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Synthesis, Molecular Docking, and Biological Evaluation of Some New Naphthalene-Chalcone Derivatives as Potential Anticancer Agent on MCF-7 Cell Line by MTT Assay

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ABSTRACT

Naphthalene chalcones (**3a-i**) with excellent yields were achieved through the use of aromatic ketones, 1-naphthaldehyde, and aqueous NaOH in the synthesis process. The synthesized chalcones were bio-evaluated as potential tubulin polymerization inhibitors for the treatment of breast cancer. The antiproliferative potential of each synthesized compound against the MCF-7 cell line was assessed. The majority of the compounds showed strong antiproliferative properties. With an IC_{50} value of 222.72 µg/mL, compound **3f** exhibited the most antiproliferative activity among them, surpassing that of 5FU (IC_{50}, 51.47 µg/mL).

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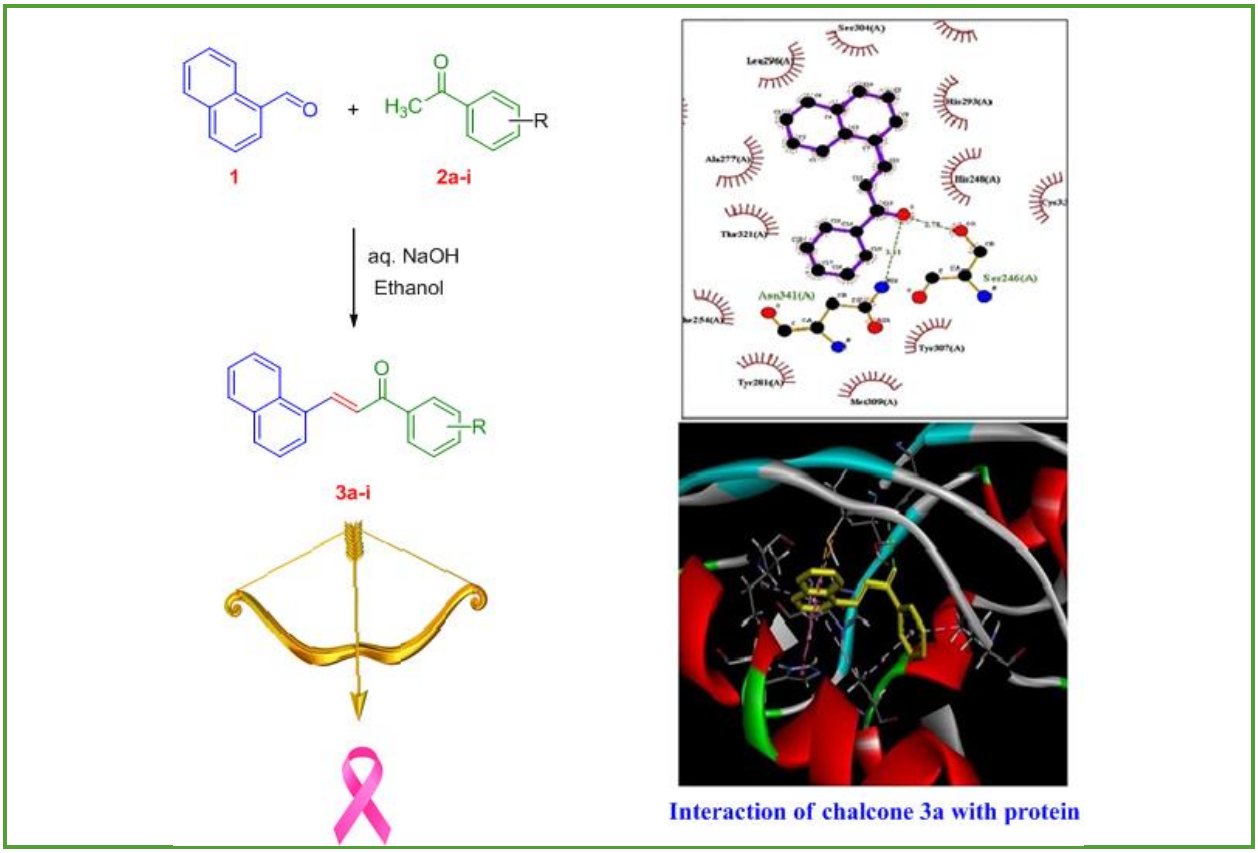
Graphical Abstract



Introduction

Chalcones are important biologically active compounds [1, 2] and important synthons used to synthesize number of biologically active compounds (Scheme 1) as like pyrazolines, pyrrolyl, etc. Pyrazolines and derivatives [3] show biological activity as like anticonvulsant activity [4], antibacterial [5], anti-inflammatory [6], antifungal [7], antidepressant activity [8], antiamoebic [9], antituberculosis, antihyperglycemic, antimalarial, antileishmanial, and anticancer [10]. Six pyrrolyl derivatives show anti-inflammatory activity, anti-proteolytic activity, and also act as promising pleiotropic bioactive molecule [11].

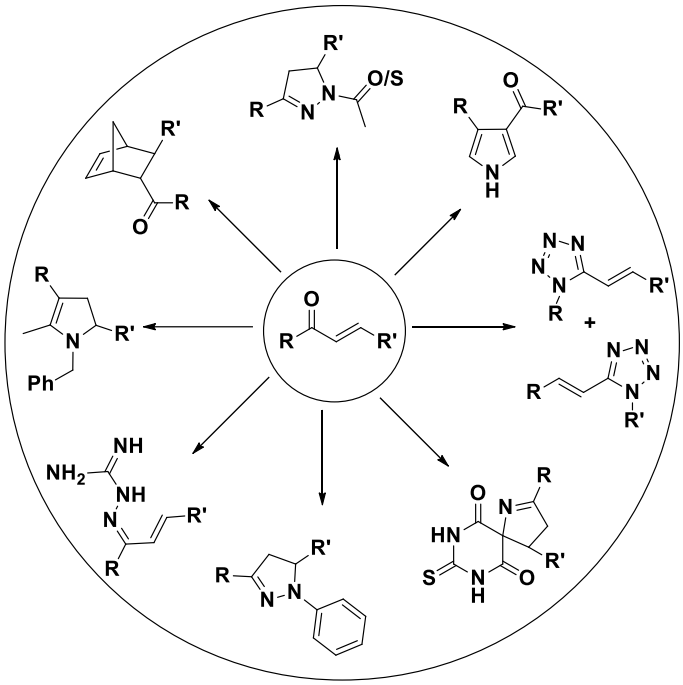
Pyrazoline derivatives containing naphthalene exhibited the most anti-EGFR and anti-A549 human lung cancer cell line activities [12]. Guanidine derivatives act as potential antiproliferative and antitubulin polymerization inhibitors [13]. Ibrahim *et al.* showed path to find biologically active compounds by structure-based identification [14]. It is well known that introduction of heterocyclic moieties in compound leads to biological activity e.g., anticancer activity in pyrrolo[2,3-b]pyridine derivatives [15], thiohydantoin derivatives [16], pyrimidine derivatives [17], etc. Metal complexes of 2-hydroxychalcones had shown good antioxidant and antimicrobial activity [18].

Chalcones are versatile starting materials for many of heterocyclic compounds [19, 20]. Thus, chalcones are one of the most important compounds in medicinal chemistry and can be

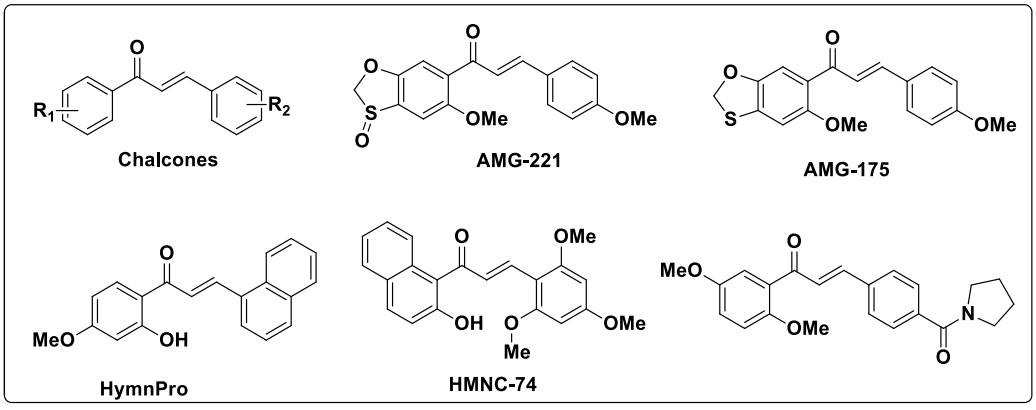
prepared using a simple but important reaction, i.e. Aldol condensation reaction.

The literature review reveals that chalcones have strong anticancer effects on various cancer cell lines [21-26]. By inhibiting tubulin polymerization, several artificial and natural chalcones shown strong anticancer efficacy against numerous cancer cell lines [22, 23, 27].

2-Hydroxy-4-methoxy-2',3'-benzochalcone (HymnPro, Scheme 2), which Shin and co-workers synthesized, has been shown to have antiproliferative activity in multiple human solid tumor cell lines and to inhibit the growth of xenografted tumors in nude mice [28]. The synthesis of 2'-hydroxy 5',6'-naphthochalcone derivatives was reported by Lee *et al.* [25]. Of these compounds, HMNC-74 (Scheme 2) has a potent inhibitory effect on the colon cancer cells SW620's ability to proliferate. Furthermore, it was shown that various substituents on the aromatic rings of chalcone might significantly alter the compounds' anticancer properties.



Scheme 1. Chalcones-source of bioactive compounds



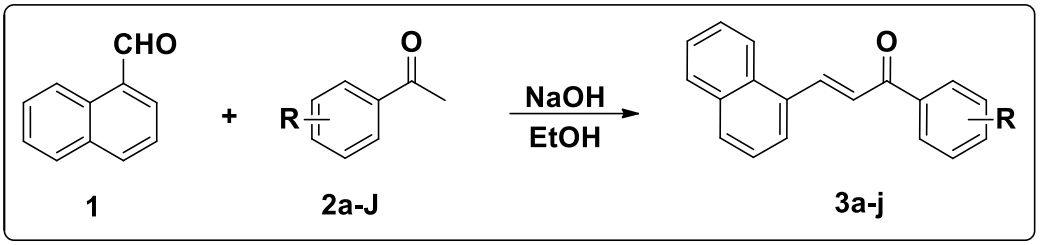
Scheme 2. Structures of some chalcones with anticancer activity

There is still plenty of room to create new chalcones with higher biological activity and investigate them, even if a number of chalcones have been synthesized and investigated for biological activities, including anticancer activity. Thus, we decided to synthesize naphthalene-chalcone derivatives and evaluate them for their anticancer activity.

Results and discussion

Chemistry

Naphthalene-chalcone derivatives **3a-i** was prepared by condensing 1-Naphthaldehyde with different aromatic ketones using aqueous sodium hydroxide (Scheme 3). Structures of ketone and product chalcone were given in Table 1 along with useful information as like absorbance, concentration, % inhibition and IC_{50} values.



Scheme 3. Synthesis of naphthalene-chalcones **3a-i**

To synthesize different substituted chalcones, 1-Naphthaldehyde (1eq.) was treated with different ketones (1 eq.) using NaOH (1 eq.) as base in ethanol. After completion of reaction (TLC monitoring), to obtain a crude solid material, ethanol was evaporated using a rotary evaporator at a lower pressure, and then small amount of water was added and extracted with ethyl acetate. Combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to get crude product. The product obtained was further purified by recrystallization.

Biological activity

MTT assay

The *in vitro* tetrazolium-based colorimetric test (MTT) is a quick technique based on the way mitochondrial enzymes in metabolically active cells cleave a yellow tetrazolium salt into purple formazan crystals [29].

The antiproliferative activity of all freshly synthesized compounds **3a-i** was assessed against MCF-7 cell lines of human breast cancer using the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, with 5FU serving as the standard medication. The IC_{50} (µg/ml) values (half maximal inhibitory concentration) of the tested compounds **3a-i** and the standard drug 5FU are listed in Table 1.

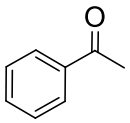
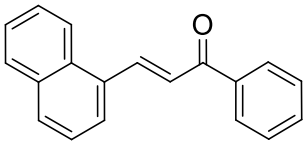
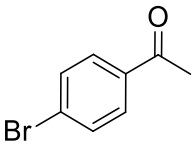
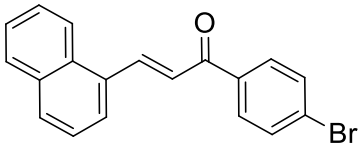
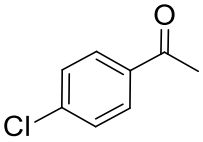
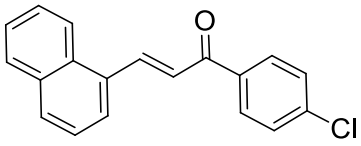
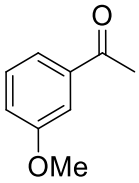
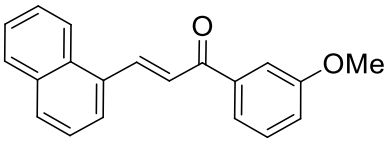
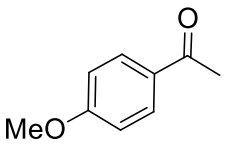
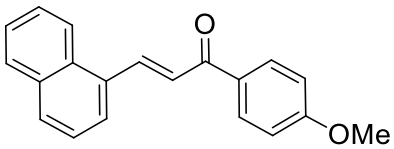
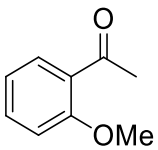
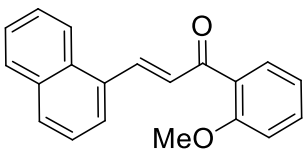
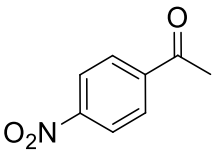
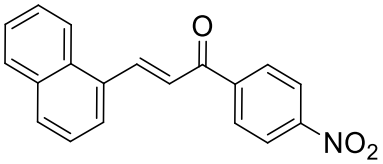
Experimental procedure

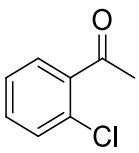
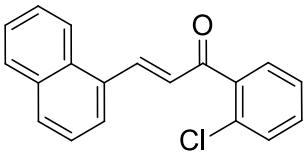
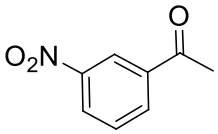
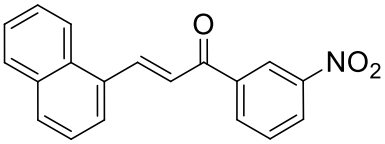
(1) The cells were cultured in culture media for 24 hours at 37 °C and 5% CO_2 at a concentration of 1×10^4 cells/mL.

(2) In micro plates (tissue culture grade, with 96 wells), cells were seeded at a density of 104 cells/well in 100 µl culture media and 100 µl of sample **3a-j** at a concentration of 1000µg/mL, respectively.

(3) Cell line and DMSO (0.2% in PBS) were cultured in control wells. Each sample underwent three rounds of incubation.

Table 1. Chalcones (**3a-i**) with concentration, absorbance, % inhibition, and IC_{50} values

Sr. N.	Ketone (Starting-2)	Chalcone (Product-3)	Conc. (µg/ml)	Absorbance (nm)	% Inhibition	IC_{50} (µg/ml)
1	 **2a**	 **3a**	10	2.422	37.78	
			30	2.390	38.60	331.05
			100	2.288	41.22	
2	 **2b**	 **3b**	10	2.310	40.66	
			30	2.261	41.92	818.18
			100	2.258	41.99	
3	 **2c**	 **3c**	10	2.900	25.50	
			30	2.813	27.74	498.77
			100	2.713	30.31	
4	 **2d**	 **3d**	10	2.876	26.12	
			30	2.802	28.02	416.37
			100	2.662	31.62	
5	 **2e**	 **3e**	10	2.701	30.61	
			30	2.564	34.13	321.69
			100	2.463	36.73	
6	 **2f**	 **3f**	10	2.524	35.16	
			30	2.401	38.32	222.72
			100	2.270	41.69	
7	 **2g**	 **3g**	10	2.999	22.96	383.82
			30	2.801	28.05	
			100	2.714	30.28	

8	 **2h**	 **3h**	10	2.902	25.45	468.14
			30	2.857	26.11	
			100	2.717	30.20	
9	 **2i**	 **3i**	10	2.891	25.73	465.60
			30	2.718	30.18	
			100	2.672	31.36	
10		**Std. 5 FU**	10	2.105	45.92	51.47
			30	1.918	50.73	
			100	1.845	52.60	
11	**Control**			3.893		

To find the proportion of live cells after culture and the survival rate of control cells, controls were kept in place.

(4) Cell cultures were placed in a CO_2 incubator (Thermo Scientific BB150) and incubated for 24 hours at 37 °C with 5% CO_2.

(5) Following the incubation period, the medium was fully extracted and 20 µl of MTT reagent (5 mg/min PBS) was added.

(6) Cells were cultured for 4 hours at 37 ^oC in a CO_2 incubator following the injection of MTT.

(7) With a microscope, examined the wells for formazan crystal development. Only live cells were able to convert the yellowish MTT to a dark-colored formazan.

(8) Completely removed the medium, added 200 µl of DMSO, let it sit for 10 minutes, and then incubated (covered in aluminum foil) at 37 ^oC.

(9) The absorbance of each of the three samples was measured using a microplate reader (Benesphera E21) set to operate at 550 nm.

Based on the acquired data, it was noted that the majority of the compounds that were synthesized demonstrated strong antiproliferative activity. At concentration 100 µg/mL, chalcones **3a**, **3e**, and **3f** showed good percent inhibition MCF-7 cell line, as compared to standard drug. The compounds **3a**, **3e**, and **3f** showed lowest IC_{50} value as compared to other compounds. It indicates these compounds showed 50% inhibition of cell growth at this concentration. It was observed that the presence of group that donate electrons on phenyl ring causes the inhibitory action to slightly increase. It was discovered that compound **3f** (IC_{50} = 222.72 µg/mL), which has methoxy at the phenyl ring's 2-position, is the most active of the group. When compared to the non-substituted ring itself, the phenyl ring's 3-methoxy substituent exhibits lesser activity and the methoxy substituent at positions 2 and 4 exhibits higher activity. Electron withdrawing substituent like $–NO_2$, -Cl, and –Br group show decreased activity. 4-Br compound **3b** shows lowest activity with IC_{50} value 818.18 µg/ml while 4-Cl compound **3c** shows IC_{50} value 498.77 µg/mL. 4-NO_2 and 3-NO_2 compounds show IC_{50} value 383.82 and 465.60 µg/mL, respectively, which are more as compared to methoxy substituent.

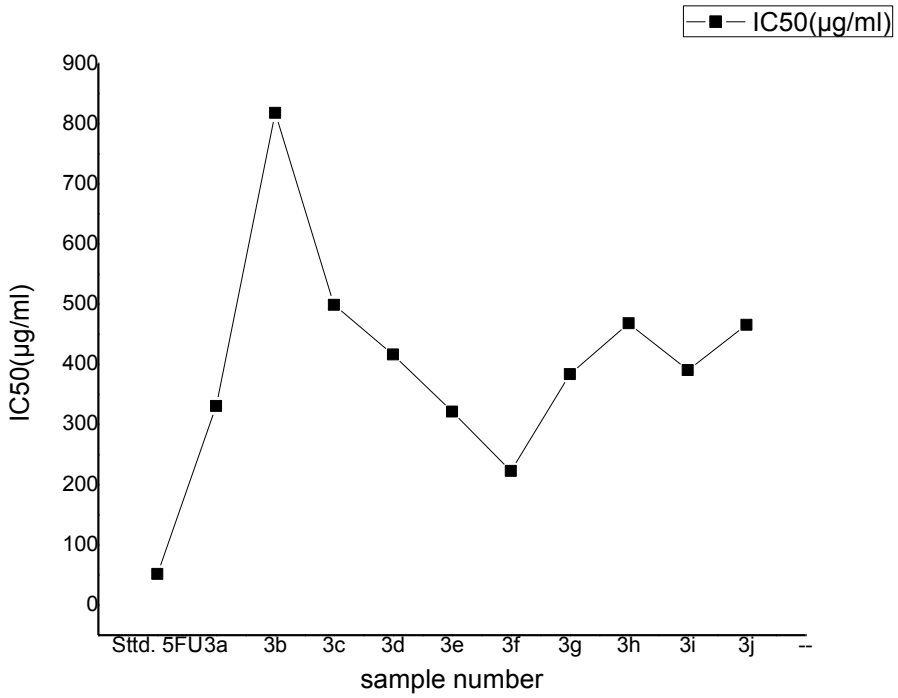


Figure 1. Graph showing IC_{50} values of different chalcones

Table 2. Docking score interaction affinity for all chalcone derivatives

Sr. No.	Entry	Affinity (kcal/mol)	(µg/mL)	H-bond formatting residue and bonds	Pi interaction
1	3a	-8.8	331.05	Ser 246 = 2.78 A^o Asn 341 = 3.11 A^o	Tyr 281
2	3b	-3.2	818.18	-	-
3	3c	-5.6	498.77	-	-
4	3d	-5.0	416.37	-	-
5	3e	-4.1	321.69	Ser 246 = 2.57 Asn 341 = 3.22	Tyr 281
6	3f	-5.3	222.72	Ser 246 = 2.70 A^o	Tyr 281
7	3g	-4.0	383.82	-	-
8	3h	-6.1	468.14	Ser 246 = 2.90 A^o	Tyr 281
9	3j	-3.6	465.60	Asn 341= 2.98 Ser 246 = 2.71	-

This indicates that electron donating substituent at 2-position increases the activity of the synthesized chalcones.

This can be cleared from the graph plotted between chalcones and corresponding IC_{50} values (Figure 1).

Molecular docking studies

Preparation of protein and ligand

The protein, whose crystal structure features a high affinity hetero dimer of the ARNT C-terminal PAS domain and HIF2α, was downloaded from the RCSB (www.rcsb.org) Protein Data Bank (PDB ID: 3F1O).

Using discovery studio to prepare the PDB format for the docking investigation, the interaction between the substituted chalcone derivatives and the aforementioned protein was investigated. The auto dock 4.2 software tool carried out the computations for molecular docking [30]. After preparing the compounds' molecular structures and minimizing their energy, the compound with the lowest free binding energy was selected for additional examination.

Docking analysis

The 3D crystal structure of HIF2α (PDBID: 3F1O) was used for this docking study. The Auto Dock Tools were used to eliminate every unattached water atom and molecule. The protein was then treated to the addition of polar hydrogen atoms and Kollman-Gesteiger charges.

We used the Lamarckian Genetic Algorithm (LGA) for all docking computations [31]. The grid box was placed at center with coordinates x: 12.378650, y: -41.613200, z: 10.343900. Docking was carried out under the same circumstances and with the same Auto Dock parameters for each compound.

Each compound's lowest binding energy conformation was chosen following the completion of the docking investigation. After comparing the propensity of each chalcone derivative to interact with protein, it was discovered that compound **3a** exhibits good inhibition (having the highest interaction affinity). Docking score interaction affinity for all chalcone derivatives are presented in Table 2 along with useful information as like H-bond formatting residue, pi interactions, etc.

Compound **3a** shows IC_{50} value of 331.05 µg/mL and in docking study shows highest affinity for protein (-8.8 kcal/mol). LigPlot [32] software shows hydrogen bonding interaction with Ser 246 (A) and Asn 341 (A) at distance of 2.78 and 3.11 A^o, respectively, depicted in Figure 2 and Figure 3. There are pi-interactions with Tyr 281(A) and hydrophobic interactions with other amino acids.

Compounds **3h** shows IC_{50} value of 468.14 µg/ml and in docking study indicates the highest affinity for protein (-6.1 kcal/mol). LigPlot software shows hydrogen bonding interaction for **3h** with Ser 246 A at distance of 2.90 A^o. Compound **3h** also shows pi-interactions with Tyr 281(A) and hydrophobic interactions with other amino acids.

Compound **3f** shows good IC_{50} value (222.72 µg/ml) and in docking study Affinity for protein (-5.3 kcal/mol). LigPlot software shows interaction with Ser 246 (A) at distance of 2.70 A^o and pi-interactions with Tyr 281(A). It also reveals hydrophobic interaction with other amino acids.

IC_{50} value of 321.69 µg/mL was obtained for compound **3e** and in docking study affinity for protein (-4.1 kcal/mol). LigPlot software shows hydrogen bonding interaction with Ser 246 (A) and Asn 341 (A) at distance of 2.57 and 3.22 A^o, respectively. It also shows pi-interactions with Tyr 281 (A) and hydrophobic interactions with other amino acids.

The correlation value between the theoretical and experimental data is provided by the Pearson correlation coefficient (R^2). Pearson's correlation coefficient shows a linear relationship between two variables that spans from +1 to -1. A complete positive linear relationship between variables is shown by a

correlation value of +1. Predicted binding free energies and actual IC_{50} values against MCF-7 human breast cancer cells are correlated. The results indicate a positive association between affinity (kcal/mol) and IC_{50} (µg/mL), as indicated by the computed Pearson correlation coefficient of 0.423756 for this study.

Experimental

General experimental procedure

After dissolving the starting ketone **2** (1eq.) in ethanol, 1eq. of sodium hydroxide was added. After agitating the reaction mixture for ten minutes at room temperature, one equivalent of 1-naphthaldehyde was added.

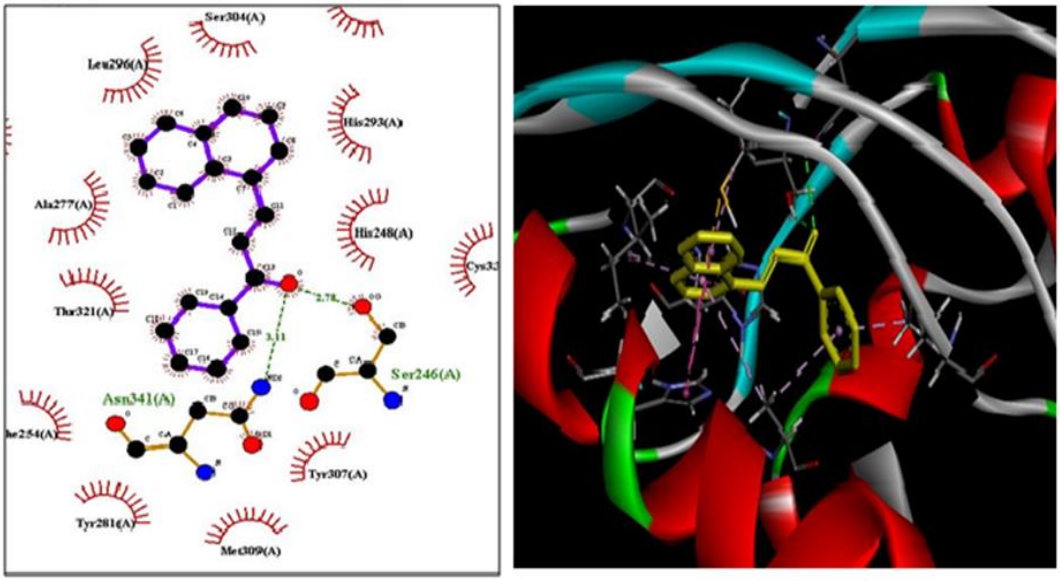


Figure 2. Interaction of compound **3a** with protein

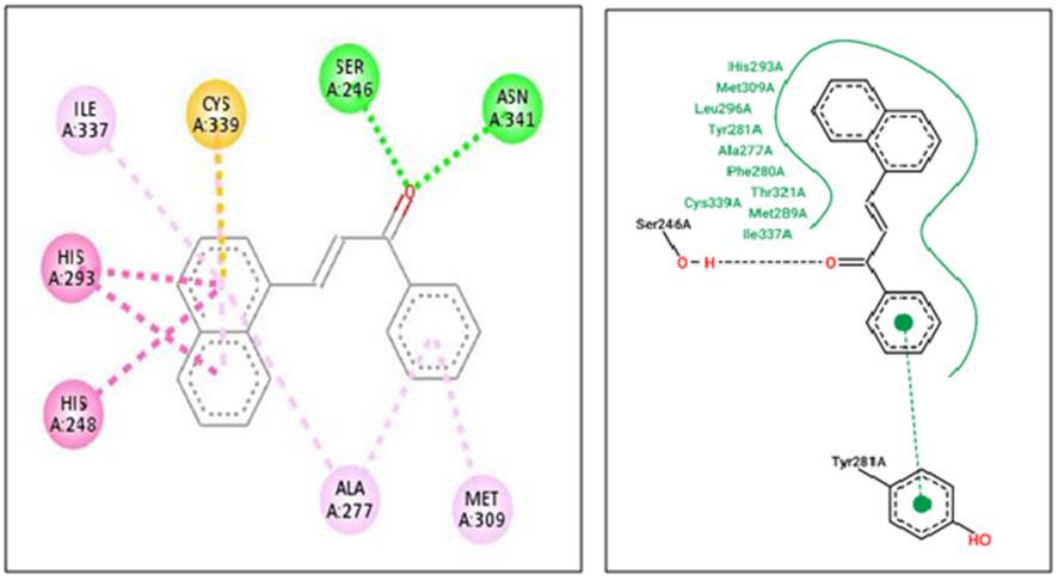


Figure 3. Compound **3a** showing 2D interaction with protein

For 30 minutes, the reaction mixture was continuously stirred. The progress of reaction was monitored by TLC analysis. Crude product was obtained by removing the solvent on a rotary evaporator under decreased pressure after the reaction was completed (TLC check). To obtain the desired product **3**, water was added to the crude product and it was extracted three times using ethyl acetate. Recrystallization was used to further purify the product.

(E)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (3a)

IR (KBr) (ν_{max}/ cm^{-1}): 3016, 1695, 1636, 1449, 1215, 744, and 666. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 15.8 Hz, 1H), 8.12 (d, J = 6.9 Hz, 1H), 7.95-7.87 (m, 4H), 7.67-7.40 (m, 7H), and 7.29 (d, J = 4.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.54, 142.93, 139.26, 136.66, 135.31, 133.76, 131.61, 131.18, 130.49, 129.58, 129.09, 128.87, 128.56, 126.98, 126.36, 125.50, 124.90, and 123.2. GC MASS= 258

(E)-1-(4-bromophenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3b)

IR (KBr) (ν_{max}/ cm^{-1}): 3059, 1659, 1593, and 590. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 15.6 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.03-7.93 (m, 3H), 7.71-7.45 (m, 6H), and 7.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189, 142, 140.1, 136.5, 136.02, 134.5, 132.01, 132, 131, 131.5, 130.02, 126.7, 126, 125.51, 125.0, 124.05, and 123. LC MASS= 351.5 (M+ Na).

(E)-1-(4-chlorophenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3c)

IR (KBr) (ν_{max}/ cm^{-1}): 3060, 1656, 1590, and 592 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (t, J = 18.5 Hz, 1H), 8.23 (t, J = 14.6 Hz, 1H), 8.01-7.81 (m, 3H), 7.74-7.63 (m, 2H), 7.66-7.50 (m, 12H), 7.40-7.23 (m, 5H), and 7.25-7.00 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.37, 158.30, 151.81, 140.06, 137.15, 133.16, 130.28, 122.54, 127.50, 124.01, 125.34, 121.02, 122.30, 119.04, 111.72, and 55.80. GC MASS= 292.

(E)-1-(3-methoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3d)

IR (KBr) (ν_{max}/ cm^{-1}): 2925, 1652, 1592, 1437, 1211, 771, and 665. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 15.6 Hz, 1H), 8.25 (t, J = 9.4 Hz, 1H), 7.89 (dt, J = 18.1, 9.5 Hz, 3H), 7.75 (d, J = 7.6 Hz, 1H), 7.66-7.47 (m, 5H), 7.11 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.69, 158.29, 139.92, 133.76, 133.11, 132.64, 131.79, 130.51, 129.70, 129.34, 128.73, 126.81, 126.21, 125.59, 125.05, 123.61, 120.85, 111.71, and 55.79. GC MASS= 289.

(E)-1-(4-methoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3e)

IR (KBr) (ν_{max}/ cm^{-1}): 2920, 1648, 1595, 1435, 1215, 770, and 660. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 15.6 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.99-7.83 (m, 3H), 7.75 (dt, J = 13.7, 6.8 Hz, 1H), 7.55 (ddd, J = 15.6, 12.7, 4.2 Hz, 5H), 7.11 (t, J = 7.3 Hz, 1H), 7.03 (t, J = 9.3 Hz, 1H), and 3.93 (d, J = 9.9 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.71, 158.30, 139.91, 133.77, 133.13, 132.60, 131.79, 130.42, 129.68, 129.31, 128.76, 126.84, 126.23, 125.51, 125.17, 123.60, 120.86, 111.73, 111.73, 55.79, and 55.46. GCMS= 289

(E)-1-(2-methoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3f)

IR (KBr) (ν_{max}/ cm^{-1}): 2923, 1654, 1590, 1440, 1219, 770, and 663. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 15.4 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 7.98-7.88 (m,

3H), 7.69-7.51 (m, 4H), 7.03 (d, *J* = 8.8 Hz, 2H), and 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 188.52, 163.52, 140.92, 133.76, 132.67, 131.79, 131.10, 130.92, 130.58, 128.73, 126.91, 126.27, 125.45, 124.99, 124.66, 123.61, 113.93, and 55.48. GC MASS= 289

(E)-3-(naphthalen-1-yl)-1-(4-nitrophenyl)prop-2-en-1-one (3g)

IR (KBr) (ν_{max}/ cm^{-1}): 3020, 1679, 1519, 1215, and 742. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.68 (m, 2H), 8.31 (m, 2H), 8.1-7.8 (m, 3H), 7.65-7.37 (m, 4H), and 7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 188.95, 140.25, 139.95, 136, 130.4, 133.1, 131, 130, 129, 126, 125, and 124. LC MASS= 325 (M+ Na).

(E)-1-(2-chlorophenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (3h)

IR (KBr) (ν_{max}/ cm^{-1}): 3061, 1650, 1592, and 595. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.40 (d, *J* = 14.5 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 8.01-7.85 (m, 4H), 7.70-7.40 (m, 5H), 7.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 189, 142, 139.6, 136, 134, 132, 131, 130.50, 130, 129, 126.50, 125, 124, and 123. LC MASS= 314.8 (M+ Na).

(E)-3-(naphthalen-1-yl)-1-(3-nitrophenyl)prop-2-en-1-one (3i)

IR (KBr) (ν_{max}/ cm^{-1}): 3025, 1672, 1522, 1212, and 740. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.68 (m, 2H), 8.25 (m, 3H), 8.01(m, 4H), 7.51 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 188.95, 142.21, 139.34, 136.51, 134, 132, 131.5, 131, 130, 128.50, 126, 125.1, 124, and 123.61. LC MASS= 325.6 (M+ Na).

Conclusion

To sum up, we designed and synthesized a range of naphthalene-chalcone derivatives (**3a-j**) and evaluated their efficacy in treating MCF-7 cell line-derived breast cancer. With an IC_{50} value of 222.70 µg/mL, compound **3f**, which carries a 2-methoxy phenyl moiety, is the most potent molecule against the MCF-7 breast cancer cell line among them. Moreover, molecular docking analyses demonstrated that these compounds show affinity for proteins.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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