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Synthesis and Anti-Proliferative Activity of Biphenyl Derived 5-Substituted-Indolin 2-Ones

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Abstract

A series of novel biphenyl derived 5-substituted-indolin-2-one derivatives were synthesized by the reaction of 6-chloro-5-(2-chloroethyl)-indolin-2-one 1 with cyclic secondary amines 2a-h followed by condensation of bromomethylcyanobiphenyl to afford the compounds 5a-h. The nitrile group of 5a-h was converted into tetrazole to obtain the compounds 7a-h and tetrazole of 7a-h was further ring transformed into oxadiazole to get compounds 8a-h. Molecular docking study of these previously unknown molecules was performed on PDB: 453D to analyze the interaction and preferred binding mode of synthesized molecules with DNA. Anti-proliferative activity of these newly synthesized compounds were evaluated against a panel of 60 human cancer cell lines at National Cancer Institute (NCI), Bethesda USA. Among these, seven (07) compounds were evaluated for their anti-cancer activity. Some of the compounds displayed potent anti-proliferative activity at 10 µM.

Keywords: Indolin-2-ones; Biphenyl; Tetrazole; Oxadiazole; Anti-proliferative activity; Docking; DNA.

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Introduction

In the recent years, cancer is one of the leading global health burden and most serious clinical problem in the world with increasing incidences every year. In spite of avoiding behavioural risk factors such as chewing tobacco, overweight and obesity, and preventive managements like dietary, medication and vaccination the disease still affects millions of people worldwide [1,2]. Most of the current anticancer drugs commonly act on metabolically active or rapidly proliferating cells, and suffer from poor preference between normal and cancerous cells. The poor endurance of current anticancer drugs and high toxicity highlights the need to identify novel molecules with potent anti-proliferative activity, cheap availability, low toxicity and with minimum side effects. Therefore, design and synthesis of novel pharmacological entities for the effective and safe cure of cancer is an active area of research in medicinal chemistry.

Indolin-2-one is a most advantageous scaffold which represents an important class of heterocyclic compounds endowed with interesting pharmacological activities such as antimicrobial [3], antioxidant [4], antiviral [5], anti-cholinesterase [6], antibacterial [7], histone deacetylase [8], and anticancer activities [9,10]. Besides, SU4984, SU6668 and BIBF1120 **(Figure 1)** are the representative drugs which have emerged from this class and are in clinical use for targeted anticancer therapies [11,12]. Especially, the structural modifications at the nitrogen-containing ring and substituted carbonyl at the second position of the 5-member indoline ring have led to increased anti-tumour activity. In this context, many synthetic indolin-2-one derivatives with anticancer activity were developed. This prompted us herein to report the synthesis, docking studies (DNA as target) and anti-proliferative assay of indolin-2-ones tailored cyclic secondary amine and biphenyl containing the tetrazole/oxadiazole [13-16]. This is because, incorporation of pharmacologically active moieties

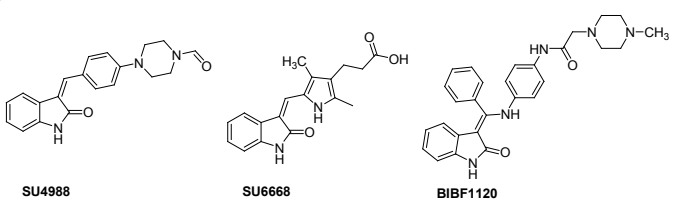


Figure 1 Representative Indolin-2-one based anti-proliferative agents.

into a core bioactive natural product provides the means for accessing wider range of pharmacological profiles, especially in the area of anticancer therapeutics. For instance, various heterocyclic ring systems such as morpholine, pyrrolidine, piperidine, dimethylmorpholine, indoline etc. have been found as the fundamental scaffold components of several drugs in the market today [17,18]. The significance of these moieties are well understood by medicinal chemists since they play important role in molecular properties or whole molecule properties such as three dimensionality, scaffold rigidity, lipophilicity or polarity, and can determine molecular reactivity, metabolic stability, cellular activity, and toxicity. Our interest in building heterocyclic systems has led us to explore the reaction of indolin-2-ones with bromomethylcyanobiphenyl resulting in the formation of cyanobiphenyl appended indolin-2one derivatives. Though many heterocyles have been introduced on biphenyls via methylene bridge, indolin-2-one is introduced for the first time. It is interesting to note that seven (07) such derivatives have been selected by National Cancer Institute, National Institute of Health, Maryland, Bethesda for anticancer activity against 60 cancer cell lines and the results are presented in this work.

Result and Discussion

Chemistry

In view of the pharmacological properties of the indolin-2-one and biphenyl derivatives, it was planned to link these bio-dynamic molecules by using simple synthetic protocols and study their Structure Activity Relationships (SAR). As presented in Scheme 1, compound 3a-h was obtained by the reaction of 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one 1 with cyclic secondary amine 2a-h by simple S_N^2 reaction. This was further reacted with bromomethylcyanobiphenyl 4 to get 4'-{[6-chloro-5-(2-(substituted)-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl} biphenyl-2-carbonitrile 5a-h. This can also be obtained by another method which involves the initial reaction between compound 1 and 4 to get 4'-{[6-chloro-5-(2-chloroethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl}biphenyl-2-carbonitrile 6. Intermediate 6 was further reacted with cyclic secondary amine 2a-h to form the compound 5a-h. The nitrile group of the compound 5a-h was converted to the tetrazole by the reaction with sodiumazide under reflux for 48 hours to get the compound 7a-h. The tetrazole of 7a-h was ring transformed into 1,3,4-oxadiazole ring to obtain the final compound 8a-h using acetic anhydride as shown in **Scheme 1**.

Molecular docking studies

Designing of organic molecules which have the proficiency of binding with bio-macromolecules like Deoxyribonucleic acid (DNA) has received immense attention since this association can regulate many biochemical functions that take place in cellular system [19]. Different loci in the DNA are involved in various dictatorial processes such as gene expression, gene transcription, carcinogenesis and mutagenesis etc. Also DNA regulates many biochemical processes occurring in the cellular system hence it is an important drug target [20]. Hence, there is a strong conviction that a molecule which interacts with DNA also exhibits great biological activities such as anticancer property [21]. During development of new therapeutic models, targeting DNA is deeply crucial, since it may restore its function or it will lead to apoptotic cell death in order to control the proliferation [22]. Therefore, molecular docking study was performed on PDB 453D, to support the interaction and preferred binding mode of synthesized molecules with DNA. The crystal structure used were B-DNA [(5'-D (*CP*GP*CP*GP*AP*AP*TP*TP*CP*GP*CP*G)-3'-benzimidazole complex)] (PDB ID: 453D) [23] obtained from Protein Data Bank. The DNA file was prepared for docking by adding polar hydrogen atom with Gästeiger-Hückel charges and water molecules were removed. The 3D structure of ligands was generated by the SKETCH module implemented in the SYBYL program (Tripos Inc., St. Louis, USA) and its energy-minimized conformation was obtained with the help of the Tripos force field using Gästeiger-Hückel charges and molecular docking was performed with Surflex-Dock program that is interfaced with Sybyl-X 2.0 [24-25] and other miscellaneous parameters were assigned with the default values given by the software.

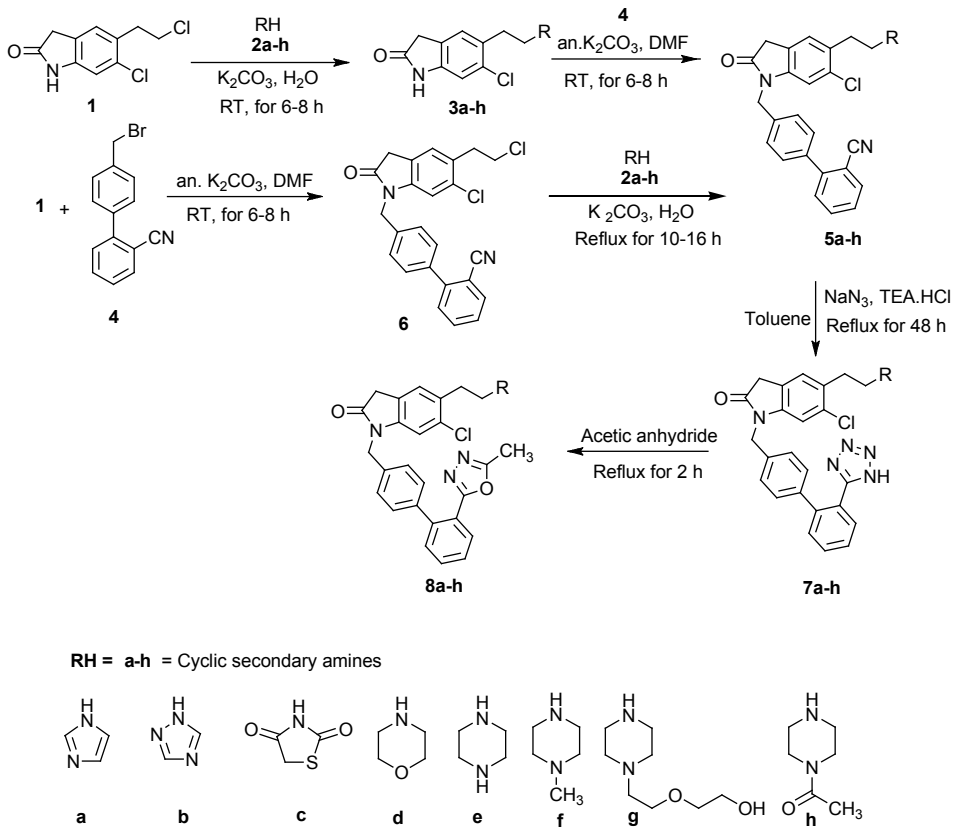
Docking on PDB 453D

The docking study revealed that amongst all the synthesized molecules, 7g acts as intercalator and it showed interaction with base pairs of DNA helix structure of PDB 453D which preferred intercalation mode of binding. As depicted in the **Figure 2**, compound 7g showed binding interaction with the base pair of DNA helix, while the hydrogen atom of amine group of tetrazole ring forms weak hydrogen bond with oxygen of DT7 base pair and hydrogen atom of terminal hydroxy group forms weak bond with oxygen atom of DC9 base pair and they may undergo threading or classical intercalation.

Biological Assay

Anticancer activity

The structures of all the newly synthesized compounds were submitted to National Cancer Institute, NIH, Bethesda, USA. Among these, seven (07) compounds viz., 5a (NSC:762890/1), 5b (NSC:762879/1), 5e (NSC:762881/1) 5f (NSC:762885/1) and 7e (NSC:762882/1), 7f (NSC:762886/1), 7g (NSC:762880/1) were selected for in vitro anticancer screening in a single high dose (10-5 M) concentration against full 60 human cancer cell lines at NCI under DTP drug discovery program. The results of single dose screen were reported as a graph of mean growth percent of the treated cells. This allows us to analyze both growth inhibition values (between 0 and 100) and cytotoxicity values (less than 0). The results of single dose screening were analyzed by COMPARE program.



Scheme 1 Synthetic route for the compounds **5a-h**, **7a-h** and **8a-h**.

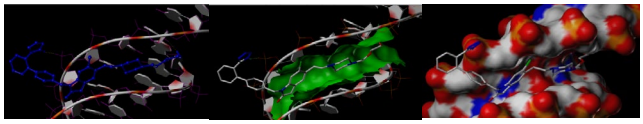


Figure 2 Interaction of compound **7g** at the binding site of DNA PDB ID: 453D.

All the 60 human cancer cell lines organized into nine sub panels derived from nine different human cancer type: viz., leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines. The sub types of these cancer cell lines are indicated in bar graphs and in table of in vitro testing results. The following are moderate percentage growth inhibition (GI % = 100 - Growth percentage) of treated cell lines at 10-5 M concentration with the compound 5a (comprising of indolin-2-one appended to imidazole): Renal Cancer UO-31 (GI% 32.45). Compound 5b (indolin-2-one appended with 1,2,4-triazole): This compound has shown moderate growth inhibition against 5 cancer cell lines viz., Melanoma UACC-62 (GI% 23.57), Ovarian Cancer NCI/ADR-RES (GI%, 24.30), Renal Cancer CAKI-1 (GI% 33.06), Prostate Cancer PC-3 (GI% 51.51), Breast Cancer T-47D (GI%, 27.84). Compound 5e (indolin-2-one annexed piperazine): This compound also has shown moderate growth inhibition against 7 cancer cell lines viz., Non-Small Cell Lung Cancer A549/ATCC (GI%, 22.02), NCI-H226 (GI%, 27.35), Renal Cancer ACHN (GI%, 20.18), CAKI-1 (GI%, 37.78), Prostate Cancer PC-3 (GI% 49.38), Breast Cancer MDA-MB-231/ATCC (GI%, 24.41), MDA-MB-468 (GI%, 36.38). Compound 5f (indolin-2-one appended to 1-methylpiperazine): This compound has shown moderate growth inhibition against 9 cancer cell lines viz., Non-Small Cell Lung Cancer EKVX (GI%, 41.13), NCI-H226 (GI%, 31.25), CNS Cancer SNB-75 (GI%, 39.91), Melanoma UACC-62 (GI%, 27.82), Renal Cancer ACHN (GI%, 23.88), CAKI-1 (GI%, 38.65), UO-31 (GI%, 34.43), Breast Cancer MDA-MB-468 (GI%, 35.5).

In case of the compounds having the tetrazole and indolin-2-one moieties viz., 7e-g the percentage of growth inhibition is very poor. However, the compound 7g (indolin-2-one appended with 2-(2-(piperazin-1-yl)ethoxy)ethanol) has exhibited good activity against the Non-Small Cell Lung Cancer EKVX (GI%, 52.63), Melanoma UACC-62 (GI%, 25.13) and Prostate Cancer PC-3 (GI%, 43.86). For the growth inhibition (GI) percentage of all these compounds please refer the (**Figures S1-S7)** in electronic **supplementary** information. From the observed anti-proliferative activity results, it may be concluded that the compounds 5b and 5e have exhibited almost 50% growth inhibition against Prostate Cancer PC-3 cell lines.

Methodology of in vitro anticancer screening

The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing fetal bovine serum (5%) and L-glutamine (2 mM). For a typical screening experiment, cells were inoculated into 96 well microtiter plates in 100 µL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37°C, 5% CO_2, 95% air and

100 % relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed in situ with TCA to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs were solubilized in Dimethylsulfoxide at 400 fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate was thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50µg/ml Gentamicin. Additional four, 10 fold or ½ log serial dilutions were made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions were added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations. Following drug addition, the plates were incubated for an additional 48 h at 37°C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay was terminated by the addition of cold TCA. Cells were fixed in situ by the gentle addition of 50 µl of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4xC. The supernatant was discarded, and the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4% (w/v) in acetic acid (1%) was added to each well, and plates were incubated for 10 minutes at room temperature. After staining, unbound dye was removed by washing 05 times with acetic acid (1%) and the plates were air dried. Bound stain was subsequently solubilized with trizma (10 mM) base, and the absorbance was read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology was the same except that the assay was terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (C) and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

$[(Ti-Tz)/(C-Tz)] \times 100$ (for concentrations for which $Ti \geq Tz$)

$[(Ti-Tz)/Tz] \times 100$ (for concentrations for which $Ti < Tz$)

Three dose response parameters were calculated for each experimental agent. Growth inhibition of 50% (GI50) was calculated from $[(Ti-Tz)/(C-Tz)] \times 100 = 50$, which was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from $[(Ti-Tz)/Tz] \times 100 = 50$. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested [26-28].

Methods

General

All the chemicals, reagents and solvents were of analytical grade purchased from Sigma-Aldrich and were used without further purification. The purity of the compounds was checked by TLC on a silica gel plate using ethyl acetate and hexane (30%) as eluent. Thin-layer chromatography (TLC) used was 0.20 mm Aluchrosep Silica Gel 60/UV 254 TLC on silica gel coated plates (Merck, Mumbai). Melting points were determined with a Coslab apparatus in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Nicolet Impact-410 FTIR spectrometer. 1H (300 MHz) and 13C (75 MHz) NMR spectra were recorded on a Brüker Avance FT NMR spectrometer with TMS as an internal standard. Mass spectra were recorded using a Finnegan MAT (Model MAT 8200) spectrometer and elemental analysis was carried out using a Heraus CHN rapid analyzer.

Experimental

General procedure for 6-chloro-5-[2-(substituted)-ethyl]-1,3-dihydro-2H-indol-2-one 3a-h

A mixture of 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2H-indol-2-one 1 (0.010 mol), anhydrous potassium carbonate (0.012 mol), secondary amine 2a-h (0.013 mol) in water (20 ml) was refluxed until the completion (TLC, about 24-48 hrs) and the reaction mass was cooled to RT and then extracted with DCM (20 ml x 3) to get crude 3a-h. Recrystallized using aqueous acetone or aqueous ethanol or methanol.

General procedure for the preparation of 4'-{[6-chloro-5-(2-chloroethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]methyl}biphenyl-2-carbonitrile 6

A mixture of 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2H-indol-2-one 1 (5.0 gm, 0.028 mol), 4'-(bromo-methyl)biphenyl-2-carbonitrile 4 (7.6 gm, 0.028 mol), anhydrous K_2CO_3 (3.8 gm, 0.028 mol) taken in DMF (30 ml) was stirred at RT for about 6-8 hrs (TLC). After completion, the reaction mass was poured into ice cold water to get crude product 6. Recrystallized using acetone and ethylacetate mixture (50:50), mp: 140-142°C.

General procedure for the preparation of the compound 5a-h

Compound 5a-h was prepared at RT by stirring equimolar ratio of compound 3a-h (0.01 mole), 4 (0.01 mole) in presence of anhydrous potassium carbonate (0.01 mole) in DMF (25 ml) followed by quenching the reaction mass in water and extraction with DCM (20 x 3). Evaporation of solvent gave crude compound 5a-h. Yield 55-70%. Purified using suitable solvent or mixture of solvents.

Compound 5a-h was also prepared by another method as follows:

4'-{[6-Chloro-5-(2-chloroethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl] methyl}biphenyl-2-carbonitrile 6 (4.22 gm, 0.010 mol) was added to a mixture containing cyclic secondary amines (0.012 m) and anhydrous K_2CO_3 (0.011 mol) in distilled water. The mixture was

refluxed for 10-16 hr (TLC). After the completion, the reaction mass was cooled to room temperature and extracted with DCM (20 x 3). Evaporation of solvent gave crude compound 5a-h. Yield 65-70%.

General procedure for the preparation of the compound 7a-h

The compound 5a-h (0.010 mole) was refluxed with NaN_3 (0.040 mole) and TEA.HCl (0.040 mole) in dry toluene (50 ml) for 48 hrs. The mixture was cooled to room temperature and extracted with 5% NaOH solution to adjust pH of alkaline solution around 6.90-7.00 to get crude compound 7a-h. Recrystallized using methanol or ethanol.

General procedure for the preparation of the compound 8a-h

Compound 7a-h (0.010 mol) was refluxed in acetic anhydride (10 ml) for about 2 hrs (TLC) and cooled to RT. The reaction mass was quenched in ice water and allowed at room temperature for 6-8 hrs. The mixture was then extracted with ethyl acetate and solvent was evaporated to get solid crude compound 8a-h, (yield 65-70%). Recrystallization was done using aqueous methanol or aqueous acetone.

Spectral Characterization

4'-{[6-Chloro-5-(2-chloroethyl)-2-oxo-2,3-dihydro-1*H*-indol-1yl]methyl}biphenyl-2-carbonitrile 6

White solid, mp. 142-4°C; IR (KBr) cm^{-1}: 2222 (CN), 3032 (Ar C-H stretch), 1619, 1718 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.33-7.75 (10H, m, ArH), 5.29 (2H, d, methylene-CH_2), 4.17 (2H, t, Cl-CH_2), 3.83 (2H, s, indolin-2-one CH_2), 3.41 (2H, t, side chain CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 172.65 (C=O), 146.50, 145.27, 138.75, 137.33, 133.45, 132.64, 132.21, 131.55, 131.18, 130.58, 129.75, 129.03, 128.95, 127.82, 117.20, 114.12, 112.56, 45.88 (Cl-CH_2), 45.00 (N-CH_2), 35.00 (indolin-2-one CH_2), 33.63 (CH_2); MS (m/z, 70 eV): 423, 421, 419, 383, 192, 177, 165, 128, 115, 97, 44; CHN Analysis: for $C_{24}H_{18}N_2Cl_2O$, Calculated: C 68.42, H 4.31, N 6.65. Found: C 68.51, H 4.40, N 6.76.

4'-{[6-Chloro-5-(2-[1*H*-imidazol-1-yl]ethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl}biphenylcarbonitrile 5a

Brown solid, mp 146-8°C; IR (KBr) cm^{-1}: 2220 (CN), 1665 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21-7.74 (10H, m, ArH), 7.05 (2H, d, imidazole- H), 6.52 (1H, s, imidazole-H), 5.24 (2H, d, CH2), 4.54-4.78 (2H, t, N-CH_2), 3.81 (2H, s, indolin-2-one CH_2), 3.15-3.36 (2H, t, C3, C-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ δ, ppm): 172.56 (C=O), 145.53, 139.25, 138.41, 137.29, 132.80, 132.40, 130.35, 129.35, 128.80, 127.85, 127.00, 123.25, 117.31, 113.25, 49.03, 44.89, 35.54 (indolin-2-one CH_2), 30.98; MS (m/z, 70 eV): 454, 452, 424, 384, 291, 270, 192, 180, 165, 152, 99, 44; CHN Analysis: for $C_{27}H_{21}N_4ClO$, Calculated: C 71.80, H 4.67, N 12.37. Found: C 71.75, H 4.75, N 12.35.

4'-{[6-Chloro-5-(2-[1*H*-1,2,4-triazol-1-yl]ethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl}biphenylcarbonitrile 5b

White solid, mp 134-6°C; IR (KBr) cm^{-1}: 2219 (CN), 1649, (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 8.23 (1H, s, triazole-H), 7.89 (1H, s, triazole-H), 7.06-7.74 (10H, m, Ar-H), 5.25 (2H, s, CH_2), 4.53-4.78 (2H, t, N-CH_2), 3.84 (2H, s, indolin-2-one CH2), 3.22-3.57 (2H, t, C-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ δ ppm): 174.88 (C=O); 153.80, 145.29, 143.92, 138.13, 137.23, 132.83, 132.50, 130.50, 129.20, 128.74, 127.73, 116.86, 113.87, 112.71, 52.08, 44.83, 34.87 (indolin-2-one CH_2), 31.08; MS (m/z, 70 eV): 455, 453, 244, 231, 218, 192, 177, 165, 143, 123, 86; CHN Analysis: for $C_{26}H_{20}N_5ClO$, Calculated: C 68.80, H 4.44, N 15.43. Found: C 68.95, H 4.52, N 15.49.

2-[-4-2-{(2,4-Dioxo-1,3-thiazolidin-3-yl)ethyl}-(6-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)benzyl] benzonitrile 5c

Pale yellow solid, mp 155-7°C; IR (KBr) cm^{-1}: 2220 (CN), 3028 (Ar C-H stretch), 1683 (N-C=O), 1755 (S-C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm.): 7.10-7.72 (10H, m, ArH), 5.19 (2H, d, CH_2), 4.13 (2H, t, N-CH_2), 3.49 (2H, s, indolin-2-one CH_2), 3.20 (2H, s, thiazolidine-CH_2), 2.99 (2H, t, C-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm.): 174.59 (thiazolidine S-C=O), 173.12 (thiazolidine N-C=O), 170.5 (indolin-2-one C=O) 145.39, 145.17, 138.92, 137.52, 132.89, 132.59, 132.29, 130.82, 129.24, 129.12, 129.00, 128.60, 127.62, 126.89, 116.32, 114.00, 112.01, 47.89, 45.00, 35.00 (indolin-2-one CH2), 31.72, 30.88; MS (m/z, 70 eV): 503, 501, 423, 367, 232, 192, 177, 165, 115, 40; CHN Analysis: for $C_{27}H_{20}N_3ClO_3S$, Calculated: C 64.60, H 4.02, N 8.37. Found: C 64.74, H 4.10, N 8.48.

4'-{[6-Chloro-5-(2-[morpholin-4-yl]-ethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]-methyl} biphenylcarbonitrile 5d

Brown solid, mp 143-5°C; IR (KBr) cm^{-1}: 2220 (CN), 1684 (C=O); ^1H NMR (300 MHz, $CDCl_3$¬, δ ppm): 7.20-7.80 (10H, m, ArH), 5.08 (2H, d, CH_2), 3.85-4.05 (4H, t, morpholine O-CH_2), 3.61(2H, s, indolin-2-one CH_2), 3.12 (2H, t, CH_2), 2.90 (2H, t, C-CH_2), 2.52-2.81 (4H, t, morpholine N-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 172.93 (C=O); 145.66, 145.23, 138.48, 137.59, 132.92, 132.56, 132.19, 130.59, 129.00, 129.08, 129.20, 129.34, 128.83, 127.33, 116.39, 114.15, 112.31, 66.99, 55.36, 44.83, 34.79 (indolin-2-one CH_2), 31.02; MS (m/z, 70 eV): 473, 471, 367, 204, 192, 177, 132, 91, 77, 44; CHN Analysis: for $C_{28}H_{26}N_3ClO_2$, Calculated: C 71.25, H 5.55, N 8.90. Found: C 71.37, H 5.64, N 8.97.

4'-{[6-Chloro-5-(2-[piperazin-1-yl]-ethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]-methyl} biphenylcarbonitrile 5e

Pale yellow, Solid mp 162-4°C; IR (KBr) cm^{-1}; 3203 br (NH), 2224 (CN), 3030 (Ar-C-H stretch), 1672, 1718 (C=O): ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.18-7.75 (10H, m, ArH), 5.06 (2H, d, CH2), 3.62 (2H, s, indolin-2-one CH_2), 3.09 (2H, t, C-CH_2), 2.89 (2H, t, C-CH_2), 2.50-2.75 (8H, m, piperazine-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 172.93 (C=O), 145.66, 145.32, 138.48, 137.59, 132.92, 132.56,

132.26, 130.59, 129.74, 129.34, 129.03, 128.83, 127.33, 116.45, 114.10, 112.81, 57.19, 55.00, 46.01, 44.85, 34.81(indolin-2-one CH_2), 31.00; MS (m/z, 70 eV): 472, 470, 459, 420, 192, 177, 165, 152, 82, 40; CHN Analysis: for $C_{28}H_{27}N_4ClO$, Calculated: C 71.40, H 5.78, N 11.90. Found: C 71.59, H 5.88, N 12.06.

4'-{[6-Chloro-5-(2-[4-methylpiperazin-1-yl]-ethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]-methyl} biphenylcarbonitrile 5f

Pale yellow solid, mp 156-8°C; IR (KBr) cm^{-1}: 2221 (CN), 3090 (Ar C-H stretch), 1619, 1718 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.19-7.79 (10H, m, ArH), 5.10 (2H, d, methylene CH_2), 3.60 (2H, s, indolin-2-one CH_2), 3.07 (2H, t, C-CH_2), 2.90 (2H, t, C-CH_2), 2.52-2.78 (8H, m, piperazine CH_2), 2.30 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm); 172.93 (C=O), 145.66, 145.12, 138.48, 137.59, 132.92, 132.56, 132.01, 130.59, 129.34, 129.08, 128.83, 127.33, 116.45, 114.10, 112.81, 57.21, 55.32, 54.91,46.52, 44.88, 34.83 (indolin-2-one CH2), 31.06 (N-CH3); MS (m/z, 70 eV): 486, 484, 459, 423, 192, 177, 165, 152, 139, 99, 41; CHN Analysis: for $C_{29}H_{29}N_4ClO$, Calculated: C 71.31, H 5.78, N 11.55. Found: C 71.46, H 5.86, N 11.70.

4-[2-(6-Chloro-2-oxo-2,3-dihydro-1-{benzyl-4-(2-cyanophenyl)}-1H-indol-5-yl)ethyl]piperazin-1-yl-ethoxyethanol 5g

Pale yellow solid mp 159-61°C; IR (KBr) cm^{-1}: 3407 (OH), 2220 (CN), 3088 (Ar C-H stretch) 1614, 1715 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm); 7.21-7.80 (10H, m, ArH), 4.99 (2H, d, methylene CH_2), 3.95 (2H, t, O-CH_2), 3.63 (2H, s, indolin-2-one CH_2), 3.43-3.60 (4H, t, O-CH_2), 2.90 (2H, t C-CH_2), 3.32 (2H, t C-CH_2), 2.41-2.68 (8H, m, piperazine CH_2), 2.22 (2H, t, N-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm); 172.93 (C=O), 145.66, 145.11, 138.48, 137.59, 132.92, 132.56, 132.21, 130.59, 129.44, 129.34, 129.01, 128.83, 128.25, 128.17, 127.33, 116.45, 114.10, 72.05, 70.59, 61.54, 57.25, 54.95, 53.94, 44.83, 34.69 (indolin-2-one CH2), 31.88; MS (m/z, 70 eV): 560, 559, 558, 441, 423, 192, 177, 165, 141, 139, 88, 66; CHN Analysis: for $C_{32}H_{35}N_4ClO_3$, Calculated: C 68.74, H 6.31, N 10.02. Found: C 68.86, H 6.42, N 10.14.

4'-{[6-Chloro-5-(2-[4-acetylpiperazin-1-yl]-ethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]-methyl} biphenylcarbonitrile 5h

Off white solid, mp. 132-134°C; IR (KBr) cm^{-1}: 2222 (CN), 3028 (Ar C-H stretch), 1687, 1719 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.15-7.80 (10H, m, ArH), 5.13 (2H, d, CH_2), 3.58 (2H, s, indolin-2-one CH_2), 3.42 (2H, t, N-CH_2), 2.83-3.25 (8H, m, piperazine CH_2), 2.53-2.67 (2H, t C-CH_2), 2.13 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm); 173.62 (C=O), 171.21, 145.29, 145.03, 138.63, 137.56, 132.99, 132.56, 132.19, 130.77, 129.34, 129.18, 129.00, 128.86, 128.66, 127.33, 116.58, 113.56, 111.87, 56.96, 53.09, 44.89, 43.72, 34.69 (indolin-2-one CH_2), 32.09, 22.06; MS (m/z, 70 eV): 514, 512, 411, 323, 192, 177, 165, 139, 81, 53; CHN Analysis: for $C_{30}H_{29}N_4ClO_2$, Calculated: C 70.23, H 5.70, N 10.92. Found: C 70.34, H 5.84, N 11.06.

6-Chloro-5-(2-[1H-imidazol-1-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7a

Pale yellow solid, mp 172-4°C, IR (KBr): cm^{-1} 3049 (Ar C-H stretch), 1688 (C=O); ^1H NMR (300 MHz, DMSO-d6, δ ppm): 7.26-7.79 (10H, m, ArH), 7.21 (1H, s, imidazole-H), 6.92 (2H, d, imidazole H), 5.03 (2H, d, CH_2), 4.21 (2H, t, CH_2), 3.60 (2H, s, indolin-2-one CH_2), 3.09 (2H, t, -CH_2); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm): 172.33 (C=O), 150.00, 145.85, 139.26, 138.29, 137.24, 135.46, 132.35, 131.00, 130.78, 129.31, 129.11, 128.65, 128.41, 127.40,127.23, 126.30, 126.12, 125.26, 122.35, 114.12, 49.56, 44.99, 35.02 (indolin-2-one CH_2), 30.49; MS (m/z, 70 eV): 497, 495, 367, 291, 270, 192, 177, 165, 152, 89, 63; CHN Analysis: for $C_{27}H_{22}N_7ClO$, Calculated: C 65.39, H 4.47, N 19.77. Found: C 65.47, H 4.58, N 19.90.

6-Chloro-5-(2-[1H-1,2,4-triazol-1-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7b

Off white solid, mp 140-2°C; IR (KBr) cm^{-1}: 3049 (Ar C-H stretch) 1688 (C=O) ^1H NMR (300 MHz, DMSO-d6, δ ppm): 8.17 (1H, s, triazole C_3H), 7.89 (1H, s, triazole C_5H), 7.37-7.73 (10H, m, ArH), 5.23 (2H, d, CH_2), 4.17-4.19 (2H, t, N-CH_2), 3.83 (2H, s, indolin-2-one CH_2), 3.26-3.27 (2H, t, CH_2); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm): 174.87 (C=O), 153.80, 150.00, 145.29, 143.92, 138.13, 137.23, 135.28, 132.83, 132.50, 131.52, 130.50, 129.43, 129.20, 128.74, 128.23, 127.73, 12741, 125.23, 113.87, 52.13, 50.03, 40.83, 34.88 (indolin-2-one CH_2), 30.99; MS (m/z, 70 eV): 498, 496, 367, 316, 270, 244, 232, 165, 139, 115, 40; CHN Analysis: for $C_{26}H_{21}N_8ClO$, Calculated: C 62.84, H 4.26, N 22.55. Found: C 62.85, H 4.26, N 22.56.

6-Chloro-5-(2,4-dioxo-1,3-thiazolidin-3-yl)ethyl)-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7c

Pale yellow solid, mp. 168-170°C; IR (KBr): 3029 (Ar C-H stretch), 1687 (N-C=O), 1735 (S-C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6, δ ppm): 7.39-7.83 (9H, m, ArH), 7.10 (1H, s, ArH), 5.10 (2H, d, CH_2), 3.99 (2H, t, CH_2), 3.52 (2H, s, thiazolidine CH_2), 3.28 (2H, s, indolin-2-one CH_2), 2.83 (2H, t, CH_2); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm): 178.33 (thiazolidine C=O), 177.92 (thiazolidine C=O), 173.12, (C=O), 149.00, 145.39, 138.42, 137.32, 135.39, 132.30, 132.01, 131.51, 130.50, 129.51, 129.20, 128.68, 128.33, 126.89, 126.32, 125.00, 112.32, 46.89, 44.95, 35.09 (indolin-2-one CH_2), 31.72, 30.48; MS (m/z, 70 eV): 546, 544, 451, 355, 238, 190, 165, 115, 52; CHN Analysis: for $C_{27}H_{21}N_6ClO_3S$, Calculated: C 59.50, H 3.88, N 15.42. Found: C 59.62, H 3.99, N 15.53.

6-Chloro-5-(2-[morpholin-4-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7d

Off white solid, mp. 175-7°C, IR (KBr) cm^{-1}: 3031 (Ar C-H stretch), 1678, (C=O); ^1H NMR (300MHz, DMSO-d6, δ, ppm): 7.12-7.70 (10H, m, ArH), 4.99 (2H, d, CH_2), 3.72 (4H, t, morpholine O-CH_2), 3.59 (2H, s, indolin-2-one CH_2), 3.10 (2H, t, CH_2), 2.87 (2H, t, side chain N-CH_2), 2.49-2.80 (4H, t, morpholine N-CH_2); ^{13}C NMR (75

MHz, DMSO-d6, δ ppm): 172.58 (C=O), 150.03, 145.66, 138.50, 137.39, 135.32, 132.50, 132.10, 130.55, 130.01, 129.40,129.23, 128.64, 128.40, 127.23, 126.83, 125.39, 112.39, 66.90, 56.21, 53.36, 44.83, 34.90 (indolin-2-one CH2), 31.02; MS (m/z, 70 eV): 516, 514, 367, 204, 192, 177, 132, 91, 77, 44; CHN Analysis: for $C_{28}H_{27}N_6ClO_2$, Calculated: C 65.30, H 5.28, N 16.32. Found: C 65.46, H 5.37, N 16.43.

6-Chloro-5-(2-[piperazin-1-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 10e

Brown solid, mp. 148-150°C; IR (KBr) cm^{-1}: 3203 (NH), 3029 (Ar C-H), 1680 (C=O), ^1H NMR (300 MHz, DMSO-d6, δ ppm): 7.09-7.79 (10H, m, ArH), 5.12 (2H, d, CH_2), 3.59 (2H, s, CH_2), 3.03 (2H, t, CH_2), 2.89 (2H, t, CH_2), 2.78 (4H, t, piperazine CH_2), 2.52 (4H, t, piperazine CH_2); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm); 172.70 (C=O), 150.13, 145.20, 138.71, 137.29, 135.32, 132.56, 132.22, 131.60, 130.71, 128.89, 128.53, 127.70, 127.53, 126.80, 126.31, 125.90, 112.81, 57.79, 56.87, 45.93, 44.88, 34.83 (inidolin-2-one CH2), 31.53; MS (m/z, 70 eV): 515, 513, 471, 188, 165, 132, 82, 66; CHN Analysis: for $C_{28}H_{28}N_7ClO$, Calculated: C 65.43, H 5.49, N 19. 07. Found: C 65.54, H 5.58, N 19.13.

6-Chloro-5-(2-[4-methyl-piperazin-1-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7f

Pale yellow solid mp 156-8°C; IR (KBr) cm-1: 3027 (Ar C-H stretch) 1682 (C=O); ^1H NMR (300 MHz, DMSO-d6, δ ppm); 7.08-7.75 (10H, m, ArH), 4.98 (2H, d, CH_2), 3.60 (2H, s, indolin-2-one CH_2), 3.07 (2H, t, CH_2), 2.90 (2H, t, N- CH_2), 2.78 (4H, t, piperazine CH_2), 2.62 (4H, t, piperazine CH_2), 2.28 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm): 172.43 (C=O), 150.31, 145.66, 138.38, 137.51, 135.32, 132.56, 131.87, 130.59, 129.38, 129.01, 128.80, 128.12, 127.33, 126.12, 125.85, 113.85, 58.33, 56.41, 55.35, 46.83, 44.86, 34.77 (indolin-2-one CH2), 31.26 (CH3); MS (m/z, 70 eV): 529, 528, 527, 419. 382, 189, 165, 150, 139, 65, 44; CHN Analysis: for $C_{29}H_{30}N_7ClO$, Calculated: C 65.96; H 5.73, N 18.57. Found: C 66.07, H 5.89, N 18.66.

4-[2-(6-Chloro-2-oxo-2,3-dihydro-1-{benzyl-4-(2'-[1H-tetrazol-5-yl]-phenyl)}-1H-indol-5-yl)ethyl] piperazin-1-yl-ethoxyethanol 7g

Pale yellow solid, mp. 159-61°C; IR (KBr) cm^{-1}: 3367 (OH), 3028 (Ar C-H stretch), 1675, 1722 (C=O); ^1H NMR (300 MHz, DMSO-d6, δ ppm): 7.18-7.78 (10H, m, ArH), 5.02 (2H, d, CH2), 3.89 (2H, t, O-CH_2), 3.60 (2H, s, indolin-2-one CH_2), 3.48-3.60 (4H, t, O-CH_2), 2.88-3.30 (4H, t, CH_2), 2.72 (4H, t, CH_2), 2.45-(4H, t, CH_2), 2.25 (2H, t, N-CH2); ^{13}C NMR (75 MHz, DMSO-d6, δ ppm): 172.43 (C=O), 150.03, 145.66, 138.48, 137.31, 135.52, 132.56, 132.24, 131.78, 130.73, 129.68, 129.27, 128.64, 128.03, 127.19, 126.83, 125.33, 114 .01, 70.59, 61.23, 58.13, 56.25, 54.11, 53.91, 44.78, 34.58 (indolin-2-one CH2), 31.53; MS (m/z, 70 eV): 603, 601, 557, 400, 192, 177, 165, 101, 139, 81, 65; CHN Analysis: for $C_{32}H_{36}N_7ClO_3$, Calculated: C 63.83, H 6.03, N 16.28. Found: C 63.92, H 6.12, N 16.39.

6-Chloro-5-(2-[4-acetyl-piperazin-1-yl]ethyl)-1-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 7h

Off white solid, mp. 162-4°C; IR (KBr) cm^{-1}: 3028 (Ar C-H stretch), 1680 (C=O); ^1H NMR (300 MHz, DMSO-d6, δ ppm): 7.35-7.80 (9H, m, ArH), 7.03 (1H, s, ArH), 4.95 (2H, d, CH_2), 3.63 (2H, s, indolin-2one CH_2), 3.28 (4H, t, piperazine CH_2), 2.90 (4H, t, piperazine CH_2), 2.87 (2H, t, CH_2), 2.73 (2H, t, CH_2), 2.06 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d6, δ, ppm): 172.59 (C=O), 170.23 (C=O), 150.11, 145.24, 138.61, 137.29, 135.43, 132.59, 132.18, 131.88, 130.57, 129.30, 129.01, 128.84, 128.35, 127.31, 126.79, 125.63, 113.85, 56.54, 53.51, 45.34, 44.21, 34.87 (indolin-2one CH_2), 31.26, 22.35; MS (m/z, 70 eV): 557, 555, 399, 343, 192, 165, 139, 77, 56; CHN Analysis: for $C_{30}H_{30}N_7ClO_2$, Calculated: C 64.80, H 5.44, N 17.63. Found: C 64.86, H 5.61, N 17.78.

6-Chloro-5-[2-(1H-imidazol-1-yl)ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl] methyl}-1,3-dihydro-2H-indol-2-one 8a

Pale yellow solid, mp. 180-2°C; IR (KBr) cm^{-1}: 3030 (Ar C-H stretch), 1672 (C=O); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.40-7.72 (10H, m, ArH), 7.31 (1H, s, imidazole C_2H), 7.14 (1H, d, imidazole C4H), 7.08 (1H, d, imidazole C5H), 4.86 (2H, d, CH2), 4.34 (2H, t, CH2), 3.58 (2H, s, indolin-2one CH2), 3.08 (2H, t, CH2), 2.31 (3H, s, CH3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.05 (C=O), 161.37, 159.33, 145.20, 139.60, 138.30, 137.29, 132.50, 132.10, 131.80, 130.68, 129.69, 129.30, 128.76, 128.34, 127.59, 127.18, 126.58, 125.66, 125.00, 123.29, 112.88, 44.23, 39.89, 35.09 (indolin-2one CH_2), 31.19 (side chain-CH_2), 9.03 (CH_3); MS (m/z, 70 eV): 511, 509, 359, 345, 311, 270, 244, 177, 165, 152, 40; CHN Analysis: for $C_{29}H_{24}N_5ClO_2$, Calculated: C 68.30, H 4.74, N 13.73. Found: C 68.40; H 4.86; N 13.86.

6-Chloro-5-[2-(1H-1,2,4-triazol-1-yl)ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl] methyl}-1,3-dihydro-2H-indol-2-one 8b

Brown solid, mp. 148-150°C; IR (KBr) cm-1: 3031 (Ar C-H stretch), 1672 (C=O); ^1H NMR (300 MHz, CDCl3, δ ppm)): 8.24 (1H, s, triazole C3H), 8.00 (1H, s, triazole C5H), 7.19-7.54 (10H, m, ArH), 5.18 (2H, d, CH^2), 3.76 (2H, t, CH_2), 3.43 (2H, s, indolin-2one CH_2), 3.22 (2H, t, side chain-CH_2), 1.78 (1H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 173.25 (C=O), 163.37, 159.05, 153.55 (triazole), 144.29, 143.27 (triazole), 139.55, 138.42, 137.66, 135.59, 132.44, 132.09, 131.59, 129.58, 129.0, 128.79, 128.38, 127.28, 126.46, 125.77, 112.20, 51.56, (CH_2), 45.41 (CH_2), 35.00 (indolin-2one CH_2), 30.00 (CH_2), 9.01 (CH_3); MS (m/z, 70 eV): 512, 511,510, 436, 411, 329, 218, 189, 165, 77, 59; CHN Analysis: for $C_{28}H_{23}N_5ClO_2$, Calculated: C 68.30, H 4.74, N 13.73. Found: C 68.48, H 4.86, N 13.85.

6-Chloro-5-[2-(2,4-dioxo-1,3-thiazolidin-3-yl) ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 8c

Off white solid, mp 135-7°C; IR (KBr): 3028 (Ar C-H stretch), 1732

and 1688 (C=O) cm−1; ^{1}H NMR $CDCl_3$, δ ppm): 7.16-7.78 (10H, m, ArH), 4.99 (2H, d, CH2), 4.05 (2H, s, thiazolidine CH2), 3.96 (2H, t,CH2), 3.55 (2H, s, indolin-2-one CH_2), 3.23 (2H, t, (CH_2), 1.74 (1H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 178.87 (thiazolidine N-COS), 177.21 (thiazolidine N-C=O), 172.48, (indolin-2-one C=O), 163.65, 159.85, 145.27, 138.25, 137.12, 135.29, 133.52, 132.80, 132.49, 130.12, 129.50, 129.00, 128.71, 128.40, 127.56, 126.31, 125.54, 113.20, 48.86 (CH_2), 45.11 (CH_2), 34.98 (indolin-2-one CH_2), 31.54 (side chain-CH_2), 30.13 (thiazolidine-CH_2), 8.99 (CH_3); MS (m/z, 70 eV): 560, 559, 558, 426, 394, 329, 238, 180, 165, 77, 63; CHN Analysis: for $C_{29}H_{23}N_4ClO_4S$, Calculated: C 62.31, H 4.15, N 10.02. Found: C 62.43, H 4.25, N 10.13.

6-Chloro-5-[2-(morpholin-4-yl)-ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl] methyl}-1,3-dihydro-2H-indol-2-one 8d

Brown solid, mp. 155-7°C; IR (KBr) cm-1: 3041 (Ar C-H stretch), 1687 (C=O); ^{1}H NMR (300 MHz, CDCl3, δ ppm): 7.23-7.81 (10H, m, ArH), 4.96 (2H, d, CH_2),3.88 (4H, t, morpholine O-CH_2), 3.59 (2H, s, indolin-2-one CH_2), 3.10 (2H, t, side chain-CH_2), 2.90 (2H, t, side chain-CH_2), 2.52-2.81 (4H, t, morpholine N-CH_2), 1.82 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 172.48 (C=O), 163.65, 159.85, 145.27, 138.25, 137.12, 135.33, 132.72, 132.49, 129.50, 129.20, 129.01, 128.63, 128.40, 127.80,127.56, 126.31, 125.68, 113.29, 65.53 (morpoline-OCH_2), 58.86, (CH_2), 53.61 (morpholine-NCH_2), 44.81 (CH_2), 34.88, (indolin-2-one CH_2), 31.44, (side chain-CH2), 9.10 (CH3); MS (m/z, 70 eV): 530, 529, 528, 406, 385, 329, 208, 189, 165, 77, 66; CHN Analysis: for $C_{30}H_{29}N_4ClO$, Calculated: C 68.11, H 5.53, N 10.59. Found: C 68.21, H 5.64, N 10.68.

6-Chloro-5-[2-(piperazin-1-yl)-ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl] methyl}-1,3-dihydro-2H-indol-2-one 8e

Off white solid, mp 166-8°C; IR (KBr) cm^{-1}: 3203 br (NH), 3028 (Ar C-H stretch), 1679 (C=O) ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): 7.11-7.79 (10H, m, ArH), 5.01 (2H, d, CH_2), 3.57 (2H, s, indolin-2-one CH_2), 3.06 (2H, t, side chain-CH_2), 2.89 (2H, t, side chain-CH_2), 2.79 (4H, t, piperazine CH_2), 2.66 (4H, t, piperazine CH_2), 1.68 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 172.75, (C=O), 163.29, 159.88, 145.66, 138.48, 137.59, 135.29, 132.92, 132.56, 132.19, 131.65, 130.59, 129.34, 129.03, 128.83, 128.66, 127.33, 126.33, 112.81, 57.19 (side chain-CH_2), 55.00 (piperazin-CH_2), 46.01 (piperazine-CH_2), 44.85 (methylene-CH_2), 34.85 (indolin-2-one CH_2), 31.00 (side chain-CH2), 9.02 (CH3); MS (m/z, 70 eV): 529, 528, 527, 470, 459, 420, 192, 177, 165, 152, 82, 40; CHN Analysis: for $C_{30}H_{30}N_5ClO_2$, Calculated: C 68.24, H 5.73, N 13.26. Found: C 68.37, H 5.80, N 13.38.

6-Chloro-5-[2-(4-methyl-piperazin-1-yl)-ethyl]-1-{[2'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 8f

Brown solid, mp. 158-60°C; IR (KBr): 3029 (Ar C-H stretch), 1669, 1728, (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.14-7.79 (10H, m, ArH), 4.96 (2H, d, methylene-CH_2), 3.63 (2H, s, indolin-2-one CH_2), 3.11 (2H, t, side chain-CH_2), 2.93 (2H, t, side chain- CH_2), 2.79 (4H, t, piperazine CH_2), 2.55(4H, t, piperazine CH_2), 2.31 (1H, s, N-CH_3), 1.73 (3H, s, oxadiazole-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 172.93 (C=O), 163.30, 159.81, 145.66, 138.48, 137.59, 135.42, 132.92, 132.56, 131.45, 130.50, 129.67, 129.34, 128.83, 128.40, 127.33, 126.54, 125.79, 112.81, 57.21 (side chain-CH_2), 55.32 (piperzine-CH_2), 44.88 (methylene-CH_2), 42.66 (CH_2), 34.83 (indolin-2-one CH_2), 31.66 (side chain-CH_2), 20.13 (CH_3), 9.3 (oxadiazole-CH_3); MS (m/z, 70 eV): 543, 542, 514, 419. 403, 189, 170, 165, 153, 130, 89, 50; CHN Analysis: for $C_{31}H_{32}N_5ClO_2$, Calculated: C 68.69 H 5.95 N 12. 92 Found: C 68.79 H 6.07 N 13.04.

4-[2-(6-Chloro-2-oxo-2,3-dihydro-1-{benzyl-4-(2'-[5-methyl-1,3,4-oxadiazol-2-yl]-phenyl)}-1H-indol-5-yl)ethyl]piperazin-1-yl-ethoxyethanol 8g

Brown solid, mp. 154-6°C; IR (KBr) cm^{-1}: 3397 (OH), 3028 (Ar C-H stretch), 1671, 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm):7.12-7.75 (10H, m, ArH), 4.93 (2H, d, CH_2), 3.89 (2H, t, O-CH_2), 3.60 (2H, s, indolin-2-one CH_2), 3.42-3.58 (4H, t, O-CH_2), 2.90-3.33 (6H, t, CH_2), 2.40-2.59 (8H, m, piperazine CH_2), 2.12 (3H, s, CH_3), 1.33 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm); 172.93 (C=O), 163.72, 160.00, 145.69, 138.48, 137.59, 135.62, 133.24, 132.92, 132.56, 132.48, 130.59, 131.26, 129.78, 129.34, 128.83, 128.54, 127.33, 126.54, 114.10, 70.59 (OCH_2), 61.25 (OCH_2), 55.23 (side chain-NCH_2), 54.68 (side chain-NCH_2), 53.94 (piperazine C), 44.83 (methylene CH_2), 34.69 (indolin-2-one CH_2), 33.25 (side chain-CH_2), 31.88 (side chain-CH_2), 9.02 (CH_3); MS (m/z, 70 eV): 617, 616, 615, 411. 383, 189, 170, 165, 129, 109, 88, 65; CHN Analysis: for $C_{34}H_{38}N_5ClO_4$, Calculated C 66.28, H 6.22, N 11.37. Found C 66.45, H 6.36, N 11.48.

6-Chloro-5-[2-(4-acetyl-piperazin-1-yl)-ethyl]-1-{[2'-(5-methyl-1,3, 4-oxadiazol-2-yl)-biphenyl-4-yl]methyl}-1,3-dihydro-2H-indol-2-one 8h

Off white solid, mp. 145-8°C; IR (KBr) cm^{-1}: 3033 (Ar C-H stretch), 1689 (C=O); ^{1}H NMR (300 MHz, CDCl3, δ ppm): 7.10-7.77 (10H, m, ArH), 5.01 (2H, d, CH_2), 3.62, (2H, t, CH_2), 3.45 (2H, s, indolin-2-one CH_2), 3.40 (4H, t, piperazine CH_2), 2.80 (4H, t, piperazine CH_2), 2.67 (2H, t, CH_2), 2.30 (3H, s, CH_3), 2.05 (3H, s CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.62 (C=O), 172.21 (C=O), 163.77, 159.64, 145.39, 138.53, 137.56, 135.62, 133.06, 132.50, 132.13, 131.50, 130.78, 129.88, 129.34, 128.86, 128.20, 126.63, 125.79, 113.56, 56.90, 53.18 (CH2), 44.80 (CH_2), 43.79 (piperazine-CH_2), 34.86 (indolin-2-one CH_2), 32.19 (side chain-CH_2), 22.76 (CH_3), 9.01 (CH_3); MS (m/z, 70 eV): 571, 570, 569, 429. 373, 189, 170, 165, 139, 88, 63; CHN Analysis: for $C_{32}H_{32}N_5ClO_3$, Calculated: C 67.42, H 5.66, N 12.28. Found: C 67.60, H 5.70, N 12.40.

Conclusion

Cancer is a widespread disease that makes millions of people around the world suffer. Due to alarming rate in the population diagnosed with cancer, medicinal chemists are implementing new strategies for the design and synthesis of anticancer scaffolds to effect the containment of this disease. In view of the above, the present report concerns about the design and synthesis of biphenyl derived 5-substituted-indolin-2-ones tailored with bioactive pharmacophore viz., cyclic secondary amines. The docking simulations with DNA were carried out to examine its

effect on DNA binding propensity which revealed the intercalative mode of binding with base pairs of DNA helix structure of PDB 453D. From the observed anti-proliferative activity results carried out at National Cancer Institute, NIH, Bethesda, USA compounds 5b and 5e have exhibited almost 50% growth inhibition against Prostate Cancer PC-3 cell lines.

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