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Synthesis and Spectral Characterization of N-Phenyl-3-Phenyl-5-Substituted Phenyl Pyrazoline and 4-Phenyl-6-Substituted Phenyl-3,4-Dihydro Pyrimidine-2-one Analogues

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ABSTRACT

The substituted chalcones (C1-5) was prepared by reaction of acetophenone (a) and aromatic aldehydes (b1-5). One series of N-phenyl pyrazoline analogues (K1-K5) were synthesized by reaction of the substituted chalcones (C1-5) with phenyl hydrazine in acidic medium. Another series of 3, 4-dihydropyrimidine-2-one analogues (K6-K10) were synthesized by reaction of substituted chalcones (C1-5) with ethanolic urea in alkali medium. The yield of the synthesized analogues ranged from 62-76%. The structures of the synthesized analogues were verified by FTIR,^{1}H-NMR, mass spectral data and physical analysis. The structures of the synthesized heterocyclics are correlated with the spectral analysis and the synthesized heterocyclics structures are well agreed with the proposed structure.

Keywords: pyrazoline, pyrimidine, chalcones, Infrared spectroscopy, Nuclear Magnetic Resonance spectroscopy and Mass spectroscopy

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INTRODUCTION

Heterocyclic's and its analogs are of the most extensively studied nucleus, which can be used as the starting material or intermediate/subunit for the synthesis of numerous pharmaceutical drugs [(1)]. The pharmaceutical chemistry of the heterocyclic analogues are attracted due to their high reactivity on the biological membranes. Many heterocyclic's compounds especially five membered like imidazoles, pyrazoles, pyrroles, thiazoles, isoxazoles and six membered heterocyclic's like pyridine, pyrimidines, pyrazines, piperazines etc have shown diversified pharmacological activity ranging from anti-infective, antibacterial, antifungal, antiprotozoal, anti-tubercular, antiviral, analgesic, anti-inflammatory, anti epileptic, anti-ulcer, diuretics, anticancer, antihypertensive, anthelminitics,[2] etc. Among that pyrazole and pyrimidine derivatives are attracted due to its fascinating biological activities. The pyrimidine heterocyclic's derivatives comprise the ring system of numerous drugs barbiturates, zidovudine, 5- fluorouracil & idoxuridine[3]. The pyrimidine nucleus derived synthetic products has different medical uses such as antihypertensive, antibacterial, antifungal, anticonvulsant, anti inflammatory[4], cyclooxygenase inhibitor[5], antitumor [6], antitubercular, alpha glucosidase inhibitors [7] and anti-oxidant properties. The pharmacological importance of these pyrazole compounds lies in the fact that they can be effectively utilized as antimicrobial, analgesic, anti-inflammatory[8], antiviral, antiparasitic, anthelmintic[9], antitubercular, anticancer [10], antiproliferative [11] and insecticidal agents. Some substituted pyrazolines and their derivatives have been reported to possess some interesting biological activities such as anticancer, insecticidal, antibacterial, antifungal, antidepressant, anticonvulsant, anti inflammatory, antimalarial[12] and anti- tumor properties [13]. Hence the synthesis of new derivatives of pyrazolines and pyrimidine heterocyclic's is being continuously reported in order to make new heterocyclic's drugs. In this way our present work involves synthesis of N-phenyl pyrazoline with phenyl substitution at third position and different substituted phenyl attachments at fifth position. Also our present work involves the synthesis of 3,4-dihydropyrimidine with phenyl substitution at fourth position and different substituted phenyl attachments at sixth position. Then the structures of the synthesized analogues were elucidated by FTIR,^{1}H-NMR, mass spectral data and physical analysis.

MATERIALS AND METHOD

Synthesis of 3-(Substituted phenyl)-1-phenylprop-2-en-1-one (Chalcones, C1-5)

The solution of 0.01mol acetophenone (a) and 0.01mol aromatic aldehydes (b1-5) named b1= 4-chloro benzaldehyde, b2 = 3,4,5-trimethoxy benzaldehyde , b3 = 4-dimethyl benzaldehyde , b4=4-

methoxy benzaldehyde, b5 = benzaldehyde, in presence of ethanol (20ml) and sodium hydroxide (0.01M) was added at room temperature with constant stirring was maintained. The reaction mixtures were stirred further until a precipitates were formed. The precipitated mixtures were diluted with ice water and neutralized by using 0.01M hydrochloric acid. The products named as 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (c1), 3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1-one (c2), 3-(4-(dimethyl amino) phenyl)-1-phenylprop-2-en-1- one (c3), 3-(4-methoxyphenyl)-1-phenylprop-2-en-1- one (c4) & 1,3-diphenylprop-2-en-1- one (c5) were filtered and recrystallized from ethanol.

Synthesis of 5-Substituted phenyl-1, 3-diphenyl-4, 5-dihydro-1H-pyrazoles (k 1-5).

To the 0.01mol of 3-(substituted phenyl)-1-phenyl prop-2-en-1-ones (C1-5) in presence of 20 ml of 1, 4-dioxane, 0.024 mol of phenyl hydrazine, 2-3 drops of sulphuric acid was added and the contents were refluxed for 4hrs , after the process 5ml of glacial acetic acid was added; again refluxed for next 2 hrs. On cooling to room temperature the contents were poured on crushed ice. As a result the solid products were 5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (k1), 5-(3,4,5-metoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (k2), 5-(4-(dimethyl amino)phenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (k3), 5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (k4) and 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (k5), were obtained which were recrystallised by using ethanol.

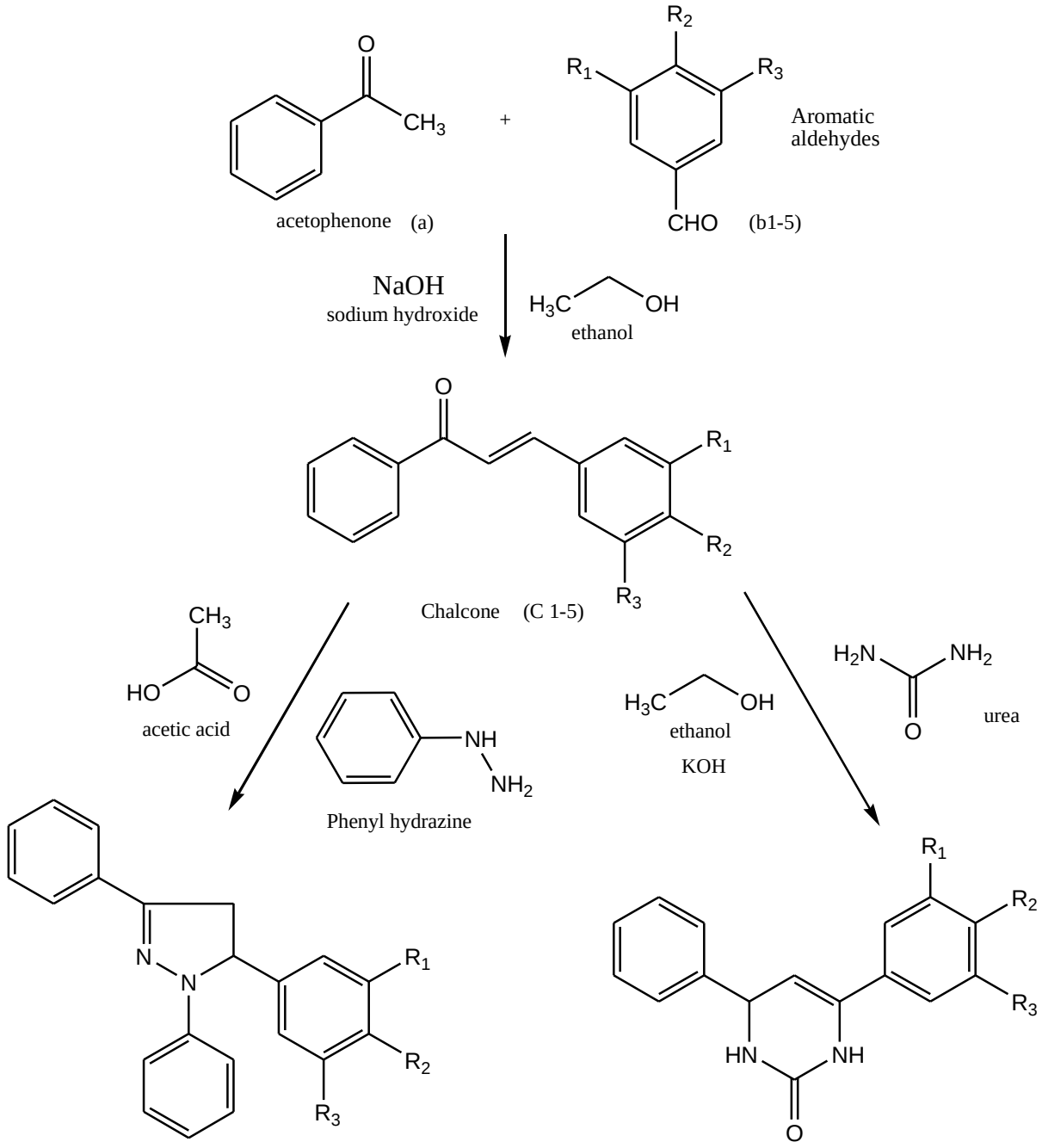
Synthesis of 6- substituted phenyl -4- phenyl -3,4-dihydropyrimidine-2-ones (k 6-10).

A mixture of 0.01Mol of 3-(substituted phenyl)-1-phenyl prop-2-en-1-ones (C1-5), 0.01Mol of urea in 25ml absolute ethanol and 10% 5ml potassium hydroxide refluxed on a water bath for 8 hours. The reactions were monitored by TLC and the precipitation was recrystallized from absolute ethanol to give pure compounds named as 6-(4-chlorophenyl)-4-phenyl-3,4-dihydro pyrimidine-2(1H)-one (k6), 4-(phenyl-6-(3,4,5-trimethoxy phenyl)-3,4-dihydropyrimidin-2(1H)-one (k7), 6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(k8),6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(k9),4,6-diphenyl-3,4-dihydro pyrimidin-2(1H)-one (k10).

The purity of the synthesized heterocyclic's was checked by TLC using silica gel-60 F_{254} aluminium sheets using as eluent and visualized in a ultra violet chamber. TLC analysis was carried out on commercially available silica gel plates of 0.5mm of thickness, as stationary phase. The melting point analysis was carried out by open capillary tube apparatus method. The mobile phase was used benzene: ethyl acetate in the ratio of 8:2 and the spots were visualized by UV chamber. IR spectra were recorded (in KBr) on FTIR 8300 Shimadzu spectrophotometer. The

^{1}HNMR spectra recorded on a Bruker AC 300 MHZ FTNMR spectrophotometer and chemical shift were recorded in parts per million downfield from TMS. The mass spectra were recorded in JEOL GC MATE II GC/MS (EI).

Scheme



K1 & K6 – R1& R3= H, R2 = Cl, K2 &K7– R1& R2& R3= OCH_3, K3 & K8 – R1& R3= H, R2 =-N-$(CH_3)_2$, K4 & K9 – R1& R3= H, R2 = OCH_3, K5 & K10 –R1& R2& R3= H.

Table 1: Physical data of the synthesized compounds

Analogues	Molecular Formula	Melting point	Soluble in	Molecular Weight	%Yield
K1	$C_{21}H_{17}ClN_2$	226.3	DMSO	332.82	74
K2	$C_{24}H_{24}N_2O_3$	321.9	DMSO	388.45	76
K3	$C_{23}H_{23}N_3$	241.9	DMSO	341.44	72
K4	$C_{22}H_{20}N_2O$	229.9	DMSO	328.40	69
K5	$C_{21}H_{18}N_2$	173.9	DMSO	298.38	65
K6	$C_{16}H_{13}ClN_2O$	247.1	DMSO	284.74	73
K7	$C_{19}H_{20}N_2O_4$	312.8	DMSO	340.37	74
K8	$C_{18}H_{19}N_3O$	262.2	DMSO	293.36	68
K9	$C_{17}H_{16}N_2O_2$	295.7	DMSO	280.32	65
K10	$C_{16}H_{14}N_2O$	204.7	DMSO	250.29	62

Table 2: Elemental composition of compounds

Compound	Elemental Composition in Percentage (%)				
	C	H	Cl	N	O
K1	84.53	6.08	10.65	8.42	-
K2	74.78	6.23	-	7.21	12.36
K3	80.90	6.79	-	12.31	-
K4	80.46	6.14	-	8.53	4.87
K5	84.53	6.08	-	9.39	-
K6	67.49	4.60	12.45	9.84	5.62
K7	67.05	5.92	-	8.23	18.80
K8	73.69	6.53	-	14.32	5.45
K9	72.84	5.75	-	9.99	11.42
K10	76.78	5.64	-	11.19	6.39

Table 3: Lipinski Properties of Synthesized Compounds

Compound	Log P	H-bond donor	H-bond acceptor	Molar refractivity	Number criteria met
K1	6.174	0	2	100.85	4
K2	5.183	0	5	115.50	4
K3	6.183	0	3	110.17	4
K4	5.88	0	3	102.40	4
K5	4.83	0	4	98.52	ALL
K6	3.728	2	3	81.13	ALL
K7	2.737	2	6	95.7	ALL
K8	3.737	2	4	91.23	ALL
K9	3.44	2	4	83.46	ALL
K10	3.106	2	3	76.91	ALL

RESULTS AND DISCUSSION

This study, two series of substituted pyrazoline and pyrimidine derivatives were prepared and their purity checked by TLC. The physical analytical studies such as melting point and elemental composition determination was carried out for conforming their identification, results were shown

in Table-1 & 2. The QSAR lipophilic parameter, polarizability parameter and hydrogen bonding forces were measured by software in order to know about binding ability of heterocyclic's analogues and their results were displayed in Table-3. The FTIR, ^{1}H-NMR, and mass spectral data of the synthesized heterocyclic's compounds were conforming the molecular structure of the pyrazoline and pyrimidine heterocyclics[14].

5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (Compound K1)

IR (ν in cm^{-1}): 1494.83 (C=C Stretching), 1587.42 (C=N Stretching), 1033.85 (C-N Stretching), 754.17 (Ar -Cl Stretching), 3061.03 (Ar-C-H Stretching)

^{1}HNMR (δ in ppm): 7.2 (m, 10H, Ar-H), 6.8 (s, 4H, Ar-H), 2.6 (s, 1H, CH)

MS : Molecular ion peak 332.82.

5-(3,4,5-metoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (Compound K2)

IR (ν in cm^{-1}): 1579 (C=C Stretching), 1548 (C=N Stretching), 1182 (C-N Stretching), 1070 (C-O-C Stretching), 3049 (Ar-C-H Stretching)

^{1}HNMR (δ in ppm): 7.8 (S,10H, Ar-H), 6.9 (S,4H, Ar-H), 3.5 (d, 9H, OCH3), 2.6 (S, 1H, CH)

MS : molecular ion peak 388.45

5-(4-(dimethyl amino)phenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (Compound K3)

IR (ν in cm^{-1}): 1548 (C=C Stretching), 1579 (C=N Stretching), 1112 (C-N Stretching), Ar-N-CH3 Stretching, 3049 (Ar-C-H Stretching)

^{1}HNMR (δ in ppm): 7.8 (10H, Ar-H), 6.9 (4H, Ar-H), 6.7 (3H, N-CH3), 2.3 (S 1H, CH)

MS : molecular ion peak 341.44

5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (Compound K4)

IR (ν in cm^{-1}): 1492 (C=C Stretching), 1500 (C=N Stretching), 1172 (C-N Stretching), 1388 (Ar-OH Stretching), 3059 (Ar-C-H Stretching)

^{1}HNMR (δ in ppm): 7.8 (S,10H, Ar-H), 6.2 (S,4H, Ar-H), 3.5 (S,3H, OCH_3), 2.4 (d,1H,CH)

MS : molecular ion peak 328.40

1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (Compound K5)

IR (ν in cm^{-1}): 1492 (C=C Stretching), 1589 (C=N Stretching), 1168 (C-N Stretching), 3059 (Ar-C-H Stretching)

^{1}HNMR (δ in ppm): 7.8 (S,10H, Ar-H), 7.5 (S, 4H, Ar-H), 2.3 (S,1H, CH)

MS : molecular ion peak 298.38.

6-(4-chlorophenyl)-4-phenyl-3,4-dihydro pyrimidine-2(1H)-one (Compound K6)

IR (ν in cm^{-1}): 1480 (C=C Stretching), 1219.01(C-N Stretching), 3059 (Ar-C-H Stretching), 688.59 (Ar-Cl Stretching), 1591 (C=O Stretching)

^{1}HNMR (δ in ppm): 7.3 (S, 5H, Ar-H), 6.9 (S,4H, Ar-H), 2.7 (S, 2H, 2NH)

MS : molecular ion peak 284.74

4-(phenyl-6-(3,4,5-trimethoxy phenyl)-3,4-dihydropyrimidin-2(1H)-one (Compound K7)

IR (ν in cm^{-1}): 1581.63 (C=C Stretching), 1178.51 (C-N Stretching), 2995.45 (Ar-C-H Stretching), 1033.85 (C-O-C Stretching), 1591.63 (C=O Stretching)

^{1}HNMR (δ in ppm): 7.3 (S, 5H, Ar-H), 6.8 (S, 4H, Ar-H), 3.5 (S, 9H, OCH_3), 2.5 (S, 2H, 2NH)

MS : molecular ion peak 340.37

6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Compound K8)

IR (ν in cm^{-1}): 1581.63 (C=C Stretching), 1020.34 (C-N Stretching), 3091 (Ar-C-H Stretching), 2933.52 (N-CH3 Stretching), 1581.63 (C=O Stretching)

^{1}HNMR (δ in ppm): 7.8 (d, 5H, Ar-H), 7.3 (S, 4H, Ar-H), 3.5 (S, 3H, N-CH_3), 2.5 (S,2H, 2NH)

MS : molecular ion peak 293.36

6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(Compound K9)

IR (ν in cm^{-1}): 1573.91 (C=C Stretching), 1213.23 (C-N Stretching), 3039.85 (Ar-C-H Stretching), 1301.95 (Ar-OH Stretching), 1600.92, (C=O Stretching)

^{1}HNMR (δ in ppm): 7.5 (S,5H, Ar-H), 7.2 (S,4H, Ar-H), 3.5 (S, 3H, OCH_3), 2.5 (S, 2H, 2NH)

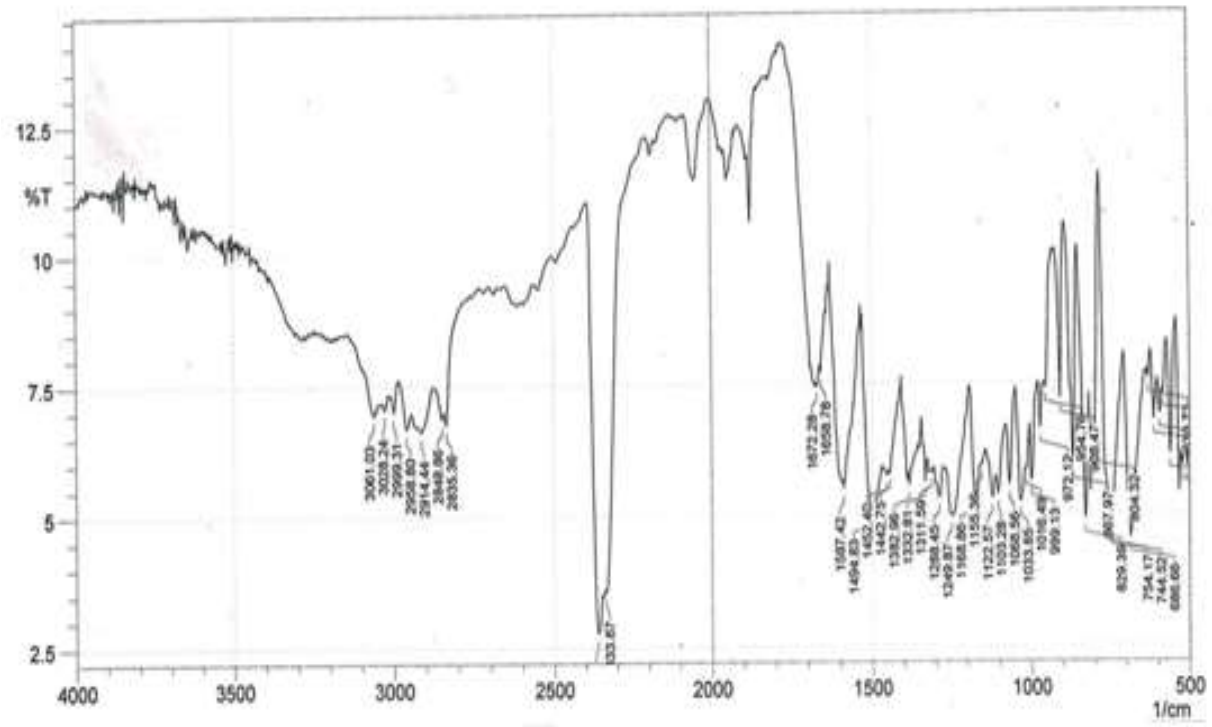
MS : molecular ion peak 280.32

4,6-diphenyl-3,4-dihydro pyrimidin-2(1H)-one (Compound K10)

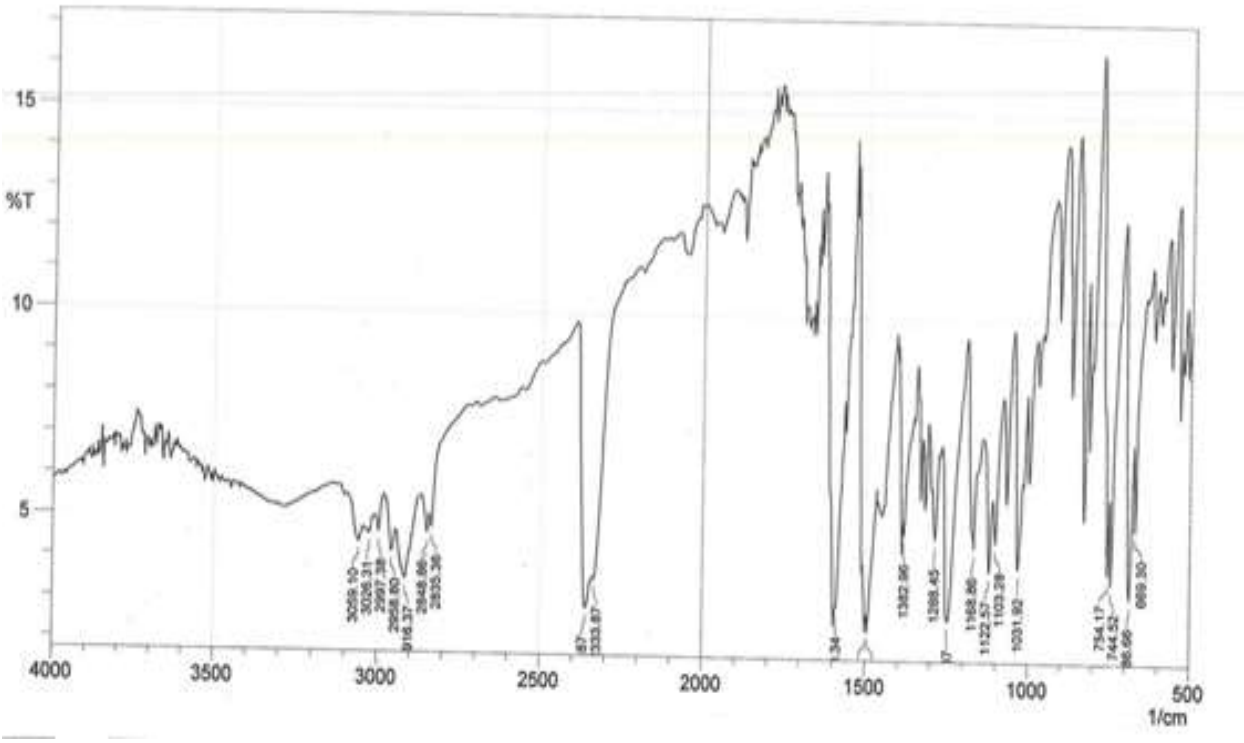
IR (ν in cm^{-1}): 1579.7(C=C Stretching), 1219.01(C-N Stretching), 3061.03 (Ar-C-H Stretching), 1598.99 (C=O Stretching)

^{1}HNMR (δ in ppm): 7.8 (S, 5H, Ar-H), 7.3 (S, 4H, Ar-H), 2.7 (S, 2H, 2NH)

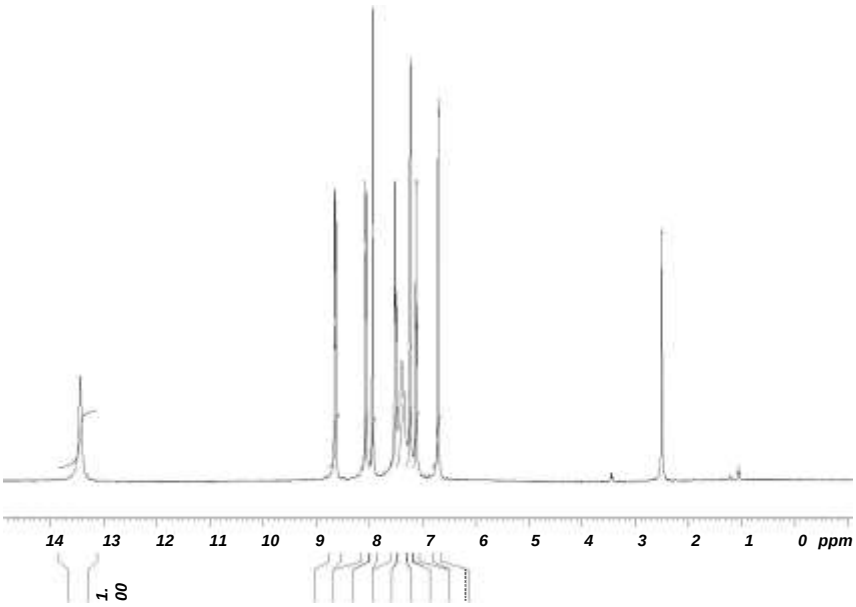
MS : molecular ion peak 250.29.



FTIR SPECTRA OF COMPOUND K1



FTIR SPECTRA OF COMPOUND K6



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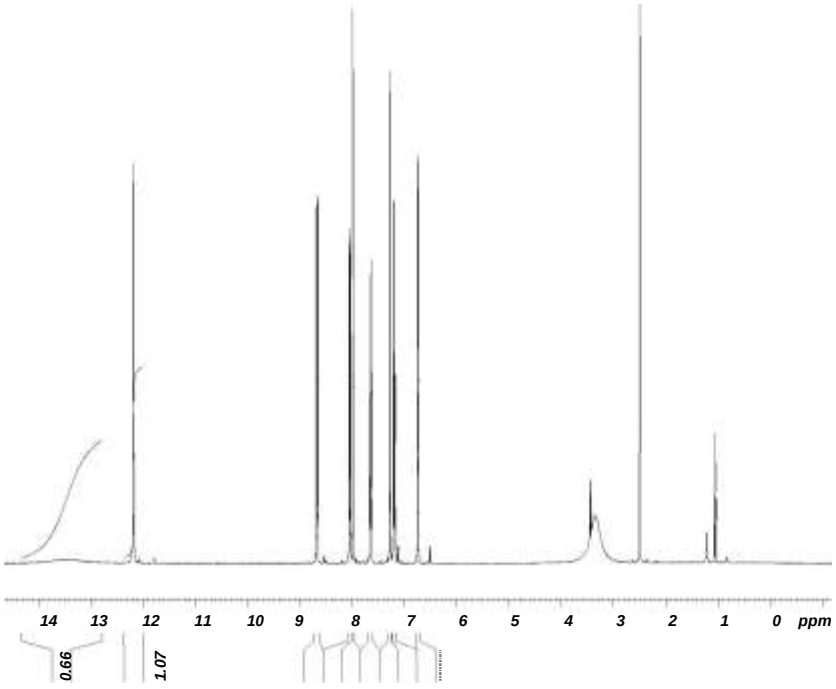

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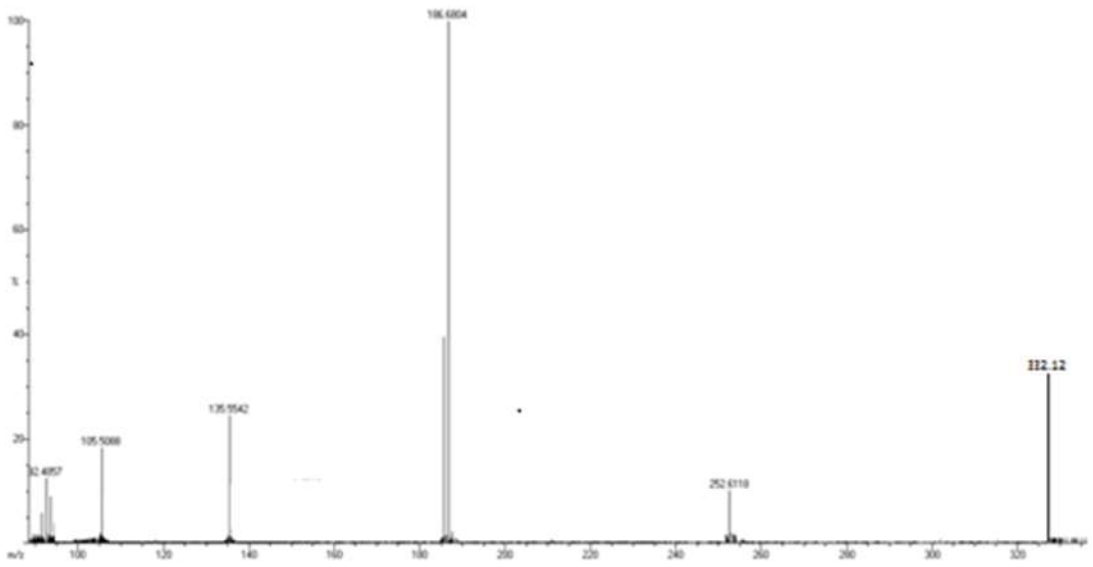
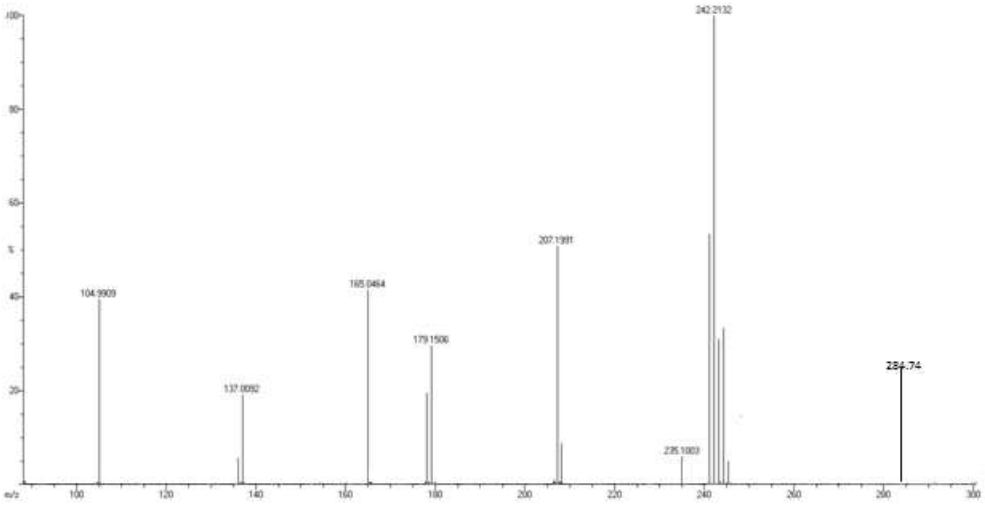


MASS SPECTRA OF COMPOUND K1



MASS SPECTRA OF COMPOUND K6

CONCLUSION

We have described the synthesis, series of two serious of N-phenyl pyrazoline derivatives (K1-K5) and 3,4-dihydropyrimidine derivatives (K6-K10) from substituted chalcones (C1-5). The molecules were designed by the software tools and the lead molecules of chalcone were synthesized by "*claisen-schmidt reaction*" followed by reaction with phenyl hydrazine and urea forms N-phenylpyrazoline and 3,4-dihydropyrimidine respectively. The structure of synthesized compounds were confirmed by FT-IR, ^{1}HNMR, MASS spectroscopy studies. The IR data's showed relevant peaks for C=C, C=N, C=O, C−O, C−N, OCH_3 groups. The ^{1}HNMR also showed

relevant correlated aromatic and aliphatic proton peaks for all the synthesized heterocyclic's compounds. The MASS spectrum confirm the molecular ion peak associated with the molecular formula of all the synthesized N-phenylpyrazoline and 3,4-dihydropyrimidine derivatives are corresponded to the molecular structure of the analogues.

REFERENCES

1. Enaiat Mohamed,K., Wesam.Shehab,S. Synthesis of Some New Condensed Pyrimidine derivatives. Journal of the Korean Chemical Society. 2011; 55: 6.
2. Atherden, L.M. Bentley and Driver's, Textbook of pharmaceutical chemistry, 8th edition, oxford Medical publications, New Delhi. 1995. P. 645-669.
3. John, H. Block (ed): Wilson and Gisvolds Textbook of organic medicinal and Pharmaceutical chemistry, 11th edition. Philadelphia: Lippincott, 2004; pp 372-561.
4. Said SA, Galli AE, Nermien MA, Mohammad S and Abdalla M: Analgesic, anticonvulsant and anti inflammatory activites of some synthesized benzodiazepine triazolo pyrimidine and bis imide derivatives, European Journal *of* Medicinal Chemistry,44(12): 2009; 4787-4792.
5. Syed Nasir Abbas Bukhari, Waqas Ahmad, Adeel Masood Butt, Naveed Ahmad,Muhammad Wahab Bin Amjad, Muhammad Ajaz Hussain, Viresh H Shah and Amit R Trivedi, Synthesis and evaluation of chalcone analogues and pyrimidines as cyclooxygenase (COX) inhibitors, African Journal of Pharmacy and Pharmacology Vol. 6(14), 2012,1064 – 1068.
6. Rao YK, Fang SH, Tzeng YM: Synthesis and biological evaluation of 3',4',5'- trimethoxy chalcone analogues as inhibitors of nitric oxide production and tumor cell proliferation, Bio-organic and Medicinal Chemistry,17(23): 2009; 7909-7914.
7. Seo WD, Kim JH, Kang JE, Ryu HW, Marcus J, Long C, Lee HS, Yang MS and Pack K: Sulfonamide chalcone as a new class of alpha glucosidase inhibitors, Bio-organic & Medicinal chemistry Letters, 15(24): 2005; 5514-5516.
8. V. H. Bhaskar, P. B. Mohite, Synthesis, analgesic, anti-Inflammatory and anti-microbial activity of some 1-[5-(substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl]-5-phenyl-1H-tetrazole, Journal of Optoelectronics and Biomedical Materials, Vol. 3, Issue 1, Jan –Mar, 2011, 7– 16.

9. Kalpesh Patel, Jayachandran E, Ravi Shah, Vijaya Javali, Sreenivasa G.M; Synthesis, characterization and anthelmintic activity of new oxadiazole incorporated with imidazole and pyrazole., International Journal of pharma and Bio sciences, 2010, Vol-1(3),01-11
10. .R.Kalirajan, Leela R, S Jubie , B. Gowramma, S Gomathy, S.Sankar, K. Elango. Microwave assisted synthesis and biological evaluation of pyrazole derivatives of benzimidazoles. Indian J.Pharm. Educ. Research. 44(4), 2010, 358-362.
11. Parekh S, Bhavsar D, Savant M, Thakrar S, Barishi, Parmar M, Vala H, Radadiya A, Pandya N and Shah A: Synthesis of some novel benzofuran-2-yl(4,5-dihydro-3,5-substituted diphenyl pyrazole-1-yl) methanones and studies on the anti-proliferative effects and reversal of multidrug resistance of huma MDR 1-gene transfected mouse lymphoma cell *in-vitro*, European Journal of Medicinal chemistry, 46(5); 2011, 1942- 1948.
12. Acharya BN, Saraswat D, Tiwali M, Shrivastra AK, Ghorpade R, Bapna S and Kaushik MP: Synthesis and antimalarial evaluation of 1,3,5-tri substituted pyrazolines, European Journal of Medicinal chemistry, 45(2): 2010; 430-438.
13. Studies on some heterocyclic entities, Part-V, studies on Pyrazoline; 110-128.
14. Robert M. Silverstein, Francis X. Webster, David J. Kiemle, David L.Bryce. Spectrophotometric Identification of Organic Compounds, Eighth Edition, Wiley, 2015, 81-187.