMR (500MHz, CDCl₃) of 4b

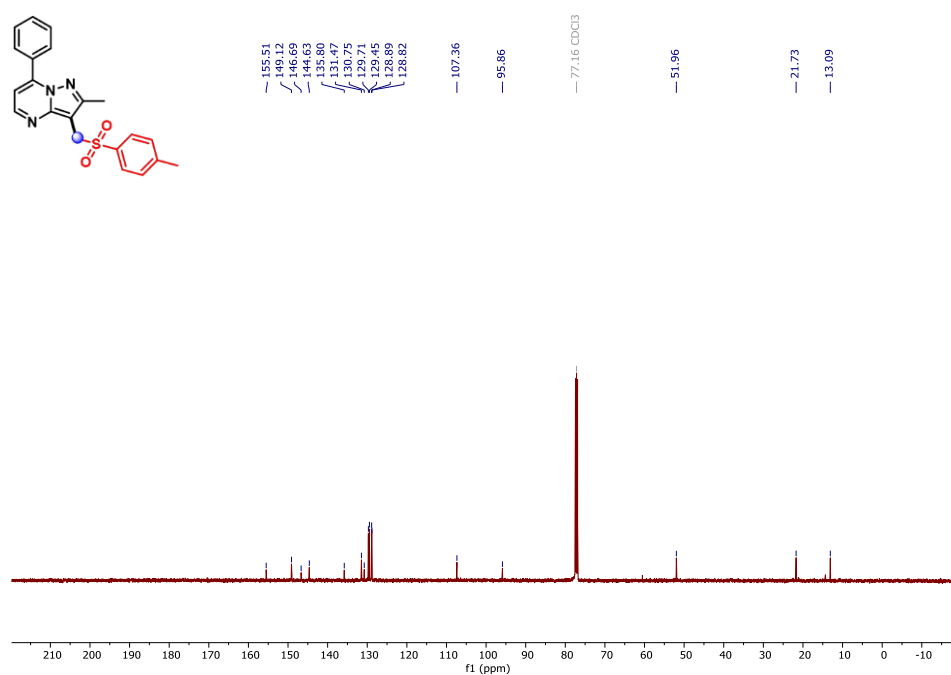


Figure 6: ¹³C NMR (126MHz, CDCl₃) of 4b

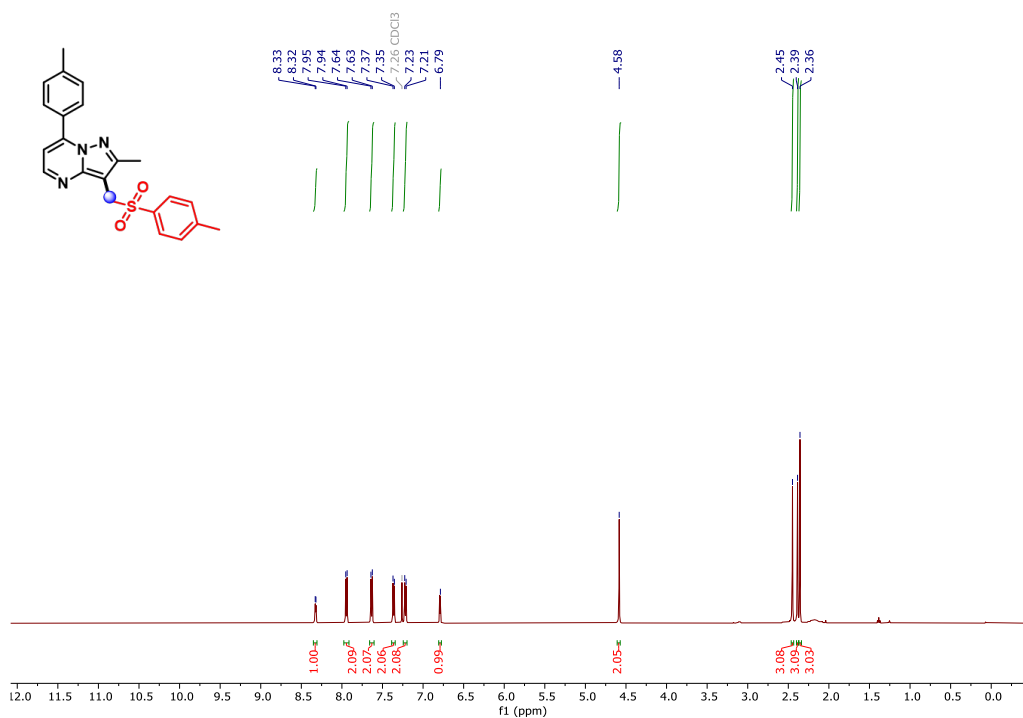


Figure 7: ¹H NMR (500MHz, CDCl₃) of 4c

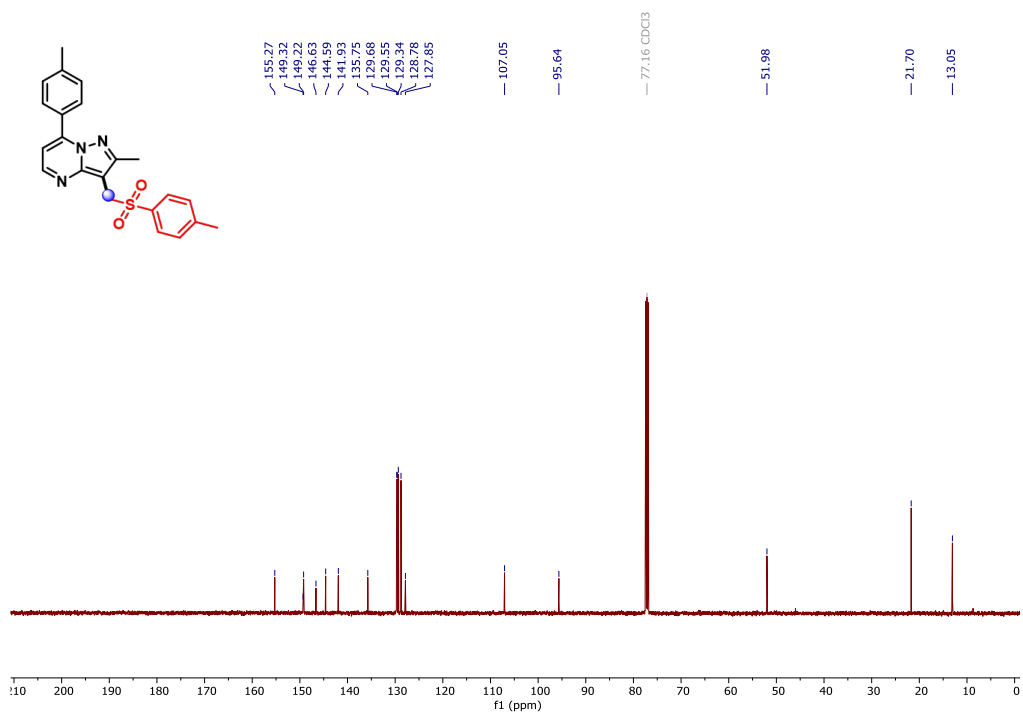


Figure 8: ¹³C NMR (126MHz, CDCl₃) of 4c

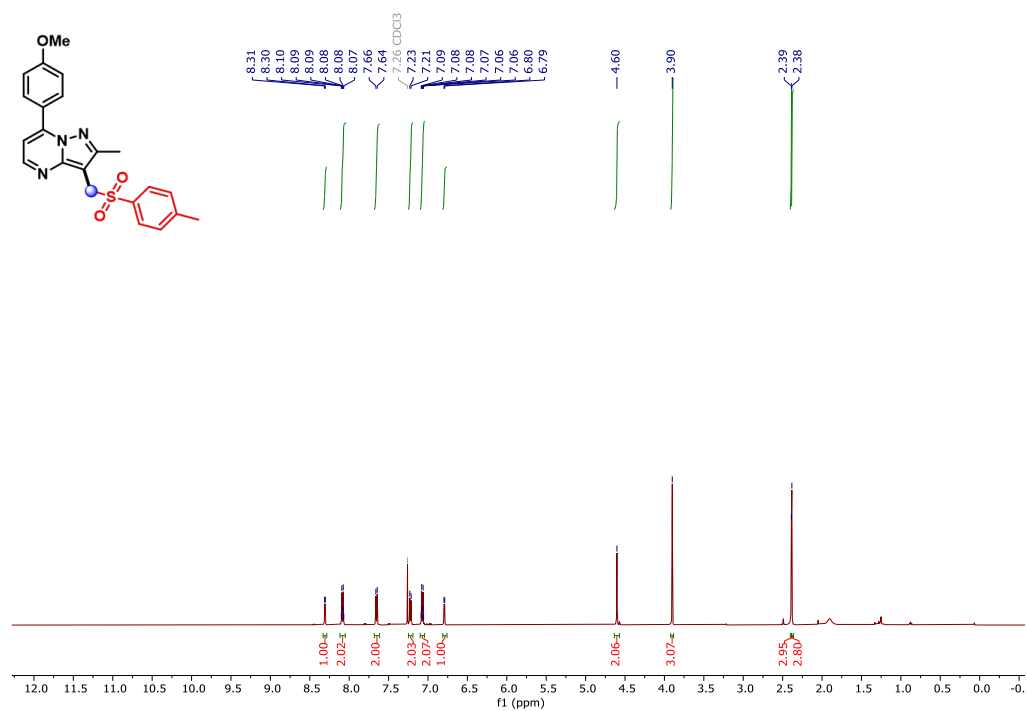


Figure 9: ¹H NMR (500MHz, CDCl₃) of 4d

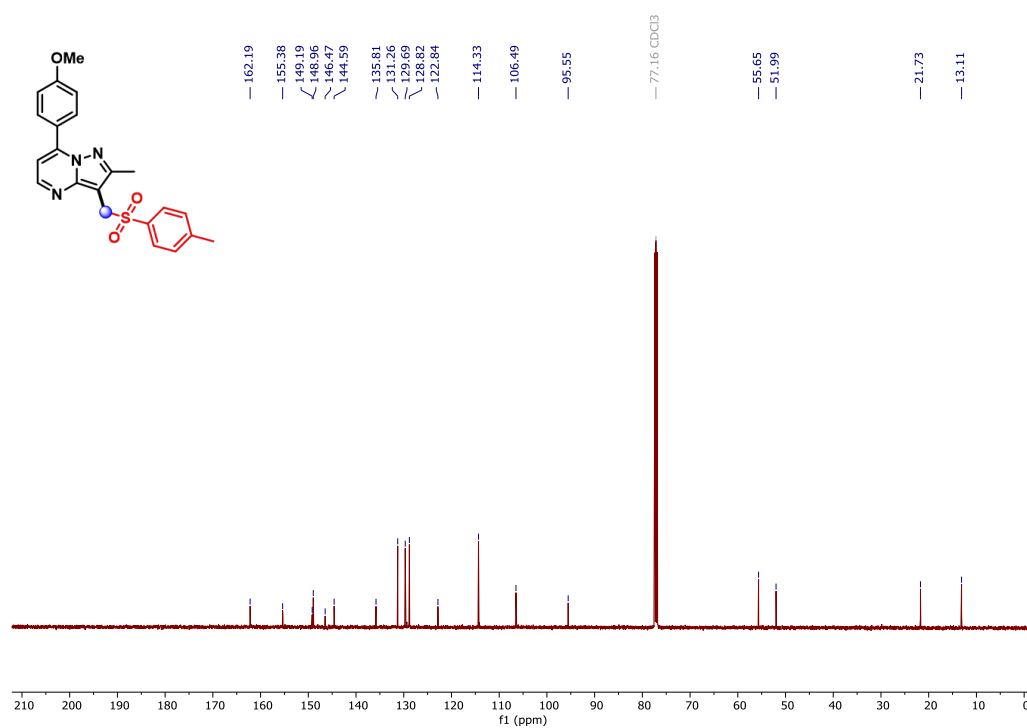


Figure 10: ¹³C NMR (126MHz, CDCl₃) of 4d

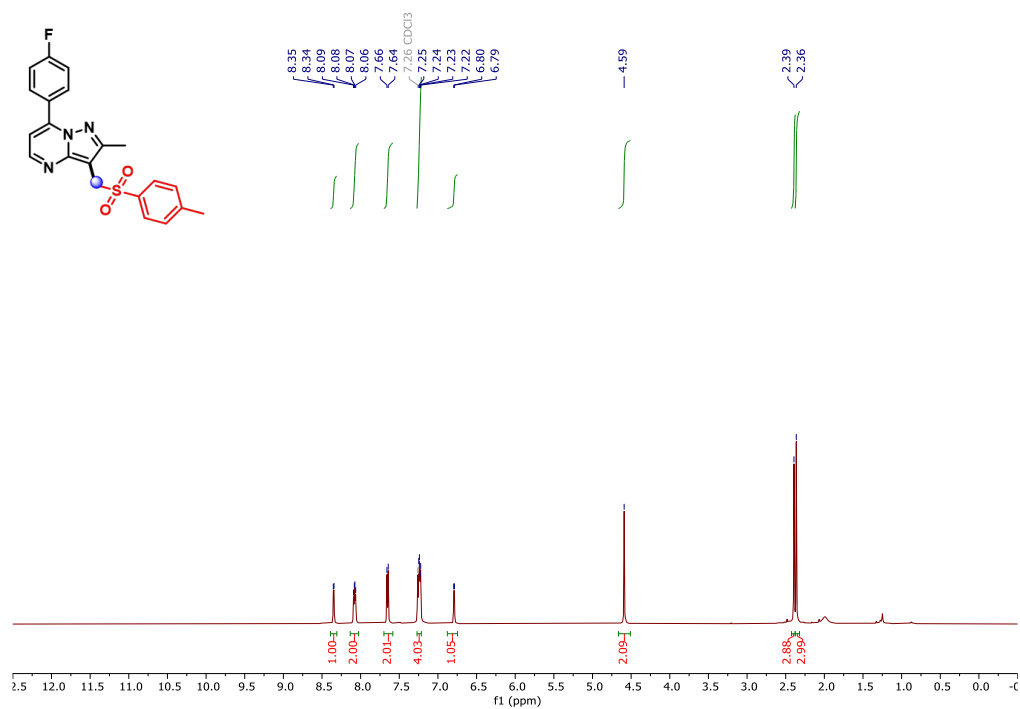


Figure 11: ¹H NMR (500MHz, CDCl₃) of 4e

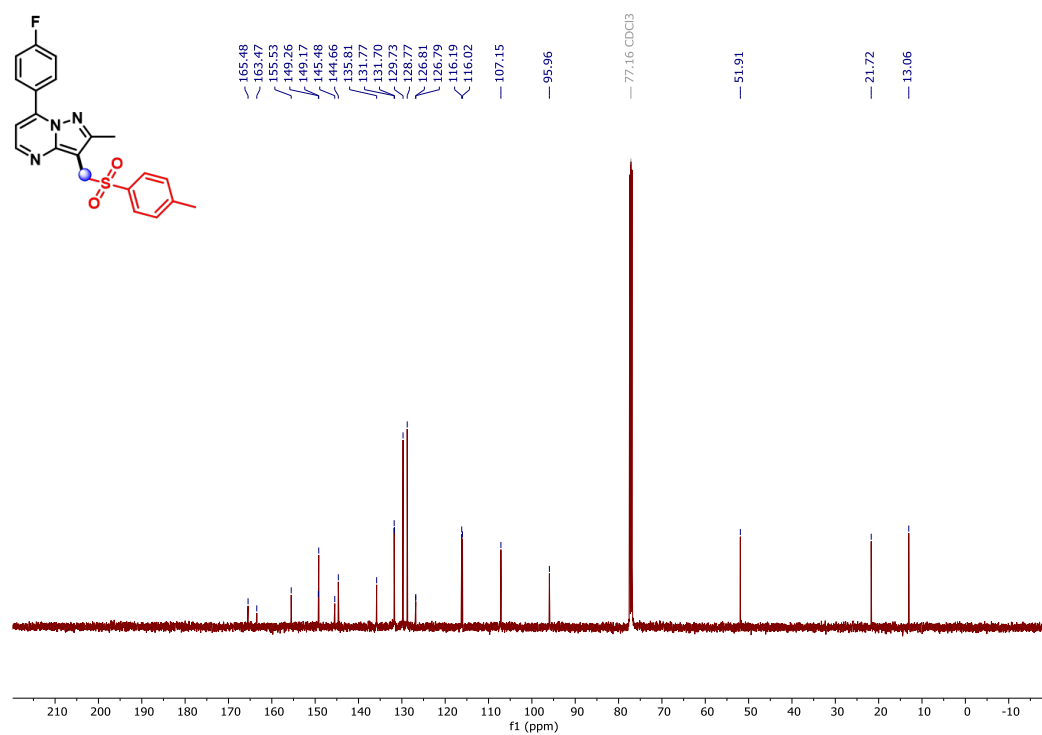


Figure 12: ¹³C NMR (126MHz, CDCl₃) of 4e

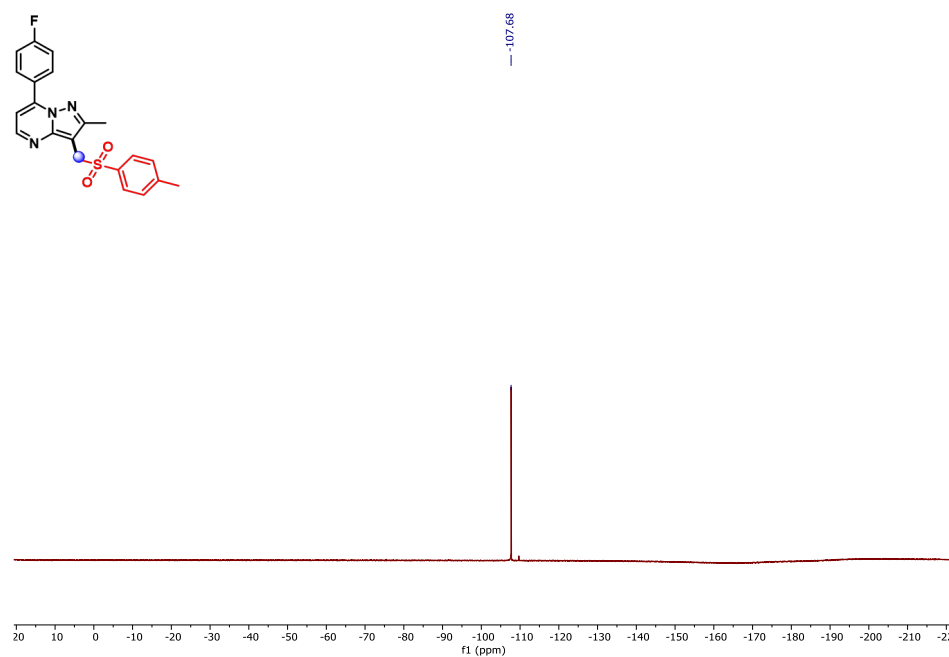


Figure 13: ^{19}F NMR (471MHz, CDCl_3) of 4e

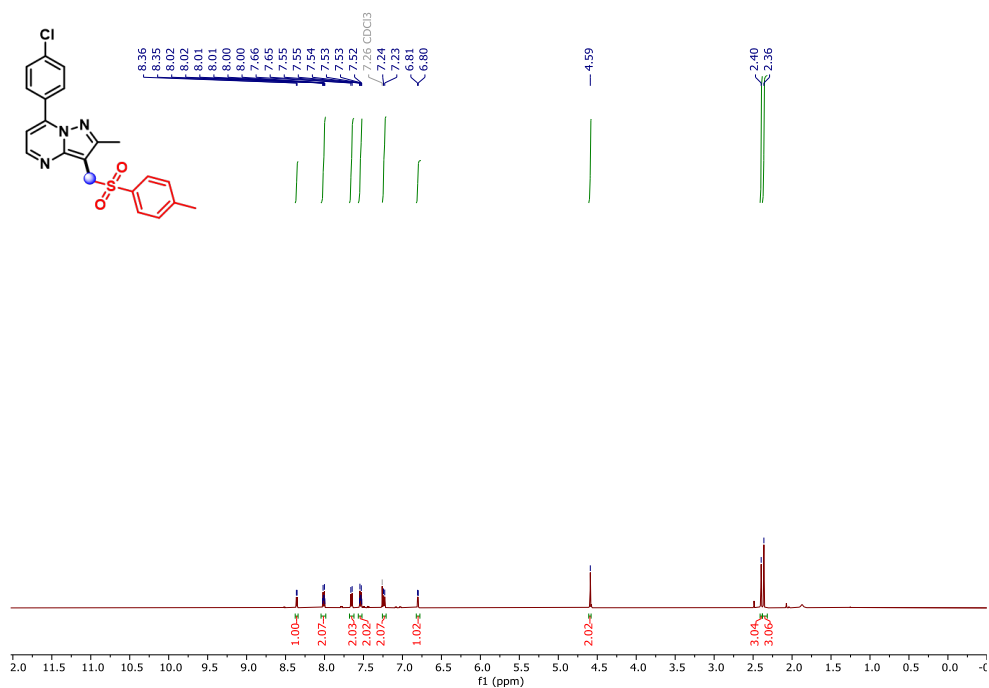


Figure 14: ¹H NMR (500MHz, CDCl₃) of 4f

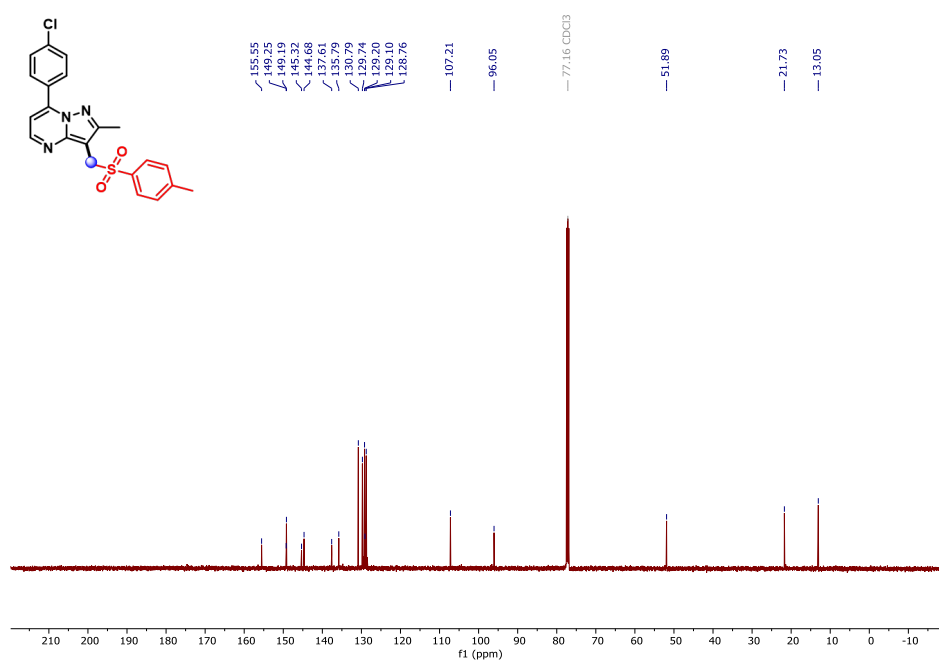


Figure 15: ¹³C NMR (126MHz, CDCl₃) of 4f

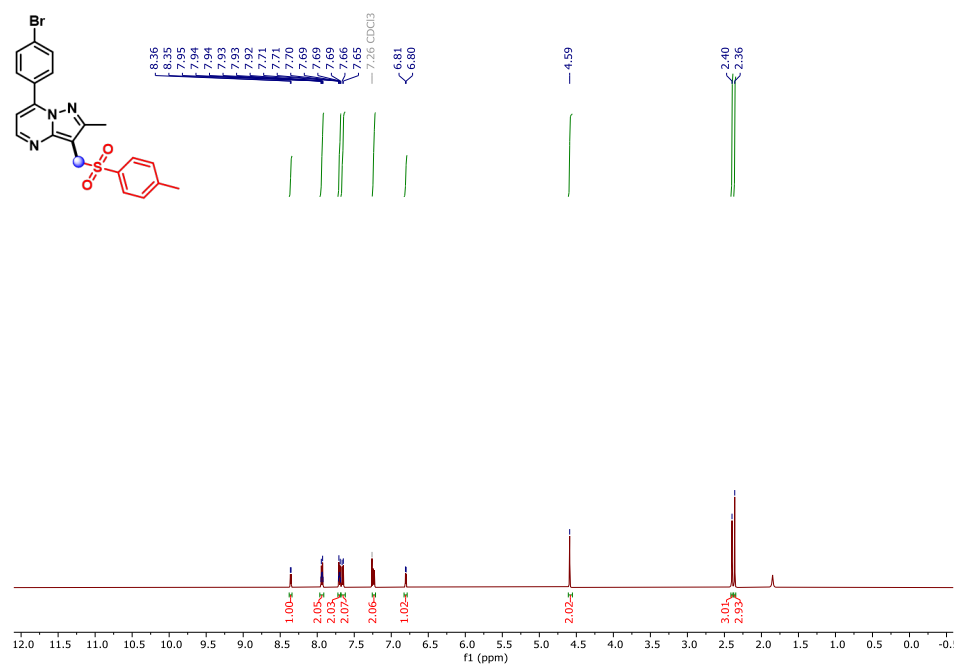


Figure 16: ¹H NMR (500MHz, CDCl₃) of 4g

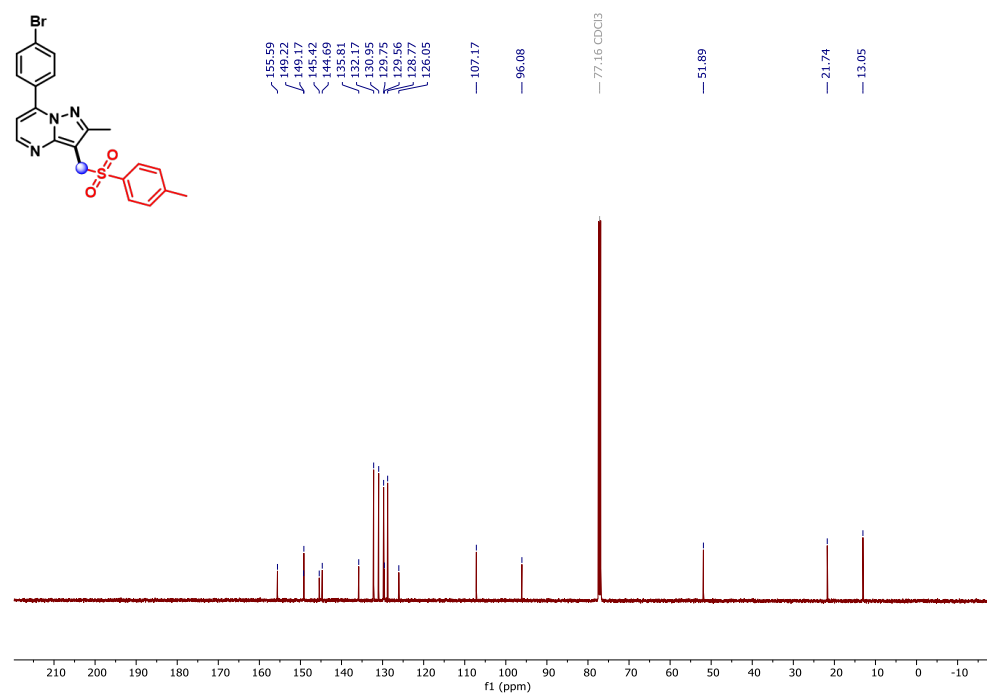


Figure 17: ¹³C NMR (126MHz, CDCl₃) of 4g

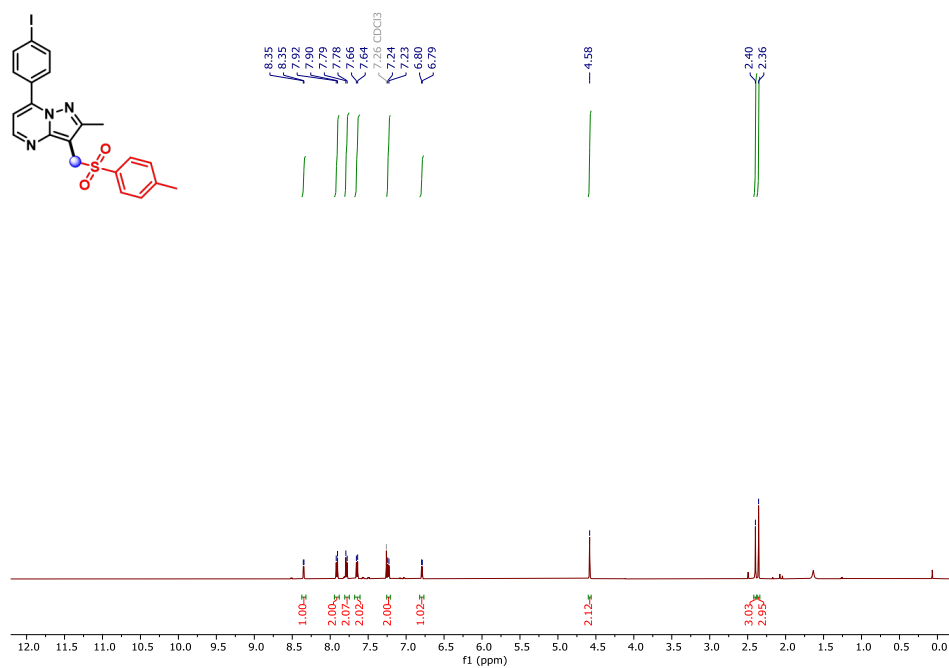


Figure 18: ¹H NMR (500MHz, CDCl₃) of 4h

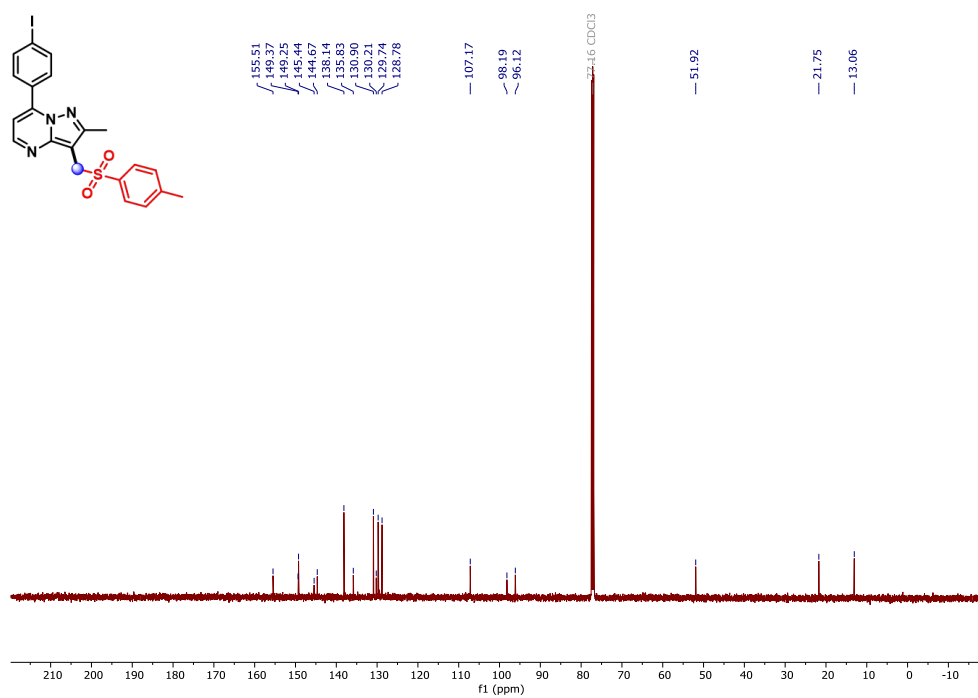


Figure 19: ¹³C NMR (126MHz, CDCl₃) of 4h

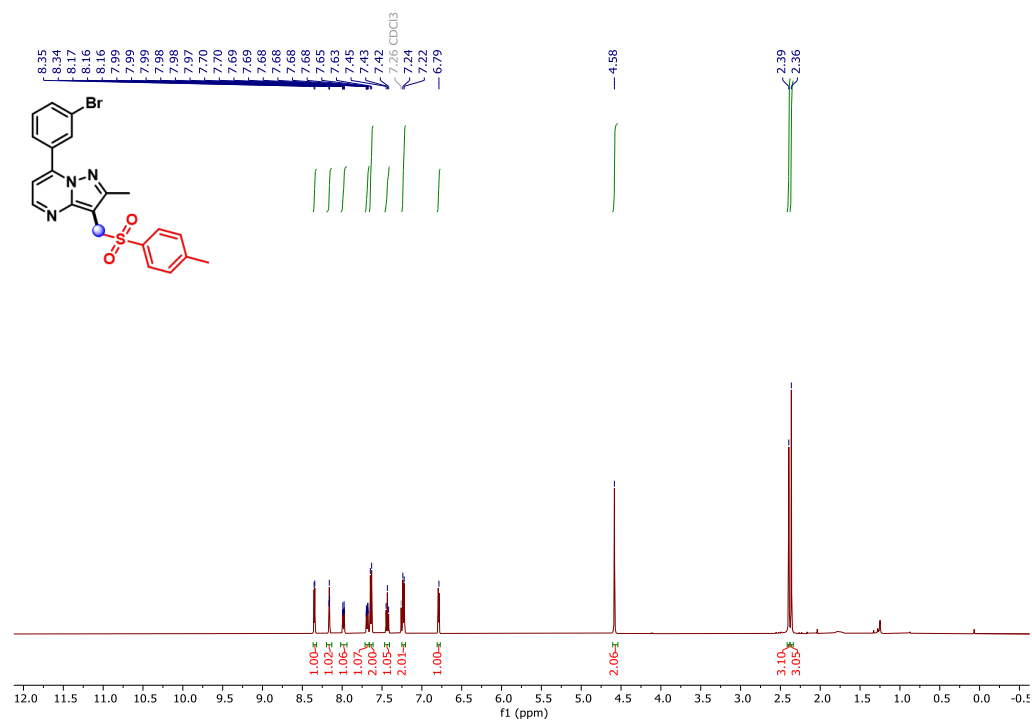


Figure 20: ¹H NMR (500MHz, CDCl₃) of 4i

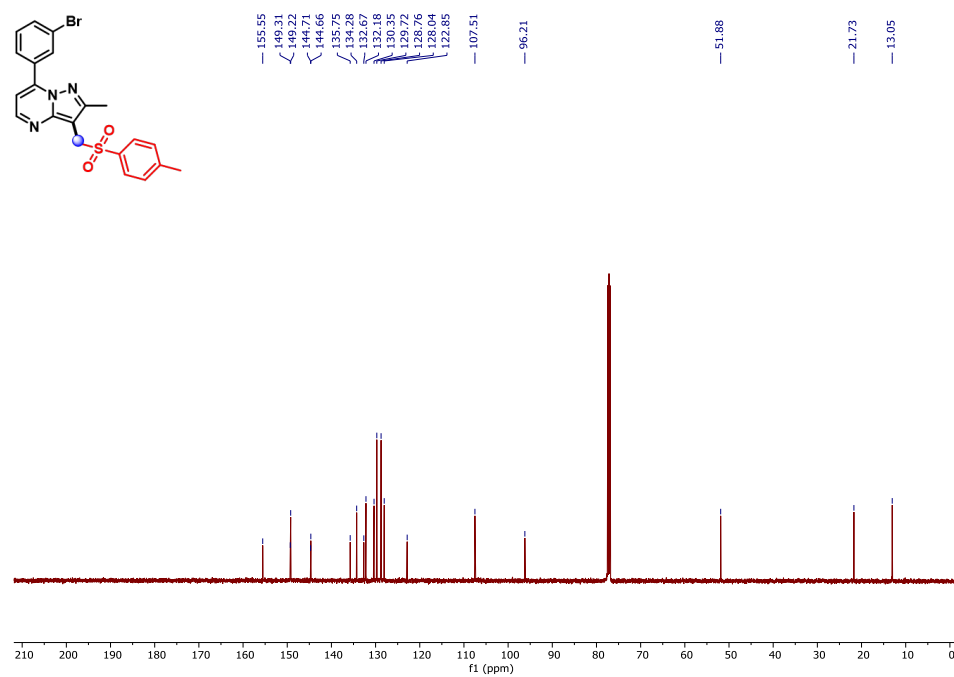
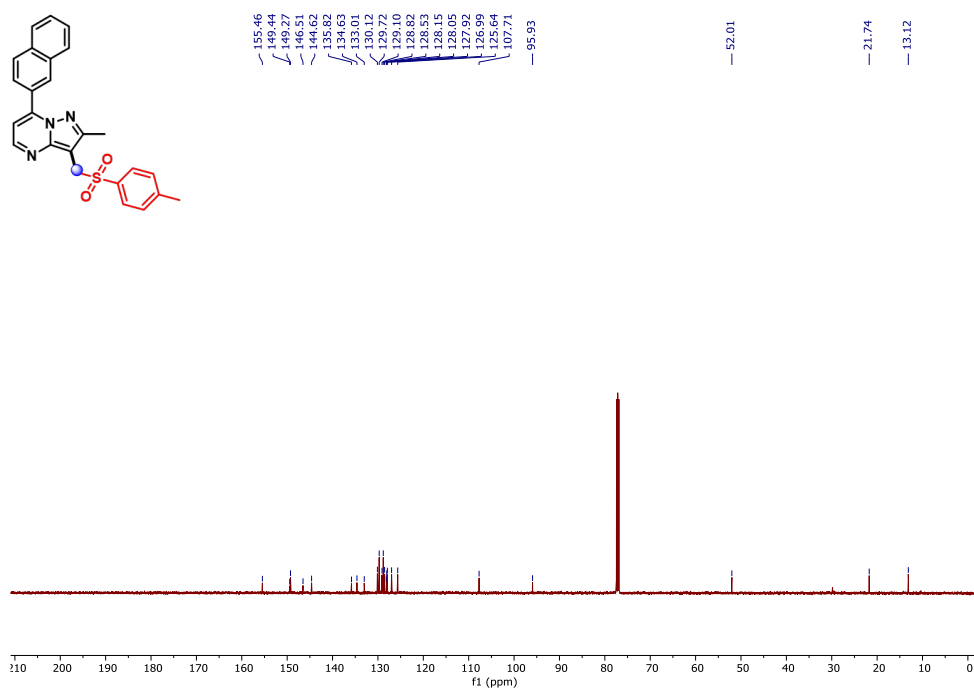
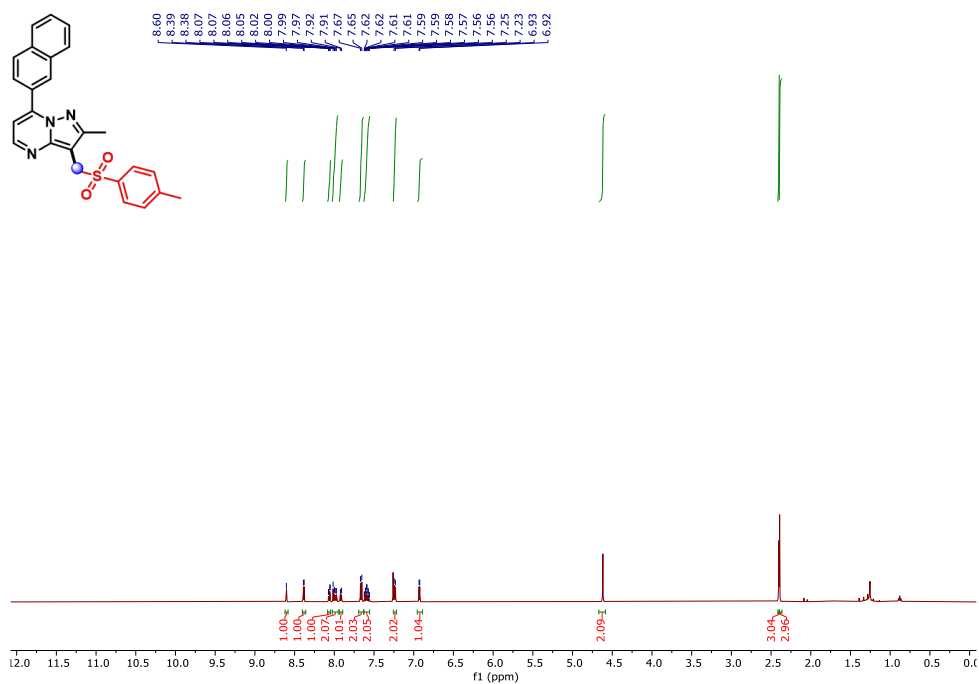


Figure 21: ¹³C NMR (126MHz, CDCl₃) of 4i



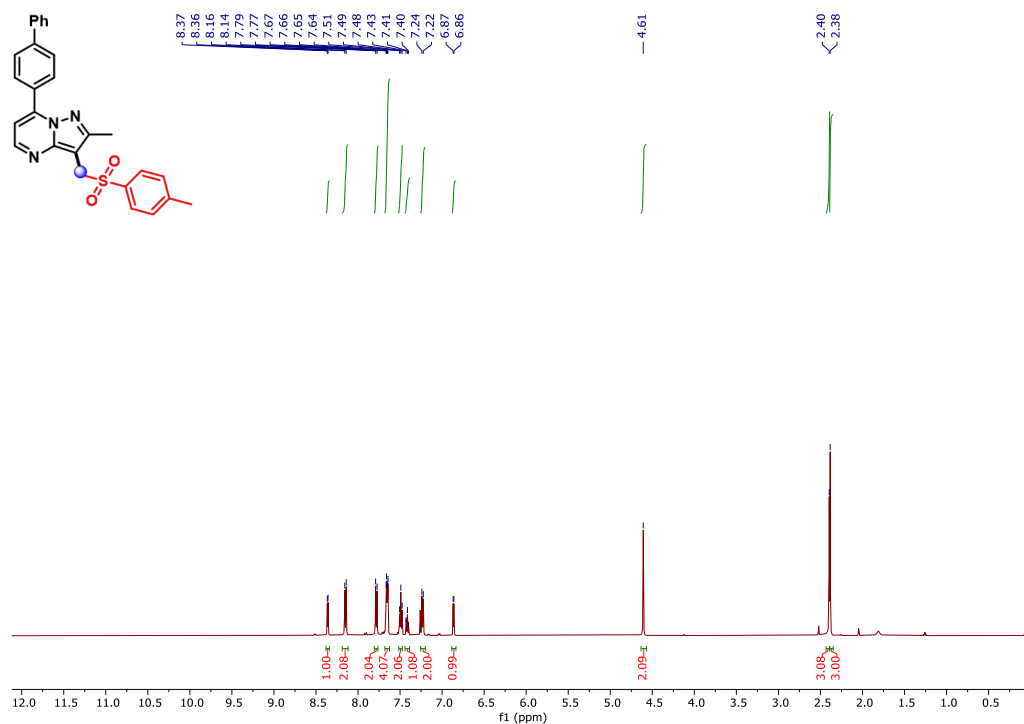


Figure 24: ¹H NMR (500MHz, CDCl₃) of 4k

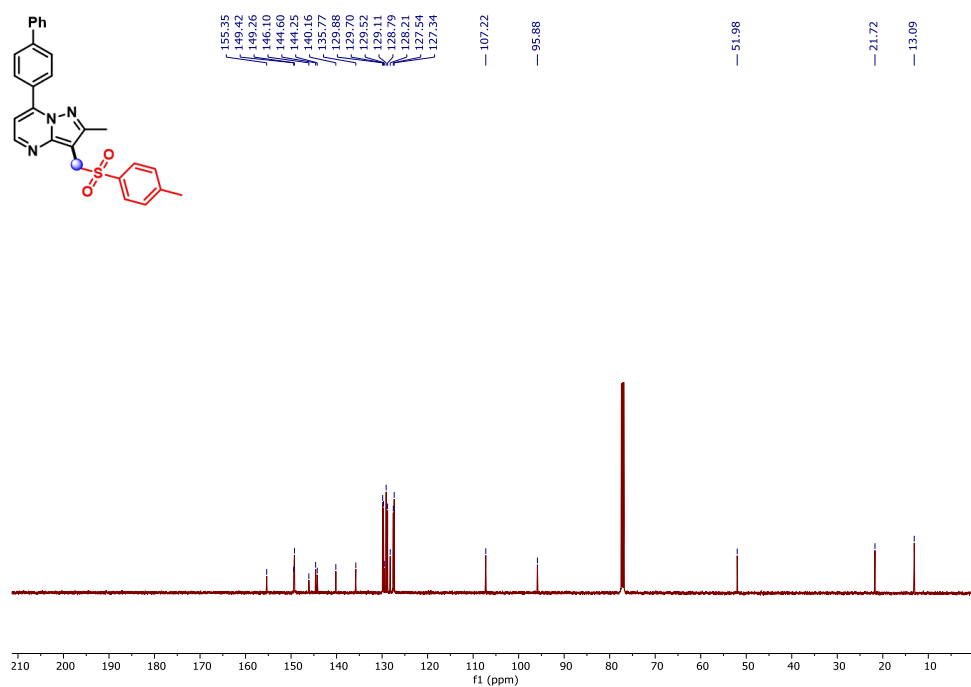


Figure 25: ¹³C NMR (126MHz, CDCl₃) of 4k

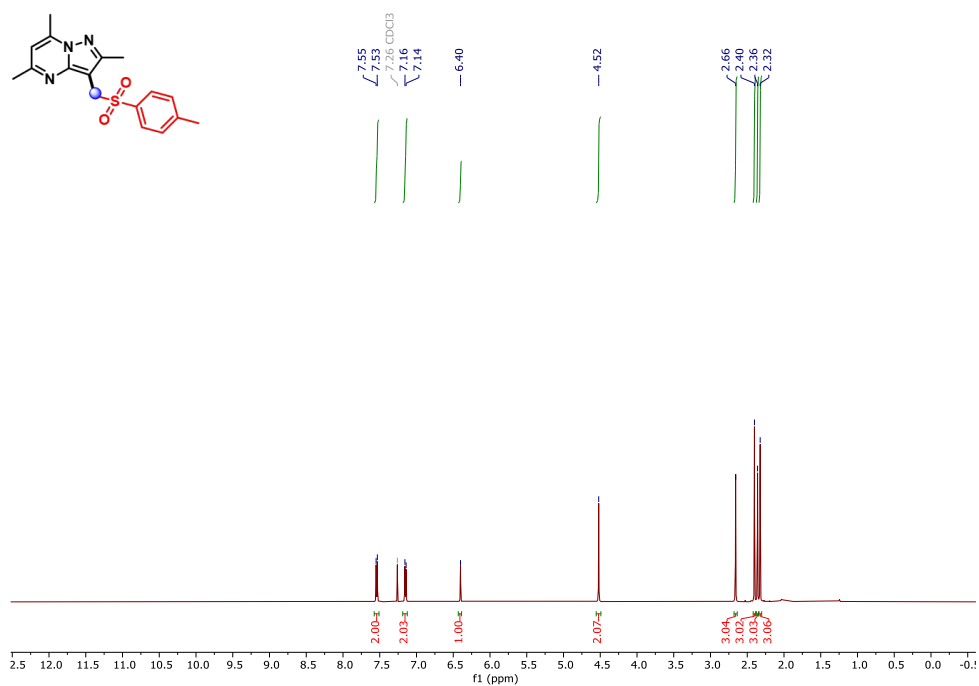


Figure 26: ¹H NMR (500MHz, CDCl₃) of 4l

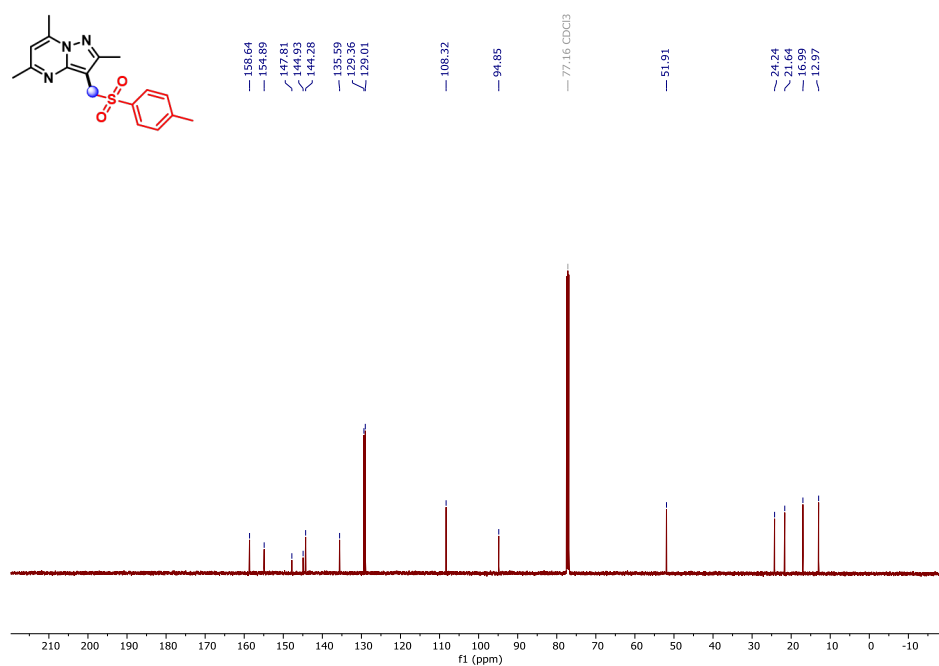


Figure 27: ¹³C NMR (126MHz, CDCl₃) of 4l

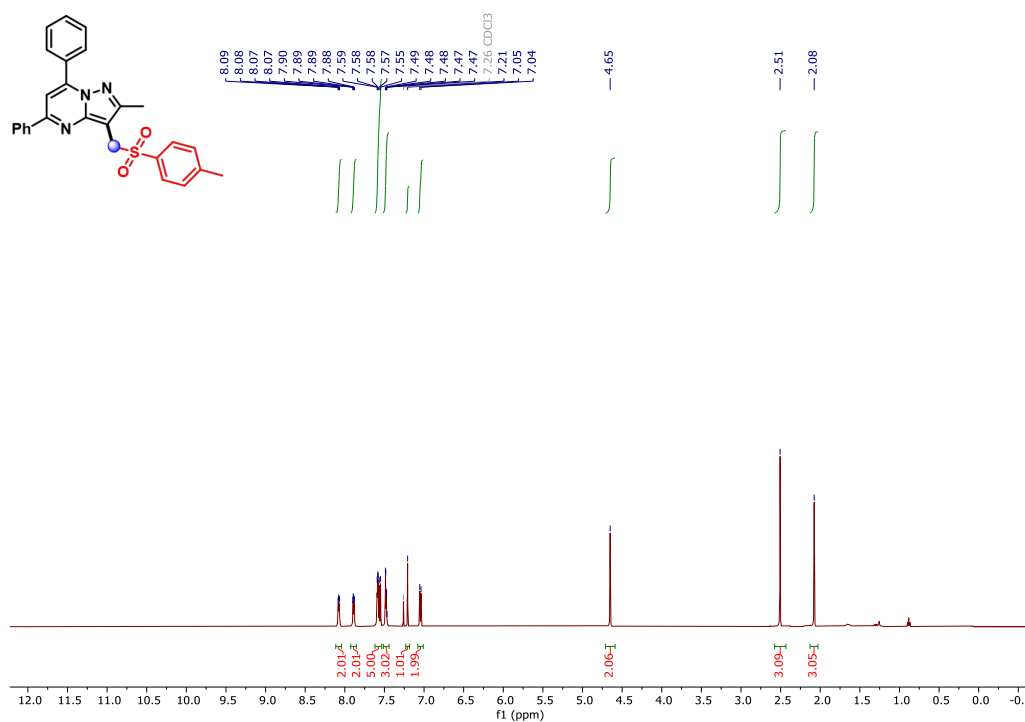


Figure 28: ¹H NMR (500MHz, CDCl₃) of 4m

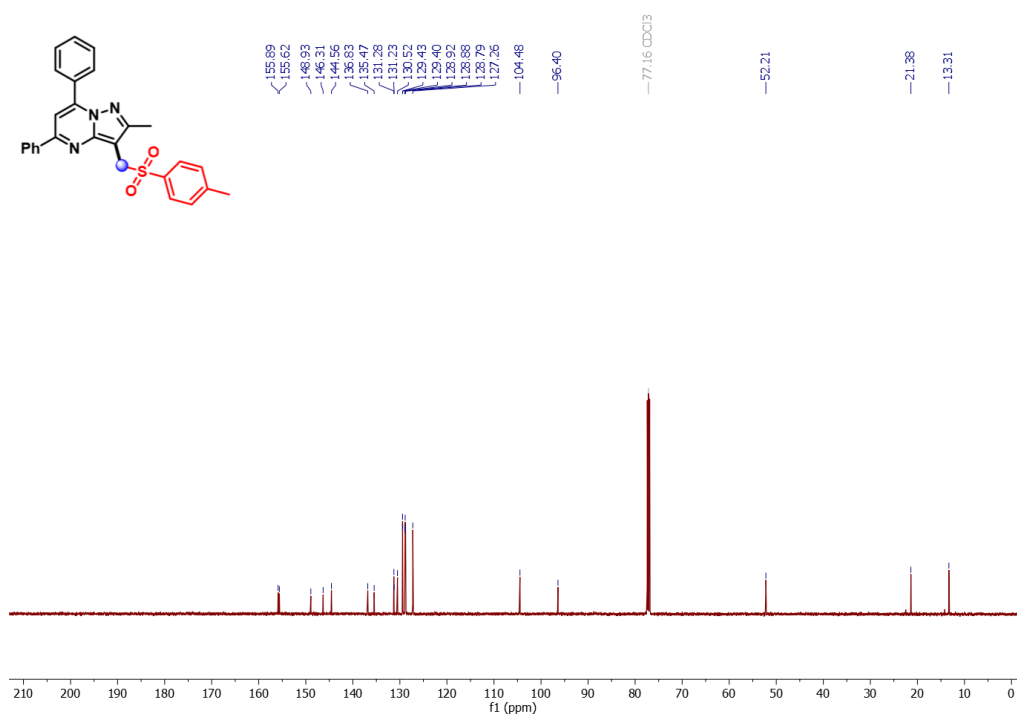


Figure 29: ¹³C NMR (126MHz, CDCl₃) of 4m

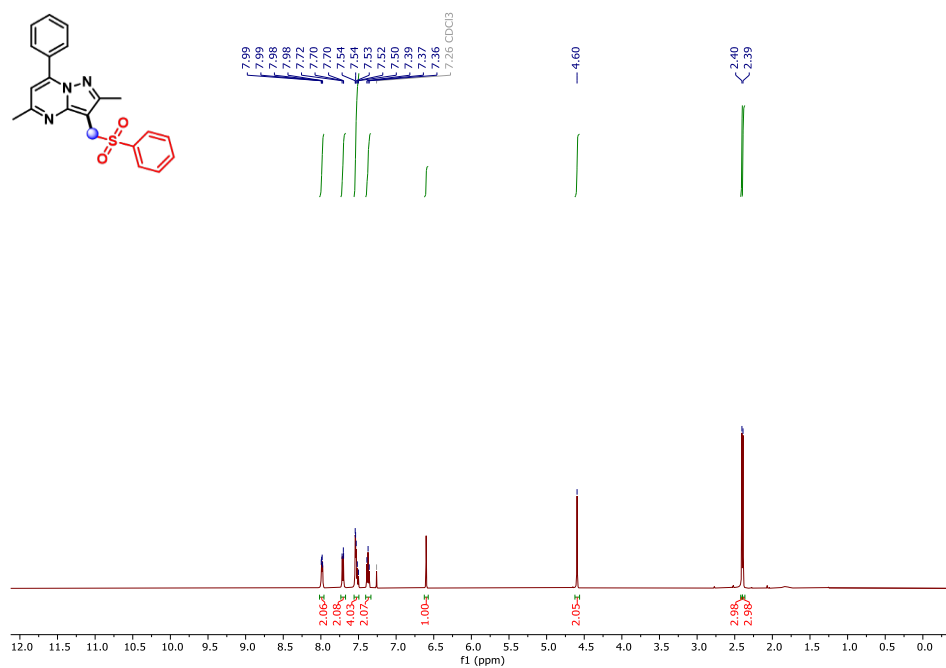


Figure 30: ¹H NMR (500MHz, CDCl₃) of 4n

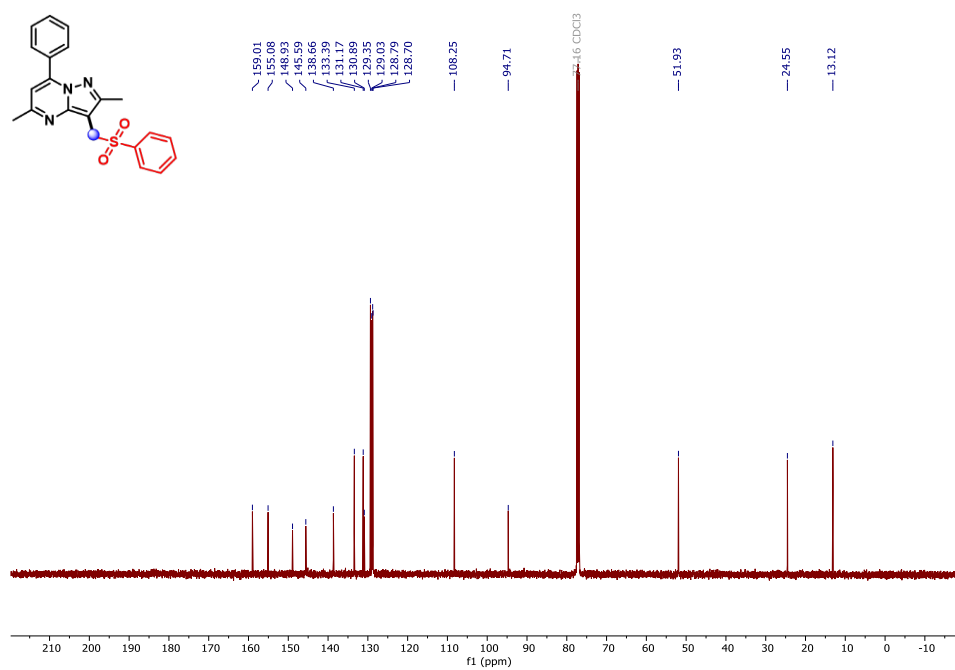


Figure 31: ¹³C NMR (126MHz, CDCl₃) of 4n

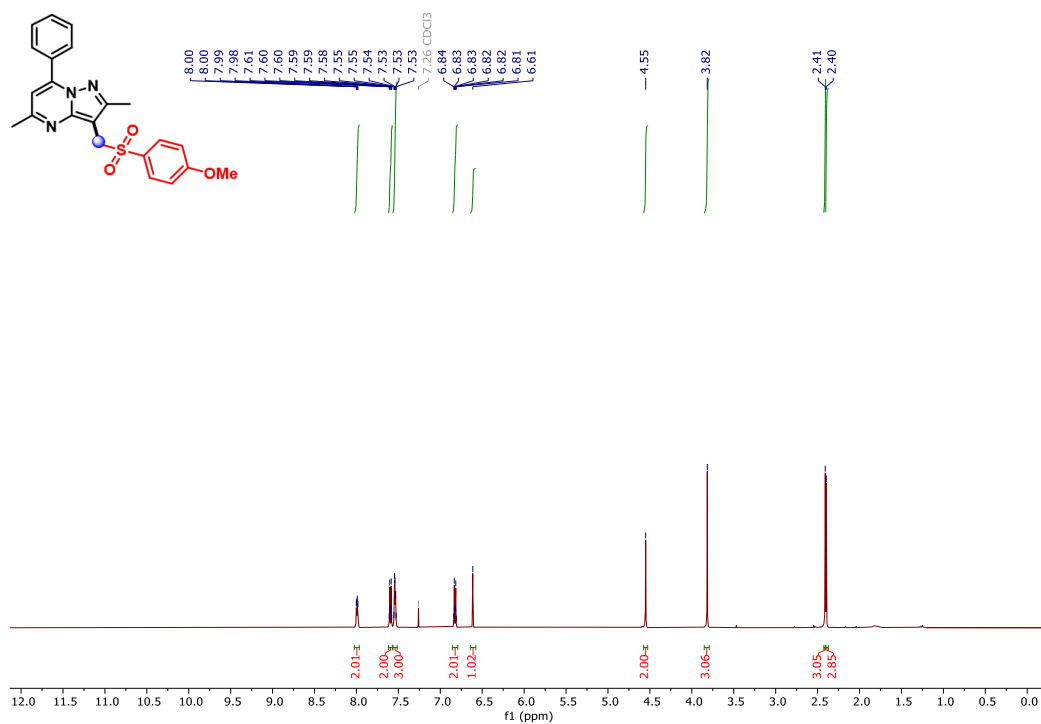


Figure 32: ¹H NMR (500MHz, CDCl₃) of 4o

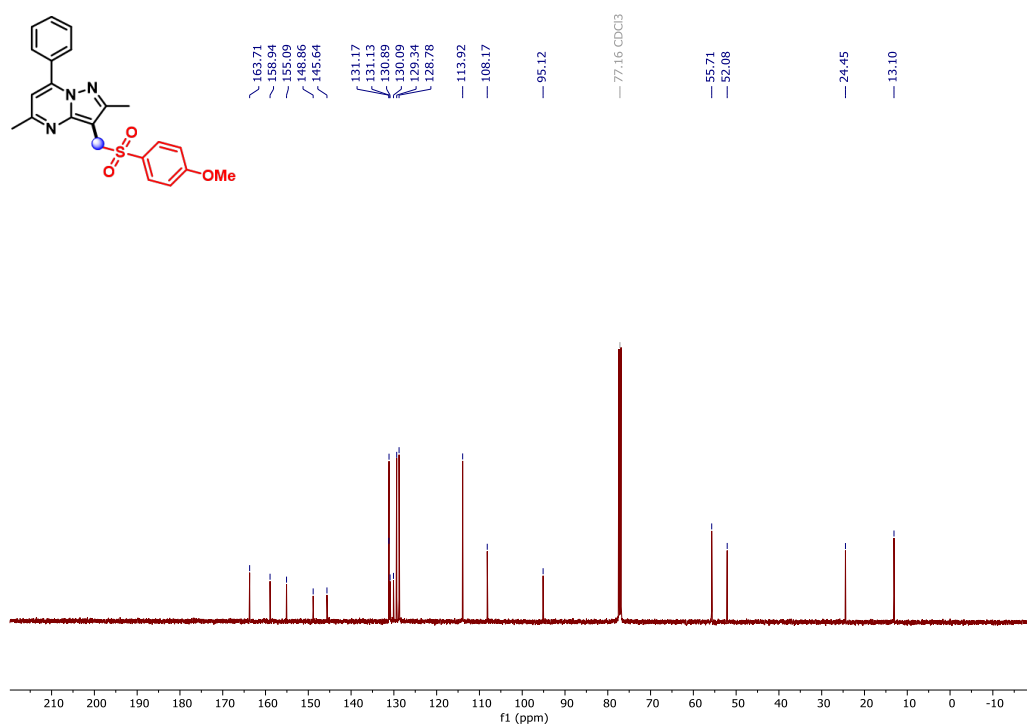


Figure 33: ¹³C NMR (126MHz, CDCl₃) of 4o

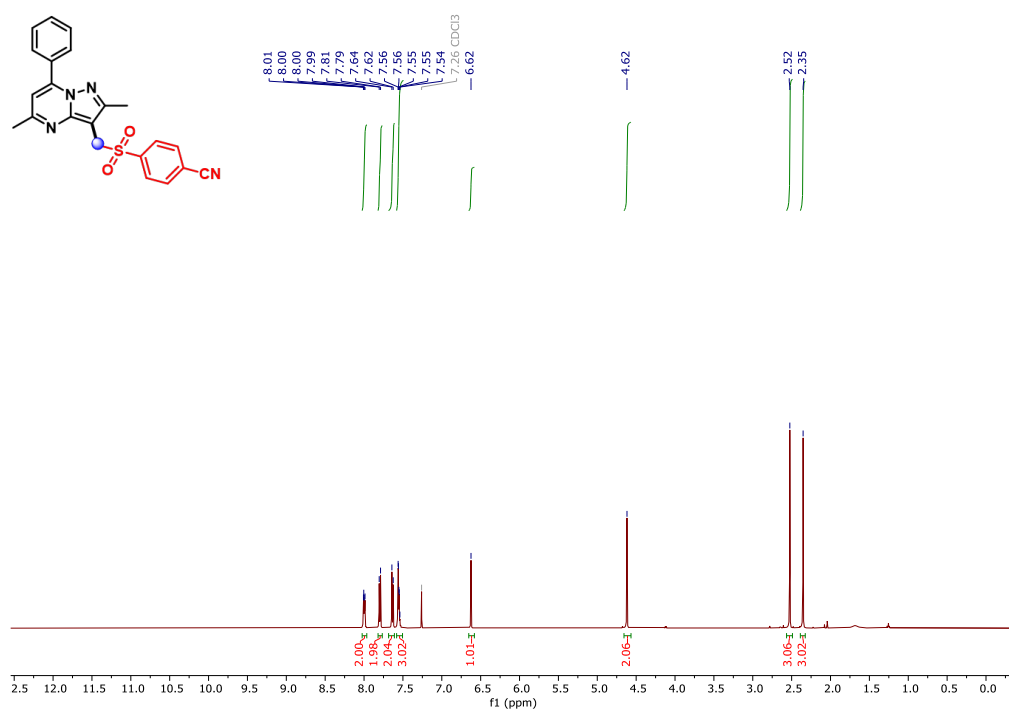


Figure 34: ¹H NMR (500MHz, CDCl₃) of 4p

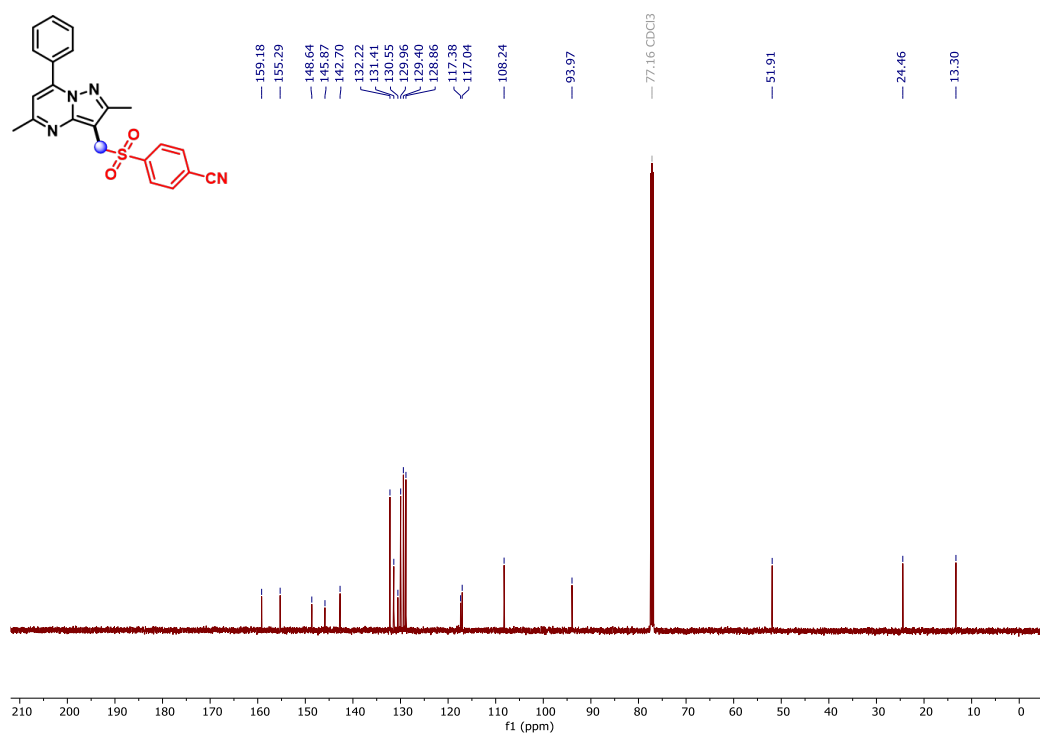


Figure 35: ¹³C NMR (126MHz, CDCl₃) of 4p

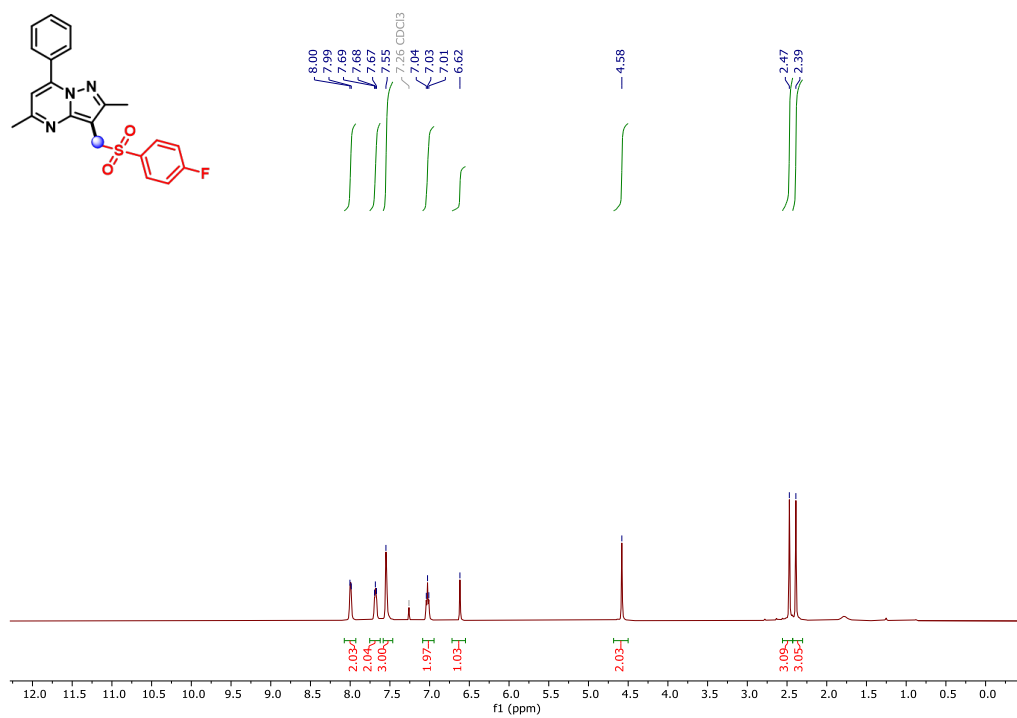


Figure 36: ¹H NMR (500MHz, CDCl₃) of 4q

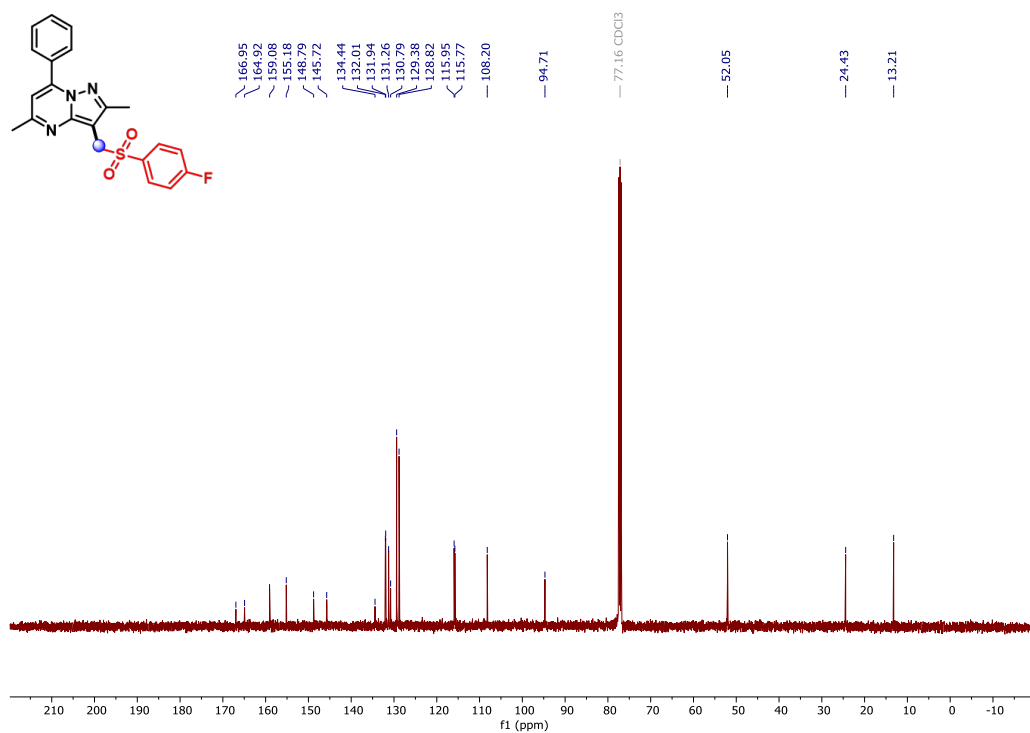


Figure 37: ¹³C NMR (126MHz, CDCl₃) of 4q

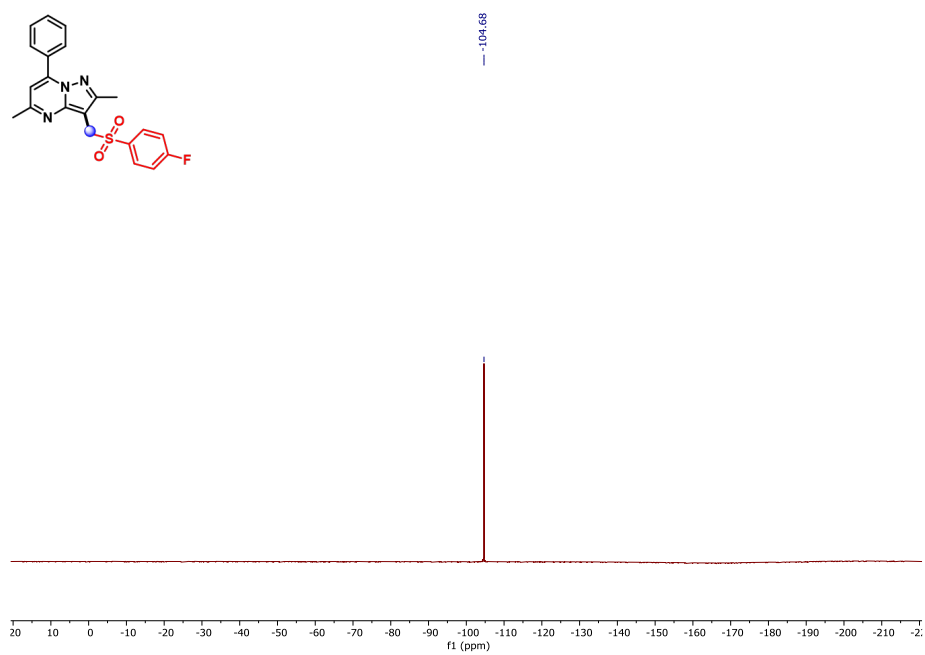


Figure 38: ^{19}F NMR (471MHz, CDCl_3) of 4q

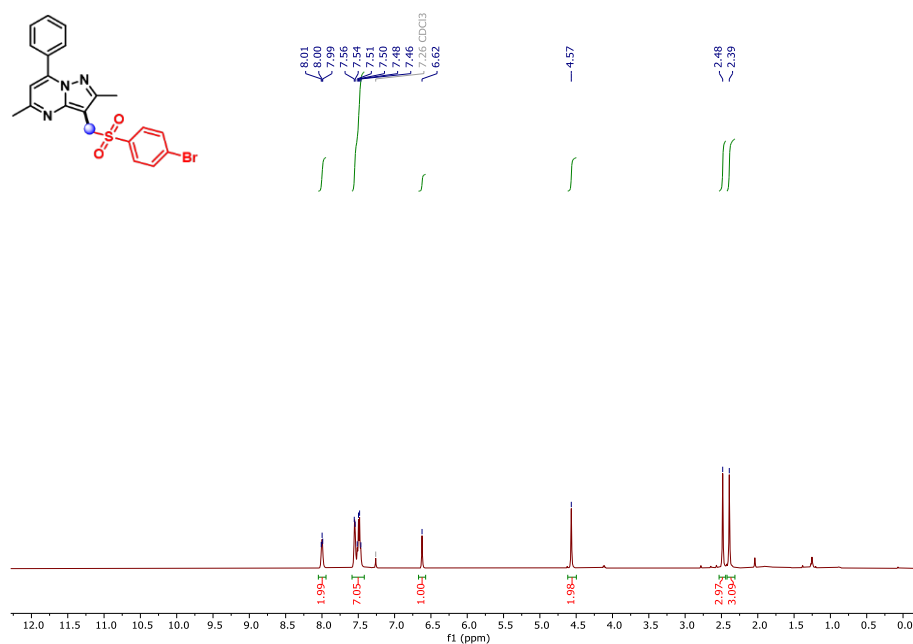


Figure 39: ¹H NMR (500MHz, CDCl₃) of 4r

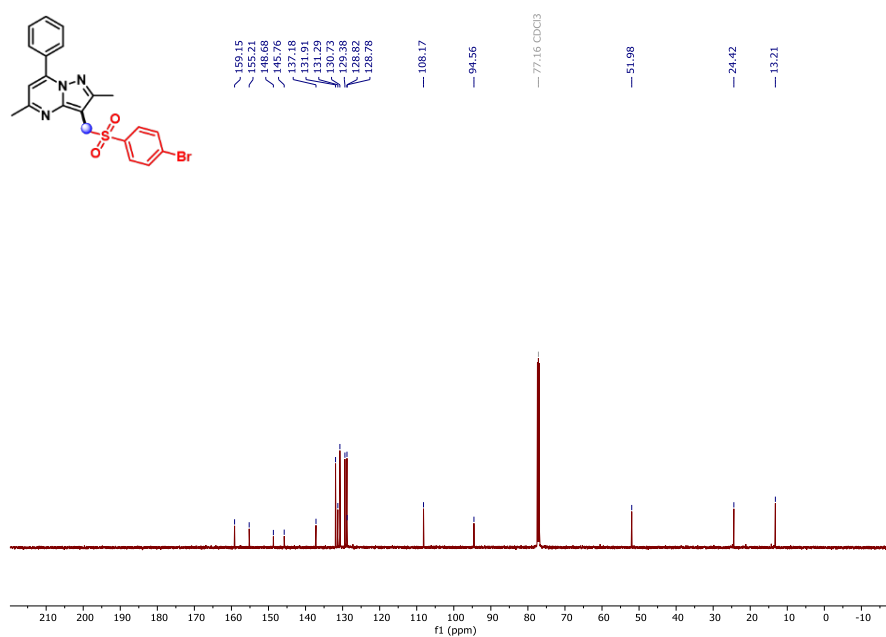


Figure 40: ¹³C NMR (126MHz, CDCl₃) of 4r

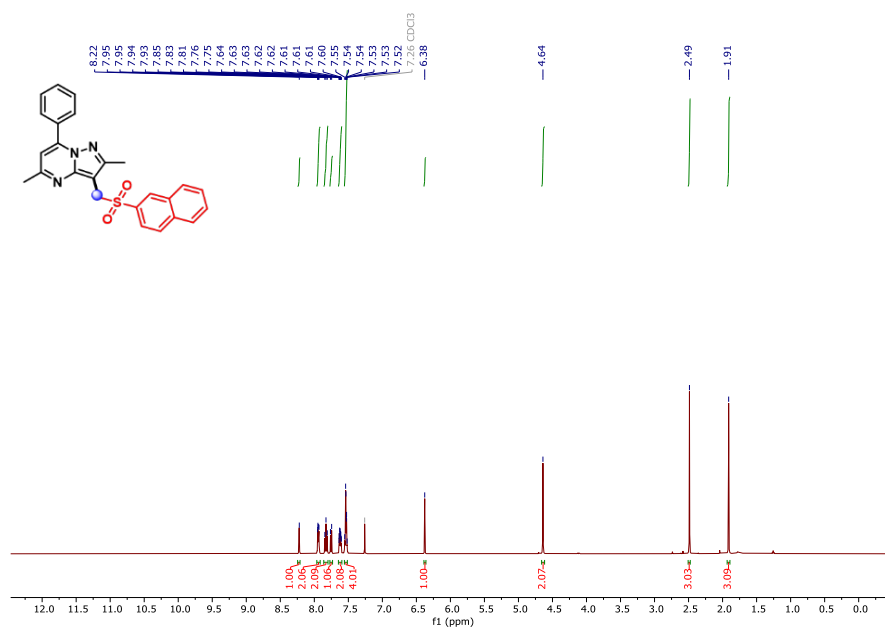


Figure 41: ¹H NMR (500MHz, CDCl₃) of 4s

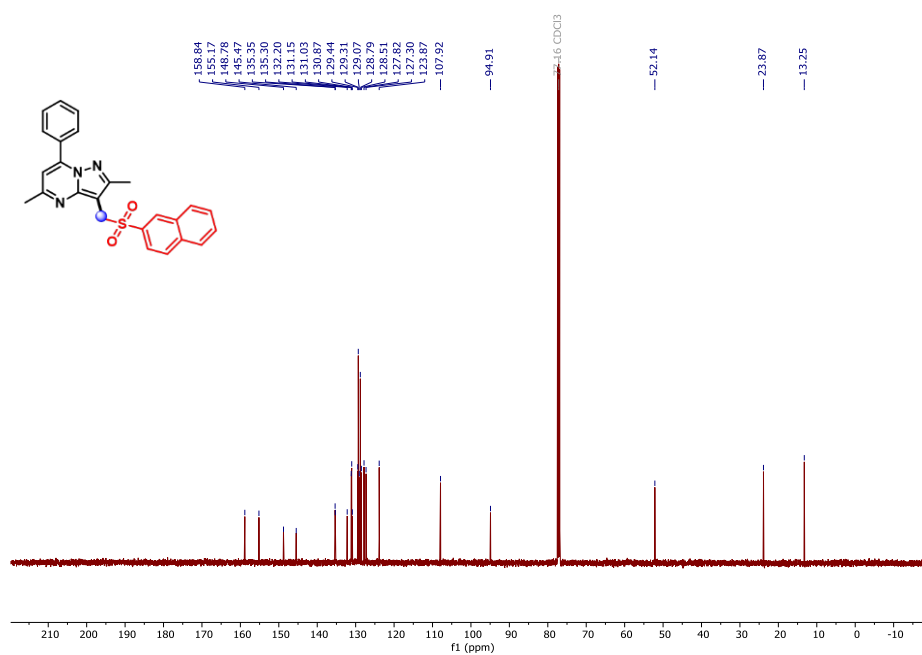


Figure 42: ¹³C NMR (126MHz, CDCl₃) of 4s

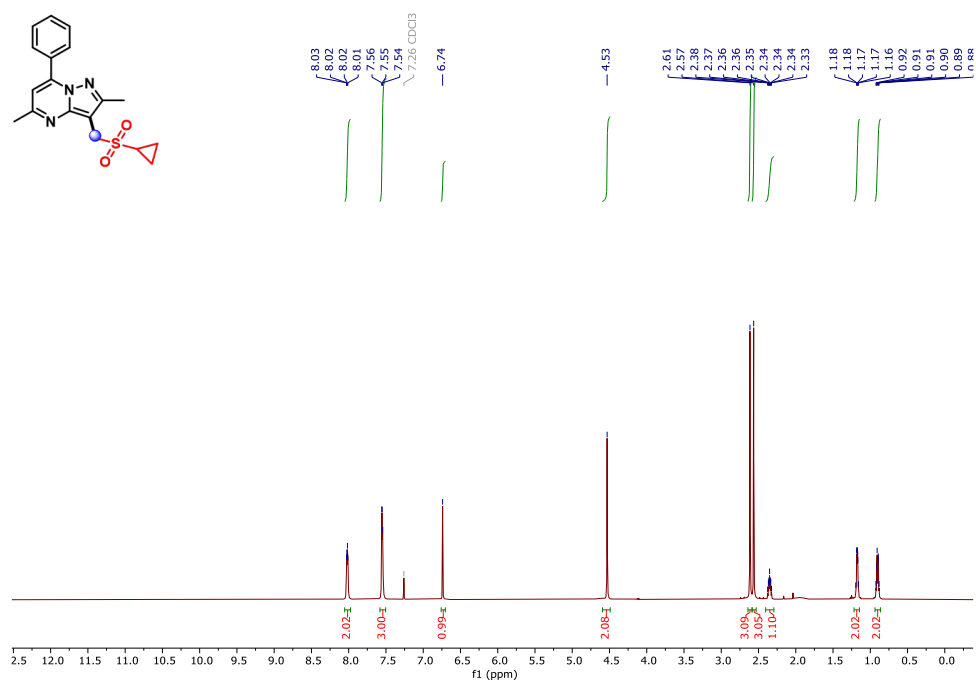


Figure 43: ¹H NMR (500MHz, CDCl₃) of 4t

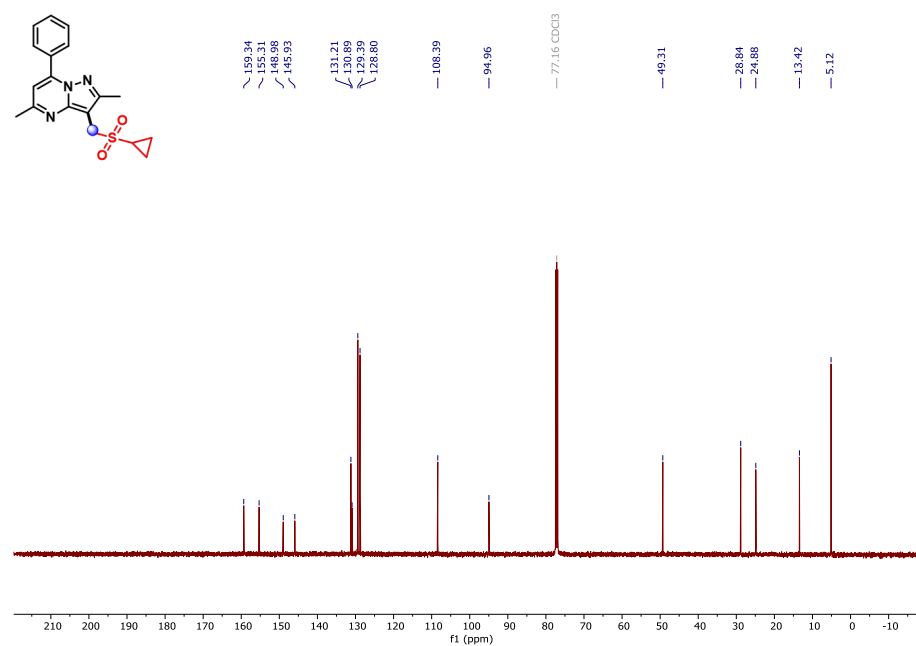


Figure 44: ¹³C NMR (126MHz, CDCl₃) of 4t

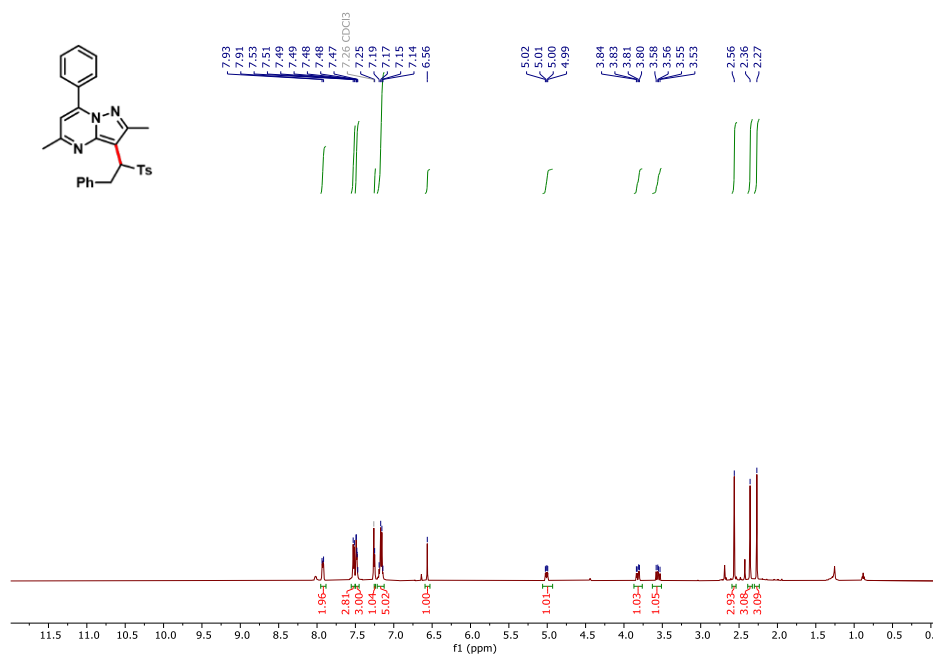


Figure 45: ¹H NMR (500MHz, CDCl₃) of 7

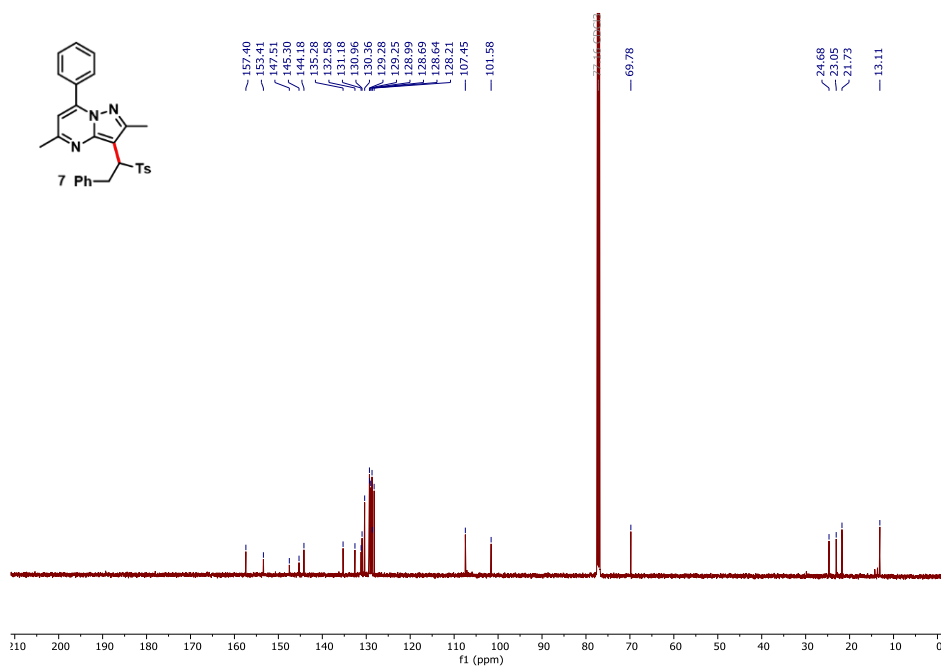


Figure 46: ¹³C NMR (126MHz, CDCl₃) of 7

CHAPTER- 5 REFERENCES

- (1) Amin, A.; Qadir, T.; Sharma, P. K.; Jeelani, I.; Abe, H. A Review on the Medicinal and Industrial Applications of N-Containing Heterocycles. *Open Med. Chem. J.* **2022**, *16*, e187410452209010. <http://dx.doi.org/10.2174/18741045-v16-e2209010>.
- (2) Kiessling, A.; Wiesinger, R.; Sperl, B.; Berg, T. Selective Inhibition of c-Myc/Max Dimerization by a Pyrazolo[1,5-*a*]Pyrimidine. *ChemMedChem* **2007**, *2*, 627–630. <https://doi.org/10.1002/cmdc.200600294>.
- (3) Kirkpatrick, W. E.; Okabe, T.; Hillyard, I. W.; Robins, R. K.; Dren, A. T.; Novinson, T. 3-Halo-5,7-Dimethylpyrazolo[1,5-*a*]Pyrimidines, a Nonbenzodiazepinoid Class of Antianxiety Agents Devoid of Potentiation of Central Nervous System Depressant Effects of Ethanol or Barbiturates. *J. Med. Chem.* **1977**, *20*, 386–393. <https://doi.org/10.1021/jm00213a014>.
- (4) Azeredo, L. F. S. P.; Coutinho, J. P.; Jabor, V. A. P.; Feliciano, P. R.; Nonato, M. C.; Kaiser, C. R.; Menezes, C. M. S.; Hammes, A. S. O.; Caffarena, E. R.; Hoelz, L. V. B.; De Souza, N. B.; Pereira, G. A. N.; Cerávolo, I. P.; Krettli, A. U.; Boechat, N. Evaluation of 7-Arylamino pyrazolo[1,5-*a*]Pyrimidines as Anti-Plasmodium Falciparum, Antimalarial, and Pf-Dihydroorotate Dehydrogenase Inhibitors. *Eur. J. Med. Chem.* **2017**, *126*, 72–83. <https://doi.org/10.1016/j.ejmech.2016.09.073>.
- (5) Castillo, J.C.; Tigreros, A.; Portilla, J. 3-Formylpyrazolo[1,5-*a*]Pyrimidines as Key Intermediates for the Preparation of Functional Fluorophores. *J. Org. Chem.* **2018**, *83*, 10887–10897. <https://doi.org/10.1021/acs.joc.8b01571>.
- (6) Tigreros, A.; Zapata-Rivera, J.; Portilla, J. Pyrazolo[1,5-*a*]Pyrimidinium Salts for Cyanide Sensing: A Performance and Sustainability Study of the Probes. *ACS Sustainable Chem. Eng.* **2021**, *9*, 12058–12069. <https://doi.org/10.1021/acssuschemeng.1c01689>.

- (7) Castellino, N. J.; Montgomery, A. P.; Danon, J. J.; Kassiou, M. Late-Stage Functionalization for Improving Drug-like Molecular Properties. *Chem. Rev.* **2023**, *123*, 8127–8153. <https://doi.org/10.1021/acs.chemrev.2c00797>.
- (8) Kerr, I. D.; Lee, J. H.; Farady, C. J.; Marion, R.; Rickert, M.; Sajid, M.; Pandey, K. C.; Caffrey, C. R.; Legac, J.; Hansell, E.; McKerrow, J. H.; Craik, C. S.; Rosenthal, P. J.; Brinen, L. S. Vinyl Sulfones as Antiparasitic Agents and a Structural Basis for Drug Design. *J. Biol. Chem.* **2009**, *284*, 25697–25703. <https://doi.org/10.1074/jbc.M109.014340>.
- (9) Meadows, D. C.; Gervay-Hague, J. Vinyl Sulfones: Synthetic Preparations and Medicinal Chemistry Applications. *Med. Res. Rev.* **2006**, *26*, 793–814. <https://doi.org/10.1002/med.20074>.
- (10) Zhang, W.; Luo, X.; Tang, H.; Tang, Z.; Huang, F.; Wan, Q.; Yu, G.; Yang, H. Structural Regulation of Sulfone-Decorated Conjugated Polymers for Boosting Photocatalysis. *J. Mater. Chem. A* **2025**, *13*, 4746–4793. <https://doi.org/10.1039/D4TA07264B>.
- (11) Xu, W.-M.; Han, F.-F.; He, M.; Hu, D.-Y.; He, J.; Yang, S.; Song, B.-A. Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing an 1,3,4-Oxadiazole Moiety. *J. Agric. Food Chem.* **2012**, *60*, 1036–1041. <https://doi.org/10.1021/jf203772d>.
- (12) Nagane, S. S.; Kuhire, S. S.; Mane, S. R.; Wadgaonkar, P. P. Partially Bio-Based Aromatic Poly(Ether Sulfone)s Bearing Pendant Furyl Groups: Synthesis, Characterization and Thermo-Reversible Cross-Linking with a Bismaleimide. *Polym. Chem.* **2019**, *10*, 1089–1098. <https://doi.org/10.1039/C8PY01477A>.
- (13) Alba, A.-N. R.; Companyó, X.; Rios, R. Sulfones: New Reagents in Organocatalysis. *Chem. Soc. Rev.* **2010**, *39*, 2018. <https://doi.org/10.1039/B911852G>.
- (14) Trost, B. M.; Kalnmals, C. A. Sulfones as Chemical Chameleons: Versatile Synthetic Equivalents of Small-Molecule Synthons. *Chem. Eur. J.* **2019**, *25*, 11193–11213. <https://doi.org/10.1002/chem.201902019>.

- (15) Ielo, L.; Touqeer, S.; Roller, A.; Langer, T.; Holzer, W.; Pace, V. Telescoped, Divergent, Chemoselective C1 and C1-C1 Homologation of Imine Surrogates: Access to Quaternary Chloro- and Halomethyl-Trifluoromethyl Aziridines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2479–2484. <https://doi.org/10.1002/ange.201812525>.
- (16) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937–2981. <https://doi.org/10.1021/acs.chemrev.5b00381>.
- (17) Bonciolini, S.; Pulcinella, A.; Leone, M.; Schirotti, D.; Ruiz, A. L.; Sorato, A.; Dubois, M. A. J.; Gopalakrishnan, R.; Masson, G.; Della Ca', N.; Protti, S.; Fagnoni, M.; Zysman-Colman, E.; Johansson, M.; Noël, T. Metal-Free Photocatalytic Cross-Electrophile Coupling Enables C1 Homologation and Alkylation of Carboxylic Acids with Aldehydes. *Nat. Commun.* **2024**, *15*, 1509. <https://doi.org/10.1038/s41467-024-45804-z>.
- (18) Grocott, M. C.; Gaunt, M. J. One-Carbon Homologation of Alkenes. *Nature* **2025**, *643*, 130–138. <https://doi.org/10.1038/s41586-025-09159-9>.
- (19) Mi, X.; Kong, Y.; Zhang, J.; Pi, C.; Cui, X. Visible-Light-Promoted Sulfonylmethylation of Imidazopyridines. *Chin. Chem. Lett.* **2019**, *30*, 2295–2298. <https://doi.org/10.1016/j.cclet.2019.09.040>.
- (20) Lu, S.; Zhu, X.; Li, K.; Guo, Y.-J.; Wang, M.-D.; Zhao, X.-M.; Hao, X.-Q.; Song, M.-P. Reactivity of *p*-Toluenesulfonylmethyl Isocyanide: Iron-Involved C–H Tosylmethylation of Imidazopyridines in Nontoxic Media. *J. Org. Chem.* **2016**, *81*, 8370–8377. <https://doi.org/10.1021/acs.joc.6b01552>.
- (21) Sun, S.; Ye, H.; Liu, H.; Li, J.; Bi, X. Iron-Catalyzed Sulfonylmethylation of Imidazo[1,2-*a*]Pyridines with N,N-Dimethylacetamide and Sodium Sulfinates. *Molecules* **2024**, *29*, 3196. <https://doi.org/10.3390/molecules29133196>.
- (22) Wu, Y.; Chen, J.; Li, L.; Wen, K.; Yao, X.; Pang, J.; Wu, T.; Tang, X. Copper-Mediated Decarboxylative Sulfonylation of Arylacetic

- Acids with Sodium Sulfinates. *Org. Lett.* **2020**, *22*, 7164–7168.
<https://doi.org/10.1021/acs.orglett.0c02516>.
- (23) Panshina, S. Yu.; Ponomarenko, O. V.; Bakibaev, A. A.; Sidelnikov, V. S.; Kurgachev, D. A.; Malkov, V. S.; Khlebnikov, A. I.; Tashenov, A. K. A Study of Products of Tetrakis(Hydroxymethyl)Glycoluril Dehydroxymethylation in Aqueous Solutions. *Russ Chem Bull* **2021**, *70*, 140–147.
<https://doi.org/10.1007/s11172-021-3068-8>.
- (24) Kalari, S.; Shinde, A. U.; Rode, H. B. Methylene-Tethered Arylsulfonation and Benzotriazolation of Aryl/Heteroaryl C–H Bonds with DMSO as a One-Carbon Surrogate. *J. Org. Chem.* **2021**, *86*, 17684–17695. <https://doi.org/10.1021/acs.joc.1c01914>.
- (25) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. HFIP in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 12544–12747.
<https://doi.org/10.1021/acs.chemrev.1c00749>.
- (26) Martins, M. A. P.; Scapin, E.; Frizzo, C. P.; Rosa, F. A.; Bonacorso, H. G.; Zanatta, N. 2-Methyl-7-Substituted Pyrazolo[1,5-*a*]Pyrimidines: Highly Regioselective Synthesis and Bromination. *J. Braz. Chem. Soc.* **2009**, *20*, 205–213.
<https://doi.org/10.1590/S0103-50532009000200003>.
- (27) Yin, L.; Liebscher, J. Convenient Synthesis of Substituted 3-Alkenylpyrazolo[1,5-*a*]pyrimidines via Heck Cross-Coupling Reaction. *Synthesis* **2004**, *2004*, 2329–2334. DOI: [10.1055/s-2004-831189](https://doi.org/10.1055/s-2004-831189).
- (28) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. Copper(I) Iodide Catalyzed Aerobic Oxidative C–N and C–S Bond Formations through C–H Activation: Synthesis of Functionalized Imidazo[1,2-*a*]Pyridines. *Asian J. Org. Chem.* **2014**, *3*, 609–613.
<https://doi.org/10.1002/ajoc.201402004>.