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COMMUNICATION

Beneficial effects of a new neuroprotective compound in neuronal cells and MPTP-administered mouse model of Parkinson's disease

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A new compound, a derivative of 3,4,5-trimethoxy-*N*-phenyl benzamide bearing an 8''-methylimidazopyridine moiety, is found to demonstrate neuroprotective effects by preventing cell death caused by oxidative stress. The compound possesses high solubility and metabolic stability, and inhibits MPTP-induced effects in vivo, indicating high potential as a therapeutic drug for Parkinson's disease.

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects 1% of individuals aged >65 years. There are over six million patients with PD worldwide.[1] There are two types of PD—sporadic and familial.[2,3] Both types show degeneration of dopaminergic neurons, which causes a decrease in dopamine levels and an increase in acetylcholine levels. [4,5] Existing agents against PD either restore the changes in dopamine or acetylcholine levels. As such, currently, there are no effective drugs to prevent the degradation of dopaminergic neurons. Recently, a worldwide meta-analysis showed that the prevalence of PD increases with age; it is over 1% in individuals aged 70 years and nearly 2% in individuals aged over 80 years.[6] Because long-term administration of existing drugs leads to dyskinesia, wearing-off, and on-off phenomena, new drugs that can completely halt the degradation of dopaminergic neurons are urgently needed. Compound-23 is as an inhibitor of oxidative stress-induced cell death in cultured cells.[7] It was discovered through *in silico* screening of the zinc compound library, which contains 2.5 million compounds targeting the DJ-1 protein, a proto-oncogene product and the causative gene product for familial PD, [8] using the FastDock software (Fujitsu) in Bioserver hardware (Fujitsu).[7] Compound-23 exhibited cell-protective activity in cultured cells at 1 μM. Moreover, treatment with 1 mg/kg of compound-23 improved PD phenotypes in both 6-hydroxydopamine-injected rat model and rotenone-induced mouse model of PD.[9] However, the molecular weight of compound-23 is 417, which is higher than the ideal molecular weight of less than 350 for drug-likeness properties, such as permeability through the blood–brain barrier (BBB), desirable for drugs targeting the central nervous system (CNS). In addition, compound-23 is sparingly soluble and precipitates in an aqueous solution. Therefore, structural optimization of compound-23 is necessary to reduce its molecular weight and improve its solubility, which could eventually lead to the development of a new lead compound. In this study, we identified compound **2** as a promising compound for further structural optimization with a focus on the substituent positions and molecular weight, and derived compound **5**.

First, we prepared 45 derivatives of compound-23 (see Supporting Information, Schemes S1–S11) to evaluate the effects of the synthesized compounds on oxidative stress-induced cell death. SH-SY5Y cells were incubated with each compound for 21 h, and then treated with or without H_2O_2 for 3 h. Cell viability was measured using an MTS assay (Fig. 1). Cell viability was approximately 20–30% of that for the untreated cells after the addition of H_2O_2 (Fig. 1). Compound-23 slightly inhibited the decrease in cell viability caused by H_2O_2 oxidative stress at a concentration of 1 μM, but no inhibition was noted at lower concentrations.

To decrease the molecular weight of compound-23, compound **1**, in which a methoxy moiety on the A ring was eliminated, was designed and synthesized. Compound **1** exhibited inhibition. Therefore, we synthesized compound **2**, which contained 3,4-difluoro substituents on the A ring instead of dimethoxy substituents to improve its water solubility. Compound **2** completely prevented the decrease in cell viability and did not affect the viability of untreated cells (Fig. 1C). In

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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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addition, the 3,5-difluoro derivative **3** showed high cell-protective activity (Fig. 1D).

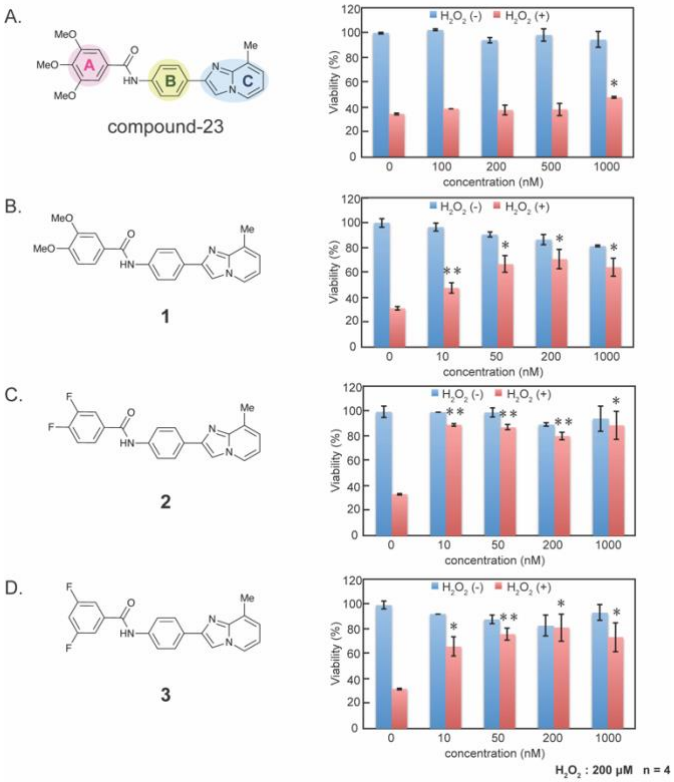

Fig. 1. Identification of new compounds and their effects on oxidative stress-induced cell death. (A) The three aromatic rings, identified as A, B, and C ring, are shown in compound-23. (A-D) Cell viability was measured by MTS assay. Significance: *p < 0.01, **p < 0.001 versus only H_2O_2 (200 μM) treated cells. The number of experiments (n) was 4.

Oxidative stress leads to neuronal cell death, which tends to cause PD.[10-12] Therefore, we investigated whether compound **2** directly ameliorates oxidative stress. The antioxidant effects of the compound **2** was measured using xanthine oxidase, NADPH oxidase, and mitochondrial electron transport systems. Positive controls, allopurinol, apocynin, and rotenone/carbonyl cyanide 3-chrolophenylhydrazone (CCCP), were evaluated using these assays (Fig. S1). Compound **2** did not show any antioxidant effect on xanthine oxidase, NADPH oxidase, or the mitochondrial electron transport system at a wide range of concentrations, although it exhibited sufficient cell-protective activity (Fig. S2).

To further determine the structure‑activity relationships (SARs) of compound **2**, the position of the methyl group in this compound was investigated. Repositioning of the methyl group on the C ring, such as **S1**, **S2**, and **S3** (Fig. S3) showed no effect on the cell-protective activity (Fig. S3). In addition, repositioning the imidazopyridine moiety on the B ring of **S4** did not affect this activity (Fig. S3). Therefore, we prepared **S5** to examine the necessity of a methyl group on the C ring (Fig. S4). We observed that 10 μM of **S5** exhibited efficacy. Furthermore, we introduced a methyl group into the amide moiety of **S6** based on **2**; however, this structural modification caused a loss of the cell-protective effect. These results indicate that the existence of the imidazopyridine moiety was important for the cell-protective activity, whereas the introduction of a methyl group into the amide moiety led to a reduction in the desired activity.

The BBB is the interface between the CNS and the blood circulation, which limits drugs from reaching the CNS owing to their relative impermeability. Molecular weight is important for drug delivery into the CNS. Therefore, we optimized the chemical structure of **2** to further reduce its molecular weight.

Substituents on the A ring were examined, as shown in Fig. 2. Compound **4** and monofluoride compounds (**5**, **6**, and **7**) completely inhibited cell death at 10 nM (Fig. 2). Furthermore, 0.5 nM of compounds **4** and **5** suppressed oxidative stress-induced cell death, whereas compounds **6** and **8** exhibited less inhibition, and **7** had little effect (Fig. 2). In particular, compounds **4** and **5** showed an ED_{50} < 1 nM, which was 1000 times lower concentration than that required for compound-**23**. The molecular weights of **4** and **5** are 327 and 345, respectively, whereas that of compound-23 is 417. Hence, these low molecular weight (<350) compounds are expected to be more suitable as CNS drugs. While compounds **2** and **5** were derived from compound-23, they showed the activity for DJ-1-knockout SH-SY5Y cells (Fig. S5), suggested that these compounds do not specifically target DJ-1.

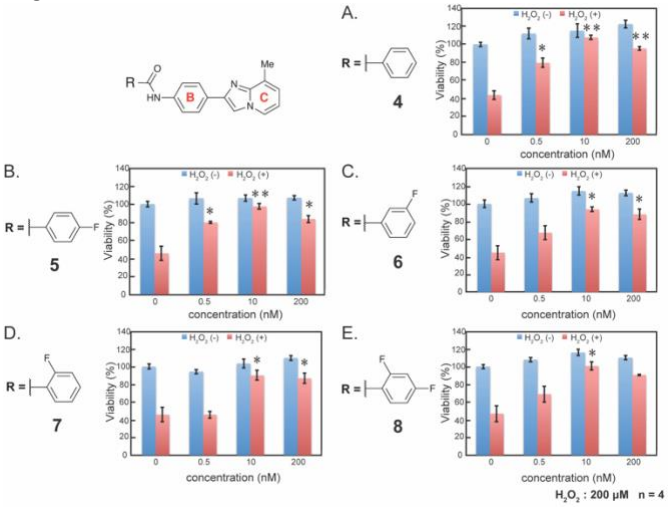

Fig. 2. Decrease in the molecular weight of compounds affects their cell death inhibition activity. Significance: *p < 0.01, **p < 0.001 versus only H_2O_2 (200 μM) treated cells. The number of experiments (n) was 4.

Because compound **5** worked effectively as an inhibitor, we performed further structural optimization by conducting a methyl scan on the A and B rings based on compound **5**. As shown in Fig. S6, **S7**, and **S8** inhibited cell death after H_2O_2 treatment, whereas **S9** had no effect. The cell-protective activity was in the following order: methyl group at the 4 > 3 > 2-position of the A phenyl ring. This suggests that the introduction of a methyl group at the 4-position on the A-ring resulted in the best activity. Methyl groups on the B ring, such as in compounds **S11** and **S12**, did not improve the cell-protective activity. These results indicated that the installation of substituents on the B ring was not effective. Furthermore, compound **S10** lost its cell-protective activity, indicating that the amide moiety was important for forming interactions via hydrogen bonding. We further designed and synthesized other derivatives to understand the SARs. Nitrogen scanning allowed minimization of conformational changes in the lead compound. Thus, nitrogen was directly introduced into the A and C rings based on compound **5**. Compounds **S13**, **S14**, and **S15** suppressed cell death after addition of H_2O_2 (Fig. S6-2). In particular, compound **S15** showed significant cell-protective activity, which was equal to that of compound **5**. Subsequently, nitrogen was introduced into the C ring. However, compounds **S16**, **S17**, and **S18** did not exhibit any activity.

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Nitrogen scanning typically prevents conformational changes but induces polarity changes in a molecule. On the contrary, the introduction of fluorine minimizes conformational changes, as does nitrogen installation, whereas the polarity changes of the entire molecule are limited.[13] Thus, we hypothesized that fluorine scanning can be applied to the C ring. As shown in Fig. S6-2, compounds **S19** and **S20** did not exhibit any cell-protective effects. These results indicate that the methyl group at the 8-position of the C-ring is essential for this activity.

Table 1. Cell viability with 1 nM compounds in MTS assay

Com*1	viability (%)	Com*1	viability (%)	Com*1	viability (%)
5	80 ± 13	**S17**	18 ± 2	**S28**	75 ± 12
S7	28 ± 4	**S18**	12 ± 6	**S29**	33 ± 7
S8	16 ± 1	**S19**	14 ± 1	**S30**	65 ± 8
S9	14 ± 2	**S20**	16 ± 4	**S31**	19 ± 4
S10	19 ± 1	**S21**	70 ± 13	**S32**	57 ± 11
S11	21 ± 2	**S22**	15 ± 3	**S33**	88 ± 3
S12	13 ± 1	**S23**	15 ± 2	**S34**	65 ± 9
S13	50 ± 10	**S24**	15 ± 1	**S35**	91 ± 2
S14	17 ± 2	**S25**	15 ± 1	**S36**	51 ± 7
S15	75 ± 9	**S26**	70 ± 7	**S37**	79 ± 5
S16	19 ± 2	**S27**	42 ± 7		

*1 Com : Compound #

We further investigated the SAR of the A ring. Compounds **S21**, **S26**, **S28**, and **S34** suppressed cell death after the addition of H_2O_2 (Fig. S6-3). All the compounds had a substituent at the 4-position of the A ring. Furthermore, **S33**, **S35**, **S36**, and **S37**, which contained substituents at the 4-position of the A ring, based on compound **S15**, strongly inhibited cell death after H_2O_2 addition, even at a concentration of 0.1 nM (Fig. S6-3). The viability of cells treated with 1 nM of the compounds is summarized in Table 1.

Metabolic stability, solubility, distribution, and oral absorption are necessary for evaluating drug development. Pharmacokinetic tests were performed on thirteen compounds (**4**, **5**, **2**, **S5**, **S6**, **6**, **7**, **8**, **S21**, **S13**, **S7**, **S33**, and **S35**) that showed high cell protective activity or improved water solubility. First, metabolic stability was measured using human or mouse liver microsomes, and the residual ratios of the compounds were assessed (Tables S1, S2, and S3). All compounds were stable in human microsomes compared to the positive control, verapamil, whereas compound **S6** was highly metabolized in mouse microsomes, and its score was lower than that of the positive control, diltiazem (Table S1 Liver microsomal stability). Thus, low metabolic stability of compounds **S6**, **S7**, and **S33**, makes them unsuitable for animal tests or oral administration, owing to the significant damage caused by the first-pass effect. It is conjectured that drug transport in the blood and brain of each mouse becomes highly variable. Next, cytochrome P450 (CYP) inhibition assays were performed, and the residual ratio of compounds (0.4, 2, 10, 50 μM) was measured after mixing with microsome containing CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Substrate activity was measured to calculate the activity. The residual ratios of the compounds were also assessed. Precipitation was observed at 50 μM for compounds with IC_{50} values higher than 10 μM. None of the compounds showed CYP inhibition under conditions of 100-fold higher concentration of ED_{50} for each compound (Table S3). Nevertheless, compounds **4**, **S5**, and **S7** displayed mechanism-based inhibition (MBI) for CYP3A4 or CYP1A2. MBI-positive compounds can cause cumulative CYP inhibition, which can lead to an increase in the concentration of concomitant drugs, causing toxicity. In addition, compound **S13** inhibited CYP3A4 even though it was MBI-negative. In addition, compounds **S6** and **S21** slightly inhibited CYP2D6 and CYP3A4 or CYP3A4. Therefore, compounds **S33** and **S35** showed slight inhibition, but the MBI evaluation of compounds **S33** and **S35** was ambiguous because the IC_{50} values were higher than the precipitation concentrations, both with and without preincubation. To evaluate the distribution, PAMPA was performed, and the membrane permeability coefficient was calculated. The pH values of the entrance and exit of the small intestine were selected as 5.0 and 7.4, respectively. However, we could not examine compound **S35** because of its insolubility. The other compounds exhibited good membrane permeability (Table S3), suggesting that these compounds have the potential to pass through the small intestine. Finally, we assessed the solubility of the compounds in FaSSIF by comparing their solubility to that of the standard solution. Table S3 shows that all the compounds had low solubility in FaSSIF, with the solubility divided by the ED_{50} score being over 100-fold. The fold solubility of compound **5** against the ED_{50} was >10,000. Thus, compound **5** was expected to present a low risk in all the four tests.

In a previous study, peripheral administration of compound-23 (1 mg/kg) protected the motor activity from damage caused by the oral administration of rotenone. To evaluate the effect of compound **5** on the motor function, we treated mice with different doses of compound **5** (0.001, 0.01, 0.1 mg/kg, orally administered for 4 days) 1 h after intraperitoneal injection of MPTP (30 mg/kg). During the administration period, the body weight of the mice did not change (Fig. 3A). As shown in Fig. 3B, the retention time of MPTP-treated mice decreased to 40% of that without MPTP, whereas compound **5**-treated mice recovered the retention time under all conditions tested. The group administered with 0.1 mg/kg of compound **5** showed significant inhibition of motility dysfunction.

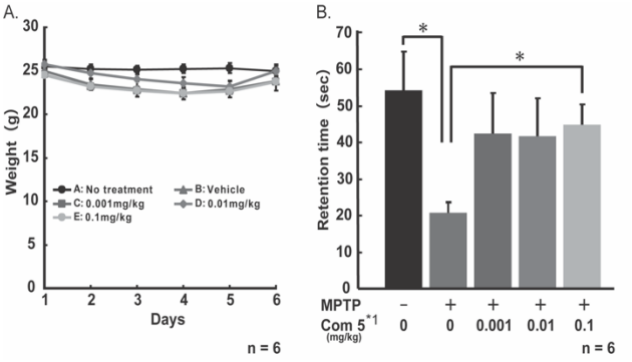

Fig. 3. The effect of compound 5 on MPTP-induced decrease in the locomotion behavior of mice. (A) The weight of mice was measured. (B) A rotor rod assay was performed for five days after the first administration. *1 Com **5**: compound **5**. Significance: *p < 0.05. The number of experiments (n) was 6.

Compound **5** prevented oxidative stress-induced death of DJ-1-knockout SH-SY5Y cells（Fig. S5）. This suggests that compound **5** affects a target different from that of compound-23. Although several drugs for PD are available, they do not retard the degradation of dopaminergic neurons. To assess the effects of these existing drugs, we performed the MTS assay using 12 Parkinson's disease drugs and one multikinase inhibitor, SU5416. The addition of 100 nM PD drugs did not prevent cell death after H_2O_2 addition (Fig. S7). This suggests that compound **5** has a different mechanism from that of existing PD drugs.

Summarizing the SARs (methyl scanning, nitrogen scanning, and fluorine scanning), derivatives with high planarity of the A-ring and amide tended to exhibit more potent activity than those with low planarity. A significant decrease in activity was observed when the derivatives were substituted at the 2-position of the A-ring and methylated at the amide moiety, which caused steric hindrance that

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disturbed the planarity of the compounds. The derivatives substituted at the 3- or 4-position of the A-ring, which did not affect or enhance the planarity of the compounds, exhibited high activity. Because both the electron-donating and electron-withdrawing groups at the 4-position of the A-ring showed the desired activity, it is suggested that the planarity of the compounds, rather than the electron distribution on the A-ring, contributes to the activity (Fig. S6-3). Moreover, the introduction of substituents on the B or C rings, except at the 8-position of the C ring, resulted in the loss of activity or only weak activity at 100 nM (Fig. S4, S6-1, and S6-2). The introduction of substituents on the B ring at the para- or meta-position, such as in compound **S4**, did not affect the cell-protective activity (Fig. S3). Consequently, derivatives that were unsubstituted or substituted with a methyl group at the 8-position of the C ring exhibited high activity.

Because the configuration of the compounds is critical for their activity, the planarity of the derivatives affects their interaction with the target protein. In contrast, modifications of the A ring showed insignificant effects on activity, suggesting that there is space around the A ring. In addition, the reverse amide (compound **S10**) or alkylated amide diminished the activity by more than 100-fold, suggesting that the amide was used to form an important interaction (Fig. S6-1). Furthermore, there is presumed to be a small space around position 8 on the C ring, whereas other positions on the C ring may fit the target-binding site. Thus, identifying its target is important for understanding the detailed mechanisms of PD pathogenesis and for developing new PD drugs.

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Conflicts of interest

There are no conflicts to declare.

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Supplementary material for

Beneficial effects of a new neuroprotective compound in neuronal cells and MPTP-administered mouse model of Parkinson's disease

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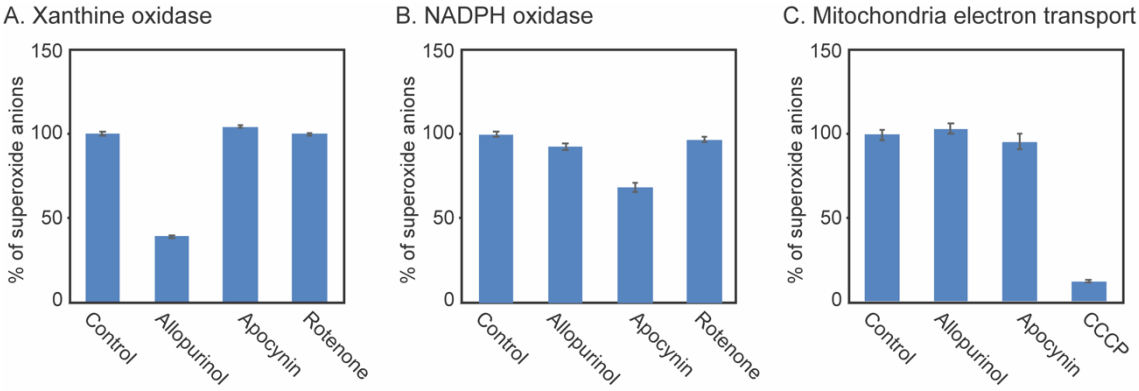
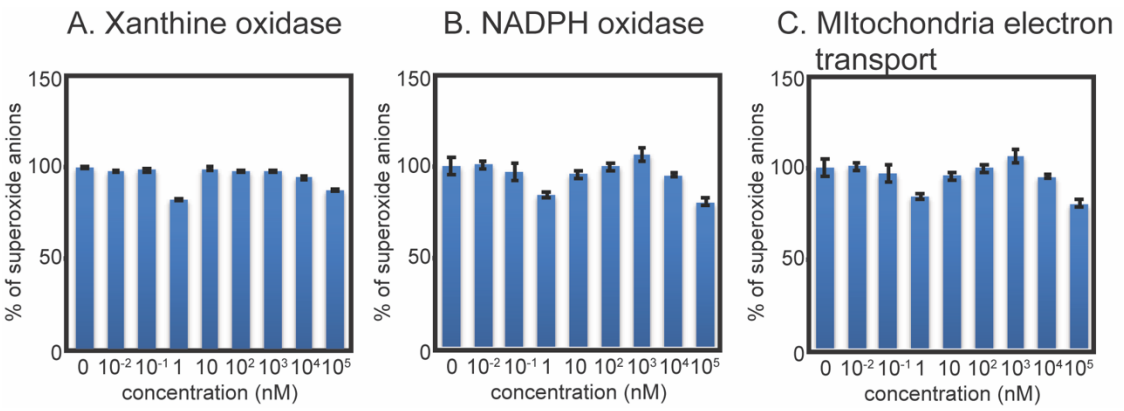
Contents

Additional file 1: Supplemental Fig. 1



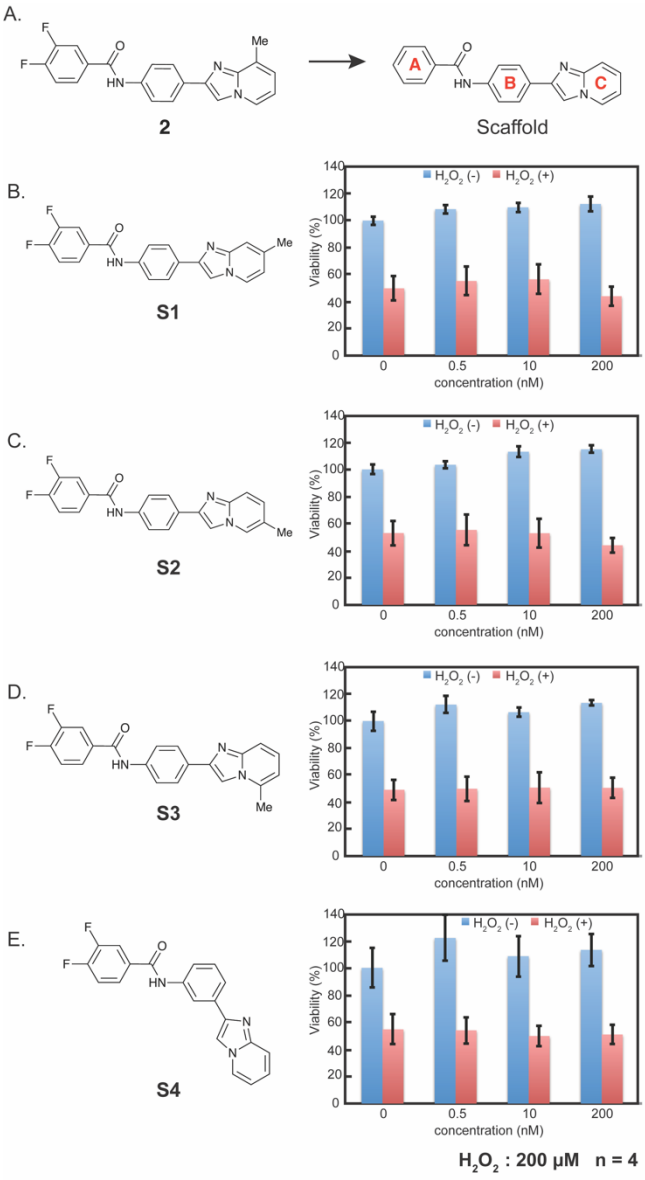
Confirmation of the evaluation system using allopurinol, apocynin, and rotenone/carbonyl cyanide 3-chrolophenylhydrazone (CCCP). The antioxidant effect was measured using the xanthine oxidase system (A), NADPH oxidase system (B), and mitochondria electron transport system (C), with an inhibitor concentration of 100 μM. The amount of ROS generated in the DMSO-added control was taken as 100%. Commercially available recombinant xanthine oxidase (A), membrane fraction protein of rat heart (B) and isolated mitochondria from rat liver (C) were used for the experiments, respectively. Because NADPH oxidase is a main source of ROS in the heart, we used the membrane fraction protein of rat heart as a source of NADPH oxidase. Superoxide anions were detected by MPEC- (A), lucigenin- (B) and lucigenin- (C) amplified chemiluminescence, respectively.

Additional file 2: Supplemental Fig. 2



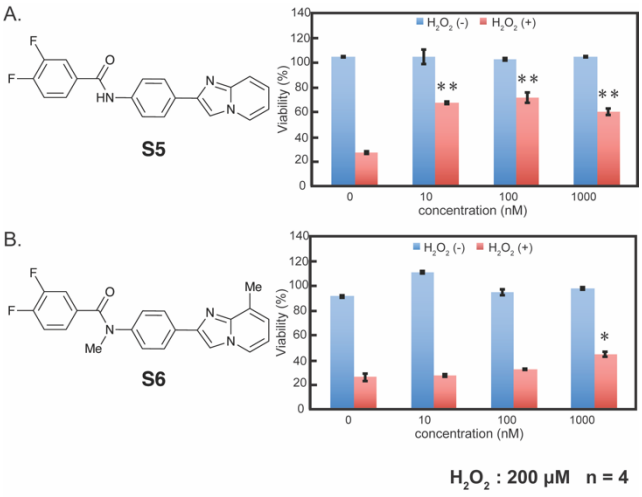
The antioxidant effect of compounds was measured by assessing their ability to scavenge superoxide anions. The antioxidant effect was measured, as shown in Fig. S1.

Additional file 3: Supplemental Fig. 3



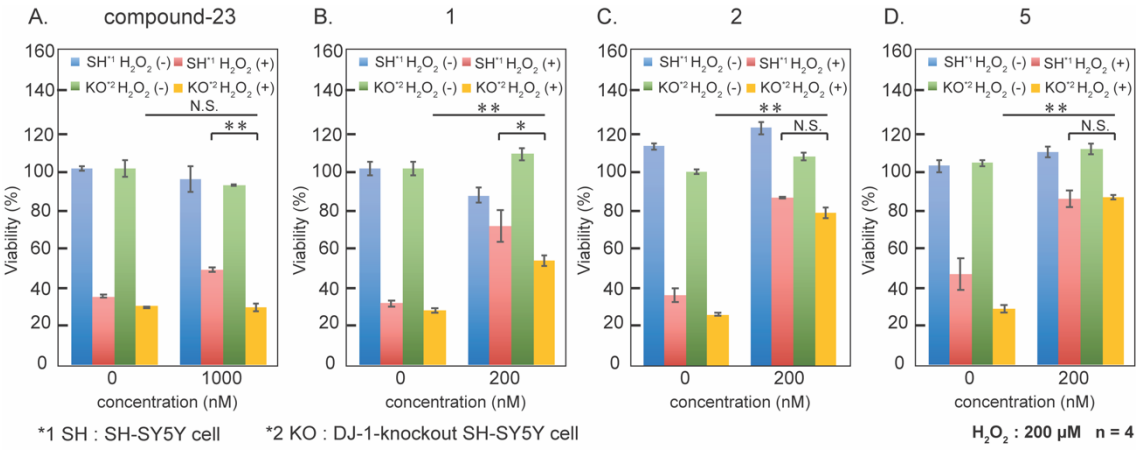
Introduction of an alkyl group on the benzene ring decreases the cell-protective activity. These compounds **S1**–**S4** lost their cell protective effects after the addition of H_2O_2 (200 μM), with the methyl group repositioned on the benzene ring. (A) The scaffold of **2** contains the three aromatic rings defined as A, B, and C ring, respectively. (B–E) Cell viability was measured using the MTS assay, as shown in Fig. 1. The number of experiments (*n*) was 4.

Additional file 4: Supplemental Fig. 4



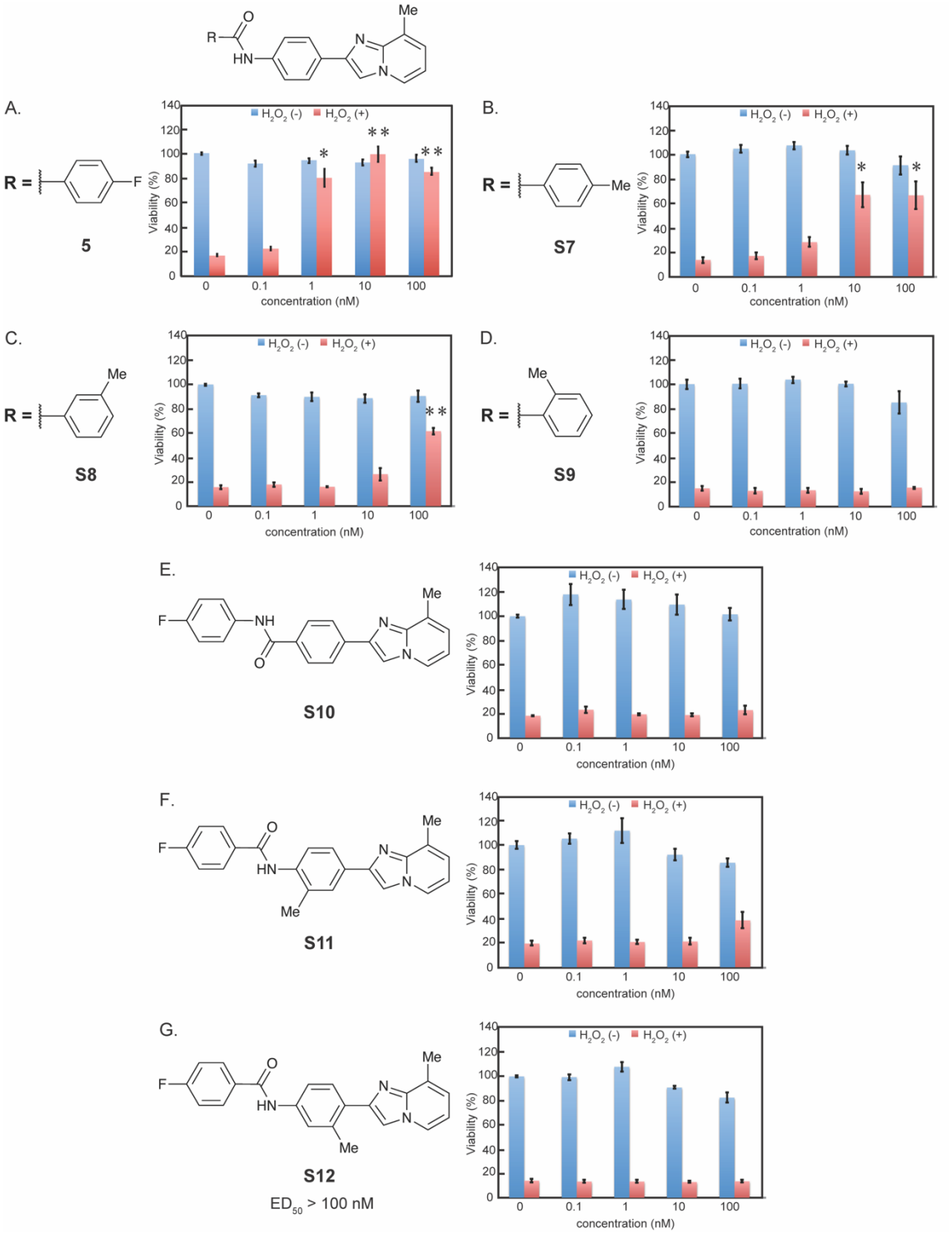
Introduction of a methyl group to the amide moiety decreases the cell-protective activity. The compounds lost their cell-protective effects after the addition of H_2O_2 (200 μM) due to the incorporation of a methyl group at the amide bond. (A-E) Cell viability was measured using the MTS assay, as shown in Fig. 1. Significance: **p* < 0.01, ***p* < 0.001 versus only H_2O_2 (200 μM) treated cells. The number of experiments (*n*) was 4.

Additional file 5: Supplemental Fig. 5

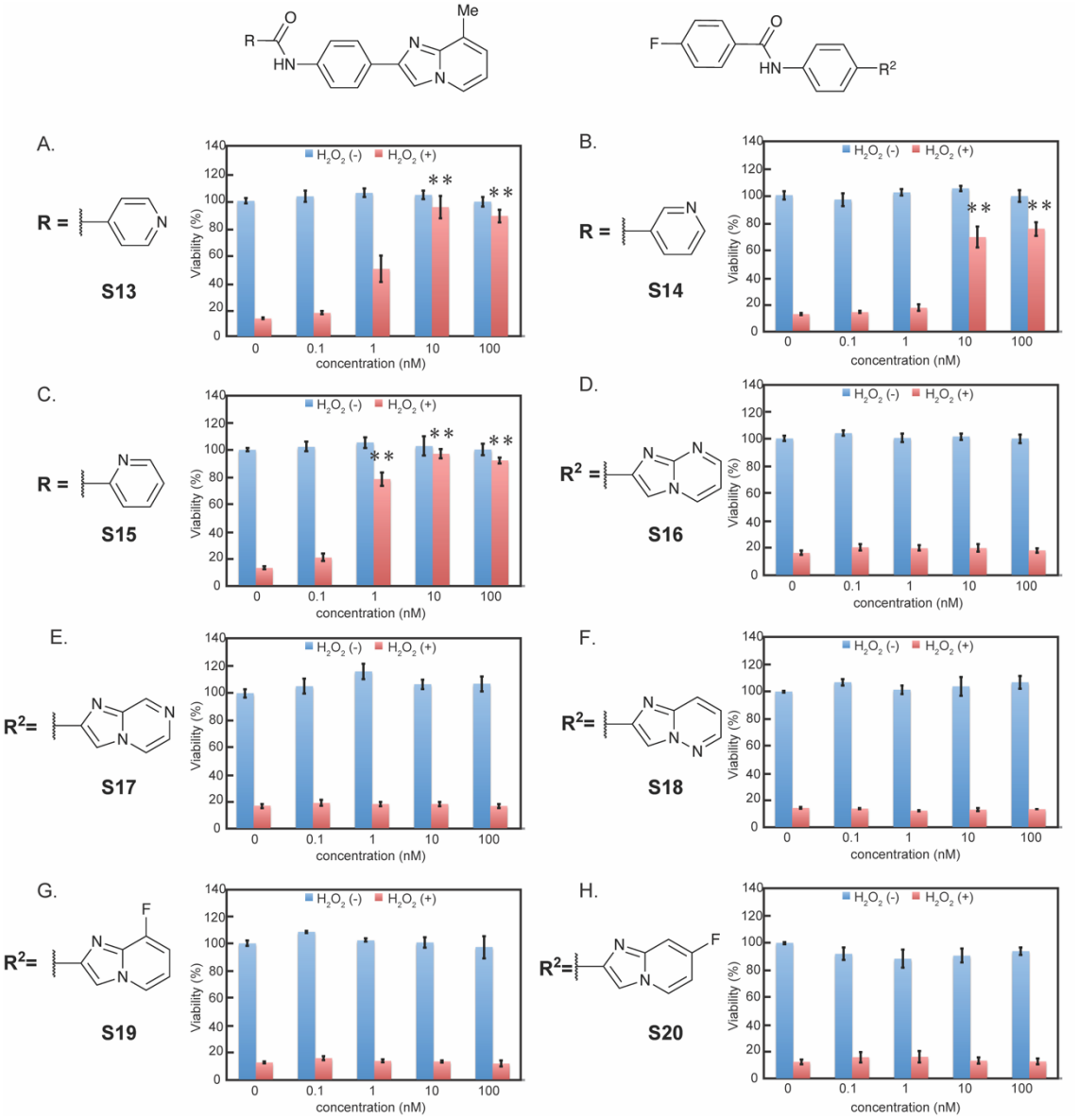


Contribution of DJ-1 to cell protective activity. DJ-1-knockout SH-SY5Y cells treated with compounds **2** and **5** demonstrate protective properties against H_2O_2 (200 μM). (A-D) Cell viability was measured using the MTS assay, as shown in Fig. 1. The values shown in panels mean ± SE (n = 4). Significance: *$p < 0.01$, **$p < 0.001$ versus only H_2O_2 (200 μM) treated cells. N.S. indicates no significance.

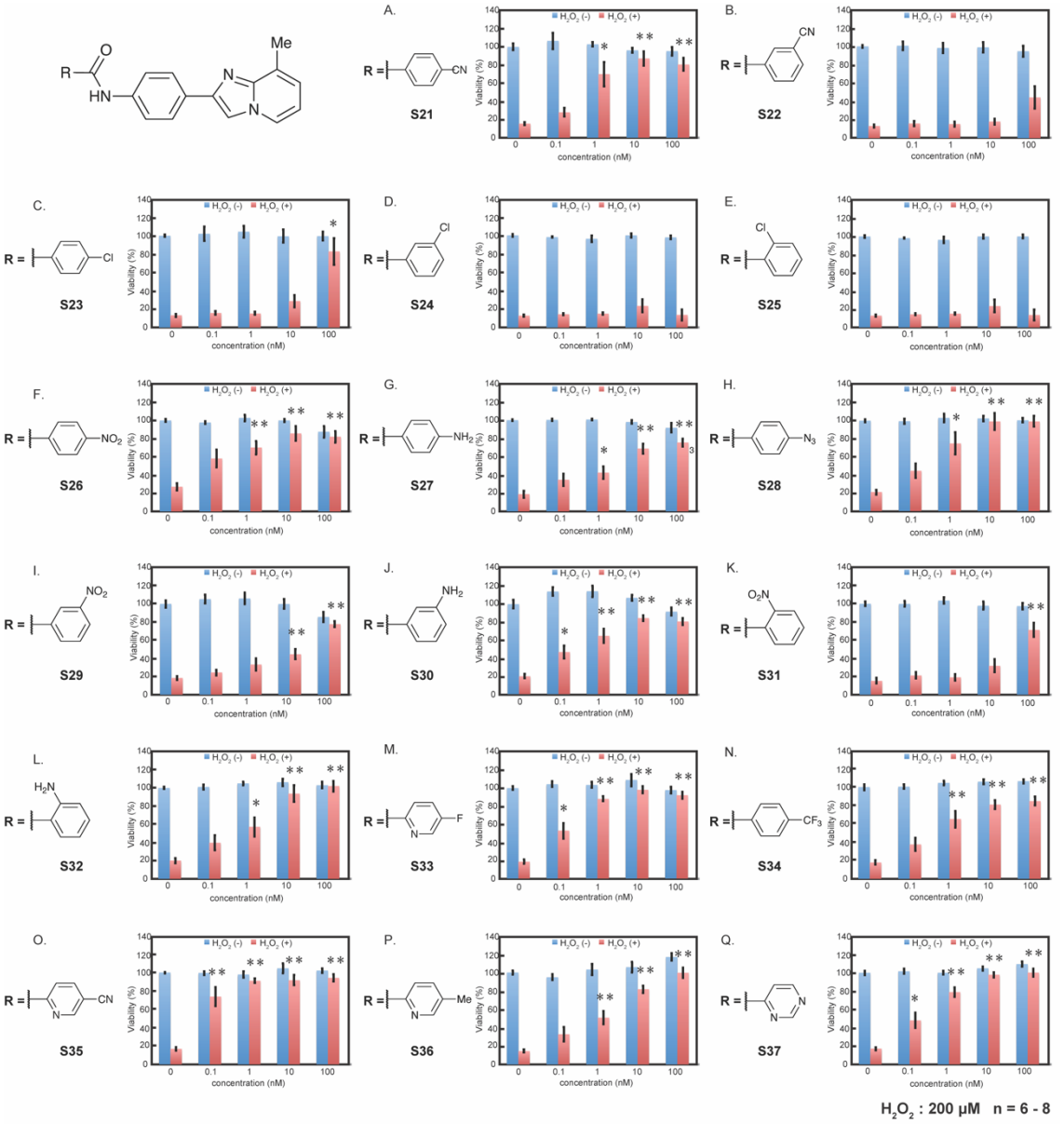
Additional file 6: Supplemental Fig. 6-1



Additional file 6: Supplemental Fig. 6-2

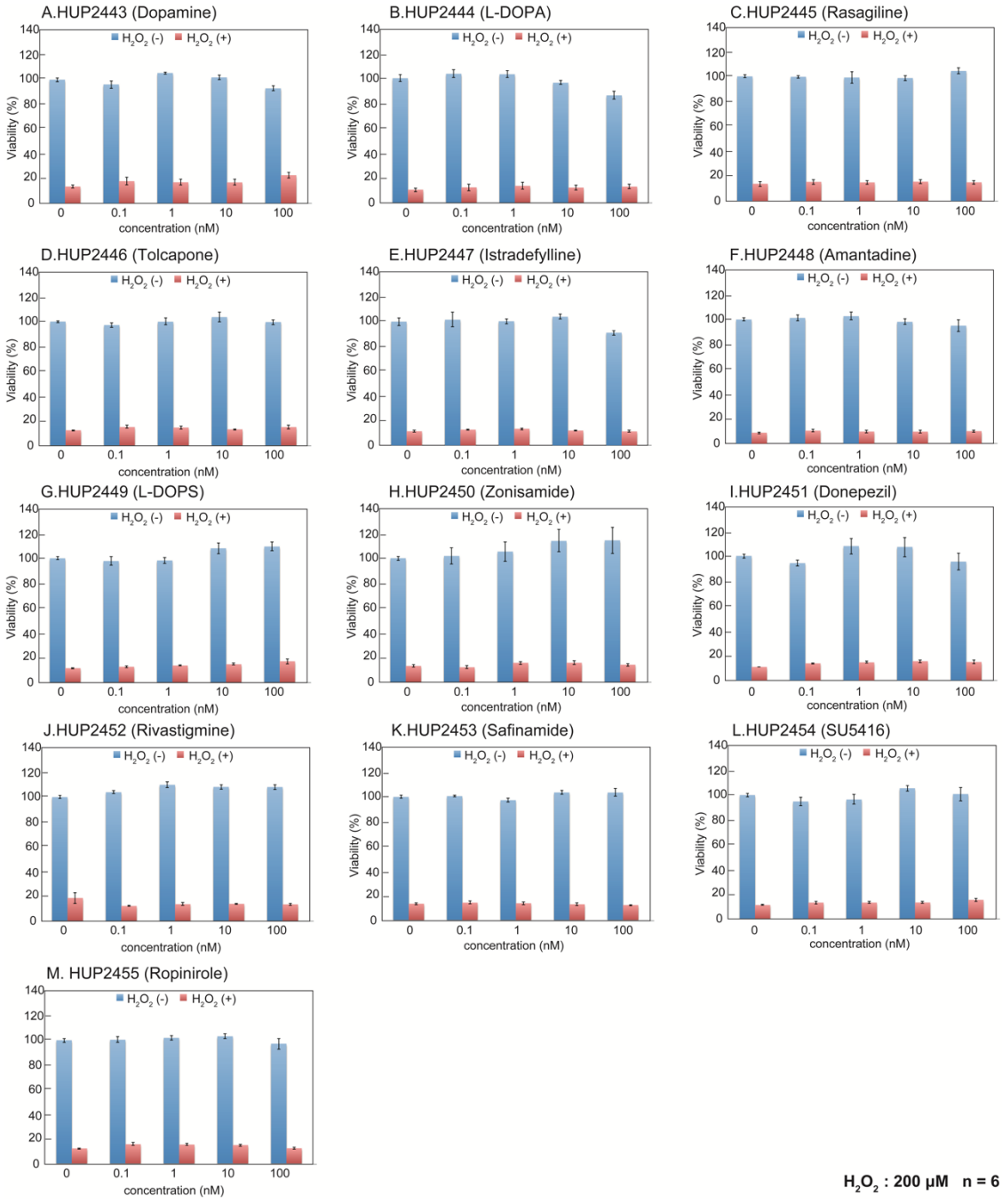


Additional file 6: Supplemental Fig. 6-3



New compounds developed based on compound 5. We synthesized new compounds to investigate their structure–activity relationships, as shown in Supplemental Fig. 6-1. Methyl scanning of compound **5** was performed along with nitrogen and fluorine scanning, as described in Supplemental Fig. 6-2 and 6-3, respectively. Various aromatic groups were tested as the A ring. Whole-cell viability was measured using the MTS assay, as described in Fig. 1. Significance: $*p < 0.01$, $**p < 0.001$ versus only H_2O_2 (200 μM) treated cells. The number of experiments (n) was 6–8.

Additional file 7: Supplemental Fig. 7



The effects of twelve existing drugs for Parkinson's disease and a multikinase inhibitor SU5416. (A–M) Cell viability was measured using the MTS assay, as described for Fig. 1. The number of experiments (*n*) was 6.

Additional file 8: Supplemental Table. 1

Table S1. The pharmacokinetic tests of 11 compounds

	Liver microsomal Stability	
Compound #	human LM *1 remained (%)	mouse LM *1 remained (%)
4	86	64
5	81	44
2	74	52
6	84	57
7	89	74
8	73	74
S5	82	72
S6	98	5
S7	68	29
S13	97	65
S21	94	47
S33	90	20
S35	87	47
Verapamil *2	26	22
Diltiazem *2	77	14

*1 LM : Liver microsomal *2 : Positive control

Additional file 9: Supplemental Table. 2

Table S2. The pharmacokinetic tests of 11 compounds

		CYP Inhibition					
Compound #	precipitation concentration (μM)	CYP1A2 inhibition IC_{50} (μM) Pre*2 (-) Pre*2 (+)	CYP2C9 inhibition IC_{50} (μM) Pre*2 (-) Pre*2 (+)	CYP2C19 inhibition IC_{50} (μM) Pre*2 (-) Pre*2 (+)	CYP2D6 inhibition IC_{50} (μM) Pre*2 (-) Pre*2 (+)	CYP3A4 inhibition IC_{50} (μM) Pre*2 (-) Pre*2 (+)	MBI *1
4	>50	>50 >50	28 29	>50 >50	>50 >50	>50 18	+
5	>10	>10 >10	>10 >10	>10 >10	>10 >10	>10 >10	-
2	>10	>10 >10	>10 >10	>10 >10	>10 >10	>10 >10	-
6	>10	>10 >10	>10 >10	>10 >10	>10 >10	>10 >10	-
7	>10	>10 >10	>10 >10	>10 >10	>10 >10	>10 >10	-
8	>10	>10 >10	>10 >10	>10 >10	>10 >10	>10 >10	-
S5	>50	>50 7.0	>50 >50	>50 >50	>50 >50	>50 >50	+
S6	>50	>50 46	6.0 6.9	6.7 9.4	>50 33	40 25	±
S7	>10	>50 >50	18 31	n/a >50	>50 >50	>50 6.9	+
S13	>50	15 14	49 >50	>50 >50	19 19	2.1 1.9	-
S21	>10	>50 >50	>50 >50	n/a >50	>50 >50	>50 42	±
S33	>10	>50 >50	>50 >50	>50 >50	>50 >50	>50 >50	±
S35	>5	>5 >5	>5 >5	>5 >5	>5 >5	>5 >5	±

*1 MBI : Mechanism-based inhibition *2 Pre : Preincubation

The pharmacokinetic tests of eleven compounds. Cytochrome P450 (CYP) inhibition was measured. The MBI criterion was as follows: an IC_{50} ratio for inhibition with and without preincubation of 3 or more was labeled as "+", and a ratio of inhibition pre (+)/pre (–) of 0.8 or less at an added concentration of 50 μM, even if IC_{50} was 50 μM or more, was labeled as "±".

Additional file 10: Supplemental Table. 3

Table S4. The pharmacokinetic tests of 11 compounds

Permeability

Compound #	PAMPA pH at 5.0 Permeability (10^{-6} cm/sec)	PAMPA pH at 5.0 Retension (%)	PAMPA pH at 7.4 Permeability (10^{-6} cm/sec)	PAMPA pH at 7.4 Retension (%)
4	27.9 ± 0.6	14 ± 2	51.6 ± 10.3	18 ± 4
5	30.9 ± 0.9	16 ± 3	38.0 ± 2.4	5 ± 4
2	39.5 ± 2.7	24 ± 4	21.7 ± 2.4	0 ± 0
6	28.7 ± 0.8	13 ± 2	20.8 ± 1.6	1 ± 1
7	39.9 ± 6.2	16 ± 3	69.4 ± 2.7	5 ± 5
8	34.9 ± 5.0	15 ± 6	13.7 ± 0.5	5 ± 1
S5	35.7 ± 2.4	10 ± 4	32.3 ± 1.6	1 ± 2
S6	33.4 ± 0.6	13 ± 2	43.3 ± 7.7	17 ± 3
S7	45.4 ± 2.2	33 ± 3	20.0 ± 0.9	3 ± 3
S13	28.8 ± 1.6	6 ± 2	46.0 ± 2.2	0 ± 0
S21	21.3 ± 0.5	7 ± 0	12.2 ± 1.3	2 ± 2
S33	42.0 ± 1.2	6 ± 5	22.7 ± 4.8	13 ± 3
S35	n/a	n/a	n/a	n/a

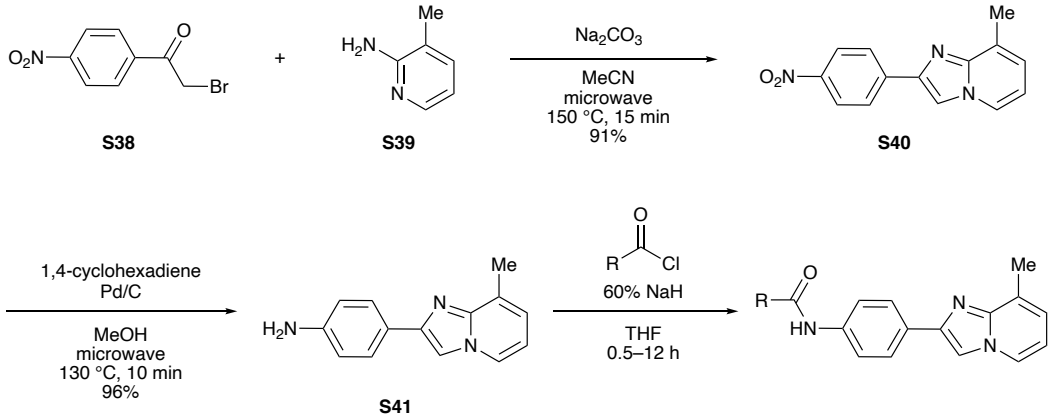
Solubility

Compound #	MW *1	ED_{50} (nM)	Solubility FaSSIF (μg/mL)	Solubility FaSSIF (μM)	Ratio of solubility and ED_{50} (fold)
4	327	1-2	3.0	9.17	>4585
5	345	0.2	1.0	2.90	14493
2	363	0.5	0.2	0.55	1102
6	345	2-5	1.0	2.90	>580
7	345	2-5	0.6	1.74	>348
8	363	2-5	1.0	2.75	>550
S5	349	1-2	2.0	5.73	>2865
S6	377	35% (100 nM)	32.0	84.88	-
S7	341	1-10	3.0	8.80	>880
S13	328	1-10	4.0	12.20	>1220
S21	352	0.1-1.0	0.5	1.42	>1420
S33	346	0.1-1.0	1.0	2.89	>2890
S35	353	<0.1	n/a	-	-

*1 MW : Molecular weight

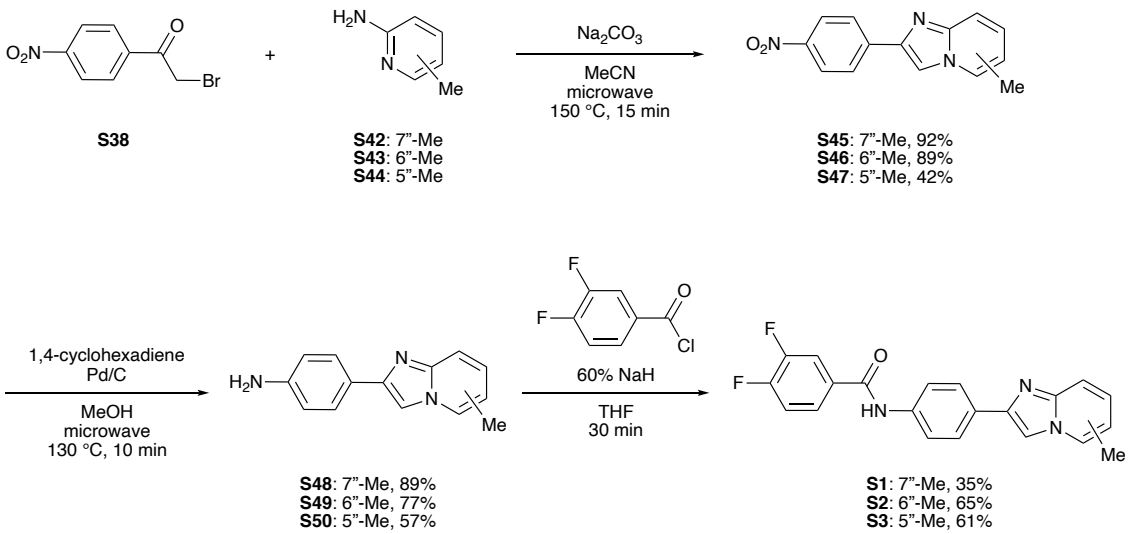
Additional file 11: Supplemental Schemes S1–S11.

Scheme S1.

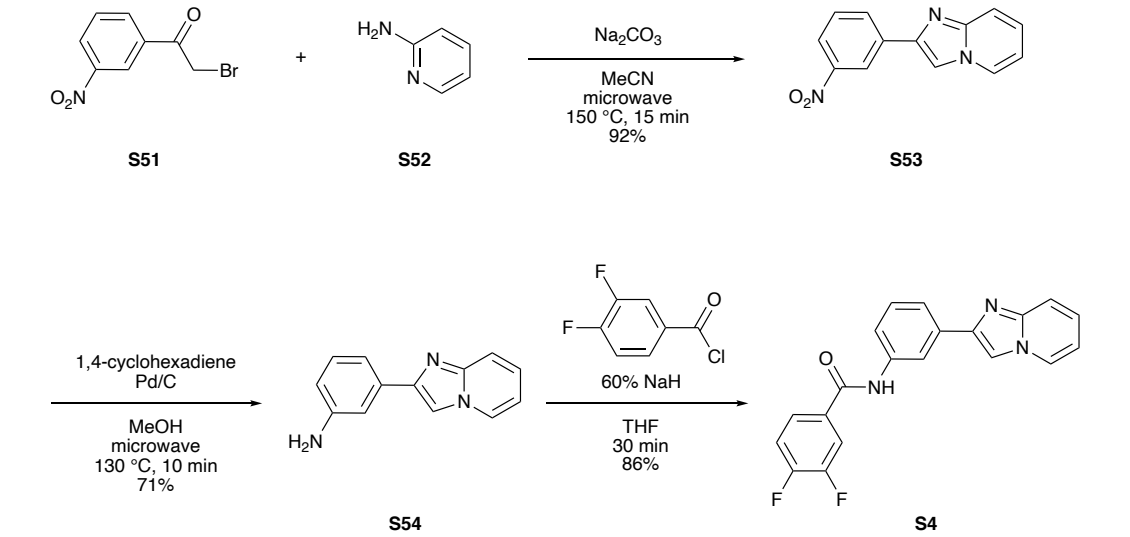


1	86%	**S7**	76%	**S23**	99%
2	68%	**S8**	38%	**S24**	65%
3	58%	**S9**	28%	**S25**	45%
4	52%	**S13**	60%	**S26**	73%
5	38%	**S14**	17%	**S28**	80%
6	43%	**S21**	55%	**S29**	69%
7	62%	**S22**	quant.	**S34**	65%
8	72%				

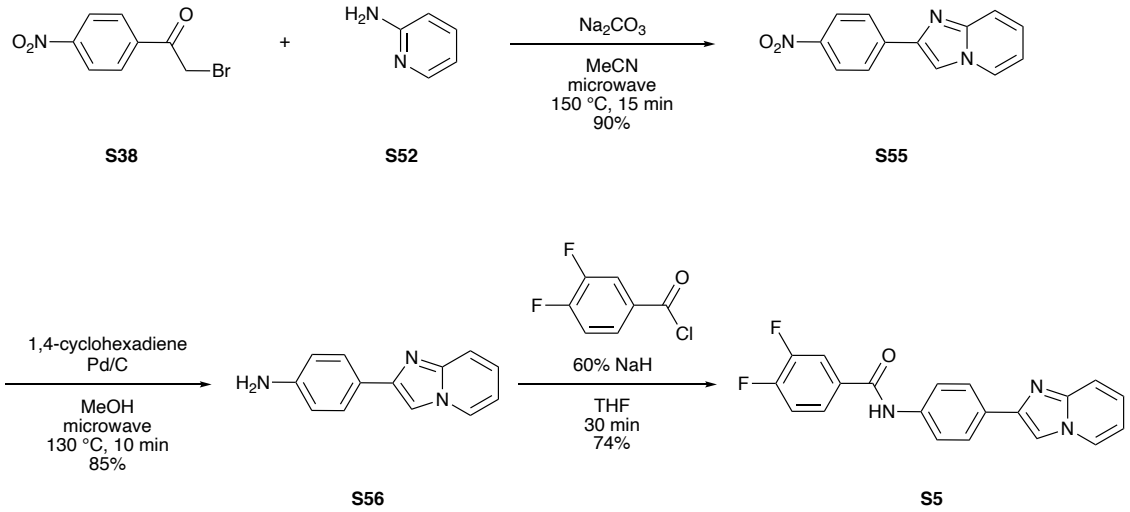
Scheme S2.



Scheme S3.

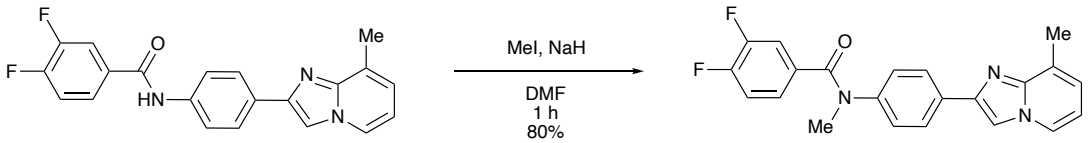


Scheme S4.



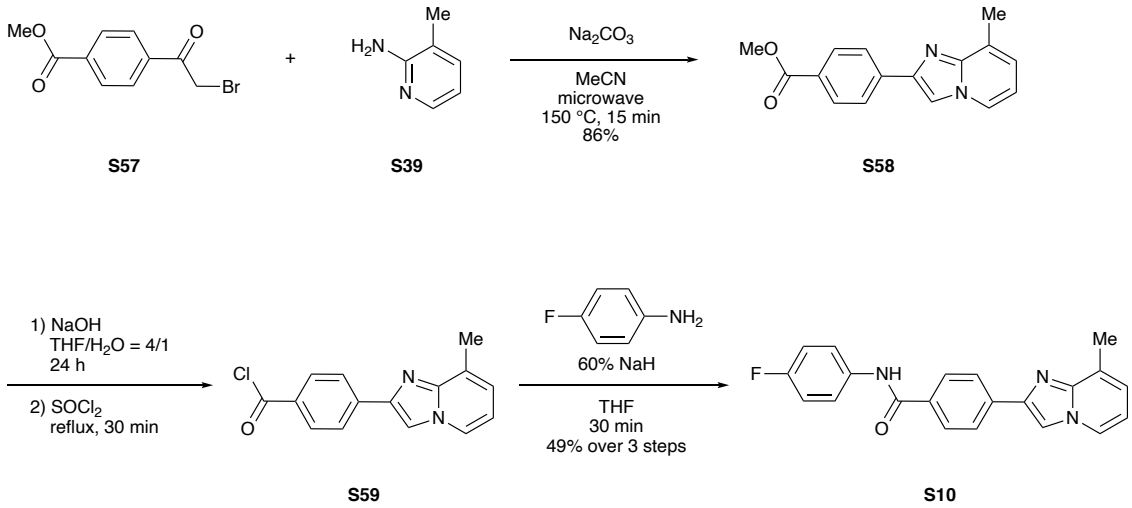
S38 **S52** **S55** **S56** **S5**

Scheme S5.

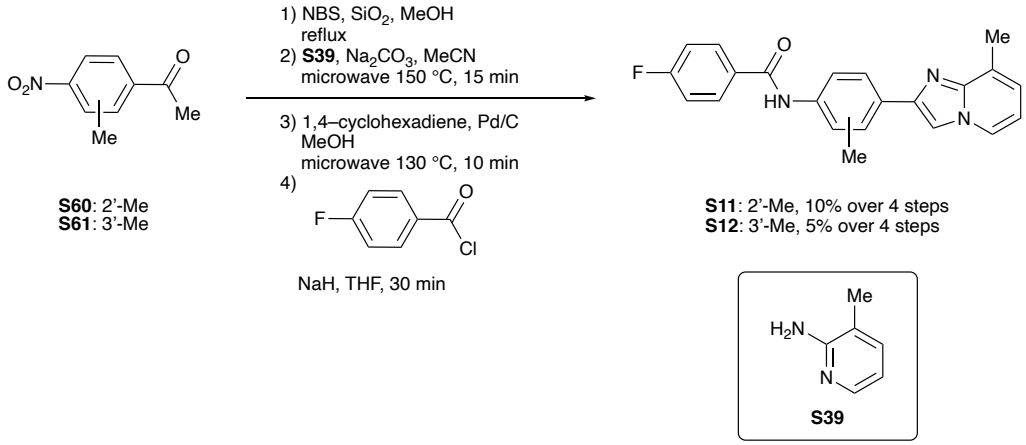


2 **S6**

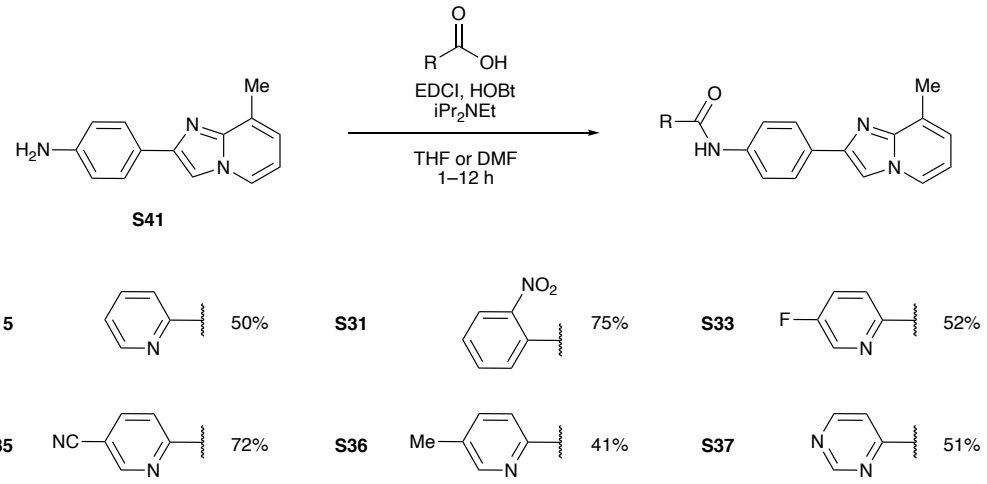
Scheme S6.



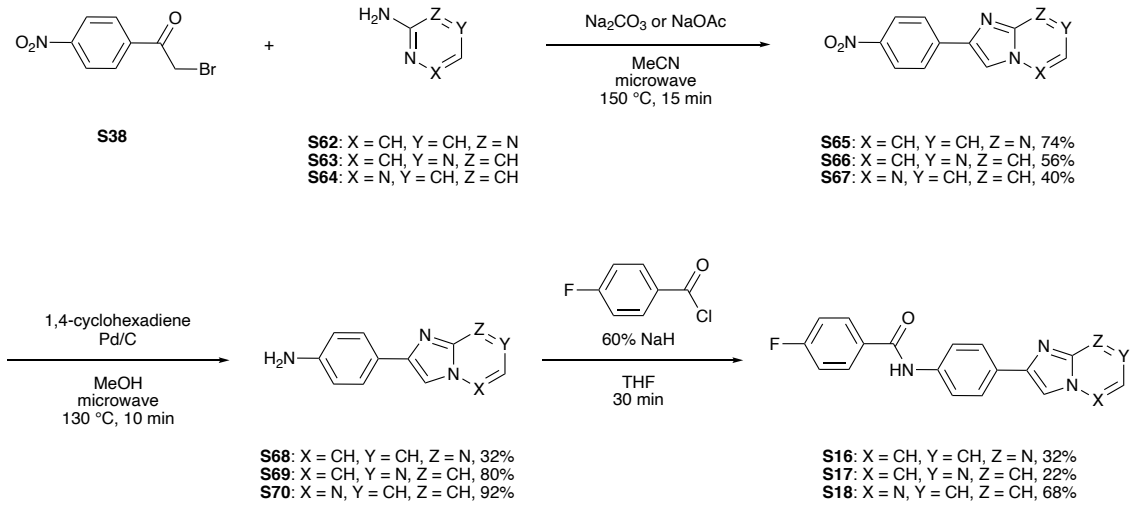
Scheme S7.



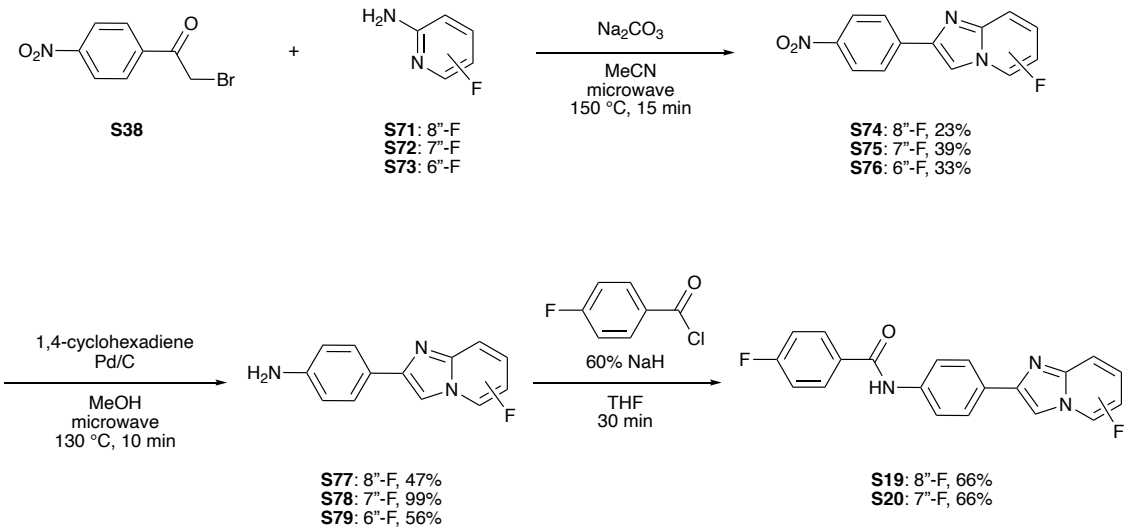
Scheme S8.



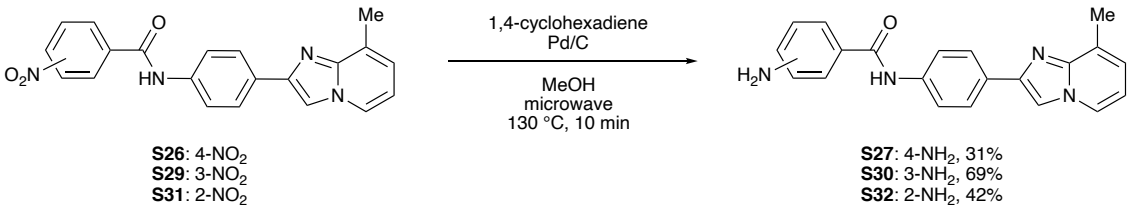
Scheme S9.



Scheme S10.



Scheme S11.



1. General experimental methods

All reactions except those carried out in aqueous phase were performed under an inert atmosphere of argon or nitrogen, unless otherwise stated. Materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. All microwave-assisted reactions were carried out under microwave irradiation conditions by using Biotage Initiator. All reactions requiring heating were heated by using SynFlex. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Flash column chromatography was performed Biotage Isolera Prime using a SNAP cartridge (Biotage). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III HD 500 MHz, JEOL NMM-EC500, JNM-ECX400P, or JNM-ECX400 spectrometer and were calibrated using residual undeuterated solvent as the internal references ($CDCl_3$: 7.26 ppm; CD_3OD: 3.31 ppm; DMSO-d_6: 2.50 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. Coupling constant (*J*) was reported in hertz (Hz). Mass spectra were obtained on Waters SQ Detector2.

Cell culture

SH-SY5Y cells and DJ-1-knockout SH-SY5Y cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum at 37 °C. DJ-1-knockout SH-SY5Y cells were established as described previously (T. Niki, J. Endo, K. Takahashi-Niki, T. Yasuda, A. Okamoto, Y. Saito, H. Ariga, S. M. Iguchi-Ariga. *Brain Res.*, 2020, **1729,** 146641).

Cell viability assay

Cells were cultured in a 96-well plate and treated with various amounts of compounds in the presence of 200 μM hydrogen peroxide (H_2O_2) added to the culture medium. Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt (MTS) assay with a cell counting kit-8 (DOJINDO, Osaka, Japan). The absorbance was measured at 450 nm using a microplate reader (En Spire; Perkin Elmer, Waltham, MA, USA).

Microsomal stability assay

The compound was diluted from a 10 μM stock to 200 nM using 0.65 mM β-NADPH solution. The assay incubation system consisted of the compound and 50 μL of 0.2 mg/mL of human microsomal (mixed sex, pool of 50 liver sample) or mouse microsomal proteins. The incubation was carried out at 37 °C for 35 min with shaking. After incubation, 400 μL of methanol was added to stop the reaction. To adjust the composition of the unreacted group, 50 μL of 0.2 mg protein/mL liver microsome solution was added. The sample was then incubated at −20 °C for 30 min and centrifuged (1830*g*, 10 min, 4 °C). The supernatant was analyzed using LC-MS/MS. HPLC liquid chromatography

system: LC-20A system (Shimadzu); analytical column: Mightysil RP-18GP, 2.0×50 mm, 3 μm (Kanto Chemical); mobile phase: (A) water/acetonitrile/acetic acid (90:10:1, v/v/v), (B) water/acetonitrile/acetic acid (20:80:1, v/v/v), 0.3 mL/min; tandem mass spectrometer: API 4000 (ESI), AB Sciex Pte. Ltd., Singapore; scan type: multiple reaction monitoring (MRM), *m*/*z* of precursor ions (Q1) and product ions (Q3) of each compound were monitored.

CYP inhibition test

The substrate cocktail contained 10 mM phenacetin, 0.6 mM bupropion hydrochloride, 0.4 mM amodiaquine dihydrochloride, 2 mM diclofenac sodium, 8 mM (*S*)-mephenytoin, 1 mM bufuralol, and 0.5 mM midazolam. The DI inhibition mixture contained 0.2 mM α-naphthoflavone, 30 mM quercetin dihydrate, 3 mM sulphaphenazole, 2 mM (*S*)-(+)- *N* -3-benzylnirvanol, 0.6 mM quinidine anhydride, and 0.2 mM ketoconazole. The mechanism-based inhibition (MBI) mixture contained 1 mM furafylline, 20 mM suprofen, 6.8 mM ticlopidine hydrochloride, 1 mM paroxetine hydrochloride, and 200 mM erythromycin. The microsomal mixture contained 0.125 M phosphate buffer (pH 7.4), 4.125 mM magnesium chloride solution, and 0.05 mg protein/mL human liver microsomal. To prepare the samples, 5 μL of the test compound solution was mixed with 295 μL of the microsome-buffer mixture. After mixing, 30 μL of the preparation sample and 50 μL of the microsomal mixture were incubated at 37 °C for 5 min. For the preincubation (-) group, 10 μL of the substrate cocktail was added, whereas for the preincubation (+) group, 10 μL of the 13 mM β-NADPH solution was added, and the mixture was incubated at 37 °C for 30 min. For the preincubation (-) group, 10 μL of 13 mM β-NADPH solution was added, whereas for the preincubation (+) group, 10 μL of the substrate cocktail was added, and the mixture was incubated at 37 °C for 10 min. The incubation was stopped by adding 50 μL of methanol and 10 μL of internal standard solution, followed by further addition of 250 μL of methanol. The samples were then centrifuged (1830*g*, 10 min, 4 °C) and the supernatant was analyzed using LC/MS/MS (API4000, AB Sciex Pte. Ltd., Singapore). The residual activity rate was calculated using the metabolite-IS area ratio in each well and the metabolite-IS area ratio in the control group. The IC_{50} values were calculated from the concentration plot. MBI (+) was assessed if the change in the IC_{50} value due to preincubation was 3-fold or more. MBI (+/-) was assessed if the IC_{50} value changed 2–3 times due to preincubation or if the preincubation (+)/preincubation (-) ratio was less than 0.8.

PAMPA permeability method

The test compound (10 mmol/L) was diluted 200-fold with 5% dimethyl sulfoxide (DMSO) solution (pH 7.4 or 5.0) (pION Inc., Billerica, MA). The 200-fold diluted solution was centrifuged at 2200*g* for 10 min at 17 °C, and the supernatant was collected and used as the test compound solution. Next, 150 μL of the prepared test compound solution was added to the UV measurement plate and the reference spectrum was measured. Two hundred microliter of the test compound solution was added

to each donor plate. Subsequently, 4 μL of GIT-0 lipid (pION Inc.) was applied to each filter of the acceptor plate, and 200 μL of ASB-7.4 acceptor sink buffer (pION Inc.) was added to the acceptor plate. The acceptor plate was placed on the donor plate and incubated at 20 °C for 4 hours. After incubation, 150 μL of the solution in acceptor and donor plates were sampled on the UV measurement plate, and the acceptor and donor spectra were measured using a UV plate reader (SpectraMax 190, Molecular Devices, San Jose, CA). If the spectrum of the compound was not observed, the concentration of the test compound on each UV measurement plate was measured using LC-MS (G1956B, Agilent, Santa Clara, CA). Finally, the membrane permeability coefficient (Pe) was calculated from the measurement results using the parallel artificial membrane permeability assay (PAMPA) software.

Solubility

Permeability was measured in fasting-state simulated intestinal fluid (FaSSIF) medium. The compound was evaporated to dryness at 40 °C for 90 min. After confirming the dryness of the powder, 3 μL of DMSO was added to dissolve it. Thereafter, 300 μL of FaSSIF was added to the mixture, which was shaken for 90 min in a constant temperature shaker at 25 °C and allowed to stand at the same temperature for 16 hours or longer. The sample was then centrifuged at 2500 × *g* for 15 min at 25 °C, and the supernatant was assayed using UPLC (ACQUITY UPLC®, Waters Inc., Milford, MA).

Administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into mice

Male wild-type C57BL/6J mice (8 weeks of age) were used in this experiment. The mice were purchased from Japan SLC, Inc and habituated to their cages for seven days. The mice were given Compound **5**, mixed with 10% DMSO and 10% 2-hydroxypropyl-beta-cyclodextrin (HPCD) in distilled water, through gavage administration. One hour before the administration of compound **5**, MPTP or saline (negative control) was injected intraperitoneally into the mice. The same combination of injections of **5** and MPTP was administered daily for four days, and rotor-rod tests were conducted five days after the first injection.

Rotarod test

The rotor-rod test was performed using the method described previously[8]. In the present study, groups were divided by a stratified continuous randomization method using the latency after acclimation by rotor-rod as an index, and we used 10 rotor speeds: 3 rpm for 2 min on the first day, 12 rpm for 2 min on the second and third days of the habituation period, and 20 rpm for the experiments using MPTP-administered mice.

Measurement of superoxide anion scavenging activity

Superoxide anions (O_2^-) are generated by the reaction between hypoxanthine and xanthine oxidase. To measure O_2^- in the xanthine oxidase system, we used 7-dihydro-2-methyl-6-(4-methoxy-phenyl) imidazo[1,2-*a*] pyrazin-3-one (MPEC) to induce oxidation. The compound was dissolved in DMSO for further evaluation. Xanthine oxidase and hypoxanthine were prepared in 0.1 M phosphate buffer [0.1 M–KHPO–NaOH (pH 7.5) and 0.05 mM ethylene diamine tetra acetic acid]. The reaction mixture for the O_2^- scavenging activity test comprised 10 μL of the test sample, 10 μL of 300 μM MPEC, 170 μL of phosphate buffer, 60 μL of xanthine oxidase-phosphate buffer (0.1 units/mL) and 50 μL of 0.72 mM hypoxanthine-phosphate buffer. The generation of O_2^- was initiated by the addition of hypoxanthine. The reaction mixture (50 μL) was poured into a 384-well plate (Becton Dickinson, Franklin Lakes, NJ, U.S.A.) and light emission was measured using a Wallac 1420 ARVOsx multilabel counter (Perkin Elmer, Wellesley, MA, USA). Superoxide anions were also generated by the reaction between $NAD(P)^+$ and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Lucigenin was used to measure O_2^- in the NADPH oxidase system. The reaction mixture for the O_2^- scavenging activity test comprised 15 μL of the test sample, 60 μL of 50 μM lucigenin, 15 μL of 2 mM NADPH, 15 μL of 2 mM NADH, and 0.1 M phosphate buffer (pH 11). Three micrograms of membrane fraction protein from the rat heart were added to the reaction solution, the total volume of the mixture was adjusted to 300 μL, and light emission was measured. Using the same method as employed for the measurement in the mitochondria electron transport system, the composition of the reaction solution for the O_2^- scavenging activity test was 3 μL of the test sample, 3 μL of 2 mM lucigenin, 3 μL of 600 mM succinate, 3 μL of 17.8 mM adenosine diphosphate (ADP), 3 μL of 200 mM NADH, 3 μL of 200 mM potassium cyanide, and 0.1 M phosphate buffer (pH 9). Three-hundred micrograms of isolated mitochondria (respiratory control index = 6.68) from rat liver was added to the reaction mixture, the total volume of the mixture was adjusted to 300 μL, and light emission was measured.

Statistical analyses

Data are expressed as mean ± standard error (SE). Statistical analyses were performed using a one-way analysis of variance (ANOVA) followed by an unpaired Student's *t*-test. The Tukey–Kramer test was used to compare multiple samples.

2. Preparation of compounds

General Procedure A: Preparation of imidazo[1,2-*a*]pyridine derivatives.

A mixture of an α-bromoketone derivative (1 equiv.), a 2-aminopyridine derivative (1–2 equiv.), and base (0.7–1 equiv.) in acetonitrile was heated at 150 ℃ under microwave irradiation conditions for 15 min. The reaction was poured into water and the precipitated solid was collected, washed with 50% aq. acetonitrile, and dried *in vacuo* to give imidazo[1,2-*a*]pyridine derivatives.

General Procedure B: Reduction of a nitro group.

A mixture of a nitro derivative (1 equiv.), 1,4–cyclohexadiene (10 equiv.), and 10% Pd/C (10% w/w) in methanol was heated at 130 ℃ under microwave irradiation conditions for 10 min, unless otherwise noted. The reaction was filtered and the residue was dried *in vacuo* to give amine derivatives.

General Procedure C: Amidation using an acid chloride.

A mixture of amine (1 equiv.) and 60% NaH (1.2–2 equiv.) in THF was stirred at ambient temperature for 10 min, then acyl chloride (1 equiv.) was added to the mixture. The whole mixture was stirred at r.t. for 0.5–28 h. The reaction was quenched by addition of sat. NH_4Cl. The mixture was extracted with ethyl acetate and the organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was washed with 20 or 50% ethyl acetate in hexane and dried *in vacuo* to give the desired product.

General Procedure D: Amidation using a carboxylic acid.

A mixture of carboxylic acid (2 equiv.), an amine derivative (1 equiv.), EDCI (2 equiv.), HOBt (2 equiv.), and DIPEA (5.5 equiv.) in DMF or THF was stirred at r.t. for 1 h–4 days. The reaction was poured into water. The water phase was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was washed with 20 or 50% ethyl acetate in hexane and dried *in vacuo* to give the desired product.

Preparation of acid chlorides

A mixture of a benzoic acid derivative in thionyl chloride was heated under reflux for 30–60 min, then the reaction mixture was poured into toluene and concentrated *in vacuo* to give the corresponding acid chloride. The product was used for the next reaction without further purification.

Scheme S1

8-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S40)

Following general procedure A using **S38** (1.0 g, 8.2 mmol), **S39** (561 μL, 4.1 mmol) and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S40** (950 mg, 3.8 mmol) was obtained in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.2 Hz, 2H), 8.13 (d, *J* = 9.2 Hz, 2H), 8.01 (d, *J* = 6.8 Hz, 1H), 7.94 (s, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.74 (t, *J* = 8.5 Hz, 1H), 2.68 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_2N_3O_2^+$ 254, found 254.

8-Methyl-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S41)

Following general procedure B using **S40** (500 mg, 2.0 mmol), 1,4-cyclohexadiene (1.8 mL, 20 mmol) and 10% Pd/C (50 mg), the title compound **S41** (423 mg, 3.8 mmol) was obtained in 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.63 (t, *J* = 7.2 Hz, 1H), 2.64 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{14}N_3^+$ 224, found 224.

3,4,5-Trimethoxy-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (Compound-23)

Following general procedure C using **S41** (48.9 mg, 0.22 mmol), 3,4,5-trimethoxybenzoyl chloride (87.6 mg, 0.36 mmol) and 60% NaH (18.4 mg, 0.46 mmol), the title compound (130 mg) was obtained in 81% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.31 (s, 1H), 8.47 (d, *J* = 6.5 Hz, 1H), 8.45 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 2H), 7.23 (d, *J* = 5.0 Hz, 1H), 6.96 (t, *J* = 6.5 Hz, 1H), 3.90 (s, 6H), 3.75 (s, 3H), 2.58 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 152.6, 144.0, 141.6, 140.4, 139.2, 129.9, 127.5, 126.2, 125.6, 125.2, 125.0, 120.7, 113.4, 109.6, 105.4, 60.1, 56.1, 16.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_3O_4^+$ 418.1761, found 418.1769.

3,4-Dimethoxy-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (1)

Following general procedure C using **S41** (48.9 mg, 0.22 mmol), 3,4-dimethoxybenzoyl chloride (53 mg, 0.26 mmol) and 60% NaH (11 mg, 0.26 mmol), the title compound **1** (73.1 mg, 0.18 mmol) was obtained in 86% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.41 (d, *J* = 6.5 Hz, 1H), 8.38 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.13 (br d, *J* = 6.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.87 (t, *J* = 6.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 151.7, 148.3, 144.6, 139.1, 128.3, 126.9, 126.0, 125.5, 124.8, 124.5, 121.1, 120.5, 112.79, 122.77, 111.05, 110.9, 109.3, 55.68, 55.64, 16.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{22}N_3O_3^+$ 388.1656, found 388.1664.

3,4-Difluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (2)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 3,4-difluorobenzoyl chloride (67 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **2** (49 mg, 0.13 mmol) was obtained in 68% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.38 (d, J = 6.5 Hz, 1H), 8.35 (s, 1H), 8.10−8.05 (m, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.92−7.88 (m, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.65 (dt, J = 10.5, 8.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.81 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.1, 151.5 (dd, $^1J_{(C–F)}$ = 250.4, $^2J_{(C–F)}$ = 12.8 Hz), 149.2 (dd, $^1J_{(C–F)}$ = 245.4, $^2J_{(C–F)}$ = 13.1 Hz), 143.5, 148.2, 145.3, 143.5, 138.3, 132.3, 129.7, 126.0, 125.9, 125.3, 124.6, 123.3, 120.5, 117.6 (d, $^2J_{(C–F)}$ = 17.5 Hz), 117.2 (d, $^2J_{(C–F)}$ = 18.3 Hz), 112.1, 109.2, 16.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 364.1263

2,5-Difluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (3)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 3,5-difluorobenzoyl chloride (67 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **3** (40 mg, 0.11 mmol) was obtained in 58% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.74−7.67 (m, 2H), 7.57−7.50 (m, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.8, 162.2 (dd, $^1J_{(C–F)}$ = 245.6, $^3J_{(C–F)}$ = 12.5 Hz), 145.3, 143.5, 138.5 (t, $^4J_{(C–F)}$ = 8.6 Hz), 138.1, 129.9, 126.0, 125.9, 124.6, 123.3, 120.6, 112.1, 111.3−111.0 (m), 109.2, 107.0 (t, $^2J_{(C–F)}$ = 26.0 Hz), 16.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 364.1261

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (4)**

Following general procedure C using **S41** (85 mg, 0.38 mmol), benzoyl chloride (76 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **4** (73.1 mg, 0.18 mmol) was obtained in 86% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.35 (s, 1H), 8.02−7.96 (m, 4H), 7.89 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.61 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 7.0 Hz, 2H), 7.05 (d, J = 7.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.5, 145.3, 143.6, 138.7, 135.0, 131.6, 129.5, 128.4, 127.7, 126.0, 125.8, 124.5, 123.3, 120.4, 112.1, 109.1, 16.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{18}N_3O^+$ 328.1444, found 328.1451.

4-Fluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (5)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 4-fluorobenzoyl chloride (60 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **5** (30 mg, 0.09 mmol) was obtained in 38% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.35 (s, 1H), 8.36 (d, J = 6.5 Hz, 1H), 8.33 (s, 1H), 8.09−8.04 (m, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.38 (t, J = 8.5 Hz, 2H), 7.05 (d, J = 7.0 Hz, 1H), 6.78 (t, J = 7.0 Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.1, 164.1 (d, $^1J_{(C–F)}$ = 247.5 Hz), 145.3, 143.6, 138.5, 131.4 (d, $^4J_{(C–F)}$ = 2.8 Hz), 130.4 (d, $^3J_{(C–F)}$ = 9.0 Hz), 129.5, 126.0, 125.8, 124.5, 123.3, 120.5, 115.3 (d, $^2J_{(C–F)}$ = 21.6 Hz), 112.1, 109.1, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{21}H_{17}FN_3O^+$ 346.1350, found 346.1361.

3-Fluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (6)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 3-fluorobenzoyl chloride (60 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **6** (34 mg, 0.10 mmol) was obtained in 43% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.38 (d, J = 7.0 Hz, 1H), 8.35 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.90−7.79 (m, 4H), 7.64−7.58 (m, 1H), 7.50−7.44 (m, 1H), 7.05 (dt, J = 7.0, 1.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.1, 161.9 (d, $^1J_{(C–F)}$ = 242.6 Hz), 145.3, 143.6, 138.3, 137.2 (d, $^3J_{(C–F)}$ = 6.8 Hz), 130.6 (d, $^3J_{(C–F)}$ = 8.0 Hz), 129.7, 126.0, 125.9, 124.5, 123.9 (d, $^3J_{(C–F)}$ = 2.6 Hz), 123.3, 120.5, 118.5 (d, $^2J_{(C–F)}$ = 21.3 Hz), 114.5 (d, $^2J_{(C–F)}$ = 22.6 Hz), 112.1, 109.1, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{21}H_{17}FN_3O^+$ 346.1350, found 346.1359.

2-Fluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (7)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 2-fluorobenzoyl chloride (60 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **7** (30 mg, 0.09 mmol) was obtained in 62% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.38 (d, J = 7.0 Hz, 1H), 8.34 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.73−7.68 (m, 1H), 7.63−7.57 (m, 1H), 7.40−7.33 (m, 2H), 7.05 (dt, J = 7.0, 1.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.7, 158.9 (d, $^1J_{(C–F)}$ = 247.1 Hz), 145.3, 143.5, 138.3, 132.5 (d, $^3J_{(C–F)}$ = 8.3 Hz), 129.9, 129.8 (d, $^2J_{(C–F)}$ = 29.3 Hz), 126.01, 125.96, 125.1 (d, $^3J_{(C–F)}$ = 15.1 Hz), 124.58, 124.54, 123.3, 119.8, 116.2 (d, $^2J_{(C–F)}$ = 21.5 Hz), 112.1, 109.1, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{21}H_{17}FN_3O^+$ 346.1350, found 346.1356.

2,4-Difluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (8)

Following general procedure C using **S41** (85 mg, 0.38 mmol), 2,4-difluorobenzoyl chloride (67 mg, 0.38 mmol) and 60% NaH (18 mg, 0.46 mmol), the title compound **8** (59 mg, 0.21 mmol) was obtained in 72% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.44 (d, J = 6.5 Hz, 1H), 8.42 (s, 1H), 8.00 (d, J = 9.0 Hz, 2H), 7.86−7.76 (m, 3H), 7.48−7.41 (m, 1H), 7.25 (td, J = 8.5, 2.0 Hz, 1H), 7.15 (d, J = 6.5 Hz, 1H), 6.89 (t, J = 6.5 Hz, 1H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.4 (dd, $^1J_{(C–F)}$ = 248.1, $^3J_{(C–F)}$ = 12.3 Hz), 161.9, 159.6 (d, $^1J_{(C–F)}$ = 250.6, $^3J_{(C–F)}$ = 12.9 Hz), 144.5, 142.2, 138.6, 131.9−131.6 (m), 128.5, 126.2, 125.5, 124.9, 124.7, 121.8−121.5 (m), 119.9, 112.9, 112.0−111.7 (m), 109.1, 104.7 (t, $^2J_{(C–F)}$ = 26.1 Hz), 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 346.1269.

4-Methyl-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S7)

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 4-methylbenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S7** (52 mg, 0.15 mmol) was obtained in 76% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.24 (s, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.33 (s, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.0 Hz, 1H), 6.80 (t, J = 6.5 Hz, 1H), 2.54 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.4, 145.2, 143.6, 141.6, 138.8, 132.1, 129.2, 128.9, 127.7, 125.9, 125.8, 124.5, 123.4, 120.4, 112.2, 109.1, 21.0, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O^+$ 342.1601, found 342.1613.

3-Methyl-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S8)

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 3-methylbenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S8** (26 mg, 0.076 mmol) was obtained in 38% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.29 (s, 1H), 8.36 (d, J = 7.0 Hz, 1H), 8.33 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.81−7.75 (m, 2H), 7.45−7.38 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.78 (t, J = 7.0 Hz, 1H), 2.54 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.6, 145.3, 143.7, 138.7, 137.7, 135.0, 132.1, 129.4, 128.3, 128.1, 126.0, 125.8, 124.8, 124.5, 123.3, 120.4, 112.1, 109.1, 21.0, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O^+$ 342.1601, found 342.1611.

2-Methyl-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S9)

Following general procedure C using **S41** (29 mg, 0.13 mmol), 2-methylbenzoyl chloride (17 uL, 0.13

mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S9** (13 mg, 0.037 mmol) was obtained in 28% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.38 (s, 1H), 8.36 (d, J = 7.0 Hz, 1H), 8.32 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.42−7.27 (m, 3H), 7.04 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 167.8, 145.3, 143.6, 138.8, 137.2, 135.2, 130.5, 129.6, 129.3, 129.2, 127.2, 126.0, 125.9, 125.6, 124.5, 123.3, 112.1, 109.1, 19.3, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O^+$ 342.1601, found 342.1606.

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)isonicotinamide (S13)**

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), isonicotinoyl chloride (35.6 mg, 0.2 mmol) and 60% NaH (20 mg, 0.5 mmol), the title compound **S13** (40 mg, 0.12 mmol) was obtained in 60% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.79 (d, J = 5.5 Hz, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.35 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.93−7.85 (m, 4H), 7.04 (d, J = 6.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.9, 150.3, 145.3, 143.5, 141.9, 138.1, 139.0, 126.0, 125.9, 124.6, 123.4, 121.6, 120.6, 112.2, 109.3, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{17}N_4O^+$ 329.1397, found 329.1417.

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)nicotinamide (S14)**

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), nicotinoyl chloride (35.6 mg, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S14** (11 mg, 0.04 mmol) was obtained in 17% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.53 (s, 1H), 9.13 (d, J = 1.0 Hz, 1H), 8.77 (d, J = 4.0 Hz, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.32 (dt, J = 8.0, 2.0 Hz, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.58 (dd, J = 8.0, 5.0 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.0, 152.1, 148.7, 145.3, 143.6, 138.3, 135.5, 130.6, 129.8, 126.0, 125.9, 124.6, 123.5, 123.3, 120.5, 112.1, 109.2, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{17}N_4O^+$ 329.1397, found 329.1407.

4-Cyano-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S21)

Following general procedure C using **S41** (1.28 g, 5.74 mmol), 4-cyanobenzoyl chloride (0.95 g, 5.74 mmol), and 60% NaH (344 mg, 8.61 mmol), the title compound **S21** (1.1 g, 3.15 mmol) was obtained in 55% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.57 (s, 1H), 8.37 (d, J = 7.0 Hz, 1H), 8.35 (s, 1H), 8.14 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 6.5 Hz, 1H), 6.80 (t, J = 6.5 Hz, 1H), 2.54 (s, 3H).
^{13}C NMR (125 MHz, DMSO-d_6): δ 164.1, 145.3, 143.5, 139.0, 138.2, 132.5, 129.9, 128.5, 126.0, 125.9, 124.5, 123.3, 120.5, 118.3, 113.8, 112.1, 109.2, 16.7.
HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{17}N_4O^+$ 353.1397, found 353.1410.

3-Cyano-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S22)
Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 3-cyanobenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (20 mg, 0.5 mmol), the title compound **S22** (81 mg, 0.22 mmol) was obtained in quantitative yield.
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.52 (s, 1H), 8.48−8.25 (m, 4H), 8.09 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 6.5 Hz, 1H), 6.81 (t, J = 6.5 Hz, 1H), 2.55 (s, 3H).
^{13}C NMR (125 MHz, DMSO-d_6): δ 163.6, 145.3, 143.5, 142.1, 138.2, 135.9, 135.0, 132.5, 131.3, 129.9, 126.0, 125.9, 124.6, 123.3, 120.5, 118.4, 112.2, 111.5, 109.2, 16.7.
HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{17}N_4O^+$ 353.1397, found 353.1403.

4-Chloro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S23)
Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 4-chlorobenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S23** (72 mg, 0.20 mmol) was obtained in 99% yield.
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.38 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 7.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.54 (s, 3H).
^{13}C NMR (125 MHz, DMSO-d_6): δ 164.4, 145.3, 143.6, 140.6, 138.4, 136.4, 133.6, 129.6, 128.5, 126.0, 125.8, 124.5, 123.3, 120.5, 112.1, 109.1, 16.7.
HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{17}ClN_3O^+$ 362.1055, found 362.1061.

3-Chloro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S24)
Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 3-chlorobenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S24** (47 mg, 0.20 mmol) was obtained in 65% yield.
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.38 (d, J = 6.5 Hz, 1H), 8.35 (s, 1H), 8.05 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.0, 145.3, 143.6, 138.3, 136.9, 133.2, 131.4, 130.3, 129.7, 127.4, 126.5, 126.0, 125.9, 124.6, 123.3, 120.5, 112.1, 109.1, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{17}ClN_3O^+$ 362.1055, found 362.1062.

2-Chloro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S25)

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 2-chlorobenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S25** (33 mg, 0.09 mmol) was obtained in 45% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.37 (d, *J* = 6.5 Hz, 1H), 8.33 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 6.5 Hz, 1H), 6.79 (t, *J* = 6.5 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 145.3, 143.5, 138.4, 127.0, 131.1, 129.9, 129.7, 129.02, 128.96, 127.3, 126.01, 125.97, 124.5, 123.3, 119.7, 112.1, 109.1, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{17}ClN_3O^+$ 362.1055, found 362.1067.

4-Nitro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S26)

Following general procedure C using **S41** (89 mg, 0.4 mmol), 4-nitrobenzoyl chloride (74 mg, 0.4 mmol) and 60% NaH (24 mg, 0.6 mmol), the title compound **S26** (108 mg, 0.29 mmol) was obtained in 73% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.40–8.33 (m, 4H), 8.21 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 6.5 Hz, 1H), 6.79 (t, *J* = 6.5 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.2, 152.2, 145.2, 143.8, 139.3, 129.4, 128.7, 126.0, 125.7, 124.5, 123.2, 121.0, 120.2, 112.6, 112.1, 108.9, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{17}N_4O_3^+$ 373.1295, found 373.1301.

4-Azido-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S28)

Following general procedure C using **S41** (250 mg, 1.12 mmol), 4-azidobenzoyl chloride (203 g, 1.12 mmol) and 60% NaH (88 mg, 2.2 mmol), the title compound **S28** (333 mg, 0.90 mmol) was obtained in 80% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.50 (d, *J* = 6.5 Hz, 1H), 8.50 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.33 (br s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.05 (t, *J* = 6.5 Hz, 1H), 2.60 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.5, 144.4 (br), 142.8, 142.2 (br), 139.0 (br), 131.2, 129.7, 126.1, 125.4 (br), 124.9 (br), 120.5, 119.0, 113.0 (br), 109.4, 16.6 (two aromatic carbons were not found, likely due to peak broadening).

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{17}N_6O^+$ 369.1458, found 369.1462.

3-Nitro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S29)

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 3-nitrobenzoyl chloride (26 μL, 0.2 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S29** (47 mg, 0.20 mmol) was obtained in 65% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.82 (t, J = 1.5 Hz, 1H), 8.47−8.41 (m, 2H), 8.38 (d, J = 6.5 Hz, 1H), 8.35 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.86 (t, J = 8.0 Hz, 1H), 7.06 (d, J = 6.5 Hz, 1H), 6.81 (t, J = 6.5 Hz, 1H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.3, 147.8, 145.2, 143.3, 138.2, 136.3, 134.2, 132.6, 130.2, 129.7, 126.2, 125.9, 124.6, 123.6, 122.4, 120.7, 112.3, 109.3, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{17}N_4O_3^+$ 373.1295, found 373.1308.

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)-4-(trifluoromethyl)benzamide (S34)**

Following general procedure C using **S41** (44.7 mg, 0.2 mmol), 4-(trifluoromethyl)benzoyl chloride (0.95 g, 5.74 mmol) and 60% NaH (12 mg, 0.3 mmol), the title compound **S34** (52 mg, 0.13 mmol) was obtained in 65% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.57 (s, 1H), 8.37 (d, J = 7.0 Hz, 1H), 8.34 (s, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 6.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.3, 145.3, 143.6, 138.8, 138.3, 131.4 (q, $^2J_{(C-F)}$ = 31.6 Hz), 129.8, 128.6, 126.0, 125.9, 125.4 (q, $^3J_{(C-F)}$ = 3.8 Hz), 124.5, 123.9 (q, $^1J_{(C-F)}$ = 270.8 Hz), 123.3, 120.5, 112.1, 109.2, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{17}F_3N_3O^+$ 396.1318, found 396.1331.

Scheme S2

7-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S45)

Following general procedure A using **S38** (1.0 g, 8.2 mmol), **S42** (443 mg, 4.1 mmol), and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S45** (468 mg, 1.8 mmol) was obtained in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, 2H), 8.07 (d, 2H), 8.02 (d, 1H), 7.90 (d, 1H), 7.39 (s, 1H), 6.66 (d, 1H), 2.42 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{12}N_3O_2^+$ 254, found 254.

6-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S46)

Following general procedure A using **S38** (500 mg, 2.0 mmol), **S43** (443 mg, 4.1 mmol), and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S46** (452 mg, 1.8 mmol) was obtained in 89% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, 2H), 8.08 (d, 2H), 7.93 (s, 1H), 7.90 (s, 1H), 7.54 (d, 1H), 7.08 (d, 1H), 2.34 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{12}N_3O_2^+$ 254, found 254.

5-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S47)

Following general procedure A using **S38** (1.0 g, 8.2 mmol), **S44** (887 mg, 8.2 mmol), and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S47** (441 mg, 1.7 mmol) was obtained in 42% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, 2H), 8.15 (d, 2H), 7.89 (s, 1H), 7.57 (d, 1H), 7.23 (t, 1H), 6.68 (d, 1H), 2.64 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{12}N_3O_2^+$ 254, found 254.

7-Methyl-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S48)

Following general procedure B using **S45** (300 mg, 1.2 mmol), 1,4-cyclohexadiene (1.1 mL, 12 mmol), and 10% Pd/C (30 mg), the title compound **S48** (236 mg, 1.1 mmol) was obtained in 89% yield.

^{1}H NMR (400 MHz,DMSO-d_6): δ 8.28 (d, 1H), 7.98 (s, 1H), 7.55 (d, 2H), 7.21 (s, 1H), 6.62 (d, 1H), 6.5 (d, 2H), 6.55 (bs, 2H), 2.28 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{14}N_3^+$ 224, found 224.

6-Methyl-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S49)

Following general procedure B using **S46** (100 mg, 0.4 mmol), 1,4-cyclohexadiene (0.36 mL, 4 mmol) and 10% Pd/C (10 mg), the title compound **S49** (68 mg, 0.30 mmol) was obtained in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 1H), 7.75 (d, 2H), 7.68 (s, 1H), 6.90 (d, 1H), 6.73 (d, 2H), 6.63 (d, 1H), 2.64 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{14}N_3^+$ 224, found 224.

5-Methyl-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S50)

Following general procedure B using **S47** (500 mg, 2.0 mmol), 1,4-cyclohexadiene (1.8 mL, 20 mmol) and 10% Pd/C (50 mg), the title compound **S50** (251 mg, 1.1 mmol) was obtained in 57% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, 2H), 7.62 (d, 1H), 7.61 (s, 1H), 7.50 (t, 1H), 6.75 (d, 2H), 6.59 (d, 1H), 3.75 (bs, 2H), 2.59 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{14}H_{14}N_3^+$ 224, found 224.

3,4-Difluoro-*N*-(4-(7-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S1)

Following general procedure C using **S48** (50 mg, 0.22 mmol), 3,4-difluorobenzoyl chloride (28 μL, 0.24 mmol) and 60% NaH (11 mg, 0.27 mmol), the title compound **S1** (29 mg, 0.08 mmol) was obtained in 35% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.40 (d, J = 7.0 Hz, 1H), 8.26 (s, 1H), 8.09−8.04 (m, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.92−7.87 (m, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.67−7.61 (m, 1H), 7.34 (s, 1H), 6.74 (dd, J = 7.0, 1.5 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.1, 151.5 (dd, $^1J_{(C–F)}$ = 249.5, $^2J_{(C–F)}$ = 13.0 Hz), 149.1 (dd, $^1J_{(C–F)}$ = 245.4, $^2J_{(C–F)}$ = 13.0 Hz), 145.2, 143.9, 138.2, 135.2, 132.3, 129.8, 126.0, 125.8, 125.4−125.1 (m), 120.5, 117.7 ($^2J_{(C–F)}$ = 17.4 Hz), 117.2 ($^2J_{(C–F)}$ = 18.3 Hz), 114.8, 114.6, 108.1, 20.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 364.1269.

3,4-Difluoro-*N*-(4-(6-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S2)

Following general procedure C using **S49** (29 mg, 0.13 mmol), 3,4-difluorobenzoyl chloride (17 μL, 0.14 mmol) and 60% NaH (8 mg, 0.2 mmol), the title compound **S2** (31 mg, 0.09 mmol) was obtained in 65% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.35 (br s, 1H), 8.30 (s, 1H), 8.21−8.15 (m, 1H), 7.99−7.95 (m, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 9.0 Hz, 2H), 7.63 (dt, J = 10.0, 8.5 Hz, 1H), 7.48 (d, J = 9.5 Hz, 1H), 7.11 (dd, J = 10.0, 1.5 Hz, 1H), 2.29 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.2, 151.6 (dd, $^1J_{(C–F)}$ = 248.0, $^2J_{(C–F)}$ = 15.0 Hz), 149.1 (dd, $^1J_{(C–F)}$ = 244.9, $^2J_{(C–F)}$ = 14.9 Hz), 144.0, 143.8, 142.2, 138.4, 132.2, 129.7, 127.8, 125.7, 125.6−125.4 (m), 124.2, 121.4, 117.6 ($^2J_{(C–F)}$ = 17.5 Hz), 117.4 ($^2J_{(C–F)}$ = 17.1 Hz), 115.9, 108.4, 17.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 364.1261.

3,4-Difluoro-*N*-(4-(5-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S3)

Following general procedure C using **S50** (50 mg, 0.0.22 mmol), 3,4-difluorobenzoyl chloride (29 mg, 0.24 mmol) and 60% NaH (14 mg, 0.35 mmol), the title compound **S3** (50 mg, 0.14 mmol) was obtained in 61% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.32 (s, 1H), 8.10−8.03 (m, 3H), 7.92−7.88 (m, 1H),

7.86 (d, J = 8.5 Hz, 2H), 7.68−7.62 (m, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.22 (dd, J = 9.0, 6.5 Hz, 1H), 6.78 (d, J = 7.0 Hz, 1H), 2.65 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.2, 151.5 (d, $^{1}J_{(C–F)}$ = 249.3, $^{2}J_{(C–F)}$ = 12.8 Hz), 149.1 (d, $^{1}J_{(C–F)}$ = 245.3, $^{2}J_{(C–F)}$ = 13.0 Hz), 145.2, 144.2, 138.3, 135.2, 132.3, 129.8, 125.9, 125.3, 124.9, 120.5, 117.7 (d, $^{2}J_{(C–F)}$ = 17.6 Hz), 117.2 (d, $^{2}J_{(C–F)}$ = 18.5 Hz), 113.9, 111.2, 106.5, 18.3.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{16}F_2N_3O^+$ 364.1256, found 364.1266.

Scheme S3

2-(3-Nitrophenyl)imidazo[1,2-*a*]pyridine (S53)

Following general procedure A using **S51** (1.0 g, 8.2 mmol), **S52** (386 mg, 4.1 mmol), and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S53** (900 mg, 3.8 mmol) was obtained in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.34 (d, 2H), 8.14 (d, 2H), 7.95 (s, 1H), 7.70–7.55 (m, 2H), 7.22 (dd, 1H), 6.82 (dd, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{10}N_3O_2^+$ 240, found 240.

2-(3-Aminophenyl)imidazo[1,2-*a*]pyridine (S54)

Following general procedure B using **S53** (500 mg, 2.1 mmol), 1,4-cyclohexadiene (2.0 mL, 21 mmol) and 10% Pd/C (50 mg), the title compound **S54** (313 mg, 1.5 mmol) was obtained in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H), 7.83 (s, 1H), 7.61 (d, 1H), 7.39 (s, 1H), 7.28 (d, 1H), 7.22 (dd, 1H), 7.16 (dd, 1H), 6.76 (d, 1H), 6.66 (d, 1H), 3.74 (bs, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{12}N_3^+$ 210, found 210.

3,4-Difluoro-N-(3-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S4)

Following general procedure C using **S54** (44.7 mg, 0.22 mmol), 3,4-difluorobenzoyl chloride (26 μL, 0.22 mmol) and 60% NaH (10 mg, 0.24 mmol), the title compound **S4** (72 mg, 0.20 mmol) was obtained in 86% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.56 (d, J = 7.0 Hz, 1H), 8.46 (t, J = 1.5 Hz, 1H), 8.39 (s, 1H), 8.14–8.08 (m, 1H), 7.96–7.91 (m, 1H), 7.79–7.75 (m, 1H), 7.73–7.57 (m, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.29–7.24 (m, 1H), 6.91 (td, J = 6.5, 1.0 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.2, 151.6 (d, $^1J_{(C–F)}$ = 249.9, $^2J_{(C–F)}$ = 12.5 Hz), 149.2 (d, $^1J_{(C–F)}$ = 245.3, $^2J_{(C–F)}$ = 13.3 Hz), 144.8, 144.2, 139.3, 134.4, 132.2, 129.0, 127.0, 125.3 (m), 125.0, 121.2, 119.7, 117.7, 117.6 (d, $^2J_{(C–F)}$ = 16.3 Hz), 117.2 (d, $^2J_{(C–F)}$ = 18.4 Hz), 116.6, 112.3, 109.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}F_2N_3O^+$ 350.1099, found 350.1120.

Scheme S4

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine (S55)

Following general procedure A using **S38** (1.0 g, 8.2 mmol), **S52** (772 mg, 8.2 mmol), and Na_2CO_3 (318 mg, 3.0 mmol), the title compound **S55** (889 mg, 3.7 mmol) was obtained in 90% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.54 (d, J = 7.0 Hz, 1H), 8.27 (d, J = 7.0 Hz, 2H), 8.20 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 9.0 Hz, 1H), 7.30−7.26 (m, 1H), 6.95−6.90 (m, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{10}N_3O_2^+$ 240, found 240.

2-(4-Aminophenyl)imidazo[1,2-*a*]pyridine (S56)

Following general procedure B using **S55** (500 mg, 2.1 mmol), 1,4-cyclohexadiene (2.0 mL, 21 mmol) and 10% Pd/C (50 mg), the title compound **S56** (372 mg, 1.8 mmol) was obtained in 85% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.41 (d, 1H), 8.07 (s, 1H), 7.59 (d, 2H), 7.12 (dd, 1H), 6.78 (dd, 1H), 6.57 (d, 2H), 5.24 (bs, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{12}N_3^+$ 210, found 210.

3,4-Difluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S5)

Following general procedure C using **S56** (209 mg, 1.0 mmol), 3,4-difluorobenzoyl chloride (17 μL, 0.38 mmol) and 60% NaH (18 mg, 1.0 mmol), the title compound **S5** (261 mg, 0.74 mmol) was obtained in 74% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.45 (s, 1H), 8.54 (d, J = 6.5 Hz, 1H), 8.37 (s, 1H), 8.12−8.06 (m, 1H), 7.98 (d, J = 9.0 Hz, 2H), 7.94−7.84 (m, 3H), 7.68−7.61 (m, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.26−7.23 (m, 1H), 6.90 (td, J = 6.5, 1.0 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 163.2, 151.5 (d, $^1J_{(C-F)}$ = 249.5, $^2J_{(C-F)}$ = 12.4 Hz), 149.1 (d, $^1J_{(C-F)}$ = 244.8, $^2J_{(C-F)}$ = 13.3 Hz), 144.8, 144.1, 138.4, 132.2 (m), 129.6, 126.8, 125.9, 125.3 (m), 124.9, 120.6, 117.6 (d, $^2J_{(C-F)}$ = 17.3 Hz), 117.2 (d, $^2J_{(C-F)}$ = 18.3 Hz), 116.5, 112.2, 108.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}F_2N_3O^+$ 350.1099, found 350.1116.

Scheme S5

3,4-Difluoro-*N*-methyl-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S6)

A solution of **2** (82 mg, 0.23 mmol), MeI (21 μL, 0.34 mmol), and 60% NaH (11 mg, 0.27 mmol) in DMF was stirred at r.t. for 1 h. The reaction was quenched by addition of sat. NH_4Cl. The mixture was extracted with ethyl acetate and the organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting material was washed with 50% ethyl acetate and water, and dried *in vacuo*. The crude material was purified by column chromatography eluting with a gradient from 30% ethyl acetate in hexane to 50% ethyl acetate in hexane to give the title compound **S6** (68 mg, 0.18 mmol) in 80% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36−8.32 (m, 2H), 7.88 (d, J = 8.5 Hz, 1H), 7.42−7.36 (m, 1H), 7.34−7.22 (m, 3H), 7.15−7.10 (m, 1H), 7.04 (d, J = 6.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 3.40 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 167.2, 149.7 (d, $^1J_{(C–F)}$ = 247.8, $^2J_{(C–F)}$ = 12.4 Hz), 148.5 (d, $^1J_{(C–F)}$ = 245.3, $^2J_{(C–F)}$ = 12.5 Hz), 145.3, 143.2, 142.7, 133.8 (m), 132.4, 127.3, 126.2, 126.1, 125.6 (m), 124.6, 123.5, 117.8 (d, $^2J_{(C–F)}$ = 18.4 Hz), 117.1 (d, $^2J_{(C–F)}$ = 17.6 Hz), 112.3, 109.9, 37.8, 16.6.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{18}F_2N_3O^+$ 378.1412, found 378.1422.

Scheme S6

Methyl 4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)benzoate (S58)

Following general procedure A using **S57** (500 mg, 1.9 mmol), **S39** (266 μL, 3.9 mmol), and Na_2CO_3 (151 mg, 1.4 mmol), the title compound **S58** (447 mg, 1.7 mmol) was obtained in 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 6.0 Hz, 2H), 8.04 (d, *J* = 6.0 Hz, 2H), 8.00 (d, *J* = 6.0 Hz, 1H), 7.93 (s, 1H), 6.98 (d, *J* = 6.8 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 3.94 (s, 3H), 2.67 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}N_2O_2^+$ 267, found 267.

4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)benzoyl chloride (S59)

A mixture of **S58** (89 mg, 0.33 mmol) and NaOH (16 mg, 0.40 mmol) in 20% aq. THF was stirred at r.t. for 24 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The carboxylic acid was dissolved in thionyl chloride, and the mixture was refluxed for 7 h. The reaction mixture was poured into toluene and the mixture was concentrated *in vacuo*. The product was used in the next step without further purification.

***N*-(4-Fluorophenyl)-4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)benzamide (S10)**

Following general procedure C using 4-fluoroaniline (31 μL, 0.32 mmol), **S59** (87 mg, 0.32 mmol), and 60% NaH (31 mg, 0.77 mmol), the title compound **S10** (103 mg, 0.29 mmol) was obtained in 50% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.29–8.22 (m, 3H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.84–7.80 (m, 3H), 7.26–7.18 (m, 3H), 7.04 (t, *J* = 7.0 Hz, 1H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.0, 158.4 (d, $^1J_{(C–F)}$ = 238.9 Hz), 143.6, 137.0, 135.5, 125.4, 134.1, 128.1, 126.8, 126.7, 124.6, 122.2 (d, $^3J_{(C–F)}$ = 7.6 Hz), 121.4, 115.2 (d, $^2J_{(C–F)}$ = 22.0 Hz), 113.8, 109.1, 16.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}FN_3O^+$ 346.1350, found 346.1360.

Scheme S7

4-Fluoro-*N*-(2-methyl-4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S11)

Following general procedure C using **S60** (227 mg, 0.96 mmol), 4-fluorobenzoyl chloride (115 μL, 0.96 mmol) and 60% NaH (80 mg, 2 mmol), the crude material was purified by column chromatography eluting with 50% ethyl acetate in hexane. The title compound **S11** (26 mg, 0.07 mmol) was obtained in 10% yield over 4 steps.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.41−8.32 (m, 2H), 8.12−8.04 (m, 2H), 7.90 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.45−7.33 (m, 3H), 7.05 (d, J = 7.0 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 2.54 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.3, 164.0 (d, $^{1}J_{(C–F)}$ = 247.6 Hz), 145.3, 143.5, 135.7, 133.8, 131.8, 131.0, 130.3 (d, $^{3}J_{(C–F)}$ = 9.0 Hz), 127.4, 126.8, 126.1, 124.6, 123.34, 123.29, 115.4 (d, $^{2}J_{(C–F)}$ = 21.6 Hz), 112.2, 109.1, 18.0, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{19}FN_3O^+$ 360.1507, found 360.1518.

4-Fluoro-*N*-(3-methyl-4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S12)

Following general procedure C using **S61** (128 mg, 0.53 mmol), 4-fluorobenzoyl chloride (64 μL, 0.53 mmol) and 60% NaH (42 mg, 1.1 mmol), the crude material was purified by column chromatography eluting with a gradient from 2% methanol in $CHCl_3$ to 5% methanol in $CHCl_3$. The title compound **S12** (103 mg, 0.29 mmol) was obtained in 5% yield over 4 steps.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.29 (s, 1H), 8.39 (d, J = 6.5 Hz, 1H), 8.15 (s, 1H), 8.10−8.04 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.75−7.70 (m, 2H), 7.38 (t, J = 9.0 Hz, 2H), 7.05 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.56 (s, 3H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.3, 164.0 (d, $^{1}J_{(C–F)}$ = 247.6 Hz), 144.3, 143.1, 138.1, 135.4, 131.0 (d, $^{4}J_{(C–F)}$ = 2.8 Hz), 130.3 (d, $^{3}J_{(C–F)}$ = 9.0 Hz), 129.3, 129.0, 126.0, 124.5, 123.2, 122.5, 117.9, 115.4 (d, $^{2}J_{(C–F)}$ = 21.6 Hz), 111.9, 111.6, 21.9, 16.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{19}FN_3O^+$ 360.1507, found 360.1516.

Scheme S8

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)picolinamide (S15)**

Following general procedure D using **S41** (100 mg, 0.45 mmol), picolinic acid (111 mg, 0.90 mmol), EDCI (173 mg, 0.90 mmol), HOBt (138 mg, 0.90 mmol), and $^{i}Pr_2NEt$ (177 μL, 1.8 mmol), the title compound **S15** (80 mg, 0.24 mmol) was obtained in 50% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.77−8.74 (m, 1H), 8.36 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.09 (td, J = 8.0, 2.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.68 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H), 7.04 (dt, J = 7.0, 1.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.4, 149.9, 148.4, 145.3, 143.6, 138.2, 137.8, 129.8, 126.9, 126.0, 125.9, 124.5, 123.3, 122.4, 120.4, 112.1, 109.2, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{17}N_4O^+$ 329.1397, found 329.1402.

2-Nitro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S31)

Following general procedure D using **S41** (152 mg, 0.68 mmol), 2-nitrobenzoic acid (137 mg, 0.82 mmol), EDCI (157 mg, 0.82 mmol), HOBt (111 mg, 0.82 mmol) and $^{i}Pr_2NEt$ (289 μL, 1.7 mmol), the title compound **S31** (191 mg, 0.51 mmol) was obtained in 75% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.79 (s, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.16 (dd, J = 8.5, 1.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.88 (td, J = 7.5, 1.0 Hz, 1H), 7.82−7.74 (m, 4H), 7.04 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.0, 146.5, 145.3, 143.5, 138.3, 134.1, 132.7, 131.0, 129.8, 129.3, 126.03, 126.02, 124.6, 124.3, 123.3, 119.8, 112.1, 109.2, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{17}N_4O_3^+$ 373.1295, found 373.1304.

5-Fluoro-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)picolinamide (S33)

Following general procedure D using **S41** (100 mg, 0.45 mmol), 5-fluoropicolinic acid (127 mg, 0.90 mmol), EDCI (173 mg, 0.90 mmol), HOBt (138 mg, 0.90 mmol) and $^{i}Pr_2NEt$ (177 μL, 1.8 mmol), the title compound **S33** (81 mg, 0.23 mmol) was obtained in 52% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.25 (dd, J = 8.5, 4.5 Hz, 1H), 8.03−7.94 (m, 5H), 7.04 (d, J = 6.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 161.9, 160.8 (d, $^{1}J_{(C–F)}$ = 256.9 Hz), 146.7 (d, $^{4}J_{(C–F)}$ = 3.5 Hz), 145.3, 143.6, 137.8, 136.8 (d, $^{2}J_{(C–F)}$ = 25.0 Hz), 129.8, 126.0, 125.9, 124.9 (d, $^{2}J_{(C–F)}$ = 18.6 Hz), 124.7 (d, $^{3}J_{(C–F)}$ = 5.8 Hz), 124.5, 123.3, 120.5, 112.1, 109.2, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{16}FN_4O^+$ 347.1303, found 347.1313.

5-Cyano-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)picolinamide (S35)

Following general procedure D using **S41** (100 mg, 0.45 mmol), 5-cyanopicolinic acid (133 mg, 0.90 mmol), EDCI (173 mg, 0.90 mmol), HOBt (138 mg, 0.90 mmol), and $^{i}Pr_2NEt$ (177 μL, 1.8 mmol), the title compound **S35** (114 mg, 0.32 mmol) was obtained in 72% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.88 (s, 1H), 9.21 (dd, J = 2.0, 0.5 Hz, 1H), 8.60 (dd, J = 8.0, 2.0 Hz, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.35 (s, 1H), 8.31 (dd, J = 8.0, 0.5 Hz, 1H), 8.03−7.96 (m, 4H), 7.05 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 161.2, 152.6, 151.5, 146.6, 142.2, 137.5, 128.0, 126.9, 126.0, 125.9, 124.6, 122.4, 120.7, 116.6, 113.6, 112.2, 111.6, 109.3, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{16}N_5O^+$ 354.1349, found 354.1366.

5-Methyl-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)picolinamide (S36)

Following general procedure D using **S41** (100 mg, 0.45 mmol), 5-methylpicolinic acid (123 mg, 0.90 mmol), EDCI (173 mg, 0.90 mmol), HOBt (138 mg, 0.90 mmol) and $^{i}Pr_2NEt$ (177 uL, 1.8 mmol), the title compound **S36** (67 mg, 0.20 mmol) was obtained in 41% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 7.0 Hz, 1H), 8.34 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 9.0 Hz, 2H), 7.96 (d, J = 9.0 Hz, 2H), 7.89 (dd, J = 8.0, 1.5 Hz, 1H), 7.04 (dt, J = 6.5, 1.0 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 2.53 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.5, 148.7, 147.5, 145.3, 143.6, 138.2, 137.9, 126.9, 129.6, 126.0, 125.9, 124.5, 123.3, 122.0, 120.3, 112.1, 109.1, 18.0, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_4O^+$ 343.1553; found 343.1566.

***N*-(4-(8-Methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrimidine-4-carboxamide (S37)**

Following general procedure D using **S41** (100 mg, 0.45 mmol), pyrimidine-4-carboxylic acid (112 mg, 0.90 mmol), EDCI (173 mg, 0.90 mmol), HOBt (138 mg, 0.90 mmol) and $^{i}Pr_2NEt$ (177 μL, 1.8 mmol), the title compound **S37** (81 mg, 0.24 mmol) was obtained in 51% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.89 (s, 1H), 9.43 (d, J = 1.0 Hz, 1H), 9.14 (d, J = 5.0 Hz, 1H), 8.36 (d, J = 6.5 Hz, 1H), 8.34 (s, 1H), 8.15 (dd, J = 5.0, 1.0 Hz, 1H), 8.02−7.96 (m, 4H), 7.04 (d, J = 6.5 Hz, 1H), 6.78 (t, J = 6.5 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 161.3, 159.9, 157.8, 156.7, 145.3, 143.5, 137.3, 130.3, 126.0, 125.9, 124.5, 123.3, 120.7, 118.9, 112.1, 109.3, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{16}N_5O^+$ 330.1349; found 330.1357.

Scheme S9

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyrimidine (S65)

Following general procedure A using **S38** (100 mg, 0.82 mmol), **S62** (78 mg, 0.41 mmol) and Na_2CO_3 (32 mg, 0.30 mmol), the title compound **S65** (73 mg, 0.30 mmol) was obtained in 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (dd, *J* = 6.9, 2.3 Hz, 1H), 8.60 (s, 1H), 8.57 (dd, *J* = 4.0, 2.3 Hz, 1H), 8.30 (d, *J* = 9.2 Hz, 2H), 8.25 (d, *J* = 9.2 Hz, 2H), 7.08 (dd, *J* = 6.9, 4.0 Hz, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{12}H_9N_4O_2^+$ 241, found 241.

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyrazine (S66)

Following general procedure A using **S38** (100 mg, 0.82 mmol), **S63** (78 mg, 0.41 mmol) and Na_2CO_3 (32 mg, 0.30 mmol), the title compound **S66** (56 mg, 0.23 mmol) was obtained in 56% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (d, *J* = 0.9 Hz, 1H), 8.84 (s, 1H), 8.64 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.36 (d, *J* = 9.0 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H), 7.95 (d, *J* = 4.5 Hz, 1H).

2-(4-Nitrophenyl)imidazo[1,2-*b*]pyridazine (S67)

Following general procedure A using **S38** (129 mg, 0.53 mmol), **S64** (50 mg, 0.53 mmol) and NaOAc (64 mg, 0.79 mmol), the title compound **S67** (50 mg, 0.21 mmol) was obtained in 40% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.56 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.33 (m, 4H), 8.18 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 4.6 Hz, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{12}H_9N_4O_2^+$ 241, found 241.

2-(4-Aminophenyl)imidazo[1,2-*a*]pyrimidine (S68)

Following general procedure B using **S65** (20 mg, 0.085 mmol), 1,4-cyclohexadiene (79 μL, 0.85 mmol) and 10% Pd/C (2 mg), the title compound **S68** (6.5 mg, 0.031 mmol) was obtained in 36% yield.

^{1}H NMR (500 MHz, CD_3OD): δ 8.78 (dd, *J* = 6.9, 1.7 Hz, 1H), 8.47 (dd, *J* = 4.0, 2.3 Hz, 1H), 8.00 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.00 (dd, *J* = 6.3, 4.6 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 2.64 (s, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{12}H_{11}N_4^+$ 211, found 211.

2-(4-Aminophenyl)imidazo[1,2-*a*]pyrazine (S69)

Following general procedure B using **S66** (56 mg, 0.23 mmol), 1,4-cyclohexadiene (215 μL, 2.3 mmol) and 10% Pd/C (6 mg), the title compound **S69** (39 mg, 0.18 mmol) was obtained in 80% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (d, *J* = 0.9 Hz, 1H), 8.45 (d, *J* = 4.5, 1.4 Hz, 1H), 8.25 (s, 1H), 7.84 (d, *J* = 4.9 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{12}H_{11}N_4^+$ 211, found 211.

2-(4-Aminophenyl)imidazo[1,2-*b*]pyridazine (S70)

Following general procedure B using **S67** (50 mg, 0.21 mmol), 1,4-cyclohexadiene (196 μL, 2.1 mmol) and 10% Pd/C (10 mg), the title compound **S70** (41 mg, 0.19 mmol) was obtained in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, *J* =4.5, 1.8 Hz, 1H), 8.16 (s, 1H), 7.91 (dd, *J* = 9.4, 0.9 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 6.99 (dd, *J* = 9.0, 4.5 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{12}H_{11}N_4^+$ 211, found 211.

4-Fluoro-*N*-(4-(imidazo[1,2-*a*]pyrimidin-2-yl)phenyl)benzamide (S16)

Following general procedure C using **S68** (104 mg, 0.50 mmol), 4-fluorobenzoyl chloride (60 μL, 0.50 mmol) and 60% NaH (28 mg, 0.70 mmol), the title compound **S16** (53 mg, 0.16 mmol) was obtained in 32% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.96 (dd, *J* = 6.5, 2.0 Hz, 1H), 8.51 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.33 (s, 1H), 8.07 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.38 (t, *J* = 9.0 Hz, 2H), 7.05 (dd, *J* = 6.5, 4.0 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.5, 164.0 (d, $^1J_{(C–F)}$ = 247.8 Hz), 150.1, 148.1, 145.2, 139.2, 134.9, 131.3, 130.4 (d, $^3J_{(C–F)}$ = 9.1 Hz), 128.8, 126.1, 120.5, 115.3 (d, $^2J_{(C–F)}$ = 21.6 Hz), 108.8, 107.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}FN_4O^+$ 333.1146, found 333.1158.

4-Fluoro-*N*-(4-(imidazo[1,2-*a*]pyrazin-2-yl)phenyl)benzamide (S17)

Following general procedure C using **S69** (39 mg, 0.18 mmol), 4-fluorobenzoyl chloride (22 μL, 0.18 mmol) and 60% NaH (10 mg, 0.25 mmol), the title compound **S17** (14 mg, 0.040 mmol) was obtained in 22% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 9.07 (s, 1H), 8.60 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.57 (s, 1H), 8.10−8.02 (m, 4H), 7.93−7.88 (m, 3H), 7.40 (t, *J* = 9.0 Hz, 2H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.5, 164.0 (d, $^1J_{(C–F)}$ = 247.4 Hz), 146.2, 142.4, 140.4, 139.4, 131.3, 130.4 (d, $^3J_{(C–F)}$ = 9.0 Hz), 129.2, 128.4, 126.4, 120.5, 120.0, 115.4 (d, $^2J_{(C–F)}$ = 21.6 Hz), 110.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}FN_4O^+$ 333.1146, found 333.1156.

4-Fluoro-*N*-(4-(imidazo[1,2-*b*]pyridazin-2-yl)phenyl)benzamide (S18)

Following general procedure C using **S70** (41 mg, 0.19 mmol), 4-fluorobenzoyl chloride (23 μL, 0.19 mmol) and 60% NaH (6 mg, 0.15 mmol), the title compound **S18** (42 mg, 0.13 mmol) was obtained in 68% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.82 (s, 1H), 8.52−8.48 (m, 1H), 8.14−8.07 (m, 3H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.41−7.33 (m, 2H), 7.26−7.20 (m, 2H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.5, 164.2 (d, $^1J_{(C–F)}$ = 247.4 Hz), 144.5, 143.8, 139.3, 138.9, 131.3, 130.5 (d, $^3J_{(C–F)}$ = 9.0 Hz), 128.7, 126.1, 124.9, 120.6, 117.7, 115.4 (d, $^2J_{(C–F)}$ = 21.8 Hz), 112.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}FN_4O^+$ 333.1146, found 333.1157.

Scheme S10

8-Fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S74)

Following general procedure A using **S38** (274 mg, 1.1 mmol), **S71** (100 mg, 1.1 mmol), and Na_2CO_3 (237 mg, 2.2 mmol), the title compound **S74** (67 mg, 0.20 mmol) was obtained in 23% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.79 (d, J = 3.4 Hz, 1H), 8.45 (d, J = 6.3 Hz, 1H), 8.40 (s, 1H), 8.32 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 9.2 Hz, 2H), 7.22 (dd, J = 11.5, 7.5 Hz, 1 H), 6.94 (m, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_9FN_3O_2^+$ 258, found 258.

7-Fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S75)

Following general procedure A using **S38** (274 mg, 1.12 mmol), **S72** (100 mg, 1.12 mmol), and Na_2CO_3 (237 mg, 2.24 mmol), the title compound **S75** (112 mg, 0.43 mmol) was obtained in 39% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.66 (t, J = 7.5 Hz, 1H), 8.31 (d, J = 9.2 Hz, 2H), 8.21 (d, J = 9.2 Hz, 2H), 7.50 (dd, J = 9.4, 2.3 Hz, 1H), 7.04 (td, J = 8.0, 2.3, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_9FN_3O_2^+$ 258, found 258.

6-Fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (S76)

Following general procedure A using **S38** (274 mg, 1.12 mmol), **S73** (100 mg, 1.12 mmol) and Na_2CO_3 (237 mg, 2.24 mmol), the title compound **S76** (94 mg, 0.36 mmol) was obtained in 33% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82 (dd, J = 4.0, 2.3 Hz, 1H), 8.64 (s, 1H), 8.31 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H), 7.71 (dd, J = 9.7, 5.2 Hz, 1H), 7.41 (td, J = 8.6, 2.3 Hz, 1H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_9FN_3O_2^+$ 258, found 258.

8-Fluoro-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S77)

Following general procedure B using **S74** (66 mg, 0.26 mmol), 1,4-cyclohexadiene (240 µL, 2.6 mmol) and 10% Pd/C (7 mg), the title compound **S77** (28 mg, 0.12 mmol) was obtained in 47% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (dd, J = 7.2, 0.9 Hz, 1H), 8.03 (d, J = 3.1 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 6.99 (ddd, J = 10.8, 7.6, 0.9 Hz, 1H), 6.80–6.74 (m, 3H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{11}FN_3^+$ 228, found 228.

7-Fluoro-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S78)

Following general procedure B using **S75** (100 mg, 0.39 mmol), 1,4-cyclohexadiene (362 µL, 3.9 mmol) and 10% Pd/C (10 mg), the title compound **S78** (88 mg, 0.39 mmol) was obtained in 99% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52 (t, J = 7.5 Hz, 1H), 8.09 (s, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.33 (dd, J = 10.3, 2.9 Hz, 1H), 6.88 (td, J = 7.5, 2.3 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 5.23 (s, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{11}FN_3^+$ 228, found 228.

6-Fluoro-2-(4-aminophenyl)imidazo[1,2-*a*]pyridine (S79)

Following general procedure B using **S76** (50 mg, 0.19 mmol), 1,4-cyclohexadiene (181 μL, 1.9 mmol) and 10% Pd/C (5 mg), the title compound **S79** (24 mg, 0.11 mmol) was obtained in 56% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−8.02 (m, 1H), 7.81−7.72 (m, 3H), 7.60−7.53 (m, 1H), 7.09−7.02 (m, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.80 (br s, 2H).

LRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{11}FN_3^+$ 228, found 228.

4-Fluoro-*N*-(4-(8-fluorolimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S19)

Following general procedure C using **S77** (28 mg, 0.12 mmol), 4-fluorobenzoyl chloride (14 μL, 0.12 mmol), 60% NaH (10 mg, 0.24 mmol), the title compound **S19** (28 mg, 0.079 mmol) was obtained in 66% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.38 (s, 1H), 8.50 (d, *J* = 3.0 Hz, 1H), 8.41 (dd, *J* = 6.5, 1.0 Hz, 1H), 8.10−8.05 (m, 2H), 8.00 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.40 (t, *J* = 9.0 Hz, 2H), 7.15 (dd, *J* = 11.5, 8.0 Hz, 1H), 6.90−6.85 (m, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.4, 164.1 (d, $^1J_{(C–F)}$ = 248.4 Hz), 150.4 (d, $^1J_{(C–F)}$ = 247.1 Hz), 144.5, 139.0, 137.2 (d, $^2J_{(C–F)}$ = 28.8 Hz), 131.4, 130.4 (d, $^3J_{(C–F)}$ = 9.0 Hz), 128.7, 126.0, 123.5 (d, $^4J_{(C–F)}$ = 4.6 Hz), 120.5, 115.4 (d, $^2J_{(C–F)}$ = 21.6 Hz), 111.3 (d, $^3J_{(C–F)}$ = 7.1 Hz), 110.4, 107.6 (d, $^2J_{(C–F)}$ = 16.0 Hz).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}F_2N_3O^+$ 350.1099, found 350.1100.

4-Fluoro-*N*-(4-(7-fluorolimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S20)

Following general procedure C using **S78** (88 mg, 0.39 mmol), 4-fluorobenzoyl chloride (47 FμL, 0.39 mmol) and 60% NaH (32 mg, 0.8 mmol), the title compound **S20** (89 mg, 0.26 mmol) was obtained in 66% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.61 (d, *J* = 6.5 Hz, 1H), 8.34 (s, 1H), 8.09−8.04 (m, 2H), 7.95 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.44 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.39 (t, *J* = 9.0 Hz, 2H), 6.97 (td, *J* = 7.5, 2.5 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 164.4, 164.1 (d, $^1J_{(C–F)}$ = 247.6 Hz), 159.7 (d, $^1J_{(C–F)}$ = 246.4 Hz), 145.3, 144.9 (d, $^3J_{(C–F)}$ = 14.4 Hz), 138.8, 131.4 (d, $^4J_{(C–F)}$ = 2.8 Hz), 130.4 (d, $^3J_{(C–F)}$ = 9.0 Hz), 129.1, 128.8 (d, $^3J_{(C–F)}$ = 10.9 Hz), 125.9, 120.5, 115.3 (d, $^2J_{(C–F)}$ = 21.8 Hz), 108.4, 104.2 (d, $^2J_{(C–F)}$ = 29.1 Hz), 100.0 (d, $^2J_{(C–F)}$ = 23.4 Hz).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}F_2N_3O^+$ 350.1099, found 350.1107.

Scheme S11

4-Amino-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S27)

Following general procedure B using **S26** (60 mg, 0.16 mmol), 1,4-cyclohexadiene (150 μL, 1.6 mmol) and 10% Pd/C (6 mg), the title compound **S27** (18 mg, 0.05 mmol) was obtained in 31% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.84 (s, 1H), 8.35 (d, J = 7.0 Hz, 1H), 8.30 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 6.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 2H), 5.77 (s, 2H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 165.2, 152.2, 145.2, 143.8, 139.3, 129.4, 128.7, 126.0, 125.7, 124.5, 123.2, 121.1, 120.2, 112.6, 112.1, 108.9, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_4O^+$ 343.1553, found 343.1559.

3-Amino-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S30)

Following general procedure B using **S29** (60 mg, 0.16 mmol), 1,4-cyclohexadiene (150 μL, 1.6 mmol) and 10% Pd/C (6 mg), the title compound **S30** (38 mg, 0.11 mmol) was obtained in 69% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.15 (s, 1H), 8.37 (d, J = 6.5 Hz, 1H), 8.32 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 2.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 6.76 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 5.37 (br s, 2H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 166.3, 148.8, 145.2, 143.6, 138.9, 135.9, 129.1, 128.8, 125.9, 125.8, 124.5, 123.4, 120.3, 116.8, 114.7, 113.0, 112.1, 109.0, 16.7.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_4O^+$ 343.1553, found 343.1562.

2-Amino-*N*-(4-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)benzamide (S32)

Following general procedure B using **S31** (100 mg, 0.27 mmol), 1,4-cyclohexadiene (250 μL, 2.7 mmol) and 10% Pd/C (10 mg), the title compound **S32** (39 mg, 0.11 mmol) was obtained in 42% yield.

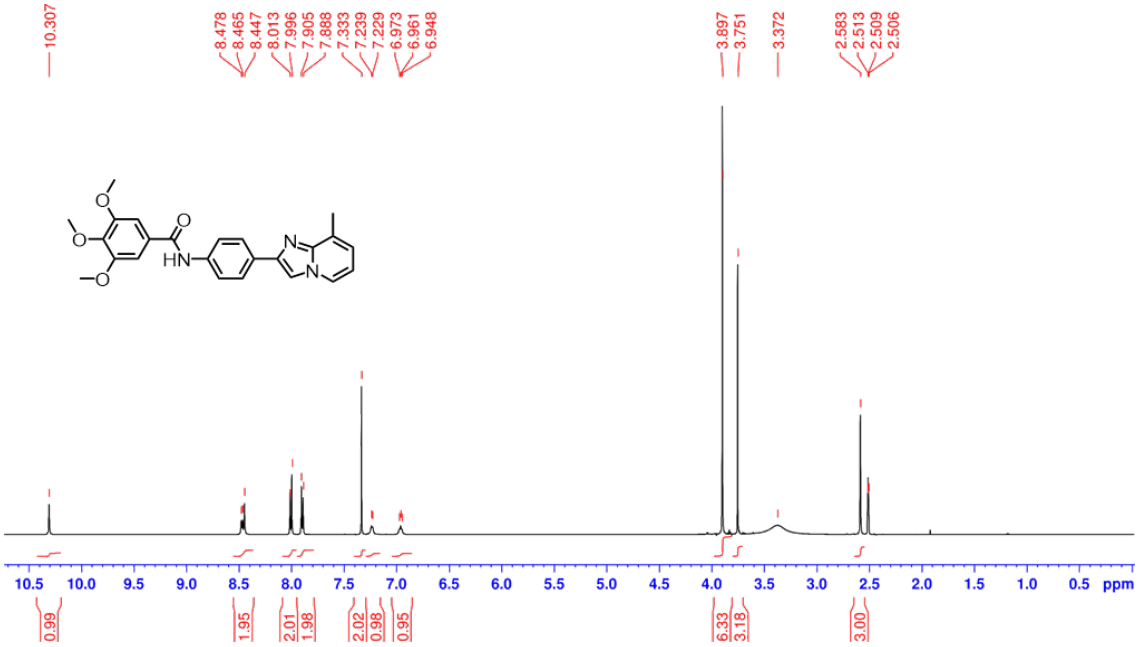
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.36 (d, J = 6.5 Hz, 1H), 8.32 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.81−6.75 (m, 2H), 6.60 (t, J = 7.0 Hz, 1H), 6.35 (br s, 2H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 167.8, 149.8, 145.3, 143.7, 138.8, 132.1, 129.2, 128.7, 126.0, 125.7, 124.5, 123.3, 120.6, 116.4, 115.2, 114.7, 112.1, 109.0, 16.7.

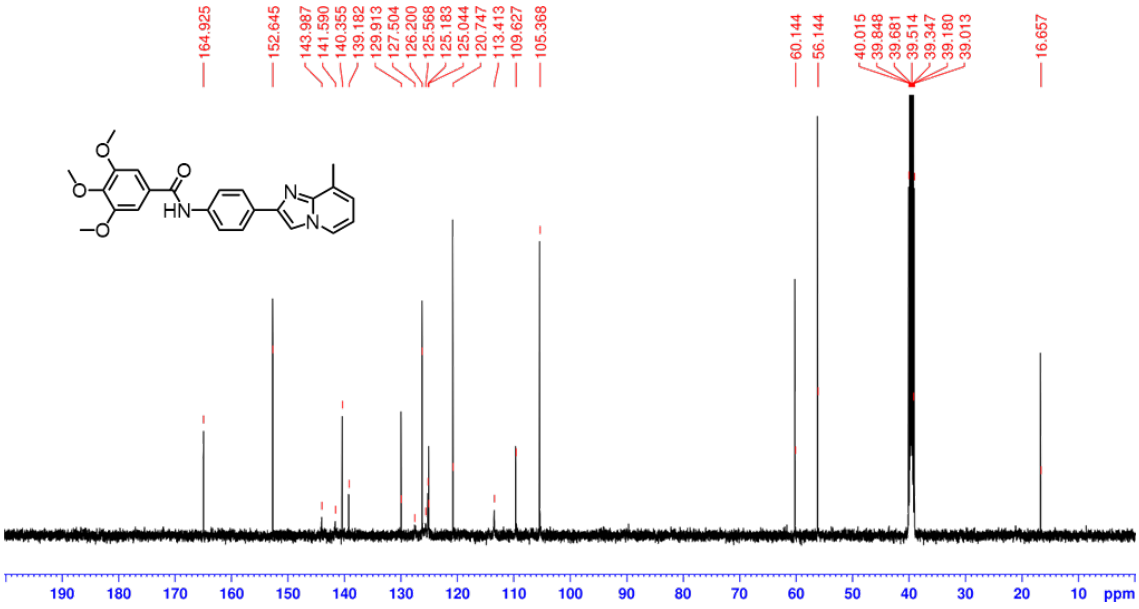
HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_4O^+$ 343.1553, found 343.1568.

NMR spectra

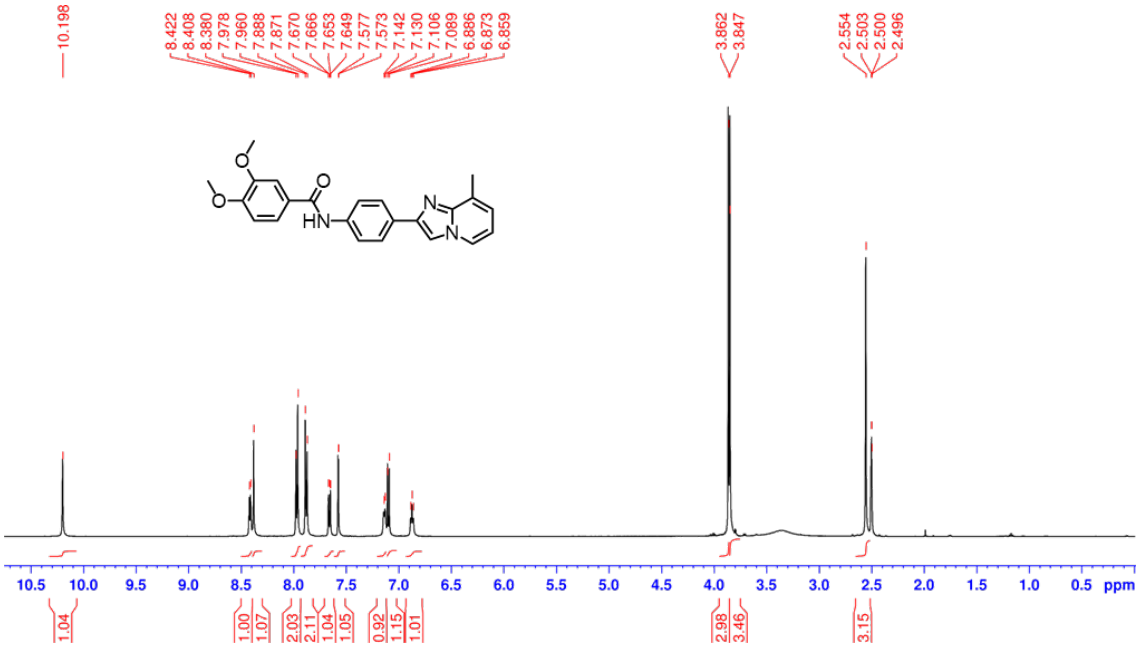
^{1}H NMR (500 MHz, DMSO-d_6) of compound-23



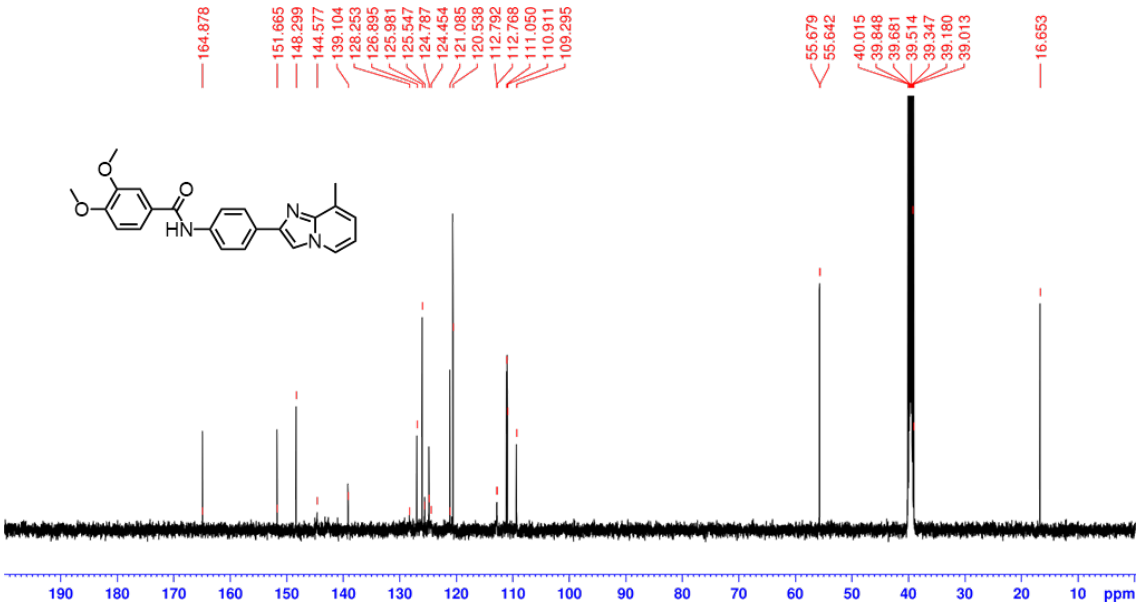
^{13}C NMR (125 MHz, DMSO-d_6) of compound-23



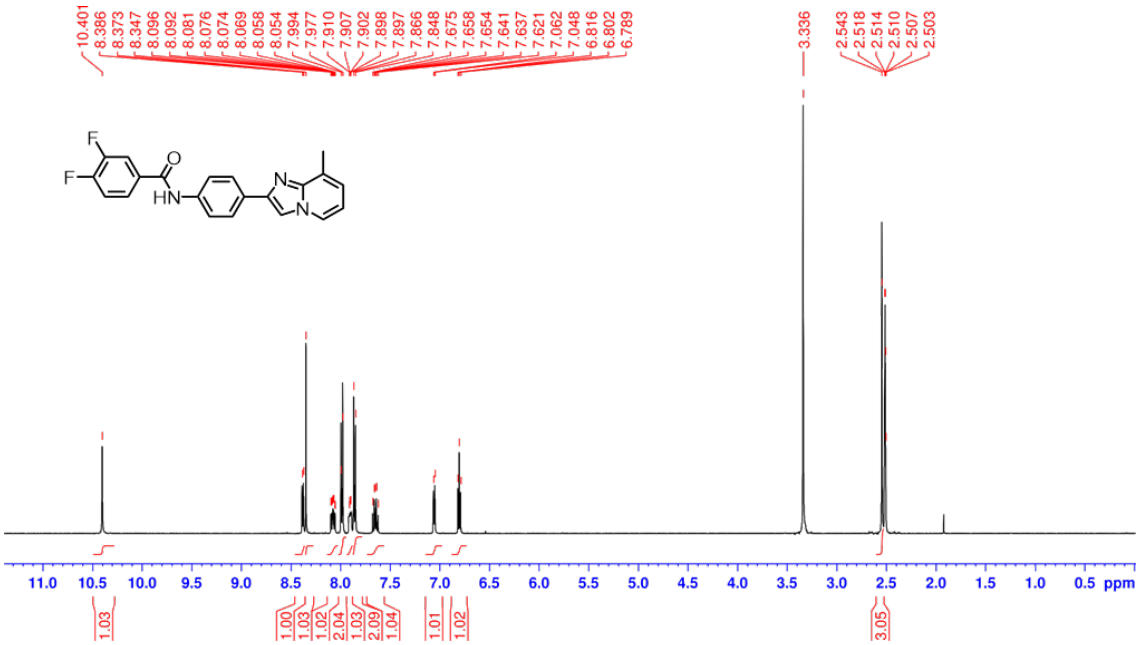
^{1}H NMR (500 MHz, DMSO-d_6) of **1**



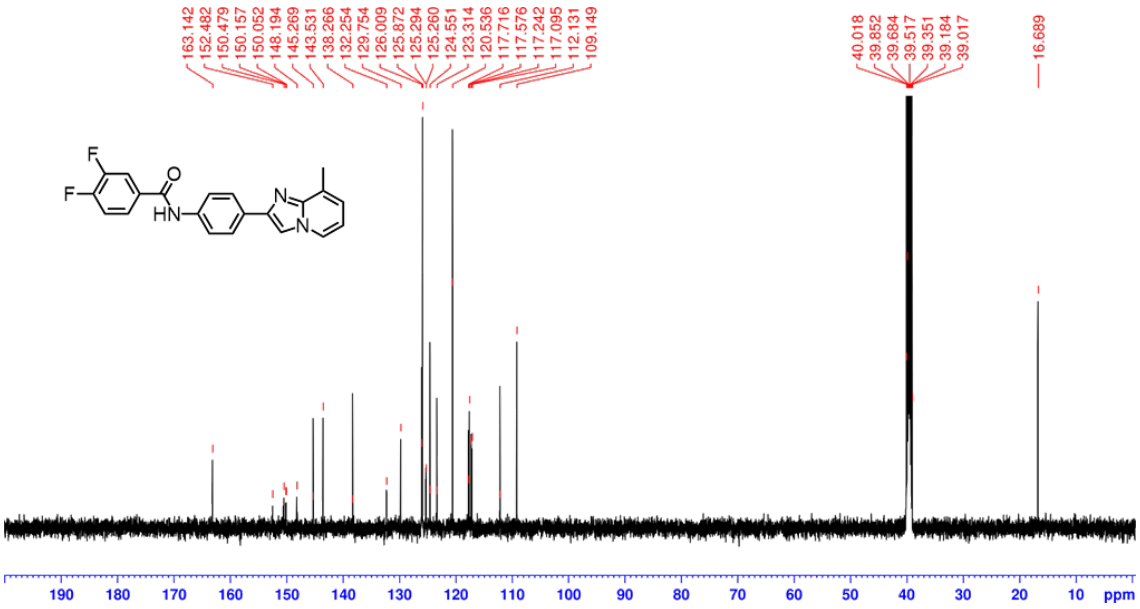
^{13}C NMR (125 MHz, DMSO-d_6) of **1**



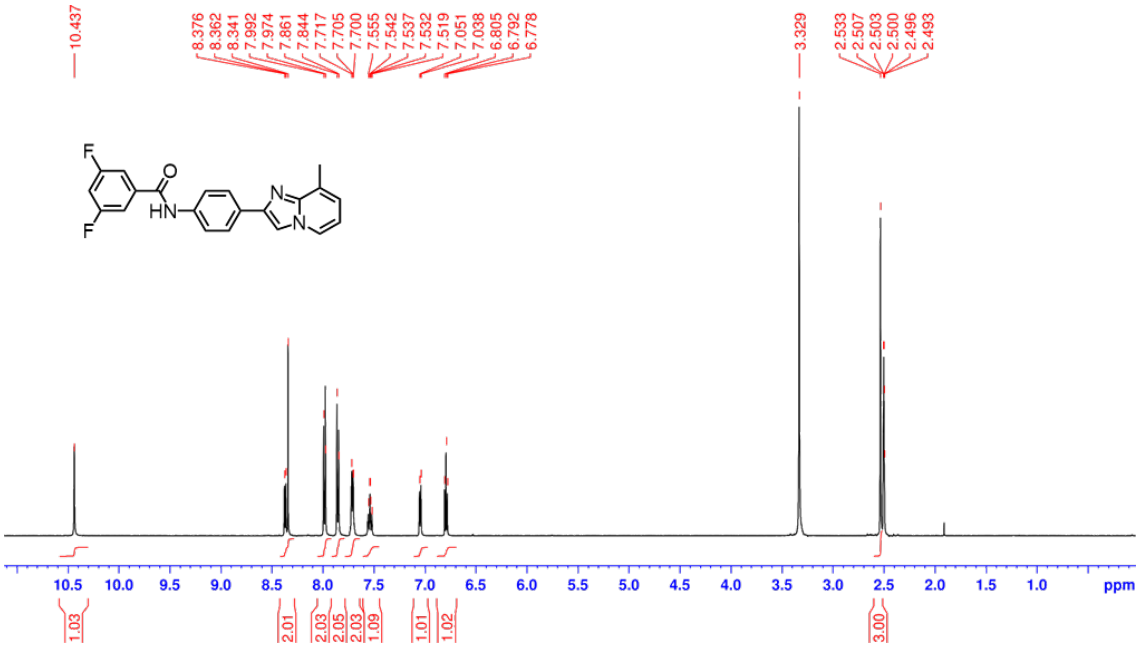
^{1}H NMR (500 MHz, DMSO-d_6) of **2**



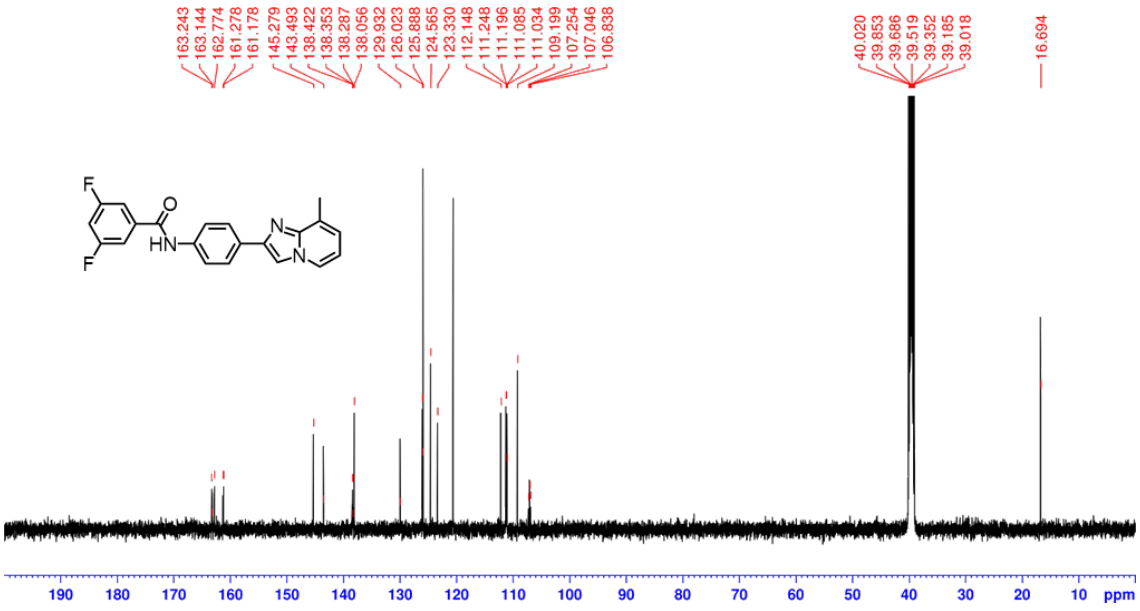
^{13}C NMR (125 MHz, DMSO-d_6) of **2**



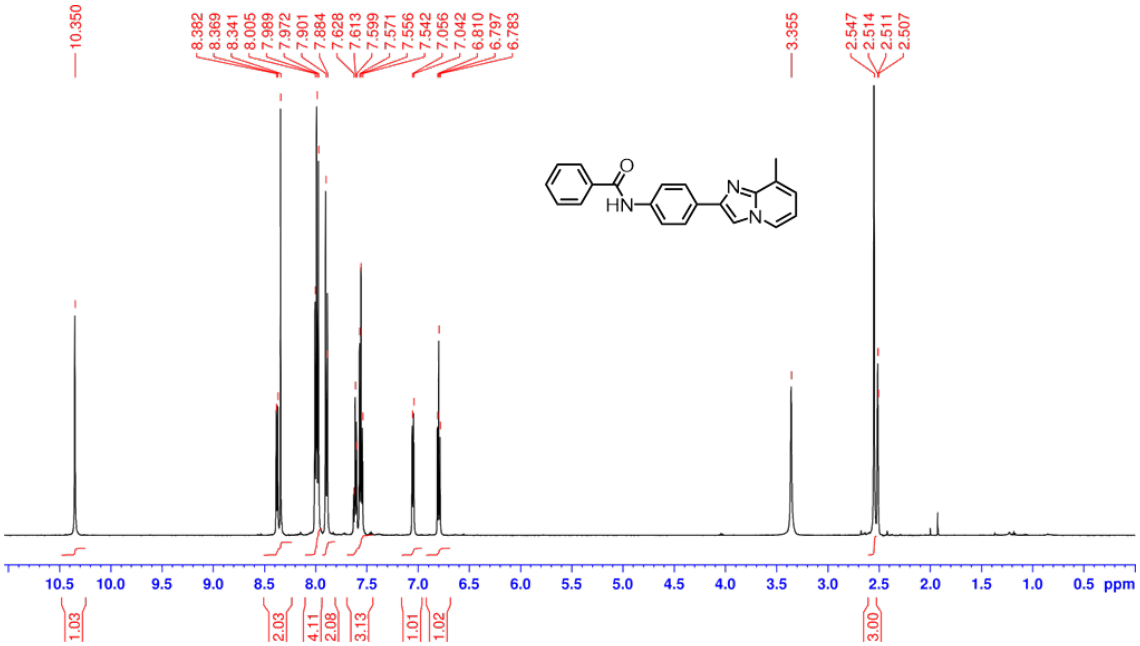
^{1}H NMR (500 MHz, DMSO-d_6) of **3**



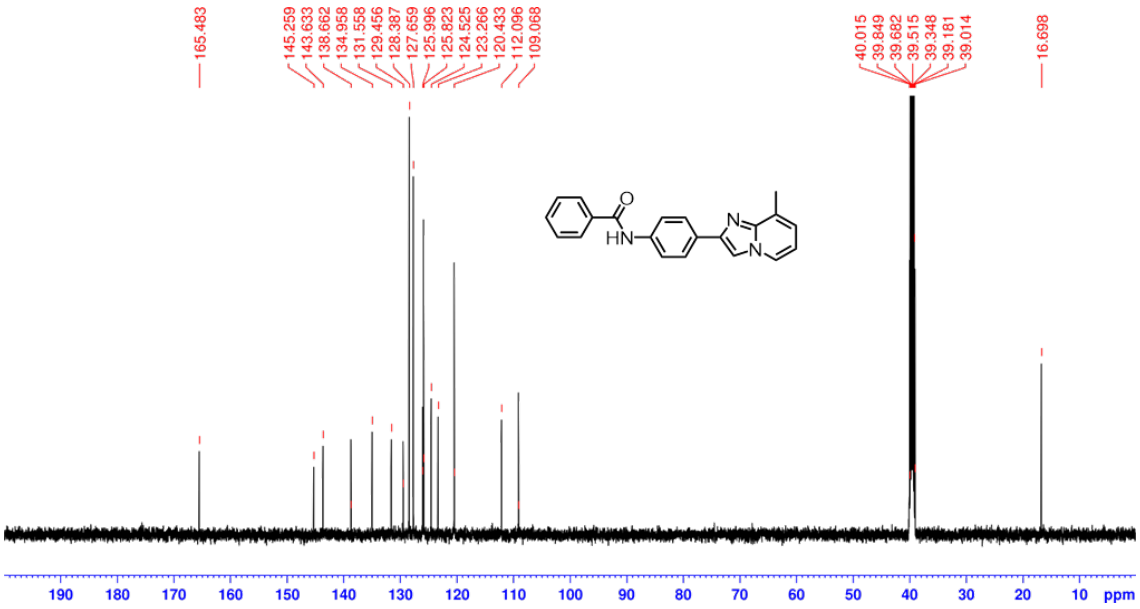
^{13}C NMR (125 MHz, DMSO-d_6) of **3**



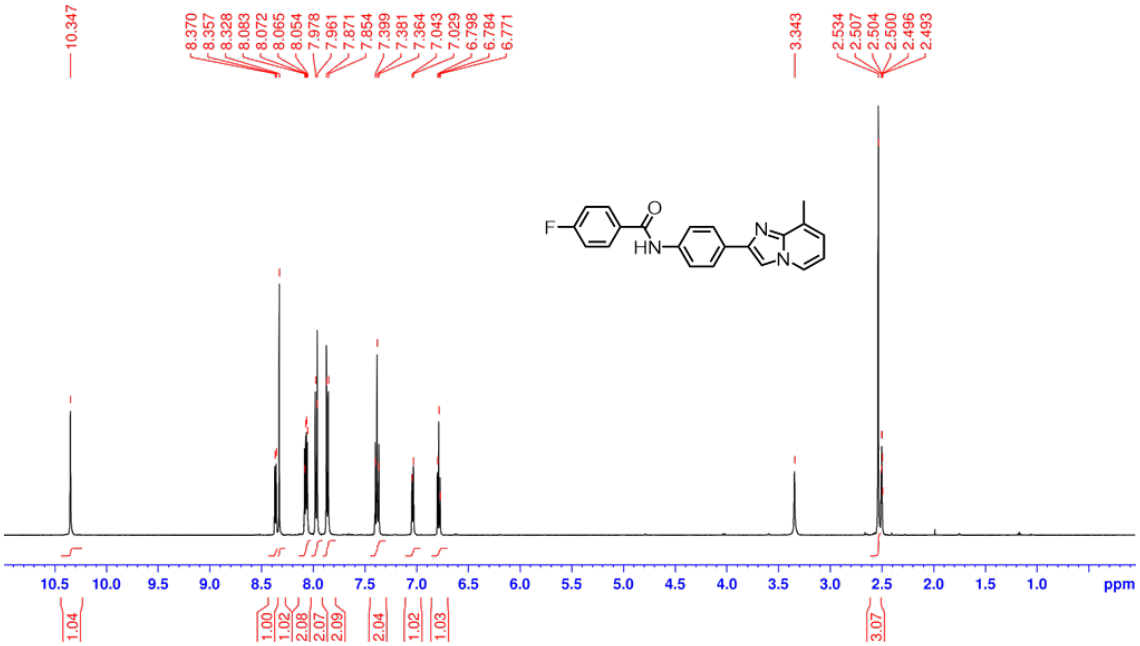
^{1}H NMR (500 MHz, DMSO-d_6) of **4**



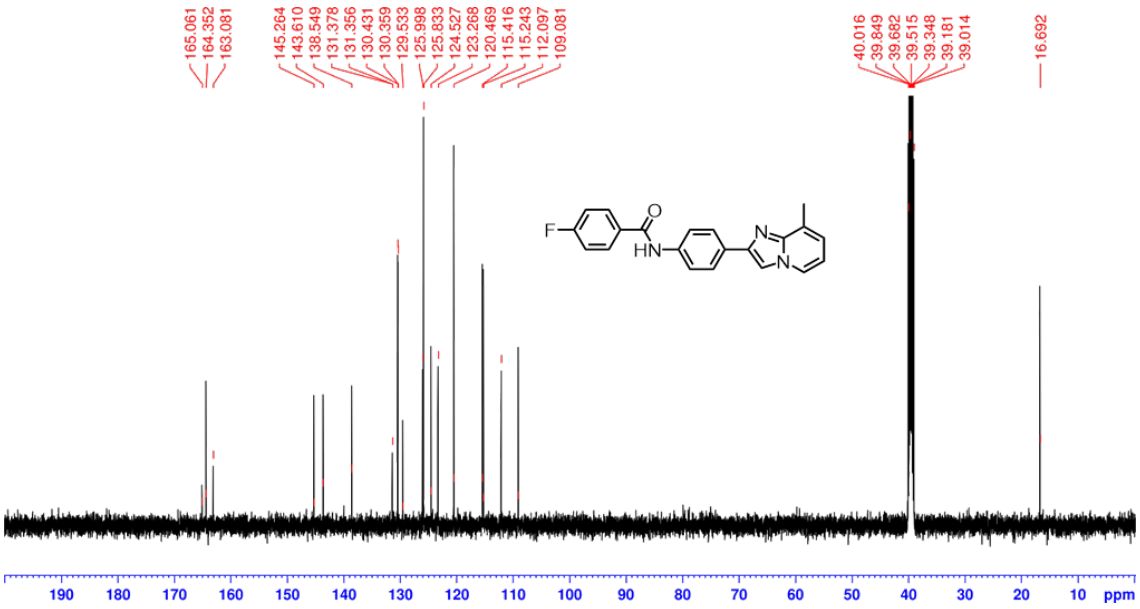
^{13}C NMR (125 MHz, DMSO-d_6) of **4**



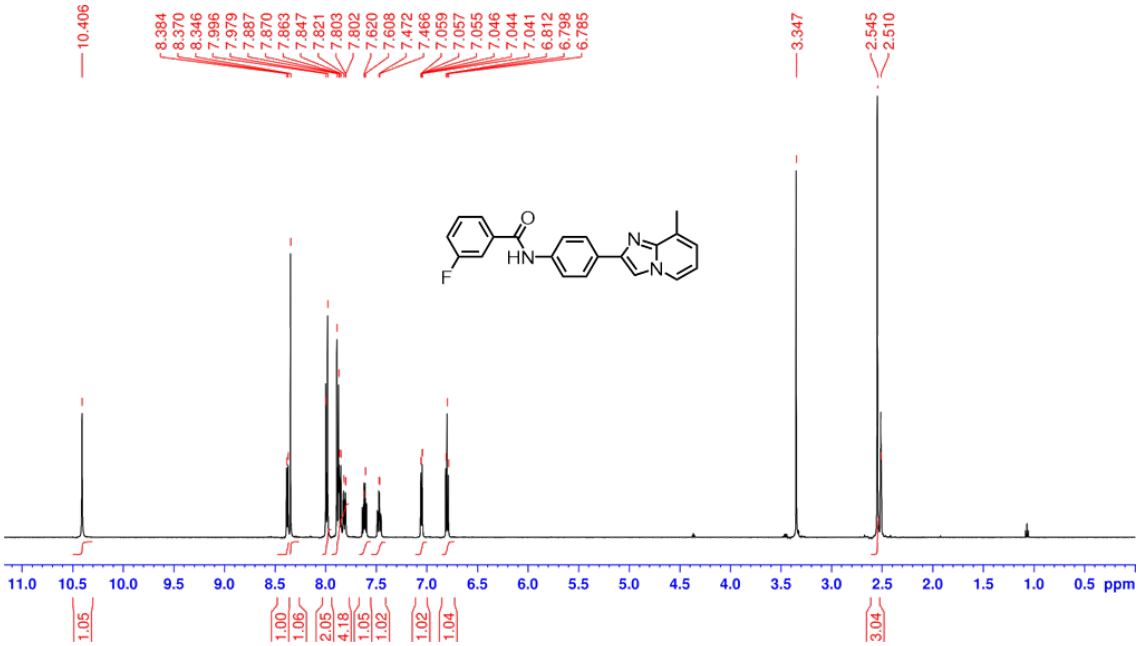
^{1}H NMR (500 MHz, DMSO-d_6) of **5**



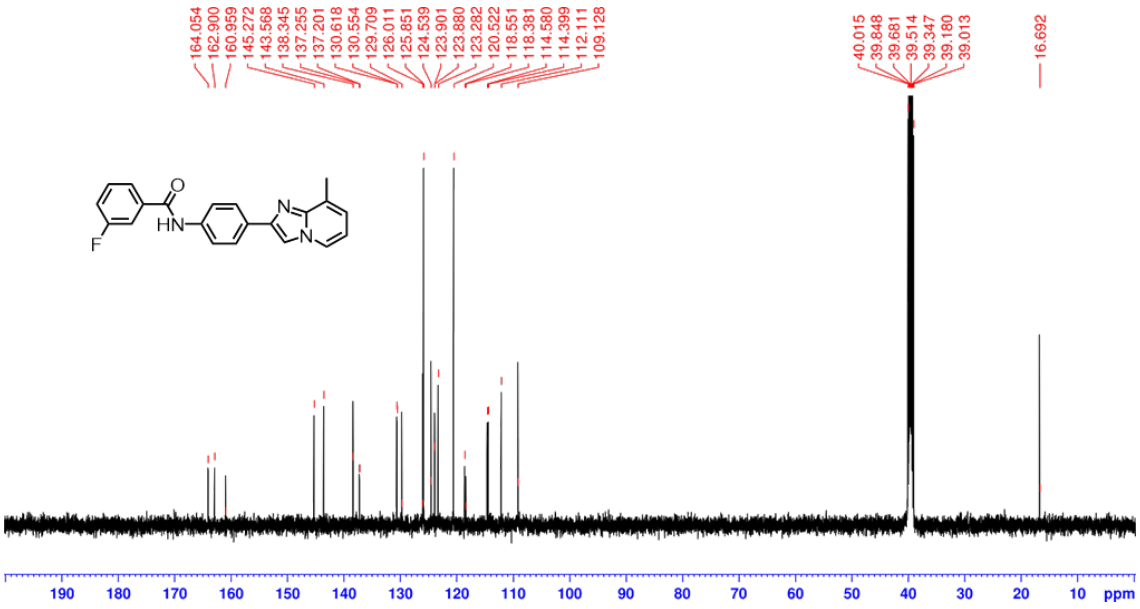
^{13}C NMR (125 MHz, DMSO-d_6) of **5**



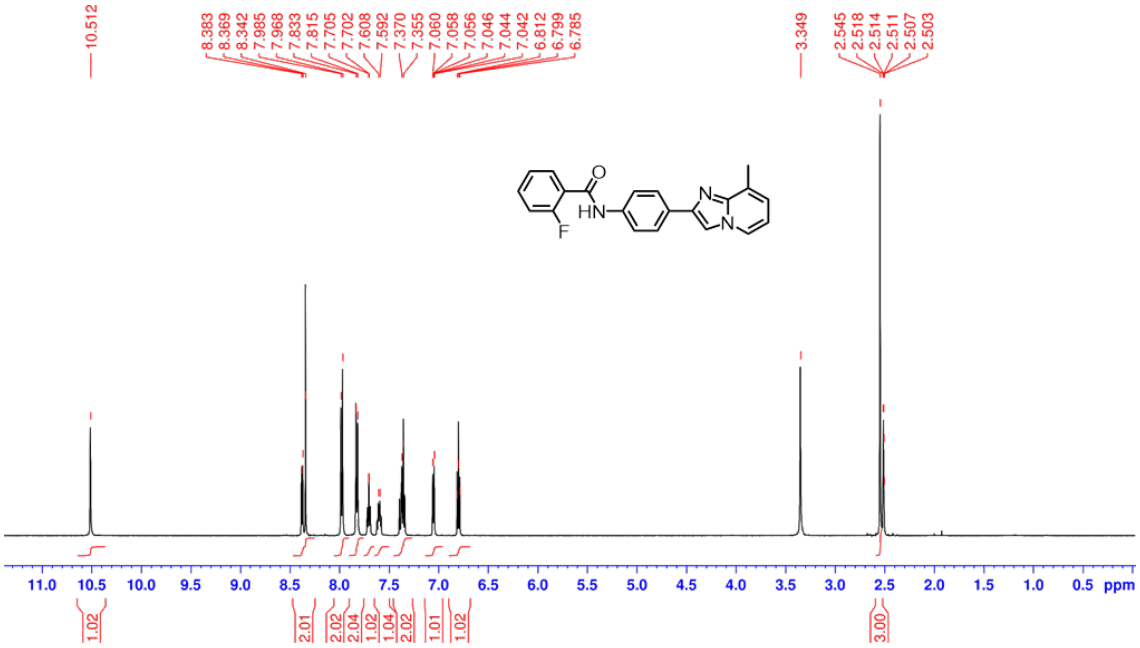
^{1}H NMR (500 MHz, DMSO-d_6) of **6**



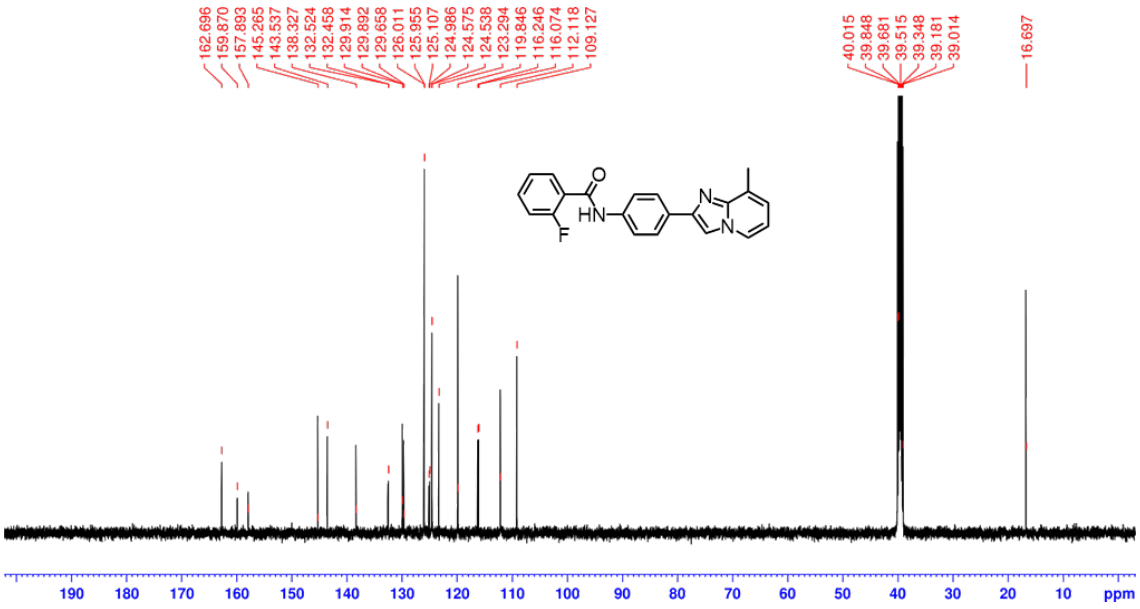
^{13}C NMR (125 MHz, DMSO-d_6) of **6**



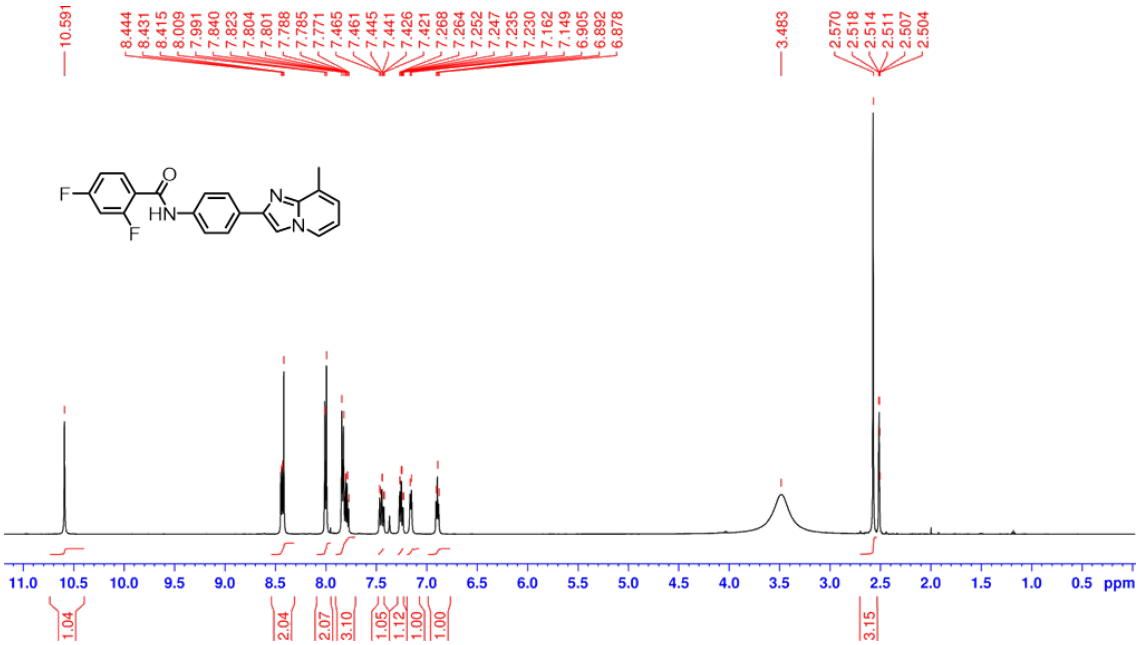
^{1}H NMR (500 MHz, DMSO-d_6) of **7**



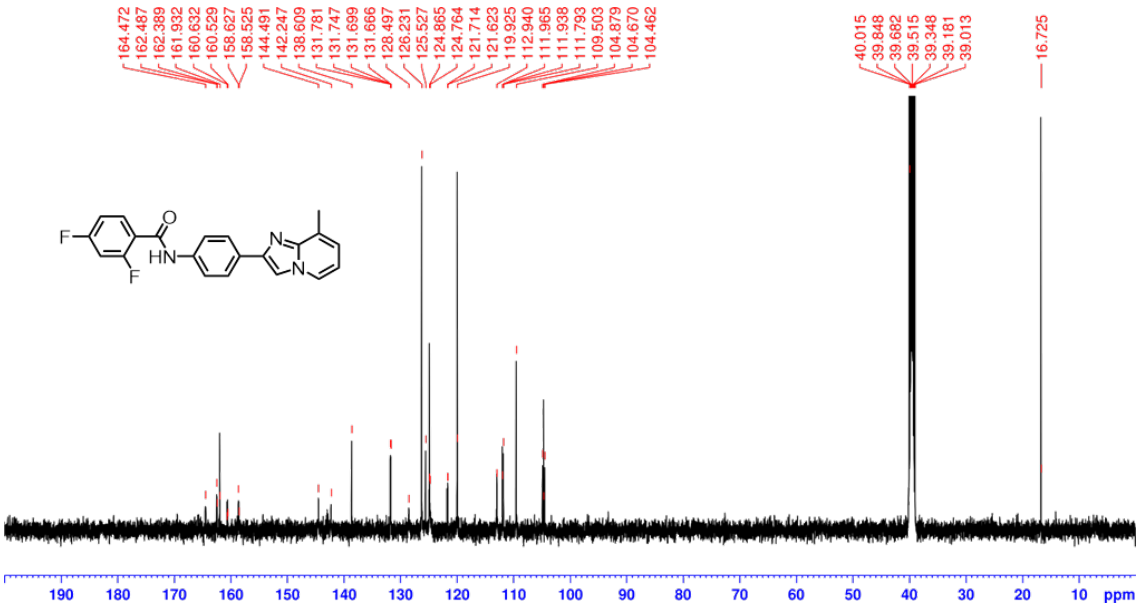
^{13}C NMR (125 MHz, DMSO-d_6) of **7**



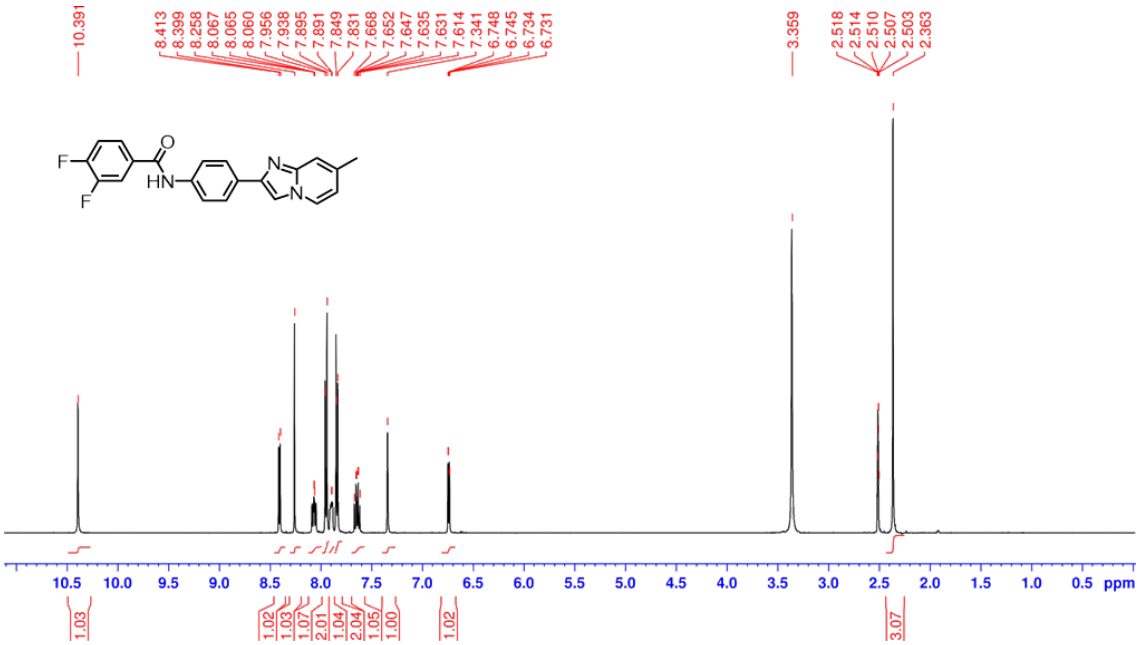
^{1}H NMR (500 MHz, DMSO-d_6) of **8**



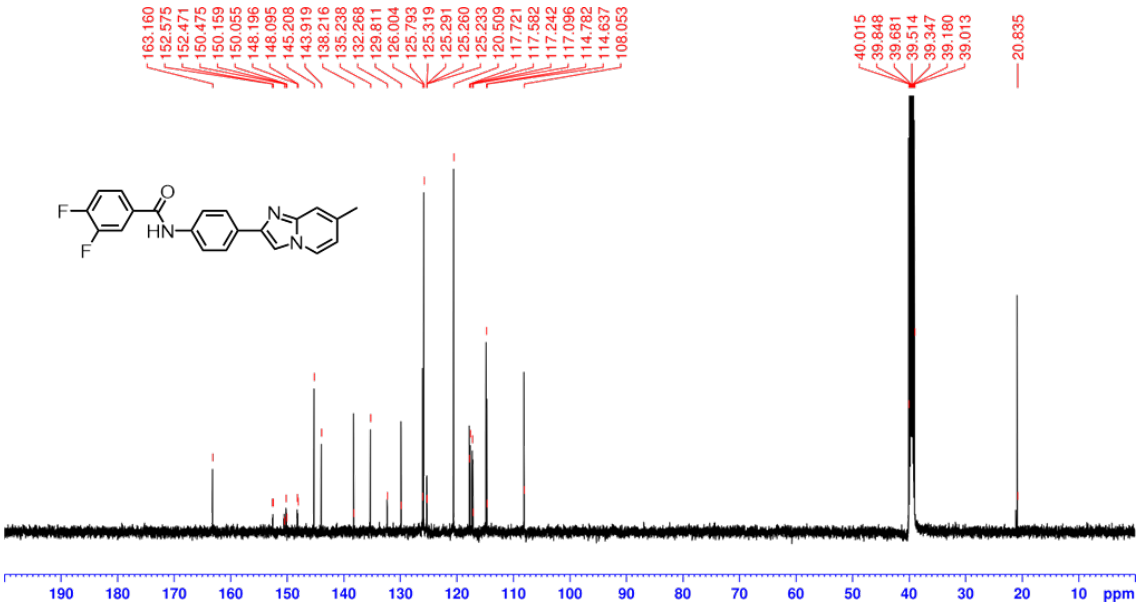
^{13}C NMR (125 MHz, DMSO-d_6) of **8**



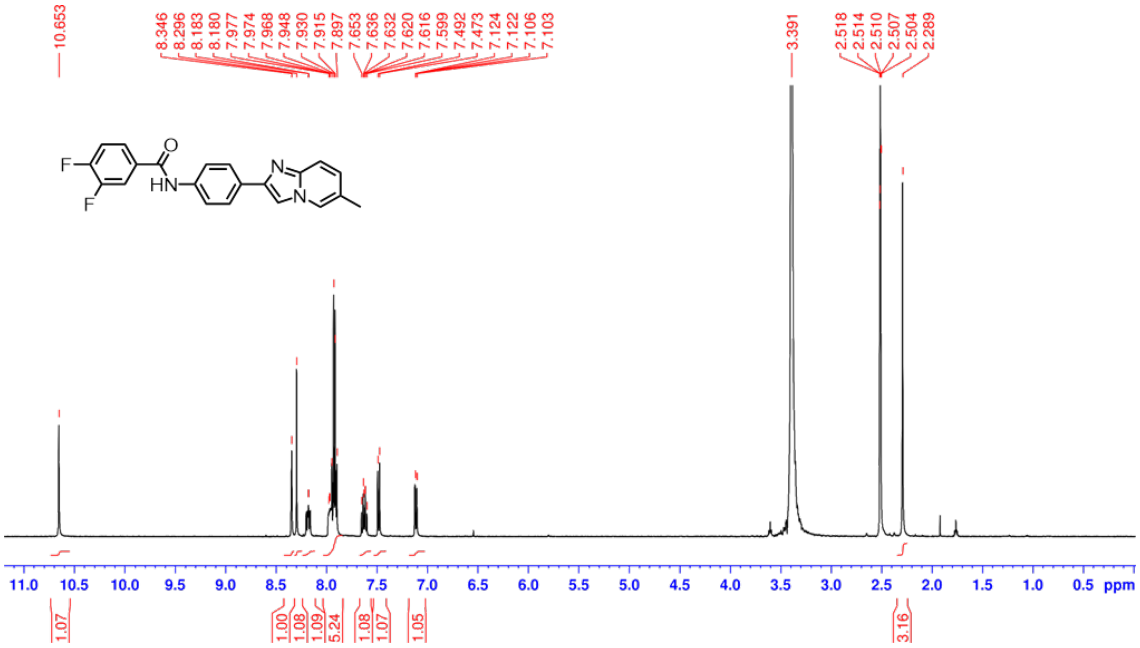
^{1}H NMR (500 MHz, DMSO-d_6) of **S1**



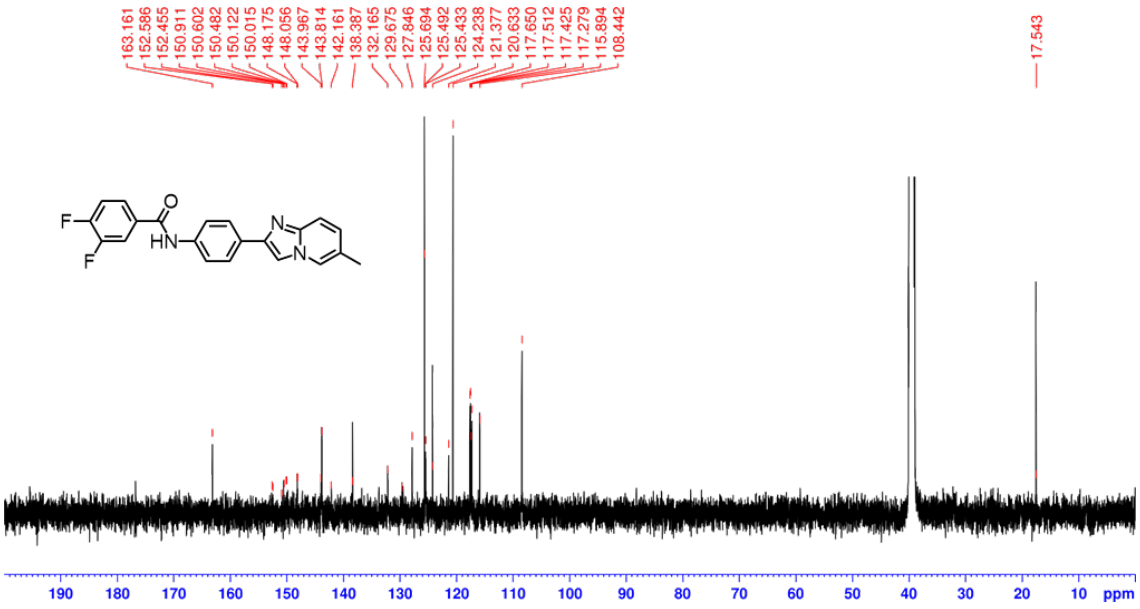
^{13}C NMR (125 MHz, DMSO-d_6) of **S1**



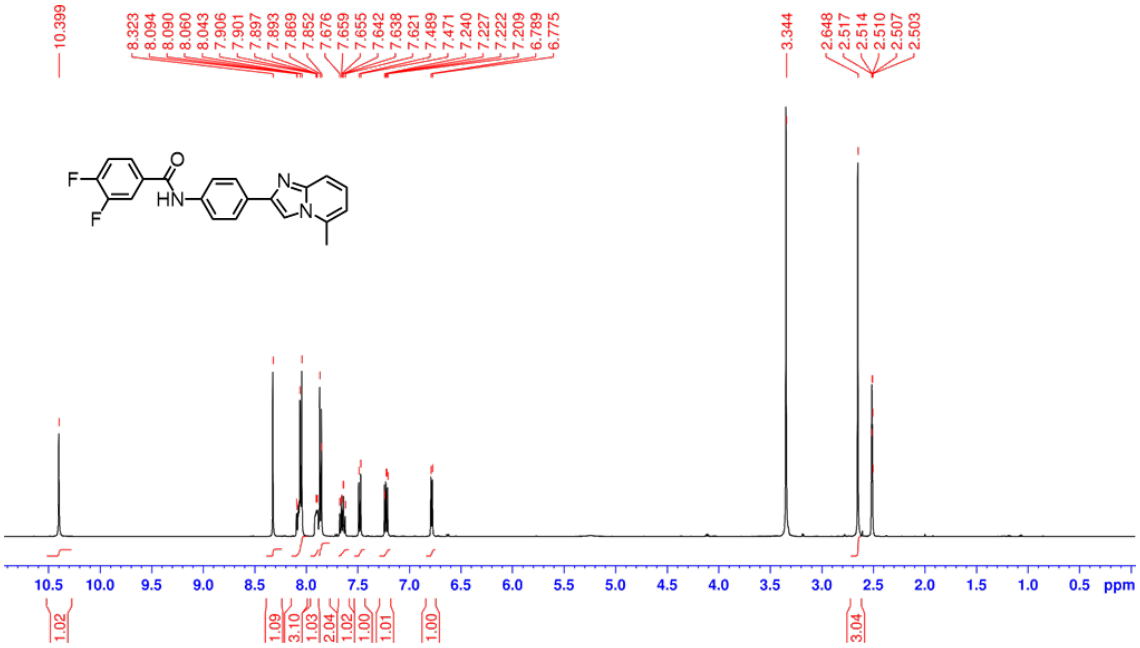
^{1}H NMR (500 MHz, DMSO-d_6) of **S2**



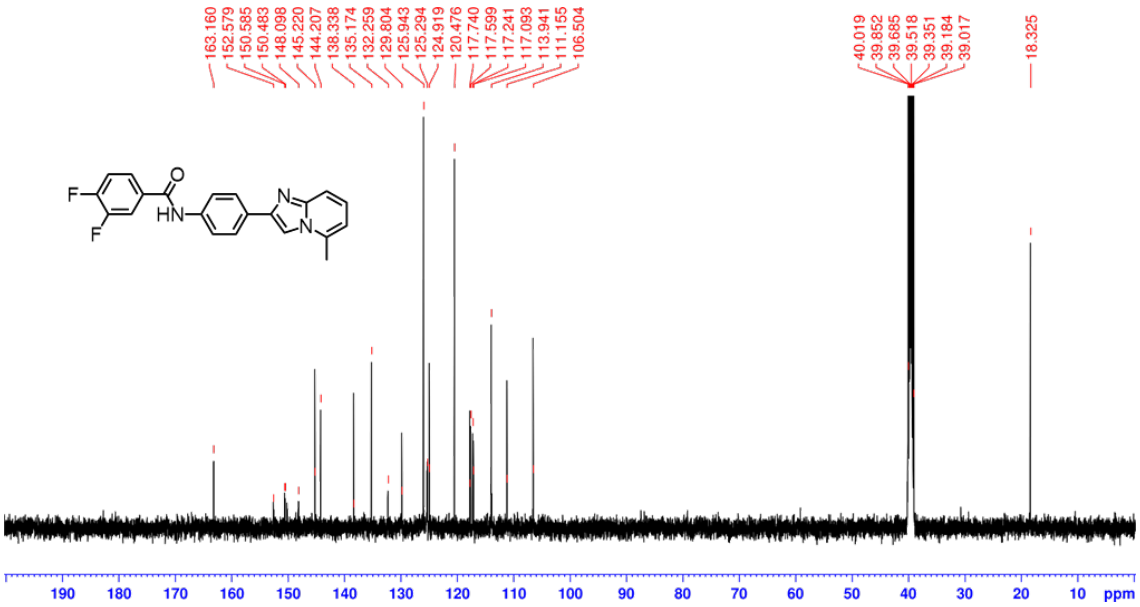
^{13}C NMR (125 MHz, DMSO-d_6) of **S2**



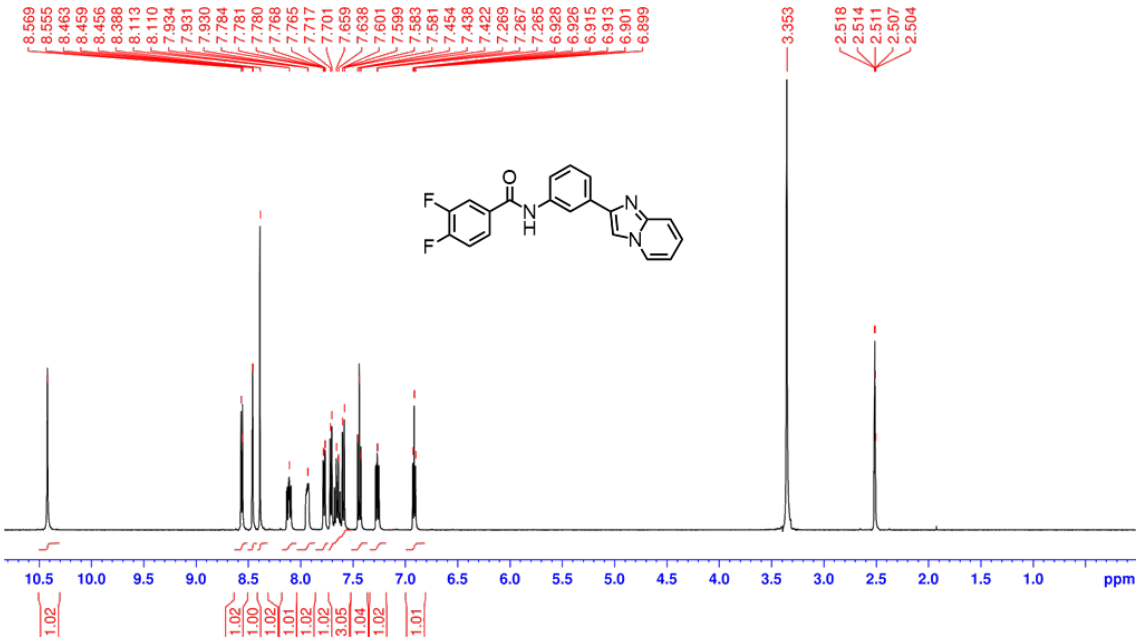
^{1}H NMR (500 MHz, DMSO-d_6) of **S3**



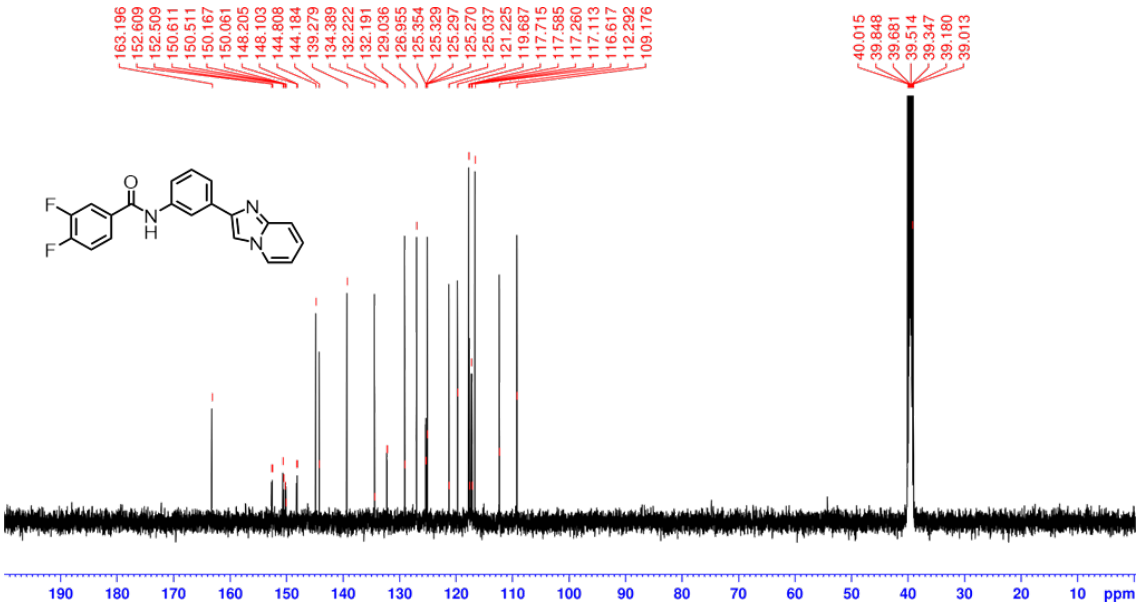
^{13}C NMR (125 MHz, DMSO-d_6) of **S3**



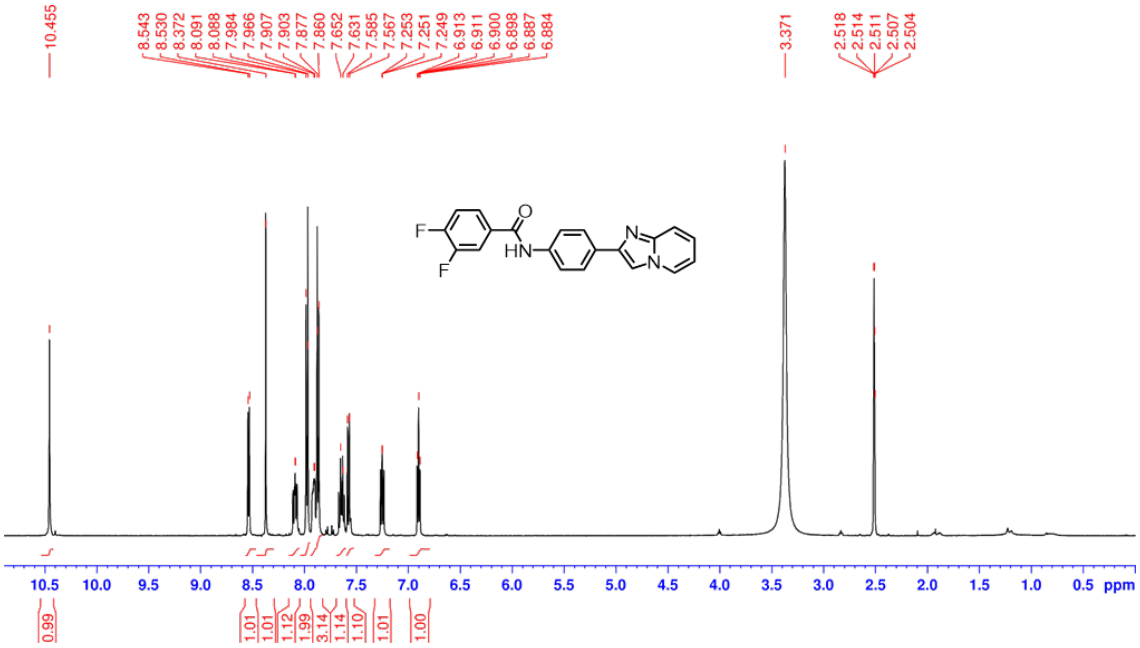
^{1}H NMR (500 MHz, DMSO-d_6) of **S4**



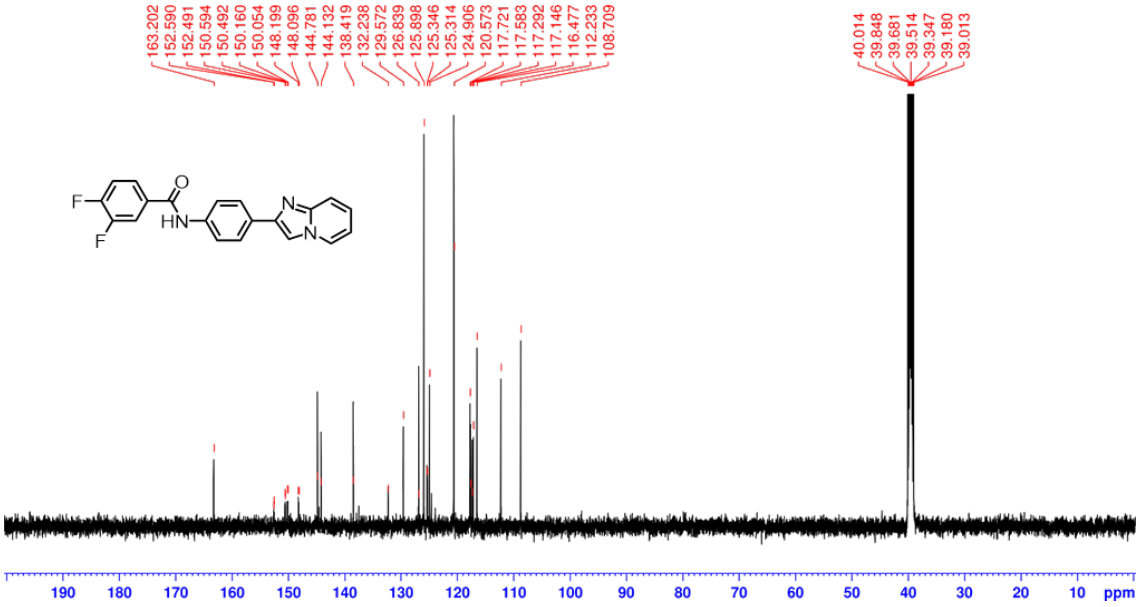
^{13}C NMR (125 MHz, DMSO-d_6) of **S4**



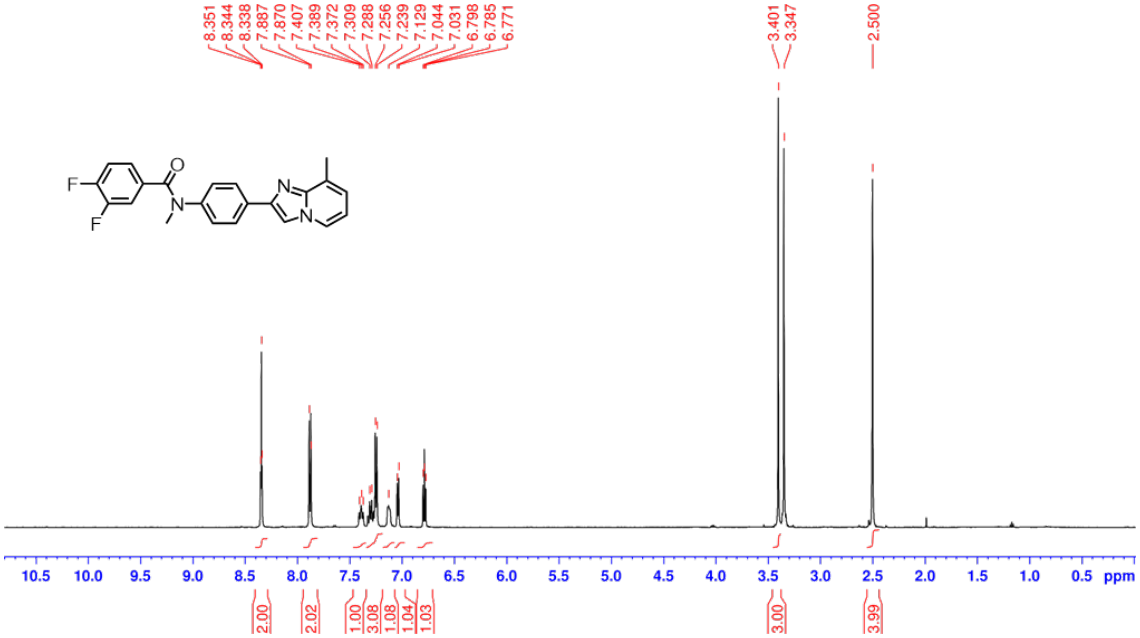
^{1}H NMR (500 MHz, DMSO-d_6) of **S5**



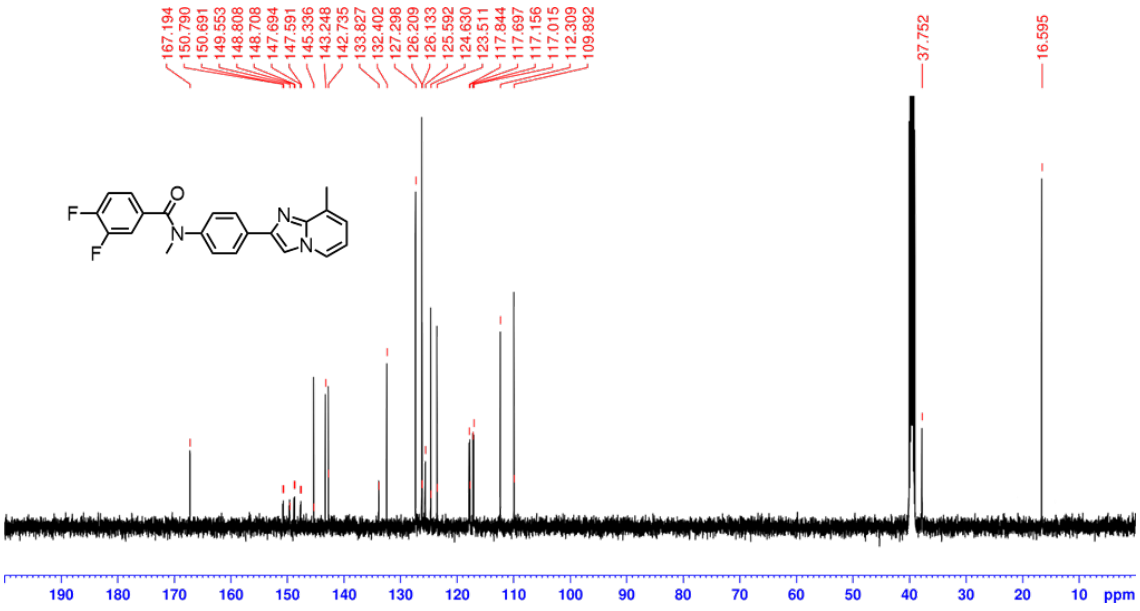
^{13}C NMR (125 MHz, DMSO-d_6) of **S5**



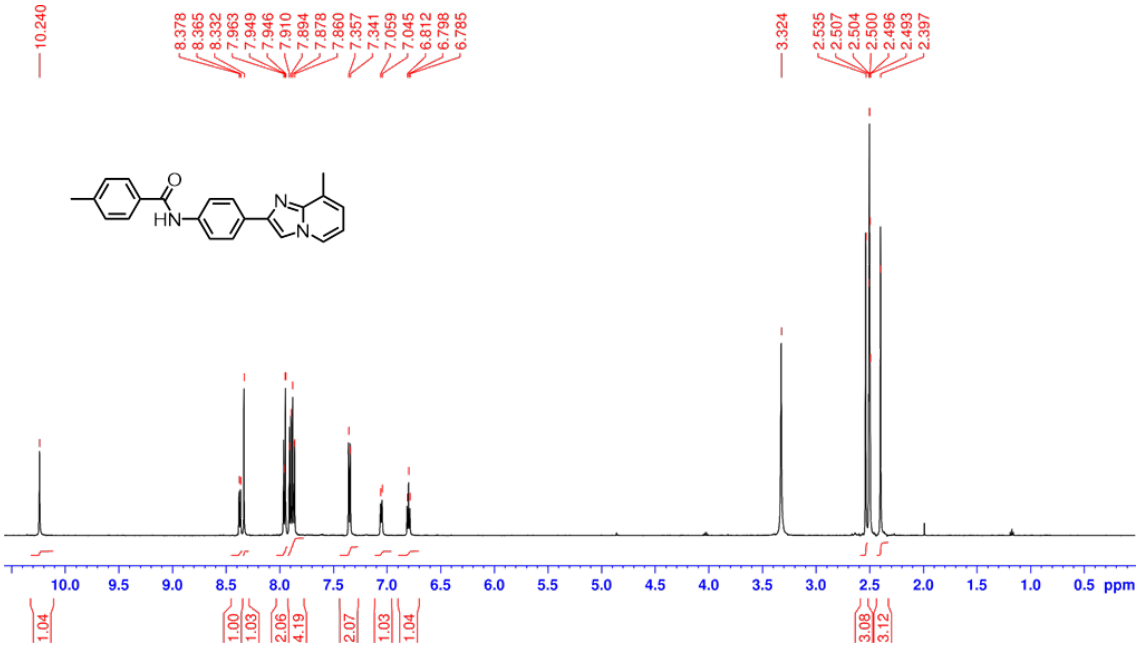
^{1}H NMR (500 MHz, DMSO-d_6) of **S6**



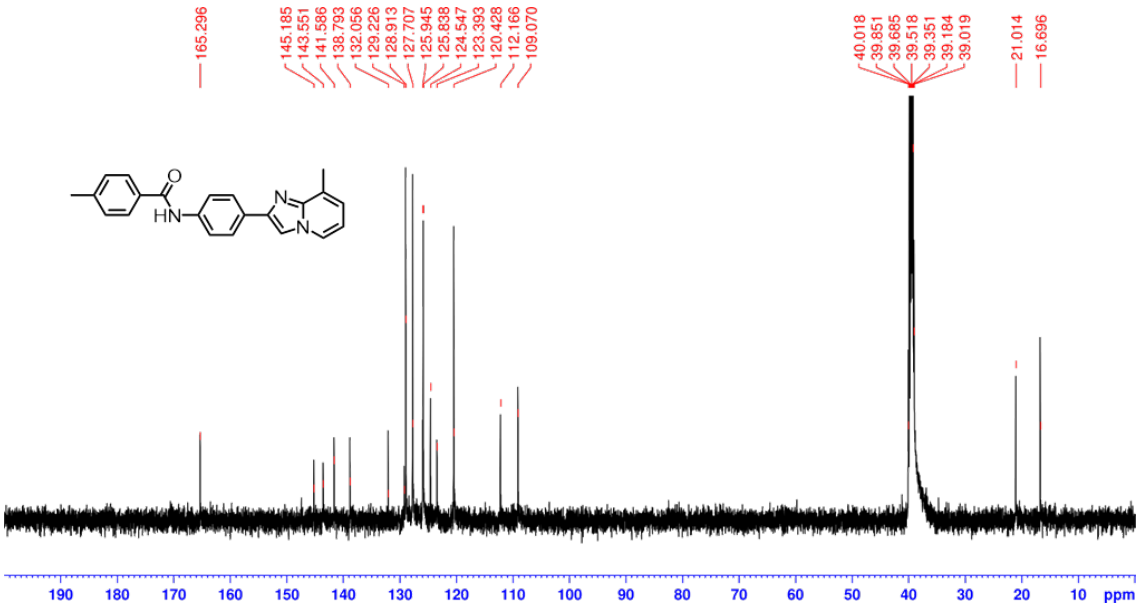
^{13}C NMR (125 MHz, DMSO-d_6) of **S6**



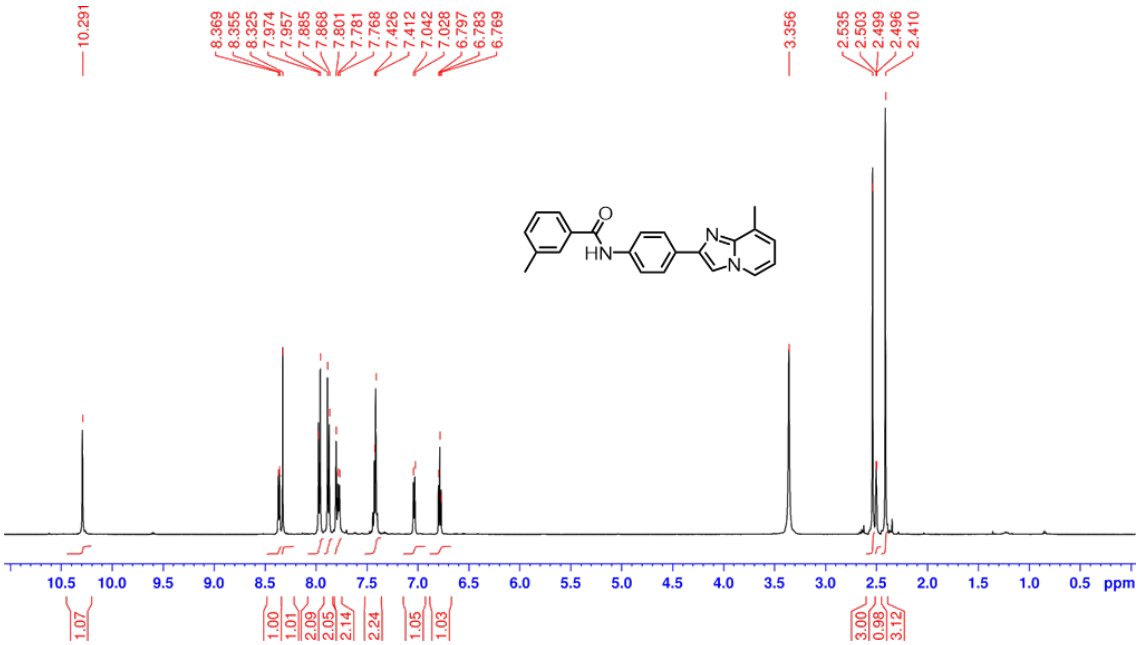
^{1}H NMR (500 MHz, DMSO-d_6) of **S7**



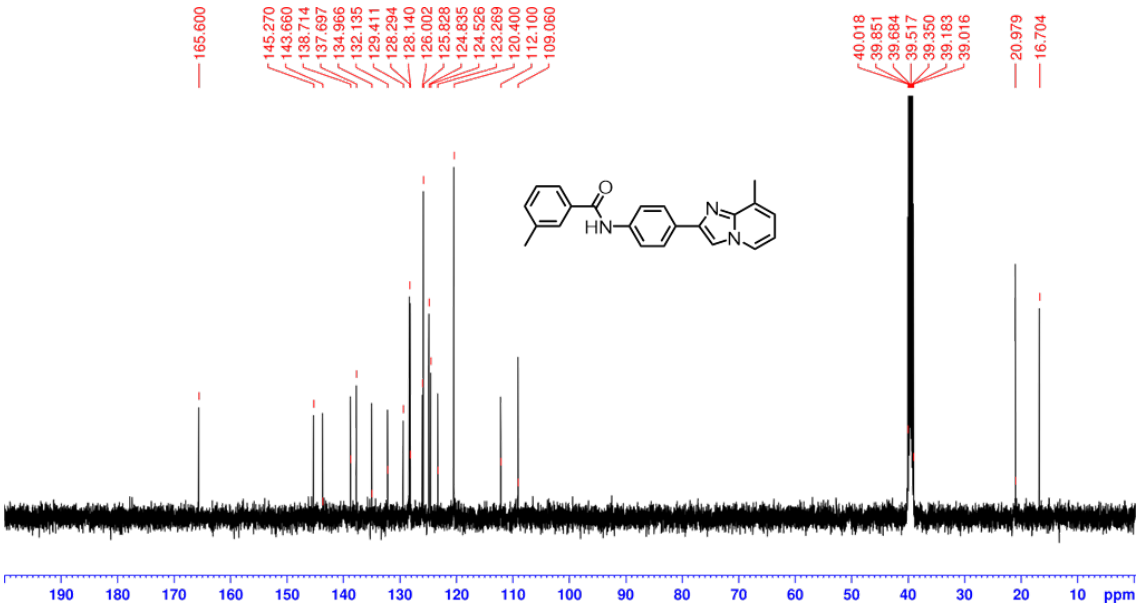
^{13}C NMR (125 MHz, DMSO-d_6) of **S7**



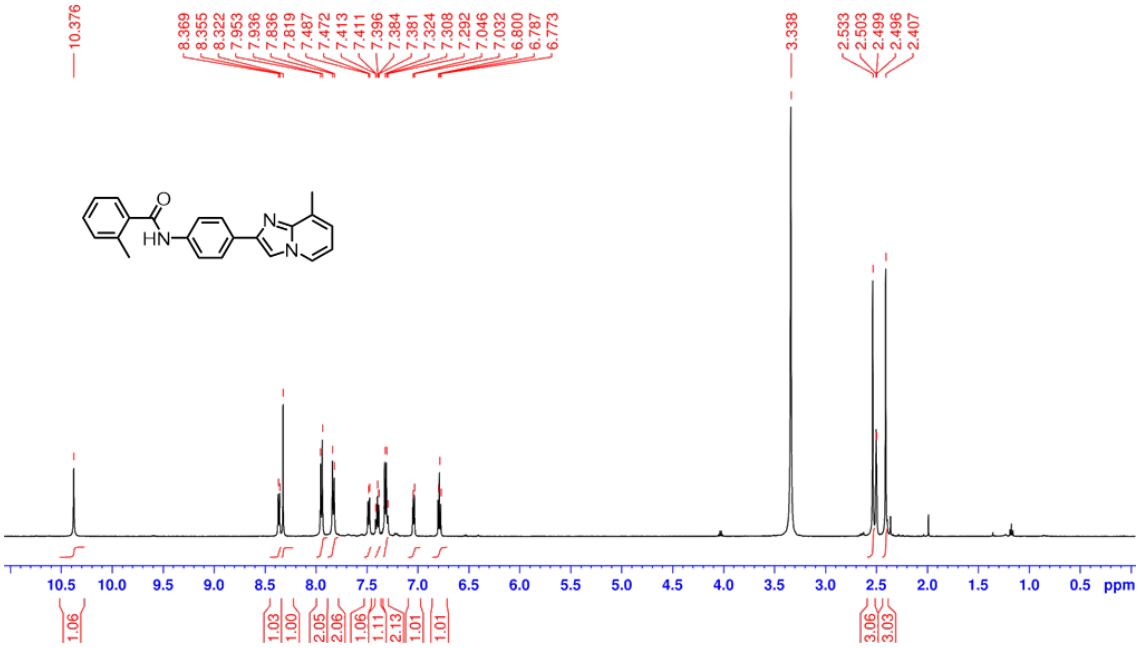
^{1}H NMR (500 MHz, DMSO-d_6) of **S8**



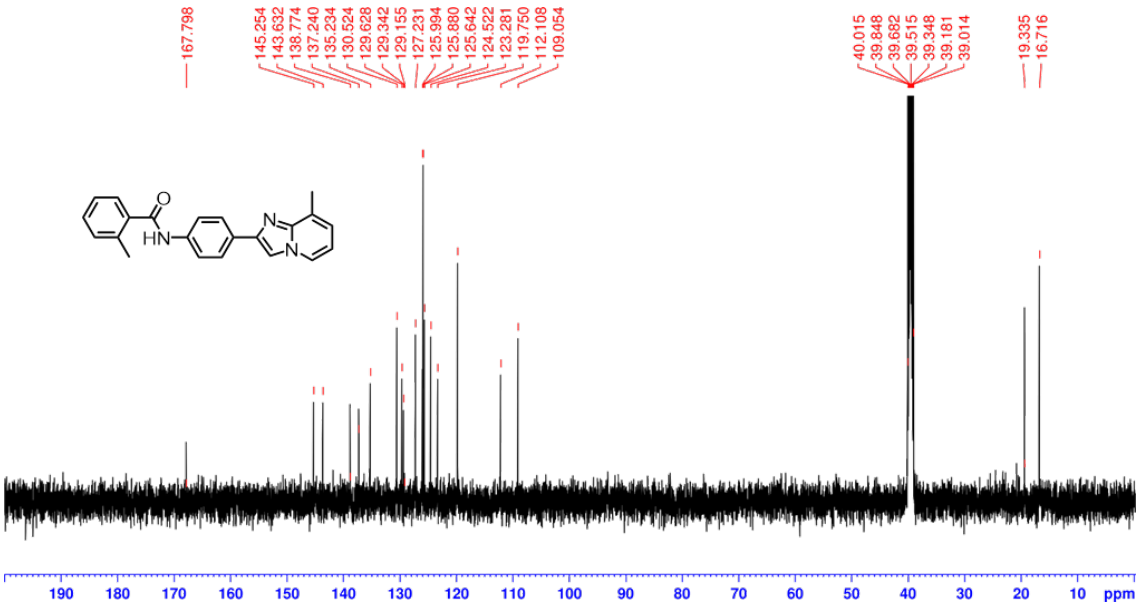
^{13}C NMR (125 MHz, DMSO-d_6) of **S8**



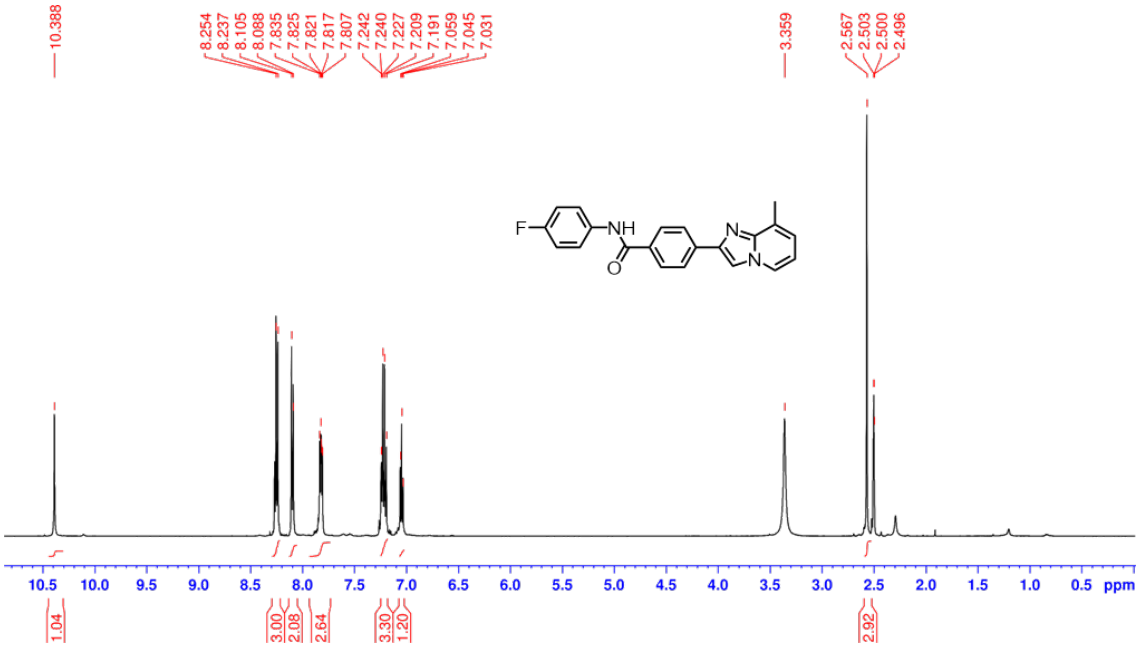
^{1}H NMR (500 MHz, DMSO-d_6) of **S9**



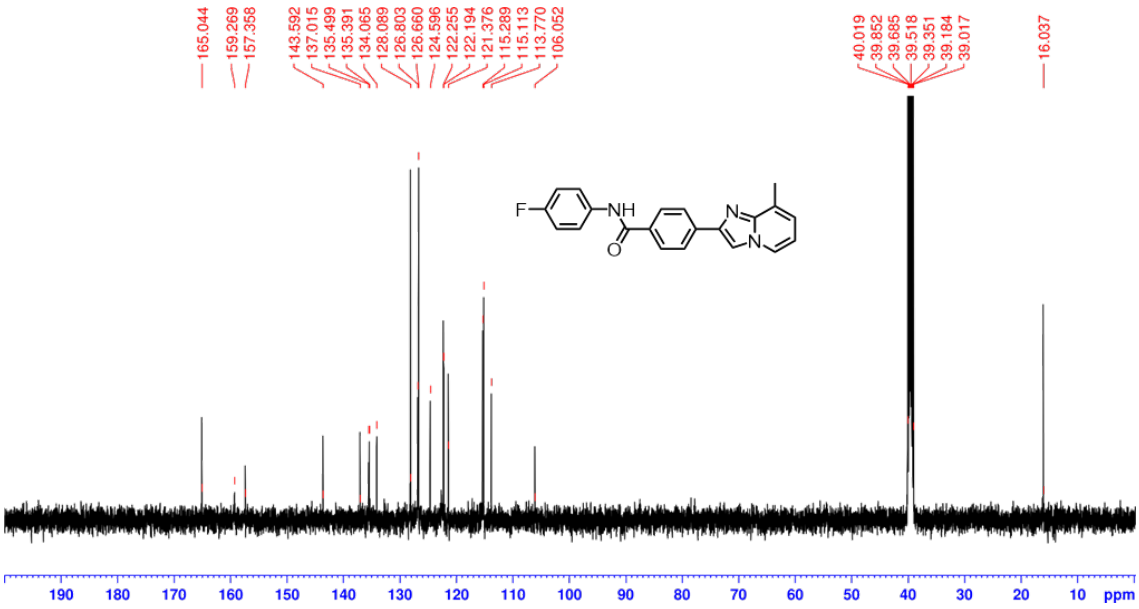
^{13}C NMR (125 MHz, DMSO-d_6) of **S9**



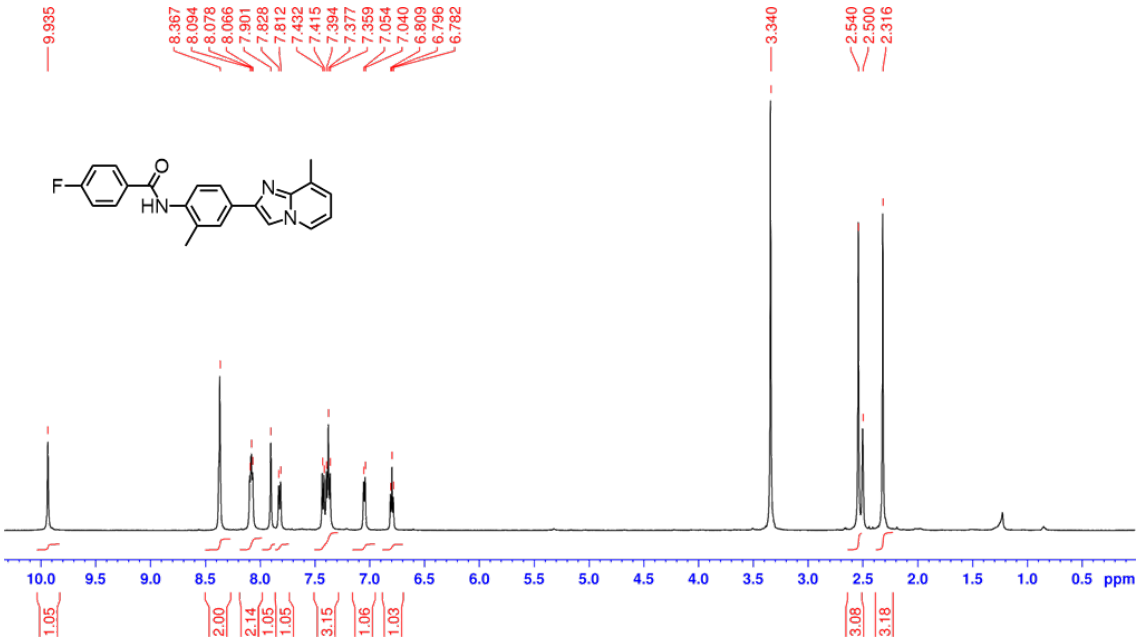
^{1}H NMR (500 MHz, DMSO-d_6) of **S10**



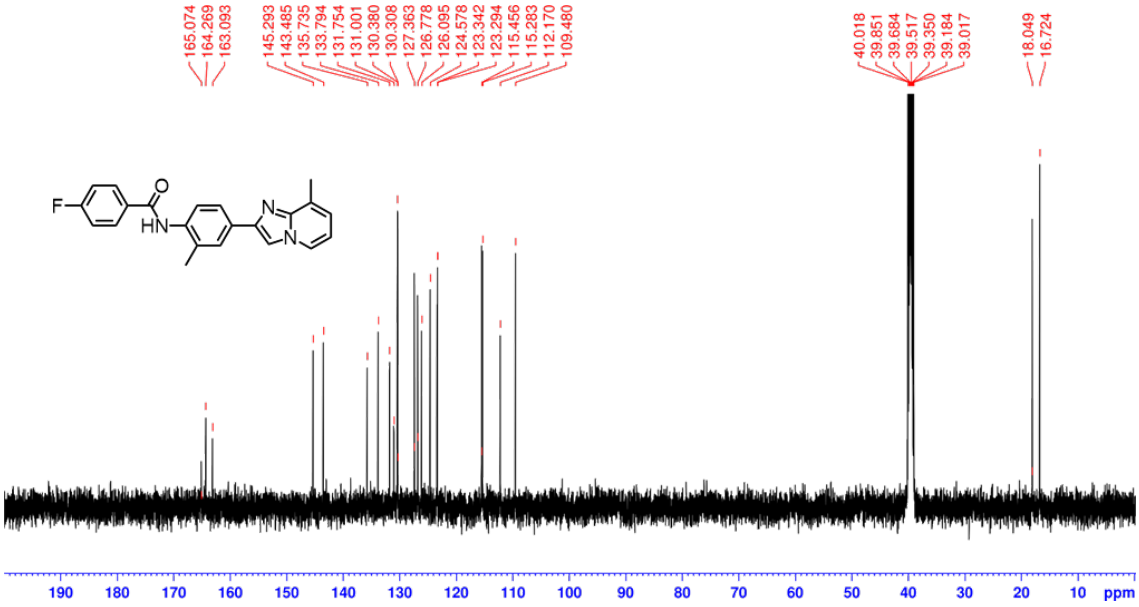
^{13}C NMR (125 MHz, DMSO-d_6) of **S10**



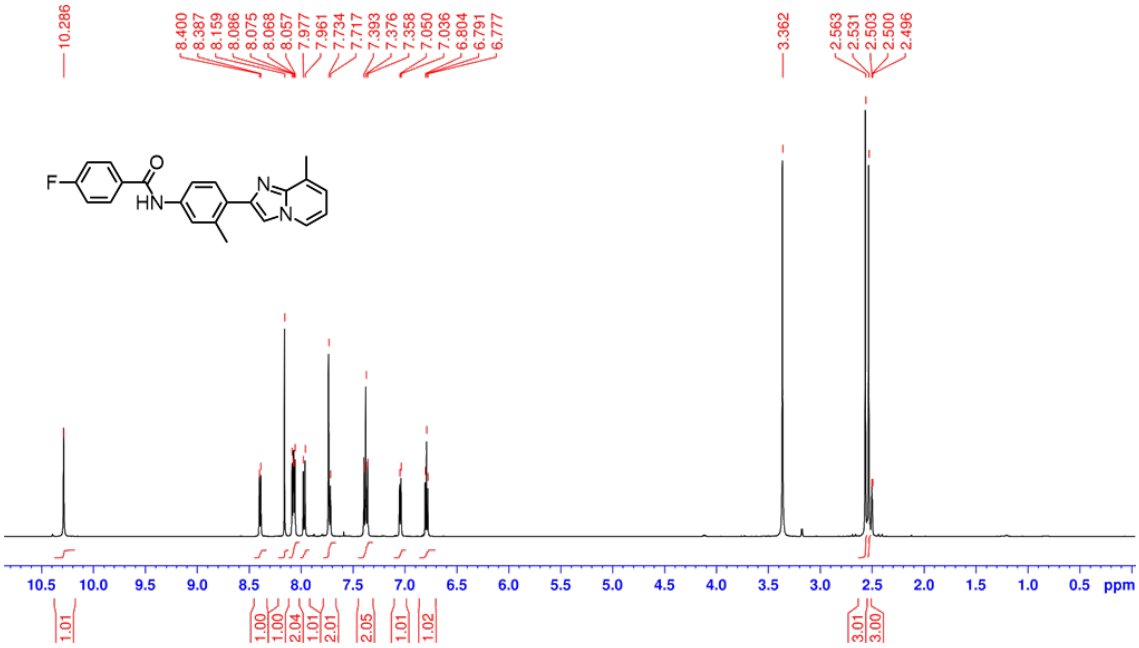
^{1}H NMR (500 MHz, DMSO-d_6) of **S11**



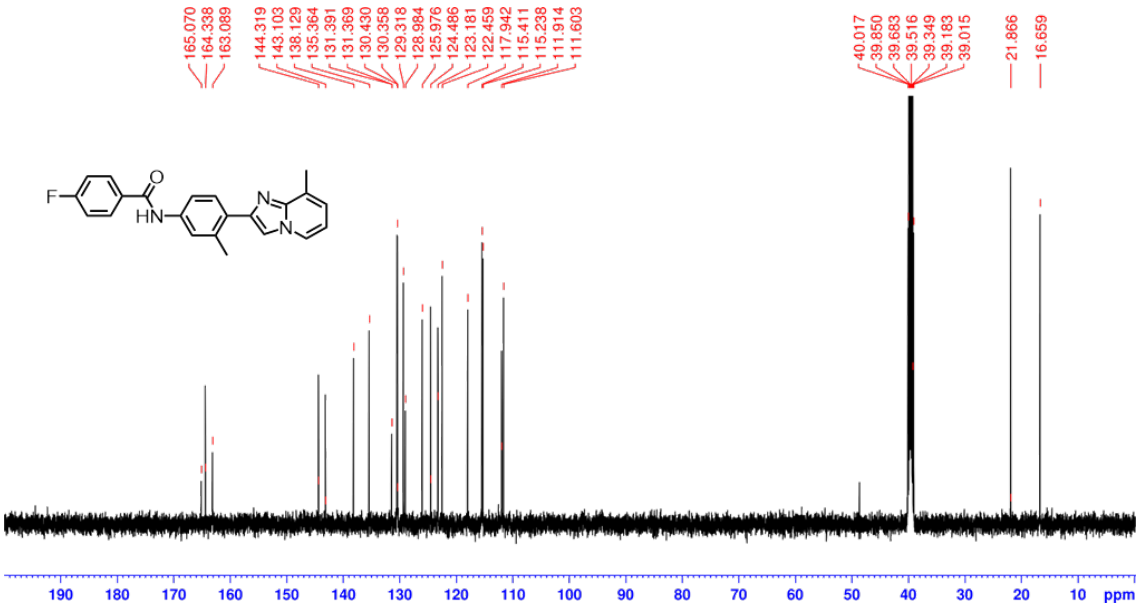
^{13}C NMR (125 MHz, DMSO-d_6) of **S11**



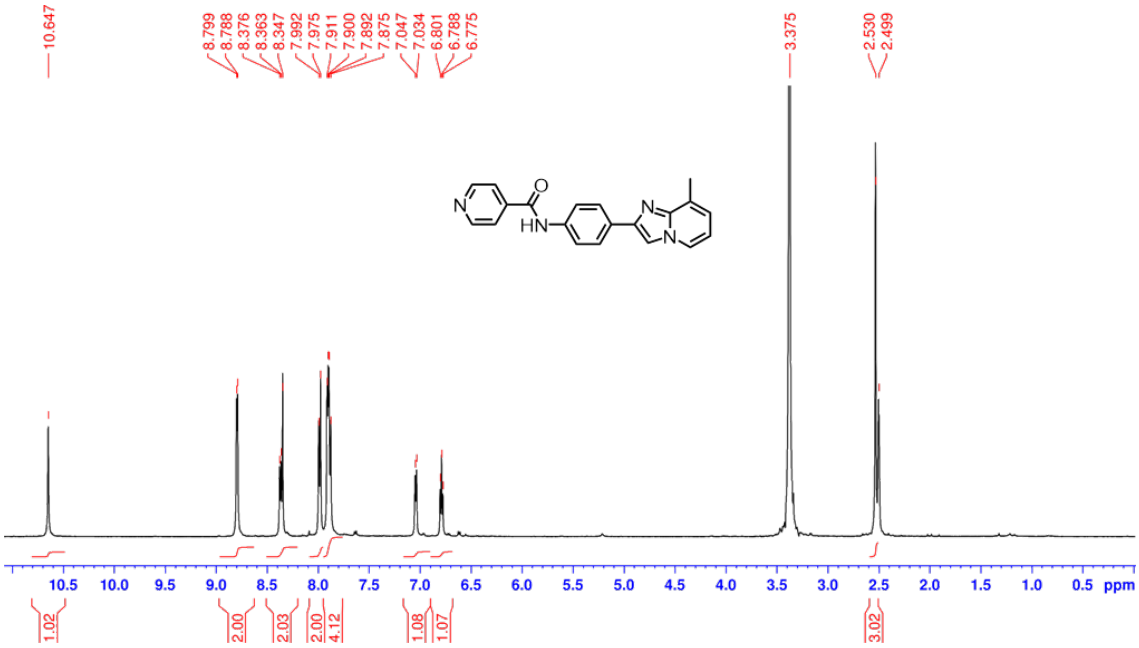
^{1}H NMR (500 MHz, DMSO-d_6) of **S12**



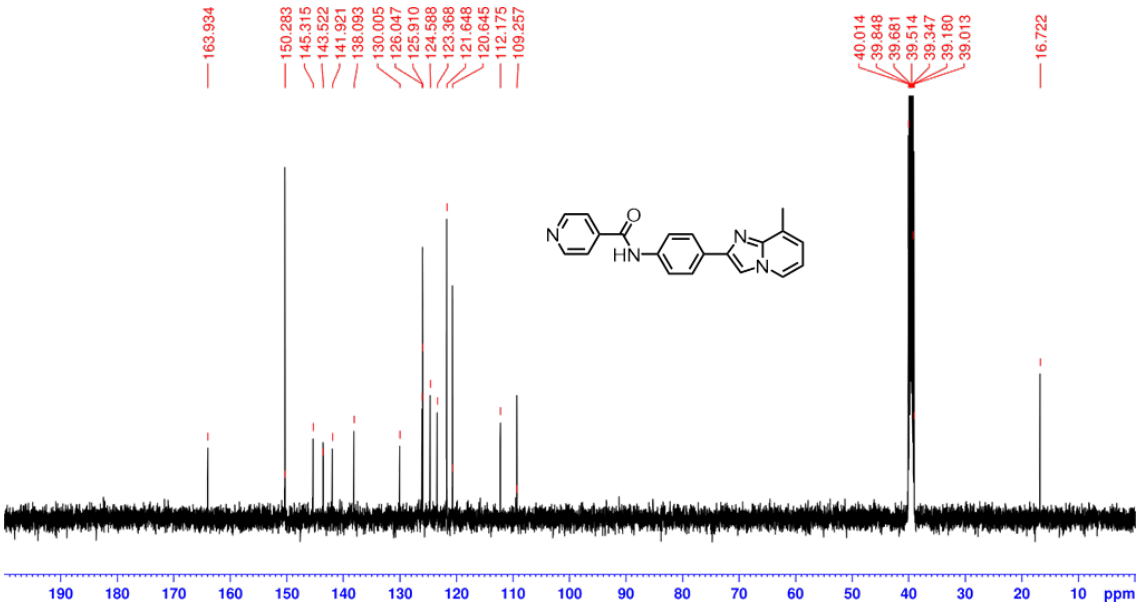
^{13}C NMR (125 MHz, DMSO-d_6) of **S12**



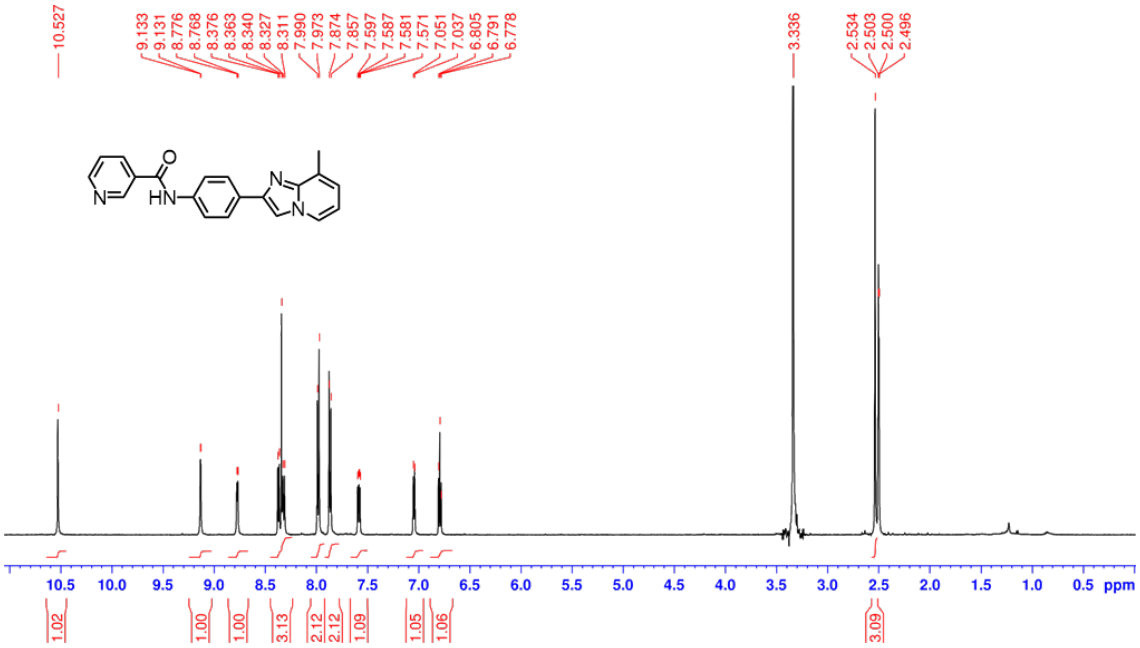
^{1}H NMR (500 MHz, DMSO-d_6) of **S13**



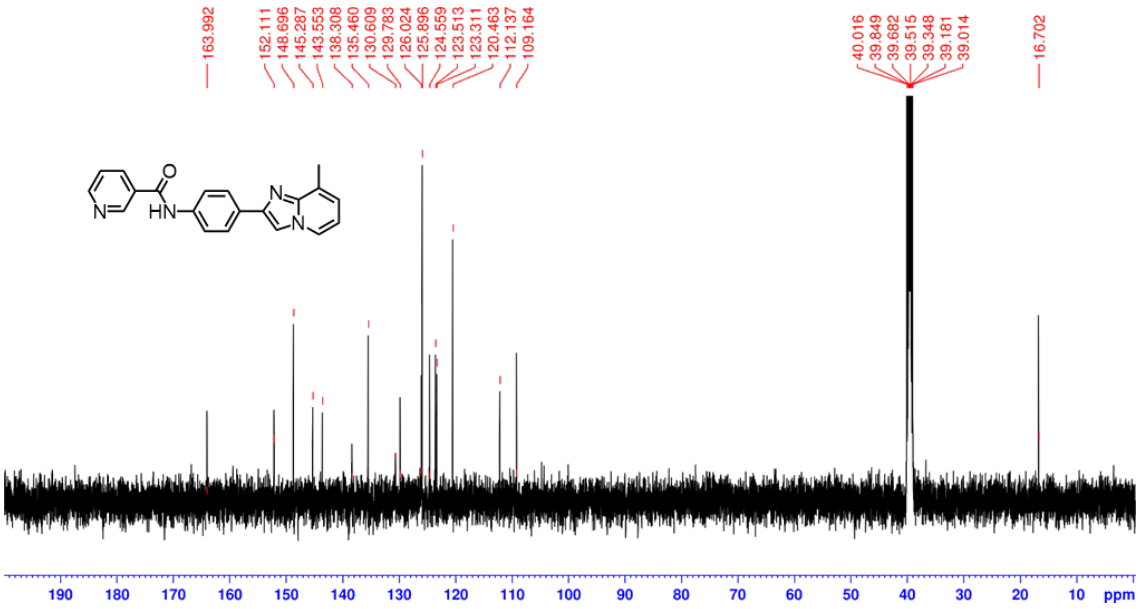
^{13}C NMR (125 MHz, DMSO-d_6) of **S13**



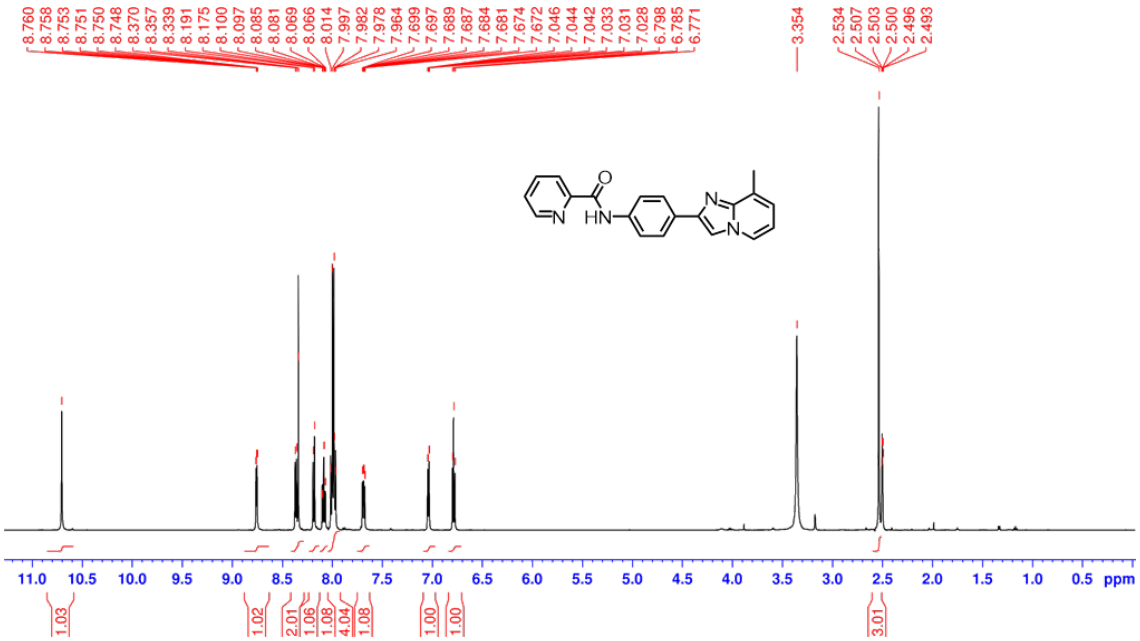
^{1}H NMR (500 MHz, DMSO-d_6) of **S14**



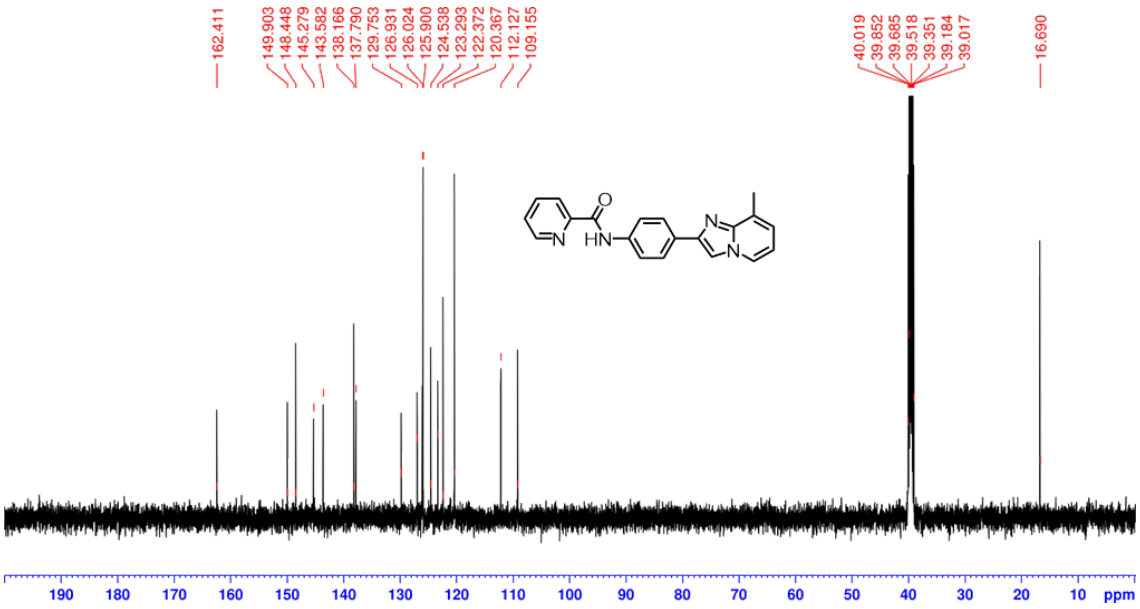
^{13}C NMR (125 MHz, DMSO-d_6) of **S14**



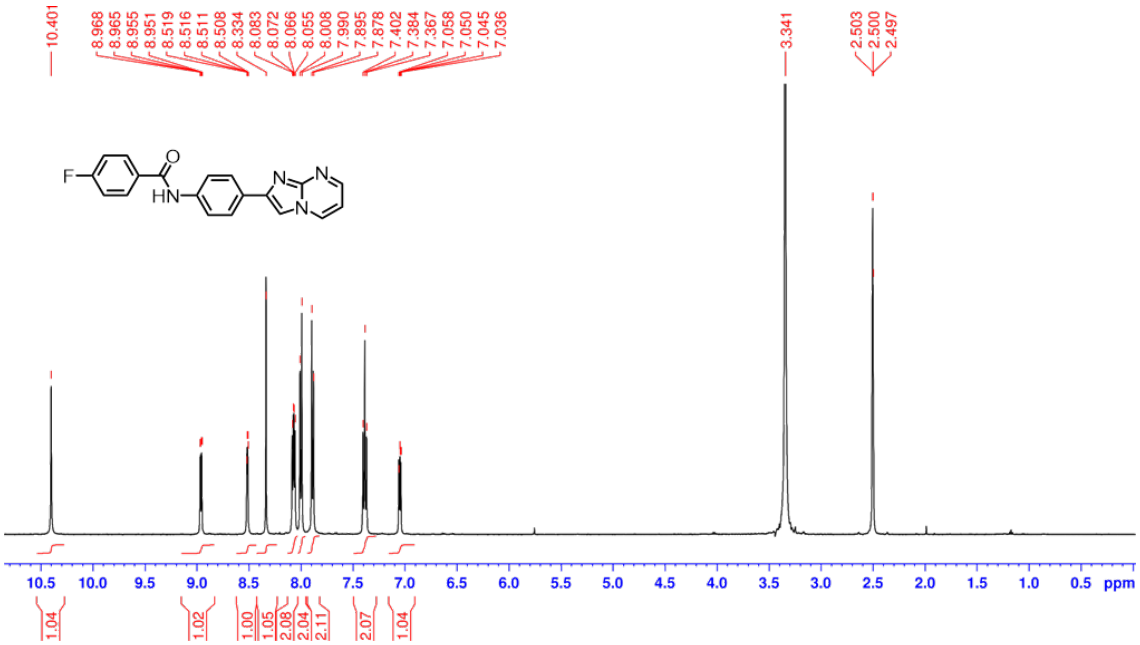
^{1}H NMR (500 MHz, DMSO-d_6) of **S15**



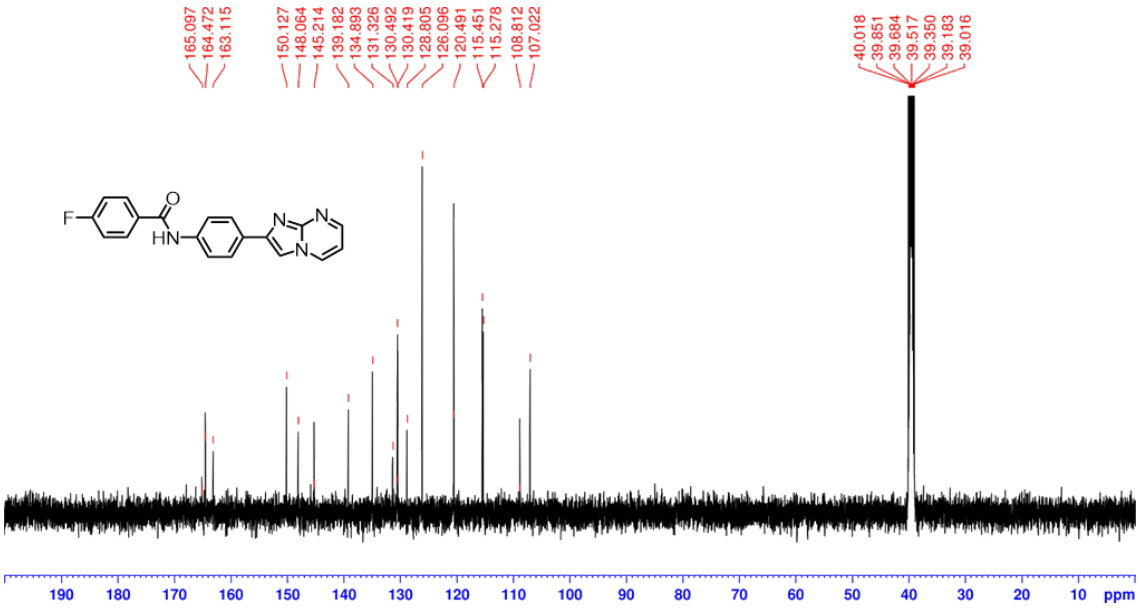
^{13}C NMR (125 MHz, DMSO-d_6) of **S15**



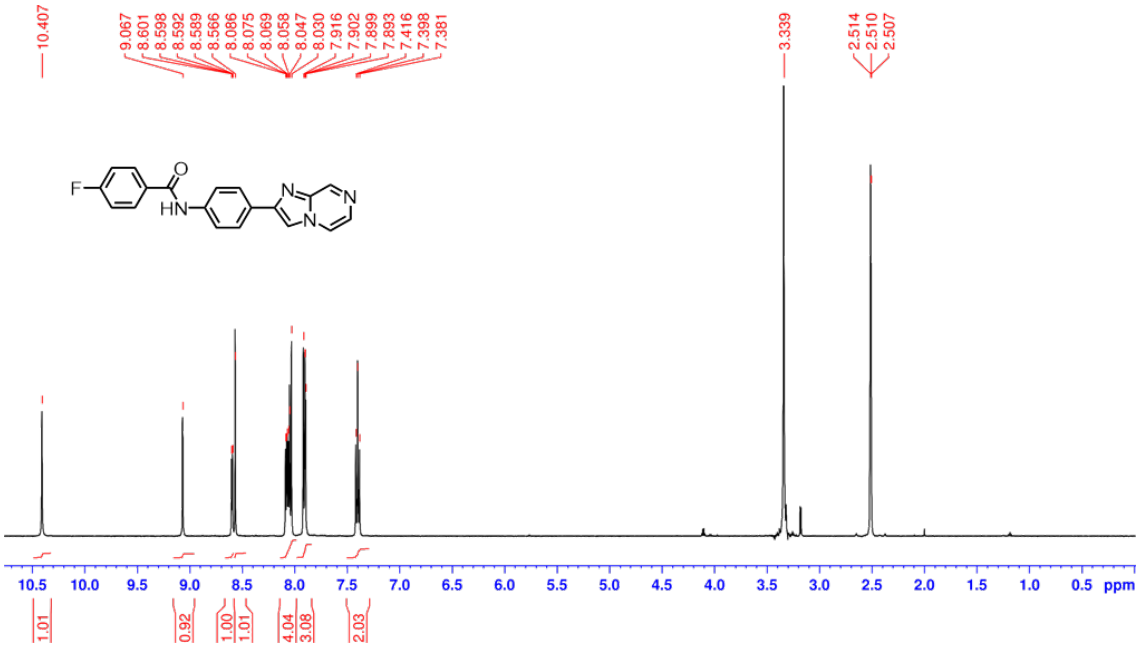
^{1}H NMR (500 MHz, DMSO-d_6) of **S16**



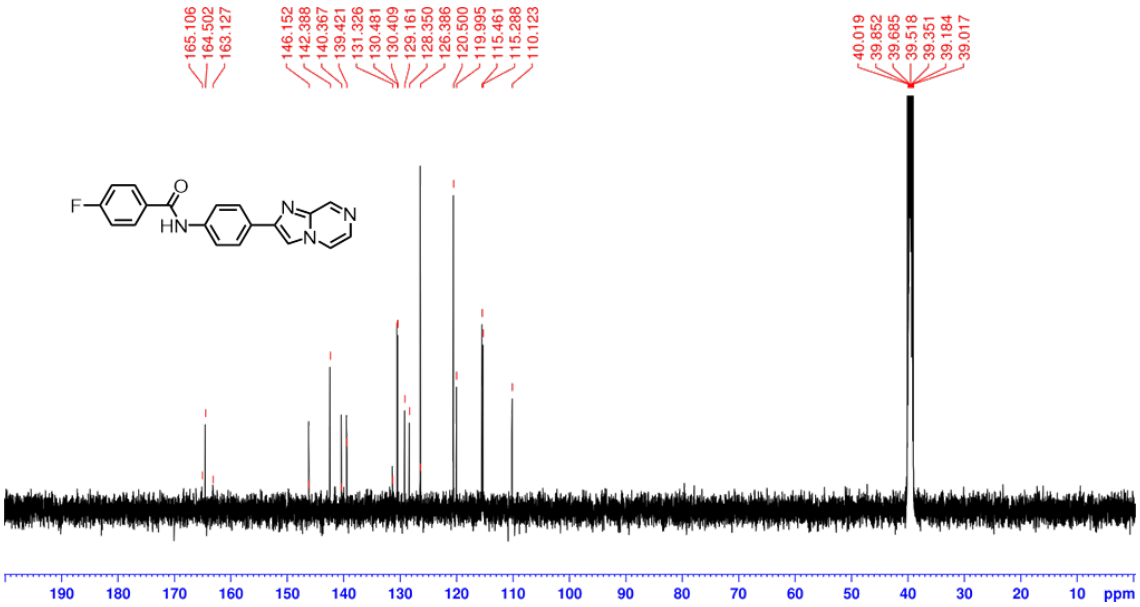
^{13}C NMR (125 MHz, DMSO-d_6) of **S16**



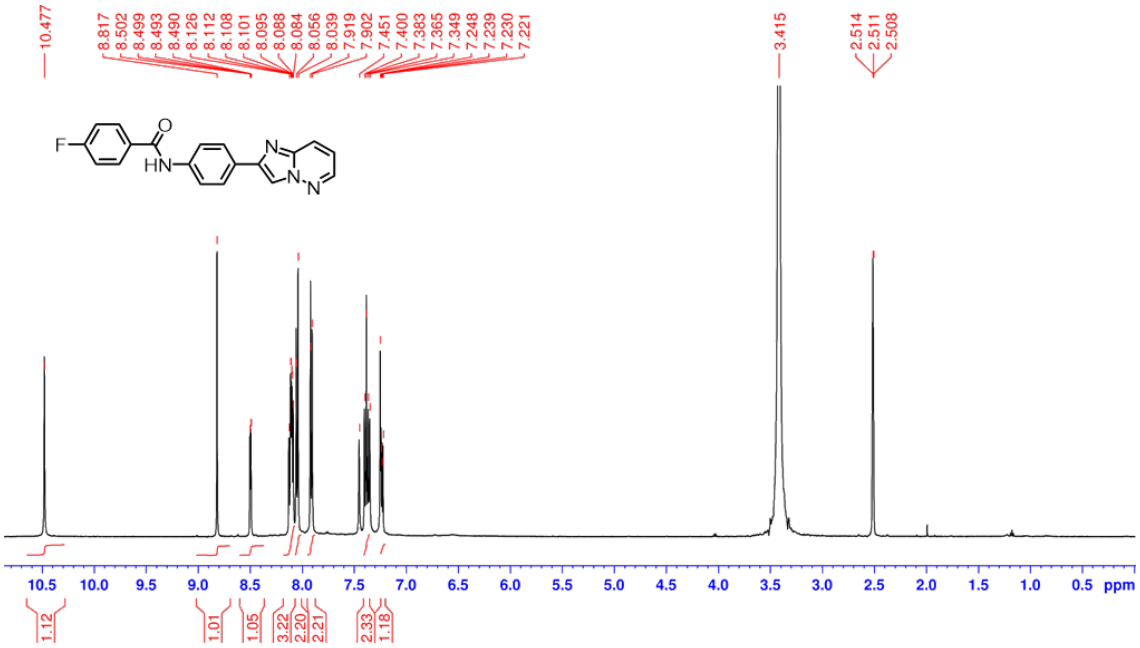
^{1}H NMR (500 MHz, DMSO-d_6) of **S17**



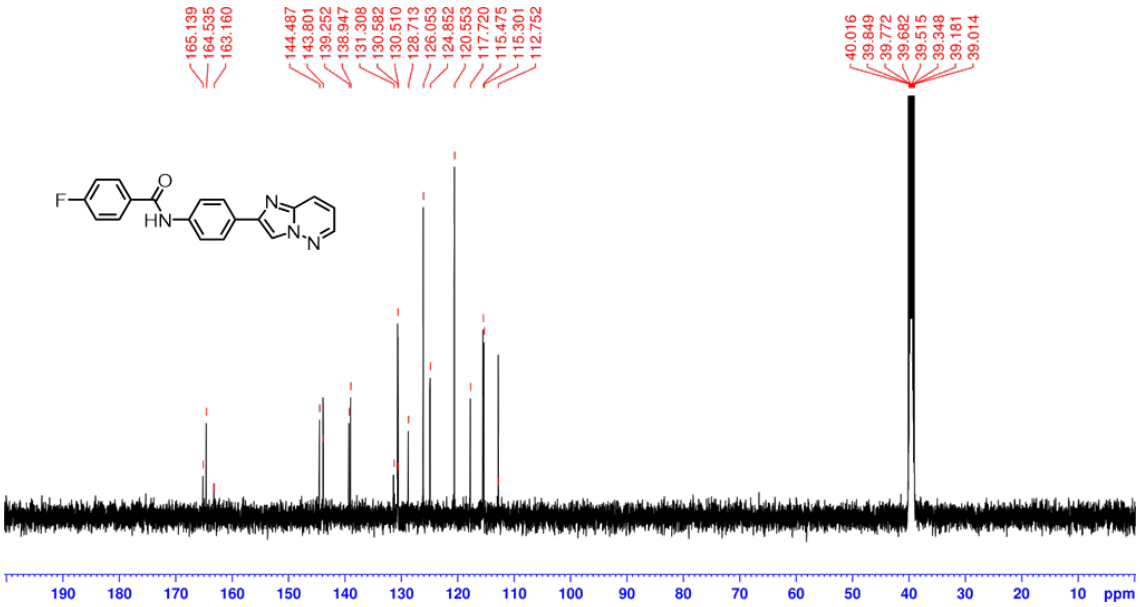
^{13}C NMR (125 MHz, DMSO-d_6) of **S17**



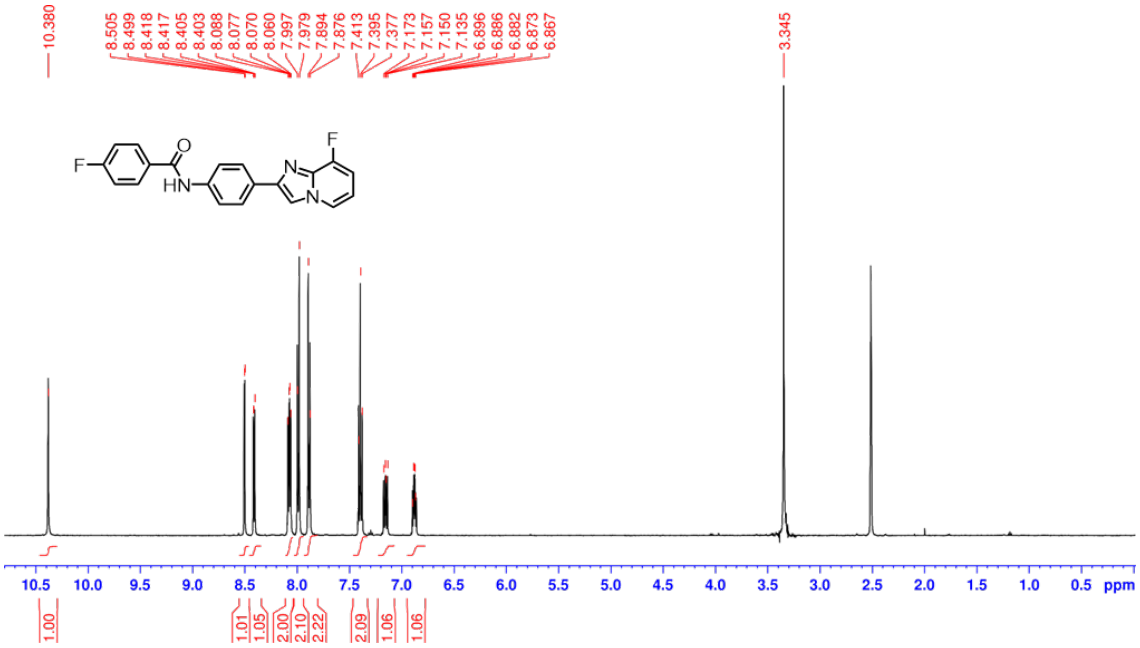
^{1}H NMR (500 MHz, DMSO-d_6) of **S18**



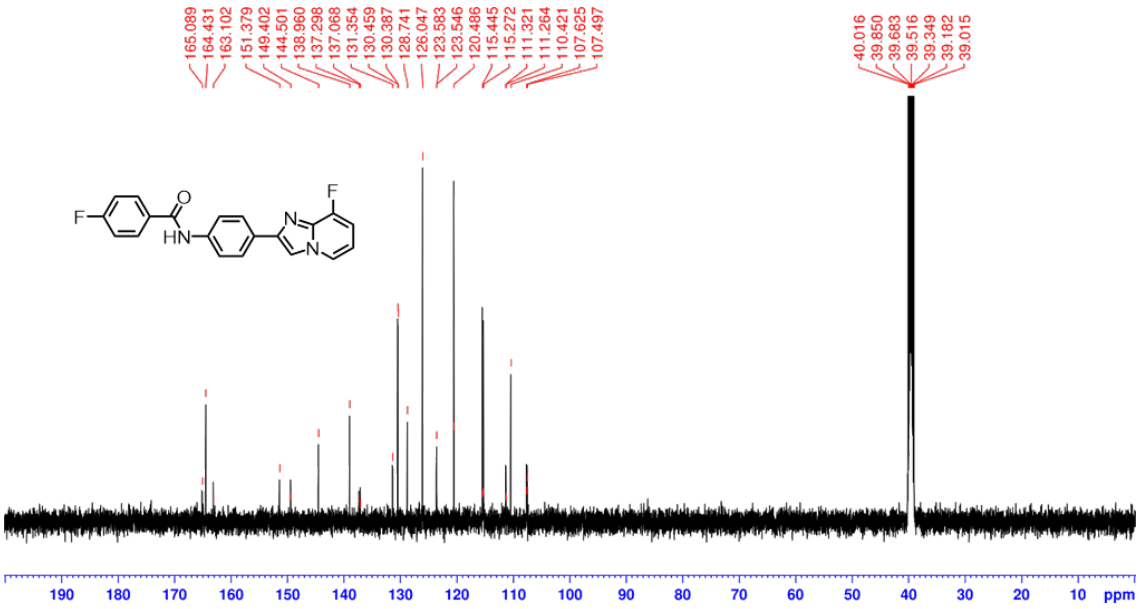
^{13}C NMR (125 MHz, DMSO-d_6) of **S18**



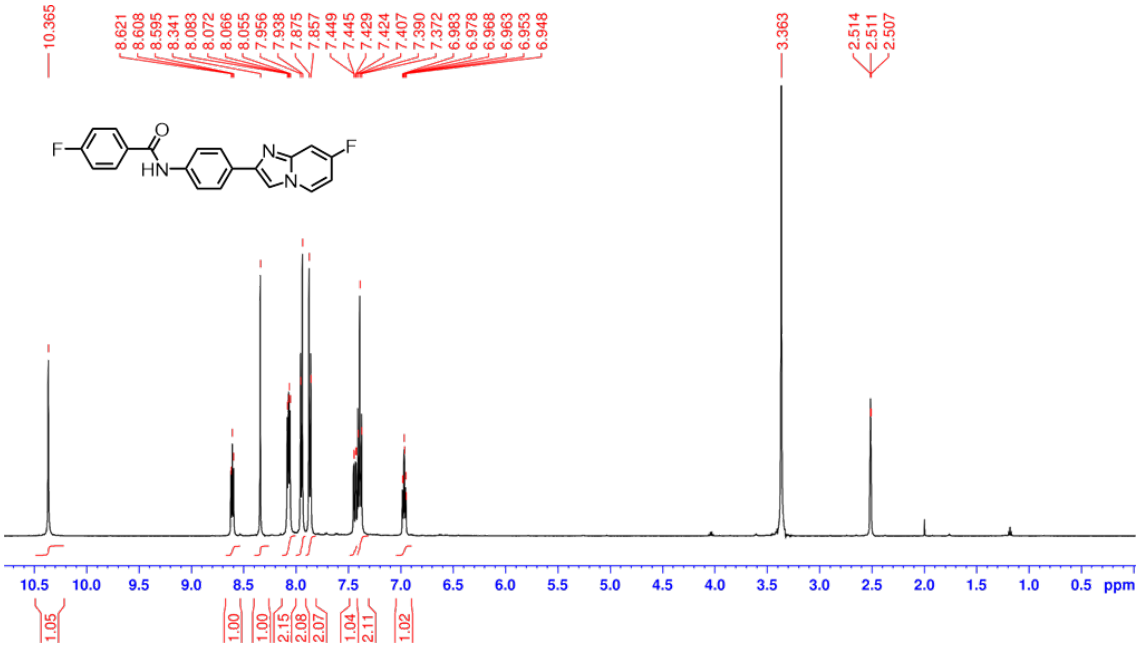
^{1}H NMR (500 MHz, DMSO-d_6) of **S19**



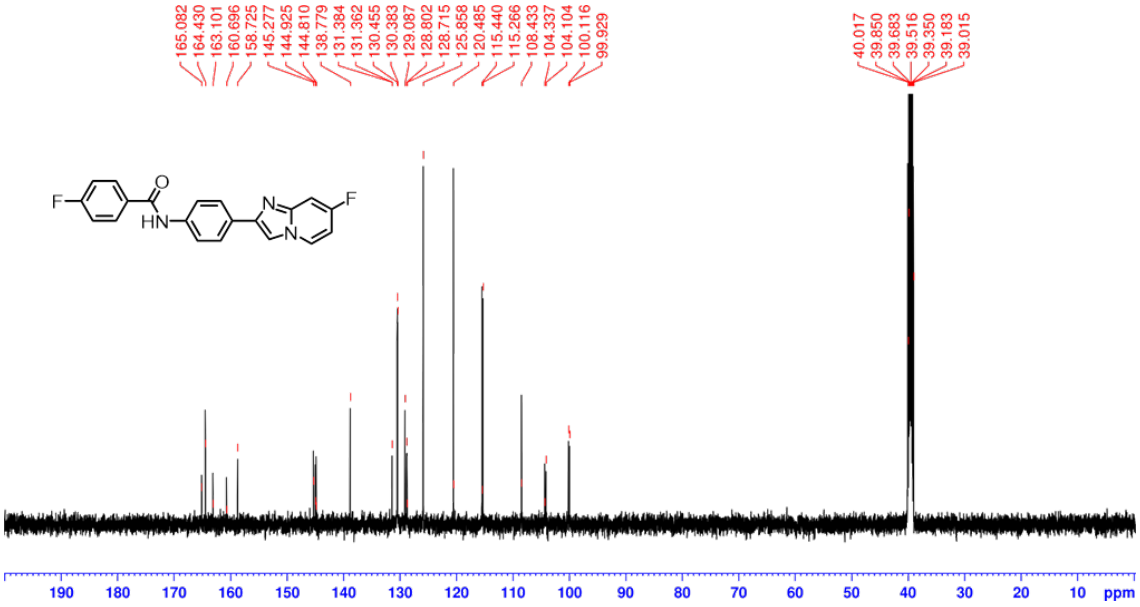
^{13}C NMR (125 MHz, DMSO-d_6) of **S19**



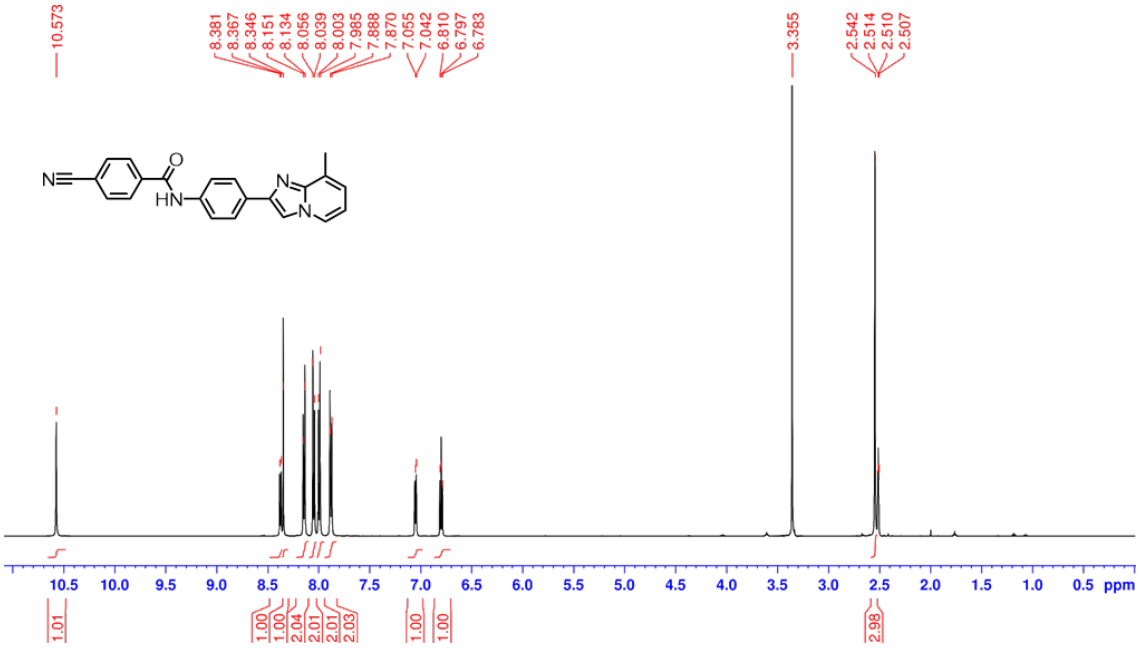
^{1}H NMR (500 MHz, DMSO-d_6) of **S20**



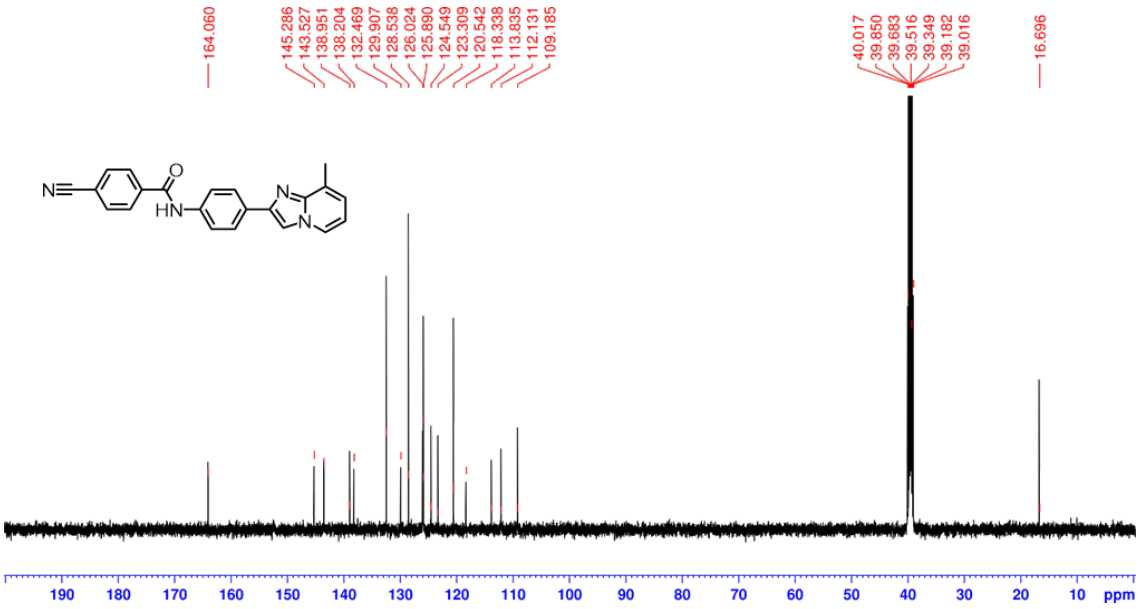
^{13}C NMR (125 MHz, DMSO-d_6) of **S20**



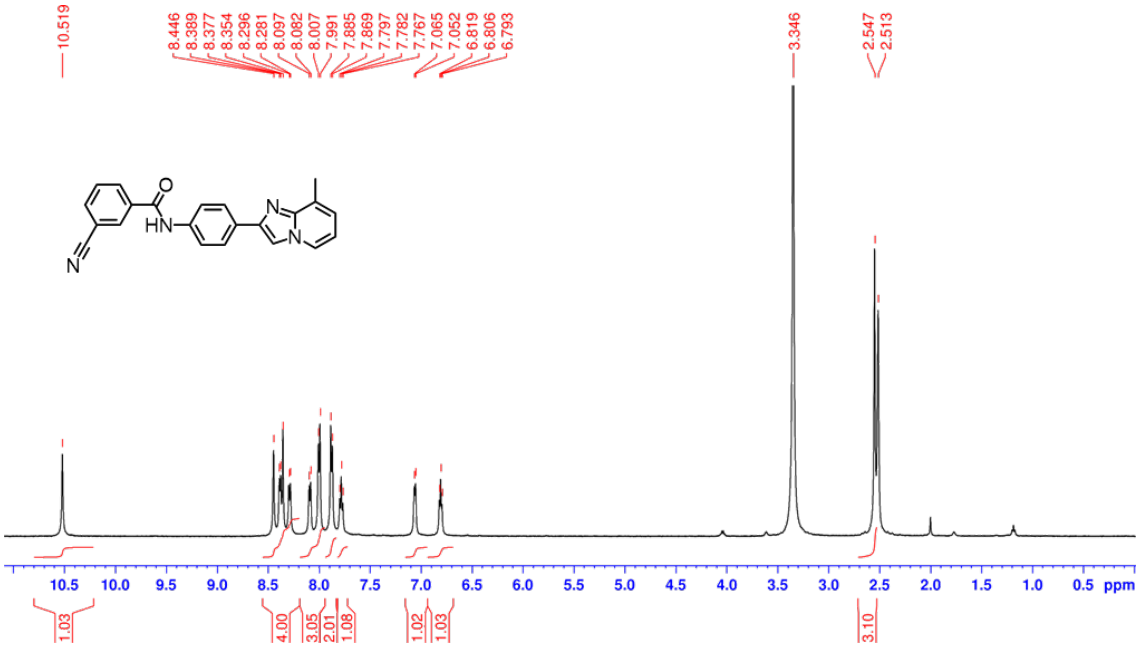
^{1}H NMR (500 MHz, DMSO-d_6) of **S21**



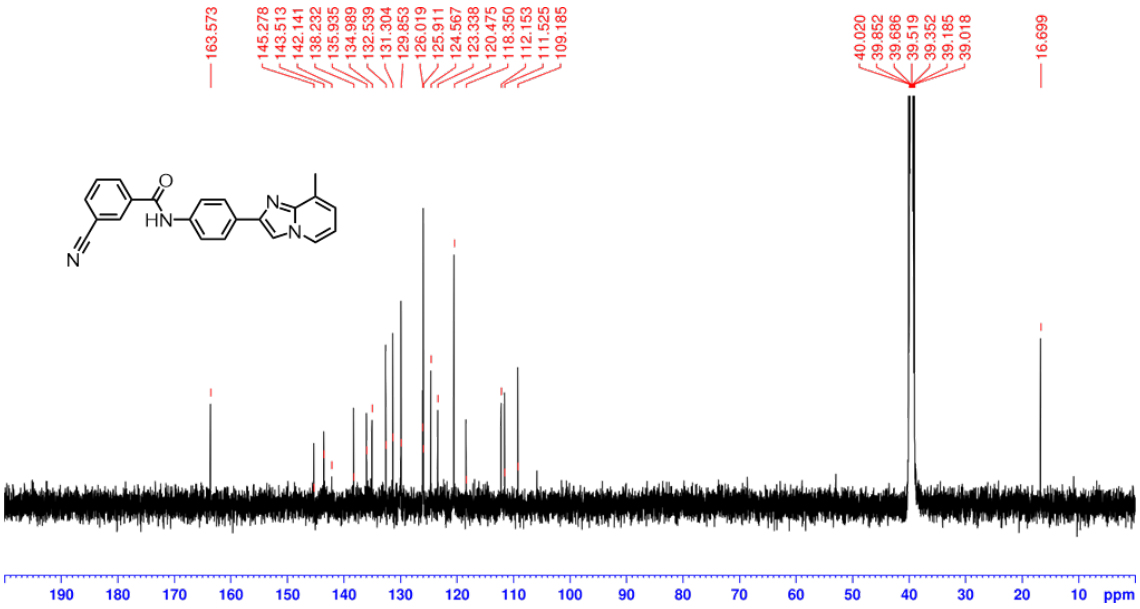
^{13}C NMR (125 MHz, DMSO-d_6) of **S21**



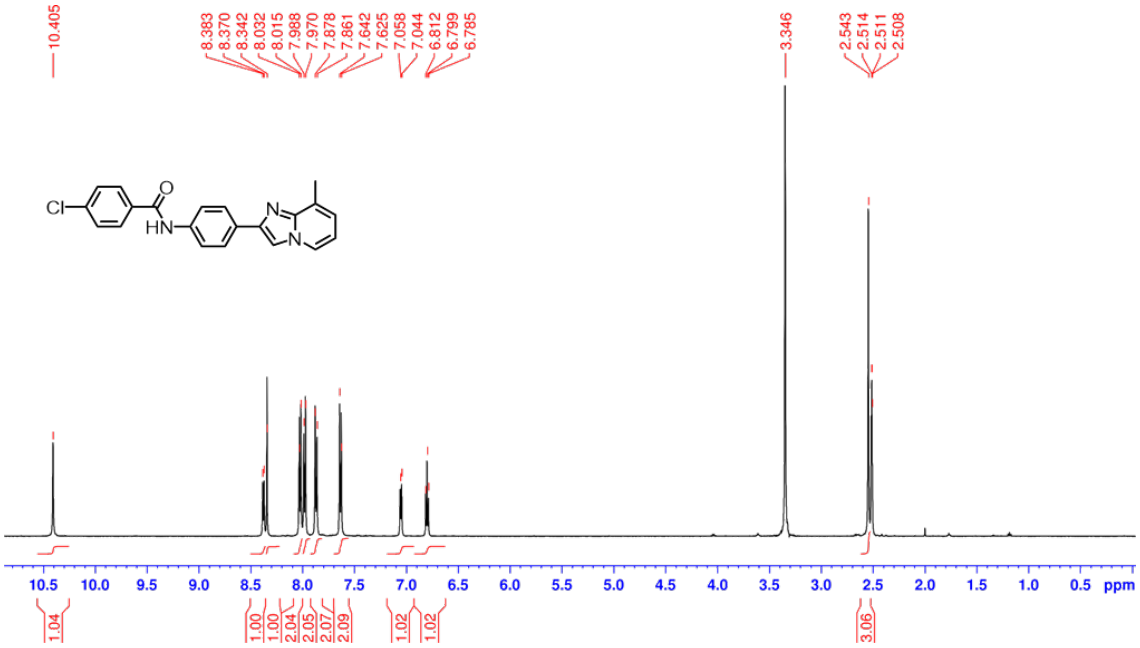
^{1}H NMR (500 MHz, DMSO-d_6) of **S22**



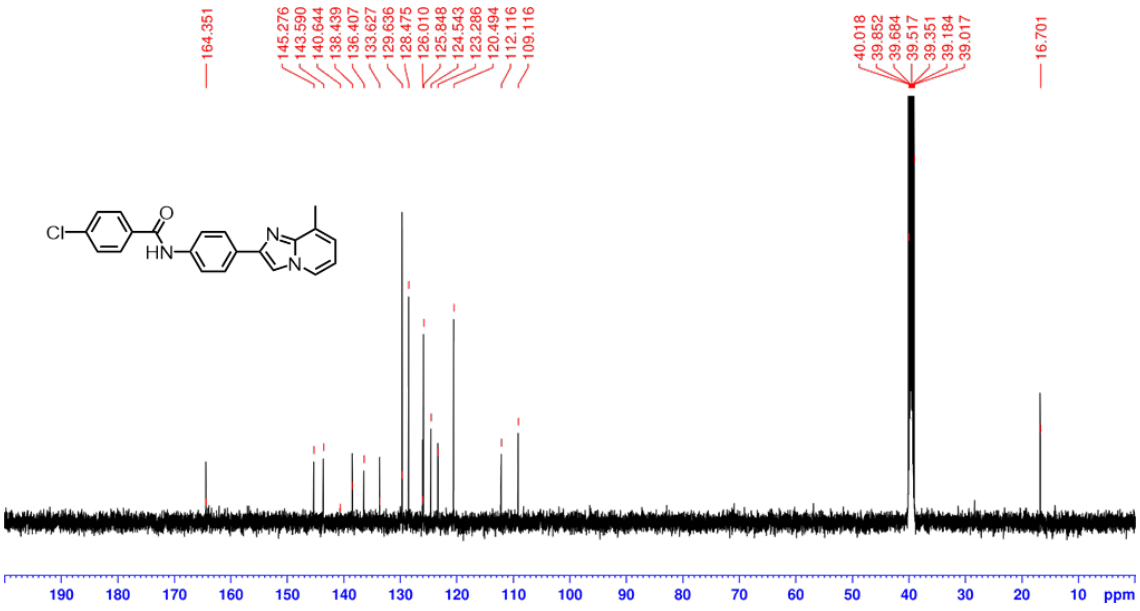
^{13}C NMR (125 MHz, DMSO-d_6) of **S22**



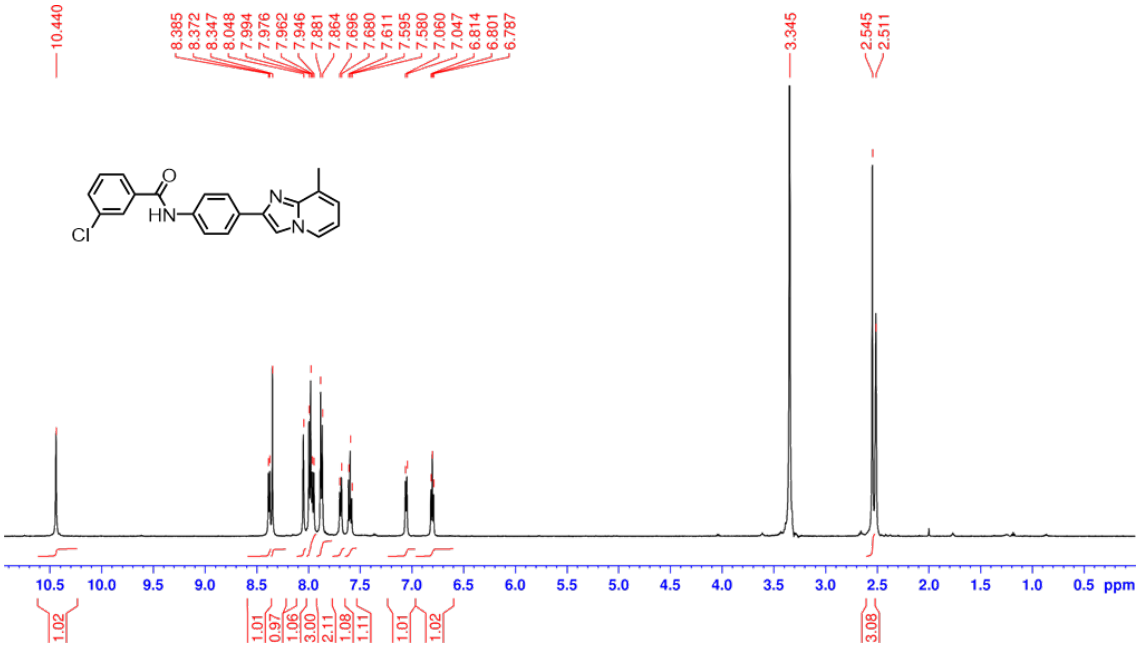
^{1}H NMR (500 MHz, DMSO-d_6) of **S23**



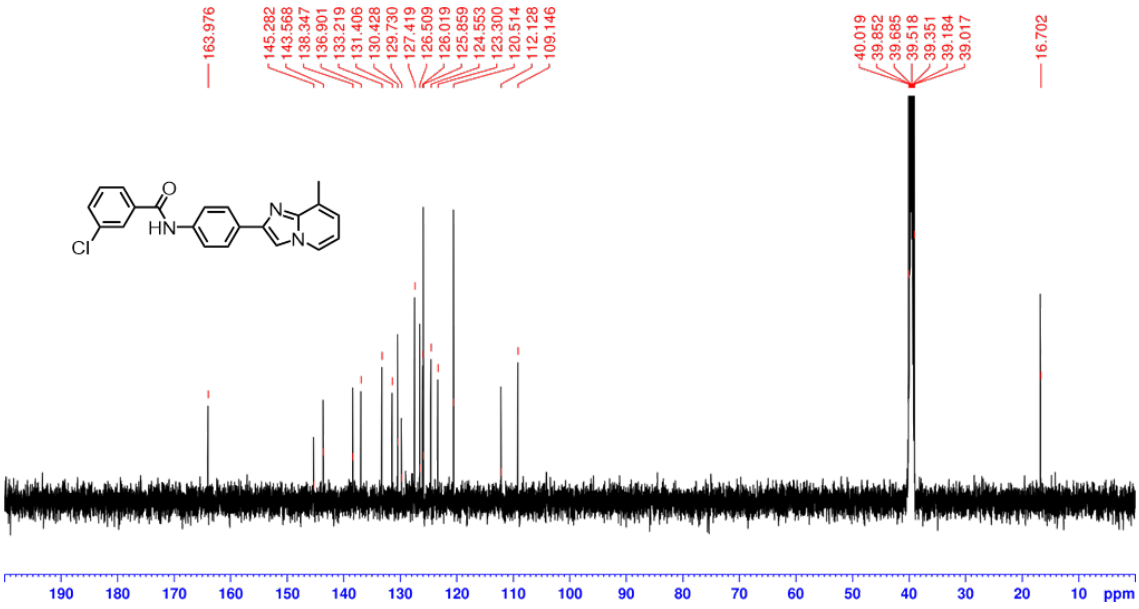
^{13}C NMR (125 MHz, DMSO-d_6) of **S23**



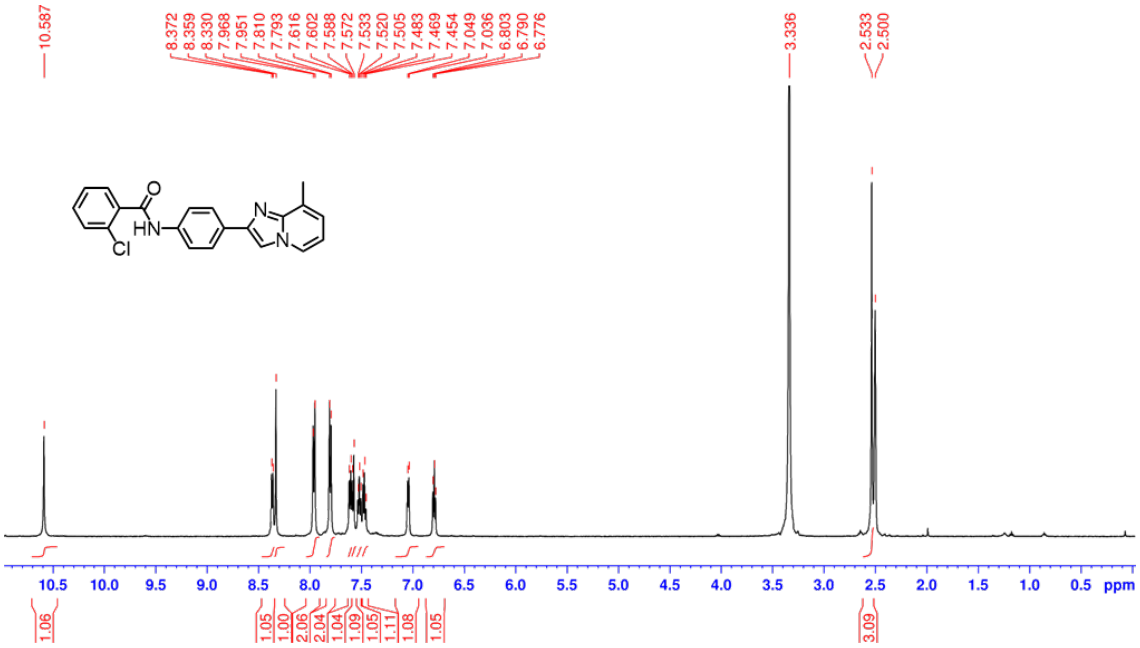
^{1}H NMR (500 MHz, DMSO-d_6) of **S24**



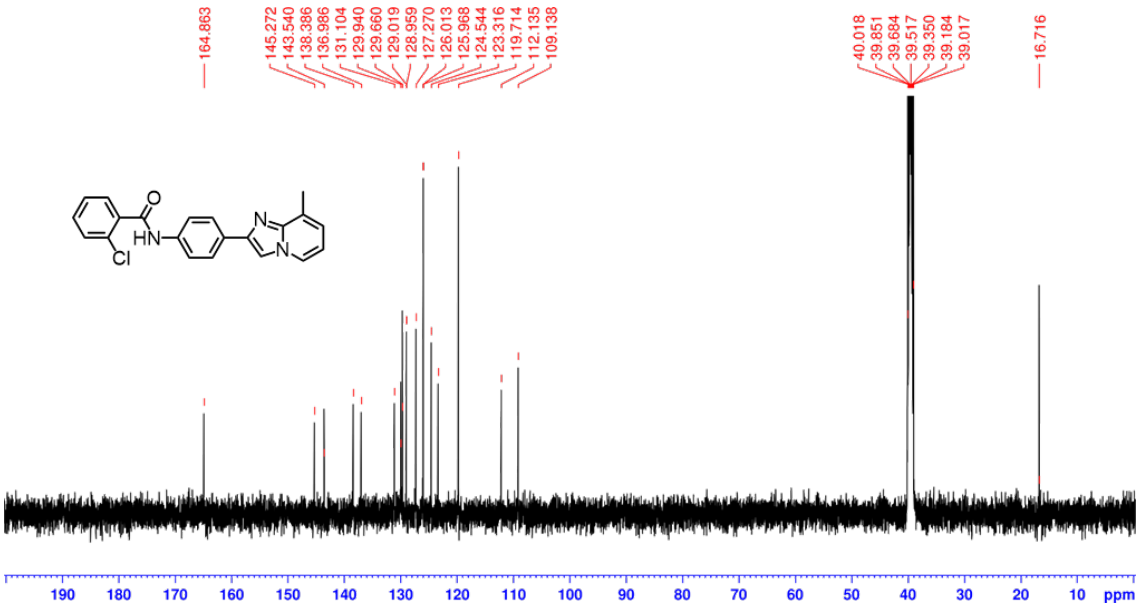
^{13}C NMR (125 MHz, DMSO-d_6) of **S24**



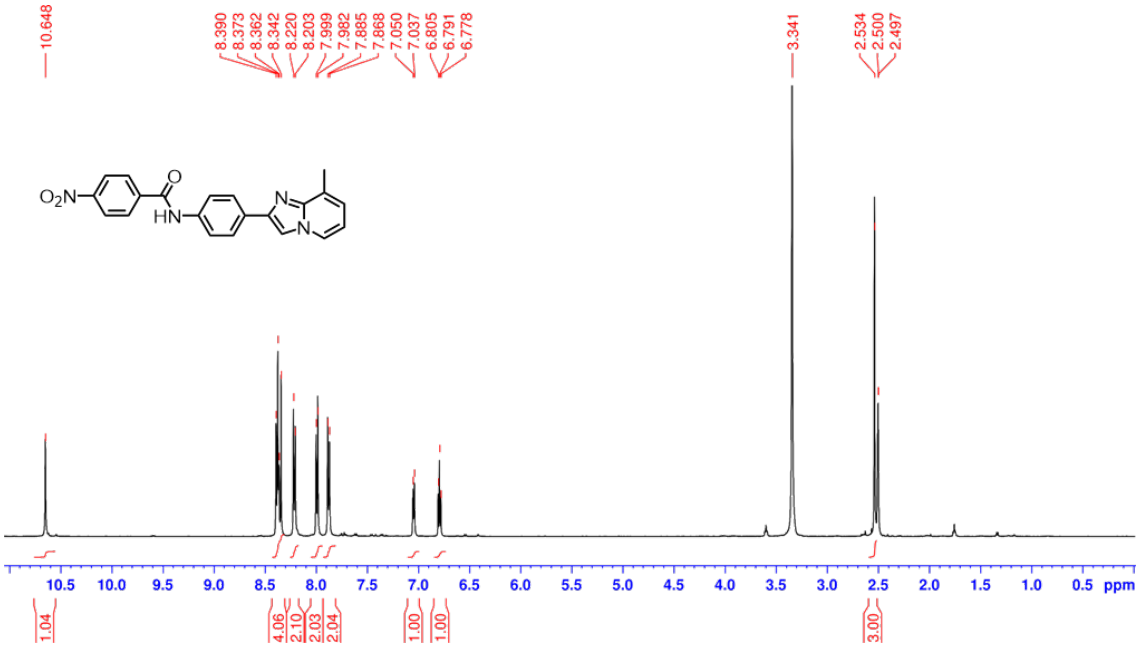
^{1}H NMR (500 MHz, DMSO-d_6) of **S25**



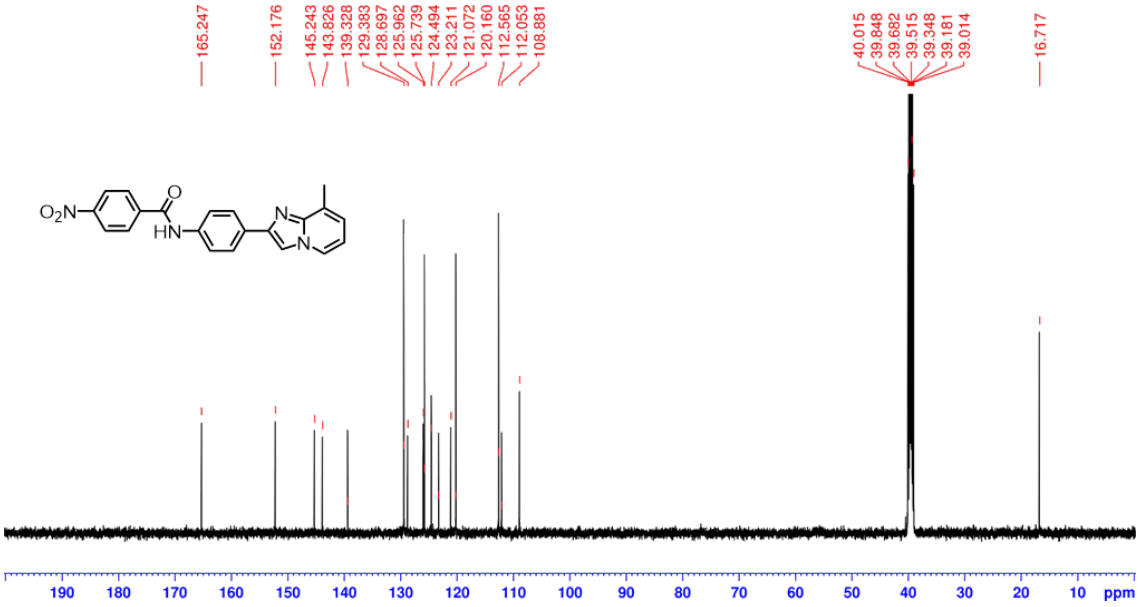
^{13}C NMR (125 MHz, DMSO-d_6) of **S25**



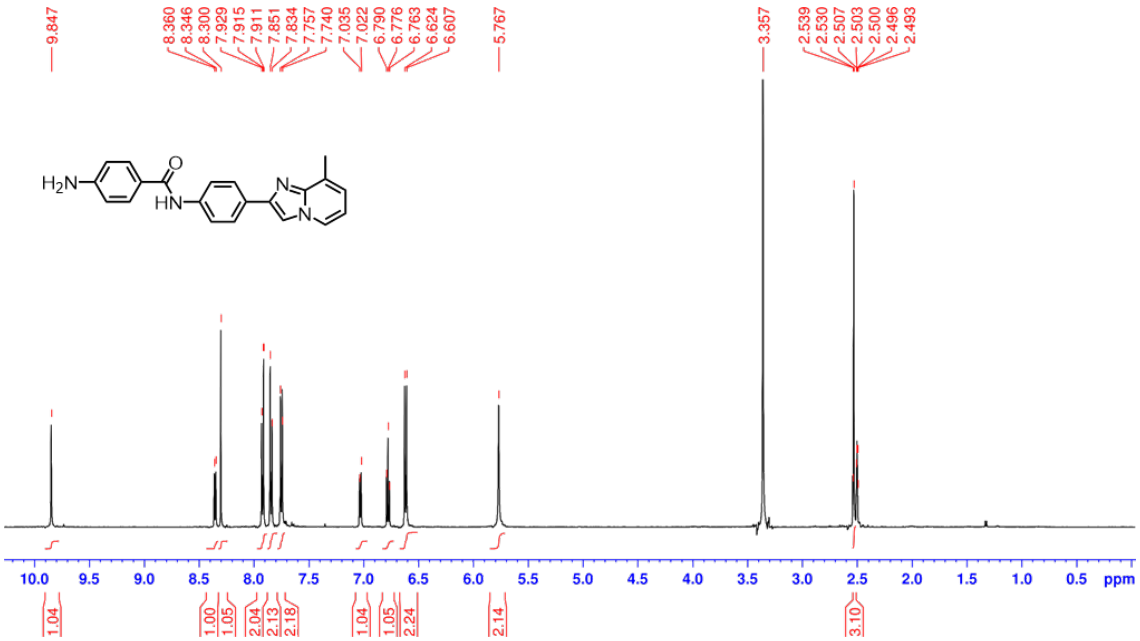
^{1}H NMR (500 MHz, DMSO-d_6) of **S26**



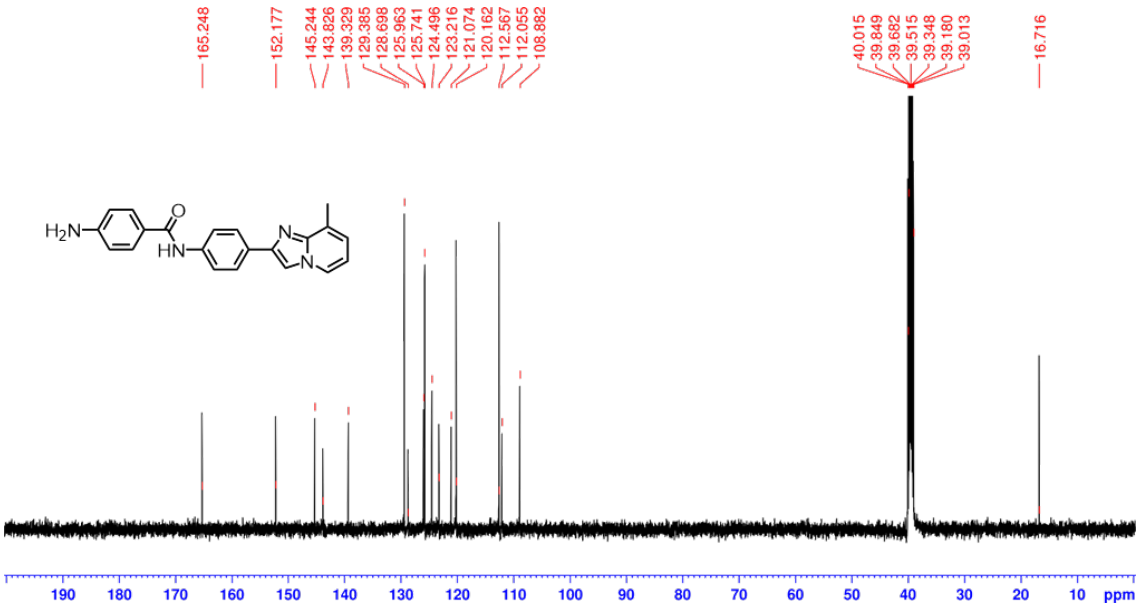
^{13}C NMR (125 MHz, DMSO-d_6) of **S26**



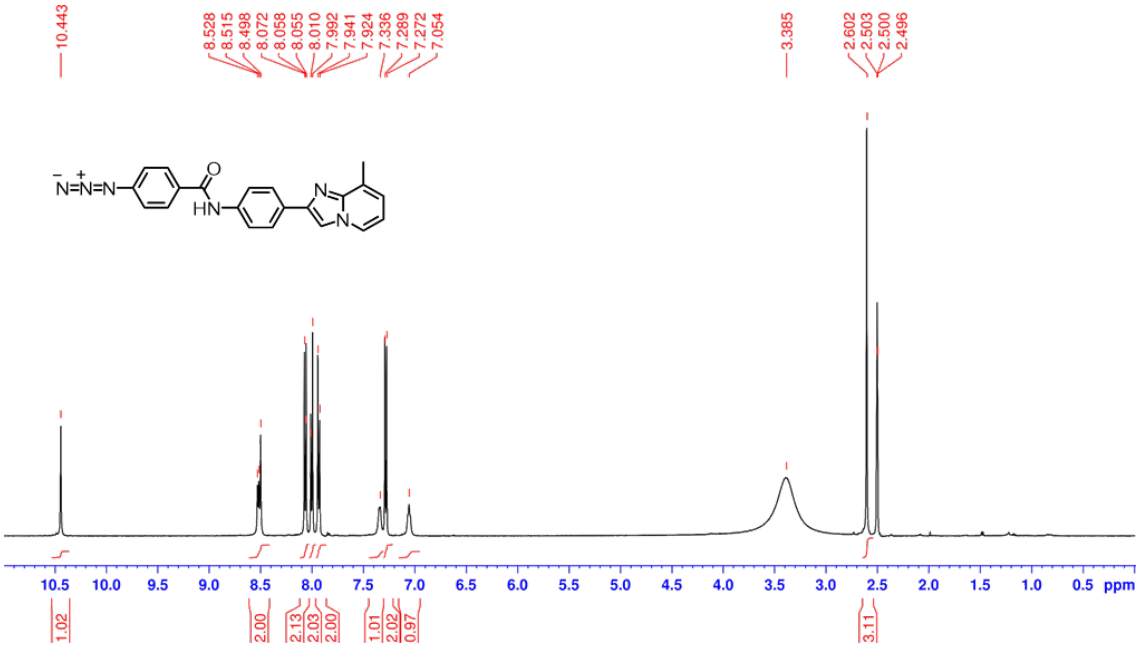
^{1}H NMR (500 MHz, DMSO-d_6) of **S27**



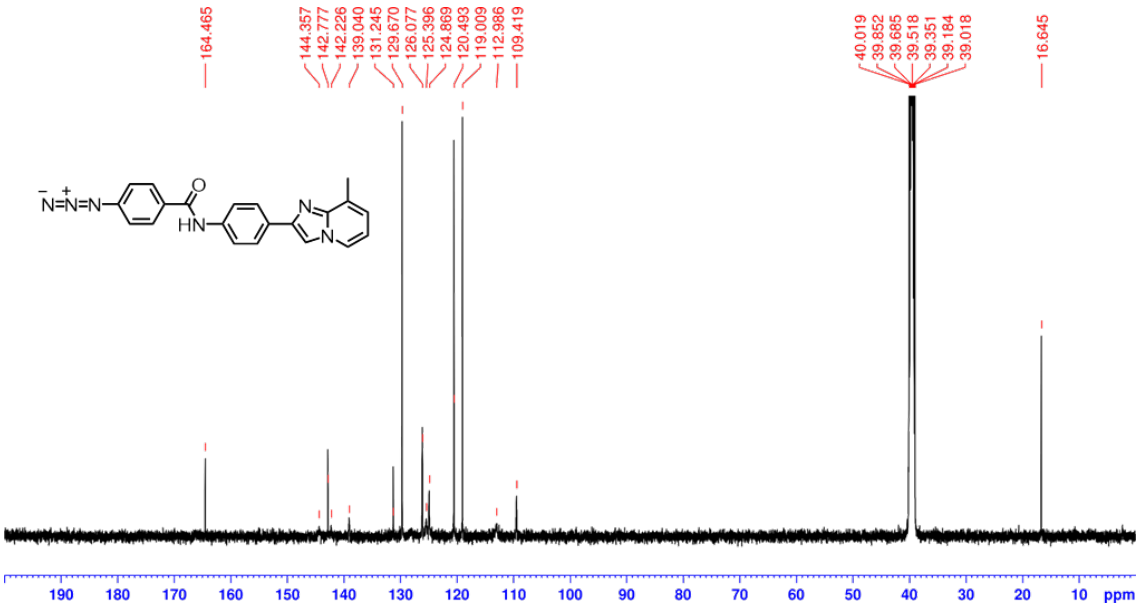
^{13}C NMR (125 MHz, DMSO-d_6) of **S27**



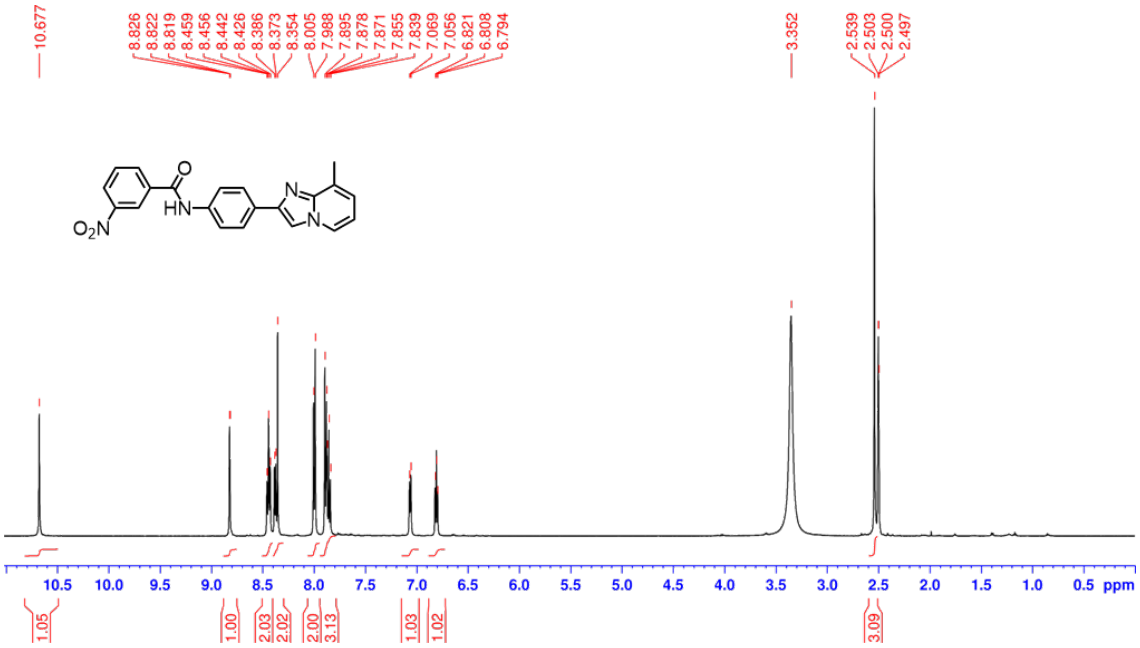
^{1}H NMR (500 MHz, DMSO-d_6) of **S28**



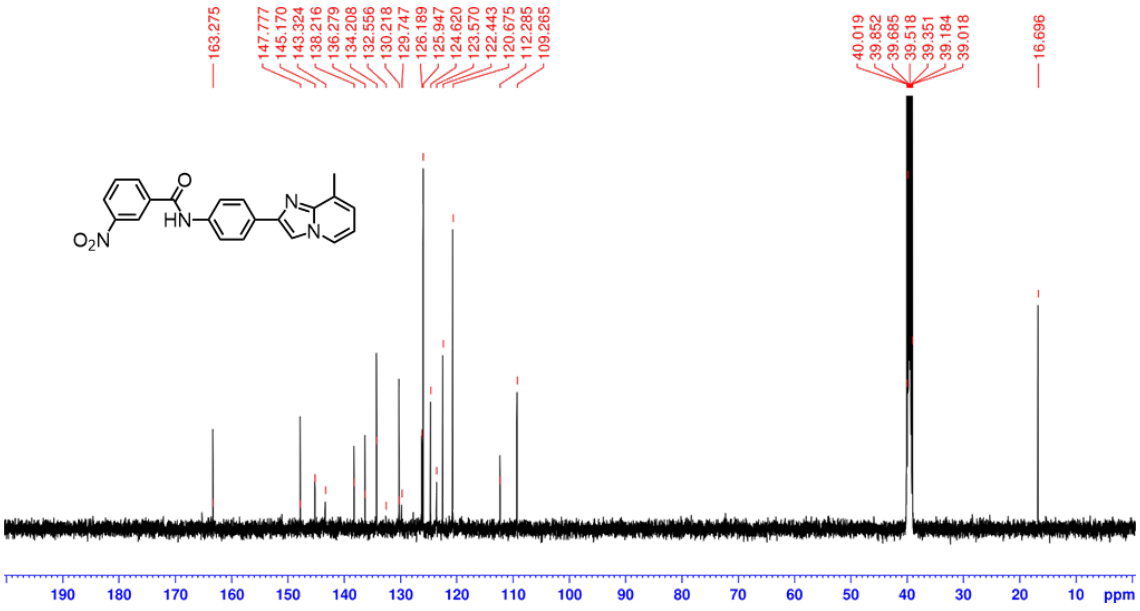
^{13}C NMR (125 MHz, DMSO-d_6) of **S28**



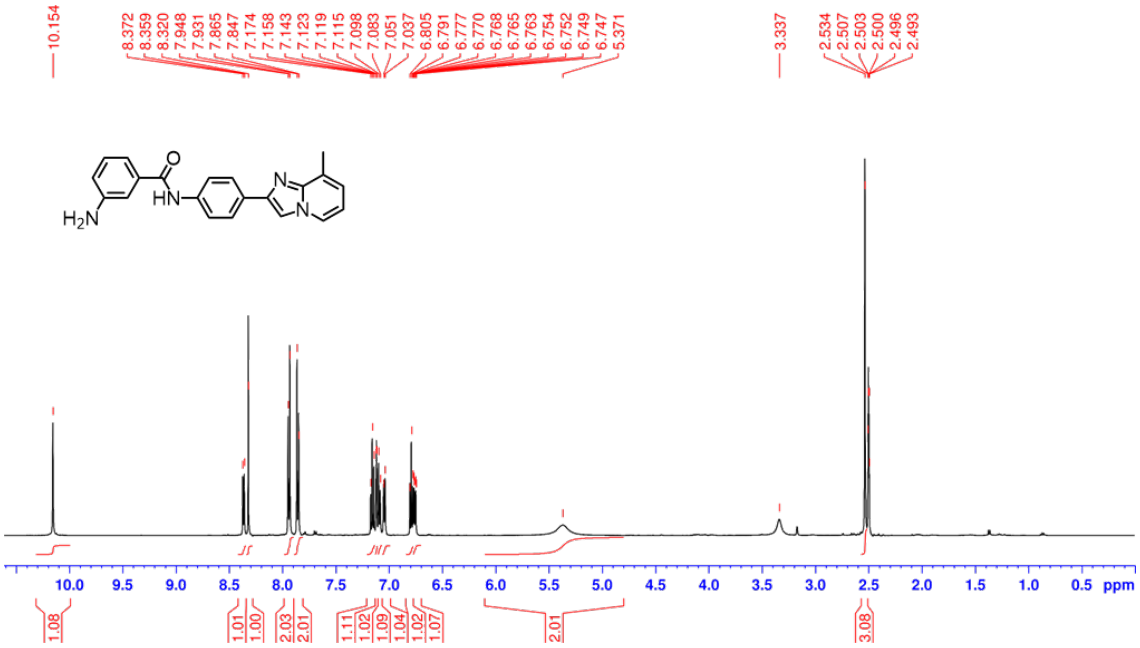
^{1}H NMR (500 MHz, DMSO-d_6) of **S29**



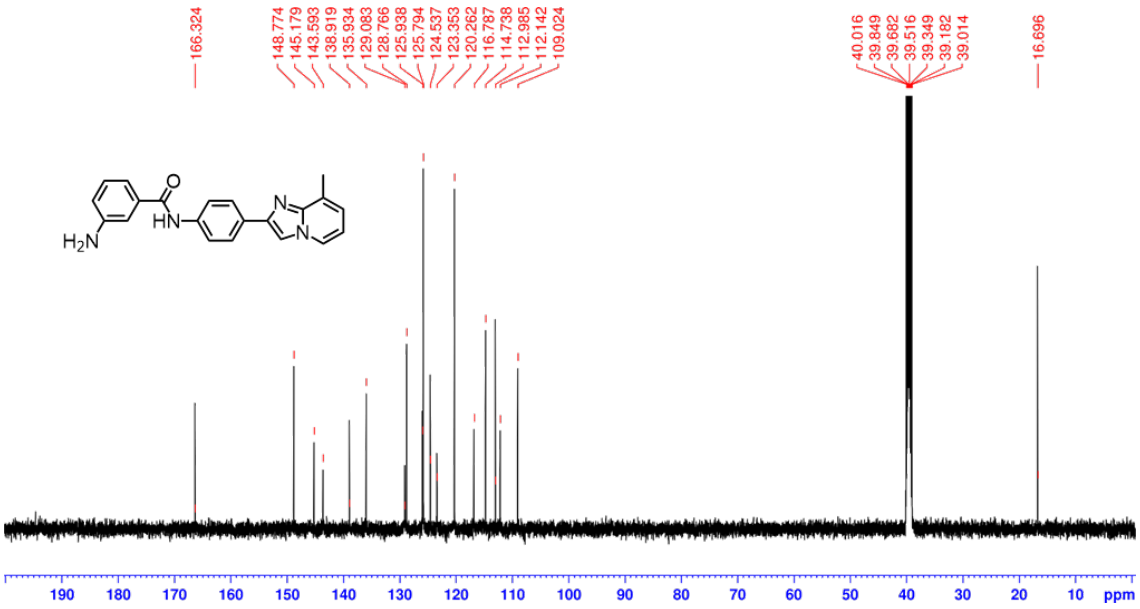
^{13}C NMR (125 MHz, DMSO-d_6) of **S29**



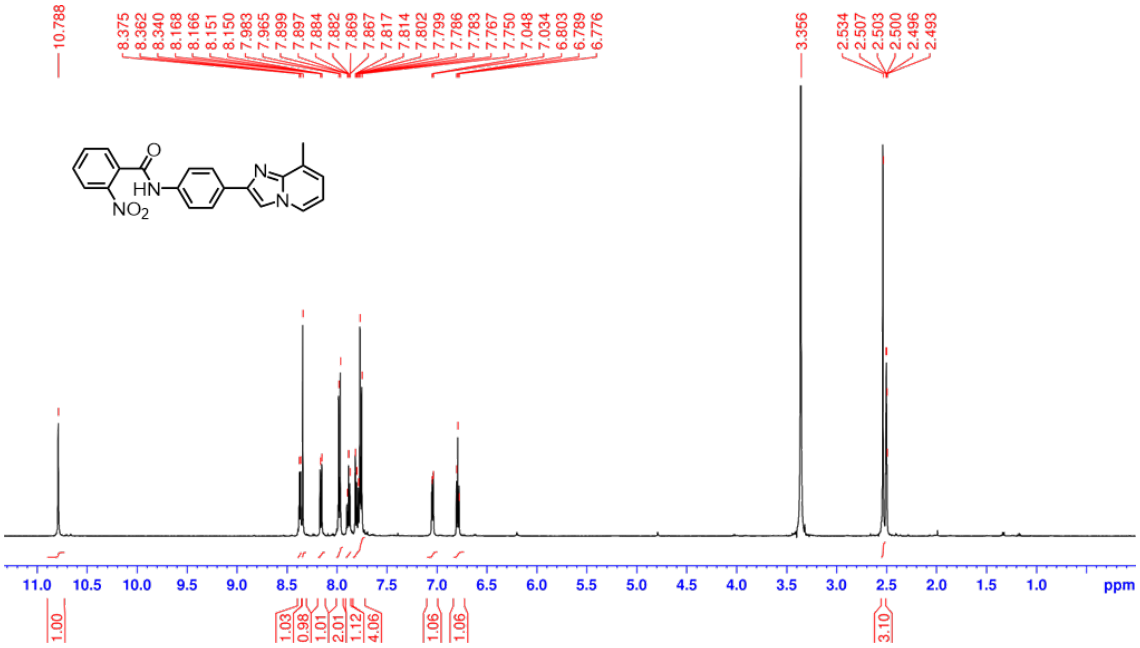
^{1}H NMR (500 MHz, DMSO-d_6) of **S30**



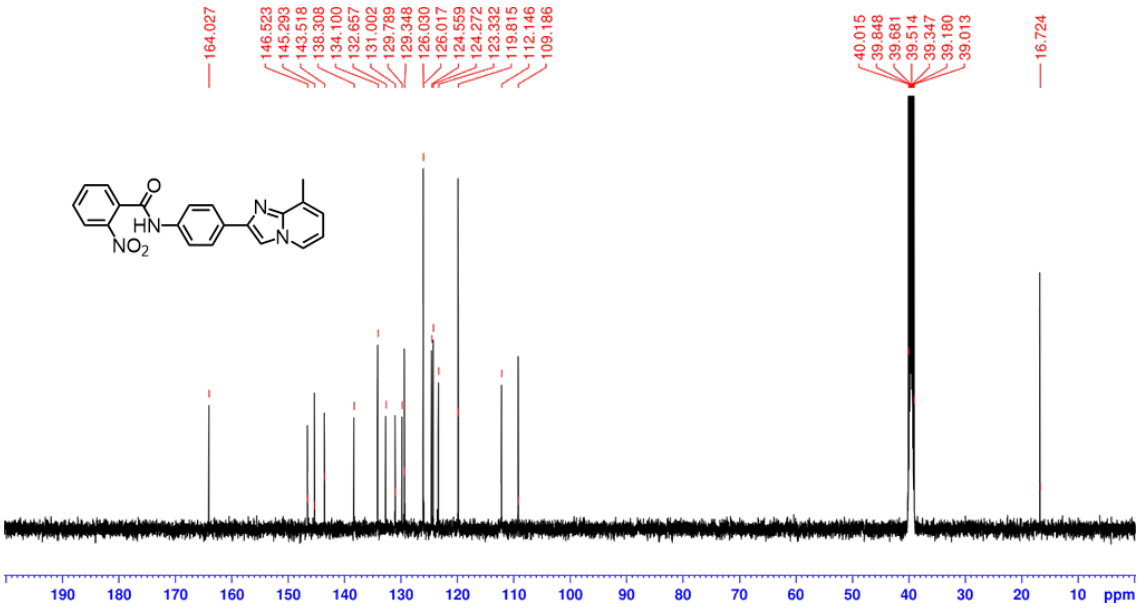
^{13}C NMR (125 MHz, DMSO-d_6) of **S30**



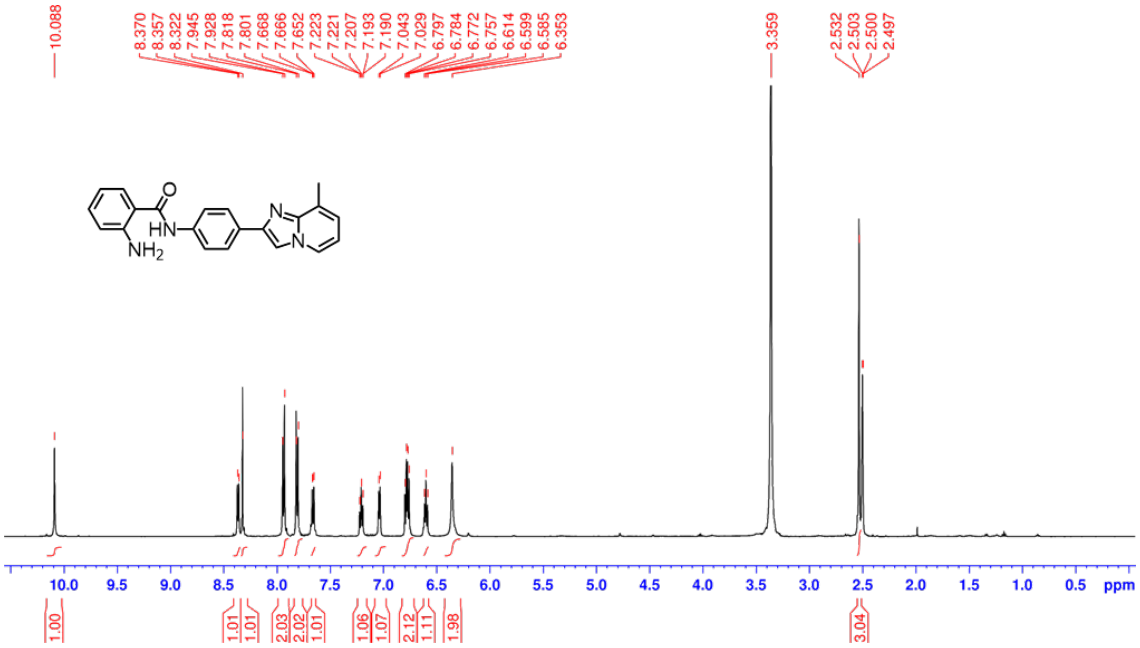
^{1}H NMR (500 MHz, DMSO-d_6) of **S31**



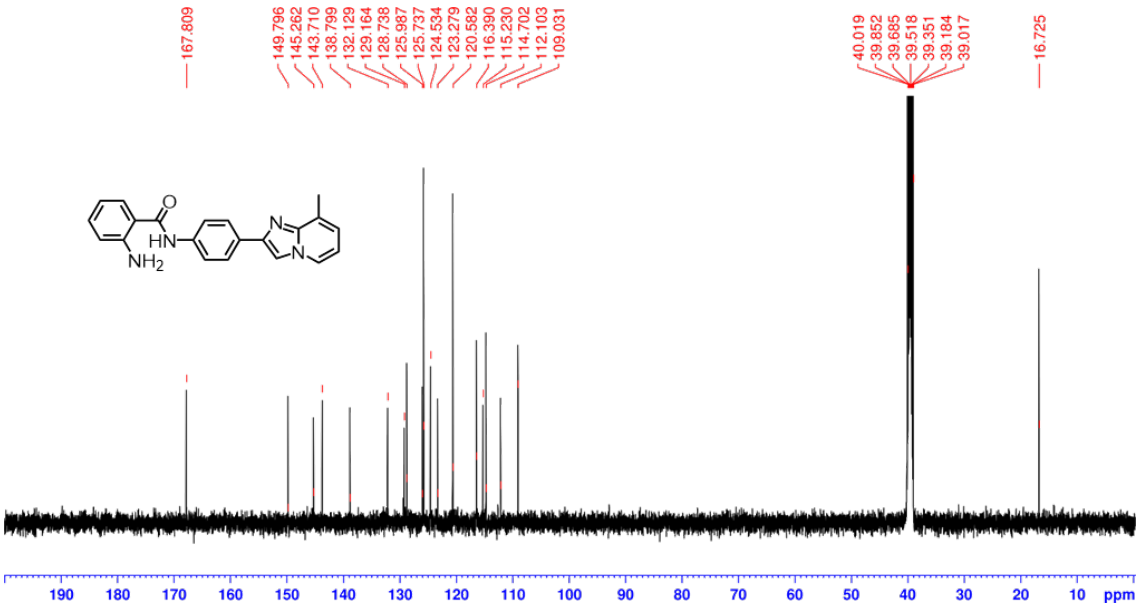
^{13}C NMR (125 MHz, DMSO-d_6) of **S31**



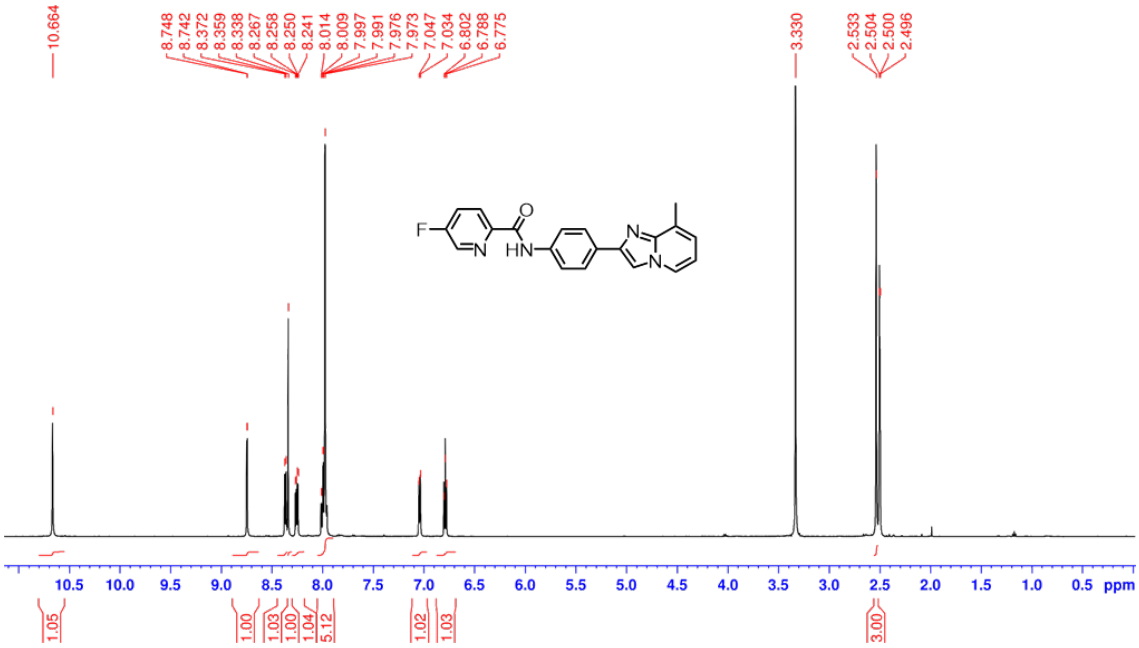
^{1}H NMR (500 MHz, DMSO-d_6) of **S32**



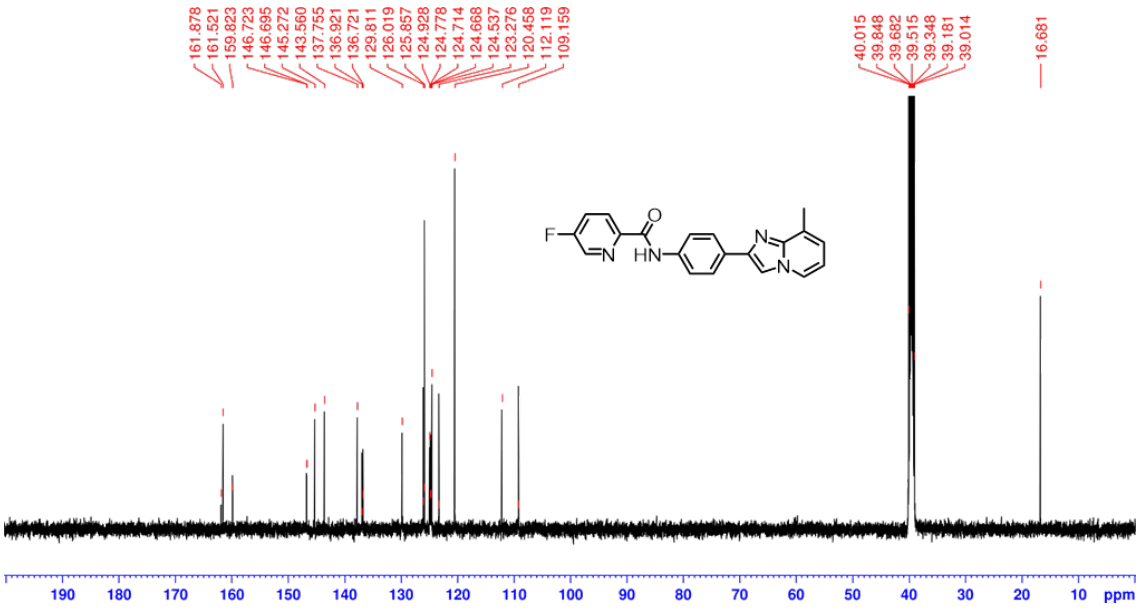
^{13}C NMR (125 MHz, DMSO-d_6) of **S32**



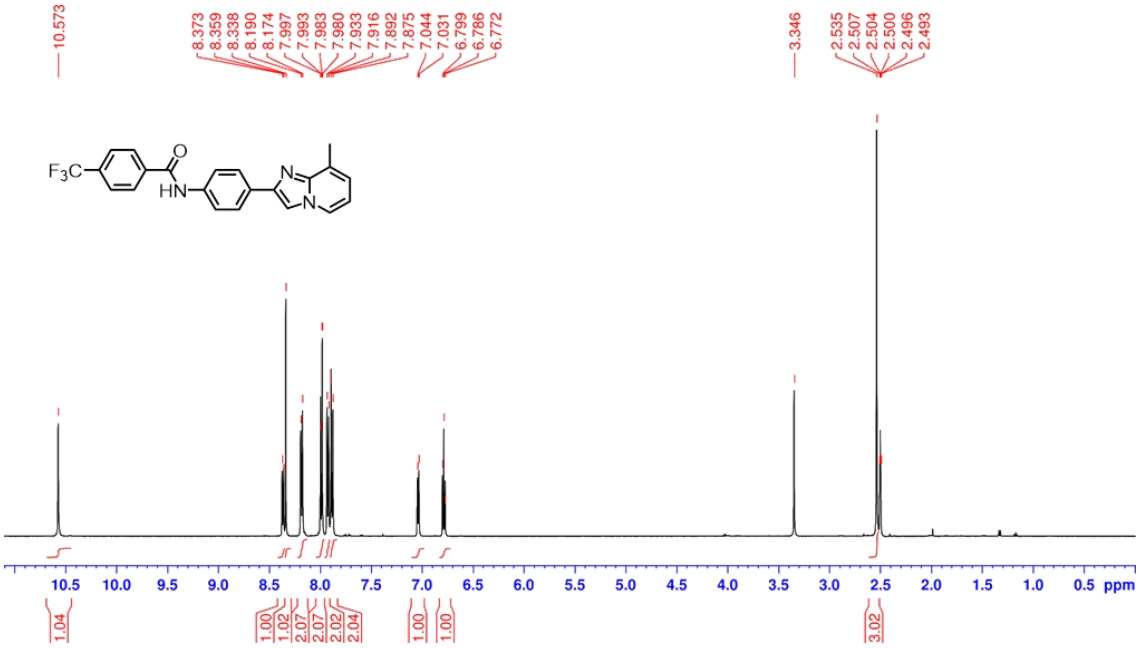
^{1}H NMR (500 MHz, DMSO-d_6) of **S33**



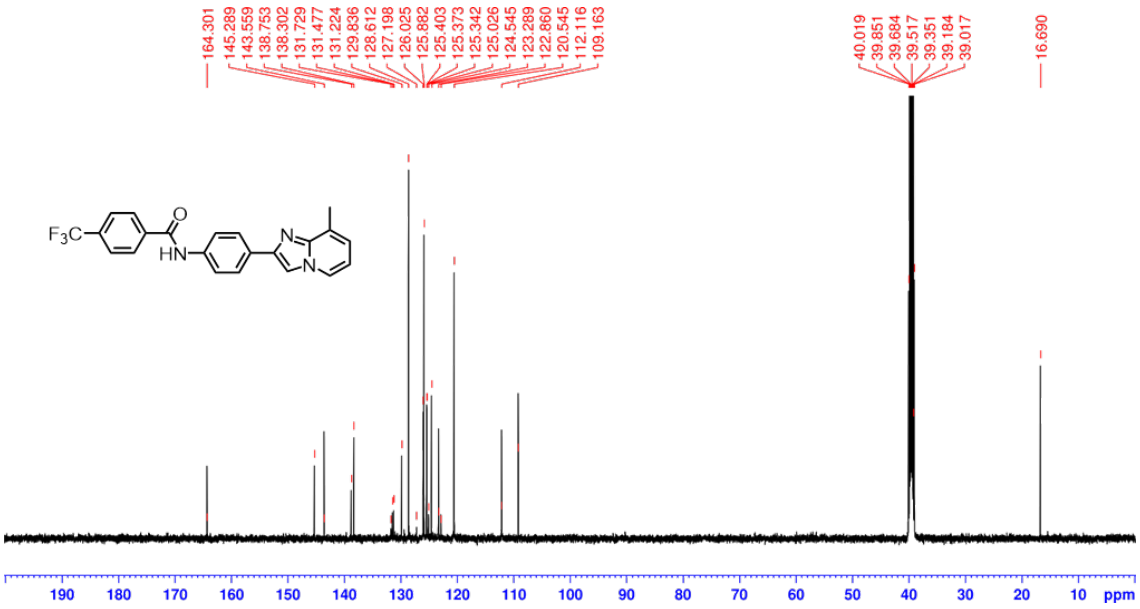
^{13}C NMR (125 MHz, DMSO-d_6) of **S33**



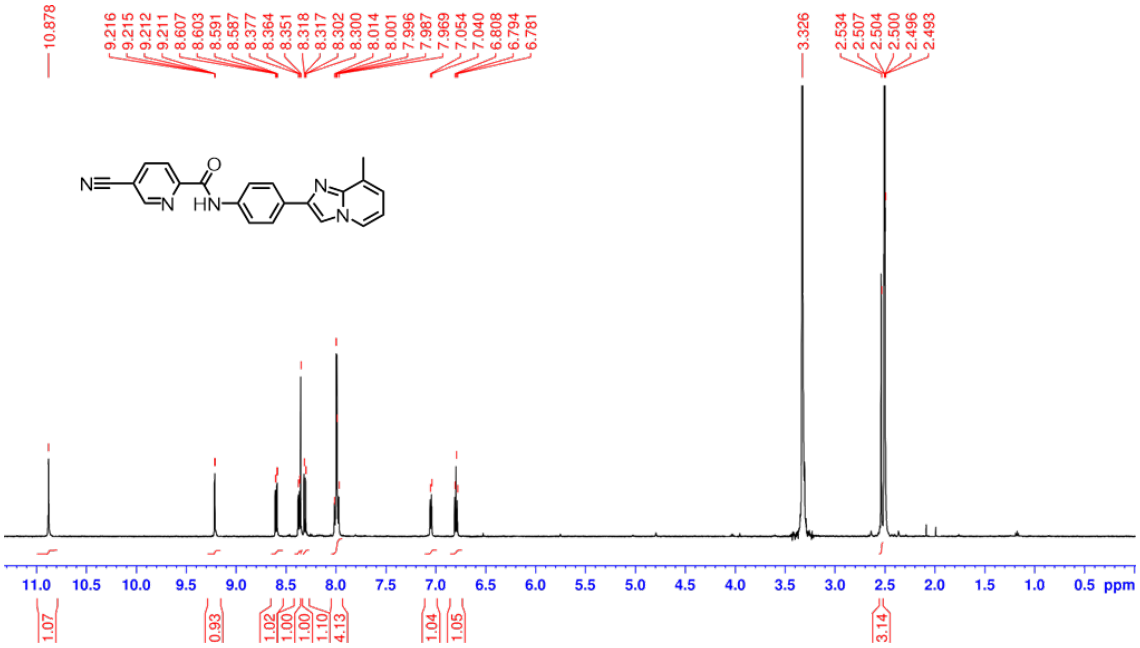
^{1}H NMR (500 MHz, DMSO-d_6) of **S34**



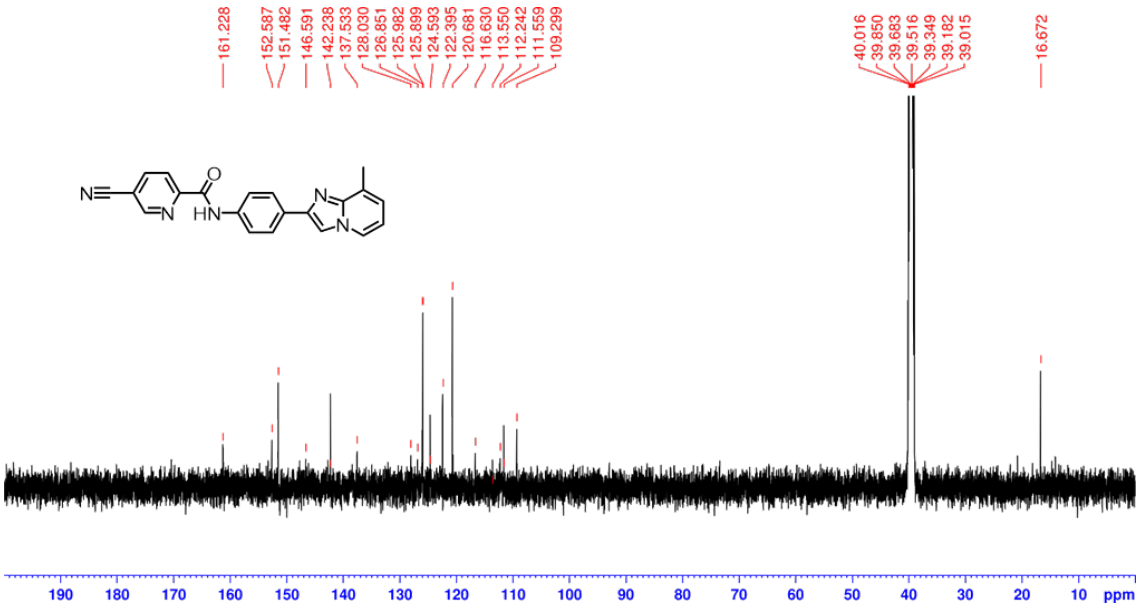
^{13}C NMR (125 MHz, DMSO-d_6) of **S34**



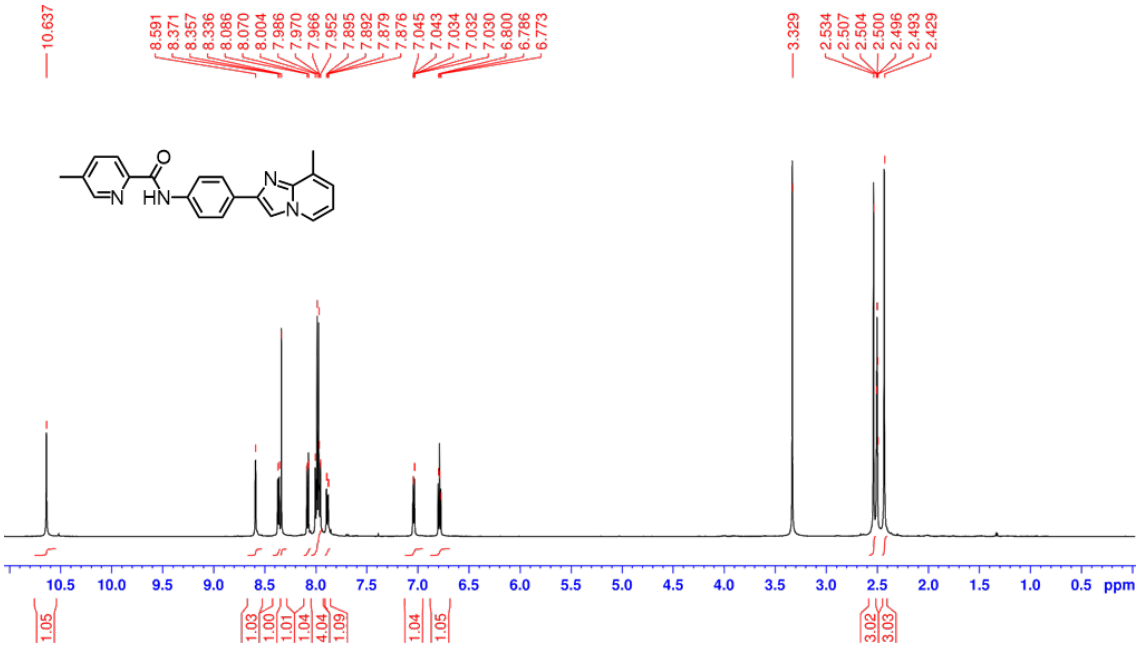
^{1}H NMR (500 MHz, DMSO-d_6) of **S35**



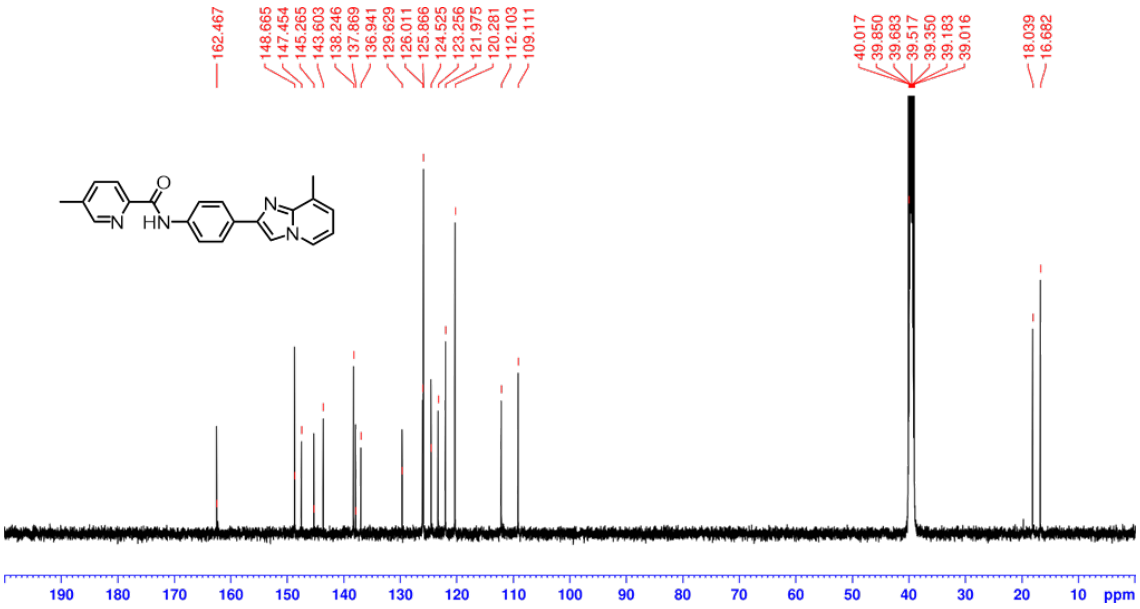
^{13}C NMR (125 MHz, DMSO-d_6) of **S35**



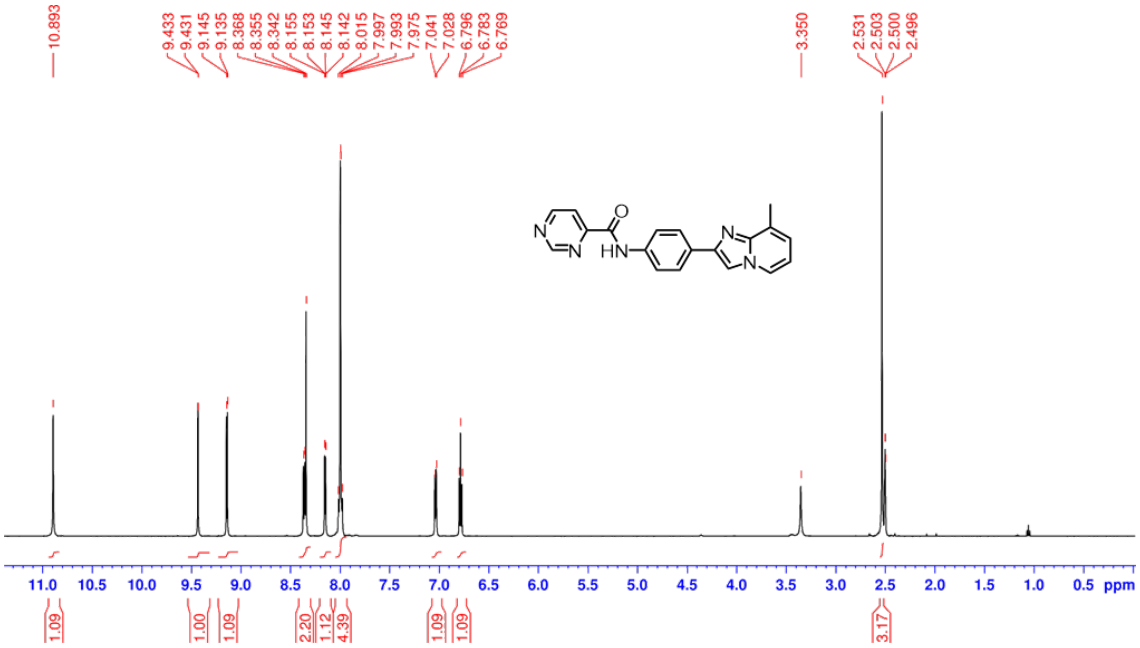
^{1}H NMR (500 MHz, DMSO-d_6) of **S36**



^{13}C NMR (125 MHz, DMSO-d_6) of **S36**



^{1}H NMR (500 MHz, DMSO-d_6) of **S37**



^{13}C NMR (125 MHz, DMSO-d_6) of **S37**