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Research Article

In silico Study of Molecular Properties, Bioactivity, and Toxicity of 2-(Substituted Benzylidene)Succinic Acids and some selected Anti-Inflammatory Drugs

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ABSTRACT

Succinic acid and its derivatives have many important uses, especially in pharmaceutical and polymer industries. The 2-(substituted benzylidene)succinic acids are also known as substituted phenylitaconic acids that are utilized in the synthesis of some lignans, lignanamides, and renin inhibitors. In view of this, the present *in silico* study aimed to calculate the molecular properties, bioactivity score, and toxicity of several benzylidenesuccinic acids, as well as, some selected anti-inflammatory drugs by computational methods. The study revealed that all the compounds obeyed Lipinski's rule of five, indicating drug-likeness properties. The bioactivity data revealed that the 2-(substituted benzylidene)succinic acids were active as nuclear receptor ligands, enzyme inhibitors, G-protein coupled receptors (GPCR) ligands, and ion channel modulators. Among all, 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid was predicted as non-toxic with better *in silico* molecular properties and bioactivity as nuclear receptor ligand, enzyme inhibitor, GPCR ligand, ion channel modulator, and protease inhibitor compared to some of the predicted anti-inflammatory drugs.

Introduction

Succinic acid is the simplest organic dicarboxylic acid recognized as an intermediate in the citric acid cycle. It is primarily used as a food additive, dietary supplement, and as an excipient in pharmaceutical products. It is also used as a precursor for various industrially important starting materials, such as, γ-butyrolactone, tetrahydrofuran, N-methylpyrrolidone, 1,4-butanediol, adipic acid, and linear aliphatic acids. Succinic acid is extensively used in polymer industry as the butanedioic acid-derived polymer is biodegradable in nature.[1,2] Itaconic acid or methylidenesuccinic acid, a succinic acid derivative used as a co-monomer in the production of acrylonitrile butadiene styrene and acrylate latexes with application in paper and architectural coating industry. Some of the itaconic acid derivatives are known to possess anti-influenza activity.[3] Phenylitaconic acid or benzylidenesuccinic acid, a derivative of itaconic acid obtained naturally from *Artemisia argyi*.[4] Further, the literature survey revealed that various substituted phenylitaconic acids or 2-(substituted benzylidene)succinic acids are utilized in the synthesis of some lignans, lignanamides, and renin inhibitors.[5-10]

Discovering or developing a new drug has been considered as an expensive and time-consuming process. Advancing the research for the effective treatment of various diseases depend on the complex financial ecosystem. The estimated time for the development of a new drug and its release into the market was nearly 15 to 25 years. Developing non-toxic drugs having

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greater efficiency and selectivity within short period of time and with less Research and Development (R & D) investments are worrying factors for the growth of the pharmaceutical industry. The use of scientific and technological innovations as a research tool combining multidisciplinary informatics, biotechnology, chemistry, and biology knowledge is essential for optimizing time and reducing cost in the drug design. Thus, the integration of these *in silico* techniques makes it possible to search for new drugs with better pharmacokinetic and toxicological profiles compared to commercially used drugs.[11] Many computer-based software are available through internet, which helps to understand the molecular properties, bioactivity, and toxicity of generated structures. Hence, the present investigation aimed to design and identify bioactive 2-(substituted benzylidene)succinic acids with good pharmacokinetic and safety profile by computational methods. The main objective of the study is to compare the *in silico* molecular properties and toxicity profile of the most bioactive 2-(substituted benzylidene)succinic acid [(E)-2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene) succinic acid] with some selected anti-inflammatory drugs possessing similar substituent fragments.

Materials and Methods

Generation of Molecular Structures and Nomenclature of 2-(Substituted Benzylidene) Succinic Acids

ChemDraw, a powerful chemical drawing tool, became the leading chemically-intelligent solution for multiple disciplines from specialty chemistry to pharmaceutical drug discovery. ChemDraw provides chemists with a rich set of easy to use tools for creating scientifically meaningful drawings of chemical structures and reactions. The software also used to find the nomenclature and stereochemistry of compounds. The chemical structures and nomenclature of some selected benzylidenesuccinic acids were developed using ChemBioDraw Ultra 11.0.

Calculation of Molecular Properties of 2-(Substituted Benzylidene)Succinic Acids and some selected Anti-Inflammatory Drugs

Drug-likeness is a qualitative concept indicated by the molecular properties that affect absorption, distribution, metabolism, and excretion (ADME) of a compound. Molinspiration online molecular property calculation toolkit (http://www.molinspriration.com) was used to evaluate the *in silico* pharmacokinetic properties of 2-(substituted benzylidene)succinic acids and some selected anti-inflammatory drugs based on Lipinski's rule of five. The rule specifies that the molecules with good membrane permeability have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5. Other rules which are important in computational prediction of drug-likeness, include number of rotatable bonds, the molecular volume, and topological polar surface area (TPSA). The number of rotatable bonds indicates conformational flexibility of a compound and ultimately binding with receptors or ion channels. Molecular volume determines transport characteristics of molecules, such as, intestinal absorption or blood-brain barrier penetration. TPSA also recognized as a good indicator of drug absorption in intestine [TPSA < 140 angstroms squared ($Å^2$)] and its penetration through blood-brain barrier (TPSA < 60 $Å^2$). The magnitude of absorption can be expressed by percentage of absorption (% ABS), which can be calculated using equation % ABS = 109 - (0.345 × TPSA).[12]

Calculation of Bioactivity Score of 2-(Substituted Benzylidene)Succinic Acids and some selected Anti-Inflammatory Drugs

Miscreen, a molinspiration virtual screening engine (http://www.molinspiration.com), used to calculate the bioactivity score of 2-(substituted benzylidene)succinic acids and some selected anti-inflammatory drugs. Virtual screening or *in silico* screening utilizes computational chemistry techniques to analyze large chemical databases in order to identify possible new drug candidates. This computational tool is used to find ligands modulating GPCR, ion channels, nuclear receptors, and to identify kinase inhibitors, protease inhibitors, and enzyme inhibitors.

The molinspiration bioactivity tool, miscreen engine first analyzes a training set of active structures and compares it with inactive molecules by using sophisticated Bayesian statistics. The analysis generates a fragment-based model (Bayesian statistical model, table of fragments with their activity contributions) and used to calculate the bioactivity score of screened molecules as sum of activity contribution of fragments in these molecules. For this kind of analysis, only SMILES and SDfile structures of active molecules are necessary but not the information about active site or binding mode. This computational tool is particularly useful in projects where structure-based approach cannot be applied due to unavailability of information about 3D receptor structure. Another advantage of this virtual screening tool is to learn general structural requirements, which are sufficient for the bioactivity and to identify new active structure classes (scaffold hopping).

Prediction of Toxicity of 2-(Substituted Benzylidene)Succinic Acids

Osiris Property Explorer (www.organic-chemistry.org/prog/peo/) an online cheminformatics tool used to determine the toxicity potential of 2-(substituted benzylidene)succinic acids. The *in silico* toxicity properties estimated are mutagenicity, tumorigenicity, irritant, and reproductive effects. The virtual toxicity results are color-coded either in green or red. The toxicity properties

shown in green indicate the molecules are safe and non-toxic. If they are expressed in red, indicates high risk of undesired effects. This computational tool also used to estimate the molecular properties, drug-likeness, and drug score. The molecular properties assessed are ClogP, solubility, molecular weight, and TPSA. The drug-likeness calculated using an equation summing up the score values of those fragments that are present in the molecule under investigation. The overall drug score of molecules estimated with an equation utilizing the values of molecule's drug-likeness, toxicity, ClogP, solubility, and molecular weight.

Results and Discussion

Computer-aided drug design plays a vital role in drug discovery and development and has become an indispensable tool in the pharmaceutical industry. Computational medicinal chemists can take advantage of all kinds of software and resources in computer-aided drug design fields for the purpose of discovering and optimizing biologically active compounds. Optimizing the chemical structure of lead candidates with respect to ADME processes has become an integral part of the current drug discovery process.

In the present research investigation, free online computational programs Molinspiration Cheminformatics and Osiris Property Explorer were used to estimate molecular properties, bioactivity, and toxicity profile of 2-(substituted benzylidene)succinic acids. Initially, the molecular structure and nomenclature of unsubstituted benzylidenesuccinic acid and twelve different 2-(substituted benzylidene)succinic acids were generated using ChemBioDraw Ultra 11.0 and the data presented in Table 1. The general molecular structure of computationally generated 2-(substituted benzylidene) succinic acid shown in Fig. 1. Among the generated structures, seven compounds (2, 4, 8, 10, 11, 12, and 13) are new and not existed or synthesized until now.

The molecular properties of all the generated structures were calculated using Molinspiration Cheminformatics, and the data presented in Table 2. The drug-likeness of all these compounds was evaluated by Lipinski's rule of five that deals with four simple physicochemical parameters (log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5). The log P measurement used to understand the substance solubility behavior and hence, its oral absorption and bioavailability. The *in silico* study revealed that the log P values of all the 2-(substituted benzylidene)succinic acids lie between 0.40 and 4.41 (within acceptable range ≤ 5). All the phenolic substituted benzylidenesuccinic acids have low log P value except compound 13 [(E)-2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid]. The log P value of compound 13 was 4.41, indicating its high lipophilicity or hydrophobicity. Thus, specify better distribution of compound 13 in the body after its absorption. All the 2-(substituted benzylidene)succinic acids have molecular weight within the acceptable range ≤ 500. Low molecular weight compounds are easily absorbed, diffused,

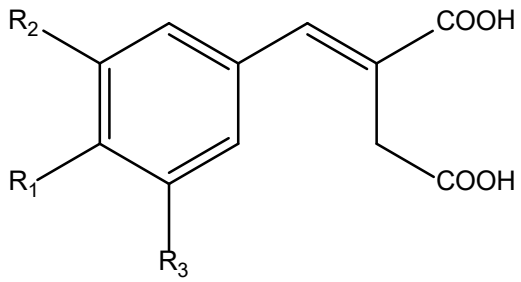

Fig. 1: General structure of 2-(substituted benzylidene)succinic acid

Table 1: Nomenclature and molecular formula of 2-(substituted benzylidene)succinic acids

Compound No.	*Nomenclature*	*Molecular formula*	*R_1*	*R_2*	*R_3*
1	(E)-2-benzylidenesuccinic acid	$C_{11}H_{10}O_4$	H	H	H
2	(E)-2-(4-hydroxybenzylidene)succinic acid	$C_{11}H_{10}O_5$	OH	H	H
3	(E)-2-(4-methoxybenzylidene)succinic acid	$C_{12}H_{12}O_5$	OCH_3	H	H
4	(E)-2-(3,4-dihydroxybenzylidene)succinic acid	$C_{11}H_{10}O_6$	OH	OH	H
5	(E)-2-(4-hydroxy-3methoxybenzylidene)succinic acid	$C_{12}H_{12}O_6$	OH	OCH_3	H
6	(E)-2-(3,4-dimethoxybenzylidene)succinic acid	$C_{13}H_{14}O_6$	OCH_3	OCH_3	H
7	(E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)succinic acid	$C_{12}H_{10}O_6$	-O- CH_2-O-		H
8	(E)-2-(4-hydroxy-3,5-dimethoxybenzylidene)succinic acid	$C_{13}H_{14}O_7$	OH	OCH_3	OCH_3
9	(E)-2-(3,4,5-trimethoxybenzylidene)succinic acid	$C_{14}H_{16}O_7$	OCH_3	OCH_3	OCH_3
10	(E)-2-(4-hydroxy-3,5-dimethylbenzylidene)succinic acid	$C_{13}H_{14}O_5$	OH	CH_3	CH_3
11	(E)-2-(3,5-diethyl-4-hydroxybenzylidene)succinic acid	$C_{15}H_{18}O_5$	OH	C_2H_5	C_2H_5
12	(E)-2-(4-hydroxy-3,5-diisopropylbenzylidene)succinic acid	$C_{17}H_{22}O_5$	OH	$CH(CH_3)_2$	$CH(CH_3)_2$
13	(E)-2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid	$C_{19}H_{26}O_5$	OH	$C(CH_3)_3$	$C(CH_3)_3$

Table 2: Molecular properties of 2-(substituted benzylidene)succinic acids

Compound	*milog P*	*M. wt*	*HBA*	*HBD*	*Volume*	*n violations*	*n rotb*	*TPSA*	*% ABS*
1	1.36	206.2	4	2	182.26	0	4	74.6	83.26
2	0.89	222.2	5	3	190.28	0	4	94.83	76.28
3	1.42	236.22	5	2	207.81	0	5	83.83	80.08
4	0.4	238.19	6	4	198.3	0	4	115.05	69.31
5	0.7	252.22	6	3	215.83	0	5	104.06	73.1
6	1.01	266.25	6	2	233.36	0	6	93.07	76.9
7	1.25	250.21	6	2	206.19	0	4	93.07	76.9
8	0.72	282.25	7	3	241.37	0	6	113.29	69.91
9	0.99	296.27	7	2	258.9	0	7	102.3	73.71
10	1.90	250.25	5	3	223.4	0	4	94.83	76.28
11	2.83	278.3	5	3	257.01	0	6	94.83	76.28
12	3.08	306.36	5	3	290.18	0	6	94.83	76.28
13	4.41	334.41	5	3	322.66	0	6	94.83	76.28
BHT	5.43	220.36	1	1	241	1	2	20.23	102.02
SA	-0.66	118.09	4	2	100.24	0	3	74.60	83.26
Darbufelone	4.18	332.47	4	3	312.82	0	3	76.94	82.46
Prifelone	6.34	316.47	2	1	305.54	1	4	37.3	96.13
Tazofelone	4.63	321.49	3	2	313.54	0	4	49.33	91.98
Tebufelone	5.71	300.44	2	1	316.08	1	6	37.3	96.13

Table 3: Bioactivity score of 2-(substituted benzylidene)succinic acids

Compound	*GPCR ligand*	*Ion channel modulator*	*Kinase inhibitor*	*Nuclear receptor ligand*	*Protease inhibitor*	*Enzyme inhibitor*
1	-0.1	0.07	-0.73	-0.04	-0.42	0.23
2	0.01	0.14	-0.56	0.22	-0.34	0.32
3	-0.04	0	-0.57	0.09	-0.34	0.21
4	0.05	0.12	-0.49	0.23	-0.3	0.33
5	0.03	0.03	-0.43	0.18	-0.33	0.27
6	0.04	-0.02	-0.4	0.16	-0.24	0.23
7	0.06	-0.02	-0.51	0.06	-0.27	0.25
8	0.09	0.03	-0.28	0.23	-0.18	0.31
9	0.1	-0.02	-0.27	0.15	-0.15	0.23
10	0.05	0.05	-0.45	0.31	-0.24	0.3
11	0.2	0.14	-0.36	0.42	-0.07	0.37
12	0.22	0.11	-0.3	0.47	-0.02	0.34
13	0.26	0.18	-0.19	0.53	0.04	0.35
BHT	-0.34	0	-0.48	-0.08	-0.57	-0.07
SA	-2.74	-2.45	-3.37	-2.68	-2.76	-2.38
Darbufelone	-0.33	-0.5	-0.05	-0.53	-0.48	-0.03
Prifelone	0.01	0.01	-0.02	0.25	-0.25	0.07
Tazofelone	0.07	-0.28	-0.57	0.2	0.01	-0.02
Tebufelone	0.16	0.28	-0.16	0.45	0.05	0.41

and transported as compared to compounds with high molecular weight greater than 500.[13] The 2-(substituted benzylidene)succinic acids also possess an adequate number of hydrogen bond acceptors and hydrogen-bond donors, ensuring efficient interaction with hydrogen bonding groups of an intractable receptor. The number of rotatable bonds explains the flexibility and conformational changes of molecules for binding to the receptors. It has been accepted that the number of rotatable bonds should be ≤ 10 to pass the oral bioavailability.[14] All the predicted compounds possess 4 to 7 rotatable bonds and, therefore, exhibit optimum conformational flexibility. TPSA is a very useful physicochemical parameter of molecules that gives information about the polarity of compounds. It is used to predict the transport properties of compounds, such as, intestinal absorption and blood-brain barrier penetration.[15] It was observed that the TPSA values of all the predicted molecules were found between 74.60 and 115.05. Using these values, % ABS were calculated and presented in Table 2. The data indicated that the benzylidenesuccinic acid and various 2-(substituted benzylidene)succinic acids exhibited good percent absorption ranging from 69.31 to 83.26. Furthermore, none of the 2-(substituted benzylidene) succinic acids violated Lipinski's parameters, making them promising drug-like molecules.

The bioactivity scores of the 2-(substituted benzylidene) succinic acids were calculated by Molinspiration Cheminformatics software and the data presented in Table 3. The bioactivity score gives information about the binding cascade of the molecules with different protein

Table 4: Toxicity and risk assessment of substituted benzylidenesuccinic acids using osiris property explorer

Compound No.	*Toxicity and risk*	*ClogP*	*Solubility*	*Molecular weight*	*TPSA*	*Drug likeness*	*Drug score*
1	Safe	1.26	-1.87	206	74.6	-0.69	0.64
2	Reproductive effect	0.91	-1.57	222	94.83	0.64	0.48
3	Reproductive effect	1.19	-1.89	236	83.83	0.76	0.48
4	Safe	0.57	-1.28	238	115	1.5	0.87
5	Safe	0.84	-1.59	252	104	1.14	0.84
6	Reproductive effect	1.12	-1.9	266	93.06	2.82	0.55
7	Safe	1.37	-2.58	250	93.06	0.73	0.77
8	Safe	0.77	-1.16	282	113.2	1.84	0.88
9	Reproductive effect	1.05	-1.92	296	102.2	3.94	0.55
10	Safe	1.6	-2.26	250	94.83	-4.03	0.47
11	Mutagenic	2.43	-2.26	278	94.83	-4.76	0.27
12	Safe	3.29	-3.31	306	94.83	-9.14	0.41
13	Safe	4.08	-3.89	334	94.83	-15.08	0.35

structures, and it is used for the identification of new functional drugs with increased binding selectivity profile and less undesirable effects. It is well documented that, if bioactivity score is more than 0, the molecules have better biological activity. If bioactivity score is -0.5 to 0, the molecules have moderate activity, and less than -0.5, the molecules have no biological activity.[16] The results of bioactivity data indicated that all the benzylidenesuccinic acids were highly active as enzyme inhibitors, nuclear receptor ligands, ion channel modulators, GPCR ligands, and moderately active as protease inhibitors. Only some compounds were predicted as moderately active kinase inhibitors, and few compounds (1, 2, 3, and 7) were inactive as kinase inhibitors. Among all the 2-(substituted benzylidene)succinic acids, the phenolic derivative exhibited greater bioactivity score as enzyme inhibitors and nuclear receptor ligands. The bioactivity data revealed that the modification of the phenolic hydroxyl group to methoxy group cause reduction in their bioactivity score. Introduction of electron releasing alkyl substituents ortho to phenolic hydroxyl group (compounds 10, 11, 12, and 13) increased their bioactivity score as nuclear receptor ligands, but does not show much variation as enzyme inhibitors.

The calculated bioactivity data revealed that the (E)-2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid (compound 13) was excellent nuclear receptor ligand, enzyme inhibitor, and GPCR ligand with highest bioactivity score 0.53, 0.35, and 0.26, respectively. The data also indicated that compound 13 was a good ion channel modulator and protease inhibitor with bioactivity score of 0.18 and 0.04, respectively. The greater bioactivity score of compound 13 was attributed to its high log P value, molecular volume, and also due to its good TPSA and % ABS values. This observation was supported by previous reports, the anti-inflammatory activity and quantitative structure activity relationship (QSAR) study of substituted 3,5-di-*tert*-butyl-4-hydroxystyrene.[17,18] Therefore, the molecular properties and bioactivity score of compound 13 was compared with its structural components, butylated hydroxytoluene (BHT), and succinic acid. The compared results revealed that compound 13 obeyed all the Lipinski's rules with zero number of violations and possess much greater bioactivity score than the antioxidant BHT and succinic acid. The better bioactivity of compound 13 was attributed to its higher number of rotatable bonds, number of hydrogen bond acceptors, and number of hydrogen bond donors responsible for conformational flexibility and receptor interaction when compared with BHT and succinic acid.

The better molecular properties and bioactivity score exhibited by (E)-2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid gave an impetus to estimate and compare the molecular properties and bioactivity score of some selected anti-inflammatory drugs, such as, darbufelone, prifelone, tazofelone, and tebufelone possessing similar structural fragment 3,5-di-*tert*-butyl-4-hydroxyphenyl ring. The generated *in silico* data presented in Tables 1 and 2. The data revealed that the above anti-inflammatory drugs obeyed Lipinski's rule of five, as it states that an orally active drug generally has no more than one violation.[19] The calculated TPSA and % ABS values of these drugs indicated good oral bioavailability. The bioactivity data revealed that the 2-(substituted benzylidene)succinic acids showed higher bioactivity scores as enzyme inhibitors than the darbufelone, prifelone, and tazolfelone, but showed lower bioactivity than tebufelone. The scores of 2-(substituted benzylidene)succinic acids range from 0.21 to 0.37 depending upon the substituents they possess. The unsubstituted benzylidenesuccinic acid also possesses good bioactivity score than the darbufelone, prifelone, and tazofelone. This observation may indicate the importance of phenylitaconic acid structure to exhibit enzyme inhibition. The estimated bioactivity score of phenolic benzylidenesuccinic acids as nuclear receptor ligands was good and appeared almost equipotent or more potent with the evaluated anti-inflammatory drugs except for darbufelone. It is observed that the bioactivity score as nuclear receptor ligands increased when phenolic benzylidenesuccinic acids substituted with one or two electron releasing substituents ortho to phenolic

hydroxyl group. The other substituted benzylidenesuccinic acids also exhibited good bioactivity scores as nuclear receptor ligands (> 0). These observations indicating the importance of not only the phenolic group, but also the other electron releasing substituents present on the benzylidenesuccnic acid.

The bioactivity prediction revealed that the prifelone, tazofelone, and tebufelone were active as GPCR ligands, but the scores were less than compounds 11, 12, and 13. The benzylidenesuccinic acid and phenolic benzylidenesuccinic acids were active as ion channel modulators, the bioactivity scores of these compounds were greater than the prifelone and lesser than the tebufelone. The bioactivity data revealed that the predicted anti-inflammatory drugs were either moderately active or inactive kinase inhibitors. The study also revealed that tazofelone, tebufelone, and compound 13 were active as protease inhibitors, indicating the importance of 3,5-di-*tert*-butyl-4-hydroxyphenyl ring system.

The toxicity of 2-(substituted benzylidene)succinic acids was assessed using Osiris Property Explorer and the data presented in Table 4. This computational tool also used to calculate ClogP, solubility, molecular weight, TPSA, drug-likeness, and drug score. The study revealed that the unsubstituted benzylidenesuccinic acid and the phenolic compounds were predicted as safe and non-toxic except compounds 2 and 11. The nonphenolic derivatives (compounds 3, 6, and 9) were predicted to possess toxic reproductive effects, whereas compound 7 was identified as safe and non-toxic molecule. The calculated ClogP values of all the benzylidenesuccinic acid were similar to that of milog P values. TPSA calculation performed by this software was found same as that of Molinspiration Cheminformatic software. The calculated drug-likeness was positive only for compounds 2 to 9. The calculated drug scores, based on ClogP, solubility, molecular weight, drug-likeness, and toxicity risks, greatly varied due to the substituents on benyzlidenesuccinic acid.

Conclusions

The *in silico* study concluded that all the 2-(substituted benzylidene)succinic acids were drug-like molecules as they satisfy Lipinski's rule. The bioactivity results indicated that these compounds were identified as better enzyme inhibitors, nuclear receptor ligands, and good GPCR ligands and Ion channel modulators. Among all, 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid (compound 13) appeared as the most potent bioactive and non-toxic molecule compared to its structural components BHT and succinic acid. This observation specifies the importance of phenylitaconic acid or benzylidenesuccinic acid structure with 3,5-di-*tert*-butyl-4-hydroxy group. Therefore, an effort has been made to compare the molecular properties and bioactivity score of 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene) succinic acid with some selected anti-inflammatory drugs, darbufelone, prifelone, tazofelone, and tebufelone, which contain the structural fragment 3,5-di-*tert*-butyl-4-hydroxyphenyl ring. The study indicated that the 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid has better *in silico* molecular properties and bioactivity score as nuclear receptor ligand and GPCR ligand than darbufelone, prifelone, tazofelone, and tebufelone. The study also indicated that the 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)succinic acid has improved bioactivity as enzyme inhibitor than darbufelone, prifelone, and tazofelone. Hence, further research is required to synthesize and evaluate the toxic and pharmacological properties of 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene) succinic acid using appropriate procedures.

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