Ind. J. Pharm. Edu. Res., 2024; 58(2):624-636.
https://www.ijper.org

Original Article

Design, Synthesis, Anticancer Activities and Comparative Molecular Docking Studies of a Novel Class of 7-Azaindole Analogs as Potent PARP-1 Inhibitors

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ABSTRACT

Background: In a research facility, 7-azaindole derivatives were designed and synthesized, and each substance was examined for its capacity to inhibit cancer growth. In the present study, the synthesized analogues were docked with PARP enzyme to find a suitable site for PARP inhibition. **Materials and Methods:** ^{1}H nuclear magnetic resonance, ^{13}C NMR, and mass spectrometry were used to characterize all synthesized analogues of 7-azindole. On the MCF-7 cell line for breast cancer, their anticancer activity was assessed. The proteins of PARP-1 inhibitors were docked against using the protein IDs 6NRF, 6NRG, 6NRH, 6NRI, 6NRJ, and 6NTU. For 7-azaindole derivatives, the two docked proteins 6NRH and 6NRF performed best. **Results**: The most active compound against MCF-7 cell lines has a GI_{50} of 15.56 µM, which is compound 4g. The compounds 4a, 4b, 4c, 4i, and 4h also exhibited good anticancer activity so these compounds have the prospective to be used as PARP inhibitors. According to additional molecular docking studies these compounds can bind to protein targets 6NRH well. These compounds offer promising potential as PARP inhibitors for the development of novel medications. **Conclusion:** The results of the study were favorable and gave direction for the synthesis of some novel potent 7-Azaindole compounds as a PARP inhibitors.

Keywords: 7-azaindole, Synthesis, Docking, Anticancer activity, PARP inhibitor.

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Received: 06-04-2023;
Revised: 09-09-2023;
Accepted: 07-01-2024.

INTRODUCTION

PARPs or Poly (ADP-ribose) polymerases are found to be an enzyme which has role in the generation of ovarian cancer, breast cancer and the other carcinomas. This enzyme displayed functioning in DNA-damage repair pathways, this mechanism was found to be an opportunity to establish new class of anticancer therapy and this class is named as PARP inhibitors.[1] In metastatic breast cancer derived from BRCA1/2 mutations PARP inhibitors are very efficacious. Pre-clinical studies stated that the specific PARP inhibitors cause cell death by inhibiting the cell growth in breast cancer cells which deficient BRCA1/2 mutations.[2-4]

Azaindole derivatives were having the various biological effects[5] like PARP1 inhibitors,[6] analgesic and anti-inflammatory agent,[7-9] protein MAPK inhibitors.[10] The Azaindole analogues also exhibited anticancer,[11-14] and anti-angiogenic activity[15,16] and IGF1-R inhibitors.[17] Effect on central nervous system[18] and affinity for serotonin receptor were also reported for Azaindole analogues. Azaindole analogues were reported active as CRTh2 receptor antagonists,[19-23] antioxidant agents,[24] antibacterial agents[25-27] and antifungal agents.[28] Azaindole derivatives were also found to be active as Chk1 inhibitors,[29] FGFR-4 inhibitors,[30] PI3Kγ Inhibitors.[31] In present studies there was synthesis of some novel Azaindole analogues which were found to be active as anticancer agent. The anticancer activity was performed by MTT assay on breast cancer MCF-7 cell line. Further, the 7-azaindole analogues were docked against different proteins of enzymes PARPs or poly (ADP-ribose) polymerases. A comparative study was performed to find the best docking protein for the synthesized 7-Azaindole ligands.

Designing of 7-Azaindole analogues (4a-4j)

According to the literature, the substrate NAD^+ occupies three of the sub-pockets that make up the catalytic pocket of enzyme PARP-1. The Phosphate-binding site (PH site), the Nicotinamide ribose binding site (NI site), and the Adenine-ribose binding (AD) site make up the first, second, and third sub-pockets, respectively[1]. Most PARP-1 suppressors are said to bind to the NI site via

DOI: 10.5530/ijper.58.2.70

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H-bonding, and some of them provide further connections to the AD site. The AD site is so spacious to accommodate a variety of molecules, which increases the effectiveness and pharmacokinetic properties of the suppressors.[2,3] Numerous studies have established that the nicotinamide moiety serves as the foundation for the production of PARP-1 inhibitors which can bind to PARP enzyme sites 4. So, among PARP-1 inhibitors, the aromatic rings and the carboxamide cores are typical pharmacophore features (Figure 1a). Many investigations have shown that the PARP inhibitors' binding affinities are enhancing (Figure 1b). Limiting the free rotation of the carboxamide significantly increases the PARP1 inhibitory activity. The carbonylamine group can be removed or it can be added in the aromatic ring heteroatoms or moieties that can form an intramolecular hydrogen bond with the amide NH. It can also be conjugated in a bicyclic system. It has been demonstrated that the 7-azaindole moiety is a crucial model for the synthesis of a few novel analogs.[15,32-35] It possess indole nucleus which is a part of endogenous serotonin, tryptophan and melatonin.[36] 7-azaindole analogues have been extensively reconnoitered over the last several years and it was observed that its chemical moiety and biological applications have significant importance for the further investigations. We attempted to correlate the structure of new Azaindole analogues (4a-4j) with that of PARP inhibitors because Azaindole is an affluent precursor and one of the key building blocks of various anticancer agents.

MATERIALS AND METHODS

General synthetic procedure

Sigma Aldrich Chemical Company provided all Reagents which were required for the synthesis and activity. The solvents used in the reactions were of the chemical grade. Pre-coated silica gel G and analytical pre-coated 0.25 mm TLC plates were taken for the monitoring of various steps of synthetic scheme as per the requirement. Iodine vapors and the spraying reagents were also used to identify the spots, along with ultraviolet light (254 nm) from the UVP UVLS-26 Series (Cambridge) instrument. On a melting point apparatus, each melting point was recorded and adjusted. Using the KBr disc and a Shimadzu IR 460 spectrophotometer, infrared spectra were measured. ^{1}H NMR and ^{13}C NMR spectra were noted using internal standard tetra methylsilane on a Bruker NMR spectrophotometer (500 MHz) using dimethyl sulfoxide as a solvent.

Chemistry

Initially 7-azaindole (2.36 g, 0.02 moles), Aluminum chloride (2.38 g, 0.02 moles) and 20 mL trichloroacetic acid were dissolved in 50 mL of dichloromethane in a beaker and reaction mixture was refluxed for 1 hr. TLC monitoring was done till the reaction completion. The crude solid product [1] was filtered using vacuum pump, dried over calcium chloride and purified by recrystallization. The compound 1 was treated with 1.90 g, 0.01 mole of Tosyl Chloride (TsCl) which afforded compound 2. It is then further treated for an additional hour on reflux with ethanolic potassium hydroxide. TLC kept an eye on the reaction process. The unfiltered solid product [2] was washed and filtered. This tosyl derivative [2] was reacted with 0.01 mole thionyl chloride and 20 mL ethanol. The reaction contents were refluxed for 45 min at 110°C and yielded the compound [3].

Synthesis of compounds (4a-4j)

N-Deprotection yielded the compound [4]. It is done by treatment of the compound [3] with in a basic medium which yielded derivative of 7-Azaindole [4]. Compound [4a-j] was produced by refluxing the compound [3] with 0.01 mol of substituted aryl amine for an hour. TLC kept an eye on the reaction process (Figure 2). The raw solid [4a-j] product was filtered and cleaned. The resulting product was recrystallized with ethanol and water mixture for the purification (Table 1).

Biological evaluation

MTT Assay: In vitro anticancer activity by using MTT assay method

Human cancer screening panel The MCF-7 breast cancer cell lines were produced by supplementing RPMI-1640 medium with 5% fetal bovine serum and 2 mM L-glutamine. Cells were plated at a density of 25000 per well on 96-well micro titer plates using a volume of 100 L. The cells were cultured on the micro titer plates for 24 hr at 5% CO_2, 37°C, 100% relative humidity, and 95% air before the experimental drugs were added. To evaluate the cell population for the cell line during the stage of drug addiction, two plates of cell line were in situ fixed with TCA (Trichloro Acetic Acid) after 24 hr (Tz). The experimental drugs were frozen before use. After that dissolved in Dimethyl Sulfoxide at 400 times the maximum test concentration necessary. Using a full medium gentamicin concentration of 50 g/mL, an amount of iced concentrate was defrosted and thinned to double the intended last highest test conc. at the time of drug administration. Additional 4, 10, 12 fold log serial dilutions were carried out to produce a total of 5 drug conc. additional power. By adding a portion of 100 µL

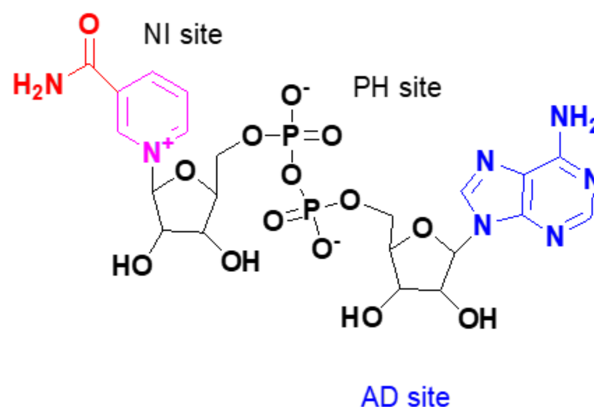

Figure 1a: Structure of PARP enzyme showing binding sites.

of each of these different drug dilutions to the appropriate micro titer wells that had already been filled with 100 μL of medium, the necessary final drug conc. was produced.[37]

Following the administration of the medication, the plates were cultured for an additional 48 hr at 5% CO_2, 37°C, 100% relative humidity, and 95% air. The test for adhering cells was terminated by the addition of cold TCA. The cells were fixed in place by a cautious injection of 50 μL of cold, 50% (w/v) TCA (last concentration, 10% TCA), after which they were gently cultured for 60 min at 4°C. After discarding the supernatant, the plates underwent five rounds of tap water rinsing before being air dried. Each well received 100 μL of a 0.4% (w/v) in 1% CH_3COOH Sulforhodamine B (SRB) sol. Plates were maturated for 10 min. at room temp. The plates were colored, then unattached stain washed off five times with 1% CH_3COOH before being left to dry by air. An automatic plate reader was used to measure the absorbance at 515 nm after the conjugated dye had been dissolved in 10 mM trizma base. With the exception of slowly pouring 50 μL of 80% TCA (last concentration, 16% TCA) to fix settling cells at the base of the walls, the procedures for suspension cells were the same. Using the seven absorbance assessments, which included Time zero (Tz), Control growth (C), and test growth with drug present at 5 concentration levels, the percentage increase at each medication concentration level was calculated (Ti). Percentage (%) growth inhibition was displayed as:

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

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

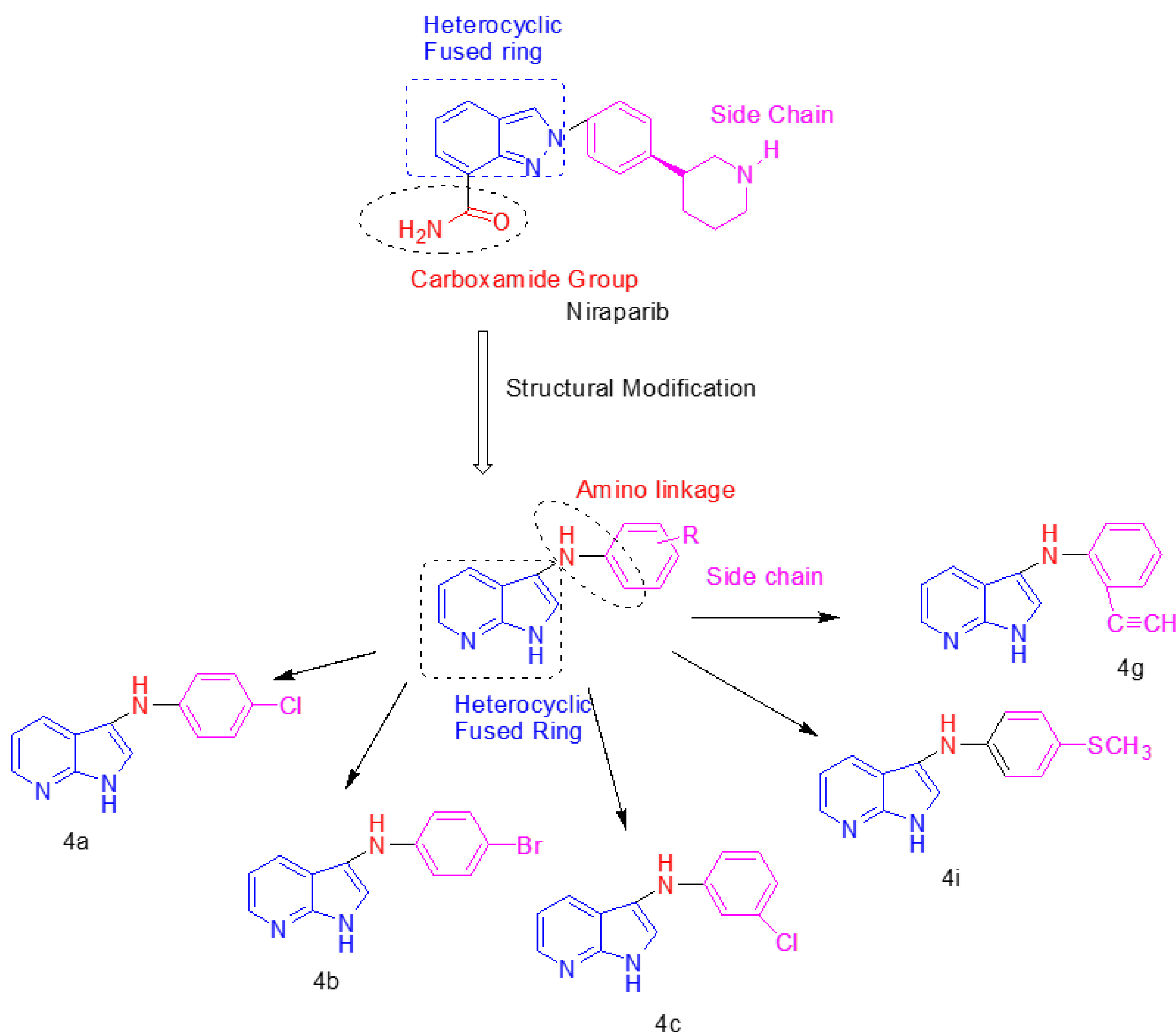

Figure 1b: Designing Approach of 7-Azaindole analogues based on PARP inhibitor.

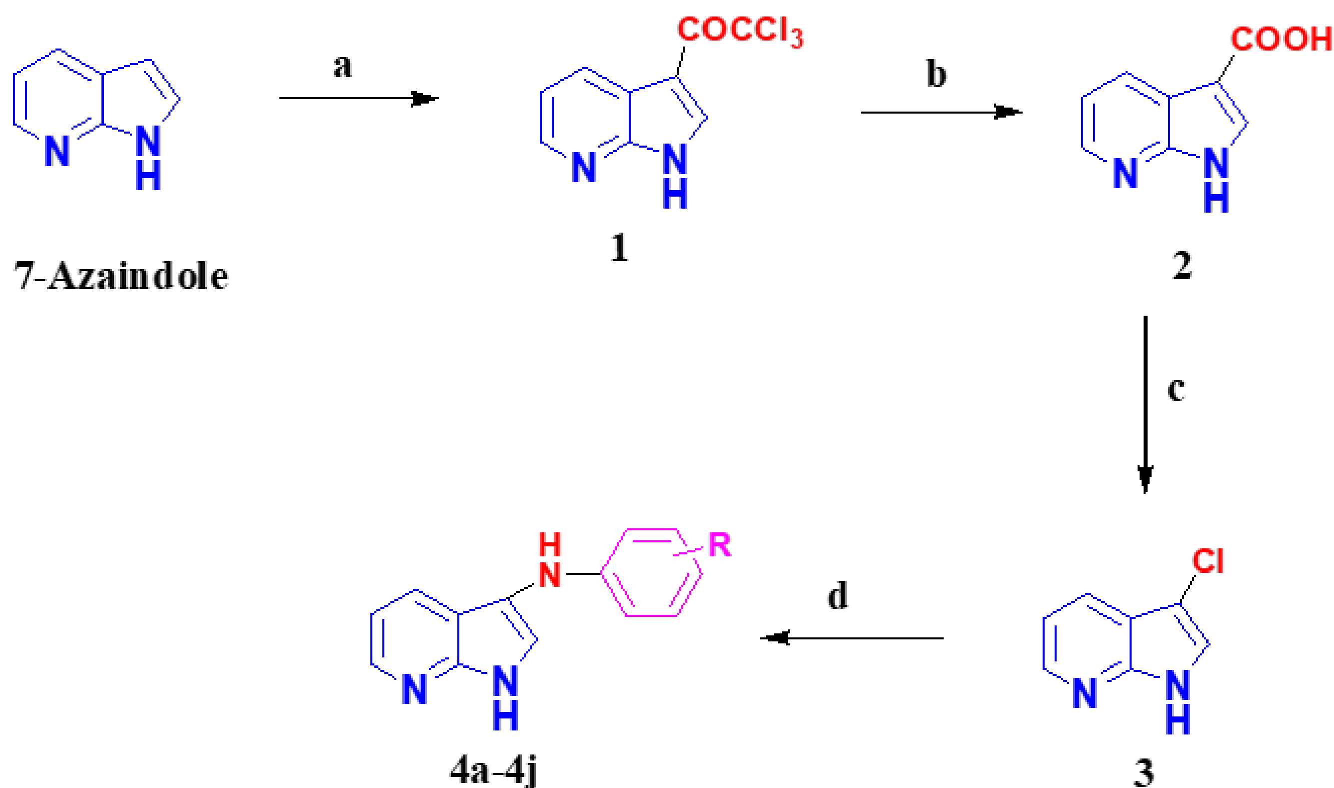

Figure 2: Scheme for synthesis of Compounds 4a-4j, Reagents, conditions used in reaction: a) CCl_3COOH, Aluminum chloride, dichloromethane b) i. Tosyl chloride, ethanol ii. KOH, C_2H_5OH c) $SOCl_2$, C_2H_5OH d) i. substituted aryl amine, C_2H_5OH, ii. KOH, Reflux

Table 1: List of Synthesized compounds (4a-j).

Compound	Substitution	Mol. Weight	R_f value*	% yield	Log P	cLog P
4a	4-Cl	243.7	0.69	56.5	3.01	4.2
4b	4-Br	288.1	0.72	45.4	3.28	4.35
4c	3-Cl	243.7	0.67	35.4	3.01	4.2
4d	4-CH_3	223.3	0.75	49.2	2.93	3.88
4e	4-C_4H_9	265.4	0.78	51.4	4.19	5.46
4f	4-OCH_3	239.3	0.82	31.5	1.17	3.64
4g	2-ethinyl	233.3	0.85	35.6	2.61	3.65
4h	2,4 di-OCH_3	269.3	0.86	44.2	2.19	3.35
4i	4-SCH_3	255.3	0.87	46.5	2.89	3.94
4j	4-Br,3-OCH_3	318.2	0.8	56.4	3.15	4.1

* Ethyl acetate: Methanol (9:1).

For every investigational drug, 3 criteria of the dosage response were computed. GI_{50} was derived using the formula (Ti-Tz)/(C-Tz)x100=50, where 50 determines the drug concentration that, when incubated with control cells, lowers the net protein rise by 50% (as shown by SRB staining). If the desired degree of activity was obtained, values were computed for every of these three criteria. The result for that factor was represented as being larger or less than the greatest or lowest concentration, respectively, if the impact was not obtained or was surpassed.

RESULTS

The spectral data of final compounds are given in the following text

Compound 4a: N-(4-chlorophenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3323.30 (NH), 3063.09 (aromatic C-H), 1572.19 (C=C), 1411.20 (Aromatic C=N), 1383.29 (C-N), 763.26

(C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6 ppm): 6.5-8.59 (m, 4H, pyridine and pyrrole ring), 5.2 ppm (s, 1H, J 7.25Hz, N-H of pyrrole ring), 6.4-7.02 ppm (m,4H, phenyl), 4.2 ppm (s, 1H, J 3.0Hz, NH).^{13}C NMR (500 MHz, DMSO-d_6 ppm): 149.1 (C, 7-azaindole), 121.9 (C, 7-azaindole), 127.4 (C, 7-azaindole),115.9 (CH, 7-azaindole), 142.3 (CH, 7-azaindole), 101.6 (C, 7-azaindole), 126 (CH, 7-azaindole),141.1 (C, aromatic), 117.5 (CH, aromatic), 129.6 (CH, aromatic), 124.3 (C, aromatic), 129.8 (CH, aromatic), 117.6 (CH, aromatic). Mass spectrum (m/z (I_{rel}, %): 243.056 (100.0), 245.053 (32.0), 244.060 (14.1), 246.057 (4.5), 244.053 (1.1). Elemental analysis: Calcd for $C_{13}H_{10}ClN_3$: C, 65.06; H, 4.15; Cl, 14.56; N, 16.23 % Found $C_{13}H_{10}ClN_3$: C, 64.27; H, 3.94; Cl, 14.25; N, 17.54%.

Compound 4b: N-(4-bromophenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3364.30(N-H), 3083.00 (aromatic C-H) 1593.09 (C=C ring), 1401.19 (Aromatic C=N), 1384.79 (C-N), 633.77 (C-Br). ^{1}H NMR (500 MHz, DMSO-d_6 ppm): 6.4-8.57 (m, 4H, pyridine and pyrrole ring), 5.12 (s, 1H,J 7.1 Hz, N-H of pyrrole ring), 6.35-7.02 (m,4H, phenyl), 4.05 (s, 1H, J 3.20 Hz, NH).^{13}C NMR (500 MHz, DMSO-d_6 ppm):), 146.8 (C, 7-azaindole), 121.1 (C, 7-azaindole), 128.3 (C, 7-azaindole), 115.7 (CH, 7-azaindole), 142.4 (CH, 7-azaindole), 101.3 (C, 7-azaindole), 126.5 (CH, 7-azaindole),142.6 (C, aromatic), 118.4 (CH, aromatic), 133.4 (CH, aromatic), 113.4 (C, aromatic), 132.6 (CH, aromatic), 118.6 (CH, aromatic). Mass spectrum (m/z (I_{rel}, %): 287.006 (100.0), 289.004 (97.3), 288.009 (14.1), 290.007 (13.7), 288.003 (1.1), 290.001 (1.1). (Elemental analysis: Calcd for $C_{13}H_{10}BrN_3$: C, 54.19; H, 3.50; Br, 27.73; N, 14.58 % Found: C, 53.14; H, 4.30; Br, 27.53; N, 14.98%.

Compound 4c: N-(3-chlorophenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3323.30 (N-H), 3063.09 (aromatic C-H) at 1572.19 (C=C ring), 1411.20(Aromatic C=N), 1383.29 (C-N), 763.26 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6 ppm):: 7.3-8.57 (m, 4H, pyridine and pyrrole ring), 5.12 (s, 1H, J 7.1 Hz, N-H of pyrrole ring), 6.34-6.95 ppm (m, 4H, phenyl), 4.2 (s, 1H, J 3.3 Hz, NH).^{13}C NMR (500 MHz, DMSO-d_6 ppm): 147.8 (C, 7-azaindole), 121.2 (C, 7-azaindole), 128.6 (C, 7-azaindole), 115.7 (CH, 7-azaindole), 142.6 (CH, 7-azaindole), 101.4 (C, 7-azaindole), 126.4 (CH, 7-azaindole), 144.6 (C, aromatic), 116.8 (CH, aromatic), 135.4 (C, aromatic), 118.7 (CH, aromatic), 131.4 (CH, aromatic), 115.6 (CH, aromatic). Mass spectrum (m/z (I_{rel}, %): 243.056 (100.0), 245.053 (32.0), 244.060 (14.1), 246.057 (4.5), 244.053 (1.1). Elemental analysis: Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; Cl, 14.55; N, 17.24. Found $C_{13}H_{10}ClN_3$: C, 64.57; H, 4.34; Cl, 14.05; N, 17.04%.

Compound 4d: N-(4-methylphenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3364.30 (N-H), 3087.20 (Aromatic C-H), 2959.20 (aliphatic C-H) 1583.10 (C=C ring), 1405.35 (Aromatic C=N), 1384.79(C-N). ^{1}H NMR (500 MHz, DMSO-d_6 ppm): 6.7-8.57 (m, 4H, pyridine and pyrrole ring), 5.15 (s, 1H, J 7.15 Hz, NH of pyrrole ring), 6.30-6.81 (m, 4H, phenyl), 4.1 (s, 1H, J 3.5 Hz, NH), 2.36 ppm (s, 3H, J 5.25 Hz, CH_3 methyl). ^{13}C NMR (500 MHz, DMSO-d_6 ppm): 148.9 (C, 7-azaindole), 121.1 (C, 7-azaindole), 142.2 (C, 7-azaindole), 116.2 (CH, 7-azaindole), 129.1 (CH, 7-azaindole), 142.2 (CH, 7-azaindole), 129.8 (CH, 7-azaindole), 127.3 (C, 7-azaindole),140.6 (C, aromatic), 117.1 (CH, aromatic), 128.1 (C, aromatic), 129.7 (CH, aromatic), 130.1 (CH, aromatic), 116.5 (CH, aromatic), 24.2 (CH_3, methyl). Mass spectrum (m/z (I_{rel}, %): 223.11 (100.0), 224.11 (15.1), 224.10 (1.1), 225.11 (1.1). Elemental analysis: Calcd for $C_{14}H_{13}N_3$: C, 74.31; H, 6.87; N, 18.82. Found C, 76.31; H, 5.75; N, 17.90%.

Compound 4e: N-(4-butylphenyl)-1H-pyrrolo [2, 3-b]pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3384.30 (N-H), 3083.00 (aromatic C-H), 1593.09 (C=C ring) 1401.19 (Aromatic C=N), 1365.70 (C-N). ^{1}H NMR (500 MHz, DMSO-d_6 ppm): 6.35-8.56 (m, 4H, pyridine and pyrrole ring), 5.0 (s, 1H, J 7.15 Hz, N-H of pyrrole ring), 6.40-6.86 (m,4H, phenyl), 4.1 (s, 1H, J 3.65 Hz, NH), 2.56 (s, 2H, J 8.5Hz, CH_2 methylene), 1.63 (s, 2H, J 8.25 Hz, CH_2 methylene),1.32 (s, 2H, J 8.45 Hz, CH_2 methylene), 1.1 (s, 3H, J 7.05 Hz, CH_3 methyl). ^{13}C NMR(500 MHz, DMSO-d_6 ppm): 147.6 (C, 7-azaindole), 122.2 (C, 7-azaindole), 128.2 (CH, 7-azaindole), 115.1 (CH, 7-azaindole), 142.6 (CH, 7-azaindole), 100.8 (C, 7-azaindole), 126.3 (CH, 7-azaindole), 140.2 (C, aromatic), 116.4 (CH, aromatic), 129.4 (C, aromatic), 128.6 (CH, aromatic), 129.1 (CH, aromatic), 115.5 (CH, aromatic), 34.9 (CH_2 methylene), 32.2 (CH_2 methylene), 22.3 (CH_2 methylene), 14.4 (CH_3, aliphatic). Mass spectrum (m/z (I_{rel}, %): 265.158 (100.0), 266.161 (18.4), 267.165 (1.6), 266.155 (1.1). Elemental analysis: Calcd for $C_{17}H_{19}N_3$: C, 76.75; H, 7.42; N, 15.84. Found $C_{17}H_{19}N_3$: C, 75.95; H, 8.02; N, 16.04%.

Compound 4f: N-(4-(methoxy) phenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3360.30 (N-H), 3092.00 (aromatic C-H), 1589.02 (C=C ring), 1411.21(Aromatic C=N), 1389.02 (C-N). ^{1}H NMR (500 MHz, DMSO-d_6 ppm): 6.6-8.46 (m, 4H, pyridine and pyrrole ring), 5.15 (s, 1H, J 7.40 Hz, N-H of pyrrole ring), 6.46-7.18 (m, 4H, phenyl), 4.1 (s, 1H, J 3.70 Hz, NH), 3.15 (s, 1H, J 6.25 Hz, CH acetylene). ^{13}C NMR (500 MHz, DMSO-d_6 ppm): 147.4 (C, 7-azaindole), 122.2 (C, 7-azaindole),128.2 (CH, 7-azaindole), 115.1 (CH, 7-azaindole), 142.6 (CH, 7-azaindole), 100.8 (C, 7-azaindole), 126.3 (CH, 7-azaindole), 140.2 (C, aromatic), 116.4 (CH, aromatic), 129.4 (C, aromatic), 128.6 (CH, aromatic), 129.1 (CH, aromatic), 115.5 (CH, aromatic), 55.8

(CH_3, aliphatic). Mass spectrum (m/z (I_{rel}, %): 239.106 (100.0), 240.109 (15.1), 240.103 (1.1), 241.113 (1.1). Elemental analysis: Calcd for $C_{14}H_{13}N_3O$: C, 71.28; H, 5.48; N, 16.56; O, 6.69. Found $C_{14}H_{13}N_3O$: C, 71.38; H, 5.48; N, 16.56; O, 6.59%.

Compound 4g: N-(2-ethinyl phenyl)-1H-pyrrolo [2,3-b]pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3359.20 (N-H), 3301.00 (aliphatic CH), 3095.00 (aromatic CH), 1587.19 (C=C ring), 1420.09 (Aromatic C=N), 1374.79 (C-N). ^1H NMR (500 MHz, DMSO-d_6, ppm): 6.5-8.58 (m, 4H, pyridine and pyrrole ring), 5.2 (s, 1H, J 7.15 Hz, N-H of pyrrole ring), 4.20 (s, 1H, J 3.45 Hz, NH), 6.6-6.98 (m, 4H, phenyl), 3.04 (s, 1H, J 6.50 Hz, CH acetylene). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 148.6 (C, 7-azaindole), 121.8 (C, 7-azaindole), 128.6 (CH, 7-azaindole), 115.7 (CH, 7-azaindole), 142.9 (CH, 7-azaindole), 101.7 (C, 7-azaindole), 126.5 (CH, 7-azaindole), 151.6 (C, aromatic), 107.9 (C, aromatic), 133.3 (CH, aromatic), 118.9 (C, aromatic), 129.2 (CH, aromatic), 116.6 (CH, aromatic),82.7 (C, acetylene), 79.2 (CH, acetylene). Mass spectrum (m/z (I_{rel}, %): 233.095 (100.0), 234.099 (16.2), 235.102 (1.2), 234.092 (1.1). Elemental analysis: Calcd for $C_{15}H_{11}N_3$: C, 76.23; H, 5.75; N, 18.01. Found $C_{15}H_{11}N_3$: C, 76.23; H, 5.55; N, 18.21%.

Compound 4h: N-(2, 4 dimethoxyphenyl)-1H-pyrrolo [2, 3-b] pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3368.05 (N-H), 3078.30 (aromatic C-H), 1579.29 (C=C ring), 1401.19 (Aromatic C=N), 1381.10 (C-N). ^1H NMR (500 MHz, DMSO-d_6, ppm): 6.7-8.56 (m, 4H, pyridine and pyrrole ring), 5.06 (s, 1H, J 7.40 Hz, N-H of pyrrole ring),

Table 2: Molecular docking and anticancer activity results.

Compound	GI 50(μM)	Protein code	LF Rank score	LF dG	Hydrogen bonding	Hydrophobic interactions
4a	27.29	6NRF	-2.375	-2.71	NME A1010 (2.9)	
		6NRG	-2.104	-2.47	GLN A912 (2.9)	ASP A914
		6NRH	-2.383	-2.61		GLN A912
		6NRI	-1.799	-1.99	SER A911 (2.0)	GLN A912,
		6NRJ	-2.24	-2.78		GLN A912, PHE A1009
4b	23.33	6NRF	-2.384	-2.63		GLN A912
		6NRG	-1.986	-2.36		GLN A912
		6NRH	-2.426	-2.69		GLN A912
		6NRI	-1.93	-2.21	LYS A1010 (1.9)	
		6NRJ	-2.154	-2.81		GLN A912, PHE A1009
4c	19.72	6NRF	-2.493	-2.78		GLN A912
		6NRG	-2.047	-2.52		ASP A914
		6NRH	-2.493	-2.78	GLY A913 (3.0), SER A911 (2.9)	GLN A912, PHE A1009
		6NRI	-1.804	-1.98	SER A911 (2.0)	GLN A912
		6NRJ	-2.034	-2.55		ASP A914
4d	33.45	6NRF	-2.289	-2.46		GLN A912
		6NRG	-1.976	-2.33	GLN A912 (2.9)	ASP A914
		6NRH	-2.239	-2.3		GLN A912
		6NRI	-2.004	-2.3	LYS A1010 (1.9)	
		6NRJ	-2.004	-2.3	GLN A912 (2.8)	ASP A914
4e	49.67	6NRF	-1.579	-2.92	GLY A913 (2.7)	ALA A828, PHE A 1009, GLN A912
		6NRG	-1.335	-2.2		GLN A912
		6NRH	-1.888	-3.07	NME A1010 (2.8)	GLN A912
		6NRI	-1.692	-2.52	ALA A828 (2.1)	PHE A1009
		6NRJ	-1.68	-2.54		GLN A912

Compound	GI 50(µM)	Protein code	LF Rank score	LF dG	Hydrogen bonding	Hydrophobic interactions
4f	122.76	6NRF	-2.221	-2.89	LYS A1010 (2.8), NME A1010 (2.5), GLY A913 (2.1)	PHE A1009, GLN A912
		6NRG	-2.221	-2.89	GLN A912 (2.9)	ASP A914
		6NRH	-2.241	-2.61	GLY A913 (2.3)	PHE A1009, GLN A912
		6NRI	-1.836	-2.61	LYS A1010 (1.9)	PHE A1009, GLN A912
		6NRJ	-1.836	-2.61	GLN A912 (2.1)	PHE A1009, GLN A912
4g	15.56	6NRF	-2.066	-2.8		GLN A912, PHE A 1009
		6NRG	-1.55	-2.13	GLN A912 (3.0)	ASP A914
		6NRH	-3.384	-4.49		TYR B527, PRO B488, CYS B483
		6NRI	-1.858	-2.09		GLN A912, PHE A1009
		6NRJ	-1.747	-2.33		GLN A912, PHE A1009
4h	49.67	6NRF	-2.134	-2.9	GLN A912 (2.0)	PHE A 1009
		6NRG	-1.559	-2.09	GLN A912 (2.0)	PHE A 1009
		6NRH	-2.152	-3	GLN A912 (2.1)	GLN A912
		6NRI	-1.033	-1.63	HIS A909 (2.0)	GLY A913(2.9)
		6NRJ	-2.152	-3	GLN A912 (2.1)	GLN A912
4i	114.17	6NRF	-1.741	-4.24	LYS A1010 (2.6), NME A1010 (2.3), GLY A913 (2.4)	PHE A1009, GLN A912
		6NRG	-1.741	-4.24		GLN A912
		6NRH	-4.284	-3.29	GLY A913 (2.6)	PHE A1009, GLN A912
		6NRI	-2.961	-2.28		GLN A912
		6NRJ	-3.878	-2.2		GLN A912
4j	62.87	6NRF	-3.339	-6.09	GLY A913 (2.1)	GLN A912
		6NRG	-2.398	-3.03	GLY A913 (2.1)	PHE A1009
		6NRH	-3.339	-6.09	GLY A913 (2.0), NME A1010 (2.9)	GLN A912, ALA A828
		6NRI	-2.21	-2.29	LYS A1010 (2.0)	GLN A912, PHE A1009
		6NRJ	-2.54	-3.63	GLY A913 (1.9)	GLN A912, PHE A1009
Niraparib	5.4	6NRF	-1.868	-3.22	GLN A912 (3.0)	GLN A912
		6NRG	-1.868	-3.22		GLN A912
		6NRH	-1.686	-3.13	ALA A828 (2.5)	GLN A912
		6NRI	-1.434	-2.18	GLN A912 (2.6)	ALA A828,PHE A1009
		6NRJ	-1.569	-3.35	GLN A912 (3.0)	GLN A912

4.12 (s, 1H,J 3.3 Hz, NH), 6.02-6.29 ppm (m, 4H, phenyl), 3.78 (s, 3H, J 8.15Hz, CH_3).^{13}C NMR (500 MHz, DMSO-d_6, ppm): 148.1 (C, 7-azaindole), 120.2 (C, 7-azaindole), 127.9 (C, 7-azaindole), 114.6 (CH, 7-azaindole), 141.7 (CH, 7-azaindole), 101.5 (C, 7-azaindole), 125.7 (CH, 7-azaindole),124.3 (C, aromatic), 146.6 (C, aromatic), 101.1 (CH, aromatic), 150.9 (C, aromatic), 108.4 (CH, aromatic), 117S.6 (CH, aromatic), 55.2 (CH_3, aliphatic), 55.2 (CH_3, aliphatic). Mass spectrum (m/z (I_{rel}, %): 269.116 (100.0), 270.120 (16.2), 271.123 (1.2), 270.113 (1.1). Elemental analysis: Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60; O, 11.88. Found $C_{15}H_{15}N_3O_2$: C, 65.50; H, 6.31; N, 15.90; O, 11.48%.

Compound 4i: N-(4-methylthiophenyl)-1H-pyrrolo [2,3-b]pyridin-3-amine

IR spectrum (KBr, ν_{max}, cm^{-1}): 3357.10 (N-H), 3076.40 (aromatic C-H), 1586.30 (C=C ring) 1405.20 (Aromatic C=N), 1388.20 (C-N). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 6.5-8.59 (m, 4H, pyridine and pyrrole ring), 5.03 (s, 1H, J 7.15Hz, N-H of pyrrole ring), 4.2 (s, 1H, J 3.20 Hz, NH), 6.38-6.94 (m, 4H, phenyl), 2.46 (s, 3H, J 1.25 Hz, S-CH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 148.4 (C, 7-azaindole), 122.6 (C, 7-azaindole), 129.7 (C, 7-azaindole),116.5 (CH, 7-azaindole), 144.5 (CH, 7-azaindole), 102.1 (C, 7-azaindole), 125.7 (CH, 7-azaindole), 138.9 (C, aromatic), 116.9 (CH, aromatic), 127.2 (CH, aromatic), 126.1 (C, aromatic), 127.8 (CH, aromatic), 115.6 (CH, aromatic), 14.5 (CH_3, aliphatic). Mass spectrum (m/z (I_{rel}, %): 255.083 (100.0), 256.086 (15.1), 257.079 (4.5), 256.080 (1.1), 257.090 (1.1). Elemental analysis: Calcd for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46; S, 12.56%. Found $C_{14}H_{13}N_3S$: C, 66.05; H, 5.43; N, 16.96; S, 12.16%.

Compound 4j: N-(4-bromo 3-methoxy phenyl)-1H-pyrrolo [2,3-b]pyridin-3-amine

IR (KBr, ν_{max}, cm^{-1}): 3371.70 (N-H), 3093.00 (aromatic C-H), 1577.20 (C=C ring), 1409.30 (Aromatic C=N), 1378.29 (C-N), 787.66 (C-Br). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 6.75-8.59 (m, 4H, pyridine and pyrrole ring), 5.12 (s, 1H, J 7.55 Hz, N-H of pyrrole ring), 5.87-7.08 (m, 4H, phenyl), 4.2 (s, 1H, J 3.75 Hz, NH),3.76 (s, 3H, J 8.15Hz, methyl). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 147.2 (C, 7-azaindole), 120.6 (C, 7-azaindole), 120.8 (CH, 7-azaindole), 115.8 (CH, 7-azaindole), 141.9(C, 7-azaindole), 125.7 (CH, 7-azaindole), 143.2 (C, aromatic), 101.5 (CH, aromatic), 156.1 (C, aromatic), 102.3 (C, aromatic), 134.4 (CH, aromatic), 111.2 (CH, aromatic), 56.3 (CH_3, aliphatic). Mass spectrum (m/z (I_{rel}, %): 317.016 (100.0), 319.014 (97.3), 318.020 (15.1), 320.018 (14.7), 318.013 (1.1), 320.011 (1.1), 319.023 (1.1), 321.021 (1.0). Elemental analysis: Calcd for $C_{14}H_{12}BrN_3O$: C, 52.85; H, 3.80; Br, 25.11; N, 13.21; O, 5.03. Found $C_{14}H_{12}BrN_3O$: C, 52.25; H, 3.80; Br, 25.71; N, 13.12; O, 5.12%.

In vitro anticancer activity

All of the synthesized derivatives (4a-4j) were screened for their efficacy against the human cancer cell line MCF-7 using the MTT assay (breast) as anticancer agents. Here, Niraparib was used as a positive control. The outcomes are reported in Table 2. For BRCA1-deficient breast cancers, PARP inhibitors (such as Olaparib, Veliparib, Talazoparib, Niraparib, and Rucaparib) have shown to be quite effective as a monotherapy. Olaparib has undergone the most testing, and it is now permitted for clinical use in breast cancer who have germ line or somatic BRCA1/2 mutations. Additionally, chemotherapy drugs that cause DNA damage have been tested in combination with PARP inhibitors. According to the literature, MCF-7, an ER+/HER2+ breast cancer cell line, and BT474 are both ER+/HER2+. According to the data, Talazoparib and Niraparib had an effect on the MCF-7 cell line between 1.1 and 5.4 µM. While Niraparib GI_{50} value is 5.4 µM, all of the synthesized derivatives tested showed good anticancer activity, with GI_{50} values ranging from 15.56 µM to 122.8 µM. The majority of the promising activity was displayed by five of the compounds: 4a, 4b, 4c, 4g, and 4i. Structure-activity relationships studies for all compounds 4a-4j were observed. The data indicated that the compound 4g (GI_{50}; MCF-7=15.56 µM), which has the highest activity in the series, which has a 4-ethinyl substitution on the phenyl ring. There is a slight drop in the GI_{50} value compared to the compound 4g when compound 4c and compound 4a have chloro groups in the third and fourth positions, respectively. Compound 4b, which had bromo group on its para position, exhibited less activity (MCF-7 GI_{50}: 23.33 µM). For the compound 4d (MCF-7 GI_{50}: 33.45 µM), in which the 4-chloro group has been replaced with a 4-methoxy substituent on the phenyl ring, there has been a decrease in anticancer activity. Contrarily, compound 4j had a 3-methoxy and 4-bromo substituent on the phenyl ring, which resulted in a lower GI_{50} (MCF-7 62.87 µM) than those of the compounds 4b and 4c. Finally, these findings showed that the best substituents for these compounds appear to be bromo, chloro, methyl, ethinyl, and single methoxy substitutions on the para position of phenyl rings.

DISCUSSION

Structure-activity relationship

Synthesized compounds 4a-j was studied for the Structure-activity relationship against the cancer cell lines. The study revealed that the compounds' anticancer activity increased when electron-withdrawing groups ethinyl and chloro, bromo were present at the para and ortho positions of the phenyl moiety, respectively. Additionally, the benzene ring has methoxy and dimethoxy groups attached to it at the ortho and para positions, both of which donate electrons. The results have shown that, at low concentrations, the presence of methyl (an electron-releasing group) at the para position of the phenyl moiety also inhibited the growth of cancer cell lines, though less so than an

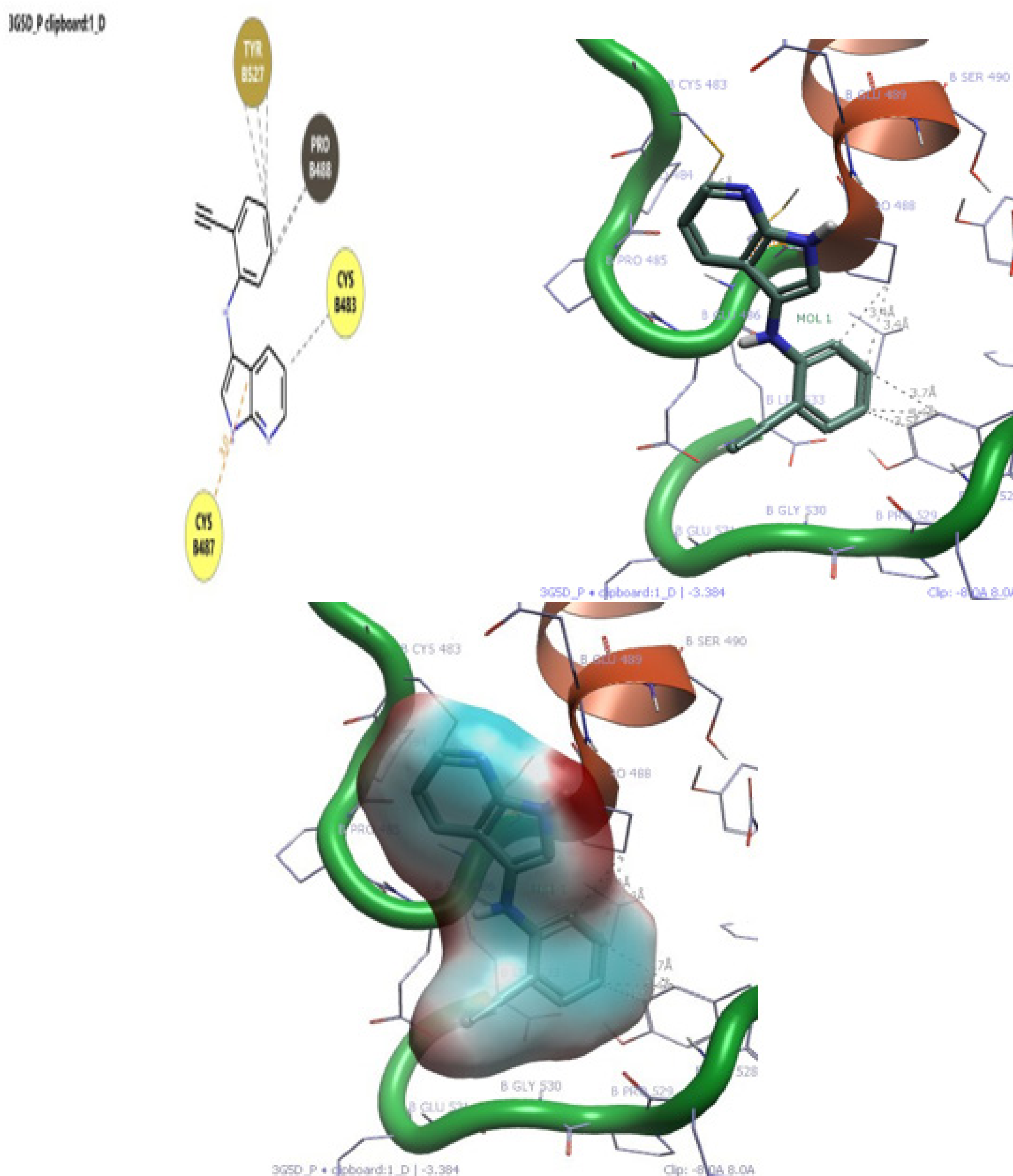

Figure 3: 2D/3D molecular docking of compound 4g with PARP protein codes (PDB id. 6NRH).

electron-withdrawing group. ChemDraw Ultra v.12 was used to compute the membrane-water partition coefficient (clog P). According to experiments, clog P of compounds 4a-4j between 2.9 and 4.4. According to Lipinski's rule,[38] these values correlate with those required to create drug-like compounds when -2 Log *P*>5.

Molecular docking

The process for docking begins with retrieving the poly (ADP-ribose) Polymerases (PARPs) enzymes' PDB structures from the RSCB PDB database. The Cresset Flare software (V6.0) was used to dock all six protein id codes: 6NRF, 6NRG, 6NRH, 6NRI, 6NRJ, and 6NTU. Cresset Flare 6.0 docking software was used to conduct the docking studies (Figures 3-5). To determine the binding efficiencies, docking studies of all Azaindole derivatives (4a-4j) in the active site of PARP (PDB ID: 6NRF, 6NRG, 6NRH, 6NRI, 6NRJ and 6NTU) were conducted. The protein data bank's 3-dimensional proteins were retrieved (PDB ID: 6NRF, 6NRG, 6NRH, 6NRI, 6NRJ and 6NTU). The results of the docking are listed in Table 2. The protein preparation wizard efficiently prepared each protein and reduced its energies. The Flare program was used to create the receptor grid that encircles their co-crystal ligands. The results of the docking in standard mode were examined, and the compounds' binding affinities

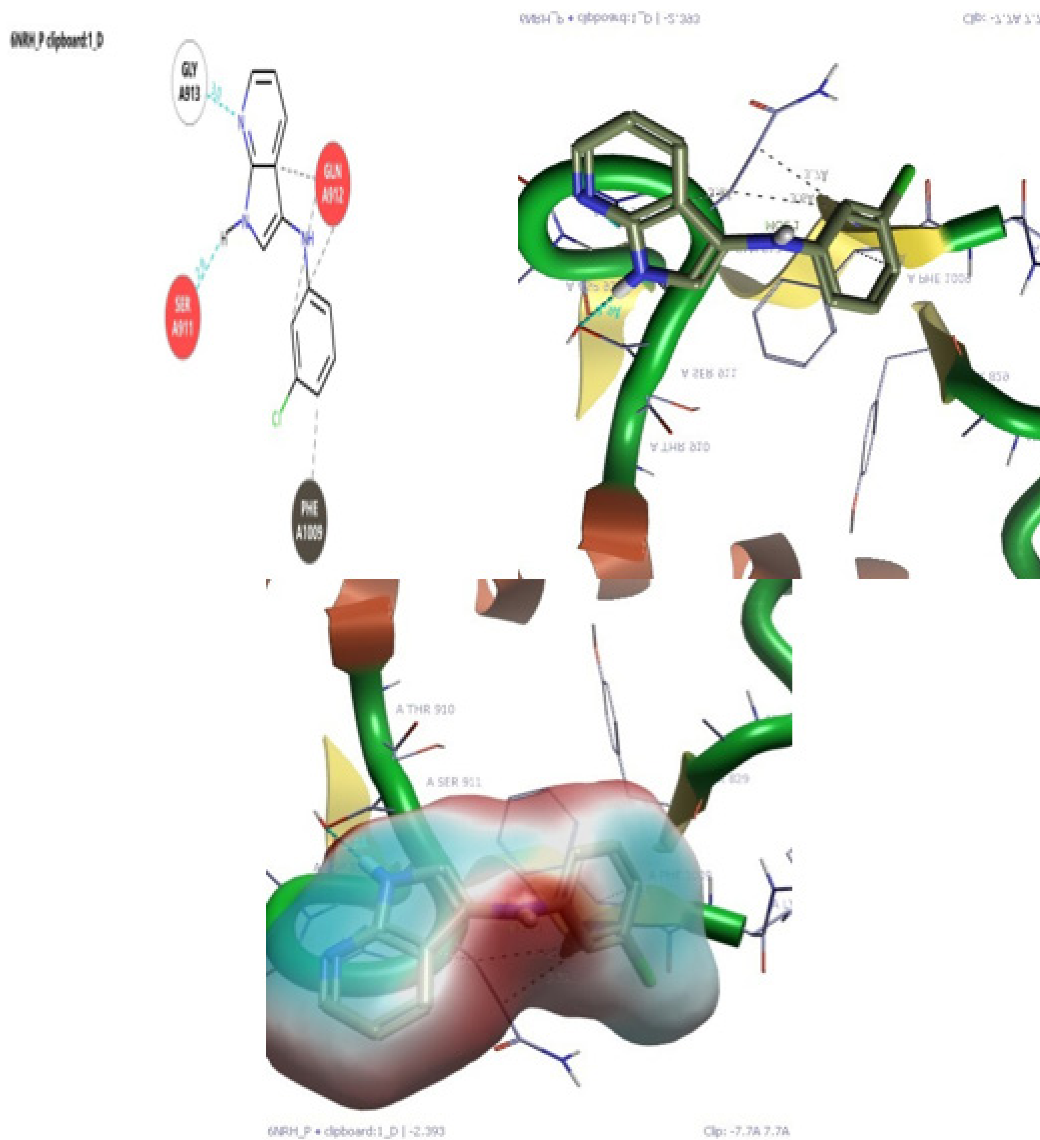

Figure 4: 2D/3D molecular docking of compound 4c with PARP protein codes (PDB id. 6NRH).

were expressed in terms of LF Rank score, negative binding energy (kcal/mole), and LF dG. More ligands with the higher protein-binding affinities will have lower negative LF Rank scores and higher dG values.[14]

Enzymes poly (ADP-ribose) polymerases PARPs (PDB ID: 6NRF, 6NRG, 6NRH, 6NRI, 6NRJ and 6NTU) molecular docking studies

Molecular interactions between the Azaindole compounds (4a-4j) and the active site of the enzyme poly(ADP-ribose) polymerases were studied and reported by conducting docking studies with cancer target molecules (PARPs).The grid is established, and the following active residues are linked to the various co-crystal ligand as per the protein codes.

PARPs (protein id code 6NRF): Co-crystal ligand was UTT103 Inhibitor (AKYV 1103),

It interacts hydrophobically with ASP A914, PHE A1009 residues and hydrogen bonding with GLN A912 (2.8) residue.

PARPs (protein id code 6NRG): Co-crystal ligand was UTT57 Inhibitor (AKYY 1101).

It interacts hydrophobically with ASP A914 residue and hydrogen bonding with GLN A912 with a bond length of 2.9.

PARPs (protein id code 6NRH): Co-crystal ligand was UTT103 Inhibitor (AKYV 1103).

It interacts hydrophobically with PHE A1009, GLN A912 and hydrogen bonding with ARG A865 (2.7), GLN A912 (2.0).

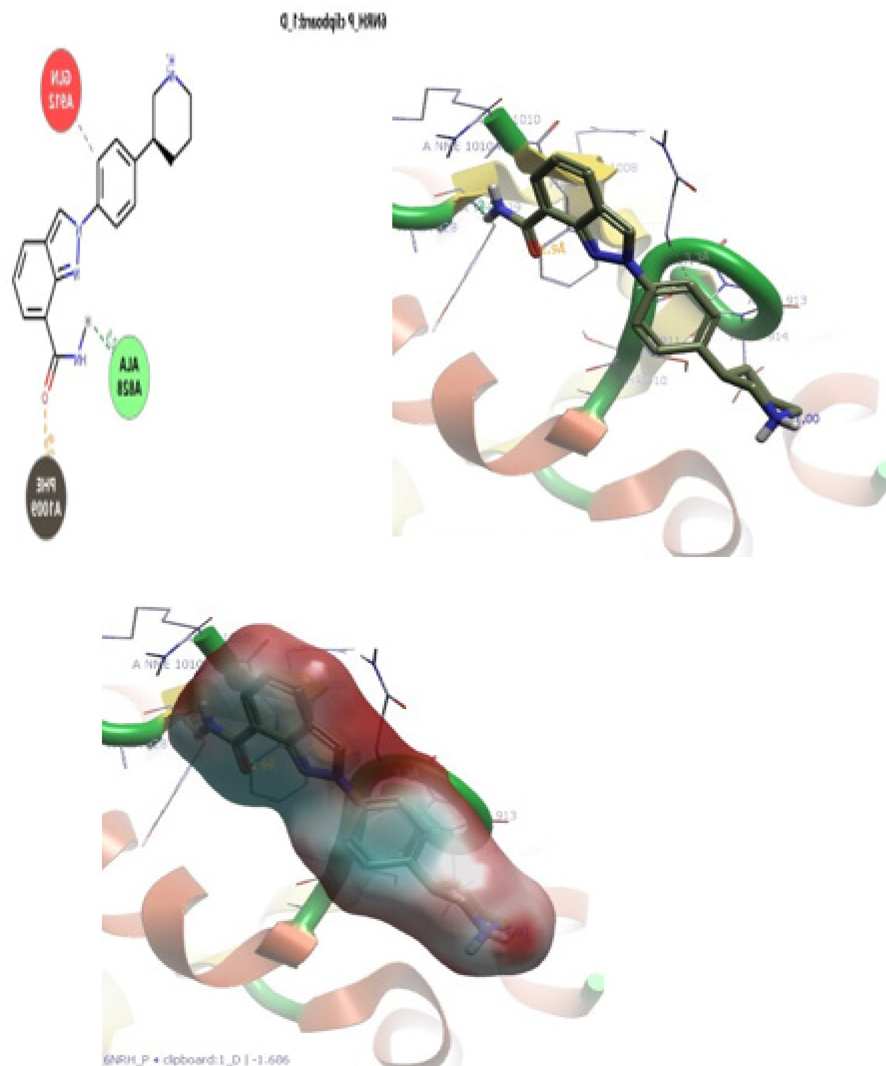

Figure 5: 2D/3D molecular docking of Niraparib with PARP protein codes (PDB id. 6NRH).

PARPs (protein id code 6NRI): Co-crystal ligand was UTT103 Inhibitor (AKYV 1103).

It interacts hydrophobically with PHE A1009 and the hydrogen bonding with GLN A912 (2.9) and GLY A913 (2.1). Free energy binding and a dG value of 2.92 kcal/mol and an LF Rank score of 0.512. All active compounds have LF Rank score in the range of 1.72 to 2.961 and dG value of in the range of 1.63 to 2.61 kcal/mol.

PARPs (protein id code 6NRJ): Co-crystal ligand was UTT103 Inhibitor (AKYV 1103).

It interacts hydrophobically with PHE A1009, GLN A912 and the hydrogen bonding with ARG A865 (2.7), GLN A912 (2.0).

PARPs (protein id code 6NRU): Not any compound was docked to UKTT15 inhibitors.

Among all protein codes the newly synthesized Azaindole analogues (4a-4j) were docked with 6NRH proteins very efficiently. LF Rank score of these compounds was in the range of 1.89 to 4.28 and dG value of ranging as 2.3 to 6.9 kcal/mol. The values were compatible with the standard drug Niraparib. The compound 4i exhibited maximum docking score with 6NRH (LF Rank score 4.28), 6NRJ (LF Rank score 3.88) and 6NRI (LF Rank score 2.961), respectively. The biologically active compounds 4a, 4b, 4c and 4g also showed good docking score with all above proteins but the maximum docking score with proteins 6NRH and 6NRF as compare to the standard PARP inhibitor Niraparib having LF Rank score 1.69 and 1.87, respectively. Compound 4g displayed maximum docking score of 3.38 and 2.09 with 6NRH and 6NRF proteins, respectively but the maximum hydrophobic interactions with TYR B527, PRO B488, CYS B483 were seen in 6NRH protein code. The compound 4i exhibited maximum docking score of 4.28 with hydrophobic interactions with PHE A1009, GLN A912 and the hydrogen bonding with GLY A913 (2.6) as compare to the standard drug Niraparib having the

hydrophobic interaction with GLN A912 and the hydrogen bonding with ALA A828 (2.5).

CONCLUSION

In conclusion, using data from mass spectrometry, ^{1}H NMR and ^{13}C NMR, we had developed a new series of 7-azaindoles (4a-4j). Each substance's anticancer properties were also examined against MCF-7 (breast) human cancer cell lines. The most encouraging activity was demonstrated by the compounds 4a, 4b, 4c, 4i, and 4h against these cancer cell lines. The compounds having substitution bromo, chloro, methyl, ethinyl, and single methoxy groups on the para position of phenyl rings, displayed maximum anticancer activity. All of these compounds, as well as compound 4i, displayed good free energy of binding interactions with poly (ADP-ribose) Polymerases (PARPs) protein id 6NRH among all the six protein codes.

ACKNOWLEDGEMENT

The authors are thankful to DST-FIST Centre at Meerut Institute of Engineering and Technology, Meerut-250005, India for providing the facilities for the research work.

CONFLICT OF INTEREST

The authors declare that there is not any conflict of interest.

ABBREVIATIONS

PARP: Poly (ADP-ribose) polymerases; **BRCA:** Breast Cancer gene; **MAPK:** Mitogen activated Protein Kinase; **IGF1-R:** Insulin Like Growth Factor-1; **CRTh2:** Chemoattractant receptor-homologous-2; **Chk1:** Checkpoint kinase1; **FGFR-4:** Fibroblast growth factor receptor 4; **PI3Kγ:** Phosphoinositide 3-kinase; **KBr:** Potassium Bromide; **TLC:** Thin Layer chromatography; **MTT:** (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); **MCF-7:** cell lines; Michigan Cancer Foundation cell lines; **PDB:** Protein data bank; **GI_{50}:** 50% Cell Growth Inhibition; **ASP:** Aspartic acid; **GLN:** Glutamine; **GLY:** Glycine; **LYS:** Lysine; **PHE:** Phenyl alanine; **PRO:** Proline; **SER:** Serine; **TYR:** Tyrosine.

SUMMARY

In the current study novel 7-Azaindole compounds were synthesized and characterized by UV, proton NMR, ^{13}C NMR and mass spectroscopy. After synthesis the compounds were evaluated for breast Cancer (MCF-7 cell lines inhibition) activity. The compounds were also docked with various protein codes of PARP enzyme for finding the potent PARP inhibitors.

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Cite this article: Sharma N, Chaudhary A, Sachdeva M. Design, Synthesis, Anticancer Activities and Comparative Molecular Docking Studies of a Novel Class of 7-azaindole Analogs as Potent PARP-1 Inhibitors. Indian J of Pharmaceutical Education and Research. 2024;58(2):624-36.