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Research Article

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Synthesis and molecular docking studies of 1-trityl-5-azaindazole derivatives

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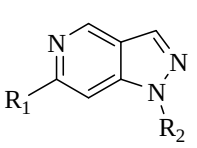
ABSTRACT

*Synthesis of a series of 3-amine/alkoxy substituted-azaindazoles (**3a-c, 5a-d**) by Ullmann coupling reaction was described. The advantage of this method includes selectivity between chloro and iodo groups to words the coupling of alcohol and amine nucleophiles which occurred only with iodo group. The selectivity was found to be almost 100 % in both amines (**2a-c**) and alcohols (**4a-d**) as incoming nucleophiles. All new compounds were subjected to molecular docking study with Murine double minutes-2(MDM2) receptor bind p53 and Pheripheral benzodiazepine receptor (PBR) cancer proteins. The results reveals that the structures **3a-c** and **5a-d** were shown more number of binding interactions with the active site amino acids such as LEU43, GLN109, ILE141, LYS140, PHE23 and LEU30 in PBR receptor protein with binding energy ranging from -2.579182e+02 to -2.863714e+02 respectively. However, the compound N-(4-methoxybenzyl)-6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (**3c**) alone exhibits very high bonding interaction with active site amino acid GLN72 and HIS73 in MDM2 receptor bind p53 protein which shows binding energy -3.592025e+02 kcal/mol.*

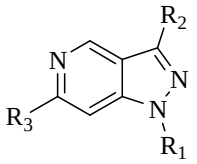
Keywords: 5-Aza indazole, Ullmann coupling, PBR, MDM2-p53, Lipinski rule.

INTRODUCTION

Indazole nucleus represents the core structure of many of pharmaceuticals which are of prime importance in medicinal chemistry [1]. The core structure displays attractive pharmacological activities such as anticancer, anti-inflammatory, analgesic male contraceptives (anti-spermatogenetic agent), anti-HIV, anti-emetic, analgesic, antipyretic, serotonin 5-HT3 receptor antagonist and anti-platelet activities [2-6]. Recently Jinho lee *et al* [7] have reported the synthesis of *N*-3-acyl-*N*5-aryl-3,5-diaminoindazoles as a anticancer drug for head and neck squamous cell carcinoma (HNSCC). Chandrasekhar *et al* [8] have reported the antibacterial and antifungal properties of indazole-3-carboxamide derivatives. Further, the Pierre *et al* [9] reported that the azaindazoles can be used as a drug in the treatment of cancer over expressing tropomyosin-related kinase protein. Nevertheless, 5-azaindazole derivatives (Figure 1a) were reported to posses anticancer activity against disorders mediated by Pim kinase(Pim-1, Pim-2, and Pim-3) inhibitors [10].



Reported structure (**a**)



Synthesized structure (**b**)

Figure 1

Regarding their synthesis, there are only a few methods, and substitution on 3rd position with nucleophiles are met with limited success only [11]. Since the lack of reactivity in traditional nucleophilic substitution reaction of indazoles, only direct amination of indazole at 3rd position was reported for 3-nitroindazole, which involves very harsh reaction condition.[3] Although many palladium catalyzed coupling reactions are known, they suffered due to low yield and use of expensive reagents [12]. Hence encouraged by our continued research on synthesis of heterocyclic compounds [13-20] for against anticancer activity, in this report our attention was turned to synthesize various *N*-trityl-3-amino/alkoxy substituted 5-azaindazoles using Ullmann coupling reaction due to the wide spectrum of biological activities of indazole nucleus. So in this work we report the Ullmann coupling reaction of 6-chloro-3-iodo-1-trityl-1*H*-pyrazolo[4,3-c]pyridine with different alcohol and amines to produce novel *N*-trityl-3-amino/alkoxy substituted 5-azaindazoles (**3a-c, 5a-d**). As a part of preliminary investigation on interaction of protein-ligand which plays a key role in rational drug design, the molecular docking was performed with all new synthesized compounds against PBR and MDM2-bind p53 cancer causing receptor proteins. Thus we were able to predict and identify most promising candidates as DNA-interactive moiety which potentially endowed with antitumor activity. Most importantly the possibility of making various derivatives was described which makes the research to produce as many as possible indazole ligands for future biological trials to test against different aliments.

EXPERIMENTAL SECTION

The chemicals and reagents obtained from HiMedia, Sigma-Aldrich Chemical Company were used as received. Melting points were determined in open capillary and were uncorrected. Purity of the compounds was checked by TLC on silica gel and compounds were purified by using column chromatography. ^{1}H NMR and ^{13}C NMR spectra were 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 were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

Typical procedure for the synthesis of 6-chloro-*N*-ethyl-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine (3a)

To a solution of ethylamine hydrochloride (0.155 g, 0.0019 mol) in DMSO 5 mL was added anhydrous potassium carbonate (0.396 g, 0.0028 mol) followed by CuI (0.036 g, 0.0001 mol) and proline (0.220 g, 0.0001 mol). The reaction mixture was stirred at ambient temperature. After 5 min, the 6-chloro-3-iodo-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (0.250 g, 0.0004 mol) was added. The resultant mixture was heated to 80 °C for 5 h. After completion of the reaction as indicated by TLC, the reaction mass was cooled to room temperature and diluted with water, the crude product was extracted into ethyl acetate (3 × 10 mL). The organic layer was washed with brain solution, dried over anhydrous sodium sulphate and concentrated to get residue. The residue was triturated with mixture of hexane and ether to get title compound **3a** (Yield = 0.78 g, 94 %) as cream white solid. Similarly all other derivatives **3b-c** and **6a-d** were synthesized.

Spectral Data:

6-chloro-*N*-ethyl-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine (**3a**)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, J = 1.2 Hz, 1H), 7.29-7.23 (m, 15H), 5.83(d, J = 0.8 Hz, 1H), 4.05 (s, 1H), 3.35-3.29 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 147.5, 146.8, 142.4, 142.1, 130.0, 127.6, 127.5, 114.2, 107.1, 38.7, 14.8 ppm; MS. *m/z* = 439.0 (M +1), 440.0 (M +2).

5-chloro-3-morpholino-1-trityl-1*H*-indazole (**3b**)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1H), 7.36-7.17 (m, 15H), 5.82 (s, 1H), 3.72 (s, 4H), 3.31 (d, J = 10 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 147.6, 143.1, 141.9, 130.2, 127.9, 114.2, 107.7, 79.1, 66.4, 49.3 ppm; MS. *m/z* = 481.0 (M +2).

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***N*-(4-methoxybenzyl)-6-chloro-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine** (**3c**)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1H), 7.33-7.16 (m, 17H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.87 (s, 1H), 4.36 (s, 2H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.1, 128.2, 128.1, 114.1, 113.5, 55.3, 16.4 ppm; MS. *m/z* = 531.0 (M +1), 532.2 (M +2).

6-chloro-3-(2,6-dimethyl-tetrahydro-2*H*-pyran-4-yloxy)-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5a**)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 0.8 Hz, 1H), 7.31-7.19 (m, 15H), 5.85 (d, *J* = 0.8 Hz, 1H), 1.95-1.91 (m, 2H), 1.58-1.36 (m, 3H), 1.33 (d, *J* = 2.8Hz, 2H), 1.15 (d, *J* = 6.4Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 147.7, 145.7, 142.4, 141.9, 130.0, 127.9, 112.6, 107.7, 79.2, 73.4, 71.3, 68.1, 36.5, 21.9 ppm; MS. *m/z* = 524.2 (M +1), 525.2 (M +2).

3-(allyloxy)-6-chloro-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5b**)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1H), 7.28-7.21 (m, 15H), 6.08-5.97 (m, 1H), 5.87 (d, *J* = 1.1 Hz, 1H), 5.38-5.25 (m, 2H), 4.75-4.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 147.8, 143.2, 143.0, 142.1, 132.3, 130.1, 127.9, 119.2, 112.2, 107.5, 78.9, 70.2, 70.1 ppm; MS. *m/z* = 452.2 (M +1), 453.2 (M +2).

6-chloro-3-ethoxy-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5c**)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 7.30-7.29 (m, 9H), 7.26-7.21 (m, 6H), 5.84 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 147.8, 143.1, 142.2, 130.1, 127.8, 112.3, 107.4, 78.8, 65.4, 14.5 ppm; MS. *m/z* = 440.4 (M +1), 441.4 (M +2).

6-chloro-3-(tetrahydrofuran-3-yloxy)-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5d**)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 7.31-7.21 (m, 15H), 5.87 (d, *J* = 0.8 Hz, 1H), 3.97 (d, *J* = 8.4 Hz, 2H), 3.91-3.90 (m, 1H), 3.86-3.82 (m, 2H), 2.16 (t, *J* = 7.6 Hz, 2H) ppm; MS. *m/z* = 452.2 (M +1), 453.2 (M +2).

***In silico* molecular docking study**
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.[21] Another protein peripheral benzodiazepine receptor (PBR) (PDBID: 1EQ1)[22] helps translocation of cholesterol and porphyrin across the mitochondrial outer membrane and helps for steroid biosynthesis [23], cellular respiration [24], proliferation [25] and apoptosis [26]. The X-ray crystal structure of MDM2 receptor bind p53 and PBR with stereochemical activity was 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 chemical structures of the synthesized compounds were drawn using ChemDraw Ultra 8.0. The docking studies were performed using HEX 6.3 software. Hex is protein docking software using spherical polar Fourier Correlations. Hex is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes.

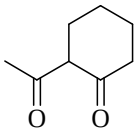
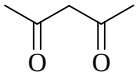
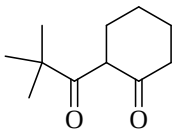
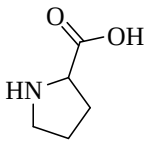
RESULTS AND DISCUSSION

To begin with our aim to synthesize *N*-trityl-3-amino/alkoxy substituted 5-azaindazoles (**3a-c**, **5a-d**, Scheme 1, 2), the azaindole **1** was selected as key intermediate. From key intermediate **1**, we opted Ullmann coupling, in which our task was not simple because, mere heating **1** with **2a** using CuI 5 mol %, K_2CO_3 did not give even traces of desired product. Hence we thought to choose the proper ligand in order to activate the copper.

Thus we successfully carried out the coupling of azaindazole **1** with ethyl amine hydrochloride **2a** in presence of proline as coupling ligands along with CuI/K_2CO_3 in the model reaction. Again the variation of solvent, temperature and mol ratio revealed that a 1:2 ratio of azaindazole **1** and ethyl amine hydrochloride **2a**, 10 mol % CuI, 10 mol % of proline and 5 equivalence of K_2CO_3 in DMSO at 80 ^oC furnished highest percentage yield of the products. Among the different coupling ligands tested the diamino ligands generated low yield. As we can observe in the table 1, among diamines the 1,10 phenanthroline generates maximum of 20 % yield. Further when the reaction was carried out by taking 1,3 diketones as ligands the yields were better but not promising. The use of ligand diketone **6** afford maximum of 25 % yield. However substantial improvement in the yield was observed when we choose *N*,*N*-

dimethyl glycine in which about 40 % yield was obtained (based on LCMS). Surprisingly, when we replace *N,N*-dimethyl glycine to proline the reaction proceeded smoothly to give 94 % yield without any side product.

Table 1. Effect of nature of ligand on the synthesis of 3a using 10 mol % CuI/K_2CO_3 in DMSO solvent

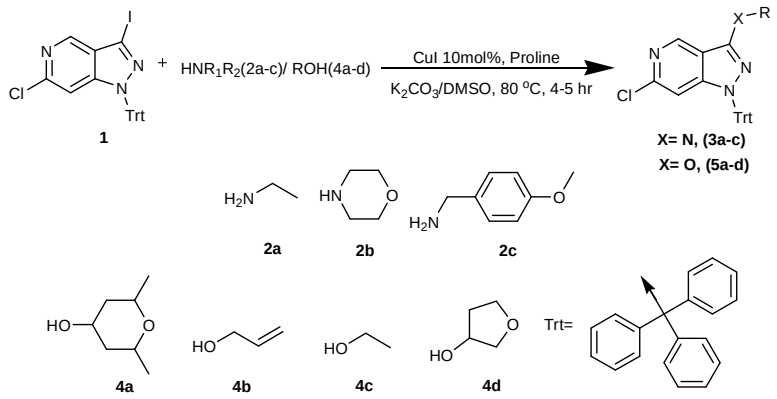
Ligand id	Ligand	Time in h	Yield of 3a %
1	1,2 diamino ethane	6	10
2	*N,N*' dimethyl ethylnene diamine	6	10
3	*N,N,N*',*N*' tetramethyl ethylene diamine	6	5
4		6	15
5		6	20
6		6	25
7		6	94
8	No ligand	6	-
9	*N,N*' Dimethyl glycine	6	40
10	1,10 phenanthroline	6	20

Further to assess the scope of this coupling reaction different amines and alcohols were chosen as nucleophiles. The results are summarized in table 3. Thus the reactions of azaindazole **1** with ether **2c** gave 95 %, with cyclic ether **4a** gave 88 % and with alkene **4b** gave 95 % of the corresponding products. Further it was noteworthy to mention that the coupling reaction did not take place with chloro substitution. Hence this coupling reaction shows selectivity with only iodo group in compound **1**.

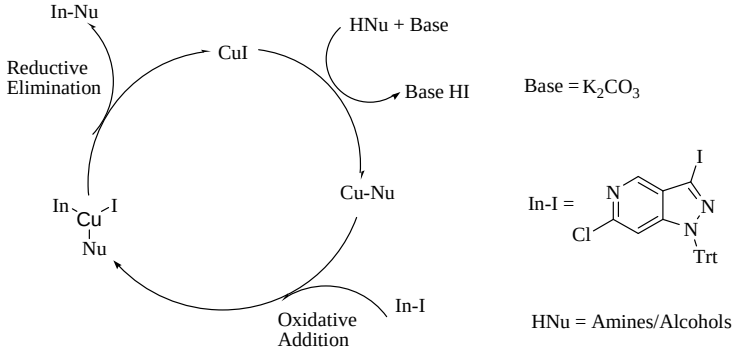
Further we compared the scope of this method with Buchwald and Hartwig coupling reaction. Thus we took 5 mol % of palladium tetrakis, palladium brettphos precatalyst and palladium Xphos precatalyst in dioxane as solvent and with Cs_2CO_3 base. The results are summarised in table 2**.** In all the cases a mixture of chloro and iodo displaced product was obtained. However the best results were obtained with palladium Xphos precatalyst i.e., 80 % desired product and 10 % of chloro displaced product. But practically all palladium catalysts were generally moisture sensitive and very expensive. But on the other hand Ullmann coupling reaction is less expensive, not moisture sensitive and so all the reactions were easily carried out.

Table 2. Selective displacement of iodo group in the presence of various catalyst for the synthesis of 3a in DMSO solvent

Reaction condition	Chloro displacement	Iodo displacement
Palladium tetrakis 5 mol %, Cs_2CO_3	-	50 %
Palladium brettphos 5 mol %, Cs_2CO_3	20 %	70 %
Palladium Xphos 5 mol %, Cs_2CO_3	10 %	80 %
CuI/proline, K_2CO_3 10 mol %	-	100 %

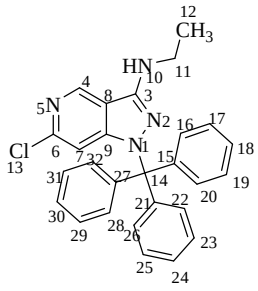


Scheme 1. Synthesis of 6-chloro-1-trityl-5-azaindazole-3-amine derivatives 3a-c and 6-chloro-1-trityl-5-azaindazole-3-ether derivatives 5a-d



Scheme 2. The plausible mechanism for copper iodide catalysed coupling reaction to give 3a-c and 5a-d

Thus synthesized derivatives **3a-c** and **5a-d** by Ullmann coupling were structurally determined by analytical methods like ^{1}H NMR and ^{13}C NMR and LCMS analysis. The structure of the compound **3a** was elucidated as discussed below.

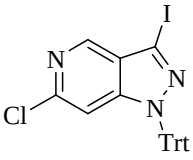
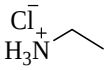
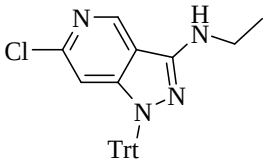
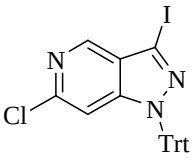
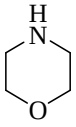
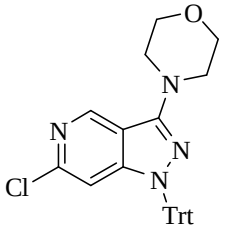
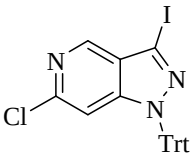
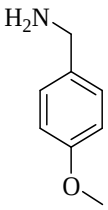
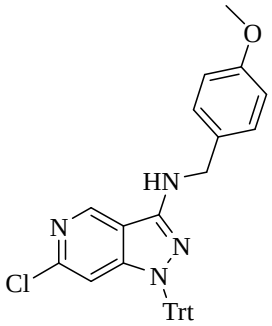
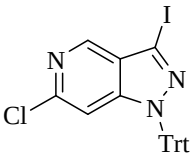
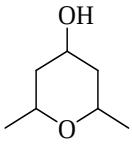
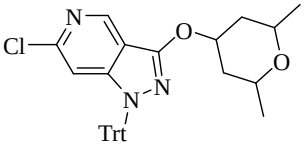
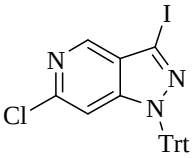
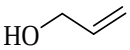
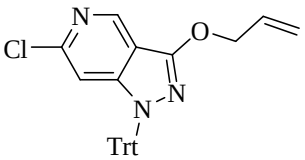
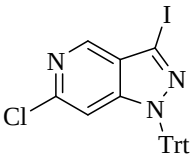
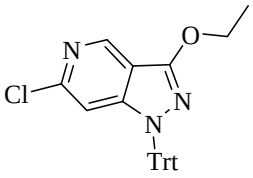
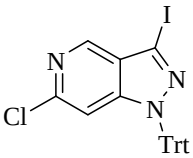
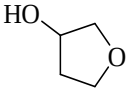
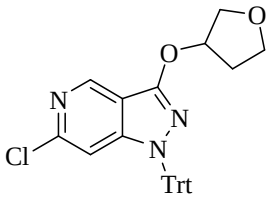


Structure of 6-chloro-*N*-ethyl-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine (3a)

The ^{1}H NMR spectrum of 6-chloro-*N*-ethyl-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine (**3a**) exhibited peak at δ = 8.52 (doublet, para coupling) corresponds to 4 ArH, peak at δ = 7.29-7.23 (Multiplet) was corresponds to aromatic proton of Trityl group and peak at δ = 5.83 (doublet, para coupling) corresponds to C_7-H of pyridine ring. The amine ($N_{10,}$H) shows broad singlet at δ = 4.05 and multiplet at δ = 3.35-3.29 corresponds to methylene group (C_{11}, H(2H)) due to coupling with amine and methyl protons. Triplet at δ = 1.21 was corresponds to methyl group ($C_{12,}$ H(3H)) with coupling constant J = 7.2 Hz, due to adjacent two methylene protons. Additional support to elucidate the structure was obtained from ^{13}C NMR spectrum. The appearance of peak at δ = 14.8 was for -CH_3(C_{12}), 38.75 for -CH_2(C_{11}), peak at δ = 78.3 was coressponds to qarternary carbon (tryphenyl methyl carbon, C_{13}). The aromatic carbon was found to appear at δ between 107.1-148.6 respectively. Further the mass spectrum of **3a** was recorded as additional evidence for the proposed structure. It was exhibited M+ peak at *m/z* 439.0 and peak at 440.0 (M+2)

shows isotopic peak due to chlorine atom. From all these spectral evidences the structure of compound **3a** was confirmed. Similarly the structures of all other derivatives were determined (Table 3).

Table 3. Physical data of 6-chloro-1-trityl-5-azaindazole-3-amine derivatives 3a-c and 6-chloro-1-trityl-5-azaindazole-3-ether derivatives 5a-d

Sl No	5-aza-indazoline	Alcohols/Amines	Products[a]	Yield (%)[b]	M.P (°C)
3a				94	204-206
3b				95	208-210
3c				95	140-142
5a				88	156-158
5b				95	124-126
5c				87	156-159
5d				88	148-150

[a]All products were characterized by ^{1}H and ^{13}C NMR and Mass spectroscopy.
[b]Isolated yields.

Molecular docking study

A series of 1-trityl-5-aza indoazole derivatives (**3a-c**, **5a-d**) were subjected to molecular docking study with MDM2 receptor bind p53 and PBR proteins. The Lipinski rule is applied on the selected molecules (**3a,c, 5a-d**) 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 4).

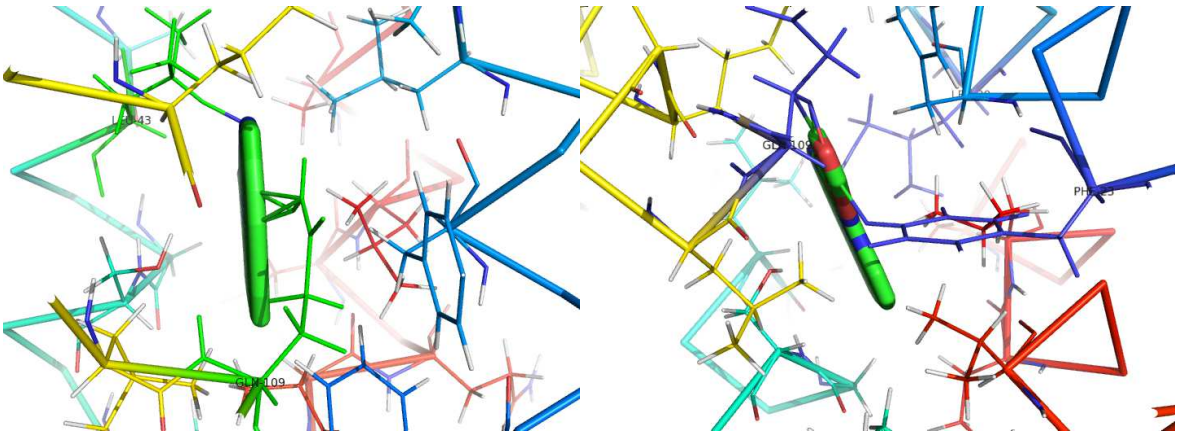
Table 4. Lipinski rule of synthesized 1-trityl-5-aza indoazole derivatives (3a, 3c and 5a-d)

Ligand	LogP	TPSA	nAtoms	MW	nON	nOHNH	nrotb	MV	nviolations
3a	6.817	42.745	32.0	438.962	4	1	6	395.12	1
3c	7.897	51.979	39.0	531.059	5	1	8	475.513	2
5a	7.741	49.186	38.0	524.064	5	o	6	473.691	2
5b	7.285	39.952	33.0	451.957	4	0	7	402.873	1
5c	7.017	39.952	32.0	439.946	4	0	6	391.702	1
5d	6.744	49.186	35.0	481.983	5	0	6	423.716	1

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.

Table 5. Molecular docking study of 1EQ1 protein complex with 1-trityl-5-azaindazole derivatives (3a-c, 5a-d)

Ligand	Binding Energy (kcal/mol)	Amino acids	Interaction	
			H-Bonds	Non-H-Bonds
3a	-2.671652e+02	LEU43 GLN109	-	1 4
3b	-2.579182e+02	-	-	0
3c	-2.863714e+02	ILE141 LYS140	-	3 3
5a	-2.712579e+02	ILE141	-	1
5b	-2.606556e+02	GLU109 LEU43	-	5 1
5c	-2.686136e+02	LEU43 GLN109	-	2 5
5d	-2.775010e+02	PHE23 LEU30 GLN109	-	1 1 2



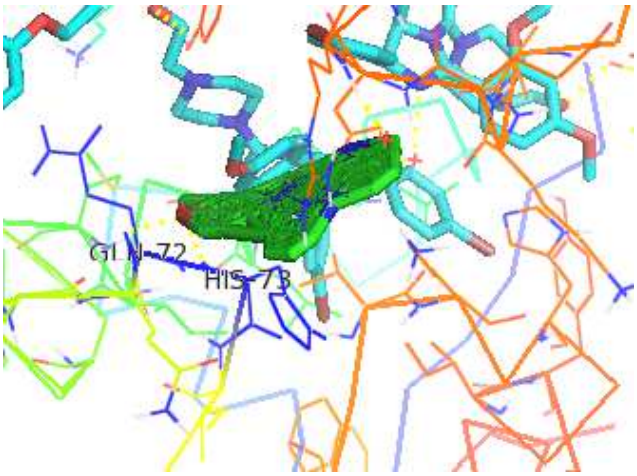
3a **6d**

Figure 3. Docking images of selected compounds with 1EQ1 showing binding of compound 3g with GLN20 and LYS 21 (1 and 2H bonds respectively) and compound 3i with LYS105, LYS107 and LEU108 (2, 1 and 1H bonds respectively)

The active crystal structures of MDM2 receptor bind p53 tumor suppressor protein and peripheral benzodiazepine receptor structure (PBR) was interacted with pharmacophores 1-trityl-5-aza indoazole derivatives **(3a-c**, **5a-d)** using

molecular docking. 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 5 and 6. 2D structures of all new ligands (**3a-c**, **5a-d**) were converted into energy minimized 3D structures and were then used for *in silico* protein-ligand docking. The docking of PBR receptor (1EQ1) protein with newly synthesized ligands **3a-c**, **5a-d** exhibited well established bonds with one or more amino acids in the receptor active pocket. Figure 3 shows the docked images of selected candidate ligands 6-chloro-*N*-ethyl-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine (**3a)** and 6-chloro-3-(tetrahydrofuran-3-yloxy)-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**6d)**. 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 -2.579182e+02 to -2.863714e+02 kcal/mol. The compound **3a**, has shown 1 and 4 non-hydrogen bond interaction (Knowledge-based (also known as statistical potentials) is based on statistical observations of intermolecular close contacts which are used to derive "potentials of mean force". This method is based on the assumptions that close intermolecular interactions between certain types of atoms or functional groups that occur more frequently than one would expect by a random distribution are likely to be energetically favorable and therefore contribute favourably to binding affinity. Knowledge-based interactions have become accepted choices for fast scoring putative protein-ligand complexes according to their binding affinities) [27] with active site amino acids LEU43 and GLN109 respectively was having binding energy of -2.671652e+02 kcal/mol. The compound 3-(allyloxy)-6-chloro-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5b)** and 6-chloro-3-ethoxy-1-trityl-1*H*-pyrazolo[4,3-c]pyridine (**5c**) shown good binding intraction with active site amino aceid such as GLU109 with 5 non-hydrogen bond and with LEU43 1, 2 non-hydrogen bonds respectively with binding energy of -2.606556e+02 and -2.686136e+02 kcal/mol. The compound **5a** binds with active site amino acid ILE141 showing 1 non-hydrogen bond and compound **5d** actively interact with active site amino acid such as PHE23, LEU30 and GLN109 exhibiting promising interaction on PBR receptor (1EQ1) protein to control the transcription regulation. The other molecules such as **3b** have no binding affinity on target PBR receptor (1EQ1) protein hence can't be considered as an inhibitor of PBR.

Similarly docking study was performed on MDM2 receptor bind p53 (1RV1) tumor suppressor protein with 1-trityl-5-azaindazole derivatives (**3a-c**, **5a-d**, Table 6). The ligands **3c** forms 1 hydrogen bond interaction with active site amino acid GLN72 and HIS73 having binding energy -3.592025e+02 kcal/mol, indicates moderate inhibitor of MDM2 receptor bind p53 protein. Figure 3 shows the docked images of selected candidate ligand *N*-(4-methoxybenzyl)-6-chloro-1-trityl-1*H*-pyrazolo[4,3-c]pyridin-3-amine **(3c)**. Other structural compounds such as **3a**, **3e**, **5a-d** have relatively no interaction with target protein and hence can't be considered as an inhibitor of MDM2 receptor bind p53 protein.



3c

Figure 2. Docking image of selected compound 3c binding with 1RV1 protein showing bonding with GLN72 and HIS73 (1H bonds each)

Table 6. Molecular docking study of 1RV1 protein complex with 1-trityl-5-azaindazole derivatives (3a-c, 5a-d)

Ligand	Binding Energy (kcal/mol)	Amino acids	Interaction	
			H-Bonds	Non-H-Bonds
3a	-3.320638e+02	-	0	-
3b	-3.405886e+02	-	0	-
3c	-3.592025e+02	GLN72 HIS73	1 1	-
5a	-3.517816e+02	-	0	-
5b	-3.363585e+02	-	0	-
5c	-3.328707e+02	-	0	-
5d	-3.304476e+02	-	0	-

CONCLUSION

In conclusion, various structurally distinct 6-chloro-1-trityl-5-azaindazole-3-amine derivatives **3a-c** and 6-chloro-1-trityl-5-azaindazole-3-ether derivatives **5a-d** were conveniently synthesized by Ullmann coupling reaction. The *in silico* docking study revealed that the compounds **3a-c** and **5a-d** found to bind efficiently with PBR (1EQ1) receptor protein. The compound **3c** alone found to bind efficiently with MDM2-bind p53 (1RV1) receptor protein with high binding energy of -3.592025e+02 kcal/mol in comparison with remaining compounds. Hence the newly synthesized compounds were found to be more selective towards PBR receptor protein when compared with MDM2-bind p53 receptor protein to control the transcription regulation. Thus this study could further widen the scope for the development of similar new 6-chloro-1-trityl-5-azaindazole-3-amines and 6-chloro-1-trityl-5-azaindazole-3-ether derivatives through our simple synthetic methodology for possible anticancer activities to find a lead molecule.

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