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Der Pharma Chemica, 2014, 6(6):411-417
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and molecular docking studies of new substituted indazole derivatives for anti-breast cancer activity

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ABSTRACT

*New substituted indazole derivatives were synthesized and studied their docking properties. Their computational docking analysis supported them as good therapeutic agents to the breast cancer aromatase enzyme and ascertained **5f** as potential molecules with good binding affinities varying from -8.0 kcal/mol and formed contacts with the NH1 & NH2 atoms of Arg115 by the distance of 3.3 & 3.2 A^{o} respectively. Compound **5g** and compound **5n** has shown similar binding energy of -7.7 kcal/mol. Majority of the compounds shown interaction with active site residues of Arg115 and Met374, respectively.*

Keywords: Indzoles , Neat synthesis, Docking studies

INTRODUCTION

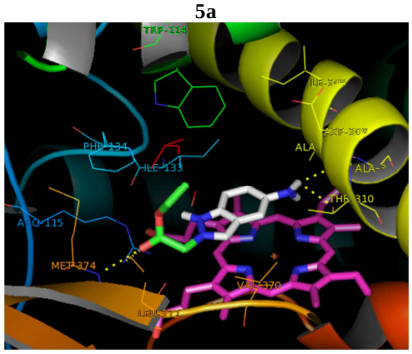
Nitrogen containing heterocycles represent an important and attractive area of organic chemistry, because of their chemical and/or biological significance. In fact, pyrazoles are known for their wide range of pharmacological applications as herbicides, antipsychotic, antibacterial, antimycotic and anti-inflammatory agents.[1-3] Benzocondensation to the pyrazole nucleus, leads to indazole derivatives. These are rare in Nature.[4] To date, only three natural products possessing the indazole ring have been isolated: Nigellicine, Nigeglanine, and Nigellidine. Moreover, Indazoles are reported to be endowed with remarkable antitumour activity by different mechanisms. Lonidamine (LND) is a potent antitumor drug, used in the treatment of several neoplasia as breast, lung, kidney, bladder as well as sarcomas of soft tissue acting via inhibition of the energy metabolism, nowadays in phase III clinical trials.5-7. However, some indazole derivatives have been developed to give leads in medicinal chemistry such as 7-NI (nitric oxide synthase inhibitor),[8] YC-1 (guanylyl cyclase activator),[9] granisetron (5HT-3 receptor antagonist),[10] lonidamine (cytotoxic modulator),[11] SE063 (HIV protease inhibitor),[12] and recently with new protein kinase Cb inhibitors[13] and oestrogen receptor ligands.[14] As mentioned in literature, numerous examples of indazolyl heterocycles exhibit biological properties as well as anticoagulating agent,[15] topoisomerase bacterium II inhibitor,[16] or for treatment of hypercholesterol,[17] tuberculosis[18]. Due to the medicinal and pharmaceutical interest concerning the specific substitution pattern of 2H-indazoles, some synthetic methods have been developed.[19] Encouraged by the above facts, the present group has been interested for design and synthesis of new indazole libraries and performed docking studies for the identification of good biological molecules leads to further biological evaluations.

MATERIALS AND METHODS

All the synthesized compounds were drawn using Chemdraw software. Crystal structure of Aromatase (PDBID: 3EQM) All the molecules were uploaded and energy minimized using Autodock Vina and PyRx (Wolf, 2009). Further, docking studies were carried out by using Lamarkian genetic algorithm (Solis, 1981) with the parameters such as number of individual population (150), max no. of energy evaluation (25000), max no of generation (27000), top individual to survive to next generation (1), gene mutation rate (0.02), crossover rate (0.8), Cauchy beta (1.0) and GA window size (10.0). The grid was set at Center_x = 83.4148, Center_y = 50.1414, Center_z = 46.3575, Size_x = 61.9584512329, Size_y = 71.94351408, Size_z = 51.4653416252 for Aromatase and exhaustiveness 8. Bond distance, bond angles, Hydrogen bonding interactions between ligand and protein molecules were assessed using PyMol.

Figures

5a



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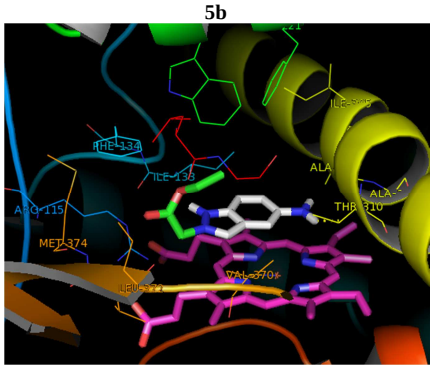

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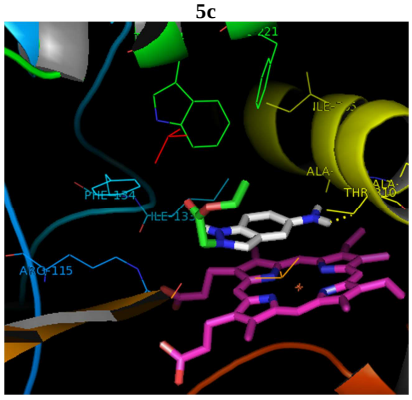

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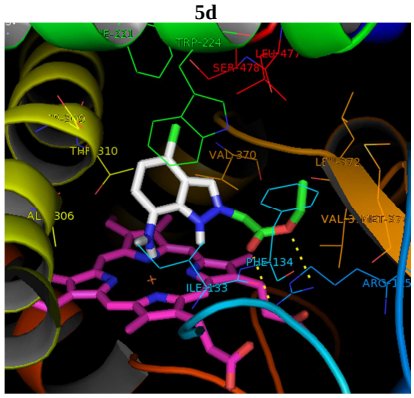

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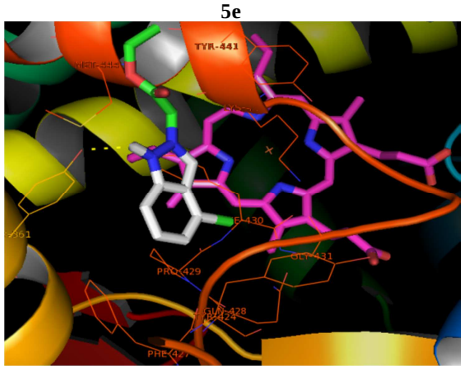

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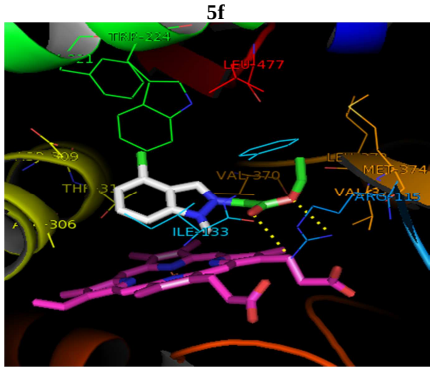

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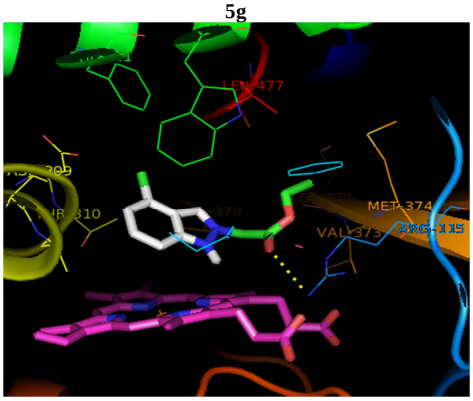

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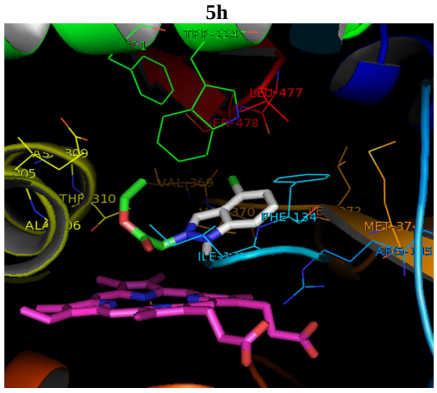

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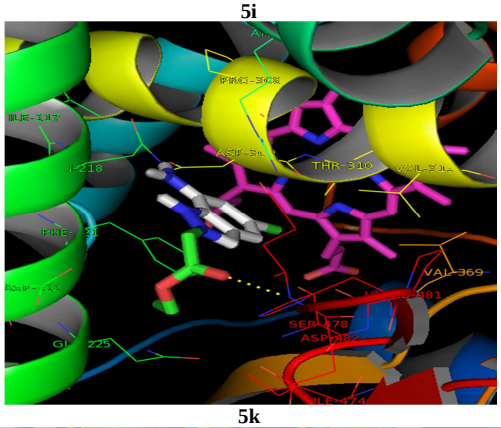

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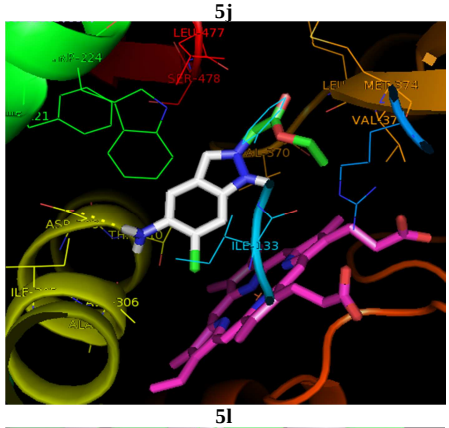

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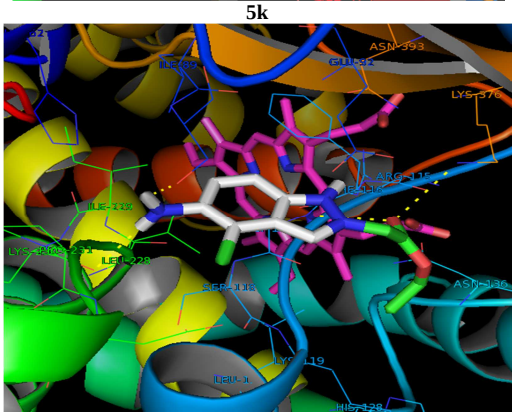

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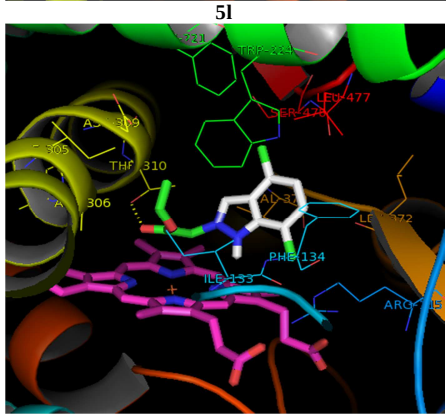

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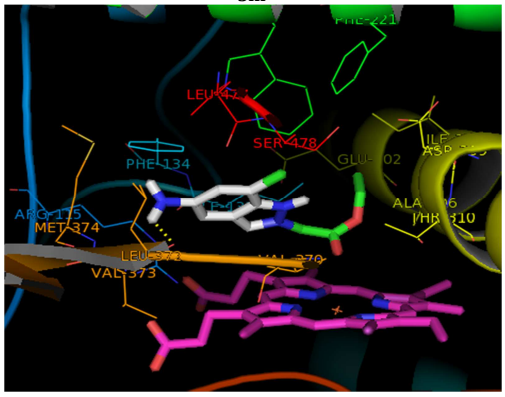

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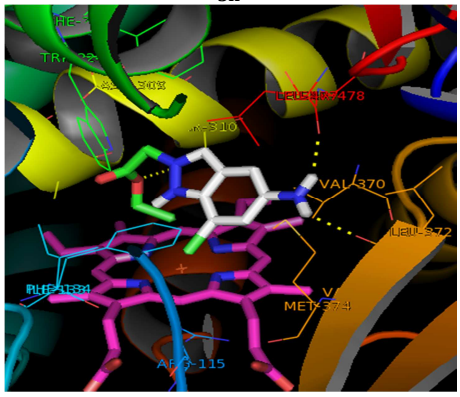


Table 1: Hydrogen bonding integrations, distances, angles, atoms involved in angle and binding energies of synthesized compound with the active site residues of aromatase

S. No	Compound	Hydrogen bonding interactions		Distance	Angle	Atoms involved in angle	Binding energy
		Protein	Ligand				
1	5a	Arg115NH1----------OC14 Met374N----------OC14 Ala306O----------HN9 Thr310OG1----------HN9		3.1 3.1 2.5 2.6	131.9 123.6 115.5 113.3	C-O-OC C-N-O C-O-HN9 CB-OG1-HN9	-7.6
2	5b	Thr310OG1----------HN9		1.9	124.1	CB-OG1-HN9	-7.5
3	5c	Thr310OG1----------HN9		1.9	125.5	CB-OG1-HN9	-7.6
4	5d	Arg115NH1----------OC19 Arg115NH2----------OC15		3.1 3.2	118.8 55.1	C-O-HN2 C-O-HN1	-7.6
5	5e	Tyr361OH----------HN11		2.1	129.7	N-H-OH	-5.7
6	5f	Arg115NH1----------OC17 Arg115NH2----------OC13		3.3 3.2	51.2 108.5	C-O-NH1 C-O-NH2	-8
7	5g	Arg115NH2----------OC13		3.1	135.6	C-O-NH2	-7.7
8	5h	Arg115, Ile133, Phe134, Met374, Trp224, Ile305, Asp309, Thr310					-7.1
9	5i	Asp309OD1----------HN11 Glu483N----------OC16		2.1 3.4	152.0 102.5	N-H-OD1 C-N-OC	-6.6
10	5j	Asp309OD1----------HN10		2.5	119.7	CG-OD2-HN10	-7.4
11	5k	Ser90OG----------HN11 Lys230O----------HN10 Gly117N----------OC15 Lys376NZ----------OC15		2.1 2.4 3.4 3.4	124.8 104.5 103.9 120.4	OG-H-N C-O-HN N-C-OC NE2-CE-OC	-6.3
12	5l	Thr310OG1----------OC14		2.9	125.0	CB-OG1-OC	-7.4
13	5m	Leu372O----------HN10		2.6	110.6	C-O-HN	-7.4
14	5n	Leu372O----------HN10 Leu477O----------HN11 Thr310OG1----------OC19		2.4 2.0 3.3	111.8 161.1 106.6	O-H-N C-O-HN CB-OG1-OC	-7.7

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were recorded on an FTIR spectrometer (KBr) and reported in reciprocal centimeters (cm^{-1}). NMR spectra were recorded for 1H NMR at 300MHz, 500MHZ and for 13C NMR at 75MHz. For 1H NMR, tetramethylsilane (TMS) served as internal standard (δ = 0) and data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t= triplet, q =quartet, m = multiplet, br = broad) and coupling constant in Hz. For 13C NMR, $CDCl_3$ (δ = 77.27) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data were obtained using Electrospray ionization (ESI) ionization.

Preparation of 2-Indazole derivatives 5(a-n)

Substituted indazole (1 eq) and bromo ethylacetate (2 eq) were heated at 120^0c for overnight then the reaction mass was cooled to room temperature and dissolved ethylacetate (20 mL), saturated sodium bicarbonate (15 mL). The organic layer was washed with brine solution, dried with sodium sulphate, concentrated. The residue was purified by silica gel column chromatography on silica gel using using Hexane/EtOAc (7:3).as eluent to afford compound **5 (a-**

ethyl 2-(5-amino-2H-indazol-2-yl)acetate (5a) :

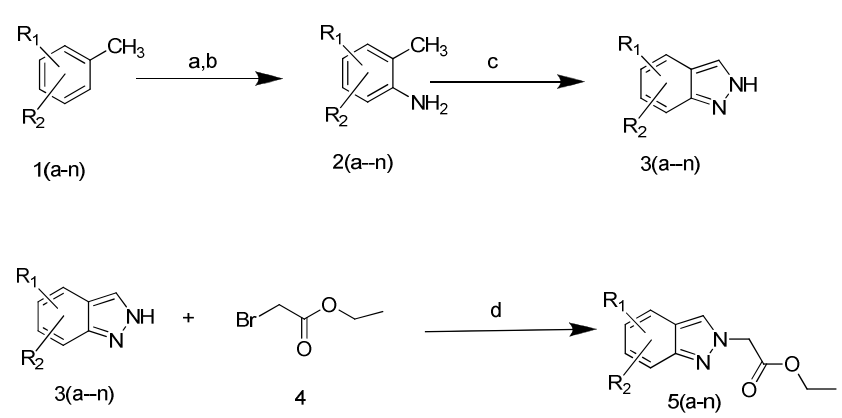
Yellow solid; **mp:** 126-128 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H), 4.26 (q, 2H), 5.15 (s, 2H), 6.52 (s, 1H), 6.75 (d, 1H), 7.56 (d, 1H), 7.76 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.1, 55.9, 60.0, 99.9, 115.2, 117.0, 121.1, 130.8, 137.9, 146.7, 166.7 ; **MASS**: m/z calcd for $C_{11}H_{13}N_3O_2$ $(M+H)^+$ 219.2.

ethyl 2-(6-amino-2H-indazol-2-yl)acetate (5b) :

Yellow solid; **mp:** 135-137 °C ; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H), 4.26 (q, 2H), 5.15 (s, 2H), 6.62 (d, 1H), 6.82 (s, 1H), 7.54 (d, 1H), 7.85 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.1, 55.8,60.0, 90.6, 108.7, 112.2, 120.2, 121.1, 145.7, 154.0, 166.7 ; **MASS**: m/z calcd for $C_{11}H_{13}N_3O_2$ $(M+H)^+$ 219.2.

ethyl 2-(7-amino-2H-indazol-2-yl)acetate (5c) :

Yellow solid; **mp:** 141-143 °C ; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.45 (t, 3H), 4.26 (q, 2H), 5.15 (s, 2H), 6.48 (d, 1H), 6.92 (t, 1H), 7.08 (d, 1H), 7.94 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.1, 55.9, 60.1, 108.5, 112.1, 119.4, 121.0, 126.0, 127.2, 131.7, 166.7 ; **MASS**: m/z calcd for $C_{11}H_{13}N_3O_2$ $(M+H)^+$ 219.2.



	R_1	R_2
a	H	NH_2
b	H	NH_2
c	H	NH_2
d	Cl	NH_2
e	Cl	H
f	Cl	H
g	Cl	H
h	Cl	H
i	Cl	NH_2
j	Cl	NH_2
k	Cl	NH_2
l	Cl	Cl
m	Cl	NH_2
n	Cl	NH_2

Synthetic route to compound 5(a–n). Reagents: (a) $SnCl_2.2H_2O$, HCl, EtOH; (b) KNO_3, H_2SO_4; (c) step-1.$NaNO_2$, HCl then $NaBF_4$, H_2O; step-2.AcOK, 18-crown-6, $CHCl_3$; (d) Neat, Reflux 120^{0}C

Scheme 1. Synthesis of indazole

n)

ethyl 2-(7-amino-4-chloro-2H-indazol-2-yl)acetate (5d) :
Yellow solid; **mp:** 166-168 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.43 (t, 3H), 4.26 (q, 2H), 5.15 (s, 2H), 6.48 (d, 1H), 7.08 (d, 1H), 7.94 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.1, 55.8, 60.6, 114.4, 116.8, 121.7, 122.6, 126.8, 129.9, 132.0, 166.8 ; **MASS**: m/z calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

ethyl 2-(4-chloro-2H-indazol-2-yl)acetate (5e) :
Yellow solid; **mp:** 112-114 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 4.29 (q, 2H), 5.35 (s, 2H), 7.16 (d, 1H), 7.22 (d, 1H), 7.62 (d, 1H), 8.12 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 13.8, 56.2, 61.4, 114.4, 118.0, 121.1, 122.6, 126.8, 129.9, 150.6, 167.4; **MASS**: m/z calcd for $C_{11}H_{11}ClN_2O_2$ $(M+H)^+$ 238.7.

ethyl 2-(5-chloro-2H-indazol-2-yl)acetate (5f) :
Yellow solid; **mp:** 139-141 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H), 4.26 (q, 2H), 5.19 (s, 2H), 7.23 (d, 1H), 7.62 (dd, 2H), 8.02 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 13.8, 56.1, 61.3, 114.9, 118.5, 121.6, 123.8, 129.5, 130.4, 150.5, 167.7; **MASS**: m/z calcd for $C_{11}H_{11}ClN_2O_2$ $(M+H)^+$ 238.7.

ethyl 2-(6-chloro-2H-indazol-2-yl)acetate (5g) :
Yellow solid; **mp:** 109-111 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.31 (t, 3H), 4.28 (q, 2H), 5.20 (s, 2H), 7.08 (d, 1H), 7.62 (d, 1H), 7.70 (s, 1H), 8.08 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.1, 55.6, 60.2, 109.6, 119.1, 120.1, 122.1, 122.9, 131.5, 151.7, 166.6; **MASS**: m/z calcd for $C_{11}H_{11}ClN_2O_2$ $(M+H)^+$ 238.7.

ethyl 2-(7-chloro-2H-indazol-2-yl)acetate (5h) :
Yellow solid; **mp:** 150-152 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H), 4.26 (q, 2H), 5.28 (s, 2H), 7.08 (t, 1H), 7.70 (d, 2H), 7.62 (d, 1H), 8.14 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.2, 55.6, 60.3, 116.5, 119.3, 121.5, 122.9, 126.4, 127.6, 149.2, 166.5; **MASS**: m/z calcd for $C_{11}H_{11}ClN_2O_2$ $(M+H)^+$ 238.7.

ethyl 2-(7-amino-5-chloro-2H-indazol-2-yl)acetate (5i) :
Yellow solid; **mp:** 121-123 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H), 4.25 (q, 2H), 5.18 (s, 2H), 6.40 (s, 1H), 7.06 (s, 1H), 7.86 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.0, 55.5, 59.8, 106.3, 112.0, 120.8, 127.5, 128.7, 131.6, 132.5, 166.6; **MASS**: m/z calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

ethyl 2-(5-amino-6-chloro-2H-indazol-2-yl)acetate (5j) :
Yellow solid; **mp:** 130-132 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132,

1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H), 4.30 (q, 2H), 5.11 (s, 2H), 6.90 (s, 1H), 7.28 (d, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.2, 55.7, 60.1, 99.6, 108.3, 116.2, 121.4, 127.1, 138.8, 139.9, 166.7; **MASS**: *m/z* calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

ethyl 2-(5-amino-4-chloro-2H-indazol-2-yl)acetate (5k) :
Yellow solid; **mp:** 133-135 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H), 4.42 (q, 2H), 5.18 (s, 2H), 6.90 (d, 1H), 7.49 (d, 1H), 7.88 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 14.0, 55.5, 59.8, 112.0, 116.4, 120.8, 121.6, 125.8, 139.5, 142.3, 166.6; **MASS**: m/z calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

ethyl 2-(4,7-dichloro-2H-indazol-2-yl)acetate (5l) :
Yellow solid; **mp:** 117-119 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 4.22 (q, 2H), 5.16 (s, 2H), 7.22 (d, 1H), 7.47 (d, 1H), 8.11 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 13.8, 56.3, 61.2, 113.1, 121.3, 123.4, 126.0, 129.2, 150.1, 156.6, 166.6; **MASS**: m/z calcd for $C_{11}H_{10}Cl_2N_2O_2$ $(M+H)^+$ 273.1.

ethyl 2-(5-amino-7-chloro-2H-indazol-2-yl)acetate (5m) :
Yellow solid; **mp:** 101-103 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H), 4.28 (q, 2H), 5.18 (s, 2H), 6.70 (s, 1H), 6.91 (s, 1H), 7.82 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 13.8, 56.3, 61.3, 113.1, 121.3, 123.4, 126.0, 129.2, 150.1, 156.6, 166.5; **MASS**: m/z calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

ethyl 2-(6-amino-4-chloro-2H-indazol-2-yl)acetate (5n) :
Yellow solid; **mp:** 144-146 °C; **IR** (KBr) 2982, 1705, 1664, 1591, 1512, 1468, 1371, 1345, 1269, 1200, 1132, 1063 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.34 (t, 3H), 4.29 (q, 2H), 5.13 (s, 2H), 6.63 (d, 2H), 7.94 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) 13.8, 56.1, 61.3, 96.0, 105.1, 116.4, 122.5, 130.2, 137.4, 145.8, 167.6; **MASS**: m/z calcd for $C_{11}H_{12}ClN_3O_2$ $(M+H)^+$ 253.7.

RESULTS AND DISCUSSION

New substituted indazoles **5(a–n)** were synthesized according to Scheme 1. Readily available starting materials and simple synthesizing procedures made this method very attractive and convenient for the synthesis of various indazole derivatives. Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C NMR and mass spectra. Indazoles were prepared from the simple, starting compounds **2(a–n)** and, **3(a–n)** were prepared as per the literature procedure [20]. Dehydrohalogenation of compound **3(a–n)** with bromoethylacetate (**4**) in ethylacetate as a solvent formed the target molecules **5(a–n).** In this reaction there is a possibility to formation of isomers. The other isomer if any formed during the course of the reaction was not isolated. However, only one pure regioisomer was isolated under the applied reaction conditions. All these synthesized compounds tested for docking properties. Encouraged by the below results we further plan to study their biological assays.

The docking study of **5(a–n)** with the therapeutically potential target of breast cancer aromatase enzyme (PDB: 3EQM) showed that multiple functional group centers of the amino acid residues of Arg115NH1, Met374N, Ala306O, Thr310OG1, Arg115NH2, OC19 of the enzyme aromatase play key role in binding the test compounds through hydrogen bonding interactions with their NH_2 and Cl groups. The results showed that all the compounds **5(a–n)** possessed good binding energy toward aromatase enzyme.

A molecular docking study was performed for the aromatase with fourteen synthesized derivatives and results furnished in Table 1. Compound **5f** showed highest binding energy of-8.0 kcal/mol and formed contacts with the NH1 & NH2 atoms of Arg115 by the distance of 3.3 & 3.2 A^o respectively (**Fig 5f**). Compound **5g** and, compound **5n** have shown similar binding energy of -7.7 kcal/mol and formed contacts with the NH2 atom of Arg115, OG1 atom of Thr310, O atom of Leu372 and O atom of Leu477 respectively (**Fig 5g&5n**). Compound **5a**, Compound **5c** & Compound **5d** have shown binding energies of -7.6kcal/mol and, formed contacts with the NH1 and NH2 atoms of Arg115, O atom of Ala306, OG1 atom of Thr310 and N atom of Met 374 respectively (**Fig 5a, 5c, 5d**). Compound **5b**, Compound **5j**, Compound **5l** & Compound **5m** have shown binding energy of -7.5, -7.4, -7.4, and -7.4 respectively and interacted with the OG1 atom of Thr310, and O atom of Leu372 respectively (**Fig 5b**, **5j**, **5l** & 5**m**). Compound **5h** has shown binding energy of -7.1 and, interacted hydrophobically with the residues of Arg115, Ile133, Phe134, Met374, Trp224, Ile305, Asp309 and, Thr310 respectively (**Fig 5h).** Compound **5i** and, Compound

5k have shown binding energies of -6.6 & -6.3 kcal/mol and, formed interactions with the OD1 atom of Asp309, N atom of Glu483, N atom of Gly117, O atom of Lys230, N atom of Lys376 and, OG atom of Ser90 respectively (**Fig 5i & 5k**). Compound **5e** has exerted moderate binding energy of -5.7 and formed one contacts with the OH atom of Thr361 respectively **(Fig 5e).** The docking results reveal that majority of the compounds were shown best binding affinities and made interaction with non polar residue of Met374 and basic residue of Arg115 which play a major role in catalysis of the testosterone to estradiol, respectivley.

CONCLUSION

We developed new substituted indazole derivatives and perfoemed their docking studies. Compound **5f** has shown highest binding energy of-8.0 kcal/mol and formed contacts with the NH1 & NH2 atoms of Arg115 by the distance of 3.3 & 3.2 A^o respectively. Compound **5g** and **5n** shown similar binding energy of -7.7 kcal/mol

Acknowledgement
The author M. Thirupalu Reddy are also thankful to Professor B. V Subba Reddy, senior scientist, organic division, Indian Institute of Chemical Science, Hyderabad, for providing laboratory facilities. And also thankful B. Vijaya Bhaskar Division of Molecular Biology, Department of Zoology, Sri Venkateswara University, Tirupati, India for Molecular Docking Studies

REFERENCES

[1] D. Nauduri, G. Reddy, *Chem. Pharm. Bull.* **1998**, *46*, 1254–1260.
[2] K. Tsuji, K. Nakamurana, N. Konishi, T. Tojo, T. Ochi, H. Scnoh, M. Masuo, *Chem. Pharm. Bull*. **1997**, *45*, 987–995.
[3] K. Brune, *Med. Chem. Toxicol*. **1986**, *1*, 1–9.
[4] A. Schmidt, *Adv. Heterocycl. Chem*. **2003**, *85*, 67–171.
[5] A. Floridi, M. G. Paggi, M. L. Marcante, B. Silvestrini, A. Caputo, C. De Martino,*J. Natl. Cancer Inst.* **1981**, *66*, 497–499.
[6] B.-Y. Oded, J. C. Lyons, W. S. Chang, B. D. Ross, *J. Neuro-Oncol*. **1998**, *36*,149–157.
[7] S. Di Cosimo, G. Ferretti, P. Papaldo, P. Carlini, A. Fabi, F. Cognetti, *Drugs Today* **2003**, *39*, 157–173.
[8] P. K. Moore, P. Wallace, Z. Gaffen, S. L. Hart, R. C. Br. Babbedge, *J. Pharmacol*. **1993**, *110*, 219–224.
[9] C. C. Wu, F. N. Ko, S. C. Kuo, F. Y. Lee, C. M. Br Teng, *J. Pharmacol*. **1995**, *116*, 1973–1978.
[10] G. J. Sanger, D. R. Nelson, *Eur. J. Pharmacol*. **1989**, *159*, 113–124.
[11] R. Villa, L. Orlandi, A. Berruti, L. Dogliotti, N. Zaffaroni, *Int. J. Oncol*. **1999**, *14*, 133–138.
[12] Patel, M.; Rodgers, J. D.; McHugh, R. J., Jr.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Ko, S. S. Bioorg. Med. Chem. Lett. 1999, 9, 3217–3220.
[13] H. C. Zhang, C. K. Derian, D. F. McComsey, K. B. White, H. Ye, L. R. Hecker, J. Li, M. F. Addo, D. Croll, A. J. Eckardt, C. E. Smith, Q. Li, W. M. Cheung, B. R. Conway, S. Emanuel, K. T. Desmarest, P. Andrade-Gordon, B. P. Damiano, B. E. Maryanoff, *J. Med. Chem.* **2005**, *48*, 1725–1728.
[14] R. J. Steffan, E. Matelan, M. A. Ashwell, W. J. Moore, W. R. Solvibile, E. Trybulski, C. C. Chadwick, S. Chippari, T. Kenney, A. Eckert, L. Borges-Marcucci, J. C. Keith, Z. Xu, L. Mosyak, D. C. Harnish, *J. Med. Chem.* **2004**, *47*, 6435–6438.
[15] A. Kranjc, L. Peterlin-Masic, J. Ilas, A. Prezelj, M. Stegnar, D. Kikelj, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 3251–3256.
[16] J. J. M. Wiener, L. Gomez, H. Venkatesan, A. Jr. Santillan, B. D. Allison, K. L. Schwarz, S. Shinde, L. Tang, M. D. Hack, B. J. Morrow, S. M. Motley, R. S. Goldschmidt, K. J. Shaw, T. K. Jones, C. A. Grice, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 2718–2722.
[17] P. J. Connolly, C. D. Westin, A. D. Loughney, L. K. Minor, *J. Med. Chem*. **1993**, *36*, 3674–3685.
[18] S. Guo, Y. Song, Q. Huang, H. Yuan, B. Wan, Y. Wang, R. He, M. G. Beconi, S. G. Franzblau, A. P. Kozikowski, *J. Med. Chem*. **2010**, *53*, 649–659.
[19] (a) A. Schimdt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, 4073–4095; (b) A. Schimdt, A. Dreger, *Curr. Org. Chem.* **2011**, *15*, 1423–1463.
[20] I. Shimada, K. Maeno, K-i. Kazuta, H. Kubota, T. Kimizuka, Y. Kimura, K-i Hatanaka, Y. Naitou, F. Wanibuchi, S. Sakamoto, S.-i. Tsukamotoa, *Bioorg. Med. Chem.* **2008** 16, 1966–1982