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ORIGINAL ARTICLE

Synthesis of novel Thiazolidinones substituted Quinoline derivatives as potent Anti-inflammatory and Analgesic agents

Sujeet Kumar Gupta* and Ashutosh Mishra
*Department of Pharmaceutical Chemistry, Hygia Institute of Pharmaceutical Education and Research, Lucknow-206020
Department of Pharmaceutical Chemistry, Acharya Narendra Deo College of Pharmacy, Babhnan, Gonda - 271313
*** Email:** sujeet20gupta2@gmail.com

ABSTRACT
A series of thiazolidinones substituted quinoline derivatives (6a-e) was synthesized starting from acetanilide. All the synthesized compounds were evaluated for their anti-inflammatory activity and analgesic activity by using carragennan induced rat paw edema model and Eddy's hot plate method respectively. The structure of the final analogues has been confirmed on the basis of elemental analysis, FTIR, 1H NMR, 13C NMR and mass spectra. Amongst all the synthesized compounds, 3-(4-methoxyphenyl)-2-(tetrazolo [1, 5-a] quinolin-4-yl)thiazolidin-4-one (6b) and 3-(2-methoxyphenyl)-2 (tetrazolo [1,5-a]quinolin-4-yl)thiazolidin-4-one (6a) showed significant anti-inflammatory activity as evidenced by % inhibition (54.19 % & 53.00 % inhibition). All the values of elemental analysis, 1H NMR, 13C NMR and mass spectra were found to be prominent. In conclusion, compounds (6b and 6a) emerged out as potent anti-inflammatory and analgesic agents.
Keywords: Vilsmeier-Haack reaction; Quinoline; thiazolidinones; Anti-inflammatory; Analgesic agents;

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INTRODUCTION

Inflammation, a complex defense mechanism is a marker of many pathological states such as gout, rheumatoid arthritis, osteoarthritis and Alzheimer's disease (AD) [1]. Throughout inflammation the body reacts to different injuries by assembling leukocytes and local fluids which ultimately eliminate the noxious stimulus. In pathological conditions, the inflammatory cells do not properly repair the development of persistent damaged tissue [2, 3]. Throughout the inflammatory process, some important mediators are released *viz.* histamine and serotonin. During inflammation, histamine is concerned in leukocyte adhesion to the vascular endothelium through the expression of P-selectin on the endothelial cell surface, sequestration of leukocytes at the inflammatory site and vasodilatation [4]. Carrageenan, a sulphated polysaccharide produces edema and inflammation. Anti-inflammatory activities of different test substances have been assessed utilizing carrageenan-induced paw edema model which is an acute model of inflammation [5]. Carrageenan induces edema and inflammation in two phases. In the early phase which lasts around 1 h, there is release of histamine, serotonin, bradykinin and to some amount prostaglandins. Throughout the second phase *viz.* the delayed phase (after 1 h), there is constant polymorphonuclear (PMN) leucocyte infiltration and generation of the prostaglandin [6-8]. Additionally, release of nitric oxide (NO), release of PMN leucocyte-derived free radicals, interleukin-1b (IL-1) and tumor necrosis factor (TNF-a) also takes place in the delayed phase [9,10].

Thus, there is a continuous need for the development of compounds with a safe anti-inflammatory profile. The synthesis of various hetero annulated Quinoline derivatives have attracted considerable attention in recent years as this class of compounds constitute structural frameworks of several naturally occurring compounds displaying a wide range of biological activities such as antituberular [11], antibacterial

[12,13], anti-inflammatory [14], antioxidant [15], antimalarial, diuretic, clastogenic, antimicrobial [16,17], antitubulin [18], antiprion agents [19]. Since quinoline moiety exerts anti-inflammatory and analgesic activities [20], and it has been noticed that introduction of additional heterocyclic rings to the quinoline core tends to exert profound influence in increasing the activity [21, 22]. Previous reports demonstrated that the efficacy and rapidity of the quinoline constructions by new metal-catalized coupling cyclizations or acid catalyzed cycloaddition of appropriate precursors may compete with classical synthesis of quinoline derivatives [23]. In view of these observations and as a part of an ongoing research program on development of newer anti-inflammatory and analgesic agents, the synthesis and pharmacological activities of a series of novel thiazolidinones scaffolds fused with the quinoline derivatives are reported herein.

MATERIALS AND METHODS

Experimental

The melting points were determined in open capillary tubes and were uncorrected. The purity of all the synthesized compounds were checked by TLC on precoated silica gel-G aluminum sheets (Type 60 GF_{254}, Merck) and the spots were detected by exposure to iodine vapors. The infrared (FT-IR) spectra were recorded on 470-Shimadzu infrared spectrophotometer using the KBr disc prepared by pressed pellet technique and υ_{max} is expressed in cm^{-1}. NMR spectra were measured in DMSO-d_6 as solvent at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a BRUKER AVANCE-300 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Spin multiplicities are given as s (singlet), d (doublet), dd (double doublet) and m (multiplet). Mass spectra were obtained on Shimadzu 2010A LC-MS spectrometer. Elemental analysis was carried on Elemental Vario EL III Carlo Erba 1108 and the values were within ±0.04% of the theoretical values. All the solvents were distilled and dried with usual desiccant.

Synthesis of 2-chloro-3-formyl quinoline (**2**)

Phosphorus oxychloride ($POCl_3$) (13.77g, 0.09 mol) was added dropwise to anhydrous dimethyl formamide (DMF) (2.19g, 0.03 mol) at 0-5 ºC & the mixture was stirred for 5 min. Acetanilide (1.35g, 0.01 mol) **(1)** was added to above mixture and refluxed for 8 h at 75-80 ºC. The reaction mixture was first cooled and then poured into crushed ice with stirring; a pale yellow precipitate of 2-chloro-3-formyl quinoline (**2**) was appeared immediately. The precipitate was filtered, washed with water and recrystallized from ethyl acetate to give compound (**2)** [24-26]. Yield 80%; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.73; Light yellow crystal; mp 142-144°C; 1H NMR: δ 6.99 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 10.21 (s, 1H, -CHO).

Synthesis of tetrazolo[1,5-1] quinoline-4-carbaldehyde (3)

A solution of compound **(2)** (0.01 mol) and absolute ethanol (50 mL) were added in sodium azide (0.015 mol) and p-toluenesulphonic acid (0.01 mol) and the reaction mixture was refluxed for 12 h. The completion of the reaction was monitored by TLC. The reaction mixture was poured onto crushed ice under continuous stirring, brown coloured precipitate of **(3)** were appeared, filtered, washed with water and dried compound was recrystallized from acetone [27]. Yield 64 %; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.63; brown colour crystal; mp 137-138°C; 1H NMR: δ 4.67 (s, 1H, Ar-H), 5.08 (s, 1H, Ar-H), 6.48-6.73 (s, 2H, Ar-H), 8.06 (s, 1H, Ar-H), 10.43 (s, 1H, -CHO).

General procedure for the synthesis of *N*-[(Z)tetrazolo[1,5-*a*]quinoline-4-ylmethyllidene] substituted amine (5a-e)

Tetrazolo[1,5-1]quinoline-4-carbaldehyde (**3**) (0.01 mol) and substituted aromatic amine **(4a-e)** (0.01 mol) were added to ethanol (50 mL) with catalytic amount of conc. HCl (2 mL) refluxed for 8 h. The completion of the reaction was monitored by TLC. The reaction mixture was poured onto crushed ice, precipitate was formed and filtered, then washed with water and (**5a-e)** were recrystallized from ethanol.

General method for the synthesis of (6a-e)

A mixture of *N*-[(Z) tetrazolo [1,5-*a*]quinoline-4-yl methyllidene]substituted amine (**5a-e)** (0.01 mol) and catalytic amount of aluminium chloride (0.05 gm) in benzene was taken in Dean Stark apparatus and to it thioglycolic acid (1.40 mL, 0.02 mol) in DMF was added slowly. The resulting mixture was refluxed for 14 h. The benzene was distilled off to get the solid mixture. This was then treated with an excess of 10% w/v sodium bicarbonate solution to remove excess of thioglycolic acid. The solid product thus obtained was filtered, washed with water and recrystallized from ethanol to give compound (**6a-e).**

3-(**2-methoxyphenyl)-2-(tetrazolo [1,5-*a*]quinolin-4-yl) thiazolidin-4-one (6a)** This compound was prepared from 2-methoxy-*N*-((tetrazolo[1,5-*a*]quinolin-4yl)methylene)benzenamine **(5a)** and thioglycolic acid as described above;Yield 59%; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.71;yellow crystal; mp 283-284 °C; FTIR (KBr, ν, cm^{-1}): 3052 (Ar C-H), 1734 (C=O), 1596 (C-N), 752 (C-S); ^{1}H NMR

(300 MHz, DMSO-d_6): 3.82 (s, 3H, OCH_3), 3.42 (d, 2H, CH-S, *J* = 7.5 Hz), 5.96 (s, 1H, CH-N), 7.42 (dd, 2H, Ar-H, *J* = 8.4Hz, 2.4 Hz), 7.54 (dd, 2H, Ar-H *J* = 8.4 Hz, 2.4 Hz), 7.61-8.04 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.9, 52.9, 55.2, 61.3, 121.4, 122.6, 125.4, 126.8, 127.3, 127.7, 128.1, 128.3, 128.9, 130.5, 134.7, 143.8, 152.1, 161.4, 172.6; EIMS (m/z): 377.42 $[M]^+$, 378.43 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{15}N_5O_2S$: C, 60.46; H, 4.01; N, 18.56. Found: C, 60.44; H, 4.02; N, 18.55 %

3-**(4-methoxyphenyl)-2-(tetrazolo [1, 5-*a*] quinolin-4-yl) thiazolidin-4-one (6b)**

This compound was prepared from 4-methoxy-*N*-((tetrazolo[1,5-*a*]quinolin-4yl)methylene)benzenamine (**5b)** and thioglycolic acid as described above; Yield 64%; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.67; yellow crystal; mp 278-279 °C; FTIR (KBr, ν, cm^{-1}): 3042 (Ar C-H), 1735 (C=O), 1593 (C-N), 756 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6): 3.63 (s, 3H, OCH_3), 3.75 (d, 2H, CH-S, *J* = 7.6 Hz), 5.94 (s, 1H, CH-N), 6.84-6.98 (m, 5H, Ar-H), 7.45 (dd, 2H, Ar-H, *J* = 8.4 Hz, 2.4 Hz), 7.56 (dd, 2H, Ar-H *J* = 8.4 Hz, 2.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): 33.6, 54.6, 55.9, 61.8, 111.2, 113.4, 114.7, 114.9, 122.6, 127.3, 127.9, 128.4, 128.9, 130.1, 134.7, 143.8, 152.1, 153.5, 157.5; EIMS (m/z): 377.42 $[M]^+$, 378.41. $[M+1]^+$; Anal. Calcd. for $C_{19}H_{15}N_5O_2S$: C, 60.46; H, 4.01; N, 18.56. Found: C, 60.45; H, 4.03; N, 18.54 %

3-benzyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)thiazolidin-4-one (6c) This compound was prepared from phenyl-*N*-((tetrazolo[1,5-*a*]quinolin-4yl)methylene)methanamine **(5c)** and thioglycolic acid as described above; Yield 54%; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.74; white solid; mp 245-246 °C; FTIR (KBr, ν, cm^{-1}): 3064 (Ar C-H), 1712 (C=O), 1588 (C-N), 762 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6): 2.48 (s, 2H, C-H), 3.27 (d, 2H, CH-S, *J* = 7.4 Hz), 5.88 (s, 1H, CH-N), 7.04-7.82 (m, 4H, Ar-H), 7.95 (dd, 2H, Ar-H, *J* = 8.4 Hz, 2.4), 8.16 (dd, 2H, Ar-H, *J* = 7.8 Hz, 1.8 Hz), 8.28 (dd, 2H, Ar-H, *J*= 7.8 Hz, 1.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): 34.5, 45.7, 53.4, 126.8, 127.4, 127.7, 128.1, 128.6, 128.9, 128.9, 129.1, 130.1, 134.7, 136.5, 152.1, 171.6; EIMS (m/z): 363.11 $[M]^+$, 364.12. $[M+1]^+$; Anal.Calcd. for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38 Found: C, 63.15; H, 4.19; N, 19.39 %

4-(4-oxo-2-(tetrazolo [1,5-*a*]quinolin-4-yl)thiazolidin-3-yl)benzoic acid (6d) This compound was prepared from 4-((tetrazolo[1,5-*a*]quinolin-4yl)methyleneamino)benzoic acid **(5d)** and thioglycolic acid as described above; Yield 48%; eluent-*n*-hexane/ethyl acetate 70:30, $R_{f=}$ 0.61; white crystal; mp255-256 °C; FTIR (KBr, ν, cm^{-1}): 3092 (Ar C-H), 1737 (C=O), 1590 (C-N), 765 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6); 3.39 (d, 2H, CH-S, *J* = 7.6 Hz), 5.92 (s, 1H, CH-N), 7.12 (dd, 2H, Ar-H, *J* = 8.6 Hz, 2.6 Hz,), 7.26 (dd, 2H, Ar-H, *J* = 8.6 Hz, 2.6 Hz), 7.46-8.12 (m, 5H, Ar-H), 11.02 (s, 1H, COOH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): 33.4, 60.9, 121.6, 121.8, 122.2, 125.8, 126.8, 127.7, 128.8, 128.9, 130.1, 130.8, 133.3, 134.7, 143.7, 146.5, 152.4, 156.3, 169.4, 171.3; EIMS (m/z): 391.40 $[M]^+$, 392.42. $[M+1]^+$; Anal. Calcd. for $C_{19}H_{13}N_5O_3S$: C, 58.30; H, 3.35; N, 17.89 Found: C, 58.32; H, 3.36; N, 17.90 %

3-(4-bromophenyl)-2-(tetrazolo[1,5-a]quinolin-4-yl)thiazolidin-4-one (6e) This compound was prepared from 4-bromo-*N*-((tetrazolo[1,5-*a*]quinolin-4yl)methylene)benzenamine **(5e)** and thioglycolic acid as described above; Yield 63%; eluent-*n*-hexane/ethyl acetate 70:30 v/v, $R_{f=}$ 0.66; brown crystal; mp 207-208 °C; FTIR (KBr, ν, cm^{-1}): 3062 (Ar C-H), 1743 (C=O), 1593 (C-N), 1099 (C-Br), 766 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6): 3.47 (d, 2H, CH-S, *J* = 8.4 Hz), 5.81 (s, 1H, CH-N), 6.12-6.95 (m, 5H, Ar-H), 7.31 (dd, 2H, Ar-H, *J* = 8.6 Hz, 1.8 Hz), 8.02 (dd, 2H, Ar-H, *J* = 8.2 Hz, 2.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.6, 60.5, 121.9, 123.5,125.7, 126.2, 127.3, 128.1, 128.9, 130.2, 131, 132.1, 133.7, 134.5, 141.5, 143.9, 152.6, 171.7; EIMS (m/z): 426.29 $[M]^+$, 427.31 $[M+1]^+$; Anal. Calcd.for $C_{18}H_{12}BrN_5OS$: C, 50.71; H, 2.84; N, 16.43. Found: C, 50.73; H, 2.82; N, 16.44 %

Pharmacological screening

Animals

Acute toxicity study and analgesic activity was performed using female Swiss Albino mice weighing 25-30 g. Anti-inflammatory activity was performed utilizing male albino Wistar rats weighing 200-220 g. Institutional animal ethical committee, Hygia Institute of Pharmaceutical Education & Research, Lucknow, India approved the study protocol with no. (1088/PO/Ere/S/07/CPCSEA). Animals used in this study were obtained from CSIR-Indian Institute of Toxicology Research, Lucknow, India. Animals were housed individually in polypropylene cages and maintained under standard conditions of 12-h light-and-dark cycles at a constant temperature (25±2°C and 35-60% relative humidity). Animals were fed with standard pellet diet and water *ad libitum*.

Acute oral toxicity study

To set up the safety profile of the test compounds, the acute toxicity study was performed according to OECD 423 guideline [28]. Briefly, Swiss albino mice of either sex weighing 25-30 g were divided into five different groups of 3 animals each for each compound. Prior to test, animals were starved for 24 h with water *ad libitum*. Different compounds were administered to different groups in an increasing dose of 5, 50, 300, 2000 and 5000 mg/kg b.w.; p.o. Animals were observed for autonomic and neurological profiles and general behavioral for 3 h and further every 30 min for next 3 h and finally for next 14days or till

death after the dosing. The study concludes that the LD_{50} of the test compounds were found to be 200 mg/kg b.w. Therefore, 1/10th of the maximum tolerated dose, i.e. 20 mg/kg; b.w. was chosen for the *in vivo* studies.

Carrageenan induced rat paw Method

Carrageenan induced rat paw edema model is widely used animal model to evaluate the anti-inflammatory activity of newly synthesized compounds. In this model measurement was done to assess the ability of the test compound to reduce local edema induced in the rat paw by injection of an irritant agent i.e. carrageenan [29]. The oedema developed by carrageenan injection, is a biphasic event. The initial phase (1-2 h) of the carrageenan induced method is mediated by the release of serotonin, histamine and increase of prostaglandin in the damaged tissue surrounding. In late phase, prostaglandin was released and mediated by leukotrienes, bradykinin and polymorphonuclear cells.

The animals were randomly divided into groups of eight. Group I served as control which received only 0.5 % carboxymethyl cellulose (CMC) solution. Group II served as the standard and received diclofenac (20 mg/kg; p.o.). Half hr after the administration of the test compounds (20 mg /kg; *p.o.*) and the standard drugs, 0.1 ml of carrageenan solution (0.1 % in sterile 0.9 % NaCl solution) was injected subcutaneously into the sub-plantar region of the right hind paw of each rat. Digital plethysmometer was utilized to measure the paw volume by saline displacement shown on the screen at 0, 1, 2, 3, and 4 h after carrageenan injection. The edema volume in the control group (*V*c) and edema volume in the test compound treated groups (*V*t) was measured and the percentage inhibition of edema was calculated using the formula [20]:

Anti-inflammatory activity (% inhibition) = 100 (*V*c–*V*t/*V*c)

Where *V*c is the paw volume of the control group and *V*t is the paw volume of the test group.

The % inhibition of control (distilled water + carrageenan) was considered as 0 % inhibition. The compounds treated groups were calculated accordingly. The data was analysed by simple arithmetic mean and standard error compare to the control. Data of the test drug were analyzed using two way ANOVA (Graph pad prism software) followed by Dunnett's test.

Eddy's hot plate method

Eddy's hot plate method was utilized to evaluate the analgesic activity of the compounds using Swiss albino mice [29]. Animals were divided into seven different groups. Animals were kept denied of nourishment 12 h before medication organization till the investigation gets finished. Hot plate was kept up at 55^{o}C. The animals were weighed and numbered appropriately. The animals were placed on the hot plate and basal reaction time was recorded by observing licking or jumping. Standard group received pentazocine (0.1 ml; 10 mg/kg) intra-peritoneally. Synthesized compounds were administered orally to the test groups (0.1 ml, 20 mg/kg). Pain relieving movement of combined mixes was assessed at equimolar measurements. The basal reaction time was recorded at 30, 60, 90 and 120 min taking after organization of the standard or the test compound. Fifteen seconds cut off period was seen to prevent tissue damage in animals.

Statistical analysis

All results were expressed as Mean ± SEM. The statistical significance was determined by Two-way analysis of variance (ANOVA) followed by Dunnett's test and the results were found significant at $P<0.05$.

RESULT AND DISCUSSION

Chemistry

In the first step, acetanilide (1) was allowed to react with Vilsmeier-Haack reagent (DMF + $POCl_3$) to form 2-chloroquinoline-3-carbaldehyde (2). The Vilsmeier-haack reagent was prepared by adding $POCl_3$ dropwise to DMF at 0-5 ^{o}C and allowed to stir. The ^{1}H NMR spectra of compound (2) indicated the presence of an aldehyde proton at δ 10.21 ppm. The compound (2) was further treated with p-toluenesulphonic acid (PTSA) and sodium azide (NaN_3) has yielded Tetrazolo[1,5-1] quinoline-4-carbaldehyde (3). The ^{1}H NMR spectra of compound (3) indicated the presence of singlet peak at δ 10.43 ppm due to an aldehyde proton. The nucleophilic reaction between formyl group and amino group of various substituted amine (4a-e) formed corresponding Schiff base intermediates (5a-e). Attempt made to derive final thiazolidinones analogues (6a-e) from Schiff base intermediates (5a-e) react with thioglycolic acid and solvent DMF in presence of catalytic amount of aluminium chloride. Various desired thiazolidinones substituted quinoline derivatives (6a-e) were prepared in multisteps summarized in Scheme 1 with good yield and high chemical purity. In the IR spectra of all final thiazolidinones analogues (6a-e) have a strong, characteristic band in the region 1588-1593 cm^{-1} due to the C-N stretching vibration. The ^{1}H NMR spectra of products (6a–e) show a doublet at δ 3.27–3.75 due to the CH-S of thiazolidinone ring which confirms the conversion of substrates into the expected products.

All the other aromatic and aliphatic protons were observed at expected regions. In the mass spectra of all compounds (6a-e) the $[M+1]^+$ peak is observed. All compounds gave satisfactory elemental analysis.

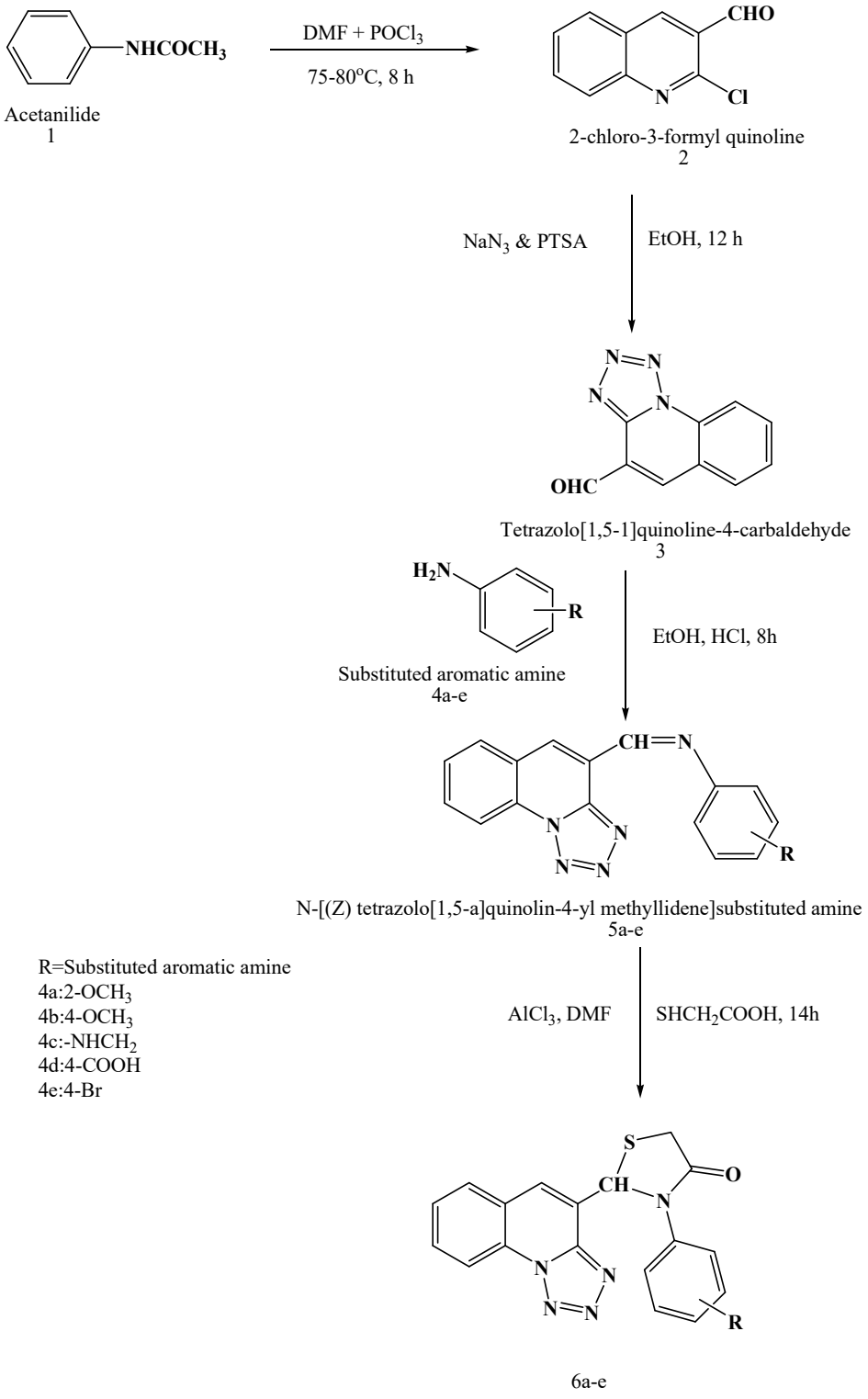

Figure 1: Scheme: Synthetic protocol of compounds **(6a-e)**

PHARMACOLOGICAL EVALUATION

Anti-inflammatory activity

As shown in Table 1, the anti-inflammatory activity test revealed that 3-(4-methoxyphenyl)-2-(tetrazolo [1, 5-*a*] quinolin-4-yl) thiazolidin-4-one (6b), exhibited the maximum anti-inflammatory activity (54.19 % inhibition) in addition to 3-(2-methoxyphenyl)-2-(tetrazolo [1, 5-*a*] quinolin-4-yl) thiazolidin-4-one (6a), showing 53.00 % inhibition, respectively. Data of percentage inhibition showed that amongst the tested compounds having methoxy groups as substituent showed highest activity as indicated by % inhibition in inflammation. Rest compounds (6c-e) showed moderate to good anti-inflammatory activity.

Table 1. Anti-inflammatory activity of compounds 6a-e in carrageenan-induced rat paw model.

Groups	Paw oedema Volume (mm)							
	0 hr	% inhibition	1 hr	% inhibition	2 hr	% inhibition	4 hr	% inhibition
Control	1.11 ± 0.23		1.34 ± 0.43		1.56 ± 0.34		1.83 ± 0.09	
Std.	1.03 ± 0.26	7.20	0.64 ± 0.03	52.23***	0.66 ± 0.03	57.69***	0.72 ± 0.06	60.65***
6a	1.06 ± 0.64	4.50	0.95 ± 0.44	29.10	0.81 ± 0.03	48.07***	0.86 ± 0.08	53.00***
6b	1.06 ± 0.52	4.50	0.83 ± 0.12	38.05**	0.72 ± 0.34	53.84***	0.82 ± 0.04	54.19***
6c	1.08 ± 0.77	2.70	1.22 ± 0.33	8.95	1.23 ± 0.78	21.15	1.27 ± 0.27	30.60*
6d	1.07 ± 0.32	3.60	1.21 ± 0.17	9.70	0.97 ± 0.39	37.82**	1.23 ± 0.51	32.78*
6e	1.09 ± 0.14	1.80	1.13 ± 0.55	15.67	1.25 ± 0.51	19.87	1.37 ± 0.89	25.13

Data are expressed as Mean ± SEM for paw edema volume. Statistical analysis was performed using two way ANOVA followed by Dunnett's test. ***P<0.001 vs control (carrageenan); **P<0.05 vs control (carrageenan);
*P<0.01 vs control (carrageenan).

Analgesic activity

Eddy's hot plate method was utilized to evaluate the compounds for their *in vivo* analgesic activity. Analgesic activity obtained for the test compounds were compared with control group. Data are expressed as Mean reaction time ± S.E.M. analyzed by One-way ANOVA followed by Dunnett test. Pentazocine at the dose of 10 mg/kg exhibited significant analgesic activity ($p < 0.01$) at all time intervals as compared to the control group. Compounds 6b, 6a at 20 mg/kg exhibited significant analgesic activity at all time intervals as compared to control group. Compounds 6c-6e show moderate analgesic activity. Almost all the derivatives showed good analgesic activity at 2 h interval as shown in Table **2**.

Table 2. Analgesic activity data of compounds using Eddy's hot plate method

Compound	Basal Reaction time (sec) before treatment (Mean ± SEM)	Basal reaction time (sec) after treatment (Mean ± SEM)			
		15 min	30 min	60 min	120 min
Control	3.72 ± 0.1121	3.20 ± 0.7265	3.42 ± 0.7865	3.19 ± 0.3498	3.66 ± 0.4532
Std.	3.52 ± 0.2342	11.56 ± 06721***	13.06 ± 0.4392***	14.66 ± 0.5567***	13.16 ± 0.2132***
6a	3.16 ± 0.5342	9.34 ± 0.2372***	11.21 ± 0.7832***	11.87 ± 0.2641***	10.82 ± 0.6452***
6b	3.26 ± 0.1924	10.07 ± 0.8142 ***	11.82 ± 0.1281***	13.15 ± 0.6512 ***	12.09 ± 0.4387***
6c	2.49 ± 0.3321	5.78 ± 0.2315 ns	6.17 ± 0.3428 ns	7.22 ± 0.3344**	6.81 ± 0.2232*
6d	2.78 ± 0.8534	6.27 ± 0.2814*	7.03 ± 0.1167**	8.12 ± 0.5572***	5.22 ± 0.4487 ns
6e	2.55 ± 0.1322	6.28 ± 0.3213*	7.05 ± 0.1526**	8.22 ± 0.1224***	7.26 ± 0.5372**

Data are expressed as Mean reaction time ± SEM. Statistical analysis was performed using two way ANOVA followed by Dunnett's test. ***P<0.001 vs control; **P<0.05 vs control; *P<0.01 vs control

CONCLUSION

An efficient and economic method for the synthesis of thiazolidinones substituted quinoline derivatives was developed. This hybrid scaffold could be promising in the discovery of new leading compounds having anti-inflammatory activity and analgesic activity. Among the derivatives, compounds **6b** and **6a** showed most promising results. This may be due to the available OCH_3 group present in **6b** & **6a**. In the current research work it was shown that substitution of methoxy group on the benzene ring increases the

potential of compound. Perhaps it is due to the electron donating property of the methoxy groups. Further research on quinoline core is indeed for the discovery of a potent anti-inflammatory agents and analgesic activity. There is enough scope for further study in developing such compounds as a good lead activity. This observation may promote a further development of this group of quinoline may lead to compounds with better pharmacological profile than standard anti-inflammatory drugs and analgesic activity.

CONFLICT OF INTEREST

None of the author has any conflict of interest in the context of this work.

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