Supporting Information

Fluorous Diastereomeric Mixture Synthesis (FDMS) of Hydantoin-fused Hexahydrochromeno[4,3-*b*]pyrroles

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Experimental procedures

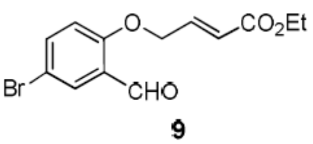
Preparation of aldehyde 9: To a solution of 5-bromo-2-hydroxybenzaldehyde (11.5 mmol, 1.15 equiv) in DMF (8 mL) was added Cs_2CO_3 (12 mmol, 1.2 equiv) and the mixture was stirred at room temperature for 20 min. Ethyl bromocrotonate (10 mmol, 1.0 equiv) in DMF (2 mL) was added dropwise under ice-water cooling. The reaction was stirred for 16 hours and quenched with ice-water. The reaction mixture was extracted with EtOAc and the organic solution was washed with K_2CO_3 and brine. The crude product was purified on FlashMaster system with 100 g of silica gel (10-30% EtOAc/hexane gradient) to afford 2.03 g (65% yield) of product **9**.

Preparation of aminoester (TFA salt) 10: To a solution of Boc-Ala (53 mmol, 1.2 equiv), $C_8F_{17}CH_2CH_2CH_2OH$ (44 mmol, 1.0 equiv), HOBt (66 mmol, 1.5 equiv) and DMAP (4.4 mmol, 0.1 equiv) in DMF (100 mL) were added DIC (66 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 20 h and quenched with ice-water. The mixture was stirred for 1 hour and then filtered. The solid was washed with water, dried and an then dissolved in 250 mL of 2:8 EtOAc/hexane. The slurry was filtered and washed with 50 mL of 2:8 EtOAc/hexane. The filtrate was washed with $NaHCO_3$, NH_4Cl, and brine and then dried over $MaSO_4$. The solution was loaded onto a plug of silica gel (400 mL). The flask was rinsed with 100 mL of 2:8 EtOAc/hexane and the solution was loaded onto the silica gel. This is the 1st fraction. The silica gel was eluted with 3 x 300 mL of 2:8 EtOAc/hexane. TLC showed the product is in fraction #2 and 3. The fractions were combined and concentrated to afford the intermediate as a white solid (22 g, 77%). The solid was then dissolved in 160 mL of DCM and then 40 mL of TFA was added. The mixture was stirred for 3 h and concentrated. The resulted solid was trituration with MeOH and toluene and then dried under vacuum to give a chunk of solid. The solid was triturated with 1:9 Et_2O/hexane, filtered, and then washed with hexane and dried under vacuum to afford the product as a white solid (22.2 g, 99%).

Formation of 1,3-dipolar cycloaddition products 11a-d: To a solution containing fluorous aminoester **10** (TFA salt, 1 mmol, 1.0 equiv) and aldehyde **9** (1.5 mmol, 1.5 equiv) in DMF (4 mL) was added Et_3N (2 mmol, 2 equiv). The reaction mixture was heated under microwave at 150 °C for 20 min. The cooled reaction mixture was loaded onto a 20 g fluorous cartridge and eluted on FlashMaster ($MeOH/H_2O$, 80% 5 min, 80-100% 5 min, 100% 10 min). The fluorous fraction was collected and concentrated on Genevac to afford the 0.549 g (65% yield) of compound **11**. The LC-MS analysis indicated it is a diastereomeric mixture of **11a-d** in a ratio of 9:4:59:28. For analytical purpose, these four diastereomers were separated by prep-scale HPLC. Compound **11a** was used for epimerization experiment shown in Scheme 5.

Formation of urea 12a-d: To a solution of diastereomeric mixture of **11a-d** (1 mmol) in 2 mL of DCM was added isocyanate (2.5 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixtures was concentrated, redissolved in 0.5 mL DMF and then loaded on to 2 g fluorous silica gel cartridge on the RapidTrace SPE apparatus. The cartridge was eluted with 2 x 6 mL of 8:2 $MeOH/H_2O$, and then 6 mL of MeOH. The MeOH fraction was concentrated to give 0.845 g (85% yield) of urea **12a-d**.

Formation of hydantoin-fused hexahydrochromeno[4,3-*b*]pyrroles 1: To a solution of diastereomeric mixture of urea **12a-d** (1 mmol) in DMF (1 mL) was added K_2CO_3 (~20 mg) and heated to 100 ºC for 30 min. The cooled reaction mixture was loaded onto a 3 g F-SPE cartridge. The reaction vial was rinsed with 1 mL of 9:1 DMF/H_2O and the liquid was loaded onto the cartridge. The cartridge was eluted with 6 mL 9:1 DMF/H_2O and the collected fraction was concentrated to give 0.273 g (53% yield) of compounds **1**. The mixture was analyzed by LC-MS which is a mixture of 8 diastereomers. Among them, 6 major were separated by prep-scale HPLC on a C_{18} stationary phase.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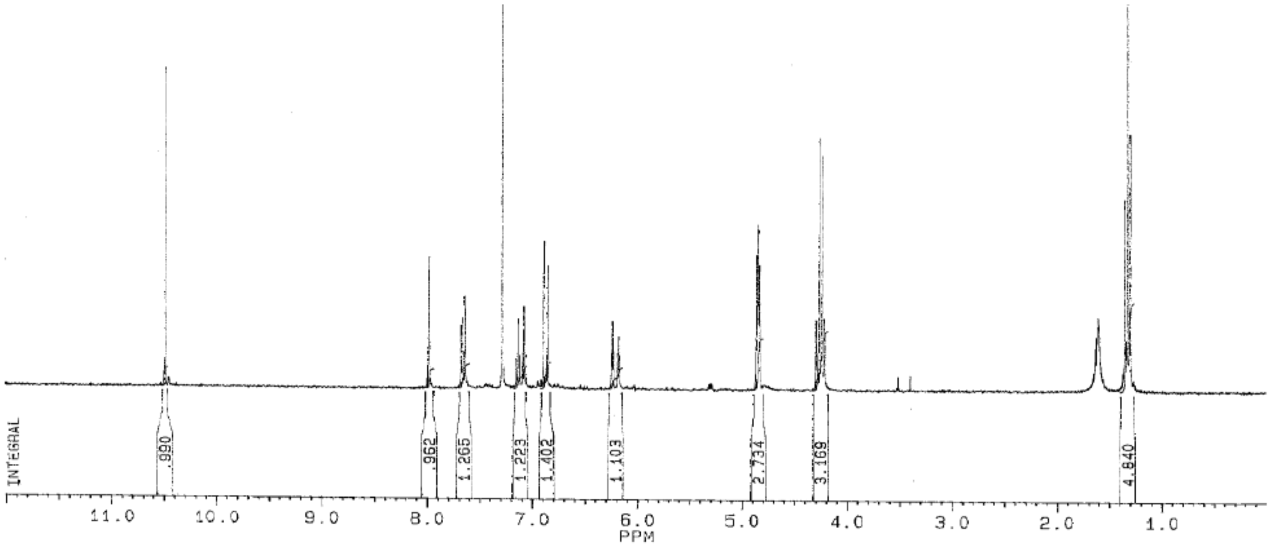
9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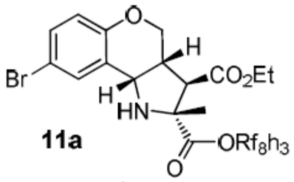
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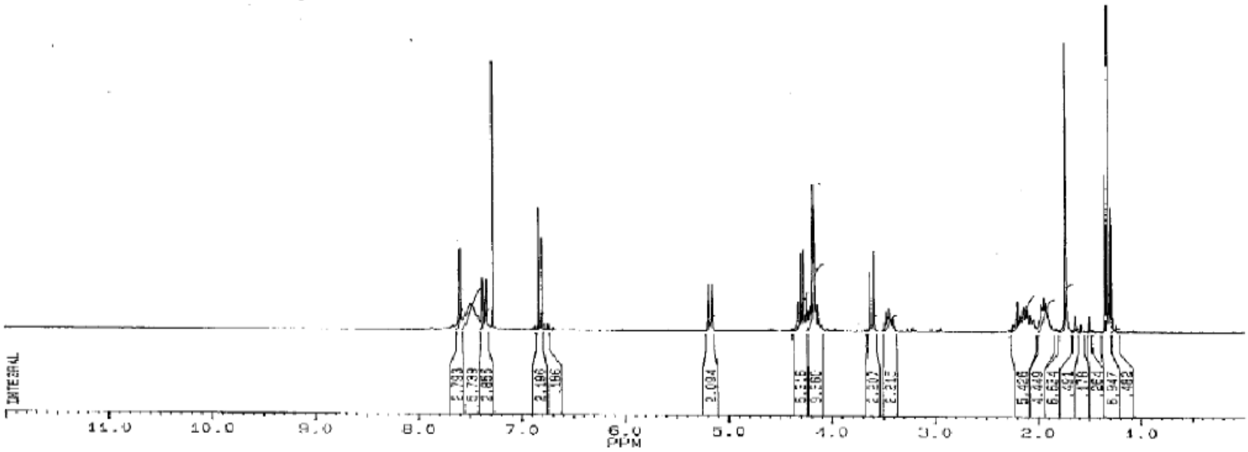
O

11a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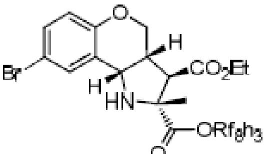
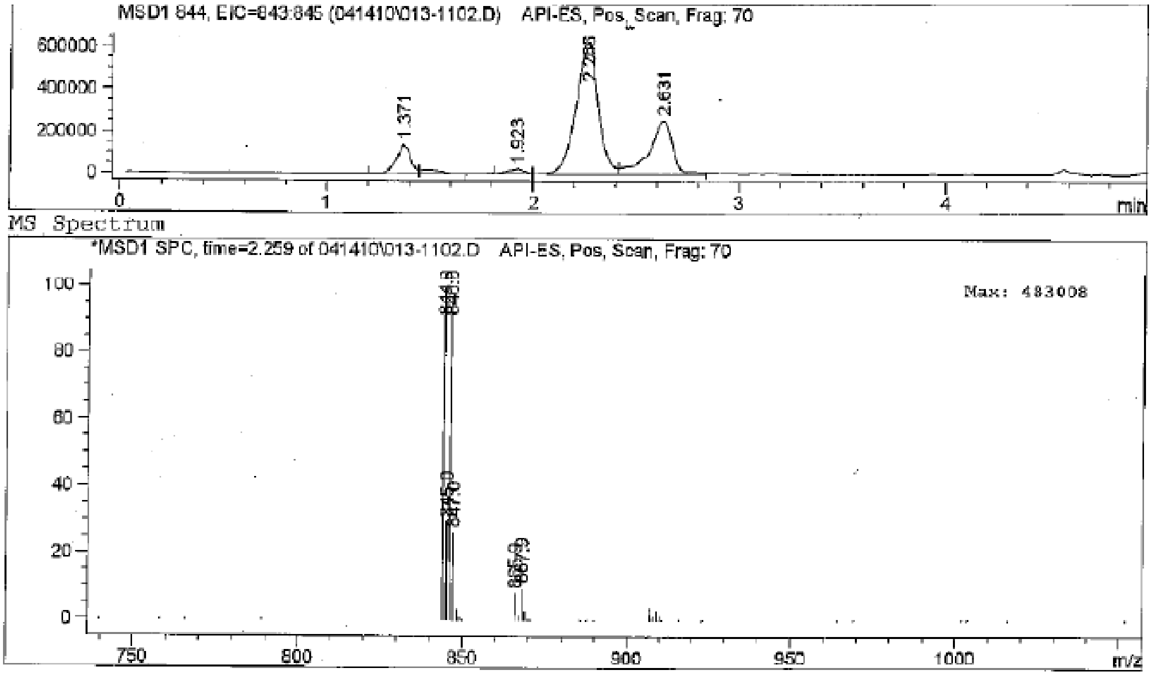
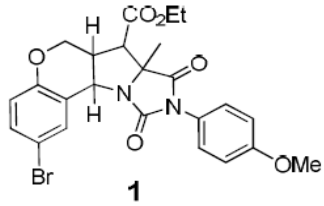


11

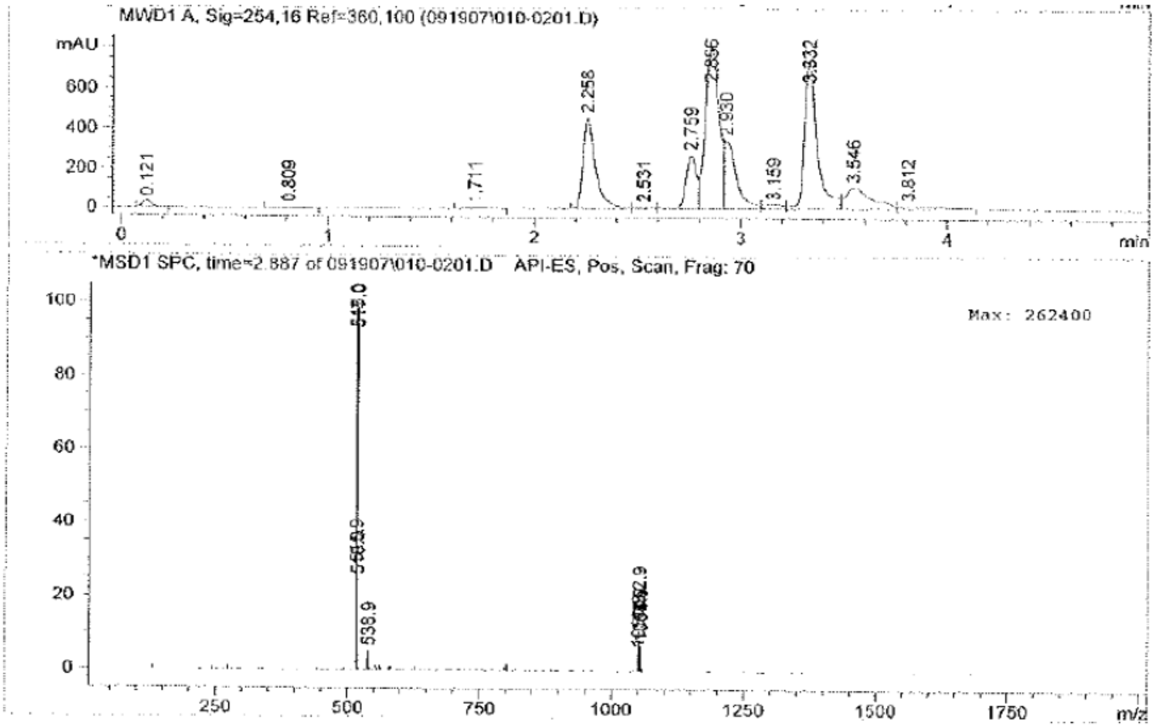
Reaction mixture has 4 major diastereomers



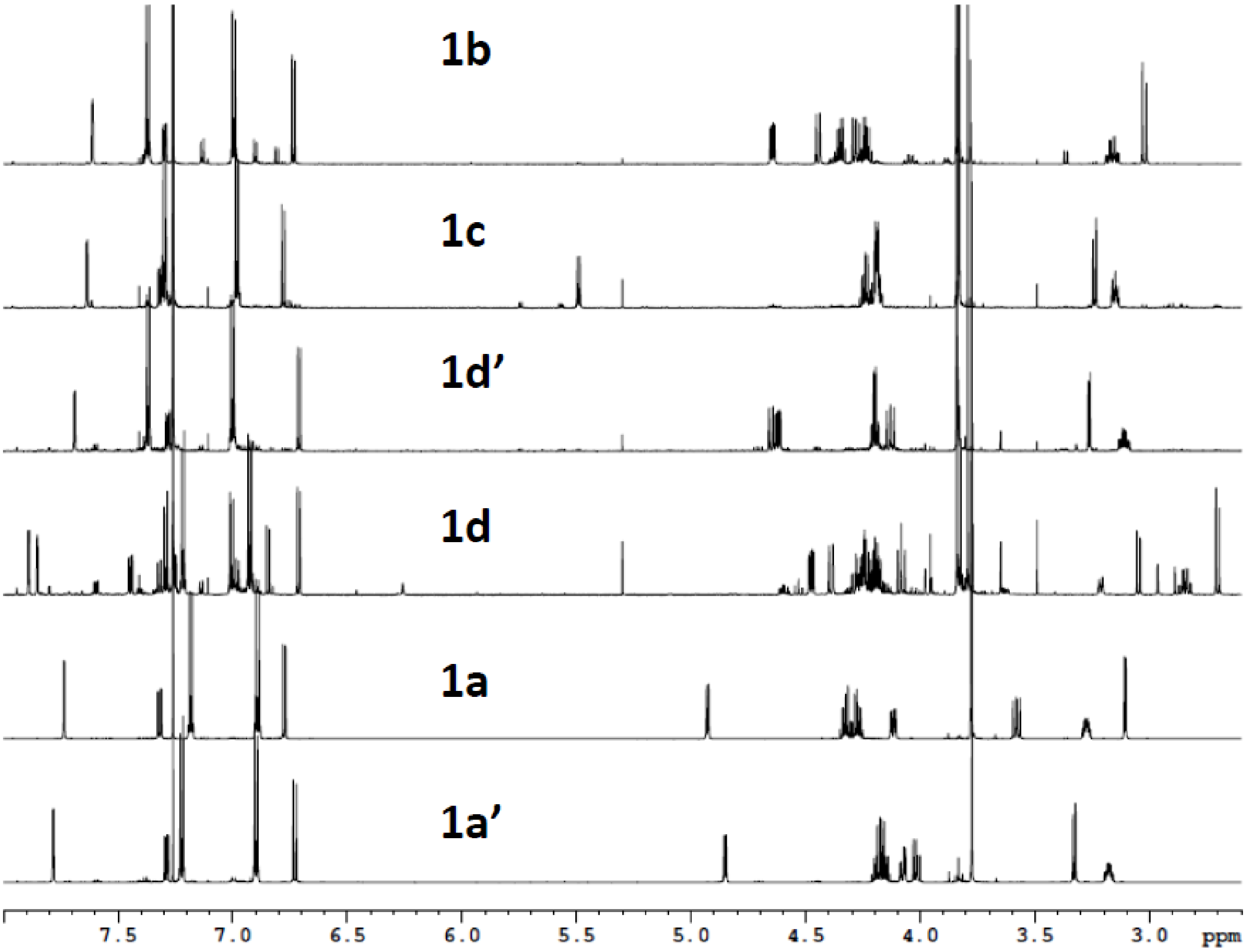


1

Reaction mixture has 8 diastereomers



^{1}NMR of 6 diastereomers of **11**



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O
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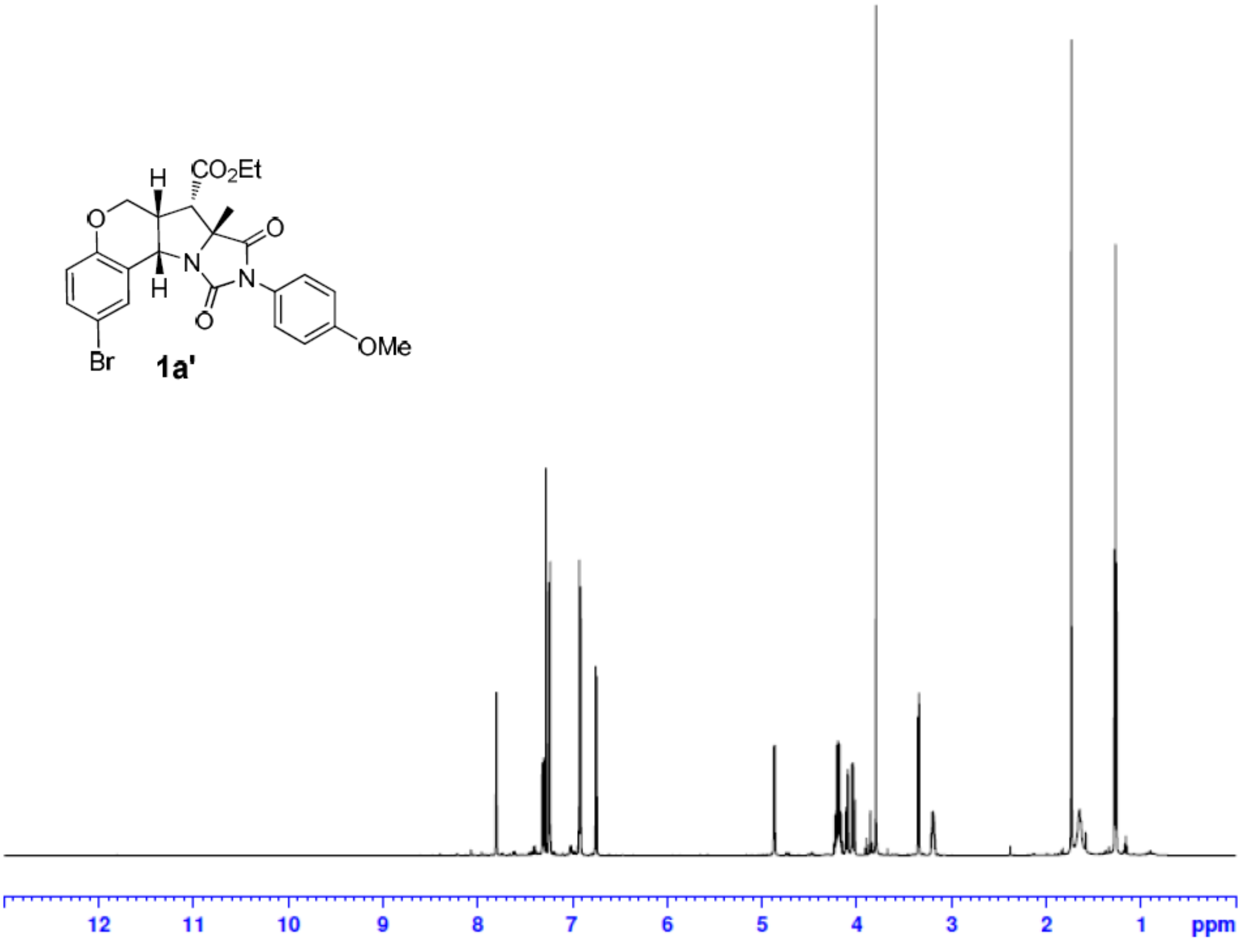
Br
OMe

1a'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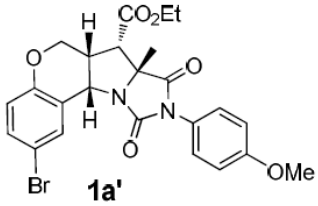
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1a'

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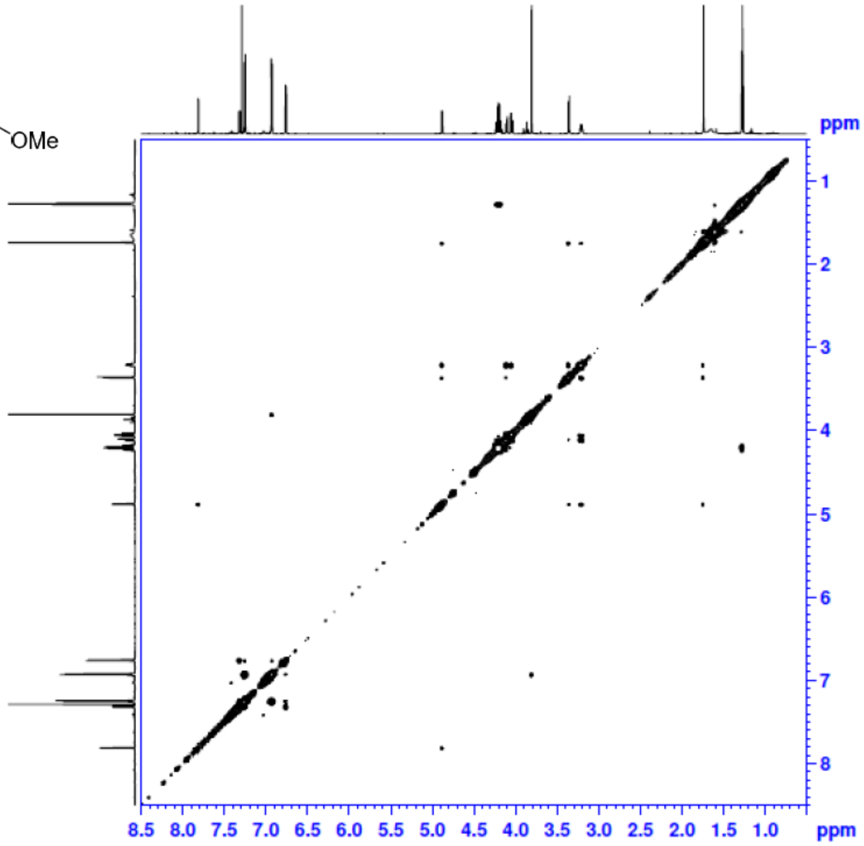
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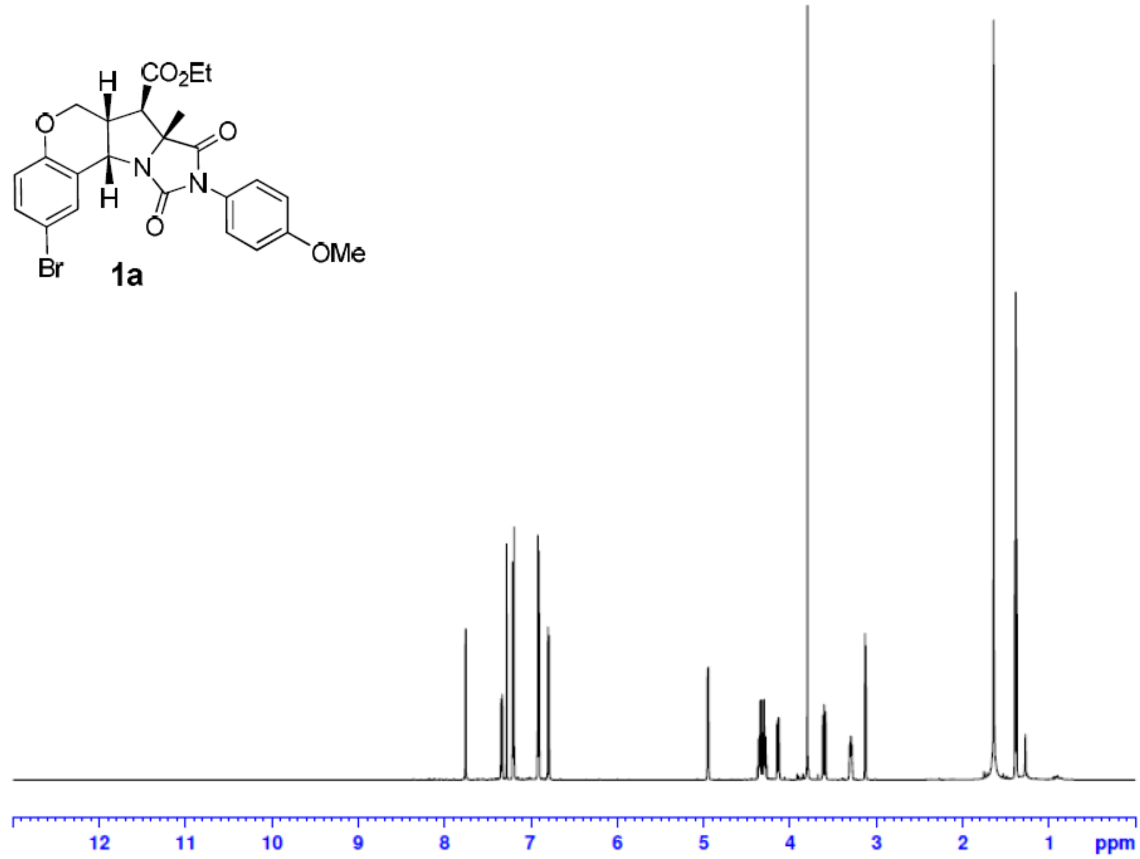

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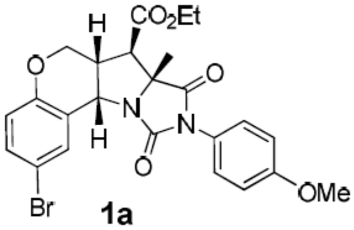

1a

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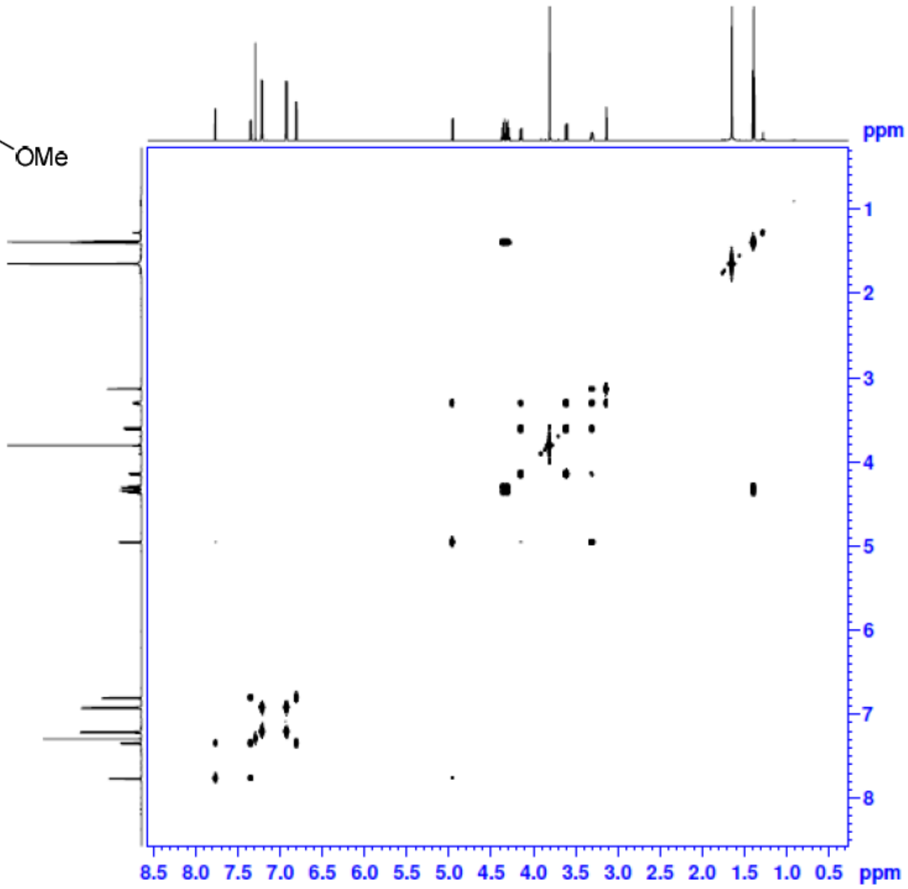

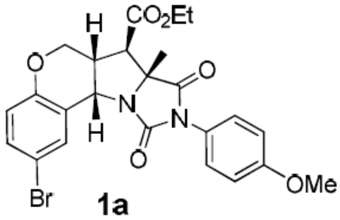

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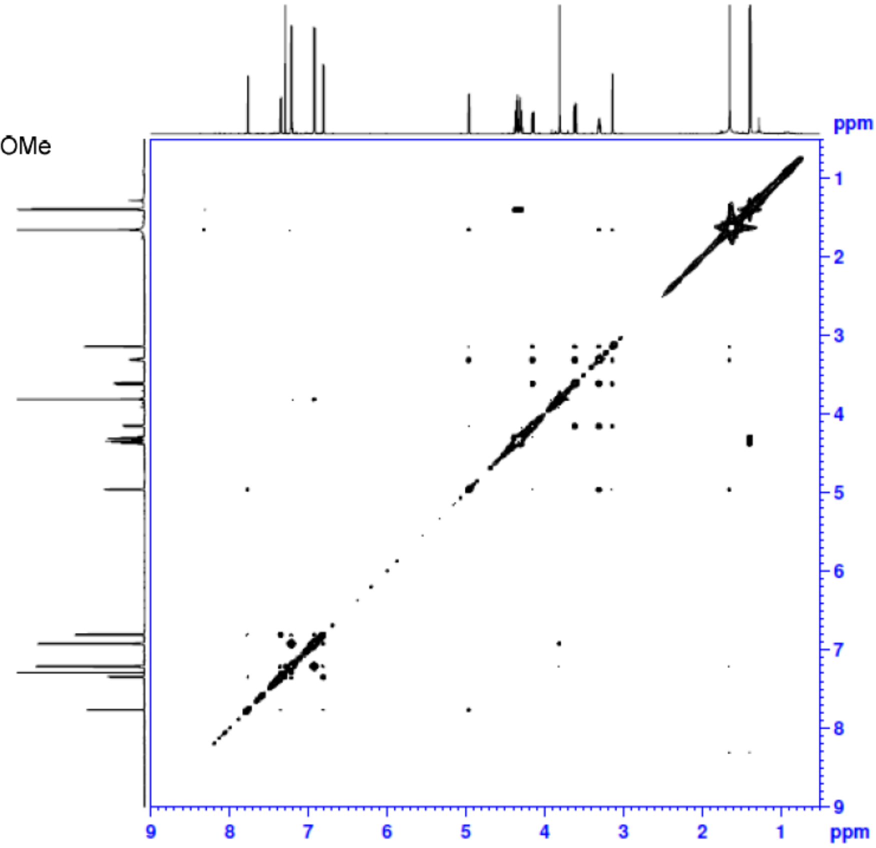

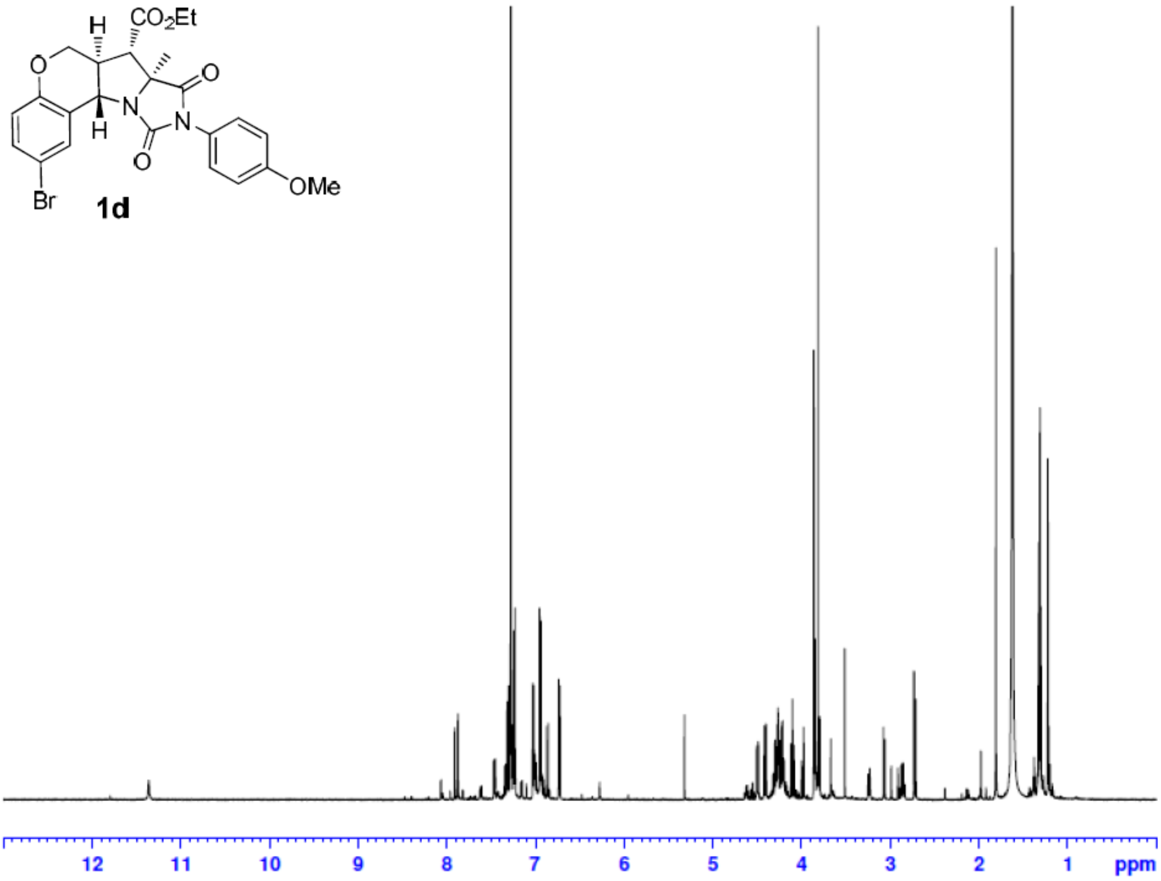
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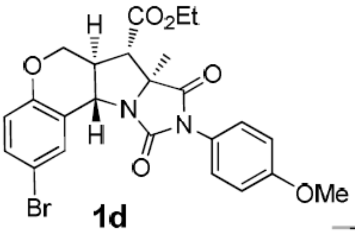

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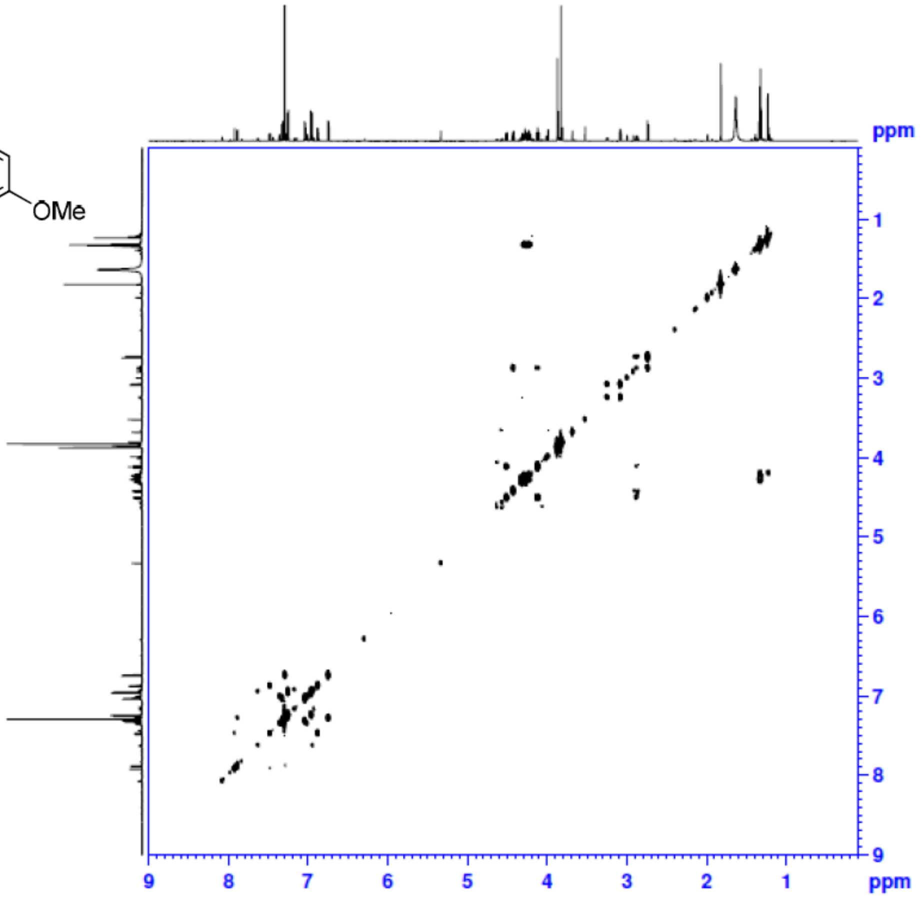

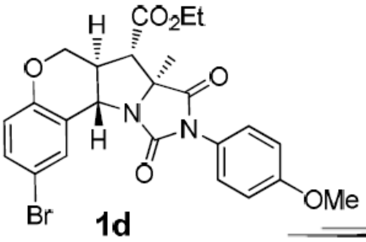

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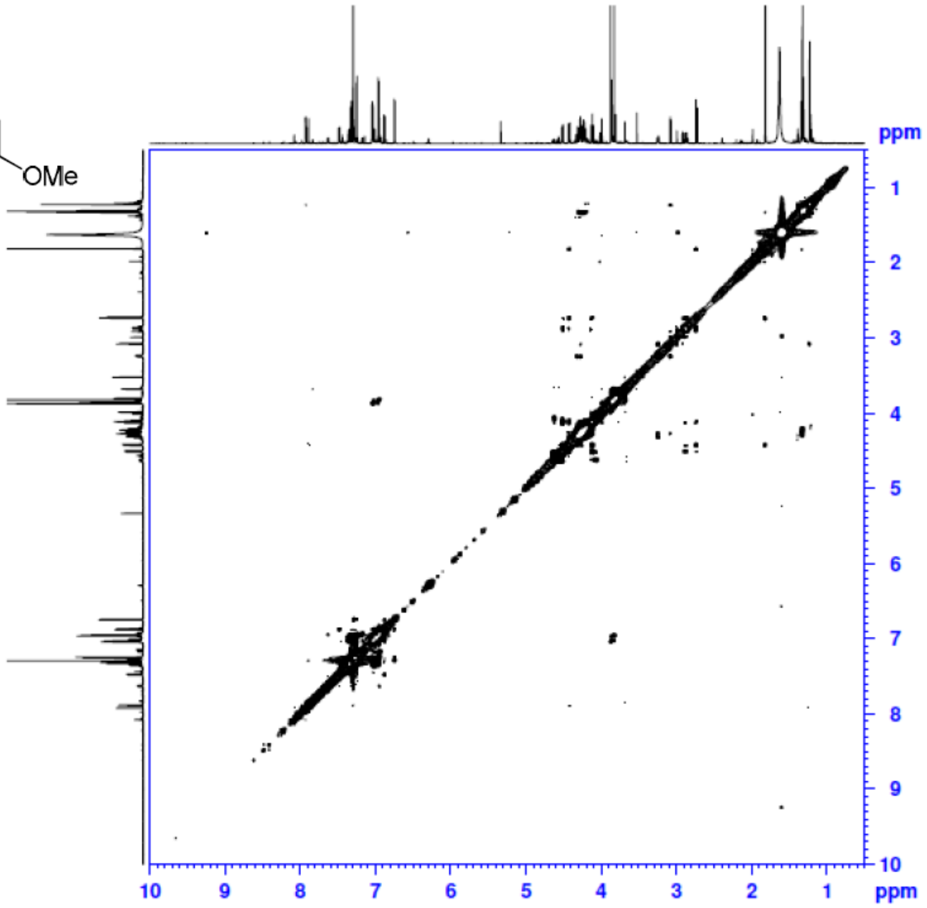

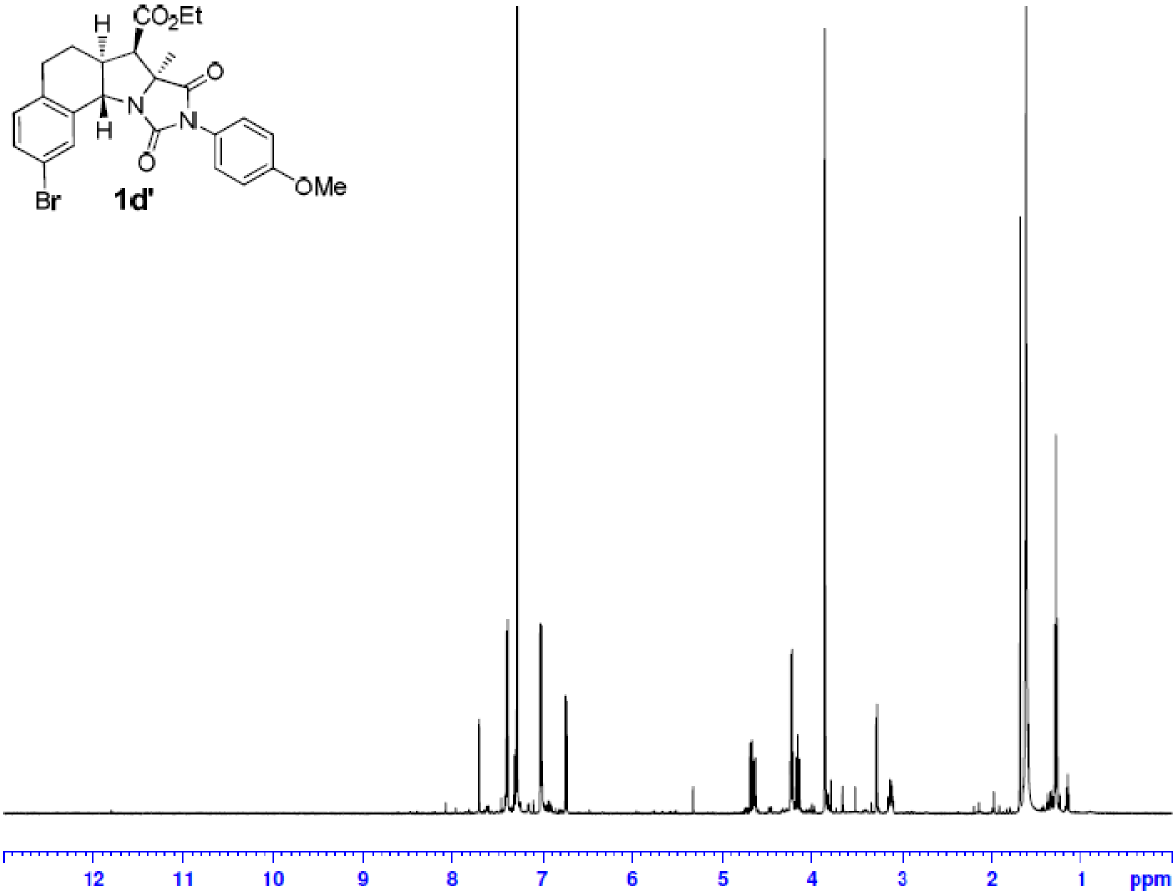
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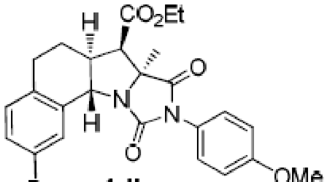

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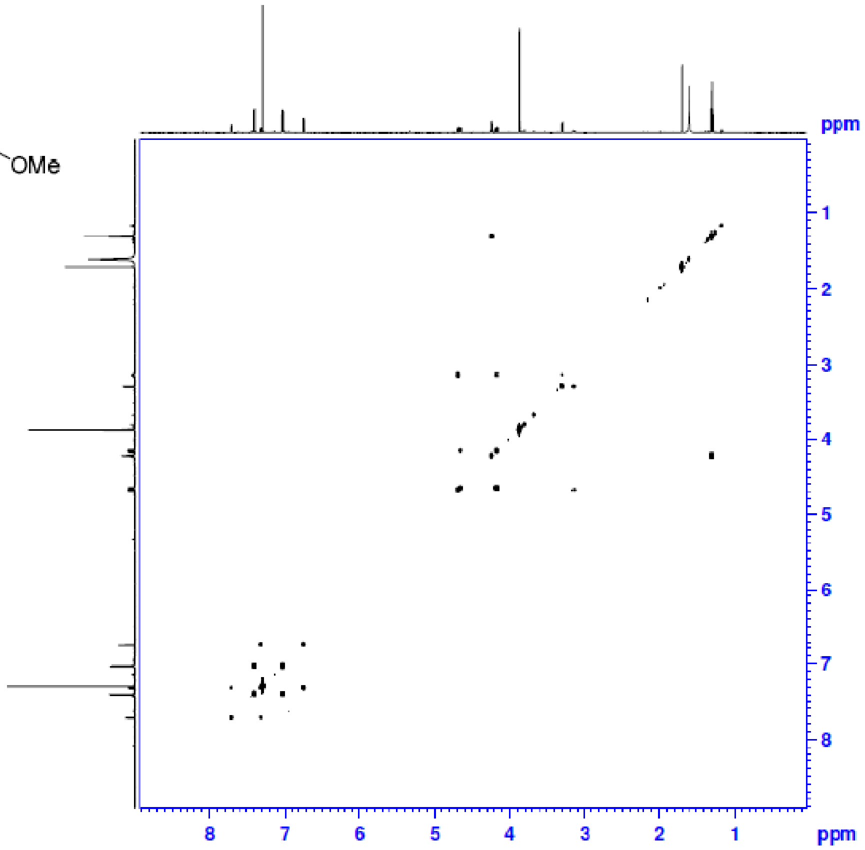

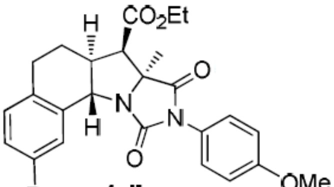

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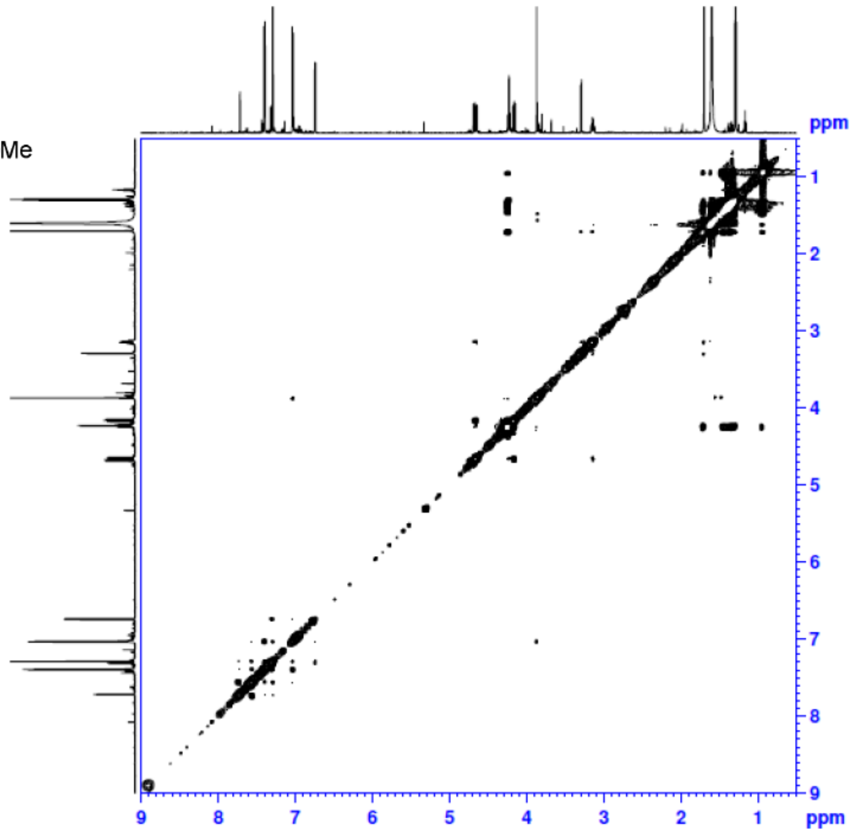

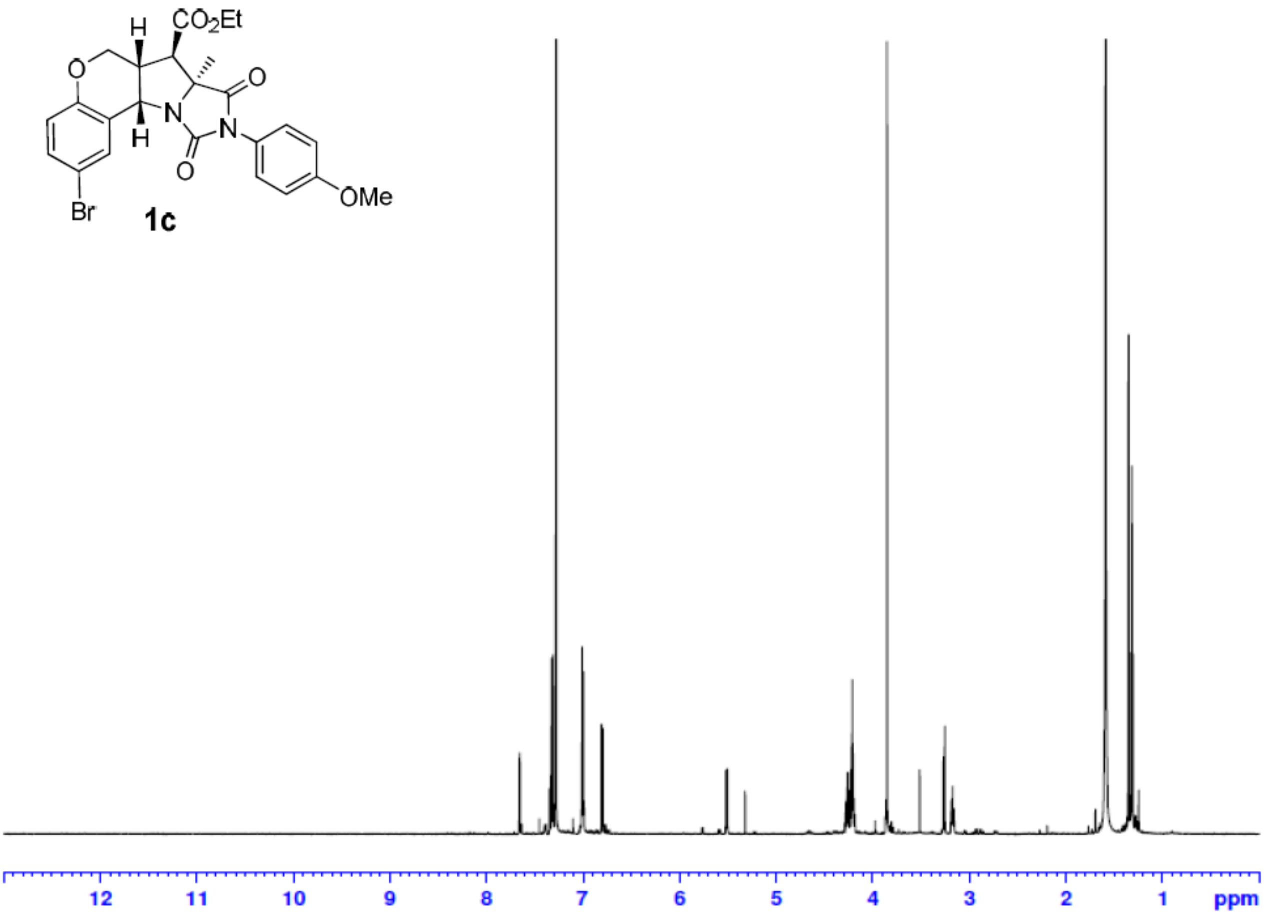

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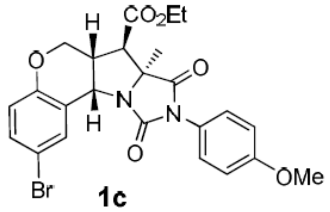

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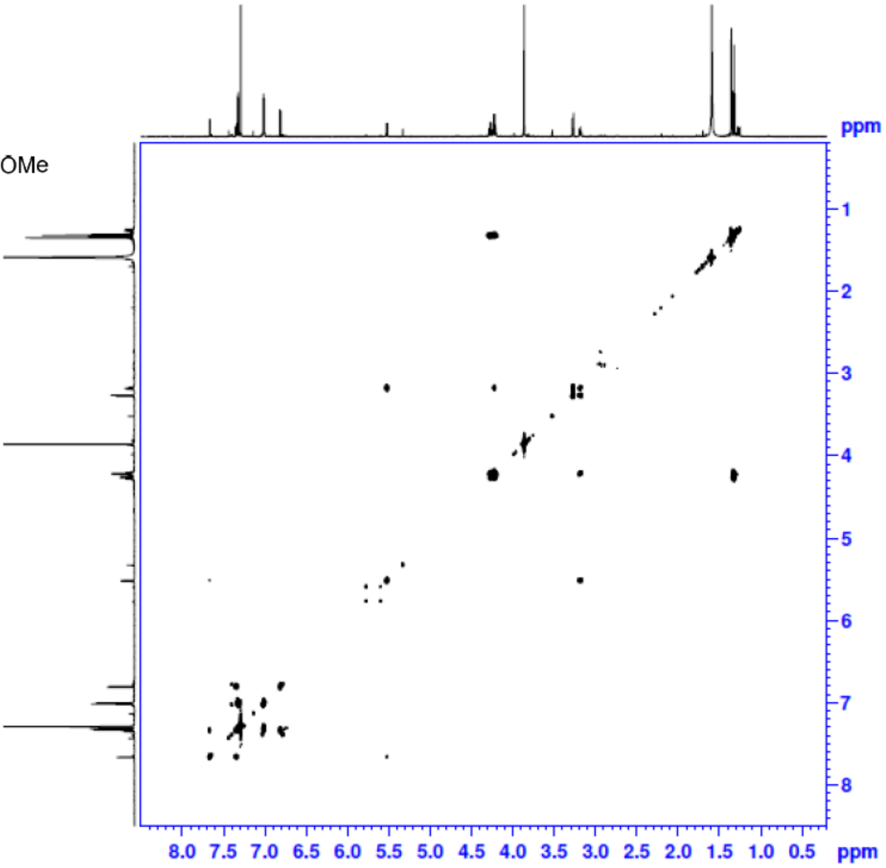

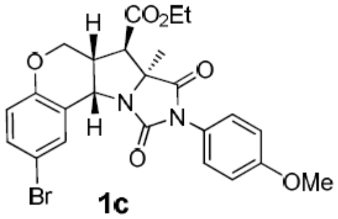

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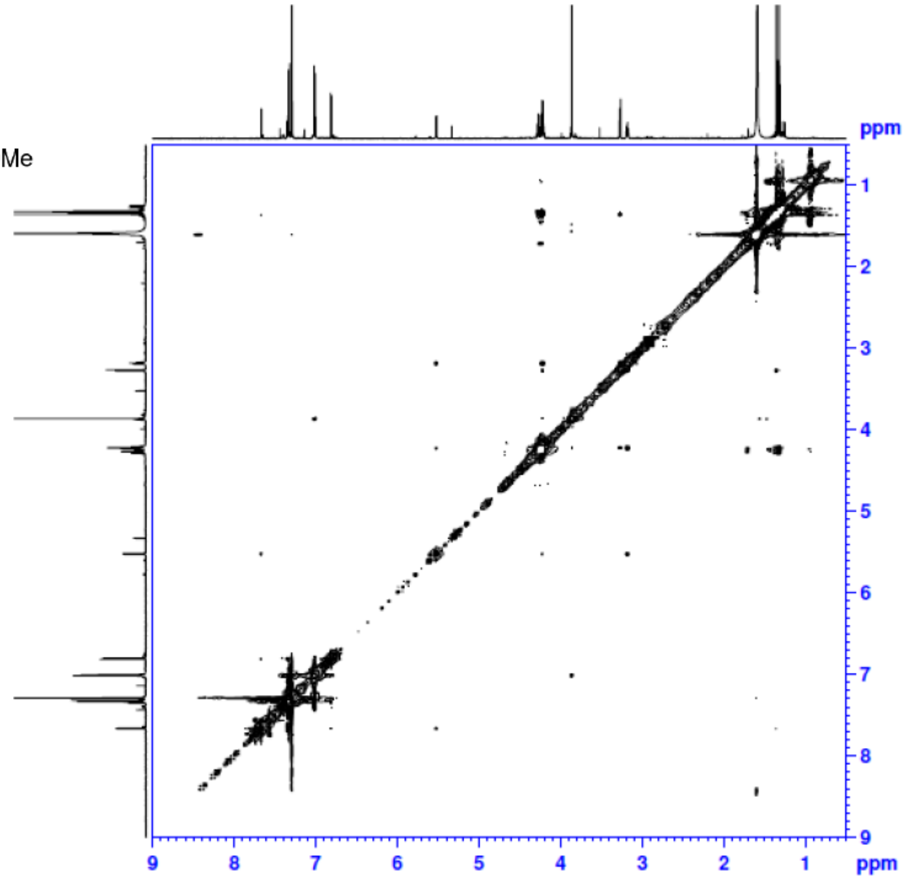

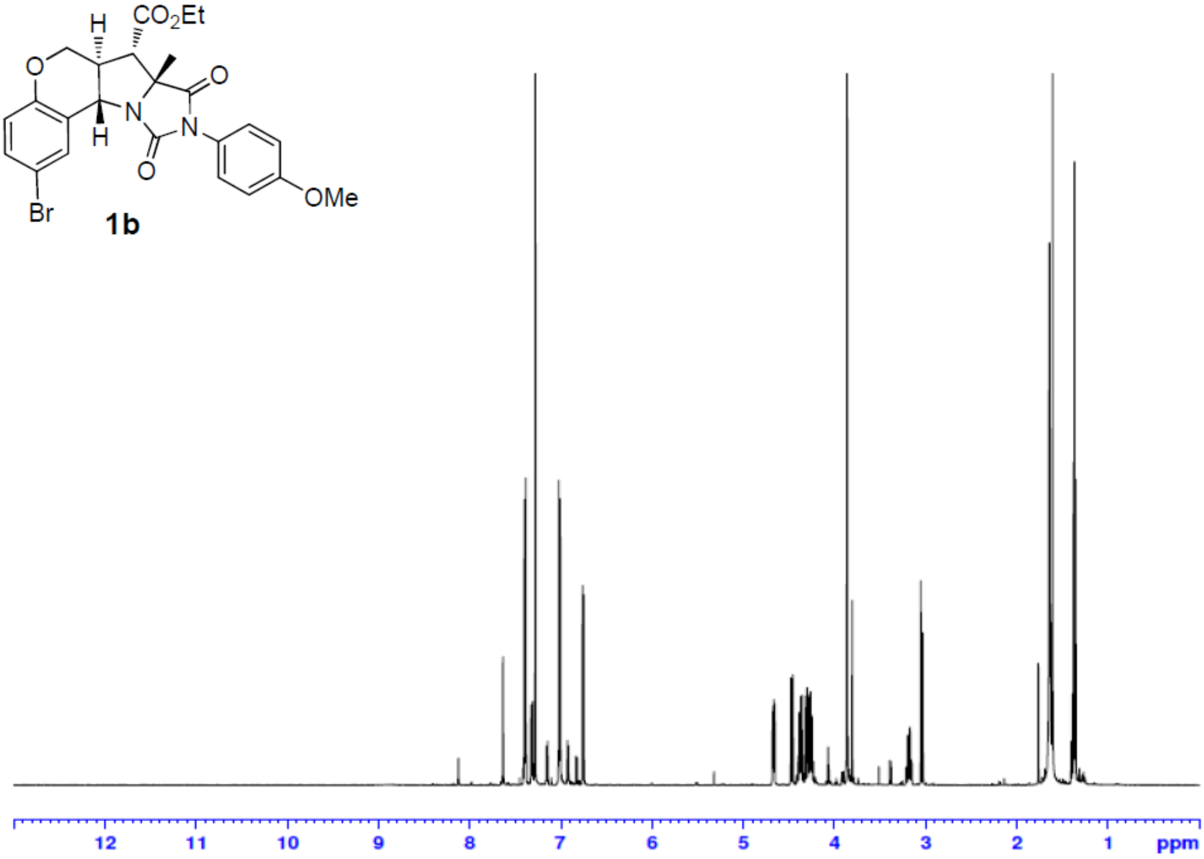

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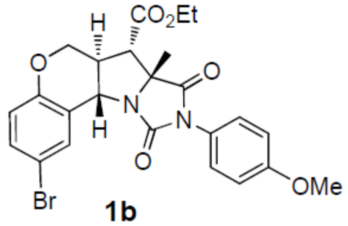

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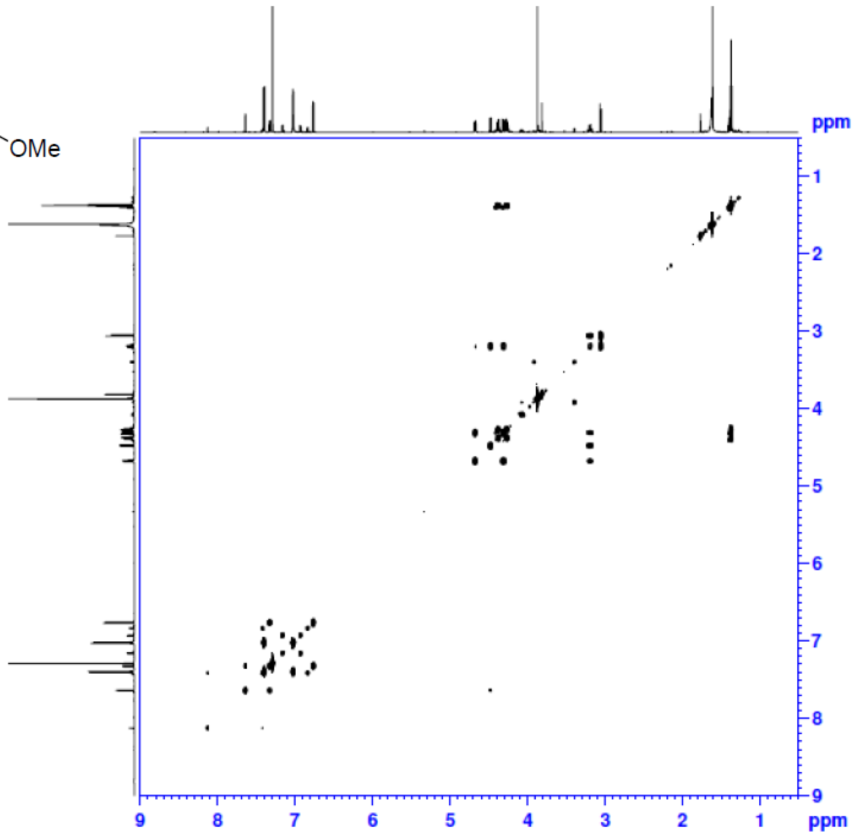

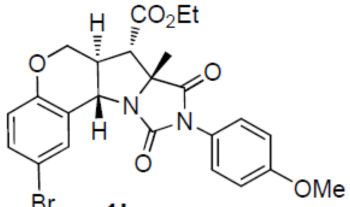

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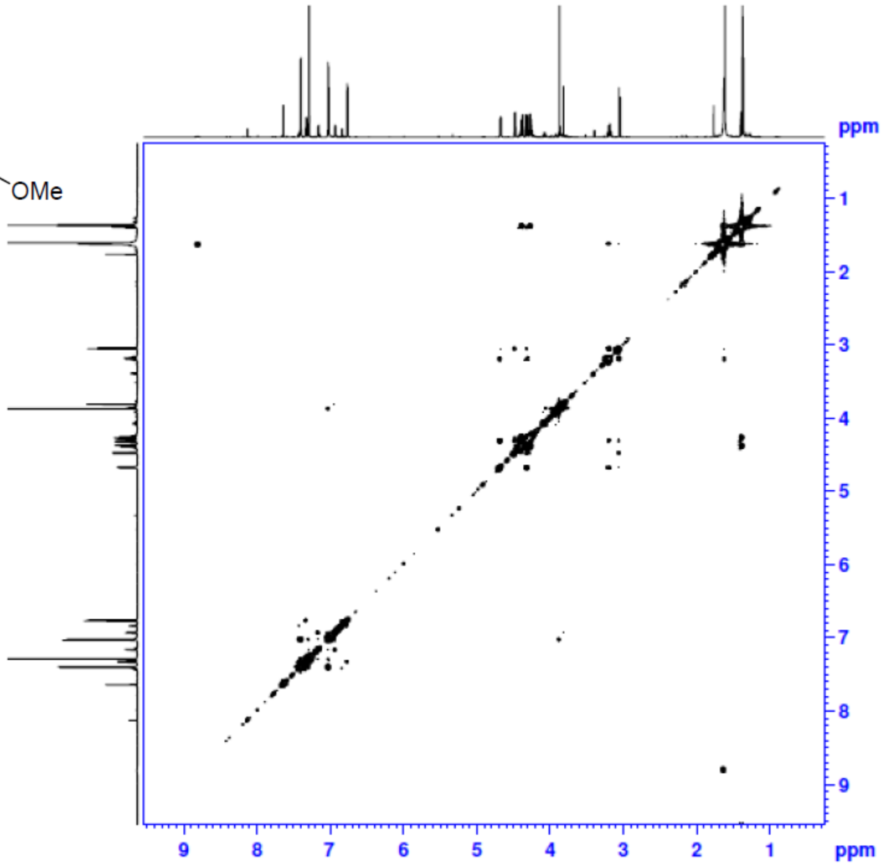

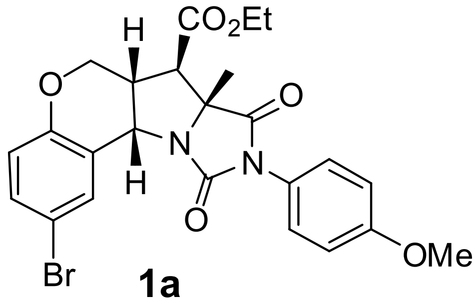
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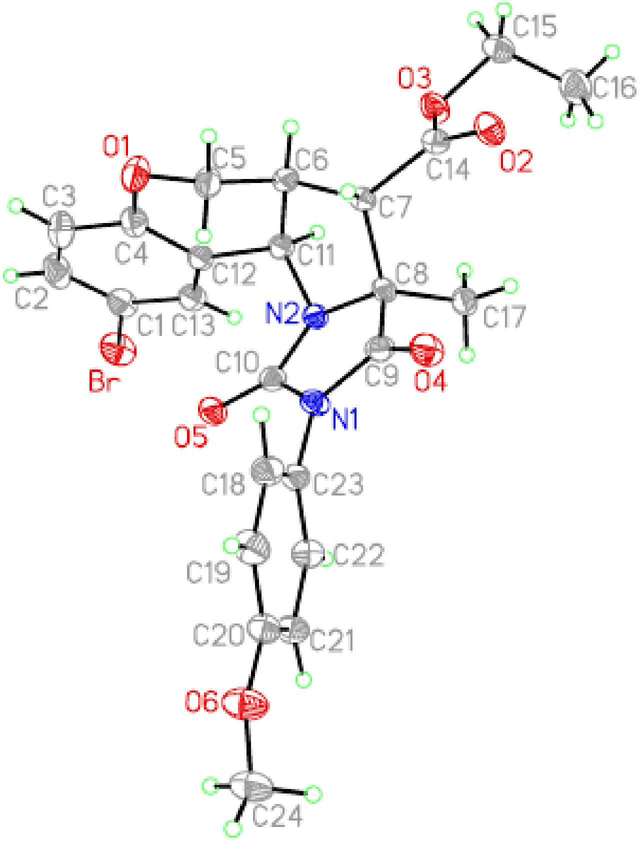
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