Supporting Information

Novel Sulfonamides Unveiled as Potent Anti-Lung Cancer Agents via Tumor Pyruvate Kinase M2 Activation

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Contents

1. General methods for synthesis

Sulfonyl chloride derivatives, Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF), N,N-Dimethylformamide dimethyl acetal (DMF-DMA), 1-Boc- piperazine, 2-aminopyridine, 2-aminopyrimidine, dimethylformamide (DMF). From Sigma Aldrich, we obtained 1,3-dichloroacetone, and trifluoroacetic acid (TFA). Thermo Fisher Scientific India Pvt. Ltd. supplied the following chemicals: acetonitrile (ACN), dichloromethane (DCM), chloroform (CHCl3), ethyl acetate, hexane, ethanol, and methanol. The Corning trans well inserts (6 mm in diameter) and polystyrene polymer (derived from tissue culture polystyrene, or TCPS) were purchased from Sigma Aldrich in India. Using Bruker NMR and internal standard tetramethylsilane (as = 0 ppm), ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR data were collected at 500 MHz, 125 MHz, and 471 MHz respectively. Values for coupling constants (J) are given in Hz. Chemical shift multiplicities were given the following abbreviations: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, and m = multiplet. MestReNova software was used to evaluate the NMR data. Mass spectra were captured using the Agilent 6545, LC/MS using a Q-TOF analyser, in positive mode. Using Agilent 1260 infinity II equipment and an eclipse C18 column (250 4.6 mM, 5 M) eluted at 1 mL/min with 0.1 percent formic acid and acetonitrile, the purity was evaluated. The compounds displayed greater than 95% purity. In the BUCHI M-560 instrument, the melting points of the produced compounds were recorded. A licenced version of Chemdraw was used to create all of the structures.[1,2]

Initially, 3.0 equivalence of DMF-DMA was applied to 2-aminopyri(mi)dine **1a-b** in the presence of methanol at 80 °C for 4 hours. The consumption of all of the 2-aminopyri(mi)dine **1a-b** was used to determine when the reaction had finished by thin layer chromatography (TLC).[1] Without additional purification, the reaction mixture was concentrated under vacuum pressure and used to furnish the Schiff base **2a-b**. The finished product was exposed to 1,3-dichloroacetone **3** for four hours at 70^{o}C in the presence of the aprotic solvent acetonitrile. The imidazopyri(mi)dine substituted chloroacetophenone adduct **4a-b** was purified by column chromatography and used as a starting material for further reactions after the reaction was finished. Next, three steps were taken to complete the synthesis. A round-bottomed flask was first filled with a mixture of

substituted sulfonyl chlorides **6** (1 equiv) and Boc-protected piperazine **5** (1.05 equiv) in 4 mL of dichloromethane. Next, triethylamine (1.2 equiv) was added while the mixture was continuously stirred at room temperature for two hours. TLC kept track of the reaction's development (Hexane: Ethyl acetate in the ratio of 70:30). The reaction mixture was first extracted with ethyl acetate after which it was washed with water, dried over anhydrous sodium sulphate, filtered, and the solvent was then evaporated using a rotary evaporator. The crude product **7** then went through the deprotection process. Trifluoroacetic acid (TFA) and DCM (3:7) were used to dissolve the dry intermediate, which was then agitated at room temperature for two hours. DCM and TFA were evaporated on the rotary evaporator after the deprotection was confirmed by TLC (Hexane: Ethyl acetate in the ratio of 50:50). Following that, DMSO was added to the deprotected intermediate **8** and it was dissolved. Then, the previously synthesised imidazopyri(mi)dine substituted chloroacetophenone adduct **4a-b** (1 equiv.) and activated K_2CO_3 (1.2 equiv.) were added, and the mixture was agitated at 80 °C for two hours. The reaction mixture was poured over crushed ice after it had finished, as determined by TLC (in 100 percent ethyl acetate), and then extracted using a DCM-water solvent system. In order to obtain the product as a yellowish-white solid, the extracted organic layer was passed over anhydrous sodium sulphate and purified by column chromatography (with mobile phase hexane: ethyl acetate in the ratio of 30:70). The ^{1}H, ^{13}C, ^{19}F NMR spectra, and HRMS readings were used to comprehensively characterise each product **9a-s** and **10a-s**.

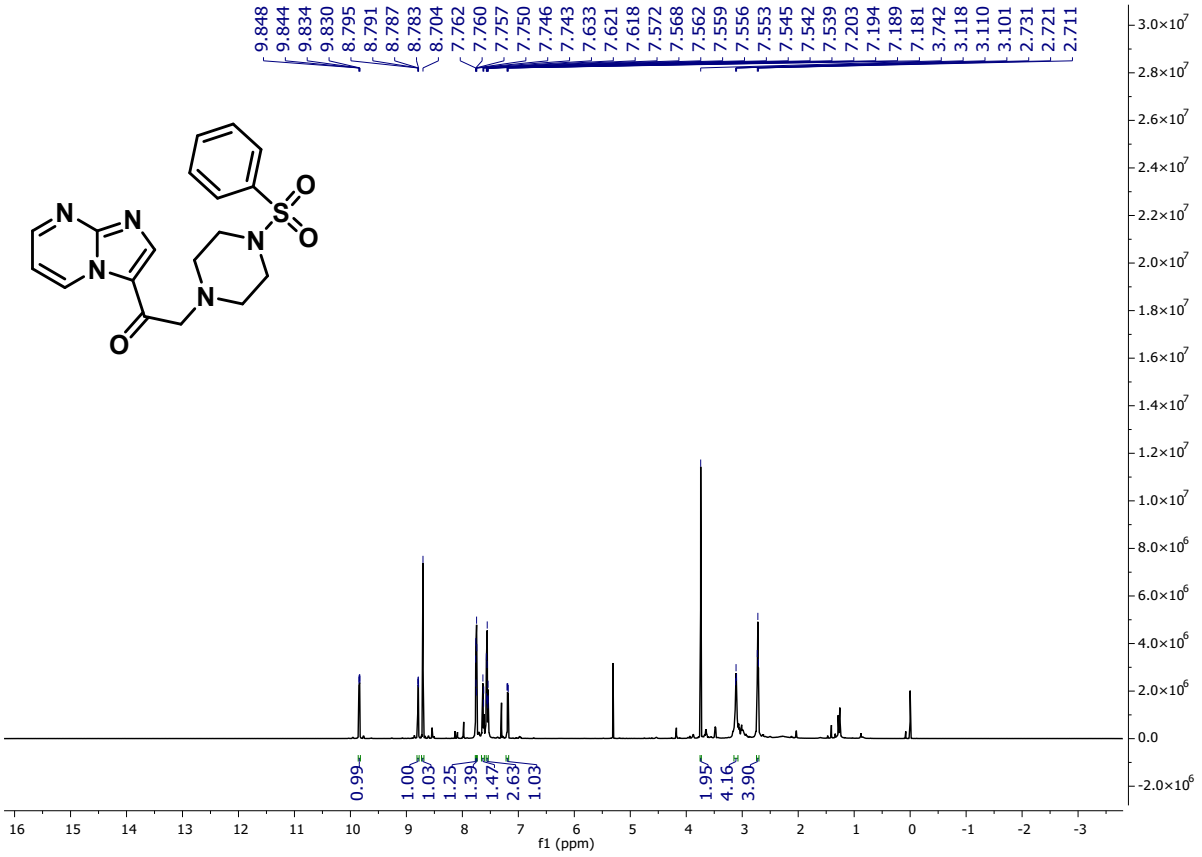
1. Rasapalli, S., Kumbam, V., Dhawane, A. N., Golen, J. A., Lovely, C. J., & Rheingold, A. L. (2013). Total syntheses of oroidin, hymenidin and clathrodin. Organic & Biomolecular Chemistry, 11(25), 4133-4137.

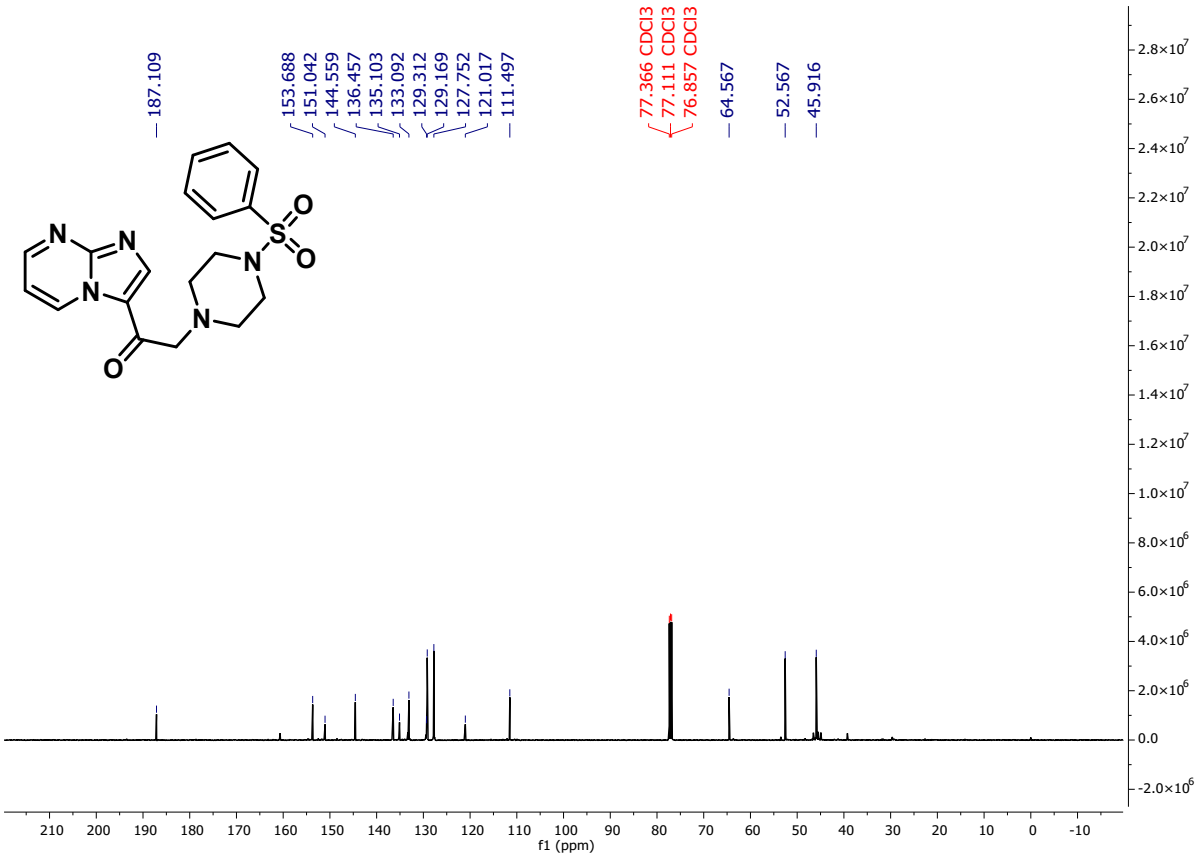
2. Vasu, K. K., Digwal, C. S., Pandya, A. N., Pandya, D. H., Sharma, J. A., Patel, S., & Agarwal, M. (2017). Imidazo [1, 2-a] pyridines linked with thiazoles/thiophene motif through keto spacer as potential cytotoxic agents and NF-κB inhibitors. Bioorganic & Medicinal Chemistry Letters, 27(24), 5463-5466.

2. NMR and HRMS spectral information of the synthesized compounds

NMR and HRMS spectra

1: 1- (imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(phenylsulfonyl)piperazin-1-yl)ethan-1-one (9b) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





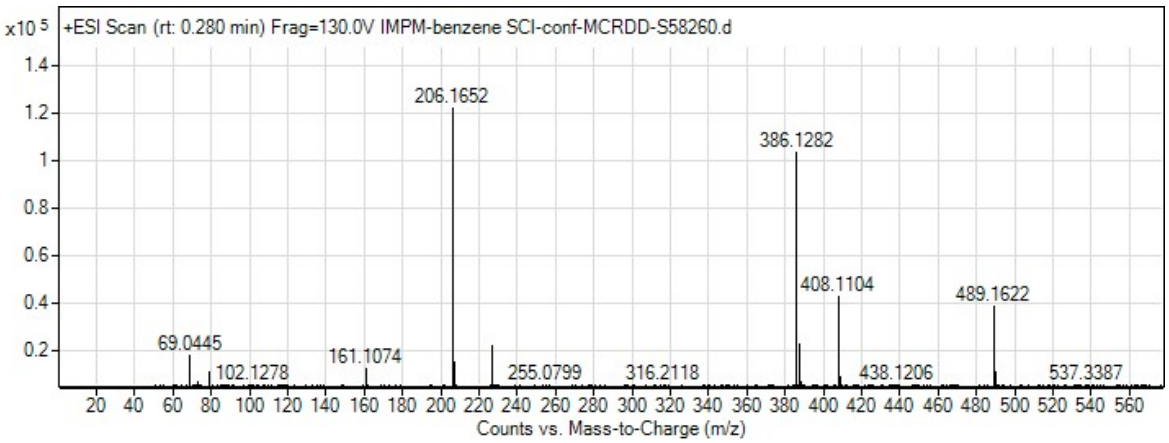
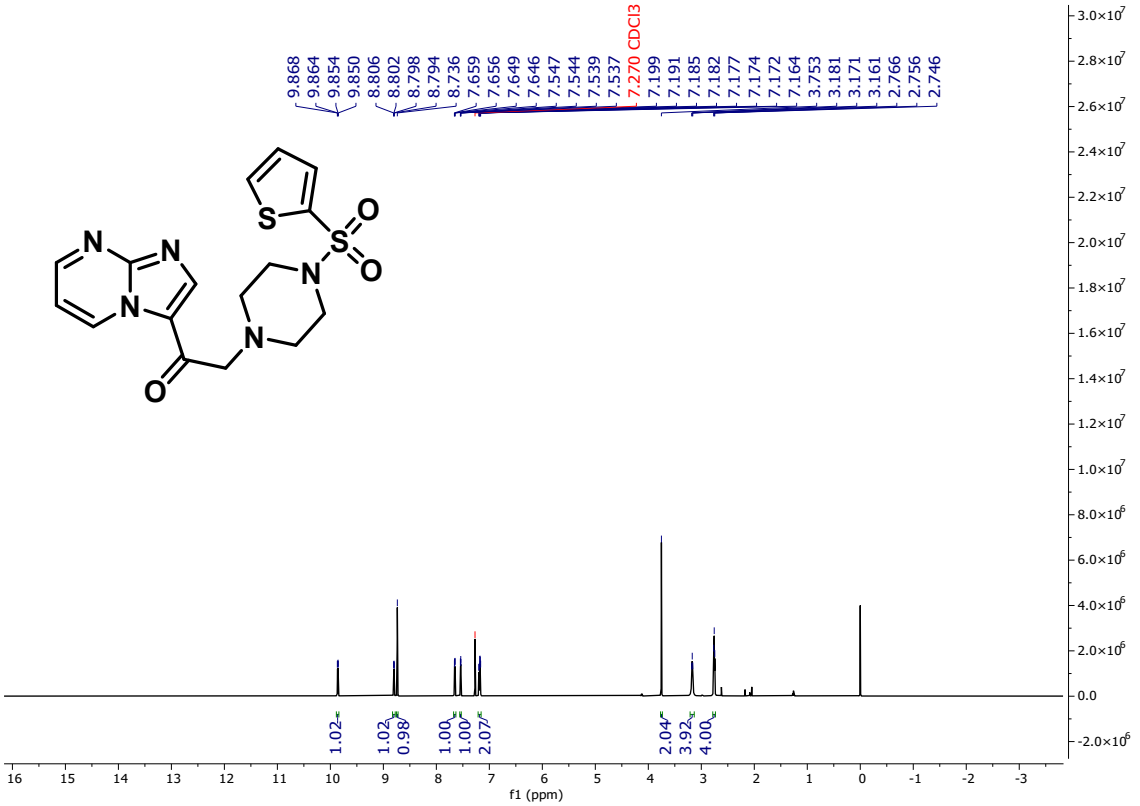
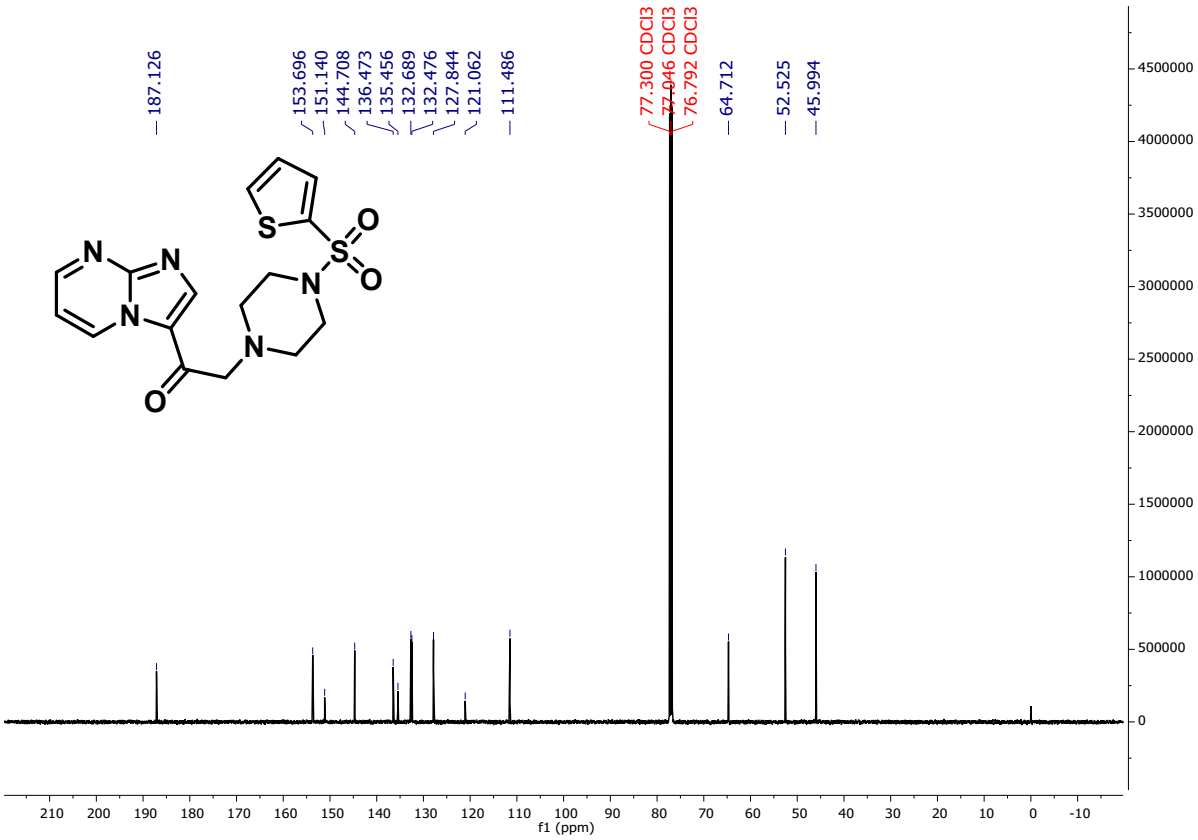


FIGURE S1: 1- (imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(phenylsulfonyl)piperazin-1-yl)ethan-1-one (9b) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

2: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)ethan-1-one (9c) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





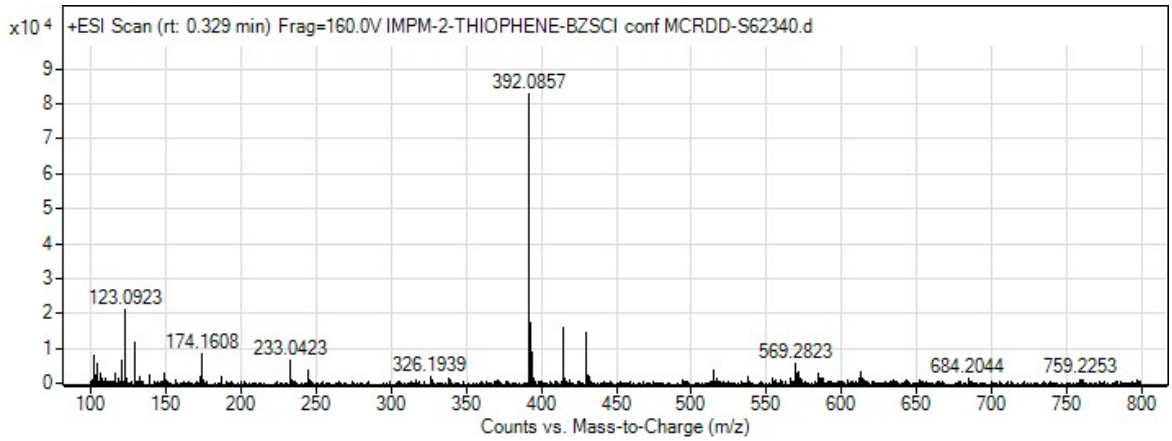
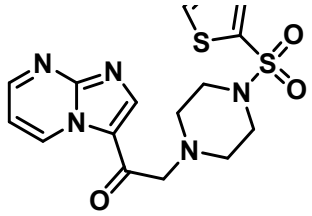
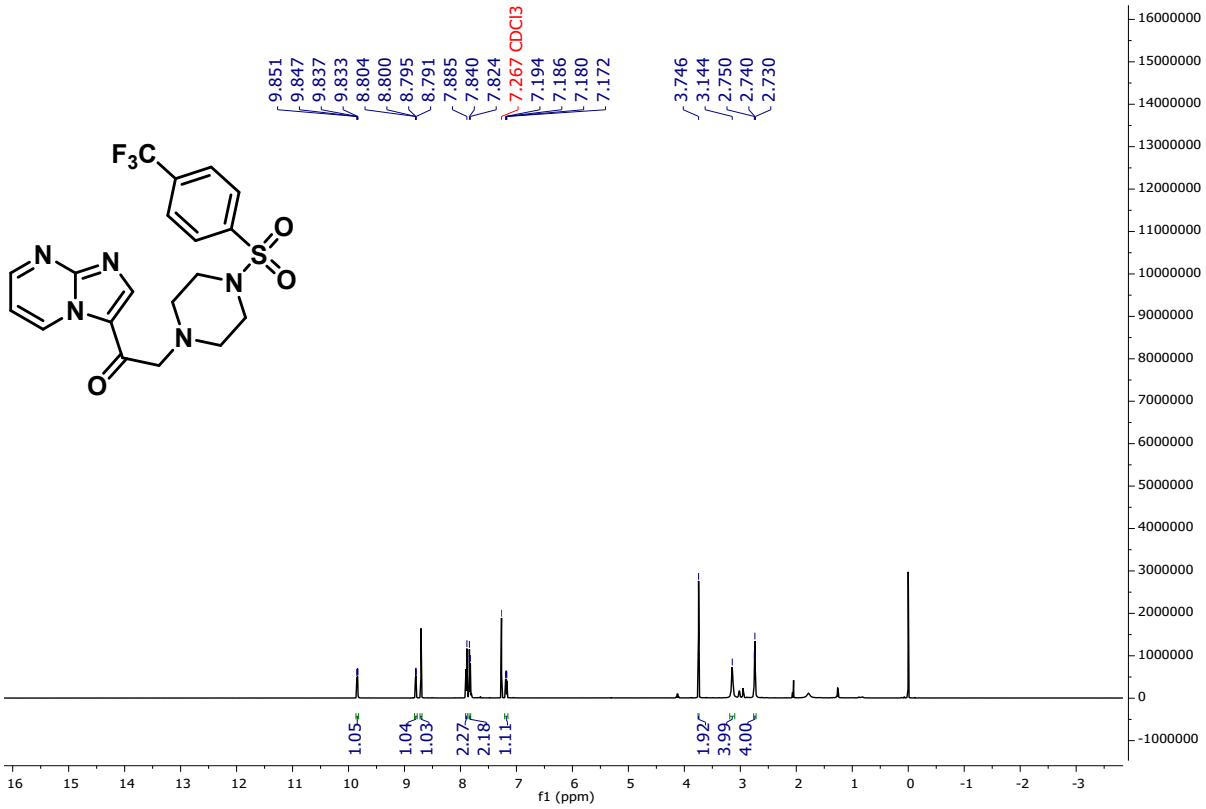
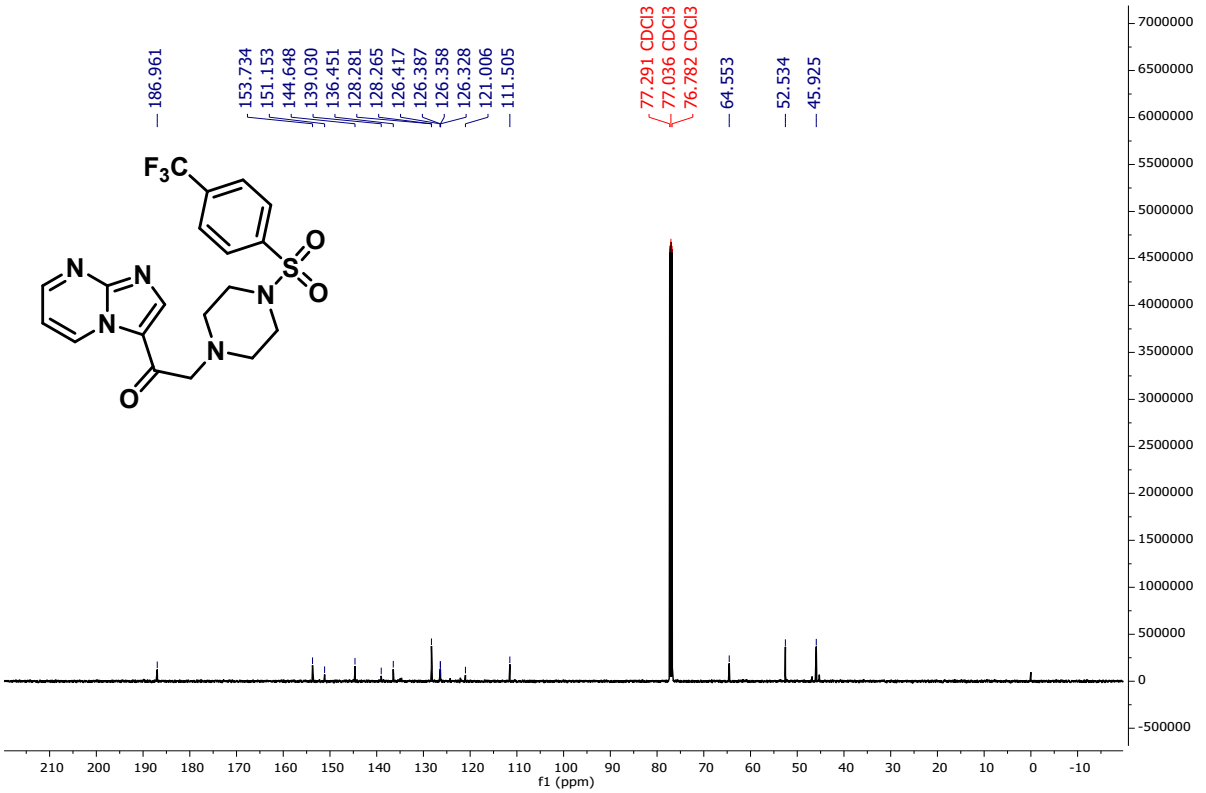


FIGURE S2: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)ethan-1-one (9c) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).



3: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9d) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)





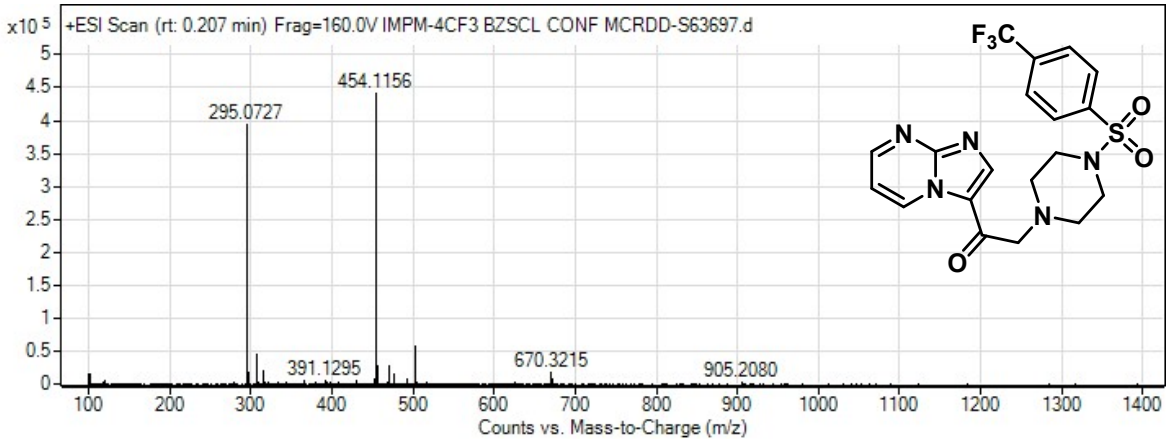
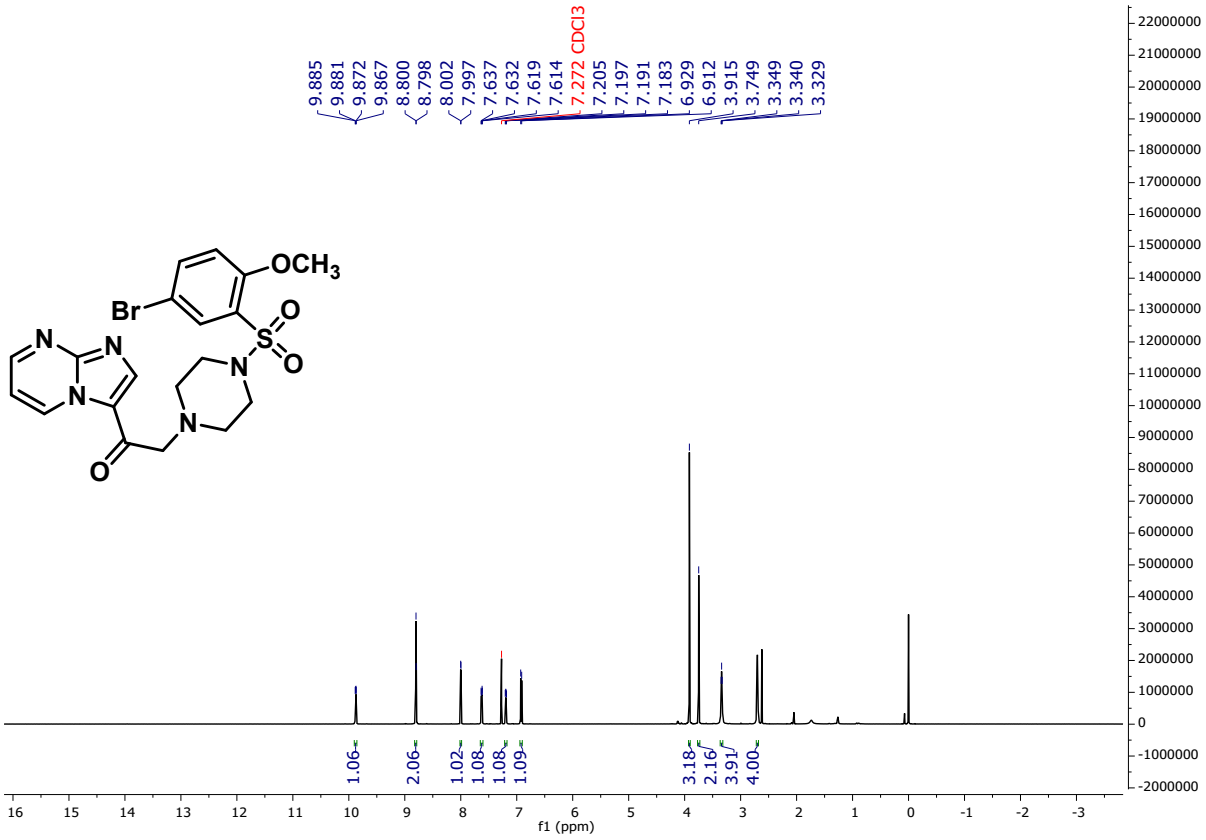
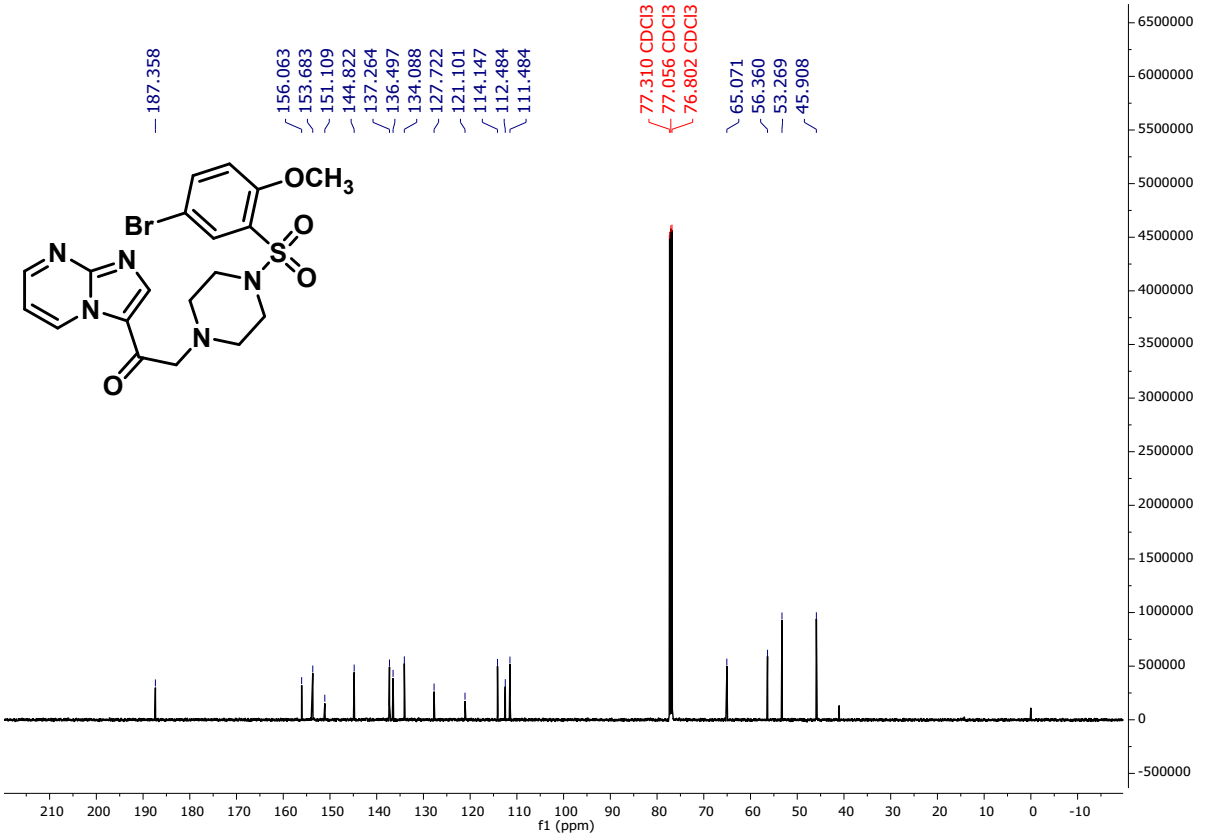


FIGURE S3: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9d) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

4: 2-(4-((5-bromo-2-methoxyphenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9j) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





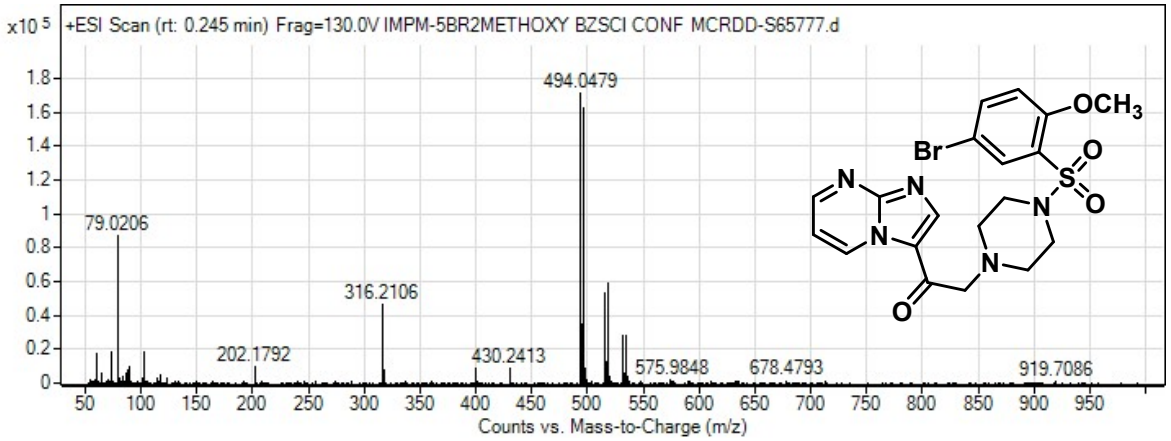
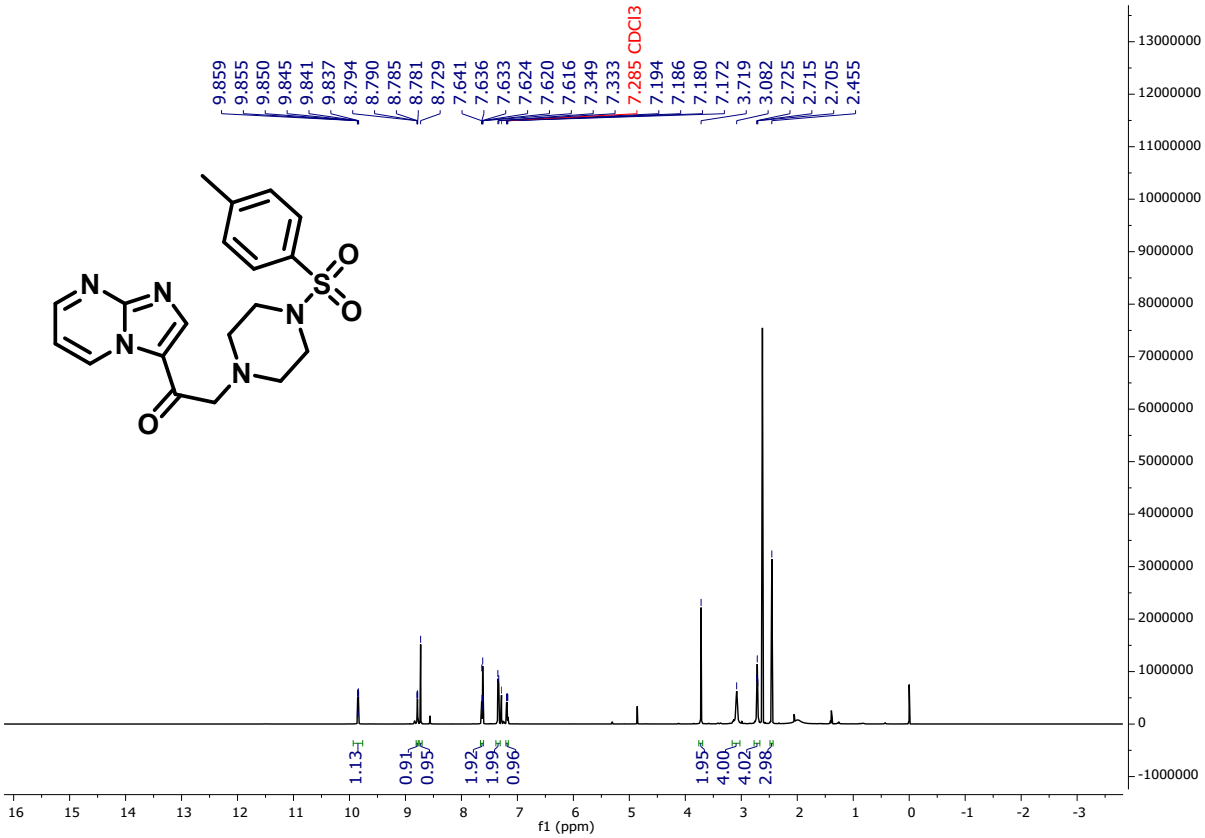
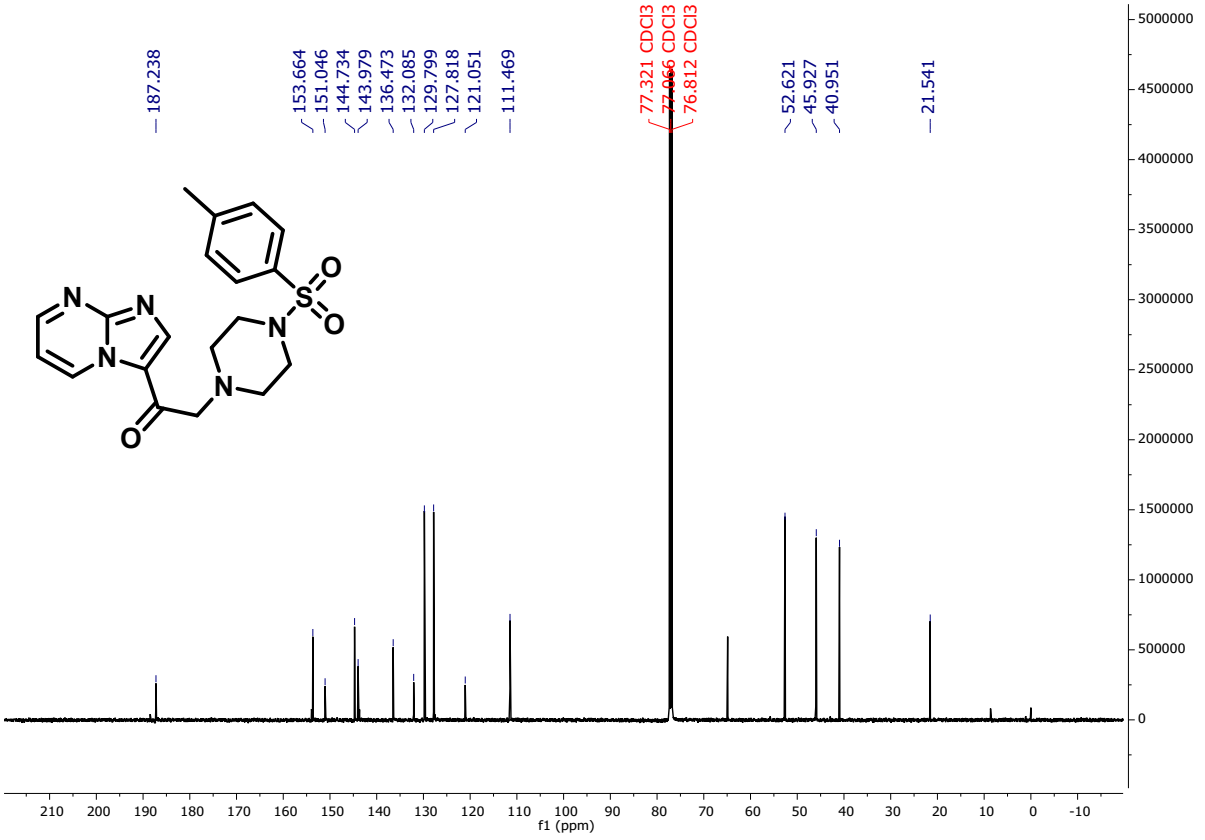


FIGURE S4: 2-(4-((5-bromo-2-methoxyphenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9j) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

5: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-tosylpiperazin-1-yl)ethan-1-one (9a) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





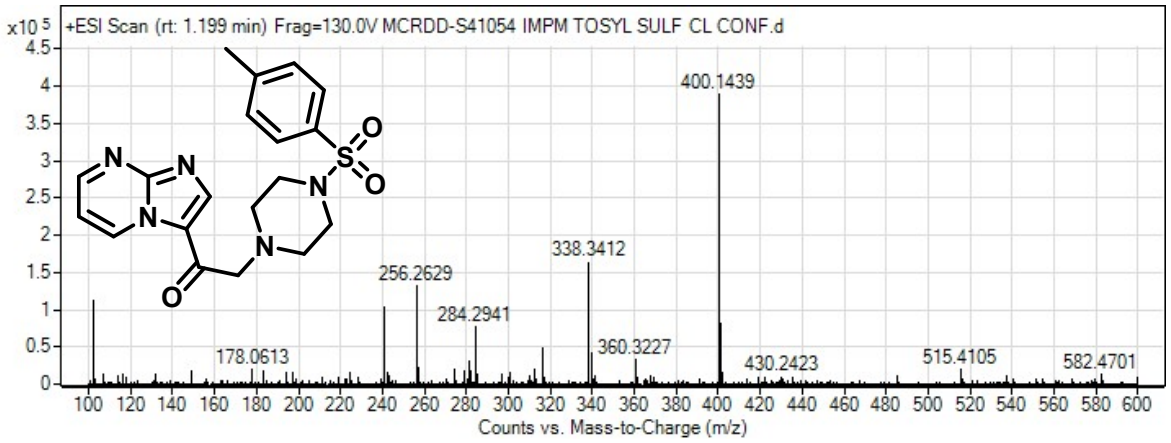
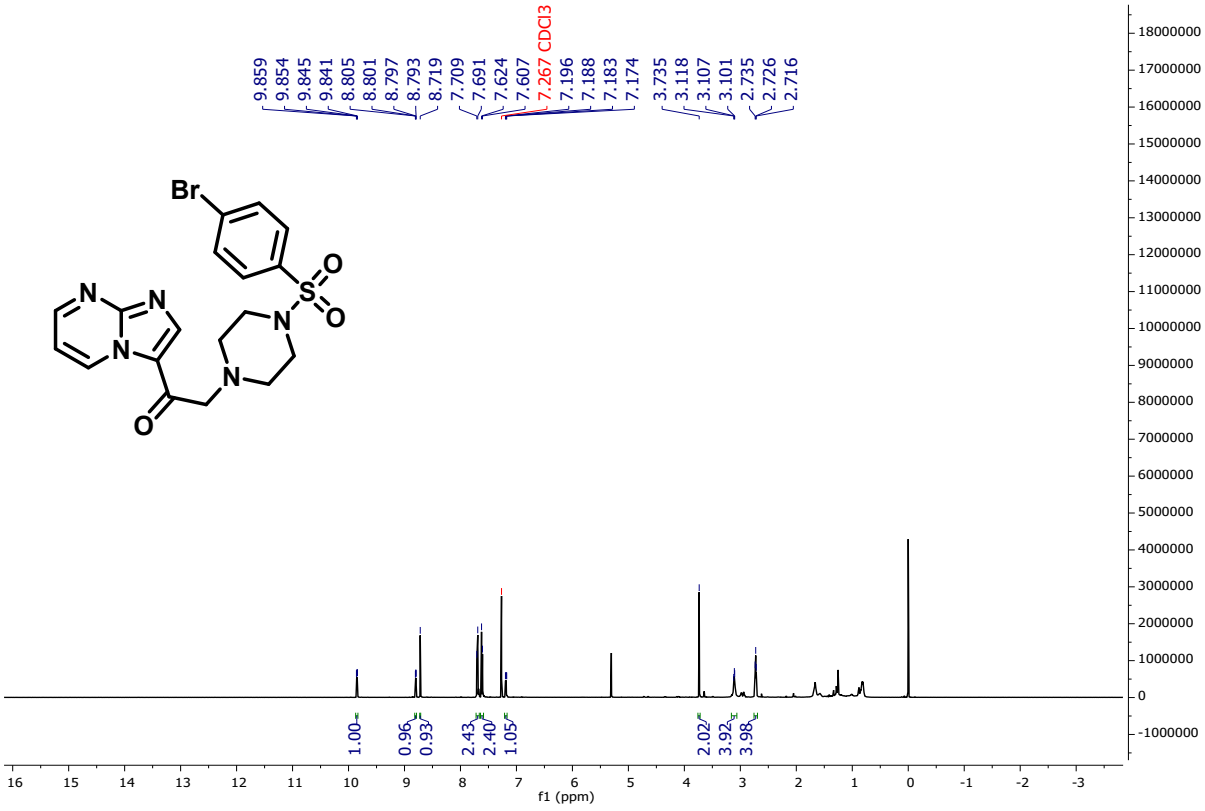
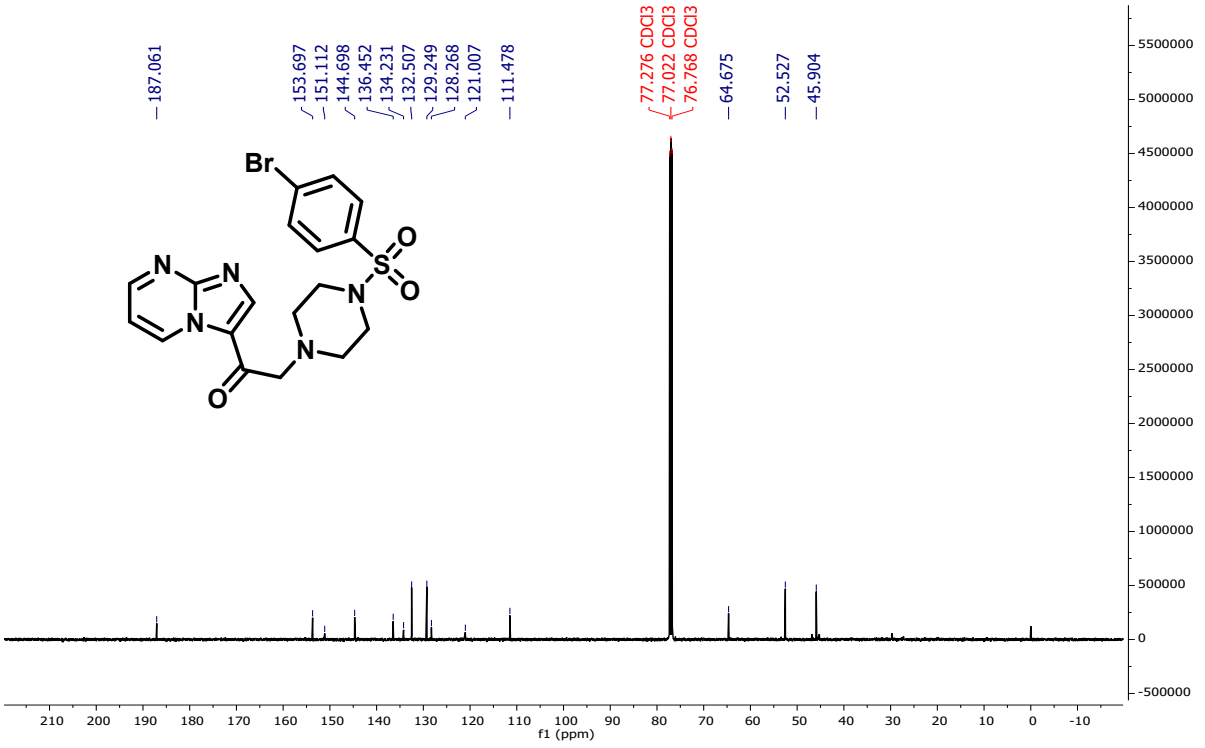


FIGURE S5: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-tosylpiperazin-1-yl)ethan-1-one (9a) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

6: 2-(4-((4-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9e)

(^{1}H NMR, ^{13}C NMR & HRMS Spectra)





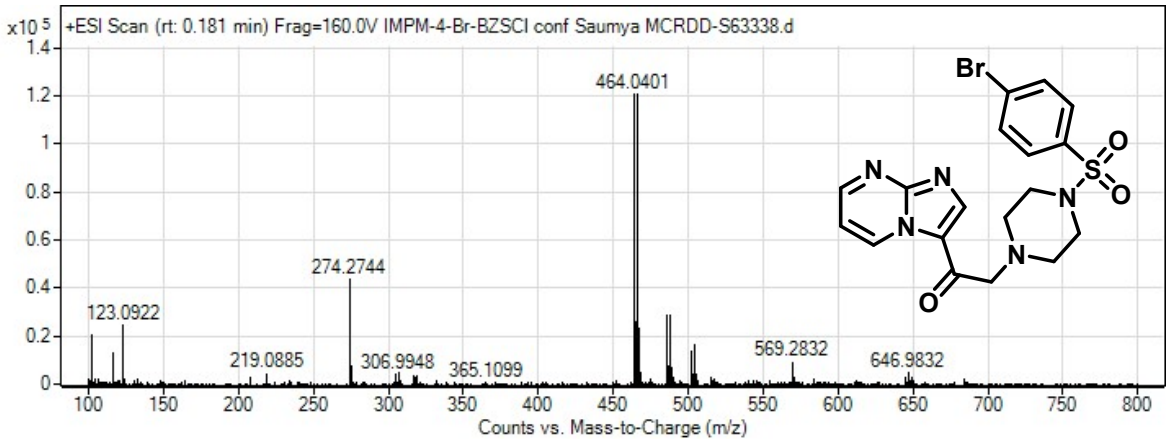
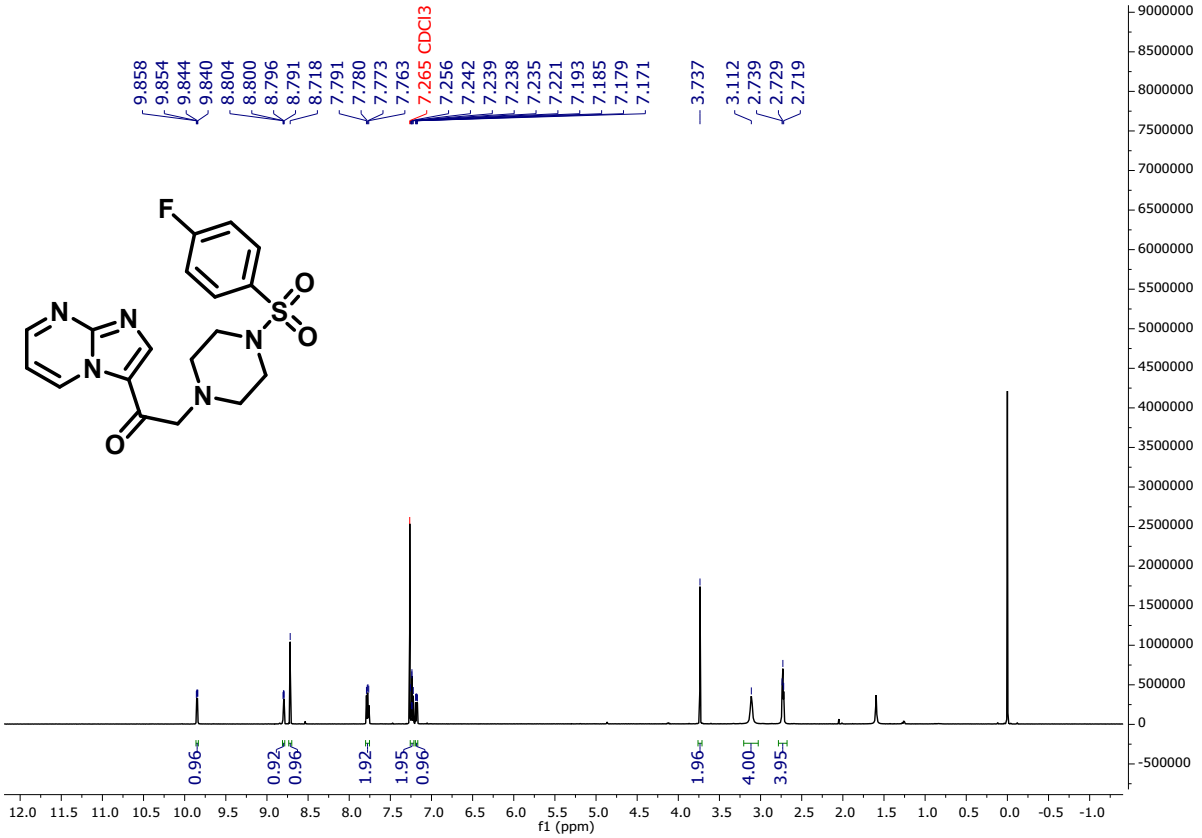
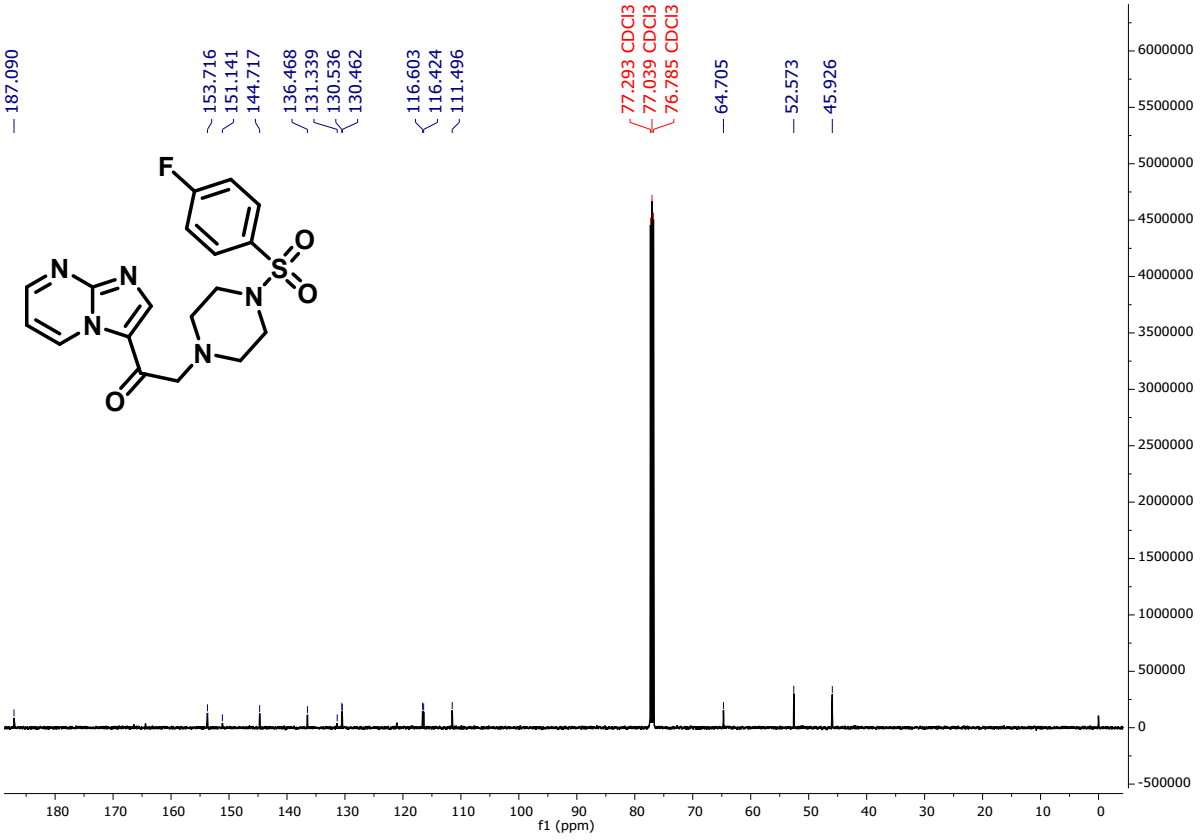


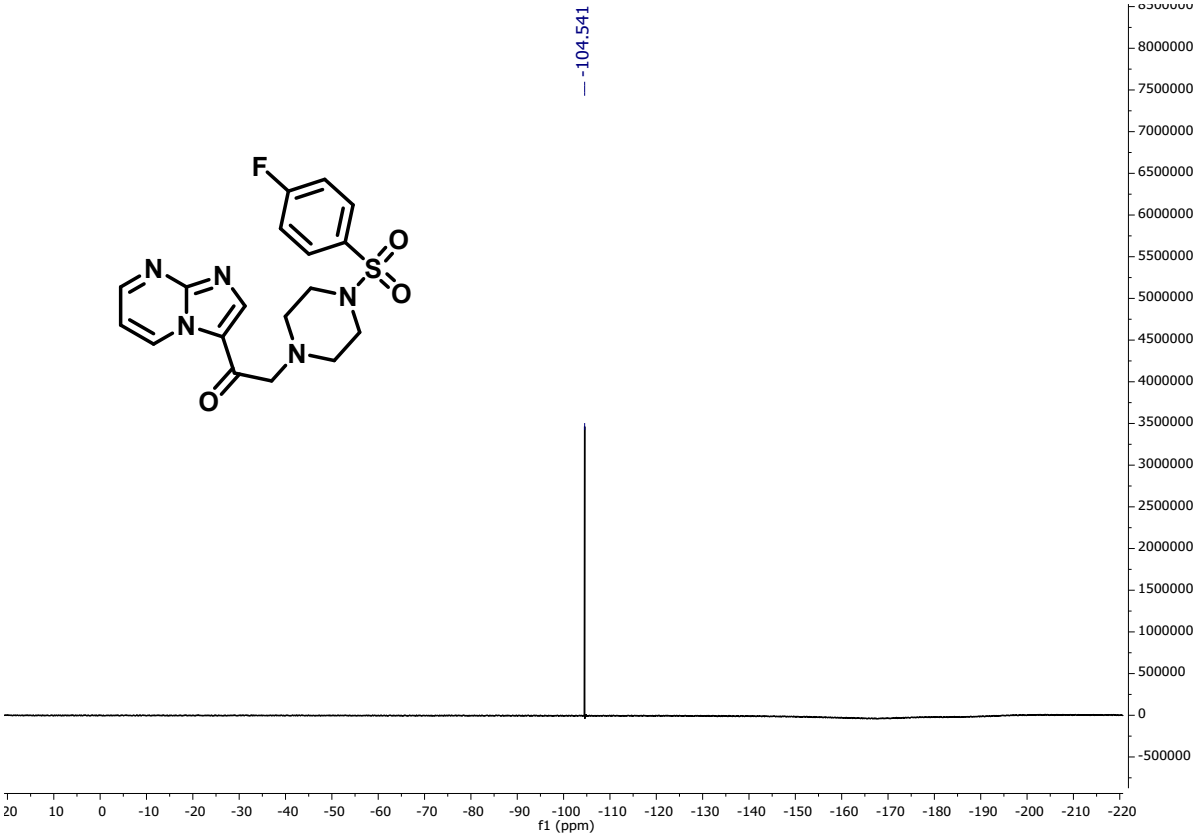
FIGURE S6: 2-(4-((4-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9e) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

7: 2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9f)

(^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)







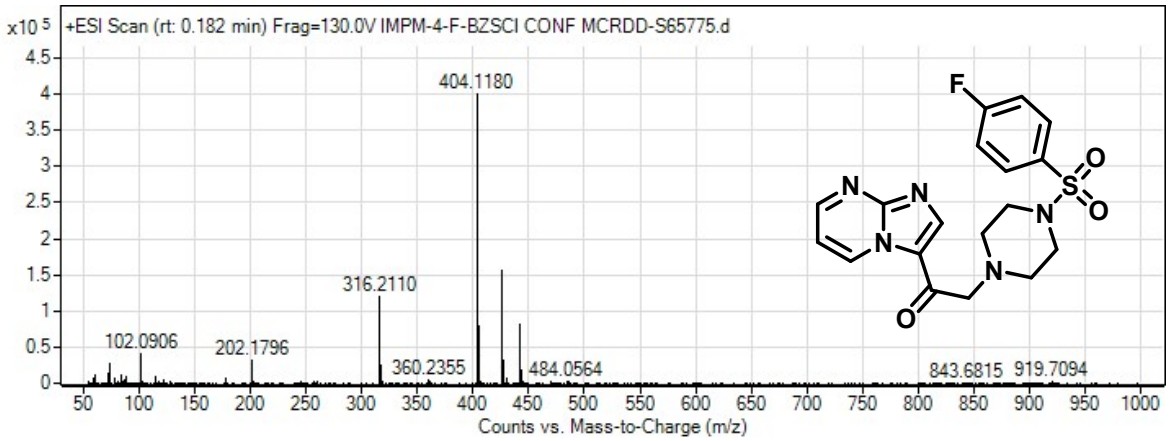
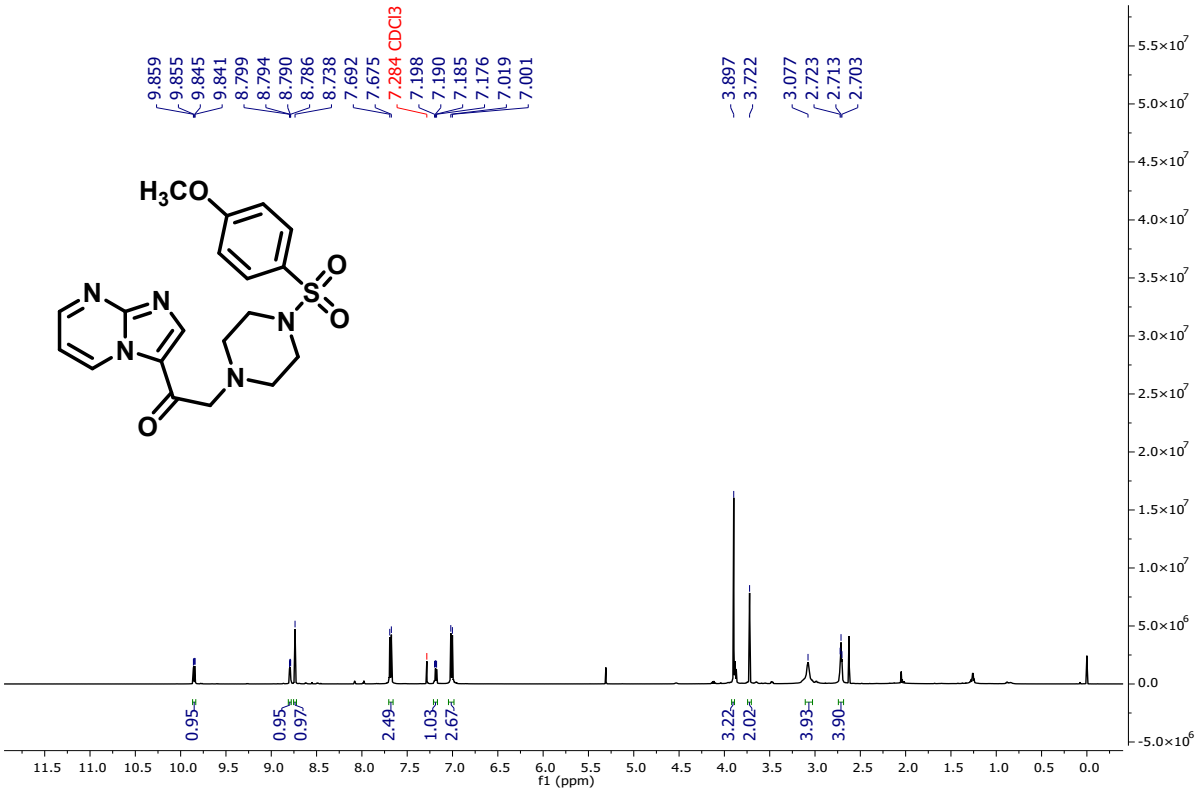
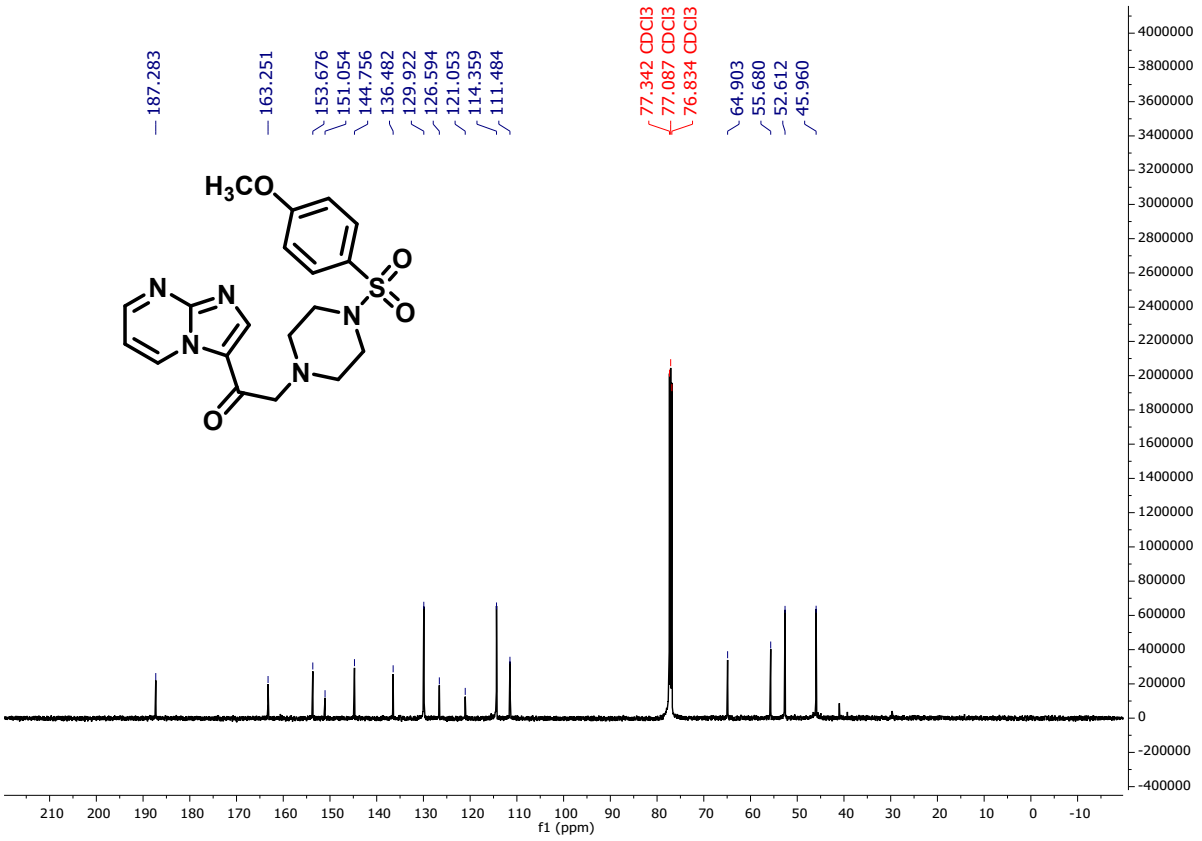


FIGURE S7: 2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9f) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

8: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9g) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





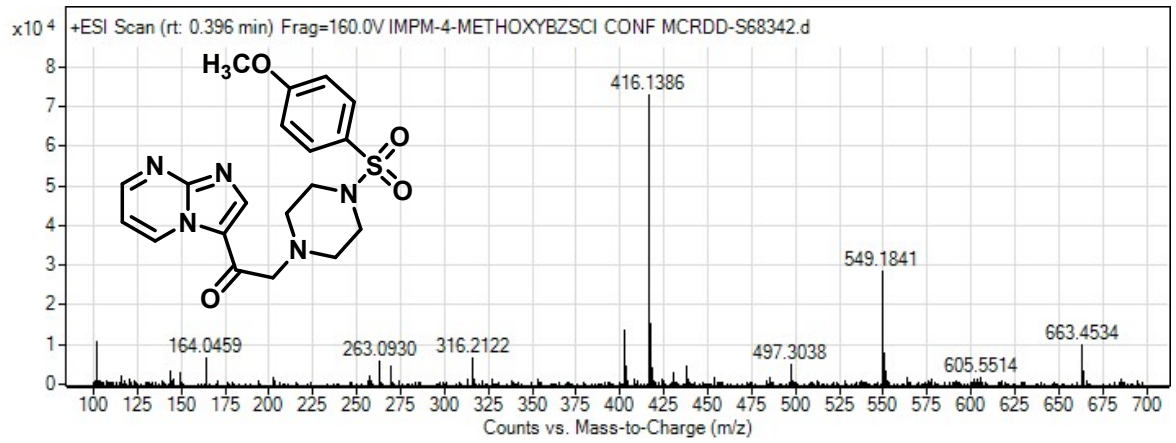
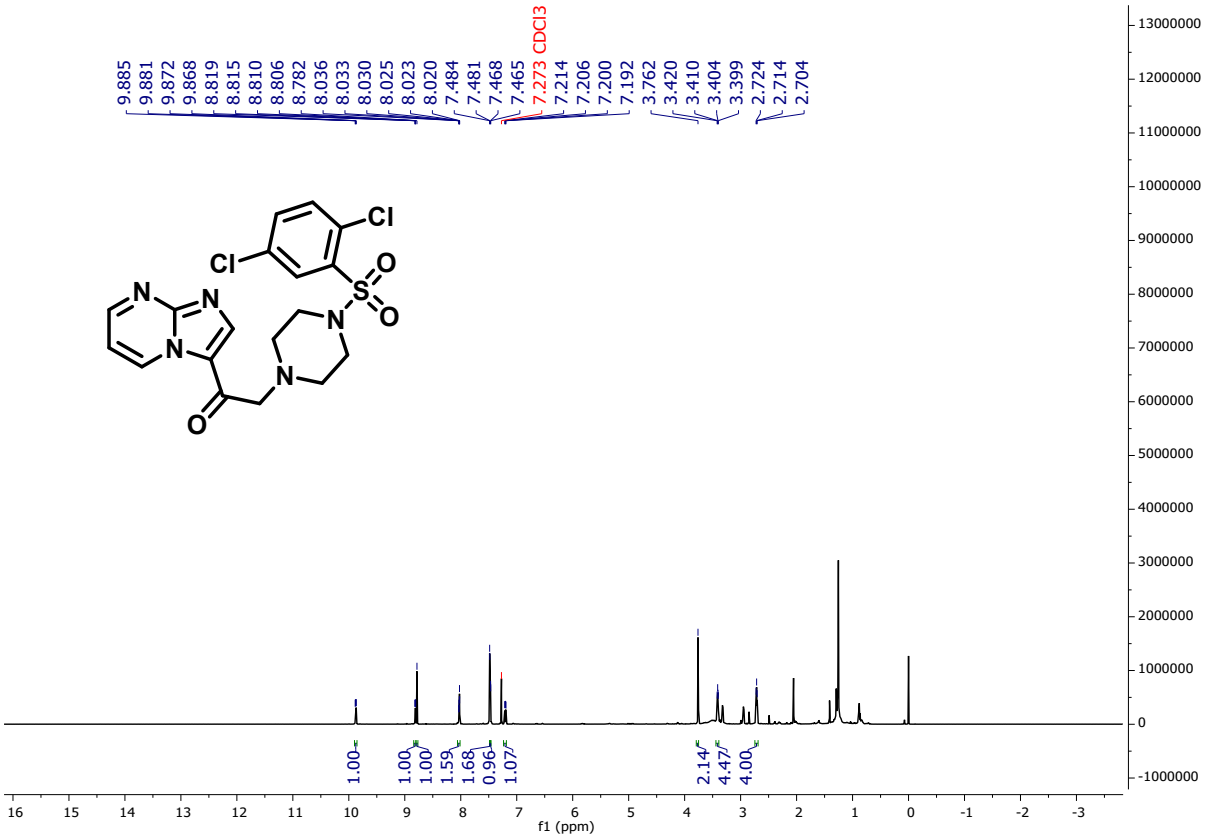
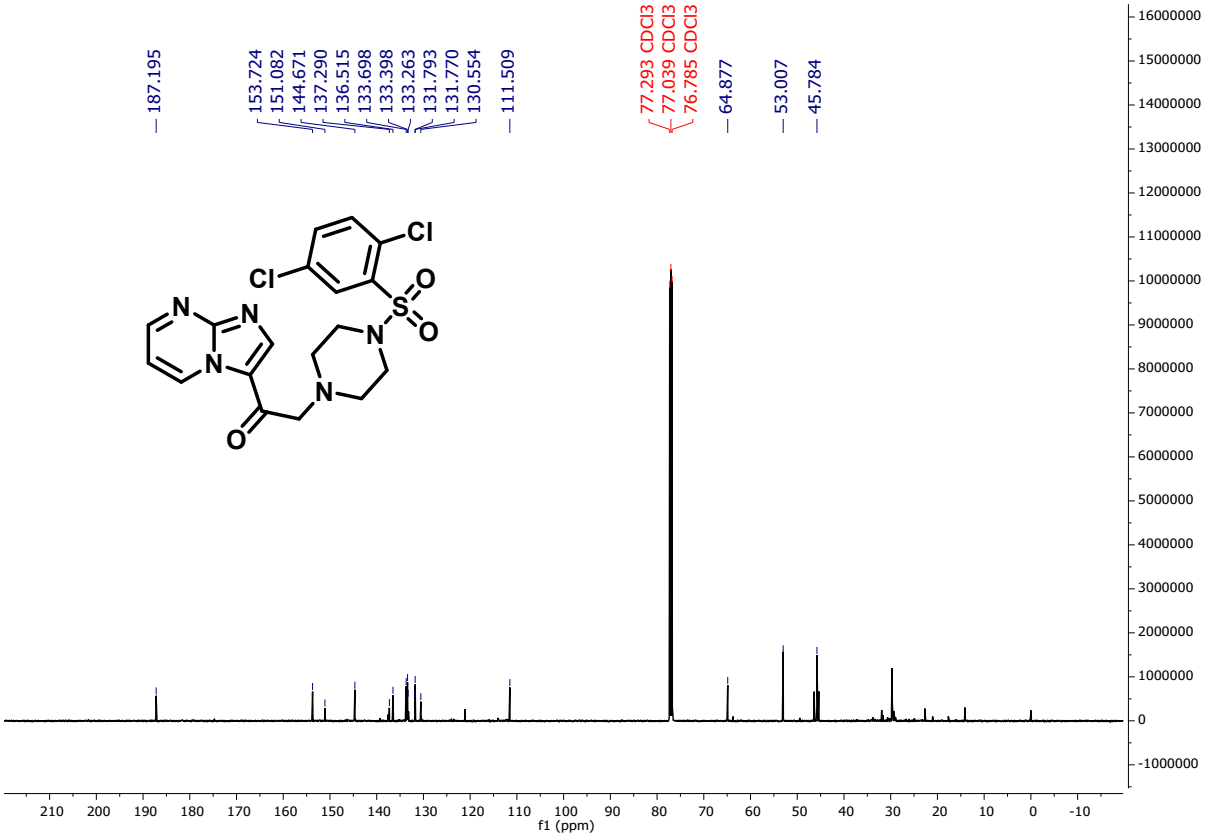


FIGURE S8: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9g) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

9: 2-(4-((2,5-dichlorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9h) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





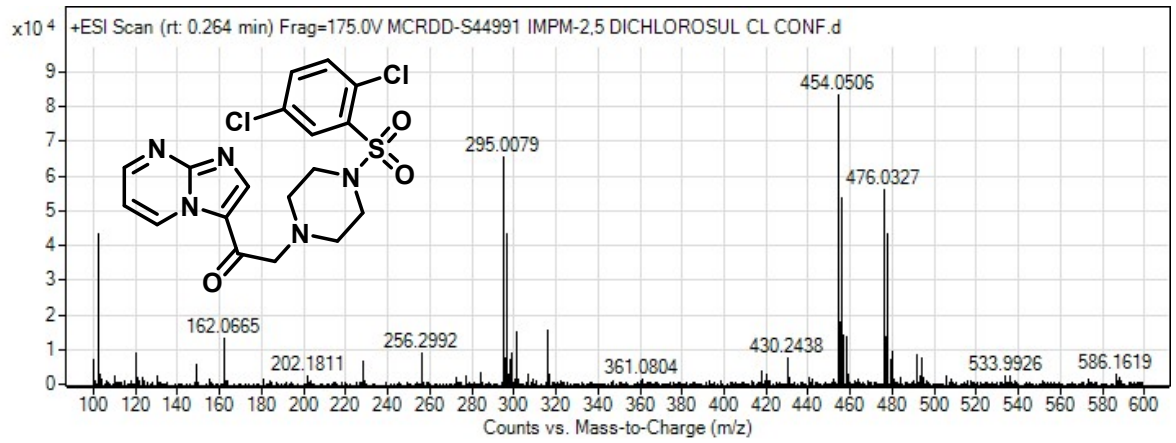
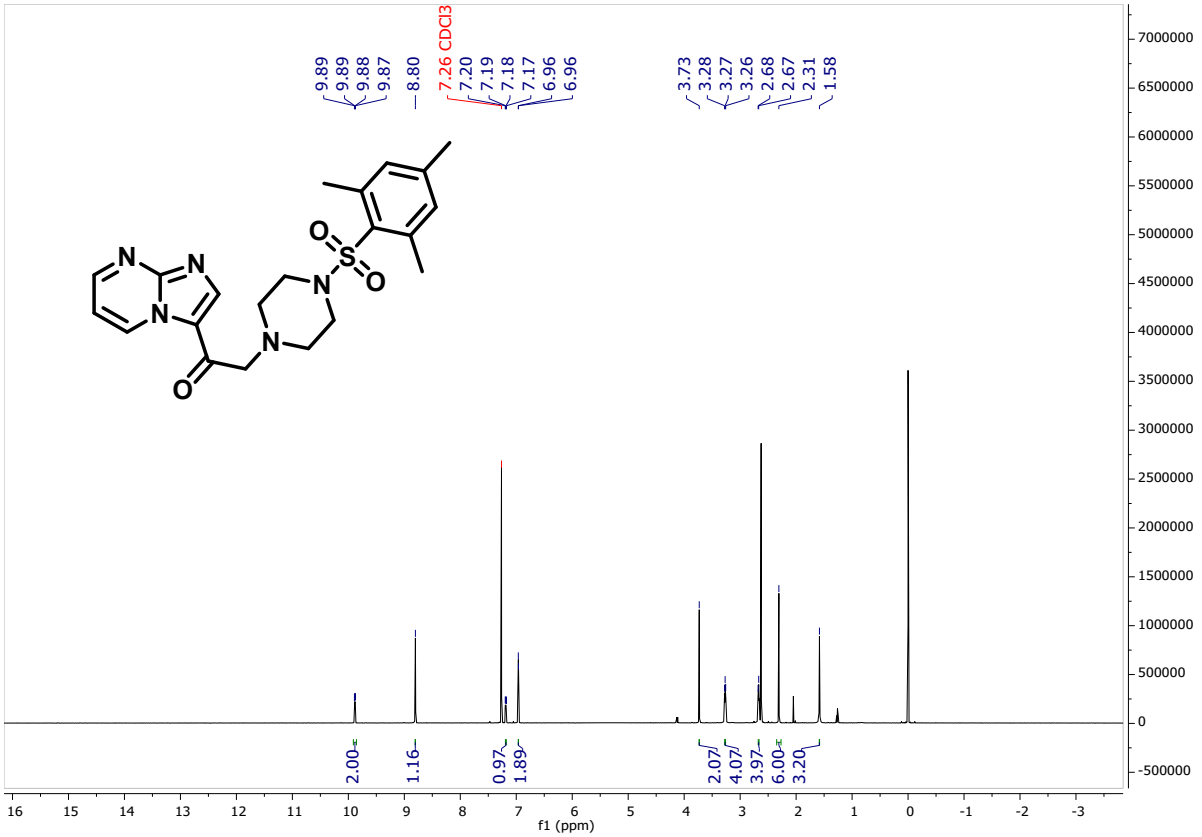
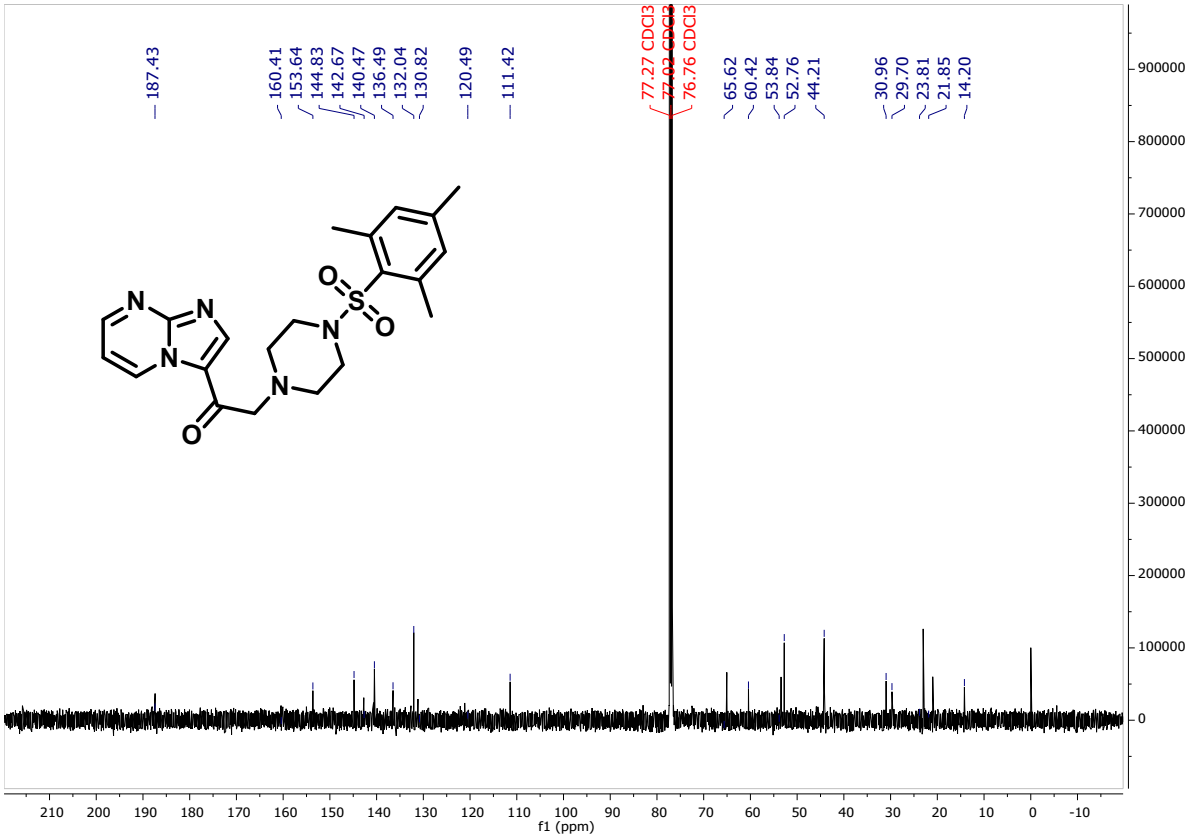


FIGURE S9: 2-(4-((2,5-dichlorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9h) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

10: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(mesitylsulfonyl)piperazin-1-yl)ethan-1-one (9i) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





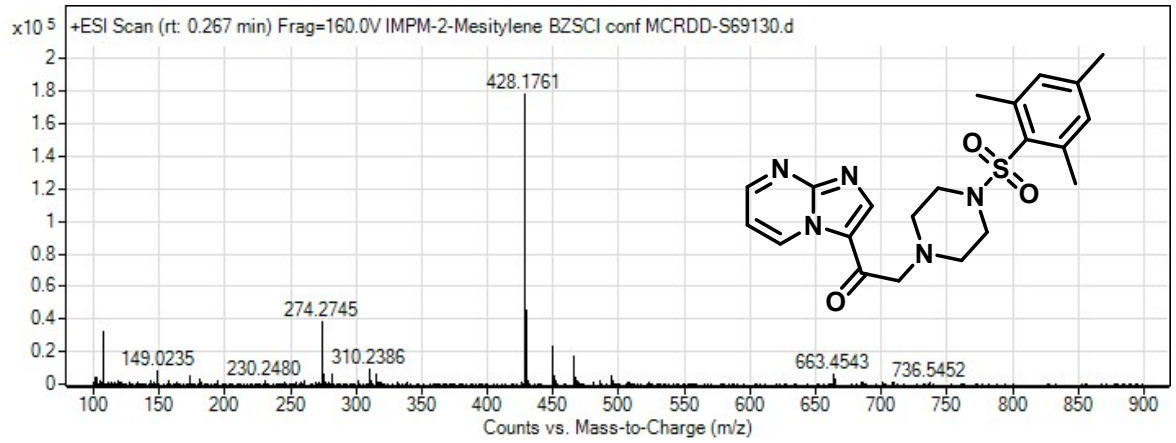
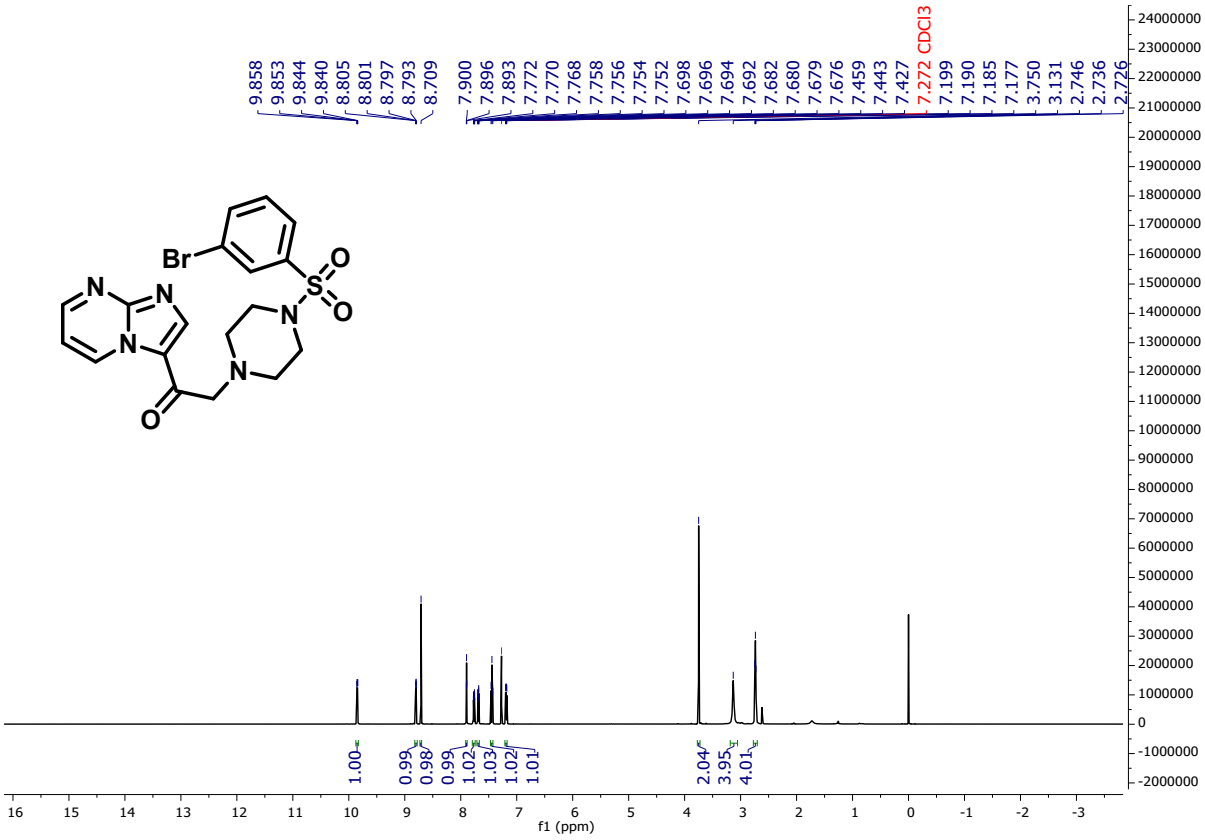
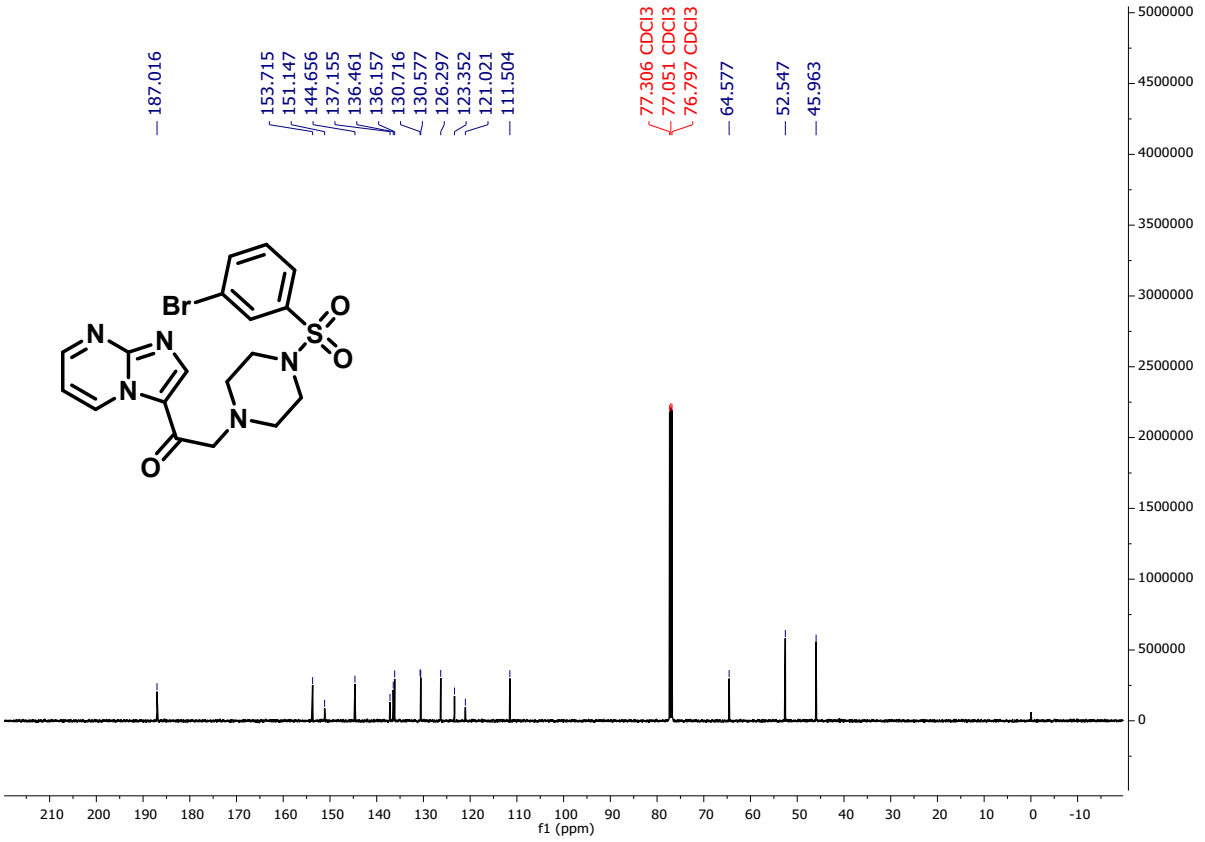


FIGURE S10: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-(mesitylsulfonyl)piperazin-1-yl)ethan-1-one (9i) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

11: 2-(4-((3-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9k) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





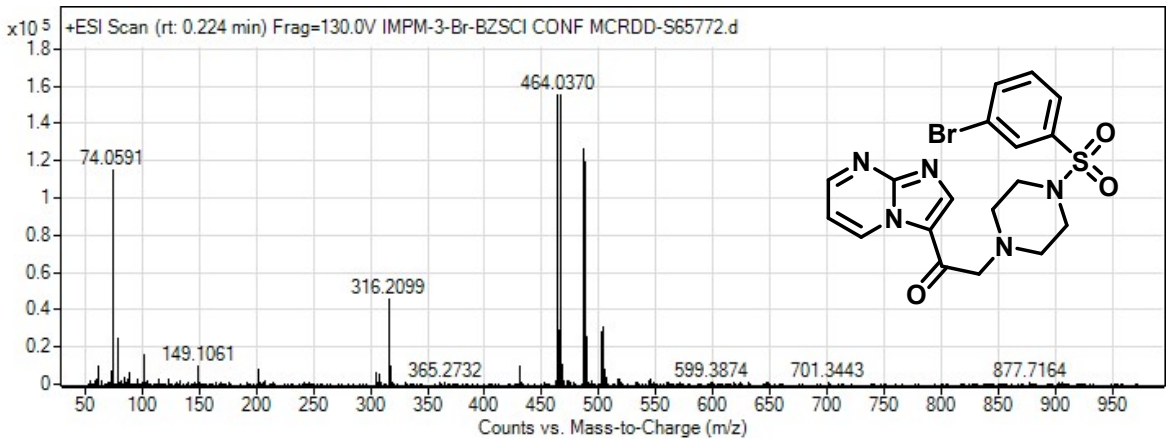
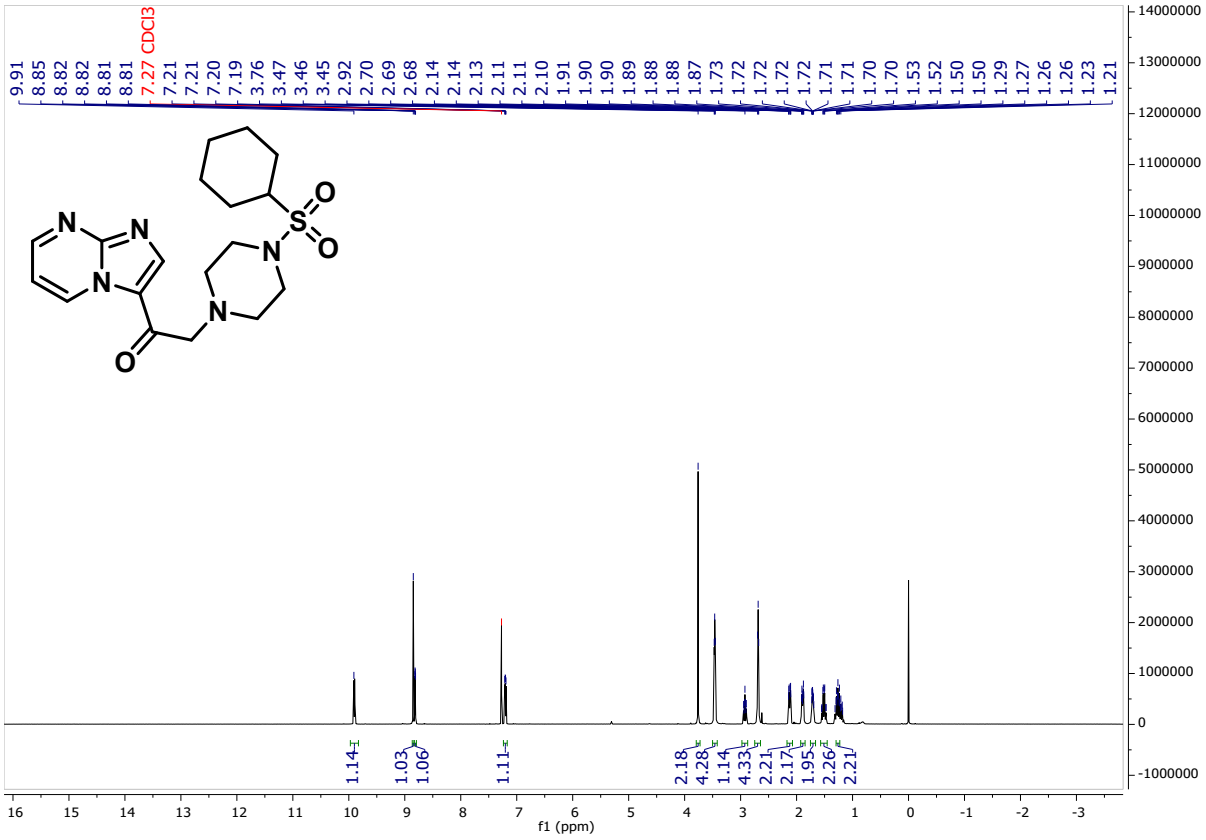
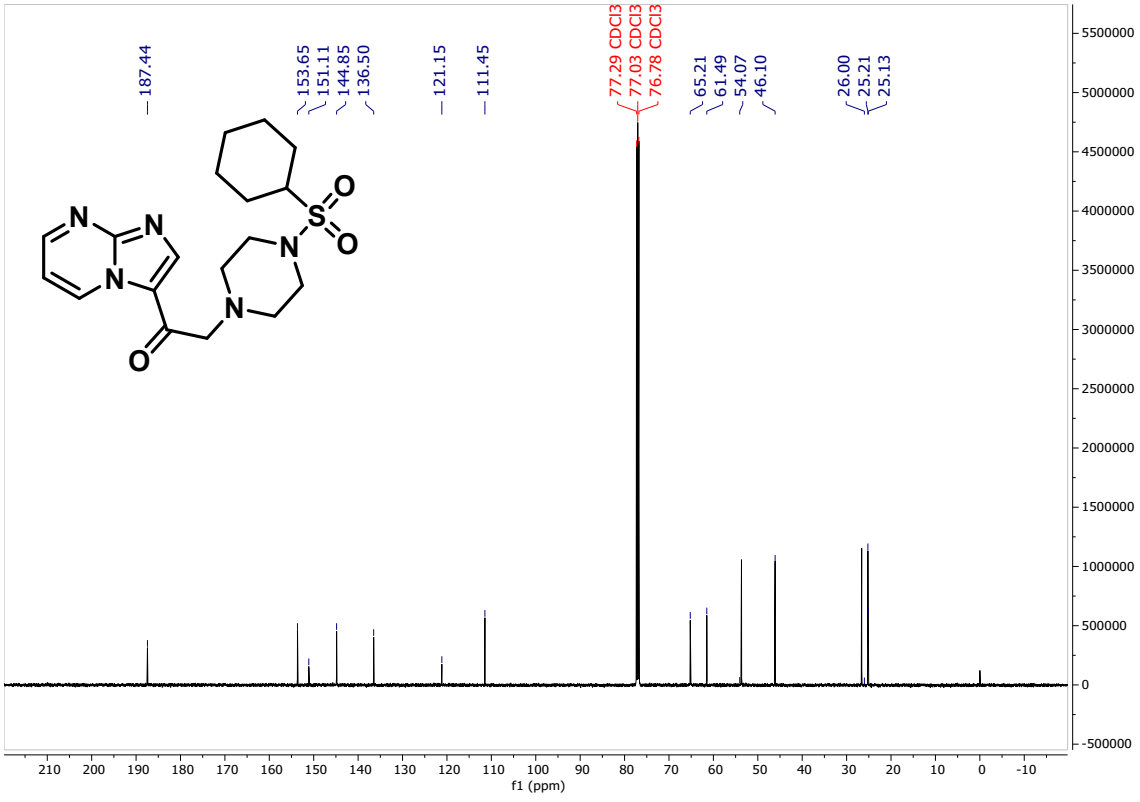


FIGURE S11: 2-(4-((3-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9k) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

12: 2-(4-(cyclohexylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9l) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





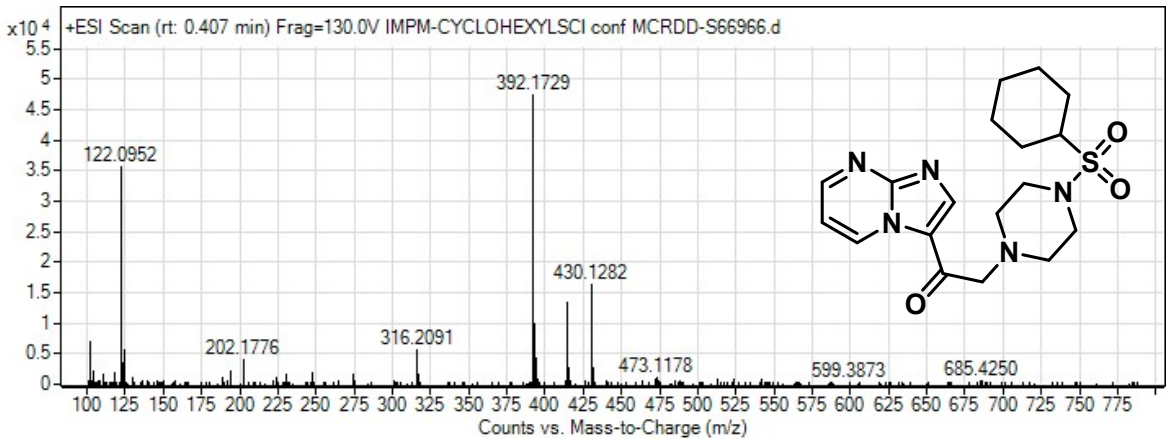
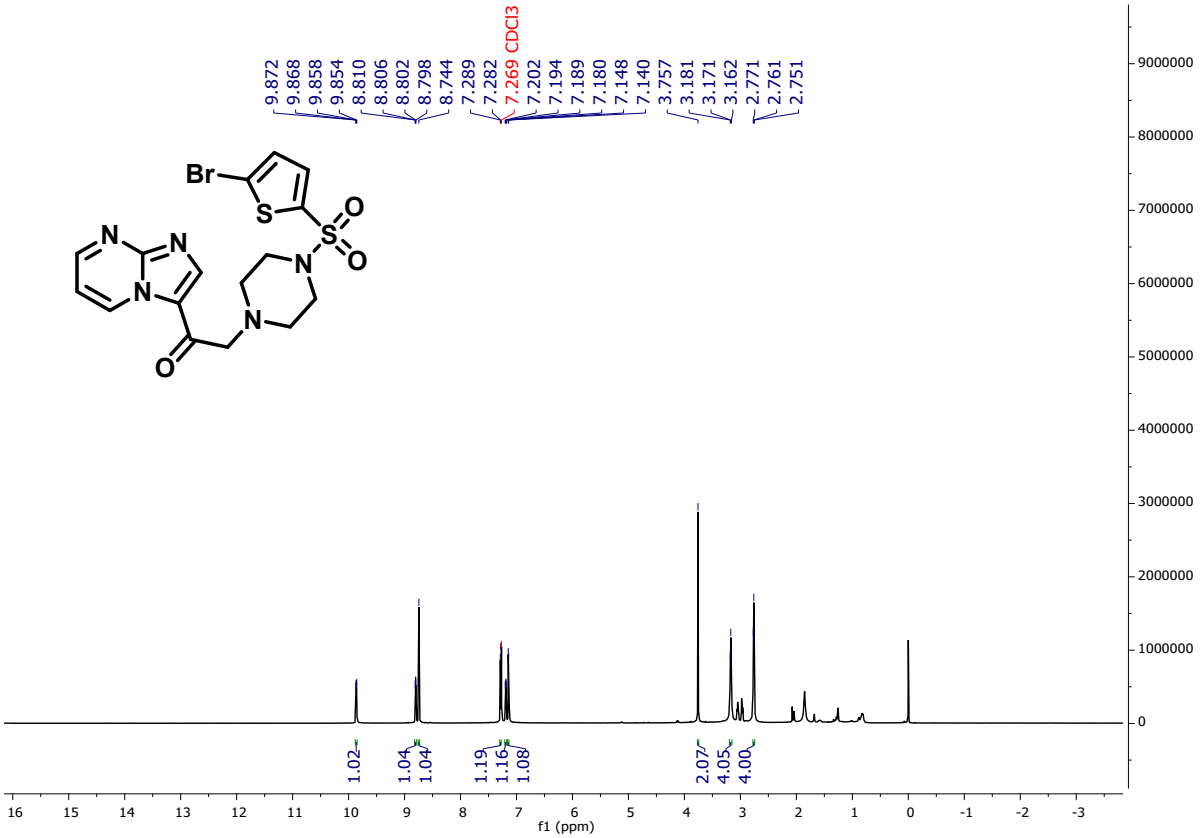
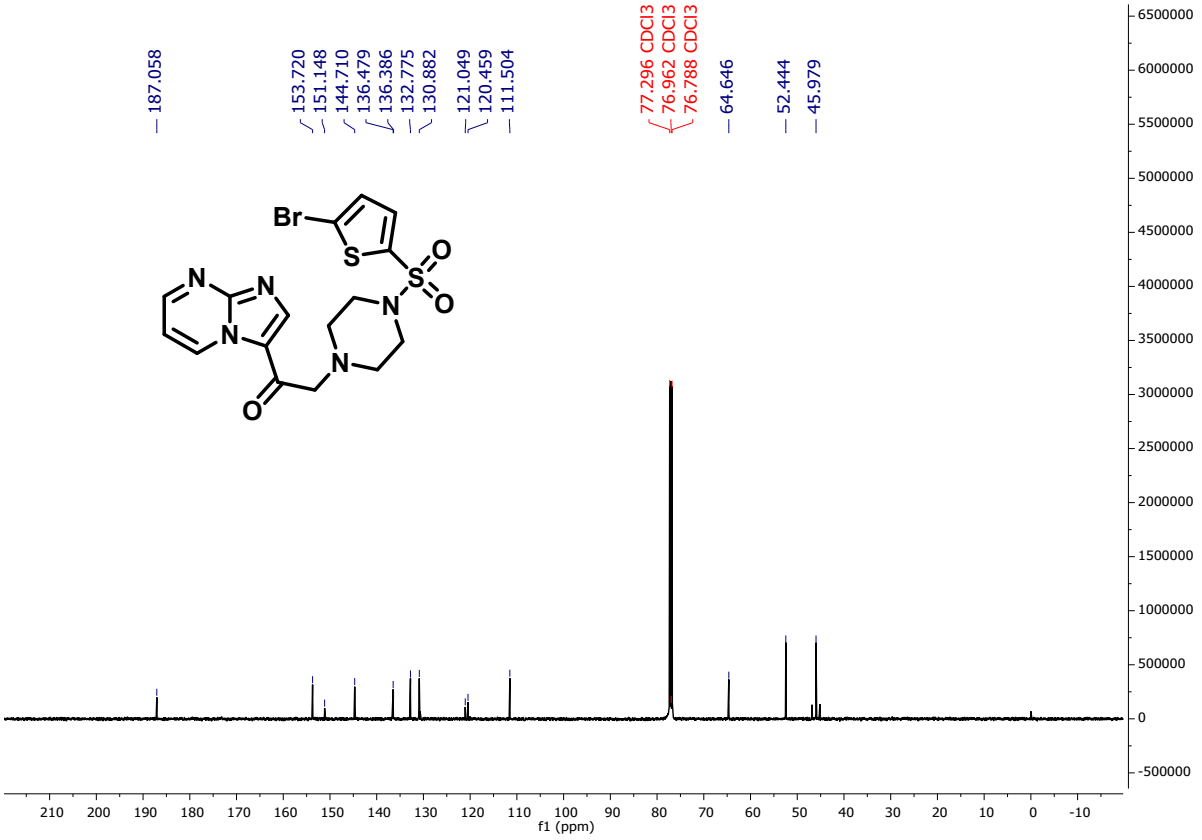


FIGURE S12: 2-(4-(cyclohexylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9l) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

13: 2-(4-((5-bromothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9m) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





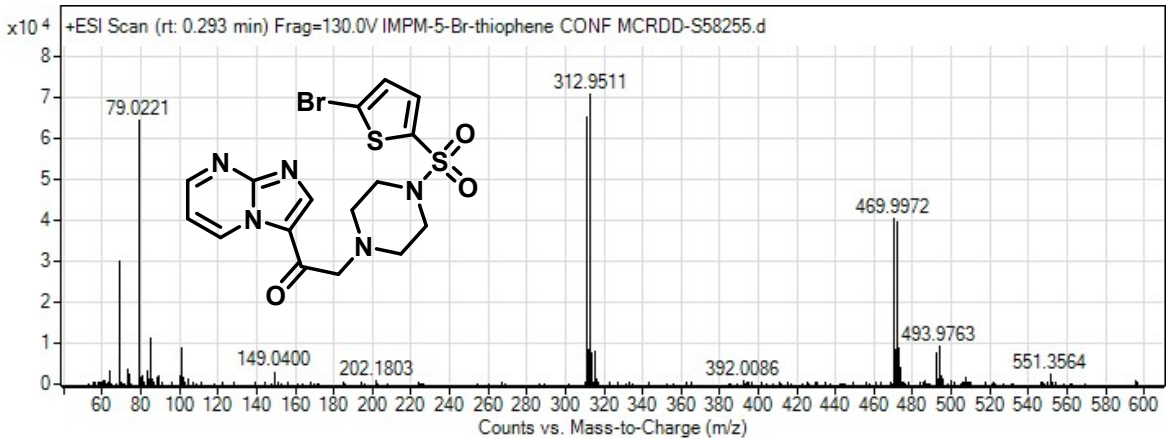
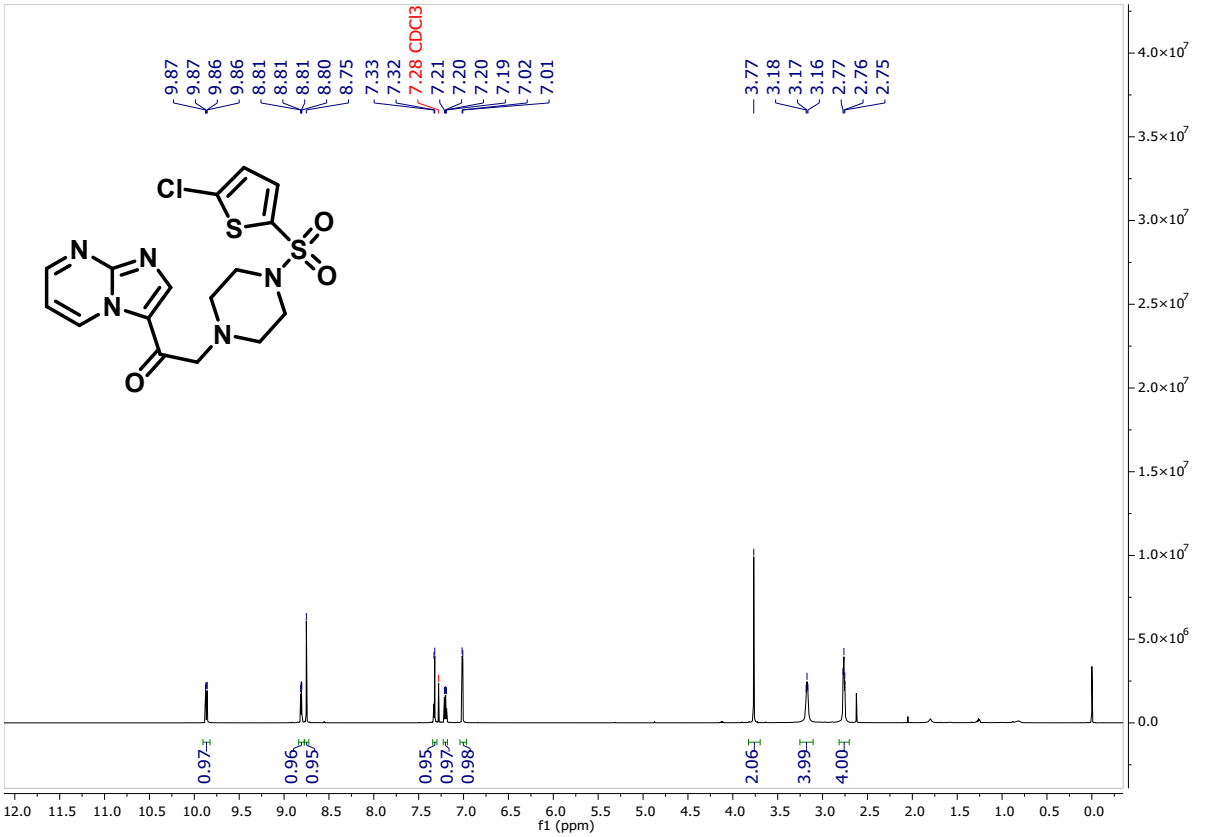
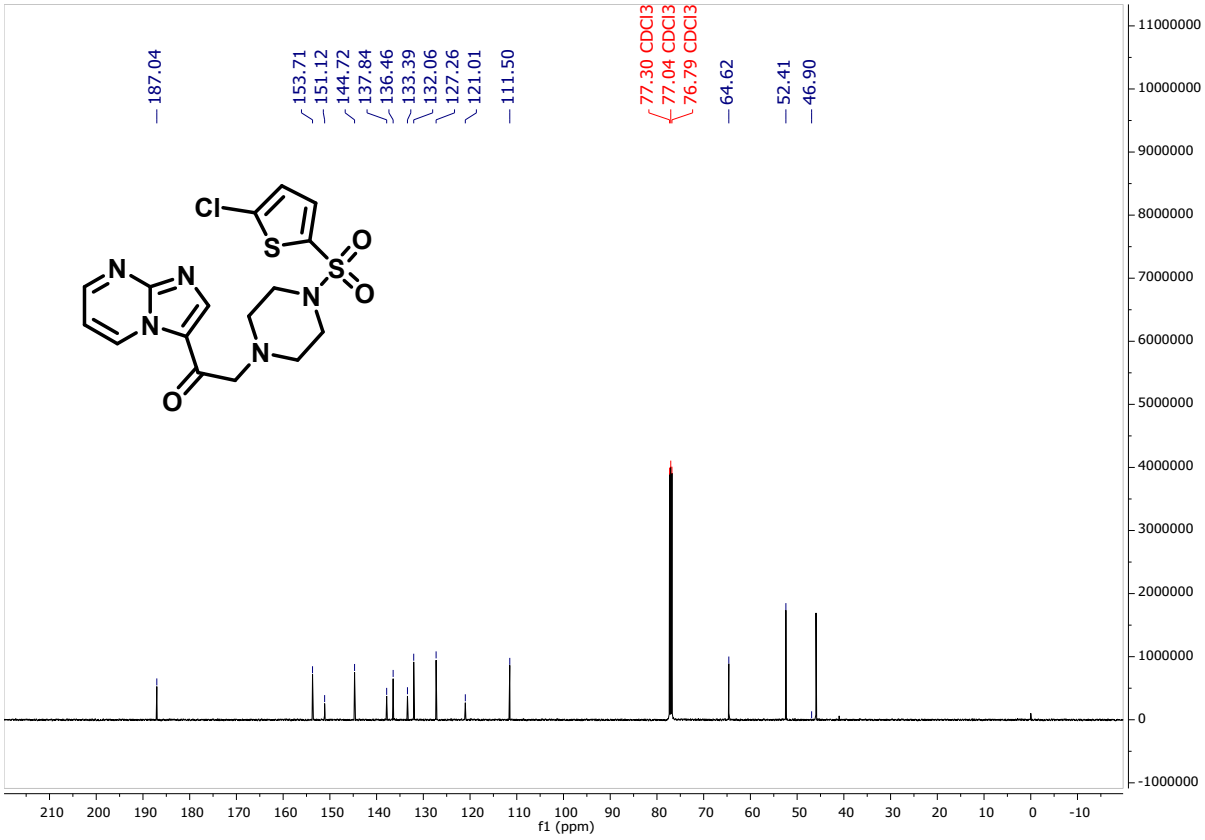


FIGURE S13: 2-(4-((5-bromothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9m) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

14: 2-(4-((5-chlorothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9q) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





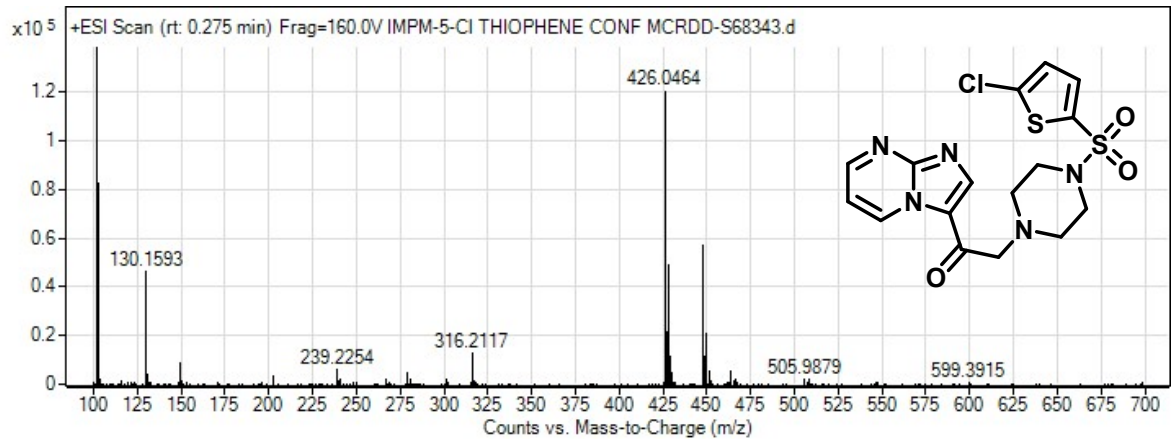
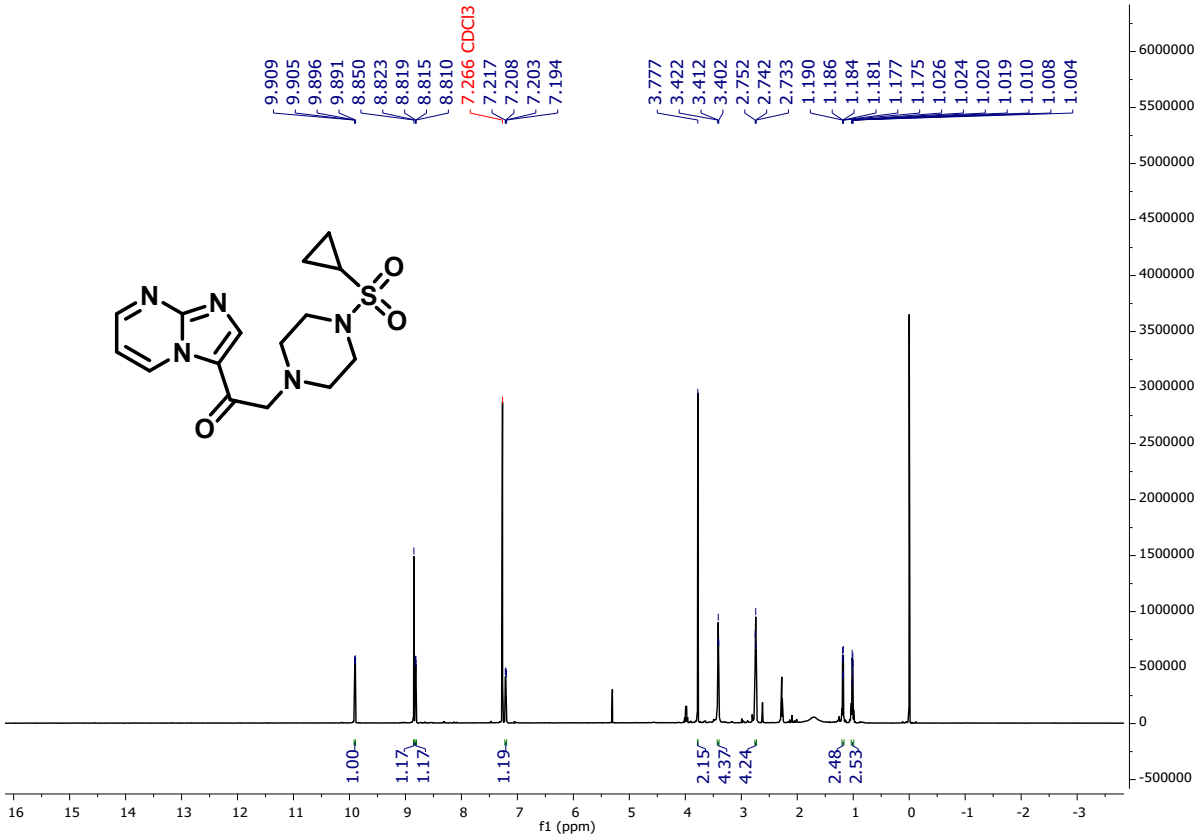
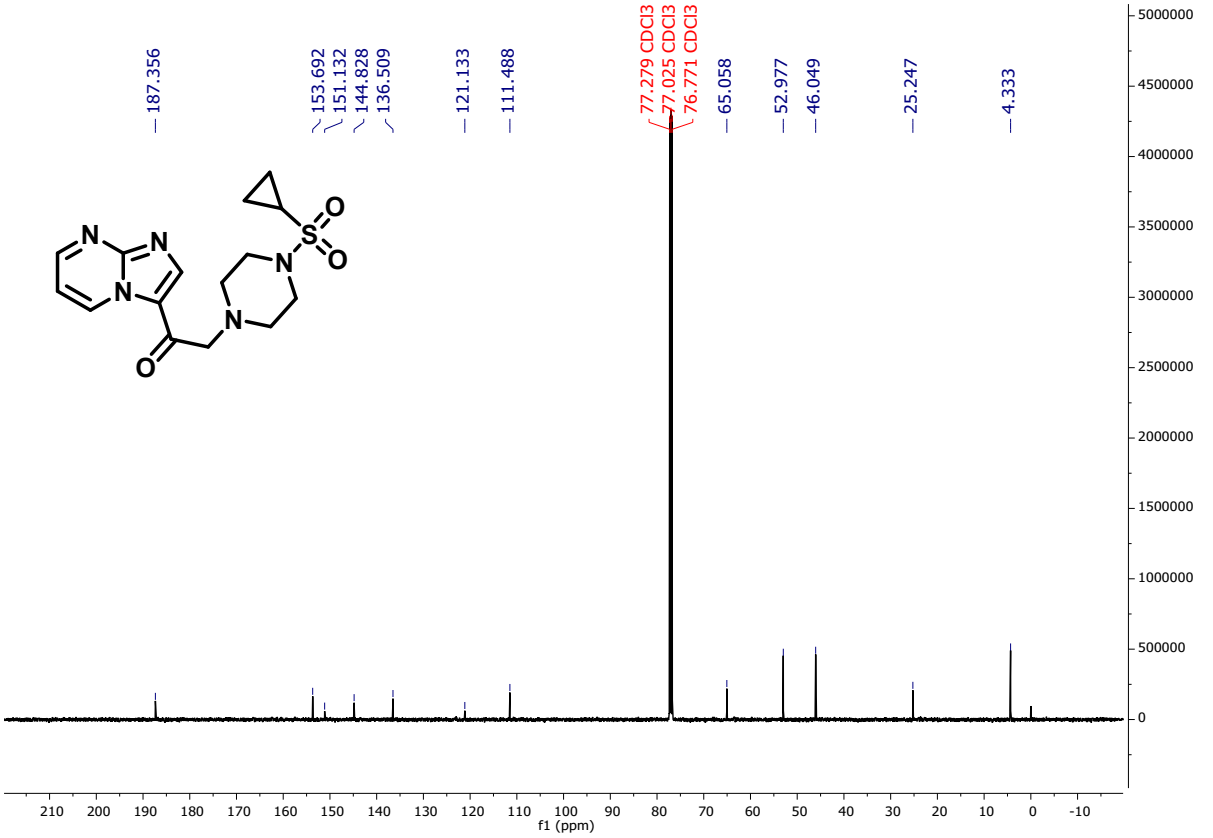


FIGURE S14: 2-(4-((5-chlorothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9q) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

15: 2-(4-(cyclopropylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9n) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





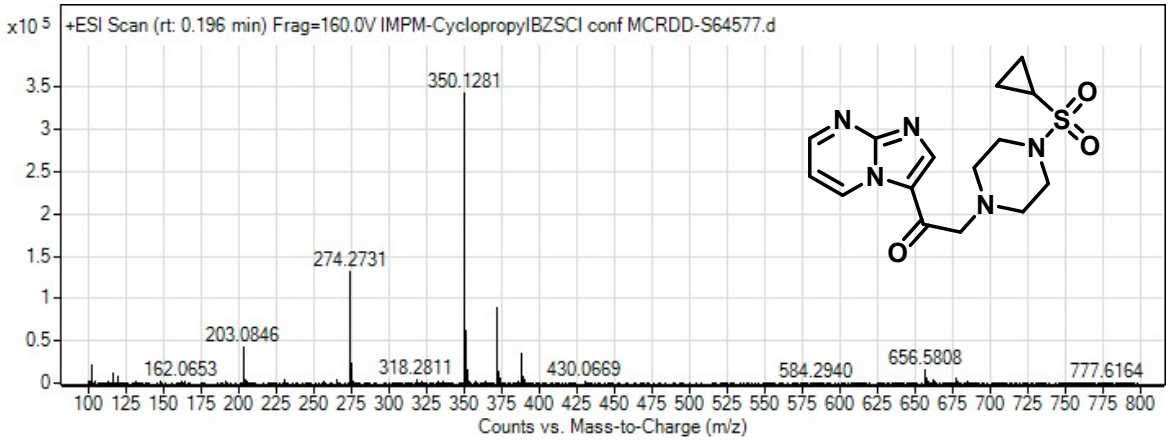
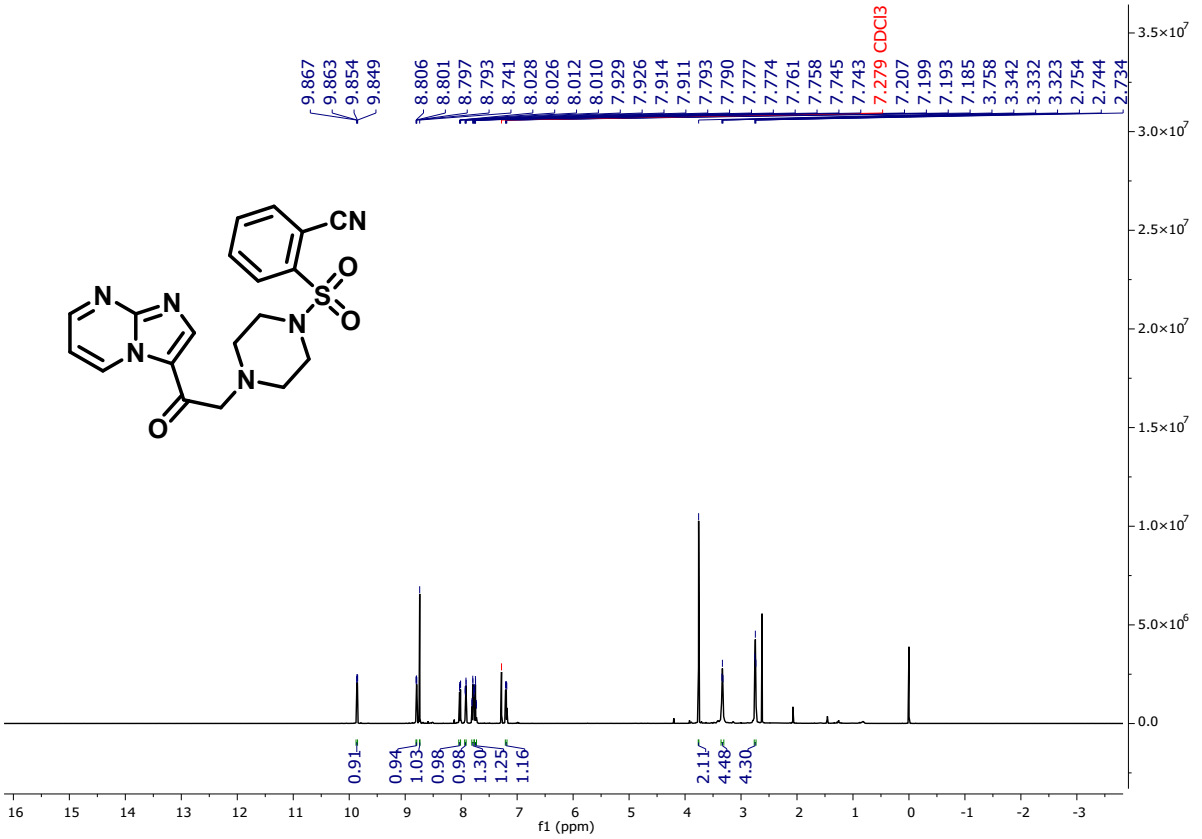
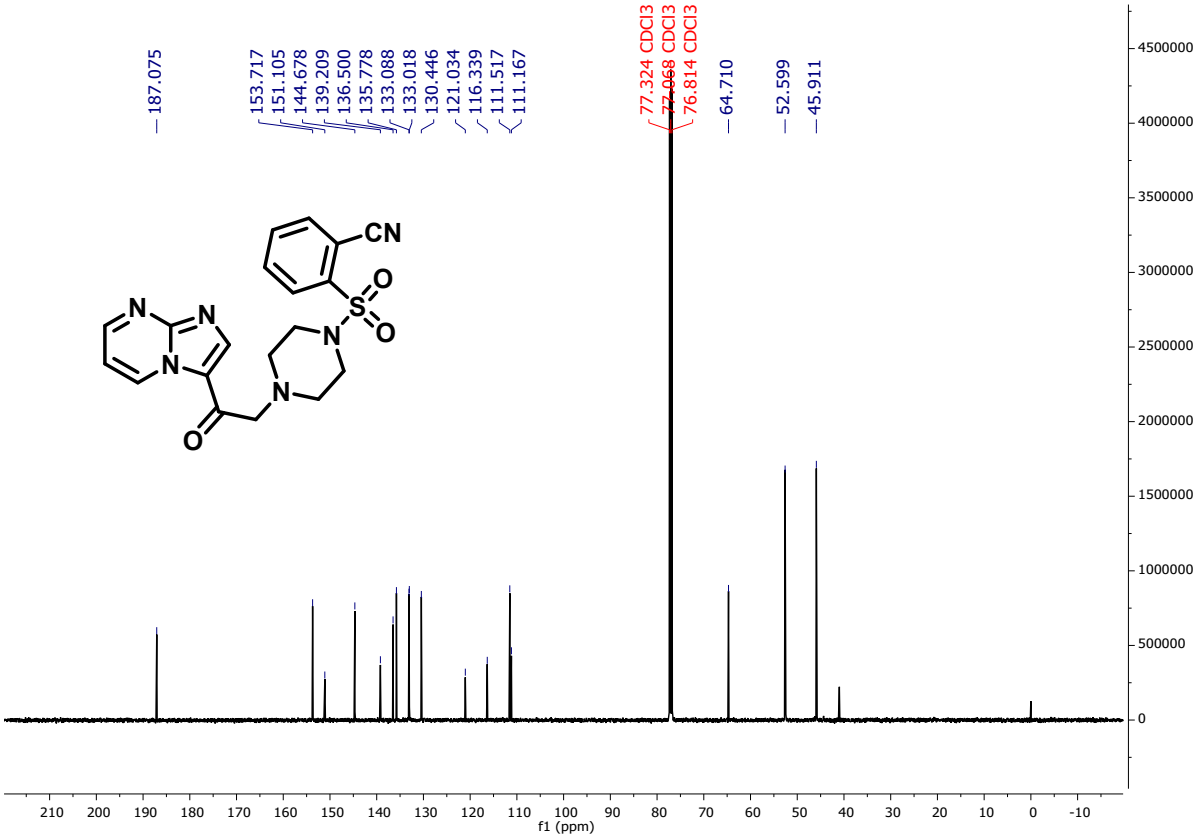


FIGURE S15: 2-(4-(cyclopropylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9n) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

16: 2-((4-(2-(imidazo[1,2-a]pyrimidin-3-yl)-2-oxoethyl)piperazin-1-yl)sulfonyl)benzonitrile (9o) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





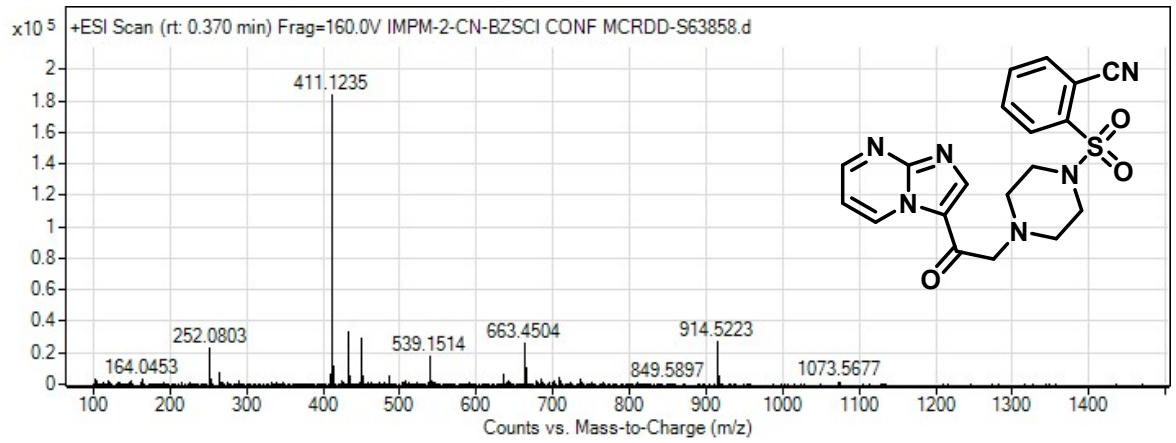
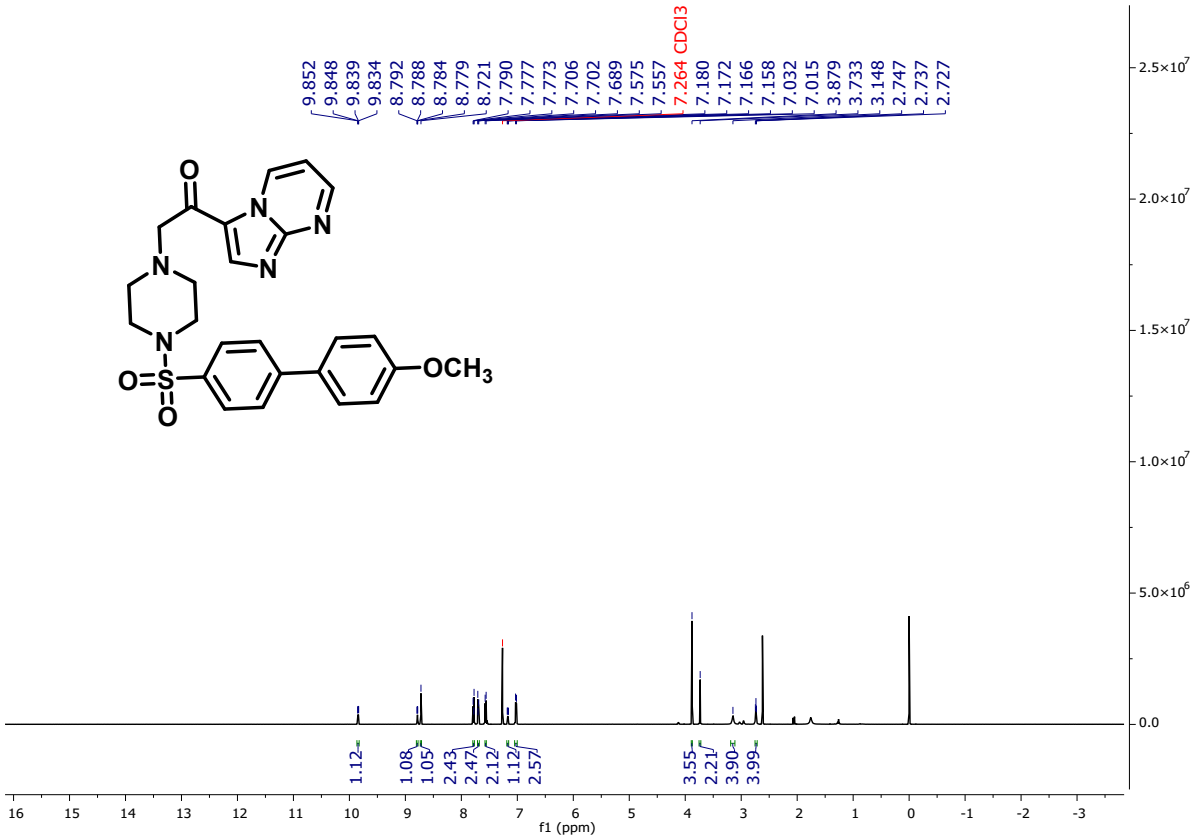
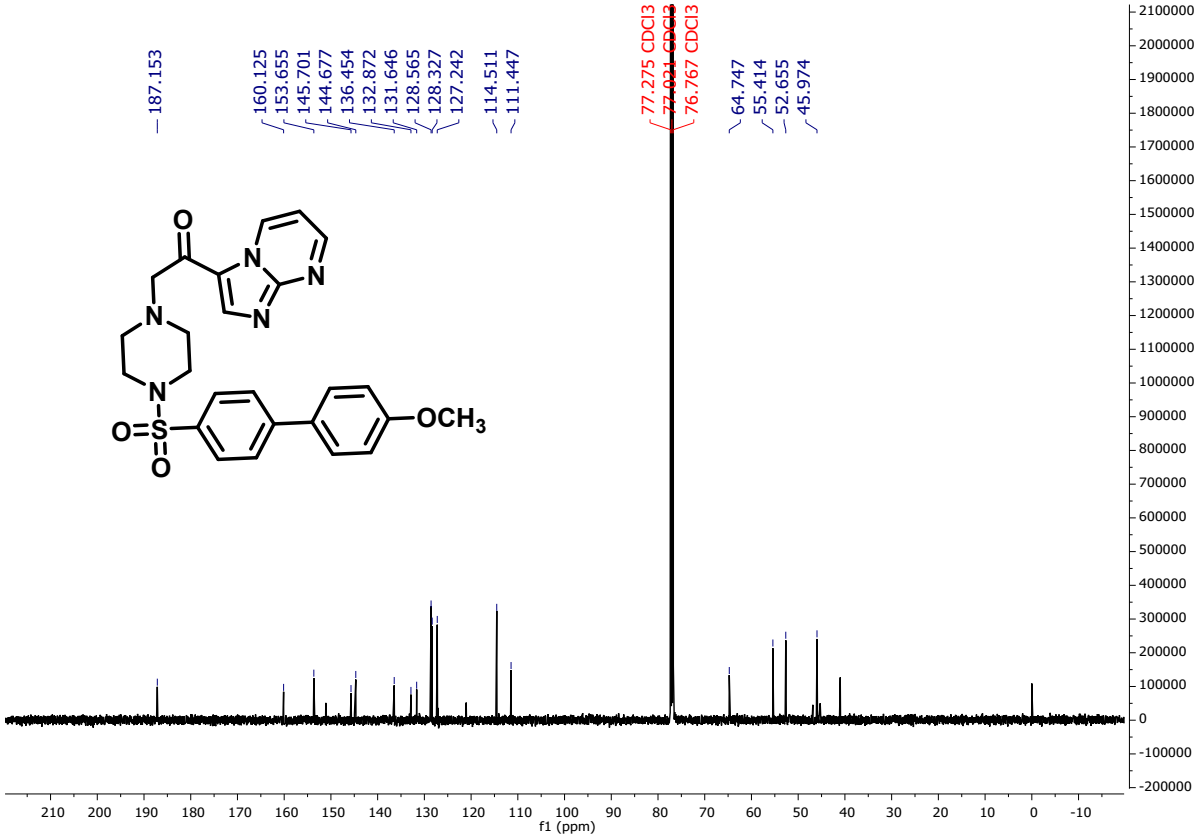


FIGURE S16: 2-((4-(2-(imidazo[1,2-a]pyrimidin-3-yl)-2-oxoethyl)piperazin-1-yl)sulfonyl)benzonitrile (9o) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

17: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4'-methoxy-[1,1'-biphenyl]-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one (9r) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





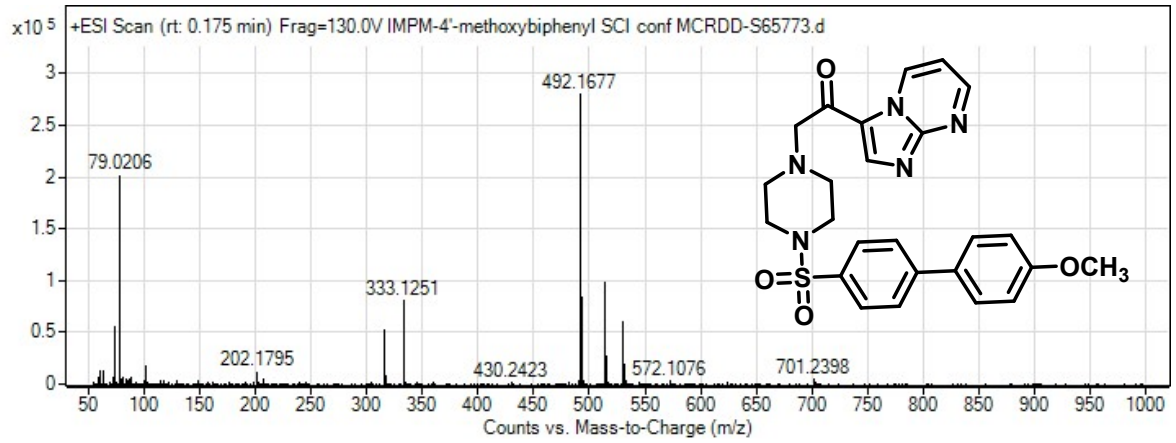
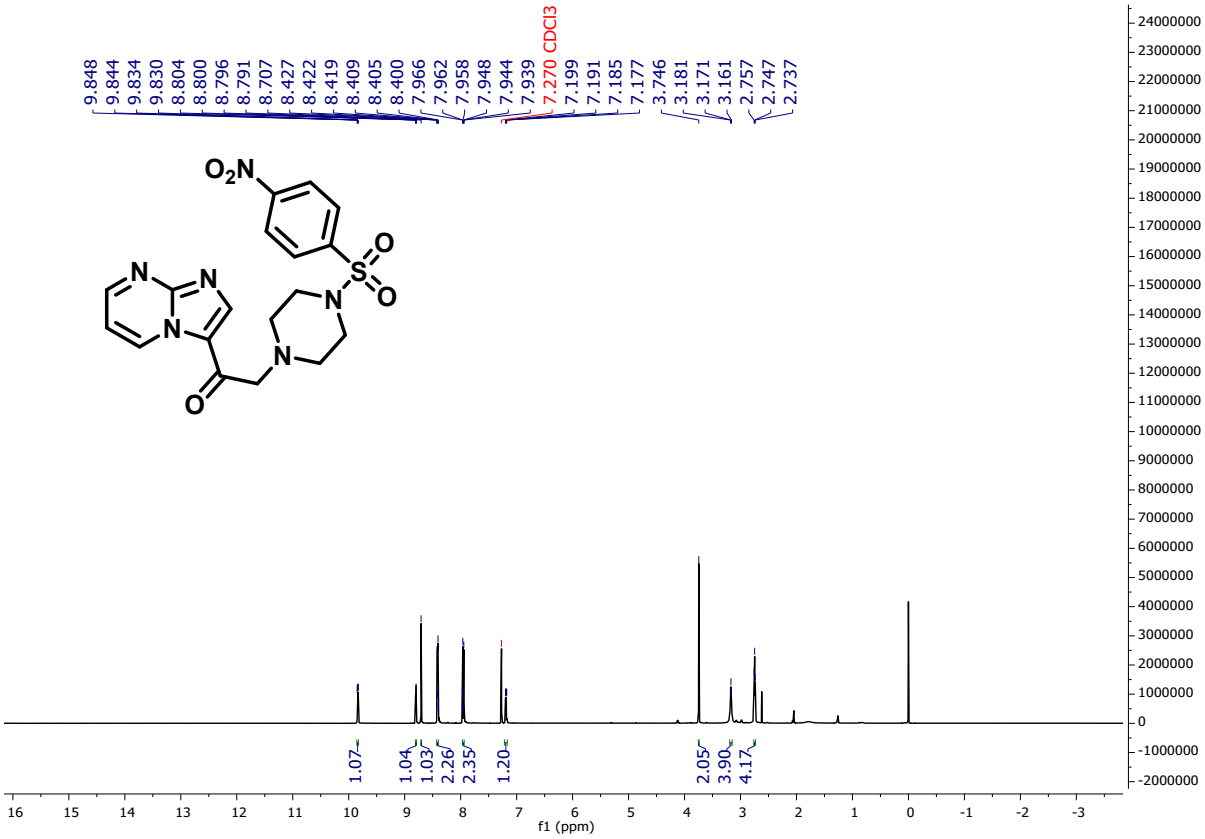
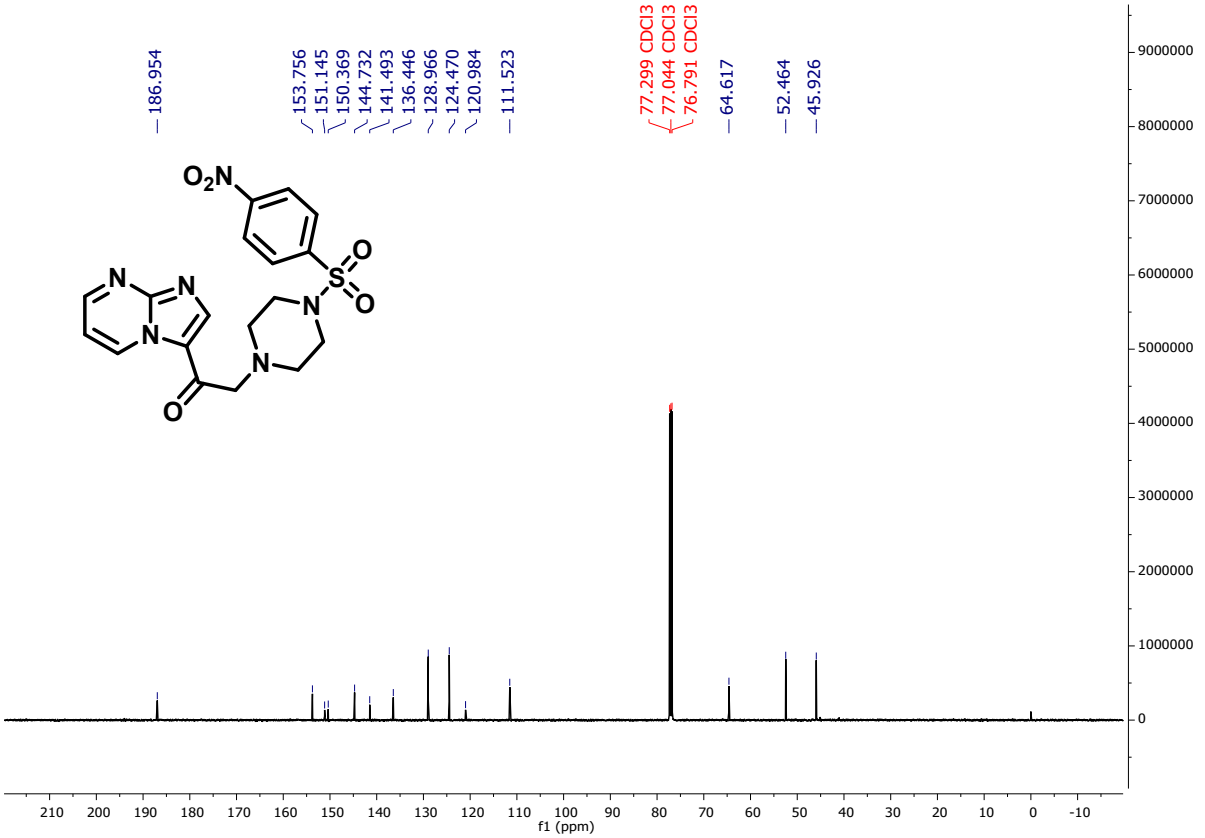


FIGURE S17: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4'-methoxy-[1,1'-biphenyl]-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one (9r) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

18: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9s)

(^{1}H NMR, ^{13}C NMR & HRMS Spectra)





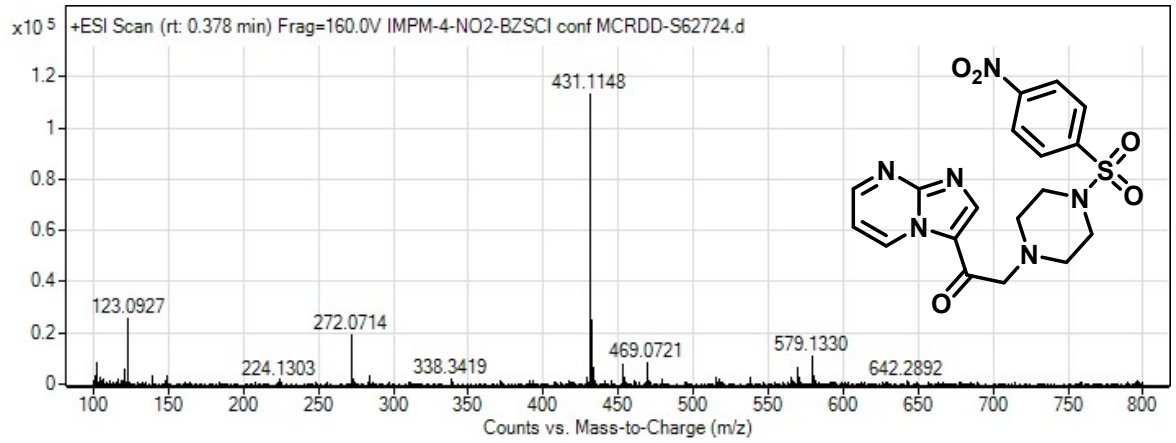
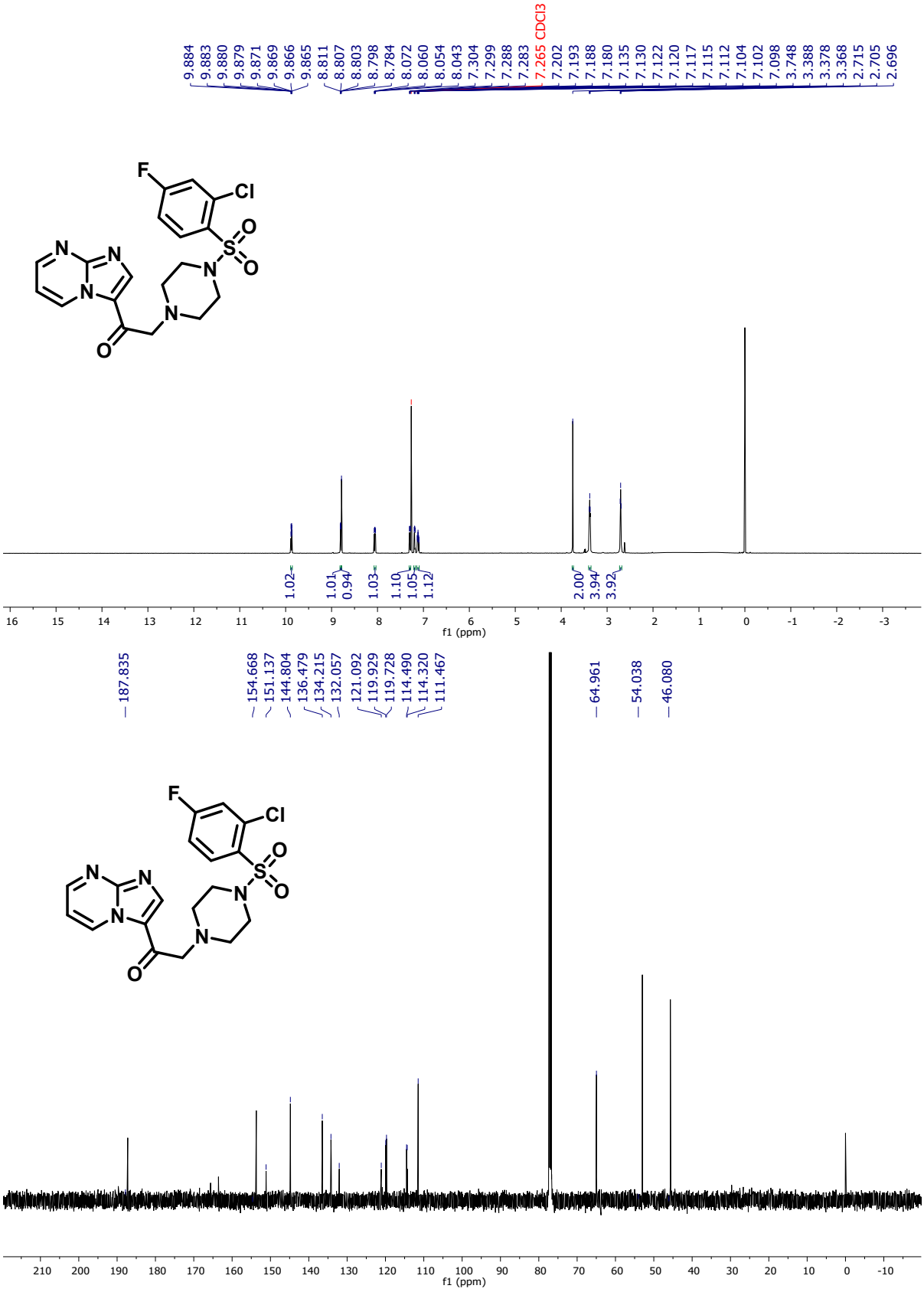
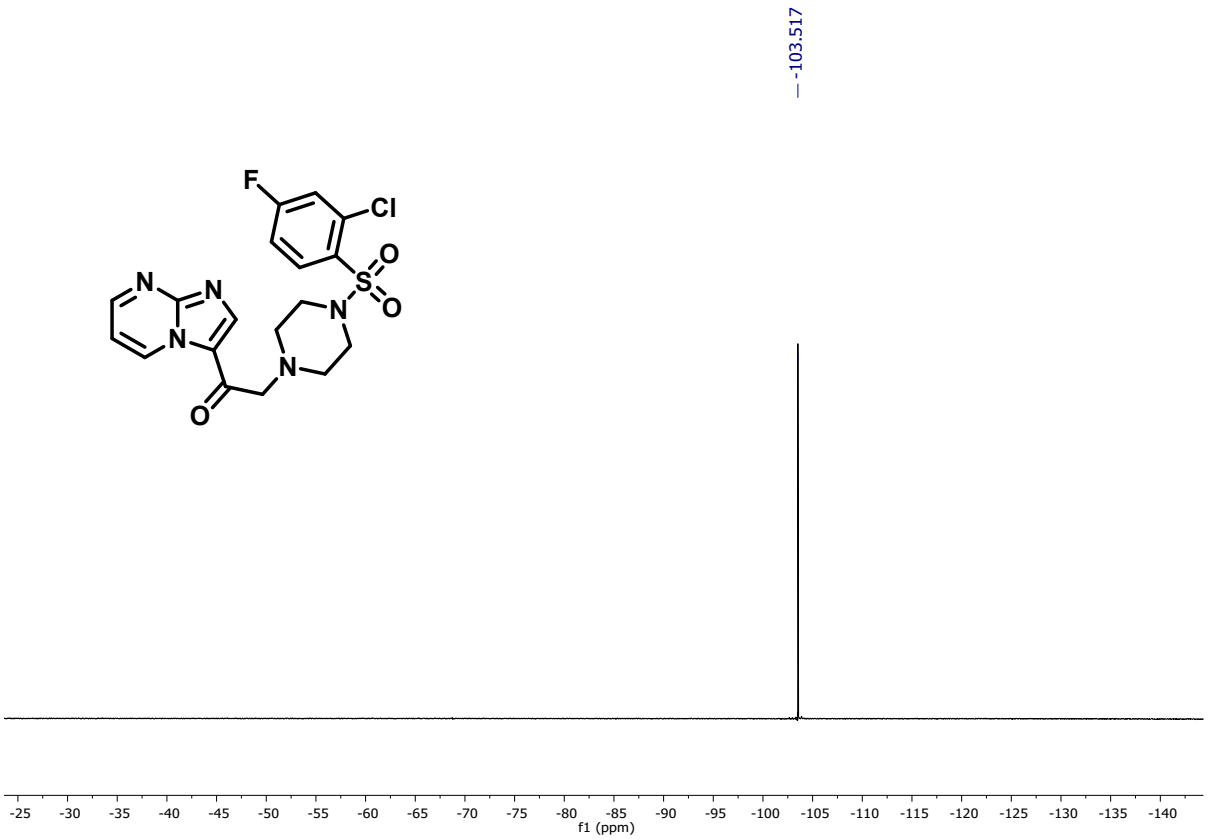


FIGURE S18: 1-(imidazo[1,2-a]pyrimidin-3-yl)-2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)ethan-1-one (9s) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

19: 2-(4-((2-chloro-4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9p) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)





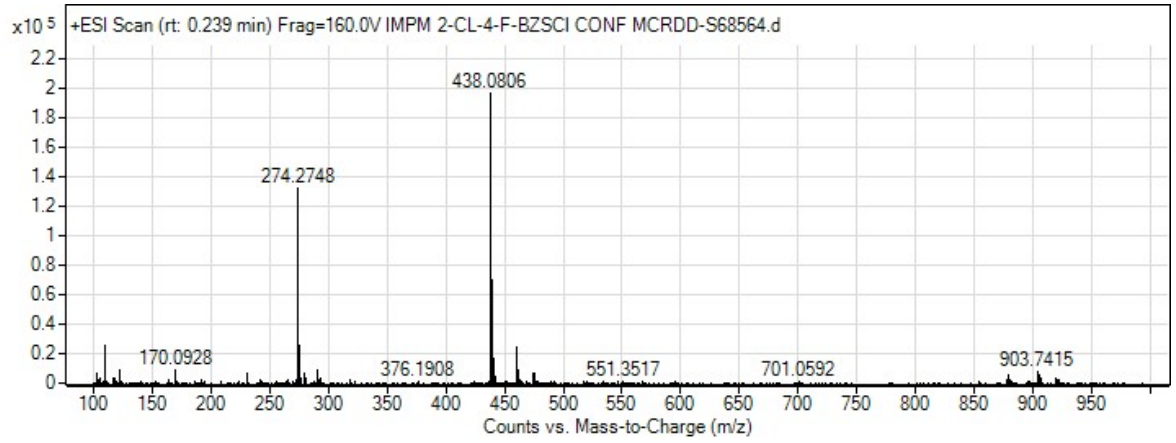
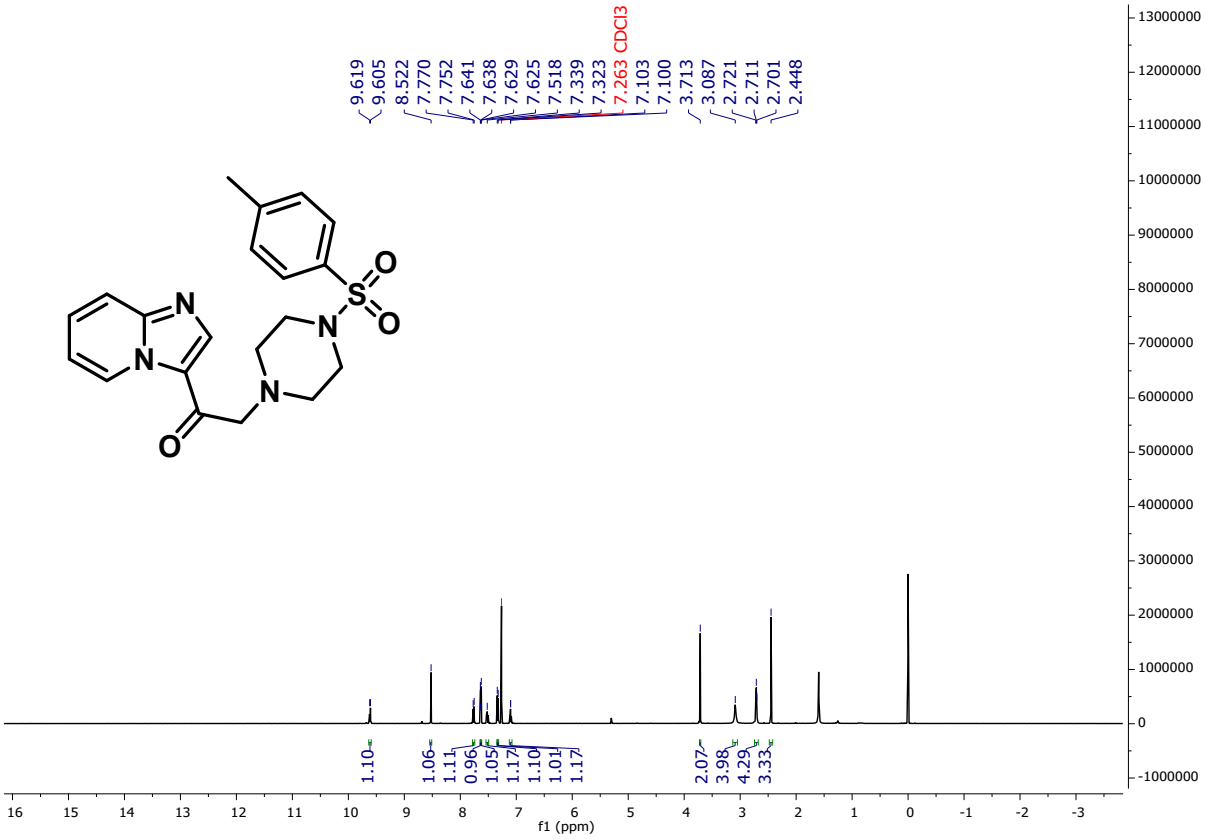
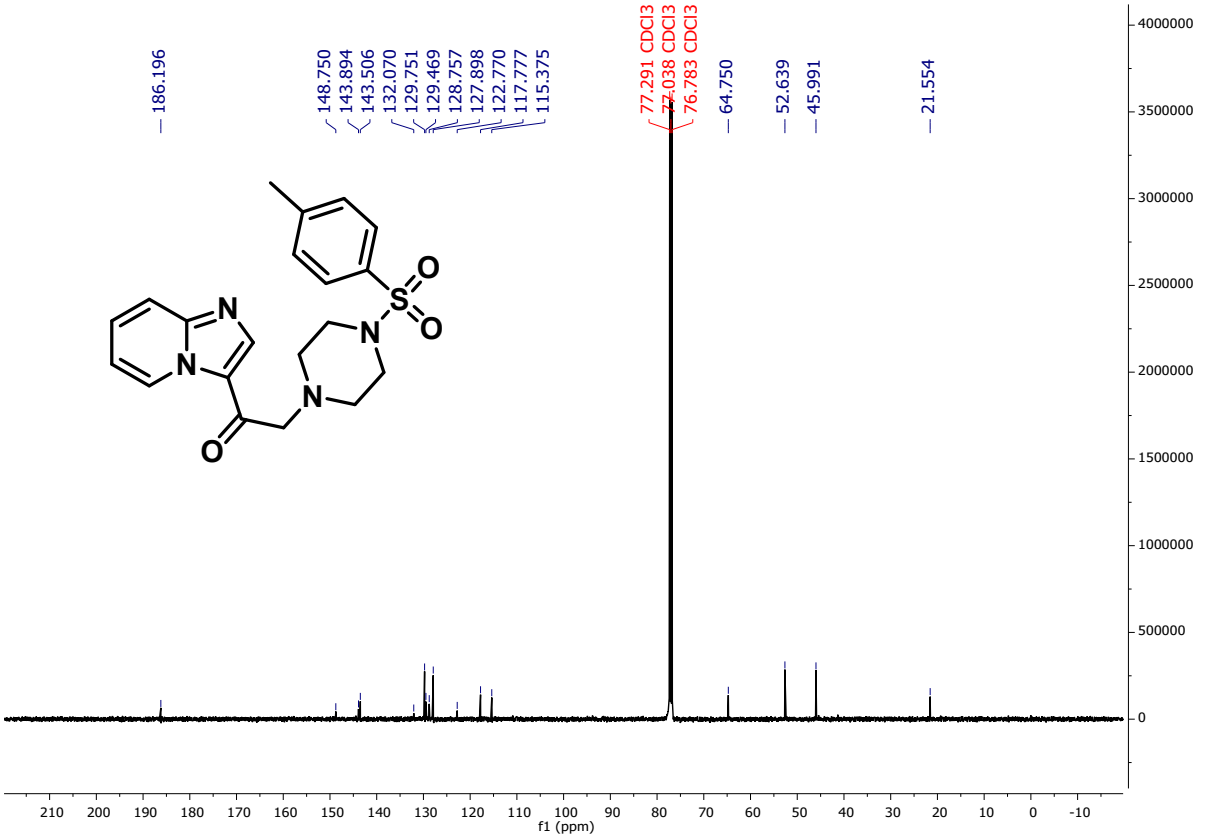


FIGURE S19: 2-(4-((2-chloro-4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyrimidin-3-yl)ethan-1-one (9p) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

20: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-tosylpiperazin-1-yl)ethan-1-one (10a) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





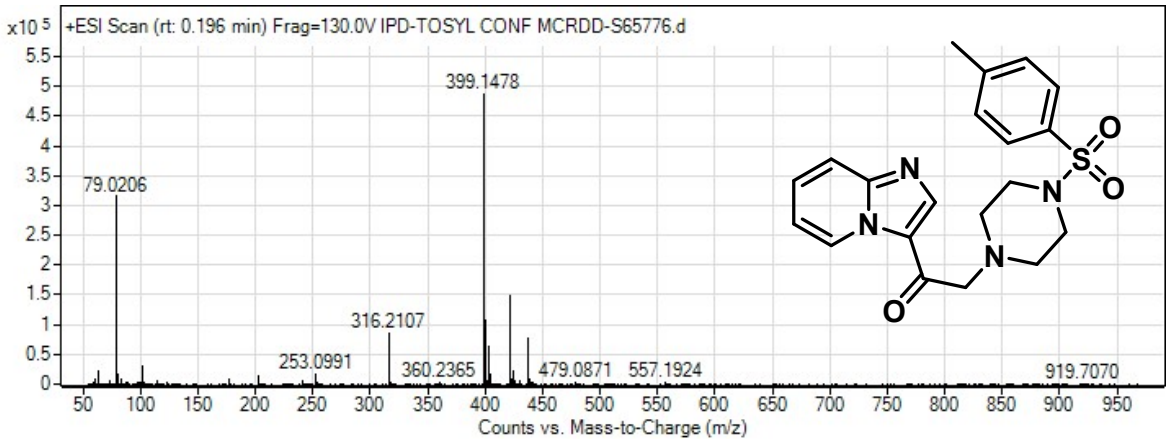
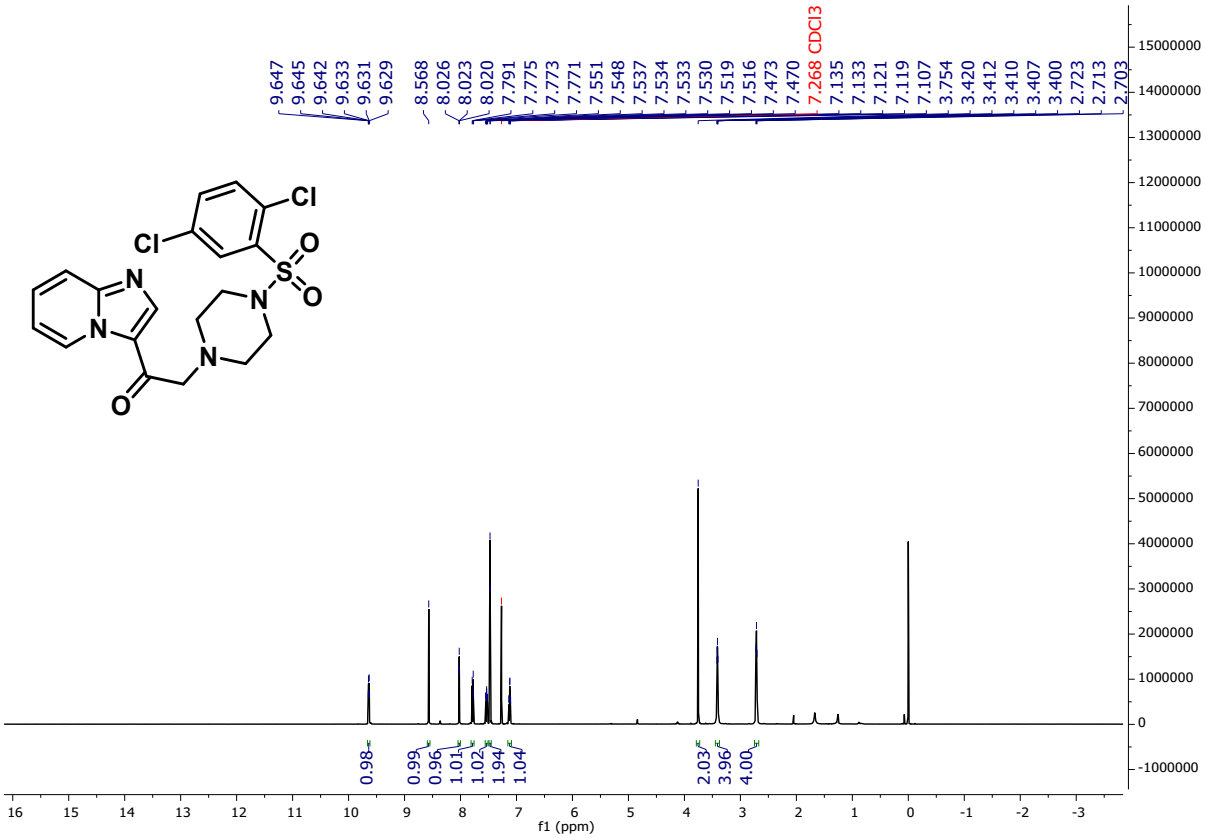
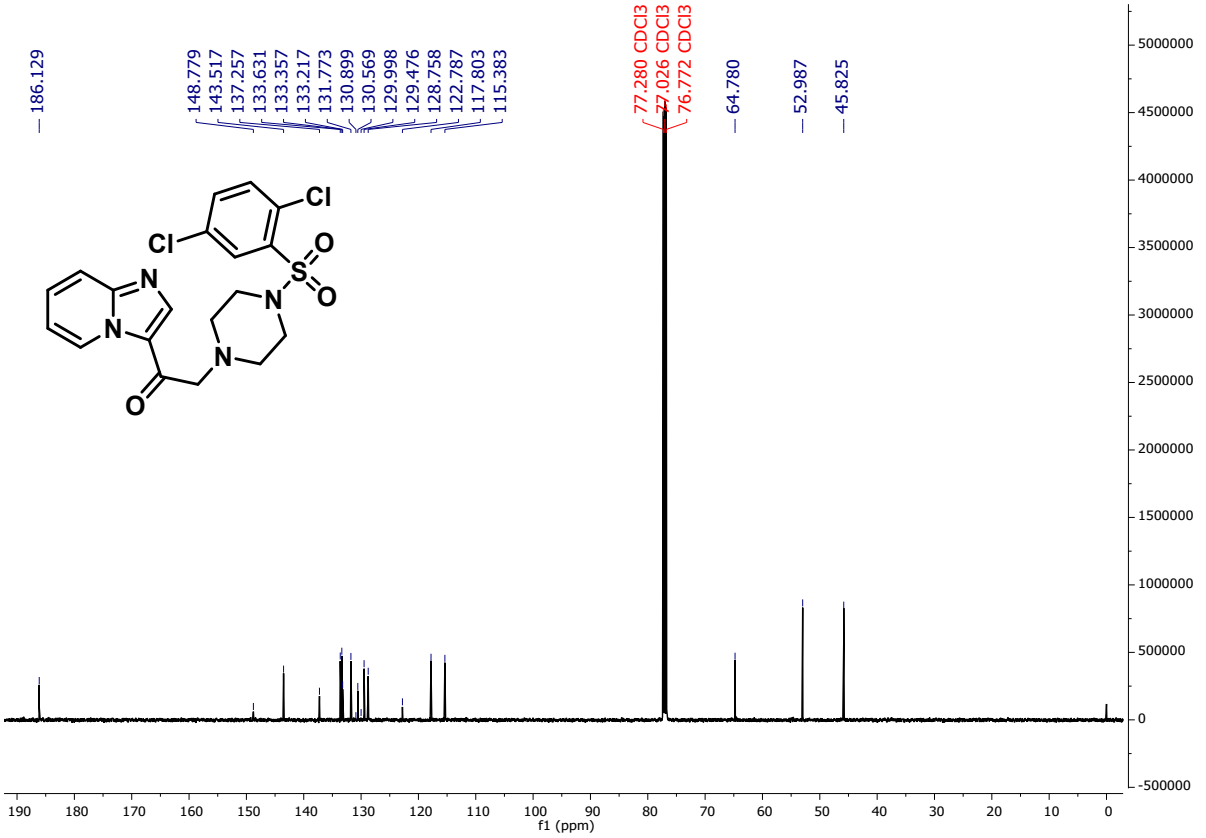


FIGURE S20: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-tosylpiperazin-1-yl)ethan-1-one (10a) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

21: 2-(4-((2,5-dichlorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10h) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





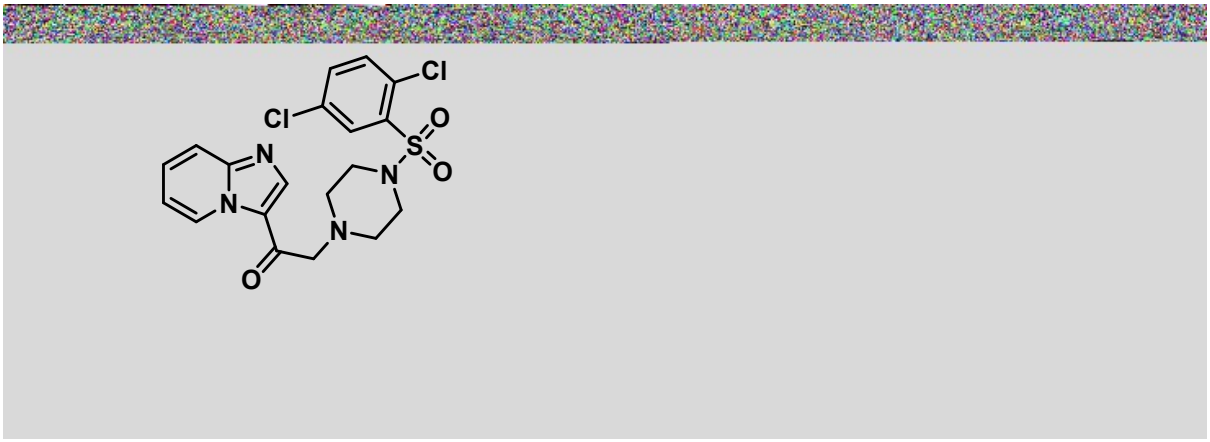
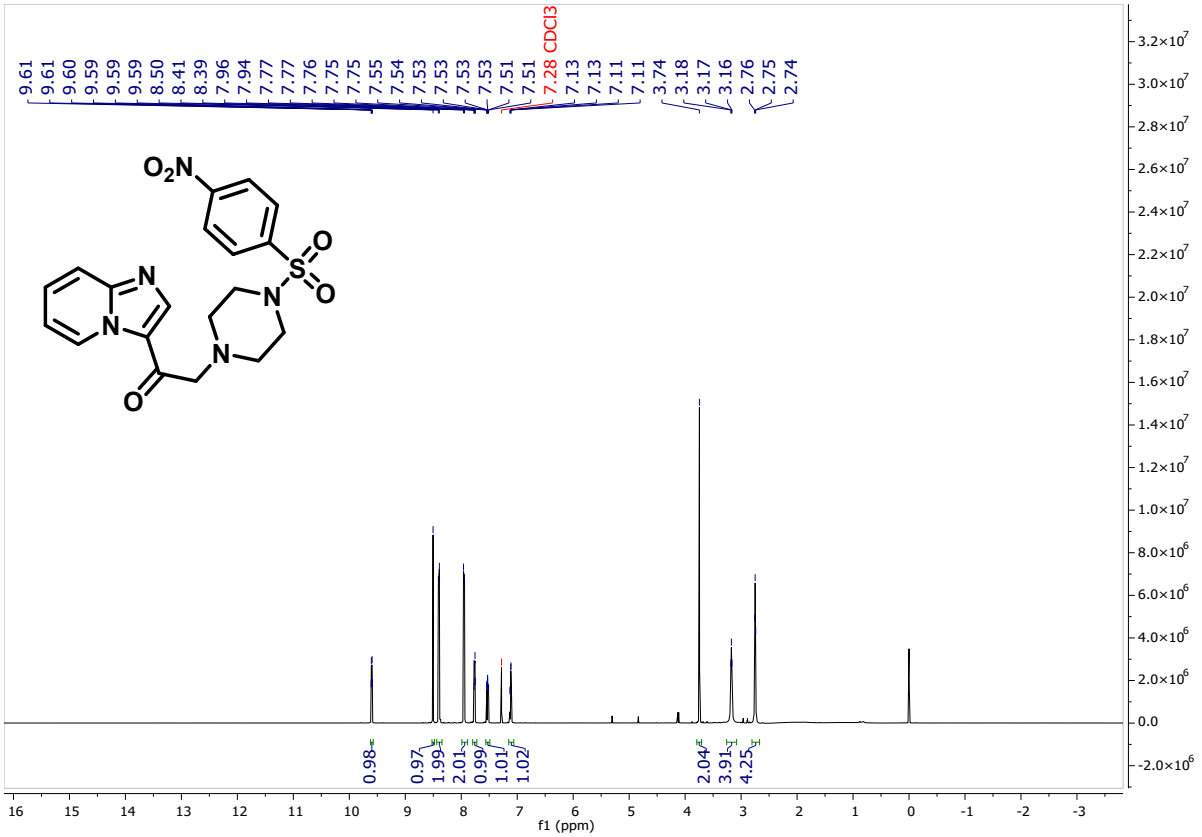
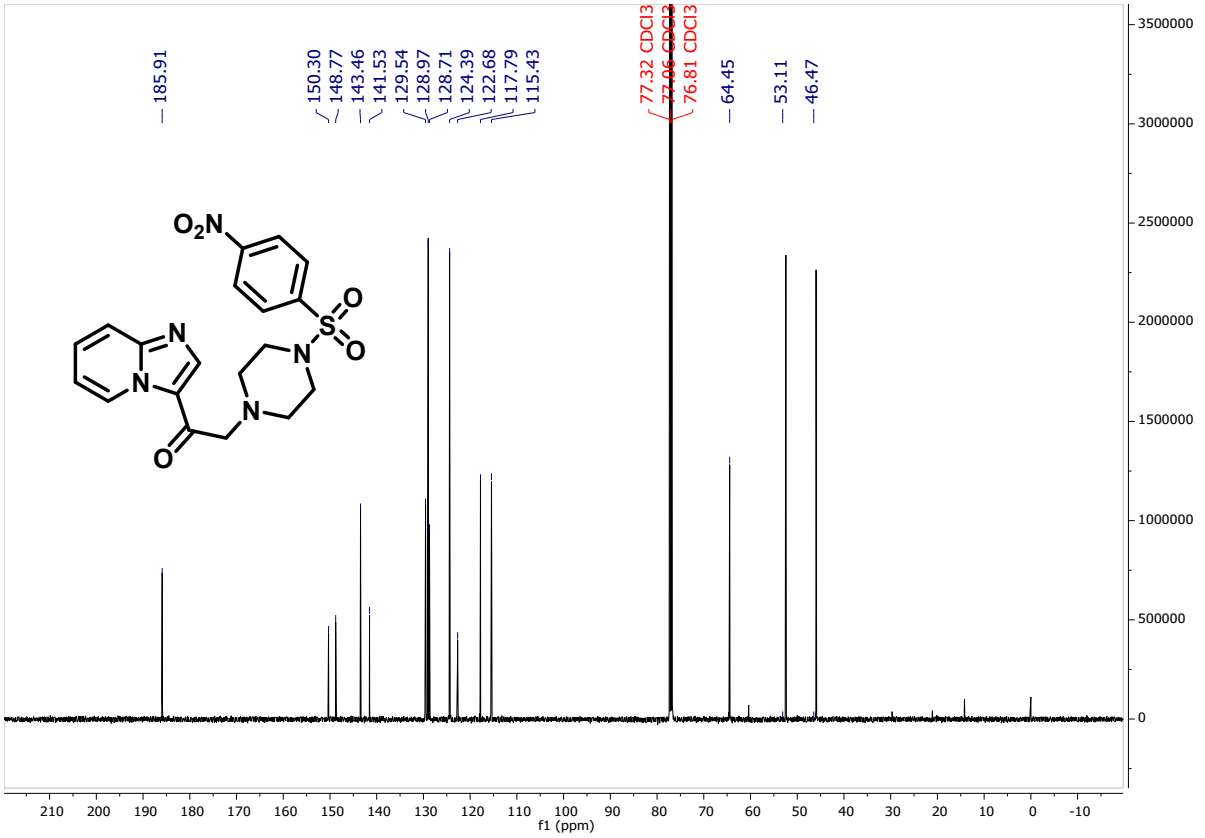


FIGURE S21: 2-(4-((2,5-dichlorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10h) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

22: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10s) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





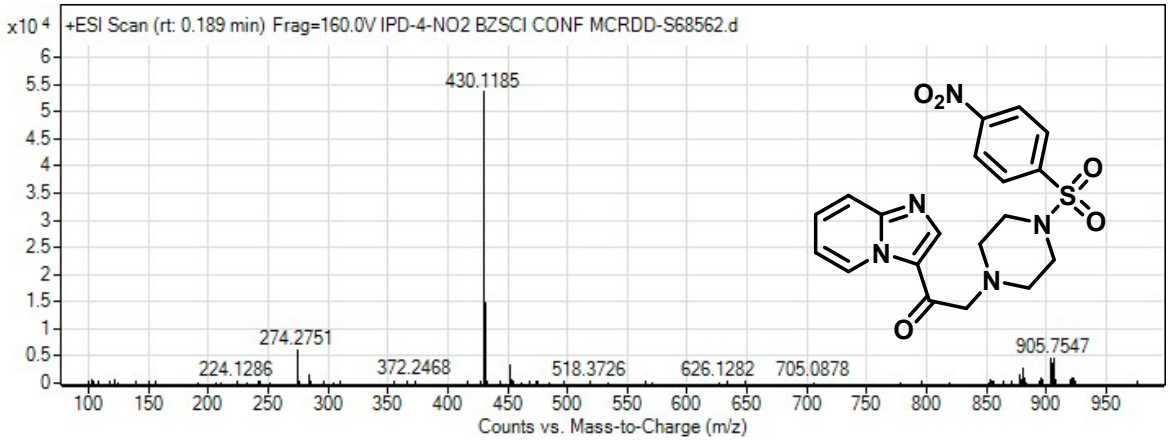
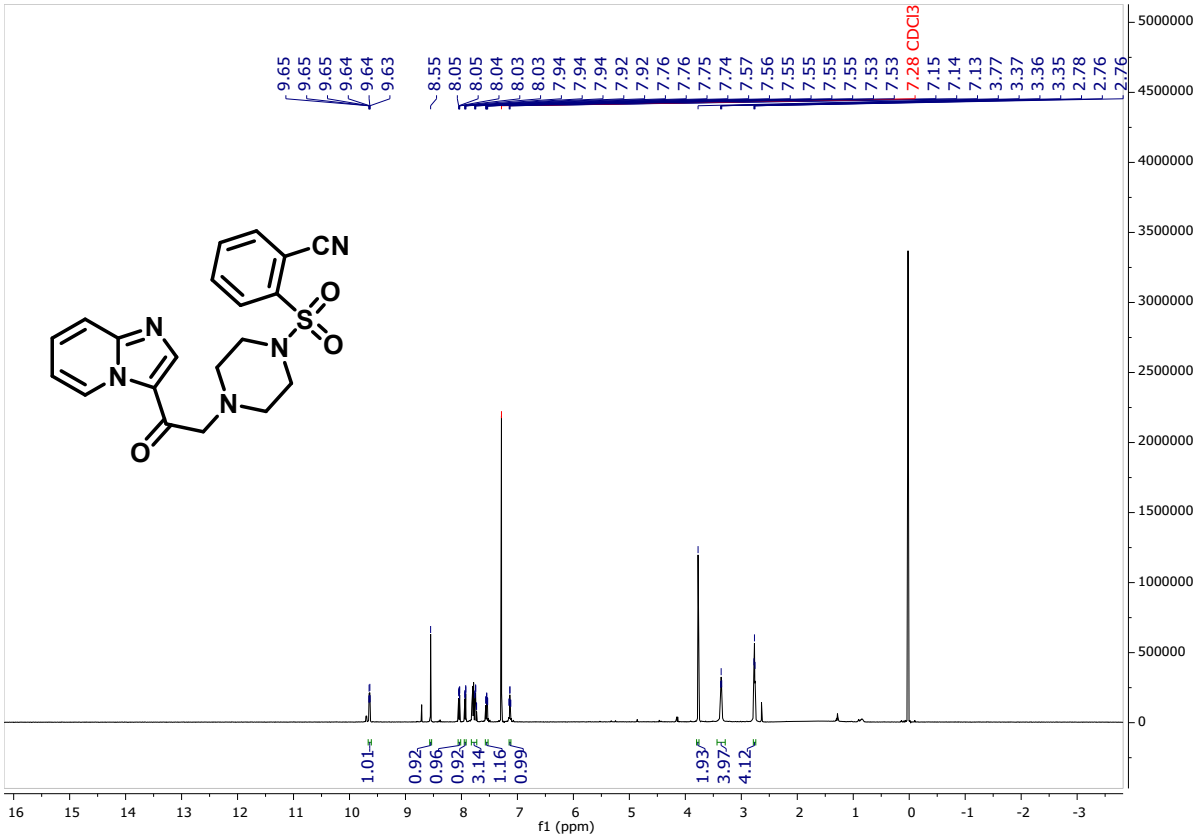
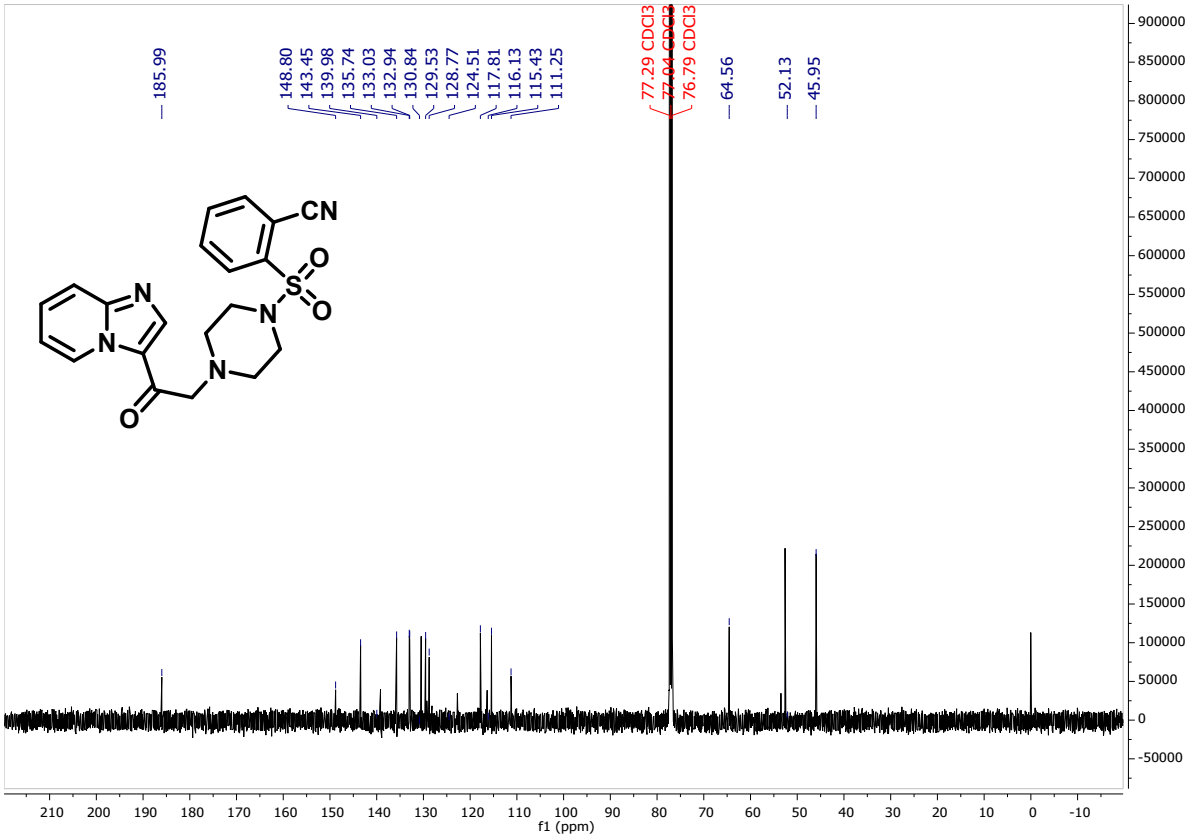


FIGURE S22: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10s) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

23: 2-((4-(2-(imidazo[1,2-a]pyridin-3-yl)-2-oxoethyl)piperazin-1-yl)sulfonyl)benzonitrile (10o) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





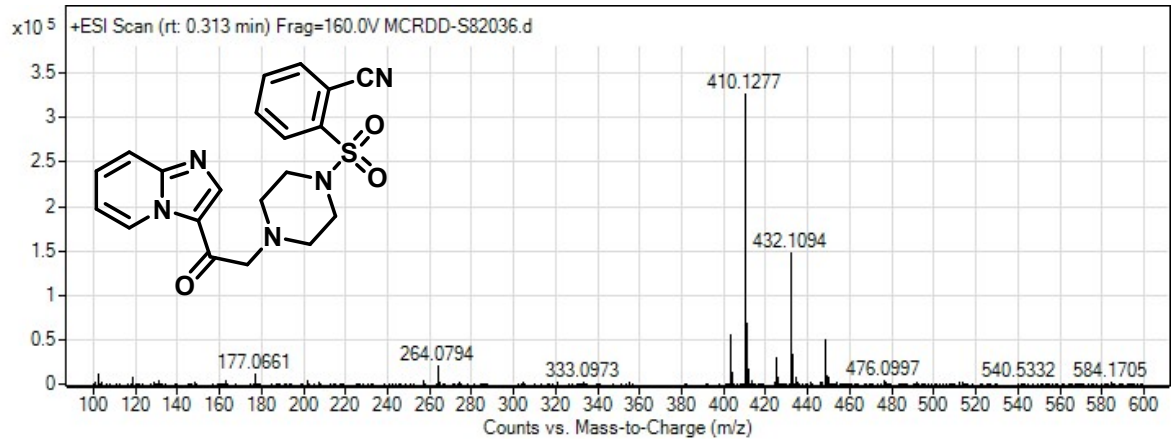
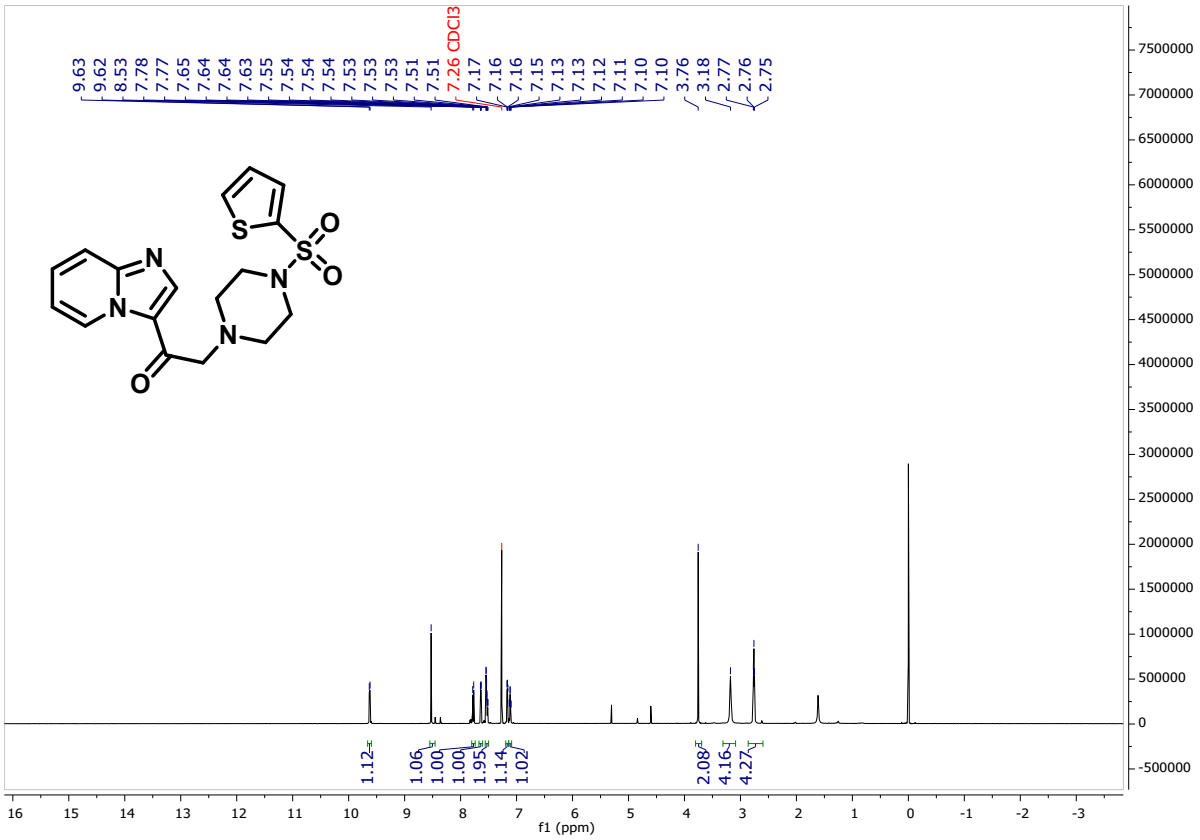
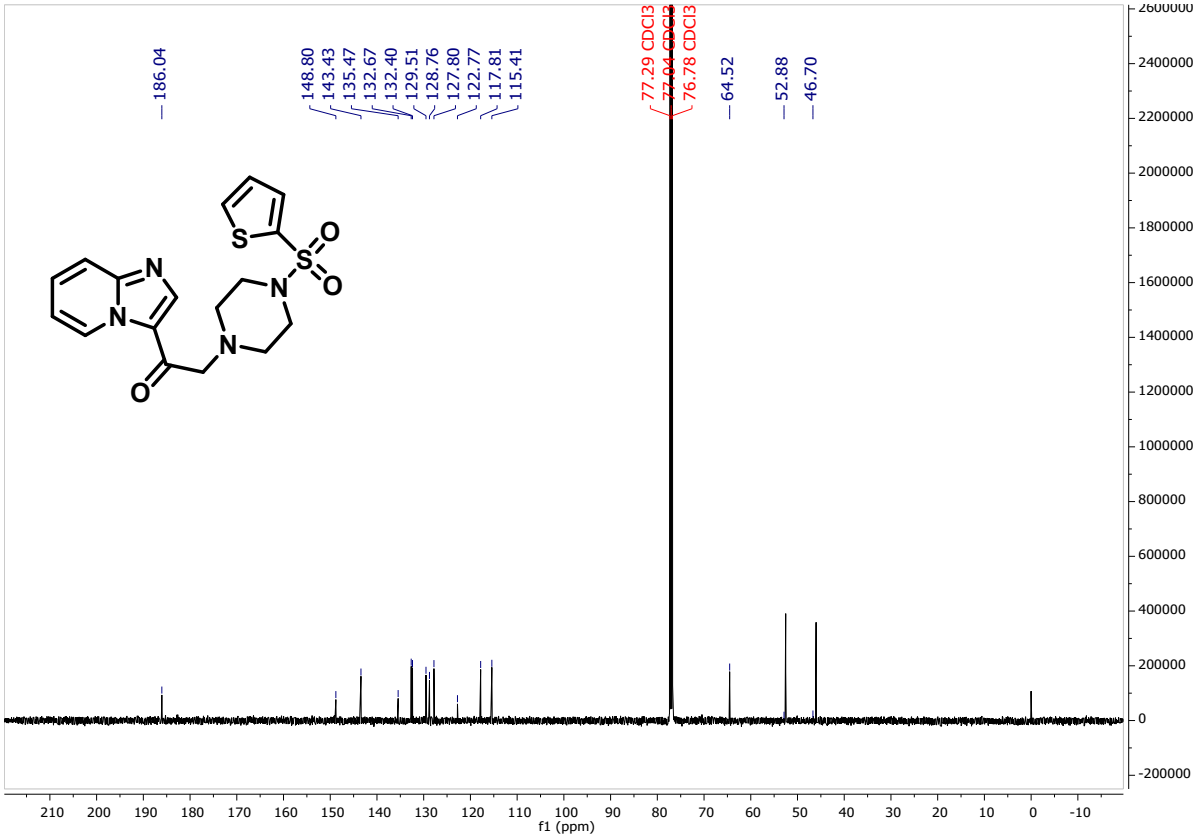


FIGURE S23: 2-((4-(2-(imidazo[1,2-a]pyridin-3-yl)-2-oxoethyl)piperazin-1-yl)sulfonyl)benzonitrile (10o) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

24: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)ethan-1-one (10c) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





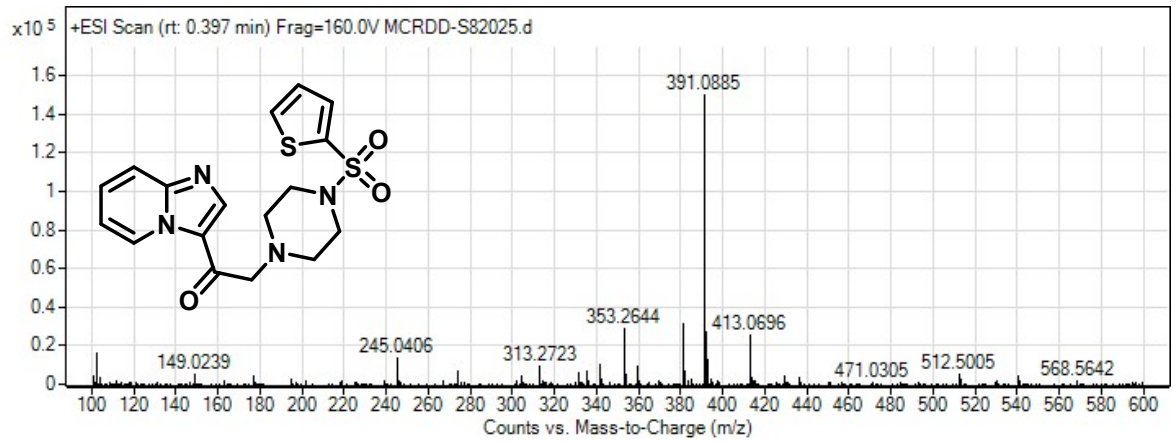
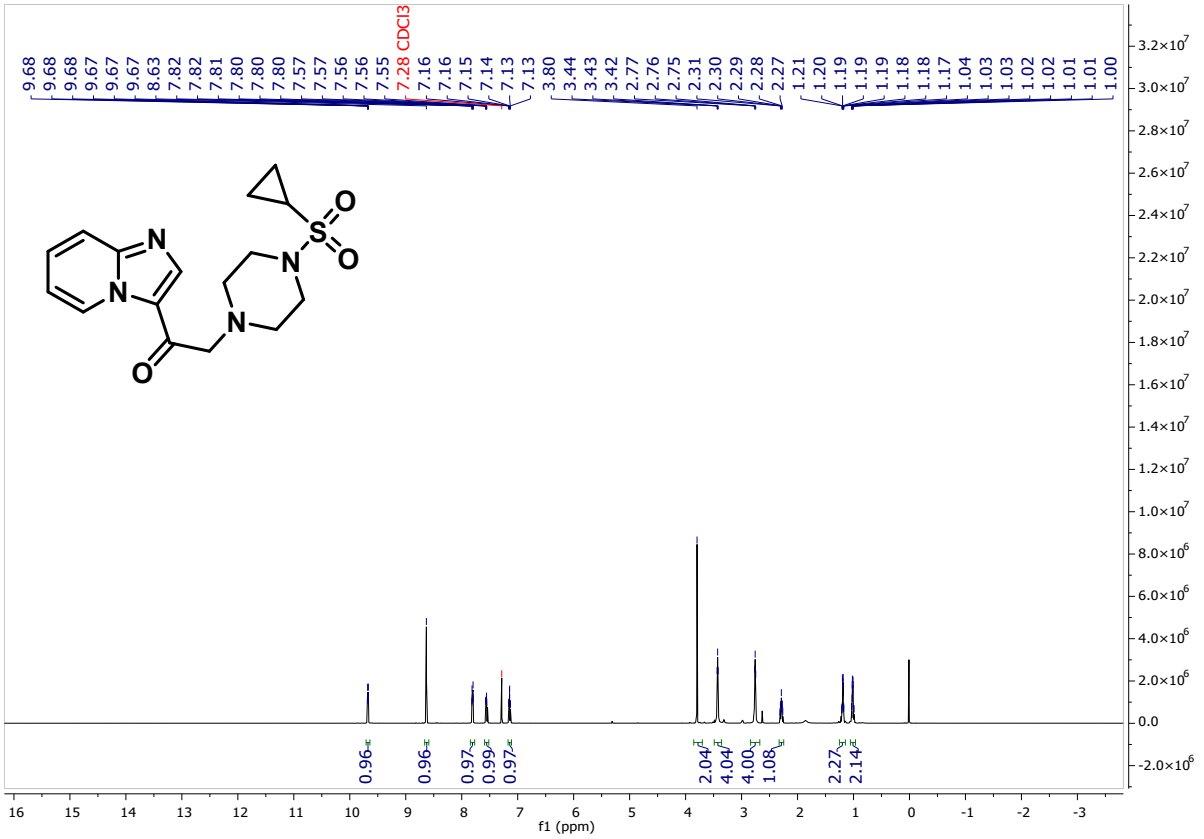
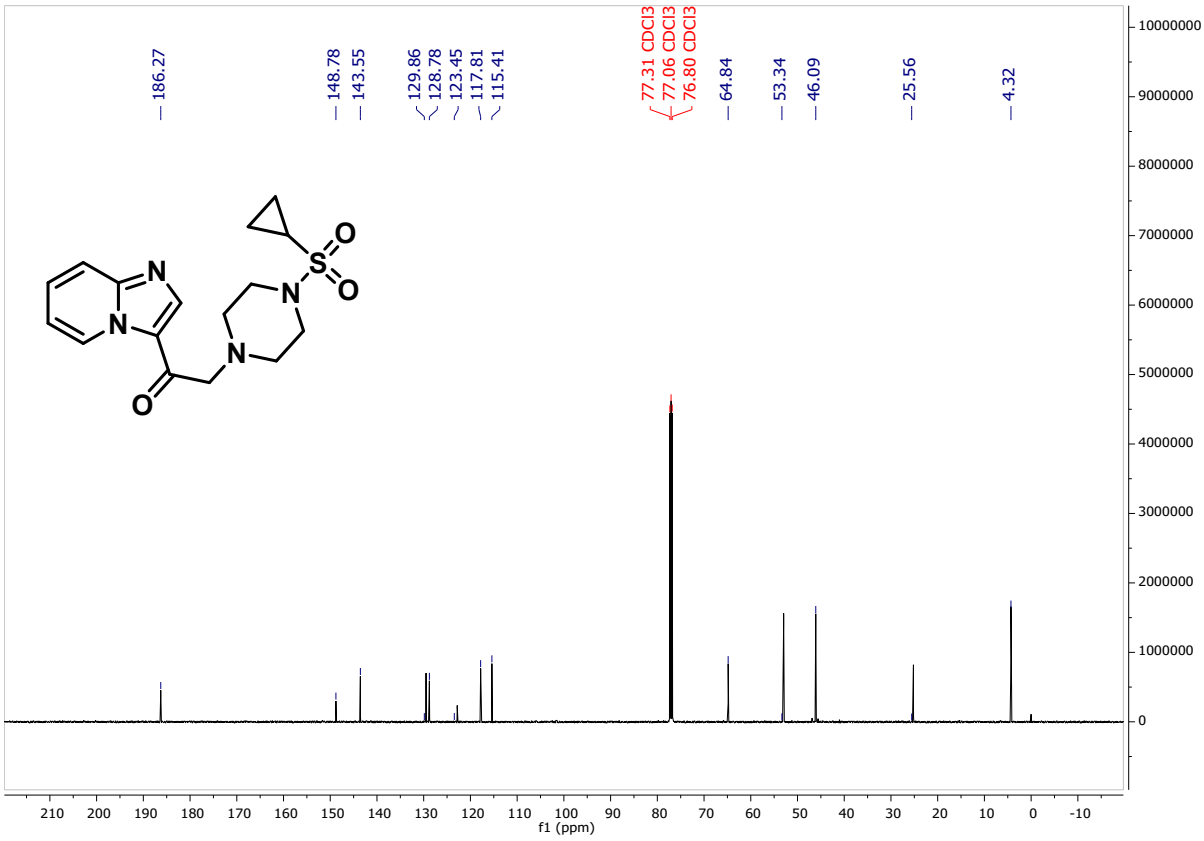


FIGURE S24: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(thiophen-2-ylsulfonyl)piperazin-1-yl)ethan-1-one (10c) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

25: 2-(4-(cyclopropylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10n) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





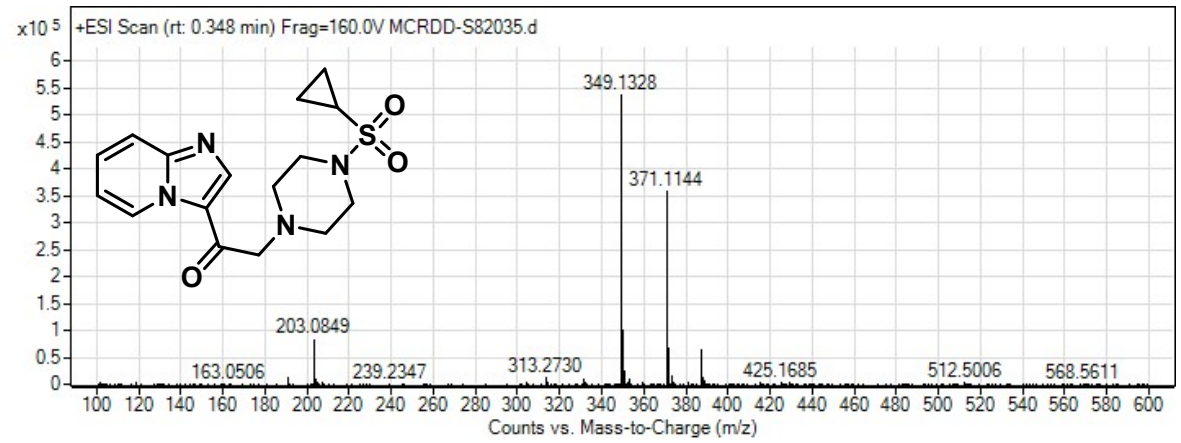
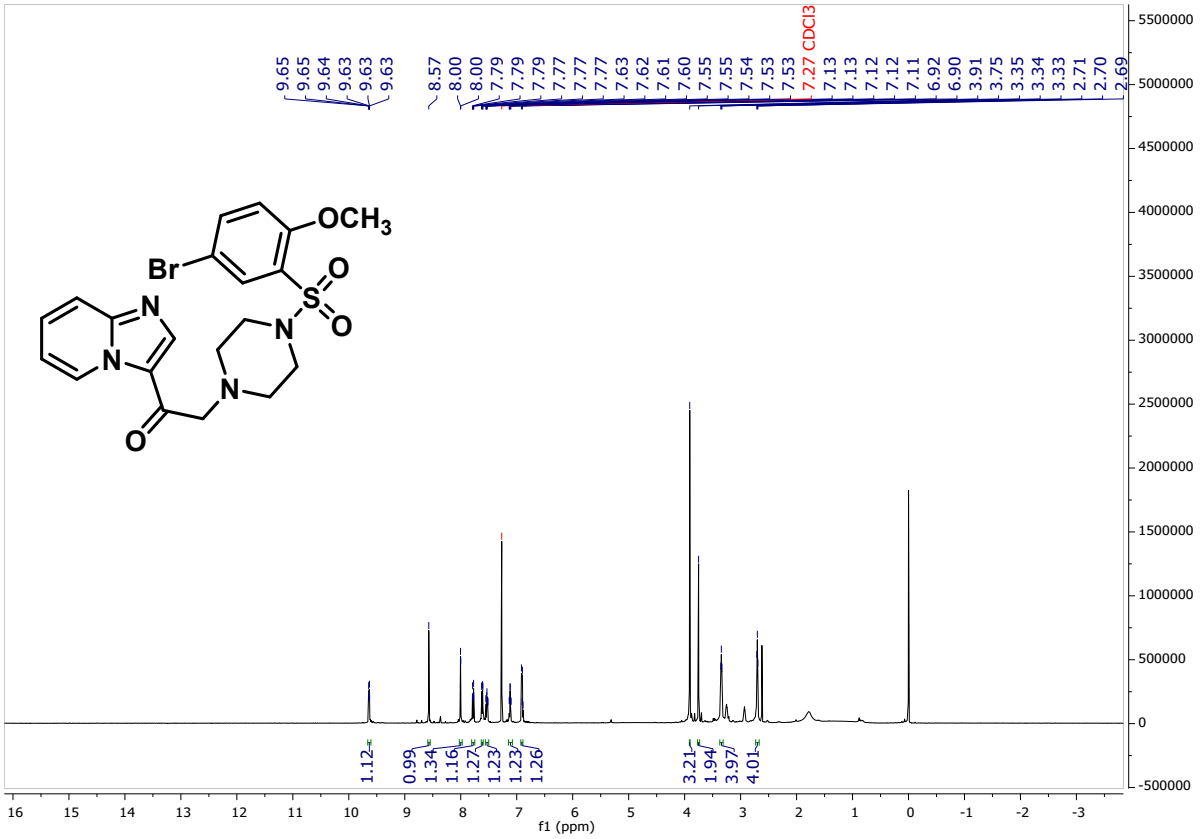
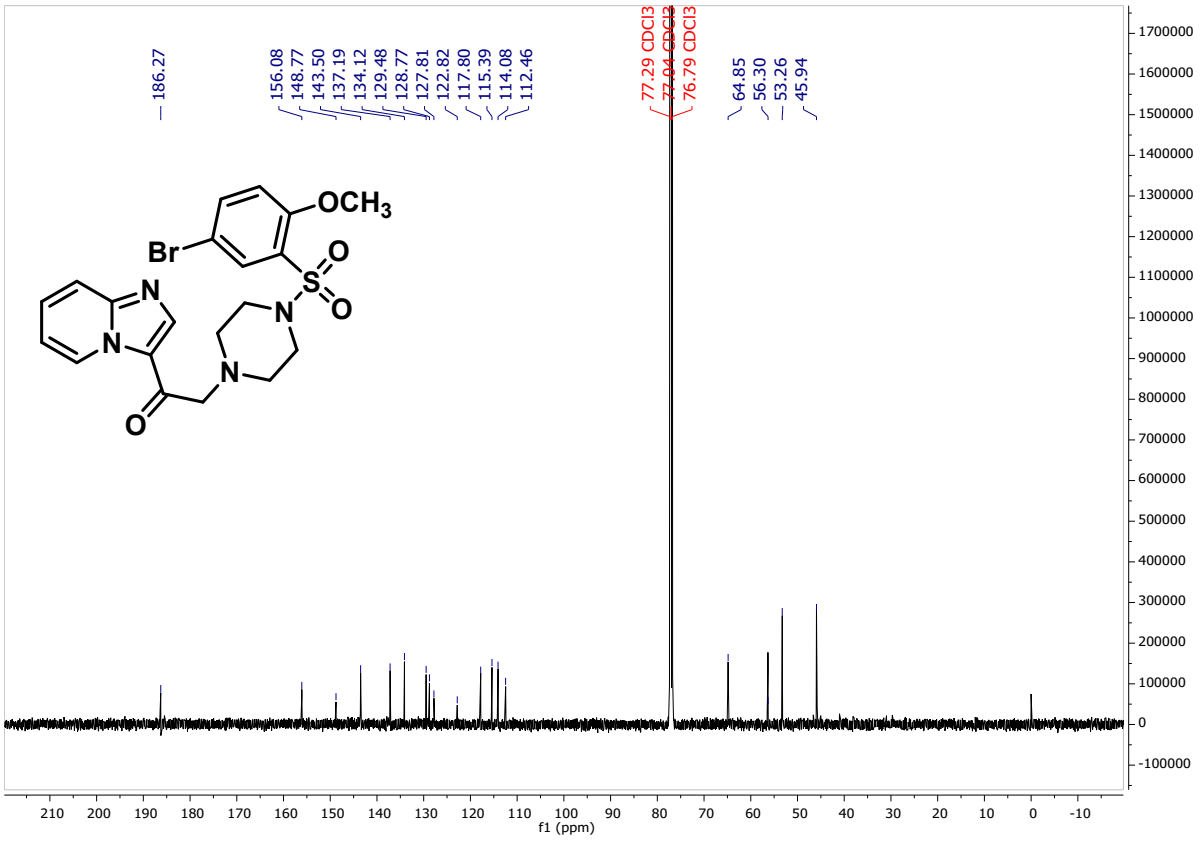


FIGURE S25: 2-(4-(cyclopropylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10n) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

26: 2-(4-((5-bromo-2-methoxyphenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]XXXyridine-3-yl)ethan-1-one (10j) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





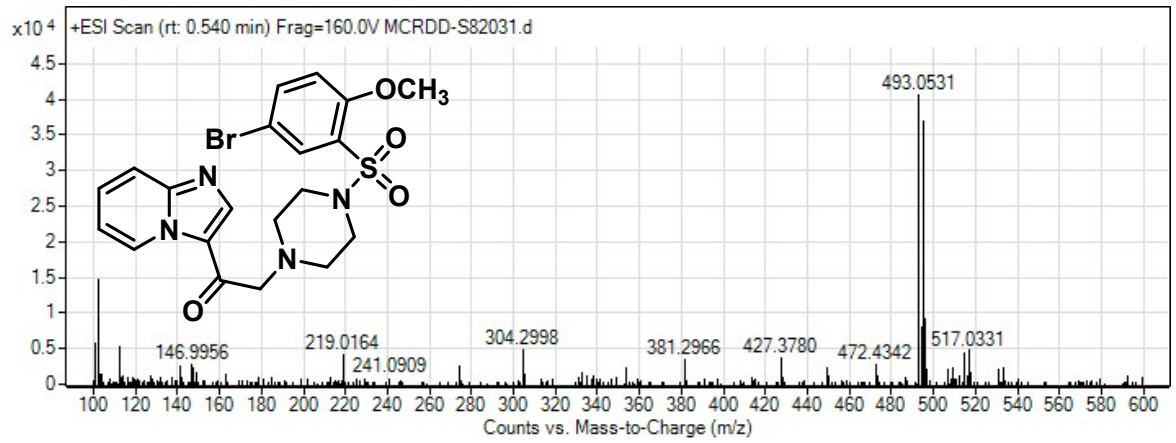
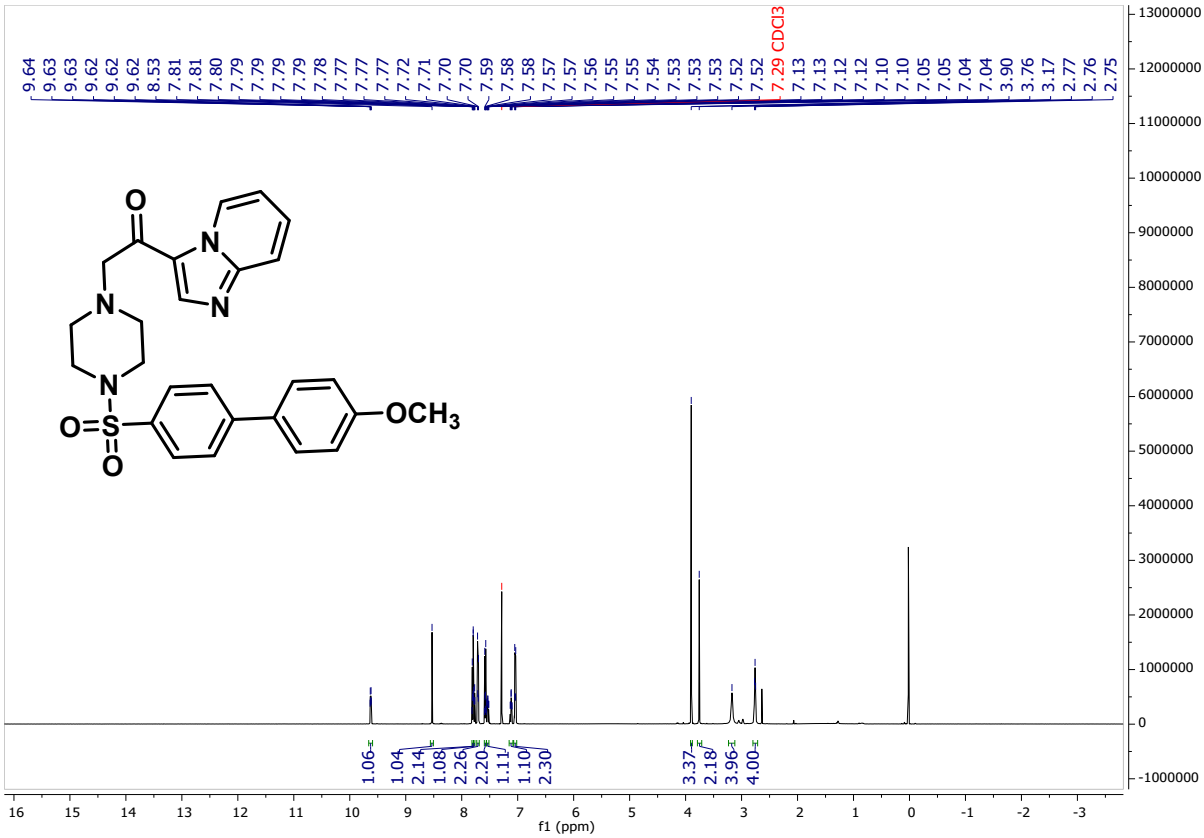
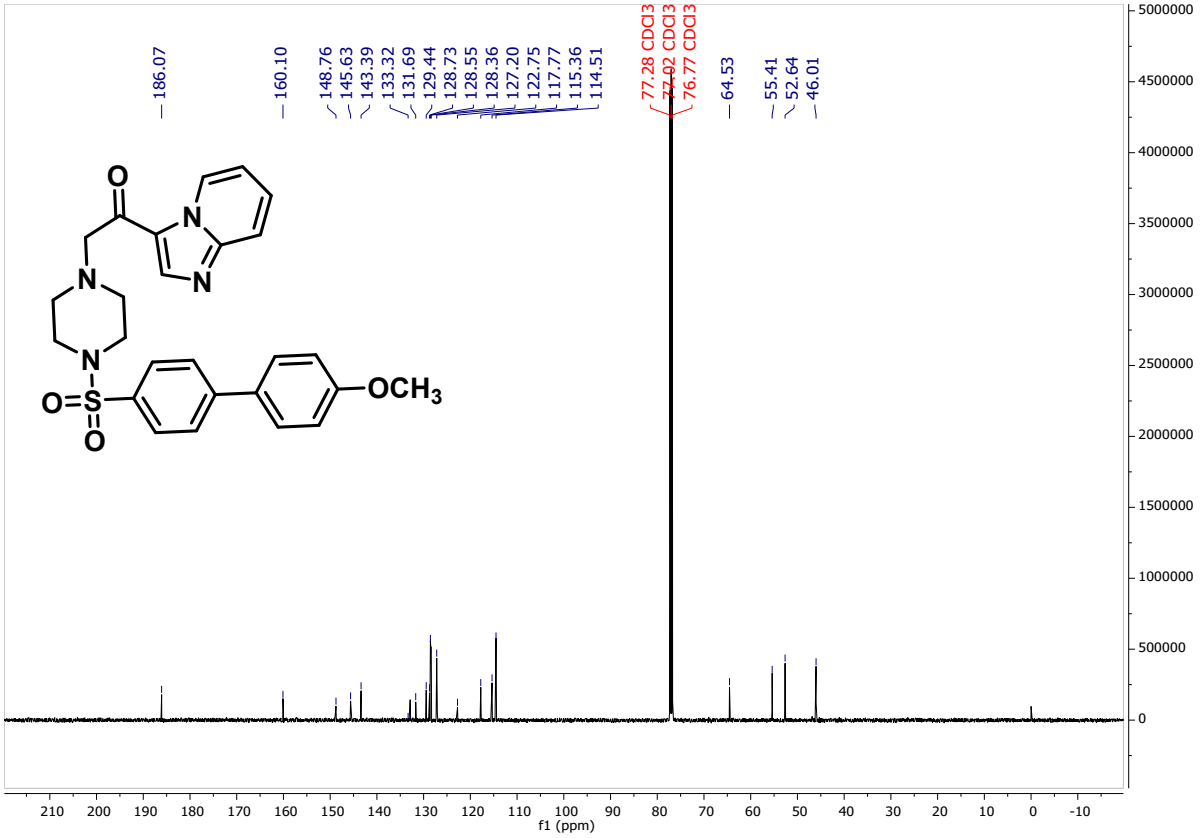


FIGURE S26: 2-(4-((5-bromo-2-methoxyphenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a] yridine-3-yl)ethan-1-one (10j) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

27: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4'-methoxy-[1,1'-biphenyl]-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one (10r) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





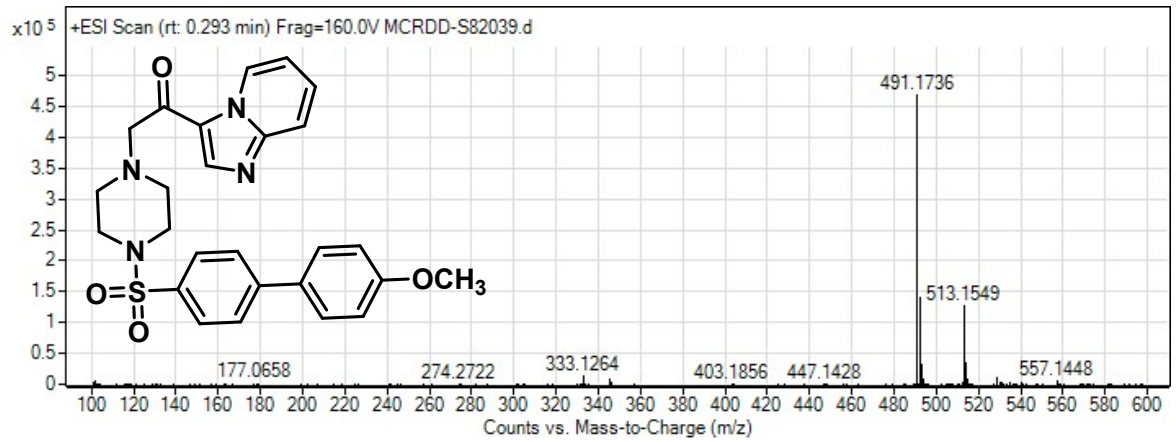
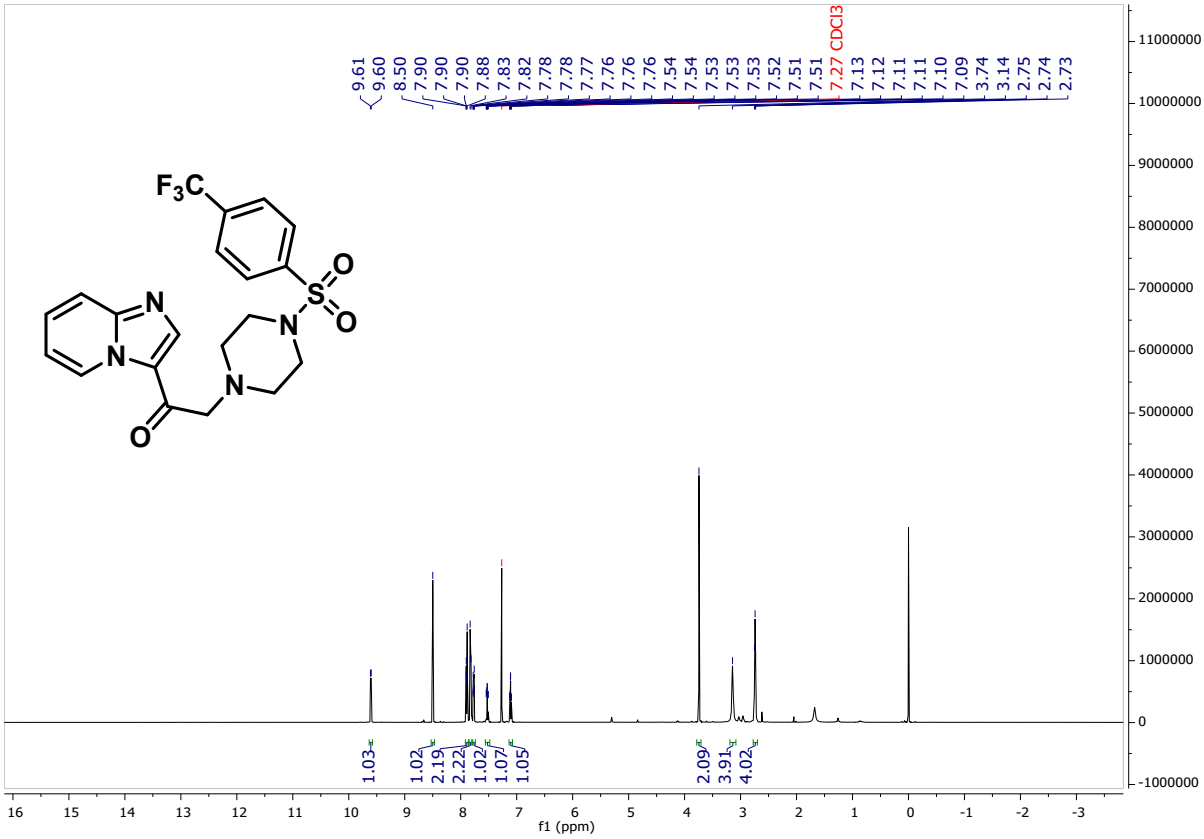
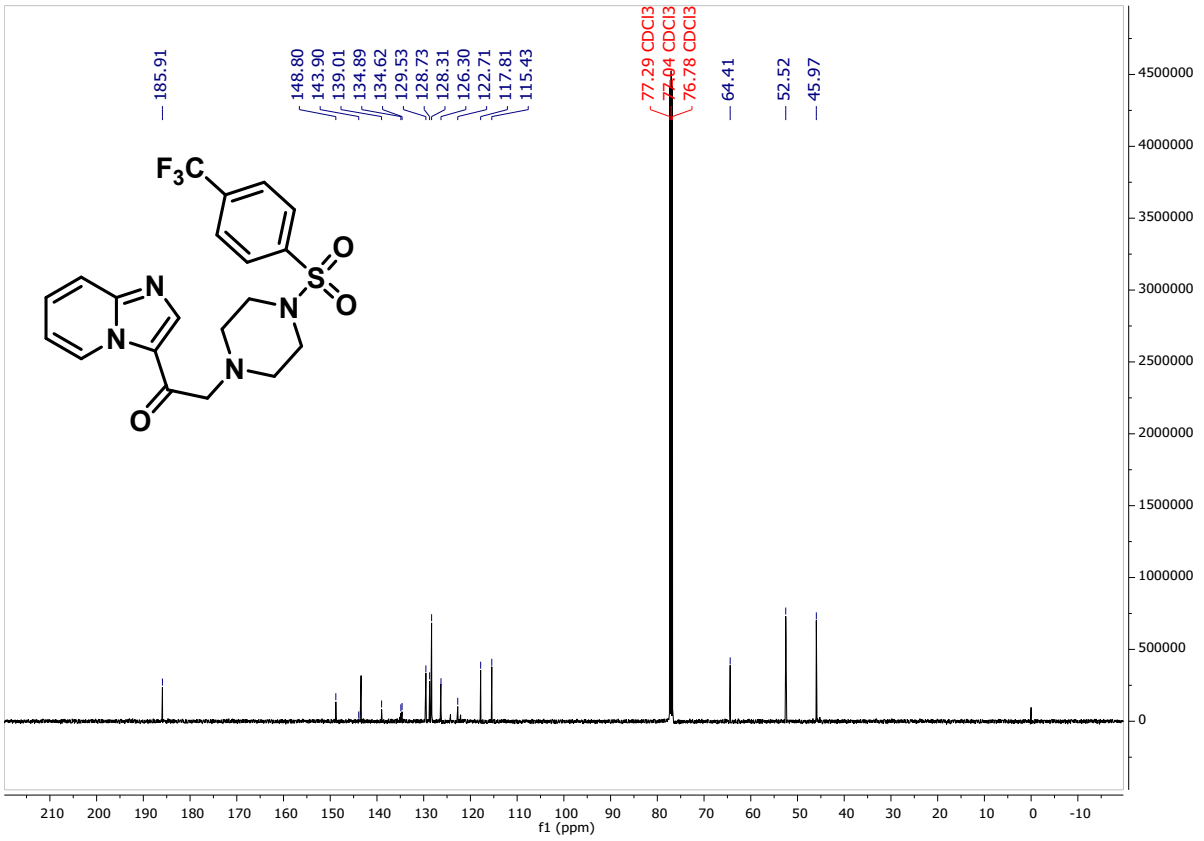


FIGURE S27: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4'-methoxy-[1,1'-biphenyl]-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one (10r) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

28: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10d) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)





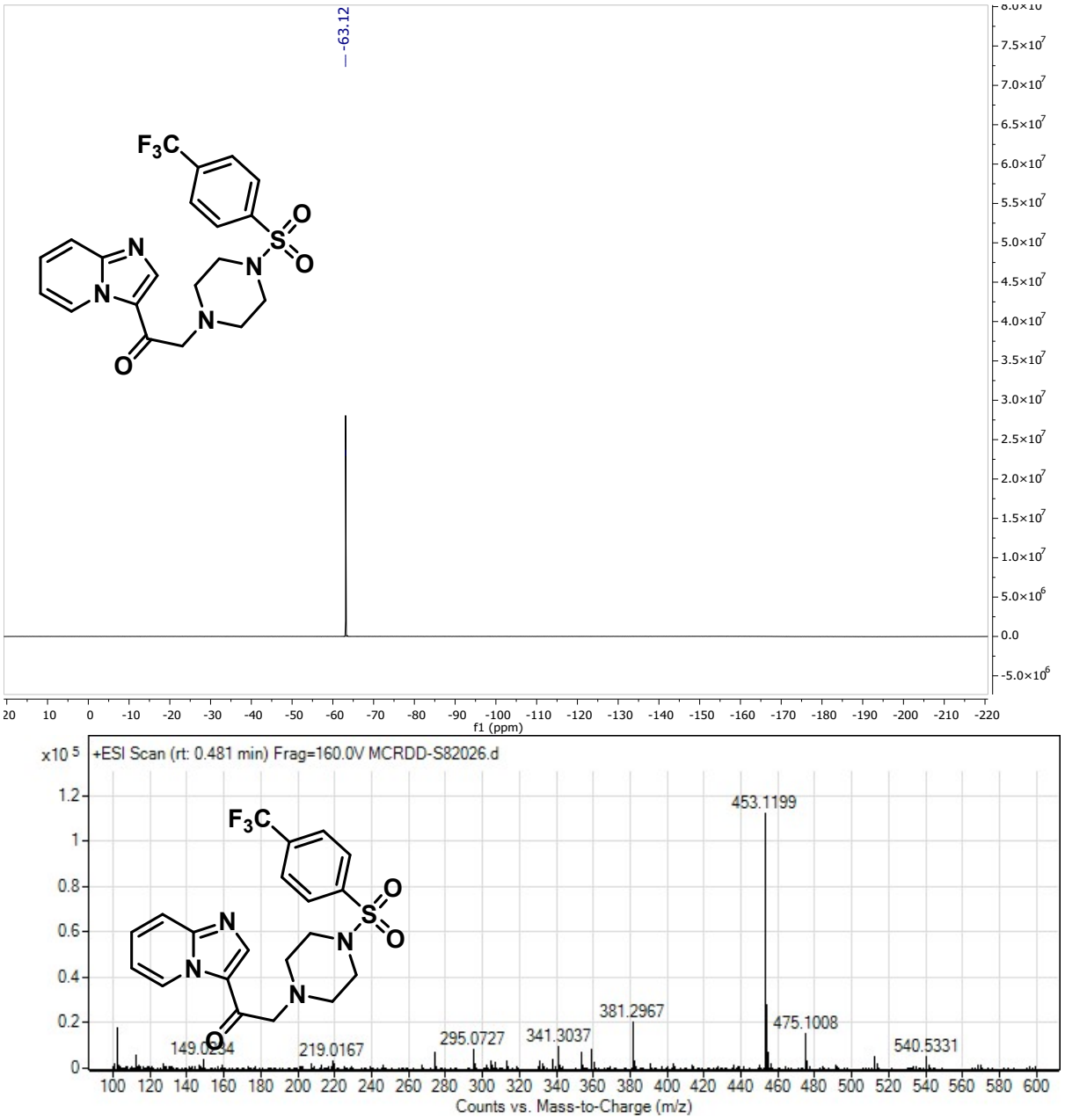
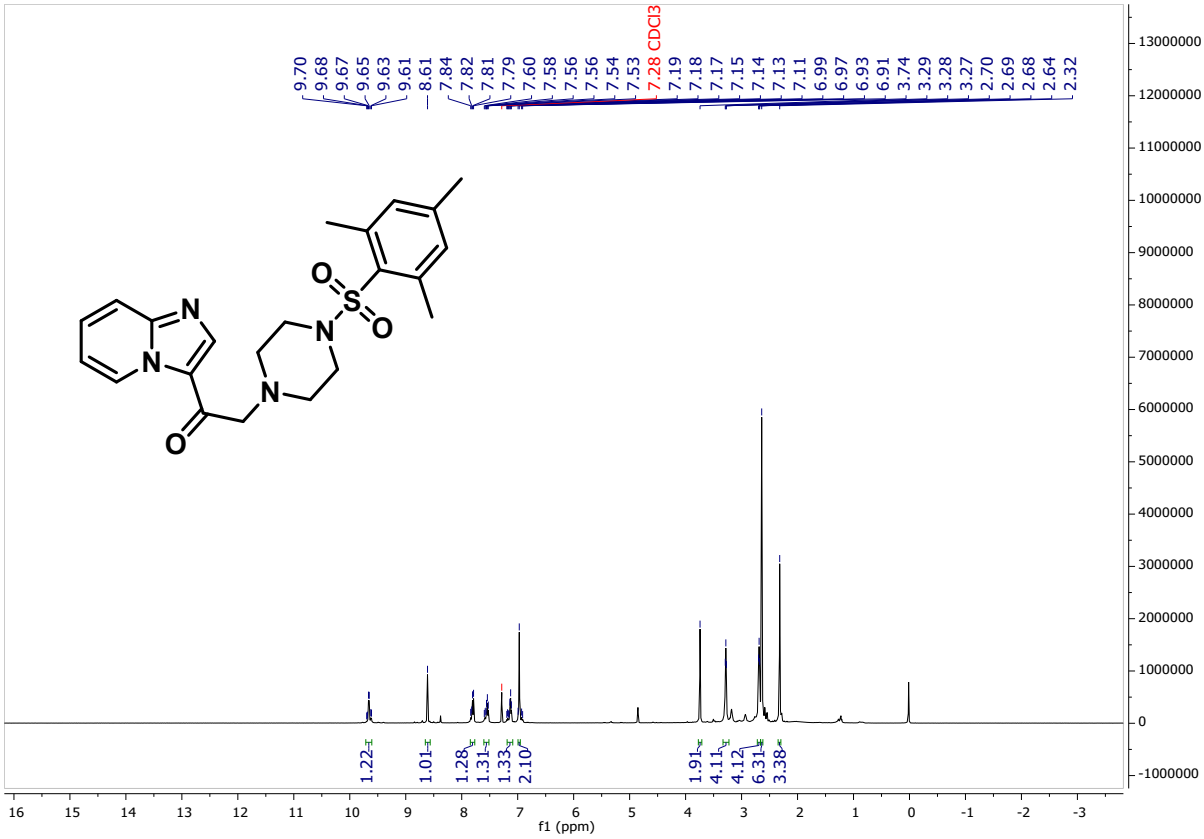
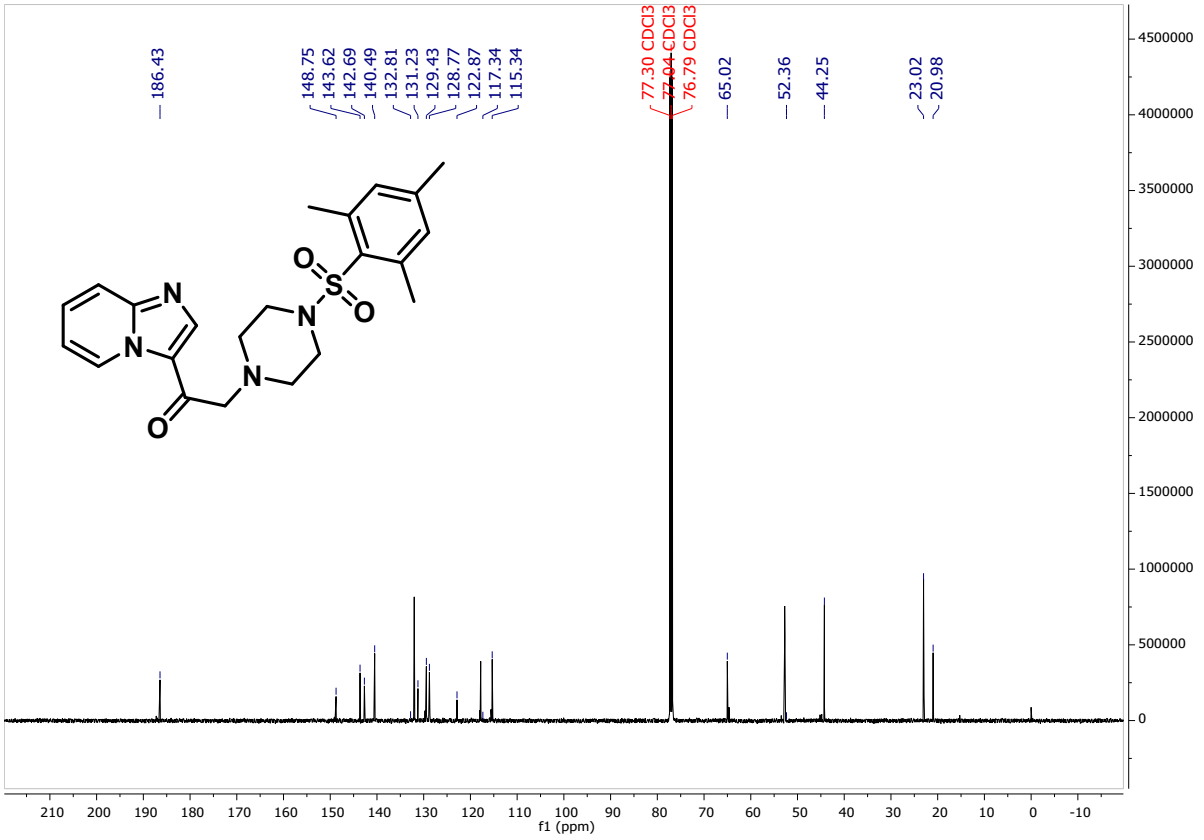


FIGURE S28: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10d) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

29: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(mesitylsulfonyl)piperazin-1-yl)ethan-1-one (10i) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





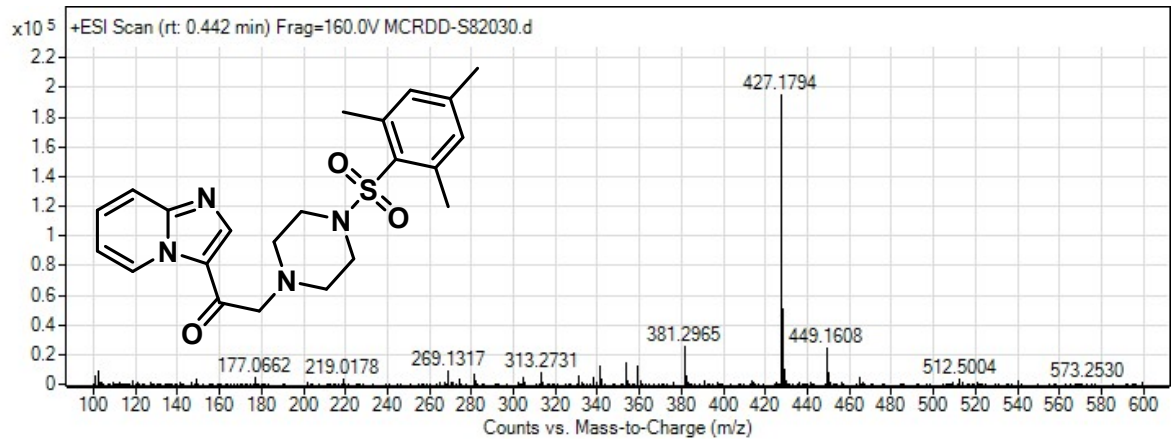
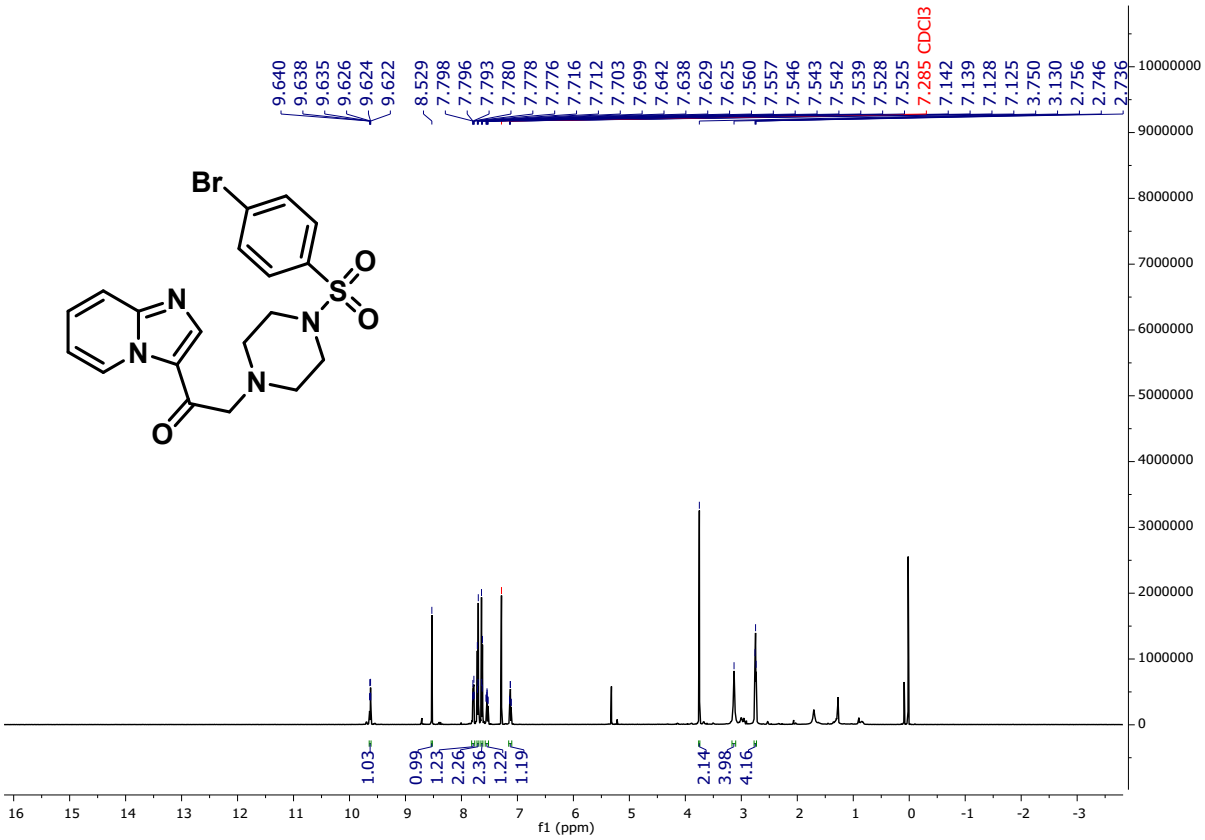
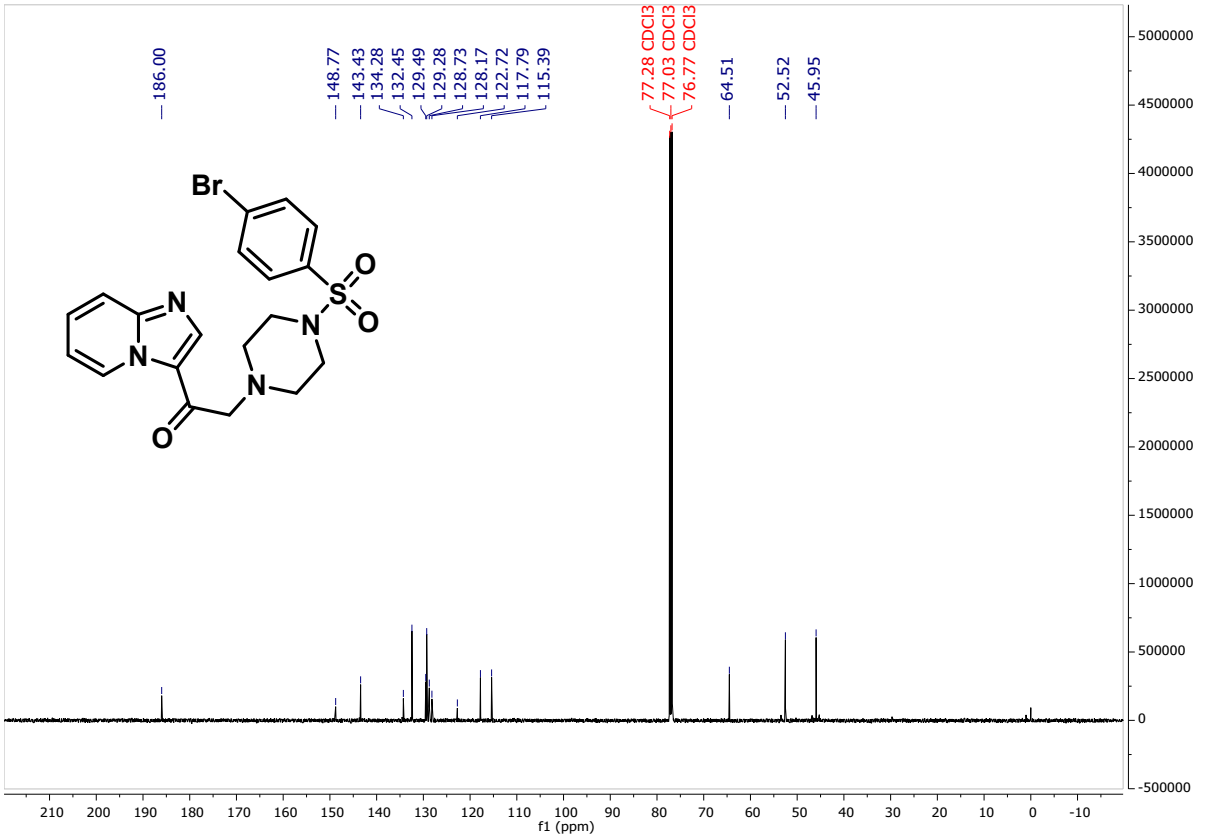


FIGURE S29: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(mesitylsulfonyl)piperazin-1-yl)ethan-1-one (10i) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

30: 2-(4-((4-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10e)

(^{1}H NMR, ^{13}C NMR & HRMS Spectra)





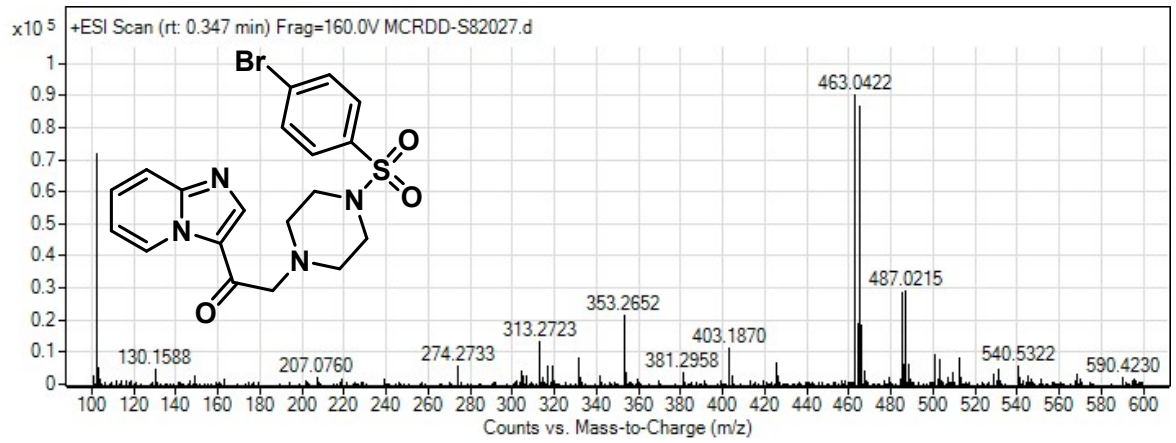
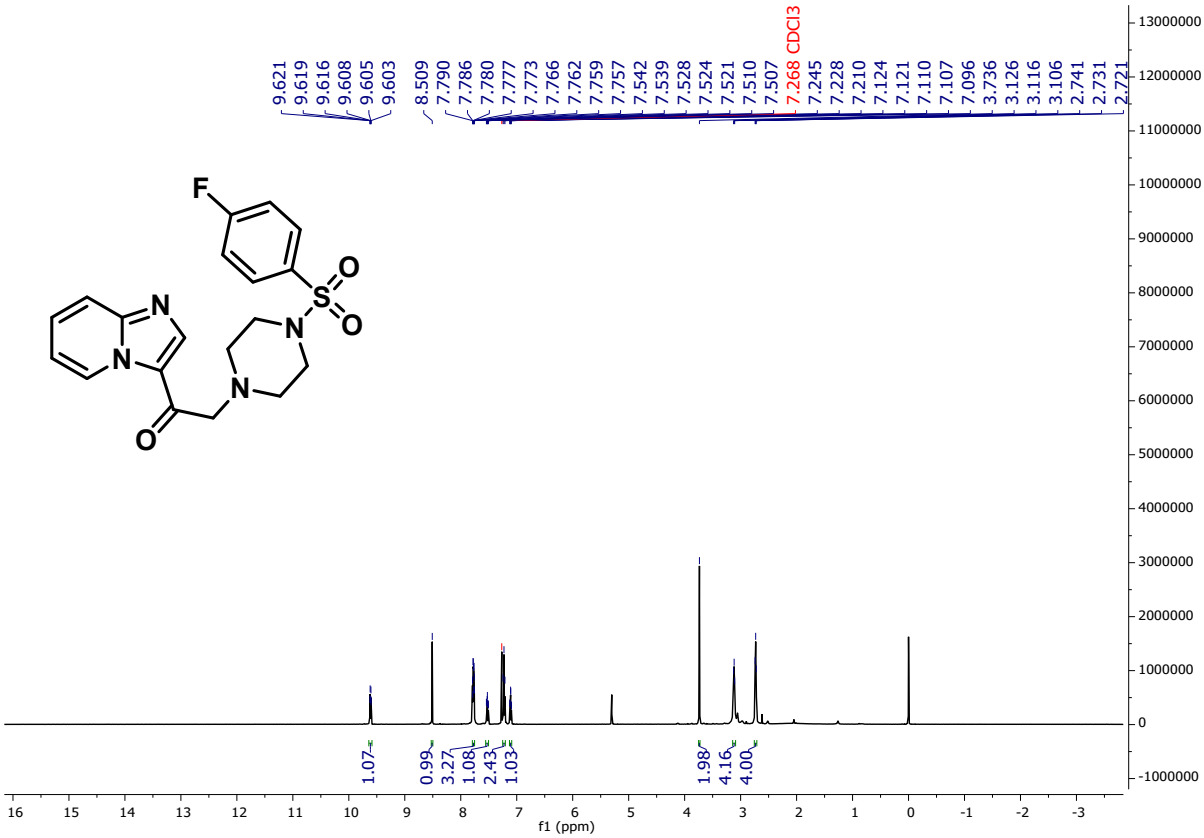
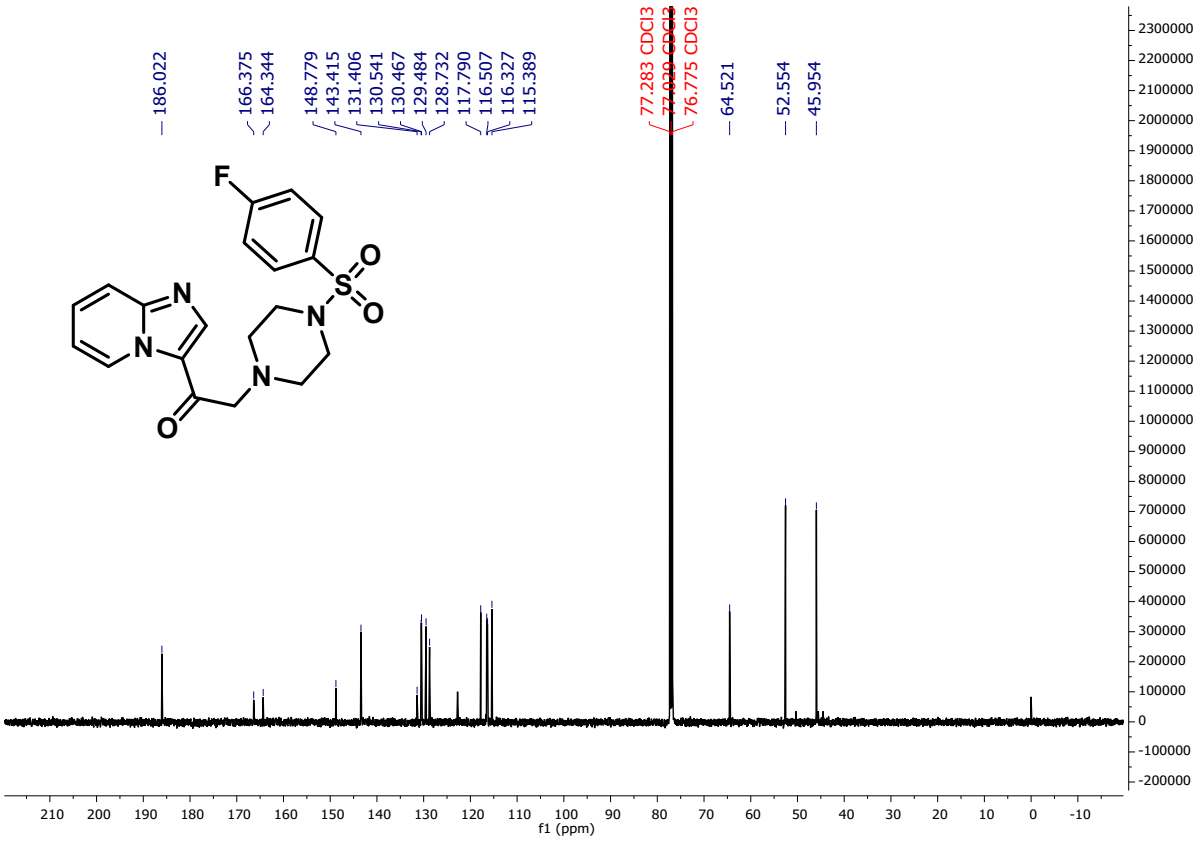
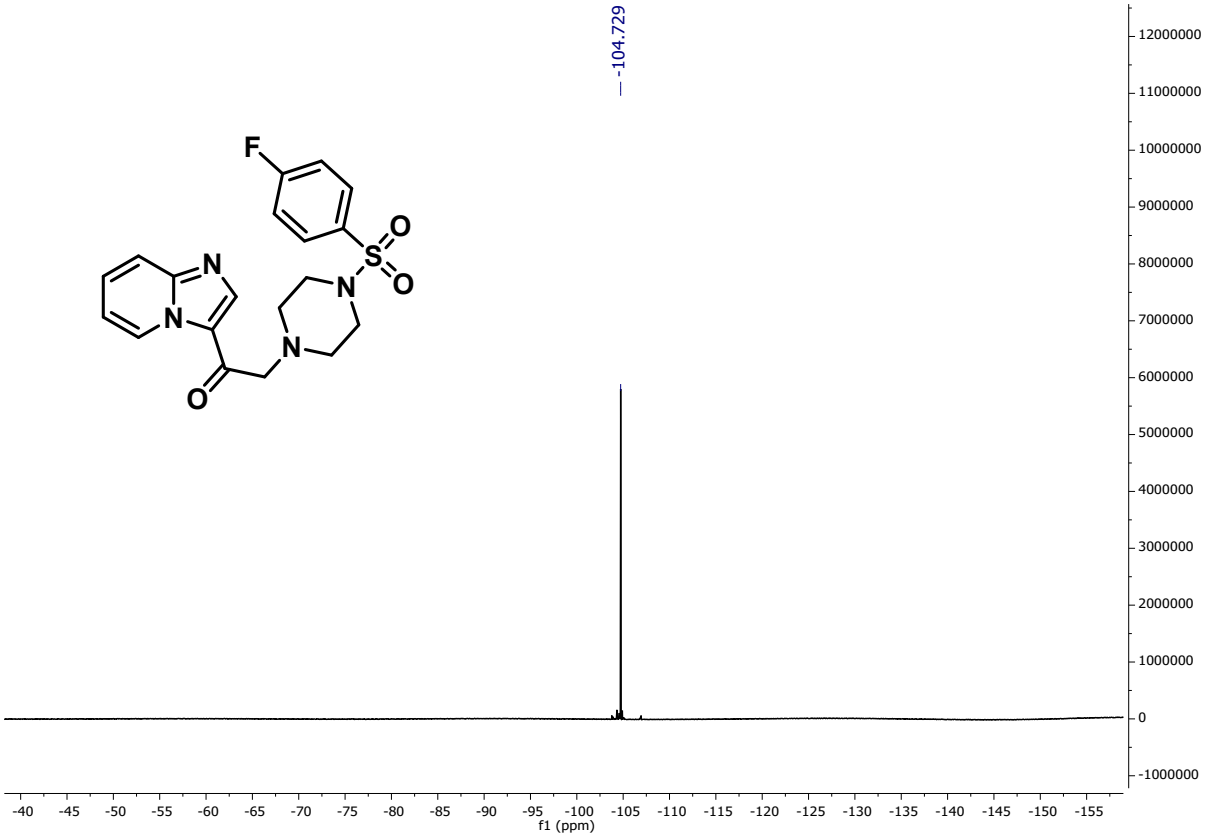


FIGURE S30: 2-(4-((4-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10e) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

31: 2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10f) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)







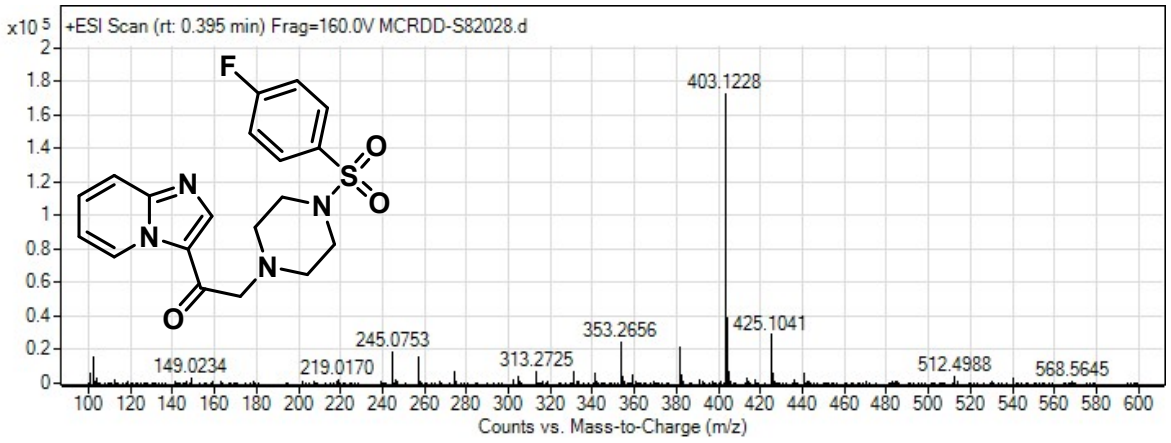
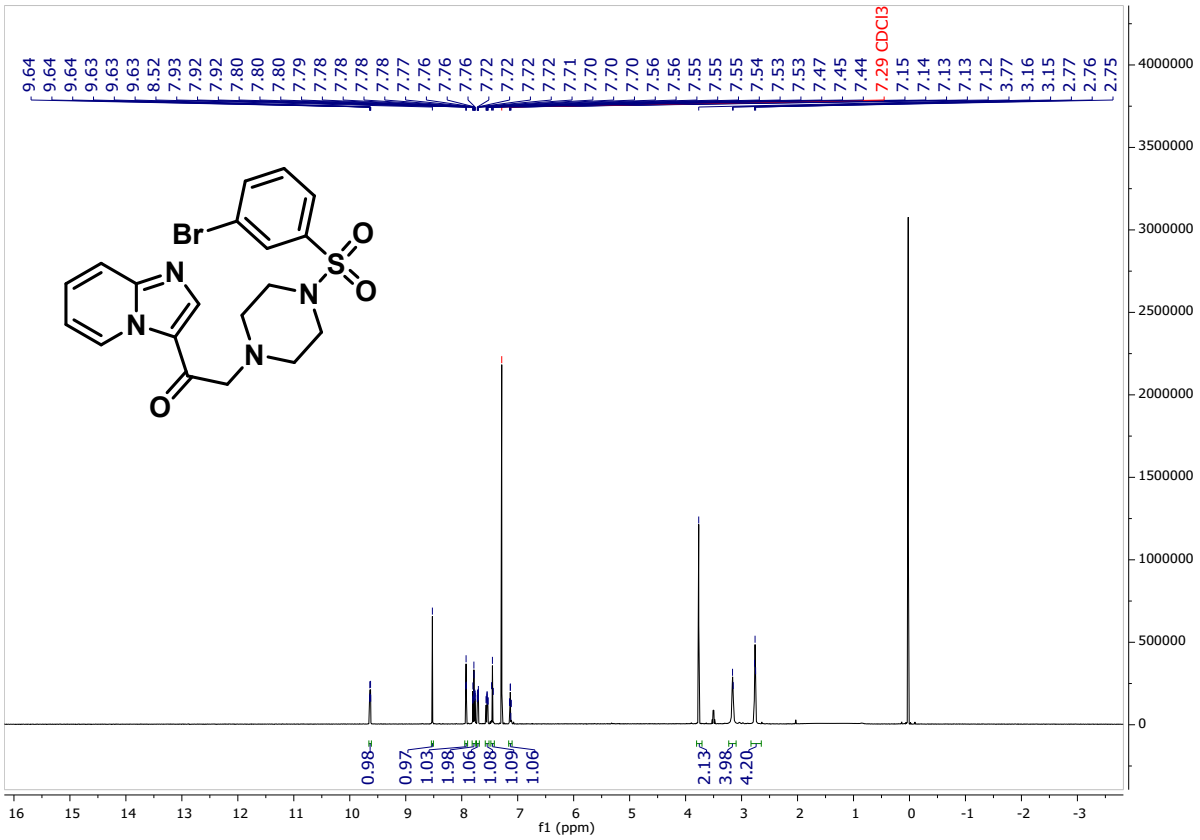
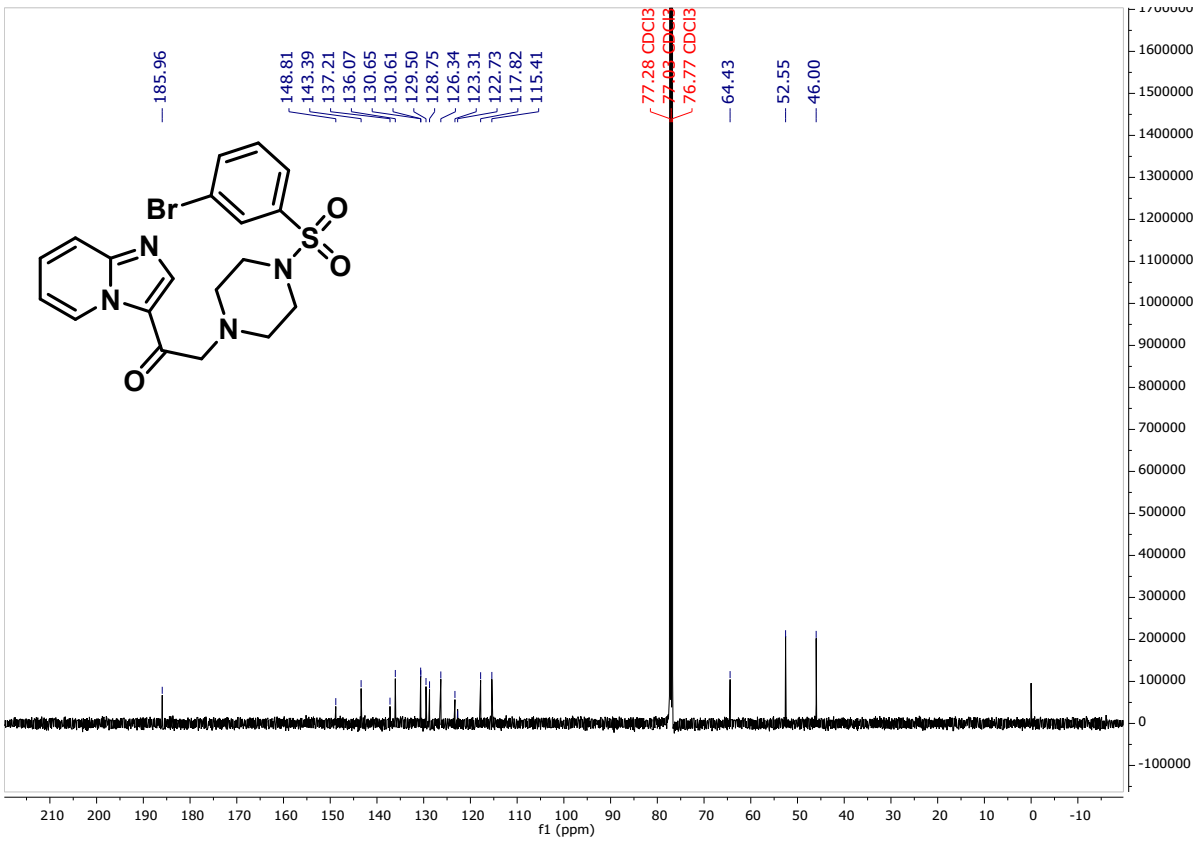


FIGURE S31: 2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10f) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

32: 2-(4-((3-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10k)

(^{1}H NMR, ^{13}C NMR & HRMS Spectra)





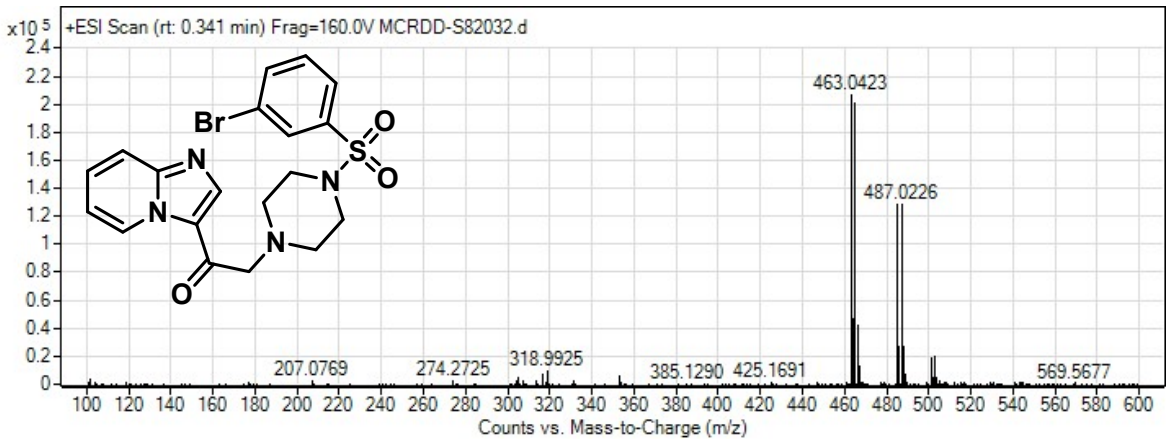
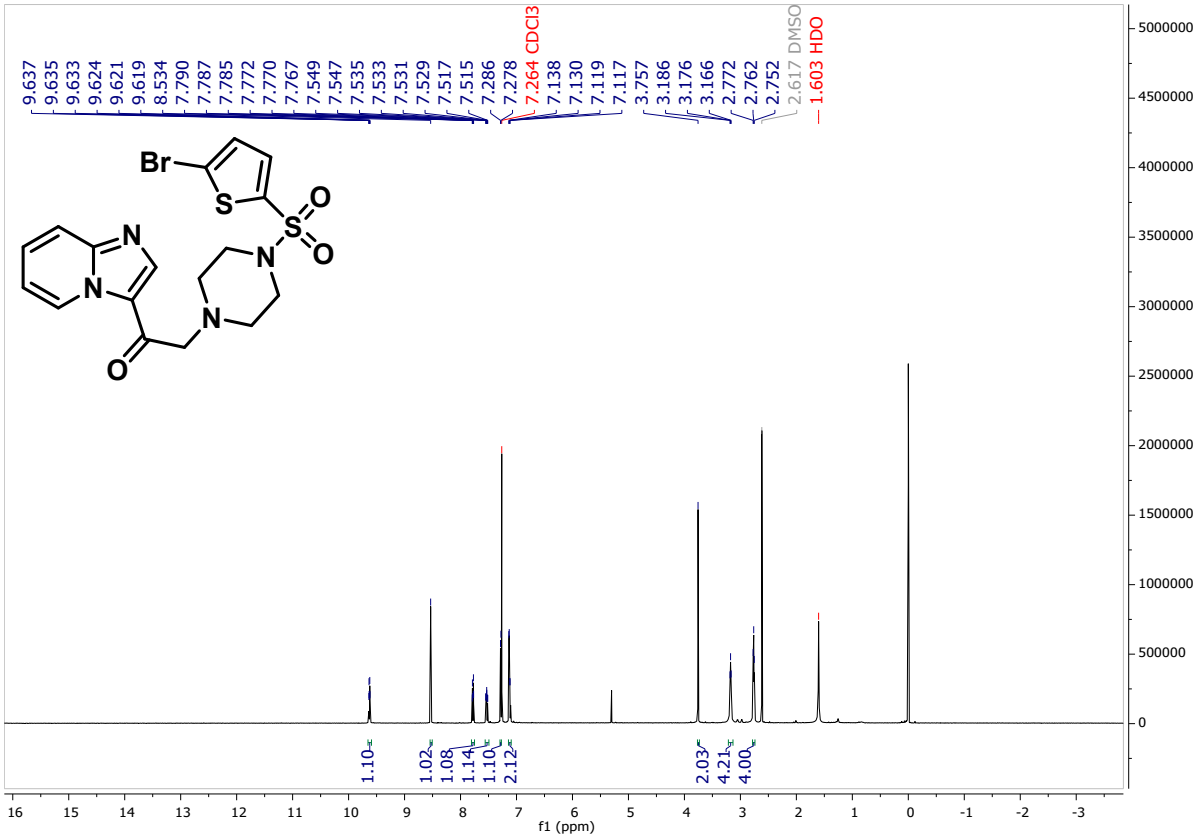
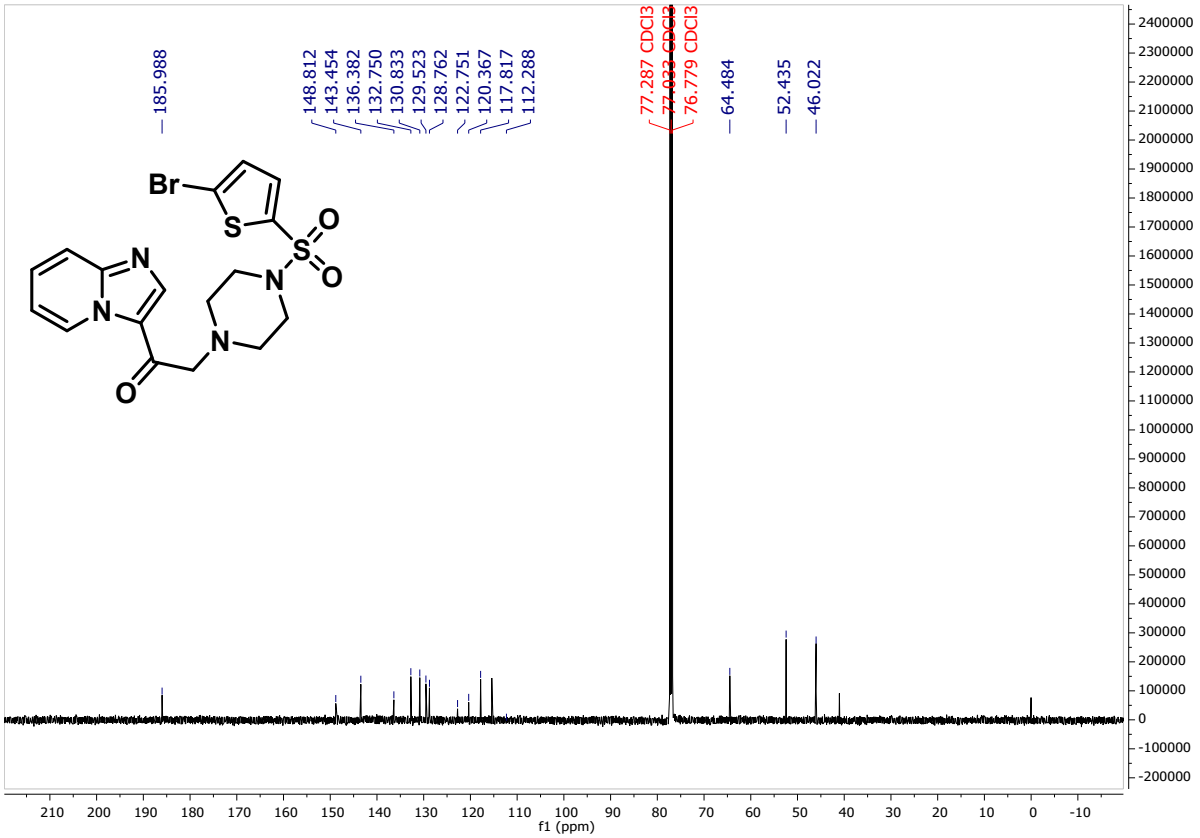


FIGURE S32: 2-(4-((3-bromophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10k) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

33: 2-(4-((5-bromothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10m) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





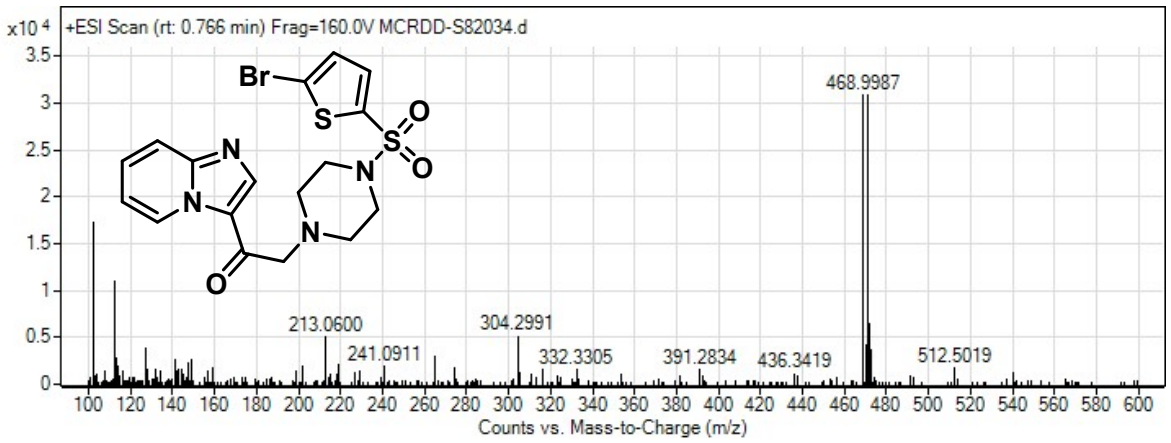
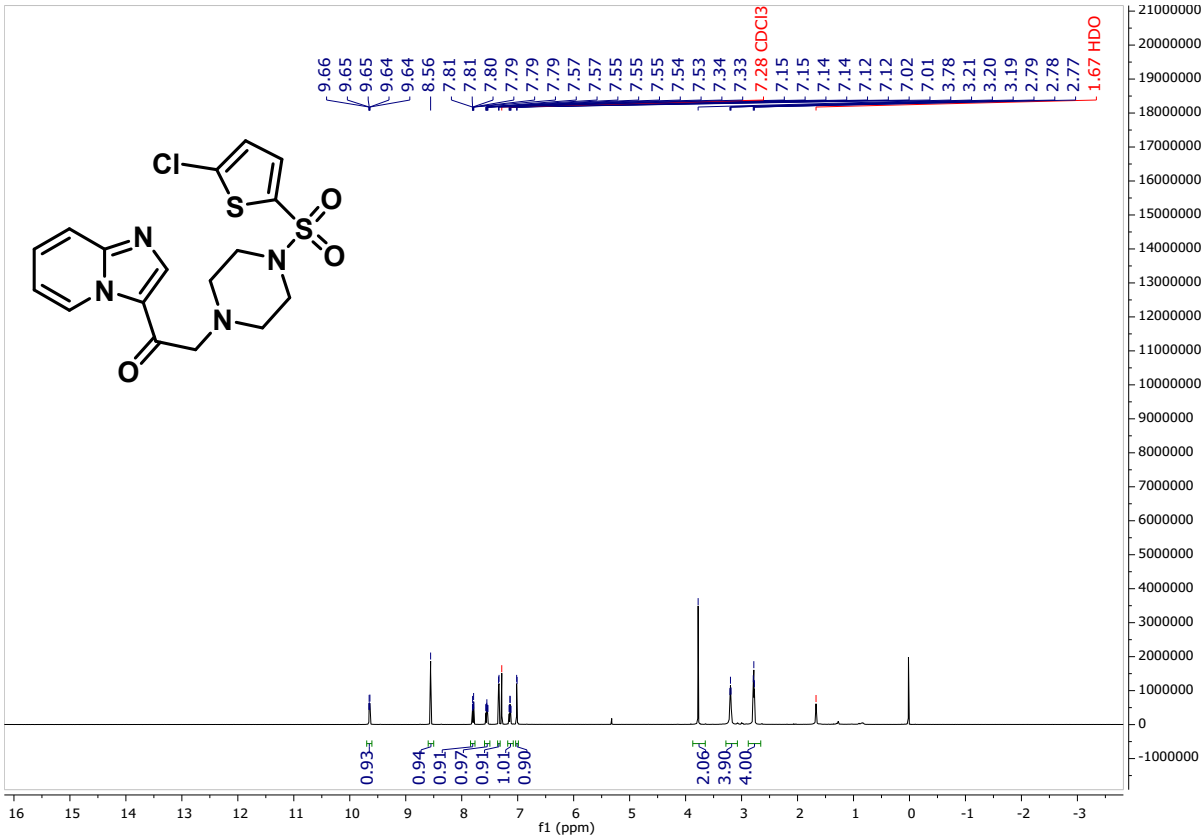
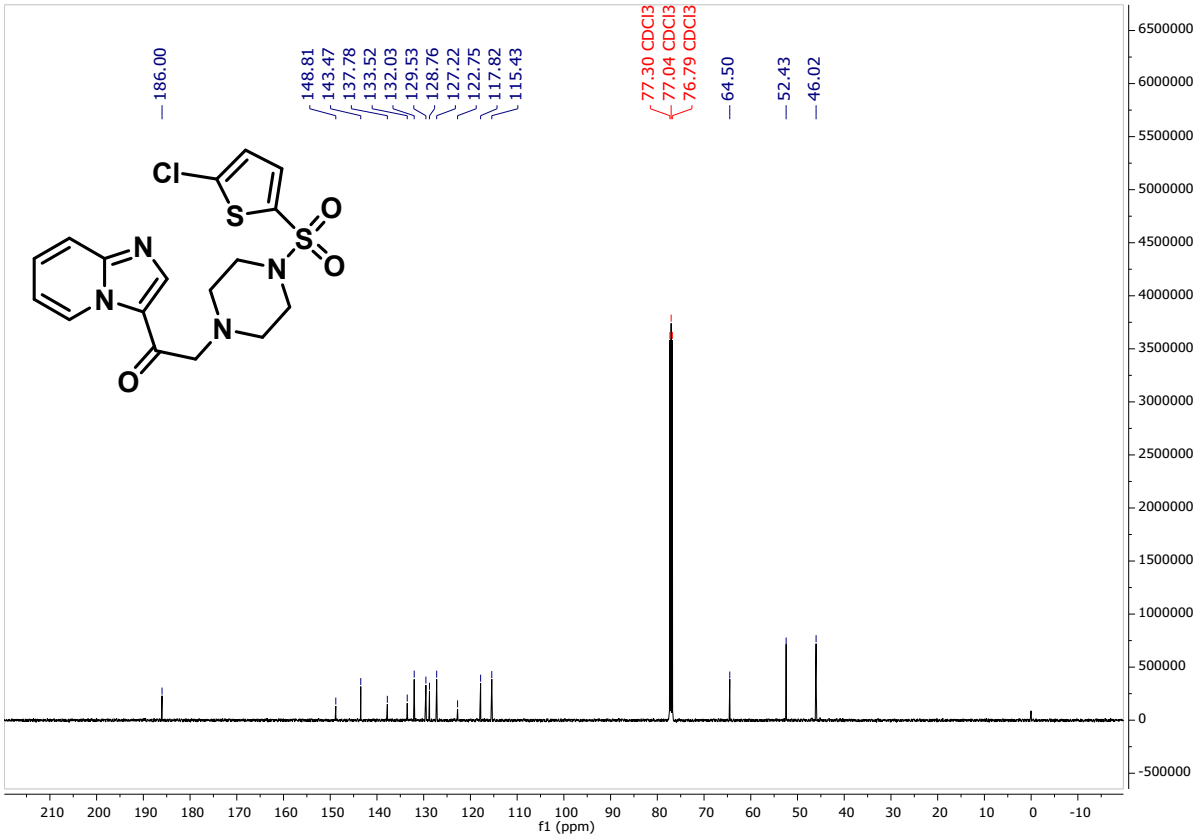


FIGURE S33: 2-(4-((5-bromothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10m) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

34: 2-(4-((5-chlorothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10q) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





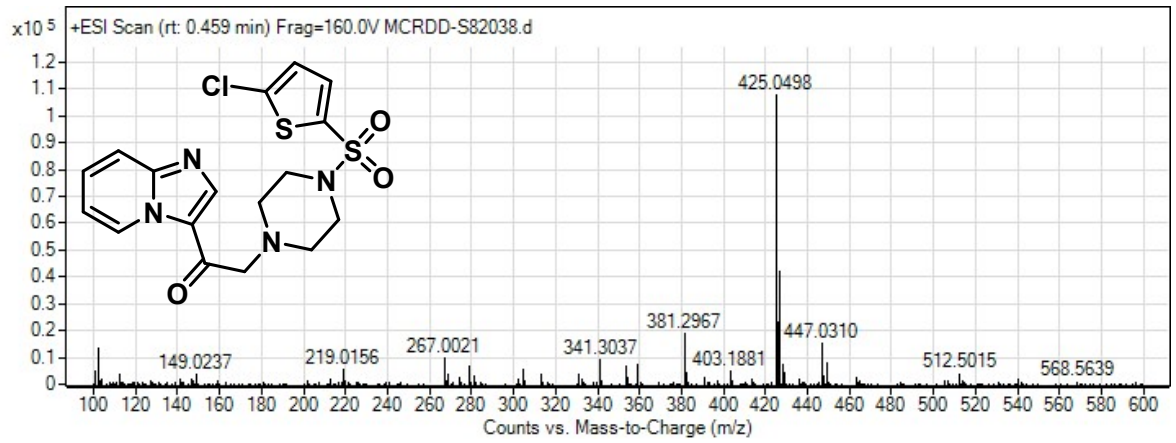
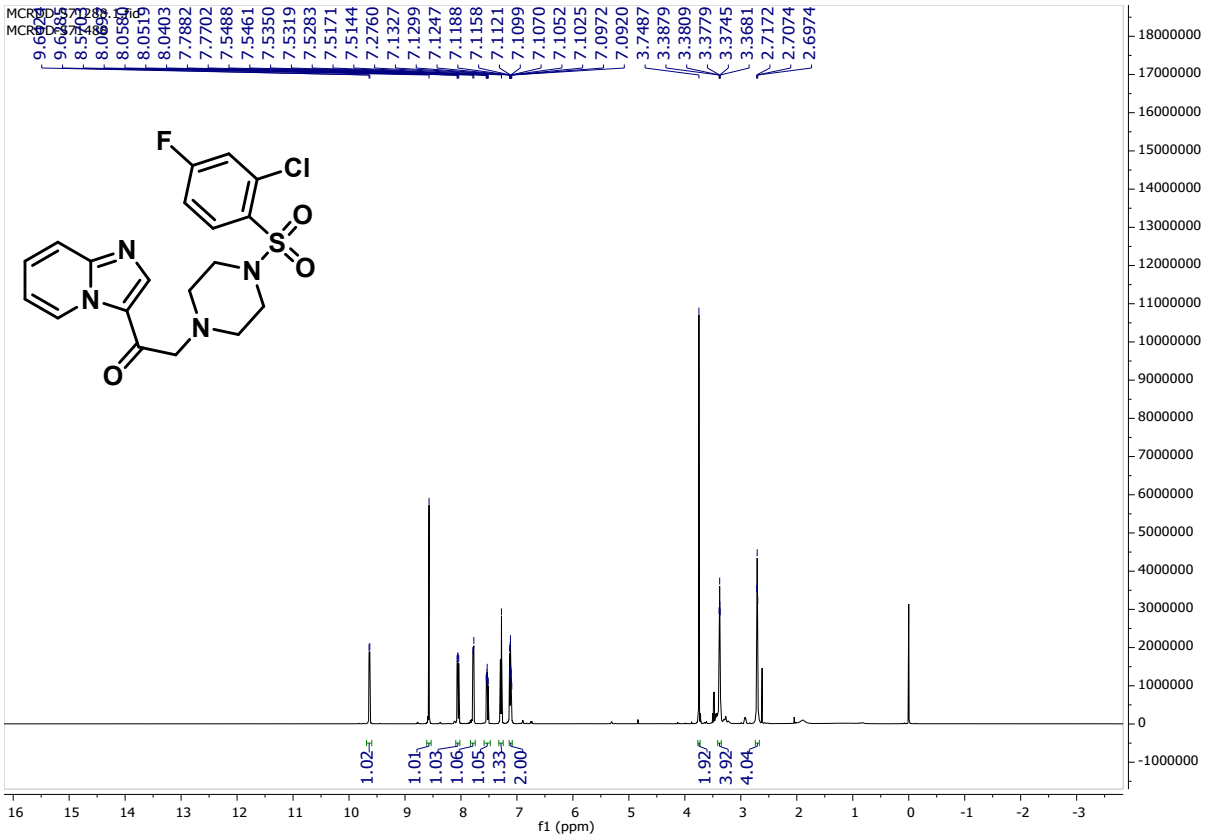
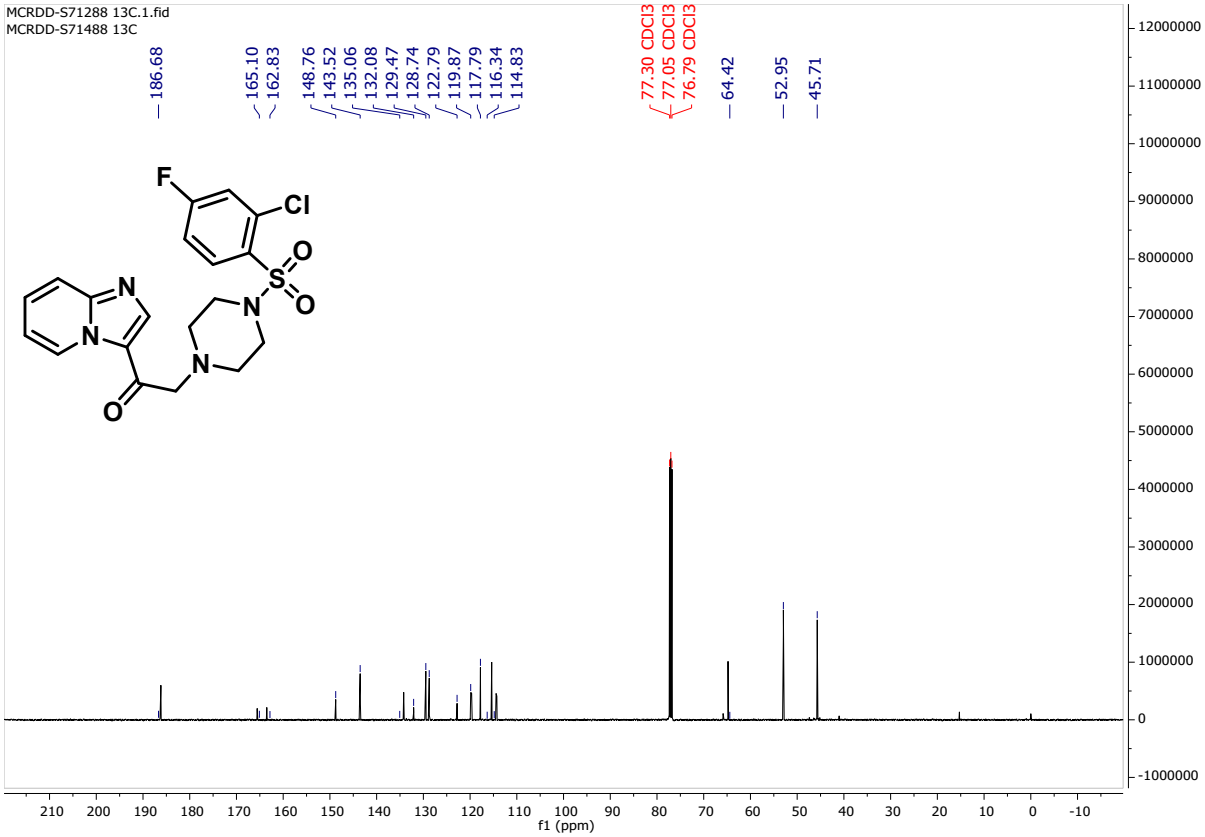


FIGURE S34: 2-(4-((5-chlorothiophen-2-yl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10q) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

35: 2-(4-((2-chloro-4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10p) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra)

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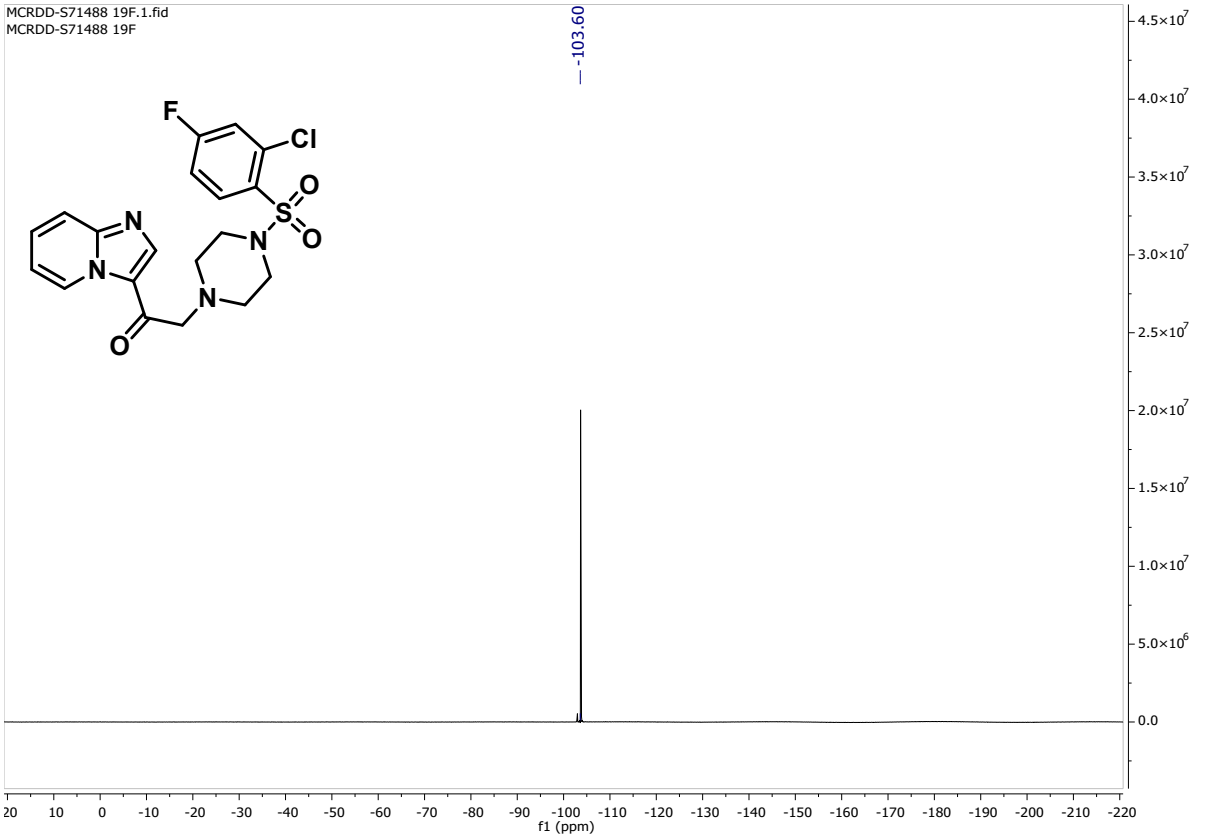
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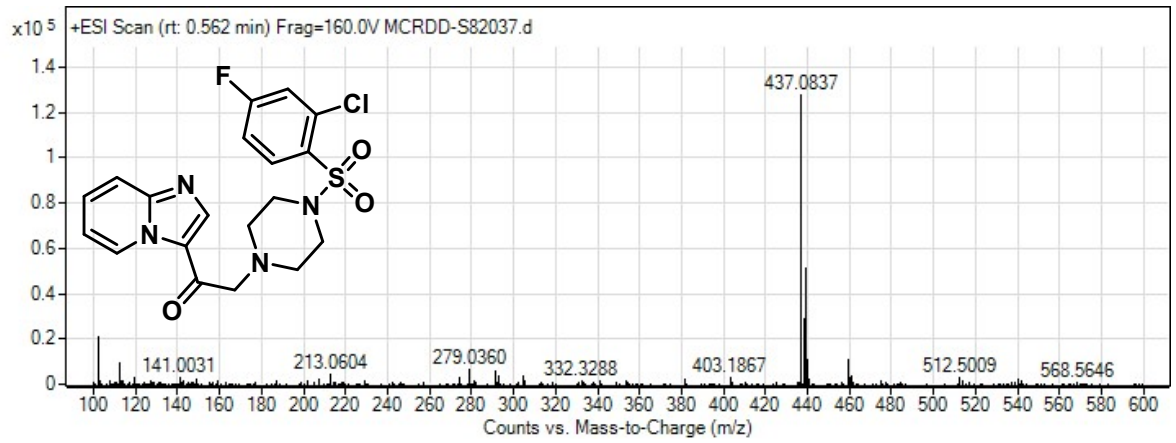
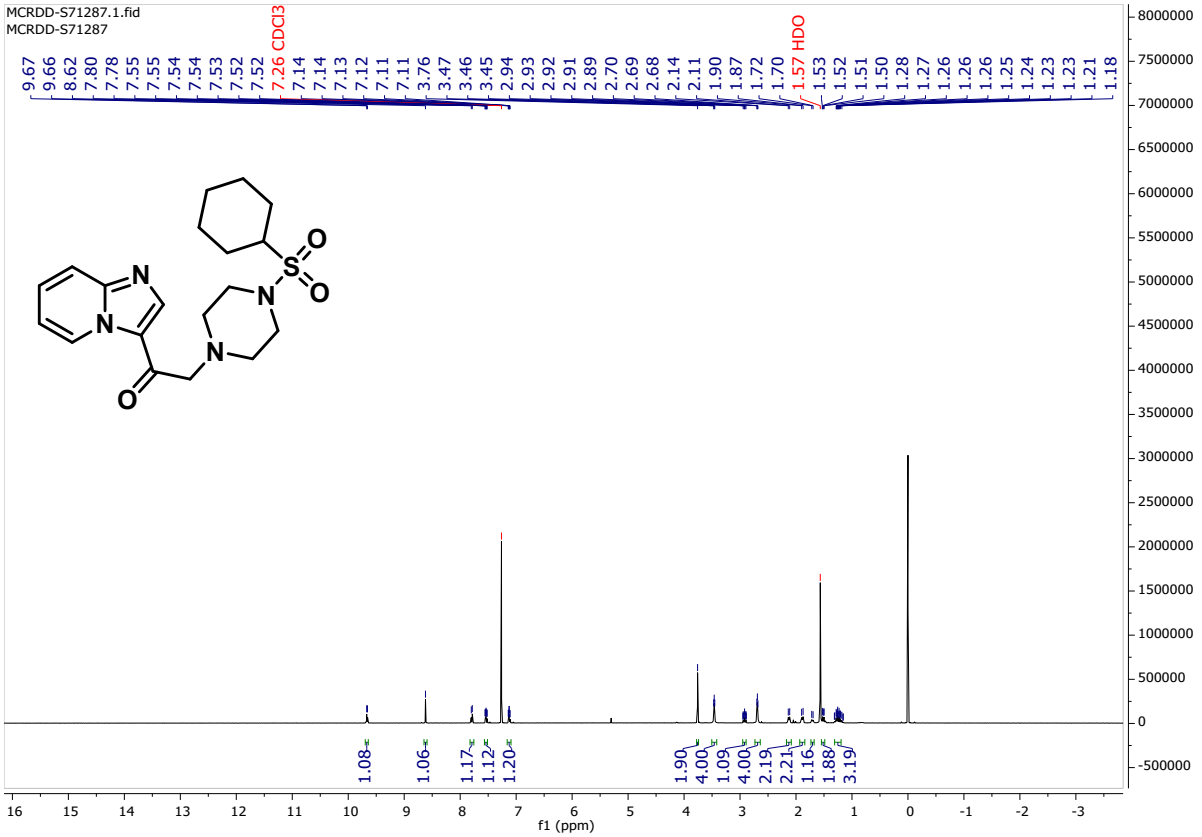
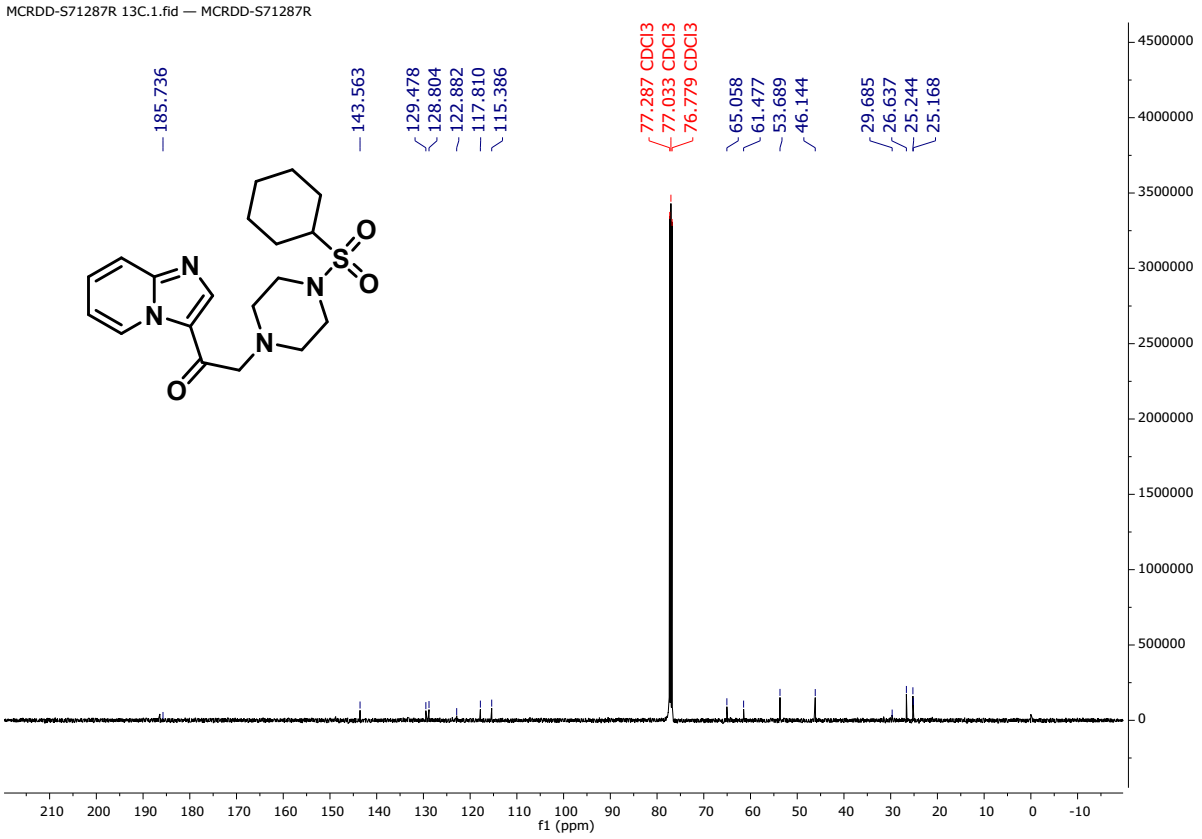


FIGURE S35: 2-(4-((2-chloro-4-fluorophenyl)sulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10p) (^{1}H NMR, ^{13}C NMR, ^{19}F NMR & HRMS Spectra).

36: 2-(4-(cyclohexylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10l) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)





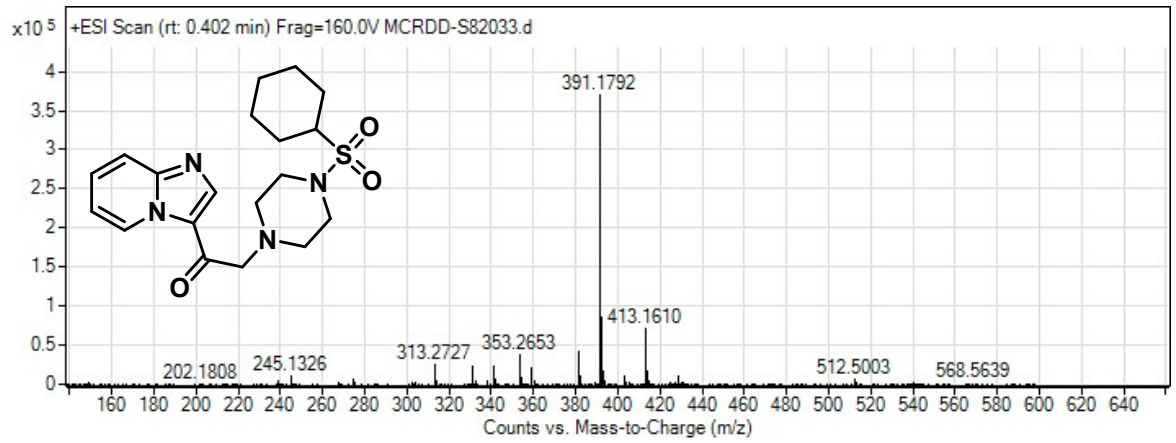
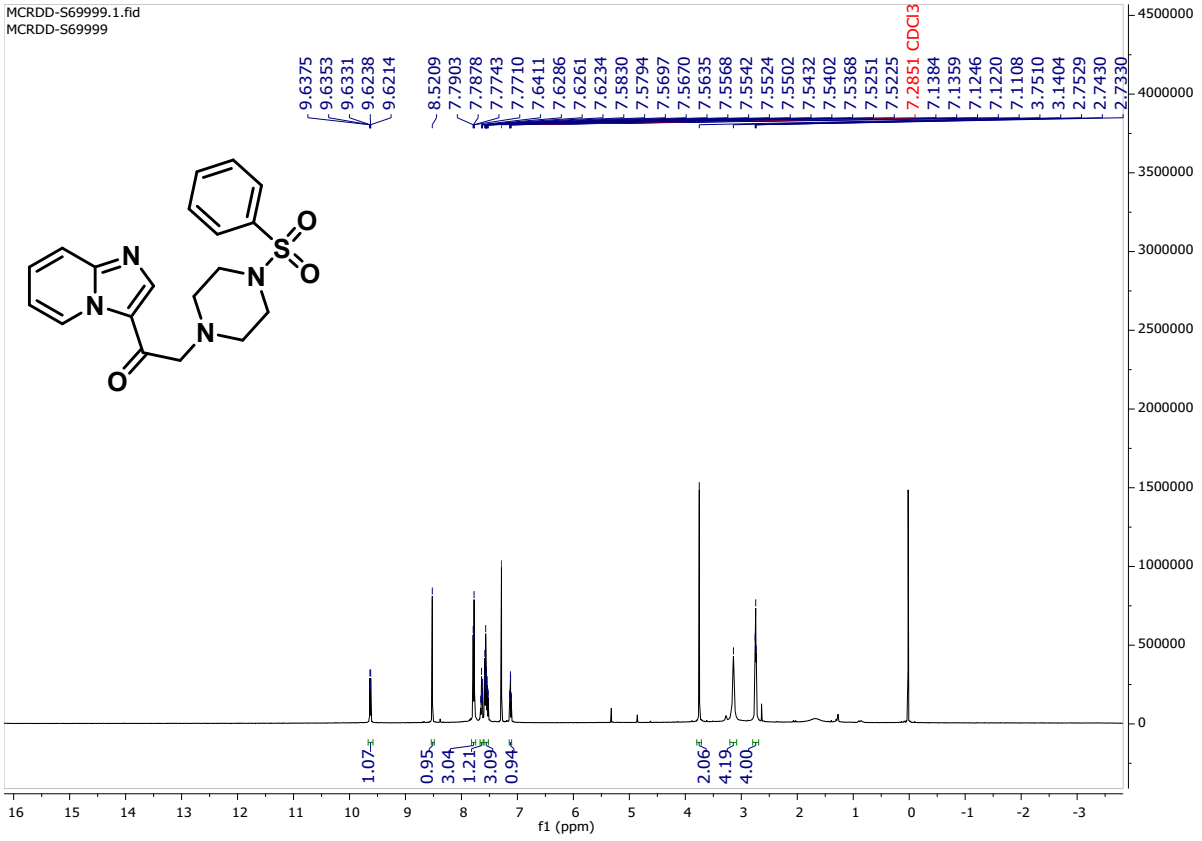


FIGURE S36: 2-(4-(cyclohexylsulfonyl)piperazin-1-yl)-1-(imidazo[1,2-a]pyridin-3-yl)ethan-1-one (10l) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

37: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(phenylsulfonyl)piperazin-1-yl)ethan-1-one (10b) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)



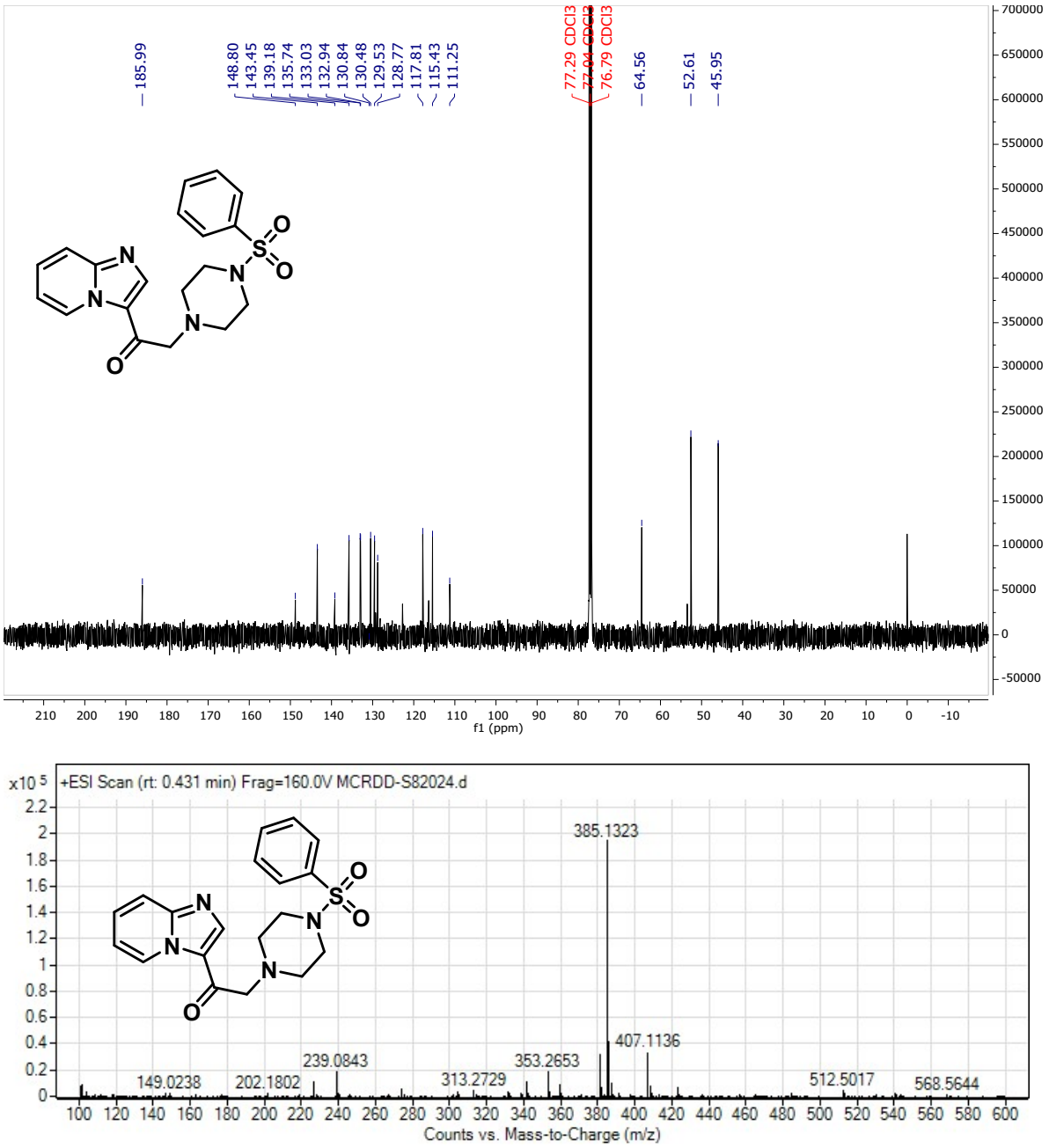
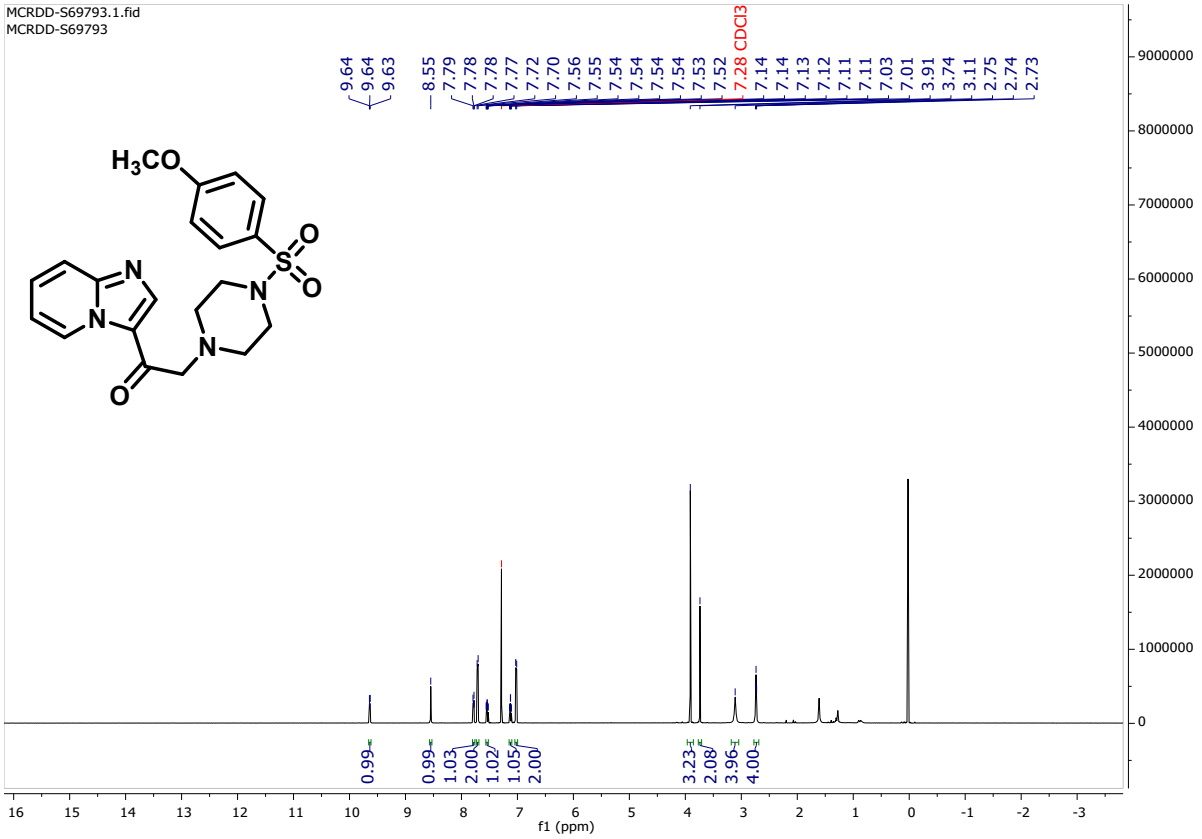


FIGURE S37: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-(phenylsulfonyl)piperazin-1-yl)ethan-1-one (10b) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

38: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10g) (^{1}H NMR, ^{13}C NMR & HRMS Spectra)



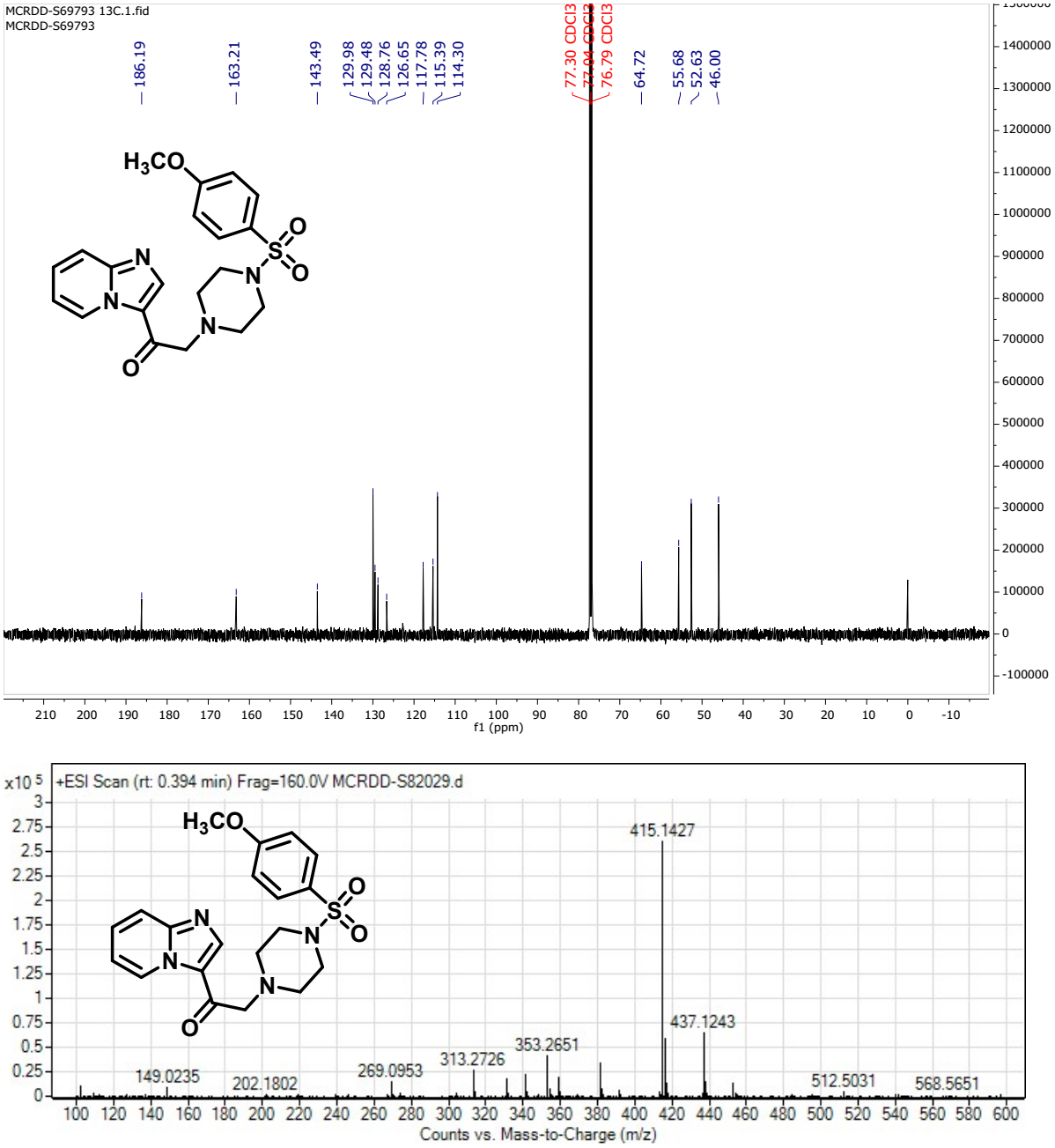
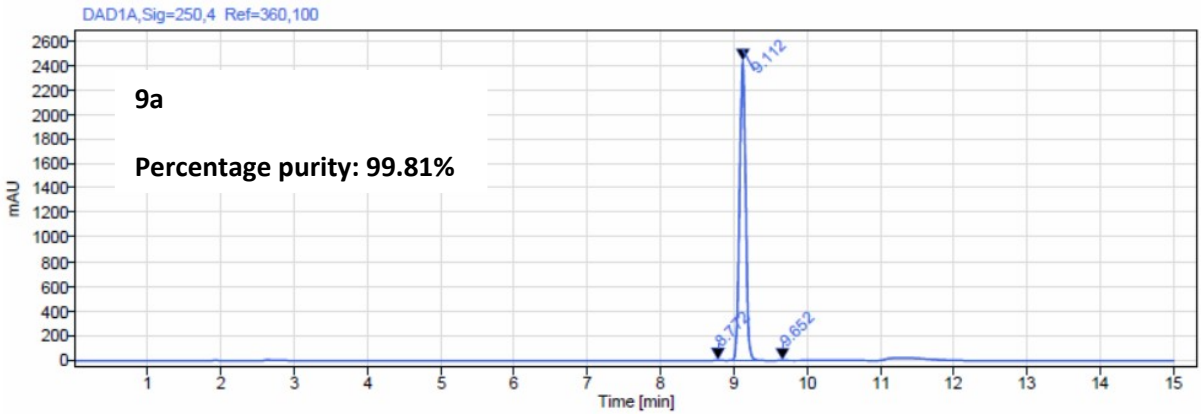


FIGURE S38: 1-(imidazo[1,2-a]pyridin-3-yl)-2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethan-1-one (10g) (^{1}H NMR, ^{13}C NMR & HRMS Spectra).

3. HPLC method and purity chromatogram of synthesized compounds

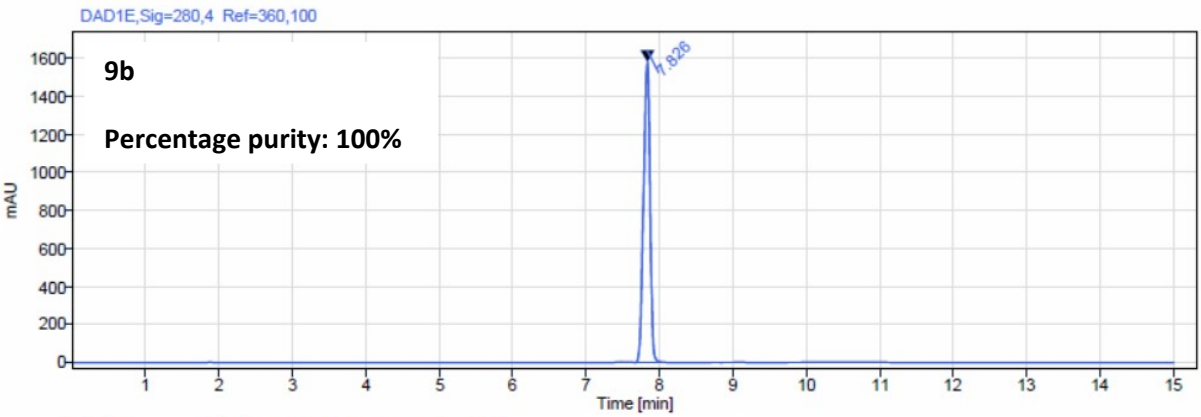
An Agilent 1260 infinity II system with phenomenix kinetic C_{18} column (250 × 4.6 mM, 5 µM) eluted at 1 mL/min with gradient elution having solvent system of water (ultrapure)+ 0.1% formic acid: methanol (procured from ualigens) was used for analyzing the purity of the compounds; 100 ppm of the analyte solution was prepared in HPLC-grade methanol. The method optimized was gradient having a duration of 15 min. The injection volume was 20 µL. The detector

utilized was diode-array detection. The chromatograms revealed purity of more than 95% as provided in the supporting information.



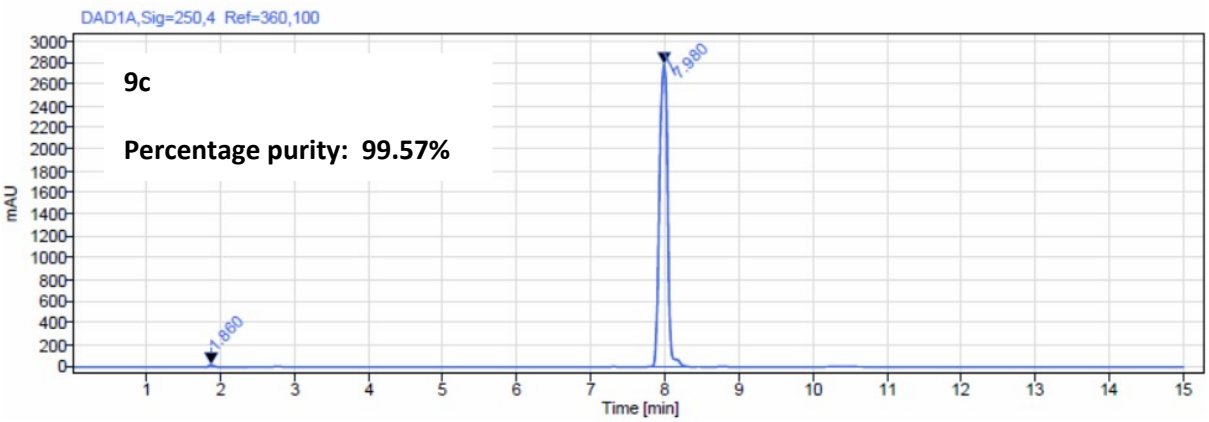
Signal: DAD1A,Sig=250,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.772	vv	0.2333	20.5350	3.1407	0.1446
9.112	vv	0.5799	14171.0470	2439.4710	99.8171
9.652	vv	0.3400	5.4310	0.6964	0.0383
		Sum	**14197.0130**		



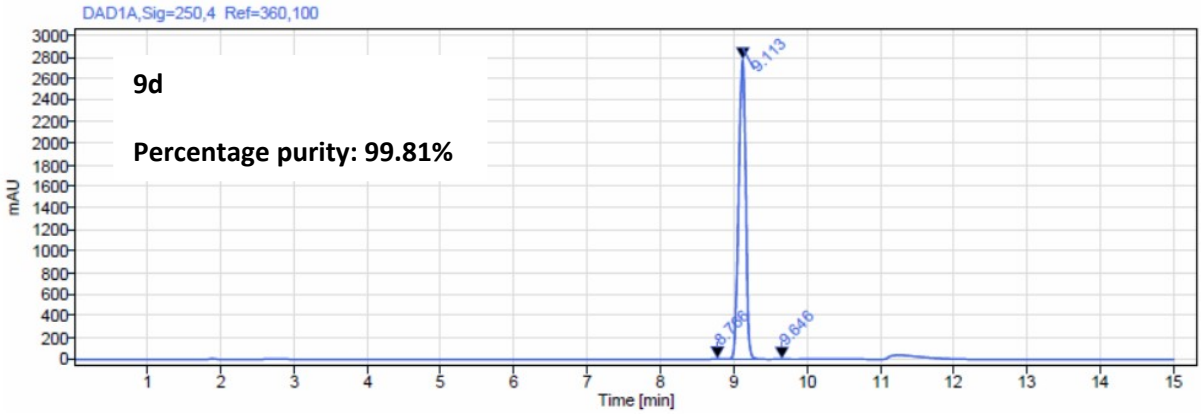
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.826	vv	0.4799	9704.7405	1583.1411	100.0000
		Sum	**9704.7405**		



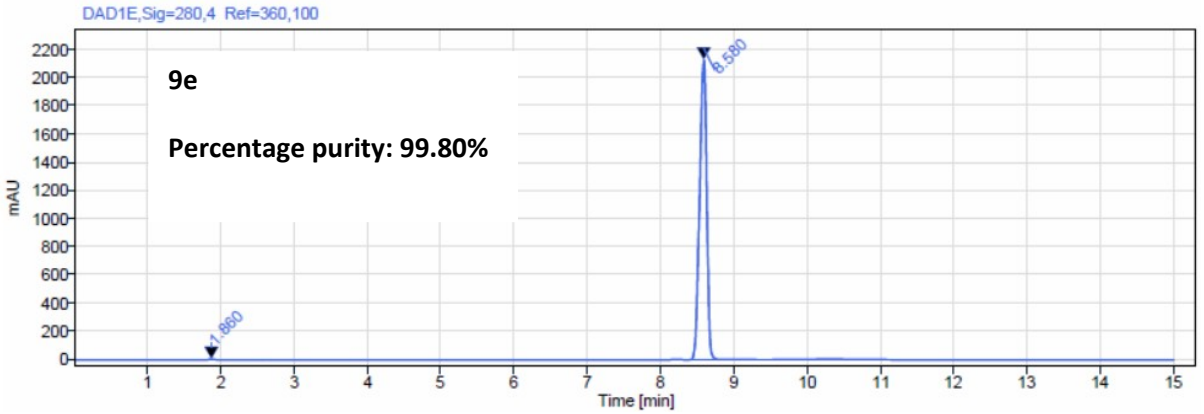
Signal: DAD1A,Sig=250,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.860	vv	0.5733	90.8027	19.6814	0.4213
7.980	vv	0.6400	21459.9336	2784.5773	99.5787
		Sum	**21550.7363**		



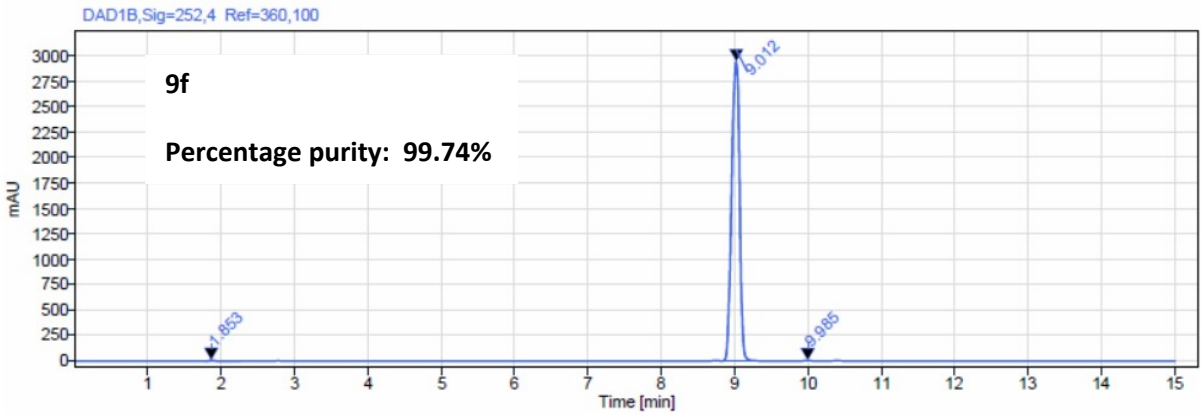
Signal: DAD1A,Sig=250,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.766	vv	0.2400	28.1798	4.1421	0.1504
9.113	vv	0.5800	18700.9105	2779.8086	99.8107
9.646	vv	0.3467	7.2926	0.8883	0.0389
		Sum	**18736.3829**		



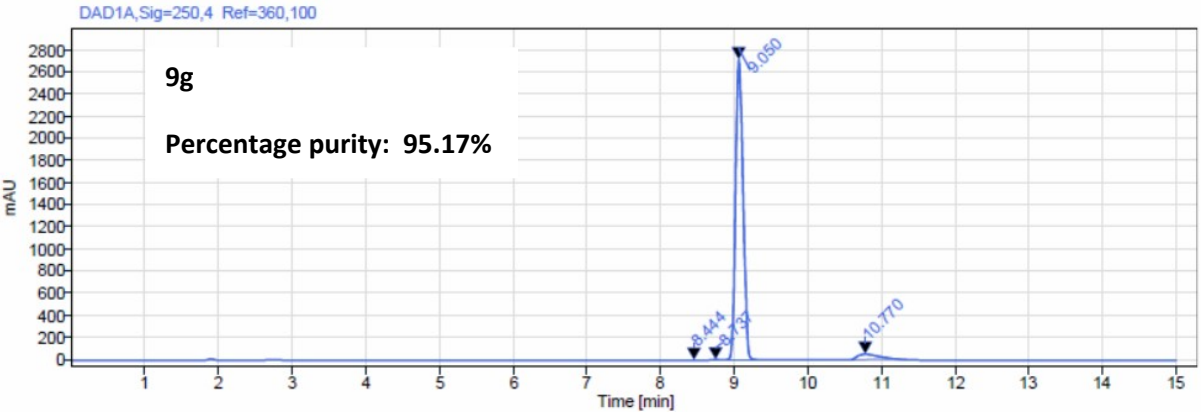
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.860	vv	0.3733	28.1430	5.7059	0.1954
8.580	vv	0.5800	14376.5338	2127.4105	99.8046
		Sum	**14404.6768**		



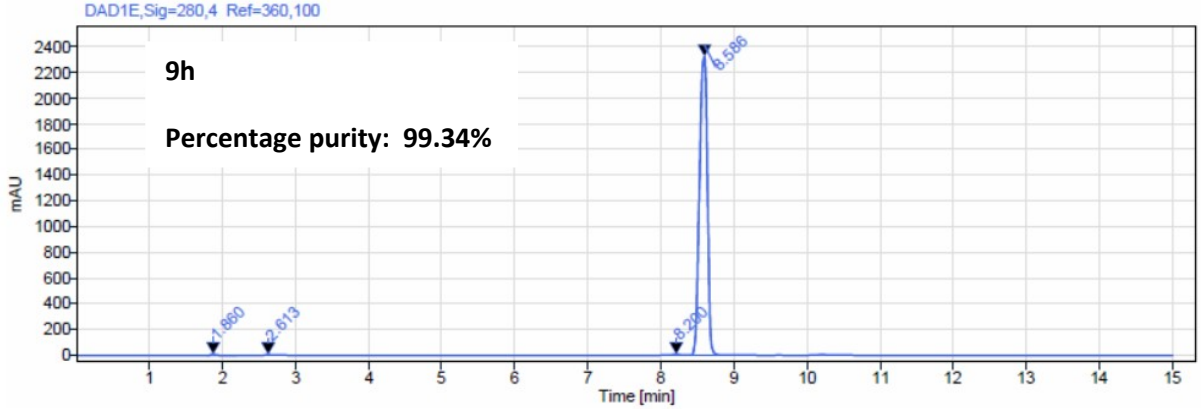
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.4799	44.7364	7.8909	0.2024
9.012	vv	0.5666	22050.9196	2950.1954	99.7402
9.985	vv	0.1666	12.7084	2.7271	0.0575
		Sum	**22108.3644**		



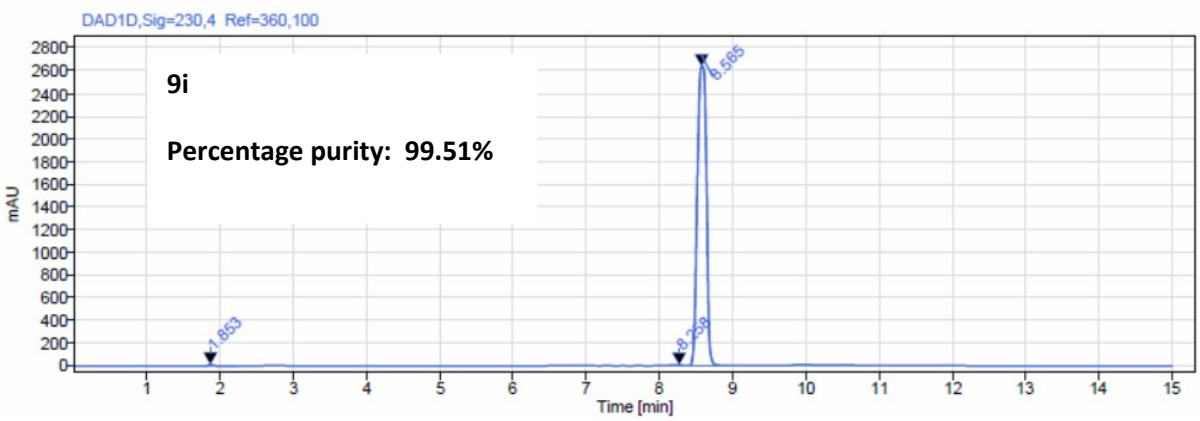
Signal: DAD1A,Sig=250,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.444	vv	0.2732	8.1023	0.8842	0.0401
8.737	vv	0.2133	22.7832	3.4676	0.1127
9.050	vv	0.6331	19235.9023	2712.5934	95.1703
10.770	vv	0.6198	945.2969	48.6155	4.6769
		Sum	**20212.0847**		



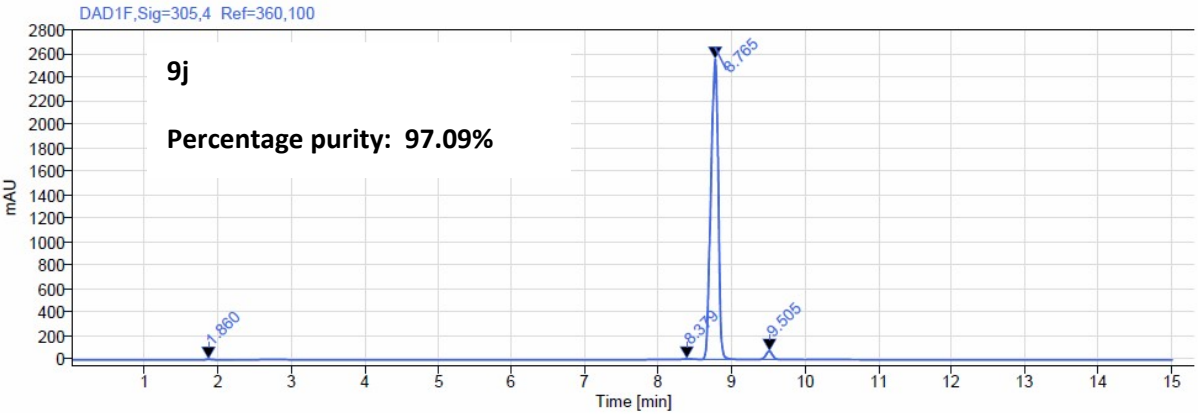
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.860	vv	0.4133	45.6900	8.3211	0.2585
2.613	vv	0.2533	30.6423	4.9430	0.1734
8.200	vv	0.2600	40.1094	6.0094	0.2269
8.586	vv	0.5933	17558.4382	2322.1548	99.3412
		Sum	**17674.8799**		



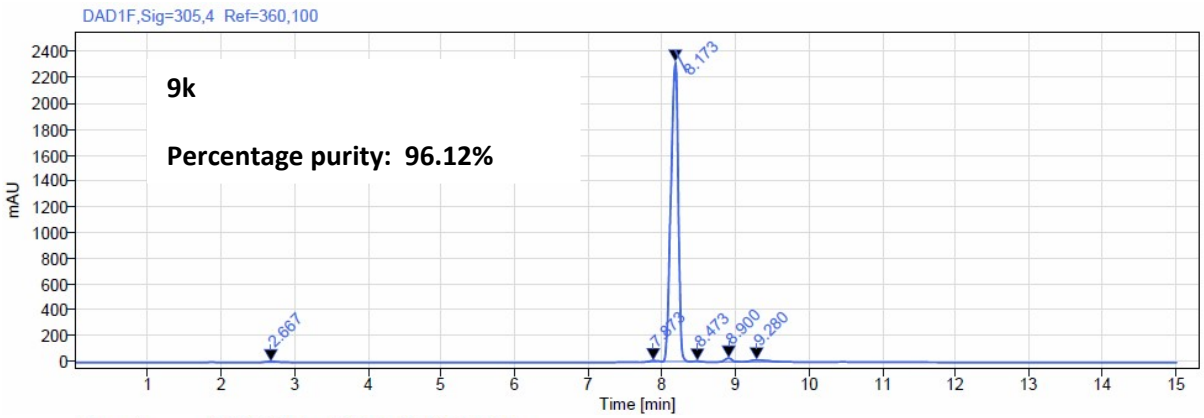
Signal: DAD1D,Sig=230,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.4532	58.2028	10.7832	0.2542
8.258	vv	0.3133	52.2405	5.3281	0.2282
8.565	vv	0.6065	22786.4224	2639.6219	99.5176
		Sum	**22896.8658**		



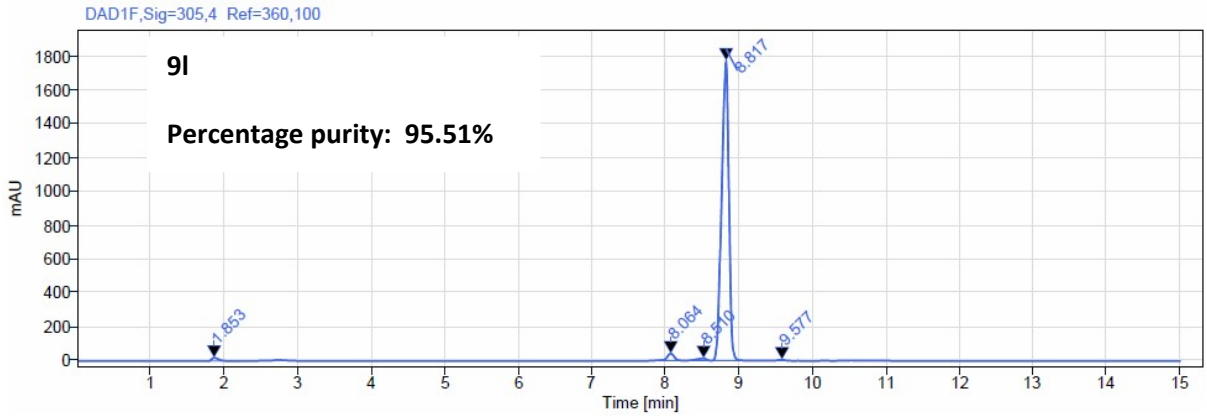
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.860	vv	0.4066	33.2518	4.9853	0.1823
8.379	vv	0.3066	53.8176	6.0174	0.2950
8.765	vv	0.5133	17714.1656	2555.3427	97.0926
9.505	vv	0.3599	443.3830	70.4871	2.4302
		Sum	**18244.6181**		



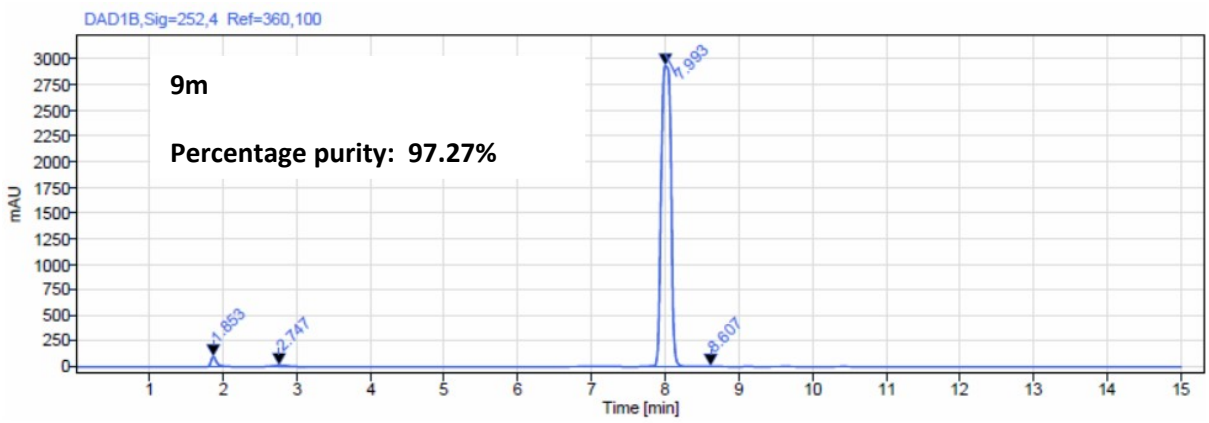
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
2.667	vv	0.4533	81.7085	5.7875	0.4884
7.873	vv	0.2667	79.1798	9.9498	0.4732
8.173	vv	0.3800	16082.8770	2318.4472	96.1244
8.473	vv	0.2067	36.2747	6.7223	0.2168
8.900	vv	0.3400	204.8590	30.0115	1.2244
9.280	vv	0.6933	246.4088	14.9429	1.4727
		Sum	**16731.3078**		



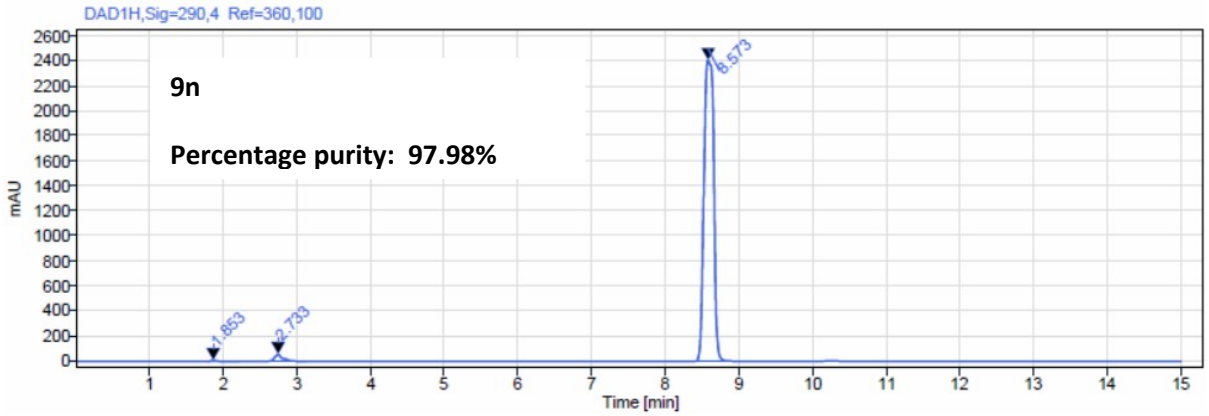
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.4399	122.4950	18.8099	0.9676
8.064	vv	0.4132	283.2826	42.0222	2.2376
8.510	vv	0.3599	126.5318	13.8704	0.9995
8.817	vv	0.5198	12091.8028	1772.6533	95.5127
9.577	vv	0.2133	35.7729	6.4974	0.2826
		Sum	**12659.8851**		



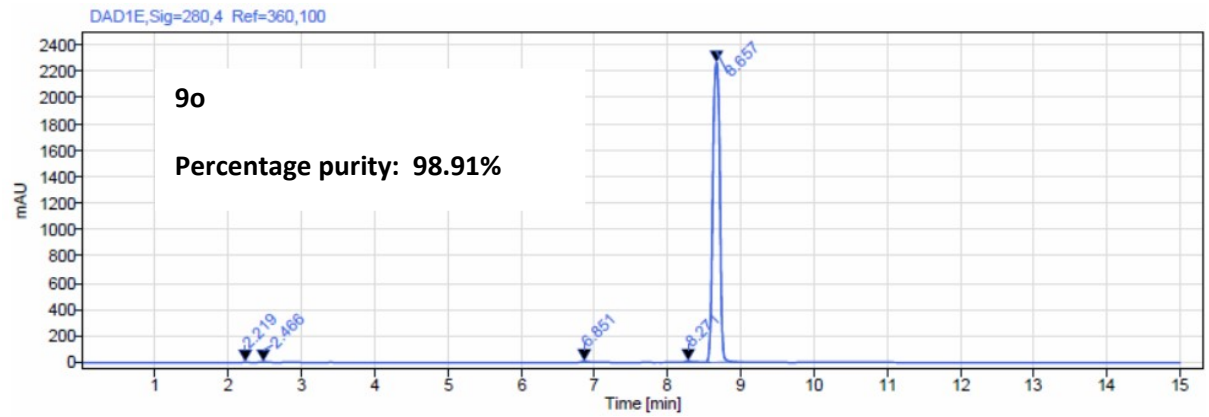
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.6133	533.5877	98.2186	1.9255
2.747	vv	0.7467	205.9766	13.1184	0.7433
7.993	vv	0.7067	26955.0131	2940.6557	97.2718
8.607	vv	0.2067	16.4572	2.6001	0.0594
		Sum	**27711.0345**		



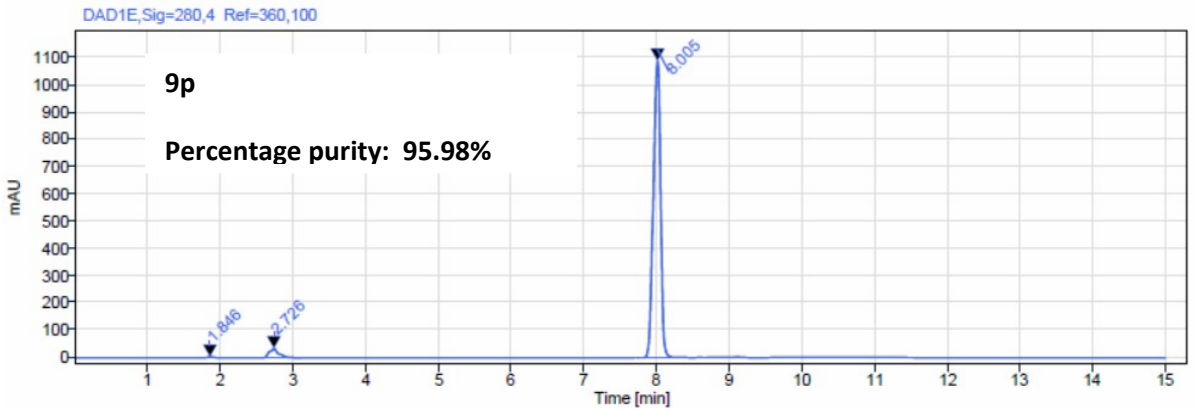
Signal: DAD1H,Sig=290,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.4400	42.1839	7.5443	0.1856
2.733	vv	0.5200	415.0866	55.6977	1.8264
8.573	vv	0.6533	22269.2835	2405.0970	97.9879
		Sum	**22726.5540**		



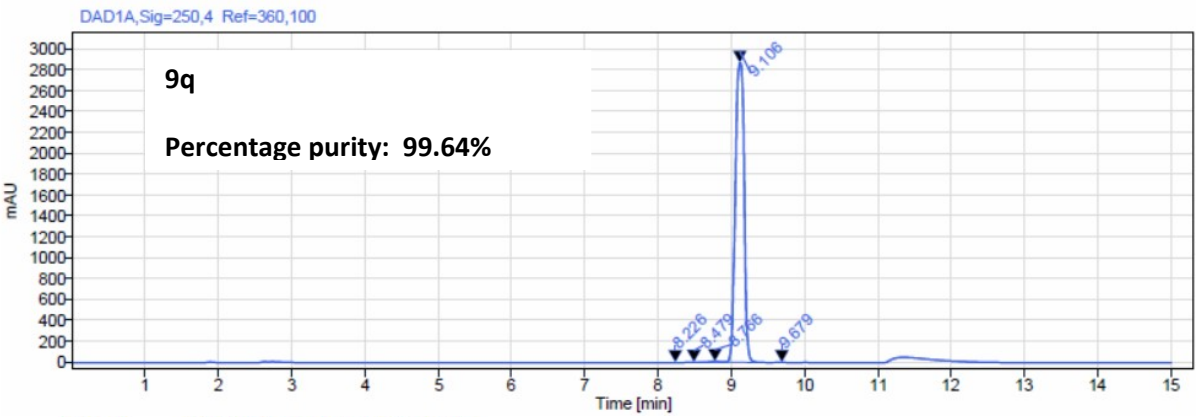
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
2.219	vv	0.1666	14.7879	3.3469	0.0977
2.466	vv	0.3665	36.4757	4.4190	0.2409
6.851	vv	0.3399	55.2425	7.3588	0.3648
8.271	vv	0.2932	57.7924	7.9042	0.3817
8.657	vv	0.5465	14977.2234	2269.0087	98.9149
		Sum	**15141.5220**		



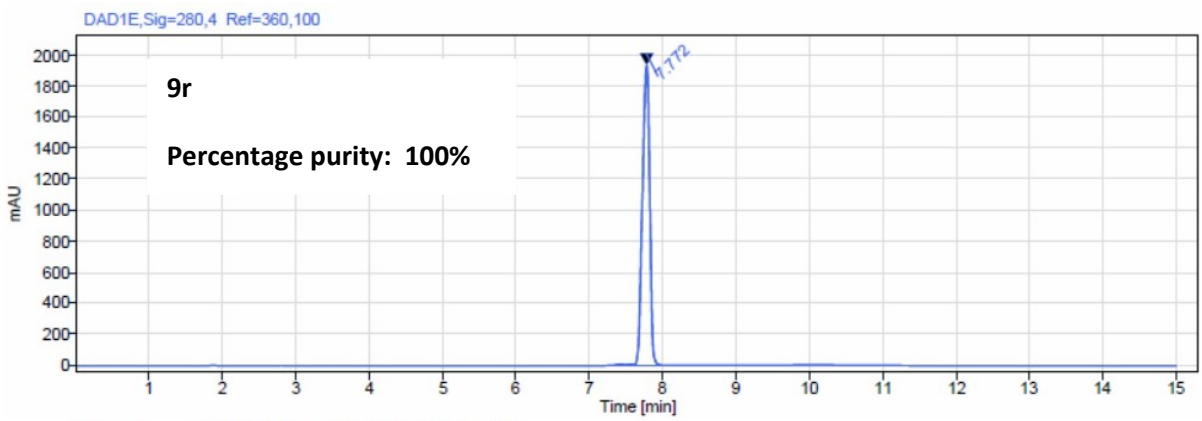
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.846	vv	0.2933	17.1509	3.5232	0.2182
2.726	vv	0.5199	298.4970	34.1620	3.7975
8.005	vv	0.4732	7544.7477	1088.4034	95.9843
		Sum	**7860.3955**		



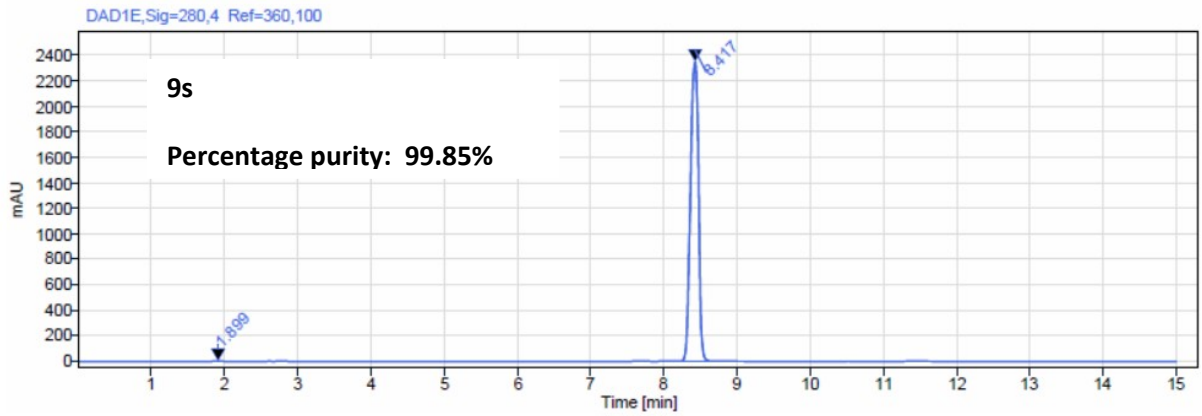
Signal: DAD1A,Sig=250,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.226	vv	0.3866	9.6552	0.6606	0.0403
8.479	vv	0.2533	9.9724	1.3360	0.0416
8.766	vv	0.3000	52.1198	7.4798	0.2175
9.106	vv	0.5733	23880.5842	2865.1959	99.6495
9.679	vv	0.3133	12.2392	1.6555	0.0511
		Sum	**23964.5709**		



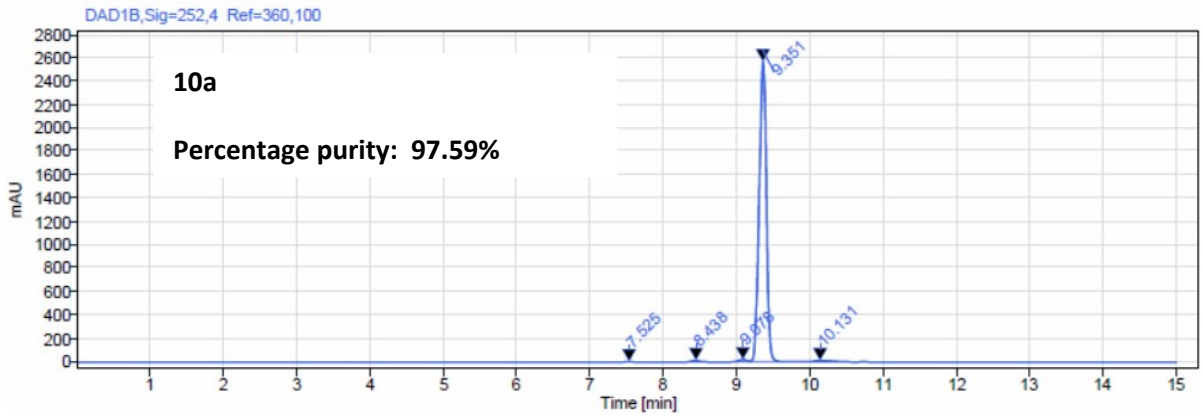
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.772	vv	0.7798	13395.8125	1933.7625	100.0000
		Sum	**13395.8125**		



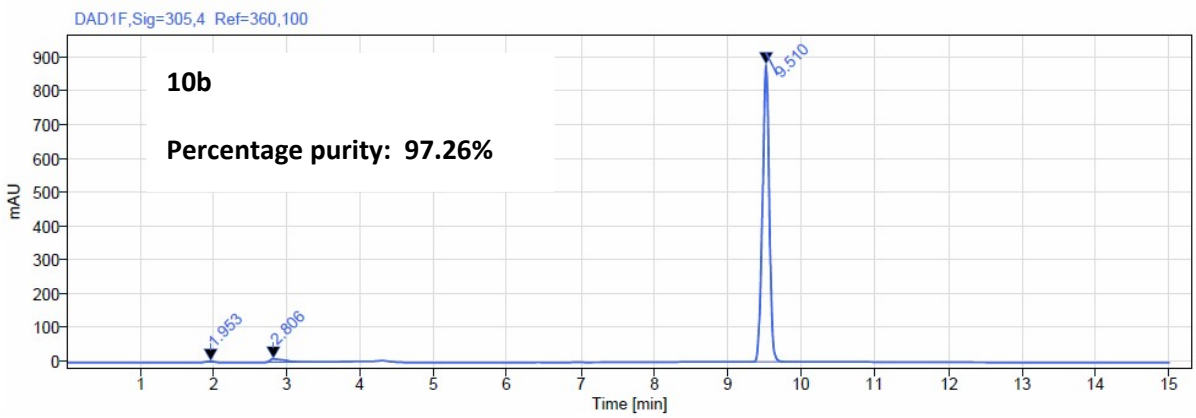
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.899	vv	0.2999	26.3706	3.4103	0.1470
8.417	vv	0.5198	17913.0833	2352.5411	99.8530
		Sum	**17939.4539**		



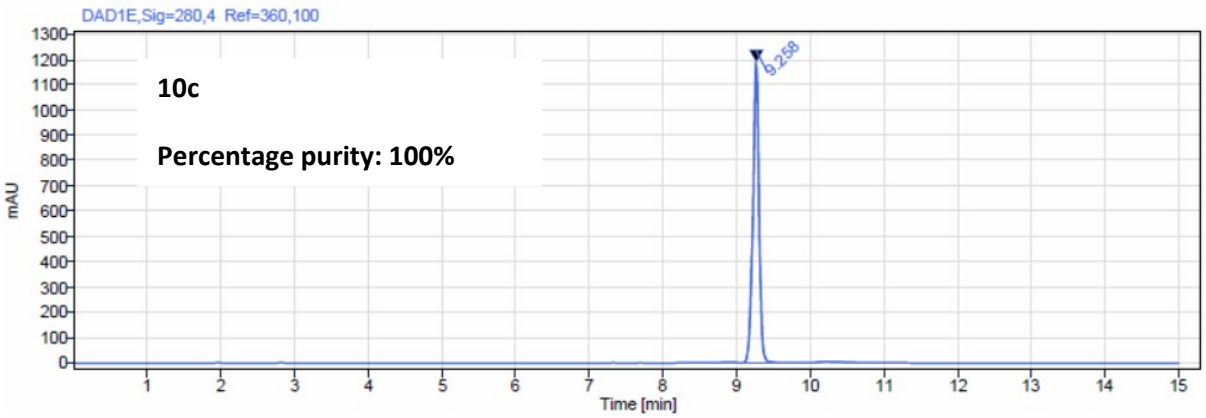
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.525	vv	0.1866	23.9422	4.1821	0.1328
8.438	vv	0.3399	96.7206	13.3148	0.5364
9.078	vv	0.2599	116.6160	17.7177	0.6468
9.351	vv	0.5199	17595.6815	2568.1155	97.5913
10.131	vv	0.8398	197.0150	11.2506	1.0927
		Sum	**18029.9753**		



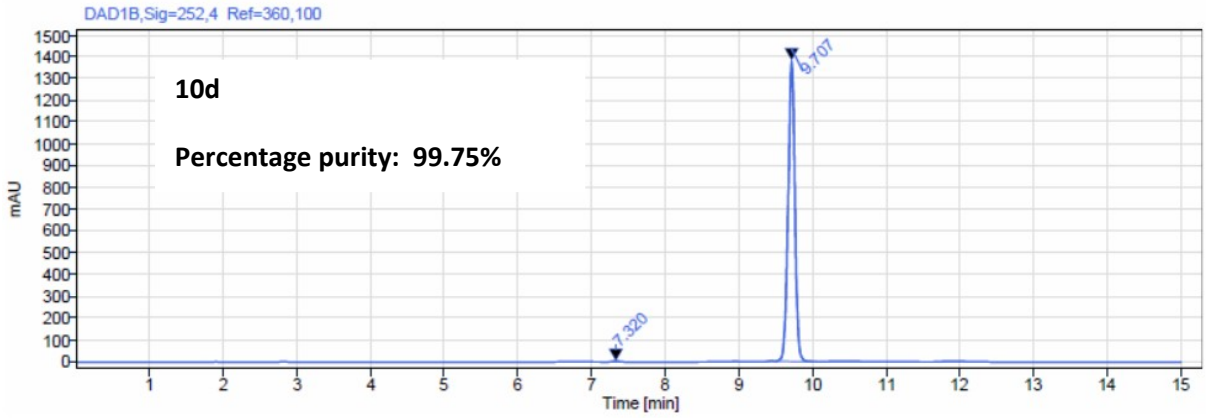
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.953	vv	0.2199	18.5197	3.3654	0.3197
2.806	vv	0.6265	139.7612	10.3722	2.4124
9.510	vv	0.6664	5635.1149	878.8148	97.2679
		Sum	**5793.3957**		



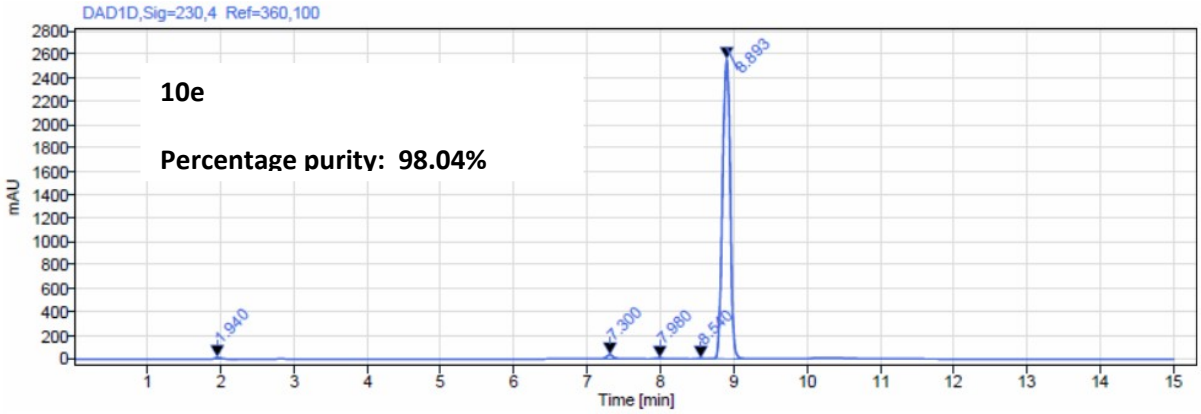
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
9.258	vv	0.5865	6832.0171	1189.9179	100.0000
		Sum	**6832.0171**		



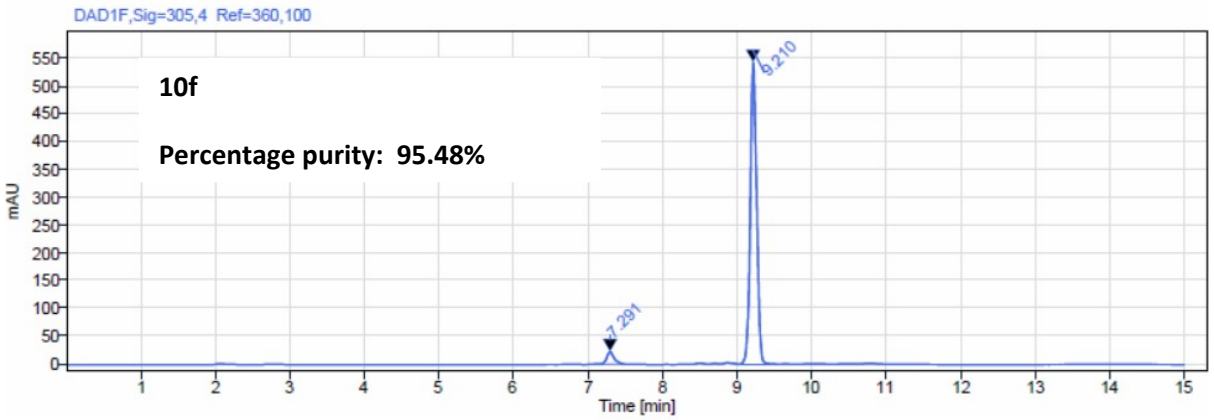
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.320	vv	0.3000	22.0272	3.7468	0.2490
9.707	vv	0.5467	8825.5994	1382.3538	99.7510
		Sum	**8847.6266**		



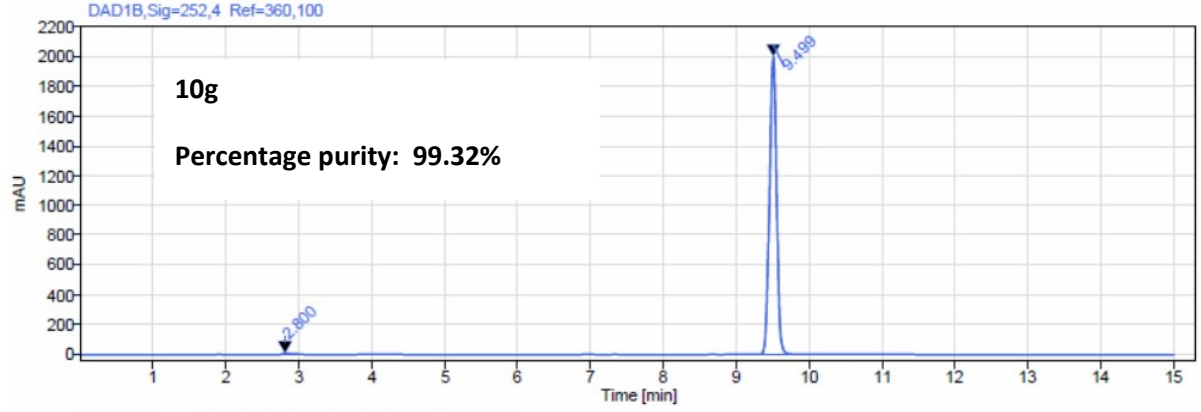
Signal: DAD1D,Sig=230,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.940	vv	0.3667	86.0832	15.0717	0.4521
7.300	vv	0.4000	225.0548	34.2710	1.1820
7.980	vv	0.2533	45.9076	6.6024	0.2411
8.540	vv	0.1733	15.3813	3.0130	0.0808
8.893	vv	0.7000	18667.7886	2562.4954	98.0440
		Sum	**19040.2156**		



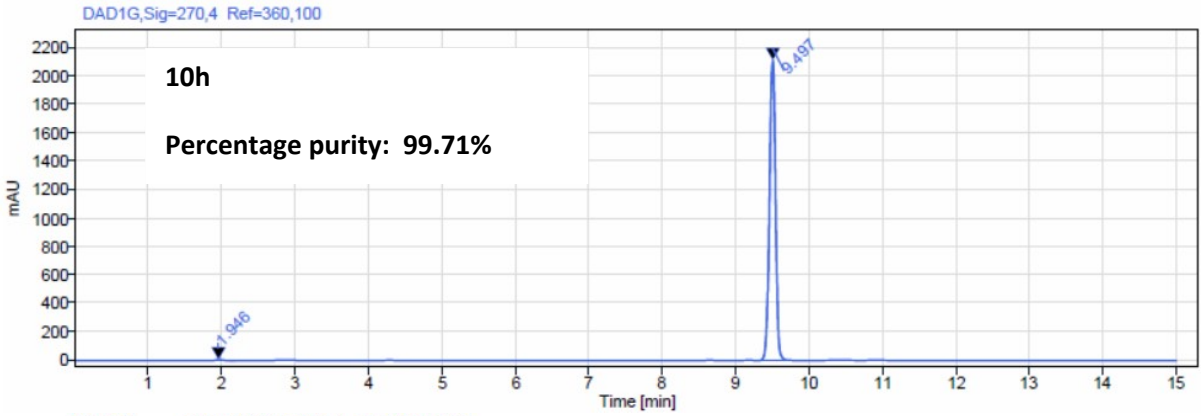
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.291	vv	0.3799	151.5867	22.5128	4.5126
9.210	vv	0.5332	3207.6310	542.5119	95.4874
		Sum	**3359.2177**		



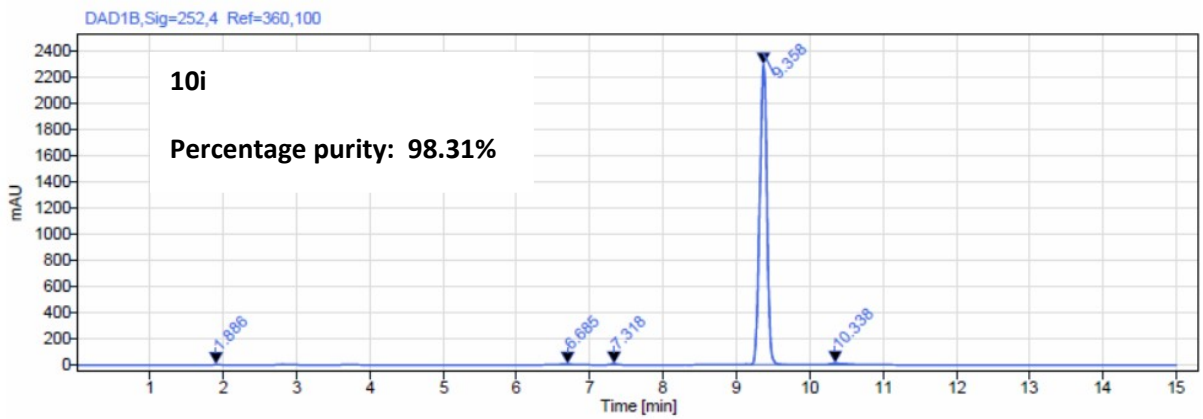
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
2.800	vv	0.4666	92.5552	8.0082	0.6744
9.499	vv	0.5933	13632.2404	2003.9324	99.3256
		Sum	**13724.7956**		



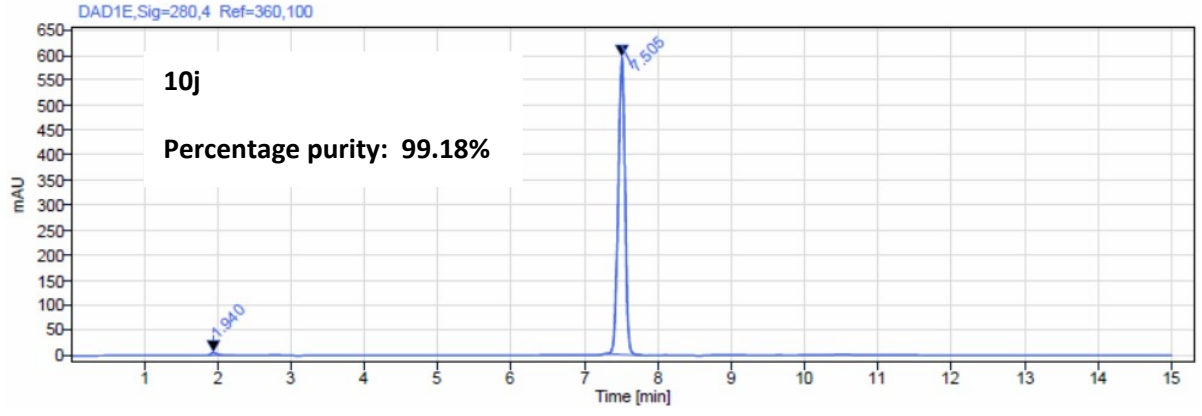
Signal: DAD1G,Sig=270,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.946	vv	0.3066	34.6383	6.2132	0.2816
9.497	vv	0.5398	12267.6148	2113.4650	99.7184
		Sum	**12302.2531**		



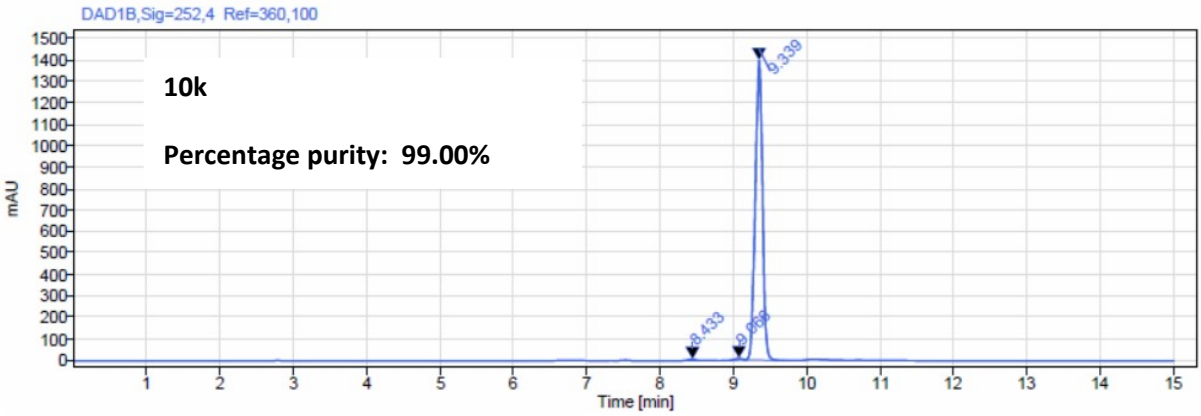
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.886	vv	0.6132	27.4555	4.1013	0.1723
6.685	vv	0.2399	32.2695	4.6925	0.2026
7.318	vv	0.3399	45.1289	7.4766	0.2833
9.358	vv	0.5066	15661.7179	2297.2160	98.3142
10.338	vv	0.6465	163.6924	11.2937	1.0276
		Sum	**15930.2642**		



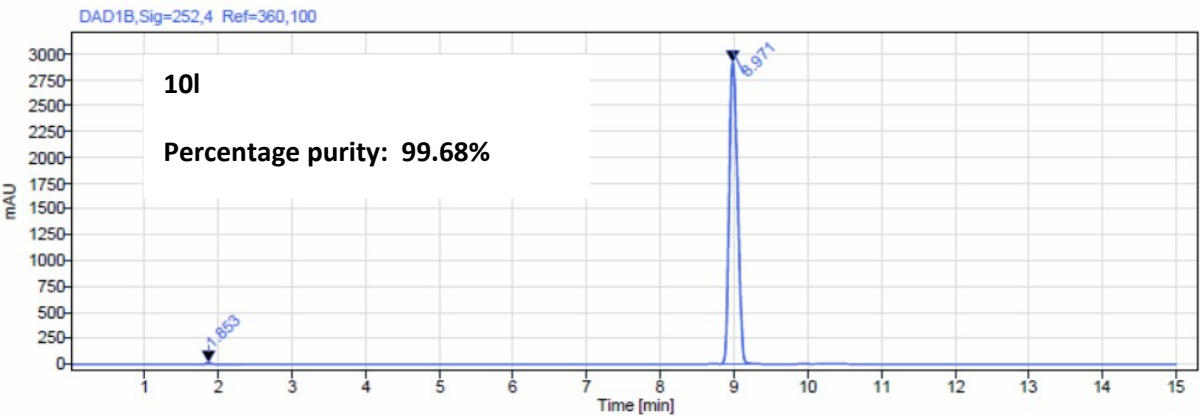
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.940	vv	0.3733	31.7439	5.6654	0.8192
7.505	vv	0.5199	3843.0104	594.9956	99.1808
		Sum	**3874.7543**		



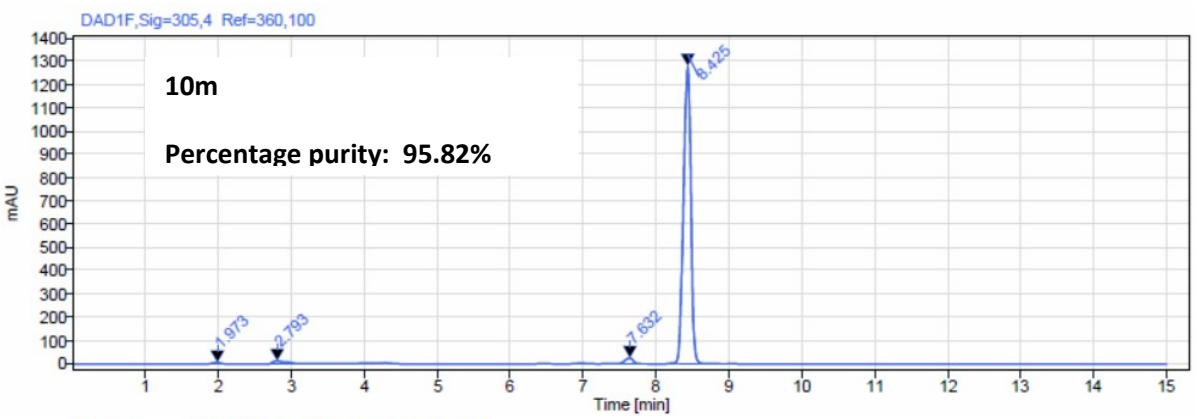
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.433	vv	0.3066	41.2627	5.6117	0.4285
9.066	vv	0.2600	54.1124	7.8843	0.5620
9.339	vv	0.5466	9533.9745	1396.2365	99.0095
		Sum	**9629.3495**		



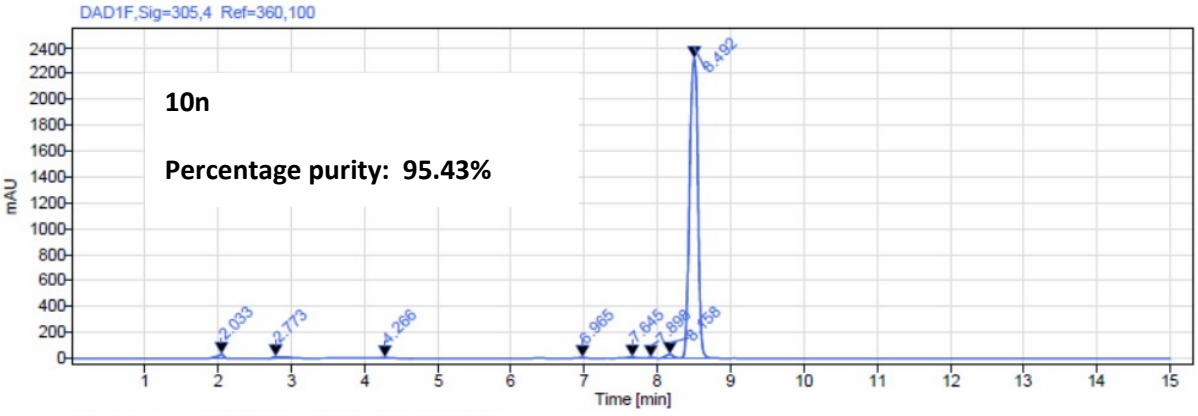
Signal: DAD1B,Sig=252,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.853	vv	0.5399	72.7946	13.0269	0.3157
8.971	vv	0.6399	22985.1671	2917.6678	99.6843
		Sum	**23057.9617**		



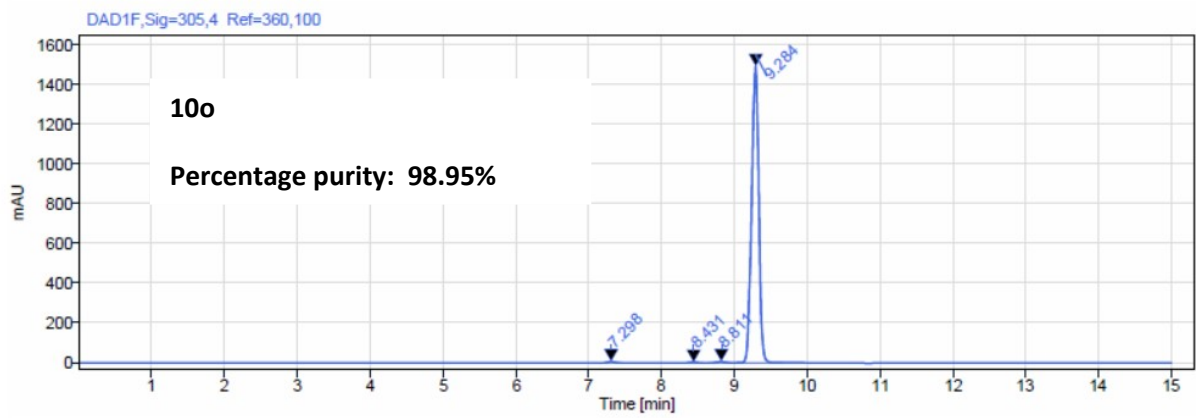
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.973	vv	0.2933	38.9589	5.2212	0.4166
2.793	vv	0.5399	165.6598	12.4023	1.7714
7.632	vv	0.3333	186.1434	24.5665	1.9904
8.425	vv	0.6665	8961.3502	1280.7858	95.8217
		Sum	**9352.1123**		



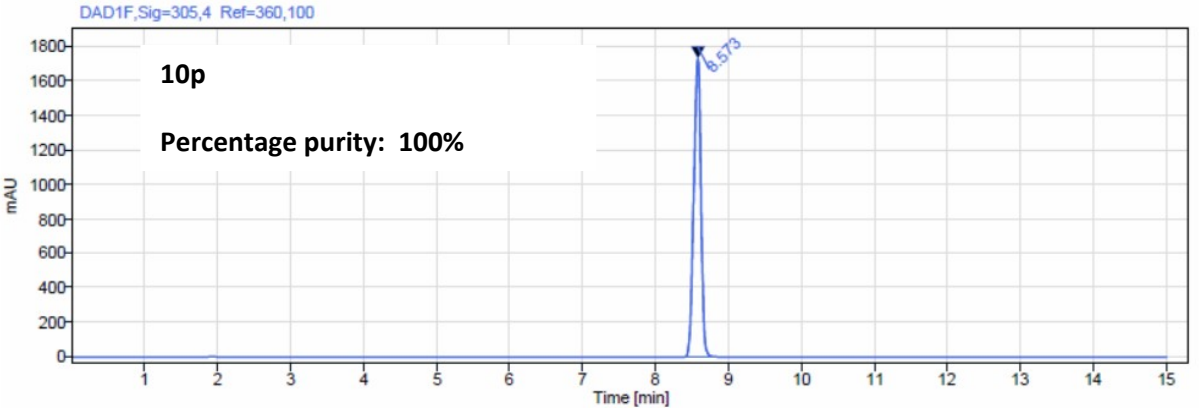
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
2.033	vv	0.4133	204.4541	31.6993	1.0746
2.773	vv	0.5666	167.6341	12.1769	0.8811
4.266	vv	1.4064	152.4847	4.9668	0.8015
6.965	vv	0.2266	31.3889	4.5454	0.1650
7.645	vv	0.5932	71.8534	7.9484	0.3777
7.898	vv	0.2133	32.0427	5.1651	0.1684
8.158	vv	0.2999	208.6237	28.5700	1.0965
8.492	vv	0.5732	18157.2442	2314.7493	95.4352
		Sum	**19025.7258**		



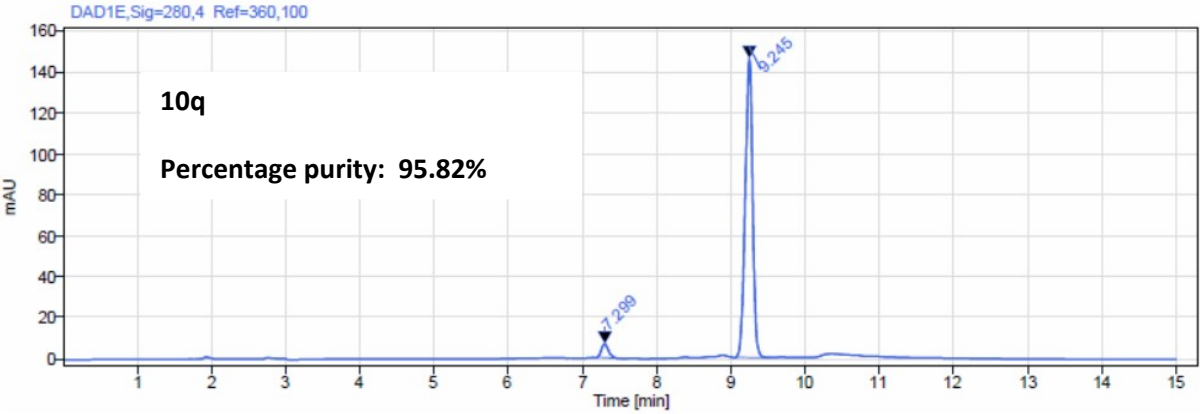
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.298	vv	0.2533	41.5162	6.7534	0.4058
8.431	vv	0.2199	16.0360	2.6829	0.1567
8.811	vv	0.3266	49.5733	6.9646	0.4845
9.284	vv	0.6998	10124.1761	1496.8453	98.9530
		Sum	**10231.3015**		



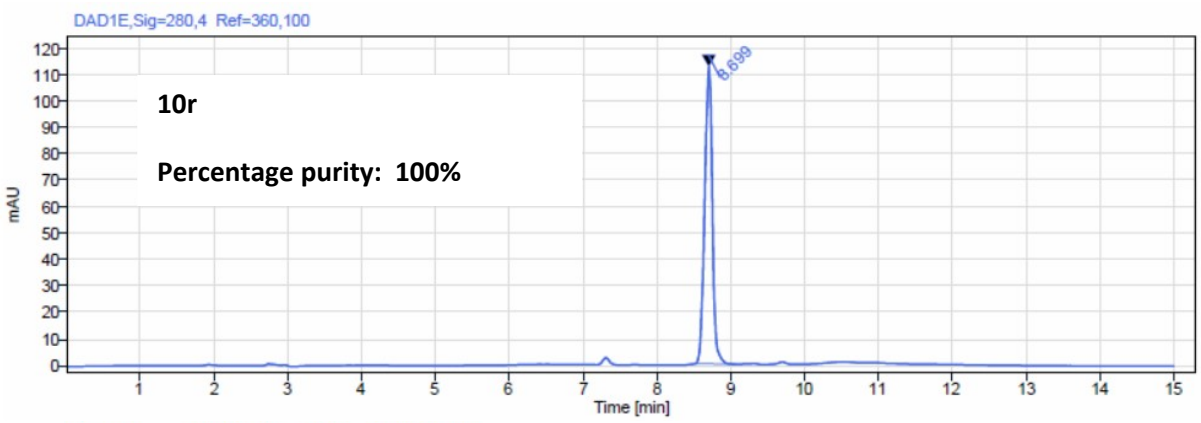
Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.573	vv	0.6933	11933.5500	1732.4507	100.0000
		Sum	**11933.5500**		



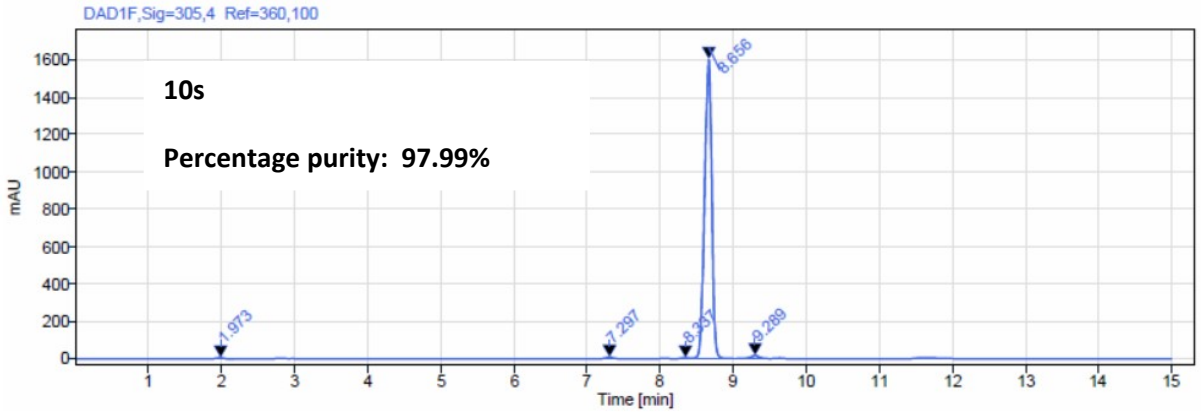
Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.299	vv	0.2933	43.9441	6.7087	4.1740
9.245	vv	0.4599	1008.8523	146.0048	95.8260
		Sum	**1052.7964**		



Signal: DAD1E,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
8.699	vv	0.5400	811.8415	112.2462	100.0000
		Sum	**811.8415**		



Signal: DAD1F,Sig=305,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
1.973	vv	0.2865	31.1650	5.3831	0.2785
7.297	vv	0.2599	43.5060	7.1168	0.3888
8.337	vv	0.1799	20.3935	3.5613	0.1823
8.656	vv	0.5798	10964.8409	1605.7181	97.9945
9.289	vv	0.4865	129.3303	15.8515	1.1558
		Sum	**11189.2357**		

FIGURE S39: HPLC chromatograms of all the synthesized compounds along with their percentage purity.

4. Lactate dehydrogenase-coupled enzyme assay results for compounds (9a-9s and 10a-10s)

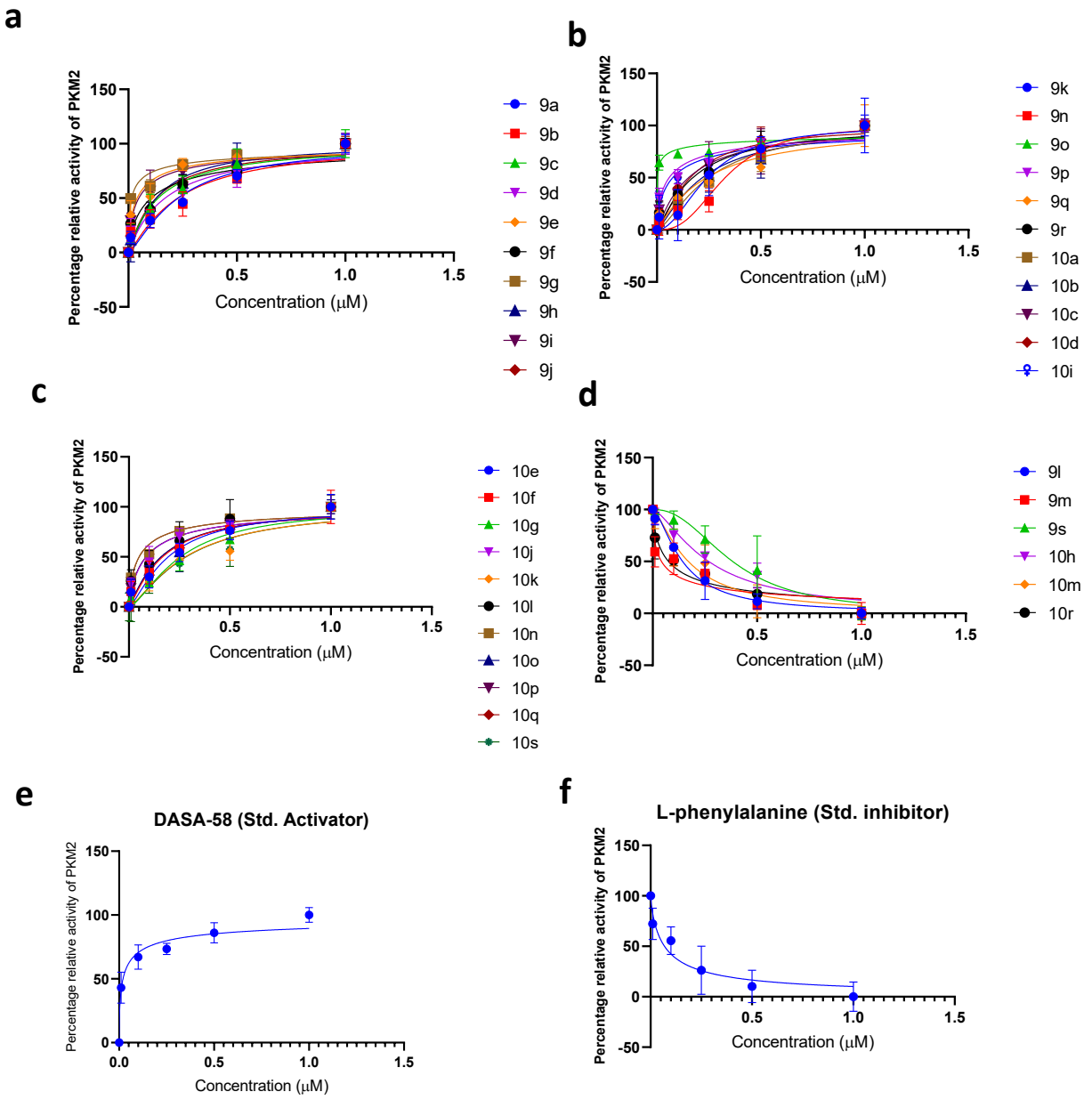


FIGURE S40: Lactate dehydrogenase-couppled enzyme assay results of the synthesized compounds. DASA-58 and L-phenylalanine has been used as the standard PKM2 activator and inhibitor.

5. Cytotoxicity (Alamar blue) assay results for compounds (9a-9s and 10a-10s)- A549 cell line

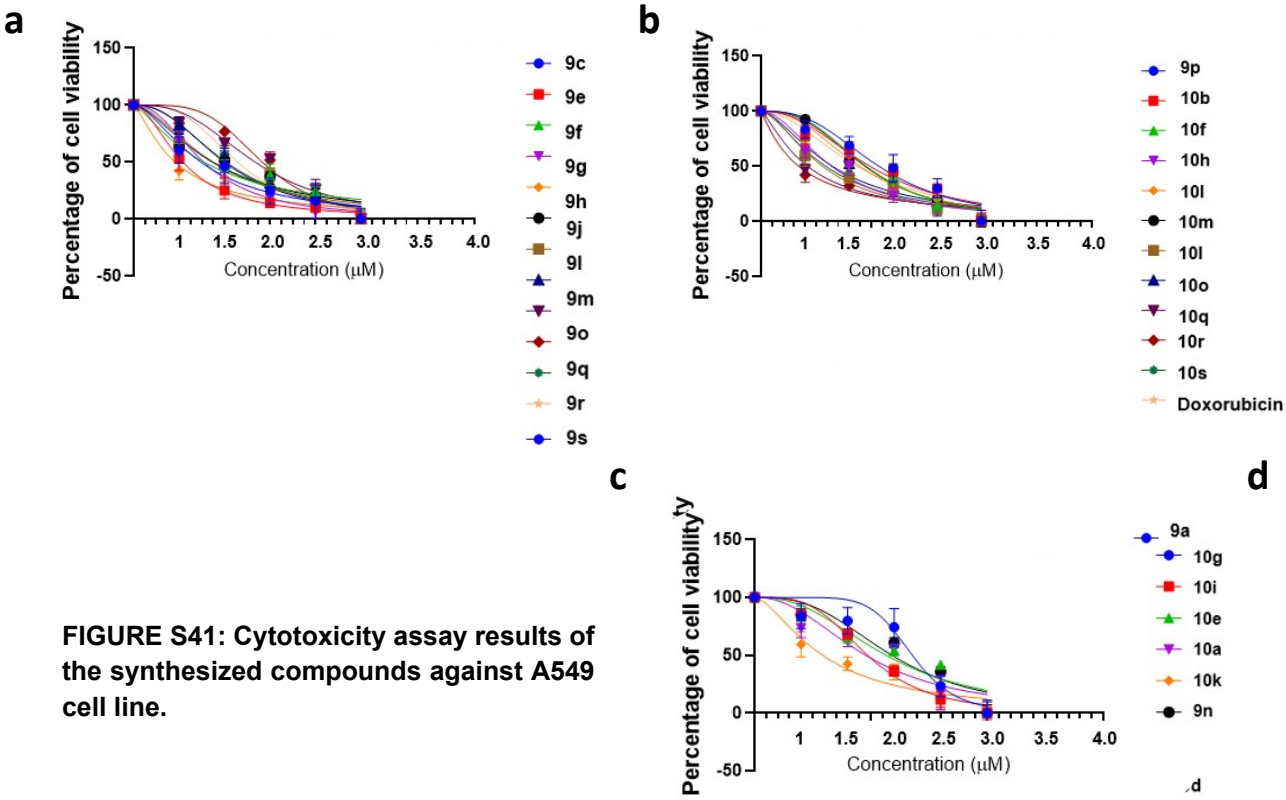
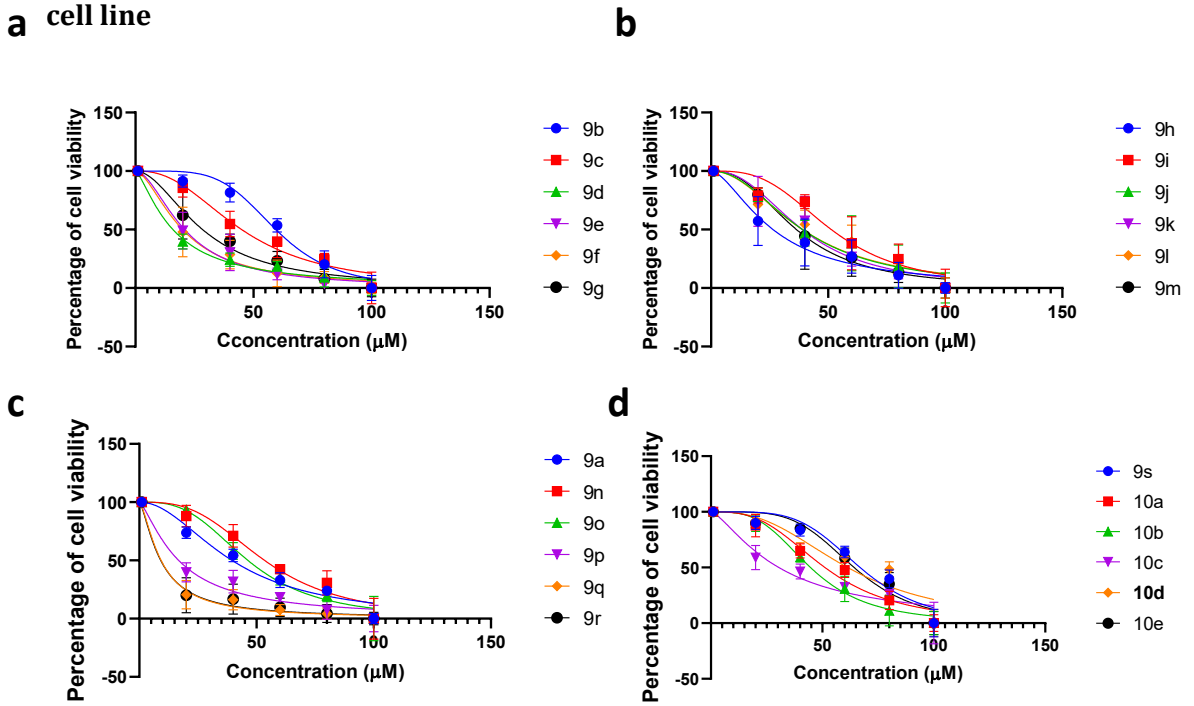


FIGURE S41: Cytotoxicity assay results of the synthesized compounds against A549 cell line.

6. Cytotoxicity (Alamar blue) assay results for compounds (9a-9s and 10a-10s)- BEAS-2B cell line



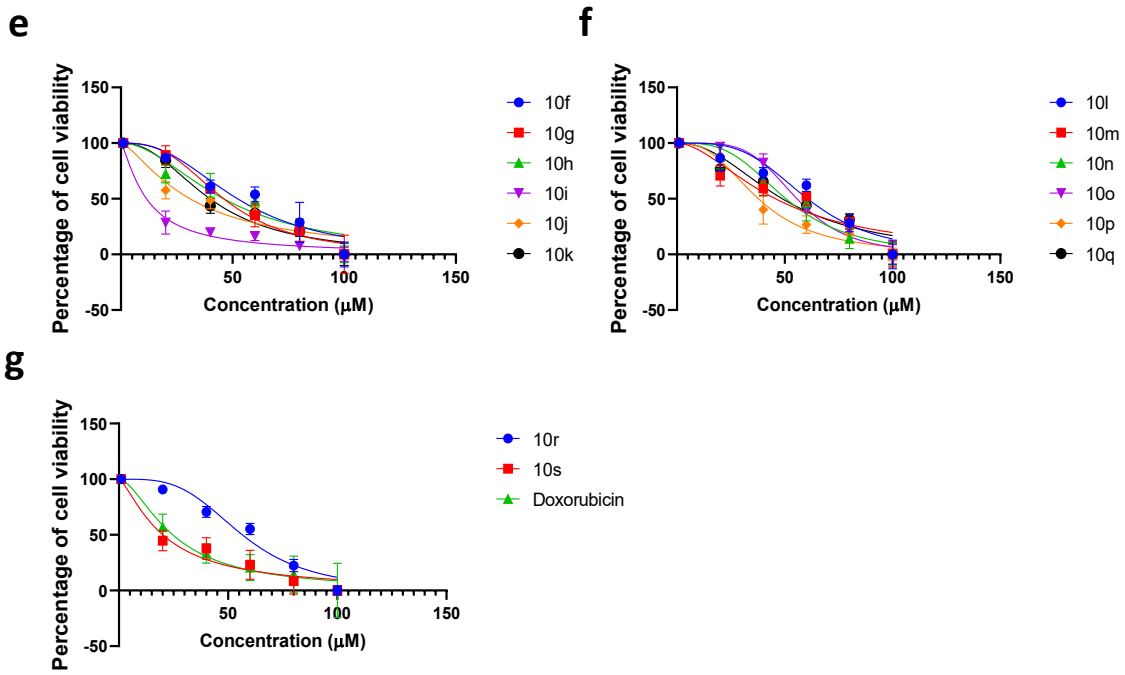


FIGURE S42: Cytotoxicity assay results of the synthesized compounds against BEAS-2B cell line.

7. Cytotoxicity (Alamar blue) assay results for compounds (9a-9s and 10a-10s)- COLO-205 cell line

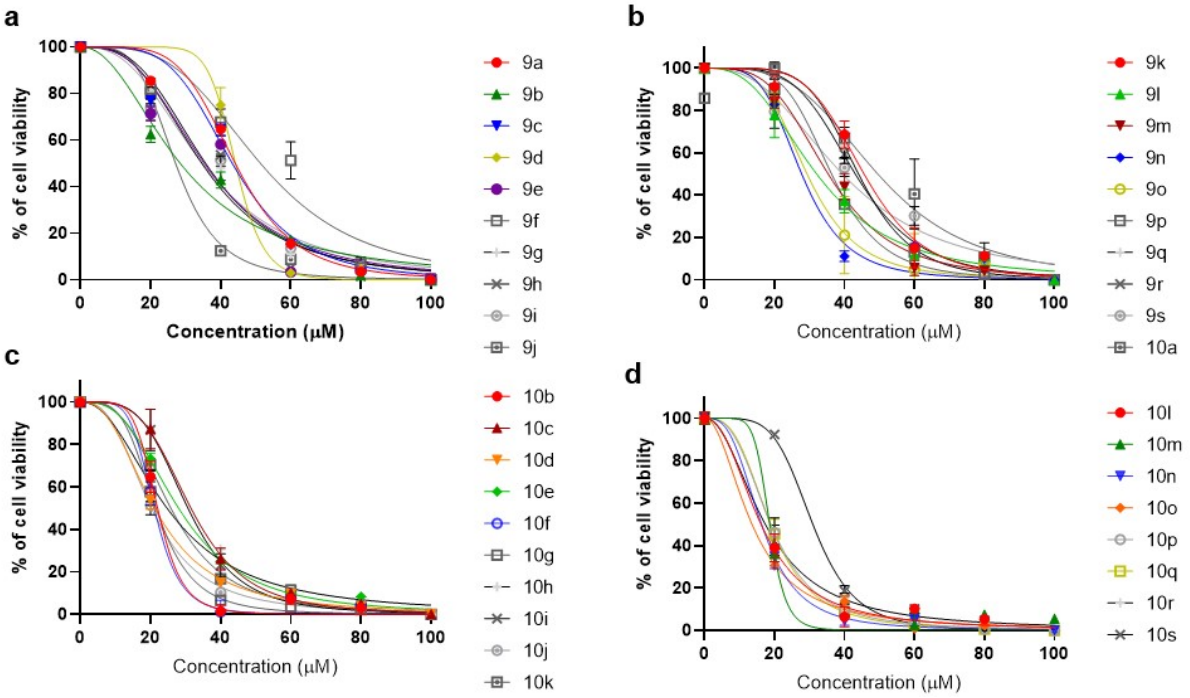


FIGURE S43: Cytotoxicity assay results of the synthesized compounds against COLO-205 cell line.

8. Cytotoxicity (Alamar blue) assay results for compounds (9a-9s and 10a-10s)- MCF-7 cell line

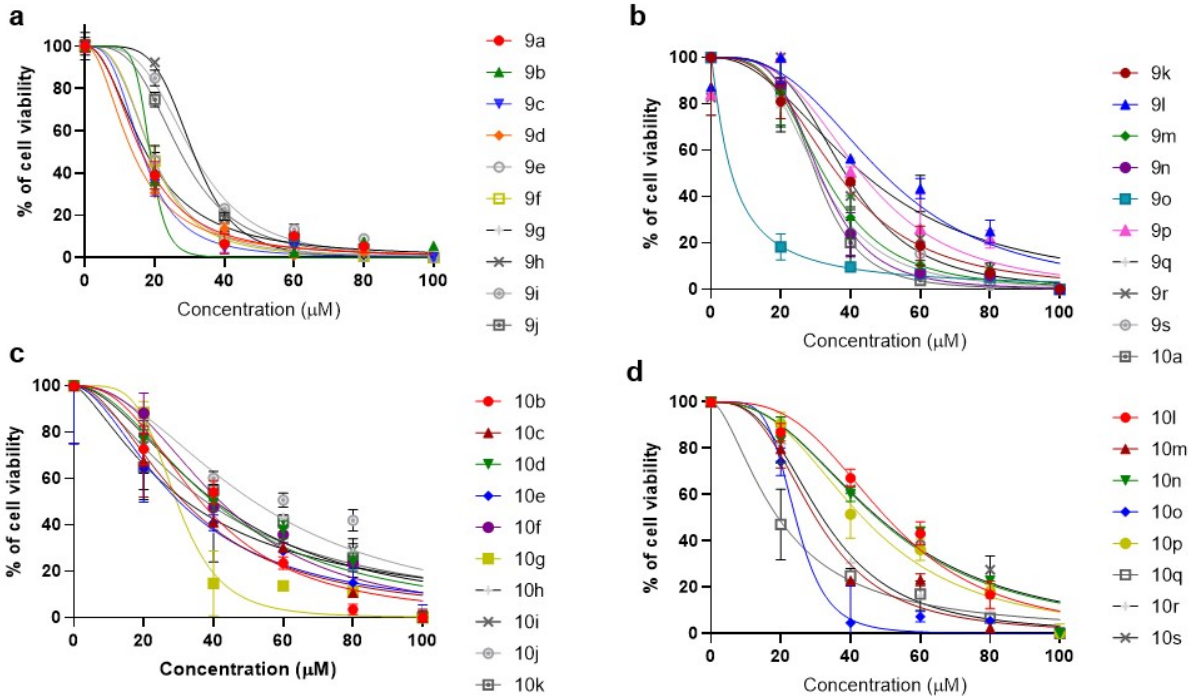


FIGURE S44: Cytotoxicity assay results of the synthesized compounds against MCF-7 cell line.

9. Cytotoxicity (Alamar blue) assay results for compounds (9a-9s and 10a-10s)- CAL-7 cell line

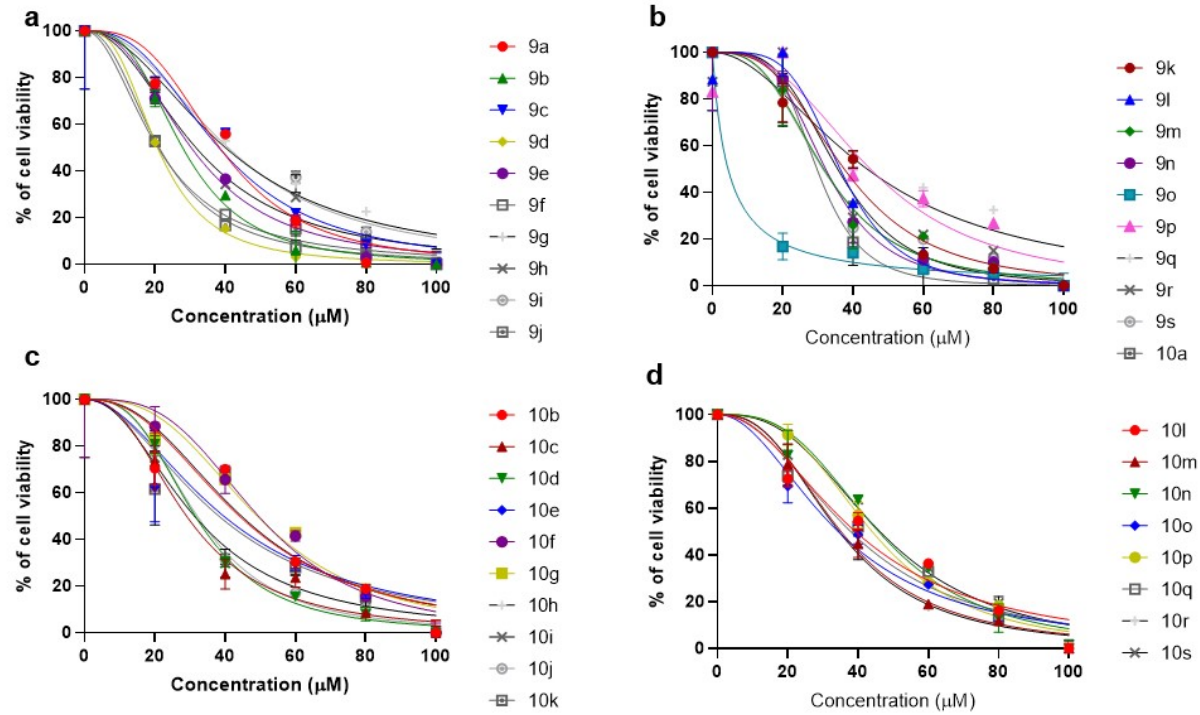
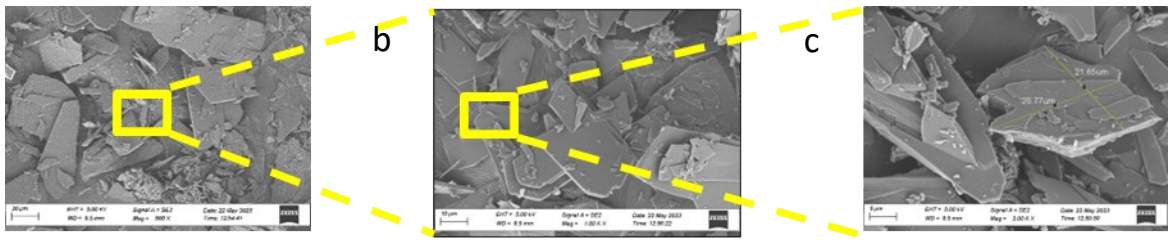


FIGURE S45: Cytotoxicity assay results of the synthesized compounds against CAL-27 cell line.

10. FE-SEM and EDAX data for compound 10q

a b c



d

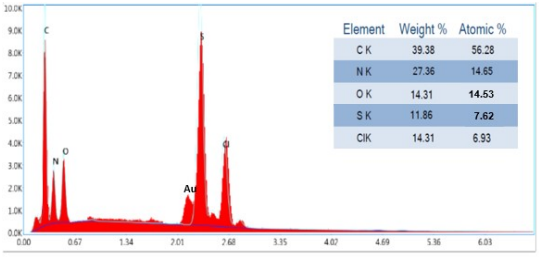


FIGURE S46: Field Emission Scanning Electron Microscopy (FE-SEM) micrographs of compound 10q at different concentrations: a) 20µM, b) 10µM, and c) 5µM. Additionally, d) Energy Dispersive X-Ray Analysis (EDX) reveals the elemental composition present in compound 10q.

Field emission scanning electron microscopy (FE-SEM) provides topographical and elemental information with an almost limitless depth of field at magnifications ranging from 10x to 300,000x. With spatial resolution down to 1.5 nanometers, FE-SEM provides images that are three to six times clearer and less electrostatically distorted than those produced by traditional scanning electron microscopy (SEM). We developed a novel series of imidazopyri(mi)dine-based sulfonamides and were curious to observe the 3D structure and morphology. The compound 10q was preferred for FE-SEM and Energy-dispersive X-ray analysis (EDAX), as we could generate crystals of this very compound that was utilized for X-RD. Therefore, 10q was chosen for these studies to establish a correlation between each of the studies undertaken (Figure S43 a-c). This FE-SEM analysis helped determine whether the compound is amorphous or crystalline owing to its surface morphology. When FE-SEM images of 10q were analyzed, it was found that the representative synthesized compound particle had dimensions of 21.65µm and 25.77µm, respectively. As work went on, it became clear that the morphological analysis was focused on the manufactured molecule's uniform size and crystal-like surface shape. The surface morphology of the molecule was sheet-like.

EDAX confirmed the presence of elements with accurate percentages further simplifying and aiding in correct structural elucidation. It showed that 10q had Carbon (weight% of 39.38 and atomic% of 56.28), Nitrogen (weight% of 27.36 and atomic% of 14.65), Oxygen (weight% of 14.31 and atomic% of 7.62), Sulfur (weight% of 11.86 and atomic% of 14.53) and Chlorine (weight% of 7.10 and atomic% of 6.93) are at par with the chemical formula $C_{17}H_{17}ClN_4O_3S_2$ of 10q (Figure S43 d).

11. Molecular dynamic simulation data for 9b-PKM2 interaction

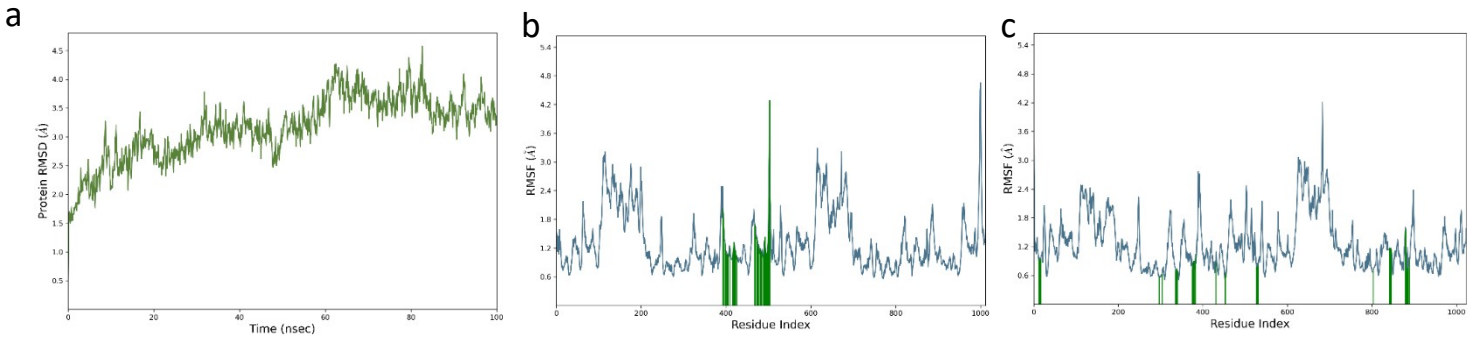


FIGURE S47: d) The RMSD graph of only PKM2 (apo), f) the RMSF graph of only PKM2, g) the RMSF graph of 9b at the activator binding site of PKM2 protein (PDB id 3GR4) after a molecular dynamics simulation of 100 ns.

12. Data related to single crystal X-ray diffraction analysis of compound 10q

Table S1. Crystal data and structure refinement for compound 10q.

Empirical formula	**$C_{17}H_{17}ClN_4O_3S_2$**
Formula weight	**424.91**
Temperature/K	**299.0**
Crystal system	**triclinic**
Space group	**P-1**
a/Å	**6.6727(9)**
b/Å	**10.1859(14)**
c/Å	**14.367(2)**
α/°	**85.903(5)**
β/°	**80.316(5)**
γ/°	**73.428(5)**
Volume/Å^3	**922.3(2)**
Z	**2**
ρ_{calc}g/cm^3	**1.530**
μ/mm^{-1}	**0.461**

F(000)	**440.0**
Crystal size/mm^3	**0.214 × 0.21 × 0.182**
Radiation	**M_oK_α (λ = 0.71073)**
2Θ range for data collection/°	**2.876 to 58.58**
Index ranges	**-8 ≤ h ≤ 8, -13 ≤ k ≤ 13, -19 ≤ l ≤ 18**
Reflections collected	**25692**
Independent reflections	**4319 [R_{int} = 0.0615, R_{sigma} = 0.0349]**
Data/restraints/parameters	**4319/0/244**
Goodness-of-fit on F^2	**1.131**
Final R indexes [I>=2σ (I)]	**R1 = 0.0600, wR_2 = 0.1466**
Final R indexes [all data]	**R1 = 0.0662, wR_2 = 0.1524**
Largest diff. peak/hole / e Å	**0.63/-0.81**

Table S2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å2×10^3) for compound 10q. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S2	-531.8(8)	5319.7(4)	7349.4(3)	40.41(16)
S1	2640.3(10)	4615.2(7)	8698.0(4)	55.22(19)
Cl1	4270.5(13)	3003.0(10)	10339.6(5)	92.5(3)
O3	7767(2)	1057.0(16)	4665.4(10)	47.9(4)
O2	-2696(2)	5335.5(18)	7409.3(12)	56.5(4)
O1	56(3)	6564.8(15)	7242.6(12)	58.5(4)
N3	9670(2)	404.1(14)	2730.2(10)	33.0(3)
N2	3461(2)	2341.4(15)	5194.5(10)	33.6(3)
N1	786(2)	4377.0(15)	6447.7(11)	35.8(3)
N4	8031(3)	950(2)	1451.2(12)	54.9(5)
C10	6671(3)	1287.3(18)	4040.3(12)	33.6(4)
C6	1164(3)	2551(2)	5384.2(14)	38.9(4)
C12	6631(3)	1356(2)	2241.4(14)	45.8(5)
C11	7549(3)	1045.4(18)	3054.6(12)	34.2(4)
C9	4275(3)	1783(2)	4256.1(13)	40.6(4)
C5	289(3)	3074.3(19)	6371.4(14)	39.9(4)
C17	11356(3)	-121.3(19)	3206.0(14)	38.9(4)
C8	3073(3)	4220(2)	6244.6(14)	40.7(4)
C3	-477(4)	3564(2)	8913.5(16)	54.7(5)
C13	9876(3)	361(2)	1755.2(13)	42.2(4)
C7	3919(3)	3648(2)	5263.7(13)	40.2(4)
C4	381(3)	4460(2)	8354.4(13)	41.6(4)
C16	13282(3)	-698(2)	2702.3(17)	48.9(5)
C14	11882(4)	-240(2)	1238.2(16)	54.1(5)
C2	704(5)	2990(3)	9646.7(17)	66.8(7)
C1	2402(4)	3459(3)	9607.2(15)	59.3(7)
C15	13557(4)	-752(2)	1711.1(18)	56.6(6)

Table S3. Anisotropic Displacement Parameters ($Å^2×10^3$) for compound 10q. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S2	46.9(3)	33.6(2)	33.4(2)	1.50(17)	-5.96(19)	-0.19(19)
S1	55.9(3)	69.1(4)	39.1(3)	-2.6(2)	-11.2(2)	-12.4(3)
Cl1	85.3(5)	123.6(7)	42.0(3)	-6.4(4)	-25.9(3)	23.7(5)
O3	42.5(7)	66.3(9)	32.4(7)	-2.5(6)	-13.4(6)	-6.6(6)
O2	41.7(8)	64.4(10)	51.1(9)	-5.0(7)	-7.0(7)	5.5(7)
O1	87.1(12)	32.5(7)	50.6(9)	0.3(6)	-9.5(8)	-9.3(7)
N3	36.4(7)	32.3(7)	30.2(7)	2.8(5)	-5.6(6)	-10.1(6)
N2	34.4(7)	38.0(7)	29.7(7)	-2.0(6)	-3.7(6)	-12.4(6)
N1	40.1(8)	34.7(7)	31.0(7)	0.5(6)	-0.6(6)	-10.9(6)
N4	52.3(10)	76.6(13)	29.0(8)	5.4(8)	-7.5(7)	-8.2(9)
C10	36.5(8)	34.9(8)	29.8(8)	2.3(6)	-8.5(7)	-9.3(7)
C6	36.1(9)	44.1(9)	39.1(9)	-5.5(7)	-4.6(7)	-15.1(7)
C12	40.5(10)	61.3(12)	31.2(9)	6.3(8)	-9.4(7)	-6.9(9)
C11	34.2(8)	38.3(9)	29.7(8)	4.7(6)	-6.8(7)	-10.1(7)
C9	35.3(9)	52.8(11)	32.7(9)	-6.4(8)	-7.0(7)	-8.5(8)
C5	39.2(9)	40.3(9)	40.8(10)	-2.0(7)	1.9(7)	-16.5(7)
C17	37.9(9)	37.8(9)	42.9(10)	0.6(7)	-11.4(7)	-11.1(7)
C8	45.1(10)	43.5(10)	37.2(9)	-5.1(7)	0.8(8)	-21.2(8)
C3	58.5(13)	55.3(12)	43.2(11)	8.8(9)	-0.5(9)	-11.2(10)
C13	47.8(10)	45.0(10)	31.2(9)	1.1(7)	-3.3(8)	-10.7(8)
C7	45.9(10)	42.3(9)	34.4(9)	-0.8(7)	2.9(7)	-20.8(8)
C4	46.2(10)	40.7(9)	31.1(9)	0.1(7)	-3.5(7)	-2.9(8)
C16	38.6(10)	44.4(10)	61.6(13)	-6.0(9)	-11.5(9)	-4.8(8)
C14	54.8(12)	57.6(12)	42.1(11)	-6.8(9)	5.1(9)	-9.0(10)
C2	78.1(17)	62.2(14)	41.0(12)	15.2(10)	1.0(11)	1.3(12)
C1	59.3(13)	68.2(14)	30.1(9)	-4.2(9)	-6.1(9)	15.0(11)
C15	44.6(11)	53.4(12)	63.6(14)	-14.0(10)	4.3(10)	-4.8(9)

Table S4. List of bond lengths for compound 10q.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S2	O2	1.4280(17)	N1	C8	1.469(2)
S2	O1	1.4218(16)	N4	C12	1.350(3)
S2	N1	1.6390(16)	N4	C13	1.338(3)
S2	C4	1.7417(19)	C10	C11	1.448(2)
S1	C4	1.714(2)	C10	C9	1.517(2)
S1	C1	1.713(3)	C6	C5	1.513(3)
Cl1	C1	1.708(2)	C12	C11	1.385(2)
O3	C10	1.221(2)	C17	C16	1.356(3)
N3	C11	1.393(2)	C8	C7	1.519(3)
N3	C17	1.372(2)	C3	C4	1.358(3)
N3	C13	1.387(2)	C3	C2	1.414(3)
N2	C6	1.466(2)	C13	C14	1.407(3)
N2	C9	1.457(2)	C16	C15	1.408(3)
N2	C7	1.461(2)	C14	C15	1.362(3)
N1	C5	1.472(2)	C2	C1	1.341(4)

Table S5. List of bond angles for compound 10q.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S2	N1	106.82(9)	N3	C11	C10	124.15(15)
O2	S2	C4	107.60(10)	C12	C11	N3	104.22(16)
O1	S2	O2	120.46(11)	C12	C11	C10	131.63(17)
O1	S2	N1	106.93(9)	N2	C9	C10	114.20(15)
O1	S2	C4	107.66(10)	N1	C5	C6	108.45(15)
N1	S2	C4	106.64(8)	C16	C17	N3	118.61(19)
C1	S1	C4	89.94(12)	N1	C8	C7	108.99(16)
C17	N3	C11	131.15(16)	C4	C3	C2	112.1(2)
C17	N3	C13	122.15(16)	N3	C13	C14	118.84(19)
C13	N3	C11	106.70(15)	N4	C13	N3	111.39(17)
C9	N2	C6	109.10(14)	N4	C13	C14	129.8(2)
C9	N2	C7	110.93(15)	N2	C7	C8	110.58(15)
C7	N2	C6	109.19(14)	S1	C4	S2	121.17(12)
C5	N1	S2	116.30(12)	C3	C4	S2	126.09(18)
C8	N1	S2	116.52(13)	C3	C4	S1	112.64(17)
C8	N1	C5	111.92(14)	C17	C16	C15	120.9(2)
C13	N4	C12	104.98(17)	C15	C14	C13	118.9(2)
O3	C10	C11	122.65(17)	C1	C2	C3	111.8(2)
O3	C10	C9	121.71(16)	Cl1	C1	S1	119.46(19)
C11	C10	C9	115.58(15)	C2	C1	S1	113.57(18)
N2	C6	C5	110.24(15)	C2	C1	Cl1	127.0(2)
N4	C12	C11	112.71(18)	C14	C15	C16	120.6(2)

Table S6. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for compound 10q.

Atom	x	y	z	U(eq)
H6A	847.24	1693.07	5320.2	47
H6B	498.76	3207.62	4927.46	47
H12	5203.71	1796.45	2239.89	55
H9A	3769.48	2482.58	3789.89	49
H9B	3704.51	1023.52	4193.14	49
H5A	-1231.54	3215.18	6493.44	48
H5B	918.35	2409.98	6832.55	48
H17	11180.84	-82.37	3860.43	47
H8A	3780.29	3602.29	6709.43	49
H8B	3343.84	5100.49	6276.3	49
H3	-1697.78	3352.56	8824.72	66
H7A	3273.09	4296.21	4798.12	48
H7B	5436.52	3517.01	5130.51	48
H16	14437.17	-1063.45	3015.84	59
H14	12060.94	-286.62	584.17	65
H2	346	2363.83	10101	80
H15	14893.18	-1141.31	1376.47	68

Table S7. A compendium of the results obtained through docking, lactate dehydrogenase coupled enzyme assay and in vitro screening of A549 human adenocarcinoma cell line where PKM2 is overexpressed. All the compounds were evaluated against normal lung epithelial cell line BEAS-2B to establish their cancer specificity.*

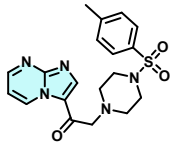
S. No.	Compound Code	Isolated yield in %	IC_{50} (µM)-A549	IC_{50} (µM) – BEAS-2B	Z	Y	AC_{50} (PKM2) in µM#	IC_{50} (PKM2) in µM#	Docking score -activator binding site (Kcal/mol)
1	**9a**	**63**	**1.00±0.365**	**39.55±5.35**	**N**	**Ph-Me**	**0.1049±0.058**		**-8.59**
2	**9b**	**68**	**0.91±0.314**	**59.46±4.53**	**N**	**Ph**	**0.03007±0.083**		**-8.09**
3	9c	72	1.47±0.141	44.99±6.76	N	Thiophene	0.0935±0.060		-7.80
4	9d	78	1.23±1.217	15.87±3.77	N	4-CF_3-Ph	0.2109±0.071		-8.16
5	9e	71	1.33±0.069	20.81±4.57	N	4-Br-Ph	0.5305±0.019		-8.24
6	9f	80	1.48±0.140	19.97±5.42	N	4-F-Ph	0.7034±0.047		-8.83
7	9g	66	1.48±0.054	28.43±5.86	N	4-OMe-Ph	0.5354±0.0081		-8.48
8	9h	74	1.26±0.16	26.46±8.21	N	2,5-dichloro-Ph	0.6478±0.049		-8.20
9	**9i**	**81**	**1.06±0.267**	**51.35±8.55**	**N**	**2,4,6-trimethyl-Ph**	**0.7253±0.021**		**-9.33**

10	9j	69	1.54±0.111	39.07±8.62	N	5-Br,2-Ome-Ph	0.6428±0.041		-7.18
11	9k	62	1.14±0.498	38.98±8.17	N	3-Br-Ph	0.6340±0.076		-8.75
12	9l	63	1.54±0.087	39.04±8.73	N	Cyclohexyl		0.7829±0.031	-7.54
13	9m	60	1.60±0.048	36.47±7.00	N	5-Br-thiophene		0.6806±0.030	-7.87
14	9n	70	1.76±0.069	53.45±6.84	N	Cyclopropyl	0.0923±0.059		-7.07
15	9o	61	1.72±0.059	46.32±5.04	N	2-cyano-Ph	0.5153±0.002		-8.53
16	9p	75	1.72±0.070	16.78±5.3	N	2-Cl,4-F-Ph	0.6121±0.415		-8.87
17	9q	77	1.75±0.043	9.29±3.76	N	5-Cl-thiophene	0.4372±0.089		-7.81
18	9r	79	1.60±0.061	9.13±4.81	N	4'-OMe-Biphenyl	0.4347±0.566		-8.26
19	9s	66	1.66±0.048	66.92±6.01	N	4-NO_2-Ph		0.0388±0.089	NA
20	10a	75	1.67±0.113	51.15±5.82	CH	Ph-Me	0.7955±0.055		-7.24
21	10b	74	1.69±0.074	44.68±4.49	CH	Ph	0.1410±0.630		-7.18
22	**10c**	**69**	**1.14±0.277**	**30.47±8.41**	**CH**	**Thiophene**	**0.1340±0.079**		**-8.75**
23	10d	69	1.30±0.145	61.36±9.97	CH	4-CF_3-Ph	0.550±0.044		-7.54
24	10e	64	1.74±0.074	64.24±5.33	CH	4-Br-Ph	0.1462±0.060		-7.87
25	10f	69	1.68±0.065	52.22±8.50	CH	4-F-Ph	0.382±0.056		-7.07
26	10g	79	1.83±0.053	46.05±5.58	CH	4-OMe-Ph	0.0416±0.048		-8.53
27	10h	72	1.50±0.084	45.95±9.06	CH	2,5-dichloro-Ph		0.6158±0.065	-7.81
28	10i	80	1.68±0.039	11.47±3.59	CH	2,4,6-trimethyl-Ph	0.1806±0.021		-9.10
29	10j	70	1.44±0.084	30.92±8.10	CH	5-Br,2-OMe-Ph	0.3285±0.035		-6.50
30	10k	77	1.67±0.120	39.90±5.16	CH	3-Br-Ph	0.6060±0.064		-8.73
31	10l	78	1.65±0.068	60.57±7.60	CH	Cyclohexyl	0.889±0.049		-5.14
32	10m	62	1.67±0.049	45.69±10.74	CH	5-Br-thiophene		0.1382±0.063	-8.17
33	10n	78	1.24±0.171	50.54±7.04	CH	Cyclopropyl	0.432±0.017		-7.40
34	10o	66	1.51±0.105	55.67±2.88	CH	2-cyano-Ph	0.1465±0.071		-8.64
35	**10p**	**62**	**0.95±0.366**	**37.80±4.73**	**CH**	**2-Cl,4-F-Ph**	**0.2046±0.071**		**-9.35**
36	10q	77	1.32±0.170	48.90±7.90	CH	5-Cl-thiophene	0.5517±0.017		-6.12
37	10r	73	1.23±0.216	56.52±5.19	CH	4'-OMe-Biphenyl		0.341±0.036	-8.13

38	10s	65	1.46±0.118	20.09±6.58	CH	4-NO_2-Ph	0.6492±0.089		NA
39	Doxorubicin		1.64±0.101	24.67±7.36					
40	DASA-58 (Std. PKM2 activator)		1.46±0.27	35.23±3.36			0.020±0.010		-8.279
41	L-phenylalanine (Std. PKM2 inhibitor)							0.055±0.042	

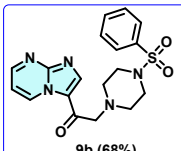
*This combined data set was analyzed for compound selection from the entire series, in case of further studies. The results of the LDH coupled enzyme assay and the cytotoxicity assay are expressed as mean ± SEM done in triplicate.

13. Chemical Structures of the synthesized compounds



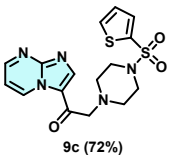
9a (63%)

$AC_{50\ (PKM2)}$: 104.9 ± 0.058 nM
$IC_{50\ (A549)}$: 1000.0 ± 0.365 nM
$IC_{50\ (BEAS\text{-}2B)}$: 39550.0 ± 5.35 nM



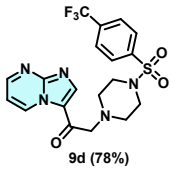
9b (68%)

$AC_{50\ (PKM2)}$: 30.07 ± 0.083 nM
$IC_{50\ (A549)}$: 910.0 ± 0.314 nM
$IC_{50\ (BEAS\text{-}2B)}$: 59460.0 ± 4.53 nM



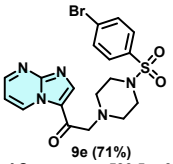
9c (72%)

$AC_{50\ (PKM2)}$: 93.5 ± 0.060 nM
$IC_{50\ (A549)}$: 1470.0 ± 0.141 nM
$IC_{50\ (BEAS\text{-}2B)}$: 44990.0 ± 6.76 nM



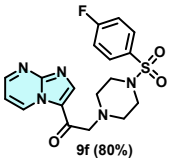
9d (78%)

$AC_{50\ (PKM2)}$: 210.9 ± 0.071 nM
$IC_{50\ (A549)}$: 1230.0 ± 1.217 nM
$IC_{50\ (BEAS\text{-}2B)}$: 15870.0 ± 3.77 nM



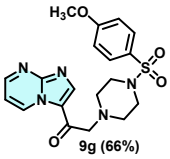
9e (71%)

$AC_{50\ (PKM2)}$: 530.5 ± 0.019 nM
$IC_{50\ (A549)}$: 1330.0 ± 0.069 nM
$IC_{50\ (BEAS\text{-}2B)}$: 20810.0 ± 4.57 nM



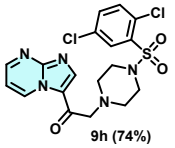
9f (80%)

$AC_{50\ (PKM2)}$: 703.4 ± 0.047 nM
$IC_{50\ (A549)}$: 1480.0 ± 0.140 nM
$IC_{50\ (BEAS\text{-}2B)}$: 19970.0 ± 5.42 nM



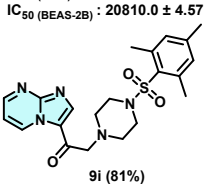
9g (66%)

$AC_{50\ (PKM2)}$: 535.4 ± 0.0081 nM
$IC_{50\ (A549)}$: 1480.0 ± 0.054 nM
$IC_{50\ (BEAS\text{-}2B)}$: 28430.0 ± 5.86 nM



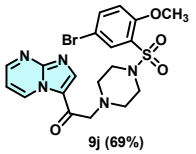
9h (74%)

$AC_{50\ (PKM2)}$: 647.8 ± 0.049 nM
$IC_{50\ (A549)}$: 1260.0 ± 0.16 nM
$IC_{50\ (BEAS\text{-}2B)}$: 26460.0 ± 8.21 nM



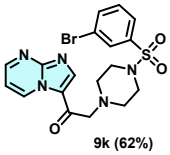
9i (81%)

$AC_{50\ (PKM2)}$: 725.3 ± 0.021 nM
$IC_{50\ (A549)}$: 1060.0 ± 0.267 nM
$IC_{50\ (BEAS\text{-}2B)}$: 51350.0 ± 8.55 nM



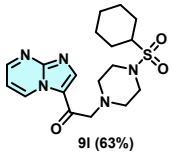
9j (69%)

$AC_{50\ (PKM2)}$: 642.8 ± 0.041 nM
$IC_{50\ (A549)}$: 1540.0 ± 0.111 nM
$IC_{50\ (BEAS\text{-}2B)}$: 39070.0 ± 8.62 nM



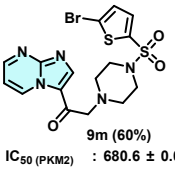
9k (62%)

$AC_{50\ (PKM2)}$: 634.0 ± 0.076 nM
$IC_{50\ (A549)}$: 1140.0 ± 0.498 nM
$IC_{50\ (BEAS\text{-}2B)}$: 38980.0 ± 8.17 nM



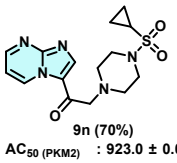
9l (63%)

$IC_{50\ (PKM2)}$: 782.9 ± 0.031 nM
$IC_{50\ (A549)}$: 1540.0 ± 0.087 nM
$IC_{50\ (BEAS\text{-}2B)}$: 39040.0 ± 8.73 nM



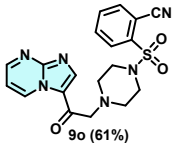
9m (60%)

$IC_{50\ (PKM2)}$: 680.6 ± 0.030 nM
$IC_{50\ (A549)}$: 1600.0 ± 0.048 nM
$IC_{50\ (BEAS\text{-}2B)}$: 36470.0 ± 7.00 nM



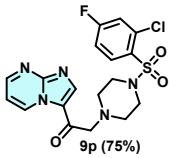
9n (70%)

$AC_{50\ (PKM2)}$: 923.0 ± 0.059 nM
$IC_{50\ (A549)}$: 1760.0 ± 0.069 nM
$IC_{50\ (BEAS\text{-}2B)}$: 53450.0 ± 6.84 nM



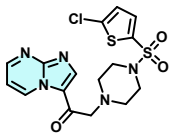
9o (61%)

$AC_{50\ (PKM2)}$: 515.3 ± 0.002 nM
$IC_{50\ (A549)}$: 1720.0 ± 0.059 nM
$IC_{50\ (BEAS\text{-}2B)}$: 46320.0 ± 5.04 nM



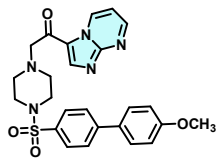
9p (75%)

$AC_{50\ (PKM2)}$: 612.1 ± 0.415 nM
$IC_{50\ (A549)}$: 1720.0 ± 0.070 nM
$IC_{50\ (BEAS\text{-}2B)}$: 16780.0 ± 5.3 nM



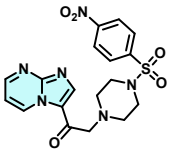
9q (77%)

$AC_{50\ (PKM2)}$: 437.2 ± 0.089 nM
$IC_{50\ (A549)}$: 1750.0 ± 0.043 nM
$IC_{50\ (BEAS\text{-}2B)}$: 9290.0 ± 3.76 nM



9r (79%)

$AC_{50\ (PKM2)}$: 434.7 ± 0.566 nM
$IC_{50\ (A549)}$: 1600.0 ± 0.061 nM
$IC_{50\ (BEAS\text{-}2B)}$: 9130.0 ± 4.81 nM



9s (66%)

$IC_{50\ (PKM2)}$: 38.8 ± 0.089 nM
$IC_{50\ (A549)}$: 1660.0 ± 0.048 nM
$IC_{50\ (BEAS\text{-}2B)}$: 66920.0 ± 6.01 nM

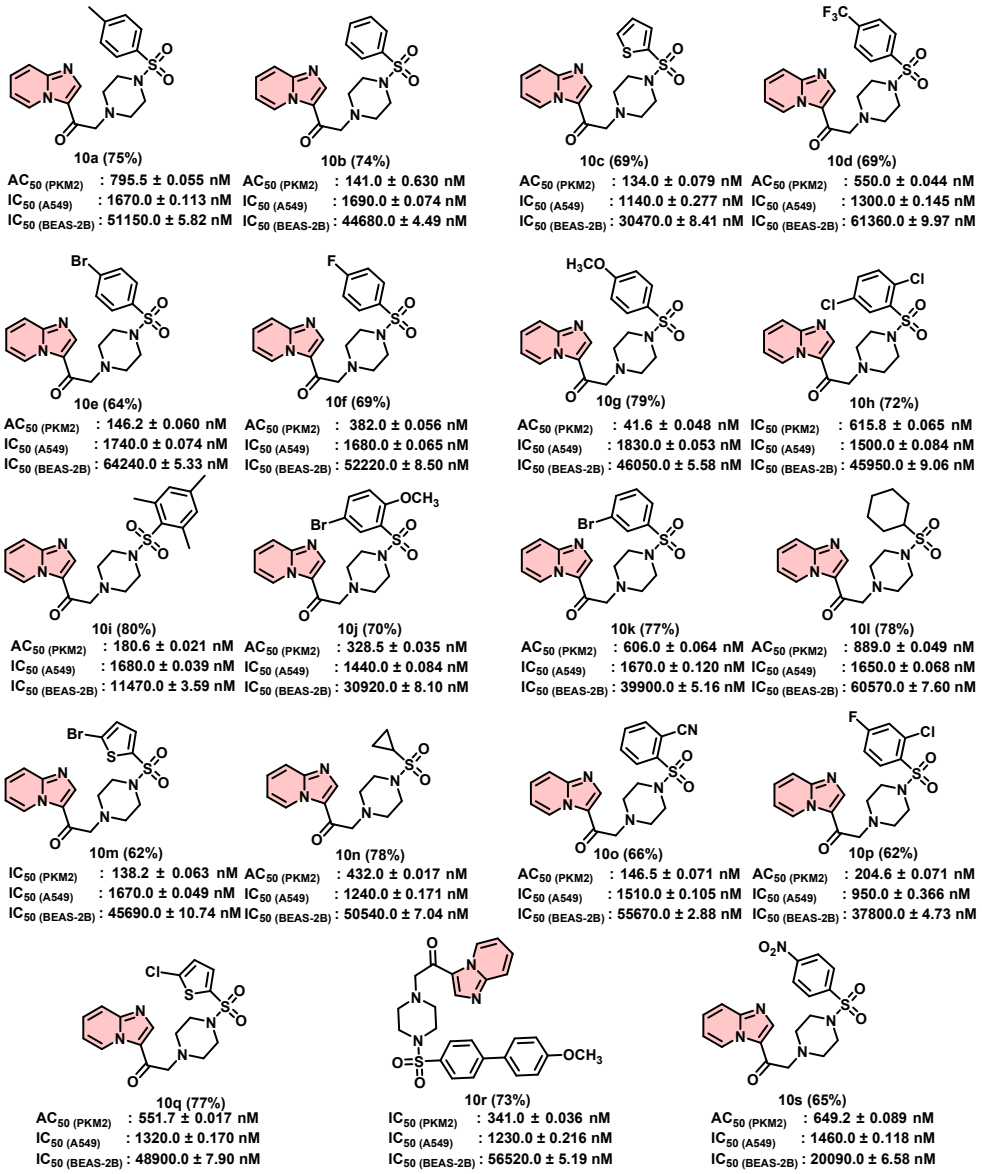


Figure S48. Chemical structures of imidazopyrimidine-flanked sulfonamide derivatives (**9a-9s**) and imidazopyridine-flanked sulfonamide derivatives (**10a-10s**) along with their respective isolated yields. The AC_{50}(PKM2) represents the concentration at which 50% of the maximum activity of PKM2 is observed, while the IC_{50}(PKM2) indicates the concentration at which 50% of the maximum inhibition of PKM2 is achieved. The results from the lactate dehydrogenase-coupled enzyme assay and the cytotoxicity assay are expressed as the mean ± SEM of triplicate measurements. Compound **9b** is the most promising candidate in the series due to its high potency and was consequently selected for further biological evaluation.