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Synthesis, Characterization and Molecular Docking Studies of 5-Chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carboxylic Acids

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A series of new 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acids (**5a-c**) was synthesized. For the synthesis of these compounds, the 1*H*-indole-2-carboxylic acids **(1a-c)** were used as core compound. The synthetic route leading to the title compounds is summarized in **Scheme-I**. The chemical structures of all intermediates and products were confirmed by their IR, ^{1}H and ^{13}C NMR, mass spectral data and elemental analysis. The molecular docking studies of title compounds was carried out to predict the binding interactions with target protein EGFR.

Keywords: Vilsmeier-Hack formylation, Indoles, Pyrazoles, Docking studies.

INTRODUCTION

An exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the heterocyclic chemistry. Pyrazoles are prominent nitrogen-containing heterocycles, which were found to possess various biological activity as antihyperglycemic [1], analgesic [2], anti-inflammatory [3], antipyretic [4], antibacterial [5], hypoglycaemic [6], sedative-hypnotic activity [7], antimicrobial [8], central nervous system [9] and immunosuppressive [10]. The indole nucleus is considered as privileged scaffolds [11]. Therefore, the synthesis and selective functionalization of indoles have been focused in by drug molecules researchers over the years [12-14]. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anticancer [15], antioxidant [16], antirheumatoidal [17], anti-HIV [18] and also play a vital role in the immune system [19,20].

Indole alkaloids are a class of alkaloids containing structural moiety of indole; many indole alkaloids also contain isoprene groups. It is one of the largest classes of alkaloids [21]. Many of them such as brevianamide **(I)**, 7-hydroxy itragynine **(II)**, ibogaine **(III)**, mesembrine **(IV)**, strychine **(V)** and yohimbine **(VI)** (Fig. 1) possess significant physiological activity and some of them are used in medicines. The tryptophan is the biochemical precursor of indole alkaloids [22].

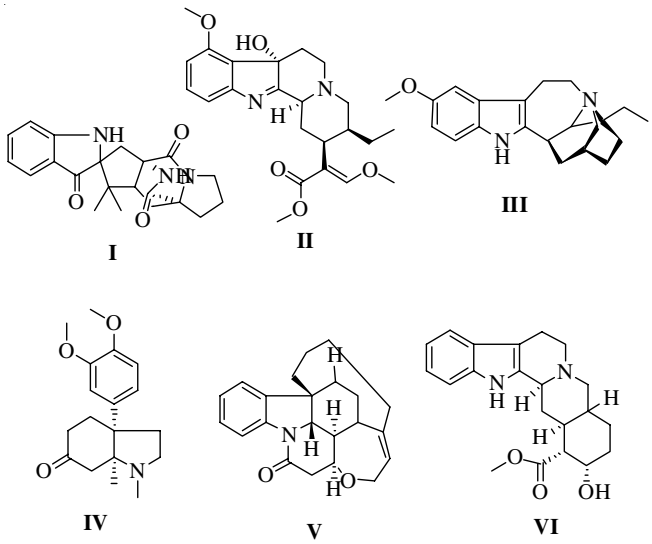


Fig. 1. Strucutre of some compounds containing indole alkaloids

In consideration of diverse biological properties of pyrazole based compounds, present work is carried out to develop simple and efficient procedures for the synthesis of new 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carboxylic acids **(5a-c)**.

EXPERIMENTAL

All the reagents and solvents were used as purchased from commercial sources and used without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR spectra were obtained using PerkinElmer BX series FT-IR 5000 spectrometer with KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 75 MHz & 300 MHz spectrometers, respectively. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of 1*H*-indole-2-carboxylic acid ethyl esters (2a-c): To a solution of 1*H*-Indole-2-carboxylic acids **(1a-c)** (0.01 mol) in absolute ethyl alcohol (15 mL) conc. H_2SO_4 (2 mL) was added. The mixture was refluxed with constant stirring for 4 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water and the obtained residue was filtered, dried and recrystallized with from ethyl acetate to get pure 1*H*-indole-2-carboxylic acid ethyl esters **(2a-c)**.

Synthesis of 1*H*-indole-2-carboxylic acid hydrazides (3a-c): A mixture of 1*H*-indole-2-carboxylic acid ethyl esters **(2a-c)** (0.01 mol) and hydrazine hydrate (0.025 mol) in absolute ethanol (20 mL) was refluxed for 8 h with uniform stirring. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give 1*H*-indole-2-carboxylic acid hydrazides **(3a-c)** in pure form.

Synthesis of 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehydes (4a-c): A homogenous solution of 1*H*-indole-2-carboxylic acid hydrazides **(3a-c)** and ethyl acetoacetate (0.025 mol) in absolute ethyl alcohol was dissolved in a cold solution of DMF (15 mL) and $POCl_3$ (12 mL). The whole solution was maintained at the ambient temperature with steady stirring for 4 h. After the completion of reaction (scanned by TLC), the resulting mixture was poured into ice-cold water (20 mL) and a saturated solution of NaOH was added to neutralize and the resultant solid was filtered, dried and recrystallized from ethyl acetate to obtain 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbalde hydes **(4a-c)** in pure form.

5-Chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehyde (4a): White solid, yield: 70%, m.p.: 113-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3328 (N-H), 3025 (C-H, Ar), 2985 (C-H, CH_3), 1732 (C=O), 1564 (C=C, Ar), 1435 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.08 (s, 1H, NH), 9.21 (s, 1H, CHO), 7.86-7.17 (m, 4H, Ar-H), 7.48 (s, 1H, =CH), 3.49 (s, 1H, CH-Cl), 2.85 (s, 1H, CH-CO), 2.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 154.6, 135.9, 132.0, 127.1, 125.4, 123.6, 119.7, 109.2, 105.3, 72.8, 64.0, 13.5; MS: 261 *m/z* (M$^+$); Elemental analysis: calcd. (found) % for $C_{13}H_{12}N_3OCl$: C, 59.66 (59.32); H, 4.62 (4.60); Cl, 13.55 (13.48); N, 16.06 (16.00); O, 6.11 (6.09).

5-Chloro-1-(5-chloro-1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehyde (4b): Yellow solid, yield: 70%, m.p.: 151-153 ºC; IR (KBr, ν_{max}, cm^{-1}): 3318 (N-H), 3028 (C-H, Ar), 2980 (C-H, CH_3), 1735 (C=O), 1572 (C=C, Ar), 1441 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.12 (s, 1H, NH), 9.32 (s, 1H, CHO), 7.78 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.65 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.56 (s, 1H, Ar-H), 7.50 (s, 1H, =CH), 3.52 (s, 1H, CH-Cl), 2.81 (s, 1H, CH-CO), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0, 154.7, 132.1, 130.5, 127.2, 126.8, 123.6, 121.7, 118.9, 106.1, 66.9, 58.7, 14.6; MS: 296 *m/z* (M$^+$); Elemental analysis: calcd. (found) % for $C_{13}H_{11}Cl_2N_3O$: C, 52.72 (52.12); H, 3.74 (3.72); Cl, 23.94 (23.69); N, 14.94 (14.81), O, 5.40 (5.37).

5-Chloro-1-(5-bromo-1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehyde (4c): Pale yellow solid, yield: 74%, m.p.: 123-125 ºC; IR (KBr, ν_{max}, cm^{-1}): 3345 (N-H), 3032 (C-H, Ar), 2970 (C-H, CH_3), 1728 (C=O), 1564 (C=C, Ar), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.95 (s, 1H, NH), 9.42 (s, 1H, CHO), 7.64 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.52 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.39 (s, 1H, Ar-H), 7.36 (s, 1H, =CH), 3.47 (s, 1H, CH-Cl), 2.89 (s, 1H, CH-CO), 2.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 150.8, 142.9, 135.9, 132.1, 127.3, 125.8, 123.6, 119.3, 118.8, 71.5, 56.0, 13.5; MS: 340 *m/z* (M$^+$); Elemental analysis: Calcd. (found) % for $C_{13}H_{11}N_3OBrCl$: C, 45.84 (45.48); H, 3.26 (3.24); Br, 23.46 (23.21); Cl, 10.41 (10.34); N, 12.34 (12.29); O, 4.70 (4.68).

Synthesis of 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acids (5a-c): To a solution of 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehydes **(4a-c)** in ethyl alcohol, a solution of $KMnO_4$ (0.01 mol) and water (5 mL) was added and the resultant solution was stirred consistently at reflux temperature for about 3 h. After completion of the reaction (monitored by TLC), the obtained solution was cooled to room temperature and neutralized by drop wise addition of NaOH solution. The resultant solid was filtered and recrystallized from ethanol to afford corresponding 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acids (**5a-c**).

5-Chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acid (5a): Brown solid, yield: 77%, m.p.: 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 3308 (N-H), 3225 (O-H), 3025 (C-H, Ar), 2970 (C-H, CH_3), 1715 (C=O), 1564 (C=C, Ar), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.21 (s, 1H, COOH), 10.84 (s, 1H, NH), 7.74-7.47 (m, 4H, Ar-H), 7.36 (s, 1H, =CH), 3.55 (s, 1H, CH-Cl), 2.91 (s, 1H, CH-CO), 2.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1, 154.7, 135.2, 134.6, 132.0, 127.9, 126.8, 123.6, 118.7, 112.4, 62.0, 54.5, 14.2; MS: 277 *m/z* (M$^+$); Elemental analysis: calcd. (found) % for $C_{13}H_{12}N_3O_2Cl$: C, 56.22 (55.89); H, 4.36 (4.35); Cl, 12.77 (12.58); N, 15.13 (15.01); O, 11.52 (11.39).

5-Chloro-1-(5-chloro-1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acid (5b): Orange solid,

yield: 74%, m.p.: 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3368 (N-H), 3248 (O-H), 3028 (C-H, Ar), 2978 (C-H, CH_3), 1718 (C=O), 1610 (C=C, Ar), 1475 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 1H, COOH), 10.92 (s, 1H, NH), 7.74 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.58 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.21 (s, 1H, =CH), 3.62 (s, 1H, CH-Cl), 2.95 (s, 1H, CH-CO), 2.84 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.7, 152.7, 135.2, 132.0, 128.4, 127.3, 125.8, 122.6, 120.6, 115.7, 66.7, 52.0, 13.5; MS: 312 *m/z* (M^+); Elemental analysis: calcd. (found) % for $C_{13}H_{11}N_3O_2Cl_2$: C, 50.02 (49.89); H, 3.55 (3.54); Cl, 22.72 (22.52); N, 13.46 (13.39); O, 10.25 (10.12).

5-Chloro-1-(5-bromo-1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acid (5c): Yellow solid, yield: 71%, m.p.: 124-126 ºC; IR (KBr, ν_{max}, cm^{-1}): 3342 (N-H), 3258 (O-H), 3014 (C-H, Ar), 2984 (C-H, CH_3), 1722 (C=O), 1605 (C=C, Ar), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.10 (s, 1H, COOH), 10.88 (s, 1H, NH), 7.56 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.41 (s, 1H, Ar-H), 7.30 (s, 1H, =CH), 3.71 (s, 1H, CH-Cl), 2.84 (s, 1H, CH-CO), 2.79 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 154.6, 135.2, 132.0, 127.3, 126.8, 126.0, 125.8, 123.6, 118.5, 114.7, 61.0, 14.20; MS: 356 *m/z* (M^+); Elemental analysis: calcd. (found) % for $C_{13}H_{11}N_3O_2BrCl$: C, 43.79 (43.36); H, 3.11 (3.10); Br, 22.41 (22.34); Cl, 9.94 (9.90); N, 11.78 (11.71); O, 8.97 (8.95).

RESULTS AND DISCUSSION

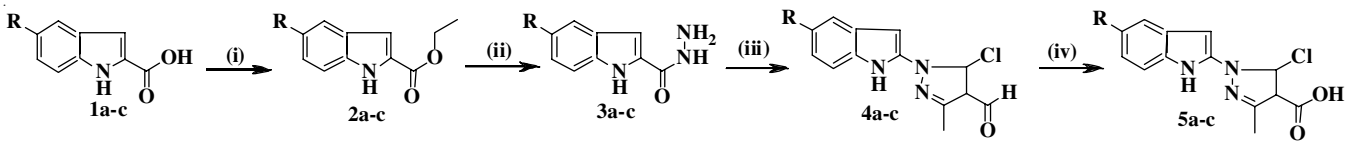
For the synthesis of the title compounds, 1*H*-indole-2-carboxylic acids **(1a-c)** was exploited as core structure. The synthetic route leading to the title compounds is summarized in **Scheme-I**. The chemical structure all intermediates and products were confirmed by their IR, ^{1}H and ^{13}C NMR, mass spectral data and elemental analysis.

The esterification of 1*H*-indole-2-carboxylic acids **(1a-c)** with absolute ethanol in presence of catalytic amount of sulphuric acid produced the corresponding 1*H*-indole-2-carboxylic acid ethyl esters **(2a-c)** in good yields. The key intermediate, 1*H*-indole-2-carboxylic acid hydrazides **(3a-c)** has been achieved in good yields from the appropriate initial intermediate **2a-c** on treatment with hydrazine hydrate in absolute ethanol at reflux temperature with constant stirring for 8 h.

Further, compound **3a-c** on cyclization with ethyl acetoacetate in ethanol followed by DMF and $POCl_3$ on steady stirring for 4 h resulted final intermediate, 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbaldehydes **(4a-c)** in good yields. The IR spectrum of compound **4a** showed the different bands at different stretching and bending frequencies corresponding to the various functional groups 3328 (N-H), 3025 (C-H, Ar), 2985 (C-H, CH_3), 1732 (C=O), 1564 (C=C, Ar), 1435 (C=N) cm^{-1}. The proton NMR spectrum of **4a** showed a signal at δ 11.08 ppm as a singlet for one proton corresponds to NH group, δ 9.21 ppm as a singlet for the proton corresponding to CHO group. The signal between δ 7.86-7.17 ppm as a multiplet for four protons is assigned to the aromatic ring, while the signal at δ 7.48 ppm as singlet for one proton is connected with =CH group. Three signals at different chemical shifts for one proton at 3.49 ppm, one proton at 2.85 ppm and three protns at 2.65 ppm are corrspond to CH-Cl, CH-CO and CH_3 groups, respectively. The ^{13}C NMR spectrum of compound **4a** exhibited signals at different δ 173.2, 154.6, 135.9, 132.0, 127.1, 125.4, 123.6, 119.7, 109.2, 105.3, 72.8, 64.0 and 13.5 ppm associated for various carbons. Mass spectrum of the compound showed peak at *m/z* 261 (M^+), confirmed the structure of compound **4a**. The chemical structure of compounds **4b** and **4c** compounds was determined by same approach.

Finally, oxidation of compound **4a-c** with $KMnO_4$ in the presence of absolute ethyl alcohol at reflux with stable stirring for 3 h produced corresponding target compounds, 5-chloro-1-(1*H*-indole-2-yl)-3-methyl-4,5-dihydro-1*H*-pyrazole-4-carbxylic acids **(5a-c)** in good yields. Emergence of the compound **5a** is established by study of its spectra. The IR spectrum of compound **5a** showed the bands at 3308 (N-H), 3225 (O-H), 3025 (C-H, Ar), 2970 (C-H, CH_3), 1715 (C=O), 1564 (C=C, Ar) and 1468 (C=N) cm^{-1}. The ^{1}H NMR spectrum of compound **5a** showed a signal at δ 11.21 ppm for one proton as singlet corresponding to COOH group. The singlet signal appeared at δ 10.84 ppm for one proton assigned to the NH group. The signals located between δ 7.74-7.47 ppm as multiplet for four protons is related to the aromatic ring. The singlet signal for one proton displayed at δ 7.36 ppm is assigned to =CH group. The CH-Cl, CH-CO and CH_3 have appeared as singlets at their corresponding protons δ 3.55 ppm, 2.91 ppm and 2.72 ppm. The ^{13}C NMR spectrum of the compound exhibited signals at δ 173.1, 154.7, 135.2, 134.6, 132.0, 127.9, 126.8, 123.6, 118.7, 112.4, 62.0, 54.5 and 14.2 ppm for various carbons. The mass spectrum of compound **5a** showed a peak at *m/z* 277 (M^+). The chemical structure of compounds **5b** and **5c** were characterized in similar strategy.

Molecular docking studies: Molecular docking studies were studied by using Auto Dock tools 4.2 software. The epidermal growth factor receptor (EGFR) was taken as the target for the study, which is a cell-surface receptor for members of the epidermal growth factor of extracellular protein ligands. The EGFR is necessary for the ductal development of mammary glands and when the protein over expressed it leads to a number of cancers, which include epithelian tumors of the head and neck and anal cancers [23-25]. It is an important target in the cancer disease and specific tyrosine kinase inhibitors [26]. The EGFR having pdb id 4HJO is downloaded from protein data bank [27].



Scheme-I: (i) EtOH, H_2SO_4, reflux, 4 h; (ii) NH_2–NH_2. H_2O, EtOH, reflux, 8 h; (iii) EAA, ethanol, DMF, $POCl_3$ RT, 4 h, (iii) $KMnO_4$, ethanol, reflux, 3 h; **1-5 a)** = H, **b)** = 5-Cl, **c)** = 5-Br

Molecular docking studies of the compounds **5a**, **5b** and **5c** revealed that they have good binding interactions with target protein EGFR (Fig. 2). Among the three compounds, **5b** has shown maximum binding energy -8.16 Kcal/mol and inhibition constant 1.05 micromolar. It has formed three hydrogen bonds with TYR845, ALA847 and LYS851 amino acid residues with

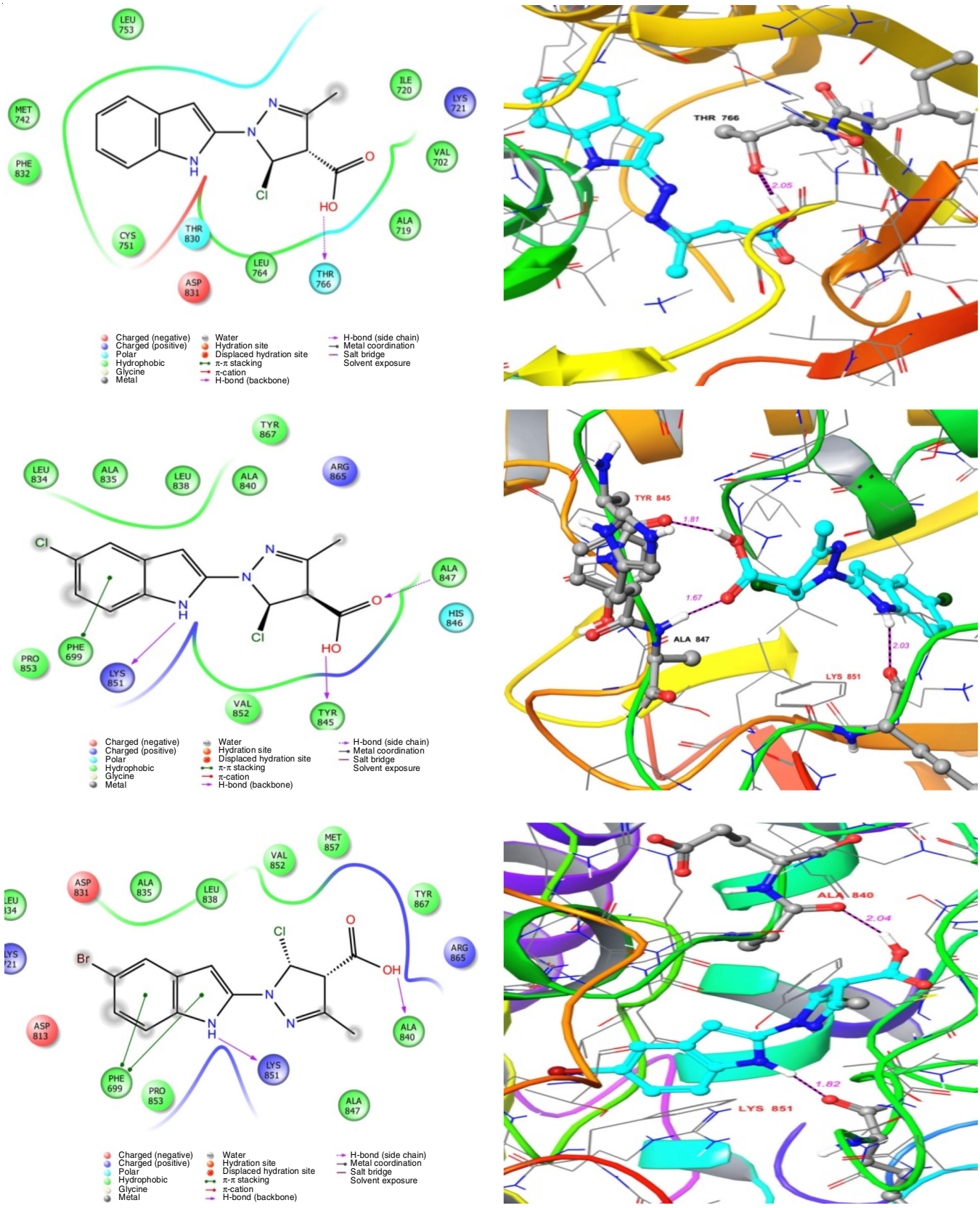


Fig. 2

TABLE-1
MOLECULAR DOCKING INTERACTION PARAMETERS OF COMPOUNDS WITH THE EPIDERMAL GROWTH FACTOR RECEPTOR (PDB ID-4HJO)

Compound entry	Binding energy (Kcal/mol)	Inhibition constant (micro molar)	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
1	-7.59	2.73	1	THR766 (2.05)
2	-8.16	1.05	3	TYR845 (1.81), ALA847 (1.67), LYS851 (2.03)
3	-7.83	1.82	2	ALA840 (2.04), LYS851 (1.82)

bond lengths 1.81 Å, 1.67 Å and 2.03 Å, respectively. It also exhibited π-π stacking with PHE699 amino acid. The compound **3** has ranked second in its interaction with EGFR and has shown -7.83 Kcal/mol binding energy and 1.82 micromolar inhibition constant. In addition to this it has also shown π-π stacking with PHE699 residue. Further two hydrogen bonds with ALA 840 and LYS851 residues with bond lengths 2.04 Å and 1.82 Å, respectively. Finally, compound **5a** has exhibited suitable binding energy (-7.59 Kcal/mol) and inhibition constant (2.73 micromolar) with the target protein. The interaction parameters are presented in Table-1.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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