Current Pharma Research
ISSN: 2230-7842
CPR 2(3), 2012, 612-619.

Design, Synthesis and Evaluation of Novel Indolyl Pyrimidine Carbohydrazides as Antifungal Agents.

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Abstract
A series of(Z)-N'-(benzylidene/ylmethylene)-4-(1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide T(1-10) and (Z)-N'- (benzylidene/ylmethylene) -2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide G (1-10) were synthesized using appropriate synthetic route. The Antifungal activity was performed using the Tube dilution technique against *Candida albicans, A. Niger, and A. clavatus*. Some of the synthesized compounds such as G-4, G-5, G-8, T-5, T-7 and T-8 were found to be equally potent as to the standard drug Griseofulvin and Nystatin.

Key Words
Indole, Tetrahydropyrimidine, carbohydrazide, Antifungal activity.

Introduction
Microorganisms are exceptionally diverse, found almost everywhere and affect the human society in countless ways. The quest for finding newer drugs to alleviate the human suffering dates back to the beginning of civilization. There is still search for drugs either of natural origin or synthetic which are highly specific in their pharmacological action with less or without toxic effect. Selective toxicity, the property of certain chemicals to destroy one form of the life without harming another is the corner stone of modern antimicrobial chemotherapy[1]. In the present work formylation of indole has been carried out by Vilsmeyer Haack method to form indole-3-carbaldehyde. In the second step indole-3-carbaldehyde was converted to ethyl 2-substituted-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, which was reacted with hydrazine hydrate and glacial acetic acid as catalyst in ethanol to form 2-substituted-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4 - tetrahydropyrimidine-5-carbohydrazide. In the last step 2-substituted-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide and substituted aldehydes were refluxed in presence of glacial acetic acid as catalyst in ethanol to give Schiff's base/imine formation. As the literature survey revealed that indole, and pyrimidine rings possess potential antimicrobial activity, it was thought worthwhile to couple the indole, and pyrimidine with the substituted aldehyde molecule so as to get enhanced bioactivity. Comparative study of the substitution pattern of the aryl and heteryl group towards antimicrobial activity has shown that electron donating groups gives the better activity while electron withdrawing groups causes moderate activity[2]. The presence of two important moieties i.e. indole and dihydropyrimidine in the final derivatives have contributed towards better antimicrobial activity. Thus the designed (Z)-2-imino-4-(1H-indol-3-yl)-N'-(4-methoxybenzylidene)-6-methyl-1, 2, 3, 4-tetra hydropyri-midine-5-carbohydrazide have shown significant antimicrobial activity.

Materials and Methods
Materials
Indole was obtained as a gift sample from Shreya life sciences Pvt. Ltd. Aurangabad. Ethanol, DMF, Phosphorous oxychloride, zinc chloride, Ethyl acetoacetate, hydrazine hydrate, Thiourea, guanidine, Aromatic and heterocyclic aldehyde was obtained as a gift sample from Merck, Sigma and Research lab. All chemicals and reagents used were of analytical grade.

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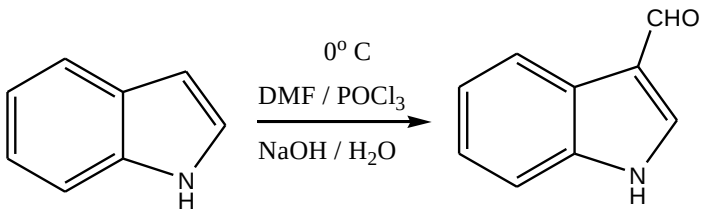
Method

General procedure for synthesis of indole-3-carbaldehyde:Formylation of indole.

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

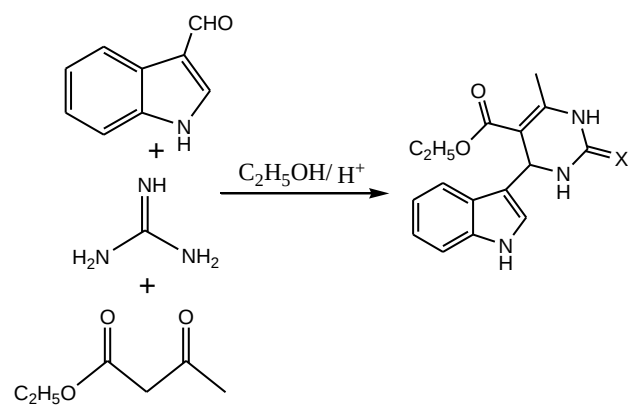
In a three-necked flask fitted with an efficient mechanical stirrer and dropping funnel is placed 28.8 ml of freshly distilled dimethylformamide. The flask and its contents are cooled in an ice-salt bath for about 0.5 hour, and 8.75 ml of freshly distilled phosphorus oxychloride is subsequently added with stirring to the dimethylformamide over a period of 0.5 hour. The pinkish color of the formylation complex is 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 10.2 ml of dimethylformamide is added to the yellow solution over a period of 1 hour during which time the temperature should not rise above 10°. Once the solution is well mixed, the dropping funnel is replaced with a thermometer and the temperature of the viscous solution is brought to 35°. The syrup is stirred efficiently at this temperature for 1 hour, or for 15 minutes longer than is necessary for the clear yellow solution to become an opaque, canary-yellow paste. At the end of the reaction period, crushed ice is added to the paste with careful stirring, producing a clear, cherry-red aqueous solution. This solution is 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 is added drop wise with stirring until about one-third of it has been added. The remaining two-thirds is added rapidly with efficient stirring , and the resulting suspension is heated rapidly to the boiling point and allowed to cool to room temperature, after which it is placed in a refrigerator overnight. The precipitate is collected on a filter and resuspended in water. Most of the inorganic material dissolves and the product is then collected on a filter, washed with water and air-dried, yielding about 12 g.(97%) of indole-3-aldehyde, m.p. 196–197°. The pure product is obtained by recrystallization from ethanol[4].



General procedure for the synthesis of indoledihydropyrimidines:

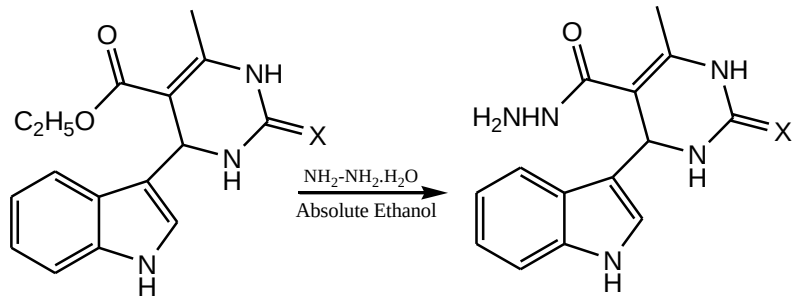
Step-2: Synthesis of ethyl 2-(thioxo/imino)-4-(1H-indol-3-yl)-6-methyl-1,2,3,4- tetrahydropyrimidine-5- carboxylate.

A mixture of indole -3-carbaldehyde **(**1 eq), urea or thiourea **(**2 eq), ethylacetoacetate **(**1 eq) in ethanol was heated under reflux in the presence of $ZnCl_2$ as 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 pure product is obtained by recrystallization from ethanol[5]. Yielding about (92%) of indole dihydropyrimidines, m.p. 228-230°



Step-3: Synthesis of 2-thioxo/imino-4-(1H-indol-3-yl)-6-methyl-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 TLC was used to monitor the progress of the reaction. Excess solvent was removed and on cooling a solid was formed. The solid was crystallized from ethanol[6].

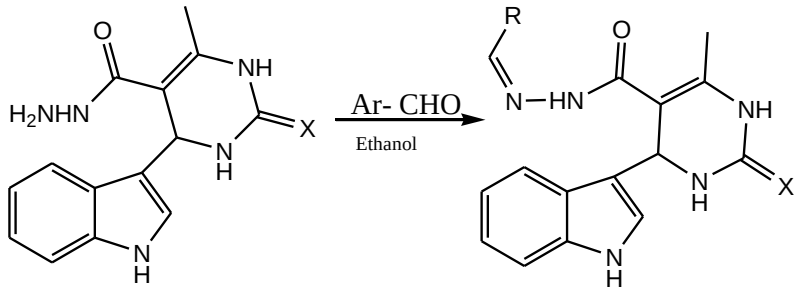


Step-4

Synthesis of (Z)-N'-(benzylidene/ylmethylene)-2-(thioxo/imino)-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide.

Procedure: Schiff's base/ imine formation**.**

Mixture of equimolar quantity of 2-substituted-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide and substituted aldehydes was refluxed in ethanol for 2-2.5 hr on heating mantle. The reaction mixture was then concentrated and cooled. Thus obtained solid was filtered and dried. The yield and MP of the product was recorded. The crude product was recrystallized from ethanol. Purity of the product was checked by TLC[7].



Antifungal activity

Antifungal activities of newly synthesized compounds were studied against the fungal organisms. The antifungal activities of synthesized compounds were studied against *Candida albicans*, *A. niger* and *A. clavatus.* The fungal cultures were inoculated into Sabouraud's broth and incubated under aerobic and at 25°C for 48 hrs.

Cup-plate method

Preparation of test solution

Test solution was prepared by dissolving 10 mg of the synthesized compound in 10 ml of sterile dimethyl formamide (DMF) to obtain a concentration of 1000 µg/ml. All the solutions were prepared under aseptic conditions. Griseofulvin and Nystatin were taken as standard drug for the comparison of the activity of the synthesized compounds[8]. The medium was prepared by dissolving the specified quantities of dehydrated medium (Hi-media) in purified water. The medium was distributed in 4 ml quantities into test tubes. The tubes were closed with cotton plug and sterilized by autoclaving at 121˚C (15 lbs PSIG) for 15 min.

Procedure

Each Petri dish containing nutrient agar medium was inoculated with one bacterial culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. In each plate cups of 6 mm diameter were made at equal distances using sterile cork borer. One cup was filled with 0.1 ml of standard drug i.e. Griseofulvin, one was filled with 0.1 ml of DMF; others were filled with 0.1 ml of synthesized compound's solution in sterile DMF. All plates were kept in the refrigerator for 30 minutes to allow the diffusion of the sample to the surrounding agar medium. The Petri dishes were incubated at 25°C for 48 hrs. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameter obtained for the test samples were compared with that produced by standard griseofulvin[9].

Determination of MIC by tube dilution technique

All the synthesized compounds were dissolved separately to prepare a stock solution containing 1000 µg/ml of DMF. 10 mg of different synthesized compounds were dissolved in 10 ml of the DMF, thus 1 ml of the resulted solution gives 1000 µg/ml. 1 ml of the above solution was transferred to 1 ml of DMF to give half the concentration of first. Thus successive concentrations like 500, 250, 125 and 62.5 so were prepared in a similar manner up to 6 dilutions from sixth one ml of the solution is discarded. The tubes were mixed well after each addition. All the tubes were inoculated with one loop full of one of the test organism. The process was repeated with different test organism. A positive control and a negative control were also prepared to confirm the nutritive property and sterility, respectively of the prepared medium. The tubes were incubated at 25^0C for 48 hours. The presence or absence of growth of organism was observed after incubation[10].

Result and Discussion

Route of synthesis

(Z)-N'-(benzylidene/ylmethylene)-4-(1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide T(1-10) and (Z)-N'- (benzylidene / ylmethylene) -2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide G (1-10) were synthesized as per the scheme of synthesis. The intermediate 1H-indole-3-carbaldehyde were synthesized by formylation of indole in presence of dimethyl formamide, Phosphorus oxychloride, NaOH and water. Ethyl 2-(thioxo/imino)-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetra hydropyrimidine-5- carboxylate was synthesized by refluxing 1H-indole-3-carbaldehyde with thiourea/guanidine and ethyl acetoacetate in presence of acid catalyst and ethanol.2--(thioxo/imino)-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbo hydrazides were synthesized by refluxing ethyl 2--(thioxo/imino)-4-

(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetra hydropyrimidine-5- carboxylate and hydrazine hydrate in presence of acid catalyst and ethanol. (Z)-N'-substituted-4-(1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4 -tetrahydropyrimidine-5 -carbohydrazide T (1-10) and (Z)-N'-substituted-2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide G (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.

Physical studies

Melting point

Melting points were recorded for each compound in open capillary tube and are uncorrected.

Thin Layer Chromatography

All the reactions were monitored by TLC using precoated TLC plates with Silica gel. The absence of TLC spots for starting materials and appearance of new TLC spot at different R_f value were ensured purity and completion of reaction. The TLC plates were visualized in glass chamber saturated with the iodine vapours. The reaction products of all the reactions were purified initially by different workup processes to remove unreacted starting materials if any and then by recrystallization using suitable solvents. Most of the steps were optimized in order to achieve quantitative yields i.e. more than 70% yields. R_f value was determined by using following equation

$$\mathbf{R_f} = \frac{\text{Distance traveled by solute front}}{\text{Distance traveled by solvent front}}$$

Spectral studies

The FTIR spectra were obtained using Jasco FTIR-4000 and peaks were expressed in terms of wave number (cm^{-1}). The PMR spectra of some compounds were scanned on Bruker advance II 400 NMR spectrophotometer in DMSO using TMS as internal standard. The chemical shifts were represented in δ ppm. The ^{1}HNMR spectra in detail are discussed in spectral characterization. Mass spectra were recorded on Micro mass Q-Tof Micro system. The spectral data is in accordance with assumed structures.

Indole

IR spectra was confirmed by the presence of aromatic N-H stretching at 3380 (m) cm^{-1}, Aromatic C-H stretching at 3150-3050 cm^{-1}, The PMR spectra of indole showed the presence of -CH at 7.27-7.00 ppm region as multiplet. Proton of –NH group of indole was observed at 10.1 ppm as broad singlet.

Intermediate Spectral characterization of 1H-indole-3-carbaldehyde.

The IR spectra were confirmed by N-H stretching bands at 3251cm^{-1} and aromatic ring stretching at 2966 cm^{-1}. Also the aldehydic -CH stretching at 2700 cm^{-1} and C=O stretching of aldehyde at 1734 cm^{-1} also confirmed the formation of 1H-indole-3-carbaldehyde. The PMR spectra of 1H-indole-3-carbaldehyde showed the presence of -NH at 10.1-10.10 ppm region. Proton of –CH group of 1H-indole-3-carbaldehyde was observed at 7.55-7.00 ppm as multiplet. The –CH of CHO found at 9.73-9.60 ppm region.

2-Imino-4-(1H-indol-3-yl)-6-methyl -1, 2, 3, 4-tetrahydropyrimidine-5-carbohy-drazide.

IR peaks shown at –NH-NH- showing secondary amine within the range of 3352 cm^{-1}, the amine stretching (NH) was found in the range 3266 cm^{-1}, C-H stretching of aromatic ring observed at 2966 cm^{-1} , C-H stretching at 2884 cm^{-1} and C=O Stretching of ester was found at 1717 $cm^{-1.}$

The PMR spectra of 2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydro pyrimidine-5-carbohydrazide showed the presence of $–CH_3$ at 2.26 ppm region -NH at 10.1 ppm region. The –NH amine was observed at 2.0 ppm region. Proton of –CH group of 2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide was observed at 7.18-7.11 ppm as multiplet. The –NH of secondary amide was found at 8.0 ppm region.

(Z)-N'-(2-Hydroxybenzylidene)-2-imino-4-(1H-indol-3-yl)-6-methyl-1,2,3,4-tetra hydropyrimidine-5-carbohydrazide:

IR peaks shown the Phenolic –OH in the range 3610 cm^{-1} , the amine stretching (NH) in the range 3266 cm^{-1}, C-H stretching of aromatic ring observed at 2966 cm^{-1} , C-H stretching at 2884 cm^{-1} , C=N stretching at 1680 cm^{-1} , C=O stretching of amide was found at 1515 cm^{-1} and C-N stretching was found at 1310 cm^{-1}. The PMR spectra of (Z)-N'-(2-Hydroxybenzylidene)-2-imino-4-(1H-indol-3-yl)-6-methyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide showed the presence of –NH amine at 2.0 ppm region. The $–CH_3$ was found at 2.26 ppm region. –CH pyrimidine at 4.16 ppm, aromatic C-OH at 5.35 ppm, -CH of aromatic ring at 6.95-7.60 ppm,

-CH of indole at 7.18 ppm, =CH of azomethine (Schiff base) at 8.78 ppm was observed. The –NH of indole found at 10.1 ppm and -NH amine was observed at 13.76 ppm region.

Antimicrobial studies

The antimicrobial study was carried out at Microcare Laboratory, Surat. In order to ensure the therapeutic efficacy of a substance, one should determine susceptibility of the microorganisms to that substance. In vitro tests like cup-plate method or the paper disc plate method or tube dilution technique are used for this purpose

Anti fungal activity

The antifungal activities of synthesized compounds were studied against *Candida Albicans, A. Niger* and *A. Clavatus.*

Conclusion

The Antifungal activity was performed using the Tube dilution technique against *Candida albicans, A. Niger, and A. clavatus* (Griseofulvin and Nistatin as a standard). Some of the synthesized compounds such as G-4 (2-hydroxyphenyl), G-5 (R= furfuryl), G-8 (R= 2, 4 Dichlorophenyl), T-5 (R= furfuryl), T-7 and T-8 (R= thiophenyl) were found to be equally potent as to the standard drug Griseofulvin and Nistatin.

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Fig. No. 1: MFC of Antifungal activity (MFC µg/ml) (T1-T10 Derivatives).

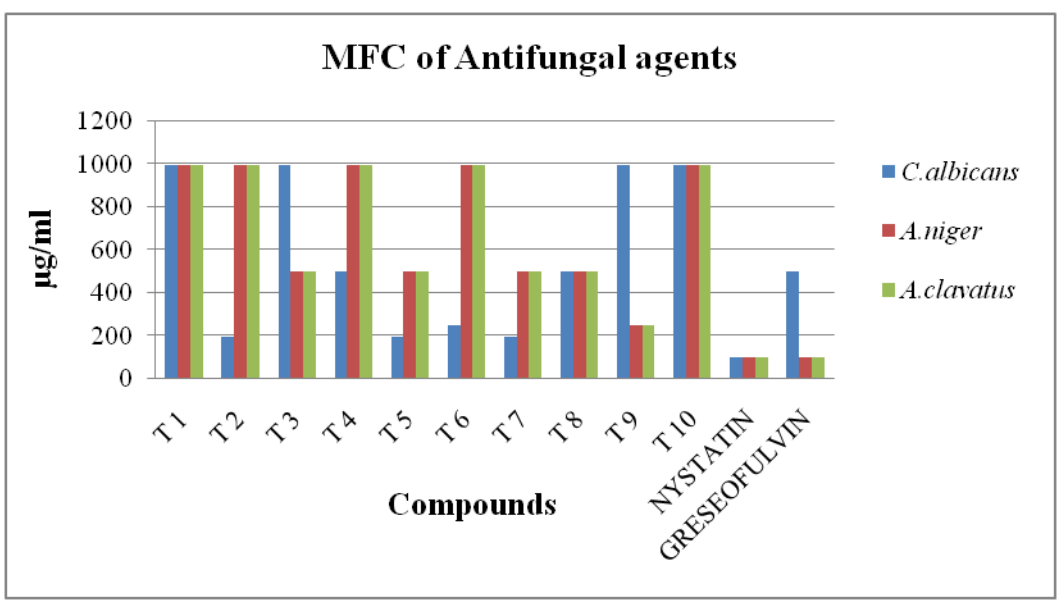


Table 1: Characterization data for (Z)-N'-substituted-4-(1H-indol-3-yl)–6-methyl -2- thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide.

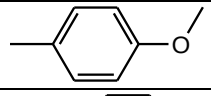
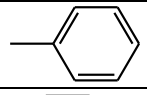
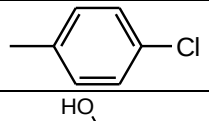
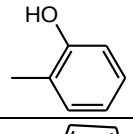
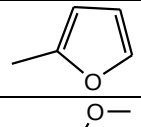
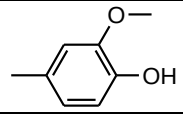
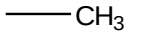
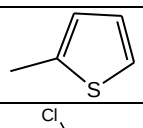
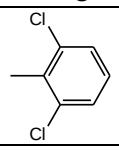
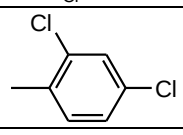
S.No.	X	R	Molecular Formula	Molecular Weight	% yield	Melting Point (^{0}C)	R_f Value
T-1	S		$C_{22}H_{21}N_5O_2S$	419.50	68.46	155	0.64
T-2	S		$C_{21}H_{19}N_5OS$	389.47	73.95	166	0.66
T-3	S		$C_{21}H_{18}ClN_5OS$	423.92	76.14	182	0.78
T-4	S		$C_{21}H_{19}N_5O_2S$	405.47	52.45	190	0.58
T-5	S		$C_{19}H_{17}N_5O_2S$	379.44	52.45	188	0.42
T-6	S		$C_{22}H_{21}N_5O_3S$	435.50	64.12	256	0.56
T-7	S		$C_{16}H_{17}N_5OS$	327.40	76.13	242	0.34
T-8	S		$C_{19}H_{17}N_5OS_2$	395.50	82.45	196	0.7
T-9	S		$C_{21}H_{17}Cl_2N_5OS$	458.36	64.76	166	0.88
T.10	S		$C_{21}H_{17}Cl_2N_5OS$	458.36	58.15	158	0.84

Table 2: Characterization data for (Z)-N'-substituted-2-imino-4-(1H-indol-3-yl)- 6- methyl- 1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide.

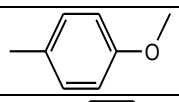
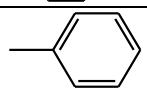
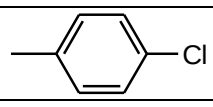
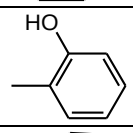
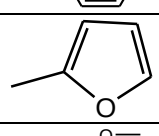
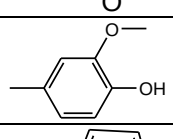
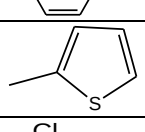
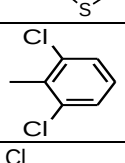
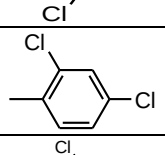
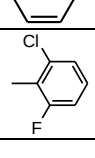
S.No.	X	R	Molecular Formula	Molecular Weight	% yield	Melting Point (^{0}C)	R_f Value
G-1	NH		$C_{22}H_{22}N_6O_2$	402.45	75.12	140	0.58
G-2	NH		$C_{21}H_{20}N_6O$	372.42	64.76	164	0.63
G-3	NH		$C_{21}H_{19}ClN_6O$	406.87	58.15	182	0.72
G-4	NH		$C_{21}H_{20}N_6O_2$	388.42	68.46	162	0.56
G-5	NH		$C_{19}H_{18}N_6O_2$	362.39	73.95	168	0.34
G-6	NH		$C_{22}H_{22}N_6O_3$	418.45	76.14	170	0.5
G-7	NH		$C_{19}H_{18}N_6OS$	378.45	52.45	122	0.64
G-8	NH		$C_{21}H_{18}Cl_2N_6O$	441.31	64.12	154	0.82
G-9	NH		$C_{21}H_{18}Cl_2N_6O$	441.31	76.13	138	0.78
G.10	NH		$C_{21}H_{18}ClFN_6O$	424.86	82.45	160	0.74

Table 3: Preparation of Sabouraud's agar medium.

Dextrose	20 mg
Agar	20 gm
Peptone	10 gm
Water	1000 ml
pH	5.4 ± 0.2

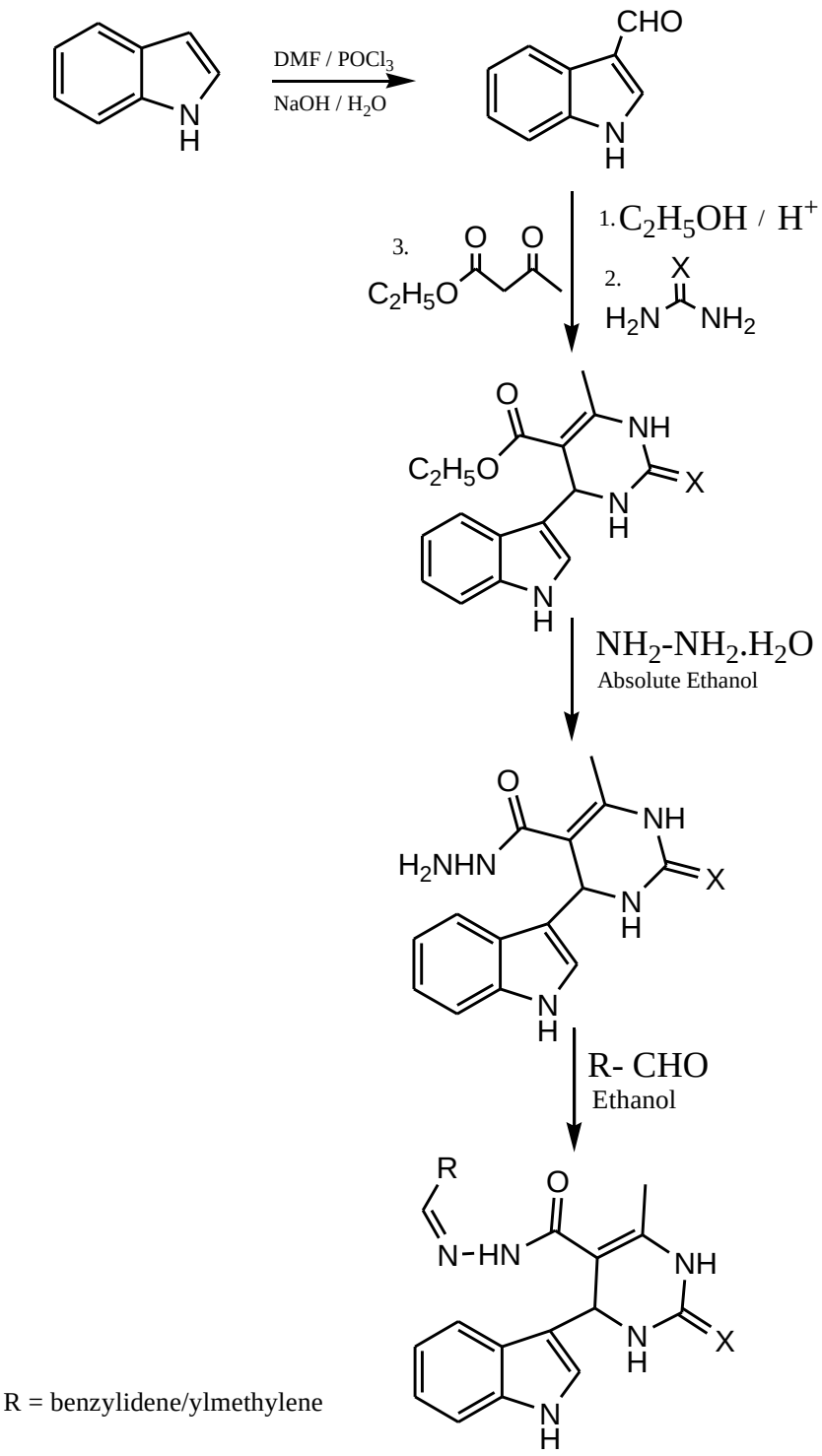
Table 4: Data of Antifungal activity (MFC µg/ml).

Compound No.	***C.Albicans MTCC 227***	***A.Niger MTCC 282***	***A.Clavatus MTCC 1323***
T-1	**125**	**125**	500
T-2	200	200	**100**
T-3	250	250	**100**
T-4	200	**125**	**100**
T-5	**125**	**100**	**125**
T-6	500	500	**62.5**
T-7	**100**	250	**125**
T-8	250	200	250
T-9	**62.5**	**125**	250
T-10	200	200	**100**
G-1	200	200	200
G-2	250	250	250
G-3	250	200	**125**
G-4	200	**100**	500
G-5	**62.5**	**100**	**100**
G-6	**100**	**125**	200
G-7	**62.5**	200	**100**
G-8	200	250	**62.5**
G-9	250	250	**100**
G-10	200	200	250
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

Table 5: MFC of Antifungal activity (MFC µg/ml) (G1-G10 Derivatives).

Compound No.	***C. Albicans MTCC 227***	***A.Niger MTCC 282***	***A. Clavatus MTCC 1323***
G-1	200	200	200
G-2	250	250	250
G-3	250	200	**125**
G-4	200	**100**	500
G-5	**62.5**	**100**	**100**
G-6	**100**	**125**	200
G-7	**62.5**	200	**100**
G-8	200	250	**62.5**
G-9	250	250	**100**
G-10	200	200	250
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

Fig. 2: Scheme of Synthesis.



X=NH (Z)-N'-(benzylidene/ylmethylene)-2-imino-4-(1H-indol-3-yl)-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**G1-G10)**

X=S (Z)-N'-(benzylidene/ylmethylene)-4-(1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**T1-T10)**

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