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ANTI-INFLAMMATORY ACTIVITIY OF NOVEL PYRAZOLINE CONTAINING QUINAZOLINONE DERIVATIVES

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ABSTRACT

In the present work, eight novel 3-[4-(1-Acetyl-5-(3,4-Disubstituted Phenyl)-4,5-Dihydro-1h-Pyrazol-3-Yl) Phenyl]-2-Substutied Phenyl Quinolin-4(3H)-One Derivatives [4a-h] were synthesized by condensation between substituted quinazolinones and hydrazine hydrate in the presence of glacial acetic acid. The structures of the synthesized compounds were characterized on the basis of IR, 1HNMR and Mass spectral data. All the synthesized compounds are screened for their anti-inflammatory activity by paw edema method, Indomethacin is employed as a reference standard. From the results it is concluded that, compounds 4b, 4e, 4f, 4g exhibited potent, rest of compounds exhibited moderate anti-inflammatory activity.

KEYWORDS

Pyrazole, Quinazolinone, Paw edema method and Anti-inflammatory activity.

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INTRODUCTION

NSAIDS - nonsteroidal anti-inflammatory drugs - reduce inflammation. Inflammation is the body's response injury or irritation and also characterized by warmth, swelling, redness and pain. NSAIDs are used to treat a variety of conditions that cause inflammation, including tendinitis and arthritis. NSAIDs are also used to treat pain from injury or other causes of chronic pain. The discovery and development of an effective drug for the treatment of inflammation continues to be a challenging problem in medicinal chemistry research.

Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds.

Several pyrazoline derivatives possess wide-spread pharmacological activities and therefore they are useful materials in drug research. These derivatives are well known for their pronounced anti-inflammatory activity[1] and are used as potent antimicrobial[2] Pyrazolines are used as antiamoebic[3], antimalarial[4] and antidiabetic[5]. Some of the pyrazoline derivatives are reported to possess antitubercular properties[6].

The quinazolones are considered to be important versatile pharmacophore in the fields of pharmacy and biology. Quinazoline-4(3H)-ones are versatile nitrogen heterocyclic compounds, displaying a broad spectrum of biological and pharmalogical activities such as anti-inflammatory and anticancer[7]. Prompted by all these observations work on the synthesis of some pyrazolines and quinazolones derivatives, herein we report the synthesis of some novel pyrazoline contain quinazolinone derivatives, which have been found to possess an interesting profile of anti-inflammatory activity.

MATERIALS AND METHODS

All the chemicals and solvents required for the study were purchased form SD Fine, Kemphasol, Ranbaxy, Hay man Ltd, fisher and S.D. Fine Chem. Ltd. All the solvents procured were purified and dried. The solvent system used for Thin Layer Chromatography in Benzene and acetone (9:1). Iodine chamber and UV Lamps were used for visualization of TLC spots; Whatmann Filter Paper (No.1, England) was used for filtration (Vacuum or ordinary). H^1 NMR spectra were recorded on 300 MHz instruments and the Mass spectra were recorded on Joel SX102/Da-600. FT-IR was recorded in Shimadzu. Melting points were determined using Sulfuric acid bath which was uncorrected.

SYNTHESIS

Synthesis of 2-Substituted Phenyl-4H-Benzo-[1,3]-Oxazin-4-One $1_{(a-b)}$

To a stirred solution of anthranilic acid (0.01 mole) in pyridine (50ml), substituted benzoyl chloride (0.01 mole) was added drop wise, maintaining the temperature near 80^0 C for 2 hour. Reaction mixture was stirred for another 3 hours at room temperature. While stirring a solid product separates out. Whole reaction mixture was neutralized with sodium bicarbonate solution. A pale yellow solid deposited which was filtered, washed with water and re-crystallized with sodium bicarbonate solution.

Synthesis of 4-(4-Oxo-2-Substituted Phenylquinazolin-3(4H)-yl) -benzaldehyde $2_{(a-b)}$

Compound $1_{(a-b)}$ (0.01 mole) was dissolved in ethanol and 4-amino benzaldehyde (0.01 mole) in ethanol was added to it with a catalytic amount of pyridine. Then the reaction mixture was refluxed for 4 hours and after cooling a crystalline product was obtained. Then it was filtered and re-crystallized from ethanol to yield needle shaped shining white crystals.

Synthesis of Compound 2-Substituted Phenyl-3-(4-(3-(Substituted Phenyl-3-oxo Prop-1-enyl) Phenyl Quniazoline-4-One: $3_{(a-h)}$

Equimolar quantities of compound 2 (a-b) and substituted acetophenone (0.01 mole) were dissolved in the minimum amount of alcohol. Then sodium hydroxide solution (0.02 mole) was added slowly and the mixture stirred for 3 hours until the entire mixture becomes very cloud and then the mixture was poured slowly in to 400 ml of water with constant stirring and kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and re-crystallized from ethanol.

Synthesis of 3-[4-(1-Acetyl-5-(3,4-Disubstituted Phenyl)-4,5-Dihydro-1h-Pyrazol-3-Yl) Phenyl]-2-Substutied Phenyl Quinolin-4(3H)-One Derivatives $4_{(a-h)}$

To a solution of chalcone 3 (a-h) (0.02 mole) in absolute alcohol (50ml), 99% hydrazine hydrate (0.04 mole) was added drop by drop with constant stirring in the presence of few drops of glacial acetic acid. The reaction mixture was refluxed for 12h, distilled of and cooled. The separated solid was cooled filtered, washed with pet.ether and re-crystallized from the appropriate solvent.

Anti-Inflammatory Activity

Anti-inflammatory activity of selected compounds was evaluated by carrageenan induced rat hind paw

edema method[8] Indomethacin used as a reference standard (100mg/kg) orally 1 hr. Paw. The results obtained were subjected to statistical analysis using ANOVA followed by Turkey-Krammer Multiple Comparison Test. Percentage inhibition of paw volume was calculated by following formula. Results are given in Table No.2.

% inhibition of edema = 1 –[⟨Vt⎪Vc⟩ X100]

Where, Vt = mean paw volume of test group.
Vc = mean paw volume of control group.

RESULTS AND DISCUSSION

Anti-inflammatory activity Anti-inflammatory activity of the selected new compounds was screened by caragennan induced acute rat hind paw edema method. a used as standard drug, which showed 57.50 % inhibition. The results of the anti-inflammatory study reveal that all the four compounds (4b, 4e,4f, 4g) have shown highly significant anti-inflammatory effect which was evident by significant reduction in the paw volume when compared to control group.

Spectral Data

Compound 4a

IR (KBr) cm-1: 3047(C-H- str, Aromatic)., 2887(C-H str, Alkyl)., 1670 (C=O str, Aromatic keto)., 1649(C=O str, Aliphatic Amide keto).,1633,1612(C=C str, Aromatic)., 1556 (C=N str).,1456,1384(C-H Bending Alkyl).,1276,1249(C-N str).,

1H NMR (DMSO) δppm: 6.292-7.864(s,18H,Ar-H).,3.828-3.870(t,1H,-CH-CH2)., 3.360-3.383(d,2H,-CH-CH2).,2.287(s,3H, CO-CH3)ESIMS (m/z): 484 (M+).

Compound 4b

IR (KBr) cm-1: 3130(C-H- str, Aromatic)., 2874(C-H str, Alkyl)., 1666 (C=O str, Aromatic keto)., 1649(C=O str, Aliphatic Amide keto)., 1599 (C=N str).,1535,1340(Aromatic Nitro)1445,1384(C-H Bending Alkyl).,1276,1249(C-N str).,

1H NMR (DMSO) δ ppm: 6.351-8.422(s,17H,Ar-H).,3.814-3.858(t,1H,-CH-CH2)., 2.695-2.718(d,2H,-CH-CH2)., 2.055(s,3H, CO-CH3) ESIMS (m/z): 529 (M+).

Compound 4c

IR (KBr) cm-1: 3126(C-H- str,Aromatic)., 2966(C-H str, Alkyl)., 2943(C-H str, Methoxy).,1678 (C=O str, Aromatic keto)., 1629(C=O str, Aliphatic Amide keto)., 1574 (C=N str).,1500,1448,1421(C-H Bending, Alkyl).,1286,(C-N str).,1222(C-O str, Methoxy).

1H NMR (DMSO) δ ppm: 7.063-7.869(s,17H,Ar-H).,3.882(s,3H.-OCH3).,3.832-3.877(t,1H,-CH-CH2)., 2.718-2.740(d,2H,-CH-CH2)., 2.055(s,3H, CO-CH3)ESIMS (m/z): 514 (M+).

Compound 4d

IR (KBr) cm-1: 3132(C-H- str,Aromatic)., 2999(C-H str, Methoxy)., 2877(C-H str, Alkyl)., 1662 (C=O str, Aromatic keto)., 1641(C=O str, Aliphatic Amide keto)., 1606(C=C str, Aromatic)., 1595 (C=N str).,1533,1340(Aromatic Nitro).,1417,1334(C-H Bending Alkyl).,1294,1249(C-N str).,1203(C-O str, Methoxy).,

1H NMR (DMSO) δ ppm: 6.759-8.330(s,16H,Ar-H).,3.886(s,3H.-OCH3).,3.896-3.942(t,1H,-CH-CH2).,2.527-2.548(d,2H,-CH-CH2)., 2.083(s,3H, CO-CH3)ESIMS (m/z): 559 (M+).

Compound 4e

IR (KBr) cm-1: 3126(C-H- str,Aromatic)., 2991(C-H str, Alkyl)., 1671 (C=O str, Aromatic keto)., 1639(C=O str, Aliphatic Amide keto)., 1579 (C=N str).,1558,1543(c=C str, Aromatic).,1402(C-H Bending Alkyl).,1151(C-N str).,

1H NMR (DMSO) δppm: 6.719-7.923(s,17H,Ar-H)., 3.896-3.942(t,1H,-CH-CH2)., 2.527-2.548 (d,2H,-CH-CH2)., 2.169(s,3H, CO-CH3).ESIMS (m/z): 519 (M+).

Compound 4f

IR (KBr) cm-1: 3097(C-H- str,Aromatic)., 2985(C-H str, Alkyl)., 1670 (C=O str, Aromatic keto)., 1639(C=O str, Aliphatic Amide keto)., 1604 (C=N str).,1539,1342(Aromatic Nitro)1477,1381(C-H Bending Alkyl).,1274,1213(C-N str).,

1H NMR (DMSO) δppm: 7.056-7.977(m,17H,Ar-H).,4.530-4.574(t,1H,-CH-CH2).,2.721-2.743(d,2H,-CH-CH2)., 2.095(s,3H, CO-CH3). ESIMS (m/z): 564 (M+).

Compound 4g

IR (KBr) cm-1: 3130(C-H- str,Aromatic)., 2874(C-H str, Alkyl)., 1651 (C=O str, Aromatic keto)., 1624(C=O str, Aliphatic Amide keto)., 1556 (C=N str).,1527,1402(Aromatic Nitro).,1242,(C-N str)., 1H NMR (DMSO) δ ppm: 6.989-7.925(m,17H,Ar-H).,4.496-4.549(t,1H,-CH-CH2).,2.726-7.747(d,2H,-CH-CH2)., 2.143(s,3H, CO-CH3).ESIMS (m/z): 529 (M+).

Compound 4h

IR (KBr) cm-1: 3057(C-H- str,Aromatic)., 2978(C-H str, Alkyl)., 1669 (C=O str, Aromatic keto)., 1639(C=O str, Aliphatic Amide keto)., 1589 (C=N str).,1531,1325(Aromatic Nitro)1460,1381(C-H Bending Alkyl).,1284,1205(C-N str).,1H NMR (DMSO) δ ppm 7.043-8.018(m,16H,Ar-H).,4.945-4.899(t,1H,-CH-CH2).,2.335-2.314(d,2H,-CH-CH2)., 2.055(s,3H, CO-CH3). ESIMS (m/z): 574 (M+).

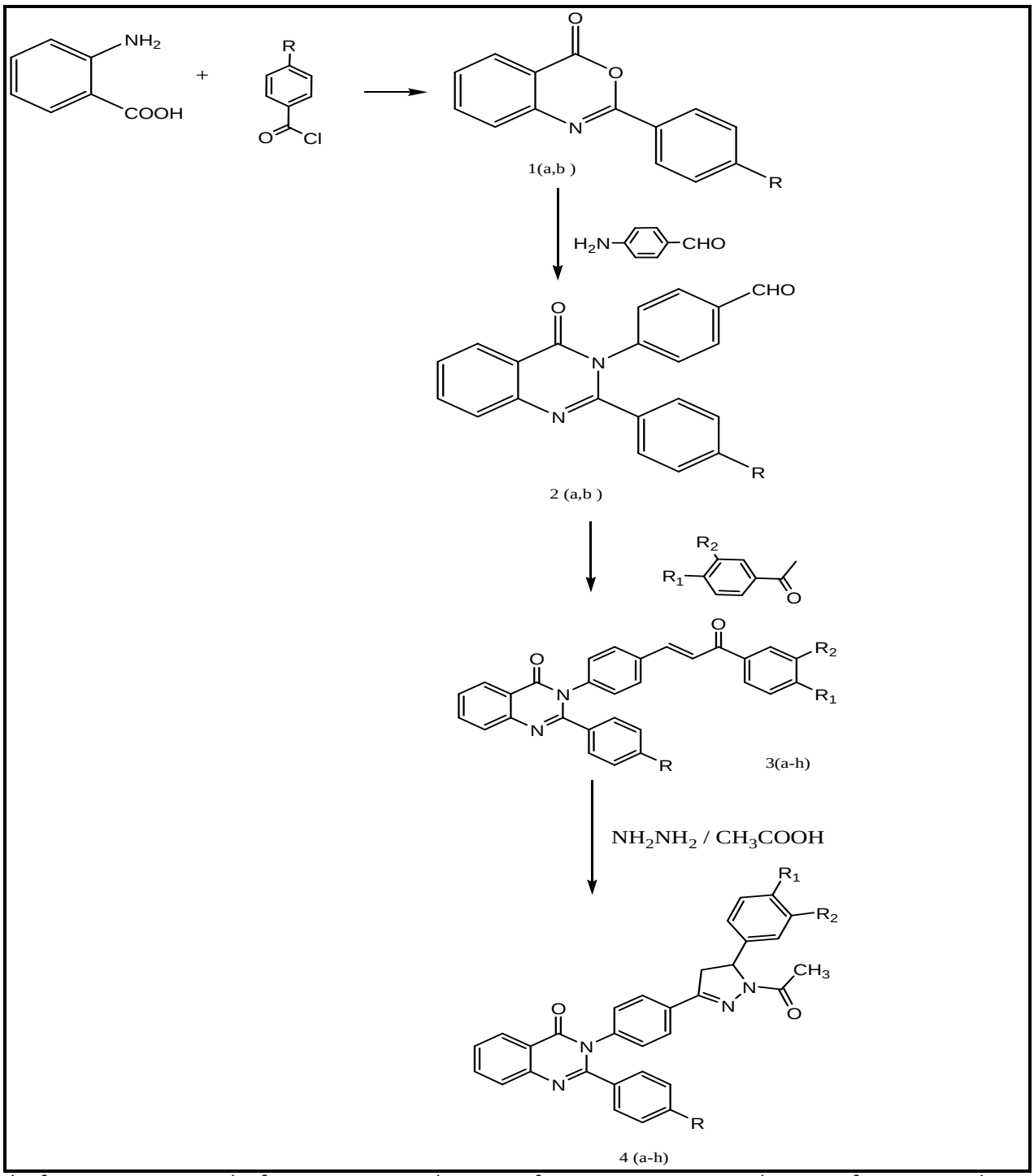
Table No.1: Characterization data of synthesized compounds 4a-h

S.No	Comound code	Melting point (^{o}C)	% yield	Molecular formula	Molecular weight
1	4a	147	75.62	$C_{31}H_{24}N_4O_2$	484
2	4b	143	73.92	$C_{31}H_{23}N_5O_4$	529
3	4c	163	77.53	$C_{32}H_{26}N_4O_3$	514
4	4d	156	74.78	$C_{32}H_{25}N_5O_5$	559
5	4e	166	77.19	$C_{31}H_{23}N_4O_2Cl$	519
6	4f	176	78.98	$C_{31}H_{22}N_5O_4$ Cl	564
7	4g	172	74.1	$C_{31}H_{23}N_5O_4$	529
8	4h	192	79.39	$C_{31}H_{22}N_6O_6$	574

Table No.2: Results of Anti-inflammatory Activity

S.No	Comound code	Mean difference in Paw volume (ml) ±SE after 4 hr	Percentage of inhibition
1	Control	3.93±0.07	-
2	Indomethacin	1.67±0.013***	57.50
3	4a	1.78±0.005*	54.70
4	4b	1.66±0.040***	62.08
5	4c	1.79±0.014*	54.45
6	4d	1.97±0.032*	48.50
7	4e	1.67±0.016***	61.00
8	4f	1.72±0.041*	59.28
9	4g	1.73±0.015***	59.54
10	4h	1.75±0.025*	55.47

Values are Mean ± S.E.M., n=5, Where *P<0.05 and ***P<0.001 vs Control.



a=R, R^1, R^2 - H , b= R- NO_2, R^1, R^2 –H , c= R- H, R^1, -OCH_3, R^2 – H d= R- NO_2, R^1,-OCH_3, R^2 -H e= R, R^1,-H, R^2 – Cl
f= R- NO_2, R^1,- H, R^2 – Cl g= R, R^1- H, R^2 - NO_2 h= R- NO_2, R^1-H, R^2 - NO_2

Physical data of synthesized compounds is given in Table No.1.

Figure No.1: Synthesized compounds

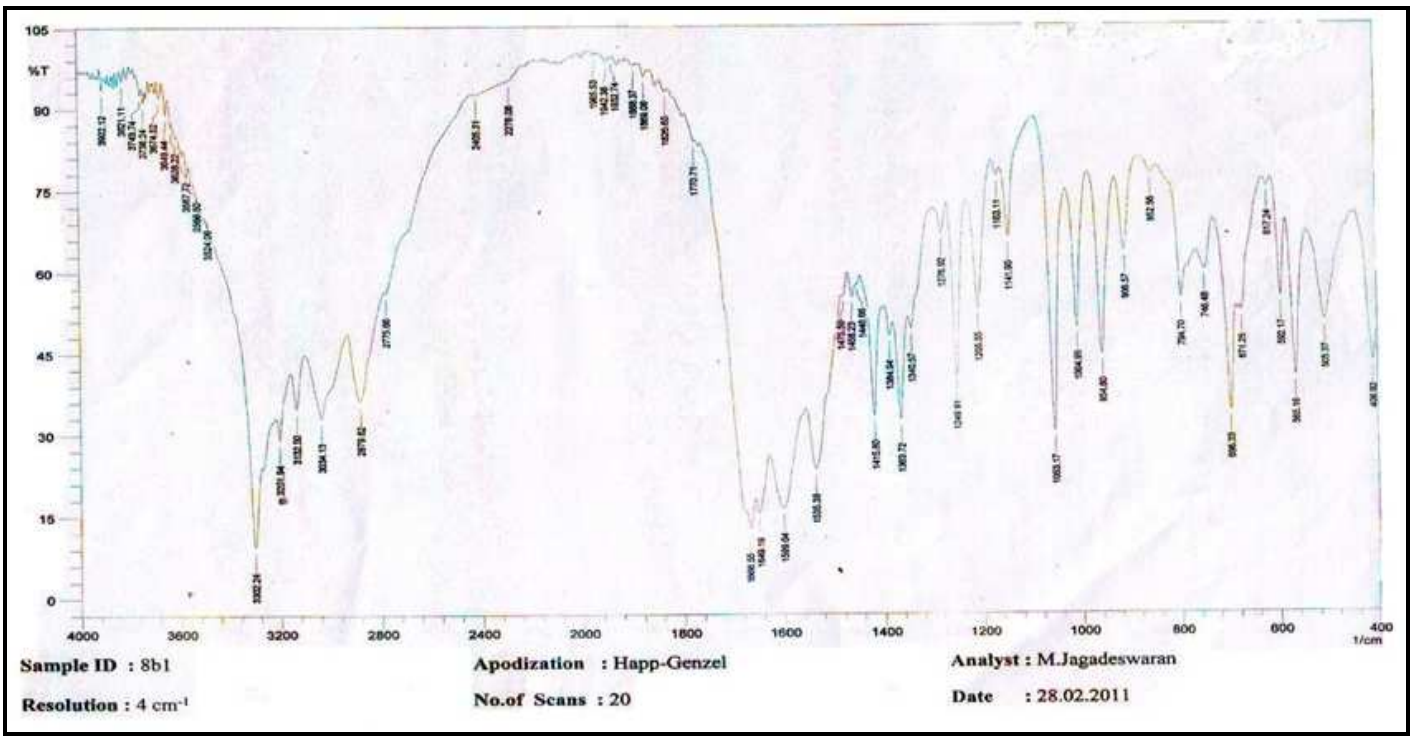


Figure No.2: IR Spectrum of Compound 4b

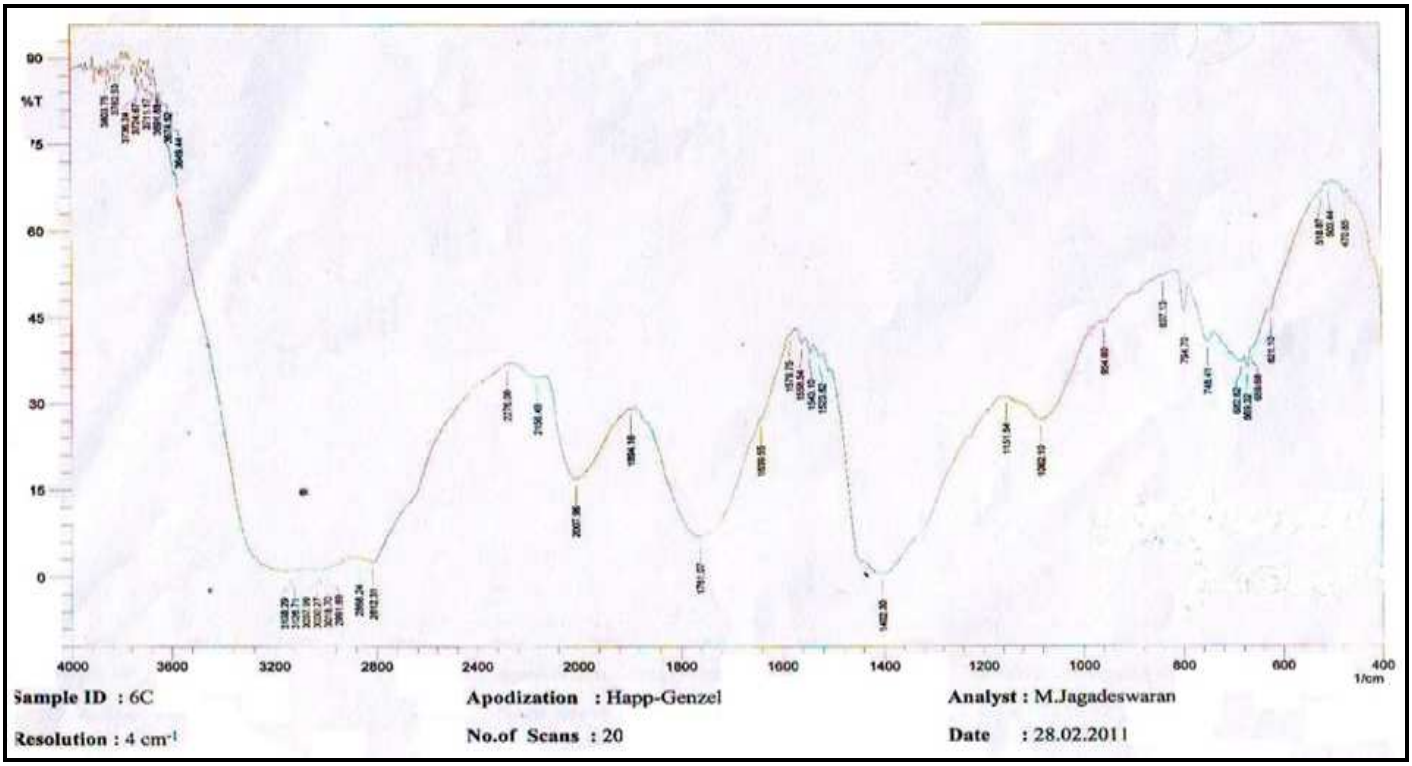


Figure No.2: IR Spectrum of Compound 4e

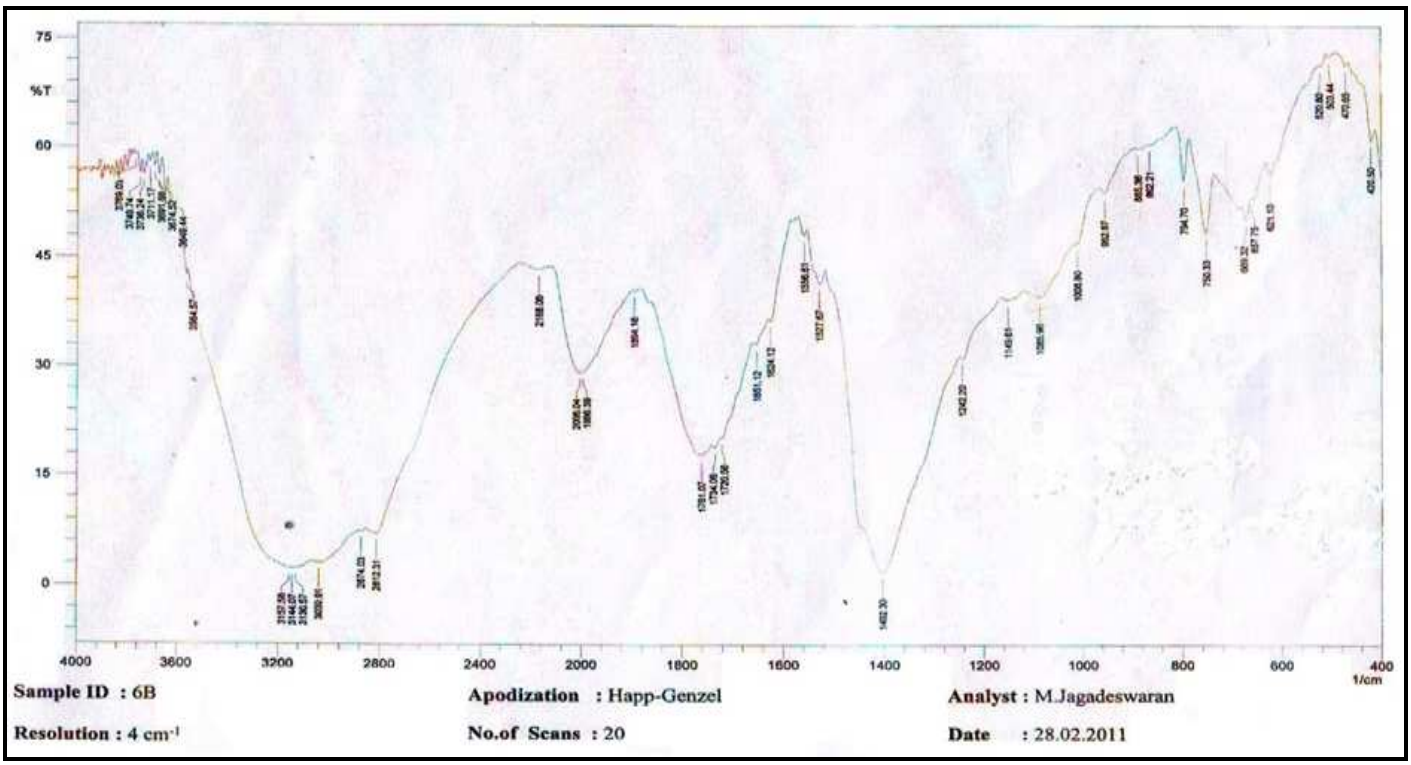


Figure No.2: IR Spectrum of Compound 4g

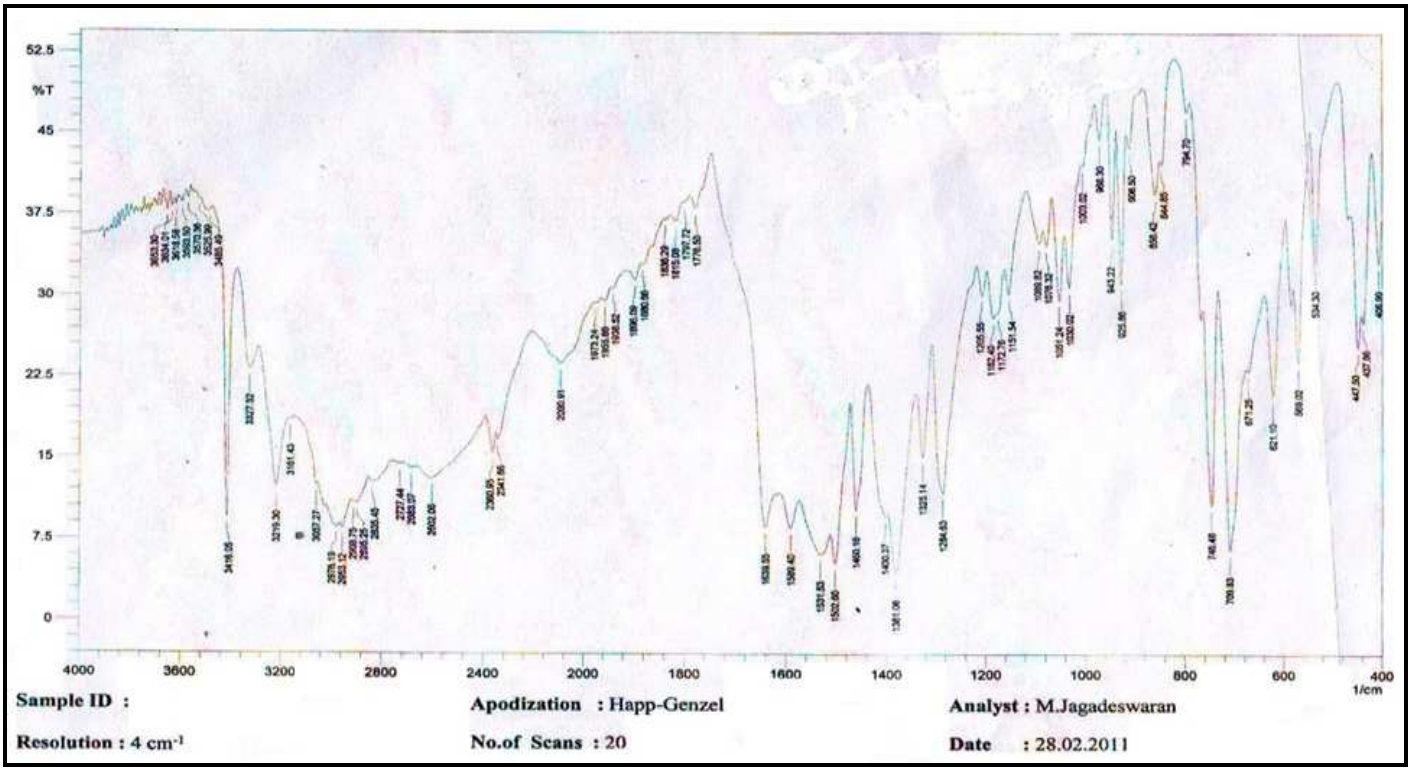


Figure No.2: IR Spectrum of Compound 4h

CONCLUSION

Eight novel pyrazoline contain quinazolone derivative have been synthesized, characterized by IR, 1HNMR and Mass spectral data Compounds C, Compounds 4a-h are screened for their anti-inflammatory using paw-odema method, indomethacin employed as a reference standard. From the results obtained it is concluded that compound 4b, 4e, 4f, 4g shown potent and compound 4a, 4c, 4d, 4h shown mild to moderate anti-inflammatory activity when compared to control indomethacin. Compounds 4b, 4e and 4f, 4h contain electron withdrawing groups like *p*-nitro and *p*-chloro which may favor potent anti-inflammatory activity when compared to compounds.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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