Design, synthesis and cancer cell growth inhibition evaluation of new aminoquinone hybrid molecules

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Molecule	Structure	ΔE 5JCB ^{a)}	ΔE 3QX3 ^{b)}	ΔΕ 2ETK ^{c)}
1a		-8.3	-8.7	-8.2
1b		-8.3	-10.4	-7.8
1c		-8.3	-10.2	-8.0
2a		8.2	-9.0	-7.6
2b	N N N N O O MeO O MeO O MeO	-7.9	-9.4	-6.9
2c		-8.1	-9.6	-6.7
3	MeO OMe	-8.4	-10.6	-7.8

Table S1. Energy data (in Kcal/mol) from docking calculation by Autodock Vina for the new ligand molecules 1a-1c, 2a-2c and 3, in comparison with original and reference ligands.

PDB original ligands and reference molecules				
Molecule	Structure	ΔE 5JCB ^{a)}	ΔE 3QX3 ^{b)}	ΔΕ 2ETK ^{a)}
HFS (original ligand)		n.d.	n.d.	-8.1
PT-262		n.d.	n.d.	-7.3
Y-27632	H ₂ N N O	n.d.	n.d.	-6.7
VP-16 (original ligand)		n.d.	-13.3	n.d.
NV4 (original ligand)	N-NH NS O MeO OMe OMe	-10.3	n.d.	n.d.
MTP	MeO MeO MeO OMe	-8.1	n.d.	n.d.

^{a)} tubulin (PDB ID: 5JCB), ^{b)}human topoisomerase II β (PDB ID: 3QX3) ^{c)} human ROCK 1 (PDB ID: 2ETK)

Table S2. ADME Prediction of compounds 1a-c, 2a-c, 3 (molecules 1-7, respectively) and	reference
compounds evaluated by online Server Swiss-ADME.	

Molecule 1	-		
			Water Solubility
H.C.	LIPO	Log S (ESOL) 📀	-5.05
CH, O		Solubility	3.75e-03 mg/ml; 8.87e-06 mol/l
CH.	FLEX	Class 📀	Moderately soluble
		Log S (Ali) 😣	-5.55
Ýî		Solubility	1.19e-03 mg/ml ; 2.80e-06 mol/l
è la		Class 📀	Moderately soluble
	POLAR	Log S (SILICOS-IT) 😣	-6.52
		Solubility	1.28e-04 mg/ml ; 3.02e-07 mol/l
· ●		Class 📀	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES COc1cc(OC2=C(N	l3CCCCC3)C(=0)c3c(C2=0)cccc3)cc(c1OC)OC	GI absorption 😣	High
Pl	nysicochemical Properties	BBB permeant 📀	Yes
Formula	C24H25NO6	P-gp substrate 📀	No
Molecular weight	423.46 g/mol	CYP1A2 inhibitor 🔞	No
Num. heavy atoms	31	CYP2C19 inhibitor 🗐	Yes
Num. arom. heavy atoms	12	CYP2C9 inhibitor 📀	Yes
Fraction Csp3	0.33	CYP2D6 inhibitor 🧐	Yes
Num. rotatable bonds	6	CYP3A4 inhibitor 🥹	Yes
Num. H-bond acceptors	6	Log Kn (skin permeation) 🥹	-5 84 cm/s
Num. H-bond donors	0	5 p. (1)	Druglikeness
Molar Refractivity	118.46	Lipinski 🔞	Yes: 0 violation
TPSA 🤨	74.30 Ų	Ghose 🧌	Yes
	Lipophilicity	Veber 🖗	Ves
Log P _{o/w} (iLOGP) 📀	3.43	Faan 🖗	Ves
Log P _{o/w} (XLOGP3) 🔞	4.28		Ves
Log P _{o/w} (WLOGP) 📀	3.49	Bioavailability Score @	0.56
Log P _{olw} (MLOGP) 📀	1.00	,	Medicinal Chemistry
Log P _{o/w} (SILICOS-IT) 📀	4.03	PAINS 🧐	1 alert: quinone_A 🥹
Consensus Log Polw 📀	3.25	Brenk 🛞	0 alert
-		Leadlikeness 📀	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 📀	3.92

Molecule 2			
Ħ 🛛 🖌			Water Solubility
H,C	LIPO	Log S (ESOL) 📀	-4.59
CH, O		Solubility	1.09e-02 mg/ml ; 2.56e-05 mol/l
осн.	FLEX	Class 📀	Moderately soluble
		Log S (Ali) 🤨	-5.06
		Solubility	3.73e-03 mg/ml : 8.80e-06 mol/l
		Class 📀	Moderately soluble
			6.15
	POLAR	Solubility	-0.10 3.03e-04.mg/ml : 7.13e-07.mol/l
		Class 0	Poorly soluble
~	INSOLU		Pharmacokinetics
SMILES COnten(OC2=C/I	N3CCCCC3)C(=Q)c3c(C2=Q)pccc3)cc(c1QC)QC	GLabsorption 0	High
DMILED COC100(002-0(1	hysicochemical Properties	BRB permeant @	No
Formula	C23H24N2O6	B an substrate	No
Molecular weight	424 45 g/mol	CVD1A2 inhibitor	No
Num heavy atoms	31	CYP1A2 IIIIIDIUI 🔮	NO
Num arom heavy atoms	12	CYP2C19 IIIIIDIUI	Tes Ves
Fraction Csp3	0.35	CYP2C9 Inhibitor 👴	Yes
Num rotatable bonds	6	CYP2D6 Inhibitor	No
Num, H-bond acceptors	7	CYP3A4 inhibitor	Yes
Num. H-bond donors	0	Log K_p (skin permeation)	-6.38 cm/s
Molar Refractivity	116.26		Druglikeness
TPSA ()	87 19 Å ²	Lipinski 🧐	Yes; 0 violation
11 0/1 -	Lipophilicity	Ghose 🛞	Yes
Log Poly (iLOGP)	3.24	Veber 🥹	Yes
	2.54	Egan 📀	Yes
	0.04	Muegge 📀	Yes
Log Poly (WLOGP)	2.88	Bioavailability Score 📀	0.56
Log P _{o/w} (MLOGP) 🧐	0.00		Medicinal Chemistry
Log P _{olw} (SILICOS-IT) 📀	3.46	PAINS 📀	1 alert: quinone_A 🤨
Consensus Log P _{o/w} 📀	2.62	Brenk 🥹	0 alert
		Leadlikeness 🛞	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 🥝	3.85

Molecule 3			
# ⊙ <i></i>			Water Solubility
H.C.	LIPO	Log S (ESOL) 🤨	-4.59
CH3 0		Solubility	1.09e-02 mg/ml; 2.56e-05 mol/l
	FLEX	Class 📀	Moderately soluble
		Log S (Ali) 🤨	-5.06
l i		Solubility	3.73e-03 mg/ml ; 8.80e-06 mol/l
		Class 📀	Moderately soluble
	INSATU	Log S (SILICOS-IT)	-6.15
		Solubility	3.03e-04 mg/ml ; 7.13e-07 mol/l
ö		Class 📀	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES COc1cc(OC2=C(N	3CCCCC3)C(=O)c3c(C2=O)cccn3)cc(c1OC)OC	GI absorption 🥹	High
Ph	ysicochemical Properties	BBB permeant <0	No
Formula	C23H24N2O6	P-gp substrate 📀	No
Molecular weight	424.45 g/mol	CYP1A2 inhibitor 📀	No
Num. heavy atoms	31	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	12	CYP2C9 inhibitor 📀	Yes
Fraction Csp3	0.35	CYP2D6 inhibitor 📀	No
Num. rotatable bonds	6	CYP3A4 inhibitor 📀	Yes
Num. H-bond acceptors	7	Log K _p (skin permeation) 📀	-6.38 cm/s
Num. H-bond donors	0		Druglikeness
Molar Refractivity	116.26	Lipinski 📀	Yes; 0 violation
TPSA 🧐	87.19 A ²	Ghose 📀	Yes
	Lipophilicity	Veber 🐵	Yes
Log P _{o/w} (ILOGP)	3.23	Egan 🛞	Yes
Log Polw (XLOGP3) 🥹	3.54	Muegge 📀	Yes
Log Polw (WLOGP) 📀	2.88	Bioavailability Score 📀	0.56
Log P _{o/w} (MLOGP) 🤨	0.00		Medicinal Chemistry
Log Polw (SILICOS-IT) 📀	3.46	PAINS ()	1 alert: quinone_A 🧐
Consensus Log Polw 🥹	2.62	Brenk 🧐	0 alert
		Leadlikeness 📀	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 🧐	3.82

Molecule 4			
👬 🕲 🖌			Water Solubility
	LIPO	Log S (ESOL) 📀	-4.27
		Solubility	2.27e-02 mg/ml ; 5.32e-05 mol/l
	FLEX SIZE	Class 🛞	Moderately soluble
		Log S (Ali) 🥹	-4.82
CH, OF T N	CH,	Solubility	6.46e-03 mg/ml ; 1.51e-05 mol/l
		Class 🛞	Moderately soluble
•	INSATU	Log S (SILICOS-IT) 😣	-6.76
CH, O		Solubility	7.33e-05 mg/ml ; 1.72e-07 mol/l
ŊС		Class 🐵	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES COc1cc(OC2=C(NCCN(C)C)C(=O)c3c(C2=O)cccc3)cc(c1OC)OC	GI absorption 😣	High
P	Physicochemical Properties	BBB permeant 📀	No
Formula	C23H26N2O6	P-gp substrate 📀	No
Molecular weight	426.46 g/mol	CYP1A2 inhibitor 📀	Yes
Num. heavy atoms	31	CYP2C19 inhibitor 📀	Yes
Num. arom. heavy atoms	12	CYP2C9 inhibitor 📀	Yes
Fraction Csp3	0.30	CYP2D6 inhibitor 📀	Yes
Num. rotatable bonds	9	CYP3A4 inhibitor 📀	Yes
Num. H-bond acceptors	7	Log Kp (skin permeation) 📀	-6.54 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	114.66	Lipinski 😗	Yes: 0 violation
TPSA 🕗	86.33 Ų	Ghose 😣	Yes
	Lipophilicity	Veber 📀	Yes
Log P _{o/w} (iLOGP) 🧐	3.75	Egan 📀	Yes
Log P _{o/w} (XLOGP3) 📀	3.33	Mueage 📀	Yes
Log P _{olw} (WLOGP) 📀	2.53	Bioavailability Score 📀	0.56
Log P _{o/w} (MLOGP) 😣	0.00		Medicinal Chemistry
Log Polw (SILICOS-IT) 📀	3.19	PAINS ()	1 alert: quinone_A 🥹
Consensus Log Poly 📀	2.56	Brenk 😣	0 alert
		Leadlikeness 📀	No; 2 violations: MW>350, Rotors>7
		Synthetic accessibility 🛞	4.02

# 0			Water Solubility
	LIPO	Log S (ESOL) 🤨	-3.82
		Solubility	6.46e-02 mg/ml; 1.51e-04 mol/l
	FLEX	Class 🛞	Soluble
		Log S (Ali) 🔞	-4.33
CH, O	CH,	Solubility	1 99e-02 mg/ml : 4 65e-05 mol/l
		Class ()	Moderately soluble
Î	INSATU POLAR	Log S (SILICOS-IT)	-6.39
Ч. 0		Solubility	1.73e-04 mg/mi ; 4.06e-07 mol/l
	INSOLU	Class 👽	Poorty soluble
			Pharmacokinetics
SMILES COC1CC(OC2=C(N	CCN(C)C)C(=O)c3c(C2=O)nccc3)cc(c1OC)OC	GI absorption 🧐	High
Pn	ysicochemical Properties	BBB permeant 🥹	No
Formula	C22H25N3O6	P-gp substrate 🧐	Yes
Molecular weight	427.45 g/moi	CYP1A2 inhibitor 📀	Yes
Num. heavy atoms	31	CYP2C19 inhibitor 📀	Yes
Num. arom. heavy atoms	12	CYP2C9 inhibitor 📀	Yes
Fraction Csp3	0.32	CYP2D6 inhibitor 📀	No
Num. rotatable bonds	9	CYP3A4 inhibitor 📀	Yes
Num. H-bond acceptors	8	Log K _p (skin permeation) 📀	-7.06 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	112.45	Lipinski 🤨	Yes; 0 violation
TPSA 🥹	99.22 A ²	Ghose 📀	Yes
	Lipophilicity	Veber 🐵	Yes
Log Polw (iLOGP)	3.06	Egan 🛞	Yes
Log Polw (XLOGP3) 📀	2.60	Muegge 🔞	Yes
Log Polw (WLOGP) 📀	1.93	Bioavailability Score 📀	0.56
Log P _{olw} (MLOGP) 📀	-0.99		Medicinal Chemistry
Log Polw (SILICOS-IT) 📀	2.62	PAINS ⁽⁹⁾	1 alert: quinone_A 🧐
Consensus Log Polw	1.84	Brenk 🐵	0 alert
		Leadlikeness 📀	No; 2 violations: MW>350, Rotors>7
		Synthetic accessibility 📀	3.94

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Molecule 6			
tt 🛛 🖌			Water Solubility
	LIPO	Log S (ESOL) 📀	-3.82
		Solubility	6.46e-02 mg/ml ; 1.51e-04 mol/l
	CH, FLEX SIZE	Class 📀	Soluble
		Log S (Ali) 😗	-4.33
CH, OF T H	- ⁻ CH ₁	Solubility	1.99e-02 mg/ml ; 4.65e-05 mol/l
		Class 📀	Moderately soluble
	INSATU	Log S (SILICOS-IT) 🔞	-6.39
CH, O		Solubility	1.73e-04 mg/ml ; 4.06e-07 mol/l
.32	INFOLL	Class 🤨	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES COc1cc(OC2=C(N	NCCN(C)C)C(=O)c3c(C2=O)cccn3)cc(c1OC)OC	GI absorption 📀	High
PI	hysicochemical Properties	BBB permeant 📀	No
Formula	C22H25N3O6	P-gp substrate 📀	Yes
Molecular weight	427.45 g/mol	CYP1A2 inhibitor 📀	Yes
Num. heavy atoms	31	CYP2C19 inhibitor 🛞	Yes
Num. arom. heavy atoms	12	CYP2C9 inhibitor 📀	Yes
Fraction Csp3	0.32	CYP2D6 inhibitor 📀	No
Num. rotatable bonds	9	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	8	Log K _n (skin permeation) 🥹	-7.06 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	112.45	Lipinski 😗	Yes: 0 violation
TPSA 🤨	99.22 Ų	Ghose ()	Yes
	Lipophilicity	Veber 🖗	Yes
Log P _{o/w} (iLOGP) 📀	2.97	Faan 🙆	Vec
Log Polw (XLOGP3) 🔞	2.60	Mueade ()	Yes
Log Polw (WLOGP) 😣	1.93	Bioavailability Score @	0.56
Log Polw (MLOGP) 📀	-0.99		Medicinal Chemistry
Log Polw (SILICOS-IT) 😣	2.62	PAINS 🥹	1 alert: quinone_A 🥹
Consensus Log Polw 📀	1.83	Brenk 😕	0 alert
		Leadlikeness 📀	No; 2 violations: MW>350, Rotors>7
		Synthetic accessibility 🥹	3.89

Molecule 7			
# 0			Water Solubility
	LIPO	Log S (ESOL) 😶	-4.09
CH, O		Solubility	3.80e-02 mg/ml ; 8.12e-05 mol/l
	FLEX	Class 📀	Moderately soluble
		Log S (Ali) 😣	-4.26
Ŷ i		Solubility	2.57e-02 mg/ml ; 5.48e-05 mol/l
		Class 🔞	Moderately soluble
\sim	INSATU	Log S (SILICOS-IT)	-5.77
		Solubility	7.99e-04 mg/ml; 1.71e-06 mol/l
HO		Class 📀	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES OCCN1CCN(CC1)C1=C(Oc2cc(OC)c(c(c2)OC)OC)C(=O)c2c(C1=O)c	GI absorption 📀	High
ccc2		BBB permeant 📀	No
P	hysicochemical Properties	P-gp substrate 🐵	Yes
Formula	G25H28N2O7	CYP1A2 inhibitor 😣	No
Molecular weight	468.50 g/moi	CYP2C19 inhibitor 🤨	Yes
Num. neavy atoms	34	CYP2C9 inhibitor 😣	Yes
Fraction Con?	12	CYP2D6 inhibitor 📀	No
Num rotatable bonds	0.00	CYP3A4 inhibitor 🥹	Yes
Num. H-bond acceptors	8	Log K _p (skin permeation) 😣	-7.34 cm/s
Num H-bond donors	1		Druglikeness
Molar Refractivity	131.24	Lipinski 🐵	Yes; 0 violation
TPSA 😕	97.77 Ų	Ghose 🙁	No; 1 violation: MR>130
	Lipophilicity	Veber 😣	Yes
Log Polw (iLOGP) 😣	3.67	Egan 😣	Yes
Log Polw (XLOGP3)	2.56	Muegge 🛞	Yes
Log Poly (WLOGP)	1.23	Bioavailability Score 📀	0.56
Log Poly (MLOGP)	-0.36		Medicinal Chemistry
	2.00	PAINS 😣	1 alert: quinone_A 🥹
	2.02	Brenk 😣	0 alert
Consensus Log Poly	1.98	Leadlikeness 📀	No; 2 violations: MW>350, Rotors>7
		Synthetic accessibility 📀	4.20

Reference Molecules

Molecule 8			
₩ ⊕ 🖌			Water Solubility
04	LIPO	Log S (ESOL) 🧐	-2.55
l l		Solubility	8.62e-01 mg/ml; 2.81e-03 mol/l
N	FLEX SIZE	Class ()	Soluble
		Log S (Ali) 🤗	-2.43
V Y		Solubility	1 15e+00 mg/ml : 3 76e-03 mol/l
0 <u> </u>		Class ()	Polublo
Ň			
\int	INSATU POLAR	Log S (SILICOS-IT)	-3.81
		Solubility	4.73e-02 mg/mi ; 1.54e-04 mol/l
NH	INSOLU	Class 👽	Soluble
SMILES October201cccc2	S(-0)(-0)N1CCNCCC1	Claboaration 0	Pharmacokinetics
SWIELS OF INCOLOR		Grabsorption 😌	nigh
Formula	C14H17N3O3S	BBB permeant	No
Molecular weight	307 37 g/mol	P-gp substrate 🐨	Tes No.
Num, heavy atoms	21	CYPIA2 Inhibitor	No
Num. arom, heavy atoms	10	CYP2C19 IIIIIDIUI 😈	No
Fraction Csp3	0.36	CYP2C9 Inhibitor	No
Num. rotatable bonds	2	CYP206 Inhibitor	No
Num. H-bond acceptors	6	Log (/ (okin permection)	7.54
Num. H-bond donors	2	Log N _p (skin permeation)	-7.51 Cm/s
Molar Refractivity	87.50		Druglikeness
TPSA 😕	90.91 Ų	Lipinski 🔮	Yes; U violation
	Lipophilicity	Gnose 😈	Yes
Log P _{o/w} (iLOGP) 😣	1.86	Veber 😈	Yes
Log Poly (XLOGP3) 😣	0.93	Egan 😈	Yes
Log Poly (WLOGP)	1.24	Muegge	Yes
Log Pow (MLOGP)	0.55		0.00 Medicinal Chemistry
Log Poly (SILICOS-IT)	0.59	PAINS ()	0 alert
	4.04	Brenk 🙆	0 alert
Consensus Log Poly	1.04		Yes
		Synthetic accessibility	2.71
		Synthetic accessibility	L.1 1

Molecule 9				
₩ ⊕ 			Water Solubility	
	LIPO	Log S (ESOL) 😣	-3.44	
		Solubility	9.97e-02 mg/ml; 3.60e-04 mol/l	
l II	FLEX SIZE	Class 😣	Soluble	
	N		2.44	
l l l		Log S (All)	-3.44	
		Class 0	1.01e-01 mg/mr, 3.65e-04 moi/i	
	\sim	CidSS 💿	Soluble	
	INSATU	Log S (SILICOS-IT) 🥹	-4.22	
\sim		Solubility	1.66e-02 mg/ml ; 6.01e-05 mol/l	
	INSOLU	Class 🥹	Moderately soluble	
			Pharmacokinetics	
SMILES CIC1=C(N2CCCCC	C2)C(=O)c2c(C1=O)nccc2	GI absorption 😣	High	
Ph	vsicochemical Properties	BBB permeant 😣	Yes	
Formula	C14H13CIN2O2	P-gp substrate 🐵	No	
Molecular weight	276.72 g/mol	CYP1A2 inhibitor 😣	Yes	
Num. heavy atoms	19	CYP2C19 inhibitor 📀	Yes	
Num. arom. heavy atoms	6	CYP2C9 inhibitor 🥹	No	
Fraction Csp3	0.36	CYP2D6 inhibitor 🤨	No	
Num. rotatable bonds	1	CYP3A4 inhibitor 😢	Yes	
Num. H-bond acceptors	3	Log K _p (skin permeation) 📀	-6.05 cm/s	
Num. H-bond donors	0		Druglikeness	
Molar Refractivity	75.57	Lipinski 🥹	Yes; 0 violation	
TPSA 🥹	50.27 A ²	Ghose 📀	Yes	
	Lipophilicity	Veber 🐵	Yes	
Log P _{o/w} (iLOGP) 🥹	1.88	Egan 😣	Yes	
Log P _{o/w} (XLOGP3) 🥹	2.73	Muegge 🔞	Yes	
Log P _{olw} (WLOGP) 😣	2.02	Bioavailability Score 😣	0.55	
Log P _{o/w} (MLOGP) 🤨	0.55		Medicinal Chemistry	
Log P _{o/w} (SILICOS-IT) 😣	2.88	PAINS 😑	2 alerts: ene_one_hal, quinone_A 🥹	
Consensus Log Polw	2.01	Brenk 😣	0 alert	
		Leadlikeness 🛞	Yes	
		Synthetic accessibility 😣	2.94	

Molecule 10						
†† 🛛 🖌			Water Solubility			
H ₂ C	LIPO	Log S (ESOL) 😣	-1.95			
		Solubility	2.75e+00 mg/ml; 1.11e-02 mol/l			
<u> </u>	FLEX	Class 🛞	Very soluble			
		Log S (Ali) 🥹	-1.97			
Ý		Solubility	2.68e+00 mg/ml; 1.08e-02 mol/l			
NH		Class (2)	Very soluble			
	INSATU	Log S (SILICOS-IT) 📀	-3.31			
		Solubility	1.20e-01 mg/ml; 4.85e-04 mol/l			
N		Class 🛞	Soluble			
	INSOLU		Pharmacokinetics			
SMILES C[C@H]([C@@H]	1CC[C@H](CC1)C(=O)Nc1ccncc1)N	GI absorption 🤨	High			
P	hysicochemical Properties	BBB permeant 📀	Yes			
Formula	C14H21N3O	P-gp substrate 📀	No			
Molecular weight	247.34 g/mol	CYP1A2 inhibitor 😣	No			
Num. heavy atoms	18	CYP2C19 inhibitor 😣	No			
Num. arom. heavy atoms	6	CYP2C9 inhibitor 📀	No			
Fraction Csp3	0.57	CYP2D6 inhibitor 📀	No			
Num. rotatable bonds	4	CYP3A4 inhibitor 📀	No			
Num. H-bond acceptors	3	Log K _p (skin permeation) 📀	-7.13 cm/s			
Num. H-bond donors	2		Druglikeness			
Molar Refractivity	72.79	Lipinski 😣	Yes: 0 violation			
TPSA 🤨	68.01 Ų	Ghose 🔋	Yes			
	Lipophilicity	Veber 🔞	Yes			
Log P _{o/w} (iLOGP) 🤫	2.20	Egan 😣	Yes			
Log P _{olw} (XLOGP3) 😣	0.95	Muegge 🙁	Yes			
Log P _{o/w} (WLOGP) 😣	1.98	Bioavailability Score 🧐	0.55			
Log Polw (MLOGP) 🥹	1.13		Medicinal Chemistry			
Log P _{o/w} (SILICOS-IT) 📀	1.56	PAINS 😕	0 alert			
Consensus Log Poly 😣	1.57	Brenk 🐵	0 alert			
		Leadlikeness 🐵	No; 1 violation: MW<250			
		Synthetic accessibility 🧐	2.73			

Molecule 11					
# @ 🖌			Water Solubility		
H,C OH	CH FLEX SIZE	Log S (ESOL) ⁽²⁾ Solubility Class ⁽²⁾	-3.75 1.05e-01 mg/ml ; 1.78e-04 mol/l Soluble		
		Log S (Ali) 🥹 Solubility Class 😔	-3.55 1.65e-01 mg/ml ; 2.81e-04 mol/l Soluble		
H,C.M., CH	INSATU POLAR	Log S (SILICOS-IT) 😣 Solubility Class 😔	-3.18 3.85e-01 mg/ml ; 6.55e-04 mol/l Soluble		
	110020		Pharmacokinetics		
COc1cc(cc(c10) SMILES (c2c1cc10COc1c ([C@H]10)0)C	DC)[C@H]1[C@H]2C(=0)OC[C@@H]2[C@@H] :2)OC10[C@@H]2C0[C@H](0[C@H]2[C@@H]	GI absorption 🤨 BBB permeant 🥝	Low No		
P	hysicochemical Properties	P-gp substrate 🧐	Yes		
Formula	C29H32O13	CYP1A2 inhibitor 🥹	No		
Molecular weight	588.56 g/mol	CYP2C19 inhibitor 🧐	No		
Num. heavy atoms	42	CYP2C9 inhibitor 🥹	No		
Num. arom. heavy atoms	12	CYP2D6 inhibitor 🥹	Yes		
Fraction Csp3	0.55	CYP3A4 inhibitor 🥹	No		
Num. rotatable bonds	5	Log K _p (skin permeation) ⁽⁹⁾	-9.46 cm/s		
Num. H-bond acceptors	13		Druglikeness		
Num. H-bond donors	3	Lipinski 📀	No; 2 violations: MW>500, NorO>10		
Molar Refractivity	139.11	Ghose 🙁	No; 3 violations: MW>480, MR>130, #atoms>70		
TPSA 😕	160.83 Ų	Veber 🙁	No; 1 violation: TPSA>140		
	Lipophilicity	Egan 😣	No; 1 violation: TPSA>131.6		
Log P _{olw} (iLOGP) 🥹	3.24	Muegge 😕	No; 2 violations: TPSA>150, H-acc>10		
Log P _{o/w} (XLOGP3) 😣	0.60	Bioavailability Score 😣	0.17		
Log P _{o/w} (WLOGP) 😢	1.01		Medicinal Chemistry		
Log Poly (MLOGP)	-0.14	PAINS 😣	0 alert		
Log Poly (SILICOS-IT)	0.95	Brenk 🥹	0 alert		
	1 12	Leadlikeness 🛞	No; 1 violation: MW>350		
Conscisus Log Folw	1.10	Synthetic accessibility 📀	6.27		

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$SMLES \begin{array}{c} Coc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H]}{Cass} \\ Coc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H]}{Cass} \\ SMLES \begin{array}{c} Coc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H]}{Cass} \\ Polar \\$
SMILES Coc1c(OC)cc(cc10C)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Moderately soluble Log S (Ali) • For any of the second seco
Image: Street
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Solubility 6.24e-04 mg/ml ; 1.26e-06 mol/l Class Moderately soluble PoLAR Log S (SILICOS-IT) INSALU FoLAR NSOLU Log S (SILICOS-IT) Solubility 2.30e-04 mg/ml ; 4.61e-07 mol/l Class Poorly soluble Pharmacokinetics Pharmacokinetics Gl absorption Low BBB permeant No P-gp substrate No
INSATU POLAR Class @ Moderately soluble INSOLU POLAR Log S (SILICOS-IT) @ -6.34 Solubility 2.30e-04 mg/ml ; 4.61e-07 mol/l Class @ Class Poorly soluble Pharmacokinetics SMILES Coc1c(OC)cc(cc10C)[C@@H]1[C@H]2C(=0)OC[C@@H]2[C@@H] Gl absorption @ Low BBB permeant @ No Pog substrate @ No
SMILES COC1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Glabsorption ● Low Physicochemical Properties Glabsorption ● No
SMILES COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Gl absorption ● Low BBB permeant ● Physicochemical Properties No
SMILES COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Class @ Poorty soluble SMILES COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Glassorption @ Low Physicochemical Properties BBB permeant @ No P-gp substrate @ No
SMILES COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Gl absorption @ Low Physicochemical Properties BBB permeant @ No P-gp substrate @ No
SMILES COc1c(OC)cc(cc1OC)[C@@H]1[C@H]2C(=O)OC[C@@H]2[C@@H] Gl absorption I Low (c2c1cc1OCOc1c2)Sc1[nH]ncn1 BBB permeant I No Physicochemical Properties P-gp substrate I No
BBB permeant No Physicochemical Properties P-gp substrate No
P-gp substrate O No
Formula C24H23N3O7S CYP1A2 inhibitor O No
Molecular weight 497.52 g/mol CYP2C19 inhibitor 😔 No
Num. heavy atoms 35 CYP2C9 inhibitor I Yes
Num. arom. heavy atoms 17 CYP2D6 inhibitor [©] Yes
Fraction CSp3 0.38 CYP3A4 inhibitor I Yes
Num. rotatable bonds 6 Log K_n (skin permeation) $=$ -6.99 cm/s
Num Hond acceptors 9 Drudikeness
Num n-bond donois in Construction (Construction)
Molai Reliatuvily 123.07 Chose 9 No: 1 violation: MW>480
LipsA Vebr Ves
Log Poly (il OGP) 2 78 Egan O No; 1 violation: TPSA>131.6
Log Poly (XLOGP3) 9 3.30 Muegge 9 Yes
Bioavailability Score O 0.55
Log Pow (VLOOP) 5.00 Medicinal Chemistry
Log Poly (MLOGP) • 1.60 PAINS • 0 alert
Log P _{0/W} (SILICOS-IT) 🔮 3.41 Brenk 😔 0 alert
Consensus Log Poly 9 2.82 Leadlikeness 9 No; 1 violation: MW>350
Synthetic accessibility 😔 5.13

Molecule 13					
# 0			Water Solubility		
	LIPO	Log S (ESOL) 😣	-4.10		
		Solubility	2.92e-02 mg/ml; 7.93e-05 mol/l		
	FLEX	Class 😟	Moderately soluble		
			4.60		
		Loy 5 (All)	-4.09		
	0-CH,	Class (2)	7.30e-03 mg/mi , 2.03e-03 mol/i		
н.с-0 мн,		Ciass 👽	Moderately soluble		
	INSATU	Log S (SILICOS-IT) 😣	-6.27		
			2.00e-04 mg/ml ; 5.42e-07 mol/l		
	INSOLU	Class 🥹	Poorly soluble		
			Pharmacokinetics		
SMILES COc1cc(cc(c1OC)	SMILES COc1cc(cc(c1OC)OC)C(=O)c1ccc2c(n1)ccc(c2N)OC		High		
Ph	ysicochemical Properties	BBB permeant 🧐	No		
Formula	C20H20N2O5	P-gp substrate 📀	No		
Molecular weight	368.38 g/mol	CYP1A2 inhibitor 😣	Yes		
Num. heavy atoms	27	CYP2C19 inhibitor 😣	Yes		
Num. arom. heavy atoms	16	CYP2C9 inhibitor 😣	Yes		
Fraction Csp3	0.20	CYP2D6 inhibitor 😣	Yes		
Num. rotatable bonds	6	CYP3A4 inhibitor 😣	Yes		
Num. H-bond acceptors	6	Log K _p (skin permeation) 😣	-6.37 cm/s		
Num. H-bond donors	1		Druglikeness		
Molar Refractivity	101.99	Lipinski 😣	Yes; 0 violation		
TPSA 🥹	92.90 A ²	Ghose 🛞	Yes		
	Lipophilicity	Veber 😢	Yes		
Log Polw (ILOGP)	3.22	Egan 📀	Yes		
Log Polw (XLOGP3)	3.07	Muegge 😣	Yes		
Log P _{o/w} (WLOGP) 😣	3.09	Bioavailability Score 😣	0.55		
Log Polw (MLOGP) 🧐	0.63		Medicinal Chemistry		
Log Polw (SILICOS-IT)	3.35	PAINS (2)	0 alert		
Consensus Log Polw	2.67	Brenk 😕	1 alert: aniline 🥹		
		Leadlikeness 📀	No; 1 violation: MW>350		
		Synthetic accessibility 🥹	2.83		



Figure S1. Overlapping of the energy minimized structures **1b** (in red), PT-262 (in green) and podophyllotoxin (in blue). Hydrogen atoms are omitted for clarity.



Figure S2. ¹HNMR spectrum (400MHz, CDCl₃) of compound 1a.



Figure S3. ¹H,¹³C correlations by HSQC experiment (400MHz, CDCl₃) of 1a.



Figure S4. ¹H,¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 1a.



Figure S5. ¹HNMR spectrum (400MHz, CDCl₃) of compound 1b.



Figure S6. ¹H, ¹³C correlations by HSQC experiment (400MHz, CDCl₃) of **1b**.



Figure S7. ¹H, ¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of **1b**.



Figure S8. ¹HNMR spectrum (400MHz, CDCl₃) of compound 1c.



Figure S9. ¹H,¹³C correlations by HSQC experiment (400MHz, CDCl₃) of 1c.



Figure S10. ¹H,¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 1c.



Figure S11. ¹HNMR spectrum (400MHz, CDCl₃) of compound 2a.



Figure S13. ¹H, ¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 2a.



Figure S15. ¹H, ¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 2b.



Figure S16. ¹HNMR spectrum (400MHz, CDCl₃) of compound 2c.



Figure S17. ¹H, ¹³C correlations by HSQC experiment (400MHz, CDCl₃) of 2c.



Figure S18. ¹H,¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 2c.



Figure S19. ¹HNMR spectrum (400MHz, CDCl₃) of compound 3.



Figure S20. ¹H, ¹³C correlations by HSQC experiment (400MHz, CDCl₃) of 3.



Figure S21. ¹H, ¹³C long range correlations by HMBC experiment (400MHz, CDCl₃) of 3.





Figure S23. ¹HNMR spectrum (400MHz, CDCl₃) of precursor 5.