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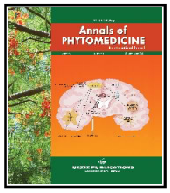

Original Article : Open Access

# Screening of coumarin derivatives as membrane integrity agonist using chem informatics approach

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**Abstract**

Investigation of oral bioavailability, absorption, distribution, metabolism, excretion, toxicity profile, and pharmacological spectra of coumarin derivatives. Coumarin is an aromatic organic chemical compound whose molecule can be described as a benzene molecule with two adjacent hydrogen atoms replaced by a lactone-like chain, forming a second six membered heterocycle that shares two carbons with the benzene ring. Coumarins have a wide range of functions such as anticancer, anti-inflammatory, anticoagulant properties, *etc*. A total of 145 coumarin derivatives were recuperated from the ChEBI database. Information such as molecular weight, molecular mass, and molecular formula along with SMILES was recuperated. Among the 145 bioactive derivatives, 32 compounds were included which showed positive drug likeness scores, exclusive of 113 derivatives which showed negative drug-likeness scores considering the modified Lipinski rule of five using Molsoft. Further, the ADMET profile of the 32 compounds was speculated for absorption, distribution, metabolism, and AMES toxicity was excluded from the study leading to the exclusion of 26 compounds that showed positive AMES test, and the 6 compounds with negative AMES toxicity proceeded for the evaluation of biological spectra. Among the 6 ligands, the biological spectra of 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin,7-hydroxy-3-(4-methoxyphenyl)-4-proply-2H-1-benzopyran-2-one and phyllocoumarin were evaluated using PASS online. Finally, 7-hydroxy-3-(4-methoxyphenyl)-4-methyl coumarin showed the highest pharmacological spectra as CYP2C12 substrate with a pharmacological activity value of 0.944 and pharmacological inactivity value of 0.004, respectively.

## 1. Introduction

Coumarin or 2H-chromen-2-one is an aromatic organic chemical compound with the formula $C_9H_6O_2$. Its molecule can be described as a benzene molecule with two adjacent hydrogen atoms replaced by a lactone-like chain (CH)=(CH)-(C-O)-O-, forming a second six membered heterocycle that shares two carbons with the benzene ring (Fylaktakidou *et al*., 2004). Coumarins have a wide variety of biological functions. It has anti-inflammatory properties and is used to treat edema (Cheng *et al*., 2004; Geddawy *et al*., 2023), antimicrobial properties (Basile *et al*., 2009; Pragyandip *et al*., 2023), anticancer properties (Küpeli Akkol *et al*., 2020; Thakur *et al*., 2015; Srivastava *et al*., 2022) and antitubercular properties (Sridevi *et al*., 2017; Kushwaha *et al*., 2022). Due to their extensive biological and pharmacological activity, coumarin derivatives are drawing more and more interest. For both natural and synthesized coumarins, we outlined their anti-inflammatory, anticoagulant, and anticancer action, among other properties.

The rule of five (ROS), also known as Lipinski's rule of five, Pfizer rule of five, or simply the Rule of five (ROS), is a rule of thumb used to assess how similar a chemical compound is to a given drug or to determine whether it possesses any properties that would make it likely to be an orally active drug in humans. As a result of a molecule's resemblance to medicine, the Lipinski rule of five forecasts a high likelihood of success or failure. In 1997, Christopher A. Lipinski developed this rule based on his observation that the majority of pharmaceuticals are made up of relatively small lipophilic molecules (Lipinski, 2004). In addition, computational approaches like molecular docking, molecular dynamics simulation, and network biology have played an important role in the identification of new lead hits that play an important role in the novel (Bhattacharya *et al*., 2023; Khanal and Patil, 2021; Kanagali *et al*., 2022).

Hence, this study aimed to identify the coumarin derivatives as membrane integrity agonists using the cheminformatics approach to predict molecules for a drug likeness score, blood brain barrier permeability, AMES toxicity, and membrane integrity agonist.

## 2. Materials and Methods

The flowline for screening coumarin derivatives for druglikeness, ADMET profile, and pharmacological spectra is presented in Figure 1.

### 2.1 Retrieval of coumarin derivatives and prediction of the drug likeness score

The reported coumarin derivatives were retrieved from the ChEBI database using the keyword "coumarin". All the basic information like molecular formula, molecular weight, and mass, including SMILES were retrieved (Matos, 2021).The drug-likeness score of each bioactive compound was calculated using the modified Lipinski rule

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of five using MolSoft (https://molsoft.com/mprop/). The calculation was based on molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, and lipophilicity (MolLogP). The molecules with positive drug likeness scores were included in further steps whereas compounds with negative drug likeness scores were excluded from further steps (Abdizadeh *et al*., 2022).

### 2.2 ADMET profiling of coumarin derivatives

The ADMET profiling of coumarin derivatives with the positive drug likeness score was predicted for absorption, distribution, metabolism, and AMES toxicity using the ADMETSAR (http://lmmd.ecust.edu.cn/admetsar1) database (Gupta*et al*.,2023). Drugs with negative AMES toxicity were excluded from the study and the rest were further queried for pharmacological spectra (Ghosh *et al*., 2016).

### 2.3 Prediction of pharmacological spectra

The pharmacological spectra of the selected ligands were further evaluated using Pass online (http://www.way2drug.com/passonline) (Stepanchikova *et al*., 2003).

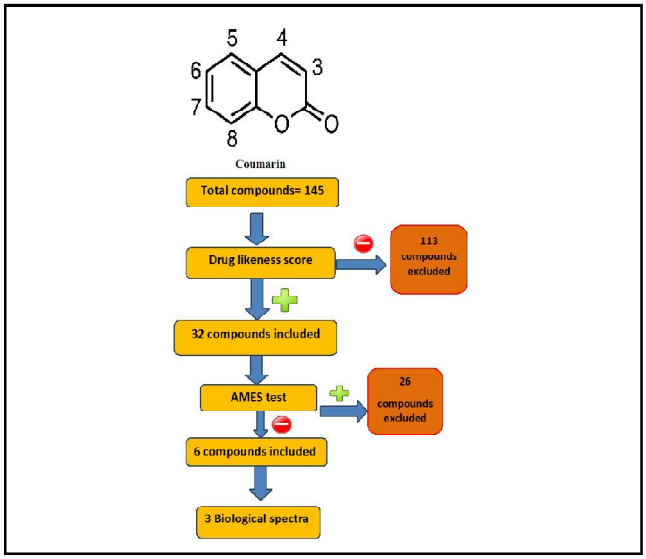



**Figure 1: Flowline for screening coumarin derivatives for drug likeness, ADMET profile, and pharmacological spectra.**

## 3. Results

### 3.1 A drug likeness score of coumarin derivatives

From the 145 different coumarin derivatives, 113 molecules were excluded from the study as they scored negative drug likeness score. Hence, 32 compounds (scored positive druglikeness score) were assumed to possess human intestinal absorptivity. Among them, Novobiocin was predicted to possess the highest drug likeness score (1.11) with 612.23 molecular weight, 11 H-bond acceptors, 6 H-bond donors, and 3.1 MolLogP.CH5126766 was predicted to possess a drug likeness score (0.95) with 383.14 molecular weight, 6 H-bond acceptors, 2 H-bond donors, and 2.15 MolLog P.6,8-Dihydroxy-5-methoxy-3-methylisocoumarin6-O-(4-O-methyl-β-D-glucopyranoside) was predicted to possess a drug likeness score (0.85) with 398.12 molecular weight, 10 H-bond acceptors, 4 H-bond and 0.24 MolLogP.8-Caffeoyl-3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin was predicted to possess a drug likeness score (0.76) with molecular weight 418.11, 7H-bond acceptors, 4 H-bond donors, and 3.67 MolLogP.5,3',4'-Trihydroxy-7-methoxy-4-phenylcoumarin 5-O-xylosyl-(1->6)-glucoside predicted for drug likeness score (0.71) with molecular weight 594.16, 15 H-bond acceptors, 8 H-bond donors, and -1.81 MolLogP. The details of each coumarin derivative with a positive drug likeness score concerning molecular formula, molecular weight, number of hydrogen bond acceptors/donors, and MolLogP are summarized in Table 1.

**Table 1: Molecular formula, molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, MolLogP, and the drug likeness score of coumarin derivatives**

| Coumarin derivatives | MF | MW | NHBA | NHBD | MolLogP | DLS |
|---|---|---|---|---|---|---|
| 6,8-Dihydroxy-5-methoxy-3-methylisocoumarin 6-O-(4-O-methyl-β-D-glucopyranoside) | $C_{18}H_{22}O_{10}$ | 398.12 | 10 | 4 | 0.24 | 0.85 |
| Phyllocoumarin | $C_{18}H_{14}0_7$ | 342.07 | 7 | 4 | 0.8 | 0.61 |
| 5-Hydroxy-6-methoxycoumarin 7-glucoside | $C_{16}H_{18}O_{10}$ | 370.09 | 10 | 5 | -0.84 | 0.36 |
| Isoglycycoumarin | $C_2H_{20}O_6$ | 368.13 | 6 | 2 | 4.09 | 0.05 |
| Isolicopyranocoumarin | $C_{21}H_{20}O_7$ | 384.12 | 7 | 3 | 3.38 | 0.23 |
| Licopyranocoumarin | $C_{21}H_{20}O_7$ | 384.12 | 7 | 3 | 3.25 | 0.37 |
| 5,7,3',4'-Tetrahydroxy-4-phenylcoumarin 5-O-glucoside | $C_{21}H_{20}O_{11}$ | 448.1 | 11 | 7 | -0.71 | 0.4 |
| 7',3',4'-Trihydroxy-5-methoxy-4-phenylcoumarin | $C_{16}H_{12}O_6$ | 300.06 | 6 | 3 | 1.55 | 0.1 |
| 5,3',4'-Trihydroxy-7-methoxy-4-phenylcoumarin 5-O-glucoside | $C_{22}H_{22}O_{11}$ | 462.12 | 11 | 6 | -0.43 | 0.41 |
| 8-Caffeoyl-3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin | $C_{24}H_{18}O_7$ | 418.11 | 7 | 4 | 3.67 | 0.76 |
| 8-p-Coumaroyl-3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin | $C_{24}H_{18}O_6$ | 402.11 | 6 | 3 | 4.06 | 0.56 |
| 8-Cinnamoyl-3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin | $C_{24}H_{18}O_5$ | 386.12 | 5 | 2 | 4.63 | 0.19 |
| 8-Hydroxy-5,7,3',4'-tetramethoxy-4-phenylcoumarin | $C_{19}H_{18}O_7$ | 358.11 | 7 | 1 | 2.1 | 0.09 |

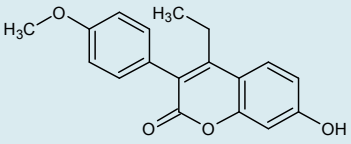
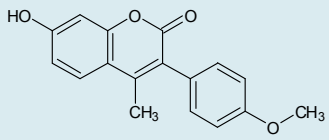
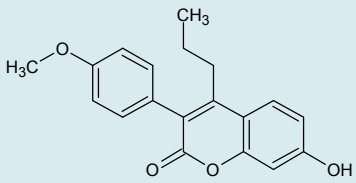
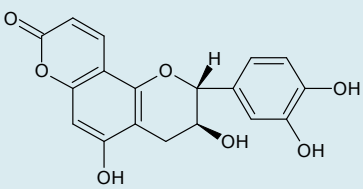
| | | | | | | |
|---|---|---|---|---|---|---|
| 5,4'-Dihydroxy-7-methoxy-4-phenylcoumarin 5-O-galactoside | $C_{22}H_{22}O_{10}$ | 446.12 | 10 | 5 | -0.04 | 0.27 |
| 5,3',4'-Trihydroxy-7-methoxy-4-phenylcoumarin 5-O-xylosyl-(1->6)-glucoside | $C_{27}H_{30}O_{15}$ | 594.16 | 15 | 8 | -1.81 | 0.71 |
| 5,2',4',5'-Tetrahydroxy-7-methoxy-4-phenylcoumarin 5-O -glucoside | $C_{22}H_{22}O_{12}$ | 478.11 | 12 | 7 | -0.36 | 0.4 |
| 4-ethyl-7-hydroxy-3-(p-methoxyphenyl)coumarin | $C_{18}H_{16}O_4$ | 296.1 | 4 | 1 | 3.77 | 0.29 |
| (2S*,3R*)-2,3-dihydro-7-methoxy-2,3-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(E)-pentenyl]-furo[3,2-c]coumarin | $C_{25}H_{28}O_5$ | 408.19 | 5 | 0 | 5.99 | 0.08 |
| Fukanefuromarin A | $C_{24}H_{28}O_5$ | 396.19 | 5 | 1 | 5.17 | 0.3 |
| Fukanefuromarin B | $C_{24}H_{28}O_5$ | 396.19 | 5 | 1 | 5.17 | 0.3 |
| Fukanefuromarin C | $C_{24}H_{28}O_5$ | 396.19 | 5 | 1 | 5.17 | 0.3 |
| Fukanefuromarin D | $C_{24}H_{28}O_5$ | 396.19 | 5 | 1 | 5.17 | 0.3 |
| Fukanefuromarin E | $C_{25}H_{28}O_5$ | 408.19 | 5 | 0 | 5.95 | 0.25 |
| Fukanefuromarin F | $C_{25}H_{28}O_5$ | 408.19 | 5 | 0 | 5.95 | 0.25 |
| Fukanefuromarin G | $C_{25}H_{28}O_5$ | 408.19 | 5 | 0 | 5.99 | 0.08 |
| 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin | $C_{17}H_{14}O_4$ | 282.09 | 4 | 1 | 3.31 | 0.08 |
| Glycycoumarin | $C_{21}H_{20}O_6$ | 368.13 | 6 | 3 | 4.75 | 0.32 |
| Novobiocin | $C_{31}H_{36}N_2O_{11}$ | 612.23 | 11 | 6 | 3.1 | 1.11 |
| 7-hydroxy-3-(4-methoxyphenyl)-4-propyl-2H-1-benzopyran -2-one | $C_{19}H_{18}O_4$ | 310.12 | 4 | 1 | 4.27 | 0.44 |
| CH5126766 | $C_{21}H_{18}FN_5O_5S$ | 471.1 | 9 | 2 | 2.15 | 0.95 |
| Glycyrin | $C_{22}H_{22}O_6$ | 383.14 | 6 | 2 | 5.08 | 0.28 |
| Cacibiocin B | $C_{15}H_8C_{12}N_2O_7$ | 397.97 | 7 | 5 | 2.2 | 0.48 |

MF: Molecular formula, DLS: Drug-likeness model score, MW: Molecular weight, NHBD: Number of hydrogen bond donors, NHBA: Number of hydrogen bond acceptor.

### 3.2 ADMET profile and AMES toxicity

Among 32 compounds, 26 were predicted for Ames toxicity, hence they were excluded from the study. 4-ethyl-7hydroxy-3-(p-methoxyphenyl), 7-hydroxy-3-(4methoxyphenyl)-4-methyl-coumarin,7-hydroxy-3-(4-methoxyphenyl)-4propyl-2H-1-benzopyran-2-one, phyllocoumarin, 8-p-coumaroyl-3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin, and 8-Cinnamoyl-3,4-dihydro-5,7-dihydroxy-4-phenyl coumarin were considered for further study as they had positive AMES toxicity. Among them, 4-ethyl-7hydroxy-3-(p-methoxyphenyl) scored 0.7144, 0.9854, 0.889 for bloodbrain barrier permeability, human intestinal absorption, and $CaCO_2$ permeability, respectively, to point to its absorptivity. In addition, it had the mitochondria as the subcellular location with 0.7498 probability, followed by high CYP inhibitory promiscuity ($p$= 0.7134). Wise, the compound was non-AMES toxic ($p$=0.9442) and non-carcinogenic ($p$= 8916).7-hydroxy-3-(4methoxyphenyl)-4-methylcoumarin scored 0.7004, 0.9793, 0.9289 for bloodbrain barrier permeability, human intestinal absorption, and $CaCO_2$ permeability, respectively, to point its absorptivity. In addition, it had the mitochondria as a subcellular location with 0.7674 probability, followed by high CYP inhibitory promiscuity ($p$=0.5343). Wise, the compound was non-AMES toxic ($p$= 0.9331) and non-carcinogenic ($p$=0.9198). 7-hydroxy-3-(4-methoxyphenyl)-4propyl-2H-1-benzopyran-2-one, scored 0.7451, 0.9863, 0.8584 for bloodbrain barrier permeability, human intestinal absorption, and $CaCO_2$ permeability, respectively, to point its absorptivity. In addition, it had the mitochondria as a subcellular location with 0.667 probability, followed by high CYP inhibitory promiscuity ($p$= 0.5793). Wise, the compound was non-AMES toxic ($p$= 0.9504) and non-carcinogenic ($p$=0.9199). Phyllocoumarin scored 0.6198, 0.9651, 0.9014 for bloodbrain barrier permeability, human intestinal absorption, and $CaCO_2$ permeability, respectively, to point to its absorptivity. In addition, it had the mitochondria as a subcellular location with 0.7416 probability, followed by high CYP inhibitory promiscuity ($p$= 0.9703). Wise, the compound was non-AMES toxic ($p$= 0.9411) and non-carcinogenic ($p$=0.96). 8-p-coumaroyl-3, 4-dihydro-5, 7-dihydroxy-4-phenylcoumarin scored 0.9223, 0.6195, human intestinal absorption and $CaCO_2$ permeability, respectively, to point its absorptivity. In addition, it had the mitochondria as a subcellular location with 0.6911 probability, followed by high CYP inhibitory promiscuity ($p$=0.5907). Wise, the compound was non-AMES toxic ($p$= 0.9404) and non-carcinogenic ($p$= 0.945). 8-Cinnamoyl-3, 4-dihydro-5, 7-dihydroxy-4-phenylcoumarin scored 0.6413, 0.9223, 0.6195 for bloodbrain barrier permeability, human intestinal absorption, and $CaCO_2$ permeability, respectively, to point its absorptivity. In addition, it had the mitochondria as a subcellular location with 0.6911 probability, followed by high CYP inhibitory promiscuity ($p$=0.5907). Wise, the compound was non-AMES toxic ($p$= 0.9404) and non-carcinogenic ($p$=0.945).The pharmacokinetic and pharmacodynamic profiles of coumarin derivatives are summarized in Table 2.

**Table 2: Pharmacokinetic and pharmacodynamic profile of coumarin derivatives**

| Compounds | Model | Result | Probability |
|---|---|---|---|
|  4-ethyl-7-hydroxy-3-(p-methoxyphenyl) coumarin | | **Absorption** | |
| | Blood brain barrier | $BBB^+$ | 0.7144 |
| | Human intestinal absorption | $HIA^+$ | 0.9854 |
| | $Caco_2$ Permeability | $Caco_2^+$ | 0.889 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.7498 |
| | CYP inhibitory promiscuity | High CYP inhibitory promiscuity | 0.7134 |
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9442 |
| | Carcinogens | Non-carcinogens | 0.8916 |
|  7-hydroxy-3-(4-methoxyphenyl) -4-methylcoumarin | | **Absorption** | |
| | Blood brain barrier | $BBB^+$ | 0.7004 |
| | Human intestinal absorption | $HIA^+$ | 0.9793 |
| | $Caco_2$ Permeability | $Caco_2^+$ | 0.9289 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.7674 |
| | | **Metabolism** | |
| | CYP inhibitory promiscuity | High CYP inhibitory promiscuity | 0.5343 |
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9331 |
| | Carcinogens | Non-carcinogens | 0.9198 |
|  7-hydroxy-3-(4-methoxyphenyl)-4 -propyl-2H-1-benzopyran-2-one | | **Absorption** | |
| | Blood brain barrier | $BBB^+$ | 0.7451 |
| | Human intestinal absorption | $HIA^+$ | 0.9863 |
| | $Caco_2$ Permeability | $Caco_2^+$ | 0.8584 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.667 |
| | | **Metabolism** | |
| | CYP inhibitory promiscuity | High CYP inhibitory promiscuity | 0.5793 |
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9504 |
| | Carcinogens | Non-carcinogens | 0.9199 |
|  Phyllocoumarin | | **Absorption** | |
| | Blood,brain barrier | $BBB^-$ | 0.6198 |
| | Human intestinal absorption | $HIA^+$ | 0.9651 |
| | $Caco_2$ Permeability | $Caco_2^+$ | 0.9014 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.7416 |
| | | **Metabolism** | |
| | CYP inhibitory promiscuity | Low CYP inhibitory promiscuity | 0.9703 |

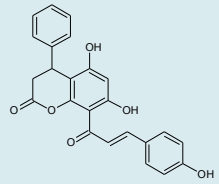
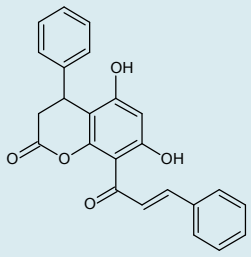
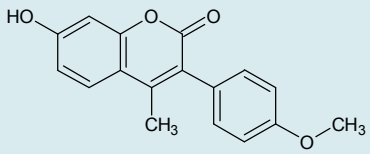
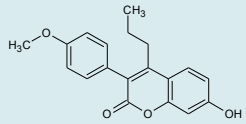
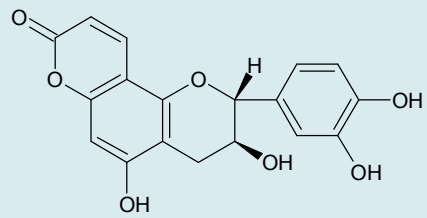
| | | | |
|---|---|---|---|
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9411 |
| | Carcinogens | Non-carcinogens | 0.96 |
|  8-p-Coumaroyl-3,4-dihydro-5,7 -dihydroxy-4-phenylcoumarin | | **Absorption** | |
| | Human intestinal absorption | HIA± | 0.9223 |
| | $Caco_2$Permeability | $Caco_2^+$ | 0.6195 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.6911 |
| | | **Metabolism** | |
| | CYP inhibitory promiscuity | Low CYP inhibitory promiscuity | 0.5907 |
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9404 |
| | Carcinogens | Non-carcinogens | 0.945 |
|  8-Cinnamoyl-3,4-dihydro-5,7 -dihydroxy-4-phenylcoumarin | | **Absorption** | |
| | Blood brain barrier | $BBB^+$ | 0.6413 |
| | Human intestinal absorption | $HIA^+$ | 0.9223 |
| | $Caco_2$Permeability | $Caco_2^+$ | 0.6195 |
| | | **Distribution** | |
| | Subcellular localization | Mitochondria | 0.6911 |
| | | **Metabolism** | |
| | CYP inhibitory promiscuity | Low CYP inhibitory promiscuity | 0.5907 |
| | | **Toxicity** | |
| | AMES toxicity | Non-AMES toxic | 0.9404 |
| | Carcinogens | Non-carcinogens | 0.945 |

**Table 3: Pharmacological spectra of selected coumarin derivatives**

| Compounds | Pa | Pi | Pharmacological spectra |
|---|---|---|---|
|  7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin | 0.950 | 0.003 | Aspulvinone dimethylallyl transferase inhibitor |
| | 0.944 | 0.004 | CYP2C12 substrate |
| | 0.909 | 0.009 | Membrane integrity agonist |
| | 0.902 | 0.004 | Aldehyde oxidase inhibitor |
| | 0.900 | 0.005 | Chlordecone reductase inhibitor |
|  7-hydroxy-3-(4-methoxyphenyl)-4-propyl-2H-1-benzopyran-2-one | 0.939 | 0.004 | Aspulvinone dimethylallyl transferase inhibitor |
| | 0.936 | 0.005 | CYP2C12 substrate |
|  Phyllocoumarin | 0.965 | 0.003 | Membrane integrity agonist |
| | 0.952 | 0.002 | UGT1A6 substrate |
| | 0.950 | 0.001 | Antimutagenic |
| | 0.946 | 0.003 | TP53 expression enhancer |
| | 0.934 | 0.002 | UGT1A substrate |
| | 0.932 | 0.001 | Free radical scavenger |
| | 0.931 | 0.006 | CYP2C12 substrate |
| | 0.919 | 0.004 | CYP1A1 substrate |
| | 0.915 | 0.001 | Pectate lyase inhibitor |
| | 0.908 | 0.004 | CYP1A substrate |
| | 0.901 | 0.002 | Sulfotransferase substrate |

### 3.3 Pharmacological spectra of non-AMES toxic compounds

Among 6 compounds, 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin,7-hydroxy-3-(4-methoxyphenyl)-4-proply-2H-1-benzopyran-2-one and phyllocoumarinwas predicted for 5 different pharmacological spectra. 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin, the scores were found to be, aspulvinone dimethylallyl transferase inhibitor (Pa = 0.950 and Pi =0.003), CYP2C12 substrate (Pa = 0.944 and Pi = 0.004), membrane integrity agonist (Pa = 0.909 and Pi =0.009), aldehyde oxidase inhibitor (Pa = 0.902 and Pi = 0.004) and chlordecone reductase inhibitor (Pa = 0.900 and Pi = 0.005).7-hydroxy-3-(-4-methoxyphenyl)-4-propyl-2H-1-benzopyran-2-one, the scores were found to be, aspulvinone dimethylallyl transferase inhibitor (Pa = 0.939 and Pi = 0.004), CYP2C12 substrate (Pa = 0.936 and Pi = 0.005). Phyllocoumarin, the scores were found to be, membrane integrity agonist (Pa = 0.965 and Pi = 0.003), UGT1A6 substrate (Pa = 0.952 and Pi = 0.002), antimutagenic (Pa = 0.950 and Pi = 0.001), TP53 expression enhancer (Pa = 0.946 and Pi = 0.003), UGT1A substrate (Pa = 0.934 and Pi = 0.002), free radical scavenger (Pa = 0.932 and Pi = 0.001), CYP2C12 substrate (Pa = 0.931 and Pi = 0.006), CYP1A1 substrate(Pa = 0.919 and Pi = 0.004), pectate lyase inhibitor (Pa = 0.915 and Pi = 0.001), CYP1A substrate(Pa = 0.908 and Pi = 0.004), sulfotransferase substrate (Pa = 0.901 and Pi = 0.002). Among them, 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin showed the highest pharmacological spectra as CYP2C12 substrate. Pharmacological spectra of selected coumarin derivatives in Table 3.

## 4. Discussion

The present study aimed to screen the ChEBI-recorded coumarin derivatives as membrane integrity agonists with human intestinal absorptivity and blood-brain barrier permeability. Previously, it has been reported that the coumarin derivative is a potential molecule in cognitive function and related activities. In addition, altered membrane integrity has been reported in the progression of neurological disorders (Dias *et al*., 2021). This may occur due to the rapid infiltration of inflammatory mediators due to an increase in blood-brain barrier leakage (Kim *et al*., 2012). This may occur due to instant cytokine-cytokine interactions in response to exogenous/endogenous infections. Previously coumarin derivatives have been reported for regulating cytokine signals followed by improvement in cognitive function, which may occur by maintaining the neuronal membrane integrity in response to high-magnitude cytokine signals. Membrane integrity plays an important role in response to metabolic disorders and cell survival. In the present study, among the top 3 lead hits for the pharmacological spectra, we identified two molecules, *i.e.,* 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin, 7-hydroxy-3-(4-methoxyphenyl)-4-propyl-2H-1-benzopyran-2-one, phyllocoumarin. These molecules were screened based on the Pfizer rule of five in which the molecules with positive drug likeness scores were considered for blood-brain barrier permeability. In this regard, 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin showed a drug-likeness score of 0.08 with 0.7004 blood-brain barrier permeability. Similarly, 7-hydroxy-3-(4-methoxyphenyl)-4-propyl-2H-1-benzopyran-2-one showed a drug likeness score of 0.44 with 0.7451 blood-brain barrier permeability. And phyllocoumarin showed a drug likeness score of 0.61 with 0.6198 blood-brain barrier permeability. The present study preliminary screens some coumarin derivatives with a positive drug likeness score, blood-brain barrier permeability, and AMES toxicity, with the possibility as membrane integrity agonist which identified 7-hydroxy-3-(4-methoxyphenyl)-4-methyl coumarin and phyllocoumarin as a lead hit.

## 5. Conclusion

The present study identified 7-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin and phyllocoumarin as membrane integrity agonist that needs to be further evaluated for neurological disorders. However, the study is based on 3 steps of preliminary competition prediction. The study needs to be further designed to evaluate their efficacy in targeting the proteins that are directly involved in neurological disorders. In addition, the findings of the present work will be evaluated using wet lab studies.

## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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