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Synthesis and molecular docking studies of 2,3-dialkylindoles and carbazoles with MDM2-p53 and PBR receptor proteins

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ABSTRACT

Fischer indolization was achieved conveniently using samarium iodide to obtain 2,3-dialkylindoles and carbazoles. The *in silico* docking study was carried out to all new compounds on Murine double minutes-2 (MDM2) receptor bind p53 and Pheripheral benzodiazepine receptor (PBR) proteins. The structures was established by ^{1}H NMR, ^{13}C NMR, and LCMS analysis for all 2,3-dialkylindoles and carbazoles. Among the test compounds, the 1,3-difluoro-6,7,8,9-tetrahydro-5*H*-carbazole **3g** and 1,3-dichloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole **3i** shown selective excellent interaction with active site amino acid such as GLN20 LYS21 with binding energy of -2.494e+2 kcal/mol and LYS105, LYS107, LEU108 with binding energy of -2.919e+2 kcal/mol in PBR protein. And, the compound 3g was also shown excellent binding interaction with active site amino acid ARG97 in MDM2-p53 protein with binding energy of -4.211446e+02 kcal/mol.

Keywords: Samarium iodide, Fischer indole synthesis, Docking, MDM2-p53, PBR.

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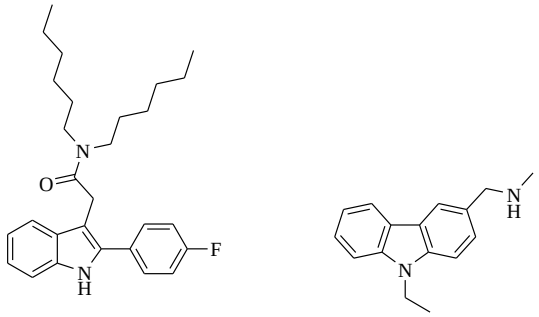
INTRODUCTION

Peripheral benzodiazepine receptor (PBR) is an 18 kDa, five trans membrane protein mainly located in the outer membrane of mitochondria[1] and widely distributed in several peripheral tissue such as kidney, steroid producing cells of the adrenals, heart, ovaries, testes and also in the central nervous system (CNS)[2]. PBR generally involved in number of biological process such as lipid metabolism, calcium homeostasis, cell growth and differentiation, apoptosis induction[3]. Upregulation of PBR reflects neuropathologic disorders including Alzheimer's and Huntington's diseases[2]. In this connection recently, FGIN-1-27 (*N*,*N*-di-n-hexyl 2-(4-fluorophenyl)indole-3-acetamide (Figure 1) have been reported to bind with the PBR[2]. Vin V et al reported SSR180575 4(7-chloro-*N*,*N*,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide) a novel PBR ligand showing high affinity on both rat heart mitochondria and on a cell line transfected with the human PBR (K(d)=1.95+/-0.22 and 4.58+/-0.83nM)[4]. Idriss et al synthesized *N*,*N*-dialkylel-(2-phenyl-1*H*-indol-3yl)glyoxylamides with high-affinity for PBR ligands[1]. Taryn et al reported the *in vitro* binding studies of *N*,*N*-dialkylel-2-phenylindol-3-yl-glyoxylamides with high affinity towards PBR[2]. Recently Federico et al and Antonio et al have also reported *N*,*N*-dialkylel-2-phenylindol-3-yl-glyoxylamides and their hydrazide derivatives as new class of potent and selective PBR ligands[3,5].

Further, various indoles were also reported as small molecule inhibitor of MDM2 receptor bind p53 protein[6]. Recently Frank et al studied the *in silico* screening of 1-(9-ethyl-9h-cabazol-3-yl-*N*-methylmetanamine (PhiKan083. Figure 1) as targeted rescue of destabilized mutant p53 tumor suppressor protein[7]. Shaomeng et al reported spirooxindole derivatives as an excellent inhibitor of MDM2-p53 protein-protein interaction with a K_i of 8.5 and 0.001 µM[8]. Melissa et al also reported that oxindole and spiroxyindole derivatives as an orally active inhibitors of the MDM2-p53 interaction[9]. More recently Yujun et al studied the structure based spiroxyindole-containing small molecule as potent inhibitor (K_i< 1nM) to MDM2 protein[10].



FIGN-1-27 PhiKan083

Figure 1

As a part of synthesizing small molecules for anticancer property, recently we have synthesized series of indoles and found them to exhibit significant cytotoxic activity against six cancer cell lines such as ACHN (human kidney adenocarcinoma), Panc1 (pancreatic), Calu1 (lung), H460 (non small cell lung), HCT116 (human colon cancer cell) and MCF10A (normal breast epithelium)[11]. Hence in continuation of our interest in efficient synthesis of indoles[12-17], quinolines[18] and their biological activity[19,20], herein we wish to report the samarium iodide in 0.1M THF as mild and efficient catalyst for the first time in the synthesis of indoles via Fischer indolization reaction to get various 2,3-dialkylindoles and carbazoles. All the new compounds were evaluated for *in silico* docking study to find out their ability to bind with MDM2 receptor bind p53 and Pheripheral benzodiazepine receptor (PBR) protein.

MATERIALS AND METHODS

Chemistry

The chemicals and reagents obtained from Hi Media, Sigma-Aldrich Chemical Company were used as received. 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. ^{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 2, 3-dimethylindole (2a)

The equivalent mole of phenylhydrazine hydrochloride 1.0g (0.0069 mol) and ethyl methyl ketone 0.49 g (0.0069 mol) was taken in a round bottom flask containing MeOH solvent added with 0.1M samarium iodide in THF (20 mole%, 1.226 ml) as catalyst. The whole reaction mixture was refluxed on water bath for appropriate time. After the completion of the reaction, as indicated by TLC the reaction mixture was cooled to room temperature and poured into water (100 mL) and extracted with EtOAc (10x2 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude solid. The crude product was purified by column chromatography with silica gel (60-120 mesh, petroleum ether: ethyl acetate, 8:2 v/v) furnished the analytically pure compound **2a**, yield **94**%. Similarly all other derivatives **2b-e** and **3a-j** were prepared.

Spectral Detail:

2,3-dimethyl-1*H*-indole (2a)

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.68 (s, 1H), 7.46 (d, *J* = 8.05 Hz, 1H), 7.24 (d, *J* = 4 Hz, 1H), 7.11 (m, *J* = 8 Hz, 2H), 2.3 (s, 3H), 2.1 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 128.1,132.2, 131.6, 110.3, 108.9, 107.5, 103.1, 102.9, 11.6, 8.4; MS. m/z =146 (M+1).

5-fluoro-2,3-dimethyl-1*H*-indole (2b)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.70 (s, 1H), 7.17 (q, *J* = 4.80 Hz, 1H), 7.07 (dd, *J* = 2.40 Hz, *J* = 10.00 Hz, 1H), 6.77 (m, 1H), 2.82 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 128.1, 132.2, 131.6, 110.3, 108.9, 107.5, 103.1, 102.9, 11.6, 8.4; MS. m/z =164.2 (M+1).

3-(2-fluorophenyl)-2-methyl-1*H*-indole (2c)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.48-7.52 (m, 2H), 7.30-7.36 (m, 2H), 7.10-7.27 (m, 4H), 2.44 (s, 3H); MS. m/z =226.2 (M+1).

3-isobutyl-5-isopropyl-2-methyl-1*H*-indole (2d)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.49 (s, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.84-6.86 (m, 1H), 2.87-2.92 (m, 1H), 2.45-2.50 (m, 2H), 2.27 (s, 3H), 1.82-1.85 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 6H), 0.88 (d, *J* = 6.8 Hz, 6H); MS. m/z =229.18 (M+1).

3-butyl-5-isopropyl-2-phenyl-1*H*-indole (2e)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.95 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.33-7.36 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.99 (q, *J* = 1.6, 8.4 Hz, 1H), 2.94-2.98 (m, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 1.57-1.63 (m, 2H), 1.33-1.39 (m, 2H), 1.25 (d, *J* = 6.8 Hz, 6H), 0.89 (t, *J* = 7.2 Hz, 3H); MS. m/z =292.0 (M+1).

3-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3a)

^{1}H NMR (400 MHz, DMSO-d_6):δ = 10.58 (s,1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.91 (m, 2H), 2.70-2.71 (m, 3H), 2.18 (t, *J* = 9.60 Hz, 1H), 1.84-1.85 (m, 2H), 1.45-1.46 (m, 1H), 1.09 (d, *J* = 6.40 Hz, 3H). ^{13}C NMR (100, MHz, DMSO-d_6): δ = 135.8, 134.0, 127.1, 119.8, 117.8, 116.9, 110.4, 107.9, 31.0, 29.1, 29.1, 22.3, 21.6; MS.m/z =186.4 (M+1).

6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (3b)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.72 (s, 1H), 7.18-7.21 (m, 1H), 7. 04-7.07 (m, 1H), 6.81 (m, 1H) , 2.56-2.70 (m, 4H),1.77-1.83 (m, 4H); MS. m/z = 190.2 (M+1).

6-fluoro-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3c)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.66 (s, 1H), 7.15 (dd, *J* = 8.8 Hz, *J* = 4.40 Hz, 1H), 7.00 (dd, *J* = 2.80 Hz, *J* = 10.0 Hz, 1H), 6.74 (m, 1H), 2.68 (d, *J* = 2.40 Hz, 3H), 2.10 (t, *J* = 9.60 Hz, 1H), 1.79-1.81 (m, 2H), 1.40-1.41 (m, 1H), 1.04 (d, *J* = 6.40 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 156.6, 135.9, 132.3, 128.1, 110.5, 108.7, 102.8, 31.2, 29.5, 29.2, 22.9,

21.6; MS. m/z = 204.2 (M+1).

1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3d)[19]

MS. m/z = 186.2 (M+1), 187.2 (M+2).

6-fluoro-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3e)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 162.3, 159.9, 149.7, 148.6, 148.5, 120.7, 120.6, 114.2, 114.0, 109,3, 109.0, 54.4, 38.5, 29.6, 29.0, 21.3, 19.7; MS. m/z = 204.2 (M+1) & 205.2 (M+2).

1,3-difluoro-8-methyl-2,3,4,9-tetrahydro-5*H*-carbazole (3f)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 2.66-2.58(m, 1H), 2.30 (t, *J* = 12.4 Hz, 2H), 1.83-1.77 (m, 2H), 1.54-1.49 (m, 1H), 1.38 (s, 3H), 1.29-1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 149.7, 131.2, 127.9, 125.6, 120.6, 38.9, 29.8, 29.2, 28.9, 19.7.

1,3-difluoro-6,7,8,9-tetrahydro-5*H*-carbazole (3g)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 136.6, 131.4, 129.8, 124.7, 120.3, 118.7, 116.1; MS. m/z = 208.2 (M+1).

3-chloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole (3h)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 134.5, 129.3, 124.8, 121.0, 117.3, 111.4, 110.6, 44.1, 42.6, 41.5, 34.9, 32.8, 27.2, 24.4, 24.3, 24.2, 21.8, 8.3; MS. m/z = 276.4 (M+1), 278.0 (M+2).

1,3-dichloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole (3i)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 131.8, 129.9, 124.6, 120.1, 118.5, 116.1, 116.0, 111.7, 42.5, 34.9, 32.8, 29.0, 24.3.24.2, 24.1, 21.8, 8.3; MS. m/z = 310.2 (M+), 312.2 (M+2).

3-(2,2-dimethylpropyl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3j)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.69-0.93 (m, 9H), 1.36-1.43 (m, 3H), 1.52-1.57 (m, 1H), 1.97-1.99 (m, 1H), 2.26-2.33 (m, 4H), 2.60-2.71 (m, 3H),6.76-6.78 (m, 1H), 7.07-7.11 (m, 2H), 10.41 (s, 1H); MS. m/z =256.2 (M+1).

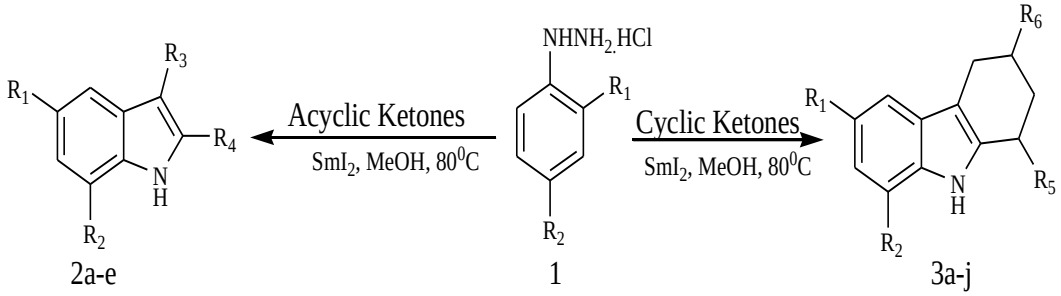
***In silico* molecular docking studies**

The crystal structure of MDM2 receptor bind p53 tumor suppressor protein (PDB ID: 1RV1) and peripheral benzodiazepine receptor (PBR) (PDBID: 1EQ1) were selected and used for docking studies. The chemical structures of synthesized compounds were drawn using ChemDraw Ultra 8.0. The docking studies were performed using HEX 6.3 software. 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

Chemistry

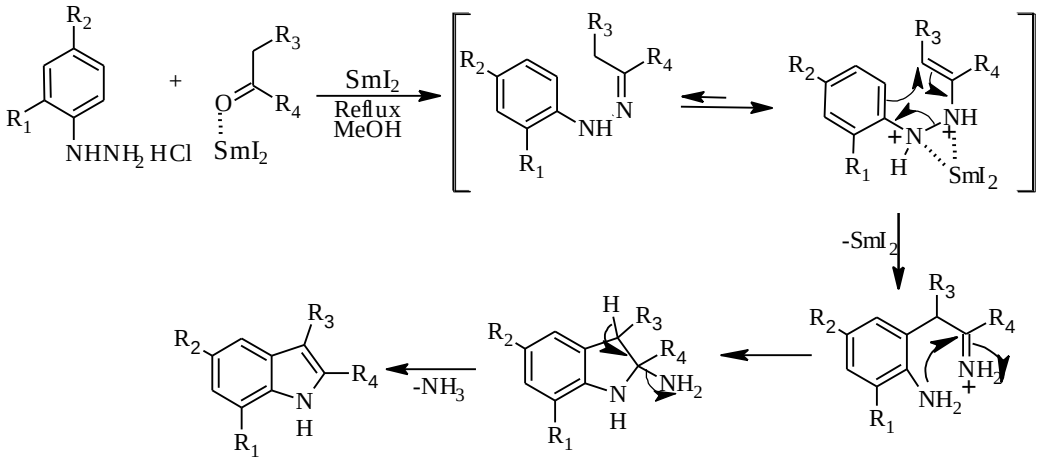
Various 2,3-dialkylindoles **2a-e** and carbazoles **3a-j** were synthesized (Table 3) via Fischer indolization reaction of 2,4-disubstituted phenyl hydrazine hydrochloride with different cyclic and acyclic ketones catalyzed by 0.1M samarium iodide in THF under methanol reflux temperature. Initially the Fischer indolization reaction was carried out in different solvent like methanol, ethanol, acetonitrile and tetrahydrofuran (Table 1) using 10 mole % of 0.1M samarium iodide in THF as catalyst, among the tested solvents methanol was found to be more suitable in which the reaction went smoothly as indicated by TLC. The product was easy to isolate with less impurities. Further the concentration of catalyst was optimized with different mole percentage such as 10, 20, 40 and 50 in methanol solvent, indicates 20 mole % of catalyst load is sufficient to carryout 3,3-sigmatropic rearrangement reaction to gave the product in good to excellent yield (Table 2). Increase in concentration of catalyst marginally affects the yield and reaction time.



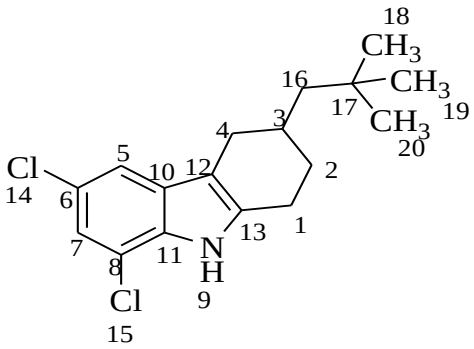
R_3= Me, n-Butyl, 2-Fluoro phenyl, t-Butyl; R_1= H, F, Cl; R_5= H, Me

R_4= Me, Phenyl; R_2= H, F, Cl, Me, Isopropyl; R_6= H, Me, Isopentyl

Scheme 1 Samarium iodide catalyzed synthesis of 2,3-dialkylindoles(2a-e) and (3a-j)



Scheme 2 The plausible reaction mechanism for the Samarium iodide catalyzed Fischer indole synthesis.



1,3-dichloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole (3i)

All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and LCMS spectroscopic technique. The ^{1}H NMR spectrum of **3i**, shows peak at δ = 11.2(singlet) corresponds to carbazole -NH, peak at δ = 7.40 was corresponds to aromatic C-7 proton, showing doublet due to meta coupling with C-5 aromatic proton (J= 1.6 Hz) and peak at δ = 7.10 was corresponds to aromatic C-5 proton, showing doublet due to meta coupling with C-5 aromatic proton (J= 1.8 Hz). Additional support to elucidate the structure was obtained from ^{13}C NMR spectrum. The appearance of peak at δ: 8.3 was corresponds to querternary carbond (C-17), peak at 21.8 is for methylene carbonn (-CH_2, C-1), peak at 24.3 was corresponds to three methyl groups (-CH_3, C-18, 19, 20), peak at 42.5 is for methylene group (–CH_2, C-16). The aromatic carbon was found to appear at δ value in between 111.7-136.7. Further the mass spectrum of **3i** was recorded as additional evidence to the proposed structure. It was exhibited M+ peak at m/z 310.2 and M+2 peak at 312.2 showed for isotopic peak due to chlorine atom. From all these spectral evidences the structure of **3i** was confirmed. Similarly the structures of all other derivatives were determined (Table 3).

Table 1: Effect of solvent polarity on Fischer indolization reaction (2a)[a]

Entry	Solvent	Mole % of catalyst	Reaction time	Yield[b] (%)
1	Methanol	10	6	93
2	Ethanol	10	7	88
3	Acetonitrile	10	7	78
4	Tetrahydrofuran	10	7	77

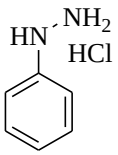
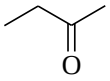
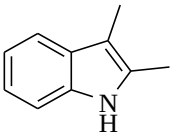
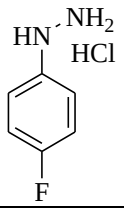
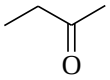
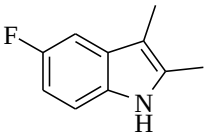
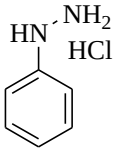
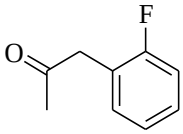
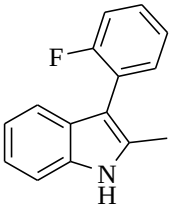
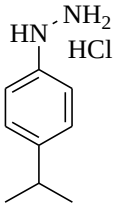
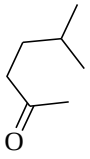
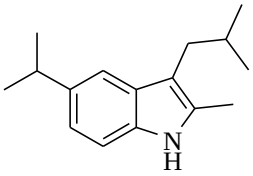
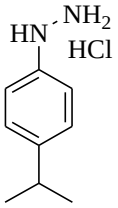
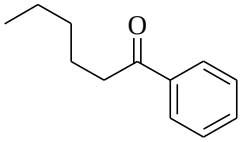
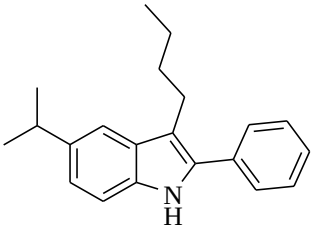
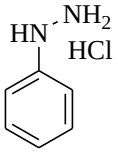
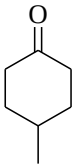
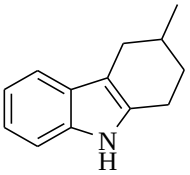
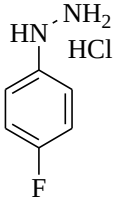
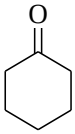
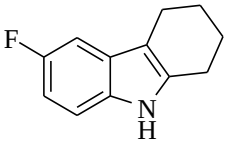
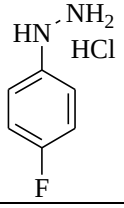
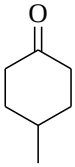
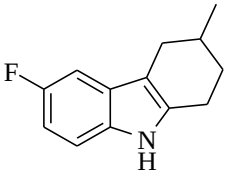
[a]All reactions were carried out at reflux temperature, [b]Isolated yields.

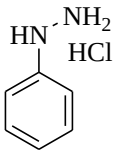
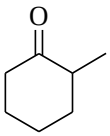
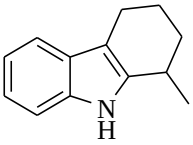
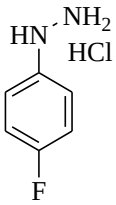
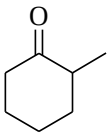
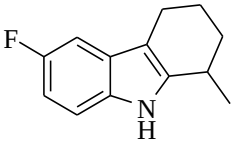
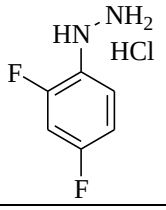
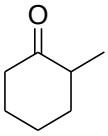
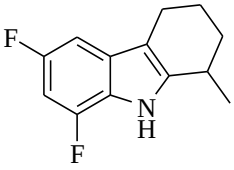
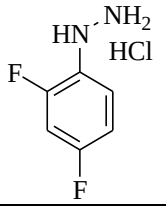
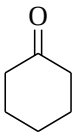
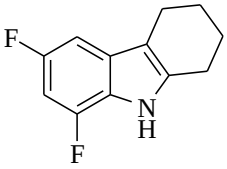
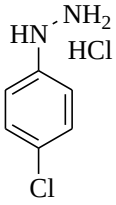
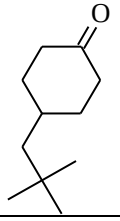
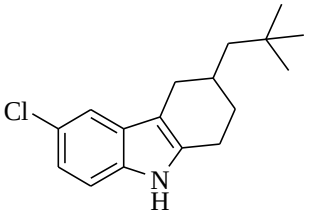
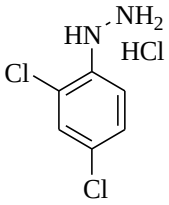
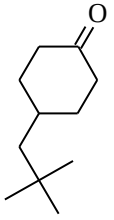
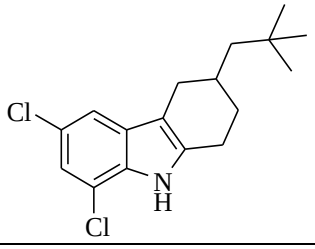
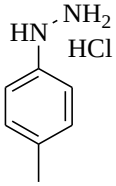
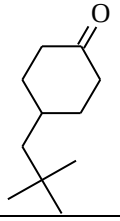
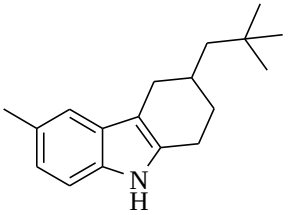
Table 2: Effect of concentration of catalyst on Fischer indolization reaction (2a)[a]

Entry	Solvent	Mole % of catalyst	Reaction time	Yield[b] (%)
1	Methanol	10	6	93
2		20		94
3		30		95
4		40		96

[a]All reactions were carried out at reflux temperature, [b]Isolated yields.

Table 3: Reaction of various phenyl hydrazine hydrochlorides with different ketones

Entry	Phenyl hydrazines	Ketones	Products[a]	Yield (%)[b]	M.P/Litr (°C)
2a				94	102-104/103-105[16]
2b				93	61-62/61-62[16]
2c				92	Gummy/ Gummy[18]
2d				95	56-58/55-58[18]
2e				91	60-61/60[18]
3a				90	109-111/108-110[51]
3b				89	94-95/94-95[16]
3c				88	104-106/105-106[16]

3d				91	63-64/63-65[21]
3e				90	98-99
3f				89	94-97
3g				90	Gummy
3h				88	Gummy
3i				89	Gummy
3j				87	Gummy/Gummy[18]

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

[b]Isolated yields.

Molecular docking studies

A series of 2,3-dialkylindole and carbazole derivatives with chemical portion plays an important role in the interaction with MDM2 receptor bind p53 and PBR proteins. 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 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 selected 2,3-dialkylindoles and carbazole derivatives

Ligand	LogP	TPSA	nAtoms	MW	nON	nOHNH	nrotb	MV	nviolations
2b	1.92	15.791	12.0	163.19	1	1	0	151.0	0
2c	4.22	15.791	17.0	225.26	1	1	1	205.9	0
3a	3.56	15.791	14.0	185.27	1	1	0	185.9	0
3b	2.50	15.791	14.0	189.23	1	1	0	174.3	0
3d	3.66	15.791	14.0	185.27	1	1	0	185.9	0
3e	2.82	15.791	15.0	203.26	1	1	0	190.9	0
3g	2.59	15.791	15.0	207.22	1	1	0	179.2	0
3h	5.81	15.791	19.0	275.82	1	1	2	265.9	1
3i	6.42	15.791	20.0	310.26	1	1	2	279.4	1
3j	5.58	15.791	19.0	255.40	1	1	2	268.9	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.

The active crystal structures of MDM2 receptor bind p53 tumor suppressor protein and peripheral benzodiazepine receptor structure (PBR) was interacted with pharmacophores 2,3-dialkylindole and carbazole derivatives 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 3 and 4. 2D structure of all new ligands **2a-e** and **3a-o** 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 **2a-e** and **3a-o** 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 1,3-difluoro-6,7,8,9-tetrahydro-5*H*-carbazole (**3g**) and 1,3-dichloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole (**3i**). Table 3 shows the binding energy and inhibition constant of fifteen compounds. *In silico* studies revealed that all the synthesized molecules showed good binding energy toward the target

protein ranging from -1.638102e+02 to -2.307832e+02 kcal/mol. The compound 1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole 3d has shown 2 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 favorably to binding affinity. Knowledge-based interactions have become accepted choices for fast scoring putative protein-ligand complexes according to their binding affinities)[22] with active site amino acids LEU108 with binding energy of -1.865589e+02 kcal/mol. The compound 1,3-difluoro-6,7,8,9-tetrahydro-5*H*-carbazole 3g and 1,3-dichloro-6-neopentyl-6,7,8,9-tetrahydro-5*H*-carbazole 3i exhibited excellent binding intraction with active site amino acids such as GLN20, LYS 21 with 1, 2 non-hydrogen bond interaction and LYS105, LYS107, LEU108 with 2,1,1 non-hydrogen bond interaction with binding energy of -2.578412e+02 and -2.919857e+02 kcal/mol respectively. On the other hand the compounds such as 3h and 3j showed poor interaction whereas the compounds 2a-e, 3a-c and 3e, 3f did not shown interaction with the target PBR receptor (1EQ1) protein hence can't be considered as an inhibitor of PBR.

Table 5: Molecular docking study of 1EQ1 protein complex with 2,3-dialkylindoles and carbazoles

Ligand	Binding Energy (kcal/mol)	Amino acids	Interaction	
			H-Bonds	Non-H-Bonds[22]
2a	-1.638102e+02	-	-	-
2b	-1.986498e+02	-	-	-
2c	-2.032324e+02	-	-	-
2d	-2.125248e+02	-	-	-
2e	-2.316314e+02	-	-	-
3a	-1.889418e+02	-	-	-
3b	-2.307832e+02	-	-	-
3c	-2.196408e+02	-	-	-
3d	-1.865589e+02	LEU108	-	2
3e	-2.264414e+02	-	-	-
3f	-2.264414e+02	-	-	-
3g	-2.578412e+02	GLN20	-	1
		LYS 21	-	2
3h	-2.494448e+02	LEU30	-	1
3i	-2.919857e+02	LYS105	-	2
		LYS107	-	1
		LEU108	-	1
3j	-2.293337e+02	SER47	-	1

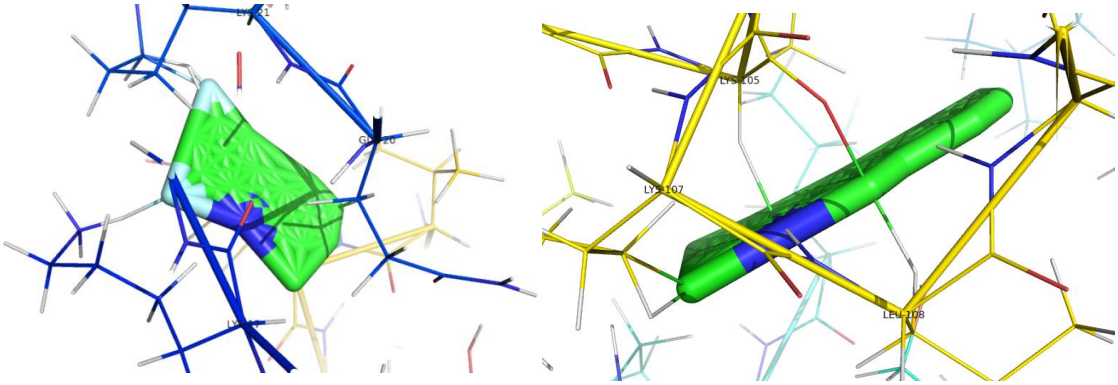
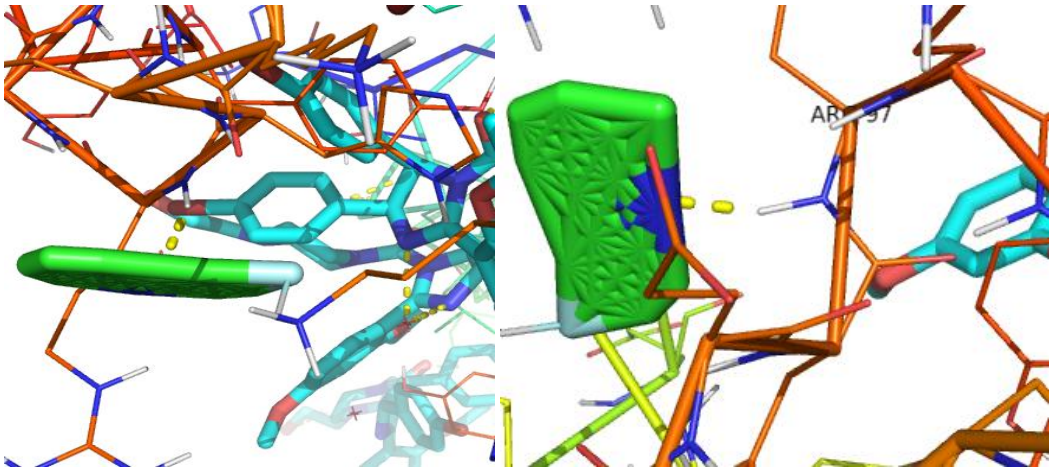


Figure 2: Docking images of selected compounds with 1EQ1 showing binding of compound 3g with GLN20 and LYS 21 (1 and 2 non-H-bond interaction respectively) and compound 3i with LYS105, LYS107 and LEU108 (2, 1 and 1 non-H-bond interaction respectively)

Similarly docking study was performed on MDM2 receptor bind p53 tumor suppressor protein with 2,3-dialkylindole and carbazole derivatives **(**Table 5). The ligands **2b-c**, **3a-b**, and **3e**, **3g** all are shown 1 hydrogen bond interaction with active site amino acid ARG97 having binding energy of -2.662056e+02 to -4.211446e+02 kcal/mol respectively, indicates moderate to good inhibitor of MDM2 receptor bind p53 protein. Figure 3 shows the docked images of selected candidate ligand 6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (**3b**) and 6-fluoro-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (**3e**). Other structural compounds in the tested series have relatively no interaction with target protein and hence can't be considered as an inhibitor of MDM2 receptor bind p53 protein.

Table 6: Molecular docking study of 1RV1 protein complex with 2,3-dialkylindoles and carbazoles

Ligand	Binding Energy (kcal/mol)	Amino acids	Interaction	
			H-Bonds	Non-H-Bonds
2a	-1.532637e+02	-	-	-
2b	-2.662056e+02	ARG97	1	-
2c	-2.749947e+02	ARG97	1	-
2d	-1.651637e+02	-	-	-
2e	-1.931431e+02	-	-	-
3a	-2.749947e+02	ARG97	1	-
3b	-2.776554e+02	ARG97	1	-
3c	-2.833571e+02	-	-	-
3d	-1.608856e+02	-	-	-
3e	-2.880477e+02	ARG97	1	-
3f	-4.212790e+02	-	-	-
3g	-4.211446e+02	ARG97	1	-
3h	-3.095031e+02	-	-	-
3i	-4.585317e+02	-	-	-
3j	-1.761182e+02	-	-	-



3b **3e**

Figure 3: Docking images of selected compounds with p53 showing binding of compound 3b and 3e with ARG97 (1 hydrogen bond interaction each)

CONCLUSION

In conclusion we have developed new protocol for the Fischer indolization reaction using Samarium iodide in 0.1M THF as catalyst to generate a series of 2,3-dialkylindoles and carbazoles. The synthesized compounds were docked with two cancer protein such as MDM2 receptor bind p53 protein and PBR protein. Compounds **3g** and **3i** were found to be more active with PBR receptor (1EQ1) protein exhibit high value of binding energy of -2.578412e+02, -2.919857e+02 and hence a strong binding affinity, whereas other derivatives display moderate to week interaction towards the selected MDM2 receptor bind p53 protein and PBR protein. Hence the docking models could provide some hint to understand the structure of the ligand suitable for efficient binding with MDM2 receptor bind p53 protein and PBR protein. Hence, with this new protocol one can generate library of indole molecules with suitable functionalization to find a small molecule inhibitor towards selected protein receptor.

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