Supplementary Materials

Expanding the Chemical Space of Arsenicin A-C Related Polyarsenicals and Evaluation of Some Analogs as Inhibitors of Glioblastoma Stem Cell Growth

Contents	Page(s):
Table S1. Relevant experimental IR data and calculated frequencies from density functional theory (DFT)-vibrational analysis using the B1B95/6-311+G(3df,2pd) basis set for compounds 8 and 9 .	S2
Figure S1. ¹ H- and ¹³ C-NMR spectra of synthetic mixture containing the sulfur nor-adamantane 10-12 .	S 3
Figure S2. EI-MS spectrum of arsenicin D (13) present in the HPLC fraction by purification of the polyarsenical mixture from workup of the sponge <i>E. bargiba</i> nti extract.	S4
Figure S3. ¹ H-NMR spectrum of the natural polyarsenicals mixture from workup of the sponge <i>E. bargibanti</i> extract; signals of arsenicin D are highlighted in yellow.	S4
Table S2. Energies calculated for the structures of arsenicin A-D (1-3 and 13) and relative stability of the corresponding structures after O/S replacement by DFT calculation <i>in vacuo</i> at B1B95/6- 311+G(3df,2pd) level of theory. The results were obtained by applying the following equations: A) $\Delta E = E (Arsenicin X) - n E(S atoms) + m E(O atoms) - E (arsenicin A) $ B) $\Delta E = E (Arsenicin Y) - m E(O atoms) + n E(S atoms) - E (arsenicin B/C/D) $ where X and Y are for B, C or D, n = number of substituted sulfur atoms and m = number of substituted oxygen atoms.	S5
Table S3. Selectivity Index (SI) values of alkyl polyarsenicals 7-9 and ATO, given by the ratio between the GI ₅₀ values of non-tumor cell lines and GSC lines, respectively.	S 6
Figure S4. Western blot for p53, p21, and actin in COMI cells treated with 100μ M of camptothecin (CTH) for 16 hours.	S 6
Table S4. GI ₅₀ values in μ M of alkyl polyarsenicals 7-9 and ATO on COMI cells grown either under normoxic conditions (normoxia), under hypoxic conditions for the duration of the treatment (hypoxia 48 h), or under hypoxic conditions for one week prior to drug treatment (hypoxia 1 week).	S 6
Figures S5-S11. Predicted physical-chemical properties and bioavailability radar for compounds 1 and 7-12 evaluated by Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).	S7-S10
Figure S12. WLOGP-versus-TPSA in Brain Or IntestinaL EstimateD permeation method (BOILED)-Egg visualization for alkyl adamantane 7-9 and dimethyl As-S compounds 10-12 in comparison with arsenicin A (1) evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).	S10
Table S5. Polar surface area (PSA), lipophilicity (LogP) and blood-brain barrier (BBB) parameters evaluated by using the indicated chemoinformatics software (Swiss-ADME: http://www.swissadme.ch/ accessed on 9 January 2023; Molsft L.L.C.: https://www.molsoft.com/ accessed on 2 March 2023; Molinspiration: https://www.molinspiration.com/ accessed on 2 March 2023).	S11
Figure S13. ¹ H- and ¹³ C-NMR spectra of compound 8.	S12
Figure S14. ¹ H- and ¹³ C-NMR spectra of compound 9.	S13
Table S6. Seeding numbers (expressed in cells/well) used for testing the alkyl polyarsenicals 7-9	S14

and ATO in 384-well plates.

IR frequency (cm^{-1})			Assignment
 intireque	incy (entr.)	Intensity	
Calculated	Experimental		
	Comp	ound 8	
463	456	strong	As-O-As bending
727	723	strong	As-C-As stretching
797	795	very strong	As-O stretching
1067	1043	medium	CH twisting
1326	1375	weak	CH ₃ symmetric bending
1413	1451	medium	CH ₃ twisting
2832	2837	weak	symmetric CH2 stretching
2867	2843	weak	symmetric CH3 stretching
2933	2923	weak	asymmetric CH3 stretching
 2941	2954	medium	asymmetric CH3 stretching
	Comp	ound 9	
458	443	strong	As-O-As bending
464	465	strong	As-O-As bending
731	717	strong	As-C-As stretching
796	789	very strong	As-O stretching
1072	1063	medium	CH twisting
1418	1461	medium	CH ₃ twisting
2820	2827	medium	symmetric CH2 stretching
2857	2852	medium	symmetric CH2 stretching
2866	2870	medium	symmetric CH3 stretching
2894	2916	medium	asymmetric CH ₂ stretching
2940	2953	medium	asymmetric CH ₃ stretching

Table S1. Relevant experimental IR data and calculated frequencies from density functional theory (DFT)-vibrational analysis using the B1B95/6-311+G(3df,2pd) basis set for compounds 8 and 9.



Figure S1. ¹H- and ¹³C-NMR spectra of sulfur derivatives mixture.



Figure S2. EI-MS spectrum of arsenicin D (**13**) present in the HPLC fraction by purification of the polyarsenical mixture from workup of the sponge *E. bargiba*nti extract.



Figure S3. ¹H-NMR spectrum of the natural polyarsenicals mixture from workup of the sponge *E. bargibanti* extract; signals of arsenicin D are highlighted in yellow.

Table S2. Energies calculated for the structures of arsenicin A-D (**1-3** and **13**) and relative stability of the corresponding structures after O/S replacement by DFT calculation *in vacuo* at B1B95/6-311+G(3df,2pd) level of theory. The results were obtained by applying the following equations:

- A) $\Delta E = |E (Arsenicin X) n E(S atoms) + m E(O atoms) E (arsenicin A)|$
- B) $\Delta E = |E (Arsenicin Y) m E(O atoms) + n E(S atoms) E (arsenicin B/C/D)|$

where X and Y are for B, C or D, n = number of substituted sulfur atoms and m = number of substituted oxygen atoms.

	Equation	Energy (a.u.)	Δ E (a.u.)	Δ E (kcal/mol)
Arsenicin A (1, C3H6As4O3)	А	-9288.336433	0.0	-
Arsenicin B (2, C ₃ H ₆ As ₄ S ₂)	А	-9859.187098	0.451145	285.96
Arsenicin C (3, C ₃ H ₆ As ₄ OS)	А	-9536.145045	0.35991	227.11
Arsenicin D (13, C ₃ H ₆ As ₄ S ₂)	А	-9859.188891	0.449352	285.27
Arsenicin A (1)		-9288.336433	-	-
3S-Arsenicin A (C3H6As4S3)	А	-10257.450842	0.285455	179.13
Arsenicin B (2)		-9859.187098		
2O-Arsenicin B (C ₃ H ₆ As ₄ O ₂) ^a	В	-9213.103230	0.182708	114.70
Arsenicin C (3)		-9536.145045		
2O-Arsenicin C (C ₃ H ₆ As ₄ O ₂) ^a	В	-9213.103230	0.091473	57.40
Arsenicin D (13)		-9859.188891		
2O-Arsenicin D(C3H6As4O2)	В	-9213.095435	0.17312	108.63
Oxygen atom		-74.964766	-	-
Sulfur atom		-398.098054	-	-

^a the same structure

Table S3. Selectivity Index (SI) values of alkyl polyarsenicals **7-9** and ATO, given by the ratio between the GI₅₀ values of non-tumor cell lines and GSC lines, respectively.

	ΑΤΟ					5	7				8				9	
	ARPE-19	MCF10A	hTERT-HPNE	Hs68	ARPE-19	MCF10A	hTERT-HPNE	Hs68	ARPE-19	MCF10A	hTERT-HPNE	Hs68	ARPE-19	MCF10A	hTERT-HPNE	Hs68
COMI	3.1	1.6	3.1	ndª	14.6	16.9	20.8	51.9	17.2	17.8	29.6	124.0	13.5	13.3	43.8	107.3
VIPI	0.7	0.3	0.7	ndª	1.8	2.1	2.6	6.5	3.9	4.0	6.7	28.2	3.0	2.9	9.7	23.8
GB6	1.0	0.5	1.0	ndª	2.0	2.3	2.8	7.1	2.5	2.6	4.4	18.2	1.6	1.6	5.1	12.6
GB7	2.1	1.1	2.1	ndª	24.3	28.2	34.7	86.4	17.2	17.8	29.6	124.0	10.8	10.6	35.0	85.8
G144	1.3	0.7	1.3	ndª	6.6	7.7	9.5	23.6	9.6	9.9	16.4	68.9	6.8	6.6	21.9	53.6
G166	0.7	0.4	0.7	ndª	1.5	1.7	2.1	5.3	2.8	2.9	4.8	20.0	2.3	2.2	7.3	17.9
GB8	0.8	0.4	0.8	ndª	1.6	1.9	2.3	5.8	2.6	2.7	4.5	18.8	1.9	1.9	6.3	15.3
GSC#1	1.4	0.7	1.4	ndª	3.3	3.8	4.7	11.8	4.5	4.7	7.8	32.6	3.0	2.9	9.7	23.8
GSC#151	0.7	0.4	0.7	ndª	3.5	4.1	5.0	12.5	7.2	7.4	12.3	51.7	3.2	3.1	10.3	25.2

 a nd: not determined. SI was not calculated since the GI₅₀ value of ATO on Hs68 was greater than the highest concentration tested (>100 μ M).



Figure S4. Western blot for p53, p21, and actin in COMI cells treated with 100 μ M of camptothecin (CTH) for 16 hours.

Table S4. GI₅₀ values^a in μ M of alkyl polyarsenicals **7-9** and ATO on COMI cells grown either under normoxic conditions (normoxia), under hypoxic conditions for the duration of the treatment (hypoxia 48 h), or under hypoxic conditions for one week prior to drug treatment (hypoxia 1 week).

	ATO	7	8	9
Normoxia	0.96 ± 0.06	0.15 ± 0.02	0.05 ± 0.07	0.040 ± 0.004
Hypoxia 48 h	0.98 ± 0.06	0.15 ± 0.05	0.07 ± 0.02	0.06 ± 0.02
Hypoxia 1 week	1.04 ± 0.07	0.14 ± 0.07	0.08 ± 0.04	0.06 ± 0.02

^a GI₅₀ values were calculated upon treating COMI cells with different compound concentrations for 48 h. The GI₅₀ values were calculated from n = 6 biological replicates, n = 3 technical replicates each, mean ± SEM.

1			S (3)
₩ 0 0 <i>Q</i>			Water Solubility
	LIPO	Log S (ESOL) 🥹	-3.02
As		Solubility	3.73e-01 mg/ml ; 9.58e-04 mol/l
	FLEX	Class 🥹	Soluble
		Log S (Ali) 😣	-1.39
10		Solubility	1.59e+01 mg/ml ; 4.09e-02 mol/l
AS	As	Class 🥹	Verv soluble
As	INSATU	Log S (SILICOS-IT) 😣	-0.90
		Solubility	4.94e+01 mg/ml ; 1.27e-01 mol/l
	INSOLU	Class 0	Soluble
			Pharmacokinetics
SMILES C1[As]2C[As]3O[A	s]1C[As](O2)O3	GI absorption 😣	High
Phy	sicochemical Properties	BBB permeant 😣	No
Formula	C3H6As4O3	P-gp substrate 📀	No
Molecular weight	389.76 g/mol	CYP1A2 inhibitor 😣	No
Num. heavy atoms	10	CYP2C19 inhibitor 😣	No
Num. arom. heavy atoms	0	CYP2C9 inhibitor 😣	No
Fraction Csp3	1.00	CYP2D6 inhibitor 🖗	No
Num. rotatable bonds	0	CVP3A4 inhibitor	No
Num. H-bond acceptors	3	Log K (ckin permection)	7.92 cm/c
Num. H-bond donors	0	Log Ap (Skill permeation)	Pruslikenees
Molar Refractivity	40.69		Drugiikeness
TPSA 🥹	27.69 Å ^z		Yes; U violation
	Lipophilicity	Gnose	No; 1 violation: #atoms<20
Log P _{o/w} (iLOGP) 😣	0.00	Veber 🥹	Yes
Log P _{o/w} (XLOGP3) 😣	1.21	Egan 🥹	Yes
Log Poly (WLOGP) 😣	-0.35	Muegge 🥹	No; 1 violation: #C<5
Log P_Au (MLOGP) (9	-1 91	Bioavailability Score 🧐	0.55
	-2.12		Medicinal Chemistry
	-2.12	PAINS 😣	0 alert
Consensus Log Po/w	-0.05	Brenk 😣	1 alert: heavy_metal 🥹
		Leadlikeness 😣	No; 1 violation: MW>350
		Synthetic accessibility 🤨	5.96

Figure S5. Predicted physical-chemical properties and bioavailability radar for arsenicin A (1) evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

7			
₩ © () 🖌			Water Solubility
	LIPO	Log S (ESOL) 🥹	-3.56
		Solubility	1.16e-01 mg/ml ; 2.77e-04 mol/l
As	CH3 FLEX SIZE	Class 😣	Soluble
Ĭ Í		Log S (Ali) 😣	-2.16
As As		Solubility	2 88e+00 mg/ml : 6 87e-03 mol/l
As		Class 😣	Colubla
1 clille	BICATI		Soluble
H ³ C .	POLAR	Log S (SILICOS-IT) 🥹	-0.65
		Solubility	9.51e+01 mg/ml ; 2.26e-01 mol/l
	INSOLU	Class 🥹	Soluble
SMILES CC1[As]20[As]30	[As]10[As](02)[C@@H]3C		Pharmacokinetics
Phy	sicochemical Properties	GI absorption 🥹	High
Formula	C4H8As4Q4	BBB permeant 🥹	No
Volecular weight	419.79 g/mol	P-gp substrate 🥹	No
Num, heavy atoms	12	CYP1A2 inhibitor 😣	No
Num arom heavy atoms	0	CYP2C19 inhibitor 🥹	No
Fraction Csp3	100	CYP2C9 inhibitor 🥹	No
Num rotatable bonds	0	CYP2D6 inhibitor 🧐	No
Num H-bond acceptors	4	CYP3A4 inhibitor 😣	No
Num H-bond donors	0	Log K _p (skin permeation) 🥹	-7.60 cm/s
Alar Refractivity	46.58		Druglikeness
TPSA ()	36 92 Å*	Lipinski 😣	Yes; 0 violation
	Lipophilicity	Ghose 🧐	Yes
00 P ((ILOGP) 😣	0.00	Veber 😐	Yes
Log P . (XLOGP3) P	1 77	Egan 😣	Yes
	0.40	Muegge 🥹	No; 1 violation: #C<5
Log P _{o/w} (WLOGP)	-0.10	Bioavailability Score 📀	0.55
Log P _{o/w} (MLOGP) ♥	-2.30		Medicinal Chemistry
Log P _{o/w} (SILICOS-IT) 🥹	-2.94	PAINS 😣	0 alert
Consensus Log P _{o/w} 😣	-0.71	Brenk 😣	1 alert: heavy_metal 🥹
		Leadlikeness 🐵	No: 1 violation: MW>350

Figure S6. Predicted physical-chemical properties and bioavailability radar for compounds 7 evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

8			
# ◎ ○ <i>Q</i>			Water Solubility
	LIPO	Log S (ESOL) 🥹	-4.05
		Solubility	3.96e-02 mg/ml ; 8.84e-05 mol/l
	CH ₃ FLEX SIZE	Class 🥹	Moderately soluble
As		Log S (Ali) 😳	-2.91
io T		Solubility	5.50e-01 ma/ml : 1.23e-03 mol/l
As As		Class 🥹	Soluble
HaC W	INSATU	Log S (SILICOS-IT) 😣	-1.43
		Solubility	1.67e+01 mg/ml ; 3.73e-02 mol/l
	INSOLU	Class 🥹	Soluble
			Pharmacokinetics
SMILES CCC1[As]20[As]3	IO[As]10[As](02)[C@@H]3CC	GI absorption 🥹	High
Phj	vsicochemical Properties	BBB permeant 😣	Yes
Formula	C6H12As4O4	P-gp substrate 📀	No
Molecular weight	447.84 g/mol	CYP1A2 inhibitor 😣	No
Num. neavy atoms	14	CYP2C19 inhibitor 😣	No
Num. arom. heavy atoms	0	CYP2C9 inhibitor 😣	No
Fraction Csp3	1.00	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	2	CYP3A4 inhibitor 😣	No
Num. H-bond acceptors	4	Log K _n (skin permeation) 🥹	-7.26 cm/s
Num. H-bond donors	0		Druglikeness
Molar Retractivity	56.20	Lipinski 😣	Yes: 0 violation
IPSA 🤍	36.92 A*	Ghose 8	Yes
1 D (1 0 0 D) 0	Lipopnii/city	Veber 🥹	Yes
Log Poly (ILUGP)	0.00	Egan 😣	Yes
Log P _{o/w} (XLOGP3) 😣	2.49	Muerre 🖗	Yes
Log P _{olw} (WLOGP) 😣	0.69	Bioavailability Score 🔍	0.55
Log P _{o/w} (MLOGP) 😣	-1.52		Medicinal Chemistry
Log P _{o/w} (SILICOS-IT) 😣	-2.62		0 alert
Consensus Log P _{o/w} 😣	-0.19	Pronk 🙆	1 alort beaux motal 9
			No: 1 violation: MW/>250
		Custosia essessibility	e 44
		Synuteuc accessibility 🐨	0.41

Figure S7. Predicted physical-chemical properties and bioavailability radar for compounds **8** evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

9			
Ħ O 🔿 🔗			Water Solubility
	LIPO	Log S (ESOL) 😣	-4.78
		Solubility	7.98e-03 mg/ml ; 1.68e-05 mol/l
	FLEX SIZE	Class 🧐	Moderately soluble
		Log S (Ali) 😣	-4.03
As As		Solubility	4.43e-02 ma/ml : 9.31e-05 mol/l
0		Class 🤨	Moderately soluble
н,с	INSATU		0.04
		Log S (SILICUS-IT)	-2.2 I
		Solupility	2.99e+00 mg/mil, o. 19e-03 Mol/l Coluble
	INSOLU	01855 🤝	Phormacekinetics
SMILES CCCC1[As]20[As	s]30[As]10[As](02)[C@@H]3CCC	CLoboardian (9)	Ligh
Ph	ysicochemical Properties	Grabsorption e	Vec
Formula	C8H16As4O4	B as substrate 8	No
Molecular weight	475.90 g/mol	CVP1A2 inhibitor	No
Num. heavy atoms	16	CVP3C10 inhibitor	No
Num. arom. heavy atoms	0	CVP2C0 inhibitor @	No
Fraction Csp3	1.00	CVP2D6 inhibitor @	No
Num. rotatable bonds	4	CVP2A4 inhibitor	No
Num. H-bond acceptors	4	Log K (ckin normanian)	6 67 cm/c
Num. H-bond donors	0	Log N _p (skin permeation) 😈	-0.07 cm/s
Molar Refractivity	65.81	Lininaki 🙆	Voc: 0 violation
TPSA 🥹	36.92 Ų	Chose 🤗	Vae
	Lipophilicity	Vahar 🙆	Tes Voc
Log P _{o/w} (iLOGP) 🥹	0.00	Face 0	Voc
Log P _{o/w} (XLOGP3) 😣	3.57	Eyan 🐨	TES Voc
Log P _{o/w} (WLOGP) 🥹	1.47	Nueyge 😎	0.55
Log P _{o/w} (MLOGP) 😣	-0.83	bioavailability Score 👽	0.00 Medicinal Chemistry
Log P _{o/w} (SILICOS-IT) 😣	-2.06	DAING ()	0 alort
Consensus Log Poly 😣	0.43	Prank 0	
			No: 2 violations: MW>250, VLOCP2>2.5
		Custostia assassibility 0	NU, 2 VIOLAUUTIS, WWV-350, XEUGP3>3.5
		Synureuc accessibility 🤝	0.00

Figure S8. Predicted physical-chemical properties and bioavailability radar for compounds **9** evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

No. Water Solubility Log S (£SOL) ● 5.24 Solubility 2.61e-03 mg/ml; 5.78e-06 mol/l Class ● Moderately soluble Log S (£MI) ● 5.24 Solubility 2.61e-03 mg/ml; 5.78e-06 mol/l Class ● Moderately soluble Log S (ÅII) ● 5.24 Solubility 1.72e-03 mg/ml; 3.80e-06 mol/l Class ● Moderately soluble Log S (ÅII) ● 5.24 Solubility 1.72e-03 mg/ml; 3.80e-06 mol/l Class ● Moderately soluble Log S (ÅII) ● 1.98 Solubility 4.59e+00 mg/ml; 1.04e-02 mol/l Class ● No Solubility 4.59e+00 mg/ml; 1.04e-02 mol/l Class ● No Num. heavy atoms 11 No Num. H-bond congs 0 No Log P _{ow} (LOGP) ● 0.00 Log P _{ow} (LOGP) ● 0.00 Log P _{ow} (MLOGP) ● 1.42 Log P _{ow} (MLOGP) ● 0.38 <th>(10</th> <th></th> <th></th> <th></th>	(10			
$ \begin{array}{c} $				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	₩ @ \) 🎸	LIPO		Water Solubility
Solubility 2.51e-03 mg/ml (5.78e-06 mol/l Class Moderately soluble Lig S (A) -5.42 Solubility 1.72e-03 mg/ml (3.80e-06 mol/l Class Moderately soluble Lig S (SILICOS-IT) -198 Solubility 4.69e+00 mg/ml (1.04e-02 mol/l Class Moderately soluble SMILES C(2@@H)1/As1/S2/(C@H)3C Formula C4H8A-4S3 Molecular weight 451.99 g/mol Num. neavy atoms 0 Fraction Csp3 1.00 Num. H-bond acceptors 0 Num. H-bond donors 0 Num. H-bond donors 0 Ligo P _{alv} (LICOP) 0.00 Log P _{alv} (LICOP) 0.00 Log P _{alv} (LICOP) 0.121 Log P _{alv} (LICOP) 0.121 Log P _{alv} (LICOP) 0.134	(гн	Log S (ESOL) 🧐	-5.24
SEEClassModerately soluble $A = A = A = A = A = A = A = A = A = A =$		2 3	Solubility	2.61e-03 mg/ml ; 5.78e-06 mol/l
$ \begin{array}{c} \label{eq:second} \begin{tabular}{lllllllllllllllllllllllllllllllllll$	S	FLEX	Class 🥹	Moderately soluble
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	As		Log S (Ali) 🤨	-5.42
$ \begin{array}{c} \label{eq:second} \\ \label{eq:second} $	As—\$—As		Solubility	1.72e-03 mg/ml ; 3.80e-06 mol/l
$\begin{array}{c c c c c c c } & \label{eq:source} \\ \hline Polark \\ H_{3}C \\ \hline \\ \hline \\ H_{3}C \\ \hline \\ \hline \\ \hline \\ H_{3}C \\ \hline \\ \hline \\ \hline \\ H_{3}C \\ \hline \\ $	As		Class 😣	Moderately soluble
$\begin{tabular}{ c $	S -S	INSATU		1.09
Fige Solubility 4.999+00 mg/ml, 1.048+02 mount SMLES C(2@@H]1[As]2S[As]3S[As]1[As](S2](CH]3C Class Solubile Formula C4H8As453 Pharmacokinetics Molecular weight 451.99 g/mol Yes Num. heavy atoms 11 CYP1A2 inhibitor No Num. rotable bonds 0 CYP22 inhibitor No Num. H-bond acceptors 0 CYP226 inhibitor No Num. H-bond donors 0 CYP226 inhibitor No No CYP242 inhibitor No Molar Refractivity 65.02 Druglikeness Log P _{olv} (ILOGP) 0.00 Charles Ves Log P _{olv} (MLOGP) 2.12 Egan Yes Log P _{olv} (SILICOS+IT) -0.98 Consensus Log P _{olv} (SILICOS+IT) -0.98 Consensus Log P _{olv} (SILICOS+IT) -0.98 0 alert Consensus Log P _{olv} (SILICOS+IT) 1.34 Egan S No; 2 violation; Wo/>2 violation;			Log S (SILICOS-IT)	- 1.90
Initial constraints Class ● Solution SMILES C[CQ@@H]1[As]2S[As]3S[As]1[As](S2](C@H]3C Class ● Pharmacokinetics Formula CdH8As4S3 CdH8As4S3 P-gp substrate ● No Num. heavy atoms 11 CYP2C9 inhibitor ● No Num. room. heavy atoms 0 CYP2C9 inhibitor ● No Fraction Csp3 1.00 CYP2C9 inhibitor ● No Num. Hoond acceptors 0 CYP2C9 inhibitor ● No Num. H-bond acceptors 0 CYP2C9 inhibitor ● No Num. H-bond acceptors 0 CYP2C9 inhibitor ● No Nolar Refractivity 65.02 Europiliance Europiliance Log P _{ow} (ILOGP) ● 0.00 Veber ● Yes Log P _{ow} (MLOGP) ● 1.42 Egan ● Yes Log P _{ow} (MLOGP) ● 1.42 Bioavaitability Score ● 0.55 Log P _{ow} (SILICOS+IT) ● -0.98 Medicinal Chemistry PanNS ● 0 alert Bernk ● 1 alert. heavy_metal ● Leadlikeness ● No; 2 violations; Wo/350, XLOGP3>3.5 Synthetic accessibility ● 6.09	13C		Solubility	4.69e+00 mg/mi ; 1.04e-02 mol/i
SMILES C(C@@H)1[As]2S[As]3S[As]1[As](S2](C@H]3C Physicochemical Properties Formula C4H8As483 Pegs substrate No Molecular weight 451.99 g/mol CYP142 inhibitor No Num. heavy atoms 1 CYP2C9 inhibitor No Num. neavy atoms 0 CYP2C9 inhibitor No Fraction Csp3 1.00 CYP2D6 inhibitor No Num. Hoad acceptors 0 CYP2D6 inhibitor No Num. Hoad acceptors 0 CYP2D6 inhibitor No Num. Hoad acceptors 0 CYP2D6 inhibitor No Num. Hoad donors 0 CYP2D6 inhibitor No Num. Hoad donors 0 CyP2D6 inhibitor No Veber Yes; Violation: #atoms<		INSOLU	Class 👽	Soluble
Formula C4H8As4S3 Molecular weight 451.99 g/mol Num. heavy atoms 11 Num. neavy atoms 0 Fraction Csp3 1.00 Num. Heavy atoms 0 Fraction Csp3 1.00 Num. Houry acceptors 0 Molar Refractivity 65.02 TPSA ● 75.90 Å ² Cip P _{obv} (ILOGP) ● 0.00 Log P _{obv} (ILOGP) ● 0.00 Log P _{obv} (ILOGP) ● 0.00 Log P _{obv} (ILOGP) ● 2.12 Log P _{obv} (ILOGP) ● 1.42 Log P _{obv} (ILCOSTI) ● -0.98 Consensus Log P _{obv} = 1.34	SMILES C[C@@H]1[As]29	[As]3S[As]1[As](S2)[C@H]3C		Pharmacokinetics
FormulaC4H8As483BBB permeantYesMolecular weight451.99 g/molP-gp substrateNoNum. heavy atoms11CYP2/12 inhibitorNoNum. heavy atoms0CYP2/19 inhibitorNoFraction Csp31.00CYP2/29 inhibitorNoNum. rotatable bonds0CYP2/29 inhibitorNoNum. H-bond acceptors0CYP2/24 inhibitorNoNum. H-bond donors0CYP2/24 inhibitorNoMolar Refractivity65.02DruglikenessDruglikenessTPSA75.90 Å ² Lipinski ©YesLog P_{olv} (ILOGP)0.00Lipinski ©YesLog P_{olv} (WLOGP)2.12Egan ©YesLog P_{olv} (SILICOS+IT)-0.980.42Medicinal ChemistryConsensus Log P_{olv} 1.34Here No1 alert heavy_metal ©LeadlikenessNo; 2 violations: WX>30, XLOGP3>3.5Synthetic accessibility6.09	Phy	sicochemical Properties	GI absorption 🥹	High
Molecular weight 451.99 g/mol P-gp substrate % No Num. heavy atoms 11 CYP1A2 inhibitor % No Num. arom. heavy atoms 0 CYP2C9 inhibitor % No Fraction Csp3 1.00 CYP2C9 inhibitor % No Mum. rotatable bonds 0 CYP2C9 inhibitor % No Num. H-bond acceptors 0 CYP2A1 inhibitor % No Num. H-bond acceptors 0 CYP3A4 inhibitor % No Num. H-bond donors 0 Log K _p (skin permeation) % -6.13 cm/s TPSA % 75.90 År LipInski % Yes; 0 volation Cop P _{olv} (ILOGP) % 0.00 Veber % Yes Log P _{olv} (ILOGP) % 0.00 Veber % Yes Log P _{olv} (ILOGP) % 1.12 Egan % Yes Log P _{olv} (ILOGP) % 1.42 Egan % Yes Log P _{olv} (ILOGP) % 1.34 PaintS % 0 alert Consensus Log P _{olv} % 1.34 Eadlikeness % No; 2 volations: Wx>350, XLOGP3>3.5	Formula	C4H8As4S3	BBB permeant 🧐	Yes
Num. heavy atoms11 $CYP142$ inhibitorNoNum. arom. heavy atoms0 $CYP2C19$ inhibitorNoFraction Csp31.00 $CYP2C29$ inhibitorNoNum. rotatable bonds0 $CYP2C29$ inhibitorNoNum. H-bond acceptors0 $CYP2205$ inhibitorNoNum. H-bond donors0 $CYP2205$ inhibitorNoMolar Refractivity65.02 $Log K_p$ (skin permeation)-6.13 cm/sTPSA75.90 ŲLipinskiYes; 0 violationLog P _{ow} (ILOGP)0.00VeberYesLog P _{ow} (MLOGP)2.12Egan OYesLog P _{ow} (MLOGP)1.42Elioavailability Score0.55Log P _{ow} (SILICOS-IT)-0.98PAINS0 alertConsensus Log P _{ow} S1.34Brenk I1 alert. heav_metalLeadlikenessNo; 2 violations; XLOGP3>3.5Synthetic accessibility6.09	Molecular weight	451.99 a/mol	P-gp substrate 🥹	No
Num. arow. heavy atoms 0 CYP2C19 inhibitor ● No Fraction Csp3 1.00 CYP2C9 inhibitor ● No Num. rotatable bonds 0 CYP2C9 inhibitor ● No Num. rotatable bonds 0 CYP2C9 inhibitor ● No Num. H-bond acceptors 0 CYP2C9 inhibitor ● No Mum. H-bond donors 0 CYP2C9 inhibitor ● No Molar Refractivity 65.02 Lips/ki ● Yes; 0 violation TPSA ● 75.90 Å* Lips/ki ● Yes; 0 violation Log P _{obv} (ILOGP) ● 0.00 Veber ● Yes Log P _{obv} (MLOGP) ● 0.00 Egan ● Yes Log P _{obv} (MLOGP) ● 2.12 Muegge ● No.1 violation: #cos Log P _{obv} (MLOGP) ● 1.42 Medicinal Chemistry Log P _{obv} (SILICOSTIT) ● -0.98 O alert Consensus Log P _{obv} ● 1.34 Brenk ● 1 alert. heavy_metal ● Leadlikeness ● No; 2 violations; XLOGP3>3.5 Synthetic accessibility ● 6.09	Num, heavy atoms	11	CYP1A2 inhibitor 🥹	No
Fraction Csp.3 1.00 CYP2C9 inhibitor ● No Num. rotatable bonds 0 CYP2D6 inhibitor ● No Num. H-bond acceptors 0 CYP3A4 inhibitor ● No Num. H-bond acceptors 0 CYP3A4 inhibitor ● No Num. H-bond donors 0 Log K _p (skin permeation) ● -6.13 cm/s Molar Refractivity 65.02 Druglikeness Druglikeness Lipinski ● Yes; 0 violation C C Log P _{olv} (iLOGP) ● 0.00 Chose ● No; 1 violation: #atoms<20	Num, arom, heavy atoms	0	CYP2C19 inhibitor 🥹	No
Num. rotatable bonds 0 Num. rotatable bonds 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 65.02 TPSA ● 75.90 Å ² Lipinski ● Yes, 0 violation Log P _{olv} (iLOGP) ● 0.00 Log P _{olv} (iLOGP) ● 0.00 Log P _{olv} (WLOGP) ● 2.12 Log P _{olv} (SILICOS+IT) ● -0.98 Consensus Log P _{olv} S 1.34	Fraction Csp3	1.00	CYP2C9 inhibitor 🥹	No
Num. H-bond acceptors 0 Num. H-bond acceptors 0 Num. H-bond donors 0 Molar Refractivity 65.02 TPSA ● 75.90 År Lipophilicity Chose ● Log P _{olv} (ILOGP) ● 0.00 Log P _{olv} (XLOGP3) ● 4.12 Log P _{olv} (MLOGP) ● 2.12 Log P _{olv} (MLOGP) ● 1.42 Log P _{olv} (SILICOS+IT) ● -0.98 Consensus Log P _{olv} = 1.34	Num, rotatable bonds	0	CYP2D6 inhibitor 🧐	No
Num. H-bond donors Log K _p (skin permeation) -6.13 cm/s Molar Refractivity 65.02 Druglikeness TPSA 75.90 Å* Lipophilicity Log P _{ow} (ILOGP) 0.00 Veber Yes Log P _{ow} (WLOGP) 2.12 Egan Yes Log P _{ow} (MLOGP) 1.42 Bioavailability Score 0.55 Log P _{ow} (SILICOS-IT) -0.98 O alert Medicinal Chemistry PAINS 0 alert Brenk 1 alert heav_metal Leadlikeness No; 2 violations; XLOGP3-3.5 Synthetic accessibility 6.99	Num H-bond acceptors	0	CYP3A4 inhibitor 😣	No
Molar Refractivity 65.02 Druglikeness TPSA ● 75.90 Å [±] Lipinski ● Yes; 0 violation Lipophilicity Ghose ● No; 1 violation: #atoms <20	Num H-bond donors	0	Log K _p (skin permeation) 🥹	-6.13 cm/s
TPSA 75.90 Ų Lipinski ● Yes; 0 violation Lipophilicity Ghose ● No; 1 violation: #atoms<20	Molar Refractivity	65.02		Druglikeness
Image: Consensus Log Poly Lipophilicity Ghose ● No; 1 violation: #atoms<20 Veber ● Veber ● Yes Log Poly (XLOGP3) ● 4.12 Egan ● Yes Log Poly (WLOGP) ● 2.12 Muegge ● No; 1 violation: #C<5	TPSA ()	75 90 Å*	Lipinski 😣	Yes; 0 violation
Log Pow (ILOGP) 0.00 Log Pow (XLOGP3) 4.12 Log Pow (WLOGP) 2.12 Log Pow (MLOGP) 2.12 Bioavailability Score 0.55 Log Pow (SLICOS-IT) -0.98 Consensus Log Pow 1.34 Brenk • 1 alert. neav_metal • Leadlikeness • No; 2 violations: WV>350, XLOGP3>3.5	11 0/10	Lipophilicity	Ghose 🧐	No; 1 violation: #atoms<20
Log P _{olw} (XLOGP3) 4.12 Log P _{olw} (WLOGP) 2.12 Bioavailability Score 0.55 Log P _{olw} (SLLCOS-IT) -0.98 Consensus Log P _{olw} 1.34	Log P_s., (iLOGP) 🥹	0.00	Veber 🧐	Yes
Log Pow (WLOGP) 2.12 Muegge No; 1 violation: #C<5 Log Pow (MLOGP) 2.12 Bioavailability Score 0.55 Log Pow (SLICOS-IT) -0.98 Medicinal Chemistry Consensus Log Pow 1.34 Brenk I 1 alert heav_metal I Leadlikeness I No; 2 violations; MW>350, XLOGP3>3.5 Synthetic accessibility 6.09		4 13	Egan 😣	Yes
Log Pow (VLOGP) @ 2.12 Bioavailability Score @ 0.55 Log Pow (MLOGP) @ 1.42 Medicinal Chemistry Log Pow (SILICOS-IT) @ -0.98 PAINS @ 0 alert Consensus Log Pow @ 1.34 Brenk @ 1 alert heavy_metal @ Leadlikeness @ No; 2 violations: MW>350, XLOGP3>3.5 Synthetic accessibility @ 6 0.9		7.12	Muegge 😣	No; 1 violation: #C<5
Log P _{ow} (NLOGP) ● 1.42 Medicinal Chemistry Log P _{ow} (SILICOS-IT) ● -0.98 PAINS ● 0 alert Consensus Log P _{ow} ● 1.34 Brenk ● 1 alert. heavy_metal ● Leadlikeness ● No; 2 violations: MW>350, XLOGP3>3.5 Synthetic caccessibility ● 6.09	LOG Po/w (WLOGP)	2.12	Bioavailability Score 😣	0.55
Log Pow (SILICOS-IT) ● -0.98 PAINS ● 0 alert Consensus Log Pow ● 1.34 Brenk ● 1 alert. heavy_metal ● Leadlikeness ● No; 2 violations: MW>350, XLOGP3>3.5 Synthetic accessibility ● 6.09	Log Po/w (MLOGP) 🥹	1.42		Medicinal Chemistry
Consensus Log P _{olv}	Log P _{o/w} (SILICOS-IT) 🥹	-0.98	PAINS 😣	0 alert
Leadlikeness No; 2 violations: MW>350, XLOGP3>3.5 Synthetic accessibility 6.09	Consensus Log P _{o/w} 😣	1.34	Brenk 🥹	1 alert: heavy_metal 🥹
Synthetic accessibility 6 6 09			Leadlikeness 🥹	No; 2 violations: MW>350, XLOGP3>3.5
			Synthetic accessibility 🥹	6.09

Figure S9. Predicted physical-chemical properties and bioavailability radar for compounds **10** evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

(11			
# ⊙ ⊘			Water Solubility
	LIPO	Log S (ESOL) 😣	-5.24
H₃C		Solubility	2.61e-03 mg/ml ; 5.78e-06 mol/l
, s	FLEX SIZE	Class 😣	Moderately soluble
As		Log S (Ali) 🤒	-5.42
As—\$—As		Solubility	1.72e-03 mg/ml ; 3.80e-06 mol/l
As		Class 😣	Moderately soluble
S-	INSATU	Log S (SILICOS-IT) 😣	-1.98
•	CH,	Solubility	4.69e+00 mg/ml ; 1.04e-02 mol/l
	INSOLU	Class 🤨	Soluble
			Pharmacokinetics
SMILES C[C@@H]1[As]2	S[As]3S[As]1[As](S2)[C@@H]3C	GI absorption 🤫	High
Ph	ysicochemical Properties	BBB permeant 😣	Yes
Formula	C4H8As4S3	P-gp substrate 🥹	No
Molecular weight	451.99 g/mol	CYP1A2 inhibitor 😣	No
Num. heavy atoms	11	CYP2C19 inhibitor 😣	No
Num. arom. heavy atoms	0	CYP2C9 inhibitor 😣	No
Fraction Csp3	1.00	CYP2D6 inhibitor 😣	No
Num. rotatable bonds	0	CYP3A4 inhibitor 9	Ne
Num. H-bond acceptors	0	Log K_ (skin permeation) @	-6.13 cm/s
Num. H-bond donors	0	Eog Ap (star permeason) -	Druglikaness
Molar Refractivity	65.02	Lininski 🖗	Yes: 0 violation
TPSA 🥹	75.90 A ^z	Chose @	No: 1 violation: #atoms<20
	Lipophilicity	Veher	Yes
Log P _{o/w} (iLOGP) 🧐	0.00	Egon 🙆	Vec
Log P _{o/w} (XLOGP3) 😣	4.12		No: 1 violation: #C<5
Log P _{o/w} (WLOGP) 🥹	2.12	Ricovoilability Score 💁	0.66
Log P _{o/w} (MLOGP) 😣	1.42	bioavailability Score 👽	0.00
Log P _{o/w} (SILICOS-IT) 😣	-0.98		0 slort
Consensus Log Pow 9	1.34	PAINS U	
2 0.4			naieri, neavy_metal 🐨
		Leadikeness 🥹	NO, 2 VIOLATIONS: MW>350, XLOGP3>3.5
		Synthetic accessibility 🧐	6.09

Figure S10. Predicted physical-chemical properties and bioavailability radar for compounds **11** evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

12			
₩ 0 0 <i>Q</i>			Water Solubility
	LIPO	Log S (ESOL) 😣	-5.24
H₃C		Solubility	2.61e-03 mg/ml ; 5.78e-06 mol/l
	FLEX	Class 📀	Moderately soluble
As			5.40
As-s-As		Log S (All)	-5.42
		Class 0	1.72e-03 mg/mi , 3.80e-00 mol/
s As		Class 🐨	Moderately soluble
	INSATU POLAR	Log S (SILICOS-IT) 🥹	-1.98
0	CH ₃	Solubility	4.69e+00 mg/ml ; 1.04e-02 mol/l
	INSOLU	Class 🥹	Soluble
9MILES 001[As]29[As]29]	Ac11(Ac1(\$2))(C@H12C		Pharmacokinetics
	nigochamical Properties	GI absorption 😣	High
Formula		BBB permeant 😣	Yes
Molocular woight	451.00 a/mol	P-gp substrate 😣	No
Num boow stoms	451.55 g/mol	CYP1A2 inhibitor 🥹	No
Num, neavy atoms	11	CYP2C19 inhibitor 😣	No
Fraction Con?	100	CYP2C9 inhibitor 😣	No
Num rotatable bonds	0	CYP2D6 inhibitor 😣	No
Num II hand cooptors	0	CYP3A4 inhibitor 😣	No
Num, H-bond dopore	0	Log K _p (skin permeation) 🥹	-6.13 cm/s
Molar Refractivity	65.02		Druglikeness
	75.00 Å?	Lipinski 😣	Yes; 0 violation
	Linophilicity	Ghose 😕	No; 1 violation: #atoms<20
Log P (il OCP) 🤗	0.00	Veber 🥹	Yes
Log R (YLOCR3)	4.10	Egan 🐵	Yes
	4.12	Muegge 😣	No; 1 violation: #C<5
Log Po/w (WLOGP)	2.12	Bioavailability Score 😣	0.55
Log Po/w (MLOGP) 😣	1.42		Medicinal Chemistry
Log Po/w (SILICOS-IT) 8	-0.98	PAINS (9)	0 alert
Consensus Log Poly 8	1.34	Brenk 😣	1 alert: heavy_metal 🥺
		Leadlikeness 😣	No; 2 violations: MW>350, XLOGP3>3.5
		Synthetic accessibility 🥹	6.09
t			

Figure S11. Predicted physical-chemical properties and bioavailability radar for compounds **12** evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).



Figure S12. WLOGP-versus-TPSA in Brain Or IntestinaL EstimateD permeation method (BOILED)-Egg visualization for alkyl adamantane **7-9** and dimethyl As-S compounds **10-12** in comparison with arsenicin A (**1**) evaluated by using Swiss-ADME software (http://www.swissadme.ch/ accessed on 9 January 2023).

Table S5. Polar surface area (PSA), lipophilicity (LogP) and blood-brain barrier (BBB) parameters evaluated by using the indicated chemoinformatics software (Swiss-ADME: http://www.swissadme.ch/ accessed on 9 January 2023; Molsft L.L.C.: https://www.molsoft.com/ accessed on 2 March 2023; Molinspiration: https://www.molinspiration.com/ accessed on 2 March 2023).

Web tool	Properties	Arsenicin A	Compound 7	Compound 8	Compound 9
SwissADME	TPSA (Ų)	27.69	36.92	36.92	36.92
	WLogP	-0.35	-0.10	0.69	1.47
	Consensus Log P	-0.63	-0.71	-0.19	0.43
	BBB permeant	No	No	Yes	Yes
Molinspiration	TPSA (Ų)	27.70	36.94	36.94	36.94
	miLog P	-3.03	-2.36	-1.35	-0.23
	BBB	-	-	-	-
Molsoft L.L.C.	MolPSA (Ų)	44.01	42.38	42.38	42.38
	MolLog P	-0.34	0.06	1.03	1.98
	BBB score ^a	3.77	4.03	4.12	4.19

^a BBB Score: 6-High, 0-Low





Figure S13. ¹H- and ¹³C-NMR spectra of compound 8.



Figure S14. ¹H- and ¹³C-NMR spectra of compound 9.

Cell Line	Seeding Number	
	(cens/wen)	
COMI	1000	
VIPI	1000	
GB6	3000	
GB7	3000	
G144	2000	
G166	1000	
GB8	1500	
GSC#1	1500	
GSC#151	1500	
ARPE-19	1500	
MCF10A	1000	
hTERT-HPNE	1500	
Hs68	1500	

Table S6. Seeding numbers (expressed in cells/well) used for testing the alkyl polyarsenicals **7-9** and ATO in 384-well plates.