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ADMET and Druglikeness Calculations of Sarin, Soman, and Their Hypothetical Derivatives

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Abstract

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) represents a numerical classification of any chemical to be a drug candidate with promising therapeutic efficacy with minimum toxicity or sensitivity depending on its chemical structures and its physicochemical properties. Sarin (GB) and Soman (GD) are nerve agents classified as chemical warfare agent containing phosphorous atom. Acetylcholine (ACh) as a neurotransmitter esterifies by acetyl cholinesterase enzyme (AChE) that can be irreversibly inhibited by (GB and GD) meaning termination of muscle function. Here, new *in Silico* predication of two nerve agents (Sarin and Soman) was done. These organophosphorous agents were hypothetically subjected to a reaction with lactic acid and various amino acids. New P-O with lactic acid and P-N linkage was between Sarin or Soman and different amino acids. Both reactions were through fluorine atom with hydroxyl group (P-O formation) and with amine (P-N). The ADMET and Druglikeness properties of the parent chemical warfare agents and their hypothetical products were subjected to MarvinSketch program and preadmet website. Sarin and Soman and their hypothetical products showed many noticeable characters such as: all 20 tested compounds were with non-inhibition character of Pgp and CYp-2D6; substrate character with CYP-3A4, negative values to skin permeability, negative to Carcino-Mouse, low risk to hERG inhibition. Other calculated predictors were varied in response between all calculated compounds.

1. Introduction

ADMET is abbreviation of Absorption, Distribution, Metabolism, Excretion, and Toxicity represents a numerical classification of any chemical to be a drug candidate with promising therapeutic efficacy depending on its chemical structures and its physicochemical properties [1, 2, 3]. Any chemical can reach optimum qualification as a drug when it easily to soluble, absorb by intestine (or other organ) and distribute by blood (or other biofluid) with minimum toxicity or sensitivity [4]. The ability of any chemical to become a drug is affected by several limitations such as its binding degree with human plasma proteins (lipoprotein, albumin, globulins, glycoproteins) and as a result its concentration in blood circulation. Also, dermal penetration (or skin permeability) is another effective character in designing and development of drug that might be administered through patient skin.

Sarin (GB) and Soman (GD) are nerve agents classified as chemical warfare agent containing phosphorous atom. Sarin looks like Soman in chemical formula except (C3H6) and both of them have the same lethal dose LD50 [5]. Acetylcholine (ACh) esterifies by acetyl cholinesterase enzyme (AChE). This important bioprocess of this neurotransmitter (ACh) can be irreversibly inhibited by nerve organophosphorus agents (GB and GD) so, for example, muscle function is terminated. Many research and review articles of Sarin, Soman, and other nerve agents have been published including bio-hydrolysis [6], detection [7], theoretical study [8], reaction [9], …etc. especially in OPCW Today. In 2016, a critical review of Sarin stated that Sarin publications in Science Direct were 12339 categorized to analysis, cholinergic, delayed, and chronic neurotoxicity, and endocrine disruption [10].

According to The Merck Index (2013), Sarin is more volatile than Soman that can be hydrolyzed by water, diluted aqueous NaOH or Na_2CO_3 to non–toxic product by removing of fluorine atom [5, 11]. Upon this scientific fact, I scheme my project in a hypothetical reaction by replacing fluorine atom with oxygen or nitrogen. This replacement was also based on known organic reactions of different amines or alcohol. My choices were hypothetical reactants (lactic acid and various amino acids (aspartic acid, glutamic acid, glycine, proline, alanine, phenylalanine, valine, and methionine) with parent chemicals (Sarin and Soman). The hypothetical products were subjected to MarvinSketch software and to preadmet [12] website. With this point our view turns into numbers. The obtained numerical information directed me to more questions and primary answers about these products: Do we need them to be synthesized as candidate drugs? What are their toxicity? The other hypothetical question of these ADMET and Druglikeness calculations is if human body forms these products: How much they are toxic? Can be excreted, metabolized, distributed, or absorbed? With these questions and primary answers, I started my calculations.

2. Theoretical Part

Our calculations were done by using Chemaxon [13] mainly depending with MarvinSketch - Version 18.15.0 as a predictor of several properties. Elemental analysis and Protonation including Molecular Weight - Formula and Isoelectric point (pI) respectively were calculated. logP as a partitioning property was calculated by Consensus and ChemAxon methods where Cl^-, Na^+, K^+ electrolyte concentration under condition of calculation 0.1 mol./dm3. Hydrophilic – Lipophilic Balance (HLB) was calculated by ChemAxon and Davies methods. Geometry was calculated as a Polar Surface Area (2D) property (PSA) without excluding Sulfur and Phosphors atoms in $(Å)^2$. The other property: Hydrogen Bond Donor (HBD)/ Acceptor (HBA) without excluding of Sulphur and phosphors atoms at pH (0-14) was the final calculated property by this program (Table 1.).

The other calculations were ADMET and Druglikeness by applying https://preadmet.bmdrc.kr website. ADME predictors (Tables 2 & 3) were including: Blood-Brain Barrier (BBB, in vivo penetration, C. Brain / C. Blood), Buffer solubility of molecule (mg/L), $CaCO_2$ (in vitro, Human colorectal carcinoma permeability), CYP 2C19, CYP 2C9, and CYP 2D6 inhibitions (in vitro cytochrome P450 inhibition), CYP 2D6 and CYP 3A4 substrate (in vitro Cytochrome P450 substrate), Human Intestinal Absorption (HIA, %), Mandin Darby Canine Kidney (MDCK, in vitro, kidney cell permeability, nm/sec.), Pgp inhibition (in vitro inhibition of P-glycoprotein), Plasma Protein Binding (in vitro, %), Pure Water Solubility (mg/L), Skin Permeability (in vitro, transdermal, logKp, cm/hr.), SK logD value (logD in pH 7.4), SK logP value (logP in pH 7.4), and SK logS (logS in pH 7.4 buffer system and pure water, mol./L).

Acute algae toxicity (algae at), Ames test (compound mutagenicity against histidine synthesis), Carcino -Mouse and -Rat (carcinogenicity bioassay with mouse and rat respectively), acute Daphnia toxicity (Daphnia- at), hERG inhibition (in vitro, human ether –a-go-go), acute fish toxicity (medaka - at and minnow- at), TA100-10RLI, TA100 – NA, TA1535 -10RLI, and TA1535 - NA (in vitro, Ames test, with (+S9) and without (-S9) metabolic activation in TA100 strain, rat liver), were calculated as toxicity predictors (Tables 2 & 3).

The other predictors that calculated by https://preadmet.bmdrc.kr website were Druglikeness predicators (Tables 4 & 5.) involving: Comprehensive Medicinal Chemistry like Rule (CMC Like Rule), CMC like Rule Violation Fields, Lead like Rule Violation, Mid-Structure, Nondrug-, and drug- like Rules (MDDR like Rule) and their Violation fields, Lipinski's Rule of Five, World Drug Index like Rule (WDI), and WDI Violation (molecular properties found in or out 90% cutoff in WDI).

Sarin and Soman were hypothetically introduced in new P-O formation with lactic acid. The other reaction was formation of P-N linkage between Sarin or Soman and different amino acids. Both reactions were through fluorine atom with hydroxyl group (P-O formation) and with amine (P-N) (Figure 1). Sarin, Soman, and their hypothetical derivatives (Figure 2) were subjected to MarvinSketch program and https://preadmet.bmdrc.kr website to calculate the above mentioned properties (Tables 1 to 5).

3. Results and Discussion

Different physicochemical characters were calculated by MarvinSketch software (Table 1), i.e. chemical formula, molecular weight, isoelectric point, logP, HLB, and PSA. All calculated compounds were with no isoelectric point. logP data were ranged from -0.58 to 3.02 (Consensus method) and from -0.37 to 3.31 (ChemAxon method). HLB by the three calculation methods were (6.32 -12.65), (4.38 – 11.32), and (8.57-15.76) for ChemAxon, Davies, and Griffin methods respectively. The other physicochemical predicator (Polar Surface Area, PSA) was (36.11 – 122.74).

ADME data as have been tabulated in Tables (2 & 3) were (0.119911.06872), (95535.5-17848800), (0.366263-34.2915), (26.0228596.38871), (0.674479-124.252), (0-93.8614), (1958.01-1071840), (3.21915-0.85576), (-1.86487-1.70873), (-0.61687-2.53794), (-0.534861.84816), and (-2.22321-0.73975) for BBB, buffer solubility, Caco2, HIA, MDCK, Plasma Protein Binding, Pure Water Solubility, Skin Permeability, SK log D, SK log P, and SK log S (buffer and pure) respectively.

Toxicity numerical data (Tables 2 & 3) were (0.029774-0.181533), (0.114382-5.16029), (0.020347-25.259), and (0.031577-7.77395) that belong to acute algae, Daphnia, Medaka, and minnow toxicities respectively.

Chemical biological response of any chemical to be a powerful drug needs many steps like ion channel and receptor tests that demand time, money, and prior preparative studies. These descriptive animal studies indicate the penetration of this target to Central Nerve System (CNS) but now these studies can be removed or reduced with the assistance of mathematical models such as ADMET.

One of ADMET calculations is Blood Brain Barrier (BBB) that determines the capability of a chemical to do its action by penetrating this barrier according to its physicochemical properties [14] such as lipophilic character, hydrogen bonding, …etc. toward CNS with easily mechanism and less required energy. CNS is a selective system between liver, intestine, blood, and brain actions of a specific chemical that can be transport by cell diffusion through the membrane, metabolize by enzyme, and pump to the blood by P-glycoprotein – ATP transfer mechanism. Candidate drug needs hydrophilic- lipophilic action to cross blood – membrane boundary and this action can be performed by the assistance of two effective parameters: first, water tendency to form hydrogen bonding with polarized molecule and second, BBB homogeneity absence as a result of lipid bilayers presence.

Candidate drug can get optimum therapeutic ability by reaching maximum selectivity with the target tissue at the required concentration and to reach this goal ADMET calculations may help scientist to quantify this ability depending upon polar groups and molecular forces that attacked by water or bonded by albumin or α-acidic glycoprotein especially with CNS drug.

Blood Brain Barrier (BBB), Buffer solubility character, logP, HLB, HBAs, and HBDs form a gate to understand other predictors which showed a different behavior sequence of Sarin, Soman, and both derivatives.

High presence of polar groups in a compound prevent or obstruct this compound from crossing this BBB and access CNS. BBB character showed that Soman and its derivatives were in high values than Sarin and its derivatives (Tables 2 & 3). Aspartic acid derivatives were with low BBB than glutamic acid (both amino acid are with dicarboxylic groups) and lactic acid derivatives. Glycine derivatives, i.e. less number of atoms and molecular weight amino acid, had less BBB than proline, valine, alanine, and phenylalanine but more than methionine. Methionine derivatives, i.e. sulphide containing amino acid, were higher than glycine, proline, valine, alanine, phenylalanine derivatives. Presence of phenyl ring increased BBB by comparison both phenylalanine and alanine derivatives because of phenyl ring steric effect in spite of HBAs, HBDs, and PSA data look alike when comparison with same parent compound. The impact of phenyl ring was resembling with logP data but in discrepancy with

HLB data. So, alanine derivatives may show different diffusion and transfer abilities than phenylalanine derivatives.

The other arrangement of comparison may be explained depending on logP, HLB, HBA, HBD, PSA, and molecular formula or structure. So more number of atoms and phenyl ring presence affected compound crossing BBB to CNS. This might be belonging to the presence of more polar atoms which agreed with the numbers of hydrogen bond acceptors (HBAs) and donors (HBDs) beside PSA data. ADMET data (except BBB) showed that Sarin (or its derivatives) gave high response in number to Buffer solubility, HIA, MDCK, Plasma Protein Binding, Pure water sol., Skin permeability, SK logP, SK logD, SK logS, algae-at, Daphnia – acute toxicity, Medaka – acute toxicity, and minnow-acute toxicity. A molecule has a good solubility and easy transfer mechanism with less energy has to be more effect than others that may be compared so it toxicity increased.

Daphnia toxicity is related to drug solubility because Daphnia for example are water organism having high speed of growth. So, Daphnia are choosing as aquatic toxicological indicators [15]. Above notifications were with more impact on Sarin (or its derivatives) according to our calculated data than Soman (or its derivatives) (see Tables 2 & 3).

Cancer this deadly disease may be caused by the toxicity of many chemicals as a simple definition of Carcinogenicity. To avoid cost and long-time of rodent in vivo testing, in Silico is the right choice. With the negative predication of Carcino–Mouse or Rat, compound under test causes cancer or it is toxic causing cancer in body. Tables (2 & 3) indicate that all tested compounds in this study were toxic to cause cancer in mouse. Carcino-Rat negative results were only with methionine derivatives (GB-ME & GD-ME).

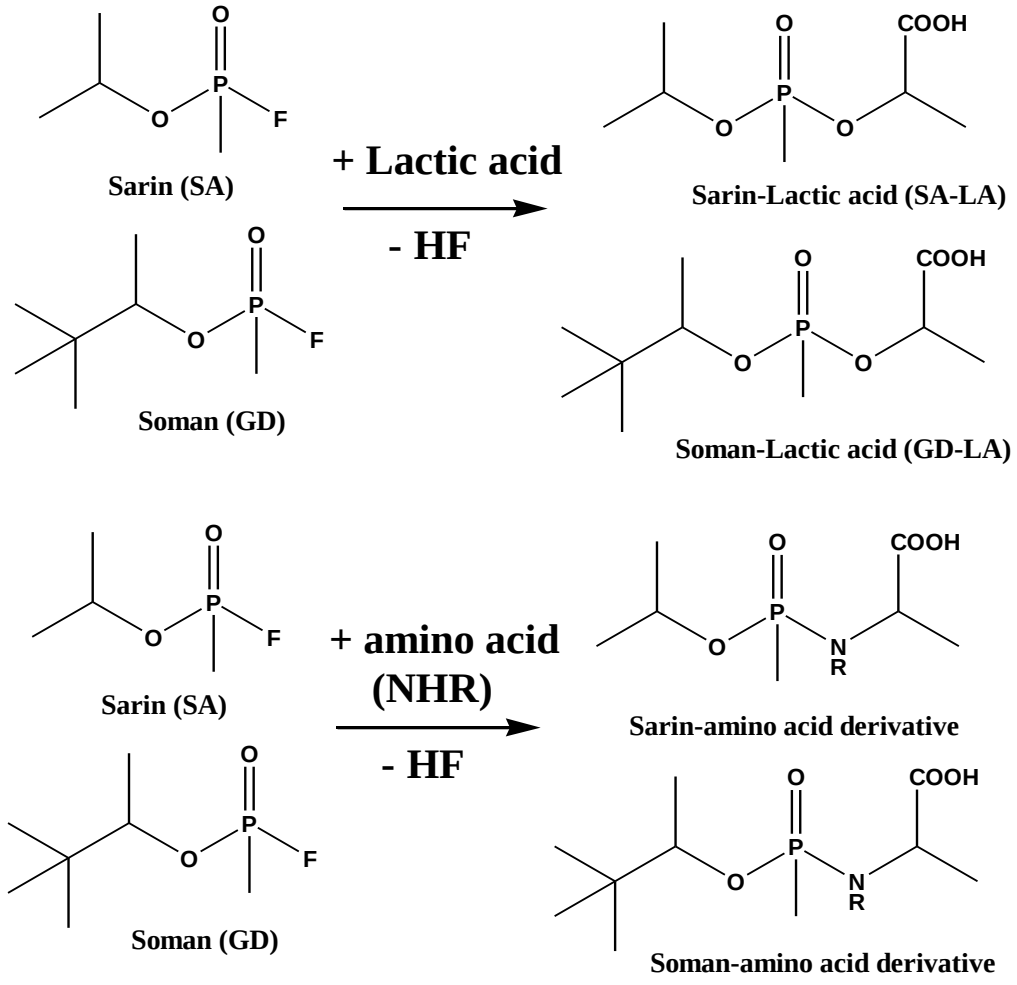

Figure (1). Hypothetical reaction of Sarin and Soman with lactic acid and different amino acids.

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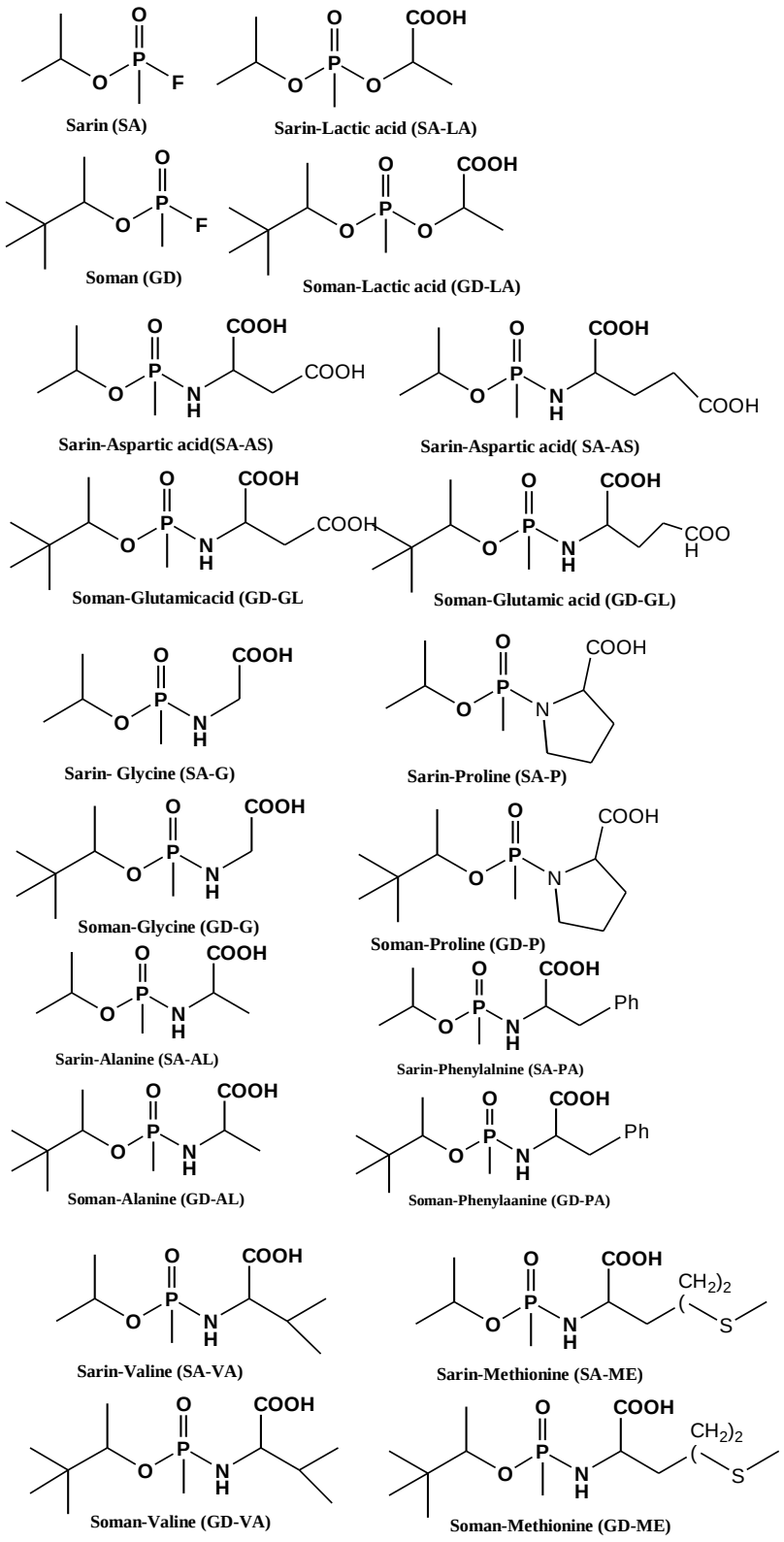

Figure (2). Sarin and Soman and their hypothetical derivatives.

Table (1). Physical properties of Sarin, Soman, and their hypothesized derivatives.

Name (Symbol)	Molecular formula	M.Wt	logP		HLB			PSA **	H-Donor*** Count Sites	H-Acceptor *** Count Sites
			Consensus	ChemAxon	ChemAxon	Davies	Griffin			
Sarin (GB)	$C_4H_{10}FO_2P$	140.094	0.77	0.97	10,56	10.18	11.14	36.11	0 0	2 5
Soman (GD)	$C_7H_{16}FO_2P$	182.175	2.08	2.35	8.68	8.75	8.57	36.11	0 0	3 6
GB-Lactic acid GB-LA	$C_7H_{15}O_5P$	210.166	0.77	0.90	12.09	11.23	13.23	82.64	1 1	3 6
GD-Lactic acid GD-LA	$C_{10}H_{21}O_5P$	252.247	2.01	2.28	10.35	9.90	11.03	82.64	1 1	3 6
GB-Aspartic acid GB-AS	C8H16NO6P	253.191	-0.58	-0.37	12.65	10.75	15.49	122.74	3 3	5 10
GD-Aspartic acid GD-AS	$C_{11}H_{22}NO_6P$	295.272	0.73	1.01	10.91	9.32	13.29	122.74	3 3	5 10
GB-Glutamic acid GB-GL	$C_9H_{16}NO_6P$	267.218	-0.30	-0.12	12.04	10.28	14.68	122.74	3 3	5 10
GD-Glutamic acid GD-GL	$C_{12}H_{24}NO_6P$	309.299	1.01	1.26	10.38	8.85	12.68	122.74	3 3	5 10
GB-Glycine GB-G	$C_6H_{14}NO_4P$	195.155	-0.47	-0.29	11.71	9.12	15.59	85.44	2 2	3 6
GD-Glycine GD-G	$C_9H_{20}NO_4P$	237.236	0.84	1.09	9.75	7.70	12.82	85.44	2 2	3 6
GB-Proline GB-P	$C_9H_{16}NO_4P$	235.220	0.32	0.48	10.20	7.70	13.95	76.65	1 1	3 6
GD-Proline GD-G	$C_{12}H_{24}NO_4P$	277.301	1.63	1.86	8.50	6.28	11.84	76.65	1 1	3 6
GB-Alanine GB-AL	$C_7H_{16}NO_4P$	209.182	0.06	0.25	10.97	8.65	14.45	85.44	2 2	3 6
GD-Alanine GD-AL	$C_{10}H_{22}NO_4P$	251.263	1.37	1.63	9.15	7.23	12.03	85.44	2 2	3 6
GB-Phenylalanine GB-PA	$C_{13}H_{20}NO_4P$	285.280	1.71	1.94	7.72	5.80	10.59	85.44	2 2	3 6

GD-Phenylalanine GD-PA	$C_{16}H_{26}NO_4P$	327.361	3.02	3.31	6.32	4.38	9.23	85.44	2 2	3 6
GB-Valine GB-VA	$C_9H_{20}NO_4P$	237.236	0.93	1.12	9.72	7.70	12.74	85.44	2 2	3 6
GD-Valine GD-VA	$C_{12}H_{26}NO_4P$	279.317	2.24	2.50	8.09	6.28	10.82	85.44	2 2	3 6
GB-Methionine GB-ME	$C_9H_{20}NO_4PS$	269.300	0.67	0.78	11.70	9.00	15.76	110.74	2 2	4 8
GD-Methionine GD-ME	$C_{12}H26_{20}NO_4PS$	311.380	1.98	2.15	10.00	7.58	13.63	110.74	2 2	4 8

*All calculated compounds were with no isoelectric point; ** for PSA calculation, P & S atoms were not excluded;

***For calculation of hydrogen acceptor, P & halogen atoms were not excluded.

Table (2). ADMET calculations of Sarin, Soman, and their hypothesized derivatives (continued).

Property		GB	GD	GB-LA	GD-LA	GB-AS	GD-AS	GB-GL	GD-GL	GB-G	GD-G
ADME	**BBB**	1.05522	1.06872	0.314296	1.30021	0.11991	0.260628	0.146437	0.188712	0.17817	0.379681
	Buffer solubility, mg/L	295032	144503	2.95742 e+6	107881	1.78488 e+7	7.8401 e+6	1.05275 e+7	4.58963 e+6	2.82891 e+6	1.29527 e+6
	Caco2	12.0517	34.2915	0.788417	19.7842	0.366263	0.393877	0.385499	0.414642	0.409251	0.658435
	CYP-2C19 inhibition	Inhibitor	Inhibitor	Inhibitor	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP-2C9 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP-2D6 inhibition	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP-2D6 substrate	Non	Weakly	Non	Weakly	Non	Non	Non	Non	Non	Non
	CYP-3A4 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Non	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP-3A4 substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate
	HIA	93.10554	96.38871	63.11209	91.55917	26.02285	35.25331	28.87075	38.91642	56.30134	67.85938
	MDCK	16.7788	46.226	58.3968	30.7031	0.674479	0.913346	0.814258	1.2079	24.8381	4.7613
	Pgp inhibition	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	Plasma Protein Binding	0.000000	8.479509	22.59407	41.93509	38.1166	28.23149	10.26311	29.34628	25.05793	16.46877
	Pure water solubility, mg/L	136339	6148.19	499635	8931.12	821862	33237.8	723812	29053.5	1.07184 e+006	45184.4

Property		GB	GD	GB-LA	GD-LA	GB-AS	GD-AS	GB-GL	GD-GL	GB-G	GD-G
	Skin Permeability	-1.29614	-0.85576	-1.45872	-0.90353	-3.21915	-2.38716	-2.97443	-2.19628	-2.75517	-1.52512
	SKlogD value	0.484950	1.70873	-0.97441	1.54181	-1.86487	-0.64109	-1.54622	-0.32244	-1.69336	-0.46958
	SKlogP value	0.484950	1.70873	0.273590	1.54181	-0.61687	0.606910	-0.29822	0.925560	-0.44536	0.778420
	SKlogS buffer	0.323450	-0.100610	1.148350	-0.365470	1.848160	1.424100	1.595460	1.171400	1.161240	0.737180
	SKlogS pure	-0.0118	-1.47174	0.376090	-1.44751	0.511350	-0.94859	0.432760	-1.02718	0.739750	-0.72019
Toxicity	algae at	0.110767	0.0565227	0.110337	0.0553809	0.164576	0.080168	0.23792	0.0578994	0.181533	0.0890447
	Ames test	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Non-Mutagen	Mutagen	Mutagen	Mutagen
	Carcino Mouse	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Carcino Rat	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
	Daphnia at	2.79091	0.859948	2.09482	0.539667	4.30276	1.31204	13.75	0.980602	5.16029	1.51529
	hERG inhibition	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Medaka at	6.69726	0.71993	4.35946	0.333536	19.4542	2.03635	190.293	1.17356	25.259	2.46614
	Minnow at	1.89027	0.260044	1.12368	0.161918	5.77321	0.886733	40.1761	0.505404	7.77395	1.17539
	TA100 10RLI	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	TA100 NA	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	TA1535 10RLI	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	TA1535 NA	Positive	Negative	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Positive

Table (3). ADMET calculations of hypothesized Sarin and Soman derivatives.

Property		GB-P	GD-P	GB-AL	GD-AL	GB-PA	GD-PA	GB-VA	GD-VA	GB-ME	GD-ME
ADME	BBB	0.286135	0.705296	0.24616	0.512072	0.426509	0.601686	0.435105	0.723752	0.166452	0.191819
	Buffer solubility, mg/L	1.50073 e+6	666376	1.61073 e+6	728730	221040	95535.5	721438	319930	4.42006 e+6	1.92497 e+6
	Caco2	16.4855	19.7689	0.443007	0.830523	1.35674	4.55654	0.682355	2.18739	0.557997	1.18702
	CYP-2C19 inhibition	Non	Non	Inhibitor	Non	Non	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor

Property		GB-P	GD-P	GB-AL	GD-AL	GB-PA	GD-PA	GB-VA	GD-VA	GB-ME	GD-ME
	CYP-2C9 inhibition	Non	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP-2D6 inhibition	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP-2D6 substrate	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP-3A4 inhibition	Non	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP-3A4 substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate
	HIA	78.27943	85.9526	60.29438	71.43586	88.69986	92.49161	67.95696	77.80378	70.53871	79.62553
	MDCK	2.92727	10.2145	2.53759	6.14886	124.252	20.0195	8.5471	38.102	3.9784	3.59644
	Pgp inhibition	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	Plasma Protein Binding	39.6127	53.30104	20.4144	29.16893	84.62024	93.8614	19.55104	59.41036	51.48572	56.94021
	Pure water solubility, mg/L	750400	30678.2	795854	33151	49203.9	1958.01	76801.4	3135.78	153638	6160.48
	Skin Permeability	-2.84528	-1.47578	-2.40147	-1.36921	-2.26904	-1.55538	-1.86838	-1.15801	-2.24956	-1.91981
	SKlogD value	-1.05427	0.169510	-1.32685	-0.10307	0.066160	1.28994	-0.53643	0.687350	-0.83694	0.386840
	SKlogP value	0.193730	1.41751	-0.07885	1.14493	1.31416	2.53794	0.711570	1.93535	0.411060	1.63484
	SKlogS buffer	0.804830	0.380770	0.886500	0.462440	-0.110800	-0.534860	0.483020	0.058960	1.215200	0.791140
	SKlogS pure	0.503820	-0.95612	0.580310	-0.87963	-0.76327	-2.22321	-0.48981	-1.94975	-0.24373	-1.70367
Toxicity	algae at	0.203281	0.0693772	0.133773	0.0665705	0.083083	0.0297741	0.0803212	0.040875	0.10594	0.0478453
	Ames test	Mutagen	Non-Mutagen	Mutagen	Mutagen	Mutagen	Non-Mutagen	Mutagen	Mutagen	Mutagen	Non-Mutagen
	Carcino Mouse	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Carcino Rat	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative
	Daphnia at	5.53088	0.703933	3.72064	0.965308	0.444622	0.114382	1.33105	0.386602	1.62803	0.457492
	hERG inhibition	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Medaka at	30.0537	0.581862	13.4638	1.04328	0.265813	0.020347	1.91231	0.183573	3.28751	0.296902
	Minnow at	7.70255	0.285541	3.37222	0.490016	0.212906	0.0315772	0.773851	0.105742	1.26889	0.168536

Property		GB-P	GD-P	GB-AL	GD-AL	GB-PA	GD-PA	GB-VA	GD-VA	GB-ME	GD-ME
	TA100 10RLI	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
	TA100 NA	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	TA1535 10RLI	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	TA1535 NA	Negative	Negative	Positive	Positive	Positive	Negative	Positive	Positive	Positive	Negative

Table (4). Druglikeness calculations of Sarin, Soman, and their hypothetical derivatives (continued).

Property	GB	GD	GB-LA	GD-LA	GB-AS	GD-AS	GB-GL	GD-GL	GB-G	GD-G
CMC like Rule	Not qualified	Qualified	Qualified	Qualified	Not qualified	Qualified	Not qualified	Qualified	Not qualified	Qualified
CMC like Rule Violation Fields	Molecular weight, A Mol Ref, No Total atoms				AlopP98 value		AlopP98 value		AlopP98_value	
CMC like Rule Violations	3	0	0	0	1	0	1	0	1	0
Lead-like Rule Violation Fields	AlopP98 value		AlopP98 value		AlopP98 value	AlopP98 value	AlopP98 value	AlopP98 value	AlopP98_value	AlopP98_value
Lead like Rule	Violated	Suitable if its binding affinity is greater than 0.1 µM	Violated	Suitable if its binding affinity is greater than 0.1 µM	Violated	Violated	Violated	Violated	Violated	Violated
Lead like Rule Violations	1	0	1	0	1	1	1	1	1	1
MDDR like Rule	Nondrug-like	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure
MDDR like Rule Violation Fields	No Rings, No Rigid bonds, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings	No Rings	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds
MDDR like Rule Violations	3	2	2	2	2	2	1	1	2	2

Property	GB	GD	GB-LA	GD-LA	GB-AS	GD-AS	GB-GL	GD-GL	GB-G	GD-G
Rule of Five	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable
Rule of Five Violation Fields										
Rule of Five Violations	0	0	0	0	0	0	0	0	0	0
WDI like Rule	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff
WDI like Rule Violation Fields	Balaban index JX	Balaban index JX, VChi_03_cluster	Balaban index JX	Balaban index JX, VChi 03 cluster	Balaban index JX	Balaban index JX, VChi_03_cluster	Balaban index JX, Kier alpha 03	Balaban index JX, Kier alpha 03, VChi 03 cluster	Balaban index JX	Balaban_index_JX, VChi_03_cluster
WDI like Rule Violations	1	2	1	2	1	2	2	3	1	2

Table (5). Druglikeness calculation of Sarin, Soman, and their hypothetical derivatives.

Property	GB-P	GD-P	GB-AL	GD-AL	GB-PA	GD-PA	GB-VA	GD-VA	GB-ME	GD-ME
CMC like Rule	Qualified	Qualified	Qualified	Qualified	Qualified	Qualified	Qualified	Qualified	Qualified	Qualified
CMC like Rule Violations	0	0	0	0	0	0	0	0	0	0
Lead-like Rule Violation Fields	AlopP 98 value		AlopP 98 value				AlopP 98 value		AlopP 98 value	
Lead like Rule	Violated	Suitable if its binding affinity is greater than 0.1 µM	Violated	Suitable if its binding affinity is greater than 0.1 µM	Suitable if its binding affinity is greater than 0.1 µM	Suitable if its binding affinity is greater than 0.1 µM	Violated	Suitable if its binding affinity is greater than 0.1 µM	Violated	Suitable if its binding affinity is greater than 0.1 µM
Lead like Rule Violations	1	0	1	0	0	0	1	0	1	0

Property	GB-P	GD-P	GB-AL	GD-AL	GB-PA	GD-PA	GB-VA	GD-VA	GB-ME	GD-ME
MDDR like Rule	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure
MDDR like Rule Violation Fields	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings	No Rings	No Rings, No Rotatable bonds	No Rings, No Rotatable bonds	No Rings	No Rings
MDDR like Rule Violations	2	2	2	2	1	1	2	2	1	1
Rule of Five	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable
Rule of Five Violations	0	0	0	0	0	0	0	0	0	0
WDI like Rule	In 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	In 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff	Out of 90% cutoff
WDI like Rule Violation Fields		VChi 03 cluster	Balaban index JX	Balaban index JX, VChi_03_cluster		Kier alpha 03, VChi 03 cluster	Balaban index JX	Balaban index JX, VChi_03_cluster	Balaban index JX	Balaban index JX, VChi 03 cluster
WDI like Rule Violations	0	1	1	2	0	2	1	2	1	2

Cytochrome P450 catalyzes many drug metabolism besides controlling lipid, steroid, or cholesterol synthesis. CYP-2C19 and CYP-2C9 are epoxygenase of unsaturated fatty acid to the corresponding epoxide derivatives. CYP-2C19 inhibition was not found in GD-LA, GB-P, GD-P, GD-AL, GB-PA, and GD-PA but this inhibitor character was found with presence of other 14 calculated compounds (Tables 2 & 3). For CYP-2C9 inhibition, only GB-P and GD-P showed non – inhibition character between all 20 calculated compounds. All tested compounds showed non – inhibition character with CYP-2D6 and Pgp (Tables 2, 3). As another remarkable note, only GD showed weakly substrate action of two CYP2D6 (Tables 2 & 3).

Non- CYP-3A4 inhibition was found in GB-AS, GD-AS, GP-P, GD-P, GB-PA, GD-PA and all evaluated ADMET compounds were CYP-3A4 substrates (Tables 2 & 3). Also, Ames mutagenic test was found negative in GD-P, GD-PA, and GD-ME while the others showed mutagenic character (Tables 2 & 3).

From Table (2), Sarin (GB) showed positive results to TA100-10RLI, TA100-NA, TA1535-10RLI, and TA1535-NA while Soman (GD) was negative to all except to TA-1535-10RLI.

Positive results toward TA100-10RLI were with GB-PA and GB-ME. Negative results toward TA100-NA were found in all tested compounds except GB as mentioned above (Tables 2 & 3). Positive TA1535-10RLI results

were found with GD, GB-LA, GB-P, and GB-AL beside GB while the rest were negative (Tables 2 & 3). This negative testing of GD, GD-P, GD-PA, and GD-ME was found toward TA2535-NA (Tables 2 & 3).

Like any other Computer –aided Molecular Design, Druglikeness prediction was computed to evaluate drug (or compound) –body interaction according to known rules and their violations that permit or restrict drug application [16]. From Tables (4 & 5), calculated Druglikeness properties were CMC like Rule, Lead like Rule, MDDR like Rule, Rule of 5, and WDI like Rule beside their violation points.
Comprehensive Medicinal Chemistry (CMC) rule in its qualification depends upon logP, molecular reactivity, molecular weight, and number of atoms. This rule is similar to Lipinski and his co- workers rule and has its limitations beside drug classification (inflammatory, infective, depressant, …). CMC like Rule of the tested compounds showed that only (GB, GB-AS, GB-GL, and GB-G) were not qualified with 3 violations for GB and one violation point for the other non-qualifiers. Also, Tables (1, 4, & 5) show that GB violated derivatives had the lowest logP values (-.037, -0.12, -0.29) for GB-AS, GB-GL, GB-G respectively. Negative logP according to Ghose et al., study classified these three GB derivatives to CMC clean, hypertensive, neoplastic, and infective drug classes [17]. Lipophilic character or Partitioning Coefficient (logP, water/oil) determine metabolism, solubility, and absorption. From Table (1), high logP value refers to low binding to hydrophilic protein directs to more toxicity. So, these GB derivatives may have low binding character to hydrophobic proteins, cytochrome P450, and hERG.

hERG is a human gene contributes with potassium ion in beating of heart [18] and this gene –ion combination is responsible of a wide death data named cardiac toxicity of drug [19]. As in Tables (2 & 3), all tested compounds were with low risk results of hERG inhibition.

AlogP98 value as a violation rule for CMC like were presented in GBAS, GB-GL, and GB-G. Also, this value represents a Lead like violation with GB, GB-LA, GB-AS, GD-AS, GB-GL, GD-GL, GB-G, GD-G, GBP, GB-AL, GB-VA, and GB-ME while the others were suitable for Lead like rule if their binding affinity >0.1µM. In general, Lead –like Rule that published by Teague et al. in 1999 stated that Lead- like Rules are three types (High affinity leads, Leadlike leads, and Druglike leads) according to molecular weight, logP, and drug binding affinity [20].

MDDR is another in Silico Druglikeness prediction classifies any chemical to non-drug, drug –like, and mid-structure depending on number of ring, rigid and rotatable bonds with exclusion of reactive functional groups like RCOX, RSO_2X, …. etc. Increasing of rings, rigid bonds and rotatable bonds contribute in choosing this chemical as a drug – like. Number of rings represented MDDR like Rule violation for all tested compounds that had Mid–structure property including GB that had nondrug – like (≤ 2). Also, the other violation in MDDR was number of rotatable bonds that in non-drug like (≤ 5) as in GB.

Lipinski and his team Five Rules re molecular weight (less or equal to 500 Da), logP (less or equal to 5), hydrogen bond donor (less or equal to 5) and acceptor (less or equal to 10). Based on these rules, any molecule has violation in two or more is not suitable for oral activity [21]. From Tables (1, 4, & 5), all 20 compound were suitable to Rule of Five without any violation where Polar Surface Area (PSA) were (36.11-122.74) and tested compounds had hydrogen acceptor counts mainly depending on oxygen atom of P=O group that found in all of them while hydrogen donor count was absent only in Sarin (GB) and Soman (GD) molecules. Also, oxygen represents the hydrogen acceptor site of C=O and OH beside sulphur in sulphide group of GB-ME and GD-ME. Hydrogen donor counts were found in hydrogen atom in OH of COOH and NH groups (Figure 2).

Brown and his group in 2001 published "Tool for designing diverse, drug-like, cost-effective combinatorial libraries" with various molecular descriptors such as molecular weight, HBDs, HBAs, logP, rotatable bonds, …etc. were in comparison with World Drug Index (WDI) [22]. Only GB-P had no WDI Violation (in 90% cutoff) while others were out having Balaban index in most of them.

4. Conclusions

A new Quantitative Structure – Activity Relationship (QSAR) of two important nerve gases (GB and GD) that hypothetically reacted with lactic acid and various amino acids showed many noticeable ADMET-Druglikeness

characters such as: all 20 tested compounds were with non- inhibition character of Pgp and CYP-2D6; substrate character with CYP-3A4, negative values to skin permeability, negative to Carcino-Mouse, low risk to hERG inhibition. Other calculated predictors were varied in response between all calculated compounds.

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