Supporting Information

for

Targeted Suppression of Oral Squamous Cell Carcinoma by Pyrimidine-Tethered Quinoxaline Derivatives

Asmita Choithramani[#a], Rudradip Das[#a], Gourav Bothra[a], Priyanka Patel Vatsa[b], Venkatesh Muthukumar[a], Bombothu Kavya Sai Bhuvana[b], Saumya Kapoor[a], Moola Deepshika[b], Moumita Ghosh Chowdhury[a], Amit Mandoli[b]* and Amit Shard[a]*

[a]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research-Ahmedabad (NIPER-A), Opposite Airforce station, Palaj, Gandhinagar, Gujarat – 382355, India.

[b]Department of Biotechnology, National Institute of Pharmaceutical Education and Research-Ahmedabad (NIPER-A), Opposite Airforce station, Palaj, Gandhinagar, Gujarat – 382355, India.

# - Equal contribution

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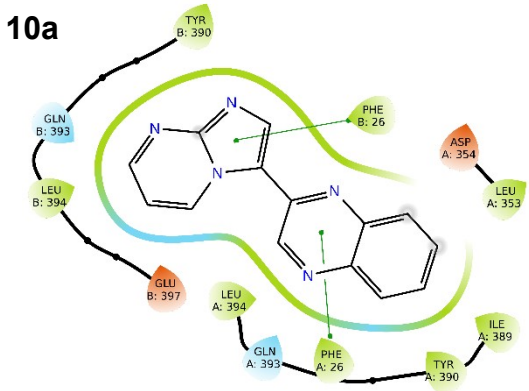
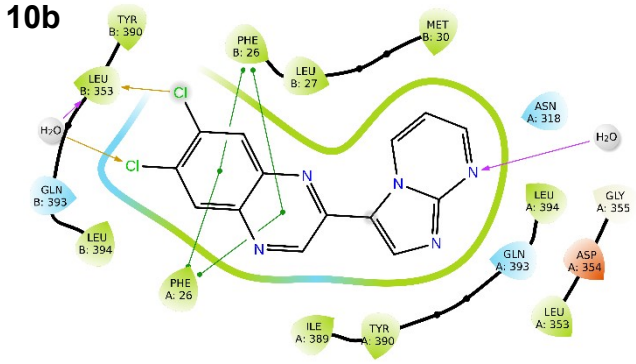
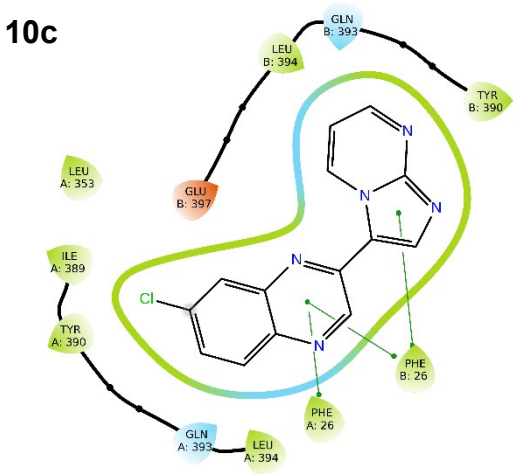
1.Molecular Docking results

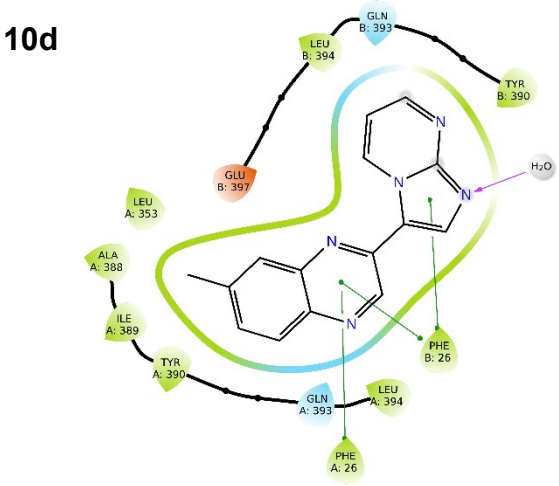
Table S1: XP Gscores of all the synthesized compounds against the PKM2 (PDB: 3GR4)

Compound	XP GScore (kcal/mol)	Compound	XP GScore (kcal/mol)
10n	**-8.993**	10g	-7.26
12d	**-8.743**	10h	-7.207
10j	**-8.269**	10a	-7.097
10f	-8.264	10c	-6.98
12a	-8.248	10e	-6.816
12c	-7.699	10d	-6.522
10p	-7.658	12g	-6.08
10b	-7.647	12b	-5.707
10i	-7.619	12e	-5.214
10l	-7.418	12i	-4.84
10o	-7.31	12h	-3.487
10m	-7.281	12f	-2.459
10k	-7.281	Standard (DASA-58)	-8.279









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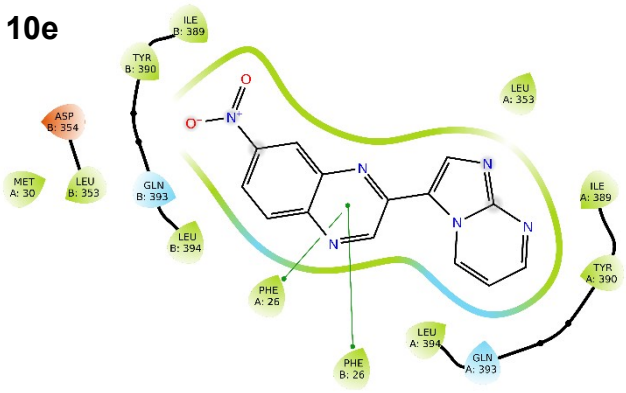

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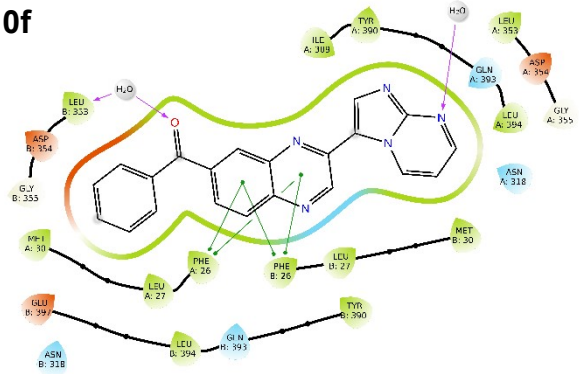

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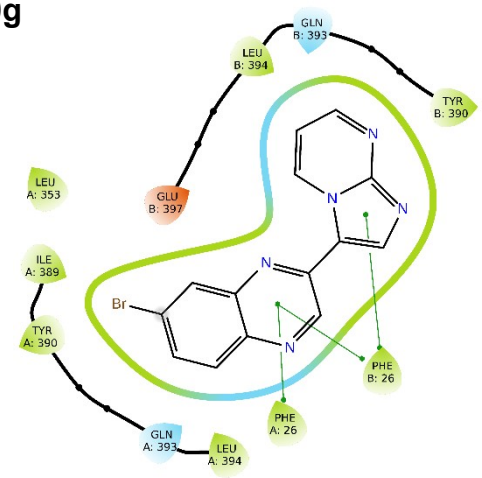

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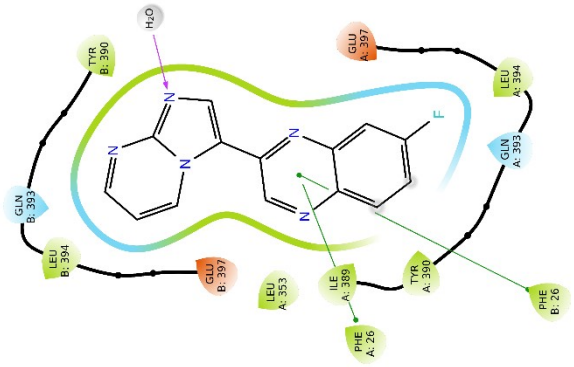

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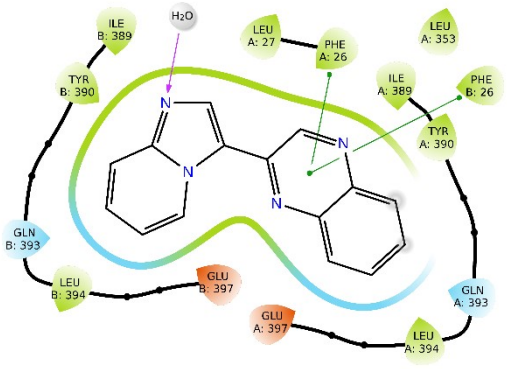

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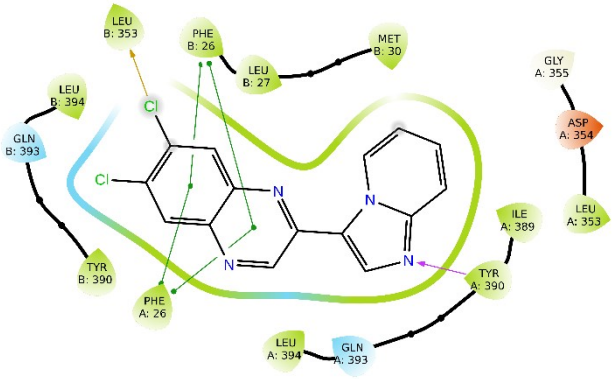

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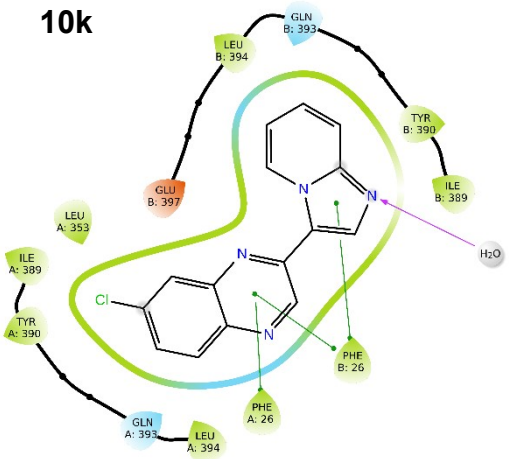

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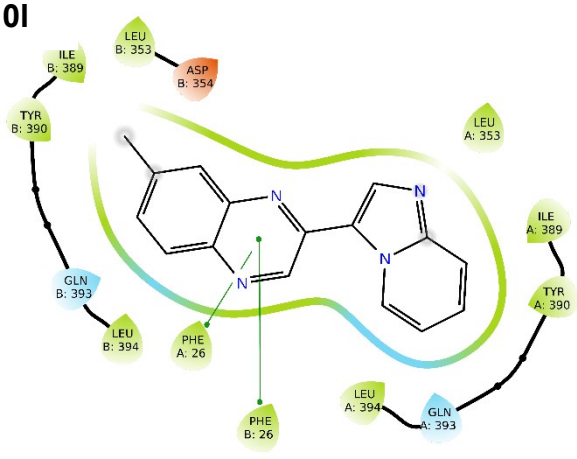

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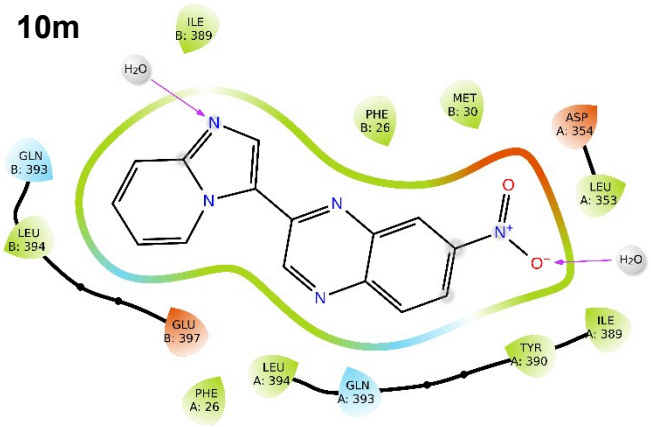

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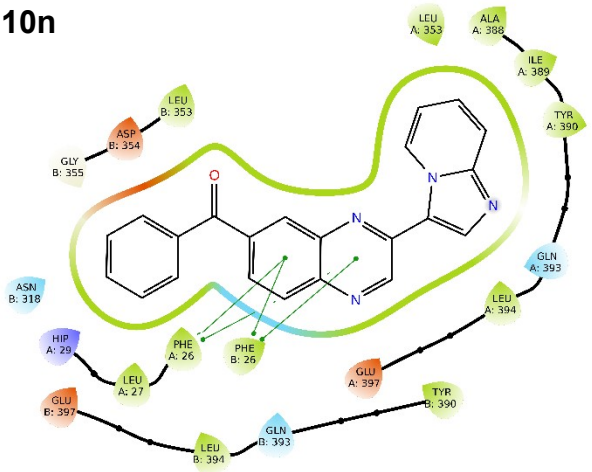

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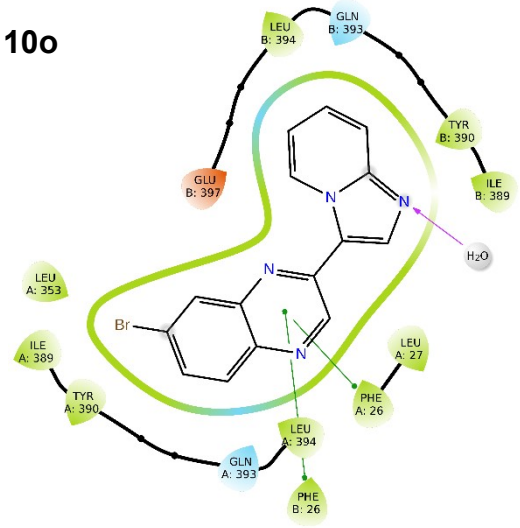

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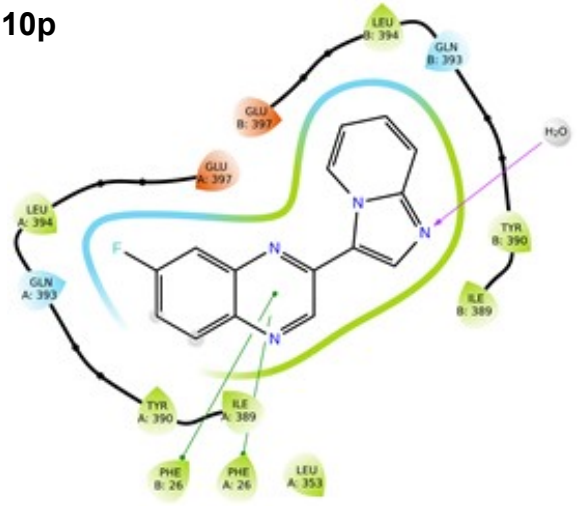

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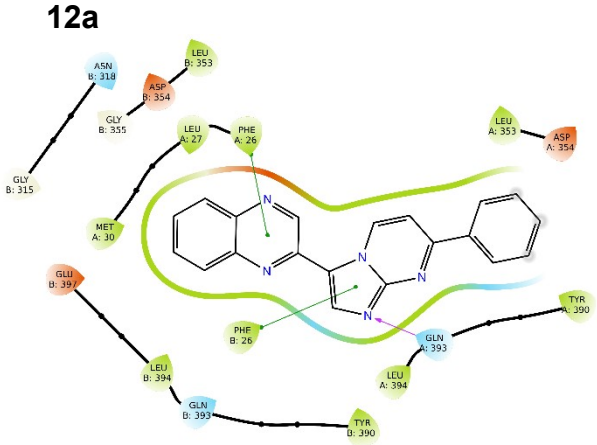

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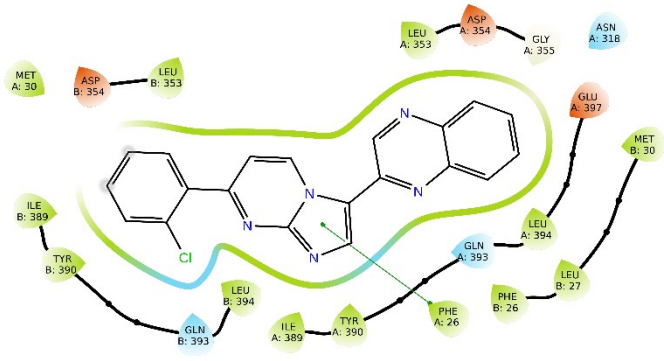

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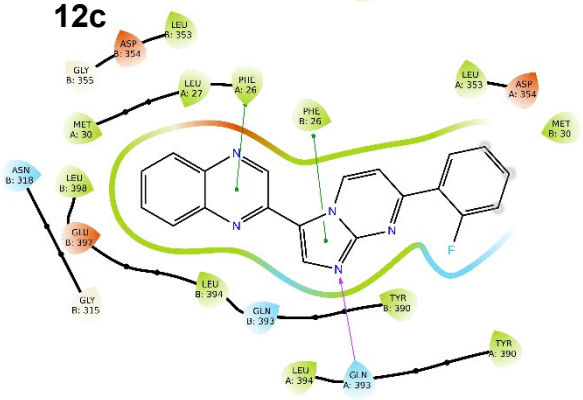

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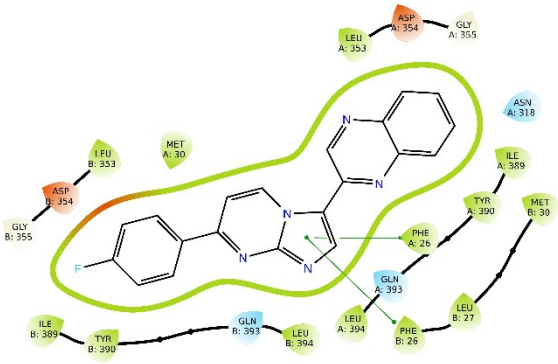

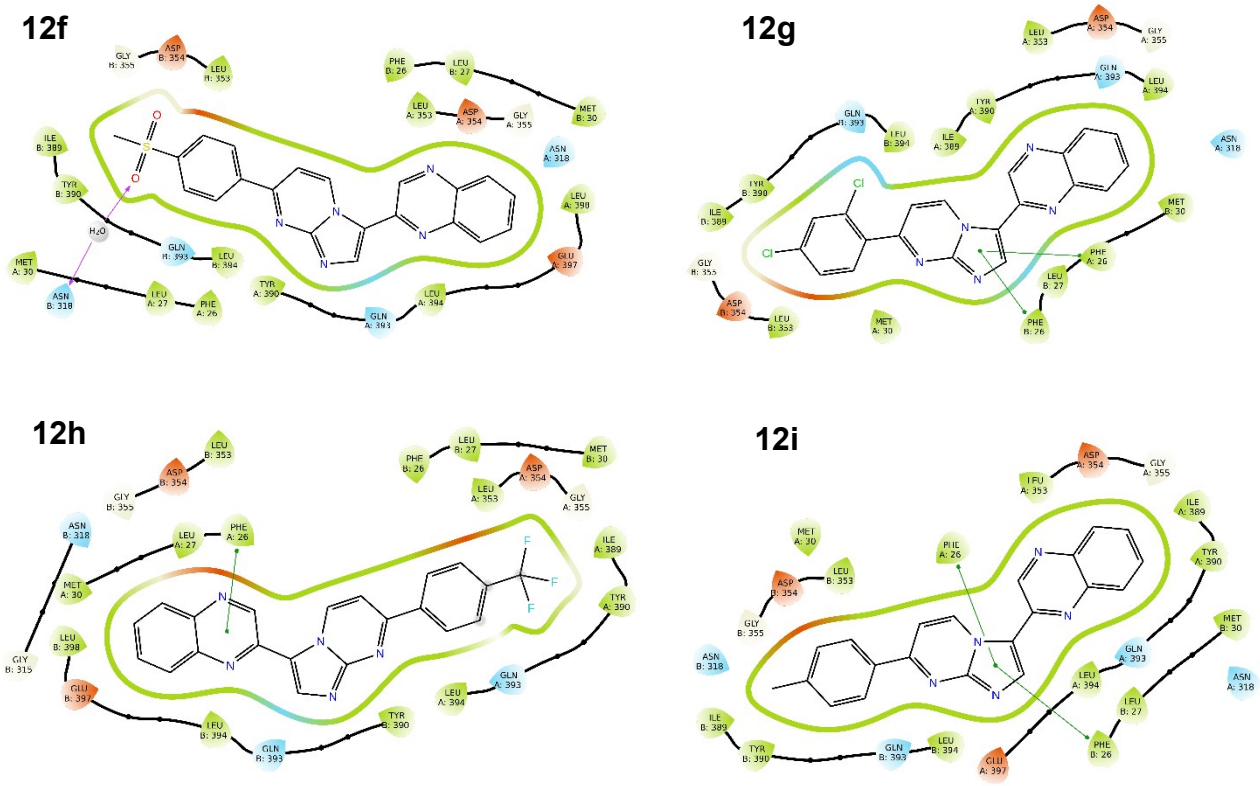

Figure S1: Interactions of synthesized molecules (**10a-10p**, and **12a-12i**) with the activator (DASA-58) binding site of Pyruvate Kinase M2 (PKM2) protein (PDB ID – 3GR4)

2.[1]H NMR, [13]C NMR, [19] F NMR, and HRMS data of the synthesized compounds

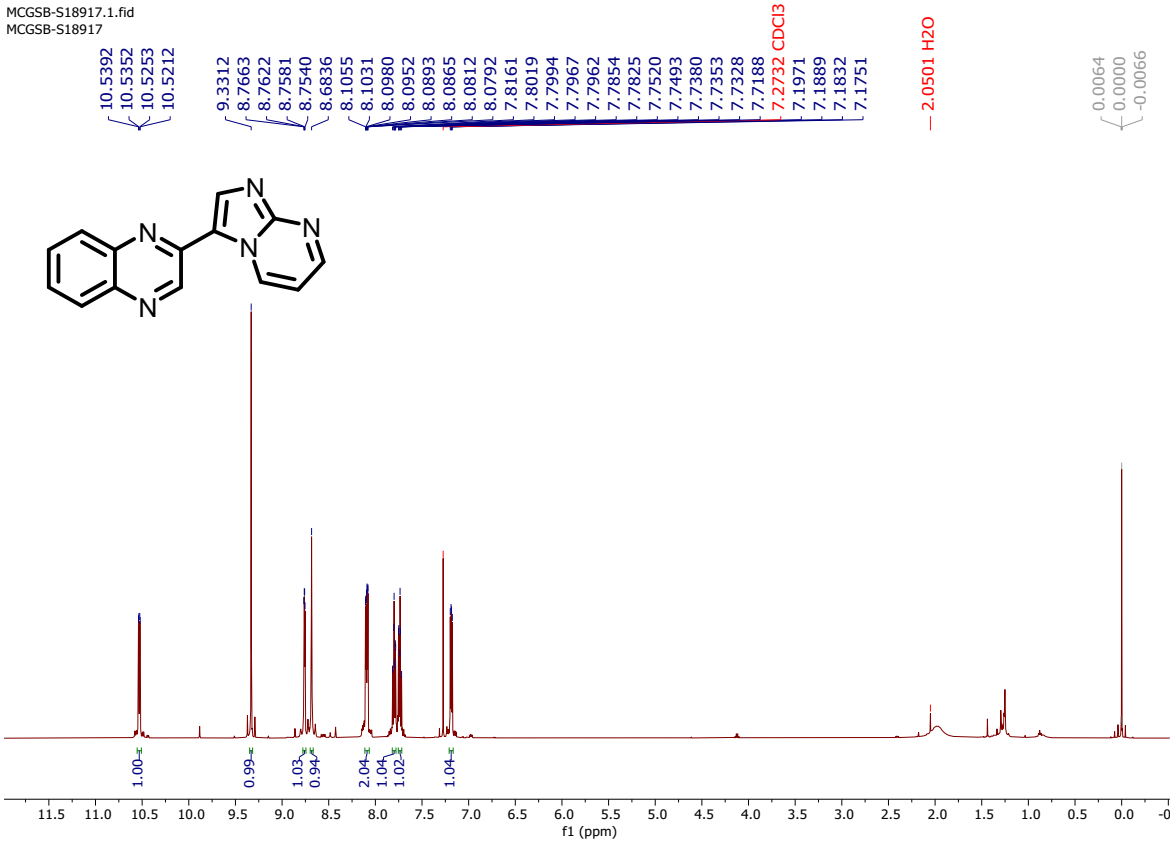

Figure S2: [1]H NMR of 2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10a**) in $CDCl_3$ at 500 MHz

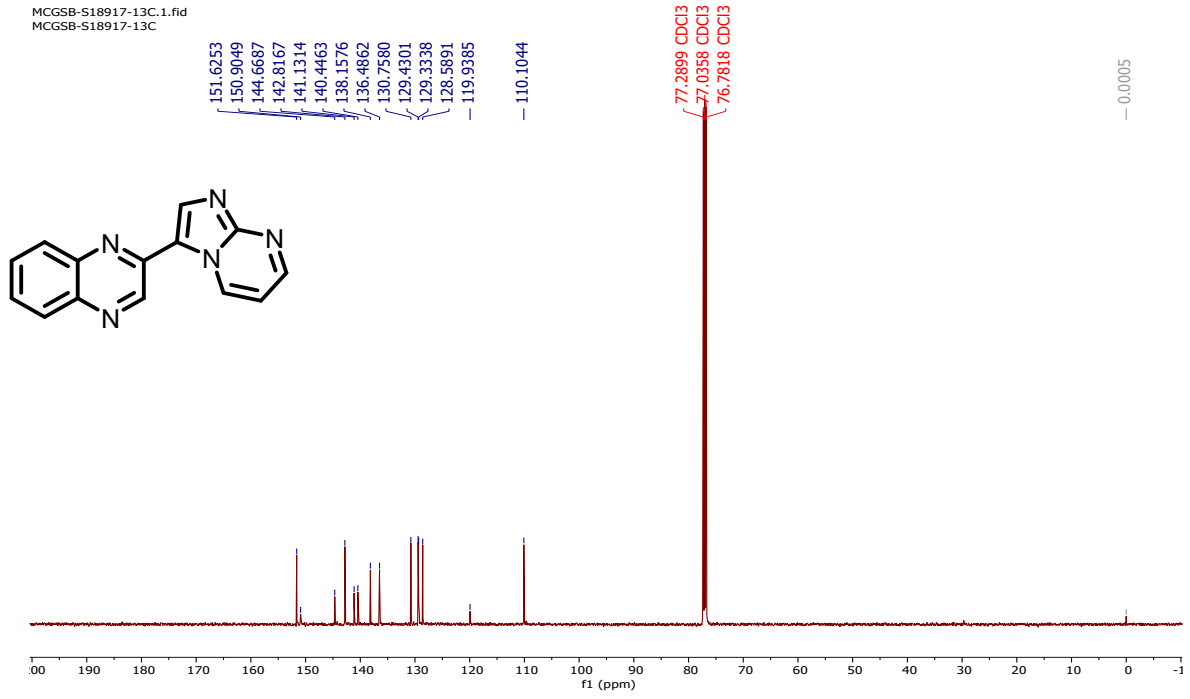

Figure S3: ^{13}C NMR of 2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10a**) in $CDCl_3$ at 125 MHz

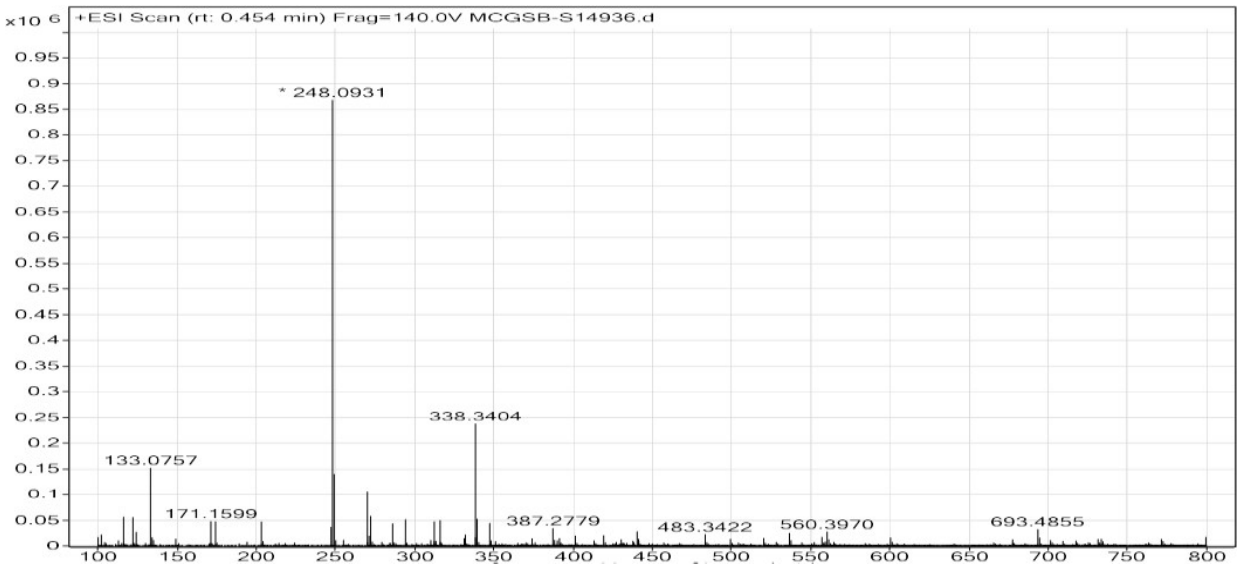

Figure S4: HRMS spectra of 2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10a**)

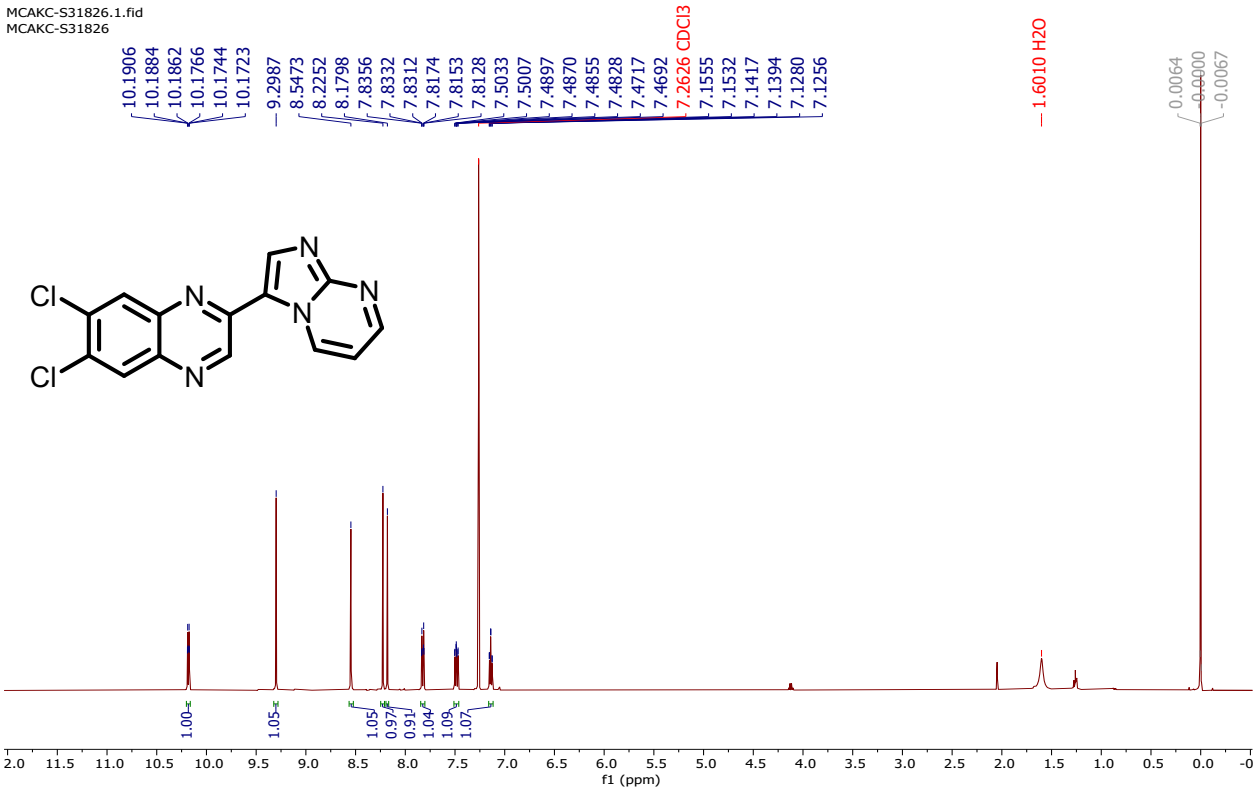

Figure S5: ^{1}H NMR of 6,7-dichloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10b**) in $CDCl_3$ at 500 MHz

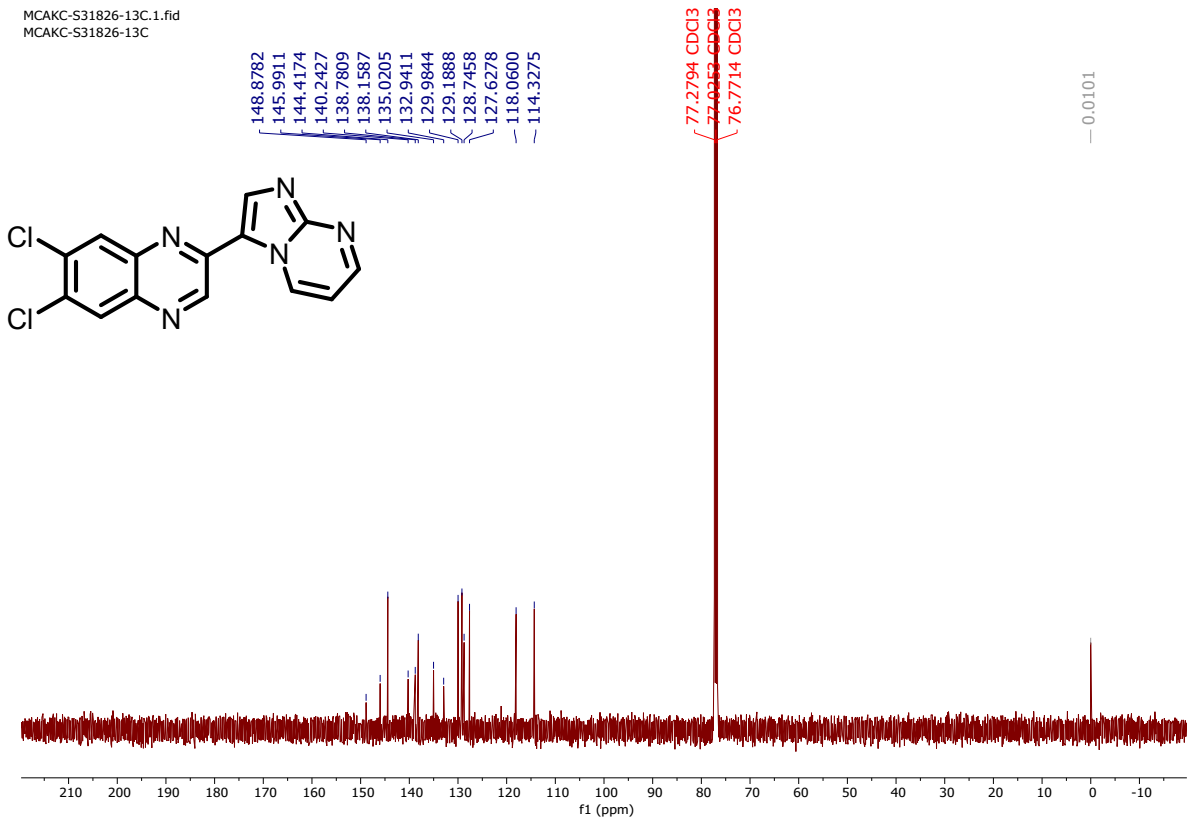

Figure S6: ^{13}C NMR of 6,7-dichloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10b**) in $CDCl_3$ at 125 MHz

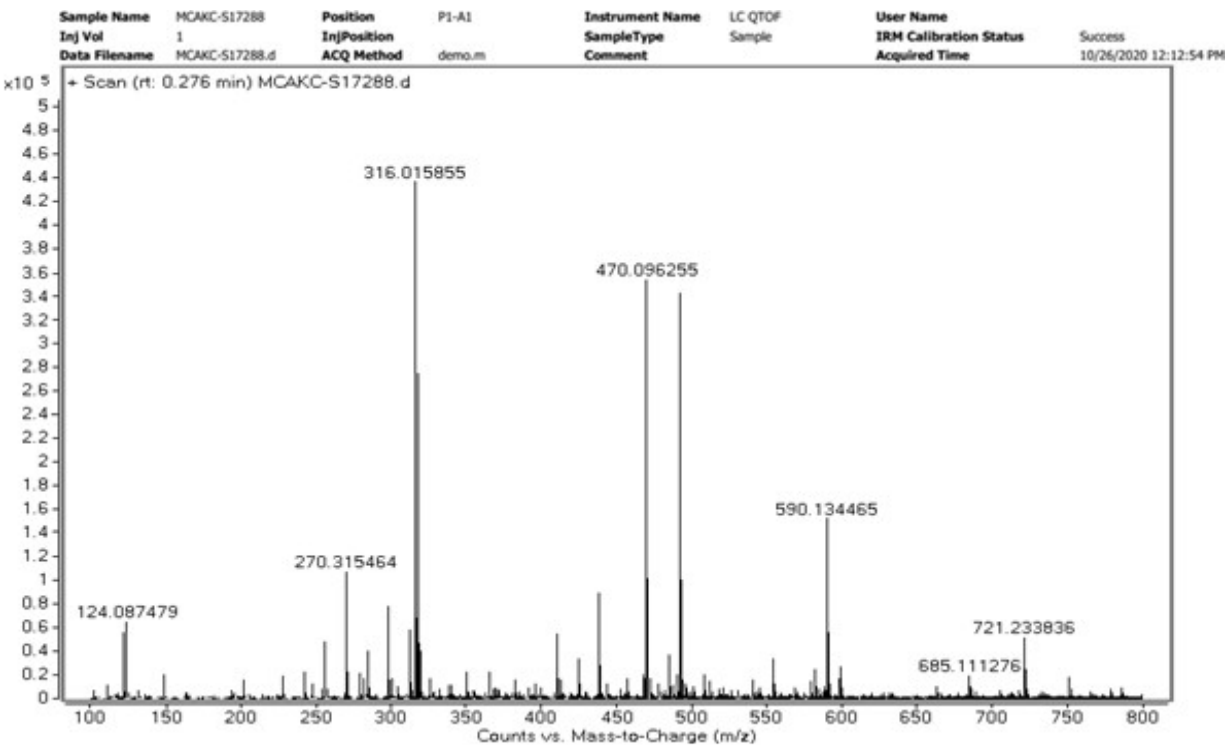

Figure 7: HRMS spectra of 6,7-dichloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10b**)

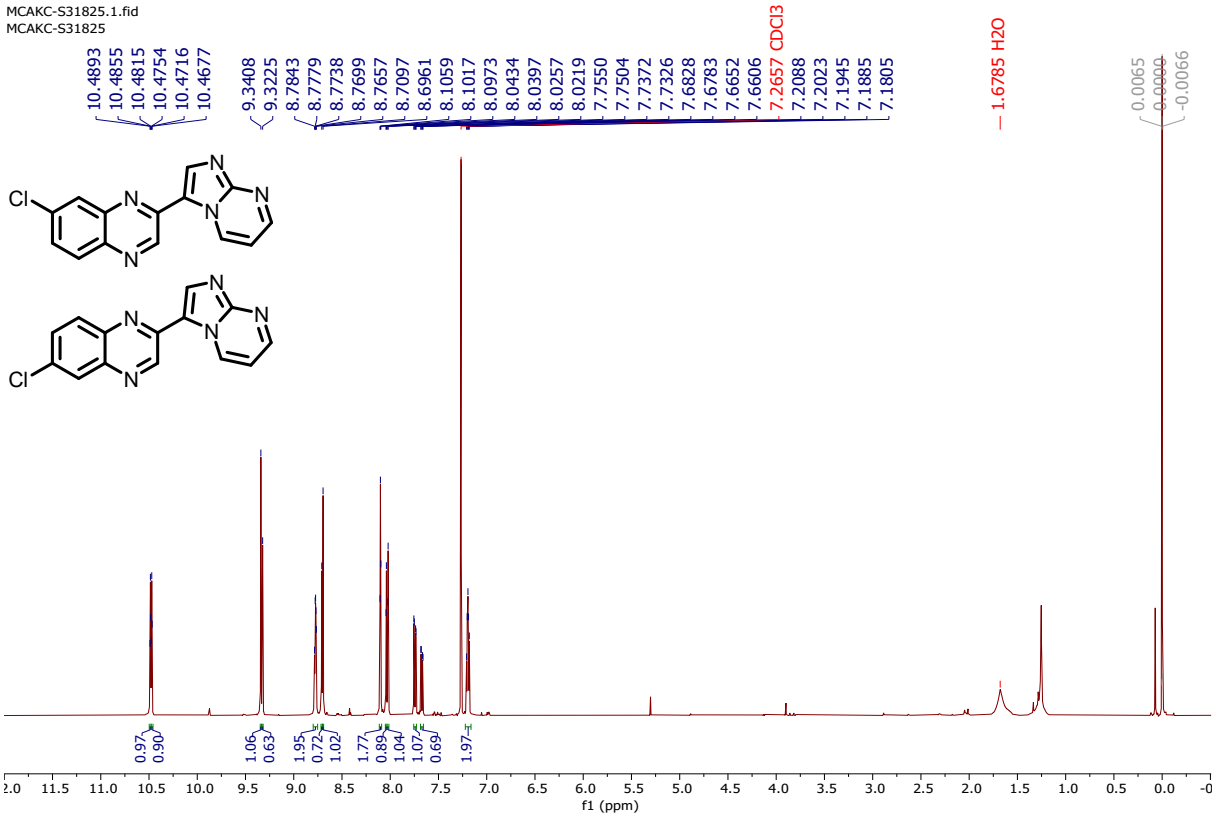

Figure S8: ^{1}H NMR of 6-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline & 7-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10c**) in $CDCl_3$ at 500 MHz

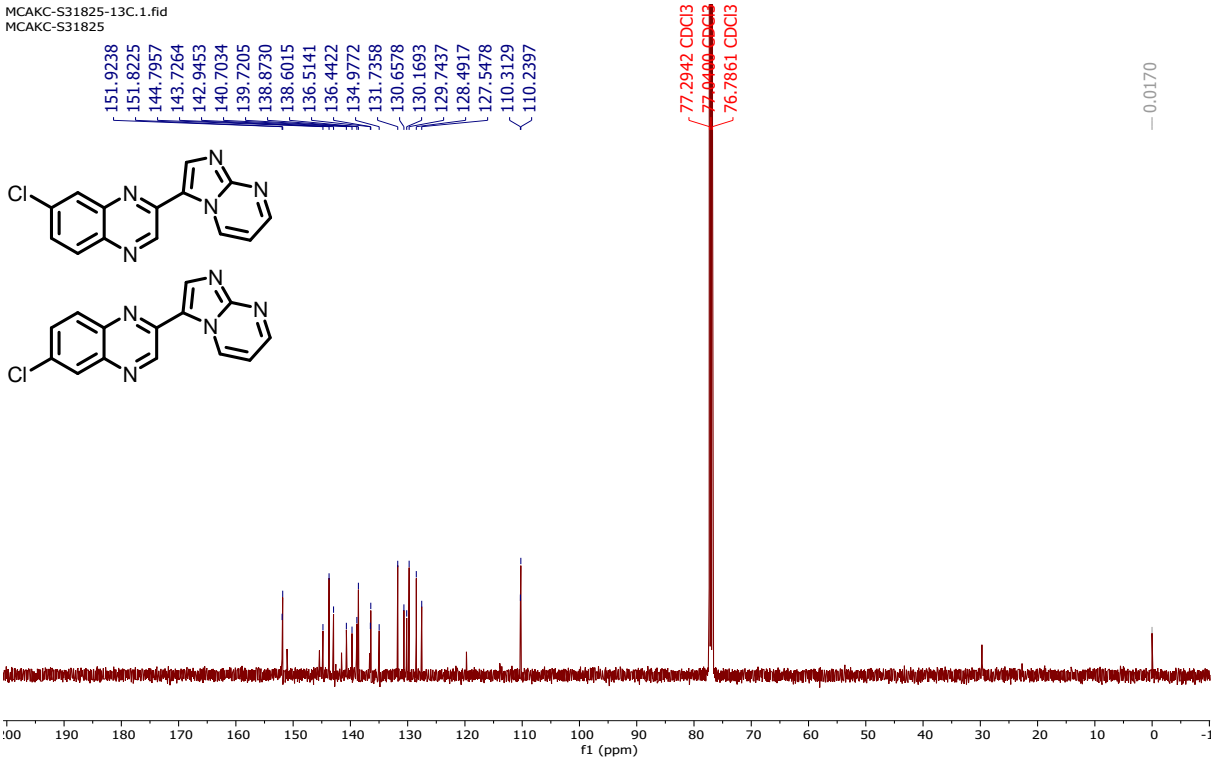

Figure S9: ^{13}C NMR of 6-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline & 7-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10c**) in $CDCl_3$ at 125 MHz

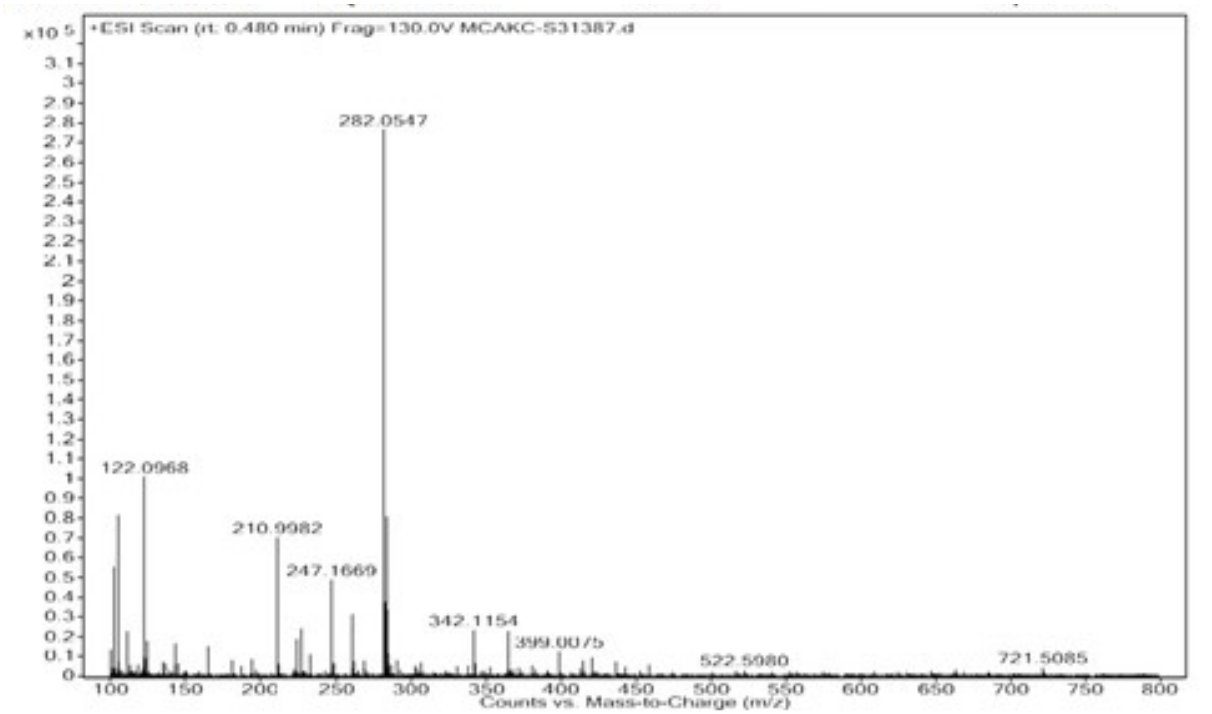

Figure S10: HRMS spectra of 6-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline & 7-chloro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10c**)

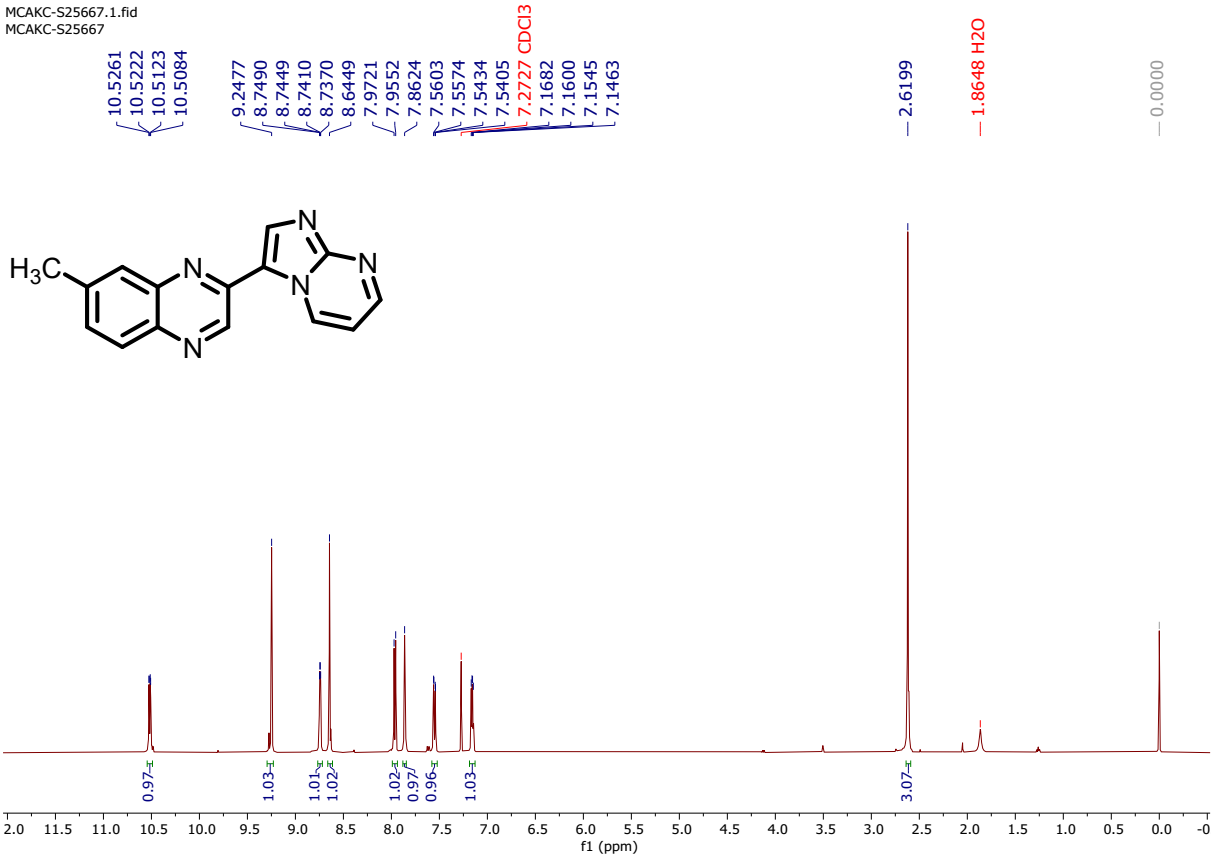

Figure S11: ^{1}H NMR of 7-methyl-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10d**) in $CDCl_3$ at 500 MHz

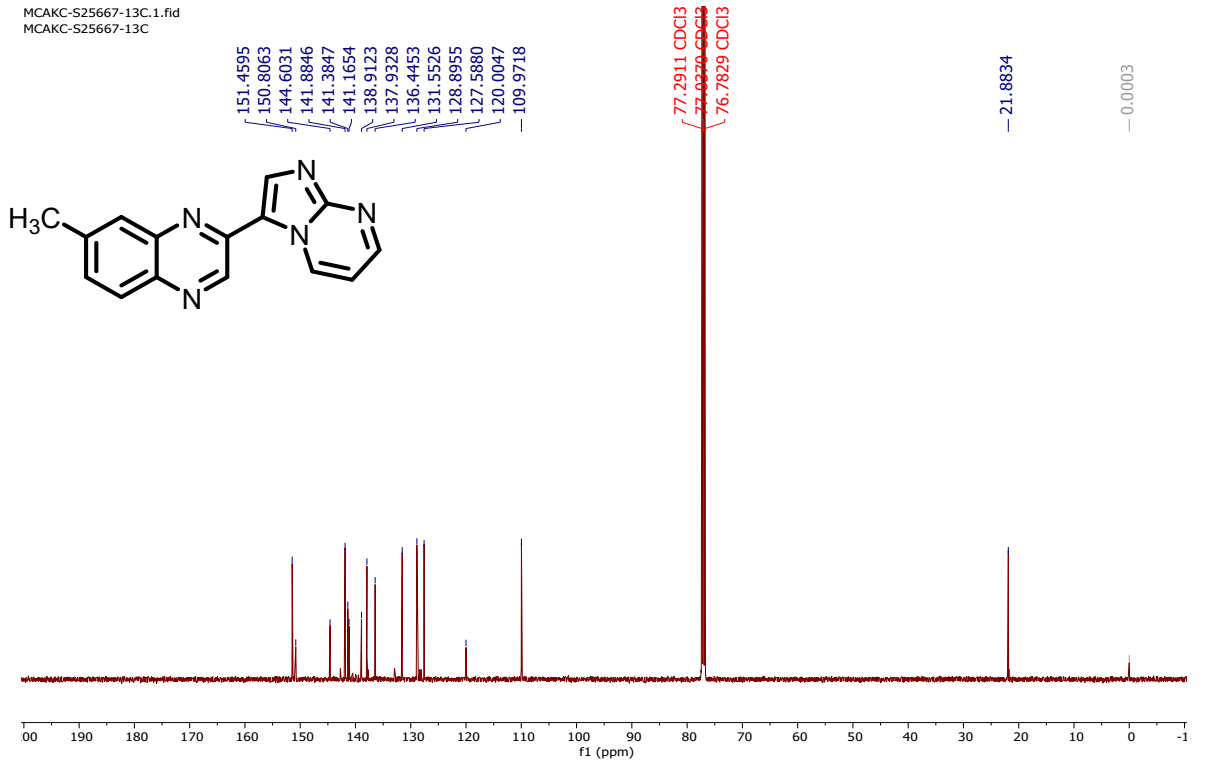

Figure S12: ^{13}C NMR of 7-methyl-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10d**) in $CDCl_3$ at 125 MHz

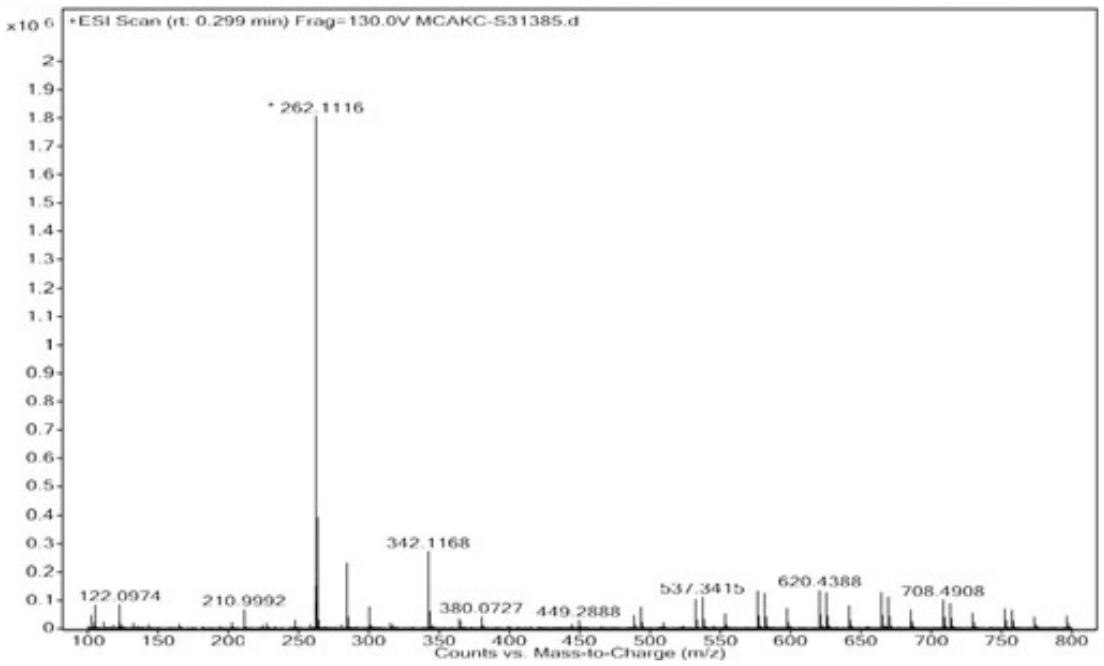

Figure S13: HRMS spectra of 7-methyl-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10d**)

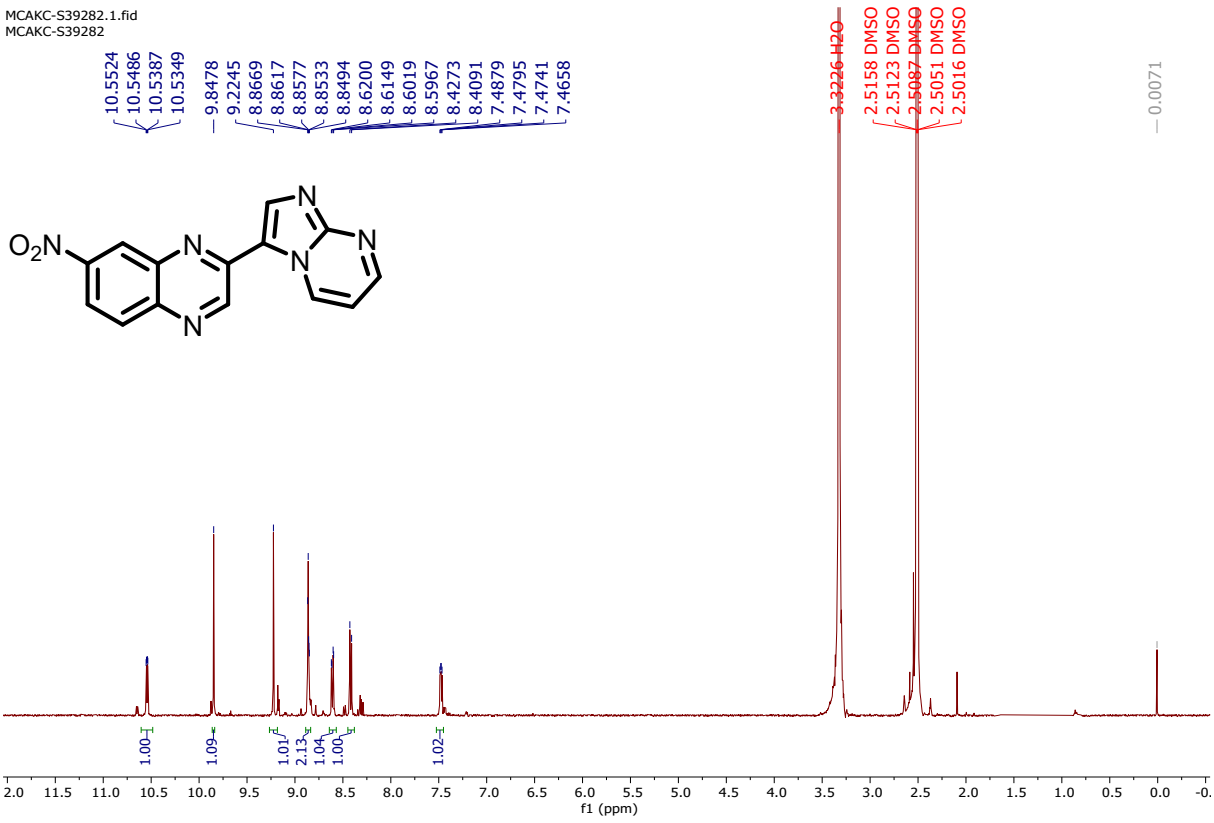

Figure S14: ^{1}H NMR of 7-nitro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10e**) in DMSO-d_6 at 500 MHz

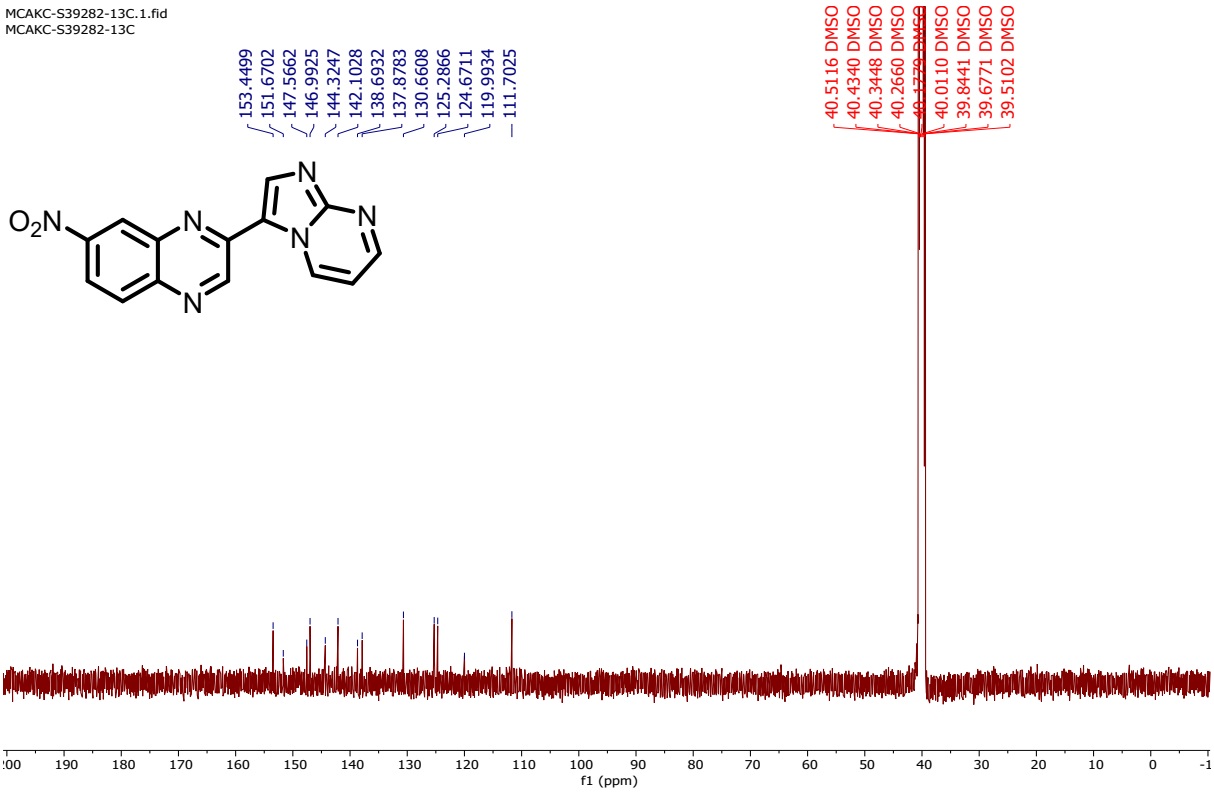

Figure S15: ^{13}C NMR of 7-nitro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10e**) in DMSO-d_6 at 125 MHz

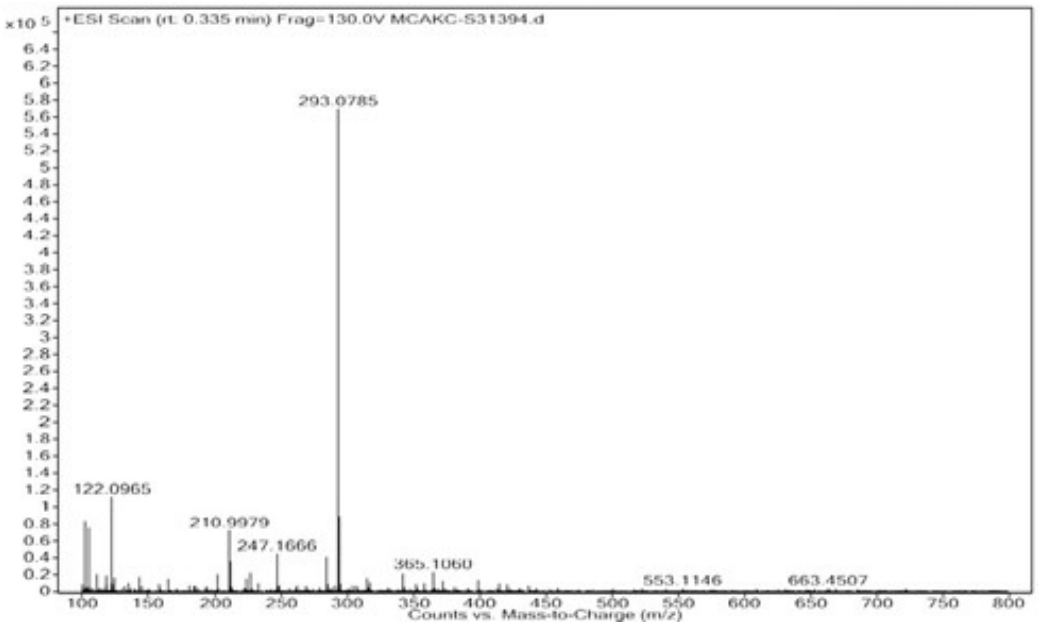

Figure S16: HRMS spectra of 7-nitro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10e**)

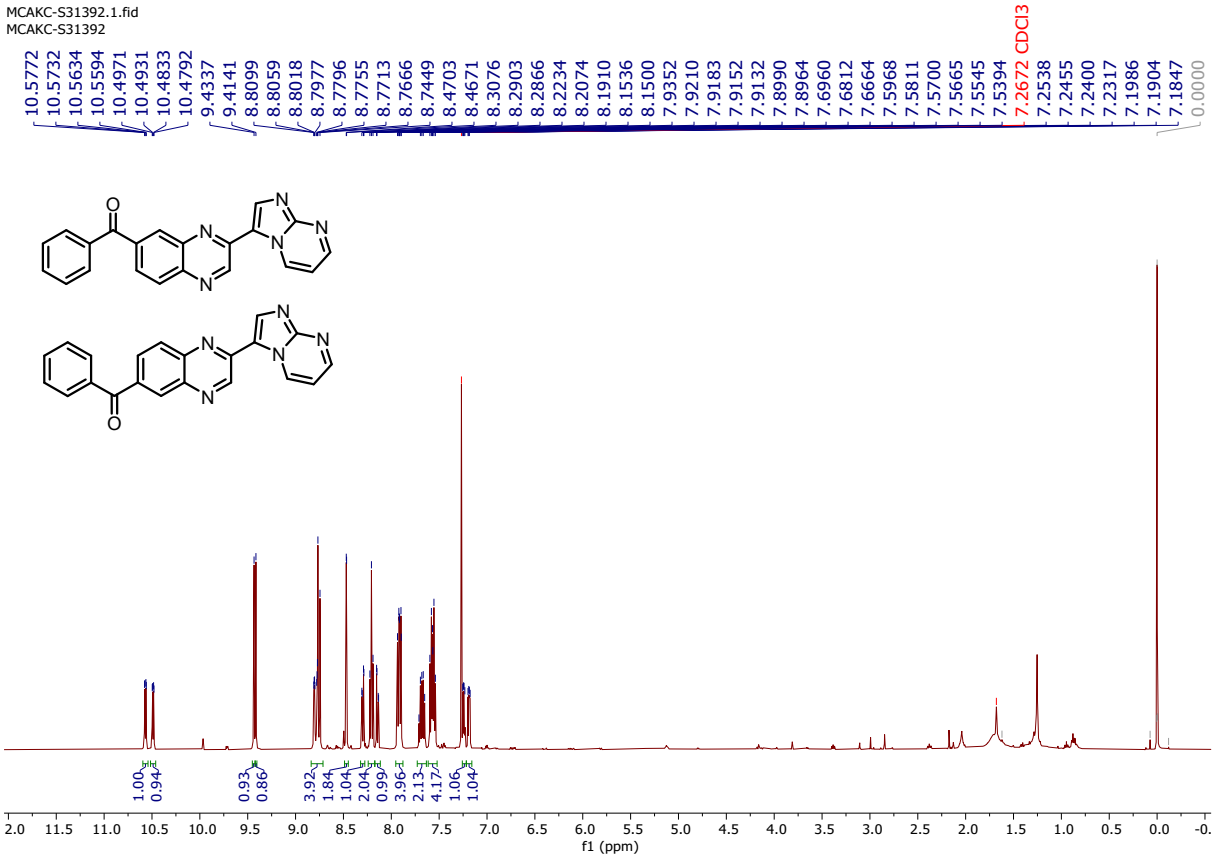

Figure S17: ^{1}H NMR of 6-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline & 7-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline **(10f)** in $CDCl_3$ at 500 MHz

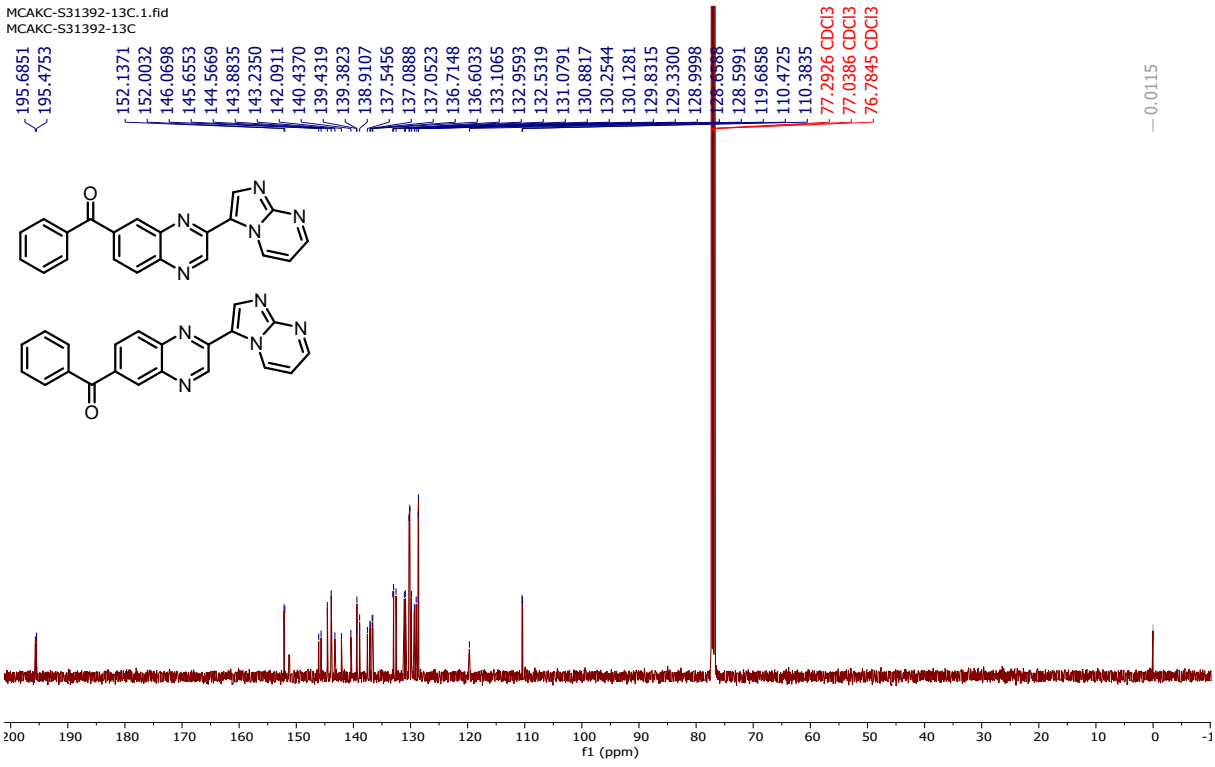

Figure S18: ^{13}C NMR of 6-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline & 7-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline **(10f)** in $CDCl_3$ at 125 MHz

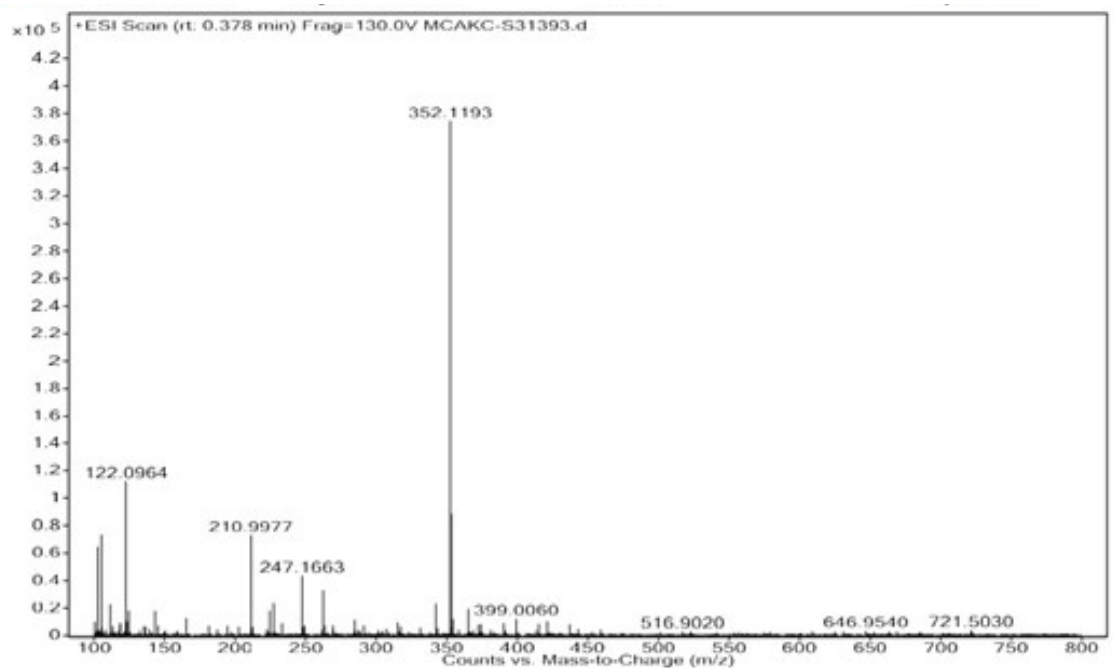

Figure S19: HRMS spectra of 6-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline & 7-phenoxy-2-(imidazo[1,2-a]pyrimidin-3-yl) quinoxaline **(10f)**

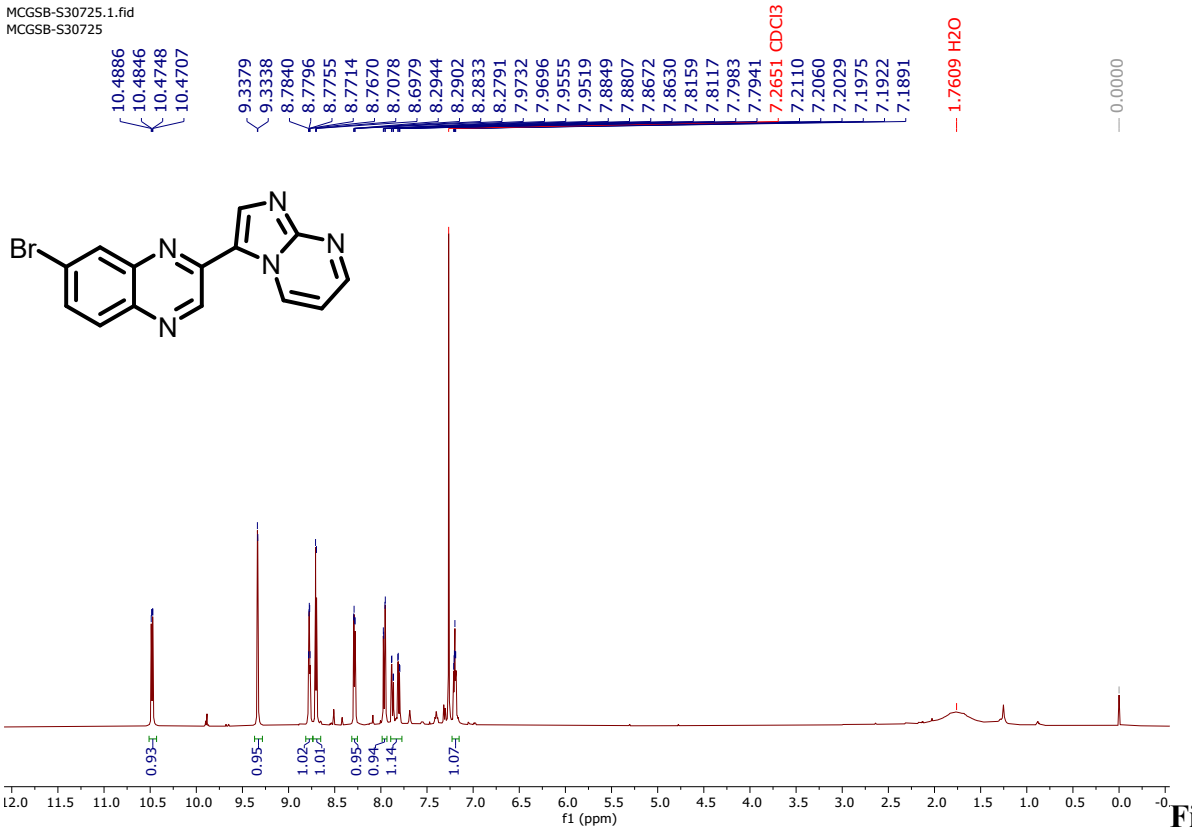

Figure S20: ^{1}H NMR of 7-bromo-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(10g)** in $CDCl_3$ at 500 MHz

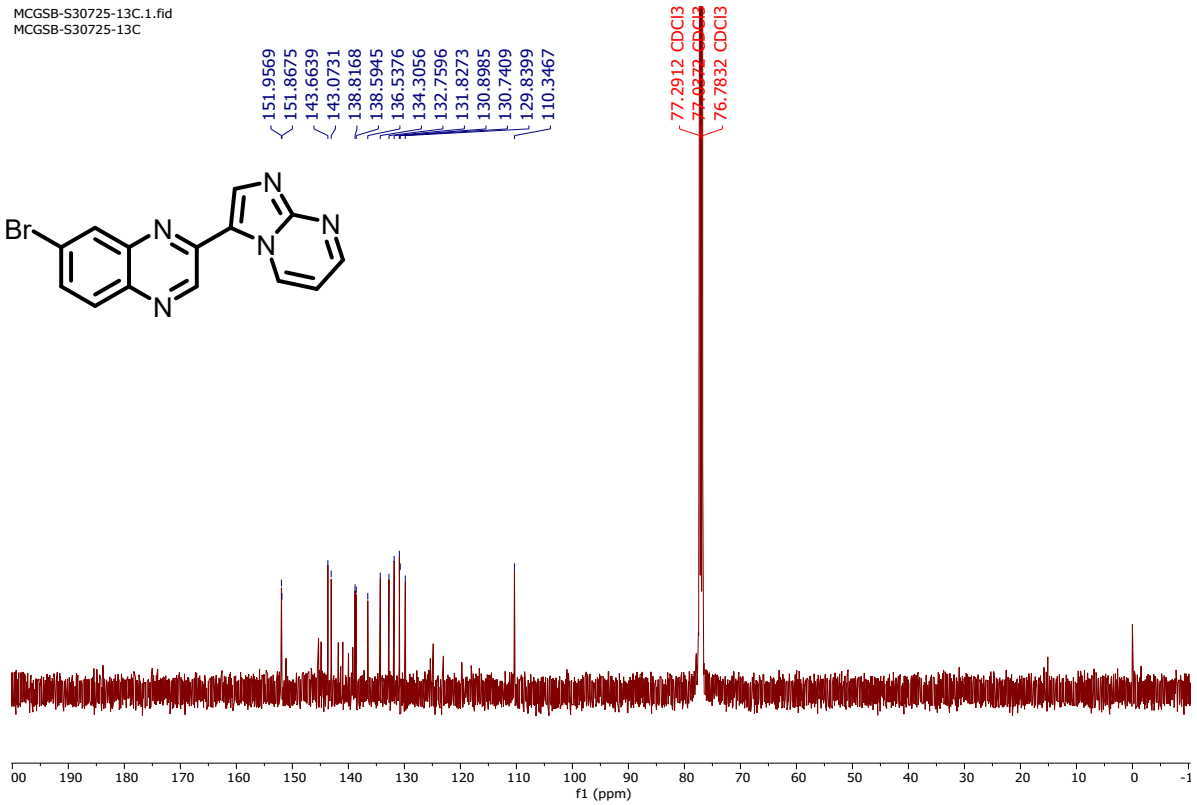

Figure S21: ^{13}C NMR of 7-bromo-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10g**) in $CDCl_3$ at 125 MHz

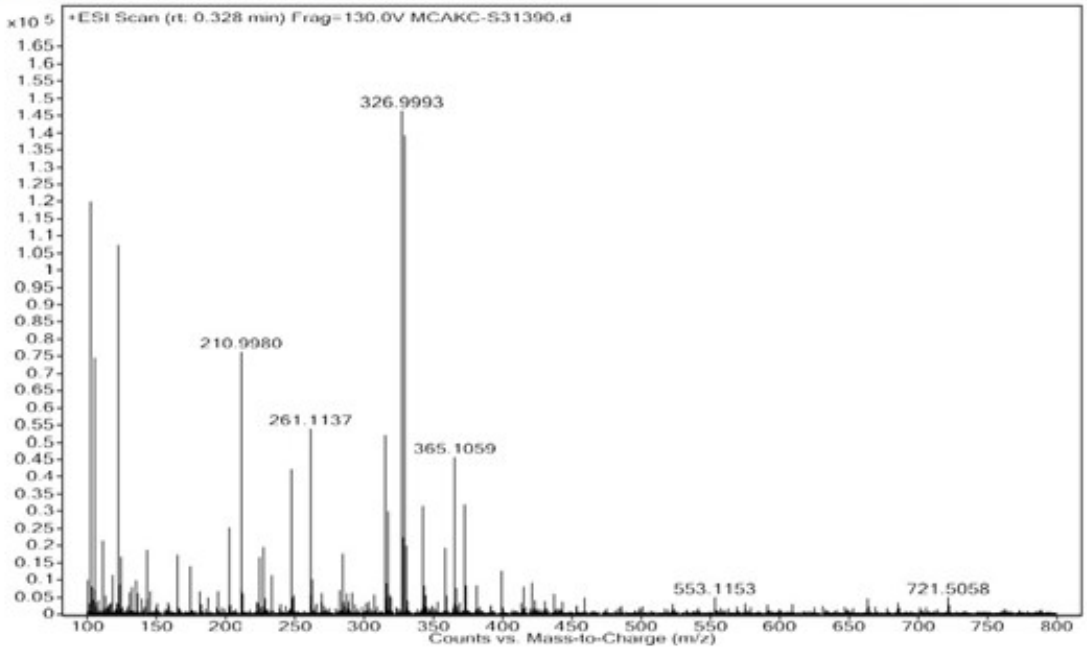

Figure S22: HRMS spectra of 7-bromo-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10g**)

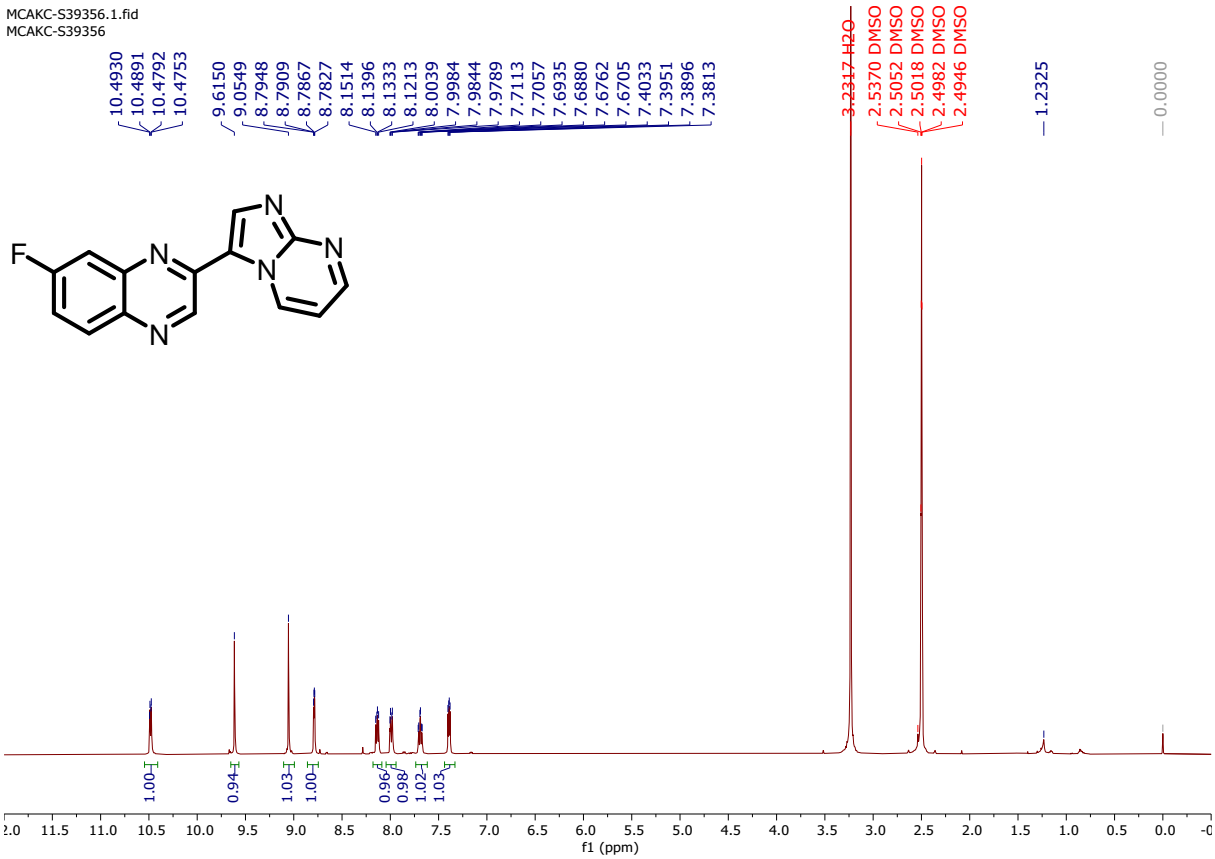

Figure S23: ^{1}H NMR of 7-fluoro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10h**) in DMSO-d_6 at 500 MHz

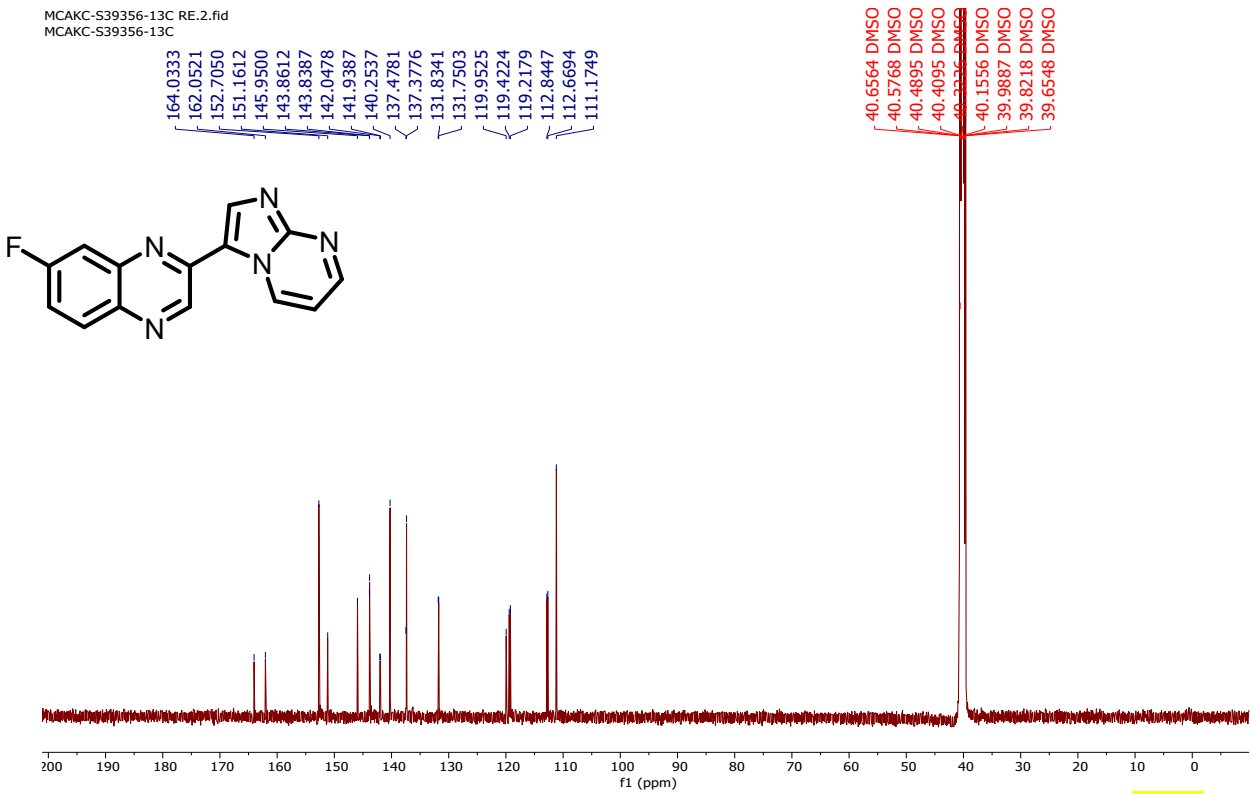

Figure S24: ^{13}C NMR of 7-fluoro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(10h)** in DMSO-d_6 at 125 MHz

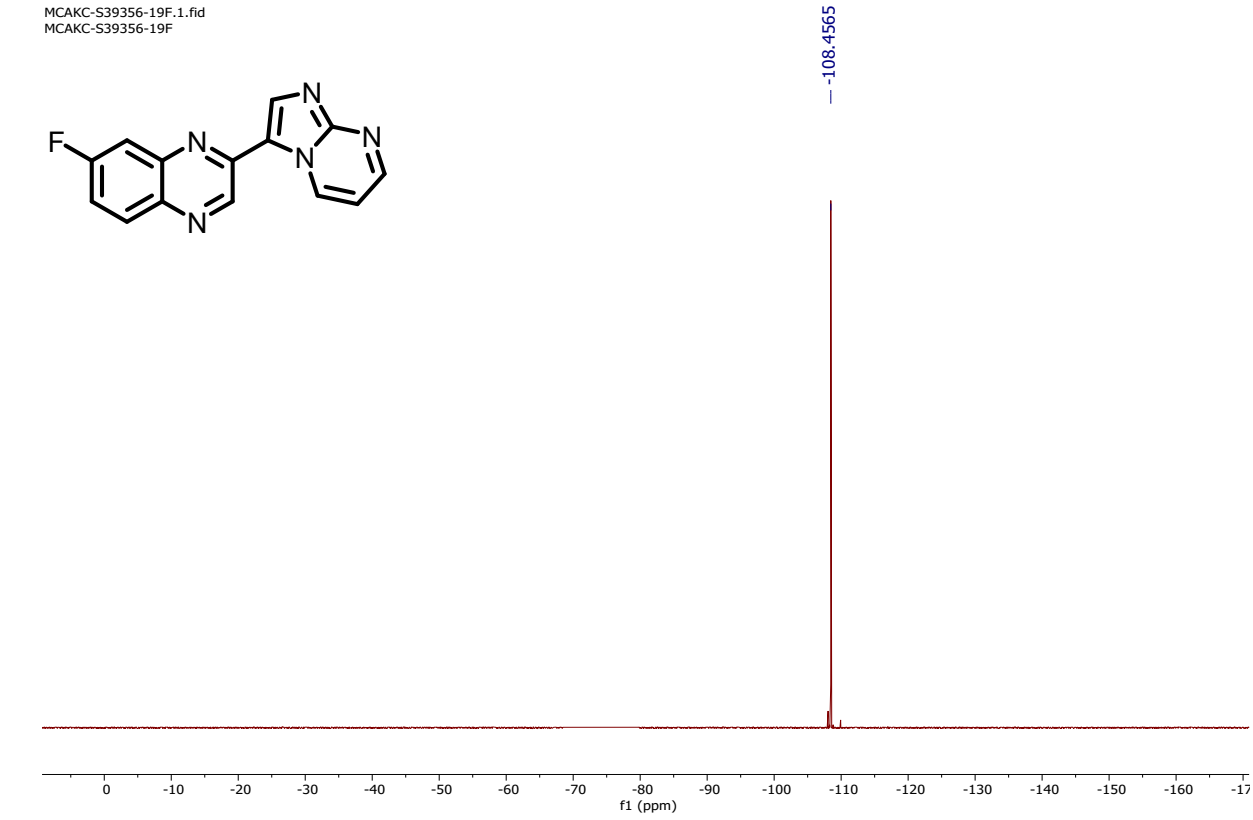

Figure S25: ^{19}F NMR of 7-fluoro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(10h)** in DMSO-d_6 at 471 MHz

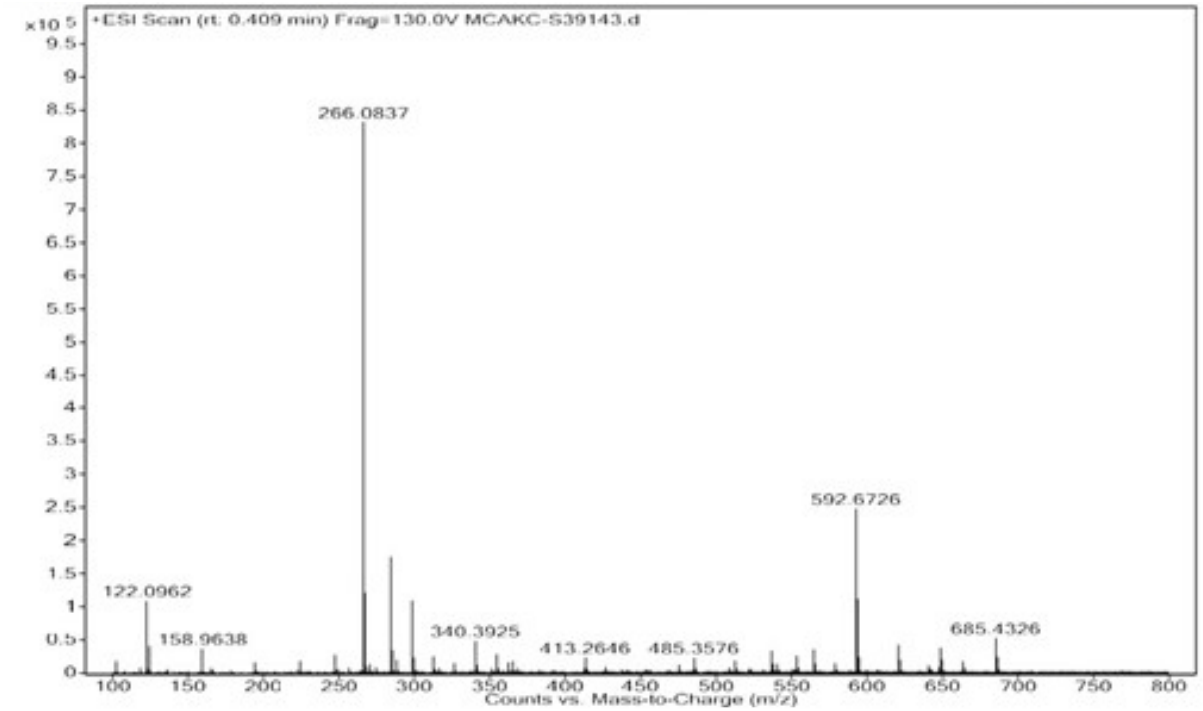

Figure S26: HRMS Spectra of 7-fluoro-2-(imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**10h**)

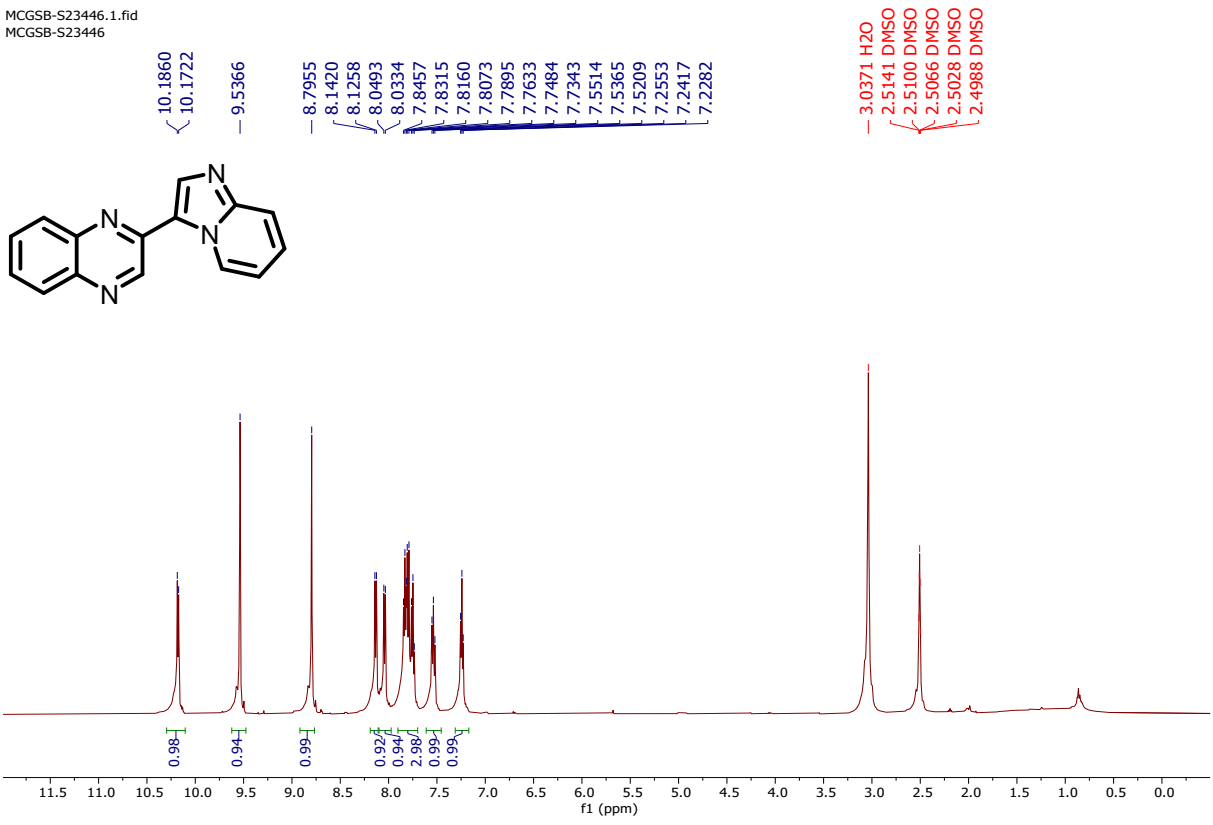

Figure S27: ^{1}H NMR of 2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10i**) in DMSO-d_6 at 500 MHz

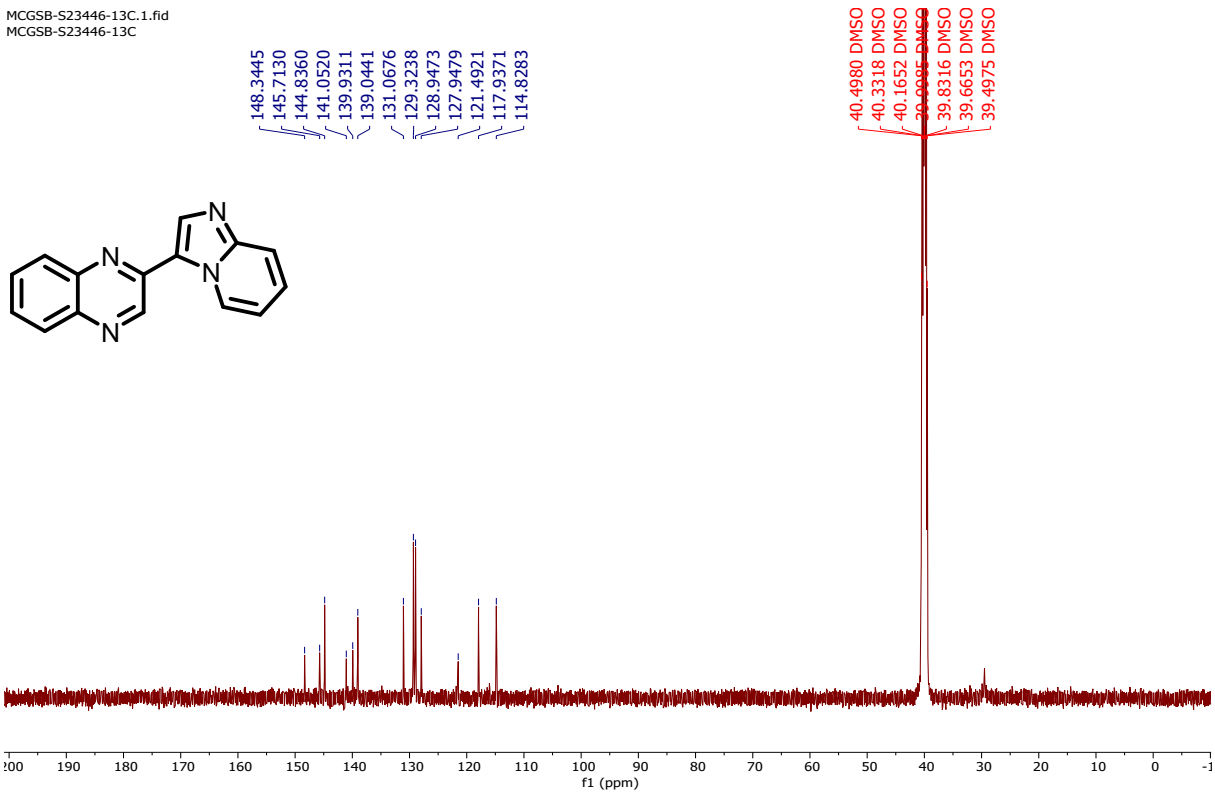

Figure S28: ^{13}C NMR of 2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10i**) in DMSO-d_6 at 125 MHz

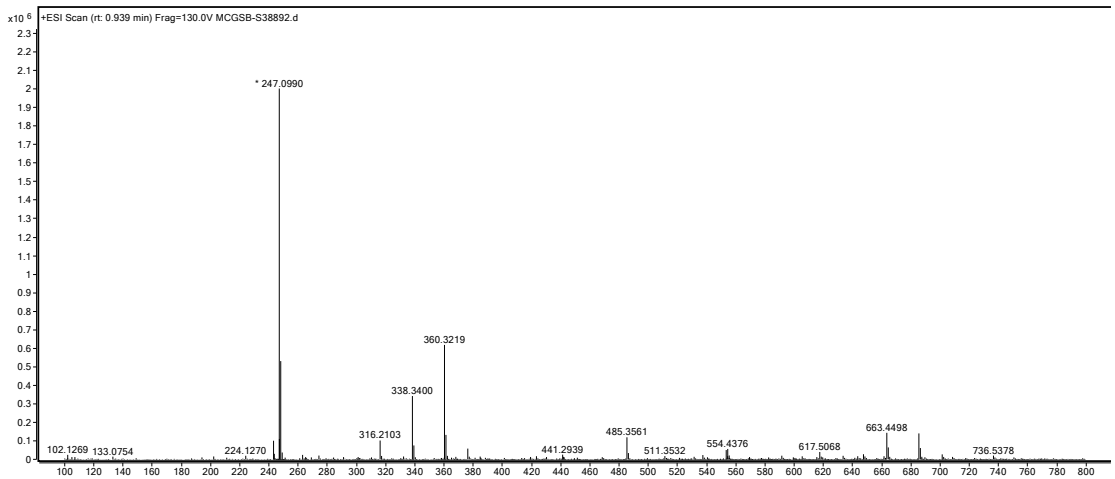

Figure S29: HRMS spectra of 2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10i**)

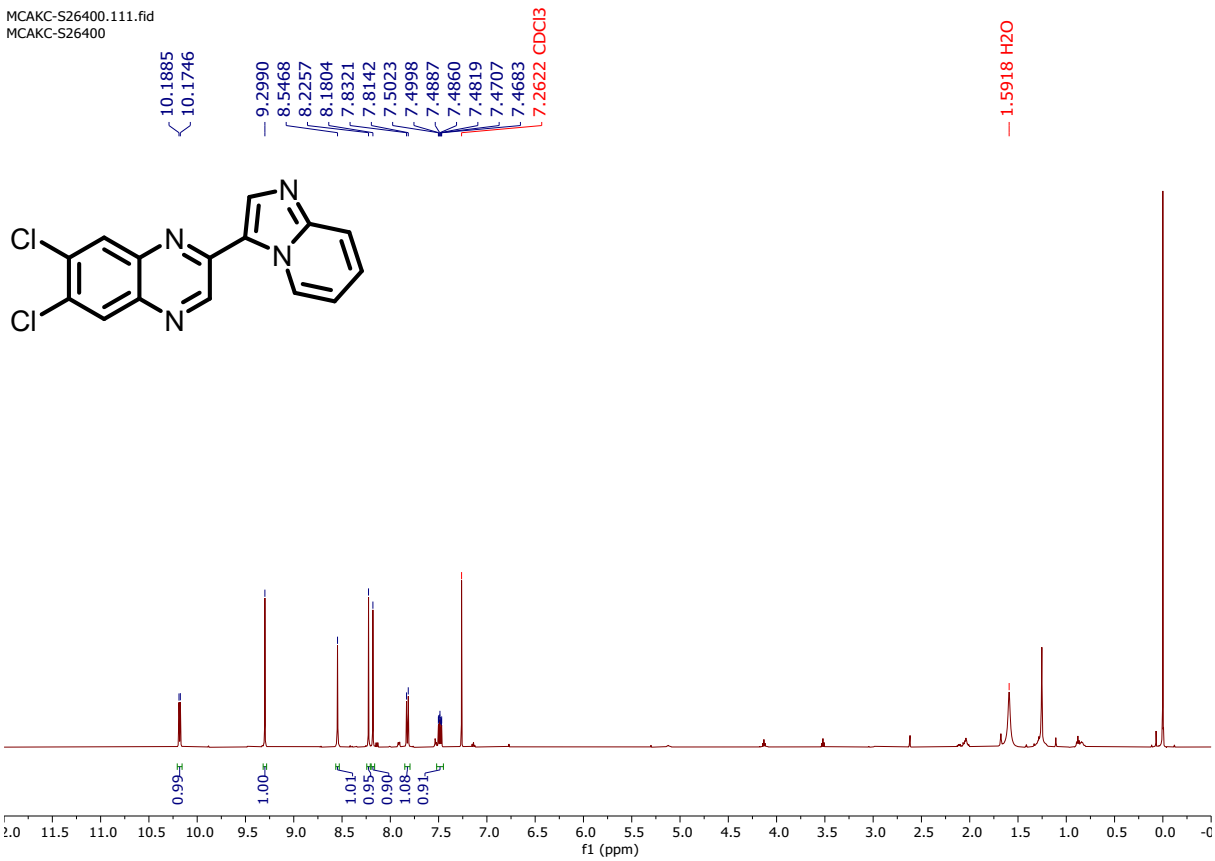

Figure S30: ^{1}H NMR of 6,7-dichloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10j**) in $CDCl_3$ at 500 MHz

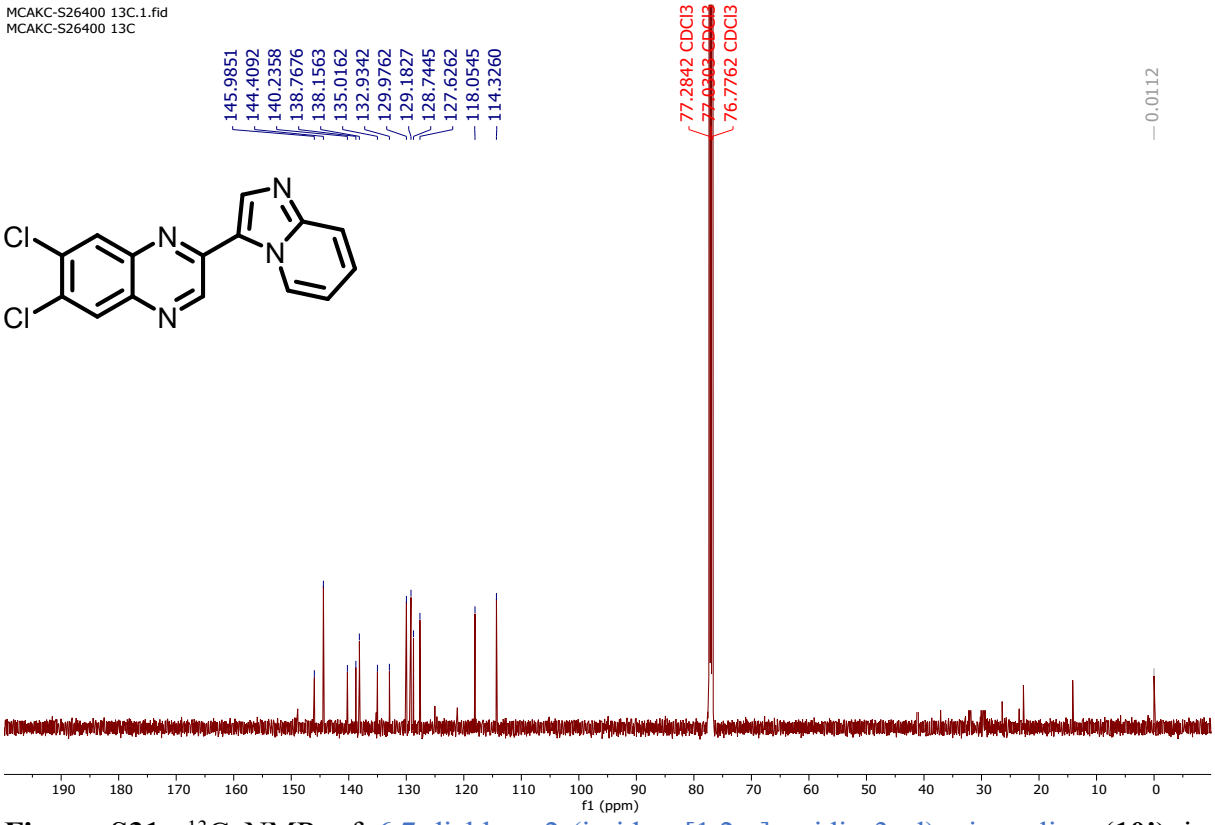

Figure S31: ^{13}C NMR of 6,7-dichloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10j**) in $CDCl_3$ at 125 MHz

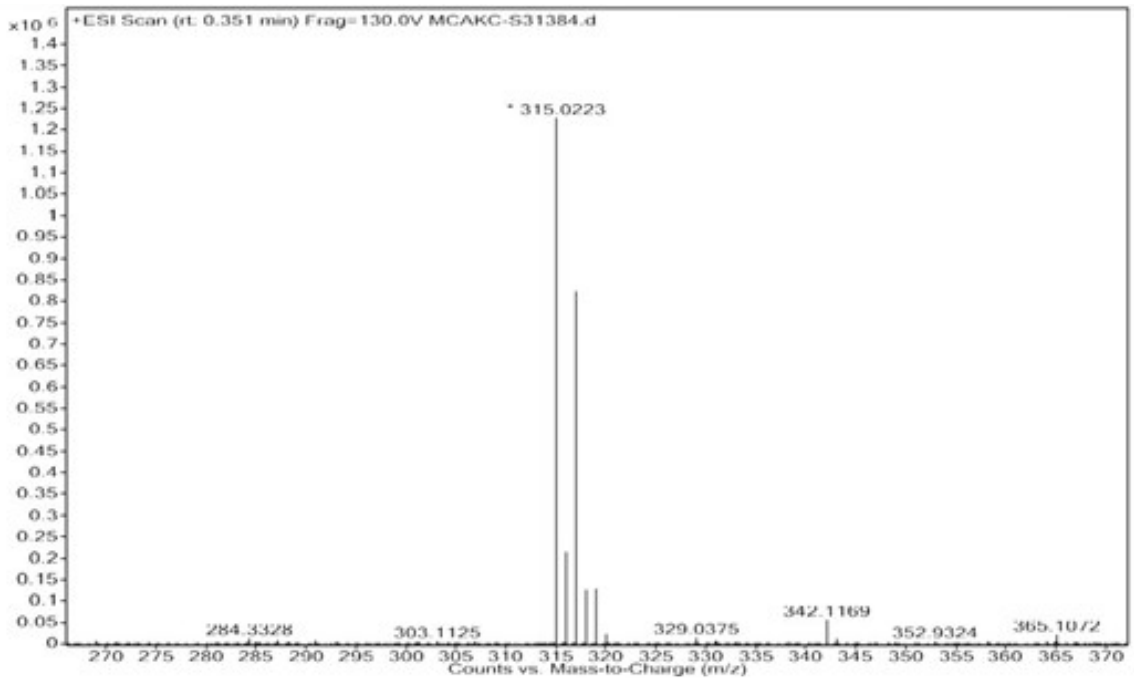

Figure S32: HRMS spectra of 6,7-dichloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10j**)

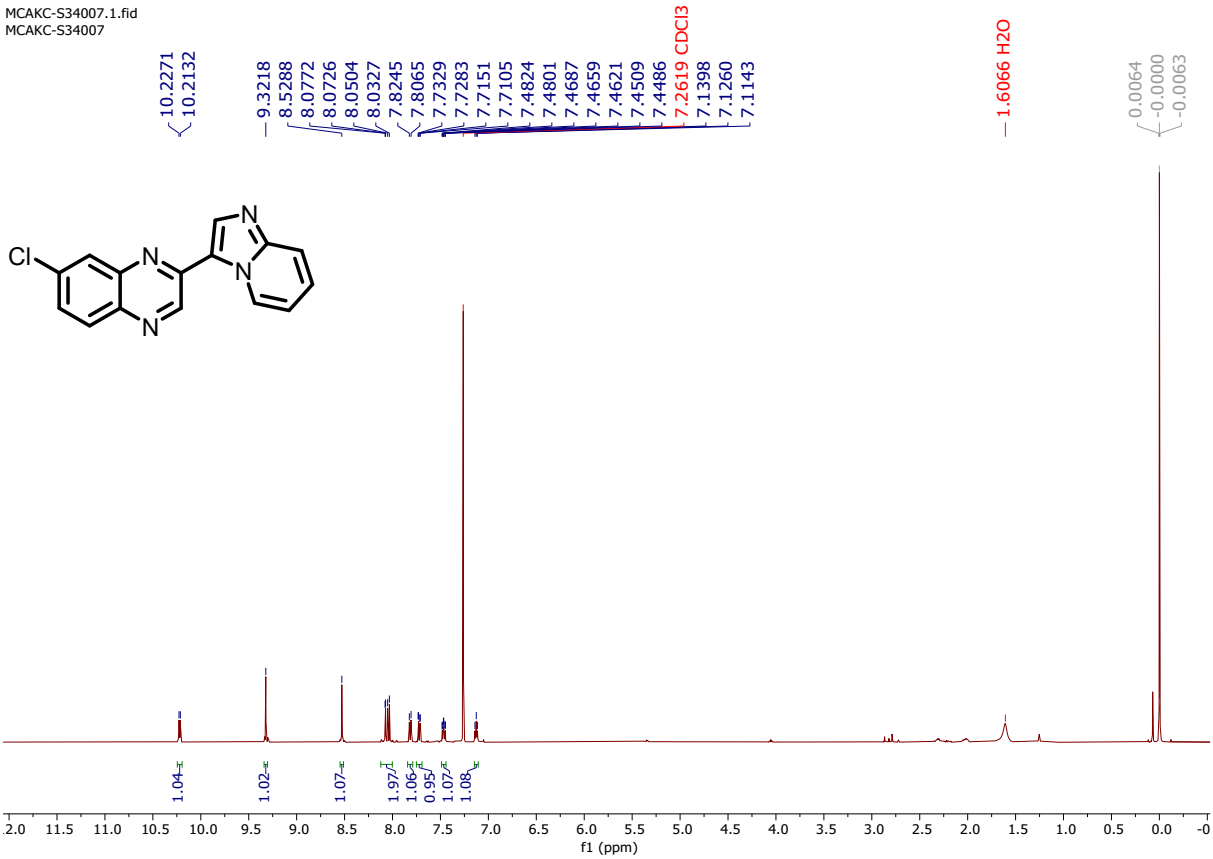

Figure S33: ^{1}H NMR of 7-chloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10k**) in $CDCl_3$ at 500 MHz

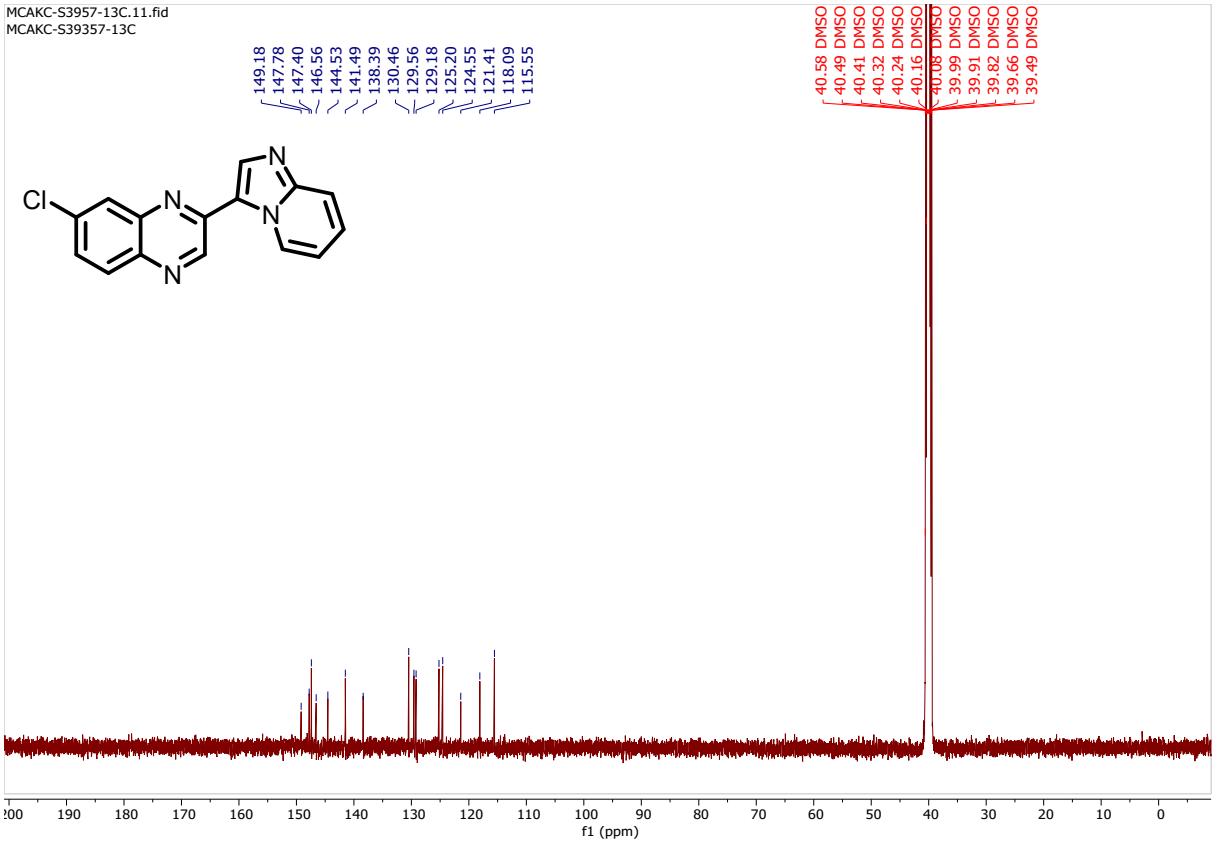

Figure S34: ^{13}C NMR of 7-chloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10k**) in $CDCl_3$ at 125 MHz

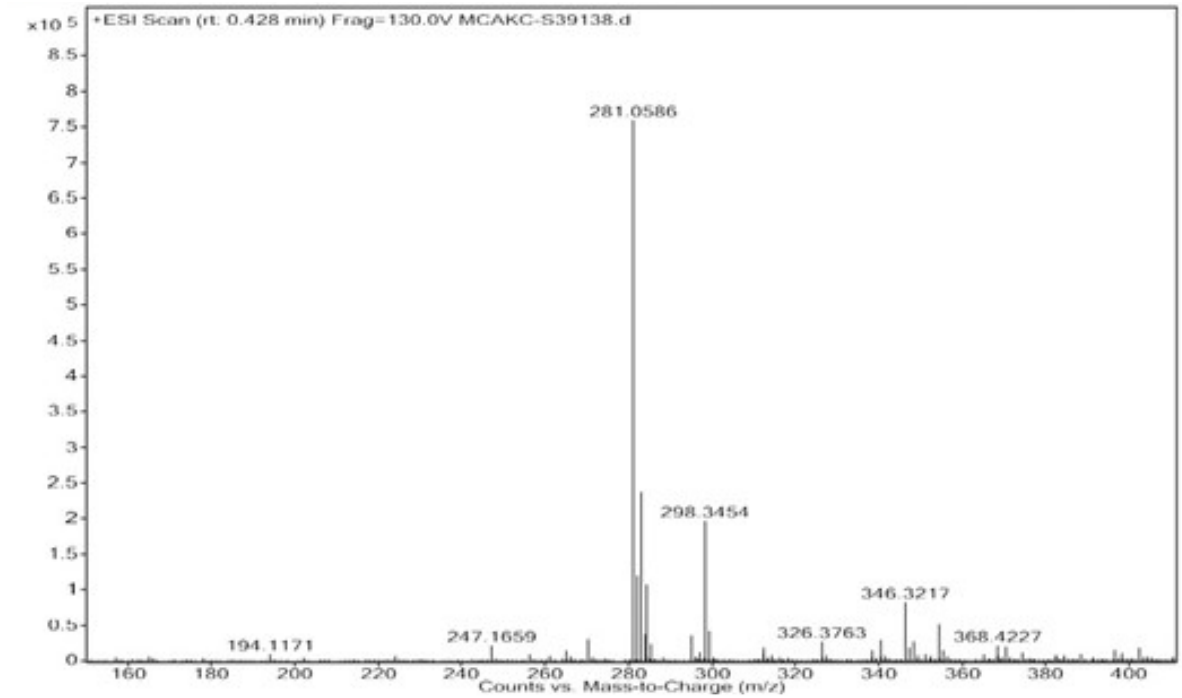

Figure S35: HRMS spectra of 7-chloro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10k**)

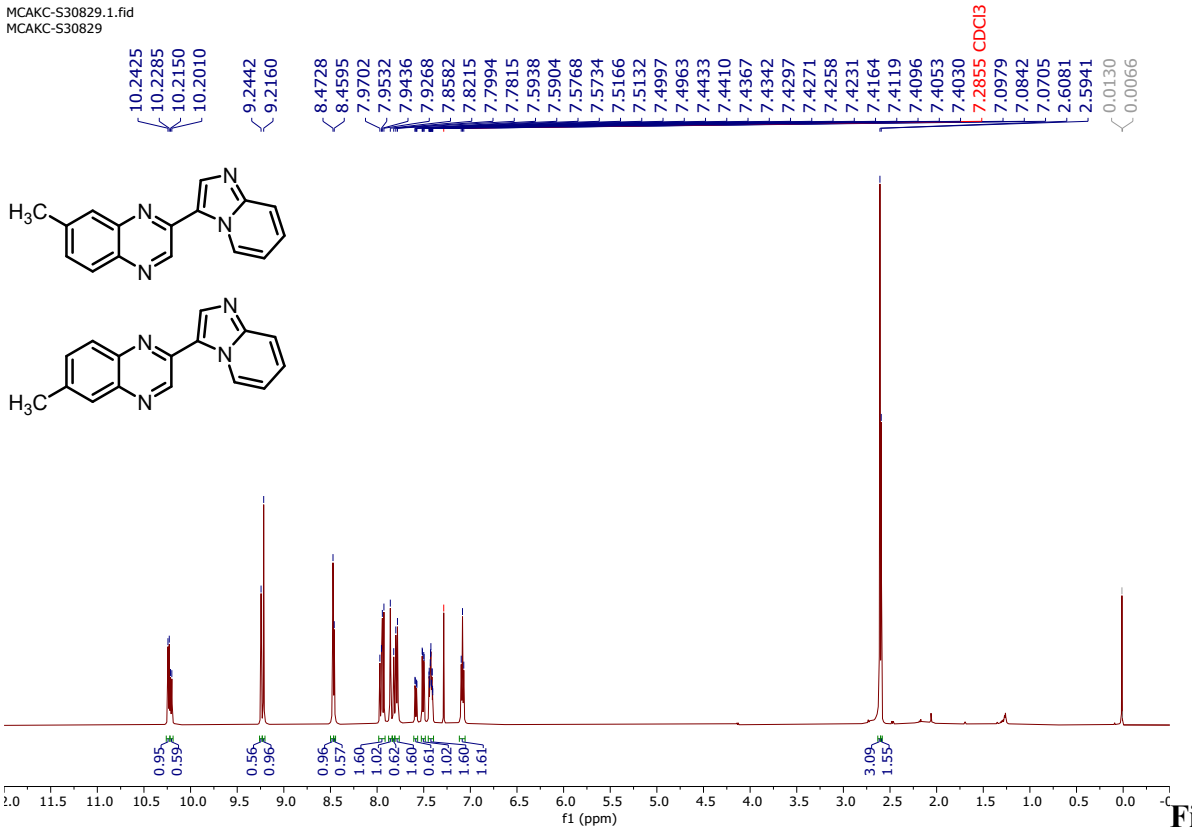

Figure S36: ^{1}H NMR of 6-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10l**) in $CDCl_3$ at 500 MHz

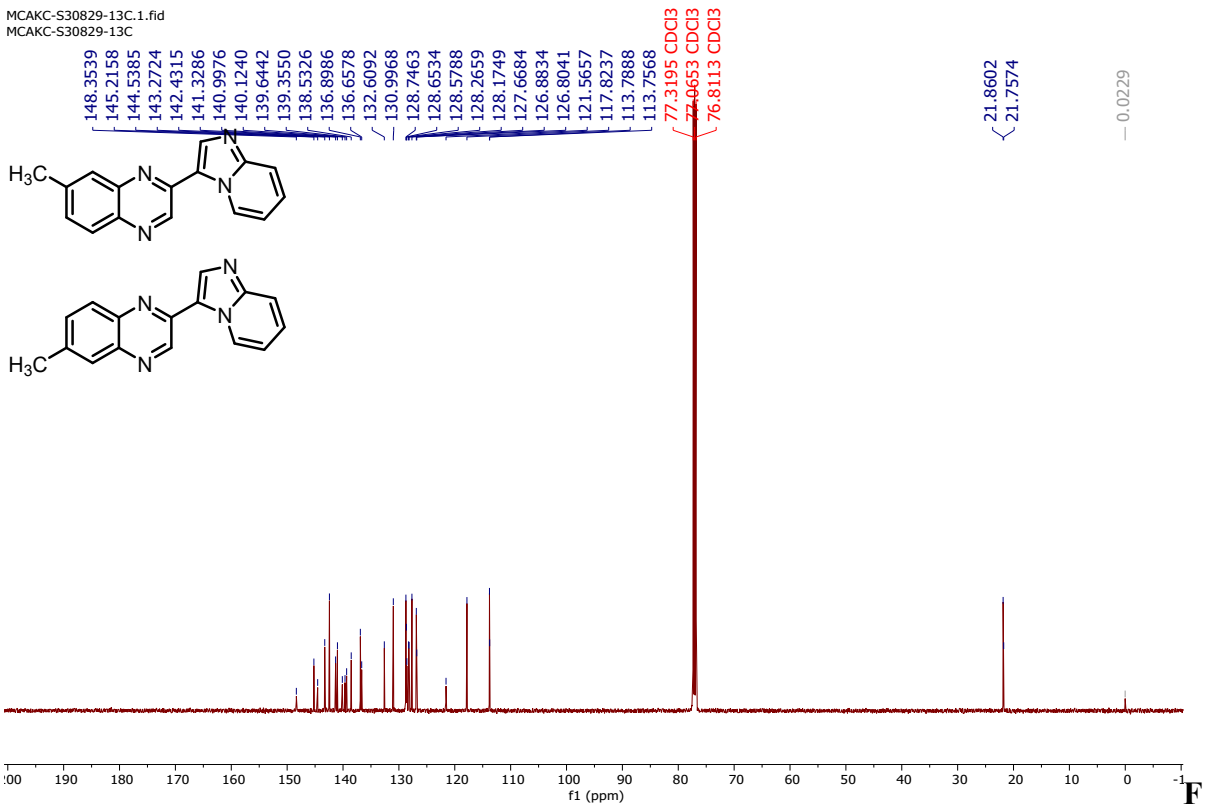

Figure S37: ^{13}C NMR of 6-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10l**) in $CDCl_3$ at 125 MHz

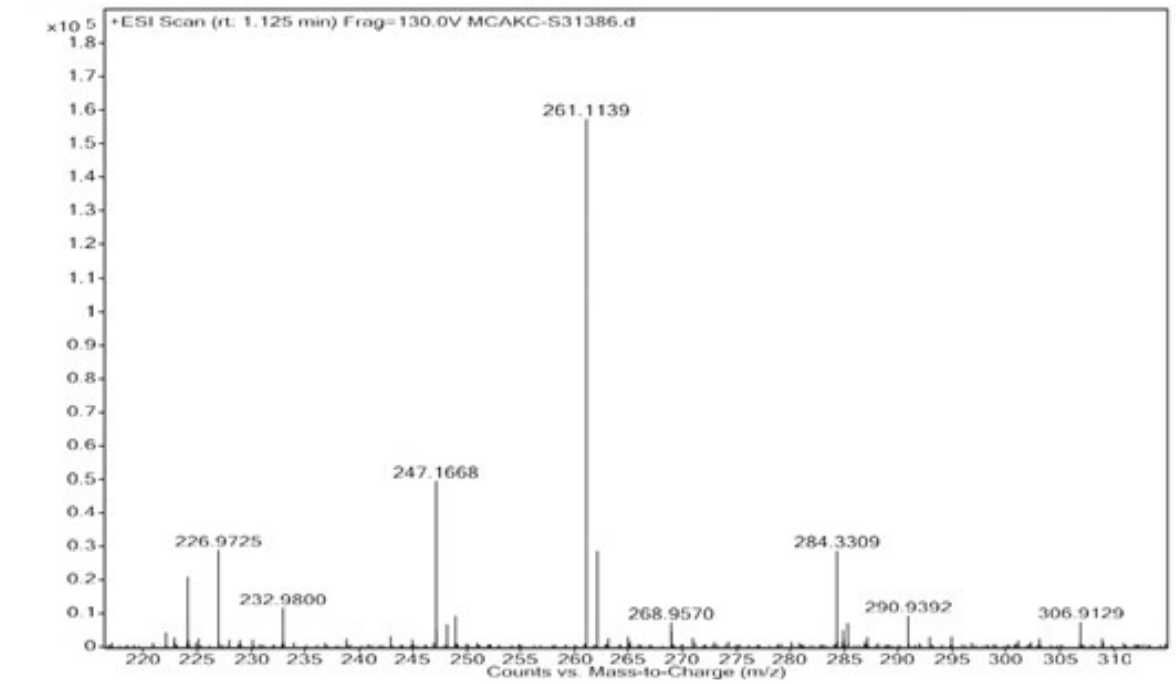

Figure S38: HRMS spectra of 6-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-methyl-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10l**)

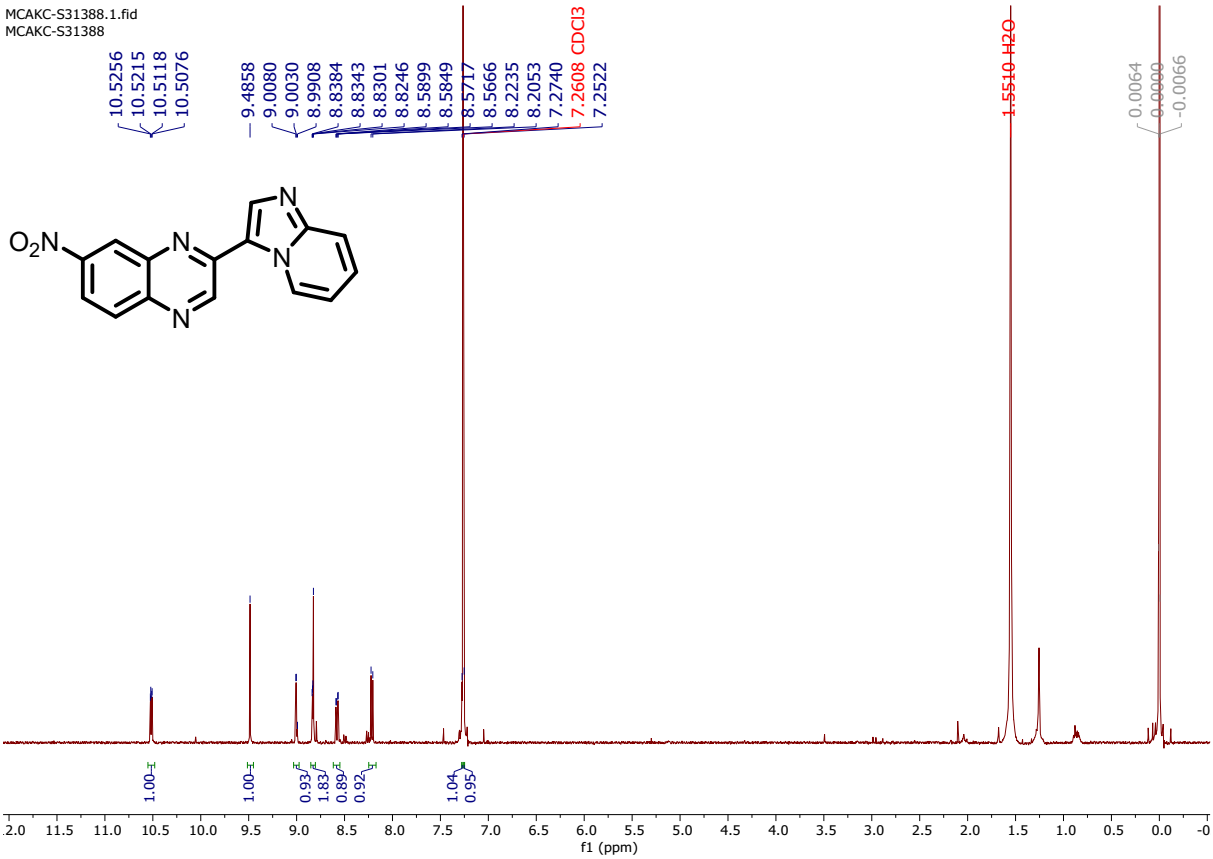

Figure S39: ^{1}H NMR of 7-nitro-2-(imidazo[1,2-a] pyridin-3-yl) quinoxaline (**10m**) in $CDCl_3$ at 500 MHz

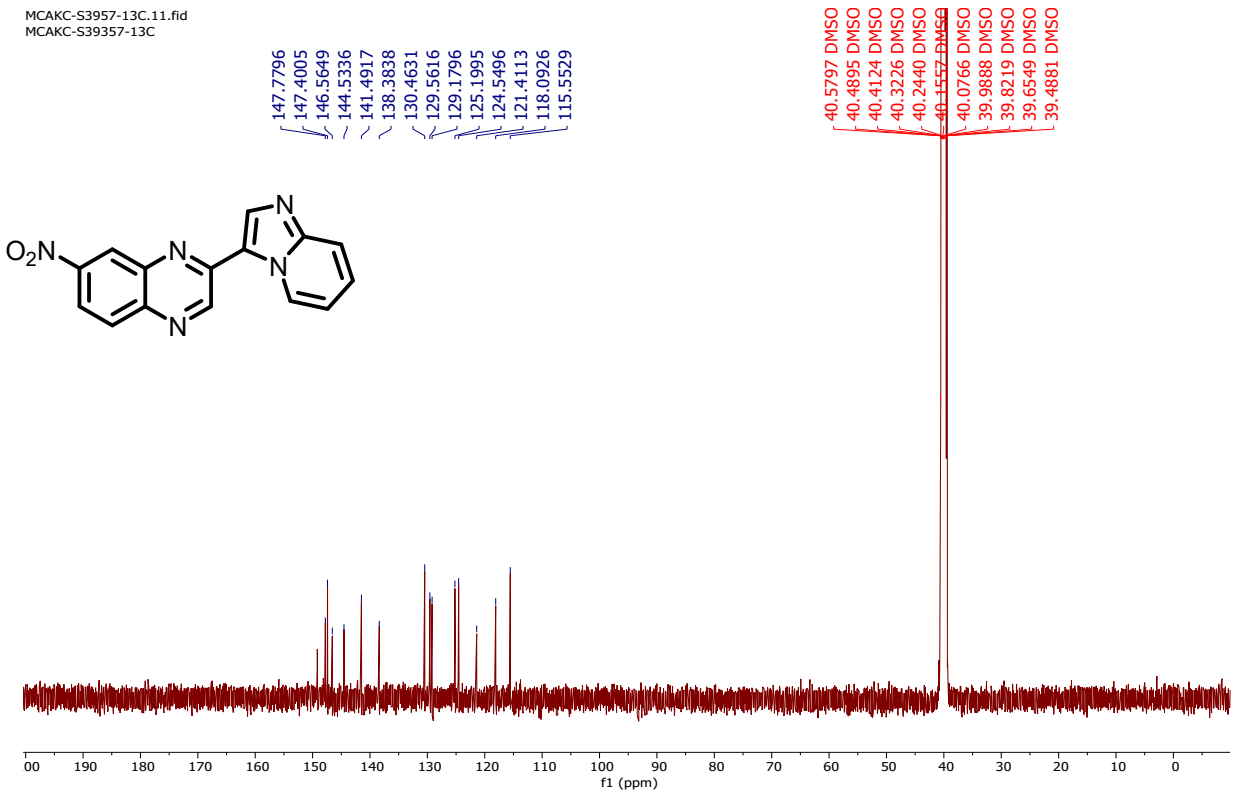

Figure S40: ^{13}C NMR of 7-nitro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10m**) in DMSO-d_6 at 125 MHz

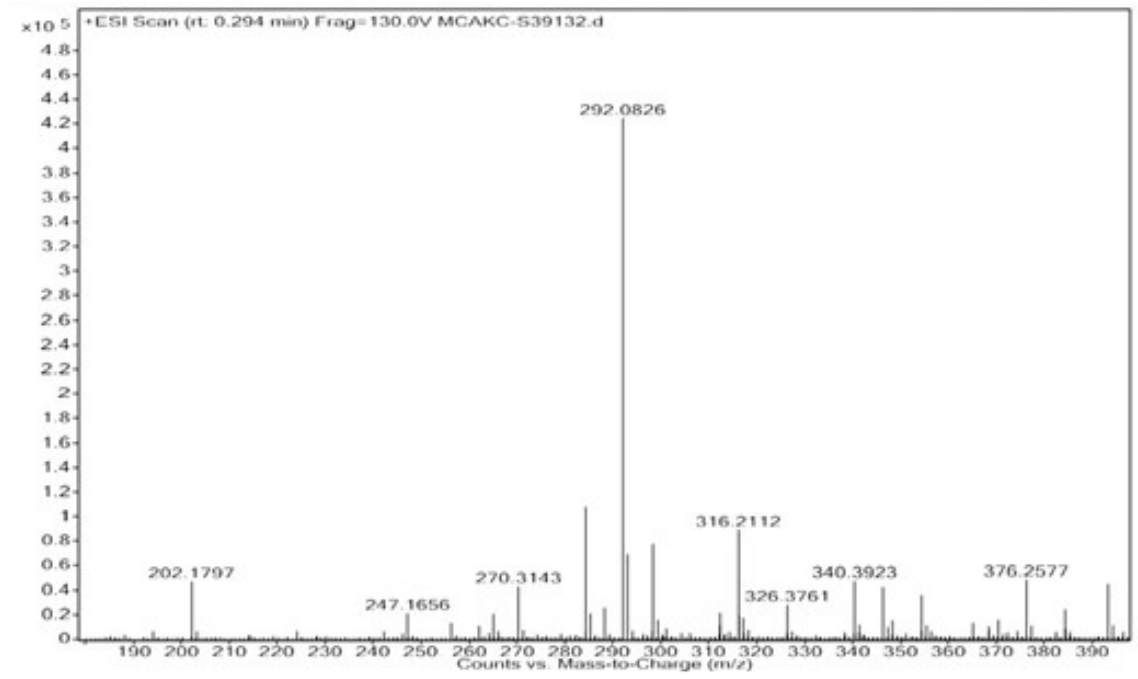

Figure S41: HRMS spectra of 7-nitro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10m**)

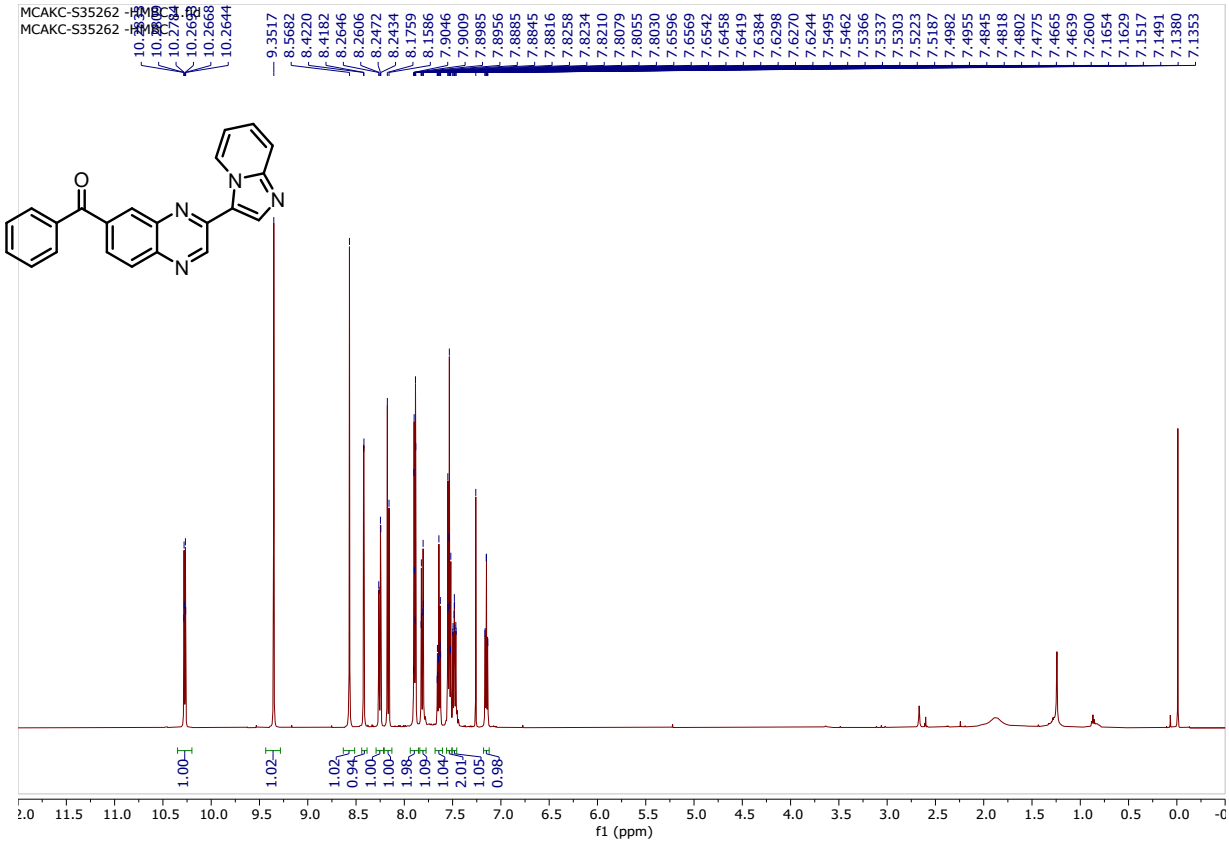

Figure S42: ^{1}H NMR of 7-phenoxy-2-(imidazo[1,2-a]pyridin-3-yl) quinoxaline (**10n**) in $CDCl_3$ at 500 MHz

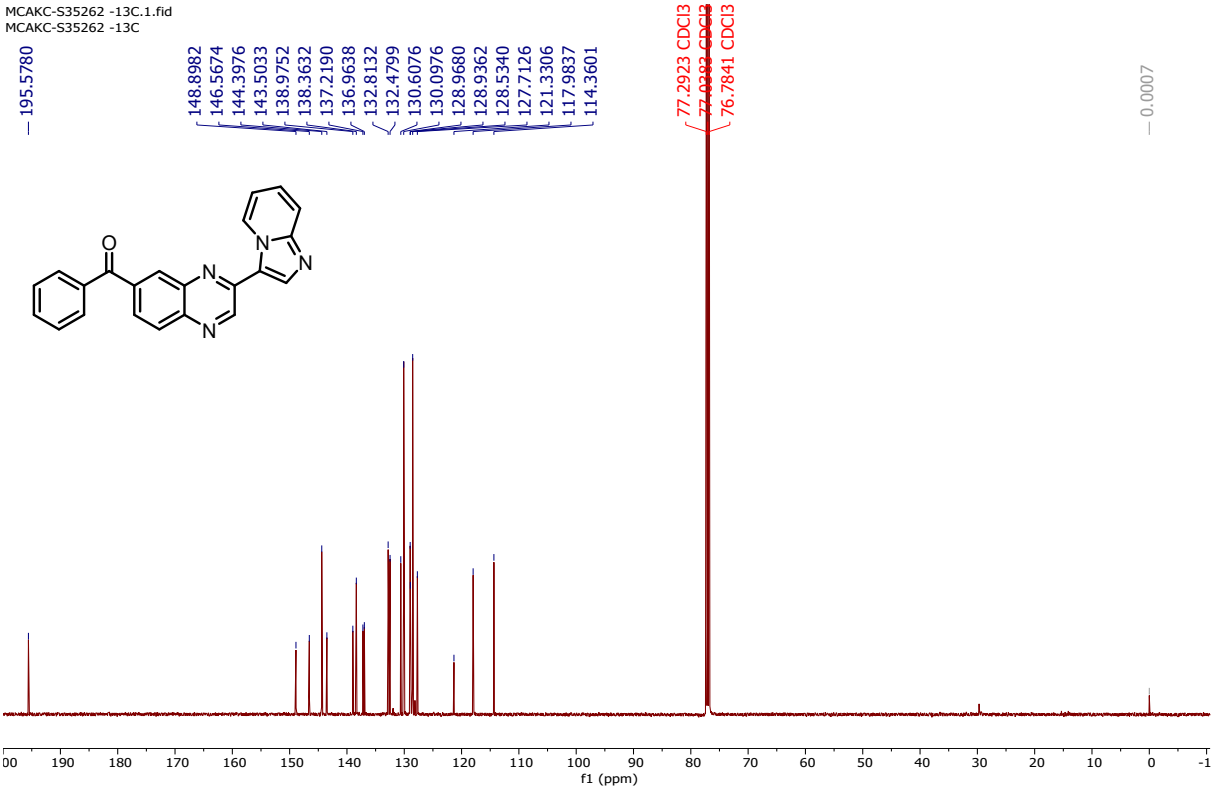

Figure S43: ^{13}C NMR of 7-phenoxy-2-(imidazo[1,2-a]pyridin-3-yl) quinoxaline (**10n**) in $CDCl_3$ at 125 MHz

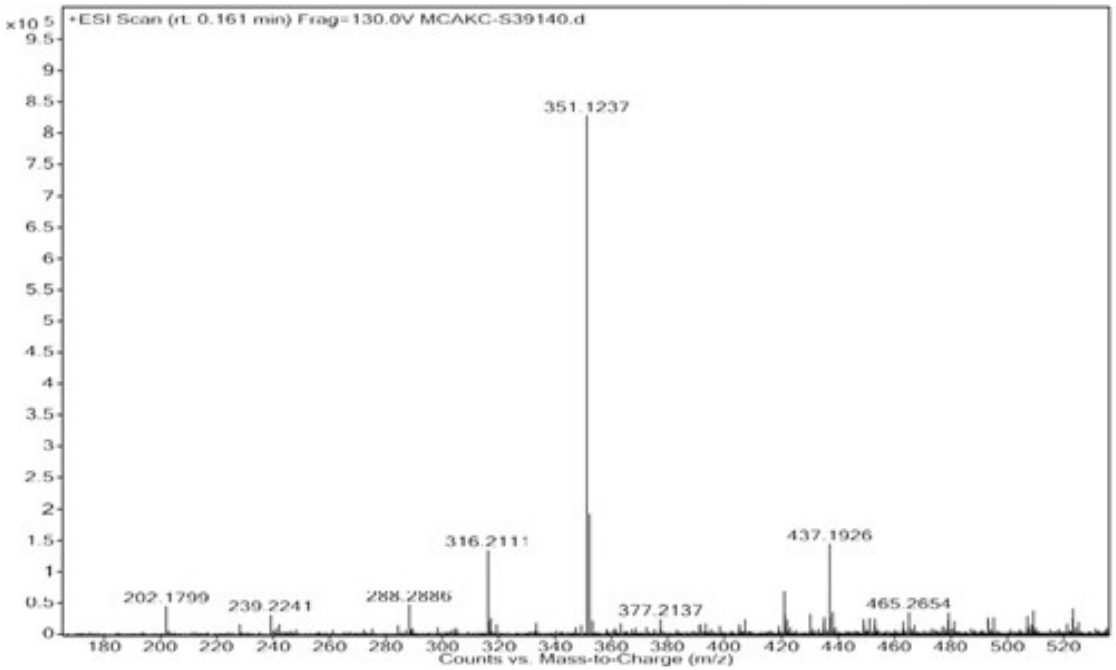

Figure S44: HRMS spectra of 7-phenoxy-2-(imidazo[1,2-a]pyridin-3-yl) quinoxaline (**10n**)

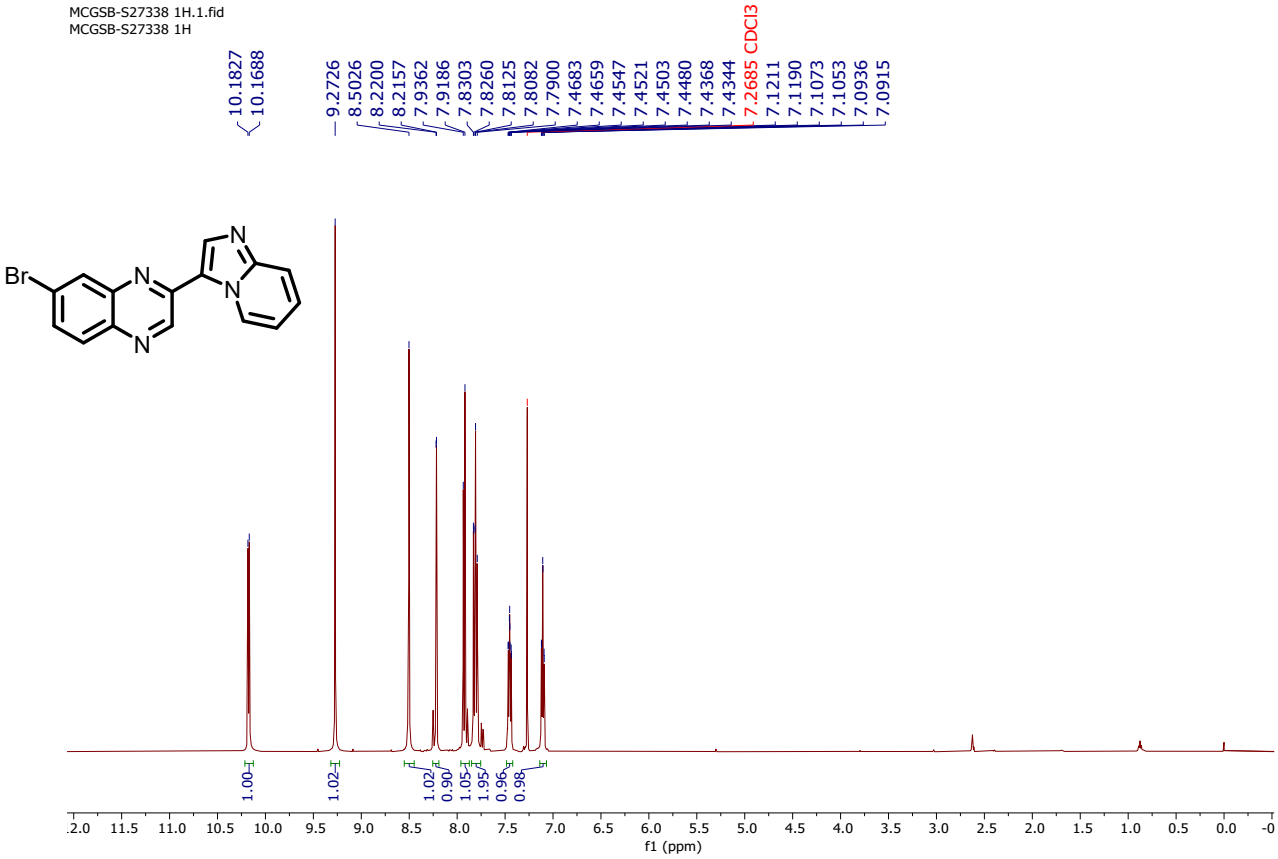

Figure S45: ^{1}H NMR of 7-bromo-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10o**) in $CDCl_3$ at 500 MHz

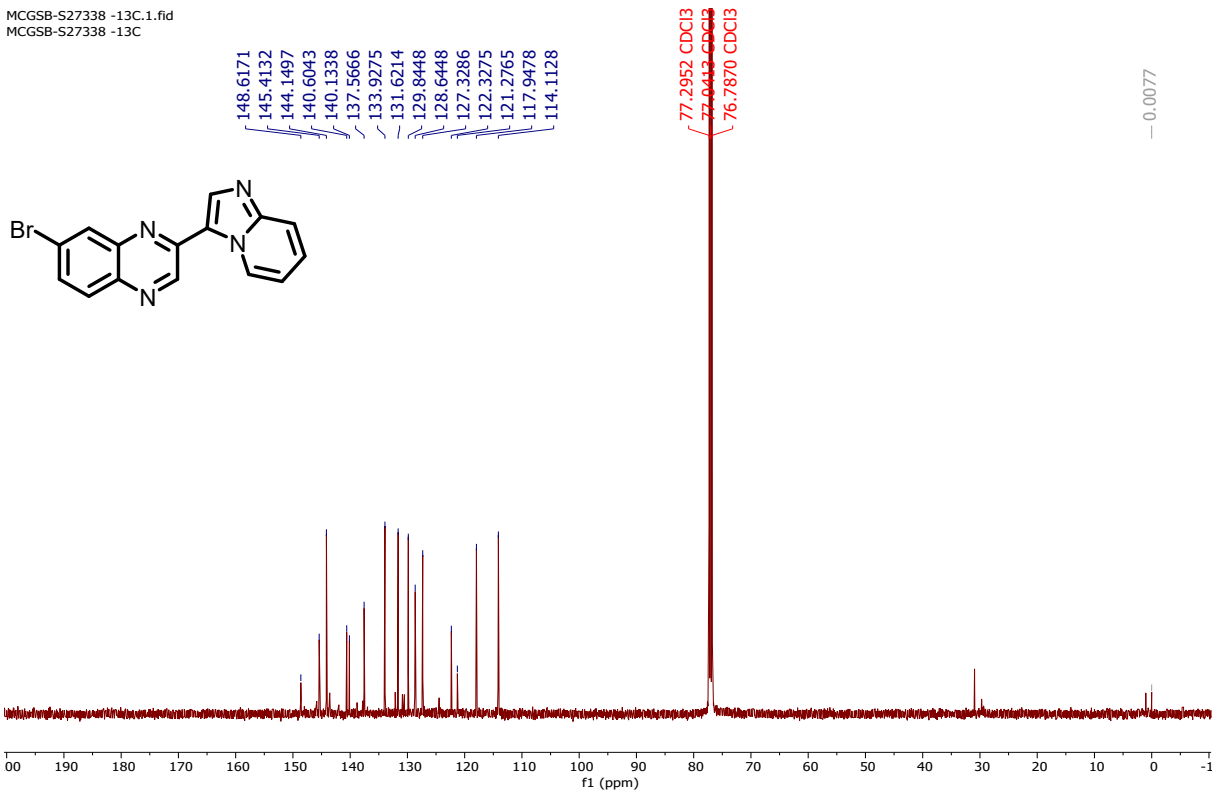

Figure S46: ^{13}C NMR of 7-bromo-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10o**) in $CDCl_3$ at 125 MHz

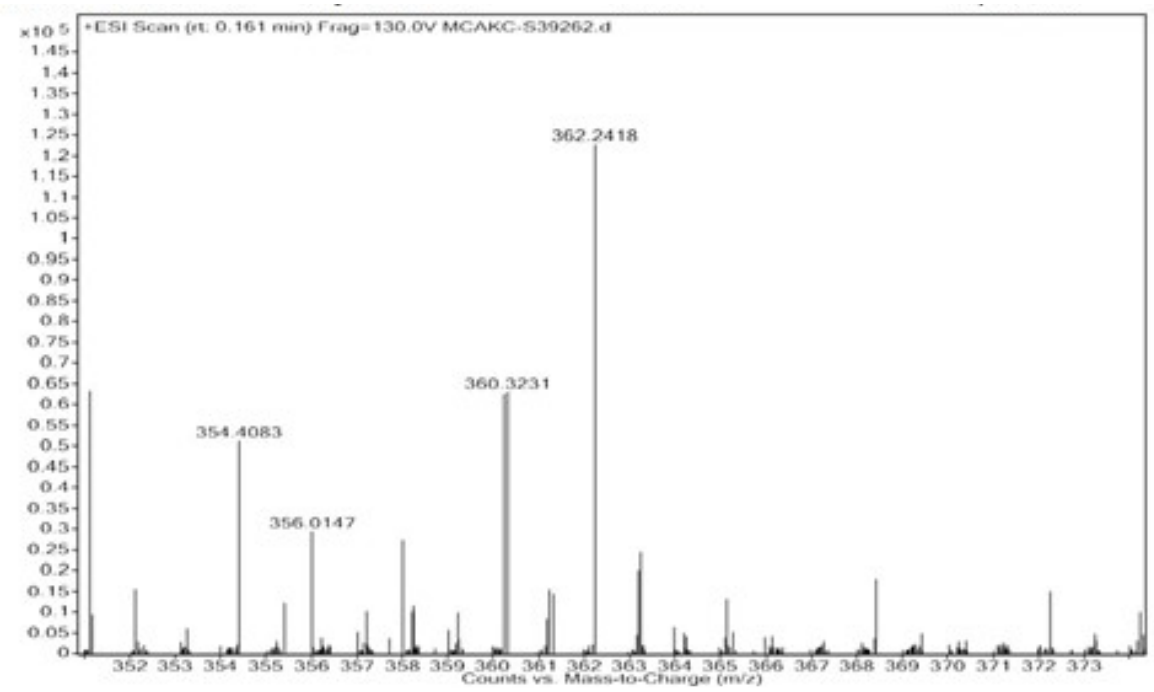

Figure S47: HRMS spectra of 7-bromo-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10o**)

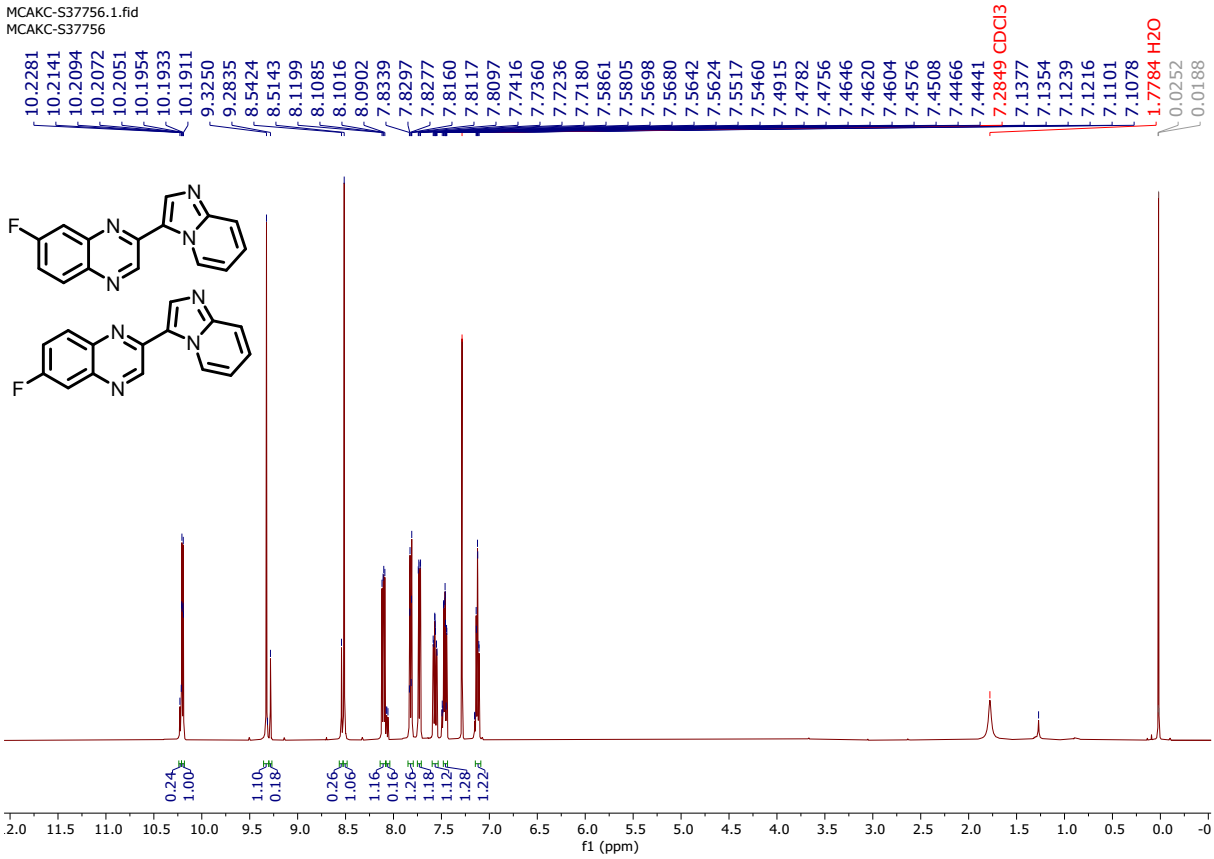

Figure S48: ^{1}H NMR of 6-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10p**) in $CDCl_3$ at 500 MHz

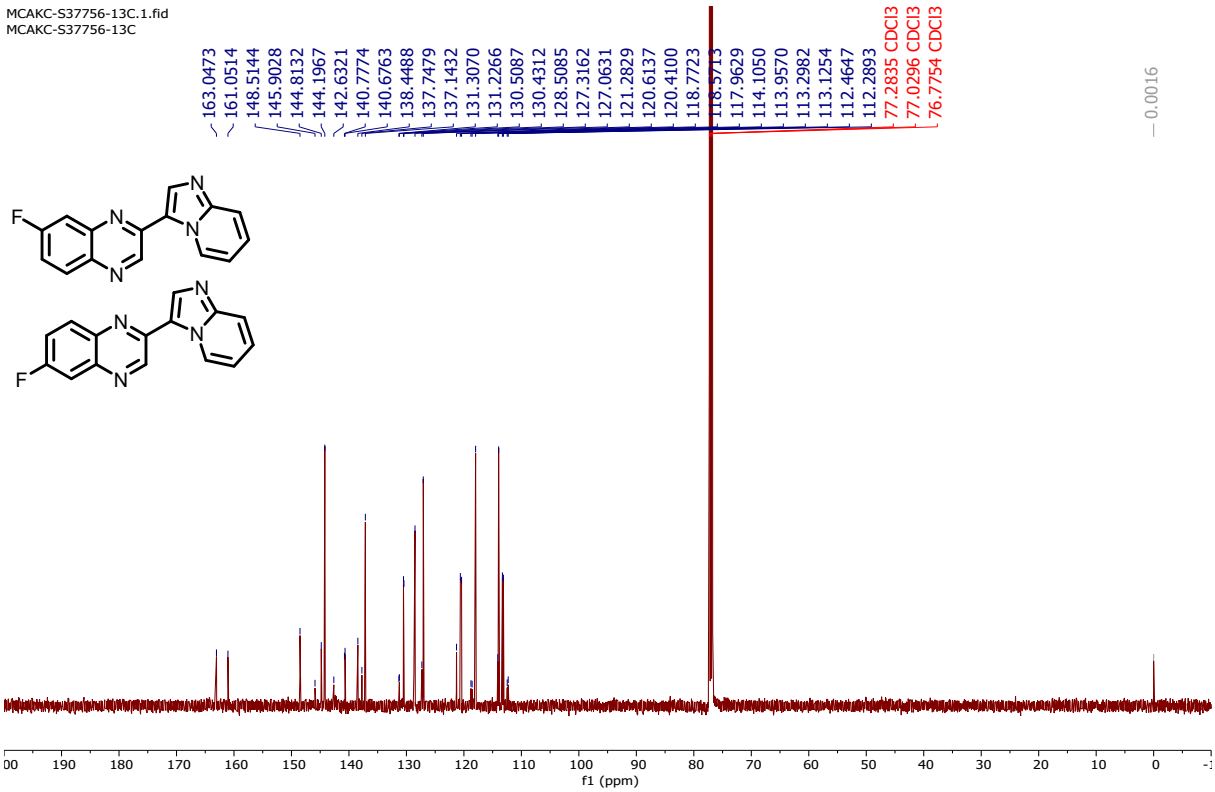

Figure S49: ^{13}C NMR of 6-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10p**) in $CDCl_3$ at 125 MHz

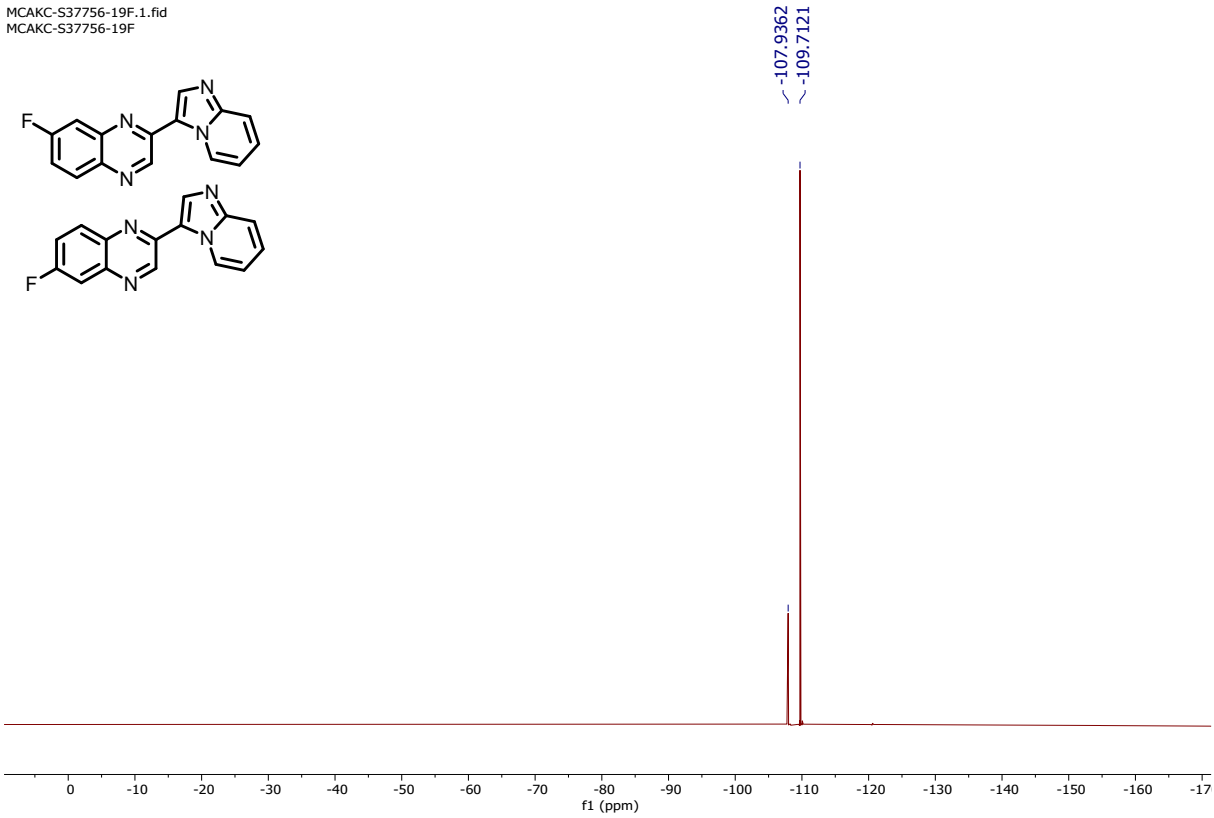

Figure S50: ^{19}F NMR of 6-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline (**10p**) in DMSO-d_6 at 471 MHz

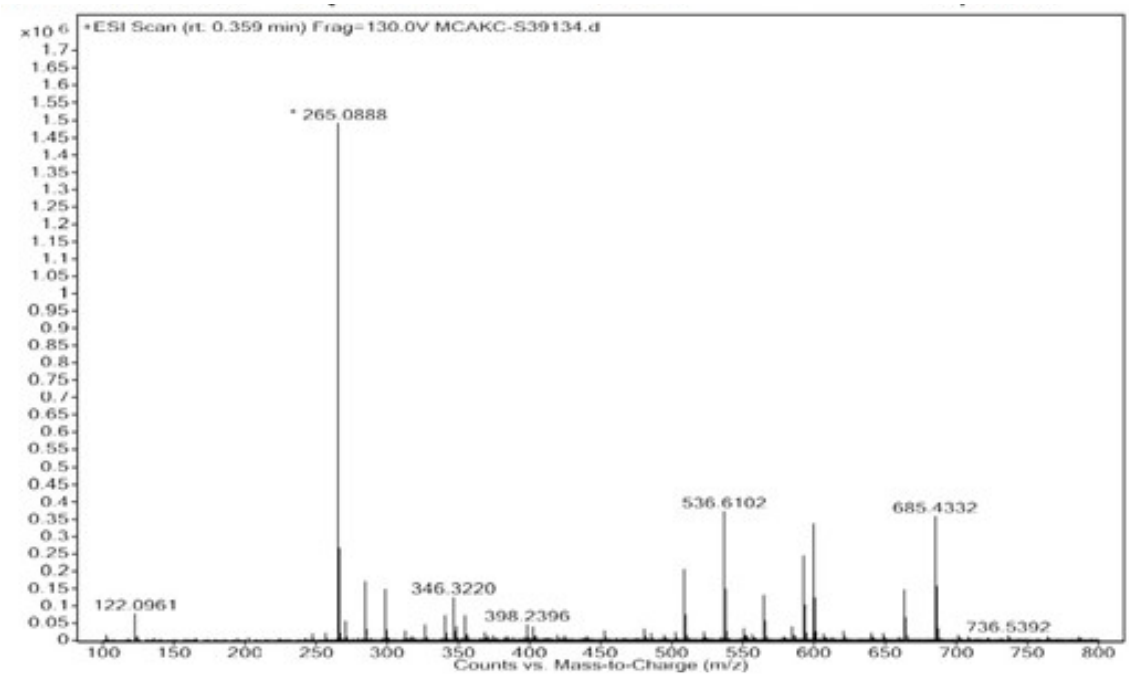

Figure S51: HRMS spectra of 6-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline & 7-flouro-2-(imidazo[1,2-a]pyridin-3-yl)quinoxaline **(10p)**

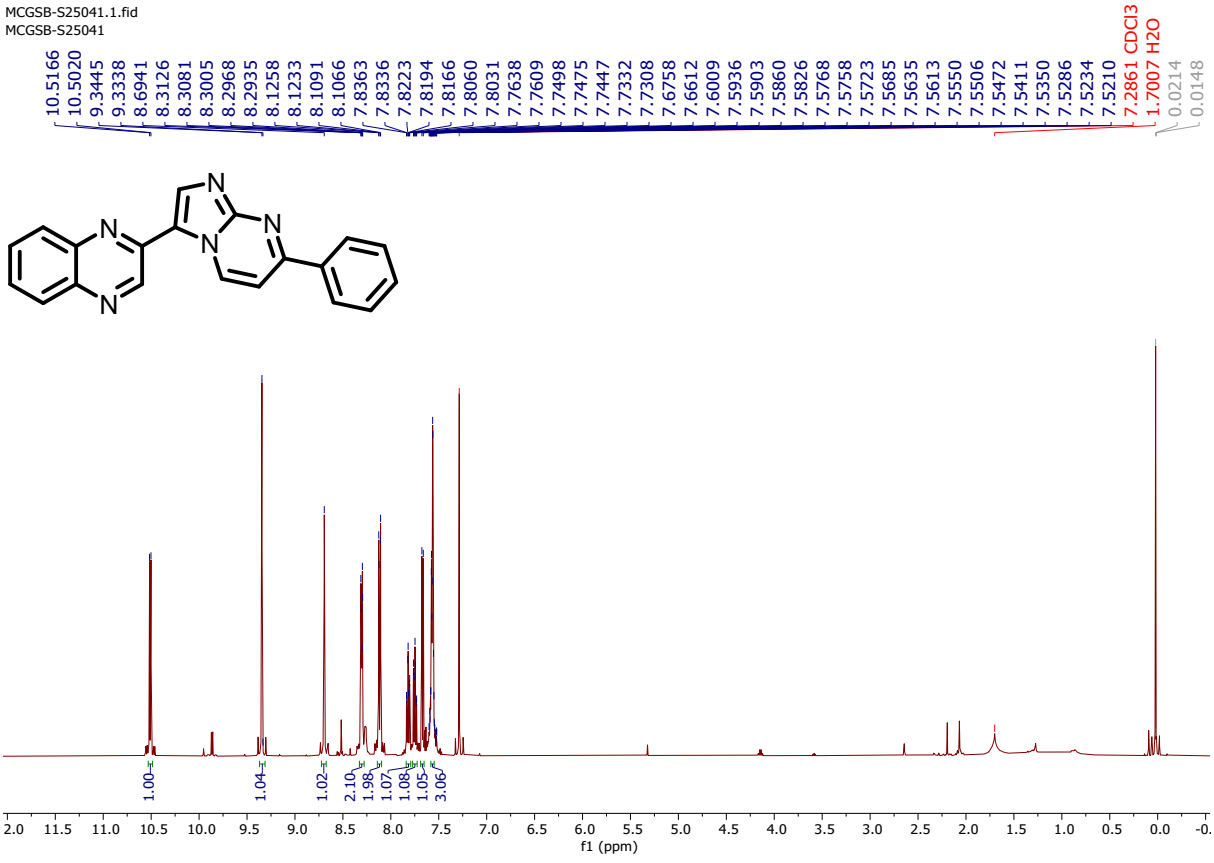

Figure S52: ^{1}H NMR of 2-(7-phenylimidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12a**) in $CDCl_3$ at 500 MHz

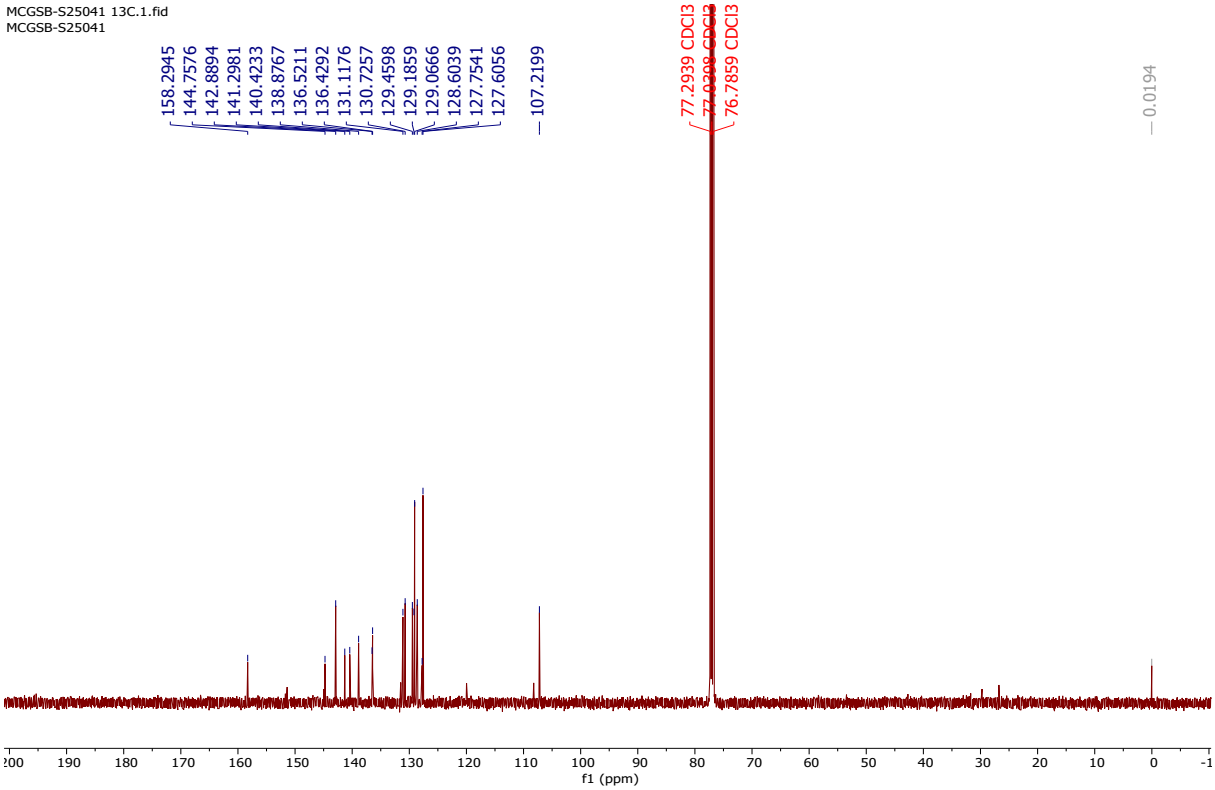

Figure S53: ^{13}C NMR of 2-(7-phenylimidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12a)** in $CDCl_3$ at 125 MHz

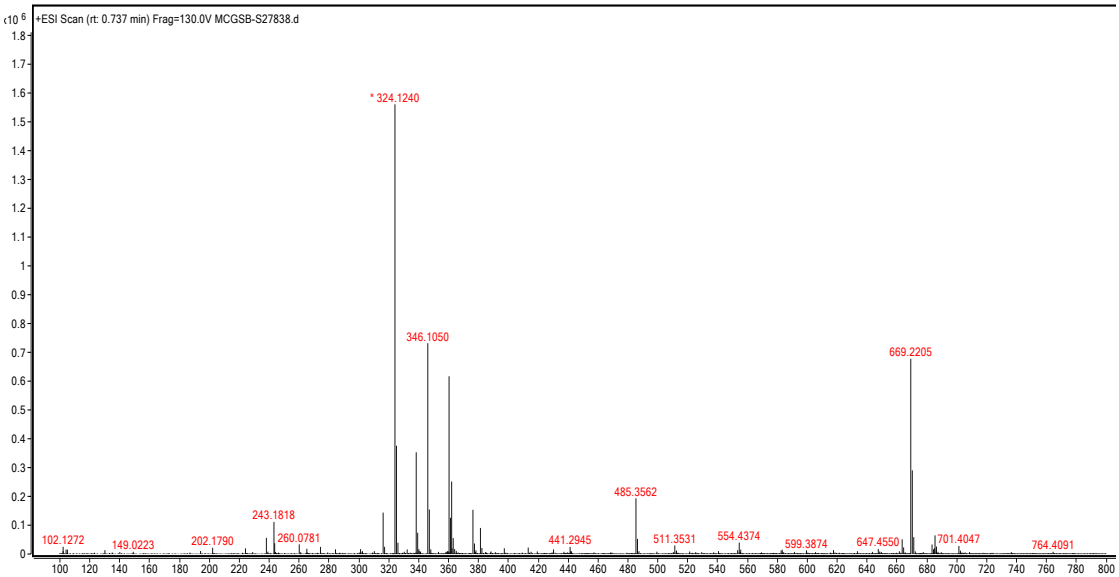

Figure S54: HRMS spectra of 2-(7-phenylimidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12a)**

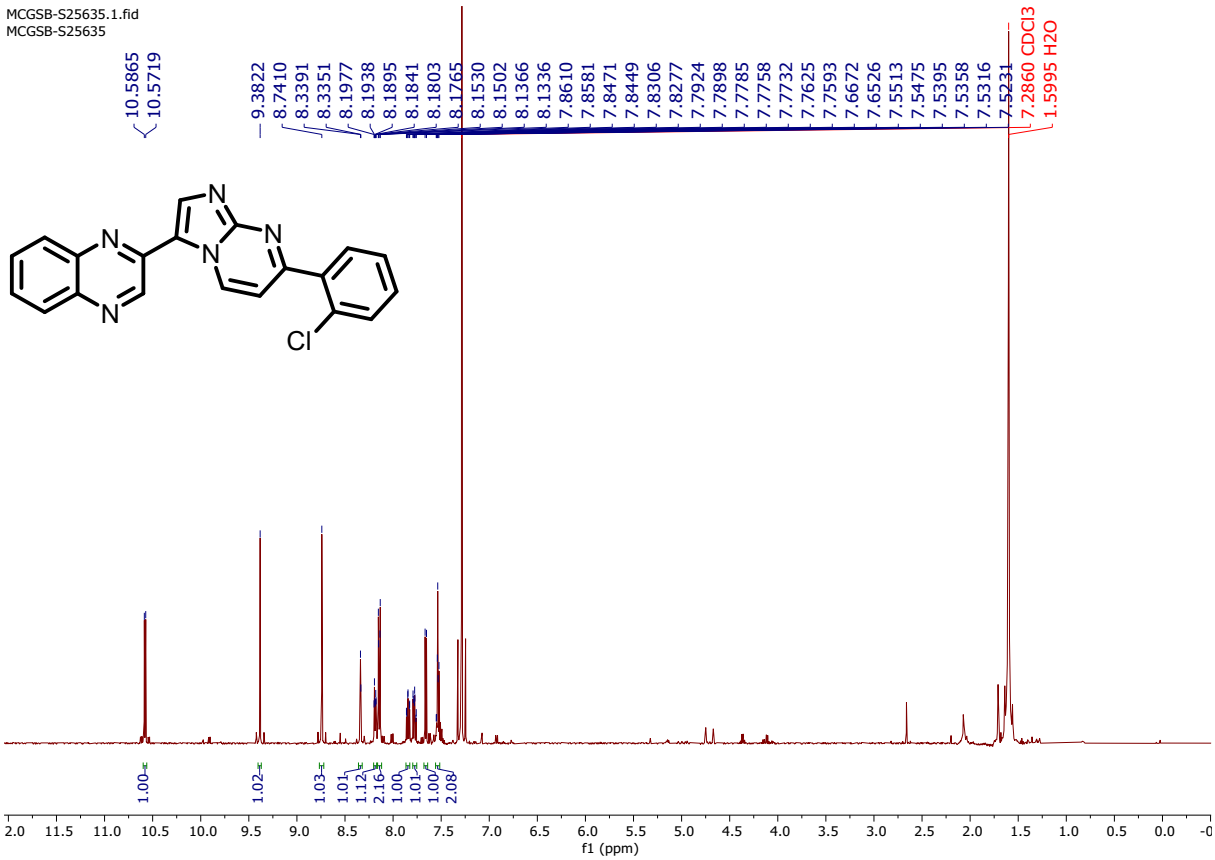

Figure S55: ^{1}H NMR of 2-(7-(2-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12b)** in $CDCl_3$ at 500 MHz

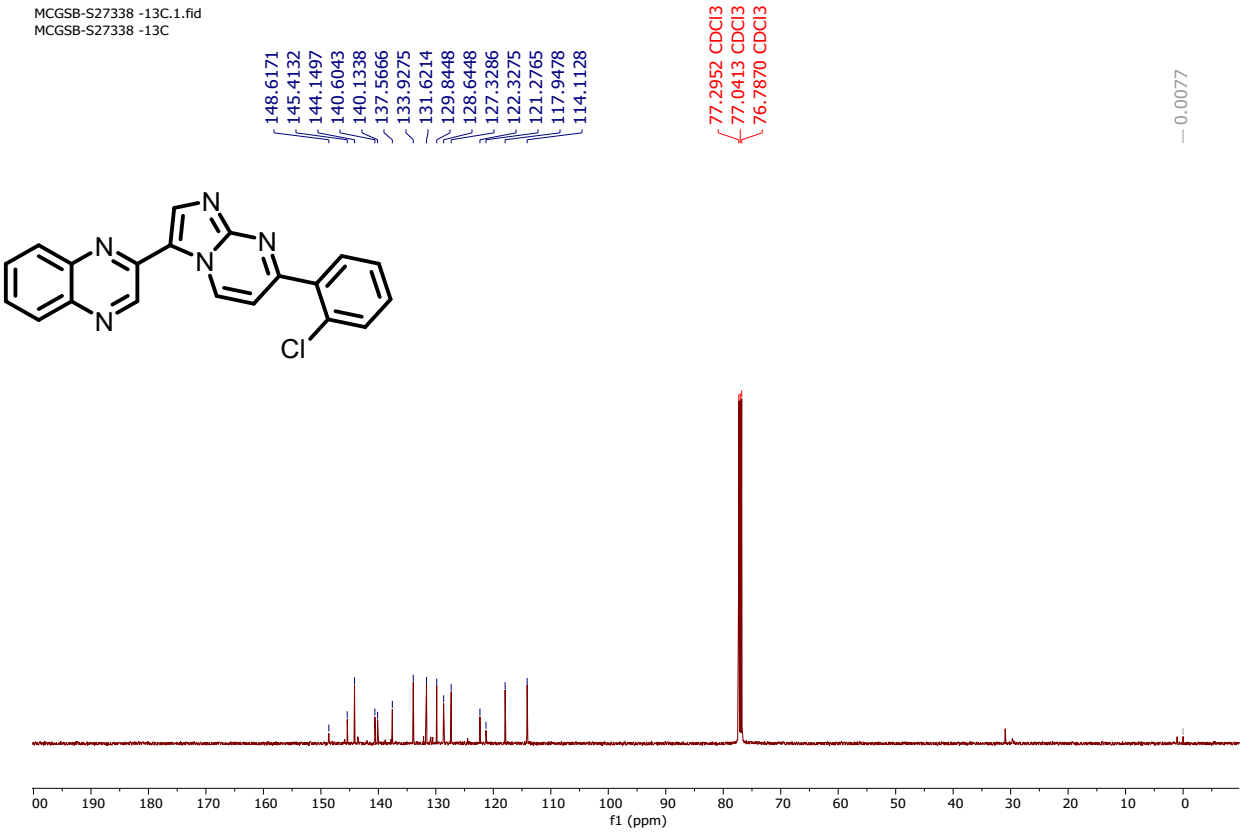

Figure S56: ^{13}C NMR of 2-(7-(2-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12b**) in $CDCl_3$ at 125 MHz

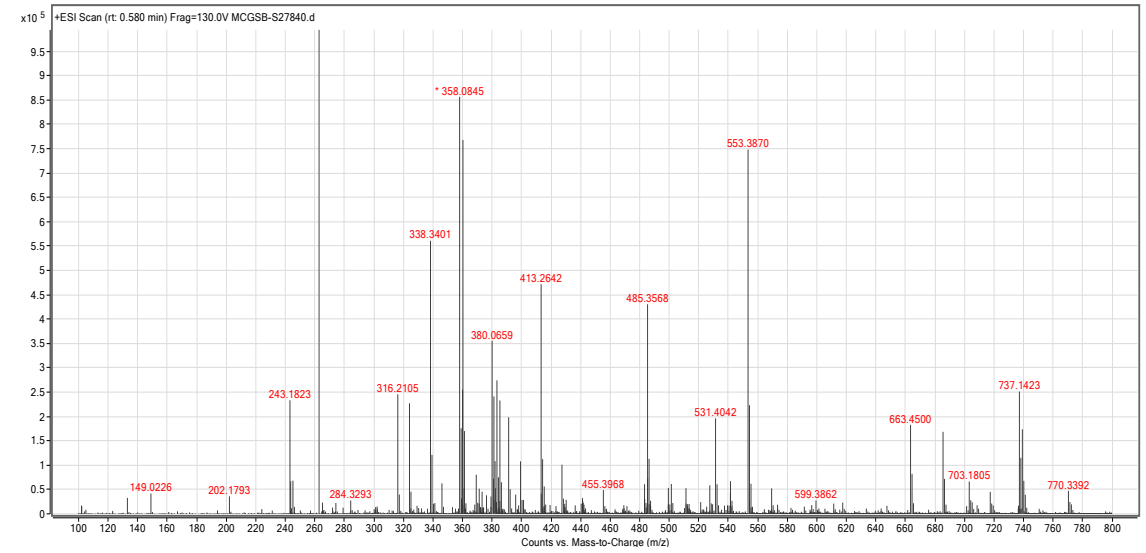

Figure S57: HRMS spectra of 2-(7-(2-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12b**)

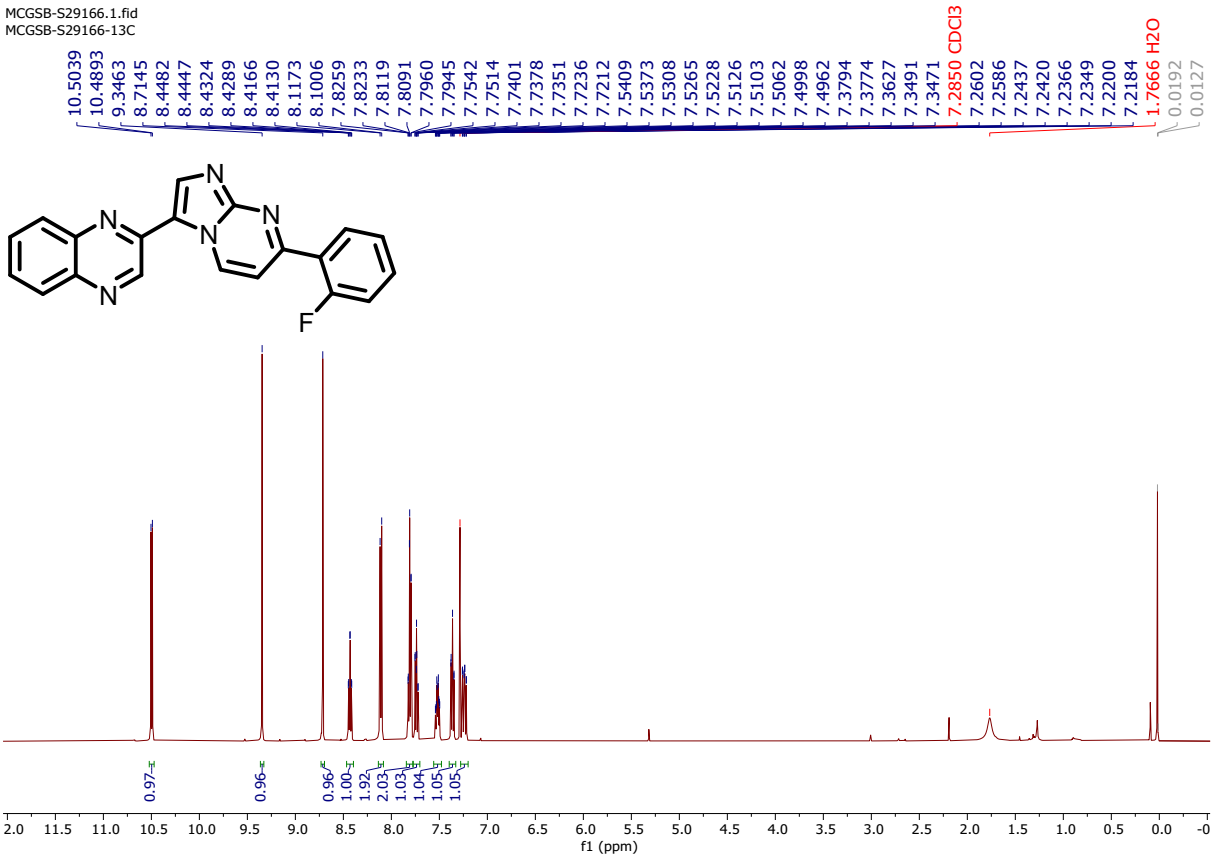

Figure S58: ^{1}H NMR of 2-(7-(2-fluorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12c**) in $CDCl_3$ at 500 MHz

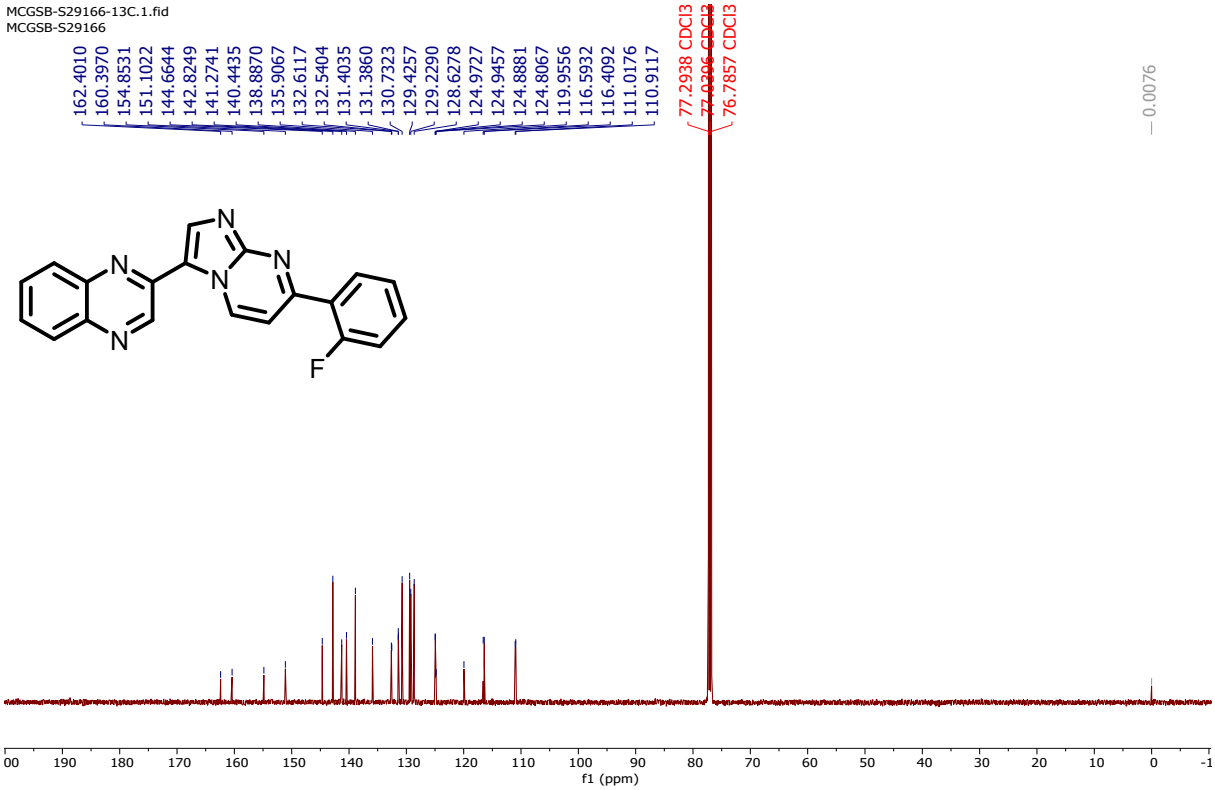

Figure S59: ^{13}C NMR of 2-(7-(2-flulorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12c**) in $CDCl_3$ at 125 MHz

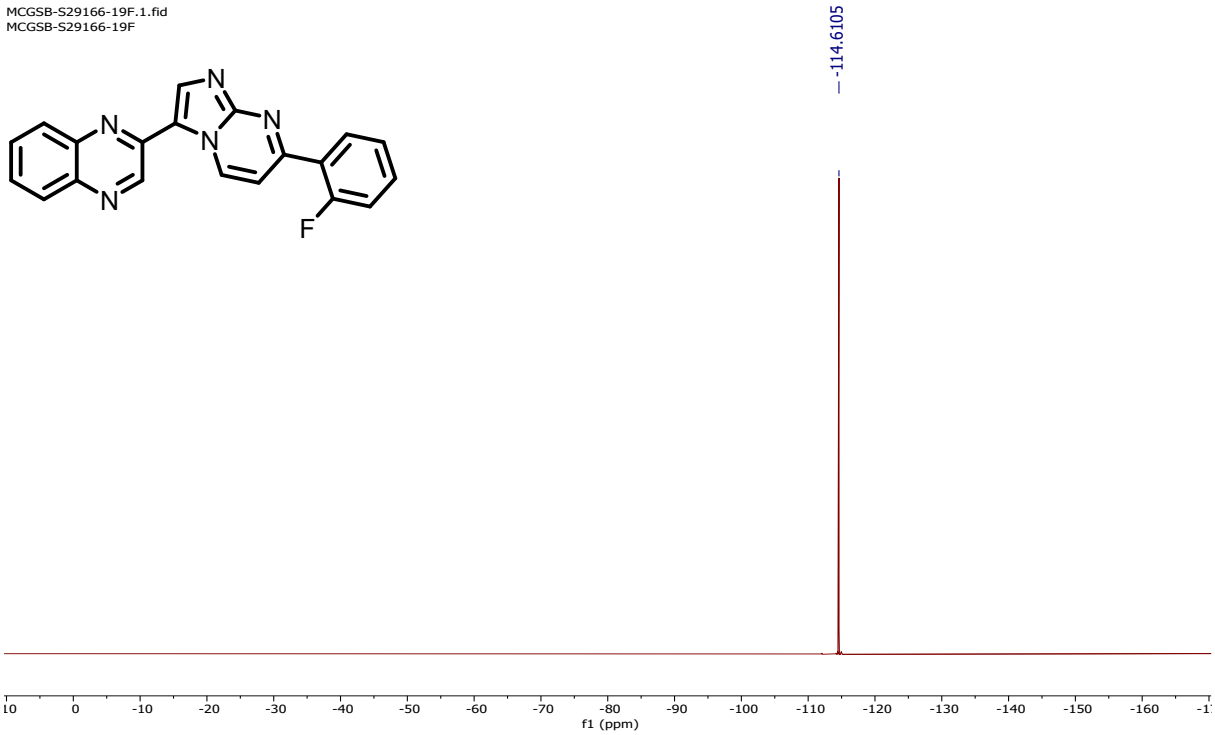

Figure S60: ^{19}F NMR of 2-(7-(2-flulorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12c**) in $CDCl_3$ at 471 MHz

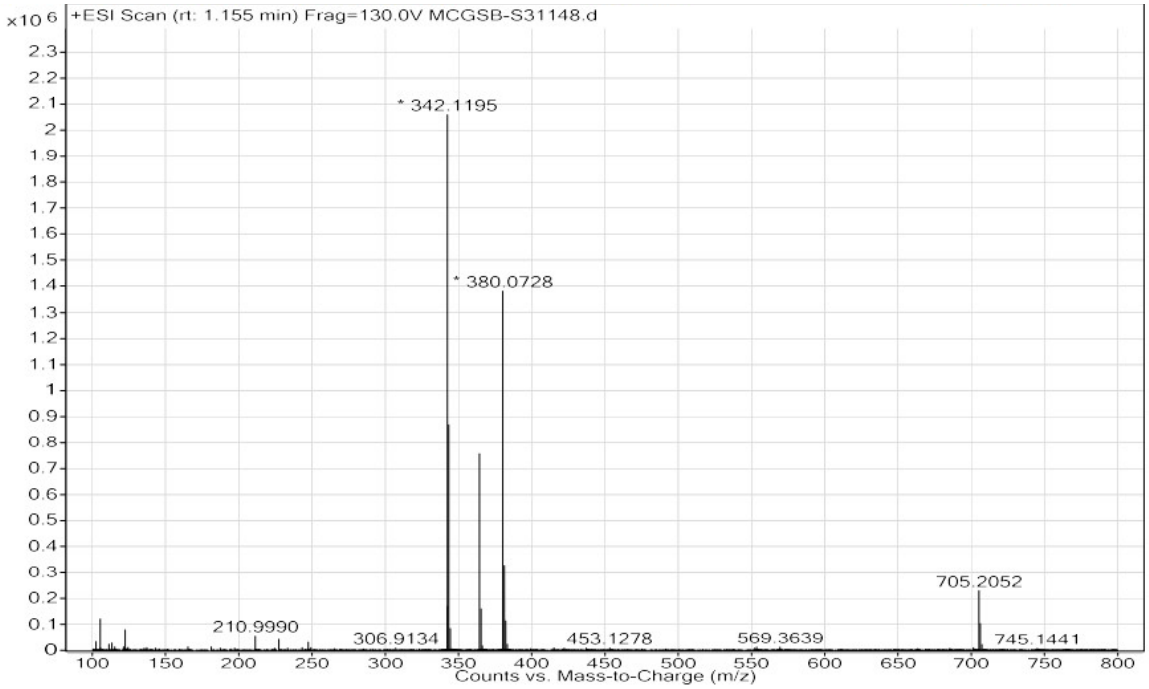

Figure S61: HRMS spectra of 2-(7-(2-fluorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12c)**

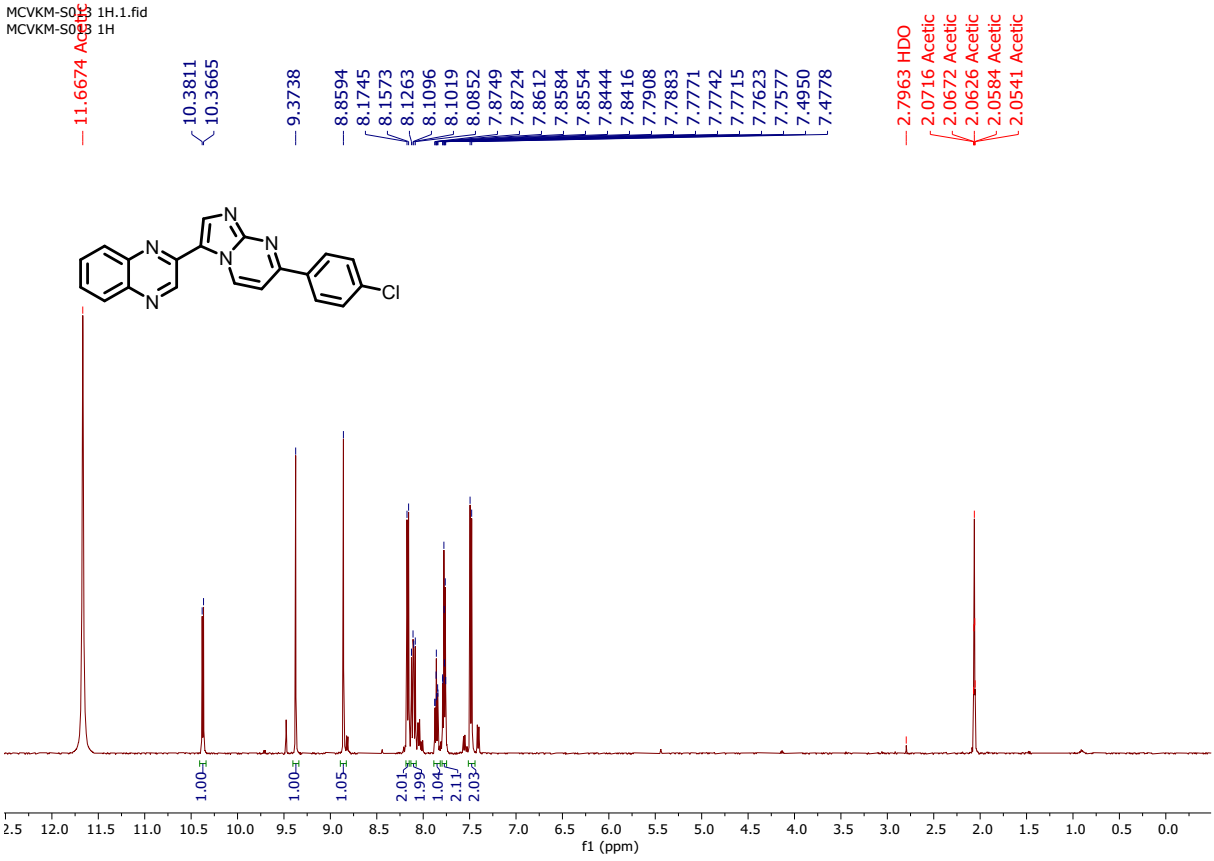

Figure S62: ^{1}H NMR of 2-(7-(4-chlorophenyl) imidazo[1,2-a] pyrimidin-3-yl) quinoxaline (**12d**) in Aceticacid-d_4 at 500 MHz

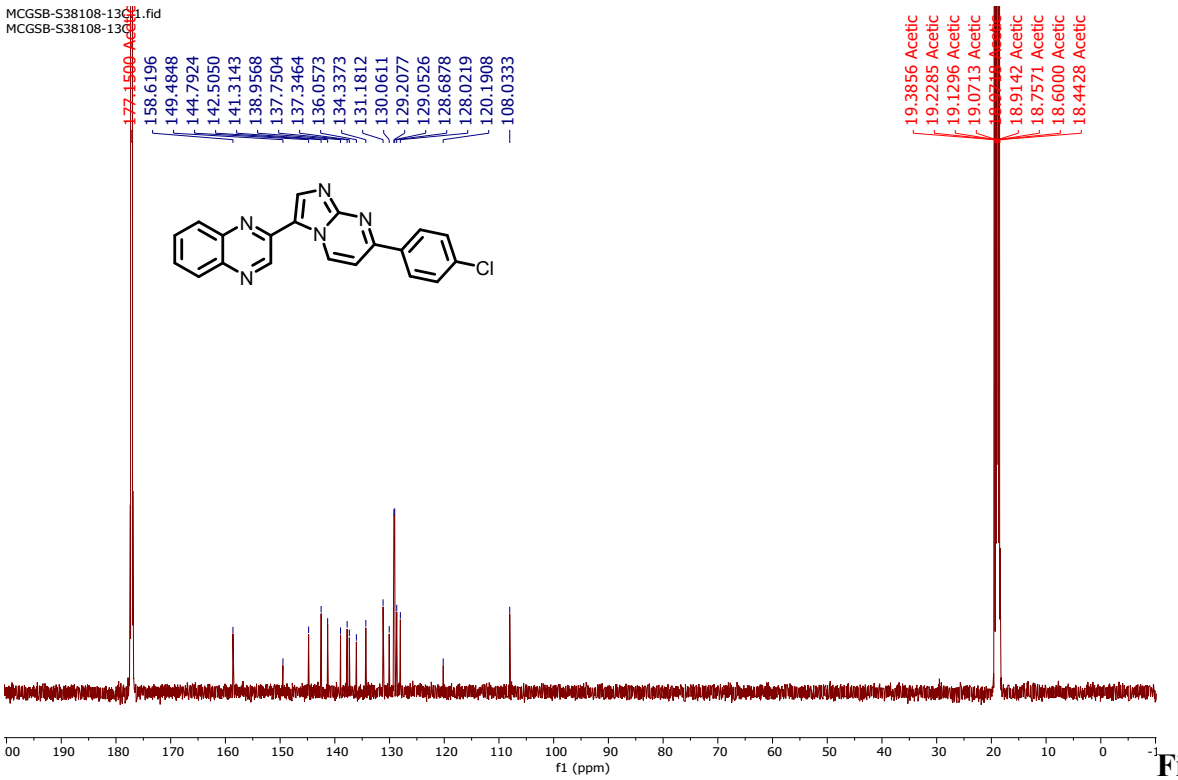

Figure S63: ^{13}C NMR of 2-(7-(4-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12d**) in Aceticacid-d_4 at 125 MHz

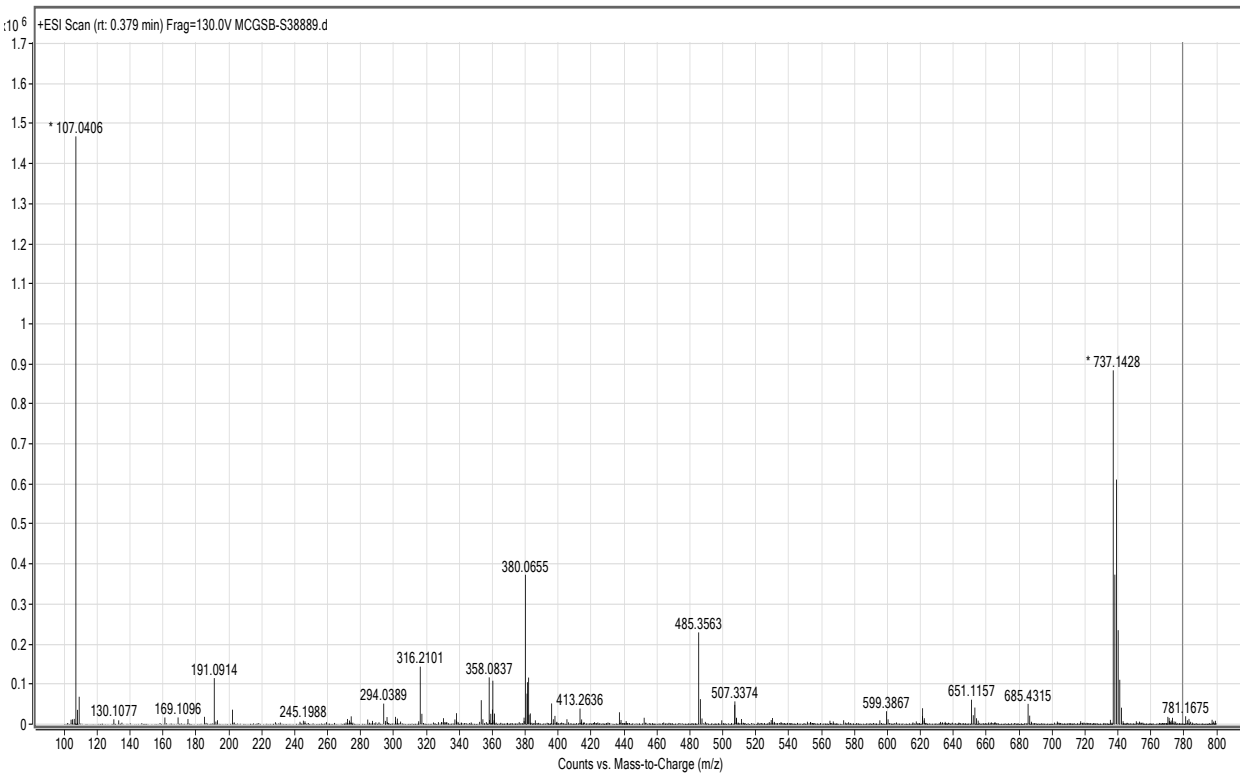

Figure S64: HRMS spectra of 2-(7-(4-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12d**)

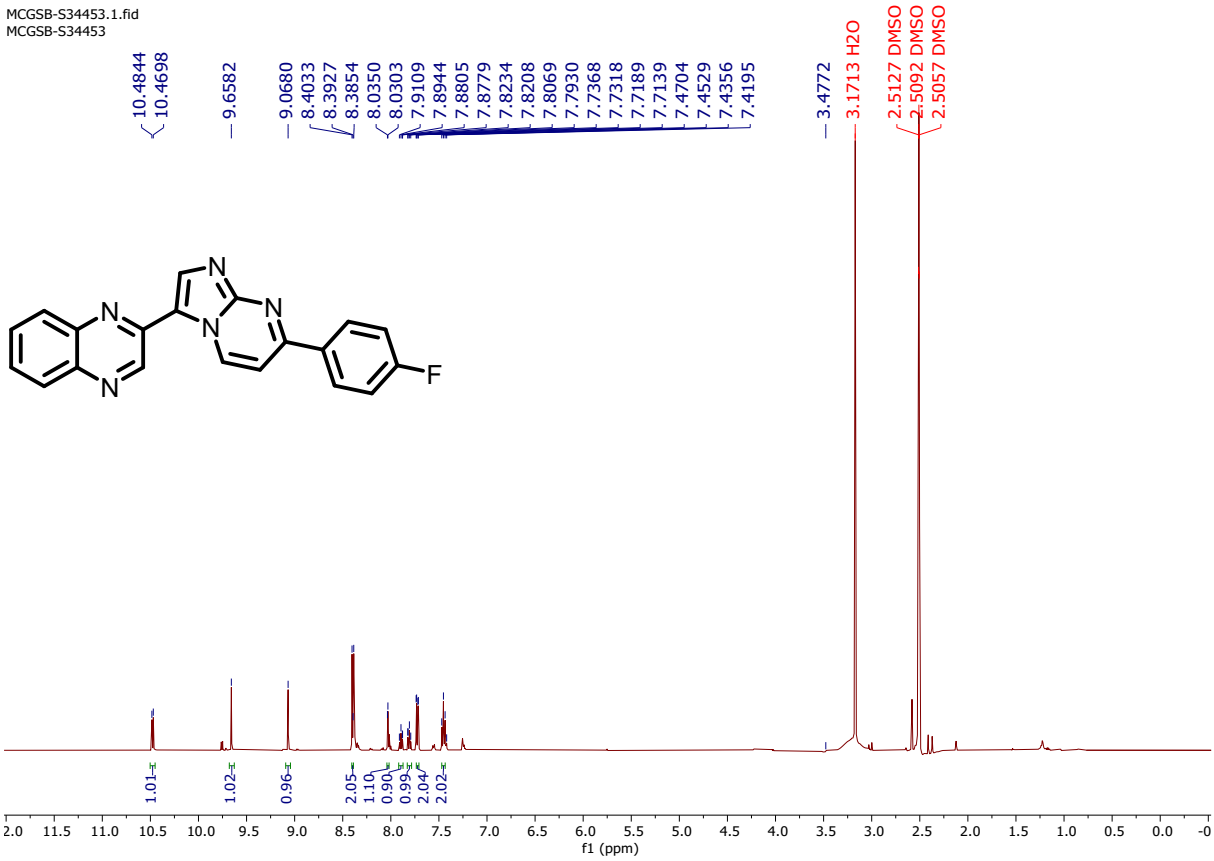

Figure S65: ^{1}H NMR of 2-(7-(4-fluorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12e**) in DMSO-d_6 at 500 MHz

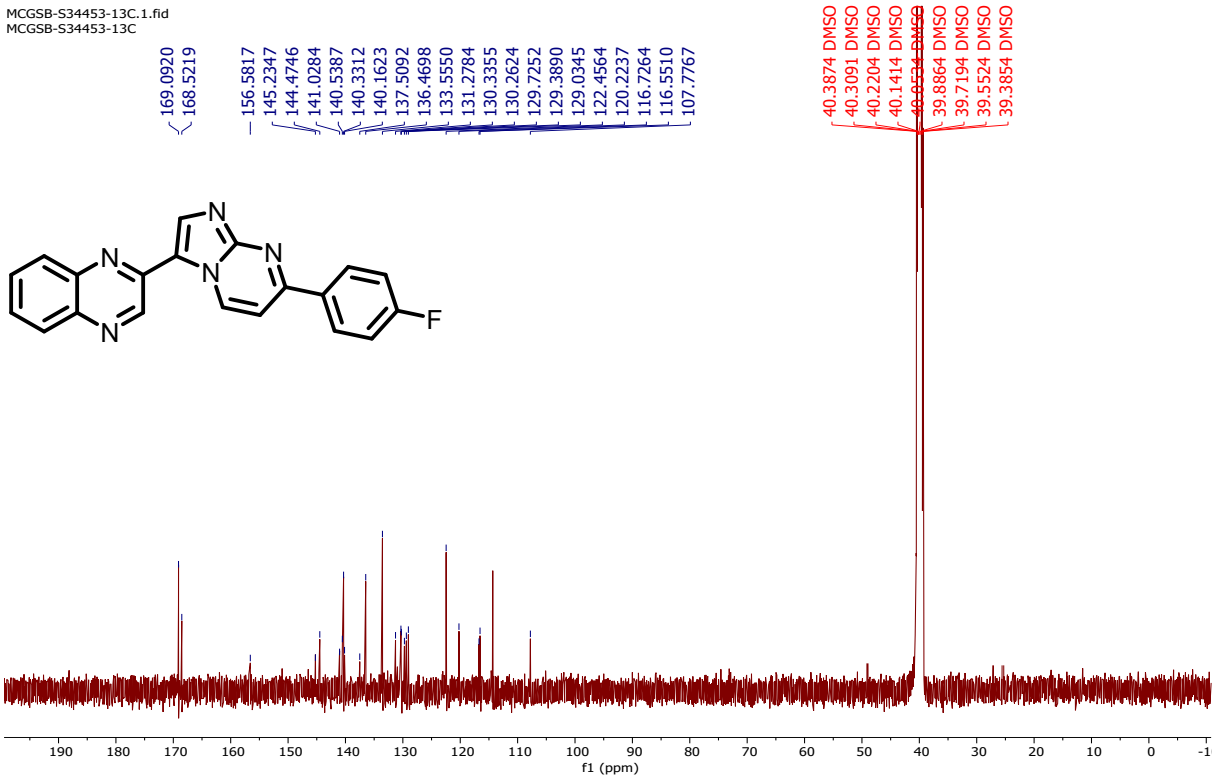

Figure S66: ^{13}C NMR of 2-(7-(4-fluorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12e**) in DMSO-d_6 at 125 MHz

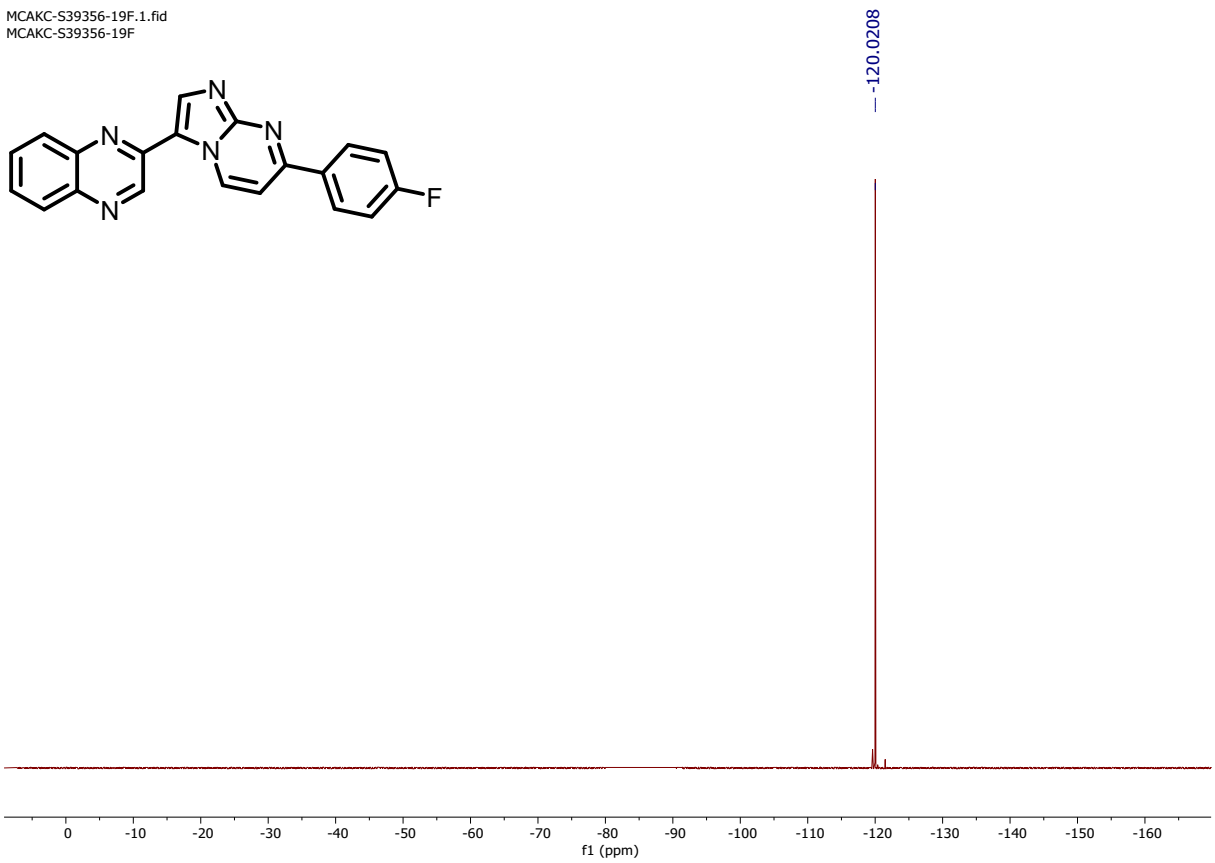

Figure S67: ^{19}F NMR of 2-(7-(4-flulorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12e**) in DMSO-d_6 at 471 MHz

Figure S68: HRMS spectra of 2-(7-(4-fluorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12e**)

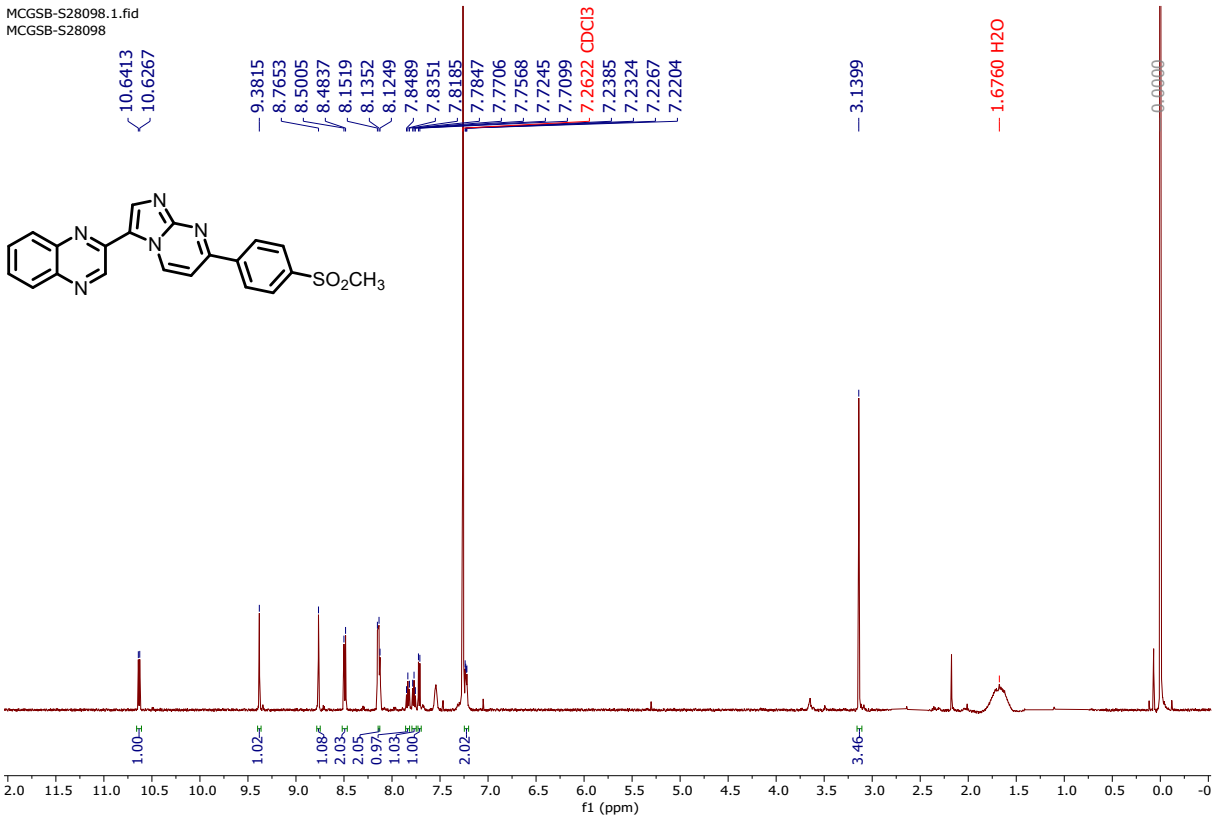

Figure S69: ^{1}H NMR of 2-(7-(4-methylsulfonyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12f**) in $CDCl_3$ at 500 MHz

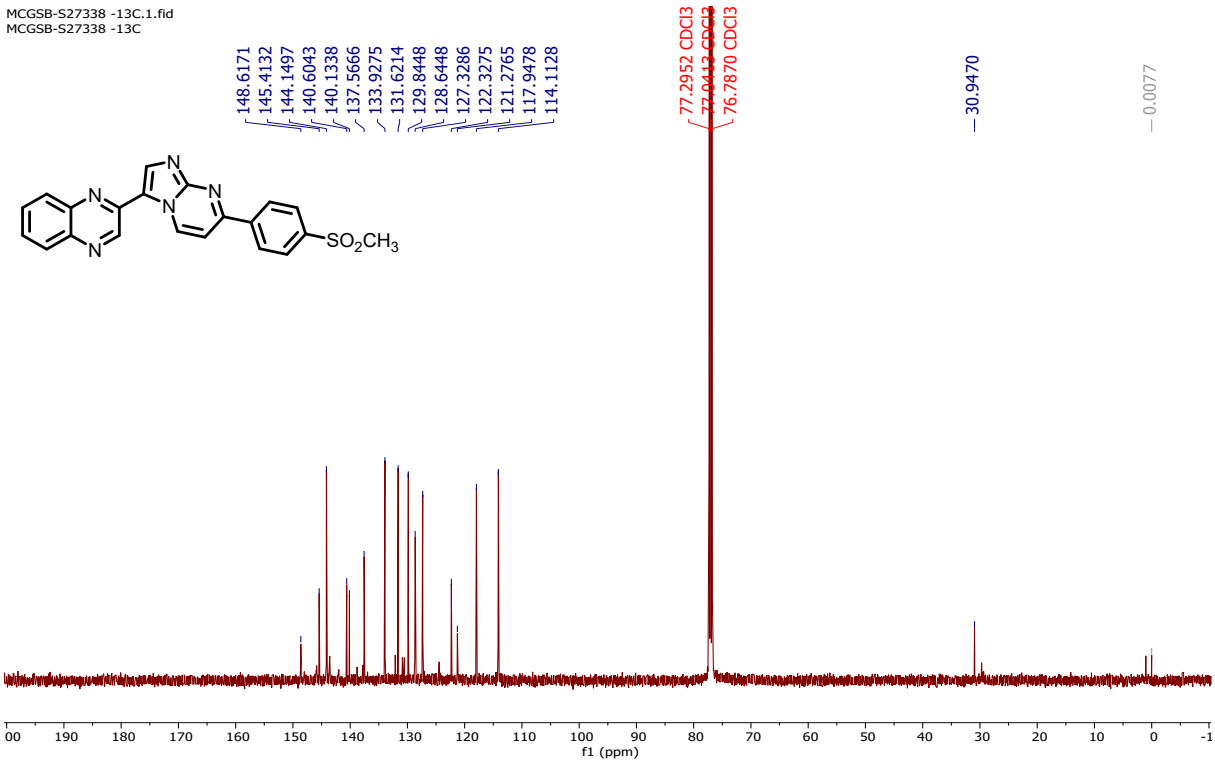

Figure S70: ^{13}C NMR of 2-(7-(4-methylsulfonyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12f**) in $CDCl_3$ at 125 MHz

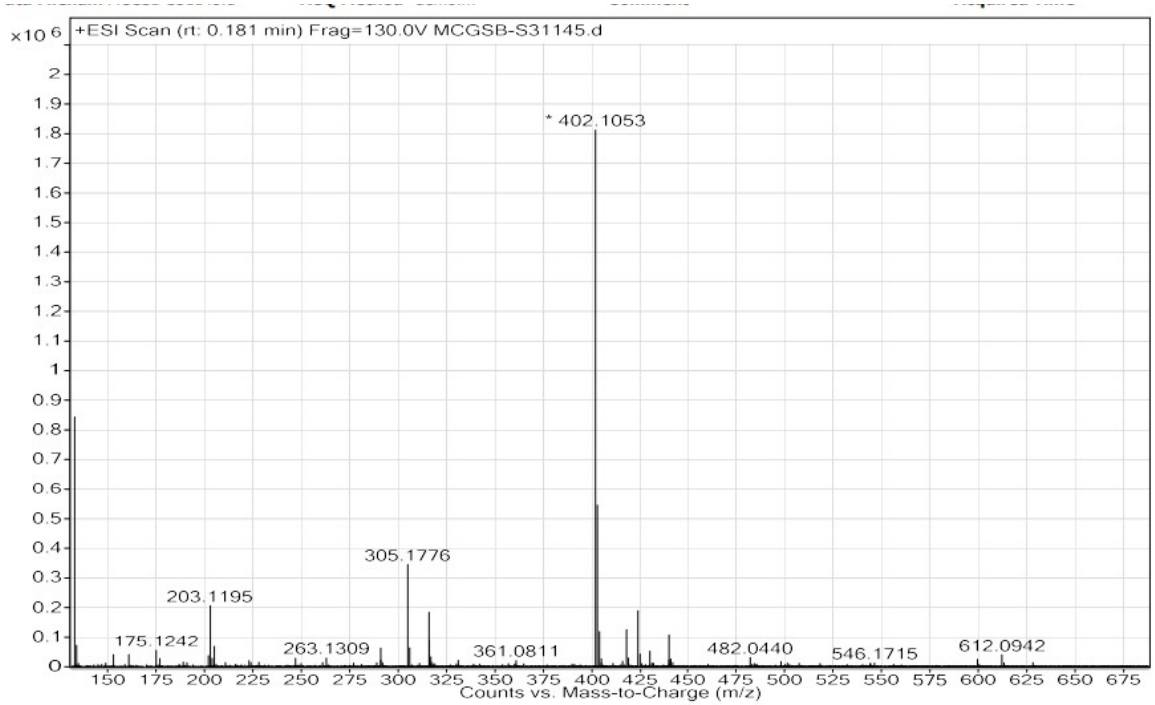

Figure S71: HRMS spectra of 2-(7-(4-methylsulfonyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline(**12f**)

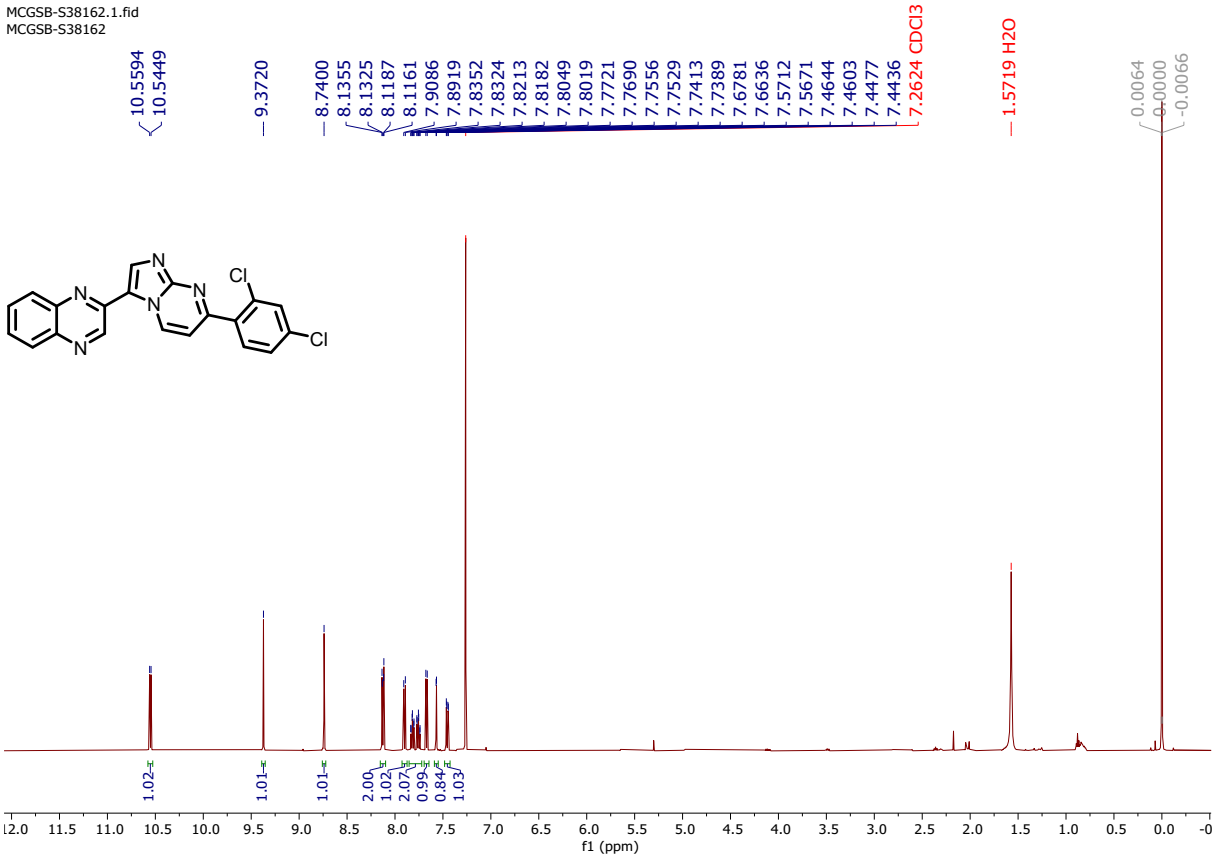

Figure S72: ^{1}H NMR of 2-(7-(2,4-dichlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12g**) in $CDCl_3$ at 500 MHz

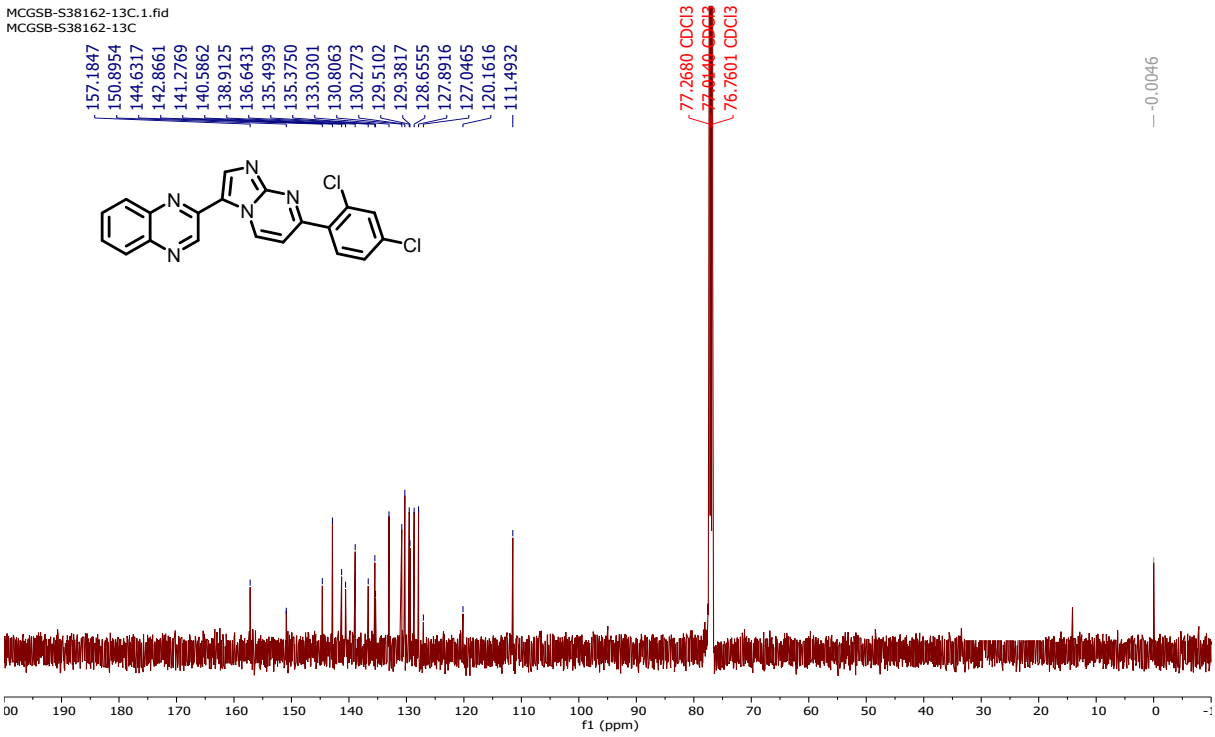

Figure S73: ^{13}C NMR of 2-(7-(2,4-dichlorophenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12g**) in $CDCl_3$ at 125 MHz

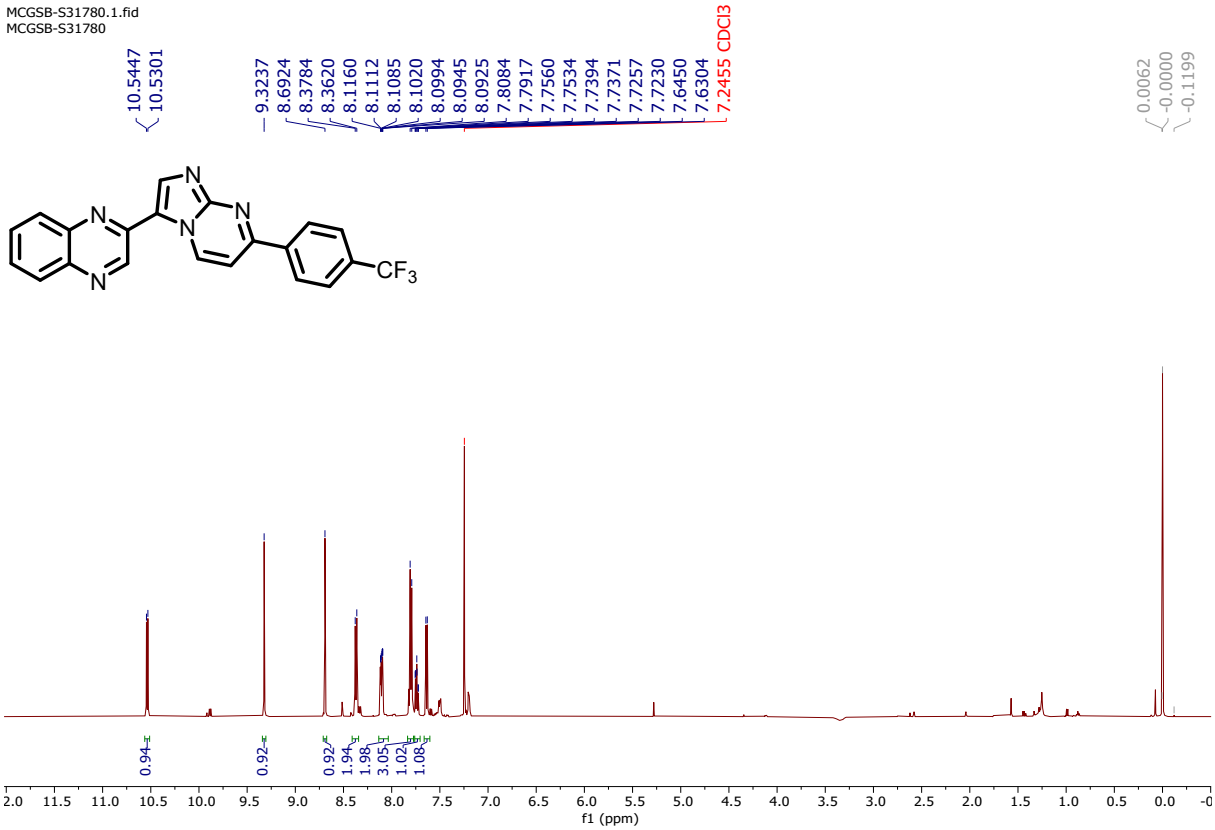

Figure S74: ^{1}H NMR of 2-(7-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12h**) in $CDCl_3$ at 500 MHz

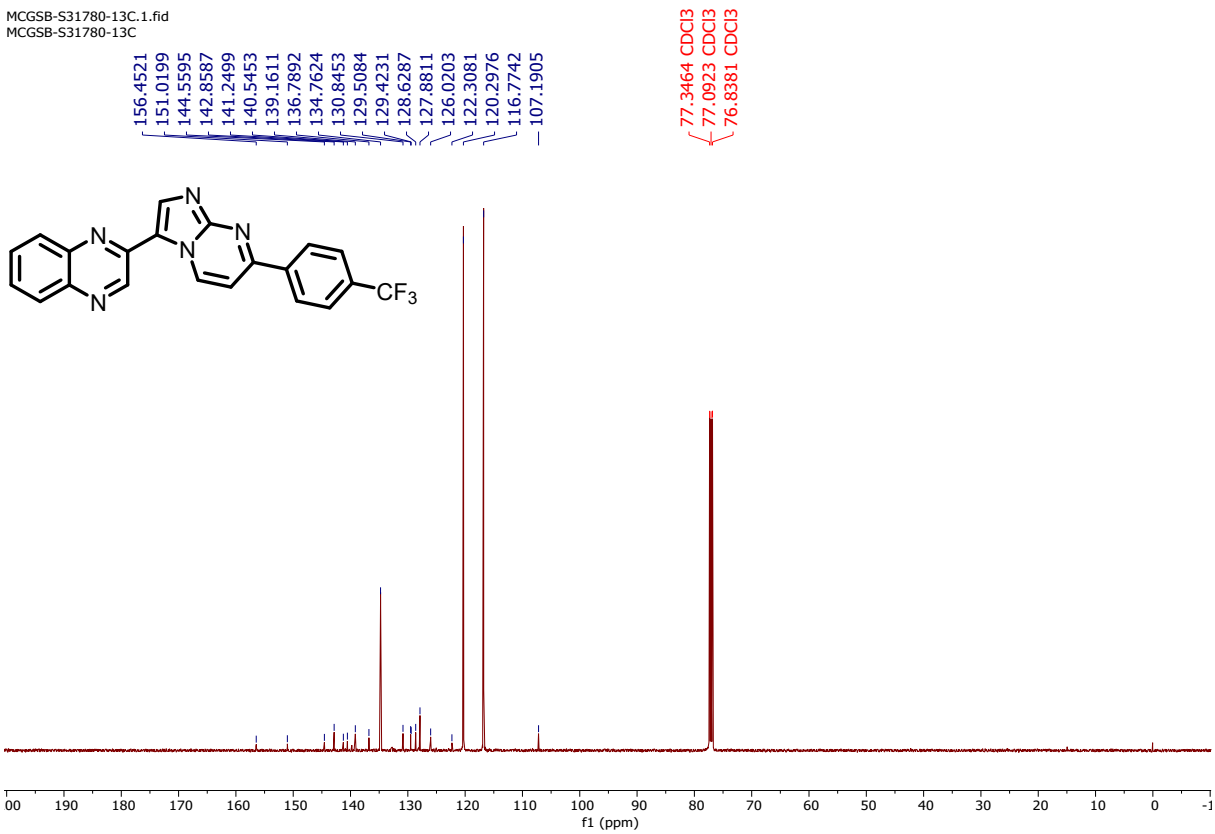

Figure S75: ^{13}C NMR of 2-(7-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12h)** in $CDCl_3$ at 125 MHz

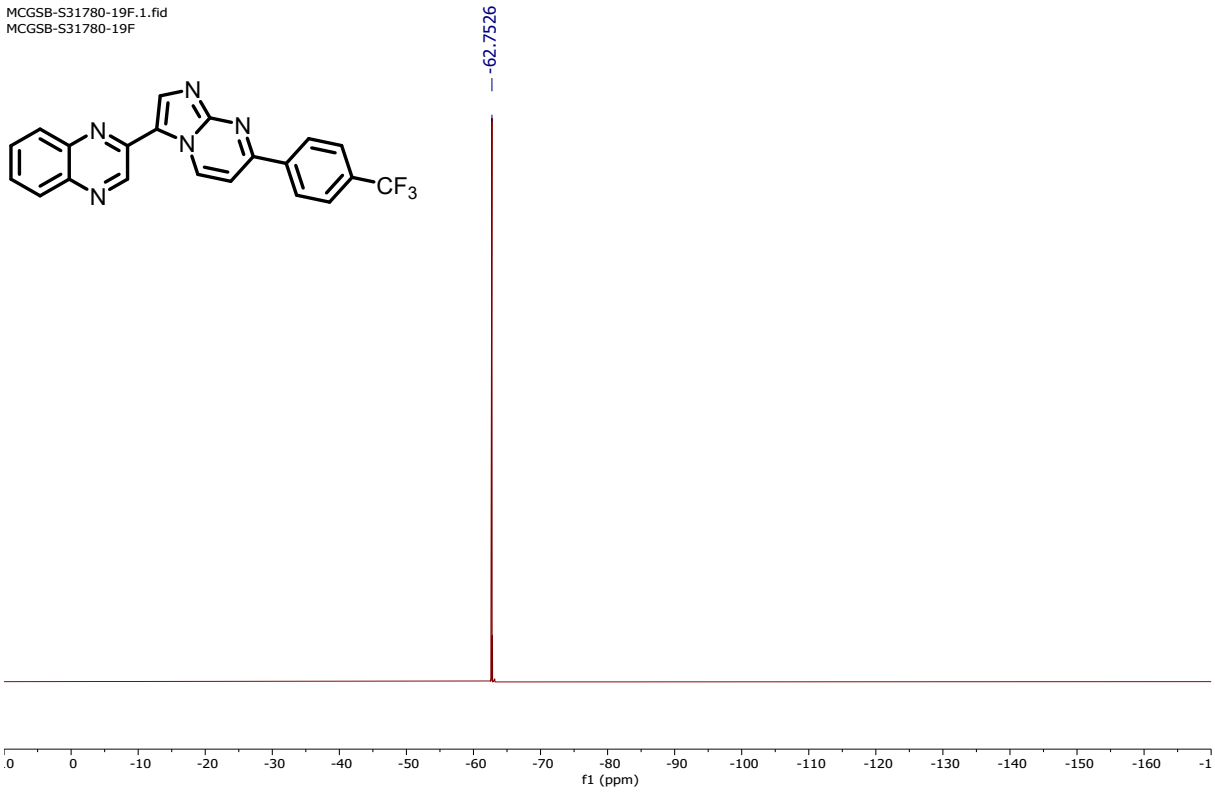

Figure S76: ^{19}F NMR of 2-(7-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline **(12h)** in $CHCl_3$ at 471 MHz

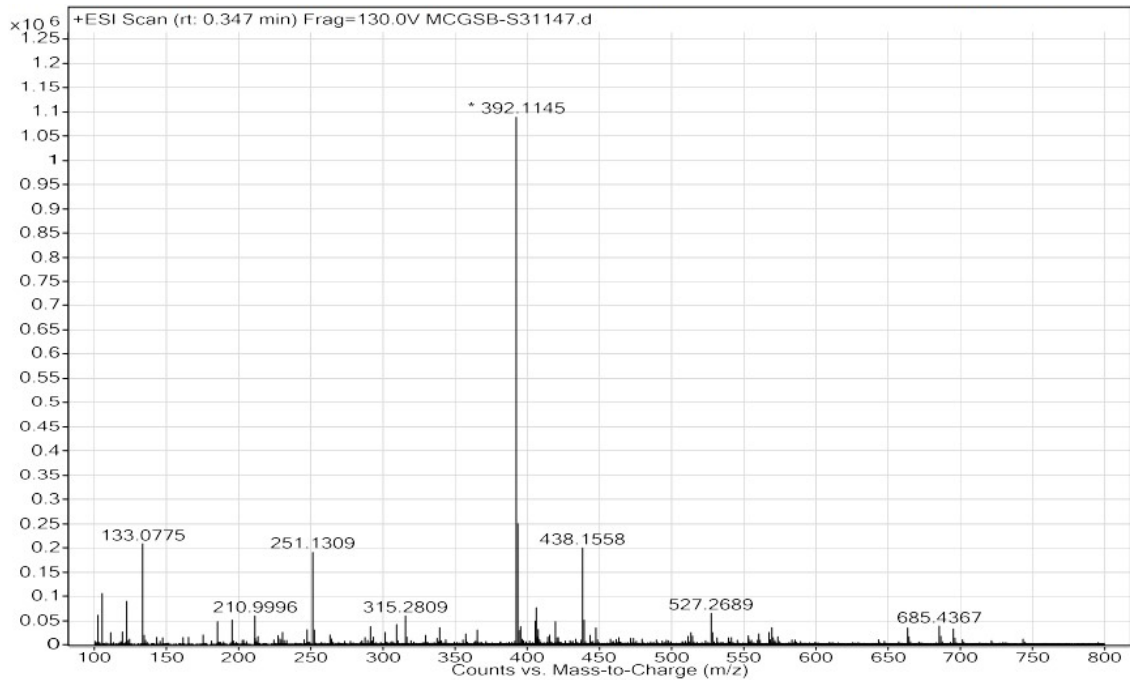

Figure S77: HRMS spectra of 2-(7-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12h**)

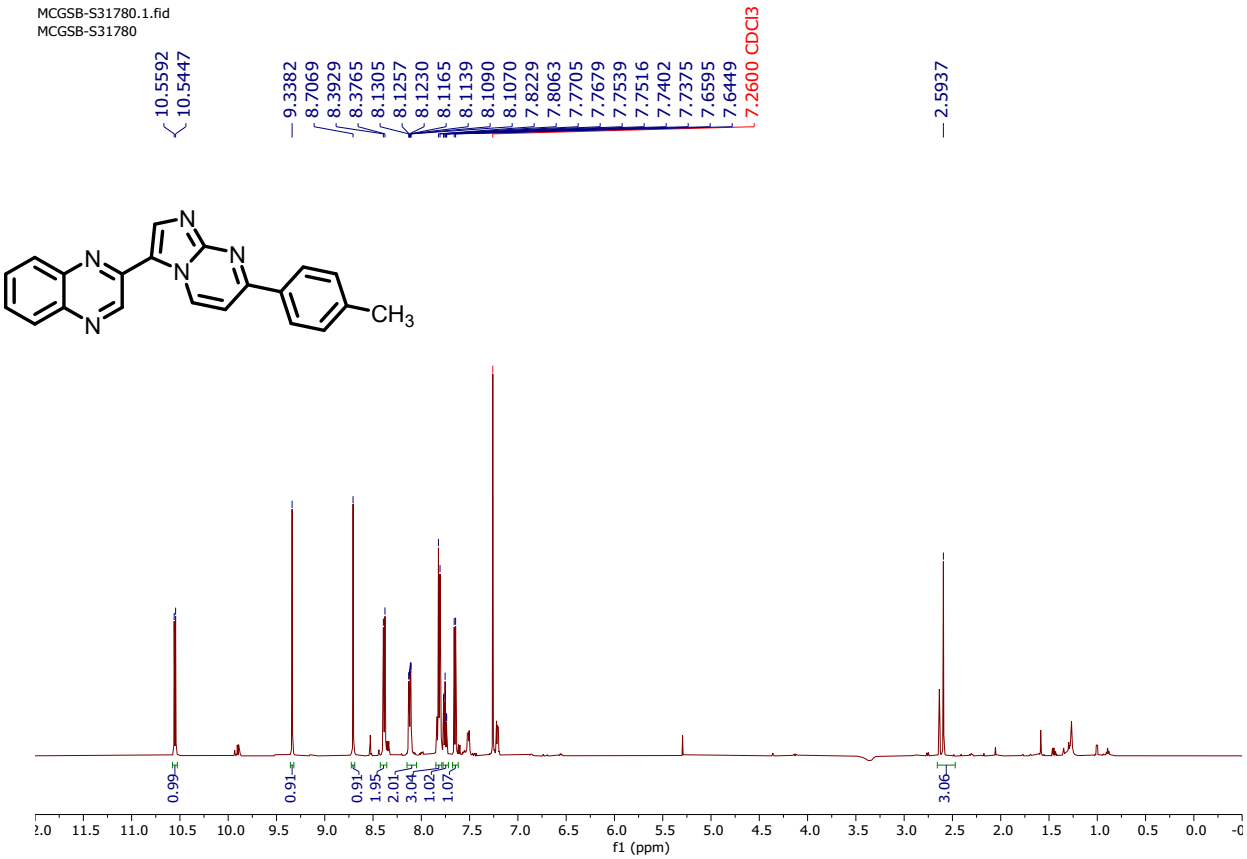

Figure S78: ^{1}H NMR of 2-(7-(4-(methyl)phenyl)imidazo [1,2-a]pyrimidin-3-yl)quinoxaline (**12i)** in $CDCl_3$ at 500 MHz

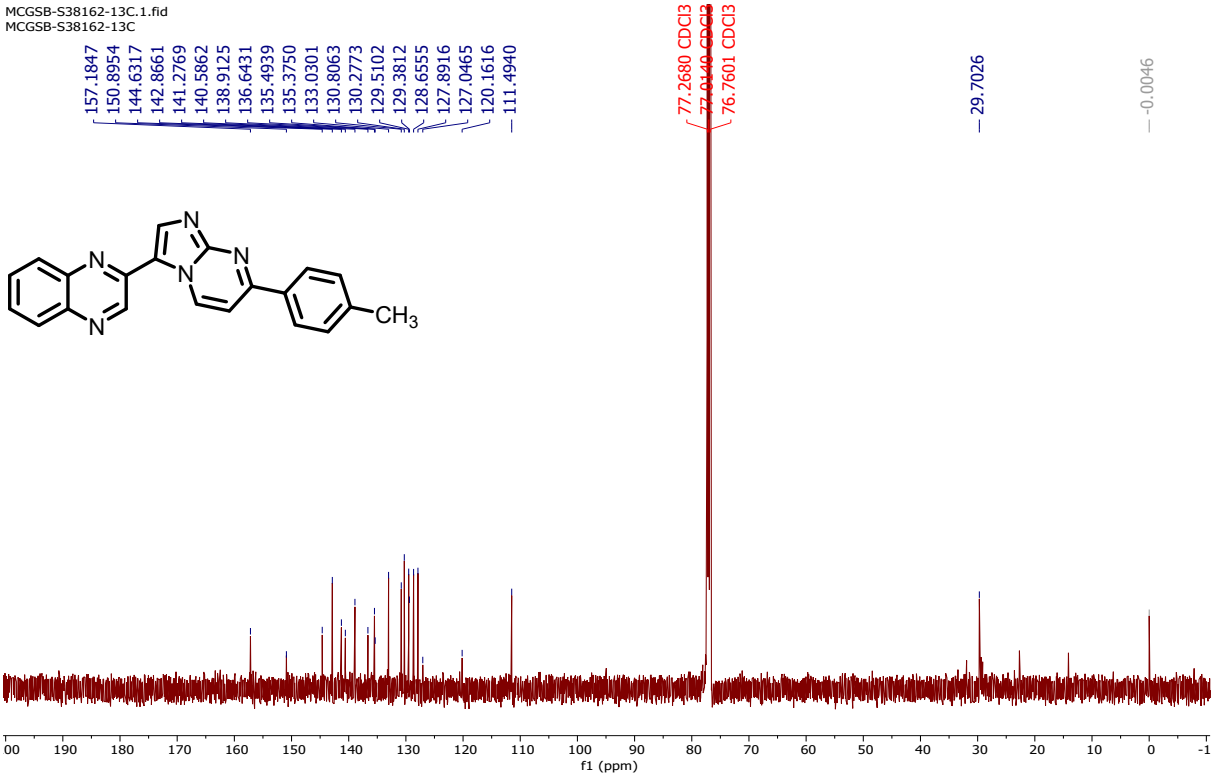

Figure S79: ^{13}C NMR of 2-(7-(4-(methyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12i**) in $CDCl_3$ at 125 MHz

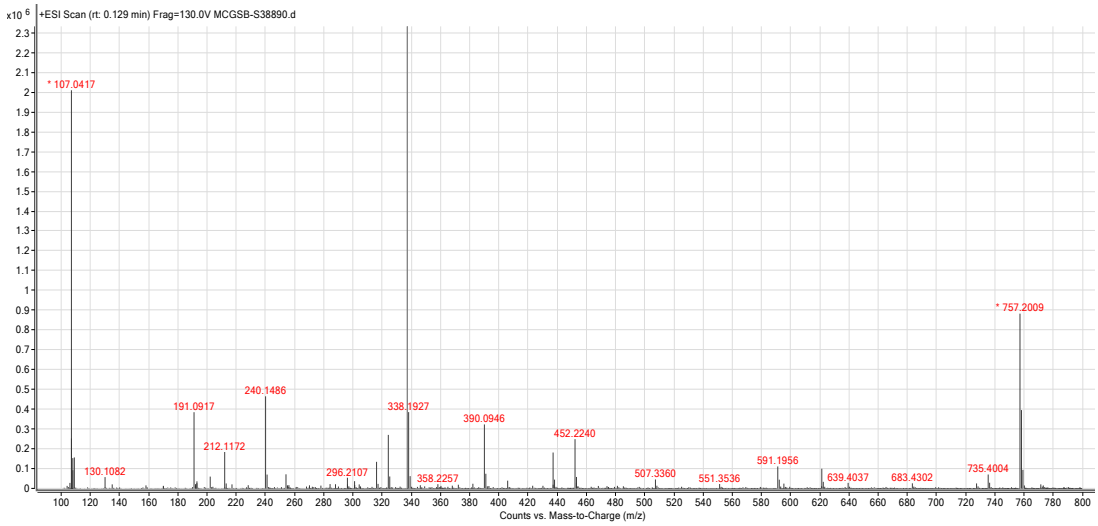

Figure S80: HRMS spectra of 2-(7-(4-(methyl)phenyl)imidazo[1,2-a]pyrimidin-3-yl)quinoxaline (**12i**)

3. in silico ADME results for the synthesized compounds

Table S2. Evaluation of the ADME properties of all the synthesized compounds.

Compound	logP	logS	Caco-2d	logHERG	PMDCK	%Human Oral

	(o/w)					Absorption
12a	3.938	-5.031	2059.967	-6.882	1080.43	100
10a	2.135	-2.864	1494.989	-5.45	764.035	96.267
10b	3.079	-4.267	1496.058	-5.347	3913.15	100
10c	2.639	-3.629	1495.535	-5.407	1882.39	100
10d	2.46	-3.47	1495.226	-5.415	764.166	100
10e	1.384	-2.918	177.561	-5.45	76.381	75.309
10f	3.755	-4.826	1494.876	-6.905	763.972	100
10g	2.718	-3.749	1495.498	-5.445	2023.92	100
10h	2.373	-3.236	1495.203	-5.343	1378.34	100
10i	2.935	-3.509	2728.62	-5.652	1464.04	100
10j	3.879	-4.642	2730.327	-5.547	7498.19	100
10k	3.361	-4.245	2728.803	-5.608	3605.89	100
10l	3.259	-4.115	2728.607	-5.616	1464.03	100
10m	2.178	-3.548	324.002	-5.632	146.322	84.632
10n	4.565	-5.51	2728.132	-7.145	1463.76	100
10o	3.503	-4.394	2728.687	-5.646	3876.95	100
10p	3.16	-3.871	2728.614	-5.545	2640.96	100
12d	4.443	-5.797	2060.387	-6.806	2664.54	100
12e	4.179	-5.412	2060.91	-6.769	1951.83	100
12f	2.452	-4.422	365.54	-6.975	167.087	87.176
12g	4.861	-6.416	1988.217	-6.714	5218.93	100
12h	4.952	-6.534	2062.103	-6.871	4760.3	100
12i	4.267	-5.65	2059.73	-6.817	1080.29	100
12b	4.354	-5.645	1987.045	-6.789	2113.56	100
12c	4.117	-5.304	2029.271	-6.787	1607.94	100

Predicted octanol/water partition coefficient log P (acceptable range -2.0 to 6.5).

Predicted aqueous solubility log S in mol/L (acceptable range: -6.5 to 0.5).

Predicted Caco-2 cell permeability in nm/s (acceptable range: < 25 is poor and > 500 is great).

Predicted IC_{50} value for blockage of HERG K^+ channels (concern below -5.0).

Predicted apparent MDCK cell permeability in nm/s (acceptable range: < 25 is poor > 500 is great).

Percentage of human oral absorption (acceptable range: < 25% is poor and > 80% is high).

4.*in vitro* study results

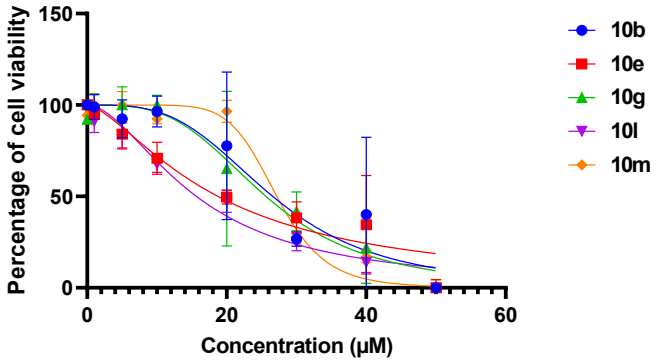

Figure S81: Cytotoxicity data for the synthesized compounds (**10b, 10e, 10g, 10l,** and **10m**) against CAL-27 cell line using alamar blue assay

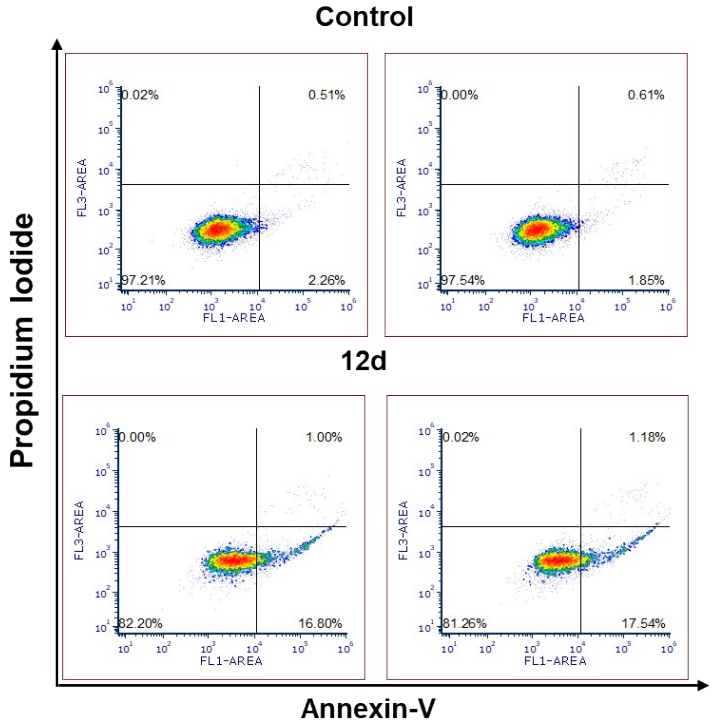

Figure S82: Apoptosis assay results of Compound **12d** performed in triplicate (n=2 and n=3 depicted here)

5.DFT results for the compound 12d

Table S3. Reactivity parameters like global electrophilicity index (ω), chemical hardness (ŋ), and electronic chemical potential (µ) as calculated for compound **12d**.

Compound	E_{HOMO}	E_{LUMO}	ΔE_{LUMO-}	µ	ŋ	ω= µ2/2ŋ

	(eV)	(eV)	HOMO (eV)	(eV)	(eV)	(eV)
12d	-5.964	2.472	3.492	4.218	3.492	2.548