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Research

Design, Synthesis and Evaluation of Novel 7-Azaindole Derivatives As Anti-Cancer Agents

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Abstract

Azaindoles are an important class of nitrogen containing heterocyclics and were identified as the most active and potent classes of compounds with wide range of biological and pharmacological activities.A new series of 7-aza indole derivatives were characterized by spectral data and evaluated for anticancer activity activity. The compounds 10m, 10n, were found to be good inhibitors of HELa and MCF-7. Most of the compounds inhibited HELa and MCF-7with the IC_{50} values, ranging from 0.68 µM 6.24 µM. Amongst them, compounds 10m, 10n with dichlorophenyl anddibromophenyl substituted molecules exhibited strongest inhibitory activity against MCF-7 and HELa with IC_{50} 0.78±1.33, 1.31±0.02 µM and 0.92±0.03, 1.91±0.02 µM respectively. when compared to standard cisplain with IC_{50} of 0.68±0.02 µM and 1.65±0.02, Thus, these new 7-aza indole derivatives have emerged as new cancer inhibitors for further exploitation as anti-cancer agents. Docking studies of all the molecules disclosed close hydrogen bond interactions within the binding site.

Keywords: 7-Azaindole derivativesm Anticancer activity, Molecular docking

INTRODUCTION

Cancer is uncontrolled, rapid proliferation of abnormal cells, is the second leading cause of mortality after cardiovascular diseases (1). About 9.6 million people die from cancer each year (2). Although anticancer medication development has made significant progress, there are still several obstacles to treating cancer, such as low efficacy, excessive toxicity, and drug resistance, which have had a significant negative impact on patients' ability to lead normal lives (3). Therefore, one of the most important areas of current cancer research is the hunt for powerful, safe anticancer agents with great selectivity(4). Indole is wide application in life sciences has stimulated the development of a number of methods for its derivative synthesis (5-9). Replacement at the C4, C5, C6, or C7 position of indole by ansp^2-hybridized nitrogen provides a skeleton containing a hydrogen-bond donor and acceptor in a rigid three-atom arrangement, respectively (10). As a natural product, 7-azaindole (1*H*-pyrrolo[2,3-b]pyridine) possesses an electron deficient pyridine ring and a [4,3]-bicyclical indene skeleton with a fused electron-rich pyrrole ring (11).

In the last few decades, a series of molecular-targeted small-molecule cancer drugs have been introduced to the clinic. Various azaheterocyclic ring systems in the structure of these drugs have taken their place in the center of medicinal chemistry studies as very useful tools and building blocks for the synthesis of these small molecule cancer therapeutics. Indole is a very important heterocyclic system as the main structure of the essential amino acid tryptophan and is the building block of many compounds of

natural origin. Therefore, it is included in the structure of many molecules such as naturally sourced proteins, receptors, hormones, enzymes, neurotransmitters, and alkaloids (12-14).

The wide variety and strong biological activity of natural compounds containing the indole ring has also attracted the attention of researchers over the years and has led to the isolation and/or synthesis of numerous compounds containing the indole ring. An important part of anti-cancer compounds are molecules that inhibit tubulin polymerization. After the isolation of vinca alkaloids vincristine and vinblastine and determination of their biological activities, one of the interesting and important biological activities of the compounds containing the indole ring is undoubtedly its anti-cancer effect (15-18).

Cediranib is an indole derivative with potent inhibitor activity of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (19). Osimertinib, for the treatment of NSCLC and advanced renal cell carcinoma, and sunitinib, for the treatment of gastrointestinal stromal tumors, are also the indole containing drugs (20). Additionally, anlotinib, a novel oral multitarget tyrosine kinase inhibitor for advanced lung cancer is also indole-derived small drug inhibitor (21).

NEED FOR THE PRESENT WORK

Design and synthesis of heterocyclic compounds, such as 4-azaindoles, 5-azaindoles, 7-azaindoles, and azaindole complexes, based on the indole and azaindole scaffold have produced a number of potent anticancer compounds, some of which have shown inhibitory activity on cancer cell lines or target at nanomolar concentration range with minimal side effects and toxicity. The fact that the NH group in indoles and azaindoles frequently forms the key hydrogen bonds with the corresponding receptor, as well as the SAR and detail mechanism of actions of active compounds. more than ten intriguing anticancer lead compounds containing indole or azaindole skeleton were found and several of them were identified effectively inhibiting the growth of solid tumors and metastasis of cancer cells. The remarkable anticancer lead compounds developed by designing indole or azaindole hybrids with other active moiety and azaindole heterocyclic scaffolds targeting on specific target are unquestionably highlights of the past few years; these accomplishments offer helpful strategies and hints for the development of better antitumor activity agents. However, it still falls short of our expectations and needs. For instance, many compounds still exert their effects at the cellular level, the majority of their mechanisms remain at the molecular docking level, and the precise binding sites between active molecules and receptors are still unknown, making it challenging to target-design active molecules has made the design of indole and azaindole molecules targeting growth factors, receptors, enzymes, and kinases into a trend. also have been elucidated as far as possible. as shown in General Structure I containing electron-withdrawing/electron-releasing substituents on azaindole.

MATERIALS AND METHODS

Chemistry

Melting points were determined by open capillary tubes using VEEGO VMP-D Digital melting point apparatus. FTIR spectra of the powdered compounds were recorded using KBr on JASCO FTIR 4100 series and are reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER-II 400 (400 MHz NMR, ^{13}C NMR 100 MHz) spectrophotometer using TMS as an internal reference. Purity of the compounds was checked on pre-coated TLC plates using silica G as stationary phase, iodine vapors and ultra-violet rays as the visualizing agent. All chemicals including standard drugs and solvents were procured from Sigma-Aldrich, Hi Media, Bangalore, India and others. The estimation of biochemical parameters was carried out using kits (Sigma-Aldrich).

EXPERIMENTAL PROCEDURE

General procedure for preparation of Ortho-iodoanilines (3a-d)

A Suspension of 4-substituted aniline **(1a-d)** (1equiv) in aqueous solution of sodium bicarbonate General procedure: Step A: A suspension of appropriately substituted aniline(0.045 mol) in aqueous solution (50.0mL) of sodium bicarbonate (0.045 mol) was stirred for 0.5h.Theniodine(0.040mol) wasaddedat5–10°Candthemixturewasstirredfor 12.0h.After completion, the reaction mixture was diluted with ethylacetate (250 ml) and extracted with ethyl acetate (3 × 250 ml). The organic layers were collected, combined, washed with saturated aqueous sodium thiosulfate solution (2 × 125 ml), dried over anhydrous Na2SO4 and concentrated under vacuum. The crude product was purified bycolumn chromatography on silica gel using 3:1, hexane-ethyl acetate to afford the desiredo-iododerivative.

Generalprotocolforsynthesisoftosylatedo-iodoanilines (5)

Toa solution of 2-iodoaniline **(3a-d)** (9mmol) in anhydrous pyridine (20ml) was added in p-toluenesulfonyl chloride **(4)** (10.8mmol).The reaction mixture was stirred for 10hrs at roomtemperatureunder nitrogen atmosphere,extracted with ethyl acetate. The combinedorganic phases were washed with brine(45ml), dried over sodium sulfate, filtered andconcentrated.Theresiduewaspurifiedbyflashchromatography,usingamixtureofethylacetateandhexane(1:10)as eluent,toaffordtheproductsaswhite solid.

Generalprotocolforsynthesisof1-vinyl-1H-pyrrolo[2,3-b]pyridine (8):

A solution of 7-azaindole **(6)** purchased from Aldrich Chemical Co., Inc. (118 mg, 1 mmol) and bromoethene**(7)** (150 mg, 1.1 mmol) in dry DMF (10 mL) was stirred for 4 h at room temperature under an atmosphere of nitrogen. After the solvent was removed, 70 mL of ether was added and the solution was washed with saturated aqueous NaHCO3 (20 mL × 2), dried (MgSO4), and concentrated in vacuume. The crude product was purified by chromatography on a silica gel column using hexane/EtOAc (8:2) to give compound (8) as colorless needles:

Generalprocedureforcouplingofvinyl indolewith tosylated o-iodoaniline:
A mixture of vinyl azaindole (0.5mmol) **(8)**, tosylated o-iodo aniline **(5)** (1mmol), Cs_2C0_3(1mmol)andacetonitrile(2ml) wasstirredatroomtemperaturefor 8hrs.Thereactionmixturewasquenched with saturated solution of $Na_2S_2O_3$ (5ml) and extracted with ethyl acetate. Thecombined organic phaseswerewashedwithbrine (45ml),dried oversodiumsulfate, filtered and concentrated. The residue was purified by flash chromatography,usinga mixture of ethyl acetate and hexane(1:10) as eluent, to afford the products as whitesolid as N-(4-chloro-2-iodophenyl)-N-(1-vinyl-1H-pyrrolo[2,3-b]pyridin-3-yl) sulfonamides **(9a-p)**.

Generalprocedurefor synthesis of (Z)-6-(sulfonyl)-6H-7,10-etheno-5,13-(metheno) pyrido[2,3-b][1,5]diazacycloundecine derivatives (10a-p):
Compounds N-(4-chloro-2-iodophenyl)-N-(1-vinyl-1H-pyrrolo[2,3-b]-pyridin-3-yl) sulfonamides (9a-p) (0.7 mmol), and Bis (triphenylphospane) palladium (0.06 gm or 0.4 mmol) in ethanol (30 mL) were refluxed for 9 hour. The residue resulted after the removal of ethanol was dissolved in dichloromethane and then washed with water. Volatilities were removed under vacuum to afford the title compounds (**10a-p**) which were purified over silica.

Scheme-I:

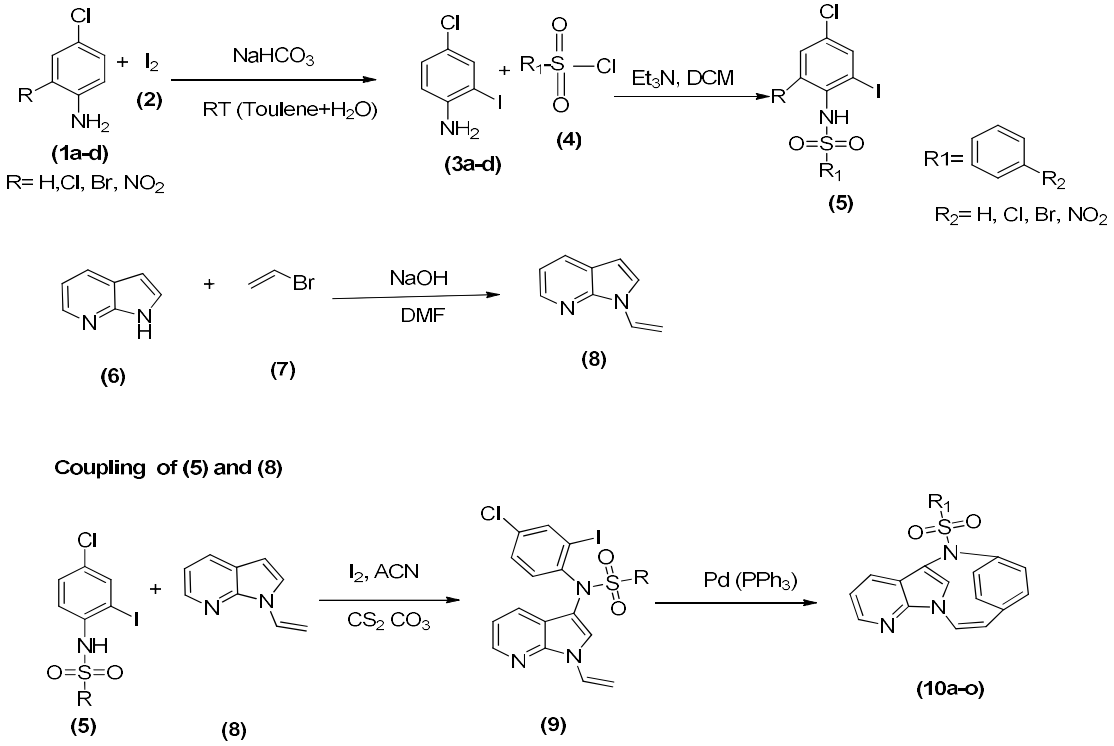

Table 1: Physical data of Synthesized compounds (10a-o)

S.No	Compound	M. Form	M.Wt	M.P	Rf*	% Yield
1	10a	$C_{16}H_{13}N_3O_2S$	311	235-237	0.7	57
2	10b	$C_{16}H_{12}ClN_3O_2S$	345	268-270	0.4	60
3	10c	$C_{16}H_{12}BrN_3O_2S$	390	203-205	0.6	75
4	10d	$C_{16}H_{12}N_4O_4S$	356	210-212	0.5	68
5	10e	$C_{21}H_{15}N_3O_2S$	373	198-200	0.8	52
6	10f	$C_{21}H_{14}ClN_3O_2S$	407	248-250	0.6	61
7	10g	$C_{21}H_{14}BrN_3O_2S$	452	263-265	0.4	38
8	10h	$C_{21}H_{14}N_4O_4S$	418	270-272	0.5	78
9	10i	$C_{19}H_{13}N_3O_2S_2$	379	169-171	0.7	57
10	10j	$C_{19}H_{12}ClN_3O_2S_2$	413	188-190	0.5	72
11	10k	$C_{19}H_{12}BrN_3O_2S_2$	458	230-232	0.5	84
12	10l	$C_{19}H_{12}N_4O_4S_2$	424	195-197	0.8	65
13	10m	$C_{21}H_{13}Cl_2N_3O_2S$	441	263-265	0.4	59
14	10n	$C_{21}H_{13}Br_2N_3O_2S$	531	190-192	0.8	81
15	10o	$C_{21}H_{13}N_5O_6S$	463	214-216	0.5	48

** Mobile phase: hexane: ethyl acetate*

Characterization of compounds:

(Z)-6-(methylsulfonyl)-6H-7,10-etheno-5,13-(metheno)-pyrido[2,3-b][1,5]di-aza cycloundecine (10a) Compound **10a** obtained as yellowish orange solid

^{1}H NMR (400MHz DMSO, δ ppm):7.906-7.927 (d, 2H, *J=8.4* Hz, Ar-H) 7.606-7.724 (t, 1H, *J*=4.0 Hz, Ar-H), 7.284-7.586 (m, 6H, Ar-H), 5.370 (s, 1H, ethylene), 2.85 (s, 3H, methyl).

^{13}C NMR (100MHz, DMSO): 142.18, 132.54, 129.35, 129.09, 128.56, 128.41, 126.88, 125.27, 124.48, 114.02, 42.18, MASS spectrum m/z: 313.14$[M+2]^{+}$,443.25$[M+4]^{+}$, Calc. for $C_{16}H_{13}N_3O_2S$; CHN: 61.72; H, 4.21; N, 13.50; S, 10.30; Found: 61.70; H, 4.26; N, 13.55; S, 10.25. **IR (KBr, cm^{-1}):** 3058.56 (C-H, Aromatic), 2976.58 (C-H, Aliphatic), 1660 (C=N), 1591.59(C=C**),** 1222.35 (S=O), 1080.34 (C-N).

(Z)-6-((chloromethyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]di-azacycloundecine (10b) : Compound **10b** obtained as white solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.906-7.927 (d, 2H, *J=8.4* Hz, Ar-H), 7.703-7.724 (d, 2H, *J*=4.0 Hz, Ar-H), 7.567-7.606 (t, 1H, Ar-H), 7.370-7.408 (m, 4H, Ar-H), 4.689 (s, 1H, ethylene), 3.066 (s, 2H, methylene).

^{13}C NMR (100MHz, DMSO): 153.78, 152.34, 143.63, 142.44, 139.59, 138.74, 136.03, 129.96, 129.40, 127.96, 127.65, 126.73, 125.01, 119.01, 122.27, 119.01, 48.15, 38.66. MASS spectrum m/z: 347.14$[M+2]^{+}$,Calc. for $C_{16}H_{12}ClN_3O_2S$; CHN: C, 55.57; H, 3.50; N, 12.15; O, 9.25; S, 9.27; Found: C, 55.50; H, 3.55; N, 12.18; O, 9.20; S, 9.22; **IR (KBr, cm^{-1}):** 3081.56 (C-H, Aromatic), 2924.43 (C-H, Aliphatic), 1638.12 (C=N), 1572.70(C=C**),** 1236.28 (S=O), 1136.97 (C-N).

(Z)-6-((bromomethyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10c): Compound **10c** obtained as yellowish orange solid.

^{1}H NMR (400MHz DMSO, δ ppm):7.928-7.923 (d, 2H, *J=8.4* Hz, Ar-H) 7.659-7.724 (t, 1H, *J*=4.0 Hz, Ar-H), 7.234-7.596 (m, 6H, Ar-H), 5.371 (s, 1H, ethylene), 2.35 (s, 2H, methylene).

^{13}C NMR (100MHz, DMSO): 161.32, 140.18, 130.54, 126.35, 126.03, 125.16, 124.41, 123.88, 122.27, 116.48, 113.02, 48.18, MASS spectrum m/z: 392.14$[M+2]^{+}$,Calc. for $C_{16}H_{13}N_3O_2S$; CHN: 49.24; H, 3.10; N, 10.77; S, 8.22; Found: 49.53; H, 3.10; N, 10.70; S, 8.20. **IR (KBr, cm^{-1}):** 3062.56 (C-H, Aromatic), 2986.18 (C-H, Aliphatic), 1650 (C=N), 1585.19 (C=C**),** 1228.15 (S=O), 1082.34 (C-N).

(Z)-6-((nitromethyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10d): Compound **10d** obtained as yellowish white solid.

^{1}H NMR (400MHz DMSO, δ ppm):7.918-7.921 (d, 3H, *J=8.4* Hz, Ar-H), 7.661-7.664 (t, 1H, *J*=4.0 Hz, Ar-H), 7.230-7.595 (m, 5H, Ar-H), 5.370 (s, 1H, ethylene), 2.30 (s, 2H, methylene).

^{13}C NMR (100MHz, DMSO): 150.25, 135.10, 128.54, 125.35, 124.03, 123.16, 120.41, 119.18, 115.27, 113.40, 110.02, 45.18, MASS spectrum m/z: 392.14$[M+2]^{+}$,Calc. for $C_{16}H_{13}N_3O_2S$; CHN: 49.24; H, 3.10; N, 10.77; S, 8.22; Found: 49.53; H, 3.10; N, 10.70; S, 8.20. **IR (KBr, cm^{-1}):** 3062.56 (C-H, Aromatic), 2986.18 (C-H, Aliphatic), 1650 (C=N), 1585.19 (C=C**),** 1228.15 (S=O), 1082.34 (C-N).

(Z)-6-(phenylsulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]di- azacycloundecine (10e):

^{1}H NMR (400MHz DMSO, δ ppm): Compound **10e** obtained as orange solid.

^{1}H NMR (400MHz DMSO, δ ppm):7.926-7.928 (d, 2H, *J=8.4* Hz, Ar-H) 7.668-7.721 (t, 1H, *J*=4.0 Hz, Ar-H), 7.238-7.535 (m, 6H, Ar-H), 5.376 (s, 1H, ethylene), 2.28 (s, 2H, methylene).

^{13}C NMR (100MHz, DMSO): 140.18, 138.12, 130.54, 126.35, 126.03, 125.16, 124.41, 123.88, 122.27, 116.48, 113.02, 48.18, MASS spectrum m/z: 392.14$[M+2]^{+}$,Calc. for $C_{16}H_{13}N_3O_2S$; CHN: 49.24; H, 3.10; N, 10.77; S, 8.22; Found: 49.53; H, 3.10; N, 10.70; S, 8.20. **IR (KBr, cm^{-1}):** 3051.89 (C-H, Aromatic), 2922.61 (C-H, Aliphatic), 1722.32 (C=O), 1588.12 (C=C, Aromatic), 1253.72(C-O).

Z)-6-((4-chlorophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10f): Compound **10f** obtained as yellowish white solid.

^{1}H NMR (400MHz DMSO, δ ppm): 7.90-7.92 (d, 2H,Ar-H), 7.72-7.75 (t, 2H, *J*=4.0 Hz, Ar-H), 7.65-7.68 (m, 4H, *J*=4.0 Hz, Ar-H), 7.55-7.60 (m, 4H, *J*=4.0 Hz, Ar-H), 5.21 (s,1H, amide), **^{13}C NMR (100MHz, DMSO):** 150.10, 138.10, 135.01, 130.10, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 114.3. **MASS spectrum m/z:** 409.14 $[M+2]^{+}$Calc. for $C_{21}H_{14}ClN_3O_2S$; CHN: C, 61.84; H, 3.46; Cl, 8.69; N, 10.30; O, 7.85; S, 7.86Found: C, 58.56; H, 3.55; N, 15.51; O, 14.28. **IR (KBr, cm^{-1}):** 3058.56 (C-H, Aromatic), 2976.58 (C-H, Aliphatic), 1724.84 (C=O**),** 1591.59 (C=C, Aromatic), 1080.34 (C-O).

(Z)-6-((4-bromophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10g) Compound **10g** obtained as white crastaline solid.

^{1}H NMR (400MHz DMSO, δ ppm): 7.94-7.96 (d, 2H,Ar-H), 7.84-7.87 (t, 2H, *J*=4.0 Hz, Ar-H), 7.62-7.68 (m, 4H, *J*=4.0 Hz, Ar-H), 7.54-7.60 (m, 4H, *J*=4.0 Hz, Ar-H), 5.35 (s,1H, amide), **^{13}C NMR (100MHz, DMSO):** 141.10, 139.20, 138.21, 135.35, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 119.75, 117.18, 118.34. **MASS spectrum m/z:** 454.14 $[M+2]^{+}$Calc. for $C_{21}H_{14}BrN_3O_2S$; CHN: C, 55.76; H, 3.12; N, 9.29; S, 7.09; Found: C, 55.78; H, 3.22; N, 9.25; S, 7.15. **IR (KBr, cm^{-1}):** 3060.21 (C-H, Aromatic), 2968.10 (C-H, Aliphatic), 1591.59 (C=C, Aromatic), 1080. 34 (C-O).

(Z)-6-((4-nitrophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10h): Compound **10h** obtained as cream colour solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.92-7.94 (d, 2H,Ar-H), 7.86-7.89 (t, 2H, *J*=4.0 Hz, Ar-H), 7.65-7.70 (m, 4H, *J*=4.0 Hz, Ar-H), 7.54-7.60 (m, 4H, *J*=4.0 Hz, Ar-H), 5.35 (s,1H, amide), **^{13}C NMR (100MHz, DMSO):** 140.32, 139.18, 138.21, 136.35, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 119.75, 117.18, 118.34. **MASS spectrum m/z:** 419.14 $[M+1]^+$Calc. for $C_{21}H_{14}N_4O_4S$; CHN: C, 55.76; H, 3.12; N, 9.29; S, 7.09; Found: C, 55.78; H, 3.22; N, 9.25; S, 7.15. **IR (KBr, cm^{-1}):** 3060.21 (C-H, Aromatic), 2968.10 (C-H, Aliphatic), 1591.59 (C=C, Aromatic), 1080.34 (C-O).

(Z)-6-(thiophen-2-ylsulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]di-azacycloundecine (10i): Compound **(10i)** obtained as yellowish solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.925-7.928 (d, 2H, *J=8.4* Hz, Ar-H), 7.86-7.89 (m, 4H, *J*=4.0 Hz, Ar-H), 7.720-7.724 (t, 2H, *J*=4.0 Hz, Ar-H), 7.484-7.586 (m, 2H, Ar-H), 5.354 (s, 1H, ethylene).
^{13}C NMR (100MHz, DMSO): 140.21, 138.21, 136.18, 132.54, 129.35, 129.09, 128.56, 128.41, 126.88, 125.27, 124.48, 114.02. MASS spectrum m/z: 380.25 $[M+1]^+$.Calc. for $C_{19}H_{13}N_3O_2S_2$; CHN: 61.72; H, 4.21; N, 13.50; S, 10.30; Found: 61.70; H, 4.26; N, 13.55; S, 10.25. **IR (KBr, cm^{-1}):** 3056.51 (C-H, Aromatic), 2978.52 (C-H, Aliphatic), 1650.12 (C=N), 1595.10 (C=C**),** 1224.32 (S=O), 1082.34 (C-N).

(Z)-6-((5-chlorothiophen-2-yl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10j): Compound **10j** obtained as white solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.82-7.86 (m, 4H,Ar-H), 7.74-7.78 (d, 2H, *J*=4.0 Hz, Ar-H), 7.55-7.58 (d, 3H, *J*=4.0 Hz, Ar-H), 7.32-7.37 (m, 2H, Ar-H), 5.315(s, 1H, ethylene). **^{13}C NMR (100MHz, DMSO):** 140.10, 139.10, 138.01,136.18, 135.10, 130.42, 129.23 128.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 114.3, **MASS spectrum m/z:** 415.14 [M+2].Calc. for $C_{19}H_{12}ClN_3O_2S_2$; CHN: C, 55.13; H, 2.92; N, 10.15; S, 15.49; Found: C, 55.15; H, 2.90; N, 10.10; S, 15.51; **IR spectrum (KBr, cm^{-1}):** 3085.98(C-H, Aromatic), 2974.62(C-H, Aliphatic), 1718.40 (C=O), 1585.10(C=C, Aromatic, 1289.04 (C-O).

(Z)-6-((5-bromothiophen-2-yl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10k): Compound **10k** obtained as white solid**. ^{1}H NMR (400MHz DMSO, δ ppm):**7.80-7.85 (d, 4H,Ar-H) 7.70-7.72 (t, 2H, *J*=4.0 Hz, Ar-H), 7.54-7.56 (d, 2H, *J*=4.0 Hz, Ar-H), 7.32-7.38 (m, 3H, Ar-H), 5.315 (s, 1H, ethylene). **^{13}C NMR (100MHz, DMSO):** 140.18, 138.10, 136.12, 135.01, 130.10, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 114.3, 110.21. **MASS spectrum m/z:** $[M+2]^+$Peak observed at 460.14.Calc. for $C_{19}H_{12}BrN_3O_2S_2$; CHN: C, 49.79; H, 2.64; N, 9.17; S, 13.99; Found: C, 49.75; H, 2.65; N, 9.19; S, 13.98; **IR (KBr, cm^{-1}):** 3065.60 (C-H, Aromatic), 2928.51 (C-H, Aliphatic), 1650.32 (S=O), 1575.18(C=C, Aromatic), 1270.70(C-O).

(Z)-6-((5-nitrothiophen-2-yl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10l); Compound **10l** obtained as yellowish cream solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.89-7.91 (d, 4H,Ar-H), 7.70-7.73 (t, 2H, *J*=4.0 Hz, Ar-H), 7.58-7.65 (m, 4H, Ar-H), 7.30-7.34 (t, 2H, Ar-H), 5.315 (s, 1H, ethylene). **^{13}C NMR (100MHz, DMSO):** 145.21, 140.12, 137.10, 136.08, 132.10, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 112.3, 110.21. **MASS spectrum m/z:** $[M+1]^+$ Peak observed at 425.15, Calc. for $C_{19}H_{12}N_4O_4S_2$; CHN: C, 57.02; H, 2.96; N, 9.50; O, 7.23; S, 7.25, Found: C, 57.02; H, 2.96; N, 9.50; O, 7.23; S, 7.25; **IR (KBr, cm^{-1}):**3068.52(C-H, Aromatic), 2980.20 (C-H, Aliphatic), 1616.34(S=O**),** 1535.12(C=C, Aromatic), 1135.18(C-N).

(Z)-6-((3,4-dichlorophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10m) :
Compound **10m** obtained as cream colour solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.75-7.80 (m, 3H,Ar-H) 7.64-7.66 (d, 2H, *J*=4.0 Hz, Ar-H), 7.55-7.58 (d, 4H, *J*=4.0 Hz, Ar-H), 7.35-7.39 (m, 1H, Ar-H), 5.125 (s, 1H). **^{13}C NMR (100MHz, DMSO):** 165.5, 150.23, 138.16, 136.15, 132.10, 130.38, 129.8 128.2, 127.08, 126.15, 126.25, 126.18, 124.52, 119.70, 118.12, 114.5, 47.18, **MASS spectrum m/z:** $[M+2]^+$ Peak observed at 444.25, $[M+4]^+$ Peak observed at 446.12; Calc. for $C_{21}H_{13}Cl_2N_3O_2S$; CHN: C, 57.02; H, 2.96; Cl, 16.03; N, 9.50; O, 7.23; S, 7.25 Found: C, 55.78; H, 3.19; N, 11.83; IR (KBr, cm^{-1}): 3103.33 (C-H, Aromatic), 2922.15 (C-H, Aliphatic), 1718.28 (C=O**),** 1590.56 (C=C, Aromatic), 1184.54 (C-O).
(Z)-6-((3,4-dibromophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]di-azacycloundecine (10n):
Compound **10n** obtained as white solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.80-7.83 (m, 4H,Ar-H) 7.60-7.63 (d, 2H, *J*=4.0 Hz, Ar-H), 7.58-7.60 (d, 3H, *J*=4.0 Hz, Ar-H), 7.40-7.45 (m, 3H, Ar-H), 5.380 (s, 1H, ethylene). **^{13}C NMR (100MHz, DMSO):** 138.15, 136.15, 132.12, 130.20, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 119.70, 117.12, 115.8, 110.25, 108.23. **MASS spectrum m/z:** 531.12 $[M+]^+$, 533.25 $[M+2]^+$, 535.31 $[M+4]^+$;Calc. for $C_{21}H_{13}Br_2N_3O_2S$; CHN: C, 47.48; H, 2.47; N, 7.91; O, 6.02; S, 6.04; Found: C, 47.40; H, 2.50; N, 7.95; O, 6.05; S, 6.04; **IR (KBr, cm^{-1}):**3082.10 (C-H, Aromatic), 2975.15 (C-H, Aliphatic), 1632.12(S=O**)**, 1541.20 (C=C, Aromatic), 1150.68(C-N).

(Z)-6-((3,4-dinitrophenyl)sulfonyl)-6H-7,10-etheno-5,13-(metheno)pyrido[2,3-b][1,5]diazacycloundecine (10o): Compound **10o** obtained as yellowish solid. **^{1}H NMR (400MHz DMSO, δ ppm):**7.92-7.98 (m, 2H,Ar-H) 7.83-7.85 (d, 2H, *J*=4.0 Hz, Ar-H), 7.56-7.60 (d, 3H, *J*=4.0 Hz, Ar-H), 7.35-7.38 (t, 3H, Ar-H), 5.312 (s, 1H, ethylene). **^{13}C NMR (100MHz, DMSO):** 140.10, 138.01, 135.10, 130.42, 129.23 128.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 114.3, 112.52, 110.35; **MASS spectrum m/z:** 463.14 $[M+]^+$,464.28 $[M+1]^+$. Calc. for $C_{21}H_{13}N_5O_6S$; CHN: C, 54.43; H, 2.83; N, 15.11; S, 6.92; Found: C, 54.45; H, 2.80; N, 15.15; S, 6.92; **IR spectrum (KBr, cm^{-1}):** 3023.18(C-H, Aromatic), 2974.62(C-H, Aliphatic), 1732.35 (S=O), 1585.25 (C=C, Aromatic, 1280.24 (C-O).

(E)-2-(1-benzyl-5-nitro-2-oxoindolin-3-ylidene)-N-(3,4-dichlorophenyl)-hydrazine-carboxamide (7o):
^{1}H NMR (400MHz DMSO, δ ppm):9.42 (s, 1H, indole amide), 7.79-7.84 (m, 4H,Ar-H), 7.72-7.74 (m, 5H, *J*=4.0 Hz, Ar-H), 7.54-7.56 (d, 2H, *J*=4.0 Hz, Ar-H), 7.30-7.35 (m, 2H, Ar-H), 7.23 (s,1H, amide), 4.35 (s, 1H). **^{13}C NMR (100MHz, DMSO):** 160.3, 151.10, 140.10, 138.21, 134.10, 130.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 114.3, 45.18. **MASS spectrum m/z:** 484.25 $[M+]^+$, 486.13 $[M+2]^+$, 488.32 $[M+4]^+$.Calc. for $C_{22}H_{15}Cl_2N_5O_4$; CHN: C, 54.56; H, 3.12; N, 14.46; Found: C, 54.50; H, 3.18; N, 14.40; IR (KBr, cm^{-1}): 3050.19 (C-H, Aromatic), 2928.65 (C-H, Aliphatic), 1720.30 (C=O), 1589.18 (C=C, Aromatic), 1263.72(C-O).

(E)-2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3,4-dibromophenyl)hydrazine-carboxamide (7p); Compound **7p** obtained as yellowish solid. **^{1}H NMR (400MHz DMSO, δ ppm):**9.44(s, 1H, indole amide), 7.89-7.91 (m, 4H,Ar-H) 7.70-7.73 (d, 2H, *J*=4.0 Hz, Ar-H), 7.58-7.61 (d, 4H, *J*=4.0 Hz, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.20 (s,1H, amide), 4.35 (s, 1H).**^{13}C NMR (100MHz, DMSO):** 160.1, 155.12, 137.10, 136.08, 132.10, 129.42, 128.23 126.14, 127.18, 126.75, 126.25, 126.18, 124.52, 118.70, 115.10, 112.3, 43.18. **MASS spectrum m/z:** 528.23 $[M+]^+$ Peak observed and 530.23 $[M+2]^+$ and 532.25 $[M+4]^+$; Calc. for $C_{22}H_{16}Br_2N_4O_2$; CHN: C, 50.03; H, 3.05; N, 10.61; Found: C, 50.13; H, 3.04; N, 10.60; IR (KBr, cm^{-1}): 3060.50(C-H, Aromatic), 2985.21 (C-H, Aliphatic), 1718.34(C=O**),** 1540.12(C=C, Aromatic), 1140.18(C-O).

E)-2-(1-benzyl-5-chloro-2-oxoindolin-3-ylidene)-N-(3,4-dibromophenyl)-hydrazine-carboxamide (7q): Compound **7q** obtained as red colour solid. **^{1}H NMR (400MHz DMSO, δ ppm):**9.30 (s, 1H, indole amide), 7.75-7.88 (m, 4H,Ar-H) 7.62-7.65 (d, 2H, *J*=4.0 Hz, Ar-H), 7.58-7.60 (d, 4H, *J*=4.0 Hz, Ar-H), 7.30-7.35 (m, 3H, Ar-H), 7.08 (s,1H, amide), 4.95 (s, 1H). **^{13}C NMR (100MHz, DMSO):** 165.5, 150.23, 138.16, 136.15, 132.10, 130.38, 129.8 128.2, 127.08, 126.15, 126.25, 126.18, 124.52, 119.70, 118.12, 114.5, 47.18; **MASS spectrum m/z:** 562.12 $[M+]^+$, 564.32 $[M+2]^+$,566.25 $[M+4]^+$ and568.23 $[M+6]^+$. Calc. for $C_{22}H_{15}Br_2ClN_4O_2$; CHN: C, 46.96; H, 2.69; N, 9.96; found C, 46.96; H, 2.69; N, 9.96; IR (KBr, cm^{-1}): 3123.33 (C-H, Aromatic), 2950.15 (C-H, Aliphatic), 1716.28 (C=O**),** 1585.56 (C=C, Aromatic), 1190.54 (C-O).

ANTICANCER ACTIVITY
MTT ASSAY
Procurement of cell line: The HElla and MCF-7 cell line with passage number 45 was procured from NCCS, Pune.
Media Preparation: Pour 20-30 ml MEM media in centrifuge. To this add 10ml of bovine serum, 0.5 ml antibiotic solution, 1.25ml HEPES and make up volume up to 50ml by appropriate media. Mix it and store at 208oC (for up to 4 weeks).
Sub culturing cells: Take above solution and remove the media and wash with PBS. Remove PBS and add 1ml trypsin-EDTA solution. Incubate the flask at 37oC in CO2 incubator.

Table 2: Protocol for MTT assay

Day 1 (Cells Suspended)	Day 2 (Drug Treatment)	Day 3 (MTT Assay)
Washing with PBS	Removed the plate form incubator to remove the media from each well	25 µl of freshly prepared MTT added in each well
Trypsinization	Drug treatment (10, 25, 50,100,200 and 300µM)	Keep in nncubator at 37°C for 2-3h
Cell Counting	Untreated / DMSO	Media was removed
Filled 96 well Plate (10000 cells/well)	Incubation (24h)	DMSO (100 µl) was added
Incubation (24h)		Kept the plate in Incubator at 37°C for overnight and recorded plate at 570nm in ELISA plate reader

Traditionally, the determination of cell growth is done by counting viable cells after staining with a vital dye. Several approaches have been used in the past. Trypan blue staining is a simple way to evaluate cell membrane integrity (and thus assume cell proliferation or death) but the method is not sensitive and cannot be adapted for high throughput screening. Measuring the uptake of radioactive substances, usually tritium-labelled thymidine, is accurate but it is also time-consuming and involves handling of radioactive substances. Yellow MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) is reduced to purple formazan in the mitochondria of living cells. The absorbance of this coloured solution can be quantified by measuring at a certain wavelength (usually between 500 and 600 nm) by a spectrophotometer.

The absorption max is dependent on the solvent employed. This reduction takes place only when mitochondrial reductase enzymes are active, and therefore conversion can be directly related to the number of viable (living) cells. When the amount of purple formazan produced by cells treated with an agent is compared with the amount of formazan produced by untreated control cells, the effectiveness of the agent in causing death of cells can be deduced, through the production of a dose-response curve. Solutions of MTT solubilized in tissue culture media or balanced salt solutions, without phenol red, are yellowish in colour.

Mitochondrial dehydrogenases of viable cells cleave the tetrazolium ring, yielding purple MTT formazan crystals which are insoluble in aqueous solutions. The crystals can be dissolved in acidified isopropanol. The resulting purple solution is spectrophotometrically measured. An increase in cell number results in an increase in the amount of MTT formazan formed and an increase in absorbance. The use of the MTT method does have limitations influenced by:

(1) the physiological state of cells.
(2) Variance in mitochondrial dehydrogenase activity in different cell types.

Nevertheless, the MTT method of cell determination is useful in the measurement of cell growth in response to mitogens, antigenic stimuli, growth factors and other cell growth promoting reagents, cytotoxicity studies, and in the derivation of cell growth curves (280).

Table 3: Anti cancer activity data against MCF-7 and HeLa cell lines

S.No	Compound	M. Form	MCF-7 IC_{50} (μM)	HELa IC_{50} (μM)
1	10a	$C_{16}H_{13}N_3O_2S$	1.10±0.02	6.17±0.02
2	10b	$C_{16}H_{12}ClN_3O_2S$	1.52±0.04	5.02±0.04
3	10c	$C_{16}H_{12}BrN_3O_2S$	1.12±0.02	2.78±0.04
4	10d	$C_{16}H_{12}N_4O_4S$	1.90±0.02	4.62±0.02
5	10e	$C_{21}H_{15}N_3O_2S$	2.80±0.02	5.35±0.03
6	10f	$C_{21}H_{14}ClN_3O_2S$	1.36±0.03	4.26±0.03
7	10g	$C_{21}H_{14}BrN_3O_2S$	1.35±0.02	3.45±0.03
8	10h	$C_{21}H_{14}N_4O_4S$	1.08±0.03	2.38±0.03
9	10i	$C_{19}H_{13}N_3O_2S_2$	2.90±0.02	7.64±0.02
10	10j	$C_{19}H_{12}ClN_3O_2S_2$	2.10±0.08	5.64±0.02
11	10k	$C_{19}H_{12}BrN_3O_2S_2$	2.02±0.04	5.59±0.02
12	10l	$C_{19}H_{12}N_4O_4S_2$	1.65±0.03	3.24±0.03
13	10m	$C_{21}H_{13}Cl_2N_3O_2S$	**0.78±0.03**	**1.31±0.02**
14	10n	$C_{21}H_{13}Br_2N_3O_2S$	**0.92±0.03**	**1.91±0.02**
15	10o	$C_{21}H_{13}N_5O_6S$	**1.12±0.05**	**1.95±0.03**
16	Cisplatin	-	0.68±0.02	1.65±0.02

RESULTS AND DISCUSSIONS

4,5 Dichloro phenyl substituted compound **10m** showed both HELa and MCF-7 with IC_{50} value of 0.78 and 1.31 μM. Most active compound among the series was found to be **10n** with IC_{50} of **0.92** and **1.91**μM and compared to 0.68, 1.65 μMof standard drug that is cisplatin against HEla and MCF-7 respectively. In general, increasing the electronegative group increasing the anti-cancer activity was found to increase significantly.

Effect of the nature of aryl group and substituents on HELa and MCF-7 inhibitory actvity was studied to understand the structure activity relationship. The simple phenyl group in 1**0e** when replaced with Cl resulted in marginal decrease in both HELa and MCF-7 inhibitory actvity. Substitution with 3-chloro group as in enhanced HELa and MCF-7 inhibitory actvity significantly and compound **10f** with Cl substituted moiety showed potent activity with IC_{50} value of 1.36 and 4.26 μM against HELa and MCF-7 cell lines respectively.

Insertion of electron withdrawing group (4-nitro) as in **10d, 10h, 10l, 10** resulted in increasing HELa and MCF-7 cell lines inhibitory activity when compared with their corresponding unsustituted compounds, **10a, 10e, 10i** which indicated that electron withdrawing groups enhance the HELa and MCF-7 cell inhibitory activity. To explore further the SAR, compounds with two Cl groups have been synthesized (**10m)** and to our expected observations. Three compounds with 4,5 di bromo phenyl groups as in **10n** have also shown enhanced activity over unsubstituted compounds, in both HELa and MCF-7 cell lines **.**

Molecular Docking

The present Series-I molecular docking studies were carried out using Schrödinger software (Schrödinger, Version 2019-1,) installed on an Intel Xenon W 3565 CPU and Ubuntu enterprise (version 14.04) as an operating system. ChemDraw 18.0 was used to create the ligands (10a-o). Using XP Visualiser (Schrödinger, Version 2019-1). The results were scrutinised. Schrodinger software (Schrodinger, Version 2019-1) (Glide module). ChemDraw software was utilised to create the ligands used as docking inputs. The docking studies were carried out utilising the OPLS3e force field in Ligprep (Dizdaroglu et al. 2020) (Version 2019-1, Schrodinger). This minimising aids in the assignment of bond ordering, as well as the addition of hydrogens to the ligands. The resulting output file containing the best ligand conformations was used for docking investigations. The protein preparation wizard was used to prepare the protein (Dizdaroglu et al. 2020). (Version 2019-1, Schrodinger). The protein was charged when hydrogen atoms were added. At pH 7.2, I generated Het states with epik. The protein was pre-processed, polished, and changed by examining workspace. Non-significant atoms were eliminated from the crystal structure. Finally, the protein was tuned using OPLS3e force filed. A receptor grid was formed around the cocrystal ligand (X-ray pose of the ligand in the protein). The centroid of the ligand was chosen to produce the grid box, and the Vander Waal radius of receptor atoms was scaled to 1.00 with a partial atomic charge of 0.25. The best-docked structure was identified from the output using the Glide docking score. XP Visualizer was used to assess the poses of the generated output of ligands after docking (Version 2019-1, Schrodinger). The results are exhibited in Table-4 and figure 1 and 2.

Table 4: Binding Energies (Kcal/mol), No. of HBs and Binding Sites

S.No	Compound	Docking score of MCF-7 (3HY3)	Docking score of HELA-6I2I
1	10a	-3.971	-3.782
2	10b	-6.707	-3.723
3	10c	-2.057	-3.415
4	10d	-2.146	-3.714
5	10e	-4.861	-3.395
6	10f	-5.504	-4.084
7	10g	-5.381	-3.484
8	10h	-4.712	-3.489
9	10i	-3.942	-3.526
10	10j	-4.386	-3.475
11	10k	-4.386	-3.241
12	10l	-3.934	-4.224
13	**10m**	**-7.270**	**-6.252**
14	**10n**	**-6.352**	**-4.721**
15	**10o**	**7.401**	**-4.711**
16	Cocrystal Ligand	5.787	-9.068

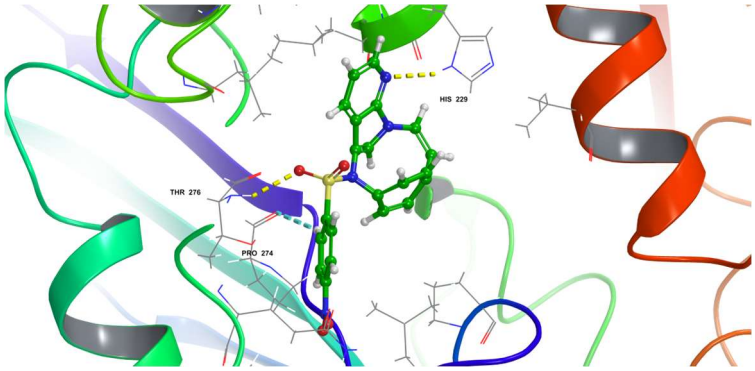

Fig 1: Docking pose of 10h (green) with HeLa (green) where hydrogen bonds are shown in blue dotted line.

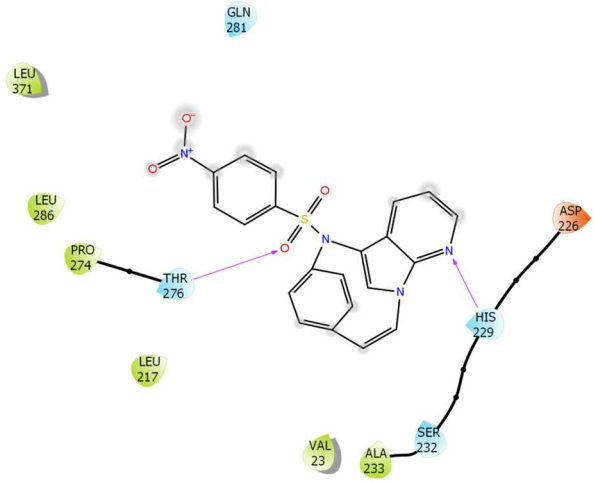

Fig 2: Binding poses and interactions of compound 10h to the binding sites of target protein HeLa receptor (6I2I)

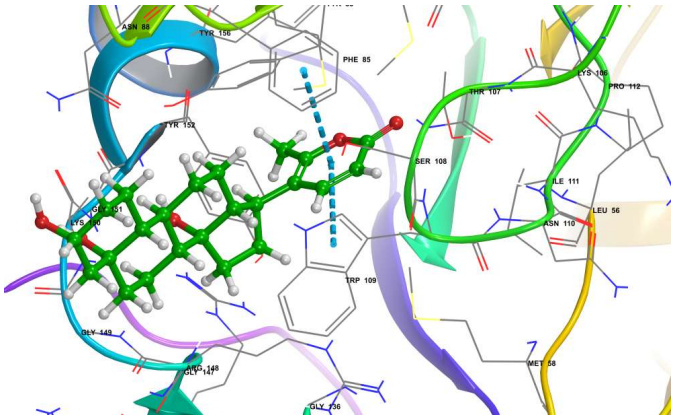

Fig 3: Binding poses and interactions of compound 10b to the binding sites of target protein MCF-7 receptor (3HY3)

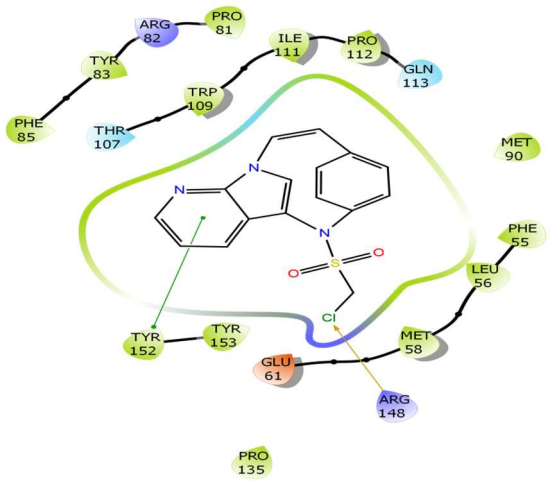

Fig 4: Binding poses and interactions of compound 10b to the binding sites of target protein MCF-7 receptor (3HY3)

RESULTS AND DISCUSSIONS

The potential anti-cancer activity of synthetic compounds was demonstrated in in-vitro tests, and among the substances, compound 10m demonstrated encouraging anti-cancer activity. These findings compelled us to carry out docking analyses to gain insight into the way synthetic chemicals bind to HeLa and MCF-7 binding pocket. The Schrodinger package's LigPrep was used to further prepare each ligand structure once it had been constructed using maestro. The Protein Preparation Wizard in the Schrodinger software was used to make the necessary corrections to the protein structure after it was retrieved from the Protein Data Bank (PDB ID: MCF-7-3HY3 and HeLa -6I2I). The docking procedure was confirmed by docking the cocrystal ligand, which produced an RMSD of docked conformation and cocrystal ligand pose of 0.6. Docking tests were carried out using the Glide docking software. the ways that substances bind to HeLa and MCF-7 cells. have been listed in Table- 3, 5.2.2, Figure-.1, 2, 3, 4.

A docking study was conducted, and binding poses of synthetic molecules with HeLa and MCF-7 cells revealed that these molecules bind strongly within the enzyme's binding pocket. The chemical with strong anti-cancer action 10m has displayed the highest binding score out of all the produced compounds (-7.584 and -6.252 against HeLa and MCF-7). As seen in Figure-5.2.1, the aromatic ring coincided with the skeleton of the cocrystal ligand in the superimposed posture of a 10 m cocrystal ligand. The enzyme hydrogen bonding interactions involving 4,5-dichlorophenyl and compound 10m, which has the highest binding score. interactions between phenyl and PhE85. While phenyl formed hydrogen bonds with Phy and Trp83, OH formed hydrogen bonds with THR 276 and SER277 (Fig2).

CONCLUSION

These new 7-aza indole derivatives have emerged as new cancer inhibitors for further exploitation as anti-cancer agents. Docking studies of all the molecules disclosed close hydrogen bond interactions within the binding site.

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