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Research Article

SYNTHESIS AND MOLECULAR DOCKING STUDY OF *N*-ALKYL/ARYL-2-ARYL INDOL-3-YL GLYOXYLAMIDES AS NOVEL ANTICANCER AGENTS

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ABSTRACT

Objective: To synthesize structurally distinct *N*-alkyl/aryl-2-aryl indol-3yl-glyoxylamides to evaluate their anticancer activity on Murine double minutes-2(MDM2) receptor bind p53 and Pheripheral benzodiazepine receptor (PBR) protein.

Methods: A series of new appropriately *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides **(2a-h)**, were synthesized by the reaction of 2-arylindoles, oxalyl chloride and different amines in one pot reaction. Structure of all the new compounds were elucidated by spectral analysis and evaluated *in silico* docking study with MDM2 receptor bind p53 and PBR protein.

Results: Among all the tested compounds, the 2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-2-oxo-*N*-propylacetamide **(2e)** showed high binding affinity on MDM2 receptor bind p53 protein. While remaining, the 2-(5-chloro-2-phenyl-1*H*-indol-3-yl)-N-(2,4-dimethylphenyl)-2-oxoacetamide **(2a)**, *N*-(4-fluorophenyl)-2-[2-(4-methylphenyl)-1*H*-indol-3-yl]-2-oxoacetamide **(2b)** and 2-[2-(4-methylphenyl)-1*H*-indol-3-yl]-2-oxoacetamide **(2c)** were shown comparably good binding affinity on PBR protein.

Conclusion: The Docking study of newly synthesized compounds revealed that the *N*-alkyl/aryl-2-aryl indol-3yl-glyoxylamides could be a very useful scaffold for anticancer therapy particularly on MDM2 receptor bind p53 and PBR protein.

Keywords: *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides; Oxalyl chloride; MDM2-p53: PBR; Docking; Lipinski rule.

INTRODUCTION

Design and synthesis of different small-molecule inhibitors that block the MDM2-p53 interaction has become an attractive strategy to activate p53 for the treatment of cancer and other human diseases. Recent advances in the design of small-molecule inhibitors of the MDM2-p53 interaction have gained much attention in recent years, and thus several compounds have reached advanced preclinical trials [1]. Hence, small-molecule such as various *N,N*-dialkyl-(2-phenyl-1*H*-lindol-3-yl)glyoxylamides containing halogens in phenyl ring were reported to be highly selective for PBR ligands [2]. The indolyl glyoxylamide D-24851 (See Figure 1) has been reported to inhibit the growth of multidrug-resistant tumors both *in vitro* and *in vivo* [3]. Also various *N*-(indol-3-ylglyoxylyl)piperidines were reported to show high affinity against agonists of human GABA-A receptors [4]. Various *N,N*-dialkyl-[2-(4'-iodo- and 4'-bromo-phenylindol-3-yl]glyoxylamides have also shown high affinity to peripheral benzodiazepine binding sites [5,6].

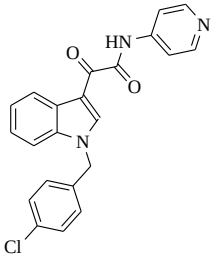


Fig. 1: *N*-(pyrin-4-yl)-[1-(4-chlorobenzyl)-indol-3yl]-glyoxyl amide (D-24851)

Various Indolyl glyoxylamides were also been investigated against several cancer cell lines, including multidrug resistance (MDR) cell lines [7-12]. Ferderico et al. also reported that *N,N*-disubstituted indol-3-ylglyoxylamides bearing different substitution represents potentially lead compounds for the treatment of anxiety disorders with high affinity for TSPO ligands [13].

Antonio Da Settimo and coworkers have been identified that a various *N*-phenylindol-3-ylglyoxylohydrazides efficiently binds to brain benzodiazepine receptors [14]. Anticancer activity of various *N*-heterocyclic indolyl glyoxylamides were studied extensively by Penthala et al [15-18].

The structure-activity relationships of various *N*-aryl(indol-3-yl)glyoxamides exhibited potent anticancer activities [19].

Covering wide range of anticancer properties of various indolyl glyoxylamides, we felt it worthwhile to study the *in silico* docking of certain new derivatives *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides **2a-h** to find out their ability to bind with MDM2 receptor bind p53 and Pheripheral benzodiazepine receptor (PBR) protein. Hence in our continuing efforts to develop small molecules, that has been reported to posses anticancer property [20, 21], in this paper we highlighted the simple and more convenient synthesis of various new *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamide derivatives (**2a-h**) as a small-molecule inhibitors of MDM2-p53 and PBR protein. And the results obtained from these efforts with their molecular docking studies have been systematically studied and presented in this paper.

MATERIALS AND METHODS

Chemistry

The chemicals used were that of analytical grade. Melting points were uncorrected, determined in open capillary. Purity of the compounds was checked by TLC on silica gel and compounds were purified by using column chromatography (pet ether/ethyl acetate 8:2 v/v). ^{1}H NMR spectra was recorded on a Bruker supercon FT NMR (400 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 and TMS as an internal standard. The chemical shifts are expressed in δ units. Mass spectra was recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer. The various 2-phenylindoles (**1a-d)** were synthesized following the literature method [14].

Typical procedure for the synthesis of 2-(5-chloro-2-phenyl-1*H*-indol-3-yl)-*N*-(2,4-dimethylphenyl)-2-oxoacetamide 2a.

To a partially dissolved solution of 5-chloro-2-phenyl-1*H*-indole (1 g, 43 mmol) in anhydrous ether (30 ml) at 0 °C was added oxalyl chloride drop wise (0.53 mL, 43 mmol) and the mixture was stirred for 1 hr. The 2,4-dimethyl aniline (0.70 mL, 5.6 mmol) in anhydrous

ether (5ml) was added drop wise slowly for 30 min into the reaction mixture under constant stirring. After the completion of the reaction as indicated by TLC (ethyl acetate/pet ether 8:2 v/v), the reaction mass was then quenched with water and extracted with ethyl acetate and dried over anhydrous $NaSO_4$. The crude product **2a** was then purified by column chromatography on silica gel (pet ether/ethyl acetate 8:2 v/v). The yield 80% of product was obtained as creamy solid (1.6 g). Similarly all other derivatives (**2b-h**) were prepared.

Spectral data

2-(5-chloro-2-phenyl-1*H*-indol-3-yl)-*N*-(2,4-dimethylphenyl)-2-oxoacetamide (2a)

^{1}H NMR(300 MHz, DMSO-d_6): δ = 12.64(s, 1H), 8.12(s, 2.4 Hz, 1H), 7.67(s, 1H), 7.51(d, *J* =4.8 Hz, 2H), 7.44-7.43(m, 3H), 7.37-7.31(m, 2H), 7.08-7.02(m, 3H), 2.49(s, 3H), 2.27(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ =186.8, 164.6, 158.5, 148.6, 135.2, 134.4, 132.4, 132.2, 131.4, 130.9, 130.7, 129.6, 128.6, 126.9, 126.6, 124.3, 123.4, 119.9, 116.2, 113.6, 108.7, 20.4, 17.4. MS: m/z=403.2 (M+1), 405.2 (M+2).

N-(4-fluorophenyl)-2-[2-(4-methylphenyl)-1*H*-indol-3-yl]-2-oxoacetamide (2b)

^{1}H NMR(400 MHz, DMSO-d_6): δ = 12.42(s, 1H), 8.15(d, *J*=7.32 Hz, 1H), 7.86-7.91(m, 3H), 7.43-7.51(m, 3H), 7.33-7.26(m, 6H), 2.21(s,3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ = 186.4, 164.6, 158.4, 157.2, 148.3, 138.9, 135.8, 134.3, 134.0, 129.3, 128.3, 128.5, 127.3, 123.4, 122.4, 122.2, 121.1, 121.3, 115.2, 115.0, 114.7, 112.0, 20.7. MS: m/z=371.0 (M-1).

2-[2-(4-methylphenyl)-1*H*-indol-3-yl]-2-oxoacetamide (2c).

^{1}H-NMR(400 MHz, DMSO-d_6): δ = 12.28(s, 1H), 8.05(d, *J*=8 Hz, 1H), 7.95(s, 1H), 7.48(m, 4H), 7.25(m, 4H), 2.39(s,3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ = 187.7, 168.6, 147.0, 138.8, 135.7, 129.5, 128,6, 127.4, 122.9, 121.9, 120.6, 111,8, 108.6, 20.9. MS: m/z=279 (M+1), 280 (M+2).

2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-*N*-(2,4-dimethylphenyl)-2-oxoacetamide (2d).

^{1}H NMR(400 MHz, DMSO-d_6): δ = 12.65(s, 1H), 8.1(d, J=2 Hz, 1H), 7.68-7.66(m, 2H), 7.55-7.47(m, 4H), 7.34-7.32(m, 2H), 6.86-7.17(m, 3H), 2.1-2.29(m, 6H). ^{13}C NMR (300 MHz, DMSO-d_6) δ = 164.6, 158.4, 148.8, 135.2, 134.7, 134.6, 134.5, 134.3, 130.9, 130.1, 129.9, 129.5, 128.9, 128,5, 128.3, 126.9, 126.7, 125.1, 123.4, 120.0, 113.8, 108.7, 20.5, 17.5. MS: m/z=403.0 (M+1), 404.0 (M+2).

2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-2-oxo-*N*-propylacetamide (2e).

^{1}H NMR(400 MHz, DMSO-d_6): δ =12.42(s, 1H), 8.50(t, *J*=6.4 Hz, 1H), 8.07(m,1H), 7.58(m, 4H), 7.49(t, *J*= 5.6Hz, 1H), 7.29(m, 2H), 2.77(q, *J*= 7.2, 13.2 Hz, 2H), 1.28(q, *J*= 7.2, 14.4 Hz, 2H), 0.79(t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ = 188.0, 166.8, 146.2, 136.2, 134.6, 131.8, 130.7, 128.5, 127.7, 123.9, 122.8, 121.4, 112.4, 110.0, 22.1, 11.9. MS: m/z= 341(M+1), 342(M+2).

2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-2-oxo-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide (2f).

^{1}H NMR(400 MHz, DMSO-d_6): δ = 12.59(s, 1H), 8.15(d, *J*= 7.2 Hz, 1H), 7.63(s, 4H), 7.51(d, *J*= 7.6 Hz, 1H), 7.31(m, 2H), 3.41(t, *J*= 4.8 Hz, 4H), 3.221(t, *J*= 4 Hz, 2H), 3.11(t, *J*= 4.4 Hz, 2H). ^{13}C NMR (300 MHz, DMSO-d_6) δ =187.0, 166.1, 146.7, 136.2, 135.1, 132.4, 129,8, 127,0, 124.2, 123.2, 121.5, 112.6, 110.4, 66.0, 65.7, 45.9. MS: m/z= 369(M+1), 370(M+2).

N-butyl-2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-2-oxoacetamide (2g).

^{1}H NMR(300 MHz, DMSO-d_6): δ =12.31(bs, 1H), 8.45(t, *J*= 5.4 Hz, 1H), 8.08(m, 1H), 7.56(m, 5H), 7.26(m, 2H), 2.50(m, 2H), 1.19(m, 4H), 0.84(q, *J*= 6, 12 Hz, 3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ =187.5, 166.3, 145.7, 135.7, 134.1, 131.3, 130.2, 128.0, 127.2, 123.3, 122.2, 120.8, 111.9, 109.5, 37.9, 30.3, 19.5, 13.5. MS: m/z= 255(M+1), 256(M+2).

2-[2-(4-bromophenyl)-1*H*-indol-3-yl]-*N*-butyl-2-oxoacetamide (2h).

^{1}H NMR(400 MHz, $CDCl_3$): δ =8.77(s, 1H), 8.18(t, *J*= 2.56, 1H), 7.53(d, *J*= 8.2 Hz 2H), 7.34(m, 5H), 6.85(s, 1H), 3.18(q, *J*= 6.6, 13.5 Hz, 2H), 1.47(m, 2H), 1.34(q, *J*= 6.8, 14.9 Hz, 2H), 0.95(d, *J*= 7.2 Hz, 3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ = 187.5, 166.2, 145.7, 135.7, 131.5, 130.9, 130.5, 127.2, 123.4, 122.8, 122.2, 120.8, 111.9, 109.5, 37.9, 30.3, 19.5, 13.5. MS: m/z=399.0 (M+), 402.0 (M+2).

***In silico* molecular docking studies**

Pharmacophore Analysis

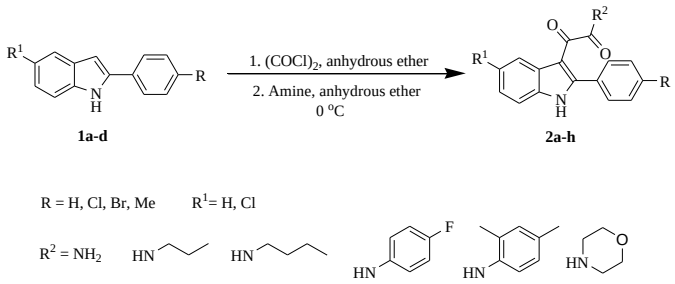
The synthesized *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (**2a-h**) compounds were used for molecular and biochemical characterization. The pharamcophore analyses of these compounds were studied with respect to chloro, bromo, methyl and fluro substituents. The chemical structures of these new compounds were drawn using ChemDraw Ultra 8.0. The Quantitative structure activity relationship (QSAR) was used to characterize the properties of each functionally derived compound with calculated molecular properties which help to understand the properties of inhibitors.

Identification of Protein structure

The crystal structure of MDM2 receptor bind p53 tumor suppressor protein (PDB ID: 1RV1) shows over expression in transcriptional inhibition and impairs the p53 function, this characteristic shows inhibition of further downstream pathways [23]. Another protein peripheral benzodiazepine receptor (PBR) (PDBID: 1EQ1) [24] helps translocation of cholesterol and porphyrin across the mitochondrial outer membrane and helps for steroid biosynthesis [25], cellular respiration [26], proliferation [27] and apoptosis [28]. The 3D integration of X-ray crystal structures with stereochemical activity were predicted using structural analysis and verification server (SAVS). The new active sites of MDM2 receptor bind p53 and PBR with nonpolar integration of valid amino acids were predicted using Q-site finder [www.bioinformatics.leeds.ac.uk/qsitefinder]. The activity of 3D structure is assumed as a ligand binding site and the whole protein structure itself is used as ligand binding site. The hydrophobic nature of active site amino acids were calculated using RMSA shows geometry accuracy of target protein structures. The resultant protein structures helps for rigid docking against the synthetic molecules (**2a-h**). The docking study was performed using AutoDockTools (ADT) v 1.5.4 and AutoDock v 4.2 program to create grid maps of different grid points for covering ligand binding pockets such as active site amino acids. Using molecular modeling and simulation algorithms such as Lamarckian genetic algorithm helps for molecular simulation and docking. Different molecular simulation parameters were used in grid point such as 80 x 80 x 80 and docking. The parameters such as population size of 150, the mutation rate of 0.02 and crossover rate of 0.8 were fixed accordingly. Secondly, the Simulations were performed up to 2.5 million energy and the evaluations were maximum at 27000 generations. Each simulation was carried about 10 times which ultimately yielded 10 docked conformations. From this, the lowest energy conformations were regarded as the best binding conformations. In the end, the reverse validation processes ensured the identified hits that fitted with generated pharmacophore models and active sites of both targets. Since all the parameters were required for molecular docking and pharmacophore mapping, they were consequently fixed and used in regular process.

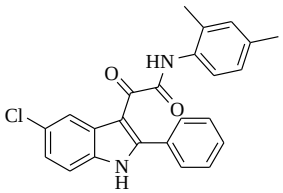
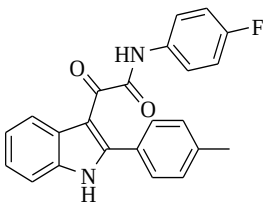
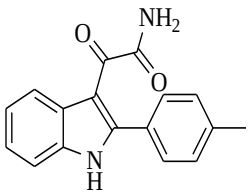
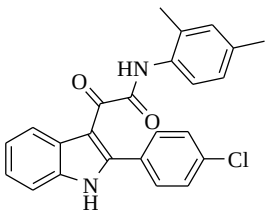
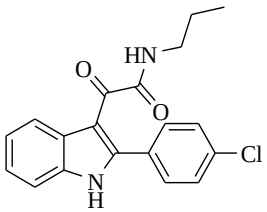
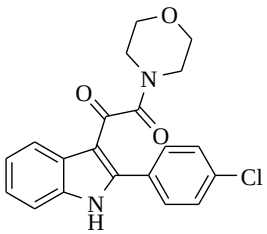
RESULTS AND DISCUSSION

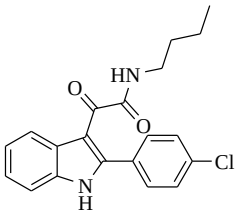
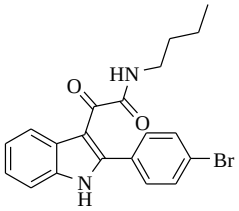
Various *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (**2a-h**) (Scheme 1 and Table 1) were synthesized via one pot multicomponent reaction. The target compounds were prepared by reacting various appropriately substituted 2-arylindoles (**1a-d)** with oxalyl chloride and different amines in presence of anhydrous ether at 0 ^{o}C in one pot by suitable modification of the reaction reported in the literature [6].



Scheme 1: Synthesis of N-alkyl/aryl-2-aryl indol-3-yl glyoxylamids (2a-h).

Table 1: Physical properties of *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamids (2a-h)

Entry	Products	Mp (°C)	Yields (%)[a]
2a		201-203	80
2b		245-246	85
2c		188-190	85
2d		211-213	81
2e		193-194	83
2f		227-228	74

2g		138-139	75
2h		241-243	79

[a] Isolated yields.

Molecular docking studies

A series of *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamide derivatives (**2a-h**) with chemical portion plays an important role in the interaction with MDM2 receptor bind p53 and PBR proteins. The Pharmacophore properties of each descriptor were predicted using Hyperchem 7.5 Professional. Each functional groups shows lower energy direction of atom position.

The QSAR properties of synthetic compounds were hailed to relate the structural descriptors of receptors with physicochemical properties and biological activities. The Lipinski rule is applied on the selected molecules (**2a-h**) are LogP (the logarithm of octanol/ water partition coefficient), molecular weight, and the number of hydrogen bond acceptors. Most "drug- like" molecules have logP ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donor's ≤ 5.

Molecular violations are occurred any of these properties is shows problem with bioavailability.

The Lipinski's rule of five parameters and total polar surface area (TPSA), which has shown to correlate with drug absorption, were obtained by using the Molinspiration program (Table 2).

Table 2: Lipinski rule of *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (2a-h)

Ligand	LogP	TPSA	nAtoms	MW	nON	nOHNH	nrotb	MV	nviolations
2a	5.566	61.96	29.0	402.881	4	2	4	352.865	1
2b	4.699	61.96	28	372.399	4	2	4	327.7	0
2c	2.464	75.956	21.0	278.311	4	3	3	250.246	0
2d	5.59	61.96	29.0	402.881	4	2	4	352.865	1
2e	3.946	61.96	24.0	340.81	4	2	5	298.499	0
2f	3.158	62.405	26.0	368.82	5	1	3	314.066	0
2g	4.505	61.96	25.0	354.837	4	2	6	315.301	0
2h	4.636	60.96	25.0	399.288	4	2	6	319.651	0

LogP=logarithm of the octanol/water partition coefficient; TPSA=topological polar surface area; nAtoms=number of atoms; MW=molecular weight; nON=number of hydrogen bond acceptors; nOHNH = number of hydrogen bond donors; nrotb=number of rotatable bonds; MV=molecular volume; nviolations=number of violations of the Lipinski's rule of five..

The active crystal structures of MDM2 receptor bind p53 tumor suppressor protein and peripheral benzodiazepine receptor structure (PBR) was interacted with pharmacophores *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (**2a-h**) using molecular docking. The potential binding surface were calculated and a cavity of 1713.3 Å was observed close to Lys51, Leu 54, Phe55, Gly58, Gln59, Ile61, Met62, Gln72, His73, Val93, His 96 and Tyr100 is predicted in 1RV1 and the resultant protein is potentially used as a drug binding sites. The PBR protein has active site surface of 514.8 Å is near to Thr22, Ala56, Ser59, Gln78, Asn82, Thr114, Gln117, Ser119, Ile141, Asp147 and Gln156. The protein structure such as MDM2 receptor (A chain) has more ligand binding sites which are predicted based on non polar interaction with the ligand molecule

Table 3: Molecular Docking study of 1RV1 protein complex with *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (2a-h)

Ligand	H-Bonds	Binding Energy (kcal/mol)	Inhibitory constant (μM)	Electrostatic Energy (kcal/mol)	RMSD	Amino acids
2a	2	-25.4927	109.877	-2.5	99.06	Lys51
2b	2	-22.7939	111.625	-1.85	95.78	Phe55, Gln59
2c	2	-25.6669	82.991	0.123	79.51	Gln72, Tyr100
2d	2	-6.73602	75.711	-2.5	28.56	His96
2e	3	-17.2424	93.201	0.134	12.86	Lys51, Gln59
2f	2	-6.5768	86.975	0.177	95.13	Val93, His96
2g	1	-16.2813	104.185	0.134	98.37	Leu54
2h	1	-8.02555	102.343	2.45	8.44	Tyr100

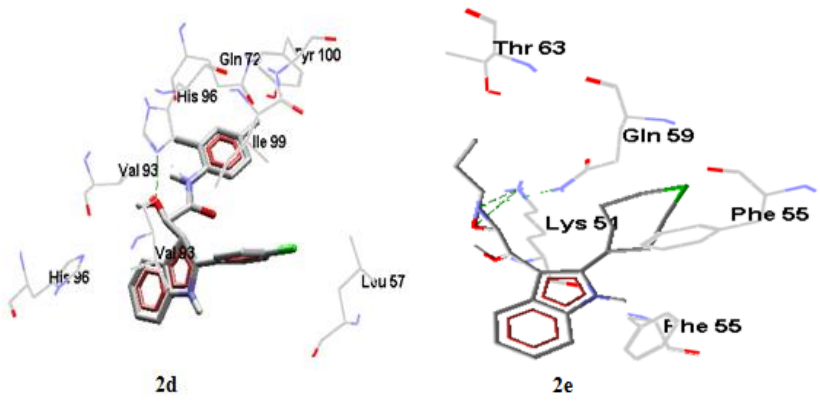


Fig. 2: Docking images of selected compounds with p53 showing binding of compound 2d with His96 (2H bonds) and compound 2e with Lys51, Gln59 (3H bonds). The blue colored dashed line denote the hydrogen bonds

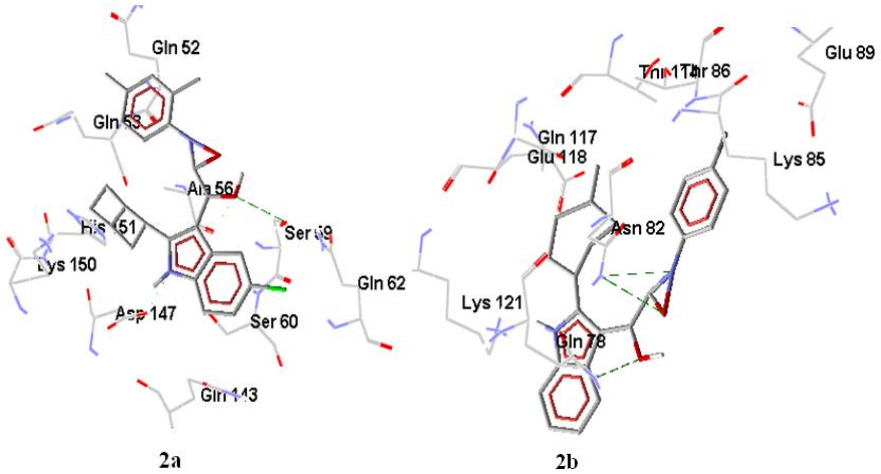


Fig. 3: Docking images of selected compounds with 1EQ1 showing binding of compound 2a with Ala56, Ser59, Asp147 (3H bonds) and compound 2b with Gln78, Asn82 (3H bonds). The blue colored dashed line denote the hydrogen bonds

The docking results are calculated according to binding energy and RMSD values. The docking score of both 1RV1 and 1EQ1 proteins were mention in Table 3 and 4. 2D structure of all new ligands **2a-h** were converted into energy minimized 3D structures and were then used for *in silico* protein-ligand docking. The docking of MDM2 receptor bind p53 tumor suppressor protein with newly synthesized ligands **2a-h** exhibited well established bonds with one or more amino acids in the receptor active pocket. Figure 2 shows the docked images of selected candidate ligands 2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-*N*-(2,4-dimethylphenyl)-2-oxoacetamide (**2d**) and 2-[2-(4-chlorophenyl)-1*H*-indol-3-yl]-2-oxo-*N*-propylacetamide (**2e**). Table 3 shows the binding energy and inhibition constant of eight compounds. *In silico* studies revealed that all the synthesized molecules showed good binding energy toward the target protein ranging from -6.57 to -25.66 kcal/mol. The compound **2e** has shown 3 hydrogen bonding interaction with active site amino acids Lys51 and Gln59 having energy -17.2424 kcal/mol exhibiting promising interaction on MDM2 receptor bind p53 protein to control the transcription regulation. The other molecules such as **2a-d** and **2f** have lesser binding affinity on target MDM2 receptor bind p53 protein

Similarly docking study was performed on PBR receptor (1EQ1) with *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides derivatives (Table 4). The ligands **2a-c** forms 3 hydrogen bonding interaction with active site amino acid Ala56, Ser59, Asp147, Gln78, Asn82, Ser119, and Ile141 having binding energy -8.8370, -15.219 and -20.597 kcal/mol respectively, indicates potent inhibitor of PBR. Figure 3 shows the docked images of selected candidate ligands 2-(5-chloro-2-phenyl-1*H*-indol-3-yl)-*N*-(2,4-dimethylphenyl)-2-oxoacetamide (**2a**) and *N*-(4-fluorophenyl)-2-[2-(4-methylphenyl)-1*H*-indol-3-yl]-2-oxoacetamide (**2b**). Other structural compounds such as **2d** and **2h** have relatively no interaction with target protein and hence can't be considered as an inhibitor of PBR.

Table 4: Molecular Docking study of 1EQ1 protein complex with *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (2a-h)

Ligand	H-Bonds	Binding Energy (kcal/mol)	Inhibitory constant (µM)	Electrostatic Energy (kcal/mol)	RMSD	Amino acids
2a	3	-8.8370	58.876	-2.69	2.21	Ala56, er59,Asp147
2b	3	-15.219	87.520	-0.13	4.33	Gln78, Asn82
2c	3	-20.597	16.016	-2.92	10.52	Ser119, Ile141
2d	-	-	-	-	-	-
2e	1	-3.025	2.660	-0.11	2.812	Thr114
2f	2	-10.136	70.341	0.177	73.26	Thr22, Gln156
2g	2	-5.1613	44.317	0.296	46.321	Thr114, Gln117
2h	-	-	-	-	-	-

CONCLUSION

Various structurally distinct *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides (**2a-h**) have been conveniently synthesized and characterized. The *in silico* docking study of *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides were revealed that the compound **2e** found to bind efficiently with 1RV1 protein whereas, compounds **2a**, **2b**, **2c** efficiently binds with 1EQ1 protein with lesser binding energy in comparison with remaining compounds. Hence this study will further widen the scope for the development of still similar new *N*-alkyl/aryl-2-aryl indol-3-yl glyoxylamides as possible potential anticancer agents.

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