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Research Article

Insilco prediction study by *Carcinopred-EL* and *Swiss-ADME* method for antiepileptic drug Carbamazepine and its interrelated impurities

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Abstract

Impurity is the substance which is present any API drug or marketed formulations which is not at all considered as chemical entity. Carcinogenicity is the material which may come with the chemical entity but which leads to the changes of DNA or gene mutation by that may occur cancer. The objective of the study was to identify the physicochemical properties, pharmacokinetics, drug-likeness of the carbamazepine and their related impurities for further screening of impurities for their biosafety by following *Carcinopred-EL* (Carcinogenicity Prediction using Ensemble Learning methods) and *Insilco Swiss-ADME*. Swiss ADME tool was used to find out the *in silico* properties. Drug release and/or dissolution from the dosage form is the only factor governing drug absorption. *Carcinopred-EL* prediction model is to concertize the structure of chemical weather it can produced carcinogenicity or not. In our study which have used as model antiepileptic drug such as carbamazepine and their related impurities. Computer simulations represent legitimate alternatives to experiments in that regard. The present impurities in the drug Bromobenzene, Nitro toluene and iminodibenzyl is producing carcinogenicity and Iminostilbene is produced toxic but not confirmed carcinogenicity. During drug development program chemical compound or drug molecules prior do the *Insilco* model for promising analysis for drug development process and impurities present the molecules. It helps to find out the impurities of physicochemical properties, pharmacokinetics, drug-likeness of the carbamazepine and their related impurities. These method helps in future to carry out their biosafety model and it will help to upgrade pharmaceutical monograph.

Keywords: *In silico*, *Swiss-ADME*, solubility, permeability, carbamazepine, iminodibenzyl, iminostilbene, nitro toluene and bromo benzene.

1. Introduction

The Carbamazepine (CBZ) is known to control seizures, treating pain from trigeminal neuralgia and is a compound known for anticonvulsant and analgesic activity. Carbamazepine, which was developed by J. R. Geigy (Novartis) in the 1950s and was marketed under the trademark Tegretol® to treat epilepsy, trigeminal neuralgia (in 1962), is the first-generation anticonvulsant authorised by the United States in 1967 and the United Kingdom in 1965. In 1965 the FDA approved this anticonvulsant molecule. It has become since then the most commonly recruited epilepsy first-line medicine. In addition, bipolar disorder is also being treated with carbamazepine. 5H-dibenzo [b,f]azepine-5-carboxamide is the chemical name. The medication is C15H12N2O as a molecular formula. The physical description of this medicine is a crystal white to yellowish white powder, odourless or almost odourless, and solubility in water and ether is virtually insoluble but ethanol-soluble. The drug has 236.27 g/mol in molecular weight. Various methods are available for profiling of the carbamazepine quantitative analysis, including GC, LC-MS/MS, HPLC, HPTLC, micellar electro-kinetic chromatography and UFLC.

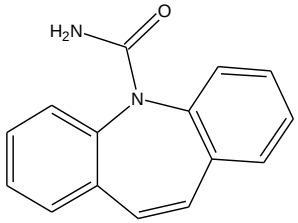
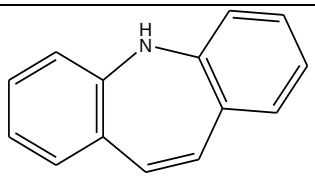
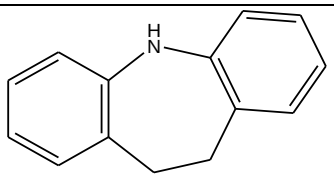
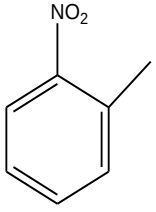
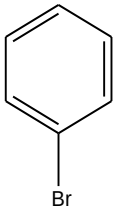
Name	Structure
Carbamazepine (CBZ)	
Impurity A (Iminostilbene)	
Impurity B (Iminodibenzyl)	
Impurity C (Nitro toluene)	
Impurity D (Bromobenzene)	

Figure 1. Carbamazepine and its related impurities

1.1 Mechanism of Action and Clinical Uses

Carbamazepine is a blocker of the sodium channel and works mainly by binding the energies inactive sodium canal into it. It also has implications for the serotonin system, but it has tentative implications for its anti-seizure action. Carbamazepine is moderately slow but well-spoken to orally. The C-10-C-11 is the most chemically, pharmacologically and metabolically reactive place in the pharmaceuticals structure. The CBZ mechanisms have not been fully revealed and have been widely debated. One of the main hypotheses is that carbamazepine prevents the firing of the sodium canal by treating the crisis. Studies in animals have shown that carbamazepine has the effects of reducing polysynaptic nerve responses and inhibiting post technic potency. Carbamazepine has shown that reduced pain is caused by the stimulation of the infraorbital nerves in both cats and rats. In other studies following the use of carbamazepine, decreased activity potential in the nucleus ventral to the brain and reticence of the lingual mandibular reflex was observed. Carbamazepine works by binding to voltage-dependent sodium channels and avoiding potentially stimulating effects on the nerves in general. Carbamazepine is also used in bipolar disorder to increase dopamine turnover, which increases transmission of GABA and to treat manic and depressive symptoms. CBZ has been used in many ways since the last five decades.

1. 2 Bioavailability and Pharmacokinetics

Carbamazepine's bioavailability range is 75-85% of the dosage taken. By one pharmacokinetics study, plasma protein binding affinity with carbamazepine reported 75%-80%. The highest portion in the liver is metabolised by Carbamazepine. The liver enzyme CYP3A4 is one of the primary enzymes that converts carbamazepine into its active metabolite, carbamazepine-10, 11-epoxide, which is additionally metabolised by the enzyme epoxide hydrolase into its trans-diol form. However, in an epileptic patient the biggest problem with this drug is the increase in drug resistance by 30%.

1.3 Side Effect of Carbamazepine

One of the major challenges nowadays is the increase of drug resistance in epileptic patients by 30 per cent, which can be attributed to the altered metabolism in modificated genotypes. Although the medicine is very effective, it has unwanted side effects. The patients report several side effects; ataxia, dizziness, sleepiness, nausea, and vomiting are commonly noted. More common side effects include blurred vision or double vision, continuous back-and-forth eye motion, and less common effects include uncontrolled action, behavioural changes, confusion, turmoil or hostility, diarrhoea, discouragement, drooling, fear, and more common effects. Feelings of unreality, headache, headache, seizure increases, lack of appetite, loss of control over balance, loss of interest or placer, shaking of muscle, jerking, stiffness or nausea, nausea, other muscle control or coordination problems, feeling of detachment from self or body; tightness and unstable walking.

This drug also exhibits serious and sometimes fatal dermatologic reactions, especially with the hereditary allelic variant HLA-B*1502. Hence, at-risk patients are to be separated prior to prescribing CBZ; and the treatment should not be started in patients that tested positive unless the benefits outweigh the risks. If there is any type of dermatologic effect then the drug must be discontinued. Research has also reported aplastic anaemia and agranulocytosis. Pre-treatment haematological trying has to be obtained and CBC must be sporadically screened. Drug termination should be considered if substantial bone marrow depression evolutions are observed.

1.4 *Swiss-ADME*

During the time and resources-intensive processes of drug discovery and development, a variety of molecular structures are tested to help synthesis, analyse and facilitate chemicals collection so as to identify patients who are best suited to becoming a successful medication. This is done according to very complex criteria. The molecules must have increased biological activity along with low toxicity. Access to the remediation target concentration is equally important in the organism. The standard method for pharmacokinetics (i.e. the fate of an organism's therapeutic agent), divides the various effects into individual parameters affecting access to the target. Computer models were promoted as a valid alternative to ADME's experimental predictions, in particular when various chemical structures have been investigated, but the availability of compounds is restricted. Bioavailability and pharmacokinetics have increased their relevance in terms of development of drugs to the study of effective potential drug molecules when the molecular physicochemical parameters in silicone are calculated. Theoretical studies play a key role in the production of accurate data quickly and easily. Recently, many free online portals were created for rapid screening, to reduce the time and cost of drug testing (no animal testing). The Swiss ADME is an inclusive tool run by the SIB, which allows the evaluation of the parameters of drug candidates for ADME (absorption, distribution, metabolism and excretion). The ADME properties, which determine whether the potential drug accesses the target or is eliminated by the organism, are necessary in the initial step of drug discovery. These parameters will be validated by in-silico experiments based on measured physicochemical needs. Lastly, lipophilicity, water solubility, molecular size, polarity, saturation or flexibility are highlighted. Lipinski et al. initially introduced the drug likeness associated with the relationship between pharmacokinetics, physical and chemical characteristics. In other words, the similarity to drugs involves improving the molecular characteristics and structures to determine if the molecules being tested are the same as the known drugs. The 'Rules of 5' (Ro5), known as the 'Rules of Pfizer's or Lipinski,' were written by Christopher Lipinski, in 1997. The assessment on the medication looks at the following factors: the molar mass (which should be ~500gmol-1), logP (alternative to 5), the number of hydrogen bond acceptors (alternative to 10) and the number of hydrogen bond donors (alternative to 5 which are included in the NH or OH group molecule function). Fermentation of the human gastrointestinal absorption (HIA) and blood/brain-barrier Swiss-ADME provides a 'Boiled-egg evaluation' (BBB). Although the generalist ADME packages are a commercial application, we felt that the key computational methods needed to include an overall assessment of the pharmaceutical profile of SMMIs concentrated on only one specific property or model in the Silico ADME tools were required. The Swiss-ADME web tool is freely available from http:/www.swissadme.ch and is intended even for the non-experts of CADD for user-friendly presentation and simple result review. Compared to state-of-the-art, free, ADME and pharmacokinetics web-based applications and to the ability to view, store, and exchange outcomes by molecule as well as intuitive and interactive global graphs, and other specialist access to specialized approaches, Swiss-ADME strengths are not exhaustive.

Methodology

2.Materialandmethods:

The free online tool Swiss-ADME has been used for the study. Swiss-ADME: a free web-enabling instrument for assessing small molecules pharmacokinetics, medicine similarity and medicinal chemistry.

2.1. Chemical Structure and Bioavailability Radar

The chemical structure in two dimensions and canonical SMILS. It shows the chemical shape of the predictions calculated. Furthermore, for a rapid drug similarity evaluation our bio-availability radar is shown. Six physical-chemical properties are calculated: lipophilicity, dimensions, polarity, solubility, flexibility and saturation. In each axis, a descriptor from Ref 23 and 24 has been described by the physicochemical range and is construed as a pink area where the radar plot of the molecule must be fully regarded as drug-like.

2.2 Physiochemical properties

The physical and physiological characteristics of the drug and the body. The oral absorption of a drug is a complex process based on these factors and their relationships. In addition, the effect on drug absorption is further demonstrated by other physicochemical properties, which influence solubility and permeability as the key physicochemical element which affects the rate and grade of oral drug absorption.

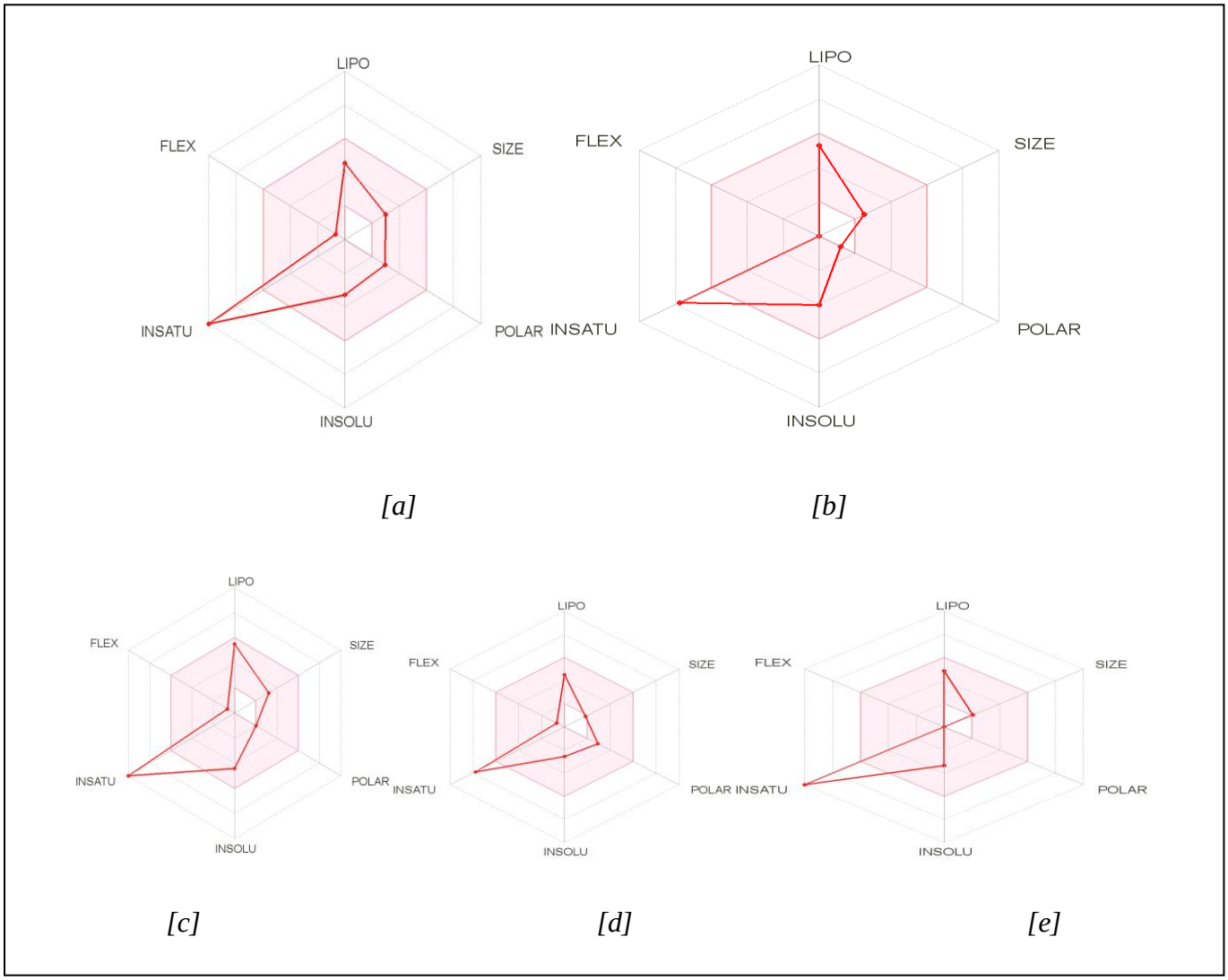


Figure 2. [a] Carbamazepine, [b] Iminodibenzyl, [c], Iminostilbene, [d] Nitro toluene. [e] Bromobenzene

2.3 Lipophilicity

Lipophilicity is defined as the lipid environment affinity of the drug. It is a critical parameter in the pharmaceutical industry that demonstrates the interaction between a drug and its molecular, pharmacokinetic and metabolic characteristics. Disposal between the organic form, typically water-saturated by n-octanol, and the water-saturated phase usually n-octanol-pre-saturated by the water can determine the lipophilicity of the substance. The partition coefficient (P) is defined as the ratio of balance levels (Ci) of the dissolved compound in a two-phase system composed of n-octanol and water.

2.4 Water solubility

The development of a CBZ and its impurities is nothing more complicated than the replication of all the dynamic phenomena leading to in vivo releasing and solubilizing of the API into the gut in a "single" in vitro environment like a paddle-stirred vessel. Compared with in vivo experiments, in vitro approaches are less systematic because USP Apparatus 1 to 4 is used for various media (HCl, clear buffer or addition of surfactants or enzymes, etc. and different technical parameters).

2.5 Pharmacokinetics

Pharmacokinetics refer to the movement of the drug in and out of the body, but often defined as what the body does with a pharmaceutical product, its absorption rate, bioavailability, distribution, metabolism and excretion. The pharmacokinetics of a medicine depend both on patient conditions and on the chemical properties of the medicinal product. A number of patient-related variables (e.g. renal function, genetic make-up, sex, age) may be used in order to predict the pharmacokinetic parameters of populations. For example, in older people, the half-life of certain drugs can be surprisingly long, in particular those which require both metabolism and excretion.

2.6 Drug likeness

Drug-like characteristics are created based on chemical structures and physicochemical properties. In terms of lipophilicity, solubility, permeability, metabolic stability and affinity the physicochemical properties are most specifically tested. In addition to the traditional physical chemistry-based laws and ratings, molecular ADMET-associated properties.

2.7 "boiled egg model"

In addition to efficacy and toxicity, poor pharmacokinetics and bio disposition are accused of several failures in drug discovery. The gastrointestinal absorption and brain access are two important pharmacokinetic activities for the estimation at different stages of medication development. For this purpose, the Brain or Intestinal estimated permeation system (BOILED-Egg) is proposed as an effective predictive model that works by measuring the lipophilic and polarity of small molecules. The simultaneous predictions for brain and intestinal permeation derive from two physicochemical Descriptors and are directly translated through molecular architecture because the model is quick, accurate, simple-conceptual and consistent graphical performance. BOILED-Egg can be used in a number of settings ranging from the filtration of chemicals libraries in the early phases of the drug research to the evaluation of growth candidates.

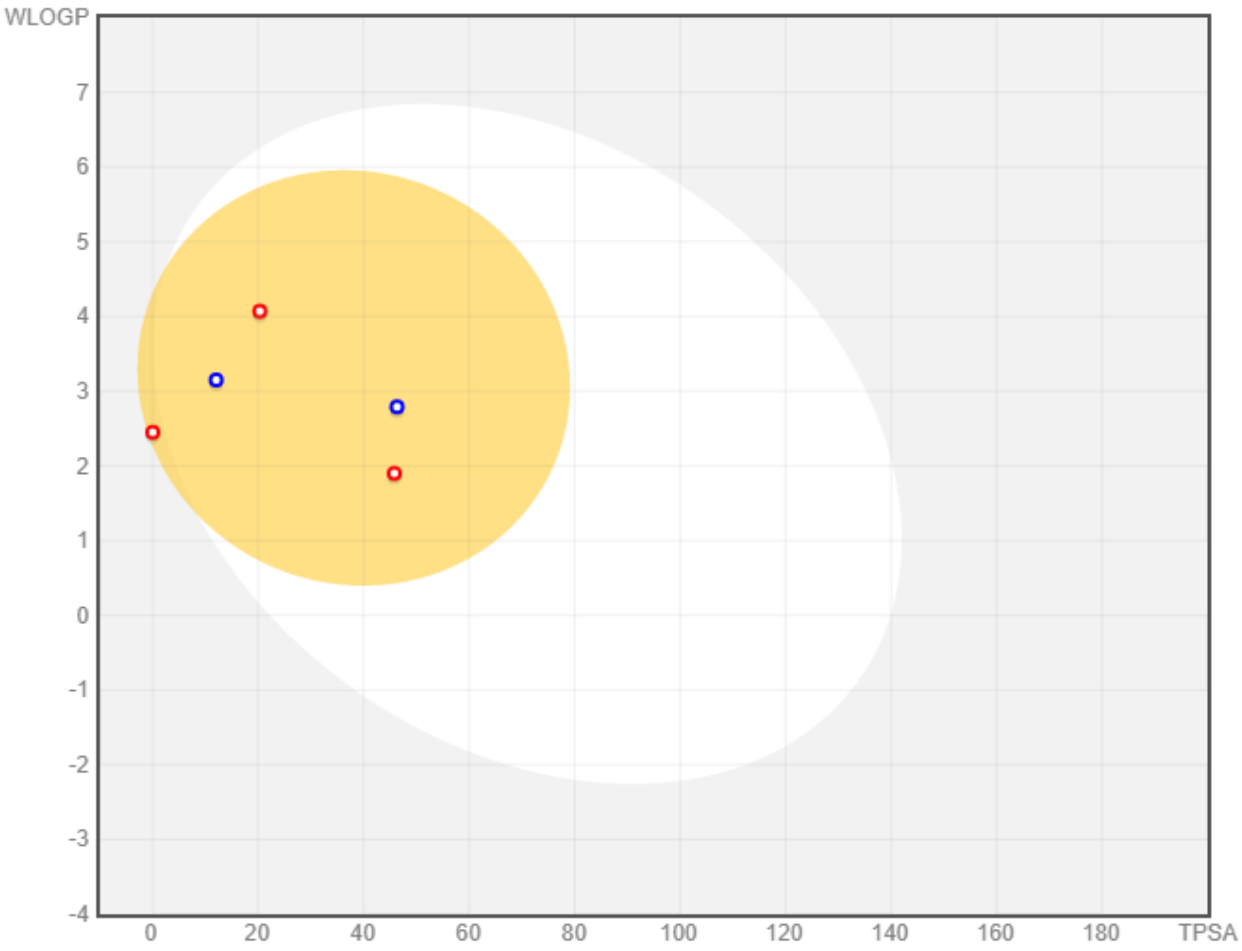


Figure 3 Boiled egg model predictions

2.8 Mutagenicity and carcinogenicity prediction

Mutagenicity and carcinogenicity are of great concern in the toxicological endpoints of chemical substances because of its grave health effects. Mutagenicity is a major endpoint of toxicity and also indicates permanent changes in the organism's DNA sequence, leading to heritable change in the organism characteristics. The mutagenic chemicals mechanism of action mainly involves DNA damage, which results in chromosomal aberrations, framework change and point mutations. Not only carcinogenesis and genotoxicity are involved in mutagens. They also involve several chronic diseases in the development and pathogenesis process, including neurodegenerative disorders, diabetes, ageing, arthritis, cardiovascular disorder, chronic inflammation, and hepatic disorders.

Discussion and Conclusion

3. Results and discussion:

3.1 Chemical Structure and Bioavailability Radar report

The Bioavailability Radar allows you to look at a molecule's drug-like character. The pink area represents the optimal range for each feature (Lipophilicity < XLOGP3 0.7 <XLOGP3 <+5.0, Size: MW between 0 Å2 < 95.97 Å2, Insolubility < 0 < log S < 6.0, Instauration: carbon fraction in the SP2

hybridization not below 0,25, and flexibility: not more than 9 rotative bonds). The pink area is of the highest possible value for the individual features of the pink area. The compound is not orally bioavailable because it is too flexible and too polar in this example (Fig 2 a-e).

3.2 Physiochemical properties

Micro molecular and dosage form design are highly affected by the identification of the active lead molecule, the identification of an appropriate drug candidate, and the creation of a marketable product. Physicochemical characterization can not only guide the selection of formulation methods, but can also influence analogue selection and optimization if it is built into the lead selection process. The final effect of considering the physicochemical properties is to minimise the risk of failure through the detection of suitable design options for dosage types and the increase in the chances of finding commercially viable leads by discovery chemists and drug development. The physiochemical properties of medication molecules were described in Table I using Swiss ADME online free tool.

Table I: Physiochemical properties of drug molecules

Physiochemical properties					
	Carbamazepine	**Iminodibenzyl**	**Iminostilbene**	**Nitro toluene**	**Bromobenzene**
Formula	C15H12N2O	C14H13N	C15H10ClNO	C7H7NO2	C6H5Br
Molecular weight	236.27 g/mol	195.26 g/mol	255.70 g/mol	137.14 g/mol	157.01 g/mol
Num. heavy atoms	18	15	18	10	7
Num. arom. heavy atoms	12	12	12	6	6
Fraction Csp3	0.00	0.14	0.00	0.14	0.00
Num. rotatable bonds	1	0	1	1	0
Num. H-bond acceptors	1	0	1	2	0
Num. H-bond donors	1	1	0	0	0
Molar Refractivity	76.05	66.74	78.14	40.23	34.14
Topological Polar surface area	46.33 Å²	12.03 Å²	20.31 Å²	45.82 Å²	0.00 Å²

3.3 Lipophilicity

Lipophilic formulations that possess a wide variety of compositional and functional properties can be used in the formulation of lipophilic drugs with advantages. Due to potential chemical and physical instable issues and lack of information on algorithms for formulation design and technology transition concerns, the establishment of lipid-based dosage types is conventionally unwilling. Nevertheless, the recent revival of interest in lipid-based dosage types is due to the potential commercial and pharmaceutical advantages as well as the industry trends towards increasingly hydrophobic (and powerful) new chemical substances (Table :II).

Table II: Lipophilicity of drug molecules

Lipophilicity					
	Carbamazepine	**Iminodibenzyl**	**Iminostilbene**	**Nitro toluene**	**Bromobenzene**
Log $P_{o/w}$ (iLOGP)	2.10	2.34	2.66	1.59	1.99
Log $P_{o/w}$ (XLOGP3)	2.45	3.76	4.08	2.37	2.99
Log $P_{o/w}$ (WLOGP)	2.79	3.15	4.07	1.90	2.45
Log $P_{o/w}$ (MLOGP)	2.99	3.48	3.72	1.19	3.05
Log $P_{o/w}$ (SILICOS-IT)	1.65	3.55	3.01	0.12	2.65
Consensus Log $P_{o/w}$	2.40	3.26	3.51	1.43	2.63

3.4 Water solubility

Released drug dosage material or solution of the active component could be a restrictive factor in the appearance of the drug in your blood when orally administering a solid dosing form by means of the bowel membrane (mainly in class III and IV of the BCS). The physicochemical characteristics of the API and not the permeability or formulation of the solubility-limited substance are the function of absorption (Class II and IV of BCS). For non-release formulations, the drug dosage type's release is limited by absorption (Table III).

Table III: Water solubility predictions

Water Solubility					
	Carbamazepine	**Iminodibenzyl**	**Iminostilbene**	**Nitro toluene**	**Bromobenzene**
Log *S* (ESOL)	-3.28	-4.01	-4.42	-2.56	-3.33

Solubility	1.25e-01 mg/ml ; 5.30e-04 mol/l	1.90e-02 mg/ml ; 9.74e-05 mol/l	9.65e-03 mg/ml ; 3.78e-05 mol/l	3.77e-01 mg/ml ; 2.75e-03 mol/l	7.32e-02 mg/ml ; 4.66e-04 mol/l
Class	Soluble	Moderately soluble	Moderately soluble	Soluble	Soluble
Log *S* (Ali)	-3.07	-3.71	-4.21	-2.97	-2.65
Solubility	2.03e-01 mg/ml ; 8.58e-04 mol/l	3.85e-02 mg/ml ; 1.97e-04 mol/l	1.57e-02 mg/ml ; 6.14e-05 mol/l	1.46e-01 mg/ml ; 1.06e-03 mol/l	3.48e-01 mg/ml ; 2.22e-03 mol/l
Class	Soluble	Soluble	Moderately soluble	Soluble	Soluble
Log *S* (SILICOS-IT)	-3.93	-5.52	-4.90	-2.14	-3.23
Solubility	2.78e-02 mg/ml ; 1.17e-04 mol/l	5.90e-04 mg/ml ; 3.02e-06 mol/l	3.20e-03 mg/ml ; 1.25e-05 mol/l	1.00e+00 mg/ml ; 7.31e-03 mol/l	9.14e-02 mg/ml ; 5.82e-04 mol/l
Class	Soluble	Moderately soluble	Moderately soluble	Soluble	Soluble

3.5 Pharmacokinetics

Modified release formulations (MR) have become an attractive alternative in novel drug delivery systems to improve the solubility and bio-availability of poorly soluble medicines because of their potential for a solubility of the medication in the gastrointestinal system. These formulations offer a variety of advantages such as reduction of the food impact and inter-individual variability, easy preparation and the ability to produce with standard marketable excipients. In spite of these benefits, relatively few drugs are available on the market today, possibly because of a failure to understand the paths behind pharmaceutical and biological aspects of MR formulations after oral administration in in vitro (for in vivo destiny provision) and because of (Table IV).

Table IV: Pharmacokinetic predictions

Pharmacokinetics					
	Carbamazepine	**Iminodibenzyl**	**Iminostilbene**	**Nitro toluene**	**Bromobenzene**
GI absorption	High	High	High	High	Low
BBB permeant	Yes	Yes	Yes	Yes	Yes

P-gp substrate	Yes	Yes	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes	No	No
CYP2C9 inhibitor	No	No	Yes	No	No
CYP2D6 inhibitor	No	Yes	No	No	No
CYP3A4 inhibitor	No	Yes	No	No	No
Log K_p (skin permeation)	-6.00 cm/s	-4.82 cm/s	-4.96 cm/s	-5.45 cm/s	-5.13 cm/s

3.6 Drug likeness

Human absorption (HIA), blood brain barrier (BBB), Cytochrome P450 (CYP) inhibitors, acts as P-gp substrates or receptors, DILI, cardiotoxicity and cytotoxicity are examples. Data groups that help drug-like study should also contain: chemical compositions, physicochemical properties, details associated with ADMET; properties of a drug-like nature (regulars and scores); and collections of pharmaceuticals and drugs (Table V).

Table V: Drug-likeness predictions

Drug likeness					
	Carbamazepine	**Iminodibenzyl**	**Iminostilbene**	**Nitro toluene**	**Bromobenzene**
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	Yes	Yes	No; 2 violations: MW<160, #atoms<20	No; 3 violations: MW<160, MR<40, #atoms<20
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	No; 2 violations: MW<200, Heteroatoms<2	Yes	No; 1 violation: MW<200	No; 2 violations: MW<200, Heteroatoms<2

Bioavailability Score	0.55	0.55	0.55	0.55	0.55

3.7 Carcinogenicity or mutagenicity prediction

Insilico model Carcinopred-EL prediction run through by four of these impurities and the result is showing that bromobenzene, Nitro toluene, Iminodibenzyl is showing carcinogenicity and Iminostelbene is not showing carcinogenicity but toxicity level is more. It shown in table VI.

Table VI: Carcinopred-EL prediction model

Name	CDK	CDK Ext	CDK Graph	KR	KRC	MACCS	PubChem	Average	Class
BB	0.7	0.71	0.83	0.59	0.55	0.79	0.82	0.71	Carcinogen
NT	0.88	0.92	0.93	0.95	0.85	0.76	0.8	0.87	Carcinogen
IMSB	0.43	0.43	0.29	0.64	0.52	0.5	0.3	0.44	Non-Carcinogen
IMDB	0.48	0.43	0.27	0.54	0.41	0.33	0.29	0.39	Carcinogen

3.8 Boiled egg model prediction

The prediction and permeation of the blood-brain barrier of passive human gastrointestinal absorption (HIA) consists of reading the BOILED-Egg model, an intuitive graphic classification model that can be seen in fig III. In our study we have selected antiepileptic drug movement and the compounds of its impurities that we have shown to cross BBB.

4. Conclusion:

During drug development program chemical compound or drug molecules prior do the *Insilco* model for promising analysis for drug development process and toxicity prediction. It helps to find out the impurities of physicochemical properties, pharmacokinetics, drug-likeness of the carbamazepine and their related impurities. These method helps in future to carry out their biosafety model by applying to this data sheet and it will help to upgrade pharmaceutical monograph regarding the drug and impurities.

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