Supplementary Information

Unveiling the action of ferruginol, tanshinone and carnosol analogues on their antiproliferative properties

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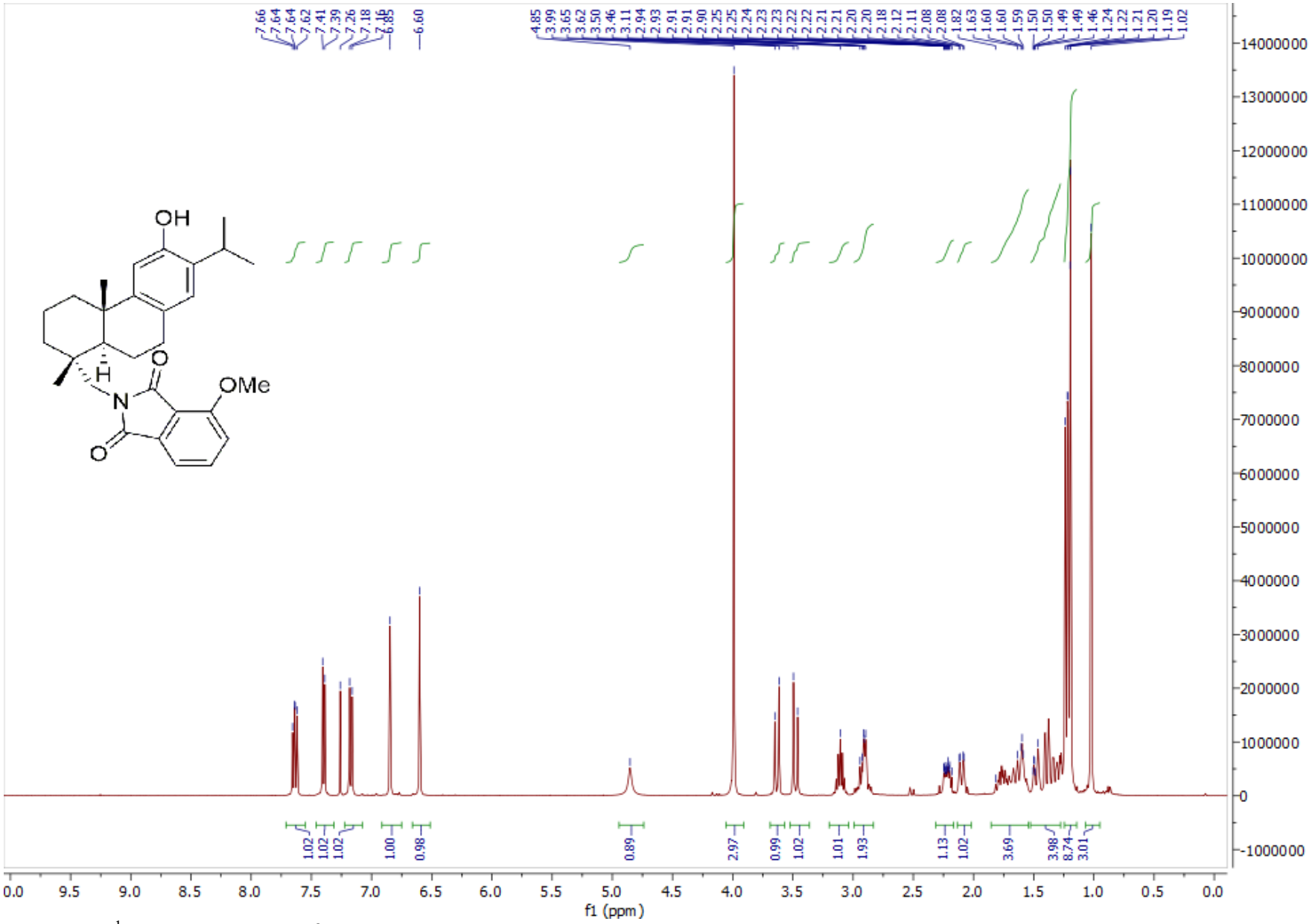


Figure S1. ^{1}H NMR spectrum of **8**.

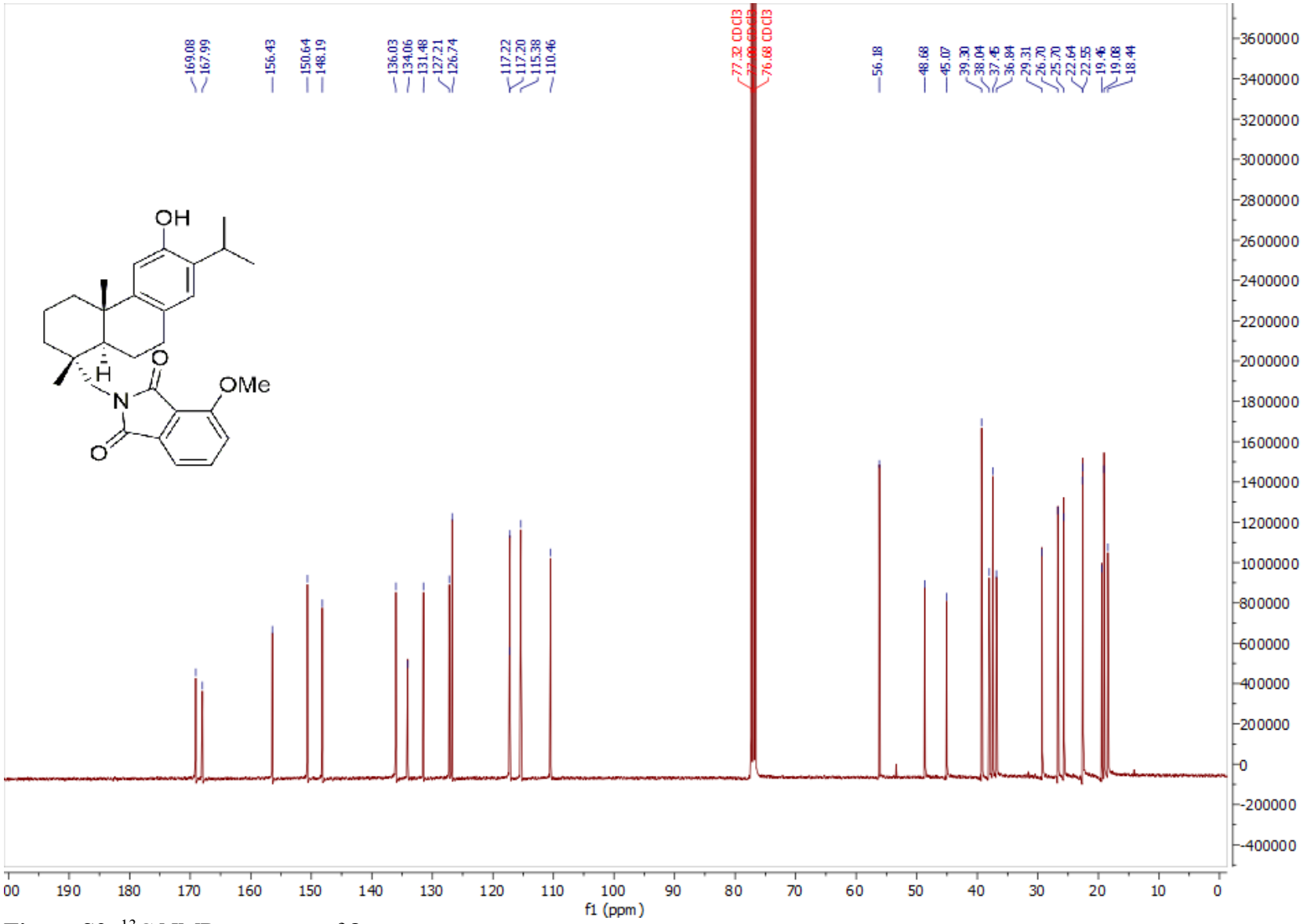


Figure S2. ^{13}C NMR spectrum of **8**.

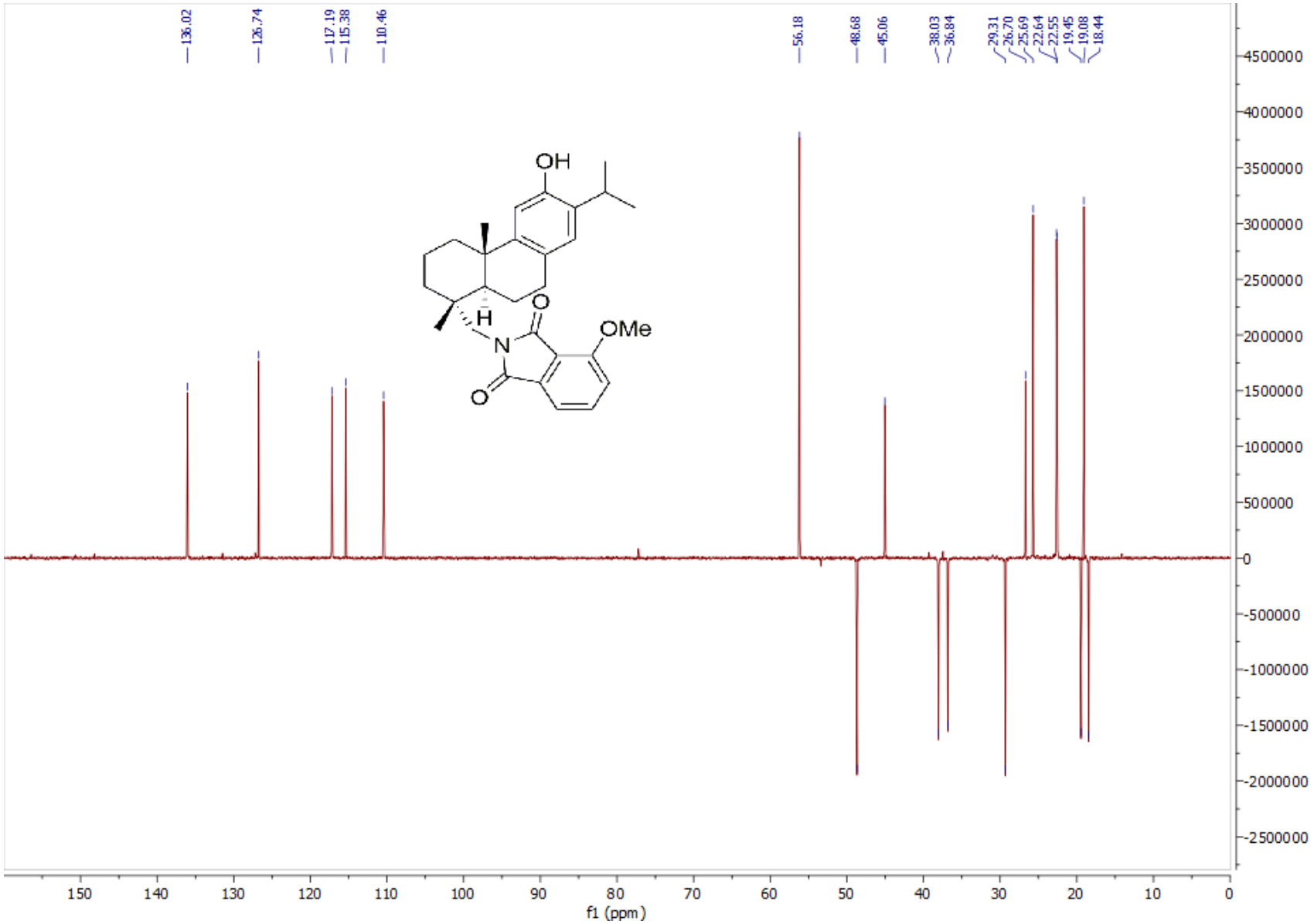


Figure S3. DEPT135 spectrum of **8**.

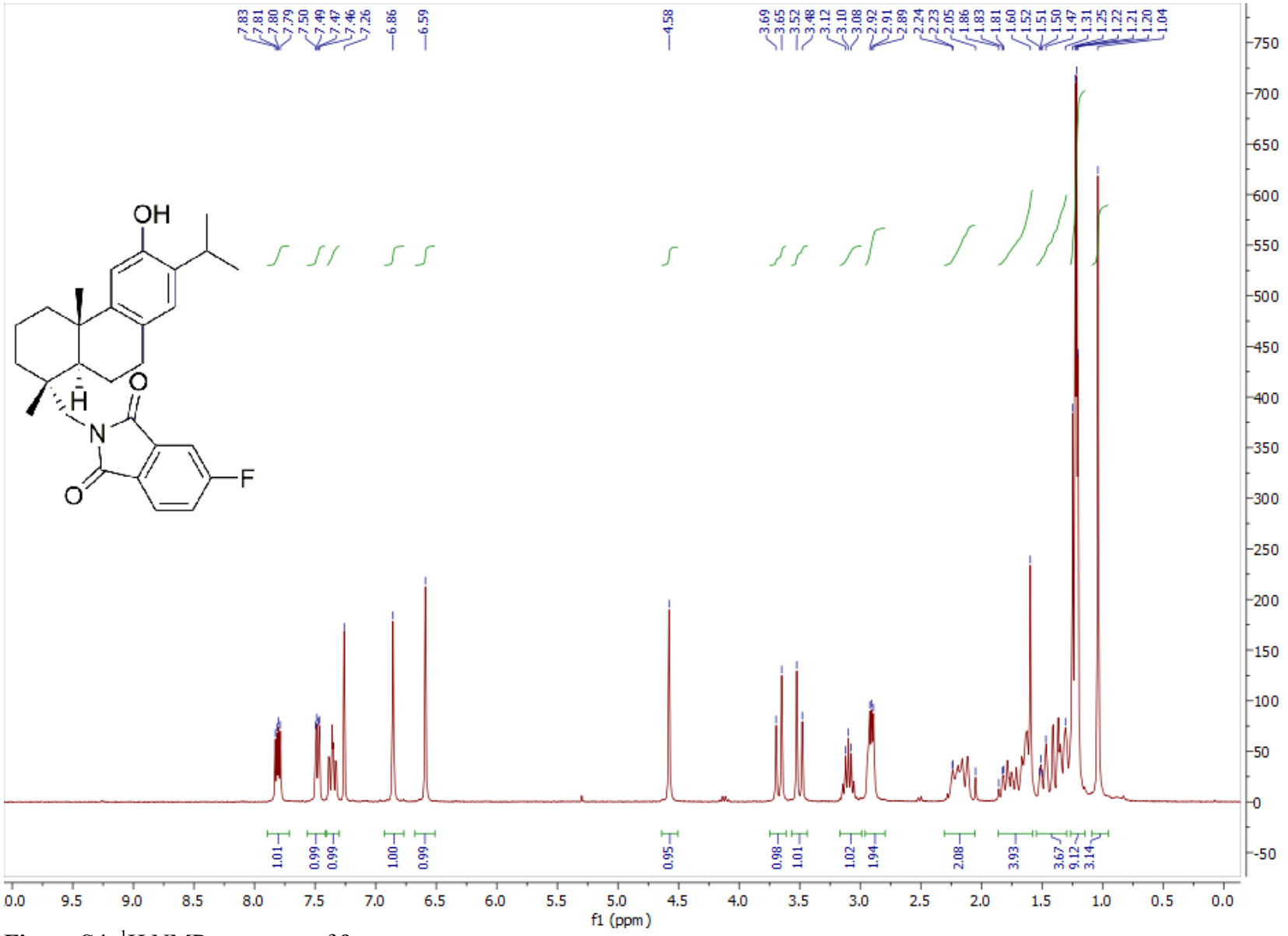


Figure S4. ^{1}H NMR spectrum of **9**.

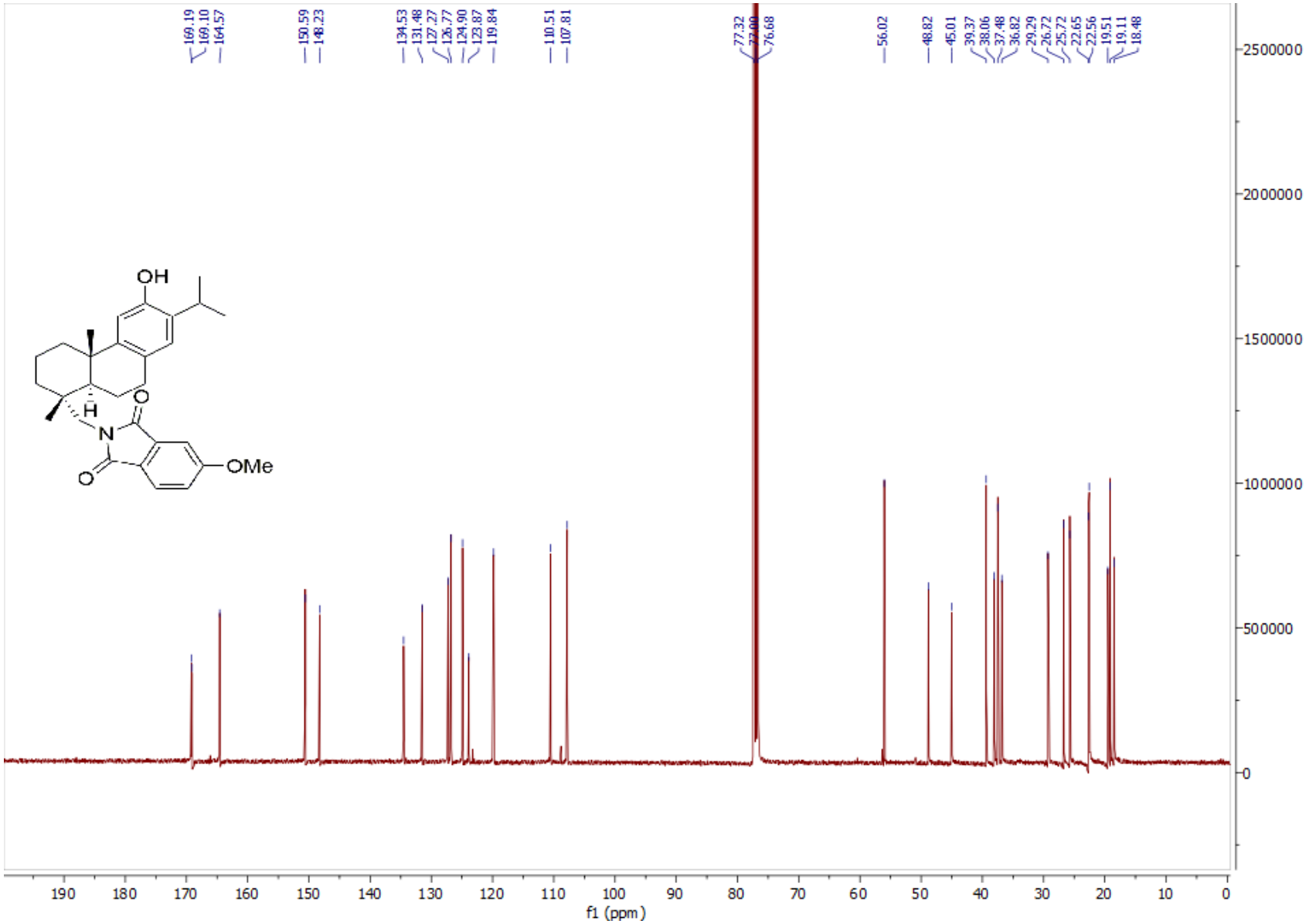


Figure S5. ^{13}C NMR spectrum of **9**.

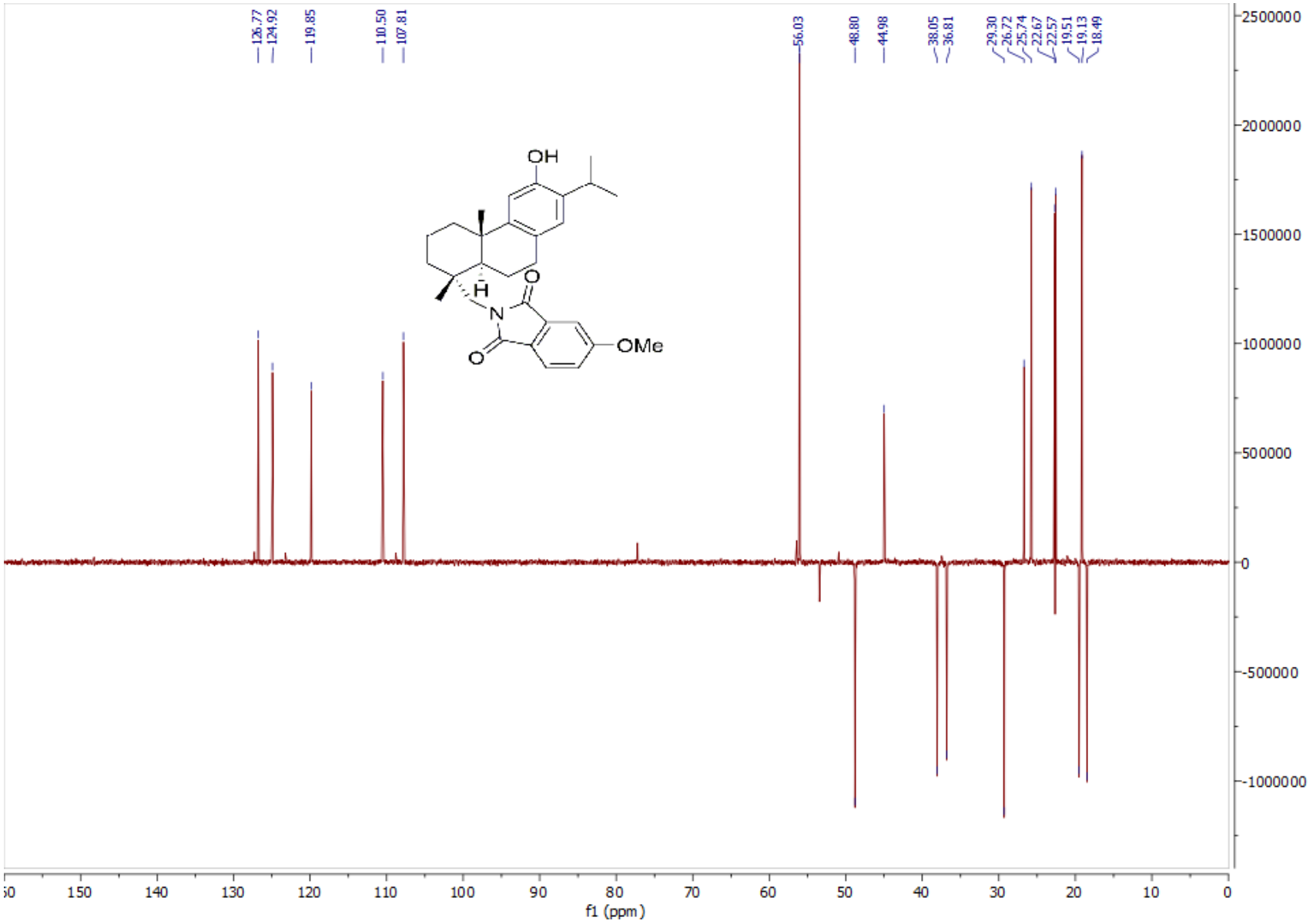
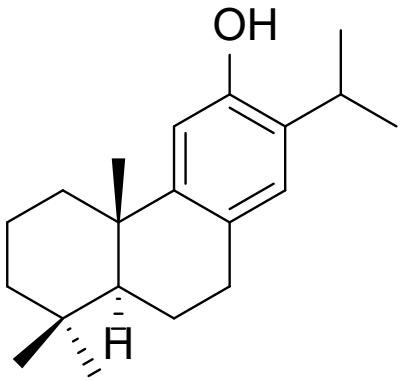
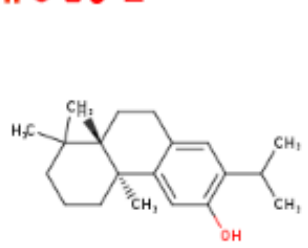
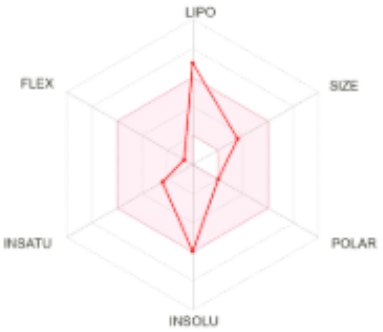


Figure S6. DEPT135 spectrum of **9**.



Molecule 1





SMILES CC(c1cc2CC[C@@H]3[C@](c2cc1O)(C)CCCC3(C)C)C

Physicochemical Properties	
Formula	C20H30O
Molecular weight	286.45 g/mol
Num. heavy atoms	21
Num. arom. heavy atoms	6
Fraction Csp3	0.70
Num. rotatable bonds	1
Num. H-bond acceptors	1
Num. H-bond donors	1
Molar Refractivity	91.63
TPSA	20.23 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.63
Log $P_{o/w}$ (XLOGP3)	6.71
Log $P_{o/w}$ (WLOGP)	5.55
Log $P_{o/w}$ (MLOGP)	4.92
Log $P_{o/w}$ (SILICOS-IT)	5.50
Consensus Log $P_{o/w}$	5.26

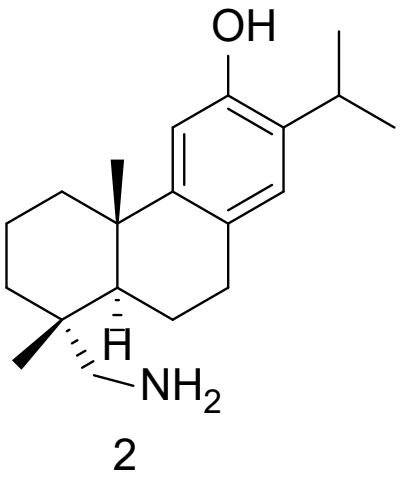
Water Solubility	
Log *S* (ESOL)	-5.99
Solubility	2.94e-04 mg/ml ; 1.03e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.94
Solubility	3.30e-05 mg/ml ; 1.15e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-5.77
Solubility	4.91e-04 mg/ml ; 1.71e-06 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.28 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 2 violations: XLOGP3>5, Heteroatoms<2
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	3.33

Figure S7. ADME-Tox and physicochemical properties of **1** predicted using the SwissADME web server (www.swissadme.ch).



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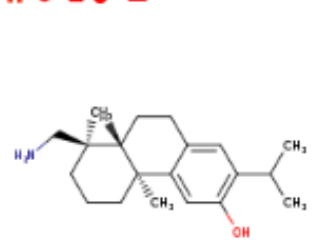
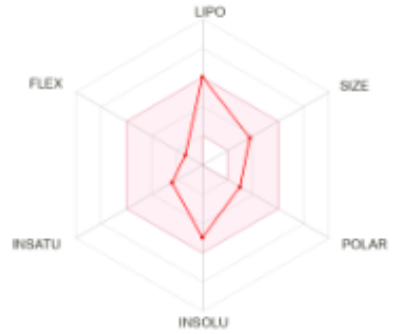
Molecule 2



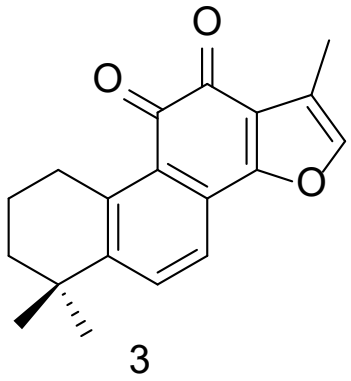


SMILES NC[C@]1(C)CCC[C@]2([C@H]1CCc1c2cc(c(c1)C(C)C)O)C

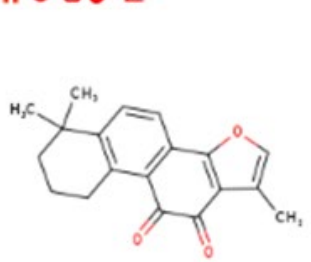
Physicochemical Properties	
Formula	C20H31NO
Molecular weight	301.47 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	6
Fraction Csp3	0.70
Num. rotatable bonds	2
Num. H-bond acceptors	2
Num. H-bond donors	2
Molar Refractivity	94.34
TPSA	46.25 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.29
Log $P_{o/w}$ (XLOGP3)	5.05
Log $P_{o/w}$ (WLOGP)	4.48
Log $P_{o/w}$ (MLOGP)	3.99
Log $P_{o/w}$ (SILICOS-IT)	4.65
Consensus Log $P_{o/w}$	4.29

Water Solubility	
Log *S* (ESOL)	-4.96
Solubility	3.30e-03 mg/ml ; 1.10e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.76
Solubility	5.20e-04 mg/ml ; 1.73e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-5.42
Solubility	1.15e-03 mg/ml ; 3.81e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.55 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	3.54

Figure S8. ADME-Tox and physicochemical properties of **2** predicted using the SwissADME web server (www.swissadme.ch).



Molecule 3



SMILES O=C1c2c3CCCC(c3ccc2c2c(C1=O)c(C)co2)(C)C

Physicochemical Properties	
Formula	C19H18O3
Molecular weight	294.34 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	11
Fraction Csp3	0.37
Num. rotatable bonds	0
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	84.70
TPSA	47.28 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.79
Log $P_{o/w}$ (XLOGP3)	4.33
Log $P_{o/w}$ (WLOGP)	4.25
Log $P_{o/w}$ (MLOGP)	2.24
Log $P_{o/w}$ (SILICOS-IT)	5.37
Consensus Log $P_{o/w}$	3.80

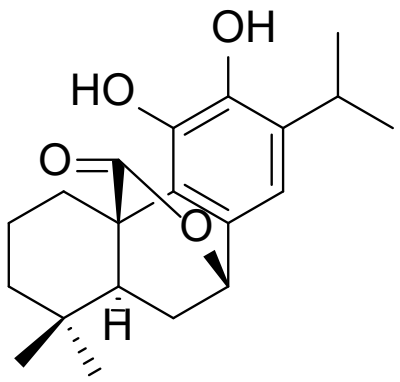
Water Solubility	
Log *S* (ESOL)	-4.76
Solubility	5.08e-03 mg/ml ; 1.73e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.04
Solubility	2.70e-03 mg/ml ; 9.18e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-6.71
Solubility	5.77e-05 mg/ml ; 1.96e-07 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.02 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	2 alerts: imine_one_A, quinone_D
Brenk	1 alert: diketo_group
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	3.66

Figure S9. ADME-Tox and physicochemical properties of **3** predicted using the SwissADME web server (www.swissadme.ch).



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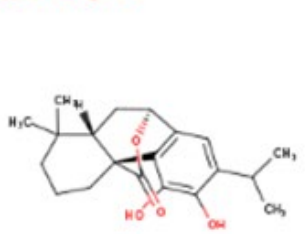
Molecule 4

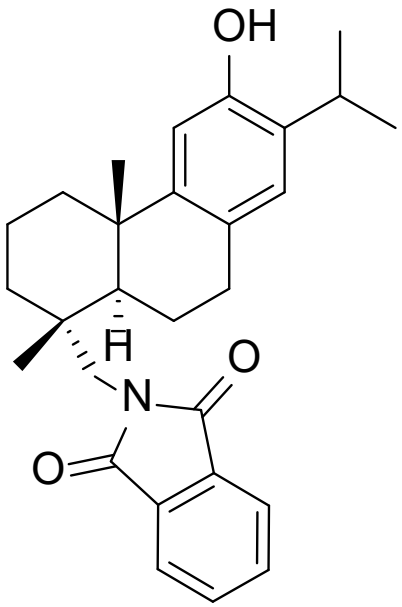


SMILES O=C1O[C@H]2C[C@@H]3[C@]1(CCCC3(C)C)c1c2cc(c(c1O)O)C(C)C

Physicochemical Properties	
Formula	C20H26O4
Molecular weight	330.42 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	6
Fraction Csp3	0.65
Num. rotatable bonds	1
Num. H-bond acceptors	4
Num. H-bond donors	2
Molar Refractivity	92.83
TPSA	66.76 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.93
Log $P_{o/w}$ (XLOGP3)	4.38
Log $P_{o/w}$ (WLOGP)	3.96
Log $P_{o/w}$ (MLOGP)	3.25
Log $P_{o/w}$ (SILICOS-IT)	4.05
Consensus Log $P_{o/w}$	3.72

Water Solubility	
Log *S* (ESOL)	-4.77
Solubility	5.65e-03 mg/ml ; 1.71e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.50
Solubility	1.05e-03 mg/ml ; 3.17e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.45
Solubility	1.16e-02 mg/ml ; 3.52e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.21 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.88

Figure S10. ADME-Tox and physicochemical properties of **4** predicted using the SwissADME web server (www.swissadme.ch).



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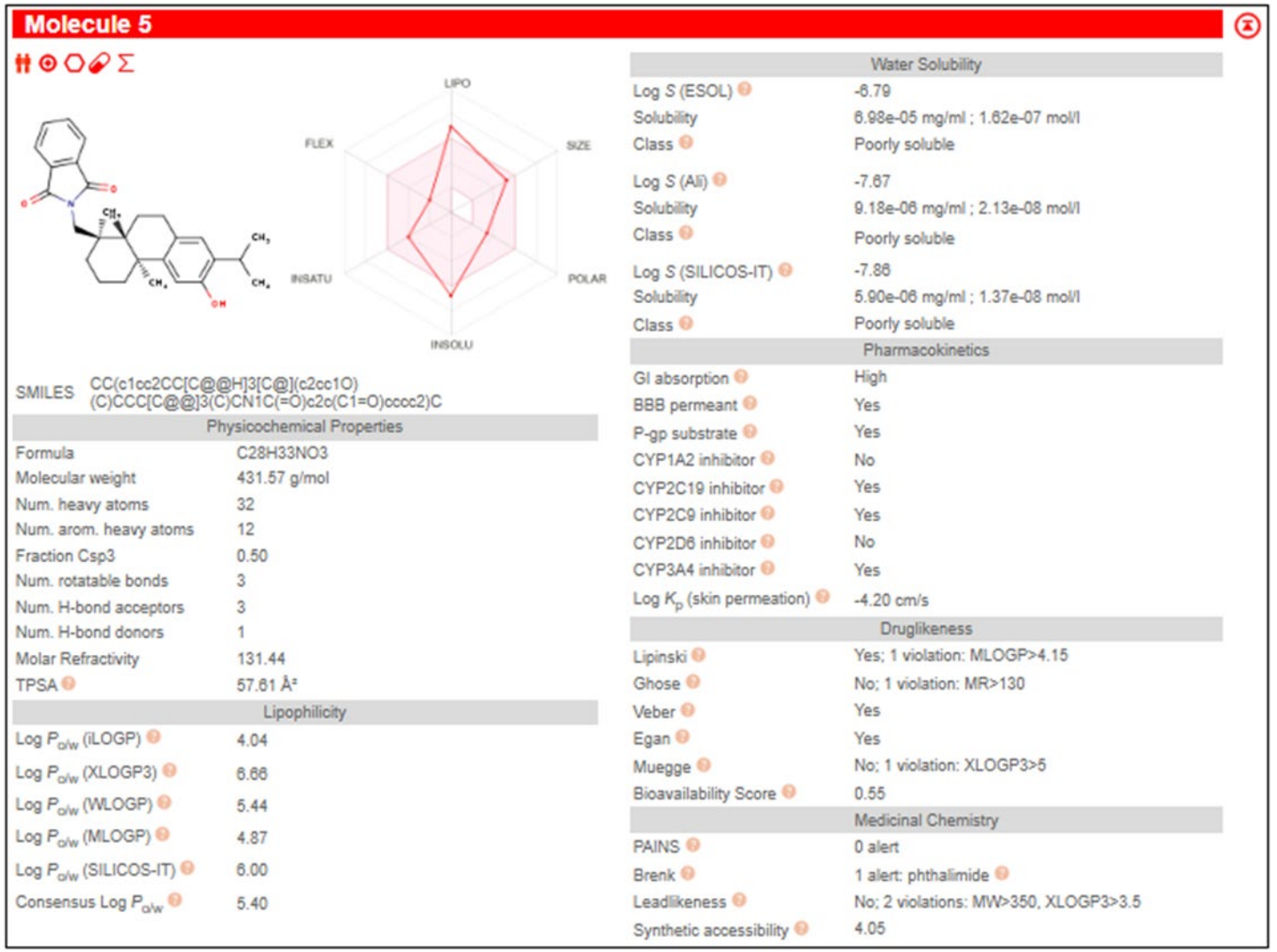
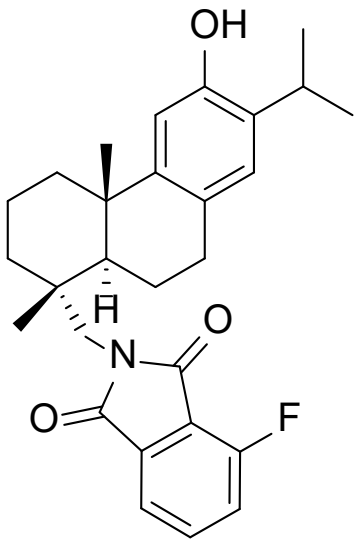
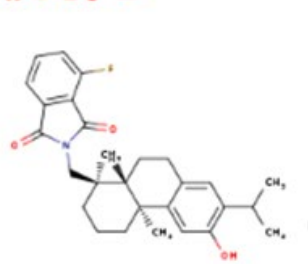


Figure S11. ADME-Tox and physicochemical properties of **5** predicted using the SwissADME web server (www.swissadme.ch).



6

Molecule 6



SMILES CC(c1cc2CC[C@@H]3[C@](c2cc1O)(C)CCC[C@@]3(C)CN1C(=O)c2c(C1=O)c(F)ccc2)C

Physicochemical Properties	
Formula	C28H32FNO3
Molecular weight	449.56 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	12
Fraction Csp3	0.50
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	131.39
TPSA	57.61 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.90
Log $P_{o/w}$ (XLOGP3)	6.76
Log $P_{o/w}$ (WLOGP)	6.00
Log $P_{o/w}$ (MLOGP)	5.24
Log $P_{o/w}$ (SILICOS-IT)	6.42
Consensus Log $P_{o/w}$	5.67

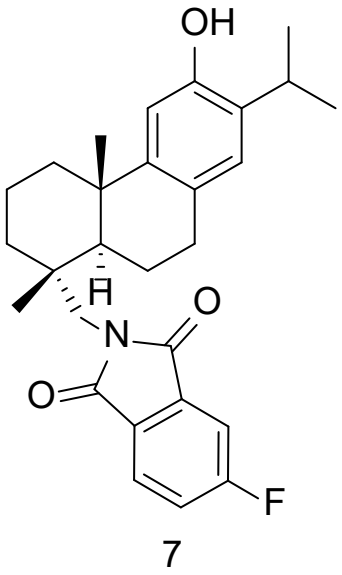
Water Solubility	
Log *S* (ESOL)	-6.96
Solubility	4.96e-05 mg/ml ; 1.10e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.78
Solubility	7.53e-06 mg/ml ; 1.68e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.13
Solubility	3.36e-06 mg/ml ; 7.48e-09 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.24 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 2 violations: WLOGP>5.6, MR>130
Veber	Yes
Egan	No; 1 violation: WLOGP>5.88
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.22

Figure S12. ADME-Tox and physicochemical properties of **6** predicted using the SwissADME web server (www.swissadme.ch).



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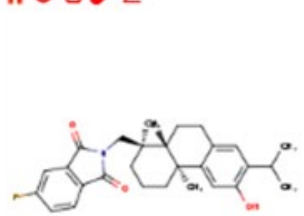
Molecule 7



SMILES Fc1ccc2c(c1)C(=O)N(C2=O)C[C@]1(C)CCC[C@]2([C@H]1CCc1c2cc(c(c1)C(C)C)O)C

Physicochemical Properties	
Formula	C28H32FNO3
Molecular weight	449.56 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	12
Fraction Csp3	0.50
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	131.39
TPSA	57.61 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.08
Log $P_{o/w}$ (XLOGP3)	6.76
Log $P_{o/w}$ (WLOGP)	6.00
Log $P_{o/w}$ (MLOGP)	5.24
Log $P_{o/w}$ (SILICOS-IT)	6.42
Consensus Log $P_{o/w}$	5.70

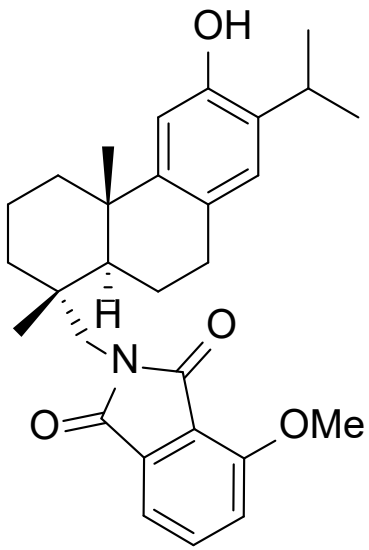
Water Solubility	
Log *S* (ESOL)	-6.96
Solubility	4.96e-05 mg/ml ; 1.10e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.78
Solubility	7.53e-06 mg/ml ; 1.68e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.13
Solubility	3.36e-06 mg/ml ; 7.48e-09 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.24 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 2 violations: WLOGP>5.6, MR>130
Veber	Yes
Egan	No; 1 violation: WLOGP>5.88
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.15

Figure S13. ADME-Tox and physicochemical properties of **7** predicted using the SwissADME web server (www.swissadme.ch).



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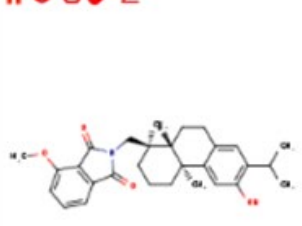
Molecule 8



SMILES COc1cccc2c1C(=O)N(C2=O)C[C@]1(C)CCC[C@]2([C@H]1CCc1c2cc(c(c1)C(C)C)O)C

Physicochemical Properties	
Formula	C29H35NO4
Molecular weight	461.59 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	12
Fraction Csp3	0.52
Num. rotatable bonds	4
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	137.93
TPSA	66.84 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.21
Log $P_{o/w}$ (XLOGP3)	6.64
Log $P_{o/w}$ (WLOGP)	5.45
Log $P_{o/w}$ (MLOGP)	4.51
Log $P_{o/w}$ (SILICOS-IT)	6.08
Consensus Log $P_{o/w}$	5.38

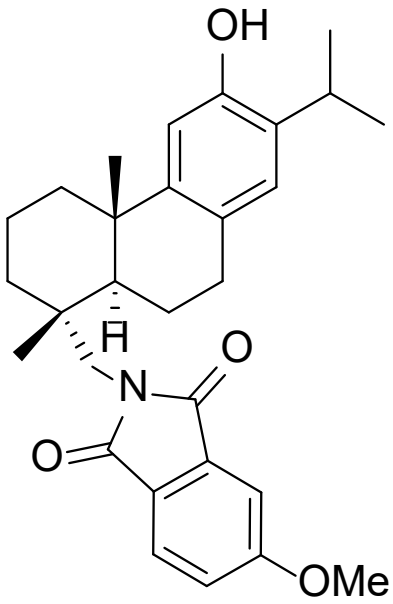
Water Solubility	
Log *S* (ESOL)	-6.88
Solubility	6.05e-05 mg/ml ; 1.31e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.85
Solubility	6.59e-06 mg/ml ; 1.43e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.96
Solubility	5.04e-06 mg/ml ; 1.09e-08 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.40 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

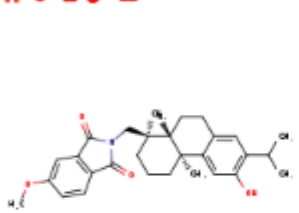
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.42

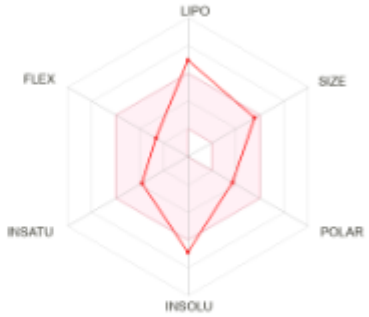
Figure S14. ADME-Tox and physicochemical properties of **8** predicted using the SwissADME web server (www.swissadme.ch).



9

Molecule 9





SMILES COc1ccc2c(c1)C(=O)N(C2=O)C[C@]1(C)CCC[C@]2([C@H]1CCc1c2cc(c(c1)C(C)C)O)C

Physicochemical Properties	
Formula	C29H35NO4
Molecular weight	461.59 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	12
Fraction Csp3	0.52
Num. rotatable bonds	4
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	137.93
TPSA	66.84 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.25
Log $P_{o/w}$ (XLOGP3)	6.64
Log $P_{o/w}$ (WLOGP)	5.45
Log $P_{o/w}$ (MLOGP)	4.51
Log $P_{o/w}$ (SILICOS-IT)	6.08
Consensus Log $P_{o/w}$	5.38

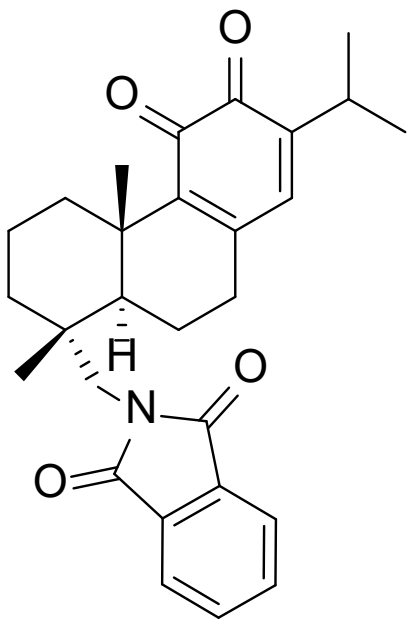
Water Solubility	
Log *S* (ESOL)	-6.88
Solubility	6.05e-05 mg/ml ; 1.31e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.85
Solubility	6.59e-06 mg/ml ; 1.43e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.96
Solubility	5.04e-06 mg/ml ; 1.09e-08 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.40 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

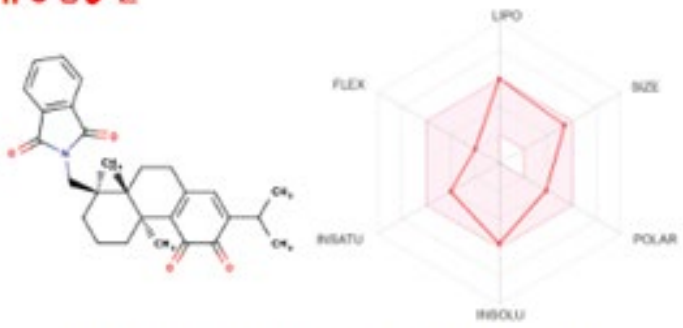
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.34

Figure S15. ADME-Tox and physicochemical properties of **9** predicted using the SwissADME web server (www.swissadme.ch).



10

Molecule 10



SMILES CC(C1=CC2=C(C(=O)C1=O)[C@@]1([C@@H](CC2)[C@@](C)(CCC1)CN1C(=O)c2c(C1=O)cccc2)C)C

Physicochemical Properties	
Formula	C28H31NO4
Molecular weight	445.55 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	6
Fraction Csp3	0.50
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	0
Molar Refractivity	130.64
TPSA	71.52 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.53
Log $P_{o/w}$ (XLOGP3)	5.03
Log $P_{o/w}$ (WLOGP)	4.54
Log $P_{o/w}$ (MLOGP)	3.70
Log $P_{o/w}$ (SILICOS-IT)	5.51
Consensus Log $P_{o/w}$	4.46

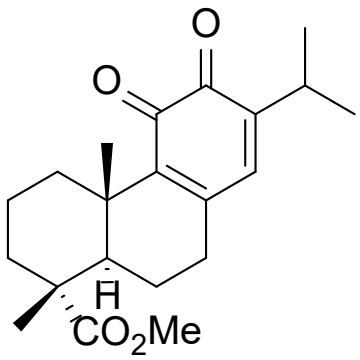
Water Solubility	
Log *S* (ESOL)	-5.71
Solubility	8.73e-04 mg/ml ; 1.96e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.27
Solubility	2.38e-04 mg/ml ; 5.34e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.08
Solubility	3.75e-05 mg/ml ; 8.41e-08 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.45 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

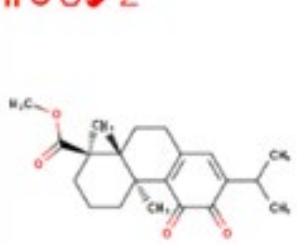
Medicinal Chemistry	
PAINS	2 alerts: imine_one_A, quinone_D
Brenk	3 alerts: chinone_2, diketo_group, phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.75

Figure S16. ADME-Tox and physicochemical properties of **10** predicted using the SwissADME web server (www.swissadme.ch).



11

Molecule 11



SMILES COC(=O)[C@]1(C)CCC[C@]2([C@H]1CCC1=C2C(=O)C(=O)C(=C1)C(C)C)C

Physicochemical Properties	
Formula	C21H28O4
Molecular weight	344.44 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	0
Fraction Csp3	0.67
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	0
Molar Refractivity	96.94
TPSA	60.44 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.18
Log $P_{o/w}$ (XLOGP3)	3.92
Log $P_{o/w}$ (WLOGP)	3.80
Log $P_{o/w}$ (MLOGP)	2.85
Log $P_{o/w}$ (SILICOS-IT)	4.48
Consensus Log $P_{o/w}$	3.65

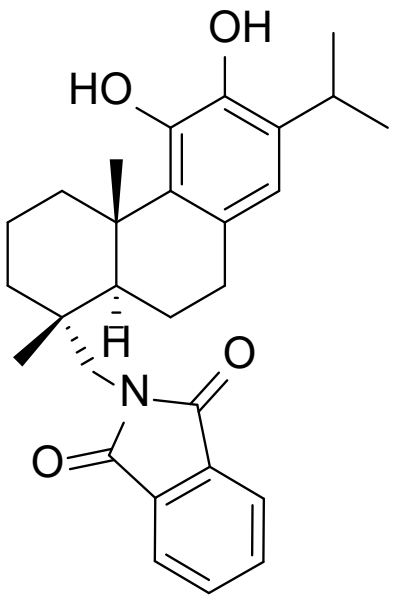
Water Solubility	
Log *S* (ESOL)	-4.25
Solubility	1.95e-02 mg/ml ; 5.66e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.89
Solubility	4.46e-03 mg/ml ; 1.29e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.65
Solubility	7.73e-03 mg/ml ; 2.24e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.62 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

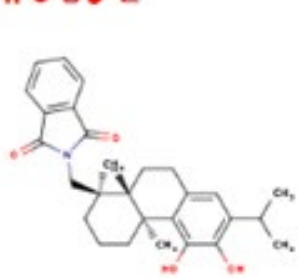
Medicinal Chemistry	
PAINS	2 alerts: imine_one_A, quinone_D
Brenk	2 alerts: chinone_2, diketo_group
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	5.11

Figure S17. ADME-Tox and physicochemical properties of **11** predicted using the SwissADME web server (www.swissadme.ch).



12

Molecule 12



SMILES CC(c1cc2CC[C@@H]3[C@](c2c(c1O)O)(C)CCC[C@@]3(C)CN1C(=O)c2c(C1=O)cccc2)C

Physicochemical Properties	
Formula	C28H33NO4
Molecular weight	447.57 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	12
Fraction Csp3	0.50
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	2
Molar Refractivity	133.46
TPSA	77.84 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.96
Log $P_{o/w}$ (XLOGP3)	6.31
Log $P_{o/w}$ (WLOGP)	5.15
Log $P_{o/w}$ (MLOGP)	4.31
Log $P_{o/w}$ (SILICOS-IT)	5.52
Consensus Log $P_{o/w}$	5.05

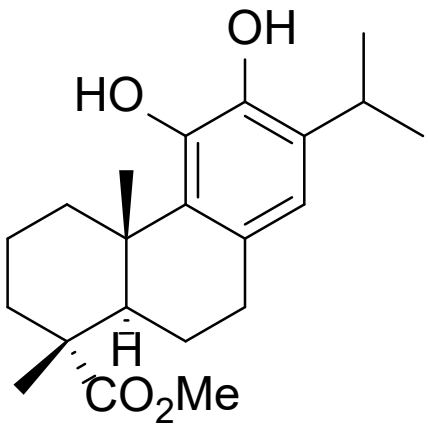
Water Solubility	
Log *S* (ESOL)	-6.66
Solubility	9.76e-05 mg/ml ; 2.18e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.73
Solubility	8.26e-06 mg/ml ; 1.85e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.27
Solubility	2.38e-05 mg/ml ; 5.32e-08 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.55 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

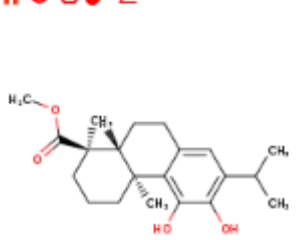
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	2 alerts: catechol, phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.16

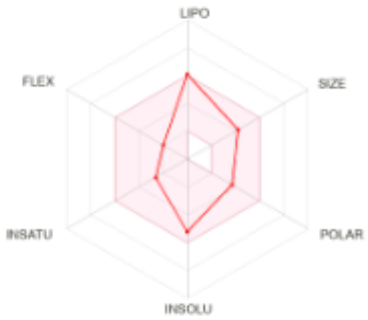
Figure S18. ADME-Tox and physicochemical properties of **12** predicted using the SwissADME web server (www.swissadme.ch).



13

Molecule 13





SMILES COC(=O)[C@]1(C)CCC[C@]2([C@H]1CCc1c2c(O)c(c(c1)C(C)C)O)C

Physicochemical Properties	
Formula	C21H30O4
Molecular weight	346.46 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	6
Fraction Csp3	0.67
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	2
Molar Refractivity	99.75
TPSA	66.76 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.53
Log $P_{o/w}$ (XLOGP3)	5.20
Log $P_{o/w}$ (WLOGP)	4.40
Log $P_{o/w}$ (MLOGP)	3.48
Log $P_{o/w}$ (SILICOS-IT)	4.50
Consensus Log $P_{o/w}$	4.22

Water Solubility	
Log *S* (ESOL)	-5.24
Solubility	1.98e-03 mg/ml ; 5.71e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.35
Solubility	1.55e-04 mg/ml ; 4.48e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.85
Solubility	4.91e-03 mg/ml ; 1.42e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.72 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	3.84

Figure S19. ADME-Tox and physicochemical properties of **13** predicted using the SwissADME web server (www.swissadme.ch).

Table S1. Predicted pharmacokinetics parameters of the examined compounds obtained by using the SwissADME server (www.swissadme.ch).

Compound	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
1	High	Yes	No	No	Yes	Yes	Yes	No	-3,28
2	High	Yes	No	No	No	No	Yes	No	-4,55
3	High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-5,02
4	High	Yes	Yes	No	No	Yes	No	No	-5,21
5	High	Yes	Yes	No	Yes	Yes	No	Yes	-4,20
6	High	No	Yes	No	No	Yes	No	Yes	-4,24
7	High	No	Yes	No	No	Yes	No	Yes	-4,24
8	High	No	Yes	No	Yes	Yes	No	Yes	-4,40
9	High	No	Yes	No	Yes	Yes	No	Yes	-4,40
10	High	Yes	No	No	Yes	Yes	No	Yes	-5,45
11	High	Yes	No	No	Yes	Yes	No	No	-5,62
12	High	No	Yes	No	Yes	Yes	No	Yes	-4,55
13	High	Yes	No	No	No	Yes	Yes	No	-4,72