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Synthesis and Molecular Docking Based Exploration of Salicylic Acid Derivatives

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In present study, four salicylic acid derivatives *viz*., 2-acetoxybenzoic acid (**2a**), 2-(1*H*-indol-2-yl)benzoic acid (**3a**), 5-chloro-2-acetoxybenzoic acid (**2b**) and 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (**3b**) were synthesized and studied for molecular docking on 3JUS and 3UPI protein selected from pdb. The studies show that all of the four synthesized compounds were found to be docked. Compound **3a** and **3b** showed the best ligand pose energy -10.8163 kcal/mol and -11.1354 kcal/mol with docking run: elapsed time 9 s and 12 s, respectively in respect of 3JUS Further, compounds **3a** and **3b** showed the best ligand pose energy -9.17851 and -9.54722 kcal/mol with docking run: elapsed time 10 and 14 s, respectively in case of 3UPI. Hence, studies showed that 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (**3b**) emerged as potent compound which might show diverse nature of biological and therapeutic activity.

Keywords: Salicylic acid, Benzoic acid, Molecular docking, Indole, Hydrazine.

INTRODUCTION

Salicylic acid is a natural occurring product which is present in the bark of the willow trees. Salicylic acid is present in the vast range of eukaryotic and prokaryotic organisms as well as in the plants. One major role which is established in plants is that salicylic acid acts as a signal molecule in plants for defense responses [1]. For more than 2000 years salicylic acid has been used to treat various skin disorders. It is a good agent as it has the ability to exfoliate *Stratum corneum*. For example acne can be treated using salicylic acid because it has anti-inflammatory property [2]. Other disorders which can be treated using salicylic acid comprises of vulgaris, freckles, photo damage, malasma and lentigines [3]. Aspirin is an acetylated form of salicylic acid which has anti-inflammatory activity which is due to its ability to inhibit the production of proinflammatory prostaglandins. Aspirin is the most commonly used synthetic medicine, which is used to treat the pain and to prevent the cardio-vascular disease [4]. Salicylic acid is the simplest aromatic carboxylic acid with the hydroxyl derivatives. Salicylic acid can be used to synthesize aspirin which further can be used to synthesize the derivative of indoles. The literature reviews of salicylic acid derivatives enlightened us about numbers of medicinal, pharmacological or therapeutic activities [5-17].

In preview of this observation, present work was the outcome of impression of diverse nature of biological activities of salicylic acid. The main purpose was to synthesize and characterize high purity aspirin followed by the formation of indole through cyclization. In this work, various salicylic acid originated derivatives were synthesized, screened by lab techniques and studied for molecular docking evaluation. The molecular docking study wasdone using ARGUS software with help of 3JUS and 3UPI proteins selected from pdb. The molecular docking study revealed that synthesized compounds, 2-(1*H*-indol-2-yl)benzoic acid (**3a**) and 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (**3b**) showed potent biological activity.

EXPERIMENTAL

Melting points of synthesized compounds were determined by open capillary and are uncorrected. The purity of compounds was checked using TLC plates (glass) coated with silica gel. The developed chromatographic plates were visualized under iodine chamber. IR spectra were recorded using KBr on Shimadzu FTIR model 8400 spectrophotometer. ^{1}H NMR spectra and mass spectra was recorded through software Chemdraw. Molecular docking studies were carried out using Argus lab 4.0.1 software.

Synthesis of 2-acetoxybenzoic acid (2a): 2-Hydroxybenzoic acid (0.01 mol) was added in 100 mL beaker followed

by 2 mL of pyridine, the mixture was kept on ice bath and then cold 2 mL of acetyl chloride was added in mixture. Conc. H_2SO_4 (0.1 mL) was added and the mixture was stirred and poured into 15 mL of distilled water. The reaction mixture was heated at 60 ºC till dissolution then kept on ice bath till crystals were formed. The crystals were filtered, washed with cold water and recrystallized with ethanol to get fine crystals of 2-acetoxybenzoic acid (**2a**). Yield: 59.23 % (180 g), m.w. $C_9H_8O_4$, m.p. 150 ºC, R_f: 0.5. Elemental analysis calcd. (found) (%): C 60.00 (60.00); H 4.46 (4.48), O 35.54 (35.52). FTIR (KBr, ν_{max}, cm^{-1}): 3238 =C-H *str*. arom. ring) , 3100-2500 (OH *str*. COOH), 1658 (C=O *str*. $COCH_3$), 1612 (C=O *str*. COOH), 1483 (C=C *str*. arom. ring), 1440 (C-H bend. arom. ring), 1296 (OH bend. carbonyl). MS: *m/z* 180.04 (100.0 %), 181.05 (10.0 %), 182.05 (1.3 %).

Synthesis of 2-(1*H*-indol-2-yl)benzoic acid (3a): In this method, 2-(1*H*-indol-2-yl)benzoic acid (**3a**) was prepared by Shaikh *et al*. method [18]. The mixture of compound **2a** (0.01 mol) and phenylhydrazene (0.01 mol) and 12 mL of ethanol was taken in round bottom flask. The reaction mixture was refluxed for 2-3 h at 25-30 ºC, cooled at room temperature and poured into 8 mL conc. H_2SO_4. The mixture was then heated and stirred for 20-30 min and poured into 20 mL of ice cold water to get solid product. The crystals were filtered, dried and recrystallized with methanol. Yield: 38.81 % (273 g), m.w. $C_{15}H_{11}O_2N$, m.p. 170 ºC, R_f: 0.9. Elemental analysis calcd. (found) (%): C 75.80 (75.90); H 4.60 (4.60), N 5.90 (5.90), O 13.35 (13.40). FTIR (KBr, ν_{max}, cm^{-1}): 3438 (NH *str*. -NH=N-) 2607, 2488, 2360 (Ar overtones), 2889 (C-H *str*. arom. ring), 1604 (C=C *str*. arom. ring), 688, 742 (C-H bend. arom. bend.). MS: *m/z* 210.12 (100.0 %), 211.12 (15.1 %), 212.12 (1.1 %).

Synthesis of 5-chloro-2-acetoxybenzoic acid (2b): 5-Chloro-2-hydroxybenzoic (0.02 mol), 2 mL of pyridine and 4 mL of toluene were heated till dissolution in 100 mL beaker. Then 2 mL of cold acetyl chloride was added followed by the addition of 0.1 mL of conc. H_2SO_4. The reaction mixture was stirred and poured into 15 mL of distilled water. It was then heated at 60 ºC till dissolution got completed and mixture was kept on ice bath to get crystals. The crystals were filtered, washed and dried. The recrystallization with ethanol yielded pure crystals of 5-chloro-2-acetoxybenzoic acid (**2b**). Yield: 95.60 % (214.5 g), m.w. $C_9H_7O_4Cl$, m.p. 80 ºC, R_f: 0.9. Elemental analysis calcd. (found) (%): C 50.48 (50.38), H 3.53 (3.29), Cl 16.60 (16.52), O 29.40 (29.81). FTIR (KBr, ν_{max}, cm^{-1}): 3236 (C-H str. arom. ring), 3300 (O-H *str*.), 1454 (C=C str. arom. ring), 1300 (C-C *str*.), 1233 (C-H bend.), 890 (O-H bend.), 800-500 (=C-H bend.). MS: *m/z* 214.00 (100.0 %), 216.00 (32.0 %), 215.01 (10.0 %), 217.00 (3.2 %), 216.01 (1.3 %).

Synthesis of 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (3b): In this method, 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (**3b**) was prepared by Shaikh *et al*. method [18]. The mixture of compound **2b** (0.01 mol), phenylhydrazene (0.01 mol) and 12 mL of ethanol was refluxed for 2-3 h at 25-30 ºC, cooled at room temperature and poured into 8 mL conc. H_2SO_4. The reaction mixture was then heated, stirred for 20-30 min and then poured into 20 mL of ice cold water to get solid product. The crystals were filtered, dried and recrystallized with methanol. Yield: 50.00 % (272.5 g), m.w. $C_{15}H_{11}O_2NCl$, m.p. 170 ºC, R_f: 0.82. Elemental analysis calcd. (found) (%): C 66.80 (66.30); H 4.60 (3.71), N 5.90 (5.16), Cl 11.35 (13.0), O 11.35 (11.78). FTIR (KBr, ν_{max}, cm^{-1}): 3449 (NH *str*. -NH=N-) 2607, 2488, 2360 (Ar overtones), 2889 (C-H *str*. arom. ring), 1604 (C=C *str*. arom. ring), 688, 742 (C-H bend. arom. bend.). MS: *m/z* 210.12 (100.0 %), 211.12 (15.1 %), 212.12 (1.1 %).

Molecular docking study: The molecular docking calculations was carried out using ArgusLab software. The molecular docking studies revealed that ligand of respective synthesized compounds **2a-b** and **3a-b** had been found docked successfully with H-bonding on the binding site (amino acids) of 3JUS (Figs. 1-4) and 3UPI protein (Figs. 5-8), selected from pdb. The best ligand pose energies had been quite remarkable in case of 3JUS as listed in Table-1. The best ligand pose energies had also been quite remarkable in case of 3UPI (Table-2).

RESULTS AND DISCUSSION

The interesting outcome of this work is the synthesis of indoles through salicylic acid followed by cyclization (**Scheme-I**). Though, low yield has been a matter of concern. As shown in the highlighted case studies, molecular docking has been able to identify promising compounds that might represent future solutions in critical areas of human health. The compounds, 2-(1*H*-indol-2-yl)benzoic acid (**3a**) and 5-chloro-2-(1*H*-indol-2-yl)benzoic acid (**3b**) showed promising activity of varying degree. The compound **3a** had been found docked with binding amino acids such as 752 GLY:coil, 580 THR:alpha helix *etc.*

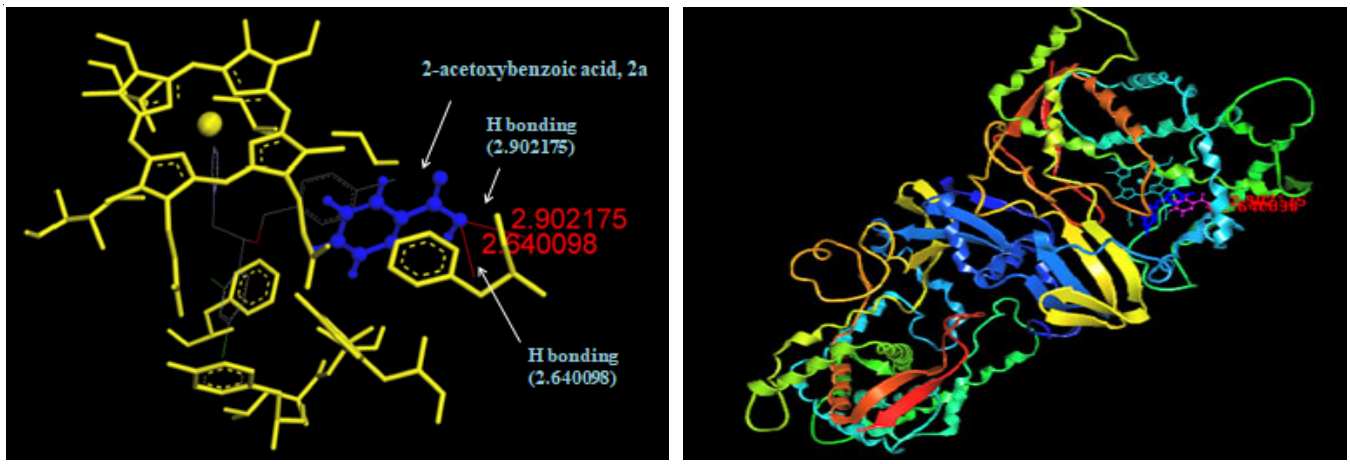


Fig. 1. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **2a** with 3JUS

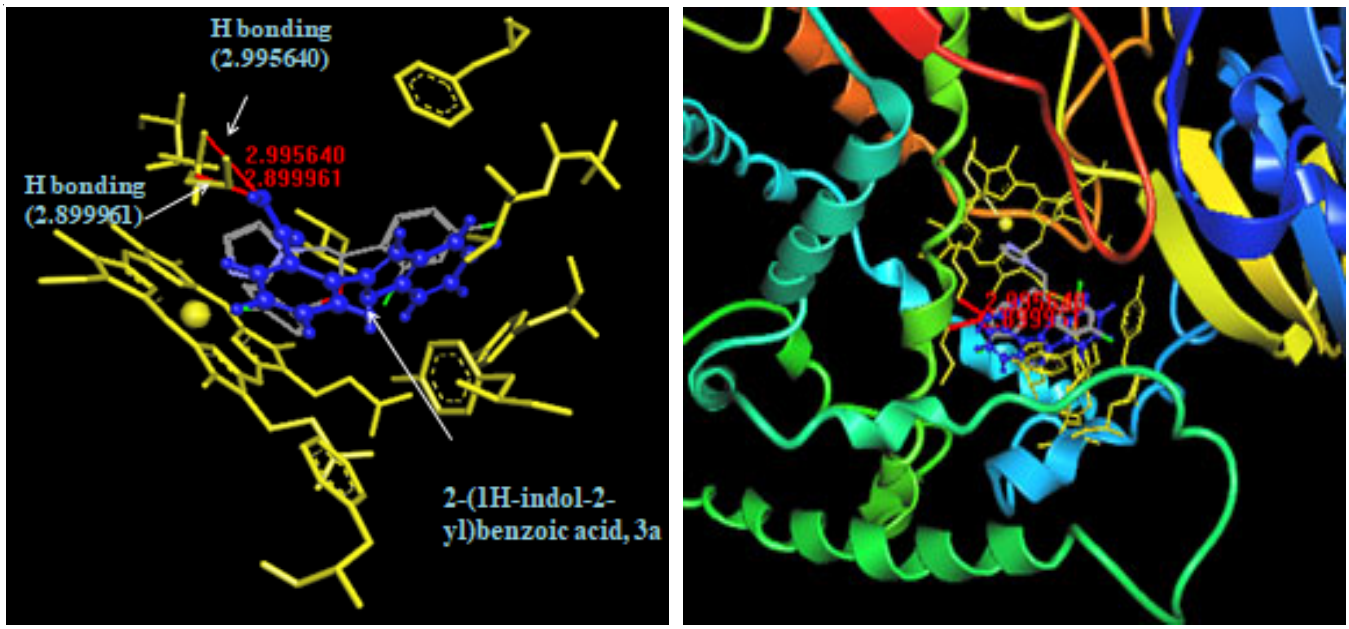


Fig. 2. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **3a** with 3JUS

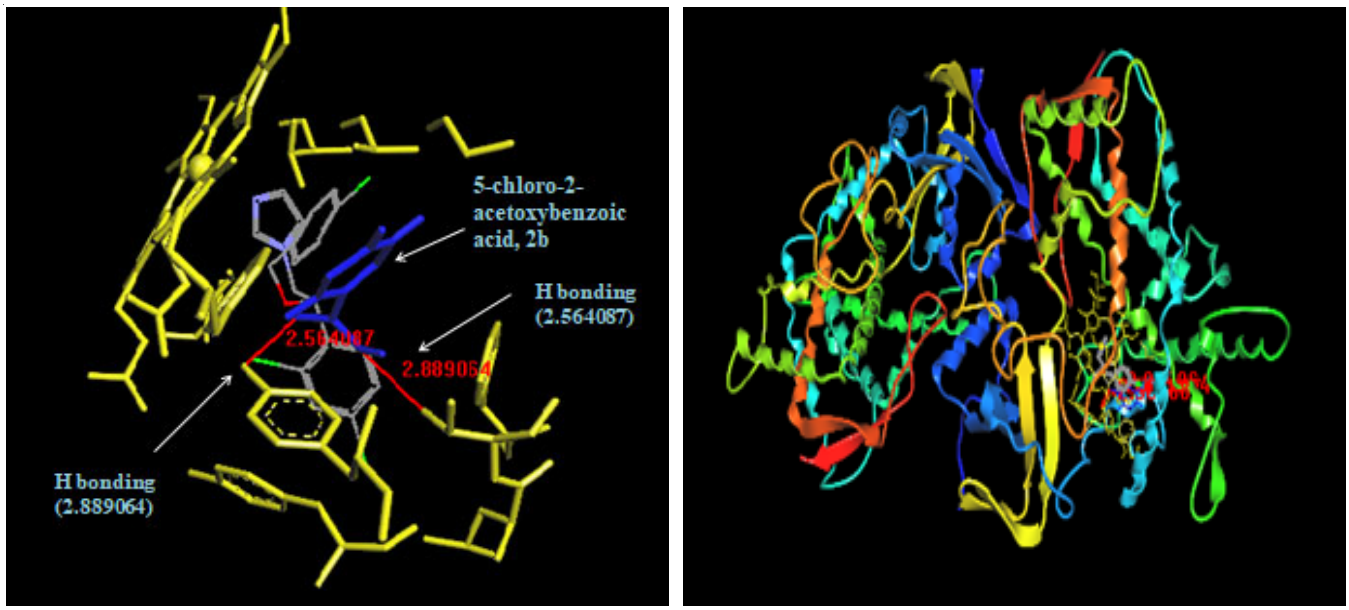


Fig. 3. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **2b** with 3JUS

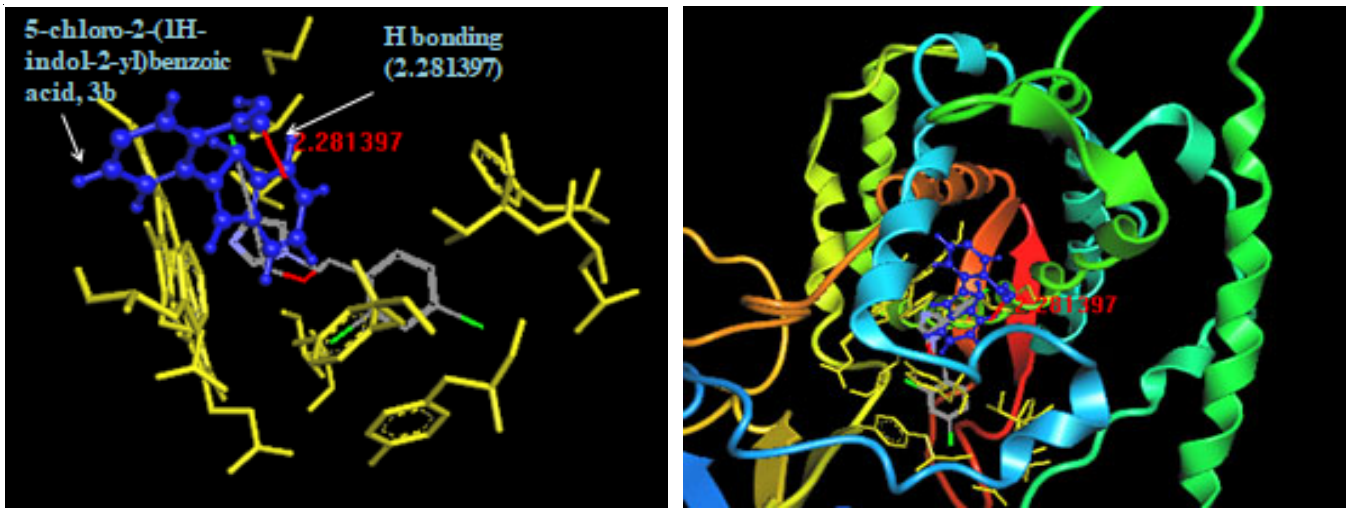


Fig. 4. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **3b** with 3JUS

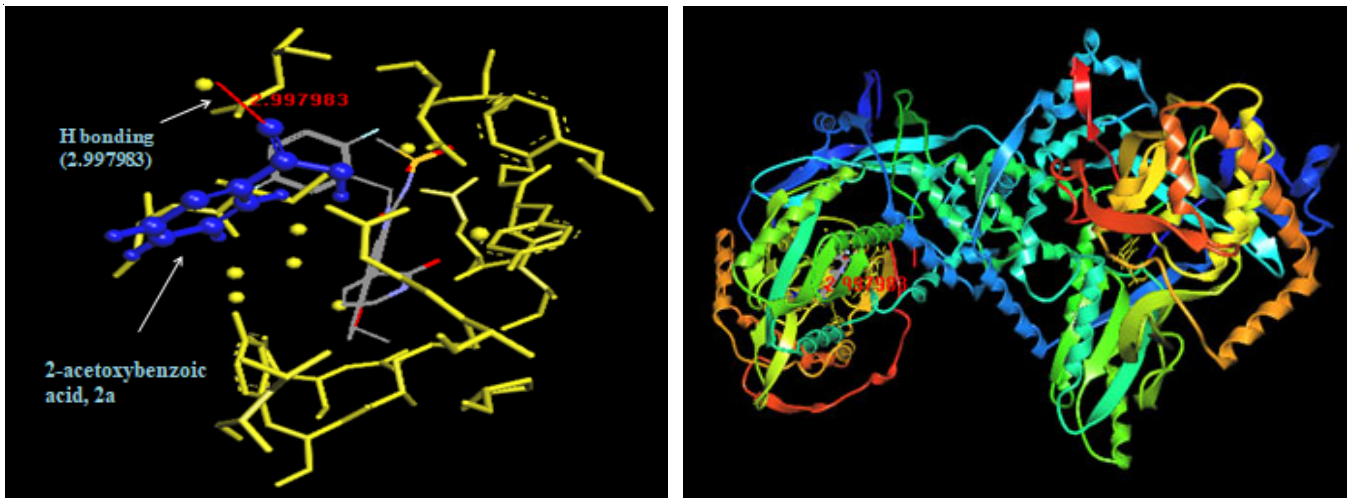


Fig. 5. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **2a** with 3UPI

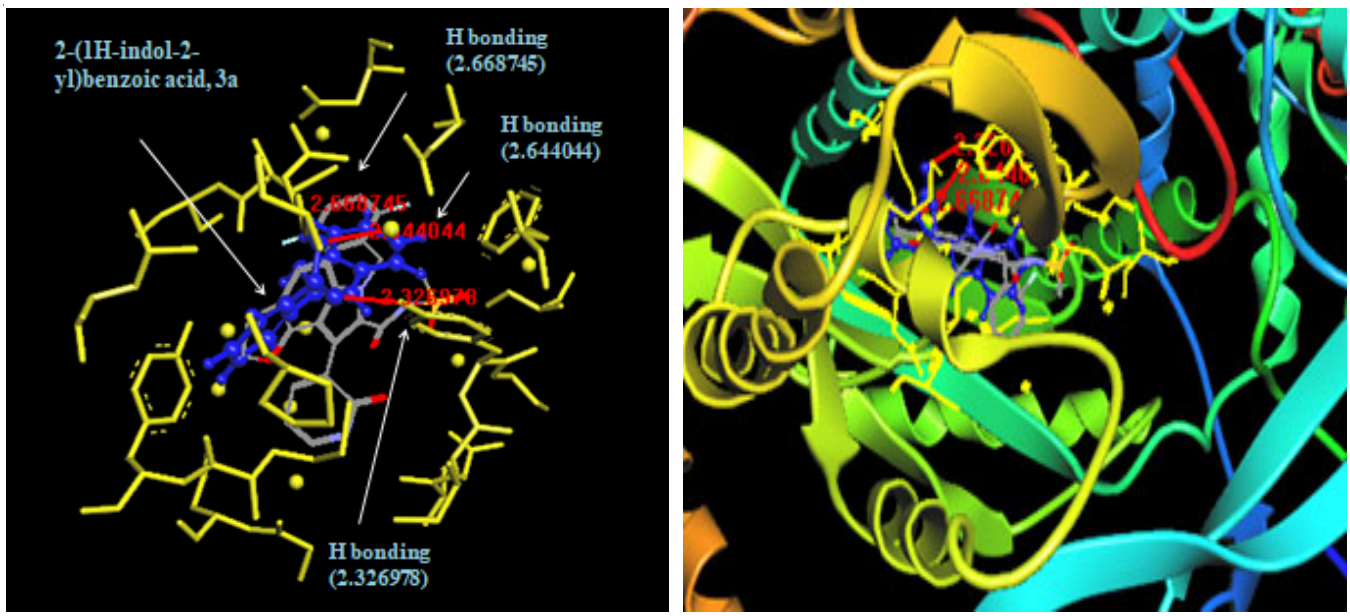


Fig. 6. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **3a** with 3UPI

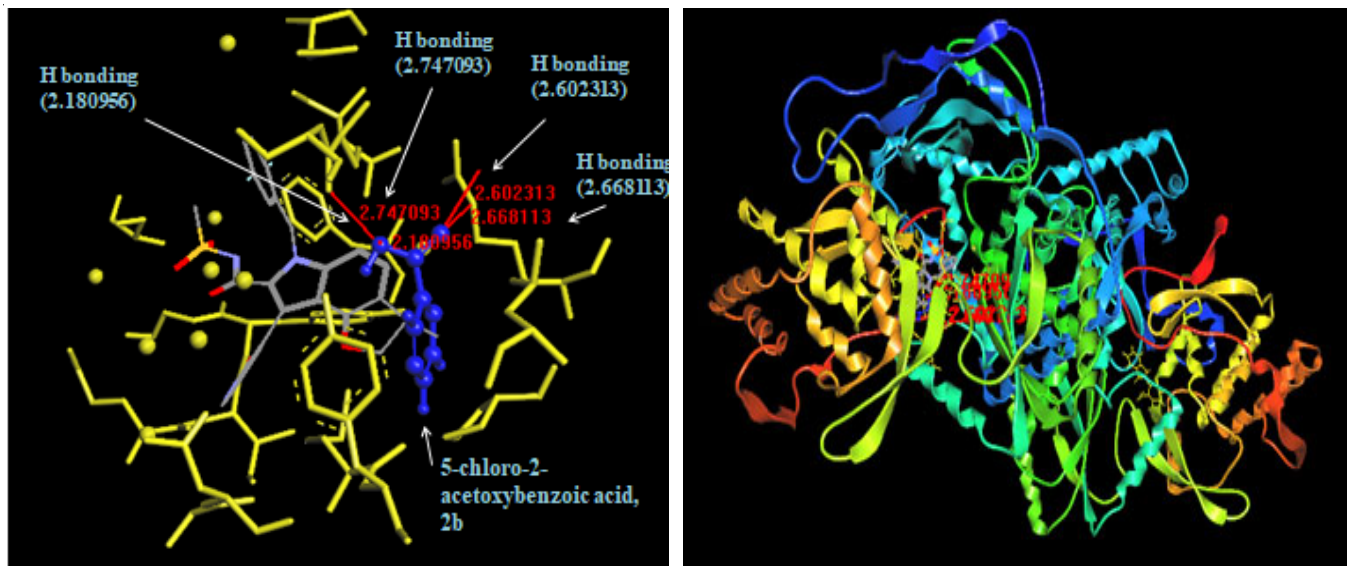


Fig. 7. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **2b** with 3UPI

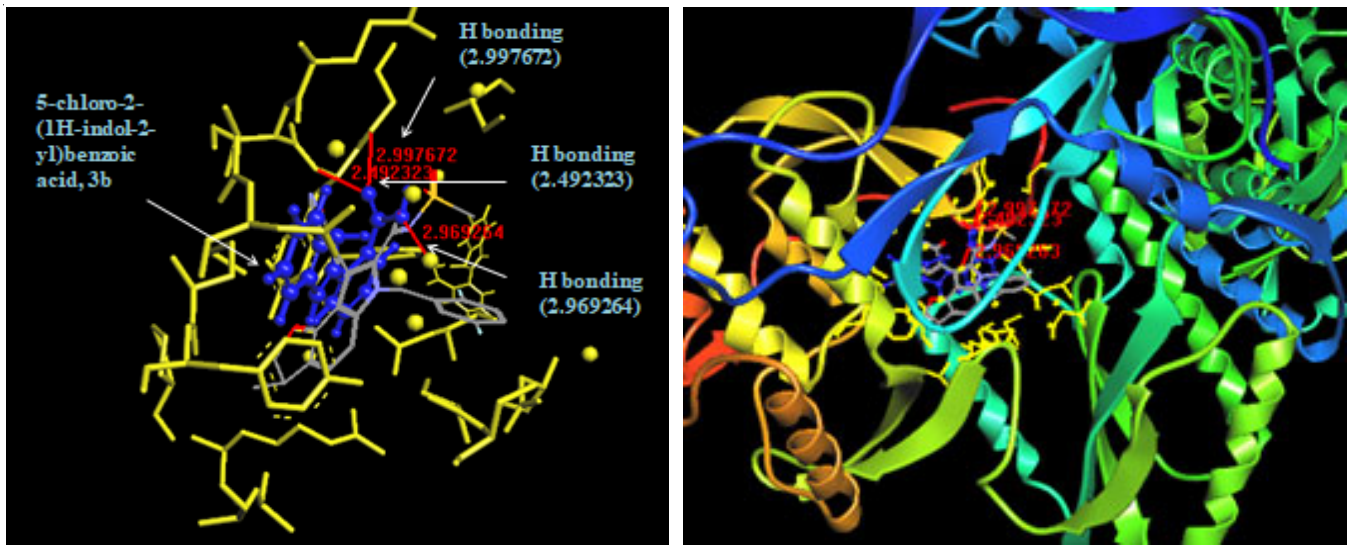


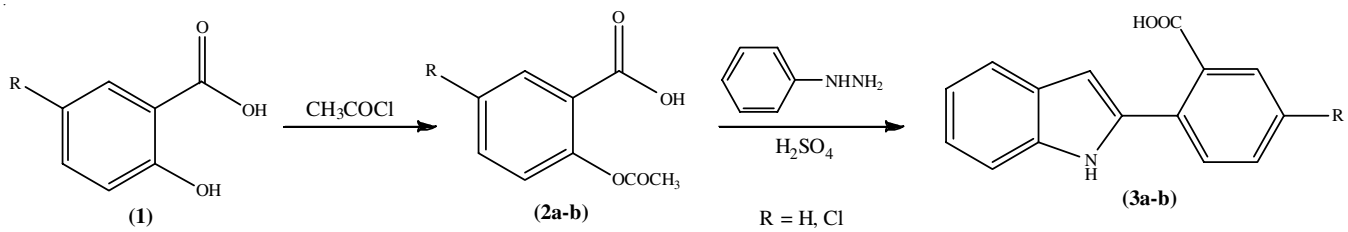
Fig. 8. Molecular docking of colour ribbon as chain position and render protein as cartoon ribbon for compound **3b** with 3UPI

TABLE-1
MOLECULAR DOCKING STUDIES OF SYNTHESIZED COMPOUNDS WITH TARGET PROTEIN 3JUS

Compd.	Clustering the final poses	Best ligand pose; energy	Docking run: Elapsed time	Few binding amino acids	H-bonding
2a	76	-8.5891 kcal/mol	14 s	579 LEU: alpha helix	2.640098
				590 TYR: coil	2.902175
3a	39	-10.8163 kcal/mol	9 s	752 GLY: coil,	2.995640
				580THR: alpha helix	2.899961
2b	81	-8.06182 kcal/mol	12 s	579 LEU: alpha helix	2.889064
				590 TYR: coil	2.564087
3b	39	-11.1354 kcal/mol	12 s	756 ALA: alpha helix	2.281397

TABLE-2
MOLECULAR DOCKING STUDIES OF SYNTHESIZED COMPOUNDS WITH TARGET PROTEIN 3UPI

Compd.	Clustering the final poses	Best ligand pose; energy	Docking run: Elapsed time	Few binding amino acids	H-bonding
2a	74	-8.14089 kcal/mol	18 s	973 GLY: alpha helix	2.997983
3a	50	-9.17851 kcal/mol	10 s	763 AGR: alpha helix	2.326978
				1009 GLY: beta strand	2.644044
				978 TYR: coil	2.668745
2b	71	-8.01004 kcal/mol	14 s	879 ASN: beta strand	2.602313
				1009 GLN: beta strand	2.668113
				973 GLY: alpha helix	2.747093
				1011 TYR: coil	2.180956
3b	44	-9.54722 kcal/mol	14 s	763 AGR: alpha helix	2.969264
				1009 GLY: beta strand	2.492323
				978 TYR: coil	2.997672



Scheme-I

through H-bonding (2.995640 and 2.899961) with best ligand pose energy -10.8163 kcal/mol with docking run: elapsed time 9 swith 3JUS protein (Fig. 2). Further, compound **3a** had been found docked with binding amino acids such as 763 AGR:alpha helix, 1009 GLY: beta strand, 978 TYR:coil, *etc*. through H-bonding (2.326978, 2.644044 and 2.668745) with best ligand pose energy -9.17851 kcal/mol with docking run: elapsed time 10 s with 3UPI protein (Fig. 6). Compound **3b** had been found docked with binding amino acid 756 ALA:alpha helix through H-bonding (2.281397) with best ligand pose energy -11.13541

kcal/mol with docking run: elapsed time 12 s with 3JUS protein (Fig. 4). Further compound **3b** had been found docked with binding amino acids such as 763 AGR: alpha helix, 1009 GLY:beta strand, 978 TYR:coil through H-bonding (2.969264, 2.492323 and 2.997672) with best ligand pose energy -9.547221 kcal/mol with docking run: elapsed time 14 s with 3UPI protein (Fig. 8). The present work clearly stated about few synthesized new salicylic acid derivatives and their pharmacological profiles which may contribute in future to synthesize various analogues and to develop new less toxic pharmacological drugs.

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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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