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β-Enaminonitrile in the Synthesis of Tetrahydrobenzo[b]thiophene Candidates with DFT Simulation, *In vitro* Antiproliferative Assessment, Molecular docking, and Modeling Pharmacokinetics

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Supporting information:

DFT study

Comnda	*E	<i>E</i> _{HOMO}	ELUMO	ΔE	μ	η	ς	μο	ω	п	Ір	EA	x
Compus.	~ <i>E</i>	(eV)	(eV)	(eV)	(Debye)	(eV)	(eV-1)	(eV)	(eV)	(eV-1)	(eV)	(eV)	(eV)
2	11.256	-6.994	0.367	7.361	-1.357	3.680	0.272	-3.313	1.491	0.671	6.994	-0.367	3.313
3	9.888	-8.164	0.366	8.530	-9.302	4.265	0.234	-3.899	1.782	0.561	8.164	-0.366	3.899
4	13.319	-7.055	0.365	7.420	-7.469	3.710	0.269	-3.345	1.508	0.663	7.055	-0.365	3.345
5	29.559	-8.065	-1.975	6.090	-3.633	0.987	1.013	5.020	12.766	0.078	8.065	1.975	5.020
6	11.020	-8.151	0.366	8.517	-8.823	4.258	0.235	-3.892	1.779	0.562	8.151	-0.366	3.892
7	14.159	-7.071	0.365	7.436	-6.829	3.718	0.269	-3.353	1.512	0.661	7.071	-0.365	3.353
8	40.965	-8.120	-3.458	8.486	-14.058	4.243	0.236	-5.789	3.949	0.253	8.120	3.458	5.789
9	23.498	-6.650	0.366	7.016	1.185	3.508	0.285	-3.142	1.407	0.711	6.650	-0.366	3.142
10	18.968	-7.618	0.366	7.984	-3.135	3.992	0.250	-3.626	1.647	0.607	7.618	-0.366	3.626
11	31.245	-7.152	-5.612	1.540	3.458	0.770	1.299	-6.382	26.448	0.038	7.152	5.612	6.382
12	47.800	-7.439	-5.463	1.976	-1.165	0.988	1.012	-6.451	21.060	0.047	7.439	5.463	6.451
Dox.	67.785	-9.189	-7.149	2.040	3.954	1.020	0.98	-8.169	32.72	0.030	9.189	7.149	8.169

Table S1. Energy level distribution of frontier orbitals and global reactivity indices of substances 2-12.

*E: Minimized Energy (kcal/mol)

Dox.: Doxorubicin

 μ : Dipole/dipole η : Global Hardness

 ς : Global Softness μ_o : Chemical Potential

 ω : Global Electrophilicity Index

n: Nucleophilicity Index

city Index Ip: Ionization Potential

tial *EA*: Electron Affinity

x: Electronegativity



Fig. S1. Optimized configurations (left), HOMO (middle), and LUMO (right) of substances **2-12**. Atom color index: grey C, white H, blue N, red O, yellow S, and green Cl.

Entry					C	ompoun	ds				
Entry	2	3	4	5	6	7	8	9	10	11	12
Molecular weight (g/mol)	254.35	296.39	296.39	338.42	282.36	282.36	638.80	281.38	330.49	387.45	384.45
Num. heavy atoms	18	21	21	24	20	20	46	20	21	28	28
Num. arom. heavy	11	11	15	11	11	15	28	15	15	17	17
Fraction Csp3	0.27	0.29	0.29	0.32	0.25	0.25	0.21	0.25	0.25	0.18	0.17
Num. rotatable bonds	1	3	1	4	3	1	8	1	1	4	2
Num. H-bond acceptor	1	2	2	3	2	2	4	2	0	4	3
Num. H-bond donors	1	1	1	0	1	1	2	1	2	0	0
Molar Refractivity	75.36	85.27	87.13	95.17	80.85	82.16	183.89	83.74	94.11	113.47	111.47
TPSA (Å ²)	78.05	81.13	73.99	89.41	81.13	73.99	162.26	80.04	124.00	110.21	89.41
Consensus Log Po/w	3.41	3.48	3.71	3.45	3.38	3.42	7.33	3.47	4.74	4.39	4.37
Lipinski's Rule	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.17	0.55	0.55	0.55	0.55
]	Pharmac	okinetics						
GI absorption	High	High	High	High	High	High	Low	High	Low	Low	High
BBB permeant	Yes	No	Yes	No	No	Yes	No	No	No	No	No
P-gp substrate	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

 Table S2. Physicochemical Properties / Lipophilicity / Drug-likeness properties of compounds 2-12.

CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No										
CYP3A4 inhibitor	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Log K _p (Skin permeation) (cm/s)	-4.91	-5.27	-5.74	-5.94	-5.17	-5.65	-3.52	-5.30	-5.28	-4.83	-5.23

(2)			3
Ħ ⊙ <i>₽</i>			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.42
	<u>^</u>	Solubility	9.72e-03 mg/ml ; 3.82e-05 mol/l
Í	FLEX	Class 😣	Moderately soluble
5		Log S (Ali) 😣	-5.50
н_м		Solubility	8.10e-04 mg/ml ; 3.19e-06 mol/l
\sim		Class 🔞	Moderately soluble
ll.	INSATU	Log S (SILICOS-IT) 😣	-4.79
ñ″		Solubility	4.09e-03 mg/ml ; 1.61e-05 mol/l
		Class 😣	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES N#Cc1c(N)sc2c10	CCC(C2)c1ccccc1	GI absorption 😣	High
Ph	ysicochemical Properties	888 permeant 😣	Yes
Formula	C15H14N2S	P-gp substrate 😣	Yes
Molecular weight	254.35 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	18	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	11	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.27	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	1	CYP3A4 inhibitor 😣	No
Num. H-bond acceptors	1	Log K _p (skin permeation) 😣	-4.91 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	/0.30 70.05 Ås	Lipinski 😣	Yes; 0 violation
IPSA 🔮	18.00 A ⁻	Ghose 😣	Yes
	2.52	Veber 😣	Yes
	2.52	Egan 😣	Yes
Log P _{olw} (XLOGP3)	4.15	Muegge 😣	Yes
Log P _{alw} (WLOGP) 😣	3.48	Bioavailability Score 😣	0.55
Log P _{alw} (MLOGP) 😣	2.50		Medicinal Chemistry
Log P _{olw} (SILICOS-IT) 😣	4.39	PAINS 😣	0 alert
Consensus Log Poly 😣	3.41	Brenk 😣	0 alert
U UW		Leadlikeness 😣	No; 1 violation: XLOGP3>3.5
		Synthetic accessibility 😣	3.28

Fig. S2. ADME of compound 2.

(3)			3
# 0 ○ <i>∕</i>			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.39
		Solubility	1.22e-02 mg/ml ; 4.10e-05 mol/l
	FLEX SZE	Class 🔞	Moderately soluble
5		Log S (Ali) 😣	-5.41
HN-K T T	* XX1	Solubility	1.16e-03 mg/ml ; 3.93e-06 mol/l
н,с		Class 😣	Moderately soluble
° //	INSATU	Log S (SILICOS-IT) 😣	-5.53
		Solubility	8.81e-04 mg/ml ; 2.97e-06 mol/l
		Class 😣	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES N#Cc1c(NC(=O)C	Disc2c1CCC(C2)c1ccccc1	GI absorption 😣	High
Ph	vsicochemical Properties	888 permeant 😣	No
Formula	C17H16N2OS	P-gp substrate 😣	No
Molecular weight	296.39 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	21	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	11	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.29	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	3	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	2	Log K,, (skin permeation) 😣	-5.27 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	85.27	Lipinski 😣	Yes; 0 violation
IPSA 🥹	81.13 A*	Ghose 😣	Yes
L B. (2.000)	Lipophilicity	Veber 🔞	Yes
Log P _{alw} (ILUGP) 😈	2.58	Egan 😣	Yes
Log P _{olw} (XLOGP3) 😣	4.00	Mueage 😣	Yes
Log P _{alw} (WLOGP) 😣	3.66	Bioavailability Score 😣	0.55
Log P _{olw} (MLOGP) 😣	2.44		Medicinal Chemistry
Log P _{olw} (SILICOS-IT) 😣	4.72	PAINS 😣	0 alert
	3.48	Brenk 😣	0 alert
00110211000 E08 1 0/W	0.70	Leadlikeness 😣	No; 1 violation: XLOGP3>3.5
		Synthetic accessibility 😣	3.53

Fig. S3. ADME of compound 3.

(4)			E
₩ @ \			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.24
		Solubility	1.71e-02 mg/ml ; 5.78e-05 mol/l
	FLEX SIZE	Class 😣	Moderately soluble
°.		Log S (Ali) 😣	-4.56
$- n^{+}$	NH III	Solubility	8.15e-03 mg/ml ; 2.75e-05 mol/l
(HO)	CH.	Class 😣	Moderately soluble
-	INSATU POLAR	Log S (SILICOS-IT) 😣	-6.28
		Solubility	1.56e-04 mg/ml ; 5.27e-07 mol/l
		Class 😣	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES Cc1nc2sc3c(c2c(=O)[nH]1)CCC(C3)c1ccccc1	GI absorption 😣	High
Pł	hysicochemical Properties	BBB permeant 😣	Yes
Formula	C17H18N2OS	P-gp substrate 😣	Yes
Molecular weight	296.39 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	21	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	15	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.29	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	1	CYP3A4 inhibitor 😣	No
Num. H-bond acceptors	2	Log K _p (skin permeation) 😣	-5.74 cm/s
Num. H-bond donors	1		Druglikeness
Molar Retractivity	87.13	Lipinski 📀	Yes; 0 violation
IF3A V	13.88 A	Ghose 😣	Yes
Log P . (il OGP) 😣	2.80	Veber 😣	Yes
	2.00	Egan 📵	Yes
Log P _{alw} (XLOGP3) 🔮	3.33	Muegge 😣	Yes
Log P _{alw} (WLOGP) 😣	3.57	Bioavailability Score 😣	0.55
Log P _{alw} (MLOGP) 😣	3.41		Medicinal Chemistry
Log P _{olw} (SILICOS-IT) 😣	5.66	PAINS 😣	0 alert
Consensus Log P	3.71	Brenk 😣	0 alert
Company 208 - 0/W	1997 - F	Leadlikeness 😣	Yes
		Synthetic accessibility 😣	3.54

Fig. S4. ADME of compound 4.

(5)			
₩ 00 <i>2</i>			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.17
		Solubility	2.30e-02 mg/ml ; 6.79e-05 mol/l
	FLEX SIZE	Class 😣	Moderately soluble
		Log S (Ali) 😣	-4.98
	Ť	Solubility	3.56e-03 mg/ml ; 1.05e-05 mol/l
н,с—		Class 😣	Moderately soluble
° //	INSATU POLAR	Log S (SILICOS-IT) 😣	-5.12
"		Solubility	2.54e-03 mg/ml ; 7.50e-06 mol/l
		Class 😣	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES N#Cc1c2CCC(Cc	2sc1N(C(=O)C)C(=O)C)c1ccccc1	GI absorption 😣	High
Ph	ysicochemical Properties	BBB permeant 😣	No
Formula	C19H18N2O2S	P-gp substrate 😣	No
Molecular weight	338.42 g/mol	CYP1A2 inhibitor 😣	No
Num. heavy atoms	24	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	11	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.32	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	4	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	3	Log K _p (skin permeation) 😣	-5.94 cm/s
Num. H-bond donors	0		Druglikeness
Molar Refractivity	90.17 90.44 Å=	Lipinski 😣	Yes; 0 violation
IPSA U	Linophilipity	Ghose 🔞	Yes
	2.04	Veber 😣	Yes
	3.04	Egan 😣	Yes
Log Palw (XLUGP3)	3.42	Muegge 😣	Yes
Log P _{olw} (WLOGP) 😣	3.79	Bioavailability Score 😣	0.55
Log P _{alw} (MLOGP) 😣	2.39		Medicinal Chemistry
Log P _{olw} (SILICOS-IT) 😣	4.58	PAINS 😣	0 alert
Consensus Log Poly 😣	3.45	Brenk 😣	0 alert
5 UW		Leadlikeness 😣	Yes
		Synthetic accessibility 😣	3.68

Fig. S5. ADME of compound 5.

(6)			(
#00₽			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.33
		Solubility	1.31e-02 mg/ml ; 4.65e-05 mol/l
	PLEX SZE	Class 😣	Moderately soluble
0 s		Log S (Ali) 😣	-5.43
	~ XX	Solubility	1.06e-03 mg/ml ; 3.75e-06 mol/l
\rightarrow		Class 😣	Moderately soluble
lli	INSATU	Log S (SILICOS-IT) 😣	-5.14
		Solubility	2.02e-03 mg/ml ; 7.16e-06 mol/l
		Class 😣	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES O=CNc1sc2c(c1C	#N)CCC(C2)c1ccccc1	GI absorption 😣	High
Ph	ysicochemical Properties	888 permeant 😣	No
Formula	C16H14N2OS	P-gp substrate 😣	No
Molecular weight	282.36 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	20	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	11	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.25	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	3	CYP3A4 inhibitor 😣	No
Num. H-bond acceptors	2	Log K _p (skin permeation) 😣	-5.17 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	80.85	Lipinski 😣	Yes; 0 violation
TPSA 🥹	81.13 A-	Ghose 😣	Yes
	Lipophilicity	Veber 😣	Yes
Log Palw (ILUGP)	2.48	Egan 😣	Yes
Log P _{alw} (XLOGP3) 😣	4.02	Muegge 😣	Yes
Log P _{olw} (WLOGP) 😣	3.27	Bioavailability Score 😣	0.55
Log P _{olw} (MLOGP) 😣	2.61		Medicinal Chemistry
Log Poly (SILICOS-IT) 😣	4.50	PAINS 😣	0 alert
Consensus Log P 9	3.28	Brenk 😣	1 alert: aldehyde 😣
	with the second s	Leadlikeness 😣	No; 1 violation: XLOGP3>3.5
		Synthetic accessibility 😣	3.45

Fig. S6. ADME of compound 6.

(7)				
₩00				Water Solubility
	LIPO		Log S (ESOL) 😣	-4.18
			Solubility	1.85e-02 mg/ml ; 6.55e-05 mol/l
	FLEX	SIZE	Class 😣	Moderately soluble
			Log S (Ali) 😣	-4.57
			Solubility	7.58e-03 mg/ml ; 2.69e-05 mol/l
(ML)			Class 😣	Moderately soluble
5	INSATU	POLAR	Log S (SILICOS-IT) 😣	-5.90
		1.00101	Solubility	3.59e-04 mg/ml ; 1.27e-06 mol/l
			Class 😣	Moderately soluble
	INSOLU			Pharmacokinetics
SMILES O=c1[nH]cnc2c1c	1CCC(Cc1s2)c1ccccc1		GI absorption 😣	High
Ph	ysicochemical Properties		BBB permeant 😣	Yes
Formula	C16H14N2OS		P-gp substrate 😣	Yes
Molecular weight	282.36 g/mol		CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	20		CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	15		CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.25		CYP2D6 inhibitor 😣	No
Num. rotatable bonds	1		CYP3A4 inhibitor 😣	No
Num. H-bond acceptors	2		Log K _p (skin permeation) 😣	-5.65 cm/s
Num. H-bond donors	1			Druglikeness
Molar Refractivity	82.10		Lipinski 😣	Yes; 0 violation
IPSA 😈	13.88 A		Ghose 🔞	Yes
Log R . (ILOGP) 9	2.47		Veber 😣	Yes
	2.17		Egan 😣	Yes
Log Palw (XLOGP3)	3.34		Muegge 😣	Yes
Log P _{alw} (WLOGP) 69	3.26		Bioavailability Score 😣	0.55
Log P _{alw} (MLOGP) 😣	3.17			Medicinal Chemistry
Log P _{alw} (SILICOS-IT) 😣	5.17		PAINS 😣	0 alert
Consensus Log Poly 😣	3.42		Brenk 😣	0 alert
- uw			Leadlikeness 😣	Yes
l			Synthetic accessibility 😣	3.40

Fig. S7. ADME of compound 7.

(8)			S (
₩ 0 0 			Water Solubility
	LIPO	Log S (ESOL) 🔞	-9.64
		Solubility	1.45e-07 mg/ml ; 2.26e-10 mol/l
	FLEX SIZE	Class 😣	Poorly soluble
i		Log S (Ali) 😣	-12.71
		Solubility	1.24e-10 mg/ml ; 1.94e-13 mol/l
Own HON'S	\sim	Class 😣	Insoluble
	DOLAR	Log S (SILICOS-IT) 😣	-12.58
		Solubility	1.69e-10 mg/ml ; 2.64e-13 mol/l
		Class 🔞	Insoluble
	INSOLU		Pharmacokinetics
N#Cc1c(NC(=O)c	2ccc(cc2)C(=O)Nc2sc3c(c2C#N)CCC(C3)c2ccccc	GI absorption 😣	Low
SMILES 2)sc2c1CCC(C2)	c1ccccc1	BBB permeant 😣	No
Ph	vsicochemical Properties	P-gp substrate 🔞	No
Formula	C38H30N4O2S2	CYP1A2 inhibitor 😣	Yes
Molecular weight	638.80 g/mol	CYP2C19 inhibitor 😣	No
Num. heavy atoms	46	CYP2C9 inhibitor 😣	No
Num. arom. heavy atoms	28	CYP2D6 inhibitor 😣	No
Fraction Csp3	0.21	CYP3A4 inhibitor 😣	No
Num. H hand apportant	0	Log K _n (skin permeation) 😣	-3.52 cm/s
Num, H-bond dopors	2		Druglikeness
Molar Refractivity	- 183.89	Lipinski 😣	No; 2 violations: MW>500, MLOGP>4.15
TPSA 😣	162.26 Å⁼	Ghose 😣	No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70
L	Lipophilicity	Veber 😣	No; 1 violation: TPSA>140
Log Poly (ILUGP)	4.70	Egan 🔞	No; 2 violations: WLOGP>5.88, TPSA>131.6
Log P _{olw} (XLOGP3) 0	9.40	Muegge 😣	No; 3 violations: MW>800, XLOGP3>5, TPSA>150
Log Poly (WLOGP)	8.22	Bioavailability Score 😣	0.17
Log P _{olw} (MLOGP) 😣	4.65	and the second s	Medicinal Chemistry
Log P _{alw} (SILICOS-IT) 😣	9.70	PAINS 8	0 alert
Consensus Log P _{alw} 😣	7.33	Brenk 😣	0 alert
		Leadlikeness Θ	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
		Synthetic accessibility 😣	5.21

Fig. S8. ADME of compound 8.

(9)			3
₩ @ () <i>@</i>			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.49
		Solubility	9.18e-03 mg/ml ; 3.26e-05 mol/l
	FLEX SIZE	Class 😣	Moderately soluble
н,		Log S (Ali) 😣	-5.21
- n		Solubility	1.75e-03 mg/ml ; 6.22e-06 mol/l
FHL		Class 😣	Moderately soluble
s	INSATU POLAS	Log S (SILICOS-IT) 😣	-5.63
		Solubility	6.58e-04 mg/ml ; 2.34e-06 mol/l
		Class 😣	Moderately soluble
	INSOLU		Pharmacokinetics
SMILES Nc1ncnc2c1c1C0	CC(Cc1s2)c1ccccc1	GI absorption 😣	High
Pł	sicochemical Properties	BBB permeant 😣	No
Formula	C16H15N3S	P-gp substrate 😣	Yes
Molecular weight	281.38 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	20	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	15	CYP2C9 inhibitor 69	Yes
Fraction Csp3	0.25	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	1	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	2	Log K _p (skin permeation) 😣	-5.30 cm/s
Num. H-bond donors	1		Druglikeness
Molar Refractivity	83.74	Lipinski 🔞	Yes; 0 violation
IPSA V	80.04 A"	Ghose 😣	Yes
Los R (LOGR) 0	2.55	Veber 😣	Yes
	2.00	Egan 🔞	Yes
Log P _{alw} (XLOGP3) 🥹	3.83	Muegge 🔞	Yes
Log P _{alw} (WLOGP) 😣	3.55	Bioavailability Score 😣	0.55
Log P _{olw} (MLOGP) 😣	3.10		Medicinal Chemistry
Log Poly (SILICOS-IT) 😣	4.31	PAINS 😣	0 alert
Consensus Log P 0	3.47	Brenk 😣	0 alert
Coursenada co8 i O/M	M-TF	Leadlikeness 😣	No; 1 violation: XLOGP3>3.5
		Synthetic accessibility 😣	3.42

Fig. S9. ADME of compound 9.

(10)			
# 0 C 2			Water Solubility
	LIPO	Log S (ESOL) 😣	-5.05
		Solubility	2.96e-03 mg/ml ; 8.95e-06 mol/l
	FLEX SIZE	Class 😣	Moderately soluble
() ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NH	Log S (Ali) 😣	-8.60
	F2	Solubility	8.37e-05 mg/ml ; 2.53e-07 mol/l
	-NH	Class 😣	Poorly soluble
ś	INSATU POLAR	Log S (SILICOS-IT) 😣	-6.19
		Solubility	2.15e-04 mg/ml ; 6.50e-07 mol/l
		Class 🔞	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES S=c1[nH]c2sc3c(c2c(=S)(nH11)CCC(C3)c1ccccc1	GI absorption 😣	Low
P	vsicochemical Properties	BBB permeant 🔞	No
Formula	C16H14N2S3	P-gp substrate 🔞	Yes
Molecular weight	330.49 g/mol	CYP1A2 inhibitor 🔞	Yes
Num. heavy atoms	21	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	15	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.25	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	1	CYP3A4 inhibitor 🔞	Yes
Num. H-bond acceptors	0	Log K _n (skin permeation) 😣	-5.28 cm/s
Num. H-bond donors	2	2 p	Druglikeness
Molar Refractivity	94.11	Lipinski 🔞	Yes: 0 violation
TPSA 😣	124.00 A=	Ghose 😣	Yes
	Lipophilicity	Veber 🔞	Yes
Log P _{alw} (iLOGP) 🕪	2.76	Egan 🔞	Yes
Log P _{alw} (XLOGP3) 😣	4.28	Muegge 🔞	Yes
Log P _{olw} (WLOGP) 😣	5.29	Bioavailability Score (9)	0.55
Log P _{olw} (MLOGP) 😣	3.16		Medicinal Chemistry
Log Poly (SILICOS-IT) 😣	8.20	PAINS 😣	0 alert
Consensus Log P	4 74	Brenk 😣	1 alert: thiocarbonyl_group 😣
Conservation 208 - 0/M	T 1 - T	Leadlikeness 🔞	No; 1 violation: XLOGP3>3.5
		Synthetic accessibility 😣	3.62

Fig. S10. ADME of compound 10.

(11)			
# O O P			Water Solubility
	LIPO	Log S (ESOL) 😣	-5.83
		Solubility	5.74e-04 mg/ml ; 1.48e-06 mol/l
	FLEX SIZE	Class 😣	Moderately soluble
Ŵ		L ag S (Ali) 9	-7.47
		Solubility	1 32a_05 ma/ml · 3 30a_08 mal/l
		Class ()	Deede eelekte
		Cidos V	Poorly soluble
	INSATU POLAR	Log S (SILICOS-IT) 😣	-7.07
		Solubility	3.29e-05 mg/ml ; 8.49e-08 mol/l
		Class 😣	Poorly soluble
	INSOLU		Pharmacokinetics
SMILES N#Cc1c(/N=C/c2c	ccc(cc2)[N+](=O)[O-])sc2c1CCC(C2)c1ccccc1	GI absorption 😣	Low
Ph	nysicochemical Properties	BBB permeant 🛞	No
Formula	C22H17N3O2S	P-gp substrate 😣	No
Molecular weight	387.45 g/mol	CYP1A2 inhibitor 😣	Yes
Num. heavy atoms	28	CYP2C19 inhibitor 😣	Yes
Num. arom. heavy atoms	17	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.18	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	4	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	4	Log K. (skin permeation) 😣	-4.83 cm/s
Num. H-bond donors	0	a · p () //	Druslikasees
Volar Refractivity	113.47	Lininghi 🔒	Var. Quialation
TPSA 😣	110.21 Å*	Chara 0	Ver
	Lipophilicity	Gnose 🖶	Tes Vie
Log P _{olw} (iLOGP) 😣	3.37	Veber 😌	Yes
Log P _{olw} (XLOGP3) 😣	5.40	Egan 👽	Ne: 1 violation: VI OCR255
Log P _{olw} (WLOGP) 😣	5.55	Ricavailability Score 😣	0.55
Log Poly (MLOGP)	2.76	bioavariability Score 🥌	Medicinal Chemistry
Log Poly (SILICOS-IT) 6	4.87	PAINS 8	0 alert
Consensus Log P _{alw} (9	4.39	Brenk 😣	3 alerts: imine_1, nitro_group, oxygen- nitrogen_single_bond 😣
		Leadlikeness 📀	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 😣	4.07

Fig. S11. ADME of compound 11.

(12)			
# O O @			Water Solubility
	LIPO	Log S (ESOL) 😣	-5.57
		Solubility	1.03e-03 mg/ml ; 2.68e-06 mol/l
	PLEX SIZ	E Class 😣	Moderately soluble
al an		Log S (Ali) 😣	-8.42
	Ť X	Solubility	1.46e-04 mg/ml ; 3.80e-07 mol/l
$\sim \sim$		Class 😣	Poorly soluble
° ///	BIGATH	Log S (SILICOS-IT) 😣	-7.26
	HOATU PO	Solubility	2.09e-05 mg/ml ; 5.43e-08 mol/l
		Class 🔞	Poorly soluble
	INSOLU		Pharmacokinetics
MILES N#Cc1c2CCC(Cc	2sc1N1C(=O)c2c(C1=O)cccc2)c1ccccc1	GI absorption 😣	High
Pł	sicochemical Properties	BBB permeant 😣	No
ormula	C23H16N2O2S	P-gp substrate 😣	No
folecular weight	384.45 g/mol	CYP1A2 inhibitor 😣	Yes
lum. heavy atoms	28	CYP2C19 inhibitor 😣	Yes
lum. arom. heavy atoms	17	CYP2C9 inhibitor 😣	Yes
Fraction Csp3	0.17	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	2	CYP3A4 inhibitor 😣	Yes
Num. H-bond acceptors	3	Log K _p (skin permeation) 6	-5.23 cm/s
Num. H-bond donors	0	r.	Druglikeness
Violar Kefractivity	111.4/	Lipinski 😣	Yes; 0 violation
IPSA 🤍	08.91 A"	Ghose 😣	Yes
R (1.000)	2 44	Veber 😣	Yes
.og P _{a/w} (ILUGP) 👽	3.11	Egan 🔞	Yes
.og P _{alw} (XLOGP3) 😣	4.81	Muegge 😣	Yes
.og P _{alw} (WLOGP) 😣	4.31	Bioavailability Score 😣	0.55
.og P _{olw} (MLOGP) 😣	4.00	-	Medicinal Chemistry
.og P _{olw} (SILICOS-IT) 😣	5.63	PAINS 😣	0 alert
	4.27	Brenk 😣	1 alert: phthalimide 😣
COW COW	7.01	Leadlikeness 😣	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 😣	3.70

Fig. S12. ADME of compound 12.



Fig. S13. BOILED-EGG chart of compounds 2-10.

Experimental

Cytotoxicity assay

Materials and methods

Cell lines

The cell lines: mammary gland breast cancer (MCF7) and hepatocellular cancer (HePG2) were obtained from ATCC *via* Holding company for biological products and vaccines (VACSERA), Cairo, Egypt. Doxorubicin was used as a reference anticancer agent for comparison.

Chemical reagents

The reagents RPMI-1640 medium, MTT, and DMSO (Sigma Co., St. Louis, USA), and Fetal bovine serum (GIBCO, UK).

MTT assay

The cell lines mentioned above were used to determine the inhibitory effects of compounds on cell growth using the MTT assay.[41] This colorimetric assay is based on the conversion of the yellow tetrazolium bromide (MTT) to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells. Cell lines were cultured in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics added were 100 units/mL penicillin and 100 mg/mL streptomycin at 37 °C in a 5% CO₂ incubator. The cell lines were seeded in a 96-well plate at a density of 1.0×10^4 cells/well at 37 °C for 48 h under 5% CO₂. After incubation, the cells were treated with different concentrations of compounds and incubated for 24 h. After 24 h of drug treatment, 20 µL of MTT solution at 5 mg/mL was added and incubated for 4 h. Dimethyl sulfoxide (DMSO) in volume of 100 µL is added into each well to dissolve the purple formazan formed. The colorimetric assay is measured and recorded at an absorbance of 570 nm using a plate reader (EXL 800, USA). The relative cell viability in percentage was calculated as (A₅₇₀ of treated samples/A₅₇₀ of untreated samples) x 100.

Statistical analysis

All data were presented as mean \pm SD (n = 3) using the SPSS 13.0 program (SPSS Inc. USA).

Molecular Docking

All molecular modeling studies were investigated using Molecular Operating Environment (MOE, 2014.0901) software. All minimizations were performed with MOE until an RMSD gradient of 0.1 kcal.mol⁻¹Å⁻¹ with the MMFF94x force field, and the partial charges were automatically calculated. The X-ray crystallographic structure of tubulin (TUB) domain complexed with colchicine (COL) (PDB ID: 5NM5) was downloaded from the protein data bank (<u>https://www.rcsb.org/structure/5NM5</u>). For the co-crystallized enzyme, water molecules and ligands, which are not involved in the binding, were removed, and the protein was prepared for the docking study utilizing the Protonate 3D protocol in MOE with default options. The co-crystallized ligand (COL) was used to define the binding site for docking. The Triangle Matcher placement method and London dG scoring function were used for docking.

ADME Profiling

The ADME properties of all compounds were studied by the SwissADME free web tool (<u>http://www.swissadme.ch/index.php</u>), accessed on 26 Feb. 2024.

Spectral Data:







	7.297 7.297 7.261 7.261 7.261 7.1242 7.1242 3.854 3.854 3.854 3.854 3.854 3.832 3.836 3.832 3.810 3.803	2.896 2.896 2.805 2.763 2.763 2.605 2.559 2.559 1.947 1.947	Current Data Parameters NAME amna-shaaban-A1-d2o EXPNO 1 PROCNO 1
Ph S O			F2 - Acquisition Parameters Date_ 20220920 Time 9.16 INSTRUM spect PROBHD 5 mm PABBO BB/ PULPROG zg30 TD 65536 SOLVENT DMSO NS 98 DS 2 SWH 8012.820 Hz FIDRES 0.122266 Hz AQ 4.0894465 sec RG 126.31 DW 62.400 usec DE 6.50 usec TE 300.0 K D1 1.0000000 sec TD0 1
			CHANNEL fl SF01 400.1524711 MHz NUC1 1H P1 12.00 usec PLW1 18.0000000 W F2 Processing parameters SI 65536 SF 400.1500000 MHz WDW EM SSB 0 LB 0.30 Hz GB 0 PC 1.00
15 14 13 12 11 10	9 8 7 6 5 4	3 2 1 ppm 3 001 3 000	



sayed-karam-A1 #190 RT: 3.20 AV: 1 SB: 26 1.21-1.34 , 0.87-1.14 NL: 4.31E8 T: {0,0} + c EI Full ms [40.00-1000.00]







	7.201 7.205 7.235 7.225 7.212 7.201	3.622 3.124 3.124 3.082 3.020 2.986 2.939 2.845 2.825 2.825 2.825 2.845 2.825 2.939 1.996 1.996 1.996 1.880	BRUKER
0			Current Data Parameters NAME amna-shaaban-A2-d2o EXPNO 2 PROCNO 1
Ph S 4			F2 - Acquisition Parameters Date_ 20220920 Time 8.56 INSTRUM spect PROBHD 5 mm PABBO BB/ PULPROG zg30 TD 65536 SOLVENT DMSO NS 85 DS 2 SWH 8012.820 FIDRES 0.122266 AQ 4.0894465 RG 205.37 DW 62.400 usec DE 6.50 usec TE 300.0 K D1 1.0000000 sec TD0 1 1
			===== CHANNEL f1 ====== === === === === === === === === === === === === === === == == == == == == == == == == == == == == == == == =
		M	F2 - Processing parameters SI 65536 SF 400.1500000 MHz WDW EM SSB 0 LB 0.30 Hz GB 0 PC 1.00
15 14 13 12 11 10 9	8 7 6	5 4 3 2 1 ppm	



Sample Name	Description	Quality Checks
A31	Sample 001 By Administrator Date Thursday, September 01 2022	The Quality Checks do not report any warnings for the sample.





















PerkinElmer Spectrum Version 10.4.2 دیسمبر, 2021 a 01:18 م 02



	Sample Name A7&	Description Sample 1388 By Administrator Date 2021 02 الخميس, ديسمبر	Quality Checks The Quality Checks give rise to a Weak Bands warning for the sample.
l			

























					7 8.841	8.411	7.250	7.239	5.245 5.221 7.3.172	r 3.088 7 3.047 7 2.922	2.896	2.508	2.025 2.025 1.995	L1.975	BR		ER	
	Ph	\bigcirc	CN S 1	CH- -N		≻no₂									Current NAME EXPNO FROCNO F2 - Acc Date_ Time INSTRUM PROBHD FULPROG TD SOLVENT NS DS SWH FIDRES AO	Data I amna- quisit: 5 mm	2arameter -shaaban- 2022091 12.4 spec PABEO BB 23 6553 DMS 12 8012.82 0.12226 4.089446	s A4 1 1 2 0 0 1 7 0 0 6 0 8 2 0 0 4 2 0 0 4 2 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
															RG DW DE TE D1 TD0 SF01 NUC1 P1 PLW1	= CHANI 40	205.3 62.40 6.5 300. 1.0000000 WEL f1 == 00.152471 1 12.0 3.0000000	7 7 0 usec 0 K 0 sec 1 1 MHz H 0 usec 0 W
							<u> </u>		1.200-01-11-2 001-0		Wall	u.M	J		F2 - Pr SI SF WDW SSB LB GB FC	ocessin 40 0 0	ng parame 6553 00.150000 E 0.3 1.0	ters 6 0 MHz M 0 Hz 0
15	14	13	12	11	10	2:02	3.94 1.12 2	6	5	4	5.17 κ 5.10 κ	3.04 2	1	ppm				





sayed-karam-A4 #62 RT: 1.05 AV: 1 SB: 26 1.21-1.34 , 0.87-1.14 NL: 3.70E2 T: {0,0} + c EI Full ms [40.00-1000.00]







sayed-karam-A21 #292 RT: 4.90 AV: 1 SB: 26 1.21-1.34 , 0.87-1.14 NL: 2.70E6 T: {0,0} + c EI Full ms [40.00-1000.00]

