SUPPLEMENTARY INFORMATION

Retro-forward synthesis design and experimental validation of potent structural analogs of known drugs.

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Section S1. User Guide for Allchemy's WebApp associated with the article

S1.1. General information

A WebApp to perform new calculations associated with this article is available for testing by academic users at https://analogs.allchemy.net/ (upon sending a registration email from an academic address, and on a rolling basis in two-week slots). Because of server limitations, some constrains for calculations were added, namely: maximum number of generations - 5, maximum time of single calculation – 30 minutes. Because the graph view of results is based on SVG2 standard, it is recommended to use Google Chrome or other browsers using the same engine, e.g., Chromium or Opera.

S1.2. Setting up new calculations

After logging in, user will be redirected to the "*New search*" tab (**Figure S1**), whereby calculations can be initiated. To set up the search, follow the instructions below:

1) Specify (optionally) allowed reaction conditions (I). It is possible to narrow down the search only to reactions occurring at particular temperatures, conditions and solvent classes.
2) Introduce the lead compound (II) using one or more input options: drawing editor, entering SMILES ("from text" option) or uploading .txt file (with SMILES) or .mol file. Only one target per calculation can be used.
3) Use "*propose*" functionality to automatically generate substrate collection or/and enter your own collection of substrates (III, from file, from editor, from text). When the "*propose*" functionality is selected, pop-up window with adjustable parameters appears (**Figure S2**).
4) Select motifs for substructure replacements. Allchemy automatically recognizes which types of motifs are present in the structure of the lead and presents the user only with possible options. All checkboxes are selected in default settings, but mind that more options selected will result in a larger set of substrates. Substructure replacements selected in calculations described in this publication were "*Non-fused 6-membered aromatic rings*" and "*Carboxylic acids*" for Ketoprofen and "*Ethers, Secondary Amines, Thioethers*" and "*Ketones*" for Donepezil. After clicking on the "*propose*" button, retrosynthetic calculations commence (it can take up to ~5 minutes) and the user will be redirected to the window with automatically generated starting materials and a set of auxiliary reagents (**Figures S3,S4**).
5) Review generated set of substrates (**Figure S3**). Generated building blocks, auxiliary reagents and compounds introduced by the user can be browsed separately, by clicking on the corresponding tabs (a). Selection of compounds via clicking on the structures (background of selected molecule(s) will change to blue) allows to remove unwanted starting materials (remove selected, b) or to narrow down the set only to selected

compounds (keep selected, c). Click on the "*next page*"/"*prev page*" buttons (d) to browse all substrates. When your set of starting materials is finalized, click on the "x" button in the top-right corner (e).

6) Displaying the target and/or substrates as well as further modifications are possible in the "*Show selected*" section (**Figure S1**, IV). Clicking on "*Show molecules*" in the "*Reactants*" section will re-open the window shown in **Figure S3**.
7) Set the number of synthetic generations (max. 5; V) and limit for maximum molecular weight for all generated molecules (typically set to 100-150 g/mol more than the molecular mass of the parent compound).
8) Adjust the beam-width (parameter *W*, VI) that prunes the molecules generated in each forward generation. Pruning slider set in the middle (default) corresponds to $W = 150$. Lower pruning translates into a higher *W* value whereas higher pruning, to a lower *W* value. Searches with higher *W* generate larger networks. They can sometimes be beneficial as they can incorporate intermediates that are, initially, not the most similar to target but, after additional modification, become so. Searches with lower *W* are more focused and more "greedy" in the sense that they accept intermediates whose similarity to target keeps increasing with synthetic generations, *G*.
9) Additional limits for intermediates can be set (optionally, VII): maximum number of heavy atoms, chiral centers and halogen atoms.
10) Set a search name for a calculation (optionally, VIII). They will be available in the "*Saved results*" tab under this name when calculations are finished.
11) Click on the "*Search*" button (IX) to start calculation. Depending on search settings and number of substrates, calculation should take between 5 and 30 minutes. Upper limit of calculation time is set to 30 minutes and after this time, calculations will be stopped and results, up to the last completed synthetic generation, will be displayed.

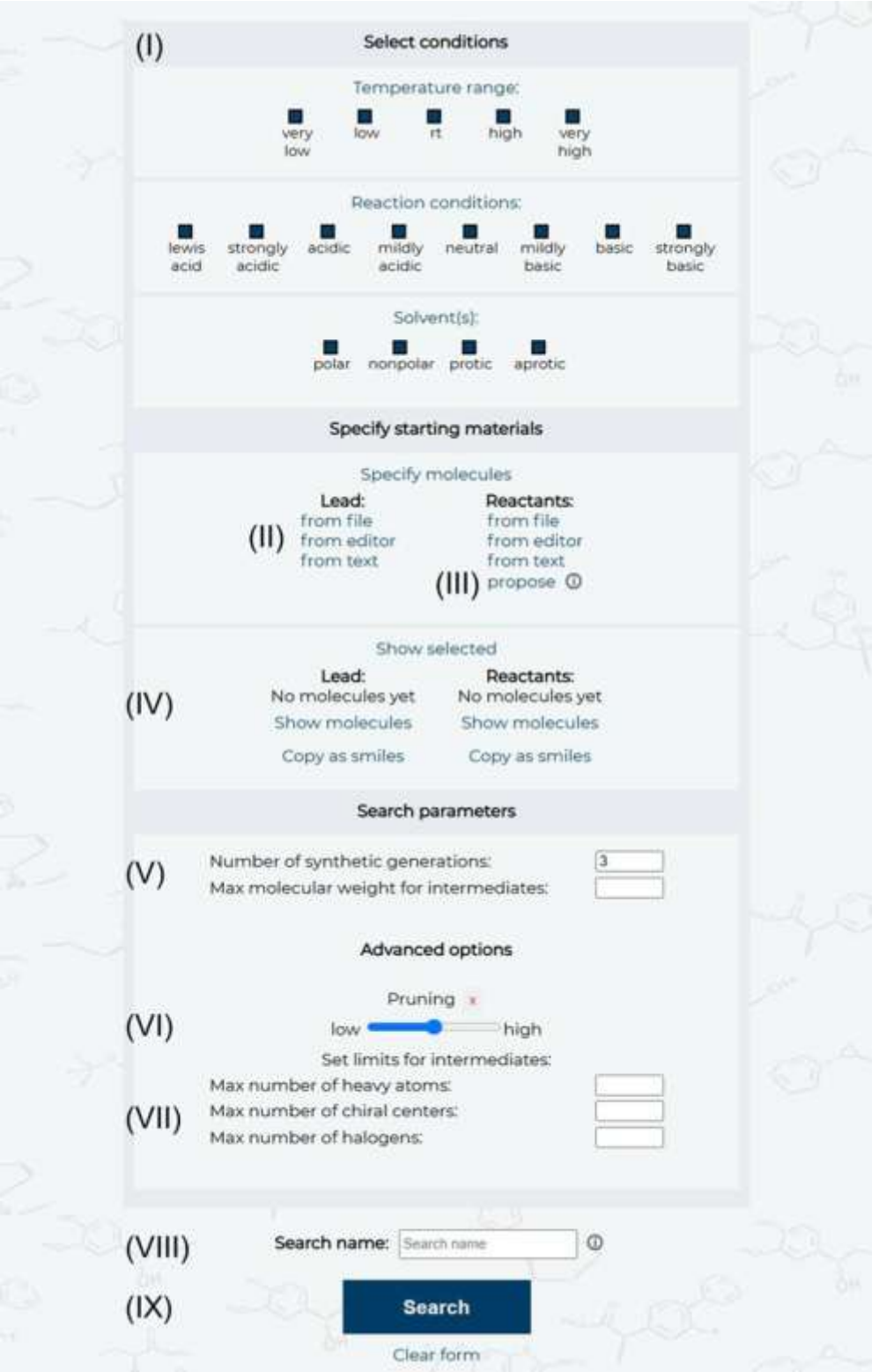


Figure S1. New search tab. Setting up a new search requires: I) Constraining (optionally) allowed reaction conditions (temperature range, reaction conditions, solvents). II) Specification of a lead compound, III) Selection of starting materials via automatic "*propose*" functionality or/and addition of one's own collection of substrates, IV) Reviewing of target and reactants (optional), V) Setting number of synthetic generations and mass limits and, optionally, VI) Adjustment of the pruning slider (beam-width parameter, *W*), VII) Setting additional limits for

intermediates, and VIII) Naming calculations. Clicking on the "*Search*" button (IX) will start the calculations.

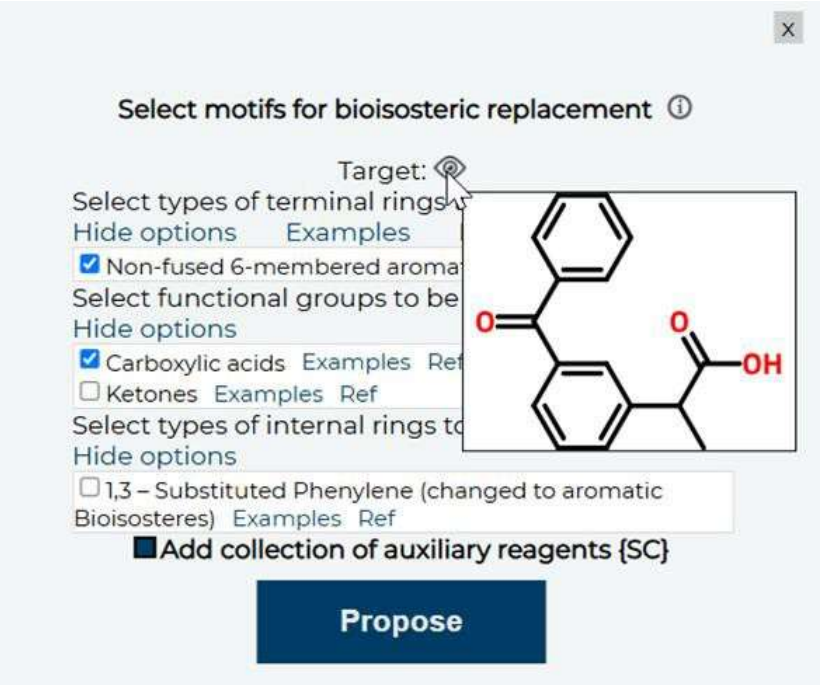


Figure S2. Allchemy's panel for the selection of substructure replacements. Allchemy automatically recognizes which types of motifs are present in the structure of the lead and presents the user with possible replacement options. All checkboxes are selected in default settings, but please mind that more options selected will result in bigger set of substrates. Hovering over an "eye" icon will display structure of the parent for which analogs are sought. The replacements are divided into three categories: terminal rings, internal rings and functional groups, with each category further split into subcategories. e.g., *Non-fused 6-membered aromatic rings*, *Fused aromatic rings*, *Aliphatic rings*. Replacement of internal rings is performed based on the substitution pattern, for example, 2,5-disubstituted thiophene and 2,5-disubstituted pyridine are proposed as replacements for 1,4-substituted benzene whereas 2,4-disubstituted furan and 2,4-disubstituted pyrimidine are replacements for 1,3-substituted benzene (based on Tables34 and 53 from *J. Med. Chem*. 2021, 64, 14046–14128).

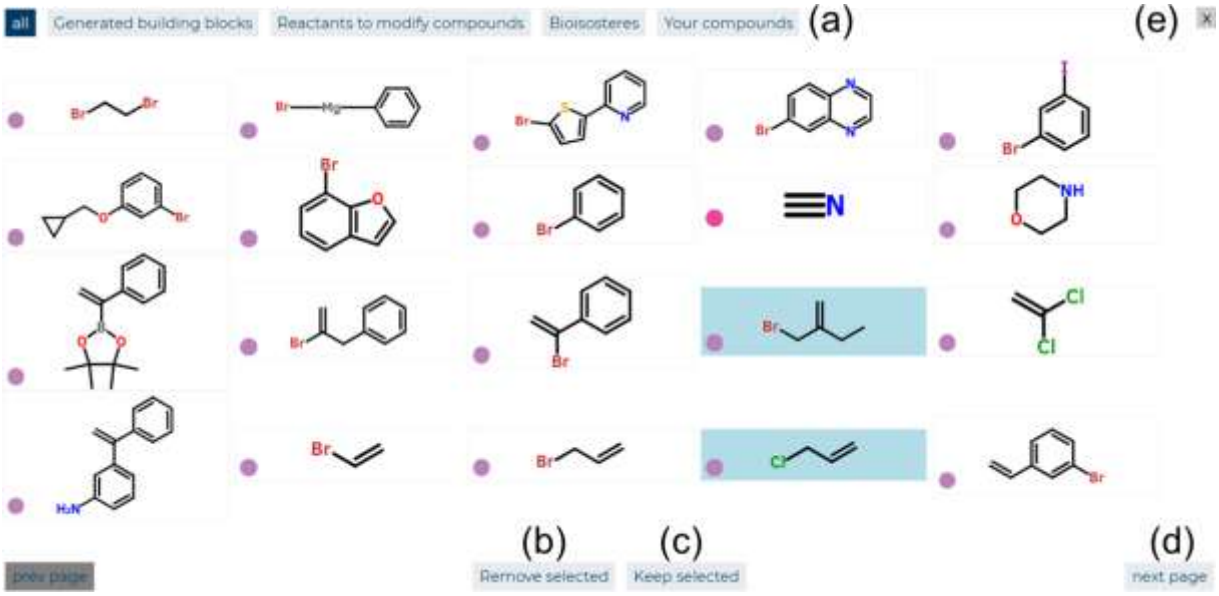


Figure S3. Browsing the set of proposed starting materials. **a)** Building blocks generated from retrosynthesis of the parent/target molecules and its "replica" molecules derived from substructure replacements, set of simple auxiliary reagents and substrates/reagents introduced by the user can be displayed separately, by clicking on the corresponding tab. Selection of compounds (left-click on the structure) allows to **b)** remove or **c)** keep selected molecules. **d)** Click on the "*next page*" and "*prev page*" buttons to browse all the substrates. **e)** Close the window using the "x" button located in the top-right corner.

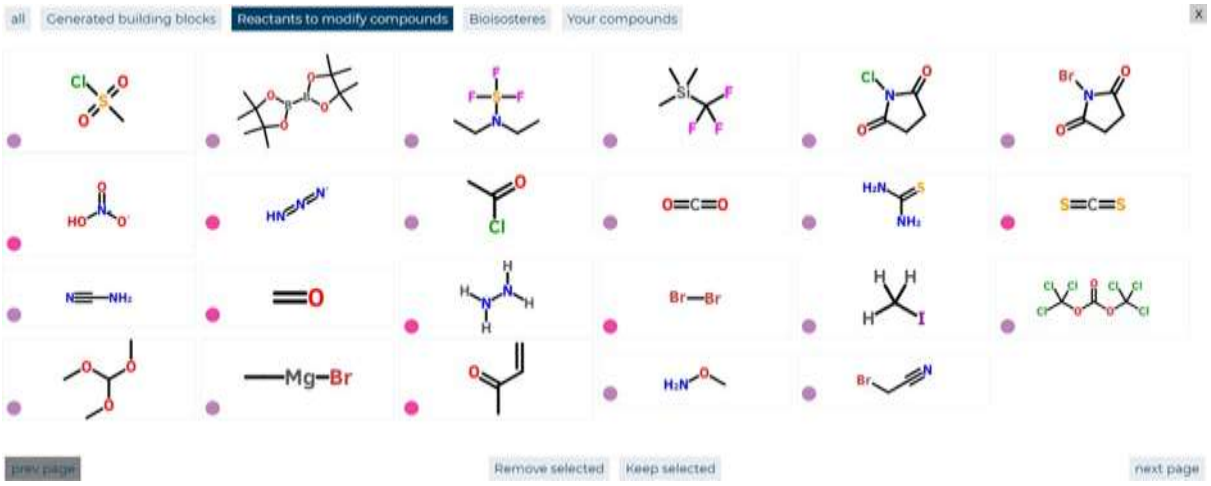


Figure S4. Set of 23 auxiliary reagents – popular chemicals chosen for synthetic versatility.

S1.3. Browsing results

After calculation finishes, the user will be redirected to the results page. Generated compounds are displayed as panels of molecular structures (**Figure S5**). To browse the structures, user can use "*next page*" and "*prev page*" buttons located under the structures or use "*go to page*"

function (by typing number of the page of interest and clicking "*go*"). To visualize the parent/target, user can hover over the "eye" icon.

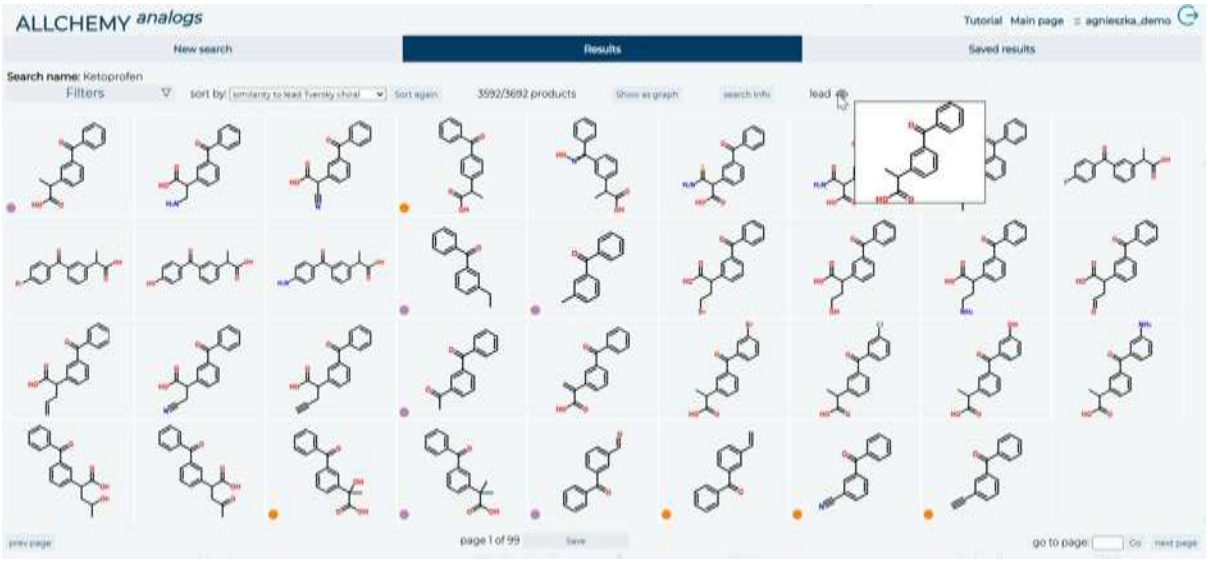


Figure S5. First page of the results of a calculation (here, analogs of Ketoprofen target) displayed as a default panel view.

Button "*search info*" located in the top panel allows the user to display information about search parameters (**Figure S6**) and lists of "replica" molecules of the lead (as list of SMILES) generated by substructure replacement as well as starting materials used in this calculation (both as structures and a list of SMILES).

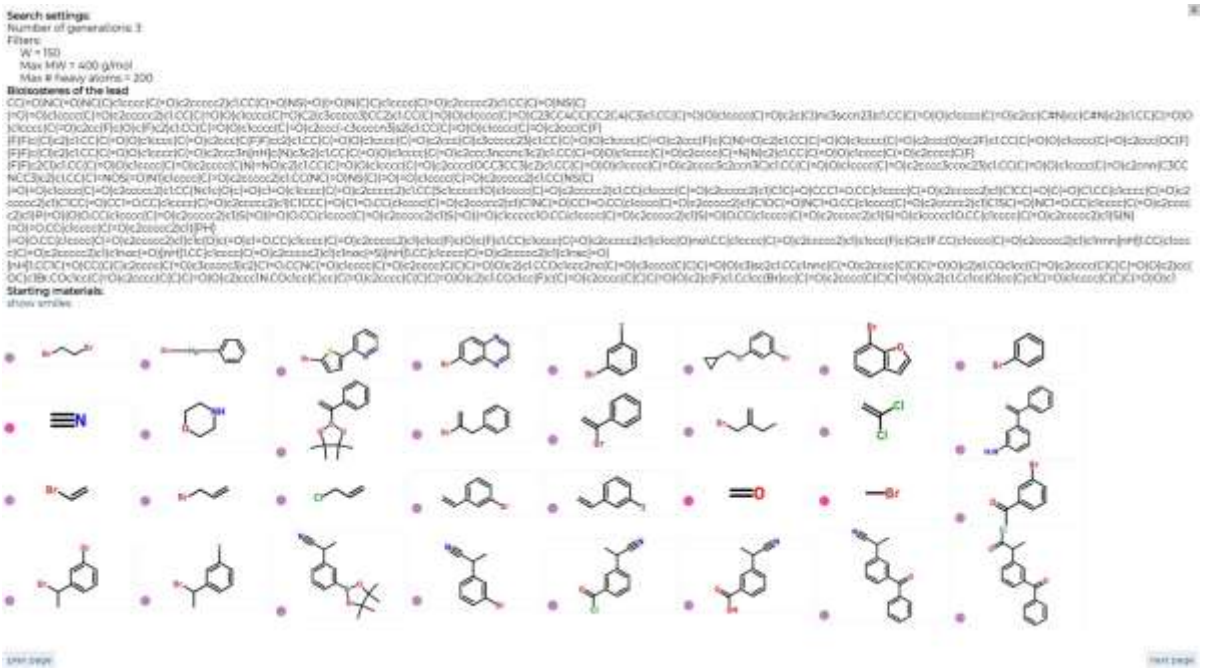


Figure S6. Information about search available after clicking "*search info*" button. Search parameters are listed at the top of the window. List of the "replica" molecules of the parent as

SMILES is available in the middle whereas structures of substrates are displayed along with corresponding list to SMILES and placed at the bottom of the pop-up window.

Clicking on any of the structures from **Figure S5**displays details of its synthesis – and, usually, multiple synthetic pathways found. As illustrated in **Figure S7**, each step lists not only the reaction scheme, but also reaction name, typical reaction conditions, typical solvent and illustrative literature reference(s) for this type of chemistry (mostly as DOI hyperlinks). Syntheses designed by the program also take into consideration environmental issues and practical aspects. In reactions involving harmful reagents or non-green solvents, greener alternatives are proposed, if a reasonable replacement is possible. For example, LiTMP is suggested as an alternative for LDA – highly flammable base (yellow frame in **Figure S7**). A practically important feature is inclusion of reaction by-products. After clicking on the flask icon, structures of by-products are displayed after the main product (green frame in **Figure S7**). In the highlighted example, diisopropylamine is generated from LDA during deprotonation of a carboxylic acid substrate. Additionally, if a proposed reaction has similar literature precedents in patent literature, "*show similar reaction(s)*" hyperlink will be available (purple frame in **Figure S7**). Clicking on the hyperlink opens a pop-up window with examples of similar reactions from patent literature. **Figure S8** shows four such reactions, similar to the specific instance of α-alkylation of active methylene compound from **Figure S8**.

Additional pathways (if available) and molecular/pKa information about the target compound can be displayed by clicking on the appropriate grey tabs at the top of the window (**Figure S9**). Predictions of machine-learning models can also be found in the "*info*" tab for every molecule, namely:

- hERG cardiotoxicity (on the 0-1 scale with values <0.5 being desirable)
- degree of human plasma protein binding, hPPB, related to drug absorption and efficacy (0-100%, with very high values less desirable)
- MDCK-MDR1 efflux rations estimating the degree to which the molecules are pumped out of the cells (values above ~2 suggest undesirable, active efflux)
- blood-brain barrier penetration (0–1, with higher values reflecting higher probability of BBB penetration)
- drug-likeness
- list of 20 protein targets for which a given molecule is predicted to have the highest affinity

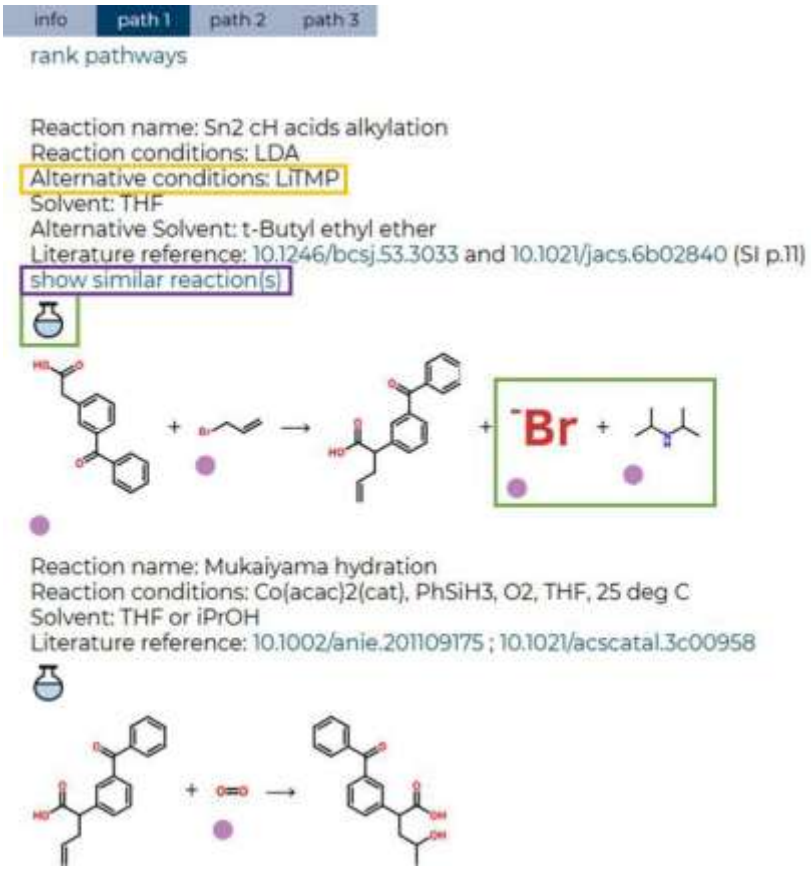


Figure S7. Example of synthetic details available upon clicking on the molecule. Additionally, other pathways (if available) and information about the molecule can be found on this page (by clicking appropriate grey buttons at the top). Each reaction scheme is accompanied by reaction name, typical reaction conditions, typical solvent and illustrative literature reference(s) for this type of chemistry**.** Alternative solvents/reagents are proposed for reactions involving harmful/non-green conditions, when reasonable replacement is possible (yellow frame). Clicking upon the flask icon displays by-products of a given reaction (green frame). "*Show similar reactions*" hyperlink, available for some of the reactions, enables the user to review instances of similar reactions from the patents (purple frame and **Figure S8**).

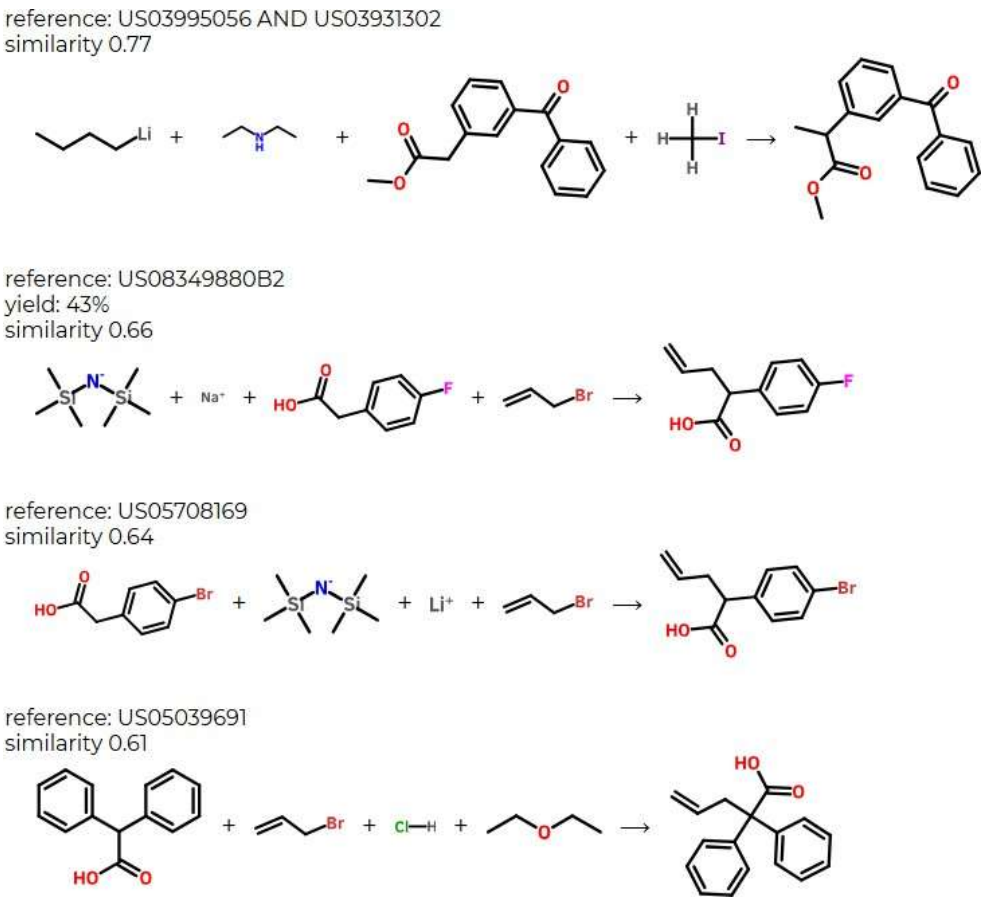
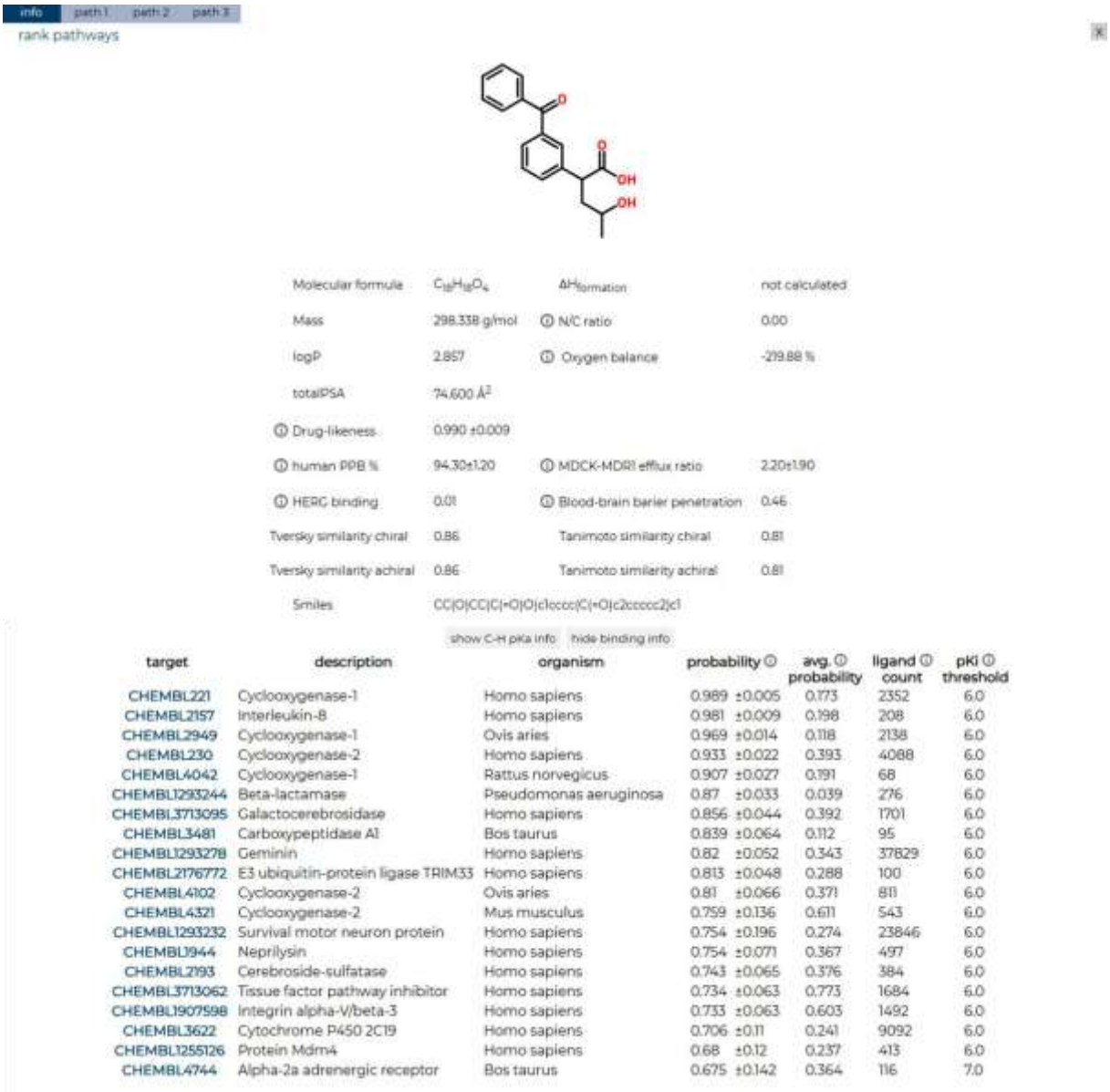


Figure S8. Examples of similar reactions. This window appears upon clicking on the "*show similar reactions*" hyperlink (purple frame in **Figure S8**). Examples are sorted by Tanimoto-based similarity to original reactions. Each reaction is accompanied by patent number(s) and similarity to original transformation. Some records contain also information about reaction yield (2nd transformation from the top). Reagents and sometimes solvents are often included in reaction visualization.

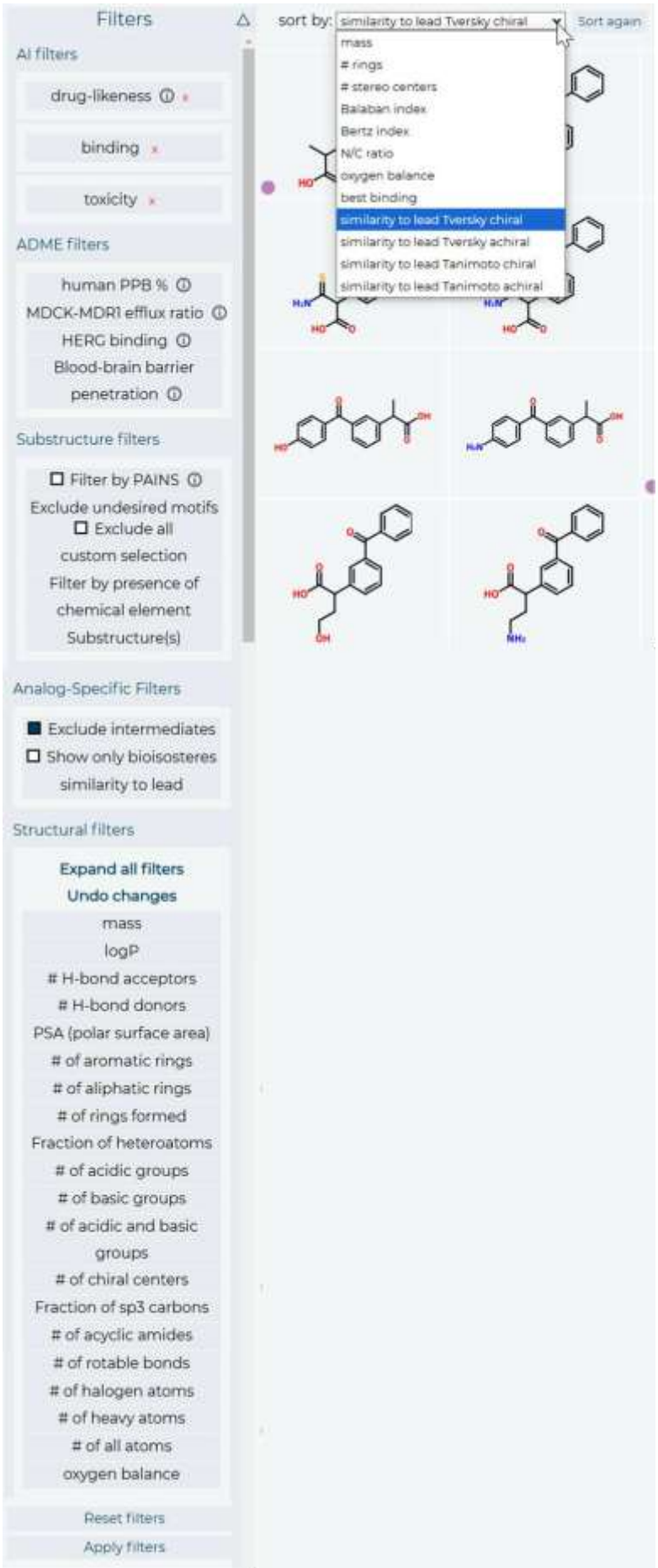


target	description	organism	probability	avg. probability	ligand count	pKi threshold
CHEMBL221	Cyclooxygenase-1	Homo sapiens	0.989 ±0.005	0.173	2352	6.0
CHEMBL2157	Interleukin-8	Homo sapiens	0.981 ±0.009	0.198	208	6.0
CHEMBL2949	Cyclooxygenase-1	Ovis aries	0.969 ±0.014	0.118	2138	6.0
CHEMBL230	Cyclooxygenase-2	Homo sapiens	0.933 ±0.022	0.393	4088	6.0
CHEMBL4042	Cyclooxygenase-1	Rattus norvegicus	0.907 ±0.027	0.191	68	6.0
CHEMBL1293244	Beta-lactamase	Pseudomonas aeruginosa	0.87 ±0.033	0.039	276	6.0
CHEMBL3713095	Galactocerebrosidase	Homo sapiens	0.856 ±0.044	0.392	1701	6.0
CHEMBL3481	Carboxypeptidase A1	Bos taurus	0.839 ±0.064	0.112	95	6.0
CHEMBL1293278	Geminin	Homo sapiens	0.82 ±0.052	0.343	37829	6.0
CHEMBL2176772	E3 ubiquitin-protein ligase TRIM33	Homo sapiens	0.813 ±0.048	0.288	100	6.0
CHEMBL4102	Cyclooxygenase-2	Ovis aries	0.81 ±0.066	0.371	811	6.0
CHEMBL4321	Cyclooxygenase-2	Mus musculus	0.759 ±0.136	0.611	543	6.0
CHEMBL1293232	Survival motor neuron protein	Homo sapiens	0.754 ±0.196	0.274	23846	6.0
CHEMBL1944	Neprilysin	Homo sapiens	0.754 ±0.071	0.367	497	6.0
CHEMBL2193	Cerebroside-sulfatase	Homo sapiens	0.743 ±0.065	0.376	384	6.0
CHEMBL3713062	Tissue factor pathway inhibitor	Homo sapiens	0.734 ±0.063	0.773	1684	6.0
CHEMBL1907598	Integrin alpha-V/beta-3	Homo sapiens	0.733 ±0.063	0.603	1492	6.0
CHEMBL3622	Cytochrome P450 2C19	Homo sapiens	0.706 ±0.11	0.241	9092	6.0
CHEMBL1255126	Protein Mdm4	Homo sapiens	0.68 ±0.12	0.237	413	6.0
CHEMBL4744	Alpha-2a adrenergic receptor	Bos taurus	0.675 ±0.142	0.364	116	7.0

Figure S9. Molecular information and predictions of machine-learning models can be displayed for any molecule upon clicking on the "*info*" tab. List of 20 molecular targets with the highest predicted probability of binding contains: ChEMBLID as a hyperlink to the ChEMBL database, name of the molecular target, organism, predicted probability of binding, average activity probability for all ChEMBL ligands, number of ligands for this target in the training set and pKi threshold for the target, which is used to determine if a ligand is active.

S1.4. Analysis of results

Analysis of the results can be performed using "sort" and "filter" functionalities. In addition to sorting by similarity to target (default setting), user can choose from the list of nine parameters, i.a., mass, number of rings and oxygen balance (right part of **Figure S10**).



List of the filters on the left comprises 5 general classes: AI filters for prediction of drug-likeness, binding to protein targets and toxicity; ADME filters - machine-learning models for prediction of human plasma protein binding, MCDK-MDR1 efflux ratio, hERG binding, blood-brain barrier penetration; Substructure filters to exclude undesired motifs, PAINS motifs or filter by presence of chemical elements or user-defined substructures; Analog-specific filters enable the user to exclude intermediates (molecules with functional groups absent in any drugs, selected by default), display only bioisosteres of the lead or molecules above user-defined similarity threshold; Structural filters with twenty physico-chemical and structural properties, i.a., mass, logP, number of aromatic or aliphatic rings (left part of **Figure S10**).

Figure S10. Analysis of results can be performed via sorting (right) and/or filtering (left). Filters comprise 5 general classes: AI filters, ADME filters, Substructure filters, Analog-specific filters and Structural filters. Multiple filters can be used simultaneously.

S1.5. Graph view

In addition to the default panel view, results of the calculation can be displayed as a reaction graph/network (**Figure S11**). This modality is useful to track synthetic pathways leading to selected molecule(s) as well as for further analysis of results. Menu in the bottom-left corner allows to color or resize nodes of the graph, corresponding to particular molecules, by multiple parameters, i.a., number of incoming or outgoing connections, similarity to drugs or agrochemicals (calculated using Tanimoto similarity between Morgan fingerprints) or combination of chemical elements the molecules contain. Additionally, checkbox "show molecules on paths" may facilitate navigating the graph by displaying all intermediates next to the nodes (when number of structures is small enough, **Figure S11.a**) or as a panel over the graph (when number of structures would be too big to assure comfortable work with the graph, **Figure S11.b**).

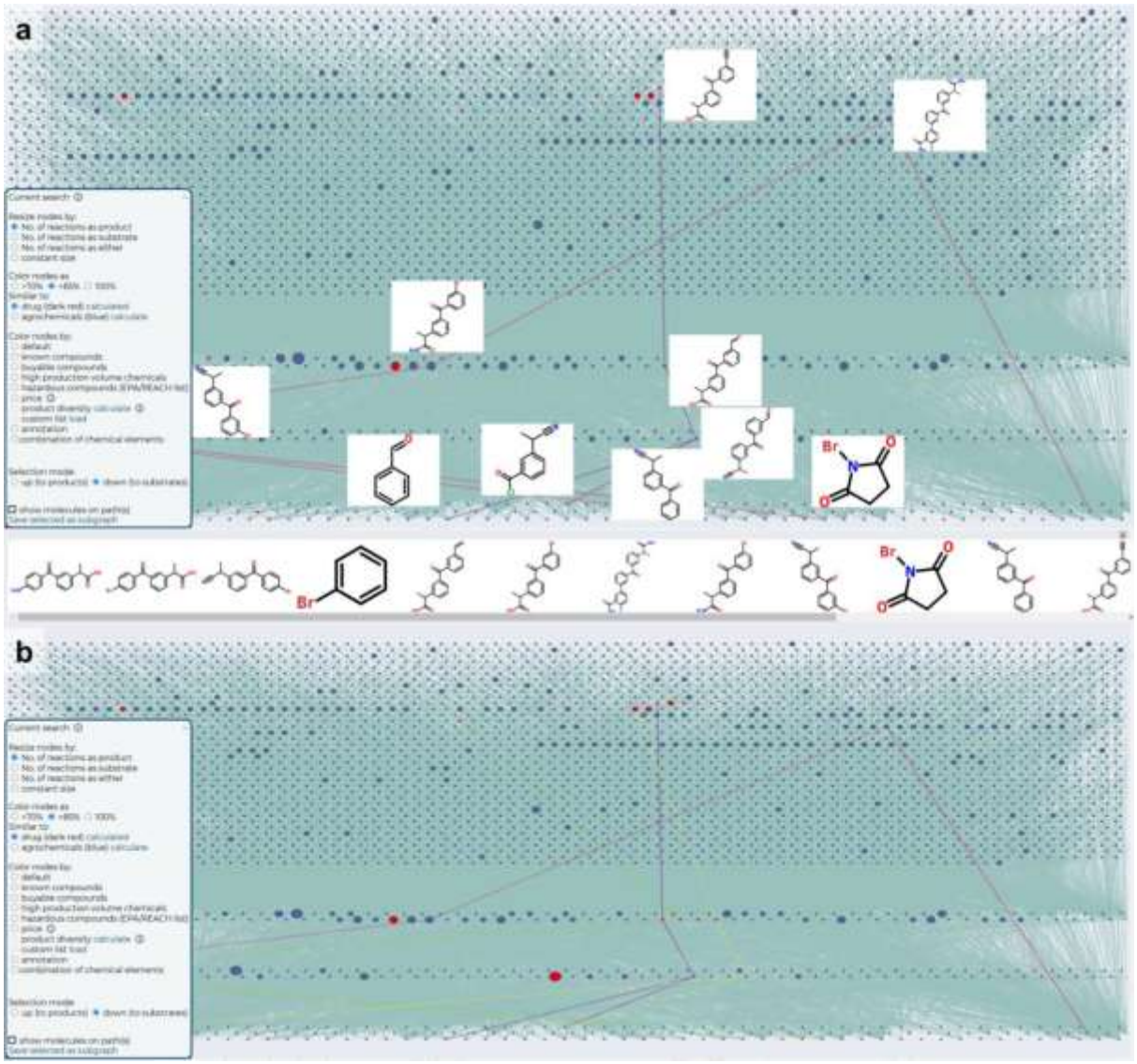


Figure S11. Results of calculations (here, for the Ketoprofen parent) presented as a reaction graph/network. All molecules resulting from particular calculations are stacked into "layers" according to the synthetic generation, G_i, in which they were produced; nodes representing

substrates are in bottom layer. Hovering over any node displays the structure of the corresponding molecule, left-clicking on the node opens a window with synthetic pathway(s), while right-clicking traces on the graph the pathway leading to this molecule (colored lines connecting product with substrates via intermediates). Expandable panel located in the bottom-left corner allows for further graph analysis. The nodes can be colored by, i.a., similarity of a given molecule to existing drugs, known or hazardous compounds. Additionally, it is possible to resize nodes by number of reactions in which a molecule serves as product (k_{in}), substrate (k_{out}) or either. Here, nodes are resized by number of incoming connections (reactions leading to the molecule) and molecules with similarity to drugs >0.85 are colored red. "*Selection mode*" section of the expandable panel allows to change the type of action resulting from right-clicking on the compound. In the default selection mode ("*down*", illustrated in this Figure), right-clicking on the node traces the pathway generated in the smallest number of generations leading to this molecule, while in mode "*up*", it traces all reactions in which the molecule serves as a substrate. Additionally, to facilitate the analysis of results, it is possible to use "*show molecules on path(s)*" checkbox. When selecting pathways with this functionality turned on, miniatures of all molecules participating in a given pathway will be displayed **a)** next to their corresponding nodes or **b)** as a panel over the graph.

S1.6. Saved results

All calculations performed by the user will be automatically saved in "*Saved results*" tab under user-specified name. If the *search name* was not provided during search set-up, calculations will be saved under software-generated name. The result name can be changed anytime, using "pencil" icon located next to the current name. Additionally, all users will be provided with pre-calculated results described in this publication under the names "Ketoprofen" and "Donepezil" (**Figure S12**). Saved results can be filtered and sorted using different key-parameters, with "Recent" option (newest calculations on the top) being default.

Figure S12. Saved results tab. All finished calculations are automatically saved and available for future analysis in the "*Saved results*" tab. Additionally, all users will be provided with pre-calculated results described in this publication under the names "Ketoprofen" and "Donepezil".

Section S2. A comment on the selection of starting materials based on the similarity to parent

One of the possible approaches to analog generation is to select starting materials based on the similarity to the parent's various substructures. This can be done either by simple substructure matching of commercially available molecules (up to some size threshold) against the parent itself or by first performing retrosynthesis of the parent and then identifying commercial chemicals that are the most similar to these building blocks. One of the problems with such approaches is that metrics of structural similarity are not necessarily indicative of functional similarity (see discussion in ref[S1-4]), and hence our "replicas"-based approach. A more mundane problem is that by simply searching for similar fragments, one may lose the reactive handles by which these fragments could later be connected (see example in **Figure S13** below). In approaches incorporating initial retrosynthesis (main-text ref. 26), one can overcome this problem – at least in part – by stipulating that the similarity search be confined to molecules retaining the necessary reactive groups. This however, does not take into account situations in which a very similar fragment may be available but with a chemically equivalent handle – say, Cl vs Br, which are formally different but, in many reactions, exhibit similar reactivity. This problem, is again, potentially surmountable by introducing tables of groups that are "exchangeable". We tried a similarity approach early on but were not satisfied with the chemical flexibility of the generated blocks whereas construction of comprehensive lists of exchangeable groups (to accommodate some 25,307 reaction types in Allchemy) proved a prohibitive undertaking.

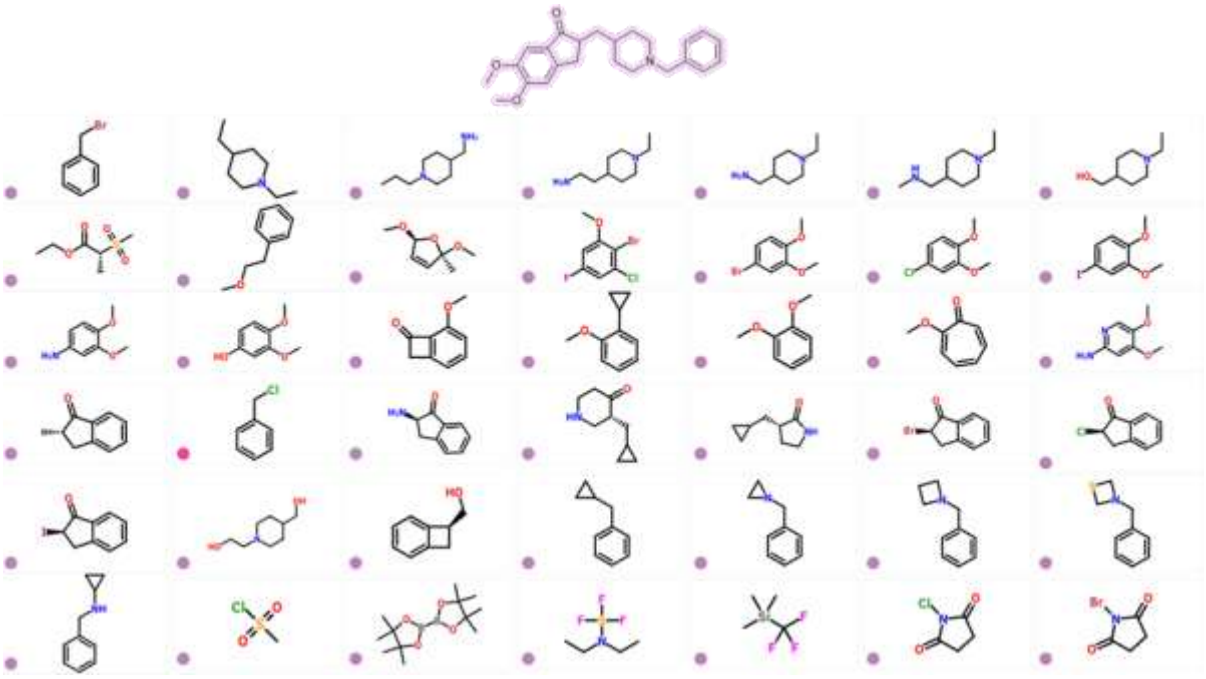


Figure S13. Substrates chosen by similarity to the target molecule (Donepezil, on the top). Some substrates lack any reactive functional group that could be used as attachment point in forward synthesis, while others, despite containing reactive functionality and structural pattern

from the target molecule, do not have a right partner to react with. For example, benzyl bromide (left-most molecule on the top) would be an excellent substrate for alkylation of 4-piperidyl fragment, but all six piperidine-containing molecules in the top-row are already substituted with ethyl/propyl groups which, as a consequence, precludes such alkylation.

Section S3. Addition of simple chemicals to the substrate set.

In this section, we compare the forward syntheses of analogs with and without the use of the set of 23 "auxiliary" reagents from **Figure S4** (i.e., for a given target, searches starting from the same set of retrosynthesis-generated substrates but with vs. without 23 auxiliaries also included). In this comparison, all searches were up to 3 synthetic generations, and the limit for molecular weight of the generated molecules was set to 550 g/mol for Donepezil and 400 g/mol for Ketoprofen.

The results are summarized in **Table S1**. For both targets, inclusion of the 23 auxiliary reagents increased the number of generated products and analogs. For the total number of products up to G3, the increase was moderate (15% for Donepezil and 7% for Ketoprofen) but became more significant for analogs with target similarity ≥0.7 (27% and 28%) and for close analogs with target similarity ≥0.85 (33% and 35%)/ . **Figure S14** shows examples of 10 close analogs for each target that are found only when the the auxiliary reagents are used.

Table S1. Comparison of forward calculations performed with and without the set of auxiliary reagents for Donepezil and Ketoprofen.

	Donepezil		*Ketoprofen*	
	Calculations **without** auxiliary reagents	Calculations **with** auxiliary reagents	Calculations **without** auxiliary reagents	Calculations **with** auxiliary reagents
Number all of products	3138	3619 (+15%)*	3459	3692 (+7%)*
*Number of analogs (similarity ≥0.7)***	1752	2222 (+27%)*	609	781 (+28%)*
*Number of close analogs (similarity ≥0.85)***	141	188 (+33%)*	69	93 (+35%)*

* - numbers in the parentheses denotes percentage increase compared to calculations without auxiliary reagents

** - similarity to target or one of target's "replicas"

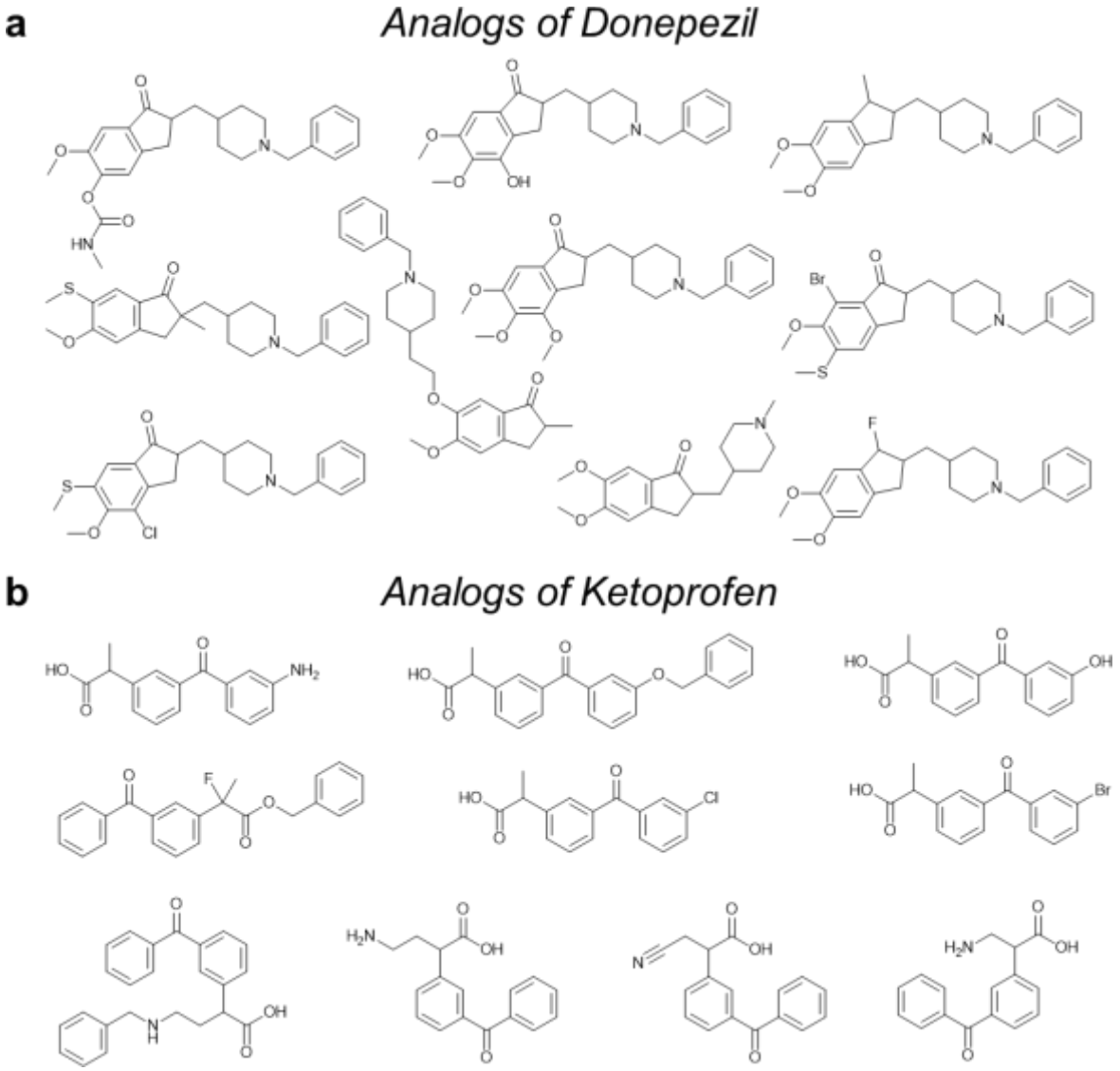


Figure S14. Close analogs (similarity to target or one of target's "replicas" ≥0.85) of Donepezil and Ketoprofen found only in calculations starting from the substrate set augmented with the collection of 23 auxiliary reagents.

Section S4. Molecular docking Studies

The crystal structures of COX-2 and AChE were extracted from the Protein Data Bank (http://www.rcsb.org, for COX-2 pdb code: 5IKR; the structure of mefenamic acid bound to human cyclooxygenase-2, resolution 2.34 Å, for AChE pdb code: *Electrophorus Electricus* acetylcholinesterase, resolution 4.20 Å). Each structure was cleaned of all water molecules and inhibitors as well as all non-interacting ions with Chimera software before being used in the docking studies. For COX-2, one of the two subunits was taken as the target structure. For AChE, one of the four subunits was taken as the target structure. Energy minimization of 3-dimensional structures of Ketoprofen and donepezil analogues were performed using Chem3D. Docking of 7 Ketoprofen analogues and Ketoprofen drug with COX-2 and 5 Donepezil analogues and donepezil drug with AChE was performed using three independent docking programs AutoDock 4.2.6, AutoDock Vina 1.2.5 and Dock 6 for comparison. The output files obtained from the docking study were visualized and analyzed by PyMol.

S4.1. AutoDock 4.2.6

Polar hydrogens were added to the protein structures and merged with non-polar hydrogens for the accurate calculation of partial Gasteiger charges. AD4 atom type was assigned. For docking simulations employing the free energy function, hydrogens were added to the ligands, partial atomic charges were assigned, and torsions were defined. The grid box size was set at 55, 55, 70 Å (x, y, z) with center x = 43.334, y = 0.932, z = 59.875 and spacing 0.375 Å for COX-2 and 60, 60, 60 Å (x, y, z) with center x = 42.095, y = 66.809, z = -81.47 and spacing 0.375 Å for AChE. Docking was performed using the Lamarckian genetic algorithm. 50 independent runs per ligand using an initial population of 300 individuals with a mutation rate of 0.02 were evolved for 27000 generations. A maximum of 2.5 million energy evaluations was applied for each experiment. The results were clustered using a tolerance of 2.0 Å. The best ranked complexes of COX-2 with Ketoprofen analogs and AChE with Donepezil analogs were selected on the basis of binding free energy value.

S4.2. Dock 6.12

First, protein and ligand for docking with Dock 6.12 were prepared using Chimera software DockPrep tool. Then, the molecular surface of the receptor, excluding hydrogen atoms and the ligand, was calculated and saved as DMS file. The Sphgen program was employed to generate spheres within the ligand binding site, which were then selected manually. Subsequently, the showbox program was used to create a box around the spheres, extending by an 8.0 Å margin in all directions. Program grid was used to precompute energy interactions between a dummy probe atom and all receptor atoms on a 0.3 Å resolution grid within the box. Grid creates the grid files necessary for rapid score evaluation. Finally, the docking was performed using the anchor-and-grow algorithm.

During docking, it was estimated that Donepezil analogs should form hydrogen bonds with Phe295, similar to crystallized Donepezil inside human acetylcholinesterase[S5]. Ketoprofen analogs were predicted to form hydrogen bonds with either Arg120 or Ser530, as is typical for most NSAID drugs.

S4.3. AutoDock Vina 1.2.5

Docking studies were also performed using AutoDock Vina 1.2.5 The input files included receptor and ligand in pdbqt formats and docking box in txt format. Output was a list of poses ranked by predicted binding energy (-ΔG in kcal/mol). Partial charges and polar hydrogens were added using AutoDock Tools and then exported as pdbqt files. The same size of the docking box was defined, 55, 55, 70 Å (x, y, z) with center x = 43.334, y = 0.932, z = 59.875 for COX-2 and 60, 60, 60 Å (x, y, z) with center x = 42.095, y = 66.809, z = -81.47 for AChE.

To obtain the maximum number of poses, we set the number of modes to 20 and the energy range to 4, exhaustiveness parameter to 100. AutoDock Vina samples the pose space based on a random seed value. Consequently, two runs with the same settings and structure files will typically produce different output poses.

Table S2. Molecular modelling of Ketoprofen, Donepezil and their analogs performed with AutoDock 4 software. Donepezil and its analogs were docked inside the active site of acetylcholinesterase from Electrophorus electricus, PDB code 1C2O. Ketoprofen and its analogs were docked inside the active site of human COX-2, PDB code 5IKR.

Compound	Binding affinity [kcal/mol]	Ki [μM]	Hydrogen bonds with aminoacids	Comment
(*S*)-Donepezil	-9.88	0.057	Tyr133, His447, Ser203	conformation 1 has inverted position inside the active site
(*R*)-Donepezil	-10.62	0.016	Phe295	-
(1*R*,2*R*)-**10**	-9.11	0.209	Gly122	conformation 1 has inverted position inside the active site, conformation 20 binds to Phe295
(1*S*,2*R*)-**10**	-9.86	0.059	Glu202, Ser125	-
(1*R*,2*S*)-**10**	-9.76	0.07	Ser203, His447	-
(1*S*,2*S*)-**10**	-9.98	0.048	Ser125, Glu202	-
(*S*)-**9**	-9.79	0.067	-	conformation 1 has inverted position inside the active site, conformation 16 binds to Phe295 and Arg296
(*R*)-**9**	-10.11	0.039	Ser125	conformation 6 binds to Phe295 and Tyr124
11	-9.77	0.069	Tyr337	-
(*R*)-**12**	-10.73	0.014	Tyr337	conformation 1 has inverted position inside the active site,

				conformation 2 binds to Phe295 and Tyr337
(*S*)-**12**	-11.12	0.007	Tyr133, Ser125	-
(1*E*,2*R*)-**8**	-10.02	0.045	Gly120, Gly120, Ser125, Tyr133	Conformation 7 binds to Phe295
(1*E*,2*S*)-**8**	-9.34	0.142	Tyr337, Tyr133, Tyr124	conformation 1 has inverted position inside the active site
(1*Z*,2*R*)-**8**	-10.75	0.013	-	-
(1*Z*,2*S*)-**8**	-10.03	0.044	Tyr133, Tyr124, Ser125	conformation 1 has inverted position inside the active site, conformation 15 binds to Phe295
(*S*)-Ketoprofen	-8.97	0.264	Arg120, Arg120, Tyr355	-
(*R*)-Ketoprofen	-8.89	0.304	Arg120, Arg120, Tyr355	-
1	-9.13	0.202	Arg120, Arg120, Tyr355	-
(*S*)-**3**	-9.15	0.197	Arg120, Arg120, Tyr355	-
(*R*)-**3**	-9.42	0.125	Ser530, Arg120, Arg120, Tyr355	-
(*S*)-**4**	-9.04	0.237	Arg120, Arg120, Arg120, Tyr355	-
(*R*)-**4**	-9.11	0.21	Arg120, Arg120, Arg120, Tyr355	-
(*S*)-**2**	-9.13	0.203	Ser530, Arg120, Arg120, Tyr355	-
(*R*)-**2**	-8.84	0.333	Arg120, Arg120, Tyr355	-
(2*R*,4*R*)-**5**	-8.95	0.277	Arg120, Arg120, Ser530, Tyr355	-
(2*R*,4*S*)-**5**	-8.61	0.492	Arg120, Arg120, Tyr355	-
(2*S*,4*R*)-**5**	-8.76	0.379	Arg120, Arg120, Tyr355	-
(2*S*,4*S*)-**5**	-9.02	0.244	Arg120, Arg120, Arg120, Ser530, Tyr355	-
(*R*)-**6**	-9.34	0.143	Arg120, Arg120, Tyr355	-
(*S*)-**6**	-9.26	0.164	Arg120, Arg120, Arg120, Tyr355, Ala527	-
(1*E*.2*R*)-**7**	-8.91	0.293	Arg120, Arg120, Tyr355, Ser530, Val523	-
(1*E*,2*S*)-**7**	-9.02	0.243	Arg120, Arg120, Tyr355, Ser530, Tyr385	-
(1*Z*,2*R*)-**7**	-9.8	0.066	Arg120, Arg120, Tyr355, Ser530	-
(1*Z*,2*S*)-**7**	-8.66	0.452	Arg120, Tyr355, Ser530	-

Table S3. Molecular modelling of Ketoprofen, Donepezil and their analogs performed with Dock 6 software. Donepezil and its analogs were docked inside the active site of acetylcholinesterase from Electrophorus electricus, PDB code 1C2O. Ketoprofen and its analogs were docked inside the active site of human COX-2, PDB code 5IKR.

Compound	Scoring	Hydrogen bonds with aminoacids	Comment
(*S*)-Donepezil	-43.4326	-	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(*R*)-Donepezil	-44.1372	Ser293	conformation 57 binds to Phe295, Tyr124;
(1*R*,2*R*)-**10**	-41.2404	-	conformation 13 binds to Phe295, Tyr337, Arg296;
(1*S*,2*R*)-**10**	-42.304	Tyr124	-
(1*R*,2*S*)-**10**	-42.8801	-	conformation 1 has inverted position inside the active site, conformation 45 binds to Phe295;
(1*S*,2*S*)-**10**	-45.7982	Tyr337	no conformation binds to Phe295;
(*S*)-**9**	-44.3883	Ser125, Tyr124	conformation 1 has inverted position inside the active site, conformation 8 binds to Phe295;
(*R*)-**9**	-40.7053	-	no conformation binds to Phe295;
11	-42.5352	-	conformation 56 binds to Phe295;
(*R*)-**12**	-44.8583	Tyr337	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(*S*)-**12**	-49.0946	Tyr124, Ser203	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(1*E*,2*R*)-**8**	-41.0654	Gln291	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(1*E*,2*S*)-**8**	-42.0311	Ser293, Ser293	no conformation with proper positioning binds to Phe295;
(1*Z*,2*R*)-**8**	-41.9395	-	no conformation binds to Phe295;

(1*Z*,2*S*)-**8**	-41.9907	Tyr124, Tyr341	conformation 1 has inverted position inside the active site, conformation 97 binds to Phe295;
(*S*)-Ketoprofen	-33.7019	-	conformation 4 binds to Arg120, Arg120, Ser530;
(*R*)-Ketoprofen	-32.3618	Arg120, Glu524	conformation 1 is docked outside the active site, conformation 8 binds to Arg120, Arg120, Tyr355, Ser530;
1	-34.8531	Ser530	-
(*S*)-**3**	-33.5769	-	conformation 1 is docked outside the active site, conformation 40 binds to Ser530;
(*R*)-**3**	-33.2132	-	conformation 1 is docked outside the active site, conformation 48 binds to Ser530,Tyr385;
(*S*)-**4**	-34.4899	-	-
(*R*)-**4**	-35.1559	Arg120, Phe470	conformation 1 is docked outside the active site, conformation 66 s docked inside but doesn't form interactions;
(*S*)-**2**	-35.2979	Arg120	conformation 1 is docked outside the active site, conformation 73 binds to Val523;
(*R*)-**2**	-33.9441	-	conformation 1 is docked outside the active site, conformation 34 is docked inside but doesn't form interactions;
(2*R*,4*R*)-**5**	-34.621	Arg120, Arg120, Arg120	conformation 1 is docked outside the active site, conformation 52 binds to Ser530;
(2*R*,4*S*)-**5**	-37.3397	Lys83	conformation 1 is docked outside the active site, conformation 60 binds to Ser530;
(2*S*,4*R*)-**5**	-38.2374	Pro84, Glu524	conformation 1 is docked outside the active site, conformation 56 is docked inside but doesn't form interactions;
(2*S*,4*S*)-**5**	-33.4627	Arg120, Arg120, Arg120, Glu524	conformation 1 is docked outside the active site, conformation 67 binds to Arg120, Arg120, Tyr355;

(*R*)-**6**	-29.1311	Arg120, Tyr355, Tyr115	conformation 1 is docked outside the active site, conformation 24 binds to Ser530, Tyr385;
(*S*)-**6**	-37.2414	-	Conformation 1 is docked outside the active site, conformation 62 binds to Arg120, Tyr355;
(1*E*.2*R*)-**7**	-41.2565	-	conformation 1 is docked outside the active site, conformation 62 binds to Arg120, Arg120, Tyr355;
(1*E*,2*S*)-**7**	-40.2117	Arg120, Arg120	conformation 1 is docked outside the active site, conformation 58 binds to Arg120, Arg120, Tyr355, Ser530, Tyr385;
(1*Z*,2*R*)-**7**	-35.3165	Arg120, Arg120, Tyr115	conformation 1 is docked outside the active site, conformation 58 binds to Ser530, Tyr385;
(1*Z*,2*S*)-**7**	-39.8196	Arg120, Arg120, Lys83	conformation 1 is docked outside the active site, conformation 60 binds to Arg120, Try355, Ser530, Tyr385;

Table S4. Molecular modelling of Ketoprofen, Donepezil and their analogs performed with AutoDock Vina software. Donepezil and its analogs were docked inside the active site of acetylcholinesterase from *Electrophorus electricus*, PDB code 1C2O. Ketoprofen and its analogs were docked inside the active site of human COX-2, PDB code 5IKR.

Compound	Binding affinity [kcal/mol]	Ki [μM]	Hydrogen bonds with aminoacids	Comment
(*S*)-Donepezil	-10	0.046	Ser203	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(*R*)-Donepezil	-10	0.046	Ser203	conformation 1 has inverted position inside the active site, conformation 4 binds to Phe295,Tyr124;

(1*R*,2*R*)-**10**	-8.6	0.488	-	conformation 1 doesn't form hydrogen bonds with protein, no conformation with correct positioning binds to Phe295;
(1*S*,2*R*)-**10**	-9	0.249	Ser203, Gly122	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(1*R*,2*S*)-**10**	-10.4	0.023	Phe295, Phe295, Arg296	-
(1*S*,2*S*)-**10**	-9.9	0.054	Ser203	conformation 1 has inverted position inside the active site, no conformation with correct positioning binds to Phe295;
(*S*)-**9**	-9.8	0.064	Phe295	-
(*R*)-**9**	-10.9	0.01	-	conformation 1 doesn't form hydrogen bonds with protein, conformation 2 binds to Phe295, Arg296, Tyr124;
11	-9.8	0.064	-	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(*R*)-**12**	-10.7	0.014	Phe295	-
(*S*)-**12**	-10.1	0.039	Tyr124, Ser125, Ser203	conformation 1 has inverted position inside the active site, no conformation with correct positioning binds to Phe295;
(1*E*,2*R*)-**8**	-9.9	0.054	Arg296, Ser293, Ser293	no conformation binds to Phe295;
(1*E*,2*S*)-**8**	-9	0.249	Tyr124	no conformation binds to Phe295;
(1*Z*,2*R*)-**8**	-10.6	0.017	Tyr124	no conformation with correct positioning binds to Phe295;

(1*Z*,2*S*)-**8**	-10.4	0.023	Ser203, Tyr341, Tyr124 inv	conformation 1 has inverted position inside the active site, no conformation binds to Phe295;
(*S*)-Ketoprofen	-8.7	0.413	Ser530	-
(*R*)-Ketoprofen	-8.3	0.812	Arg44, Lys137, Tyr130	conformation 2 binds to Ser530;
1	-8.7	0.413	Arg120, Tyr355	conformation 4 binds to Ser530;
(*S*)-**3**	-8.5	0.579	Arg44, His39, Gln461	conformation 1 is docked outside the active site, conformation 10 is docked inside the active site and binds to Met522;
(*R*)-**3**	-8.5	0.579	His39, Gln461, Phe381, Arg44	conformation 1 is docked outside the active site, no conformation binds to Arg120 or Ser530;
(*S*)-**4**	-8.1	1.138	His39, Cys41, Cys37	conformation 1 is docked outside the active site, conformation 9 binds to Ser530;
(*R*)-**4**	-8.1	1.138	Gln461, Arg44, His39	conformation 1 is docked outside the active site, conformation 11 is docked inside but doesn't form hydrogen bonds;
(*S*)-**2**	-8.6	0.489	His39, Cys41	conformation 1 is docked outside the active site, conformation 2 binds to Arg120, Arg120, Tyr355;
(*R*)-**2**	-8.1	1.138	Arg44, Cys41, Cys41	conformation 1 is docked outside the active site, no conformation is docked inside;
(2*R*,4*R*)-**5**	-8.5	0.579	His39, Cys41, Phe367	conformation 1 is docked outside the active site, conformation 10 binds to Arg120, Arg120;
(2*R*,4*S*)-**5**	-8.5	0.579	His39	conformation 1 is docked outside the active site,

				conformation 7 binds to Arg120, Arg120, Tyr355;
(2*S*,4*R*)-**5**	-8.5	0.579	Arg44, Arg44, Cys47, Gly45	conformation 1 is docked outside the active site; conformation 11 binds to Arg120, Tyr355;
(2*S*,4*S*)-**5**	-8.7	0.413	Arg120, Arg120, Ser530, Tyr355	-
(*R*)-**6**	-8.6	0.489	Arg469, Arg44, Arg44, Tyr130, Gly45	conformation 1 is docked outside the active site, conformation 12 binds to Ser530;
(*S*)-**6**	-8.7	0.413	Asn43, His39, Arg44	conformation 1 is docked outside the active site, conformation 16 binds to Tyr385, Try385;
(1*E*.2*R*)-**7**	-8.2	0.961	His39, Gln461	conformation 1 is docked outside the active site, conformation 8 binds to Arg120, Arg120, Tyr355, Ser530, Ser530;
(1*E*,2*S*)-**7**	-8.5	0.579	Arg120, Tyr355, Ser530, Tyr385	-
(1*Z*,2*R*)-**7**	-8.7	0.413	Cys47, His39, Cys36	conformation 1 is docked outside the active site, no conformation binds inside;
(1*Z*,2*S*)-**7**	-8.8	0.349	Gln42, Lys468, Glu465, Arg44, Cys47	conformation 1 is docked outside the active site, no conformation binds inside;

Section S5. Procedures of the biological analysis

S5.1. Cyclooxygenase-2 (COX-2) inhibition assay

The synthesized compounds were assessed for their COX-2 inhibitory potential using an adapted literature procedures[S6,7]. This procedure was carried out with a fluorescence-based assay by measuring the effects of the compounds on the peroxidase activity of COX-2 enzyme using 10-acetyl-3,7-dihydroxyphenoxazine (Amplex Red = Ampliflu) as a fluorescent probe. Under the action of the COX-2 enzyme, arachidonic acid is converted to prostaglandin G2 (PG2). The fluorescence produced by the probe is directly proportional to the PG2 formation.

Recombinant human COX-2 enzyme stock solution was prepared by diluting 5 μL of ≥8000 units/mg protein solution supplied from Sigma–Aldrich with 35 μL of buffer solution of pH 8.0. It was then divided into 4 batches of 10 μL each, and kept at -78 ºC. At the time of measurement, one batch at a time was used and stored between -50 ºC and -20 ºC. 1 mM stock solution of Hemin was prepared by dissolving Hemin in anhydrous DMSO. 2 mM solution of test compounds in DMSO was diluted in buffer solution of pH 8.0, to prepare appropriate working solutions. Arachidonic acid (AA) working solution was prepared by mixing 100 uL of 10 mM AA solution in ethanol, 100 uL solution of 0.1M KOH and 800 uL of ddH_2O.

COX-2 enzyme (1 μL from stock solution, 2.5U per cuvette), hemin cofactor (1 μL from 1 mM solution in DMSO, final concentration: 10 μM), test compounds or the standard drugs (10 μL, final concentrations ranged from 0.1 μM to 100 μM) were incubated in reaction buffer (100 mM Tris-HCl-EDTA buffer, 77 μL, pH 8.0) in a thermoshaker for a period of 15 min at room temperature and at 300 rpm. The reaction was initiated by addition of Amplex red reagent (Sigma-Aldrich, 1 μL from 10 mM solution in DMSO, final concentration: 100 μM), followed by arachidonic acid/NaOH solution (10 μL from 1 mM AA/NaOH stock solution). The assay was performed in a final volume of 100 μL. After 2 min of incubation in the thermoshaker at room temperature and 300 rpm, the assay was immediately quantified (F6000, Shimadzu) based on the generated fluorescence of resorufin (λ_{ex} = 535 nm, λ_{em} = 601 nm). Any delay in the measurement would lead to inaccurate and asynchronous results. The measured fluorescence for the final results was calculated after subtraction of background activity. The mean fluorescence values were calculated to determine the percentage of residual activity achieved by treatment of the enzyme with each compound. Enzyme control (10 μL of buffer was added instead of an inhibitor) serves as 100% activity. IC_{50} values were determined from dose-response curves. Celecoxib and Ketoprofen served as standard drugs for comparison. Each experiment was conducted in triplicate.

Volume	Solution
1 μL	COX-2 from stock solution, final conc. 2.5U/100
1 μL	Hemin from 1 mM stock solution, final conc. 10 μM
77 μL	100 mM Tris-HCl-EDTA, pH 8.0
10 μL	Inhibitor or drug from working solutions, final conc. ranged from 0.1 μM to 100 μM
1 μL	Ampliflu from 10 mM solution in DMSO, final conc.100 μM
10 μL	arachidonic acid/NaOH solution from 1 mM stock solution

S5.2. Acetylcholinesterase (AChE) inhibition assay

The synthesized compounds were assessed for their AChE inhibitory potential using a modified Ellman's method[S6]. This protocol involves a two-step reaction, starting with the hydrolysis of acetylthiocholine iodide, catalyzed by the AChE enzyme, to produce thiocholine and acetic acid. In the second step, resultant thiocholine reacts with Ellman's reagent (5,5-dithiobis(2-nitro) benzoic acid, DTNB) generating TNB (5-thio-2-nitrobenzoic acid). TNB can be quantitatively measured at λ = 412 nm.

100 U/mL enzyme stock solution was prepared by dissolving 292.5 U/mg protein supplied from Sigma-Aldrich (AChE, E.C. 3.1.1.7, as lyophilized powder) with ddH_2O. 5 U/mL of AChE working solution was prepared directly before performing experiments by diluting stock solution with ddH_2O. 2 mM solution of test compounds in DMSO was diluted in ddH_2O to prepare appropriate working solutions. 2 mM stock solutions of potential inhibitors were prepared in dimethyl sulfoxide (DMSO). DdH_2O was used to prepare different dilutions of inhibitors to obtain less than 2% (v/v) DMSO to avoid false positive results.

Each reaction was initiated by mixing sodium phosphate buffer (384 μL, 50 mM, pH 7.4), the test compounds or the standard drugs (6 μL final concentrations ranged from 0.1 μM to 100 μM), acetylcholinesterase enzyme from electric eel origin (10 μL from 5U/mL to get final concentration of 0.05U per cuvette). The working solution was then incubated at room temperature for 15 min, after which 100 μL of 2 mM acetylthiocholine iodide in sodium phosphate buffer and 100 μL of 0.66 mM DTNB (5,5-dithiobis(2-nitro) benzoic acid) in sodium phosphate buffer were added. Reaction was incubated for 5 min at rt. Absorption corresponding to the formed chromophore was detected at 412 nm using a Shimadzu UV-1900 spectrophotometer. The assay was performed in a final volume of 600 μL. A background reaction was also performed under the same conditions but without the inclusion of enzyme. In this assay, the blank consisted of sodium phosphate buffer. The mean absorbance values were calculated to determine the percentage of residual activity achieved by treatment of the enzyme with each compound. Enzyme control (6 μL of buffer was added instead of an inhibitor) serves as 100% activity. IC_{50} values were determined from dose-response curves. Donepezil served as standard drug for comparison. Each experiment was conducted in triplicate.

Volume	Solution
384 µL	sodium phosphate buffer (50 mM, pH 7.4)
6 µL	Inhibitor or drug from working solutions, final conc. ranged from 0.1 µM to 100 µM
10 µL	AChE from 5U/mL working solution to get final concentration of 0.05U per cuvette
100 µL	acetylthiocholine iodide from 2 mM stock solution in sodium phosphate buffer
100 µL	DTNB from 0.66 mM stock solution in sodium phosphate buffer

Section S6. Synthetic details

General information. All starting materials and reagents were purchased from Aldrich, Fisher, Alfa Aesar, TCI, or Ambeed and used without purification. All solvents used were freshly distilled prior to use. ^{1}H NMR spectra were recorded at 400, 500 or 600 MHz, and ^{13}C NMR spectra were recorded at 100, or 150 MHz with complete proton decoupling. Chemical shifts are given in δ relative to the residual signals of the deuterated solvents. High-resolution mass spectra were acquired using electron ionization (EI) or electrospray ionization (ESI) mode with a time-of-flight detector. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer as a thin film on a NaCl plate (film). Elemental analysis was performed in the automatic analyzer UNIcube by Elementar, at a temperature of 1150 °C, and by the analysis of the percentage of C, H, N, S atoms. TLC was performed with aluminium plates coated with 60 F254 silica gel. Plates were visualized with UV light (254 nm) and by treatment with ethanolic *p*-anisaldehyde with sulfuric and glacial acetic acid followed by heating, aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating, or aqueous potassium permanganate with sodium hydroxide and potassium carbonate solution followed by heating or ethanolic vanillin with sulfuric acid followed by heating. Reaction products were purified by flash chromatography using silica gel 60 (230-400 mesh).

Section S6.1. Ketoprofen's analogs described in main-text Figure 3.a

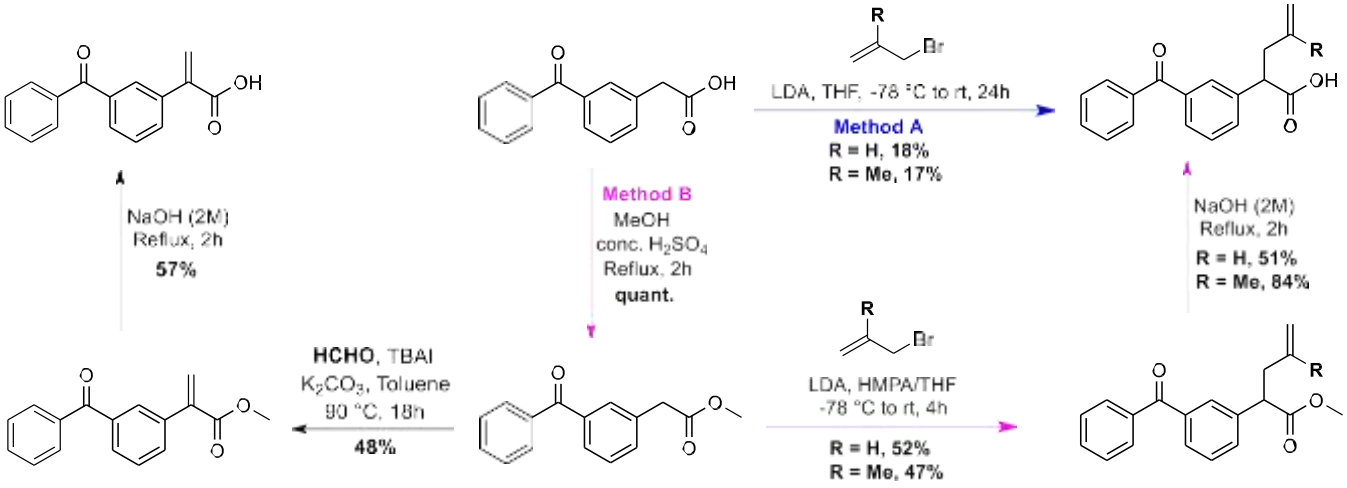


Figure S15. Reactions of compounds S6.1.1 to S6.1.7 described in main-text Figure 3.a.

General procedure S6.I for Method A

LDA (2M in THF, 2.5 equiv.) was added to 1 mL of anhydrous THF at -78 °C under Ar atmosphere. A solution of 2-(3-benzoylphenyl)acetic acid (1 equiv.) was then added to the mixture. The reaction mixture was then slowly allowed to warm up to 0 °C, and stirred at that temperature for 1 h. Afterwards, the reaction mixture was again cooled down to -78 °C, and the corresponding allyl bromide (4 equiv.) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. It was then quenched with water (5 mL) followed by 1N HCl (5 mL), then extracted with ethyl acetate (3x10 mL). The combined organic layers were collected, washed with brine, dried over $MgSO_4$, and concentrated under

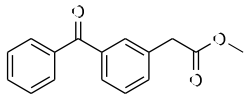
reduced pressure to obtain the crude product, which was then purified by column chromatography with hexane/EtOAc/AcOH (84/15/1) mixture, to afford the final compound.

General procedure S6.II for Method B

To a solution of 2-(3-benzoylphenyl)acetic acid (1 equiv.) in MeOH (0.5 mL), was added 2 drops of concentrated H_2SO_4 at room temperature, and then was refluxed for 2 h. Upon completion of the reaction (monitored by TLC), the volatiles were removed under reduced pressure. The resultant residue was diluted with EtOAc (10 mL) and then neutralized with aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (3x10 mL). The combined organic phase was collected, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford methyl 2-(3-benzoylphenyl)acetate as yellow liquid (60 mg, quant.), which was used for the next step without further purification.

LDA (2M in THF, 1.2 equiv.) was added to 2 mL of anhydrous THF at -78 °C under argon atmosphere. A solution of methyl 2-(3-benzoylphenyl)acetate (1 equiv.) in dry THF (2 mL) was added to it dropwise, and the reaction mixture was then slowly allowed to warm up to 0 °C and stirred at that temperature for 1 h. Afterwards, the reaction mixture was again cooled back to -78 °C before HMPA (2 equiv.) and the corresponding allyl bromide (2 equiv.) were added. The reaction mixture was then allowed to warm up to room temperature and stirred for extra 4 h. It was then quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, using hexane/EtOAc (90/10), to afford the desired product.

The latter obtained ester (1 equiv.) was added to an aqueous solution of 2N NaOH (0.5 mL) and the reaction mixture was refluxed for 2 h. After cooling down to room temperature, water (10 mL) was added and the resulting mixture was extracted with diethyl ether (10 mL). The aqueous layer was then acidified with 3N aqueous HCl solution (pH<1, checked by litmus paper), and extracted with ethyl acetate (3x20 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude mixture. It was then purified by column chromatography, with hexane/EtOAc/AcOH (84/15/1), to afford the desired final product.



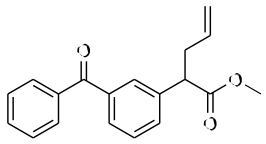
Methyl 2-(3-benzoylphenyl)acetate S6.1.1

Following the general procedure S6.II for method B, using 2-(3-benzoylphenyl)acetic acid (60.06 mg, 0.25 mmol, 1 equiv.) in MeOH (0.5 mL), to afford the desired product methyl 2-(3-benzoylphenyl)acetate **S6.1.1**, as yellow liquid (62 mg, quant.).

The spectral data match those reported in the literature[S8];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2 H), 7.73-7.68 (m, 2 H), 7.61-7.57 (m, 1 H), 7.53-7.42 (m, 4 H), 3.71 (s, 3 H), 3.70 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.4, 137.8, 137.4, 134.2, 133.2, 132.4, 130.8, 129.9, 128.8, 128.4, 128.2, 52.0, 40.8.



Methyl 2-(3-benzoylphenyl)pent-4-enoate S6.1.2

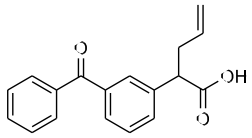
Following the general procedure S6.II for method B, using LDA (2M in THF, 1.2 mL, 2.359 mmol, 1.2 equiv.) in THF (2 mL), methyl 2-(3-benzoylphenyl)acetate (500 mg, 1.966 mmol, 1 equiv.) in THF (2 mL), HMPA (0.68 mL, 3.932 mmol. 2 equiv.) and neat allyl bromide (0.34 mL, 3.932 mmol, 2 equiv.), to afford desired product, methyl 2-(3-benzoylphenyl)pent-4-enoate **S6.1.2**, as colorless liquid (301 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2 H), 7.74-7.73 (m, 1 H), 7.70-7.67 (m, 1 H), 7.61-7.54 (m, 2 H), 7.50-7.42 (m, 3 H), 5.76-5.66 (m, 1 H), 5.09-5.00 (m, 2 H), 3.73 (t, *J* = 7.76 Hz, 1 H), 3.67 (s, 3 H), 2.88-2.81 (m, 1 H), 2.58-2.51 (m, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 173.4, 138.8, 137.9, 137.5, 134.8, 132.5, 131.9, 130.1, 129.7, 129.2, 128.6, 128.3, 117.4, 52.1, 51.2, 37.4;

HRMS (ESI) m/z: [M]+ Calc. for $C_{19}H_{18}O_3Na$: 317.1154, found: 317.1159;

IR (film, $CDCl_3$): 3063, 2951, 1737, 1669, 1598, 1438, 1317, 1280, 1229, 1198, 1164, 919, 718 cm^{-1}.



Methyl 2-(3-benzoylphenyl)pent-4-enoate S6.1.3

Following the general procedure S6.I for method A, using LDA (2M in THF, 0.78 mL, 1.560 mmol, 2.5 equiv.) in THF (1 mL), 2-(3-benzoylphenyl)acetic acid (150 mg, 0.624 mmol, 1 equiv.) in THF (1 mL) and neat allyl bromide (0.22 mL, 2.497 mmol, 4 equiv.), to afford 2-(3-benzoylphenyl)pent-4-enoic acid **S6.1.3**, as colorless oil (31.5 mg, 18% yield).

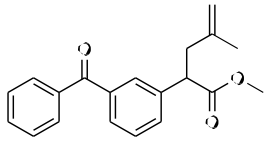
Following the general procedure S6.II for method B, using methyl 2-(3-benzoylphenyl)pent-4-enoate (25 mg, 0.0849 mmol, 1 equiv.) and 2N NaOH (0.5 mL), to afford 2-(3-benzoylphenyl)pent-4-enoic acid **S6.1.3**, as colorless oil (12.1 mg, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 3 H), 7.71-7.69 (m, 1 H), 7.60-7.55 (m, 2 H), 7.49-7.43 (m, 3 H), 5.77-5.67 (m, 1 H), 5.11-5.02 (m, 2 H), 3.74 (t, *J* = 7.69 Hz, 1 H), 2.87-2.82 (m, 1 H), 2.60-2.53 (m, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 178.0, 138.2, 138.0, 137.4, 134.4, 132.5, 132.0, 130.1, 129.8, 129.4, 128.7, 128.3, 117.7, 51.0, 37.1;

HRMS (ESI) m/z: [M]+ Calc. for $C_{18}H_{16}O_3Na$: 303.0997, found: 303.0996;

IR (film, $CDCl_3$): 3067, 2921, 1734, 1708, 1658, 1597, 1318, 1281, 1178, 919, 720 cm^{-1}**.**



Methyl 2-(3-benzoylphenyl)-4-methylpent-4-enoate S6.1.4

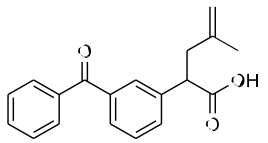
Following the general procedure S6.II for method B, using LDA (2M in THF, 0.3 mL, 0.594 mmol, 1.2 equiv.) in THF (2 mL), methyl 2-(3-benzoylphenyl)acetate (126 mg, 0.495 mmol, 1 equiv.) in THF (2 mL), HMPA (0.17 mL, 0.99 mmol, 2 equiv.), and neat 3-bromo-2-methylprop-1-ene (0.1 mL, 0.99 mmol, 2 equiv.) to afford methyl 2-(3-benzoylphenyl)-4-methylpent-4-enoate **S6.1.4**, as colorless liquid (72 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.75 (m, 3 H), 7.69-7.67 (m, 1 H), 7.61-7.56 (m, 2 H), 7.50-7.41 (m, 3 H), 4.76 (s, 1 H), 4.68 (s, 1 H), 3.91-3.87 (m, 1 H), 3.66 (s, 3 H), 2.85 (dd, *J* = 14.6, 8.7 Hz, 1 H), 2.48 (dd, *J* = 14.6, 6.9 Hz, 1 H), 1.72 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 173.6, 142.1, 139.0, 137.9, 137.5, 132.5, 131.8, 130.1, 129.6, 129.1, 128.5, 128.3, 112.6, 52.1, 49.8, 41.2, 22.5;

HRMS (ESI) m/z: [M]+ Calc. for $C_{20}H_{20}O_3Na$: 331.1310, found: 331.1316;

IR (film, $CDCl_3$): 3073, 2951, 1737, 1659, 1598, 1579, 1445, 1316, 1281, 1194, 1159, 718 cm^{-1}.



2-(3-benzoylphenyl)-4-methylpent-4-enoic acid S6.1.5

Following the general procedure S6.I for method A, using LDA (2M in THF, 0.52 mL, 1.04 mmol, 2.5 equiv.) in THF (1 mL), 2-(3-benzoylphenyl)acetic acid (100 mg, 0.416 mmol, 1 equiv.) in THF (1 mL) and 3-bromo-2-methylprop-1-ene (0.17 mL, 1.664 mmol, 4 equiv.), to afford 2-(3-benzoylphenyl)-4-methylpent-4-enoic acid **S6.1.5,** as colorless oil (21 mg, 17% yield).

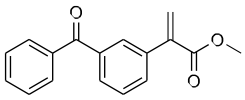
Following the general procedure S6.II for method B, using methyl 2-(3-benzoylphenyl)-4-methylpent-4-enoate (25 mg, 0.081 mmol, 1 equiv.) and 2N NaOH (0.5 mL), to afford 2-(3-benzoylphenyl)-4-methylpent-4-enoic acid **S6.1.5**, as white sticky solid (20 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.77 (m, 3 H), 7.70-7.68 (m, 1 H), 7.60-7.56 (m, 2 H), 7.48-7.42 (m, 3 H), 4.77 (s, 1 H), 4.70 (s, 1 H), 3.88 (t, *J* = 7.79 Hz, 1 H), 2.87-2.81 (m, 1 H), 2.52-2.47 (m, 1 H), 1.71 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 178.6, 141.7, 138.3, 137.9, 137.4, 132.5, 132.0, 130.1, 129.8, 129.4, 128.6, 128.3, 112.9, 49.6, 40.8, 22.5;

HRMS (ESI) m/z: [M]+ Calc. for $C_{19}H_{18}O_3Na$: 317.1154, found: 317.1155;

IR (film, $CDCl_3$): 3074, 2967, 2926, 1735, 1708, 1658, 1597, 1446, 1282, 1178, 719 cm^{-1}.



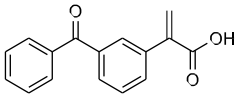
Methyl 2-(3-benzoylphenyl)acrylate S6.1.6

To a solution of methyl 2-(3-benzoylphenyl)acetate (60 mg, 0.236 mmol, 1 equiv.) in toluene (1 mL), were added paraformaldehyde (21.26 mg, 0.708 mmol, 3 equiv.), tetrabutylammonium iodide (3.50 mg, 0.0094 mmol, 4 mol%) and K_2CO_3 (97.8 mg, 0.708 mmol, 3 equiv.) at room temperature. The resulting mixture was stirred at 90 °C for 18 h. After completion of the reaction, water (20 mL) was added and the aqueous phase was extracted with EtOAc (2x20 mL). The combine organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude mixture was purified by column chromatography, using hexane/EtOAc (90/10) to afford methyl 2-(3-benzoylphenyl)acrylate **S6.1.6**, as yellow liquid (30 mg, 48% yield).

The spectral data match those reported in the literature[S9];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 3 H), 7.78-7.74 (m, 1 H), 7.65-7.63 (m, 1 H), 7.61-7.57 (m, 1 H), 7.50-7.45 (m, 3 H), 6.43 (d, *J* = 0.9 Hz, 1 H), 5.95 (d, *J* = 0.9 Hz, 1 H), 3.82 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 166.7, 140.4, 137.5, 137.4, 136.9, 132.5, 132.3, 130.1, 129.9, 129.8, 128.3, 128.1, 128.0, 52.3.



2-(3-benzoylphenyl)acrylic acid S6.1.7

Following the hydrolysis step in the general procedure S6.II for method B, using Methyl 2-(3-benzoylphenyl)acrylate (26.6 mg, 0.0998 mmol, 1 equiv.) and 2N NaOH (0.5 mL), to afford 2-(3-benzoylphenyl)acrylic acid **S6.1.7** as light yellow sticky oil (12 mg, 47% yield).

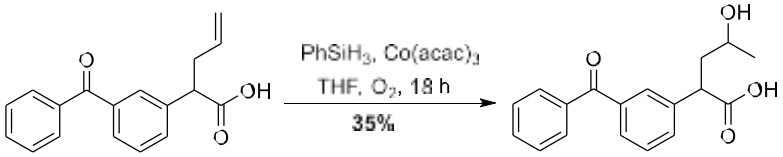
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.88 (m, 1 H), 7.84-7.81 (m, 2 H), 7.80-7.77 (m, 1 H), 7.69-7.66 (m, 1 H), 7.61-7.57 (m, 1 H), 7.51-7.47 (m, 3 H), 6.61 (s, 1 H), 6.10 (s, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 170.3, 139.6, 137.6, 137.4, 136.3, 132.6, 132.4, 130.4, 130.13, 130.10, 130.0, 128.3, 128.1.;

HRMS (ESI) m/z: [M]+ Calc. for $C_{16}H_{12}O_3H$: 253.0865, found: 253.0869;

IR (film, $CDCl_3$): 2923, 2852, 1698, 1659, 1597, 1447, 1318, 1277, 1216, 707 cm^{-1}.

Synthesis of 2-(3-benzoylphenyl)-4-hydroxypentanoic acid S6.1.8



Scheme S1. Reaction scheme of compound S6.1.8 described in main-text Figure 3.a.

Under inert atmosphere, and to a solution of 2-(3-benzoylphenyl)pent-4-enoic acid **S6.1.3** (43.0 mg, 0.153 mmol, 1 equiv.) in anhydrous THF (1 mL), was added phenylsilane (33.2 mg, 0.306 mmol, 2 equiv.), and $Co(acac)_3$ (2.71 mg, 0.0076 mmol, 5 mol%). An oxygen balloon was connected to the reaction system, and it was stirred for 24 h at room temperature. EtOAc (10 mL) and water (10 mL) were then added to the reaction mixture. The aqueous layer was extracted with EtOAc (3x20 mL), and the combined organic layers were collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain the crude product, which was then purified by column chromatography, with hexane/EtOAc/AcOH (87/12/1) mixture, to afford 2-(3-benzoylphenyl)-4-hydroxypentanoic acid **S6.1.8**, as colorless liquid (16 mg, 35% yield).

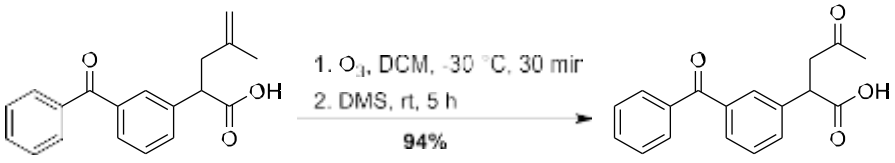
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.78 (m, 4 H), 7.74-7.69 (m, 4 H), 7.62-7.53 (m, 4 H), 7.51-7.46 (m, 6 H), 4,87-4.79 (m 1 H), 4.69-4.60 (m, m, 1 H), 4.04-3.95 (m, 2 H), 2.85-2.78 (m, 1 H), 2.63-2.55 (m, 1 H), 2.32-2.36 (m, 1 H), 2.11-2.02 (m, 1 H), 1.51 (d, *J* = 6.1 Hz, 3 H), 1.47 (d, *J* = 6.3 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 196.2, 176.6, 176.3, 138.3, 138.1, 137.4, 137.3, 136.9, 132.6, 132.6, 132.1, 131.7, 130.1, 130.1, 129.6, 129.5, 129.4, 129.1, 128.9, 128.8, 128.4, 128.4, 75.1, 75.1, 47.5, 45.3, 39.5, 37.6, 21.0, 20.7;

Elemental analysis: Calc. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08; O, 21.45. Found: C, 73.38; H, 5.79; O, 20.83;

IR (film, $CDCl_3$): 3060, 2977, 2927, 1769, 1658, 1283, 1716, 1135, 1056, 718 cm^{-1}.

Synthesis of 2-(3-benzoylphenyl)-4-oxopentanoic acid S6.1.9



Scheme S2. Reaction scheme of compound S6.1.9 described in main-text Figure 3.a.

Under inert atmosphere, the compound 2-(3-benzoylphenyl)-4-methylpent-4-enoic acid **S6.1.5** (15 mg, 0.051 mmol, 1 equiv.) was dissolved in 7 mL of anhydrous DCM, and the mixture was purged with stream of ozone at -30 °C, until the color of the reaction mixture turned into dark blue. The reaction mixture was then brought to 0 °C, and dimethyl sulfide (0.038 mL, 0.510 mmol, 10 equiv.) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 5 h. After that, the reaction mixture was concentrated and

partitioned between diethyl ether (10 mL) and water (10 mL), the aqueous layer was extracted with diethyl ether (2x10 mL). the combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was then purified by column chromatography, with hexane/EtOAc/AcOH (84/15/1) mixture, to obtain 2-(3-benzoylphenyl)-4-oxopentanoic acid **S6.1.9**, as colorless oil (14.2 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.74 (m, 3 H), 7.69-7.67 (m, 1 H), 7.60-7.57 (m, 1 H), 7.54-7.52 (m, 1 H), 7.49-7.42 (m, 3 H), 4.20 (dd, *J* = 9.92, 4.52 Hz, 1 H), 3.38 (dd, *J* = 17.9, = 9.84 Hz, 1 H), 2.78 (dd, *J* = 18.0, 4.6 Hz, 1 H), 2.17 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 196.3, 177.5, 138.2, 137.9, 137.2, 132.6, 132.0, 130.1, 129.6, 129.4, 128.8, 128.3, 46.3, 45.8, 29.9;

HRMS (ESI) m/z: [M]+ Calc. for $C_{18}H_{16}O_4Na$: 319.0946, found: 319.0948;

IR (film, $CDCl_3$): 3061, 3027, 2956, 2924, 1714, 1658, 1597, 1318, 1283, 1163, 720 cm^{-1}.

Illustration of compounds S6.1.10 to S6.1.12 described in main-text Figure 3.a

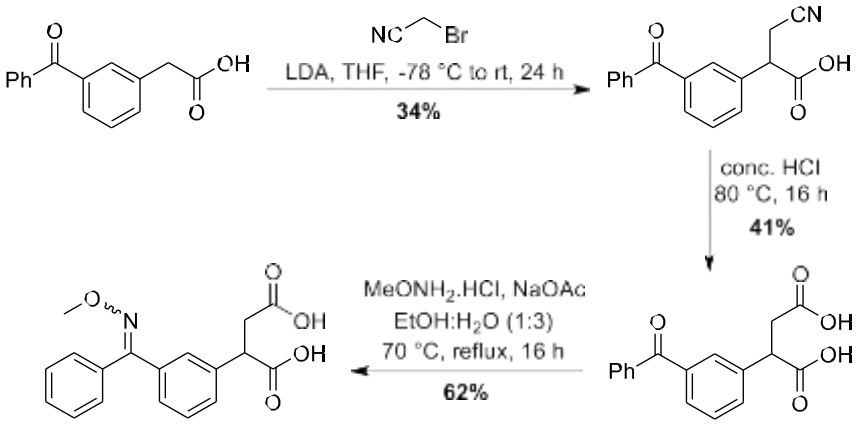
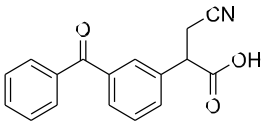


Figure S16. Synthesis of compounds S6.1.10 to S6.1.12 described in main-text Figure 3.a.



2-(3-benzoylphenyl)-3-cyanopropanoic acid S6.1.10

LDA (2M in THF, 0.94 mL, 1.873 mmol, 2.5 equiv.) was added to 1 mL of anhydrous THF at -78 °C under argon atmosphere. A solution of 2-(3-benzoylphenyl)acetic acid (180 mg, 0.750 mmol, 1 equiv.) in THF (1 mL) was then added, and the reaction mixture was slowly allowed to warm up to 0 °C, and stirred at that temperature for 1 h. After that, the reaction mixture was again cooled down to -78 °C, and neat 2-bromoacetonitrile (0.078 mL, 1.125 mmol, 1.5 equiv.) was added at -78 °C. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. Then, quenched with water (5 mL), followed by 1N HCl (5 mL), and it was extracted with ethyl acetate (3x10 mL). The combined organic layers were collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to

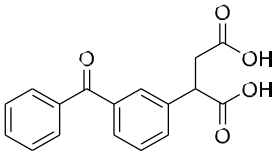
obtain the crude product, which was then purified by column chromatography, with hexane/EtOAc/AcOH(79/20/1) mixture, to afford 2-(3-benzoylphenyl)-3-cyanopropanoic acid **S6.1.10**, as yellow sticky oil (71.2 mg, 34% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.75 (m, 4 H), 7.62-7.54 (m, 2 H), 7.52-7.46 (m, 3 H), 4.05 (t, *J* = 7.5 Hz, 1 H), 3.05 (dd, *J* = 16.9, 7.0 Hz, 1 H), 2.88 (dd, *J* = 16.9, 7.9 Hz, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 175.1, 138.4, 136.9, 135.6, 132.9, 131.7, 130.5, 130.1, 129.3, 128.4, 117.1, 47.2, 21.2;

HRMS (ESI) m/z: [M]+ Calc. for $C_{17}H_{13}NO_3Na$: 302.0793, found: 302.0797;

IR (film, $CDCl_3$): 2958, 2925, 2853, 2252, 1712, 1658, 1598, 1494, 1447, 1318, 1281, 1185, 1081, 718 cm^{-1}.



2-(3-benzoylphenyl)succinic acid S6.1.11

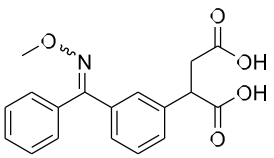
The obtained compound **S6.1.10** (71 mg, 0.254 mmol, 1 equiv.) was refluxed with 1 mL of conc. HCl for 16 h. After this, water (10 mL) and EtOAc (20 mL) were added to the reaction mixture, and was extracted with EtOAc (3x20 mL). The combined organic layers were collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to get the crude product, which was then purified by column chromatography, with hexane/EtOAc/AcOH (74/25/1) mixture, to afford 2-(3-benzoylphenyl)succinic acid **S6.1.11**, as colorless oil (31 mg, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (m, 3 H), 7.70 (d, *J* = 7.6 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.48-7.43 (m, 3 H), 4.18 (dd, *J* = 11.3, 3.96 Hz, 1 H), 3.28 (dd, *J* = 17.4, 11.4 Hz, 1 H), 2.73 (dd, *J* = 17.4, 4.04 Hz, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 178.3, 177.3, 138.3, 137.2, 137.0, 132.7, 131.7, 130.1, 129.9, 129.4, 129.0, 128.4, 46.9, 37.3;

HRMS (ESI) m/z: [M]+ Calc. for $C_{17}H_{14}O_5Na$: 321.0739, found: 321.0741;

IR (film, $CDCl_3$): 3027, 2926, 1712, 1658, 1597, 1416, 1319, 1284, 1718, 1001, 720 cm^{-1}.



2-(3-((methoxyimino)(phenyl)methyl)phenyl)succinic acid S6.1.12

To a solution of compound **S6.1.11** (33.7 mg, 0.113 mmol, 1 equiv.) in EtOH:H_2O (1:3, 1.33 mL), was added methoxamine hydrochloride (25.48 mg, 0.305 mmol, 2.7 equiv.) followed by anhydrous sodium acetate (40.78 mg, 0.497, 4.4 equiv.). The mixture was then refluxed for 16

h. EtOAc (10 mL) and water (10 mL) were then added to the reaction mixture. The organic layer was extracted with EtOAc (3x20 mL). The combined organic layer was collected, washed with brine dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain the crude product, which was then purified by column chromatography, with hexane/EtOAc/AcOH (84/15/1) mixture, to afford the target 2-(3-((methoxyimino)(phenyl)methyl)phenyl)succinic acid **S6.1.12**, as light yellow sticky oil (23 mg, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 7.45-7.39 (m, 6 H), 7.37-7.28 (m, 11 H), 4.14-4.08 (m, 2 H), 3.98 (s, 3H), 3.95 (s, 3 H), 3.29-3.20 (m, 2 H), 2.74-2.65 (m, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 178.9, 177.8, 177.8, 156.1, 156.0, 137.2, 136.6, 136.3, 136.1, 134.0, 132.9, 129.4, 129.1, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.1, 62.5, 62.4, 47.0, 46.9, 37.4;

HRMS (ESI) m/z: [M]+ Calc. for $C_{18}H_{17}NO_5Na$: 350.1004, found: 350.1008;

IR (film, $CDCl_3$): 3026, 2936, 1712, 1442, 1422, 1289, 1252, 1216, 1184, 1054, 758 cm^{-1}.

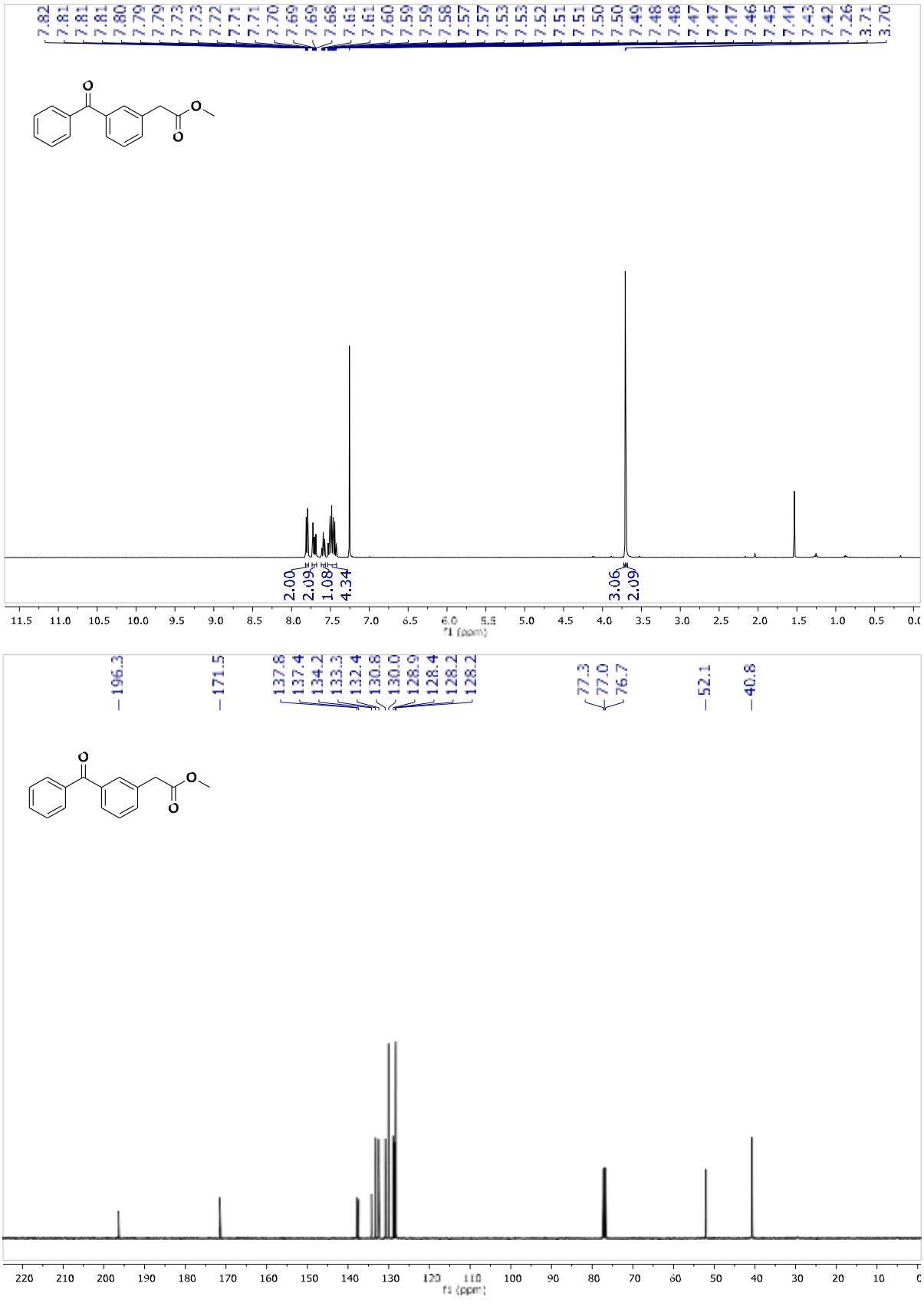


Figure S17. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.1**.

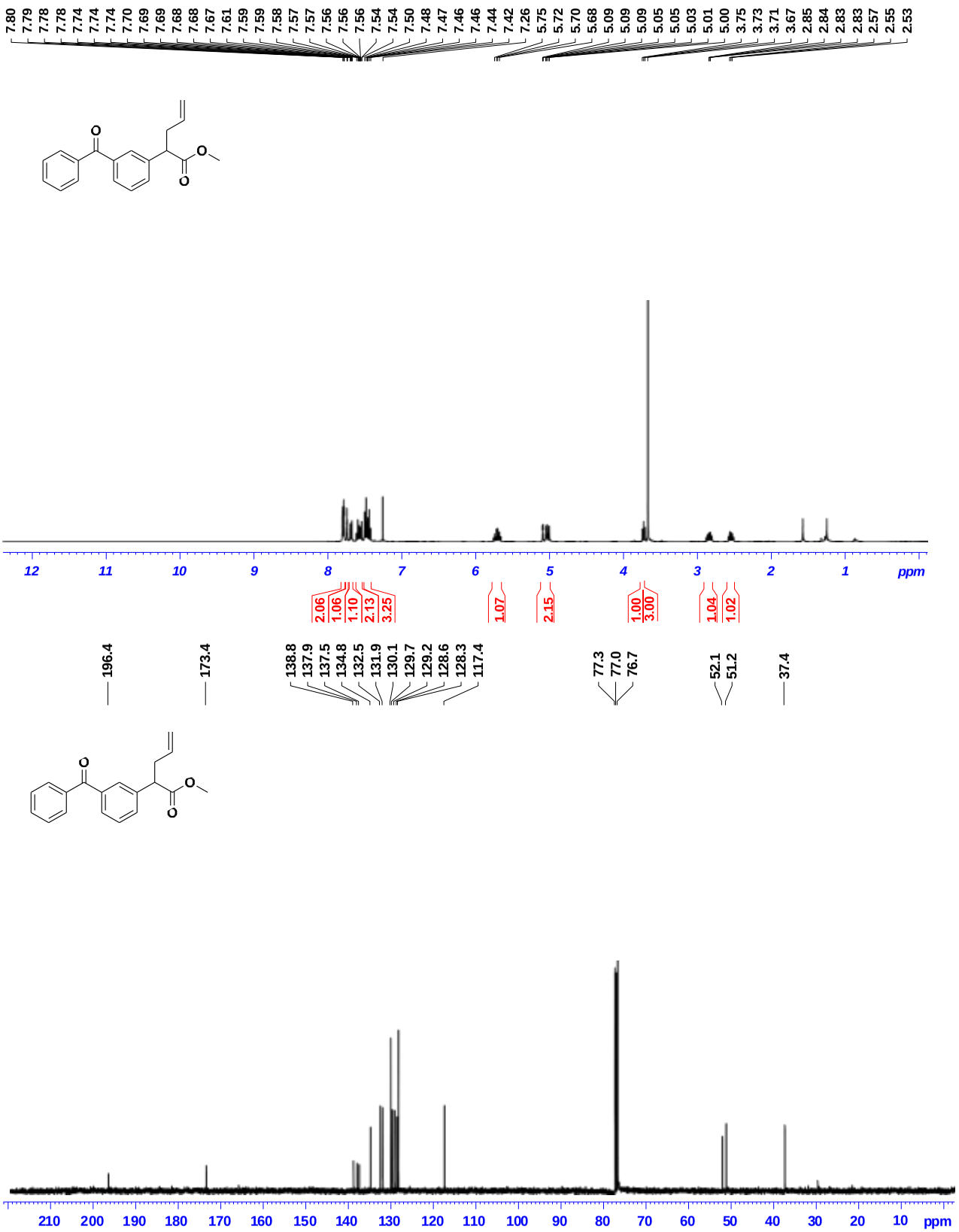


Figure S18. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.2**.

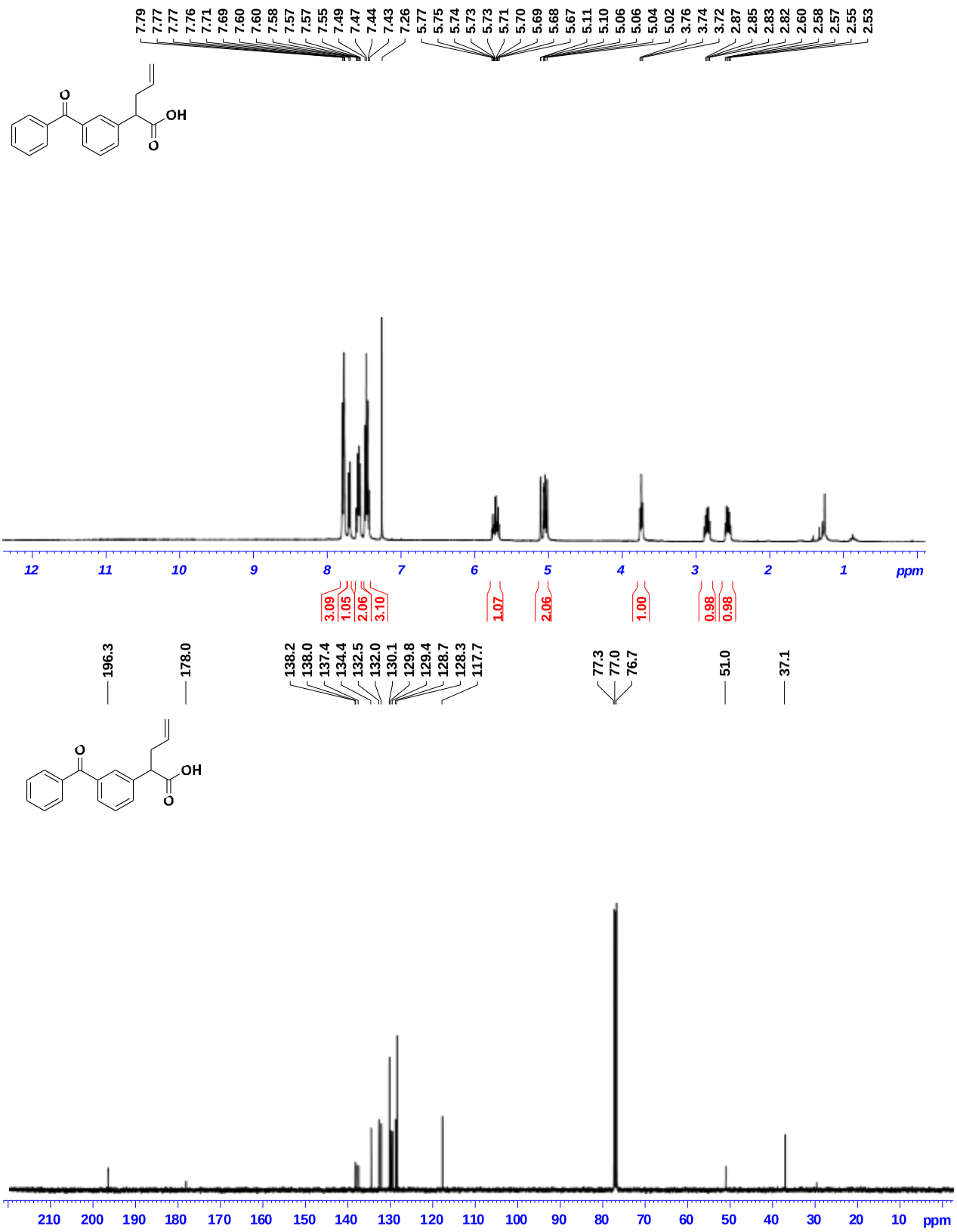


Figure S19. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.3**.

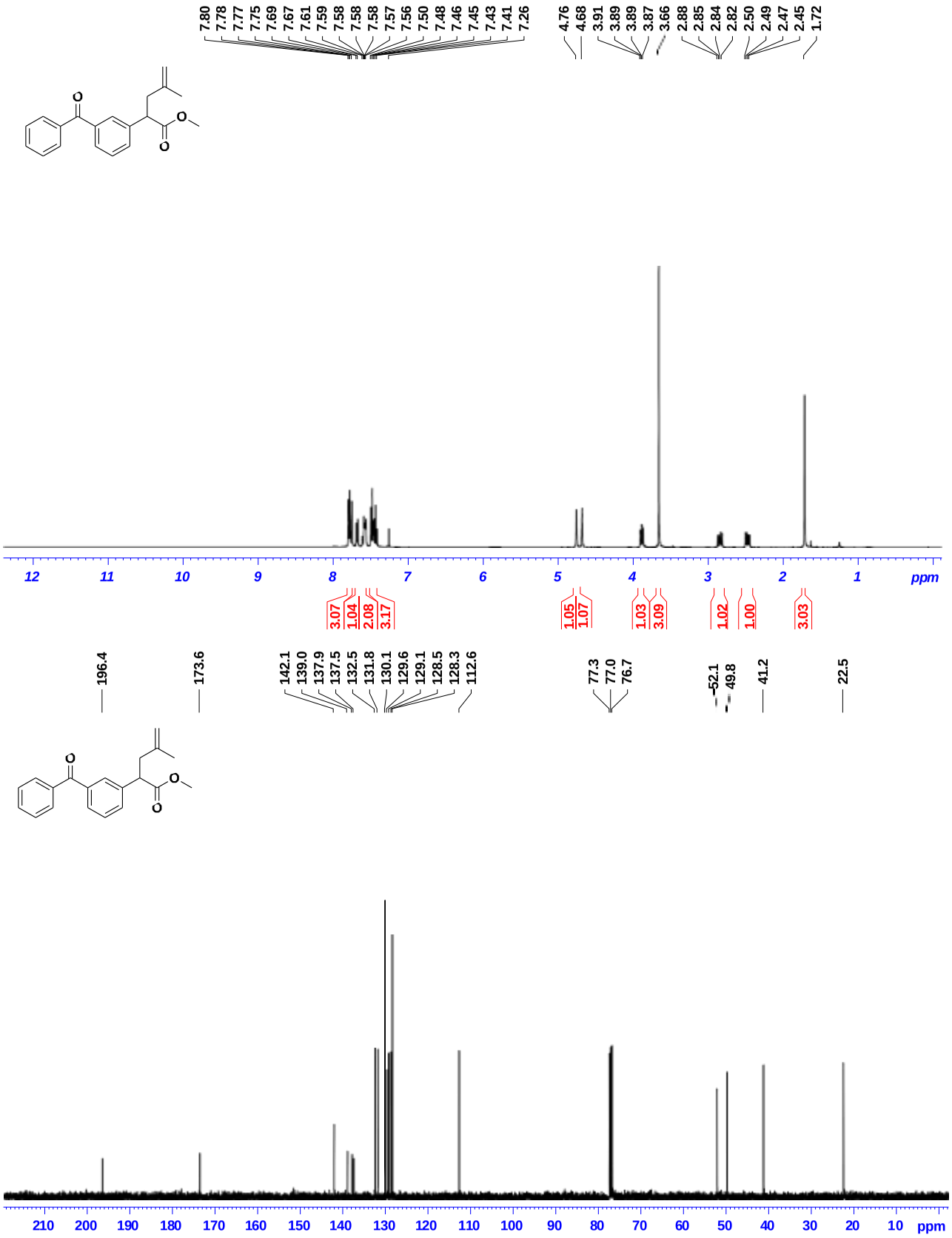


Figure S20. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.4**.

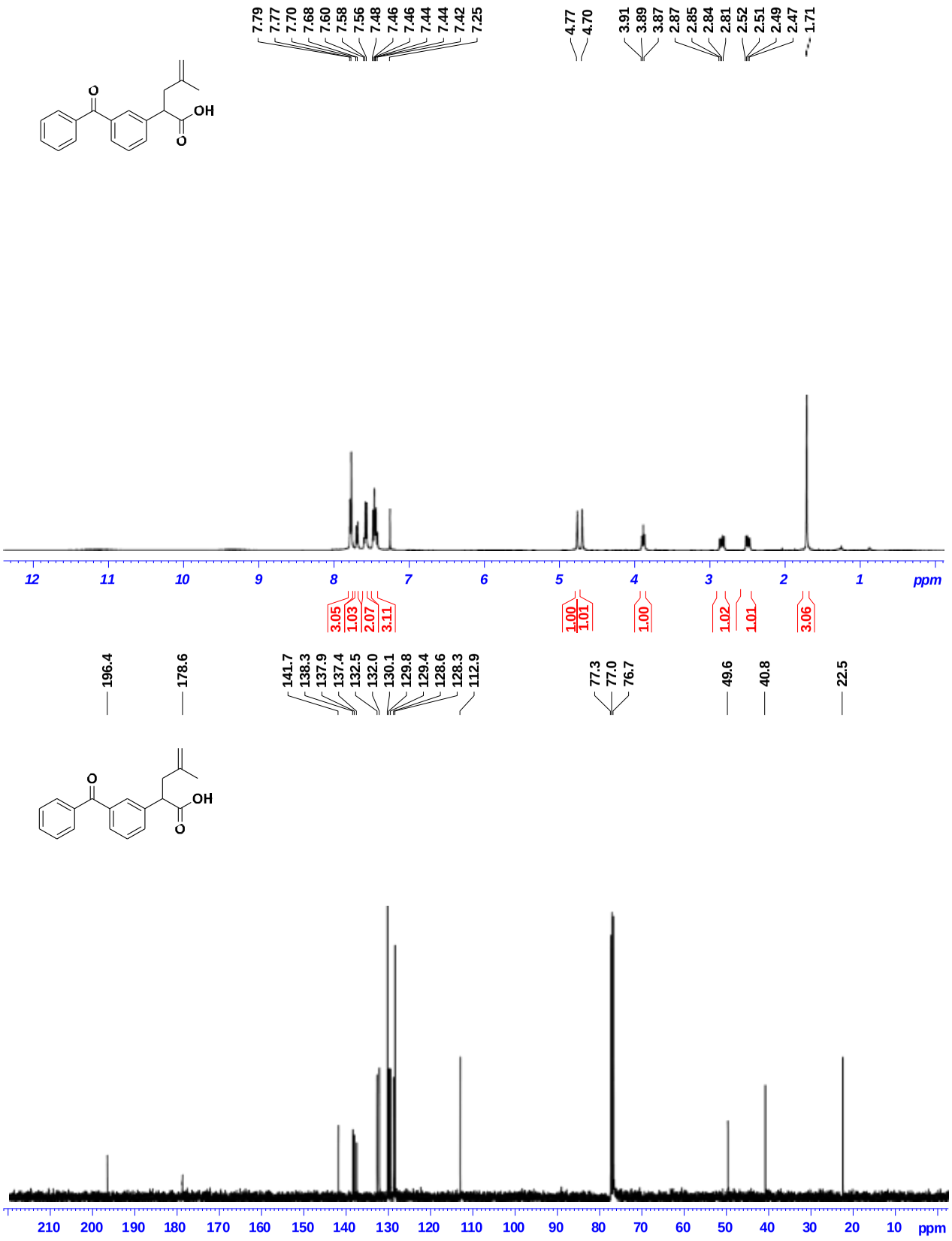


Figure S21. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.5**.

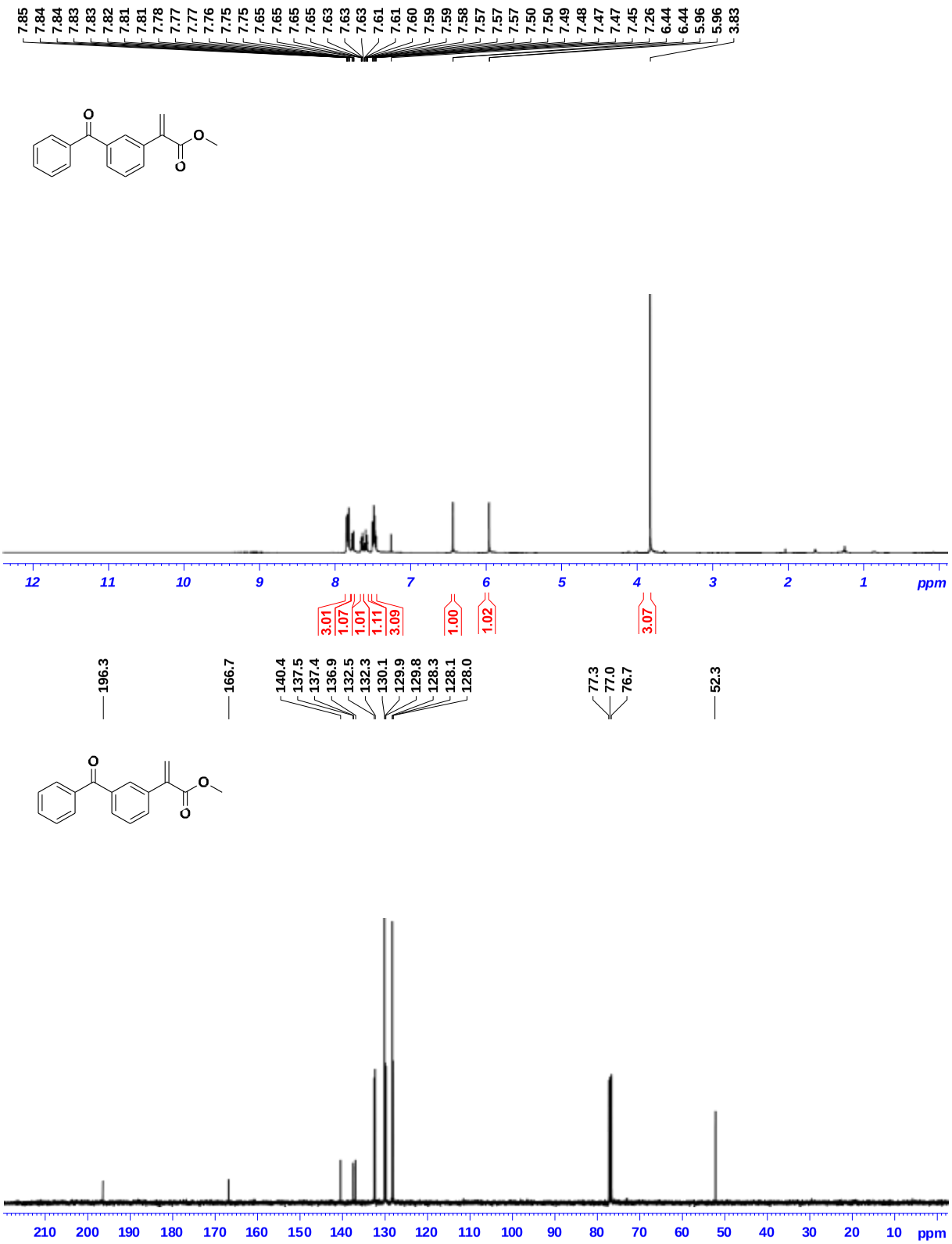


Figure S22. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.6.**

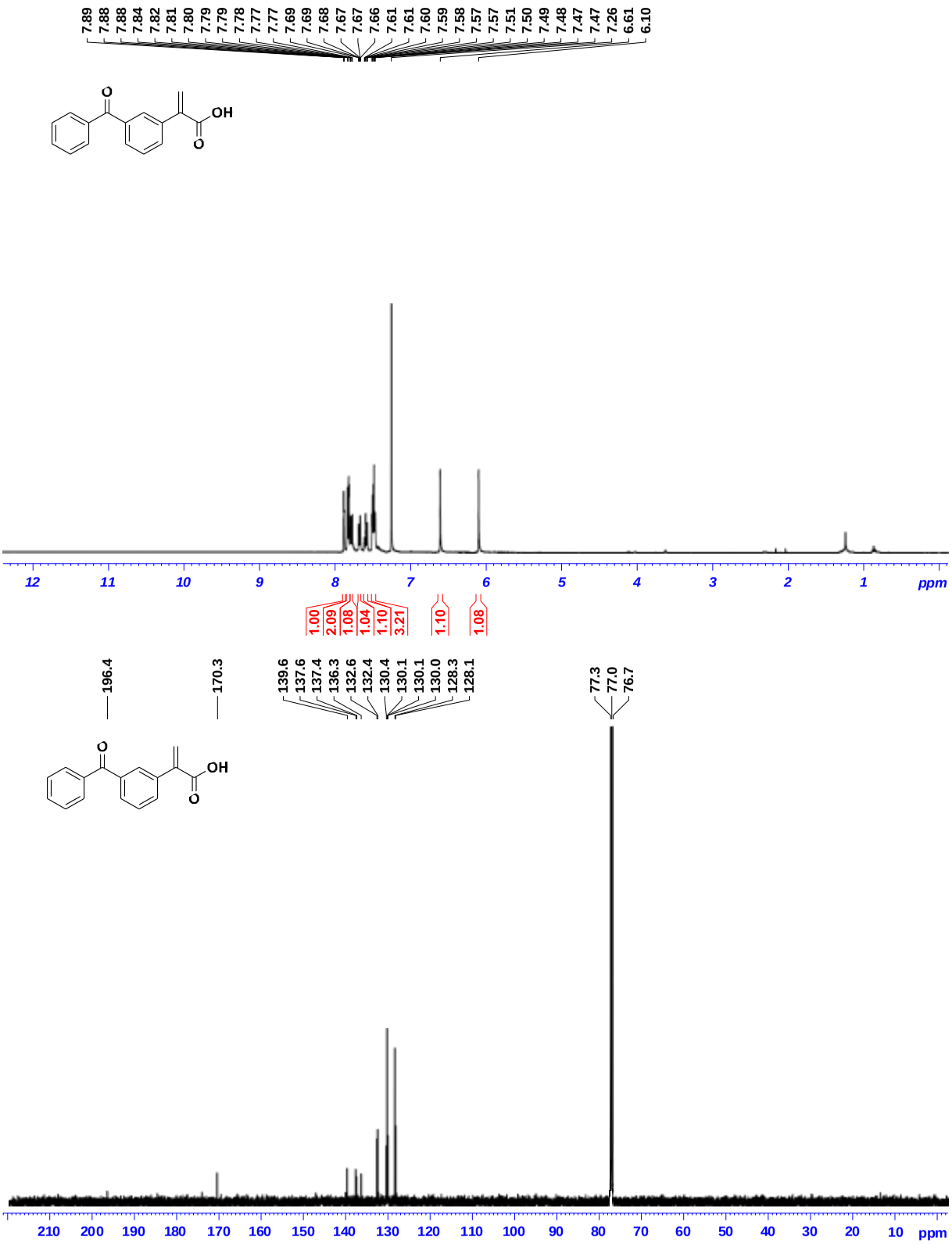


Figure S23. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.7.**

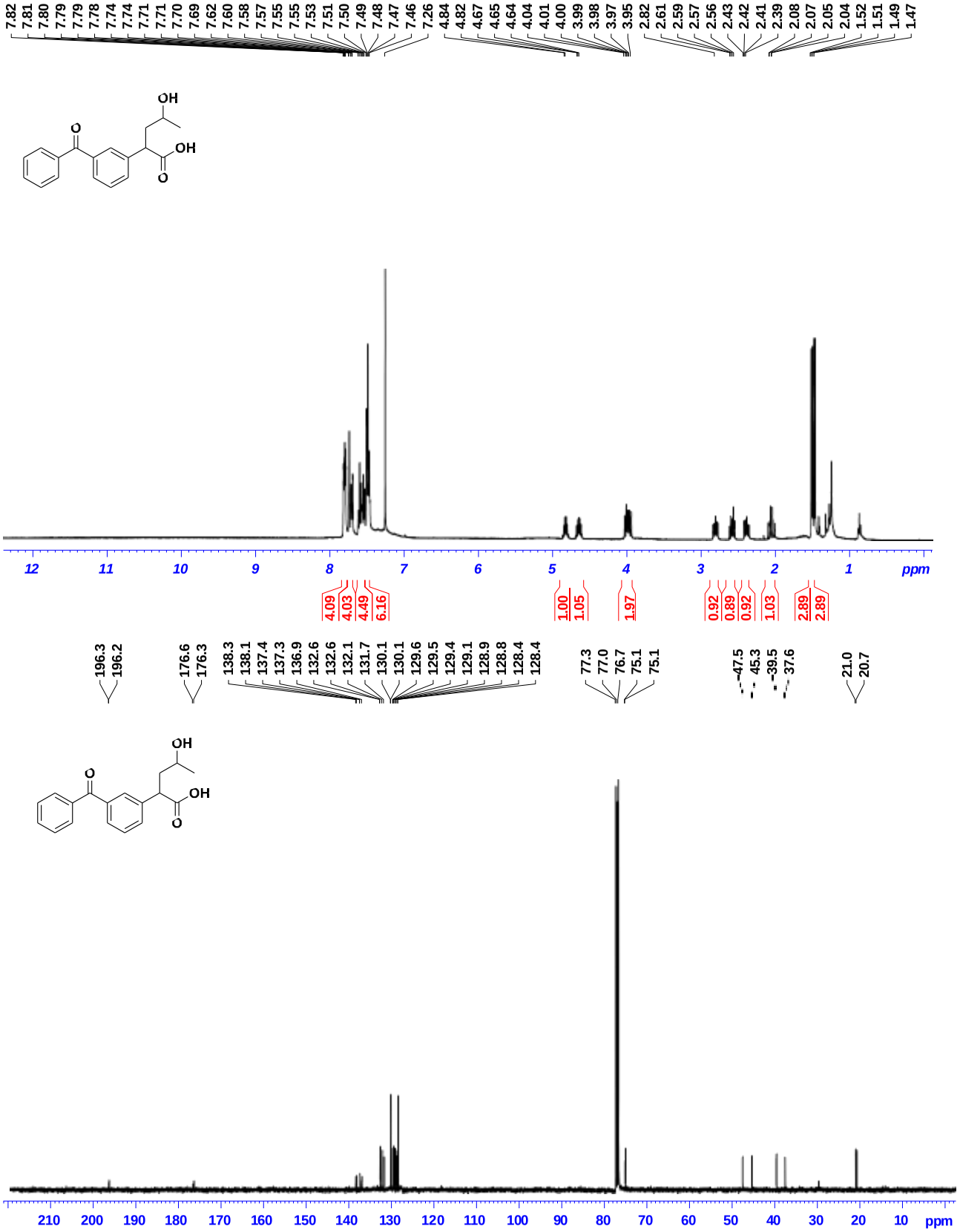


Figure S24. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.8**.

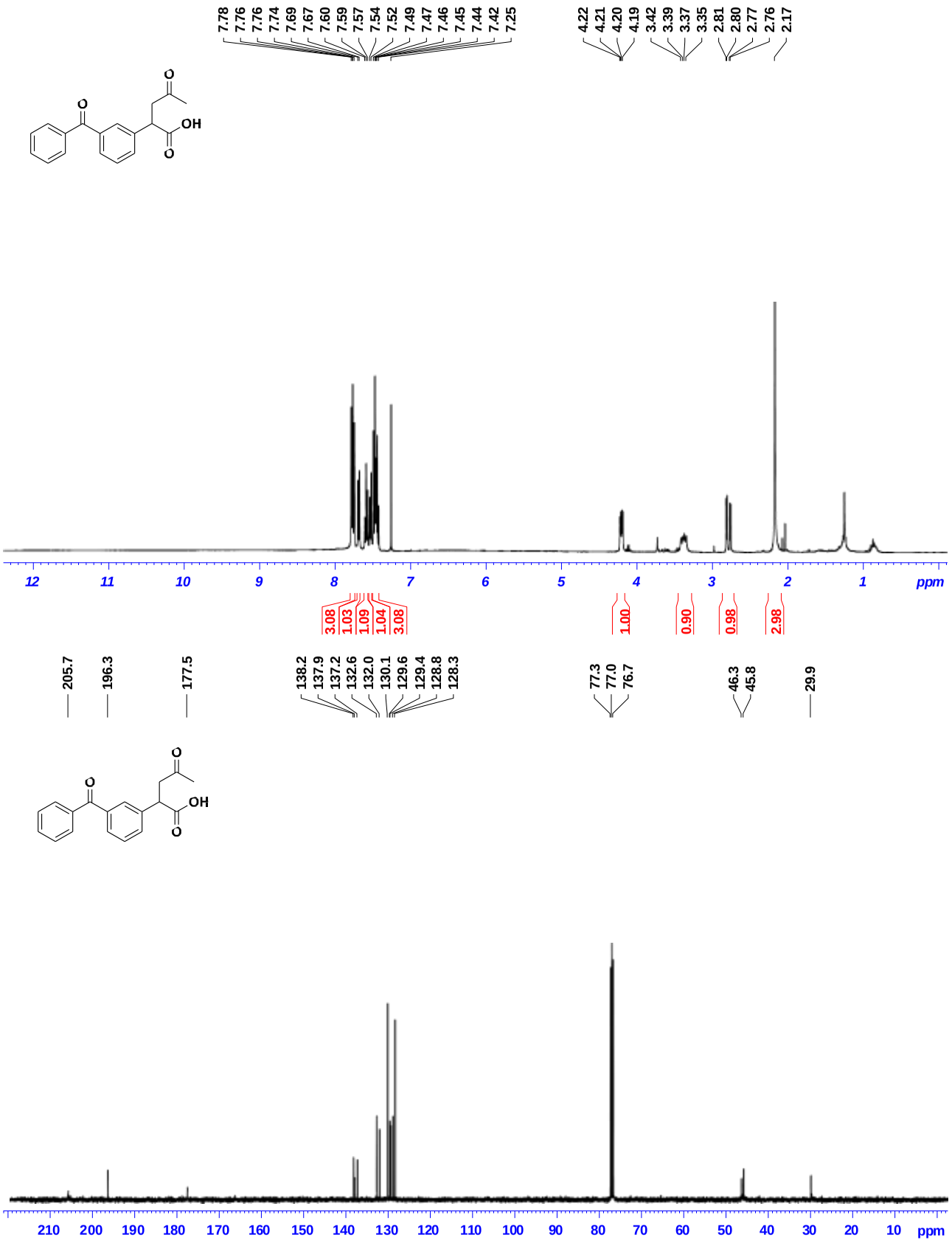


Figure S25. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.9.**

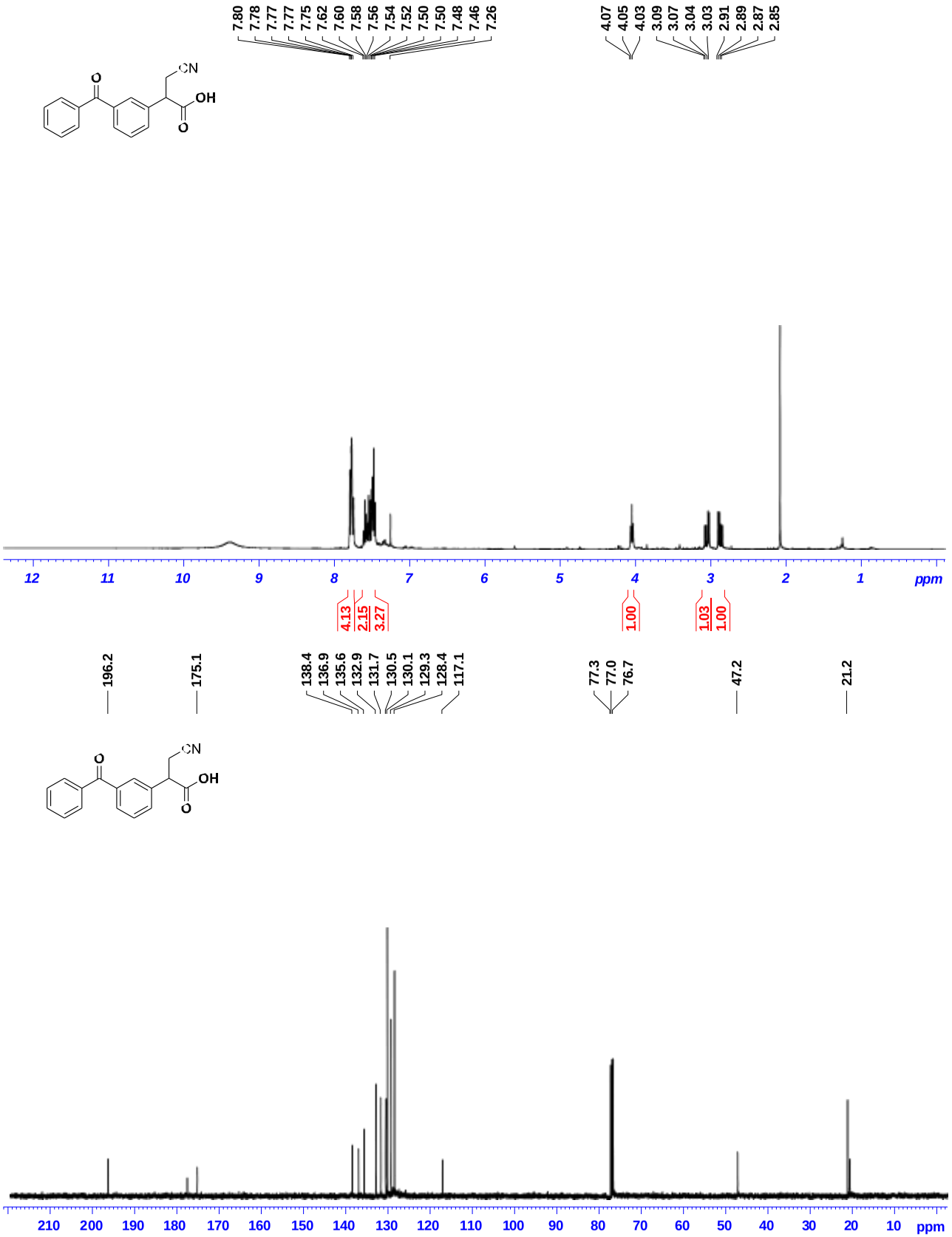


Figure S26. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.10.**

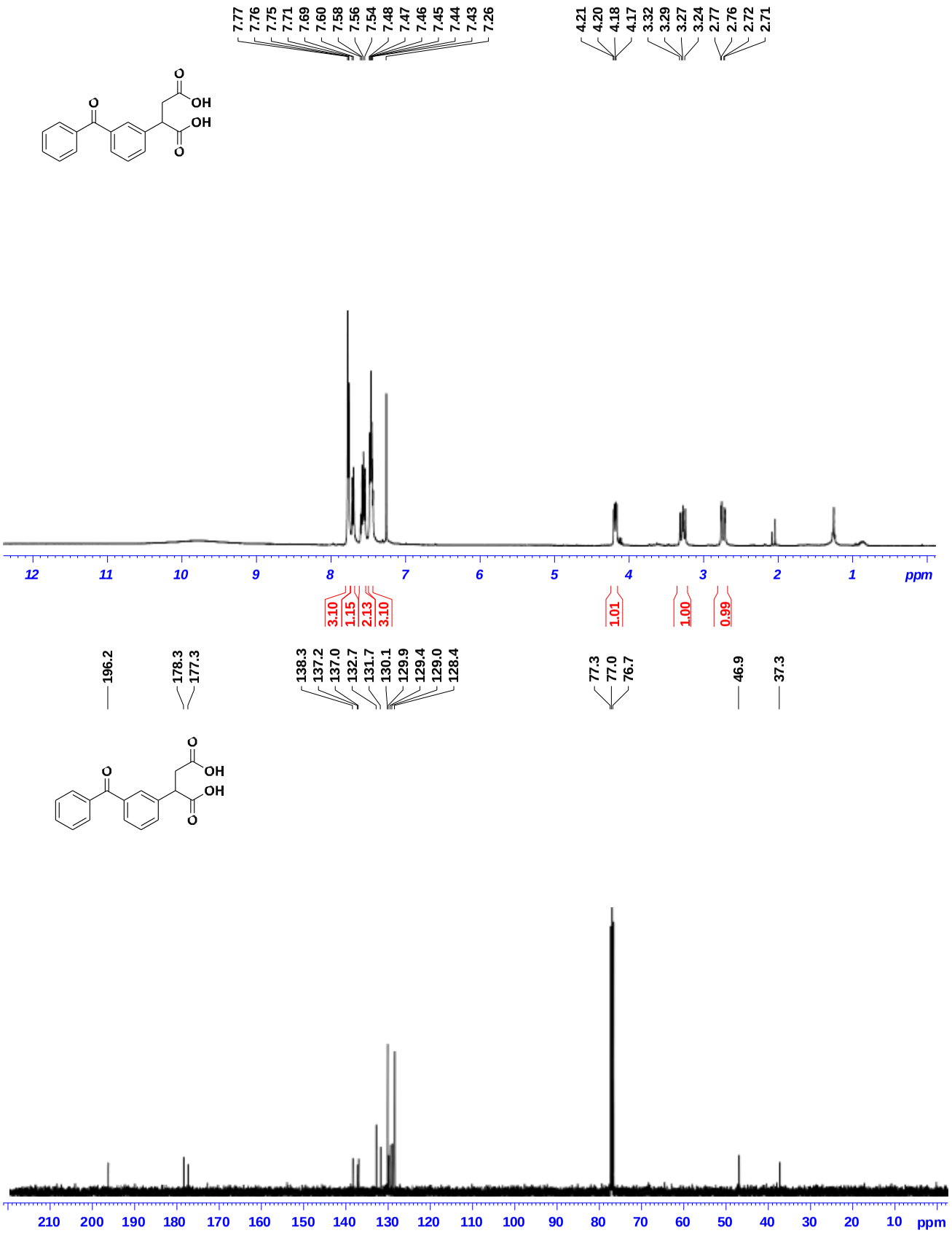


Figure S27. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.11.**

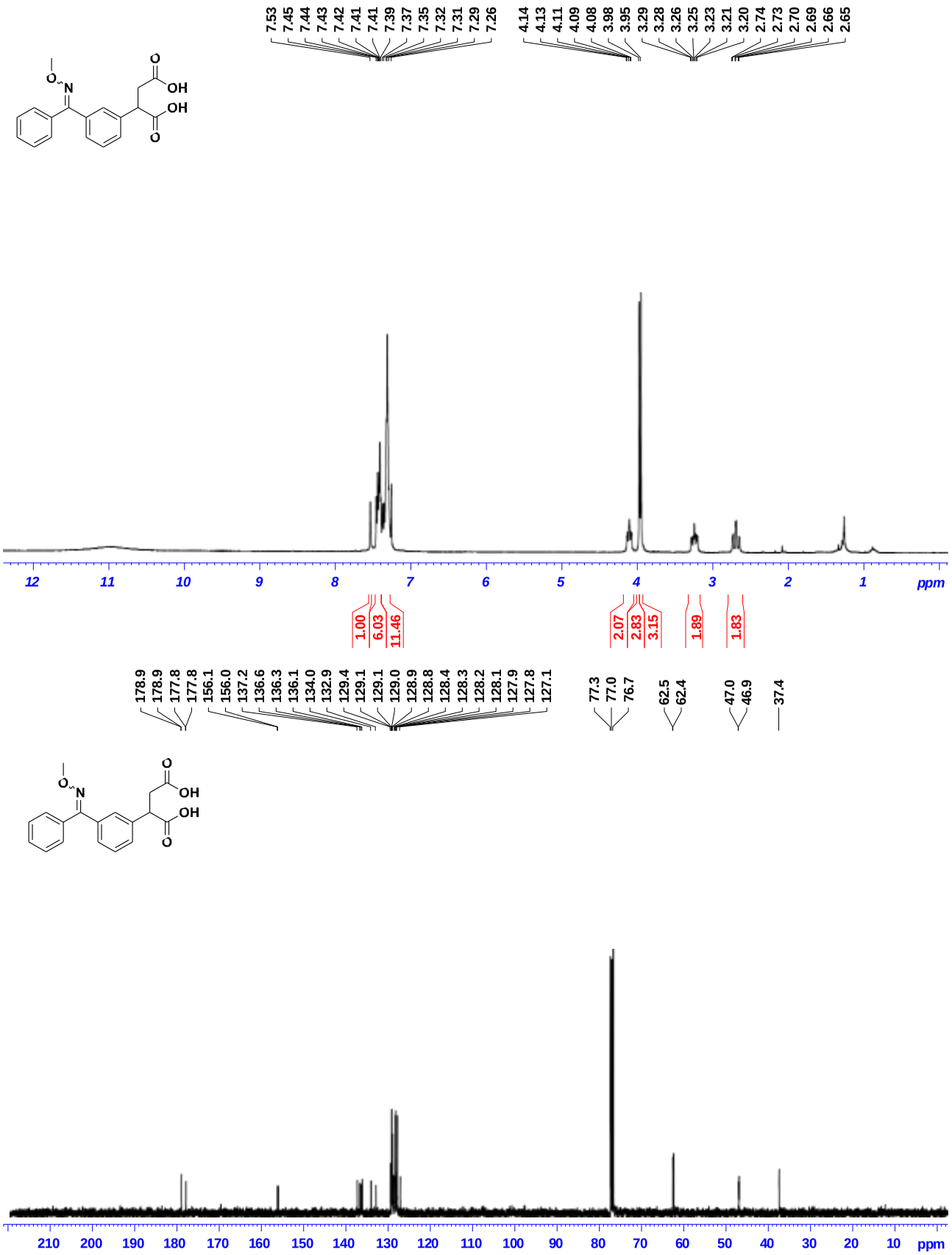
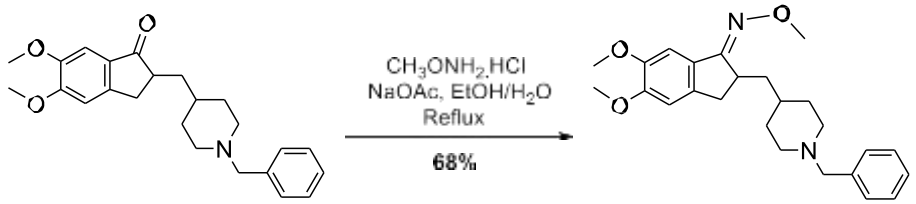


Figure S28. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.1.12.**

Section S6.2. Donepezil's analogs described in main-text Figure 4.a

Synthesis of (E)-2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one O-methyl oxime S6.2.1



Scheme S3. Reaction scheme of compound S6.2.1 described in main-text Figure 4.a.

To a solution of donepezil hydrochloride (100 mg, 0.240 mmol, 1 equiv.) in EtOH/H_2O (1.0/2.5 mL), was added O-methyl hydroxylamine hydrochloride (54.3 mg, 0.650 mmol, 2.7 equiv.) and sodium acetate (87.0 mg, 1.06 mmol, 4.4 equiv.) at room temperature. It was then refluxed for 20 h. The solvents mixture was directly evaporated, and the crude was purified on column chromatography with EtOAc/MeOH/acetic acid (90/10/2, v/v/v), to afford the desired product **S6.2.1** (67 mg, 68%), as light-yellow sticky oil.

^{1}H NMR (400 MHZ, CDCl3). δ 7.54-7.53 (m, 2H), 7.42-7.41 (m, 3H), 7.08 (s, 1H), 6.73 (s, 1H), 4.02 (s, 2H), 3.91-3.89 (m, 9H), 3.42-3.37 (m, 1H), 3.31-3.28 (m, 2H), 3.13-3.07 (m, 1H), 2.58-2.54 (m, 3H), 1.87-1.78 (m, 5H), 1.42-1.37 (m, 1H), 1.29 (m, 1H);

^{13}C NMR (101 MHZ, CDCl3). δ 164.99, 151.84, 149.05 (overlapped), 139.55, 130.98 (overlapped), 129.38, 129.02 (overlapped), 127.47, 107.47, 103.27, 61.85, 61.15, 56.05, 55.96, 52.30, 52.13, 38.63, 37.80, 36.02, 32.91, 30.13, 29.69;

HRMS (ESI) m/z: [M]+ Calc. for $C_{25}H_{33}N_2O_3$ 409.2491; Found 409.2497;

IR (film, CDCl3): 2952, 2926, 1717, 1602, 1500, 1460, 1332, 1043, 733 cm^{-1}.

General synthesis of the substrate 2-(1-benzylpiperidin-4-yl)acetaldehyde S6.2.5, described in main-text Figure 4.a

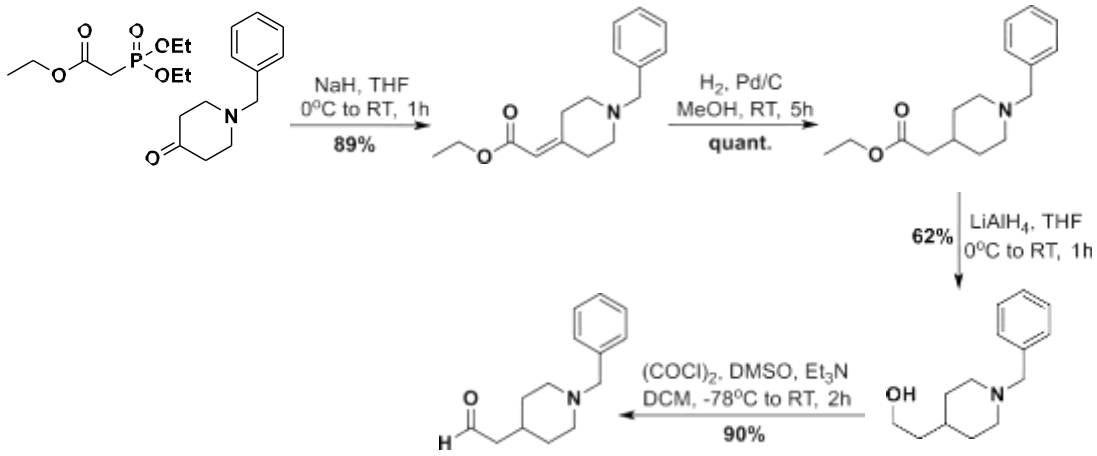
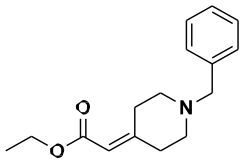


Figure S29. Synthesis of compounds S6.2.2 to S6.2.5.



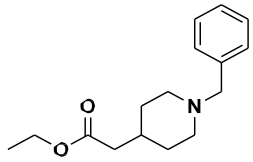
Ethyl 2-(1-benzylpiperidin-4-ylidene)acetate S6.2.2

Sodium hydride (60% in mineral oil, 0.253 g, 6.34 mmol, 1.2 equiv.) was added to anhydrous THF (8 mL) and the resulting mixture was stirred for 10 min in an ice bath. Then, triethyl phosphonoacetate (1.42 g, 6.34 mmol, 1.2 equiv.) was slowly added at the same temperature. The resulting solution was stirred for 30 min at RT, and cooled in an ice bath, followed by adding a solution of 1-benzyl-4-piperidone (1 g, 5.28 mmol, 1 equiv.) in anhydrous THF (3 mL). The resulting solution was stirred for no longer than 30 min at room temperature under inert atmosphere. The reaction mixture was then cooled back to 0 °C and a saturated aqueous solution of NH_4Cl was added. The aqueous layer was extracted twice with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The concentrate was purified by Flash chromatography (Hex./EtOAc, 7/3, v/v) to afford the desired product **S6.2.2** (1.23 g, 89%), as a colorless liquid.

The spectral data match those reported in the literature[S10];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.35-7.32 (m, 4H), 7.30-7.26 (m, 1H), 5.66 (s, 1H), 4.19-4.14 (q, *J* = 7.13 Hz, 2H), 3.55 (s, 2H), 3.03-3.00 (t, *J* = 5.59 Hz, 2H), 2.56-2.53 (m, 4H), 2.36-2.33 (t, *J* = 5.58 Hz, 2H), 1.31-1.28 (t, *J* = 7.14 Hz, 3H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 166.56, 159.56, 138.32, 129.05 (overlapped), 128.24 (overlapped), 127.07, 114.03, 62.59, 59.58, 54.54, 54.10, 36.82, 29.45, 14.32.



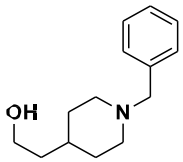
Ethyl 2-(1-benzylpiperidin-4-yl)acetate S6.2.3

Following the procedure for the synthesis of compound **S6.2.3**[S10]. **S6.2.2** (1.22 g, 4.70 mmol) and Pd/C (0.035 g) in MeOH (8 mL) were used at RT. A colorless liquid of **S6.2.3** (quant.) was obtained, no further purification was required.

The spectral data match those reported in the literature[S10];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.33-7.28 (m, 4H), 7.26-7.23 (m, 1H), 4.16-4.13 (m, 2H), 3.50 (s, 2H), 3.09-3.06 (d, *J* = 11.93 Hz, 2H), 2.88-2.86 (d, *J* = 11.76 Hz, 2H), 2.67-2.61 (dd, *J* = 13.01, 11.16 Hz, 2H), 2.24-2.23 (m, 3H), 2.03-1.96 (m, 2H), 1.28-1.26 (m, 3H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 172.79, 138.57, 129.14 (overlapped), 128.12 (overlapped), 126.87, 63.40, 60.16, 53.52 (overlapped), 41.29, 32.97, 32.11 (overlapped), 14.27.



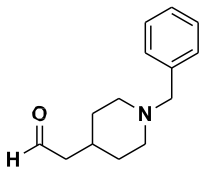
2-(1-benzylpiperidin-4-yl)ethan-1-ol S6.2.4

Following a modified procedure for the synthesis of compound **S6.2.4**[S10]. Compound **S6.2.3** (0.930 g, 3.55 mmol, 1 equiv.) and $LiAlH_4$ (1M in THF, 9.9 mmol, 2.5 equiv.) in THF (16 mL) were used. The temperature was allowed to warm up from 0^{o}C to RT, and the reaction was kept stirring for 1h at RT. A colorless liquid of **S6.2.4** (0.480 g, 62%) was obtained, no further purification was required.

The spectral data match those reported in the literature[S10];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.33-7.30 (m, 4H), 7.28-7.24 (m, 1H), 3.70-3.66 (t, *J* = 6.64 Hz, 2H), 3.50 (s, 2H), 2.90-2.87 (d, *J* = 11.68 Hz, 2H), 2.27 (m, 1H), 2.00-1.93 (m, 2H), 1.69-1.66 (m, 2H), 1.55-1.50 (m, 2H), 1.45-1.41 (m, 1H), 1.35-1.28 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 138.40, 129.27 (overlapped), 128.12 (overlapped), 126.90, 63.52, 60.41, 53.81 (overlapped), 39.46, 32.33, 32.31 (overlapped).



2-(1-benzylpiperidin-4-yl)acetaldehyde S6.2.5

Following the same procedure for **S6.2.5** synthesis[S10]. Compound **S6.2.4** (0.475 g, 2.16 mmol, 1 equiv.) in anhydrous DCM (1 mL), oxalyl chloride (0.548 g, 4.32 mmol, 2 equiv.) in anhydrous DCM (11 mL), Et_3N (0.931 g, 9.2 mmol, 4.25 equiv.), and DMSO (0.37 mL) were used at -78°C. Purification was done by using silica gel column chromatography (Hex./EtOAc, 4/6 to 2/8, v/v) to afford the desired product **S6.2.5** (0.420 g, 90%) as a colorless liquid.

The spectral data match those reported in the literature[S10];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 9.79 (m, 1H), 7.32-7.30 (m, 3H), 7.28-7.24 (m, 2H), 3.51 (s, 2H), 2.90-2.87 (d, *J* = 11.82 Hz, 2H), 2.39-2.37 (m, 2H), 2.06-1.99 (m, 2H), 1.95-1.88 (m, 1H), 1.72-1.69 (m, 2H), 1.42-1.31 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 202.18, 129.15 (overlapped), 128.16 (overlapped), 126.95, 63.39, 53.49 (overlapped), 50.49, 32.21 (overlapped), 30.66.

General figure of compounds S6.2.6 to S6.2.8, described in main-text Figure 4.a

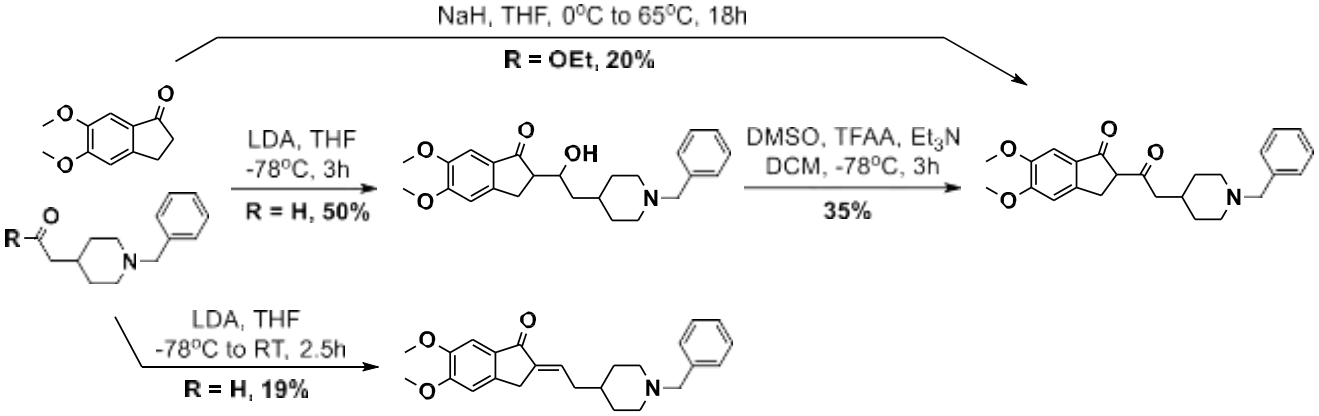
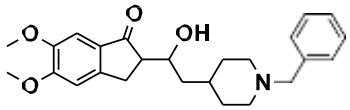


Figure S30. Reactions of compounds S6.2.6 to S6.2.8.



2-(2-(1-benzylpiperidin-4-yl)-1-hydroxyethyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one S6.2.6.

Under inert atmosphere, diisopropylamine (0.088 g, 0.87 mmol, 1.2 equiv.) was added to a flask containing anhydrous THF (2 mL), n-butyllithium (1.6 M in hexanes, 0.80 mmol, 1.1 equiv.) was added dropwise at -78 °C, and the mixture was stirred for 1 h at that temperature. To the reaction mixture was added 5,6-dimethoxy-1-indanone (0.140 g, 0.728 mmol, 1 equiv.) dissolved in THF (2 mL), and it was stirred at 0 °C for 1 h. The temperature was cooled back to -78 °C, and a solution of **S6.2.5** (0.190 g, 0.87 mmol, 1.2 equiv.) in THF (2 mL) was added. The reaction was stirred for 3 h between -78 °C and -50 °C before it was quenched with 2M HCl solution, and then extracted with EtOAc (2 x 30 mL). The organic extracts were washed with sat. $NaHCO_3$ and brine, then dried with anhydrous $MgSO_4$. The solvent was removed in

vacuo, and the residue was purified using silica gel column chromatography (EtOAc/MeOH, 9/1, v/v) to afford the desired product **S6.2.6** (0.150 g, 50%), as white solids.

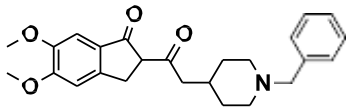
m.p. = 261-263 ºC;

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.33-7.30 (m, 4H), 7.27-7.23 (m, 1H), 7.18 (s, 1H), 6.90 (s, 1H), 4.54 (bs, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.91-3.86 (m, 1H), 3.50 (s, 2H), 3.22-3.16 (m, 1H), 2.90-2.87 (d, *J* = 11.35 Hz, 2H), 2.71-2.63 (m, 2H), 2.06-1.96 (m, 2H), 1.84-1.81 (m, 1H), 1.74-1.67 (m, 2H), 1.64-1.57 (m, 1H), 1.39-1.30 (m, 2H), 1.28-1.15 (m, 1H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 208.4, 156.1, 149.7, 149.3, 138.7, 129.2 (overlapped), 129.1, 128.1 (overlapped), 126.8, 107.3, 104.3, 70.3, 63.5, 56.3, 56.1, 53.9, 53.7, 52.5, 43.0, 33.6, 31.6, 31.5, 29.7;

HRMS (ESI) m/z: [M]+ Calc. for $C_{25}H_{32}NO_4$ 410.2331; Found 410.2332;

IR (film, $CDCl_3$) 3443, 2923, 1683, 1501, 1316, 1265, 1121, 1040, 747 cm^{-1}.



2-(2-(1-benzylpiperidin-4-yl)acetyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one S6.2.7

Method A:

To a solution of DMSO (47 μL) in DCM (0.5 mL) was added TFAA (0.067 g, 0.319 mmol, 2.9 equiv.) dropwise at -78 ºC under argon. The resulting mixture was stirred at that temperature for 45 min. Then, a precooled solution of **S6.2.6** (0.045 g, 0.11 mmol, 1 equiv.) in DCM (0.4 mL) was added. The reaction mixture was stirred at -78 ºC for 30 min, then at -15 ºC for 15 min, and cooled back to -78ºC. Et_3N (0.100 g, 0.99 mmol, 9 equiv.) was then added, and the mixture was stirred at -78 ºC for 45 min. The reaction was quenched by addition of sat. aqueous solution of NH_4Cl and the mixture warmed to room temperature. The two phases were separated and the aqueous phase was extracted with DCM (3x) and then EtOAc (1x). The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 9/1, v/v) to afford the desired product **S6.2.7** (0.016 g, 35%) as white solids.

Method B:

To a suspension of NaH (60% in mineral oil, 37.44 mg, 1.2 equiv.) in THF (0.5 mL) was added 5,6-dimethoxy-1-indanone (0.150 g, 0.78 mmol, 1 equiv.) in THF (1 mL) at 0 ºC. After stirring for 10 min, **S6.2.3** (0.490 g, 1.87 mmol, 2.4 equiv.) was added dropwise. This mixture was refluxed for 18 h, cooled back to r.t. and poured onto ice-cold 1 M HCl (4 mL). Extraction was performed with EtOAc (15x3 mL), the organic phase was washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 9/1, v/v) to afford the desired product **S6.2.7** (0.063 g, 20%), as white solids.

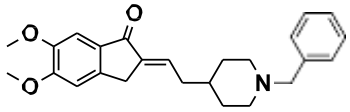
m.p. = 265-267 ºC;

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.33-7.32 (m, 5H), 7.27-7.24 (m, 1H), 6.96 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.93-3.91 (m, 1H), 3.51 (s, 2H), 2.91-2.88 (m, 3H), 2.32-2.30 (d, *J* = 7.18 Hz, 2H), 2.07-1.97 (m, 3H), 1.78-1.72 (m, 3H), 1.41-1.35 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 203.3 (194.5), 198.1 (172.9), 154.5 (154.4), 149.7 (149.5), 143.2 (144.5), 138.5 (138.7), 131.3 (134.6), 129.1 (overlapped), 128.1 (overlapped), 126.9 (126.8), 110.8 (overlapped), 107.4 (107.3), 63.4 (63.4), 61.9 (104.4), 56.2 (56.2-56.1), 53.8 (53.6) (overlapped), 40.6 (40.6), 34.0 (34.0), 32.5 (32.4-32.0), 29.6 (31.4);

HRMS (ESI) m/z: [M]+ Calc. for $C_{25}H_{30}NO_4$ 408.2175; Found 408.2176;

IR (film, $CDCl_3$) 2933, 1689, 1655, 1500, 1291, 1222, 1128, 750 cm^{-1}.



(E)-2-(2-(1-benzylpiperidin-4-yl)ethylidene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one S6.2.8

Lithium diisopropylamide, LDA (2M in THF, 2.71 mmol, 2.0 equiv.) was added to 2 mL of anhydrous THF, the mixture was cooled to -78 ºC before 5,6-dimethoxy-1-indanone (0.438 g, 2.28 mmol, 1.65 equiv.) in THF (5 mL) and (0.5 mL) of HMPA were added. The reaction mixture was stirred at that temperature for 15 min. A solution of **S6.2.5** (0.300 g, 1.38 mmol, 1 equiv.) in THF (5 mL) was then added, and the temperature was allowed to gradually increase to room temperature, followed by stirring for 2 h. An aqueous 1% ammonium chloride solution was added thereto, and the reaction mixture was extracted with EtOAc, The organic layers were collected, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (DCM/MeOH, 95/5, v/v) to afford the desired product **S6.2.8** (100 mg, 19%) as white solid.

m.p. = 243-245 ºC;

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.34-7.32 (m, 4H), 7.31 (s, 1H), 7.29-7.28 (m, 1H), 6.93 (s, 1H), 6.82-6.78 (t, *J* = 7.83 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.57-3.55 (m, 4H), 2.98-2.95 (m, 2H), 2.28-2.24 (t, *J* = 7.30 Hz, 2H), 2.06-2.01 (m, 2H), 1.77-1.73 (m, 2H), 1.60-1.53 (m, 1H), 1.46-1.40 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 192.12, 155.33, 149.53, 144.56, 137.90, 134.38, 131.85, 129.88, 129.53, 129.49, 128.37, 128.25, 127.26, 107.31, 105.07, 63.01, 56.25, 56.14, 53.42, 53.23, 36.68, 35.73, 31.98, 29.84, 29.69;

HRMS (ESI) m/z: [M]+ Calc. for $C_{25}H_{30}NO_3$ 392.2226; Found 392.2228;

IR (film, $CDCl_3$) 2924, 1694, 1650, 1501, 1307, 1254, 1129 cm^{-1}.

General synthesis of the substrate 1-benzylpiperidine-4-carbaldehyde S6.2.12, described in main-text Figure 4.a

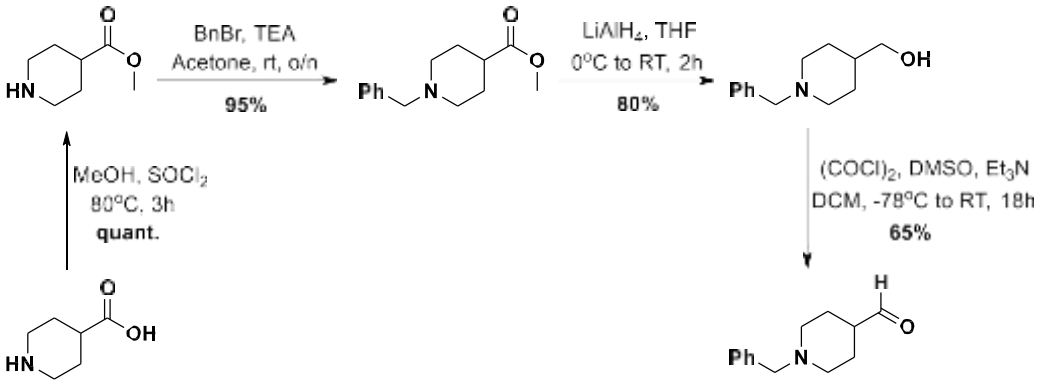
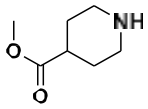


Figure S31. Synthesis of compounds S6.2.9 to S6.2.12.

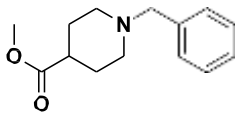


Methyl piperidine-4-carboxylate S6.2.9

To a solution of 4-piperidinecarboxylic acid (2 g, 15.48 mmol, 1 equiv.) in methanol (12 mL) was added thionyl chloride (1.84 g, 15.48 mmol, 1 equiv.) drop-wisely, the reaction is exothermic, so the temperature was gradually increased during the dropwise addition. Then, the mixture was set at 80 ^{o}C, and kept stirring for 3 h. After that, it was concentrated under reduced pressure to give the desired product **S6.2.9** (2.2 g, quant.), as white solids.

^{1}H NMR (400 MHZ, DMSO). δ 3.63 (s, 3H), 3.20-3.17 (m, 2H), 2.92-2.86 (m, 2H), 2.51 (m, 1H), 1.98-1.95 (m, 2H), 1.84-1.74 (m, 2H);

^{13}C NMR (101 MHZ, DMSO). δ 174.1, 52.2, 42.5 (overlapped), 38.1, 24.8 (overlapped).



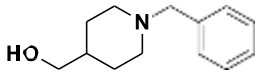
Methyl 1-benzylpiperidine-4-carboxylate S6.2.10

To a solution of methyl piperidine-4-carboxylate **S6.2.9** (2.2 g, 15.36 mmol, 1 equiv.) in acetone (18 mL), triethylamine (4.3 mL, 30.72 mmol, 2 equiv.) was added at r.t., followed by benzyl bromide (1.82 mL, 15.36 mmol, 1 equiv.). The mixture was stirred at r.t. for 16 h, and then it was quenched with water, and extracted with DCM. The organic layers were collected, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude yellow liquid was purified by flash chromatography (Hexane/EtOAc, 8/2, v/v) to afford the desired product **S6.2.10** (3.43 g, 95%), as light-yellow liquid.

The spectral data match those reported in the literature[S11];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.34-7.30 (m, 4H), 7.29-7.25 (m, 1H), 3.69 (s, 3H), 3.53 (s, 2H), 2.89-2.87 (m, 2H), 2.37-2.29 (m, 1H), 2.10-2.05 (m, 2H), 1.93-1.90 (m, 2H), 1.85-1.75 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 175.7, 138.4, 129.1 (overlapped), 128.2 (overlapped), 127.0, 63.2, 52.9 (overlapped), 51.6, 41.1, 28.3 (overlapped).



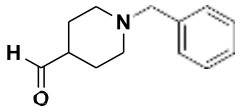
(1-benzylpiperidin-4-yl)methanol S6.2.11

To a suspension of $LiAlH_4$ (1.67 g, 44.10 mmol, 3 equiv.) in 30 mL of anhydrous THF was added, dropwise, a solution of methyl ester **S6.2.10** (3.43 g, 14.70 mmol, 1 equiv.) in 30 mL of anhydrous THF, while maintaining the temperature at 0 °C. After the addition was completed, the reaction mixture was allowed to stir at r.t. for 2 h. The reaction was then cooled back to 0 °C, and 40 mL of cold water was added with vigorous stirring. Insoluble material was filtered off, and the filtrate was concentrated in vacuo to remove THF. The resulting aqueous suspension was extracted with EtOAc and dried over $MgSO_4$, filtered and concentrated in vacuo to give us an oily liquid (2.4 g, 80%), as the desired product **S6.2.11**.

The spectral data match those reported in the literature[S11];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.34-7.30 (m, 4H), 7.28-7.26 (m, 1H), 3.52-3.50 (m, 4H), 2.95-2.92 (m, 2H), 2.02-1.96 (m, 2H), 1.75-1.71 (m, 2H), 1.57-1.47 (m, 1H), 1.36-1.26 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 138.5, 129.2 (overlapped), 128.1 (overlapped), 126.9, 68.0, 63.5, 53.4 (overlapped), 38.6, 28.8 (overlapped).



1-benzylpiperidine-4-carbaldehyde S6.2.12

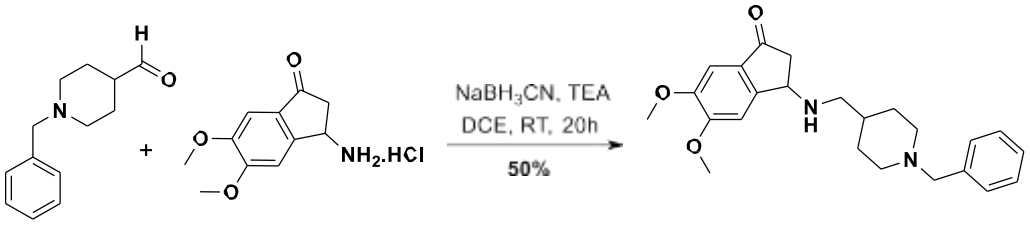
To a solution of oxalyl chloride (0.387 mL, 4.57 mmol, 2 equiv.) in 11 mL of anhydrous DCM was added dropwise dimethyl sulfoxide (0.4 mL, 5.63 mmol, 2.45 equiv.) at -60 °C. The reaction mixture was stirred at the same temperature for 10 min before adding the solution of the alcohol **S6.2.11** (0.470 g, 2.29 mmol, 1 equiv.) in 1 mL of anhydrous DCM. After 15 min, trimethylamine (1.36 mL, 9.728 mmol, 4.25 equiv.) was added dropwise. Then, reaction mixture was warmed to ambient temperature over 3 h, and then poured into water. The organic phase was separated, and the aqueous phase was extracted twice with DCM. The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by flash chromatography (Hexane/EtOAc, 7/3, v/v) to afford the desired product **S6.2.12** as oily liquid (300 mg, 65%).

The spectral data match those reported in the literature[S11];

^{1}H NMR (400 MHZ, $CDCl_3$). δ 9.67 (s, 1H), 7.34-7.33 (m, 4H), 7.30-7.26 (m, 1H), 3.53 (s, 2H), 2.86-2.83 (m, 2H), 2.29-2.23 (m, 1H), 2.16-2.11 (m, 2H), 1.92-1.89 (m, 2H), 1.77-1.67 (m, 2H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 204.0, 129.1 (overlapped), 128.2 (overlapped), 127.1, 63.2, 52.5 (overlapped), 48.0, 25.4 (overlapped).

Synthesis of 3-(((1-benzylpiperidin-4-yl)methyl)amino)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one S6.2.13



Scheme S4. Reaction scheme of compound S6.2.13 described in main-text Figure 4.a.

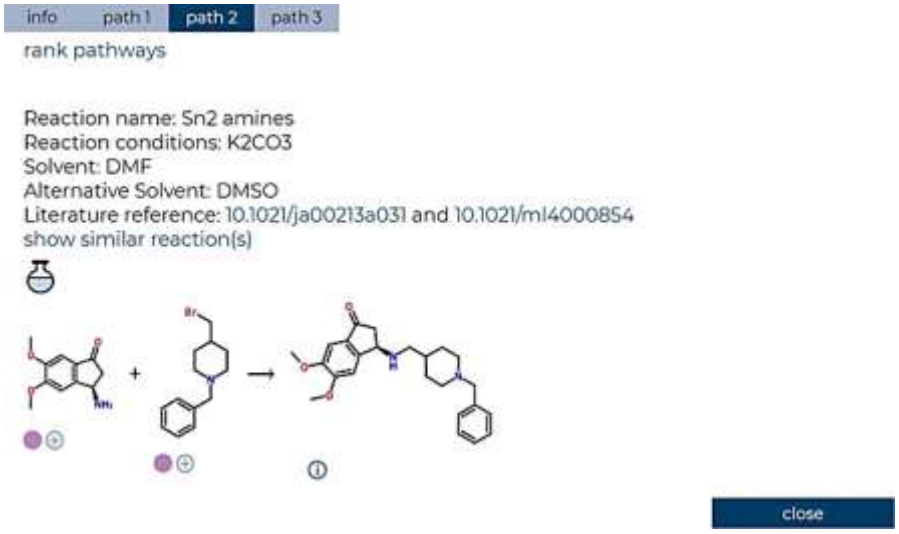


Figure S32. A screenshot from Allchemy showing the route of synthesis for compound S6.2.13.

Under inert atmosphere, to a solution of 3-amino-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one hydrochloride[S12] (0.180 g, 0.738 mmol, 1.3 equiv.) in DCE (2 mL) was added trimethylamine (0.134 mL, 0.965 mmol, 1.7 equiv.) dropwise at room temperature. 1-benzylpiperidine-4-carbaldehyde **S6.2.12** (0.116 g, 0.568 mmol, 1 equiv.) and $NaBH_3CN$ (0.064 g, 1.02 mmol, 1.8 equiv.) were then added portion-wise, and the mixture was kept stirring at room temperature for 20 h. The reaction was monitored by TLC. The reaction was then quenched with aq. $NaHCO_3$, extracted with EtOAc, the combined organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the crude mixture was purified by flash chromatography (EtOAc /MeOH, 5/5, v/v) to give the desired product **S6.2.13** (113 mg, 50%), as colorless sticky oil.

^{1}H NMR (400 MHZ, $CDCl_3$). δ 7.41-7.38 (m, 5H), 7.17 (s, 1H), 7.11 (s, 1H), 4.43-4.41 (dd, *J* = 2.48, 6.46 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.87 (s, 2H), 3.26-3.23 (m, 2H), 2.98-2.91 (dd,

J = 6.60, 18.57 Hz, 1H), 2.65-2.55 (m, 2H), 2.52-2.47 (dd, *J* = 2.72, 18.57 Hz, 1H), 2.38-2.32 (m, 2H), 1.89-1.86 (m, 2H), 1.35-1.27 (m, 3H);

^{13}C NMR (101 MHZ, $CDCl_3$). δ 202.8, 155.7, 150.5, 130.2 (overlapped), 129.9, 128.7 (overlapped), 128.4, 106.8, 103.7, 62.1, 56.4, 56.2, 56.0, 52.8, 52.7, 52.1, 44.3, 35.8, 29.7, 28.9;

HRMS (ESI) m/z: [M]+ Calc. for $C_{24}H_{31}N_2O_3$ 395.2335; Found 395.2337;

IR (film, $CDCl_3$) 3408, 2923, 2850, 1698, 1500, 1390, 1311, 1272 cm^{-1}.

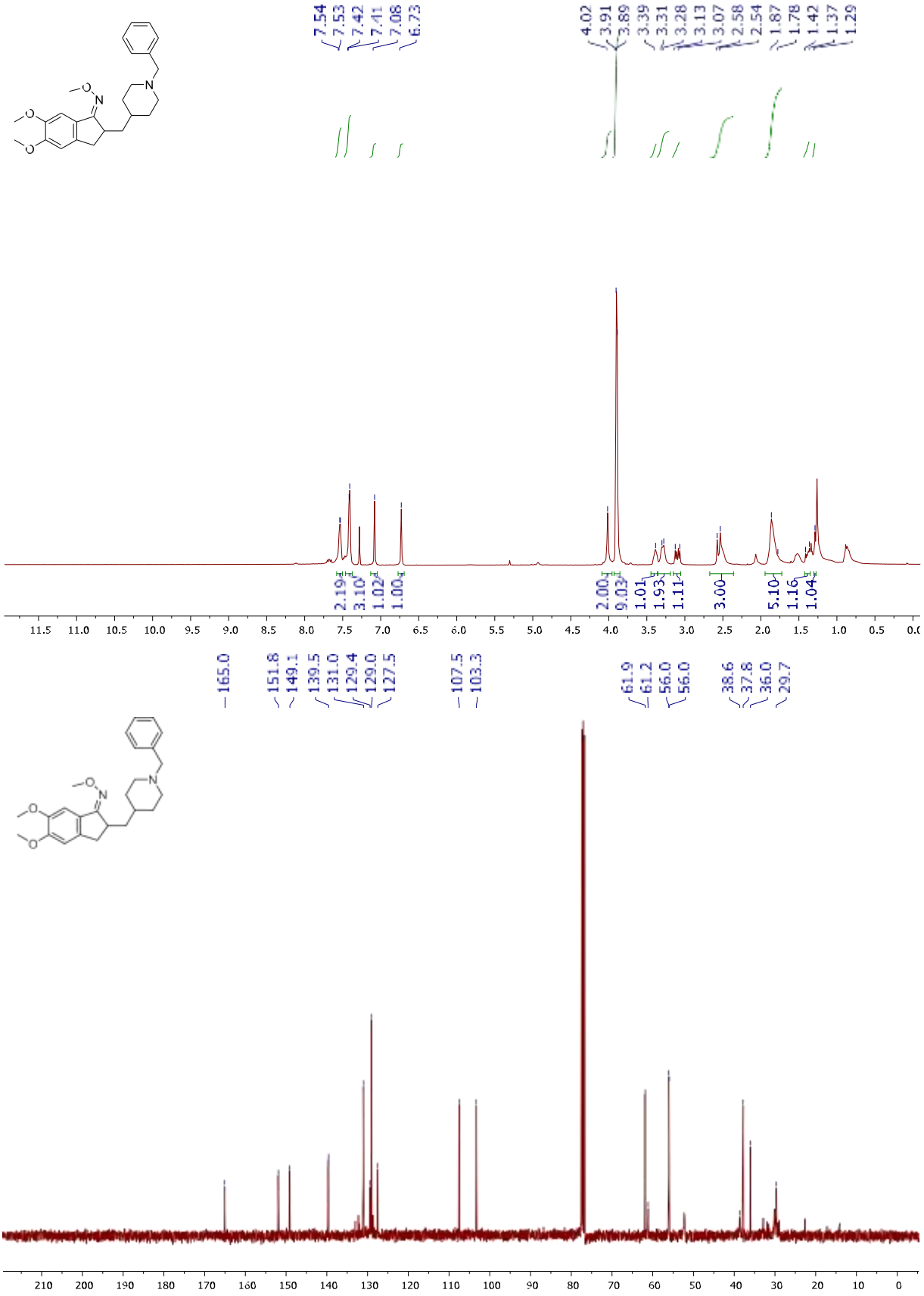


Figure S33. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.1.**

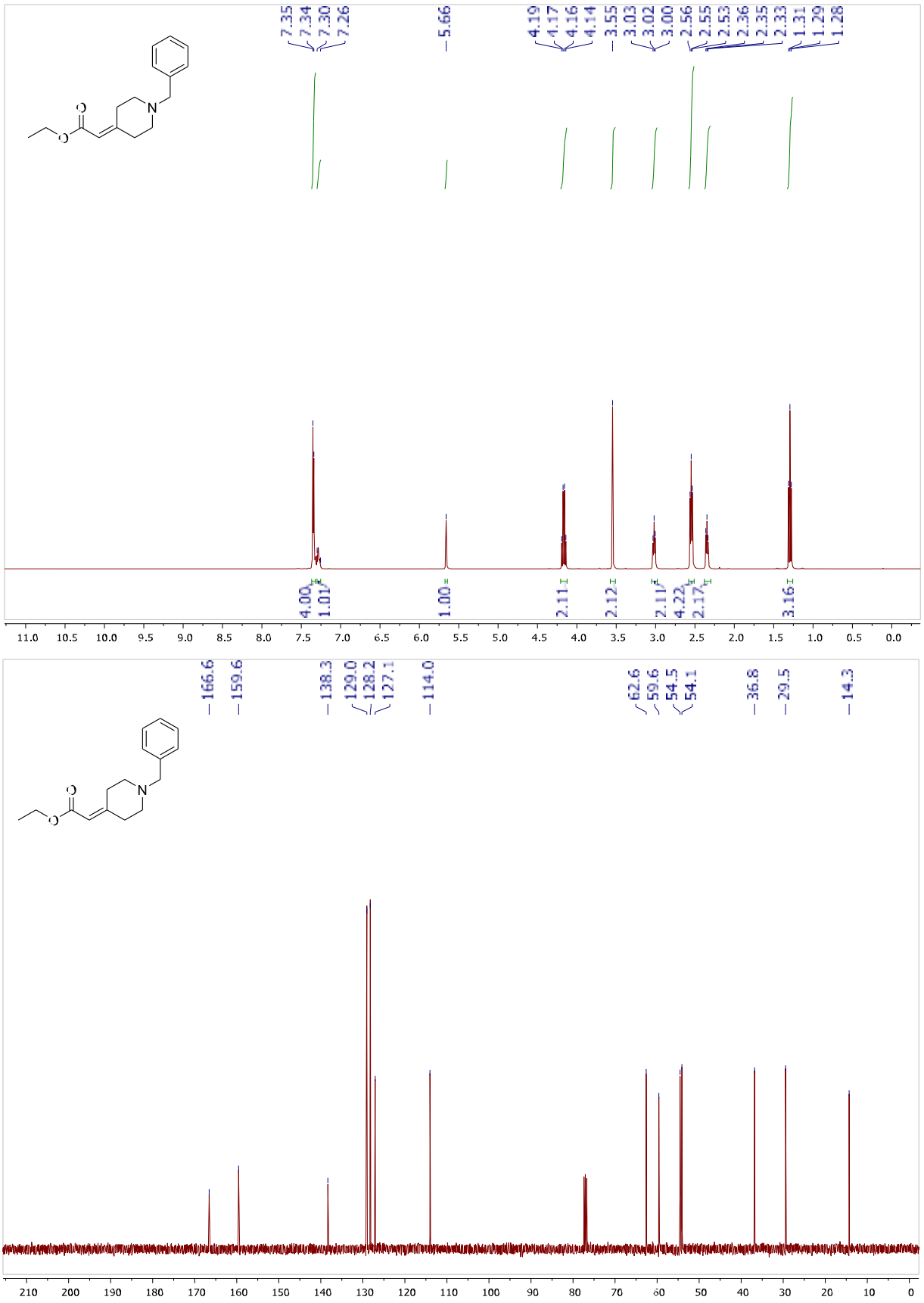


Figure S34. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.2.**

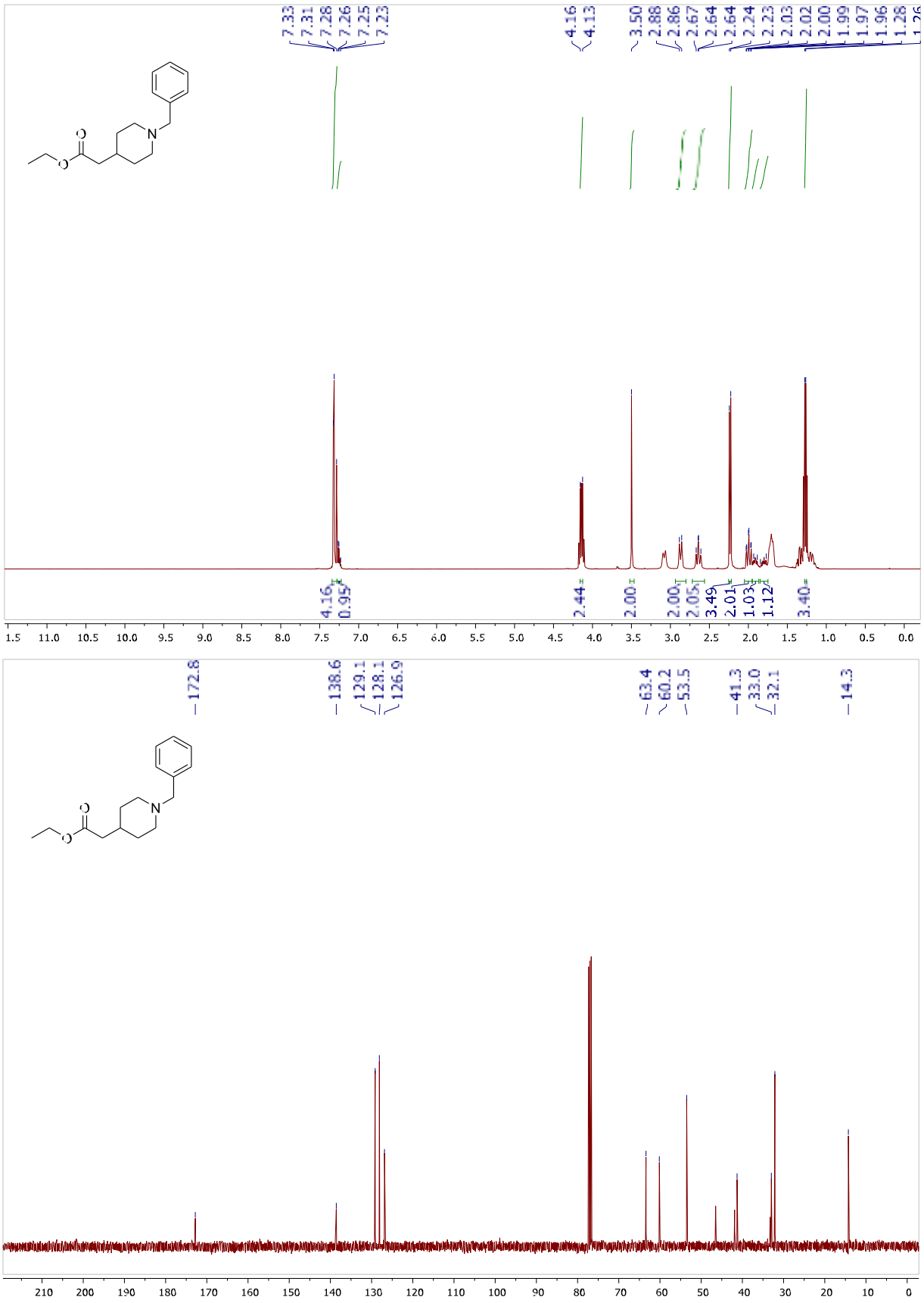


Figure S35. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.3.**

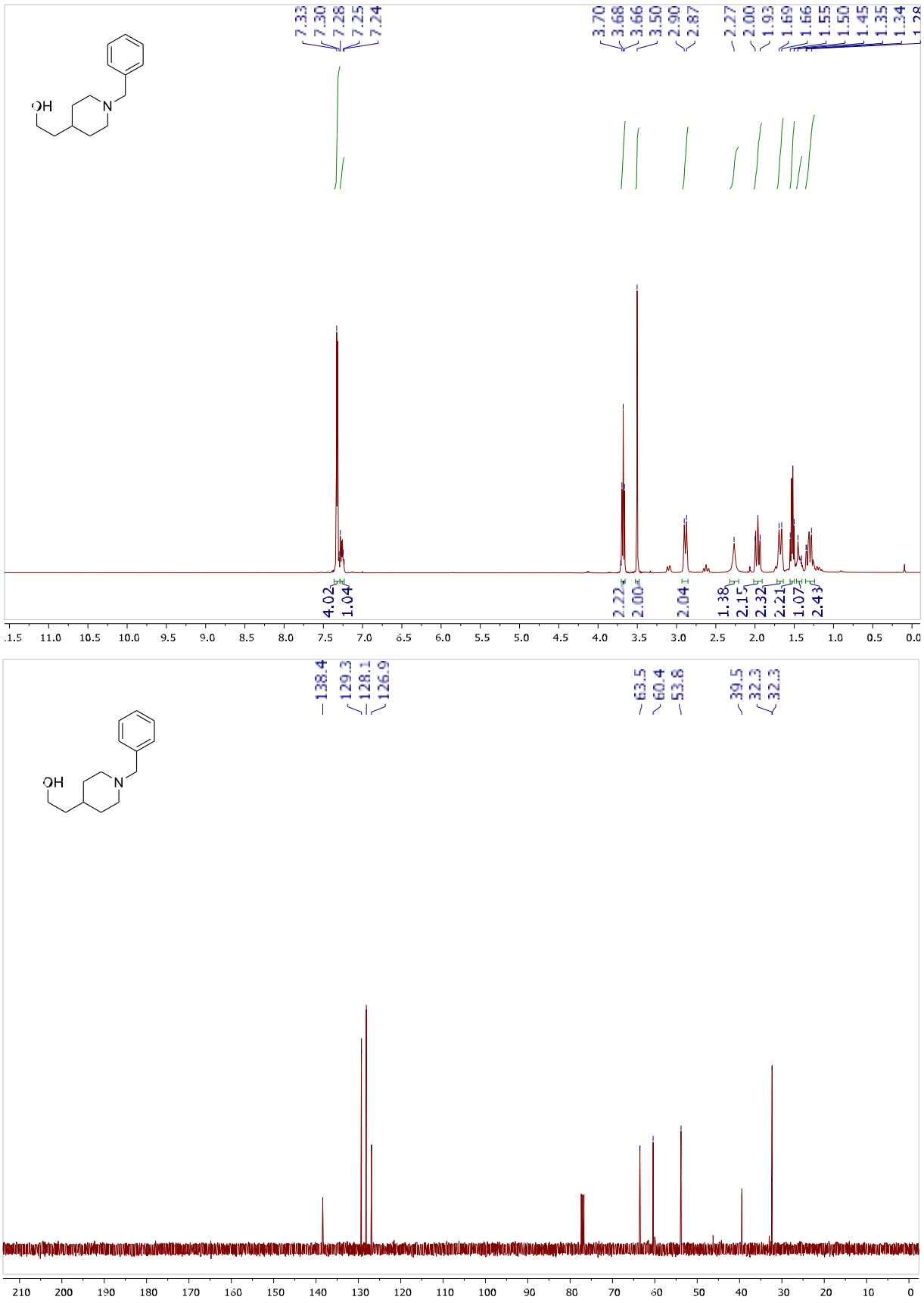


Figure S36. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.4.**

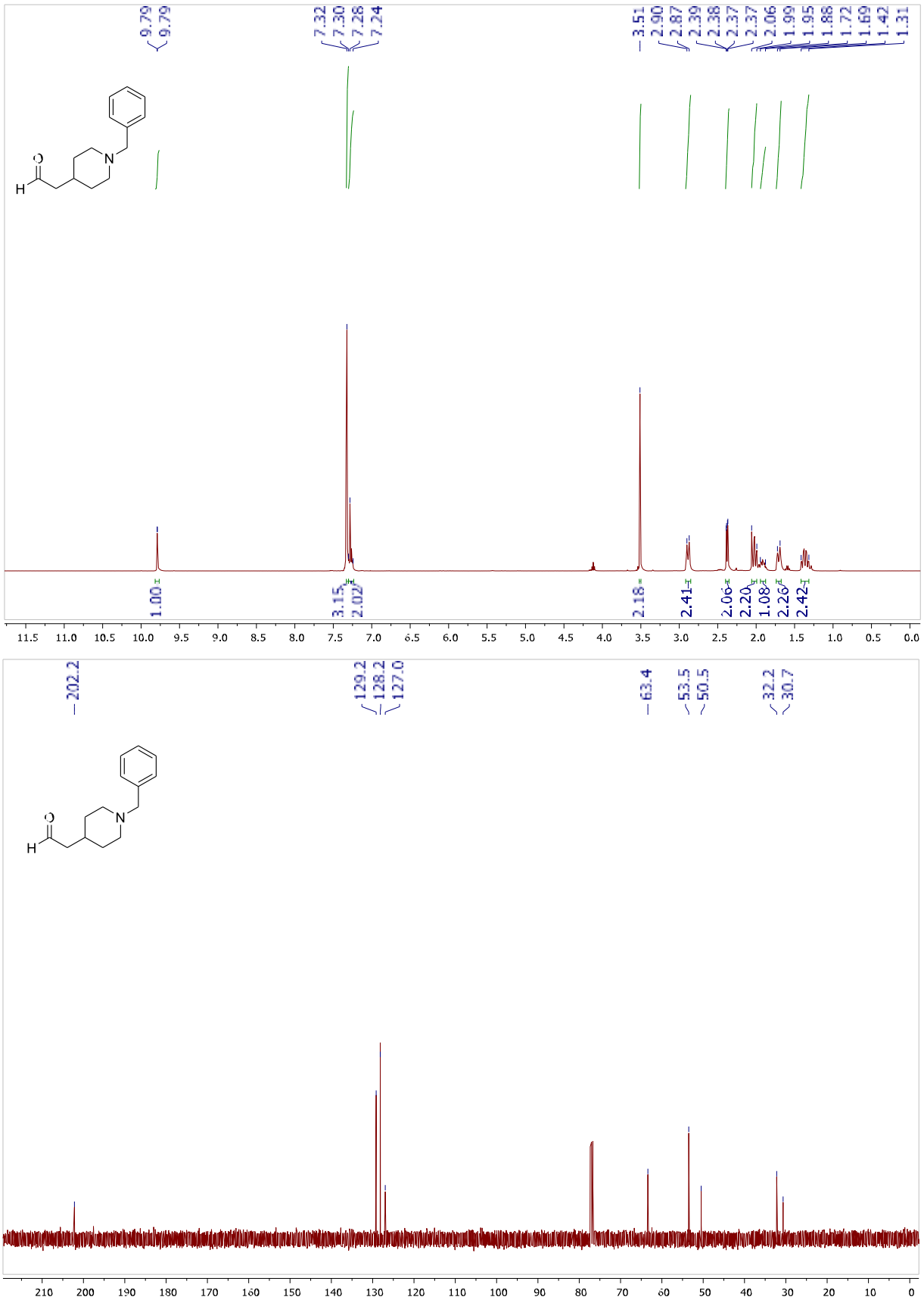


Figure S37. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.5.**

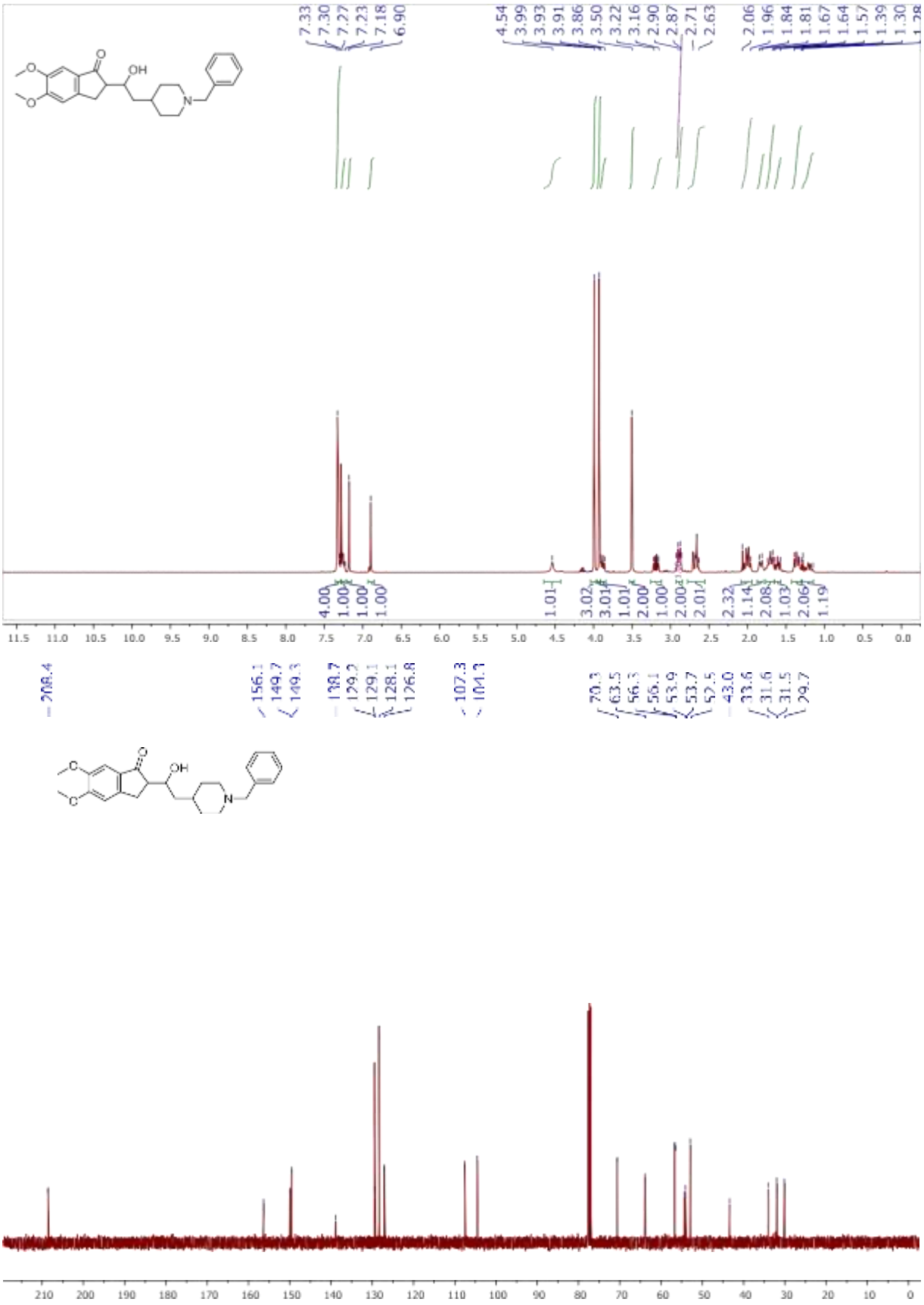


Figure S38. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.6.**

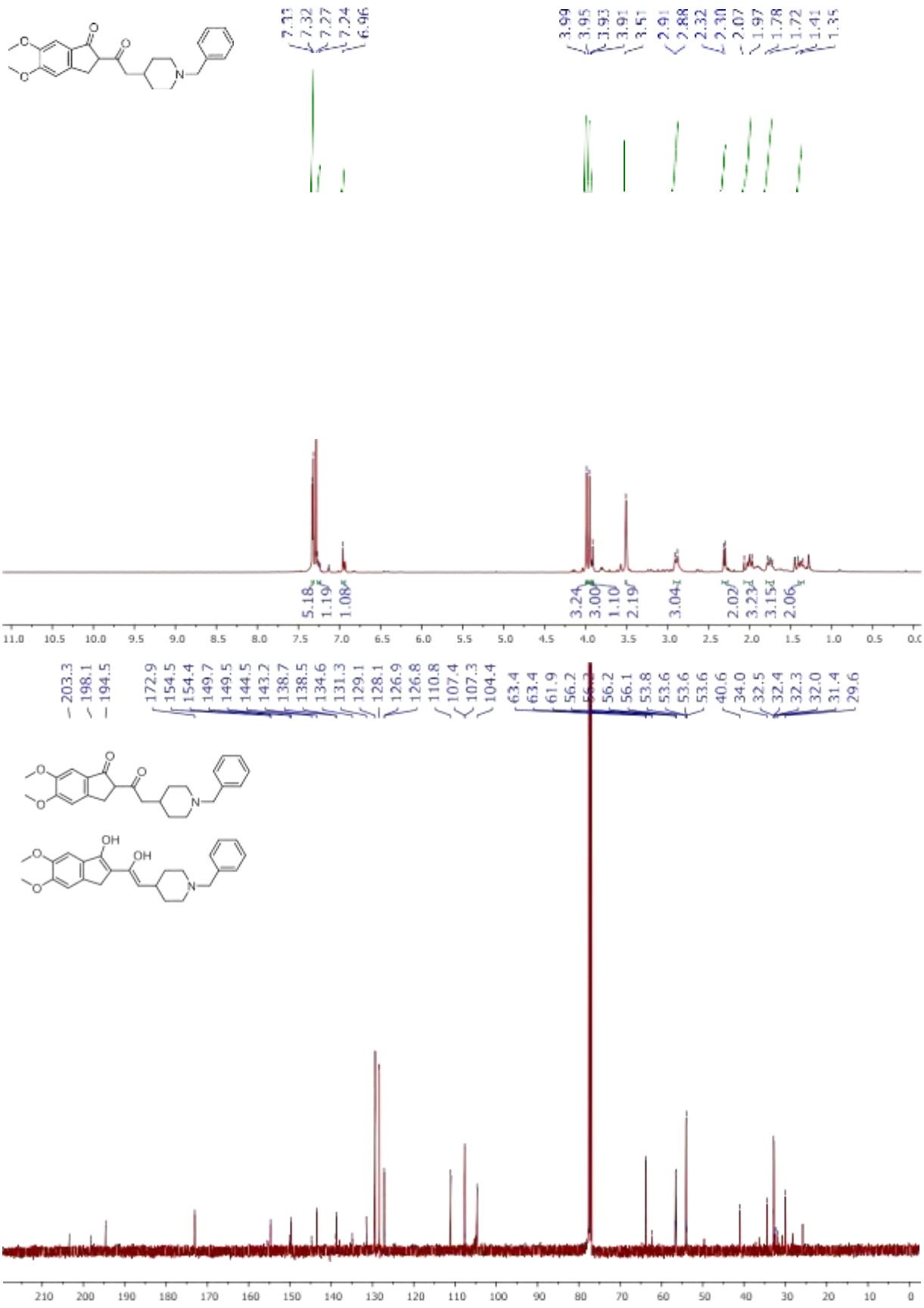


Figure S39. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.7.**

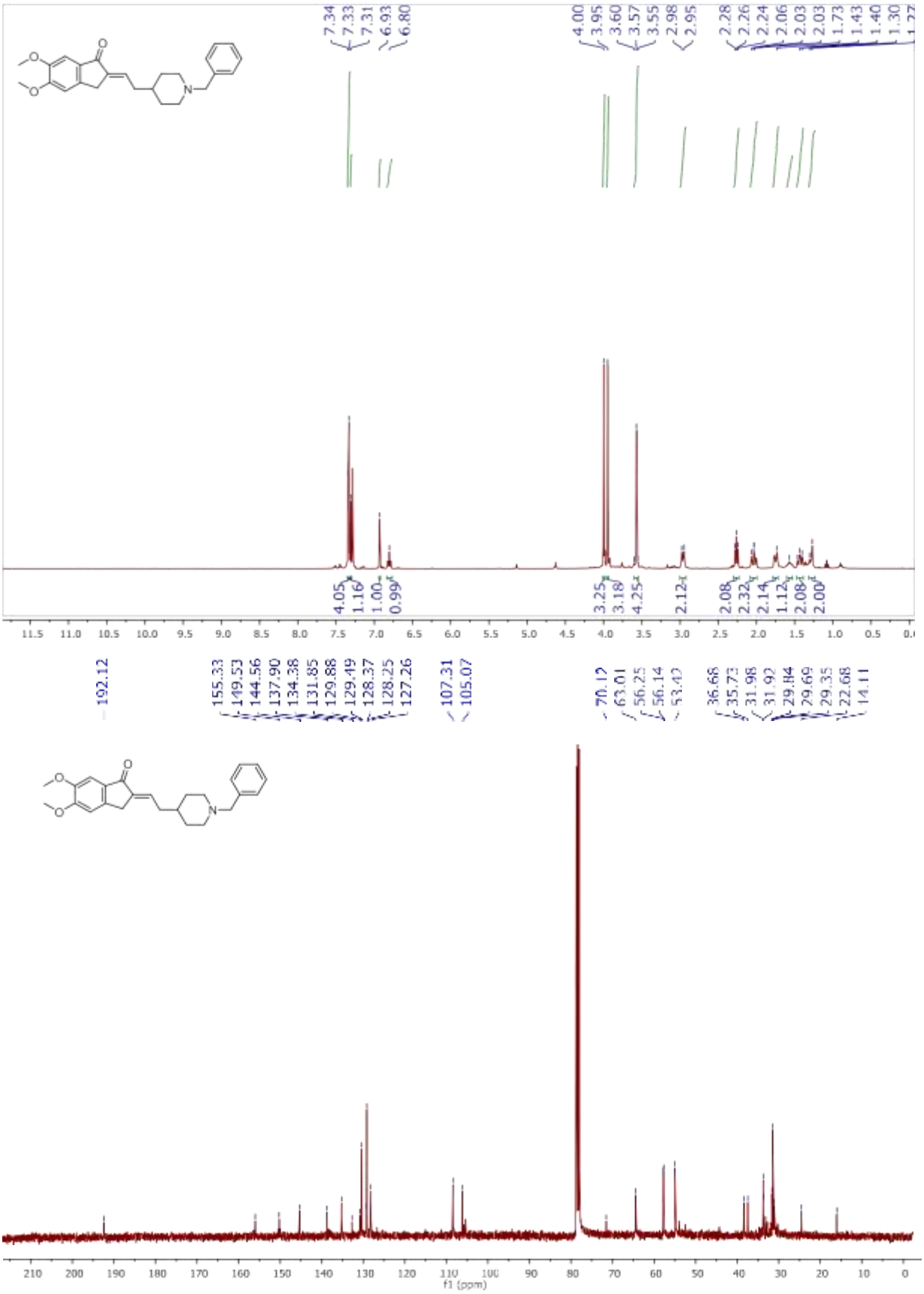


Figure S40. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.8.**

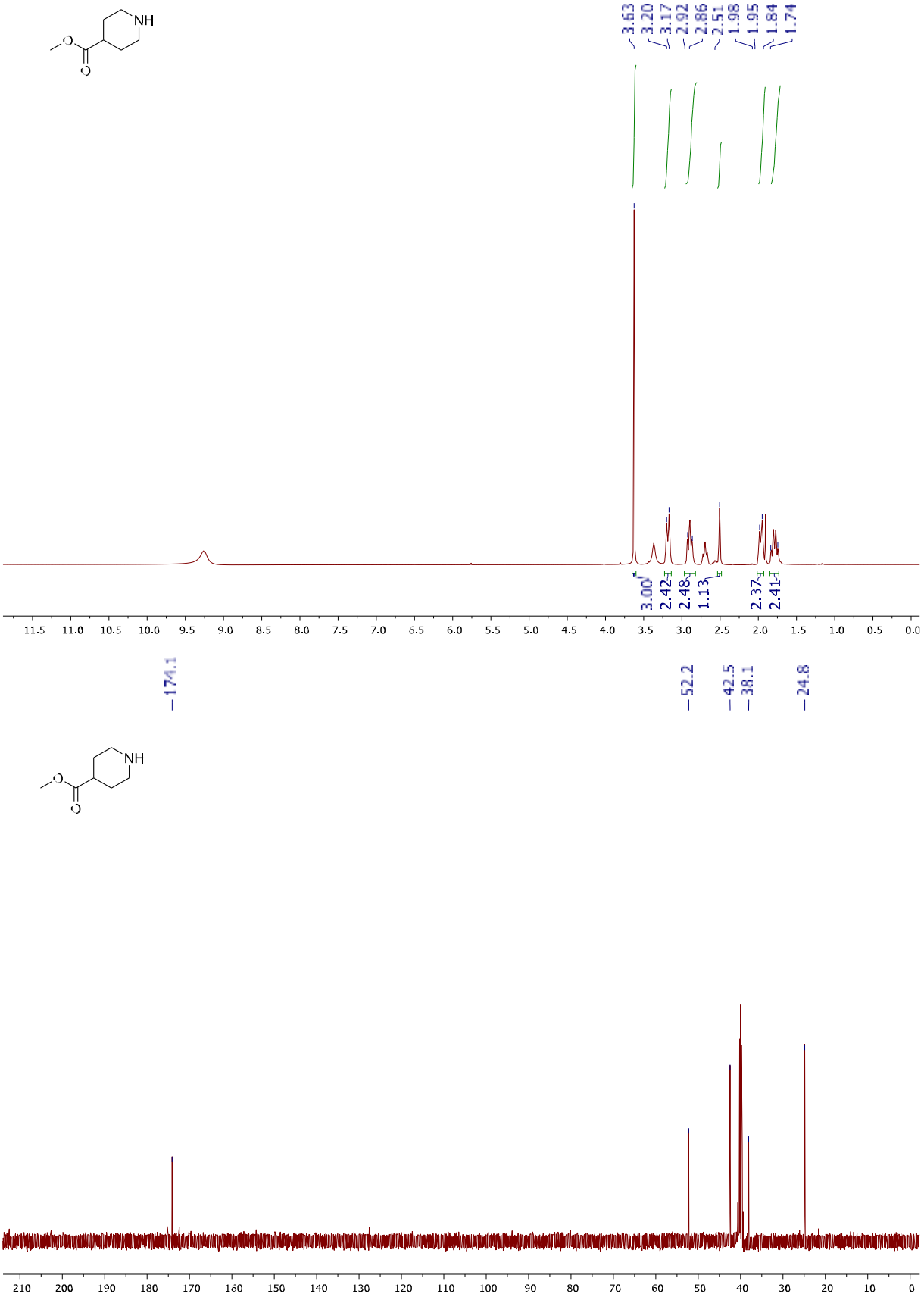


Figure S41. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.9.**

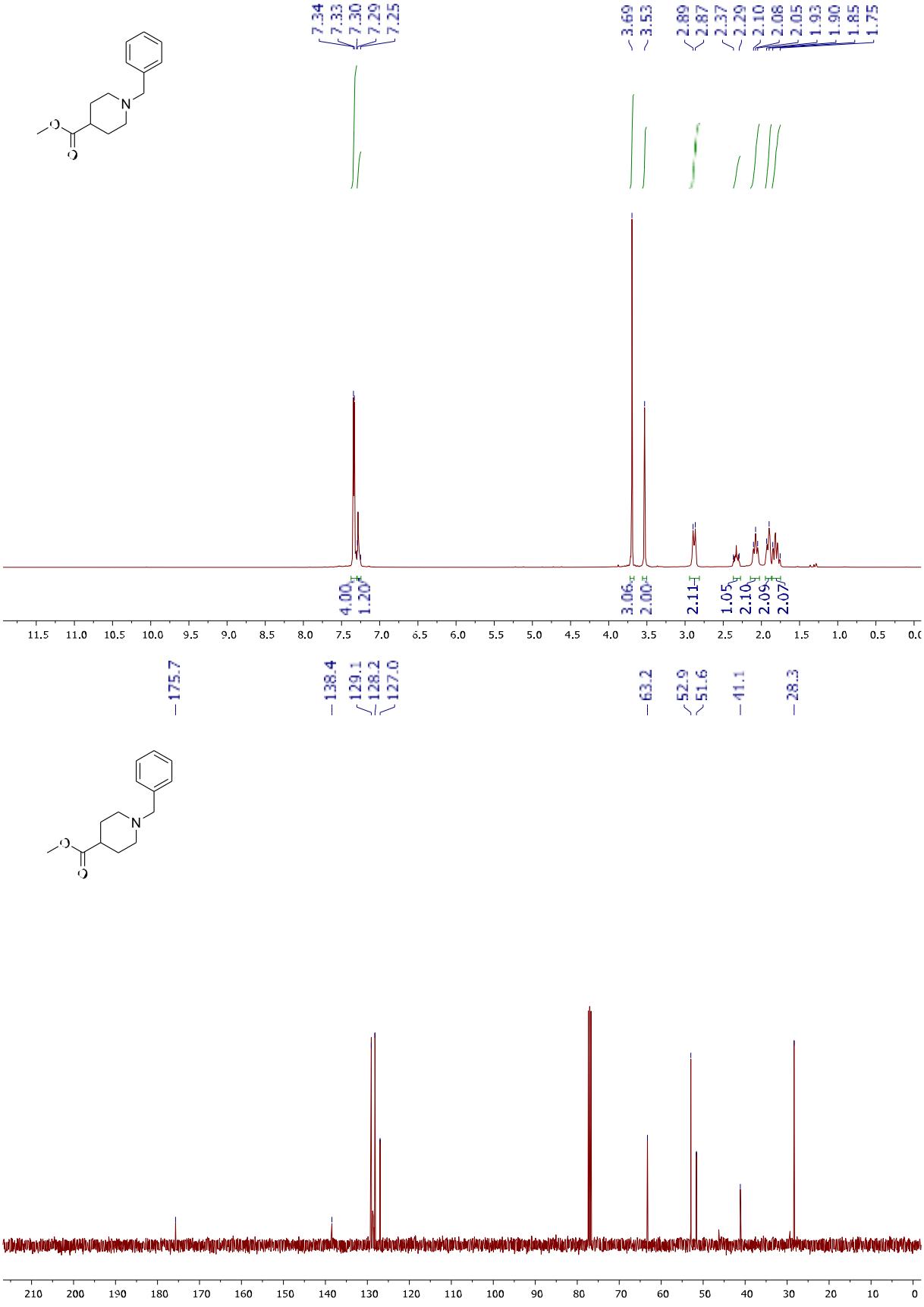


Figure S42. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.10.**

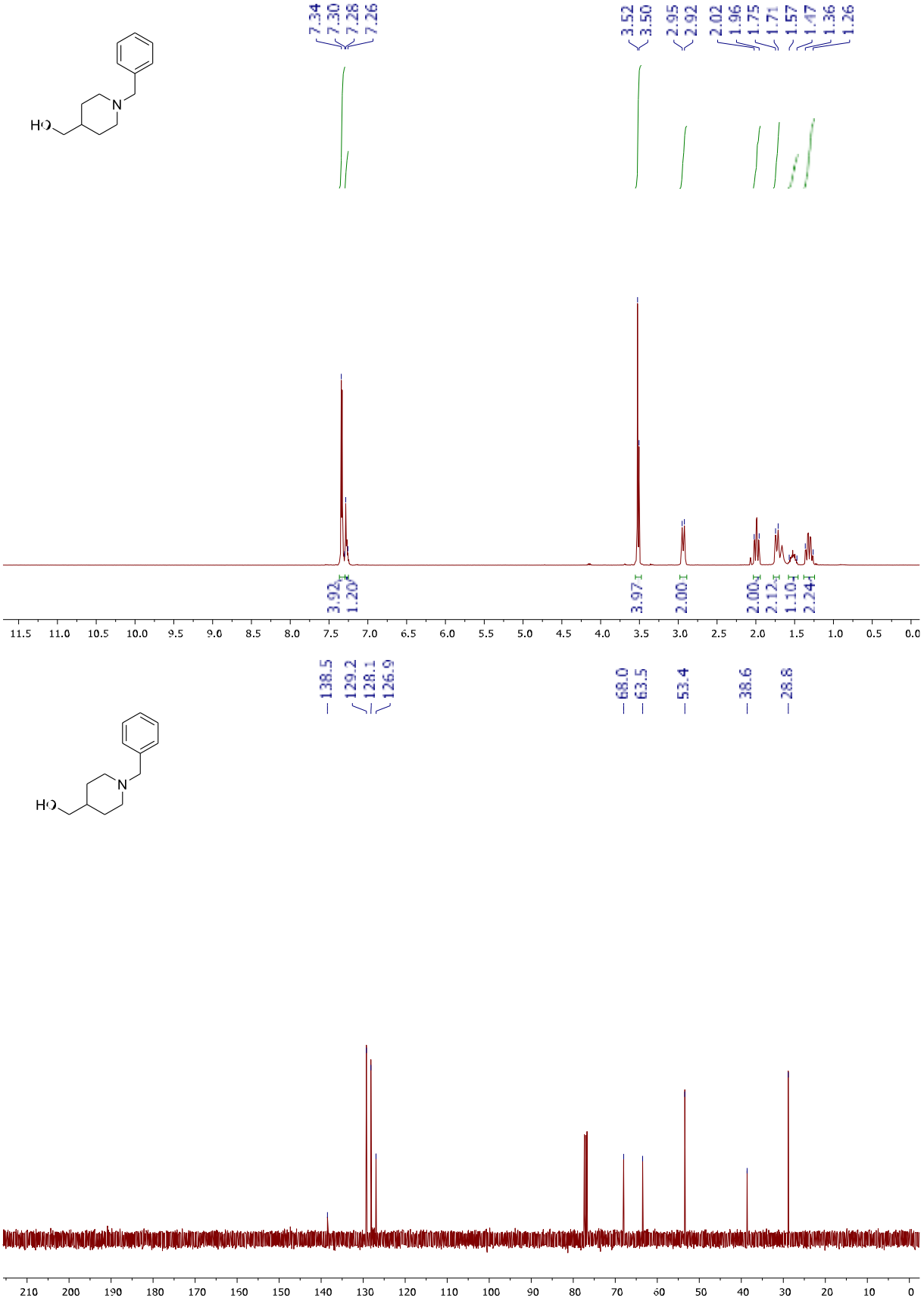


Figure S43. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.11.**

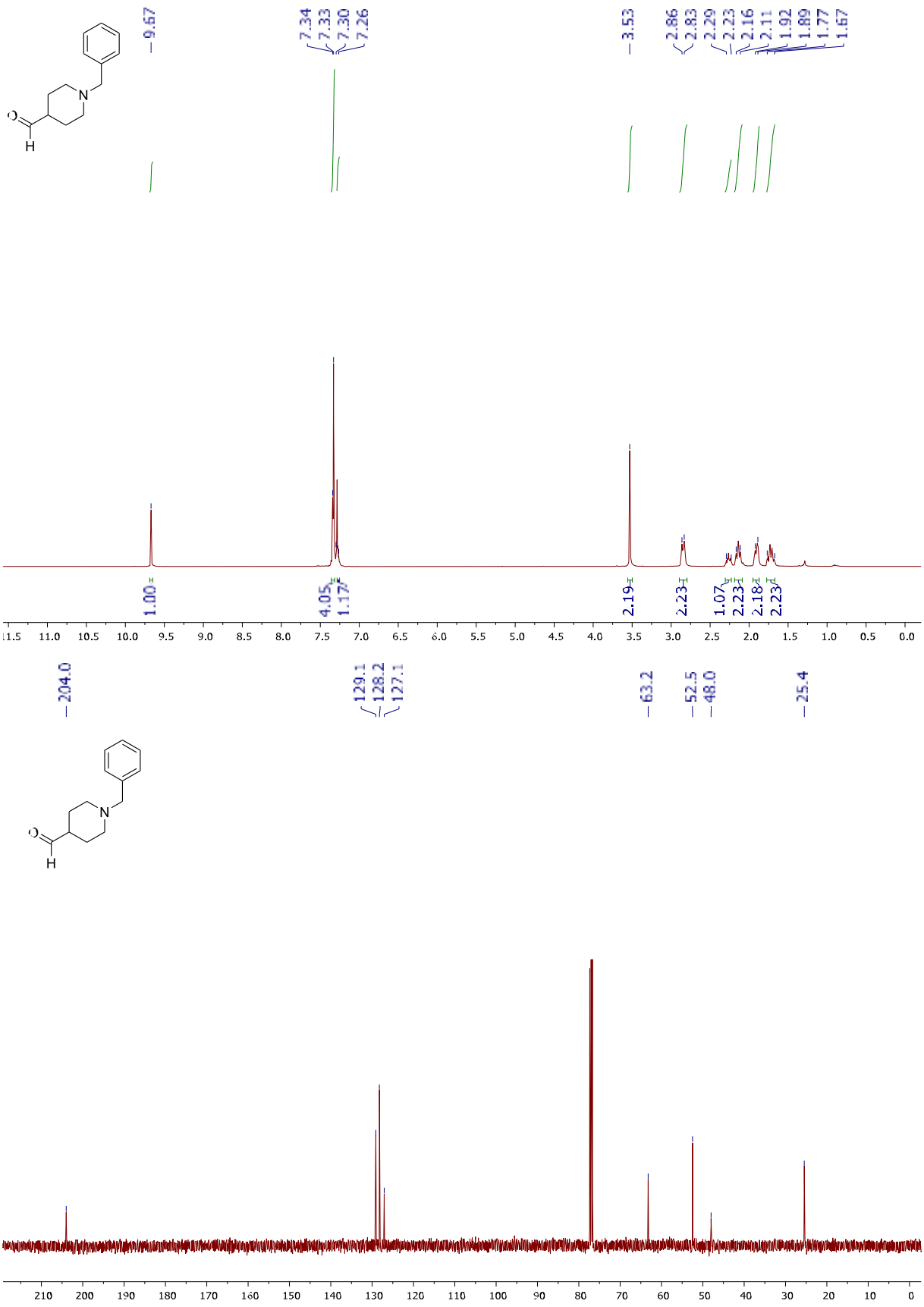


Figure S44. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.12.**

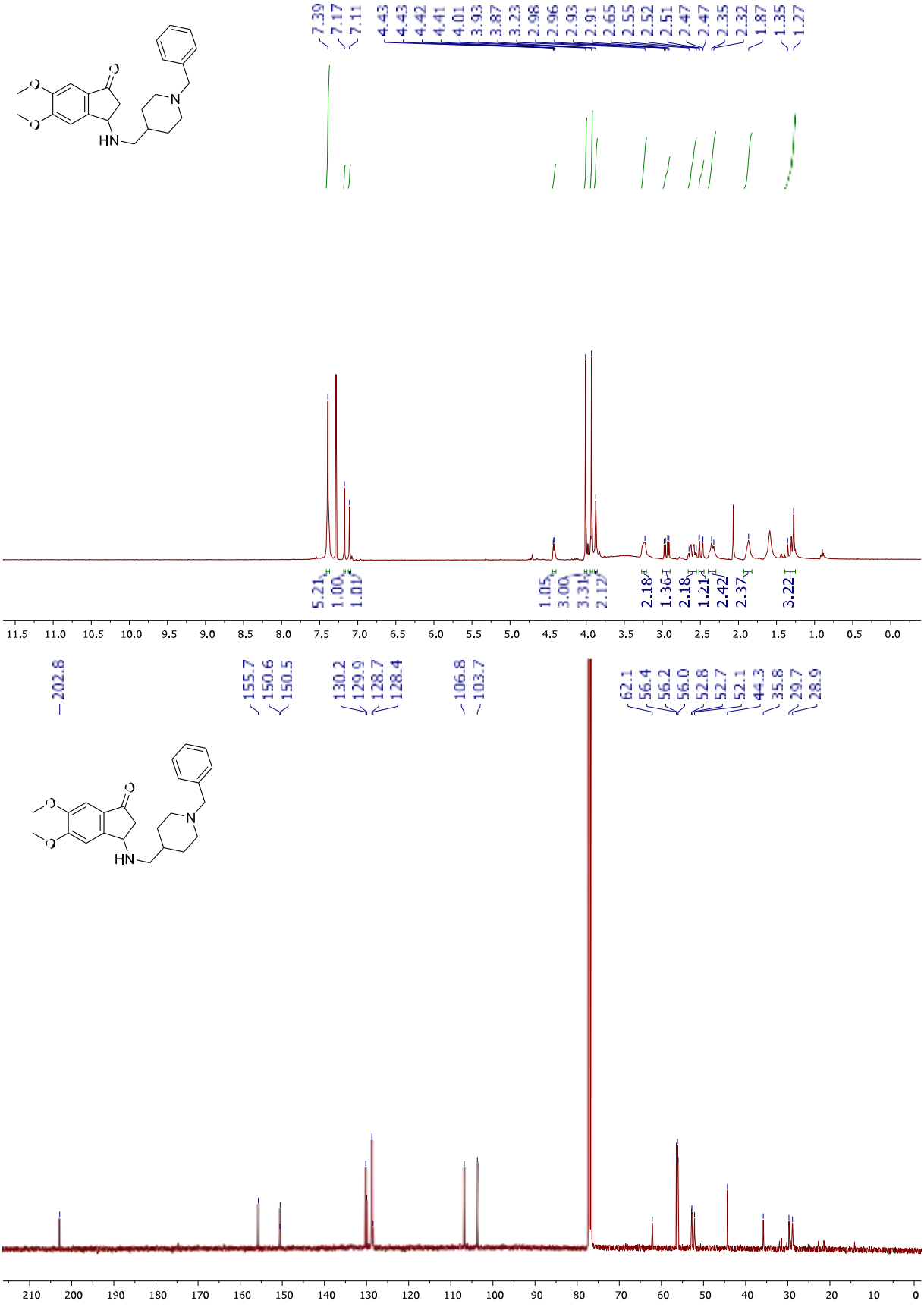


Figure S45. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **S6.2.13.**

Section S7. Tutorial for reaction rule coding.

All synthetic analyses presented in the Manuscript were performed using *Analogs* module of the Allchemy software. This module uses two distinct components:

i. retrosynthetic analysis of target replicas to obtain appropriate building blocks;
ii. forward-synthesis analysis commencing from the obtained building blocks (along with added simple chemicals) to generate the structural analogs of the parent molecule.

The first component is limited to 180 reaction rules, covering chemistries most commonly used in medicinal chemistry. In contrast, the second component utilizes the entire collection of reaction rules available in Allchemy, totaling 25,307 rules. As in all previous works involving the Allchemy software, these rules are expert-coded (rather than machine extracted) to minimize the incorrect predictions in both retrosynthetic and forward-synthesis analyses. In this Section of Supporting Information, we provide general guidelines related to the coding of such reaction rules, and illustrate these guidelines with examples of reaction rules used for generation of Ketoprofen's and Donepezil's analogues.

The coding of each reaction rule begins with a careful examination of the underlying reaction mechanism, aiming to generalize the rule beyond published precedent(s). At this stage, the strict reaction "core" (the atoms that change their environments) and the admissible substituents flanking this core are determined. The scope of the admissible substituents must account for appropriate electronic (e.g., the presence of electron-withdrawing groups in CH-alkylations or aldol-type condensations) and steric (e.g., the lack of steric hindrance in SN_2-type substitutions) environments to minimize incorrect predictions. The reaction template is then written in the SMARTS notation (*https://www.daylight.com/dayhtml/doc/theory/theory.smarts.html*) which is a machine-readable notation representing molecules and reactions as alphanumeric strings. This notation allows for defining the lists of admissible substituents and incorporation of full atom mapping across the reaction. The reaction template is written in the forward direction, with set of substrates on the left side of the reaction arrow and main product and byproducts on the right side of the reaction arrow (*Substrate1.Substrate2.Substrate3*>>*MainProd.Byprod1.Byprod2*). Additionally, the same reaction template is written in the retrosynthetic direction (with main product and byproducts on the left side of reaction arrow and set of substrates on the right side of reaction arrow) to be available for both (retro and forward-synthesis) modalities available in Allchemy.

In the next step, the list of functional groups beyond that are outside of the reaction core and can interfere with expected reaction outcome needs to be defined. At this stage, the reaction conditions (e.g., the presence of strong acids or bases, reducing or oxidizing reagents, or the presence of water or other nucleophilic solvents) and reacting partners (nucleophilic, electrophilic or radical species) are carefully evaluated. Without this list of incompatible structural fragments, the software would predict implausible reaction outcomes which would fail in the experimental validation due to cross-reactivity, non-selectivity or degradation of unstable substrates (e.g., due to hydrolysis) under the conditions necessary to perform the given reaction.

In the third step, the additional reaction details are provided. Here, the reaction conditions are classified with respect to:

i. general conditions (strongly acidic, acidic, neutral, basic, strongly basic, Lewis Acid);
ii. temperature (very low, low, room temperature (rt), high, very high);
iii. solvent classification (polar/nonpolar and protic/aprotic).

These classifications enable running the analyses avoiding unwanted reaction conditions, e.g., requiring extreme (cryogenic or very high) temperatures. These considerations can be included in the search settings as shown in the topmost part of Figure S1. Finally, the additional reaction metadata such as typical reaction conditions, literature reference illustrating a given type of chemistry, reaction name, or reaction byproducts (derived from reagents used) are added. All these data are available to the user and are displayed upon entering synthetic details (**Figure S7**).

With these general guidelines in mind, we will discuss in detail two examples of reaction rules used for disconnecting the parent Ketoprofen and Donepezil targets (and their structural replicas) and reassembling their structural analogues.

Example 1: Reductive amination.

This type of chemistry allows for the preparation of secondary amines from primary amines and aldehydes. From a mechanistic point of view, this one-pot, two-stage reaction proceeds via

i. formation of an imine via addition of an amine to an aldehyde and elimination of water and
ii. reduction of the imine via addition of the hydride delivered by a borohydride reducing agent.

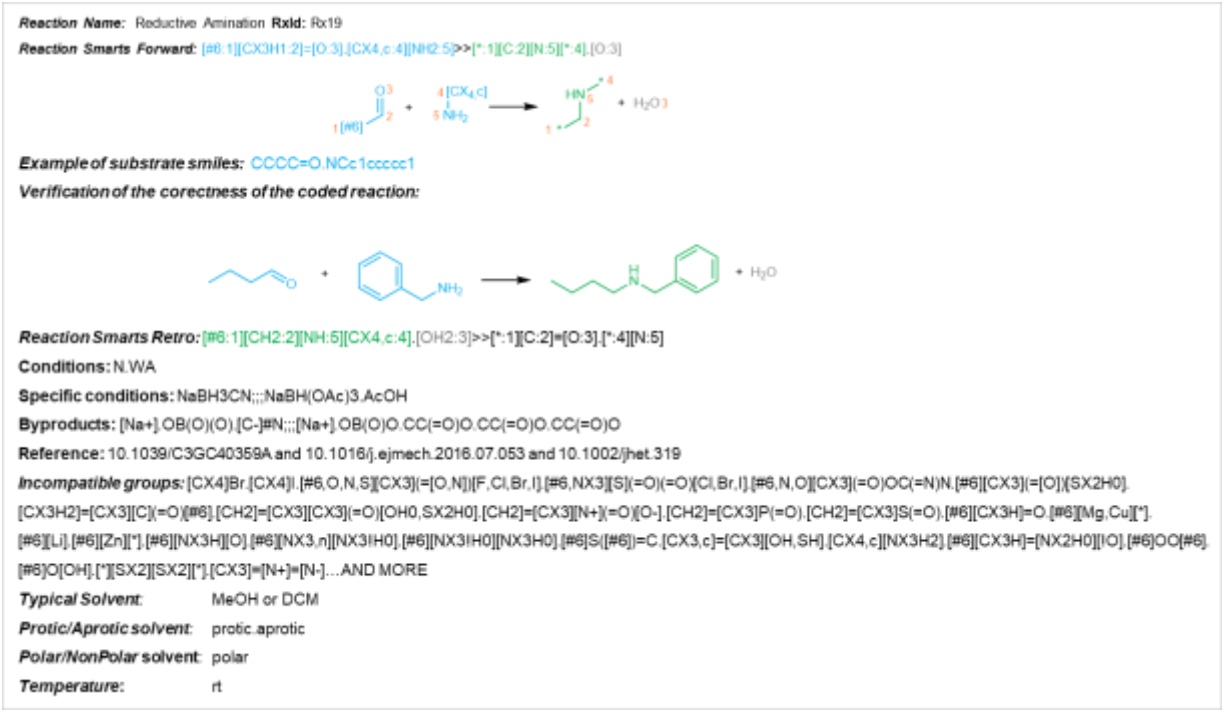


Figure S46. Coding of reaction rules used in the *Analogs* module. Example of a reaction rule for reductive amination used for preparation of Donepezil analogue **16**.

With reference to **Figure S46**, we begin coding the reaction template in forward direction by defining the set of substrates participating in this reaction. First, we specify the aldehyde starting material with atoms #1-#3. Here, the reaction core (atoms which change their environments) is defined with atoms #2 and #3 and represents the monosubstituted carbonyl group of an aldehyde which is written as [CX3H1:2]=[O:3] in SMARTS notation. The flanking substituent (#1) can be either aromatic or aliphatic sp3, sp2 or sp hybridized carbon atom, which is written as [#6:1] in SMARTS notation with #6 denoting carbon's atomic number. Next, we define the primary amine participating in the reductive amination reaction with atoms #4 and #5. The amino group of primary amine with two hydrogen atoms attached is encoded as [NH2:5] in SMARTS notation, while the flanking substituent (#4) can be either an aliphatic or an aromatic carbon atom which is written as [CX4,c:4] in SMARTS. No additional constrains are added to aliphatic carbons at position #4 because this type of chemistry is validated even for very hindered amines with nitrogen atom attached to a quaternary carbon. With all substrates thus coded in SMARTS notation, we move to the product side of the reaction and start coding the reaction product and byproduct templates. As the software uses the substrates defined on the left side of reaction arrow to check applicability ofa given reaction transform, the right side do not require the precise specification of substituents. Here, we code the template of the secondary amine with atoms #1,#2,#4,#5 as [*:1][C:2][N:5][*:4] and water byproduct with atom #3. Importantly,

all atoms which were lists or pseudolists such as [#6:1] defining various types of atoms (here, both aliphatic and aromatic) are written as "dummy" atoms denoted with stars. In this example, we use this "dummy" atom notation to code substituents flanking the carbonyl group of the aldehyde ([*:1]) and the amine ([*:4]). Finally, we rewrite the reaction template in the retro direction – now, with main reaction product (*green*) and byproducts (*grey*) on the left side of reaction arrow and substrate set (*blue*) on the right side of reaction arrow. In this example, the secondary amine main product is SMARTS-encoded as [#6:1][CH2:2][NH:5][CX4,c:4] while the water byproduct is written as [OH2:3].

In the next step, we provide an example of substrates for which a given reaction template can be applied and verify the corectness of coded reaction templates by i) running the forward template for these substrates and ii) running the retro template with products generated by the forward template – if both templates are correct we "regenerate" the original set of substrates. This tests are performed within the freely available RDKit (https://www.rdkit.org/) cheminformatics package.

After validation of the coded reaction templates, we move to the specification of functional groups present outside the reaction core and interfering with the expected reaction outcome. In this particular case, the reaction requires borohydride reducing agent and proceeds between an aldehyde electrophile and amine nucleophile. Accordingly, the list of competing functional groups includes:

1. strongly electrophilic groups which may react with amine nucleophile, e.g., alkyl bromides ('[CX4]Br'), alkyl iodides ('[CX4]I'), acyl halides ('[#6,O,N,S][CX3](=[O,N])[F,Cl,Br,I]), sulfonyl halides ('[#6,NX3][S](=O)(=O)[Cl,Br,I]'), activated carboxylic acids ('[#6,N,O][CX3](=O)OC(=N)N'), thioesters ('[#6][CX3](=[O])[SX2H0]'), β-unsubstituted Michael acceptors ('[CX3H2]=[CX3][C](=O)[#6]', '[CH2]=[CX3][CX3](=O)[OH0,SX2H0]', '[CH2]=[CX3][N+](=O)[O-]', '[CH2]=[CX3]P(=O)', '[CH2]=[CX3]S(=O)'), and competitive aldehydes ('[#6][CX3H]=O')
2. strongly nucleophilic groups which may react with aldehyde substrate and/or imine intermediate, e.g., organomagnesium, organolithium, organozinc and organocuprates compounds ('[#6][Mg,Cu][*]', '[#6][Li]', '[#6][Zn][*]'), NH-hydroxylamines ('[#6][NX3H][O]'), NH-hydrazines ('[#6][NX3,n][NX3!H0]', '[#6][NX3!H0][NX3H0]'), ylides ('[#6]S([#6])=C'), enols and thioenols ('[CX3,c]=[CX3][OH,SH]'), and competitive primary amines ('[CX4,c][NX3H2]')

3. functional groups prone to reduction, e.g., aldimines (‘[#6][CX3H]=[NX2H0][!O]’), peroxides(‘[#6]OO[#6]’), hydroperoxides (‘[#6]O[OH]’), disulfides(‘[*][SX2][SX2][*]’), diazo (‘[CX3]=[N+]=[N-]’)

In the next step, we classify the reaction conditions ($NaBH_3CN$ or $NaBH(OAc)_3$.AcOH) – here, the general reaction conditions are classified as ‘neutral or weakly acidic’ (*N.WA*), the temperature is classified as room temperature (*rt*) while the typical solvent (MeOH or DCM) is classified as *polar, protic* or *aprotic*.

Finally, the “Reaction name” (“*Reductive Amination*”), reaction identifier (RxId, “*Rx19*”) reaction byproducts generated from reagents (‘[Na+].OB(O)(O).[C-]#N’ from $NaBH_3CN$ and ‘[Na+].OB(O)O.CC(=O)O.CC(=O)O.CC(=O)O’ from $NaBH(OAc)_3$) and references to illustrative examples of application of such reductive aminations are added.

Example 2: C-H alkylation

In this example, we illustrate coding of a reaction rule covering the alkylation of enolates with primary alkyl bromides. This reaction transform allows for the preparation of functionalized ketones, esters or amides and was the key step in reassembling Ketoprofen’s analogues. From the mechanistic point of view, this one-pot two-stage reaction is carried out by i) deprotonation and enolisation of C-H acids and ii) SN_2-type substitution of the obtained enolate nucleophile with alkyl bromide electrophile. Accordingly, the coded reaction template must account for the presence of appropriate electron withdrawing groups (enabling the deprotonation and formation of the enolate) and define the steric environment surrounding the electrophilic center of primary alkyl bromide (excluding unreactive and sterically hindered neopentyl-type electrophiles).

With reference to **Figure S47**, we start coding the reaction template by defining the participating nucleophile with atoms #1-#5. First, we define the strict reaction core – here, atom #4 changes its environment and is limited to sterically unhindered aliphatic carbon atom with two hydrogens attached, which is written as [CX4H2:4] in SMARTS notation. Next, we move to the specification of electron withdrawing groups acidifying the #4 positions. In this particular reaction template, the allowed groups are limited to carboxylic acid esters, amides or ketones. The carbonyl group of each of these fragments is coded on atoms #2 and #3 and written as [C:2](=[O:3]) in SMARTS notation while atom #1 defines the flanking alkoxy-, amino- or carbon fragment behind the carbonyl group and is coded as [CX4H0,c,CX3,CX2,OH0,NX3H0:1]. The alkoxy- fragment of carboxylic acid esters is coded as “OH0” – oxygen atom with no hydrogens attached. The amino fragment of amides is limited

to amides with no hydrogens at nitrogen atom because N-H amides are preferentially deprotonated and alkylated at nitrogen rather than at α-CH position. This requirement is written as `NX3H0` is SMARTS notation representing sp3-hybridized nitrogen atom with no hydrogens attached. Finally, the ketones are allowed to have acidic hydrogens at only a single α-position #4 to avoid non-selective reaction outcomes. Thus, position #1 of ketones is limited to alkyl carbons with no attached hydrogens (`CX4H0`), aromatic ('c') or aliphatic sp2 (`CX3`) or sp ('CX2') hybridized carbons. Finally, we define the list of substituents at position #5 flanking the reaction center. Here, we allow for the aliphatic ('CX4','CX3','CX2') or aromatic ('c') carbons, n-bound heterocycles ('n') and nitrogen, sulfur, oxygen or silicon heteroatoms with no attached hydrogens ('NX3H0', 'SX2H0', 'OX2H0', 'SiX4H0'). We note the alkylation of C-H acids with two electron withdrawing groups (e.g., ketoesters, ketoamides or diketones) is coded in the separate reaction rule because such alkylations can be performed under much milder conditions (with no strong base involved) and their scope of incompatible groups is quite different.

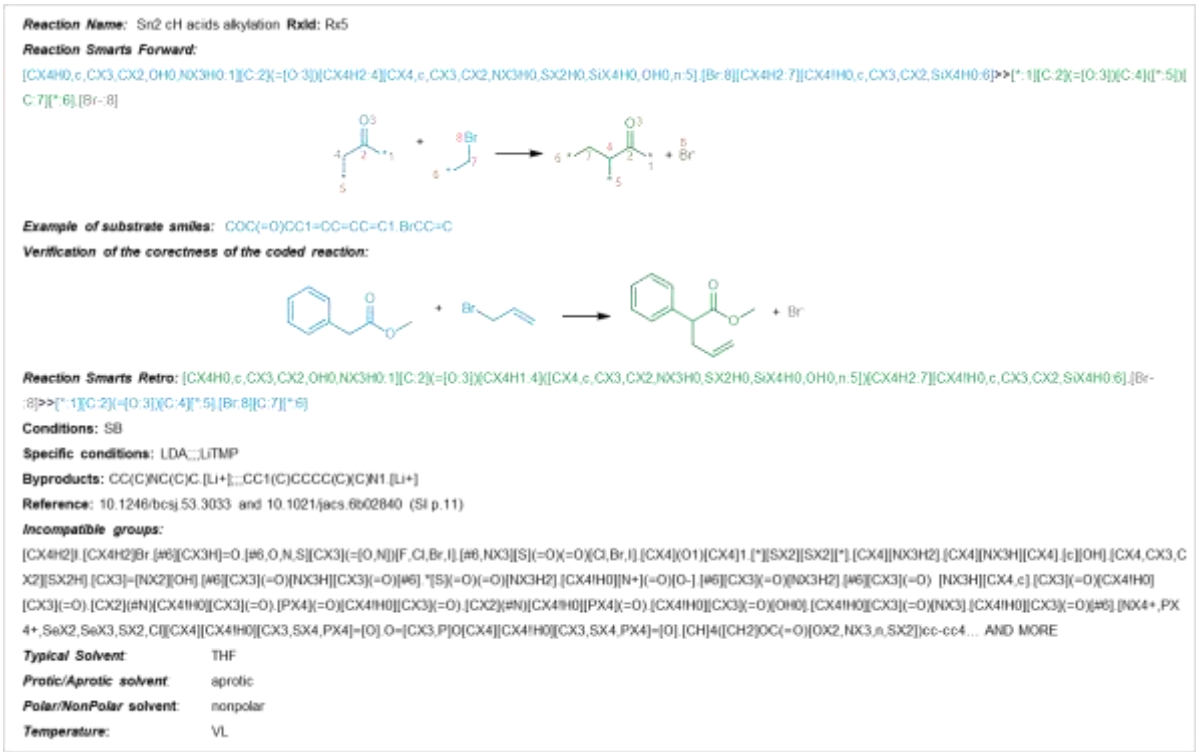


Figure S47. Coding of reaction rules used in the *Analogs* module. Example of a reaction rule for the alkylation of CH acids used here in the preparation of Ketoprofen's analogues.

Next, we continue the coding of reaction template by defining the alkyl bromide electrophile with atoms #6-#8. First, we define the strict reaction core: bromide leaving group ([Br:8]) and

the carbon atom of primary alkyl bromide involved in S_N2-type displacement (#7), the latter limited to aliphatic carbon atom with two hydrogens attached ([CX4H2:7]). The neighboring position #6 ([CX4!H0,c,CX3,CX2,SiX4H0:6]) allows for the presence of aromatic ('c') or aliphatic sp2 ('CX3') or sp ('CX2') hybridized carbons (defining highly reactive benzyl, allyl and propargyl bromides as electrophiles) or silicon atom. Aliphatic, sp3-hybridized carbons are also allowed but are required to have at least one hydrogen attached ([CX4!H0]) excluding sterically hindered and unreactive neopentyl-type electrophiles. With all substrates thus defined, we move to the coding of the main reaction product (*green* in **Figure S47**) with atoms #1-#7 and the bromide leaving group ([Br-:8], *grey* in **Figure S47**). As in the previous example, we replace all lists of substituents (here, at #1, #5 and #6) with 'dummy' atoms ([*:1], [*:5] and [*:6]). Finally, we provide the example of substrates for which this reaction rule can be applied, rewrite the forward reaction template in retro direction with the main reaction product coded as [CX4H0,c,CX3,CX2,OH0,NX3H0:1][C:2](=[O:3])[CX4H1:4]([CX4,c,CX3,CX2,NX3H0, SX2H0,SiX4H0,OH0,n:5])[CX4H2:7][CX4!H0,c,CX3,CX2,SiX4H0:6], and validate both reaction templates in the *rdkit* package.

In the next step, we define the list of incompatible functional groups. The reaction proceeds between the alkyl bromide electrophile and enolate nucleophile, the latter generated with strong, non-nucleophilic base such as LDA or LiTMP. Accordingly, the list of functional groups interfering with the expected reaction outcome contains:

1) strongly electrophilic groups which may react with the enolate nucleophile, e.g., alkyl iodides ('[CX4H2]I') and bromides ('[CX4H2]Br'), aldehydes ('[#6][CX3H]=O'), acyl halides ('[#6,O,N,S][CX3](=[O,N])[F,Cl,Br,I]'), sulfonyl halides ('[#6,NX3][S](=O)(=O)[Cl,Br,I]'), epoxides ('[CX4](O1)[CX4]1'), disulfides ('[*][SX2][SX2][*]')
2) nucleophilic groups which may react (especially, after deprotonation) with alkyl bromide electrophile, e.g., aliphatic amines ('[CX4][NX3H2]' and '[CX4][NX3H][CX4]'), phenols ('[c][OH]'), thiols ('[CX4,CX3,CX2][SX2H]'), oximes ('[CX3]=[NX2][OH]'), imides ('[#6][CX3](=O)[NX3H][CX3](=O)[#6]'), sulfonamides ('*[S](=O)(=O)[NX3H2]')
3) acidic groups which may interfere with the deprotonation and formation of enolate, e.g., nitroalkanes ([CX4!H0][N+](=O)[O-]), amides ('[#6][CX3](=O)[NX3H2]' and '[#6][CX3](=O)[NX3H][CX4,c]'), active methylene compounds ('[CX3](=O)[CX4!H0][CX3](=O)','[CX2](#N)[CX4!H0][CX3](=O)','[PX4](=O)[CX4!H0][CX3](=O)', '[CX2](#N)[CX4!H0][PX4](=O)') and competing enolizable esters ([CX4!H0]

[CX3](=O)[OH0]), amides ([CX4!H0][CX3](=O)[NX3]) and ketones ([CX4!H0][CX3](=O)[#6])

4) groups unstable under basic conditions, e.g., fragments prone to β-elimination ('[NX4+,PX4+,SeX2,SeX3,SX2,Cl][CX4][CX4!H0][CX3,SX4,PX4]=[O]' and 'O=[CX3,P]O[CX4][CX4!H0][CX3,SX4,PX4]=[O]') or Fmoc protecting group ('[CH]4([CH2]OC(=O)[OX2,NX3,n,SX2])cc-cc4').

In the next step, we classify the reaction conditions (LDA or LiTMP) – here, the general reaction conditions are classified as 'strongly basic' (*SB*) due to presence of LDA or LiTMP bases used for deprotonation (with pKa's ~36), the temperature at which such alkylations are usually performed (-78°C) is classified as very low (*VL*) while the typical solvent (THF) is classified as *nonpolar*, *aprotic*.

Finally, the "Reaction name" ("*Sn2 cH acids alkylation*"), reaction identifier (RxId, "*Rx5*"), reaction byproducts generated from reagents ('CC(C)NC(C)C.[Li+]' from LDA and 'CC1(C)CCCC(C)(C)N1.[Li+]' from LiTMP) and references to illustrative examples of application of such alkylations are added.

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