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Supporting Information

Design, Synthesis and Evaluation of 2,4-Diaminoquinazoline Derivatives as Potential Tubulin Polymerization Inhibitors

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Author Contributions

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F.M.-M. Data curation:Equal; Formal analysis:Equal; Methodology:Equal
R.A.-O. Investigation:Equal; Methodology:Equal; Software:Lead; Visualization:Lead; Writing - Review & Editing:Equal
L.D. Formal analysis:Equal; Investigation:Equal; Methodology:Equal; Software:Lead; Supervision:Equal; Writing - Review & Editing:Equal
T.R.-A. Data curation:Equal; Investigation:Equal; Methodology:Equal
L.Y.-M. Investigation:Lead; Methodology:Lead; Supervision:Lead; Validation:Lead; Writing - Review & Editing:Lead

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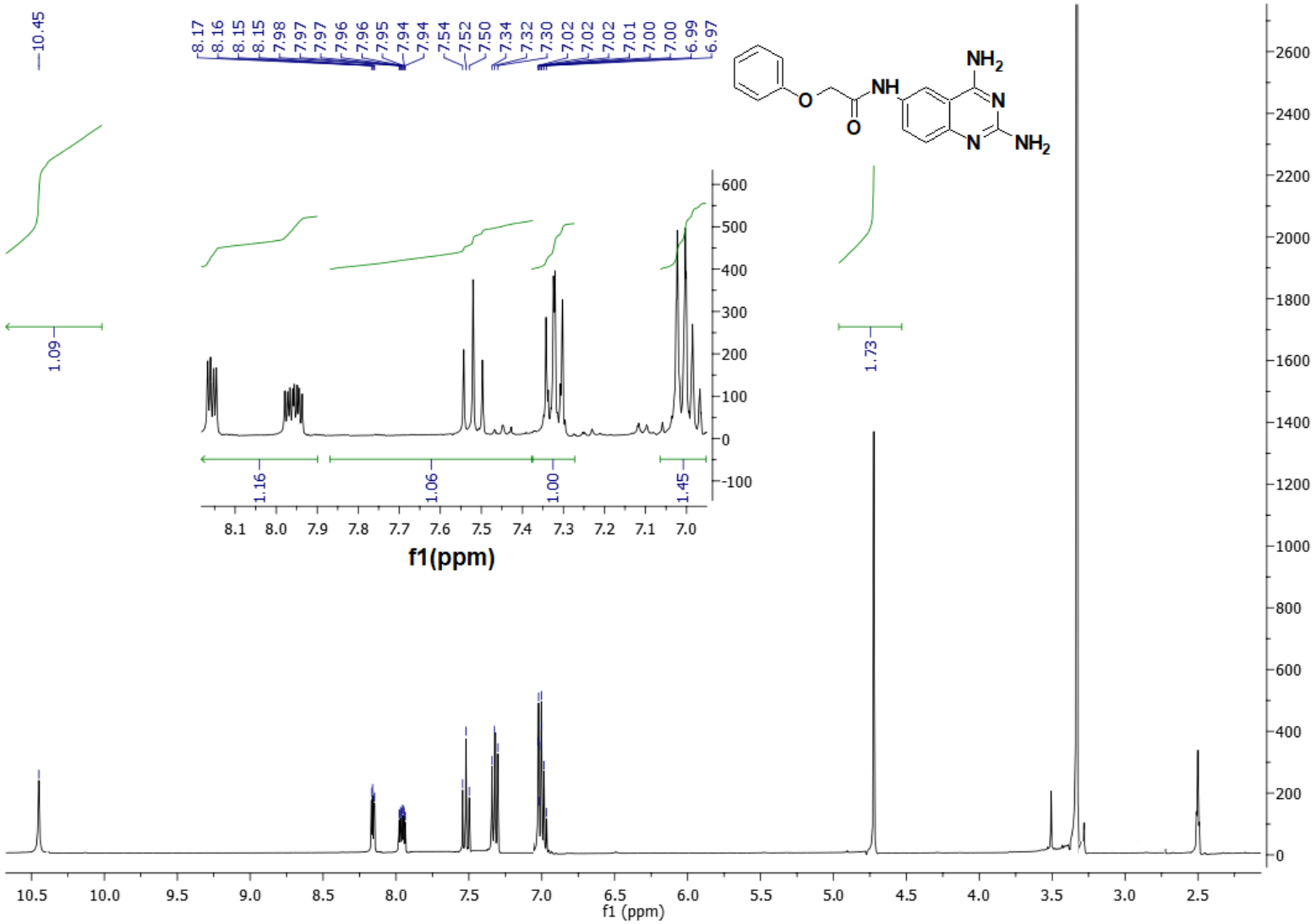

Figure S1. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-phenoxyacetamide* (***4a***).

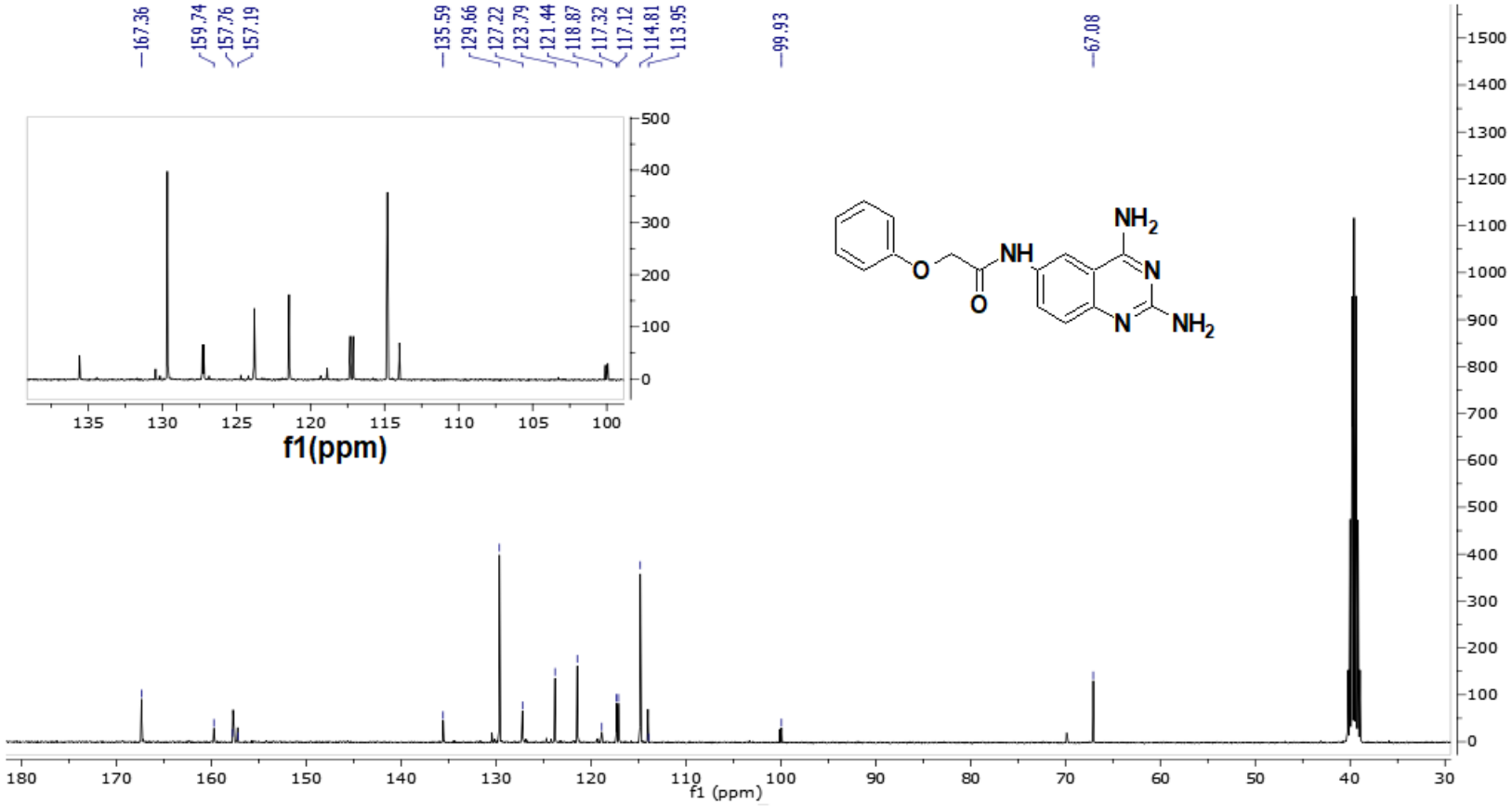

Figure S2. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-phenoxyacetamide (**4a**)*.

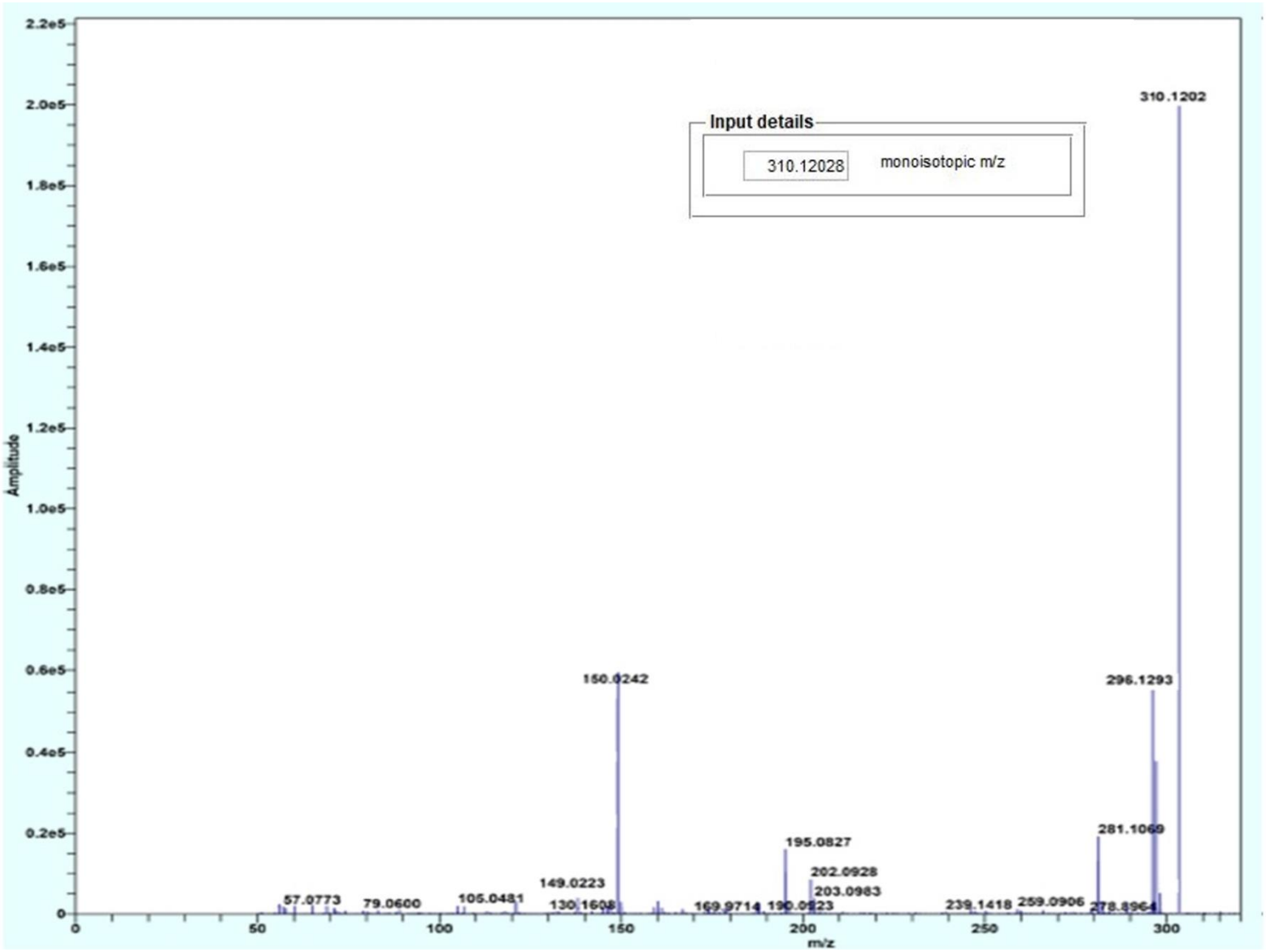

Figure S3. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-phenoxyacetamide (**4a**)*.

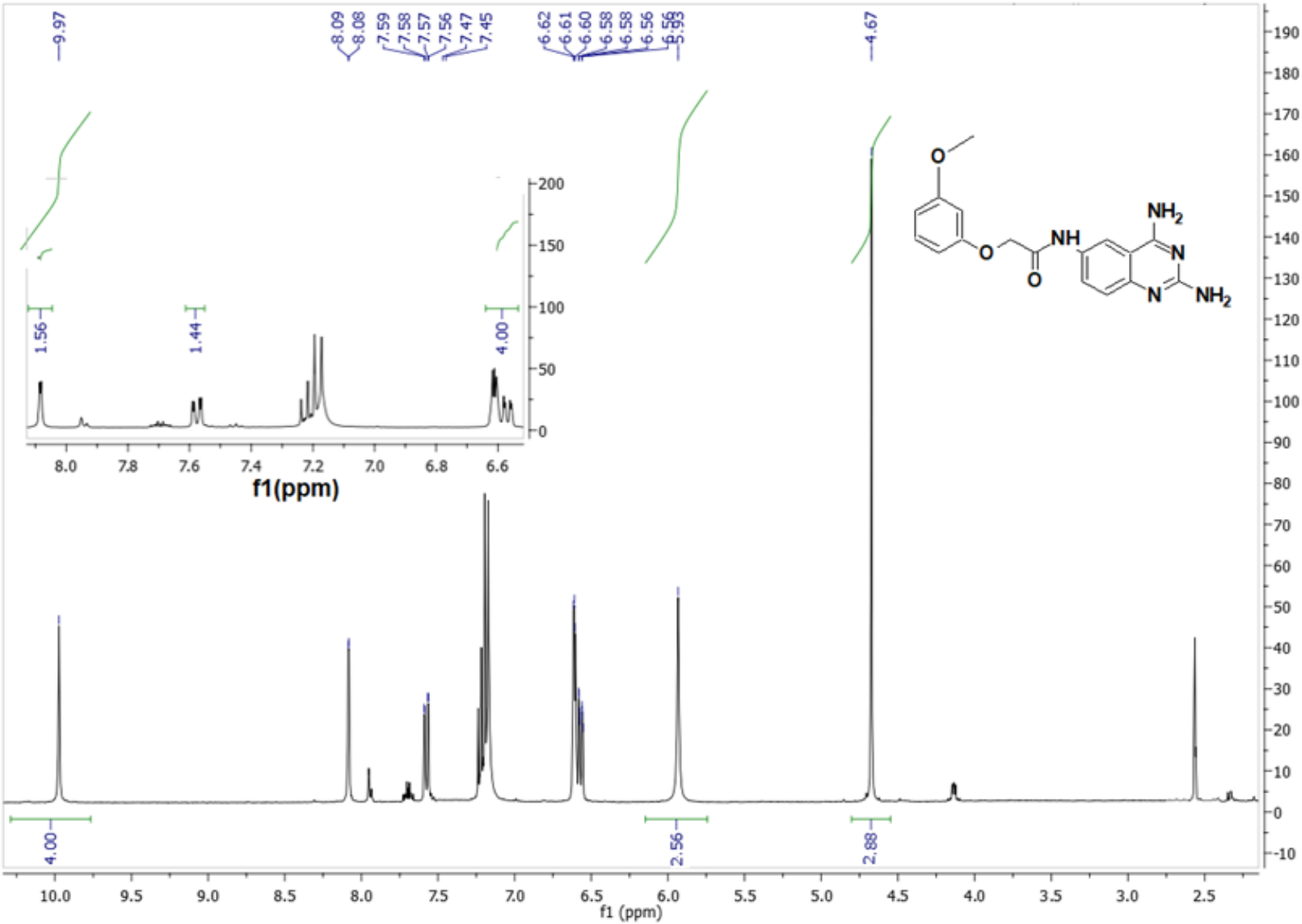

Figure S4. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methoxyphenoxy)acetamide (**4b**)*.

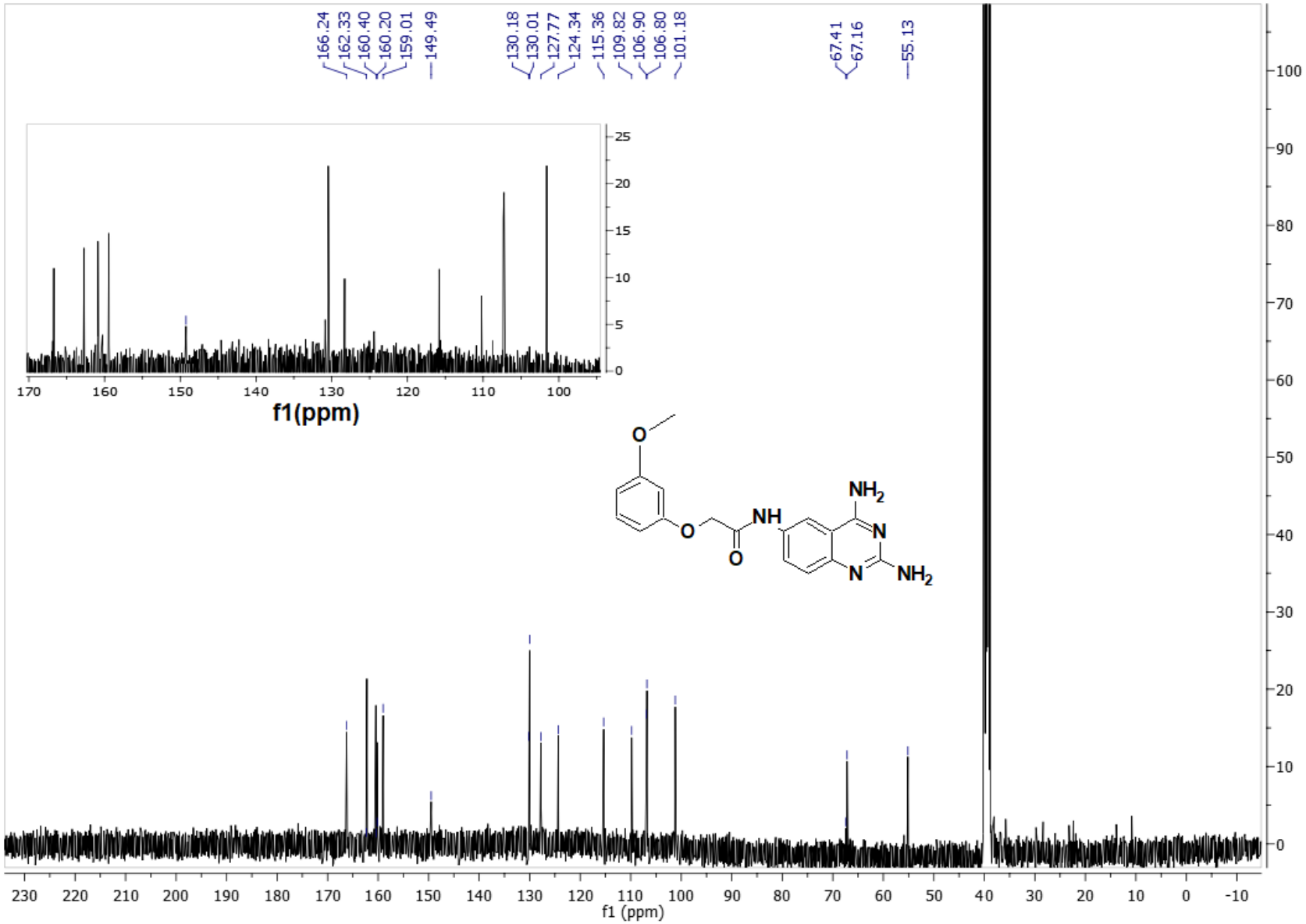

Figure S5. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methoxyphenoxy)acetamide (**4b**)*.

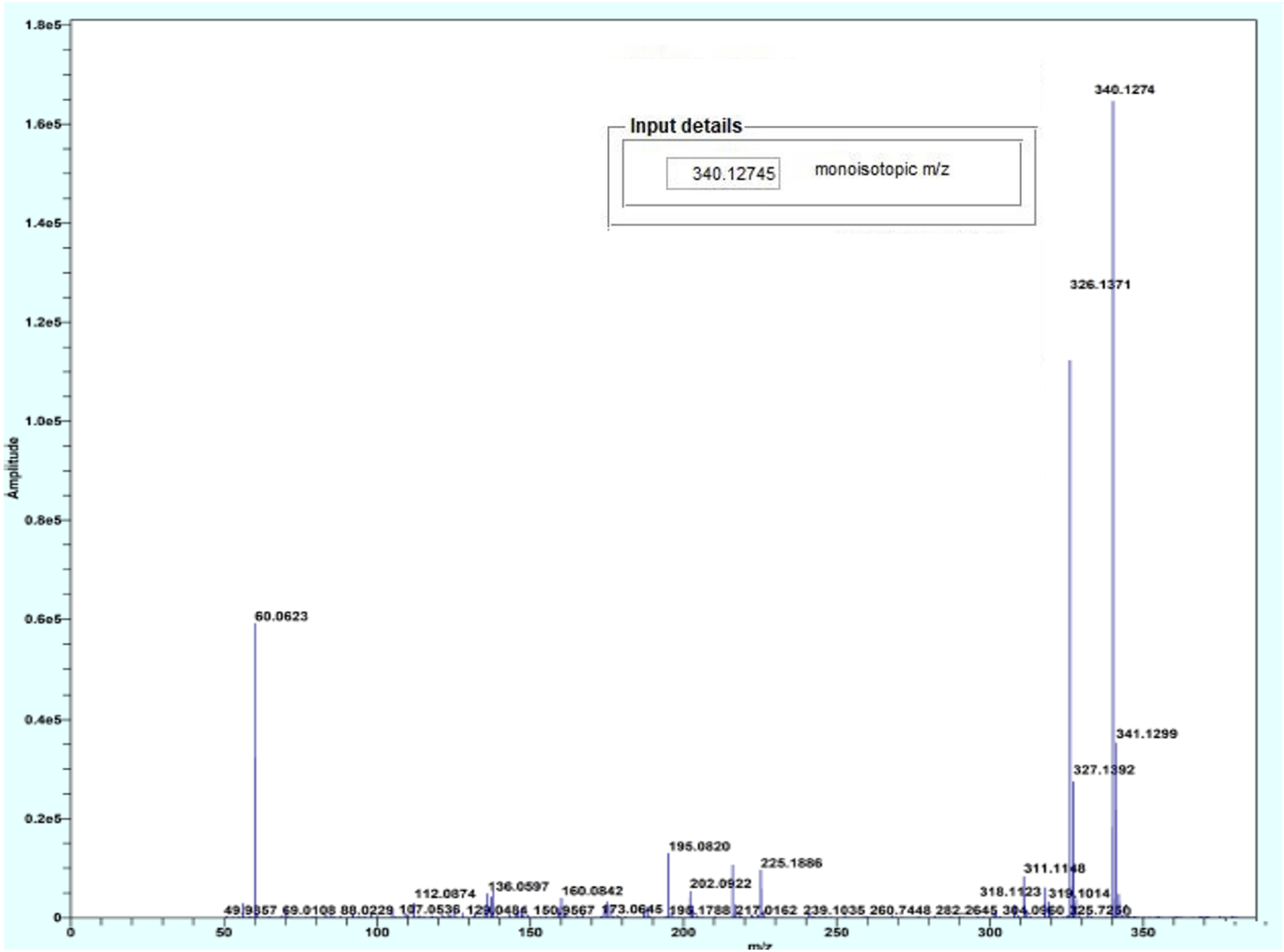

Figure S6. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methoxyphenoxy)acetamide* (***4b***).

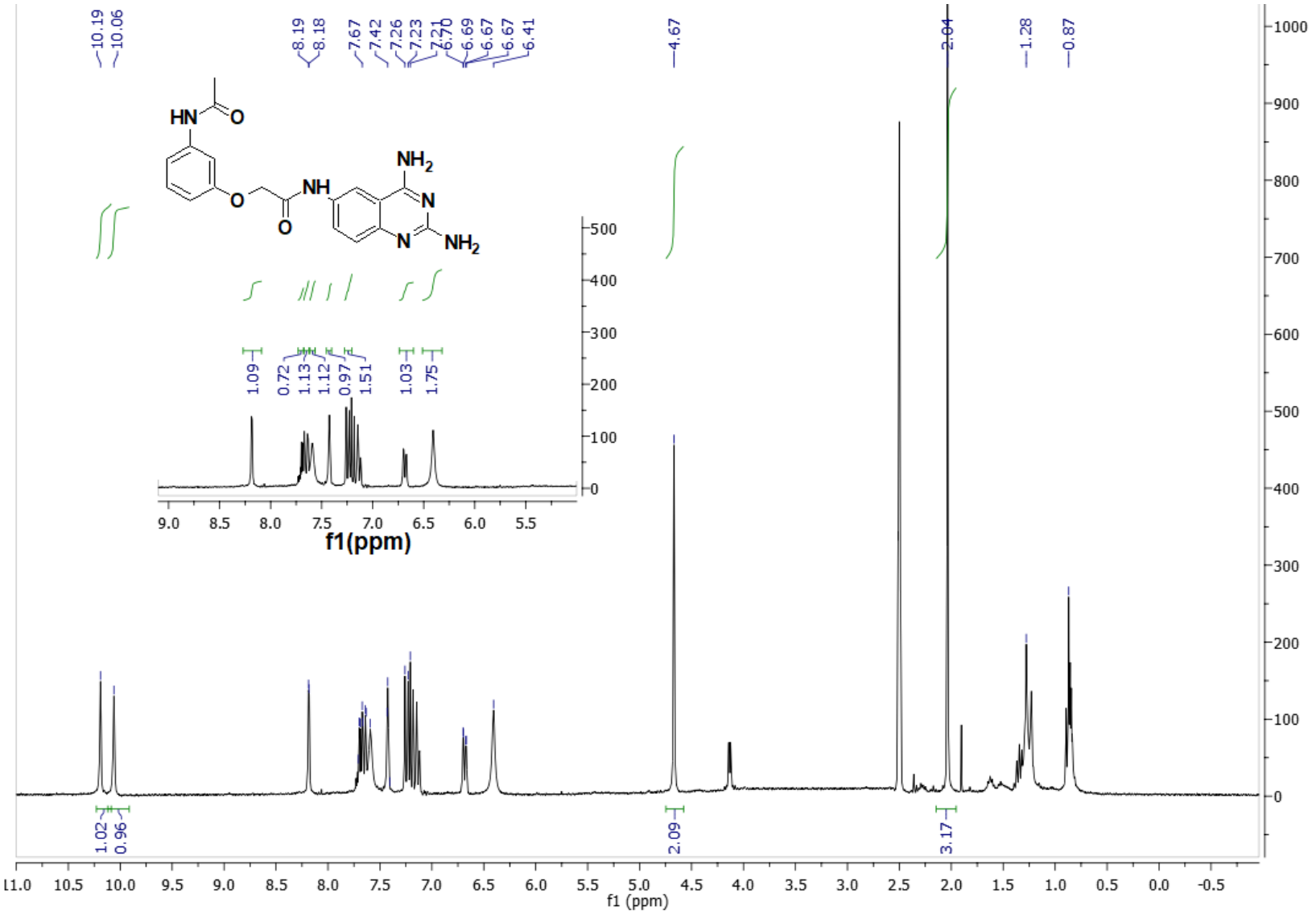

Figure S7. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *2-(3-acetamidophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4c**).*

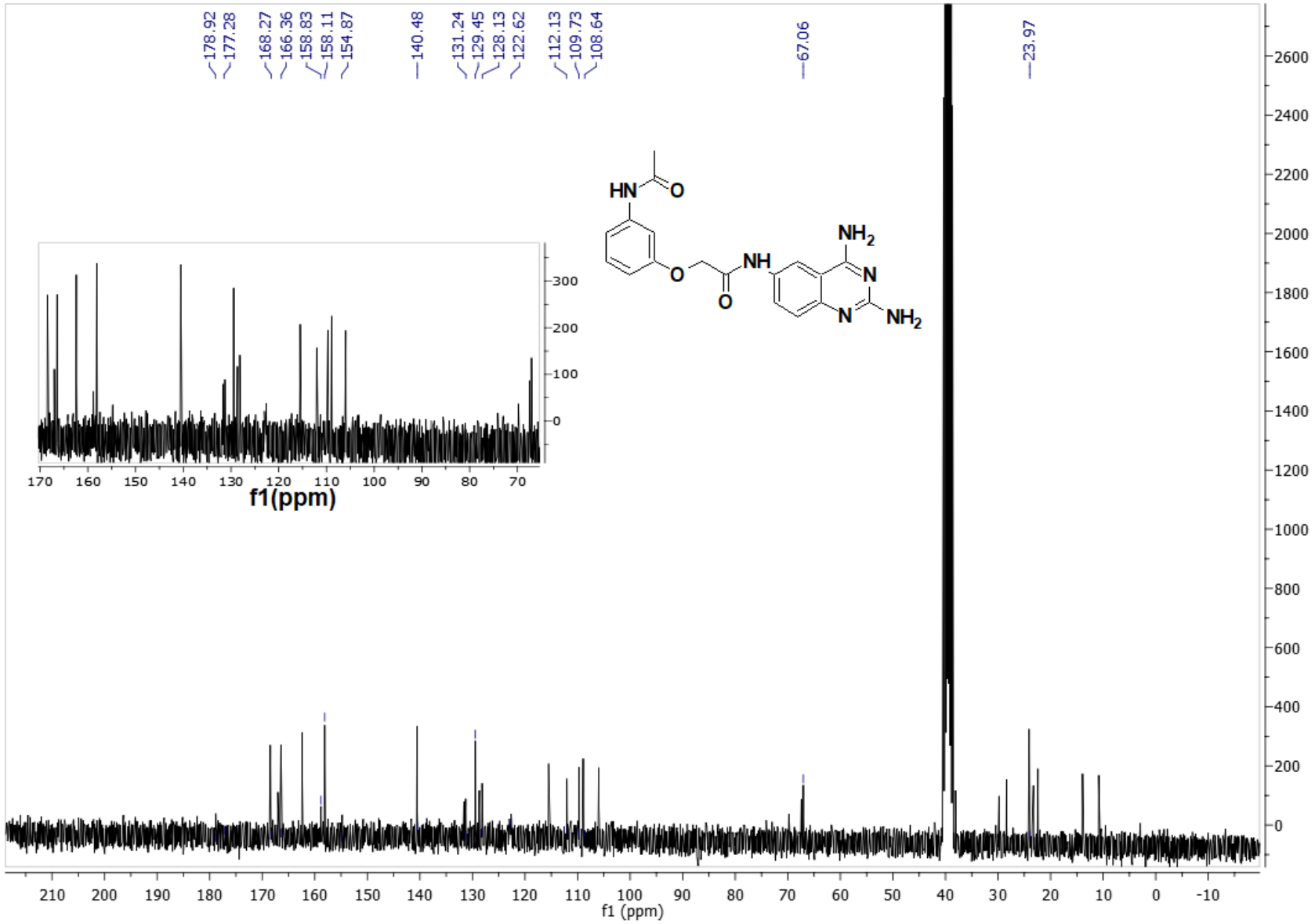

Figure S8. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *2-(3-acetamidophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4c**).*

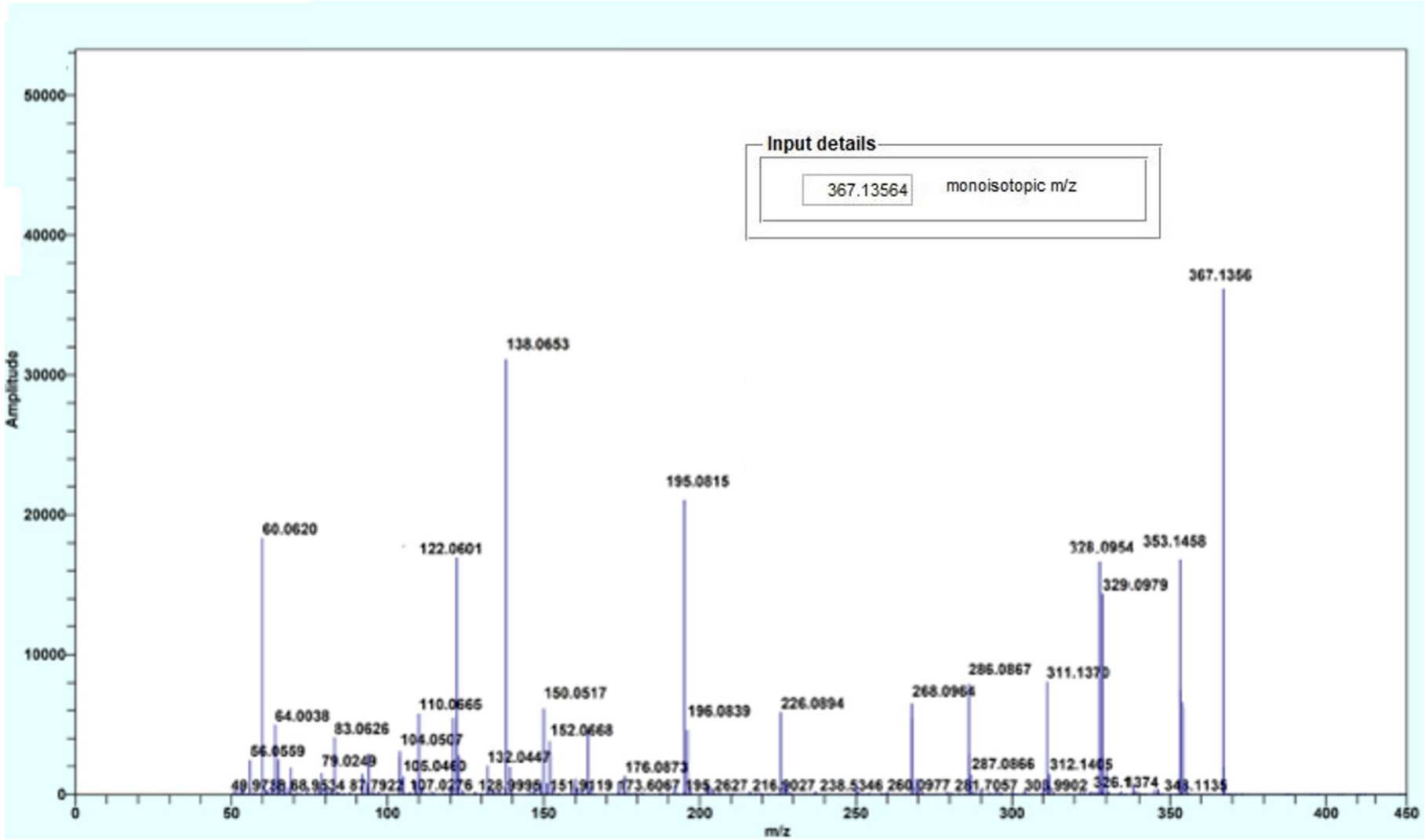

Figure S9. HRMS (APCI+) for *2-(3-acetamidophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4c**).*

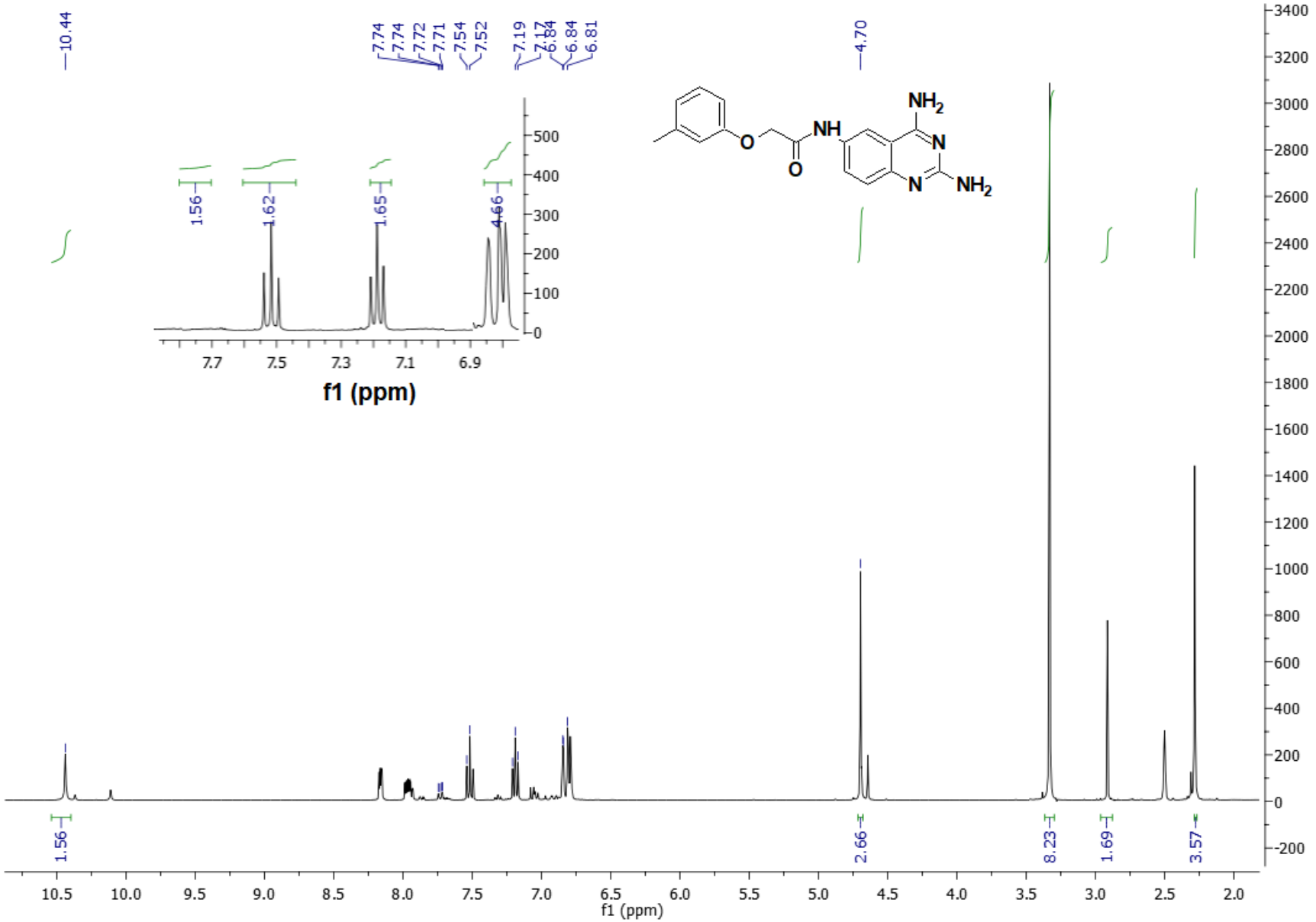

Figure S10. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methylphenoxy)acetamide (**4d**)*.

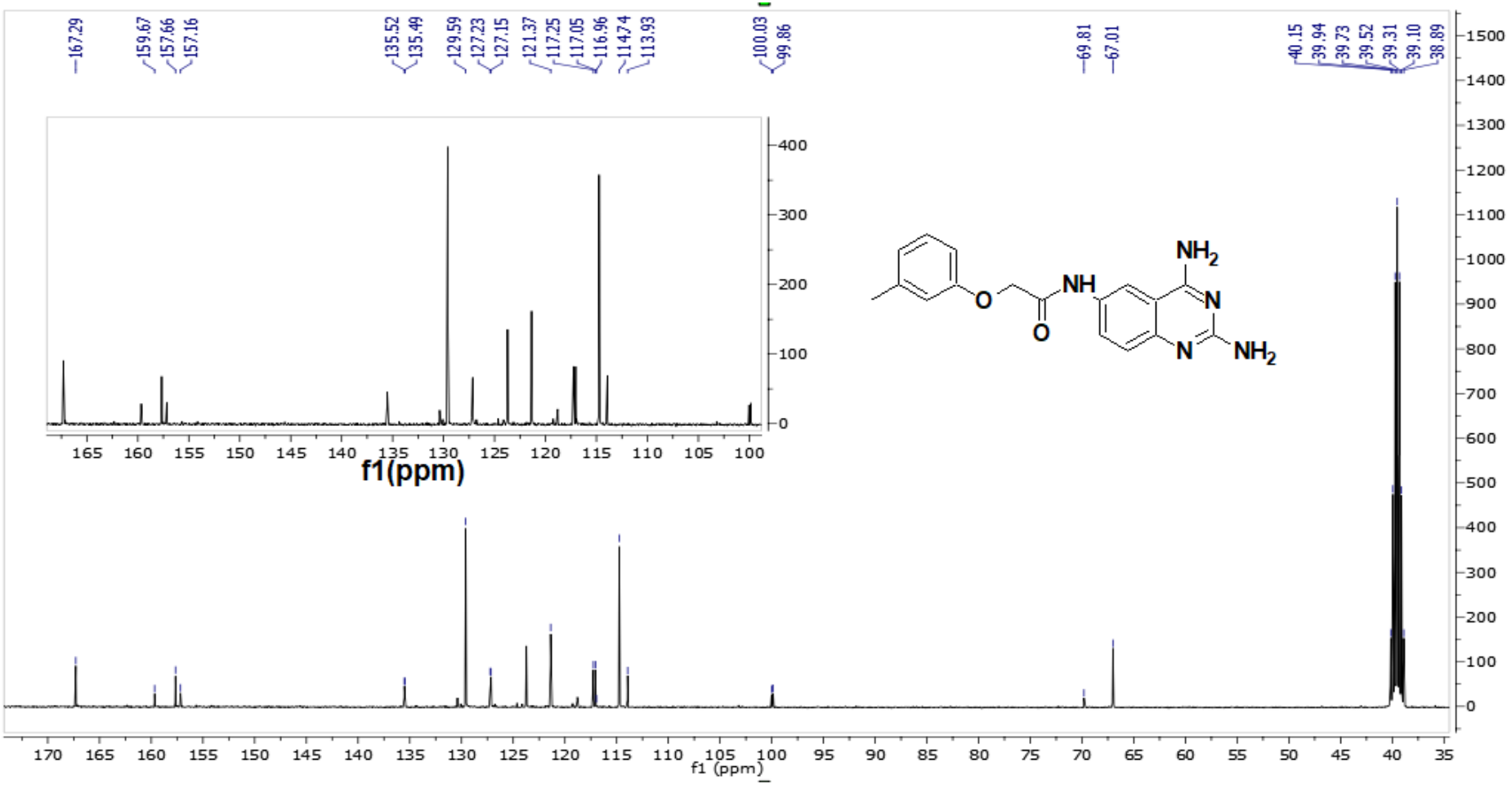

Figure S11. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methylphenoxy)acetamide (**4d**)*.

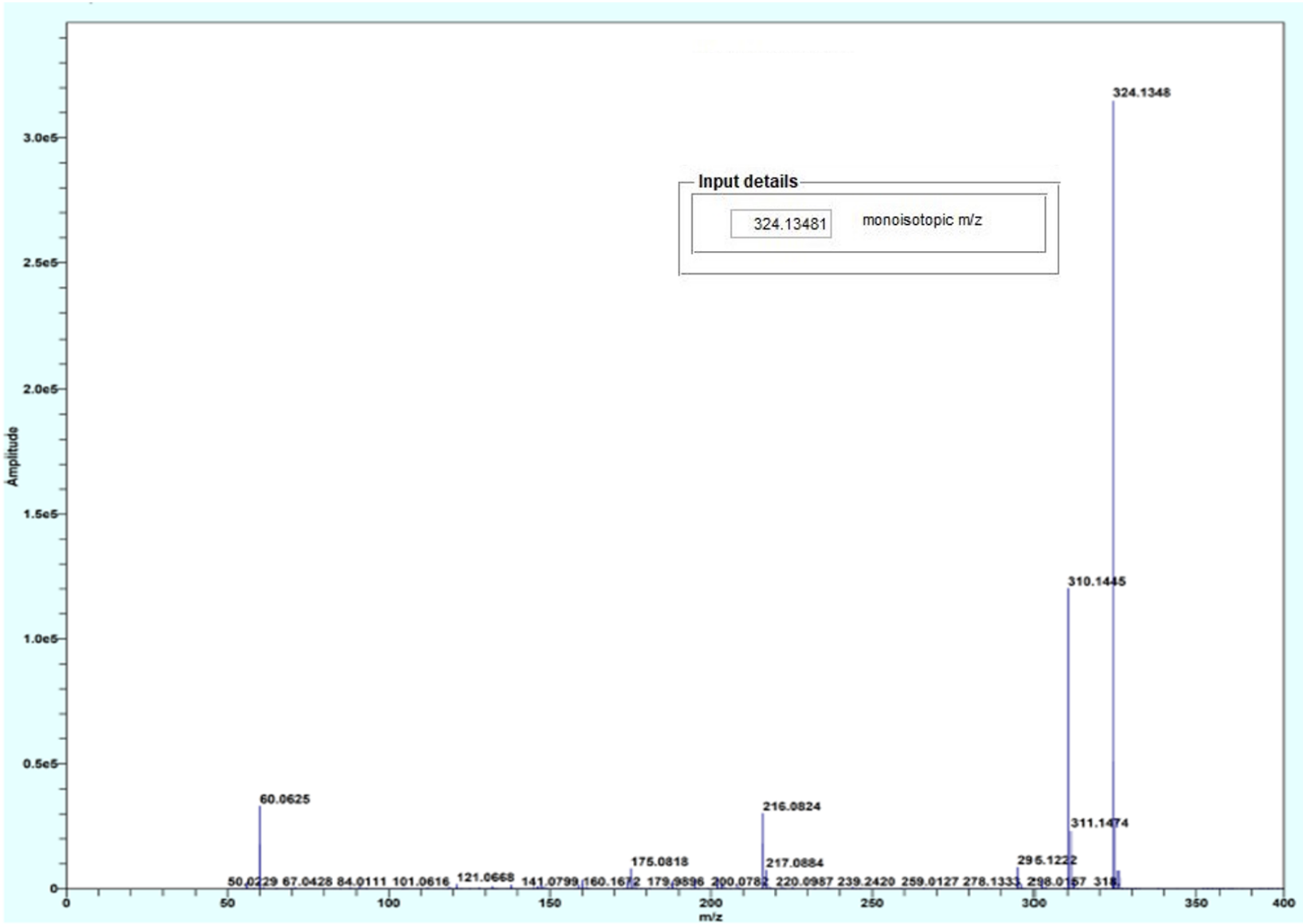

Figure S12. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-methylphenoxy)acetamide (**4d**)*.

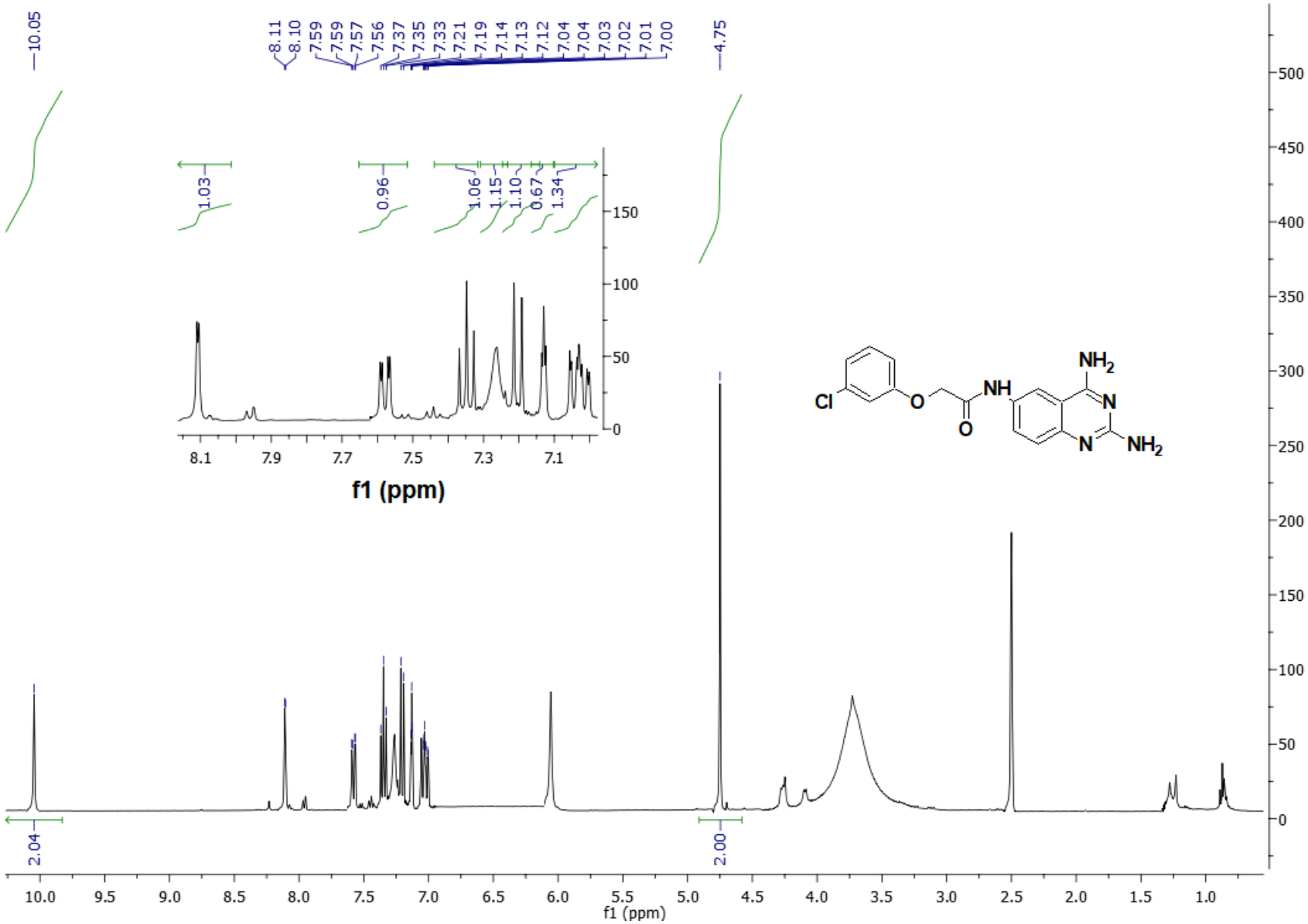

Figure S13. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *2-(3-chlorophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide* (***4e***).

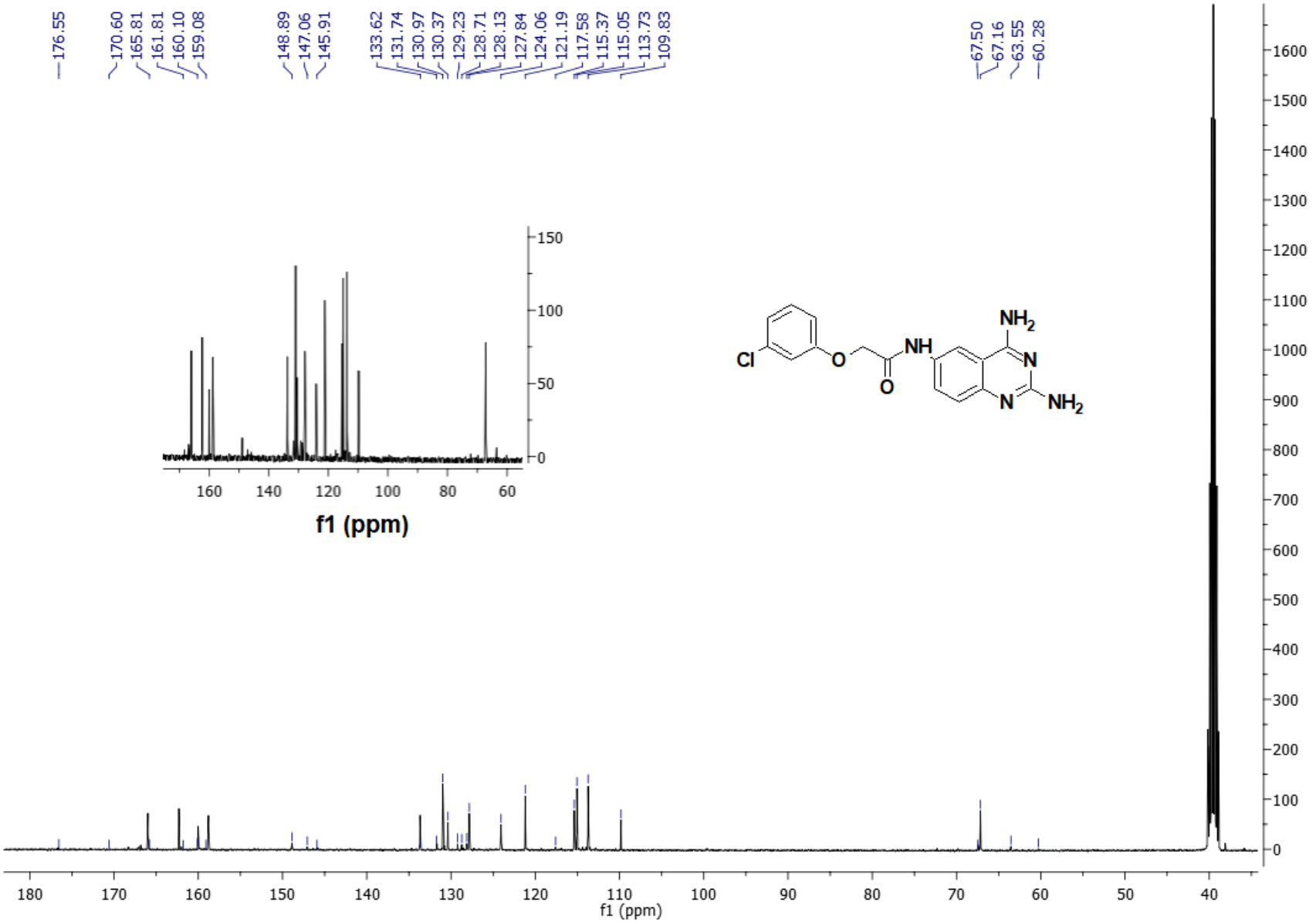

Figure S14. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *2-(3-chlorophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4e**)*.

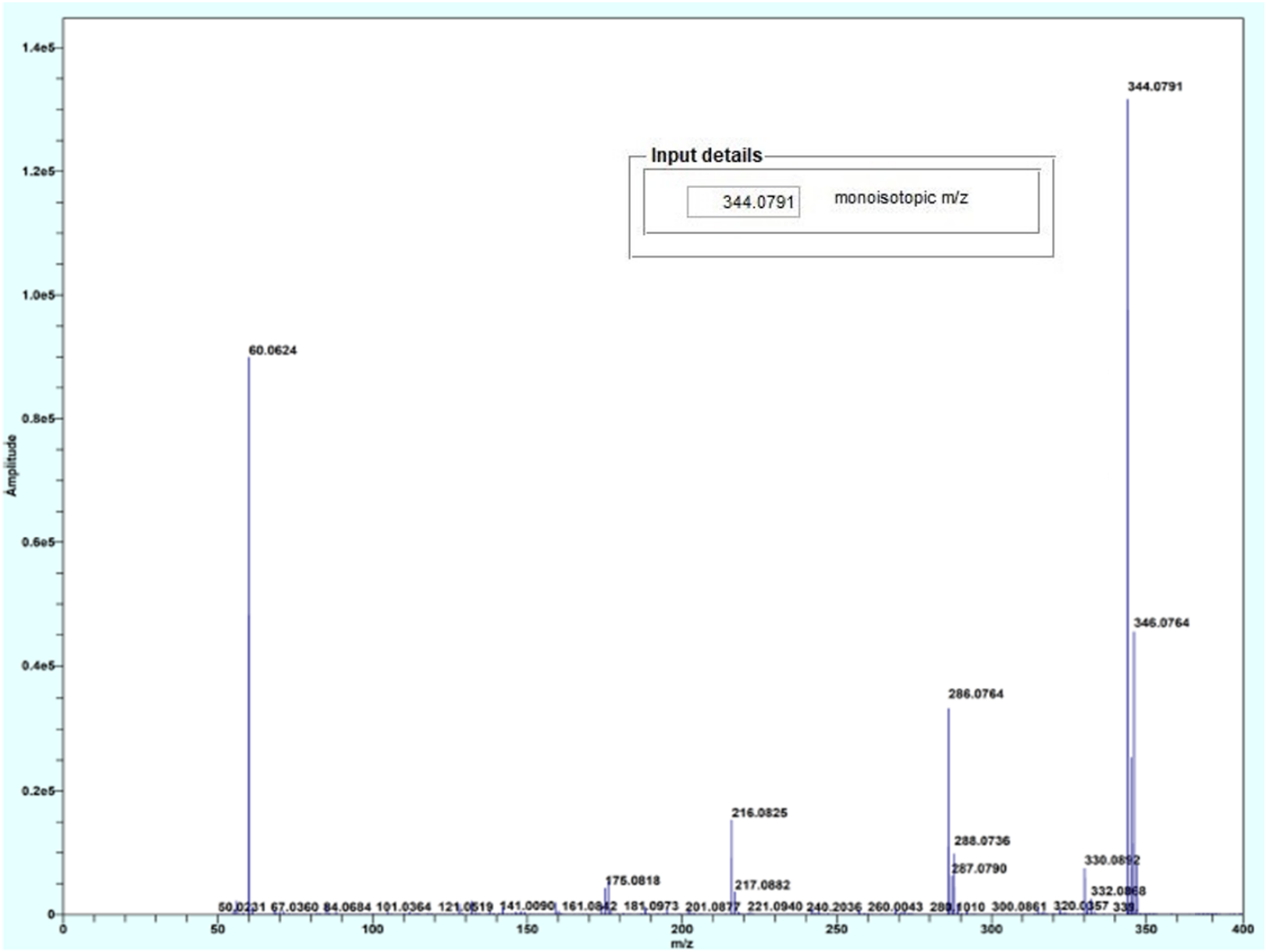

Figure S15. HRMS (APCI+) for *2-(3-chlorophenoxy)-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4e**)*.

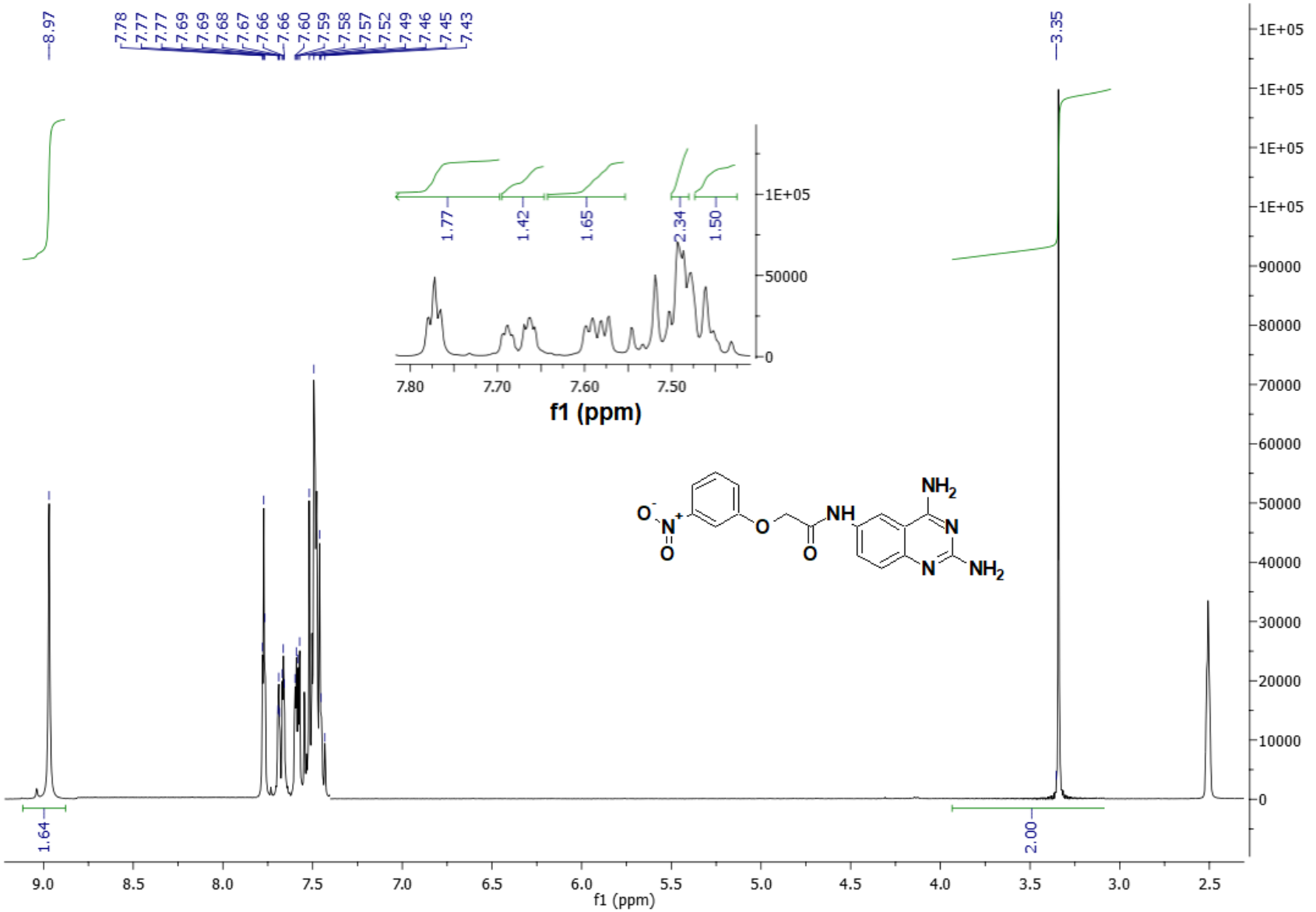

Figure S16. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-nitrophenoxy)acetamide* (***4f***).

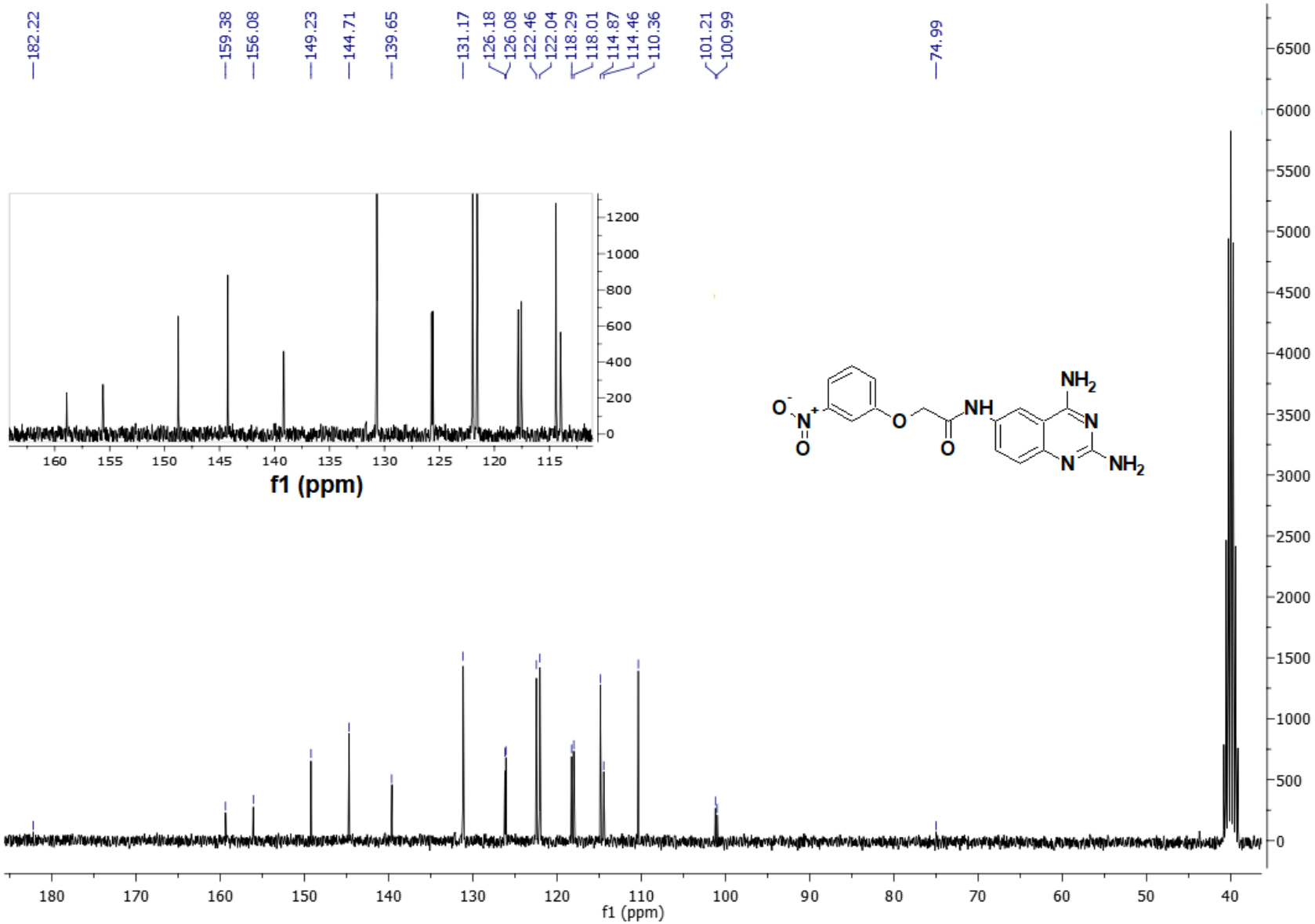

Figure S17. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-nitrophenoxy)acetamide* (***4f***).

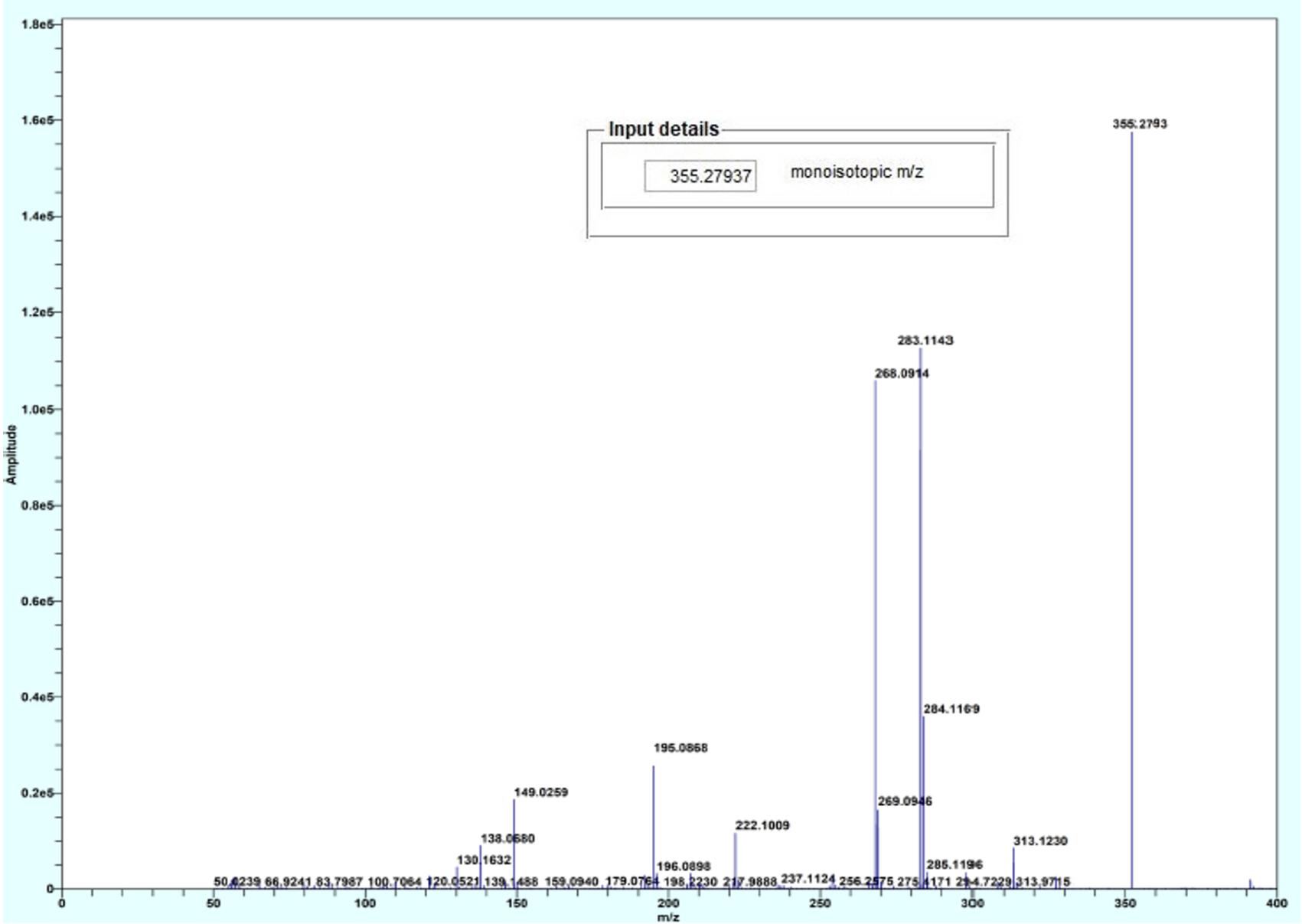

Figure S18. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3-nitrophenoxy)acetamide* ***(4f)***.

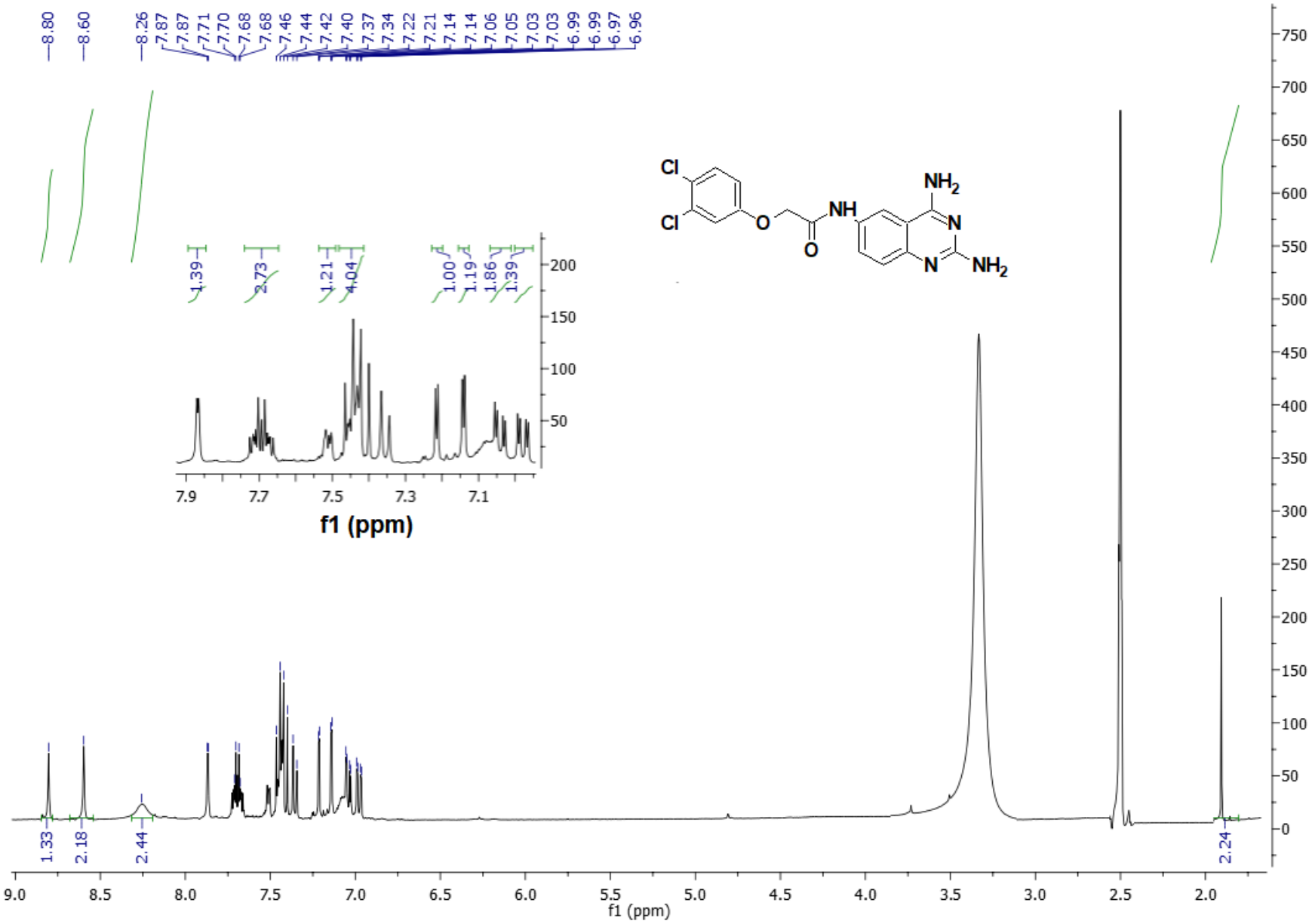

Figure S19. [1]H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3,4-dichlorophenoxy)acetamide* (***4g***).

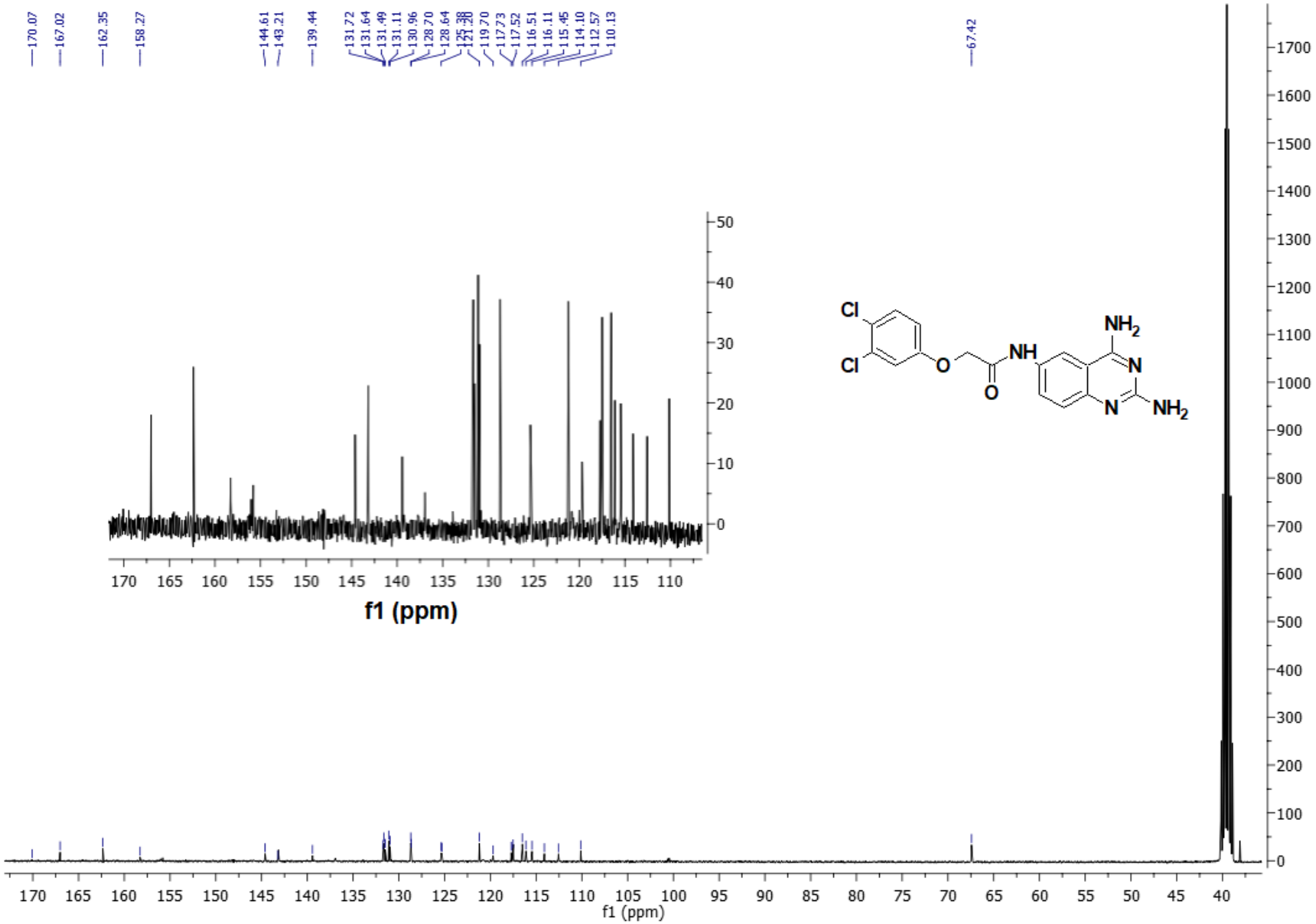

Figure S20. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3,4-dichlorophenoxy)acetamide* (***4g***).

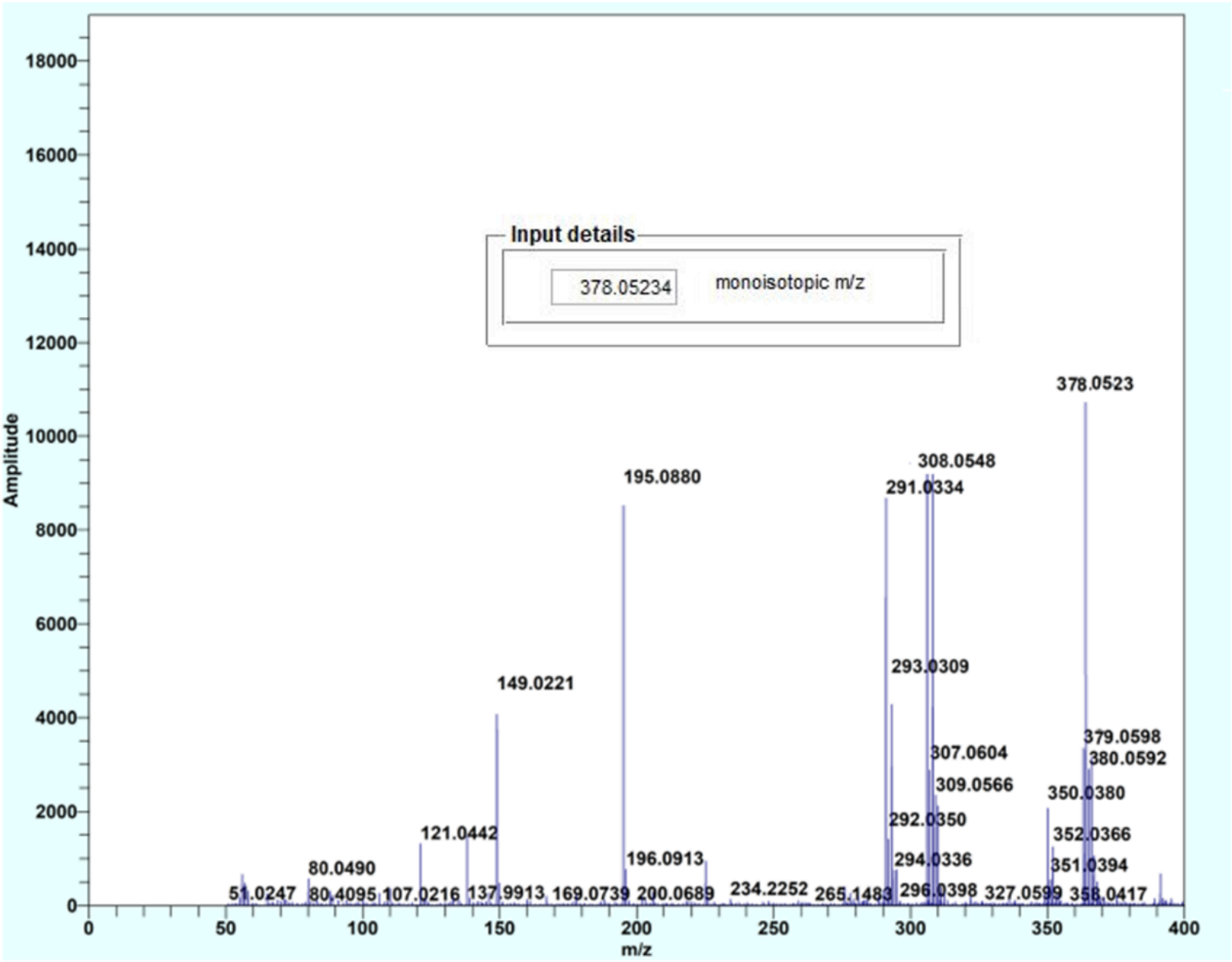

Figure S21. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-(3,4-dichlorophenoxy)acetamide (**4g**)*.

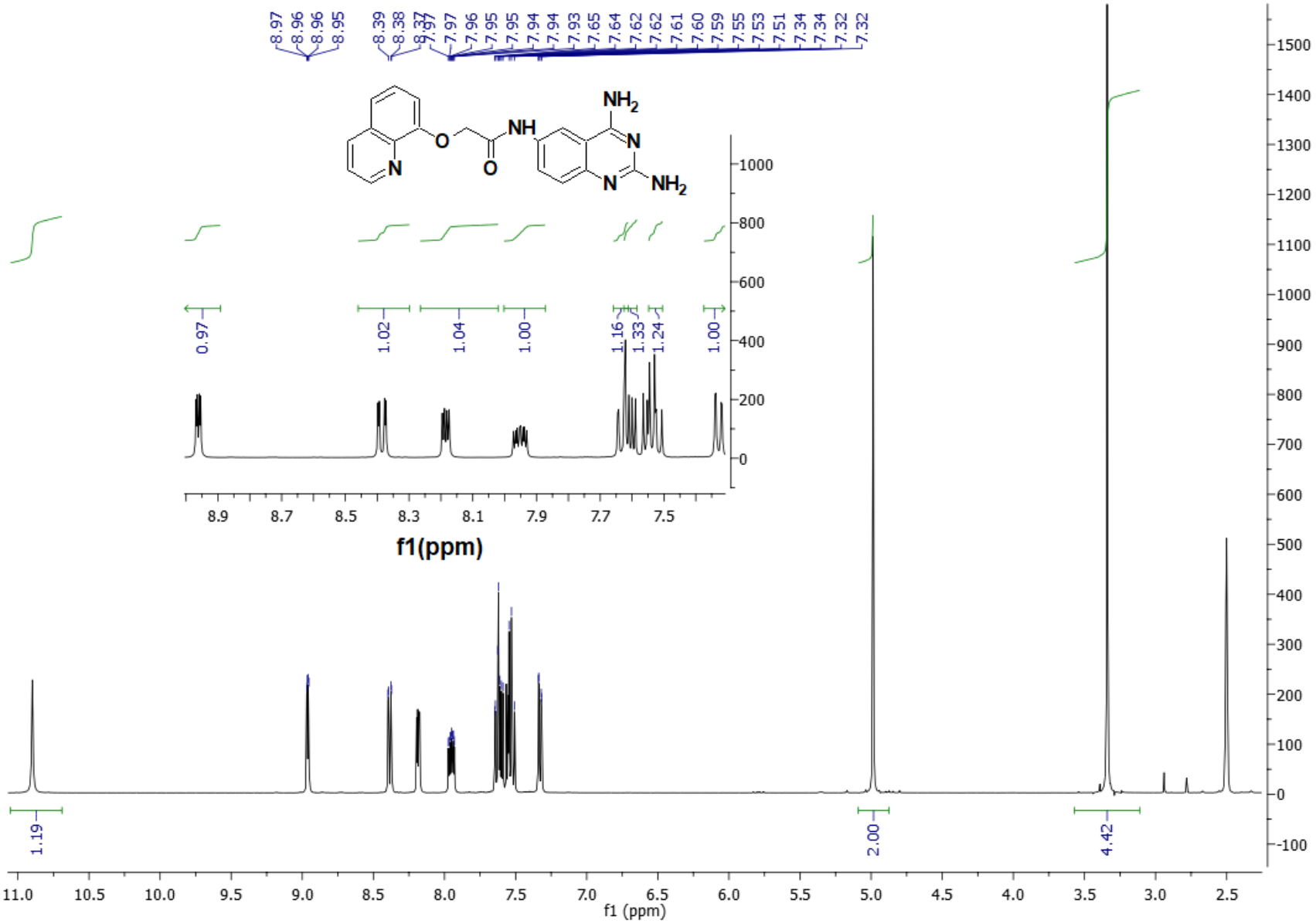

Figure S22. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-[(quinolin-8-yl)oxy]acetamide (**4h**)*.

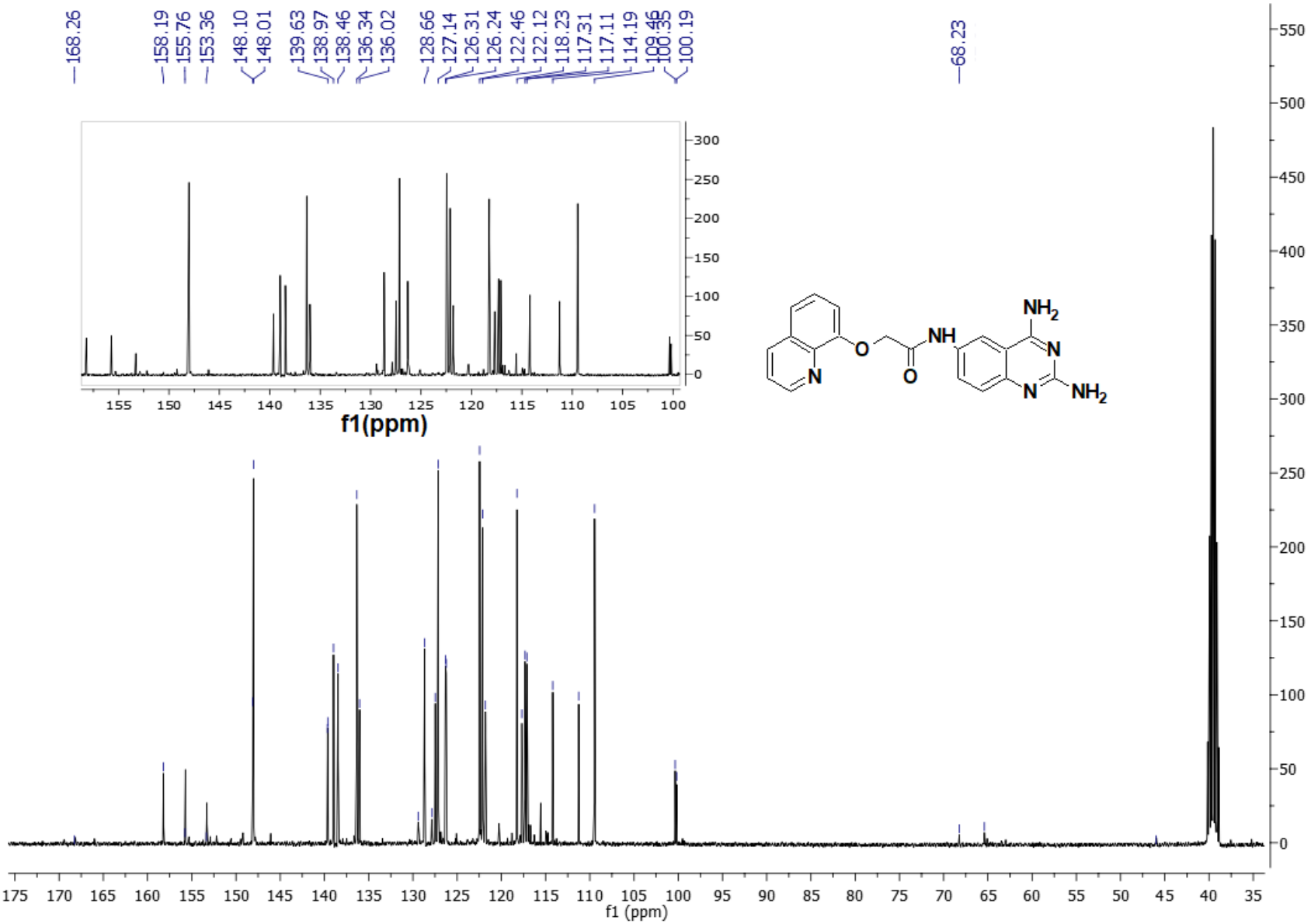

Figure S23. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *N-(2,4-diaminoquinazolin-6-yl)-2-[(quinolin-8-yl)oxy]acetamide* (***4h***).

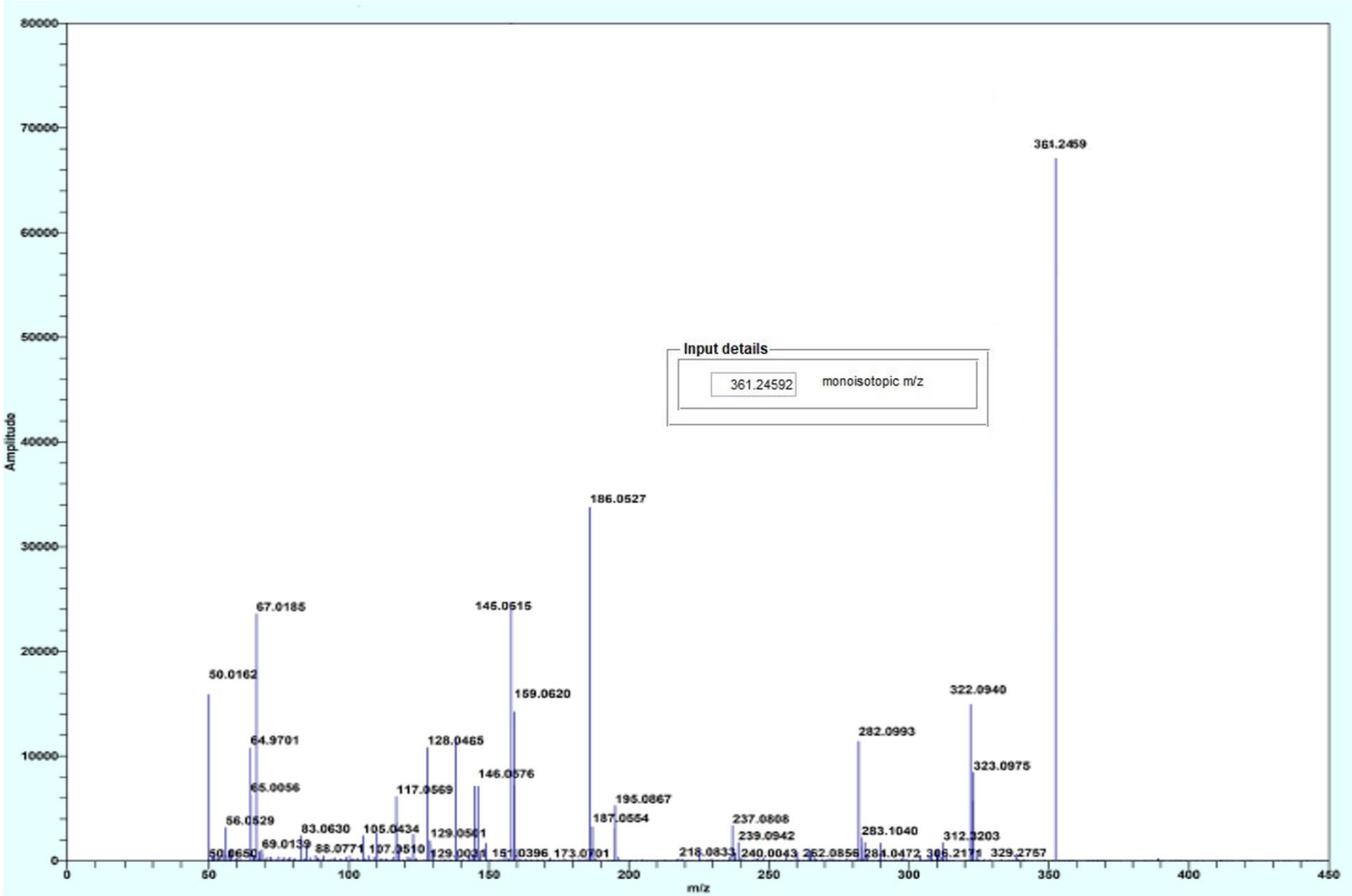

Figure S24. HRMS (APCI+) for *N-(2,4-diaminoquinazolin-6-yl)-2-[(quinolin-8-yl)oxy]acetamide* (***4h***).

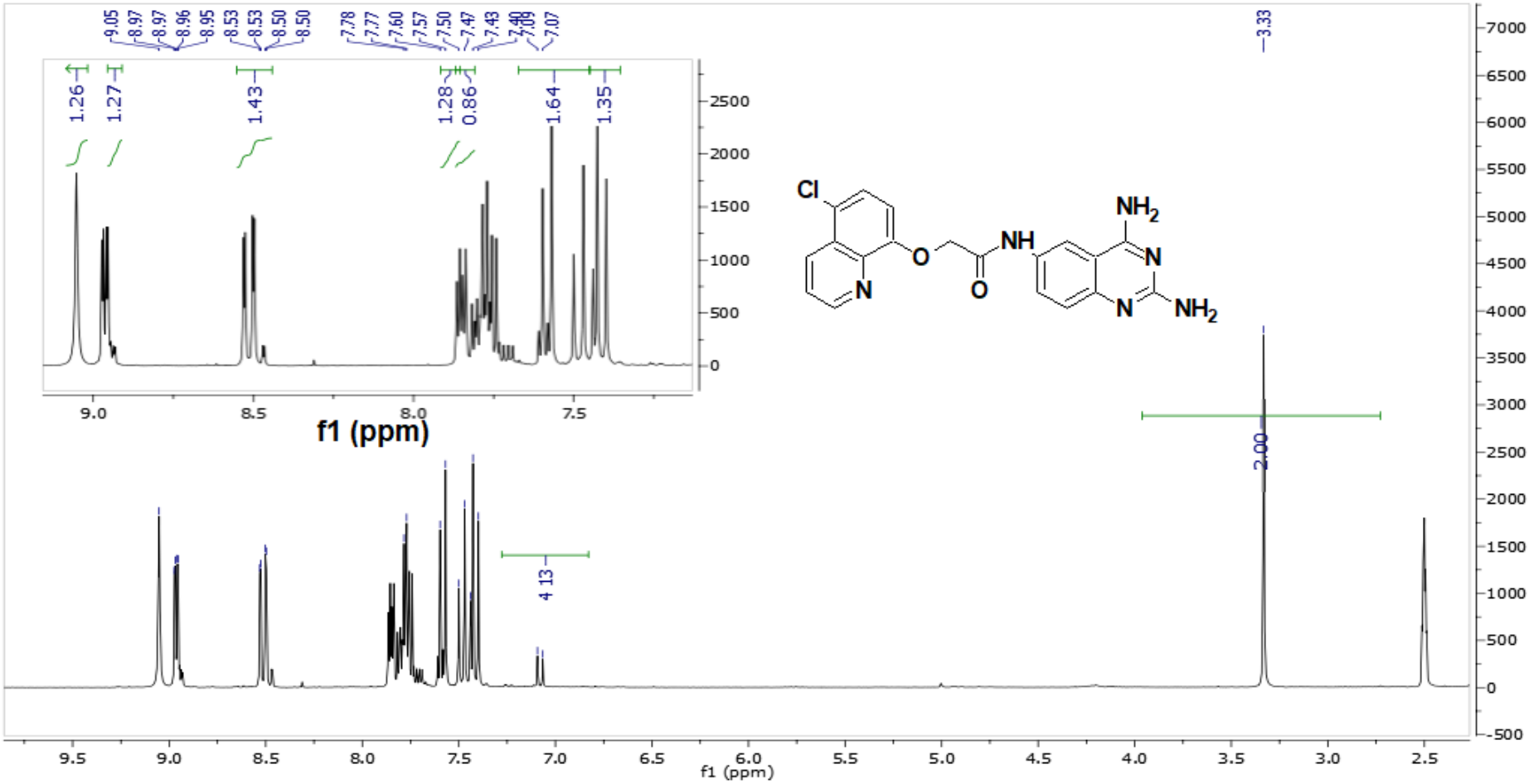

Figure S25. ^{1}H NMR (400 MHz Dimethyl sulphoxide-$_{d6}$) for *2-[(5-chloroquinolin-8-yl)oxy]-N-(2,4-diaminoquinazolin-6-yl)acetamide* (***4i***).

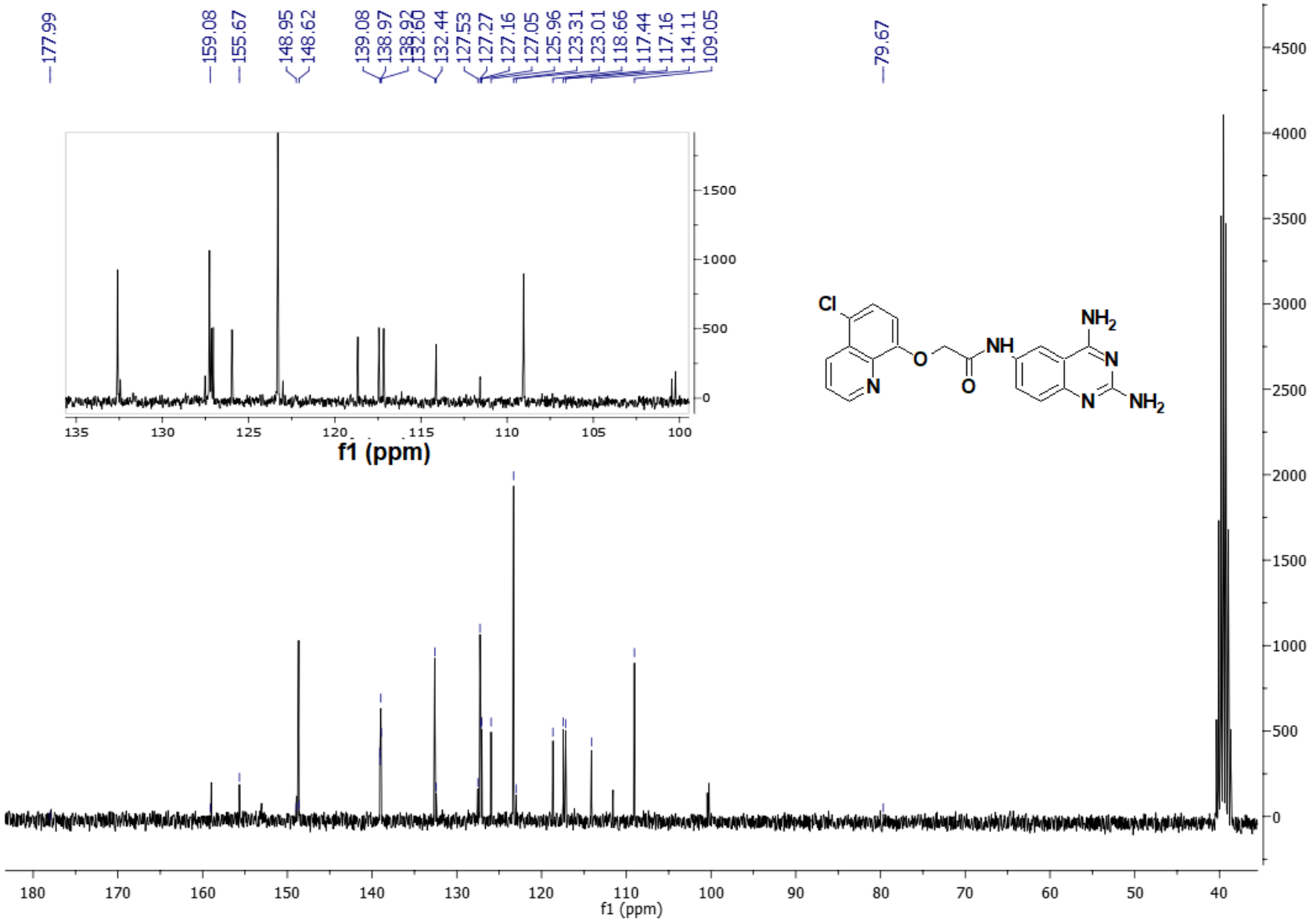

Figure S26. ^{13}C NMR (75 MHz Dimethyl sulfoxide -$_{d6}$) for *2-[(5-chloroquinolin-8-yl)oxy]-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4i**)*.

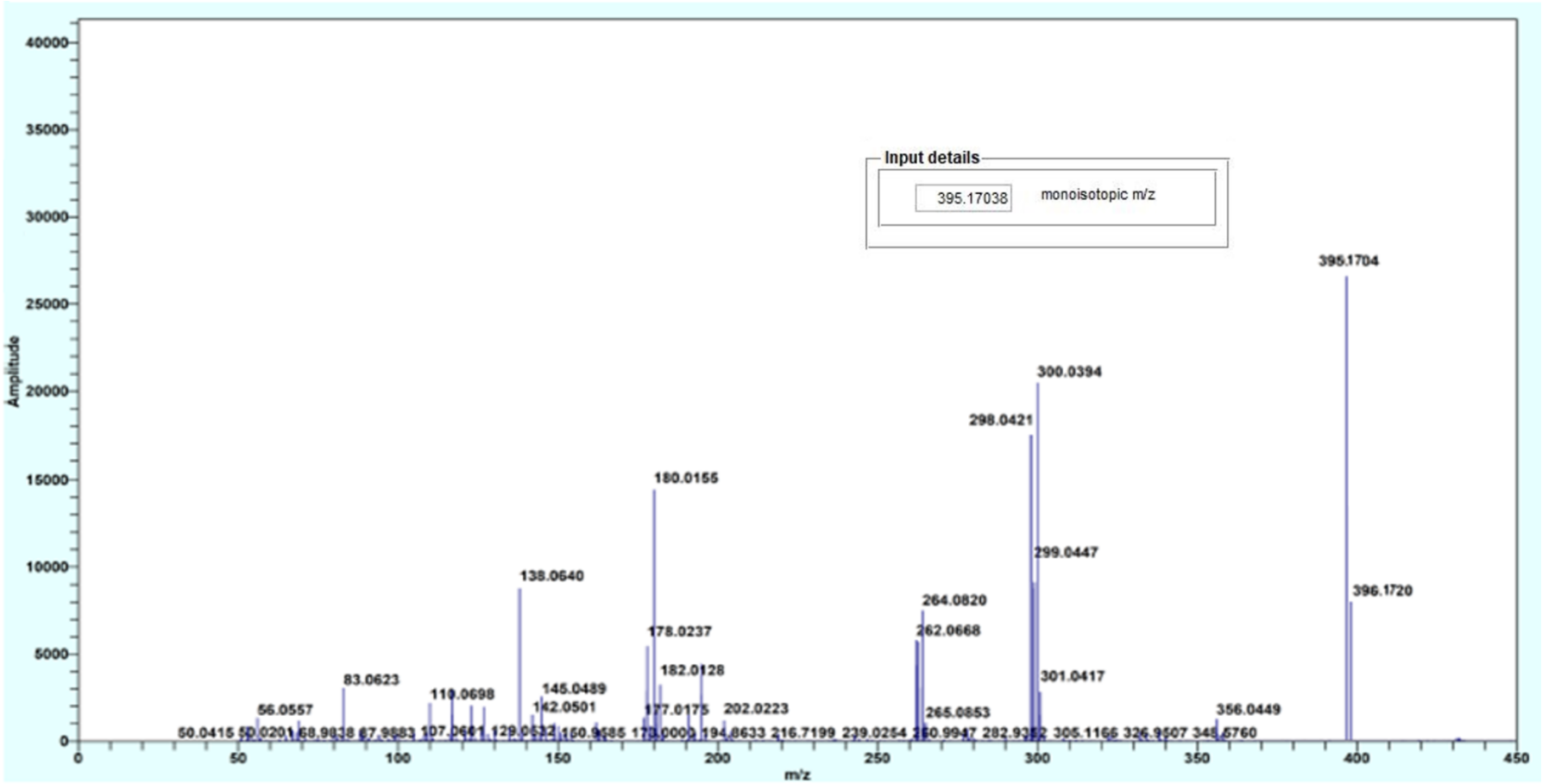

Figure S27. HRMS (APCI+) for *2-[(5-chloroquinolin-8-yl)oxy]-N-(2,4-diaminoquinazolin-6-yl)acetamide (**4i**)*.

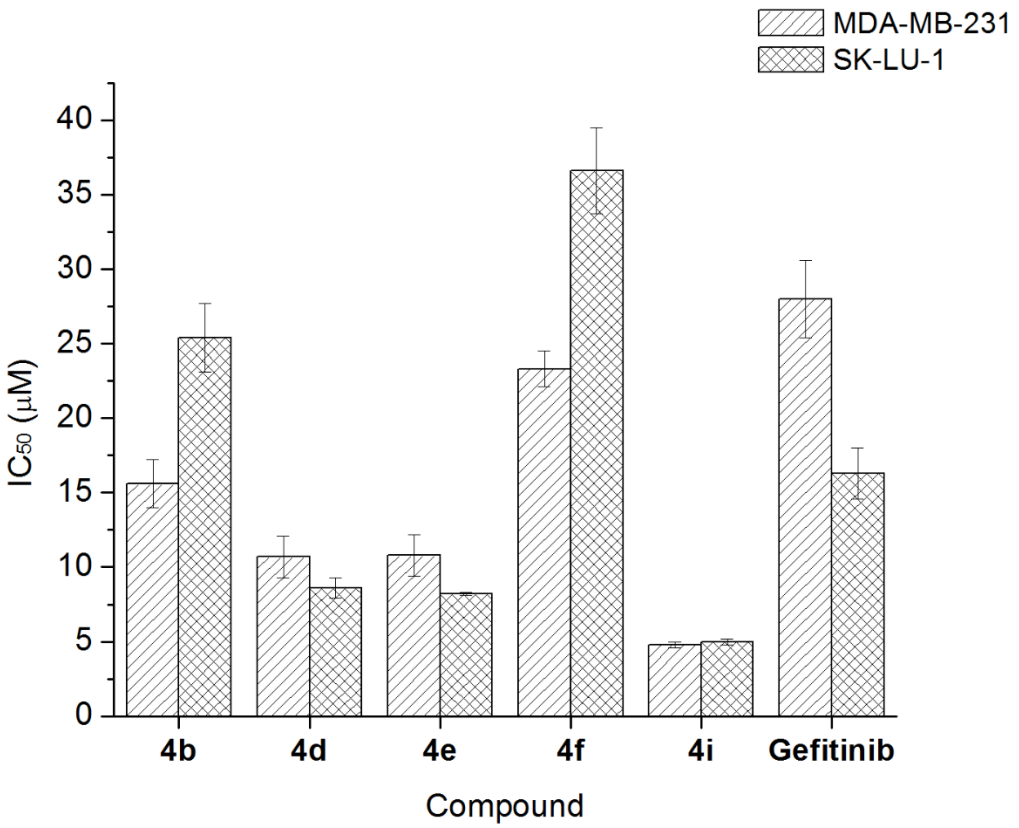

Figure S28. Histogram of the experimentally determined IC_{50} values (μM) in MDA-MB-231 and SK-LU-1.

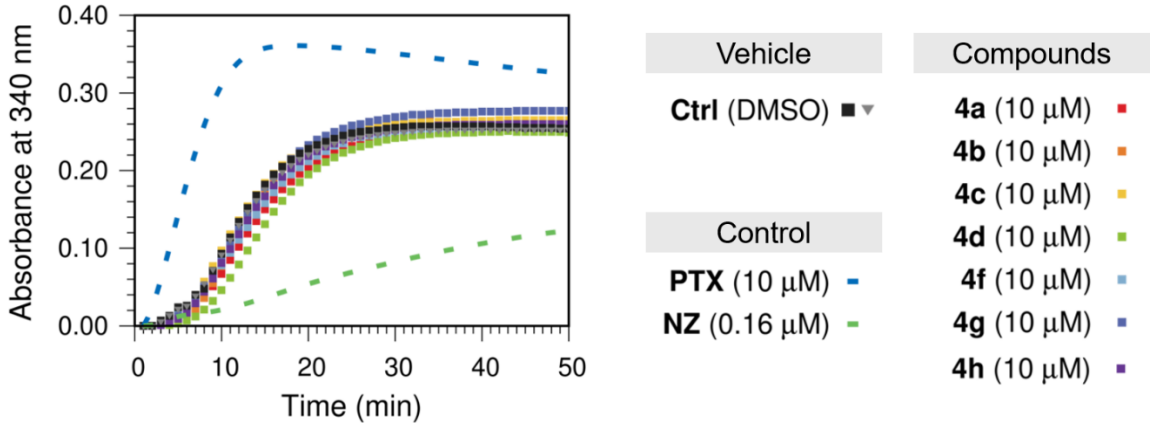

Figure S29. Tubulin polymerization curves of purified porcine brain tubulin in the absence (Ctrl, DMSO) and presence of quinazoline derivatives (**4a** – **4d** and **4f** – **4h**) at 10 μM. Curves of reference compounds **PTX** (10 μM) and **NZ** (0.16 μM) are shown as colored dotted lines.

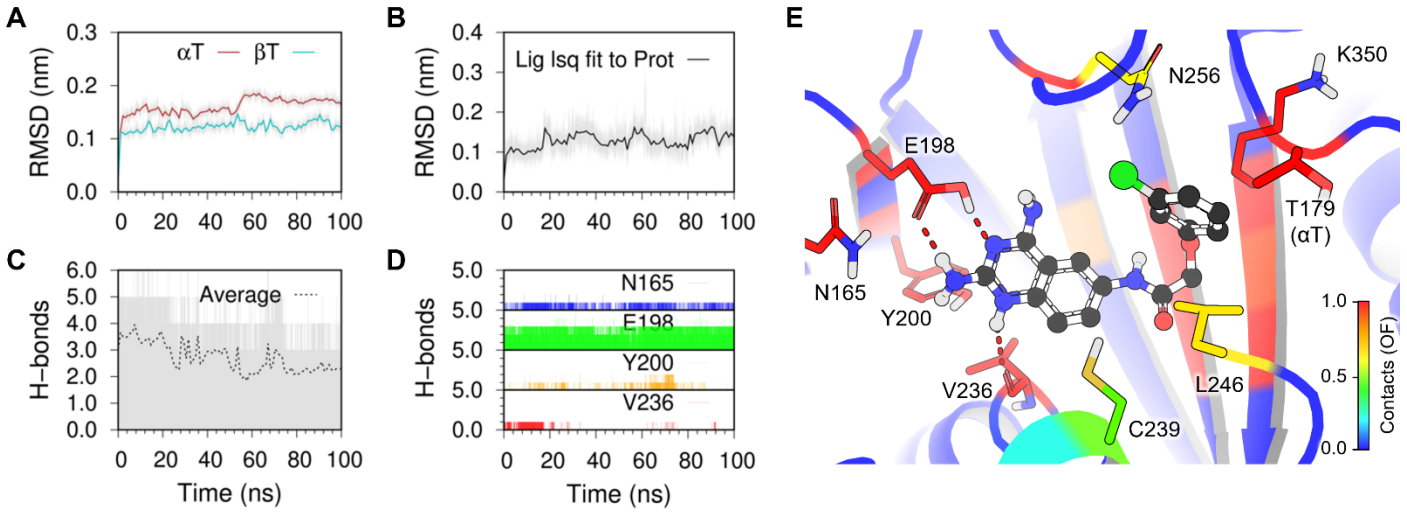

Figure S30. Analysis of the 100 ns MD simulation of αβ-tubulin-**4e** complex. Root-mean-square deviation (RMSD) of (A) αβ-tubulin backbone and (B) **4e** structure calculated from the least-square fit to the heterodimer. (C) Average and (D) per amino acid number of H-bonds of **4i** with the **NZ**/**COL** binding site through the simulation. (E) Depiction of residues involved in the interaction of **4i** with αβ-tubulin. The color scale shows the residues with the higher (red) to the lower (blue) value of the occupancy fraction (OF) with the compound.