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SYNTHESIS, CHARACTERIZATION AND ANTIINFLAMMATORY ACTIVITY OF SOME NOVEL QUINOLINE DERIVATIVES

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ABSTRACT

The Inflammation is a serious health problem in industrialized country due increase in pollution. In the present study a series of new quinoline derivatives (3a-l) were synthesized and evaluated for their anti-inflammatory activity by using the model of carrageenan induced mice paw edema in adult albino rat on comparison with standard Indomethacin. The maximum anti-inflammatory activity was recorded by the compound 3i and 3j having 71% protection of edema followed by compound 3c and 3d showed 69%, compound 3b and 3e having 64% protection of edema. The compound 3i and 3j showed more percentage protection of edema with compared with standard drug Indomethacin (75%). It has been found that the extent of increase in paw volume reduces significantly up to 5 hrs when compared with solvent control.

KEYWORDS: Anti-inflammatory activity, Carrageenan, Indomethacin, Quinoline.

INTRODUCTION

Inflammatory reaction, typically characterized by redness, swelling, heat, and pain, is one of the most important host defense mechanisms against invading pathogens. However, persistent or over-inflammation leads to tissue damage and possibly the failure of organs. Pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β) are produced in large quantities by activated macrophages/monocytes that stimulate cellular responses via increasing prostaglandins (PGs) and reactive oxygen species (ROS). Additionally, lipid peroxidation (malondialdehyde, MDA) is produced by free radicals attacking the cell membranes. Thus, inflammatory effect results in the accumulation of MDA.[1]

Among all the widely used therapeutic agents Nonsteroidal anti-inflammatory drugs (NSAIDs) primarily important for the treatment of inflammation and pain. Most currently used nonsteroidal anti-inflammatory drugs (NSAIDs) have limitations for therapeutic use since they cause gastrointestinal and renal side effects that are inseparable from their pharmacological activities. Therefore, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years.

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties.[2] Quinolines are nitrogenous bicyclic systems in the area of heterocyclic chemistry. Historically quinolines are the most important antimalarial drugs. The quinoline ring system is found in a myriad of naturally occurring as well as medicinally active synthetic drug substances.Moreover, the quinoline ring system occurs in various natural products, especially in alkaloids and is often used for the design of many synthetic compounds with diverse pharmacological properties. There are number of natural products of quinoline skeleton used as a medicine or employed as lead molecule for the development newer and potent molecules.[3]

The search for new drugs which treat both infectious and inflammatory states without side effects remains a major challenge in biomedical studies. The advanced studies are enriched with progressive findings about the preparation and medicinal properties of heterocycles bearing quinoline moiety are reported to display a broad spectrum of pharmacological effects such as anti-malarial,[4] anti-inflammatory,[5-7] anti-asthmatics,[8] antibacterial,[9] antihypertensive[10] and tyrosine kinase PDGF-RTK inhibiting agents, anti-protozoal,[11] anti-fungal,[12] anti-platelet, anti-tubercular,[13] anti-helmintic,[14] anti-alzhemeric,[15] anti-HIV,[16] anti-cancer,[17] anti oxidant, anti-atherosclerotic,[18] antiamoebic[19] antiviral,[20] antipsychotic,[21] and anti-anxiety agents.

In light of the aforementioned findings and our interest in the synthesis of novel heterocycles of biological importance, we have synthesized some new quinoline derivatives incorporated carboxamide linkage to evaluate their anticipated antiinflammatory activities.

MATERIAL AND METHOD

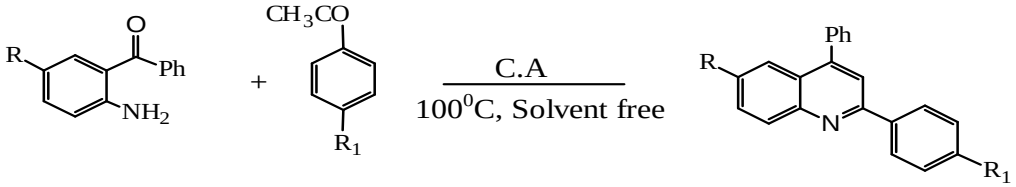
Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (MERCK). Visualization was made with UV light (254 and 365nm) or

with an iodine vapor. IR spectra were recorded on a SHIMADZU-FOURIER TRANSFORM INFRA RED **(**FTIR)-8400 Spectrophotometer using KBr disc. 1H NMR spectra were recorded on a BRUKER DPX-400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. The mass spectral data were obtained with a SHIMADZU-GCMS-QC-2010**.**

Experimental

General Procedure for the synthesis of 2,4-disubstituted of Quinolines[3a-l]

A mixture of acetophenone (0.1ml, 1.0 mmol), 2-aminobenzophenone (0.1972gm, 1.0 mmol), and 0.5 equi (0.09606 gm) of citric acid were heated on an oil bath at 100°C for 4-6 hr. After completion of the reaction monitered by TLC, extracted with dichloromethane the solid product was purified by column using solvent system (hexane : EtOAc 9:1) and product was recrystallized from ethanol to afford substituted quinolines % of yields and melting points were calculated. All the products were characterized by IR, mass and ^{1}H NMR spectral data.



1a&b
R=H,Cl

2a-f
R_1=H, OH, Cl, Br, OCH_3, NO_2

3a-l

Acute oral toxicity - acute toxic class method[22]

Acute oral toxicity defines to those adverse effects occurring within a short time following oral administration of a single dose of a substance or multiple doses given within 24 hours. The toxicity of the compounds was tested using a stepwise procedure, each step using three rats of a single sex. The rats were fasted prior to dosing (food was with held but not water) for 3-4 hours. After 4 hours, the synthesized compounds were suspended in Tween – 80 and administered orally in a dose of 2000 mg/kg body weight. The animals were kept under observation for 14 days. As no mortality was observed with the above dose, a dose of 200 mg/kg body weight was selected for the evaluation of anti inflammatory activity.

Screening for Anti-Inflammatory activity[23]

Carrageenan-induced acute paw oedema in rats

Rats of either sex were randomly divided into 6 groups. Each group composed of 6 animals.

Group. 1: Received 1 ml/kg body weight (sub-planter regions) of carrageenan 1% w/v. This group served as control.

Group 2: Received 100 mg/kg body weight (p.o) of synthesized compound 3b.

Group 3: Received 100 mg/kg body weight (p.o) of synthesized compound 3c.

Group 4: Received 100 mg/kg body weight (p.o) of synthesized compound 3d.

Group 5: Received 100 mg/kg body weight (p.o) of synthesized compound 3e.

Group 6: Received 100 mg/kg body weight (p.o) of synthesized compound 3h.

Group 7: Received 100 mg/kg body weight (p.o) of synthesized compound 3i.

Group 8: Received 100 mg/kg body weight (p.o) of synthesized compound 3j.

Group 9: Received 100 mg/kg body weight (p.o) of synthesized compound 3k.

.Group 10: Received 10 mg/kg body weight (i.p) of indomethacin. This group served as standard control.

After half an hour of test compounds administration 0.1 ml of carrageenan was injected into the lateral malleolus of the sub-planter region of the left hind paw. The inflammation of the paw was measured for all animals by using plethysmograph before the administration of carrageenan and after the administration of carrageenan at 60, 120, 180, 240 and 300 min.

The percentage protection was calculated as follows

$$\% \text{ Protection} = \frac{\text{Control-test}}{\text{Control}} \times 100$$

Spectral data for synthesized compounds[3a-l]

2,4 diphenyl quinolone[3a]: Yellow solid; Yield: 85%; m.p. 112-114^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19-8.23(m, 3H,Ar-H), 7.38-7.92(m, 12H,Ar-H); IR(KBr): 1588(C=N), 1488(C=C), 1357(C-N)cm^{-1}; Mass (ESI-MS): 282(M^+ +1).

2-(4-hydroxyphenyl)-4-phenyl quinolone[3b]: Yellow solid; Yield: 78%; m.p. 137^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.38-7.99 (m, 7H,Ar-H), 6.74-6.83 (m, 7H,Ar-H); IR (KBr): 1590(C=N), 1545(C=C), 1353(C-O in C-OH), 1279(C-N) cm^{-1}; Mass (ESI-MS): 298(M^+ +1).

2-(4-chlorophenyl)-4-phenyl quinolone[3c]: White solid; Yield: 78%; m.p. 126^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ8.15 (d, J = 8.684, 2H,Ar-H), 7.42-7.84 (m.12H, Ar-H).; IR (KBr): 1589(C=N), 700(C-Cl), 1543(C=C), 1353(C-N) cm^{-1}; Mass (ESI-MS): 316(M^+ +1).\

2-(4-bromophenyl)-4-phenyl quinolone[3d]

Yellow solid; Yield: 76%; m.p. 138^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-8.18(m, 2H,Ar-H), 7.32-7.909(m, 12H, Ar-H); IR (KBr): 1590(C=N), 1543(C=C), 584(C=Br), 1262(CN) cm^{-1}; Mass (ESI-MS): 298(M^+ +1).

2-(4-methoxyphenyl)-4-phenyl quinolone[3e]

White solid; Yield: 70%; m.p. 124^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d,J=8.8Hz,1H,Ar-H),7.31-7.82(m,4H,Ar-H); 6.97-7.03(m,9H,Ar-H), 3.89 (3H, S,OCH_3 ; IR (KBr): 1600(C=N), 1511 (C=C), 2841(C-H in O-CH3), 1074 (C-O in CH3) 1256(C-N) cm^{-1}; Mass (ESI-MS): 316(M^+).

2-(4-nitrophenyl)-4-phenyl quinolone[3f]

White solid; Yield: 74%; m.p. 161^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ8.34-8.43(m,2H,Ar-H), 8.21(d,J=8.30Hz.1H, Ar-H), 7.84(1H,S), 7.73-7.78(m,3H,Ar-H), 7.28-7.89(m,7H,Ar-H); IR(KBr): 1589(C=N), 1461(C=C), 1512(N=O), 1261(C-N) cm^{-1}; Mass (ESI-MS): 327(M^+).

6 -chloro-2,4 diphenyl quinolone[3g]

Yellow solid; Yield: 84%; m.p. 127 ^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.46-7.59(m, 5H); 7.66 -7.698(m, 4H); 7.894(S, 1H), 8.16-8.22(m, 4H) ; IR(KBr): 1588(C=N), 1488(C=C), 1379(C-N)cm^{-1}; Mass (ESI-MS): 316(M^+).

6-chloro-2-[4 hydroxphenyl]–4-phenyl quinolone[3h]

Yellow solid; Yield: 76%; m.p. 157 ^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 6.930 (d,J=8.30,2H), 7.560-7.668(m,5H),7.77-7.81(m,6H), 8.11(d,J=8.30; 2H); IR(KBr): 1590(C=N), 1545(C=C), 1359(C-Oin C-OH)cm^{-1}; Mass (ESI-MS): 332(M^+).

6-chloro-2-[4 chlorophenyl]–4-phenyl quinolone[3i]

White solid; Yield: 76%; m.p. 157 ^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.1-8.3(m,5H), 7.82 7.91 (d,J=7.01,3H) 7.5-7.75(m,5H); IR(KBr): 1591(C=N), 700(C-Cl), 1540(C=C), 1353(C-N) cm^{-1} Mass (ESI-MS): 350(M^+).

6-chloro-2-[4 bromophenyl]–4-phenyl quinolone[3j]: Yellow solid; Yield: 82%; m.p. 186 ^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.1-8.2(m,5H), 7.5 7.75 (m,5H), 7.8-7.9(d,3H,J=7.02); IR(KBr): 1586(C=N), 1539(C=C), 586(C-Br), 1266(C-N) cm^{-1} Mass (ESI-MS): 350(M^+).

6-chloro-2-[4 methoxyphenyl]–4-phenyl quinolone[3k]

White solid; Yield: 72%; m.p. 148 ^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): 3.8(S,3H),6.75(d,J=6.79,2H),6.8-7.09(m,2H),7.2-7.4(m,4H),8.2-8.3(m,2H); IR(KBr): 1602(C=N), 1521(C=C), 2929(C-H in CH_3), 1080(C-Oin CH_3), 1242(C-N) cm^{-1}; Mass (ESI-MS): 346(M^+).

6-chloro-2-[4 nitrophenyl]–4-phenyl quinolone[3l]

White solid; Yield: 74%; m.p. 176^{O}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ8.34-8.43(m,2H,Ar-H), 8.21(d,J=8.30Hz.1H, Ar-H), 7.84(1H,S), 7.73-7.78(m,3H,Ar-H), 7.28-7.89(m,7H,Ar-H); IR(KBr): 1589(C=N), 1461(C=C), 1512(N=O), 1261(C-N) cm^{-1}; Mass (ESI-MS): 362(M^+)

RESULT AND DISCUSSION

Acute oral Toxicity – Acute Toxic Class Method

Acute oral toxicity studies were performed based on organization of economical cooperation and development guidelines for the synthesized compounds **3b, 3c, 3d, 3e, 3h, 3i, 3j, 3k** and. No toxicity or death was observed for all the compounds on administration of 2000mg/kg body weight. So further anti-inflammatory testing was carried out at 100mg/kg body weight in which no death was observed. Form this study, the compounds **3b, 3c, 3d, 3e, 3h, 3i, 3j, 3k** had no mortality even at 2000mg/kg body weight. So these compounds might consider as safe(X-unclassified).

Anti-inflammatory Studies

Among the twelve synthesized compounds eight compounds **3b, 3c, 3d, 3e, 3h, 3i, 3j, 3k** were screened for anti-inflammatory activity against carrageenan induced paw oedema using indomethacin as standard drug whose data was given in table-1.

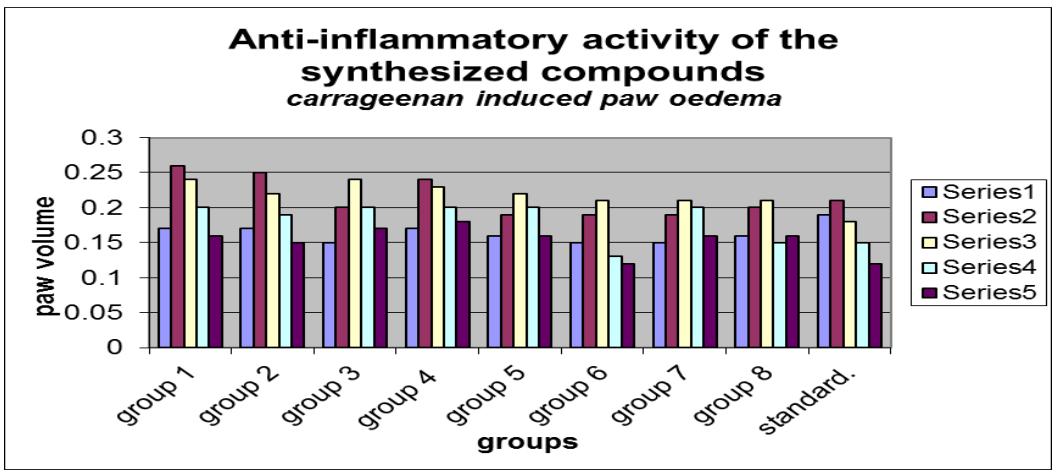
And all the compounds exhibited significant anti-inflammatory activity. Among the eight compounds **3i** and **3j** at 200 mg/kg (p.o.) showed significant reduction in paw oedema. when compared to the other compounds. The compound **3i** and **3j** showed 71.4% protection, compound **3c & 3d** showed 69% and compound **3b** and **3e** showed 64% protection. The standard indomethacin showed 75% protection. The compounds did not cause mortality up to 2000 mg/kg in acute oral toxicity studies (OECD-423 guidelines) and were considered as safe (X-unclassified).

Table. 1: Carrageenan induced Paw Oedema.

Group	1 hr	2 hr	3 hr	4 hr	5 hr
Group I Control 1% CMC (1 ml/kg)	0.16 ± 0.003	0.22 ± 0.006	0.3 ± 0.005	0.38 ± 0.004	0.42 ± 0.005
Group II Compound – **3b** (200 mg/kg)	0.17 ± 0.002** (7.82%)	0.26 ± 0.006** (18.40%)	0.24 ± 0.004** (34.37%)	0.20± 0.004*** (52.61%)	0.16 ± 0.006*** (64%)
Group III Compound – **3c** (200 mg/kg)	0.17 ± 0.003** (7.82%)	0.25 ± 0.003** (26.00%)	0.22± 0.003*** (48.72%)	0.19± 0.005*** (61.04%)	0.15 ± 0.004*** (69%)
Group IV Compound – **3d** (200 mg/kg)	0.15 ± 0.003** (17.66%)	0.20 ± 0.006** (27.92%)	0.24± 0.004*** (51%)	0.20± 0.003*** (63.88%)	0.17 ± 0.004*** (69%)
Group V Compound – **3e** (200 mg/kg)	0.17 ±0.002** (18.38%)	0.24 ±0.002** (28.92%)	0.23±0.004*** (44%)	0.20± 0.005*** (56.72%)	0.18 ± 0.004*** (64%)
Group VI Compound **3h** (200mg/kg)	0.16 ± 0.003** (18.66%)	0.19 ± 0.003** (28.64%)	0.22 ± 0.003** (36.73%)	0.20± 0.004*** (48.48%)	0.16 ± 0.003*** (66%)
Group VI Compound – **3i** (200 mg/kg)	0.15 ± 0.002** (16.66%)	0.19 ± 0.007** (26.92%)	0.21± 0.003*** (50%)	0.13± 0.004*** (63.88%)	0.12 ± 0.004*** (71.4%)
Group VII Compound – **3j** (200 mg/kg)	0.15 ± 0.004** (16.66%)	0.19 ± 0.004** (26.92%)	0.21 ± 0.004** (34.37%)	0.20± 0.003*** (44.44%)	0.16 ± 0.003*** (71.4%)
Group IX Compound **3k** (200mg/kg)	0.16±0.004** (15.38%)	0.20±0.003** (24.73%)	0.21±0.004*** (38.54%)	0.15± 0.005*** (47.56%)	0.16 ± 0.004*** (61.9%)
Group X Standard Indomethacin (20 mg/kg)	0.19± 0.003*** (5.55%)	0.21± 0.007*** (26.92%)	0.18± 0.005*** (50%)	0.15± 0.003*** (66.66%)	0.12 ± 0.002*** (75%)

All values are mean ± SEM values using 6 animals in each group.

Significant differences with respect to control group was evaluated by ANOVA, Dunnets 't' test. *P < 0.05, **P < 0.01, ***P < 0.001.



CONCLUSION

The present study concluded the beneficial effect of synthesized novel quinoline derivatives in the Carrageenan induced acute inflammation in rats. This study confirms the rational basis for its use in synthesized novel quinoline and its derivatives for the treatment of inflammation in patients. Further pharmacological investigations are under way to characterize active novel quinolone and to establish exact mechanism of inflammation action, which may have fewer side effects. This work, we believe, will be useful for further inflammation research works.

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