



Insilico Design and Synthesis, Evaluation of Anti-Colon Cancer Activity of Novel Stilbene Hybrids

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Various biologically important Stilbene analogues were competently synthesized using inexpensive, non-toxic, and readily available amino acids and Stilbene; the systematic study was carried out to characterize parameters such as TLC, melting point, IR, ¹H NMR and mass spectral studies. The synthesized compounds were screened for anticancer activities. The molecular docking studies have been performed by using software Autodock 4.2, Autodock vina. The targeted proteins are P450a2 & Estrogen.

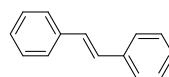
The reaction of phenylacetic acid substituted Benzaldehyde, and triethylamine in acetic anhydride was irradiated in a microwave oven for 3 minutes at 700W afforded (2E)-3-(substituted phenyl)-2-phenylacrylic acid. The above compound, after irradiating with hydrazine provided (2E)-3-(substituted phenyl)-2-phenyl acrylic acid hydrazide. Anti-Cancer activity for synthesized compounds was evaluated using the MTT assay technique against colon cancer. The results were obtained as a percentage in cell lysis data. The I_{C50} value of the compounds was between 0.037-0.0257 μM/lit. Among all the compounds, tyrosine derivatives exhibited the more potent activity. Insilico studies PCB-arg having more binding affinity with the receptor Cytochrome P450 A2 and PCB-try having more binding affinity with the receptor estrogen beta when compared to other derivatives.

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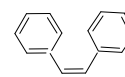
Keywords: Stilbene; colon cancer; characterization; anti-cancer activity; cytotoxicity.

ABBREVIATIONS

MIC : Minimum Inhibitory Concentration,
TLC : Thin layer chromatography
FTIR : Fourier transform infrared
NMR : nuclear magnetic resonance
IC₅₀ : half-maximal inhibitory concentration
µg/ml : microgram per milliliter



(E)-1,2-
diphenylethylene(or)
(E)-Stilbene , trans –
Stilbene

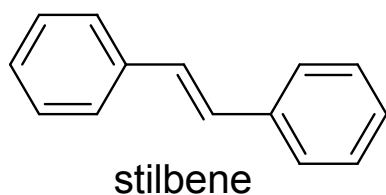


(Z)-Stilbene , Cis –
Stilbene
(Z)-1,2-
diphenylethylene

1. INTRODUCTION

Drugs are the greatest contributions of the 20th century to therapeutics. Their advent changed the outlook of diseases. They are one of the few curative drugs. Their importance is magnified in developing countries, where infectious diseases predominate. As a class, they are one of the most frequently used as well as misused drugs.

Early types of anti-microbial substances were not specifically anti-microbial but were usually toxic to all living cells [1]. They were of value only in so far as they could be employed without severe damage to the host. The search for more suitable anti-microbial agents resulted in the preparation and testing of many substances of the widely different constitution. From the systematic empirical investigations of one such class of chrysoidine dyestuff, knowledge of the activity of sulphanilamide arises. The growing evidence that the anti-microbial action of sulphonyl drugs [2] was due to competition with an enzymic metabolic process suggested that Fildes (1940) approach the problem.



A common name for trans-1,2-diphenyl ethylene is stilbene, or more specifically, stilbene is the alkene, ethene with two phenyl groups on other carbon of parent chain. The name was derived from the Greek word stilbos, which means shinning (Cis-trans isomerism E/Z notation/Z)-stilbene, which is sterically hindered and less stable. It is noticed that (Z)-stilbene has a melting point of 5^oC to 6^oC while the melting point of (E)-stilbene is 125^oC. This shows the significant difference between the two because (E)-stilbene is more common than (Z)-stilbene.

Stilbenes, produced by several plants in response to pathogen attacks, regulate many biological functions. In agreement with their role as antifungal [3], antibacterial [4], and cytotoxic activities [5] have been reported. Some of them, such as resveratrol, exert antioxidant activity, which modulates the synthesis of lipids, inhibit ribonucleotide reductase and DNA polymerase increase the activity of Map-kinase, an enzyme potentially related to neurodegenerative diseases such as Alzheimer's and Parkinson's, inhibit platelet aggregation and after the eicosanoid synthesis, both effects probably related the inhibition of the cyclooxygenase and hydroperoxides activities. These findings have stimulated the study of these compounds as anti-inflammatory [6] cardiotoxic and anti-platelet aggregating agents, anti-convulsant [7].

Also, many scientists have carried out the synthesis and biological activities of stilbene derivatives, which revealed that stilbene plays a significant role in the biomedical field. Pharmacological Studies have established that stilbene inhibits the synthesis of eicosanoids by platelets, reducing the incidence of coronary heart disease. It has also shown significant anticancer [8] antifungal [3], antimicrobial [9], antioxidant [8], anti-inflammatory [6], anticonvulsant activity, and synthesized stilbene derivatives using Wittig reaction [10], But the yield was inferior (10%). Inhibitory activities of stilbene from medicinal plants on the expression of cell adhesion molecules on THP1 cells [11]. there is a new synthesis of trans stilbenes [12,13] and chemoprotective properties resveratrol [14-15] and hydroxy stilbenoids [16] and cytotoxicity activity of hydroxylated resveratrol analogues [17]. synthesis of diaryl ethylene's [18].

1.1 Types of Cancer in the Colon and Rectum

Adenocarcinomas: More than 95% of colorectal cancers are a type of cancer known as

adenocarcinomas. These cancers start in cells that form glands that make mucus lubricate inside the colon and rectum. Other, less common types of tumours may also begin in the colon and rectum.

These include:

Gastrointestinal carcinoid tumours
Gastrointestinal stromal tumours (GISTs)
Lymphomas

1.2 Microwave Technology in the Synthesis of Organic Drugs

Several synthetic transformations in pharmaceutical and organic chemistry require prolonged heating and reflux of several hours. However, microwave-induced organic reaction enhancement chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis, where the microwave oven is the source of heating. Experiments involving heating time up to 6 hours in conventional methods, namely preparation of Benzocaine, Butamben, Phenytoin, 3-methyl-1-Phenyl pyrazole-5-one and Fluorescein. All these compounds were prepared easily in high yields in less than 10 minutes of microwave heating, and Purification, recrystallization, and drying of products were completed one day. This method is economical due to the savings of energy, fuel, and chemicals.

Significant limitations of classical chemistry practical are long time, elaborate and tedious apparatus setup, higher cost, longer reaction time and environmental pollution due to large quantities of solvents/reagents. On the other hand, microwave-induced organic reaction enhancement chemistry provides a non-conventional technique for the rapid synthesis of organic molecules.

The application of microwave irradiation is used for carrying out chemical transformations which are pollution-free and eco-friendly [10]. A commercial microwave oven is used as a convenient source of heat in the laboratory. The microwave-assisted organic reactions occur more rapidly, safely and with higher chemical yields, render the microwave method superior to the conventional method [19].

2. METHODS

TLC was employed for the confirmation of reaction progress and product formation. The

melting point and its range were determined by the open capillary tube method. While functional nature of carbons and protons of the structure was assigned by IR (Jasco-510 FT-IR Spectrophotometer at 4 cm⁻¹ using KBr pellet disc), ¹H-NMR (Varian VXR Unity at 400MHz using TMS as internal standard and DMSO-d₆/CHCl₃ as solvent), and mass spectral (Agilent LC/MS, positive mode, ESI) studies. All chemicals used for synthesis were AR grade purchased from Sd fine chemicals, Mumbai. All six compounds are soluble in the chloroform and the mobile phase for TLC ethyl acetate and petroleum ether in ratio 6:4 ratio. The purification of products was carried out by recrystallization, TLC and column chromatography. The synthesized compounds were confirmed by FTIR, ¹H-NMR, MASS spectroscopy.

2.1 Synthetic Procedures

1. Synthesis of (2E)-3-(substituted phenyl)-2-phenyl acrylic acid :

A mixture of phenylacetic acid (2 millimoles) substituted benzaldehyde (2 millimoles) and triethylamine (0.5milli moles) in acetic anhydride (5ml) was irradiated in a microwave oven for 3 minutes at 700W. The product obtained was poured into a hot saturated sodium carbonate solution (50ml) and left overnight. The mixture was extracted with ethanol, and the ether extracts were discharged, the aqueous solution was acidified with dilute HCl and the precipitated product was filtered and dried.

2. Synthesis of (2E)-3-(substituted phenyl)-2-phenyl acrylic acid hydrazide:

(2E)-3-(substituted phenyl)-2-phenylacrylic acid(0.01mole) and Hydrazine (0.01mole) in 40ml of methanol with a catalytic amount of glacial acetic acid were irradiated in a microwave oven for 2 minutes at 700W. The reaction mixture was cooled & poured onto crushed ice. The resultant solid was filtered& washed with water & recrystallized with 90% ethanol.

3. Synthesis of (2E)-3-(substituted phenyl)-2-phenylacrylic acid amide:

(2E)-3-(substituted phenyl)-2-phenylacrylic acid hydrazide (0.01mole) and amino acid(0.01mole) in 40ml of methanol with a catalytic amount of glacial acetic acid were irradiated in a microwave oven for 2 minutes at 700W. The reaction mixture was cooled & poured onto crushed ice.

The resultant solid was filtered & washed with water & recrystallized with 90% ethanol.

2.2 Spectral Data

(E)-2-amino (3-(4-chlorophenyl)-2-phenylacrylohydrazino-propanoic acid (PCB-ala): m.p.175-177°C, Rf value 0.88, IR : (KBr pellet, Cm^{-1}), 3423.22 NH (Sec. amine) stretching, 3076.87 C=C (aliphatic) stretching, 3020.68 C-H (aromatic) stretching, 2916.57 C-H (aliphatic) stretching, 1655.12 C=O stretching, $^1\text{H NMR}$: (DMSO $-\text{d}^6$, δ ppm): 11 (CONH), 8 NH (sec.amine), 7.11 – 7.48 CH (Aromatic), 1.43 CH (Methyl), 4.64 CH (Ethylene). **Mass** : (M+1) – 343.81

(E)-2-amino (3-(4-chlorophenyl)-2-phenylacrylohydrazino-3-(4-hydroxyphenyl)-propanoic acid (PCB-tyr): m.p.181-183°C, Rf value 0.62 IR: (KBr pellet, Cm^{-1}): 1487.77 - C=C stretching (aromatic), 3007.22 C-H(aromatic) stretching, 3087.36 C=C (aliphatic) stretching, 3104.06 Sec-NH, 2990.60 C-H (aliphatic) stretching, 763 C-Cl stretching. $^1\text{H NMR}$: (DMSO $-\text{d}^6$, δ ppm): 11 OH (Acid), 8 NH (sec.amine),

7.48 H (Ethylene) 7.11 – 7.42 CH (Aromatic), 6.68 CH (Ethylene). **Mass** : (M+1)– 435.13

(E)-2-amino-N- (3-(4-chlorophenyl)-2-phenylacrylohydrazino)-5-guanidinopentanoic acid (PCB-arg): m.p.170-172°C, Rf value 0.98, IR : (KBr pellet, Cm^{-1}) : 3545.25 (Sec. Amine) stretching, 3456.23 Ar(C-H), 1617.70 – C=O stretching (acid), 1492.30 – Aromatic (C=C) stretching. $^1\text{H NMR}$: (DMSO $-\text{d}^6$, δ ppm): 11 (CONH), 8 NH (Sec. amine), 7.11 - 7.42 CH (Aromatic), 4.46 CH (Ethylene). **Mass** : (M+1) - 429.15

(E)-2-amino-N-(3-(4-chlorophenyl)-2-phenylacrylohydrazino)-3-(1H-indol-3-yl)-propanoic acid (PCB-try): m.p.190-192°C, Rf value 0.54, IR : (KBr pellet, Cm^{-1}): 2891.49 Ar(-NH) stretching, 1617.70 C=O stretching, 1556.24 –CONH stretching, 1492.30 Ar (C=C) stretching, 836.70 Cl stretching. $^1\text{H NMR}$: (DMSO $-\text{d}^6$, δ ppm): 11 OH (Carboxylic acid), 10.1 NH (Pyrrole), 8 NH (sec. amine), 7.18 CH (Pyrrolo benzene), 7.11 – 7.42 CH (Benzyl), 4.54 CH (Ethylene). **Mass** : (M+1) – 458.2

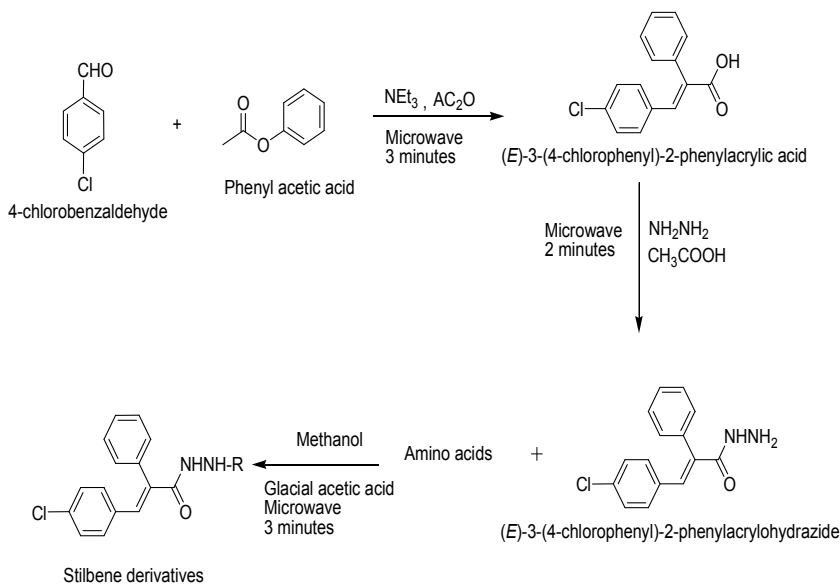
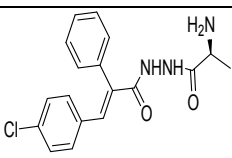
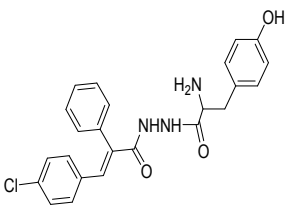
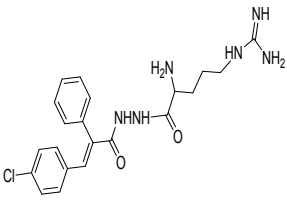
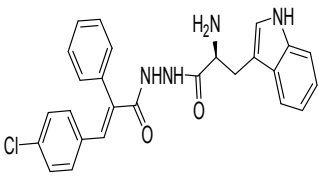
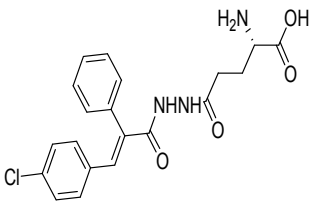
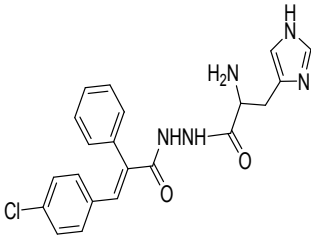


Fig.1. Synthetic scheme 1

Table 1. Characterization of compounds

Compound code	Structure	Molecular formula	Molecular weight g/mole	Percentage yield (%)
PCB-ala		C ₁₉ H ₂₀ ClN ₃ O ₂	343.81	90
PCB-tyr		C ₂₄ H ₂₂ ClN ₃ O ₃	435.13	58
PCB-arg		C ₂₁ H ₂₅ ClN ₆ O ₂	428.17	67
PCB-try		C ₂₄ H ₂₂ ClN ₄ O ₂	458.15	55
PCB-glu		C ₂₀ H ₂₀ ClN ₃ O ₄	401.84	97
PCB-his		C ₂₁ H ₂₀ ClN ₅ O ₂	409.87	20.3

(E)-2-amino(3-(4-chlorophenyl)-2-phenylacryloylhydrazino-3-(1H-imidazole-4-yl)-pentanedioic acid (PCB-glu): m.p.187-188°C, Rf value 0.90 IR : (KBr pellet, Cm^{-1}) : 3076.82 – COOH stretching, 3051.05 Aliphatic (C=C)stretching, 3020.46 Aromatic C-H stretching, 1596.85 C=O stretching, 1451.21 Aromatic C=Cstretching. $^1\text{H NMR}$: (DMSO $-d_6$, δ ppm): 11 OH (Acid), 8 NH (sec. amine), 7.11 – 7.42 CH (Aromatic), 4.42 CH (Ethylene), 2.05 – 2.23 CH_2 (Ethane).Mass : (M+1) – 467.1

(E)-2-amino (3-(4-chlorophenyl)-2-phenylacryloylhydrazino-3-(1H-imidazole-4-yl) propanoic acid (PCB-his) :m.p.184-186°C,Rf value 0.76,IR : (KBr pellet, Cm^{-1}) : 1492.30 Aromatic (C=C) stretching, 3456.23 Aromatic (CH)stretching,1701.20 C=O stretching, 1617.70, Aromatic (-NH bending), 749.92 –Cl stretching.

2.3 Biological Evaluation

In vitro Anticancer activity of synthesized stilbene derivatives:

MTT Assay:

1. MTT solution preparation (stock solution): 5 mg in 1 ml of PBS.
2. Cell culture:

The cell line used for the study were HEK-293, HT-29, HepG2, K562, A549 and KB Mouth (human procured from NCCS, Pune). The cell lines were maintained in 96 wells microtiter plate containing MEM media supplemented with 10% heat-inactivated fetal calf serum (FCS), including 5% of a mixture of Gentamicin (10 μg), Penicillin (100 Units/ ml) and Streptomycin (100 μg /ml) in the presence of 5% CO_2 at 37°C for 48-72 hours.

3. Cytotoxicity Assay:

In vitro growth inhibition effect of test compound was assessed by colorimetric or spectrophotometric determination of conversion of MTT into "Formazan blue" by living cells.

A) Remove the supernatant from the plate and add fresh MEM solution and treat with different concentrations of extract or compound appropriately diluted with DMSO. The Control group contains only DMSO. In your study, 10, 20, 25, 30 and 50 μl of the stock solution (10 mg/ml prepared in DMSO) were added to respective wells containing 100 μl of the medium. So, the final concentrations were 10, 20, 25, 30 and 50 μg / ml.

B) After 48hrs incubation at 37°C in a humidified atmosphere of 5% CO_2 , a stock solution of MTT was added to each well (20 μl , 5mg per ml in sterile PBS) for further 4 hr incubation.

C) The supernatant was carefully aspirated. The precipitated crystals of "Formazan blue" were solubilised by adding DMSO (100 μl), and optical density was measured at a wavelength of 570nm using LISA plus.

4. The results represent the mean of five readings. The concentration at which the OD of treated cells was reduced by 50% with respect to the untreated control.
5. Formula:

$$\text{Surviving cells (\%)} = \frac{\text{Mean OD of test compound} \times 100}{\text{Mean OD at control}}$$

2.4 Principle of the Assay

This is a colourimetric assay that measures the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria, reduced to an insoluble, coloured (dark purple) formazan product. The cells are then solubilized with an organic solvent (e.g., DMSO, Isopropanol) and the released, solubilized formazan reagent is measured spectrophotometrically. Since the reduction of MTT can only occur in metabolically active cells, the activity level is a measure of the viability of the cells.

3. RESULTS

3.1 Anti -Cancer Activity of Novel Stilbene Derivatives

There was a total of six compounds synthesized in this study. Separate studies established all the compounds' structure. The TLC technique authenticated the purity of the compounds. The Anti –Cancer activity for the five synthesized compounds was carried out using the MTT assay technique. The results were obtained as a percentage in cell lysis data. The $\mu\text{g}/\text{ml}$ concentration IC_{50} was converted into $\mu\text{M}/\text{lt}$ concentration using a molecular weight of the compounds, and the results are presented in the table above. The IC_{50} value of the compounds was between 0.037-0.0257 $\mu\text{M}/\text{lt}$. Among all the compounds, tyrosine derivatives exhibited the more potent activity. The critical difference (CD 5%) value was found to be 0.01 or less.

However, the difference in cytotoxicity among the synthesized compounds was significantly less. This indicated the presence and consideration of amino acids for Anti Cancer activity.

3.2 Cell line - HT 29

Least concentration to show 50% inhibition of cell line was found to be 10 μ g.

3.3 Docking Protocol

Procedure for molecular docking

1. Draw structure of synthesized molecule with Chemdraw 16.0 and cleanup the structure.
2. Copy the structure and past it in Chem 3D, and save it as a (.mol) file
3. Using open babble software, convert the (.mol) file to (.pdb) file
4. Open PDB and download the suitable protein.
5. For the activity, we used estrogen receptor beta and cytochrome P450A2 receptor as

- a protein and do0..wnload them in PDB format
6. Open and optimize the protein by removing water molecules and pre ligands from the structure and save as (.pdb) file.
 7. Open Autodock and load the molecule
 - Add polar hydrogen
 - Save as (.pdbqt) format
 - Draw grid box
 - Save the box
 8. Later load ligand and add energy (the software will auto-detect that and add some energy to the molecule)
 9. Add torsion root
 10. Save as (.pdbqt) format
 11. Run Autodock vina to get results.
 12. AutoDock 4.2 is currently being distributed free of charge as open-source under a GPL license at the WWW site: <http://autodock.scripps.edu>. ADT is being distributed free of charge as part of the MGL Tools package at the WWW site: <http://mgltools.scripps.edu/downloads>.

Table. 2. Results for anti-cancer activity

S.No.	Sample	Concentration	Absorbance (nm)	Results as observed	IC50 (μ g)	Micro moles/lt
1.		10	0.282	50% lysis		
2.		20	0.281	50% lysis		
3.	PCB-arg	25	0.279	50% lysis	10 μ g	0.0241
4.		30	0.272	50% lysis		
5.		50	0.250	>50%lysis		
6.		10	0.293	50% lysis		
7.		20	0.286	50% lysis		
8.	PCB-glu	25	0.281	50% lysis	10 μ g	0.0257
9.		30	0.281	50% lysis		
10.		50	0.279	50% lysis		
11.		10	0.295	50% lysis		
12.	PCB-tyr	20	0.254	>50%lysis	10 μ g	0.0237
13.		25	0.252	>50%lysis		
14.		30	0.244	>50%lysis		
15.		50	0.226	>50%lysis		
16.		10	0.291	50% lysis		
17.		20	0.282	50% lysis		
18.	PCB-try	25	0.274	50% lysis	10 μ g	0.0247
19.		30	0.273	50% lysis		
20.		50	0.270	50% lysis		
21.		10	0.292	50% lysis		
22.		20	0.254	>50%lysis		
23.	PCB-ala	25	0.249	>50%lysis	10 μ g	0.0252
24.		30	0.245	>50%lysis		
25.		50	0.237	>50%lysis		
26.	Control	00	0.589	No lysis		

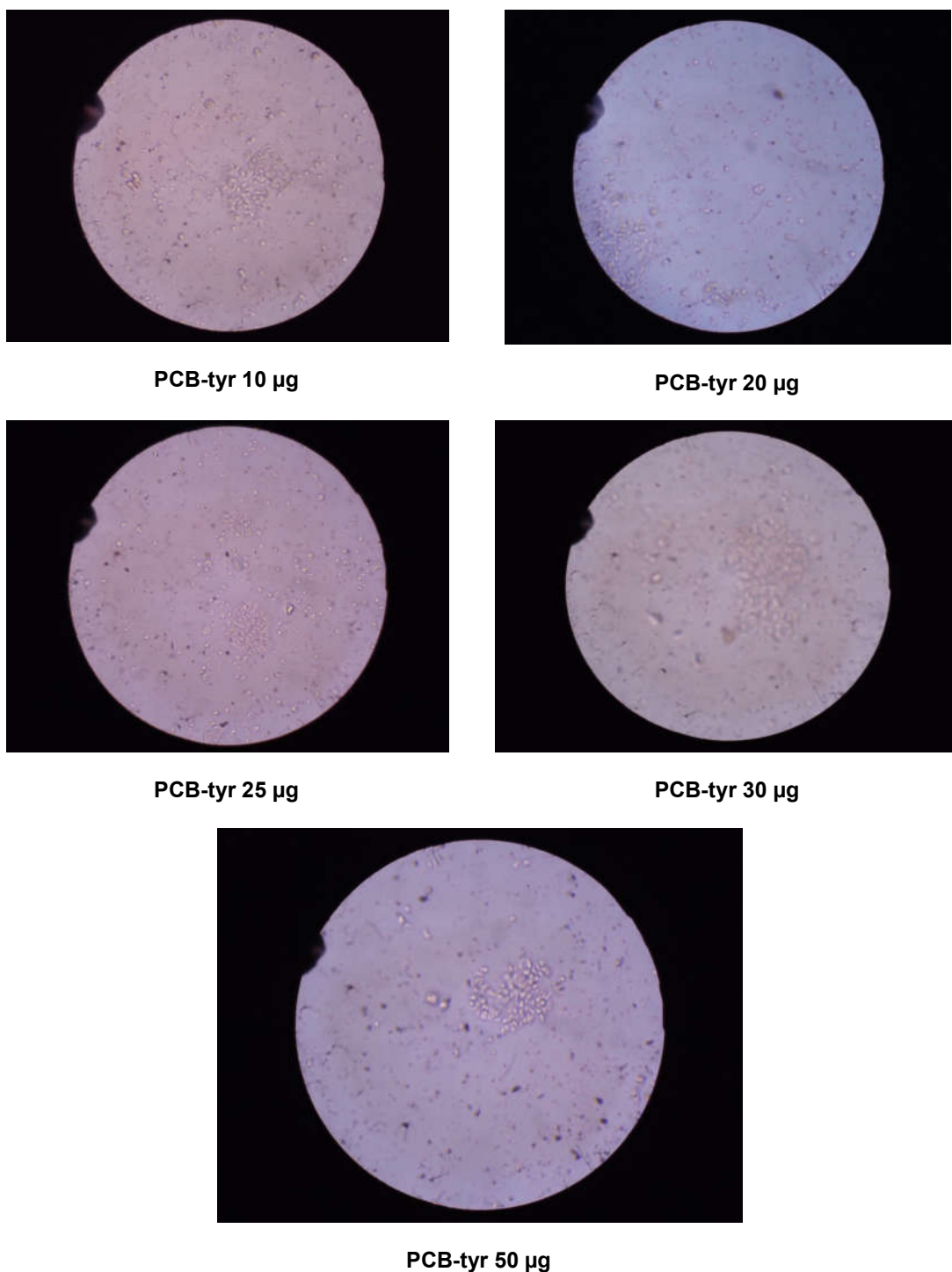


Fig. 2. photographs showing Anti-cancer activity of compound PCB-tyr

The ligand has shown the attractive charge with the amino acids arginine, glutamic acid and conventional hydrogen bond interactions with the amino acid proline, unfavorable donor-donor

interactions with the amino acid valine, pi-cation and pi-anion interactions with the amino acid glutamic acid and histidine and pi-alkyl interactions with the amino acid leucine.

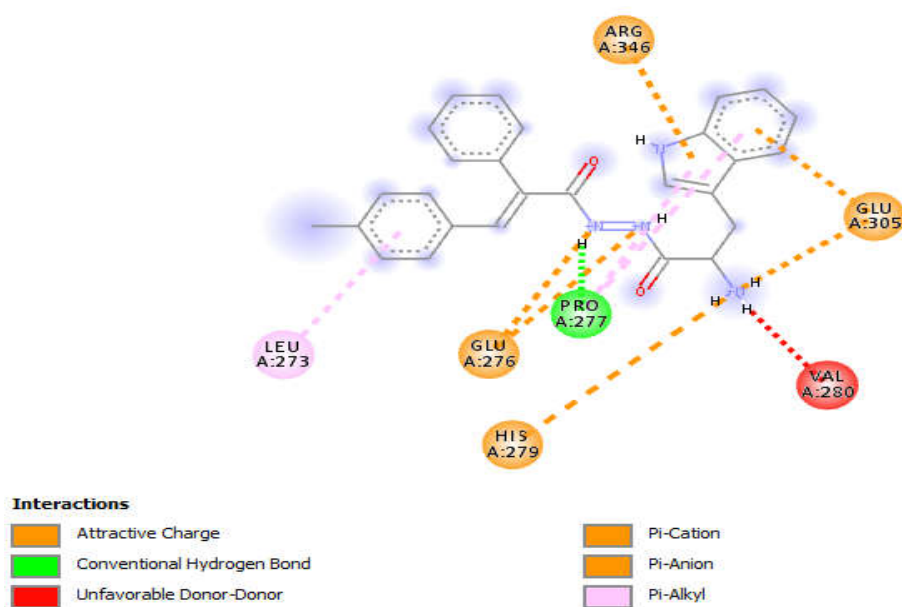


Fig. 3. PCB-try and 2D interaction with estrogen receptor beta

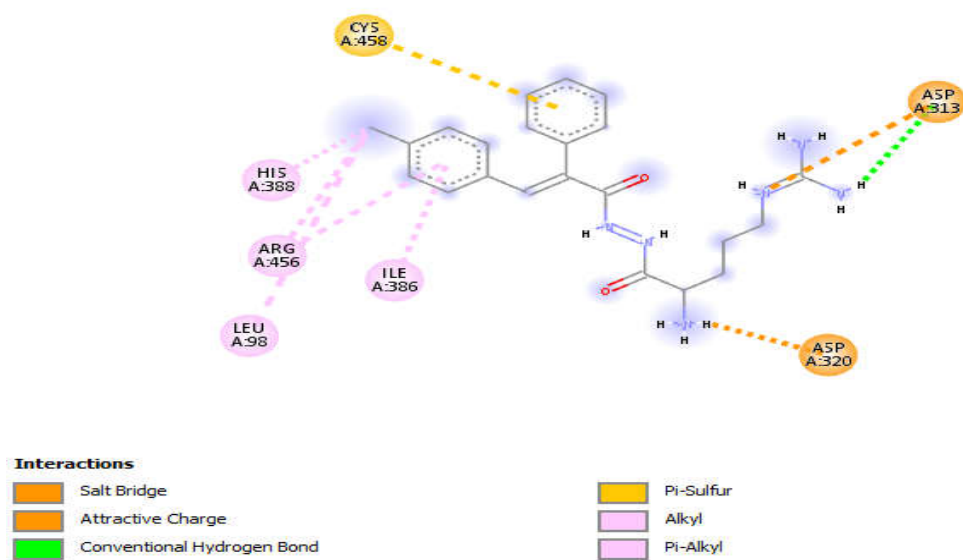


Fig. 4. PCB-arg and 2D interactions with cytochrome P450A2 receptor

Table 3. Docking scores for synthesized compounds

Compound code	Binding energy (Kcal/mol) P450a2 receptor	Binding energy (Kcal/mol) Estrogen receptor beta
PCB-ala	-7.4	-6.7
PCB-tyr	-7.5	-7.0
PCB-arg	-8.9	-7.7
PCB-try	-8.5	-8.3
PCB-glu	-6.9	-6.0
PCB-his	-7.2	-5.7

The ligand has shown the salt and attractive charge with the amino acid asparagine and conventional hydrogen bond and pi-sulfur interactions with the amino acid cysteine, alkyl and pi-alkyl interactions with the amino acid leucine.

4. DISCUSSION

Results are described above and can be discussed as follows. The Stilbene derivatives interfered with prostaglandin E2 (PGE2) generation in murine intestinal mucosa in vivo and colon derivative cells in-vitro. The ability of Stilbene derivatives to interfere with Adenomatous polyposis coli (APC). Adenoma development was paralleled by inhibition of PGE2 production, which might be involved as an antitumour promotional mechanism. The superior inhibition of colon cell growth in-vitro by (methylated derivative of resveratrol) DMU-212 compared to resveratrol is not reflected by a corresponding difference in potency as far as inhibition of PGE2 production invitro is concerned. Resveratrol and other Stilbene derivatives bind and activate (Estrogen Receptor Alpha and beta) ER- α as well as ER- β . Resveratrol acts as a selective estrogen receptor modulator, and the effects of resveratrol depend on cell type and target organs and the presence of endogenous estrogens.

ER- β is present in colon. Stilbenes prevent colon cancer via estrogenic action and interaction with ER- β in the colon. Stilbene derivatives show the growth-inhibiting action through cell-cycle arrest induced by upregulation of P21, P27, P53 and downregulation of cyclin D₁ and cyclin E. Apoptosis action by upregulating the expression of PUMA (p53 upregulated modulator of apoptosis), downregulating (tumour necrosis factor) TNF related apoptosis-inducing ligand [20].

Two targeted proteins were selected for docking subsequently, the studies were carried out. Docking studies carried out using autodock 4.2 reveals that the PCB-arg has a more binding affinity towards cytochrome p450 A2 receptor when compared with the other synthesized derivatives. Compared with the other synthesized products, the PCB-try has shown a more binding affinity with the estrogen receptor beta. The PCB-try, PCB-tyr, PCB-ala has shown the medium binding affinity with the cytochrome p450 A2 receptor. The PCB-arg, PCB-tyr, and PCB-ala have shown medium binding affinity

with the estrogen receptor beta. Cytochrome p450 plays an important role in the metabolism of endogenous and exogenous substances, especially drugs. Moreover, many p450 can serve as targets for disease therapy [11,21].

5. CONCLUSION

The synthesized stilbene derivatives are considered a promising molecules for fighting cancer. Some of these newly synthesized compounds have stimulating effects. Stilbene derivatives of tyrosine and alanine are the most active, while other compounds have moderate activity. Comparing the compounds indicates that protecting groups like hydroxyl and amine groups lead to better action. Moreover, the absence of the methoxy groups provides a better lipophilic property.

In most cases, the efficacy of the other synthesized compounds has less activity compared to tyrosine and alanine, which have the most potent activity. Furthermore, the lack of effect on non-tumour cells demonstrates the selectivity of these molecules for tumour cells, which is an essential aspect for therapeutic applications. In vitro cell culture experiments and preclinical animal studies with stilbene derivatives suggest a multitude of mechanisms for the pharmacological activity of this group of compounds. Elucidation of mechanisms of action and in-vivo efficacy of stilbenes may lead to new approaches for the treatment and prevention of various neoplasms, including colon cancer. Docking studies revealed that PCB-arg has a more binding affinity with the receptor Cytochrome P450 A2. PCB-try has a more binding relationship with the receptor Estrogen beta compared to other derivatives. [22-23] This study showed that the ligands might have high tumour suppressing properties and explain about medium tumour suppressing properties of other derivatives.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICS APPROVAL

It is not applicable.

AVAILABILITY OF DATA AND MATERIAL

All data and material are available upon request

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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