Heterocyclic Letters
Vol. 16| No.1|145-152 |Nov-Jan|2026
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

IN SILICO PREDICTION OF MEDICINAL PROPERTIES AND TARGET ANALYSIS OF 1-(1,3-BENZOTHIAZOL-2-YL)-3-PYRIDIN-2-YL THIOUREA - A SWISSADME STUDY

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ABSTRACT:
The ADME analysis of 1-(1,3-benzothiazol-2-yl)-3-pyridin-2-yl thiourea (**A**) has been performed using SwissADME software. The selected molecule (**A**) was further studied to find the targets by Swiss Target prediction to bind with enzymes. The results show that the molecule can possess good combination with enzymes responsible for auto-oxidation, auto-immune and inflammatory diseases, blood cell production, reproductive functions and various neurological processes.

KEYWORDS: Thiourea, ADME properties, cheminformatics, target prediction and SwissADME.

INTRODUCTION

Synthesis of small structurally diverse molecules which can bind macromolecules can serve as the starting points for the synthesis of drugs. Organic chemists can synthesize moieties fit for pharmaceutical formulations[i]. The eye-catching aspect of synthetic chemistry is to change the chemical and physical properties of the nitrogen containing molecule by just changing substitutions on nitrogen atom. Compounds containing heteroatoms, being important in biological as well as for industrial and such compounds are considered as one of the largest parts of organic chemistry. Among heteroatoms, sulfur and nitrogen containing compounds are of special interest for the researchers[ii-viii].

Thiourea is a versatile group of organic reagents possessing considerable range of applications[ix]. Many researchers have documented that thioureas have great medicinal applications as well as non-medicinal activities in industry, analytical chemistry and metallurgy. Thioureas have a number of medicinal applications and a number of thioureas are in clinical use. Medicinal applications of thioureas are increasing with the passage of time. In the field of agriculture, thioureas are used as insect growth regulator, anti-fungal agents and herbicides. Obtained experimental data are indicating the developed new method for

thionization of sugar carbamides, which opens up broad possibilities for synthesis of various carbohydrate derivatives of thiourea. Thiourea derivatives are promising bactericidal, fungicidal and anti-inflammatory drugs. Therefore, the preparation of thiourea derivatives and the study of their properties remain topical tasks in the field of chemistry[x].

Using the innovative knowledge of biological targets through various softwares, drugs are being designed. The smaller organic molecules interact with proteins by either inhibiting it or activating it and in consequence organism benefits therapeutically[xi]. 1-(1,3-benzothiazol-2-yl)-3-pyridin-2-yl thiourea has been modelled and the structural and biological properties of the compound have been analysed recently using DFT. Molecular docking studies were reported to explore the interactions between **A** and BRAF (V600E) protein kinase[xii].

Based on the above points, this work focuses on the study of physicochemical properties, drug-likeness and medicinal properties of the selected candidate, 1-(1,3-benzothiazol-2-yl)-3-pyridin-2-yl thiourea (**A**) using SwissADME software[xiii,xiv]. The plausible targets with which the studied molecule can have connection is reported.

METHODOLOGY

SwissADME

SwissADME software and web-servers were utilized to study the physicochemical and pharmacokinetic properties of **A**. It is publicly accessible web server that suggest various properties of the active chemical entity by using accurate algorithms. Swiss ADME, free web tool was utilized to study the ADME properties of A in this present work.

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 < Fraction Csp3 < 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 absorption and Brain Blood Barrier permeation were studied.

Druglikeness

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

Medicinal Chemistry

The SWISS ADME web tool was very much useful to analyse the medicinal chemistry of the molecules in this work. Leadlikeness and Synthetic accessibility of the selected molecule have been noted for analysis.

RESULTS AND DISCUSSION

The Bio-availability radar, physicochemical properties, pharmacokinetics, druglikeness and medicinal chemistry of **A** (Figure 1.) have been analyzed by Swiss ADME web tool and all results are shown in Table 1. In the bio-availability radar shown in Figure 1., it is noted that Limitations of Lipinski's rule are highly obeyed. All promising factors, except insaturation, are within the pink area. Two pharmacokinetic activities important for estimating at different stages of the drug development process are gastrointestinal absorption and brain access. The result indicates that the gastrointestinal (GI) absorption is high for the studied compound and it has no blood brain barrier (BBB) permeation. Therfore, it possesses no effect on central nervous system.

Bioavailability score (0.55) and synthetic accessibility (2.62) of the studied compound is greater. To this end, as an effective predictive model that operates by measuring the lipophilicity and polarity of small molecules, the Brain or IntestinaL EstimateD permeation system (BOILED egg) is proposed.

Due to the speed, accuracy, conceptual simplicity and consistent graphical performance of the model, concomitant predictions for both brain and intestinal permeation are derived from the same two physicochemical descriptors and directly converted through molecular architecture. From the filtering of chemical libraries at the early stages of drug research to the assessment of drug candidates for growth, BOILED egg can be used in a number of settings. Boiled egg predicts the penetration of the drug through gastro intestinal and blood brain barrier (BBB). It is very useful for statistical method in drug designing. The white region shows the probability of passive absorption in the GI tract and yellow is the brain penetration. The studied molecule (shown in the white portion in Figure 2.) indicates that it has high gastrointestinal absorption.

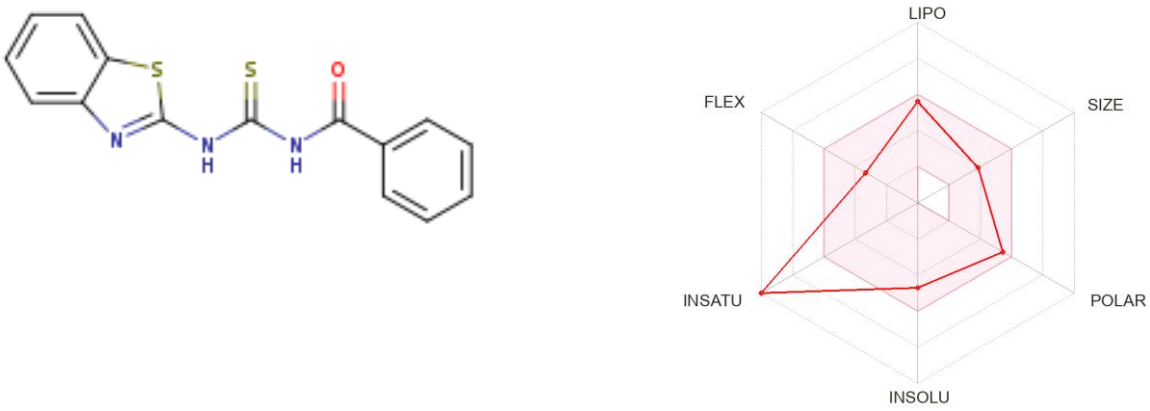


Figure 1. Modelled structure and Bio-availability radar of A using SwissADME software

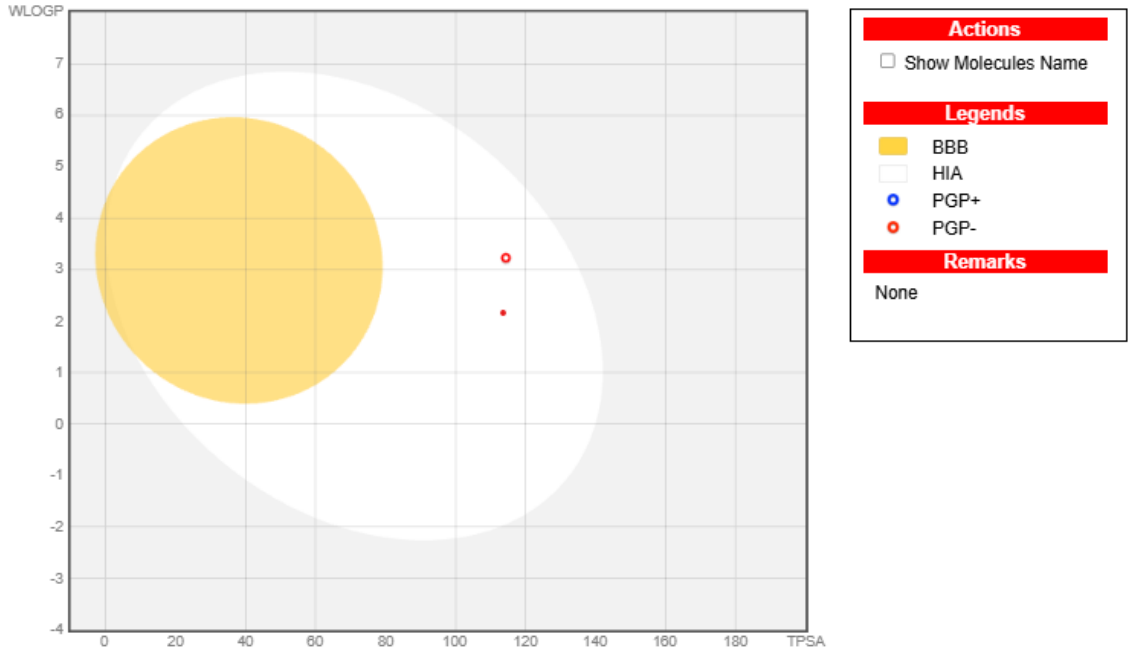


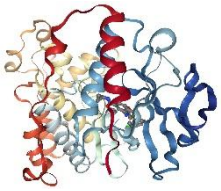
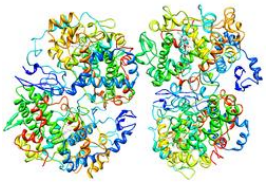
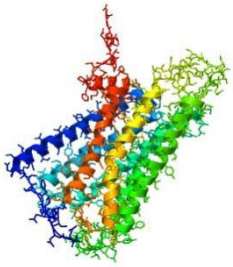
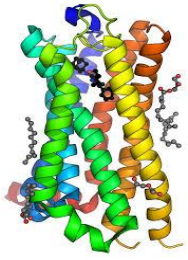
Figure 2. BOILED Egg of A using SwissADME software

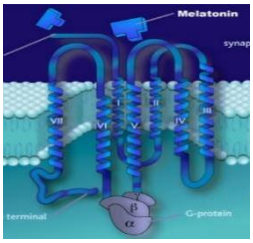
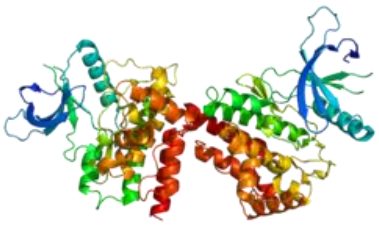
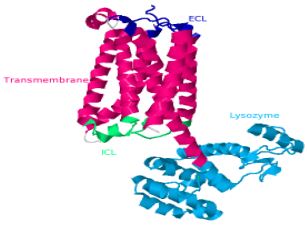
Table 1. Physicochemical and Medicinal properties of A using SwissADME software

SMILES	S=C(NC(=O)c1ccccc1)Nc1nc2c(s1)cccc2
Formula	$C_{15}H_{11}N_3OS_2$
Molecular weight	313.40 g/mol
Num. heavy atoms	21
Num. arom. heavy atoms	15
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	2
Molar Refractivity	89.23
TPSA	114.35 Å²
Lipophilicity, Log $P_{o/w}$	3.34
Water solubility, Log *S* (ESOL)	-4.70
GI absorption	High
BBB permeant	No
Log K_p (skin permeation)	-5.15 cm/s
Lipinski	Yes; 0 violation
Bioavailability Score	0.55
PAINS	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.62

Figure 3. Target prediction of A using SwissADME software

Table 2. Selected targets of A using SwissADME software

S. No.	Target	Structure
1	MAP kinase p38 alpha (MAPK14)	
2	Cyclooxygenase-2 (PTGS2)	
3	Cannabinoid receptor 1 (CNR1) Cannabinoid receptor 2 (CNR2)	 (CNR1)  (CNR2)

4	Melatonin receptor 1A (MTNR1A)	
5	Tyrosine-protein kinase (JAK2)	
6	Metabotropic glutamate receptor 5 (GRM5)	

SwissADME target prediction

Using SwissADME target prediction the chosen candidate, **A** has been analysed for the suitable targets to bind with. The results are displayed in Figure 3 and Table 2.

MAP kinase p38 alpha

The selected molecule (**A)** can bind with MAP kinase p38 alpha. A large body of evidences indicates that p38MAPK activity is critical for normal immune and inflammatory response. The p38MAPK pathway is a key regulator of pro-inflammatory cytokines biosynthesis at the transcriptional and translational levels, which makes different components of this pathway potential targets for the treatment of autoimmune and inflammatory diseases[xv].

Cyclooxygenase-2

Binding is possible between **A** and Cyclooxygenase-2 (PTGS2), an enzyme also known as prostaglandin-endoperoxide synthase 2. This enzyme plays a crucial role in the production of prostaglandins, which are involved in various biological processes, including inflammation, pain, and fever. PTGS2 is often upregulated in inflammatory conditions and certain cancers. The conversion of arachidonic acid to PGG_2 can be shown as a series of radical reactions analogous to polyunsaturated fatty acid autoxidation[xvi].

Cannabinoid receptor 1 (CNR1)

The studied compound **A** combines with CNR1 which is widely expressed in all major regions of the postnatal day 14 mouse brain, but is conspicuously absent in much of the thalamus. CB1 receptors are expressed most densely in the central nervous system and are largely responsible for mediating the effects of cannabinoid binding in the brain[xvii].

Cannabinoid receptor 2 (CNR2)

There is a possibility of **A** to unite with Cannabinoid receptor 2 (CNR2), a G protein-coupled receptor that plays a significant role in the immune system and is also found in the nervous system. It is primarily expressed in immune cells and tissues, as well as in some brain regions

and is involved in regulating inflammation, immune responses and potentially neuro-inflammation[xviii,xix] .

Melatonin receptor 1A (MTNR1A)

Melatonin receptor 1A (MTNR1A), also known as MT1, is a G-protein coupled receptor that binds to the hormone melatonin and plays a crucial role in regulating circadian rhythms and reproductive functions in mammals[xx]. The selected molecule **A** can react with MTNR1A as the result from SwissADME target prediction.

Tyrosine-protein kinase (JAK2)

Union of **A** and Tyrosine-protein kinase (JAK2) is feasible. JAK2 is a non-receptor tyrosine kinase that plays a crucial role in cellular signalling, particularly in the hematopoietic system (blood cell production) and in response to cytokines (small proteins that act as messengers between cells). It's a key component of the Janus kinase (JAK) family and is involved in various cellular processes, including cell growth, differentiation, and immune responses[xxi].

Metabotropic glutamate receptor 5 (GRM5)

It has been noted that the studied molecule **A** can combine with Metabotropic glutamate receptor 5 (mGluR5) is a protein encoded by the GRM5 gene, belonging to the G-protein coupled receptor family. It plays a crucial role in regulating synaptic transmission and plasticity in the brain. mGluR5 is involved in various neurological processes and has been implicated in conditions like Alzheimer's disease, Fragile X Syndrome and anxiety disorders[xxii,xxiii].

CONCLUSION:

The ADME properties of 1-(1,3-benzothiazol-2-yl)-3-pyridin-2-yl thiourea (**A**) were analysed using SwissADME software. The result reveals that **A** has good GI absorption and great synthetic accessibility. Swiss target prediction was also used to determine the targets for the chosen candidate (**A**) to bind with enzymes. The findings demonstrate that the molecule can work well with enzymes involved in blood cell creation, several biological functions, such as immunological responses, cell division and development as well as neurological reactions.

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Received on September4, 2025.