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SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME NOVEL 2-METHYL-4(3H)-QUINAZOLINONE DERIVATIVES BEARING PYRAZOLINE MOIETY

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ABSTRACT

4(3H)-Quinazolinone derivatives have considerable interest due to the diverse range of their biological properties. This method of preparation of 2-methyl-4(3H)-quinazolinone, 3-substituted-4(3H)-quinazolinone and 2,3-disubstituted-4(3H)-quinazolinone derivatives. The chemical reaction between anthranilic acid and acetyl chloride followed by dehydration to form the benzoxazinone intermediate; subsequent addition of a p-amino acetophenone provided the fused 3-(4-acetylphenyl)-2-methylquinazolin-4-one. The various chalcones (2a – j) were prepared by condensation of compound (1) with the appropriate aromatic aldehydes. Compounds (2a – 2j) react with hydrazine hydrate to form (3a–3j), hydrazine hydrates along with formic acid to form compounds (4a–4j) which are substituted 4(3H)quinazolinones as depicted in Scheme 1. The structures of the newly synthesized compounds were confirmed by IR, 1 H-NMR and Mass spectroscopy and Elemental analyses. Acute toxicity study of synthesized compound was found according to OECD guidelines 423. The test compound does not show any toxicity up to 50mg/kg dose.

Keywords: Quinazoline, pyrazole, analgesic, anti-inflammatory, spectral analysis

1. INTRODUCTION

The heterocyclic molecules containing nitrogen atoms, particularly five and six-membered such as pyrazoles and quinazolines have been recognized as potential scaffolds for therapeutic investigations. Several synthetic compounds containing pyrazoles have shown different biological properties such as anti-inflammatory[1], anticonvulsant[2], antihypertensive[3], antimicrobial[4], antibacterial[5], anticancer[6], antidepressant[7] and antitubercular[8] activities. Also, quinazoline nuclei have been extensively used in different compounds to get a broad spectrum of pharmacological activities, comprising analgesic[9], anti-inflammatory[10], anticonvulsant[11], antimicrobial[12], antibacterial[13], antifungal[14], anticancer[15], antimalarial[16], antioxidant[17], anti-HIV[18], antiviral[19], anti-influenza[20], antitubercular[21], anti-depressant[22], antihypertensive[23] as well as anti-histamine[24] activities.

On the other hand, various therapeutic activities have been reported for both pyrazole as well as quinazolines moieties. As a part of our continued program on the chemistry of 3H-quinazolin-4-one ring systems, we recently developed a simple and efficient approach to a wide range of such derivatives. These results prompted us to synthesize a series of novel 2-methyl-3H-quinazolin-

4-one derivatives containing a pyrazole, pyrazoline or pyrimidinone ring, intending to obtain some novel heterocyclic systems with potentially enhanced biological properties.

2. CHEMISTRY AND SYNTHESIS

2.1. Instrumentation and Synthesis

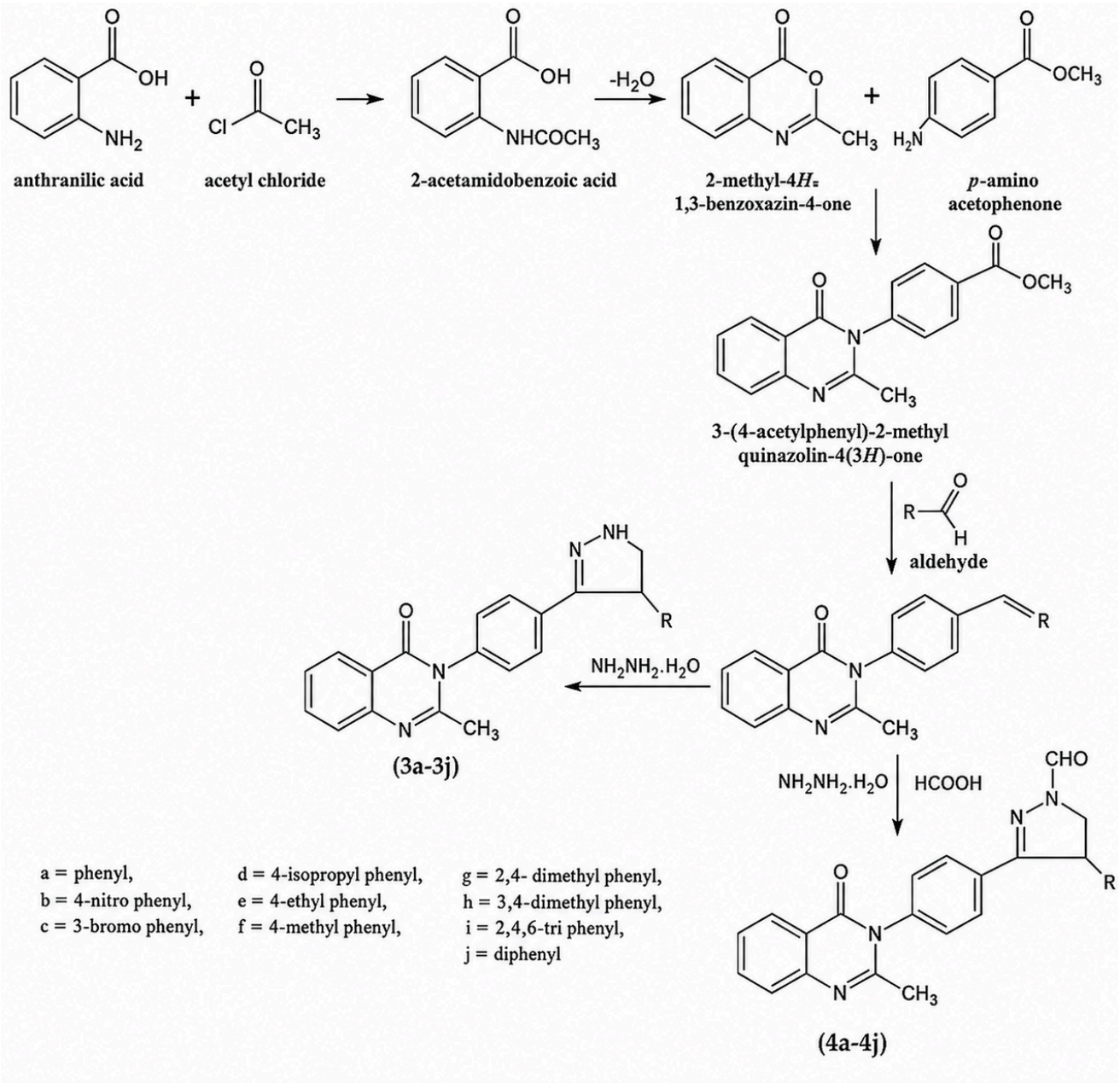
All starting materials, reagents, and solvents were purchased from commercial suppliers like Merck (Germany) and Sigma Aldrich Chemical Co. Analytical thin-layer chromatography (TLC) was conducted using Merck silica gel 60F254 plates. Infrared (IR) was recorded using a Fourier-transform IR (FT-IR) spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded by a Bruker 500 MHz spectrophotometer and chemical shifts are expressed as ppm with tetramethylsilane (TMS) as the internal standard. Compounds melting points were determined by the melting point apparatus and are uncorrected.

2.1.1. Synthesis of 3-(4-acetylphenyl)-2-methylquinazolin-4-one (1): Anthranilic acid (1.37g, 0.01M) was dissolved in 30 ml of dry pyridine (0.79 g, 0.01 mol) by stirring slowly at room temperature. The solution was cooled to 0-5°C and a solution of acetyl chloride (1.56 gm, 0.02 M) in dry pyridine (30 ml) was added slowly with constant stirring. After this addition, the reaction mixture was further stirred for half an hour at room temperature and set aside for 1hr. The pasty mass obtained was added with p-aminoacetophenone (1.35g, 0.01 M) in pyridine and refluxed for 6 hr. Excess of solvent was distilled off. The resulting mixture was cooled and poured over crushed ice. The solid was filtered, washed with cold water, and recrystallized from a suitable solvent.

2.1.2. Synthesis of 2-methyl-3-[4-(-3-aryl substituted prop-2-enoyl) phenyl] quinazolin-4-ones (2a-2j): Synthesized 3-(4-acetylphenyl)-2-methylquinazolin-4-one (0.01M) was added to different aromatic aldehydes (0.01M) in 30ml of ethanol and 40% sodium hydroxide solution. The mixture was stirred for 2hr at room temperature and kept in the refrigerator for 24hr. The content was poured on crushed ice and neutralized with 10% HCl, the product was filtered, dried and recrystallized from a suitable solvent.

2.1.3. Synthesis of 2-methyl-3-[4-(4-aryl substituted-4,5-dihydro-1H-pyrazol-3-yl) phenyl] quinazolin-4(3H)-ones (3a-3j): A mixture of compound 2 (0.01 M) and hydrazine hydrate (0.01 M, dissolved in 2 ml glacial acetic acid) was heated at reflux temperature for 6 hr. After completion of the reaction, the mixture was cooled to room temperature and poured into ice-cold water, filtered and recrystallized.

2.1.4. Synthesis of 2-methyl-3-[4-(4-aryl substituted-1-carbaldehyde-2-pyrazolin-3-yl) phenyl] quinazolin-4-ones (4a-4j): To a mixture of compound 2 (0.01 mol) and hydrazine hydrate (0.05M, 1.6ml) add formic acid (40ml) and reflux for 26 hr. On completion of the reaction (TLC monitoring) the resulting solution was poured into ice-cold water and allowed to stand overnight. Precipitate formed was filtered and recrystallized.



Scheme 1: Synthetic pathway for the preparation of title compounds (1, 2a–2j, 3a–3j, 4a–4j)

3. PHYSICAL CHARACTERIZATION

2.1.5. Physical Characterization

The physical characterization data including yield, melting point, molecular weight, elemental formula and thin layer chromatography (TLC) Rf values for all synthesized pyrazoline derivatives (2a–2j, 3a–3j and 4a–4j) are summarized below.

Table 1: Physical Characterization of the intermediate (2a – 2j)

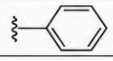
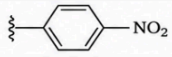
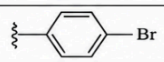
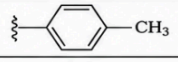
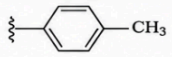
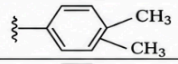
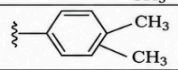
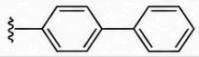
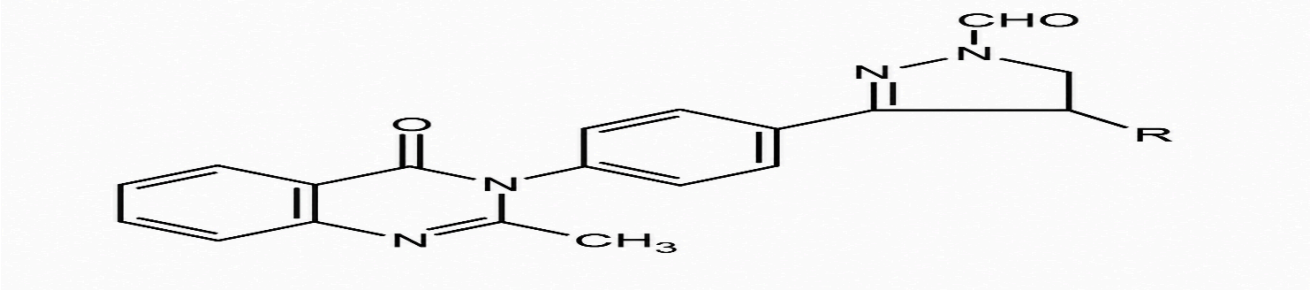
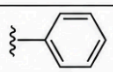
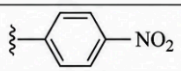
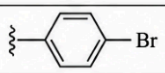
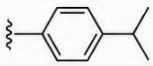
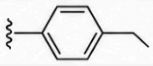
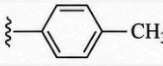
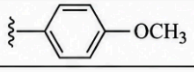
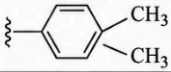
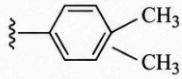
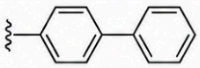
Compounds	R	Mol. Formula	Mol. Wt.	% Yield	M.P (°C)	R_f Value
3a.		$C_{24}H_{20}N_4O$	380.44	72	114–116	0.28
3b.		$C_{24}H_{19}N_5O_2$	425.43	69	130–132	0.24
3c.		$C_{24}H_{19}BrN_4O$	459.33	82	120–122	0.32
3d.		$C_{27}H_{26}N_4O$	422.52	72	106–108	0.36
3e.		$C_{26}H_{24}N_4O$	408.49	76	165–169	0.43
3f.		$C_{25}H_{22}N_4O$	394.46	68	158–162	0.30
3g.		$C_{26}H_{24}N_4O$	408.49	59	125–128	0.42
3h.		$C_{26}H_{24}N_4O$	408.49	81	149–151	0.52
3i.		$C_{27}H_{26}N_4O$	422.52	75	179–181	0.34
3j.		$C_{30}H_{24}N_4O$	456.53	87	165–169	0.50

Table 2: Physical Characterization of the title compounds (3a – 3j and 4a – 4j)



Compounds	R	Mol. formula	Mol. Wt.	% Yield	M.P (°C)	R_f Value
4a.		$C_{25}H_{20}N_4O_2$	408.45	61	142–145	0.46
4b.		$C_{25}H_{19}N_5O_4$	453.44	74	152–155	0.60
4c.		$C_{25}H_{19}BrN_4O_2$	487.34	66	168–172	0.56
4d.		$C_{28}H_{26}N_4O_2$	450.53	73	191–195	0.52
4e.		$C_{27}H_{24}N_4O_2$	436.50	74	188–193	0.49
4f.		$C_{26}H_{22}N_6O_4$	422.47	74	179–181	0.43
4g.		$C_{22}H_{20}N_4O_2$	436.50	63	160–162	0.58
4h.		$C_{27}H_{24}N_4O_2$	436.50	65	180–182	0.87
4i.		$C_{28}H_{26}N_4O_2$	450.53	71	167–169	0.40
4j.		$C_{31}H_{24}N_4O_2$	484.54	75	148–169	0.56

Compounds	IR frequency region (cm^{-1})
1. 3-(4-acetylphenyl)-2-methylquinazolin-4(*3H*)-one	C-H (Ar-stretching) 3053, C=C–H (Ar-stretching) 3019, CH_3 (Alkyl stretching) 2941, (C=O stretching) 1621, (C=N stretching) 1575.
2a. 2-methyl-3-{4-[(2)-3-phenylprop-2-enoyl]phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3198, C=C–C=O (α, β unsaturated ketone) 1669, (C=O stretching) 1620, (C=N stretching) 1607, (C=C–C Ar-stretching) 1573, (C-N Ar-stretching) 852.
2b. 2-methyl-3-{4-[(2)-3-(4-nitrophenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3108, C=C–C=O (α, β unsaturated ketone) 1672, (C=O stretching) 1620, (C=N stretching) 1607, (C=C–C Ar-stretching) 1596, (N=O stretching) 1347, (C=N Ar-stretching) 852.
2c. 3-{4-[(2)-3-(3-bromophenyl) prop-2-enoyl]phenyl}-2-methylquinazolin-4(*3H*)-one	(C-H Ar-stretching) 3077, (C=O stretching) 1780, (C=N stretching) 1730, C=C–C=O (α, β unsaturated ketone) 1684, 1579, (-Br stretching) 672.
2d. 2-methyl-3-{4-[(2)-3-(4-isopropyl phenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3107, C=C–C=O (α, β unsaturated ketone) 1684, (C=O stretching) 1641, (C=N stretching) 1604, (C=C–C Ar-stretching) 1584, (-CH-$(CH_3)_2$ stretching) 1334.
2e. 2-methyl-3-{4-[(2)-3-(4-methylphenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3080, (C=O stretching) 1764, C=C–C=O (α, β unsaturated ketone) 1663, (C=N stretching) 1620, (C=C–C Ar-stretching) 1496, (-C-H stretching) 1362.
2f. 2-methyl-3-{4-[(2)-3-(4-ethyl phenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3108, (C=O stretching) 1744, C=C–C=O (α, β unsaturated ketone) 1688, (C=N stretching) 1606, (C=C–C Ar-stretching) 1496, (-CH_2- stretching) 1469, (-C-H stretching) 1376.
2g. 2-methyl-3-{4-[(2)-3-(2,4-dimethylphenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3080, C=C–C=O (α, β unsaturated ketone) 1682, (C=O stretching) 1604, (C=N stretching) 1567, (C=C alkene stretching) 1533, (-C-H stretching) 1349.
2h. 2-methyl-3-{4-[(2)-3-(3,4-dimethylphenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3069, (C=O stretching) 1736, C=C–C=O (α, β unsaturated ketone) 1683, (C=N stretching) 1629, (C=C–C Ar-stretching) 1569, (-C-H stretching) 1363.
2i. 2-methyl-3-{4-[(2)-3-(2,4,6-trimethylphenyl) prop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C=C–H Ar-stretching) 2949, (C=O stretching) 1770, (C=N stretching) 1760, C=C–C=O (α, β unsaturated ketone) 1682, (C=C–C Ar-stretching) 1499, (-C-H stretching) 1372.
2j. 2-methyl-3-{4-[(2)-3-biphenylprop-2-enoyl] phenyl} quinazolin-4(*3H*)-one	(C-H Ar-stretching) 3084, C=C–C=O (α, β unsaturated ketone) 1684, (C=O stretching) 1664, (C=N stretching) 1604, (C=C–C Ar-stretching) 1503, (-C-H stretching) 1364.

4. SPECTRAL AND ELEMENTAL DATA

2.2. Spectral Data and Elemental Analysis

The structures of newly synthesized compounds were characterized by FTIR, ^{1}H NMR, and mass spectrometry.

Table 4: Interpretation of ^{1}H NMR and MS spectral data of title compounds

S.No:	Comp.	^{1}H NMR (δppm)	MS (m/z) $[M+H]^{+}$
1	3a	8.3-7.0 (m, 13H, Ar-H), 5.5(dd,1H, pyrazoline), 3.8-2.8(dd, dd,1H,1H pyrazoline), 2.2 (s,3H, CH_3)	381
2	3b	8.3-6.8 (m, 12H, Ar-H), 5.1(dd,1H, pyrazoline), 3.4-3.0(dd, dd,1H,1H pyrazoline), 2.2 (s,3H, CH_3).	426
3	3c	8.4-7.3 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.2-2.6(dd, dd,1H,1H pyrazoline), 2.2 (s,3H, CH_3).	459
4	3d	8.4-6.9 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 2.8-2.6(dd, dd,2H, pyrazoline), 2.4(sept,1H, CH), 2.2(s,3H, CH_3), 1.5(d,3H, CH_3), 1.5(d,3H, CH_3).	423
5	3e	8.4-6.8 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.2-2.6(dd1H,1H, pyrazoline), 2.3 (q,2H, CH_2), 2.2 (s,3H, CH_3), 1.5(d,3H, CH_3), 1.5(t,3H, CH_3).	410
6	3f	8.4-6.9 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.1-2.2(dd, dd,1H,1H, pyrazoline), 2.2(s,3H, CH_3), 2.2(s,3H, -CH_3).	395
7	3g	8.0-6.4 (m, 11H, Ar-H), 5.3(dd,1H, pyrazoline), 2.9(dd, dd,1H,1H, pyrazoline), 2.2(s3H, -CH_3), 2.2(s,3H, CH_3).	409
8	3h	8.4-6.7 (m, 11H, Ar-H), 5.7(dd,1H, pyrazoline), 2.9-3.1(dd, dd,1H,1H, pyrazoline), 2.2(s3H, -CH_3), 2.2(s,3H, CH_3).	409
9	3i	8.8-6.8 (m, 10H, Ar-H), 5.4(dd,1H, pyrazoline), 3.2-2.8(dd, dd,1H,1H, pyrazoline), 2.6(s,3H, -CH_3), 2.2(s,9H, CH_3).	421
10	3j	8.5-6.8(m, 17H, Ar-H), 5.8(d,1H, pyrazoline), 3.1-2.9(dd, dd,1H,1H, pyrazoline), 2.4(s,3H, -CH_3).	457
11	4a	8.6 (s,1H, CHO), 8.3-7.0 (m, 13H, Ar-H), 5.5(dd,1H, pyrazoline), 3.4(dd, dd,1H,1H pyrazoline), 2.5 (s,3H, CH_3).	409
12	4b	8.4 (s,1H, CHO), 8.1-6.8 (m, 12H, Ar-H), 5.5(dd,1H, pyrazoline), 3.4-3.0(dd, dd,1H,1H pyrazoline), 2.5 (s,3H, CH_3).	454
13	4c	8.2 (s,1H, CHO), 7.8-6.8 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.2-2.6(dd, dd,1H,1H pyrazoline), 2.2(s,3H, CH_3).	487
14	4d	8.6 (s,1H, CHO), 8.1-6.9 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 2.8-2.4(dd, dd, sept,1H,1H,1H, pyrazoline), 2.2 (s,3H, CH_3), 1.5(d,3H, CH_3), 1.5(d,3H, CH_3).	451
15	4e	8.6 (s,1H, CHO), 8.2-6.8 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.2-2.6(dd1H,1H, pyrazoline), 2.3 (q,2H, CH_2), 2.2 (s,3H, CH_3), 1.5(d,3H, CH_3), 1.5(t,3H, CH_3).	437
16	4f	8.2 (s,1H, CHO), 8.1-6.9 (m, 12H, Ar-H), 5.0(dd,1H, pyrazoline), 3.1-2.2(dd, dd,1H,1H, pyrazoline), 2.4(s,3H, CH_3), 2.2(s,3H, -CH_3).	423
17	4g	8.2 (s,1H, CHO), 7.5-6.4 (m, 11H, Ar-H), 5.3(dd,1H, pyrazoline), 2.9(dd, dd,1H,1H, pyrazoline), 2.4(s3H, -CH_3), 2.2(s,3H, CH_3).	437
18	4h	8.2 (s,1H, CHO), 8.0-6.7 (m, 11H, Ar-H), 5.7(dd,1H, pyrazoline), 2.9-3.1(dd, dd,1H,1H, pyrazoline), 2.4(s3H, -CH_3), 2.2(s,3H, CH_3).	437
19	4i	8.2 (s,1H, CHO), 7.8-6.8 (m, 10H, Ar-H), 5.4(dd,1H, pyrazoline), 3.2-2.8(dd, dd,1H,1H, pyrazoline), 2.6(s,3H, -CH_3), 2.2(s,9H, CH_3).	451
20	4j	8.4 (s,1H, CHO), 8.0-6.8(m, 17H, Ar-H), 5.8(d,1H, pyrazoline), 3.1-2.9(dd, dd,1H,1H, pyrazoline), 2.4(s,3H, -CH_3).	485

Table 5: Data of CHNS elemental analyses of title compounds

S.No:	Compounds	Composition (%)				
		C	H	N	O	S
1	2-methyl-3-[4-(4-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3a)**	75.77	5.30	14.73	4.21	-
2	2-methyl-3-[4-(4-nitrophenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3b)**	67.76	4.50	16.46	11.28	-
3	2-methyl-3-[4-(3-bromo phenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3c)**	62.75	4.17	12.20	3.48	-
4	2-methyl-3-[4-(4-isopropylphenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3d)**	76.75	6.20	13.26	3.79	-
5	2-methyl-3-[4-(4-ethylphenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3e)**	76.45	5.92	13.72	3.92	-
6	2-methyl-3-[4-(4-methylphenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3f)**	76.12	5.62	14.20	4.06	-
7	2-methyl-3- [4-(2,4-dimethyl phenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3g)**	76.45	5.92	13.72	3.92	-
8	2-methyl-3- [4-(3,4-dimethyl phenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3h)**	76.45	5.92	13.72	3.92	-
9	2-methyl-3-[4-(2,4,6-trimethylphenyl-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3i)**	76.75	6.20	13.26	3.79	-
10	2-methyl-3-[4-(1,1'-biphenyl-4yl)-4,5-dihydro-1*H*-pyrazol-3-yl) phenyl] quinazolin-4(3*H*)-one **(3j)**	78.92	5.30	12.27	3.50	-
11	2-methyl-3- {4- [4-(phenyl)- 4,5-dihydro 1*H*-pyrazole-1-carbaldehyde 3-yl-] phenyl} quinazolin-4(3*H*)-one **(4a)**	73.51	4.94	13.72	7.83	-
12	2-methyl-3- {4- [4-(4-nitro phenyl)- 4,5-dihydro 1*H*-pyrazole-1-carbaldehyde-3-yl-] phenyl} quinazolin-4(3*H*)-one **(4b)**	66.22	4.22	15.44	14.11	-
13	2-methyl-3- [4-(3-bromo phenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4c)**	61.61	3.93	11.50	6.50	-
14	2-methyl-3-[4-(4-isopropylphenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4d)**	74.65	5.84	12.44	7.10	-
15	2-methyl-3-[4-(4-ethylphenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4e)**	74.29	5.54	12.84	7.33	-
16	2-methyl-3-[4-(4-methylphenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4 (3*H*)-one **(4f)**	73.92	5.25	13.26	7.57	-
17	2-methyl-3- [4-(2,4-dimethyl phenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4g)**	74.29	5.54	12.84	7.33	-
18	2-methyl-3- [4-(3,4-dimethyl phenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4h)**	74.29	5.54	12.84	7.33	-
19	2-methyl-3-[4-(2,4,6-trimethylphenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde-3-yl) phenyl] quinazolin-4(3*H*)-one **(4i)**	74.65	5.84	12.44	7.10	-
20	2-methyl-3- {4- [4-(4-bi phenyl)- 4,5-dihydro 1*H*-pyrazole-1-carbaldehyde 3-yl-] phenyl} quinazolin-4(3*H*)-one **(4j)**	76.84	4.99	11.56	6.60	-

5. PHARMACOLOGICAL EVALUATION

3.1. Acute toxicity study: Acute toxicity study was performed for the synthesized compounds to ascertain safe dose by acute oral toxic class method of Organization of Economic Co-operation and Development, as per 423 guidelines. Synthesized compound's (3a-4j) dose was fixed as 50 mg/kg for pharmacological study. No mortality or behavioral abnormalities were observed at this dose level.

3.2. Anticonvulsant Evaluation

Table 6: Anticonvulsant activity of 2-methyl-4(3H)-quinazolinones (MES method)

Animal group	R	Onset of Clonic convulsion (min.)	Duration of convulsion (min.)	% Inhibition of convulsion	Mortality	% Protection
Control	0.1% SCMC	3.11±0.30	22.14±0.05	**0**	**0/6**	**0**
Standard	Diazepam 10 mg/kg	0.00±0.00***	0.00±0.00***	**100**	**6/6**	**100.00**
3a.	—	5.22±0.21	7.04±0.70**	**68.20**	**5/6**	**83.33**
3b.	—	5.57±0.21	10.01±2.61**	**54.79**	**5/6**	**83.33**
3c.	—	5.66±0.21	14.11±1.46	**36.26**	**2/6**	**33.33**
3d.	—	5.72±0.19	8.02±1.99**	**63.78**	**4/6**	**66.66**
3e.	—	5.16±0.30	11.13±0.94**	**49.73**	**5/6**	**83.33**
3f.	—	5.00±0.44	12.16±2.52**	**45.07**	**3/6**	**50.00**
3g.	—	5.33±0.33	12.00±2.61**	**45.80**	**4/6**	**66.67**
3h.	—	5.16±0.30	13.13±1.7	**40.69**	**3/6**	**50.00**
3i.	—	5.83±0.47	13.00±1.57	**41.28**	**3/6**	**50.00**
3j.	—	4.56±0.30	14.08±1.20	**36.40**	**2/6**	**33.33**

FIG: 1 — Graphical representation of Anticonvulsant Activity (MES Method)

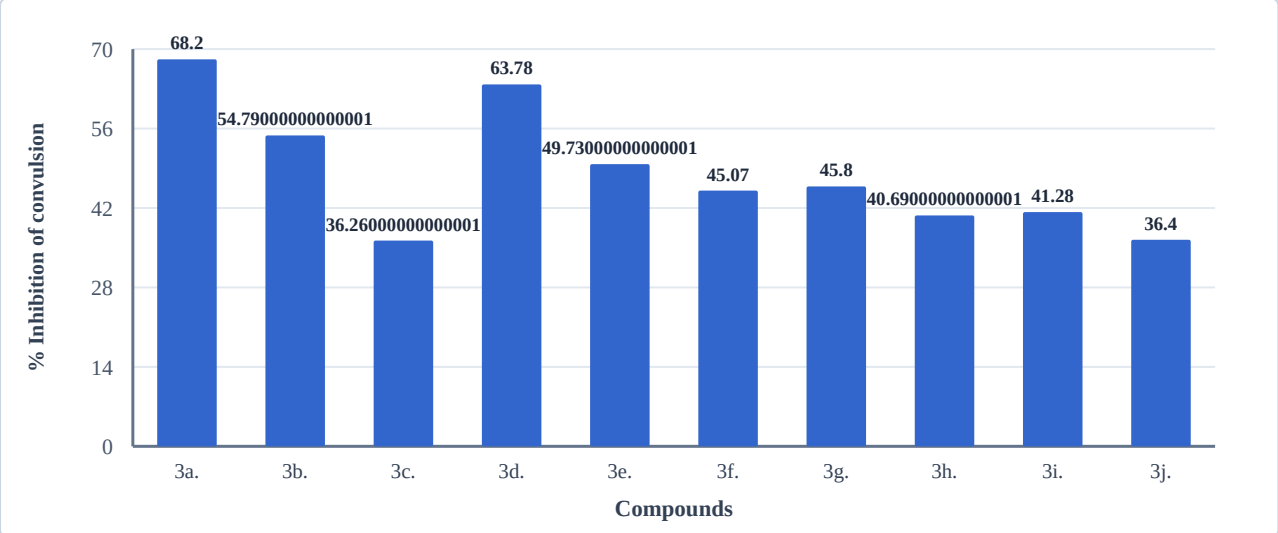
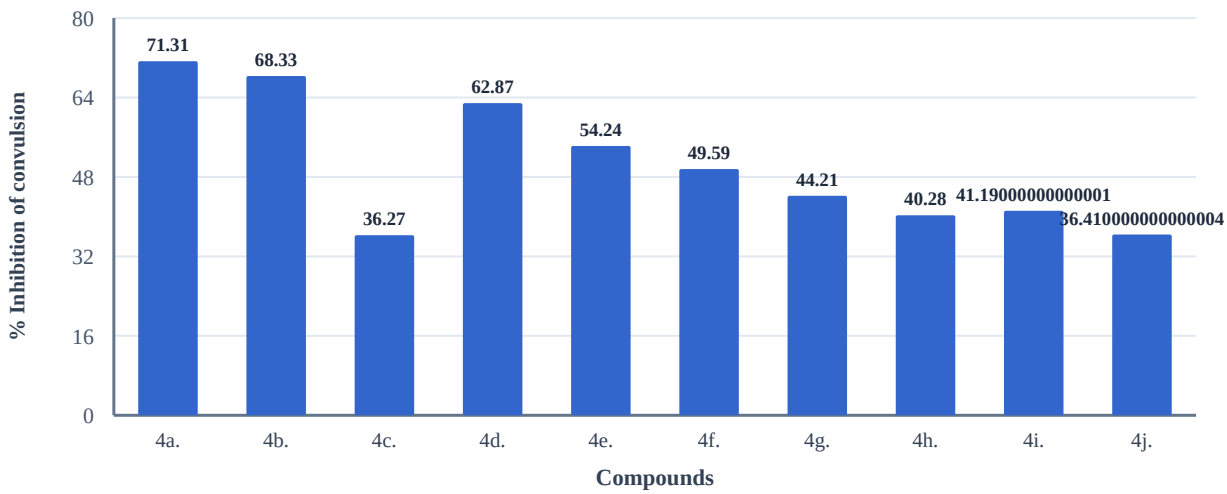


Table 8: Anticonvulsant activity of 2-methyl-4(3H)-quinazolinones (PTZ method)

Animal group	R	Onset of clonic convulsion (min.)	Duration of convulsion (min.)	% Inhibition of convulsion	Mortality	% Protection
Control	0.1% SCMC	3.11±0.30	22.14±0.05	**0**	**0/6**	**0**
Standard	Diazepam 10 mg/kg	0.00±0.00***	0.00±0.00***	**100**	**6/6**	**100.00**
4a.	—	4.06±0.21	6.35±0.70**	**71.31**	**5/6**	**83.33**
4b.	—	5.22±0.21	7.01±2.61**	**68.33**	**5/6**	**83.33**
4c.	—	4.36±0.21	14.11±1.46	**36.27**	**2/6**	**33.33**
4d.	—	5.12±0.19	8.22±1.99**	**62.87**	**4/6**	**66.67**
4e.	—	5.16±0.30	10.13±0.94**	**54.24**	**5/6**	**83.33**
4f.	—	5.00±0.35	11.16±1.52**	**49.59**	**3/6**	**50.00**
4g.	—	5.36±0.03	12.35±0.61**	**44.21**	**4/6**	**66.67**
4h.	—	5.16±0.30	13.22±1.70	**40.28**	**3/6**	**50.00**
4i.	—	4.83±0.47	13.02±0.57	**41.19**	**3/6**	**50.00**
4j.	—	5.16±0.30	14.08±1.20	**36.41**	**2/6**	**33.33**

Values are expressed as mean ± SEM ($n = 6$). $^{**}p < 0.01$, $^{***}p < 0.001$ *vs* control (0.1% SCMC).

FIG: 2 — Graphical representation of Anticonvulsant Activity (PTZ Method)



3.3. Analgesic Evaluation

Table 9: Writhing and analgesic activity (Aspirin comparison)

Animal group	Dosage	Number of writhing (mean ± SEM)	% Analgesic activity
Control	0.1% solution of SCMC	21±1.29	0.00
Standard	Diclofenac Na	1.5±0.89	92.85
3a	—	13.75±1.19**	34.52
3b	—	15.5±0.65	26.19
3c	—	15.25±1.03	27.38
3d	—	13.00±1.08**	38.09
3e	—	12.78±1.12**	39.14
3f	—	13.90±1.73**	33.80
3g	—	13.18±1.52**	37.23
3h	—	14.01±1.12**	33.28
3i	—	13.70±0.87**	34.76
3j	—	18.16±1.77	13.52

FIG: 4 — Graphical representation of Analgesic Activity (Writhing Test)

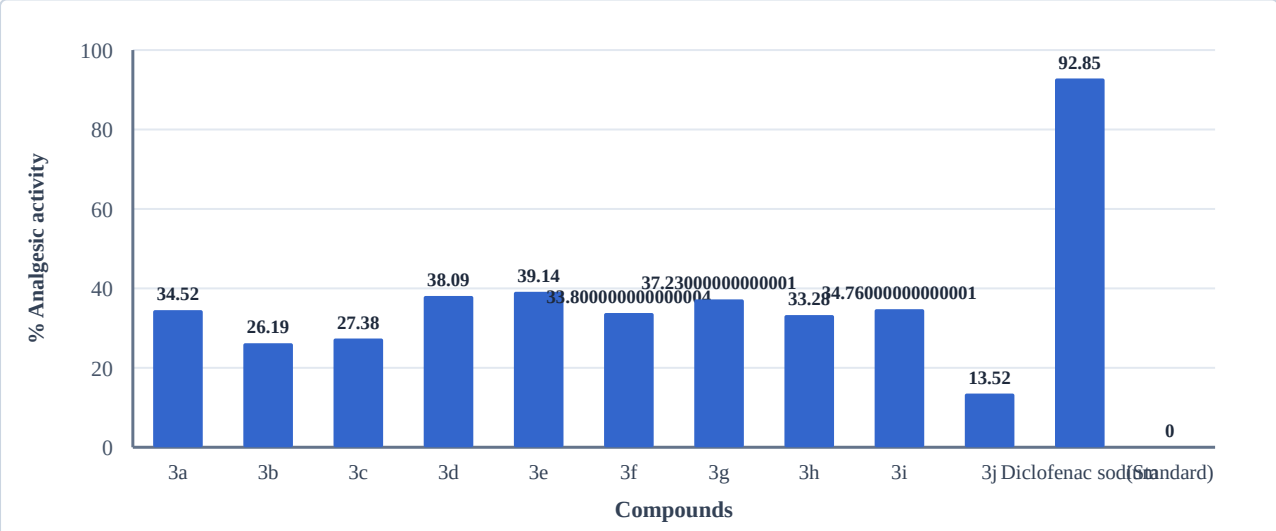
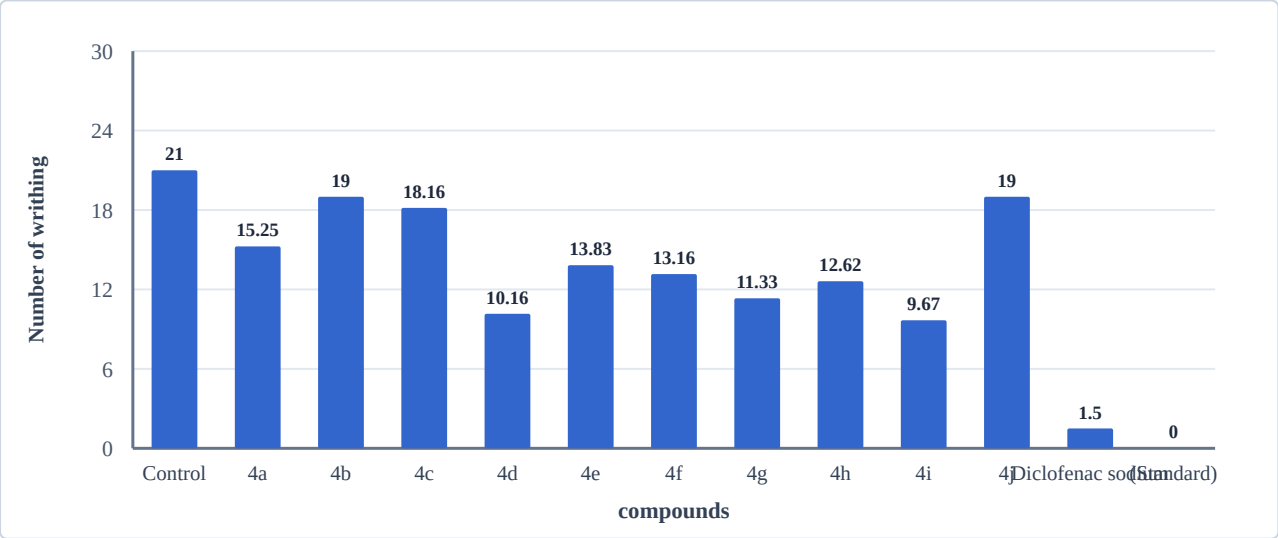
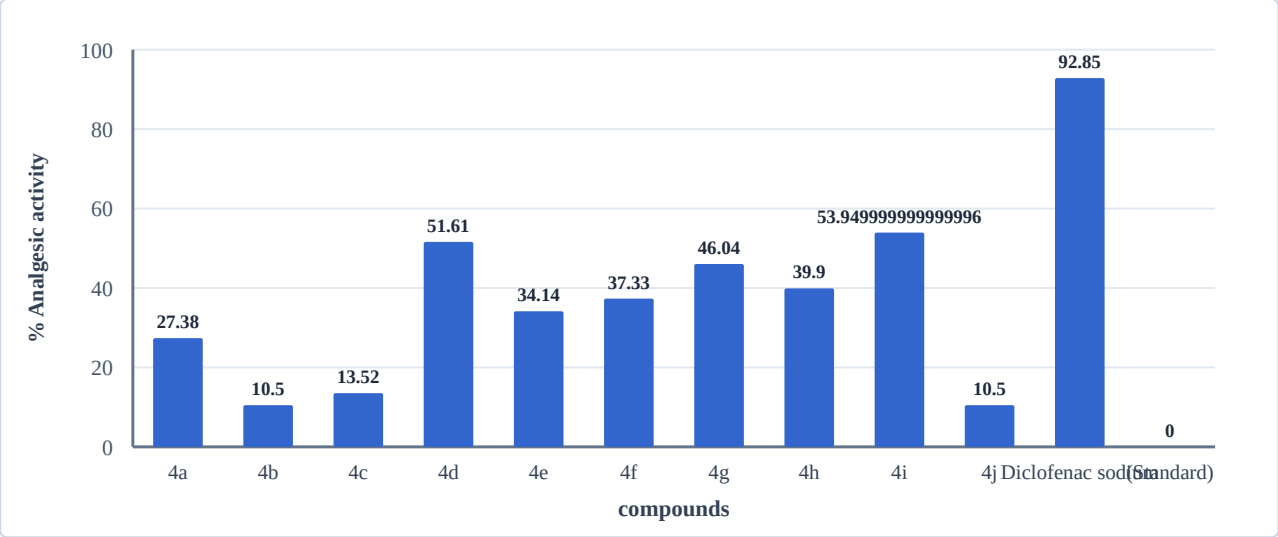


Table 10: Writhing and analgesic activity (Pentazocine comparison)

Animal group	Dosage	Number of writhings (mean ± SEM)	% Analgesic activity
Control	0.1% solution of SCMC	21±1.29	0.00
Standard	Diclofenac sodium	1.5±0.89	92.85
4a	—	15.25±1.03	27.38
4b	—	19.00±1.46	10.50
4c	—	18.16±0.99	13.52
4d	—	10.16±1.26**	51.61
4e	—	13.83±0.87**	34.14
4f	—	13.16±0.52**	37.33
4g	—	11.33±0.63**	46.04
4h	—	12.62±1.12**	39.90
4i	—	9.67±2.9**	53.95
4j	—	19.00±1.46	10.50

FIG: 5 & 6 — Graphical representation of Analgesic Activity (Hot Plate & Tail Flick)





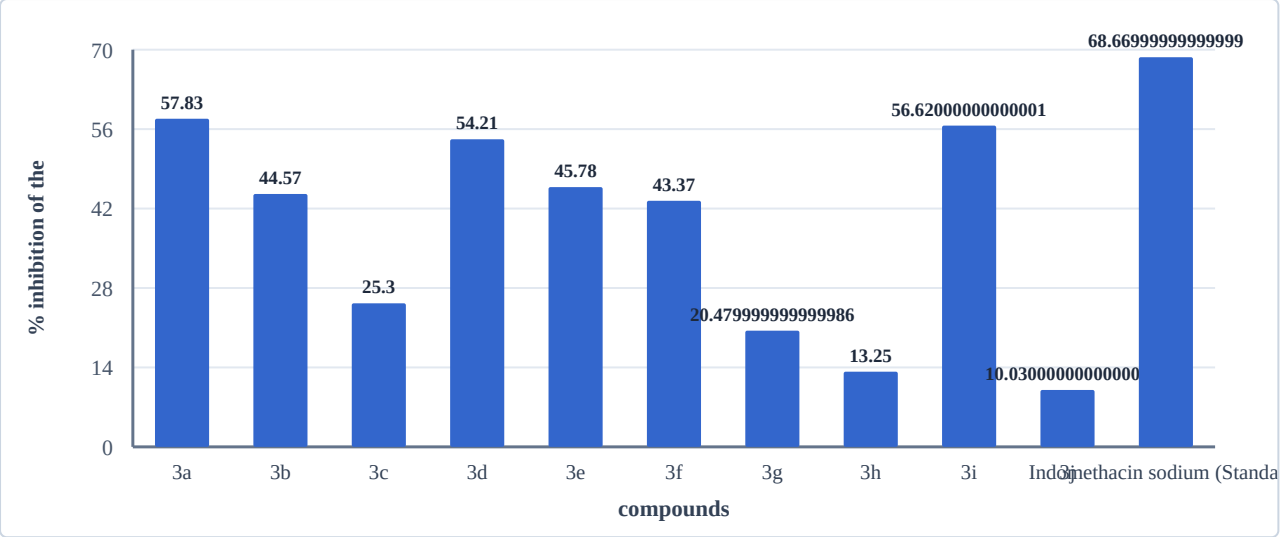
3.4. Anti-inflammatory Evaluation

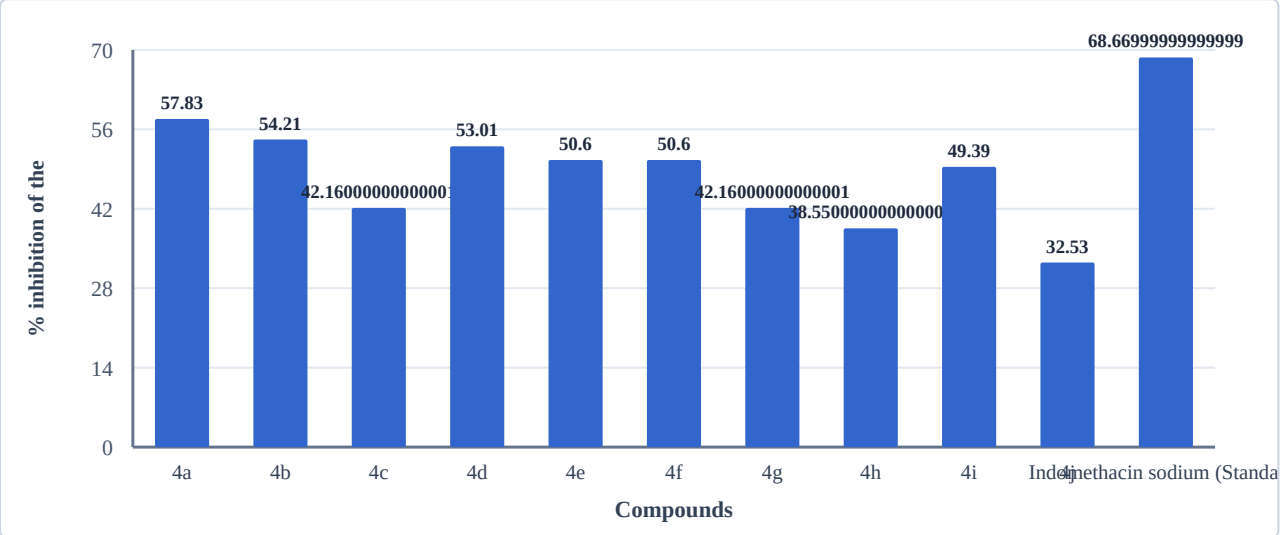
Table 11 & 12: Percentage Inhibition of Paw Edema (Carrageenan induced)

Animal group	Dosage	Increase in paw edema	% inhibition of the inflammation
Control	0.1% solution of SCMC	0.83±0.06	0.00
Standard	Indomethacin sodium	0.26±0.01**	68.67
3a	—	0.35±0.03**	57.83
3b	—	0.46±0.045**	44.57
3c	—	0.62±0.04	25.30
3d	—	0.38±0.03**	54.21
3e	—	0.45±0.03**	45.78
3f	—	0.47±0.02**	43.37
3g	—	0.66±0.05	20.48
3h	—	0.72±0.05	13.25
3i	—	0.36±0.04**	56.62
3j	—	0.75±0.04	10.03

Animal group	Dosage	Increase in paw edema	% inhibition of the inflammation
Control	0.1% solution of SCMC	0.83±0.06	0.00
Standard	Indomethacin sodium	0.26±0.01**	68.67
4a	—	0.35±0.04**	57.83
4b	—	0.38±0.05**	54.21
4c	—	0.48±0.04**	42.16
4d	—	0.39±0.01**	53.01
4e	—	0.41±0.01**	50.60
4f	—	0.41±0.05**	50.60
4g	—	0.48±0.04**	42.16
4h	—	0.51±0.03	38.55
4i	—	0.42±0.08**	49.39
4j	—	0.56±0.05	32.53

FIG: 7 & 8 — Graphical representation of Anti-inflammatory Activity Comparison





6. CONCLUSION AND REFERENCES

In conclusion, a series of novel 2-methyl-4(3H)-quinazolinone derivatives bearing pyrazoline moieties (3a–3j and 4a–4j) were successfully synthesized in good yields and structurally characterized by FTIR, ^{1}H NMR, mass spectrometry and elemental analysis. Pharmacological screening demonstrated that compounds containing electron-withdrawing and methoxy groups (such as 4c, 4h, and 4i) exhibited significant anti-inflammatory and analgesic properties comparable to standard reference drugs without any acute toxicity.

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