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# ADMET properties of novel 5-*O*-benzoylpinostrobin derivatives

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**Abstract:**
**Background:** Prediction of the properties of absorption, distribution, metabolism, excretion, and toxicity (ADMET) from a compound is essential, especially for modified novel compounds. Previous research has successfully designed several modified compounds of 5-*O*-benzoyl derivatives from pinostrobin, a flavanone that has cytotoxic activity. This study aims to describe the properties of ADMET from the 5-*O*-benzoylpinostrobin derivative.
**Methods:** Prediction of the properties of ADMET was carried out using three web servers consisting of SwissADME, pkCSM, and ProTox-II. The observed parameters are divided into ADMET parameters.
**Results:** In general, absorption parameters indicate that the 5-*O*-benzoylpinostrobin derivative has lower water solubility than the parent pinostrobin. Distribution parameters show mixed results for distribution through the blood-brain barrier. Metabolism parameters showed different results with generally inhibitory activity shown in CYP2C19, CYP2C9, and CYP3A4. The excretion parameters showed a higher total clearance than pinostrobin except in the trifluoromethyl derivative. The toxicity parameters showed both pinostrobin and the 5-*O*-benzoylpinostrobin derivatives, including the class IV toxicity category with the lowest $LD_{50}$ value indicated by the nitro derivative of 1500, with the possible target of the androgen receptor and prostaglandin G/H synthase 1.
**Conclusions:** Overall, the 5-*O*-benzoylpinostrobin derivative has the predicted ADMET profile that is relatively similar to pinostrobin, with the most noticeable difference being shown in the absorption parameters where all 5-*O*-benzoylpinostrobin derivatives have lower water solubility than pinostrobin.

**Keywords:** 5-*O*-benzoylpinostrobin, ADMET prediction, pinostrobin, toxicity
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## Introduction

The properties of absorption, distribution, metabolism, excretion, and toxicity (ADMET) are phenomena that are closely related to the fate of a chemical in the human body. Each of the properties of ADMET will reflect the outcome of a chemical compound when interacting with various organs in the body. Prediction of the ADMET properties from a compound is essential, especially for foreign chemical compounds that are consumed in the long term or large concentrations [1], [2]. Information about the properties of ADMET from a compound is mainly needed in the development of a new drug compound, where the information can be used to predict various pharmacokinetic phenomena of these compounds, which can then be used as necessary information in the further development of new drug compounds [3].

Previously, researchers have succeeded in designing several modified compounds of 5-*O*-benzoyl derivatives from pinostrobin, a flavanone with various pharmacological activities, one of which is cytotoxic activity and has the potential to be developed in the treatment of several types of cancer. The 5-*O*-benzoylpinostrobin derivatives are novel compounds designed by reacting pinostrobin with benzoyl chloride reagents and variants of their substituents. Feasibility tests have been carried out for this compound and are predicted to be synthesized by the mechanism of the Schotten-Baumann reaction under alkaline conditions. Pinostrobin can be extracted in sufficient quantities from fingerroot (*Boesenbergia pandurata*) rhizomes with extraction solvents

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that are nonpolar like *n*-hexane [4], [5]. Modifications of pinostrobin to increase cytotoxic activity have been conducted before, such as a study by Poerwono et al. (2010), which reported that prenyl derivatives from pinostrobin have higher cytotoxic activity in several types of cancer cells [6]. Prenyl and benzoyl derivatives have some similarities, as they are both relatively nonpolar. Therefore, modification of the benzoyl derivative from pinostrobin is also predicted to increase its cytotoxic activity. For this reason, it is necessary to predict the properties of ADMET from the 5-*O*-benzoylpinostrobin derivatives. These properties will be beneficial initial information in the development of the compound.

This study aims to describe the properties of ADMET from the 5-*O*-benzoylpinostrobin derivative. Information on the properties of ADMET is obtained by sending molecular structures to several ADMET server prediction properties. The results obtained are grouped into ADMET parameters, and conclusions are drawn from the comparison of the results of each test server [7].

## Materials and methods

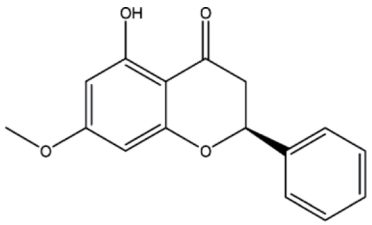
### Materials

The hardware used is the ASUS A46CB series Ultrabook with an Intel™ Core i5-3337U@1.8 GHz and Windows 7 Ultimate 64-bit SP-1 operating system. The software used is ChemDraw® Ultra 8.0.3 from CambridgeSoft and OpenBabel 2.4.1 from OpenBabel.org. The ADMET prediction servers used are SwissADME (http://swissadme.ch/) from the Swiss Institute of Bioinformatics, pkCSM (http://biosig.unimelb.edu.au/pkcsm/) from the Biosig Lab University of Melbourne, and ProTox-II (http://tox.charite.de/protox_II/) from Charite University of Medicine.

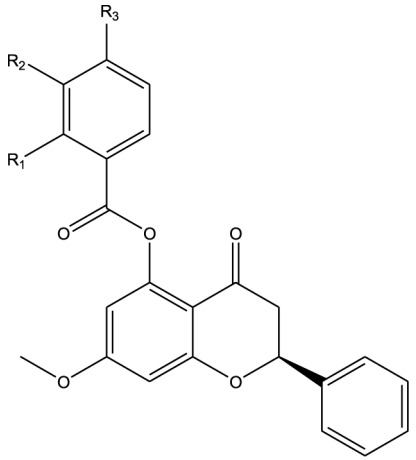
### Test molecular preparation

The test molecules used were 28 compounds consisting of pinostrobin, 5-*O*-benzoylpinostrobin, and 26 derivatives with variations in substituents on the benzoyl group at the position of C numbers 2, 3, and 4. Variations in substituents used were chlorine groups, fluorine, bromine, trifluoromethyl, nitro, methyl, methoxy, and *t*-butyl. The three-dimensional structure of molecular sketch test used ChemDraw® Ultra 8.0.3 software and stored in the. cdx format. The test molecule is then converted to the SMILES format (.smiles) using the OpenBabel 2.4.1 software [8]. The structure and the code of the SMILES of all test compounds are presented in Table 1.

**Table 1:** The 2D structure and code of the SMILES of all test compounds.




Pinostrobin




-*O*-Benzoylpinostrobin

| No. | Compound | SMILES | Functional group | | |
|---|---|---|---|---|---|
| | | | $R_1$ | $R_2$ | $R_3$ |
| 1 | Pinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)O)c1ccccc1 | – | – | – |
| 2 | 5-*O*-Benzoylpinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)OC(=O)c1ccccc1)c1ccccc1 | H | H | H |
| 3 | 2-Chloro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2Cl)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | Cl | H | H |
| 4 | 3-Chloro-5-*O*-benzoylpinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)OC(=O)c1cccc(c1)Cl)c1ccccc1 | H | Cl | H |
| 5 | 4-Chloro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)Cl)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | Cl |
| 6 | 2,4-Dichloro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2Cl)Cl)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | Cl | H | Cl |
| 7 | 3,4-Dichloro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(c(c2)Cl)Cl)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | Cl | Cl |
| 8 | 2-Fluoro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2F)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | F | H | H |
| 9 | 3-Fluoro-5-*O*-benzoylpinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)OC(=O)c1cccc(c1)F)c1ccccc1 | H | F | H |
| 10 | 4-Fluoro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)F)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | F |
| 11 | 2-Bromo-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2Br)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | Br | H | H |
| 12 | 3-Bromo-5-*O*-benzoylpinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)OC(=O)c1cccc(c1)Br)c1ccccc1 | H | Br | H |
| 13 | 4-Bromo-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)Br)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | Br |
| 14 | 2-Trifluoromethyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2C(F)(F)F)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | $CF_3$ | H | H |
| 15 | 3-Trifluoromethyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2cccc(c2)C(F)(F)F)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | $CF_3$ | H |
| 16 | 4-Trifluoromethyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)C(F)(F)F)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | $CF_3$ |
| 17 | 2-Nitro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2[N](=O)O)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | $NO_2$ | H | H |
| 18 | 3-Nitro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2cccc(c2)[N](=O)O)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | $NO_2$ | H |
| 19 | 4-Nitro-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)[N](=O)O)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | $NO_2$ |
| 20 | 2-Methyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2C)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | $CH_3$ | H | H |

| | | | | | |
|---|---|---|---|---|---|
| 21 | 3-Methyl-5-*O*-benzoylpinostrobin | COc1cc2O[C@@H](CC(=O)c2c(c1)OC(=O)c1cccc(c1)C)c1ccccc1 | H | $CH_3$ | H |
| 22 | 4-Methyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)C)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | $CH_3$ |
| 23 | 2-Methoxy-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2OC)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | $OCH_3$ | H | H |
| 24 | 3-Methoxy-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2cccc(c2)OC)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | $OCH_3$ | H |
| 25 | 4-Methoxy-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)OC)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | $OCH_3$ |
| 26 | 2-*t*-butyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccccc2C(C)(C)C)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | $(CH_3)_3$ | H | H |
| 27 | 3-*t*-butyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2cccc(c2)C(C)(C)C)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | $(CH_3)_3$ | H |
| 28 | 4-*t*-butyl-5-*O*-benzoylpinostrobin | COc1cc(OC(=O)c2ccc(cc2)C(C)(C)C)c2c(c1)O[C@@H](CC2=O)c1ccccc1 | H | H | $(CH_3)_3$ |

### ADMET prediction

Test molecules in the SMILES format are submitted one by one to each web server. SwissADME provides information consisting of formulas; molecular weight; number of heavy atoms and aromatic heavy atoms; fraction Csp3; number of rotatable bonds; H-bond acceptors; dan H-bond donors; molecular mass (MR); topological polar surface area (TPSA); implicit Log P (iLOGP); XLOGP3; WLOGP; MLOGP; SILICOS-IT Log P; Consensus Log P; ESOL Log S; ESOL Solubility; ESOL Class; Ali Log S; Ali Solubility; Ali Class; SILICOS-IT LogSw; SILICOS-IT solubility; SILICOS-IT class; gastrointestinal (GI) absorption; blood-brain barrier (BBB) permeant; P-glycoprotein (Pgp) substrate; CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 inhibitors; human skin permeability coefficients (log Kp); number of Lipinski's rule-of-five; Ghose's filter, Veber's filter, Egan's filter, and Muegge's filter violations; bioavailability score; number of PAINS and Brenk alerts; number of lead-likeness violations; and synthetic accessibility (SA) score [1]. The pkCSM provides information similar to some additional parameters such as Caco-2 permeability, Pgp I and II inhibitors, volume of distribution at steady state ($VD_{ss}$), central nervous system (CNS) permeability, total clearance, renal organic cation transporter 2 (OCT2) substrate, AMES toxicity, maximum recommended tolerated dose (MRTD) human, the human Ether-à-go-go-Related Gene (hERG) I and II inhibitors, oral rat acute toxicity ($LD_{50}$) and chronic toxicity-lowest observed adverse effect (LOAEL), hepatotoxicity, skin sensitization, *Tetrahymena pyriformis* toxicity, and fathead minnow toxicity ($LC_{50}$) [3].

ProTox-II provides more comprehensive information for a variety of toxicity parameters, including predicted median $LD_{50}$; predicted toxicity class; average similarity and prediction accuracy with three most similar toxic compounds from the data set with the known rodent oral toxicity value; organ toxicity, including hepatotoxicity, carcinogenicity, mutagenicity, immunotoxicity, and cytotoxicity; and various toxicological pathways, including aryl hydrogen receptor, androgen receptor (AR), androgen receptor ligand-binding domain (AR-LBD), aromatase, estrogen receptor alpha (ER), estrogen receptor ligand-binding domain (ER-LBD), peroxisome proliferator-activated receptor gamma, nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element, heat shock factor response element, mitochondrial membrane potential, phosphoprotein tumor suppressor, and ATPase family AAA domain-containing protein 5. In addition, information was also obtained in the form of predictions of toxicity targets based on 15 different targets from the Novartis *in vitro* safety panels of the protein targets linked to adverse drug reactions, such as adenosine receptor A2a, beta-2 adrenergic receptor, androgen receptor (ANDR), amine oxidase (flavin-containing) A (AOFA), corticotropin-releasing factor receptor 1, D(3) dopamine receptor, estrogen receptor alpha (ESR1) and beta (ESR2), glucocorticoid receptor, histamine H1 receptor, nuclear receptor subfamily 1 group I member 2, Kappa-type opioid receptor, Mu-type opioid receptor/MOR-1, cAMP-specific 3′,5′-cyclic phosphodiesterase 4D, prostaglandin G/H synthase 1/COX-1 (PGH1), and progesterone receptor [9]. The results obtained from each server for each test molecule are then compared with each other and divided broadly into five test parameters consisting of ADMET. However, not all information obtained is used in the analysis process of ADMET prediction results, and only important ADMET information is compared with each other [10].

## Results

The SwissADME test results showed that for most parameters, substituted 5-*O*-benzoylpinostrobin derivatives gave higher values than pinostrobin and 5-*O*-benzoylpinostrobin alone, whereas 5-*O*-benzoylpinostrobin was slightly higher than pinostrobin. Notable results are shown on some absorption parameters, including solubility, where ESOL solubility, Ali solubility, and SILICOS-IT solubility indicate that almost all 5-*O*-benzoylpinostrobin derivatives are more difficult to dissolve in water than pinostrobin. Consistently, 5-*O*-benzoylpinostrobin derivatives substituted with two chlorine and *t*-butyl groups show lower water solubility than other test molecules. This certainly can be a problem in the activity testing process later, where compounds that are difficult to dissolve in water require separate treatment to be tested for their activity. Besides, all test molecules are predicted to be well absorbed in the GI tract.

For distribution parameters, most compounds are thought to pass through the BBB except for 5-*O*-benzoylpinostrobin derivatives substituted with two chlorine groups, trifluoromethyl, nitro, and *t*-butyl groups. For metabolism parameters, an exciting result is shown in CYP2D6, where all test molecules except pinostrobin are predicted not to have potential as CYP2D6 inhibitors. In contrast to CYP3A4, all test molecules except the 5-*O*-benzoylpinostrobin derivative substituted with the nitro group are predicted to have activity as CYP3A4 inhibitors. SwissADME also predicts the SA score of all test molecules, where the lowest value is indicated by pinostrobin and the highest value is indicated by the 5-*O*-benzoylpinostrobin derivative substituted by the *t*-butyl group. The complete results of the test with SwissADME are presented in Table 2.

**Table 2:** The results of the ADMET test with SwissADME.

| Compound no. | Formula | MR | TPSA | iLOGP | XLOGP3 | WLOGP | MLOGP | Silicos-IT Log P | Consensus Log P | ESOL Log S |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | C16H14O4 | 74.02 | 55.76 | 2.75 | 3.2 | 2.78 | 1.52 | 3.06 | 2.66 | −3.84 |
| 2 | C23H18O5 | 103.39 | 61.83 | 3.53 | 4.42 | 4.3 | 3.07 | 4.56 | 3.97 | −5.09 |
| 3 | C23H17ClO5 | 108.4 | 61.83 | 3.61 | 4.91 | 4.95 | 3.55 | 5.2 | 4.44 | −5.6 |
| 4 | C23H17ClO5 | 108.4 | 61.83 | 3.84 | 5.04 | 4.95 | 3.55 | 5.2 | 4.52 | −5.68 |
| 5 | C23H17ClO5 | 108.4 | 61.83 | 3.77 | 5.04 | 4.95 | 3.55 | 5.2 | 4.5 | −5.68 |
| 6 | C23H16Cl2O5 | 113.41 | 61.83 | 3.73 | 5.54 | 5.6 | 4.02 | 5.84 | 4.95 | −6.19 |
| 7 | C23H16Cl2O5 | 113.41 | 61.83 | 3.94 | 5.54 | 5.6 | 4.02 | 5.84 | 4.99 | −6.19 |
| 8 | C23H17FO5 | 103.35 | 61.83 | 3.5 | 4.39 | 4.86 | 3.44 | 4.98 | 4.23 | −5.17 |
| 9 | C23H17FO5 | 103.35 | 61.83 | 3.61 | 4.52 | 4.86 | 3.44 | 4.98 | 4.28 | −5.25 |
| 10 | C23H17FO5 | 103.35 | 61.83 | 3.61 | 4.52 | 4.86 | 3.44 | 4.98 | 4.28 | −5.25 |
| 11 | C23H17BrO5 | 111.09 | 61.83 | 3.72 | 4.98 | 5.06 | 3.65 | 5.24 | 4.53 | −5.92 |
| 12 | C23H17BrO5 | 111.09 | 61.83 | 3.85 | 5.11 | 5.06 | 3.65 | 5.24 | 4.58 | −6 |
| 13 | C23H17BrO5 | 111.09 | 61.83 | 3.92 | 5.11 | 5.06 | 3.65 | 5.24 | 4.59 | −6 |
| 14 | C24H17F3O5 | 108.4 | 61.83 | 2.98 | 5.17 | 6.47 | 3.59 | 5.63 | 4.77 | −5.86 |
| 15 | C24H17F3O5 | 108.4 | 61.83 | 3.85 | 5.39 | 6.47 | 3.59 | 5.63 | 4.99 | −6 |
| 16 | C24H17F3O5 | 108.4 | 61.83 | 3.77 | 5.3 | 6.47 | 3.59 | 5.63 | 4.95 | −5.94 |
| 17 | C23H18NO7 | 110.64 | 111.49 | −5.47 | 3.65 | 4.62 | 2.15 | 2.39 | 1.47 | −4.78 |
| 18 | C23H18NO7 | 110.64 | 111.49 | −5.53 | 3.65 | 4.62 | 2.15 | 2.39 | 1.46 | −4.78 |
| 19 | C23H18NO7 | 110.64 | 111.49 | −5.28 | 3.78 | 4.62 | 2.15 | 2.39 | 1.53 | −4.86 |
| 20 | C24H20O5 | 108.36 | 61.83 | 3.7 | 4.65 | 4.6 | 3.28 | 5.09 | 4.26 | −5.31 |
| 21 | C24H20O5 | 108.36 | 61.83 | 3.84 | 4.87 | 4.6 | 3.28 | 5.09 | 4.34 | −5.45 |
| 22 | C24H20O5 | 108.36 | 61.83 | 3.85 | 4.78 | 4.6 | 3.28 | 5.09 | 4.32 | −5.39 |
| 23 | C24H20O6 | 109.89 | 71.06 | 3.67 | 4.26 | 4.31 | 2.73 | 4.62 | 3.92 | −5.08 |
| 24 | C24H20O6 | 109.89 | 71.06 | 3.85 | 4.39 | 4.31 | 2.73 | 4.62 | 3.98 | −5.16 |
| 25 | C24H20O6 | 109.89 | 71.06 | 3.81 | 4.39 | 4.31 | 2.73 | 4.62 | 3.97 | −5.16 |
| 26 | C27H26O5 | 122.66 | 61.83 | 4.12 | 5.96 | 5.59 | 3.89 | 5.95 | 5.1 | −6.28 |
| 27 | C27H26O5 | 122.66 | 61.83 | 4.31 | 6.18 | 5.59 | 3.89 | 5.95 | 5.19 | −6.42 |
| 28 | C27H26O5 | 122.66 | 61.83 | 4.32 | 6.09 | 5.59 | 3.89 | 5.95 | 5.17 | −6.37 |

| Compound no. | ESOL class | Ali Log S | Ali class | Silicos-IT LogSw | Silicos-IT class | GI absorption | BBB permeant | Pgp substrate | CYP1A2 inhibitor | CYP2C19 inhibitor |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Soluble | −4.04 | Moderately soluble | −4.7 | Moderately soluble | High | Yes | No | Yes | Yes |
| 2 | Moderately soluble | −5.44 | Moderately soluble | −7.42 | Poorly soluble | High | Yes | No | Yes | Yes |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Moderately soluble | −5.94 | Moderately soluble | −8.01 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 4 | Moderately soluble | −6.08 | Poorly soluble | −8.01 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 5 | Moderately soluble | −6.08 | Poorly soluble | −8.01 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 6 | Poorly soluble | −6.6 | Poorly soluble | −8.59 | Poorly soluble | High | No | No | No | Yes | |
| 7 | Poorly soluble | −6.6 | Poorly soluble | −8.59 | Poorly soluble | High | No | No | No | Yes | |
| 8 | Moderately soluble | −5.41 | Moderately soluble | −7.68 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 9 | Moderately soluble | −5.54 | Moderately soluble | −7.68 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 10 | Moderately soluble | −5.54 | Moderately soluble | −7.68 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 11 | Moderately soluble | −6.02 | Poorly soluble | −8.2 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 12 | Moderately soluble | −6.15 | Poorly soluble | −8.2 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 13 | Moderately soluble | −6.15 | Poorly soluble | −8.2 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 14 | Moderately soluble | −6.21 | Poorly soluble | −8.25 | Poorly soluble | High | No | No | No | Yes | |
| 15 | Moderately soluble | −6.44 | Poorly soluble | −8.25 | Poorly soluble | High | No | No | No | Yes | |
| 16 | Moderately soluble | −6.35 | Poorly soluble | −8.25 | Poorly soluble | High | No | No | No | Yes | |
| 17 | Moderately soluble | −5.68 | Moderately soluble | −6.76 | Poorly soluble | High | No | Yes | No | Yes | |
| 18 | Moderately soluble | −5.68 | Moderately soluble | −6.76 | Poorly soluble | High | No | Yes | No | Yes | |
| 19 | Moderately soluble | −5.81 | Moderately soluble | −6.76 | Poorly soluble | High | No | Yes | No | Yes | |
| 20 | Moderately soluble | −5.67 | Moderately soluble | −7.8 | Poorly soluble | High | Yes | No | No | Yes | |
| 21 | Moderately soluble | −5.9 | Moderately soluble | −7.8 | Poorly soluble | High | Yes | No | No | Yes | |
| 22 | Moderately soluble | −5.81 | Moderately soluble | −7.8 | Poorly soluble | High | Yes | No | No | Yes | |
| 23 | Moderately soluble | −5.46 | Moderately soluble | −7.52 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 24 | Moderately soluble | −5.6 | Moderately soluble | −7.52 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 25 | Moderately soluble | −5.6 | Moderately soluble | −7.52 | Poorly soluble | High | Yes | No | Yes | Yes | |
| 26 | Poorly soluble | −7.03 | Poorly soluble | −8.58 | Poorly soluble | High | No | Yes | No | Yes | |
| 27 | Poorly soluble | −7.26 | Poorly soluble | −8.58 | Poorly soluble | High | No | Yes | No | Yes | |
| 28 | Poorly soluble | −7.17 | Poorly soluble | −8.58 | Poorly soluble | High | No | Yes | No | Yes | |

| Compound no. | CYP2D6 inhibitor | CYP3A4 inhibitor | Log Kp, cm/s | Lipinski violations | Ghose violations | Bioavailability score | PAINS alerts | Brenk alerts | Lead-likeness violations | Synthetic accessibility |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Yes | Yes | −5.68 | 0 | 0 | 0.55 | 0 | 0 | 0 | 3.07 |
| 2 | No | Yes | −5.45 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.54 |
| 3 | No | Yes | −5.31 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.59 |
| 4 | No | Yes | −5.22 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.58 |
| 5 | No | Yes | −5.22 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.54 |
| 6 | No | Yes | −5.07 | 0 | 1 | 0.55 | 0 | 1 | 2 | 3.64 |
| 7 | No | Yes | −5.07 | 0 | 1 | 0.55 | 0 | 1 | 2 | 3.62 |
| 8 | No | Yes | −5.58 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.55 |
| 9 | No | Yes | −5.48 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.56 |
| 10 | No | Yes | −5.48 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.53 |
| 11 | No | Yes | −5.53 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.62 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 12 | No | Yes | −5.44 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.61 |
| 13 | No | Yes | −5.44 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.57 |
| 14 | No | Yes | −5.33 | 0 | 1 | 0.55 | 0 | 1 | 2 | 3.76 |
| 15 | No | Yes | −5.17 | 0 | 1 | 0.55 | 0 | 1 | 2 | 3.73 |
| 16 | No | Yes | −5.24 | 0 | 1 | 0.55 | 0 | 1 | 2 | 3.68 |
| 17 | No | No | −6.27 | 0 | 0 | 0.55 | 0 | 2 | 2 | 3.81 |
| 18 | No | No | −6.27 | 0 | 0 | 0.55 | 0 | 2 | 2 | 3.74 |
| 19 | No | No | −6.18 | 0 | 0 | 0.55 | 0 | 2 | 2 | 3.68 |
| 20 | No | Yes | −5.37 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.69 |
| 21 | No | Yes | −5.21 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.7 |
| 22 | No | Yes | −5.28 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.67 |
| 23 | No | Yes | −5.74 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.71 |
| 24 | No | Yes | −5.65 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.79 |
| 25 | No | Yes | −5.65 | 0 | 0 | 0.55 | 0 | 1 | 2 | 3.69 |
| 26 | No | Yes | −4.69 | 0 | 0 | 0.55 | 0 | 1 | 2 | 4.07 |
| 27 | No | Yes | −4.54 | 0 | 0 | 0.55 | 0 | 1 | 2 | 4.06 |
| 28 | No | Yes | −4.6 | 0 | 0 | 0.55 | 0 | 1 | 2 | 4 |

Testing with PKCSM gives results that are slightly different from SwissADME, especially on absorption, distribution, and metabolism parameters. For absorption parameters such as water solubility, the lowest solubility is predicted by 5-*O*-benzoylpinostrobin derivatives substituted with two chlorines and trifluoromethyl. Also, intestinal absorption value predicts that the most absorbable test molecule is the 5-*O*-benzoylpinostrobin derivative substituted with the nitro group, whereas the least absorbed is pinostrobin. All test molecules other than pinostrobin are also thought to have acted as Pgp I and II inhibitors, where no test molecule becomes the Pgp substrate. For distribution parameters, in contrast to SwissADME results, all test molecules other than pinostrobin are predicted to have negative BBB permeability values, indicating that the compound can penetrate BBB. All test molecules also show negative CNS permeability values, which means they can penetrate CNS, where the most negative values are indicated by the 5-*O*-benzoylpinostrobin derivative substituted with the nitro group.

For metabolism parameters, exciting results are shown where all test molecules become CYP3A4 substrates, but none of them become CYP2D6 substrates. Almost all test compounds become inhibitors of CYP2C19, CYP2C9, and CYP3A4, but none of them become CYP2D6 inhibitors. For excretion parameters, the total value of test molecular clearance shows variable results, where the lowest value is indicated by the 5-*O*-benzoylpinostrobin derivative substituted with the trifluoromethyl group, whereas the highest is indicated by the 5-*O*-benzoylpinostrobin derivative substituted with the nitro group. Among all the test molecules, only the 5-*O*-benzoylpinostrobin derivative substituted with a nitro group, which is thought to be an OCT2 renal substrate. Toxicity parameters show exciting results, where the AMES test results suggest that only pinostrobin and 4-nitro-5-*O*-benzoylpinostrobin are active as mutagens. The highest MRTD value is indicated by the 5-*O*-benzoyl pinostrobin derivative substituted with chlorine and fluorine groups, whereas the 5-*O*-benzoylpinostrobin derivative substituted with a nitro group results in a negative MRTD value. All test molecules are also predicted not to be hepatotoxic except for 5-*O*-benzoylpinostrobin derivative substituted with nitro and *t*-butyl groups. Complete results of testing with PKCSM are presented in Table 3.

**Table 3:** The results of the ADMET test with pkCSM.

| Compound no. | LOGP | Surface area | Water solubility | Caco2 permeability | Intestinal absorption | Skin permeability | Pgp substrate | Pgp I inhibitor | Pgp II inhibitor | $VD_{ss}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.1073 | 116.125 | −3.478 | 1.311 | 92.733 | −2.827 | No | No | No | −0.072 |
| 2 | 4.6209 | 162.028 | −5.71 | 1.169 | 96.08 | −2.733 | No | Yes | Yes | −0.773 |
| 3 | 5.2743 | 172.331 | −5.998 | 1.165 | 94.419 | −2.734 | No | Yes | Yes | −0.739 |
| 4 | 5.2743 | 172.331 | −5.998 | 1.165 | 94.419 | −2.734 | No | Yes | Yes | −0.739 |
| 5 | 5.2743 | 172.331 | −5.998 | 1.165 | 94.419 | −2.734 | No | Yes | Yes | −0.739 |
| 6 | 5.9277 | 182.635 | −6.247 | 1.162 | 92.758 | −2.735 | No | Yes | Yes | −0.703 |
| 7 | 5.9277 | 182.635 | −6.247 | 1.162 | 92.758 | −2.735 | No | Yes | Yes | −0.703 |
| 8 | 4.76 | 166.194 | −5.835 | 1.174 | 95.226 | −2.735 | No | Yes | Yes | −0.89 |
| 9 | 4.76 | 166.194 | −5.835 | 1.174 | 95.226 | −2.735 | No | Yes | Yes | −0.89 |
| 10 | 4.76 | 166.194 | −5.835 | 1.174 | 95.226 | −2.735 | No | Yes | Yes | −0.89 |
| 11 | 5.3834 | 175.896 | −6.045 | 1.163 | 94.352 | −2.735 | No | Yes | Yes | −0.722 |
| 12 | 5.3834 | 175.896 | −6.045 | 1.163 | 94.352 | −2.735 | No | Yes | Yes | −0.722 |
| 13 | 5.3834 | 175.896 | −6.045 | 1.163 | 94.352 | −2.735 | No | Yes | Yes | −0.722 |
| 14 | 5.6397 | 180.89 | −6.214 | 1.174 | 92.806 | −2.736 | No | Yes | Yes | −0.745 |
| 15 | 5.6397 | 180.89 | −6.214 | 1.174 | 92.806 | −2.736 | No | Yes | Yes | −0.745 |
| 16 | 5.6397 | 180.89 | −6.214 | 1.174 | 92.806 | −2.736 | No | Yes | Yes | −0.745 |
| 17 | 3.5359 | 178.808 | −3.68 | 1.101 | 96.429 | −2.745 | No | Yes | Yes | −0.335 |
| 18 | 3.5359 | 178.808 | −3.947 | 1.024 | 98.538 | −2.763 | No | Yes | Yes | −0.217 |
| 19 | 3.5359 | 178.808 | −4.272 | 1.043 | 98.532 | −2.769 | No | Yes | Yes | −0.093 |
| 20 | 4.92932 | 168.393 | −5.846 | 1.168 | 95.877 | −2.734 | No | Yes | Yes | −0.723 |
| 21 | 4.92932 | 168.393 | −5.846 | 1.168 | 95.877 | −2.734 | No | Yes | Yes | −0.723 |
| 22 | 4.92932 | 168.393 | −5.846 | 1.168 | 95.877 | −2.734 | No | Yes | Yes | −0.723 |
| 23 | 4.6295 | 173.507 | −5.933 | 1.301 | 95.981 | −2.735 | No | Yes | Yes | −0.833 |
| 24 | 4.6295 | 173.507 | −5.933 | 1.301 | 95.981 | −2.735 | No | Yes | Yes | −0.833 |
| 25 | 4.6295 | 173.507 | −5.933 | 1.301 | 95.981 | −2.735 | No | Yes | Yes | −0.833 |
| 26 | 5.9184 | 187.488 | −5.704 | 1.176 | 94.748 | −2.735 | No | Yes | Yes | −1.061 |
| 27 | 5.9184 | 187.488 | −5.843 | 1.181 | 94.521 | −2.735 | No | Yes | Yes | −1.008 |
| 28 | 5.9184 | 187.488 | −5.912 | 1.147 | 94.489 | −2.735 | No | Yes | Yes | −0.969 |

| Compound no. | BBB permeability | CNS permeability | CYP2D6 substrate | CYP3A4 substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor | Total clearance |
|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.159 | −1.991 | No | Yes | Yes | Yes | Yes | No | No | 0.187 |
| 2 | −0.083 | −1.843 | No | Yes | Yes | Yes | Yes | No | Yes | 0.557 |
| 3 | −0.084 | −1.729 | No | Yes | No | Yes | Yes | No | Yes | 0.378 |
| 4 | −0.084 | −1.729 | No | Yes | No | Yes | Yes | No | Yes | 0.249 |
| 5 | −0.084 | −1.729 | No | Yes | No | Yes | Yes | No | Yes | 0.188 |
| 6 | −0.085 | −1.614 | No | Yes | Yes | Yes | Yes | No | Yes | 0.302 |
| 7 | −0.085 | −1.614 | No | Yes | Yes | Yes | Yes | No | Yes | 0.373 |
| 8 | −0.171 | −2.687 | No | Yes | Yes | Yes | Yes | No | Yes | 0.394 |
| 9 | −0.171 | −2.687 | No | Yes | Yes | Yes | Yes | No | Yes | 0.391 |
| 10 | −0.171 | −2.687 | No | Yes | Yes | Yes | Yes | No | Yes | 0.384 |
| 11 | −0.086 | −1.706 | No | Yes | No | Yes | Yes | No | Yes | 0.136 |
| 12 | −0.086 | −1.706 | No | Yes | No | Yes | Yes | No | Yes | 0.227 |
| 13 | −0.086 | −1.706 | No | Yes | No | Yes | Yes | No | Yes | 0.166 |
| 14 | −0.072 | −1.686 | No | Yes | Yes | Yes | Yes | No | Yes | 0.092 |
| 15 | −0.072 | −1.686 | No | Yes | Yes | Yes | Yes | No | Yes | 0.085 |
| 16 | −0.072 | −1.686 | No | Yes | Yes | Yes | Yes | No | Yes | 0.077 |
| 17 | −0.718 | −3.054 | No | Yes | No | Yes | No | No | Yes | 0.468 |
| 18 | −0.781 | −3.054 | No | Yes | No | Yes | No | No | Yes | 0.566 |
| 19 | −0.839 | −3.053 | No | Yes | No | No | No | No | Yes | 0.615 |
| 20 | −0.071 | −1.769 | No | Yes | No | Yes | Yes | No | Yes | 0.569 |
| 21 | −0.071 | −1.769 | No | Yes | No | Yes | Yes | No | Yes | 0.565 |
| 22 | −0.071 | −1.769 | No | Yes | No | Yes | Yes | No | Yes | 0.558 |
| 23 | −0.679 | −2.749 | No | Yes | Yes | Yes | Yes | No | Yes | 0.527 |
| 24 | −0.679 | −2.749 | No | Yes | Yes | Yes | Yes | No | Yes | 0.52 |
| 25 | −0.679 | −2.749 | No | Yes | Yes | Yes | Yes | No | Yes | 0.513 |
| 26 | −0.208 | −1.487 | No | Yes | No | Yes | Yes | No | No | 0.503 |
| 27 | −0.173 | −1.487 | No | Yes | No | Yes | Yes | No | No | 0.495 |
| 28 | −0.159 | −1.49 | No | Yes | No | Yes | Yes | No | No | 0.488 |

| Compound no. | Renal OCT2 substrate | AMES toxicity | MRTD, log mg/kg/-day | hERG I inhibitor | hERG II Inhibitor | LD50 | LOAEL | Hepatotoxicity | *T. pyriformis* toxicity | Minnow toxicity |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | No | Yes | 0.112 | No | No | 2.192 | 2.037 | No | 0.919 | 1.222 |
| 2 | No | No | 0.775 | No | Yes | 2.427 | 1.483 | No | 0.305 | −0.699 |
| 3 | No | No | 0.791 | No | Yes | 2.55 | 1.281 | No | 0.302 | −1.013 |
| 4 | No | No | 0.791 | No | Yes | 2.55 | 1.281 | No | 0.302 | −1.013 |
| 5 | No | No | 0.791 | No | Yes | 2.55 | 1.281 | No | 0.302 | −1.013 |
| 6 | No | No | 0.807 | No | Yes | 2.666 | 1.078 | No | 0.298 | −1.327 |
| 7 | No | No | 0.807 | No | Yes | 2.666 | 1.078 | No | 0.298 | −1.327 |
| 8 | No | No | 0.805 | No | Yes | 2.506 | 1.361 | No | 0.291 | −1.232 |
| 9 | No | No | 0.805 | No | Yes | 2.506 | 1.361 | No | 0.291 | −1.232 |
| 10 | No | No | 0.805 | No | Yes | 2.506 | 1.361 | No | 0.291 | −1.232 |
| 11 | No | No | 0.794 | No | Yes | 2.561 | 1.27 | No | 0.301 | −1.159 |
| 12 | No | No | 0.794 | No | Yes | 2.561 | 1.27 | No | 0.301 | −1.159 |
| 13 | No | No | 0.794 | No | Yes | 2.561 | 1.27 | No | 0.301 | −1.159 |
| 14 | No | No | 0.784 | No | Yes | 2.738 | 0.98 | No | 0.296 | −0.812 |
| 15 | No | No | 0.784 | No | Yes | 2.738 | 0.98 | No | 0.296 | −0.812 |
| 16 | No | No | 0.784 | No | Yes | 2.738 | 0.98 | No | 0.296 | −0.812 |
| 17 | Yes | No | −0.054 | No | Yes | 2.493 | 2.064 | Yes | 0.285 | −1.291 |
| 18 | Yes | No | −0.173 | No | Yes | 2.5 | 2.045 | Yes | 0.286 | −1.282 |
| 19 | Yes | Yes | −0.186 | No | Yes | 2.498 | 2.012 | Yes | 0.286 | −1.674 |
| 20 | No | No | 0.778 | No | Yes | 2.468 | 1.508 | No | 0.303 | −0.796 |
| 21 | No | No | 0.778 | No | Yes | 2.468 | 1.508 | No | 0.303 | −0.796 |
| 22 | No | No | 0.778 | No | Yes | 2.468 | 1.508 | No | 0.303 | −0.796 |
| 23 | No | No | 0.793 | No | Yes | 2.495 | 1.407 | No | 0.291 | −1.299 |
| 24 | No | No | 0.793 | No | Yes | 2.495 | 1.407 | No | 0.291 | −1.299 |
| 25 | No | No | 0.793 | No | Yes | 2.495 | 1.407 | No | 0.291 | −1.299 |
| 26 | No | No | 0.504 | No | Yes | 2.501 | 1.102 | No | 0.287 | −1.792 |
| 27 | No | No | 0.547 | No | Yes | 2.542 | 1.141 | Yes | 0.287 | −1.813 |
| 28 | No | No | 0.562 | No | Yes | 2.576 | 1.161 | Yes | 0.287 | −1.825 |

Unlike the two previous test results, ProTox-II is more specific for testing toxicity parameters. An important parameter obtained from ProTox-II is predicted $LD_{50}$, where almost all test molecules have an $LD_{50}$ of 2000 mg/kg, except for the 5-*O*-benzoylpinostrobin derivative substituted with a nitro group, which shows an $LD_{50}$ value of 1500 mg/kg. All test molecules are also predicted to be in toxicity class IV ($300 < LD50 \leq 2000$), indicating that the compound is harmful if swallowed. The prediction is obtained from a comparison of the data set with average percentage similarity ranges from 65% to 78%, and percentage prediction accuracy ranges from 68% to 69%. Almost all test molecules except the 5-*O*-benzoylpinostrobin derivative substituted with a nitro group are also predicted to have toxicity targets on ANDR and PGH1. Complete results of the ProTox-II test are presented in Table 4.

**Table 4:** The results of the ADMET test with ProTox-II.

| Compound no. | $LD_{50}$, mg/kg | Toxicity class | Average similarity, % | Prediction accuracy, % | Hepatotoxicity | Carcinogenicity | Immunotoxicity | Mutagenicity | Cytotoxicity | Toxicity targets | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | ANDR | AOFA | PGH1 |
| 1 | 2000 | 4 | 78.47 | 69.26 | Inactive | Active | Inactive | Inactive | Inactive[a] | Yes | No | Yes |
| 2 | 2000 | 4 | 72.75 | 69.26 | Inactive[a] | Active | Inactive | Inactive | Inactive[a] | Yes | No | Yes |
| 3 | 2000 | 4 | 67 | 68.07 | Inactive | Active | Active | Active | Inactive | Yes | No | Yes |
| 4 | 2000 | 4 | 67.38 | 68.07 | Inactive | Active | Active | Active | Inactive | Yes | No | Yes |
| 5 | 2000 | 4 | 68.34 | 68.07 | Inactive | Active | Active | Active | Inactive | Yes | No | Yes |
| 6 | 2000 | 4 | 65.3 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | No | Yes |
| 7 | 2000 | 4 | 66.09 | 68.07 | Inactive | Active | Active | Active | Inactive | Yes | No | Yes |
| 8 | 2000 | 4 | 67.44 | 68.07 | Inactive | Active | Active | Active | Inactive | Yes | No | Yes |
| 9 | 2000 | 4 | 67.44 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | No | Yes |
| 10 | 2000 | 4 | 69.54 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | No | Yes |
| 11 | 2000 | 4 | 67.89 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | No | Yes |
| 12 | 2000 | 4 | 69.07 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | No | Yes |
| 13 | 2000 | 4 | 69.73 | 68.07 | Inactive | Active | Active[a] | Active | Inactive | Yes | Yes | Yes |
| 14 | 2000 | 4 | 65.67 | 68.07 | Inactive | Inactive | Active[a] | Inactive | Inactive | Yes | No | Yes |
| 15 | 2000 | 4 | 67.72 | 68.07 | Inactive | Active | Active | Inactive | Inactive | Yes | No | Yes |
| 16 | 2000 | 4 | 67.83 | 68.07 | Inactive | Active | Active | Inactive | Inactive | Yes | No | Yes |
| 17 | 1500 | 4 | 68.88 | 68.07 | Inactive | Active | Inactive | Active[a] | Inactive | No | No | No |
| 18 | 1500 | 4 | 69.62 | 68.07 | Inactive | Active | Inactive[a] | Active[a] | Inactive | No | No | Yes |
| 19 | 1500 | 4 | 72.72 | 69.26 | Inactive | Active | Active | Active[a] | Inactive | No | No | Yes |
| 20 | 2000 | 4 | 70.69 | 69.26 | Inactive[a] | Inactive | Inactive | Inactive | Inactive[a] | Yes | No | Yes |
| 21 | 2000 | 4 | 72.15 | 69.26 | Inactive[a] | Active | Inactive[a] | Inactive | Inactive[a] | Yes | No | Yes |
| 22 | 2000 | 4 | 71.68 | 69.26 | Inactive[a] | Active | Inactive[a] | Inactive | Inactive[a] | Yes | No | Yes |
| 23 | 2000 | 4 | 71.98 | 69.26 | Inactive[a] | Inactive | Active[a] | Inactive | Inactive[a] | Yes | No | Yes |
| 24 | 2000 | 4 | 72.62 | 69.26 | Inactive[a] | Active | Active | Inactive | Inactive[a] | Yes | No | Yes |
| 25 | 2000 | 4 | 73.4 | 69.26 | Inactive[a] | Active | Active | Inactive | Inactive[a] | Yes | No | Yes |
| 26 | 2000 | 4 | 68.8 | 68.07 | Inactive[a] | Active | Active[a] | Inactive | Inactive | Yes | No | Yes |
| 27 | 2000 | 4 | 71.55 | 69.26 | Inactive[a] | Active | Active | Inactive | Inactive | Yes | No | Yes |
| 28 | 2000 | 4 | 71.18 | 69.26 | Inactive[a] | Active | Active[a] | Inactive | Inactive | Yes | No | Yes |

[a]High probability (≥0.70).

## Discussion

Despite the varying results, the prediction results of ADMET properties of the 5-*O*-benzoylpinostrobin derivative show a consistent pattern: There is not much difference from each parameter between the pinostrobin and the 5-*O*-benzoylpinostrobin derivative. The most noticeable difference is in the absorption parameter, where almost all 5-*O*-benzoylpinostrobin derivatives except with nitro group substituents are predicted to be more difficult to dissolve in water than pinostrobin. This is implied by several parameters such as Log S variant, Log P, and water solubility, where pinostrobin almost always has better water solubility than other test molecules. This is not surprising because the properties of the benzoyl groups are relatively nonpolar, so the addition of the benzoyl group has been predicted to reduce the solubility in water from the derivatives of these compounds [11]. However, one of the advantages of adding benzoyl groups to position O is the formation of the moiety of esters. The formation of esters is known to be able to increase the solubility of a compound in water, so it is expected that a decrease in the solubility parameters in the water can be compensated by the formation of the ester compound [12]. If individually viewed from absorption parameters only, the test molecule with the most

beneficial absorption properties is the 5-*O*-benzoylpinostrobin derivative substituted with the nitro group. In some parameters such as iLOGP, SILICOS-IT Log P, and P Consensus Log, even the value is better than pinostrobin. However, solubility in water is only one factor considered in the development of drug compounds, and there are still other factors that must also be taken into account [13].

Distribution is one of the critical ADMET parameters, especially for compounds with high toxicity potential and compounds with systemic pharmacological activity. Some essential parameters for distribution include BBB permeability [14]. The ability of a drug to enter the brain is an important parameter that needs to be considered to reduce side effects and toxicity or to increase the efficacy of drugs whose pharmacological activity is in the brain. The BBB permeability was calculated *in vivo* as a log BB, the logarithmic ratio of the brain-to-plasma drug concentration. The molecule can cross the BBB immediately when log BB is higher than 0.3, but compounds with log BB smaller than −1 hardly reach the brain [3], [15].

The test molecule shows varying results between testing with SwissADME and PKCSM, where several test molecules are said to pass through BBB in the SwissADME results, but none can pass through the results of PKCSM. The difference in results is due to differences in approaches and modules used on each web server, so the difference in results obtained is not astonishing. The difference in results here shows that to obtain convincing results, ADMET predictions properties should not be done using only one web server or software application, but rather the results of a comparison of several testing algorithms [16]. When compared with the results of testing with SwissADME and PKCSM, the test molecules that are consistently predicted not to pass through the BBB are of sufficient size, consisting of the 5-*O*-benzoylpinostrobin derivative with two chlorine groups, trifluoromethyl, nitro, and the *t*-butyl group. The similarity of the results is probably due to the algorithm used in SwissADME, one of which considers the size of the test molecule, where smaller-sized molecules are predicted to pass through the BBB more comfortable [17].

The metabolic parameters show more consistent results, where some results from SwissADME and PKCSM show harmonious results. Among them are shown in CYP2D6 and CYP3A4, where differences are only shown in the results of pinostrobin prediction. Both are known to be the main responsible isoforms for drug metabolism, wherefrom both types of cytochrome in almost all test molecules are predicted to inhibit CYP3A4, but none inhibits CYP2D6. Thus, the test molecule is predicted to influence the metabolism of other drug compounds metabolized by CYP3A4 such as acetaminophen, codeine, ciclosporin, diazepam, and erythromycin [15], [18].

Excretion parameters were obtained mainly from pkCSM, which consisted of total clearance, OCT2 substrate renal. Almost all test molecules except for the 5-*O*-benzoylpinostrobin derivative substituted with the trifluoromethyl group have a higher total clearance value than pinostrobin, suggesting that the 5-*O*-benzoylpinostrobin derivative is relatively more rapidly excreted from the body than pinostrobin [19]. The OCT2 is a protein transporter that has a vital contribution in the renal uptake, disposition, and clearance of drugs compounds. Evaluating the transfer of a candidate compound by OCT2 offers useful information regarding not only its clearance but also its potential contraindications [3], [15]. The pkCSM results show that only the 5-*O*-benzoylpinostrobin derivative substituted with a nitro group, which is an OCT2 substrate, so the compound is predicted to undergo a renal uptake process and stay longer in the body.

Essential parameters for toxicity include $LD_{50}$ and toxicity class, where all test molecules are predicted to have $LD_{50}$ not less than 1500 mg/kg/day and included in the category IV Globally Harmonized System, which means they are slightly toxic if swallowed as shown in the ProTox-II results [9]. The potential for toxicity is mainly related to the presumed carcinogenicity of most test molecules, as well as the potential for immunotoxicity and mutagenicity of some test molecules. However, the probability of the potential toxicity is relatively low, except for immunotoxicity, which has a high probability on average (≥0.70). Of the 15 target toxicity models available, most test molecules show potential toxicity to ANDR and PGH1. These results imply that the side effects that may occur due to the consumption of test compounds may be related to the two types of receptors, such as fertility disorders due to interference with the ANDR and digestive disorders due to interference with PGH1 [20], [21].

## Conclusions

This study has successfully predicted the ADMET properties of the 5-*O*-benzoylpinostrobin derivative. Overall, the 5-*O*-benzoylpinostrobin derivative has an ADMET profile that is relatively similar to pinostrobin, where some parameters indicate that the 5-*O*-benzoylpinostrobin derivative may have lower water solubility than pinostrobin. The three web servers that are used provide results that are not very different for each parameter. The difference in prediction results from the web server used is most likely due to differences in modules and algorithms used on each web server. Therefore, it is vital to obtain ADMET properties by not only relying on one

web server. For future research, the results obtained from this study provide excellent guidelines, especially in the stages of synthesis and testing of the pharmacological activities of each 5-*O*-benzoylpinostrobin derivative.

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