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Molecular Modeling Based Synthesis and Evaluation of *In vitro* Anticancer Activity of Indolyl Chalcones

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Rajendra Singh Bhakuni

Abstract: A series of twenty one chalcone derivatives having indole moiety were synthesized and were evaluated against four human cancer cell lines. Indolyl chalcones **1a**, **1b**, **1d**, **1f-1j**, **2c**, **2e**, **2i** showed good anticancer activity. Chalcones **1b** and **1d** were the most active and selective anticancer agents with IC_{50} values <1μg/ml and 1.51μg/ml, against WRL-68 cell line, respectively. Molecular mechanism was explored through in silico docking & ADMET studies.

Keywords: 1,3-Diaryl-2-propen-1-ones, Anticancer agents, Indolyl chalcones.

1. INTRODUCTION

Cancer, the uncontrolled growth of cells is a major cause of death worldwide and is responsible for 8.2 million deaths in 2012 which is around 13% of total deaths [1,2]. While great efforts have been made to tackle the disease over past few decades, it still continues to be a major health menace. Medicinal chemists are tirelessly exploring for a better and more suitable cancer therapeutic. Chalcones (1, 3-diaryl-2-propen-1-ones), constituting an enone system between two aromatic rings are an important class of natural products which exhibit interesting pharmacological activities [3,4]. Chalcones, originating from natural and synthetic routs possess several biological activities, such as cytotoxic [5-8] antimalarial [9,10], antileishmanial [11,12], anti-inflammatory [13,14], anti-HIV [15], antifungal [16] and as tyrosine kinase inhibitors [17]. Because of very high pharmacological interest, these molecules have attracted medicinal chemists to design and synthesize further large number of chalcones with different functional groups. In the recent years, the development of anticancer agents was achieved by structural modification of chalcones to increase their bioavailability and to study the effect of various substituents on aryl or heteroaryl rings [18].

Indoles, the heteroaryl rings are widely distributed in nature and possess a variety of significant biological activities. The indole ring is an important moiety in many pharmacologically active compounds in which some studies related to anticancer effectiveness have been reported in the literature [19-22]. Some of the individual anticancer compounds in which the indole ring is responsible for the activity are panobinostat [23,24], cediranib [25], indole-3-carbinol [26] (Fig. **1**). Basically, indolyl chalcones are not much explored for their anticancer potential [27-29]. In the present study, we have synthesized two different series (Fig. **2**) of novel indolyl chalcones **1a-j** (Scheme **1**) and **2a-k** (Scheme **2**) and evaluated their *in vitro* anticancer activity against four human cancer cell lines.

2. RESULT AND DISCUSSION

General methods for the preparation of chalcones involve Claisen-Schmidt condensation of appropriate aryl methyl ketones and aldehydes in presence of acid or base [30]. We have prepared both series of indolyl chalcones by using aforementioned reference conditions in good yields. Indolyl chalcones **1a-j** were prepared by the reaction of appropriate acetophenone **4** with indol-3-carboxaldehyde **5** in the presence of NaOH at RT (Scheme **1**) [30]. Indolyl chalcones **2a-k** were prepared by the reaction of 3-acetylindole **6** with appropriate aldehyde **7** in the presence of $SOCl_2$ (Scheme **2**) [31]. Acetophenones (**4h-4j**) for the preperation of the compounds **1h-1j** were prepared by etherification of o-hydroxy (**3h**), p- hydroxy (**3i**) and o,p-hydroxy (**3j**) acetophenones respectively with allylbromide in the presence of KBr in acetone using refluxing condition.

All these indolyl chalcones were assayed for their *in vitro* cytotoxicity against four human cancer cell lines: breast (MCF-7), liver (WRL-68), prostate (PC-3) and colon (CACO2). The IC_{50} and IC_{90} values were used to determine the growth inhibition of these cancer cell lines. From the IC_{50} values summarized in Table **1**, the compounds **1b** and **1d** have shown significant cytotoxicity. Furan moieties are present in many natural products [2]. Chalcone **1d** bearing benzofuran ring is most active in this series and selectively cytotoxic against WRL-68 and MCF-7 cancer cell lines with an IC_{50} value of <1μg/ml whereas compound **1b** bearing

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#RG and DKY share equal contribution and authorship

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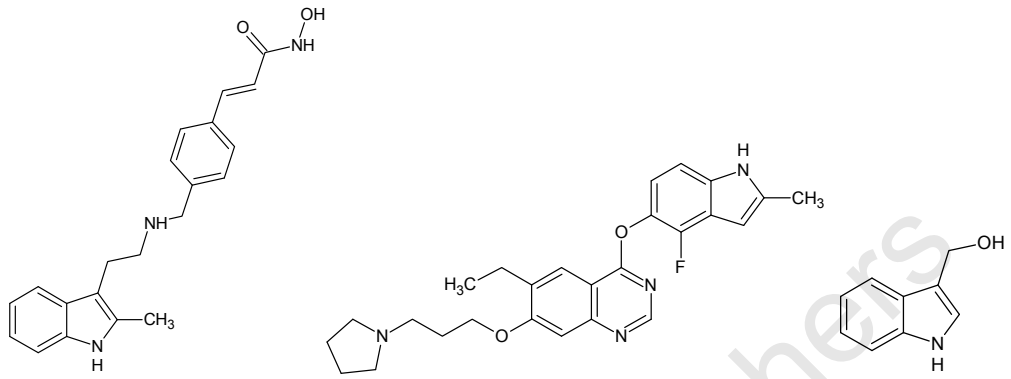


Fig. (1). Some anti-cancer drugs having indole ring.

benzyloxy group in the aromatic ring is as active as **1d,** IC_{50} <1µg/ml against WRL-68 cancer cell line. Compound **1g** with o-hydroxy group is moderately cytotoxic against all the four cell lines without any selectivity. Introduction of m-allylic group in the aryl ring i.e. compound **1h** is beneficial for the activity as compared to compound **1g**. In other series, Compound **2i** has displayed significant cytotoxicity against WRL-68 with an IC_{50} values 1.5 1µg/ml. Indolyl chalcone **2c** with a 3, 4, 5-trimethoxy substituent and **2e** with 3-ethoxy-4-hydroxy substituent were moderately active and selective against WRL-68 and MCF-7 respectively with an IC_{50} value of 10 1µg/ml (Table **2**).

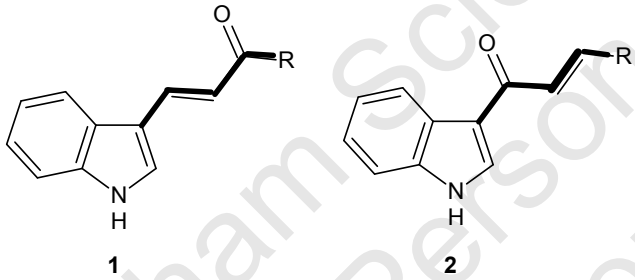
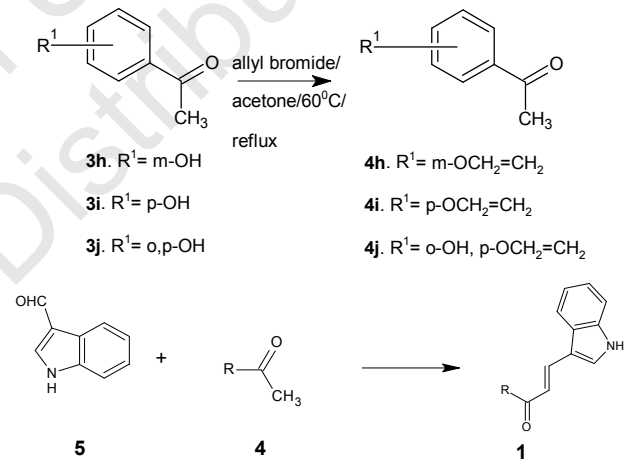


Fig. (2).

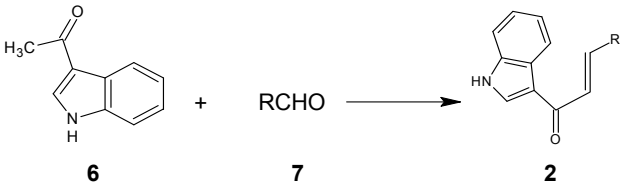
2.1. Molecular Docking Studies

The molecular docking study was performed to elucidate whether the compounds **1b** and **1d** modulates the anticancer target, and also to identify the actual binding pocket against molecular target tubulin and LRH-1. We docked compound **1d** at 'tubulin binding site' and compounds **1b** and **1d** also at 'LRH-1 site'. The orientations and binding affinities were explored in terms of total score. Surflex-dock software was used in reproducing the experimentally was observed binding mode for paclitaxel. Crystallography data of LRH-1 showed that the amino acid ASP-389 is the "gatekeeper" residue, an important determinant of stabilizing specificity in the LRH-1 binding pocket.

The docking results for compound **1d** and doxorubicin against target protein showed binding affinity, total docking score of 7.9867 (Fig. **3C**) and 3.9428 (Fig. **3A**). The amino acid residues within a selection radius of 4Å from bound compound **1d** (ligand) were hydrophobic residue VAL-406 (Valine), PHE-342, ILE-378, ILE-387 (isoleucine), MET-345, MET-348, MET-428 (Methione); nucleophilic (polar, hydrophobic) e.g., THR-352 (Threonine); basic ARG-393, (Arginine), GLN-432(Glutamine), HIS-390 (Histidine), CYS-346(cysteine); acidic (polar, negative charged) e.g., ASP-389, (Aspartic acid), Hydrophobic e.g., ALA-431, ALA-513, (Alanine), LEU-386, LEU-405, LEU-424, LEU-427, LEU-517 (Leucine), and aromatic (hydrophobic), i.e. TYR-516 (tyrosine), the bound compound **1d** showed strong hydrophobic interactions with tubulin, thus leading to more stability and activity (Fig. **3A**).



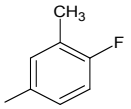
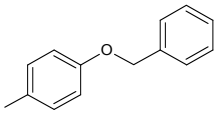
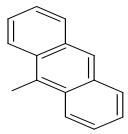
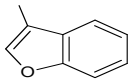
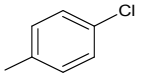
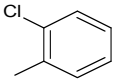
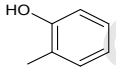
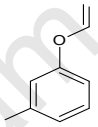
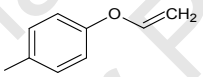
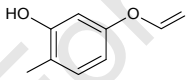
Scheme 1. Reagents and conditions: NaOH, methanol, 1- 15 h., RT.



Scheme 2. Reagents and conditions: $SOCl_2$, methanol, 1- 2 h., RT.

Similarly, compounds **1b** and **1d** was docked at LRH-1 binding pocket as indicated by docking score in the form of total score was i.e. 7.9867 and 5.2861 respectively. While, the docking scores of doxorubicin was 4.6342 only. The docked view of compounds **1b** and **1d** (Fig. **1C** and **1D**), shows the formation of a H-bond of length 2.4Å to the polar

Table 1. ***In vitro*** **cytotoxicity data of indolyl chalcones (1a-j).**

Compounds	R	WRL-68 IC_{50}µg/ml C_{90}µg/ml		PC-3 IC_{50}µg/ml IC_{90}µg/ml		CaCO-2 IC_{50}µg/ml IC_{90}µg/ml		MCF-7 IC_{50}µg/ml IC_{90}µg/ml	
1a		6.6	>100	NO	NO	96	>100	7	50
1b		<1	8.4	8.3	66	7.4	47	6.4	10
1c		81	>100	NO	NO	100	>100	78	>100
1d		<1	>100	NO	NO	52	>100	<1	>100
1e		54	>100	NO	NO	NO	NO	8.15	>100
1f		5.4	9.4	9.8	86	7.8	68	7.4	10
1g		3.7	72	8.8	74	7.8	78	9.4	80
1h		3.7	6.6	8	88	8.7	87	7.8	68
1i		5	66	NO	NO	NO	NO	NO	NO
1j		10	82	NO	NO	NO	NO	NO	NO
Doxorubicin		0.85		5.0		3.5		2.1	

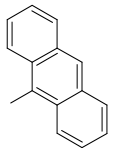
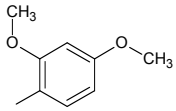
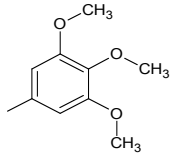
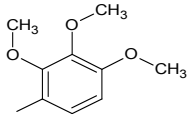
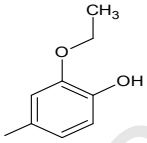
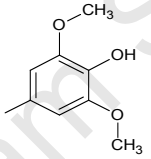
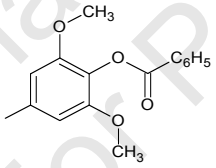
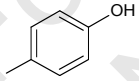
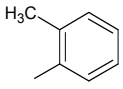
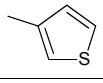
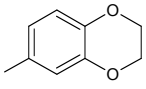
WRL-68=liver cancer cell line, CaCO2=colon cancer, MCF-7=breast cancer, PC-3=prostate cancer.
Doxorubicin SigmaD-1515 is the standard used.

hydrophobic residue ASP-389. The amino acid residues within a selection radius of 4Å from bound ligand were hydrophobic residue VAL-406(Valine), PHE-342 (Phenylalanine), ASP-389 (Aspartic acid), HIS-390 (Histidine), LEU-386, LEU-424, LEU-427, LEU-405, LEU-517(Leucine), ALA-431, ALA-513 (Alanine), ILE-387 (isoleucine), MET-345, MET-348, MET-428 (Methione); nucleophilic (polar, hydrophobic), i.e. CYS-386 (cysteine), THR-352 (Threonine); basic ARG-393, (Arginine), aromatic (hydrophobic), i.e. TYR-516 (tyrosineas) and polar amide, e.g. GLN-432 (glutamine), as a result bound compound showed high molecular interaction in compare to doxorubicin, which causes more stability and activity in this compound. Overall, docking studies clearly indicates that compound **1b** and **1d** binds well with tublin and LRH-1 binding site and hence may exhibit similar inhibition effects on microtubules and LRH-1. These results were further substantiated by wet lab experiments.

2.2. Compliance with Pharmacokinetic Parameters Assessment

Pharmacokinetic parameters used for *in silico* screening of compounds **1b** and **1d** were absorption, distribution, metabolism and excretion (ADME) which showed close

Table 2. ***In vitro*** **cytotoxicity data of indolyl chalcones (2a-k).**

Compounds	R	WRL-68 IC_{50}µg/ml IC_{90}µg/ml		PC-3 IC_{50}µg/ml IC_{90}µg/ml		CaCO-2 IC_{50}µg/ml IC_{90}µg/ml		MCF-7 IC_{50}µg/ml IC_{90}µg/ml	
2a		NO	NO	NO	NO	NO	NO	NO	NO
2b		20	>100	NO	NO	NO	NO	91	>100
2c		10	>100	NO	NO	74	>100	84	>100
2d		NO	NO	NO	NO	NO	NO	NO	NO
2e		70	>100	88	>100	88	>100	10	90
2f		NO	NO	NO	NO	NO	NO	NO	NO
2g		15	>100	NO	NO	32	>100	61	>100
2h		NO	NO	NO	NO	NO	NO	38	90
2i		1.5	>100	8.8	81	7.4	68	8.1	70
2j		NO	NO	40	>100	NO	NO	NO	NO
2k		NO	NO	NO	NO	NO	NO	NO	NO
Doxorubicin		0.85		5.0		3.5		2.1	

WRL-68=liver cancer cell line, CaCO2=colon cancer, MCF-7=breast cancer, PC- 3=prostate cancer.
Doxorubicin SigmaD-1515 is the standard used.

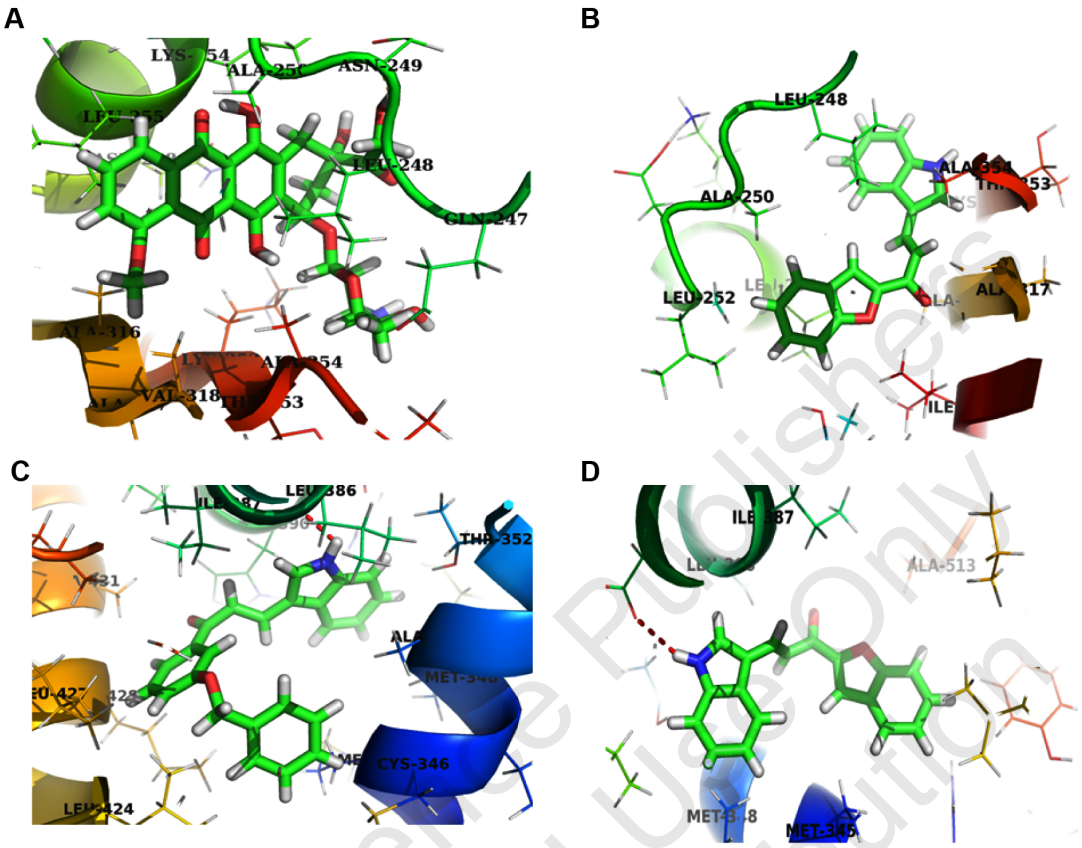


Fig. (3). *In-silico* molecular docking studies elucidating the possible mechanisms of compound **1b** and **1d** induced modulation of tubulin (PDB: 1TUB) and LRH-1 protein receptor (PDB: 3PLZ). The docking studies were carried out using SYBYL-X 2.0, Tripos International. The control compound doxorubicin was docked into the binding site of tubulin crystallized conformation and a total docking score of 3.9428(A) and a H-bond of length 2.0Å to the binding pocket residue Leu-248 was observed. Compound **1d** docked on to tubulin with high binding affinity, as indicated by a total docking score of 5.4569 (B) and compound **1b** and **1d** docked on LRH-1form a H-bond of length 2.4Å to the binding pocket residue Asp-389 and total score 7.9867 (C) and 5.2861 (D) was observed.

correspondence with those of control compound doxorubicin and were within the standard range of values exhibited by 95% of all known drugs. Results revealed that chalcone derivatives have compliance with standard range of pharmacokinetics parameters (Table **3**).

2.3. Compliance with Toxicity Risk Assessment Parameters

Results of toxicity risk assessment calculated through OSIRIS calculator. Toxicity screening results showed that both compounds **1b** and **1d** possess risk of mutagenicity toxicity, however indicate significant docking and experimental based anticancer activity (Table **4**). Thus, there is a need for more qualitative safety evaluation of chalcone. This is particularly important because of the fact that chalcone derivatives are used very frequently in clinical and non clinical settings. The compliance of active chalcone derivatives namely, compounds **1b** and **1d** with computational toxicity risks parameters indicate that these compounds are active and safe except mutagenicity toxicity risk at high doses or long term use similar to standard anticancer drug namely doxorubicin. Therefore lead optimization of these active chalcone derivatives is a subject of further research work. Results of ADMET revealed that the overall drug scores of predicted active compounds are comparable to that of standard drugs and also in accordance with *in vitro* experimental data (Table **1**) tested in MCF-7 and WRL-68 cancer cell line.

3. EXPERIMENTAL SECTION

Chemistry. General Methods. Melting point was determined on a Toshniwal melting point apparatus and is uncorrected. IR spectra were recorded on a Perkin Elmer 1719 FT-IR spectrophotometer. NMR spectra were obtained in acetone-d_6, DMSO-d_6 and pyridine-d_5 on a Bruker Avance, 300 MHz instrument using TMS as internal standard. The chemical shift values are reported in ppm and coupling constants in Hz. ESI-MS spectra were recorded on a Perkin Elmer Turbo Mass/ Shimadzu LC-MS. TLC analyses were carried out on precoated silica gel 60 F_{254} plates (Merck) using solvent system, hexane: ethyl acetate (7:3). The compounds were visualized by either exposure of TLC plates to I_2 vapors or by spraying with vanillin-sulfuric acid reagent, followed by heating at 110°C for 15 minutes. Si-gel, 60-120 mesh (spectrochem) was used in the column chromatography for the purification of metabolites. HPLC analyses were carried out on waters spherisorb ODS2 (250x4.6mm i.d.,10µm) column using binary gradient elution with acetonitrile and water mobile phase (70:30) at a flow rate of 0.6mL/min, column

Table 3. Compliance of active chalcones to computational parameters of pharmacokinetics (ADME).

Compounds	log S for aq. Solubility	log Khsa, Serum Protein Binding	log BB for Brain/ Blood	No. of Metabolic Reactions	Predicted CNS Activity	log HERG for K+ Channel Blockage	Apparent Caco-2 Permeability nm/sec	Apparent MDCK Permeability nm/sec	log Kp for Skin Permeability	% Human Oral Absorption in GI (+-20%)	Qual Model for Human oral Absorption
1b	-5.293	0.825	-0.506	2	-1	-6.390	2157.263	1135.692	-0.365	100	High
1d	-4.432	-4.432	-0.410	1	-1	-6.179	1783.35	924.50	-1.001	100	High
Doxorubicin	-2.162	-0.628	-2.633	9	-2	-5.916	3.982	1.394	-7.423	0	Low
Stand. Range*	(-6.5 / 0.5)	(-1.5 / 1.5)	(-3.0 / 1.2)	(1.0 / 8.0)	-2 in-active +2 active	concern below -5	<25 poor, >500 great	<25 poor, >500 great	-8 to -1, Kp in cm/hr	<25% is poor	>80% is high

Table 4. Compliance of active chalcones to computational toxicity risks parameters (i.e., mutagenicity, tumorogenicity, irritation and reproduction).

Compounds	Toxicity Risk Parameters			
	Mutagenicity	Tumorogenicity	Irritation (Skin)	Reproductive toxicity
1b	High risk	No risk	No risk	No risk
1d	High risk	No risk	No risk	No risk
Doxorubicin	No risk	No risk	No risk	No risk

temperature of 25º and UV detection at λ230nm. The compounds were identified by their spectral IR, ID (^{1}H, ^{13}C, DEPT) and 2D (COSY, HSQC, HMBC) ESIMS) NMR and ESIMS analysis.

3.1. Synthesis of Indolyl Chalcones, series 1

To a solution of indol-3-carboxaldehyde **5** (1 mmol) and appropriate acetophenone **4** (1 mmol) in anhydrous methanol (20 mL) was added 10%-40% sodium hydroxide (2 mL) and stirred the reaction mixture at RT for 2-8 h. The contents of reaction mixture were poured into ice-cold water and neutralized with dilute hydrochloric acid. The solid so obtained was filtered, column chromatographed and recrystallized from ethanol to afford pure **1a-j**.

Trans-3-(1H-indol-3-yl)-1-(4'-flouro-3'-methylphenyl)-2-propen-1-one (**1a**): Orange powder; 20% yield obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-3-(1H-indol-3-yl)-1-(4'-benzyloxyphenyl)-2-propen-1-one (**1b**): Yellow solid; 60%, yield obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-3-(1H-indol-3-yl)-1-(anthracenyl)-2-propen-1-one (**1c**): Yellow powder; 80% yield; mp 108-109°C; IR ν^{max} (KBr)**:** 3395, 1561, 1164, 746 (NH), 1649 (chalcone C=O), 1515, 1483, 1430 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 7.16 (2H, d, J=7.8 Hz, H-4'', H-12''), 7.23 (2H, m, H-5', H-6'), 7.26 (4H, m, H-5'', H-6'', H-10'', H-11''), 7.44 (1H, d, J=2.1 Hz, H-8''), 7.51 (1H, dd, J=8.1, 2.1 Hz, H-4'), 7.59 (2H, d, J=7.8 Hz, H-3'', H-13''), 7.87 (1H, d, J=15.6 Hz, H-2), 7.89 (1H, brs, H-2'), 8.21 (1H, dd, J=8.1, 2.1 Hz, H-7'), 8.55 (1H, d, J=15.6 Hz, H-3), 13.05 (1H, brs, NH); ^{13}C NMR (75 MHz, acetone-d_6): δ 111.65 (C-5'', C-11''), 112.53 (C-4'', C-12''), 113.06 (C-4'), 114.23 (C-1'), 116.45 (C-3'', C-13''), 121.11[a] (C-7'), 121.89[a] (C-2, C-6'), 123.15[b] (C-6'', C-10''), 123.48[b] (C-5'), 124.15 (C-8''), 126.40 (C-3'), 128.15 (C-1''), 133.50 (C-2'), 138.88 (C-8'), 139.30 (C-3), 155.35[c] (C-7'', C-9''), 155.91[c] (C-2'', C-14''), 179.72 (C-1) (a,b,c=interchangable); ESI-MS, MeOH (Positive): m/z 348 $[M+H]^+$, 346$[M-H]^-$, $C_{25}H_{17}NO$.

Trans-3-(1H-indol-3-yl)-1-(benzofuran)-2-propen-1-one (**1d**): Dark brown solid; 40%, yield obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-3-(1H-indol-3-yl)-1-(4'-chlorophenyl)-2-propen-1-one (**1e**): Yellow fluffy crystals, 60% yield, obtained and analysed by spectroscopic data as described by an earlier method [29].

Trans-3-(1H-indol-3-yl)-1-(2'-chlorophenyl)-2-propen-1-one (**1f**): Yellow shiny crystals, 85% yield, obtained and analysed by spectroscopic data as described by an earlier method [29].

Trans-3-(1H-indol-3-yl)-1-(2'-hydroxyphenyl)-2-propen-1-one (**1g**): Light brown crystals, 55% yield, obtained and analysed by spectroscopic data as described by an earlier method [32].

Trans-3-(1H-indol-3-yl)-1-(3'-allyloxyphenyl)-2-propen-1-one (**1h**): Light brown powder; 65% yield; **mp 90-92°C;** IR ν^{max} (KBr): 3389 1564, 1211, 739 (NH), 1653 (chalcone C=O), 1523, 1458, 1420 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.64 (2H, d, J=5.1 Hz, H_2-7''), 5.26 (1H, dd, J=10.5, 0.9 Hz, Ha-9''), 5.40 (1H, dd, J=17.4, 1.5 Hz,

Hb-9''), 6.05 (1H, m, H-8''), 7.24 (3H, m, H-5', H-6', H-4''), 7.49 (2H, d, J=8.1 Hz, H-4', H-5''), 7.54 (1H, s, H-2''), 7.60 (1H, d, J=15.6 Hz, H-2), 8.03 (1H, d, J=6.6 Hz, H-7'), 8.06 (1H, d, J=15.6 Hz, H-3), 8.09 (1H, d, J=2.1 Hz, H-2'), 7.70 (1H, d, J=8.1 Hz, H-6''), 9.90 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 69.20 (C-7''), 113.42 (C-4'), 113.60 (C-1'), 114.44 (C-2''), 116.31 (C-2), 118.42 (C-9''), 119.82 (C-4''), 121.09 (C-7'), 121.59 (C-6''), 122.07 (C-6'), 123.59 (C-5'), 126.05 (C-3'), 130.72 (C-5''), 134.10 (C-2'), 134.39 (C-8''), 138.44 (C-8'), 140.08 (C-3), 140.90 (C-1''), 159.25 (C-3''), 189.60 (C-1); ESI-MS, MeOH (Positive): m/z 304$[M+H]^+$, Negative: 302$[M-H]^-$, $C_{20}H_{17}NO_2$.

Trans-3-(1H-indol-3-yl)-1-(4'-allyloxyphenyl)-2-propen-1-one (**1i**): Light brown powder; 30%; mp 110-111°C; IR ν^{max} (KBr): 3372 1561, 1205, 736 (NH), 1651 (chalcone C=O), 1511, 1470, 1406 (aromatics) cm^{-1};^{1}H NMR (300 MHz, DMSO-d_6): δ 4.65 (2H, d, J=5.04 Hz, H_2-7''), 5.28 (1H, d, J=10.52 Hz, Hb-9''), 5.42 (1H, d, J=17.21 Hz, Ha-9''), 6.05 (1H, m, H-8''), 7.08 (2H, d, J=8.64 Hz, H-3'', H-5''), 7.24 (1H, m, H-5', H-6'), 7.53 (1H, m, H-4'), 7.67 (1H, d, J=15.40 Hz, H-2), 8.06 (1H d, J=15.56 Hz, H-3), 8.09 (2H, m, H-2', H-7'), 8.13 (1H, d, J=8.72 Hz, H-2''), 8.13 (1H, d, J=8.72 Hz, H-6''), 9.91 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 68.86 (C-7''), 113.00 (C-4'), 113.19 (C-1'), 115.02 (C-3'', C-5''), 115.66 (C-2), 118.36 (C-9''), 120.74 (C-7'), 121.53 (C-6'), 123.07 (C-5'), 125.66 (C-3'), 130.85 (C-6''), 131.80 (C-1''), 130.85 (C-2''), 133.37 (C-2'), 133.65 (C-8''), 138.06 (C-8'), 138.74 (C-3), 162.05 (C-4''), 187.76 (C-1); ESI-MS, MeOH (Positive): m/z 304$[M+H]^+$, Negative: 302$[M-H]^-$, $C_{20}H_{17}NO_2$.

Trans-3-(1H-indol-3-yl)-1-(4'-allyloxy-2'-hydroxyphenyl)-2-propen-1-one (1j): Yellow powder; 30% yield; mp 110-111°C; IR ν^{max} (KBr): 3569 1559, 1229, 735 (NH), 3380 (OH), 1621 (chalcone C=O), 1497, 1439, 1369 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.65 (2H, d, J=4.92 Hz, H_2-7''), 5.29 (1H, d, J=10.68 Hz, Hb-9''), 5.42 (1H, d, J=17.32 Hz, Ha-9''), 6.04 (1H, m, H-8''),), 6.50 (1H, s, H-3''), 6.58 (1H, dd, J=8.92, 2.08 Hz, H-5''), 7.25 (2H, m, H-5', H-6'), 7.52 (dd, J=7.92, 2.52 Hz, H-4'), 7.54 (1H, dd, J=7.92, 2.52 Hz, H-4'), 7.68 (1H, d, J=15.3 Hz, H-2), 8.11 (1H, dd, J=7.92, 2.52 Hz, H-7'), 8.14 (1H, s, H-2'), 8.17 (1H, d, J=15.3 Hz, H-3), 8.19 (1H, m, H-6''), 9.45 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 69.00 (C-7''), 113.10 (C-4'), 113.36 (C-1'), 102.20 (C-3''), 107.93 (C-5''), 114.11 (C-2), 114.51 (C-1''), 118.46 (C-9''), 120.85 (C-7'), 121.81 (C-6'), 123.30 (C-5'), 125.63 (C-3'), 132.46 (C-6''), 165.89 (C-2''), 134.43 (C-2'), 133.47 (C-8''), 138.14 (C-8'), 139.90 (C-3), 164.43 (C-4''), 192.08 (C-1); ESI-MS, MeOH (Positive): m/z 320$[M+H]^+$, Negative: 318$[M-H]^-$, $C_{20}H_{17}NO_3$.

3.2. Synthesis of Indolyl Chalcones 2(a-k)

To a solution of 3-acetylindole **6** (1 mmol) and appropriate aldehyde **7** (1 mmol) in methanol (20 mL) was added $SOCl_2$ (2 mL) and stirred the reaction mixture for 2 h. The contents of reaction mixture were poured into ice-cold water. The solid so obtained was filtered, dried and recrystallized from ethanol to afford pure **2(a-m)**.

Trans-1-indolyl-3-(anthracenyl)-2-propen-1-one (**2a**): Yellow powder; 70% yield; mp 190-191°C, IR ν^{max} (KBr): 3398, 1570, 1234, 728 (NH), 1639 (chalcone C=O), 1518, 1442, 1419, 1381 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, pyridine-d_5): δ 6.90 (4H, m, H-5', H-5'', H-6'', H-11'), 6.83(2H, m, H-4', H-12'), 6.95 (2H, m, H-3', H-13'), 7.16 (1H, d, J=15.6 Hz, H-2), 7.53 (1H, d, J=7.8 Hz, H-4''), 7.83 (2H, d, J=8.1 Hz, H-6', H-10'), 7.96 (1H, brs, H-8'), 8.07 (1H, brs, H-2''), 8.45 (1H, d, J=15.56 Hz, H-3), 8.63 (1H, d, J=7.8 Hz, H-7''), 12.81 (1H, brs, NH); ^{13}C NMR (75 MHz, pyridine-d_5): δ 113.08 (C-4''), 119.2 (C-1''), 123.02 (C-6'', C-7''), 123.32 (C-5''), 124.23 (C-4', C-12'), 126.04 (C-5', C-11'), 126.10 (C-6', C-10'), 126.81 (C-3', C-13'), 127.49 (C-3''), 128.34 (C-8'), 130.19 (C-1'), 131.67 (C-2', C-14'), 132.01 (C-7', C-9'), 134.39 (C-2), 137.57 (C-3), 135.04 (C-2''), 138.47 (C-8''), 184.37 (C-1); ESI-MS, MeOH (Positive): m/z 348 [M+H]+, 370 $[M+Na]^+$, $C_{25}H_{17}NO$.

Trans-1-indolyl-3-(2',4'-dimethoxyphenyl)-2-propen-1-one (**2b**)*:* Creamish white crystals, 10% yield, obtained and analysed by spectroscopic data as described by an earlier method [29].

Trans-1-indolyl-3-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (**2c**)*:* Light orange crystals; 70% yield; mp 191-192°C; IR ν^{max} (KBr): 3448 1581, 1197, 755 (NH), 1642 (chalcone C=O), 1515, 1459, 1426 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (3H, s, OC<u>H</u>$_3$), 3.71 (6H, s, 2 x OC<u>H</u>$_3$), 7.18 (2H, brs, H-2', H-6'), 7.24 (2H, m, H-5'', H-6''), 7.51 (1H, dd, J=6.3, 2.1 Hz, H-4''), 7.62 (1H, d, J=15.6 Hz, H-2), 7.78 (1H, d, J=15.6 Hz, H-3), 8.38 (1H, dd, J=6.3, 2.1 Hz, H-7''), 8.75 (1H, d, J=3 Hz, H-2''), 12.12 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.97 (2 x O<u>C</u>H$_3$), 60.99 (O<u>C</u>H$_3$), 106.92 (C-2', C-6'), 113.04 (C-4''), 118.68 (C-1''), 122.70 (C-6'', C-7''), 123.97 (C-5''), 124.77 (C-3), 126.81 (C-3''), 131.69 (C-1'), 135.52 (C-2''), 137.79 (C-8''), 140.07 (C-4'), 140.84 (C-2), 154.01 (C-3', C-5'), 184.54 (C-1); ESI-MS, MeOH (Positive): m/z 338 $[M+H]^+$, $C_{20}H_{19}NO_4$.

Trans-1-indolyl-3-(2'3',4'-trimethoxyphenyl)-2-propen-1-one(**2d**) : Creamish powder; 70% yield obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-1-indolyl-3-(3'-ethoxy-4-hydroxyphenyl)-2-propen-1-one(**2e**): Light brown crystals; 70% yield; mp 154-155°C; IR ν^{max} (KBr): 3535 1557, 1204, 746 (NH), 3394 (OH), 1641 (chalcone C=O), 1512, 1479, 1403 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, J=6.9 Hz, CH_3), 3.99 (2H, q, J=6.9 Hz, OC<u>H</u>$_2$-), 7.35 (1H, d, J=8.1 Hz, H-5'), 7.39 (1H, d, J=8.1 Hz, H-6'), 7.47 (2H, m, H-5'', H-6''), 7.55 (1H, d, J=1.5 Hz, H-2'), 7.67 (1H, d, J=7.5 Hz, H-4''), 7.85 (1H, d, J=3.0 Hz, H-2''), 8.06 (1H, d, J=15.3 Hz, H-2), 8.35 (1H, d, J=15.3 Hz, H-3), 9.21 (1H, d, J=7.8 Hz, H-7''), 13.23 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.07 (<u>C</u>H$_3$), 65.89 (O<u>C</u>H$_2$-), 113.90 (C-4''), 114.33 (C-2', C-14'), 118.24 (C-5', C-11'), 120.84 (C-1''), 123.47 (C-2), 123.76 (C-6''), 124.59 (C-7''), 124.77 (C-5''), 125.02 (C-6', C-10'), 128.78 (C-3''), 129.10 (C-1'), 135.34 (C-2''), 139.48 (C-8''), 142.96 (C-3), 149.57 (C-3', C-13'), 152.04 (C-4', C-12), 186.47 (C-1); ESI-MS, MeOH (Positive): m/z 308 $[M+H]^+$, Negative: 306$[M-H]^+$, $C_{19}H_{17}NO_3$.

Trans-1-indolyl-3-(3',5'-dimethoxy-4'-hydroxyphenyl)-2-propen-1-one (2f): Creamy crystals; 70% yield and analysed

by spectroscopic data as described by an earlier method [31b].

Trans-1-indolyl-3-(3',5'-dimethoxy-4'-benzyloxyphenyl)-2-propen-1-one (**2g**): Creamish crystals; 70% yield; mp 209-210°C; IR ν^{max} (KBr): 3440 1576, 1203, 739 (NH), 1655 (chalcone C=O), 1742 (ester CO), 1512, 1466, 1426 (aromatics) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (1H, dd, J=7.5, 1.5 Hz, H-10'), 7.31 (2H, d, J=7.5 Hz, H-3', H-6'), 7.54 (2H, dd, J=8.4, 2.7 Hz, H-9', H-11'), 7.58 (2H, m, H-5'', H-6''), 7.68 (1H, d, J=15.3 Hz, H-2), 8.70 (1H, br s, H-2''), 7.72 (1H, dd, J=7.2, 1.2 Hz, H-4''), 7.88 (1H, d, J=15.3 Hz, H-3), 8.12 (2H, d, J=7.5 Hz, H-8', H-12'), 8.38 (1H, dd, J=6.6, 2.1 Hz, H-7''), 12.20 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 106.79 (C-2', C-6'), 113.12 (C-4''), 118.67 (C-1''), 122.77 (C-6'', C-7''), 123.23 (C-5''), 125.90 (C-2), 126.79 (C-3''), 129.32 (C-1'), 129.90 (C-9', C-11'), 130.85 (C-8', C-12'), 134.96 (C-10'), 135.77 (C-2''), 137.83 (C-8''), 140.43 (C-3), 153.02 (C-3', C-4', C-5'), 164.48 (CO), 184.42 (C-1); ESI-MS, MeOH (Positive): m/z 428[M-H]$^+$, 450 [M+Na]$^+$, Negative: 428[M-H]$^-$, $C_{26}H_{21}NO_5$.

Trans-1-indolyl-3-(4'-hydroxyphenyl)-2-propen-1-one(**2h**): Dark brown powder, 85% yield, obtained and analysed by spectroscopic data as described by an earlier method [33].

Trans-1-indolyl-3-(2'-methylphenyl)-2-propen-1-one (**2i**): Obtained as brown solid; 80% yield, obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-1-indolyl-3-(thiophenyl)-2-propen-1-one (**2j**)*:* Creamish white powder; 70% yield, obtained and analysed by spectroscopic data as described by an earlier method [31b].

Trans-1-indolyl-3-(benzodioxanyl)-2-propen-1-one (**2k**): Light orange, 90% yield; mp 154-155°C; IR ν^{max} (KBr): 3449 1580, 1251, 752 (NH), 1638 (chalcone C=O), 1509, 1439, 1291 (aromatics) cm^{-1}**;** ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.25 (2H, s, H-5', H-6'), 6.88 (1H, d, J=8.4 Hz, H-3'), 7.21 (2H, m, H-5'', H-6''), 7.28 (1H, dd, J=8.4, 1.5 Hz, H-2'), 7.42 (1H, d, J=1.5 Hz, H-8'), 7.48 (1H, dd, J=6.6, 2.7 Hz, H-4''), 7.52 (1H, d, J=15.3 Hz, H-2), 7.66 (1H, d, J=15.6 Hz, H-3), 8.33 (1H, dd, J=6.3, 2.4 Hz, H-7''), 8.68 (1H, brs, H-2''), 12.04 (1H, brs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 64.86* (C-4'), 65.21* (C-5'), 122.66 (C-6'', C-7''), 123.26 (C-8'), 123.70 (C-2), 123.94 (C-5''), 126.76 (C-3''), 129.56 (C-1'), 135.34 (C-2''), 137.71 (C-8''), 140.28 (C-3), 144.45 (C-6'), 145.97 (C-3'), 184.69 (C-1) (*=interchangable); ESI-MS, MeOH (Positive): m/z 306 [M+H]$^+$, Negative: 304 [M-H]$^-$, $C_{19}H_{15}NO_3$.

3.3. Biology

3.3.1. MTT Anti-Proliferative Activity Assay

In vitro anti-cancer activity of phytomolecules is done by using MTT assay. Cytotoxicity testing *in vitro* was done by the method of Woerdenbag *et al.* 1-2X 10^4cells/well were incubated in the 5% CO_2 incubator for 24 h to enable them to adhere properly to the 96-well polystyrene microplate (Grenier, Germany). Test compound dissolved in 100% DMSO (Merck, Germany) in at least five doses was added and left for 6 h after which the compound plus media was replaced with fresh media and the cells were incubated for another 48 h in the CO_2 incubator at 37°C. The concentration of DMSO used in our experiments never exceeded 1.25%, which was found to be non-toxic to cells. Then, 10 ul MTT [3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide; Sigma M 2128] was added, and plates were incubated at 37°C for 4 h. One hundred microlitres of dimethyl sulfoxide (DMSO, Merck, Germany) was added to all wells and mixed thoroughly to dissolve the dark blue crystals. After a few minutes at room temperature to ensure that all crystals were dissolved, the plates were read on a spectrofluorometer FLUOstar Omega (BMG Labtech) at 570 nm. Plates were normally read within 1 h of adding the DMSO. The experiment was done in triplicate and the inhibitory concentration (IC) values were calculated as follows:

%inhibition=(1-OD at 570nm of sample well/OD at 570nm of control well)X100.

IC_{50} is the concentration mg/mL required for 50% inhibition of cell growth as compared to that of untreated control.

IC_{90} is the concentration lg/mL required for 90% inhibition of cell growth as compared to that of untreated control.

3.4. Molecular Modeling Parameters and Energy Minimization

To find the possible interactions of indolyl chalcones derivatives compound **1b** and **1d** with microtubule and liver receptor homolog-1 (LRH-1), we docked compound at 'microtubule binding site' and also at LRH-1site. Sybyl X 2.0 interfaced with Surflex-Dock module was used for molecular docking. The X-ray crystallographic structures of tubulin complex with ligand [PDB: 1SA0] [34] and LRH-1 [PDB: 3PLZ] [35] were taken from the protein data bank (PDB) and modified for docking calculations. Co-crystallized ligand was removed from the structure, water molecules were removed, H atoms were added and side chains were fixed during protein preparation. Protein structure minimization was performed by applying Tripos force field and partial atomic charges were calculated by Gasteiger-Huckel method [36-41].

3.5. Screening Through Pharmacokinetic Properties

In discovery process most of drugs fail to cross clinical trials because of poor pharmacokinetics. Thus, screening through pharmacokinetic properties was done according to our previous published papers [36-44] (Schrödinger, USA, 2011).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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