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Proceeding Paper

Synthesis of a novel series of substituted1-(3,6-dimethyl-4- phenyl-1 H-indazol-5-yl) ethan-1-one derivatives and evaluations of their antimicrobial, antioxidant activity with Insilco docking study†

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Abstract

We describe here the in silico design, synthesis and biological evaluation of four novel effective 1-(3,6-dimethyl-4-phenyl-1H-indazol-5-yl)ethan-1-one derivatives synthesized from the treatment of hydrazine hydrates in MeOH/H+ with 1,1'-(3-hydroxy-4'-methoxy-5-methyl-[1,1'-biphenyl]-2,6-diyl) bis(ethan-1-one). The structures of all new compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis. The synthesized compounds are screened for their antimicrobial, antioxidant activity, the compounds 1-(3,6-dimethyl-4-phenyl- 1*H*- indazol-5-yl) ethan-1-one 5a, 1-(4-(3,4-dimethoxyphenyl)-3,6-dimethyl-1H- indazol-5-yl) ethan-1-one 5b, and 1-(3,6-dimethyl-4- (2,3,4-trimethoxyphenyl)-1H-indazol-5-yl)ethan-1-one 5d display prominent antimicrobial, antioxidant activity. Finally, a molecular docking analysis was performed to investigate the binding mode and interactions of the most active compounds to the active site of DNA gyrase enzyme 1KZN.

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Keywords : MultisubtitutedIndazole, NH_2-NH_2-H_2O, Molecular docking, antimicrobial, antioxidant activity

Introduction :

Indazole is an organic heterocyclic compound called isoindazole or benzo[c]pyrazole, 1,2-benzothiazole [1]. Indazole was initially named by Emil Fisher as a 'pyrazole ring fused with the benzene ring [2]. The continuous research on indazole due to its interesting chemical and biological properties. Indazole belongs to the azole family and posses' ten π-electron aromatic heterocyclic like that of pyrazole molecule and indazoles resemble pyridine and pyrrole. The indazole exists in 1H-, 2H- and 3H- three tautomeric [3]. However 3*H*-indazole have only few example are known, which carry alkyl or aryl groups on the five member ring and not calculated by this way because alkyl or aryl groups on the five members ring.[4]The example Pkb values for 1- methyl-1*H*-indazole is 0.42 but Pkb values for 2-methyl-2H-indazole is 2.02 that mean the 2H tautomer is stronger base than 1H tautomer. For identification of 1*H* tautomer and 2*H* tautomer the spectral studies ^{1}H, ^{13}C, ^{14}N and ^{15}N NMR is used [5-6]. World's largest trading drugs are nitrogen-containing heterocycles[7]. Indazole heterocyclic has two nitrogen atoms in the five-member ring. It is because of their availability all over in nature, they make them key scaffold of many biological and medicinally important molecules[8]. Indazole moiety has biological, agricultural, and industrial applications [9]. Indazole derivatives are medicinally important as they form the prin-

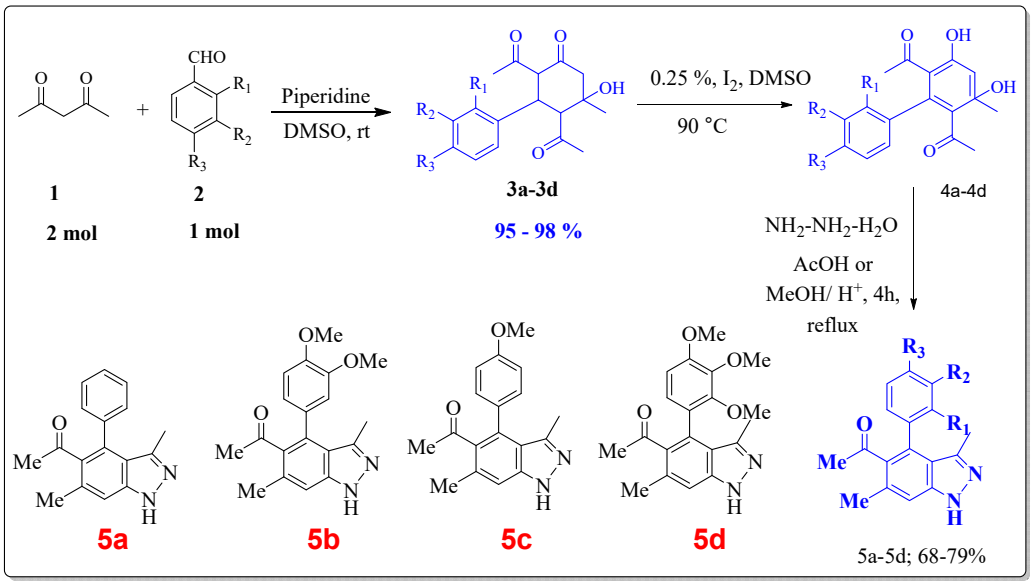
cipal skeleton of several drug molecules, such as Granisetron,[10]5-HT3 receptor antagonist used in cancer chemotherapy, and benzydamine an anti-inflammatory agent.[11] anti-tumor,[12]anti-HIV,[13] Antimicrobial,[14] and strongly Estrogen receptor.[15]This has aroused great interest in the development of novel indazole based therapeutic agent. The indazole scaffold ring skeleton is of great current interest as the partial structure of biologically active compounds. Some feature of pharmacological properties of indazoles has been reviewed in 2005.16,9 As per literature survey the indazole such as 1H-indazole, 2H-indazole and benzo[g]indazole has biological activity on their number of substitution on the ring[17].

In the pursuit of developing novel antimicrobial agents, herein we report the synthesis of some novel multi substituted hybrids indazole derivatives to investigate their potential antimicrobial activities.

Our research group is always interested in finding new heterocyclic compounds for biological testing [18]. In continuation of ongoing research aiming at finding new leads molecules with potential antimicrobial activities. Considering the medicinal utility of indazole, we attempted the molecular docking of novel multi substituted indazole derivatives with attractive targets Crystal Structure of E. coli 24kDa Domain in Complex with Clorobiocin [19].

Results and Discussion :

The starting precursor multisubstituted cyclohexanone derivatives (3a-3d) were prepared by the reaction of Knoevenagel/Michael/Aldol condensation of aromatic aldehyde and β-keto ketones in the presence of piperidine [20] Scheme 1. Next, the multisubstituted cyclohexanone derivatives were treated with 0.25 Equiv. of I_2/ DMSO in combination with 10 % Pd/C reagent at 90 °C afforded desired compound 4a-4d with 55-65% yield. The products were easily purified by column chromatography and confirmed by 1H, 13C NMR spectroscopy method. The 1HNMR product show singlet at 16.47 for 1H corresponding to the OH group. The peak at 2.26 is singlet for (s, 3H, CH3) and the peak at 1.71 and 1.70 for (two s, 6H, COCH3). The ^{13}CNMR shows the two signals at the downfield region at 205.60, 204.19 belong to the carbonyl carbon group. Based on the spectral signal the structure of the 4a was assigned to the exact structure. In continuation of our ongoing research of indazoles, then we move towards the synthesis of multi substituted indazole derivatives are prepared by treatment of 1,1'-(3-hydroxy-5-methyl- [1,1'-biphenyl] -2,6-diyl)bis(ethan-1-one) 4a with hydrazine hydrates in AcOH or MeOH/H+ solvent gave desired product 5a with 79% (Scheme 1).



Scheme 1. Synthesis of Multisubtituted indazole derivatives

The structures of all newly synthesized compounds were confirmed by IR, 1H NMR, 13C NMR, and mass spectral analysis. The IR spectra showed a peak at 3226 cm-1 is for the NH proton. The

peak at 1647 is for the carbonyl CO group. The ^{1}HNMR spectrum of compound 1-(3,6-dimethyl-4-phenyl-1H-indazol-5-yl)ethan-1-one 5a showed the signal at 13.23 for 1H proton corresponding to NH proton. The aromatic proton shows following signal 7.51 (s, 1H), 7.32 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), The one Singlet appears at δ2.21 (s, 3H) and the other two singlet appear at 2.11 (s, 3H), 2.01 (s, 3H).of CO-CH_3. In ^{13}C NMR spectrum of compound 1-(3,6-dimethyl-4-phenyl-1*H*-indazol-5-yl)ethan-1-one 5a showed the signals at 205.54 ppm corresponding to the carbon of Carbonyl of CH_3CO and three singles appear at shielded region belong to three methyl groups. The m/z (M+H) calculated for Chemical Formula: $C_{17}H_{16}N_2O$, 264.1263 was found at 265. From the spectral data, the structure of 1-(3,6-dimethyl-4-phenyl-1*H*-indazol-5-yl)ethan-1-one compound 1-(3,6-dimethyl-4- phenyl-1*H*-indazol -5-yl) ethan-1-one 5a was confirmed.

Table 1. Physico-chemical data of compound 5a to 5e

Sr/No	Comp.	R_1	R_2	R_3	m.p °C	Yield %
1	**5a**	H	H	H	198-199	79
2	**5b**	H	OMe	OMe	120-124	74
3	**5c**	H	H	OMe	Liquid	68
4	**5d**	OMe	OMe	OMe	146-150	77
5	**5e**	H	H	Cl	167-168	72

Mechanism :

The mechanism of the reaction involves, the compound reacts with hydrazine hydrate gives intermediates hydrazone B, under acidic conditions the phenolic –OH group intermediates B tautomerizes to a keto-hydrazine C, which undergoes dehydration (-H_2O) to afford the indazole F. (figure 2).

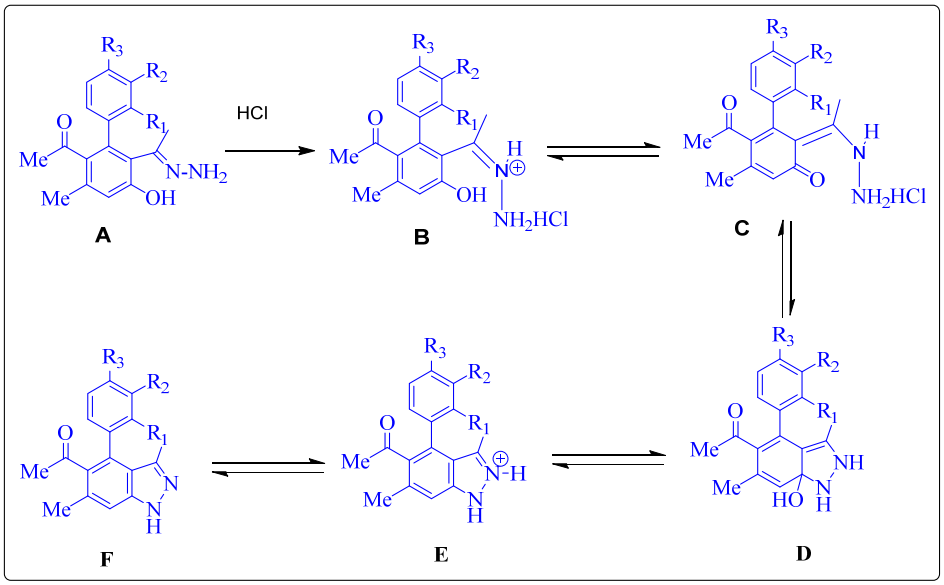


Figure 2. Proposed mechanism

Molecular Docking Analysis :

The docking analysis of 1-(3,6-dimethyl-4-phenyl-1H-indazol-5-yl)ethan-1-one 5a-5d derivatives was carried out by Autodocksoftware (Dallakyan S. et al. 2015). Based on the overall structural configuration of the synthesized molecules and the co-crystalized drug molecules CLOROBIOCIN, we performed the molecular docking against the DNA gyrase target, The DNA gyrase target is a known target for antibacterial agents since its blocking induces bacterial death. The three- dimensional crystal structure of E. coli 24kDa Domain with PDB: 1KZN in a Complex with ligand Clorobiocin was retrieved from the Protein Data Bank (http:// www.rscb.org/pdb).

The compound 1-(4-(3,4-dimethoxyphenyl)-3,6-dimethyl-1H-indazol-5-yl)ethan-1-one 5b (Figure 3) shows a similar orientation in the binding pocket of DNA gyrase (PDB code 1KZN). enzyme with a binding energy of -7.7 kcal/mol. The compound 5b, OMe formed a bond with ASN-46(A) N---O and having bond distance 2.79Å, as well as the indazole N-H display H-bond with ASP-73 with bond distance 2.64Å. The compound 1-(4-(3,4-dimethoxyphenyl)-3,6-dimethyl-1H- indazol-5-yl)ethan-1-one 5b also exhibits drophobic/hydrophilic interaction with amino acids like MET-91, VAL120, ILE90, ILE-8, ALA-47, THR165, GLU-50 ANS ASP-49 amino acids, which is responcible for the biochemical mechanism in the cell. The compound 1-(3,6-dimethyl-4-(2,3,4-trimethoxyphenyl)-1H-indazol-5-yl)ethan-1-one 5d also showed hydrogen bond with MET-91, ASP-49 amino acids (Figure 5).

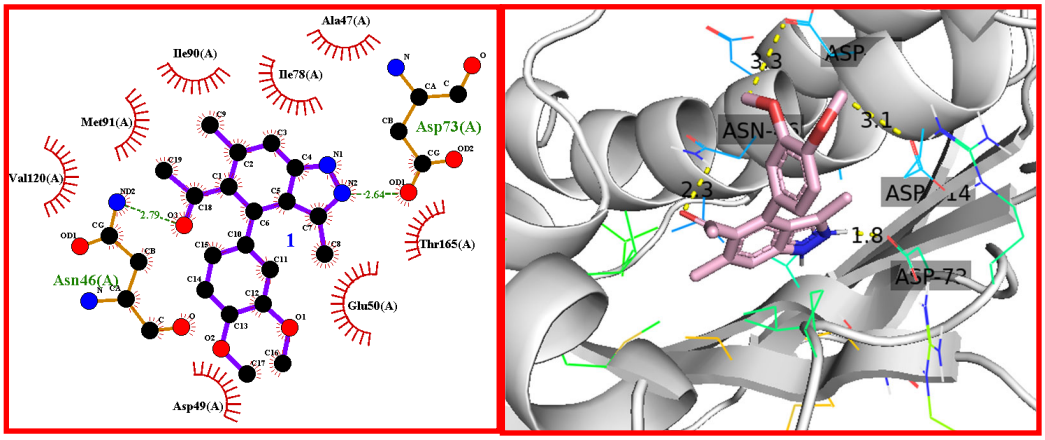


Figure 3. A) 2D structure showing hydrogen bonding and hydrophobic interactions of 5b with DNA gyrase (PDB code 1KZN) complex. .B). Binding interactions between 5b and DNA gyrase (PDB code 1KZN).

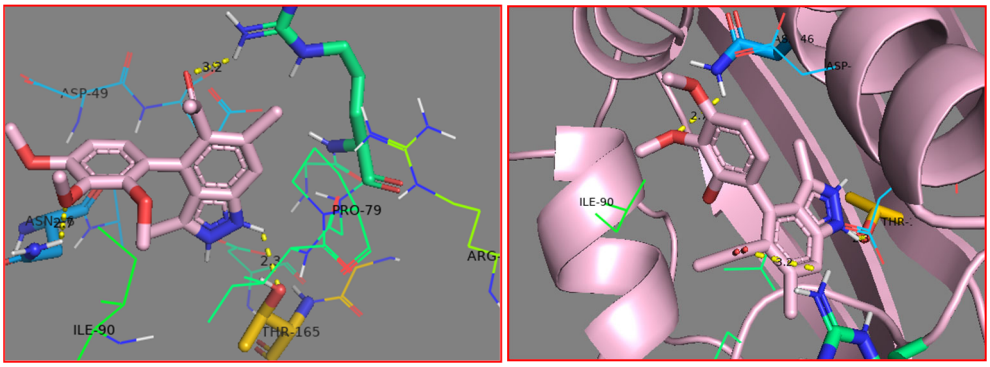


Figure 4. A) 2D structure showing hydrogen bonding and hydrophobic interactions of 5d with DNA gyrase (PDB code 1KZN) complex. .B). Binding interactions between 5d and DNA gyrase (PDB code 1KZN).

The molecular docking studies revealed that the synthesized compounds can target attractive antimicrobial targets like 1kzn DNA gyrase inhibitor.

Conclusions :

This study demonstrates a novel, efficient, method for the synthesis of novel series of 1-(3,6-dimethyl-4-phenyl-1H-indazol-5-yl)ethan-1-one derivatives. The molecular docking studies releveled that the synthesized compounds can target the attractive antimicrobial targets with DNA gyrase (PDB code 1KZN).

Experimental section :

General procedure for preparation of 1-(3,6-dimethyl-4-phenyl-1H-indazol-5-yl) ethan-1-one (5a); A mixture of 1,1'-(3,5-dihydroxy-3-methyl-3 l 5-[1,1'-biphenyl]-2,6-diyl) bis(ethan-1-one) 4a (1 equiv) in acetic acid/ MeOH (10 ml) and hydrazine hydrate (1.5 Equiv.) was added followed at 0 °C and the resulting mixture was stirred at 70 °C temperature. Once TLC confirms the formation of 5a the reaction mixture was quenched with cold water. The crude product was purified by column chromatography using ethyl acetate: hexane to obtain the desired compounds

Light yellow solid, m.p. 198 °C 1H NMR (300 MHz,cdcl3) δ 13.23 (s, 1H), 7.51 (s, 1H), 7.32 – 7.26 (m,1H), 7.25 – 7.21 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H),6.95 (d, J = 2.4 Hz, 1H),2.21 2.01 (s, 3H).

1-(4-(3,4-dimethoxyphenyl)-3,6-dimethyl-1H-indazol-5-yl)ethan-1-one (5b):White solid (198mg, 68%); 1H NMR (300 MHz, CDCl3) δ12.57 (s, 1H), 7.10 (s, 1H), 6.88 (d, J = 8.9 Hz, 1H), 6.84 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.70 (s, 3H), 2.17 (s, 3H), 1.53 (s, 3H)

1-(4-(4-methoxyphenyl)-3,6-dimethyl-1H-indazol-5-yl)ethan-1-one (5c): Semisolid, 1H NMR (300 MHz, CDCl3)12.47 (s, 1H), δ 7.65(s, 1H), 7.45(d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H),4.17 (s, 3H),2.10 (s, 3H), 1.97 (s, 3H), 1.71 (s, 3H).

1-(4-(4-chlorophenyl)-3,6-dimethyl-1H-indazol-5-yl)ethan-1-one(5e): Yellow solid m.p. decomposed 184 °C; 1H NMR (300 MHz,cdcl3) δ 11.59 (s, 1H), 7.72 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 6.5 Hz, 2H), 7.35 (s, 1H), 2.11 (s, 3H), 2.00 (s, 3H), 1.77 (s,3H)

Supplementary Materials: The following are available online at

Author Contributions: S.G. has done experimental& writing part , S.P. help for literature search

Conflicts of Interest: The authors declare no conflict of interest.

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