SUPPORTING INFORMATION FOR:

In vitro and *In vivo* Studies of Dehydroxylated-isoquines and -Isotebuquines Against Trypanosomatids: A Preclinical Drug Candidate for Treatment of Cutaneous Leishmaniasis

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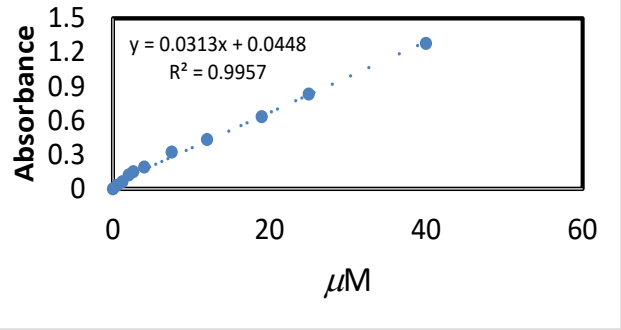
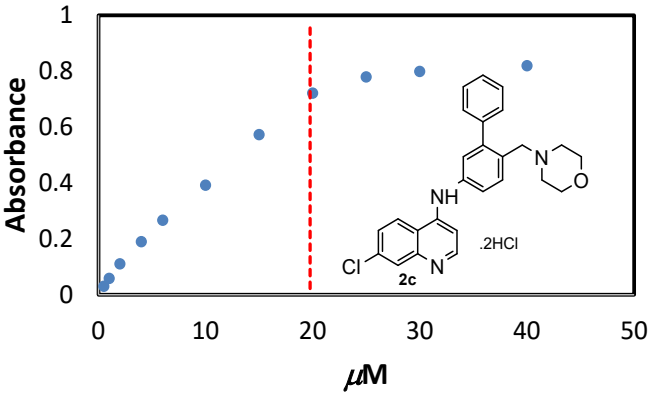
1. Experimental ADME-properties Data

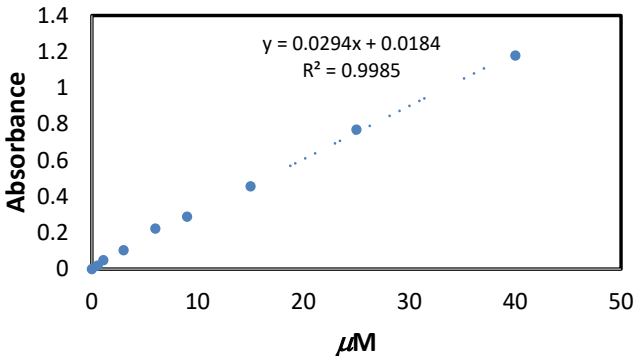
Table S1. Water-solubility determination data for compound **2c**.

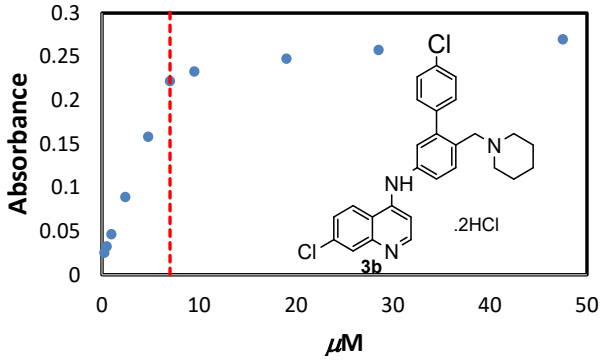




Entries	Sample (mg/mL)	[M]	Dilution 1/200, [M]	[μM]	Absorbance
1	20 mg/mL	0.04	0.00004	30	0.8
2	15 mg/mL	0.03	0.00003	25	0.78
3	10 mg/mL	0.02	0.00002	20	0.72233
4	7.5 mg/mL	0.015	0.000015	15	0.57332
5	5 mg/mL	0.01	0.00001	10	0.39222
6	3 mg/mL	0.006	0.000006	6	0.2667
7	2 mg/mL	0.004	0.000004	4	0.19032
8	1 mg/mL	0.002	0.000002	2	0.111
9	0.5 mg/mL	0.001	0.000001	1	0.05884
10	0.25 mg/mL	0.0005	0.0000005	0.5	0.031

Table S2. Water-solubility determination data for compound **3b**.

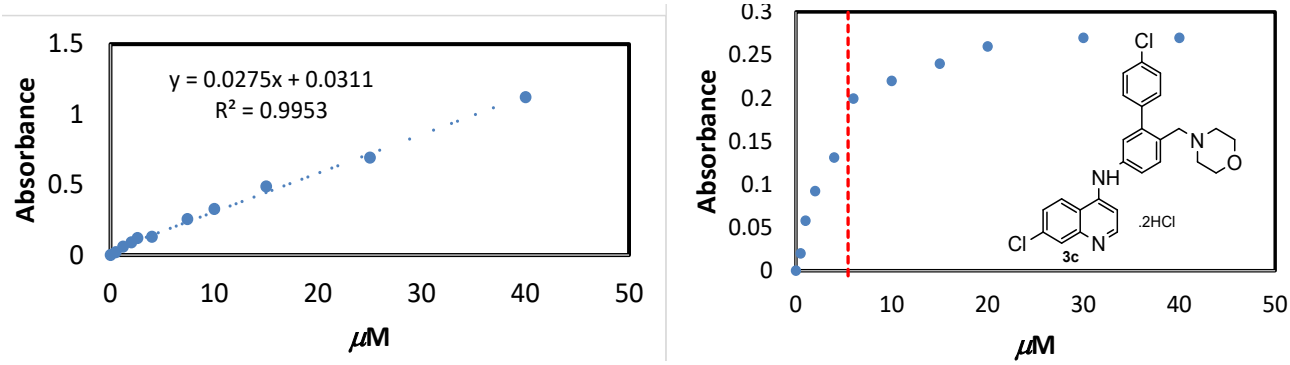




Entries	Sample (mg/mL)	[M]	Dilution 1/200, [M]	[μM]	Absorbance

1	5	0.0095	0.0000475	47.5	0.27
2	3	0.0057	0.0000285	28.5	0.25777
3	2	0.0038	0.000019	19	0.24776
4	1	0.0019	0.0000095	9.5	0.233
5	**0.75**	**0.0014**	**0.000007**	**7**	**0.222**
6	0.5	0.00095	0.00000475	4.75	0.15805
7	0.25	0.00048	0.0000024	2.4	0.08896
8	0.10	0.00019	0.00000095	0.95	0.04633
9	0.05	0.000095	4.75E-07	0.475	0.03237
10	0.025	0.000048	0.00000024	0.24	0.0253

Table S3. Water-solubility determination data for compound **3c**.



Entries	Sample (mg/mL)	[M]	Dilution 1/200, [M]	[μM]	Absorbance
1	20 mg/mL	0.04	0.00004	40	0.27
2	15 mg/mL	0.03	0.00003	30	0.27
3	10 mg/mL	0.02	0.00002	20	0.26
4	7.5 mg/mL	0.015	0.000015	15	0.24
5	5 mg/mL	0.01	0.00001	10	0.22
6	3 mg/mL	0.006	0.000006	6	0.1995
7	2 mg/mL	0.004	0.000004	4	0.13111
8	1 mg/mL	0.002	0.000002	2	0.09221
9	0.5 mg/mL	0.001	0.000001	1	0.057888
10	0.25 mg/mL	0.0005	0.0000005	0.5	0.02

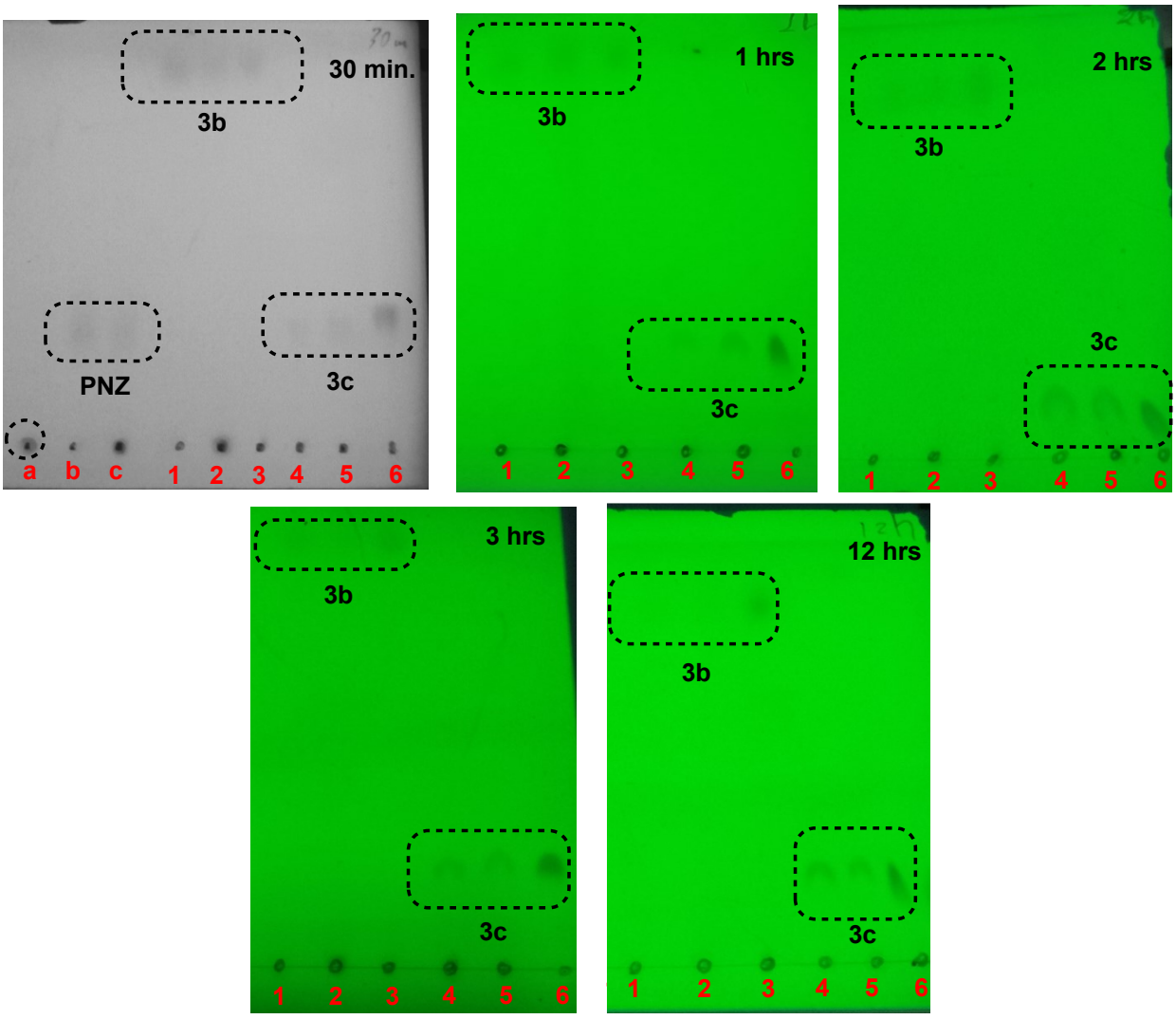


Figure S1. Metabolic stability studies at 30 minutes, 1 hour, 2 hours 3 hours and 12 hours. Experiments were analyzed from silice gel TLC using *n*-hexane/ethyl acetate (7:3). N^1,N^5-phenazine-dioxide (PNZ) was used as positive control. No metabolic conditions (medium) involve the following lanes with corresponding compound: lane **a** (N^1,N^5-phenazine-dioxide), lane **1** (compound **3b)** lane **4** (compound **3c)**. Experiments in microsomal environment involve the following lanes with corresponding compounds: lane **b** (N^1,N^5-phenazine-dioxide), lane **2** (compound **3b)** and lane **5** (compound **3c)**. Experiments in cytosolic environment involve lane **c** (N^1,N^5-phenazine-dioxide), lane **3** (compound **3b)** and lane **6** (compound **3c).**

Table S4. Summary about metabolic study from TLC experimentation for N^1,N^5-phenazine-dioxide and quinolínic compounds **3b** and **3c**.

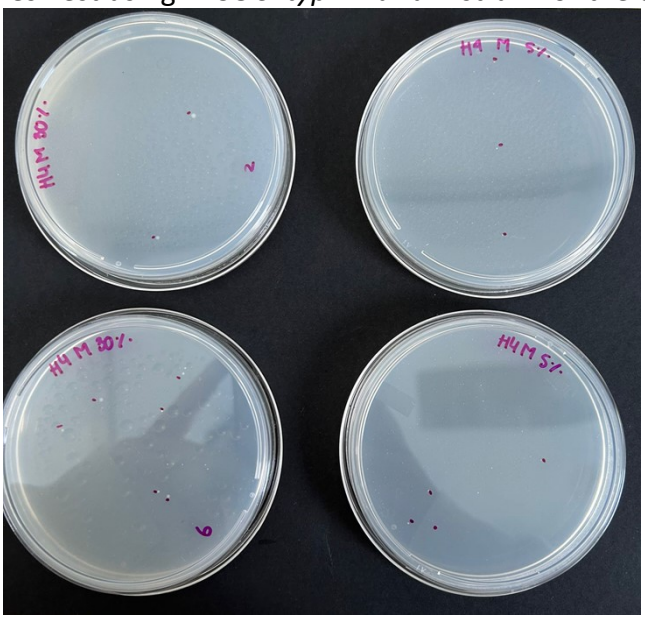
Compounds	**Conditions**	R_f			
		30 min.	**1 h**	**2 h**	**3 h**
PNZ	**No metabolic**	0.05	---	---	---

	Microsomal	0.32	---	---	---
	Cytosolic	0.32 0.05 (trace)	---	---	---
	Result	Transform under hepatic microsomal and cytosolic environments			
3b	**No metabolic**	**0.92**	**0.92**	**0.92**	**0.92**
	Microsomal	**0.92**	**0.92**	**0.92**	**0.92**
	Cytosolic	**0.92**	**0.92**	**0.92**	**0.92**
	Result	Stable under hepatic microsomal and cytosolic environments			
	No metabolic	**0.31**	**0.31**	**0.31**	**0.31**
3c	**Microsomal**	**0.31**	**0.31**	**0.31**	**0.31**
	Cytosolic	**0.31**	**0.31**	**0.31**	**0.31**
	Result	Stable under hepatic microsomal and cytosolic environments			

Table S5a. Ames Test using TA98 *S. typhimurium* strain for the compound **3b**.

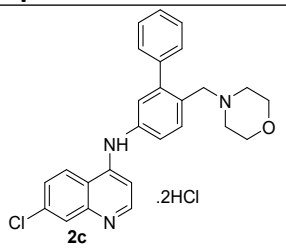
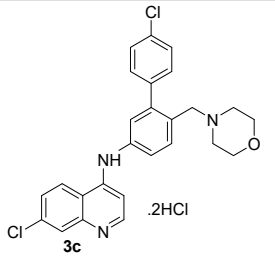
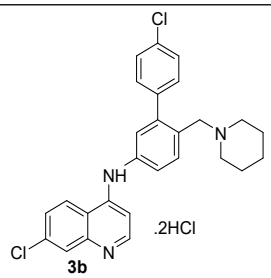
Entries	**[mM]**	**Number of revertants**		
		TA98	**TA98+S9 (30%)**	**TA98+S9(5%)**
1	18.7	5.1 ± 2.1	4.0 ± 2.0	3.5 ± 0.7
2	6.2	3.8 ± 0.7	5.0 ± 2.0	3.0 ± 1.0
3	2.1	---	4.5 ± 2.1	3.5 ± 0.7
4	0.7	4.0 ± 1.0	3.0± 0.0	4.0 ± 0.0
5	0.2	3.0 ± 1.0	3.0 ± 1.0	4.5 ± 0.7
6	C-	9 ± 4		
7	C + (NPA)	102		

Table S5b. Ames Test using TA98 *S. typhimurium* strain for the compound **3c**.



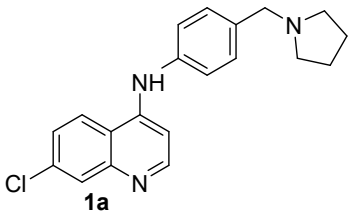
Entries	[mM]	Number of revertants		
		TA98	TA98+S9 (30%)	TA98+S9(5%)
1	18.7	5.1 ± 2.1	4.0 ± 2.0	3.5 ± 0.7
2	6.2	3.8 ± 0.7	5.0 ± 2.0	3.0 ± 1.0
3	2.1	---	4.5 ± 2.1	3.5 ± 0.7
4	0.7	4.0 ± 1.0	3.0± 0.0	4.0 ± 0.0
5	0.2	3.0 ± 1.0	3.0 ± 1.0	4.5 ± 0.7
6	C-	9 ± 4		
7	C + (NPA)	102		

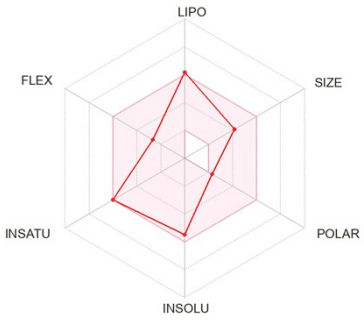
Table S6. *In vitro* hematotoxicity data using human erythrocytes for compounds **2c, 3b** and **3c**.

Compound	[μM]	% Lysis	IC_{50} (μM)
 **2c**	50	8.20 ± 1.73	
	100	25.10 ± 3.83	
	200	47.77 ± 4.84	
	500	98.03 ± 10.70	208.8
 **3c**	50	6.69 ± 0.88	
	100	7.99 ± 0.55	
	200	30.39 ± 4.56	
	500	79.72 ± 7.75	323.4
 **3b**	50	0.00 ± 0.10	
	100	2.02 ± 1.12	
	200	16.80 ± 1.51	
	500	50.83 ± 6.24	493.6

2. Predicted ADME-properties Data

Table S7. Predicted ADME-properties from Swiss-ADME for quinoline **1a**.

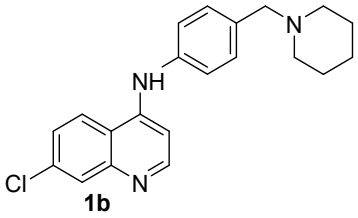


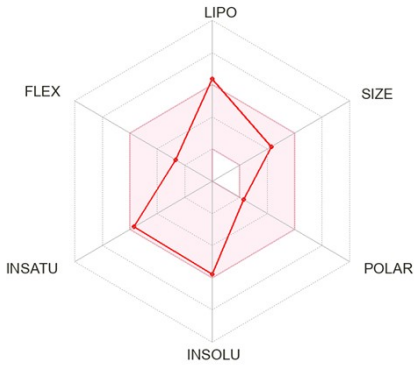


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(cc1)CN1CCCC1
Physicochemical Properties	
Formula	C20H20ClN3
Molecular weight	337.85 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	16
Fraction Csp3	0.25
Num. rotatable bonds	4
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	105.19
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.61
Log $P_{o/w}$ (XLOGP3)	5.29
Log $P_{o/w}$ (WLOGP)	4.69
Log $P_{o/w}$ (MLOGP)	3.69
Log $P_{o/w}$ (SILICOS-IT)	4.51
Consensus Log $P_{o/w}$	4.36
Water Solubility	
Log *S* (ESOL)	-5.50
Solubility	1.08e-03 mg/ml ; 3.19e-06 mol/l

Class	Moderately soluble
Log *S* (Ali)	-5.63
Solubility	7.88e-04 mg/ml ; 2.33e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.70
Solubility	6.68e-06 mg/ml ; 1.98e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.60 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	2.25

Table S8. Predicted ADME-properties from Swiss-ADME for quinoline **1b**.

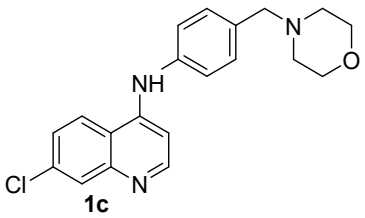


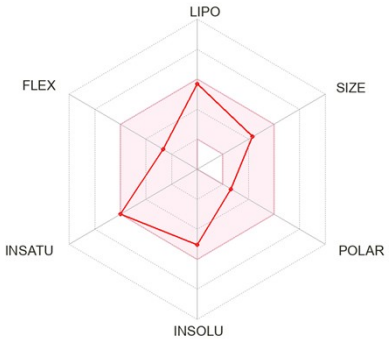


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(cc1)CN1CCCCC1
Physicochemical Properties	
Formula	C21H22ClN3
Molecular weight	351.87 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	16
Fraction Csp3	0.29
Num. rotatable bonds	4
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	109.99
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.91
Log $P_{o/w}$ (XLOGP3)	5.65
Log $P_{o/w}$ (WLOGP)	5.09
Log $P_{o/w}$ (MLOGP)	3.91
Log $P_{o/w}$ (SILICOS-IT)	4.74
Consensus Log $P_{o/w}$	4.66
Water Solubility	
Log *S* (ESOL)	-5.79
Solubility	5.70e-04 mg/ml ; 1.62e-06 mol/l
Class	Moderately soluble

Log *S* (Ali)	-6.01
Solubility	3.47e-04 mg/ml ; 9.87e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.97
Solubility	3.74e-06 mg/ml ; 1.06e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.43 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; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	2.35

Table S9. Predicted ADME-properties from Swiss-ADME for quinoline **1c**.

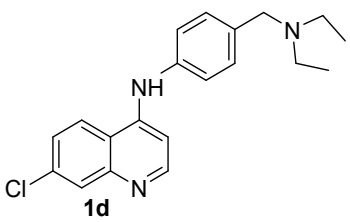


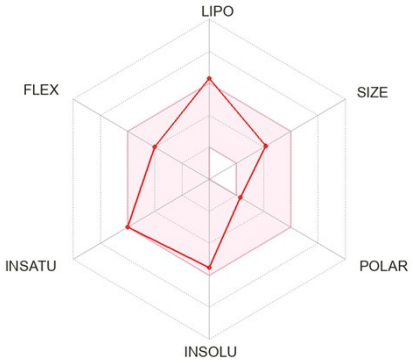


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(cc1)CN1CCOCC1
Physicochemical Properties	
Formula	C20H20ClN3O
Molecular weight	353.85 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	16
Fraction Csp3	0.25
Num. rotatable bonds	4
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	106.27
TPSA	37.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.50
Log $P_{o/w}$ (XLOGP3)	4.43
Log $P_{o/w}$ (WLOGP)	3.93
Log $P_{o/w}$ (MLOGP)	2.84
Log $P_{o/w}$ (SILICOS-IT)	4.10
Consensus Log $P_{o/w}$	3.76
Water Solubility	
Log *S* (ESOL)	-5.03
Solubility	3.27e-03 mg/ml ; 9.24e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.93

Solubility	4.12e-03 mg/ml ; 1.17e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.43
Solubility	1.30e-05 mg/ml ; 3.68e-08 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)	-5.31 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	2.44

Table S10. Predicted ADME-properties from Swiss-ADME for quinoline **1d**.

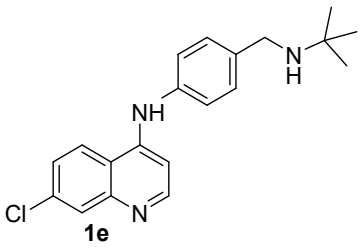


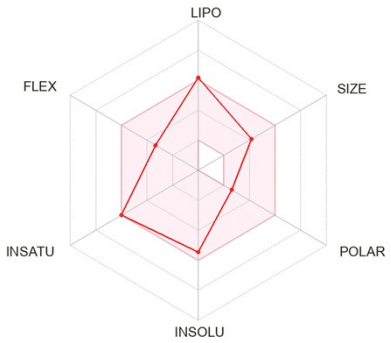


SMILES	CCN(Cc1ccc(cc1)Nc1ccnc2c1ccc(c2)Cl)CC
Physicochemical Properties	
Formula	C20H22ClN3
Molecular weight	339.86 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	16
Fraction Csp3	0.25
Num. rotatable bonds	6
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	103.39
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.82
Log $P_{o/w}$ (XLOGP3)	5.54
Log $P_{o/w}$ (WLOGP)	5.32
Log $P_{o/w}$ (MLOGP)	3.69
Log $P_{o/w}$ (SILICOS-IT)	4.60
Consensus Log $P_{o/w}$	4.59
Water Solubility	
Log *S* (ESOL)	-5.53
Solubility	9.92e-04 mg/ml ; 2.92e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.89

Solubility	4.36e-04 mg/ml ; 1.28e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-8.18
Solubility	2.26e-06 mg/ml ; 6.65e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.44 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	2.40

Table S11. Predicted ADME-properties from Swiss-ADME for quinoline **1e**.

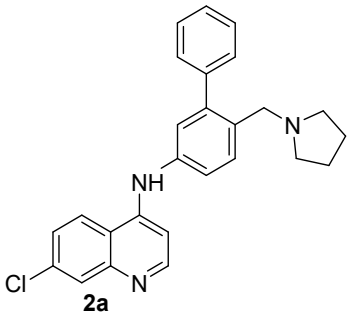


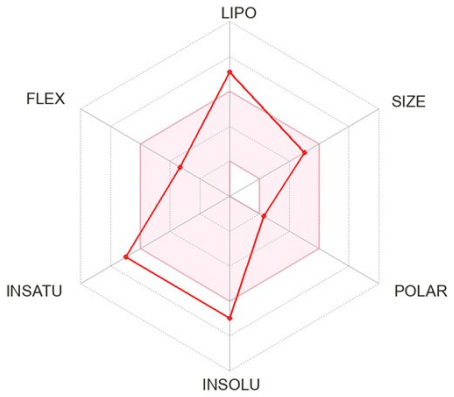


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(cc1)CNC(C)(C)C
Physicochemical Properties	
Formula	C20H22ClN3
Molecular weight	339.86 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	16
Fraction Csp3	0.25
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	2
Molar Refractivity	103.33
TPSA	36.95 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.79
Log $P_{o/w}$ (XLOGP3)	5.32
Log $P_{o/w}$ (WLOGP)	5.37
Log $P_{o/w}$ (MLOGP)	3.69
Log $P_{o/w}$ (SILICOS-IT)	4.72
Consensus Log $P_{o/w}$	4.58
Water Solubility	
Log *S* (ESOL)	-5.46
Solubility	1.17e-03 mg/ml ; 3.45e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.85
Solubility	4.83e-04 mg/ml ; 1.42e-06 mol/l

Class	Moderately soluble
Log *S* (SILICOS-IT)	-8.52
Solubility	1.03e-06 mg/ml ; 3.03e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.60 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	2.38

Table S12. Predicted ADME-properties from Swiss-ADME for quinoline **2a**.

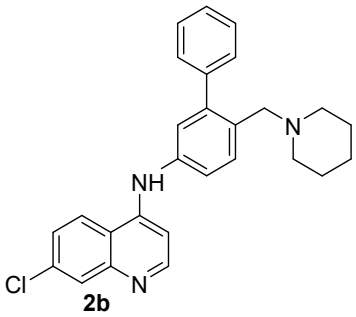


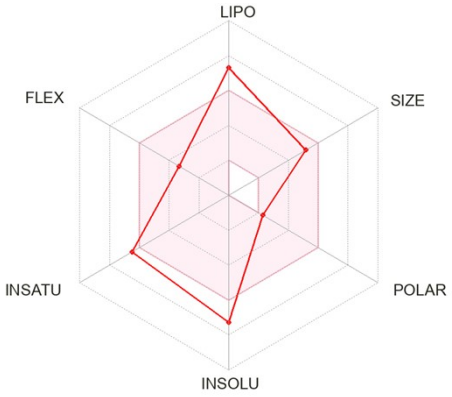


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(c(c1)c1ccccc1)CN1CCCC1
Physicochemical Properties	
Formula	C26H24ClN3
Molecular weight	413.94 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	130.62
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.15
Log $P_{o/w}$ (XLOGP3)	6.92
Log $P_{o/w}$ (WLOGP)	6.36
Log $P_{o/w}$ (MLOGP)	4.72
Log $P_{o/w}$ (SILICOS-IT)	6.05
Consensus Log $P_{o/w}$	5.64
Water Solubility	
Log *S* (ESOL)	-6.98
Solubility	4.35e-05 mg/ml ; 1.05e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.32

Solubility	1.97e-05 mg/ml ; 4.75e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.16
Solubility	2.85e-08 mg/ml ; 6.89e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-3.91 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	2.94

Table S13. Predicted ADME-properties from Swiss-ADME for quinoline **2b**.

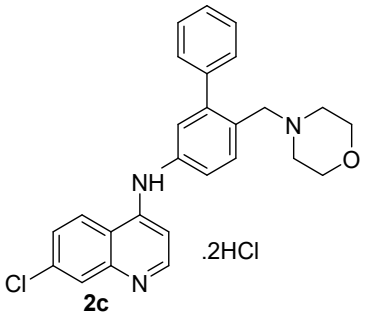




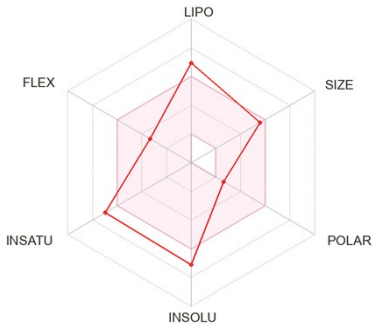
SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(c(c1)c1ccccc1)CN1CCCCC1
Physicochemical Properties	
Formula	C27H26ClN3
Molecular weight	427.97 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	135.43
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.32
Log $P_{o/w}$ (XLOGP3)	7.28
Log $P_{o/w}$ (WLOGP)	6.75
Log $P_{o/w}$ (MLOGP)	4.92
Log $P_{o/w}$ (SILICOS-IT)	6.28
Consensus Log $P_{o/w}$	5.91
Water Solubility	
Log *S* (ESOL)	-7.27
Solubility	2.27e-05 mg/ml ; 5.31e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.70

Solubility	8.60e-06 mg/ml ; 2.01e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.43
Solubility	1.60e-08 mg/ml ; 3.73e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.74 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.03

Table S14. Predicted ADME-properties from Swiss-ADME for quinoline **2c**.



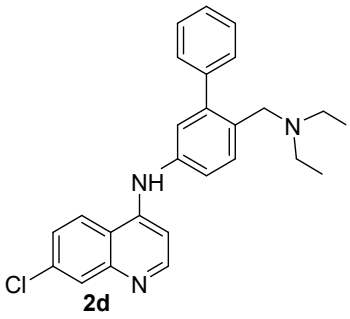
2c

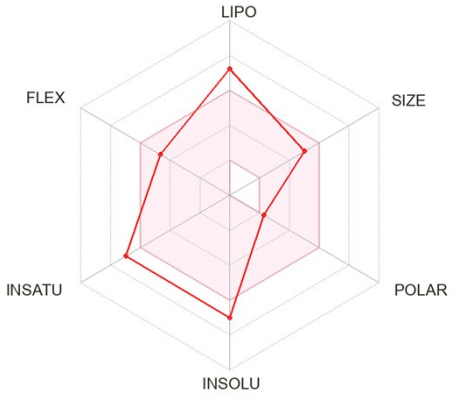


SMILES	Clc1ccc2c(c1)nccc2Nc1ccc(c(c1)c1ccccc1)CN1CCOCC1
Physicochemical Properties	
Formula	C26H24ClN3O
Molecular weight	429.94 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	131.71
TPSA	37.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.98
Log $P_{o/w}$ (XLOGP3)	6.06
Log $P_{o/w}$ (WLOGP)	5.60
Log $P_{o/w}$ (MLOGP)	3.87
Log $P_{o/w}$ (SILICOS-IT)	5.63
Consensus Log $P_{o/w}$	5.03
Water Solubility	
Log *S* (ESOL)	-6.52
Solubility	1.30e-04 mg/ml ; 3.03e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-6.62
Solubility	1.02e-04 mg/ml ; 2.37e-07 mol/l
Class	Poorly soluble

Log *S* (SILICOS-IT)	-9.89
Solubility	5.58e-08 mg/ml ; 1.30e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.612 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	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.08

Table S15. Predicted ADME-properties from Swiss-ADME for quinoline **2d**.

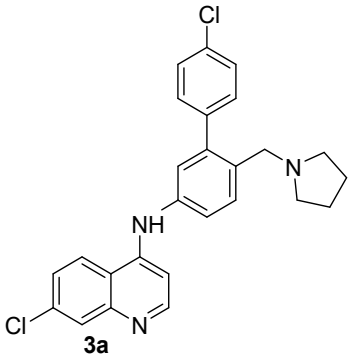


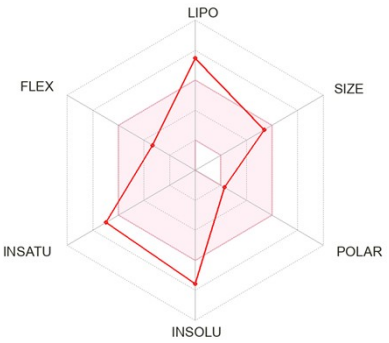


SMILES	CCN(Cc1ccc(cc1c1ccccc1)Nc1ccnc2c1ccc(c2)Cl)CC
Physicochemical Properties	
Formula	C26H26ClN3
Molecular weight	415.96 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	7
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	128.82
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.13
Log $P_{o/w}$ (XLOGP3)	7.16
Log $P_{o/w}$ (WLOGP)	6.99
Log $P_{o/w}$ (MLOGP)	4.72
Log $P_{o/w}$ (SILICOS-IT)	6.21
Consensus Log $P_{o/w}$	5.84
Water Solubility	
Log *S* (ESOL)	-7.01
Solubility	4.06e-05 mg/ml ; 9.76e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.57

Solubility	1.11e-05 mg/ml ; 2.68e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.63
Solubility	9.64e-09 mg/ml ; 2.32e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-3.75 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: WLOGP>5.6
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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.11

Table S16. Predicted ADME-properties from Swiss-ADME for quinoline **3a**.

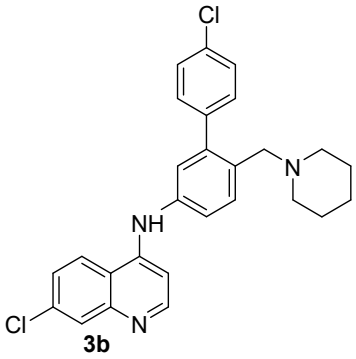


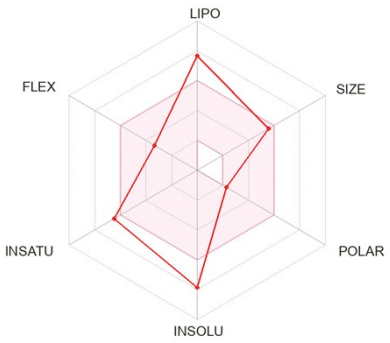


SMILES	Clc1ccc(cc1)c1cc(ccc1CN1CCCC1)Nc1ccnc2c1ccc(c2)Cl
Physicochemical Properties	
Formula	C26H23Cl2N3
Molecular weight	448.39 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	135.63
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.43
Log $P_{o/w}$ (XLOGP3)	7.55
Log $P_{o/w}$ (WLOGP)	7.02
Log $P_{o/w}$ (MLOGP)	5.19
Log $P_{o/w}$ (SILICOS-IT)	6.68
Consensus Log $P_{o/w}$	6.17
Water Solubility	
Log *S* (ESOL)	-7.57
Solubility	1.20e-05 mg/ml ; 2.68e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.98
Solubility	4.73e-06 mg/ml ; 1.05e-08 mol/l

Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.74
Solubility	8.07e-09 mg/ml ; 1.80e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.67 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	2.97

Table S17. Predicted ADME-properties from Swiss-ADME for quinoline **3b**.

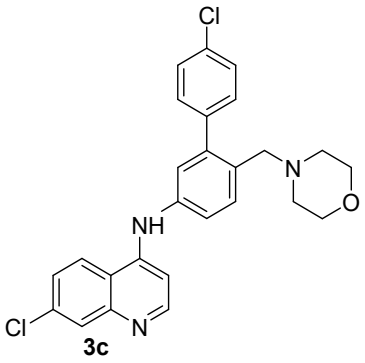


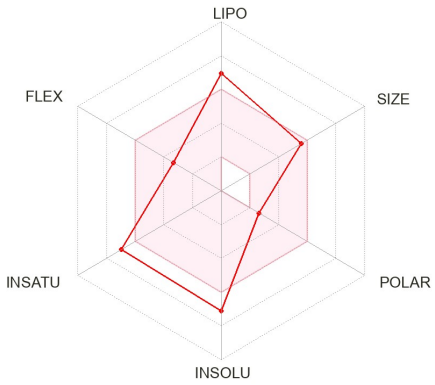


SMILES	Clc1ccc(cc1)c1cc(ccc1CN1CCCCC1)Nc1ccnc2c1ccc(c2)Cl
Physicochemical Properties	
Formula	C27H25Cl2N3
Molecular weight	462.41 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	140.44
TPSA	28.16 Å²
1Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.66
Log $P_{o/w}$ (XLOGP3)	7.90
Log $P_{o/w}$ (WLOGP)	7.41
Log $P_{o/w}$ (MLOGP)	5.39
Log $P_{o/w}$ (SILICOS-IT)	6.91
Consensus Log $P_{o/w}$	6.45
Water Solubility	
Log *S* (ESOL)	-7.86
Solubility	6.34e-06 mg/ml ; 1.37e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-8.34
Solubility	2.11e-06 mg/ml ; 4.57e-09 mol/l

Class	Poorly soluble
Log *S* (SILICOS-IT)	-11.01
Solubility	4.53e-09 mg/ml ; 9.79e-12 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.51 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.07

Table S18. Predicted ADME-properties from Swiss-ADME for quinoline **3c**.

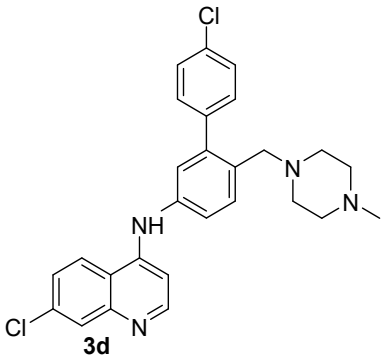


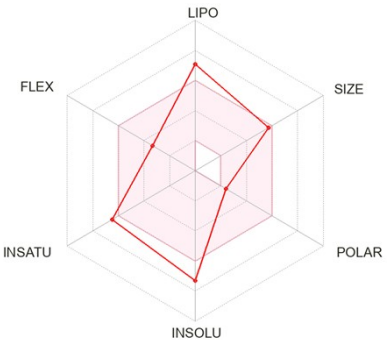


SMILES	Clc1ccc(cc1)c1cc(ccc1CN1CCOCC1)Nc1ccnc2c1ccc(c2)Cl
Physicochemical Properties	
Formula	C26H23Cl2N3O
Molecular weight	464.39 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	136.72
TPSA	37.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.14
Log $P_{o/w}$ (XLOGP3)	6.68
Log $P_{o/w}$ (WLOGP)	6.25
Log $P_{o/w}$ (MLOGP)	4.34
Log $P_{o/w}$ (SILICOS-IT)	6.26
Consensus Log $P_{o/w}$	5.54
Water Solubility	
Log *S* (ESOL)	-7.11
Solubility	3.64e-05 mg/ml ; 7.83e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.27
Solubility	2.50e-05 mg/ml ; 5.39e-08 mol/l

Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.47
Solubility	1.58e-08 mg/ml ; 3.40e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.39 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.11

Table S19. Predicted ADME-properties from Swiss-ADME for quinoline **3d**.

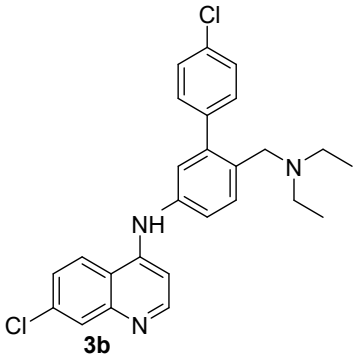




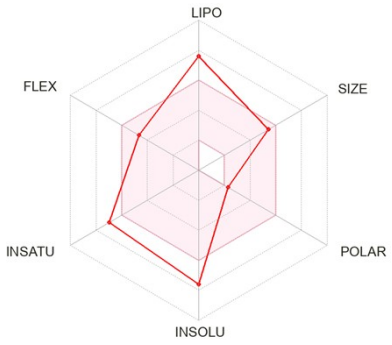
SMILES	CN1CCN(CC1)Cc1ccc(cc1c1ccc(cc1)Cl)Nc1ccnc2c1ccc(c2)Cl
Physicochemical Properties	
Formula	C27H26Cl2N4
Molecular weight	477.43 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	147.25
TPSA	31.40 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.52
Log $P_{o/w}$ (XLOGP3)	6.87
Log $P_{o/w}$ (WLOGP)	5.79
Log $P_{o/w}$ (MLOGP)	4.54
Log $P_{o/w}$ (SILICOS-IT)	5.89
Consensus Log $P_{o/w}$	5.52
Water Solubility	
Log *S* (ESOL)	-7.29
Solubility	2.44e-05 mg/ml ; 5.11e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.34
Solubility	2.18e-05 mg/ml ; 4.58e-08 mol/l

Class	Poorly soluble
Log *S* (SILICOS-IT)	-10.44
Solubility	1.74e-08 mg/ml ; 3.65e-11 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.33 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 2 violations: WLOGP>5.6, MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.27

Table S20. Predicted ADME-properties from Swiss-ADME for quinoline **3e**.



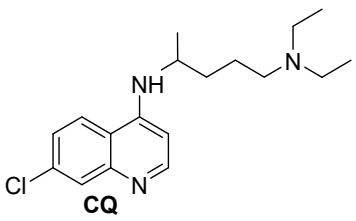
3b

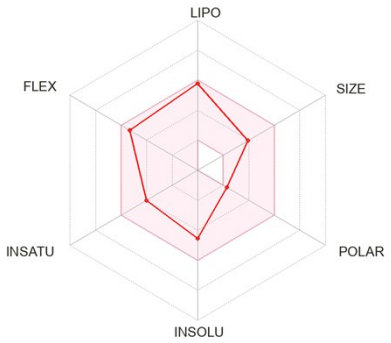


SMILES	CCN(Cc1ccc(cc1c1ccc(cc1)Cl)Nc1ccnc2c1ccc(c2)Cl)CC
Physicochemical Properties	
Formula	C26H25Cl2N3
Molecular weight	450.40 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	7
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	133.83
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.35
Log $P_{o/w}$ (XLOGP3)	7.79
Log $P_{o/w}$ (WLOGP)	7.64
Log $P_{o/w}$ (MLOGP)	5.19
Log $P_{o/w}$ (SILICOS-IT)	6.85
Consensus Log $P_{o/w}$	6.36
Water Solubility	
Log *S* (ESOL)	-7.60
Solubility	1.12e-05 mg/ml ; 2.49e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-8.23
Solubility	2.68e-06 mg/ml ; 5.94e-09 mol/l

Class	Poorly soluble
Log *S* (SILICOS-IT)	-11.22
Solubility	2.73e-09 mg/ml ; 6.05e-12 mol/l
Class	Insoluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-3.52 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	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.14

Table S21. Predicted ADME-properties from Swiss-ADME for chloroquine.





SMILES	CCN(CCCC(Nc1ccnc2c1ccc(c2)Cl)C)CC
Physicochemical Properties	
Formula	C18H26ClN3
Molecular weight	319.87 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	10
Fraction Csp3	0.50
Num. rotatable bonds	8
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	97.41
TPSA	28.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.95
Log $P_{o/w}$ (XLOGP3)	4.63
Log $P_{o/w}$ (WLOGP)	4.62
Log $P_{o/w}$ (MLOGP)	3.20
Log $P_{o/w}$ (SILICOS-IT)	4.32
Consensus Log $P_{o/w}$	4.15
Water Solubility	
Log *S* (ESOL)	-4.55
Solubility	9.05e-03 mg/ml ; 2.83e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.95
Solubility	3.61e-03 mg/ml ; 1.13e-05 mol/l

Class	Moderately soluble
Log *S* (SILICOS-IT)	-6.92
Solubility	3.86e-05 mg/ml ; 1.21e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.96 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: Rotors>7, XLOGP3>3.5
Synthetic accessibility	2.76

3. *In vivo* Efficacy Data

Table S22. Footpad lesion weight and diameter at end of the treatment.

Entries	Treatment	Footpad lesion weight (g)[a,b]	Footpad lesion diameter (cm)[a,b]
1	PBS	0.4993 ± 0.0522	10.10 ± 0.81
2	Glucantime	0.3995 ± 0.0436 (*)	7.17 ± 1.01 (*)
3	**2c**	0.4308 ± 0.0395 (*)	8.08 ± 0.87 (**)
4	**3b**	0.2219 ± 0.0281 (*)	7.33 ± 0.79 (*)

[a]Results are expressed as the mean ± SD of the groups (n=6, number of treated mice). (*) and (**) indicates statistically significant difference compared to the non-treated control (water group) ($P < 0.01$ and $P < 0.05$, respectively).

Table S23. Footpad lesion thickness diameter (mm) weekly.

Entries	Time (week)	Untreated[a,b]	Glucantime[a,b]	3b	3c
1	0	2.00 ± 0.10	2.00 ± 0.12	2.00 ± 0.15 (*)	2.00 ± 0.10 (*)
2	7	3.25 ± 0.18 (*)	3.17 ± 0.16 (*)	3.00 ± 0.18 (*)	3.25 ± 0.19 (*)
3	**14**	3.42 ± 0.22 (*)	3.83 ± 0.25 (**)	3.25 ± 0.21 (*)	3.50 ± 0.24 (*)
4	**21**	3.83 ± 0.30 (*)	4.58 ± 0.36 (*)	3.75 ± 0.31 (*)	3.92 ± 0.30 (*)
5	**28**	5.63 ± 0.41 (*)	5.08 ± 0.42 (*)	4.42 ± 0.38 (*)	5.20 ± 0.45 (*)
6	**35**	8.5 ± 0.65 (*)	6.42 ± 0.50 (*)	5.67 ± 0.45 (*)	7.10 ± 0.60 (*)
7	**42**	10.0 ± 0.72 (*)	7.17 ± 0.60 (*)	7.33 ± 0.62 (**)	8.00 ± 0.70 (*)

[a]Results are expressed as the mean ± SD of the groups (n=6, number of treated mice). (*) and (**) indicates statistically significant difference compared to the non-treated control (water group) ($P < 0.01$ and $P < 0.05$, respectively).