Journal of Advances and Scholarly Researches in Allied Education
Vol. XV, Issue No. 1, April-2018, ISSN 2230-7540

An Efficient Synthesis of Chalcone, Acetyl Pyrazzoline and Amino Pyrimidine Derivatives Incorporate Indole Nucleus as Antimycobacterial and Antimicrobial Agents

Jayesh R. Patel[1*] Amrendra Kumar Singh[2] Rajanikant B. Patel[3] Kinchit S. Desai[4] Riki P. Tailor[5]

[1] Department of Chemistry, Veer Bahadur Singh Purvanchal University, Jaunpur

[2] Department of Chemistry, Veer Bahadur Singh Purvanchal University, Jaunpur

[3] Department of Chemistry, Veer Narmad South Gujarat University, Surat, India

[4] Department of Chemistry, Veer Narmad South Gujarat University, Surat, India

[5] Department of Chemistry, Government College Daman

Abstract – Due to increasing microbial drug resistance, it is to more necessary to develop new antimycobacterial and antimicrobial agents. For this purpose, we developed some new indole base chalcone (Va-e) analogs and converted into 1-acetyl-2-yrazoline (VIa-e) and 2-amino pyrimidine (VIIa-e) derivatives. Target compounds were evaluated for their antimycobacterial efficacy against Mycobacterium tuberculosis H_{37}Rv and antimicrobial activity against four common pathogenic bacterial and three common fungal strains. Structures of entire newly synthesized compounds were assigned on the basis of FTIR, ^{1}H NMR, ^{13}C NMR, LCMS as well as elemental analysis. Three derivatives (Vb, Vc, VIb, VId, VIIa, VIIb, VIIe) displayed significant antitubercular activity. In terms of antimicrobial activity, most compounds exhibited moderate to potent activity against the bacteria, and the antifungal activities.

Keywords: 5-Methoxy-1H-indole-3-Carbaldehyde, Claisen-Schmidt Condensation, 1-Acetyl Pyrazoline, 2-Amino Pyrimidine, Antimycobacterial Activity, Antimicrobial Activity.

----------X----------

INTRODUCTION

Antimicrobial diseases, caused by microbial species, are one of the most important diseases worldwide [1]. Tuberculosis (TB) is one of the most important chronic communicable bacterial diseases caused by *Mycobacterium tuberculosis*. TB is one of the major causes of morbidity and mortality throughout the world. Approximately 32% of the world's population is currently living with this infectious disease. It is a fatal disease and one of the leading causes of the death all over the world especially in the developing countries like India. The incidences of failure in the treatment of microbial infections have increased because of the emergence of multidrug-resistant strains due to misuse of antimicrobial drugs. Therefore, the synthesis of effective, novel antimicrobial compounds has become extremely important [2].

Chalcones (1,3-diaryl-2-propene-1-ones) and other biogenetically-related compounds belonging to the flavonoid family are natural substances found in a number of plants or prepared synthetically. They consist of two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system [3]. Chalcones have been found to exhibit many pharmacological activities, including anti-microbial [4] and anti-tuberculosis [5], anticancer [6], anti-inflammatory [7], antioxidant [8] etc activities. Pyrazolines are an important class of heterocyclic compounds containing two nitrogen atoms in the five membered ring. Pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in the diverse biological activities. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Considerable attention has been focused on the pyrazolines and substituted pyrazolines due to their

interesting biological activities. These compounds have been found to possess anti-tumor [9], anticonvulsant [10], antimicrobial [11], antitubercular [12] etc. Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities and clinical applications [13]. The pyrimidines represent one of the most active classes of compounds possessing wide spectrum of biological activities like significant in vitro activity against antimicrobial [14], antileishmanial [15], anti-inflammatory [16], analgesic [17], antimycobacterial [18] etc. In view of the above mentioned knowledge of different pharmacophores, we have designed and synthesized some new chalcones and converted into its analogues acetyl pyrazolines and amino pyrimidine having indole scaffold. Compounds were subjected to evaluation of their antimicrobial and antimycobacterial potency against various strains.

MATERIAL AND METHODS

The reagents and solvents used for reaction were of analytical reagent (AR) grade. Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on Shimadzu FTIR 8401 spectrophotometer using potassium bromide pellets. ^{1}H NMR and 13C NMR spectra were recorded on a Bruker Avance 400 F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using $CDCl_3$ as a solvent and TMS as an internal standard at 400 MHz frequency respectively. Chemical shifts are reported in parts per million (ppm) and coupling constant (J) are reported in Hertz. Elemental analysis was carried out by Perkin-Elmer 2400 series-II elemental analyser (Perkin-Elmer, USA). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan). TLC was run on E-Merck pre-coated 60 F254 plates and the spots were rendered visible by exposing to UV light or iodine chamber. Reference drugs antimicrobial and antitubercular activity are Ampicillin, Chloramphenicol, Ciprofloxacin, Griseofulvin, Nystatin, Rifampicin and Isoniazid used of commercial grade.

Preparation of 1-benzyl-5-methoxy-1H-indole-3-carbaldehyde (III)

5-Methoxy-1H-indole-3-carbaldehyde **(I)** (0.01 mol), benzyl chloride **(II)** (0.01 mol) and anhydrous K_2CO_3 in dimethylformamide (DMF) were charged in a 100 ml round bottomed flask, fitted with a reflux condenser. The reaction mixture was heated under reflux temperature for 5-6 hours. After completion of the reaction as monitored by TLC, the reaction mixture was cooled, and poured onto water· The precipitated solid was filtered off, washed with water, dried and recrystallized from ethanol gives 1-benzyl-5-methoxy-1H-indole-3-carbaldehyde **(III)**. FTIR (KBr, $v_{max,}$ cm^{-1}): 3012 (aromatic =CH streching), 2925 (C-H streching of alkane), 1712 (C=O streching), 1512 (aromatic C=C streching), 1247 (C-N streching), 1220 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8 (s, 3H, -OC<u>H</u>$_3$), 3.9 (s, 2H, -C<u>H</u>$_2$), 10.5 (s, 1H, -C<u>H</u>O), 6.5 to 8.6 (m, 9H, 08 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 51.2 (CH_2), 54.2 (OCH_3), 103.4 (CH), 105.6 (CH), 112.4 (CH), 114.5 (CH), 118.1 (CH), 126.3 (CH),131.4 (CH), 132.5 (C), 136.0 (CH), 139.1 (CH), 133.2 (CH), 137.2 (CH), 141.8 (C), 143.2 (C), 151.2 (C), 152.4 (C-N), 175.2 (CO); LCMS (m/z): 266.1 (M+1).

General method for the preparation of 3-(1-benzyl-5-methoxy-1H-indol-3-yl)-1-(substitutedphenyl)prop-2-en-1-one (Va-e)

Substituted acetophenone **(IVa-e)** (0.01 mol) and 1-benzyl-5-methoxy-1H-indole-3-carbaldehyde (0.01 mol) **(III)** dissolved in isopropyl alcohol was taken in a 100 ml conical flask. The reaction proceed by applying classical Claisen-Schmidt condensation reaction i.e. To make it alkaline, solution of 40% KOH (5ml) was added in it. Then the reaction mixture was stirred for 24 hours on a magnetic stirrer at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, neutralized with dilute hydrochloric acid and the mixture was agitated for 4 hours a yellow solid was obtained. Finally, the product was isolated by filtration, crystallized from ethanol gives product 3-(1-benzyl-5-methoxy-1H-indol-3-yl)-(1-substitutedphenyl)prop-2-en-1-one **(Va-e)**.

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (Va)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3015 (aromatic =CH streching), 2970 (C-H streching of alkane), 1640 (C=O streching), 1550 (CH=CH streching), 1512 (aromatic C=C streching), 1416 (-OCH_3 streching), 1262 (C-N streching), 1225 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8-4.0 (m, 9H, -OC<u>H</u>$_3$), 4.2 (s, 2H, -C<u>H</u>$_2$), 5.8 (1H, d, CO-C<u>H</u>=, *J* = 6.2 Hz), 6.9 to 8.3 (m, 12H, 11 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety), 8.2 (1H, d, Ar-C<u>H</u>=, *J* = 6.1Hz); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 50.0 (CH_2), 54.2, (OCH_3), 111.4 (CH), 113.0 (CH), 115.2 (CH), 116.7 (CH), 118.4 (CH), 121.3 (=CH), 120.5 (CH), 121.4 (C), 130.2 (C), 136.7 (CH), 138.9 (CH), 140.5 (CH), 142.3 (CH), 144.2 (=CH), 151.8 (C), 150.3 (C), 154.9 (C), 161.3 (C-N), 178.2 (CO); LCMS (m/z): 398.9 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (Vb)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3506 (-OH streching), 3026 (aromatic =CH streching), 2925 (C-H streching of

alkane), 1635 (C=O streching), 1560 (CH=CH streching), 1518 (aromatic C=C streching), 1412 (-OCH_3 streching), 1260 (C-N streching), 1220 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.9 (m, 3H, -OC<u>H</u>$_3$), 5.3 (m, 3H, -O<u>H</u>), 5.5 (m, 3H, -O<u>H</u>), 4.9 (s, 2H, -C<u>H</u>$_2$), 6.1 (1H, d, CO-C<u>H</u>=, *J* = 8.1 Hz), 6.9 to 8.3 (m, 12H, 11 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety), 8.2 (1H, d, Ar-C<u>H</u>=, *J* = 8.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 48.2 (CH_2), 55.1, (OCH_3), 112.3 (CH), 114.5 (CH), 116.3 (CH), 118.3 (CH), 119.3 (CH), 120.2 (=CH), 122.1 (CH), 123.7 (C), 128.8 (C), 131.4 (CH), 133.2 (CH), 139.3 (CH), 143.5 (CH), 145.8 (=CH), 150.2 (C), 157.1 (C), 159.4 (C), 162.5 (C-N), 172.5 (CO); LCMS (m/z): 400.5 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (Vc)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3069 (aromatic =CH streching), 2978 (C-H streching of alkane), 1630 (C=O streching), 1563 (CH=CH streching), 1532 (aromatic C=C streching), 1420 (-OCH_3 streching), 1259 (C-N streching), 1212 (asymmetric C-O-C streching of ether linkage), 786 (C-Cl streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8 (m, 3H, -OC<u>H</u>$_3$), 4.3 (s, 2H, -C<u>H</u>$_2$), 6.3 (1H, d, CO-C<u>H</u>=, *J* = 7.5 Hz), 6.8 to 8.0 (m, 12H, 11 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety), 8.3 (1H, d, Ar-C<u>H</u>=, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 39.1 (CH_2), 56.5, (OCH_3), 109.4 (CH), 112.1 (CH), 114.8 (CH), 116.5 (CH), 117.4 (CH), 119.8 (=CH), 121.0 (CH), 122.9 (C), 125.7 (C), 130.0 (CH), 132.5 (CH), 134.6 (CH), 140.8 (CH), 142.8 (=CH), 152.3 (C), 155.0 (C), 160.6 (C-N), 169.3 (CO); LCMS (m/z): 434.5 (M-1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (Vd)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3025 (aromatic =CH streching), 2956 (C-H streching of alkane), 1649 (C=O streching), 1563 (CH=CH streching), 1518 (aromatic C=C streching), 1420 (-OCH_3 streching), 1260 (C-N streching), 1221 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.6-4.0 (m, 12H, -OC<u>H</u>$_3$), 4.6 (s, 2H, -C<u>H</u>$_2$), 5.1 (1H, d, CO-C<u>H</u>=, *J* = 5.9 Hz), 7.0 to 8.1 (m, 11H, 10 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety), 8.3 (1H, d, Ar-C<u>H</u>=, *J* = 5.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 39.4 (CH_2), 55.6, (OCH_3), 110.5 (CH), 112.5 (CH), 114.7 (CH), 116.8 (CH), 117.0 (CH), 123.5 (=CH), 124.0 (CH), 126.7 (C), 131.2 (C), 134.6 (CH), 137.8 (CH), 142.6 (CH), 143.0 (CH), 145.7 (=CH), 150.5 (C), 152.8 (C), 153.0 (C), 160.8 (C-N), 169.0 (CO); LCMS (m/z): 458.2 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(3-chloro-4-pyridine)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (Ve)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3069 (aromatic =CH streching), 2967 (C-H streching of alkane), 1643 (C=O streching), 1551 (CH=CH streching), 1509 (aromatic C=C streching), 1410 (-OCH_3 streching), 1260 (C-N streching), 1232 (asymmetric C-O-C streching of ether linkage), 769 (C-Cl streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8 (m, 3H, -OC<u>H</u>$_3$), 3.9 (s, 2H, -C<u>H</u>$_2$), 6.3 (1H, d, CO-C<u>H</u>=, *J* = 5.7 Hz), 6.5 to 7.9 (m, 12H, 11 Ar-<u>H</u>, C<u>H</u> of indole and C<u>H</u> of pyridine moiety), 8.0 (1H, d, Ar-C<u>H</u>=, *J* = 5.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) : 36.5 (CH_2), 57.2, (OCH_3), 108.3 (CH), 111.2 (CH), 113.4 (CH), 115.2 (CH), 117.9 (CH), 120.5 (=CH), 122.4 (CH), 123.7 (C), 126.7 (C), 132.0 (CH), 134.7 (CH), 138.3 (CH), 141.9 (CH), 143.1 (=CH), 149.0 (C), 151.4 (C), 153.2 (C), 159.0 (C-N), 170.1 (CO); LCMS (m/z): 401.0 (M-1)

General method for the preparation of 1-(3-(1-benzyl-5-methoxy-1H-indol-3-yl)-5-(substitutedphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VIa-e)

An appropriate chalcone (**Va-e**) (0.01 mol) and hydrazine hydrate (0.015 mol) was charged in a 100 ml round bottomed flask, fitted with a reflux condenser. To make the mixture acidic catalytic amount of glacial acetic acid (5 ml) was added. The reaction mixture was heated under reflux temperature for 5-6 hours. The progress of the reaction was investigated by TLC using toluene: methanol (12:6 v/v) eluent as mobile phase. After completion of the reaction, the mixture was cooled to room temperature then poured into crushed ice and neutralised with Na_2CO_3. The solid mass separated was collected by filtration, washed well with hot water and recrystallised from ethanol gives product (**VIa-e**) in good yield.

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VIa)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3012 (aromatic =CH streching), 2925 (C-H streching of pyrazoline moiety), 1663 & 1576 (C=O and C=N streching of pyrazoline moiety), 1512 (aromatic C=C streching), 1354 (CH_3 streching of pyrazoline moiety), 1248 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.6 (s, 3H, -COC<u>H</u>$_3$), 3.2 (dd, 1H, -C<u>H</u>$_x$-CH, *J* = 11.3 & 14.1 Hz), 3.6 (dd, 1H, -C<u>H</u>$_y$-CH, *J* = 11.4 & 13.9 Hz), 4.8 (dd, 1H, -C<u>H</u>-CH_2-Ar, *J* = 5.2 & 13.9 Hz), 3.8-3.9 (m, 9H, OC<u>H</u>$_3$), 7.2 to 8.2 (m, 12H, 11 Ar-<u>H</u> and 1-C<u>H</u> of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 22.5 (CH_3, pyrazoline moiety), 37.5 (CH_2, methylene, pyrazoline moiety), 41.3 (CH_3), 55.0 (OCH_3), 61.0 (CH-Ar), 110.5 (CH), 114.5 (CH), 115.2 (CH), 118.3 (CH), 120.0 (CH), 122.7 (CH), 125.9 (CH), 128.3 (CH), 130.1 (C), 132.4 (CH), 133.2 (C), 143.4 (C), 150.2 (C), 151.7 (C-OCH_3), 160.2 (C=N), 169.0 (CO pyrazoline moiety); LCMS (m/z): 482.5 (M-1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VIb)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3405 (-OH streching), 3016 (aromatic =CH streching), 2963 (C-H streching of pyrazoline moiety), 1659 & 1571 (C=O and C=N streching of pyrazoline moiety), 1510 (aromatic C=C streching), 1350 (CH_3 streching of pyrazoline moiety), 1224 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.2 (s, 3H, -COC$\underline{H}_3$), 3.5 (dd, 1H, -C$\underline{H}_x$-CH, *J* = 10.4 & 14.5 Hz), 3.7 (dd, 1H, -C$\underline{H}_y$-CH, *J* = 10.5 & 13.9 Hz), 5.0 (dd, 1H, -C$\underline{H}$-CH_2-Ar, *J* = 6.2 & 13.8 Hz), 3.8 (s, 3H, OC$\underline{H}_3$), 5.2 (s, 2H, O$\underline{H}$), 7.0 to 8.3 (m, 12H, 11 Ar-$\underline{H}$ and 1-C$\underline{H}$ of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 19.2 ($CH_{3,}$ pyrazoline moiety), 36.3 ($CH_{2,}$ methylene, pyrazoline moiety), 38.1 (CH_3), 50.2 (OCH_3), 62.4 (CH-Ar), 111.6 (CH), 113.0 (CH), 116.7 (CH), 118.5 (CH), 122.4 (CH), 123.8 (CH), 124.1 (CH), 127.5 (CH), 129.2 (C), 131.2 (CH), 132.7 (C), 140.5 (C), 151.0 (C), 155.8 (C-OCH_3), 158.2 (C=N), 167.2 (CO pyrazoline moiety); LCMS (m/z): 456.1 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VIc)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3110 (aromatic =CH streching), 2925 (C-H streching of pyrazoline moiety), 1669 & 1546 (C=O and C=N streching of pyrazoline moiety), 1512 (aromatic C=C streching), 1359 (CH_3 streching of pyrazoline moiety), 1229 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.9 (s, 3H, -COC$\underline{H}_3$), 3.0 (dd, 1H, -C$\underline{H}_x$-CH, *J* = 9.8 & 12.1 Hz), 3.4 (dd, 1H, -C$\underline{H}_y$-CH, *J* = 9.7 & 12.4 Hz), 5.3 (dd, 1H, -C$\underline{H}$-CH_2-Ar, *J* = 9.6 & 12.4 Hz), 3.9 (s, 3H, OC$\underline{H}_3$), 6.9 to 8.2 (m, 12H, 11 Ar-$\underline{H}$ and 1-C$\underline{H}$ of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 18.6 ($CH_{3,}$ pyrazoline moiety), 31.0 ($CH_{2,}$ methylene, pyrazoline moiety), 39.4 (CH_3), 58.2 (OCH_3), 68.2 (CH-Ar), 112.5 (CH), 113.3 (CH), 116.2 (CH), 118.4 (CH), 121.3 (CH), 125.2 (CH), 129.0 (CH), 130.1 (CH), 132.4 (C), 133.0 (CH), 135.0 (C), 137.5 (C), 143.4 (C), 151.3 (C-OCH_3), 156.1 (C=N), 160.8 (CO pyrazoline moiety); LCMS (m/z): 492.6 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VId)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3026 (aromatic =CH streching), 2910 (C-H streching of pyrazoline moiety), 1665 & 1570 (C=O and C=N streching of pyrazoline moiety), 1508 (aromatic C=C streching), 1356 (CH_3 streching of pyrazoline moiety), 1242 (asymmetric C-O-C streching of ether linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.1 (s, 3H, -COC$\underline{H}_3$), 3.1 (dd, 1H, -C$\underline{H}_x$-CH, *J* = 11.5 & 13.2 Hz), 3.3 (dd, 1H, -C$\underline{H}_y$-CH, *J* = 11.4 & 13.2 Hz), 4.2 (dd, 1H, -C$\underline{H}$-CH_2-Ar, *J* = 5.9 & 13.9 Hz), 3.7-3.9 (m, 16H, OC$\underline{H}_3$), 6.5 to 8.1 (m, 11H, 10 Ar-$\underline{H}$ and 1-C$\underline{H}$ of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 22.5 ($CH_{3,}$ pyrazoline moiety), 37.5 ($CH_{2,}$ methylene, pyrazoline moiety), 38.2 (CH_3), 54.2 (OCH_3), 62.3 (CH-Ar), 111.4 (CH), 113.2 (CH), 114.5 (CH), 117.2 (CH), 118.3 (CH), 121.6 (CH), 123.7 (CH), 129.2 (CH), 132.9 (C), 134.8 (CH), 135.1 (C), 145.3 (C), 151.0 (C), 156.7 (C-OCH_3), 161.8 (C=N), 168.2 (CO pyrazoline moiety); LCMS (m/z): 483.2 (M+1).

1-(3-(1-Benzyl-5-methoxy-1H-indol-3-yl)-5-(3-chloro-4-pyridine)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (VIe)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3020 (aromatic =CH streching), 2960 (C-H streching of pyrazoline moiety), 1645 & 1525 (C=O and C=N streching of pyrazoline moiety), 1512 (aromatic C=C streching), 1356 (CH_3 streching of pyrazoline moiety), 1220 (asymmetric C-O-C streching of ether linkage), 789 (C-Cl streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.6 (s, 3H, -COC$\underline{H}_3$), 3.5 (dd, 1H, -C$\underline{H}_x$-CH, *J* = 10.4 & 14.5 Hz), 3.6 (dd, 1H, -C$\underline{H}_y$-CH, *J* = 10.6 & 13.8 Hz), 5.2 (dd, 1H, -C$\underline{H}$-CH_2-Ar, *J* = 6.2 & 13.7 Hz), 3.9 (s, 3H, OC$\underline{H}_3$), 7.2 to 8.1 (m, 13H, 12 Ar-$\underline{H}$ and 1-C$\underline{H}$ of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 18.4 ($CH_{3,}$ pyrazoline moiety), 34.2 ($CH_{2,}$ methylene, pyrazoline moiety), 39.3 (CH_3), 51.6 (OCH_3), 63.3 (CH-Ar), 112.4 (CH), 114.5 (CH), 115.2 (CH), 116.4 (CH), 119.5 (CH), 121.3 (CH), 122.5 (CH), 128.4 (CH), 129.1 (C), 131.2 (CH), 132.7 (C), 142.7 (C), 150.1 (C), 156.8 (C-OCH_3), 159.3 (C=N), 168.0 (CO pyrazoline moiety); LCMS (m/z): 429.2 (M+1).

General method for the preparation of 4-(1-benzyl-5-methoxy-1H-indol-3-yl)-6-(substitutedphenyl)pyrimidin-2-amine (VIIa-e)

Compound (**Va-e**) (0.01 mol) condensed with guanidine hydrochloride (0.01mol) in the presence of alkaline medium (5 ml 40% KOH) in ethanol at refluxed temperature for 5-6 hours in 100 ml round bottomed flask. The progress of the reaction was monitored by TLC using toluene: methanol (10:3 v/v) eluent as mobile phase. After completion of the reaction, the reaction mixture was poured into crushed ice and neutralised with dilute HCl. Finally, the product was filtered, washed with water, dried and recrystallised in acetone gives product (**VIIa-e**) with good yield.

4-(1-Benzyl-5-methoxy-1H-indol-3-yl)-6-(2,5-dimethoxyphenyl)pyrimidin-2-amine (VIIa)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3426 (NH_2 str. 1^0 amine of pyrimidine moiety), 3061 (aromatic =CH streching), 2975 (C-H streching of pyrimidine moiety), 1652 (C=N streching of pyrimidine moiety), 1529 (aromatic C=C streching), 1221 (asymmetric C-O-C streching of ether linkage), 1129 (OCH_3 streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.7-4.0 (m, 9H, OC$\underline{H}_3$), 5.2 (s, 2H,-NH_2), 6.7 - 8.2 (m, 14H, 13 Ar-$\underline{H}$ and 1-C$\underline{H}$ of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 19.4 (CH_2), 59.2 (OCH_3), 103.2 (CH, pyrimidine moiety), 110.2 (CH), 113.5 (CH), 118.3 (CH), 120.4 (CH), 121.2 (CH), 130.8 (CH), 133.7 (CH), 137.0 (CH), 137.2 (C), 139.5 (C), 142.3 (C),

152.4 (C), 152.2, 154.3, 159.6 (C, pyrimidine moiety); LCMS (m/z): 467.2 (M+1).

4-(1-Benzyl-5-methoxy-1H-indol-3-yl)-6-(2,4-dihydroxyphenyl)pyrimidin-2-amine (VIIb)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3526 (OH str.), 3426 (NH_2 str. 1^0 amine of pyrimidine moiety), 1121 (OCH_3 streching) 3054 (aromatic =CH streching), 2965 (C-H streching of pyrimidine moiety), 1640 (C=N streching of pyrimidine moiety), 1525 (aromatic C=C streching), 1221 (asymmetric C-O-C streching of ether linkage), 1129 (OCH_3 streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8-3.9 (m, 3H, OCH_3), 5.4 (s, 2H,-NH_2), 5.6-5.7 (s, 4H,-OH), 6.9 - 8.1 (m, 14H, 13 Ar-H and 1-CH of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 21.2 (CH_2), 56.5 (OCH_3), 104.7 (CH, pyrimidine moiety), 108.7 (CH), 112.0 (CH), 114.5 (CH), 119.7 (CH), 123.0 (CH), 131.7 (CH), 134.0 (CH), 136.8 (CH), 139.0 (C), 140.0 (C), 143.8 (C), 150.8 (C), 151.0, 152.4, 156.7 (C, pyrimidine moiety); LCMS (m/z): 409.5 (M+1).

4-(1-Benzyl-5-methoxy-1H-indol-3-yl)-6-(2,4-dichlorophenyl)pyrimidin-2-amine (VIIc)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3356 (NH_2 str. 1^0 amine of pyrimidine moiety), 3019 (aromatic =CH streching), 2969 (C-H streching of pyrimidine moiety), 1620 (C=N streching of pyrimidine moiety), 1556 (aromatic C=C streching), 1241 (asymmetric C-O-C streching of ether linkage), 1076 (C-F streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.9 (s, 3H, OCH_3), 5.6 (s, 2H,-NH_2), 6.9 - 8.3 (m, 13H, 12 Ar-H and 1-CH of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 32.5 (CH_2), 59.7 (OCH_3), 99.5 (CH, pyrimidine moiety), 110.7 (CH), 113.5 (CH), 115.7 (CH), 117.0 (CH), 119.8 (CH), 123.3 (CH), 130.7 (CH), 132.8 (CH), 134.9 (C), 136.8 (C), 139.7 (C), 153.7 (C), 155.4, 156.7, 161.2 (C, pyrimidine moiety); LCMS (m/z): 446.3 (M+1).

4-(1-Benzyl-5-methoxy-1H-indol-3-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (VIId)

3427 (NH_2 str. 1^0 amine of pyrimidine moiety), 3066 (aromatic =CH streching), 2971 (C-H streching of pyrimidine moiety), 1663 (C=N streching of pyrimidine moiety), 1531 (aromatic C=C streching), 1236 (asymmetric C-O-C streching of ether linkage), 1136 (OCH_3 streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.8-4.1 (m, 12H, OCH_3), 5.3 (s, 2H,-NH_2), 6.7 - 8.1 (m, 14H, 13 Ar-H and 1-CH of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 19.6 (CH_2), 59.2 (OCH_3), 104.5 (CH, pyrimidine moiety), 111.3 (CH), 112.3 (CH), 114.1 (CH), 119.2 (CH), 122.3 (CH), 125.4 (CH), 130.6 (CH), 135.3 (CH), 138.8 (C), 139.1 (C), 143.0 (C), 153.5 (C), 154.5, 155.2, 158.5 (C, pyrimidine moiety); LCMS (m/z): 437.2 (M+1).

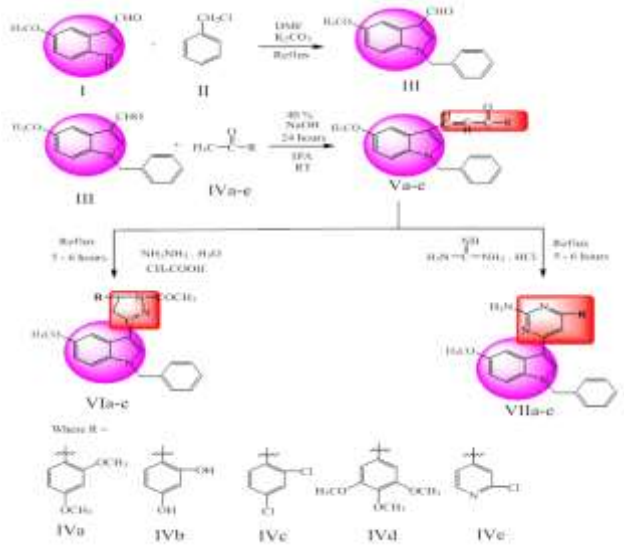
4-(1-Benzyl-5-methoxy-1H-indol-3-yl)-6-(3-chloro-4-pyridine)pyrimidin-2-amine (VIIe)

FTIR (KBr, $v_{max,}$ cm^{-1}): 3436 (NH_2 str. 1^0 amine of pyrimidine moiety), 3010 (aromatic =CH streching), 2953 (C-H streching of pyrimidine moiety), 1654 (C=N streching of pyrimidine moiety), 1524 (aromatic C=C streching), 123 (asymmetric C-O-C streching of ether linkage), 1123 (OCH_3 streching),789 (OCH_3 streching); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.9 (m, 3H, OCH_3), 5.4 (s, 2H,-NH_2), 6.9 - 8.2 (m, 14H, 13 Ar-H and 1-CH of indole moiety); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 19.2 (CH_2), 56.1 (OCH_3), 102.5 (CH, pyrimidine moiety), 110.2 (CH), 112.1 (CH), 115.3 (CH), 116.2 (CH), 123.7 (CH), 129.5 (CH), 134.0 (CH), 136.5 (CH), 138.8 (C), 139.5 (C), 141.2 (C), 153.4 (C), 150.2, 153.2, 156.8 (C, pyrimidine moiety); LCMS (m/z): 416.7 (M+1).

RESULT AND DISCUSSION

Chemistry

The reaction sequence for title the starting precursors **(III)** and chalcones **(Va-e)** are depicted in **Scheme 1**. The key intermediate chalcone **(Va-e)** is subjected to a cycloaddition condensation reaction with hydrazine hydrate and guanidine hydrochloride gives corresponding 1-acetylpyrazoline and 2-aminopyrimidine derivatives respectively as depicted synthetic path in Scheme 2. The formation of all these new heterocyclic derivatives were fully characterised by means of spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and LCMS. As an example, in the IR spectrum of compound **Va**, a strong absorption band is observed at 1550 and 1640 cm^{-1} which corresponds to the stretching vibration of the CH = CH and C=O functionality of α, β- unsaturated carbonyl group of chalcone moiety. The C=C functionality of aromatic ring was observed at 1512 cm^{-1} respectively.



Scheme 1. Methodical synthetic route for the target compounds (**Va-g**), (**VIa-g**) and (**VIIa-g**)

The ^{1}H NMR spectrum of compound **Va** showed a doublet at δ 5.8 (J = 6.2 Hz) ppm for the -CO-CH= and at δ 8.2 (J = 6.1 Hz) ppm for the Ar-CH= of α, β unsaturated carbonyl group protons. The other remaining eleven aromatic and indole protons appeared as a multiplet signal at δ 6.9-8.3 ppm. Finally, the ^{13}C NMR spectra of the compound **Va** was recorded in $CDCl_3$ and the spectral signals were in good agreement with the proposed structure. In the ^{13}C NMR spectrum of compound **Va**, the most deshielded signal that appeared at δ 178.2 ppm was assigned to the carbonyl carbon of the chalcone moiety. The signal for CH = CH functionality of α, β-unsaturated carbonyl group was appeared at δ 121.3 and 144.2 ppm. The signals for aromatic carbons appeared between at δ 111.4-154.9 ppm in the ^{13}C spectrum.

In the IR spectrum of compound **VIa**, a strong absorption band is observed at 1663 cm^{-1} which corresponds to the stretching vibration of the C=O functionality of acetyl group attached at N_1 position in pyrazoline ring. A broad stretching band for the C=N functionality of pyrazoline unit and C=C functionality of aromatic ring is observed at 1576 and 1512 cm^{-1} respectively. The C_4''-H stretching of pyrazoline ring was observed at 2925 cm^{-1}. A strong absorption band was observed at 1354 cm^{-1} due to the presence of the CH_3 group. The ^{1}H NMR spectrum of compound **VIa** showed a singlet at δ 2.6 ppm for the $COCH_3$ protons. The pro-chiral methylene protons C_4''-H of pyrazoline appeared as two distinct doublets of a doublet at δ 3.2 ppm (*J* = 11.3 & 14.1 Hz) and at δ 3.6 ppm (*J* = 11.4 & 13.9 Hz) for the CHx-CH and CHy-CH protons, thereby indicating that both the protons are magnetically non-equivalent and diastereotopic while the chiral C_5''-H proton of pyrazoline appeared as a doublets of a doublet at δ 4.8 ppm (*J* = 5.2 & 13.9 Hz) due to CH-CH_2-Ar proton. The other remaining twelve aromatic protons appeared as a multiplet signal at δ 7.2 - 8.2 ppm. Finally, the ^{13}C NMR spectra of the cyclised product were recorded in $CDCl_3$ and the spectral signals were in good agreement with the proposed structures. In the ^{13}C NMR spectrum of compound **VIa**, the shielded signal at δ 37.5 and 41.3 ppm was assigned to the methylene and methyl carbon of pyrazoline ring. The most deshielded signal that appeared at δ 169.0 ppm was assigned to the carbonyl carbon of the acetyl group attached with the pyrazoline unit. The signals for aromatic carbons appeared between δ 110.5-151.7 ppm in the ^{13}C spectrum.

The IR spectrum of compound **VIIa** showed a strong characteristic band at 1652 cm^{-1} and 3426 cm^{-1} due to the C=N and NH_2 group of pyrimidine ring. The C_5''-H stretching of pyrimidine ring was observed at 2975 cm^{-1}. The aromatic C=C stretching was observed at 1529 cm^{-1} respectively. The ^{1}H NMR spectrum of compound **VIIa** showed a sharp singlet at δ 5.2 due to the NH_2 protons, and it also showed a sharp singlet at δ 7.3 due to HC=C, which confirmed the cyclisation of the chalcone into a pyrimidine ring. The other remaining fourteen aromatic protons resonate as a multiplet signal at δ 7.2-8.0 ppm. ^{13}C NMR spectrum of compound **VIIa** showed a signal at 103.2 due to the –CH carbon of pyrimidine ring and signal at δ 152.4, 154.3 and 159.6 ppm assigned to the C=N carbon of pyrimidine ring which assigned the pyrimidine unit. The signals for aromatic carbons appeared between δ 113.4-156.5.0 ppm in the ^{13}C spectrum. The obtained elemental analysis values are in good agreement with theoretical data. Further, mass spectra of all the title compounds showed molecular ion peak M^{+} corresponding to their exact mass which is in agreement with its proposed structure.

Table 1. The physical data of synthesised compounds III, (Va-e), (VIa-e) and (VIIa-e).

Compd	Molecular Formula	Yield	Melting Point °C	Elemental Analysis					
				% of C		% of H		% of N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
III	$C_{23}H_{17}NO$	85	106	81.68	81.60	5.57	5.50	5.95	5.60
Va	$C_{25}H_{19}O_2N$	82	148	75.86	75.83	5.89	5.86	3.28	3.24
Vb	$C_{25}H_{21}O_4N$	76	131	75.17	75.20	5.30	5.35	3.51	3.47
Vc	$C_{25}H_{19}O_2Cl_2N$	70	116	68.82	68.80	4.39	4.45	3.21	3.17
Vd	$C_{26}H_{27}O_3N$	65	176	73.51	73.45	5.95	5.90	3.06	3.10
Ve	$C_{24}H_{19}O_2N_2Cl$	79	162	71.55	71.50	4.75	4.78	6.95	6.91
VIa	$C_{28}H_{25}O_4N_3$	74	138	72.03	72.07	6.04	6.08	8.69	8.60
VIb	$C_{27}H_{23}N_3O_4$	81	134	71.19	71.14	5.53	5.50	9.22	9.20
VIc	$C_{27}H_{23}N_3O_2Cl_2$	86	116	65.86	65.80	4.71	4.65	8.53	8.50
VId	$C_{28}H_{31}O_5N_3$	79	157	70.16	70.12	6.08	6.10	8.18	8.14
VIe	$C_{28}H_{23}N_4O_2Cl$	76	169	68.04	68.02	5.05	5.00	12.21	12.18
VIIa	$C_{28}H_{29}O_4N_3$	82	174	72.09	72.05	5.62	5.58	12.01	12.03
VIIb	$C_{28}H_{27}N_4O_3$	70	123	71.22	71.20	5.06	5.10	12.78	12.74
VIIc	$C_{29}H_{20}N_4Cl_2O$	69	116	65.69	65.72	4.24	4.20	11.79	11.75
VIId	$C_{28}H_{29}O_4N_4$	73	142	70.15	70.10	5.68	5.61	11.28	11.24
VIIe	$C_{28}H_{28}N_5OCl$	76	136	67.95	67.90	4.56	4.50	15.85	15.80

In vitro antimicrobial activity

Antimicrobial activity [19] was screened against Staphylococcus aureus (MTCC 96) Streptococcus pyogenes (MTCC 442), Escherichia coli MTCC 443, Pseudomonas aeruginosa (MTCC 441) by using ampicillin, chloramphenicol and ciprofloxacin as the standard antibacterial drugs. Antifungal activity was screened against three fungal species Candida albicans (MTCC 227), Aspergillus niger (MTCC 282) and Aspergillus clavatus (MTCC 1323) by using griseofulvin and nystatin were used as the standard antifungal drugs. The minimal inhibitory concentration (MIC) of all the synthesised compounds was determined by the broth micro dilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [20]. All the synthesised compounds (**Va-e**), (**VIa-e**) and (**VIIa-e**) were screened for their antibacterial and antifungal activities in three sets against bacteria and fungi used in the present protocol. The results are summarised in **Table 2**.

Antimicrobial screening data of compounds chalcone (**Va-e**), 1- acetyl pyrazoline (**VIa-e**) and 2-amino pyrimidine derivatives (**VIIa-e**) shows that compound **Vc** and **VIe** showed an outstanding inhibitory effect i.e. MIC = 62.5 and 50 µg/ml against Staphylococcus aureus as compared ampicillin (MIC = 250 µg/ml) and moderate to chloramphenicol and ciprofloxacin

(MIC = 50 µg/ml) whereas compounds **Vd, VIb, VIIc** and **VIIe** (MIC = 100 µg/ml) showed better activity compared to ampicillin (MIC = 250 µg/ml) and poor to chloramphenicol and ciprofloxacin (MIC = 50 µg/ml) against Staphylococcus aureus.

In the case of pathogenic Streptococcus pyogenes, compound **Ve** and **Vic** (MIC = 62.5 µg/ml) showed an outstanding inhibitory effect whereas compound **Vb, Vc, Vd, VIb, VID, VIe, VIIa, VIIb** and **VIId** (MIC = 100 µg/ml) were found to be comparable to ampicillin (MIC = 100 µg/ml) and moderate to chloramphenicol and ciprofloxacin (MIC = 50 µg/ml).

Against Gram negative bacteria, compound **Vc** (MIC = 62.5 µg/ml) showed maximum activity against Escherichia coli as compared to ampicillin while compounds **Va, Vb, Vd, VIc, VIe, VIIb** and **VIIc** (MIC = 100 µg/ml) showed similar activity against Escherichia coli upon comparison with the standard drug ampicillin and lowest to chloramphenicol (MIC = 50 µg/ml) and ciprofloxacin (MIC = 25 µg/ml). Compound **VIIc** (MIC = 50 µg/ml) and **Va** and **VIe** (MIC = 62.5 µg/ml) showed excellent activity to ampicillin (MIC = 100 µg/ml) and modest to chloramphenicol (MIC = 50 µg/ml) and ciprofloxacin (MIC = 25 µg/ml) against Pseudomonas aeruginosa. The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and were found less effective than the employed standard drugs. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-positive bacteria rather than Gram-negative bacteria.

From in vitro antifungal activity data, it is found that compounds **Vc, VIc** and **VIe** (MIC = 100 µg/ml) displayed highest antifungal activity against Candida albicans as compared to griseofulvin (MIC = 500 µg/ml) and equivalent to nystatin (MIC = 100 µg/ml). Compounds **Ve, VIa, VId, VIIa, VIIb, VIIc** and **VIId** showed the same potency as griseofulvin (MIC = 500 µg/ml) against Candida albicans. Compound **Vc, VIc** and **VIIc** (MIC = 100 µg/ml) showed equipotent to griseofulvin (MIC = 100 µg/ml) and nystatin (MIC = 100 µg/ml) against Aspergillus niger. While compound **Ve** and **VIe** (MIC = 100 µg/ml) were found to be active against the fungal pathogen Aspergillus clavatus.

Table 2. Antimicrobial activity data of synthesised compounds (Va-e), (VIa-e) and (VIIa-e)

Compd	Minimal bactericidal concentration MIC - µg/ml				Minimal fungicidal concentration MIC - µg/ml		
	Gram positive		Gram negative				
	S. a	S. p	E. c	P. a	C. a	A. n	A. c
Va	200	125	100	62.5	>1000	500	>1000
Vb	250	100	100	100	>1000	1000	>1000
Vc	62.5	100	62.5	100	100	100	200
Vd	100	100	100	125	>1000	>1000	500
Ve	50	62.5	200	100	500	500	100
VIa	250	125	200	200	500	>1000	250
VIb	100	100	200	125	200	>1000	>1000
VIc	125	62.5	100	100	100	100	500
VId	200	100	250	125	500	>1000	500
VIe	50	100	100	62.5	100	500	100
VIIa	200	100	125	125	500	>1000	1000
VIIb	250	100	100	100	500	>1000	>1000
VIIc	100	125	100	50	500	100	500
VIId	125	100	125	250	500	>1000	200
VIIe	100	200	200	100	200	1000	100
Ampi.	125	100	100	100	-	-	-
Chlo.	50	50	50	50	-	-	-
Cipr.	50	50	25	25	-	-	-
Gris.	-	-	-	-	500	500	500
Nyst.	-	-	-	-	100	100	100

S. a.: Staphylococcus aureus, S. p.: Streptococcus pyogenes, E. c.: Escherichia coli, P. a.: Pseudomonas aeruginosa, C. a.: Candida albicans, A. n.: Aspergillus niger, A. c.: Aspergillus clavatus. Ampi: Ampicillin, Chlo.: Chloramphenicol, Cipr.: Ciprofloxacin, Gris.: Greseofulvin, Nyst.: Nystatin. '-': not tested.

In vitro antimycobacterial activity

The *in vitro* antitubercular activity of all the newly synthesized compounds were determined by using Lowenstein-Jensen medium (conventional method) against *Mycobacterial tuberculosis* H37Rv strain [20]. The observed results are presented in **Table 3** in the form of inhibition (%), relative to that of standard antitubercular drugs isoniazid and rifampicin. Compounds demonstrating more than 90% inhibition in the primary screening were retested at lower concentration (MIC) in a Lowenstein–Jensen medium and evaluated for their MIC values. Among the compounds screened for antitubercular activity, compounds **Vb** (MIC = 50 µg/ml), **Vc** (MIC = 62.5 µg/ml), **VIb** (MIC = 50 µg/ml) **VId** (MIC = 100 µg/ml), **VIIa** (MIC = 62.5 µg/ml), **VIIb** (MIC = 100 µg/ml) and **VIIe** (MIC = 62.5 µg/ml) were found to possess the greatest potency against Mycobacterium tuberculosis with **82, 86, 84, 90, 96, 83** and **99** % inhibition respectively (**Table 3**). Other derivatives showed moderate to poor antitubercular activity.

Table 3. In vitro antitubercular activity (% inhibition) of the synthesized compounds (Va-e), (VIa-e) and (VIIa-e) at concentration 250 µg/ml

Compd	Inhibition (%)
Va	79
Vb	82
Vc	86
Vd	64
Ve	76
VIa	26
VIb	84
VIc	74
VId	90
VIe	68
VIIa	96
VIIb	83
VIIc	71
VIId	65
VIIe	99
Rifampicin	98

Table 3. In vitro antitubercular activity of compounds exhibiting greater inhibition

Compd	Inhibition (%)	MIC (µg/ml)
Vb	82	50
Vc	86	62.5
VIb	84	50
VId	90	100
VIIa	96	62.5
VIIb	83	100
VIIe	99	62.5
Isoniazid	99	0.20
Rifampicin	98	40

CONCLUSION

A new class of chalcone and its derivatives, as a novel class of ant tubercular and antimicrobial agents was synthesized. The newly synthesized novel heterocyclic showed good ant tubercular and antimicrobial activities against both drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis as well as antimicrobial species. These results make new indole clubbed chalcone, pyrazoline and pyrimidine derivatives interesting lead molecules for further synthetic and biological evaluation.

ACKNOWLEDGEMENT

The authors are grateful thankful to RSIC Punjab University for the FTIR analysis, ^{1}H NMR, and ^{13}C NMR spectral analysis as well as elemental analysis and Microcare Laboratory, Surat, for antimicrobial and ant tubercular activity.

REFERENCES

1. K. D. Olczak, M. Daszkiewicz, K. Slawinska, D. B. Baginska, D. Gozdowski, P. Daszkiewicz, B. Fronc, K. Semczuk (2012). ***J. Oral Pathol. Med.***, 41, p. 568.

2. A. P. Magiorakos, A. Srinivasan, R. B. Carey, et. al. (2012). ***Clin. Microbiol. Infect.***, 18, p. 268.

3. I. Jantan, S. N. Bukhari, O. A. Adekoya, I. Sylte (2014). ***Drug Des. Dev. Ther.***, **2014**, 16, 1405.

3. A. Soalnkee, R. Tailor (2015). ***Chem Sci. Trans.***, 4, p. 1057.

4. M. N. Gomes, R. C. Braga, E. M. Grzelak, B. J. Neves, E. Muratov, R. Ma, L. L. Klein, S. Cho, G. R. Oliveira, S. G. Franzblau, C. H. Andrade (2017). ***Eur. J. Med. Chem.***, 8, 137, p. 126.

5. D. K. Mahapatra, S. K. Bharti, V. Asati (2015). ***Eur. J. Med. Chem.***, 98, p. 69.

6. Z. Nowakowska (2007). ***Eur. J. Med. Chem.***, 42, p. 125.

7. S. A. Lahsasni, F. H. Al Korbi, N. Ab. Aziz Aljaber (2014). ***Chem Cent J.***, 8, p. 32.

8. Shamsuzzaman, H. Khanam, A. Mashrai, A. Sherwani, M. Owais, N. Siddiqui (2013). ***Steroids***, 78, 12, p. 1263.

9. P.Y. Rajendra, R.A. Lakshmana, L. Prasoona, K. Murali, K.P. Ravi (2005). ***Bioorg. Med. Chem. Lett.***, 15, p. 5030.

10. A. Solankee & R. Tailor (2015). ***ILCPA***, 57, p. 13.

11. A. Solankee & R. P. Tailor (2016). ***Chemistry International***, 2, p. 189.

12. R. C. Elderfield (1957). ***Heterocyclic Compounds***, **1957**, vol. 6, John Wiley & Sons, New York, NY, USA.

13. Y. K. Gupta, V. Gupta, S. Singh (2013). ***J. Pharm. Res.***, 7, p. 491.

14. K. F. M. Atta, T. M. Ibrahim, O. O. M. Farahat, T. Q. Al-Shargabi, M. G. Marei, A. A. Bekhit, E. S. H. El Ashry (2017). ***Future Med. Chem.***, 9, p. 1913.

15. S. M. Sondhi, N. Singh, M. Johar, A. Kumar (2005). ***Bioorg. Med. Chem.***, 13, p. 6158.

16. J. K. Gupta, P. K. Sharma, R. Dudhe, S. C. Mondal, A. Chaudhary, P. K. Verma (2011). ***Acta Pol Pharm.***, 68, pp. 785.

17. M. T. Chhabria, M. H. Jani (2009). ***Eur. J. Med. Chem***, 44, p. 38377.

18. National Committee for Clinical Laboratory Standards. 2000. Methods for Dilution, antimicrobial susceptibility tests for bacteria that grow aerobically approved standard, (M7A5) (5th edition). National Committee for Clinical Laboratory Standards, Wayne, PA.

19. A. Rattan (2000). Antimicrobials in laboratory medicine. B.L. Churchill, Livingstone, New Delhi, pp. 85-105.

Corresponding Author

Jayesh R. Patel*

Department of Chemistry, Veer Bahadur Singh Purvanchal University, Jaunpur

jayesh77777@yahoo.co.in