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DEVELOPMENT OF FUNCTIONALIZED IMIDAZOLES AS POTENTIAL THERAPEUTIC AGENTS

by

Drew C. Morgan

A Thesis

Submitted to the
Department of Chemistry & Biochemistry
College of Science & Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
February 23, 2019

Thesis Chair: Subash C. Jonnalagadda, Ph.D.

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Dedication

This body of work is dedicated to my family; to my wife Brynn, to my son Drew Thomas, and to my daughter Isla Rose. I love you all and I appreciate the support that you've given me to make this possible.

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Acknowledgments

To Prof. Subash Jonnalagadda, I would like to show my sincere thanks for the help and guidance you've given me throughout my academic career. For what seemed to be an insurmountable task at the beginning, this research project was only possible because of the guidance and knowledge you've given me. I appreciate the opportunity of being on your team and I hope that my contribution benefits the group as much as I have benefited from my own involvement. I would also like to show my appreciation to Dr. Suman Pathi for all of his hard work and mentorship throughout this process.

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Abstract

Drew Morgan
DEVELOPMENT OF FUNCTIONALIZED IMIDAZOLES AS POTENTIAL THERAPEUTIC AGENTS
2018-2019
Subash Jonnalagadda, Ph.D.
Master of Science in Pharmaceutical Sciences

Imidazoles are heterocyclic small molecules that play a major role in medicinal chemistry and drug discovery. There are several drugs in the market which contain imidazoles as the pharmacophore. Metronidazole, an imidazole containing compound, is a prominent antibiotic and antiprotozoal medication used for the treatment of a variety of infections such as amoebiasis, trichomoniasis, bacterial vaginosis, etc. The current work involves the synthesis of small molecule libraries of imidazoles derived from metronidazole using Baylis-Hillman (BH) reaction. BH reaction is a carbon-carbon bond forming reaction and involves the coupling of aldehydes or imines with activated alkenes such as acrylates, acrolein, or vinyl ketones to produce functionalized allylic alcohols and amines. These products were further functionalized with metronidazole derived amines for potential use as therapeutic agents.

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Chapter 1

Introduction

Imidazoles, members of the azole family, are heteroaromatic compounds that are prevalent in both nature and in medicine (**Figure 1**). In the human body, imidazole plays a critical role in many systems, and the electron rich ring structure is found in various biological structures such as histamine and histidine. This electron rich ring structure allows the imidazole group to bind to various receptors and enzymes. This enables the imidazole ring to exhibit many biological properties ranging from anti-microbial (eg. oroidin), anti-neoplastic (eg. temozolomide), and anti-fungal agents (eg. metronidazole). The mechanism of action for imidazoles, and azoles in general, as antifungal agents is by the inhibition of the fungal cytochrome p450 14 alpha demethylase by coordinating with the iron loaded heme group present in the cytochrome. This binding interrupts the conversion of lanosterol to ergosterol. Ergosterol is a component of the fungal cell membrane which houses the eukaryotic cell. While both human and fungal cells are eukaryotes, humans have a different sensitivity to azoles and hence imidazoles are able to selectively act as anti-fungal agents. It was also observed that the electron rich ring of imidazole was able to coordinate with and affect the production of ferritin. Using ferritin harvested from the spleen of a horse, researchers found that increasing the concentration of imidazole inhibited the formation of ferritin, thus inhibiting iron formation due to the possible binding to active sites found on the ferritin molecule. Functionalized imidazoles have also shown to be able to penetrate the blood brain barrier in molecules such as theophylline and caffeine.

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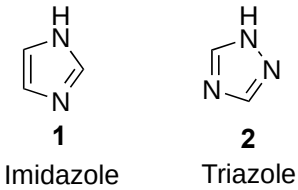

Figure 1. Azaheteroaromatic compounds.

Imidazoles have also already been the focus in the studies involving their use as a treatment for Alzheimer's disease. Functionalized imidazoles have been prepared in the literature, in an attempt to target multiple sites in the brain that are thought to be connected to the Alzheimer's disease. Some of these synthetic molecules showed promise as a brain penetrant agent and were effective at reaching proposed targets.[1] Given the previous research linking of Alzheimer's disease with both a microbial presence and the overabundance of ferritin, our group began to investigate small molecules that have known effects on both fungal infections and can influence iron containing groups. The continued interest of our group in heterocyclic chemistry[2-14] led to the hypothesis that small functionalized imidazoles may not only be able to pass through the blood brain barrier, but the electron rich imidazole ring would be able to strongly coordinate with the iron present in ferritin associated with the Alzheimer's affected brain.

We envisioned the synthesis of the highly substituted imidazoles using the Baylis-Hillman reaction.[15-22] The Baylis-Hillman reaction involves coupling of activated alkenes **4** with aldehydes **3** or imines, the products of which are highly functionalized allylic alcohols and amines **5** (**Figure 2**). These alcohols can be further functionalized as acetates and subjected to further substitution with variety of nucleophiles.

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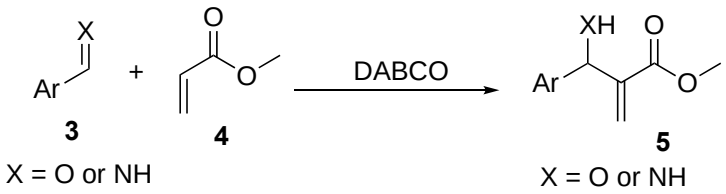

Figure 2. Baylis Hillman Reaction.

Given the correlation between Alzheimer's disease and the microbial presence, as well as the versatility of the Baylis-Hillman reaction, we decided to investigate the structure activity relationship of the functionalized imidazoles derived utilizing BH reaction. We envisioned multiple sites for derivatization on the BH template including changes on the aryl ring, ester position, as well as the nucleophile used for substitution of BH acetates. Our group has synthesized >150 molecules based on imidazole containing cinnamates using Baylis Hillman chemistry using the scheme outlined below **(Figures 3-6)**. All the compounds were evaluated for their anti-fungal, anti-bacterial, and anti-cancer activities. Most of these compounds were found to be selectively toxic towards fungal organisms (C. Neoformans). The microbial activity was evaluated via MIC assay and the cytotoxicity against cancer cells was evaluated via sulphorhodamine assay outlined below.

Minimum Inhibitory Concentration (MIC) assays were performed on samples that showed zones of inhibition greater than 1.5 cm. A fresh preparation of the stock inoculum described above was diluted 1000-fold in the modified RPMI medium. Each 100 mM DMSO stock solution was diluted to 200 μM in the modified RPMI medium. One hundred μL of the diluted C. albicans or C. neoformans inoculum was added to each well of a round-bottom 96-well plate containing two-fold serial dilutions of each stock antifungal

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compound solution yielding a range of concentrations beginning at 100 μM with a DMSO-only control in the final well of each row. The plates were incubated at 37 °C in a non-CO_2 incubator, and the absorbance at 600 nm was measured using a Molecular Devices M5 plate reader after 24 and 48 hours. The reported MICs corresponded to the lowest compound dilution that significantly inhibited growth (more than 20% relative to control). Each compound was tested in at least triplicate, and Fluconazole was used as a positive control, returning MIC values consistent with published data.

Cytotoxicity assay: MCF-7 cells were incubated in 5% CO_2 atmosphere at 37^{o}C in IMEM medium containing 10% Hyclone-III and 1% Antibiotic (500,000 units pen-strep) in sterile conditions at 100% humidity. The growth media was changed every 2-3 days. MCF-7 cells were trypsinized, diluted in growth media and seeded at a concentration of approximately $5x10^5$ cells per mL in 48 well plates such that each well contains 400 μL of media and incubated for 24 hours. The test compounds were initially diluted in DMSO and diluted 1000 times in growth media so that the final DMSO concentration was <0.1%. Growth media was removed from 48 well plates and test compound in 400 μL of growth media were added. Taxol, DMSO and growth media were used as controls. All the compounds were tested in triplicates at 100, 50 and 10 μM. These plates were incubated for 72 hours. After removing the media, the cells were washed with 400μL of 1% DPBS. The plates were dried and SRB assay was performed. 100μL of 0.5% SRB (in 1% acetic acid) was added in each well and incubated at 37^{o}C for 45 minutes. SRB solution was removed and the wells were washed 5 times with 1% acetic acid solution and dried. The cells were dissolved in 400 μL of 10 mM Tris base (pH 10) and absorbance was recorded.

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The series of compounds synthesized utilizing this protocol are shown in **Figures 3-6** below. Initially, the allylic alcohol **5** was obtained via the reaction of a variety of aromatic aldehydes with methyl acrylate and was subsequently treated with acetic anhydride followed by imidazole in the presence of potassium carbonate to furnish aryl substituted α-imidazolylmethyl cinnamates **6**. Some of the aryl groups introduced include phenyl, tolyl, cyanophenyl, nitrophenyl, anisyl, trimethoxyphenyl, napthyl, fluorophenyl, chlorophenyl, diflorophenyl, dichlorophenyl, etc. (**Figure 3**). We further probed the use of different nucleophiles such as morpholine, N-methylpiperazine, and dibenzylamine, as a replacement for the imidazole moiety (**Figure 4**). We also probed the substitutions on imidazole unit itself to include 2-methylimidazole, 2-ethylimidazole, 2-phenylimidazole, 2-isopropylimidazole, and 4-methylimidazole (**Figure 5**). Finally, we also investigated the effect of changing ester groups to replace methyl acrylate in the BH reaction with ethyl acrylate, ^{n}propyl acrylate, ^{n}butyl acrylate, benzyl acrylate, 2,2,2-trifloroethyl acrylate, and 2-hydroxyethyl acrylate, etc. (**Figure 6**).

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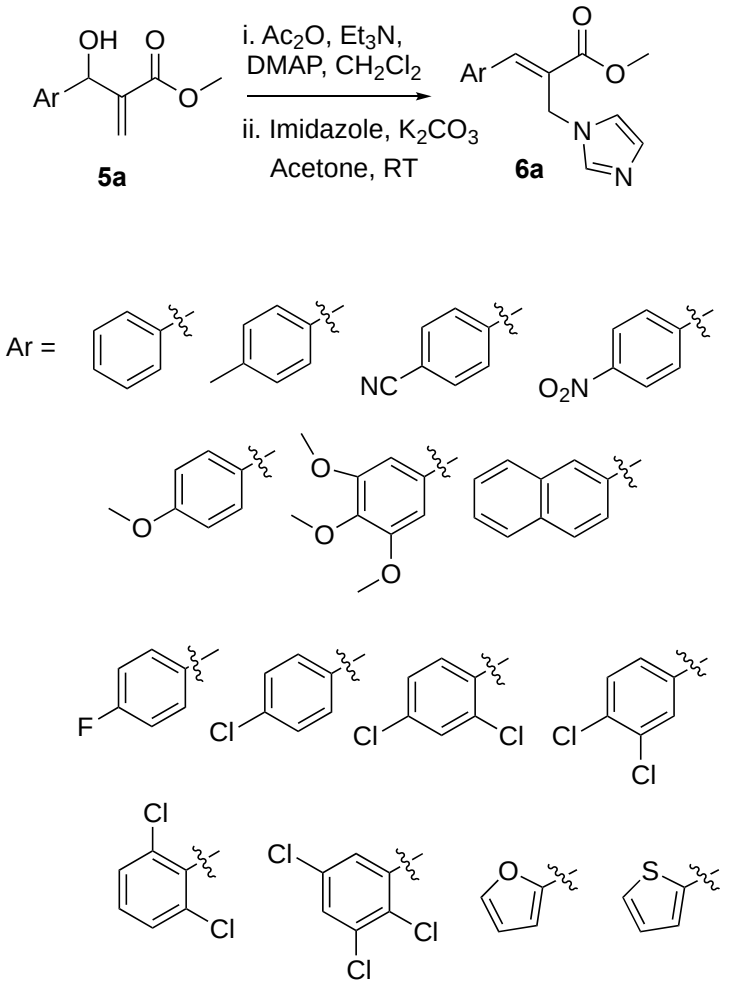

Figure 3. α-Imidazolylmethyl cinnamates.

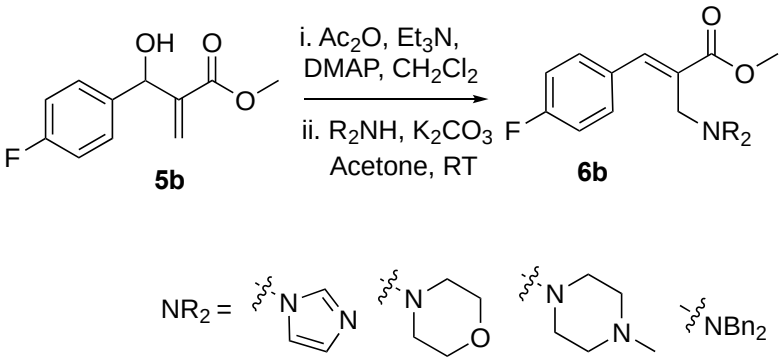

Figure 4. α-Aminomethyl cinnamates.

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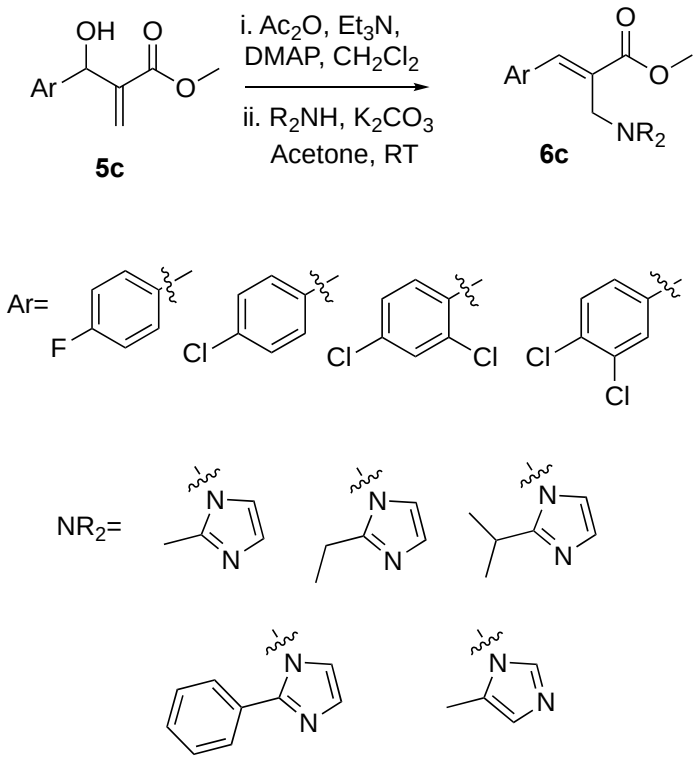

Figure 5. Functionalized α-Imidazolylmethyl cinnamates.

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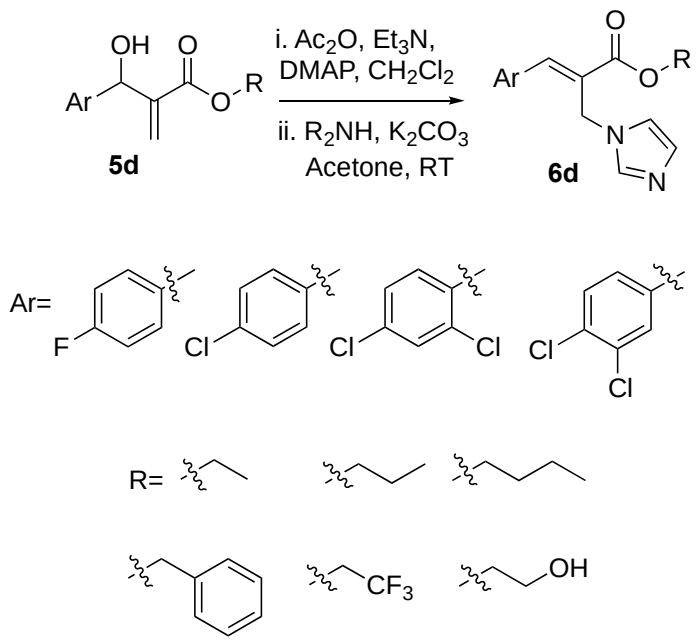

Figure 6. Ester functionalization of α-imidazolylmethyl cinnamates.

We wanted to investigate if the compounds synthesized above in **Figures 3-6** were acting as readily hydrolyzed prodrugs. In order to achieve this, we synthesized allyl alcohols **5e** derived from the BH reaction of aryl aldehydes with ^{t}butyl acrylate and further functionalized these alcohols with acetic anhydride followed by treatment with imidazole/triazole/4-nitro-2-methylimidazole (**Figure 7**).

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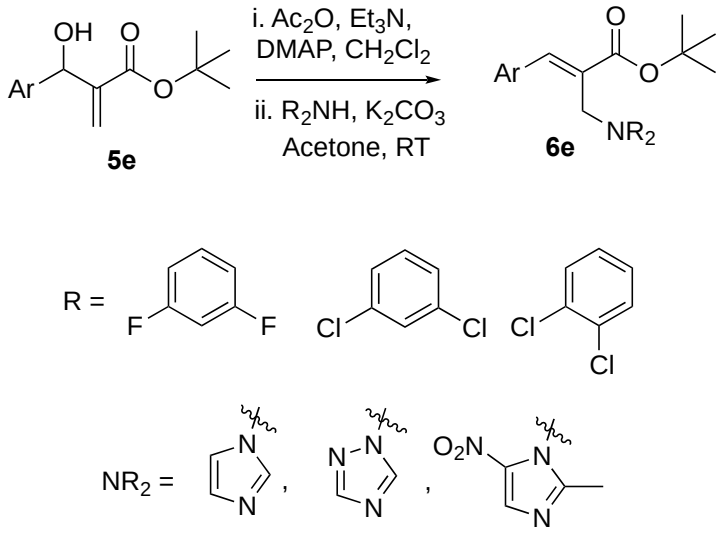

Figure 7. ^{t}Butyl ester functionalization of α-imidazolylmethyl cinnamates.

In addition to the less readily hydrolyzed ^{t}butyl ester derivatives **6e** reported above in **Figure 7**, we prepared amide derivatives **8**, **10**, and **12** as well to investigate the mechanism of action for these drug candidates. The amide analogs **8** were synthesized starting from the corresponding ester derivative **6f** via hydrolysis followed by coupling with amines under EDCI and HOBt conditions. Some of the amines used for coupling include morpholine, 2,6-dimethylmorpholine, *N*-methylpiperazine, *N*-hydroxyethyl piperazine, *N*-Boc-piperazine, isobutylamine, diflorobenzylamine, and ^{t}butylamine (**Figure 8**). Other amide derivatives 10 and 12 were synthesized under similar conditions employing 4-nitro-2-methylimidazole (**Figure 9**) and triazole (**Figure 10**) as nucleophiles.

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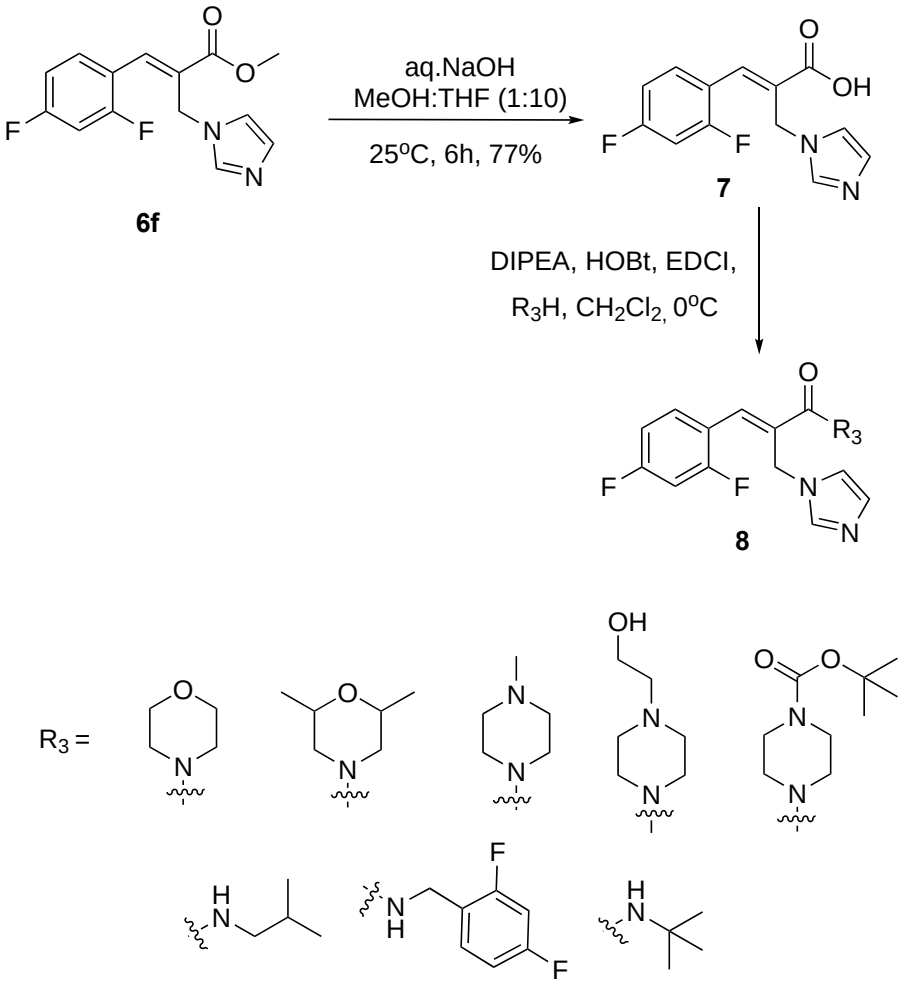

Figure 8. α-Imidazolylmethyl cinnamamides.

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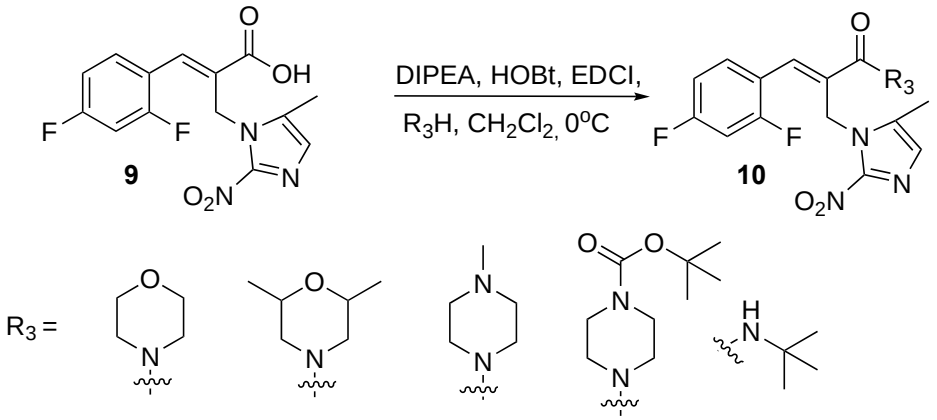

Figure 9. α-2-Nitro-4-methylmidazolylmethyl cinnamamides.

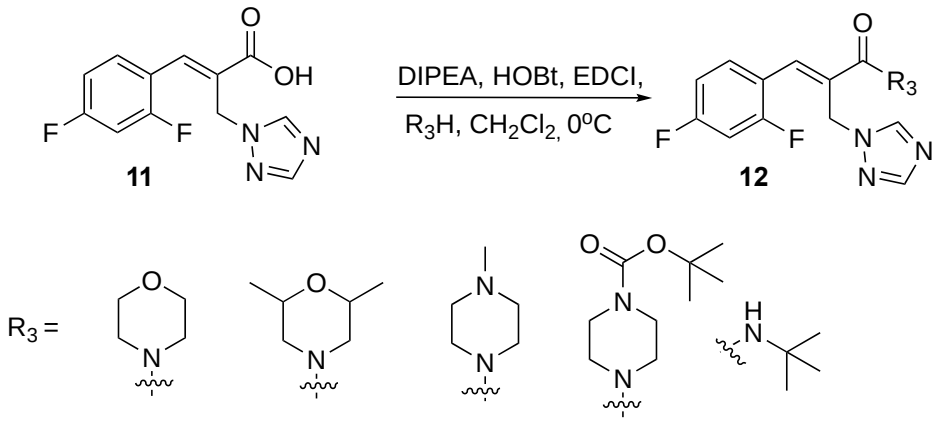

Figure 10. α-Triazolylmethyl cinnamamides.

Based on these investigations, it was determined that the greatest biological activity was achieved with florophenyl and chlorophenyl substituents on the aldehyde, methyl and ethyl substituions on the acrylate, and imidazole as the nucleophile. These results shaped the first generation lead molecule and led to the next stage of drug development.

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Chapter 2

Preparation of α-Imidazolyl Cinnamamide Conjugates

Metronidazole **13** (**Figure 11**) is an antimicrobial drug has been on the market since 1960 and has been used to treat microbial infections.[23,24] It is on the World Health Organization's list of essential medicines and remains the diagnostic standard for the management and prevention of anaerobic infections. Metronidazole is highly active against both gram-negative and gram-positive bacteria. It acts by passively diffusing into the bacterial cell as a prodrug, which is then activated by the cytoplasm inside of the bacteria or protozoa.[24] This activation of the prodrug causes the molecule to fragment and the resulting imidazole leads to cell death and it has shown activity against a broad range of microbes.[25,26] The nitro group in metronidazole is also believed to function as a strong radical oxidant.[27] Some studies have found that in very rare occasions, patients that were using this drug developed neurological and cognitive symptoms that improved once administration of the drug was discontinued.[28,29] Given the success of this compound, we envisioned the preparation of α-imidazolyl cinnamamides using Baylis-Hillman reaction and coupling reaction with metronidazole.

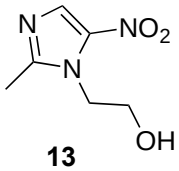

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Figure 11. Metronidazole.

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Synthesis of α-Imidazolyl Cinnamic Acid

The synthesis of these molecules necessitated the hydrolysis of BH reaction derived cinnamate ester to carboxylic acid followed by coupling with metronidazole derived amine. Briefly, the reaction of benzaldehyde with methyl acrylate in the presence of DABCO at room temperature afforded the corresponding allylic alcohol, which was further dissolved in dichloromethane and treated with acetic anhydride, 4-dimethylaminopyridine (DMAP), and triethylamine to yield the acetate. The nucleophilic addition of the imidazole group to the acetate was accomplished in the presence of potassium carbonate (K_2CO_3) in acetone furnishing the cinnamate ester **14**. Similarly, the cinnamate ester **16** was obtained by replacing imidazole with nitromethylimidazole. To obtain the necessary carboxylic acid **15** or **17**, hydrolysis of the cinnamate ester was attempted with NaOH dissolved in methanol/water or methanol/THF solvent mixtures. The compounds containing nitromethylimidazole group were dissolved in methanol/THF mixture and hydrolyzed upon dropwise addition of aqueous NaOH and stirring overnight (**Figure 12**). The compounds containing the more polar imidazole group were dissolved in methanol/water mixture and hydrolyzed upon dropwise addition of aqueous NaOH at 0^{o}C and stirring overnight (**Figure 12**).

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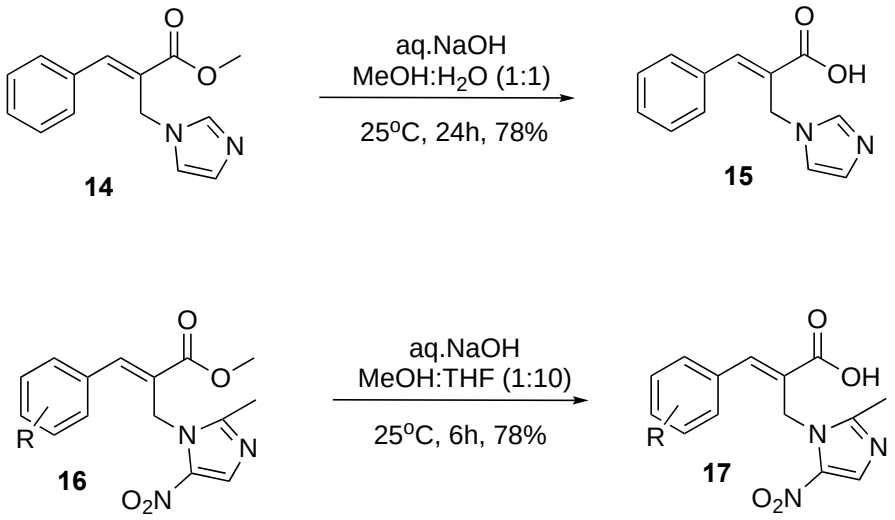

Figure 12. Synthesis of α-Imidazolyl Cinnamic acid.

Synthesis of Metronidazole Amine

Metronidazole **13** was dissolved in dichloromethane and cooled to 0°C. To the cooled solution were added tosyl chloride, triethyl amine, and DMAP and allowed to stir overnight. The resulting tosylate **18** was then heated in the presence of sodium azide (NaN_3) in DMF at 100°C to yield the azide **19**. To generate the necessary amine from **19**, the azide was dissolved in dry tetrahydrofuran (THF) and cooled to 15°C. Triphenophosphine flakes were dissolved in dry THF and added to the solution. The reaction was allowed to proceed under nitrogen atmosphere. After three hours, concentrated hydrochloric acid was added and the solution was allowed to stir under reflux conditions for 5 hours. The target amine **20** was obtained in 59% yield under these conditions (**Figure 13**).

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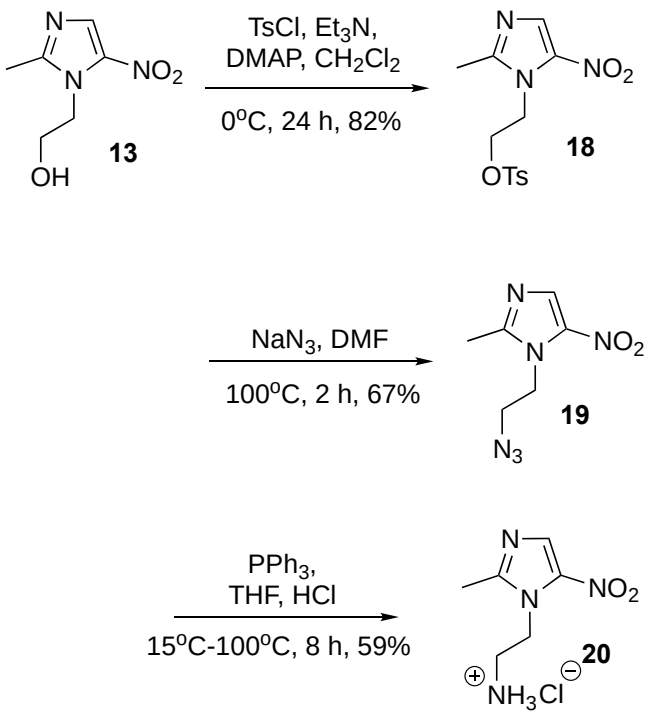

Figure 13. Synthesis of Metronidazole Amine.

Synthesis of Metronidazole-Cinnamamide Conjugates

The cinnamic acids synthesized in **Figure 12** were coupled with metronidazole amine **20**. The coupling was performed by dissolving the acids **17** in dichloromethane at 0°C under nitrogen atmosphere by using 1-hydroxybenzotriazole (HOBt), 1-ethyl-3-(-3-dimethylamino propyl) carbodimide hydrochloride (EDCI), and *N*,*N*-diisopropylethylamine (Hunig's base). The amine salt **20** was added after half an hour and the coupling produced the desired α-imidazolyl cinnamamides **21-23**. All of these compounds were characterized using proton and carbon NMR as well as mass spectral analysis (**Figures 14-17**).

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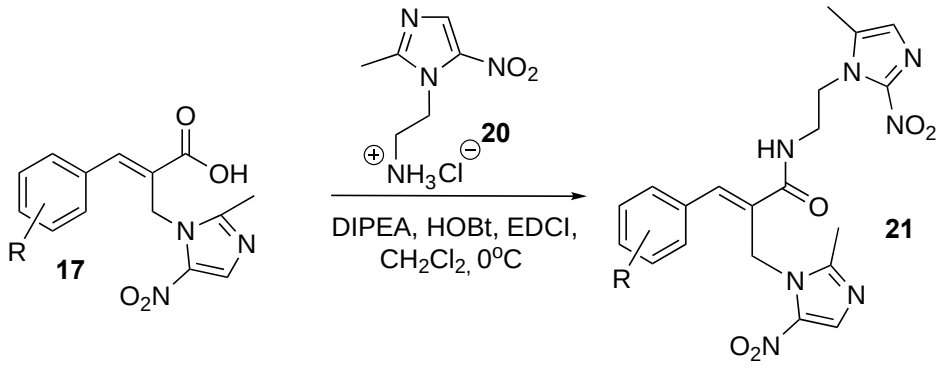

Figure 14. Synthesis of Metronidazole-Cinnamamide Conjugates.

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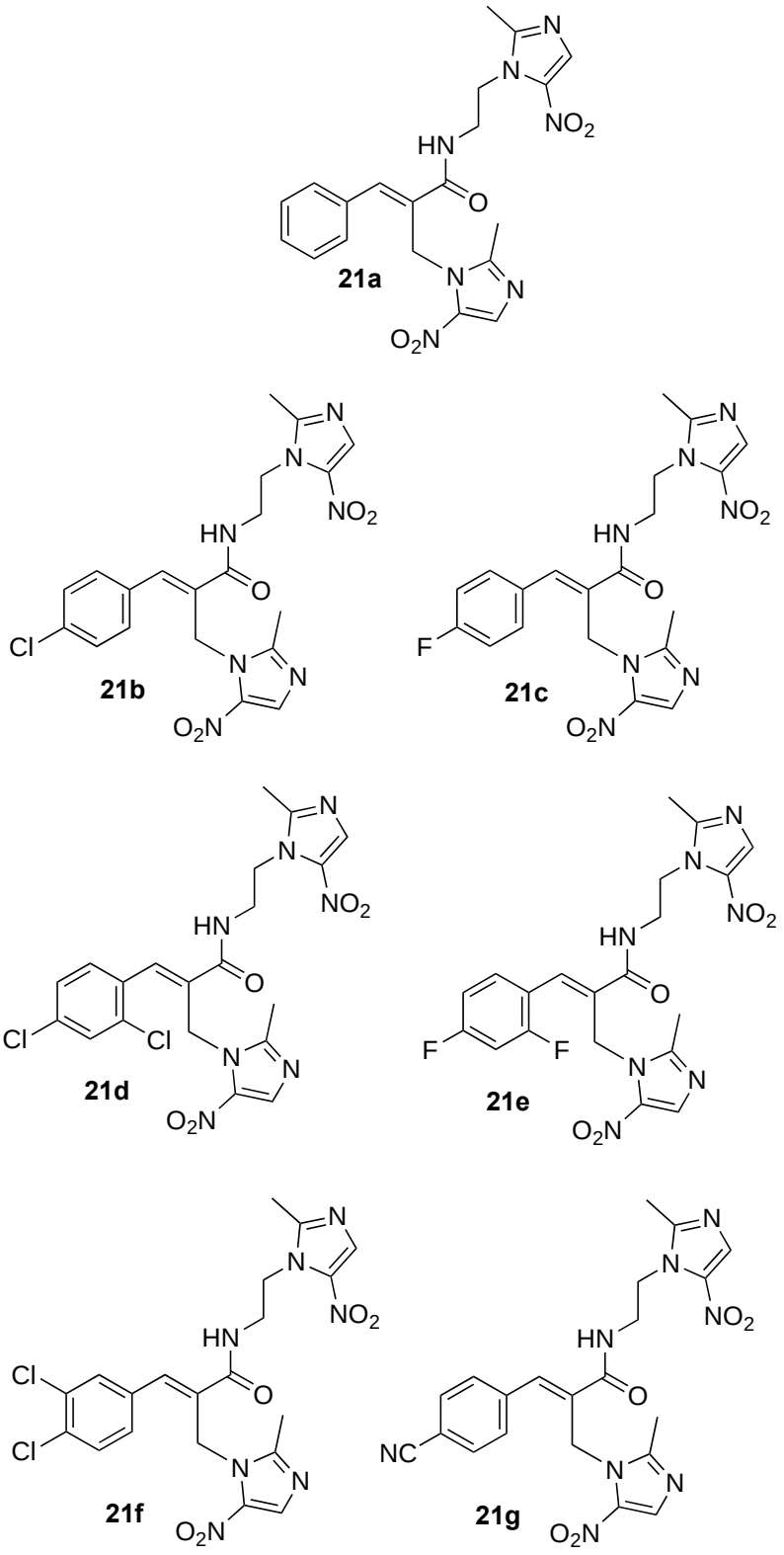

Figure 15. α-Nitromethylimidazolylmethyl cinnamamide-metronidazole conjugates.

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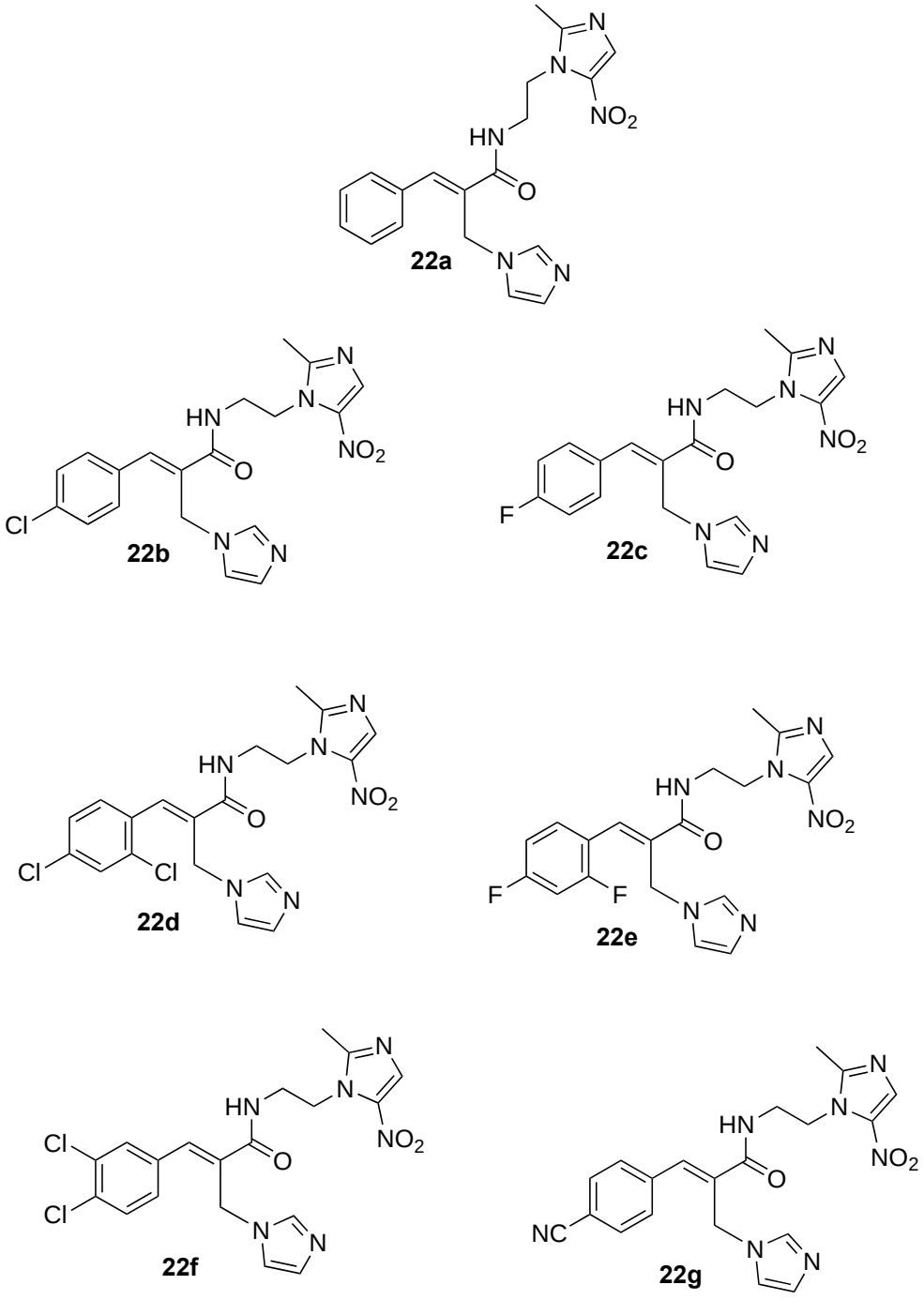

Figure 16. α-Imidazolylmethyl cinnamamide-metronidazole conjugates.

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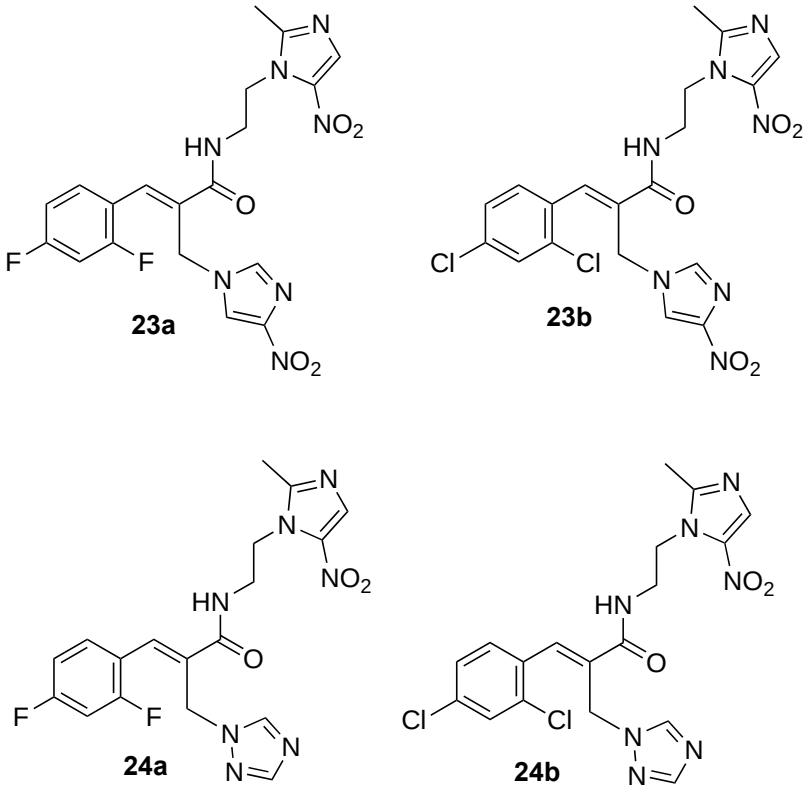

Figure 17. α-Nitroimidazolyl/α-triazolylmethyl cinnamamide-metronidazole conjugates.

Preparation of Glycine-Metronidazole-Cinnamamide Conjugates

We then ventured into the synthesis of metronidazole cinnamamide conjugates employing glycine as a linker to evaluate the SAR profile of these derivatives. The coupling of *N*-Boc-glycine **25** with metronidazole amine salt **20** was performed by dissolving the acid **25** in dichloromethane at 0°C under nitrogen atmosphere, by using 1-hydroxybenzotriazole (HOBt), 1-ethyl-3-(-3-dimethylamino propyl) carbodimide hydrochloride (EDCI), and *N*,*N*-diisopropylethylamine (Hunig's base). The amine salt **20** was added after half an hour and the solution was allowed to stir overnight. Further, deprotection of the Boc group in **26** was achieved by dropwise addition of a solution

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of 4 N dioxane/HCl, resulting in the formation of amine hydrochloride **27** (**Figure 18**). The final target compounds 28 were synthesized via another peptide coupling between **17** and **27** under identical (HOBt-EDCI) conditions (**Figures 19-20**).

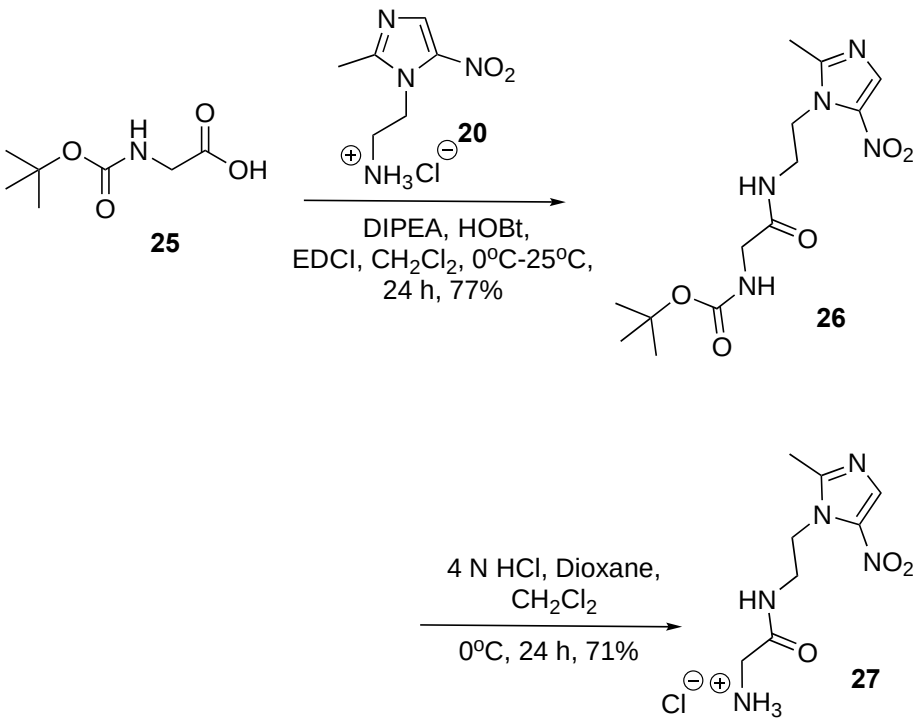

Figure 18. Preparation Glycine-Metronidazole Conjugate.

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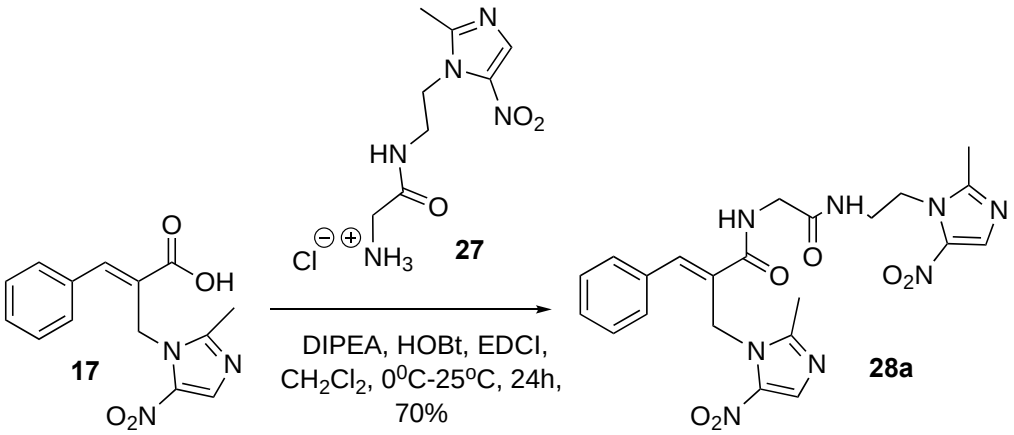

Figure 19. Preparation of Glycine-Metronidazole-Cinnamamide Conjugates.

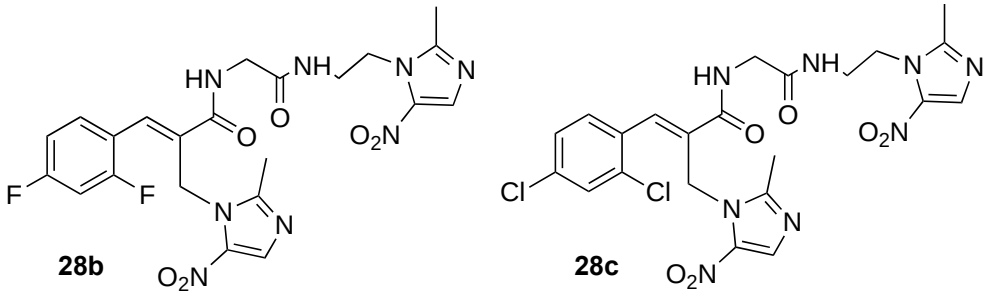

Figure 20. Glycine-Metronidazole-Cinnamamide Conjugates.

Synthesis of Metronidazole-Cinnamate Conjugates

Eventually, metronidazole-cinnamate conjugate **29** was also accomplished via the coupling of metronidazole tosylate **18** with carboxylic acid **17** dissolved in dimethylformamide in the presence of potassium carbonate and heating at 100°C for five hours. The mixture was allowed to stir for five hours and worked up to obtain the target compounds **29a-b** (**Figures 21-22**). The biological evaluation of the new compounds is

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underway and the data obtained in this project will provide insights into the next stage of drug development.

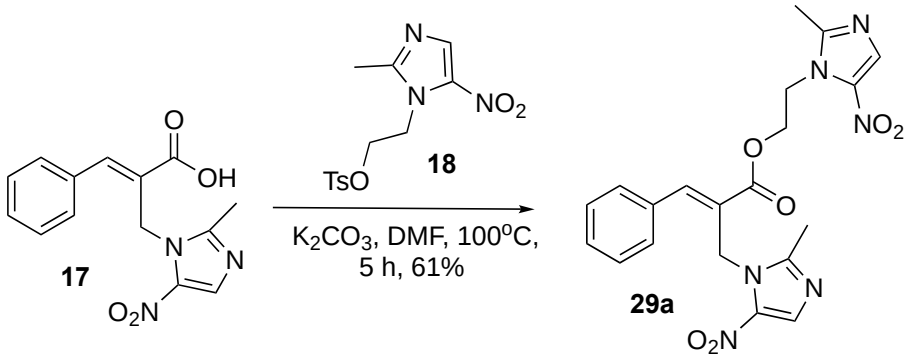

Figure 21. Synthesis of Metronidazole-Cinnamate Conjugates.

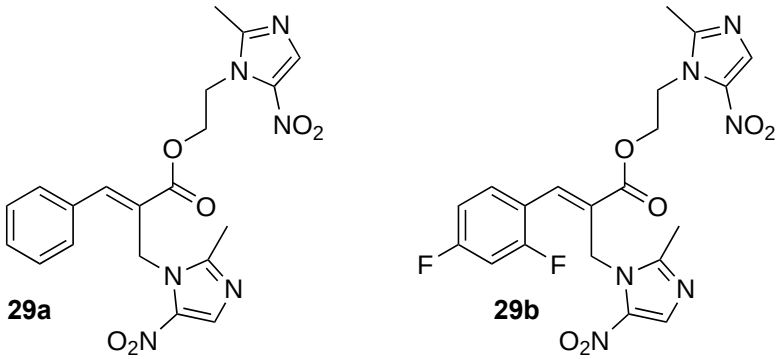

Figure 22. Metronidazole-Cinnamate Conjugates.

Conclusions

We have been involved in the development of methodologies for the preparation of small molecule libraries utilizing Baylis- Hillman reaction for potential development

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as therapeutic agents. In this regard, we took up a project involving the synthesis of functionalized imidazoles as potential medicinal agents and were able to identify few lead derivatives. The ease of synthesis coupled with the versatility of the Baylis-Hillman reaction renders interest for this project among the synthetic and medicinal community.

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Chapter 3

Experimental Procedures

Materials and Methods

All the reactants were of reagent grade, purchased from Acros Organics, Alfa Aesar or Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific. All operations were carried out under an inert atmosphere of nitrogen. Glassware for all reactions was oven dried at 125 °C and cooled under nitrogen prior to use. Liquid reagents and solvents were introduced by oven-dried syringes or cannulas through septa sealed flasks under a nitrogen atmosphere.

Instrumentation

Nuclear Magnetic Spectroscopy (NMR) spectra were produced using a Varian 400 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 400 MHz for ^{1}H NMR, and 101 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures

General amide-coupling procedure A. *N*,*N*-diisopropylethylamine (2.0 mmol), HOBt (1.1 mmol), and EDCI (1.1 mmol) were added at 0 °C to a stirred solution of the appropriate acid (1.0 mmol) in dichloromethane (10.0 mL) and the reaction was stirred for 30 min. The appropriate amine (1.0 mmol) was added in one portion and the reaction was stirred overnight at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and worked up with dichloromethane (2 x 10.0 mL). The combined extracts were washed with

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brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain pure amides in good yields.

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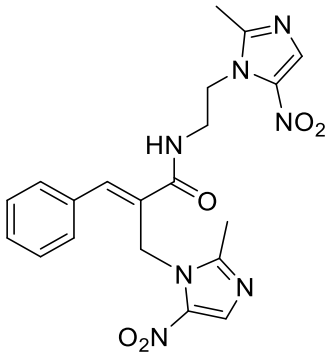

(E)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)-3-phenylacrylamide (21a): White solid; yield: 167 mg; mp 168°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 (s, 1H), 7.44 (s, 2H), 7.42 (d, *J* = 3.9 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 2H), 6.97 (d, *J* = 5.1 Hz, 1H), 4.95 (s, 2H), 4.44 (t, *J* = 6.4 Hz, 2H), 3.68 (q, *J* = 6.3 Hz, 2H), 2.46 (s, 3H), 2.22 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 167.8, 151.3, 146.1, 145.5, 139.0, 138.4, 133.4, 130.3, 129.6, 129.1, 128.4, 120.1, 44.9, 43.4, 39.4, 29.6, 13.9, 12.9.

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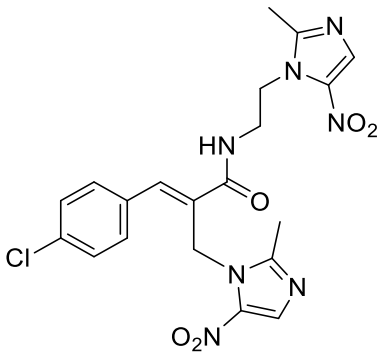

(E)-3-(4-chlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21b): White solid; yield: 190mg; mp: 245 °C ^{1}H – NMR (400 MHz, DMSO– d_6) δ 8.69 (t, *J* = 5.8 Hz, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.30 (s, 1H), 4.91 (s, 2H), 4.31 (t, *J* = 5.6 Hz, 2H), 3.48 (d, *J* = 5.5 Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H). ^{13}C–NMR (101 MHz, DMSO-d_6): δ (ppm) 167.6, 151.7, 145.7, 139.0, 136.4, 134.1, 133.6, 133.2, 131.4, 131.0, 129.3, 121.8, 45.5, 43.8, 38.7, 14.1, 13.1.

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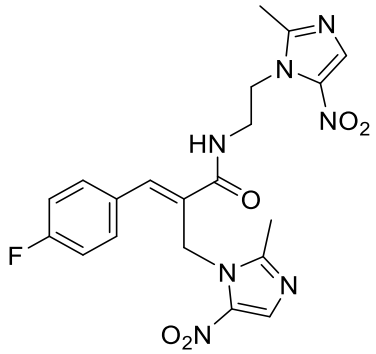

(E)-3-(4-fluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21c): White solid; yield: 107; mp 217°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.66 (t, *J* = 5.5 Hz, 1H), 7.96 (s, *J* = 1.6 Hz, 1H), 7.84 (s, *J* = 1.9 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.31 (s, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 4.91 (s, 2H), 4.30 (t, *J* = 5.4 Hz, 2H), 3.48 (d, *J* = 5.7 Hz, 2H), 2.29 (s, 3H), 2.13 (d, *J* = 1.8 Hz, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ (ppm) 167.7, 163.9, 161.4, 151.7, 145.7, 145.6, 139.0, 136.7, 133.6, 131.5, 131.5 (d, *J* = 8.5 Hz), 131.4, 130.8, 130.8 (d, *J* = 3.2 Hz), 130.8, 130.7, 121.8, 116.3 (d, *J* = 21.7 Hz), 45.6, 43.8, 38.8, 14.1, 13.1.

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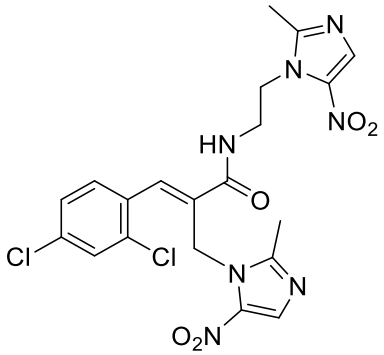

(E)-3-(2,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21d): Cream white solid; yield: 124mg; mp: 223°C; ^{1}H– NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.64 (s, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 6.1 Hz, 1H), 4.81 (s, 2H), 4.44 (t, *J* = 6.2 Hz, 2H), 3.69 (d, *J* = 6.0 Hz, 2H), 2.48 (s, *J* = 15.5 Hz, 3H), 2.22 (s, *J* = 3.7 Hz, 3H). ^{13}C –NMR (101 MHz, $CDCl_3$) δ (ppm) 167.0, 151.2, 146.0, 145.5, 138.3, 136.2, 134.5, 134.2, 133.1, 130.6, 130.5, 130.0, 127.7, 120.3, 44.9, 43.7, 39.3, 13.9, 12.8.

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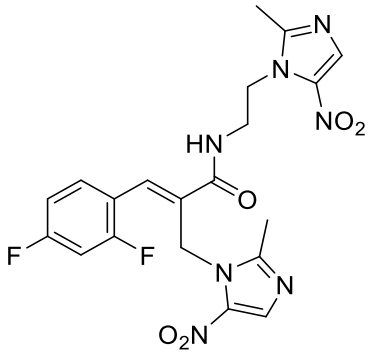

(E)-3-(2,4-difluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21e): Cream solid; yield: 121 mg; mp 209 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.69 (t, *J* = 5.9 Hz, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.33 – 7.45 (m, 2H), 7.13 – 7.19 (m, 2H), 4.84 (s, 2H), 4.30 (t, *J* = 5.8 Hz, 2H), 3.48 (q, *J* = 5.7 Hz, 2H), 2.29 (s, 3H), 2.12 (s, 3H). ^{13}C – NMR (101 MHz, DMSO-d_6): δ (ppm) 166.9, 163.0 (dd, *J* = 12.0, 249.0 Hz), 159.9 (dd, *J* = 12.4, 249.4 Hz), 151.6, 145.6, 145.6, 138.9, 133.8, 133.6, 132.2 (dd, *J* = 3.9, 9.8 Hz), 129.3, 122.1, 118.5 (dd, *J* = 4.0, 14.9 Hz), 112.5 (dd, *J* = 3.3, 21.8 Hz), 104.9 (t, *J* = 26.3 Hz), 45.5, 44.4, 38.8, 14.0, 12.9;

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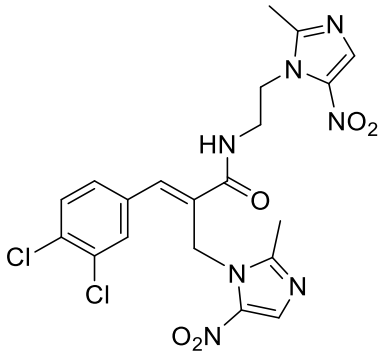

(E)-3-(3,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21f): White solid; yield: 105mg; mp: 240°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.67 (s, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 4.93 (s, 2H), 4.29 (t, *J* = 5.3 Hz, 2H), 3.48 (d, *J* = 4.8 Hz, 2H), 2.29 (s, *J* = 20.2 Hz, 3H), 2.14 (s, *J* = 20.1 Hz, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ (ppm) 167.4, 151.7, 145.7, 145.6, 139.0, 135.1, 134.78, 133.6, 132.7, 131.9, 131.9, 131.3, 130.9, 129.2, 122.1, 45.5, 43.8, 38.8, 14.1, 13.1.

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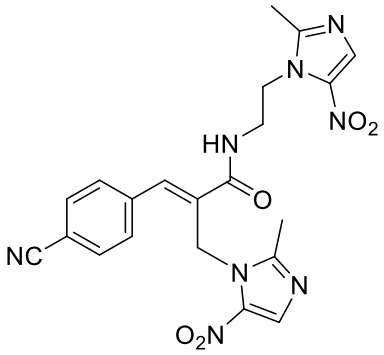

(E)-3-(4-cyanophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (21g): gummy yellow solid; yield: 50 mg; mp 108 °C; ^{1}H– NMR (400 MHz, DMSO– d_6) δ 8.71 (t, *J* = 5.9 Hz, 1H), 7.95 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.86 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.33 (s, 1H), 4.91 (s, 2H), 4.30 (t, *J* = 5.9 Hz, 2H), 3.52 – 3.45 (m, 2H), 2.29 (s, 3H), 2.12 (s, 3H). ^{13}C– NMR (101 MHz, DMSO– d_6) δ (ppm) 167.3, 151.7, 145.7, 139.2, 139.0, 135.7, 133.6, 133.1, 133.1, 130.0, 122.0, 118.9, 111.7, 45.5, 43.8, 38.8, 14.1, 13.1.

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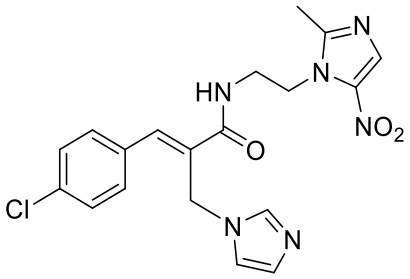

(E)-2-((1H-imidazol-1-yl)methyl)-3-(4-chlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide(22b): Gummy brown solid: yield: 86 mg; mp:78°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.85 (s, 1H), 7.37 (s, 2H), 7.35 (s, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.94 (s, 1H), 6.86 (s, 1H), 4.96 (s, 2H), 4.41 (t, *J* = 6.3 Hz, 2H), 3.62 (dd, *J* = 12.1, 6.1 Hz, 2H), 2.39 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 168.4, 151.3, 138.4, 137.1, 135.4, 133.4, 132.3, 132.0, 129.9, 129.3, 128.7, 119.4, 44.8, 43.4, 39.4, 29.7, 14.0.

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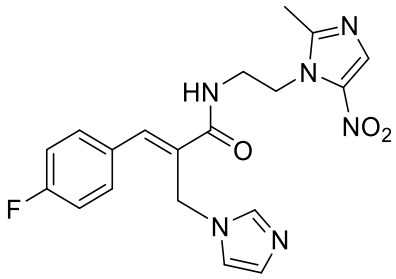

(E)-2-((1H-imidazol-1-yl)methyl)-3-(4-fluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (22c): Gummy brown solid; yield: 112 mg; mp 88°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.69 (d, *J* = 5.4 Hz, 1H), 7.35 (s, 2H), 7.24 – 7.16 (m, 2H), 7.12 – 7.05 (m, 2H), 6.90 (d, *J* = 31.2 Hz, 2H), 4.96 (s, 2H), 4.42 (t, *J* = 6.4 Hz, 2H), 3.62 (dd, *J* = 12.3, 6.2 Hz, 2H), 2.38 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 168.6, 164.2, 161.7, 151.3, 138.4, 137.2, 133.3, 131.4, 130.5 (d, *J* = 8.4 Hz), 129.9 (d, *J* = 3.4 Hz), 116.2(d, *J* = 21.8 Hz), 44.8, 43.3, 39.4, 30.9, 13.9.

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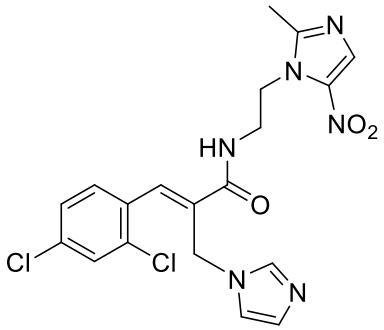

(E)-2-((1H-imidazol-1-yl)methyl)-3-(2,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (22d): Tan solid; yield: 98 mg; mp 62°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 4.85 (s, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 3.65 (q, *J* = 6.3 Hz, 2H), 2.43 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ (ppm) 167.8, 151.3, 138.4, 135.9, 134.5, 134.4, 133.7, 133.4, 131.0, 130.4, 129.9, 127.7, 127.6, 113.8, 44.8, 43.5, 39.5, 29.7, 14.0.

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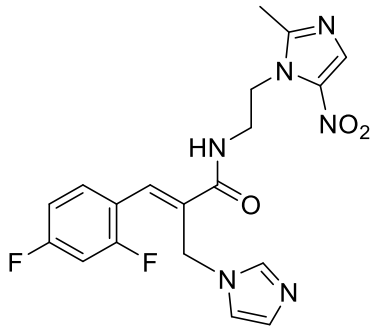

(E)-2-((1H-imidazol-1-yl)methyl)-3-(2,4-difluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (22e): Tan solid; yield: 120 mg; mp 54°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.72 (t, *J* = 5.9 Hz, 1H), 7.38 (s, 1H), 7.28 – 7.23 (m, 1H), 7.15 (dd, *J* = 14.8, 8.1 Hz, 1H), 6.94 (dd, *J* = 20.1, 8.6 Hz, 3H), 6.85 (s, 1H), 4.89 (s, 2H), 4.39 (t, *J* = 6.4 Hz, 2H), 3.61 (q, *J* = 6.3 Hz, 2H), 2.39 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 168.1, 163.4 (dd, *J* = 253.0, 12.0 Hz), 160.0 (dd, *J* = 251.7, 12.2 Hz), 151.3, 138.3, 136.9, 134.7, 133.4, 130.9, 130.8, 129.5, 128.8, 119.4, 117.9 (dd, *J* = 14.9, 4.0 Hz), 112.1 (dd, *J* = 21.6, 3.7 Hz), 104.7 (t, *J* = 25.6 Hz). 44.8, 43.8, 39.4, 13.9.

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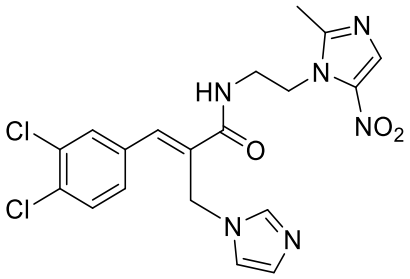

(E)-2-((1H-imidazol-1-yl)methyl)-3-(3,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (22f): Tan solid; yield: 113; mp 123°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.57 (s, 2H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.33 (s, 1H), 7.28 (s, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 44.9 Hz, 2H), 4.97 (s, 2H), 4.41 (t, *J* = 6.0 Hz, 2H), 3.63 (d, *J* = 6.0 Hz, 2H), 2.41 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 168.1, 151.3, 138.4, 135.6, 133.8, 133.5, 133.4, 133.3, 133.1, 133.0, 131.0, 130.4, 127.7, 44.8, 43.4, 39.4, 30.9, 14.0.

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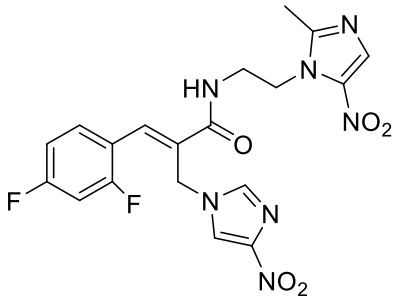

(E)-3-(2,4-difluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((4-nitro-1H-imidazol-1-yl)methyl)acrylamide (23a): Cream solid; yield: 330 mg; mp 149°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.70 (d, *J* = 5.7 Hz, 1H), 8.03 (s, 1H), 7.96 (s, 1H), 7.61 (s, 1H), 7.43 (dd, *J* = 16.8, 9.4 Hz, 1H), 7.37 (t, *J* = 9.9 Hz, 1H), 7.24 (s, 1H), 7.16 (t, *J* = 8.3 Hz, 1H), 4.92 (s, 2H), 4.33 (t, *J* = 5.5 Hz, 2H), 3.51 (d, *J* = 5.7 Hz, 2H), 2.30 (s, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ 167.0, 151.7, 147.2, 139.0, 137.7, 133.6, 133.5, 132.1 (dd, *J* = 10.1, 4.1 Hz), 130.2, 121.5, 118.5 (dd, *J* = 15.4, 3.5 Hz), 112.6 (dd, *J* = 21.5, 3.4 Hz), 105.0 (t, *J* = 25.9 Hz) 45.6, 45.0, 38.9, 14.1.

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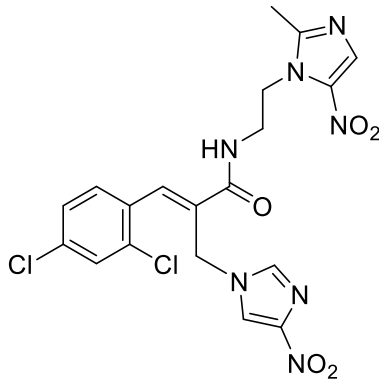

(E)-3-(2,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-2-((4-nitro-1H-imidazol-1-yl)methyl)acrylamide (23b): White solid; yield: 87 mg; mp 208°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.71 (t, *J* = 5.6 Hz, 1H), 8.02 – 7.90 (m, 2H), 7.74 (t, *J* = 2.2 Hz, 1H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.48 (t, *J* = 5.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 4.86 (s, 2H), 4.34 (t, *J* = 5.2 Hz, 2H), 3.53 (d, *J* = 5.1 Hz, 2H), 2.32 (s, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ (ppm) 166.7, 151.7, 147.2, 139.0, 137.7, 134.8, 134.4, 133.8, 133.6, 131.9, 131.8, 129.6, 128.3, 121.5, 45.6, 44.7, 38.9, 14.2.

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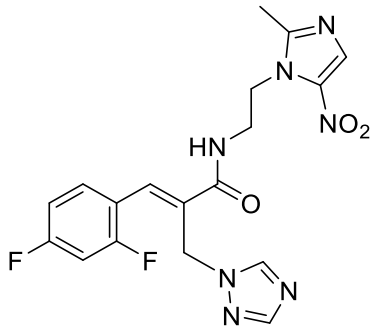

(E)-2-((1H-1,2,4-triazol-1-yl)methyl)-3-(2,4-difluorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (24a): Tan solid; yield: 137 mg; mp 150°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.60 (t, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 7.99 (s, 1H), 7.96 (s, 1H), 7.95 – 7.91 (m, 1H), 7.38 (t, *J* = 9.8 Hz, 1H), 7.26 (s, 1H), 7.21 (t, *J* = 9.2 Hz, 1H), 5.04 (s, 2H), 4.30 (t, *J* = 5.9 Hz, 2H), 3.47 (q, *J* = 6.0 Hz, 2H), 2.21 (s, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ 167.0, 163.2 (dd, *J* = 249.4, 12.1 Hz), 160.5 (dd, *J* = 250.2, 12.4 Hz), 152.0, 151.7, 145.4, 138.9, 133.7, 133.2, 132.1, 129.1, 118.9 (dd, *J* = 14.0, 3.8 Hz), 112.5 (dd, *J* = 21.3, 3.6 Hz), 104.9 (t, *J* = 26.0 Hz) 46.1, 45.6, 38.9, 14.0.

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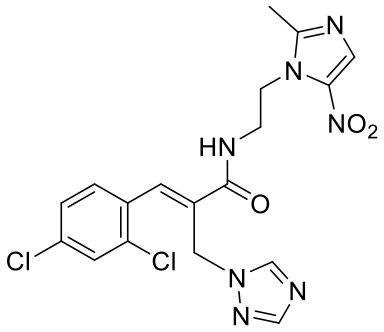

(E)-2-((1H-1,2,4-triazol-1-yl)methyl)-3-(2,4-dichlorophenyl)-N-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)acrylamide (24b): White solid; yield: 180 mg; mp 153°C; ^{1}H–NMR (400 MHz, DMSO– d_6) δ 8.61 (t, *J* = 5.9 Hz, 1H), 8.38 (d, *J* = 1.2 Hz, 1H), 7.99 (d, *J* = 1.3 Hz, 1H), 7.97 (d, *J* = 1.3 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 2.0 Hz, 1H), 7.54 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.29 (s, 1H), 4.98 (s, 2H), 4.31 (t, *J* = 5.8 Hz, 2H), 3.49 (q, *J* = 5.9 Hz, 2H), 2.23 (s, 3H). ^{13}C–NMR (101 MHz, DMSO– d_6) δ (ppm)166.8, 152.0, 151.8, 145.4, 138.9, 134.9, 134.5, 133.7, 133.3, 133.1, 132.1, 132.0, 129.6, 128.2, 46.0, 45.7, 38.9, 14.1.

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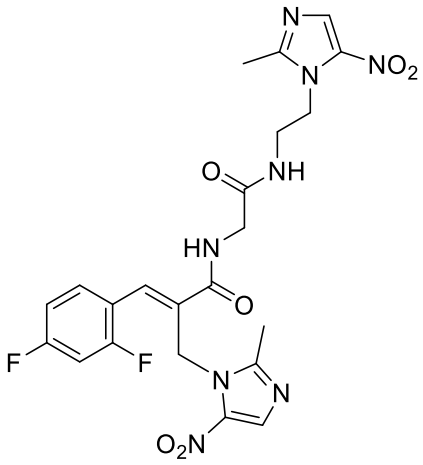

(E)-3-(2,4-difluorophenyl)-N-(2-((2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)amino)-2-oxoethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (28b): Light tan solid; yield: 60 mg; mp 98°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.86 (t, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 0.9 Hz, 1H), 7.38 (s, 1H), 7.32 (t, *J* = 5.3 Hz, 1H), 7.21 (dd, *J* = 14.7, 8.4 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.84 (s, 2H), 4.43 (t, *J* = 6.3 Hz, 2H), 3.88 (d, *J* = 5.3 Hz, 2H), 3.59 (q, *J* = 6.3 Hz, 2H), 2.48 (s, 3H), 2.24 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 169.6, 166.8, 163.6 (dd, *J* = 253.5, 11.8 Hz), 159.9 (dd, *J* = 251.2, 12.2 Hz), 151.3, 146.0, 145.5, 138.5, 133.2, 133.1, 131.2 (dd, *J* = 9.9, 4.1 Hz), 130.6, 120.5, 117.5 (dd, *J* = 15.0, 3.8 Hz), 112.4 (dd, *J* = 21.7, 3.1 Hz), 104.9 (t, *J* = 25.7 Hz)., 45.0, 44.2, 43.2, 38.9, 29.6, 14.0, 12.8.

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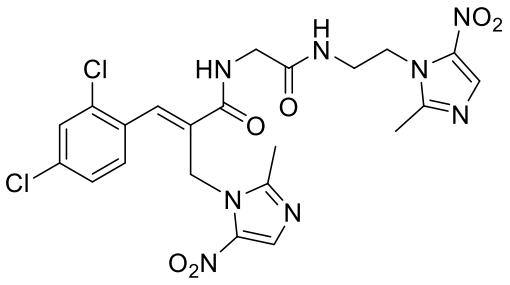

(E)-3-(2,4-dichlorophenyl)-N-(2-((2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)amino)-2-oxoethyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylamide (28c): Cream solid; yield: 76 mg; mp 105°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.45 (s,1H), 7.35 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.93 (s, 1H), 4.82 (s, 2H), 4.43 (t, *J* = 6.3 Hz, 2H), 3.90 (d, *J* = 5.3 Hz, 2H), 3.61 (q, *J* = 6.2 Hz, 2H), 2.48 (s, 3H), 2.21 (s, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 169.8, 167.3, 151.2, 138.5, 135.8, 134.4, 134.2, 133.9, 133.1, 131.1, 130.6, 129.9, 128.7, 127.6, 45.1, 43.7, 43.2, 38.9, 29.7, 14.0.

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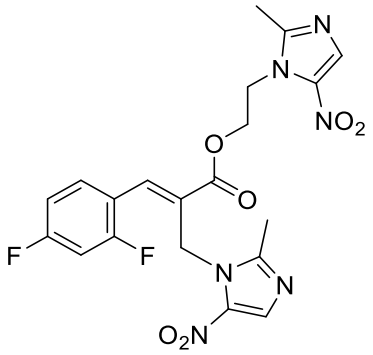

2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl (E)-3-(2,4-difluorophenyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylate (29b): Brown solid; yield: 92 mg; mp 83°C; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.3 Hz, 1H), 7.78 (s, 1H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.27 – 7.15 (m, 1H), 7.09 – 6.86 (m, 2H), 4.78 (s, 2H), 4.67 (t, *J* = 5.3 Hz, 2H), 4.55 (t, *J* = 5.4 Hz, 2H), 2.49 (s, *J* = 22.0 Hz, 3H), 2.27 (s, *J* = 27.2 Hz, 3H). ^{13}C–NMR (101 MHz, $CDCl_3$) δ 164.2 (dd, *J* = 255.4, 12.3 Hz), 160.1 (dd, *J* = 21.5, 13.3 Hz), 150.4, 145.2, 131.1 (dd, *J* = 9.9, 3.7 Hz), 138.0, 127.3, 119.4, 117.1 (dd, *J* = 14.6, 4.1 Hz), 112.7 (dd, *J* = 21.9, 3.5 Hz), 105.2 (t, *J* = 25.5 Hz), 63.5, 44.6, 43.5, 14.2, 13.0.

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Chapter 4

Spectral Characterization

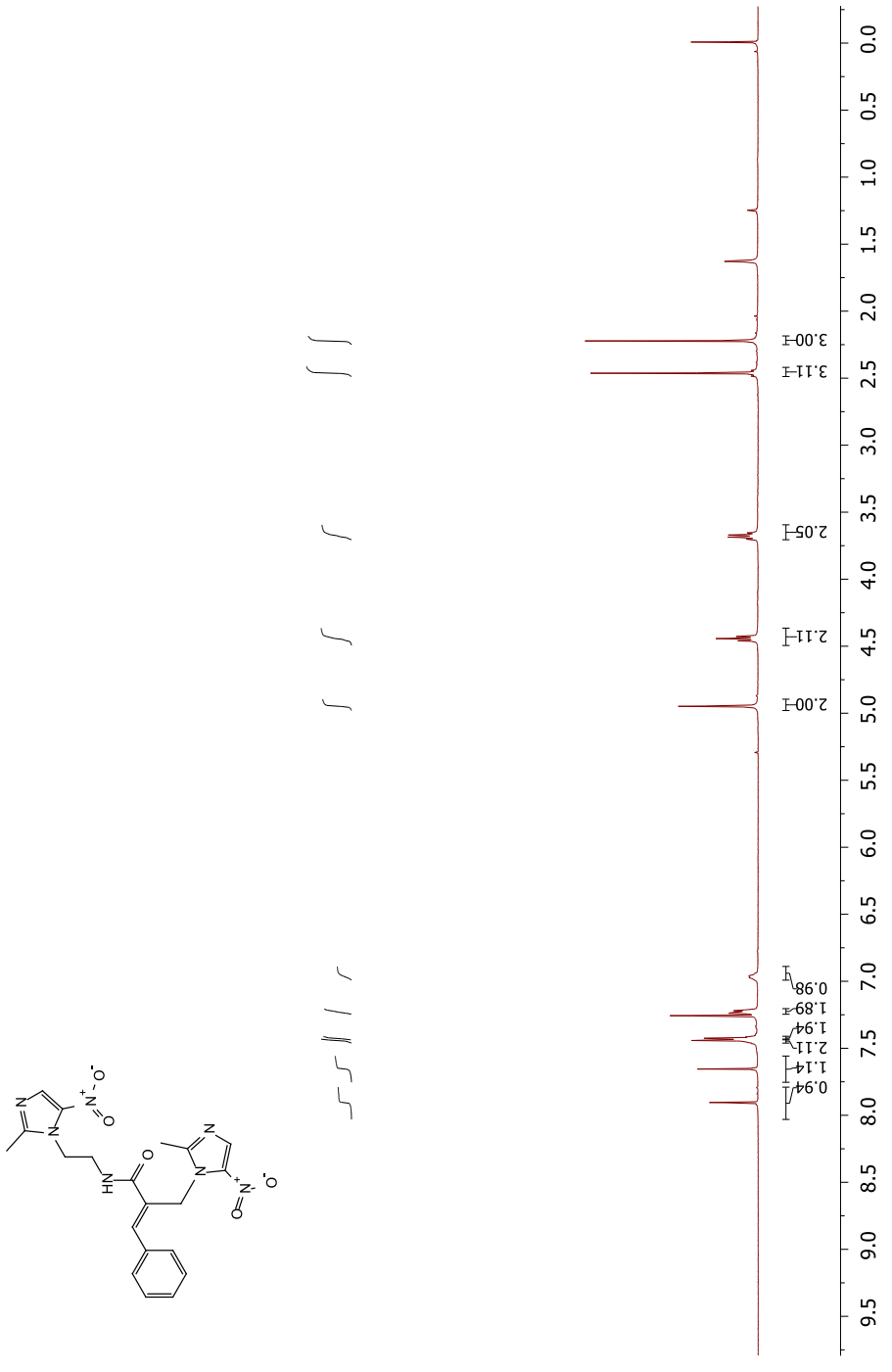

Figure 23. 400 MHz ^{1}H–NMR of Compound **21a** in $CDCl_3$.

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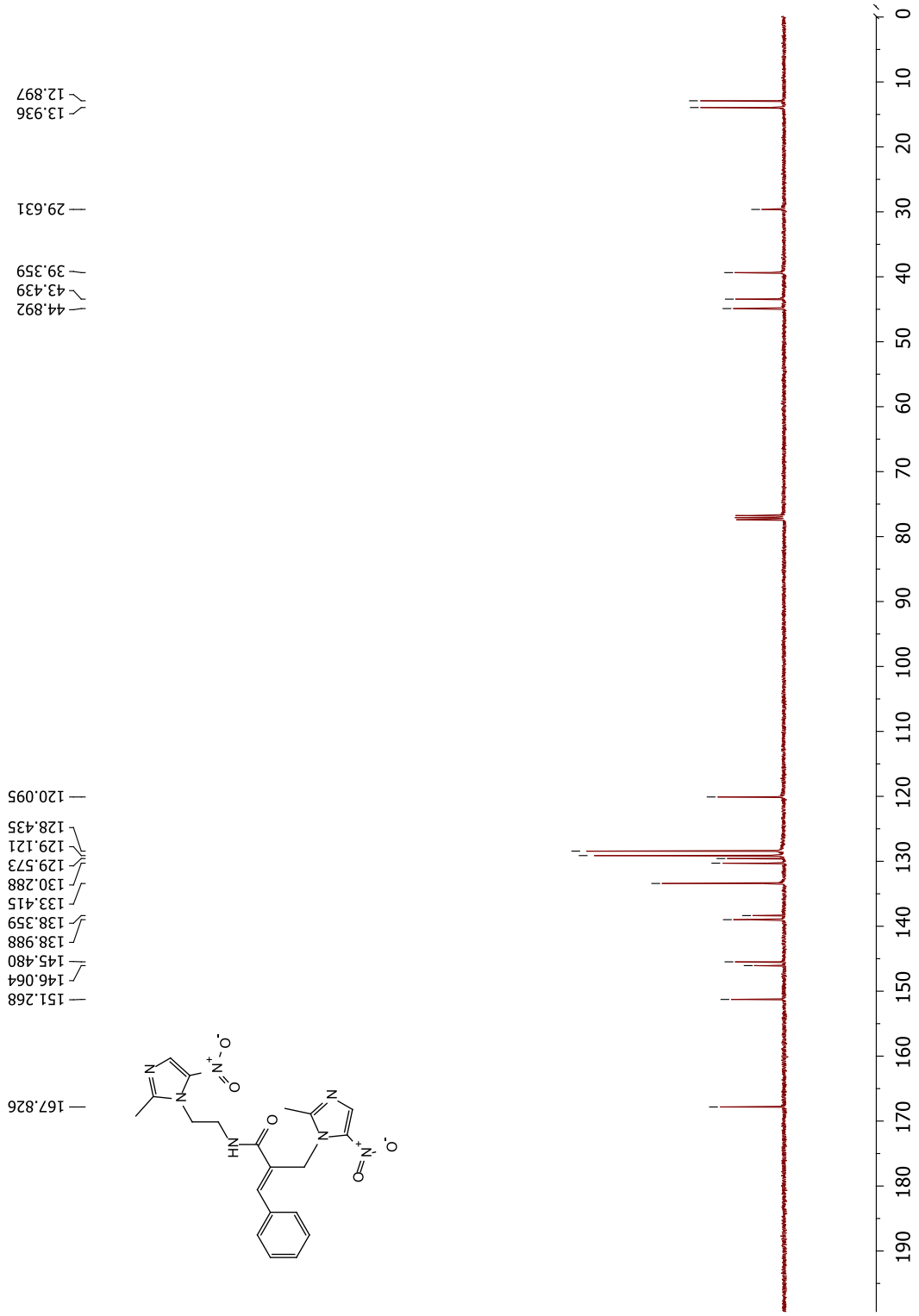

Figure 24. 101 MHz ^{13}C–NMR of Compound **21a** in $CDCl_3$.

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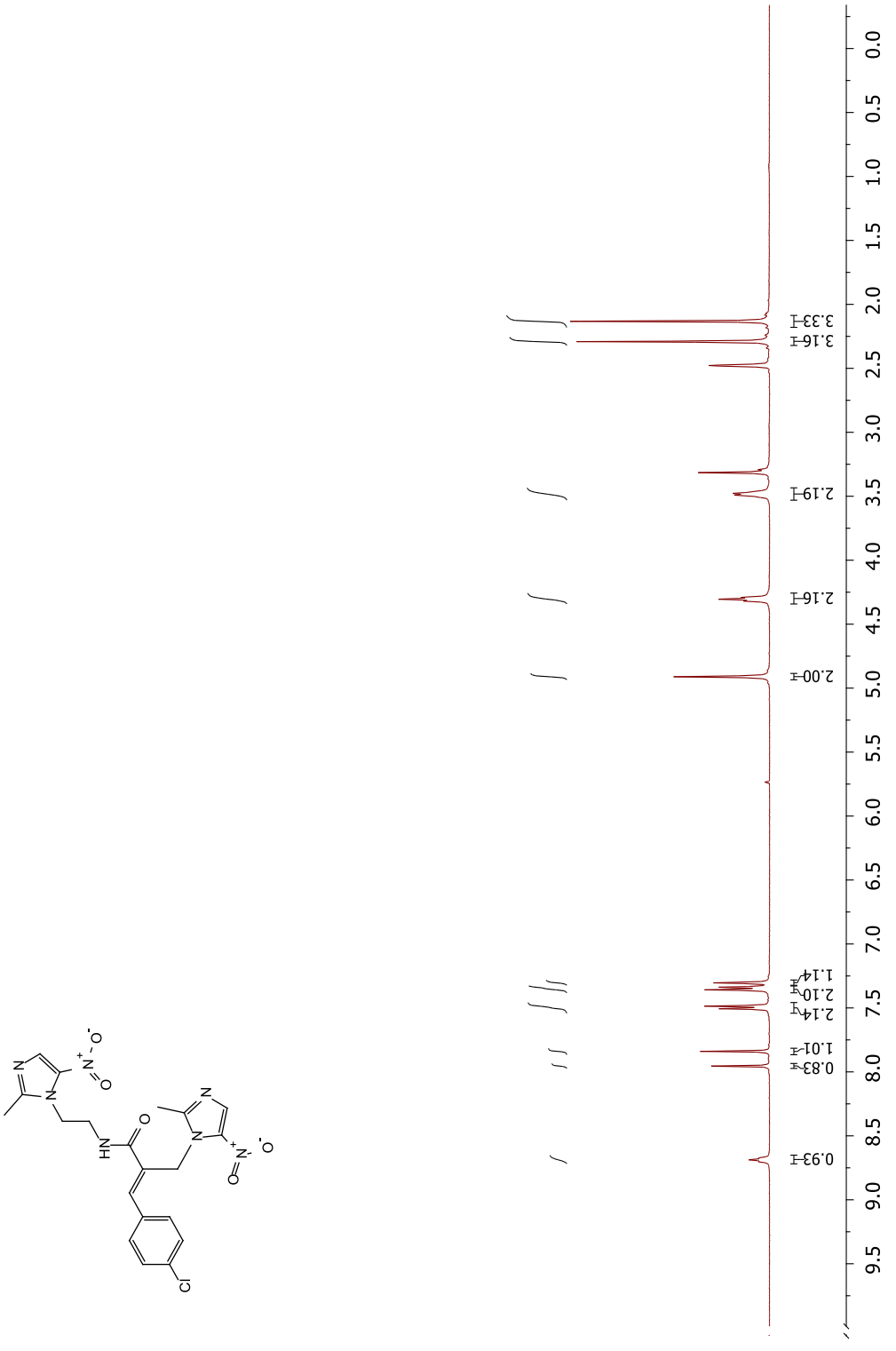

Figure 25. 400 MHz ^{1}H–NMR of Compound **21b** in DMSO-d_6.

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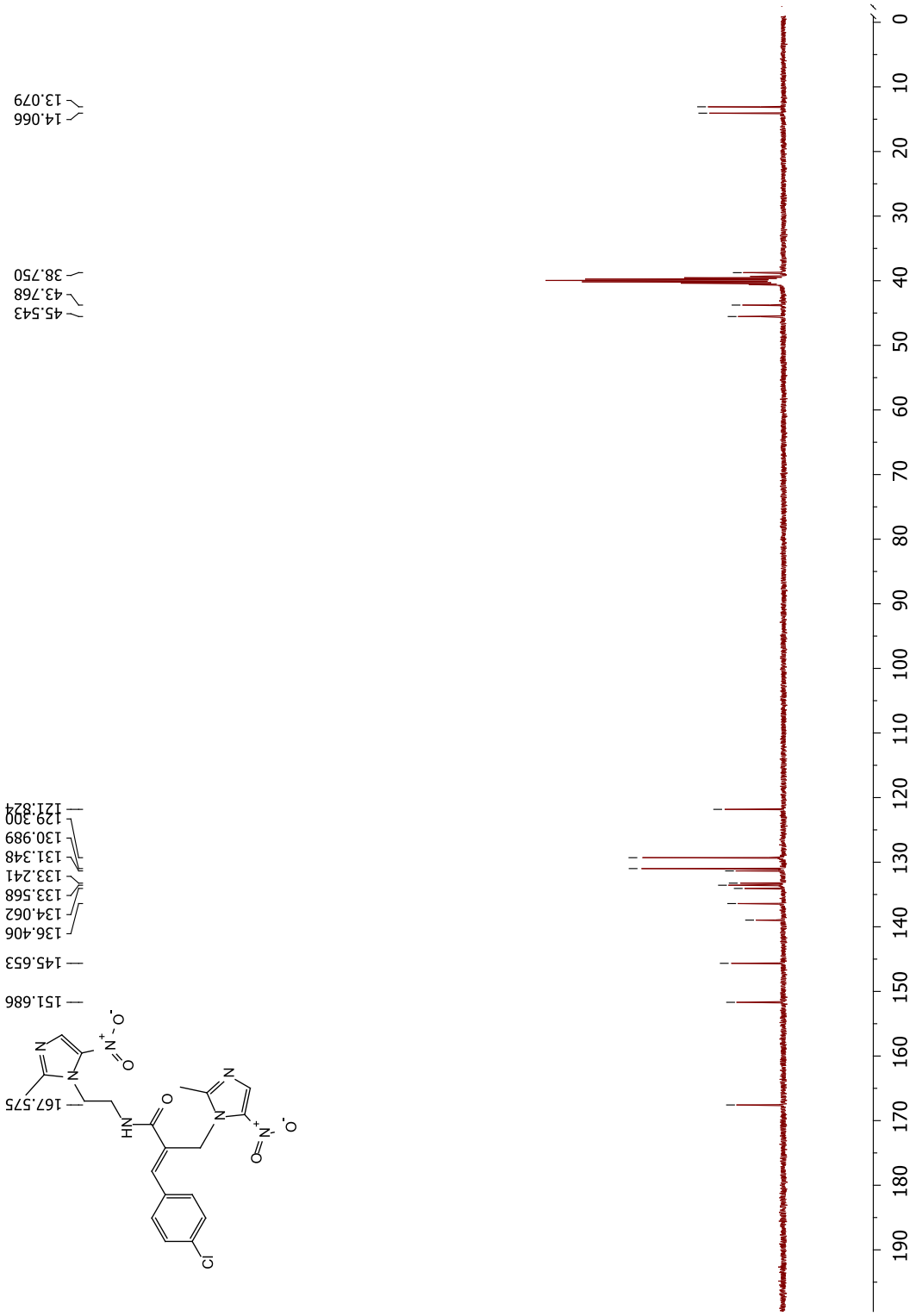

Figure 26. 101 MHz ^{13}C–NMR of Compound **21b** in DMSO-d_6.

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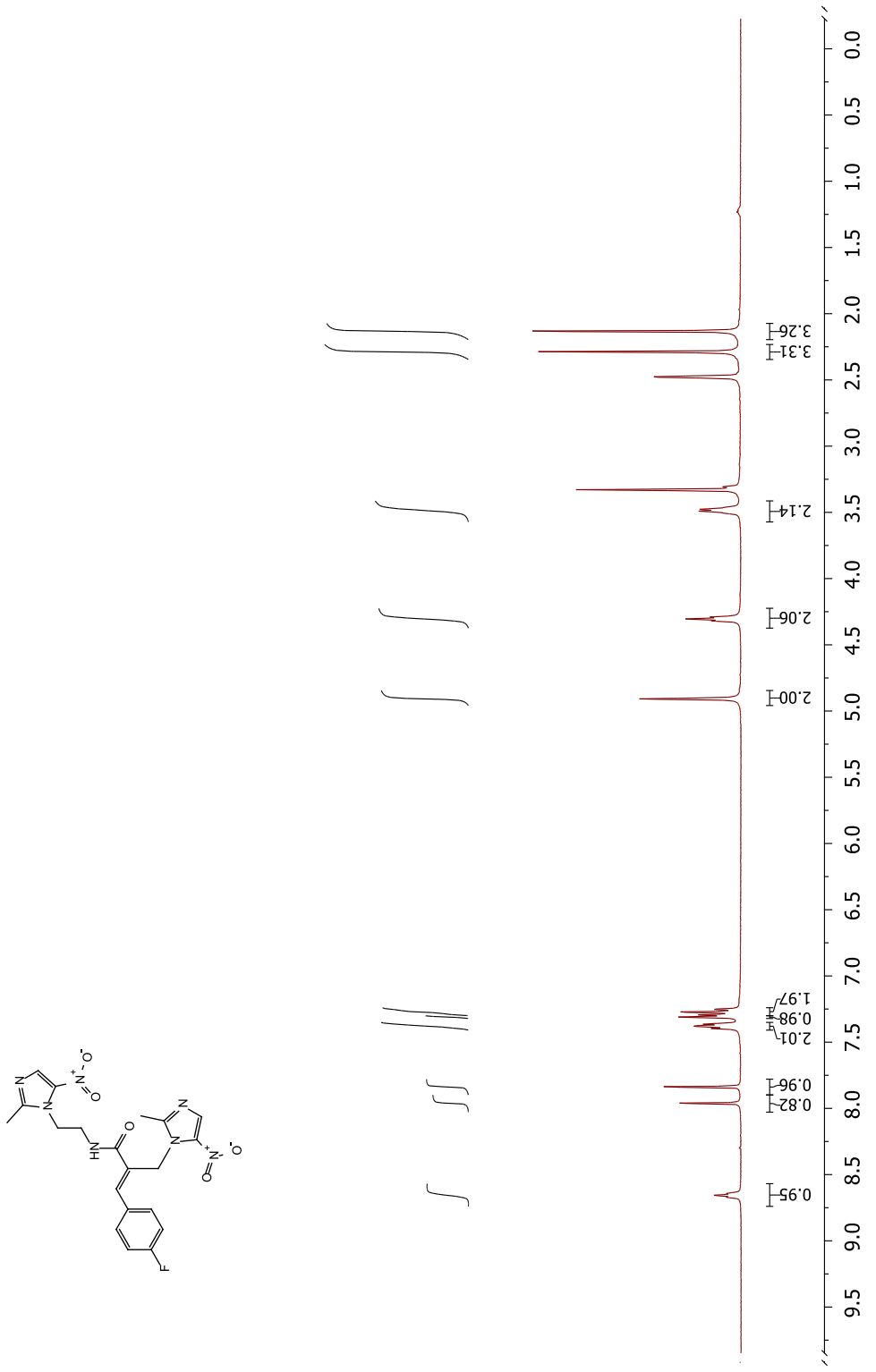

Figure 27. 400 MHz ^{1}H–NMR of Compound **21c** in DMSO-d_6.

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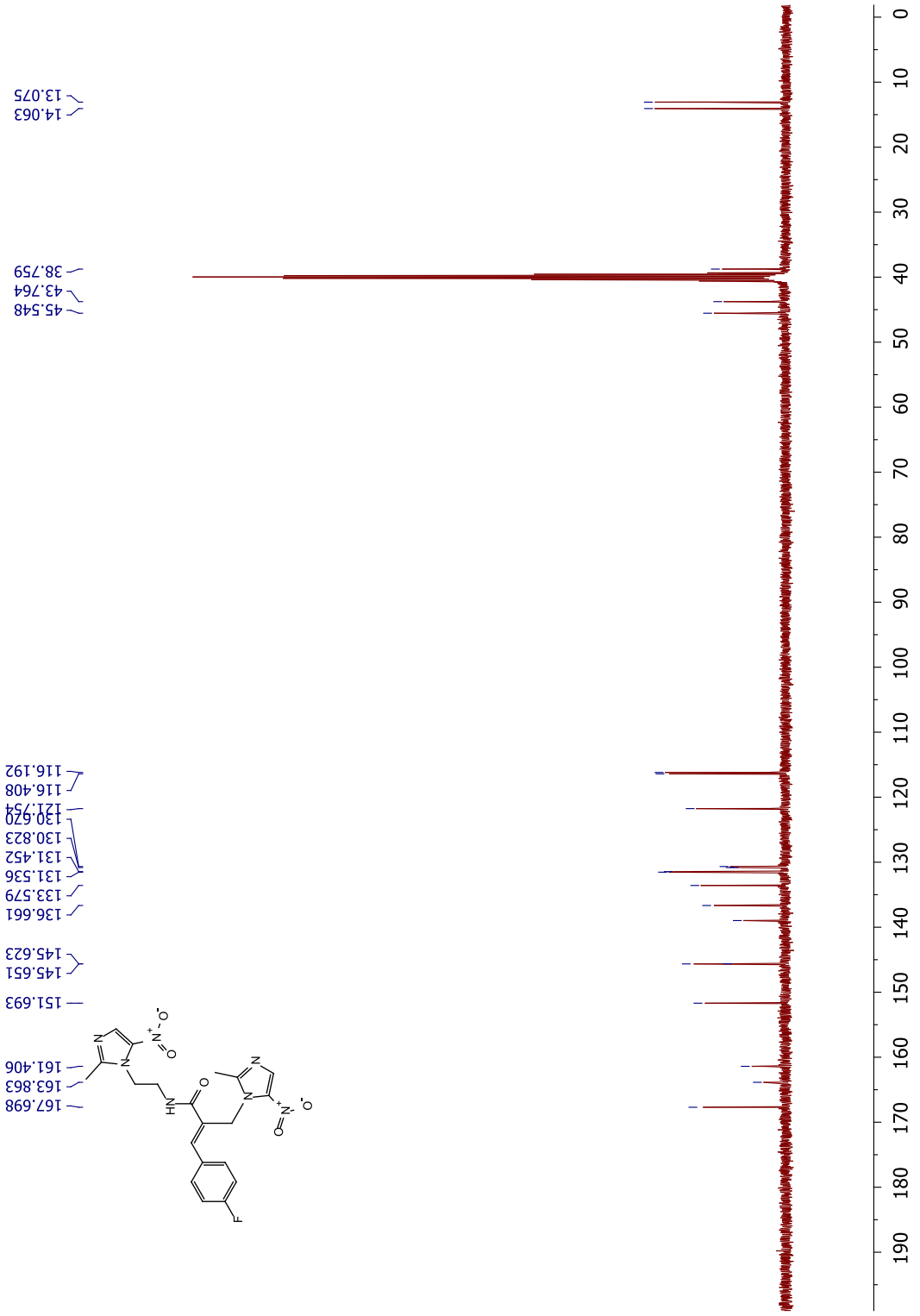

Figure 28. 101 MHz ^{13}C–NMR of Compound **21c** in DMSO-d_6.

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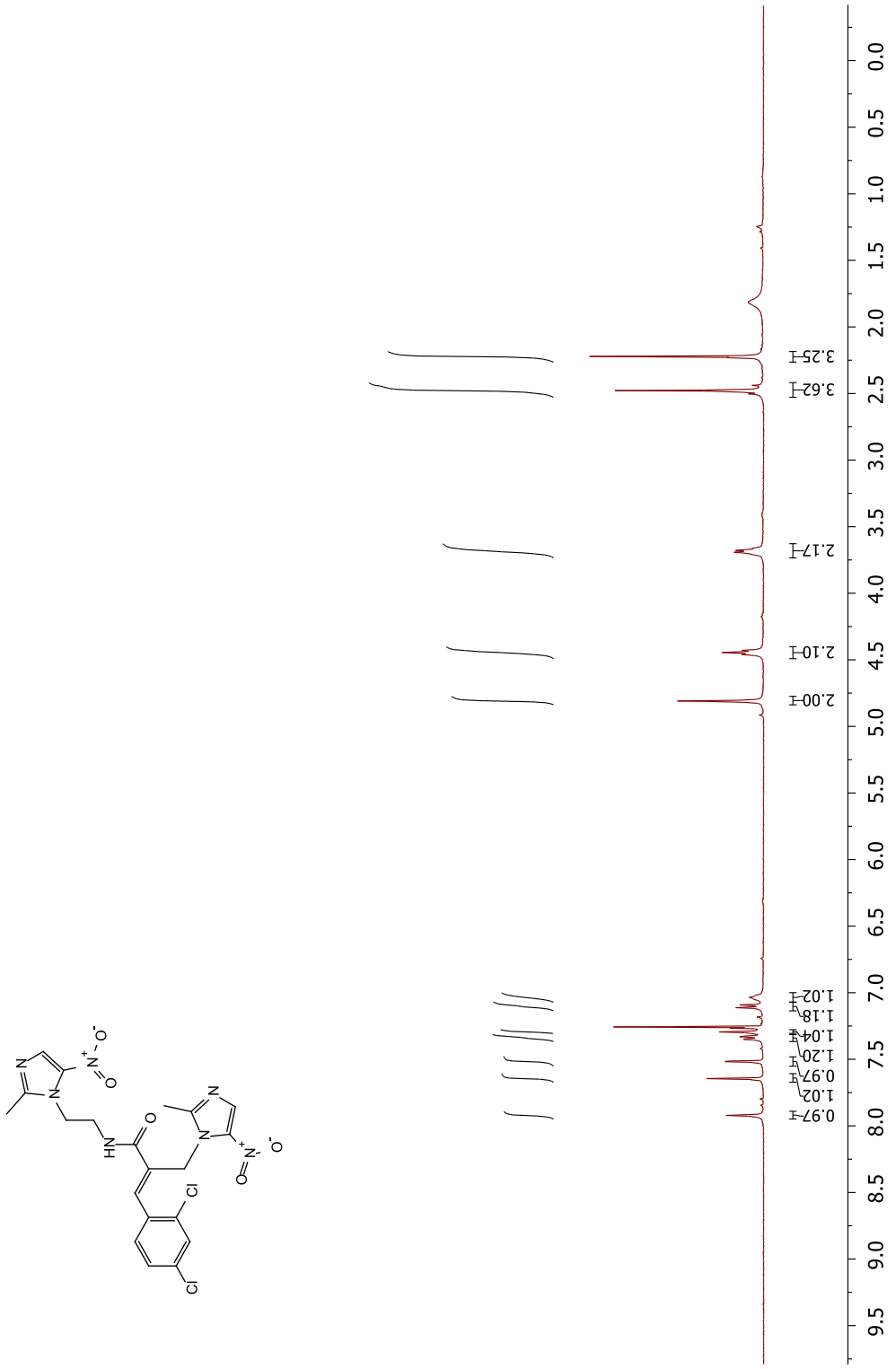

Figure 29. 400 MHz ^{1}H–NMR of Compound **21d** in $CDCl_3$.

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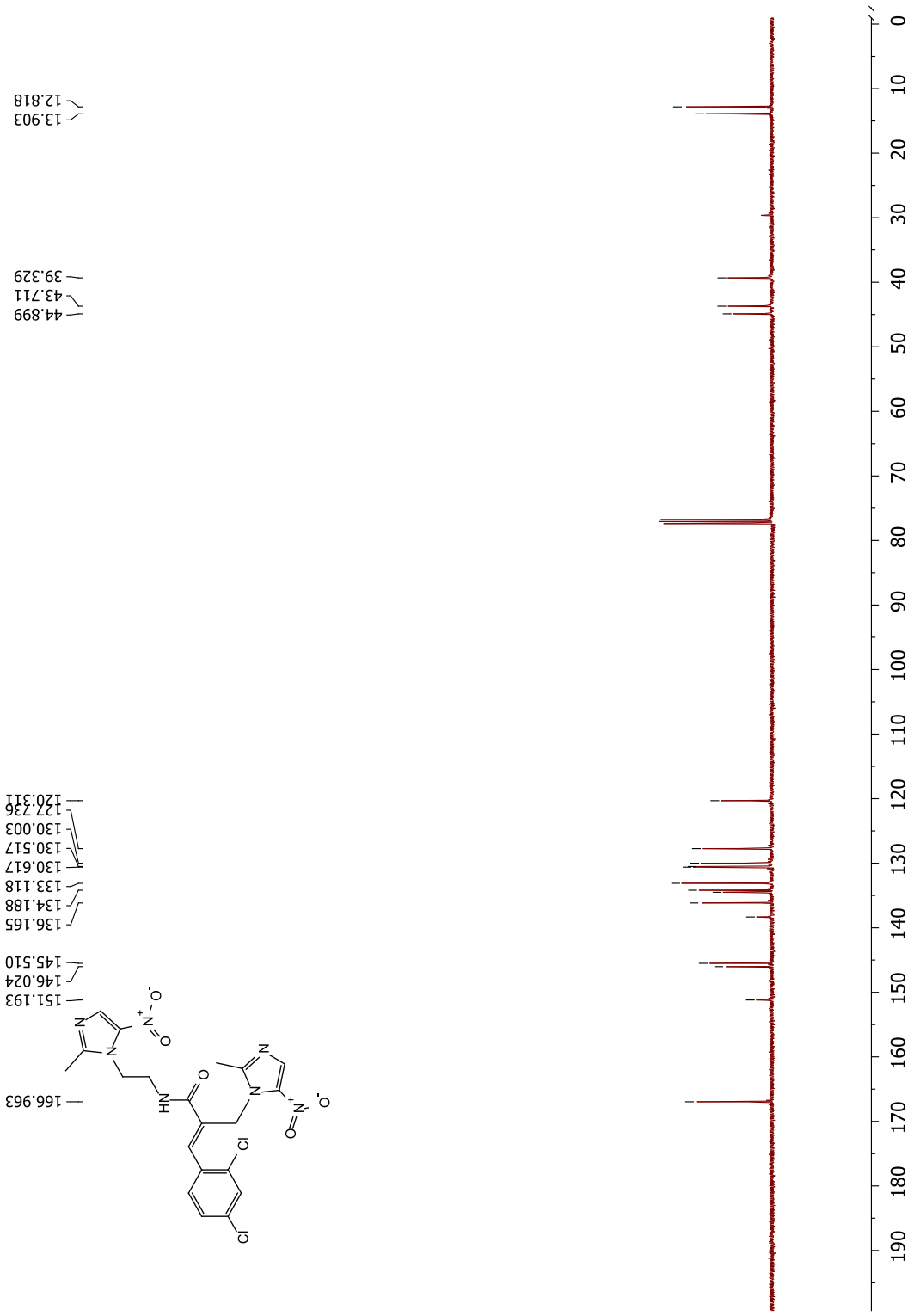

Figure 30. 101 MHz ^{13}C–NMR of Compound **21d** in $CDCl_3$.

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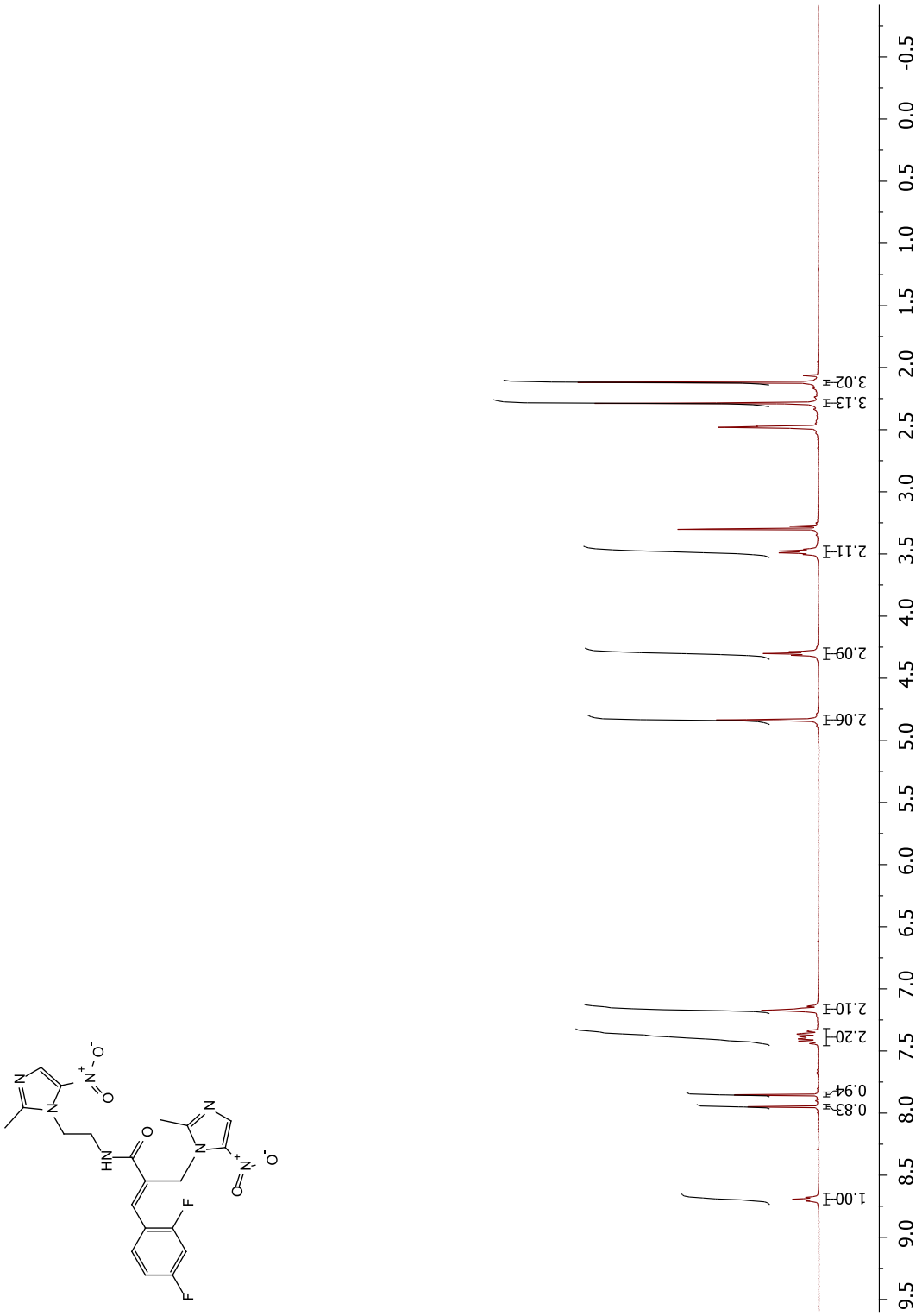

Figure 31. 400 MHz ^{1}H–NMR of Compound **21e** in DMSO-d_6.

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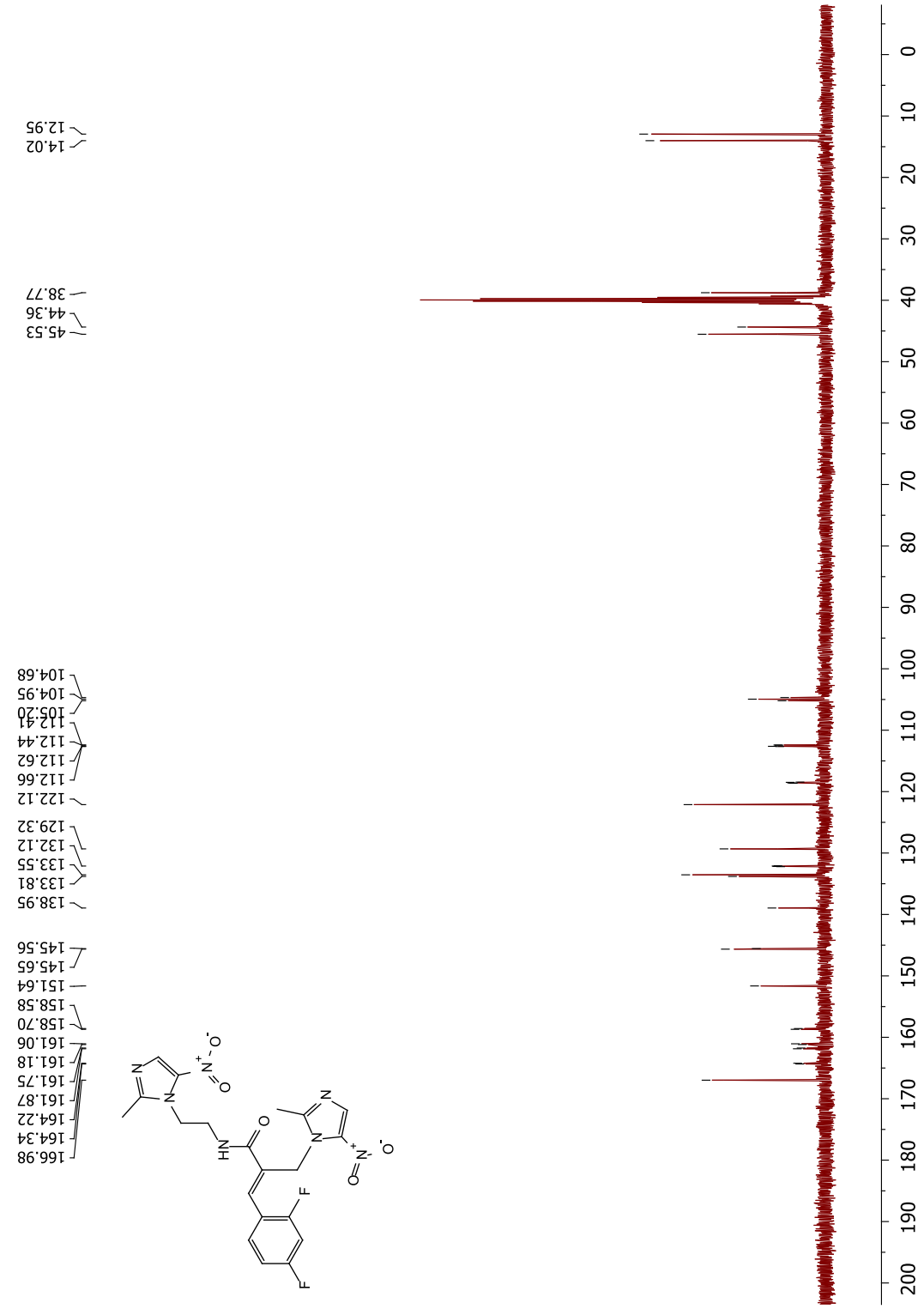

Figure 32. 101 MHz ^{13}C–NMR of Compound **21e** in DMSO-d_6.

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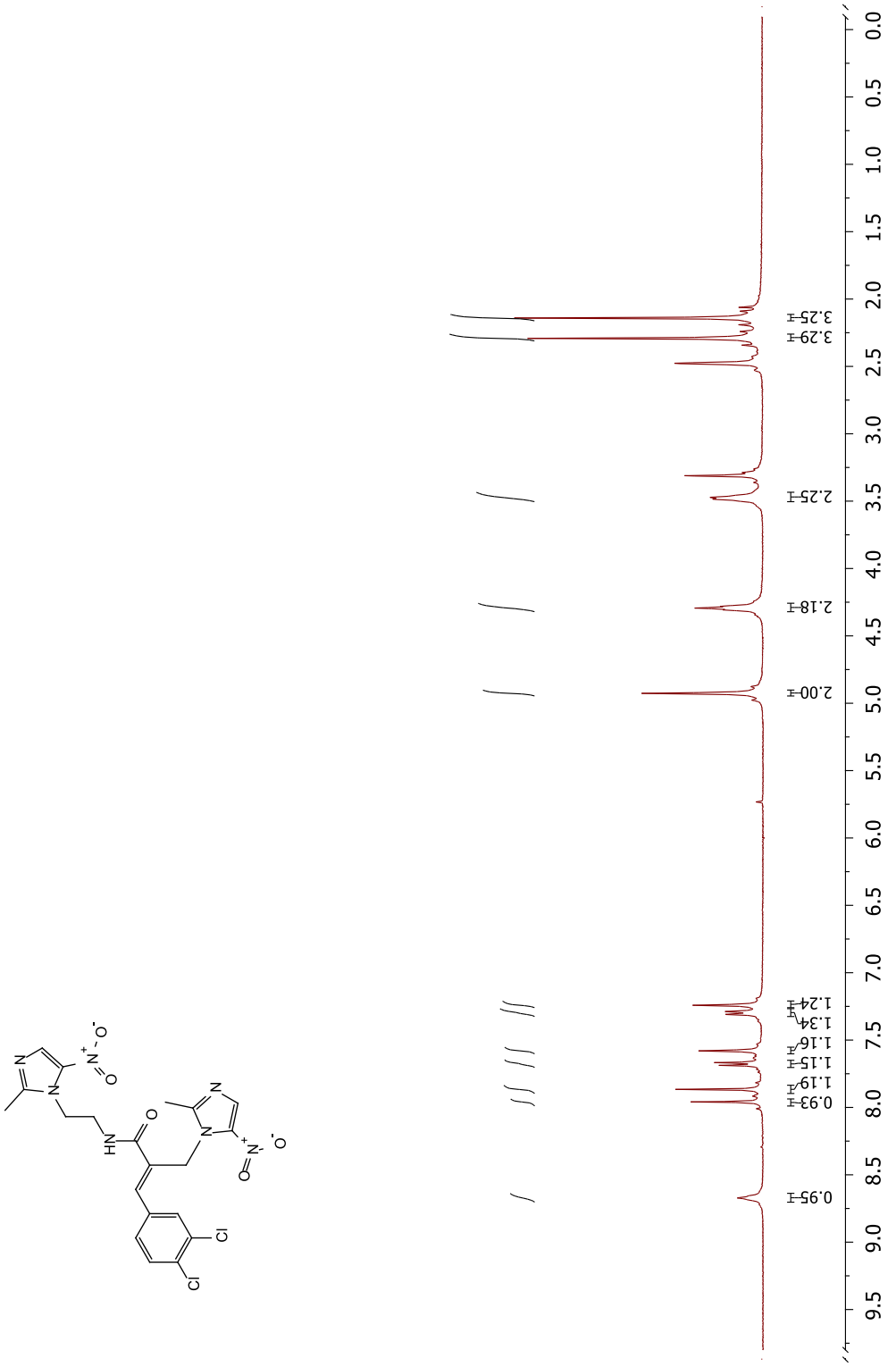

Figure 33. 400 MHz ^{1}H–NMR of Compound **21f** in DMSO-d_6.

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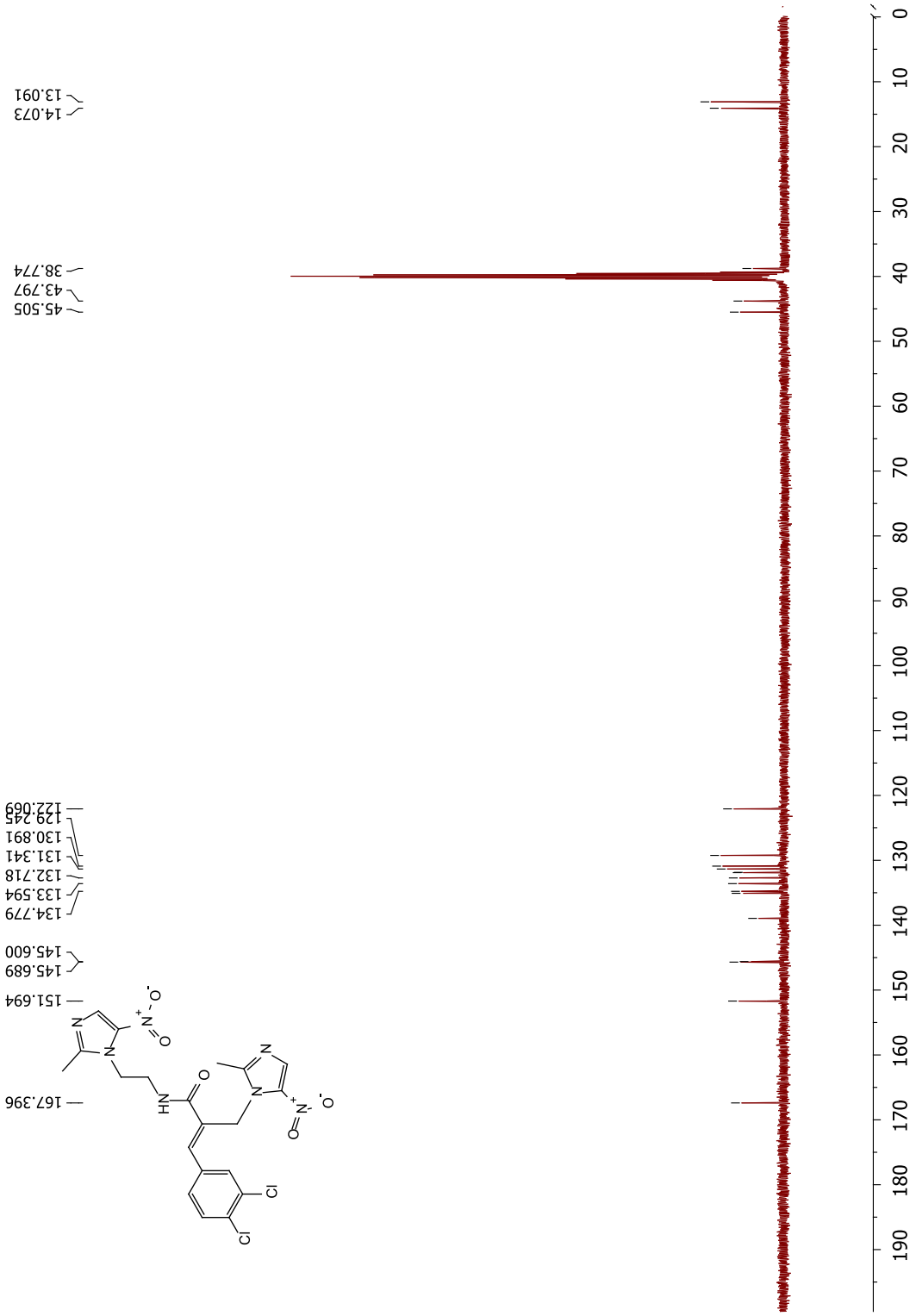

Figure 34. 101 MHz ^{13}C–NMR of Compound **21f** in DMSO-d_6.

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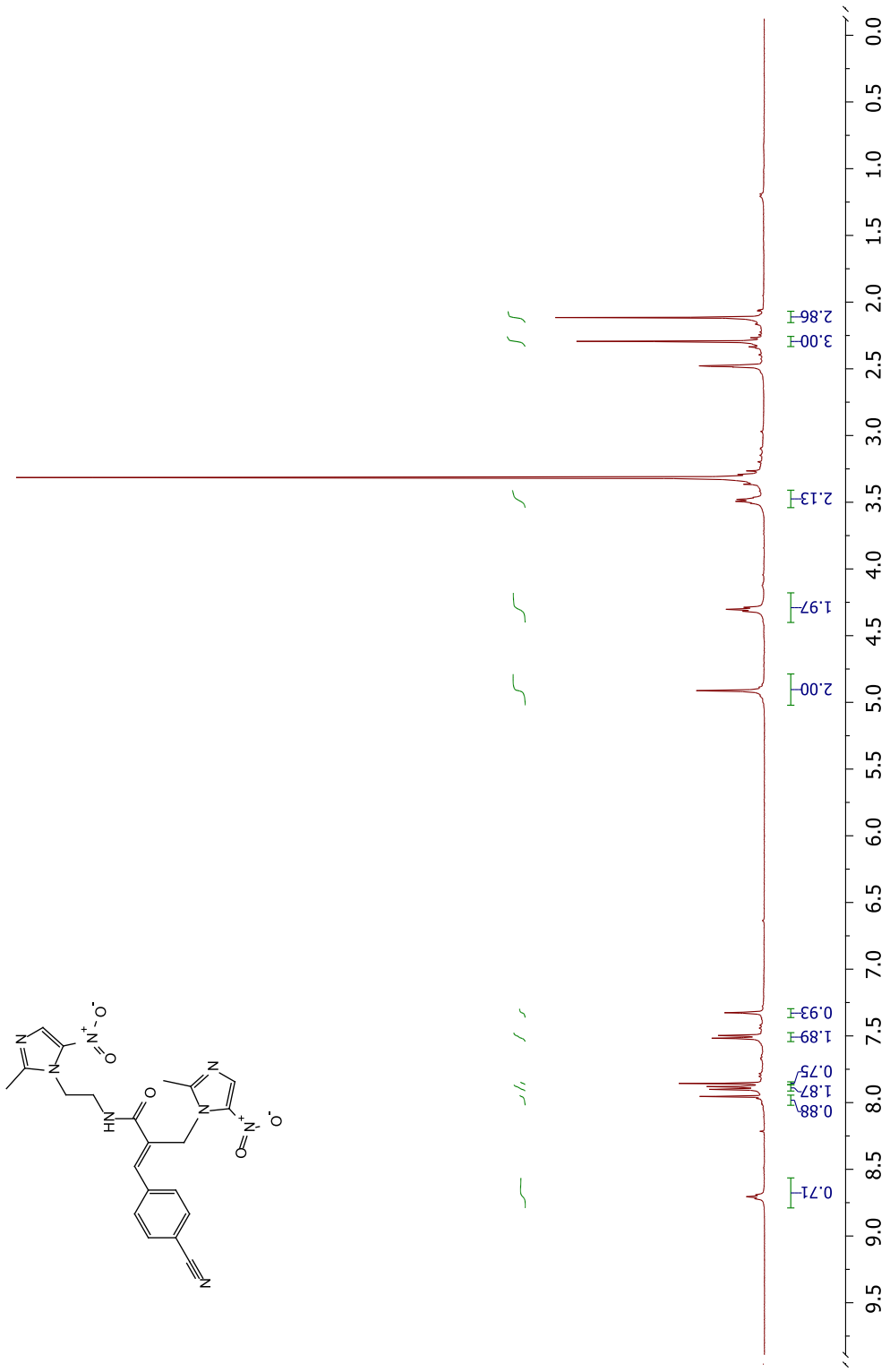

Figure 35. 400 MHz ^{1}H–NMR of Compound **21g** in DMSO-d_6.

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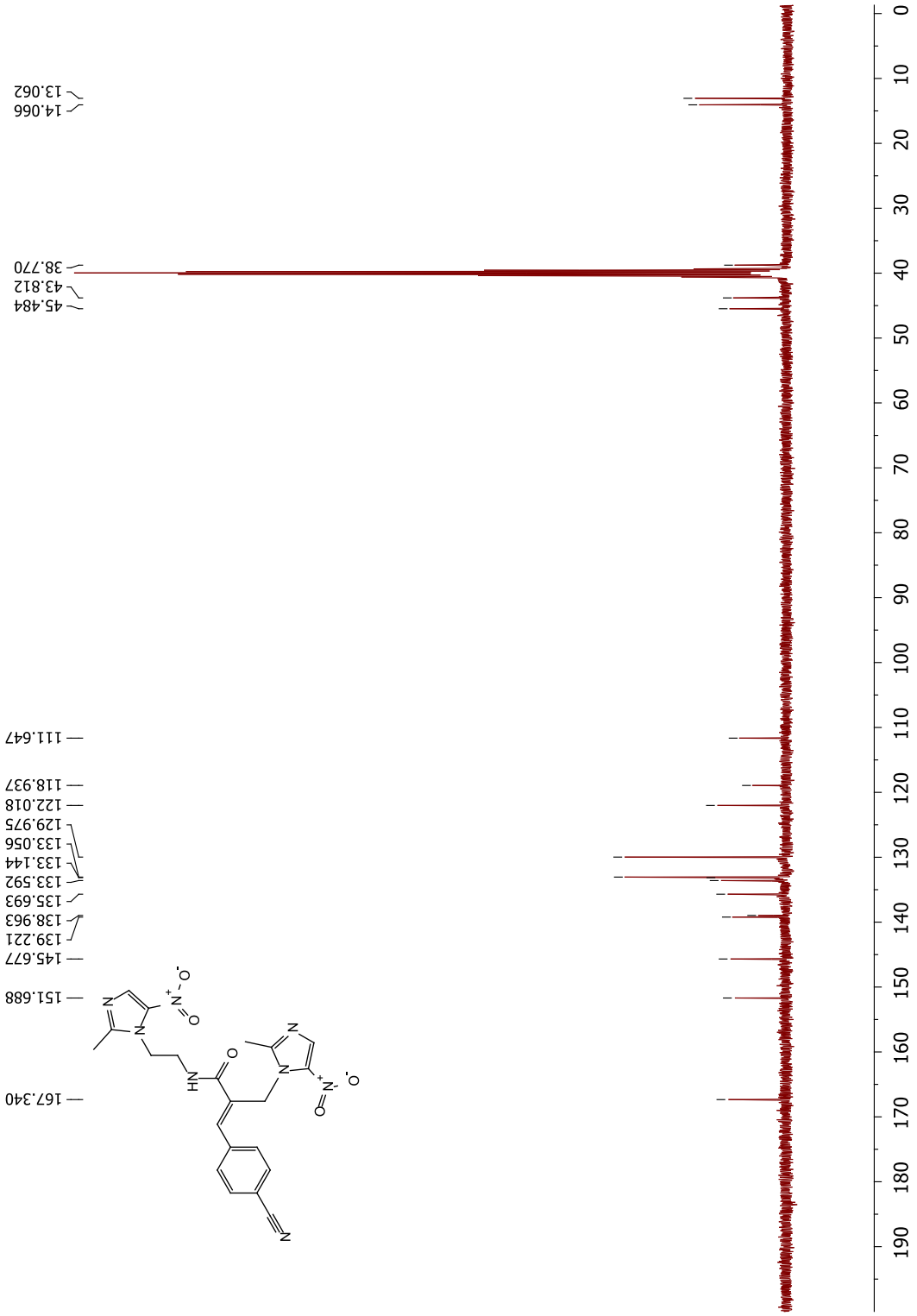

Figure 36. 101 MHz ^{13}C–NMR of Compound **21g** in DMSO-d$_6$.

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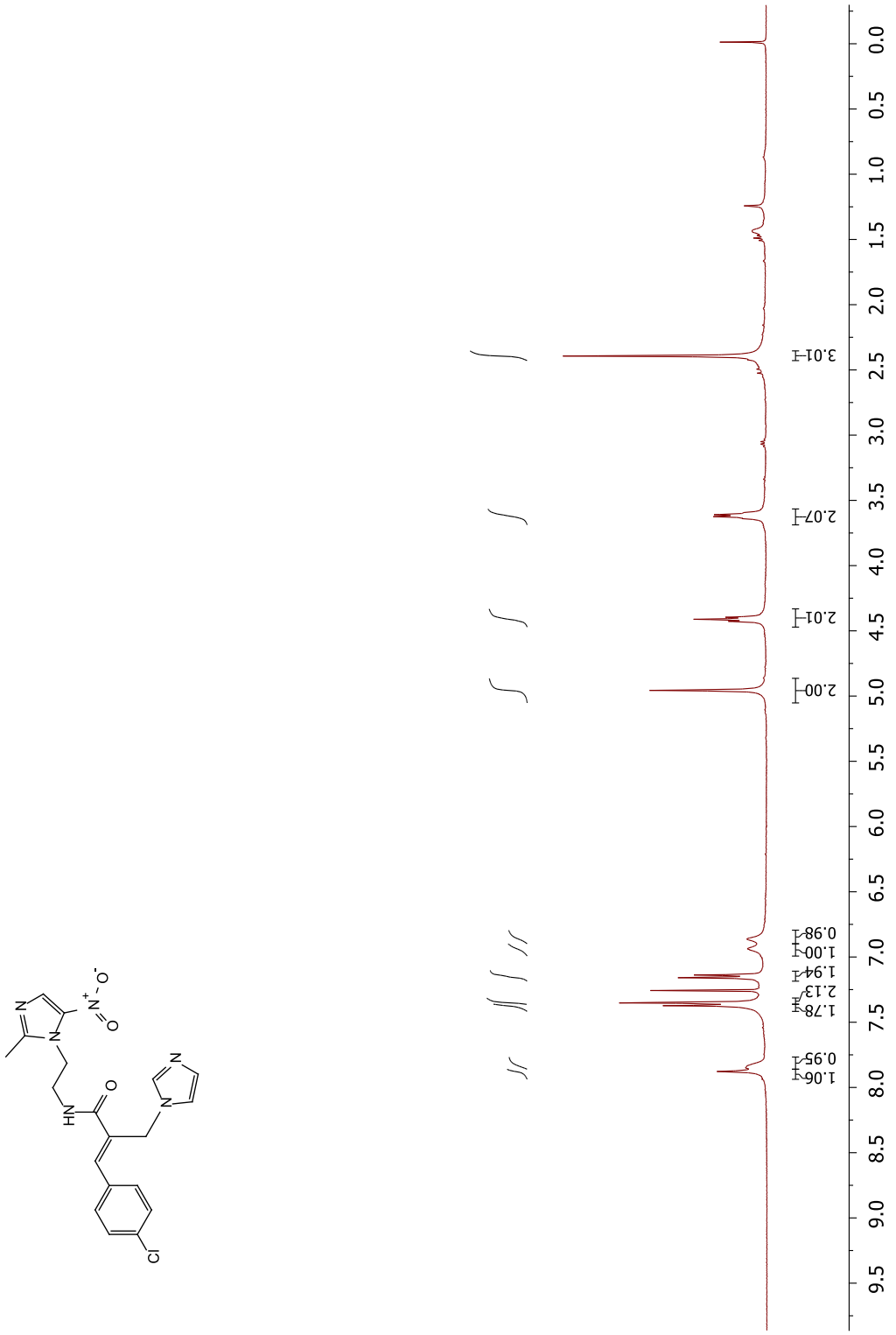

Figure 37. 400 MHz ^{1}H–NMR of Compound **22b** in $CDCl_3$.

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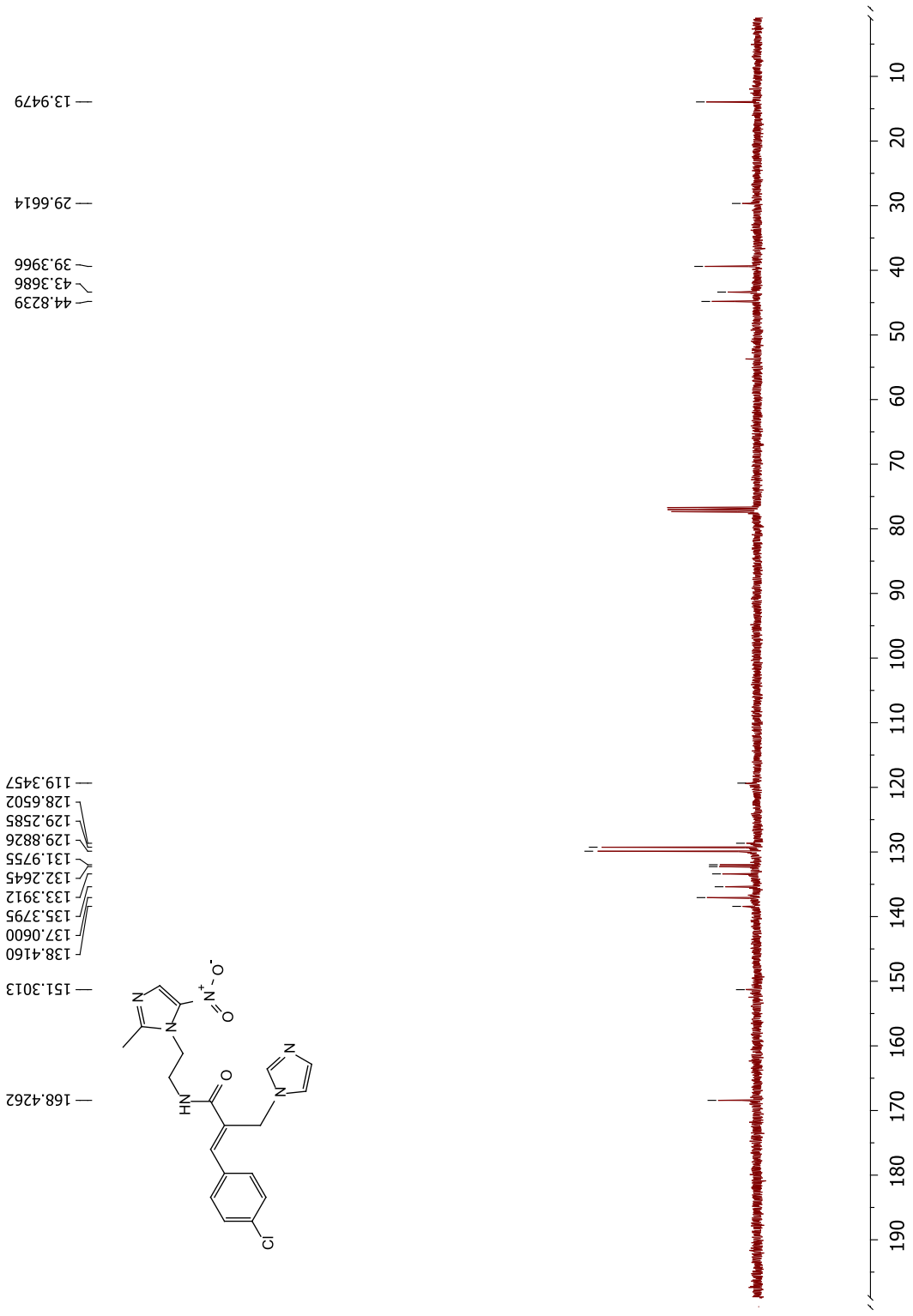

Figure 38. 101 MHz ^{13}C–NMR of Compound **22b** in $CDCl_3$.

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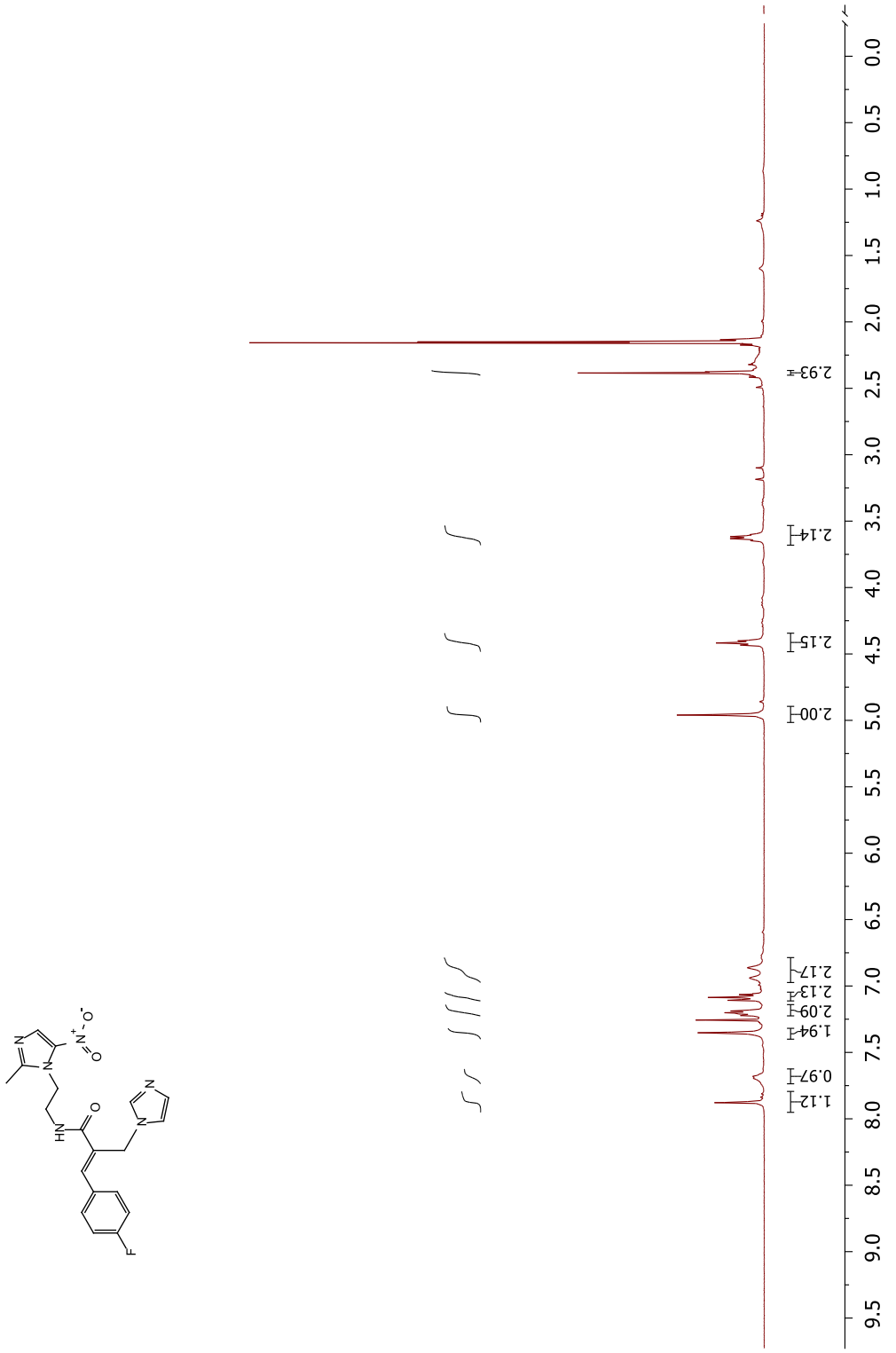

Figure 39. 400 MHz ^{1}H–NMR of Compound **22c** in $CDCl_3$.

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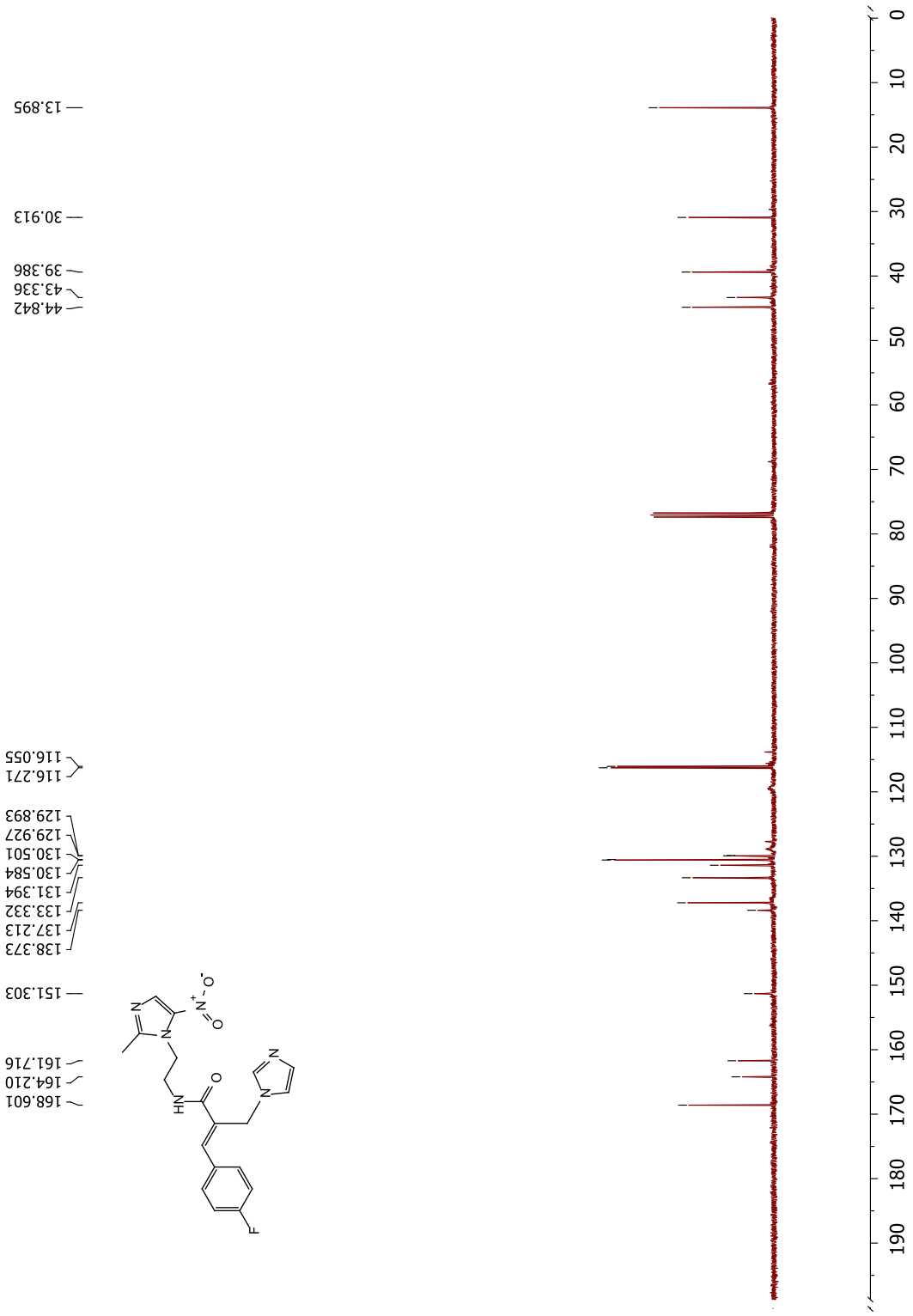

Figure 40. 101 MHz ^{13}C–NMR of Compound **22c** in $CDCl_3$.

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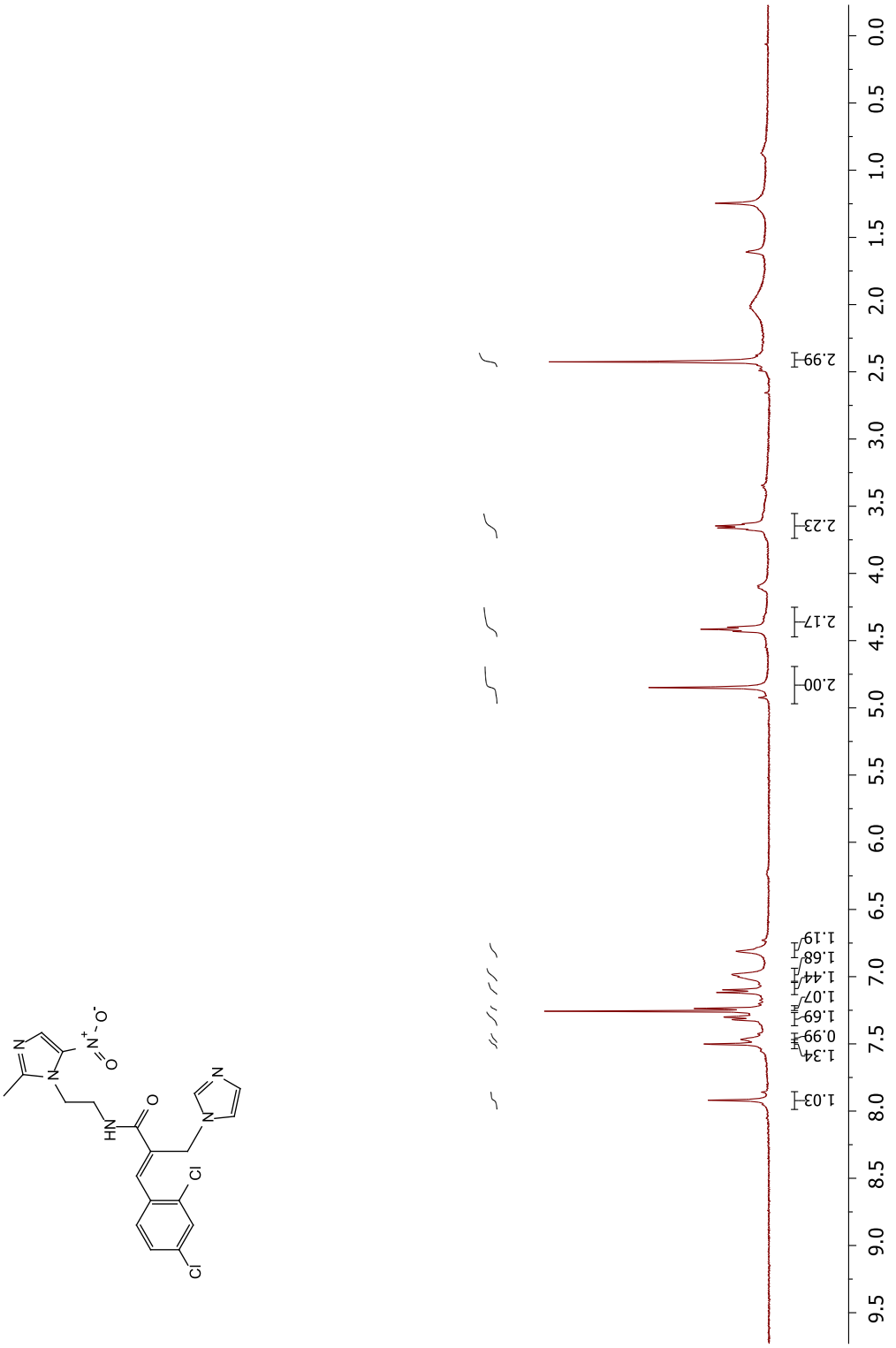

Figure 41. 400 MHz ^{1}H–NMR of Compound **22d** in $CDCl_3$.

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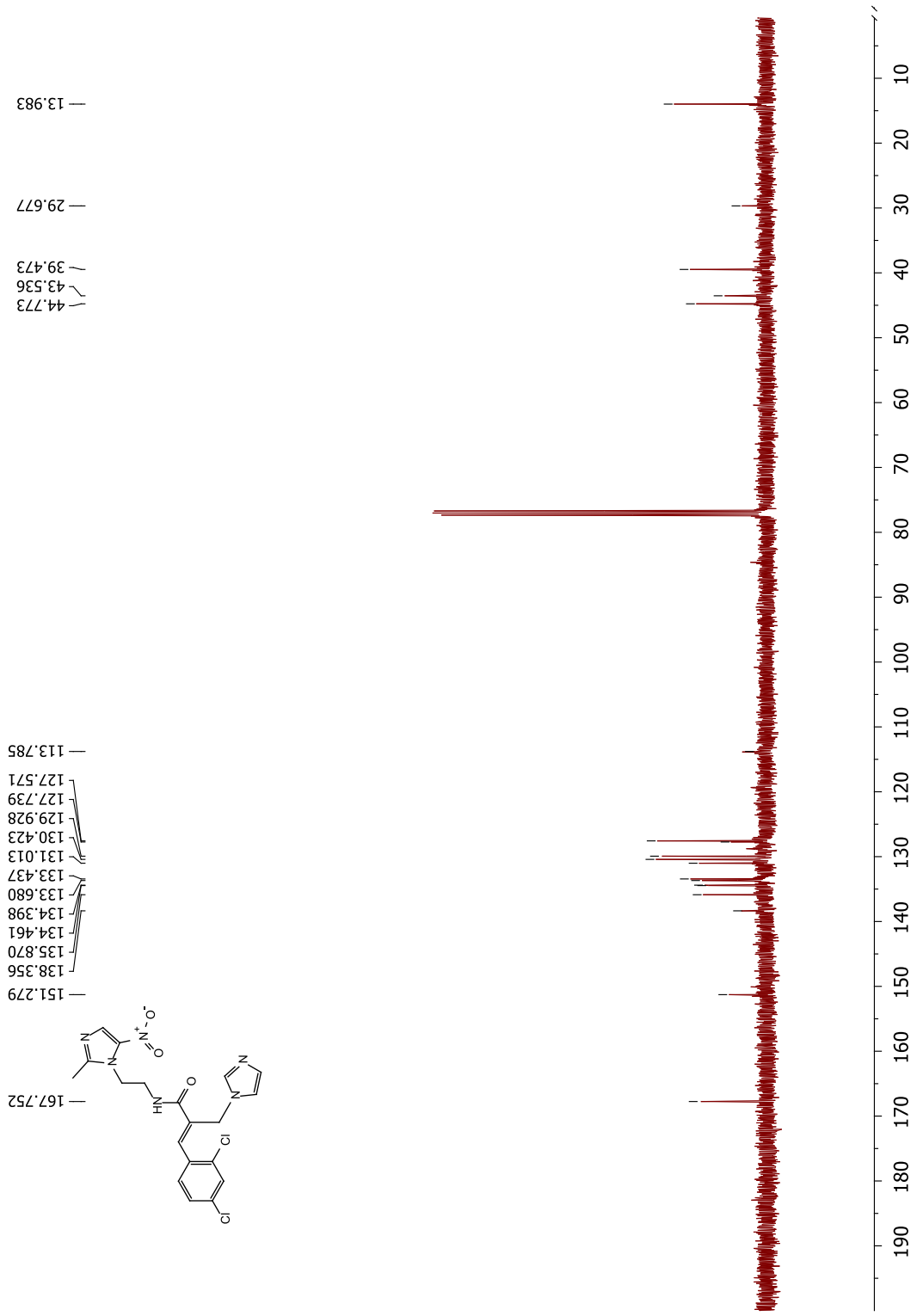

Figure 42. 101 MHz ^{13}C–NMR of Compound **22d** in $CDCl_3$.

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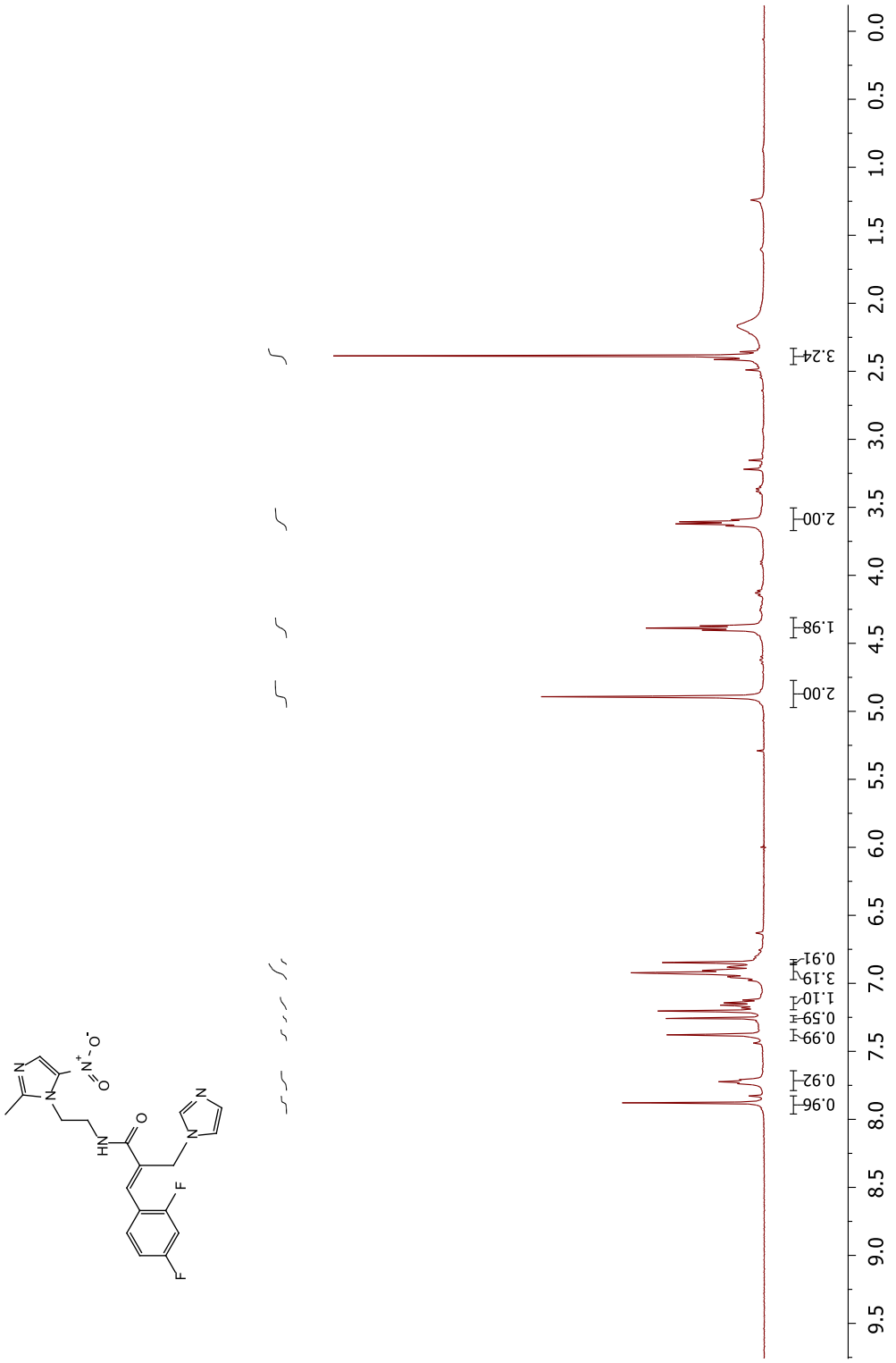

Figure 43. 400 MHz ^{1}H–NMR of Compound **22e** in $CDCl_3$.

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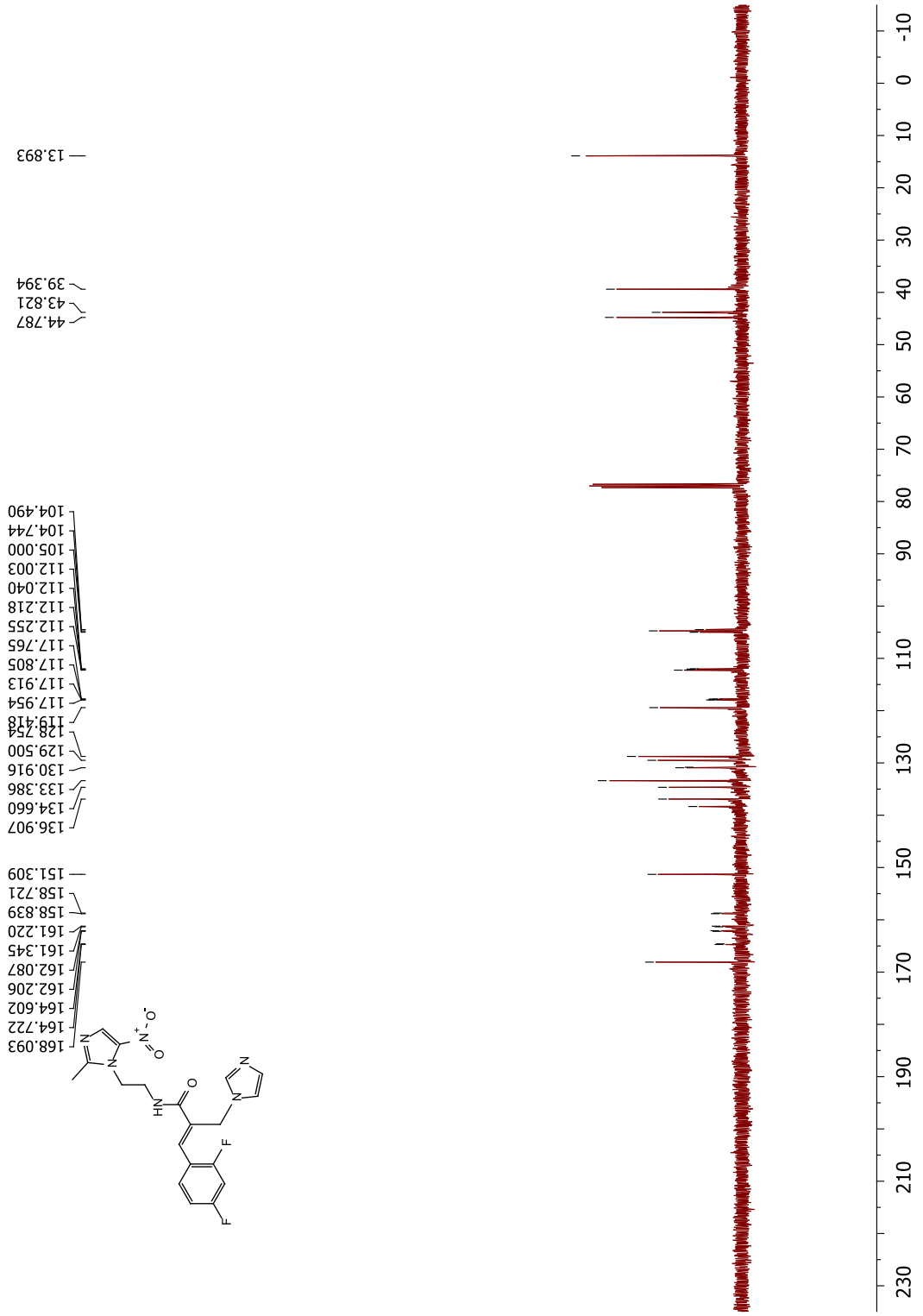

Figure 44. 101 MHz ^{13}C–NMR of Compound **22e** in $CDCl_3$.

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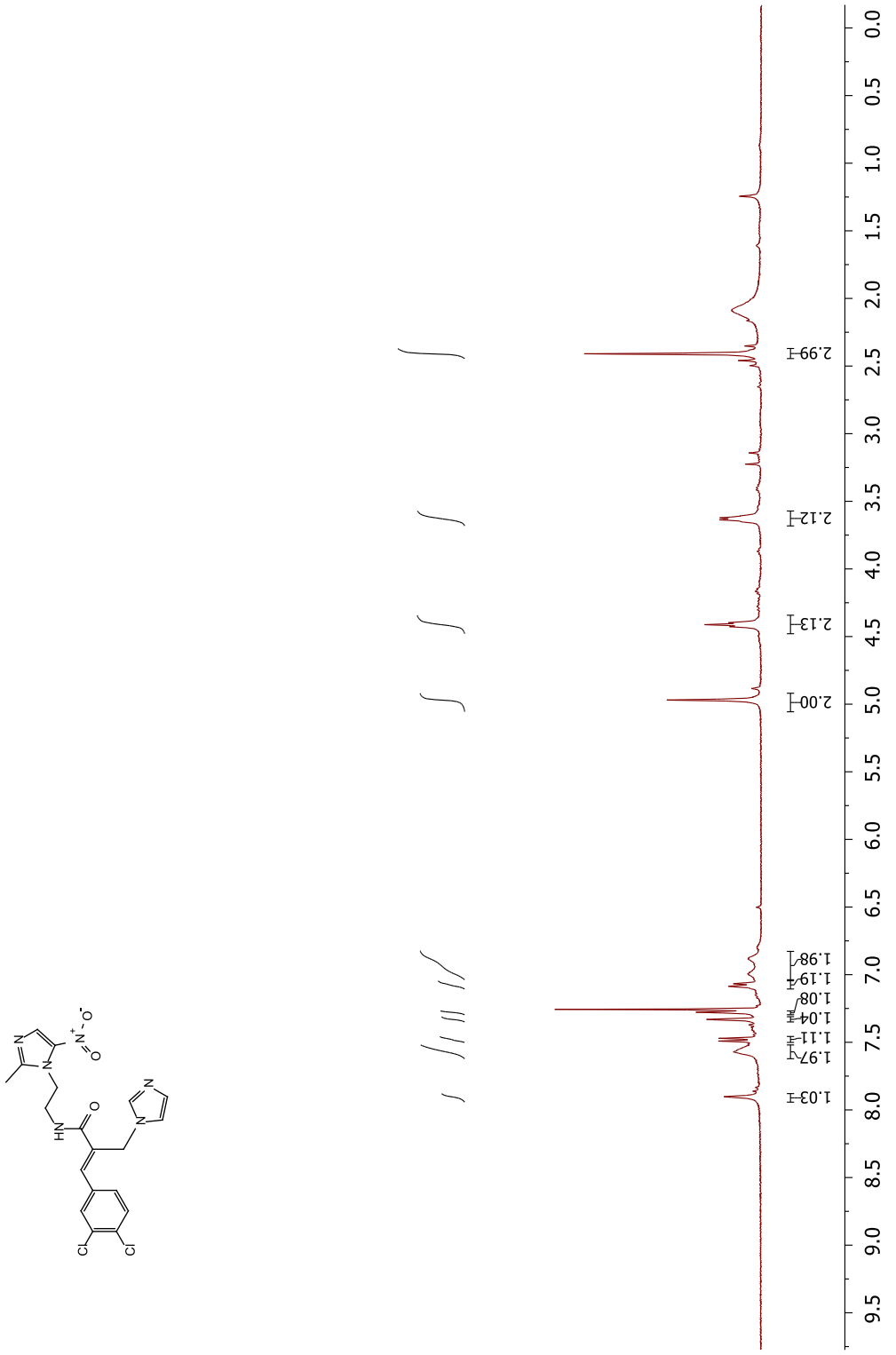

Figure 45. 400 MHz ^{1}H–NMR of Compound **22f** in $CDCl_3$.

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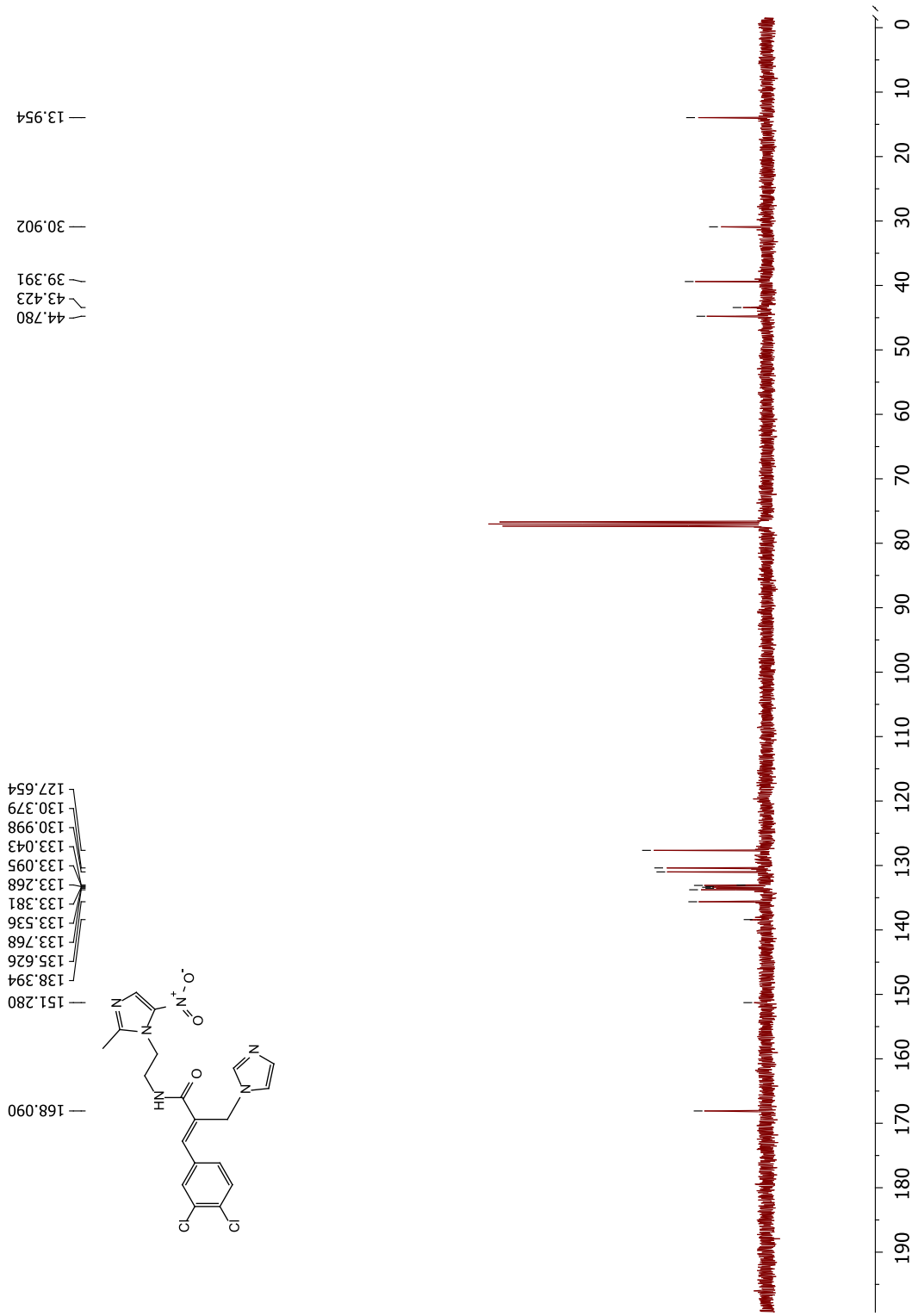

Figure 46. 101 MHz ^{13}C–NMR of Compound **22f** in $CDCl_3$.

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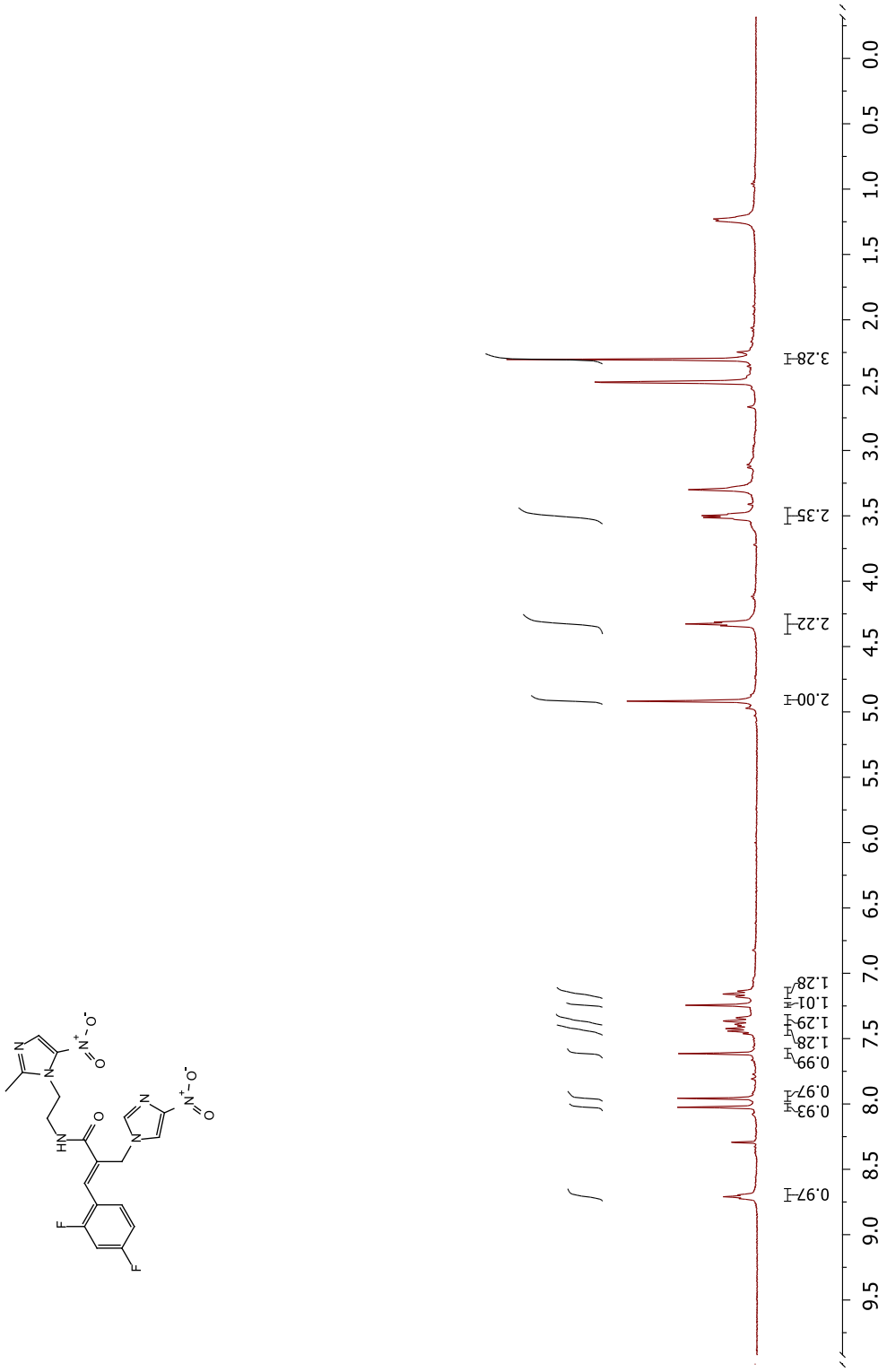

Figure 47. 400 MHz ^{1}H–NMR of Compound **23a** in DMSO-d_6.

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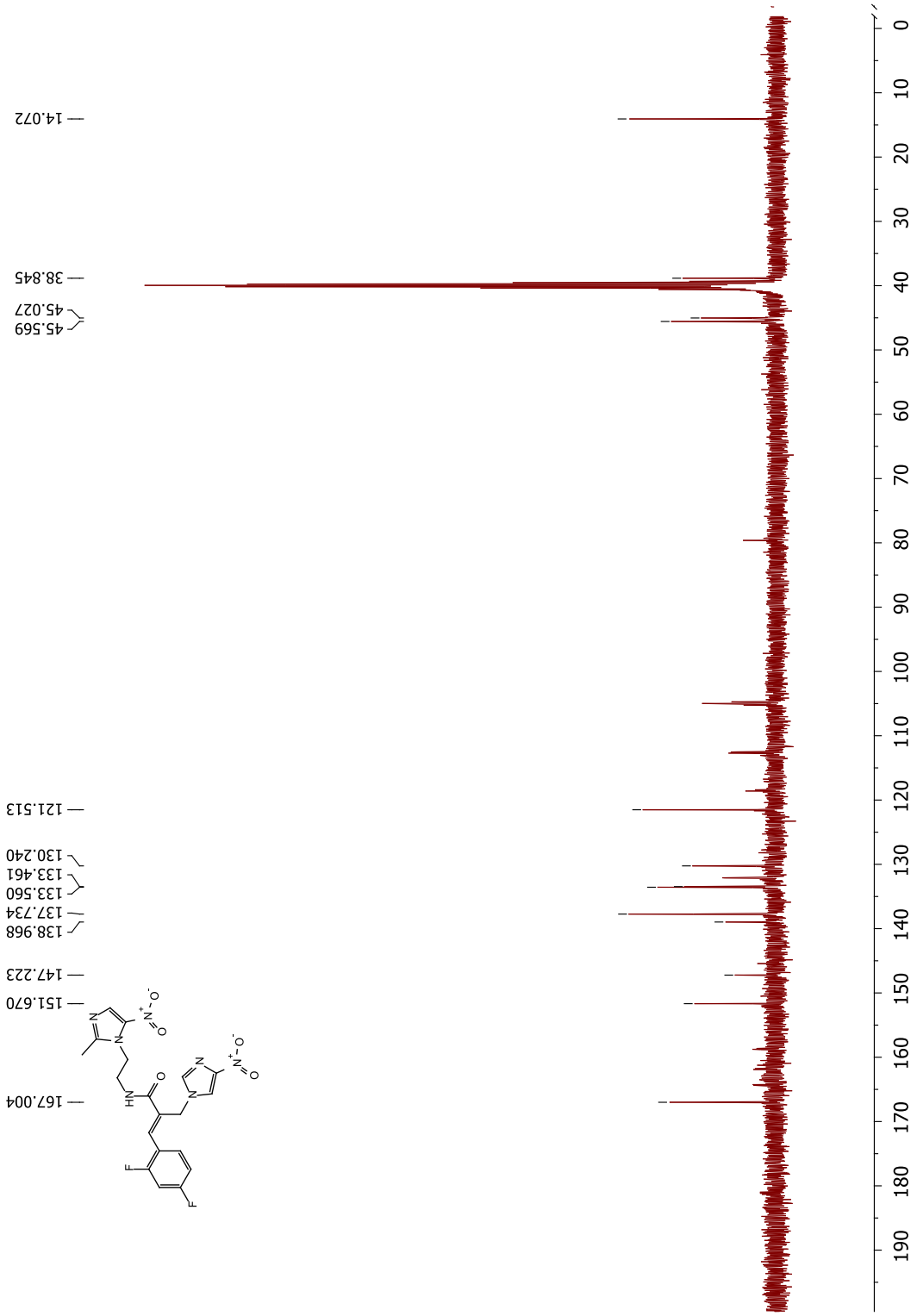

Figure 48. 101 MHz ^{13}C–NMR of Compound **23a** in DMSO-d_6.

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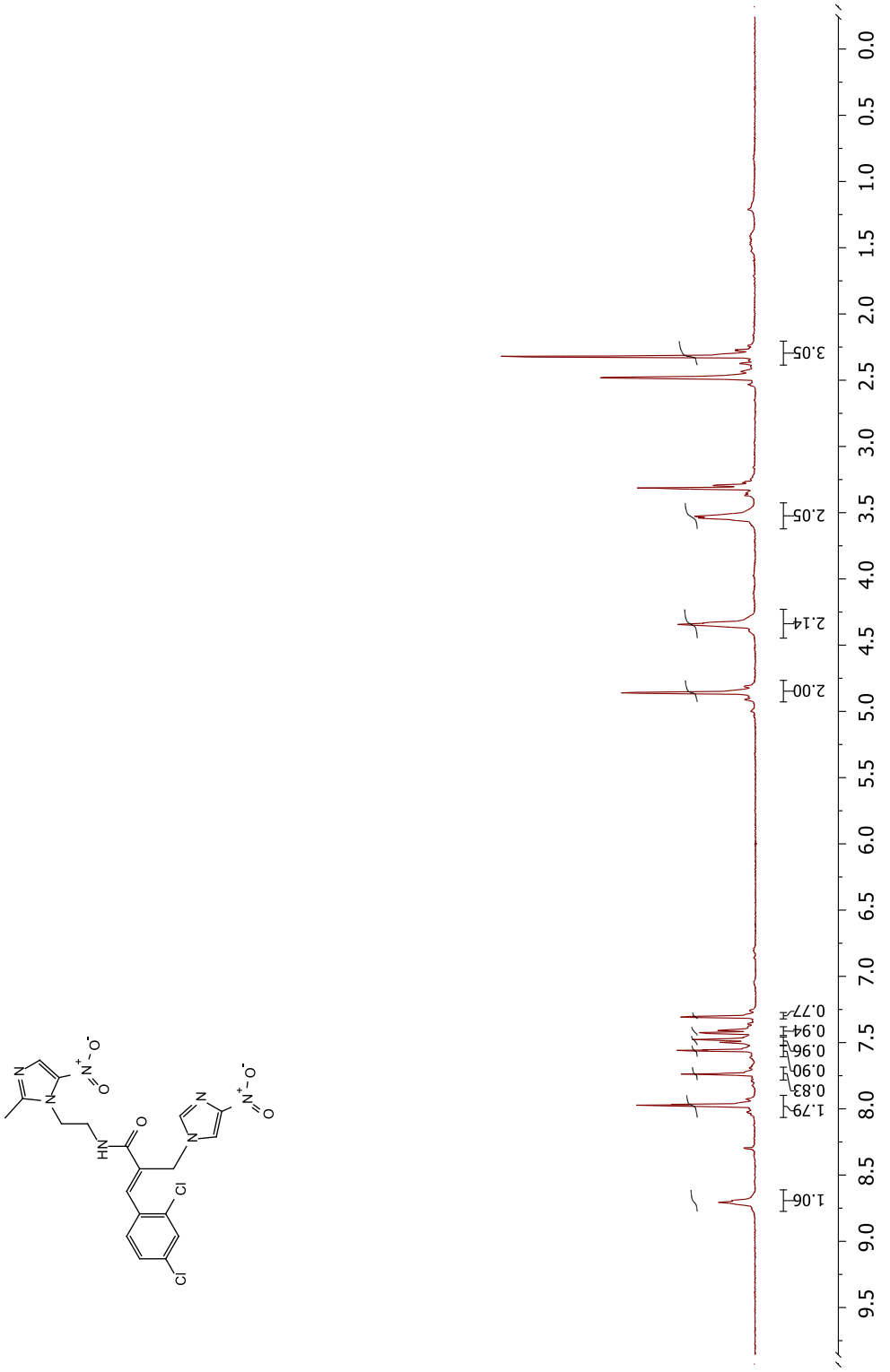

Figure 49. 400 MHz ^{1}H–NMR of Compound **23b** in DMSO-d_6.

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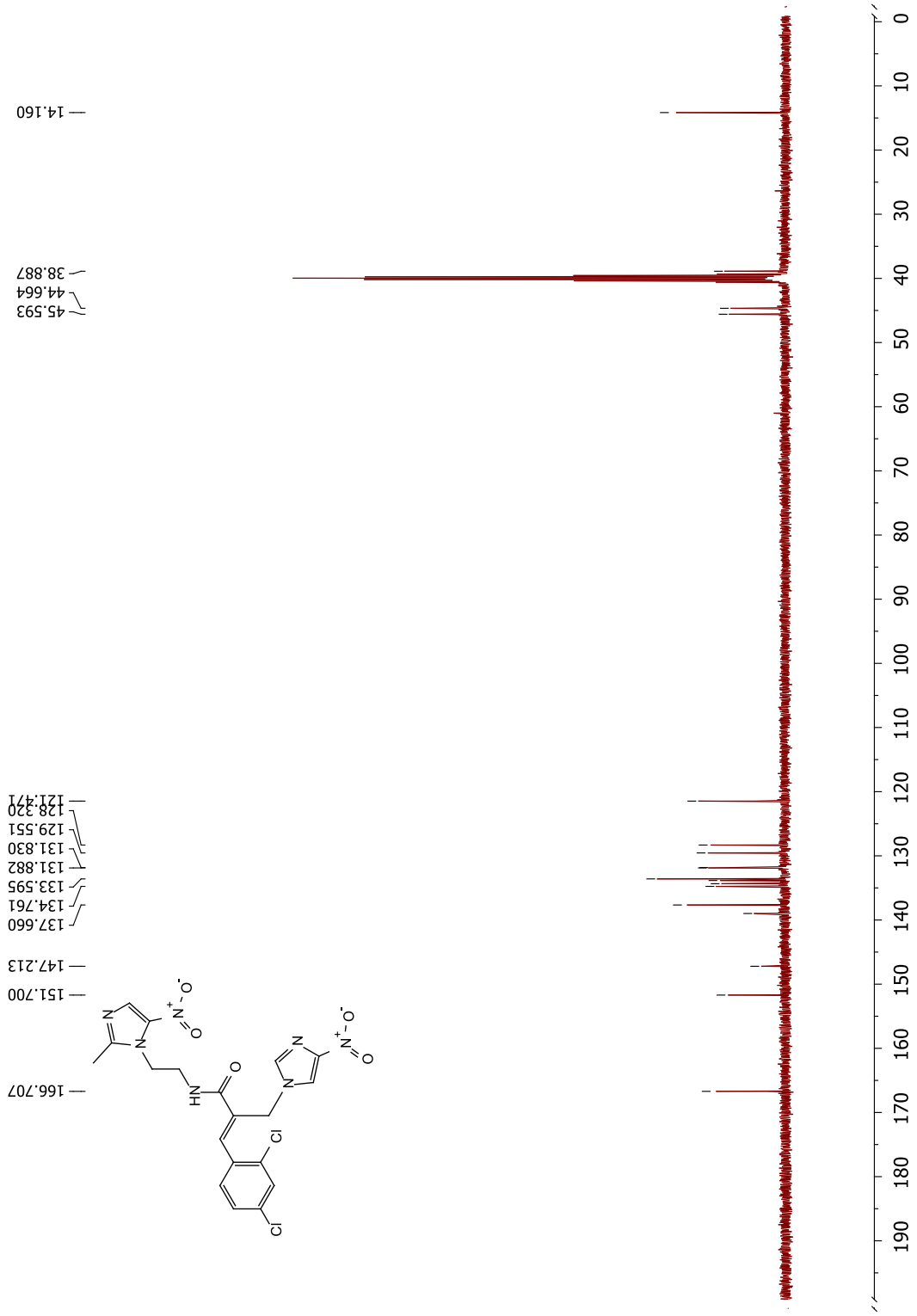

Figure 50. 101 MHz ^{13}C–NMR of Compound **23b** in DMSO-d$_6$.

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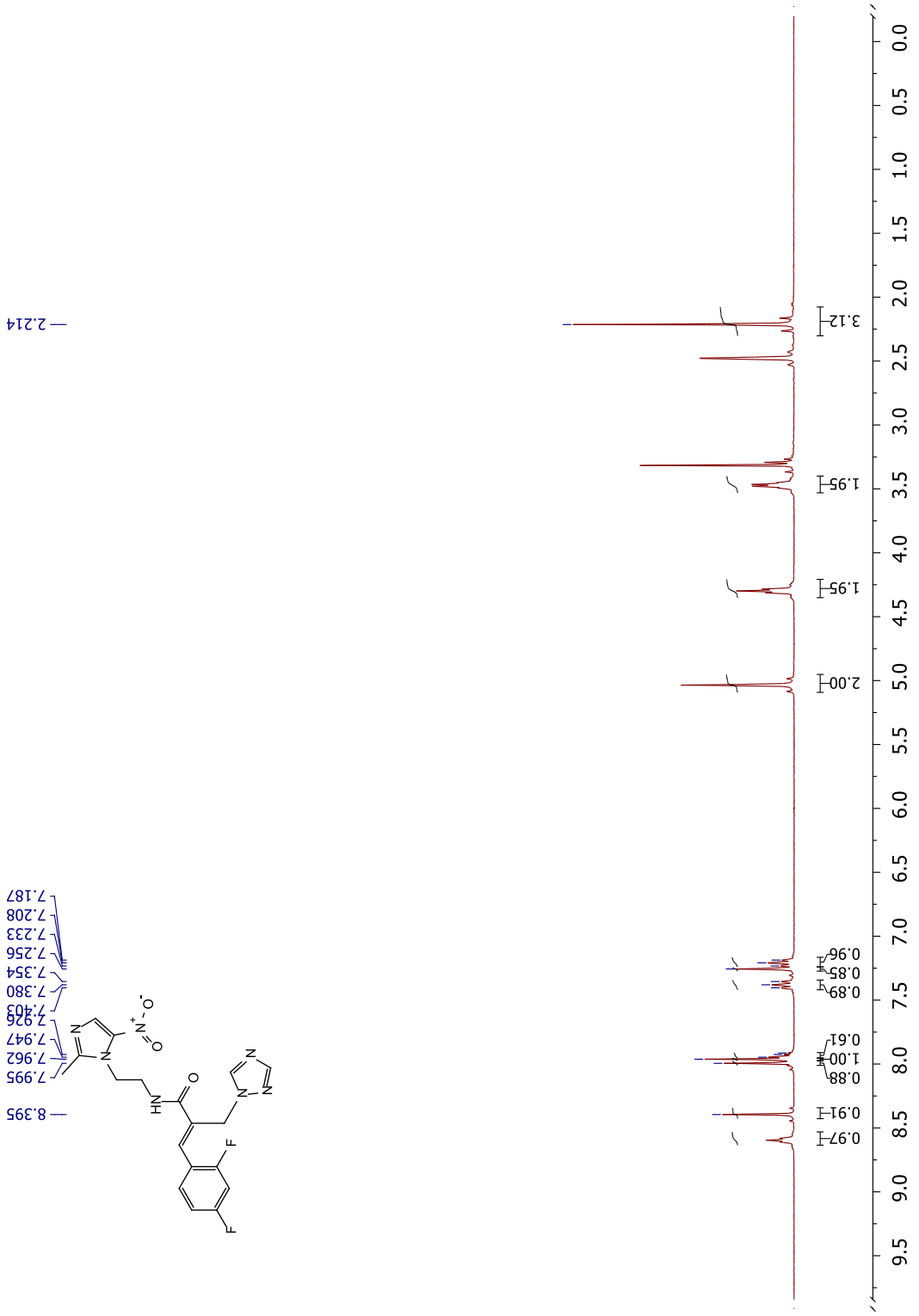

Figure 51. 400 MHz ^{1}H –NMR of Compound **24a** in DMSO-d_6.

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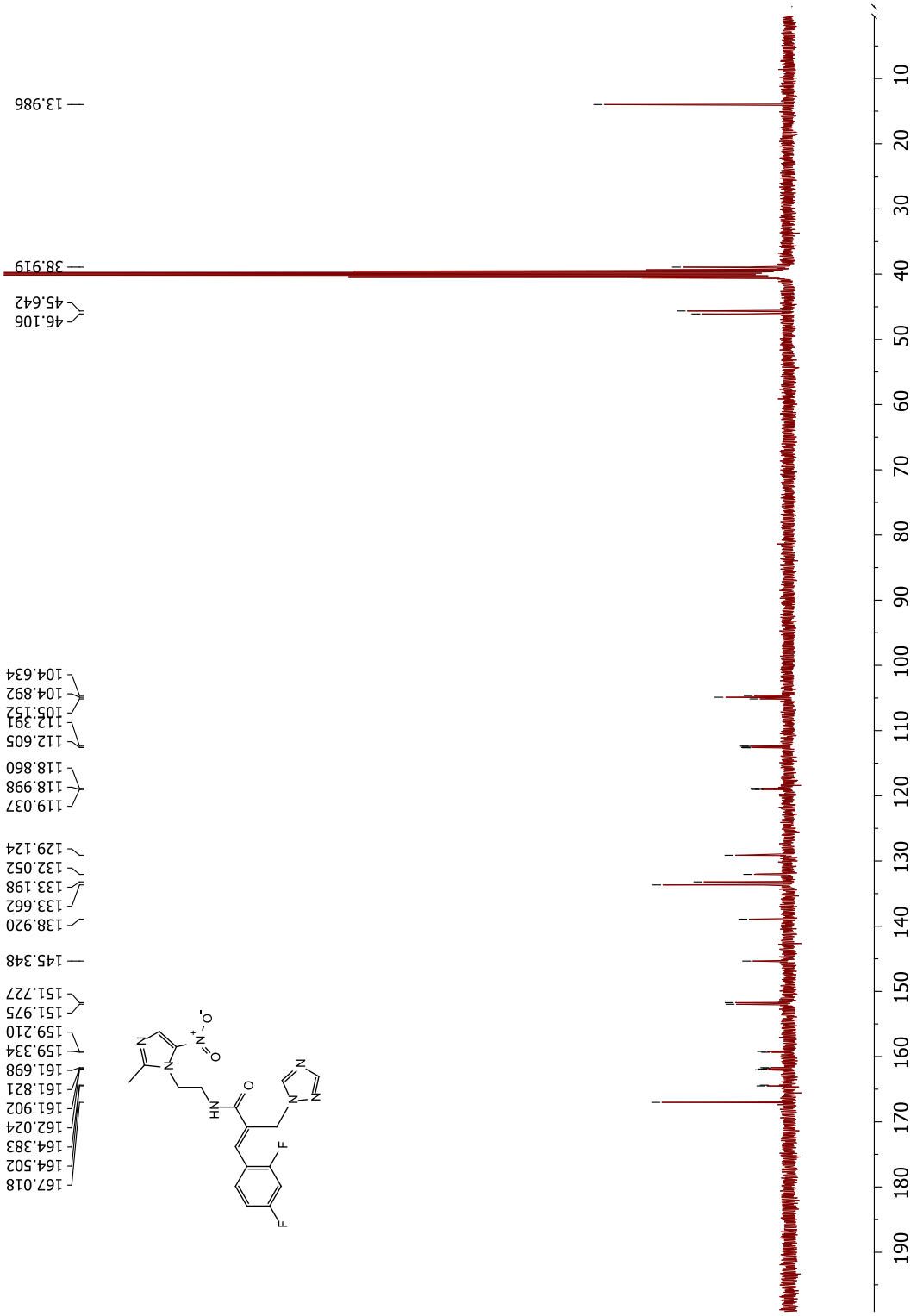

Figure 52. 101 MHz ^{13}C–NMR of Compound **24a** in DMSO-d_6.

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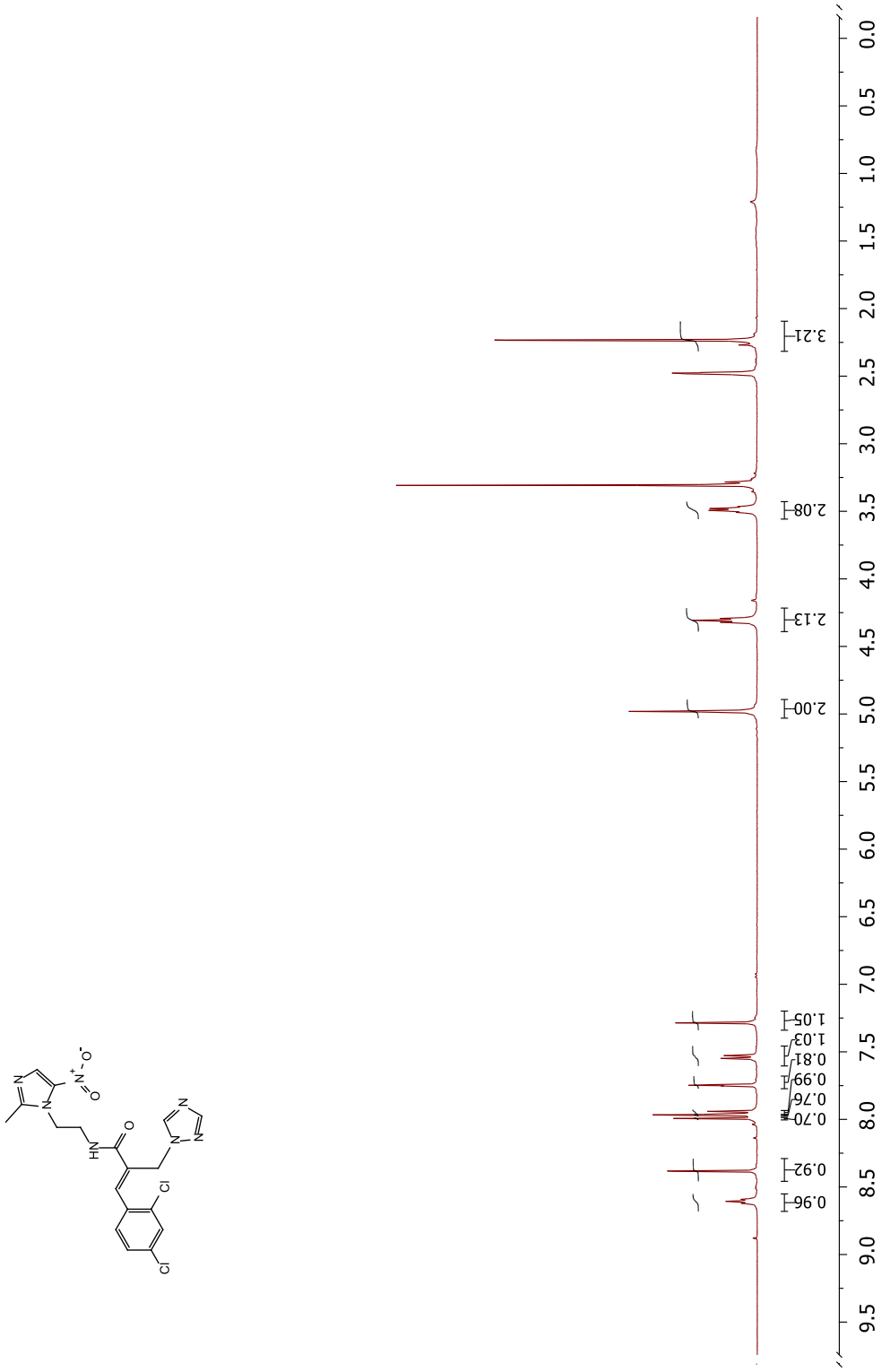

Figure 53. 400 MHz ^{1}H–NMR of Compound **24b** in DMSO-d_6.

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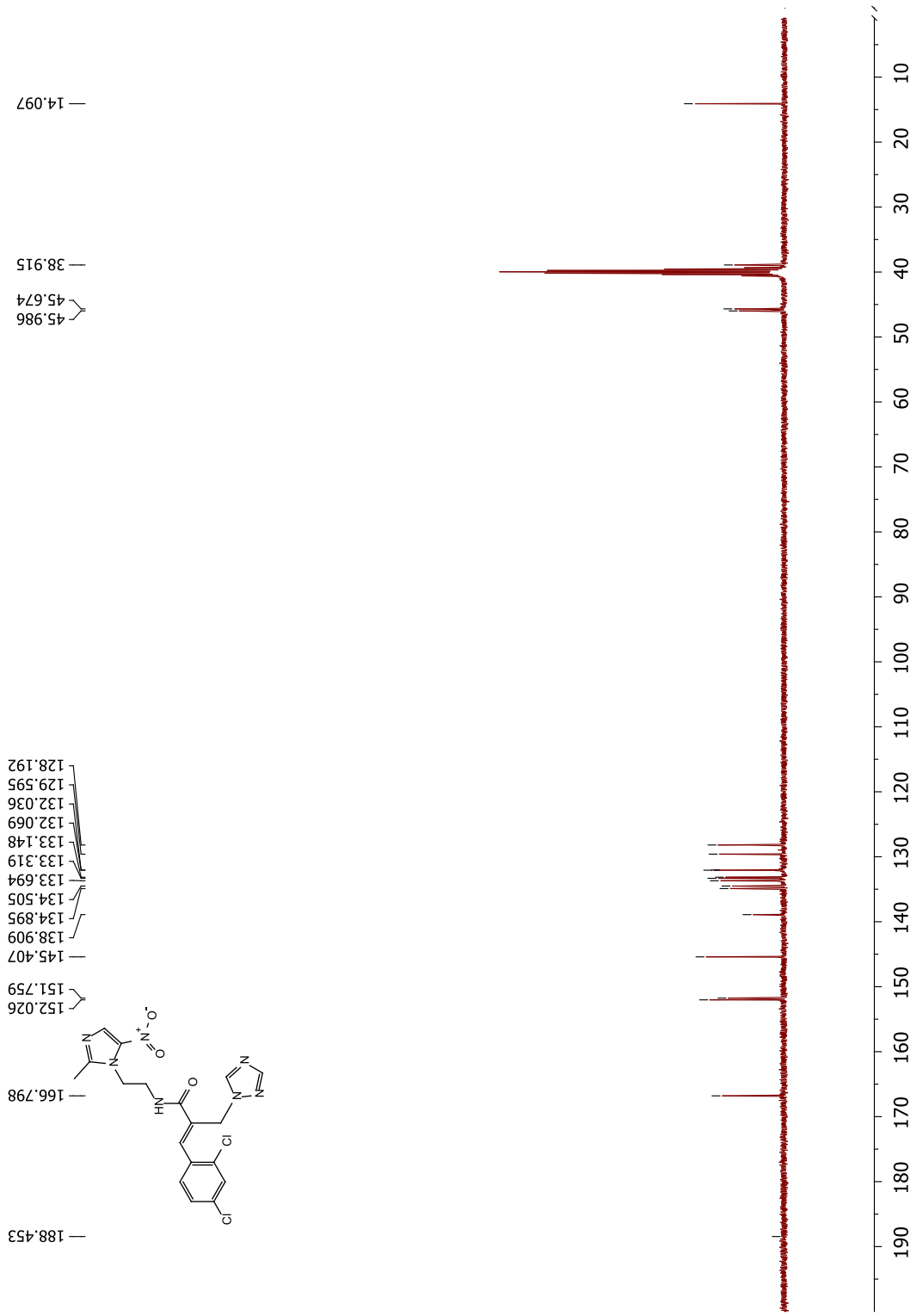

Figure 54. 101 MHz ^{13}C–NMR of Compound **24b** in DMSO-d$_6$.

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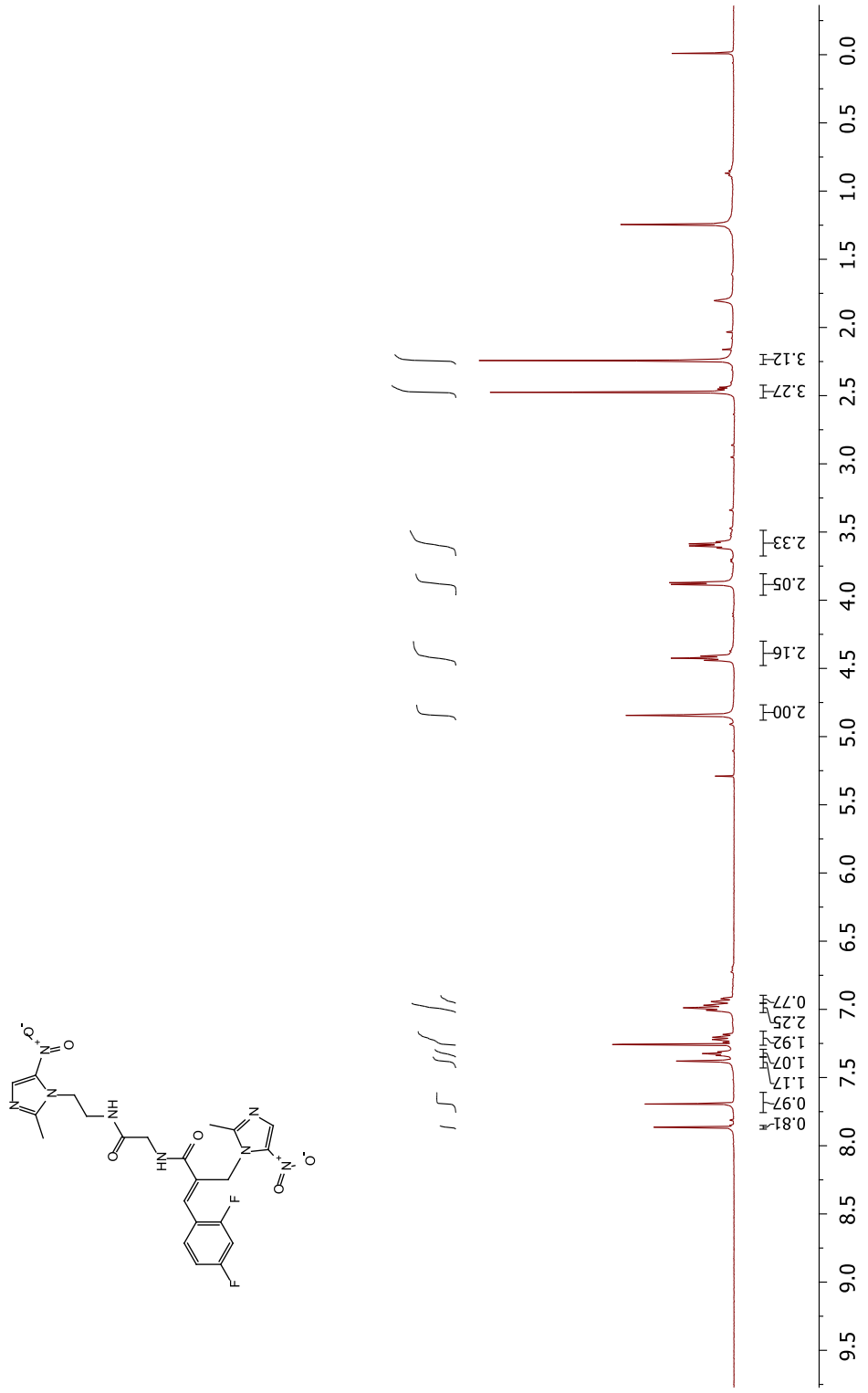

Figure 55. 400 MHz ^{1}H–NMR of Compound **28b** in $CDCl_3$.

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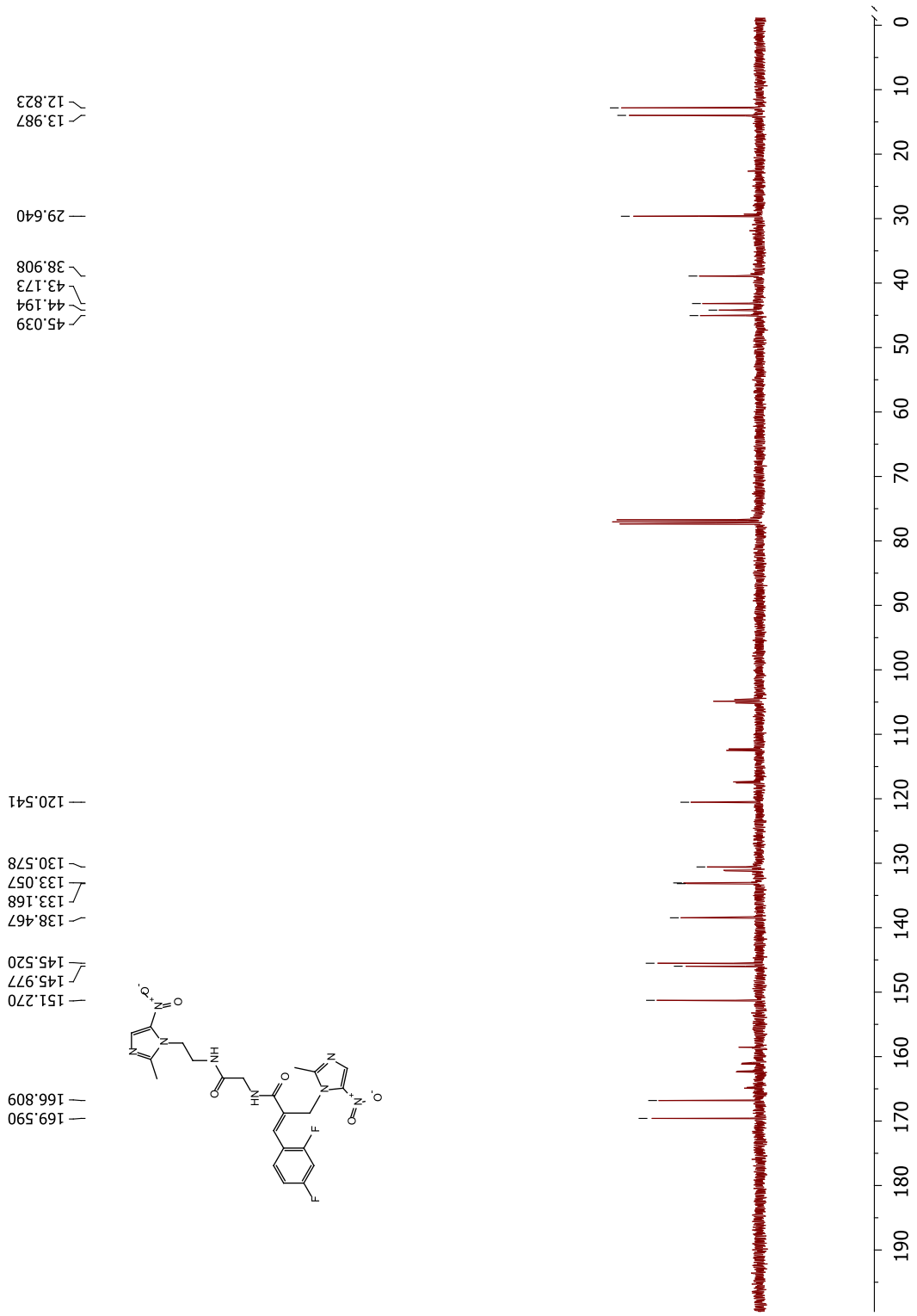

Figure 56. 101 MHz ^{13}C–NMR of Compound **28b** in $CDCl_3$.

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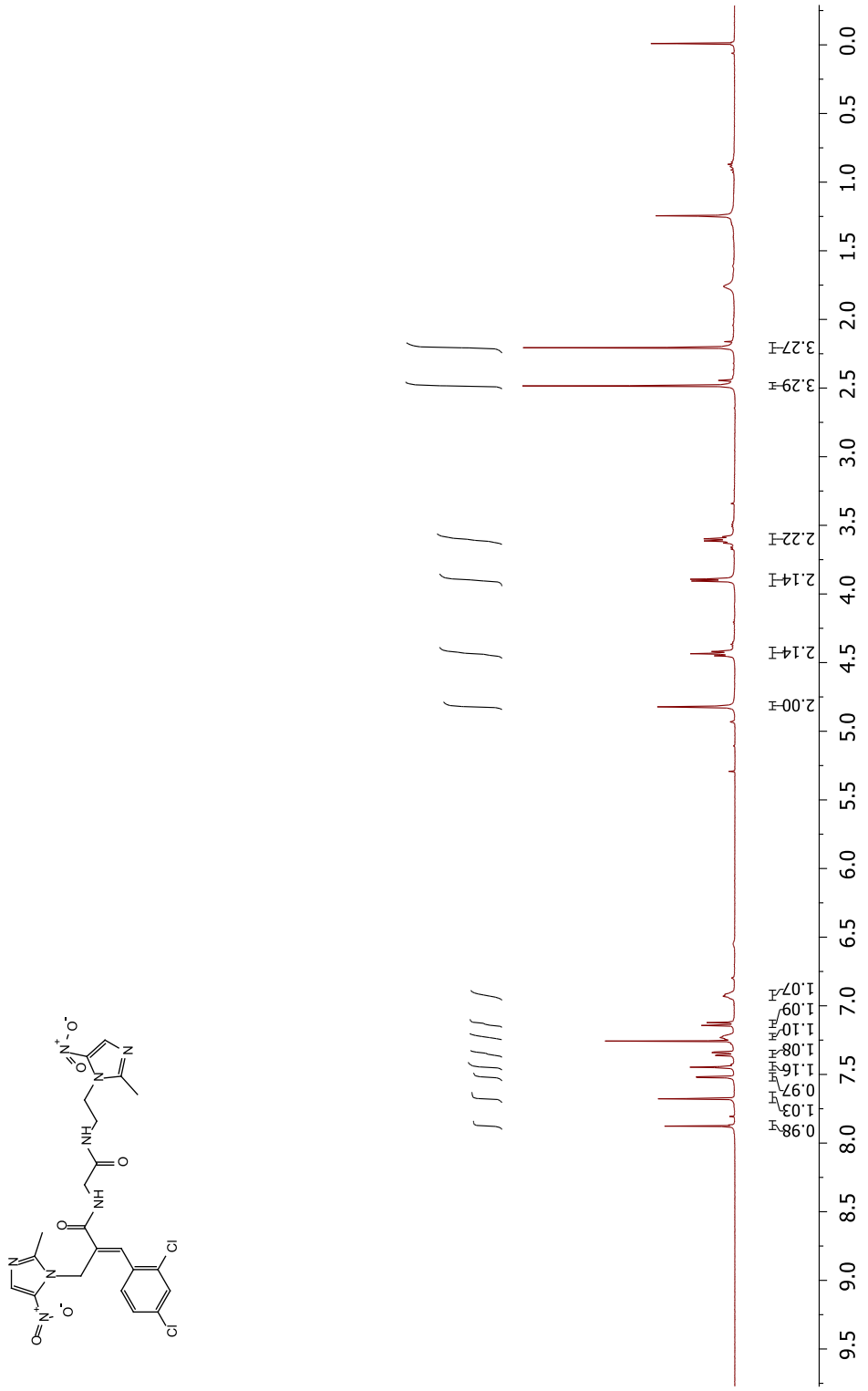

Figure 57. 400 MHz ^{1}H–NMR of Compound **28c** in $CDCl_3$.

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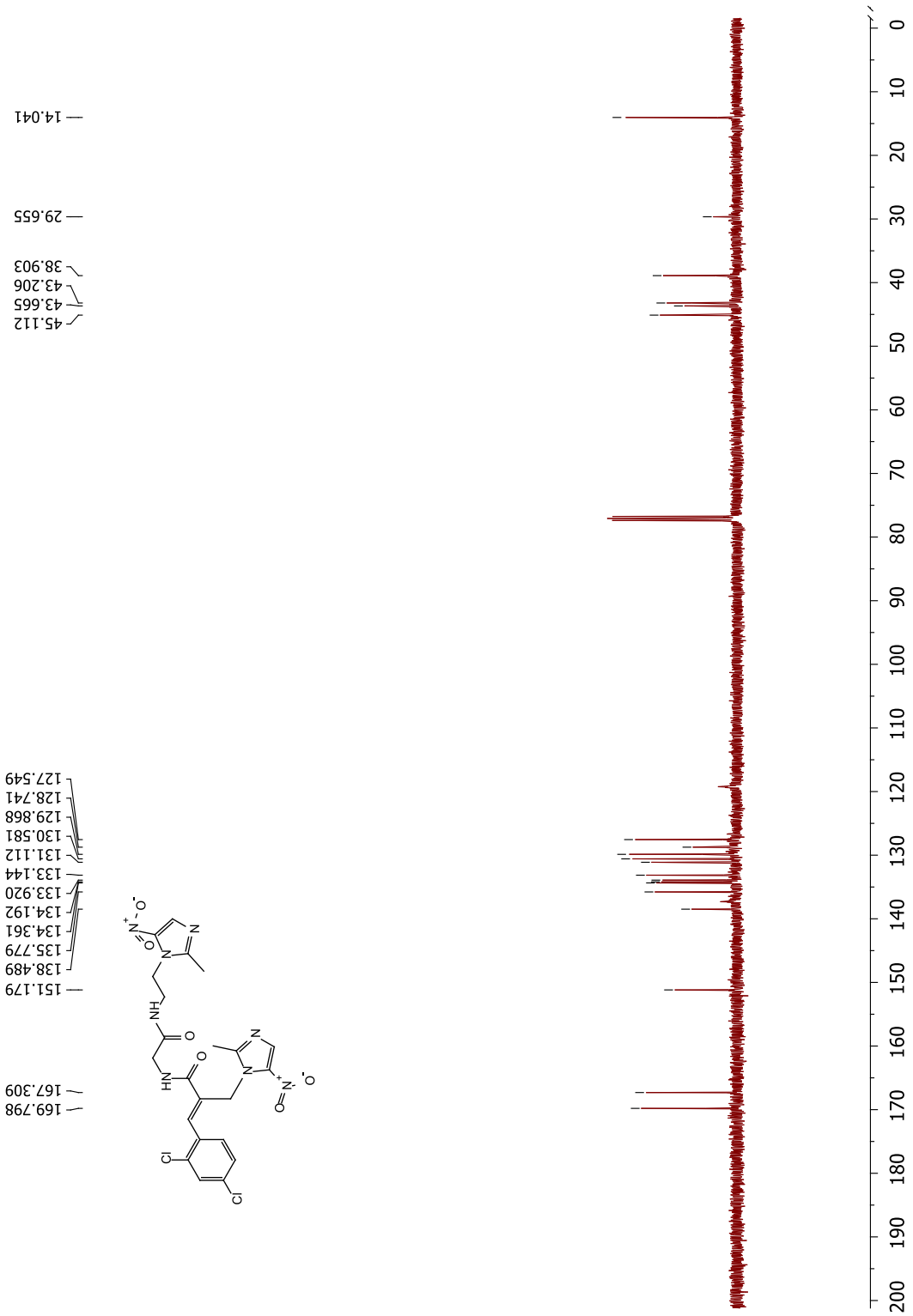

Figure 58. 101 MHz ^{13}C–NMR of Compound **28c** in $CDCl_3$.

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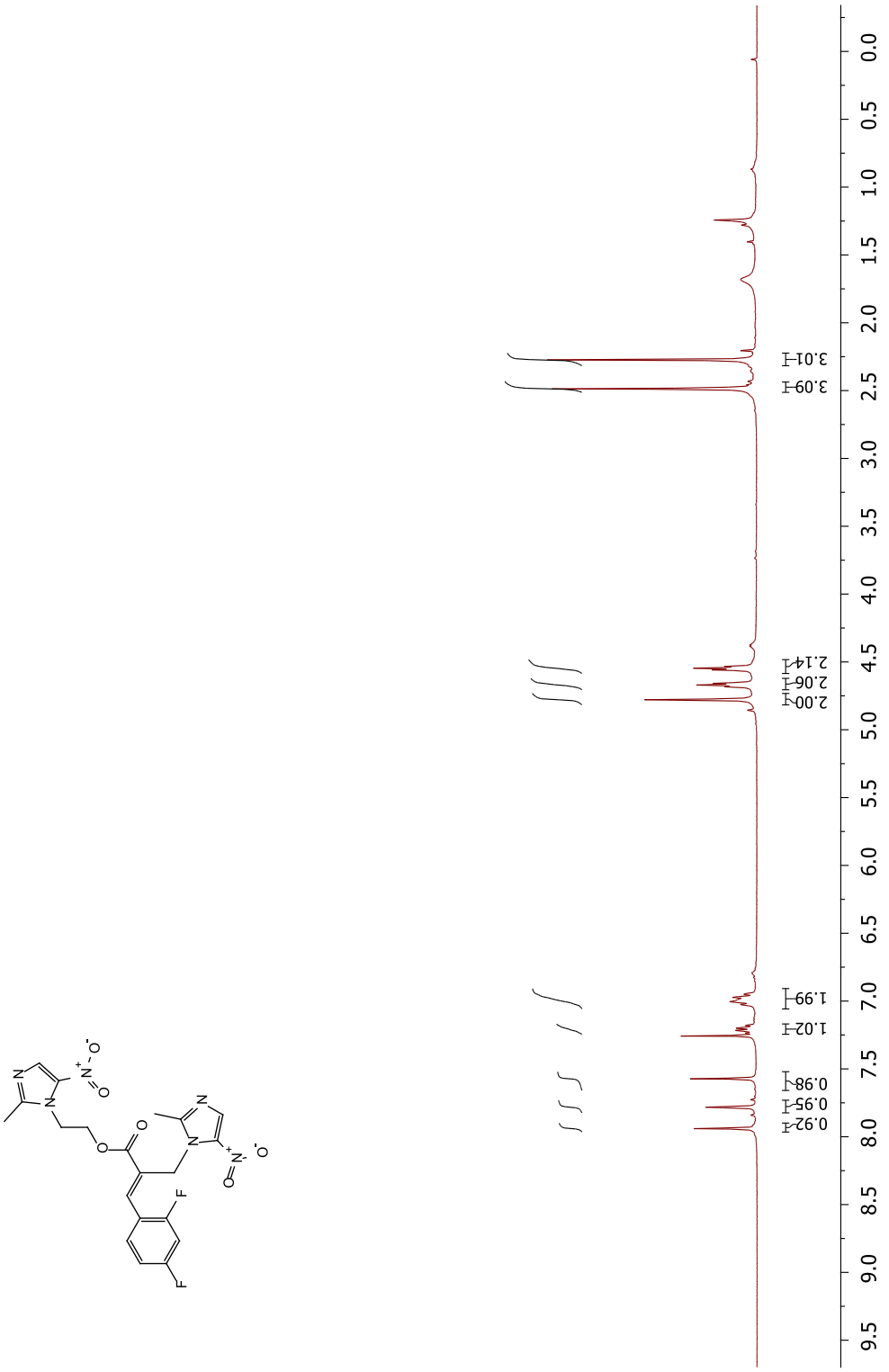

Figure 59. 400 MHz ^{1}H–NMR of Compound **29b** in $CDCl_3$.

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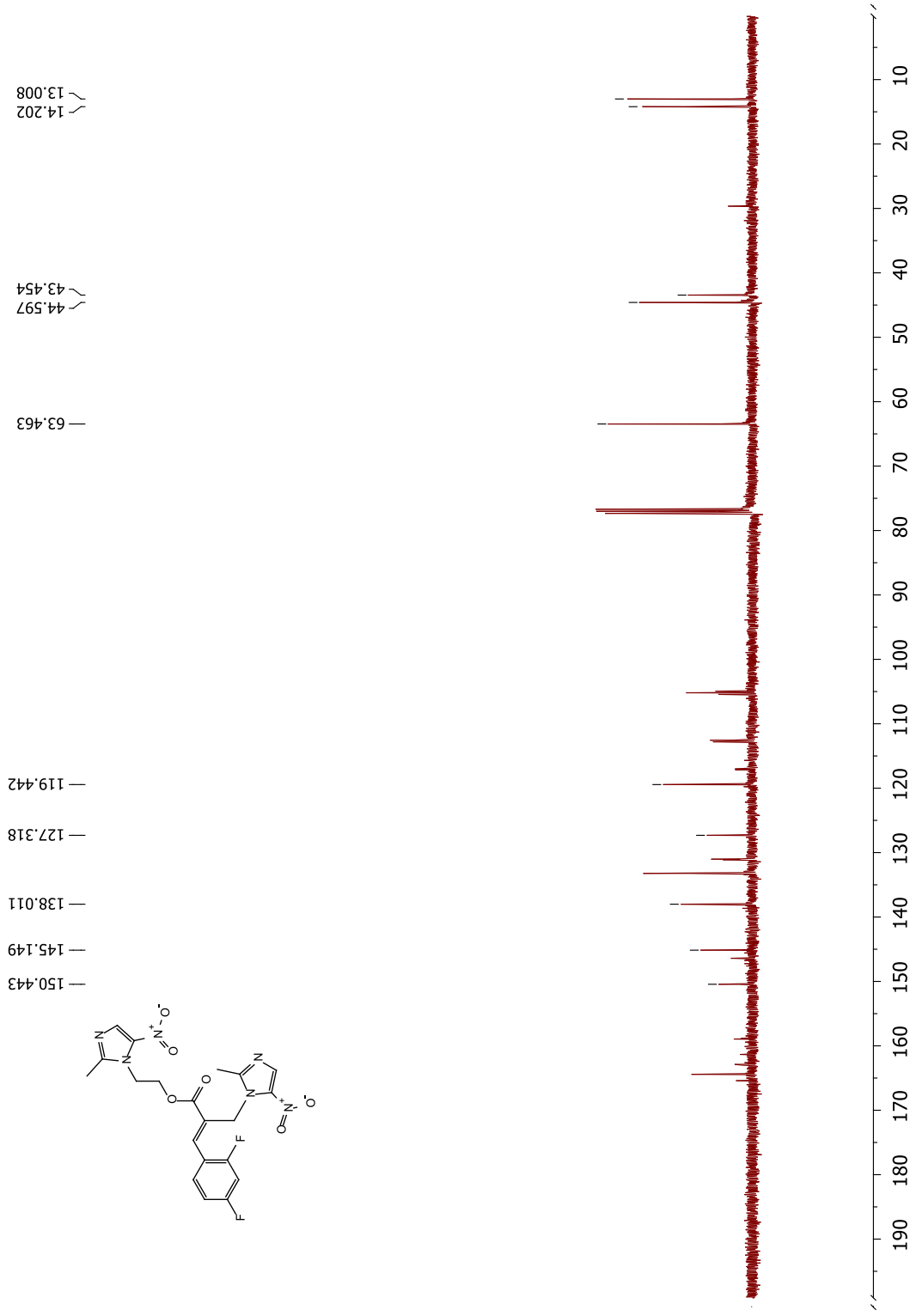

Figure 60. 101 MHz ^{13}C–NMR of Compound **29b** in $CDCl_3$.

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