

Screening of ADME properties of biphenyl ether

Shubhangi Sakpal and Kalpana Padmanaban

Department of Chemistry, K.L.E. Society's Science and Commerce College, Kalamboli, Navi Mumbai - 410 218, India.

ABSTRACT

Biphenyl ether (**I**), an antimicrobial agent was selected and modelled by SwissADME database and physicochemical, pharmacokinetics, drug-likeness and medicinal properties were analysed. The results indicate that all studied molecules obey Lipinski rule and possess positive gastrointestinal (GI) absorption with keen blood brain barrier (BBB) permeation. **I** exhibits remarkable bioavailability score with good synthetic accessibility.

KEYWORDS: Biphenyl ether, Theoretical analysis, SwissADME web tool and ADME properties

I. INTRODUCTION

Biphenyls and diphenyl ethers are widely described natural structural motifs with antimicrobial potential. Among the others, naturally occurring phlorotannins consist of both structural units (known as fucols and phloroethols); however, difficult isolation processes from their natural matrices make synthetic efforts necessary for a proper biological evaluation. Natural and nature-derived biphenyls and diphenyl ethers were prepared and tested as antifungal and antibacterial agents. Notably, none of the natural compounds were able to completely inhibit fungal growth at the tested concentrations, while diphenyl ethers and showed significant inhibition of the mycelium growth of *P. oryzae* and *B. cinerea*, with lower activity observed against *F. culmorum*. The most promising compounds were all characterized by the presence of a (poly) methylated diphenyl ether nucleus. Indeed, the methylation pattern together with the C–O–C fragment seemed to heavily affect the interaction with the biological target. Conversely, no antibacterial effect was detected. Further investigations are needed to deepen the structure–activity relationship to enhance the antifungal activity, and the key structural features required by these scaffolds to act as antibacterial agents[1-7].

To the best of our knowledge, no theoretical research has been documented on the selected biphenyl ether molecule (**I**) so far. Therefore, this work concentrates on the medicinal properties of **I** by utilizing SwissADME software [8].

II. METHODOLOGY

In this study, physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry of the silicic acid and its methylated analogues (I-V) have been screened by SwissADME web tool. The 2D structure of the selected molecule was first modelled (shown in Fig. 1) and converted into corresponding SMILES (Simplified Molecular Input Line Entry System) which has been displayed in Table 1 and the program was further simulated to study the ADME properties of the molecules (shown in Fig. 2).

III. RESULTS AND DISCUSSION

Study of physicochemical properties

The physicochemical properties of I screened by SwissADME server have been shown in Table 1. From the result it is inferred that the rotatable bond (RB) is observed as 2 and it is responsible for the medicinal properties. It is confirmed with the decrease of topological polar surface area (TPSA) of the chosen compound. All are showing positive results for a suitable drug and more solubility nature of the compounds offer the notable point towards the drug development.

Pharmacokinetics

The selected compounds were examined for pharmacokinetics and drug-likeness properties and shown in Table 1. From the results, it is inferred that the gastrointestinal (GI) absorption is high with positive blood brain barrier (BBB) permeation and it is exhibited in the yellow portion of the BOILED egg (Fig 3.) It is good indication of I to efficiently act on central nervous system. The studied molecule has good skin permeation also.

Lipinski's rule

Lipinski rule of 5 helps to distinguish between drug-like and non-drug-like molecules [9,10]. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules.

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

I is obeying Lipinski's rule (shown in Fig. 2) thereby eligible for being an oral drug at the preliminary stage of drug discovery.

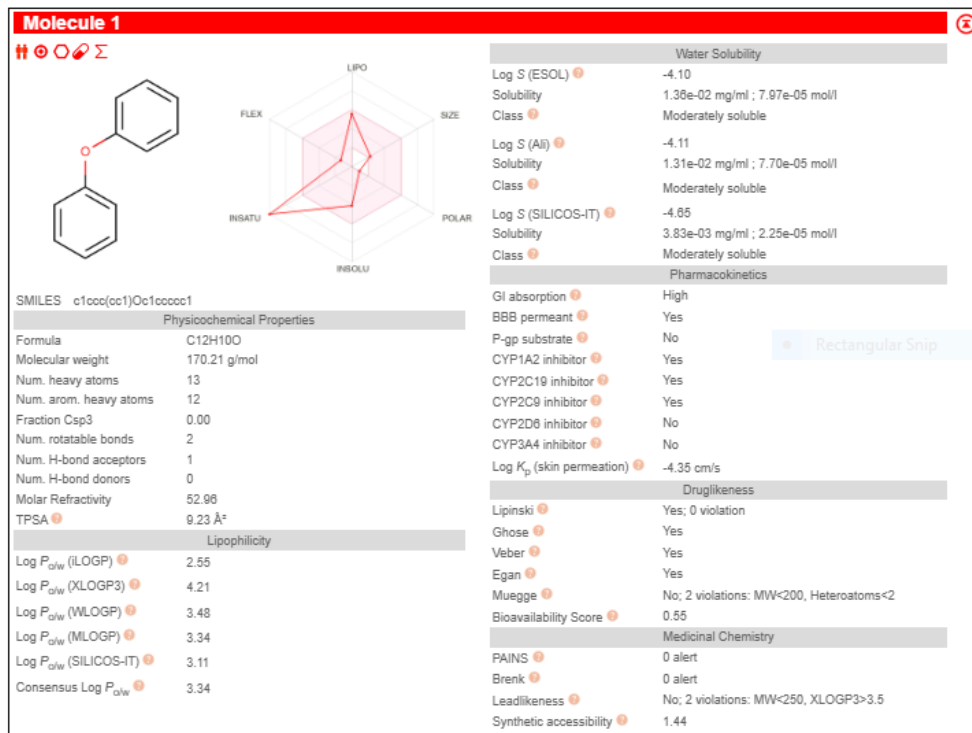
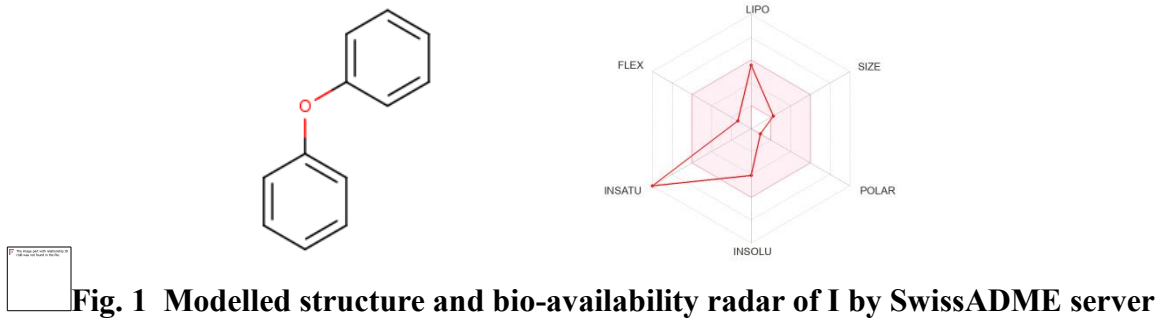


Fig. 2 SwissADME analysis of I

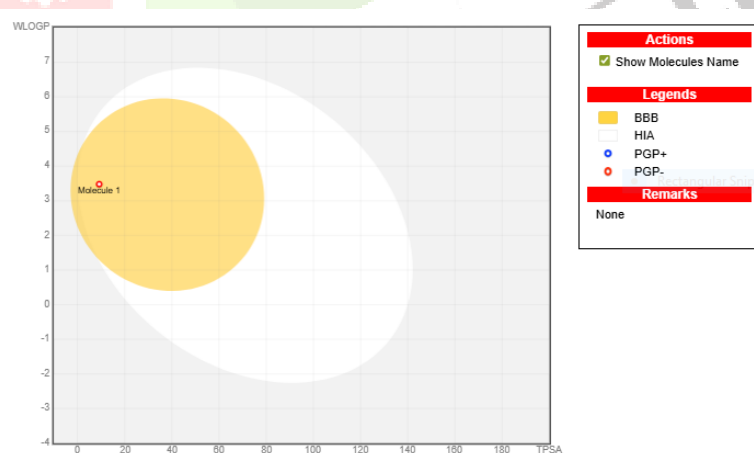


Fig. 3 BOILED egg of I using SwissADME web tool

Table 1. Physicochemical and ADME descriptors of I by SwissADME web tool

Descriptor	I
SMILES	c1ccc(cc1)Oc1ccccc1
MF	C ₁₂ H ₁₀ O
MW (g/mol)	170.21
NRB	2
NHA	1
NHD	0
MR	52.96
TPSA (Å ²)	9.23
Log P _{o/w}	3.34
Log S (ESOL)	-4.10
GI absorption	High
BBB permeant	Yes
Log K _p (skin permeation) (cm/s)	-4.35
Lipinski Rule	Yes; 0 violation
Bio-availability Score	0.55
Synthetic accessibility	1.44

Analysis of Bio-availability Radar

The modelled structure and bio-availability radar of the selected compound (**I**) has been presented in Fig 2. In bio-availability radar of the compounds Pink / Red area is shown in the plot which reflects the maximum range of Lipophilicity, Size, Polarity, Insolubility, Instauration and Flexibility. By examining the radar of **I**, it is showing promising results for all the characteristics of medicinal properties which offers the good pathway in drug designing.

Medicinal chemistry

Bio-availability score is also remarkable for the selected molecule under study. Affirmative result of lead-likeness with good synthetic accessibility score makes **I** as suitable candidate to be examined by *in vitro* study.

IV. CONCLUSION

Biphenyl ether motif has very strong potential against micro-organisms in the medicinal field. Therefore, this theoretical predictions on ADME properties of **I** unravels the therapeutic properties and showing well-fixed chances for the *in vitro* analysis to proceed further in the drug development.

V. REFERENCES

1. Liu. J. C., Yang. J., Lei. S. X., Wang. M. F., Ma. Y. N., Yang. R. (2023). Natural phytoalexins inspired the discovery of new biphenyls as potent antifungal agents for treatment of invasive fungal infections. *Eur. J. Med. Chem.* 261, 115842.
2. Chatterjee. S., Kuang. Y., Splivallo. R., Chatterjee. P., Karlovsky. P. (2016). Interactions among filamentous fungi *Aspergillus niger*, *Fusarium verticillioides* and *Clonostachys rosea*: fungal biomass, diversity of secreted metabolites and fumonisin production. *BMC Microbiol.* 16, 83,
3. Ke. S., Gao. Z., Zhang. Z., Liu. F., Wen. S., Wang. Y. (2023). Discovery of Novel Carboxamide Derivatives Containing Biphenyl Pharmacophore as Potential Fungicidal Agents Used for Resistance Management. *J. Agric. Food Chem.* 71, 14505– 14516.
4. Ming-Xin Guo. M. M., Wu. X., Feng. Y. F., Hu. Z. Q. (2023). Research Progress on the Structural Modification of Magnolol and Honokiol and the Biological Activities of Their Derivatives. *Chem. Biodiversity.* 20, e202300754.
5. Mottagh. S., Abbaszadeh. H. (2022). Natural Lignans Honokiol and Magnolol as Potential Anticarcinogenic and Anticancer Agents. A Comprehensive Mechanistic Review. *Nutr. Cancer.* 74, 761– 778.
6. Gao. Y., Yang. J., Yang. X., Zhang. L., Wang. J. and Li. Q. (2021). Novel dibenzofuran and biphenyl phytoalexins from *Sorbus pohuashanensis* suspension cell and their antimicrobial activities. *Fitoterapia*, 152, 104914.
7. Chizzali. C., Beerhues. L. (2012) Phytoalexins of the Pyrinae: Biphenyls and dibenzofurans. *Beilstein J. Org. Chem.* 8, 613– 620.
8. Daina. A., Michielin. O., & Zortr. V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports.* 7, 42717.
9. Lipinski. C. A., Lombardo. F., Dominy. B.W., & Feeney. P.J, (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings 1 PII of original article: S0169-409X(96)00423-1. The article was originally published in *Advanced Drug Delivery Reviews* 23 (1997) 3–25. 1 *Advanced Drug Delivery Reviews.* 46 (1), 3.
10. Kalpana P. and Rani P. (2025). Swissadme analysis of some selected analogues of pyrrole, *IJCRT*, 3(4), k925-k929.