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In Silico Taste–Toxicity Study of New Hypothetical Hetero-Abiraterone Derivatives

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Abstract

First Iraqi attempt to study drug used for prostate cancer treatment (Abiraterone) that hypothetically reacted with known chemicals classified as Anticancer drug: Tirapazamine (T) and 5-Fluorouracil (F), food additive and preservative: Butylated Hydroxy Toluene (B) and Ethoxyquin (E), and sweeteners: P-4000 (P), Sodium Cyclamate (CS), Alitame (AT), and Saccharin (SA). The second step in this work was computational study of all reactants and the formed products having newly ether, amine, and carboxylic acid ester, and sulphonate bonds by online websites. Taste, toxicity, and ADMET were calculated by three online websites related to Charite University of Medicine, Institute for Physiology, Germany and University of Melbourne, Australia. SMILES of the reactants were obtained from National Library of Medicine/ National Center for Biotechnology Information websites while products were drawn by the molecular editor CS ChemDraw Ultra and rechecked by MarvinSketch program. This in Silico study showed various results of the formed products compared to Abiraterone (A) that predicated it as sour chemical belongs to Class 4 as a harmful substance if swallowed. Abiraterone (A) toxicity on liver organ was 61% probability percentage as hepatotoxicity while carcinogenicity, Immunotoxicity, Mutagenicity, cytotoxicity, AhR, AR, Aromatase, ER, HSE, and p53 were more than 70 % to bind Progesterone or Androgen. Also, Abiraterone (A) has a poor water solubility leading to high intestinal absorption, moderate total clearance, and giving inhibition reaction to Cytochrome P450 type CYP2C19, hERG II, and Ames test. These results confirmed that Abiraterone is structurally less harmful acute class with highly chance to interact with cell components resulting lethal response. All Abiraterone hypothetical products had a harmful reaction if swelled (Class 4), sour taste. All toxicological characters may be highly affected by its water solubility and intestinal absorption towards CNS, BBB, and $CaCO_2$ permeability, skin sensation, and Ames test issues. For example, this in Silico- QSAR foundations about Abiraterone – Saccharin (A-SA) suggest that A-SA is structurally safe and there are several possibilities of becoming an active–multiple toxicological compound.

1. Introduction

One of men health problems is prostate cancer combined with pain, weakness, erectile dysfunction, and/or urination difficulties. Now day's treatments include drugs, hormones, vaccines, radiation, surgery, chemotherapy, beside complementary and alternative medicines like nutrition and dietary supplements. Many drugs have been approved and used as a prostate cancer treatment such as Abiraterone acetate, Lupron group, Flutamide, Radium 223 dichloride, and others [1-6].

Safety of environment is a critical issue when it related to the research and development sectors. In chemistry, new materials can be synthesized to perform new or known applications like biological, electrical, photo, and others. This new material can be / or not used by human and animal according to many limitations related to safety of environmental species and the planet. To reduce synthesis of new compound with remarkable toxicity, in Silico method can predict this toxicity. Also, it provides the researcher a primary alert to avoid these complex issues of toxicity- cost-chemicals- experimental tools – characterization instrumentations – biological effects. In biological section, this new material can be candidate as promising drug in specific way of exposure (oral, skin, injection, inhalation…etc). So, it is important to specify it toxicity with in vitro, in vivo, and / or in Silico methods. In Silico is a computational methodology predicates toxicity and other important characters with no – living species under test [7, 8, 9]. This computer –aided or in Silico methodology is popular approach used to evaluate chemical activity and develop or/ and candidate it to be bio-inhibitor of specific disease or bio-activator to particular biological route. In these research directions and others, many articles were published [10-12].

In this paper, Abiraterone was chosen to be a start in Silico study point of hypothetical reactions. The hypothetical products and the reactants were introduced in online prediction websites to characterize their influence on living cell or organs.

2. Experimental Procedure

Abiraterone (A) enters hypothetical reactions with known compounds classified as Anticancer drug: Tirapazamine (T) and 5-Fluorouracil (F), food additive and preservative: Butylated Hydroxy Toluene (B) and Ethoxyquin (E), and sweeteners: P-4000 (P), Sodium Cyclamate (CS), Alitame (AT), and Saccharin (SA). The reactions involved formation of ether and ester and amine linkages. (Figure 1.)

This paper contains online calculations for both of the reactants and the hypothetical products of prostate cancer drug (Abiraterone) (Figure 1.) where their names, identity, SMILES, and logP are in (Table 1.). Taste, toxicity, and ADMET were calculated by three online websites related to Charite University of Medicine, Institute for Physiology, Germany and University of Melbourne, Australia (Tables 2. and 3.) [13]. SMILES of the reactants were obtained by National Library of Medicine/ National Center for Biotechnology Information websites while products were drawn by the molecular editor CS ChemDraw Ultra and rechecked by MarvinSketch program [14]. Also, logP character in Table (1). was calculated by MarvinSketch for all compounds [14b].

Table (1). Isomeric SMILES and logP of the reactants and Hypothetical products.

Reactant Name, Identity	Isomeric SMILES*	logP**	Product Name, Identity	Isomeric SMILES*	logP**
Abiraterone, A	C[C@]12CC[C@@H](CC1=CC[C@@H]3[C@@H]2CC[C@]4([C@H]3CC=C4C5=CN=CC=C5)C)O	4.12	Abiraterone - Butylated hydroxyl Toluene, A -B	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OC1=C(C=C(C)C=C1C(C)(C)C)C(C)(C)C	10.20
Abiraterone acetate, AA	CC(=O)O[C@H]1CC[C@@]2([C@H]3CC[C@]4([C	4.55	Abiraterone - Butylated hydroxyl	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H]	10.40

Reactant Name, Identity	Isomeric SMILES*	logP**	Product Name, Identity	Isomeric SMILES*	logP**
	@H]([C@@H]3CC=C2C1)CC=C4C5=CN=CC=C5)C)C		Toluene, A – B1	(CC[C@]12C)OCOC1=C(C=C(C)C=C1C(C)(C)C)C(C)(C)C	
Ethoxquin, E	CCOC1=CC2=C(C=C1)NC(C=C2C)(C)C	3.03	Abiraterone - Ethoxquin, A-E	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OCCN1C2=CC=C(OCC)C=C2C(C)=CC1(C)C	8.24
5-Fluorouracil, F	C1=C(C(=O)NC(=O)N1)F		Abiraterone - 5-Fluorouracil, A-F	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OC1=CNC(=O)NC1=O	4.11
Tirapazamine T	C1=CC=C2C(=C1)[N+](=C(N=[N+]2[O-])N)[O-]	0.30	Abiraterone-Tirapazamine, A-T	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OCCNC1=[N+]([O-])C2=CC=CC=C2[N+]([O-])=N1	5.17
Butylated hydroxyl Toluene, B	CC1=CC(=C(C(=C1)C(C)(C)C)O)C(C)(C)C	-0.08	Abiraterone - Saccharin, A-SA	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OCCN1C(=O)C2=C(C=CC=C2)S1(=O)=O	5.12
Saccharin, SA	C1=CC=C2C(=C1)C(=O)NS2(=O)=O	0.36	Abiraterone - Sodium Cyclomate, A-CS	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OS(=O)(=O)NC1CCCCC1	5.67
Sodium Cyclomate, CS	[Na+].O=S([O-])(=O)NC1CCCCC1		Abiraterone - Alitame, A-AT	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OC(=O)CC(N)C(=O)N[C@H](C)C(=O)NC1C(C)(C)SC1(C)C	3.56
Alitame, AT	C[C@H](C(=O)NC1C(SC1(C)C)(C)C)NC(=O)[C@H](CC(=O)O)N	-1.16	Abiraterone - P-4000, A-P	[H][C@@]12CC=C(C3=CC=CN=C3)[C@@]1(C)CCC1[C@@]2([H])CC=C2C[C@H](CC[C@]12C)OCNC1=C(OCCC)C=CC=C1[N+]([O-])=O	7.67
P-4000, P	CCCOC1=C(C=C(C=C1)[N+](=O)[O-])N	2.43	*SMILES of the reactants were obtained from PubChem website and MarvinSketch program but for products by the help of MarvinSketch program. **logP was calculated by MarvinSketch program		

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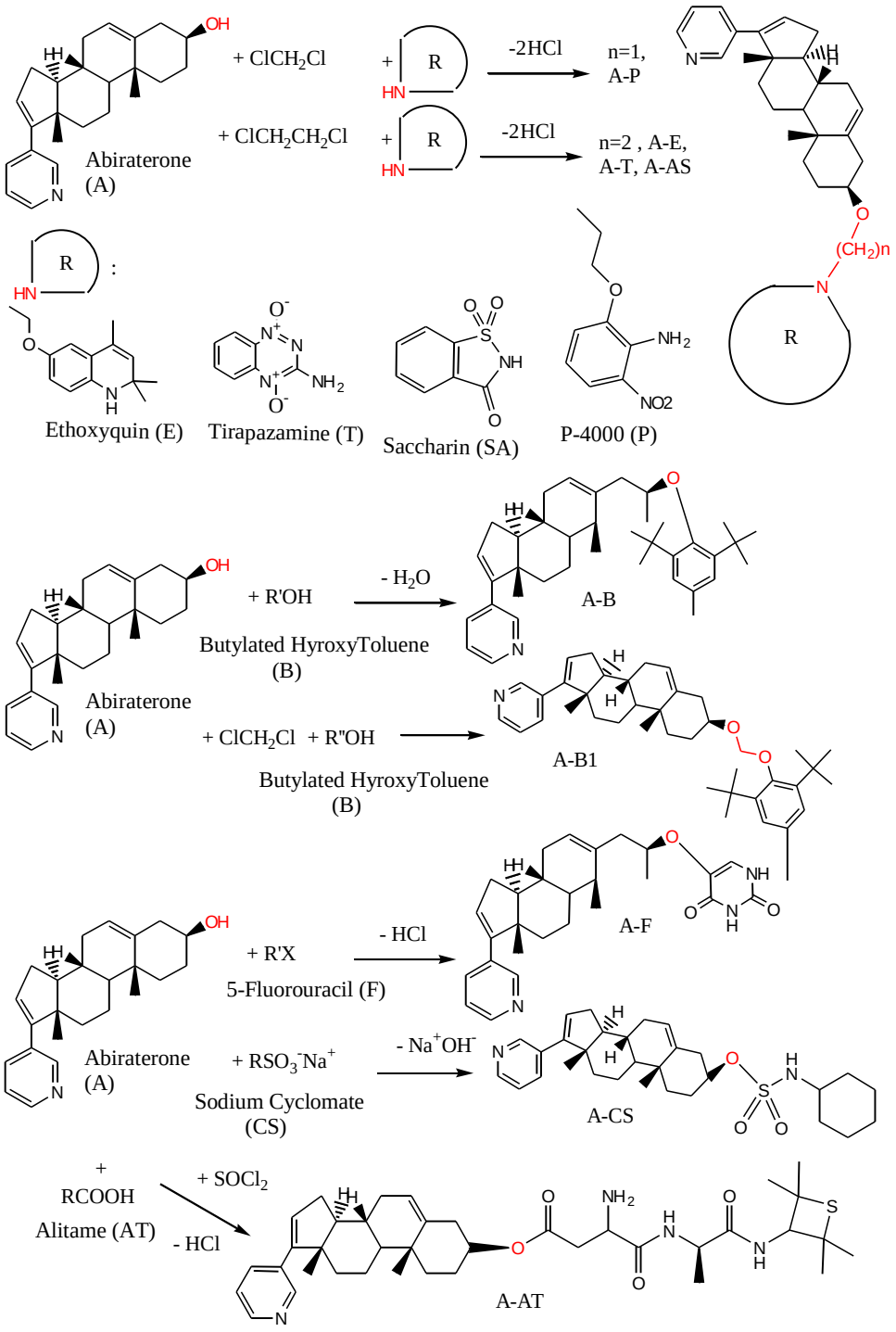

Figure (1). Formation of Hypothetical Abiraterone derivatives.

Table (2). Taste and Some toxicological predictors of the reactants and the hypothetical products calculated by [13].

Category	Character	A	AA	E	A-E	F	A-F	T	A-T	B	A-B	A-B1	SA	A-SA	CS	A-CS	AT	A-AT	P	A-P
Taste	Bitter	0.764	0.782	0.717	0.923	0.914	0.728	0.826	0.761	0.609	0.748	0.64	0.664	0.786	0.53	0.657	0.546	0.667	0.89	0.642
	Sweet	0.886	0.632	0.796	0.839	0.887	0.679	0.813	0.754	0.992	0.754	0.619	0.993	0.648	0.982	0.533	0.987	0.512	0.693	0.638
	sour	0.973	0.982	0.99	0.997	0.977	0.994	0.989	0.991	0.93	0.986	0.979	1.0	0.999	0.98	0.996	0.995	0.995	1.0	0.996
Oral toxicity	LD_{50}	830	680	800	750	1923	830	1550	1000	650	830	1000	14200	1200	680	800	4000	2500	1500	500
	Class	4	4	4	4	4	4	4	4	4	4	4	6	4	4	4	5	5	4	4

Category	Character	A	AA	E	A-E	F	A-F	T	A-T	B	A-B	A-B1	SA	A-SA	CS	A-CS	AT	A-AT	P	A-P
Organ toxicity	Hepato.	0.61	0.62	0.66	0.86	0.78	0.60	0.60	0.62	0.78	0.70	0.70	0.64	0.60	0.73	0.61	0.75	0.65	0.65	0.59
Toxicity end points	Carcino.	0.70	0.52	0.85	0.53	0.85	0.56	0.67	0.55	0.52	0.62	0.56	0.86	0.68	0.72	0.55	0.78	0.56	0.51	0.54
	Immuno.	0.87	0.97	0.79	0.99	0.99	0.95	0.96	0.99	0.98	0.98	0.98	0.99	0.66	0.99	0.79	0.99	0.99	0.73	0.99
	Muta.	0.85	0.88	0.90	0.71	0.88	0.63	0.73	0.58	0.99	0.80	0.80	0.86	0.67	0.56	0.52	0.80	0.71	0.86	0.63
	Cyto.	0.83	0.74	0.75	0.62	0.93	0.76	0.98	0.62	0.91	0.83	0.78	0.75	0.58	0.65	0.65	0.60	0.62	0.70	0.56
Tox21-Nuclear receptor signalling pathways	AhR	0.96	0.97	1.0	0.74	0.94	0.87	0.52	0.78	1.0	0.85	0.81	0.98	0.92	0.98	0.89	0.93	0.94	0.57	0.8
	AR	0.70	0.83	0.99	0.93	0.99	0.84	0.95	0.91	1.0	0.87	0.83	0.99	0.89	0.99	0.71	0.92	0.87	0.98	0.89
	Aromatase	0.74	0.87	0.89	0.83	0.99	0.88	0.93	0.84	0.99	0.74	0.75	0.99	0.92	0.99	0.83	0.98	0.89	0.95	0.82
	ER	0.77	1.0	0.94	0.83	0.98	0.83	0.86	0.85	1.0	0.54	0.60	0.77	0.89	0.94	0.64	0.91	0.81	0.85	0.85
Tox21-Stress response pathways	HSE	0.87	0.89	0.79	0.88	0.99	0.91	0.91	0.87	1.0	0.80	0.82	0.98	0.88	0.99	0.93	0.97	0.9	0.94	0.85
	MMP	0.55	0.86	0.89	0.69	0.95	0.59	0.75	0.74	0.96	0.55	0.73	0.94	0.69	0.86	0.66	0.94	0.72	0.60	0.50
	p53	0.88	0.93	0.93	0.85	1.0	0.81	0.85	0.90	0.99	0.88	0.90	0.95	0.86	0.98	0.80	0.96	0.73	0.92	0.82

Table (3). ADMET-pKCSM predication of the reactants and the hypothetical products.

Character	A	AA	E	F	T	B	SA	CS	AT	P	A-E	A-F	A-T	A-B	A-B1	A-SA	A-CS	A-AT	A-P
Water sol.*	2.168 E-6	9.816 E-7	0.000116	0.0685157	0.1027595	0.0006538	0.0455783	0.2322126	0.0418554	0.002848	2.42 E-7	1.021 E-5	0.0003407	4.538 E-7	2.804 E-7	1.259 E-6	7.887 E-7	8.572 E-6	2.327 E-7
Caco2 perm.	1.234	1.187	1.332	0.607	0.156	0.494	1.307	0.603	-0.346	0.922	1.222	0.985	0.689	1.033	1.119	0.795	0.679	0.634	0.604
Intest. Abs.	96.968	97.559	92.233	92.348	80.075	92.27	81.045	88.524	33.238	92.632	94.455	95.669	100	94.059	93.748	97.225	93.793	94.701	90.969
Skin Perm.	-2.904	-3.012	-2.251	-3.938	-2.92	-2.729	-3.015	-2.76	-2.735	-2.688	-2.73	-3.151	-2.742	-2.724	-2.718	-2.846	-3.349	-2.849	-2.722
P-glycopro. Subs.	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes
P-glycopro Inh.I	Yes	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P-glycopro Inh.II	No	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BBB perm.	0.25	0.09	0.359	-0.449	-0.319	0.362	-0.297	-0.359	-1.212	-0.262	0.267	-0.451	-0.563	0.321	0.443	-0.675	-0.362	-1.003	-0.15
CNS perm.	-2.667	-2.82	-2.176	-3.046	-2.927	-0.631	-2.952	-3.101	-3.92	-2.421	-1.547	-2.858	-1.844	-1.07	-1.136	-1.621	-2.809	-2.181	-1.509
CYP1A2 inh.	No	No	Yes	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No
CYP2C19 inh.	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes
CYP2C9 inh.	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
CYP2D6 inh.	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No
CYP3A4 inh.	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Total Clearance	0.486	0.417	0.279	0.609	0.355	0.876	0.656	0.324	0.217	0.224	-0.171	0.066	0.205	-0.402	-0.385	0.084	0.226	0.026	0.068
OCT2 subs.	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No
AMES	No	No	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	Yes
Max. dose	-0.242	-0.227	0.407	1.192	0.086	-0.283	0.781	0.77	1.38	0.441	0.388	-0.356	0.012	0.242	0.291	0.151	-0.564	-0.888	0.155
hERG I inh.	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

Character	A	AA	E	F	T	B	SA	CS	AT	P	A-E	A-F	A-T	A-B	A-B1	A-SA	A-CS	A-AT	A-P
hERG II inh.	Yes	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Oral Rat Acute LD_{50}	2.423	1.881	2.417	1.874	2.177	2.093	2.321	2	1.658	1.965	2.503	2.481	2.797	2.576	2.564	2.621	2.586	2.809	3.283
Oral Rat Chronic LOAEL	1.655	1.78	1.732	1.585	1.384	3.301	2.088	0.621	2.666	1.546	1.469	0.805	1.502	2.269	2.08	1.966	0.83	1.036	1.289
Hepato.	Yes	No	No	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	No
Skin Sens.	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No

3. Results and Discussion

Abiraterone or its acetate form is a known cure agent of prostate cancer that minimizes androgen action. Working of this cure agent is basing on biosynthesis inhibition of this steroid hormone (androgen) synthesis in testes or adrenal glands. This inhibition pathway can be processed by blocking Cytochrome P450 enzyme [3-5].

Octanol to water solubility or logP that in this study was calculated by ChemAxon method provides researchers a primary predication of chemical behaviour in different phases. In this paper, Hypothetical Abiraterone products were higher than their reactants as an indicator of their low water solubility and high Octanol (organic medium) solubility (Table 1, Figure 2.).

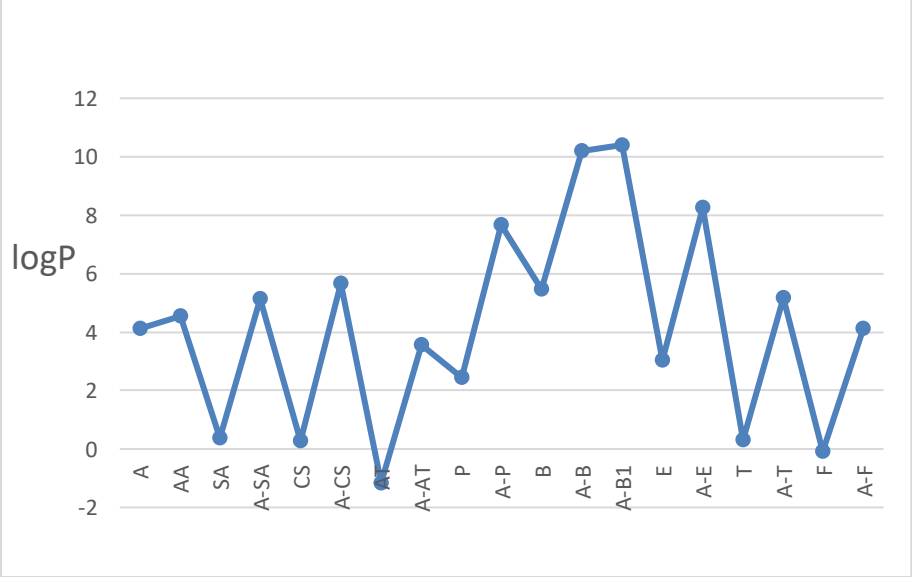

Figure (2). logP of reactants and products.

For example, A and P were 4.12 and 2.43 respectively compared to their product A-P which was 7.67. Low logP indicates spontaneous permeation of chemical through membrane by lipid (organic) phase association. Also, poor membrane permeability is a result of high hydrophilicity resulting chemical with negative logP value. Low hydrophilicity or high lipophilicity is the researcher target of any candidate drug because human or animal have a lipid nature in their cell membrane that demand biological action [15]. Acceptable balance between lipid and water phases permits suitability of absorption, drug design and formulation. This required balance mainly depends upon chemical structure [16].

Minimum to maximum range of the calculated data in Table 2. is presenting as below showing the predication probability of taste (bitter, sweet, and sour), toxicity as Oral toxicity (LD50), Organ toxicity (Hepato.), Toxicity end points (Carcino., Immuno., Muta., and Cyto.), Tox21-Nuclear receptor signalling pathways (AhR, AR, Aromatase, ER) and Tox21-Stress response pathways (HSE, MMP, and p53) (Table 4.).

Table 4. Summary of the prediction probability according to each character.

All reactants and hypothetical products						Only hypothetical products					
Character	**Min.**	**Max.**	**Character**	**Min.**	**Max.**	**Character**	**Min.**	**Max.**	**Character**	**Min.**	**Max.**
Bitter	0.53	0.923	Hepato.	0.59	0.86	Bitter	0.609	0.923	Hepato.	0.59	0.86
Sweet	0.512	0.993	Carcino.	0.51	0.86	Sweet	0.512	0.992	Carcino.	0.52	0.68
sour	0.93	1	Immuno.	0.66	0.99	sour	0.93	0.999	Immuno.	0.66	0.99
LD_{50}	500	14200	Muta.	0.52	0.99	LD_{50}	500	2500	Muta.	0.52	0.99
AhR	0.52	1	Cyto.	0.56	0.98	AhR	0.74	1	Cyto.	0.56	0.91
AR	0.7	1	HSE	0.79	1	AR	0.71	1	HSE	0.8	1
Aromatase	0.74	0.99	MMP	0.5	0.96	Aromatase	0.74	0.99	MMP	0.5	0.96
ER	0.54	1	p53	0.73	1	ER	0.54	1	p53	0.73	0.99

Taste is a sensation character of material through direct contact. It is a useful primary identification of human or animal with the help of mouth or throat receptors to permit its likeness. This primary likeness is a gate of toxicity recognition or acceptable take. From (Table 2.) and (Figure 3.), it can be noticed that taste probability was in its higher values in sour taste. Also, presence of highly sweet taste reactants (B, SA, CS, and AT) did not convert AA or AB to sweeter material. It can be noticed that taste property of the hypothetical products was more sour than the reactants themselves.

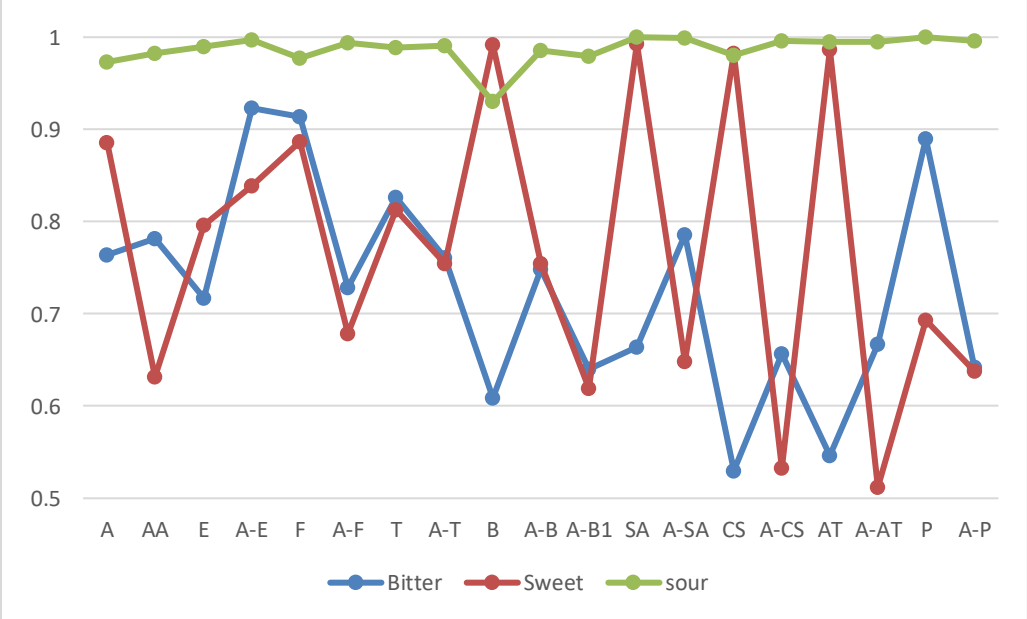

Figure (3). Taste predication according to http://virtualtaste.charite.de/VirtualTaste/

Oral toxicity calculations in this study included toxicity class and LD_{50} or "the medium dose predicted to kill 50% of a given test population" as it defined of acute lethality hazard indicator of chemicals. The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) integrates LD_{50} as warning based on animal testing protocols [17].

In oral toxicity category, LD_{50} values were in good signs of acceptable hypothetical products to be taken by human or towards environmental species in spite of their low values compared to the reacted material with Abiraterone. Also, it can be noticed that Abiraterone converted SA from its highest LD_{50} value (14200) mg/kg to (1200) mg/Kg

or from toxicity class (6; LD_{50} greater than 5000 mg/Kg; nontoxic) to (4; LD_{50} < 2000 mg/Kg, harmful if swallowed) but this dramatic conversion did not hypothetically produce a high toxic product (A-SA) (Table 2.).

In general, most reactant and hypothetical products were with harmful if swallowed toxicity class (Class 4) except AT and its A-AT were class 5 as may be harmful if swallowed and their LD_{50} were less than 5000 mg/Kg as Globally Harmonized System (GHS) categorizes LD_{50} (Figure 4., Table 2.).

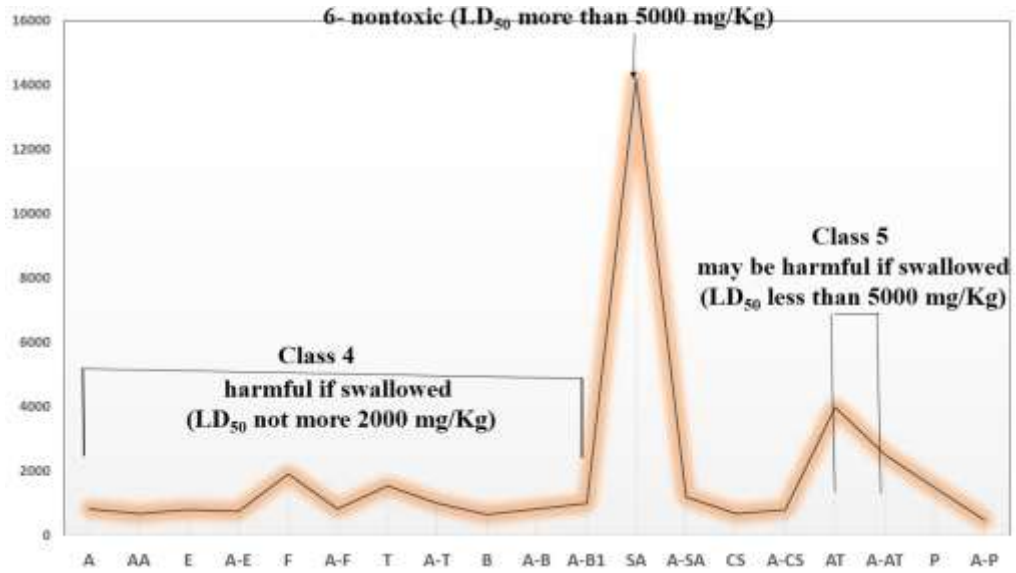

Figure (4). Representative LD_{50} and GHS Classes of Toxicity.

Many botanical and environmental hepatotoxins are rapidly absorbed by gastrointestinal tract and reached liver causing inhibition of two important pathways protein synthesis and mRNA production. Liver damage is not only the major toxicity issue, there are Central Nerve System (CNS) function disability, renal failure, and others. Hepatotoxic materials are in foodstuffs like grains contaminated by potential fungal mycotoxins, mushroom (approx. 100 among 5000 classified as poisonous plants), Chemicals, herbal, and dietary supplements [18].

Mitochondria and Plasma membrane (cellular structures) mange many functions such as generation of energy and cell safety that damaged by highly hepatotoxins. This harming of liver cells is a result of irreversible protein, lipid, or nucleic acid reaction with toxin by covalent bond. This unwanted binding deactivates enzyme or protein function and produces molecular danger through immunological destructive steps [19].

Table 2. and Figure 5. present general decreasing of hepatotoxic prediction probability of hypothetical Abiraterone derivatives compared to their reactants that reacted with Abiraterone except A-T and A-E. According to hepatotoxic probability in this study, high covalent binding of A-T and A-E to cellular components may destruct liver cell and deactivate hepatocyte performance.

Predication of hepatotoxicity with Yes/ No response as presented in Table 3. displayed (Yes) response of A, A-F, A-T, A-SA, and A-T while others with (No). By comparing hepatotoxicity prediction probability in both Tables 2 and 3., only A-T that showed high value compared to its reactants revealed Yes response.

Carcinogenicity (Carcino.), Immunotoxicity (Immuno.), Mutagenicity (Muta.), and Cytotoxicity (Cyto.) are four toxicological endpoint models predicted in this work [20]. Carcino. (incidence of tumour) by chemical represents 1% and 19% of exposure resulting adversely influence on human depending upon duration time of exposure, chemical sensitivity, environmental factors, work type, and others [21]. In this *in Silico* study, only A-B, A-B1, and A-P had more carcinogenicity probability than their parent reactants (A, AA, B, and P) compared to the other Abiraterone derivatives (Table 2., Figure 5.).

Immune system provides an advanced protection walls to minimize cell damage, prevent tumour cell from increasing and surveillance, and direct system to kill pathogens or at least innate immunity [22]. Immunotoxicity (Immuno.) or growth inhibition in immune system of chemicals is affective when chemical concentration is less than 10 µM by negative regulator and checkpoints centres [23]. Current online calculations of the reactants and Abiraterone products showed immunotoxicity predication probability with (≥0.95) except A-SA (0.66) and A-CS (0.79). So, both A-SA and A-CS are suggested to be safer Abiraterone derivatives to human with less tumour cell growth probability.

Mutagenicity (Muta.) or abnormal changing in DNA resulting disease by chemical material is another predictor of Abiraterone hypothetical reactions. Radiation and chemicals as environmental components, synthesized, or used in chemotherapies by both internal and external exposure attack genetic information causing DNA modifications and mutagenic templates. DNA modifications faced by complex repair mechanism to the original state. Repairing consequences outcome in known and new genetic disorder diseases and of course premature aging [24]. Mutagenicity prediction showed a decreasing in its probability of all Abiraterone derivatives compared to the reactants and these results are a good founding in materials candidate as drugs (Table 2. And Figure 5.).

Cytotoxicity (Cyto.) is cell damage leading to activated or programed death or tumour by toxic compound. DNA cleavage and / or cytoplasmic shrinking are/ is cytological steps force cell to terminate its metabolism and characteristic shape (no longer presence of membrane). Cytotoxic material threats cells by preventing growth, non-controlling of mitochondria functions so energy production, and decreasing or inhibition of cellular protein and nucleic acid syntheses. Inhibition by chemical and biological cytotoxic agent may be including biosynthesis of purine, pyrimidine, RNA, DNA, nucleoprotein, energy, and other important biological processes [25]. From Table (2). and Figure (5)., *in Silico* prediction presents a good finding of these hypothetical Abiraterone products where they had less cytostatic compared to their reactants except A-CS and A-AT.

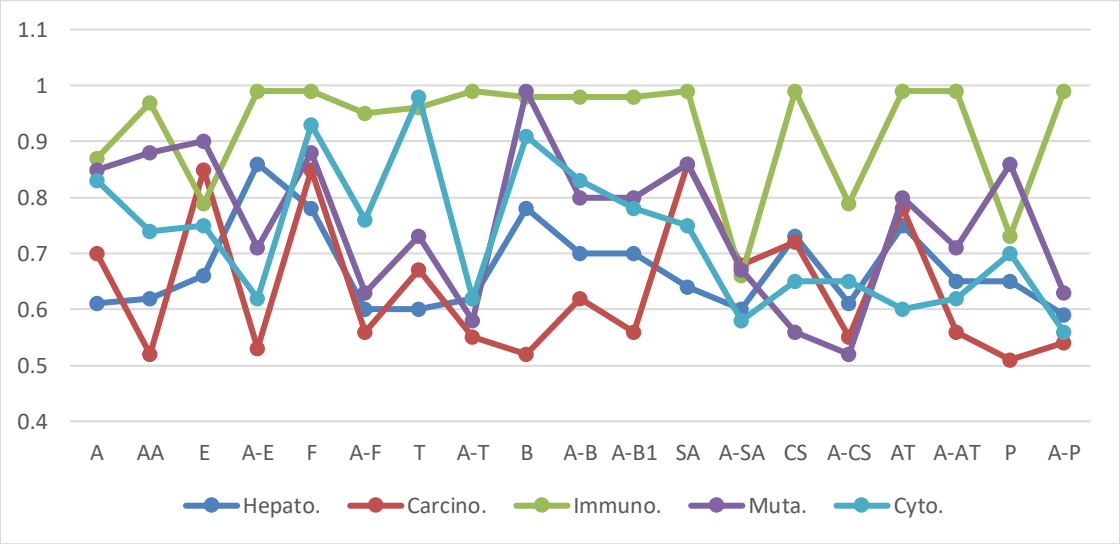

Figure (5). Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity, and Cytotoxicity prediction probability.

Adsorption-Distribution-Metabolism- Excretion- Toxicity (ADMET) characters were calculated and presented in (Table 3.) in Numerical and Yes/No results. Numerical Adsorption property calculation contains water solubility (log mol./L), Caco2 permeability (log P_{app} in 10^{-6} cm/Sec.), Intestinal absorption in human (% absorbed), Skin Permeability (log Kp); Distribution property includes BBB and CNS permeability in log BB and PS respectively; Excretion property contains total Clearance (log, mL/min./Kg); and Toxicity property consists of maximum tolerated dose for human (log, mg/Kg. day), and oral rat chronic toxicity (LOAEL, log, mg/kg of body weight/day). These numerical results predicated by pKCSM website (Table 3.) were ranged as below:

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Table 5. Summary of the ADMET prediction probability according to each character.

All reactants and hypothetical products						Only hypothetical products					
Character	**Min.**	**Max.**	**Character**	**Min.**	**Max.**	**Character**	**Min.**	**Max.**	**Character**	**Min.**	**Max.**
Water Sol.	2.33E-07	0.232	Total clearance	0.396	7.52	Water Sol.	2.33E-07	3.41E-04	Total clearance	0.396	1.68
Skin perm.	1.15E-04	5.61E-03	Max. dose	0.129	24	Skin perm.	4.47E-04	1.91E-03	Max. dose	0.129	2.44
BBB	6.13E-02	2.77	Caco2	0.451	21.5	BBB	0.0993	2.77	Caco2	4.02	16.7
CNS	1.20E-04	0.234	LOAEL	4.18	2000	CNS	0.00139	0.0851	LOAEL	6.38	186

From Table (3). and Figure (6)., water solubility of the produced Abiraterone derivatives hypothetically formed were with increasing pattern compared to Abiraterone itself where A-T has the highest value. The increasing in water values may be attributed to the presence of more heteroatoms especially N and O that are capable to form more hydrogen bonding with water molecules.

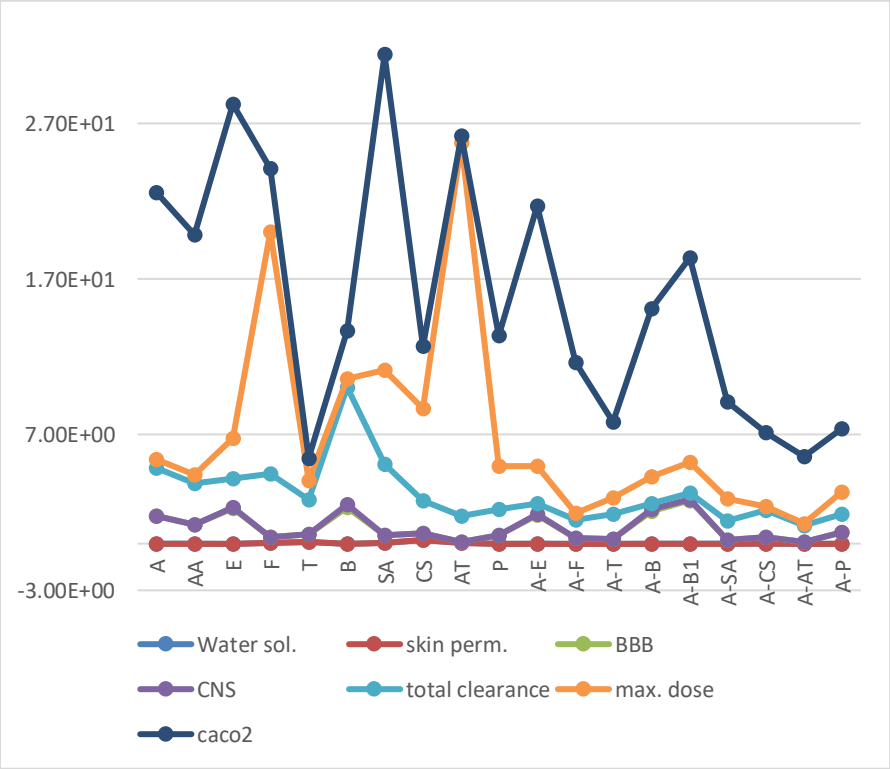

Figure (6). Water solubility, skin permeability, BBB, CNS, Total clearance, maximum dose, and Caco-2 predicators of the reactants and the products.

In experimental toxicological studies of chemicals, important guidelines must be followed on animal oral doses, time, repeating, food type, … that provide an expansion and updating of human hazard database. Caco-2 permeability is another character predicted in this study that is highly related to drug and chemical absorption in human by small intestine [26]. *In vitro* and *in Silico* studies were performed to predict oral delivered absorption of material in small intestine [27]. Here, a new *in Silico* attempt to predict hypothetical oral absorption influence of hypothetical Abiraterone products and their effects on human cancer cell line. These products revealed lower Caco-2 response than Abiraterone itself (Table 3 and Figure 6.).

Pharmaceutical characteristics, molecular and physicochemical descriptors like particle size, lipophilicity, dissociation, intra- and / or intermolecular hydrogen bonding, molecular and / or polar surface, weight, formation of Zwitter ion, charge at neutralization stage, and compound-membrane interaction control molecule bio-transport and candidate the target molecule to be drug or safe consumed material [28].

Predication of intestinal absorption in human showed the same pattern of Caco-2 response to Abiraterone products compared to Abiraterone itself with one difference in A-T intestinal absorption was with 100% (more than A, AA, all reactants, and products). This difference may be related to the ionic oxygen structure of Tirapazamine (T) with high presence of Nitrogen atom.

Skin – chemical relationships are in two ways: penetration or remaining (non- penetration) of the chemical on the external human surface in both directions: in- or out of the body. Sunscreens are examples of topical materials. Dermal infections and their medications are examples of easy accessibility to this homeostatic barrier that also control losing of water. Many medical limitations are considered in dermal topical treatments such as drug location, diffusion into bloodstream, stability in gastrointestinal system, hepatic pass, and interaction with other medications or clinic situation of patients. During drug development under ethical considerations especially in topical and transdermal subjects, many expensive and time-consuming studies are proceeded. To minimize cost, time and other related experimental conditions, computational studies are good options now days which are under development issue because there no standardization in formal way for dermal treatments [29]. In this work, skin permeability character in logKp term of Abiraterone products were higher in negative values than both Abiraterone forms (A and AA) and their reactants except A-CS and A-F (Table 3. and Figure 6.).

P-glycoprotein is trans-membrane regulator, protects cells from toxic substance in brain, liver, intestine, testis, kidney, and pancreas. Also, this protein system controls drugs or toxins efflux over plasma membrane and may secret them into bile or eliminate through the urine. This important action of p-glycoprotein has a side effect that is failure of many treatment strategies. There are two main classified roles of p-glycoprotein: substrate and inhibitor. The first one is merge action of compound with this protein system while the other compound may prohibit p-glycoprotein action [30].

Predication of p-glycoprotein behaviour as substrate and inhibition types I and II showed Yes/ No of A, AA and Abiraterone products (Table 3.). In p-glycoprotein substrate prediction, both Abiraterone forms (A and AA) showed (No) response like its hypothetical products except A-F, A-T, A-B, and A-P showed (Yes) response. In p-glycoprotein inhibition type I, both Abiraterone forms and all their products showed (Yes) response. While in inhibition Type II, Abiraterone (A) (not AA) and its products showed (Yes) response.

Blood Brain Barrier (abbreviated as BBB) is the key control of brain metabolic activities that functionalizes normal brain and Central Nerve System (NCS) roles (Figure 7.). This largest dynamic biological interface is a primary block of exogenous compounds or various pathological conditions to access CNS [31]. Table 3. and Figure 6. show an increasing in BBB permeability towards A-E, A-B, and A-B1 while other Abiraterone products showed a decrease in this predicated character.

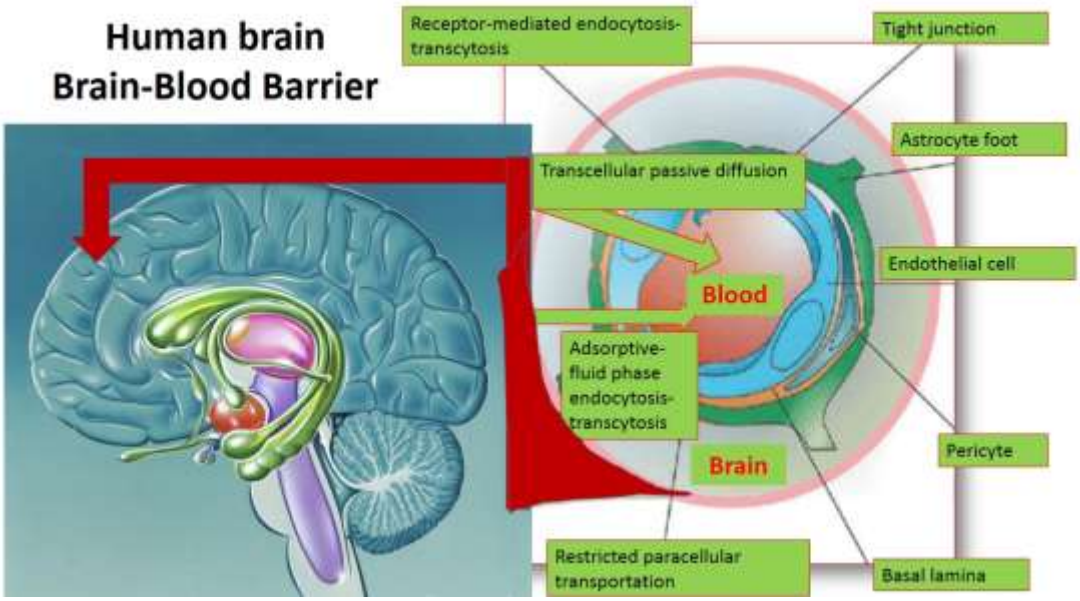

Figure 7. Brain-Blood Barrier structure and functions.

Any drug, toxin or other chemical substance needs to penetrate the brain-blood influx and efflux barrier that is so sensitive to any changing in biological signals. *In vivo* or *in vitro* BBB models predict chemical substance BBB passage into the brain with some correlations. *In Silico* predication is an important tool to avoid losing more than $100 million as a result of clinic failure in a drug candidate [32]. As shown in Table (3) and Figure (6), this work predicts that only A-F had a decrease in CNS permeability while other Abiraterone products had an increasing even with slightly number like A-CA.

Chemical substance may have metabolized by cytochrome P450 enzymes in reversible or irreversible competitive, non- competitive mechanisms depending on concentration, time, overuse of medication, enzyme activity, and drug-drug interaction in multi-administration of more than one chronic disease. CYP450 systems based upon active site of protein, substrate, inhibitor, and binding affinity. Inhibition process is a consequence of chemical substance (drug, substrate, toxin...etc) binding to the active site of the target enzyme. Inhibition is a selective mechanism may have occurred in one or more enzymes from the same family [33].

Table (3). with Yes/ No response displays CYP450 enzymatic inhibition towards Abiraterone, other reactants, and their hypothetical products as shown below:

- CYP1A2 inhibition confirmed by all chemicals under test.
- CYP2C19 inhibition was with Yes response towards Abiraterone forms, and (A-E, A-T, A-SA, A-CA, and A-P).
- CYP2C9 inhibition was with No response to both Abiraterone forms and (A-T, A-B, A-B1, A-SA, A-CA, A-AT, and A-P) but not (A-E and A-F).
- CYP2D6 inhibition was with Yes reaction only to A-T.
- CYP3A4 inhibition was with No to Abiraterone forms and A-T, A-B, AND A-B1.

Drug or any chemical substance enters human body to perform specific action then this material or its metabolic(s) remove(s) by various organs according to their clearance mechanisms: renal, hepatic, and biliary. Total clearance is the body capacity to eliminate the target by all needed mechanisms according to volume of blood per time (mL/minute) [34]. In this work, this important excretion factor presents a numeric decreasing issue of Abiraterone products compared to both Abiraterone forms (Figure 6., Table 3.).

OCT2 is an uptake and secretion transporter of organic cationic substrate at physiological pH to brain, kidney, and liver and it differs from OCT1 and OCT3 in its capacity to transform (kinetic rate) low molecular weight of

hydrophilic organic cationic material. Various OCT2 substrates have been characterized such as choline, dopamine, cisplatin, histamine, and others [35]. Both Abiraterone s showed a No response to OCT2 substrate beside most of their products; A-SA and A-T showed Yes to this transporter (Table 3.).

Salmonella or *Escherichia coli* strains may be reversibly gene-mutated by chemicals that inactivate synthesis of histidine or tryptophan respectively. This bacterial mutation assay is DNA damage by base substitution and known as Ames test [36]. In this work, online prediction of Ames test showed that all Abiraterone products except A-T and A-P were genetically safe to the tested bacteria (Table 3.).

The other remarkable character in Quantitative- Structure Activity Relationship (QSAR) in Toxicity state is maximum tolerated dose for human that is identified as "the highest dose of the test agent given during the chronic study that can be predicted not to alter the animal". This character is necessary in serious numerous diseases such as cardiovascular, mental, epilepsy, or others that used antidepressant, stimulants, antipsychotics in early or late phase of illness. It is major factor in avoiding probable carcinogenicity and getting efficient acceptable dose for long – term treatment especially in chronic diseases of renal tract, liver, or heart in the elderly [37]. Present work showed that Abiraterone – F,-CA, and At products were significantly lower that Abiraterone themselves (Table 3, Figure 6.).

Lowest Observed Adverse Effect Levels (LOAEL) is another QSAR character has an extreme relationship between toxicity and exposure duration in long- term (chronic, (52-104) weeks) or short – term (subchronic, 13 weeks) studies. There is a lack in toxicity studies in critical fields such as food constituents, additives, or contaminants in oral uptake. The lack is partially a consequence of legal requirements of using laboratory animals which is known as 3R (replace, reduce, and refine) [38]. With this risk assessment guide, our online – toxicity work presents a computational path of toxicity where only A-B, A-B1, and A-SA were higher (4.1, 2.7, and 2.05) times respectively than Abiraterone (A) (Table 3, Figure 8.).

Rat Acute dose (LD_{50}) was also calculated as presented in (Table 3. and Figure 8.) and exhibited an increase value of all Abiraterone products compared to Abiraterone even in slightly rise as in A-F.

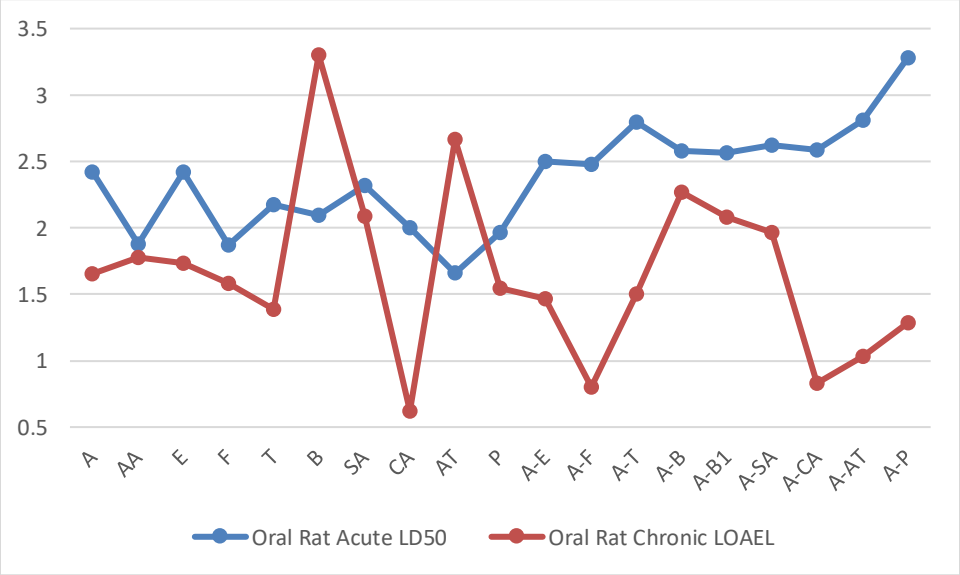

Figure (8). Oral Rat toxicity in acute and chronic terms.

hERG is a human gene related to potassium ion (K^+) and cardiac action potential where its mainly role is cardiac repolarization that can be blocked by drug and causing lethal ventricular tachycardia [39]. From a preclinical safety in drug discovery and development, concentration of any candidate compound required IC_{50} (50% blockage) at maximal current of this voltage gated K^+ channel. By the exploring gate in drug industry, *in Silico* predication is an important model in drug –hERG screening that possess fast-economic method compared to in vitro or in vivo

methods [40]. In this work, hERG Type I inhibition was with (No) response of A, AA, and all Abiraterone products while in Type II A, AA, and all hypothetical products except (A-SA and A-CA) showed (Yes) response (Table 3).

So, hERG type II (not Type I) contribution to coordinate heart beating by conducting electric current across membrane with presence of A, AA, and most of hypothetical Abiraterone products can be inhibited. hERG inhibition may generate fatal disorder or Inherited Rhythm Disorder (IRD), cancer of leukemic cell, or changing in nervous cell functions [41].

Skin sensation is the last prediction character in this work. It is defined as "sensory reaction triggered by contactors and/or environmental factors (cold, heat, sun, pollution, moisture), usually without a visible clinical manifestation" but can be characterized to hypersensitivity, irritation, intolerance, or skin hyperreactivity by skin stinging, itching, burning, tingling, or thickening. Conducting Time, physical type of the chemical (product or environmental), concentration, repeat of use and cumulative rate determine skin sensation [42]. Both Abiraterone forms and all its hypothetical products showed No response to skin sensation prediction (Table 3.).

4. Conclusions

First Iraqi attempt to study drug used for prostate cancer treatment (Abiraterone) that hypothetically reacted with known chemicals (Anti-cancer drug, food additive and preservative, and sweetener). The second step in this work was online computational study of all reactants and the formed products having newly ether, amine, and carboxylic acid ester, and sulphonate bonds.

This *in Silico* study showed various results of the formed products compared to their parent reactants as shown: Abiraterone, Saccharin, and their product A-SA:

Abiraterone (A) predicated as sour chemical with 0.973 probability having LD_{50}: 840 mg/Kg which is too much less than 2000 mg/Kg that belong to Class 4 as a harmful substance if swallowed. Abiraterone (A) toxicity on liver organ was 0.61 probability as hepatotoxicity. Other studied toxicological categories (carcinogenicity, Immunotoxicity, Mutagenicity, cytotoxicity, and toxicological pathways: AhR, AR, Aromatase, ER, HSE, p53) were more than 70 % as probability percentage to bind Progesterone or Androgen. Also, Abiraterone (A) has a poor water solubility leading to high intestinal absorption, moderate total clearance, and giving inhibition reaction to Cytochrome P450 type CYP2C19, hERG II, and Ames test. These results confirmed that Abiraterone is structurally less harmful acute class with highly chance to interact with cell components resulting lethal response.

Saccharin (SA) is a known sweetener that predicated in this work. Its predication gave 100% sour probability percentage than sweet 99.3% belonging to non-toxic Class 6 with LD_{50} equal to 14200 mg/Kg with high confidence score in most of toxicological categories. This sweetener is high soluble compound compared to Abiraterone (A) but less intestinal absorption (81.045%) with negative inhibition response to p-glycoprotein, cytochrome P450, and hERG. Also, its negative response was predicted in Ames test and skin sensation but it gave positive prediction toward hepatotoxicity with 62% probability. So, Saccharin is more structurally safe than Abiraterone (A) however, its cellular interaction in particular points must be taken under considerations.

Finally, hypothetical Abiraterone –Saccharin product has a harmful reaction if swelled (Class 4), sour taste, and LD_{50} (1200 mg/Kg) more than Abiraterone but less than Saccharin. Its liver hepatotoxicity, carcinogenicity, Immunotoxicity, Mutagenicity, and cytotoxicity were less than its reactants. Its response probability towards toxicity pathways varied compared to Abiraterone (A) and saccharin (SA) but in general they were more than 60%. These toxicological characters may be highly affected by its lower water solubility and high intestinal absorption towards more CNS permeability but not BBB and Caco2 permeability. Also, it is safe in skin sensation and Ames test issues. This *in Silico*- QSAR foundations about A-SA suggest that A-SA is structurally safe and there are several possibilities of becoming an active –multiple toxicological compound.

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