Focused On Fungal Disease Covering Prominent Targets and the Potent Compounds

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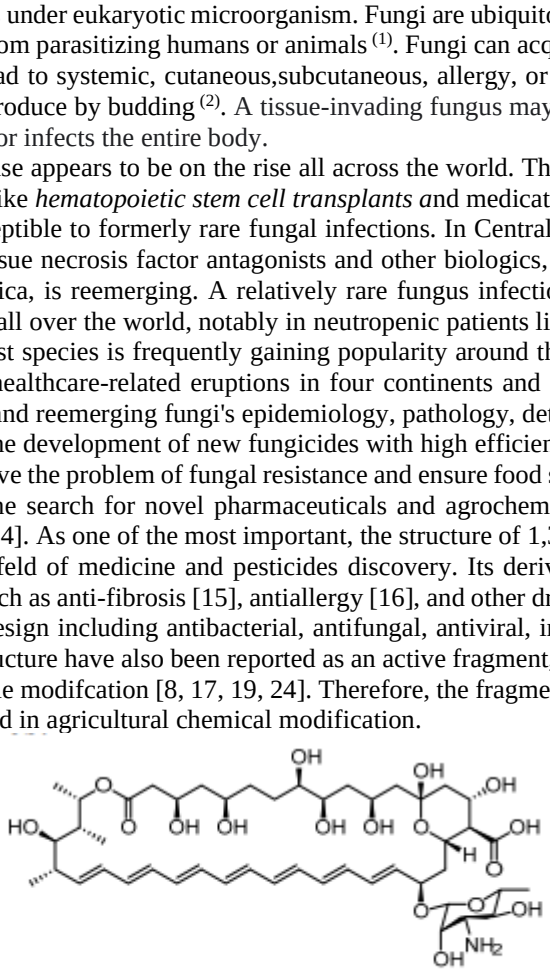
Abstract: In individuals with immunocompromised system, fungal infection is a common problem that frequently result in high rates of morbidity and mortality. Five separate antifungal drug classes are used in current therapy, four of which concentrate on ergosterol and cell wall glucan production. However, there are several disadvantages to using the antifungals that are now on the market, including poor oral bioavailability, limited therapeutic indices, and the development of drug resistance as a result of their use. Recent improvements in the research and development of antifungaldrugs can be seen in the appearance of several novel compounds that are now in various phases of development.

Keywords : CYP51, Squalene epoxidase, Drug targets, Antifungal, Fluconazole.

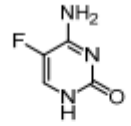
Fungi comes under eukaryotic microorganism. Fungi are ubiquitous and found throughout the worldas free-living saprobes that gain no benefit from parasitizing humans or animals [(1)]. Fungi can acquirethe shape of yeasts, moulds, and a combination of both. Some fungi can lead to systemic, cutaneous,subcutaneous, allergy, or superficial illnesses. Yeasts are microscopic fungus with solitary cells thatreproduce by budding [(2)]. A tissue-invading fungus may result in a sickness that affects only the skin,extends to the bones and organs, or infects the entire body.

Fungal disease appears to be on the rise all across the world. This may be partially explained by the surge in immune-suppressing procedures like *hematopoietic stem cell transplants a*nd medications like tissue necrosis factor antagonists, which have made more people susceptible to formerly rare fungal infections. In Central and South America, as well as among patients in North America receiving tissue necrosis factor antagonists and other biologics, the fungus Histoplasma capsulatum,which is native to North and South America, is reemerging. A relatively rare fungus infection calledfusarium species is reemerging in immunocompromised populations all over the world, notably in neutropenic patients like those who have undergone hematopoietic stem cell transplants. A novel yeast species is frequently gaining popularity around the world: Candida auris was previously unknown. It is generating large-scale healthcare-related eruptions in four continents and spreading around the world thanks to patient travel. These three developing and reemerging fungi's epidemiology, pathology, detection, and therapy will be covered in this review.

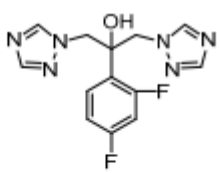
Therefore, the development of new fungicides with high efficiency, low toxicity, and no cross-resistance undoubtedly an effective means to solve the problem of fungal resistance and ensure food security. Nitrogen-containing heterocycles are known as a research hotspot in the search for novel pharmaceuticals and agrochemicals due to their unique structural characteristics and biological activity [8–14]. As one of the most important, the structure of 1,3,4-oxadiazole group is an active pharmacophoreore which widely used in the feld of medicine and pesticides discovery. Its derivatives have been reported to possess a wide range of biological activities, such as anti-fibrosis [15], antiallergy [16], and other drugs [17, 18]. It has also been widely used as a scafold in pesticides molecular design including antibacterial, antifungal, antiviral, insecticidal, and herbicidal [19–29]. The derivatives of oxadiazole biphenyl structure have also been reported as an active fragment, which can obtain the compound with excellent biological activity just by simple modifcation [8, 17, 19, 24]. Therefore, the fragment of 1,3,4-oxadiazole or its biphenyl derivatives can be used as an active scafold in agricultural chemical modification.



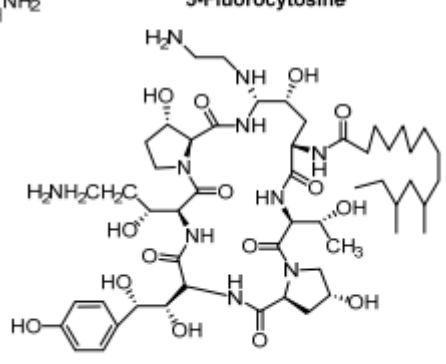
Amphotericin B



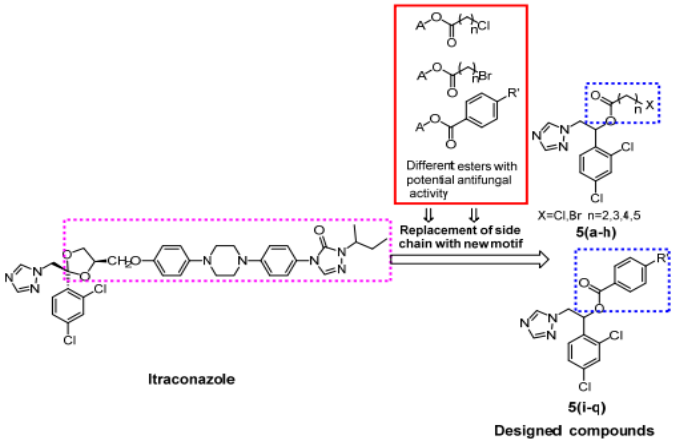
5-Fluorocytosine



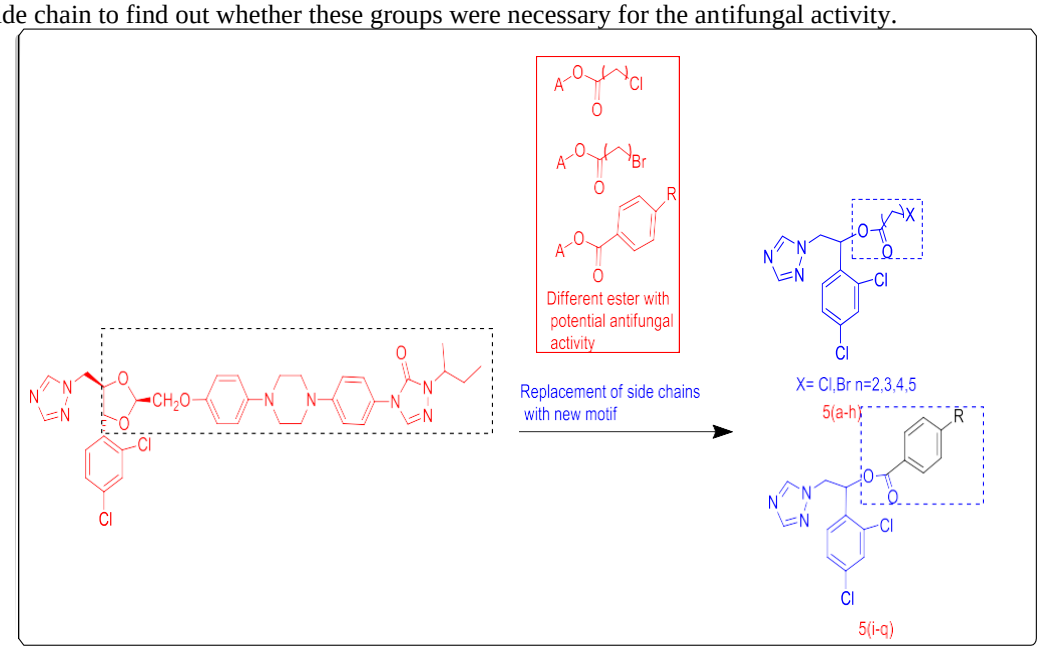
Fluconazole



Caspofungin

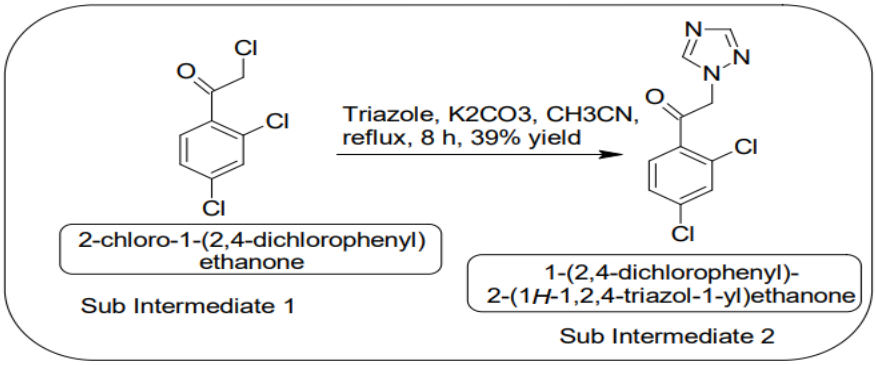


Studies showed that16) the antifungal triazoles featured a core structure composed of a triazole, a halophenyl ring, while differing in the side chains. The development of triazole drugs is primarily driven through structure optimization especially of the side chains as well as SAR study. Itraconazole (Fig. 2) is the triazole antifungal drug available in the market and widely used for candidiasis. The long side chain of itraconnazole containing four linearly linked cyclic rings might attribute to its low solubility and erratic bioavailability, which drove the research to design novel agents with medium side chains.17) Therefore, replacing the long side chain in the itraconazole structure with different ester moieties containing aryl rings and halogenated alkyl chain might result in novel triazole antifungal drugs. Furthermore, molecular docking study indicated that the triazole bound to the heme iron of CYP51, and the halo phenyl ring could locate into the hydrophobic pocket.18) We hypothesized that the ester moieties might accommodate in the deep cavity of CYP51, as well as providing in hydrophobic pockets of the biological targets which contribute to improve the potency, stability and specificity of the binding site. In addition, the ester groups were to be introduced in the target compounds because they could be further removed to reduce molecular weight. The halogen as a strong electron-withdrawing group could affect the charge distribution and hydrophobility of drug molecules and the time of drug action. Thus, the halogenated alkyl chain was to be introduced to leave large space for further optimization. The above mentioned promoted us to design and synthesize a series of 1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethyl derivatives containing a triazole ring, a dichlorophenyl group, and ester groups in the side chain. In our design, the structure of itraconazole was altered as a platform and different ester groups were insert into the side chain to find out whether these groups were necessary for the antifungal activity.



The procedure of Intermediate I 2-Chloro-1-(2,4- dichlorophenyl) ethenone • To the stirred solution of 1,3-Dichlorobenzene in 15ml methylene dichloride (DCM) at 0 °C for 1 hour in Round Bottom Flask. An inert atmosphere was provided by attaching a nitrogen balloon with RBF. • Chloro acetyl chloride (49.65mml, 6.875ml) was added dropwise in the reaction vessel. Monitoring of the ongoing reaction was performed by the TLC analysis in Benzene and ethyl acetate (5%) solvent system; the reaction was completed After 8 hour that was detected by TLC. • Ethyl acetate was taken to extract the mixture (3 times) after it was diluted with water. After drying the mixed organic layers over sodium sulphate and washing them with water, the solvent was removed to reveal the solid result.

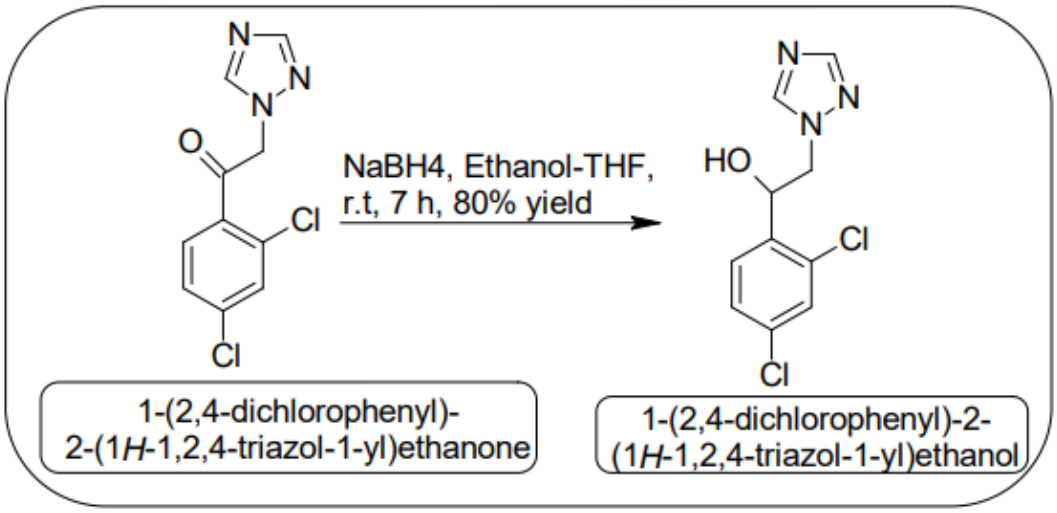
• Reaction Scheme of Sub Intermediate II (1-(2,4-dichlorophenyl)-2-(1H1,2,4-triazol-1-yl) ethenone)



The procedure of Intermediate II (1-(2,4-dichlorophenyl)-2-(1H-1,2,4- triazol-1-yl) ethenone)

The mixture of 2-Chloro-1-(2,4-dichlorophenyl) ethenone (7.15mmol, 2g) and 1,2,4- triazole and K2CO3(17.8mmol, 1.16g) in 10 ml Acetonitrile were taken in RBF. The reaction blend was heated at 70-90°C. After 5-6 hours the TLC monitoring in Benzene and ethyl acetate (2.5%) indicated complete consumption of reactants, after decreasing to room temperature, the solution was poured into chilled water and extracted with ethyl acetate (3 times). Sodium sulphate was used to dry the mixed organic layers after they had been rinsed with water and brine. To get the raw material, the solvent was evaporated.

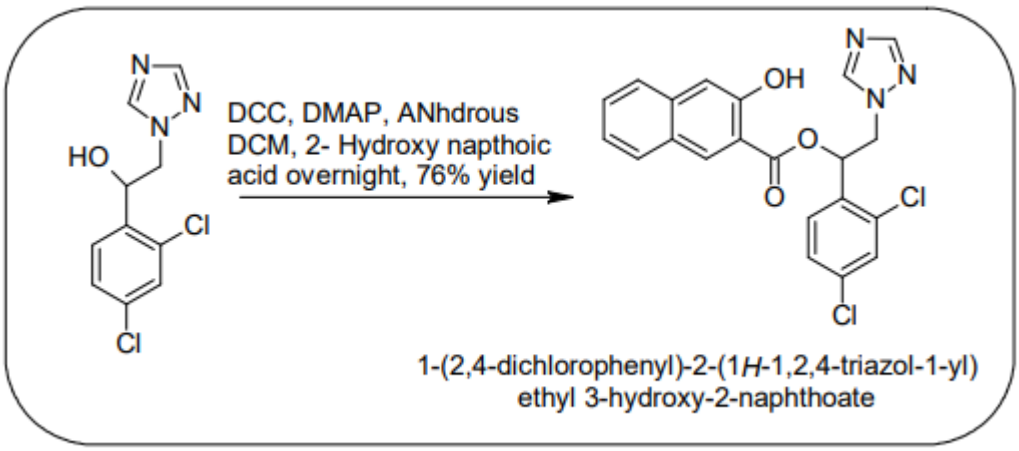
Reaction Scheme of Intermediate III 1-(2,4-dichlorophenyl)-2-(1H-1,2,4- triazol-1-yl) ethanol.

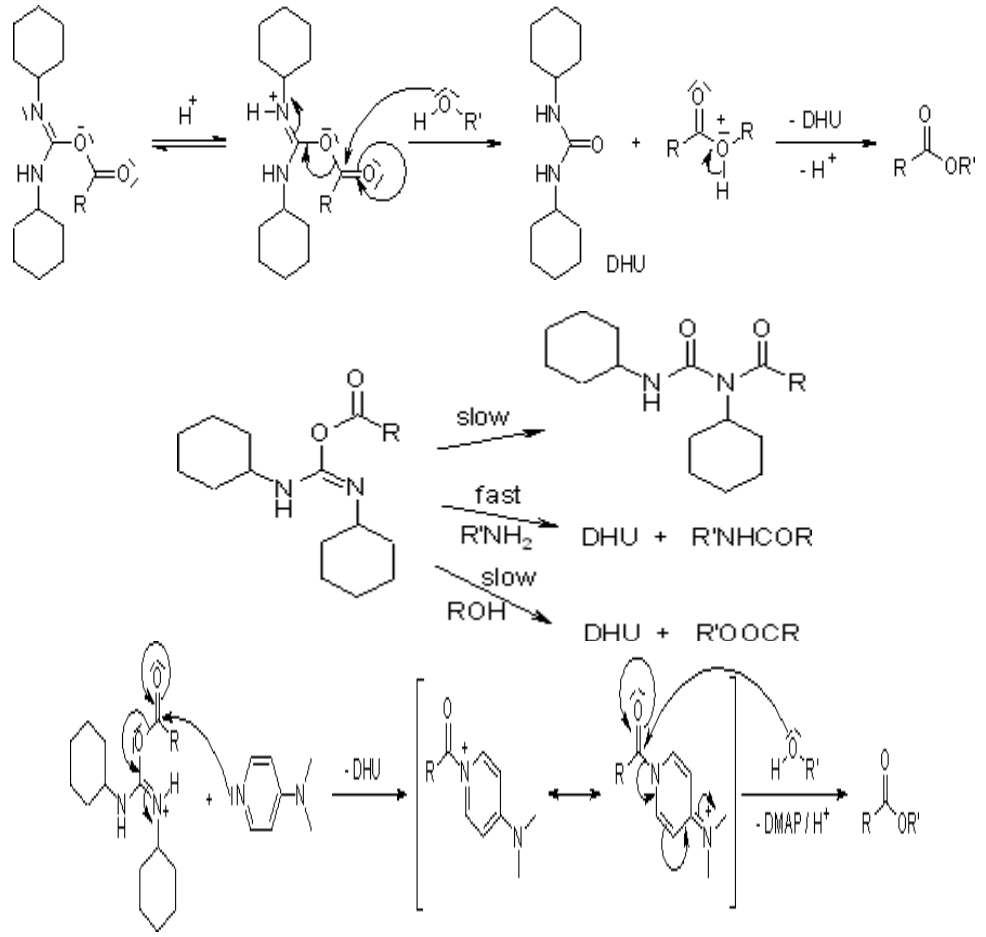


The procedure of Intermediate III 1-(2,4-dichlorophenyl)-2-(1H-1,2,4- triazol-1-yl) ethanol.

- Sodium borohydride (14.97mmol,2.5 g) was dissolved in 7ml of ethanol in RBF. Tetra hydro furan (THF) (16.46mmol, 2.27ml) were added to the reaction vessel.
- The reaction was stimulated for 1 hour at room temperature then TLC was checked in Hexane and ethyl acetate (5%) solvent system which detected that the reaction was completed in 1 hour.
- Subsequently, the mixture was transferred into ice-cold water; the precipitate was formed and collected by filtration.

General reaction scheme of substitution (here we take different acids)





DCC (dicyclohexylcarbodiimide) and the carboxylic acid can combine to create an intermediate called O-acylisourea, which has properties that are comparable to thoseof the equivalent carboxylic acid anhydride:

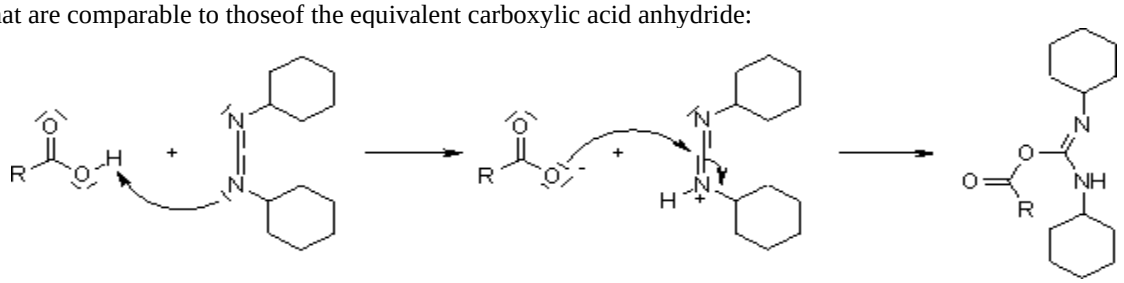
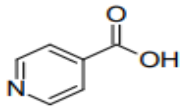
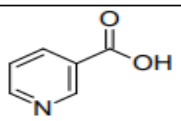
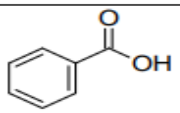
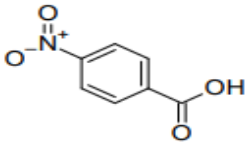
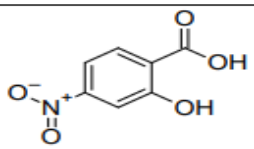
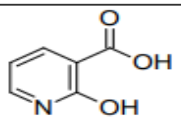
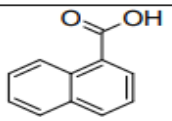
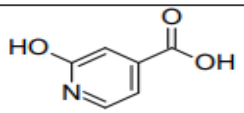
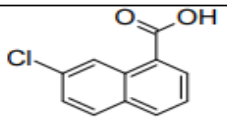


Table 2: Different substituted R groups

S. No.	R group	Name of the group
1.		Nicotinic acid
2.	 Iso-nicotinic acid	Iso-nicotinic acid
3.		Benzoic acid
4.		4-Nitro Benzoic acid
5.		4- nitro 2-hydroxy benzoic acid
6.		2-hydroxynicotinic acid
7.		Naphthoic acid
8.		2-hydroxy iso-nicotinic acid
9.		7-chloro-1-naphthoic acid

RESULTS AND DISCUSSION

The main objective of the present study is to design different trifluoromethyl containing quinolone derivatives against the CYP51 target as anti-tubercular About 21 derivatives were designed and a GLIDE score was obtained using the GLIDE module (Grid-based Ligand Docking with Energetics, version Schrodinger 9.1, LLC, New York 2010, at CADD laboratories, S.G.S.I.T.S, Indore.

Characterization of compounds

Characterization of compounds was performed via the following methods:

- Thin layer Chromatography
- Melting Point determination
- IR Spectroscopy
- NMR Spectroscopy
- Mass Spectroscopy

Thin layer Chromatography:

Rf value and the optimized mobile phase for the given compounds are reported inTable no. 3

Rf value of synthesized compounds along with the solvent system Table 3: Mobile Phase and Rf value of synthesized compounds

Sr. No.	Compound Code	Rf Value	Mobile Phase
1	AP1	0.38	Benzene: Ethyl Acetate (6: 4)
2	AP2	0.36	Benzene: Ethyl Acetate (6: 4)
3	AP3	0.53	Benzene: Ethyl Acetate (6: 4)
4	AP4	0.54	Benzene: Ethyl Acetate (6: 4)
5	AP5	0.35	Benzene: Ethyl Acetate (5: 5)
6	AP6	0.44	Benzene: Ethyl Acetate (6: 4)
7	AP7	0.28	Benzene: Ethyl Acetate (6: 4)
8	AP8	0.51	Benzene: Ethyl Acetate (6: 4)
9	AP9	0.31	Benzene: Ethyl Acetate (6: 4)

During progression of reaction TLC has been checked to confirm whether thecompound or intermediate is formed or not. Here, the table No. 3 indicated that the compounds had given single spot with these above Rf value.

Melting Point Determination and Practical Yield:

Melting Point determination and Practical yield of the given compounds are reportedin table no.

Compound Code, Molecular Weight, % Yield, and Melting Point

Table 4: Compound Code, Molecular Weight, % Yield, and Melting Point

npoundCode	**lolecular Weight**	**MolecularFormula**	**leltingPoint**	**Yield ofCrude Product**	**Yield ofPure Product**
AP- 01	182.22	$C_{12}H_{10}N_2$	170-172°C	56.365%	54.127%
AP- 02	216.67	$C_{12}H_9ClN_2$	103°C-105°C	63.550%	15.65%
AP- 03	225.29	$C_{14}H_{15}N_3$	225°C-230°C	75.560%	40.175%
AP- 04	225.29	$C_{12}H_9ClN_2$	202°C-204°C	42.501%	47.021%
AP- 05	198.22	$C_{12}H_{10}N_2O$	183°C-186°C	66.933%	41.92%
AP- 06	196.25	$C_{13}H_{12}N_2$	150°C-154°C	72.976%	25.66%
AP- 07	216.67	$C_{12}H_9ClN_2$	188°C-191°C	50.843%	46.91%
AP- 08	198.22	$C_{12}H_{10}N_2O$	196°C-201°C	52.402%	40.00%
AP- 09	196.25	$C_{13}H_{12}N_2$	184°C-187°C	74.853%	71.005%
AP-10	253.34	$C_{16}H_{19}N_3$	215°C-221°C	41.978%	33.18%

According to the table no.4, the synthesized compounds having melting point in range that suggests us that the synthesized compounds is good and can be allowed tosend it for further pharmaceutical analysis.

IR- Spectroscopy

AP- 01

(IR (KBr): υ 3379 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 02(IR (KBr): υ 3379 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),

1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 03

(IR (KBr): υ 3308 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 04

(IR (KBr): υ 3369 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 05

(IR (KBr): υ 3359 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 06

(IR (KBr): υ 3330 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 07

(IR (KBr): υ 3379 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 08

(IR (KBr): υ 3328 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

AP - 09

(IR (KBr): υ 3379 (O-H peak), 780 (C-H Stretching), 1708 (aliphatic ketone),1768(C=C bonding), 690 (C-Cl bonding) cm^{-1}.

6.0.1 1H NMR Spectroscopy

^{1}H NMR of the given compounds are reported below:

AP- 01

^{1}H NMR (500 MHz, DMSO3) δ 8.68 (d, J = 8.8 Hz, 1H,ArH), 8.27 (m, 2H,ArH), 7.65 (dd, J = 8.5, 1.4 Hz,1H,ArH), 7.45 (s, 1H,ArH), 7.38 (d, J = 8.5 Hz, 2H,ArH), 5.54 (s,2H,CH_2), 4.43 (q, J = 7.1 Hz, 2H,CH_2), 1.43 (t, J = 7.1Hz, 3H,CH_3).

AP- 02

^{1}H NMR (500 MHz, DMSO) δ 8.65 (m, 2H, ArH), 7.62 (m, 1H, ArH), 7.39 (dt, J = 11.3,6.6 Hz, 3H, ArH), 7.21 (m, 1H, ArH), 5.43 (s, 2H, CH_2), 4.42 (qd, J = 7.2,2.4 Hz, 2H,CH_2), 1.42 (td, J = 7.1, 1.9 Hz, 3H,CH_3).

AP- 04

^{1}H NMR (500 MHz, DMSO) δ 8.64 (t, *J* = 4.2 Hz, 2H, ArH), 7.62 (dd, *J* = 8.4, 1.4 Hz, 1H, ArH), 7.54 (m, 3H, ArH), 7.08(d, *J* = 8.2 Hz, 2H, ArH), 5.38 (s, 2H,CH_2), 4.42 (q, *J* = 7.1 Hz, 2H,CH_2), 1.42 (t, *J* = 7.1 Hz, 3H,CH_3).

AP- 05

^{1}H NMR (500 MHz, DMSO) δ 8.66 (d, J = 7.9 Hz, 2H, ArH), 7.62 (m, 2H ArH), 7.20 (m, 2H,ArH), 7.10 (t, J = 8.5 Hz, 2H, ArH),5.40 (s, 2H,CH_2), 4.42 (q, J = 7.1 Hz, 2H,CH_2), 1.43 (t, J = 7.1 Hz, 3H,CH_3).

AP- 07

^{1}H NMR (500 MHz, DMSO) δ 8.65 (d, J = 9.4 Hz, 2H, ArH), 7.63 (dd, J = 8.4, 1.5 Hz, 1H, ArH), 7.56 (s, 1H,ArH),7.38 (m, 2H, ArH), 7.15 (d, J = 8.2 Hz, 2H, ArH),5.39 (s, 2H,CH_2), 4.42 (q, J = 7.1 Hz, 2H,CH_3), 1.43 (t, J = 7.2Hz,3H,CH_3).

Mass- Spectroscopy:

ADMET Prediction:

ADME Results:

Predicted Result ADME of Compounds

Table 5: ADME of synthesized compounds

ompound Code	**pinskiRule**	**Log P[a]**	**Caco-2[b]**	**PPB[c]**	**BBB Penetration[d]**	**learance[e]**
AP- 01	Accepted	3.883	-4.712	98.50%	0.255	2.87
AP- 02	Accepted	3.998	-4.817	97.70%	0.439	3.518

AP- 03	Accepted	3.054	-4.625	95.43%	0.573	2.064
AP- 04	Accepted	4.767	-4.841	98.02%	0.412	2.377
AP- 05	Accepted	4.091	-4.779	98.27%	0.397	3.657
AP- 06	Accepted	4.6	-4.833	98.88%	0.254	3.447
AP- 07	Accepted	3.728	-4.801	98.17%	0.586	5.189
AP- 08	Accepted	3.771	-4.833	98.20%	0.566	5.538
AP- 09	Accepted	3.776	-4.886	98.02%	0.609	5.508
AP- 10	Accepted	5.444	-5.319	99.46%	0.091	2.864

*a- Optimal:0-3,b- Optimal higher than -5.319 log unit, c-Optimal-15ml/min/kg; moderate: 5-15 ml/min/kg; low:
According, to ABMET tool 2.0, the synthesized compound's that is AP- 01 to AP- 10, can easily obeys Lipinski rule, all compounds fallen in the accepted range. So, that why we can subsequently predict that these compounds can easily cross BBB andthereby their renal clearance is also acceptable.

Toxicity Results:

Predicted Result of Toxicity

Table 6: Toxicity profile of synthesized compound

S. N0	**Compound code**	**HerGBlockers**	**Carcinogeni city (Category 1: carcinogens)(Category 0:noncarcinog ens)**	**Respiratory Toxicity (Categor y**
1	AP1	0.368	0.143	0.754
2	AP2	0.07	0.152	0.816
3	AP3	0.168	0.349	0.89
4	AP4	0.02	0.163	0.711
5	AP5	0.105	0.551	0.962
6	AP6	0.068	0.033	0.959
7	AP7	0.077	0.151	0.992
8	AP8	0.034	0.164	0.829
9	AP9	0.075	0.456	0.755
10	AP10	0.217	0.281	0.487

According, to ABMET tool 2.0, the synthesized compound's that is AP- 01 to AP-

10, These above compounds are having carcinogenicity parameter and respiratorytract toxicity and thereby we can conclude that these compounds are not carcinogenic.

6.1 Biological Evaluation

Table 7: Synthesized compound with % inhibition

Compound Code	**% Inhibition**
IM- 01	**75**
IM- 02	**50.62**
IM- 04	**50**
IM- 05	38.65
IM- 07	**50.27**
Reference	
Nystatin	75
Griseofulvin	50

Among Five compounds, three compounds showed relatively greater percentage inhibition. We compared the biological activity by the result that had been came fromMicrocare Laboratory, Surat. In which they mentioned that the nystatin and griseofulvin is showed the value of 250 and the literature suggested that if any compound fallen below the 250 value that compound can be regarded as potent compounds IM- 01, IM- 02, IM- 05 respectively.

1. Reference:-

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