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MEDICINAL PROPERTIES OF CLOTRIMAZOLE – A VIRTUAL ANALYSIS

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ABSTRACT:
Clotrimazole has been modelled to virtually screen for extended medicinal properties using cheminformatics tools such as SwissADME and Molinspiration. The molecule was further analysed to find the target by Swiss Target prediction to bind with enzymes. The results reveal that the selected candidate has positive value to combine strongly with G protein-coupled receptors, which catalyses cell production and signalling, enzymes responsible for oxidation and gene creation.
KEYWORDS: Clotrimazole, ADME properties, Cheminformatics, SwissADME and Molinspiration.

INTRODUCTION:

Clotrimazole is currently a field of intensive research for the continued development of pharmaceuticals. The use of clotrimazole as the principal compound for design studies in structural preparations is being developed as a pharmaceutic to identify novel clinical indicators of treatment and to improve the administration of manufactured goods[i]. Marketed clotrimazole topical formulations (A & B) were applied on the pre-marked forearms of the subjects as per the dosing schedule. This study has demonstration that all the pharmacokinetic parameters calculated for test formulations A were close to those of the reference formulation B and there was no statistically significant difference between the two formulations. Test formulation A and Reference formulations B were bioequivalent with respect to the rate and extent of Diclofenac absorption[ii]. Clotrimazole is a broad-spectrum antimycotic drug mainly used for the treatment of *Candida albicans* and other fungal infections. It has been reviewed that the pharmaceutical chemistry, application and pharmacology of clotrimazole and discuss future prospects for its further development as a chemotherapeutic agent[iii,iv].

To the best of our knowledge there has been no report on virtual screening of clotrimazole by SwissADME web tool[v-vii]. Therefore, this work focuses on the modelling and analysis of physicochemical and medicinal properties of clotrimazole using SwissADME and Molinspiration[viii] web tools to predict the possibility of extended drug properties. The drug properties are computationally studied by Swiss target prediction[ix].

METHODOLOGY:

SwissADME

SwissADME, is publicly accessible web server that suggests various properties of the active chemical entity by using accurate algorithms. Swiss ADME, free web tool was utilized to screen the ADME properties of clotrimazole in this present study.

Physicochemical properties

The physicochemical properties of the selected molecule such as canonical SMILES, molecular formula, molecular weight, number of such as canonical SMILES, formula, molecular weight, rotatable bonds, H-bond acceptors, H- bond donors, etc. were collected from web-based online server such as SwissADME.

Bioavailability Radar

Bioavailability radar for the Studied molecule has been obtained from SwissADME database. All the parameters in bioavailability radar have been analysed and the results were shown accordingly.

The bioavailability radar gives graphical interpretation of properties such as lipophilicity, compound size, insolubility, polarity, instaurations and flexibility in its six hexagonal vertices which help to evaluate scopes of improvement of bioavailability score.

For each feature anticipated to be orally accessible, the optimum physicochemical environment is illustrated by the pink area as LIPO: -0.7 < XLOGP3 < +5.0, SIZE (Molecular weight (MW)) 150 g/mol < MW < 500 g/mol, POLAR (Polarity) 20A Molecular polar surface area (TPSA) < 130 A2, INSOLU (Insolubility) -6 < Log S(ESOL) < 0, INSATU (Insaturation) 0.25 < FractionCsp3 < 1 and FLEX (Flexibility) 0 < RP (Number of rotatable bonds) < 9 are the six physicochemical qualities that are taken into consideration.

Pharmacokinetics

The Pharmacokinetics study of the Selected molecule was performed by the utilization of Swiss ADME web server. In particular, Gastrointestinal (GI) absorption and Brain Blood Barrier (BBB) permeation were studied.

Drug-likeness

In this work, drug-likeness was studied for the selected was molecules whether Lipinski rule was obeyed and bioavailability score was noted using web tool.

Medicinal Chemistry

The SwissADME web tool was very much useful to analyze the medicinal chemistry of the molecules in this study. Lead-likeness and Synthetic accessibility of the selected molecule have been noted for analysis.

Molinspiration

Molinspiration[viii] offers a broad range of cheminformatics software tool supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. It supports also fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform. Molinspiration interactive web services are available from now not only on desktop computers, but also on touch devices including iPhone, iPad and Android phones and tablets. A molecule structure 8 input to our property calculation and bioactivity prediction services is powered by the JSME molecule editor written in JavaScript. Also our Galaxy 3D molecule visualizer that allows interactive display of molecules in various modes and visualization of surface molecule lipophilicity potential and polar surface area is written in JavaScript.

Molinspiration Molecule Viewer

Molinspiration Molecule Viewer allows visualization of collection of molecules encoded as SMILES or SDF file. SMILES is automatically transformed into molecule 2D representation by depiction engine. Display of associated data, selection of molecules, built-in substructure search and export of selected molecules is supported.

Swiss target prediction

Swiss target prediction is a web interface designed by Swiss instituted of bioinformatics[ix]. It can predict the targets for any bioactive drug molecule. It enables us to select species like Homo sapiens, Mus musculus, Rattus. The input is provided with SMILES are through graphical interface proved by chemaxon. The list of targets and their details are available.

RESULTS AND DISCUSSION:

The modelled molecule chosen for virtual screening and drug action studies is shown in Figure 1.

Figure 1. Modelled structure and Bio-availability Radar of clotrimazole by SwissADME server

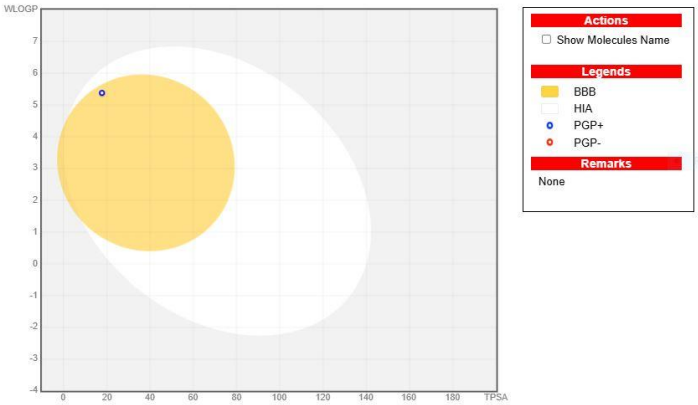


Figure 2. BOILED Egg of clotrimazole by SwissADME web tool

Table 1. Physicochemical and Medicinal poperties of clotrimazole using SwissADME server

SMILES	C1=CC=C(C=C1)C(C2=CC=CC=C2)(C3=CC=CC=C3Cl)N4C=CN=C4
Formula	$C_{22}H_{17}ClN_2$
Molecular weight	344.84 g/mol

Num. heavy atoms	24
Num. arom. heavy atoms	23
Num. rotatable bonds	4
Num. H-bond acceptors	1
Num. H-bond donors	0
Molar Refractivity	101.84
TPSA	17.82 Å^2
Lipophilicity, Log $P_{o/w}$	4.64
Water solubility, Log *S* (ESOL)	-5.80 (Moderately soluble)
GI absorption	High
BBB permeant & P-gp substrate	Yes & Yes
Log K_p (skin permeation)	-4.56 cm/s
Lipinski	Yes; 1 violation: MLOGP>4.15
Bioavailability Score	0.55
PAINS	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.25

The Bio-availability radar (Figure 1.), physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry of clotrimazole have been analyzed by SwissADME web tool and all results are shown in Table 1. In the bio-availability radar shown in Figure 1., it is noted that all promising factors except insaturation are within the pink area. The result indicates that the gastrointestinal (GI) absorption is high for the studied compound. It has blood brain barrier (BBB) and P-glycoprotein substrate permeation also. Therfore, it possesses good and promising effect on central nervous system. This result is supported in the BOILED Egg representation displayed in Figure 2 as well. Even though MLOGP > 4.15, is slightly higher than the limitation of Lipinski's rule, bioavailability score (0.55) and synthetic accessibility (2.25) of the studied compound is greater.

Molinspiration

Molinspiration software has been utilized for this analysis. The modelled 2D and 3D structures of the chosen candidate are shown in Figure 3. The results (Figure 4.) obtained from the Molinspiration web tool are aligned with SwissADME software predictions. Therefore, clotrimazole has greater support in ADME properties to be experimented for a reliable drug.

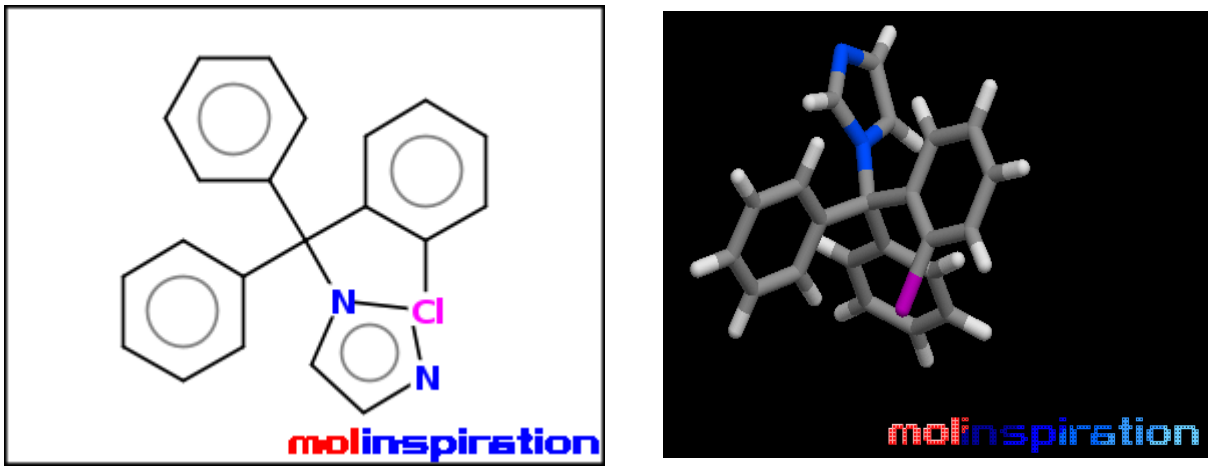
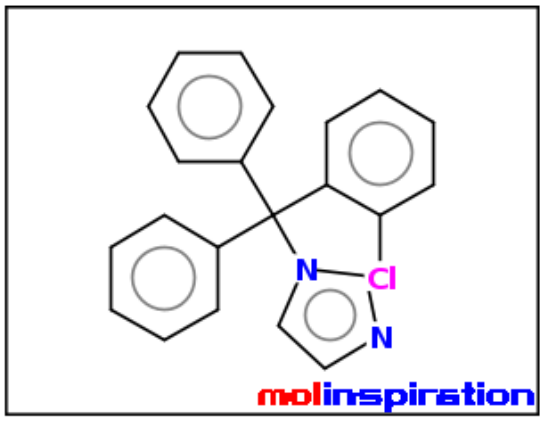


Figure 3. Modelled structure of clotrimazole by Molinspiration Galaxy 3D Structure Generator v2023.08



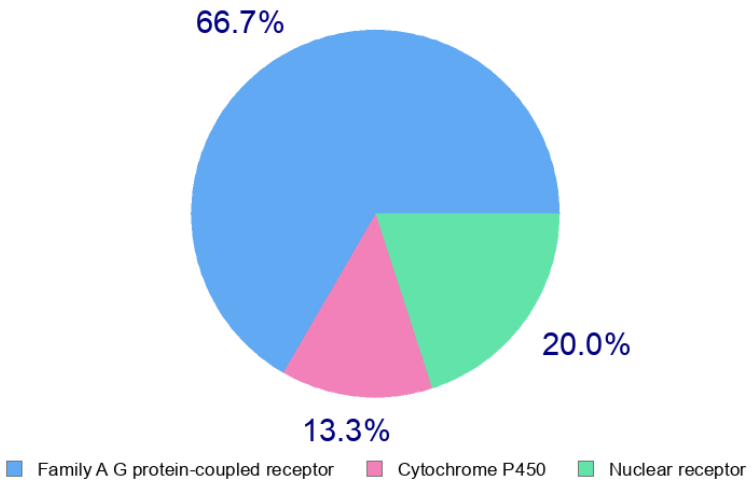
Molinspiration property engine v2022.08

miLogP	5.47
TPSA	17.83
natoms	25
MW	344.85
nON	2
nOHNH	0
nviolations	1
nrotb	4
volume	309.52

Figure 4. Physicochemical properties of clotrimazole by Molinspiration software

Swiss Target prediction analysis

The result from SwissADME target prediction shows that clotrimazole can bind with G protein-coupled receptors (GPCRs) which are a large family of membrane proteins that play a crucial role in cellular signalling and are key targets for drug development.



Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Dopamine D2 receptor	DRD2	P14416	CHEMBL217	Family A G protein-coupled receptor		5 / 9
Dopamine D4 receptor	DRD4	P21917	CHEMBL219	Family A G protein-coupled receptor		1 / 4
Norepinephrine transporter	SLC6A2	P23975	CHEMBL222	Electrochemical transporter		7 / 6
Alpha-1d adrenergic receptor	ADRA1D	P25100	CHEMBL223	Family A G protein-coupled receptor		20 / 3
Serotonin 2a (5-HT2a) receptor	HTR2A	P28223	CHEMBL224	Family A G protein-coupled receptor		12 / 7
Serotonin 2c (5-HT2c) receptor	HTR2C	P28335	CHEMBL225	Family A G protein-coupled receptor		11 / 6
Adenosine A1 receptor	ADORA1	P30542	CHEMBL226	Family A G protein-coupled receptor		6 / 4
Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter		25 / 6
Histamine H1 receptor	HRH1	P35367	CHEMBL231	Family A G protein-coupled receptor		5 / 1
Neurokinin 2 receptor	TACR2	P21452	CHEMBL2327	Family A G protein-coupled receptor		3 / 6
Mu opioid receptor	OPRM1	P35372	CHEMBL233	Family A G protein-coupled receptor		2 / 10
Dopamine D3 receptor	DRD3	P35462	CHEMBL234	Family A G protein-coupled receptor		4 / 6
Delta opioid receptor	OPRD1	P41143	CHEMBL236	Family A G protein-coupled receptor		9 / 8
Kappa Opioid receptor	OPRK1	P41145	CHEMBL237	Family A G protein-coupled receptor		4 / 7
Dopamine transporter	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter		46 / 5

Figure 5. Target classes of clotrimazole using SwissADME target prediction server

The candidate of the study combines with Cytochrome P450 (CYP) enzymes which are a superfamily of heme-containing monooxygenases that play a crucial role in the metabolism of drugs, toxins and various biological compounds. It is possible for clotrimazole to unite with nuclear receptors which are a class of intracellular proteins that regulate gene expression in response to specific ligands, playing crucial roles in various biological processes such as development, metabolism and homeostasis.

CONCLUSION:

Clotrimazole exhibits high GI absorption, indicating their potential for usage as oral medications. It possesses BBB and P-gp substrate penetration. Therefore, it can be used for illnesses relating to the brain. The bio-availability and synthetic accessibility scores are also worthy. The selected molecule exhibits efficient binding for G protein-coupled receptors, which catalyzes cell proliferation and signalling. The nuclear receptor enzyme, which directly controls the transcription of genes that govern a wide range of biological activities, including cell proliferation, development, metabolism, and reproduction, is bound by the candidate with less percentage. UA7 binds to nuclear receptors and secreted proteins with a high proportion. The fact that all of the compounds have positive nuclear receptor interaction values indicates that they play a part in gene creation, which may have an impact on reproduction and anti-carcinogenic properties.

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