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INDOLE 1,2,3,4-TETRAHYDROPYRIMIDINONE: SYNTHESIS, CHARACTERIZATION AND IT'S BIOLOGICAL APPLICATIONS

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Keywords:

Indole, Substituted 1,2,3,4-tetrahydropyrimidine, Biginelli reaction, Antibacterial, Antifungal activity

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ABSTRACT: The present research work involves the use of exclusively and commercially available indole-3-carbaldehyde as a starting material to synthesize novel pyrimidine analogues. The synthesis of series of indole and pyrimidine containing N-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro-pyrimidine-5-carbohydrazide U(1-10) has been done by using principle of Biginelli condensation reaction.Indole-3-carbaldehyde was prepared by formylation of indole (Vilsmeier Haack reaction) using dimethylformamide and phosphorus oxychloride (1). The intermediate indole dihydropyrimidines was synthesized from a mixture of indole-3-carbaldehyde, urea and ethyl acetoacetate in the presence of zinc chloride as acid catalyst (2). The intermediate compound then refluxed with hydrazine hydrate by the addition of catalytic amount of conc. sulphuric acid, led to formation of parent compound 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide(3). The parent compound 3 was used for synthesis of N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo- 1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide and substituted aldehydes U (1-10), and/or Schiff bases of N'-substituted-4-(1H-indol- 3- yl)- 6- methyl- 2- oxo- 1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide. Elemental analysis, FT-IR, ^{1}H-NMR, and Mass spectral data supports the structures of synthesized compounds. The selected synthesized compounds were screened for antibacterial and antifungal activities. Test compounds (U-5) and (U-7) were showed excellent antibacterial activity against all the bacterial strains. For antifungal activity, test compounds (U-5), (U-7), and (U-8) exhibited considerable activity compared to the standard compound.

INTRODUCTION: Bacterial infection is a leading cause of hospitalization and death through-out the world and has primarily been treated with antibiotics over the past half-century; hence it is increasingly important to understand bacterial virulence and survival mechanisms in order to identify new therapeutic approaches to combat bacterial infection and bacterial resistant strains [1].

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Compounds containing heterocycles are rich in nature and are most valuable to life as their structural analogues present in various natural products like hormones, vitamins, and antibiotics; hence they have concerned significant focus on the design and development of therapeutic active candidates and advanced organic chemistry [2].

The aza-heterocycles such as indole, pyrimidine, pyrazole, morpholine, piperidine, pyrrolidine, and triazine are serving as templates of a number of clinically used anti-inflammatory, antifungal, antileukemic, and neuroprotective agents [3]. Besides this, dihydropyrimidinones (DHPMs) and their analogues have shown a attractive assortment in

natural, synthetic, pharmacological, therapeutic and bioorganic chemistry mainly due to their wide range of biological activities [4]. Tetrahydro-pyrimidines, Dihydropyrimidinones (DHPMs) or Pyrimidinones are well recognized for their wide range of bioactivities, and their applications in the field of drug research have stimulated the invention of synthetic methods for their preparation and chemical transformations [5]. Indole is found in essential oils, coal tar, molasses tar, and also found along with pus in the liver, pancreas, brain, and bile. It is present in number of physiologically significant compounds like serotonin, tryptophan, indole-3-acetic acid, gramine, abrine, reserpine, yohimbine, physostigmine, lysergic acid, diethyl amide, and also in important antibiotics like mitomycin and glitoxin [6]. Indole linked to pyrimidine moiety has been reported for many decades [7]. Also found to exhibit a wide range of pharmacological activities and used as a drug in the market [8]. Some of the structures of active pharmaceuticals containing indole, pyrimidine, and indole pyrimidine hybrid are highlighted in **Fig. 1.**

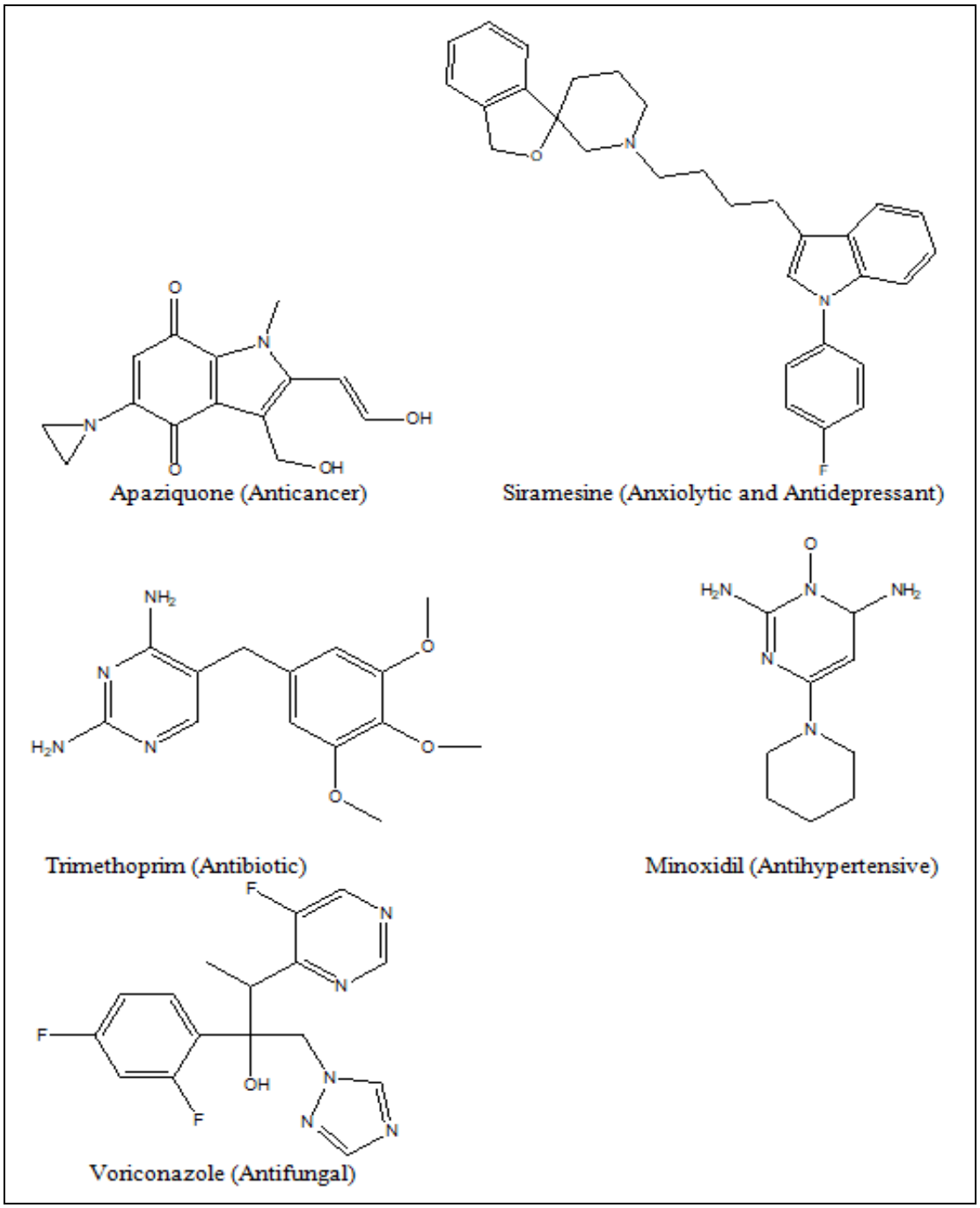


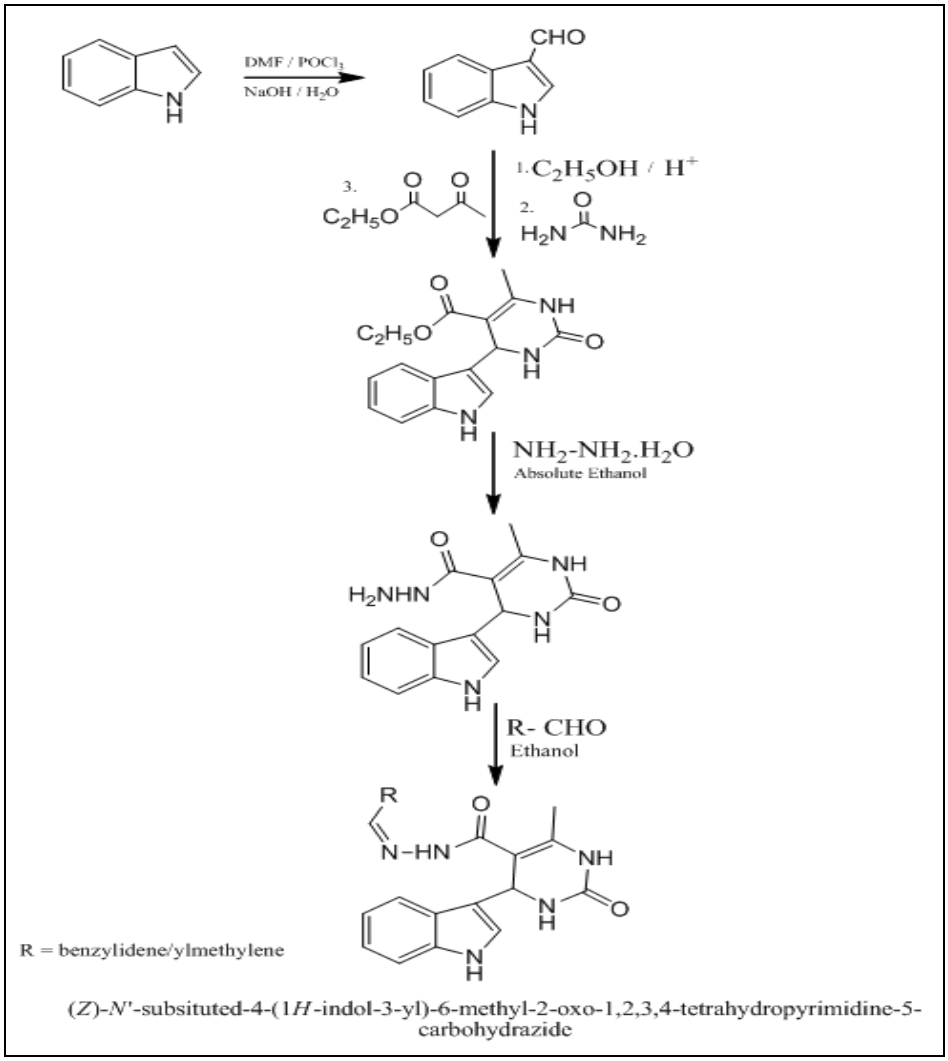
FIG. 1: CHEMICAL STRUCTURE OF ACTIVE PHARMACEUTICALS HAVING INDOLE AND PYRIMIDINE NUCLEUS

Hybrid of indole-pyrimidine nucleus possesses wide range of biological activities, such as anti-bacterial, [9-11] antifungal, [12-14] anticancer [15-17] *etc*. Synthesis of indole-pyrimidine scaffold is beneficial to get new biologically active derivatives.

In this study, we report on synthesis of indole derivatives linked to pyrimidine, and different reactions were carried out to get title compounds U (1-10) as per the scheme depicted to get desired biological activities.

MATERIALS AND METHODS:

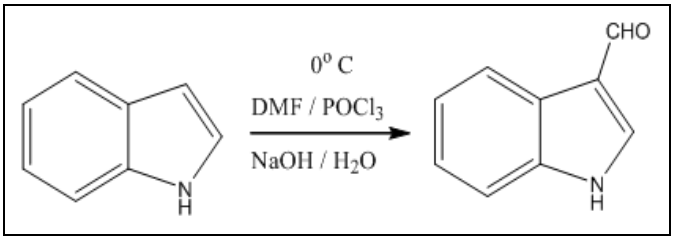
Chemistry: All the chemicals used for synthesis were of Merck, Sigma and Qualigens make. Melting points were determined in open capillaries using a conventional method. The progress of reaction was monitored by thin-layer chromato-graphy (TLC). The TLC plates were visualized in glass chamber saturated with the iodine vapors, using benzene and methanol solvent system. The absence of TLC spots for starting materials and the appearance of new TLC spot at different R_f value were ensured for purity and completion of reaction. The infrared spectra were scanned on FT-IR Shimadzu within 4000-400 cm^{-1} wavelength range, ^{1}HNuclear magnetic resonance (NMR) spectra of the synthesized compounds were recorded on Varian Mercury YH 300 NMR Spectrometer in $CDCl_3$ at 300 mhz frequency and bruker avance II 400 spectrometer, using trimethyl silane (TMS) as internal standard. The chemical shifts were represented in δ ppm. The peak multiplicities were specified as: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were recorded on Micro mass Q-Tof Microsystem. Elemental analysis was recorded on FLASHEA112 series.



SCHEME 1: SYNTHETIC SCHEME FOR THE CONSTRUCTION OF N'-SUBSTITUTED-4-(1H-INDOL-3-YL)-6-METHYL-2-OXO-1, 2, 3, 4-TETRAHYD ROPYRIMIDINE-5-CARBOHYDRAZIDE U (1-10)

General Procedure for the Synthesis of 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetra hydro-pyrimidine-5-carbohydrazide and Schiff bases U (1-10):

Step-1: Synthesis of 1H-indole-3-carbaldehyde

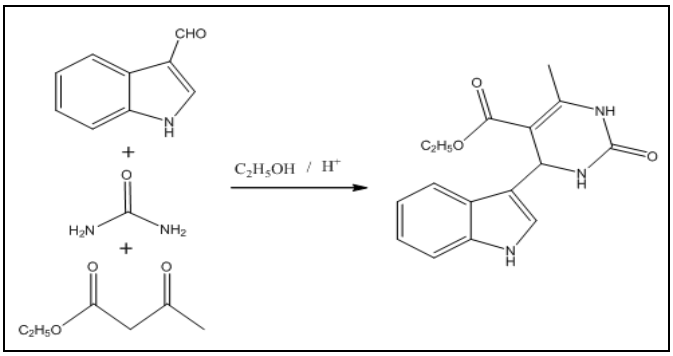


Formylation of Indole: In a three-necked flask fitted with an efficient mechanical stirrer and dropping funnel was placed 28.8 ml of freshly distilled dimethylformamide. The contents of the flask were cooled in an ice bath for 30 min and 8.7 ml of freshly distilled phosphorus oxychloride was subsequently added with stirring to the dimethyl-formamide over a period of 0.5 h. The pinkish color of the formylation complex was observed during this step. The 125-ml. dropping funnel is replaced with a 200-ml. dropping funnel, and a solution of 9.94 gm of indole in 10.0 ml of dimethylformamide was added to the yellow solution over a period of 1 hour during which time the temperature should not rise above 10 °C. Whenever the solution was mixed well, then the funnel was substituted with a thermometer, and the temperature of the viscous solution is brought to 35 °C. The mixture was stirred properly at this temperature till the clear yellow solution to become an opaque, canary-yellow paste. At the end of the reaction period, crushed ice was added to the paste with careful stirring, producing a clear, cherry-red aqueous solution.

This solution was transferred with water to a three-necked flask containing crushed ice and fitted with an efficient mechanical stirrer and a separatory funnel containing a solution of 37.6 gm of sodium hydroxide in water. The aqueous base was added dropwise with stirring until about one-third of it has been added. The rest of part was mixed properly with sufficient stirring and it was heated rapidly to the boiling point and allowed to cool to room temperature, after which it was placed in a refrigerator overnight. The precipitate was collected on a filter and resuspended in water.

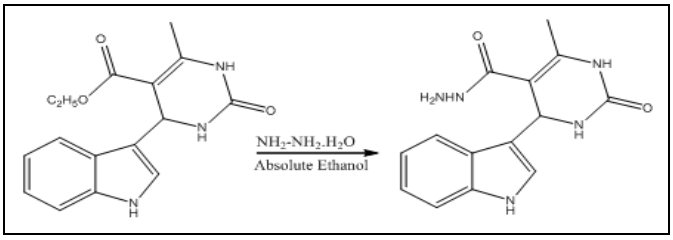
Almost inorganic substances were and collected on a separate filter paper sheet and then washed with water and air-dried, yielding about 12 g.(97%) of indole-3-aldehyde, m.p. 196-197°C. The pure product was obtained by recrystallization from ethanol.

Step-2: Synthesis of ethyl 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate



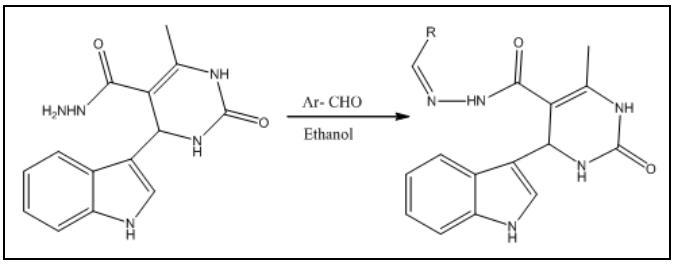
A mixture of indole -3-carbaldehyde **(**1 eq), urea **(**2 eq), and ethyl acetoacetate **(**1 eq) in ethanol was heated under reflux in the presence of $ZnCl_2$ as an acid catalyst. TLC was used to monitor the progress of the reaction. After completion, the reaction mixture was poured on crushed ice and filtered under suction; the precipitate was washed with water. The product was recrystallized by using ethanol. The yield was about (92%) of indole dihydro-pyrimidines, m.p. 228-230°C.

Step-3: Synthesis of 4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide.



To 0.1 mole of indole dihydropyrimidines in ethanol (20 ml), hydrazine hydrate (0.1 mole) was added followed by the addition of a catalytic amount of conc. H_2SO_4 (3 drops). The mixture was refluxed for two to three hours, and the progress of the reaction was monitored by using TLC. Excess solvent was removed, and on cooling a solid was formed. The solid was crystallized from ethanol.

Step-4: Synthesis of (Z)-N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro-pyrimidine-5-carbohydrazide (Schiff's base/imine formation).



A mixture of equimolar quantity of 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide and substituted aldehydes was refluxed in ethanol for 2-2.5 hrs, on the heating mantle. The reaction mixture was then concentrated and cooled. Thus obtained solid was filtered and dried. The crude product was recrystallized from ethanol, and the purity of the product was checked by TLC. Similarly, the other Schiff bases U (1-10) were prepared by following a similar procedure, and their physicochemical parameters are tabulated in **Table 1**.

4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetra hydropyrimidine-5-carbohydrazide: FT-IR (KBR) *v* (cm^{-1}): 3352 (NH-NH), 3,266 (NH), 2,966 (C-H), 1,717 (C=O); ^{1}H (NMR) δ=13.76 (s, 1H, NH-pyrimidine), 10.1 (d, 1H, NH-indole), 7.11-7.60 (m, 4H, ArH), 2.26 (s, 1H, CH_3); Elemental analysis calculated for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N,24.55; Found: C, 56.53; H, 4.56; N, 22.61; MS: *m/z* =401.59 (M^+).

N'- (4-methoxybenzylidene)- 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide (U-1): FT-IR (KBR) *v* (cm^{-1}): 3,466 (NH), 1,655 (C=O), 1,310 (C-N), 1,109 (C-O); ^{1}H (NMR) δ=13.76 (s, 1H, NH-amine), 10.1 (d, 1H, NH-indole), 7.11-7.77 (m, 8H, ArH), 2.21 (s, 3H, CH_3); Elemental analysis calculated for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36; Found: C, 66.26; H, 4.87; N, 16.31; MS: *m/z* = 428.16 (M^+).

N'-benzylidene- 4- (1H-indol-3-yl)- 6- methyl- 2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydr-azide(U-2): FT-IR (KBR) *v* (cm^{-1}): 3,466 (NH), 2,966 (CH), 1,730 (C=O), 1,310 (C-N), 740 (C-C); Elemental analysis calculated for $C_{19}H_{18}N_5O_2$: C, 67.55; H, 5.13; N, 18.36; Found: C, 68.74; H, 5.05; N, 17.55.

N'- (4-chlorobenzylidene)- 4- (1H-indol-3-yl)- 6-methyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide (U-3): FT-IR (KBR) *v* (cm^{-1}): 3,266 (NH), 2,966 (C-H), 1,655 (C=O), 1,310 (C-N), 780 (C-Cl); ^{1}H (NMR) δ=13.76 (s, 1H, NH-amine), 10.1 (d, 1H, NH-indole), 7.11-7.77 (m, 8H, ArH), 2.26 (s, 3H, CH_3); MS: *m/z* =407.85 (M^+).

N'- (2- hydroxybenzylidene)-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide (U-4): FT-IR (KBR) *v* (cm^{-1}): 3,610 (OH), 3,266 (NH), 2,966 (C-H), 1,730 (C=O); 1,680 (C=N); ^{1}H (NMR) δ=13.76 (s, 1H, NH-amine), 10.1 (d, 1H, NH-indole), 7.02-7.66 (m, 8H, ArH), 5.35 (s, 1H, OH), 2.26 (m, 3H, CH_3); MS: *m/z* =426.09 (M^+).

N'-(furan-2-yl methylene)- 4- (1H-indol- 3- yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide (U-5): FT-IR (KBR) *v* (cm^{-1}): 3,266 (NH), 2,966 (C-H), 1,655 (C=O), 1,240 (C-O); ^{1}H (NMR) δ=10.1 (d, 1H, NH-indole), 7.5 (s, 1H, CH-furan), 7.2 (s, 5H, ArH), 1.8 (s, 3H, CH_3); MS: *m/z* =363.19 (M^+).

N'- (4- hydroxy, 3-methoxybenzylidene)-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro-pyrimidine-5-carbohydrazide (U-6): FT-IR (KBR) *v* (cm^{-1}): 3,216 (NH), 2,359 (C-H), 1,716 (C=O), 1,683 (C=N); ^{1}H (NMR) δ=12.76 (s, 1H, NH-pyrimidine), 10.1 (d, 1H, NH-indole), 7.11-7.60 (m, 4H, ArH), 2.26 (s, 1H, CH_3); MS: *m/z* =419.43 (M^+).

N'- (thiophen-2-yl methylene)- 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide (U-7): FT-IR (KBR) *v* (cm^{-1}): 3,395 (NH), 1,716 (C=O), 1,647 (C=N), 1370 (C-S); ^{1}H (NMR) δ=11.76 (s, 1H, NH-pyrimidine), 10.1 (d, 1H, NH-indole), 7.11-7.60 (m, 4H, ArH), 2.21 (s, 3H, CH_3).

N'- (2, 6-dichlorobenzylidene)-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide (U-8): FT-IR (KBR) *v* (cm^{-1}): 3,356 (NH), 1,745 (C=O), 1,317 (C=N), 760 (C-Cl); ^{1}H (NMR) δ=13.76 (s, 1H, NH amine), 10.1 (d, 1H, NH-indole), 7.11-7.60 (m, 4H, ArH), 2.06 (s, 1H, CH_3).

N'- (2, 4-dichlorobenzylidene)-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide (U-9): FT-IR (KBR) *v* (cm^{-1}): 3,356 (NH), 1,730 (C=O), 1,317 (C=N), 860 (C-Cl); ^1H (NMR) δ=13.76 (s, 1H, NH-amine), 10.1 (d, 1H, NH-indole), 8.36 (CH-azomethine), 7.11-7.60 (m, 4H, ArH), 2.06 (s, 1H, CH_3).

N'-(2-chloro,6-fluorobenzylidene)-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine -5-carbohydrazide (U-10): FT-IR (KBR) *v* (cm^{-1}): 3,266 (NH), 2,966 (C-H), 1,717 (C=O); ^1H (NMR) δ=13.76 (s, 1H, NH-amine), 10.1 (d, 1H, NH-indole), 7.4 (m, 8H, ArH), 2.26 (s, 3H, CH_3).

Biological Activity:

Antibacterial Activity: The antibacterial activity of the synthesized compounds was performed by using cup plate method, and minimum inhibitory concentration (MIC) was determined by tube dilution techniques against two Gram-positive bacteria *Staphylococcus aureus* (MTCC 96) and *Staphylococcus pyrogenus* (MTCC 443) and Gram-negative bacteria *Escherichia coli* (MTCC 442) and *Pseudomonas aeruginosa* (MTCC 441). The tested compounds exhibited mild to moderate antibacterial activity against above-mentioned microorganisms when compared with different standard compounds by taking DMF as a control. The antibacterial results of synthesized compounds are tabulated in **Table 2**.

Antifungal Activity: The antifungal activity of the synthesized compounds was tested against three different strains of fungi namely, *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*, by tube dilution technique at 1000 µg/ml concentrations. The Petri dishes were incubated at 25 °C for 48 h, and after incubation, the diameter of the zone of inhibition was measured, and the average diameter for each sample was calculated. Griseofulvin and Nystatin were used as standard drugs and dimethylforfamide as a control. The results of antifungal activity are tabulated in **Table 3**.

RESULTS AND DISCUSSION: N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo- 1, 2, 3, 4-tetrahydro-pyrimidine-5-carbohydrazide U (1-10) were synthesized as per the scheme of synthesis. The intermediate 1H- indole- 3- carbaldehyde were synthesized by formylation of indole in the presence of dimethyl formamide, Phosphorus oxychloride, NaOH and water. 4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2,3, 4-tetra hydropyrimidine-5-carboxylate was synthesized by refluxing 1H-indole-3-carbaldehyde with urea and ethyl acetoacetate in presence of glacial acetic acid as catalyst and ethanol. 4-(1H-indol- 3- yl)- 6-methyl-2-oxo-1, 2, 3, 4-tetrahydro-pyrimidine-5-carbohydrazides were synthesized by refluxing 4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2,3,4 -tetra hydropyrimidine-5-carboxylate and hydrazine hydrate in presence of acid catalyst and ethanol. Schiff bases of N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide, U (1-10) were synthesized by condensation with various substituted aromatic aldehydes in presence of acid catalyst and ethanol. The reaction was performed by conventional method.

Synthesis of indole -3-carbaldehyde (1) involves the formylation of indole using dimethyl formamide (DMF) and phosphorus oxychloride (Vilsmeier Haack method). The compound (2) involves the synthesis of ethyl 4-(1H-indol-3-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (Indole dihydropyrimidines) with the trimolecular Biginelli condensation of indole -3-carbaldehyde, urea, and ethyl acetoacetate in ethanol. The formation of the intermediate compounds 1 and 2 have been confirmed. Compound 2, when refluxed with hydrazine hydrate in ethanol led to the formation of parent compound N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbohydrazide (3), which was the key intermediate for the synthesis of target compounds U (1-10).

The IR spectrum of compound 3 exhibited stretching bands at 3,266, 2,966, and 1,717 cm^{-1} due to NH, CH, and C=O, respectively. ^1H NMR spectrum of parent compound 3 taken in DMSO exhibited multiplet at δ 7.11-7.60 and singlet at δ 2.26 toward three aromatic protons and *N*-methyl protons, respectively. Two characteristic signals for NH and NH_2 at δ 13.76 and 10.1, respectively. The mass spectrum of the compound exhibited its molecular ion peak at *m/z* 401.59 correspondings to its molecular weight.

The compound 3 was refluxed with methoxy benzaldehyde in ethanol with a catalytic amount of

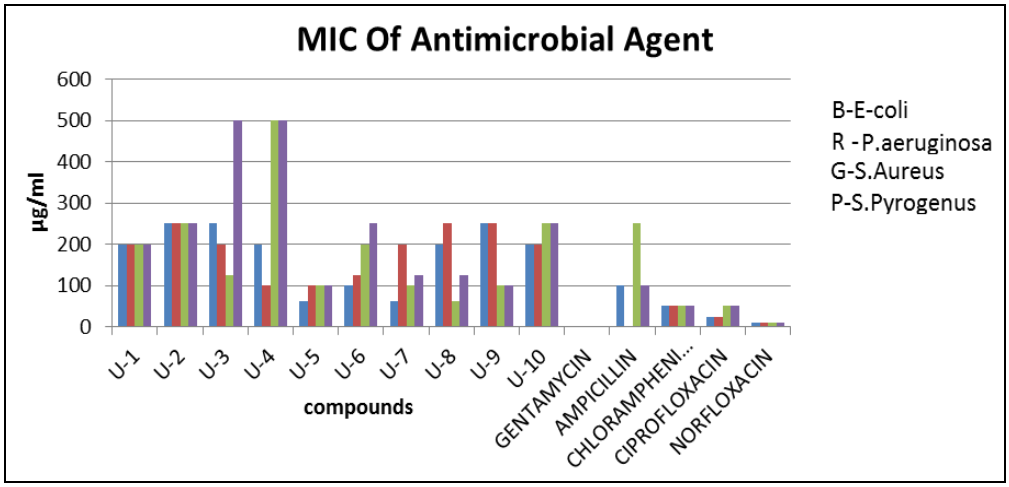
sulfuric acid for 2 h to yield 4-methoxy-benzylidene-4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2, 3,4-tetrahydropyrimidine-5-carbohydrazide (U-1). The IR spectrum of compound (U-1) exhibited peaks at 3,466, 1,655, 1,310, and 1,109 cm^{-1} due to NH, C=O, C-N, and C-O groups, respectively. ^1H NMR spectrum of the same compound recorded in DMSO, exhibited a peak at δ 13.76 corresponding to one proton of amine, at 10.1 for NH-indole, multiplet between 7.11 and 7.77 corresponds to eight aromatic protons, singlet at 2.21 belongs to three protons of N-CH_3. The structure of (U-1) was further confirmed by Elemental analysis calculated for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36; Found: C, 66.26; H, 4.87, and by the appearance of a molecular ion peak at *m/z* =428.16 (M^+) in its mass spectrum. Similarly, compounds U (1-10) were prepared by using the corresponding aldehydes.

The detailed experimental procedure, analysis data for the compounds mentioned above have been incorporated in the experimental section. The structures of all synthesized derivatives have been elucidated by IR, ^1H NMR, Mass, and Elemental analysis. Some of the selected compounds were tested for antibacterial and antifungal activities, and its results have been discussed.

TABLE 1: PHYSICOCHEMICAL DATA OF *N*-SUBSTITUTED-4-(1H-INDOL-3-YL)-6-METHYL-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOHYDRAZIDE (U 1-10)

S. no.	R	Molecular Formula	Molecular Weight	% yield	Melting Point (°C)	R_f Value
U-1	4-OCH_3,C_6H_5	$C_{22}H_{21}N_5O_3$	403.43	75.12	140-144	0.58
U-2	C_6H_5	$C_{21}H_{19}N_5O_2$	373.41	64.76	164-168	0.63
U-3	4-Cl,C_6H_5	$C_{21}H_{18}ClN_5O_2$	407.85	58.15	182-186	0.72
U-4	2-OH,C_6H_5	$C_{21}H_{19}N_5O_3$	389.41	68.46	162-165	0.56
U-5	Furan	$C_{19}H_{17}N_5O_3$	363.37	73.95	168-170	0.57
U-6	4-OH,3-OCH_3,C_6H_5	$C_{22}H_{21}N_5O_4$	419.43	76.14	170	0.82
U-7	Thiophene	$C_{19}H_{17}N_5O_2S$	379.44	52.45	122	0.64
U-8	2,6-dichloro	$C_{21}H_{17}C_{l2}N_5O_2$	442.30	64.12	154	0.82
U-9	2,4-dichloro	$C_{21}H_{17}C_{l2}N_5O_2$	442.30	76.13	138	0.78
U-10	2-Chloro,6-fluoro	$C_{21}H_{17}ClFN_5O_2$	425.84	82.45	160	0.74

[a] Compounds purification by recrystallization method using ethanol as solvent.

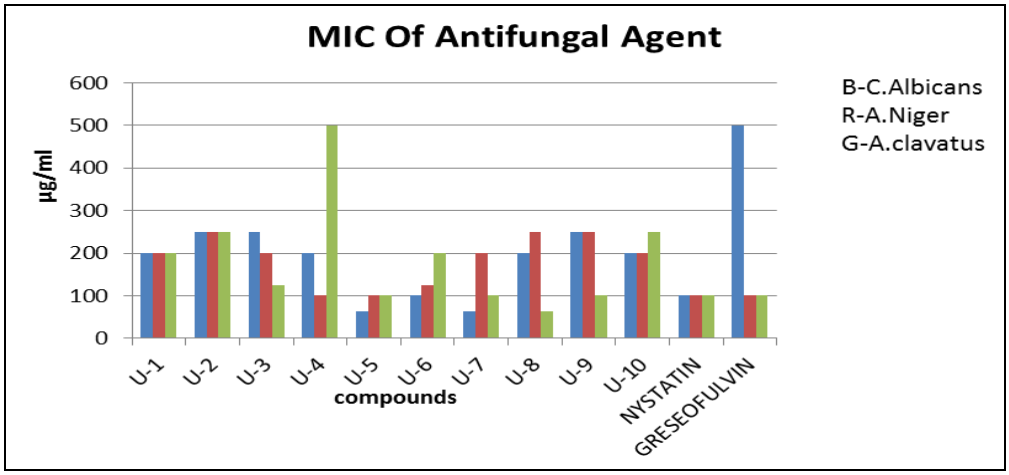


GRAPH 1: MIC OF ANTIBACTERIAL ACTIVITY (MIC µG/ML) OF TEST COMPOUNDS U (1-10)

TABLE 2: ANTIBACTERIAL ACTIVITY OF TEST COMPOUNDS U (1-10) DERIVATIVES) AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA IN COMPARISON WITH STANDARD AND CONTROL

Compound no.	R	*E. coli* *MTCC 442* 1000 µg/ml	*P. aeruginosa* *MTCC 441* 1000 µg/ml	*S. aureus* *MTCC 96* 1000 µg/ml	*S. pyrogenus* *MTCC 443* 1000 µg/ml
U-1	4-OCH_3,C_6H_5	200	200	200	200
U-2	C_6H_5	250	250	250	250
U-3	4-Cl,C_6H_5	250	200	125	500
U-4	2-OH,C_6H_5	200	100	500	500
U-5	Furan	62.5	100	100	100
U-6	4-OH,3-OCH_3, C_6H_5	100	125	200	250

U-7	Thiophen	62.5	200	100	125
U-8	2,6-dichloro	200	250	62.5	125
U-9	2,4-dichloro	250	250	100	100
U-10	2-Chloro,6-fluoro	200	200	250	250
DMF		-	-	-	-
GENTAMYCIN		0.05	1	0.25	0.5
AMPICILLIN		100	--	250	100
CHLORAMPHENICOL		50	50	50	50
CIPROFLOXACIN		25	25	50	50
NORFLOXACIN		10	10	10	10



GRAPH 2: MIC OF ANTIFUNGAL ACTIVITY (MIC µG/ML) OF TEST COMPOUNDS U (1-10)

TABLE 3: ANTIFUNGAL ACTIVITY OF TEST COMPOUNDS U (1-10) AGAINST THREE DIFFERENT FUNGAL STRAINS IN COMPARISON WITH STANDARD AND CONTROL

Compound no.	**R**	***C. Albicans* *MTCC 227* 1000 µg/ml**	***A.Niger* *MTCC 282* 1000 µg/ml**	***A. Clavatus* *MTCC 1323* 1000 µg/ml**
U-1	4-OCH_3,C_6H_5	200	200	200
U-2	C_6H_5	250	250	250
U-3	4-Cl,C_6H_5	250	200	125
U-4	2-OH,C_6H_5	200	100	500
U-5	Furan	62.5	100	100
U-6	4-OH,3-OCH_3, C_6H_5	100	125	200
U-7	Thiophen	62.5	200	100
U-8	2,6-dichloro	200	250	62.5
U-9	2,4-dichloro	250	250	100
U-10	2-Chloro,6-fluoro	200	200	250
DMF		-	-	-
NYSTATIN		100	100	100
GRISEOFULVIN		500	100	100

CONCLUSION: The reactions were performed to achieve Schiff bases of parent compound N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-oxo-1,2, 3,4-tetrahydropyrimidine-5-carbohydrazide (3) were eco-friendly and yields obtained were satisfactory. Purification of synthesized compounds was achieved by using recrystallization method, and purity was determined by thin layer chromatography method. Characterization of the compounds was carried out by spectral analysis. Compounds (U-5) and (U-7) showed excellently antibacterial activity against all the bacterial strains.

Compounds (U-5), (U-7), and (U-8) exhibited considerable antifungal activity compared to the standard substance. Noteworthy results are tabulated. Novel indole substituted 1, 2, 3, 4-tetrahydropyrimidine derivatives were synthesized and had shown prominent antibacterial and antifungal activity; results encourage us for further lead optimization of this series of compounds.

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REFERENCES:

1. Biswas N, Kutty S, Barraud N, Iskander G, Griffith R, Rice S, Willcox M, Black D and Kumar N: Indole-based novel small molecules for the modulation of bacterial signaling pathways. Org Biomol Chem 2015; 13: 925-37.
2. Vinita S, Nitin C and Ajay KA: Significance and Biological Importance of Pyrimidine in the Microbial World. Int J Med Chem 2014; 1-31.
3. Kaur S, Kumari P, Singh G, Bhatti R and Singh P: Design and Synthesis of Aza-/Oxa Heterocycle-Based Conjugates as Novel Anti-Inflammatory Agents Targeting Cyclooxygenase 2. ACS Omega 2018; 3: 5825-45.
4. Zhang Y, Wang B, Zhang X, Huang J and Liu C: An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones and Thiones Catalyzed by a Novel Brønsted Acidic Ionic Liquid under Solvent-Free Conditions. Molecules 2015; 20: 3811-20.
5. Phucho IT, Nongpiur A, Tumtin S, Nongrum R and Nongkhlaw RL: Recent progress in the chemistry of Dihydropyrimidinones. Rasayan J Chem 2009; 2: 662-76.
6. Rabindranath M, Margareth Melo, Cid A, Eric G and Bhupesh D: Trinervine, a New Indole Alkaloid from Strychnos trinervis. Heterocycles 1990; 31(10): 1819-22.
7. Peng CD, Qiu L, Meng JH, Yu FM, Wen WY, Kwon HH and Pei LZ: Synthesis and biological evaluation of novel indole-pyrimidine hybrids bearing morpholine and thiomorpholine moieties. Eur J Med Chem 2017; 134: 110-18.
8. Nikhila G, Udayakumar D and Manjunatha K: Facile synthesis of indole-pyrimidine hybrid and evaluation of their anticancer and antimicrobial activity. J Saudi Chem Society 2017; 7(21): 761-75.
9. Hanane Z, Assia B, Adnane A, Tahar L and Mohamed B: Antibacterial study of 3-(2- amino-6-phenylpyrimidin-4-yl)-N-cyclopropyl-1-methyl-1Hindole-2-carboxamide derivatives:CoMFA, CoMSIA analyses, molecular docking and ADMET properties prediction. J Molecular Structure 2018; 1-20.
10. Roberto R, Maria AC, Agata C, Giulia M, Lucia V, Daniela I, Gianluigi B and Salvatore VG: Synthesis and Biological Evaluation of Pyrimidine-oxazolidin-2-arylimino Hybrid Molecules as Antibacterial Agents. Molecules 2018; 23: 1754-59.
11. Heda LC, Rashmi S, Pareek C and Chaudhari P: Synthesis and antimicrobial activity of some derivatives of 5-substituted indole dihydropyrimidines. E-Journal of Chemistry 2009; 6(3): 772-74.
12. Asmaa SS, Naema AM, Anhar AA, Mona AM and Doaa ME: Synthesis, reactions and antimicrobial activity of some new 3-substituted indole derivatives. Int J Org Chem 2015; 5: 81-99.
13. Nikhila G, Udayakumar D and Manjunatha K: Facile synthesis of indole-pyrimidine hybrid and evaluation of their anticancer and antimicrobial activity. J Saudi Chem Society 2015; 1-37.
14. Kamiar Z, Hamid RS, Sahar M, Keyvan P, Saeed M, Niusha S and Seyed AJ: The study on the Antifungal Activities of Novel Derivatives of Indole, Benzofuran and Dihydropyrimidine against Candida, Aspergillus and Dermatophytes Species by Broth Micro-Dilution Method. J. of Advancement in Medical and Life Sciences 2016; 4: 1-8.
15. Sanjiv K, Siong ML, Kalavathy R, Mani V, Syed AA, Manikandan S and Balasubramanian N: Synthesis, molecular docking and biological evaluation of bis-pyrimidine Schif base derivatives. Chemistry Central Journal 2017; 1: 11-16.
16. Meng JH, Bei Z, Hai K, Yang L, Yu R, Tian Z, Ling L, Wen W and Pei L: Design, synthesis and molecular docking studies of novel indole-pyrimidine hybrids as tubulin polymerization inhibitors. Chem Biol Drug Des 2015; 86: 1491-1500.
17. Peng CD, Qiu L, Meng JH, Yu FM, Wen WY, Kwon HH and Pei LZ: Synthesis and biological evaluation of novel indole-pyrimidine hybrids bearing morpholine and thiomorpholine moieties. Eur J Med Chem 2017; 134: 110-18.
18. Anantnarayan R and Panikar CKJ: Textbook of Microbiology. 2nd Ed. Orient Longman Publication Chennai 1996; 85-88.
19. Furniss BS, Hannaford AJ, Smith PW and Tatchell AR: Vogel's textbook of practical organic chemistry. 6th Ed. Pearson education publication, London 2005; 1243-45.
20. John HB, John MB: Wilson and Griswold's Textbook of Organic, Medicinal and Pharmaceutical Properties. 11th Ed. Lippincott Williams and Wilkins Publication, New York 2004; 657-89.
21. Keshab BM, Katharigatta VN, Pradip KM, Raquel MG, Deepak C, Daniel G, Bharati O and Sushant KN: Larvicidal study of tetrahydropyrimidine scaffolds against *Anopheles arabiensis* and structural insight by single crystal X-ray studies. Chem Biol Des 2018; 92: 1924-32.
22. Kavitha S, Kannan K and Gnanavel S: Synthesis, characterization and biological evaluation of novel 2, 5 substituted- 1, 3, 4 oxadiazole derivatives, Saudi Pharm J 2017; 25(3): 337-45.
23. Kokare CR: Pharmaceutical Microbiology Principles and Application.1st Ed. Nirali Prakashan, Pune 2005; 65-74.
24. Pavia DL, Lampman GM and Kriz GS: Introduction to Spectroscopy: a Guide for students of organic chemistry. 5th Ed. Hartcourt College publishers, Singapore 2001; 587-96.
25. Pelczar MJ, Chan EC and Krieg NR: Microbiology. 4th Ed. Tata McGraw Hill publishing company Ltd. New Delhi. 1993; 421-40.
26. Sanjay BB and Nitin GH: Design, synthesis and molecular docking study of thienopyrimidin- 4(3H)-thiones as antifungal agents. J Saudi Chem Soc 2017; 21: 264-74.
27. Thomas LL and David AW: Foye's principles of medicinal Chemistry. 6th Ed. Lippincott Williams and Wilkins, Philadelphia 2013; 945-48.
28. Tripathi KD: Essentials of medical pharmacology. 6th Ed. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd. 2008; 708-09.
29. Valeriya V, Patrick B, Pavel I, Albert K, Sergey L, Konstantin K, Boris N, Konstantin M and Alexander A:

Synthesis and antituberculosis activity of indole-pyridine derived hydrazides, hydrazide-hydrazones, and thiosemicarbazones. Bio & Med Chem Lett 2015; 26(3): 978-85.

30. Watt B, Rayner A and Harris G: Practical Medical Microbiology. 2nd Ed. New York: Churchill Livingstone 1996; 87-89.
31. Sharma BK: Instrumental Method of Chemical Analysis. 5th Ed. GOEL Publishing House Meerut. 2002; 721-25.
32. Silverstein RM, Bassler GC and Morril TC: Infrared Spectroscopy, NMR Spectroscopy. In Spectrometric Identification of Organic Compounds. 4th Ed. John Wiley & sons Inc, New York 2006; 322-36.
33. Skoog DA, Holler FJ and Nieman TA: Principles of Instrumental Analysis. 3rd Ed. Thomson Asia Pvt. Ltd. Singapore 2005; 489-93.
34. Jadhav VB, Hollab HV, Tekale AC and Pawar RP: Bioactive dihydro pyrimidines: An overview. Der Chemica Sinica 2012; 3(5): 1213-28.
35. Rajasekaran S, Rao GK, Pai S and Ajay AK: Design, synthesis and biological activity of substituted dihydro pyrimidine-2-(1H)-thiones. International Journal of PharmTech Research. (CODEN (USA): IJPRIF ISSN: 0974- 4304) 2011; 3(2): 626-31.
36. Sara R, Lotfollah S and Afshin F: Conformational properties of novel 1, 2, 3, 4-tetrahydropyrimidinone (thione) derivatives: A DFT study. Journal of Reports in Pharmaceutical Sciences 2012; 1(2): 110-18.
37. Kadre T, Srinivasa RJ, Bhatewara A, Paliwal P and Jain S: Green protocol for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones using TBAB as a catalyst and solvent free condition under microwave irradiation. Archives of Applied Science Research 2012; 4(2): 988-93.
38. Thirupathi G, Venkatanarayana M, Dubey PK and Bharathi KY: Facile and green syntheses of 5-arylidene - pyrimidine-2, 4, 6-triones and 5-arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones using L-tyrosine as an efficient and eco-friendly catalyst in aqueous medium. Chemical Science Transactions 2013; 2(2): 441-46

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