

Directed C–H Activation of 13 α -Estrone: A Pathway to Promising AKR1C Inhibitors *via* Docking and Biological Studies

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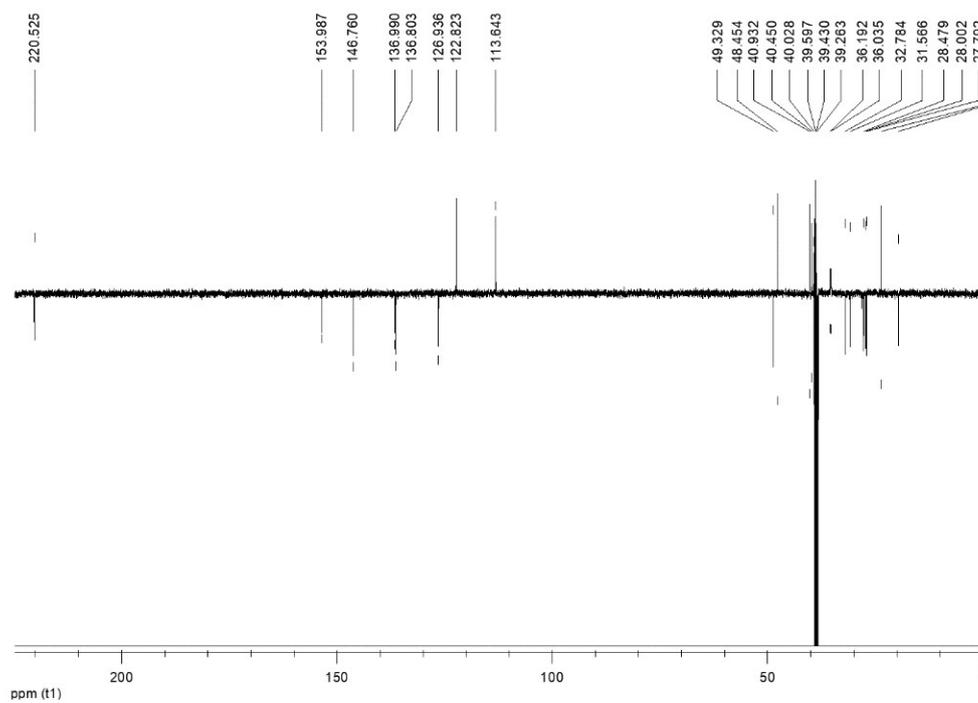
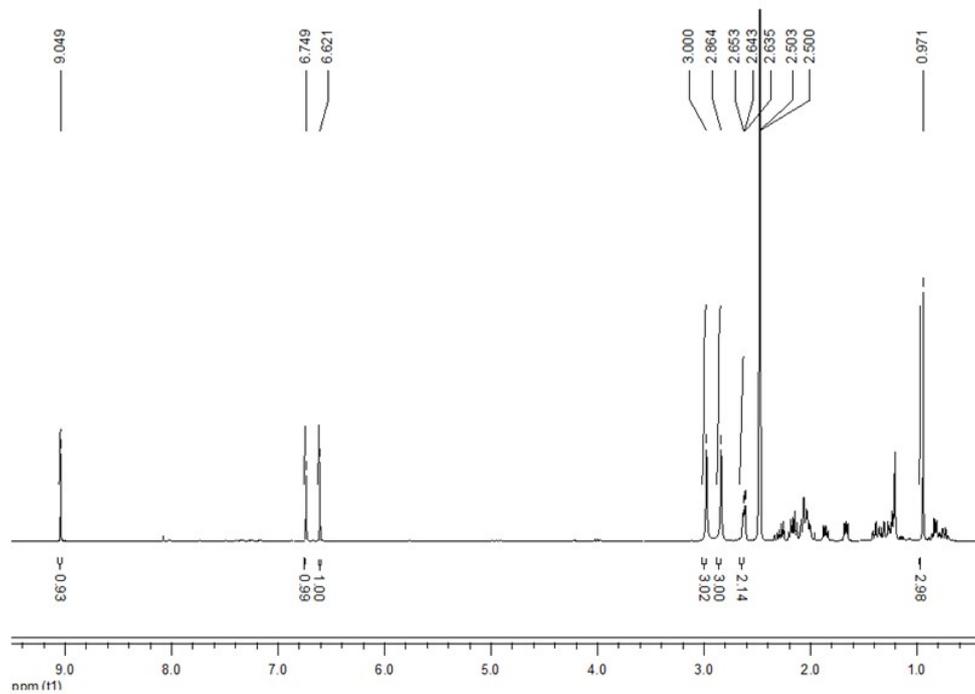
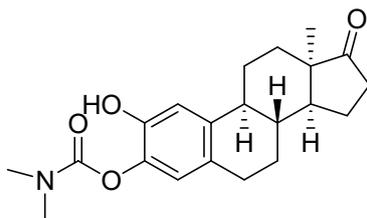
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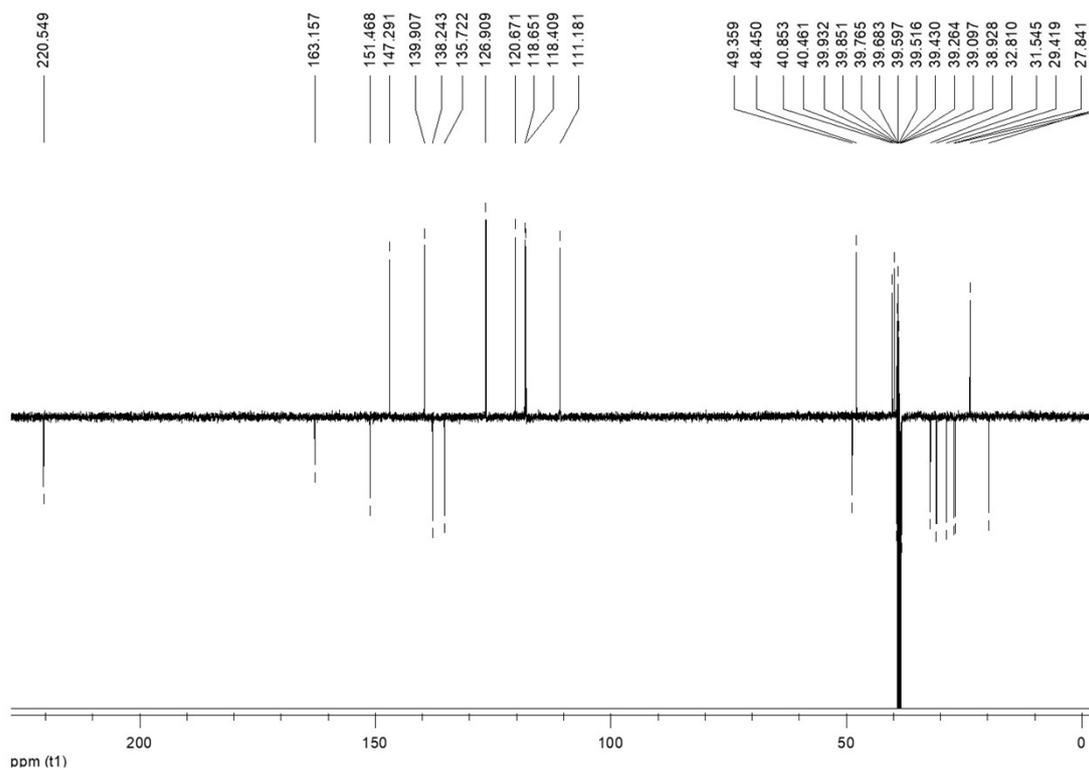
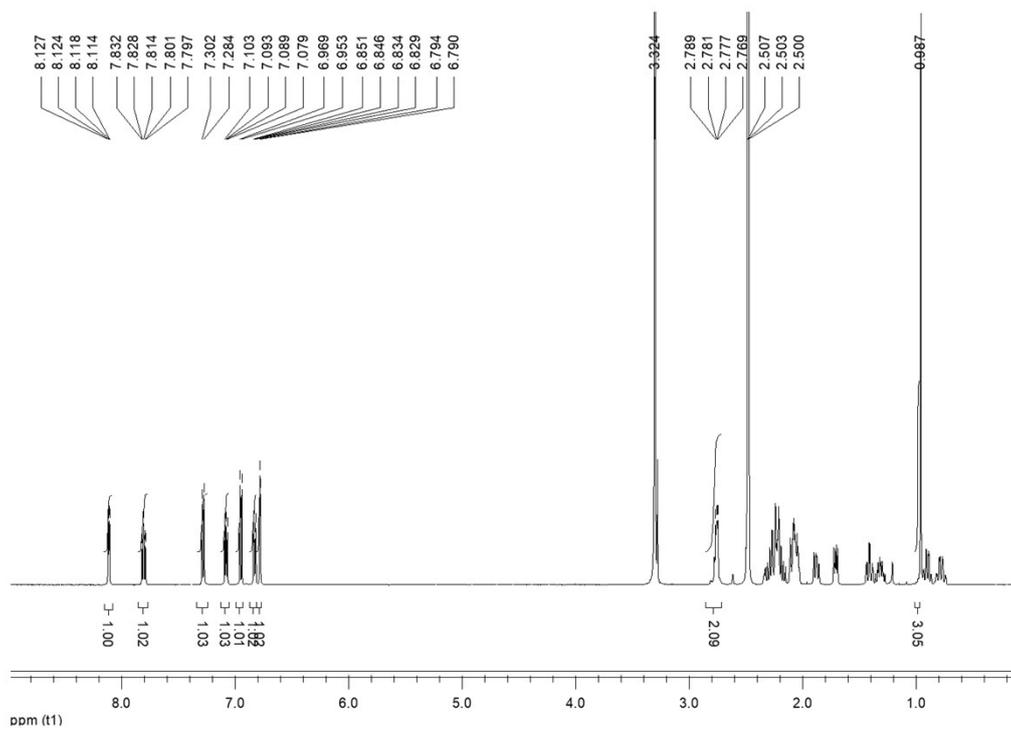
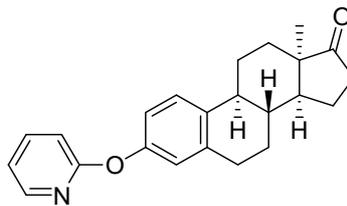
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¹H and ¹³C NMR spectra of the compounds

¹H and ¹³C-NMR spectrum of compound 5



^1H and ^{13}C -NMR spectrum of compound **6a**



^1H and ^{13}C -NMR spectrum of compound **6b**

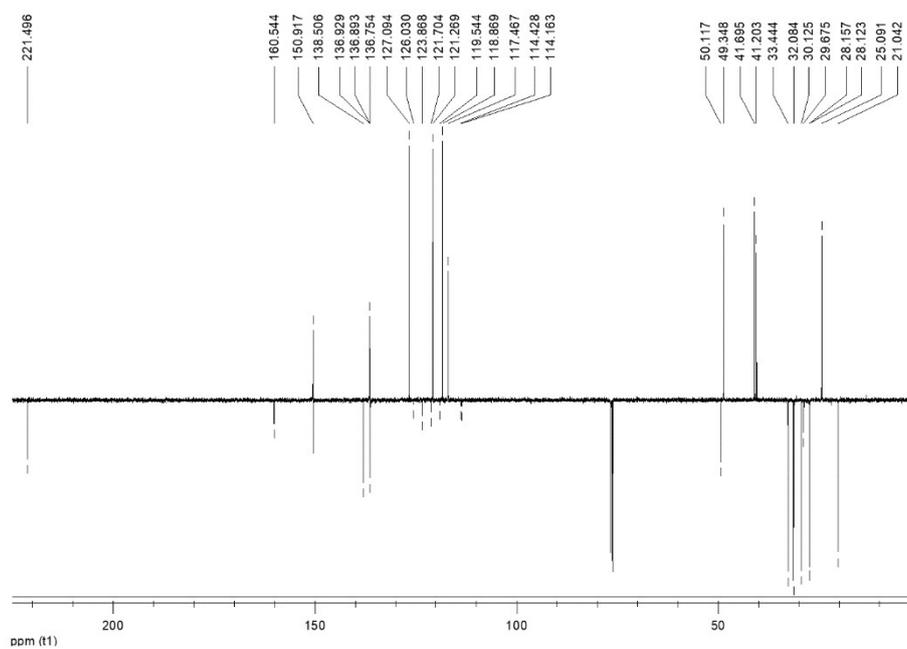
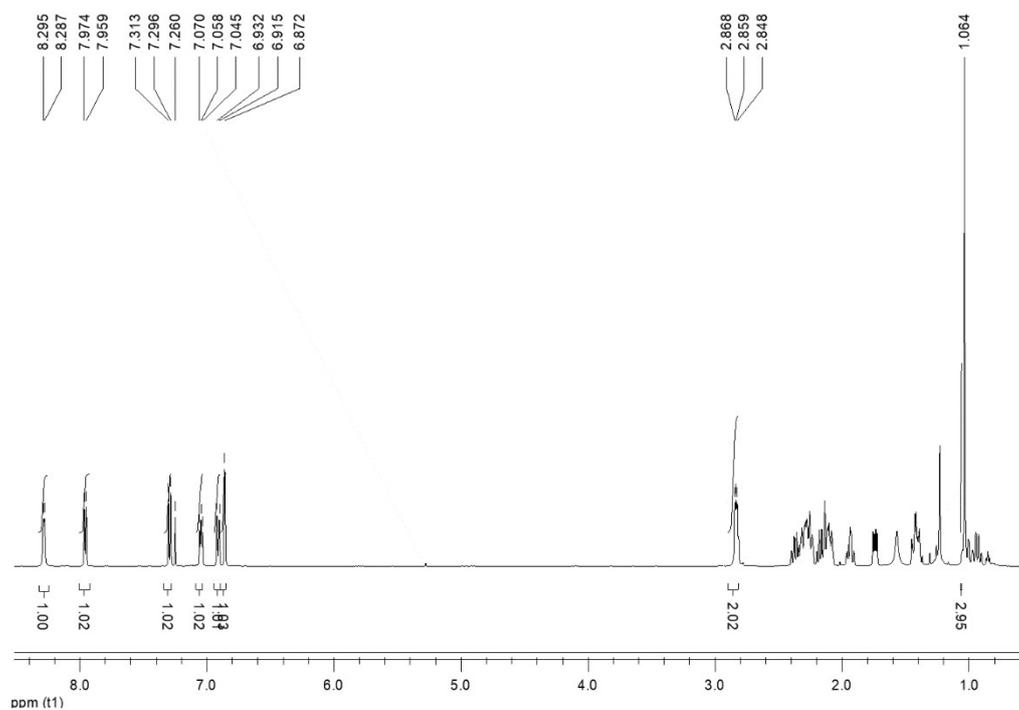
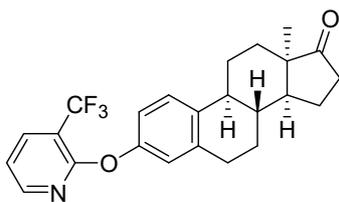
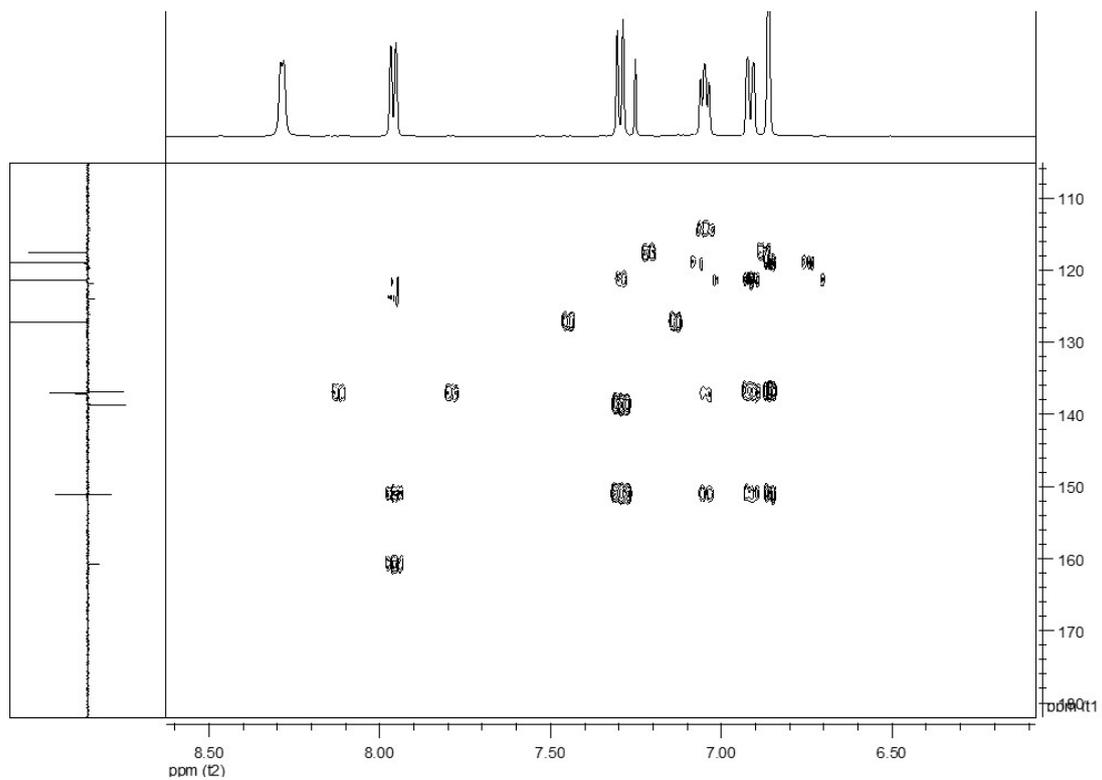
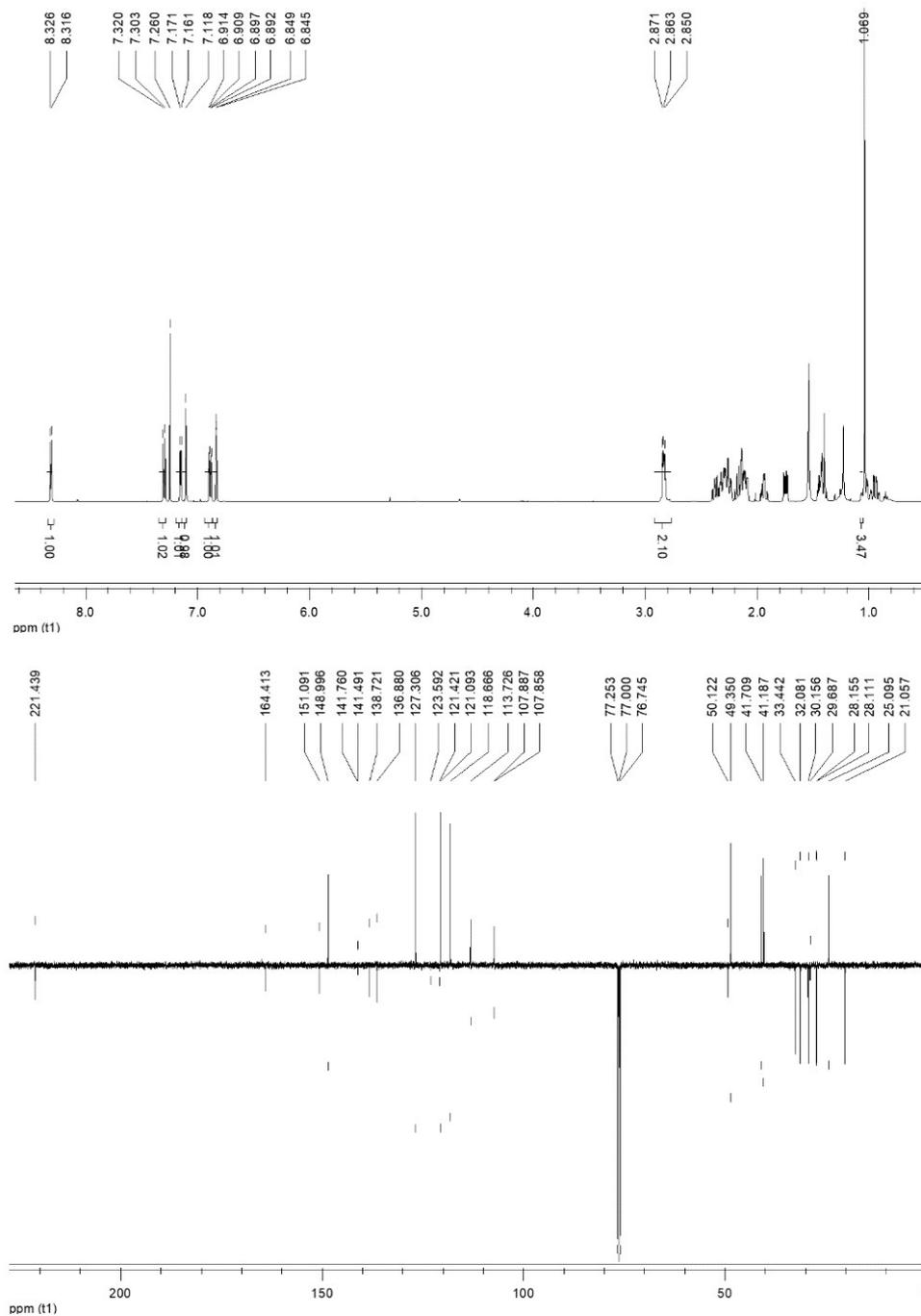
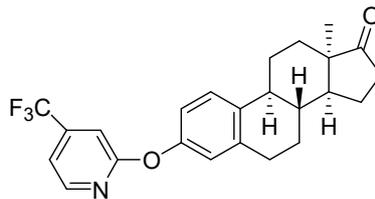


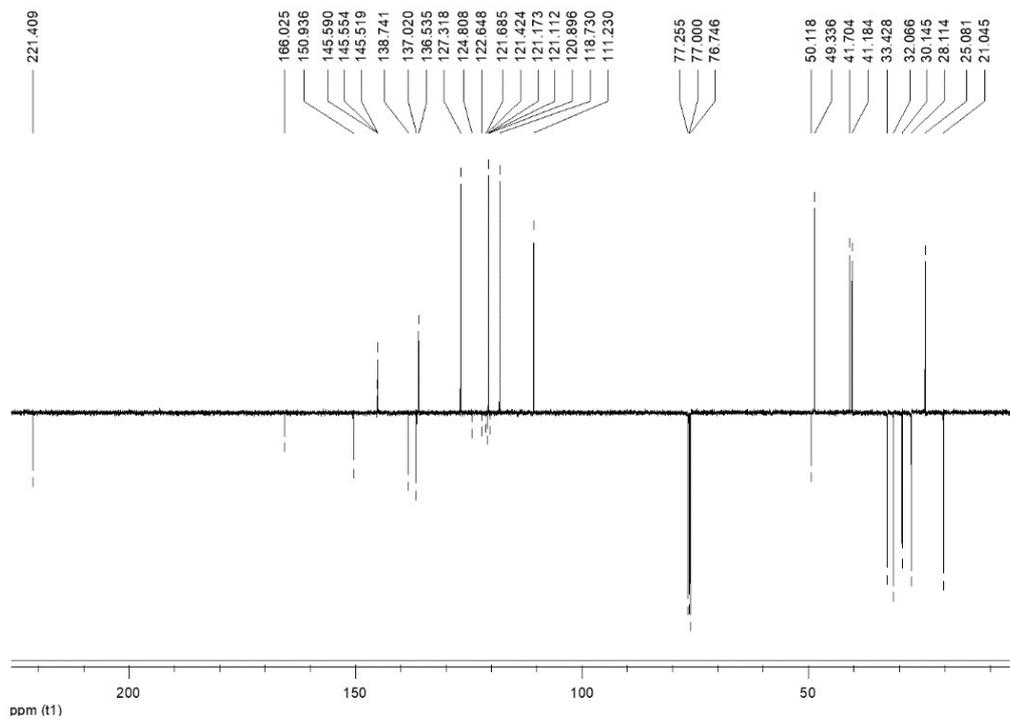
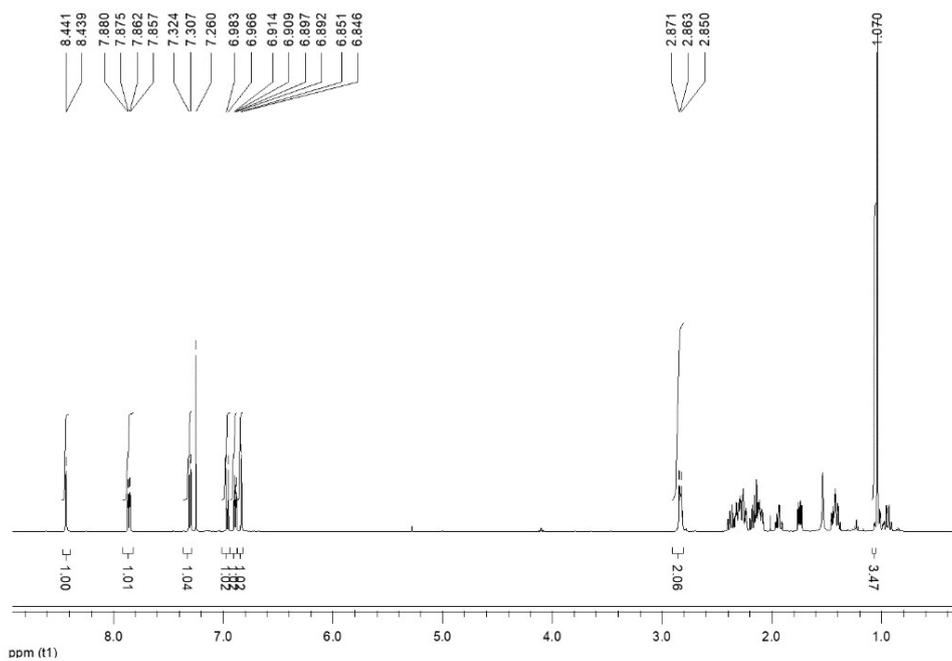
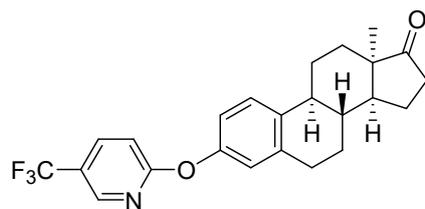
Figure SHMBC: A relevant region of the HMBC spectrum of compound **6b**



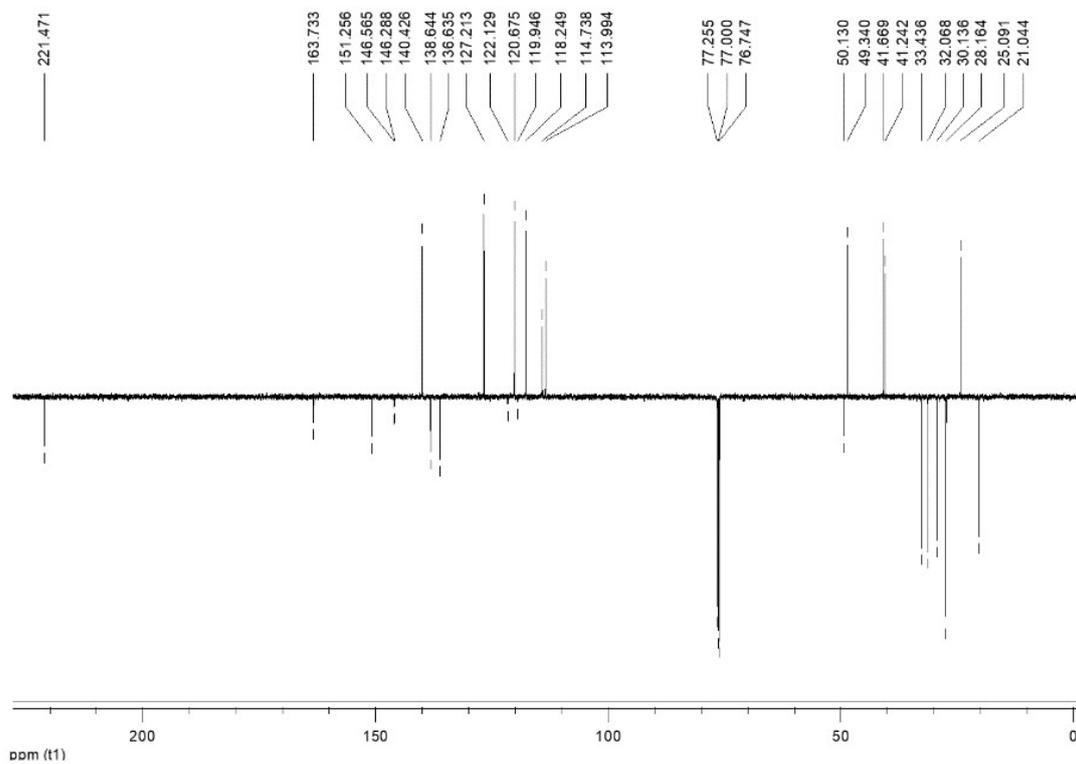
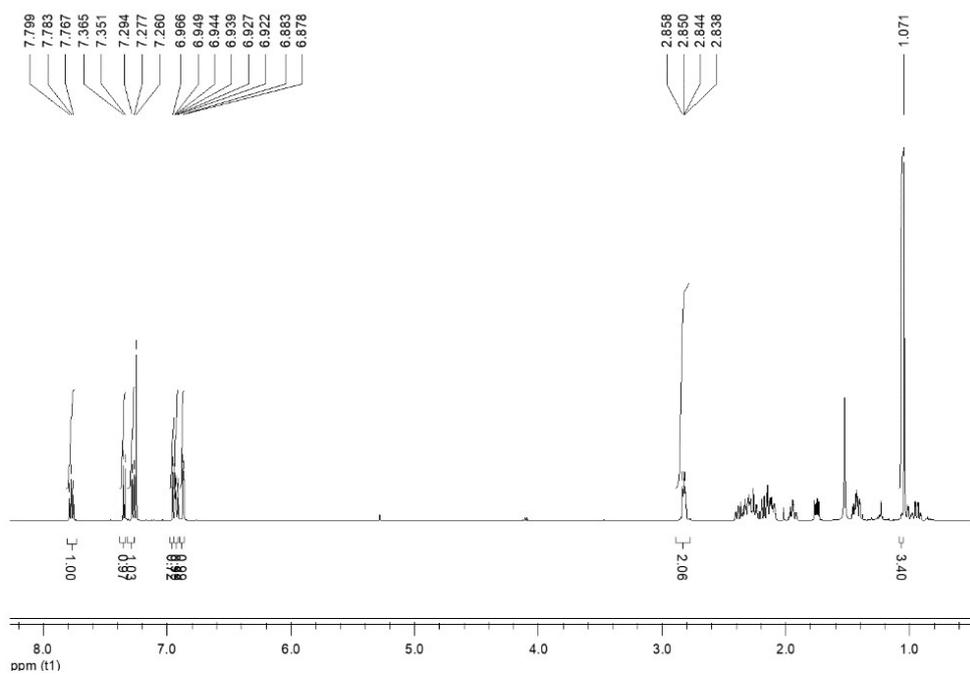
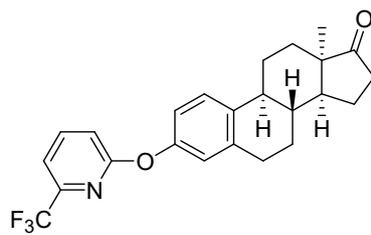
¹H and ¹³C-NMR spectrum of compound **6c**



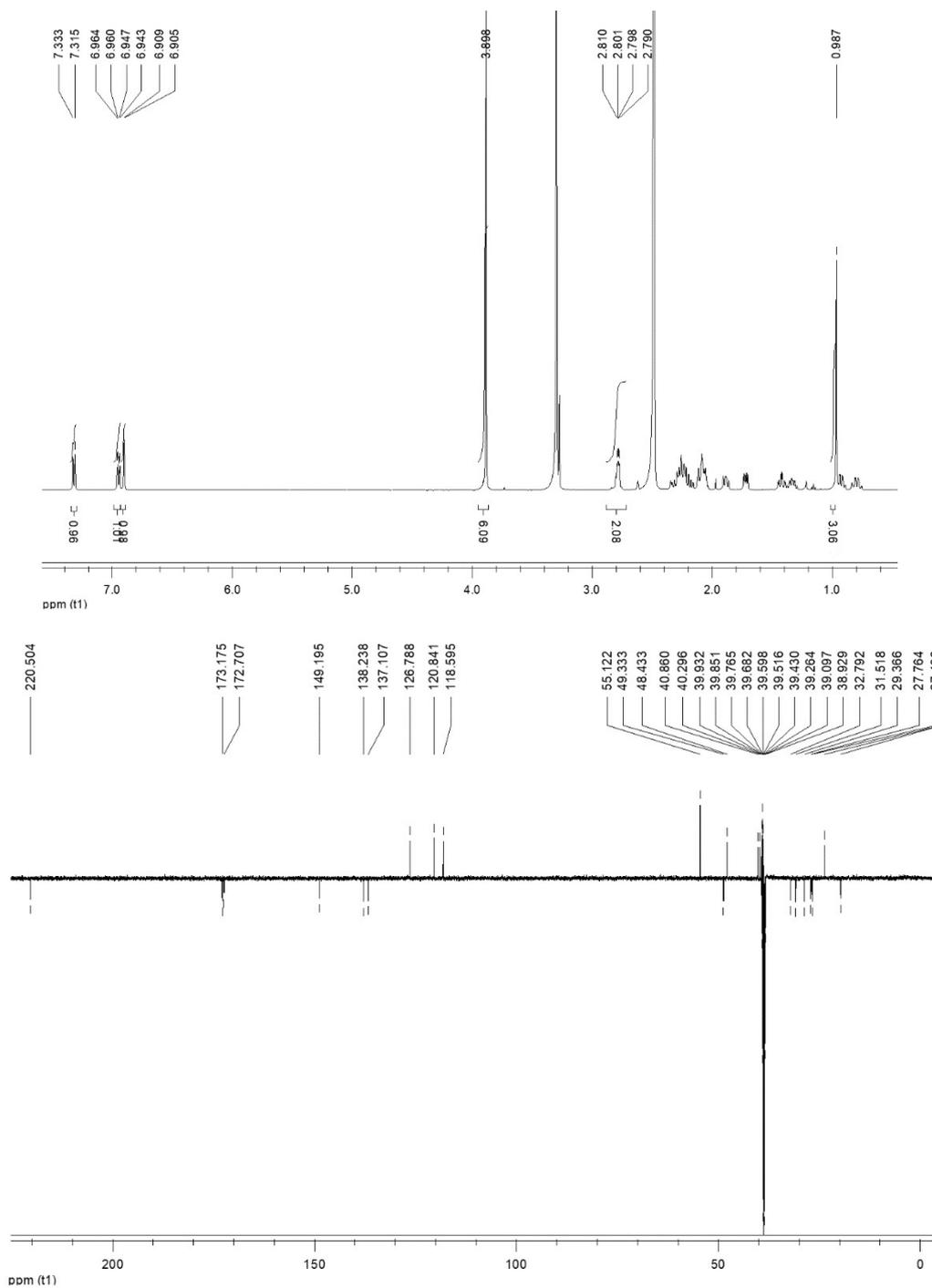
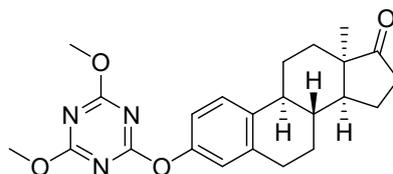
¹H and ¹³C-NMR spectrum of compound **6d**



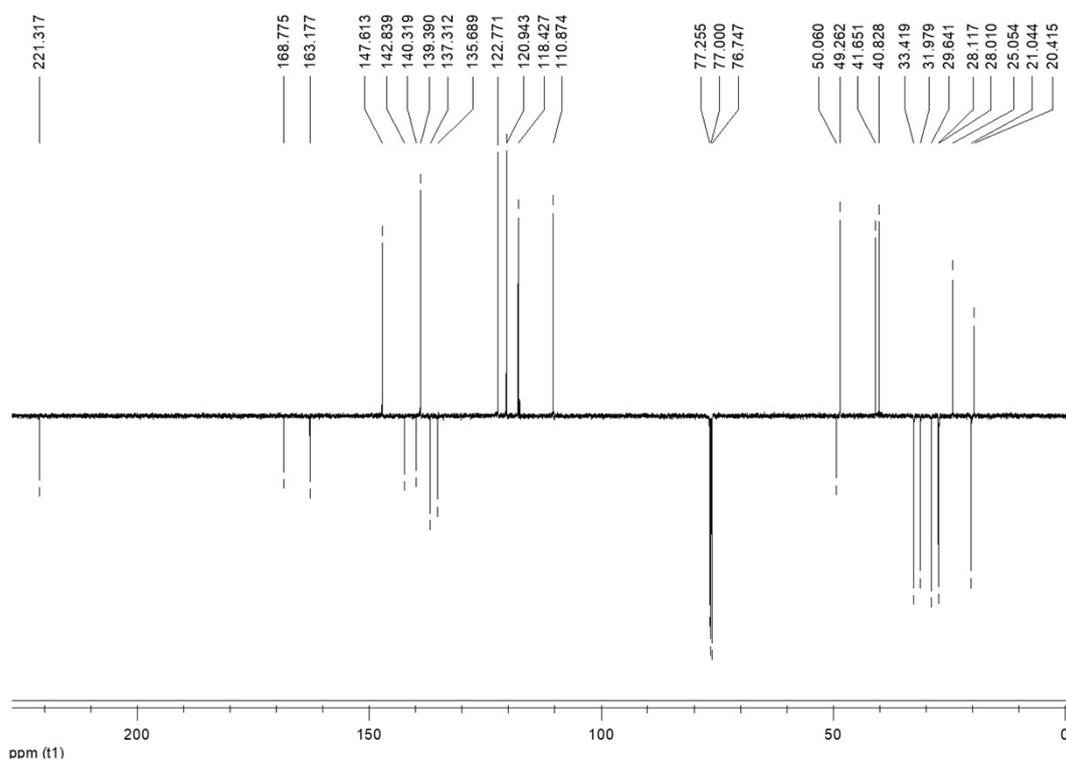
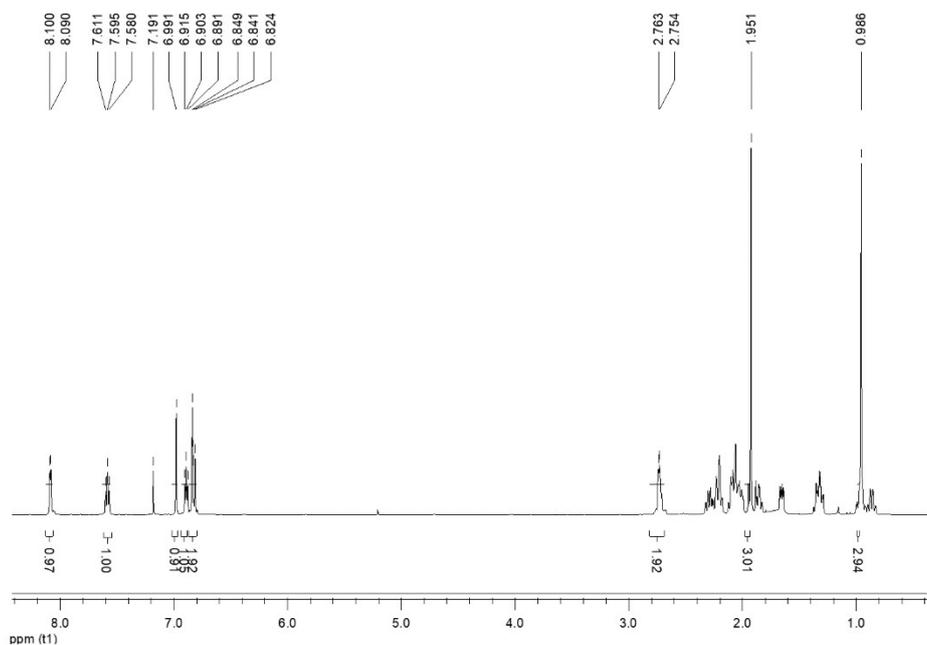
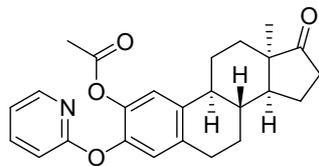
¹H and ¹³C-NMR spectrum of compound 6e



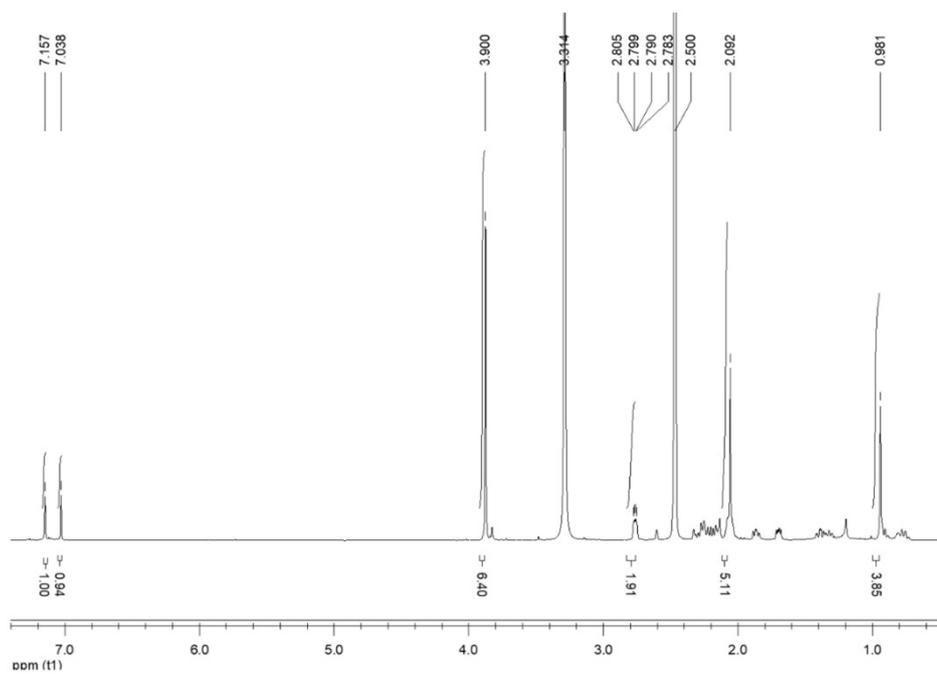
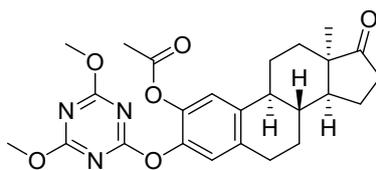
¹H and ¹³C-NMR spectrum of compound 7

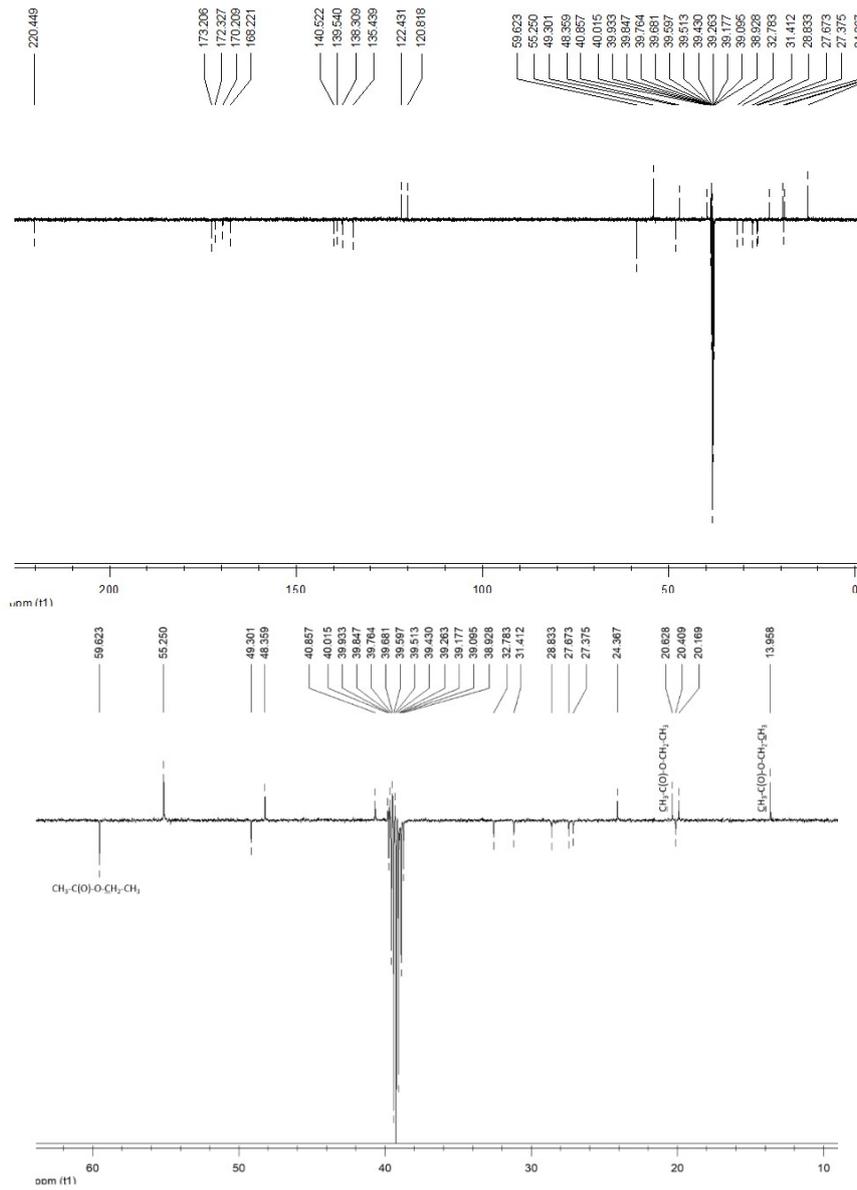


¹H and ¹³C-NMR spectrum of compound **8**

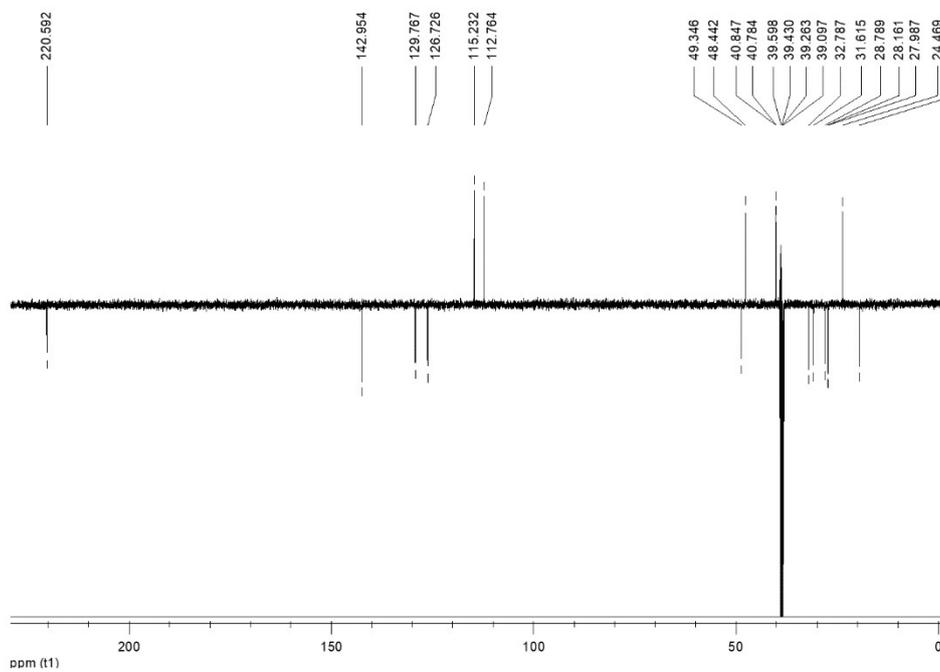
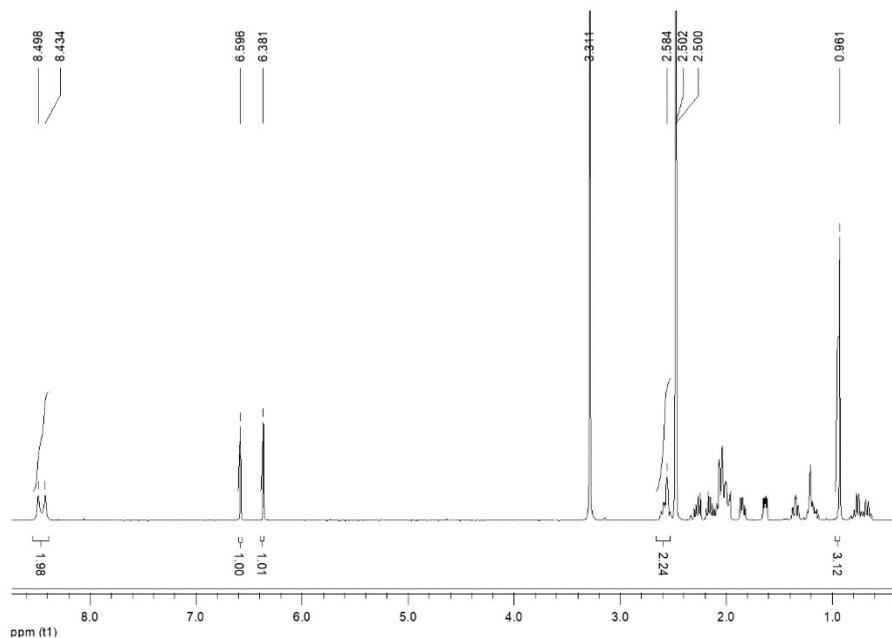
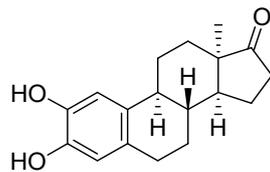


^1H and ^{13}C -NMR spectrum of compound **9**

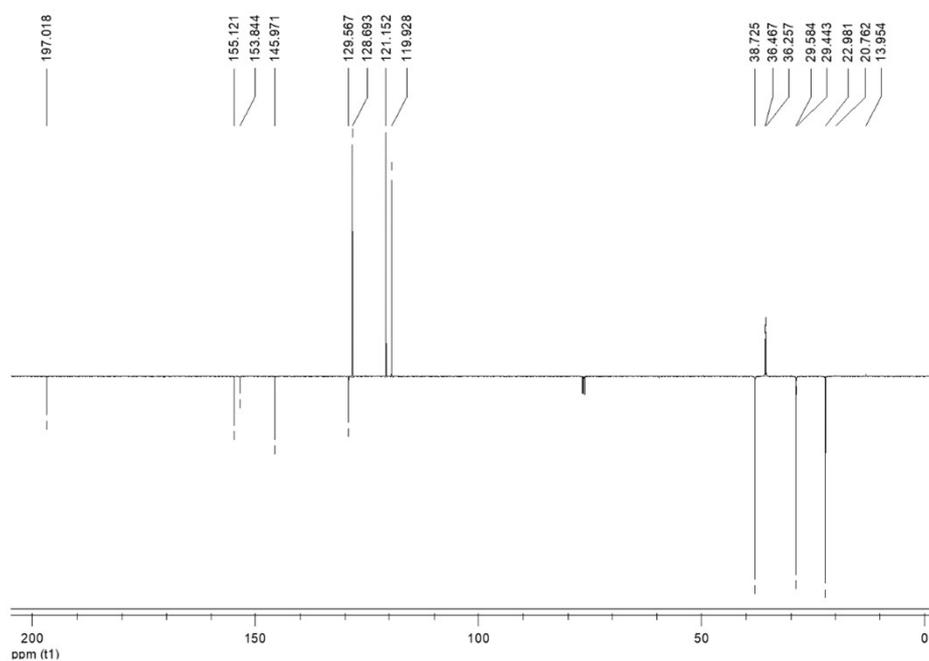
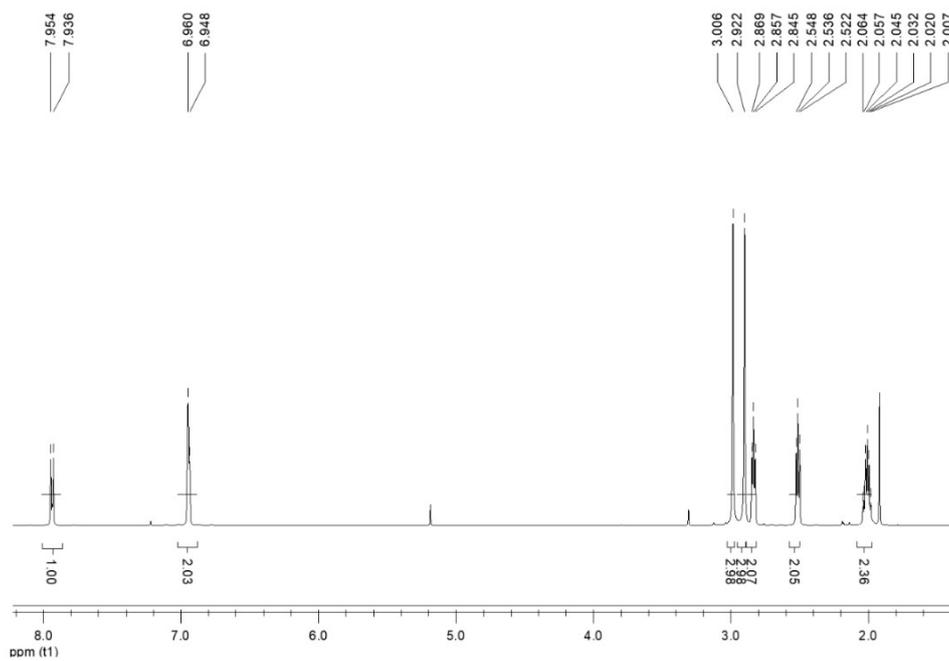
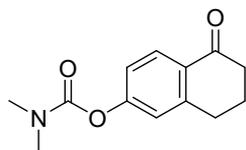




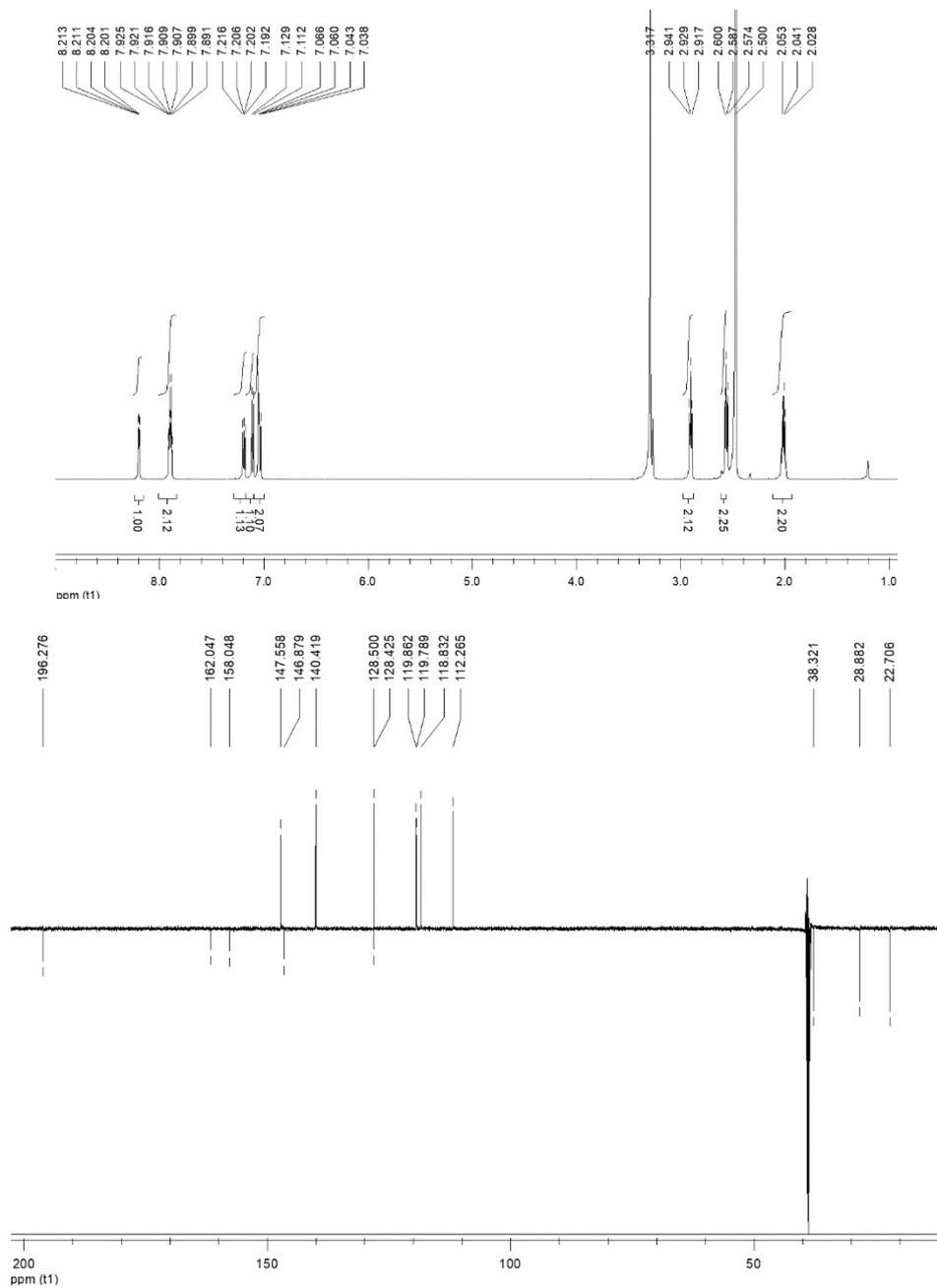
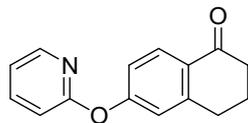
^1H and ^{13}C -NMR spectrum of compound **11**



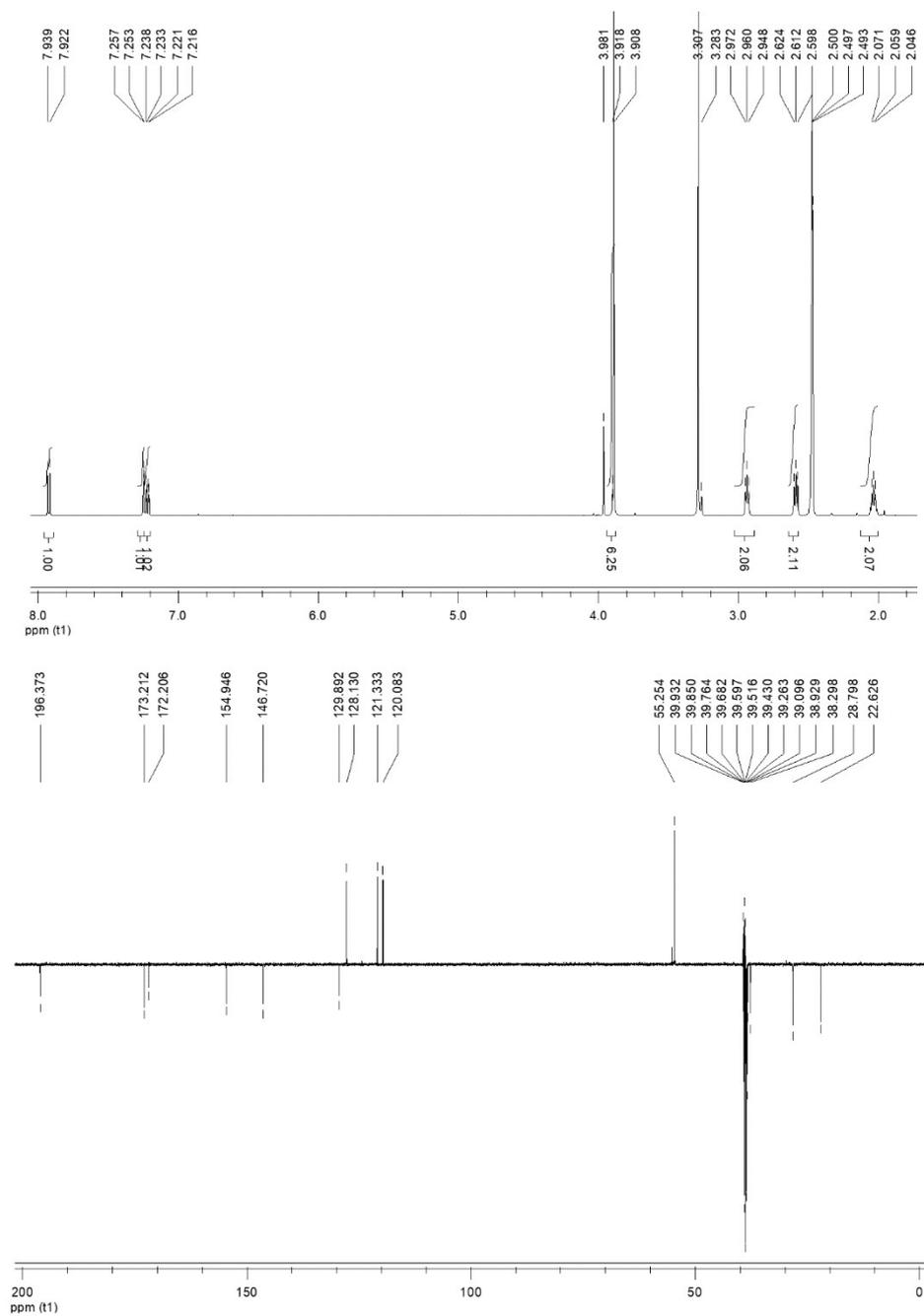
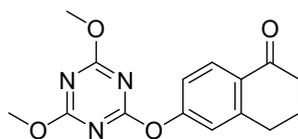
^1H and ^{13}C -NMR spectrum of compound **13**

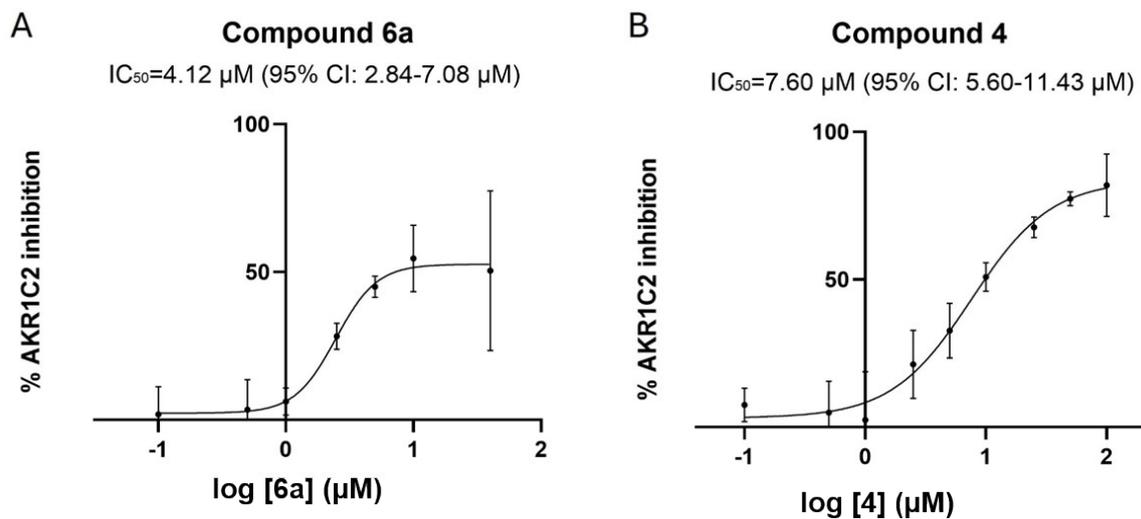


^1H and ^{13}C -NMR spectrum of compound **14**



¹H and ¹³C-NMR spectrum of compound **15**





In silico studies

Table: Target selection. UNIPROT – Uniprot protein code, PDBID - RCSB PDB protein code, resolution – resolution of X-ray crystal structure in Å, ligand – presence of a ligand in protein active site and RCSB PDB ligand code, cofactor - presence of a co-factor in the protein co-factor site and RCSB PDB co-factor code, chain – selected chain in the crystal complex. Selected crystal complex denoted by “OK”.

UNIPROT: AK1C1_HUMAN

AKR1C1,
Q04828 DDH, DDH1

PDB: AKR1C1

| PDBID | resolution | ligand | cofactor | chain | |
|-------|------------|--------|-----------|-------|----|
| 1MRQ | 1,59 | STR | NAP | A | OK |
| 3C3U | 1,8 | C2U | NAP+,Zn2+ | A | |
| 3NTY | 1,87 | 5P3 | NAP+,Zn2+ | A | |
| 4YVP | 2,6 | GBM | NAP | A | |
| 6A7A | 2,37 | 9S0 | NAP | A | |
| 6IJX | 2,2 | JMS | NAP | A | |

UNIPROT: AK1C2_HUMAN

AKR1C2,
P52895 DDH2

PDB: AKR1C2

| PDBID | resolution | ligand | cofactor | chain | |
|-------|------------|--------|----------|-------|----|
| 1IHI | 3 | IU5 | NAP | A | |
| 1J96 | 1,25 | TES | NAP | A | OK |

| | | | | |
|------|------|-----|---------|---|
| 1XJB | 1,9 | | NAP | A |
| 2HDJ | 2 | | NDP | A |
| 4JQ1 | 1,6 | NPS | NAP | A |
| 4JQ2 | 1,75 | SUZ | NAP | A |
| 4JQ3 | 1,75 | ZOM | NAP | A |
| 4JQ4 | 1,52 | IMN | NAP | A |
| 4JQA | 1,45 | ID8 | NAP,NA+ | A |
| 4JTQ | 1,6 | FLP | NAP | A |
| 4JTR | 1,3 | IZP | NAP | A |
| 4L1W | 2,2 | STR | NAP | A |
| 4L1X | 2 | STR | NAP | A |
| 4XO6 | 1,2 | 5SD | NAP | A |
| 4XO7 | 1,75 | ASD | NAP | A |

UNIPROT: AK1C3_HUMAN

| | | | | |
|-------------|--|--------|----------|----|
| P42330 | AKR1C3, DDH1, HSD17B5, KIAA0119, PGF | | | |
| PDB: AKR1C3 | | | | |
| PDBID | resolution | ligand | cofactor | |
| 1RY0 | 1,69 | PG2 | NAP | |
| 1RY8 | 1,69 | RUT | NDP | |
| 1ZQ5 | 1,3 | E04 | NAP | OK |
| 4DBS | 1,85 | 0HV | NAP | |
| 4DBU | 2,53 | BT9 | NAP | |
| 4DBW | 1,8 | 511 | NAP | |
| 4YVV | 2,3 | GBM | NAP | |

| | | | |
|------|------|-----|-----|
| 4YVX | 2,3 | GMR | NAP |
| 4ZFC | 2 | GCZ | NAP |
| 6A7B | 2,37 | 9S0 | NAP |

Table: Scoring. AKR1C* systems scored by Cmd scoring funcion (CMD score, unit is kcal/mol; although authors declare this is unit-less docking score).

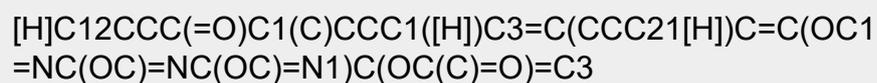
| compounds | CMD score | | |
|-----------|-----------|--------|--------|
| | AKR1C1 | AKR1C2 | AKR1C3 |
| 1 | -4,19 | -3,75 | -5,62 |
| 2 | -4,47 | -4,01 | -4,73 |
| 3 | -4,24 | -3,98 | -5,27 |
| 4 | -4,25 | -3,87 | -6,12 |
| 5 | -4,98 | -4,95 | -5,68 |
| 6 | -5,63 | -6,76 | -6,48 |
| 7 | -4,36 | -6,05 | -5,35 |
| 8 | -4,11 | -4,08 | -3,92 |
| 9 | -4,53 | -5,52 | -6,44 |
| 10 | -5,91 | -5,82 | -5,08 |
| 11 | -3,56 | -4,04 | -4,23 |
| 13 | -5,04 | -4,72 | -5,45 |
| 14 | -4,21 | -4,6 | -5,29 |
| 15 | -4,82 | -4,57 | -5,37 |
| 16 | -3,96 | -4,47 | -5,31 |
| 17 | -4,58 | -4,37 | -4,95 |
| 19 | -5,12 | -4,7 | -6,32 |
| 20 | -5,48 | -5,77 | -6,57 |
| Min | -5,91 | -6,76 | -6,57 |

| model | pdb | pdb | pdb |
|-------|-----|-----|-----|
|-------|-----|-----|-----|

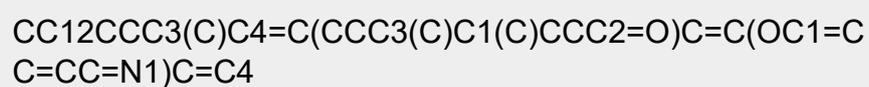
Table: Compound reference. Compounds are denoted by SMILES strings for the benefit of the reader and future *in-silico* work.

| compounds | smiles |
|-----------|---|
| 1 | <chem>CN(C)C(=O)OC1=CC2=C(C=C1)C(=O)CCC2</chem> |
| 2 | <chem>CC(C)(C)C(=O)OC1=CC2=C(C=C1)C(=O)CCC2</chem> |
| 3 | <chem>CN(C)S(=O)(=O)OC1=CC2=C(C=C1)C(=O)CCC2</chem> |
| 4 | <chem>O=C1CCCC2=C1C=CC(OC1=CC=CC=N1)=C2</chem> |
| 5 | <chem>COC1=NC(OC2=CC3=C(C=C2)C(=O)CCC3)=NC(OC)=N1</chem> |
| 6 | <chem>[H]C12CCC(=O)C1(C)CCC1([H])C3=C(CCC21[H])C=C(OC1=NC(OC)=NC(OC)=N1)C=C3</chem> |

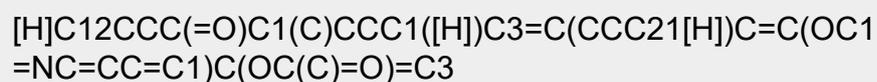
7



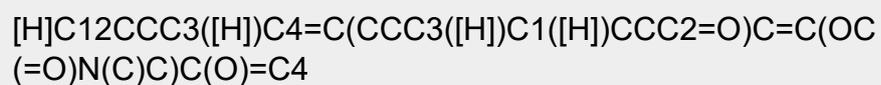
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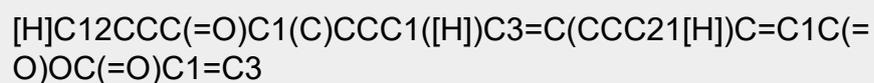
9



10



11



13

CC12CCC3C(CCC4=C3C=CC(OC3=CC=C(C=N3)C(F)(F)F)=C4)C1CCC2=O

14

CC12CCC3C(CCC4=C3C=CC(OC3=C(Br)C=C(C=N3)C(F)(F)F)=C4)C1CCC2=O

15

CC12CCC3C(CCC4=C3C=CC(OC3=NC(=CC=C3)C(F)(F)F)=C4)C1CCC2=O

16

CC12CCC3C(CCC4=C3C=CC(OC3=C(C=CC=N3)C(F)(F)F)=C4)C1CCC2=O

17

CC12CCC3C(CCC4=C3C=CC(OC3=CC(=CC=C3)C(F)(F)F)=C4)C1CCC2=O

19

CN(C)C(=O)OC1=CC2=C(C=C1)C1CCC3(C)C(CCC3=O)C1CC2

20

CC12CCC3C(CCC4=C3C=C(O)C(O)=C4)C1CCC2=O
