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Functionalized heterocyclics as potential therapeutics

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FUNCTIONALIZED HETEROCYCLICS AS POTENTIAL THERAPEUTICS

by

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A Thesis

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

Dedication

This thesis is dedicated to my beloved family. Your patience and encouragement influenced me to undertake higher studies and face the eventualities of life with zeal and enthusiasm. Thank you for your support along the way and in the years to come.

Acknowledgments

I owe my deepest gratitude to Prof. Subash Jonnalagadda for imparting his knowledge and expertise during this research. I thank Dr. Suman Pathi for his guidance in the lab. I am grateful to all my friends who were a constant source of support during my research and beyond.

Abstract

Anupama Indukuri
FUNCTIONALIZED HETEROCYCLICS AS POTENTIAL THERAPEUTICS
2018-2019
Subash Jonnalagadda, Ph.D.
Master of Science in Pharmaceutical Sciences

Heterocyclic compounds play an important role in pharmaceutical drug development. Several natural products and biologically active compounds contain heterocyclic motifs in them. Multicomponent coupling reactions offer an excellent platform for the synthesis of diverse libraries of heterocyclic compounds. We have been working on the synthesis of novel heterocyclic small molecules utilizing reactions such as Baylis-Hillman reaction, Passerini reaction, Click reaction, reductive amination aldol condensation, etc.

In the current project, we prepared three series of heterocyclic compounds using Passerini and Baylis-Hillman reactions as key steps. Owing to the importance of heterocyclic chemistry in drug discovery and the ease of synthesis, the current work would be of interest to medicinal and natural product chemists.

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Chapter 1

Preparation of Heterocyclic Compounds

Introduction

Heterocyclic moieties are present in many natural products and medicinally important compounds.[1-8] Heterocyclic compounds exhibit wide variety of biological activities such as anti-cancer,[9] anti-bacterial,[10-13] anti-fungal,[14] anti-tuberculosis,[15] anti-malarial,[16] anti-asthma,[17] and other activities.[18-22] Several drugs also contain heterocyclic motifs in them (eg. Fezolamin,[23] Celecoxib,[24] Rimonabant,[25] Ruxolitinib,[26] Pyrazofurin,[27] Crizotinib,[28] Tepoxalin[29] Ionazolac[30], etc.).[31-33] We have been working on the development of novel heterocyclic compounds for the past several years.[34-46]

Multicomponent coupling reactions play an important role not only in medicinal chemistry but in organic synthesis as well particularly in the preparation of heterocyclic compounds.[47] We have also been working on the synthesis of diverse library of compounds via multicomponent coupling reactions. Some of the famous multicomponent coupling reactions include Passerini reaction,[48-52] Ugi reaction,[53] Baylis-Hillman reaction,[54-61] aldol condensation, reductive amination, Click reaction, [62-65] etc. The two key reactions involved in the present study include Passerini reaction (Figure 1) and Baylis-Hillman reaction (Figure 2).

Passerini Reaction

Passerini reaction involves the synthesis of α-acyloxy carboxamides **4** via a three-component coupling reaction between aldehyde/ketones **1**, carboxylic acids **2**, and isocyanides **3**, while Ugi reaction involves a four-component coupling of aldehydes/ketones **1**, carboxylic acids **2**, isocyanides **3**, and amines **5** towards the synthesis of α-acylamino amides **6** (Figure 1).

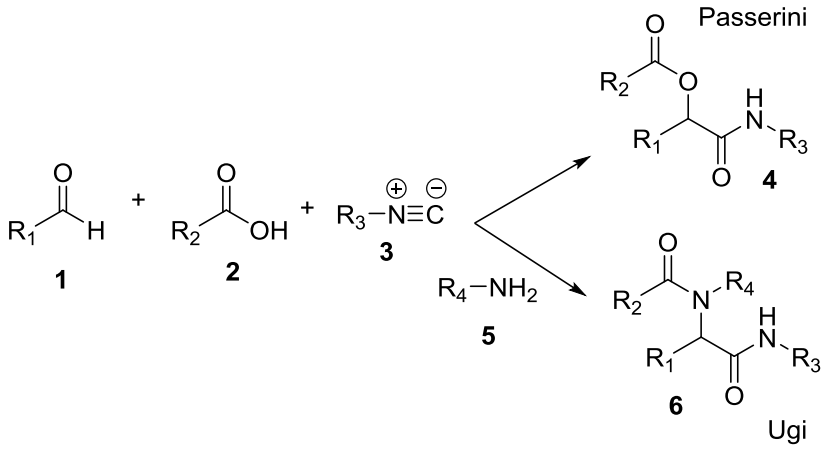


Figure 1. Passerini Reaction

Baylis-Hillman Reaction

Baylis-Hillman reaction involves the coupling of activated olefins such as acrylates, vinyl ketones, and acrolein **8** with aldehydes **7** to produce densely functionalized allylic alcohols **9** in high yields (Figure 2).[66] While this reaction does tolerate wide variety of functional groups, it does have a drawback of being extremely slow (often this reaction

takes two weeks or longer for completion) and multiple efforts have been made accordingly towards increasing the rate of this reaction.[67-74] Baylis-Hillman reaction has been reported with olefins such as acrylate,[75,76] vinyl ketone,[77,78,79] acrolein,[71,80] acrylamide,[69] acrylonitrile, [78,81] vinyl sulfone,[82] vinyl sulfoxide,[83] vinyl phosphonate, and allenyl esters[84,85] leading to the formation of corresponding allylic alcohols. These allylic alcohols can be further functionalized via acetylation followed by nucleophilic substitution to generate diverse library of compounds **11** (Figure 2).

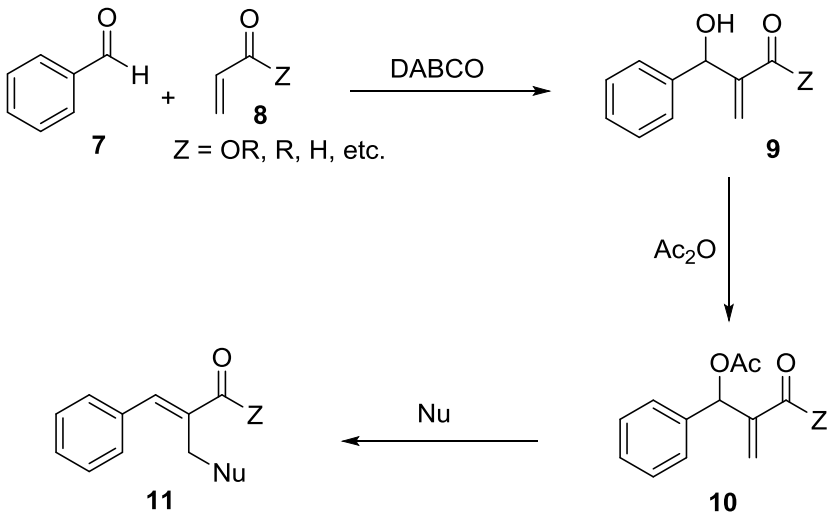


Figure 2. Baylis-Hillman Reaction

Proposed Target Compounds

Based on our interest involving the applications of heterocyclic chemistry in medicinal compounds, we undertook the synthesis of conjugates **12-14** using Baylis-Hillman and Passerini reactions as key steps (Figure 3).

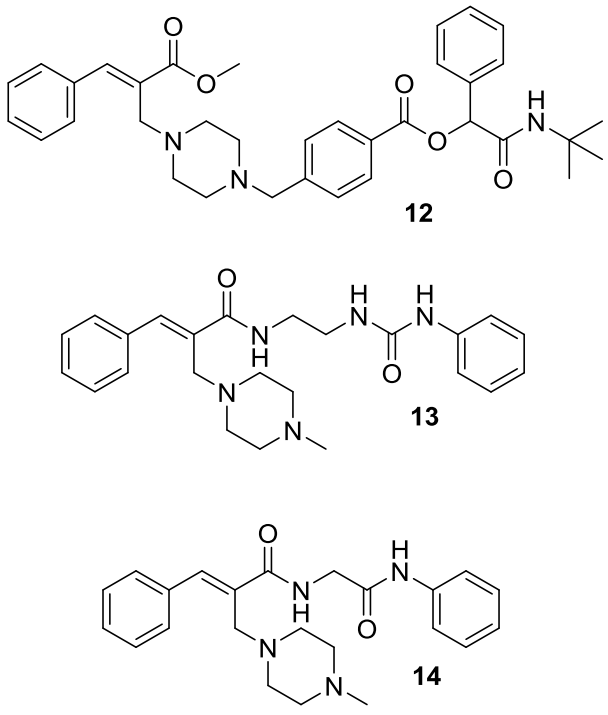


Figure 3. Target Compounds

Proposed Synthesis of Target 12

We hypothesized the synthesis of **12** via Passerini reaction of bromomethyl benzoic acid **15** with isocyanide **16**, and benzaldehyde **17** followed by sequential nucleophilic substitution with piperazine as shown in Figure 4.

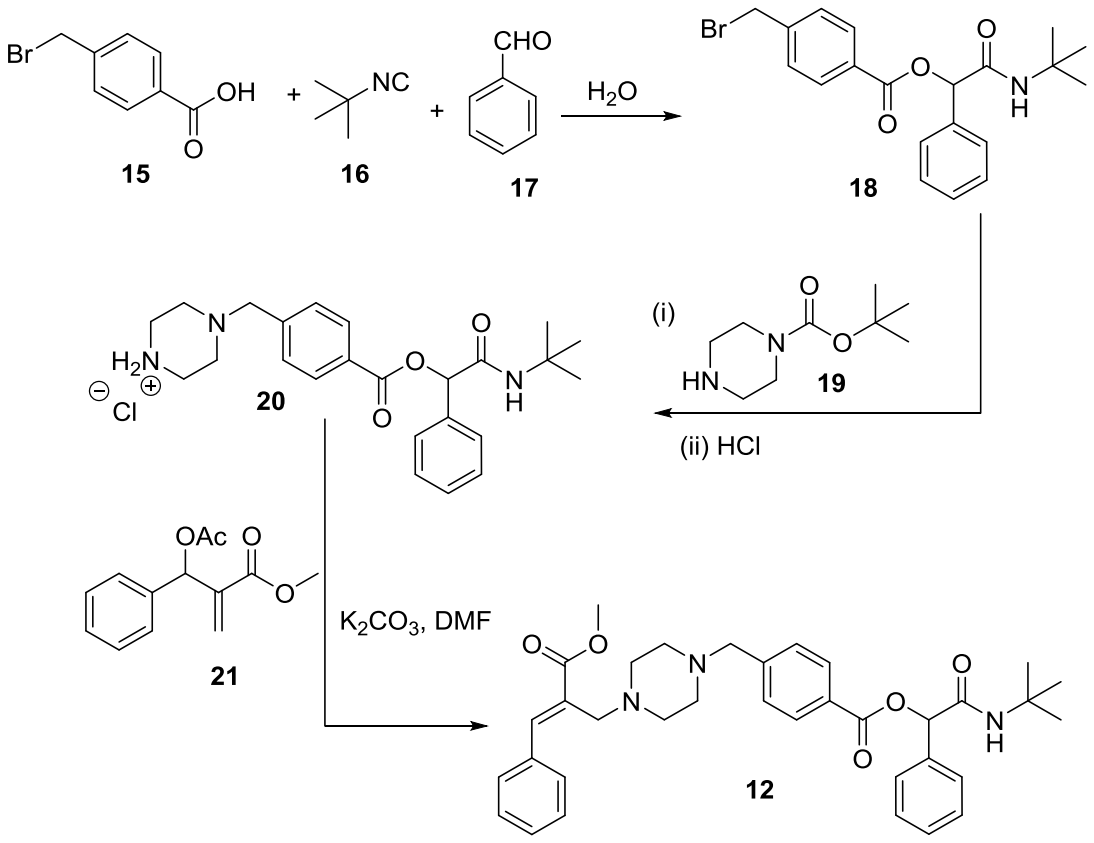


Figure 4. Proposed Synthesis of Target Compound **12**

Proposed Synthesis of Target 13

The synthesis of conjugate **13** was envisioned via conversion of amine **22** into isocyanate **23** followed by reaction with monoprotected ethylenediamine **24** and amide coupling with Baylis-Hillman reaction derived α-piperazinylmethylcinnamic acid **27**. The synthesis of compound **27** was in turn hypothesized via substitution of BH acetate **21** with *N*-methylpiperazine **26** (Figure 5).

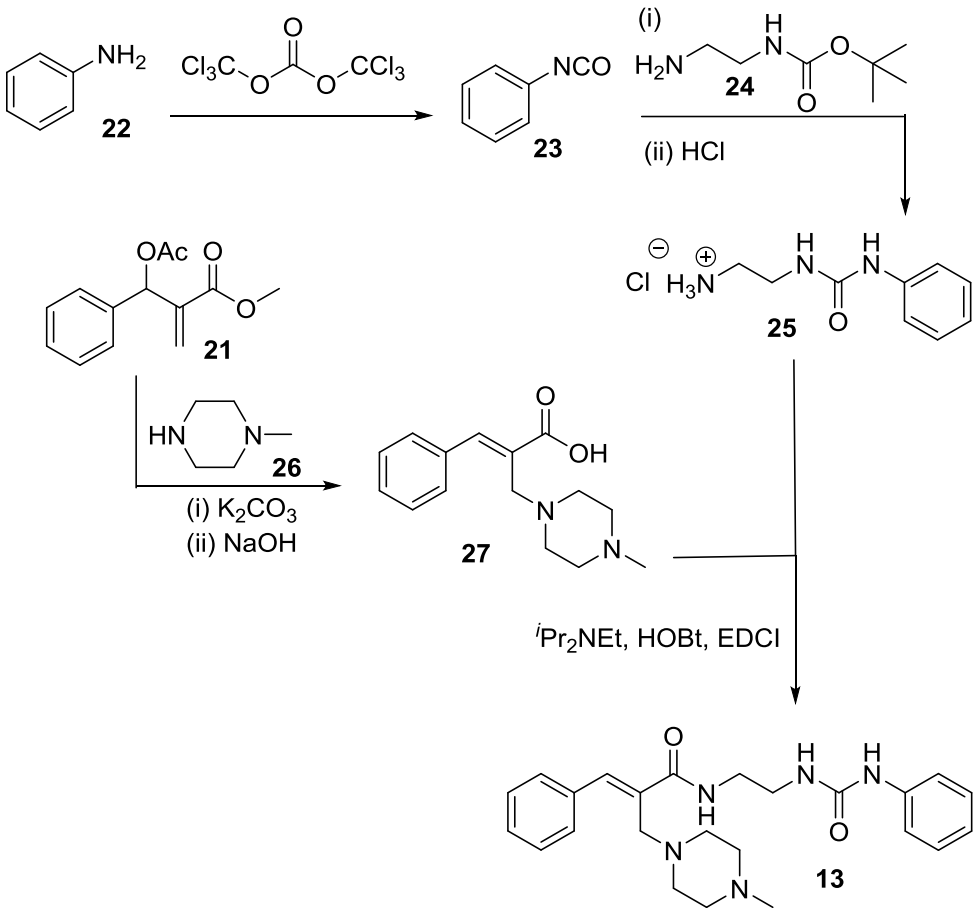


Figure 5. Proposed Synthesis of Target Compound **13**

Proposed Synthesis of Target 14

The synthesis of **14** was proposed via sequential coupling of glycine analog **28** with aniline **22** and α-piperazinylmethylcinnamic acid **27** (Figure 6).

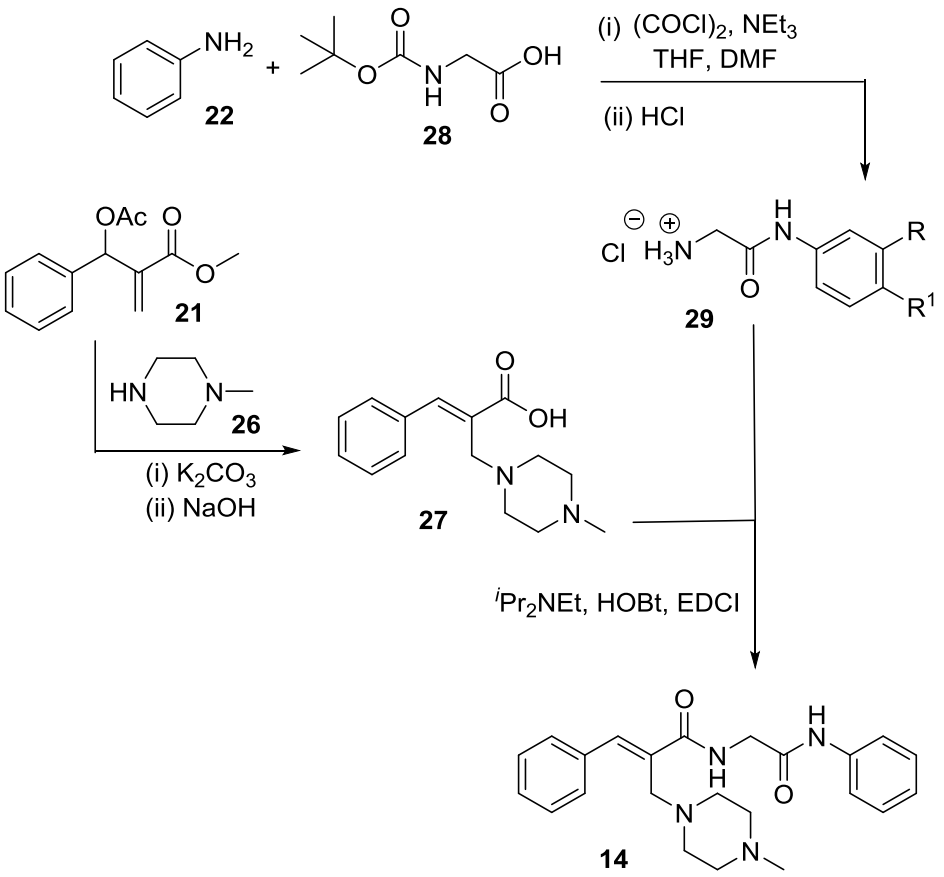


Figure 6. Proposed Synthesis of Target Compound **14**

Preparation of Target Compound 12

The synthesis of compound **12** was initiated with the Passerini reaction of *p*-bromomethylbenzoic acid **15**. **15** was in turn was synthesized via benzylic halogenation of *p*-toluic acid using potassium bromate and sodium thiosulfate.[86] *p*-Bromomethylbenzoic acid **15** was further reacted with *t*-butyl isocyanide and three aldehydes (benzaldehyde, *p*-fluorobenzaldehyde, and *p*-cyanobenzaldehyde) **17a-c** in water and stirred at room temperature overnight to obtain the α-acyloxy amides **18a-c** in very good yield (Figure 7). The compounds synthesized via Passerini reaction are shown in Figure 8.

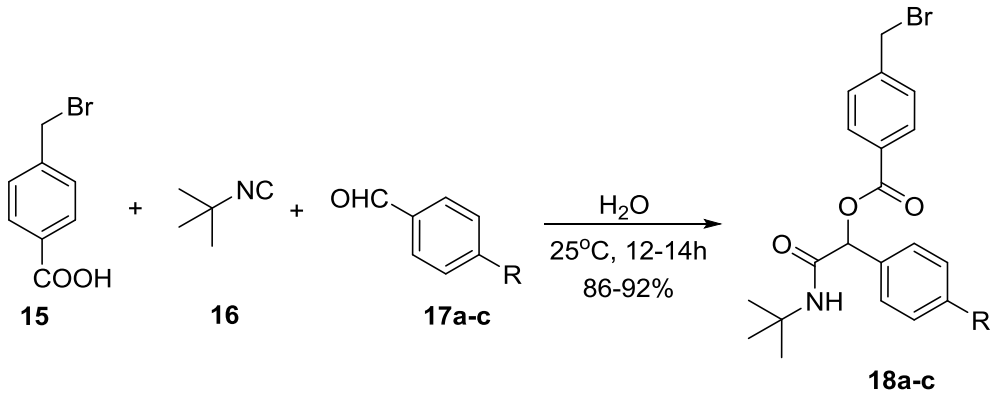


Figure 7. Preparation of **18a-c** via Passerini Reaction

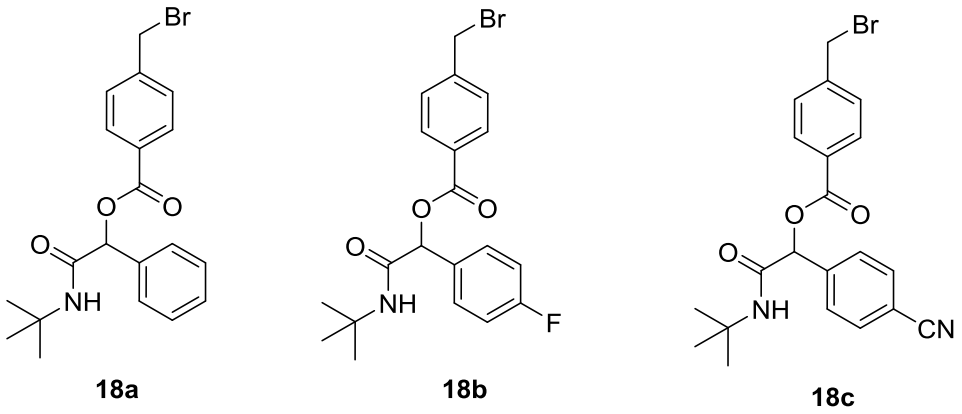


Figure 8. Compounds Synthesized via Passerini Reaction

The α-acyloxyamides **18a-c** obtained via Passerini reaction were further reacted with *N*-Boc piperazine **19** in the presence of potassium carbonate and DMF to obtain *N*-Boc piperazinylmethyl benzoates **30a-c** (Figure 9). The compounds synthesized via this protocol are shown in Figure 10.

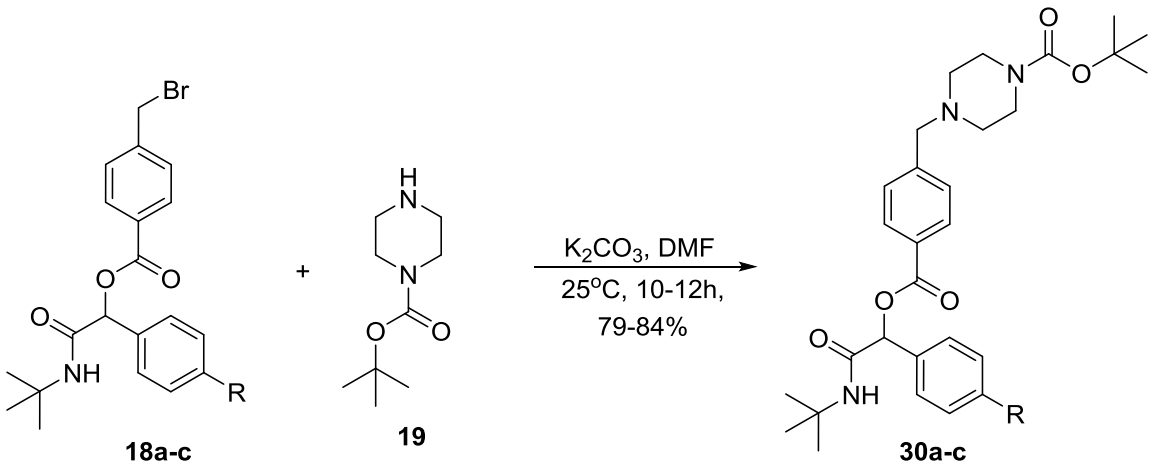


Figure 9. Preparation of **30a-c** via Nucleophilic Substitution

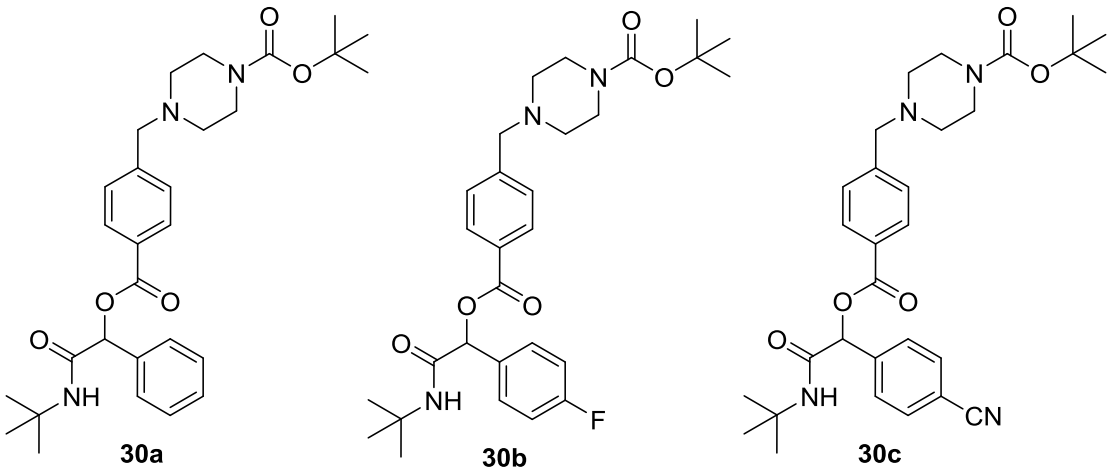


Figure 10. Compounds synthesized via Nucleophilic Substitution

The Boc protecting group in **30a-c** was cleaved via treatment with hydrochloric acid in dioxane to obtain the piperazine analogs **20a-c** (Figure 11). The compounds synthesized via this protocol are shown in Figure 12.

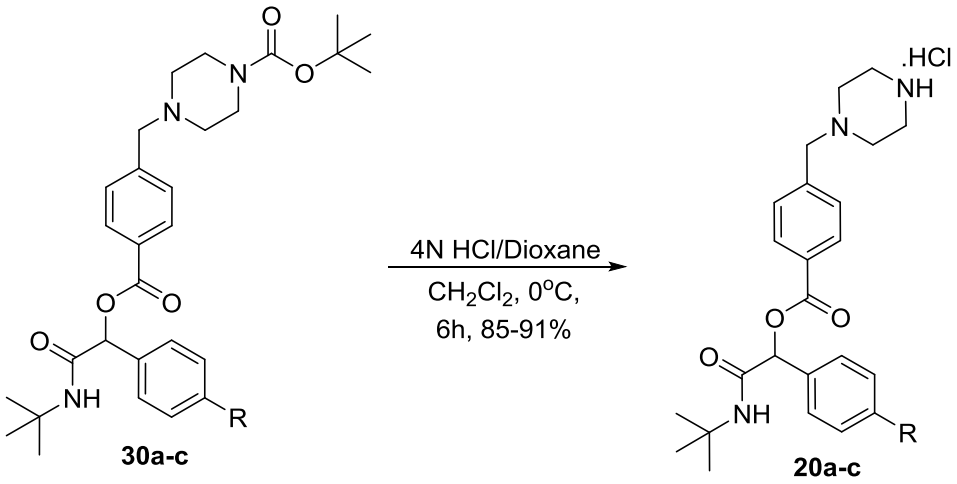


Figure 11. Deprotection of *N*-Boc-piperazine

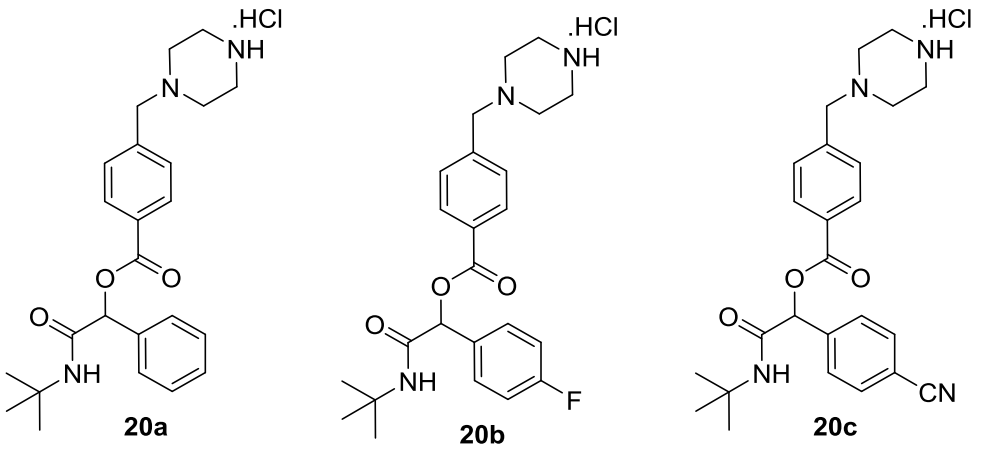


Figure 12. Compounds synthesized via Boc deprotection

The acetates **21a-d** required for coupling with piperazines **20a-c** were prepared via Baylis-Hillman reaction. Treatment of methyl acrylate **32** with benzaldehyde, p-fluorobenzaldehyde, p-cyanobenzaldehyde, and p-anisaldehyde **31a-d** in the presence of diazabicyclo[2.2.2]octane yielded the allylic alcohols **33a-d**, which were further subjected to acetylation with acetic anhydride and triethyl amine to yield the requisites acetates **21a-d** (Figure 13). The acetates prepared via this protocol are shown in Figure 14.

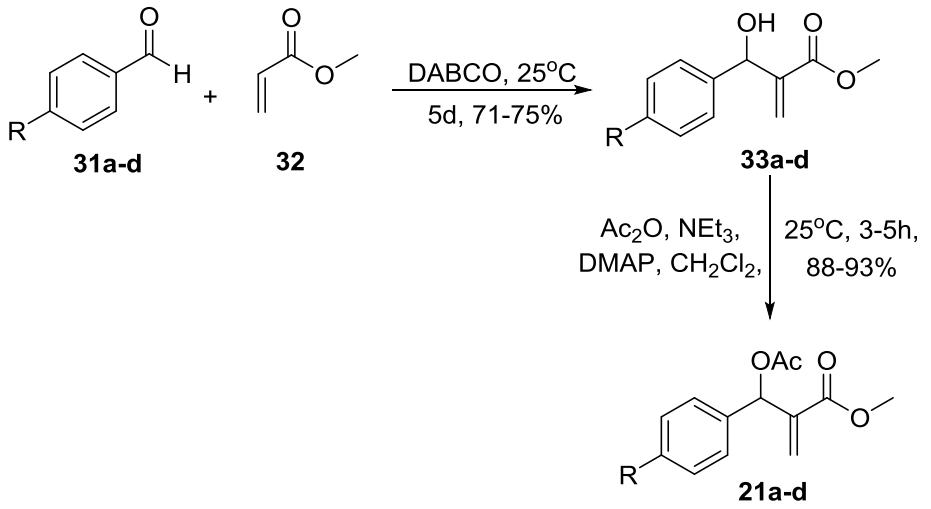


Figure 13. Preparation of Allylic Acetates **21a-d** via Baylis-Hillman Reaction

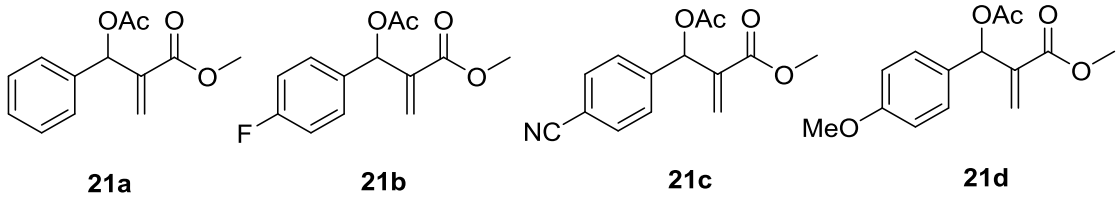


Figure 14. Acetates synthesized via Baylis-Hillman Reaction

The target compounds **12a-f** were eventually synthesized via the reaction of piperazine hydrochloride **20a-c** with acetates **21a-d** in the presence of potassium carbonate and DMF (Figure 15). The target compounds synthesized via this protocol (Figure 16) were rigorously characterized using proton and carbon NMR spectroscopy as well as mass spectrometry.

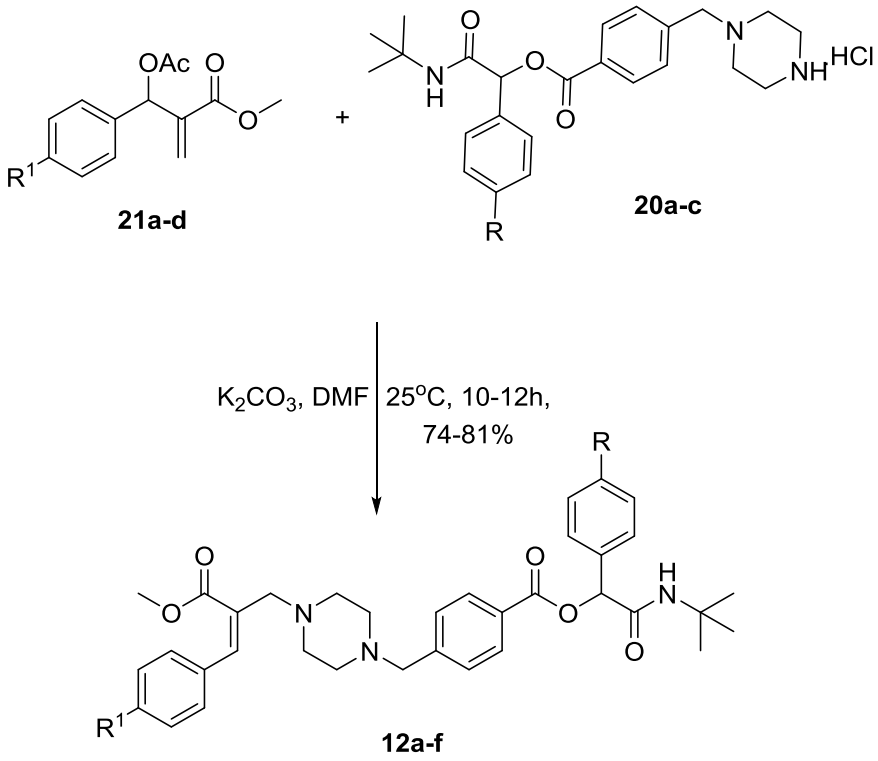


Figure 15. Preparation of Target Compounds **12a-f**

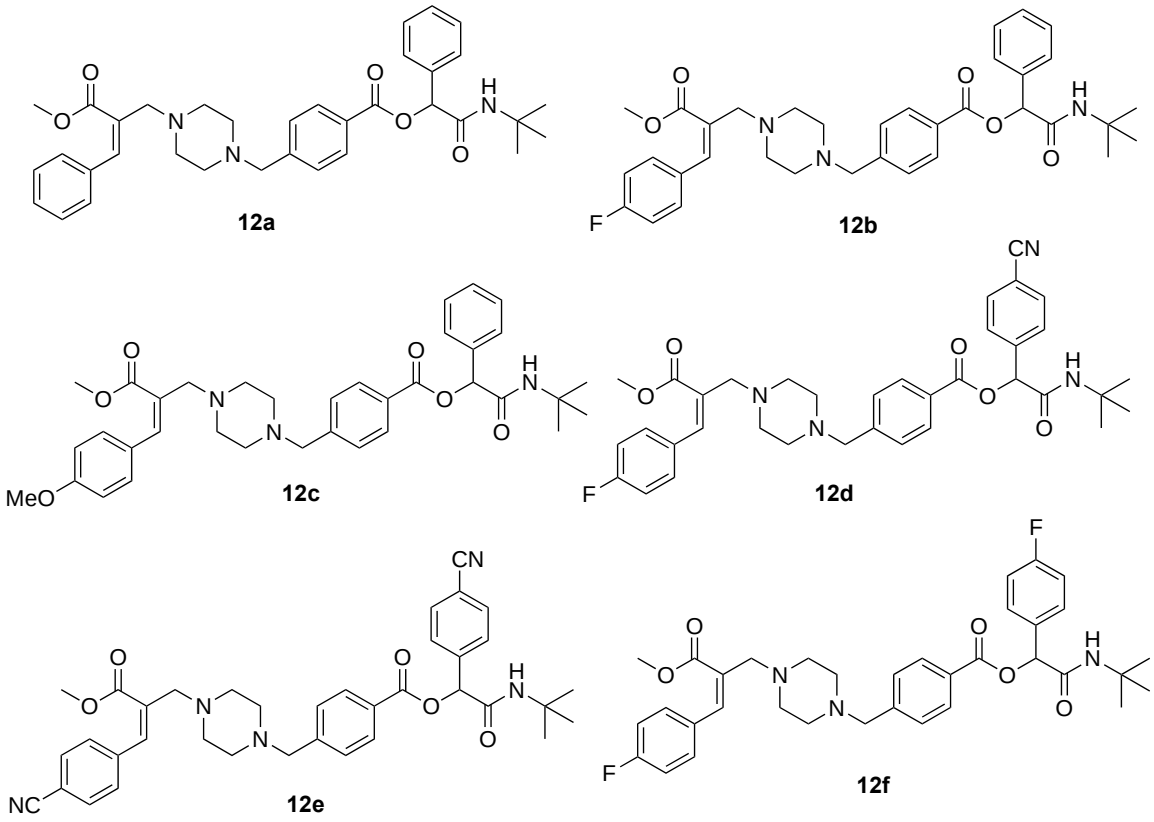


Figure 16. Target Compounds **12a-f** Synthesized via S_N2' Substitution

Preparation of Target Compound 13

The synthesis of target compound **13** was initiated with the preparation of ureas **25a-c** (Figure 17). Isocyanates **23a-c** were obtained upon treatment of aniline, 4-cyano-3-trifloromethylaniline, and 4-nitro-3-trifloromethylaniline (**22a-c**) with triphosgene. The isocyanates **23a-c** were further treated with *N*-boc-ethylenediamine **24** in the presence of triethylamine to afford the ureas **34a-c**, which were further deprotected via acid treatment yielding the amine hydrochlorides **25a-c** (Figure 17). The compounds synthesized via this protocol are shown in Figure 18.

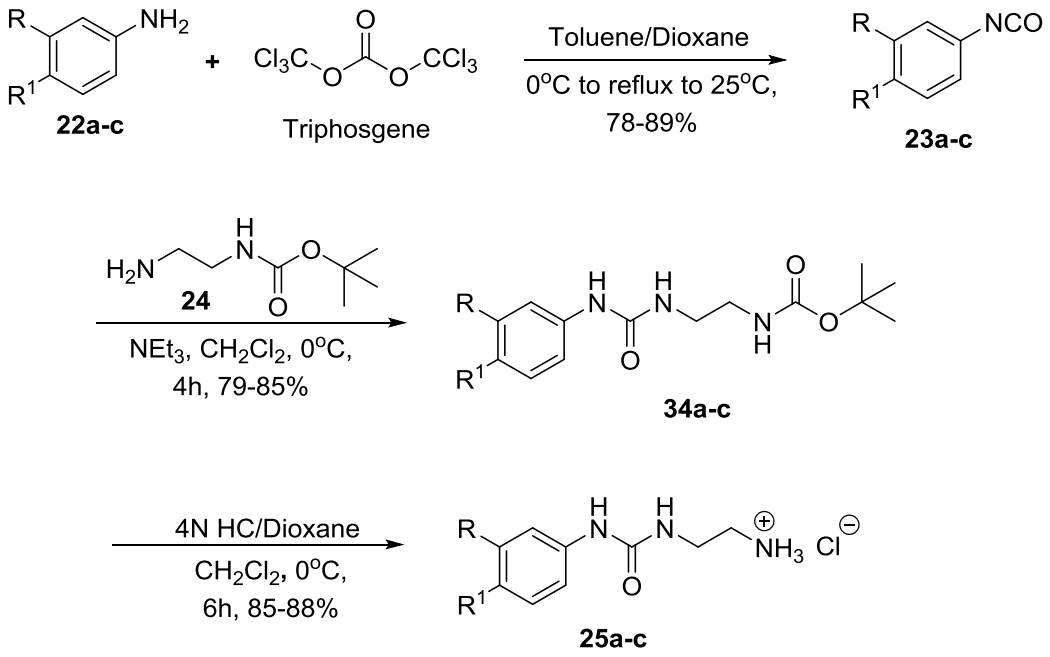


Figure 17. Preparation of *N*-Phenyl-*N*'-2-aminoethyl ureas **25a-c**

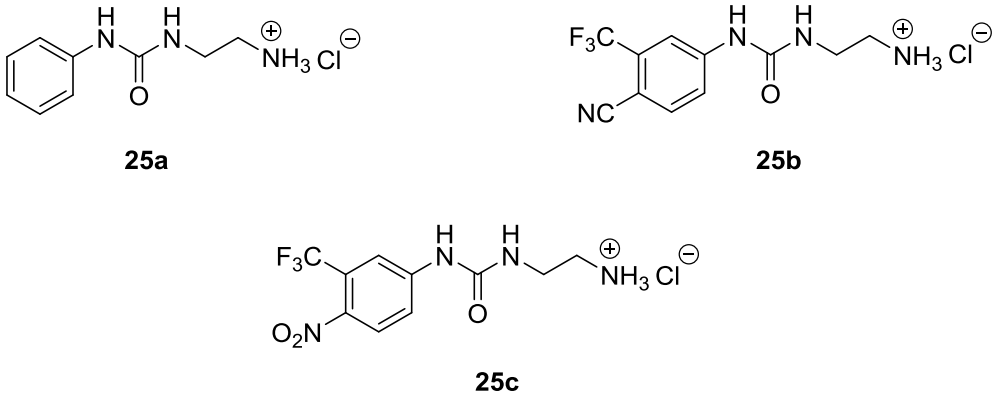


Figure 18. *N*-Phenyl-*N*'-2-aminoethyl ureas **25a-c**

Final target compounds **13a-c** were synthesized via EDCI-HOBt coupling of amine hydrochlorides **25a-c** with Baylis-Hillman reaction derived α-piperazinylmethylcinnamic acid **27**. The cinnamic acid **27** was synthesized in two steps from Baylis-Hillman acetate **21** via nucleophilic substitution with *N*-methylpiperazine **26** followed by alkaline hydrolysis of the resulting a-piperazinylmethylcinnamate **35** (Figure 19). The target compounds synthesized via this protocol are shown in Figure 20. The two compounds **13b** and **13c** were inspired from the chemotherapeutic drugs such as nilutamide and bicalutamide.

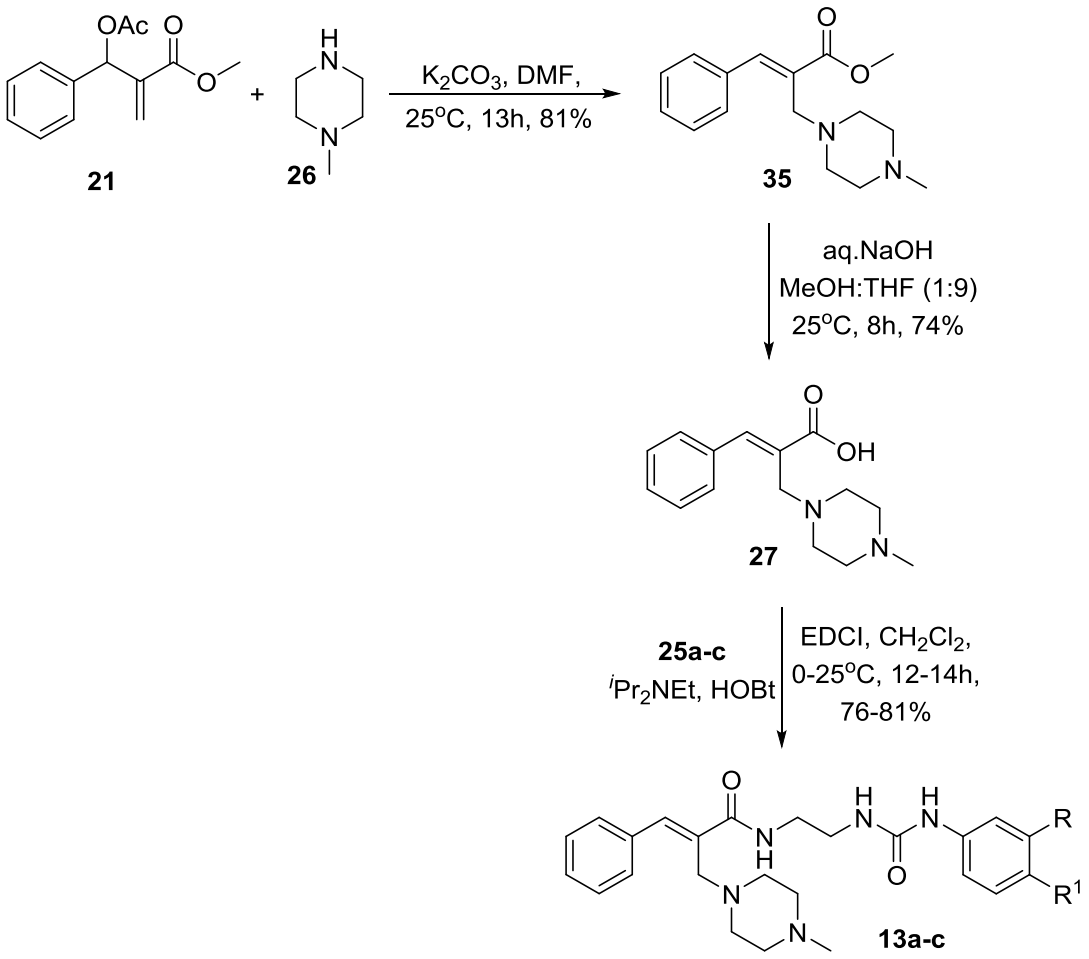


Figure 19. Preparation of Target Compounds **13**

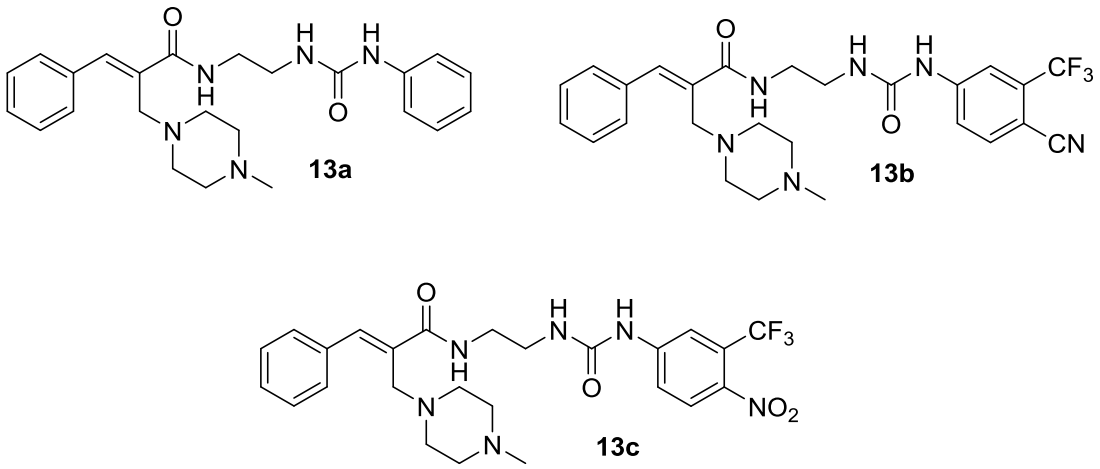


Figure 20. Target Compounds **13** Synthesized via Peptide Coupling

Preparation of Target Compound 14

Finally, the target compounds **14a-b** were synthesized starting from N-Boc glycine **28**. Coupling of **28** with amines **22a-b** in the presence of oxalyl chloride and triethyl amine resulted in the formation of amides **36a-b**, which were further deprotected using HCl and dioxane to yield the amine hydrochlorides **29a-b**. The N-methylpiperazinylmethyl cinnamic acid **27** synthesized above (Figure 19) was used for reaction with amine hydrochlorides **29a-b** under EDCI and HOBt coupling conditions to generate the final target compounds **14a-b** (Figure 21). The compounds synthesized via this protocol are shown in Figure 22. The biological evaluation of these compounds as potential *anti*-cancer agents is underway.

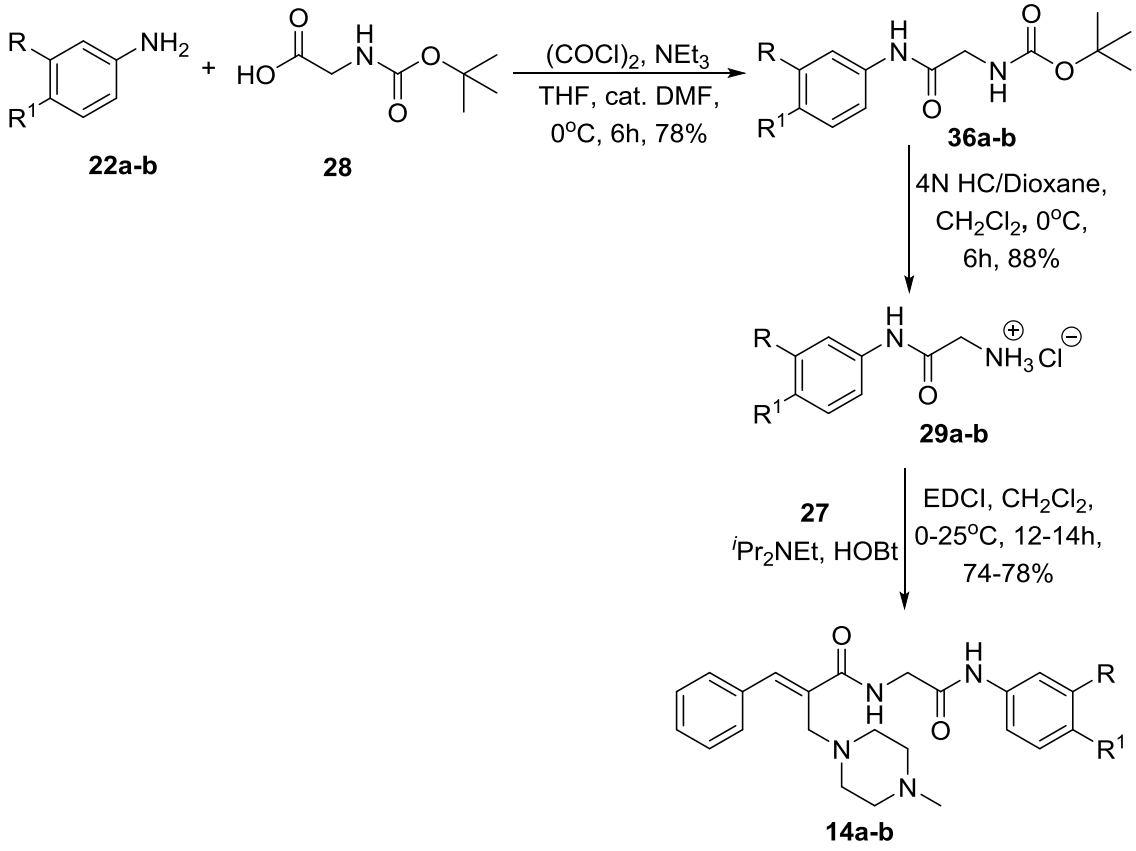


Figure 21. Preparation of Target Compounds **14**

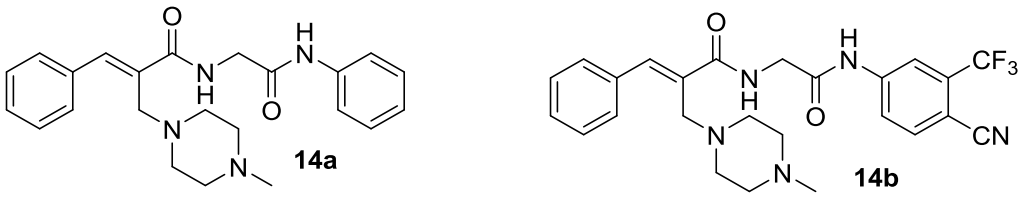


Figure 22. Target Compounds **14** Synthesized via Peptide Coupling

Conclusions

Heterocyclic compounds play in important role in medicinal chemistry and drug discovery. In this project, we have prepared three series of heterocyclic compounds using Passerini and Baylis-Hillman reactions as key steps. Once the preliminary biological screening has been completed, the ease of synthesis of the above-mentioned protocols coupled with the versatility of the multicomponent coupling reactions, will enable us to synthesize diverse library of compounds for potential drug-design applications.

Chapter 2

Experimental Procedures and Spectral Characterization

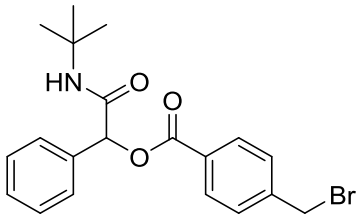
Materials

All the reactants were of reagent grade, and 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.

Instrumentation

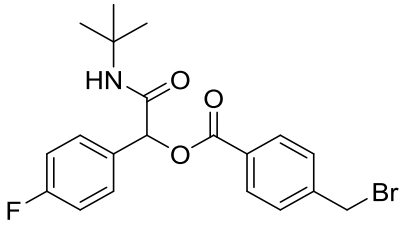
Nuclear Magnetic Spectroscopy (NMR) spectra were produced using the Varian 400 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures



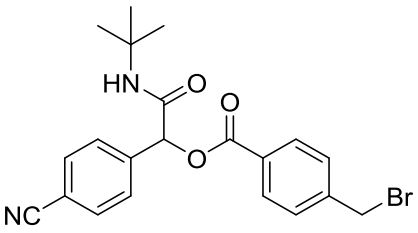
Preparation of 2-(tert-Butylamino)-2-oxo-1-phenylethyl 4-(bromomethyl)benzoate ***18a****:* To a stirred solution of benzaldehyde **17a** (500 mg, 4.7 mmol) and 4-

(bromomethyl)benzoic acid **15** (1.2 g, 5.6 mmol) in water (5.0 mL), was added ^{t}butyl isocyanide (469 mg, 5.6 mmol) and stirred overnight at room temperature. Upon completion as indicated by thin layer chromatography (TLC), the reaction mixture was washed with saturated $NaHCO_3$ followed by extraction with ethyl acetate (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by triturating with hexanes to obtain pure 1.7 g (92%) of **18a** as white solid. Mp 155 – 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.54 (m, 4H), 7.35 – 7.42 (m, 3H), 6.20 (s, 1H), 5.92 (s, 1H), 4.50 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.3, 164.4, 143.4, 135.8, 130.3, 129.3, 129.2, 128.9, 128.8, 127.5, 76.2, 51.6, 32.1, 28.7. ESIMS: m/z calculated for $C_{20}H_{22}BrNO_3$ $(M+H)^+$ 404.09, found 404.02.

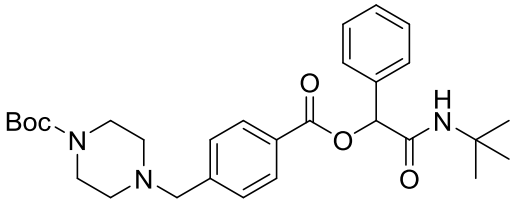


*Preparation of 2-(tert-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl 4-(bromomethyl)benzoate **18b**:* Procedure similar to that of **18a**. The reaction of 4-fluoro benzaldehyde **17b** (400 mg, 3.2 mmol), 4-(bromomethyl)benzoic acid **15** (832 mg, 3.86 mmol), and ^{t}butyl isocyanide (320 mg, 3.86 mmol) yielded 1.2 g (89%) of **18b** as white solid. Mp 167 – 169 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ (ppm) 8.04 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.53 (m, 4H), 7.07 (t, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 5.98 (s, 1H), 4.50 (s, 2H), 1.37

(s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.1, 164.3, 162.9 (d, *J* = 248.0 Hz), 143.5, 131.7 (d, *J* = 3.3 Hz), 130.2, 129.4 (d, *J* = 8.5 Hz), 129.3, 129.1, 115.8 (d, *J* = 21.8 Hz), 75.4, 51.7, 31.9, 28.7. ESIMS: m/z calculated for $C_{20}H_{21}BrFNO_3$ $(M+Na)^+$ 444.06, found 444.05.

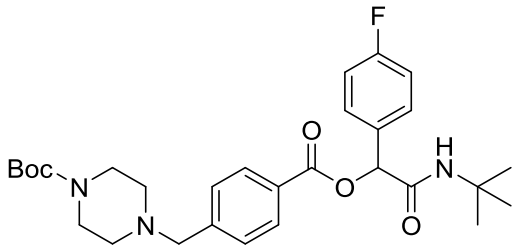


*Preparation of 2-(tert-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl 4-(bromomethyl)benzoate **18c**:* Procedure similar to that of **18a**. The reaction of 4-cyano benzaldehyde **17c** (500 mg, 3.8 mmol), 4-(bromomethyl)benzoic acid **15** (984 mg, 4.6 mmol), and ^{t}butyl isocyanide (379 mg, 4.6 mmol) yielded 1.4 g (86%) of **18c** as white solid. Mp 161 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 6.07 (s, 1H), 4.51 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 166.1, 164.0, 143.9, 140.9, 132.5, 130.2, 129.4, 128.6, 127.9, 118.4, 112.7, 75.2, 51.9, 31.8, 28.6. ESIMS: m/z calculated for $C_{21}H_{21}BrN_2O_3$ $(M+Na)^+$ 451.06, found 451.05.



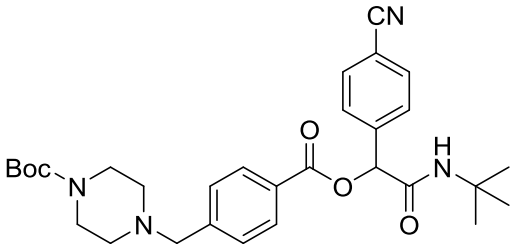
*Preparation of tert-Butyl 4-(4-((2-(tert-butylamino)-2-oxo-1-phenylethoxy)carbonyl)benzyl) piperazine-1-carboxylate **30a**:* Potassium carbonate

(513 mg, 3.7 mmol) was added to a stirred solution of *tert*-butyl piperazine-1-carboxylate (507 mg, 2.7 mmol) and **18a** (1.0 g, 2.5 mmol) in *N*,*N*-dimethylformamide (10.0 mL) at room temperature and stirred overnight at room temperature. Upon completion, the reaction mixture was diluted with cold water to affect the precipitation of solid. The resulting solid was filtered and dried under vacuum to furnish 1.06 g (84%) of **30a** as white solid. Mp 97 – 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 6.8 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.41 (m, 3H), 6.20 (s, 1H), 5.98 (s, 1H), 3.56 (s, 2H), 3.36 – 3.47 (m, 4H), 2.33 – 2.43 (m, 4H), 1.45 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.4, 164.8, 154.7, 144.3, 135.9, 129.8, 129.1, 128.8, 128.7, 128.2, 127.4, 79.6, 75.9, 62.5, 52.9, 51.5, 43.9, 43.1, 28.7, 28.4; ESIMS: m/z calculated for $C_{29}H_{39}N_3O_5$ $(M+Na)^+$ 532.28, found 532.25.

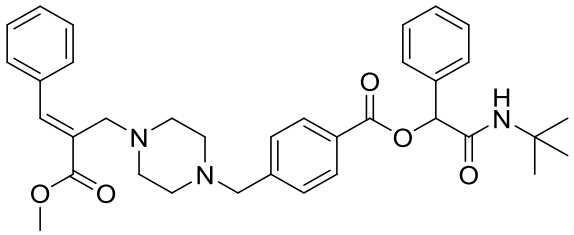


*Preparation of tert-Butyl 4-(4-((2-(tert-butylamino)-1-(4-fluorophenyl)-2-oxoethoxy) carbonyl) benzyl) piperazine-1-carboxylate (**30b**):* Procedure similar to that of **30a**. The reaction of **18b** (1.0 g, 2.4 mmol) with *tert*-butyl piperazine-1-carboxylate (484 mg, 2.6 mmol) in presence of potassium carbonate (488 mg, 3.5 mmol) yielded 1.0 g (82%) of **30b** as white solid. Mp 127 – 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (d, *J* = 8.0 Hz, 2H), 7.49 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.18 (s, 1H), 6.03 (s, 1H), 3.56 (s, 2H), 3.42 (t, *J* = 4.6 Hz, 4H), 2.38 (t, *J* = 4.6 Hz, 4H),

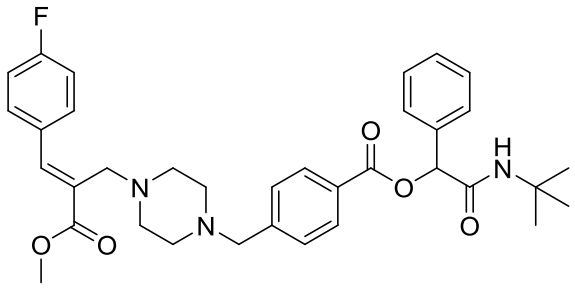
1.45 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.2, 164.7, 162.9 (d, *J* = 247.8 Hz), 154.7, 144.5, 131.9 (d, *J* = 3.1 Hz), 129.8, 129.3 (d, *J* = 8.4 Hz), 129.1, 128.1, 115.7 (d, *J* = 21.7 Hz), 79.6, 75.2, 62.5, 52.9, 51.6, 43.9, 43.2, 28.6, 28.4; ESIMS: m/z calculated for $C_{29}H_{38}FN_3O_5$ $(M+Na)^+$ 550.27, found 550.35.



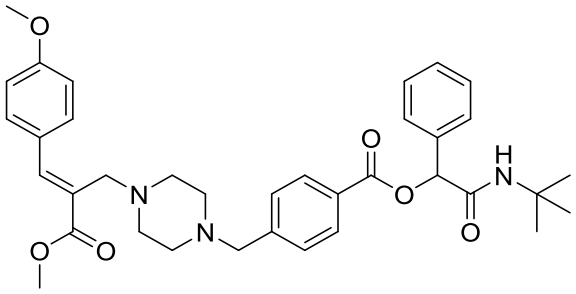
Preparation of tert-Butyl 4-(4-((2-(tert-butylamino)-1-(4-cyanophenyl)-2-oxoethoxy)carbonyl) benzyl)piperazine-1-carboxylate ( ): Procedure similar to that of **30a**. The reaction of **18c** (900 mg, 2.1 mmol) with *tert*-butyl piperazine-1-carboxylate (429 mg, 2.3 mmol) in presence of potassium carbonate (432 mg, 3.1 mmol) yielded 883 mg (79%) of **30c** as white solid. Mp 158 – 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.23 (s, 1H), 6.13 (s, 1H), 3.58 (s, 2H), 3.43 (t, *J* = 4.6 Hz, 4H), 2.39 (t, *J* = 4.6 Hz, 4H), 1.45 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 166.3, 164.4, 154.7, 144.9, 141.1, 132.4, 129.8, 129.2, 127.8, 127.6, 118.4, 112.5, 79.7, 74.9, 62.5, 52.9, 51.8, 43.9, 43.0, 28.6, 28.4; ESIMS: m/z calculated for $C_{30}H_{38}N_4O_5$ $(M+H)^+$ 557.27, found 557.36.



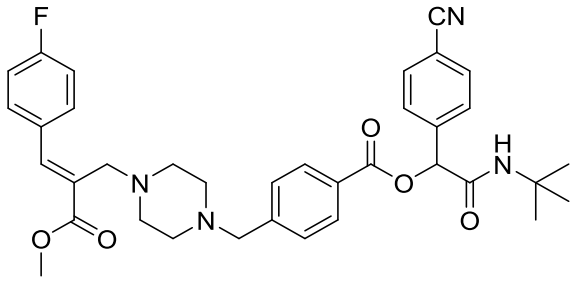
*Preparation of 2-(tert-Butylamino)-2-oxo-1-phenylethyl-4-((4-(2-(methoxycarbonyl)-3-phenylallyl) piperazin-1-yl)methyl)benzoate **12a**:* To a stirred solution of acrylate **21a** (150 mg, 0.64 mmol) in *N*,*N*-dimethylformamide (10.0 mL), was added compound **20a** (313 mg, 0.7 mmol) and followed by addition of K_2CO_3 (132 mg, 0.96 mmol). The reaction was stirred for 10 h and diluted with cold water upon completion. The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Further purification of the crude product by chromatography (silica gel, hexanes: ethyl acetate, 4:1) yielded **12a** as white solid (291 mg, 78%). Mp 124 – 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.63 – 7.66 (m, 2H), 7.51 (dd, *J* = 1.5, 7.8 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.39 (m, 6H), 6.21 (s, 1H), 6.02 (s, 1H), 3.81 (s, 3H), 3.54 (s, 2H), 3.36 (s, 2H), 2.37 – 2.58 (m, 8H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.3, 167.7, 165.0, 145.1, 143.6, 136.3, 135.6, 130.7, 129.9, 129.4, 129.2, 129.0, 128.9, 128.6, 128.3, 127.6, 76.2, 62.8, 53.5, 53.4 (2C), 52.8, 52.3, 51.8, 28.9; ESIMS: m/z calculated for $C_{35}H_{41}N_3O_5$ $(M+H)^+$ 584.3, found 584.4, HPLC purity 94.2%.



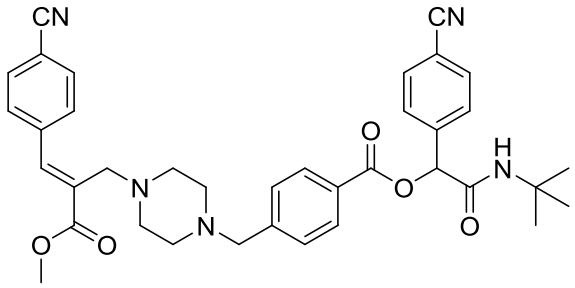
Preparation of 2-(tert-butylamino)-2-oxo-1-phenylethyl-4-((4-(3-(4-fluorophenyl)-2-methoxycarbonyl)allyl) piperazin-1-yl)methyl)benzoate ***12b****:* Procedure similar to that of **12a**. The reaction of **21b** (150 mg, 0.59 mmol) with compound **20a** (292 mg, 0.65 mmol) in presence of potassium carbonate (123 mg, 0.88 mmol) yielded 266 mg (75%) of **12b** as white solid. Mp 98 – 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (d, *J* = 8.0 Hz, 2H), 7.81 (s, 1H), 7.70 (dd, *J* = 5.6, 8.8 Hz, 2H), 7.51 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.39 (m, 3H), 7.07 (t, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 6.00 (s, 1H), 3.80 (s, 3H), 3.55 (s, 2H), 3.33 (s, 2H), 2.36 – 2.60 (m, 8H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.2, 167.6, 165.0, 163.27 (d, *J* = 250.3 Hz), 145.0, 142.8, 136.2, 132.94 (d, *J* = 8.1 Hz), 131.76 (d, *J* = 3.2 Hz), 129.9, 129.3, 129.1, 128.9, 128.3, 127.6, 115.63 (d, *J* = 21.5 Hz), 76.1, 62.7, 53.5, 53.4 (2C), 52.7, 52.4, 52.3, 51.8, 28.9; ESIMS: m/z calculated for $C_{35}H_{40}FN_3O_5$ $(M+H)^+$ 602.3, found 602.4; HPLC purity 89.2%.



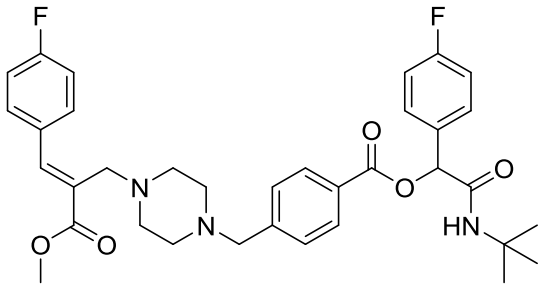
*Preparation of 2-(tert-butylamino)-2-oxo-1-phenylethyl-4-((4-(2-(methoxycarbonyl)-3-(4-methoxyphenyl)allyl) piperazin-1-yl)methyl)benzoate **12c**:* Procedure similar to that of **12a**. The reaction of **21d** (150 mg, 0.56 mmol) with compound **20a** (275 mg, 0.61 mmol) in presence of potassium carbonate (116 mg, 0.84 mmol) yielded 254 mg (74%) of X as white solid. Mp 95 – 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.32 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.13 (s, 1H), 6.01 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.46 (s, 2H), 3.27 (s, 2H), 2.26 – 2.56 (m, 8H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5, 167.7, 165.0, 160.6, 145.1, 143.8, 136.3, 132.9, 129.9, 129.4, 129.0, 128.9 (2C), 128.3, 127.6, 127.2, 114.1, 76.2, 62.7, 55.5, 53.6, 53.4, 53.3, 52.7, 52.2, 52.2, 51.8, 28.9; ESIMS: m/z calculated for $C_{36}H_{43}N_3O_6$ $(M+H)^+$ 614.3, found 614.4; HPLC purity 90.2%.



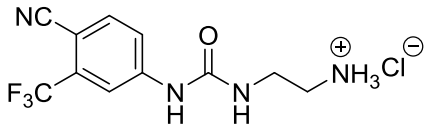
Preparation of 2-(tert-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl-4-((4-(3-(4-fluorophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate ***12d****:* Procedure similar to that of **12a**. The reaction of **21b** (150 mg, 0.59 mmol) with compound **20c** (308 mg, 0.65 mmol) in presence of potassium carbonate (122 mg, 0.88 mmol) yielded 292 mg (79%) of X as white solid. Mp 86 – 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (d, *J* = 8.4 Hz, 2H), 7.82 (s, 1H), 7.60 – 7.74 (m, 6H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.24 (s, 1H), 6.13 (s, 1H), 3.81 (s, 3H), 3.57 (s, 2H), 3.33 (s, 2H), 2.39 – 2.58 (m, 8H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.2, 166.5, 164.6, 163.3 (d, *J* = 250.4 Hz), 145.6, 142.8, 141.3, 132.9 (d, *J* = 8.2 Hz), 132.7, 131.7 (d, *J* = 3.2 Hz), 129.9, 129.5, 129.3, 128.1, 127.6, 118.7, 115.6 (d, *J* = 21.4 Hz), 112.8, 75.2, 62.7, 53.5, 53.4, 52.7, 52.4, 52.1, 28.9; ESIMS: m/z calculated for $C_{36}H_{39}FN_4O_5$ $(M+H)^+$ 627.3, found 627.4; HPLC purity 91.3%.



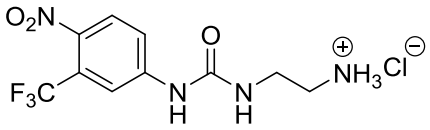
Preparation of 2-(tert-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl-4-((4-(3-(4-cyanophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate ***12e****:* Procedure similar to that of **12a**. The reaction of **21c** (150 mg, 0.57 mmol) with compound **20c** (295 mg, 0.62 mmol) in presence of potassium carbonate (118 mg, 0.86 mmol) yielded 274 mg (76%) of **12e** as cream color solid. Mp 89 – 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (d, *J* = 8.4 Hz, 2H), 7.77 – 7.82 (m, 3H), 7.62 – 7.69 (m, 6H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.23 (s, 1H), 6.12 (s, 1H), 3.83 (s, 3H), 3.56 (s, 2H), 3.31 (s, 2H), 2.36 – 2.57 (m, 8H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.6, 166.5, 164.6, 145.5, 141.4, 141.3, 140.1, 132.7, 132.7, 132.2, 131.1, 129.9, 129.5, 128.9, 128.1, 127.7, 118.8, 118.6, 112.8, 112.4, 75.2, 62.6, 53.4, 53.4, 52.7, 52.6, 52.1, 28.9; ESIMS: m/z calculated for $C_{37}H_{39}N_5O_5$ $(M+H)^+$ 634.3, found 634.4; HPLC purity 96.2%.



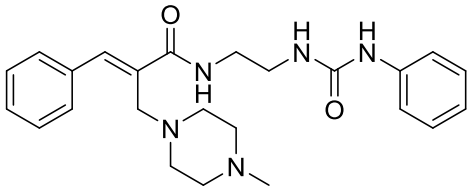
Preparation of 2-(tert-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl-4-((4-(3-(4-fluorophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate ***12f****:* Procedure similar to that of **21a**. The reaction of **21b** (150 mg, 0.59 mmol) with compound **20b** (301 mg, 0.65 mmol) in presence of potassium carbonate (122 mg, 0.88 mmol) yielded 296 mg (81%) of **12f** as white solid. Mp 94 – 96 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, *J* = 7.9 Hz, 2H), 7.73 (s, 1H), 7.62 (dd, *J* = 5.7, 7.8 Hz, 2H), 7.42 (dd, *J* = 5.7, 8.0 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 6.97 (t, *J* = 8.5 Hz, 4H), 6.11 (s, 1H), 6.07 (s, 1H), 3.71 (s, 3H), 3.46 (s, 2H), 3.24 (s, 2H), 2.24 – 2.55 (m, 8H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.2, 167.4, 164.9, 163.3 (d, *J* = 250.2 Hz), 163.2 (d, *J* = 247.8 Hz), 145.2, 142.8, 132.9 (d, *J* = 8.2 Hz), 132.2 (d, *J* = 3.3 Hz), 131.8 (d, *J* = 3.3 Hz), 129.9, 129.6 (d, *J* = 8.4 Hz), 129.4, 129.4, 128.1, 115.9 (d, *J* = 21.7 Hz), 115.6 (d, *J* = 21.5 Hz), 75.4, 62.7, 53.5, 53.4, 52.7, 52.4, 51.9, 28.9; ESIMS: m/z calculated for $C_{35}H_{39}F_2N_3O_5$ $(M+H)^+$ 620.3, found 620.4; HPLC purity 96.5%.



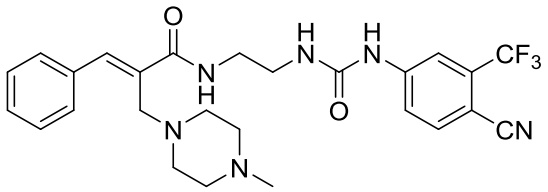
Preparation of 2-(3-(4-cyano-3-(trifluoromethyl)phenyl)ureido)ethan-1-aminiumchloride ***25b****:* Procedure similar to that of **25a-c**. Yield: 85%; pale cream solid; mp 233 – 236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.44 (s, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.03 (br s, 3H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.73 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.06 (t, *J* = 5.8 Hz, 1H), 3.30 – 3.38 (m, 2H), 2.82 – 2.92 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 155.5, 145.8, 136.6, 132.1 (q, *J* = 31.3 Hz), 123.0 (q, *J* = 273.6 Hz), 120.5, 116.6, 115.0 (q, *J* = 4.7 Hz), 99.18 (q, *J* = 2.9 Hz),, 37.5, 36.9; ESIMS: m/z calculated for $C_{11}H_{12}ClF_3N_4O$ $(M)^+$ 273.10, found 272.95;



Preparation of 2-(3-(4-nitro-3-(trifluoromethyl)phenyl)ureido)ethan-1-aminiumchloride ***25c****:* Procedure similar to that of **25a-c**. Yield: 87%; pale cream solid; mp 220 – 224 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.34 – 10.45 (m, 1H), 8.21 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 7.96 (br s, 3H), 7.77 (dd, *J* = 2.2, 9.0 Hz, 1H), 6.99 – 7.06 (m, 1H), 3.35 (q, *J* = 6.0 Hz, 2H), 2.83 – 2.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 155.4, 146.2, 139.7, 128.3, 123.7 (q, *J* = 33.0 Hz), 122.6 (q, *J* = 262.4 Hz), 120.4, 115.8 (q, *J* = 6.0 Hz), 39.4, 37.6; ESIMS: m/z calculated for $C_{10}H_{12}ClF_3N_4O_3$ $(M)^+$ 293.09, found 293.00.

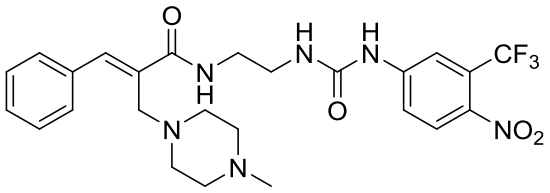


*Preparation of (E)-2-((4-methylpiperazin-1-yl)methyl)-3-phenyl-N-(2-(3-phenylureido) ethyl) acrylamide **13a**:* The reaction of acid **27** (150 mg, 0.58 mmol), with amine **25a**(150 mg, 0.70 mmol) yielded 198 mg (81%) of **13a** as pale cream solid. Mp 104 – 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.02 (t, *J* = 5.1 Hz, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.34 (m, 3H), 7.11 – 7.21 (m, 4H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.40 (br s, 1H), 3.44 – 3.54 (m, 4H), 3.40 (s, 2H), 2.26 – 2.77 (m, 8H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5, 156.4, 140.5, 139.6, 135.0, 129.7, 128.9, 128.9, 128.4, 128.2, 122.3, 119.0, 54.9, 54.6, 52.1, 45.6, 39.9, 39.6; ESIMS: m/z calculated for $C_{24}H_{31}N_5O_2$ $(M+H)^+$ 422.26, found 422.21; HPLC purity 98.2%.

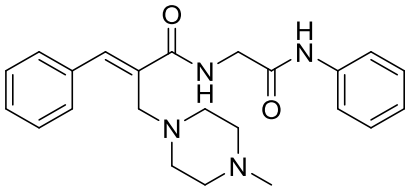


*Preparation of (E)-N-(2-(3-(4-cyano-3-(trifluoromethyl)phenyl)ureido)ethyl)-2-((4-methyl-piperazin-1-yl)methyl)-3-phenylacrylamide **13b**:* The reaction of acid **27** (130 mg, 0.50 mmol), with amine **25b** (185 mg, 0.60 mmol) yielded 196 mg (76%) of **13b** as pale cream solid. Mp 119 – 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.35 – 10.43 (m, 1H), 9.00 (br s, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.37 (m, 3H), 7.10 – 7.16 (m, 2H), 6.67 (br s, 1H), 3.48 – 3.58 (m, 4H),

3.46 (s, 2H), 2.31 – 2.67 (m, 8H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 170.3, 155.2, 144.5, 141.0, 135.6, 134.4, 133.7 (q, *J* = 32.3 Hz), 129.3, 128.8, 128.7, 128.6, 122.3 (q, *J* = 274.1 Hz), 119.9, 116.1, 115.5 (m), 101.1 (m), 54.9, 54.6, 52.1, 45.7, 39.8, 29.7; ESIMS: m/z calculated for $C_{26}H_{29}F_3N_6O_2$ $(M+H)^+$ 515.24, found 515.19; HPLC purity 99.8%.

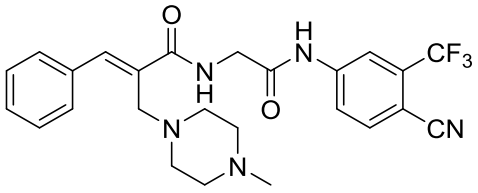


Preparation of (E)-2-((4-methylpiperazin-1-yl)methyl)-N-(2-(3-(4-nitro-3-trifluoromethyl) phenyl)ureido)ethyl)-3-phenylacrylamide ***13c****:* The reaction of acid **27** (110 mg, 0.42 mmol), with amine **25c** (166 mg, 0.51 mmol), yielded 175 mg (78%) of **13c** as pale yellow solid. Mp 128 – 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.46 (t, *J* = 5.1 Hz, 1H), 9.14 (s, 1H), 7.79 – 7.91 (m, 3H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.36 (m, 3H), 7.10 – 7.15 (m, 2H), 6.71 (br s, 1H), 3.49 – 3.59 (m, 4H), 3.45 (s, 2H), 2.29 – 2.65 (m, 8H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 170.3, 155.2, 144.9, 140.9, 140.6, 134.3, 129.3, 128.8, 128.6, 128.5, 127.4, 125.2 (q, *J* = 33.6 Hz), 121.9 (q, *J* = 273.4 Hz), 119.7, 116.4 (m), 55.0, 54.6, 52.2, 45.8, 39.9, 39.8; ESIMS: m/z calculated for $C_{25}H_{29}F_3N_6O_4$ $(M+H)^+$ 535.23, found 535.27; HPLC purity 98.3%.



Preparation of (E)-2-((4-methylpiperazin-1-yl)methyl)-N-(2-oxo-2-(phenylamino)ethyl)-3-phenylacrylamide ***14a****: N,N*-diisopropylethylamine (239 µL, 1.38 mmol), HOBt (68 mg, 0.51 mmol), and EDCI (97 mg, 0.51 mmol) were added at 0 °C to a stirred solution of the

acid **28** (120 mg, 0.46 mmol), in dichloromethane (10.0 mL) and the reaction was stirred for 30 min. The amine **29** (103 mg, 0.55 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 extracted with dichloromethane (2 x 10.0 mL). The combined extracts were washed with 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 140 mg (78%) of pure amide **14a** as pale cream solid. Mp 115 – 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.51 (t, *J* = 5.2 Hz, 1H), 8.94 (s, 1H), 8.00 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.23 – 7.40 (m, 6H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.20 (d, *J* = 5.6 Hz, 2H), 3.48 (s, 2H), 2.32 – 2.86 (m, 8H), 2.28 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.4, 167.7, 141.1, 138.1, 135.1, 129.2, 129.0, 128.9, 128.4, 128.2, 124.1, 119.8, 54.8, 54.7, 52.3, 45.8, 45.6; ESIMS: m/z calculated for $C_{23}H_{28}N_4O_2$ $(M+H)^+$ 393.23, found 393.31; HPLC purity 96.9%.



*Preparation of (E)-N-(2-((4-cyano-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-((4-methyl- piperazin-1-yl)methyl)-3-phenylacrylamide **14b**:* Procedure similar to that of **14a**. The reaction of acid **28** (130 mg, 0.50 mmol), with amine **29** (168 mg, 0.60 mmol) yielded 180 mg (74%) of **14b** as pale cream solid. Mp 122 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.05 (br s, 1H), 10.42 (s, 1H), 8.04 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.96 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.44 (m, 5H), 4.39 (d, *J* = 4.5 Hz, 2H), 3.53 (s, 2H), 2.37 – 2.93 (m, 8H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.7, 167.9, 142.7, 141.3, 135.6, 134.7, 133.7 (q, *J* = 32.6 Hz), 129.1, 128.9, 128.5, 128.5, 122.1 (q, *J* = 274.1 Hz), 121.8, 117.2 (q, *J* = 4.9 Hz), 115.6, 103.7 (m), 54.8 (2C), 52.3, 45.8, 45.3; ESIMS: m/z calculated for $C_{25}H_{26}F_3N_5O_2$ $(M+H)^+$ 486.21, found 486.22; HPLC purity 98.4%.

Chapter 3: Proton and Carbon NMR Spectra

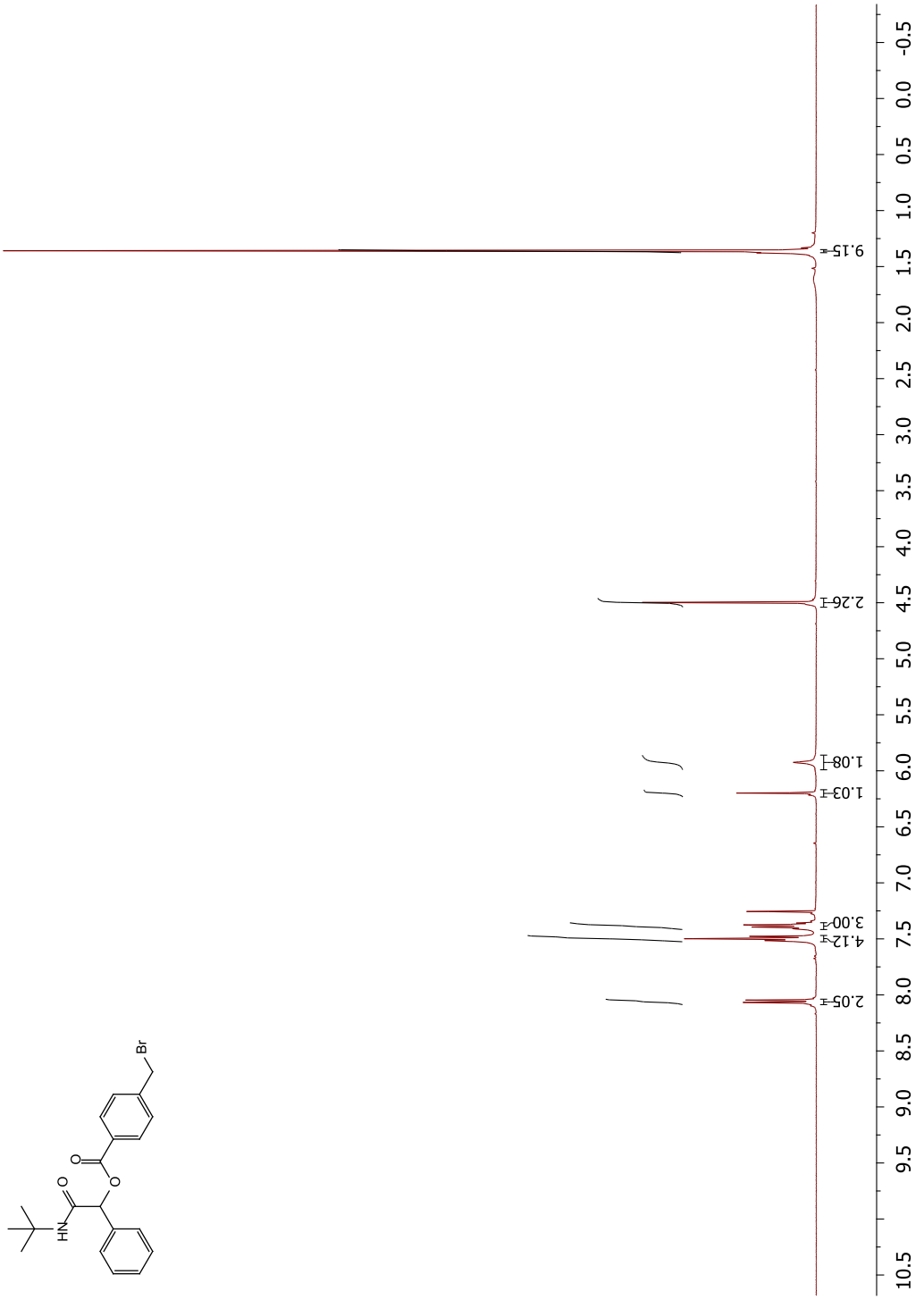


Figure 23. 400 MHz ^{1}H NMR of Compound **18a** in $CDCl_3$

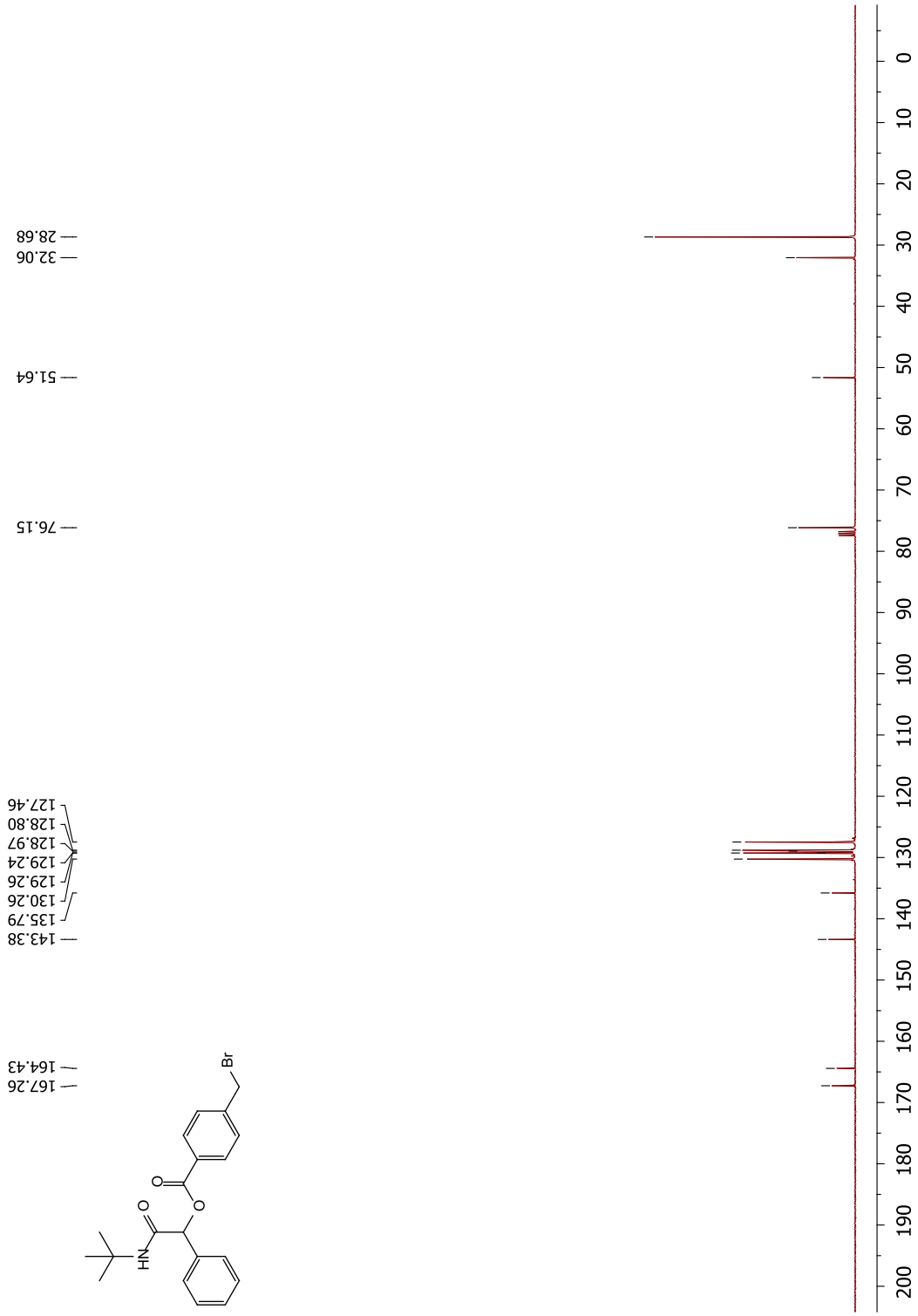


Figure 24. 101 MHz ^{13}C NMR of Compound **18a** in $CDCl_3$

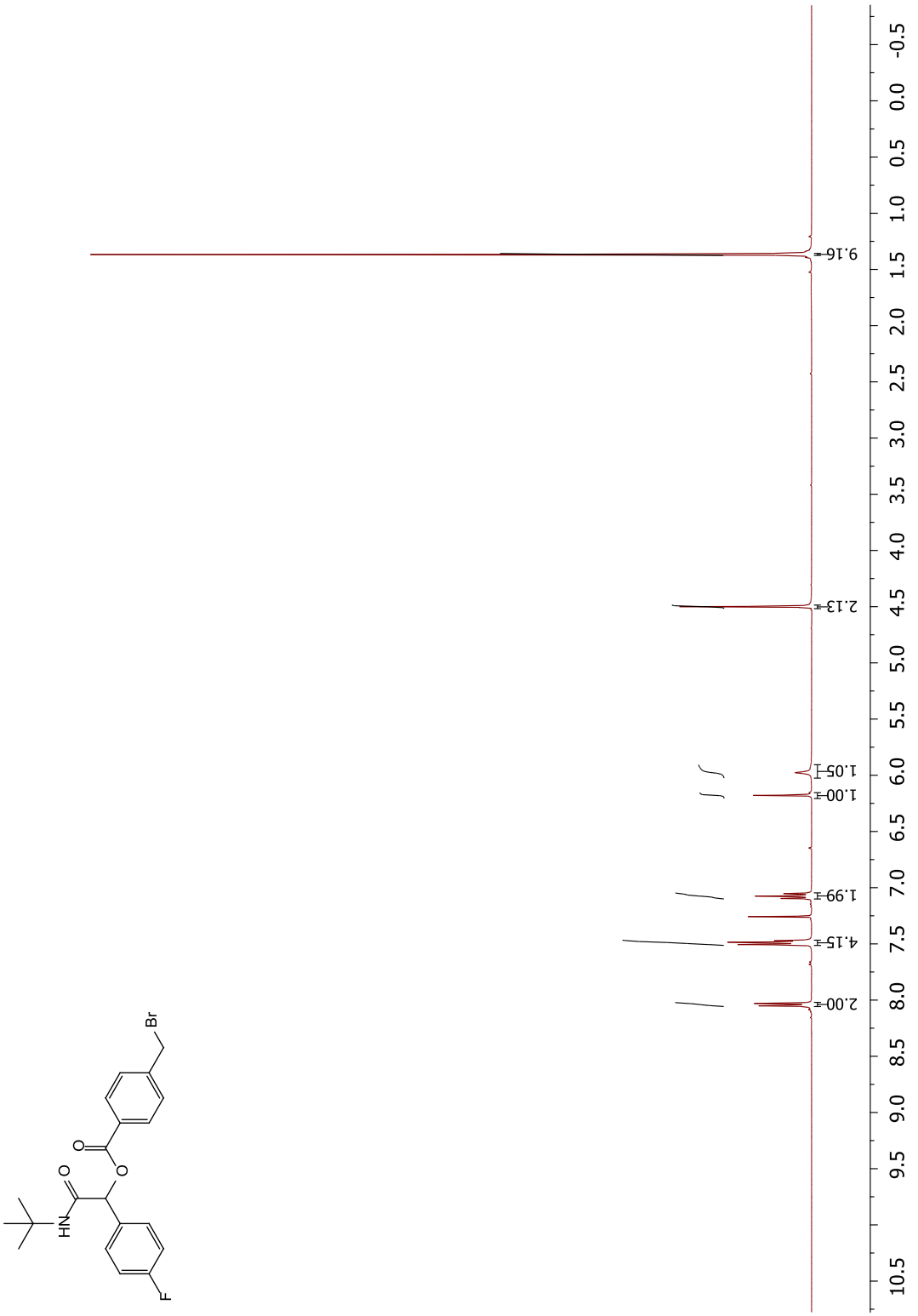


Figure 25. 400 MHz ^{1}H NMR of Compound **18b** in $CDCl_3$

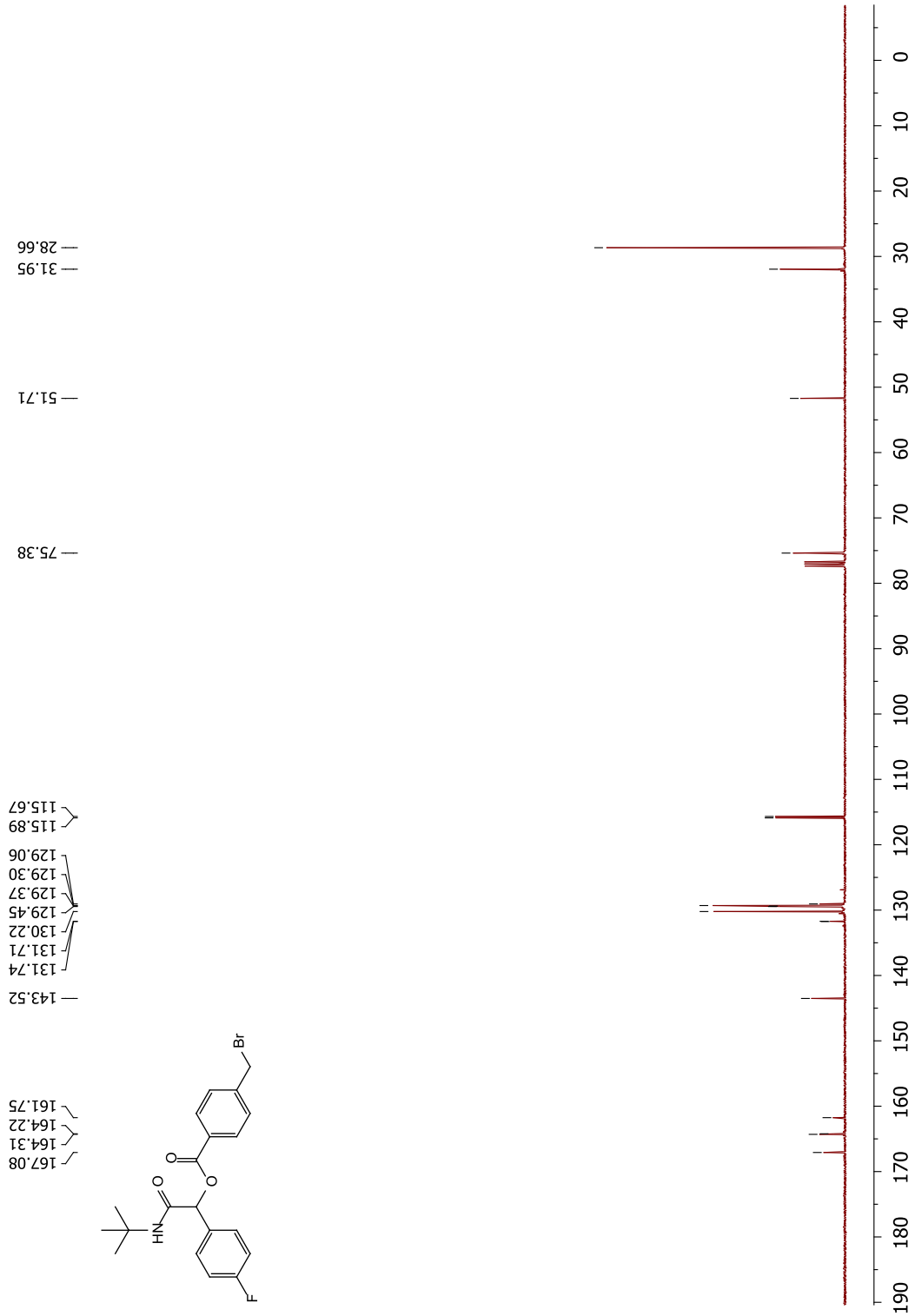


Figure 26. 101 MHz ^{13}C NMR of Compound **18b** in $CDCl_3$

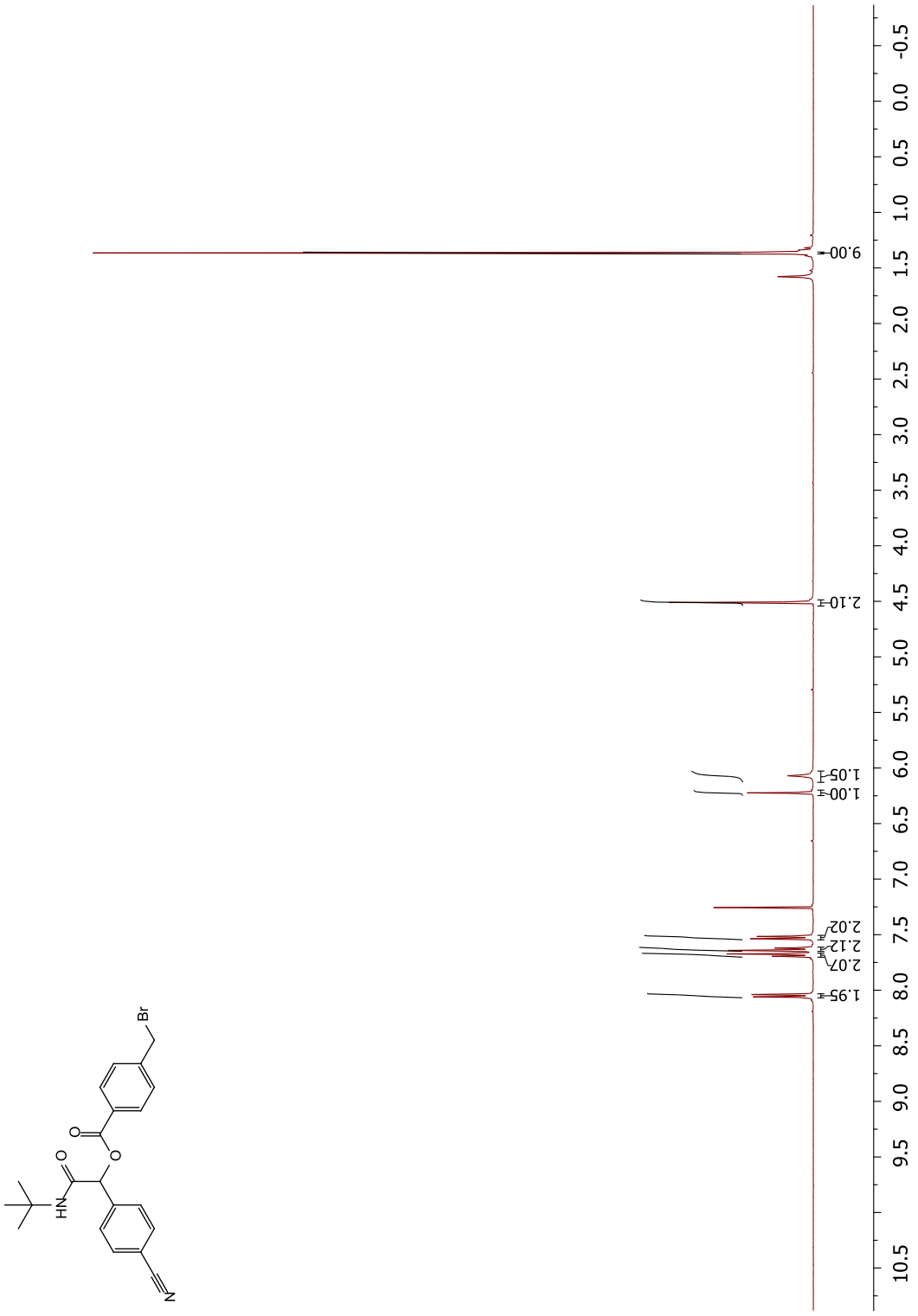


Figure 27. 400 MHz ^{1}H NMR of Compound **18c** in $CDCl_3$

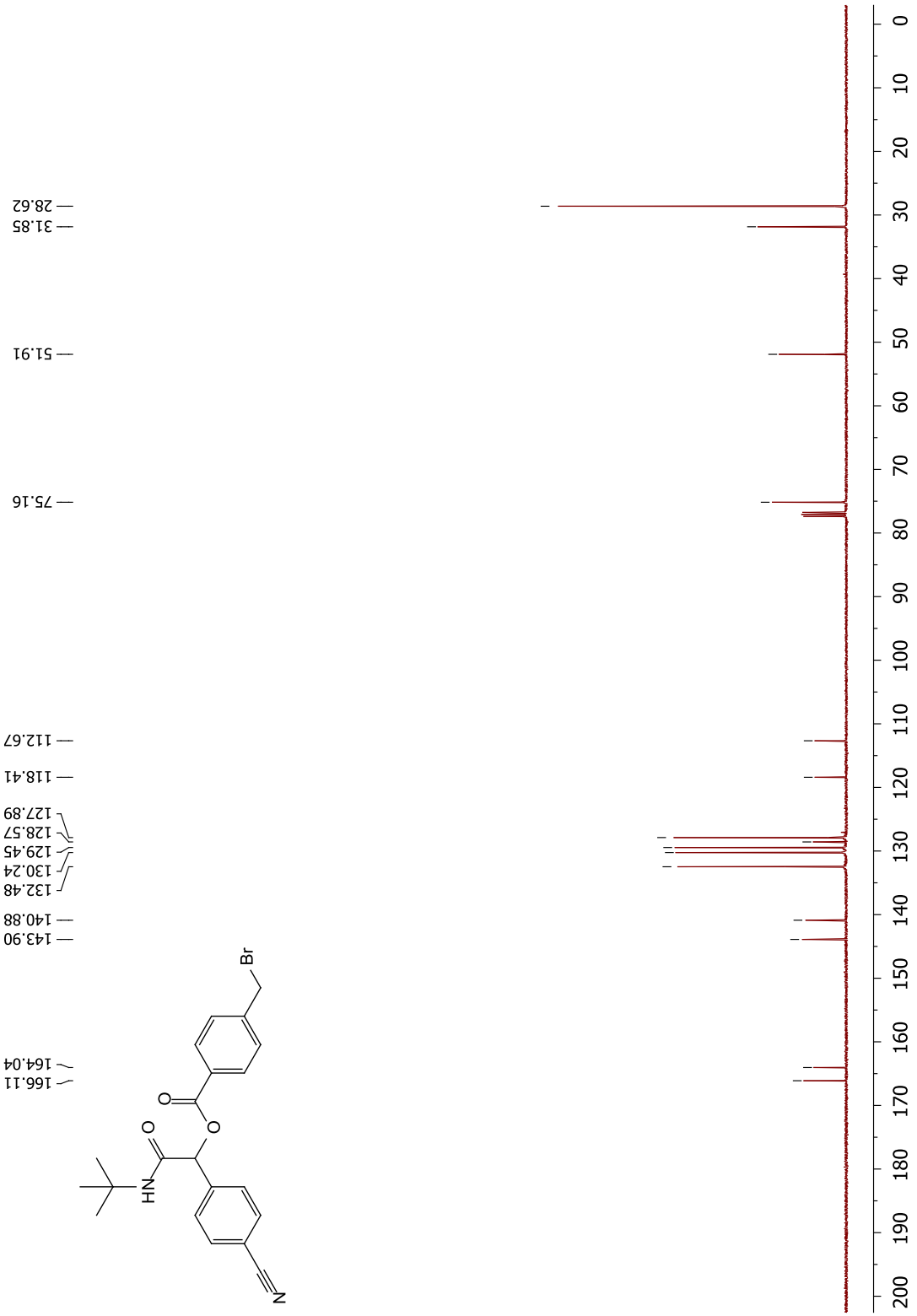


Figure 28. 101 MHz ^{13}C NMR of Compound **18c** in $CDCl_3$

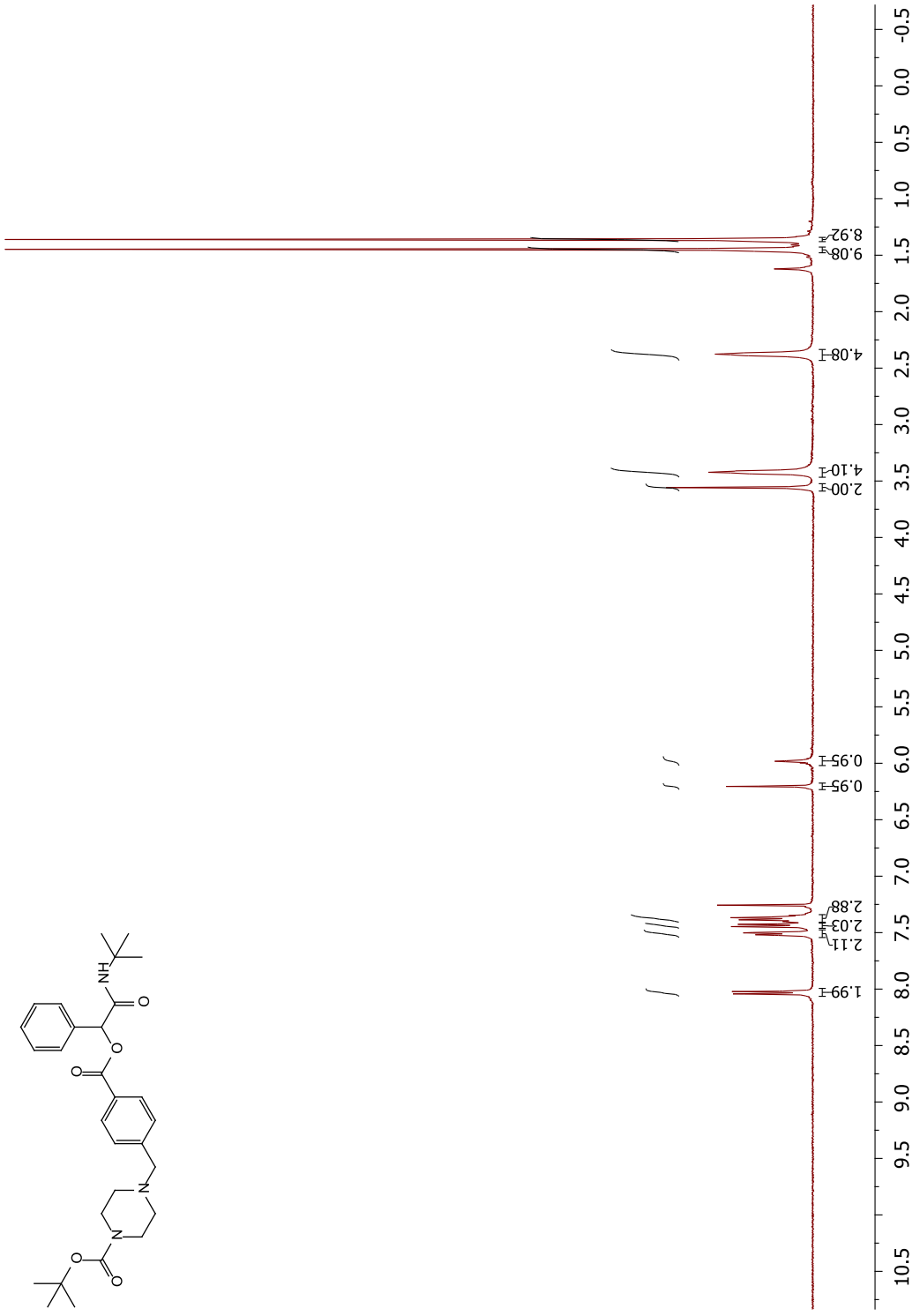


Figure 29. 400 MHz ^{1}H NMR of Compound **30a** in $CDCl_3$

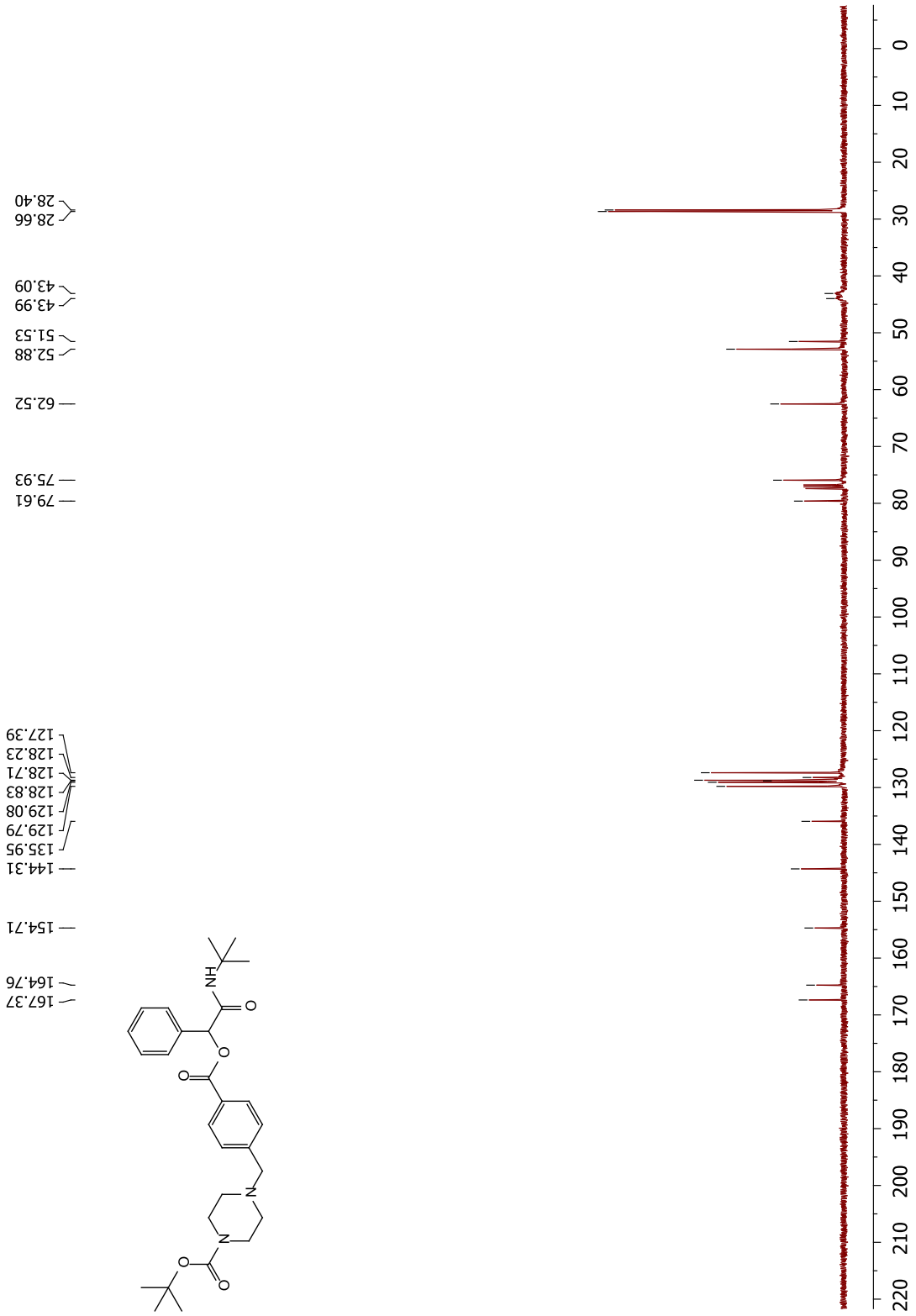


Figure 30. 101 MHz ^{13}C NMR of Compound **30a** in $CDCl_3$

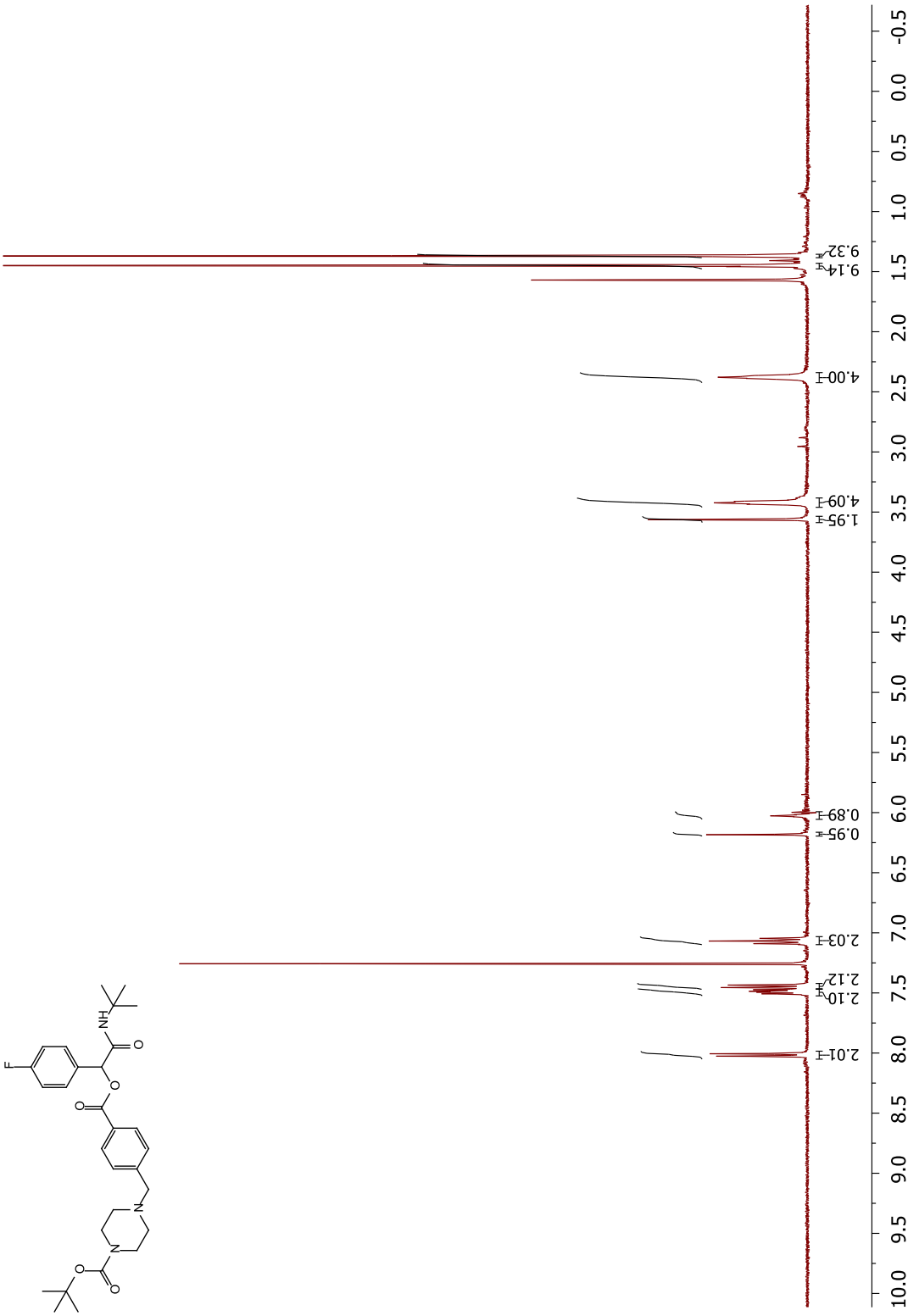


Figure 31. 400 MHz ^{1}H NMR of Compound **30b** in $CDCl_3$

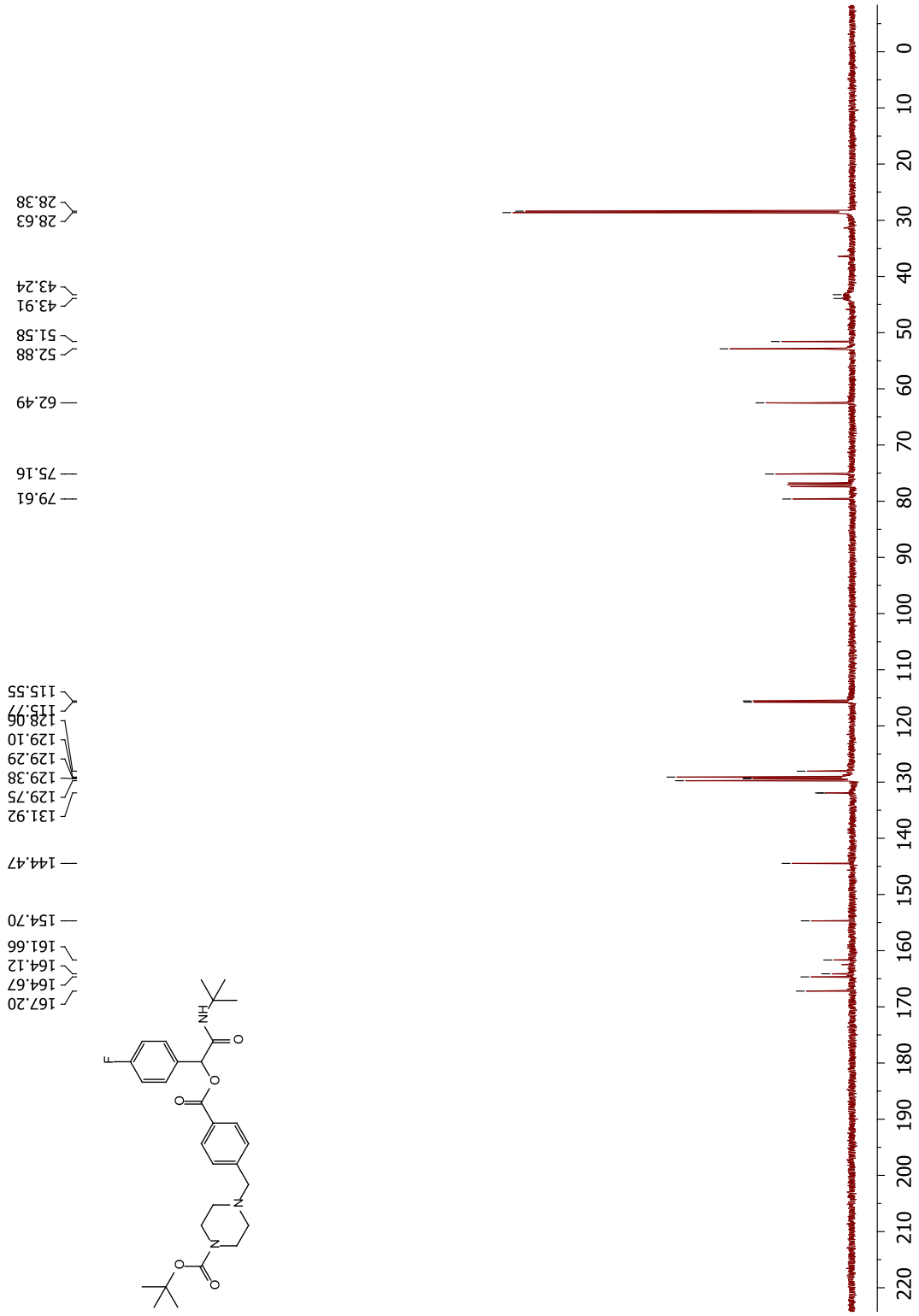


Figure 32. 101 MHz ^{13}C NMR of Compound **30b** in $CDCl_3$

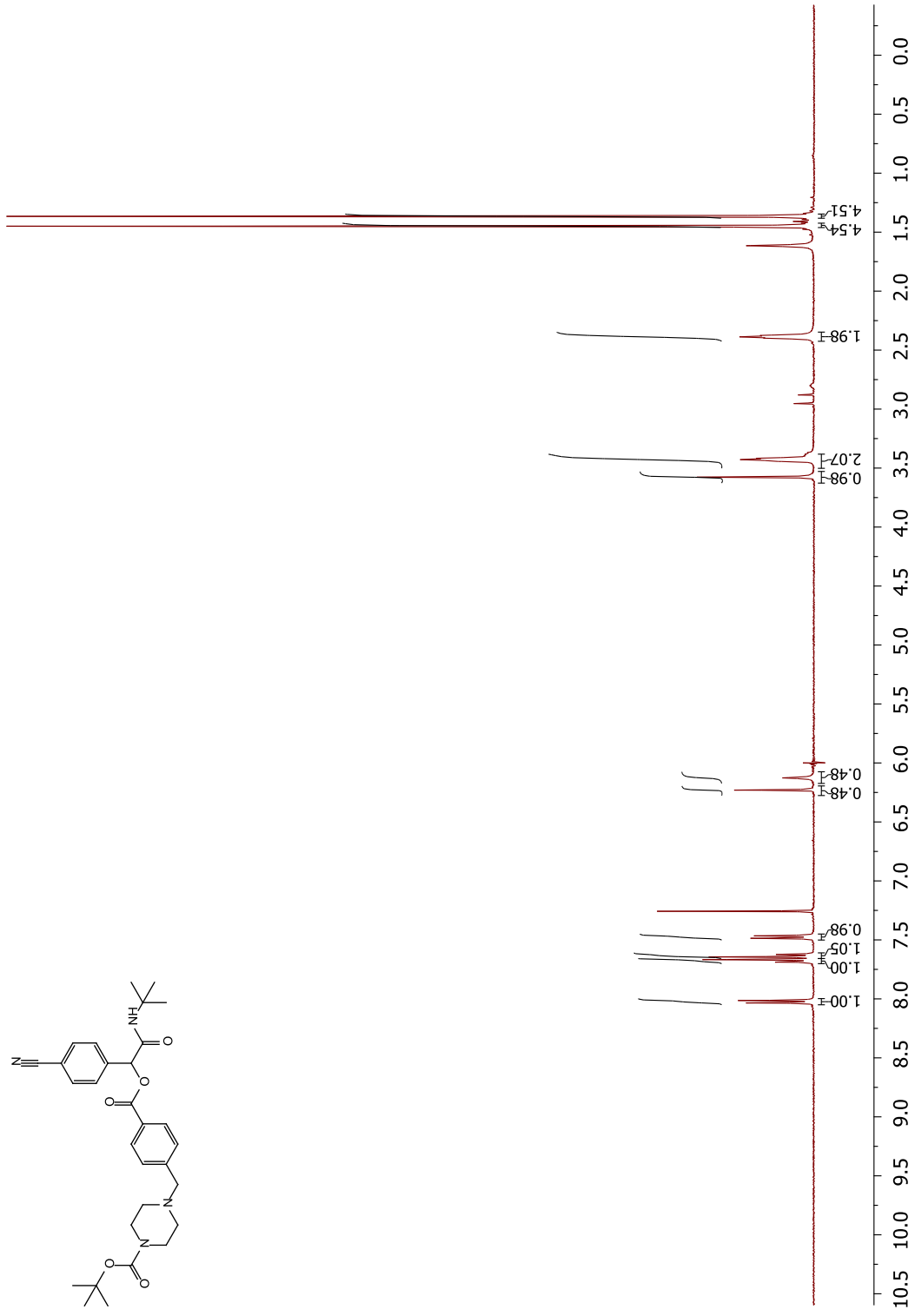


Figure 33. 400 MHz ^{1}H NMR of Compound **30c** in $CDCl_3$

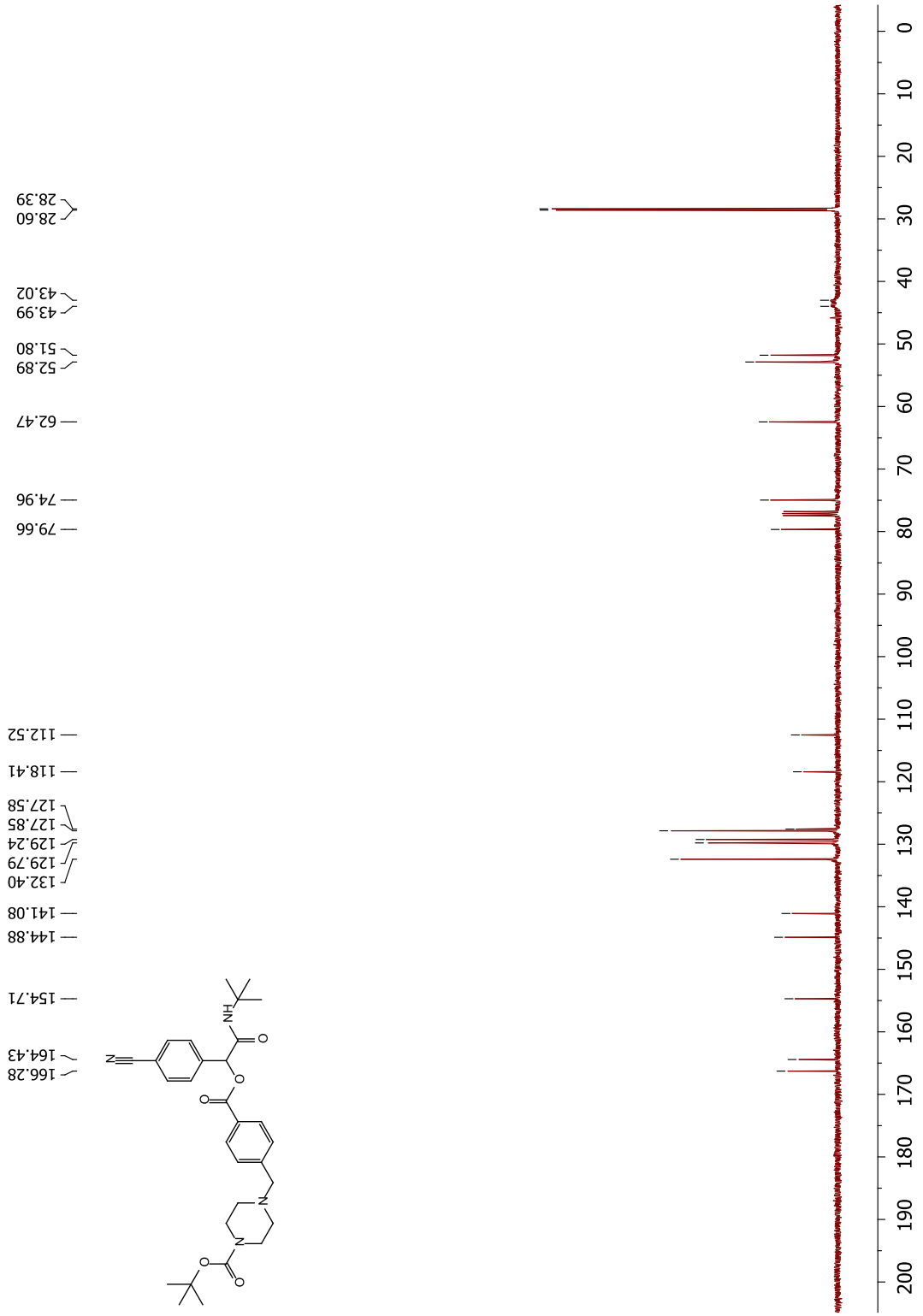


Figure 34. 101 MHz ^{13}C NMR of Compound **30c** in $CDCl_3$

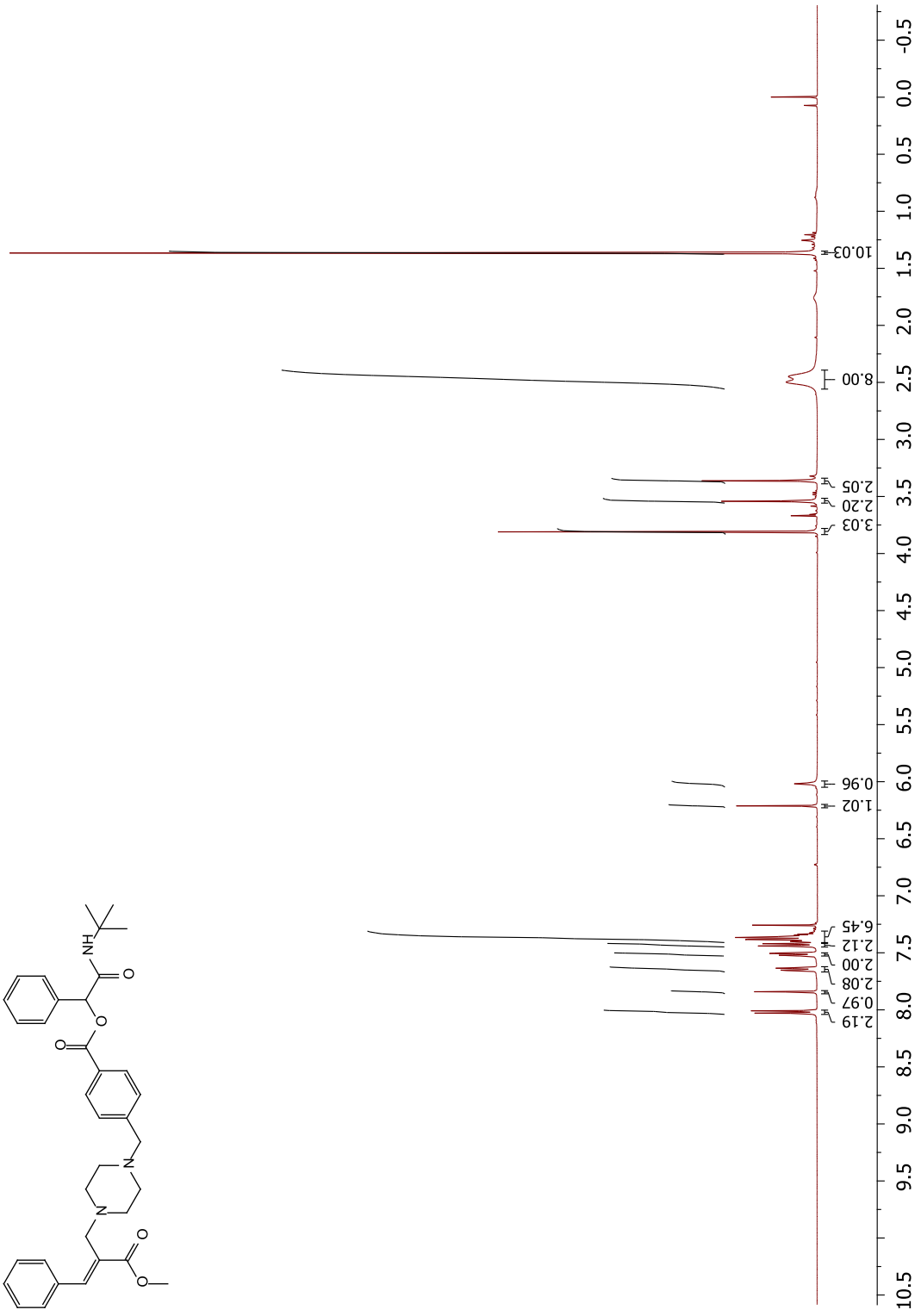


Figure 35. 400 MHz ^{1}H NMR of Compound **12a** in $CDCl_3$

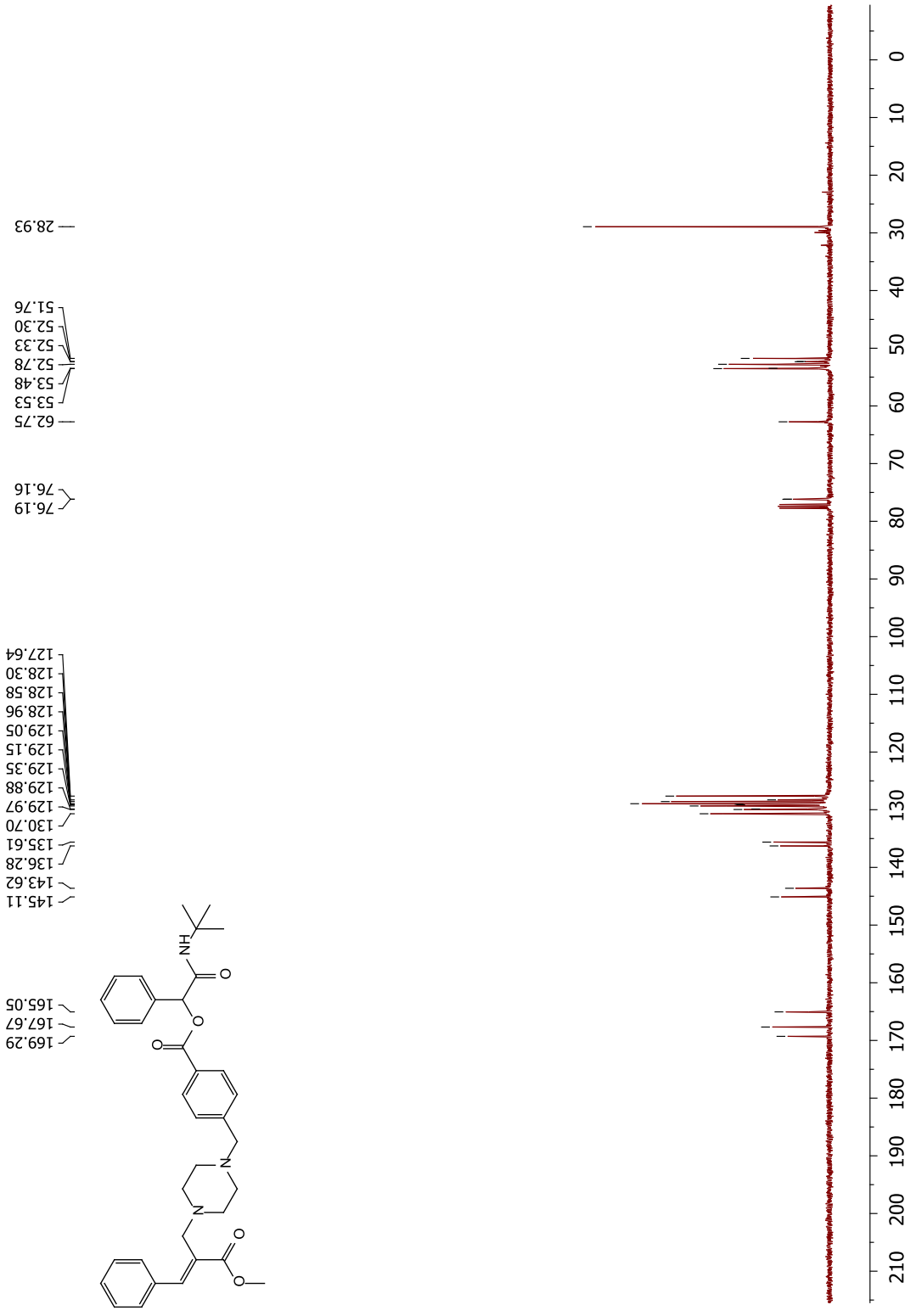


Figure 36. 101 MHz ^{13}C NMR of Compound **12a** in $CDCl_3$

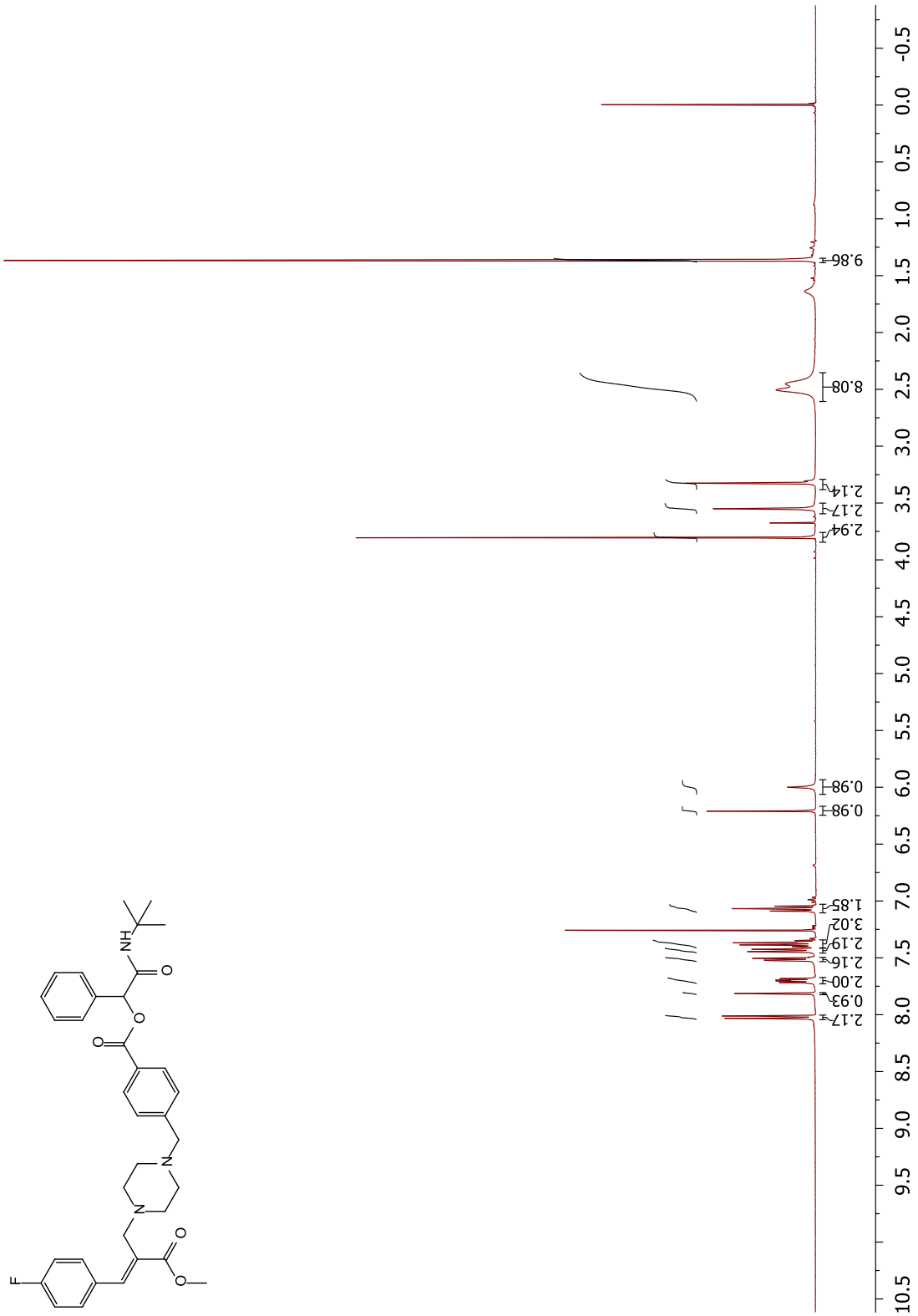


Figure 37. 400 MHz ^{1}H NMR of Compound **12b** in $CDCl_3$

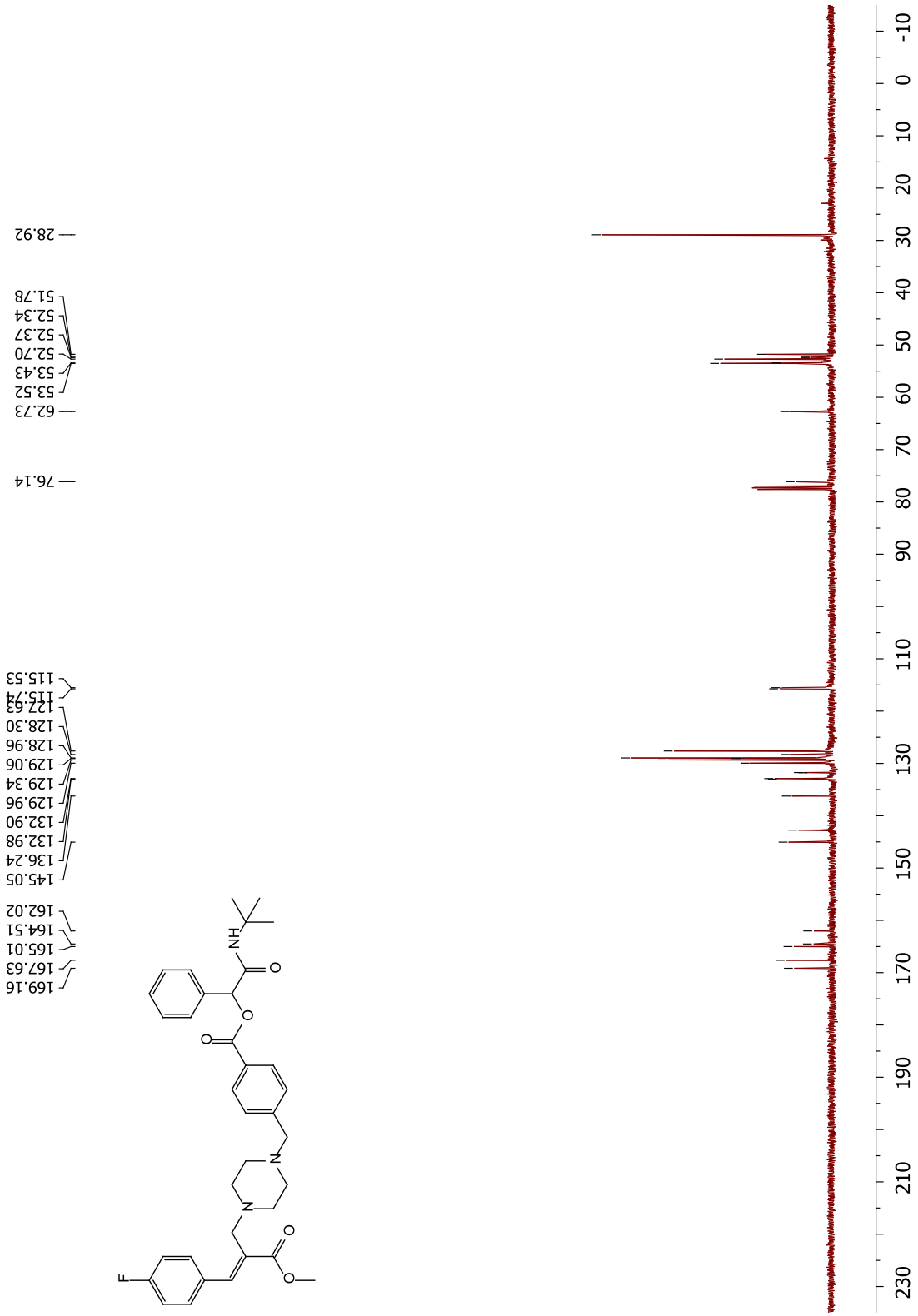


Figure 38. 101 MHz ^{13}C NMR of Compound **12b** in $CDCl_3$

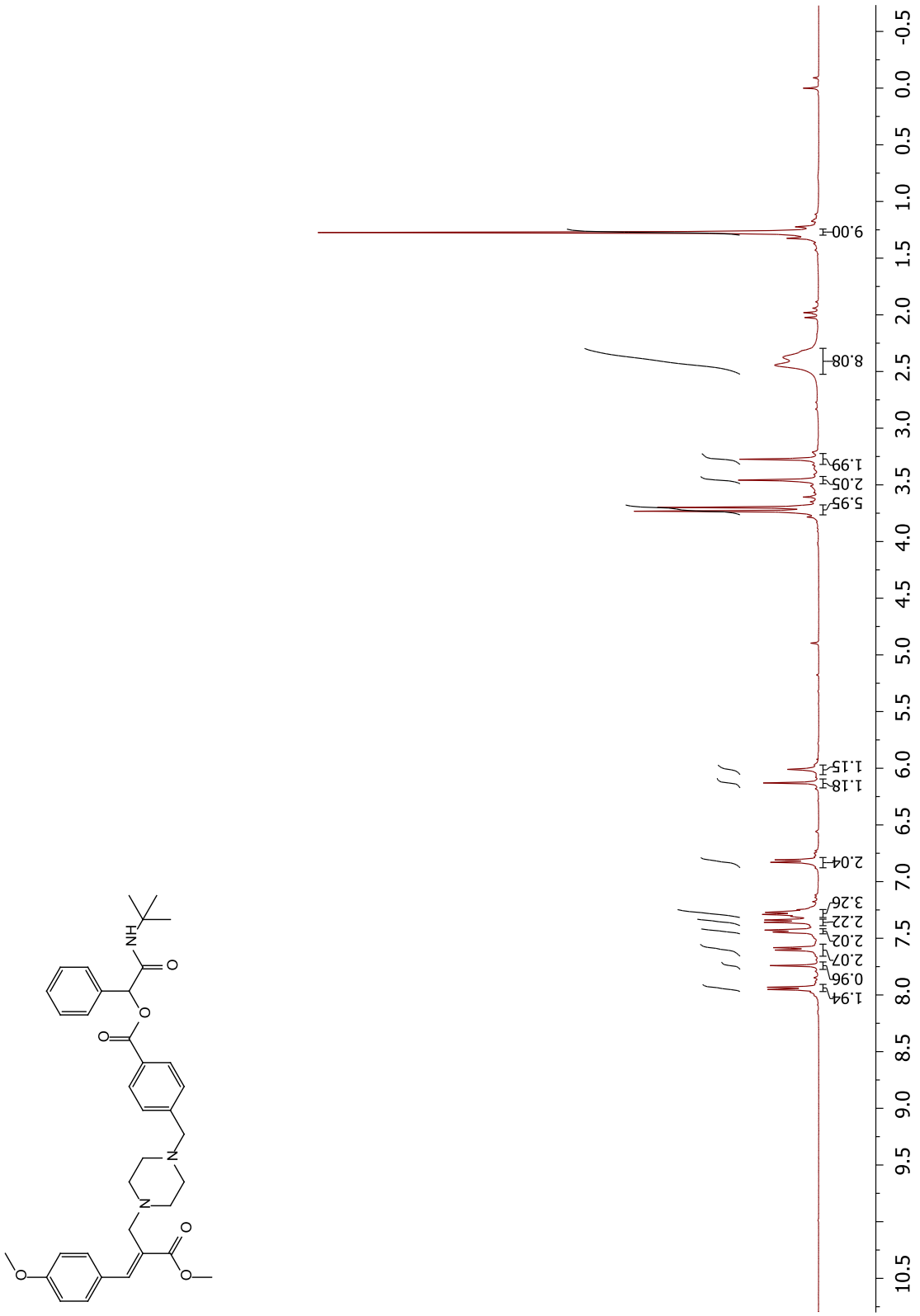


Figure 39. 400 MHz ^{1}H NMR of Compound **12c** in $CDCl_3$

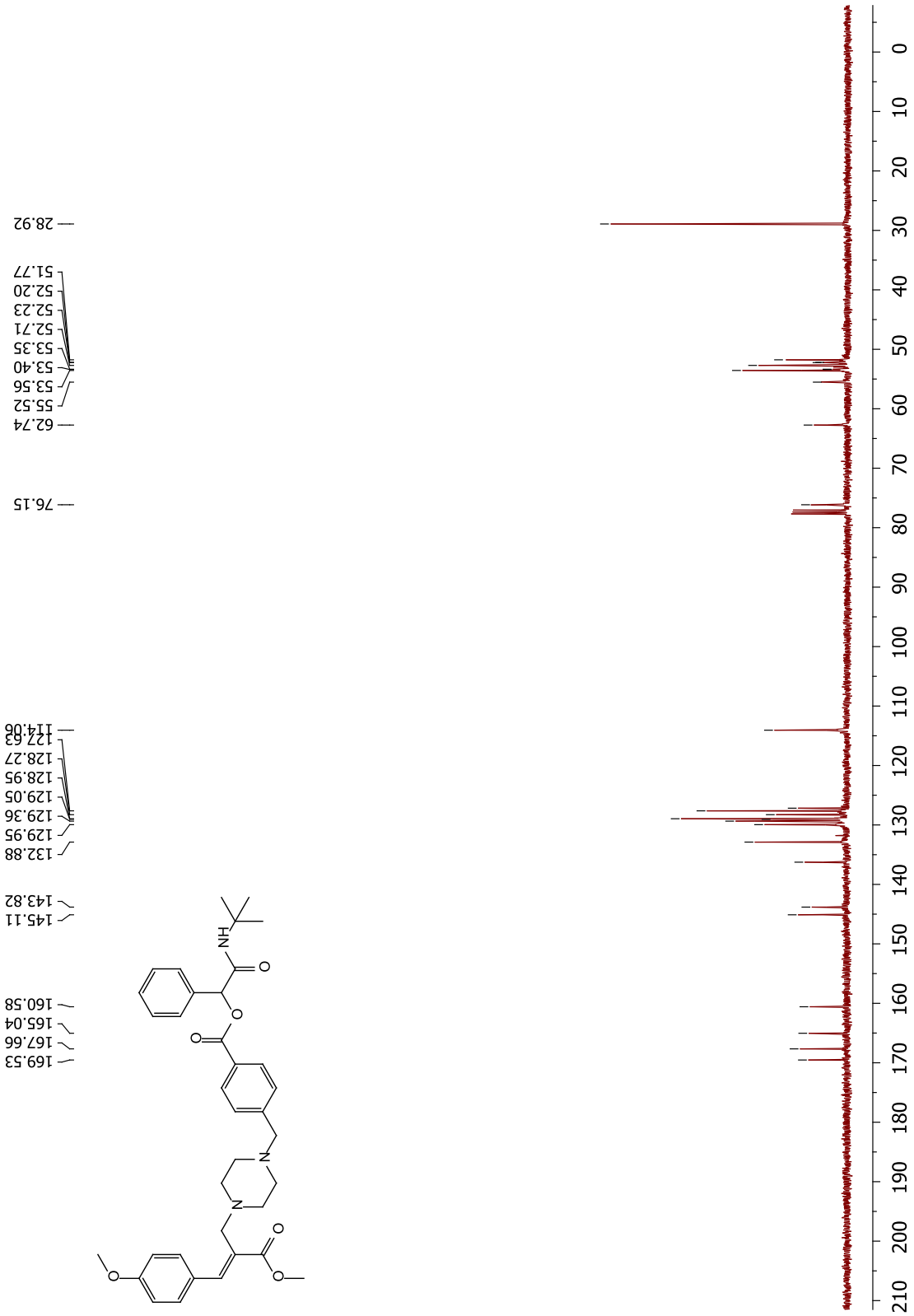


Figure 40. 101 MHz ^{13}C NMR of Compound **12c** in $CDCl_3$

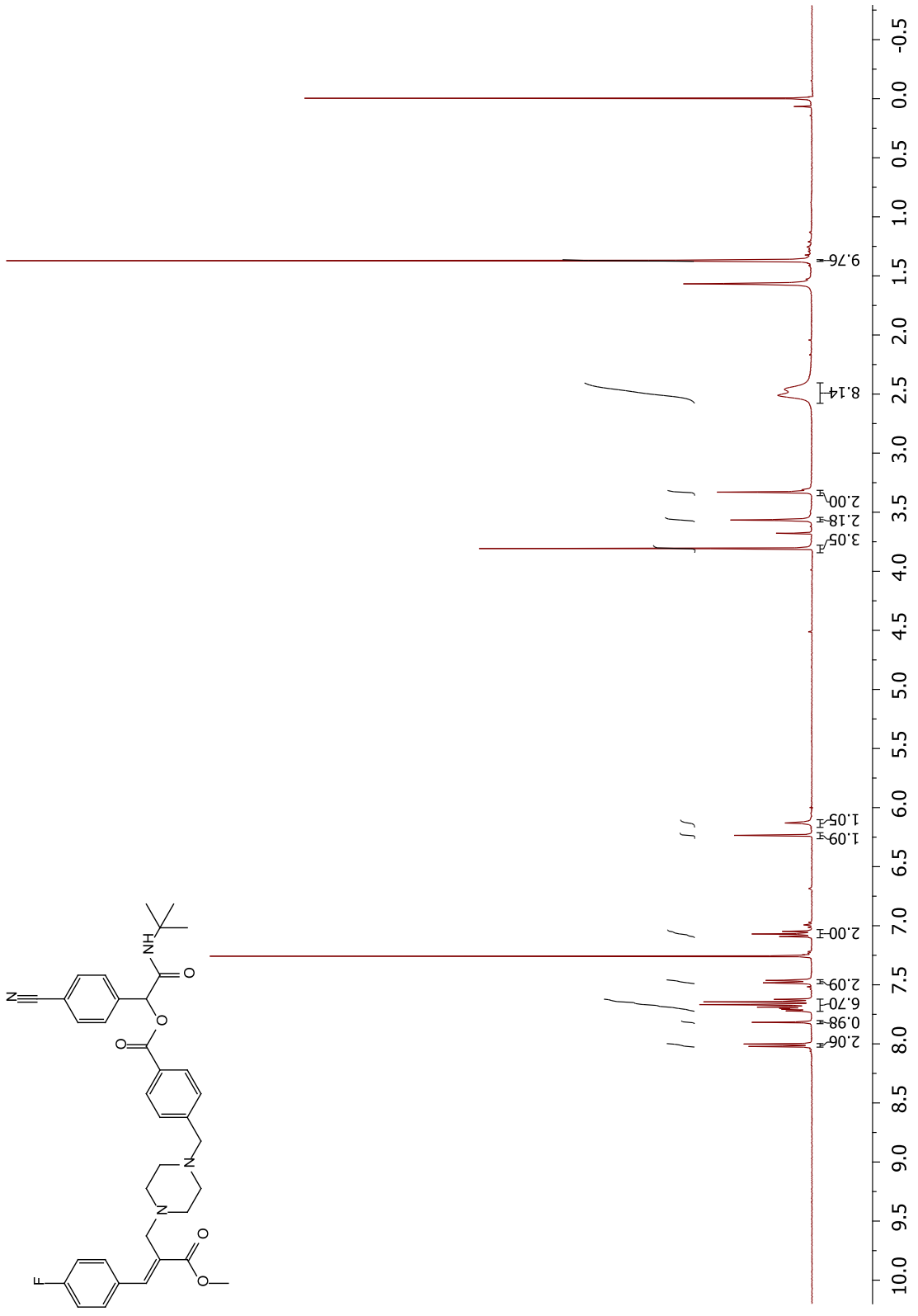


Figure 41. 400 MHz ^{1}H NMR of Compound **12d** in $CDCl_3$

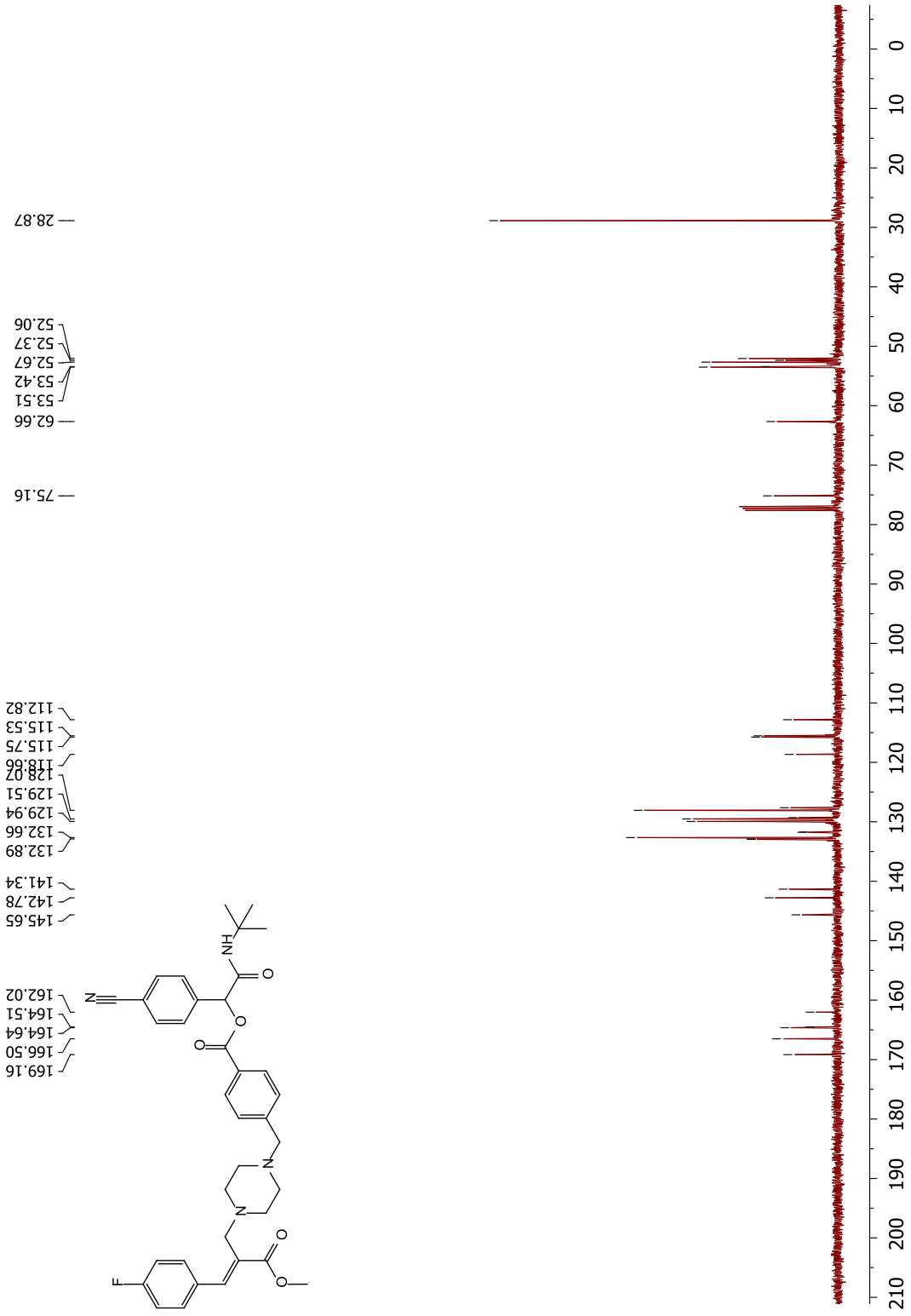


Figure 42. 101 MHz ^{13}C NMR of Compound **12d** in $CDCl_3$

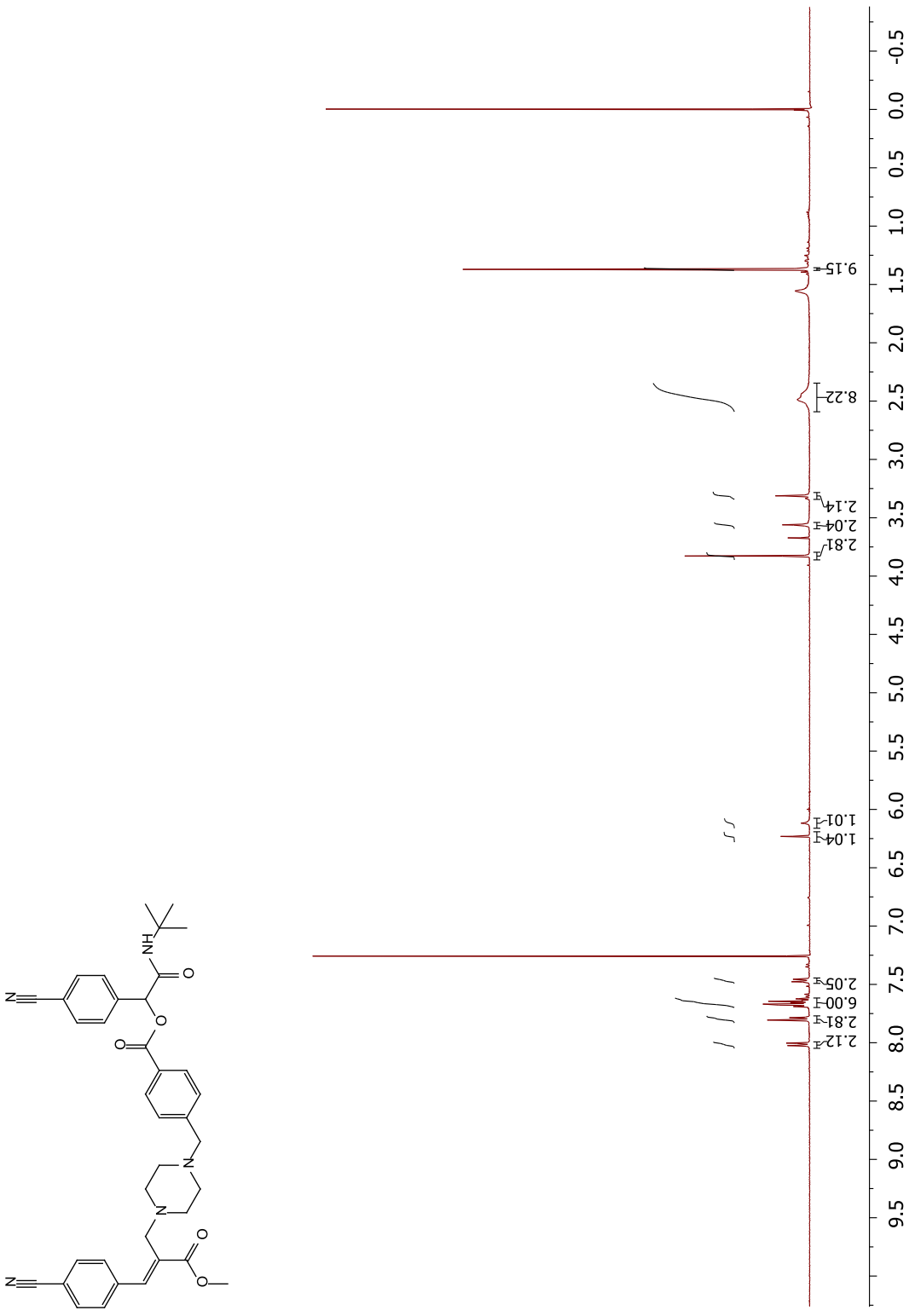


Figure 43. 400 MHz ^{1}H NMR of Compound **12e** in $CDCl_3$

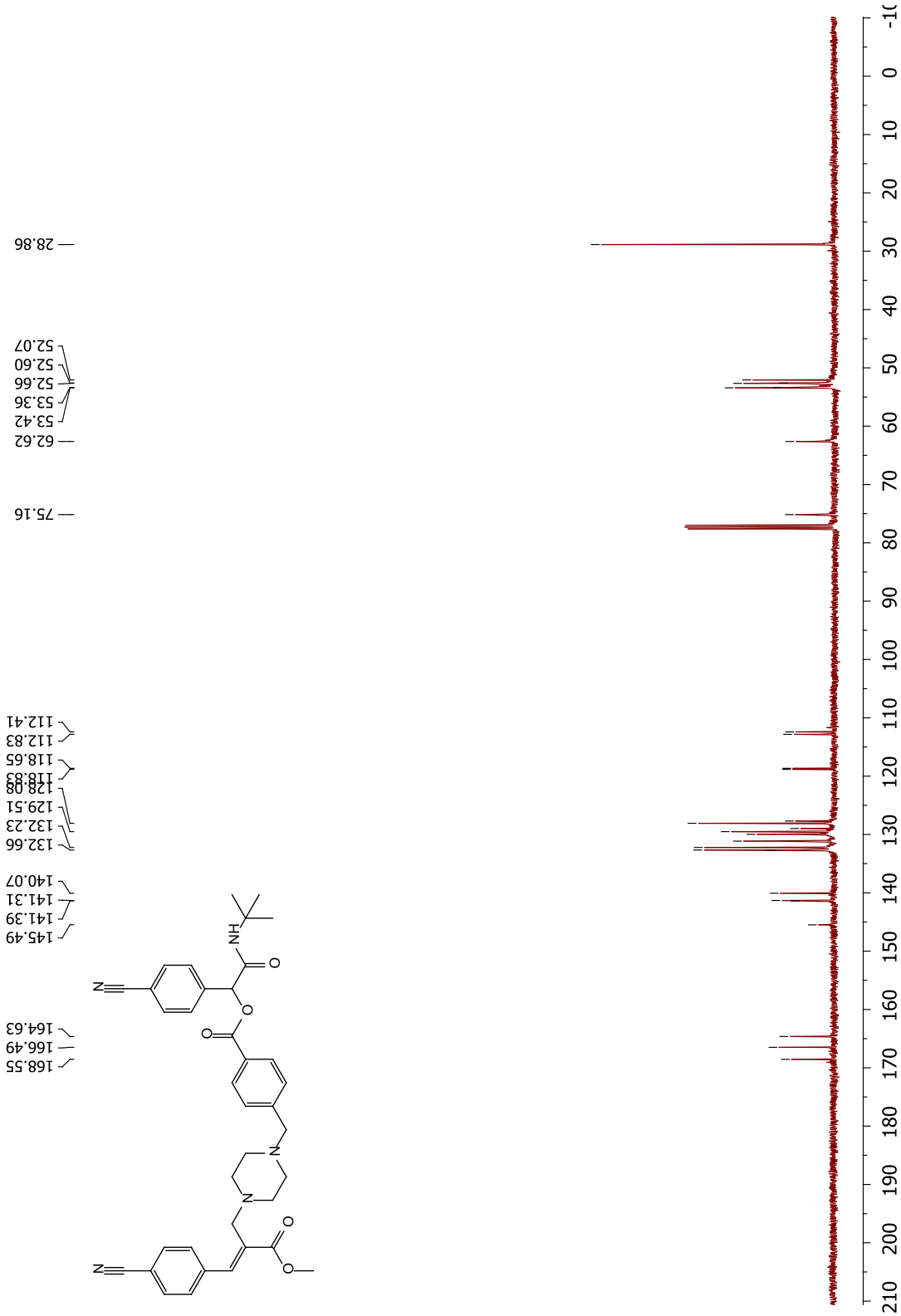


Figure 44. 101 MHz ^{13}C NMR of Compound **12e** in $CDCl_3$

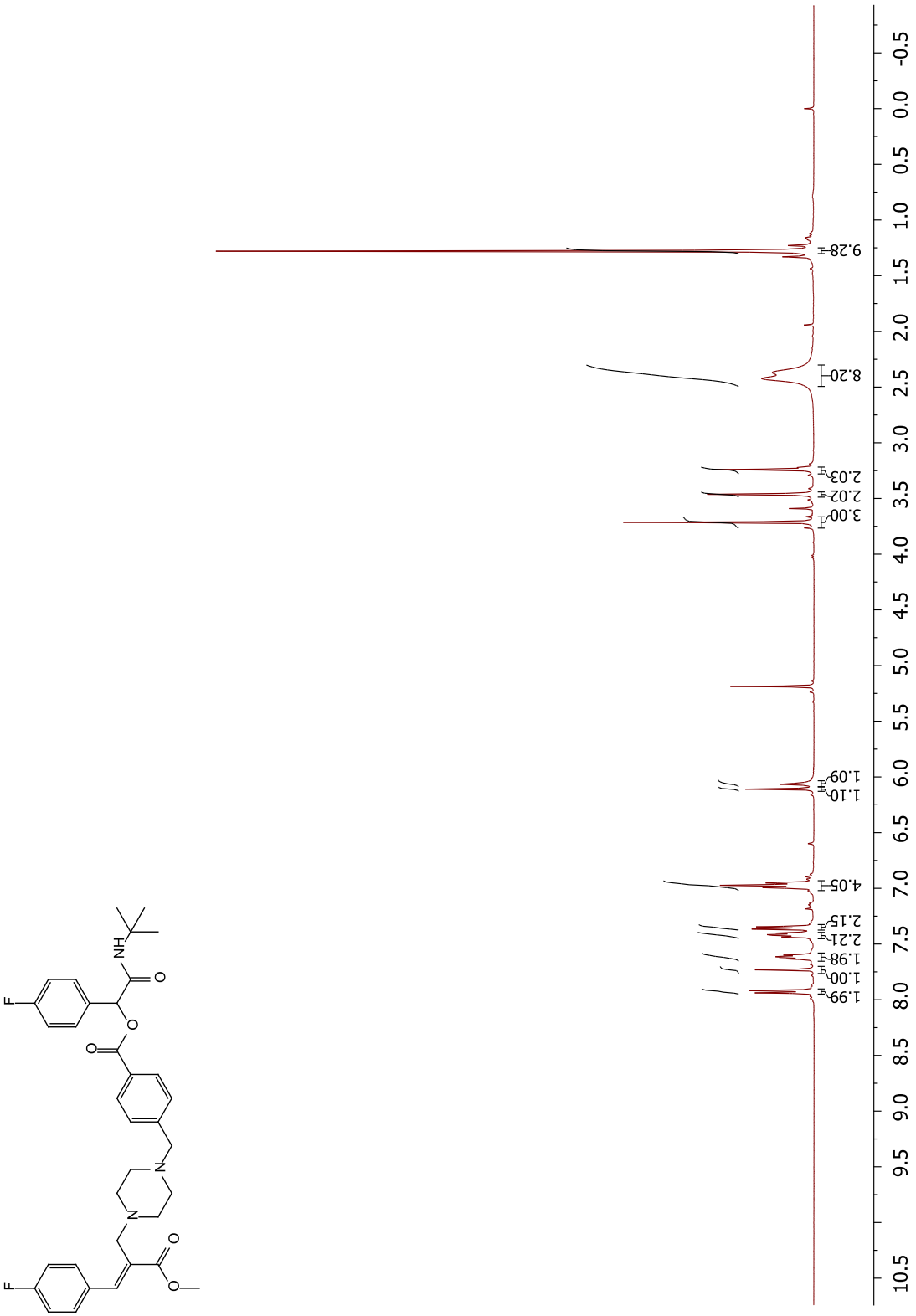


Figure 45. 400 MHz ^{1}H NMR of Compound **12f** in $CDCl_3$

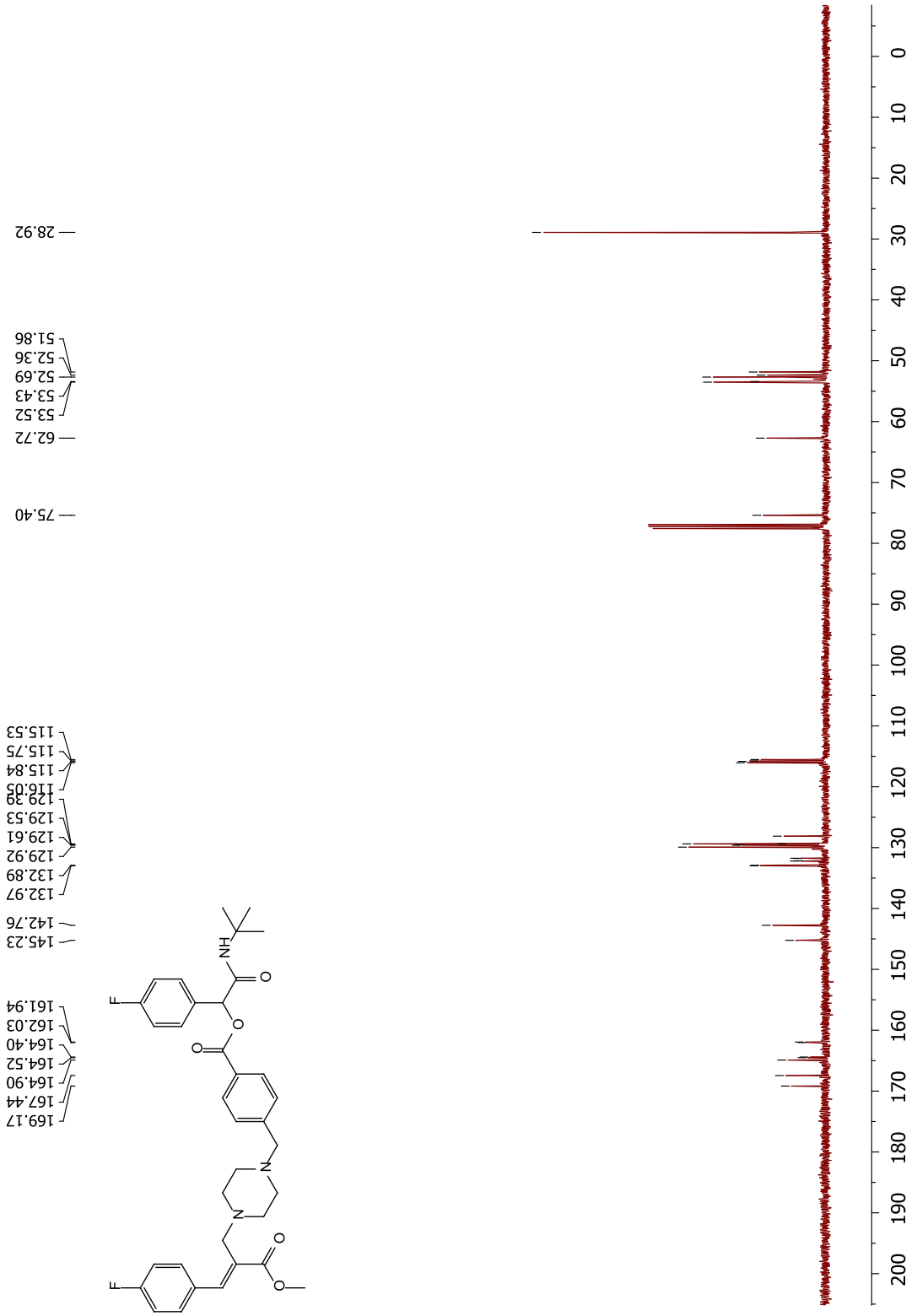


*Figure 46.*101 MHz ^{13}C NMR of Compound **12f** in $CDCl_3$

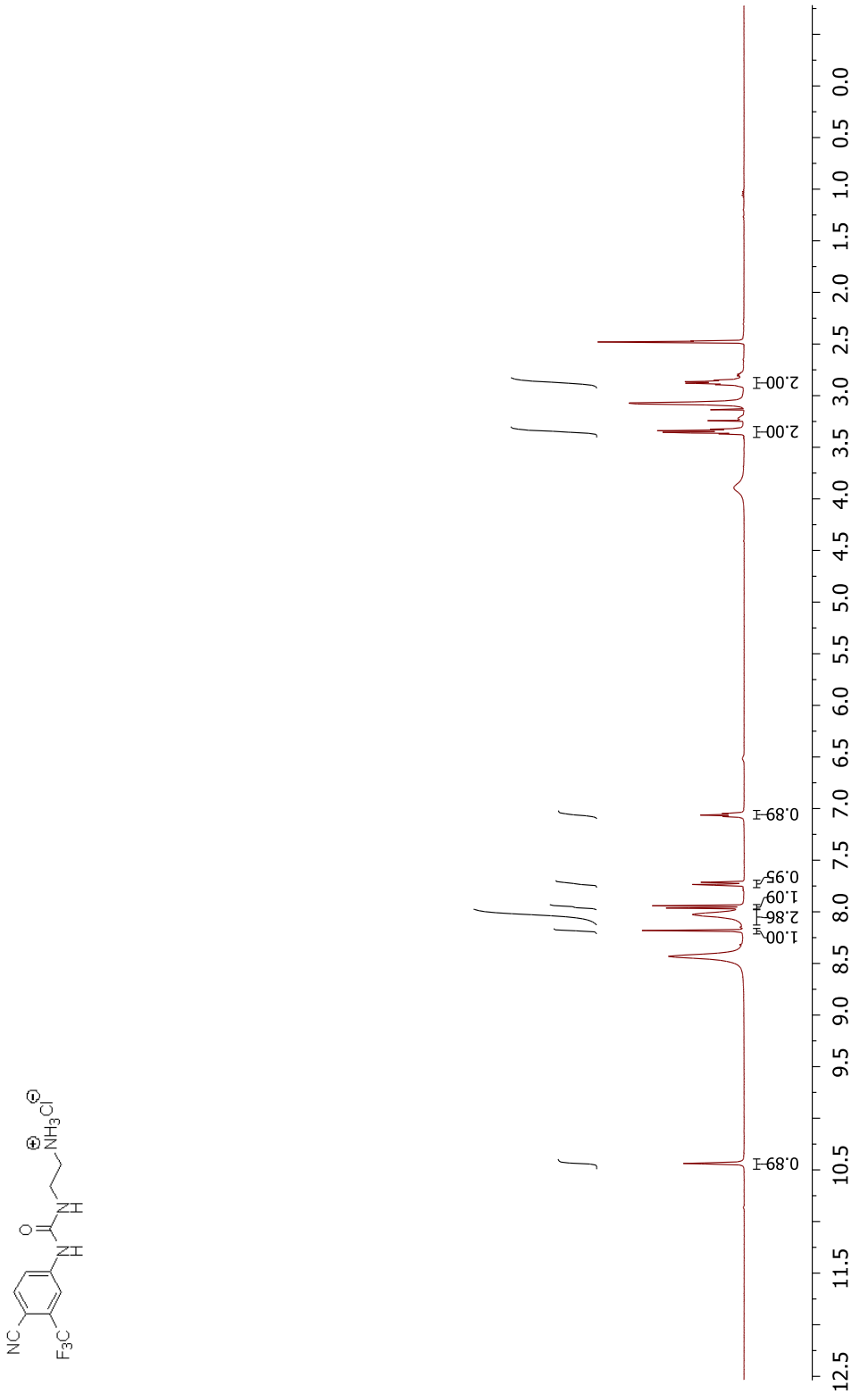


Figure 47. 400 MHz ^{1}H NMR of Compound **25b** in DMSO-d_6

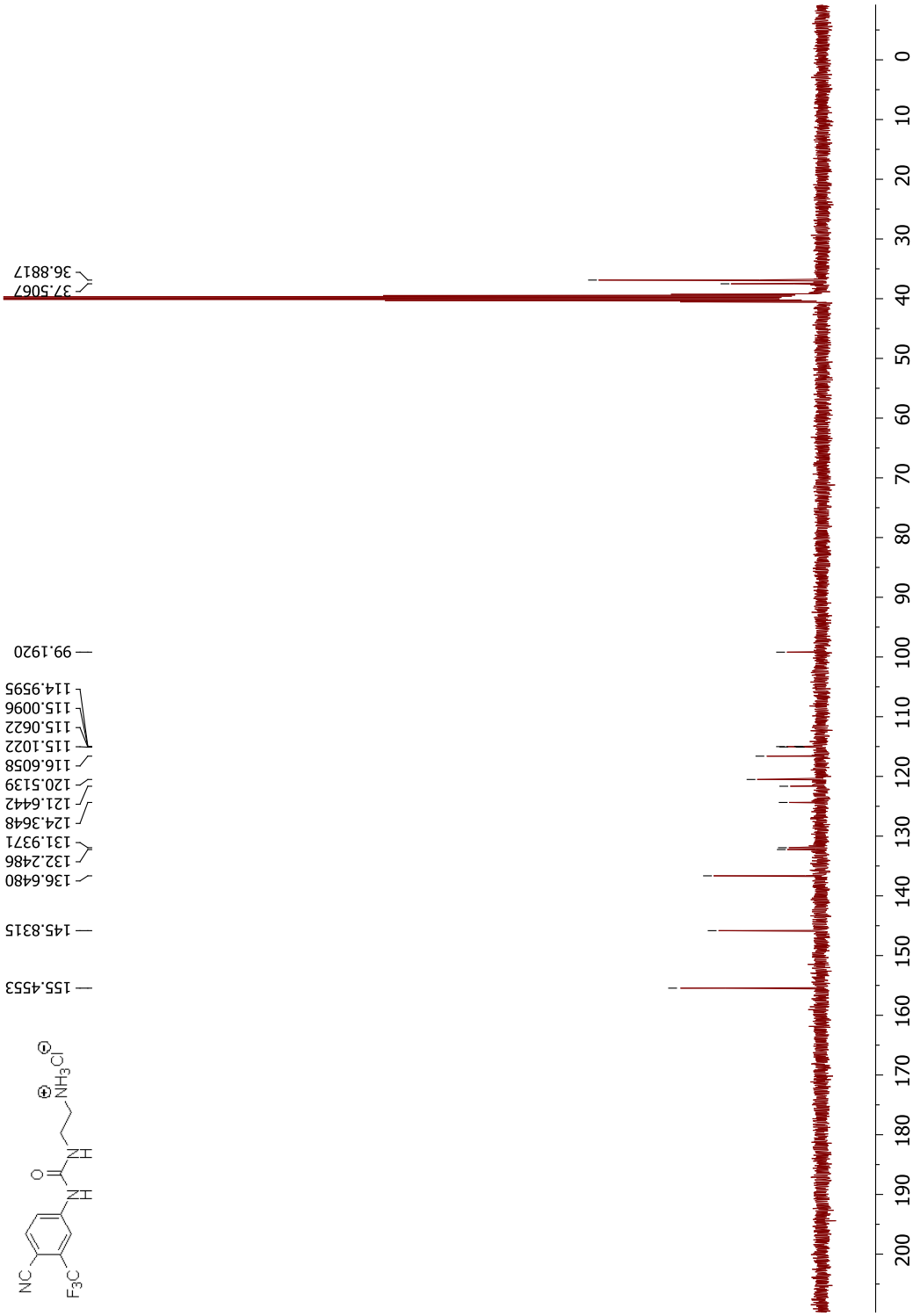


Figure 48. 101 MHz ^{13}C NMR of Compound **25b** in DMSO-d_6

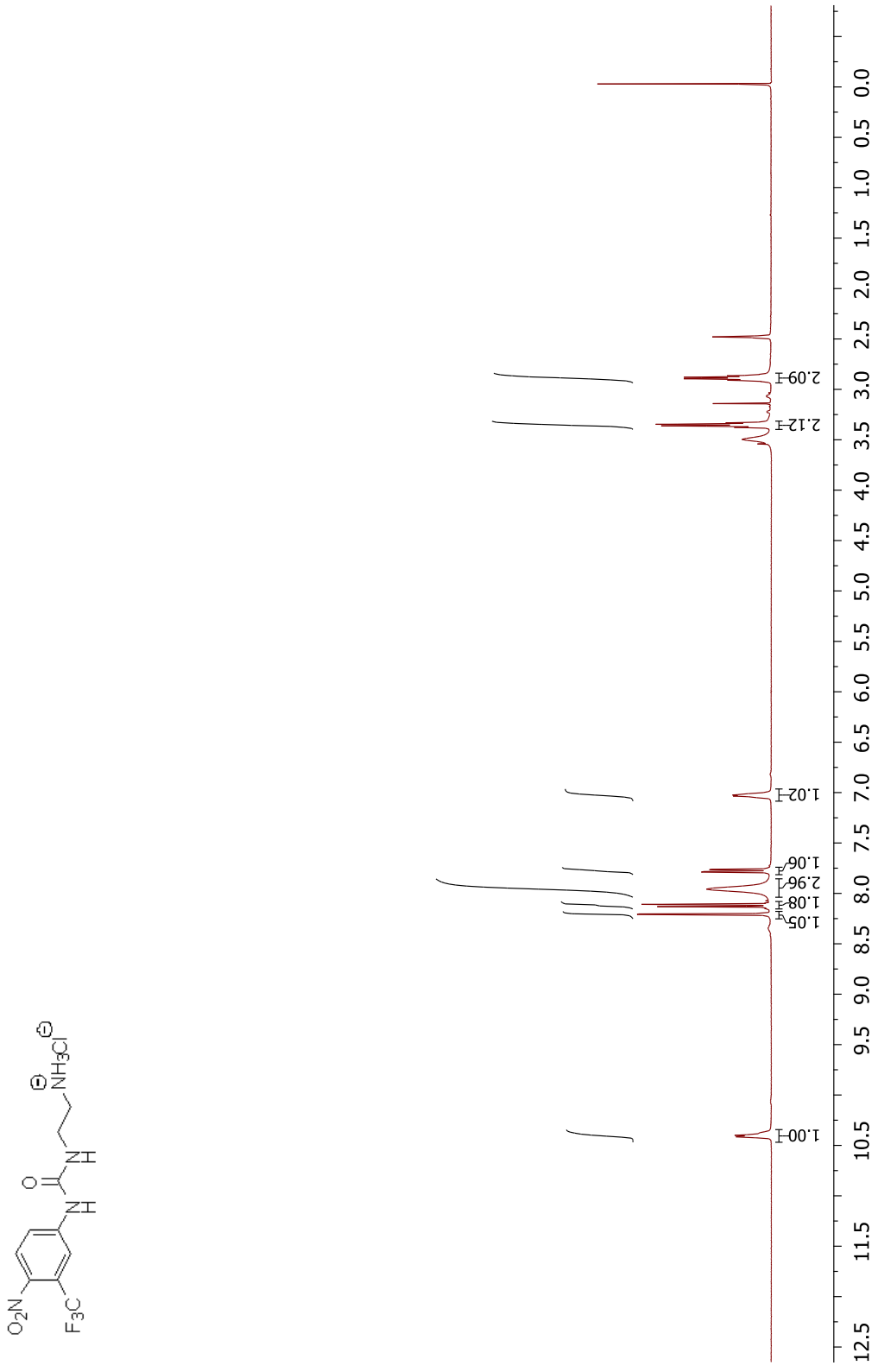


Figure 49. 400 MHz ^{1}H NMR of Compound **25c** in DMSO-d_6

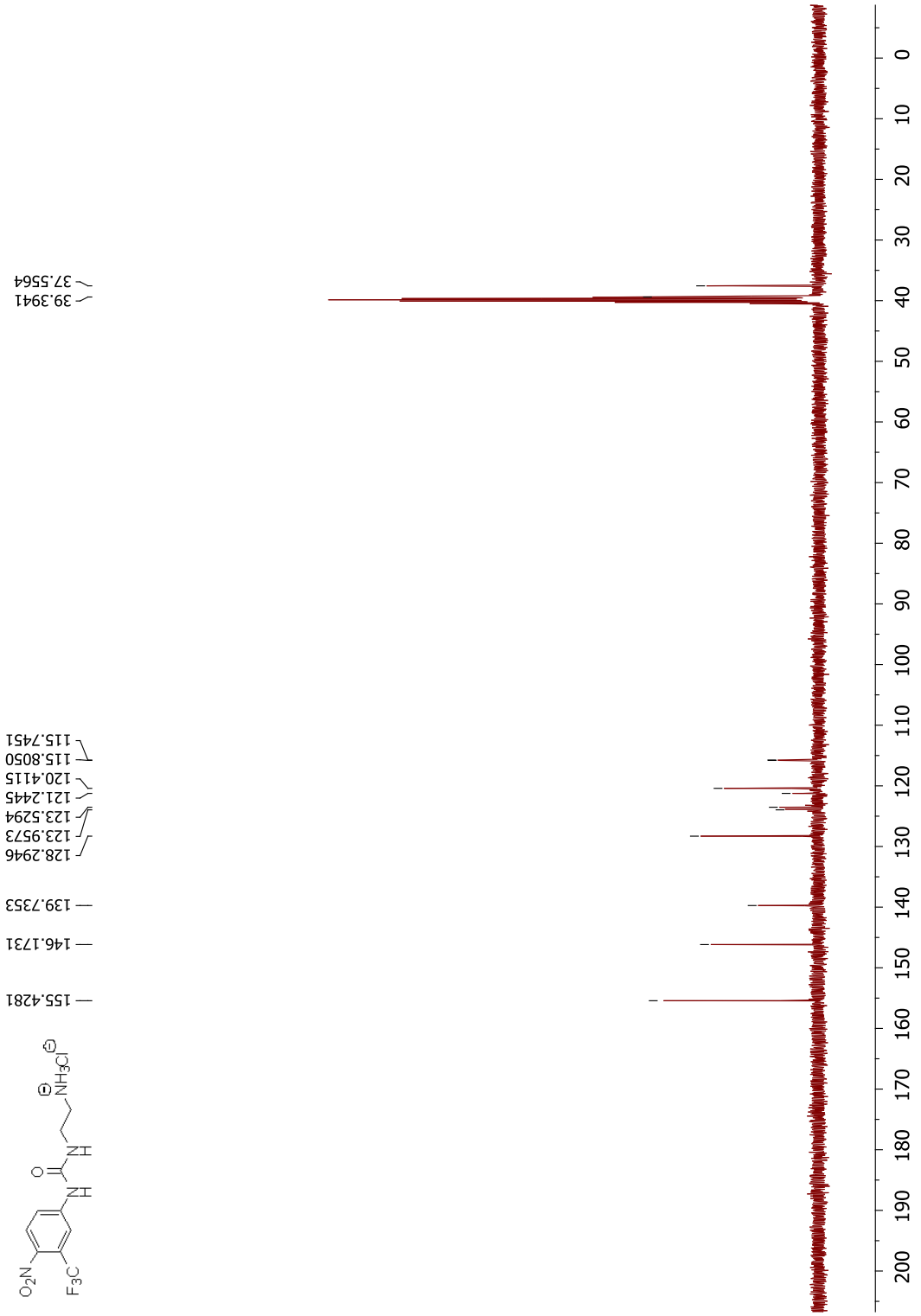


Figure 50. 101 MHz ^{13}C NMR of Compound **25c** in DMSO-d_6

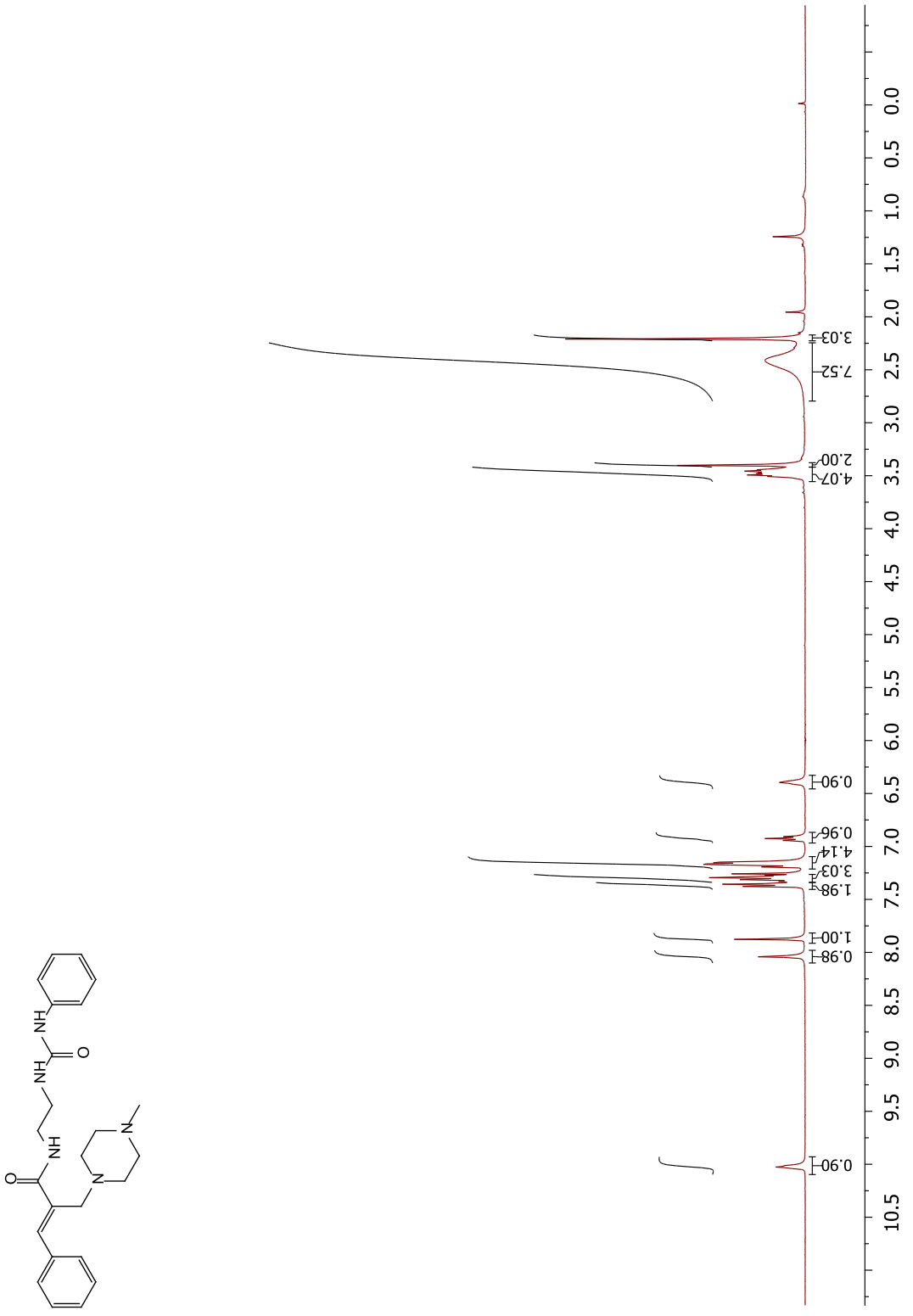


Figure 51. 400 MHz ^{1}H NMR of Compound **13a** in $CDCl_3$

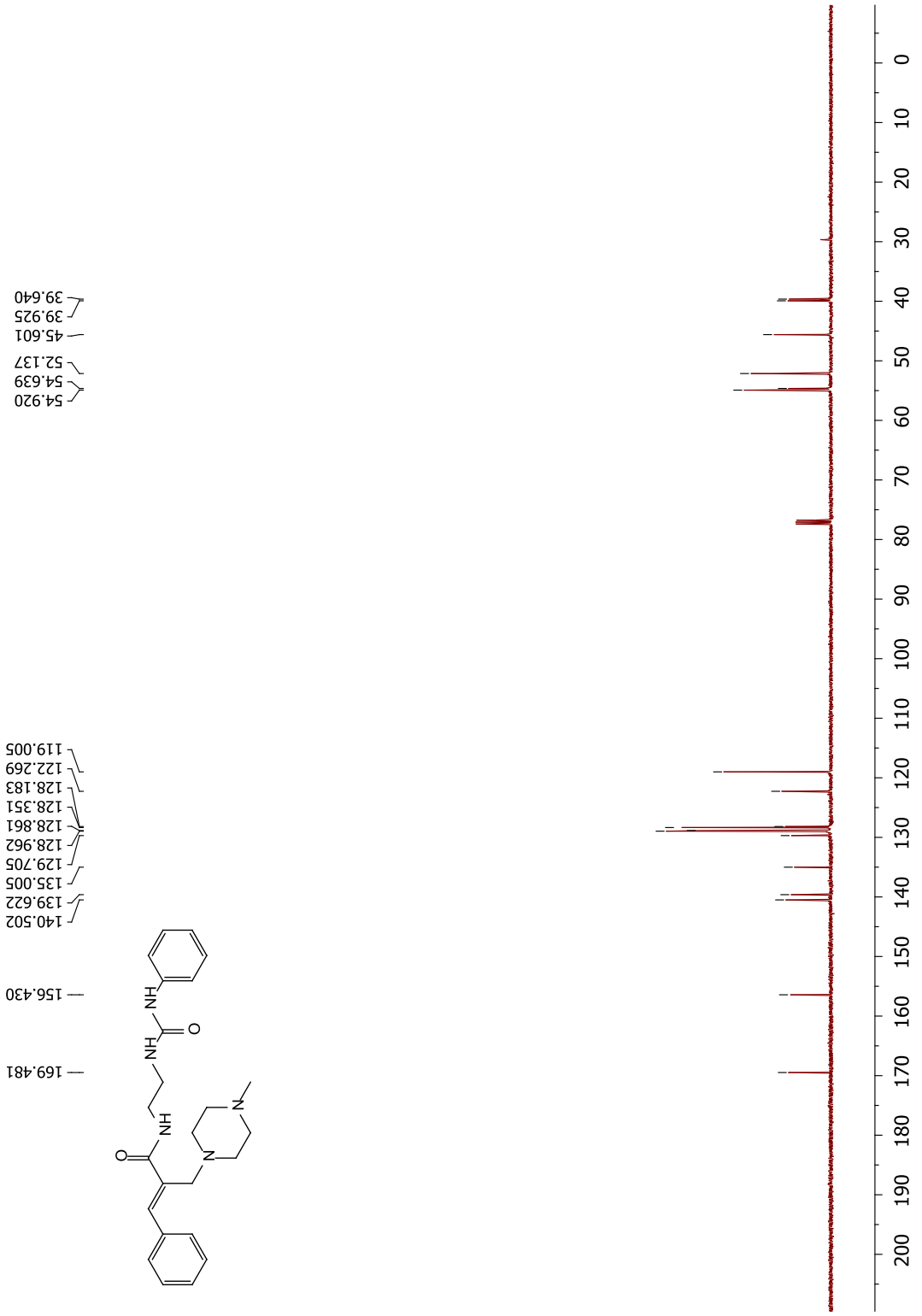


Figure 52. 101 MHz ^{13}C NMR of Compound **13a** in $CDCl_3$

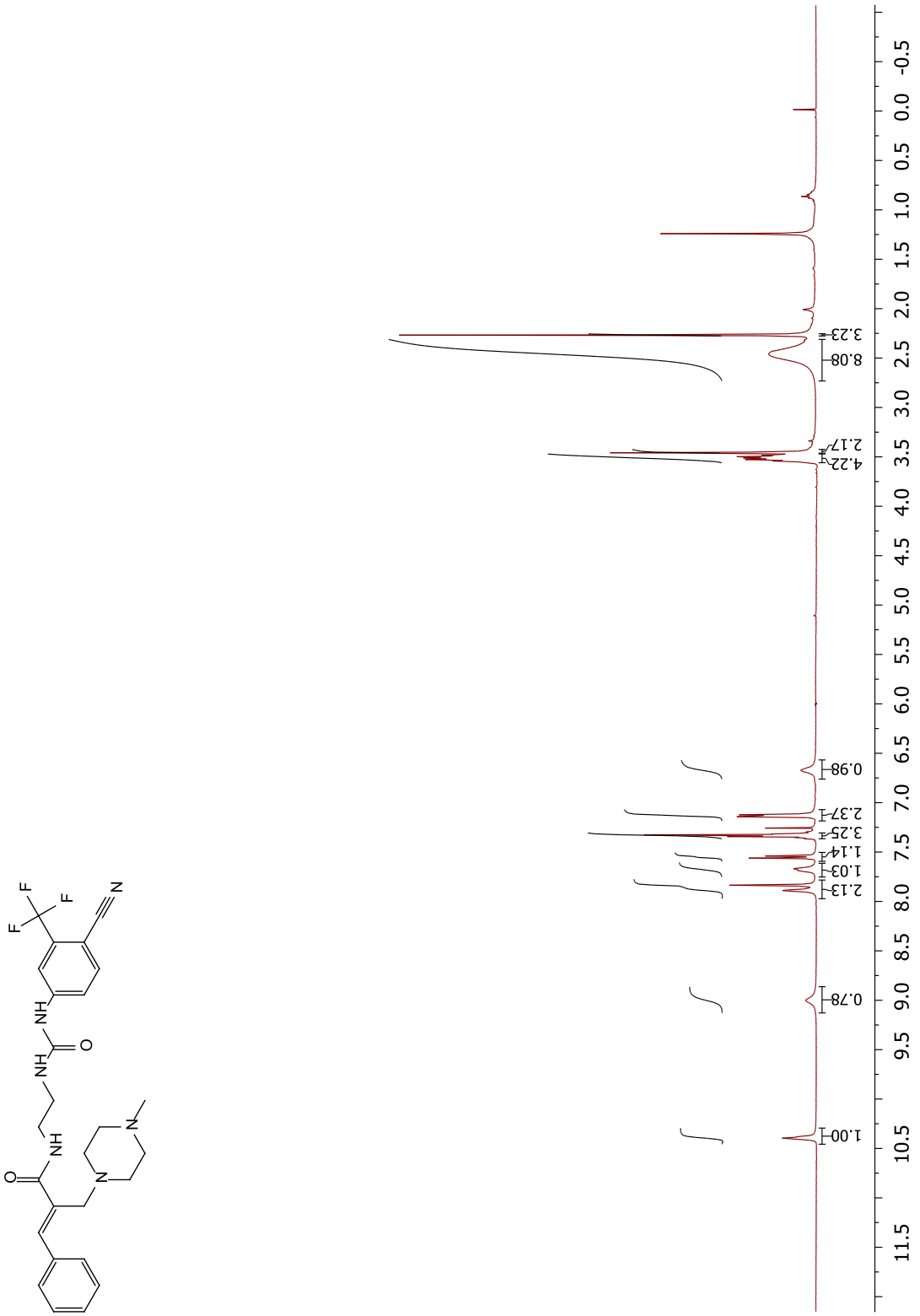


Figure 53. 400 MHz ^{1}H NMR of Compound **13b** in $CDCl_3$

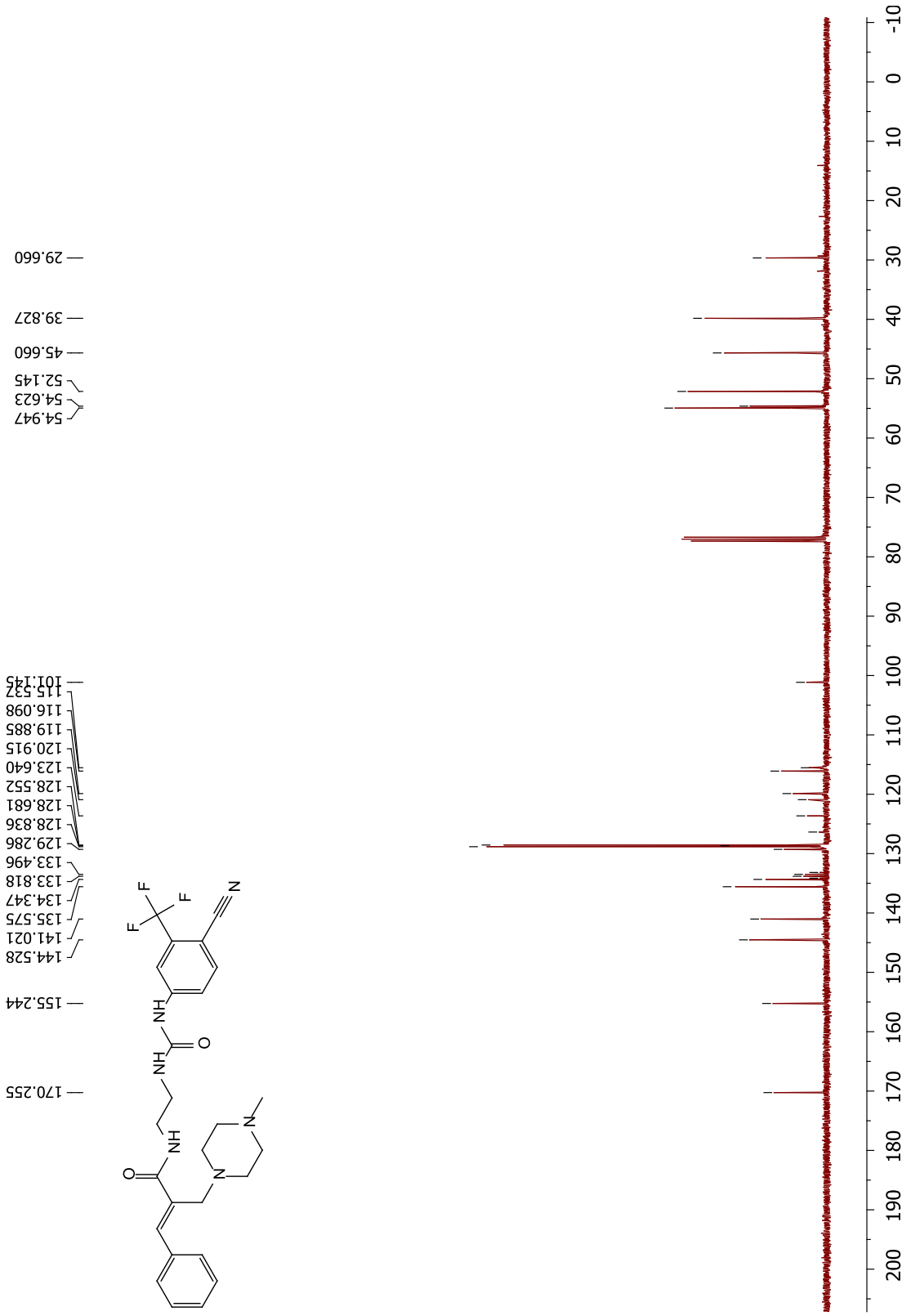


*Figure 54.*101 MHz ^{13}C NMR of Compound **13b** in $CDCl_3$

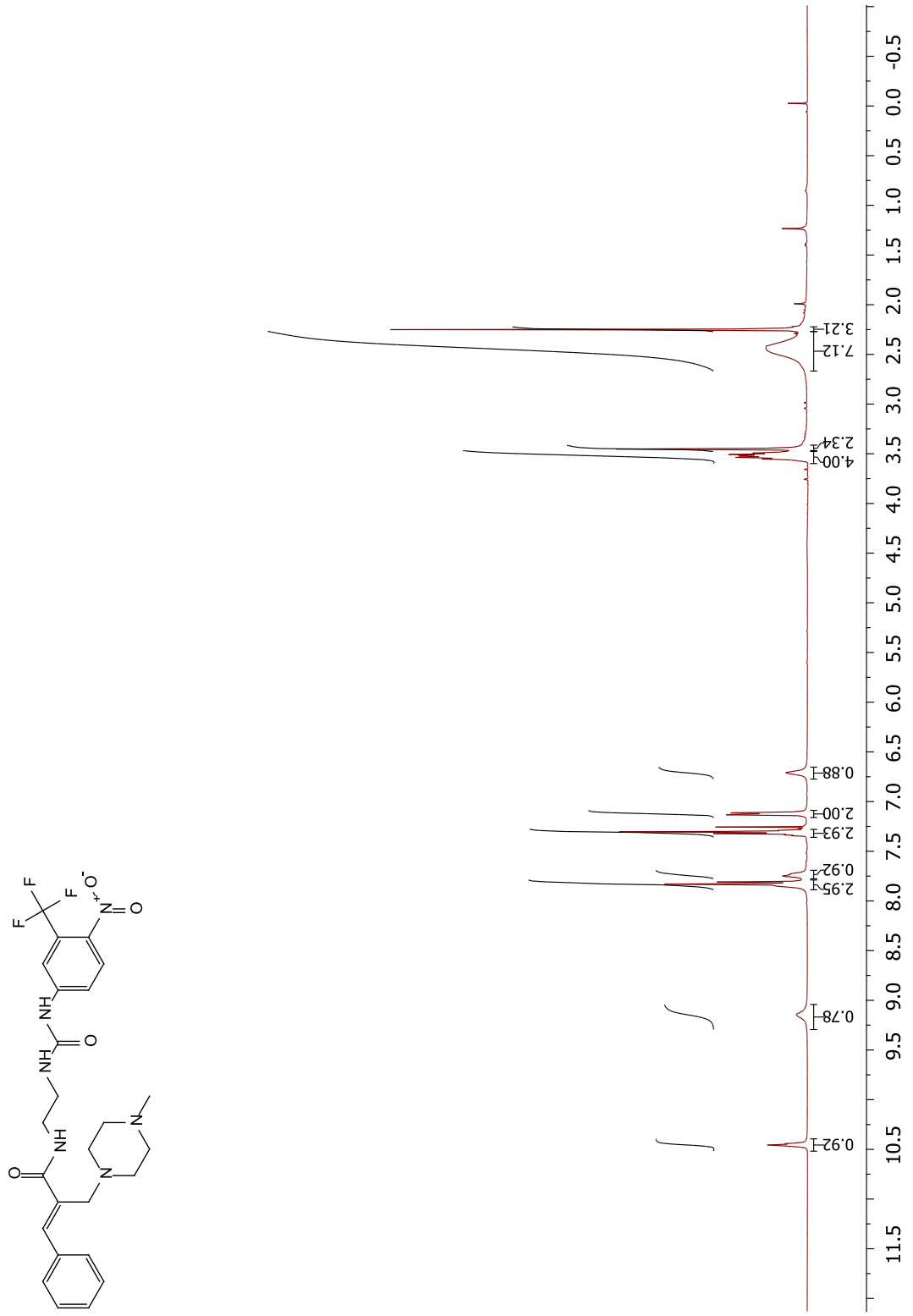


Figure 55. 400 MHz ^{1}H NMR of Compound **13c** in $CDCl_3$

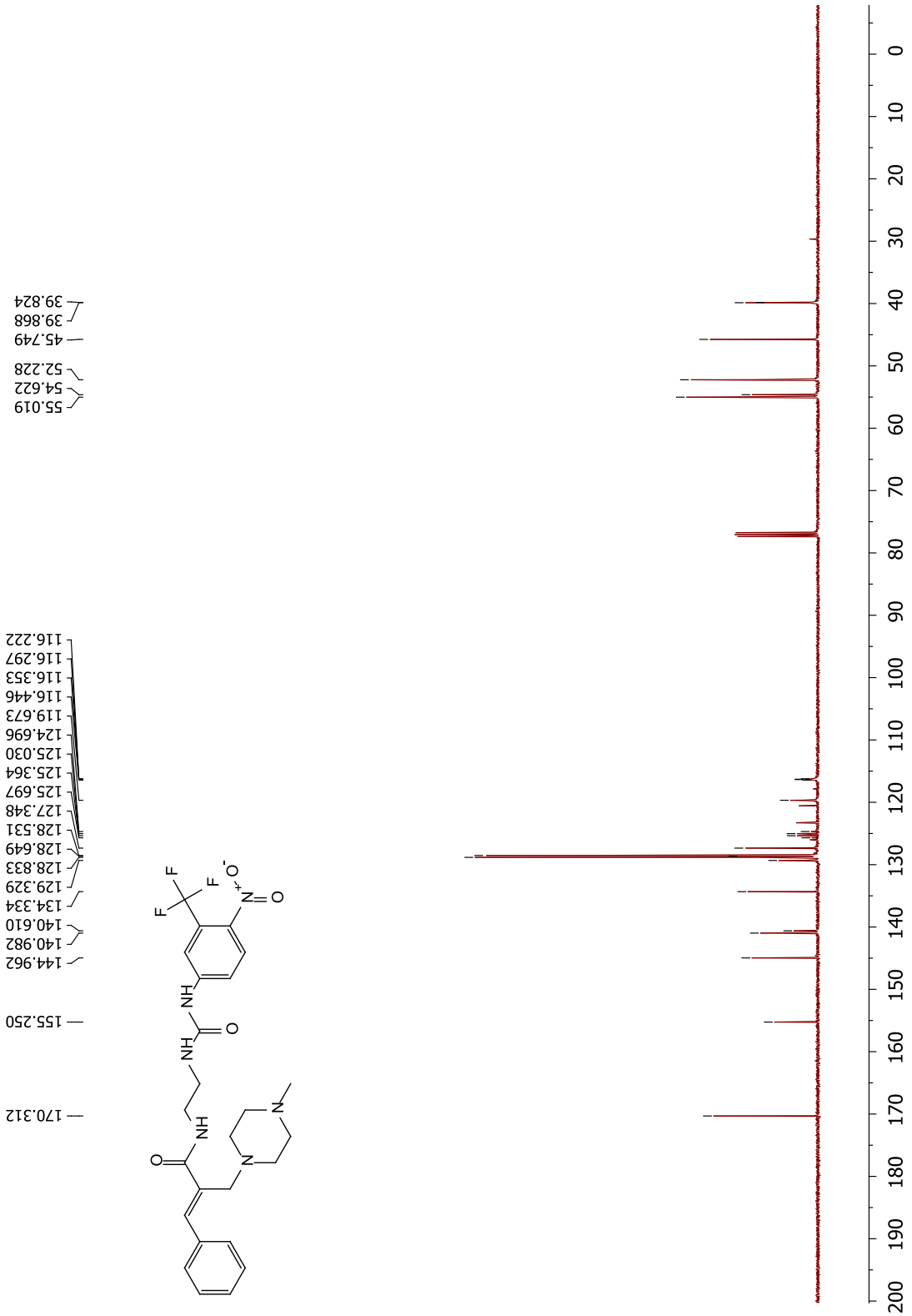


Figure 56. 101 MHz ^{13}C NMR of Compound **13c** in $CDCl_3$

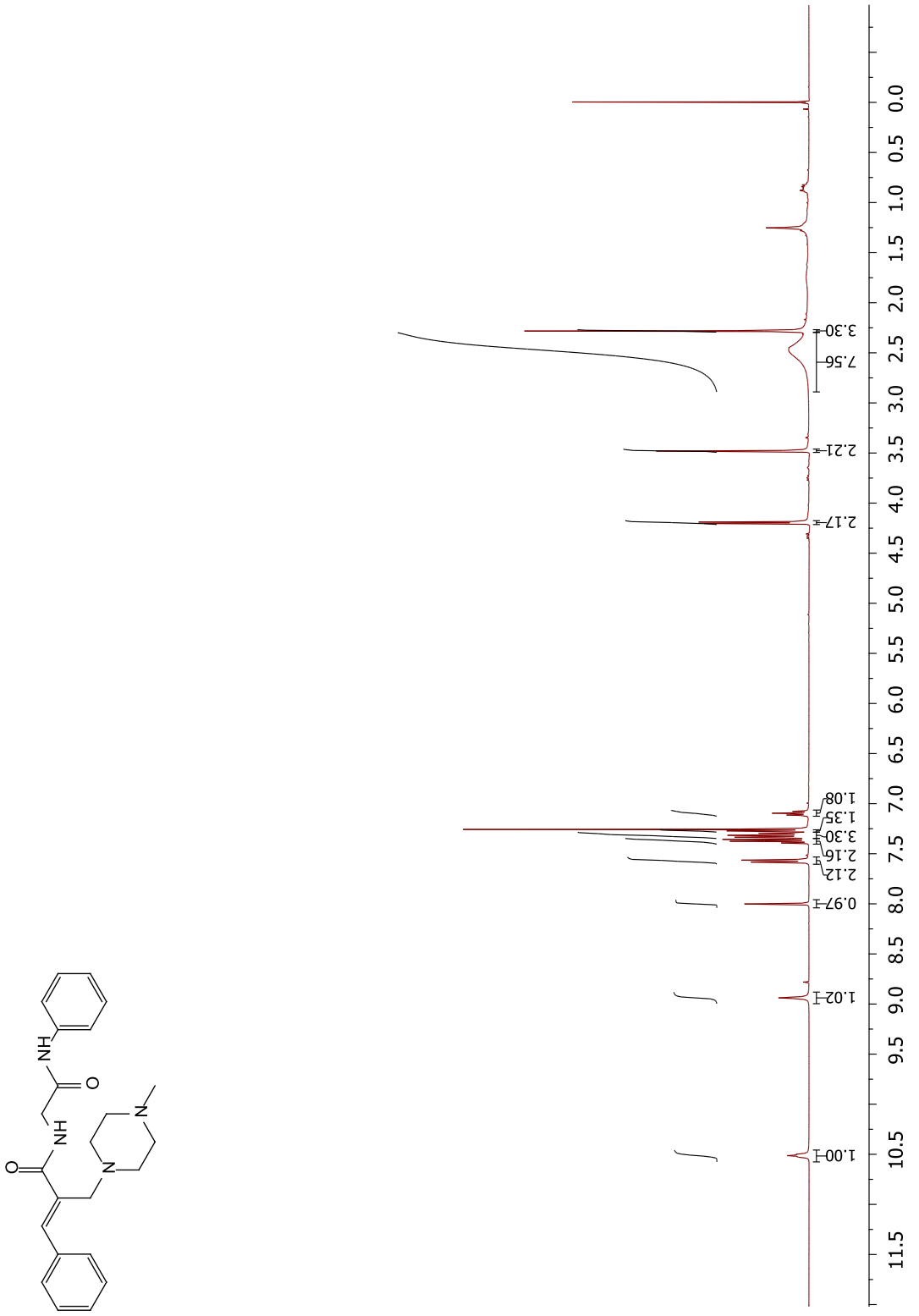


Figure 57. 400 MHz ^{1}H NMR of Compound **14a** in $CDCl_3$

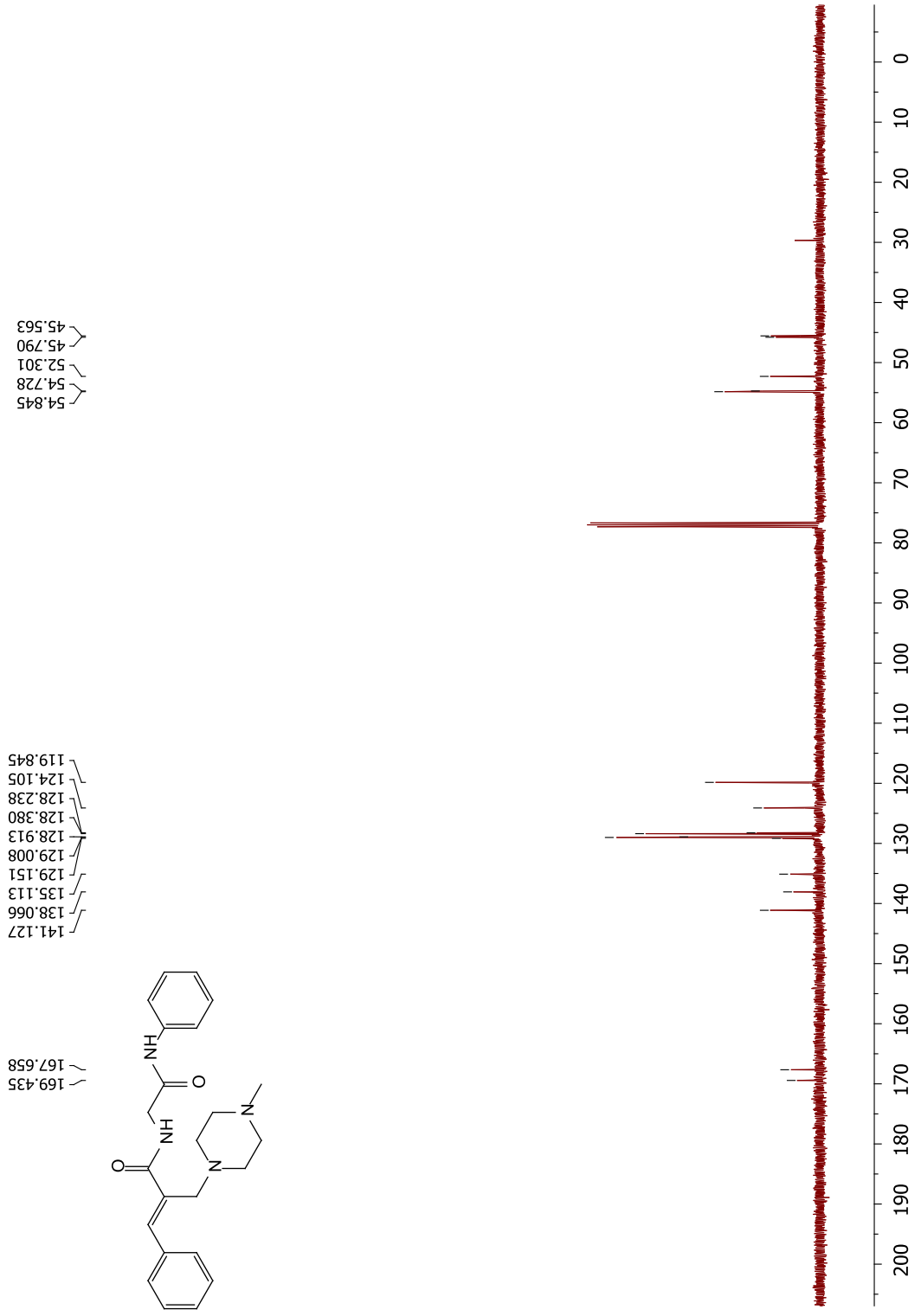


Figure 58. 101 MHz ^{13}C NMR of Compound **14a** in $CDCl_3$

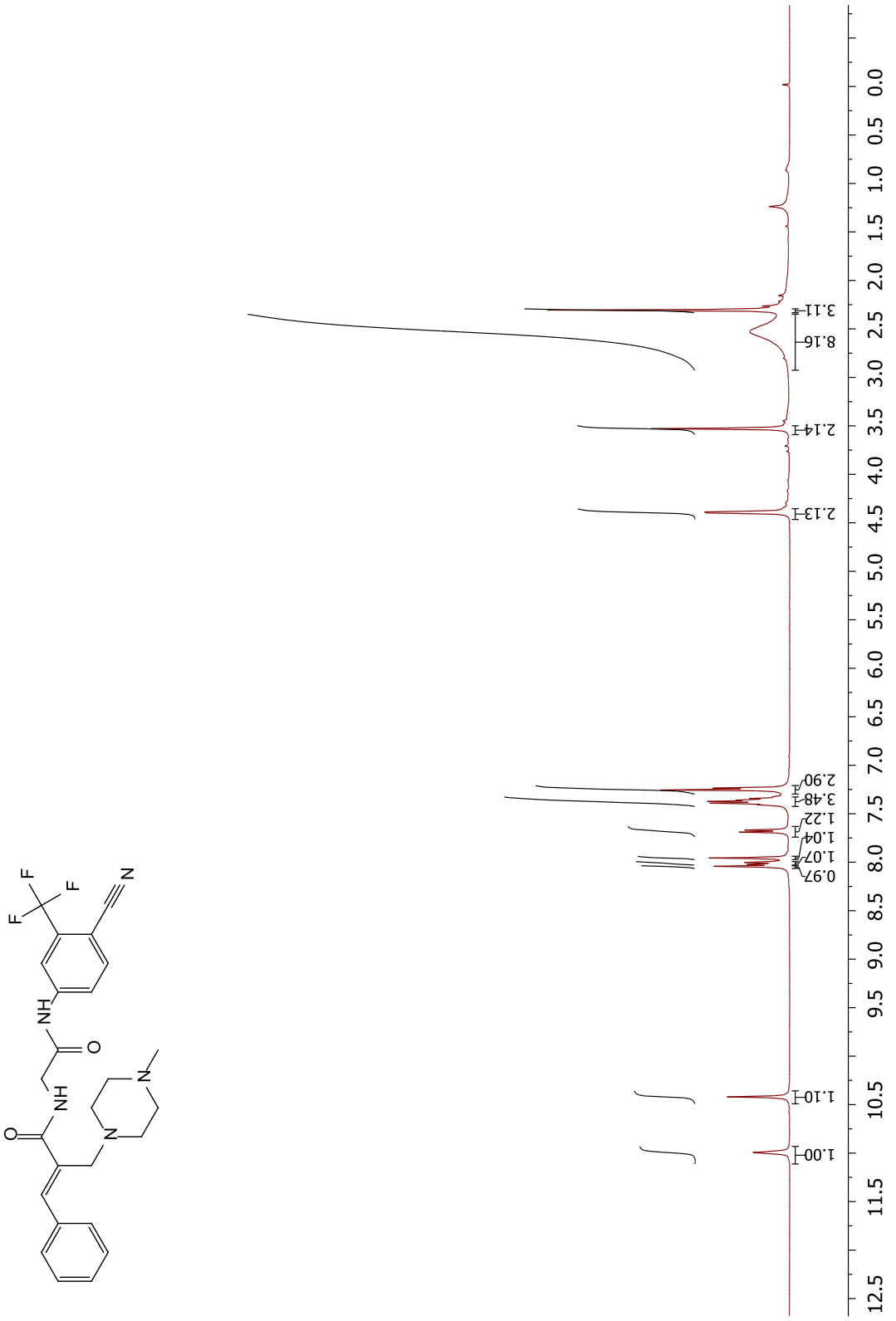


Figure 59. 400 MHz ^{1}H NMR of Compound **14b** in $CDCl_3$

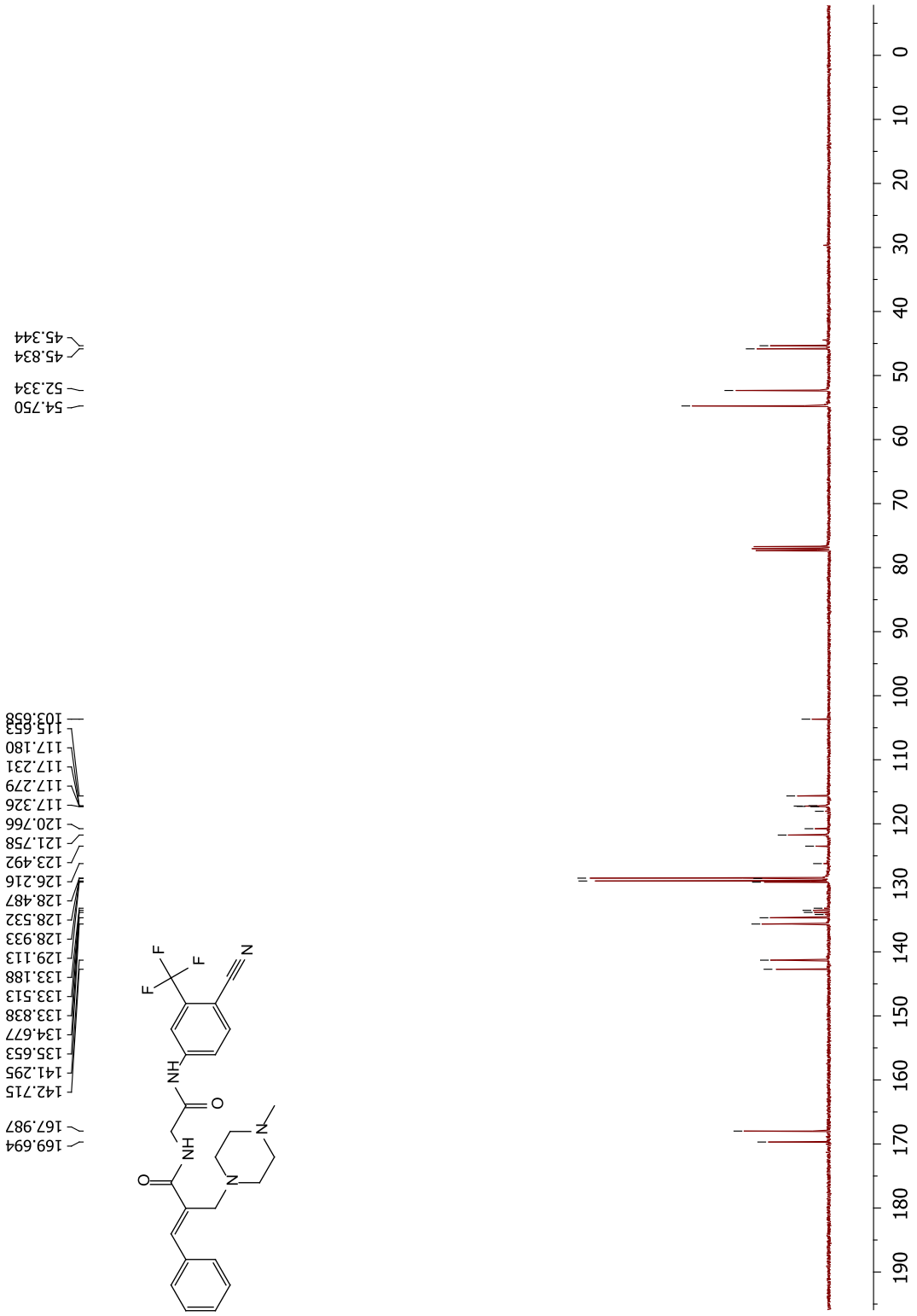


Figure 60. 101 MHz ^{13}C NMR of Compound **14b** in $CDCl_3$

References

1. Fang, Y.; Xiao, M.; Hu, A.; Ye, J.; Lian, W.; Liu, A. *Chin. J. Chem.* **2016**, 34, 403-411.

2. Jauhari, S.; Mistry, B.M. *Med. Chem. Res.* **2013**, 22, 647-658.

3. Marella, A.; Tanwar, O.; Saha, R.; Rahmat Ali, M.; Srivastava, S.; Akhter, M.; Shaquiquzzaman, M.; Mumtaz Alam, M. *Saudi Pharm. J.*, **2013**, 21, 1-12

4. Karad, S.C.; Purohit, V.B.; Thakor, P.; Thakkar, V.R.; Raval, D.K. *Eur. J. Med. Chem.* **2016**, 112, 270-279.

5. Srivastava, V.; Lee, H. *Bioorg. Med. Chem.* **2015**, 23, 7629-7640

6. Jain, P.P.; Degani, M. S.; Raju, A.; Anantram, A.; Seervi, M.; Sathay, S.; Ray, M.; Rajan, M.G.R. *Bioorg. Med. Chem. Lett*. **2016**, 26, 645-649.

7. Nichols,D.E; Lloyd, D.H.; Hoffman, A.J.;Nichols, M.B.; Yim,G.K. *J. Med. Chem.***1982,**25,530-535.

8. Deshpande, S.R.; Nagrale, S.N.; Patil, M.V.; Chavan, P.S. *Ind. J. Pharm. Sci*. **2015**, 77, 24-33

9. Redd, W.H.; Manne, S.L.; Peters, B; Jacobsen, P.B.; Schmidt, H. *J. Magn. Reson. Imagin.* **1994,** 4, 623-626.

10. Pandya, K.M.; Patel, R.J. *Int. J.Pharm. Res. Scholars.*, **2014,** 3, 905-913.

11 . Marzano, I. M.; Franco, M. S.; Silva, P. P.; Augusti, R.; Santos, G. C.; Fernandes, N. G.; Bucciarelli-Rodriguez, M.; Chartone-Souza, E.; Pereira-Maia, E. C. *Molecules.* **2013**, 18, 1464-1476

12. Bowles,B.L.; Juneja, V.K. *J. Food Saf.* **1998,** 18,101-112.

13. Mahamoud,A.; Chevalier,J.; Davin-Regli,A.;Berbe, J. *Current drug targets,* **2006,** 7,843-847.

14. Pandya, K.M.; Desai,P.S. *Int. J. Pharm. Res. Scholars*., **2013,** 2, 179-183.

15. A.Lilienkampf,J.; Mao,B.; Wan,Y.;S.G.Franzblau,A.;Kozikowski. *J.Med.Chem.* **2009,** 52, 2109-2118.

16. Nasved,P.; Kitchener,S. *Trans. R. Soc. Trop. Med. Hyg.* **2005,** 99, 2-5.

17. Varma,R.; Prakash,R.; Prasad,C. *J. Chem. Soc. Pak.* **1986,** 8, 117-123.

18. Joule, J.A.; Mills, K.; Smith, G.F. *Heterocyclic Chem.* 3rd Ed **1995**, 94-104

19. Chaubey, A.; Pandey, S.N. *Asian J. Pharm. Clin. Res.* **2011**, 4, 5-8

20. Huttrer, C.P.; Djerassiv, W.L.; Beears, R.; Mayer, L.; Scholz, C.R. J. *Am. Chem. Soc.* **1946**, 68, 1999-2002.

21 Sebille, S.; de Tullio, P.; Boverie, S.; Antoine, M.H.; Lebrun, P.; Pirotte, B. *Curr. Med. Chem.* **2004**, 11, 1213-1222

22. De Melos, J.R.L; Torres-Santos, E.C.; Faioes,V.D.S,;De Nigris Del Cistia,C.; Sant'Anna,C.M.R.; Rodrigues-Santos,C.E.; Echevarria,A. *Eur. J. Med. Chem.* **2015,** 103, 409-917.

23. Akbas, E.; Berber, I. *Eur. J. Med. Chem.* **2005,** 40, 401-405.

24. Ranatunge, R.R.; Garvey, D.S.; Janero, D.R.; Letts, L.G.; Martino, A.M.; Murty, M.G.; Richardson, S.K.; Young, D.V.; Zemetseva, I.S. *Bioorg. Med. Chem.* **2004,** 12, 1357-1366

25. Deprez-Poulain,R.; Cousaert,N.; Toto, P.; Willand, N.; Deprez, B. *Eur. J. Med. Chem.***2011,** 46, 3867-3876.

26. Gavegnano, C.; Detorio,M.; Montero, C.; Bosque, A.; Planelles, V.; Schinazi, R.F. *Antimicrob. Agents. Chemother.* **2014,** 58, 1977-1986.

27. Bekhit, A.A.; Ashour, H.M.A,; Abdel Ghany, Y.S.; Bekhit A.E.; Barka,A. *Eur. J. Med. Chem.* **2008,** 43, 456-463.

28 Bronson, J.; Dhar,M.; Ewing, W.; Lonberg, N. *Ann. Rep. Med. Chem.* **2012,** 47, 525.

29. Charlier, C.; Michaux, C. *Eur. J. Med. Chem.* **2003,** 38, 645-659.

30. Liu,X.H.; Cui,P.; Song,B.A.; Bhadury, P.S.; Zhu, H.L.; Wang, S.F. *Bioorg. Med. Chem.* **2008,** 16, 4075-4082.

31. Pandya, K.; Patel. R. *J.Chem. & Cheml. Sci.* **2017**, 7, 1331-1341.

32. Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman. *New J. Chem.* **2017**, 41, 16-41.

33. Keri, R.S.; Chand, K.; Ramakrishnappa, T.; Nagaraja, B. M. *Arch. Pharm. Chem. Life. Sci.* **2015**, 348, 299-314.

34. Mereddy, G. R.; Chakradhar, A.; Rutkoski, R. M.; Jonnalagadda, S. C., *J. Organomet. Chem.* **2018,** *865*, 12-22.

35. Suman, P.; Patel, A.; Solano, L. N.; Jampana, G.; Gardner, Z.; Holt, C. M.; Jonnalagadda, S. C., *Tetrahedron* **2017**, *73*, 4214-4226.

36. Alam, M. A.; Arora, K.; Gurrapu, S.; Jonnalagadda, S. K.; Nelson, G. L.; Kiprof, P.; Jonnalagadda, S. C.; Mereddy, V. R., *Tetrahedron*. **2016**, *72*, 3795-3801.

37. Suman, P.; Patel, B. P.; Kasibotla, A. V.; Solano, L. N.; Jonnalagadda, S. C., *J. Organomet. Chem.* **2015,** *798*, 125-131.

38. Tekkam S.; Alam, M. A.; *Just, M. J.;* Johnson J. L.; Jonnalagadda S. C.; Mereddy V. R., *Anti-Cancer Agents in Medicinal Chemistry* **2013,** *13*, 1514-1530.

39. Tekkam S.; Johnson J. L.; Jonnalagadda S. C.; Mereddy, V. R., *J. Het. Chem.* **2013**, *50*, 969-972.

40. Tekkam S.; Johnson J. L.; Jonnalagadda S. C.; Mereddy V. R., *J. Het. Chem.* **2013**, *50*, 955-958.

41. Kumar, J. S.; Alam, M. A.; Gurrapu, S.; Nelson, G.; Williams, M.; Corsello, M. A.; Johnson, J. L.; Jonnalagadda, S. C.; Mereddy, V. R., *J. Het. Chem.* **2013**, *50*, 814-820.

42. Tekkam, S.; Alam, M. A.; Jonnalagadda, S. C.; Mereddy, V. R., *Chem. Commun.* **2011**, *47*, 3219-3221.

43. *Just, M. J.;* Tekkam, S.; Alam, M. A.; Jonnalagadda, S. C.; Johnson, J. L.; Mereddy, V. R., *Tetrahedron Lett.* **2011**, *52*, 5349-5351.

44. Kumar, J. S.; *Bashian, C. M.; Corsello, M. A.;* Jonnalagadda, S. C.; Mereddy, V. R., *Tetrahedron Lett.* **2010**, *51*, 4482-4485.

45. Kumar, J. S.; Jonnalagadda, S. C.; Mereddy, V. R., *Tetrahedron Lett.* **2010**, *51*, 779-782.

46. Gopala, J.; Jonnalagadda, S. C.; Mereddy, V. R., *Org. Chem. Ind. J.* **2008**, *4*, 513-517.

47. Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.

48. Passerini, M. *Gazz. Chim. Ital*., **1921**, 51, 126.

49. Banfi,L.; Riva,R. *Org. React.* **2005,** 65, 1-140.

50. Passerini, M.; Ragni,G. *Gazz. Chim. Ital.* **1931,** 61, 964-969.

51. Passerini, M.; Simone,L. *Gazz. Chim. Ital.* **1921,** 51, 126-129.

52. Domling,A.; Ugi,I. *Angew. Chem. Int. Ed. Engl.* **2000,** 39, 3168-3210.

53. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, 71, 386.

54. Drewes, S.E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653-4670.

55. Basavaiah, D.; Rao P. D.; Hyma, R. S. *Tetrahedron*, **1996**, *52*, 8001-8062.

56. Ciganek, E. *Organic Reactions*, **1997**, *51*, 201-350.

57. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.

58. Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**; *26*, 1581-1588.

59. Declerck, V.; Martinez, J.; Lamaty F. *Chem. Rev.* **2009**, *109*, 1-48.

60. Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.

61. Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev*. **2012**; *41*, 68-78.

62. Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689-5743.

63. Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086-3240.

64. Alonso, F.; Moglie, Y.; Radivoy, G. *Acc. Chem. Res.* **2015**, *48*, 2516-2528.

65. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

66. Baylis, A. B.; Hillman, M. E. D. *German Patent* 2155113, **1972**; *Chem. Abstr*. **1972**, *77*, 34174q.

67. Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611-5614.

68. Basavaiah, D.; Gowriswari, V.V.L. *Synth. Commun*. **1989**, *19*, 2461-2465.

69. Kundu, M. K.; Mukherjee, S. B.; Balu, N; Padmakumar, R.; Bhat, S.V. *Synlett* **1994**, *6*, 444.

70. Auge, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett*. **1994**, *35*, 7947-7952.

71. Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett*. **1986**, *27*, 5007-5010.

72. Hill, J. S.; Isaacs, N. S. *J. Chem. Res*. (S) **1988**, *10*, 330-331.

73. Schuurman, R. J. W.; V. D. Liden, A.; Grimbergen, R.P.F.; Nolte, R.J.M.; Scheeren, H.W. *Tetrahedron*, **1996**, *52*, 8307-8314.

74. Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun*. **1988**, *18*, 495-500.

75. Drewes, S. E.; Emslie, N.D. *J. Chem. Soc.Perkin Trans.* **1982**, *1*, 2079-2083.

76. Hoffmann, H.M.R.; Rabe, J. *Angew. Chem. Int. Ed. Engl*. **1983**, *22*, 795-796.

77. Basavaiah, D.; Gowriswari, V.V.L. *Tetrahedron Lett*. **1986**, *27*, 2031-2032.

78. Amri, H.; Villiereas, J. *Tetrahedron Lett*. **1986**, *27*, 4307-4308.

79. Basavaiah, D.; Bharathi, T.K.; Gowriswari, V.V.L. *Synth. Commun.* **1987**, *17*, 1893-1896.

80. Strunz, G.M.; Bethell, R.; *Sampson*, G.; White, P. *Can. J. Chem.* **1995**, 73, 1666-1674.

81. Basavaiah, D.; Gowriswari, V.V.L. *Synth. Commun*. **1987**, *17*, 587-591.

82. Auvray, P.; Konchel, P.; Normant, J.F. *Terahedron Lett.* **1986**, 27, 5095-5098.

83. Wang, S.-Z.; Yamamto, K.; Yamada, H.; Takahashi, T. *Tetrahedron* **1992**, *48*, 2333-2348

84. Tsuboi, S.; Takatsuka, S.; Utaka, M. *Chem. Lett.* **1988**, 17, 2003-2004.

85. Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukava, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1993**, *58*, 5952-5957.

86. Kikuchi, D.; Sakaguchi, S.; Ishii, Y.; *J. Org. Chem.* **1998**, 63, 6023-6026.