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RESEARCH ARTICLE

A facile one pot synthesis of pyrazolyl pyrimidines through multcomponent reaction

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Abstract

A series of new pyrimidine derivatives containing pyrazole moiety were designed and synthesized. In addition, various substituents were introduced in to the entering pyrazole aldehyde ring and β-keto ester with the purpose of exploring the influence of substituent on anticancer activity by regulating the electronic and steric effects. The synthesized compounds were characterized by various spectroscopic techniques.

Introduction:-

Pyrimidine and their derivatives play a vital role in the field of drugs and agricultural **c**hemicals. They are structural components in many natural compounds, such as nucleotides, nucleic acids, vitamins and antibiotics. In all organisms, pyrimidine nucleotides serve essential functions in nucleic acids as well as in cell metabolism. Pyrimidine nucleotides have been shown to be involved in many extracellular processes. Pyrimidine derivatives are of interest due to their pharmacological properties such as antitumor,[1-4] antiviral,[5] antifungal, anticancer,[6] antibacterial,[7] antiinflammator,[8-11] analgesic,[12] antimicrobial,[13] anti-HIV,[14] antithrombotic[15] and antifilarial[16] activities, suggesting the importance of this class of compound as broad spectrum drugs. Both pyrimidine and pyrazole are a significant pharmacophore and exhibits outstanding biological activities.

In view of these observations, it was thought of interest to study the influence of pyrimidine moiety and pyrazole framework combination; so that the two combined substructures may be expected to exhibit enhanced biological activities. Therefore, a series of new pyrimidine derivatives containing pyrazole moiety were designed and synthesized. In addition, various substituents were introduced in to the pyrazole aldehyde ring and β-keto ester with the purpose of exploring the influence of substituent on anticancer activity by regulating the electronic and steric effects.

Material and Methods:-

Chemicals and reagents:-

All chemicals were purchased from Sigma-Aldrich U.S.A. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany.)

Equipments and analytical instruments:-

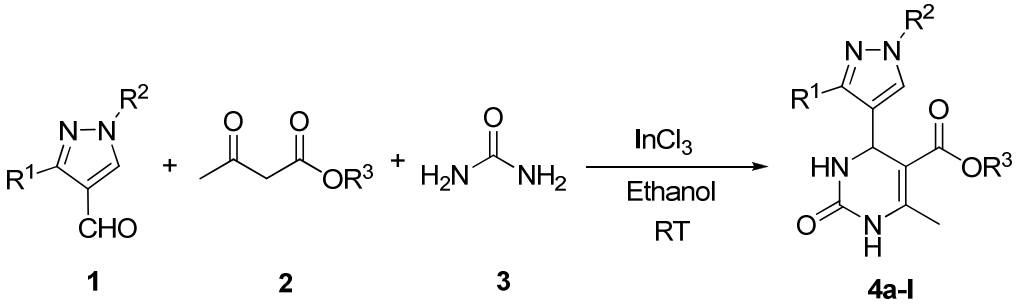
^{1}H and ^{13}C NMR spectra were recorded in DMSO using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz respectively. Chemical shifts are given in parts per million (ppm). The mass spectra (LCMS) were recorded by using an Electrospray Ionisation method with Thermo Finnigan mass spectrometer Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer.

General procedure for the synthesis of pyrimidine derivatives 4a-l:-

To a stirred mixture of pyrazole aldehyde (1 mmol) and ethylacetoacetate (1 mmol) in ethyl alcohol (15ml), urea (1 mmol) and indium chloride (0.5 mmol) were added. The reaction mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the mixture was extracted with ethyl acetate and column chromatographed with 15% ethyl acetate–petroleum ether (bp. 60–80^{o}C) mixture to produce highly substituted pyrazolyl pyrimidine in good to excellent yields (Table 1).

Result and Discussion:-

An equimolar mixture of a substituted pyrazole aldehyde **1,** β-keto ester **2** and urea **3** were mixed with ethanol and stirred after adding 5 mol% of $InCl_3$ for about six hours. Then the mixture was extracted with ethyl acetate and column chromatographed with 15% ethyl acetate–petroleum ether (bp. 60–80^{o}C) mixture to produce highly substituted pyrazolyl pyrimidine in good to excellent yields (**Scheme 1**). The structures of these products were thoroughly characterized with various spectroscopic techniques like ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis as described in the experimental section. The results are summarized in table **1.**

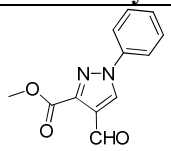
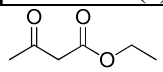
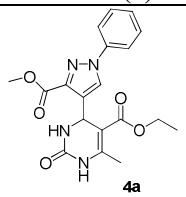
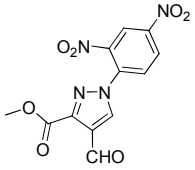
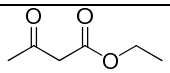
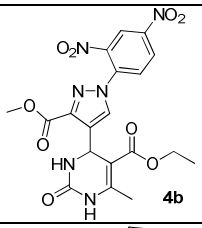
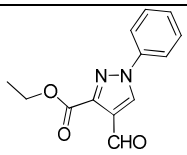
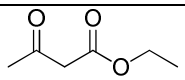
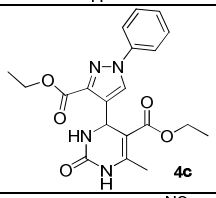
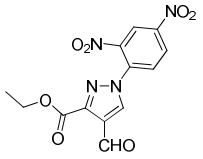
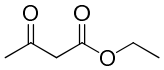
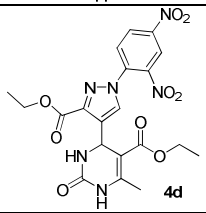
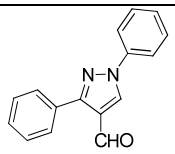
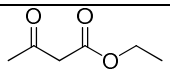
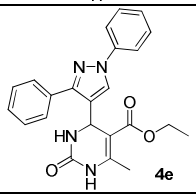
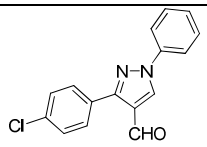
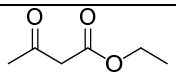
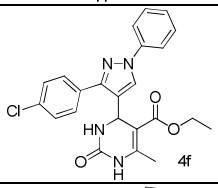
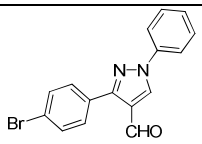
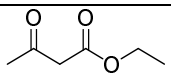
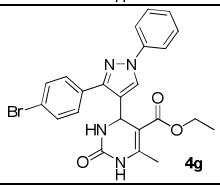
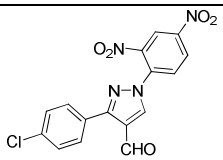
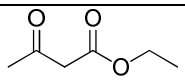
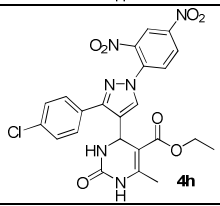


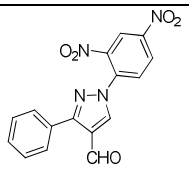
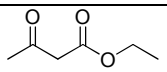
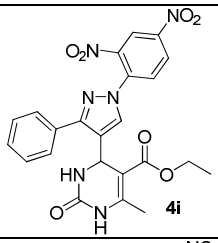
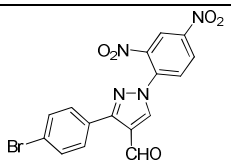
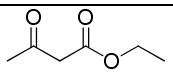
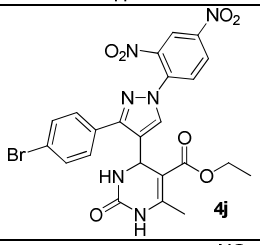
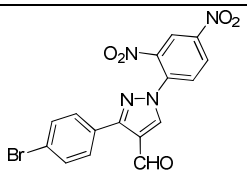
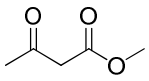
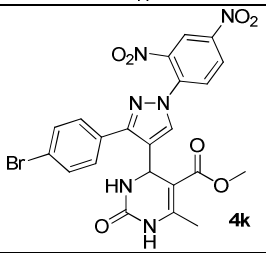
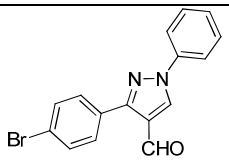
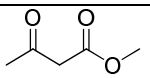
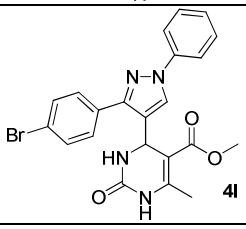
Scheme 1. Synthesis of pyrazolyl pyrimidines

The ^{1}H NMR spectrum of compound **4a** exhibited a two singlet at 7.23 and 7.39 ppm reveals that the presence of two -NH group. The two singlets at 5.74 and 9.22 ppm were assigned to pyrimidine and pyrazole ring protons respectively. The singlet at 2.51 ppm was assigned to pyrimidine methyl protons. Three protons, triplet at 1.04 ppm and two protons, quartet at 3.97 ppm clearly shows that the presence of ethyl ester group (CH_3-CH_2-O-CO-). The methyl proton of methyl ester group in the pyrazole ring appears at singlet at 3.89 ppm. The peaks at 7.41-8.36 ppm were attributed to aromatic protons (**fig 1.1**).

In the ^{13}C NMR spectra, the peaks at 149.9 ppm and the range between 119-140 ppm were assigned to imide carbonyl carbon and aromatic carbon respectively (**fig 1.2**). The peaks at 162.9 ppm and 165.6 ppm were attributed to two ester carbonyl carbons. The mass spectrum revealed the molecular ion peak $(M+H)^{+}$ at m/z 386. The formation of the product was further confirmed by elemental analysis.

Table 1. Synthesis of pyrazolyl pyrimidines

Entry	Pyrazole aldehyde (1)	β-keto ester (2)	Product (4)[a]	Time(h)	Yield[b](%)
1			 4a	5	87
2			 4b	5.5	76
3			 4c	4	80
4			 4d	6	72
5			 4e	5	85
6			 4f	4	82
7			 4g	4	78
8			 4h	5	82

9				6	80
10				6	85
11				4.5	90
12				5.5	85

[a]All products were characterized by IR, [1]HNMR, [13]CNMR and mass spectroscopy
[b]Isolated yield after column chromatography.

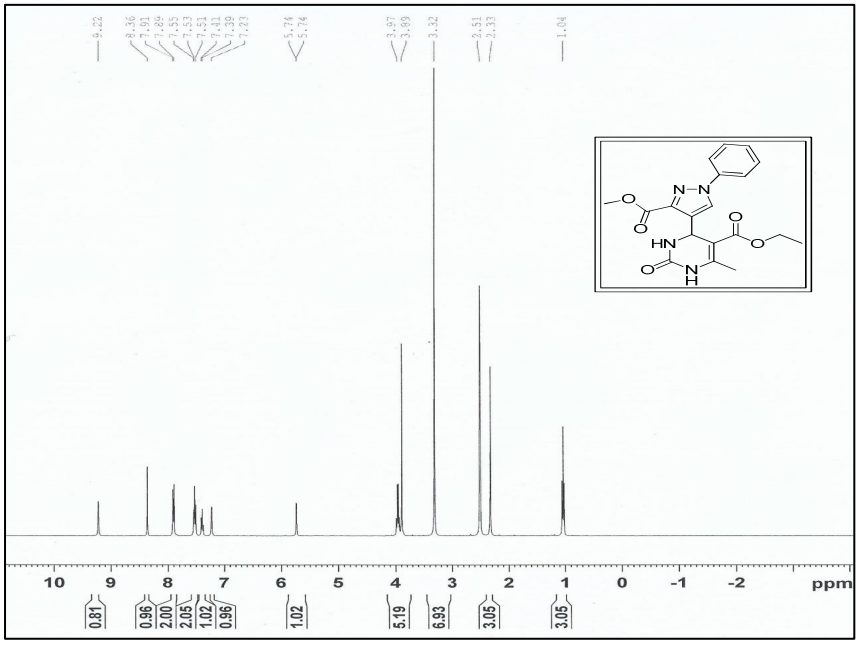


Figure 1.1 [1] HNMR spectrum of compound 4a

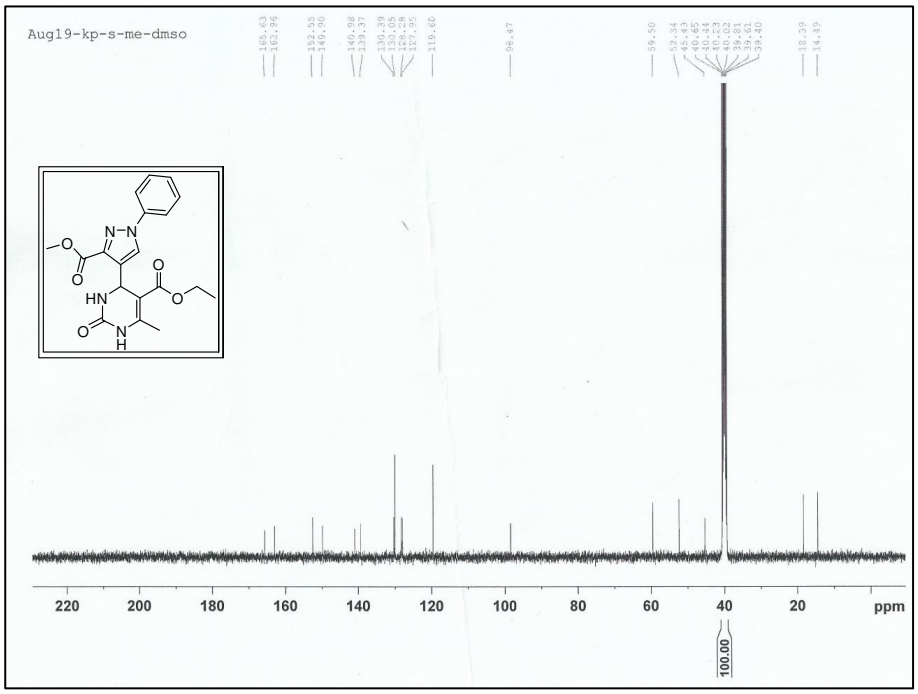


Figure 1.2 ^{13}C NMR spectrum of compound 4a

Characterization of compounds 4a-l

Compound4a; Ethyl 4-(3-(methoxycarbonyl)-1-phenyl-1H-pyraole-4yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydopyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.04 (t, 3H, *J*= 6.8 Hz),2.51 (s, 3H), 3.89 (s, 3H), 3.97 (q, 2H, *J*=7.4 Hz), 5.74 (s, 1H), 7.23 (s, 1H), 7.39 (S, 1H), 7.41-8.36 (m, 5H), 9.22 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.5, 19.4, 45.4, 52.3, 59.0, 98.5, 119.6, 127.9, 128.3, 130.0, 130.4, 139.4, 140.9, 149.9, 152.6, 162.9, 165.6; LC-MS (m/z): 386 (M+H); Anal. (%) for $C_{19}H_{20}N_4O_5$ Calcd. C, 59.37; H, 5.24; N, 14.58; O, 20.81; Found: C, 59.26; H, 5.18; N, 14.32; O, 20.75.

Compound 4b; Ethyl 4-(1-(2, 4-dinitrophenyl)-3-(methoxycarbonyl)--1H-pyraole-4yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydopyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.14 (t, 3H, *J*=6.4 Hz),2.54 (s, 3H), 3.90 (s, 3H), 3.99 (q, 2H, *J*=7.2 Hz), 5.74 (s, 1H), 6.96 (s, 1H), 7.02 (S, 1H), 7.8 (s, 1H), 7.5 (d, 2H, *J*=12.4 Hz), 9.10 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.5, 19.8 ,44.4, 53.0, 59.6, 97.9, 119.2, 126.9, 127.2, 128.0, 130.6, 131.4, 139.1, 142.8, 146.3, 140.9, 149.9, 152.6, 162.9, 165.6; LC-MS (m/z): 476 (M+H); Anal. (%) for $C_{19}H_{18}N_6O_9$ Calcd. C, 48.11; H, 3.82; N, 17.72; O, 30.35; Found: C, 47.89; H, 3.76; N, 17.52; O, 30.22.

Compound 4c; Ethyl 4-(3-(ethoxycarbonyl)-1-phenyl-1H-pyraole-4yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydopyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.29 (m, 6H), 2.56 (s, 3H), 4.02 (q, 2H, *J*=7.4 Hz), 4.31(q, 2H, *J*=7.8 Hz), 5.74 (s, 1H), 7.10 (s, 1H), 6.98 (S, 1H), 7.64 (m, 5H), 9.34 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.2, 19.6, 45.1, 52.6, 59.2, 60.9, 98.2, 120.2 127.4, 128.8, 131.2, 131.7, 139.2, 141.6, 149.2, 152.3, 162.6, 165.2; LC-MS (m/z): 400 (M+H); Anal. (%) for $C_{20}H_{22}N_4O_5$ Calcd. C, 60.29; H, 5.57; N, 14.06; O, 20.08; Found: C, 60.42; H, 5.50; N, 14.24; O, 20.63.

Compound 4d; Ethyl 4-(1-(2, 4-dinitrophenyl)-3-(ethoxycarbonyl)--1H-pyraole-4yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydopyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.20 (m, 6H),2.54 (s, 3H), 3.97 (q, 2H, *J*=7.6 Hz), 4.24 (q, 2H, *J*=7.84 Hz), 5.76 (s, 1H), 6.92 (s, 1H), 7.00 (S, 1H), 8.2 (d,2H, *J*=12.40 Hz), 8.8 (s, 1H), 9.24 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.5, 19.8 ,44.4, 53.0, 59.6, 97.9, 119.2, 126.9, 127.2, 128.0, 130.6, 131.4, 139.1, 142.8, 146.3, 140.9, 149.9, 152.6, 162.9, 165.6. LC-MS (m/z): 489 (M+H); Anal. (%) for $C_{20}H_{20}N_6O_9$ Calcd. C, 49.18; H, 4.13; N, 17.21; O, 29.48; Found: C, 49.12; H, 4.02; N, 17.18; O, 29.44.

Compound 4e; Ethyl 4-(1, 3-diphenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.24 (t, 3H, *J*=6.84 Hz), 2.56 (s, 3H), 4.21 (q, 2H, *J*=7.84 Hz), 5.24 (s, 1H), 6.56 (s, 1H), 6.82 (S, 1H), 7.4-7.6 (m, 5H), 7.8 (m, 5H), 9.34 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.6, 19.2, 45.4, 53.6, 56.4, 62.7, 96.2, 120.6,123.9, 127.8, 129.8, 131.4, 132.6, 139.0, 141.2, 148.2, 152.8, 161.6, 166.4; LC-MS (m/z):404 (M+H); Anal. (%) for $C_{23}H_{22}N_4O_3$ Calcd. C, 68.64; H, 5.51; N, 13.92; O, 11.93; Found: C, 60.42; H, 5.50; N, 13.24; O, 11.85.

Compound 4f; Ethyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo1,2,3,4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.26 (t, 3H *J*=6.24 Hz), 2.52 (s, 3H), 4.21 (q, 2H, *J*=7.45 Hz), 5.23 (s, 1H), 6.54 (s, 1H), 6.84 (S, 1H), 7.0-7.2 (m, 5H), 7.5(d, 2H, *J*=7.65Hz), 7.9 (d, 2H, *J*=7.84Hz), 9.21 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.0, 19.8, 45.2, 52.6, 54.4, 62.2, 96.8, 121.6, 123.4, 126.4, 129.8, 130.4, 134.6, 139.2, 142.2, 147.1, 154.6, 162.6, 168.4; LC-MS (m/z):437 (M+H); Anal. (%) for $C_{23}H_{21}ClN_4O_3$ Calcd. C, 63.23; H, 4.84; Cl, 8.11, N, 12.82; O, 10.99; Found: C, 63.22; H, 4.78; Cl, 8.08, N, 12.64; O, 10.85.

Compound 4g; Ethyl 4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.24 (t, 3H *J*=6.24 Hz), 2.53 (s, 3H), 4.22 (q, 2H, *J*=7.65 Hz), 5.24 (s, 1H), 6.56 (s, 1H), 6.74 (S, 1H), 7.0-7.5 (m, 5H), 7.92(d, 2H, *J*=7.85Hz), 8.14(d, 2H, *J*=7.86Hz), 9.32 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.0, 19.6, 45.2, 52.2, 54.2, 62.6, 94.8, 122.6, 123.4, 126.4, 128.8, 130.4, 134.8, 139.8, 142.6, 147.8, 155.6, 162.6, 169.2; LC-MS (m/z):481 (M+H); Anal. (%) for $C_{23}H_{21}BrN_4O_3$ Calcd. C, 57.39; H, 4.40; Br, 16.60, N, 11.64; O, 9.97; Found: C, 57.36; H, 4.38; Br, 16.56, N, 11.61; O, 9.87.

Compound 4h; Ethyl 4-(3-(4-chlorophenyl)-1-(2, 4-dinitrophenyl)-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.21 (t, 3H *J*=6.64 Hz), 2.56 (s, 3H), 4.24 (q, 2H, *J*=7.85 Hz), 5.34 (s, 1H), 6.46 (s, 1H), 6.84 (S, 1H), 7.98(d, 2H, *J*=7.85Hz), 8.24(d, 2H, *J*=7.86Hz), 8.66(d,2H, *J*=12.40 Hz), 8.92 (s, 1H), 9.62 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.6, 19.8, 46.2, 52.2, 54.8, 66.6, 97.8, 122.8, 123.9, 126.2, 127.8, 131.4, 134.8, 139.8, 142.6, 146.2, 147.5, 149.1, 154.6, 164.6, 169.9; LC-MS (m/z):527 (M+H); Anal. (%) for $C_{23}H_{19}ClN_6O_7$ Calcd. C, 52.43; H, 3.63; Cl, 6.73, N, 15.95; O, 21.26; Found: C, 52.40; H, 3.53; Cl, 6.53, N, 15.75; O, 21.18.

Compound 4i; Ethyl 4-(1-(2, 4-dinitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-6methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.26 (t, 3H *J*=6.85 Hz), 2.50 (s, 3H), 4.21 (q ,2H, *J*=7.65 Hz), 5.36 (s, 1H), 6.20 (s, 1H), 6.22 (S, 1H), 7.2-7.8 (m, 5H), 8.58(d,2H, *J*=12.40 Hz), 8.90 (s, 1H), 9.67 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.6, 19.6, 46.0, 52.4, 54.3, 66.1, 98.2, 123.2, 127.8, 128.5, 129.6, 132.4, 134.7, 139.6, 142.0, 145.2, 147.6, 149.4, 154.6, 163.4, 168.2; LC-MS (m/z):493 (M+H); Anal. (%) for $C_{23}H_{20}N_6O_7$ Calcd. C, 56.10; H, 4.09; N, 17.07; O, 22.74; Found: C, 55.08; H, 4.02; N, 17.01; O, 22.62.

Compound 4j; Ethyl 4-(3-(4-bromophenyl)-1-(2, 4-dinitrophenyl)-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.21 (t, 3H *J*=6.65 Hz), 2.54 (s, 3H), 4.24 (q, 2H, *J*=7.65 Hz), 5.36 (s, 1H), 6.46 (s, 1H), 6.84 (S, 1H), 7.96(d, 2H, *J*=7.85Hz), 8.22(d, 2H, *J*=7.92Hz), 8.60(d, 2H, *J*=12.65 Hz), 8.86 (s, 1H), 9.62 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 14.0, 19.2, 45.1, 52.4, 55.1, 65.6, 98.3, 122.8, 123.8, 126.2, 127.6, 131.5, 134.6, 139.8, 142.9, 146.4, 147.4, 149.2, 155.6, 164.2, 169.8; LC-MS (m/z):571 (M+H); Anal. (%) for $C_{23}H_{19}BrN_6O_7$ Calcd. C, 48.35; H, 3.35; Br, 13.99, N, 14.71; O, 19.60; Found: C, 48.30; H, 3.32; Br, 13.93, N, 14.64; O, 19.54.

Compound 4k; Methyl 4-(3-(4-bromophenyl)-1-(2, 4-dinitrophenyl)-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.64 (s, 3H), 3.86 (s, 3H), 5.26 (s, 1H), 6.64 (s, 1H), 6.92 (S, 1H), 7.96(d, 2H, *J*=7.95Hz), 8.29(d, 2H, *J*=7.92Hz), 8.56 (d, 2H, *J*=12.85 Hz), 8.89 (s, 1H), 9.20 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 13.9, 19.4, 45.2, 52.4, 554, 66.6, 98.8, 122.0, 123.6, 126.4, 127.8, 132.4, 134.2, 138.6, 142.3, 1454, 147.9, 149.0, 156.6, 164.2, 168.8; LC-MS (m/z):557 (M+H); Anal. (%) for $C_{22}H_{17}BrN_6O_7$ Calcd. C, 47.41; H, 3.07; Br, 14.34, N, 15.08; O, 20.10; Found: C, 47.41; H, 3.07; Br, 14.34, N, 15.08; O, 20.10.

Compound 4l; Methyl 4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.62 (s, 3H), 3.76 (s, 3H), 5.48 (s, 1H), 6.48

(s, 1H), 6.82 (S, 1H), 7.4-7.6 (m, 5H), 7.64(d, 2H, *J*=7.65Hz), 7.89 (d, 2H, *J*=7.95Hz), 9.02 (S, 1H); ^{13}C NMR (125 MHz DMSO) δ = 17.6, 45.2, 52.6, 54.8, 64.6, 96.8, 122.0, 123.8, 126.2, 129.0, 130.2, 134.6, 139.2, 142.4, 146.8, 154.6, 161.6, 168.2; LC-MS (m/z):467 (M+H); Anal. (%) for $C_{22}H_{19}BrN_4O_3$ Calcd. C, 56.54; H, 4.10; Br, 17.10; N, 11.99; O, 10.27; Found: C, 56.54; H, 4.10; Br, 17.10; N, 11.99; O, 10.27.

Conclusion:-

In conclusion, we have described a convenient one pot, three component reaction that offers a simple method for the synthesis of multisubstituted biologically important pyrimidine derivatives from substituted pyrazole aldehydes, β-keto ester and urea in ethanol using indium chloride as catalyst. This method offers several advantages like milder reaction conditions, shorter reaction time, high yield, no toxic byproduct and simple experimental and isolation procedures making it an efficient route to the synthesis of pyrimidine derivatives. In addition, we expect that the enhanced biological activity for the synthesized pyrimidine derivatives due to the presence of pyrazole and pyrimidine heterocyclic units in the same molecule.

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