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PII: S0040-4020(13)00661-3

DOI: 10.1016/j.tet.2013.04.101

Reference: TET 24301

To appear in: *Tetrahedron*

Received Date: 5 March 2013

Revised Date: 18 April 2013

Accepted Date: 24 April 2013

Please cite this article as: Suryavanshi PA, Sridharan V, Menº ndez JC, A new CAN-catalyzed domino process related to the Nenitzescu reaction: Very concise access to fused *ortho*-indolequinones from simple precursors, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.04.101.

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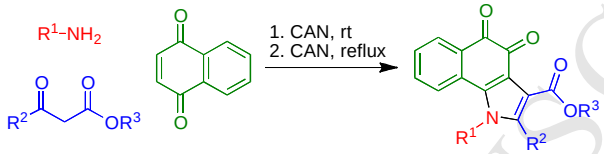

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 Quinones
Keyword_2 Fused indoles
Keyword_3 Multicomponent reactions
Keyword_4 Cerium(IV) ammonium nitrate
Keyword_5 Nenitzescu indole synthesis

ABSTRACT

The CAN-catalyzed three-component reaction between primary amines, β-ketoesters and naphthoquinone in ethanol at room temperature afforded as the main products the corresponding Michael adducts, oxidized to the quinone stage. When these compounds were refluxed in ethanol in the presence of CAN, they afforded tricyclic *ortho*-quinones derived from the benzo[*g*]indole-4,5-dione framework *via* a domino mechanism comprising a sequence of 5-*exo*-*trig* cyclization, elimination, Michael addition, oxo-enol tautomerism and hydroquinone oxidation individual steps.

1. Introduction

Quinones are a very important class of compounds owing to the relevance of the biochemical roles of compounds such as ubiquinone, plastoquinone and phylloquinone (vitamin K_1). Furthermore, quinone moieties are essential structural fragments of a large number of pharmacologically active compounds, specially in the anticancer field.[1] Due to the fact that heterocycles are the most important single class of compounds in the pharmaceutical and agrochemical industries, comprising around 60% of all drug substances in therapeutic use, heterocyclic quinones can be considered as particularly relevant.[2] Most compounds in this cathegory are *para*-quinones, but some *ortho*-quinones are also known.

Indole is a widespread structural motif found in a large number of natural products and its derivatives can be considered as one of the most important single class of heterocyclic systems.[3] They possess a wide range of therapeutically interesting biological activities,[4] and indeed indole derivatives have been included in the "privileged scaffolds" cathegory[5] because they constitute "a molecular framework able to provide ligands for diverse receptors", thus satisfying the definition originally proposed by Evans and widely employed as a guide to drug design.[6] Indole-4,7-quinones related to the natural product mitomycin (Figure 1) are well known as anticancer agents acting by alkylation of the DNA minor groove.[7] The mitosenes, such as WV15 (**1**) and the aziridinylindolequinones, such as EO9 (**2**), constitute typical examples. On the other hand, *ortho*-quinones derived from indole frameworks are not well represented in the

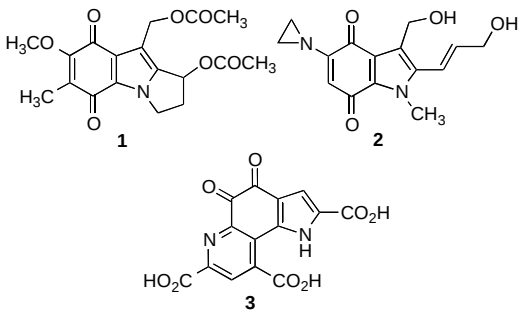

Figure 1 Examples of bioactive indole-4,7-quinones and indole-4,5-quinones

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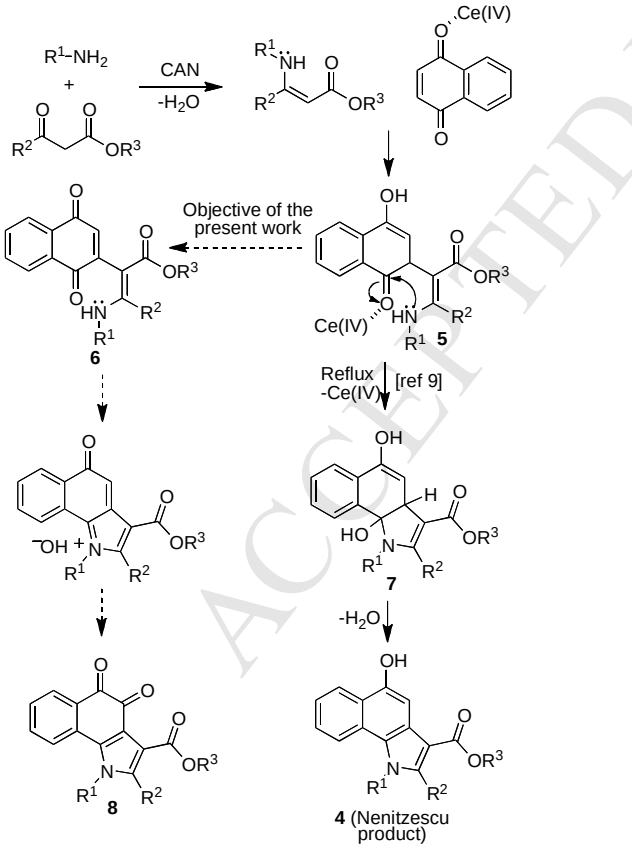
literature. Probably the most important one is pyrroloquinoline-quinone (PQQ, **3**), which plays crucial roles as a cofactor and is involved in a range of biochemical reactions including oxidative deaminations and free-radical redox reactions.[8]

In this context, we became interested in developing a fast route for the synthesis of indole derivatives containing an *ortho*-quinone moiety. We were stimulated to undertake this work by our recent development[9] of a three-component version of the Nenitzescu indole synthesis catalyzed by cerium(IV) ammonium nitrate[10,11] in refluxing ethanol and affording benzo[*g*]indoles **4**. We found that this reaction did not seem to follow the conventional Nenitzescu mechanism, in which the initial Michael addition of the enaminone to the quinone gives **5** (a hydroquinone tautomer). Air oxidation of the latter intermediate gives quinone **6** whose formation, even in trace amounts, may trigger a redox cycle involving cyclization of **6** to an iminium derivative, which is then reduced by **5** to give another molecule of **6** and the observed product **4**.[12] However, treatment of one of the quinones **6** (isolated in minor amounts from one of the reactions, see below) with one equivalent of externally added hydroquinone under our standard reaction conditions (5 mol% of CAN in refluxing ethanol) did not afford the corresponding compound **4**. For this reason, we proposed a non-redox alternative mechanism in which the presence of the Lewis acid catalyst promoted the cyclization of **5** to **7**, which was finally dehydrated to the final products **4**,[13] with traces of **6** being sometimes isolated from a side reaction involving the air oxidation of the hydroquinone tautomer of **5** (Scheme 1, first column).

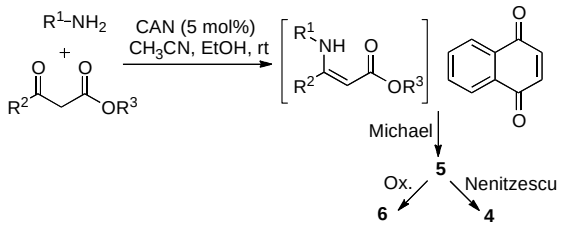


Scheme 1 A summary of our previous work on the CAN-catalyzed reaction between primary amines, β-ketoesters and naphthoquinone[Error! Bookmark not defined.] and our plan for the synthesis of benzo[*g*]indole-4,5-diones

Against this background, we became intrigued by the possibility of using this chemistry for the preparation of *ortho*-quinone derivatives. More specifically, we wished to ascertain whether compounds **6** might be suitable precursors to iminium derivatives **9**, the putative intermediates of the conventional redox mechanism. We reasoned that, in the absence of reductive species, these intermediates should behave as excellent Michael acceptors able to trap hydroxide, acting as a nucleophile, thereby afording compounds dioxygenated at the 4 and 5 positions of the indole ring, which should be easy to transform into the target *ortho*-quinones **8** (Scheme 2). It is relevant to mention at this point that this transformation was rendered particularly significant by the observation that we were unable to obtain compounds **8** from **4** by oxidation with Fremy's salt under a variety of conditions.[14] We were also encouraged to attempt this transformation by the fact that the benzo[*g*]indole-4,5-dione framework present in **8** is almost unknown in the literature, and its preparation normally requires multistep sequences.[15,16] There is a report of the synthesis of three benzo[*g*]indole-4,5-diones in a two-step sequence from 2,3-dichloronaphthoquinone and N-substituted β-aminocrotonic esters, but it has very clear disadvantages, including the need to prepare the starting enaminones in a separate step, its very narrow scope, its poor atom economy owing to the release of two molecules of HCl and the very harsh reaction conditions required for the cyclization step, which led to "strong resinification of the reaction medium".[17]

2. Results and discussion

As a first step towards our goal, we needed to establish reliable conditions for the preparation of compounds **6**, bearing in mind the competition with the formation of the Nenitzescu-like product **4**. After extensive manipulation of the reaction conditions, we established that the best option to shift the processes summarized in Scheme 1 towards the formation of **6**



Scheme 2 Synthesis of quinones **6**

Table 1 Results obtained in the preparation of compounds **6**

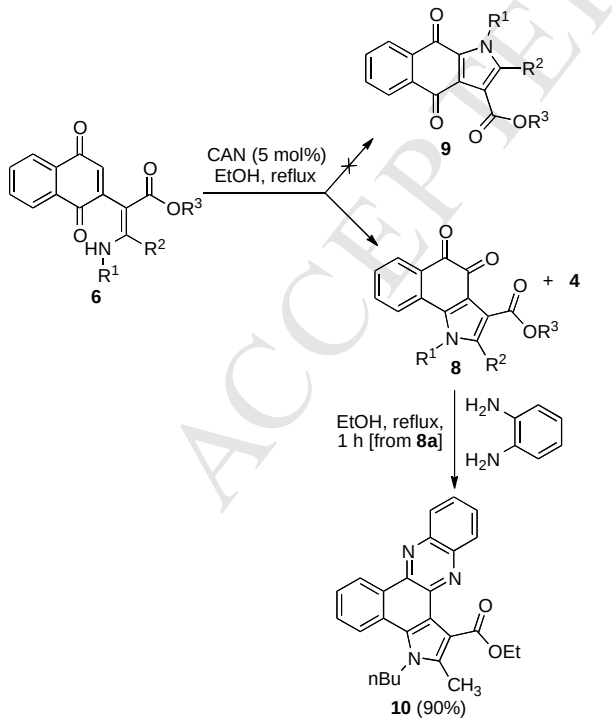
Entry	Cmpd.	R^1	R^2	R^3	Time, h	**6**/**4** ratio[a]	Yield of **6**, %[b]
1	**6a**	*n*-Bu	Me	Et	1.5	85:15	65
2	**6b**	*n*-Bu	Me	^{t}Bu	1	80:20	68
3	**6c**	Allyl	Me	Et	1	75:25	62
4	**6d**	*n*-Bu	Me	Me	1.5	75:25	60
5	**6e**	*n*-Bu	Me	Allyl	1.5	78:22	65
6	**6f**	*n*-Pr	Me	Et	1	70:30	58
7	**6g**	Bn	Me	Et	1.5	65:35	62
8	**6h**	*n*-Bu	*n*-Pr	Et	1	65:35	60

[a]Determined on the crude ^{1}H-NMR spectra. [b]Isolated yields after chromatography.

involved the reaction in ethanol between primary amines, β-ketoesters and naphthoquinone in the presence of 5% CAN, at room temperature in a flask open to the air and using as solvent a 5:1 mixture of acetonitrile and ethanol. Under these conditions, the **6**/**4** ratios ranged betwen 85:15 and 65:35 (Scheme 2 and Table 1). The intermediacy of an enaminone was verified by carrying out the reaction from an isolated example, prepared by a literature method.[18]

With compounds **6** in hand, we could study the final step of our route. After some experimentation, we discovered that a simple reflux in ethanol containing CAN allowed their one-pot transformation into the target *ortho*-quinones **8**, again with small amounts of compounds **4** as side products (Scheme 3 and Table 2). The spectral data, specially the very close chemical shifts for the carbonyl ^{13}C-NMR signals,[14,19] fitted the expected structure for the final products, but in view of the possibility of a cyclization pathway leading to a linear *para*-quinone system **9** *via* an aza-Michael addition of the enamine nitrogen onto the quinone moiety in **6**, we considered it desirable to have independent chemical evidence for the presence of an *ortho*-quinone unit in **8**. To achieve this goal, we treated **8a** with *o*-phenylenediamine in refluxing ethanol, and this reaction afforded the fused quinazoline derivative **10** in 90% yield, a result that confirmed the *ortho*-quinone structure.

Regarding the mechanism of this transformation, we propose the sequence of reactions summarized in Scheme 4, where compound **6** undergoes a 5-*exo*-*trig* cyclization followed by extrusion of hydroxyde anion to give iminium salt **11**. Conjugate addition of the hydroxide anion to the position 4 of compound **11**, conjugated with the iminium group, followed by tautomerization would afford intermediate catechol **12**, whose oxidation by air would afford the final product **8**. On the other hand, according to the conventional Nenitzescu mechanism, the oxidation of **12** could be coupled to the reduction of **11**, explaining the isolation of small amounts of **4** from the reaction. On the basis of this rationalization, an effort was made to



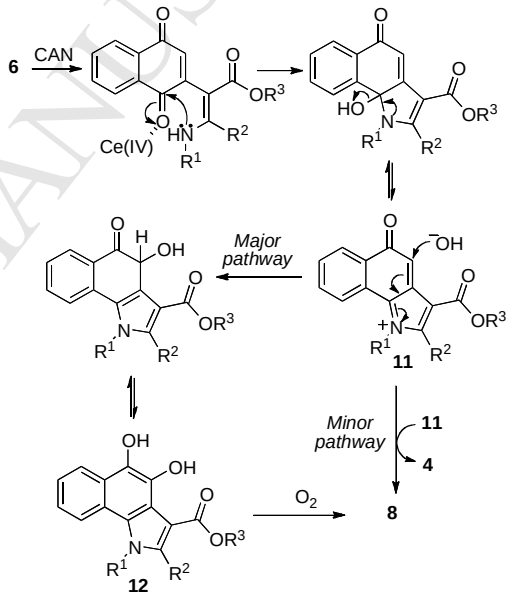
Scheme 3 Preparation of compounds **8** and confirmation of their angular *ortho*-quinone structure

Table 2 Results obtained in the synthesis of compounds **8**

Entry	Cmpd.	R^1	R^2	R^3	Time, h	**8**/**4** ratio[a]	Yield of **8**, %[b]
1	**8a**	*n*-Bu	Me	Et	2	75:25	61
2	**8b**	*n*-Bu	Me	^{t}Bu	1	75:25	55
3	**8c**	Allyl	Me	Et	2	85:15	56
4	**8d**	*n*-Bu	Me	Me	0.5	65:35	58
5	**8e**	*n*-Bu	Me	Allyl	1	73:27	55
6	**8f**	*n*-Pr	Me	Et	2	75:25	59
7	**8g**	Bn	Me	Et	2	80:20	57
8	**8h**	*n*-Bu	*n*-Pr	Et	1	85:15	60

[a]Determined on the crude ^{1}H-NMR spectra. [b]Isolated yields after chromatography.

increase the **8**/**4** ratio by carrying out the reaction in an oxygen atmosphere and in the presence of hydroxide anion in order to facilitate the oxidation of intermediates **12** without the intervention of **11** and was also employed for the same purpose, but only complex mixtures were obtained.



Scheme 4 Mechanistic rationalization of the reaction leading to compounds **8**

Finally, in view of the similarity in the reaction conditions for both steps of our route, we examined the possibility of carrying out the whole sequence in one pot, avoiding the isolation of intermediates **6**. Thus, treatment of an ethanol solution of butylamine with ethyl acetoacetate followed by naphthoquinone in the presence of 5% CAN for 1.5 h was followed by reflux in the same solvent, leading to a yield of **8a** virtually identical to the one obtained in the two-step method. Unfortunately, the one-pot protocol seems to lack generality and failed for other cases (**8c** and **8g**), giving complex mixtures.

3. Conclusions

In conclusion, we have developed a two-step method for the synthesis of pharmacologically relevant *ortho*-quinones derived from the benzo[*g*]indole-4,5-dione system, which combines two multibond-forming processes. The first step of the route consists of a three-component room temperature reaction between

primary amines, β-ketoesters and naphthoquinone comprising β-enaminone formation and dehydrogenative coupling (*i.e.*, Michael addition followed by hydroquinone oxidation) individual steps. In the second step, which is achieved by simply heating the product of the first reaction in ethanol containing CAN, 5-*exo-trig* cyclization, elimination, Michael addition, oxo-enol tautomerism and hydroquinone oxidation steps are achieved in a single operation. Taken in the aggregate, the two-step sequence involves up to nine individual reactions and achieves the generation of two C-N and one C-C bonds from very simple starting materials and catalysts with a very high atom economy, since the only by-product is a molecule of water.

4. Experimental section

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40-63 μm) or neutral alumina (Merck S22). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

4.1. Synthesis of quinones 6: General procedure

A solution of the suitable β-ketoester (1 mmol), the suitable primary amine (1 mmol) and CAN (5 mol %) in acetonitrile (0.5 mL) was stirred at room temperature for 30 min. A solution of 1,4-naphthoquinone (158 mg, 1 mmol) in EtOH (110 μL) was added, and stirring at room temperature was continued for 30 min. Thereafter, the reaction was diluted with water (3 mL) and extracted with dichloromethane (4 x 5 mL). The combined organic phases were evaporated to dryness, and then the crude product was purified by flash column chromatography eluting with petroleum ether-ethyl acetate. Characterization data for the major products **6** are given below; the side products **4** were known compounds.[9]

*4.1.1. (E)-Ethyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)but-2-enoate (**6a**).*

Dark red viscous liquid; IR (neat): 2960, 2931, 1706, 1652, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.40-1.54 (m, 2H), 1.60-1.71 (m, 2H), 1.97 (s, 3H), 3.30 (q, *J* = 6.8 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 6.76 (s, 1H), 7.71-7.78 (m, 2H), 8.07-8.15 (m, 2H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.2, 14.7, 17.5, 20.5, 32.3, 43.7, 59.6, 89.7, 126.2, 127.2, 132.8, 133.3, 133.7, 133.8, 137.5, 149.4, 162.0, 169.2, 185.9, 186.0. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; Found: C, 70.04; H, 6.79; N, 4.00.

*4.1.2. (E)-tert-Butyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (**6b**).*

Dark red viscous liquid; IR (neat): 2973, 2932, 1691, 1665, 1596, 1547, 1529, 1501, 1460, 1390, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 9H), 1.48-1.52 (m, 2H), 1.60-1.69 (m, 2H), 1.99 (s, 3H), 3.29 (q, *J* = 6.8 Hz, 2H), 6.68 (s, 1H), 7.72-7.76 (m, 2H), 8.08-8.14 (m, 2H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.2, 17.4, 20.5, 28.6, 32.5, 43.8, 79.8, 91.6, 126.1, 127.0, 132.7, 133.5, 133.6, 133.7, 136.2, 150.3, 161.4, 169.0, 186.0. 186.3. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79; Found: C, 71.27; H, 7.09; N, 3.53.

*4.1.3. (E)-Ethyl 3-(allylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (**6c**).*

Dark red viscous liquid; IR (neat): 2981, 1649, 1593, 1300, 1252, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): 1.12 (t, *J* = 7.1 Hz, 3H), 1.96 (s, 3H), 3.93-3.98 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 5.23-5.36 m, 2H), 5.86-5.99 (m, 1H), 6.77 (s, 1H), 7.74-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): 14.6, 17.2, 46.1, 59.7, 90.5, 117.1, 126.2, 127.2, 132.8, 133.2, 133.7, 133.9, 134.2, 137.8, 149.2, 161.9, 169.1, 185.7, 186.0. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; Found: C, 69.85; H, 6.04; N, 3.88.

*4.1.4. (E)-Methyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (**6d**).*

Dark red viscous liquid; IR (neat): 2954, 1650, 1592, 1439, 1323, 1299, 1259, 1220, 1143, 1069, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.40-1.55 (m, 2H), 1.61-1.72 (m, 2H), 1.96 (s, 3H), 3.32 (q, *J* = 6.8 Hz, 2H), 3.58 (s, 3H), 6.78 (s, 1H), 7.72-7.79 (m, 2H), 8.10-8.15 (m, 2H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.2, 17.5, 20.5, 32.3, 43.7, 51.1, 89.1, 126.2, 127.3, 132.8, 133.1, 133.8, 133.9, 138.0, 149.0, 162.2, 169.6, 185.7, 186.0. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; Found: C, 69.58; H, 6.41; N, 4.19.

*4.1.5. (E)-Allyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (**6e**).*

Dark red viscous liquid; IR (neat): 2926, 2339, 1650, 1592, 1455, 1324, 1298, 1252, 1142, 1055, 1015, 992 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.40-1.54 (m, 2H), 1.60-1.71 (m, 2H), 1.97 (s, 3H), 3.32 (q, *J* = 6.8 Hz, 2H), 4.51-4.54 (m, 2H), 5.06-5.18 (m, 2H), 5.74-5.89 (m, 1H), 6.79 (s, 1H), 7.73-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.2, 17.6, 20.5, 32.3, 43.8, 64.2, 89.2, 117.0, 126.2, 127.3, 132.7, 133.2, 133.3, 133.8, 133.9, 137.9, 149.1, 162.4, 168.7, 185.8, 186.0. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96; Found: C, 71.06; H, 6.31; N, 3.87.

*4.1.6. (E)-Ethyl 2-(1,4-dioxo-1,4-dihydronaphth-2-yl)-3-propylaminobut-2-enoate (**6f**).*

Dark red viscous liquid; IR (neat): 2966, 2362, 1646, 1593, 1458, 1323, 1298, 1259, 1221, 1142, 1064, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.02-1.15 (m, 6H), 1.63-1.75 (m, 2H), 1.98 (s, 3H), 3.30 (q, *J* = 6.9 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 6.76 (s, 1H), 7.73-7.77 (m, 2H), 8.09-8.14 (m, 2H), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.9, 14.7, 17.5, 23.6, 45.7, 59.6, 89.7, 126.2, 127.2, 132.8, 133.3, 133.7, 133.8, 137.5, 149.4, 162.0, 169.2, 185.9, 186.0. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; Found: C, 69.92; H, 6.29; N, 4.07.

*4.1.7. (E)-Ethyl 3-(benzylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (**6g**).*

Dark red viscous liquid; IR (neat): 3272, 1645, 1594, 1448, 1414, 1299, 1258, 1220, 1098, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.12 (t, *J* = 7.1 Hz, 3H), 1.98 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 5.8 Hz, 2H), 6.78 (s, 1H), 7.29-7.44 (m, 5H), 7.74-7.78 (m, 2H), 8.10-8.15 (m, 2H), 10.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.6, 17.6, 47.8, 59.8, 90.9, 126.3, 127.2, 127.3, 128.0, 129.3, 132.7, 133.2, 133.8, 133.9, 137.8, 138.1, 149.1, 161.8, 169.1, 185.7, 186.0. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73; Found: C, 73.26; H, 5.36; N, 3.42.

*4.1.8. (E)-Ethyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)hex-2-enoate (**6h**).*

Dark red viscous liquid; IR (neat): 2961, 2932, 2873, 1667, 1649, 1595, 1665, 1363, 1324, 1253, 1142, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 0.86-1.01 (m, 6H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.40-1.55 (m, 4H), 1.60-1.72 (m, 2H), 2.19-2.25 (m, 2H), 3.30 (q, *J* = 6.8 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 6.80 (s, 1H), 7.73-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.2, 14.6, 14.7, 20.5, 22.2, 32.2, 32.6, 43.3, 59.6, 89.2, 126.2, 127.2, 132.7, 133.2, 133.7, 133.9, 137.3, 149.5, 165.4, 169.4, 186.0, 186.1. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79; Found: C, 71.44; H, 7.24; N, 3.59.

4.2. Synthesis of compounds 8: General procedure

To a suspension of the suitable quinone **6** (0.5 mmole) in EtOH (1.5 mL) and CAN (5 mol %) was refluxed for the time indicated in table 2. After the disappearance of starting material, as indicated by tlc, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were evaporated under reduced pressure and crude residue thus obtained was purified by silica gel column chromatography, eluting with 20% petroleum ether/ethyl acetate. Characterization data for compounds **8** are given below.

*4.2.1. Ethyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8a**).*

Purple solid ; mp 112 ºC; IR (neat) 2961, 2931, 2873, 1693, 1666, 1650.3, 1594, 1548, 1503, 1469, 1302, 1223, 1127, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.04 (t, *J* = 7.1 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.47-1.61 (m, 2H), 1.81-1.61 (m, 2H), 2.47 (s, 3H), 4.19 (t, *J* = 8.0 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.32-7.39 (m, 1H), 7.54-7.60 (m, 2H), 8.10 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.3, 14.0, 14.5, 20.3, 32.2, 46.5, 61.4, 115.2, 120.5, 122.7, 128.6, 130.3, 130.7, 131.8, 135.5, 136.6, 139.6, 165.4, 174.4, 182.6. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; Found: C, 70.93; H, 6.28 ; N, 4.18.

*4.2.2. tert-Butyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8b**).*

Red solid; mp 145 ºC; IR (neat) 2996, 1691, 1660, 1593, 1502, 1462, 1366, 1321, 1278, 1153, 1132, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.47-1.59 (m, 2H), 1.64 (s, 9H), 1.80-1.93 (m, 2H), 2.45 (s, 3H), 4.17 (t, *J* = 8.1 Hz, 2H), 7.32-7.38 (m, 1H), 7.53-7.63 (m, 2H), 8.11 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.1, 14.0, 20.3, 28.4, 31.3, 32.2, 46.4, 82.2, 117.0, 122.6, 128.5, 130.3, 130.8, 131.8, 135.5, 136.2, 138.8, 164.8, 174.0, 182.5; Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81; Found: C, 71.69; H, 6.68; N, 3.98.

*4.2.3. Ethyl 1-allyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8c**).*

Red solid; mp 114-115 ºC; IR (neat) 2918, 2850, 1709, 1666, 1594, 1548, 1492.9, 1462, 1407, 1302, 1273, 1228, 1139, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.43 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.87 (br s, 2H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.46 (d, *J* = 10.4 Hz, 1H), 6.10-6.23 (m, 1H), 7.28-7.41 (m, 1H), 7.54-7.56 (m, 2H), 8.11 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 10.8, 14.5, 48.7, 61.5, 115.2, 118.8, 120.2, 123.3, 128.8, 130.2, 130.3, 131.0, 131.6, 135.4, 137.9, 140.4, 165.2, 174.6, 182.8; Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33; Found: C, 70.36; H, 5.48; N, 4.11.

*4.2.4. Methyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8d**).*

Red solid; mp 125-126 ºC; IR (neat): 2958, 2873, 1710, 1666, 1650, 1594, 1548, 1536, 1502, 1468, 1442, 1402, 1312, 1223, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.50-1.59 (m, 2H), 1.83-1.95 (m, 2H), 2.49 (s, 3H), 3.92 (s, 3H), 4.21 (t, *J* = 7.7 Hz, 2H), 7.34-7.38 (m, 1H), 7.40-7.62 (m, 2H), 8.12 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.3, 14.0. 20.3, 32.2, 46.5, 52.4, 114.7, 120.6, 122.7, 128.7, 130.4, 130.7, 131.8, 135.5, 136.7, 139.9, 165.7, 174.7, 182.7. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; Found: C, 69.96; H, 5.90; N, 4.44.

*4.2.5. Allyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8e**).*

Red solid; mp 145-146 ºC; IR (neat): 2959, 1701, 1666, 1593, 1499, 1466, 1267, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.07 (t, *J* = 7.3 Hz, 3H), 1.50-1.63 (m, 2H), 1.82-1.94 (m, 2H), 2.48 (s, 3H), 4.20 (t, *J* = 7.8 Hz, 2H), 4.83-4.86 (m, 2H), 5.29 (dd, *J* = 1.4, 10.3 Hz, 1H), 5.44 (dd, *J* = 1.4, 17.2, 1H), 6.03-6.19 (m, 1H), 7.30-7.40 (m, 1H), 7.55-7.61 (m, 2H), 8.12 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.3, 14.0, 20.3, 32.2, 46.5, 66.2, 114.7, 119.0, 120.5, 122.7, 128.6, 130.3, 130.6, 131.7, 132.6, 135.5, 136.7, 140.1, 165.0, 174.4, 182.5. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99; Found: C, 71.63; H, 6.26; N, 4.19.

*4.2.6. Ethyl 2-methyl-4,5-dioxo-1-propyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8f**).*

Purple solid; mp. 79-80 ºC; IR (neat) 3014, 2925, 2853, 1697, 1666, 1595, 1536, 1501, 1465, 1366, 1271, 1128, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.13 (t, *J* = 7.4 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.89-1.99 (m, 2H), 2.49 (s, 3H), 4.17 (dd, *J* = 6.3, 8.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.34-7.40 (m, 1H), 7.53-7.61 (m, 2H), 8.13 (dd, *J* = 1.4, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.3, 11.4, 14.5, 23.6, 48.0, 61.4, 115.2, 120.5, 122.6, 128.6, 130.3, 130.7, 131.8, 135.5, 136.6, 139.6, 165.3, 174.4, 182.6. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; Found: C, 70.30; H, 5.52; N, 4.08.

*4.2.7. Ethyl 1-benzyl-2-methyl-4,5-dioxo-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8g**).*

Red solid; mp. 200-201 ºC; IR (neat): 2981, 2928, 1710, 1666, 1594, 1494, 1462, 1302, 1203, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.45 (t, *J* = 7.1 Hz, 3H), 2.41 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 5.51 (s, 2H), 7.17 (d, *J* = 6.6 Hz, 2H), 7.27-7.45 (m, 6H), 8.08-8.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.1, 14.5, 50.1, 61.5, 115.3, 120.4, 123.2, 125.7, 128.7, 128.8, 130.0, 130.1, 130.2, 131.6, 134.7, 135.5, 138.0, 140.6, 165.1, 174.4, 182.5. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75; Found: C, 73.78; H, 5.35; N, 3.41.

*4.2.8. Ethyl 1-butyl-4,5-dioxo-2-propyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8h**).*

Red solid; mp. 114-115 ºC; IR (Neat): 2962, 2933, 2873, 1711, 1667, 1594, 1502, 1466, 1308, 1218, 1126, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.02-1.10 (m, 6H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.50-1.59 (m, 2H), 1.62-1.71 (m, 2H), 1.81-1.94 (m, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 4.20 (t, *J* = 8.0 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.33-7.40 (m, 1H), 7.59-7.61 (m, 2H), 8.13 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.0, 14.3, 14.5, 20.3, 23.7, 27.0, 32.8, 46.2, 61.4, 115.2, 120.8, 122.7, 128.6, 130.4, 130.9, 131.8, 135.5, 136.4, 143.6, 165.3, 174.5, 182.6. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81; Found: C, 71.69; H, 6.72; N, 3.90.

4.3. Ethyl 3-butyl-2-methyl-3*H*-benzo[*a*]pyrrolo[2,3-*c*]phenazine-1-carboxylate (10).

To a solution of compound **8a** (339 mg, 1 mmol) in ethanol (5 mL) was added *o*-phenylenediamine (108 mg, 1 mmol). The resulting solution was refluxed for 1 h, cooled and a mixture of water (10 mL) and ethyl acetate (15 mL) was added. The aqueous phase was extracted with additional ethyl acetate (3 x 15 mL). The combined extracts were dried over Na_2SO_4 and evaporated to yield 370 mg (90%) of compound **10**, as a yellow solid; mp 167 ºC; IR (neat): 2957, 2921, 2855, 1712, 1577, 1544, 1508, 1463, 1412, 1343, 1277, 1232, 1172, 1121, 1071, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.09 (t, *J* = 7.2 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.56-1.65 (m, 2H), 1.95-2.07 (m, 2H), 2.65 (s, 3H), 4.53 (t, *J* = 7.5 Hz, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 7.66-7.83 (m, 4H), 8.17-8.24 (m, 2H), 8.31-8.35 (m, 1H), 9.60 (dd, *J* = 1.4, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 11.8, 14.2, 14.5, 14.9, 20.5, 23.1, 29.7, 30.0, 30.1, 32.3, 32.6, 46.6, 61.5, 121.0, 125.7, 126.6, 127.8, 128.7, 129.9, 130.1, 130.2, 140.9, 168.5. Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21; Found: C, 75.63; H, 6.03; N, 10.05.

Acknowledgments

Financial support from MICINN and MINECO (grant CTQ2012-33272-BQU) is gratefully acknowledged. We also thank Agencia Española de Cooperación Internacional y Desarrollo (AECID) for a predoctoral fellowship to Padmakar Suryavanshi.

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Supporting Information

A CAN-catalyzed domino process allowing two-step access to fused ortho-indolequinones from simple precursors

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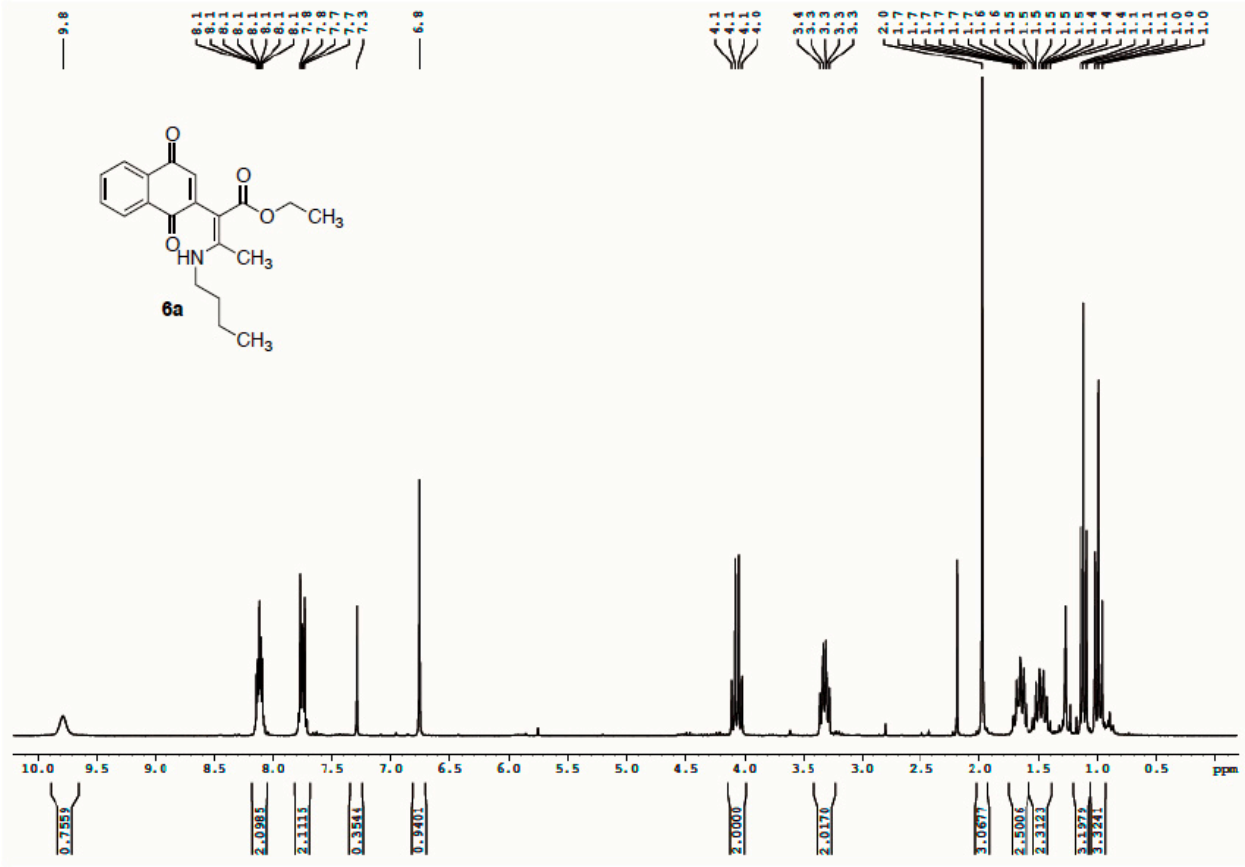
Contents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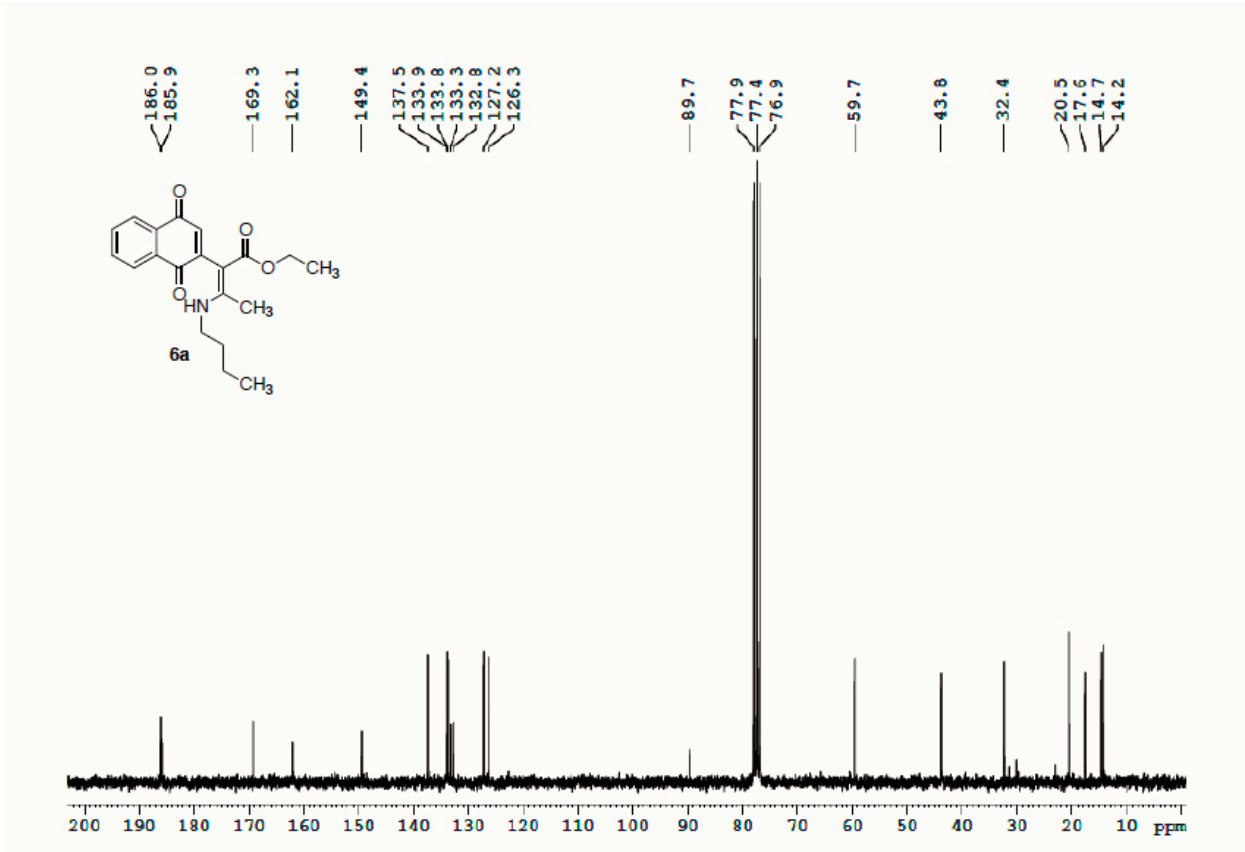
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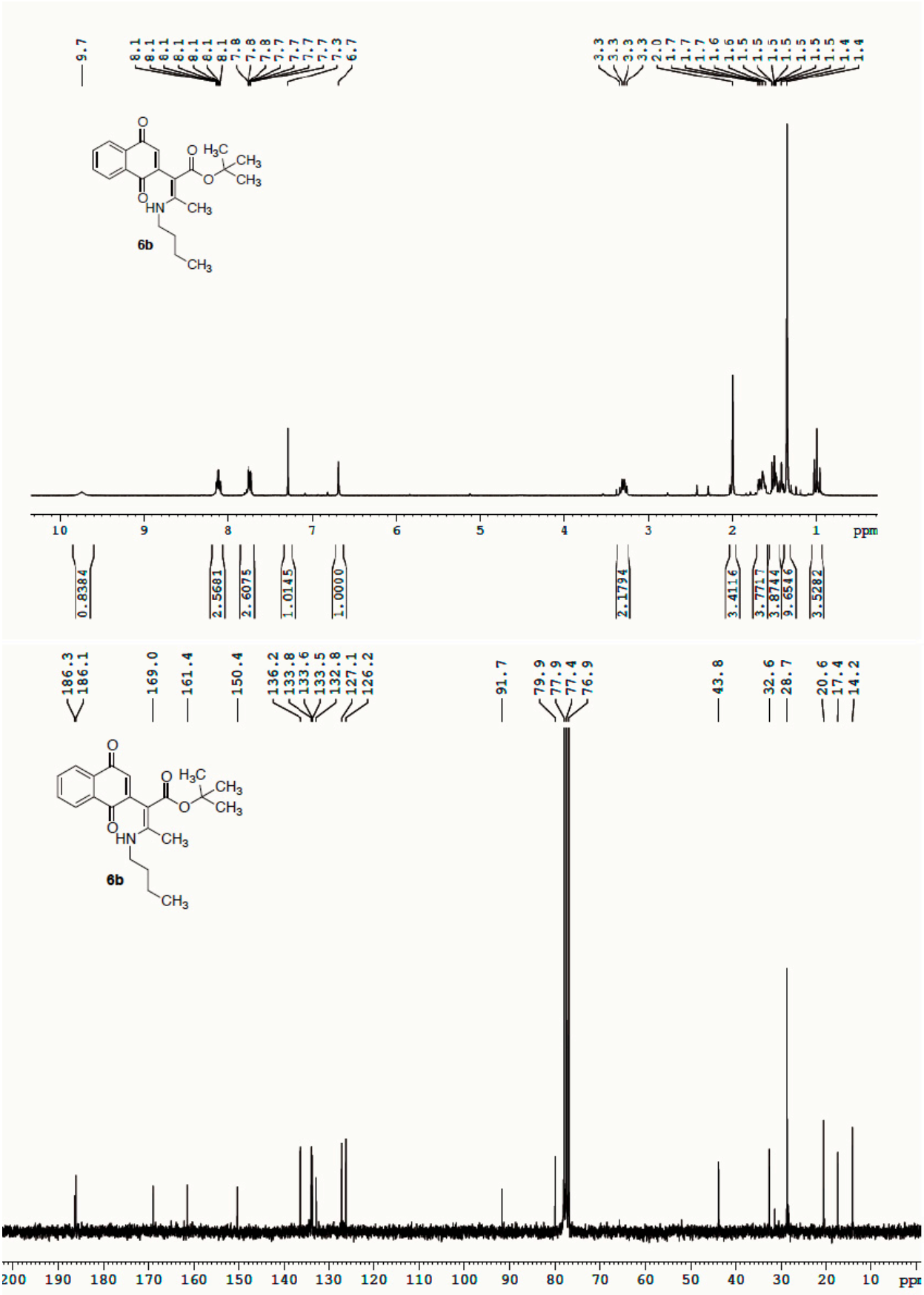
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169.0
161.4
150.4
136.2
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133.6
133.5
132.8
127.1
126.2
91.7
79.9
77.9
77.4
76.9
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32.6
28.7
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17.4
14.2
6b
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160
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70
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30
20
10
ppm


9.9
8.1
8.1
8.1
8.1
8.1
8.1
7.8
7.8
7.8
7.7
7.3
6.8
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6.0
6.0
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5.9
5.9
5.9
5.9
5.9
5.4
5.4
5.3
5.3
5.3
5.3
5.2
5.2
4.1
4.1
4.1
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4.0
4.0
4.0
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3.9
2.0
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1.1
1.1
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O
O
CH3
HN
CH3
6c
CH2
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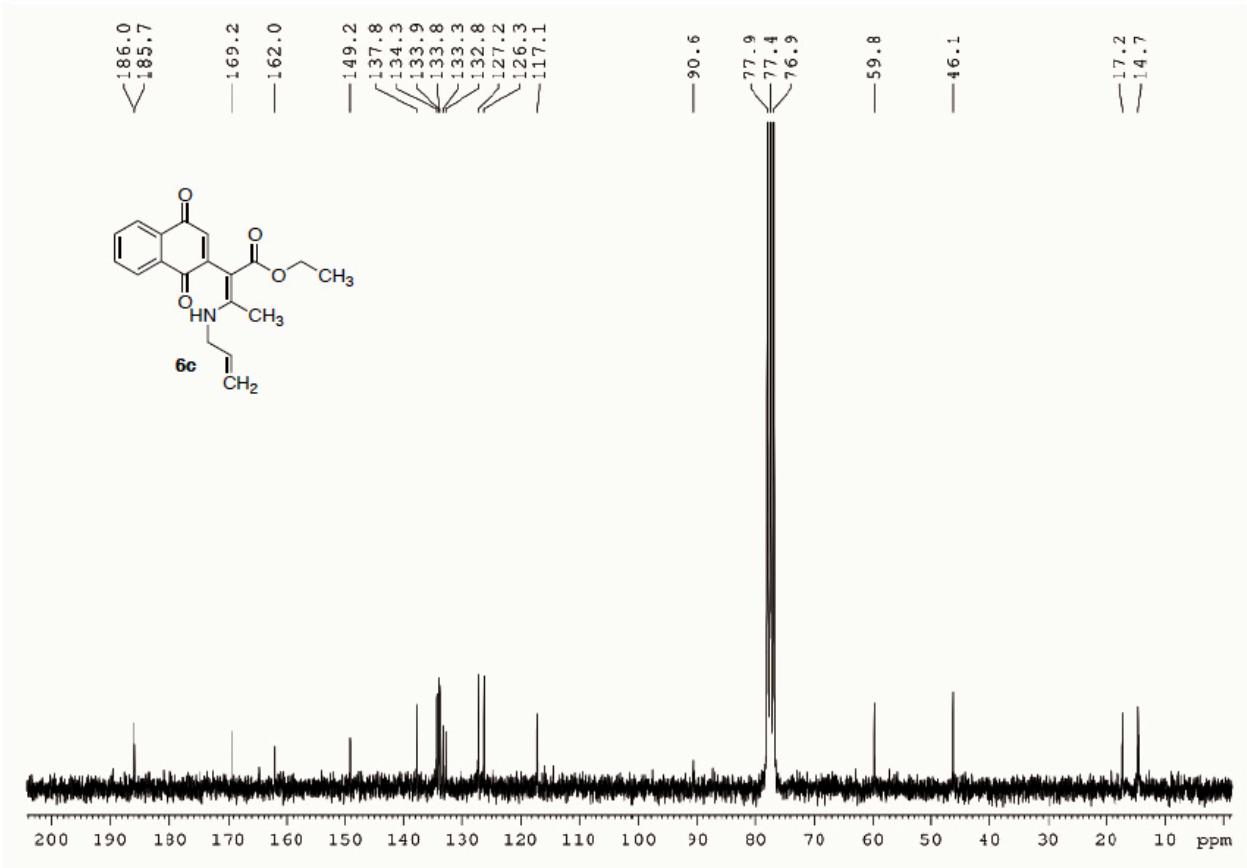
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6c
CH2
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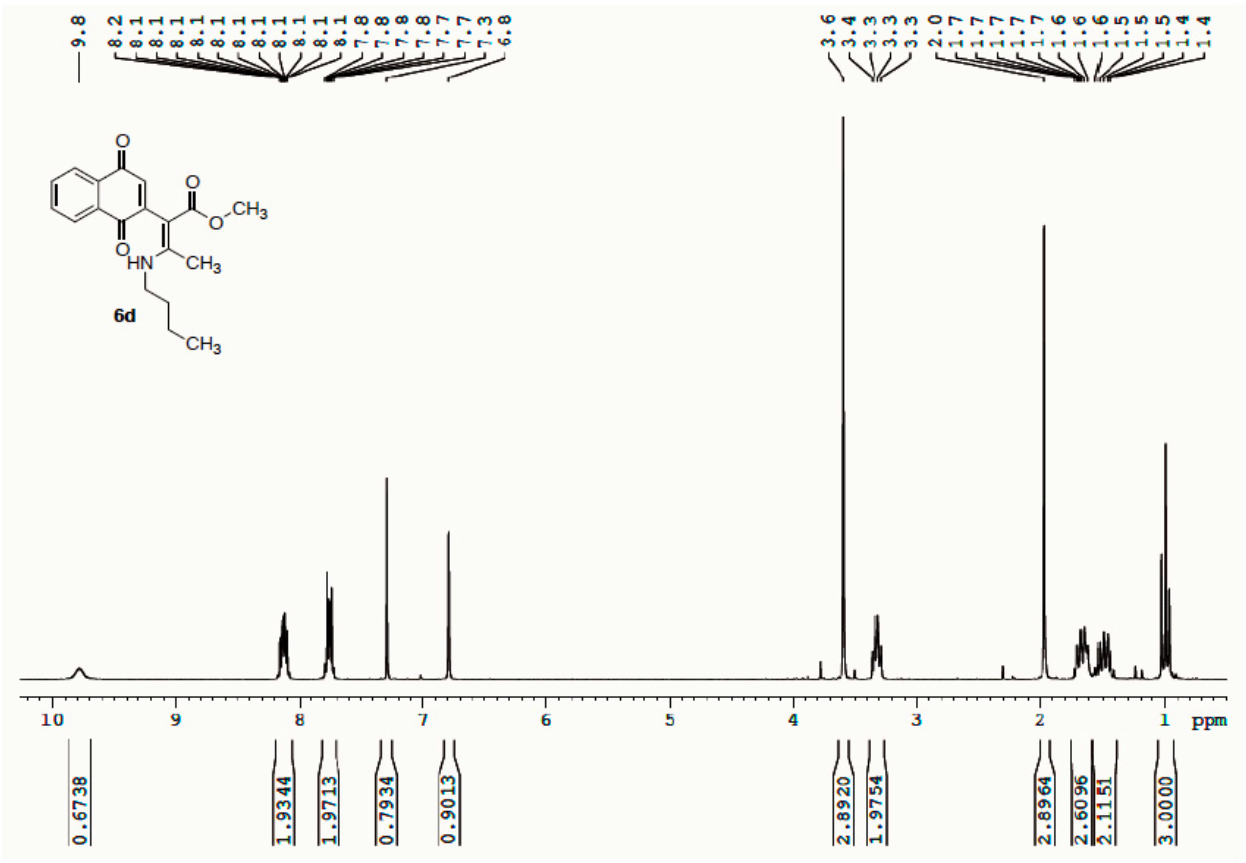
10
ppm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3.4
3.3
3.3
3.3
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1.6
1.6
1.5
1.5
1.5
1.4
1.4
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CH3
10
9
8
7
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5
4
3
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1
ppm
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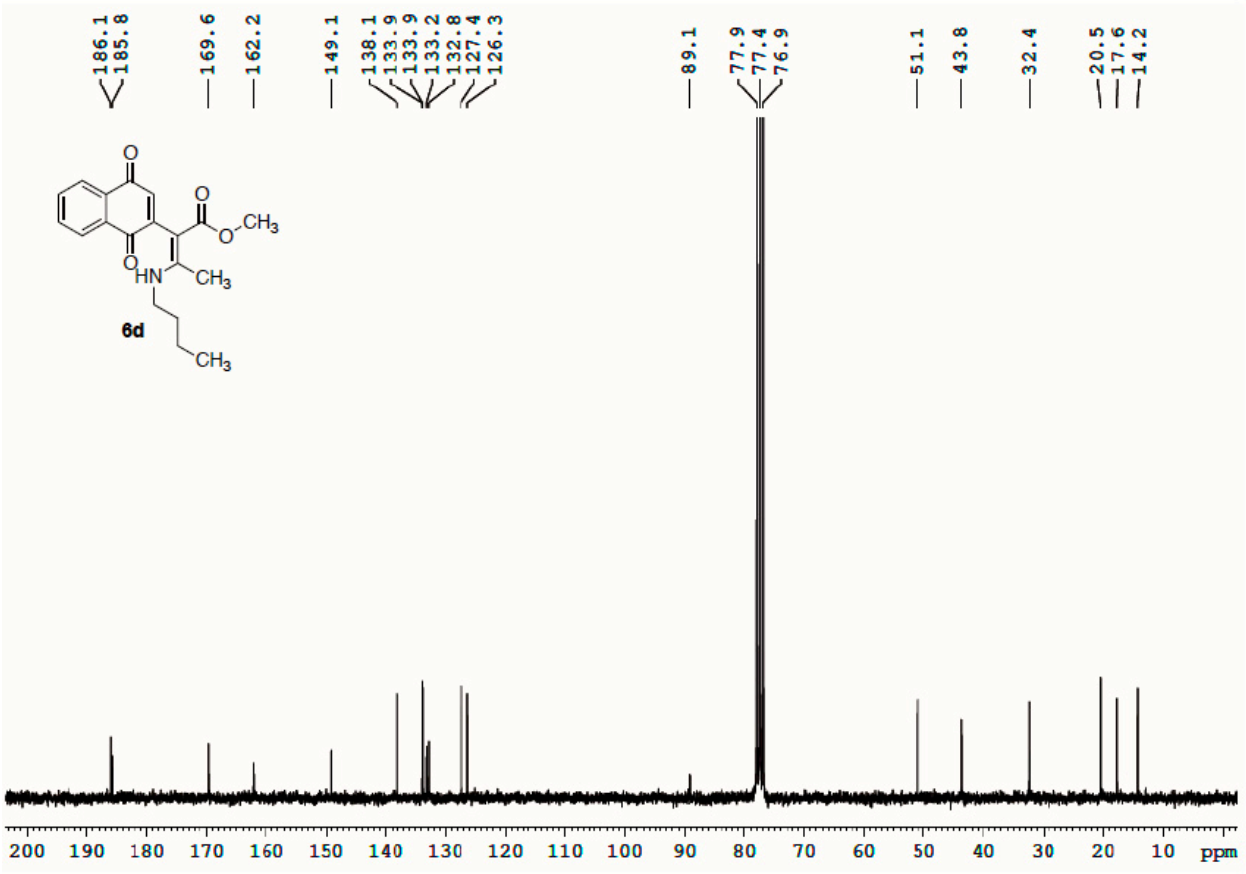
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76.9
51.1
43.8
32.4
20.5
17.6
14.2
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O
O
O
CH3
HN
CH3
6d
CH3
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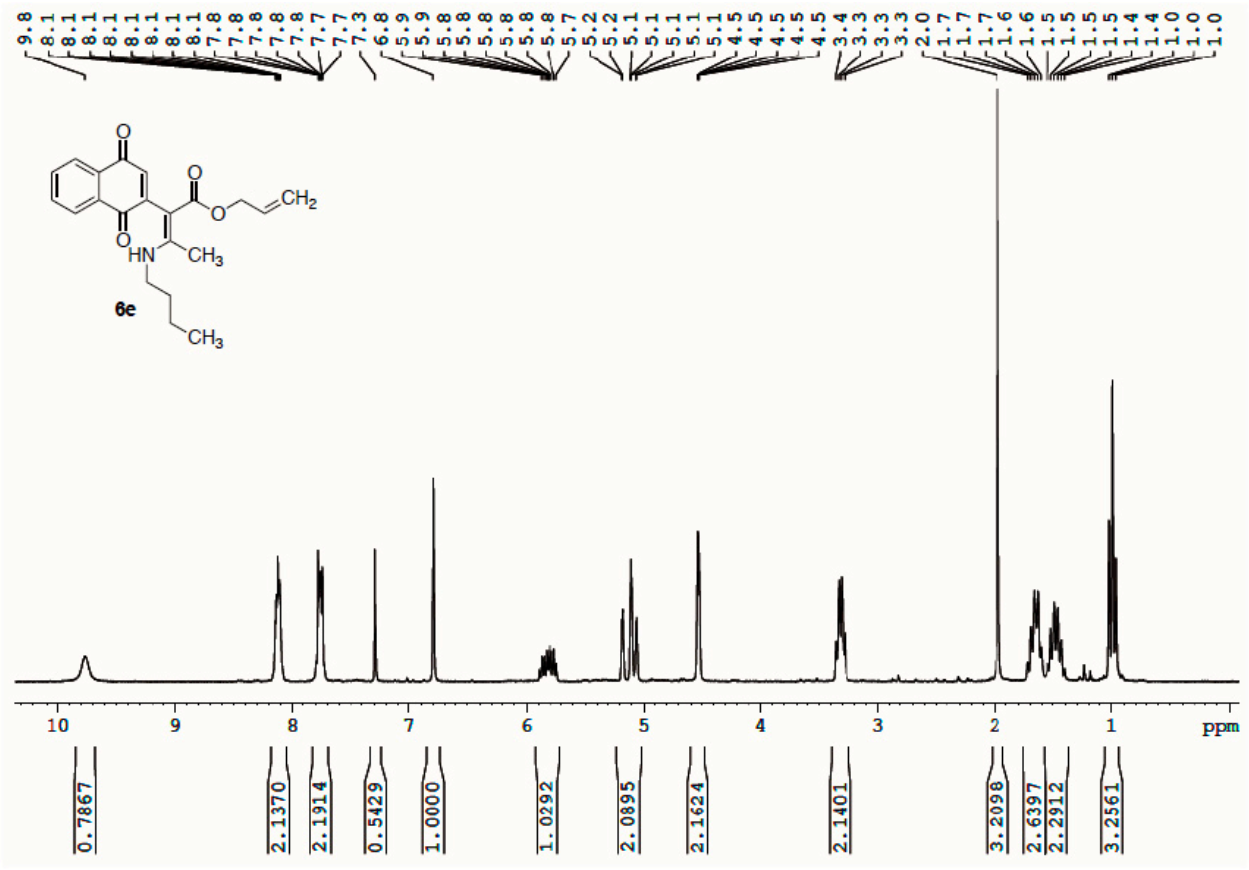
30
20
10
ppm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O
O
O
O
HN
CH3
CH2
CH3
6e
10 9 8 7 6 5 4 3 2 1 ppm
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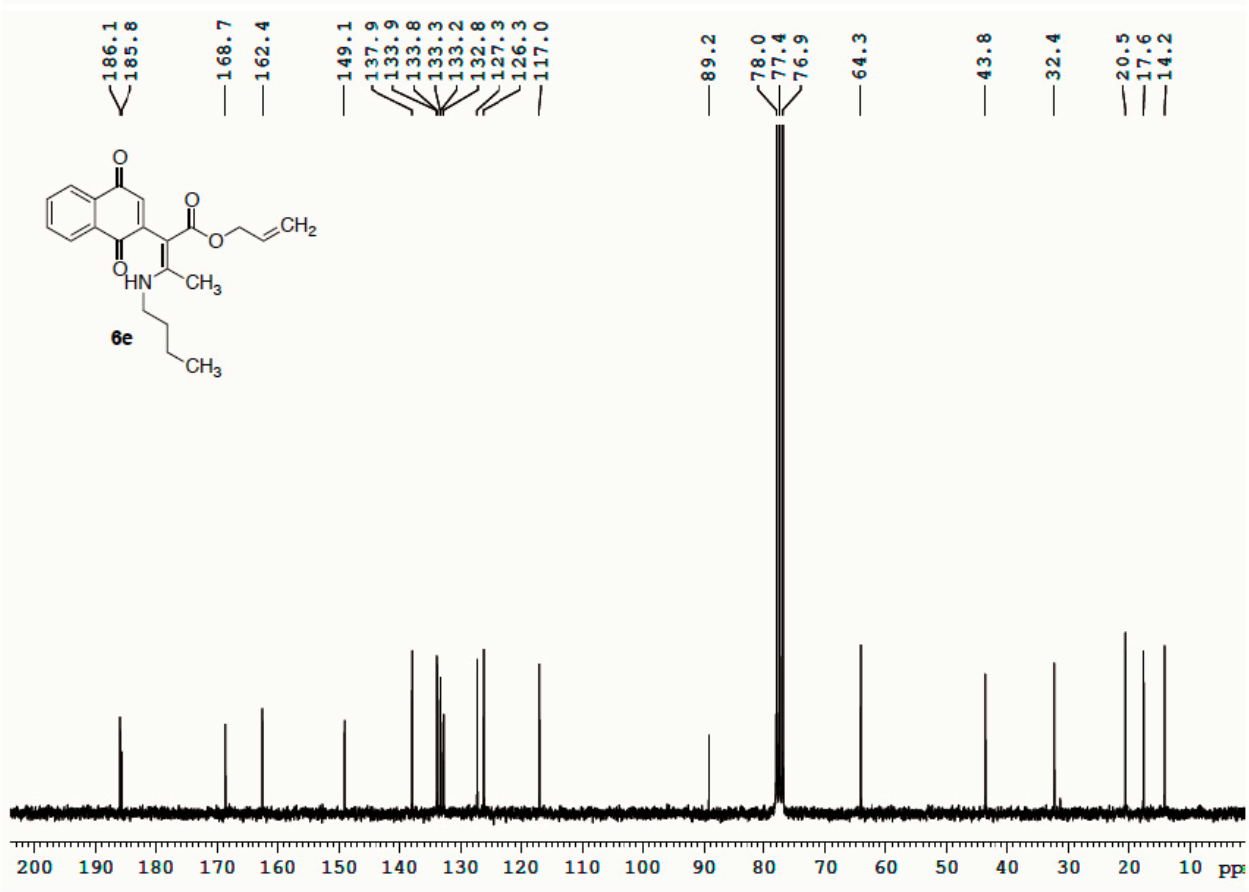
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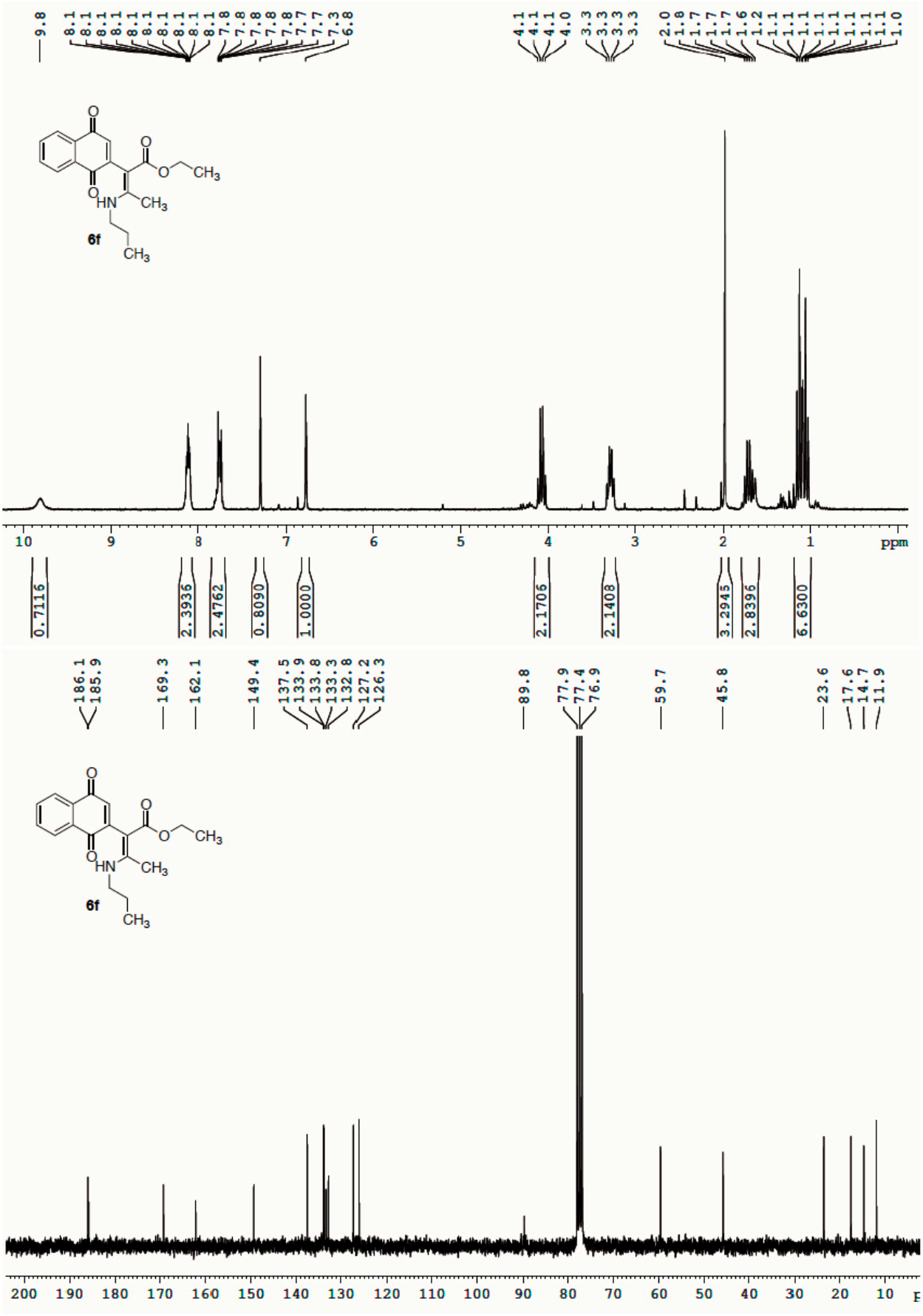
O
O
HN
CH3
CH2
CH3
6e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.8
7.7
7.7
7.3
6.8
4.1
4.1
4.1
4.0
3.3
3.3
3.3
3.3
2.0
1.8
1.7
1.7
1.7
1.6
1.2
1.1
1.1
1.1
1.1
1.1
1.1
1.1
1.0
O
O
O
O
HN
CH3
CH3
CH3
6f
10
9
8
7
6
5
4
3
2
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ppm
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2.4762
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3.2945
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6.6300
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185.9
169.3
162.1
149.4
137.5
133.9
133.8
133.3
132.8
127.2
126.3
89.8
77.9
77.4
76.9
59.7
45.8
23.6
17.6
14.7
11.9
O
O
O
O
HN
CH3
CH3
CH3
6f
200
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160
150
140
130
120
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80
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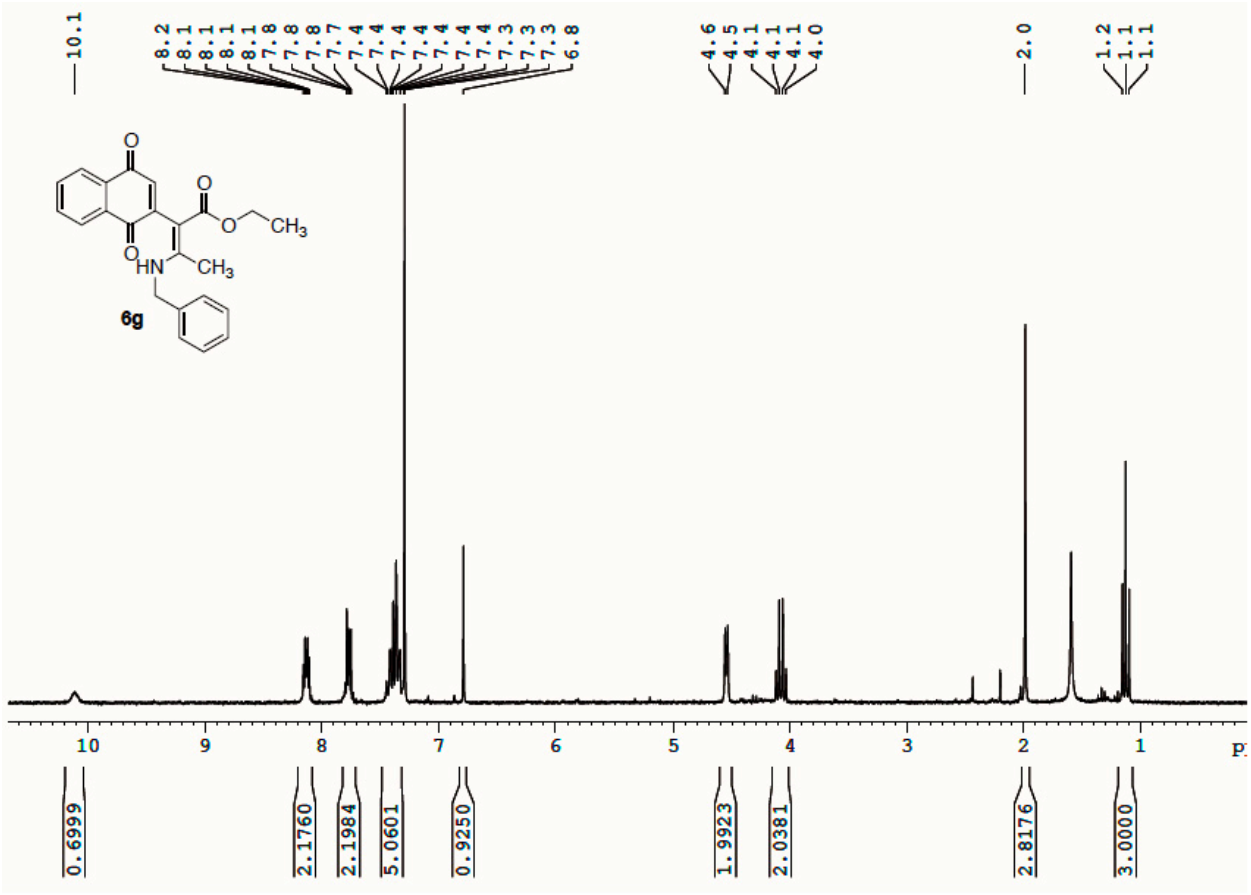
20
10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7.7
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7.4
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7.4
7.4
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7.4
7.3
7.3
7.3
6.8
4.6
4.5
4.1
4.1
4.1
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1.2
1.1
1.1
O
O
O
O
CH3
HN
CH3
6g
10
9
8
7
6
5
4
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1.9923
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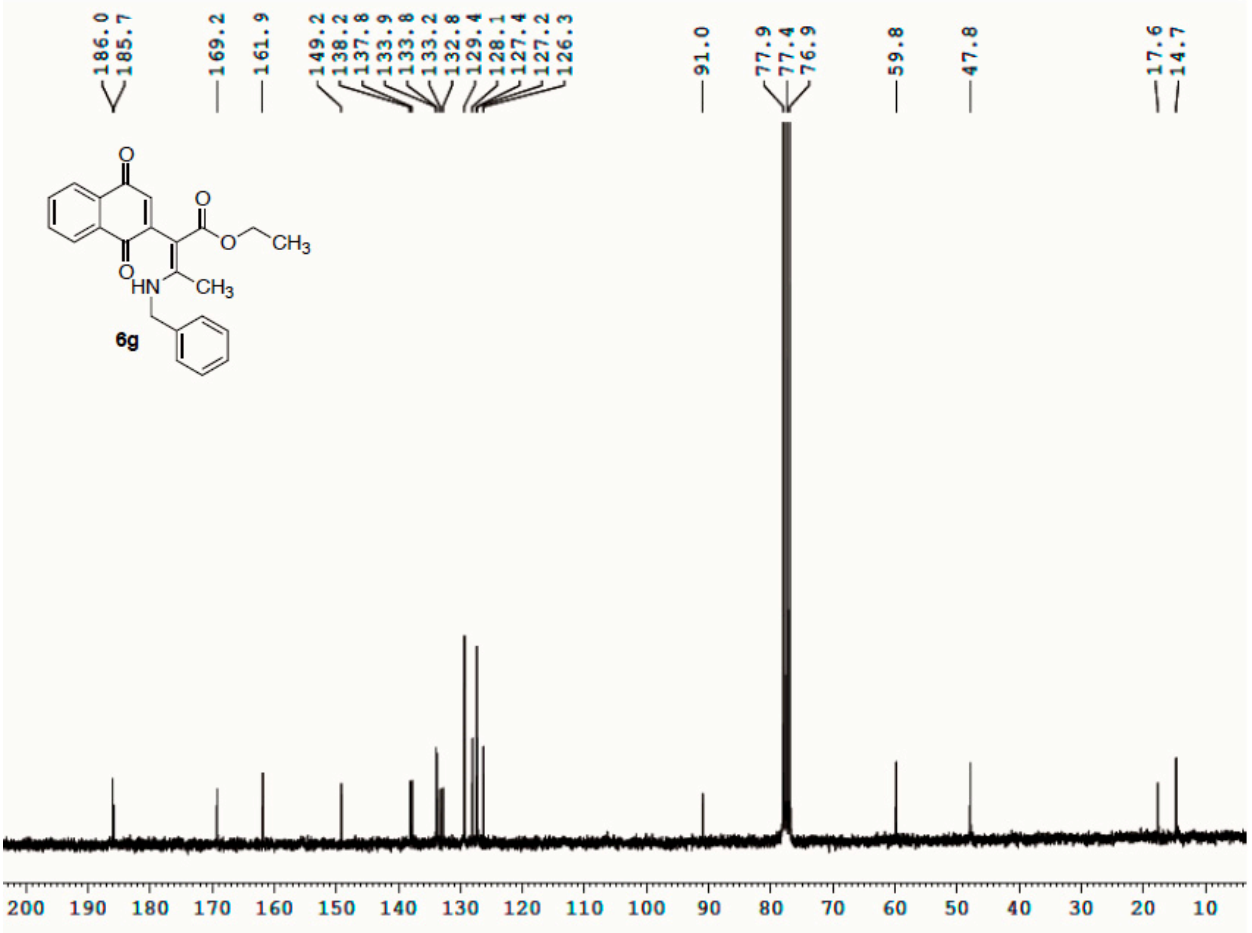
2.8176
3.0000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161.9
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138.2
137.8
133.9
133.8
133.2
132.8
129.4
128.1
127.4
127.2
126.3
91.0
77.9
77.4
76.9
59.8
47.8
17.6
14.7
O
O
O
O
CH3
HN
CH3
6g
200
190
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160
150
140
130
120
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80
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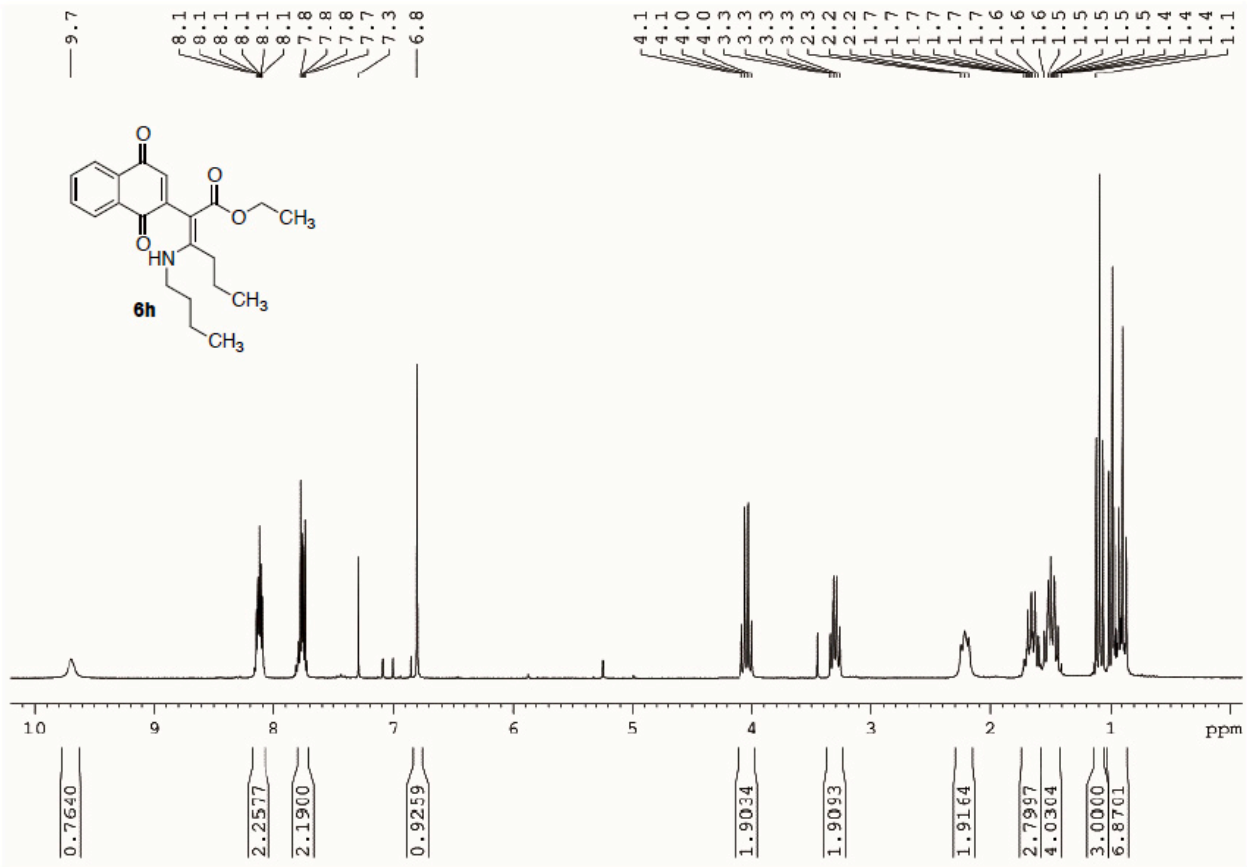
40
30
20
10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7.3
6.8
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4.0
4.0
3.3
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1.5
1.5
1.5
1.5
1.4
1.4
1.4
1.1
O
O
O
O
HN
CH3
CH3
CH3
6h
10
9
8
7
6
5
4
3
2
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ppm
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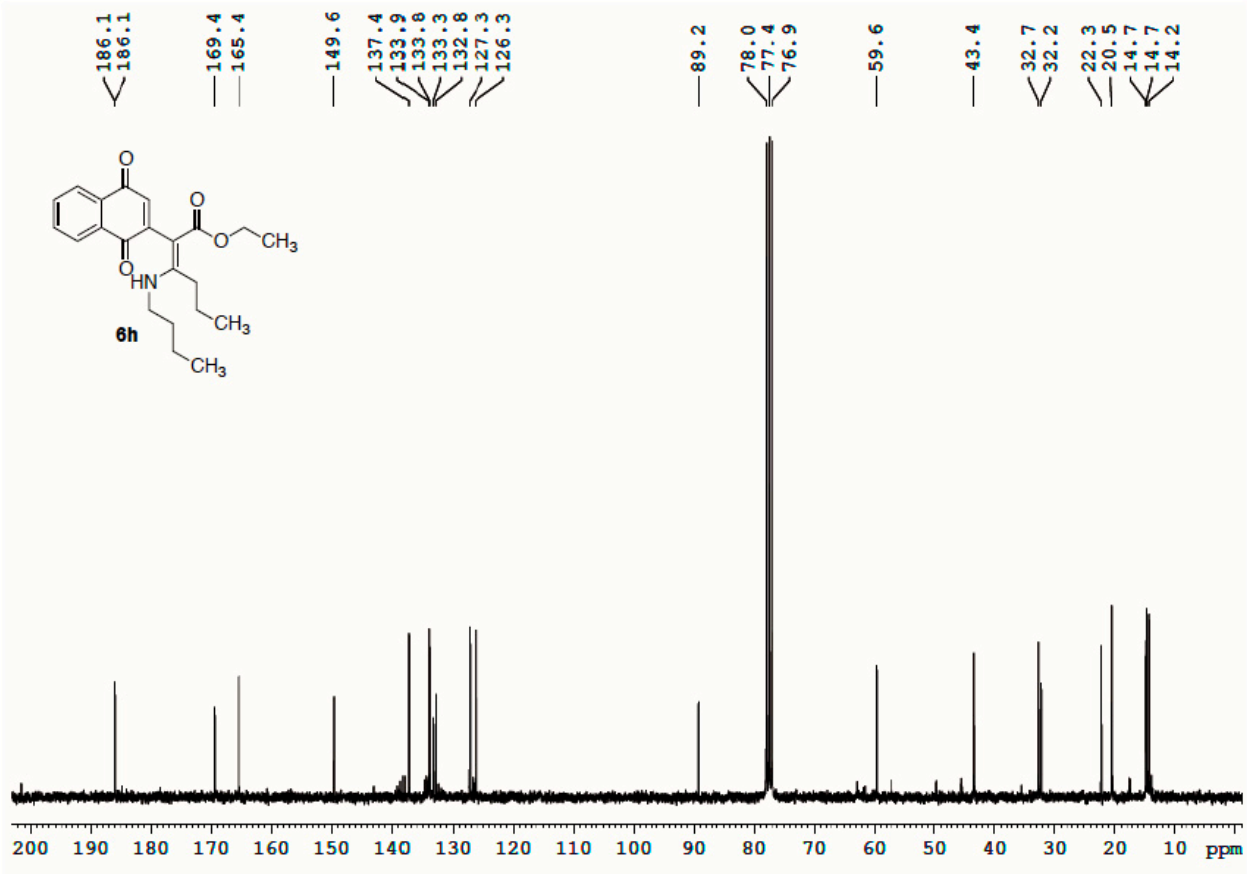
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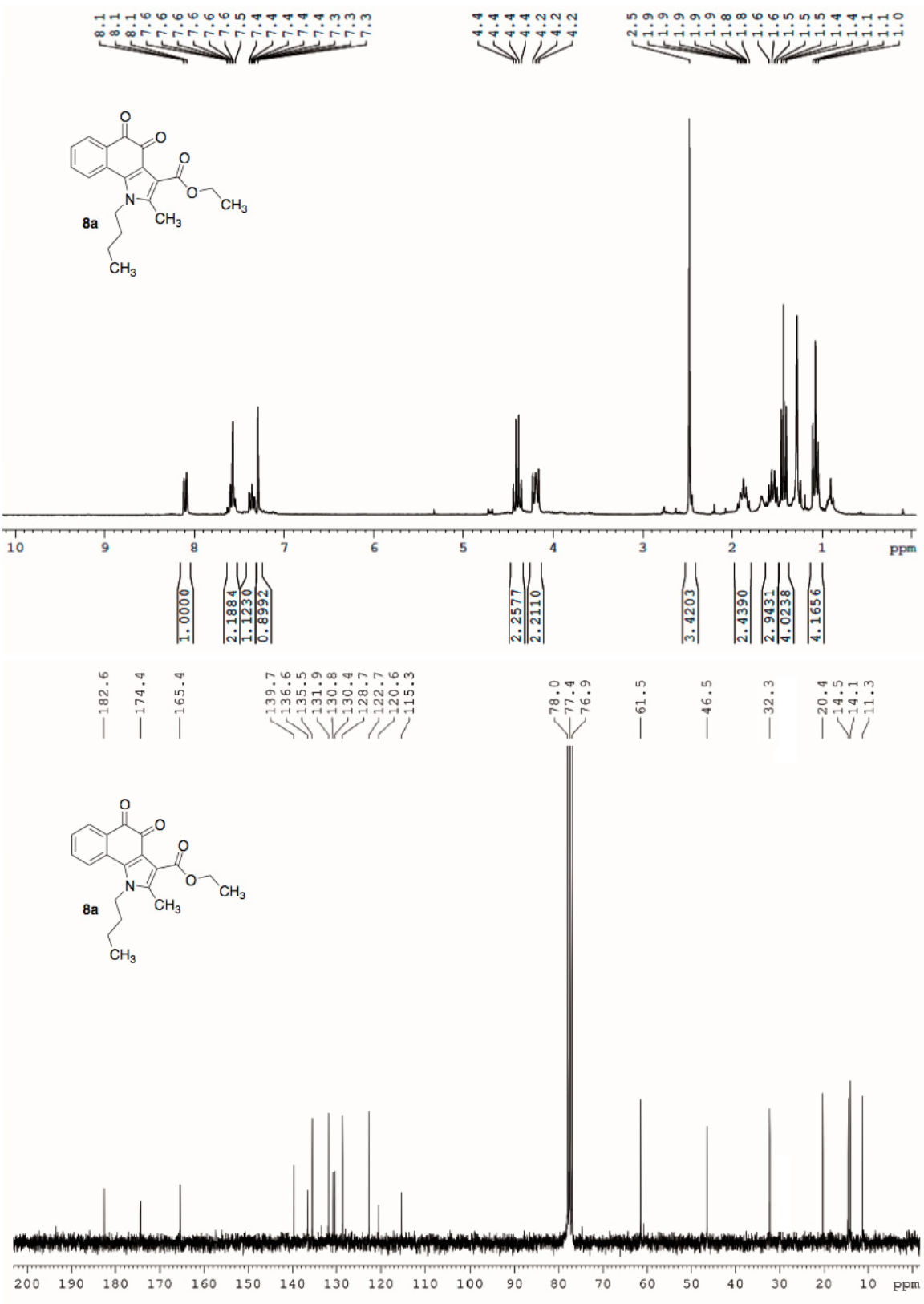
137.4
133.9
133.8
133.3
132.8
127.3
126.3
89.2
78.0
77.4
76.9
59.6
43.4
32.7
32.2
22.3
20.5
14.7
14.7
14.2
O
O
O
O
HN
CH3
CH3
CH3
6h
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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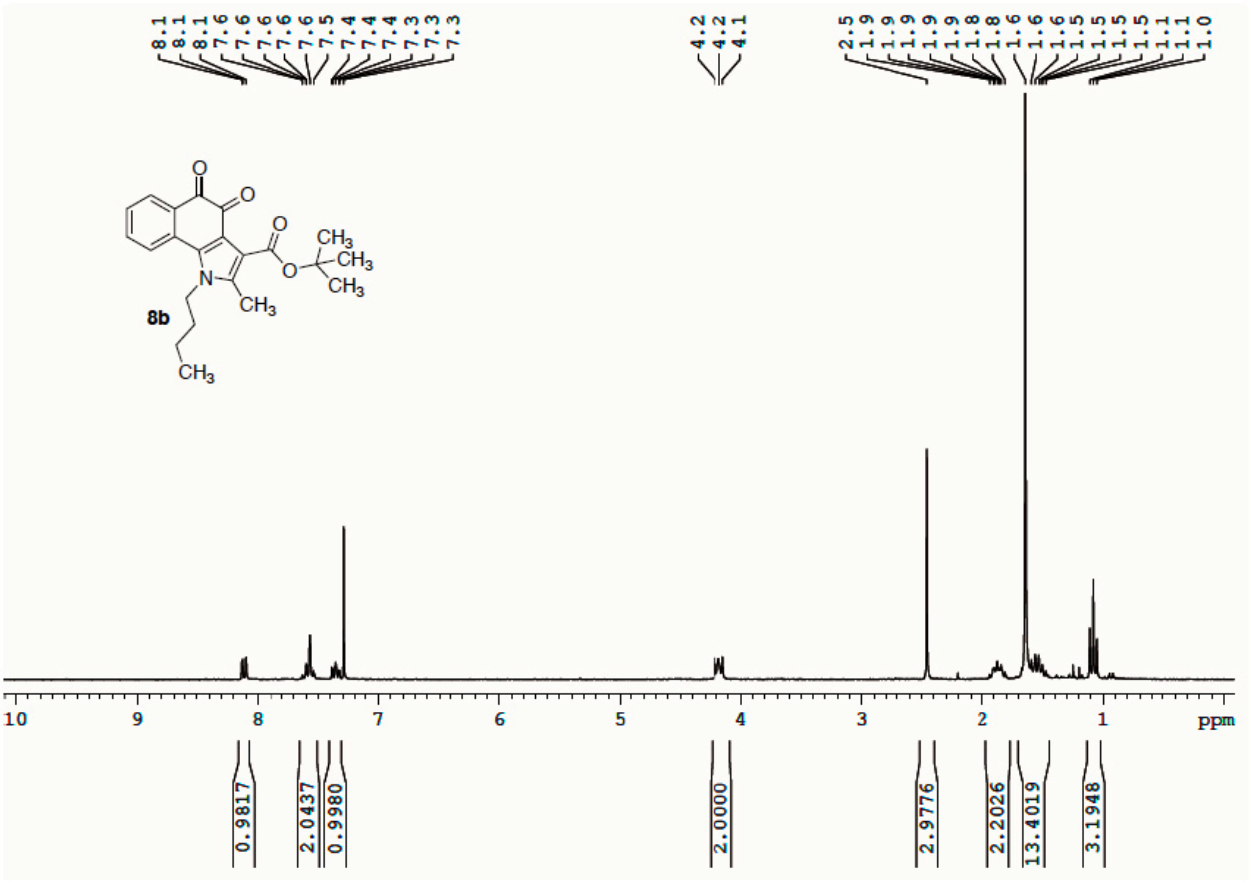
ppm
8a
ppm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7.6
7.6
7.5
7.4
7.4
7.4
7.3
7.3
7.3
4.2
4.2
4.1
2.5
1.9
1.9
1.9
1.9
1.8
1.8
1.6
1.6
1.6
1.5
1.5
1.5
1.5
1.1
1.1
1.0
8b
10
9
8
7
6
5
4
3
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ppm
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0.9980
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2.9776
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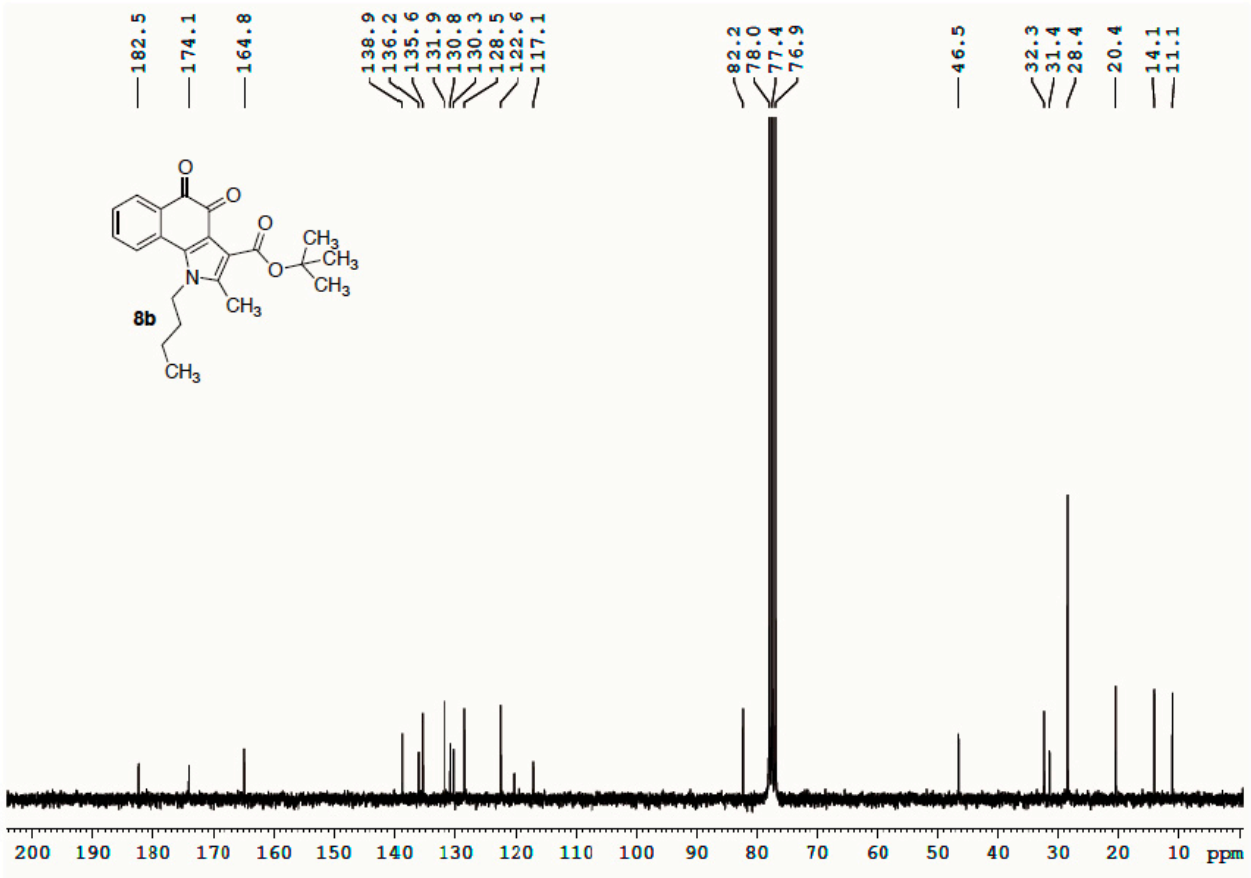
13.4019
3.1948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138.9
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131.9
130.8
130.3
128.5
122.6
117.1
82.2
78.0
77.4
76.9
46.5
32.3
31.4
28.4
20.4
14.1
11.1
8b
200
190
180
170
160
150
140
130
120
110
100
90
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70
60
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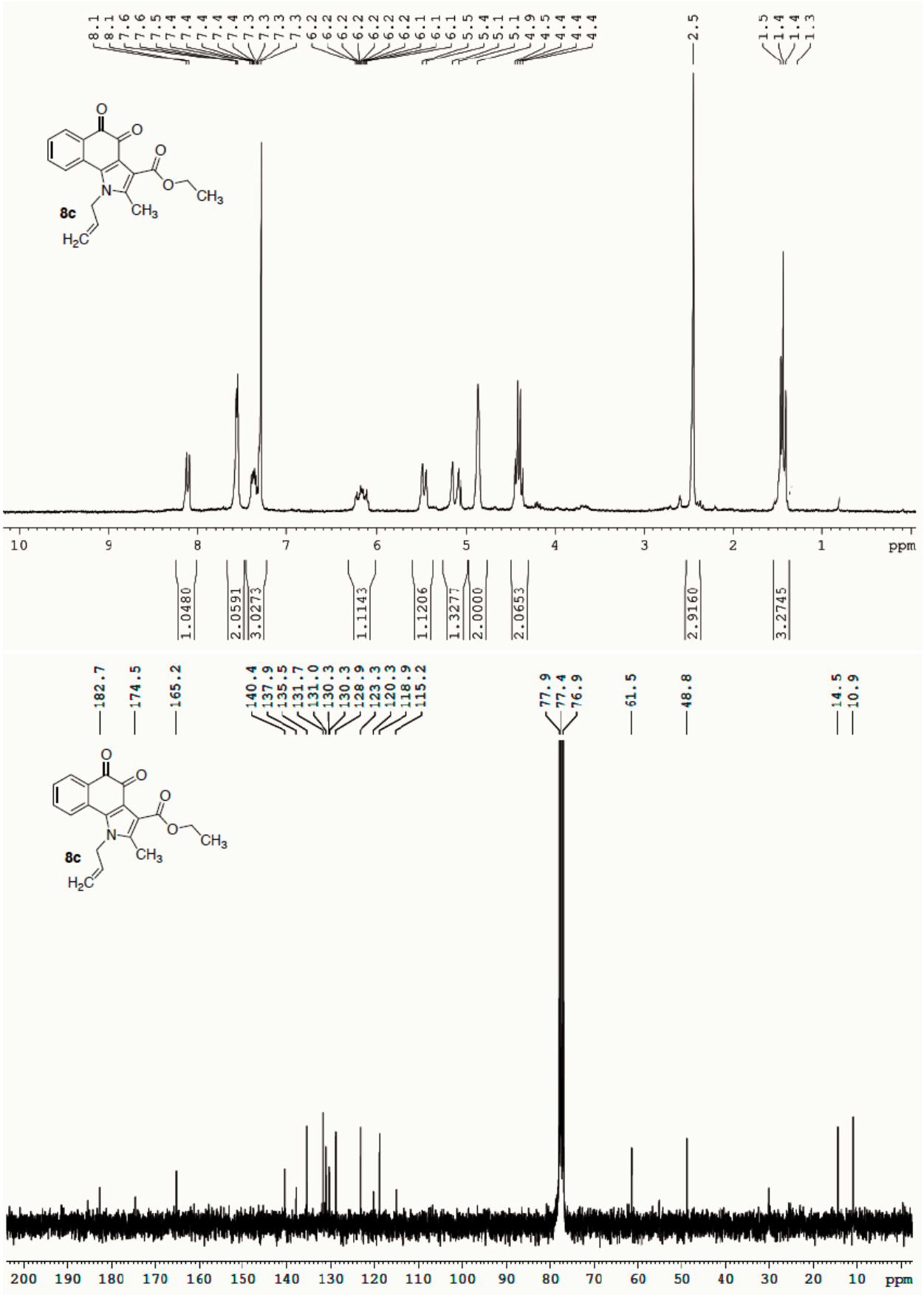
30
20
10
ppm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O
O
O
O
N
CH3
8c
H2C
10 9 8 7 6 5 4 3 2 1 ppm
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182.7 174.5 165.2 140.4 137.9 135.5 131.7 131.0 130.3 130.3 128.9 123.3 120.3 118.9 115.2 77.9 77.4 76.9 61.5 48.8 14.5 10.9
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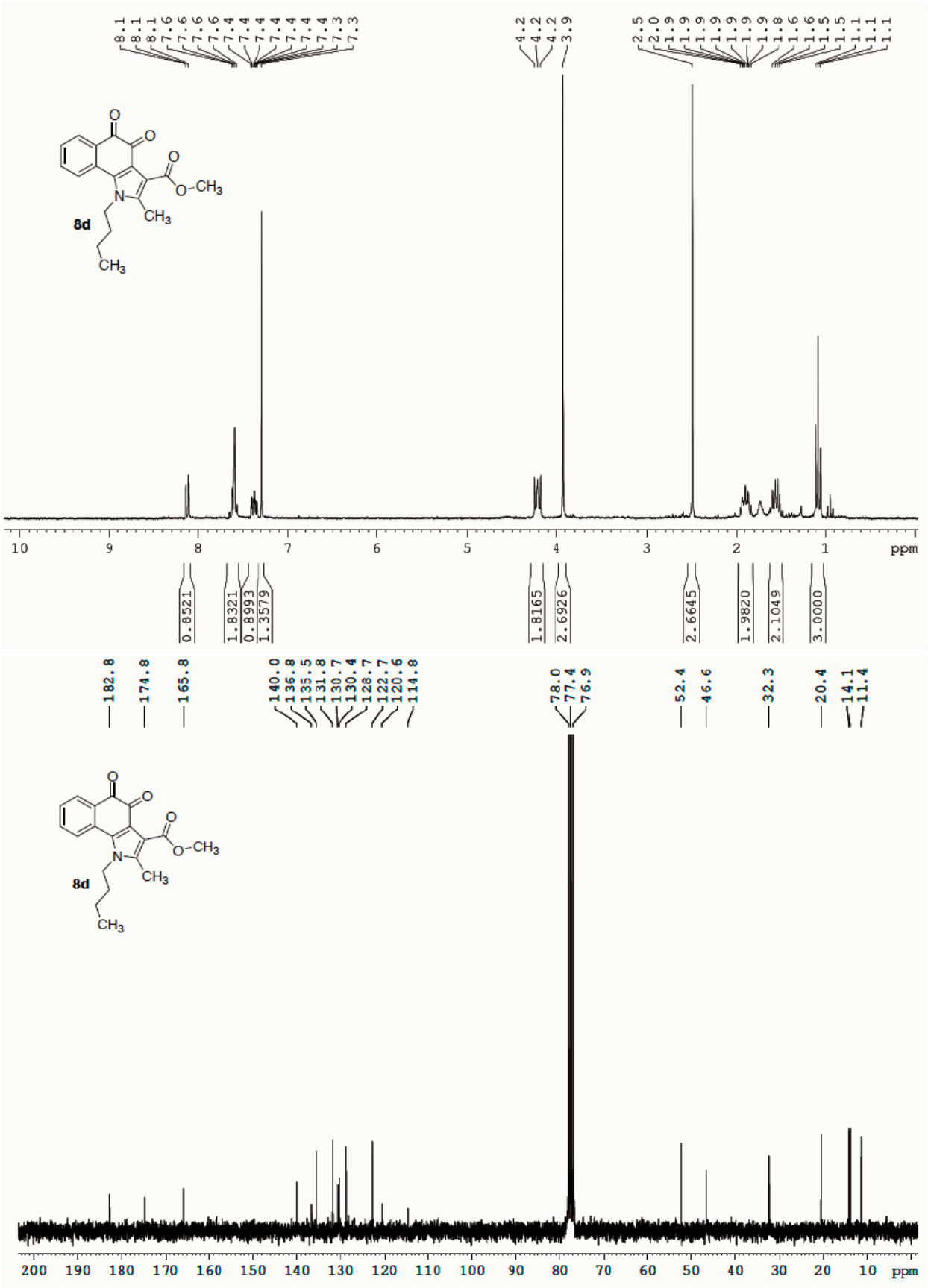
O
O
O
N
CH3
8c
H2C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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4.2 4.2 4.2 3.9
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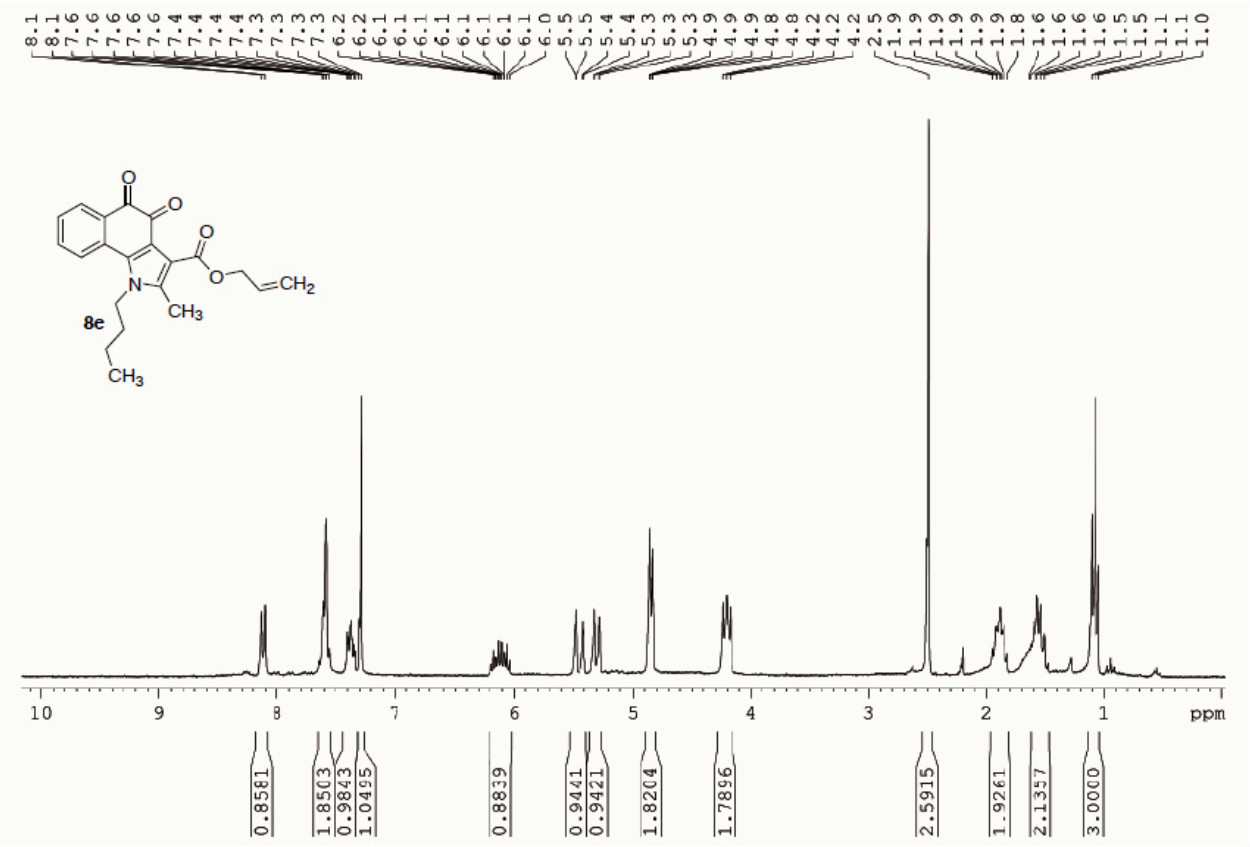
O
O
O
O-CH3
N
CH3
8d
CH3
10 9 8 7 6 5 4 3 2 1 ppm
0.8521 1.8321 0.8993 1.3579 1.8165 2.6926 2.6645 1.9820 2.1049 3.0000
182.8 174.8 165.8 140.0 136.8 135.5 131.8 130.7 130.4 128.7 122.7 120.6 114.8
78.0 77.4 76.9
52.4 46.6 32.3 20.4 14.1 11.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8e
CH3
CH2
ppm
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0.9441
0.9421
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1.7896
2.5915
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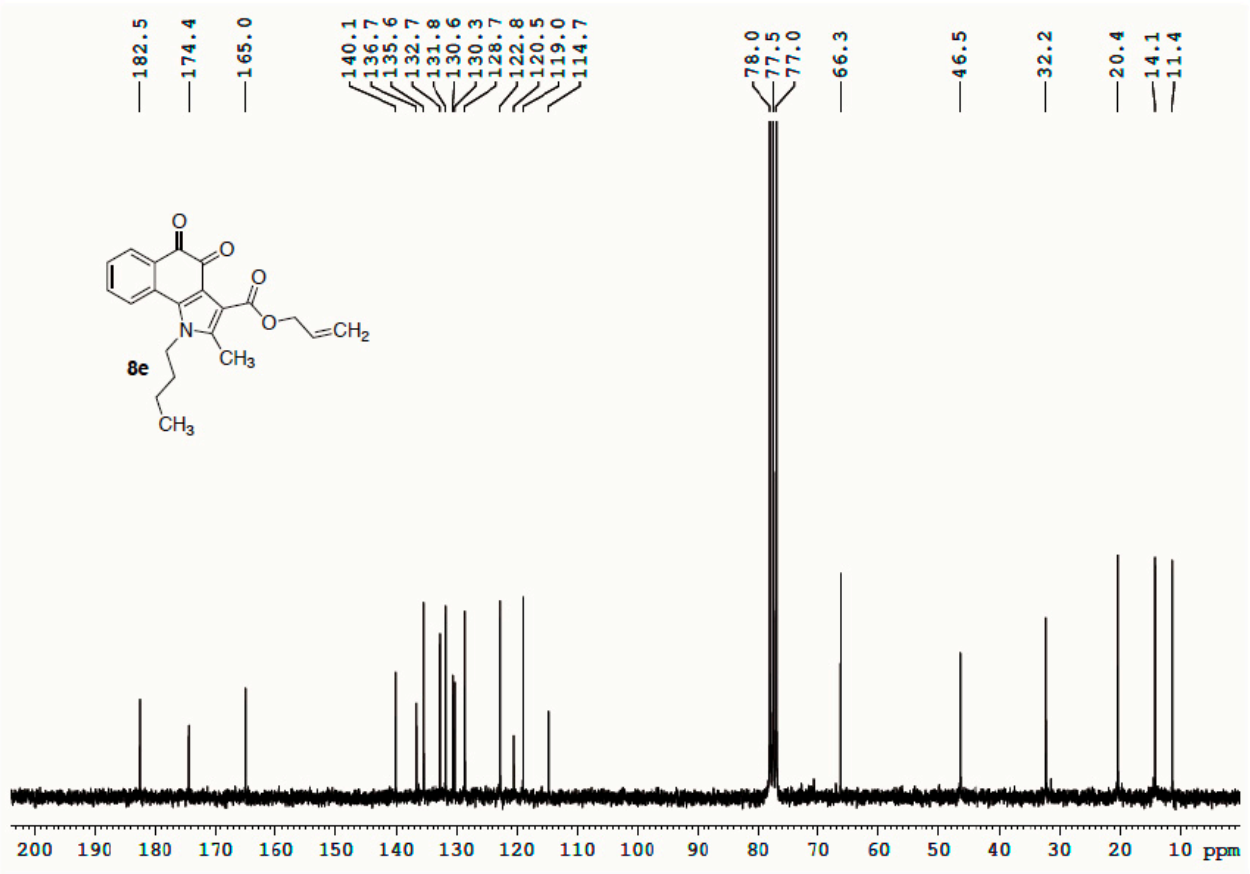
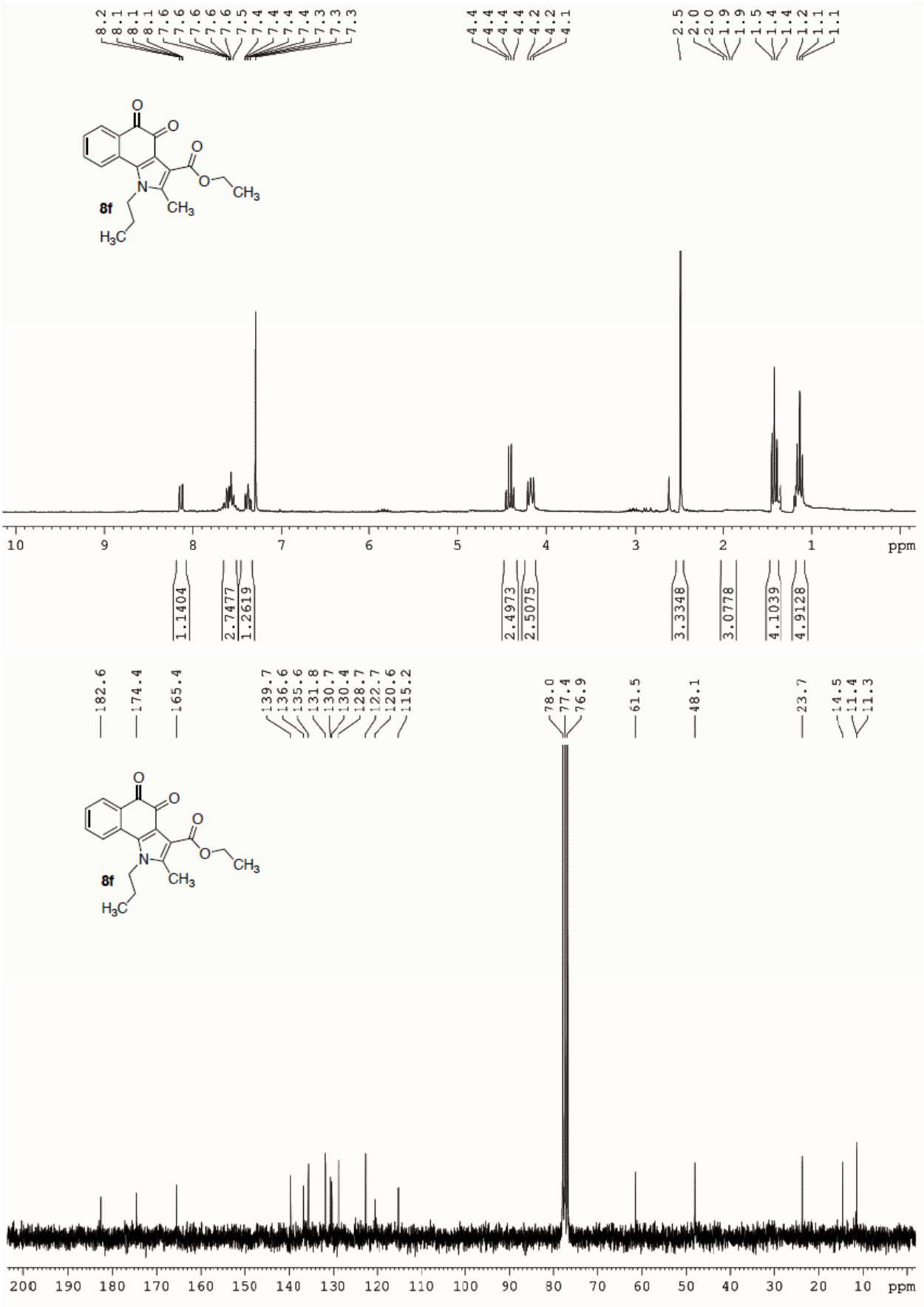
2.1357
3.0000


8e
CH3
CH2
ppm
182.5
174.4
165.0
140.1
136.7
135.6
132.7
131.8
130.6
130.3
128.7
122.8
120.5
119.0
114.7
78.0
77.5
77.0
66.3
46.5
32.2
20.4
14.1
11.4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7.5
7.4
7.4
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7.4
7.3
7.3
7.3
4.4
4.4
4.4
4.4
4.2
4.2
4.1
2.5
2.0
2.0
1.9
1.9
1.5
1.4
1.4
1.2
1.1
1.1
O
O
O
O
N
CH3
CH3
8f
H3C
10
9
8
7
6
5
4
3
2
1
ppm
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1.2619
2.4973
2.5075
3.3348
3.0778
4.1039
4.9128
182.6
174.4
165.4
139.7
136.6
135.6
131.8
130.7
130.4
128.7
122.7
120.6
115.2
78.0
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76.9
61.5
48.1
23.7
14.5
11.4
11.3
O
O
O
O
N
CH3
CH3
8f
H3C
200
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150
140
130
120
110
100
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80
70
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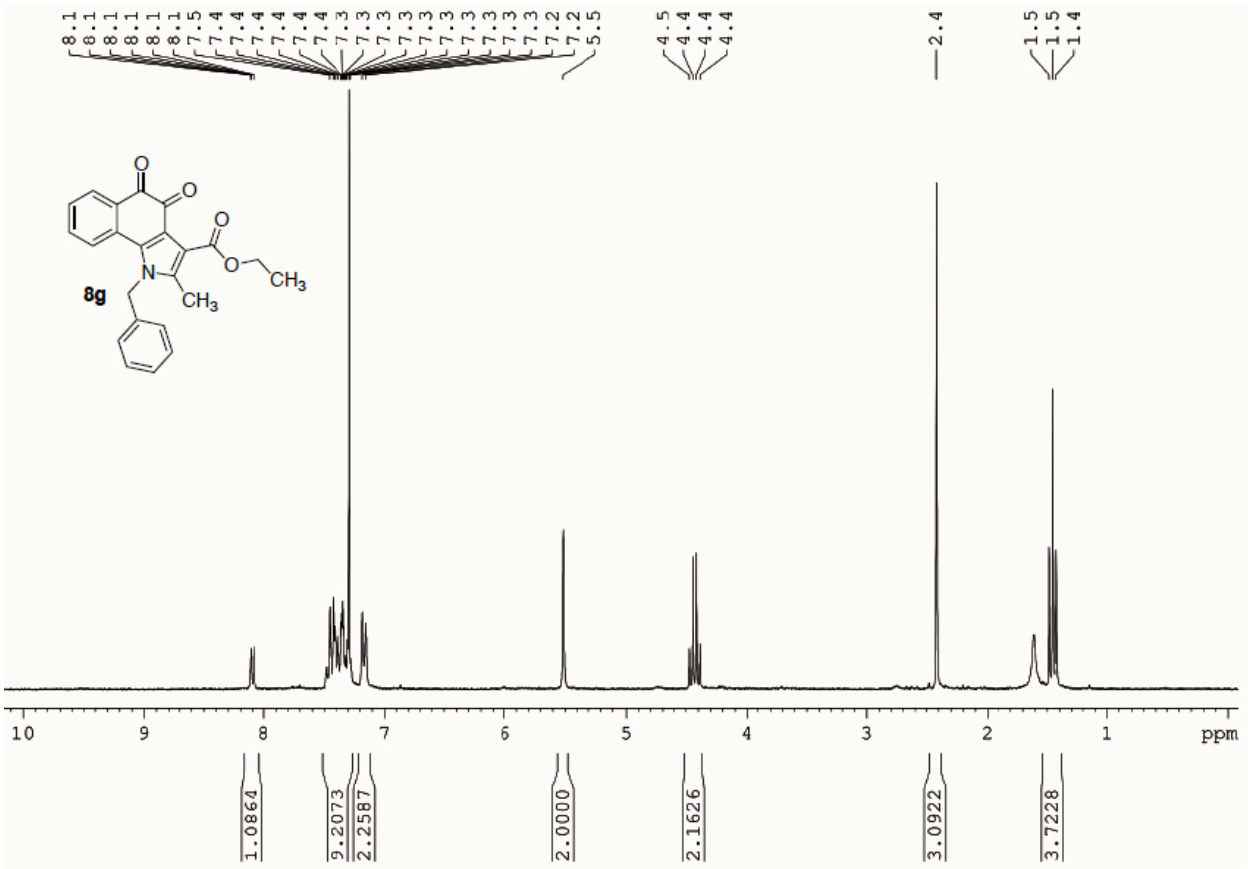
30
20
10
ppm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7.5
7.4
7.3
7.2
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4.5
4.4
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1.5
1.4
8g
10
9
8
7
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ppm
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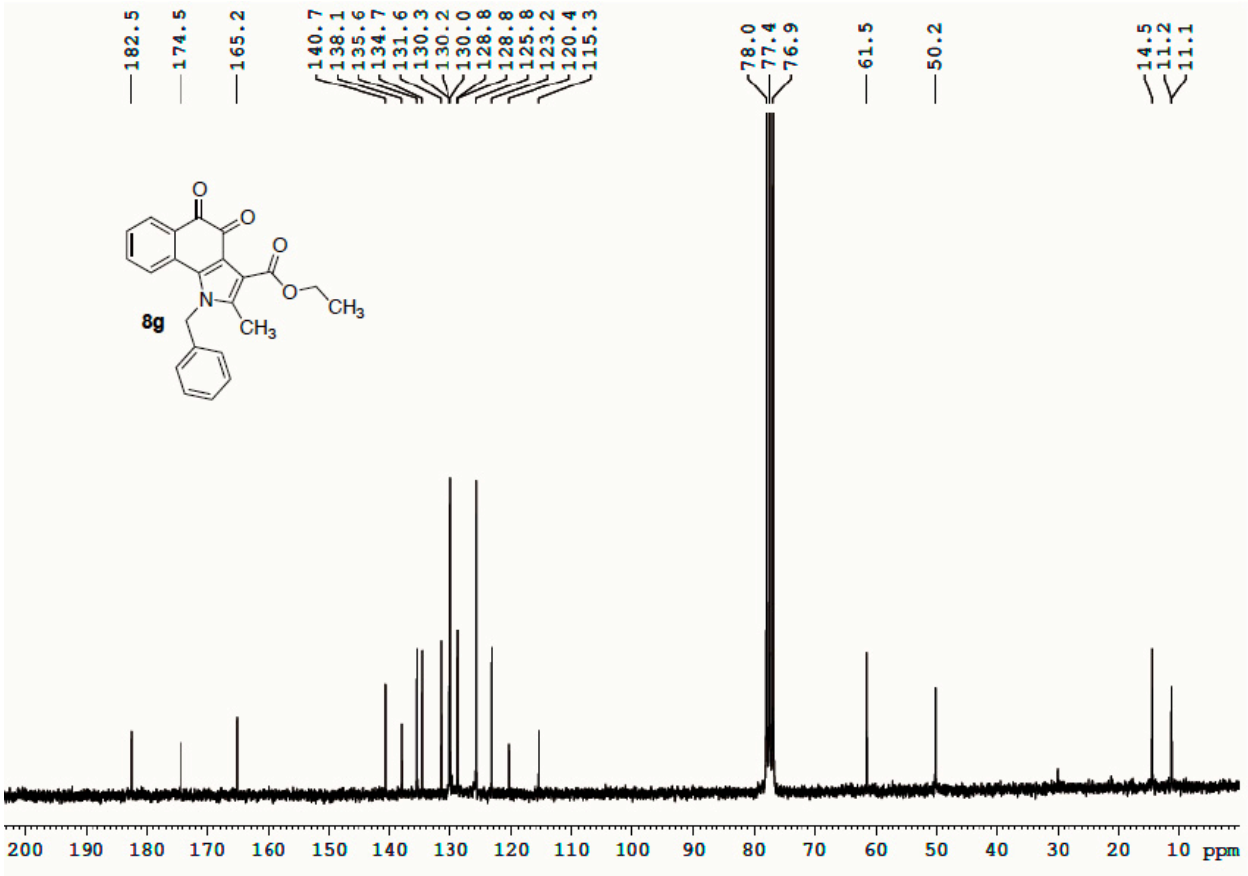
3.7228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174.5
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138.1
135.6
134.7
131.6
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130.2
130.0
128.8
128.8
125.8
123.2
120.4
115.3
78.0
77.4
76.9
61.5
50.2
14.5
11.2
11.1
8g
200
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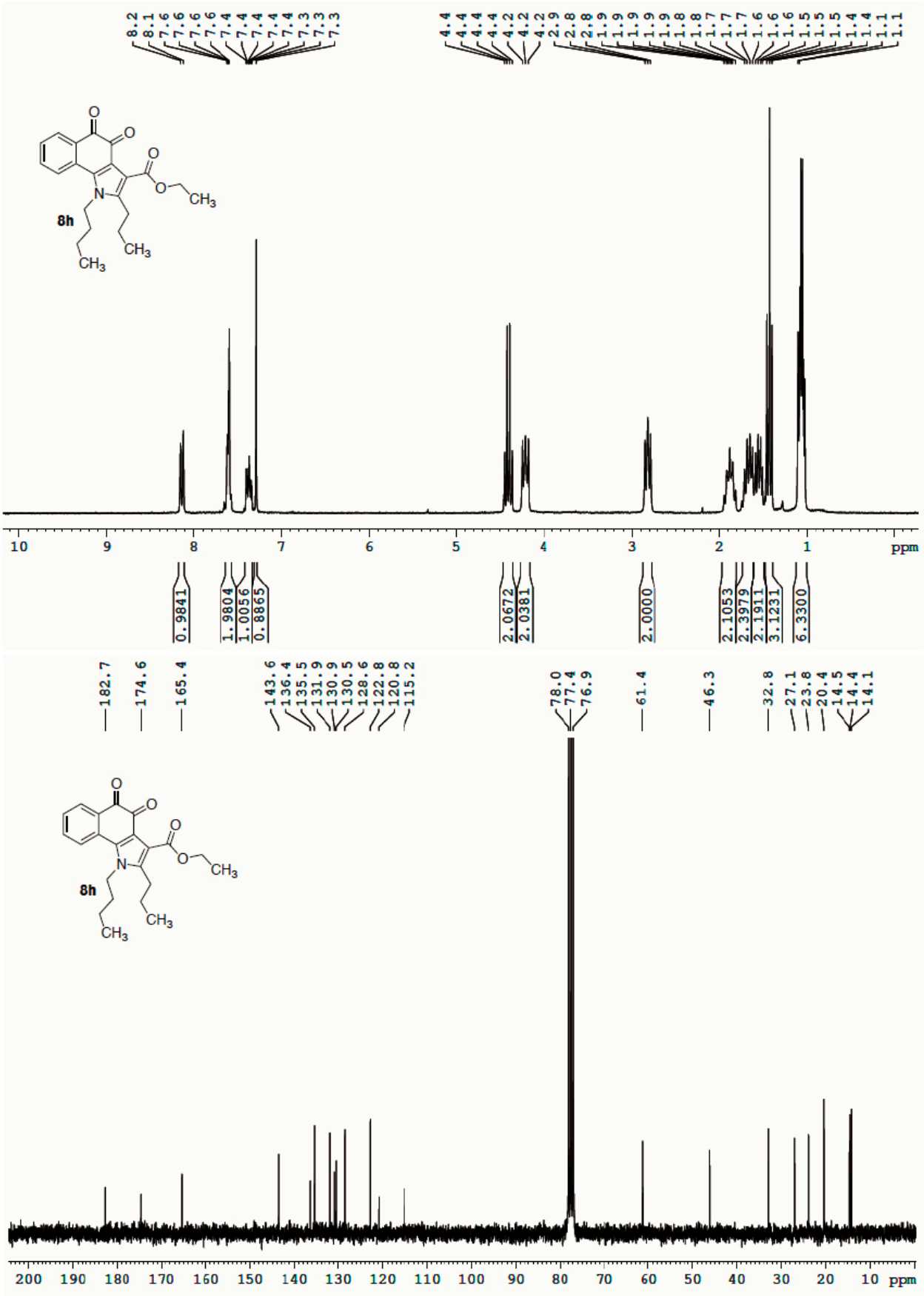
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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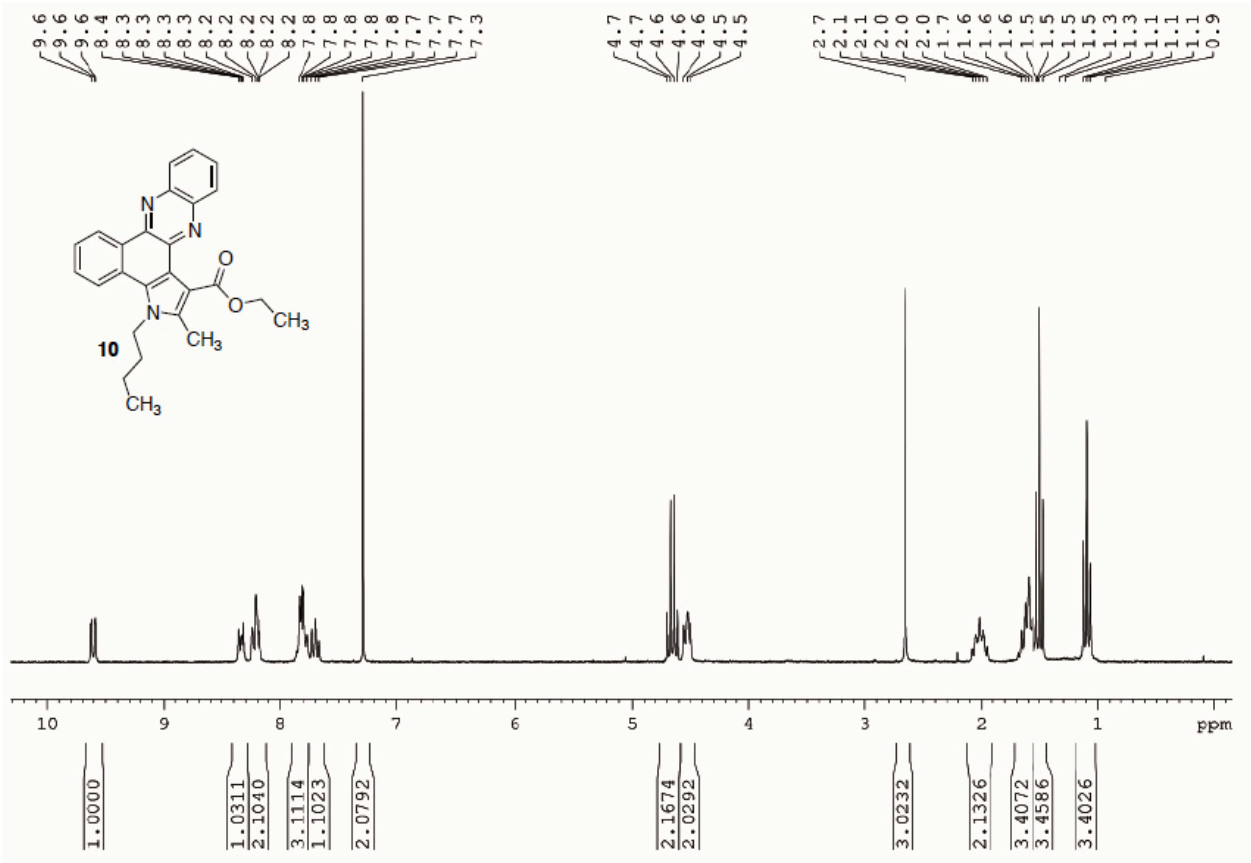
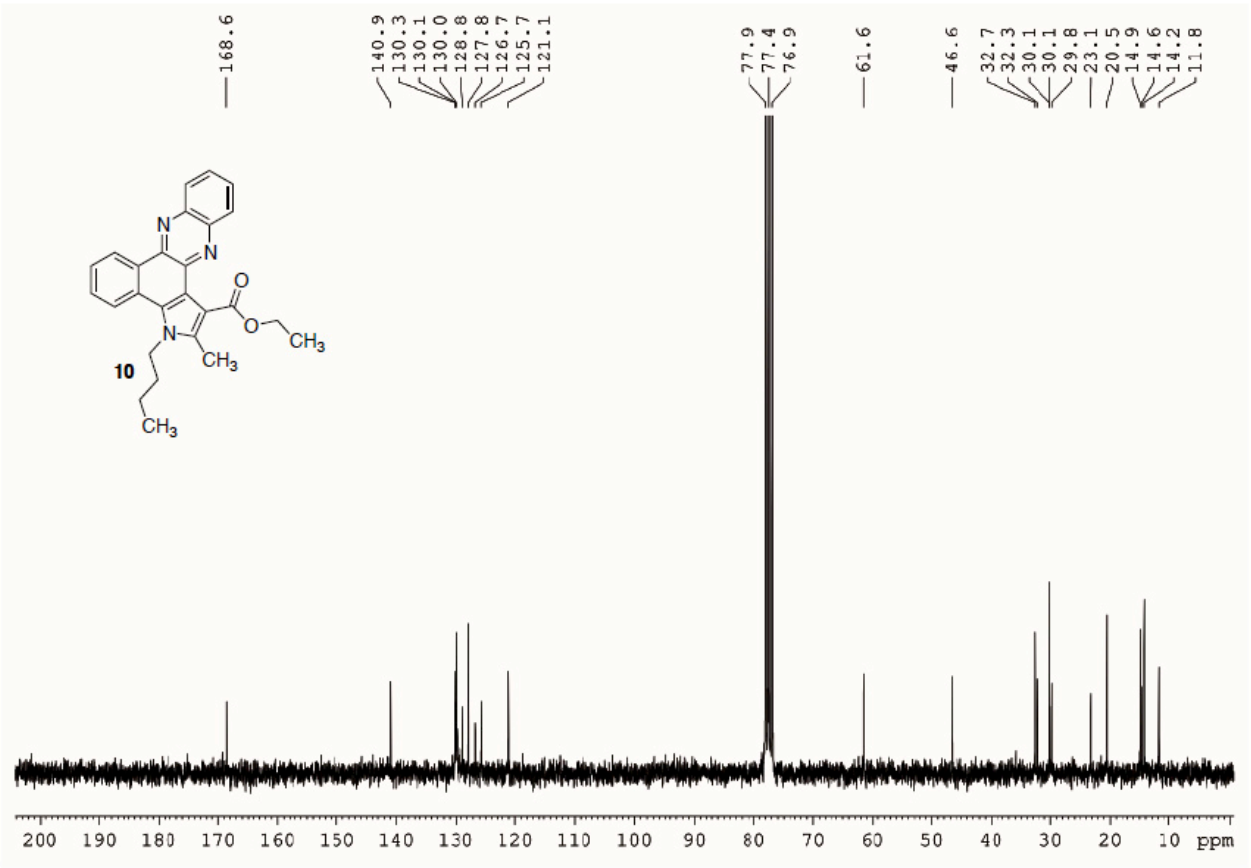
4.4 4.4 4.4 4.4 4.2 4.2 4.2 2.9 2.8 2.8 1.9 1.9 1.9 1.9 1.9 1.8 1.8 1.7 1.7 1.7 1.6 1.6 1.6 1.5 1.5 1.5 1.4 1.4 1.1 1.1
O
O
O
O
N
CH3
CH3
CH3
8h
10 9 8 7 6 5 4 3 2 1 ppm
0.9841
1.9804
1.0056
0.8865
2.0672
2.0381
2.0000
2.1053
2.3979
2.1911
3.1231
6.3300
182.7 174.6 165.4 143.6 136.4 135.5 131.9 130.9 130.5 128.6 122.8 120.8 115.2
78.0 77.4 76.9 61.4 46.3 32.8 27.1 23.8 20.4 14.5 14.4 14.1
O
O
O
O
N
CH3
CH3
CH3
8h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.6 9.6 9.6 8.4 8.3 8.3 8.3 8.3 8.2 8.2 8.2 8.2 8.2 7.8 7.8 7.8 7.8 7.7 7.7 7.7 7.3
4.7 4.7 4.6 4.6 4.6 4.5 4.5
2.7 2.1 2.1 2.0 2.0 2.0 1.7 1.6 1.6 1.5 1.5 1.5 1.5 1.3 1.3 1.1 1.1 1.1 0.9
N
N
O
O
CH3
N
CH3
10
CH3
10 9 8 7 6 5 4 3 2 1 ppm
1.0000
1.0311
2.1040
3.1114
1.1023
2.0792
2.1674
2.0292
3.0232
2.1326
3.4072
3.4586
3.4026


168.6
140.9 130.3 130.1 130.0 128.8 127.8 126.7 125.7 121.1
77.9 77.4 76.9
61.6
46.6
32.7 32.3 30.1 30.1 29.8 23.1 20.5 14.9 14.6 14.2 11.8
N
N
O
O
CH3
N
CH3
10
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm