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DRUG SYNTHESIS

MICROWAVE ASSISTED ONE POT SYNTHESIS OF SOME PYRAZOLE DERIVATIVES AS A SAFER ANTI-INFLAMMATORY AND ANALGESIC AGENTS

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Abstract: A series of pyrazolo[3,4-b]quinolines have been synthesized using one-pot water mediated synthetic route under microwave irradiation involving the condensation of 2-chloroquinoline-3-carbaldehydes with semicarbazide or 2,4-dinitrophenyl hydrazine. The compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation actions. The pharmacological evaluation showed that the compounds are good at inhibiting edema induced by carrageenan and also showed prominent analgesic activity with lesser GI toxicity as indicated by severity index and LPO values.

Keywords: pyrazoloquinolines, green chemistry, microwave, anti-inflammatory, analgesic

The quinoline nucleus is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities, such as anti-malarial (1, 2), antibacterial (3, 4), antifungal (5), anthelmintic (6), cardiotonic (7, 8), anticonvulsant (9), anti-inflammatory (10), analgesic (11), antiviral (12), anticancer (13), antiobesity (14), which can be well illustrated by a variety of formulations possessing this heterocyclic moiety. The quinolones derivatives are extensively used as antibiotics in eradicating many infections (15, 16).

Pyrazole and its derivatives are gaining importance in medicinal and synthetic chemistry due to their diverse types of biological properties such as antibacterial (17), anti-inflammatory (18), analgesic (19), antiviral (20) etc. Even condensed pyrazoles are known for biological activities like pyrazolo[3,4-b]quinolines as potential antivirals (21) and antibacterials (22).

Due to the presence of versatile biological activities in pyrazolo[3,4-b]quinolines, several attempts are made to provide convenient synthetic route for this fused ring system. According to the available literature 2-chloroquinoline-3-carbaldehyde has been used as precursor for the synthesis of pyrazolo[3,4-b]quinolines. They can be prepared by refluxing 2-chloroquinoline-3-carbaldehyde with hydrazine hydrate using ethanol (23) or microwave assisted one pot condensation of 2-chloroquinoline-3-carbaldehyde with semicarbazide or 2,4-dinitrophenylhydrazine using organic catalyst PTSA (22, 24). These reactions were found to involve an intermediate Schiff's base formation which at the end of reaction gives an impurity to the final product.

The literature available showed that water can be used to perform organic transformation using thermal or microwave resources (25). It is also reported that boiling water under microwave irradiation behaves as hydrophobic medium and helps to form homogenous mass with organic substrates and accelerates the reaction rate (26).

Keeping in view the diverse activities of both pyrazole and quinoline nucleus and difficulties arising from synthetic methods we have tried to synthesize molecules using 2-chloroquinoline-3-carbalde-

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hyde and semicarbazide or 2,4-dinitrophenyl hydrazine in the presence of water to give eco friendly and economic synthetic one pot route for pyrazolo[3,4-b]quinolines and evaluated their anti-inflammatory and analgesic activity.

EXPERIMENTAL

Chemicals were purchased from Merck and Sigma-Aldrich as 'synthesis grade' and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 analyzer and found within ±0.4% of theoretical values. The IR spectra were measured as potassium bromide pellets using a Buck Scientific M-500 Infrared spectrophotometer. ^{1}H-NMR spectra were recorded in DMSO as a solvent (using TMS as an internal standard). ^{13}C-NMR of compound **3a** was recorded as a prototype using DMSO-d_6 as a solvent. The NMR and mass spectra were recorded on Bruker Avance-400 MHz and JEOL BX 102/DA-6000 mass spectrometers, respectively. Purity of the compounds was checked by TLC on silica gel G plates using toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v) as solvent system and the spots were located either under ultra violet light or through exposure to iodine vapors. The reactions were carried out in a Catalyst microwave oven having a maximum power output of 1000 W. Compounds **1**(**a**-**d**) and **2**(**a**-**d**) were prepared by reported methods of Kidwai et al. (27) (Scheme 1).

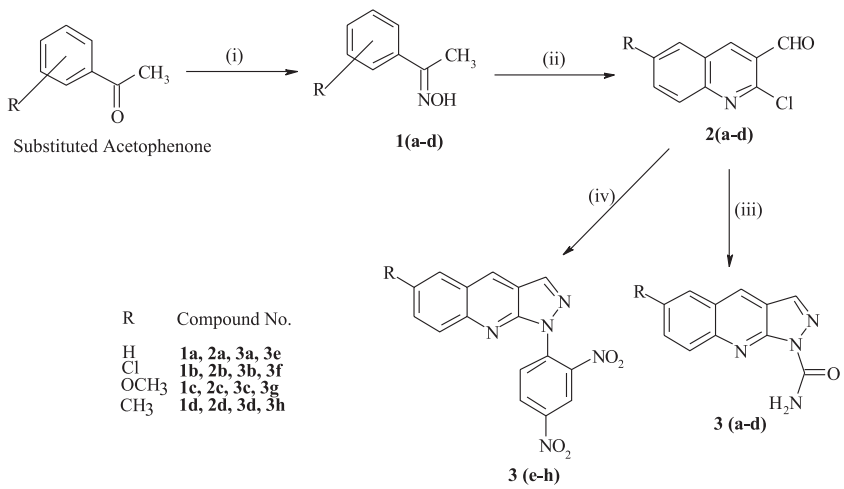
General procedure for the synthesis of 1-carboamidopyrazolo[3,4-b]quinolines (3a-h)

Conventional method

A mixture of 2-chloroquinoline-3-carbaldehyde (1 mmol) and 2,4-dinitrophenylhydrazine or semicarbazide (1.25 mmol) was refluxed in ethanol (20 mL). The reaction was monitored by TLC using toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v). After completion of reaction, the ethanol was concentrated to half of its volume and poured into ice water. The precipitate obtained was filtered, washed with water and recrystallized from ethanol.

Non-conventional (microwave irradiation) method

A mixture of 2-chloroquinoline-3-carbaldehyde (1 mmol) and 2,4-dinitrophenylhydrazine or semicarbazide (1.25 mmol) was refluxed with stirring in water (5 mL) under microwave irradiation at 1000 W for 2-5 minutes. The reaction was monitored by TLC using toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v). After completion of reaction, the reaction mixture was cooled and solid obtained was filtered, washed with water and recrystallized from ethanol.



Reagents and Condition: (i) Sodium acetate, Hydroxylamine, Hydrochloric acid; (ii) Dimethyl formamide, Phosphorus oxychloride;(iii) Semicarbazide, Water, MW-1000 W; (iv) 2,4-Dintirophenylhydrazine, Water, MW-1000 W

Scheme 1.

1-Carboamidopyrazolo[3,4-b]quinoline (3a)

Yield: 96%, m.p. 230-232°C, R_f: 0.84, IR (cm^{-1}): 3375, 3310 (NH_2), 1667 (C=O), 1610 (C=N), 1580 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 6.32 (s, 2H, NH_2), 7.51 (t, 1H, *J* = 7.2 Hz, H-6), 7.73 (t, 1H, *J* = 7.6 Hz, H-7), 7.84 (d, 1H, *J* = 8.4 Hz, H-5), 8.01 (d, 1H, *J* = 7.6 Hz, H-8), 8.25 (s, 1H, H-3), 8.30 (s, 1H, H-4); ^{13}C-NMR (δ, ppm): 122.63, 126.16, 128.45, 130.08, 132.10, 132.82, 136.07, 140.32, 142.46, 147.86, 162.18; MS (m/z): 212 (M^+). Analysis: calcd. for $C_{11}H_8N_4O$ (212.2): C, 62.25; H, 3.80; N, 26.41%; found: C, 62.18; H, 3.85; N, 26.43%.

6-Chloro-1-carboamidopyrazolo[3,4-b]quinoline (3b)

Yield: 92%; m.p. 258-260°C; R_f: 0.78, IR (cm^{-1}): 3380, 3315 (NH_2), 1664 (C=O), 1608 (C=N), 1575 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 6.34 (s, 2H, NH_2), 7.62 (d, 1H, *J* = 2.4 Hz, H-5), 7.76 (dd, 1H, *J* = 8.0, 2.4 Hz, H-7), 7.90 (d, 1H, *J* = 8.0 Hz, H-8), 8.22 (s, 1H, H-3), 8.34 (s, 1H, H-4); MS (m/z): 246 (M^+). Analysis: calcd. for $C_{11}H_7N_4OCl$ (246.7): C, 53.66; H, 2.87; N, 22.74%; found: C, 53.48; H, 2.85; N, 22.76%.

6-Methoxy-1-carboamidopyrazolo[3,4-b]quinoline (3c)

Yield: 96%; m.p. 238-240°C; R_f: 0.80, IR (cm^{-1}): 3365, 3290 (NH_2), 1668 (C=O), 1610 (C=N), 1570 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.76 (s, 3H, OCH_3), 6.30 (s, 2H, NH_2), 7.18 (d, 1H, *J* = 2.8 Hz, H-5), 7.42 (dd, 1H, *J* = 7.6, 2.8 Hz, H-7), 7.84 (d, 1H, *J* = 7.6 Hz, H-8), 8.28 (s, 1H, H-3), 8.42 (s, 1H, H-4); MS (m/z): 242 (M^+). Analysis: calcd. for $C_{12}H_{10}N_4O_2$ (242.2): C, 59.50; H, 4.17; N, 23.14. Found: C, 59.68; H, 4.15; N, 23.16.

6-Methyl-1-carboamidopyrazolo[3,4-b]quinoline (3d)

Yield: 92%; m.p. 235-238°C; R_f: 0.74, IR (cm^{-1}): 3367, 3285 (NH_2), 1676 (C=O), 1611 (C=N), 1570 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 3H, CH_3), 6.22 (s, 2H, NH_2), 7.53 (d, 1H, *J* = 2.4 Hz, H-5), 7.67 (dd, 1H, *J* = 7.2, 2.4 Hz, H-7), 7.94 (d, 1H, *J* = 7.2 Hz, H-8), 8.20 (s, 1H, H-3), 8.28 (s, 1H, H-4); MS (m/z): 226 (M^+). Analysis: calcd. for $C_{12}H_{10}N_4O$ (226.2): C, 63.72; H, 4.46; N, 24.77%; found: C, 63.82; H, 4.44; N, 24.76%.

1-(2,4-Dinitrophenyl)pyrazolo[3,4-b]quinoline (3e)

Yield: 94%, m.p. > 300°C, R_f: 0.86, IR (cm^{-1}): 1618 (C=N), 1586 (C=N), 1524 (-NO_2), 1325 (-NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 7.54 (t, 1H, *J* = 7.2 Hz, H-6), 7.79 (t, 1H, *J* = 7.6 Hz, H-7), 7.87 (d, 1H, *J* = 8.4 Hz, H-5), 8.05 (d, 1H, *J* = 7.6 Hz, H-8), 8.18 (d, 1H, *J* = 8.4 Hz, H-6, phenyl ring), 8.38 (s, 1H, H-4), 8.69 (d, 1H, *J* = 8.4 Hz, H-5, phenyl ring), 8.79 (s, 1H, H-3), 9.04 (s, 1H, H-3, phenyl ring); MS (m/z): 335 (M^+). Analysis: calcd. for $C_{16}H_9N_5O_4$ (335.3): C, 57.31; H, 2.70; N, 20.89%; found: C, 57.19; H, 2.72; N, 20.87%.

6-Chloro-1-(2,4-dinitrophenyl)pyrazolo[3,4-b]quinoline (3f)

Yield: 84%, m.p. >.300°C, R_f: 0.84, IR (cm^{-1}): 1615 (C=N), 1582 (C=N), 1520 (-NO_2), 1321 (-NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 7.70 (d, 1H, *J* = 2.4 Hz, H-5), 7.82 (dd, 1H, *J* = 8.0, 2.4 Hz, H-7), 7.96 (d, 1H, *J* = 8.0 Hz, H-8), 8.23 (d, 1H, *J* = 8.4 Hz, H-6, phenyl ring), 8.42 (s, 1H, H-4), 8.56 (s, 1H, H-3), 8.71 (d, 1H, *J* = 8.4 Hz, H-5, phenyl ring), 9.06 (s, 1H, H-3, phenyl ring); MS (m/z): 369 (M^+). Analysis: calcd. for $C_{16}H_8N_5O_4Cl$ (369.7): C, 52.03; H, 2.18; N, 18.97%. found: C, 52.21; H, 2.17; N, 18.95%.

6-Methoxy-1-(2,4-dinitrophenyl)pyrazolo[3,4-b]quinoline (3g)

Yield: 94%, m.p. > 300°C, R_f: 0.82, IR (cm^{-1}): 1620 (C=N), 1591 (C=N), 1522 (-NO_2), 1326 (-NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.80 (s, 3H, OCH_3), 7.22 (d, 1H, *J* = 2.8 Hz, H-5), 7.44 (dd, 1H, *J* = 7.6, 2.8 Hz, H-7), 7.88 (d, 1H, *J* = 7.6 Hz, H-8), 8.20 (d, 1H, *J* = 8.4 Hz, H-6, phenyl ring), 8.36 (s, 1H, H-4), 8.52 (s, 1H, H-3), 8.62 (d, 1H, *J* = 8.4 Hz, H-5, phenyl ring), 8.96 (s, 1H, H-3, phenyl ring); MS (m/z): 365 (M^+). Analysis: calcd. for $C_{17}H_{11}N_5O_5$ (365.3): C, 55.89; H, 3.03; N, 19.17%; found: C, 55.72; H, 3.01; N, 19.15%.

6-Methyl-1-(2,4-dinitrophenyl)pyrazolo[3,4-b]quinoline (3h)

Yield: 94%, m.p. 271-272°C, R_f: 0.78, IR (cm^{-1}): 1622 (C=N), 1594 (C=N), 1524 (-NO_2), 1326 (-NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.48 (s, 3H, CH_3), 7.58 (d, 1H, *J* = 2.4 Hz, H-5), 7.73 (dd, 1H, *J* = 7.2, 2.4 Hz, H-7), 7.96 (d, 1H, *J* = 7.2 Hz, H-8), 8.26 (d, 1H, *J* = 8.4 Hz, H-6, phenyl ring), 8.46 (s, 1H, H-4), 8.58 (s, 1H, H-3), 8.65 (d, 1H, *J* = 8.4 Hz, H-5, phenyl ring), 8.99 (s, 1H, H-3, phenyl ring); MS (m/z): 349 (M^+). Analysis: calcd. for $C_{17}H_{11}N_5O_4$ (349.3): C, 58.45; H, 3.17; N, 20.05%; found: C, 58.27; H, 3.15; N, 20.08%.

Animals

Wistar rats and albino mice used in the present study were housed and kept in accordance with the

Hamdard University Animal Care Unit, which applies the guidelines and rules laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Wistar rats and albino mice of either sex weighing 120-150 g and 22-25 g, were used. The animals were housed in groups of six and acclimatized to room conditions for at least 2 days before the experiments. Food and water were freely available up to the time of experiments. The food was withdrawn 12h/24h before the start of experiment, but free access to water was allowed.

Anti-inflammatory activity

The synthesized compounds were evaluated for their anti-inflammatory activity using carrageenan-induced paw edema method of Winter et al. (28). The animals were randomly divided into groups of six. Group I was kept as control, and received only 0.5% carboxymethyl cellulose (CMC) solution. Group II was kept as standard and received ibuprofen (20 mg/kg *p.o.*). Carrageenan solution (0.1% in sterile 0.9% NaCl solution) in a volume of 0.1 mL was injected subcutaneously into the subplantar region of the right hind paw of each rat, 30 min after the administration of the test compounds and standard drugs. The paw volume was measured by saline displacement shown on screen of digital plethysmometer (Ugo Basile) at 2 and 3 h after carrageenan injection. Thus the edema volume in control group (V_c) and edema volume in groups treated with test compounds (V_t) was measured and the percentage inhibition of edema was calculated using the formula:

$$\text{Anti-inflammatory activity (\% inhibition)} = = [(V_c - V_t)/ V_c] \times 100$$

where, V_c = paw volume of control group, V_t = paw volume of test group.

Analgesic activity

Compounds which showed anti-inflammatory activity above 70% of ibuprofen inhibition were screened for analgesic activity. Analgesic activity was done by acetic acid-induced writhing method (29) at 20 mg/kg using ibuprofen as reference drug. Swiss albino mice (25–30 g) of either sex were divided into groups of six in each. A 1% aqueous acetic acid solution (*i.p.* injection in a volume of 0.1 mL) was used as writhing induced agent. Mice were kept individually in the test cage, before acetic acid injection and habituated for 30 min. Screening of analgesic activity was performed after *p.o.* administration of test drugs at a dose of 20 mg/kg. Group I was taken as control and received CMC suspension only, group II received reference drug ibuprofen and rest of the groups were treated with test drugs (20 mg/kg) suspended in 1.0% CMC orally. After 1 h of drug administration, 0.10 mL of 1% acetic acid solution was given to mice intraperitoneally. Stretching movements consisting of arching of the back, elongation of body and extension of hind limbs were counted for 5–15 min after acetic acid injection. The analgesic activity was expressed in terms of percentage inhibition.

$$\%\text{Analgesic activity} = \{(n - n')/ n\} \times 100$$

where, n = mean number of writhes of control group, n' = mean number of writhes of test group.

Acute ulcerogenesis

Acute ulcerogenesis test was done according to method of Cioli et al. (30). Albino rats (150–200 g) were divided into different groups consisting of six animals in each group. Ulcerogenic activity was evaluated after *p.o.* administration of test compounds or ibuprofen at the dose of 60 mg/kg. Control rats received *p.o.* administration of vehicle (suspension of 1% methylcellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed with normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in normal saline. The mucosal damage was examined by means of a magnifying glass. For each stomach the mucosal damage was assessed according to the following scoring system: 0.5: redness, 1.0: spot ulcers, 1.5: hemorrhagic streaks, 2.0: ulcers > 3 but < 5, 3.0: ulcers > 5. The mean score of each treated group minus the mean score of control group was regarded as severity index of gastric mucosal damage.

Lipid peroxidation

Lipid peroxidation studies were carried out as a measure of damage to gastric mucosa. It was determined according to the method of Ohkawa et al. (31). After screening for ulcerogenic activity, the gastric mucosa were scraped with two glass slides and 10% of that tissue was homogenized at 10,000 rpm in 1.8 mL of 1.15% ice-cold KCl solution. 1 mL of suspension medium was taken from the supernatant, 0.5 mL of 30% trichloroacetic acid (TCA) followed by 0.5 mL of 0.8% thiobarbituric acid (TBA) reagent were added to it. The tubes were covered with aluminium foil and kept in a shaking water bath for 30 min at 80°C. After 30 min, tubes were taken out and kept in ice cold water for 10 min.

These were then centrifuged at 3000 rpm for 15 min. The absorbance of supernatant was read at 540 nm at room temperature against the blank on UV spectrophotometer.

The standard curve was used for estimating the concentration of malondialdehyde (MDA) prepared by using 1,1,3,3,-tetraethoxypropane. The results are presented as nM MDA/mg of protein (Fig. 1).

Statistical analysis

Data were expressed as the mean ± standard error (S.E.) of the mean. For a statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA) with *post hoc* analysis. The Tukey-Kramer test *post hoc* was applied to identify significance among groups; $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Chemistry

Eight new pyrazolo[3,4-b]quinolines (**3a**-**h**) were synthesized as outlined in Scheme 1. The title compounds were synthesized by refluxing 3-chloroquinoline-3-carbaldehyde (**2a**-**d**) with semicarbazide or 2,4-dinitophenylhydrazine with stirring in water under microwave irradiation. The boiling water under microwave irradiation behaves as hydrophobic medium and helps to form homogenous mass with reagents and accelerates the rate of reaction. The synthesized compounds under microwave irradiation give the same compound as that of conventional method but with lesser time, higher yield, free from impurities and eco-friendly-economic condition.

In general, the IR spectral data of all the compounds showed characteristic peaks around 3375, 3310 cm^{-1} for NH_2, 1667 cm^{-1} for C=O, 1610 and 1580 cm^{-1} for C=N supports the formation of 1-carboxamido-pyrazolo[3,4-b]quinoline derivatives. Similarly, characteristics peaks around 1618 and 1586 cm^{-1} for C=N, 1524 and 1325 cm^{-1} for NO_2 also confirms the formation of 1-(2,4-dinitrophenyl)pyrazolo[3,4-b]quinoline derivatives.

In ^{1}H-NMR spectral data, all the compounds showed characteristic peak at appropriate δ values. The structure of the compounds was further supported by mass spectral data. The synthesized compounds gave M^+ peak in reasonable intensities.

Pharmacology

The *in vivo* anti-inflammatory activity of the synthesized compounds was evaluated by carageenan induced rat paw edema method as described by Winter et al. (28). Ibuprofen was used as a standard. Three of the eight tested compounds showed statistically significant anti-inflammatory activity. Compounds **3b**, **3c** and **3g** have shown the maximum percentage of anti-inflammatory activity i.e., 61.38, 67.07 and 63.41%, respectively. The compound **3f**, also showed promising anti-inflammatory activity.

The obtained pharmacological results revealed that the 1-carboxamido-pyrazolo[3,4-b] quinoline

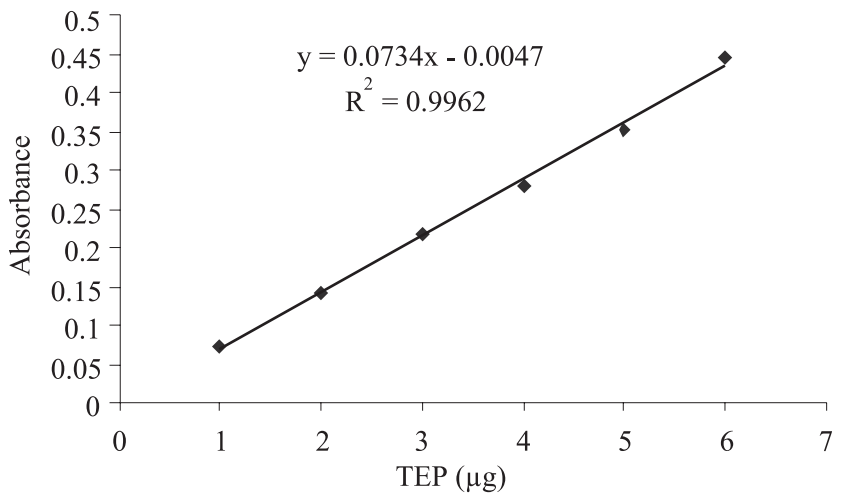


Figure 1. The standard curve for estimation of the concentration of malondialdehyde prepared by using 1,1,3,3,-tetraethoxypropane (TEP). The results are presented as nM MDA/mg of protein

Table 1. Anti-inflammatory and analgesic activity along with ulcerogenic and lipid peroxidation effect of the synthesized compounds **3a-h**.

Compound	% Inhibition ± SEM[b]		% Inhibition with respect to ibuprofen		Severity index[a]	Lipid peroxidation[†]	Analgesic activity (writhing test)
	After 2 h	After 3 h	After 2 h	After 3 h			% protection
Control	-	-	-	-	0.00 ± 0.00	0.239 ± 0.007[b,***]	-
Ibuprofen	69.52 ± 1.26	78.04 ± 0.71	100	100	0.92 ± 0.15**	0.597 ± 0.007[a,***]	61.89
3a	33.09 ± 1.13***	50.00 ± 1.13***	47.95	64.06	-	-	-
3b	46.42 ± 2.01***	61.38 ± 1.62***	67.27	78.63	0.34 ± 0.17	0.341 ± 0.008[ab,***]	42.65
3c	54.52 ± 1.45***	67.07 ± 0.71***	79.01	85.91	0.17 ± 0.11	0.327±0.009[ab,***]	47.09
3d	28.57 ± 1.22***	44.51 ± 2.11***	41.40	57.01	-	-	-
3e	35.00 ± 1.32***	49.59 ± 1.12***	50.72	63.52	-	-	-
3f	38.09 ± 2.23***	56.50 ± 1.39***	55.20	72.37	-	-	-
3g	45.71 ± 1.52***	63.41 ± 1.41***	66.24	81.22	0.17 ± 0.11	0.347 ± 0.005[ab,***]	44.35
3h	24.52 ± 2.00***	42.27 ± 1.43***	35.53	54.14	-	-	-

*p < 0.05; **p < 0.01; ***p < 0.001. [a]Relative to their respective control and data were analyzed by one-way ANOVA followed by Tukey test for n = 6. [b]Relative to the standard (ibuprofen) and data were analyzed by one-way ANOVA followed by Tukey test for n = 6. [†]Lipid peroxidation activity is expressed as nmoles of MDA / mg of protein

derivatives have better anti-inflammatory-analgesic profile as compared to 1-(2,4-dinitrophenyl)pyrazolo[3,4-b]quinoline derivatives. Furthermore, the activity is higher in case of substitution with negative hydrophobic and electronic constants (methoxy substitution) as compared to that of the substitutions with both positive or negative hydrophobic and electronic constants; as was seen with the methyl and chloro substitution. However, the activity was found to decline in compounds with no substitution.

Test compounds that exhibited above 75% of anti-inflammatory activity of ibuprofen (**3b**, **3c** and **3g**) were further evaluated for their analgesic and ulcerogenic activity and lipid peroxidation.

The compounds were evaluated for analgesic effects using acetic acid induced writhing method. The results of analgesic activity (Table 1) indicated that compounds **3b**, **3c** and **3g** showed 42.65, 44.35 and 47.09% protection against acetic acid-induced writhings. The analgesic activity of compounds followed same pattern as anti-inflammatory activity.

The tested compounds showed low ulcerogenic activity ranging from 0.17 ± 0.11 to 0.34 ± 0.17 whereas the standard drug ibuprofen showed high severity index of 0.92 ± 0.15. The maximum reduction in ulcerogenic activity (0.17 ± 0.11) was found in the compounds **3c** and **3g**. The LPO was measured as nmoles of malondialdehyde (MDA)/mg of protein. Ibuprofen exhibited high lipid peroxidation 0.597 ± 0.007 whereas control group showed 0.239 ± 0.002.

Thus, these compounds showed superior GI safety profile along with reduction in LPO in comparison with ibuprofen. Results are presented in Table 1.

As our interest was to develop pyrazole derivatives as safer anti-inflammatory and analgesic agents using eco-friendly and economic method, the synthesized compounds were found potent as anti-inflammatory and analgesic agent with lesser GI irritation. Compound **3c** was found to be most active potent anti-inflammatory and analgesic agent.

CONCLUSION

Title compounds were successfully synthesized by following Scheme 1. The devel-

oped one-pot microwave assisted synthesis provides a safe, economic and convenient synthetic route for bioactive pyrazolo[3,4-b]quinolines.

The pharmacological evaluation showed that the compounds are good at inhibiting edema induced by carrageenan and also showed prominent analgesic activity with lesser GI toxicity as indicated by severity index and LPO values.

Among the newer derivatives, it can be concluded that compound **3c** can be taken as lead to develop safer anti-inflammatory analgesic agents. It is conceivable that these derivatives could be further modified to develop potent and safer anti-inflammatory and analgesic agents. Further studies to acquire more information about quantitative structure-activity relationship (QSAR) are in progress in our laboratory.

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