Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 2 Issue 10 October 2021

Research Article

A Novel Anticancer Organic Drug Based on the Natural Product Synthesis

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Received: August 26, 2021

Published: September 18, 2021

Abstract

Despite the outstanding ongoing research on anticancer activity the limited availability from the natural resources has barred drug discovery in researchers. The present work has been carried in achieving 99 percent pure synthesized chalcone derivative (2E)-1-(4-aminophenyl)-3-(4-benzyloxyphenyl)-prop-2-en-1-one (APBPP) with simple, cost effective method under room temperature conditions. As per the unique results obtained APBPP significantly augment anticancer effects theoretically.

Keywords: DFT; Chalcones; Anticancer; Docking

Introduction

The past few decades have seen a rapid rise in cancer research, particularly in chemicals which exhibit proactive and degenerative biological behavior when interacting with cancerous tissues. Chalcones have proven to be a very promising class of chemicals in such research. Chalcones are polyphenolic, plant-derived compounds belonging to the flavonoid family, they are aromatic ketones and enones and have shown promising antineoplastic properties on inspections through infrared spectroscopy and DFT calculations [1]. The chalconoid Butein which can be found in Toxicodendron vernicifluum, Dahlia, Butea and Coreopsis has displayed antioxidative and anti-cancer properties, it has also displayed a high ability to inhibit and/or control aromatase process in the human body and hence its effects of breast cancer and estrogen production are being thoroughly studied [2]. In addition, the apigenin falvone glucoside Vitexin found in the passion flower, Vitex agnus castus (Chaste tree) and bamboo (Phyllostachys nigra) has displayed anti-tumor and degenerative properties when dealing with cancerous cells and the chemical 2,4 dihydroxychalcone [3] isolated from Herba oxytropis has displayed a high pro-apoptosis properties inducing large scale cell death when interacting with cancer cells and has been studied widely as a potential treatment for prostate cancer. In this study we aim to compile research data regarding the biological and pharmacological activities of the chalcone (2E)-1-(4-aminophenyl)-3-(4-benzyloxyphenyl)-prop-2-en-1-one (APBPP) and to reach a scientifically viable statistical conclusion about their general effectiveness in cancer treatment and therapy.

Experimental procedure

The title compound was synthesised by Claisenschmidt condensation reaction method. And the reported procedure is as follows : In a 250 ml beaker the sample was stirred well for re-crystallization with cost effective solvent ethanol and was kept for drying [4].

Computational details

The structure of the compound was optimised using B3LYP/6-31++G(d,p) level of theory with Gaussian 09 software [5] and Mercury crystal structure visualisation (3.8) software. The compound was virtually analysed using Auto dock tools [6] to investigate the pharmaceutical nature of the title compound.

Results and Discussion

Computational geometry

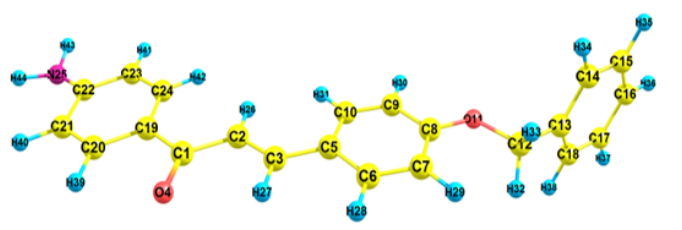

Figure 1: Optimized geometric structure of APBPP.

The B3LYP optimised structure using B3LYP/6-31++G(d,p) basis set is presented in Fig 1. The x,y,z planes shows identity and the 1/2 -x, 1/2 +y, 1/2-z planes shows screw fold (2-axis) symmetry with direction [0,1,0] at 1/4,y, 1/4 with screw component [0,1/2,0]. The compound exhibits inversion at [0,0,0] in -x,-y,-z directions. A maximum torsion angle of 179° A is observed at C1,C5,C7,C12,C13,C17,C20,H6,H11 and H12atoms and is shown in table 1. The experimental and theoretical bond length and bond angles are in good agreement with each other [7].

Number	Atom1	Atom2	Atom3	Atom4	Torsion
1	C6	C1	C2	H2	-179.7
2	C6	C1	C2	C3	0.3(5)
3	N1	C1	C2	H2	1
4	N1	C1	C2	C3	-179.0(3)
5	C2	C1	C6	C5	0.2(5)
6	C2	C1	C6	H6	-179.8
7	N1	C1	C6	C5	179.5(4)
8	N1	C1	C6	H6	-0.5
9	C2	C1	N1	H1B	-12(3)
10	C2	C1	N1	H1A	-173(4)
11	C6	C1	N1	H1B	168(3)
12	C6	C1	N1	H1A	8(4)
13	C1	C2	C3	H3	-179.9
14	C1	C2	C3	C4	0.2(5)
15	H2	C2	C3	H3	0.1
16	H2	C2	C3	C4	-179.9
17	C2	C3	C4	C5	-1.1(4)
18	C2	C3	C4	C7	179.1(3)
19	H3	C3	C4	C5	179
20	H3	C3	C4	C7	-0.9
21	C3	C4	C5	H5	-178.4
22	C3	C4	C5	C6	1.5(4)
23	C7	C4	C5	H5	1.4
24	C7	C4	C5	C6	-178.6(3)
25	C3	C4	C7	C8	-172.4(3)
26	C3	C4	C7	O1	5.6(4)
27	C5	C4	C7	C8	7.8(4)
28	C5	C4	C7	O1	-174.2(3)
29	C4	C5	C6	C1	-1.2(5)
30	C4	C5	C6	H6	178.8
31	H5	C5	C6	C1	178.8
32	H5	C5	C6	H6	-1.2
33	C4	C7	C8	H8	-17.3
34	C4	C7	C8	C9	162.7(3)
35	O1	C7	C8	H8	164.7
36	O1	C7	C8	C9	-15.4(5)
37	C7	C8	C9	H9	2.4
38	C7	C8	C9	C10	-177.7(3)
39	H8	C8	C9	H9	-177.7
40	H8	C8	C9	C10	2.2
41	C8	C9	C10	C11	-3.7(5)
42	C8	C9	C10	C15	175.3(3)
43	H9	C9	C10	C11	176.2
44	H9	C9	C10	C15	-4.8
45	C9	C10	C11	H11	-2.1
46	C9	C10	C11	C12	177.8(3)
47	C15	C10	C11	H11	178.9
48	C15	C10	C11	C12	-1.2(5)
49	C9	C10	C15	C14	-178.2(3)
50	C9	C10	C15	H15	1.8
51	C11	C10	C15	C14	0.9(5)
52	C11	C10	C15	H15	-179.2
53	C10	C11	C12	H12	179.9
54	C10	C11	C12	C13	-0.1(6)
55	H11	C11	C12	H12	-0.1
56	H11	C11	C12	C13	179.8
57	C11	C12	C13	C14	1.7(5)
58	C11	C12	C13	O2	-172.0(4)
59	H12	C12	C13	C14	-178.3
60	H12	C12	C13	O2	8
61	C12	C13	C14	H14	178.1
62	C12	C13	C14	C15	-2.0(5)
63	O2	C13	C14	H14	-9.7
64	O2	C13	C14	C15	170.3(4)
65	C12	C13	O2	C16	-179.3(4)
66	C14	C13	O2	C16	7.8(7)
67	C13	C14	C15	C10	0.7(5)
68	C13	C14	C15	H15	-179.3
69	H14	C14	C15	C10	-179.3
70	H14	C14	C15	H15	0.7
71	C13	O2	C16	H16A	58.5

72	C13	O2	C16	H16B	-60.2
73	C13	O2	C16	C17	179.1(5)
74	O2	C16	C17	C18	-38.2(8)
75	O2	C16	C17	C22	142.2(8)
76	H16A	C16	C17	C18	82.2
77	H16A	C16	C17	C22	-97.3
78	H16B	C16	C17	C18	-159
79	H16B	C16	C17	C22	21
80	C16	C17	C18	H18	4
81	C16	C17	C18	C19	-176.4(7)
82	C22	C17	C18	H18	-176.7
83	C22	C17	C18	C19	3(1)
84	C16	C17	C22	C21	176.4(8)
85	C16	C17	C22	H22	-4
86	C18	C17	C22	C21	-3(1)
87	C18	C17	C22	H22	176.8
88	C17	C18	C19	H19	179.6
89	C17	C18	C19	C20	-0(1)
90	H18	C18	C19	H19	0

Number	Atom1	Atom2	Atom3	Atom4	Torsion
91	H18	C18	C19	C20	179.6
92	C18	C19	C20	H20	177
93	C18	C19	C20	C21	-3(2)
94	H19	C19	C20	H20	-3
95	H19	C19	C20	C21	177
96	C19	C20	C21	H21	-177
97	C19	C20	C21	C22	3(2)
98	H20	C20	C21	H21	3
99	H20	C20	C21	C22	-177
100	C20	C21	C22	C17	0(1)
101	C20	C21	C22	H22	-180
102	H21	C21	C22	C17	-179.7
103	H21	C21	C22	H22	0
104	C28	C23	C24	H24	-179.9
105	C28	C23	C24	C25	0.2(4)
106	N2	C23	C24	H24	-1.9
107	N2	C23	C24	C25	178.2(3)
108	C24	C23	C28	C27	0.4(4)
109	C24	C23	C28	H28	-179.7
110	N2	C23	C28	C27	-177.7(3)
111	N2	C23	C28	H28	2.3
112	C24	C23	N2	H2B	170(3)
113	C24	C23	N2	H2A	13(3)
114	C28	C23	N2	H2B	-12(3)
115	C28	C23	N2	H2A	-169(3)
116	C23	C24	C25	H25	-179.8
117	C23	C24	C25	C26	0.1(4)
118	H24	C24	C25	H25	0.2
119	H24	C24	C25	C26	-179.8
120	C24	C25	C26	C27	-0.9(4)
121	C24	C25	C26	C29	179.7(2)
122	H25	C25	C26	C27	179
123	H25	C25	C26	C29	-0.4
124	C25	C26	C27	H27	-178.5
125	C25	C26	C27	C28	1.5(4)
126	C29	C26	C27	H27	0.9
127	C29	C26	C27	C28	-179.1(2)
128	C25	C26	C29	C30	164.7(2)
129	C25	C26	C29	O3	-12.8(4)
130	C27	C26	C29	C30	-14.6(4)
131	C27	C26	C29	O3	167.8(3)
132	C26	C27	C28	C23	-1.2(4)
133	C26	C27	C28	H28	178.8
134	H27	C27	C28	C23	178.8
135	H27	C27	C28	H28	-1.2
136	C26	C29	C30	H30	14.7
137	C26	C29	C30	C31	-165.3(2)
138	O3	C29	C30	H30	-167.8
139	O3	C29	C30	C31	12.2(4)
140	C29	C30	C31	H31	-1.3
141	C29	C30	C31	C32	178.7(2)
142	H30	C30	C31	H31	178.7
143	H30	C30	C31	C32	-1.3
144	C30	C31	C32	C33	-165.2(3)
145	C30	C31	C32	C37	15.2(4)
146	H31	C31	C32	C33	14.8
147	H31	C31	C32	C37	-164.8
148	C31	C32	C33	H33	0.4
149	C31	C32	C33	C34	-179.6(2)
150	C37	C32	C33	H33	-179.9
151	C37	C32	C33	C34	0.0(4)
152	C31	C32	C37	C36	178.6(2)
153	C31	C32	C37	H37	-1.4
154	C33	C32	C37	C36	-1.1(4)
155	C33	C32	C37	H37	179
156	C32	C33	C34	H34	-178.9
157	C32	C33	C34	C35	1.1(4)
158	H33	C33	C34	H34	1.1
159	H33	C33	C34	C35	-179
160	C33	C34	C35	C36	-1.1(4)
161	C33	C34	C35	O4	177.5(2)
162	H34	C34	C35	C36	178.8
163	H34	C34	C35	O4	-2.5
164	C34	C35	C36	H36	-180
165	C34	C35	C36	C37	0.1(4)
166	O4	C35	C36	H36	1.3
167	O4	C35	C36	C37	-178.7(2)

Number	Atom1	Atom2	Atom3	Atom4	Torsion
168	C34	C35	O4	C38	5.8(4)
169	C36	C35	O4	C38	-175.5(2)
170	C35	C36	C37	C32	1.0(4)
171	C35	C36	C37	H37	-179
172	H36	C36	C37	C32	-178.9
173	H36	C36	C37	H37	1
174	H38A	C38	C39	C40	-65.7
175	H38A	C38	C39	C44	115.8
176	H38B	C38	C39	C40	52.8
177	H38B	C38	C39	C44	-125.7
178	O4	C38	C39	C40	173.5(3)
179	O4	C38	C39	C44	-5.0(4)
180	H38A	C38	O4	C35	66.3
181	H38B	C38	O4	C35	-52.3
182	C39	C38	O4	C35	-173.0(2)
183	C38	C39	C40	H40	1.5
184	C38	C39	C40	C41	-178.5(3)
185	C44	C39	C40	H40	-179.9
186	C44	C39	C40	C41	0.1(5)
187	C38	C39	C44	C43	178.3(3)
188	C38	C39	C44	H44	-1.7
189	C40	C39	C44	C43	-0.2(5)
190	C40	C39	C44	H44	179.8
191	C39	C40	C41	H41	179.4
192	C39	C40	C41	C42	-0.7(5)
193	H40	C40	C41	H41	-0.7
194	H40	C40	C41	C42	179.3
195	C40	C41	C42	H42	-178.8
196	C40	C41	C42	C43	1.3(6)
197	H41	C41	C42	H42	1.2
198	H41	C41	C42	C43	-178.8
199	C41	C42	C43	H43	178.6
200	C41	C42	C43	C44	-1.3(5)
201	H42	C42	C43	H43	-1.4
202	H42	C42	C43	C44	178.7
203	C42	C43	C44	C39	0.8(5)
204	C42	C43	C44	H44	-179.2
205	H43	C43	C44	C39	-179.1
206	H43	C43	C44	H44	0.9

Table 1: Torsion angles of APBPP.

Molecular docking

Molecular docking was done to predict the best binding conformation of ligand to a macromolecule. Here in the best pose ligands for four different cancer were selected from their lowest binding energy and presented [8]. The crystal structure of 5JMS (Liver cancer) [9], 5W2L (Bone cancer) [10], 6DYV (stomach cancer) [11], 6LU4(Breast cancer) [12] were derived from RCSB Protien data bank. All the water, co-crystallized inhibitors and interacting ions were removed and polar hydrogens were added also the charges namely Kollman and Gasteiger were obtained to examine the PDBQT files. Using Grid box centres were confirmed in Autodock tools. The title chalcone acts as ligand and the docking were done to various types of cancer proteins of which the best conformations are only presented in this study. The APBPP molecule in comparison with the approved drug Erlotinib is tabulated. From the Table 2 it was observed that the binding energy of APBPP is comparable with Erlotinib and hence could be of use clinically. The structure of the standard drug was obtained from Drug bank database. The ligand with torsion information was added and saved as PDBQT file. The synthesized chalcone binds tightly into the inhibition sites of all types of cancer and is comparable with that of the approved drug Erlotinib. These results portray the pharmocopore nature of the title compound to be a suitable drug for various types of Liver, Bone, stomach and Breast cancer treatment. This work can be further extended with experimental analysis to validate theoretical results.

Protein PDB	Bonded residue	Hydrogen bonds	Binding Energy (Kcal/mol)	Inhibition-constant (μ mol)
5JMS	ARG30, LIG1:H	2	-5.83	151.76
5W2L	PHE80, GLU80	2	-3.57	2.42mMol
6DYV	CY52:H, GLY3:H	2	-4.22	800.04
6LU4	GLY227, LIG1:H, LEU225	3	-4.93	242.78
Erlotinib (Drug)	LEU654, GLY678 GLY684, THR759	4	-7.11	2.67mMol

Table 2: Docking parameters of APBPP.

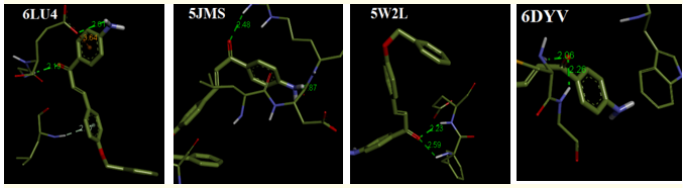

Figure 2: Docking conformations of APBPP.

Conclusion

Cancer active pharmocopore was synthesized using simple Claisen-Schmidt method. The synthesis of the title compound is easily scalable for large scale manufacture, biocompatible and economically feasible. The present study explores the wide potent anticancer activity of the title compound with molecular docking studies and compared with standard drug using Auto dock tools. The results observed showcases the title chalcone as an effective anticancer drug in pharmaceutical industry with minimal side effects as the product is of organic nature. Hence this work paves way for the researchers to confine their drug design according to their need in anticancer therapy by modifying the positioning of functional groups in the title compound.

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