

# An efficient synthesis and antimicrobial evaluation of some new pyrazoline, pyrimidine and benzodiazepine derivatives bearing 1,3,5- triazine core

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**ABSTRACT.** In our present investigation a new class of diverse sets of acetyl pyrazolines (**6a-e**), amino pyrimidines (**7a-e**) and 1,5-benzodiazepines (**8a-e**) bearing 1,3,5-triazine core were synthesised from chalcones (**5a-e**). Treatment of chalcone with hydrazine hydrate, guanidine hydrochloride and *o*- phenylenediamine afforded the corresponding acetyl pyrazoline, amino pyrimidine and 1,5-benzodiazepine derivatives respectively. The structures of all the newly synthesised compounds were assigned on the basis of FTIR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectral data as well as elemental analysis. *In vitro* antimicrobial proficiency of the title compounds were assessed against selected pathogens *S. aureus* MTCC 96, *S. pyogenes* MTCC 442, *E. coli* MTCC 443 and *P. aeruginosa* MTCC 1688 bacteria for antibacterial activities as well as antifungal activities against *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 were used. The minimum inhibitory concentration (MIC) was determined by broth dilution method and recorded at the lowest concentration inhibiting growth of the organism. Among the synthesised compounds **6b**, **6c**, **7b**, **8b**, **8d** and **8e** exhibited excellent antimicrobial activity and said to be the most proficient members of the series.

## 1. INTRODUCTION

Varieties of infectious diseases caused by microbes are increasing rapid in recent year and still a major threat to public health in the world [1], even though incredible development in medicinal chemistry. Owing to non-availability of requisite medicines and emergence of prevalent drug resistance, the impact is more delicate in developing countries. Scientists and doctors are still struggling to find solutions with various forms of medications. Thus the demand for designing of new antimicrobial agents having excellent potential with high beneficial index with novel structural classes and mechanisms is necessary. 1,3,5-Triazine has received an enormous attention among the researchers and chemists as a consequence of essential role in novel drug discovery owing to three-fold symmetry, allows for versatile modifications, uncomplicated by region chemical concerns and has proven a useful biological target with diverse pharmacological properties of the molecules [2-3]. And therefore, it is an ongoing effort to synthesise novel antimicrobial agents bearing 1,3,5-triazine core. Chalcones are compounds of chalconoid group chemically known as 1,3-diarylprop-2-en -1- one and key precursors in the synthesis of a large array of biologically important heterocycles [4-8]. It is therefore, not surprising that many synthetic methods have been developed for the preparation of heterocycles starting from chalcones precursors. Pyrazoline is an important five member heterocyclic compound containing nitrogen as a hetero atom and various methods have been worked out for their synthesis. Due to the interesting activity of variously substituted pyrazolines as biological agents considerable attention has been focused on this class of compounds. They are used as anti-inflammatory [9], antitumor [10], anticancer [11], antimicrobial [12] etc... Among the existing various pyrazoline type derivatives, 1-acetyl pyrazolines have been identified as one of the most promising derivatives. In view of the importance of these derivatives, the title compound (**6a-e**) is achieved. Pyrimidine is a six member heterocyclic compound

containing four carbon and two nitrogen atoms and is pharmacologically inactive but its synthetic derivatives possess an important role in modern medicine. In medicinal chemistry pyrimidine derivatives have been very eminent for their therapeutic applications like anti-infective [13], antibacterial [14], analgesic [15], diuretic [16] etc... . 1,5-Benzodiazepine is a vital nitrogen containing seven member heterocyclic compound in pharmaceutical research because they possess a variety of bioactivities. Various methods have been worked out for their synthesis and numerous derivatives have been published in the literature with a diverse range of biological activities such as antimicrobial [17], anticonvulsant, antianxiety, analgesic, sedative [18] as well as cholecystokinin - 2 receptor antagonists [19]. In light of the above considerations, we herein report the reaction of 2-(3'-trifluoromethylphenylamino)-4-(tetrahydro-1',4'-oxazine)-6-[4'-{3'- aryl-2''-propanon-1''-yl}phenylamino]-1,3,5- triazines (**5a-e**) with hydrazine hydrate, guanidine hydrochloride and o-phenylenediamine furnished subsequent conversion to products acetyl pyrazolines (**6a-e**), amino pyrimidines (**7a-e**) and 1,5- benzodiazepines (**8a-e**) derivatives respectively.

## 2. EXPERIMENTAL

### 2. 1. Material

All the chemicals and solvents used for reaction were of analytical reagent (AR) grade. All the melting points were resolute in open capillary method and are uncorrected. IR spectra were recorded on Shimadzu FTIR 8401 spectrophotometer using potassium bromide pellets. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 400 F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using CDCl<sub>3</sub>, DMSO as a solvent and TMS as an internal standard at 400 MHz. 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). Purity of the compounds were checked by thin layer chromatography using TLC aluminum sheets Silica Gel 60 F-254 (Merck) plates of 0.25 mm thickness and detection of the components were made by exposure to UV light or keeping the plates in iodine chamber.

### 2. 2. Method

#### 2. 2 A. General procedure for the compounds (A), (B), (C) and chalcones (5a-e)

The starting precursors **A**, **B** and **C** were prepared by the reported procedure [20]. The chalcones (**5a-e**) were prepared by the reported method [12] in good yields by a base catalysed Claisen-Schmidt condensation of appropriately substituted benzaldehydes and substituted ketone (**C**).

#### 2. 2 B. Preparation of 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4' - oxazine) - 6 - [4' - {1'' - acetyl - 5''- (4''' - methoxyphenyl) - 2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5 - triazines (**6a**)

A 100 ml round bottomed flask, fitted with a reflux condenser was charged with a mixture of chalcone (**5a**) (0.01 mol, 5.76 gm in 30 ml ethanol) and hydrazine hydrate (0.015 mol, 0.75 gm in 5 ml ethanol). 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<sub>2</sub>CO<sub>3</sub>. The solid mass separated was collected by filtration, washed well with hot water and recrystallised from methanol to get product (**6a**) in good yield with high purity. Similarly, the remaining compounds (**6b-e**) were synthesised by this given method.

## 2. 2 C. 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6''- (4''' - methoxyphenyl) - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazines (7a)

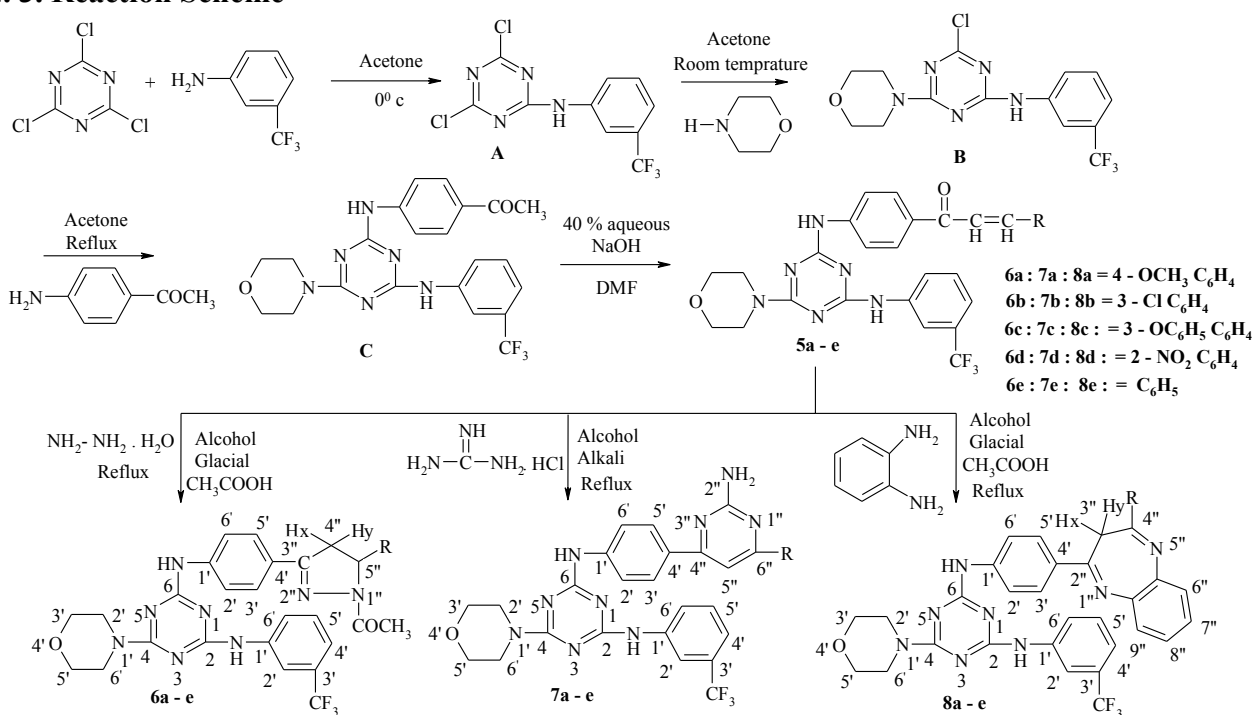
Compound (5a) (0.01 mol, 5.76 gm in 30 ml ethanol) and guanidine hydrochloride (0.015 mol, 1.43 gm in 5 ml ethanol) dissolved in ethanol was mixed in 100 ml round bottomed flask. To make this mixture alkaline 40% KOH (5 ml) was added to the reaction mixture and refluxed for 4-5 hours. The progress of the reaction was investigated by TLC using toluene: methanol (15:9 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 from methanol to get product (7a) in good yield with high purity. Similarly, the remaining compounds (7b-e) were prepared by this method. All the newly synthesised compounds (7a-e) were characterised by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectroscopy as well as elemental analysis. The characteristic data of the entire synthesised compounds are given in spectral and physical analysis data are given in spectral analysis data (3).

## 2. 2 D. Preparation of 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4''- (4''' - methoxyphenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazines (8a)

Compound (5a) (0.01 mol, 5.76 gm in 30 ml ethanol) condensed with o- phenylenediamine (0.01 mol, 1.0 gm) in the presence of catalytic amount of glacial acetic acid (5 ml) 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 (12:8 v/v) eluent as mobile phase. After completion of the reaction, the reaction mixture was poured into crushed ice and neutralised with Na<sub>2</sub>CO<sub>3</sub>. Finally, the product was filtered, washed with water, dried and recrystallised from methanol to get product (8a) in good yield with high purity. In the same way, the remaining compounds (8b-e) were prepared by this given method.

All the newly synthesised compounds (6a-e), (7a-e) and (8a-e) were characterised by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectroscopy as well as elemental analysis. The spectral and physical analysis data of the entire synthesised compounds are given in spectral analysis data (3).

## 2. 3. Reaction Scheme



### 3. SPECTRAL ANALYSIS DATA

**Compound (6a):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1',4' - oxazine) - 6 - [4' - {1''- acetyl 5''- (4''' - methoxyphenyl)2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5- triazine: Yield: 78%; mp: 147 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3358 (-NH str.), 3007 (=CH str. aromatic), 2900 (C-H str. pyrazoline moiety), 1610 (C=O str.), 1583 (C=N str. pyrazoline moiety), 1546 (-NH bend.), 1510 (C=C str. aromatic), 1365 (CH<sub>3</sub> str.), 1247 (asymmetric C-O-C str. ether linkage), 1176 (OCH<sub>3</sub> str.), 1070 (C-F str.), 833 (C-H bend. 1,4 disubstituted benzene ring), 800 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.4 (s, 3H, -COCH<sub>3</sub>), 3.0 (dd,  $J = 9.7$  & 15.4 Hz, 1H, -CH<sub>x</sub>-CH), 3.6 (dd,  $J = 9.7$  & 12.4 Hz, 1H, -CH<sub>y</sub>-CH), 5.6 (dd,  $J = 4.0$  & 11.5 Hz, 1H, -CH-CH<sub>2</sub>-Ar), 3.94 (s, 3H, 4-OCH<sub>3</sub>), 3.73 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.84 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 6.7 - 8.1 (m, 13H, 12 Ar-H and 1-NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 23.4 (CH<sub>3</sub>), 40.9 (CH<sub>2</sub>, methylene, pyrazoline moiety), 48.9 (CH<sub>2</sub>, oxazine), 55.9 (OCH<sub>3</sub>), 65.4 (CH-Ar), 66.9 (CH<sub>2</sub>, oxazine), 111.4 (CH), 115.1 (CH), 116.7 (CH), 121.3 (CH), 123.6 (CF<sub>3</sub>), 126.5 (CH), 126.9 (C), 127.7 (CH), 128.5 (CH), 129.7 (CH), 130.2 (CH), 131.8 (C), 141.7 (C), 142.2 (C), 142.8 (C), 146.2 (C), 151.6 (C=N of pyrazoline moiety), 166.2 (C=N of 1,3,5- triazine), 168.7 (C=N of 1,3,5- triazine), 168.5 (C=O), 175.4 (C=N of 1,3,5- triazine); M.S. (m/z): 632.5 (M<sup>+</sup>); Anal. Calcd. for C<sub>32</sub>H<sub>31</sub>N<sub>8</sub>F<sub>3</sub>O<sub>3</sub>: C, 60.76; H, 4.93; N, 17.71%. Found: C, 60.79; H, 4.90; N, 17.69%.

**Compound (6b):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4' - oxazine) - 6 - [4' - {1''- acetyl 5''- (3''' - chlorophenyl) 2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5- triazine: Yield: 71%; mp: 129 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3289 (-NH str.), 3078 (=CH str. aromatic), 2956 (C-H str. pyrazoline moiety), 1678 (C=O str.), 1597 (C=N str. pyrazoline moiety), 1551 (-NH bend.), 1489 (C=C str. aromatic), 1370 (CH<sub>3</sub> str.), 1220 (asymmetric C-O-C str. ether linkage), 1089 (C-F str.), 826 (C-H bend. of 1,4 disubstituted benzene ring), 809 (C=N str. 1,3,5- triazine), 659 (C-Cl); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.1 (s, 3H, -COCH<sub>3</sub>), 3.3 (dd,  $J = 11.2$  & 16.5 Hz, 1H, -CH<sub>x</sub>-CH), 3.9 (dd,  $J = 12.3$  & 16.5 Hz, 1H, -CH<sub>y</sub>-CH), 5.1 (dd,  $J = 4.5$  & 12.4 Hz, 1H, -CH-CH<sub>2</sub>-Ar), 3.53 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.78 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 7.1 - 8.3 (m, 13H, 12 Ar-H and 1-NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 24.7 (CH<sub>3</sub>), 39.4 (CH<sub>2</sub>, methylene, pyrazoline moiety), 46.1 (CH<sub>2</sub>, oxazine), 64.2 (CH-Ar), 65.8 (CH<sub>2</sub>, oxazine), 110.8 (CH), 114.7 (CH), 115.2 (CH), 122.2 (CH), 124.7 (CF<sub>3</sub>), 125.1 (CH), 126.3 (C), 128.4 (CH), 129.1 (CH), 130.5 (CH), 131.4 (CH), 132.0 (C), 134.3(C), 140.9 (C), 141.5 (C), 143.2 (C), 150.3 (C=N of pyrazoline moiety), 162.1 (C=N of 1,3,5- triazine), 166.5 (C=N of 1,3,5- triazine), 167.9 (C=O), 172.0 (C=N of 1,3,5- triazine); M.S. (m/z): 637.9 (M<sup>+</sup>); Anal. Calcd. for C<sub>31</sub>H<sub>28</sub>N<sub>8</sub>F<sub>3</sub>O<sub>2</sub>Cl: C, 58.45; H, 4.43; N, 17.59%. Found: C, 58.44; H, 4.41; N, 17.58%.

**Compound (6c):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4' - oxazine) - 6 - [4' - {1''- acetyl 5''- (3''' - phenoxyphenyl) 2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5- triazine: Yield: 79%; mp: 139 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3156 (-NH str.), 3016 (=CH str. aromatic), 2947 (C-H str. pyrazoline moiety), 1656 (C=O str.), 1590 (-NH bend.), 1578 (C=N str. pyrazoline moiety), 1460 (C=C str. aromatic), 1367 (CH<sub>3</sub> str.), 1268 (C-O-C str. phenoxy), 1254 (asymmetric C-O-C str. ether linkage), 1099 (C-F str.), 836 (C-H bend. of 1,4 disubstituted benzene ring), 804 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.9 (s, 3H, -COCH<sub>3</sub>), 3.0 (dd,  $J = 10.8$  & 15.2 Hz, 1H, -CH<sub>x</sub>-CH), 3.4 (dd,  $J = 9.6$  & 15.2 Hz, 1H, -CH<sub>y</sub>-CH), 4.8 (concealed d, 1H, -CH-CH<sub>2</sub>-Ar), 3.67 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.92 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 6.7 - 8.4 (m, 18H, 17 Ar-H and 1-NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 23.9 (CH<sub>3</sub>) 39.7 (CH<sub>2</sub>, methylene, pyrazoline moiety), 48.1 (CH<sub>2</sub>, oxazine), 66.2 (CH-Ar), 67.9 (CH<sub>2</sub>, oxazine), 110.6 (CH), 112.4 (CH), 114.1 (CH), 116.5 (CH), 119.1 (CH), 121.2 (CH), 123.7 (CF<sub>3</sub>), 125.4 (CH), 126.8 (C), 127.1 (CH), 129.2 (CH), 129.9 (CH), 131.6 (CH), 132.4 (CH), 133.0 (C), 137.7 (C), 141.8 (C), 142.1 (C), 148.9 (C=N of pyrazoline moiety), 156.7 (C), 157.3 (C), 163.2 (C-N of 1,3,5- triazine), 166.8 (C-N of 1,3,5- triazine), 169.1 (C=O), 173.5 (C-N of 1,3,5- triazine); M.S. (m/z): 694.3 (M<sup>+</sup>); Anal. Calcd. for C<sub>37</sub>H<sub>33</sub>N<sub>8</sub>F<sub>3</sub>O<sub>3</sub>: C, 63.97; H, 4.78; N, 16.13%. Found: C, 63.95; H, 4.75; N, 16.16%.

**Compound (6d):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4' - oxazine) - 6 - [4' - {1''- acetyl 5''- (2''' - nitrophenyl) 2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5 - triazine: Yield: 69%; mp: 119 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3316 (-NH str.), 3058 (=CH str. aromatic), 2919 (C-H str. pyrazoline moiety), 1687 (C=O str.), 1597 (-NH bend.), 1590 (C=N, str. pyrazoline moiety), 1539 (C-NO<sub>2</sub>), 1503 (C=C str. aromatic), 1369 (CH<sub>3</sub> str.), 1221 (asymmetric C-O-C str. ether linkage), 1026 (C-F str.), 831 (C-H bend. 1,4 disubstituted benzene ring), 799 (C-N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.6 (s, 3H, -COCH<sub>3</sub>), 3.3 (dd,  $J = 9.3$  & 15.9 Hz, 1H, -CH<sub>x</sub>-CH), 3.9 (dd,  $J = 9.3$  & 13.4 Hz, 1H, -CH<sub>y</sub>-CH), 4.2 (dd,  $J = 4.5$  & 12.2 Hz, 1H, -CH-CH<sub>2</sub>-Ar), 3.51 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.73 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 7.0 - 8.2 (m, 13H, 12 Ar-H and 1-NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 23.9 (CH<sub>3</sub>), 41.3 (CH<sub>2</sub>, methylene, pyrazoline moiety), 48.6 (CH<sub>2</sub>, oxazine), 65.6 (CH-Ar), 67.1 (CH<sub>2</sub>, oxazine), 111.2 (CH), 113.8 (CH), 114.5 (CH), 120.3 (CH), 122.8 (CF<sub>3</sub>), 124.9 (CH), 125.7 (C), 127.3 (CH), 128.1 (CH), 129.0 (CH), 131.8 (CH), 133.7 (C), 137.6 (C), 140.9 (C), 142.7 (C), 148.3 (C), 152.1 (C=N of pyrazoline moiety), 163.4 (C=N of 1,3,5- triazine), 167.6 (C=N of 1,3,5- triazine), 169.2 (C=O), 173.8 (C=N of 1,3,5- triazine); M.S. (m/z): 647.4 (M<sup>+</sup>); Anal. Calcd. for C<sub>31</sub>H<sub>28</sub>N<sub>9</sub>F<sub>3</sub>O<sub>4</sub>: C, 57.50; H, 4.35; N, 19.47%. Found: C, 57.53; H, 4.39; N, 19.44%.

**Compound (6e):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4' - oxazine) - 6 - [4' - {1''- acetyl 5''- phenyl 2'' - pyrazolin 3''- yl} phenylamino] - 1,3,5 - triazine: Yield: 70%; mp: 156 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3187 (-NH str.), 3008 (=CH str. aromatic), 2987 (C-H str. pyrazoline moiety), 1648 (C=O str.), 1591 (-NH bend.), 1583 (C=N str. pyrazoline moiety), 1497 (C=C str. aromatic), 1372 (CH<sub>3</sub> str.), 1239 (asymmetric C-O-C str. ether linkage), 1064 (C-F str.), 838 (C-H bend. 1,4 disubstituted benzene ring), 803 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 1.9 (s, 3H, -COCH<sub>3</sub>), 2.6 (dd,  $J = 11.8$  & 16.2 Hz, 1H, -CH<sub>x</sub>-CH), 3.1 (concealed d, 1H, -CH<sub>y</sub>-CH), 3.7 (dd,  $J = 4.7$  & 11.6 Hz, 1H, -CH-CH<sub>2</sub>-Ar), 3.39 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.61 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 7.2 - 8.3 (m, 14H, 13 Ar-H and 1-NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm) : 25.7 (CH<sub>3</sub>), 38.2 (CH<sub>2</sub>, methylene, pyrazoline moiety), 46.5 (CH<sub>2</sub>, oxazine), 64.6 (CH-Ar), 66.8 (CH<sub>2</sub>, oxazine), 109.7 (CH), 111.2 (CH), 113.7 (CH), 117.4 (CH), 124.1 (CF<sub>3</sub>), 124.9 (CH), 126.2 (C), 127.8 (CH), 129.3 (CH), 130.7 (CH), 132.3 (CH), 134.4 (C), 138.6 (C), 141.2 (C), 142.0 (C), 149.6 (C=N, pyrazoline moiety), 162.4 (C=N of 1,3,5- triazine), 165.9 (C=N of 1,3,5- triazine), 170.8 (C=O), 172.6 (C=N of 1,3,5- triazine); M.S. (m/z): 602.6 (M<sup>+</sup>); Anal. Calcd. for C<sub>31</sub>H<sub>29</sub>N<sub>8</sub>F<sub>3</sub>O<sub>2</sub>: C, 61.79; H, 4.85; N, 18.6%. Found: C, 61.82; H, 4.82; N, 18.62%.

**Compound (7a):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6''- (4'''- methoxyphenyl) - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazine: Yield: 73%; mp: 143 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3307 (-NH str. 1<sup>o</sup> amine of pyrimidine moiety), 3109 (-NH str.), 3064 (=CH str. aromatic), 1672 (C=N str. pyrimidine moiety), 1577 (-NH bend.), 1510 (C=C str. aromatic), 1247 (asymmetric C-O-C str. ether linkage), 1165 (OCH<sub>3</sub> str.), 1068 (C-F str.), 831 (C-H bend. 1,4 disubstituted benzene ring), 802 (C=N str. of 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 3.89 (s, 3H, 4-OCH<sub>3</sub>), 3.43 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.69 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 5.18 (s, 2H, -NH<sub>2</sub>), 6.9 - 8.2 (m, 14H, 13 Ar-H and 1 -NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 47.3 (CH<sub>2</sub>, oxazine), 55.6 (OCH<sub>3</sub>) 68.7 (CH<sub>2</sub>, oxazine), 101.7 (CH, pyrimidine moiety), 114.8 (CH), 115.1 (CH), 116.4 (CH), 116.8 (CH), 121.1 (CH), 123.8 (CF<sub>3</sub>), 125.8 (C), 128.1 (C), 128.3 (CH), 128.8 (CH), 129.3 (CH), 131.4 (C), 138.6 (C), 142.2 (C), 160.6 (C), 161.1 (C=N of 1,3,5- triazine), 162.0 (C, pyrimidine moiety), 163.8 (C=N of pyrimidine moiety), 165.2 (C of pyrimidine moiety), 166.4 (C=N of 1,3,5- triazine), 172.6 (C=N of 1,3,5- triazine); M.S. (m/z): 615.1 (M<sup>+</sup>); Anal. Calcd. for C<sub>31</sub>H<sub>28</sub>N<sub>9</sub>F<sub>3</sub>O<sub>2</sub>: C, 60.48; H, 4.58; N, 20.48%. Found: C, 60.52; H, 4.56; N, 20.51%.

**Compound (7b):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6'' - (3'''- chlorophenyl) - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazine: Yield: 70%; mp: 130 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3390 (-NH str. 1<sup>o</sup> amine of pyrimidine moiety), 3209 (-NH

str.), 3026 (=CH str. aromatic), 1618 (C=N str. pyrimidine moiety), 1559 (-NH bend.), 1499 (C=C str. aromatic), 1234 (asymmetric C-O-C str. ether linkage), 1082 (C-F str.), 840 (C-H bend. 1,4 disubstituted benzene ring), 809 (C=N str. 1,3,5- triazine), 679 (C-Cl);  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ,  $\delta$  ppm): 3.81 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 4.06 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 5.2 (s, 2H,  $-\text{NH}_2$ ), 7.1 - 8.1 (m, 14H, 13 Ar-H and 1 -NH);  $^{13}\text{C}$  NMR (400 MHz, DMSO,  $\delta$  ppm): 46.2 ( $\text{CH}_2$ , oxazine), 67.1 ( $\text{CH}_2$ , oxazine), 103.4 (CH, pyrimidine moiety), 112.5 (CH), 114.2 (CH), 115.0 (CH), 116.3 (CH), 120.2 (CH), 124.1 ( $\text{CF}_3$ ), 126.7 (C), 127.2 (C), 128.9 (CH), 129.2 (CH), 130.5 (CH), 132.9 (C), 134.8 (C), 139.7 (C), 141.3 (C), 162.4 (C=N of 1,3,5- triazine), 163.1 (C=N of pyrimidine moiety), 163.7 (C, pyrimidine moiety), 166.3 (C, pyrimidine moiety), 168.1 (C=N of 1,3,5- triazine), 171.6 (C=N of 1,3,5- triazine); M.S. (m/z): 620.1 ( $\text{M}^+$ ); Anal. Calcd. for  $\text{C}_{30}\text{H}_{25}\text{N}_9\text{F}_3\text{OCl}$ : C, 58.12; H, 4.06; N, 20.33%. Found: C, 58.11; H, 4.03; N, 20.30%.

**Compound (7c):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6'' - (3'''- phenoxyphenyl) - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazine: Yield: 69%; mp: 165  $^{\circ}\text{C}$ ; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3368 (-NH str. 1 $^{\circ}$  amine of pyrimidine moiety), 3226 (-NH str.), 3034 (=CH str.), 1597 (C=N str. pyrimidine moiety), 1526 (-NH bend.), 1487 (C=C str. aromatic), 1289 (C-O-C str. phenoxy), 1223 (asymmetric C-O-C str. of ether linkage), 1061 (C-F str.), 834 (C-H bend. 1,4 disubstituted benzene ring), 797 (C=N str. 1,3,5- triazine);  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ,  $\delta$  ppm): 3.79 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 3.97 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 4.9 (s, 2H,  $-\text{NH}_2$ ), 6.8 - 8.3 (m, 19H, 18 Ar-H and 1 -NH);  $^{13}\text{C}$  NMR (400 MHz, DMSO,  $\delta$  ppm): 48.3 ( $\text{CH}_2$ , oxazine), 65.9 ( $\text{CH}_2$ , oxazine), 99.1 (CH, pyrimidine moiety), 113.4 (CH), 114.8 (CH), 115.3 (CH), 116.7 (CH), 118.7 (CH), 120.1 (CH), 121.8 (CH), 123.5 ( $\text{CF}_3$ ), 126.2 (C), 127.0 (C), 128.1 (CH), 128.6 (CH), 130.2 (CH), 131.3 (CH), 133.0 (C), 138.4 (C), 140.3 (C), 157.6 (C), 157.9 (C), 164.6 (C=N of 1,3,5- triazine), 165.3 (C=N of pyrimidine moiety), 167.2 (C, pyrimidine moiety), 169.0 (C, pyrimidine moiety), 172.2 (C=N of 1,3,5- triazine), 173.5 (C=N of 1,3,5- triazine); M.S. (m/z): 677.0 ( $\text{M}^+$ ); Anal. Calcd. for  $\text{C}_{36}\text{H}_{30}\text{N}_9\text{F}_3\text{O}_2$ : C, 63.81; H, 4.46; N, 18.60%. Found: C, 63.79; H, 4.51; N, 18.57%.

**Compound (7d):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6'' - (2''' - nitrophenyl) - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazine: Yield: 78%; mp: 137  $^{\circ}\text{C}$ ; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3379 (-NH str. 1 $^{\circ}$  amine of pyrimidine moiety), 3256 (-NH str.), 3039 (=CH str. aromatic), 1625 (C=N str. pyrimidine moiety), 1563 (-NH bend.), 1548 (C- $\text{NO}_2$ ), 1448 (C=C str. aromatic), 1256 (asymmetric C-O-C str. ether linkage), 1031 (C-F str.), 829 (C-H bend. 1,4 disubstituted benzene ring), 806 (C=N str. of 1,3,5- triazine);  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ,  $\delta$  ppm): 3.33 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 3.68 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 5.4 (s, 2H,  $-\text{NH}_2$ ), 6.6 - 8.0 (m, 14H, 13 Ar-H and 1 -NH);  $^{13}\text{C}$  NMR (400 MHz, DMSO,  $\delta$  ppm): 47.6 ( $\text{CH}_2$ , oxazine), 64.2 ( $\text{CH}_2$ , oxazine), 102.9 (CH, pyrimidine moiety), 113.1 (CH), 114.5 (CH), 115.7 (CH), 116.8 (CH), 119.3 (CH), 122.8 ( $\text{CF}_3$ ), 125.4 (C), 126.6 (C), 127.7 (CH), 128.9 (CH), 131.2 (CH), 132.5 (C), 142.4 (C), 143.8 (C), 146.0 (C), 162.7 (C=N of pyrimidine moiety), 164.9 (C=N of 1,3,5- triazine), 165.0 (C, pyrimidine moiety), 168.2 (C, pyrimidine moiety), 168.8 (C=N of 1,3,5- triazine), 174.2 (C=N of 1,3,5- triazine); M.S. (m/z): 630.8 ( $\text{M}^+$ ); Anal. Calcd. for  $\text{C}_{30}\text{H}_{25}\text{N}_{10}\text{F}_3\text{O}_3$ : C, 57.14; H, 3.99; N, 22.21%. Found: C, 57.17; H, 3.96; N, 22.24%.

**Compound (7e):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {2''- amino - 6'' - phenyl - pyrimidin - 4''- yl} phenylamino] - 1,3,5 - triazine: Yield: 64%; mp: 125  $^{\circ}\text{C}$ ; IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3326 (-NH str. 1 $^{\circ}$  amine of pyrimidine moiety), 3229 (-NH str.), 3036 (=CH str. aromatic), 1629 (C=N str. pyrimidine moiety), 1549 (-NH bend.), 1472 (C=C str. aromatic), 1251 (asymmetric C-O-C str. ether linkage), 1091 (C-F str.), 843 (C-H bend. 1,4 disubstituted benzene ring), 812 (C=N str. 1,3,5- triazine);  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ,  $\delta$  ppm): 3.82 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 4.13 (concealed t, 4H,  $-\text{CH}_2$ , oxazine ring), 4.7 (s, 2H,  $-\text{NH}_2$ ), 7.2 - 8.4 (m, 15H, 14 Ar-H and 1 -NH);  $^{13}\text{C}$  NMR (400 MHz, DMSO,  $\delta$  ppm): 46.2 ( $\text{CH}_2$ , oxazine), 66.8 ( $\text{CH}_2$ , oxazine), 101.5 (CH, pyrimidine moiety), 114.6 (CH), 114.8 (CH), 116.2 (CH), 117.3 (CH), 118.7 (CH), 125.0 ( $\text{CF}_3$ ), 126.2 (C), 126.8 (C), 127.4 (CH), 128.1 (CH), 129.3

(C), 131.8 (CH), 134.9 (C), 143.5 (C), 144.2 (C), 162.1 (C=N of pyrimidine moiety), 164.3 (C=N of 1,3,5- triazine), 166.2 (C, pyrimidine moiety), 167.8 (C, pyrimidine moiety), 169.5 (C=N of 1,3,5- triazine), 172.7 (C=N of 1,3,5- triazine); M.S. (m/z): 585.2 ( $M^+$ ); Anal. Calcd. for  $C_{30}H_{26}N_9F_3O$ : C, 61.53; H, 4.47; N, 21.53%. Found: C, 61.50; H, 4.51; N, 21.56%.

**Compound (8a):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4'' - (4''' - methoxyphenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazine: Yield: 70%; mp: 107 °C; IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3346 (-NH str.), 3067 (=CH str. aromatic), 1610 (C=N str. benzodiazepine moiety), 1581 (-NH bend.), 1494 (C=C str. aromatic), 1241 (asymmetric C-O-C str. ether linkage), 1157 (OCH<sub>3</sub> str.), 1100 (C-F str.), 848 (C-H bend. 1,4 disubstituted benzene ring), 805 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.72 (dd,  $J = 6.2$  & 13.0 Hz, 1H, CH<sub>x</sub>, diazepine moiety), 2.44 (dd,  $J = 6.2$  & 14.2 Hz, 1H, CH<sub>y</sub>, diazepine moiety), 3.78 (s, 3H, 4-OCH<sub>3</sub>), 3.44 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.74 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 6.9 - 8.1 (m, 17H, 16 Ar-H and 1 - NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 37.8 (CH<sub>2</sub>, methylene, diazepine moiety), 49.8 (CH<sub>2</sub>, oxazine), 57.9 (4 - OCH<sub>3</sub>), 69.7 (CH<sub>2</sub>, oxazine), 110.4 (CH), 113.8 (CH), 116.3 (CH), 118.7 (CH), 120.1 (CH), 122.5 (CH), 124.4 (CF<sub>3</sub>), 127.3(C), 128.5 (CH), 130.2 (CH), 131.8 (C), 132.1 (CH), 133.1 (CH), 137.8 (C), 141.3 (C), 143.8 (C), 149.2 (C), 157.3 (C=N), 162.7 (C), 166.2 (C=N of 1,3,5- triazine), 169.4 (C=N of 1,3,5- triazine), 171.4 (C=N of 1,3,5- triazine); M.S. (m/z): 664.0 ( $M^+$ ); Anal. Calcd. for  $C_{36}H_{31}N_8F_3O_2$ : C, 65.05; H, 4.70; N, 16.86%. Found: C, 65.01; H, 4.74; N, 16.83%.

**Compound (8b):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4'' - (3''' - chlorophenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazine: Yield: 70%; mp: 107 °C; IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3378 (-NH str.), 3034 (=CH str. aromatic), 1599 (C=N str. benzodiazepine moiety), 1583 (-NH bend.), 1496 (C=C str. aromatic), 1249 (asymmetric C-O-C str. ether linkage), 1039 (C-F str.), 835 (C-H bend. 1,4 disubstituted benzene ring), 801 (C=N str. 1,3,5- triazine), 650 (C-Cl); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.87 (concealed d, 1H, CH<sub>x</sub>, diazepine moiety), 3.26 (concealed d, 1H, CH<sub>y</sub>, diazepine moiety), 3.56 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.83 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 7.2 - 8.3 (m, 17H, 16 Ar-H and 1 - NH); <sup>13</sup>C NMR (100 MHz, DMSO,  $\delta$  ppm): 38.2 (CH<sub>2</sub>, methylene, diazepine moiety), 48.6 (CH<sub>2</sub>, oxazine), 67.3 (CH<sub>2</sub>, oxazine), 111.6 (CH), 112.5 (CH), 115.1 (CH), 116.0 (CH), 118.3 (CH), 120.2 (CH), 123.7 (CF<sub>3</sub>), 126.2 (C), 129.1 (CH), 131.6 (CH), 132.4 (C), 133.9 (CH), 134.7 (CH), 135.0 (C), 138.2 (C), 142.8 (C), 144.1 (C), 147.9 (C), 155.8 (C=N of diazepine moiety), 164.1 (C=N of 1,3,5- triazine), 167.0 (C=N of 1,3,5- triazine), 172.9 (C=N of 1,3,5- triazine); M.S. (m/z): 669.4 ( $M^+$ ); Anal. Calcd. for  $C_{36}H_{31}N_8F_3O_2$ : C, 65.05; H, 4.70; N, 16.86%. Found: C, 65.01; H, 4.74; N, 16.83%.

**Compound (8c):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4'' - (3''' - phenoxyphenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazine: Yield: 80%; mp: 126 °C; IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3362 (-NH str.), 3059 (=CH str. aromatic), 1594 (C=N str. benzodiazepine moiety), 1587 (-NH bend.), 1480 (C=C str. aromatic), 1291 (C-O-C str. phenoxy), 1226 (asymmetric C-O-C str. ether linkage), 1049 (C-F str.), 842 (C-H bend. 1,4 disubstituted benzene ring), 798 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 3.45 (dd,  $J = 6.4$  & 13.5 Hz, 1H, CH<sub>x</sub>, diazepine moiety), 3.78 (dd,  $J = 7.0$  & 13.5 Hz, 1H, CH<sub>y</sub>, diazepine moiety), 3.36 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.56 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 6.8 - 8.2 (m, 22H, 21 Ar-H and 1 - NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 39.8 (CH<sub>2</sub>, methylene, diazepine moiety), 46.1 (CH<sub>2</sub>, oxazine), 66.9 (CH<sub>2</sub>, oxazine), 109.1 (CH), 111.3 (CH), 113.8 (CH), 115.7 (CH), 117.0 (CH), 118.2 (CH), 119.6 (CH), 121.4 (CH), 124.2 (CF<sub>3</sub>), 125.6 (C), 127.1 (CH), 128.0 (CH), 130.9 (CH), 131.3 (C), 132.4 (CH), 133.8 (CH), 136.0 (C), 140.2 (C), 142.6 (C), 145.9 (C), 153.6 (C=N of diazepine moiety), 156.3 (C), 158.4 (C), 165.6 (C=N of 1,3,5- triazine), 166.3 (C=N of 1,3,5- triazine), 170.2 (C=N of 1,3,5- triazine); M.S. (m/z): 726.6 ( $M^+$ ); Anal. Calcd. for  $C_{41}H_{33}N_8F_3O_2$ : C, 67.76; H, 4.57; N, 15.42%. Found: C, 67.74; H, 4.53; N, 15.45%.

**Compound (8d):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4'' - (2''' - nitrophenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazine: Yield: 65%; mp: 117 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3306 (-NH str.), 3071 (=CH str. aromatic), 1592 (C=N str. benzodiazepine moiety), 1577 (-NH bend.), 1539 (C-NO<sub>2</sub>), 1502 (C=C str. aromatic), 1219 (asymmetric C-O-C str. ether linkage), 1085 (C-F str.), 831 (C-H bend. 1,4 disubstituted benzene ring), 806 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 2.96 (concealed d, 1H, CH<sub>x</sub>, diazepine moiety), 3.54 (dd,  $J = 6.8$  & 14.2 Hz, 1H, CH<sub>y</sub>, diazepine moiety), 3.78 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 4.02 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 7.0 - 8.1 (m, 17H, 16 Ar-H and 1 - NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 38.6 (CH<sub>2</sub>, methylene, diazepine moiety), 48.3 (CH<sub>2</sub>, oxazine), 68.6 (CH<sub>2</sub>, oxazine), 110.4 (CH), 112.1 (CH), 114.7 (CH), 115.8 (CH), 117.2 (CH), 119.8 (CH), 124.8 (CF<sub>3</sub>), 125.9 (C), 127.4 (CH), 130.0 (CH), 133.7 (C), 134.2 (CH), 135.1 (CH), 137.9 (C), 140.9 (C), 143.2 (C), 145.6 (C), 150.9 (C), 156.5 (C=N of diazepine moiety), 165.8 (C=N of 1,3,5- triazine), 168.8 (C=N of 1,3,5- triazine), 174.1 (C=N of 1,3,5- triazine); M.S. (m/z): 679.0 (M<sup>+</sup>); Anal. Calcd. for C<sub>35</sub>H<sub>28</sub>N<sub>9</sub>F<sub>3</sub>O<sub>3</sub>: C, 61.85; H, 4.15; N, 18.55%. Found: C, 61.83; H, 4.19; N, 18.52%.

**Compound (8e):** 2 - (3' - trifluoromethylphenylamino) - 4 - (tetrahydro - 1', 4'- oxazine) - 6 - [4' - {4'' - (phenyl) - 3'' H - benzo - 1'', 5''- diazepin - 2''- yl} phenylamino] - 1,3,5 - triazine: Yield: 72%; mp: 100 °C; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3319 (-NH str.), 3061 (=CH str. aromatic), 1598 (C=N str. benzodiazepine moiety), 1571 (-NH bend.), 1489 (C=C str. aromatic), 1243 (asymmetric C-O-C str. ether linkage), 1054 (C-F str.), 844 (C-H bend. 1,4 disubstituted benzene ring), 803 (C=N str. 1,3,5- triazine); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 3.64 (dd,  $J = 7.2$  & 14.2 Hz, 1H, CH<sub>x</sub>, diazepine moiety), 4.03 (dd,  $J = 7.2$  & 13.9 Hz, 1H, CH<sub>y</sub>, diazepine moiety), 3.49 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 3.81 (concealed t, 4H, -CH<sub>2</sub>, oxazine ring), 6.8 - 8.3 (m, 18H, 17 Ar-H and 1 - NH); <sup>13</sup>C NMR (400 MHz, DMSO,  $\delta$  ppm): 40.9 (CH<sub>2</sub>, methylene, diazepine moiety), 46.2 (CH<sub>2</sub>, oxazine), 66.1 (CH<sub>2</sub>, oxazine), 108.1 (CH), 110.7 (CH), 112.2 (CH), 113.4 (CH), 115.6 (CH), 117.1 (CH), 122.3 (CF<sub>3</sub>), 126.7 (C), 128.9 (CH), 130.8 (CH), 131.6 (CH), 133.4 (C), 135.2 (CH), 136.0 (CH), 138.8 (C), 142.1 (C), 144.4 (C), 148.9 (C), 154.0 (C=N of diazepine moiety), 162.1 (C=N of 1,3,5- triazine), 166.4 (C=N of 1,3,5- triazine), 170.2 (C-N, 1,3,5 - triazine); M.S. (m/z): 634.7 (M<sup>+</sup>); Anal. Calcd. for C<sub>35</sub>H<sub>29</sub>N<sub>8</sub>F<sub>3</sub>O: C, 66.24; H, 4.60; N, 17.66%. Found: C, 66.27; H, 4.58; N, 17.63%.

## 4. RESULT AND DISCUSSION

### 4. 1. Chemistry

The aim of the present study was to develop an efficient protocol with good to excellent yields in a short span of time without formation of any side product. The formation of designed compounds was confirmed by their IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral and elemental analysis. The IR spectrum of compound **6a** exhibited a strong band at 1610  $\text{cm}^{-1}$  for C=O stretching of acetyl group attached at N<sub>1</sub> position in pyrazoline ring. The C-H stretching was observed at 2900  $\text{cm}^{-1}$ . Characteristic band of C=N stretching of pyrazoline moiety appeared at 1583  $\text{cm}^{-1}$ . A strong absorption band was observed at 1365  $\text{cm}^{-1}$  due to the presence of the CH<sub>3</sub> group. The aromatic C-H bending vibrations for 1,4 disubstituted benzene ring and C=N stretching of 1,3,5-triazine core were observed at 833 and 800  $\text{cm}^{-1}$  respectively. The <sup>1</sup>H NMR spectrum of compound **6a** showed a singlet at  $\delta$  2.4 ppm for the COCH<sub>3</sub> protons. The pro-chiral methylene protons C<sub>4</sub>''-H of pyrazoline appeared as two distinct doublets of a doublet at  $\delta$  3.0 ppm ( $J = 9.7$  & 15.4 Hz) and at  $\delta$  3.6 ppm ( $J = 9.7$  & 12.4 Hz) for the CH<sup>x</sup>-CH and CH<sup>y</sup>-CH protons, thereby indicating that both the protons are magnetically non-equivalent and diastereotopic. The chiral C<sub>5</sub>''-H proton of pyrazoline appeared as a doublets of a doublet at  $\delta$  5.6 ppm ( $J = 4.0$  & 11.5 Hz) due to CH-CH<sub>2</sub>-Ar proton. The other remaining twelve aromatic protons appeared as a multiplet signal at  $\delta$  6.7-7.0 ppm. In the <sup>13</sup>C NMR spectrum of compound **6a**, the signal appeared at  $\delta$  23.4 ppm was assigned to the methyl carbon and the most deshielded signal that appeared at  $\delta$  168.5 ppm was assigned to the carbonyl carbon of the acetyl group attached with the pyrazoline unit. The signals for aromatic carbons appeared between  $\delta$



111.4-146.2 ppm in the  $^{13}\text{C}$  spectrum. The IR spectrum of compound **7a** showed a strong characteristic band at  $1672\text{ cm}^{-1}$  and  $3307\text{ cm}^{-1}$  due to the C=N and  $\text{NH}_2$  group of pyrimidine ring. The aromatic C=C stretching and C-H bending vibrations for 1,4 disubstituted benzene ring were appeared at  $1510$  and  $831\text{ cm}^{-1}$  respectively. The  $^1\text{H}$  NMR spectrum of compound **7a** showed a singlet at  $\delta$  5.18 ppm due to  $\text{NH}_2$  proton on pyrimidine nucleus which confirmed the cyclisation of pyrimidine moiety. The other remaining thirteen aromatic protons resonate as a multiplet signal at  $\delta$  6.9-8.0 ppm.  $^{13}\text{C}$  NMR spectrum of compound **7a** showed a signal at  $\delta$  163.8 ppm assigned to the C=N carbon of pyrimidine ring which assigned the pyrimidine unit. The signals for aromatic carbons appeared between  $\delta$  114.8-142.6 ppm in the  $^{13}\text{C}$  spectrum. The IR spectrum of compound **8a** exhibited a strong band at  $1556\text{ cm}^{-1}$  due to the C=N of diazepine unit. Aromatic C=C and C-H bending vibrations for 1,4 disubstituted benzene ring were appeared at  $1494$  and  $848\text{ cm}^{-1}$  respectively. The  $^1\text{H}$  NMR spectrum of compound **8a** showed  $\text{C}_3$ -H as doublet of doublet at  $\delta$  2.72 ppm ( $J = 6.2$  &  $13.0$  Hz) and at  $\delta$  3.44 ppm ( $J = 6.2$  &  $14.2$  Hz). The other remaining seventeen aromatic protons resonate as a multiplet signal at  $\delta$  6.9-8.0 ppm. In the  $^{13}\text{C}$  NMR spectrum of compound **8a** showed a shielded signal at  $\delta$  37.8 signal for methylene carbon and the most deshielded signal appeared at 157.3 ppm due to the C=N of diazepine ring which confirmed diazepine moiety. The signals for aromatic carbons appeared between  $\delta$  110.4-149.2 ppm in the  $^{13}\text{C}$  spectrum. There are no absorptions in the region of  $1600$  - $1700\text{ cm}^{-1}$  in IR spectra of compound **7a** and **8a** which indicating the absence of a C=O group of chalcone moiety in these structures and further confirmed the cyclisation of chalcone in to its derivatives. Moreover, distinctive singlet around  $\delta$  3.65 - 4.21 ppm stands for methoxy group of aryl ring attached to pyrazoline, pyrimidine and diazepine unit, singlet around  $\delta$  8.1- 8.5 ppm stands for secondary amine attached with 1,3,5-triazine. Further, mass spectra of compound **6a**, **7a** and **8a** showed molecular ion peak  $\text{M}^+$  at  $m/z$  632.5, 615.1 and 664.0 (100%) along with other fragment peaks, which also supported the structure of compound **6a**, **7a** and **8a** respectively. The obtained elemental analysis values within  $\pm 0.4\%$  of theoretical values of all the synthesised compounds were good agreement with the molecular formula.

#### 4. 2. Antimicrobial evaluation

The antibacterial and antifungal activity of newly synthesised compounds (**6a-e**), (**7a-e**) and (**8a-e**) was carried out by broth dilution method [21] according to National Committee for Clinical Laboratory Standards (NCCLS, 2002). It is one of the non automated *in vitro* bacterial / fungal susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms which is carried out in tubes. Upon reviewing antimicrobial data (**Table 1**) it has been observed that in Gram positive bacterial strains, compounds **7b** (MIC =  $50\text{ }\mu\text{g/mL}$ ), **8d** and **8e** (MIC =  $62.5\text{ }\mu\text{g/mL}$ ) exhibited excellent activity against *Staphylococcus aureus* (MTCC 96) compared to Ampicillin (MIC =  $250\text{ }\mu\text{g/mL}$ ) and equipotent activity to Chloramphenicol and Ciprofloxacin (MIC =  $50\text{ }\mu\text{g/mL}$ ) while **8c** (MIC =  $100\text{ }\mu\text{g/mL}$ ), **6a**, **6d**, **6e**, **7c** and **7d** (MIC =  $125\text{ }\mu\text{g/mL}$ ) were found to be more potent compared to Ampicillin (MIC =  $250\text{ }\mu\text{g/mL}$ ) and less potent to Chloramphenicol and Ciprofloxacin (MIC =  $50\text{ }\mu\text{g/mL}$ ) against *Staphylococcus aureus* (MTCC 96). Compounds **6b**, **6c** and **8b** (MIC =  $62.5\text{ }\mu\text{g/mL}$ ) were found to possess excellent activity compared to Ampicillin (MIC =  $250\text{ }\mu\text{g/mL}$ ) and equivalent to Chloramphenicol and Ciprofloxacin (MIC =  $50\text{ }\mu\text{g/mL}$ ) against *Streptococcus pyogenes* (MTCC 442) whereas compounds **6a**, **6d**, **6e**, **7b** and **8e** (MIC =  $100\text{ }\mu\text{g/mL}$ ), **7c**, **7d** and **8d** (MIC =  $125\text{ }\mu\text{g/mL}$ ) were found equally potent to Ampicillin (MIC =  $100\text{ }\mu\text{g/mL}$ ) and less potent to Chloramphenicol and Ciprofloxacin (MIC =  $50\text{ }\mu\text{g/mL}$ ) against *Streptococcus pyogenes* (MTCC 442). Compounds **6b**, **7a** and **8a** (MIC =  $200\text{ }\mu\text{g/mL}$ ) were found to be more active than Ampicillin (MIC =  $250\text{ }\mu\text{g/mL}$ ) while compounds **6c**, **7e** and **8b** (MIC =  $250\text{ }\mu\text{g/mL}$ ) were exerted equally potent to Ampicillin (MIC =  $250\text{ }\mu\text{g/mL}$ ) and modest to Chloramphenicol and Ciprofloxacin (MIC =  $50\text{ }\mu\text{g/mL}$ ) against *Staphylococcus aureus*. On the other hand in Gram negative bacterial strains, compound **6b** (MIC =  $50\text{ }\mu\text{g/mL}$ ) showed excellent potency against *Escherichia coli* (MTCC 443) compared to Ampicillin (MIC =  $100\text{ }\mu\text{g/mL}$ ), comparable to Chloramphenicol (MIC =  $50\text{ }\mu\text{g/mL}$ ) and modest to Ciprofloxacin (MIC =  $25\text{ }\mu\text{g/mL}$ ) whereas

compounds **6e**, **7c**, **8b** and **8e** (MIC = 100 µg/mL), **6c**, **8a** and **8d** (MIC = 125 µg/mL) were found to have comparable potency to Ampicillin (MIC = 100 µg/mL) against *Escherichia coli* (MTCC 443). Compounds **6b** and **8e** (MIC = 100 µg/mL), **7c** and **8b** (MIC = 125 µg/mL) exerted equally active to Ampicillin (MIC = 100 µg/mL) and less active to Chloramphenicol (MIC = 50 µg/mL) and Ciprofloxacin (MIC = 25 µg/mL) against *Pseudomonas aeruginosa* (MTCC 441). The antifungal screening data (Table 1) revealed that compound **8b** (MIC = 100 µg/mL) exhibited excellent activity against *Candida albicans* (MTCC 227) compared to Greseofulvin (MIC = 500 µg/mL) and significant to Nystatin (MIC = 100 µg/mL) whereas compounds **6c**, **6d**, **7a**, **7b**, **7d**, **8a**, **8c** and **8d** (MIC = 500 µg/mL) were found to have equipotent activity to Greseofulvin (MIC = 500 µg/mL) against *Candida albicans* (MTCC 227). None of the compound showed promising antifungal activity against *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323).

**Table - 1. In Vitro antimicrobial activity of synthesised compounds (6a-e), (7a-e) and (8a-e)**

| Compd | Minimal bactericidal concentration<br>MIC (µg/mL) |                     |                     |                     | Minimal fungicidal<br>concentration MIC (µg/mL) |                     |                      |
|-------|---|---------------------|---------------------|---------------------|---|---------------------|----------------------|
|       | Gram positive                                     |                     | Gram negative       |                     | C. a<br>MTCC<br>227                             | A. n<br>MTCC<br>282 | A. c<br>MTCC<br>1323 |
|       | S. a<br>MTCC<br>96                                | S. p<br>MTCC<br>442 | E. c<br>MTCC<br>443 | P. a<br>MTCC<br>441 |   |                     |                      |
| 6a    | 125   | 100                 | 200                 | 200                 | 1000  | 1000                | 500                  |
| 6b    | 200   | 62.5                | 50                  | 100                 | 1000  | 500                 | 500                  |
| 6c    | 250   | 62.5                | 125                 | 200                 | 500   | 250                 | 1000                 |
| 6d    | 125   | 100                 | 200                 | 200                 | 500   | >1000               | >1000                |
| 6e    | 125   | 100                 | 100                 | 250                 | >1000   | >1000               | >1000                |
| 7a    | 200   | 250                 | 250                 | 250                 | 500   | 250                 | 500                  |
| 7b    | 50  | 100                 | 250                 | 250                 | 500   | 1000                | 500                  |
| 7c    | 125   | 125                 | 100                 | 125                 | 1000  | >1000               | >1000                |
| 7d    | 125   | 250                 | 500                 | 500                 | 500   | >1000               | >1000                |
| 7e    | 250   | 125                 | 250                 | 200                 | 1000  | >1000               | 250                  |
| 8a    | 200   | 200                 | 125                 | 200                 | 500   | 250                 | >1000                |
| 8b    | 250   | 62.5                | 100                 | 125                 | 100   | 500                 | 1000                 |
| 8c    | 100   | 250                 | 200                 | 200                 | 500   | 1000                | >1000                |
| 8d    | 62.5  | 125                 | 125                 | 200                 | 500   | 500                 | 500                  |
| 8e    | 62.5  | 100                 | 100                 | 100                 | >1000   | >1000               | >1000                |
| A     | 250   | 100                 | 100                 | 100                 | -   | -                   | -                    |
| B     | 50  | 50                  | 50                  | 50                  | -   | -                   | -                    |
| C     | 50  | 50                  | 25                  | 25                  | -   | -                   | -                    |
| D     | -   | -                   | -                   | -                   | 500   | 100                 | 100                  |
| E     | -   | -                   | -                   | -                   | 100   | 100                 | 100                  |

Sa.: *Staphylococcus aureus*; Sp.: *Streptococcus pyogenes*; Ec.: *Escherichia coli*; Pa.: *Pseudomonas aeruginosa*; Ca.: *Candida albicans*; An.: *Aspergillus niger*; Ac.: *Aspergillus clavatus*; A: Ampicillin; B: Chloramphenicol; C: Ciprofloxacin; D: Greseofulvin; E: Nystatin. MTCC: Microbial Type Culture Collection. '-' represents 'not tested'.

## 5. CONCLUSION

In summary, the synthesis of biologically important three elegant protocols (acetyl pyrazolines, amino pyrimidines and 1,5- benzodiazepines) has been developed using the potential of chalcones with the hope of generating new pharmacologically important molecules that could be useful as potent antimicrobial agents. The method reported in this investigation is effective in giving excellent conversion to the product, less - energy consuming and apparently substituent insensitive. There is no necessary to do any extra or special work during isolation of product. The results indicated that all the derivatives of new chemical entities exhibited appreciable activities against multidrug-resistant bacteria. Among the fifteen newly synthesised compounds, analogs **6b**, **6c**, **7b**, **8b**, **8d** and **8e** were found to be the most proficient members of the series. It is interesting to note that compounds bearing the electron withdrawing chloro group in the aryl moiety **6b**, **7b** and **8b** showed the highest antibacterial and antifungal activities. Further in depth SAR study of the active scaffolds and the mechanism research are also required. These result suggest that chalcones and their derivatives have an opportunity to behave as generation of newer antimicrobial agents and have excellent scope for further development as commercial antimicrobial agents.

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