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SYNTHESIS AND CHARACTERIZATION OF NOVEL PYRIMIDINE-4,5-DIAMINE/ PYRIMIDINE-2,4,5-TRIAMINE AS ANTITB AGENT

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Keywords:

Pyrimidine-4,5-diamine, Pyrimidine-2,4,5-triamine, anti TB

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ABSTRACT: Pyrimidine derivative had a wide range of biological activities, including antiTB activity. In this view, pyrimidine moiety containing N N_5-(3-substituted benzylidene)-N_4-phenyl and N_5-(2-substituted benzylidene)-N_2,N_2-dimethyl-N_4-phenyl compounds was designed, and a novel series of N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F]/N5-(2-substituted benzylidene)-N2,N2-dimethyl-N4-phenyl pyrimidine-2,4,5-triamine [5a-5f], were synthesized, evaluated for their antiTB activity against *MTB* H37Ra strain by MABA screening. Among the all 12 derivatives tested, N_5-(4-methoxybenzylidene)-N_4-phenylpyrimidine-4,5-diamine[5A], N_5-(4-chloro benzylidene)-N_4-phenylpyrimidine-4,5-diamine [5C], N_5-(4-chloro benzylidene)-N_2, N_2-dimethyl-N_4-phenyl pyrimidine-2,4,5-triamine [5c], and N_5-(4-amino benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5E**]** was found to have potent activity against *MTB* H37Ra strain. The compounds bearing electron-withdrawing, donating group's substitution, and its positioning function was important to produce significant activity proved. The obtained results showed that the most active compounds could be useful as a template for future design, structural modification, and investigation to produce more active analogs.

INTRODUCTION: Tuberculosis is the most common disease which is caused by various mycobacterium species in the world. In the developed country the effect of this *Mycobacterium tuberculosis* (*MTB*) diminished but in developing countries, it is a major health problem that affects a major portion of the population in those countries with high mortality rates. The *MTB* has developed resistance against most of the antituberculosis agents that already exist, so the development of a new anti-tuberculotic agent has been done [1, 2].

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Infections caused by *Mycobacterium* species like *MTB*, *M. avium*, *M. kansasaii*, *M. bovis* are known to express multidrug-resistance toward most chemicals, disinfectants, and a number of antibiotics and chemotherapeutics as a consequence of single point mutations [3].

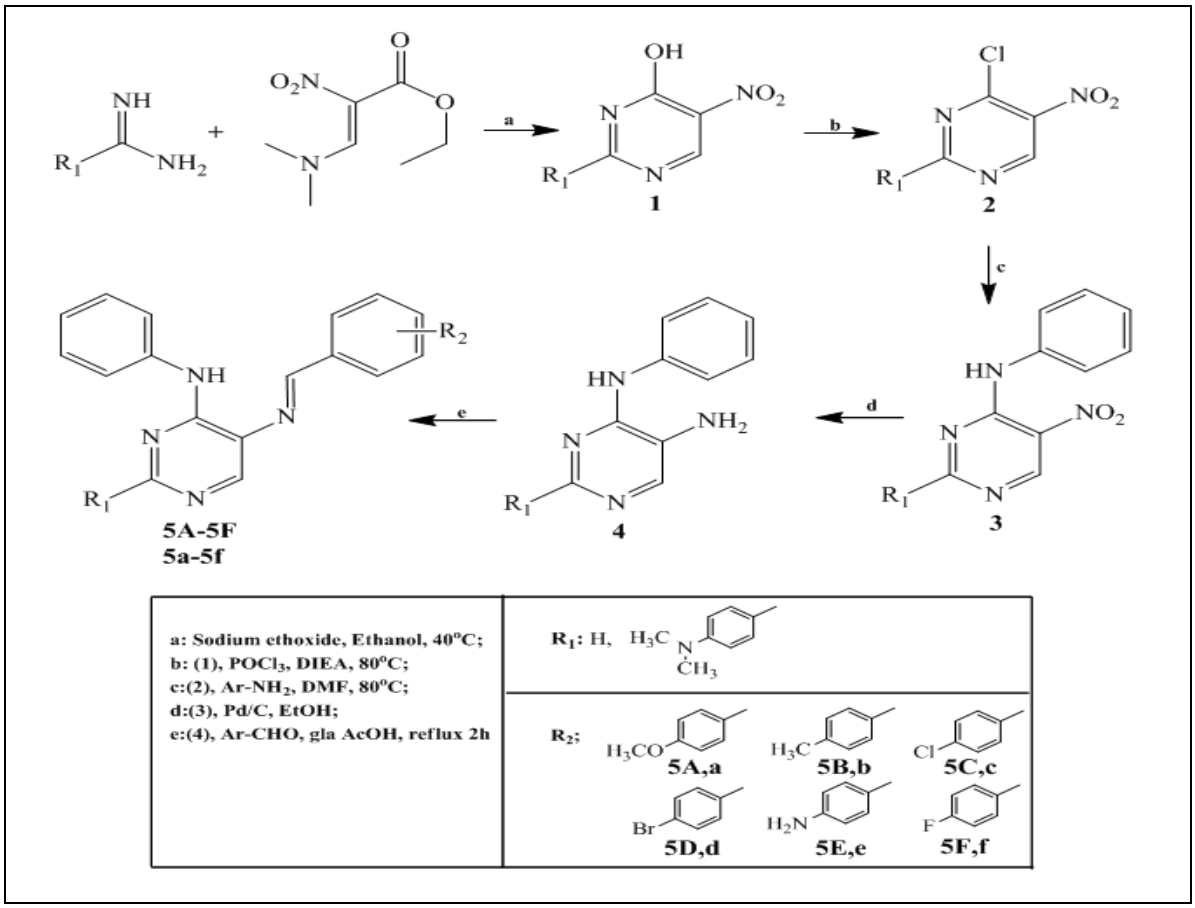
Pyrimidine moiety is present in various biologically active natural products; due to this distinct nature its having a unique place in the field of medicinal chemistry; in addition its having wide spectrum of biological activities such as anti allergic, antitumor, anti-inflammatory, and antiparasitic activities and it was exhibited by synthetic pyrimidine based scaffolds, a number of analogues have garnered a considerable amount of attention [2, 4-15]. Moreover, the pyrimidine derivatives are potential inhibitors of dihydrofolate reductase, an important drug target for the development of anti-infective agents.

Recent studies of pyrimidine-based compounds were found to be maximum drug-likeness model scores and the most promising antitubercular agent [4]. In order to gain more insight into the pyrimidine series, and particularly with regard to their anti TB performance, we have designed to synthesize novel N_5-(3-substituted benzylidene)- N_4-phenyl pyrimidine-4, 5-diamine [5A-5F]/N5-(2-substituted benzylidene)-N2,N2-dimethyl-N4-phenyl pyrimidine -2,4,5-triamine [5a-5f] derivatives which have been characterized by spectral data and elemental analysis.

EXPERIMENTAL SECTION:

Materials: All solvents used were of laboratory grade and were obtained from SD fine chemicals (Mumbai, India), and Merck (Mumbai, India). Rifampicin is received as gift samples from Dr. Reddy's Laboratories, Hyderabad, India. Melting points were determined in open glass capillary tubes and are uncorrected. Compounds were routinely checked for their purity on silica gel G (Merck) thin layer chromatography (TLC) plates; iodine chamber and UV lamp were used for visualization of TLC spots. The IR spectra were recorded in KBr pellets on FT-IR spectro-photometer. ^{1}H-NMR spectra were recorded on Bruker DPX-300 NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm scale. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. Elemental analyses were performed on a Perkine Elmer model 24 °C analyzer and were within ±0.4 % of the theoretical values.

Methods: The synthetic strategy to prepare the target compounds is depicted in **Scheme 1**. To construct pyrimidine nucleus [16-18] in the first step the equimolor quantity of formimidamide/ 4-(dimethylamino)benzimidamide [10mmol], sodium ethoxide, (0.5 g in 5mL water), in 25 ml of ethanol were stirred mechanically 05 min, then ethyl 3-(dimethylamino)- 2- nitroacrylate (10mmol) was added, and the mixture was subjected to heat for 1 hr at 40 °C. The reaction was monitored by TLC to finalize the title compound. The crude product was purified by recrystallized by using ethyl alcohol to obtain pure product 5-nitropyrimidin-4-ol/2-(4-(dimethylamino)phenyl)-5-nitropyrimidin-4-ol [1].



SCHEME 1: SYNTHESIS OF PYRIMIDINE DIAMINE AND TRIAMINE DERIVATIVES

A mixture of 5-nitropyrimidin-4-ol/2-(4-(dimethyl-amino)phenyl)- 5- nitropyrimidin- 4-ol (1) under gone under chlorination by using (10mmol) $POCl_3$ (10mmol) and 10mL of N, N-Diisopropyl-ethylamine [DIEA], further it was refluxed for 30 min on 80 °C. End of reaction was observed via TLC and the purified compound was obtained by recrystalized by using ethyl alcohol to get pure product 4-chloro-5-nitropyrimidine/4-(4-chloro-5-nitropyrimidin-2-yl)-N,N-dimethylaniline (2).

A mixture of 4-chloro-5-nitropyrimidine/4-(4-chloro- 5 -nitro pyrimidin-2-yl)-N, N-dimethyl-aniline (2) (10mmol) reacted with aniline (10mmol) in 10mL of DMF at 80 °C and quenched in ice-water to get the precipitate was filtered, washed with water and recrystallized from ethyl alcohol to give 5- nitro- N- phenylpyrimidin- 4-amine/2-(4-(dimethylamino) phenyl)- 5- nitro- N- phenyl pyrimidin-4-amine (3). A mixture of 5-nitro-N-phenylpyrimidin- 4- amine/2- (4- (dimethylamino) phenyl)- 5- nitro-N-phenyl pyrimidin-4-amine (3) (10mmol) reacted with Zn (3 mmol), $CuSO_4$ (3 mmol) in water on magnetic stirrer 3 h under room temperature to give N_4-phenylpyrimidine-4,5-diamine/2- (4-(dimethylamino)phenyl)-N_4-phenyl-pyrimidine-4,5-diamine (4). A mixture of 10mmol N_4-phenylpyrimidine-4, 5-diamine/2- (4-(dimethyl-amino)phenyl)- N_4-phenylpyrimidine- 4, 5-diamine (4) was added to a solution of an appropriate substituted aromatic aldehyde (10 mmol) in glacial acetic acid (20 mL) containing anhydrous sodium acetate (0.82 g, 10 mmol). The reaction mixture was heated under reflux for 2 h, and then the solvent was evaporated under reduced pressure. The produced solid was dried to get crystallized from of N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F]/N5-(2-substituted benzylidene)-N2,N2-dimethyl-N4-phenyl pyrimidine-2,4,5-triamine [5a-5f].

Spectral Analysis:

N_5-(4-methoxybenzylidene)-N_4-phenylpyrimidine-4,5-diamine[5A]: IR: 3147 (NH), 3059 (Ar-CH), 1643 (C=N), 1591 (C=C), 1076 (C-O-C); ^{1}H NMR: 3.12 (s, 3H, OCH_3), 3.74 (s, 1H, =CH linkage), 5.15 (s, 1H, NH), 6.43-7.91 (m, 11H, Ar-H); Mass: $C_{18}H_{16}N_4O$; calcd, 304 [M+], found, 304 [M+]; Elemental Analysis: calcd, C, 71.04; H, 5.30; N, 18.41; O, 5.26; found, C, 71.06; H, 5.32; N, 18.40; O, 5.23.

N_5-(4-methoxybenzylidene)-N_2,N_2-dimethyl-N_4-phenylpyrimidine-2,4,5-triamine[5a]: IR: 3119 (NH), 3062 (Ar-CH), 1698 (C=N), 1645 (C=C), 1071 (C-O-C); ^{1}H NMR: 2.03 (s, 6H, CH_3), 2.47 (s, 3H, OCH_3), 3.43 (s, 1H, =CH linkage), 5.05 (s, 1H, NH), 6.51-7.54 (m, 10H, Ar-H); Mass: $C_{20}H_{21}N_5O$; calcd, 347 [M+], found, 347 [M+]; Elemental Analysis: calcd, C, 69.14; H, 6.09; N, 20.16; O, 4.61; found, C, 68.43; H, 5.72; N, 21.07; O, 4.82.

N_5-(4-methylbenzylidene)-N_4-phenylpyrimidine-4,5-diamine [5B]: IR: 3122 (NH), 3081 (Ar-CH), 1642 (C=N), 1623 (C=C); ^{1}H NMR: 2.31 (s, 3H, CH_3), 3.82 (s, 1H, =CH linkage), 5.34 (s, 1H, NH), 6.51-7.13 (m, 11H, Ar-H); Mass: $C_{18}H_{16}N_4$; calcd, 288 [M+], found, 288 [M+]; Elemental Analysis: calcd, C, 74.98; H, 5.59; N, 19.43; found, C, 74.96; H, 5.57; N, 19.44.

N_5- (4- methylbenzylidene)- N_2, N_2-dimethyl-N_4-phenylpyrimidine-2,4,5-triamine [5b]: IR: 3365 (NH), 3035 (Ar-CH), 1682 (C=N), 1611 (C=C);^{1}H NMR: 2.32 (s, 6H, CH_3), 2.72 (s, 3H, CH_3), 3.12 (s, 1H, =CH linkage), 5.42 (s, 1H, NH), 6.52-7.32 (m, 10H, Ar-H);Mass: $C_{20}H_{21}N_5$; calcd, 331[M+], found, 331[M+];Elemental Analysis: calcd, C, 72.48; H, 6.39; N, 21.13; found, C, 72.47; H, 6.35; N, 21.12.

N_5-(4-chloro benzylidene)-N_4-phenylpyrimidine-4,5-diamine [5C]: IR: 3120 (NH), 3061 (Ar-CH), 1641 (C=N), 1595 (C=C), 726 (C-Cl); ^{1}H NMR: 3.11 (s, 1H, =CH linkage), 5.16 (s, 1H, NH), 7.19-7.82 (m, 11H, Ar-H); Mass: $C_{17}H_{13}ClN_4$; calcd, 308 [M+], found, 310 [M+2]; Elemental Analysis: calcd, C, 66.13; H, 4.24; Cl, 11.48; N, 18.15; found, C, 66.16; H, 4.25; Cl, 11.47; N, 18.17.

N_5- (4-chlorobenzylidene)-N_2, N_2- dimethyl- N_4-phenylpyrimidine-2,4,5-triamine [5c]: IR: 3363 (NH), 3033 (Ar-CH), 1673 (C=N), 1594 (C=C), 873 (C-Cl); ^{1}H NMR: 2.23 (s, 6H, CH_3), 3.23 (s, 1H, =CH linkage), 5.13 (s, 1H, NH), 6.63-7.83 (m, 10H, Ar-H); Mass: $C_{19}H_{18}ClN_5$; calcd, 351[M+], found, 353 [M+2]; Elemental Analysis: calcd, C, 64.86; H, 5.16; Cl, 10.08; N, 19.91; found, C, 64.84; H, 5.17; Cl, 10.12; N, 19.93.

N_5-(4-bromo benzylidene)-N_4-phenylpyrimidine-4,5-diamine [5D]: IR: 3385 (NH), 3176 (Ar-CH), 1668 (C=N), 1548 (C=C), 668 (C-Br); ^{1}H NMR: 3.01 (s, 1H, =CH linkage), 5.41 (s, 1H, NH), 7.27-

7.92 (m, 11H, Ar-H); Mass: $C_{17}H_{13}BrN_4$; calcd, 352 [M+], found, 354 [M+2]; Elemental Analysis: calcd, C, 57.81; H, 3.71; Br, 22.62; N, 15.86; found, C, 57.84; H, 3.73; Br, 22.63; N, 15.85.

N_5- (4-bromobenzylidene)-N_2, N_2- dimethyl- N_4-phenylpyrimidine-2,4,5-triamine [5d]: IR: 3082 (NH), 2952 (Ar-CH), 1692 (C=N), 1604 (C=C), 794 (C-Br); ^{1}H NMR: 2.94 (s, 6H, CH_3), 3.14 (s, 1H, =CH linkage), 5.14 (s, 1H, NH), 6.14-8.14 (m, 10H, Ar-H); Mass: $C_{19}H_{18}BrN_5$; calcd, 396 [M+], found, 398 [M+2]; Elemental Analysis: calcd, C, 57.59; H, 4.58; Br, 20.16; N, 17.67; found, C, 57.61; H, 4.60; Br, 20.18; N, 17.69.

N_5-(4-aminobenzylidene)-N_4-phenylpyrimidine-4,5-diamine [5E]: IR: 3351 & 3031(NH), 2961 (Ar-CH), 1664 (C=N), 1604 (C=C); ^{1}H NMR: 3.52 (s, 1H, =CH linkage), 4.72 (s, 2H, NH_2), 5.52 (s, 1H, NH), 6.62-7.14 (m, 11H, Ar-H); Mass: $C_{17}H_{15}N_5$; calcd, 289 [M+], found, 289 [M+]; Elemental Analysis: calcd, C, 70.57; H, 5.23; N, 24.21; found, C, 70.59; H, 5.22; N, 24.22.

N_5- (4-aminobenzylidene)-N_2, N_2- dimethyl-N_4-phenylpyrimidine-2,4,5-triamine [5e]: IR: 3354 (NH), 3024 (Ar-CH), 1664 (C=N), 1624 (C=C); ^{1}H NMR: 2.74 (s, 6H, CH_3), 4.14 (s, 2H, NH_2), 3.54 (s, 1H, =CH linkage), 5.44 (s, 1H, NH), 7.54-7.74 (m, 10H, Ar-H); Mass: $C_{19}H_{20}N_6$; calcd, 332 [M+], found, 332 [M+]; Elemental Analysis: calcd, C, 68.65; H, 6.06; N, 25.28; found, C, 68.67; H, 6.10; N, 25.29.

N_5-(4-fluorobenzylidene)-N_4-phenylpyrimidine-4,5-diamine [5F]: IR: 3126 (NH), 3086 (Ar-CH), 1656 (C=N), 1606 (C=C), 1166 (C-F); ^{1}H NMR: 3.26 (s, 1H, =CH linkage), 5.26 (s, 1H, NH), 7.36-7.96 (m, 11H, Ar-H); Mass: $C_{17}H_{13}FN_4$; calcd, 292 [M+], found, 292 [M+]; Elemental Analysis: calcd, C, 69.85; H, 4.48; F, 6.50; N, 19.17; found, C, 69.83; H, 4.46; F, 6.53; N, 19.14.

N_5- (4-fluorobenzylidene)-N_2, N_2-dimethyl-N_4-phenylpyrimidine-2,4,5-triamine [5f]: IR: 3376 (NH), 3037 (Ar-CH), 1678 (C=N), 1619 (C=C), 1043 (C-F); ^{1}H NMR: 2.23 (s, 6H, CH_3), 3.24 (s, 1H, =CH linkage), 5.18 (s, 1H, NH), 6.61-7.83 (m, 10H, Ar-H); Mass: $C_{19}H_{18}FN_5$; calcd, 335 [M+], found, 335 [M+]; Elemental Analysis: calcd, C, 68.04; H, 5.41; F, 5.66; N, 20.88; found, C, 68.08; H, 5.43; F, 5.68; N, 20.87.

MABA Assay Protocol [2]: A stock solution of Rifampicin was prepared in dimethylformamide (DMF) (10mg/mL), aliquoted, and stored at –20 °C. Alamar dye (Invitrogen) was purchased. Antimycobacterial bioassay was performed using the microplate Alamar blue assay (MABA) [18]. Briefly, representative colonies of *MTB* H37Ra from Lowenstein-Jensen (LJ) slope were suspended in 1 mL distilled water, and the turbidity was adjusted to match McFarland tube No.1 (10^7 CFU/mL) and further diluted to 1:25 in 7H9 (Middlebrook 7H9 [Becon Dicinson] supplemented with 0.2% glycerol, 0.1% casitone, and 10% albumin-dextrose, pH 6.8) and used as inoculums. 100µL of the bacterial suspension was added to each well of a microtiter plate together with the synthesized compounds N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F]/ N5-(2-substituted benzylidene)-N2, N2-dimethyl-N4-phenyl pyrimidine-2,4,5-triamine [5a-5f] in Middlebrook 7H9 medium to the final volume of 200 µL, and the final concentration of the test compounds [5A-5F]/[5a-5f] were ranging from 31.25 µg/mL to 0.97 µg/mL.

A growth control well and a sterile control well were also included. Plates were covered and sealed with parafilm and incubated at 37 °C. After incubation for about 7 days, 20 µL of Alamar blue dye was added to the wells. The plates were re-incubated overnight. A color change from blue to pink indicated bacterial growth. MIC was defined as the lowest concentration of the drug that showed no color change, and the ranges were 0.0047–0.0095 (µg/mL).

RESULTS AND DISCUSSION:

Chemistry: The series of heterocycles, N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F]/ N5-(2-substituted benzylidene)-N2, N2- dimethyl- N4- phenyl pyrimidine- 2, 4, 5-triamine [5a-5f] were synthesized by the reaction of formimidamide / 4-(dimethylamino) benzimid-amide with an appropriate solution of sodium ethoxide as presented in **Scheme 1**. The novel compounds were characterized by FTIR, 1H-NMR, mass spectroscopy. The IR spectrum of compounds [5A-5F]/ [5a-5f] showed bands of NH group at 3118-3385 cm^{-1}. In [5A-5F]/ [5a-5f], Ar-CH stretching bands appears at 2951-3089 cm^{-1}. The appearance of a strong intensity band in the IR

spectra of compounds [5A-5F]/ [5a-5f] in the range of 3118-3385 cm^{-1} attributable to -NH stretching and provides strong evidence for the confirmation of the conversion chlorine to -NH. The proton magnetic resonance spectra of [5A-5F]/ [5a-5f] and their corresponding derivatives have been recorded in CDCl3. In this [5A-5F]/ [5a-5f] has =CH linkage signals appear at 3.01-3.53 ppm respectively. The presence of =CH linkage proton signals in the 1H-NMR spectra of final compounds confirms that the formation of benzylidine moiety **Fig. 1**.

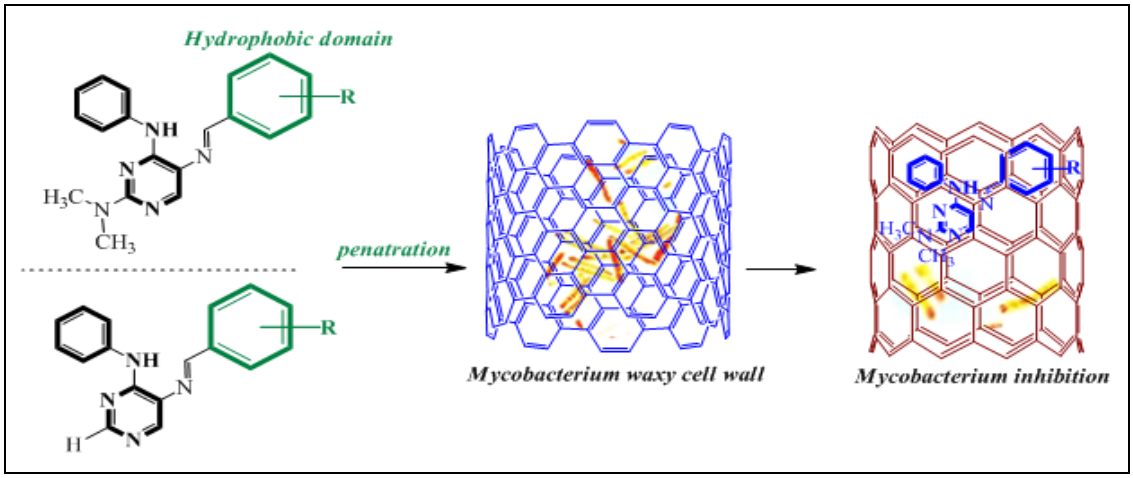


FIG. 1: PYRIMIDINE-4,5-DIAMINE/PYRIMIDINE-2,4,5-TRIAMINE [5A-5F] & [5A-5F] PERMEATION IN *MTB* CELL WALL

All these observed facts clearly envisages that the N5-(3-substituted benzylidene)-N4-phenyl pyrimidine-4,5-diamine[5A-5F]/N5-(2-substituted benzylidene)-N2, N2-dimethyl-N4-phenyl pyrimidine-2, 4, 5-triamine [5a-5f] formation as indicated in Scheme and confirms the proposed structure [5A-5F]/ [5a-5f].

AntiTB Activity: The derivatives of pyrimidine were evaluated for its *in-vitro* antitubercular activity. The effect of these synthetic compounds on the growth of *MTB* H_{37} Ra was recorded by MABA method after 7 days of incubation R 37 °C. The antitubercular activities performed by using six different concentrations, namely 0.97, 1.95, 3.90, 7.81, 15.62 and 31.25µg/mL were used, and the data of screening reveals that the compounds 5a, 5B, 5b, 5d, 5F, and 5f were inactive in all concentration against *MTB* H_{37}Ra strain. In the MABA screening, amongst the tested compounds, 5A, 5C, 5c, and 5E was active 1.95µg/mL, 5D was active R 7.81µg/mL, and 5e, was active 15.62 µg/mL concentrations, respectively. The promising nature of the compounds may be attributed to the substitutions R the distal aryl ring. These compounds had electron-withdrawing groups R the *para* position of the distal aryl ring. In general, it was observed that the substituted derivatives were more active derivatives. This may be because of the fact that the substituted derivatives are better fitted into the receptor site. It was highlighted that the most active compounds had substitution R, the *para* -position of the distal aryl ring, which resulted in increased antitubercular activity. It is interesting to note that compounds 5A, 5C, 5c, and 5E showed enhanced activity, and this compound was considered as a most potent analogue against *MTB* strain and was found to have significant potency. *MTB* is unique surrounded by a thick and waxy cell wall; hence efficient antitubercular drugs should have reasonable lipophilicity to penetrate the cell wall.

The most frequently encountered heterocycles are reported to have a strong lipophilic character **Fig. 1** which plays an essential role in permeation in *MTB* cell wall. The values for the antitubercular studies of the selected N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F]/ N_5-(2-substituted benzylidene)-N_2,N_2-dimethyl-N_4-phenyl pyrimidine- 2, 4, 5- triamine [5a-5f] series compounds and the standard are represented in **Table 1**. It has been well established that electron-donating groups (-OCH_3, -CH_3 and -NH_2), electron-withdrawing groups (-F, -Cl, and -Br) substituted molecules have a significant level of importance in modern medicinal chemistry, and it may be explained that it possesses preferable lipophilicity and show optimal membrane permeability.

TABLE 1: *IN-VITRO* ANTITB ACTIVITY OF THE CHOSEN SYNTHESIZED COMPOUNDS FROM [5A-5F] & [5A-5F] SERIES AGAINST MTB H37RA

Compounds		MIC (µg/mL)
Rifampicin (control)		0.0095 µg/mL
5A	4-Methoxy	1.95 µg/mL
5a		NIL
5B	4-Methyl	NIL
5b		NIL
5C	4-Chloro	1.95 µg/mL
5c		1.95 µg/mL
5D	4-Bromo	7.81 µg/mL
5d		NIL
5E	4-Amino	1.95 µg/mL
5e		15.62 µg/mL
5F	4-Fluoro	NIL
5f		NIL

CONCLUSION: In the view of the above findings and the new candidates N_5- (3- substituted benzylidene)-N_4-phenyl pyrimidine-4, 5-diamine [5A-5F]/ N_5-(2-substituted benzylidene)-N_2,N_2-dimethyl-N_4-phenyl pyrimidine-2,4,5-triamine [5a-5f] that may value in significant anti-TB agents. Thus we can promise here that the synthesized analogues will generate a very good impact to the chemists and research scholars for further investigations in this field of pyrimidine and its selective influence of electronic effects as well as a change in the basic nucleus.

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CONFLICTS OF INTEREST: The authors declare no competing financial interest.

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