ADME studies of TUG-770 (a GPR-40 inhibitor agonist) for the treatment of type 2 diabetes using SwissADME predictor: *In silico* study

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**ARTICLE INFO**
Received on: 11/12/2021
Accepted on: 05/02/2022
Available Online: 05/04/2022

**Key words:**
SwissADME, TUG-770, ChemiDraw, *in silico* prediction.

**ABSTRACT**
*In vivo* absorption, delivery, metabolism, and elimination (ADME) testing is considered expensive, time-consuming, and animal lives put at risk, while *in silico* ADME testing is safer, easier, and faster. The aim of this study is to predict the ADME profile of drug candidates prior to their synthesis. TUG-770 *in silico* ADME experiments will be predicted in this study to tell what to expect from the clinical trials, to find a link between *in vivo* and *in silico* findings, and to improve the structure of TUG-770 so that biological activity is not harmed (unaffected) while unwanted ADME effects are reduced. The 2D and 3D structures of TUG-770 were drawn using ChemDraw 3D-Ultra version 19.0.0.22 by minimizing the energy using MM2 and Molecular Orbital Package (MOPAC) with the minimum Root-Mean-Square (RMS) gradient set to 0.01. The bioavailability radar revealed that the colored areas were bioavailable, which have properties like lipophilicity, flexibility, saturation scale, and polarity, which are the most favorable physicochemical environments for oral bioavailability and solubility. The molecular formula of the molecule, according to its physicochemical properties, is $C_{19}H_{14}FNO_2$ [307.32 (g/mol)]. This compound has 23 heavy atoms and 12 aromatic heavy atoms. In the sp³ hybridization, 0.16% of carbon atoms are active.

**INTRODUCTION**
Drug research entails determining the safety and toxicity of potential new drugs, as well as developing a target receptor hypothesis for a specific condition and screening the new drug candidates’ *in vitro* and/or *in vivo* biological activities. Conducting drug metabolism and pharmacokinetics tests, also known as ADMET, which means absorption, delivery, metabolism, elimination, and toxicity experiments, is an important part of drug discovery (Guoli et al., 2021; Leonardo and Adriano, 2019; Longfei et al., 2019; Yuhua et al., 2019). The use of early absorption, delivery, metabolism, and excretion (ADME) assessment has significantly reduced the number of compounds that fail clinical trials (Akbar et al., 2017; Kaitin, 2008; Mishra and Dahima, 2019).

Preclinical ADME’s main goal is to remove poor drug candidates early in the drug development process, allowing resources to be spent on promising candidates (Mishra and Dahima, 2019). Since the 1950s, regulatory agencies have focused on *in vivo* research to predict how new molecules would behave in the body of humans (Arora et al., 2008). Bioavailability, pharmacokinetics, metabolism, tissue distribution, and toxicity are usually evaluated in one non-rodent and one rodent species preceding administering a medication to a person in a clinical trial (dog or nonhuman primate) in phase 1. Radioactively labeled compounds are commonly used in the appropriate technique for biodistribution assessment. Animal studies and synthesizing enough radioactively labeled compounds both take time and resources (Oldendorf, 1970).
As a result, these assays are used later in the preclinical research process, when there are more tools available to study the few molecules that have made it that far. Thanks to advancements in cell and molecular biology, high-throughput sampling, and miniaturization technology in the 1990s, as well as stem cell-derived models at the turn of the century, early in silico ADME experiments have been developed to predict in vivo animal and human outcomes at a pace and cost-effectiveness suitable for the early discovery period (Mishra and Dahima, 2019; Oldendorf, 1970).

Preclinical drug testing necessitates the use of animals, which is time-consuming and expensive, as well as potentially causes individual pain. This has compelled scientists to look for ways to cut down on not just the time expended on drug detection experiments, but also the number of animals involved and their care by humans. To achieve this end, several new in silico techniques known as “alternatives” or “substitutes” for animal use in drug research have been developed (Arora et al., 2008).

The benefits of these choices involve a reduction in the number of animals utilized, the capability to deliver results rapidly, cost savings, and the versatility to monitor the experiment’s variables (Mishra and Dahima, 2019). The advancement of ADME profiling has reduced the number of drug candidates failing in clinical trials due to ADME issues, while also providing critical early information for drug candidate safety and toxicity prediction.

The SwissADME web tool is a free piece of software that predicts the following: physicochemical properties, distribution, metabolism, elimination, absorption, and also pharmacokinetic properties of molecules under investigation, all of which are important steps in the process of moving forward with clinical trials (Mishra and Dahima, 2019; Yusuf et al., 2020). Lipophilicity, flexibility, saturation, polarity, size, and solubility are among the six most significant physicochemical properties considered (Pires et al., 2018).

Parameters in druglikeness can be investigated using a collection of rules developed by different pharmaceutical companies, which establish the correlation between biological activities and properties of pharmacokinetic, and that must be followed for in vivo action (Cheng et al., 2012). For instance, Pfizer established the Lipinski rule of five which states that the molecule’s molecular weight should be less than 500 Da, also the H-bond acceptor is less than 10, the H-bond donor should be higher than 5, the logP value should be less than 5, and biological transporters should be avoided (Mishra and Dahima, 2019).

The logP value must range from −0.4 to +5.6; the molar refractivity must be between 40 and 130; the molecular weight must be within the range of 180–480; and the number of the atoms must be between 20 and 70, including hydrogen bond donor and acceptor, according to Amgen’s Ghose rule (Cheng et al., 2012). The Egan rule notes that the logP value and topological polar surface area (TPSA) should not exceed 5.88 and 131.6, respectively, for predicting human intestinal absorption (Mishra and Dahima, 2019).

Based on small molecule lipophilicity and polarity computations, the BOILED-egg model is proposed as an efficient predictive model. The permeability glycoprotein (P-gp) substrate is used to measure active efflux across biological membranes. It defends the Central Nervous System (CNS) from xenobiotics and is overexpressed in tumor cells. Five main isoforms, namely CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, are substrates for 50%–90% of molecules. Inhibition of these isoenzymes is likely to be one of the more frequent sources of pharmacokinetics-related drug–drug interactions and can result in toxic ADME due to drug/metabolite accumulation (Potts and Guy, 1992).

TUG-770, 3-(4-((2-(cyanomethyl)phenyl)ethynyl)-2-fluorophenyl)propanoic acid, is a GPR-40 inhibitor in clinical trials (Fig. 1). This study aims to predict the in silico ADME experiments of TUG-770, to understand the predictable outcome of clinical trials, to find a link between in vivo and in silico outcomes, and to enhance TUG-770’s structure such that biological activity is not harmed while unwanted ADME effects are decreased. To our

![chemical structure of TUG-770](image-url)
knowledge, this is the first research using SwissADME predictor to conduct in silico ADME studies of TUG-770 for the treatment of type 2 diabetes.

MATERIALS AND METHODS

SwissADME is a free online platform for determining the drug-likeness, pharmacokinetics, and medicinal chemistry related to the stability of small molecules (Noemi et al., 2020; Tianshu et al., 2021). In comparison to the state-of-the-art of ADME (free web-based tools) and pharmacokinetics, such as pk-CSM (Pires et al., 2018) and admetSAR (Cheng et al., 2012), and aside from unique access to proficient methods, such as ilogP (Daina et al., 2014) or the BOILED-egg (Daina and Zoete, 2016), strong points of SwissADME include input methods diverse, computation for various molecules, and the ability to display, save, and exchange results (per-molecule basis) or via global, and interactive graphs. SwissADME is considered now part of the SwissDrugDesign workspace (Daina et al., 2014; Daina and Zoete, 2017).

ChemDraw was used to draw the 2D structure of TUG-770, and ChemDraw 3D-Ultra version 19.0.0.22 was used to draw the 2D and 3D structures by minimizing energy with MM2 and MOPAC, with the minimum RMS gradient set to 0.01. The structure smiley was introduced after the structure was imported. The results of the SwissADME drug design study have been recorded.

RESULTS AND DISCUSSION

According to Verber, a GlaxoSmithKline (GSK) pharmaceuticals spokesperson, some drugs, such as steroids, should have a molecular weight of more than 500 Da, 10 or even lower rotatable bonds, and a polar surface area of lower than 140 A². The Muegge rule, proposed by Bayer Pharmaceuticals, defined the following parameters: number of rings (> 7), number of carbon atoms (< 4), number of heteroatoms (> 1), number of rotatable bonds (< 15), hydrogen bond donor atoms (< 5), and hydrogen bond acceptor (> 10). Molecular weight ranged from 200 to 600 D; logP was between the range −2 and +5; the topological surface area was < 150; and the F-value of Abbott bioavailability does not exceed 10% (Oldendorf, 1970).

For oral bioavailability and absorption, a drug must have strong aqueous solubility. Based on the latter, three methods, namely Estimated SOLubility (ESOL), A method to compute log S and to estimate the water solubility (ALI) logS, and (SILICOS-IT) logS (Vázquez-Tato et al., 2021), are used to estimate the water solubility. The ESOL model is an acronym for calculating aqueous solubility straight from chemical molecular structure, then through molecular weight, the heavy atoms proportion found in the aromatic system, and rotatable bonds number. The model predicted solubility correctly within a factor of 5–8 through three validation sets (Arora et al., 2008; Cheng et al., 2012). The in-silico prediction model of aqueous solubility utilizing logS (ALI) considers the effect of TPSA. By using a fragmental form, Log (SILICOS-IT) calculates the negative sign logarithm of a compound’s water solubility. The logS scale ranges from −10 (insoluble), −6 (poorly soluble), −4 (soluble), −2 (extremely soluble), and 0 (highly soluble) (Mishra and Dahima, 2019).

A drug’s lipophilic character must be strong enough to allow it to cross the cell membrane and have good biological activity. Several methods can be used to evaluate the lipophilicity parameter. The ilogP (in-house physics-based approach) is based on solvation-free energies using n-octanol and water measured using the model of a generalized born and solvent accessible surface area. On the other hand, XlogP3 is an atomistic approach that uses the XlogP software to measure corrective factors and a knowledge-based library. WlogP is a fragmental atomistic process. MlogP is a topological approach that uses 13 molecular descriptors in a linear relationship. A Belgian consultancy company that was founded in 2010 and that is specialized in computational drug design (SILICOS-IT) logP (hybrid method) uses fragment and topological descriptors; logP is a hybrid method. The arithmetic mean of the five lipophilic character predictions is the consensus of logP (Cheng et al., 2012).

Figure 2 shows that the radar of bioavailability, revealed by the colored zone, is the best physicochemical space indicator for oral bioavailability when lipophilicity, saturation, size, flexibility, polarity, and solubility are considered. LogP can have lipophilicity of −0.7 to +5.0. The molecular weight can be anywhere between 150 and 500 (g/mol). Between 20 and 130 Å³ is the TPSA (Antoine et al., 2017). The logS (ESOL) insolubility ranges from 0 to 6. The number of rotatable bonds should range from 0 to 9 and the unsaturation fraction ranges from 0.25 to 1.0, indicating that the carbon atom fraction in sp³ hybridization cannot be less than 0.25.

According to its physicochemical properties, the compounds’ molecular formula is C₁₄H₁₄FNO₅. The molecular mass was 307.32 (g/mol). This complex comprises 23 heavy atoms and 12 aromatic heavy atoms. 0.16% of carbon atoms are active in the sp³ hybridization. There are four rotatable bonds, four hydrogen bond acceptors, and one H-bond donor in this structure. The molar refractivity was found to be 84.70, and the TPSA was measured to be 61.09 Å² (Mishra and Dahima, 2019). The logPo/w (ilogP), logPo/w (XlogP3), logPo/w (WlogP), logPo/w (MlogP), Po/w (SILICOS-IT), and consensus logPo/w were 2.66, 3.64, 3.81, 3.71, 4.91, 3.71, respectively. The logP values mean that the compound is lipophilic in general. With a logS (ESOL) value of −4.05, the compound’s water solubility was measured, meaning that it is moderately water-soluble.

The BOILED-egg model was used to study the pharmacokinetic properties. The BOILED-egg model helps in performing the computation of derivative polarity as well as lipophilicity since it generates datasets with high precision, speed, and transparency (Fahmina et al., 2020; Sabitu et al., 2020). Also, it aids in drug production by allowing chemical libraries to be purified. This model helps for intuitive estimation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) concerning the direction of the molecules (Fig. 3). The yolk (yellow region) represents a high likelihood of brain invasion, while the white area (intestinal tract) represents a high likelihood of passive absorption by the GI tract. It is not appropriate for white and yolk areas to be mutually exclusive.

TUG-770 has a high degree of gastrointestinal absorption and easily passes through the blood–brain barrier. There will be no problems with opioid excretion since there is no P-gp substrate. P-gp is necessary for drug removal and absorption. P-gp has a stronger impact on limiting drug absorption from blood circulation into the brain and from the intestinal lumen into epithelial cells due to its localization than it does on facilitating drug excretion.
from hepatocytes and renal tubules into the neighboring luminal space due to its localization. Since it activates the isoenzymes CYP2C19 and CYP2D6, there is a risk of aggregation or drug–drug reactions, which could lead to toxicity.

With a bioavailability score of 0.85, the parameter of drug-likeness is considered high, since it fits the Lipinski, Verber, and Egan rule. The score of Synthetic Accessibility of SwissADME is based on the premise that the occurrence of molecular fragments in “really” obtainable molecules is related to synthesis ease. For typical chemical moieties, the fragmental contribution to Synthetic Accessibility should be beneficial, but for uncommon moieties, it should be unfavorable. The synthetic usability score was discovered to be 2.72, suggesting that the molecule is not difficult to synthesize. There is no alarm about Pan-Assay Interference Compounds (PAINS), suggesting that it is a very particular compound.

**OUTPUT**

We used its incorporation into SwissADME to improve the graphical efficiency by predicting P-gp substrates, which is the most effective active efflux mechanism found in biological barriers. The state of the computation is shown immediately after
### Table 1. SwissTargetPrediction.

| Target                                           | Common name                                      | Uniprot ID | ChEMBL ID   | Target class                      | Probability* | Known actives (3D/2D) |
|--------------------------------------------------|--------------------------------------------------|------------|-------------|-----------------------------------|--------------|-----------------------|
| Free fatty acid receptor 1                       | FFAR1                                            | O14842     | CHEMBL4422  | Family A G protein-coupled receptor | 1.0          | 174 / 19              |
| G-protein-coupled receptor 120                   | FFAR4                                            | Q5NUL3     | CHEMBL5339  | Family A G protein-coupled receptor | 1.0          | 21 / 22               |
| Aldose reductase (by homology)                   | AKR1B1                                           | P15121     | CHEMBL1900  | Enzyme                            | 0.101613854776 | 310 / 0              |
| Matrix metalloproteinase 13                      | MMP13                                            | P45452     | CHEMBL280   | Protease                          | 0.101613854776 | 93 / 0               |
| Matrix metalloproteinase 14                      | MMP14                                            | P50281     | CHEMBL3869  | Protease                          | 0.101613854776 | 23 / 0               |
| Aldo-keto-reductase family 1 member C3           | AKR1C3                                           | P42330     | CHEMBL4681  | Enzyme                            | 0.101613854776 | 104 / 0              |
| Fatty acid-binding protein, liver (by homology)  | FABP1                                            | P07148     | CHEMBL5421  | Fatty acid binding prote family   | 0.101613854776 | 3 / 0                |
| Steroid 5-alpha-reductase 2                      | SRD5A2                                           | P31213     | CHEMBL1856  | Oxidoreductase                    | 0.101613854776 | 48 / 0               |
| Matrix metalloproteinase 16                      | MMP16                                            | P51512     | CHEMBL2200  | Protease                          | 0.101613854776 | 3 / 0                |
| Matrix metalloproteinase 8                       | MMP8                                             | P22894     | CHEMBL4588  | Protease                          | 0.101613854776 | 75 / 0               |
| Matrix metalloproteinase 3                       | MMP3                                             | P08254     | CHEMBL283   | Protease                          | 0.101613854776 | 74 / 0               |
| Thyroid hormone receptor alpha                   | THRA                                             | P10827     | CHEMBL1860  | Nuclear receptor                  | 0.101613854776 | 41 / 0               |
| Thyroid hormone receptor beta-1                  | THR8                                             | P10828     | CHEMBL1947  | Nuclear receptor                  | 0.101613854776 | 49 / 0               |
| HMG-CoA reductase                                | HMGCR                                            | P04035     | CHEMBL402   | Oxidoreductase                    | 0.101613854776 | 62 / 0               |
| Thromboxane-A synthase                           | TBXAS1                                           | P24557     | CHEMBL1835  | Cytochrome P450                    | 0.101613854776 | 270 / 0              |
| Mitogen-activated protein kinase kinase 8        | MAP3K8                                           | P41279     | CHEMBL4899  | Kinase                            | 0.101613854776 | 18 / 0               |
| Plasminogen                                      | PLG                                              | P00747     | CHEMBL1801  | Protease                          | 0.101613854776 | 2 / 0                |
| G protein-coupled receptor 44                    | PTGDR2                                           | Q9Y5Y4     | CHEMBL5071  | Family A G protein-coupled receptor | 0.101613854776 | 66 / 0               |
| Leukotriene B4 receptor 1                        | LTB4R                                            | Q15722     | CHEMBL3911  | Family A G protein-coupled receptor | 0.101613854776 | 41 / 0               |
| Solute carrier family 22 member 12               | SLC22A12                                         | Q96837     | CHEMBL6120  | Family A G protein-coupled receptor | 0.101613854776 | 1084 / 0             |
| Prostanoid EP4 receptor                          | PTGER4                                           | P35408     | CHEMBL1836  |                                    |              |                       |
| Target                                           | Common name                        | Uniprot ID | ChEMBL ID  | Target class                          | Probability   | Known actives (3D/2D) |
|-------------------------------------------------|------------------------------------|------------|------------|---------------------------------------|---------------|-----------------------|
| Angiotensin-converting enzyme (by homology)     | ACE                                | P12821     | CHEMBL1808 | Protease                              | 0.101613854776 | 237 / 0               |
| Prostanoid IP receptor                          | PTGIR                              | P43119     | CHEMBL1995 | Family A G protein-coupled receptor   | 0.101613854776 | 30 / 0                |
| Thromboxane A2 receptor                         | TBXA2R                             | P21731     | CHEMBL2069 | Family A G protein-coupled receptor   | 0.101613854776 | 246 / 0               |
| Hematopoietic cell protein-tyrosine phosphatase | PTPN22                             | Q9Y2R2     | CHEMBL2889 | Phosphatase                           | 0.101613854776 | 17 / 0                |
| Peroxisome proliferator-activated receptor delta| PPARD                              | Q03181     | CHEMBL3979 | Nuclear receptor                      | 0.101613854776 | 125 / 0               |
| Carbonic anhydrase II                           | CA2                                | P00918     | CHEMBL205  | Lyase                                 | 0.101613854776 | 94 / 0                |
| Carbonic anhydrase I                            | CA1                                | P00915     | CHEMBL261  | Lyase                                 | 0.101613854776 | 66 / 0                |
| Glutathione reductase                           | GSR                                | P00390     | CHEMBL2755 | Oxidoreductase                        | 0.101613854776 | 2 / 0                 |
| Carbonic anhydrase XII                          | CA12                               | O43570     | CHEMBL3242 | Lyase                                 | 0.101613854776 | 26 / 0                |
| Carbonic anhydrase IX                           | CA9                                | Q16790     | CHEMBL3594 | Lyase                                 | 0.101613854776 | 30 / 0                |
| Cytochrome P450 11B2                            | CYP11B2                            | P19099     | CHEMBL2722 | Cytochrome P450                        | 0.101613854776 | 1 / 0                 |
| Retinoid X receptor alpha                       | RXRA                               | P19793     | CHEMBL2061 | Nuclear receptor                      | 0.101613854776 | 52 / 0                |
| Phosphodiesterase 5A                           | PDE5A                              | O76074     | CHEMBL1827 | Phosphodiesterase                     | 0.101613854776 | 5 / 0                 |
| Fatty acid binding protein adipocyte            | FABP4                              | P15090     | CHEMBL2083 | Fatty acid binding protein family     | 0.101613854776 | 39 / 0                |
| Phosphodiesterase 3                            | PDE3A                              | Q14432     | CHEMBL241  | Phosphodiesterase                     | 0.101613854776 | 4 / 0                 |
| Phosphodiesterase 7A                           | PDE7A                              | Q13946     | CHEMBL3012 | Phosphodiesterase                     | 0.101613854776 | 14 / 0                |
| Prostanoid EP2 receptor                         | PTGER2                             | P43116     | CHEMBL1881 | Family A G protein-coupled receptor   | 0.101613854776 | 102 / 0               |
| Prostanoid EP3 receptor                         | PTGER3                             | P43115     | CHEMBL3710 | Family A G protein-coupled receptor   | 0.101613854776 | 40 / 0                |
| Protein farnesyltransferase                     | FNTA                               | P49354     | CHEMBL2094108 | Enzyme                           | 0.101613854776 | 139 / 6               |
| MMP2                                            | P08253                             | P12821     | CHEMBL333  | Protease                              | 0.101613854776 | 1084 / 0              |
| MMP12                                           | P39900                             | P11837     | CHEMBL1781 | Isomerase                             | 0.101613854776 | 2 / 0                 |
| VCP                                             | P55072                             | CHEMBL1075145 | Primary active transporter                   | 0.101613854776 | 19 / 0                |
| Target name                                      | Common name                   | Uniprot ID | ChEMBL ID | Target class           | Probability | Known activs (3D/2D) |
|-------------------------------------------------|-------------------------------|------------|-----------|------------------------|-------------|----------------------|
| Peroxisome proliferator-activated receptor gamma| PPARG                         | P7231      | CHEMBL225 | Nuclear receptor        | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor alpha| PPARG                         | Q7869      | CHEMBL239 | Nuclear receptor        | 0.101613854776 | 0 / 0                |
| PKB/Akt                                         | PRKAB                         | O6054      | CHEMBL318 | Kinase                 | 0.101613854776 | 0 / 0                |
| PKC                                             | PROK1                         | Q13258     | CHEMBL427 | Family AG protein-coupled | 0.101613854776 | 0 / 0                |
| MAP kinase-activated protein kinase-1            | MAPK14                        | Q18591     | CHEMBL260 | Kinase                 | 0.101613854776 | 0 / 0                |
| MAPK                                             | MAPK14                        | Q18591     | CHEMBL260 | Kinase                 | 0.101613854776 | 0 / 0                |
| Interleukin-8                                    | CXCL8                         | Q13258     | CHEMBL427 | Secreted protein        | 0.101613854776 | 0 / 0                |
| Prostaglandin D1 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D2 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D3 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Dihydroxyacetone dehydrogenase                   | DHODH                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor gamma| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor alpha| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAP kinase-activated protein kinase-1            | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAPK                                             | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Interleukin-8                                    | CXCL8                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D1 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D2 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D3 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Dihydroxyacetone dehydrogenase                   | DHODH                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor gamma| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor alpha| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAP kinase-activated protein kinase-1            | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAPK                                             | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Interleukin-8                                    | CXCL8                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D1 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D2 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D3 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Dihydroxyacetone dehydrogenase                   | DHODH                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor gamma| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor alpha| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAP kinase-activated protein kinase-1            | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAPK                                             | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Interleukin-8                                    | CXCL8                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D1 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D2 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D3 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Dihydroxyacetone dehydrogenase                   | DHODH                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor gamma| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Peroxisome proliferator-activated receptor alpha| PPARG                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAP kinase-activated protein kinase-1            | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| MAPK                                             | MAPK14                        | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Interleukin-8                                    | CXCL8                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D1 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D2 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Prostaglandin D3 receptor                        | PTGDR                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Dihydroxyacetone dehydrogenase                   | DHODH                         | Q13258     | CHEMBL427 | Oxidoreductase         | 0.101613854776 | 0 / 0                |
| Target                                                                 | Common name                  | Uniprot ID | ChEMBL ID          | Target class          | Probability | Known actives (3D/2D) |
|----------------------------------------------------------------------|------------------------------|------------|--------------------|-----------------------|-------------|-----------------------|
| Monocarboxylate transporter 4                                         | SLC16A3                      | O15427     | CHEMBL2073663      | Electrochemical transporter | 0.101613854776 | 4 / 0 |
| Peptidyl-glycine alpha-amidating monoxygenase                        | PAM                          | P19021     | CHEMBL2544         | Enzyme                | 0.101613854776 | 3 / 0 |
| Peptidyl-prolyl cis-trans isomerase NIMA- interacting 1               | PIN1                         | Q13526     | CHEMBL2288         | Enzyme                | 0.101613854776 | 41 / 0 |
| Epoxide hydratase                                                    | EPHX2                        | P34913     | CHEMBL2409         | Protease              | 0.101613854776 | 53 / 0 |
| Telomerase reverse transcriptase                                      | TERT                         | O14746     | CHEMBL2916         | Enzyme                | 0.101613854776 | 2 / 0 |
| Nuclear receptor ROR-gamma                                           | RORC                         | P51449     | CHEMBL1741186      | Nuclear receptor       | 0.101613854776 | 9 / 0 |
| Hepatocyte growth factor receptor                                    | MET                          | P08581     | CHEMBL3717         | Kinase                | 0.101613854776 | 5 / 0 |
| Serine/threonine-protein kinase Aurora-A                              | AURKA                        | O14965     | CHEMBL4722         | Kinase                | 0.101613854776 | 49 / 0 |
| Histone deacetylase 3                                                | HDAC3                        | O15379     | CHEMBL1829         | Eraser                | 0.101613854776 | 1 / 0 |
| Histone deacetylase 6                                                | HDAC6                        | Q9UBN7     | CHEMBL1865         | Eraser                | 0.101613854776 | 2 / 0 |
| Xanthine dehydrogenase                                               | XDH                          | P47989     | CHEMBL1929         | Oxidoreductase         | 0.101613854776 | 1 / 0 |
| Histone deacetylase 2                                                | HDAC2                        | Q92769     | CHEMBL1937         | Eraser                | 0.101613854776 | 1 / 0 |
| Methionyl-tRNA synthetase                                            | MARS                         | P56192     | CHEMBL2870         | Enzyme                | 0.101613854776 | 15 / 0 |
| Histone deacetylase 8                                                | HDAC8                        | Q9BY41     | CHEMBL3192         | Eraser                | 0.101613854776 | 1 / 0 |
| Histone deacetylase 1                                                | HDAC1                        | Q13547     | CHEMBL325          | Eraser                | 0.101613854776 | 1 / 0 |
| Histone deacetylase 10                                               | HDAC10                       | Q96988     | CHEMBL5103         | Eraser                | 0.101613854776 | 1 / 0 |
| Phosphodiesterase 4D                                                 | PDE4D                        | Q08499     | CHEMBL288          | Phosphodiesterase     | 0.101613854776 | 74 / 0 |
| Casein kinase II alpha                                               | CSNK2A1                      | P68400     | CHEMBL3629         | Kinase                | 0.101613854776 | 128 / 0 |
| Autotaxin                                                            | ENPP2                        | P13822     | CHEMBL3691         | Enzyme                | 0.101613854776 | 28 / 0 |
| Lysosomal protective protein                                          | CTSA                         | P10619     | CHEMBL6115         | Protease              | 0.101613854776 | 311 / 0 |
| Neprilysin (by homology)                                             | MME                          | P08473     | CHEMBL1944         | Protease              | 0.101613854776 | 189 / 0 |
| Phospholipase A2 group IIA                                           | PLA2G2A                      | P14555     | CHEMBL3474         | Enzyme                | 0.101613854776 | 80 / 0 |
| P2X purinoceptor 7                                                    | P2RX7                        | Q99572     | CHEMBL4805         | Ligand-gated ion channel | 0.101613854776 | 1 / 0 |
| Arachidonate 5-lipoxygenase                                          | ALOX5                        | P09917     | CHEMBL215          | Oxidoreductase        | 0.101613854776 | 83 / 0 |
| Lysine-specific demethylase 5A                                        | KDM5A                        | P29375     | CHEMBL2424504      | Eraser                | 0.101613854776 | 7 / 0 |
| Lysine-specific demethylase 5B                                        | KDM5B                        | Q9UGL1     | CHEMBL3774295      | Eraser                | 0.101613854776 | 5 / 0 |
| Lysine-specific demethylase 2B                                        | KDM2B                        | Q8NHM5     | CHEMBL3779760      | Eraser                | 0.101613854776 | 3 / 0 |
| MAP kinase ERK2                                                      | MAPK1                        | P28482     | CHEMBL4040         | Kinase                | 0.101613854776 | 7 / 0 |
| Hydroxyacid oxidase 1                                                | HA01                         | Q9UJ89     | CHEMBL4229         | Enzyme                | 0.101613854776 | 9 / 0 |
| Apoptosis regulator Bcl-X                                            | BCL2L1                       | Q07817     | CHEMBL4625         | Other ion channel      | 0.101613854776 | 29 / 0 |
| G protein-coupled receptor kinase                                    | GRK6                         | P43250     | CHEMBL6144         | Kinase                | 0.101613854776 | 16 / 0 |
| Lysine-specific demethylase 4C                                        | KDM4C                        | Q9H3R0     | CHEMBL6175         | Eraser                | 0.101613854776 | 18 / 0 |

*Probability for the query molecule-assumed as bioactive – to have this protein as target.
application, beginning with validation of structure. This transient page communicates with the workload management system (Slurm version 17.11.2) to inform the user that his or her job has been queued or is being worked on. The consumer will see the various stages of the computation and observe the overall procedure on a progress bar. Starting calculations take between 15 and 20 seconds for a compound the size of a druglike molecule. Predictions are shown on the first performance page until the progression bar is filled (Antoine et al., 2017).

The most valuable piece of information on this result page is the tabulated list of potential protein targets (Table 1), as determined by the dual-score ligand-dependent reverse screening of the query molecule against the collection of known actives. The table rows are ranked by default based on the likelihood of the related protein being the real target of the query molecule. Protein complex targets are now provided incomplete names (linked to a particular ChEMBL ID), with their subunits/components linked to Genecard and Uniprot separately in version 2019.

The probability values, shown as green bars, are calculated using the combined scores of the most closely related compounds to the query molecule (in 2D and 3D) that are active on a given protein as previously stated, and outlined in detail elsewhere (Antoine et al., 2019; Gfeller et al., 2014). Importantly, this value accurately depicts the likelihood of a bioactive molecule having a specific protein as a goal, but not the likelihood of being bioactive. Furthermore, targets labeled with the phrase “by homology” are projections focused on related molecules active on proteins with a high degree of homology (Antoine et al., 2017).

A common example is an orthology in which a target is expected for a given species depending on the question molecule’s similarities to compounds active on ortholog proteins. In the last column, you can see the number of compounds that are active on each listed target and are extremely like the query molecule. You may adjust the number of planned targets shown on a website to 15 (default), 25, 50, or all using page scanning (maximum 100). Furthermore, by clicking on the header, the table can be arranged by any column, and the results can be filtered using a search box.

Furthermore, users can use advanced export options by clicking on dedicated icons. The table can be saved in a variety of formats such as CSV, Excel, and PDF, copied or printed straight from the browser. A pie chart created with JPgraph is shown in a box located on the top-right of the result sheet (Fig. 4) as a description of the forecast target groups (column 5 of Table 1) (version 4.2.6). The percentages equate to the top 15 proteins by design, but the user can change this by selecting the top 25, 50, or all expected targets using the buttons on the left of the column. By clicking on the pie-chart, a full-size image would appear in a new tab of the window, allowing for more saving or printing. The user’s question molecule’s chemical composition is shown in a box located on the top-left side of the result sheet (Fig. 4), the molecular modeling group of the SIB Swiss Institute of Bioinformatics has created four icons that appear within this box and allow for the clear submission of the molecule of interest to other web resources provided. These interoperability symbols can be used in all boxes referring to the chemical compositions of known actives, as well as a reference to the ChEMBL Compound Report Card.

The above is classified in order of their similarity to the question molecules, from most to least. The “twins” icon sends the molecule to SwissSimilarity for ligand-based direct screening (Daina and Zoete, 2017), the “target” icon resubmits the aim prediction (on a different animal, for example), and the “pill” icon uses SwissADME to approximate physicochemical, ADME, or pharmacokinetic parameters (Zoete et al., 2016). The proposed expansion of interoperability by adding other in-house software is also in the works, so more icons will be added to the various websites in the future (Antoine et al., 2017). Obtaining the molecule’s SMILES through the fourth symbol also makes it easier to use it as a possible input to other, potentially external, processes. The ChEMBL ID, SMILES, similarity attribute to the query molecule, and, if applicable, the source species of the experimentally identified homologous target are all included in the file (Antoine et al., 2017).

Figure 4 shows a brief of the various target groups present among the projected targets in a pie chart. The chance calculated
from the goal scores is shown as a horizontal bar in the fifth column. 
Ligands are sorted by how close they are to the question molecule. 
The ligands have a relation to their ChEMBL entries, and the 
resemblance to the question molecule is suggested. We propose 
that you explore the ligands manually that are closest and the query 
molecule to see how accurate the projections are, and which types 
of ligands have the most similarities to the query molecule. Finally, 
there are support pages along with interactive screenshots of the 
website, a FAQ page to help users, and a download page to get a 
little of the raw data used in the predictions process.

CONCLUSION

Traditional clinical trial methods require a significant 
expenditure in time and resources, and it is possible that the 
molecule will fail. Thus, to minimize or change the structure, in silico 
trials can be pursued rather than aggressively pursuing 
monopoly and running to animal studies. The SwissADME web tool 
allows users to calculate vital pharmacokinetic, physicochemical, 
and similar parameters for one or more molecules. It was inferred 
from the analysis that the compound’s aqueous solubility, as well as 
the sp² hybridized carbon atoms fraction, should be increased. 
Further changes to the lead structure are needed to guarantee that 
the molecule does not hinder metabolizing enzymes.

SwissTargetPrediction is considered part of the Swiss 
Institute of Bioinformatics’ valuable initiative to offer online 
resources for computer-assisted drug design. SwissTargetPrediction 
can be combined further with these methods in the future, for 
example, by forecasting possible linking modes with SwissDock (Gabriela and Walter, 2019; Gfeller et al., 2014).

TUG-770 has a high degree gastrointestinal absorption 
rate and quickly passes the blood-brain barrier. Because there is 
no P-gp substrate, there will be no issues with opioid excretion. 
Also, with its bioavailability score of 0.85, the drug-likeness 
parameter is considered high, since it meets the Lipinski, Verber, 
and Egan rules. Additionally, TUG-770 synthetic usability score 
was determined to be 2.72, indicating that the molecule is not 
difficult to synthesis. Moreover, the logP values indicate that 
the compound is lipophilic in general. The compound’s water 
solubility was determined with a logS (ESOL) value of ~4.05, 
indicating that it is moderately water-soluble.

ACKNOWLEDGMENT

Declared None declared.

FUNDING

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this 
research article.
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How to cite this article:
Al Azzam KM, Negim ES, Aboul-Enein HY. ADME studies of TUG-770 (a GPR-40 inhibitor agonist) for the treatment of type 2 diabetes using SwissADME predictor: In silico study. J Appl Pharm Sci, 2022; 12(04):159–169.