



SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SUBSTITUTED QUINOLINE DERIVATIVES

NEHA GARG[#], TRILOK CHANDRA AND ASHOK KUMAR*

Department of Pharmacology, Medicinal Chemistry Division, L.L.R.M. Medical College, Meerut (U.P.)-250004, India

Email: rajputak09@gmail.com

Received: 17 Jan 2010, Revised and Accepted: 29 Jan 2010

ABSTRACT

In the present study we report the synthesis and anticonvulsant evaluation of several new 3-(4-(2-(4-methylquinolin-2-yl) hydrazinyl)oxazol-2-yl)-2-substituted phenylthiazolidin-4-ones 9-12 and 3-(4-(2-(4-methylquinolin-2-yl) hydrazinyl) thiazol-2-yl)-2-substituted phenylthiazolidin-4-ones 9'-12'. The structures of the synthesized compounds were confirmed by their elemental analysis, spectroscopic data (IR and ¹H NMR). All these compounds were screened in vivo, for their anticonvulsant activity and acute toxicity. Compound 11' was found to be most potent compound of this series and was compared with the reference drug phenytoin sodium.

Keywords: Quinolinyloxazoles, Quinolinythiazoles, Quinolinythiazolidinone, Anticonvulsant activity, Toxicity studies.

INTRODUCTION

Epilepsy is a neurological disorder characterized by unprovoked 50 million people worldwide. There is a continuing demand for the development of new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available drugs. About one third patients do not respond well to current multiple drug therapy¹⁻². Therefore, the need for more effective and less toxic antiepileptic drugs still exists. Substituted heterocyclic nucleus quinoline remarkably increases the anticonvulsant activity and they have been found to possess potent wide spectrum biological activities like anticonvulsant³⁻⁶, anti-inflammatory⁷⁻⁸ and antidepressant⁹. In the light of these observations this prompted us to synthesize a new series of quinoline derivatives by incorporation the oxazole, thiazole, thiazolidinone moieties at 2nd

EXPERIMENTAL

Melting points were taken in open capillaries tubes and are uncorrected. Analytical data of C, H, N were within $\pm 0.4\%$ of the theoretical values. IR spectra (cm⁻¹) were recorded on Bruker IFS-66 V FT-IR. The ¹H NMR spectra were recorded by Bruker 300 FT-NMR instrument using CDCl₃ as solvent and tetramethyl silane (TMS) as internal reference standard. Homogeneity of the synthesized compounds was routinely checked by thin layer chromatography on Silica Gel-G plates. The eluent was a mixture of different polar and nonpolar solvent in different proportion and spots were located under iodine chamber. The All exchangeable protons were confirmed by the addition of D₂O. All Chemical shift values were recorded in ppm.

2-Chloro-4-methylquinoline (1).

The starting compound 2-hydroxy-4-methyl quinoline was prepared by the reported method Kidwai [10]. Which on treated with POCl₃/PCl₅ gave 2-chloro-4-methyl quinoline 1 [11]. Yield 70% ; IR (KBr) [cm⁻¹]: 1632 (C=N), 1550 (C=C of aromatic ring), 710 (C-Cl); ¹H NMR (CDCl₃) δ [ppm] : 7.90-7.55 (m, 5H, Ar-H), 2.35 (s, 3H, CH₃); Anal. Calcd for C₁₀H₈ClN : C, 67.62 ; H, 4.54 ; N, 7.89 ; Found C, 67.55 ; H, 4.45 ; N, 7.70 %. MS : [M]⁺ at m/z 177.63.

7.87-7.64 (m, 6H, 5 H Ar-H, 1 H of oxazole), 7.42 (brs, 2H, NHNH exchangeable with D₂O), 6.42 (s, 2H, NH₂ exchangeable with D₂O), 2.35 (s, 3H, CH₃); Anal. Calcd for C₁₃H₁₃N₅O : C, 61.17 ; H, 5.13 ; N, 27.43 ; Found C, 61.29 ; H, 5.26 ; N, 27.52 %. MS : [M]⁺ at m/z 255.28.

2-(2'-Amino thiazol-4-yl-hydrazinyl)-4-methyl quinoline (4').

A mixture of 2-(2-chloro-acetohydrazinyl)-4-methylquinoline 3 (0.02 mol), thiourea (0.02 mol) and acetone (60 mL) were refluxed for 12 h. The completion of the reaction was monitored by TLC it

2-Hydrazinyl-4-methylquinoline (2).

A mixture of 2-chloro-4-methylquinoline 1 (0.1 mol) and hydrazine hydrate (99%) (0.2 mol) in methanol was refluxed for 10 h. The excess of solvent was distilled off and the reaction mixture was poured onto ice. The solid thus obtained was filtered, washed with water, dried and recrystallized from methanol. Yield 68% ; m.p 2200C ; IR (KBr) [cm⁻¹]: 3300 (NH,NH₂), 1630 (C=N), 1552 (C=C of aromatic ring), 1265 (N-N), 1224 (C-N); ¹H NMR (CDCl₃) δ [ppm] : 7.85-7.62 (m, 5H, Ar-H), 6.42 (s, 2H, NH₂ exchangeable with D₂O), 5.61 (s, 1H, NH-NH₂), 2.32 (s, 3H, CH₃); Anal. Calcd for C₁₀H₁₁N₃ : C, 69.34 ; H, 6.40 ; N, 24.26 ; Found C, 69.49 ; H, 6.30 ; N, 24.40 %. MS : [M]⁺ at m/z 173.21.

2-(2-Chloro-acetohydrazinyl)-4-methylquinoline (3).

To the solution of 2-hydrazinyl-4-methylquinoline 2 (0.01 mol) in dry benzene and chloro acetylchloride (0.02 mol) was added gradually with stirring under cool condition. The reaction mixture was further stirred for 2 h at room temperature and then refluxed for 4 h. Benzene was removed by distillation, to yield the product, which was finally recrystallized from methanol. Yield 68% : m.p 2180C ; IR (KBr) [cm⁻¹]: 2956 (C-H aliphatic), 1632 (C=N), 1554 (C=C of aromatic ring), 1272 (N-N), 1225 (C-N); ¹H NMR (CDCl₃) δ [ppm] : 7.80-7.61 (m, 5H, Ar-H), 7.41 (brs, 2H, NHNH exchangeable with D₂O), 6.40 (s, 2H, NH₂ exchangeable with D₂O), 2.32 (s, 3H, CH₃); Anal. Calcd for C₁₂H₁₂ClN₃O : C, 57.72 ; H, 4.84 ; N, 16.83 ; Found C, 57.59 ; H, 4.72 ; N, 16.70 %. MS : [M]⁺ at m/z 249.07.

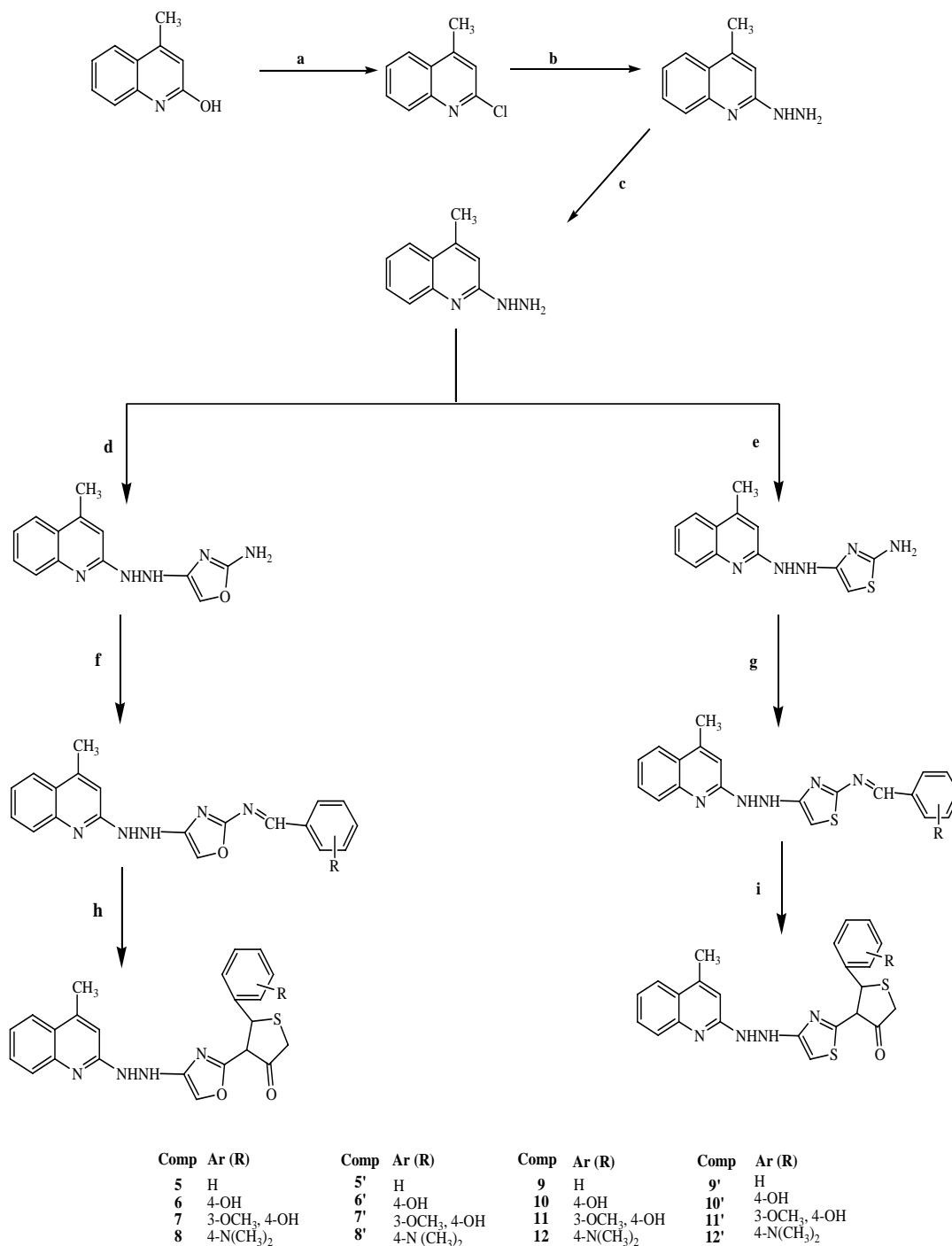
2-(2'-Amino oxazol-4-yl-hydrazinyl)-4-methyl quinoline (4).

A mixture of 2-(2-chloro-acetohydrazinyl)-4-methylquinoline 3 (0.02 mol), urea (0.02 mol) and acetone (60 mL) was refluxed for 12 h. The completion of the reaction was monitored by TLC it was then concerted and cooled where upon the obtained was washed with 2% saturated sodium carbonate solution and water to liberate the base completely dried and recrystallized from ethanol. Yield 68% : m.p 2500C ; IR (KBr) [cm⁻¹]: 3390 (N-H), 2950 (C-H aliphatic), 1630 (C=N), 1550 (C=C of aromatic ring), 1270 (N-N), 1220 (C-N), 1030 (C-O-C); ¹H NMR (CDCl₃) δ [ppm]:

was then concerted and cooled where upon the obtained was washed with 2% saturated sodium carbonate solution and water to liberate the base completely dried and recrystallized from ethanol. Yield 60% : m.p 2520C ; IR (KBr) [cm⁻¹]: 3392 (N-H), 2955 (C-H aliphatic), 1632 (C=N), 1554 (C=C of aromatic ring), 1272 (N-N), 1220 (C-N); ¹H NMR (CDCl₃) δ [ppm] : 7.84-7.72 (m, 6H, 5 H Ar-H, 1 H of thiazole), 7.36 (brs, 2H, NHNH exchangeable with D₂O), 6.40 (s, 2H, NH₂ exchangeable with D₂O), 2.38 (s, 3H, CH₃); Anal. Calcd for C₁₃H₁₃N₅S : C, 57.54 ; H, 4.83 ; N, 25.81 ; Found C, 57.44 ; H, 4.66 ; N, 25.72 %. MS : [M]⁺ at m/z 271.34.

General procedure for the preparation of 2-(2'-Substituted benzylidene amino oxazol-4-yl)-hydrazinyl)-4-methyl quinoline (5-8). To the solution of 2-(2'-amino oxazol-4-yl)-hydrazinyl)-4-methyl quinoline 4 (0.01 mol) in methanol (80 mL), substituted benzaldehyde (0.01 mol) with few drops of glacial acetic acid was

added and then reaction mixture refluxed for 10 h ,completion of the reaction was monitored by TLC. After distillation of excess of solvent the reaction mixture was cooled, diluted with cold water and filtered. The solid thus obtained was recrystallized from suitable solvent.



Reactions and Conditions: (a) $\text{PCl}_3/\text{POCl}_3$; (b) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$; (c) ClCOCH_2Cl ; (d) NH_2CONH_2 ; (e) NH_2CSNH_2 ; (f) Ar (R)CHO ; (g) $\text{gl CH}_3\text{COOH/ Ar-CHO}$
 (h) Thioglycolic acid/ ZnCl_2 (i) Thioglycolic acid/ ZnCl_2

Scheme 1: Synthetic protocol of the titled compounds

Table 1: Anticonvulsant activity of compounds 1-4, 4', and 5-8, 5'-8', 9-12 and 9'-12'

Compound No.	R	Dose (mg/kg i.p.)	Anticonvulsant activity (SMES) ^c		ALD ₅₀ (mg/kg i.p.)
			No. of animals exhibiting convulsions	%seizure protection	
	P.G.a	2 ml	10	0	
	Phenytoin sodiumb	30	2	80***	
1	-	30	7	30	> 1000
2	-	30	6	40	>1000
3	-	30	7	30	> 1000
4	-	30	6	40	>1000
4'	-	30	6	40	>1000
5	H	30	5	50*	>1000
6	4-OH	30	4	60*	>1000
7	3-OCH ₃ ,4-OH	30	3	70**	>1000
8	OH	30	5	50*	>1000
5'	4-N(CH ₃) ₂ H	30	4	60*	>1000
6'	4-OH	30	5	50*	> 1000
7'	3-OCH ₃ ,4-OH	30	5	70**	> 1000
8'	OH	30	2	60*	> 1000
9	4-N(CH ₃) ₂ H	30	4	60*	> 1000
10	H	30	4	70**	> 1000
	4-OH	7.5	7	30	
11	OH	15	5	50*	> 1000
	3-OCH ₃ , 4-OH	30	2	80**	
12	OH	30	5	50*	> 1000
9'	OH	30	4	50*	> 1000
10'	4-N(CH ₃) ₂ H	30	3	70**	> 1000
	H	7.5	6	40	> 1000
11'	4-OH	15	4	60**	> 1000
	OH	30	1	90***	> 2000
12'	3-OCH ₃ ,4-OH	30	3	70**	> 1000
	4-N(CH ₃) ₂				

* P < 0.05 ** P < 0.01, *** P < 0.001. a. P.G.- Propylene glycol standard for control, b. Phenytoin sodium reference standard drug for anticonvulsant activity, c. Supramaximal electroshock seizure pattern test

2-(2'-Benzylidene amino oxazol-4-yl)-hydrazinyl-4-methyl quinoline (5).

Yield 65% (Methanol): m.p : 2530C ; IR (KBr) [cm-1]: 3395 (N-H), 2952 (C-H aliphatic), 1638 (C=N), 1552 (C=C of aromatic ring), 1275 (N-N), 1222 (C-N), 1062 (C-O-C); 1H NMR (CDCl₃) δ [ppm] : 7.81-7.53 (m, 11H, 10 H Ar-H, 1 H of oxazole), 7.40 (brs, 2H, NHHN exchangeable with D₂O), 8.20 (s, 1H, N=CH-Ar), 2.32 (s, 3H, CH₃) ; Anal. Calcd for C₂₀H₁₇N₅O : C, 69.96 ; H, 4.99 ; N, 20.40 ; Found C, 69.84 ; H, 4.80 ; N, 20.35 %. MS : [M]⁺ at m/z 343.38.

2-(2'-(4-Hydroxybenzylidene)-amino oxazol-4-yl)-hydrazinyl-4-methyl quinoline (6).

Yield 60% (Acetone): m.p 2450C ; IR (KBr) [cm-1]: 3485 (OH), 3394 (N-H), 2953 (C-H aliphatic), 1632 (C=N), 1554 (C=C of aromatic ring), 1277 (N-N), 1225 (C-N), 1065 (C-O-C); 1H NMR (CDCl₃) δ [ppm] : 11.02 (s, 1H, Ar-OH exchangeable), 7.85-7.56 (m, 10H, 9 H Ar-H, 1 H of oxazole), 7.39 (brs, 2H, NHHN exchangeable with D₂O), 8.25 (s, 1H, N=CH-Ar), 2.34 (s, 3H, CH₃) ; Anal. Calcd for C₂₀H₁₇N₅O₂ : C, 66.84 ; H, 4.77 ; N, 19.49 ; Found C, 66.74 ; H, 4.86 ; N, 19.32 %. MS : [M]⁺ at m/z 359.38.

2-(2'-(3-Methoxy-4-hydroxybenzylidene)-amino oxazol-4-yl)-hydrazinyl-4-methyl quinoline (7).

Yield 68% (Ethanol): m.p 2550C ; IR (KBr) [cm-1]: 3482 (OH), 3390 (N-H), 2956 (C-H aliphatic), 1630 (C=N), 1550 (C=C of aromatic

ring), 1272 (N-N), 1226 (C-N), 1061 (C-O-C); 1H NMR (CDCl₃) δ [ppm] : 11.02 (s, 1H, Ar-OH exchangeable), 7.82-7.61 (m, 9H, 8 H Ar-H, 1 H of oxazole), 7.44 (brs, 2H, NHHN exchangeable with D₂O), 8.27 (s, 1H, N=CH-Ar), 3.20 (s, 3H, OCH₃), 2.30 (s, 3H, CH₃) ; Anal. Calcd for C₂₁H₁₉N₅O₃ : C, 64.77 ; H, 4.92 ; N, 17.98 ; Found C, 64.64 ; H, 4.82 ; N, 17.80 %. MS : [M]⁺ at m/z 389.41.

2-(2'-(4-N,N-Dimethyl benzylidene)-amino oxazol-4-yl)-hydrazinyl-4-methyl quinoline (8).

Yield 72% (DMF/ Water): m.p 2580C ; IR (KBr) [cm-1]: 3395 (N-H), 2952 (C-H aliphatic), 1625 (C=N), 1553 (C=C of aromatic ring), 1270 (N-N), 1224 (C-N), 1066 (C-O-C); 1H NMR (CDCl₃) δ [ppm] : 7.69-6.70 (m, 10H, 9 H Ar-H, 1 H of oxazole), 7.51 (brs, 2H, NHHN exchangeable with D₂O), 8.24 (s, 1H, N=CH-Ar), 2.36 (s, 3H, CH₃), 2.18 (s, 6H, 2 X CH₃) ; Anal. Calcd for C₂₂H₂₂N₆O : C, 68.38 ; H, 5.74 ; N, 21.75 ; Found C, 68.49 ; H, 5.85 ; N, 21.89 %. MS : [M]⁺ at m/z 386.45.

General procedure for the preparation of 2-(2'-Substituted benzylidene amino thiazol-4-yl)-hydrazinyl-4-methyl quinoline (5'-8').

To the solution of 2-(2'-amino thiazol-4-yl)-hydrazinyl-4-methyl quinoline 4' (0.01 mol) in methanol (80 mL), substituted benzaldehyde (0.01 mol) with few drops of glacial acetic acid was added and then reaction mixture refluxed for 10 h, completion of the

reaction was monitored by TLC. After distillation of excess of solvent the reaction mixture was cooled, diluted with cold water and filtered. The solid thus obtained was recrystallized from suitable solvent.

2-(2'-(Benzylidene amino thiazol-4-yl)-hydrazinyl)-4-methyl quinoline (5').

Yield 72% (Acetone): m.p 2540C ; IR (KBr) [cm-1]: 3396 (N-H), 2954 (C-H aliphatic), 1640 (C=N), 1553 (C=C of aromatic ring), 1276 (N-N), 1224 (C-N), 690 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 7.77-7.53 (m, 11H, 10 H Ar-H, 1 H of thiazole), 7.35 (brs, 2H, NHHN exchangeable with D2O 8.20 (s, 1H, N=CH-Ar), 2.34 (s, 3H, CH3) ; Anal. Calcd for C20H17N5S : C, 66.83 ; H, 4.77 ; N, 19.48 ; Found C, 66.64 ; H, 4.63 ; N, 19.55 %. MS : [M]⁺ at m/z 359.45.

2-(2'-(4-Hydroxybenzylidene)-amino thiazol -4-yl)-hydrazinyl-4-methyl quinoline (6').

Yield 70% (Methanol): m.p 2480C ; IR (KBr) [cm-1]: 3488 (OH), 3395 (N-H), 2956 (C-H aliphatic), 1730 (C=O of quinoline ring), 1636 (C=N), 1556 (C=C of aromatic ring), 1278 (N-N), 1226 (C-N), 692 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 11.06 (s, 1H, Ar-OH exchangeable), 7.75-7.59 (m, 10H, 9 H Ar-H, 1 H of thiazole), 7.40 (brs, 2H, NHHN exchangeable with D2O), 8.17 (s, 1H, N=CH-Ar), 2.38 (s, 3H, CH3) ; Anal. Calcd for C20H17N5O5S : C, 63.98 ; H, 4.56 ; N, 18.65 ; Found C, 63.84 ; H, 4.66 ; N, 18.52 %. MS : [M]⁺ at m/z 375.45.

2-(2'-(3-Methoxy-4-hydroxybenzylidene)-amino thiazol-4-yl)-hydrazinyl-4-methyl quinoline (7').

Yield 68% (Ethanol): m.p 2420C ; IR (KBr) [cm-1]: 3486 (OH), 3395 (N-H), 2958 (C-H aliphatic), 1726 (C=O of quinoline ring), 1632 (C=N), 1554 (C=C of aromatic ring), 1274 (N-N), 1224 (C-N), 696 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 11.10 (s, 1H, Ar-OH exchangeable), 7.80-7.42 (m, 9H, 8 H Ar-H, 1 H of thiazole), 7.46 (brs, 2H, NHHN exchangeable with D2O), 8.23 (s, 1H, N=CH-Ar), 3.22 (s, 3H, OCH3), 2.36 (s, 3H, CH3) ; Anal. Calcd for C21H19N5O2S : C, 62.21 ; H, 4.72 ; N, 17.27 ; Found C, 62.34 ; H, 4.84 ; N, 17.38 %. MS : [M]⁺ at m/z 405.13.

2-(2'-(4-N,N Dimethyl benzylidene)-amino thiazol -4-yl)-hydrazinyl-4-methyl quinoline (8').

Yield 72% (DMF/ Water): m.p 2600C ; IR (KBr) [cm-1]: 3396 (N-H), 2955 (C-H aliphatic), 1726 (C=O of quinoline ring), 1628 (C=N), 1555 (C=C of aromatic ring), 1272 (N-N), 1228 (C-N), 691 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 7.81-7.54 (m, 10H, 9 H Ar-H, 1 H of thiazole), 7.34 (brs, 2H, NHHN exchangeable with D2O), 8.19 (s, 1H, CH-Ar), 2.38 (s, 3H, CH3), 2.22 (s, 6H, 2 X CH3) ; Anal. Calcd for C22H22N6S : C, 65.65 ; H, 5.51 ; N, 20.88 ; Found C, 66.49 ; H, 5.65 ; N, 20.69 %. MS : [M]⁺ at m/z 402.52.

General procedure for the preparation of 3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)oxazol-2-yl)-2- substituted phenylthiazolidin-4-ones (9'-12').

A mixture of compounds 2-(2'-Substituted benzylidene amino oxazol-4-yl)-hydrazinyl-4-methyl quinoline 5-8 (0.01 mol), thioglycolic acid (0.01 mol) and anhydrous ZnCl₂ (2 g) in absolute ethanol was refluxed for 10 h. The progress and completion of reaction was checked by TLC. After refluxing, excess of solvent was distilled off and residue was poured in cold water, filtered, dried and finally the product was recrystallized from appropriate solvent.

3-(4-(2-(4-Methylquinolin-2-yl)hydrazinyl)oxazol-2-yl)-2-phenyl thiazolidin-4-one (9').

Yield 68% (Acetone): m.p 2600C ; IR (KBr) [cm-1]: 3390 (N-H), 2950 (C-H aliphatic), 1721 (C=O of quinoline ring), 1636 (C=N), 1550 (C=C of aromatic ring), 1274 (N-N), 1223 (C-N), 1065 (C-O-C); 1H NMR (CDCl3) δ [ppm] : 7.88-7.62 (m, 11H, 10 H Ar-H, 1 H of oxazole), 7.36 (brs, 2H, NHHN exchangeable with D2O), 5.20 (s, 2H, CH₂-CO), 5.95 (s, 1H, N-CH-Ar), 2.36 (s, 3H, CH₃) ; Anal. Calcd for

C22H19N5O2S : C, 63.29 ; H, 4.59 ; N, 16.78 ; Found C, 63.44 ; H, 4.70 ; N, 16.92 %. MS : [M]⁺ at m/z 417.48.

2-(4-Hydroxyphenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)oxazol-2-yl)thiazolidin-4-one (10).

Yield 70 % (Methanol): m.p 2650C ; IR (KBr) [cm-1]: 3486 (OH), 3394 (N-H), 2952 (C-H aliphatic), 1724 (C=O of quinoline ring), 1635 (C=N), 1555 (C=C of aromatic ring), 1276 (N-N), 1226 (C-N), 1070 (C-O-C); 1H NMR (CDCl3) δ [ppm] : 11.10 (s, 1H, Ar-OH exchangeable), 7.72-7.50 (m, 10H, 9 H Ar-H, 1 H of oxazole), 7.32 (brs, 2H, NHHN exchangeable with D2O), 5.22 (s, 2H, CH₂-CO), 5.91 (s, 1H, N-CH-Ar), 2.36 (s, 3H, CH₃) ; Anal. Calcd for C22H19N5O3S : C, 60.96 ; H, 4.42 ; N, 16.16 ; Found C, 60.84 ; H, 4.30 ; N, 16.10 %. MS : [M]⁺ at m/z 433.48.

2-(4-Hydroxy-3-methoxyphenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)oxazol-2-yl)thiazolidin-4-one (11).

Yield 72 % (Methanol): m.p 2700C ; IR (KBr) [cm-1]: 3488 (OH), 3398 (N-H), 2955 (C-H aliphatic), 1726 (C=O of quinoline ring), 1640 (C=N), 1558 (C=C of aromatic ring), 1280 (N-N), 1225 (C-N), 1075 (C-O-C); 1H NMR (CDCl3) δ [ppm] : 11.15 (s, 1H, Ar-OH exchangeable), 7.72-7.61 (m, 9H, 8 H Ar-H, 1 H of oxazole), 7.37 (brs, 2H, NHHN exchangeable with D2O), 5.21 (s, 2H, CH₂-CO), 5.96 (s, 1H, N-CH-Ar), 3.25 (s, 3H, OCH₃), 2.40 (s, 3H, CH₃) ; Anal. Calcd for C23H21N5O4S : C, 59.60 ; H, 4.57 ; N, 15.11 ; Found C, 59.76 ; H, 4.42 ; N, 15.23 %. MS : [M]⁺ at m/z 463.13.

2-(4-(4-N,N-Dimethyl amino)phenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)oxazol-2-yl)thiazolidin-4-one (12).

Yield 68 % (Acetone): m.p 2680C ; IR (KBr) [cm-1]: 3398 (N-H), 2954 (C-H aliphatic), 1723 (C=O of quinoline ring), 1636 (C=N), 1552 (C=C of aromatic ring), 1282 (N-N), 1224 (C-N), 1072 (C-O-C); 1H NMR (CDCl3) δ [ppm] : 7.75-7.32 (m, 10H, 9 H Ar-H, 1 H of oxazole), 7.44 (brs, 2H, NHHN exchangeable with D2O), 5.24 (s, 2H, CH₂-CO), 5.93 (s, 1H, N-CH-Ar), 2.41 (s, 3H, CH₃), 2.24 (s, 6H, 2 X CH₃) ; Anal. Calcd for C24H24N6O2S : C, 62.59 ; H, 5.25 ; N, 18.25 ; Found C, 62.70 ; H, 5.38 ; N, 18.12 %. MS : [M]⁺ at m/z 460.55.

General procedure for the preparation of 3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)thiazol-2-yl)-2-substituted phenylthiazolidin-4-ones (9'-12').

A mixture of compounds 2-(2'-substituted benzylidene amino thiazole-4-yl)-hydrazinyl-4-methyl quinoline 5'-8' (0.01 mol), thioglycolic acid (0.01 mol) and anhydrous ZnCl₂ (2 g) in absolute ethanol was refluxed for 10 h. The progress and completion of reaction was checked by TLC. After refluxing, excess of solvent was distilled off and residue was poured in cold water, filtered, dried and finally the product was recrystallized from appropriate solvent.

3-(4-(2-(4-Methylquinolin-2-yl)hydrazinyl)thiazol-2-yl)-2-phenyl thiazolidin-4-one (9').

Yield 70% (Methanol): m.p 2640C ; IR (KBr) [cm-1]: 3392 (N-H), 2954 (C-H aliphatic), 1724 (C=O of quinoline ring), 1635 (C=N), 1555 (C=C of aromatic ring), 1278 (N-N), 1226 (C-N), 695 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 7.84-7.51 (m, 11H, 10 H Ar-H, 1 H of thiazole), 7.35 (brs, 2H, NHHN exchangeable with D2O), 5.25 (s, 2H, CH₂-CO), 5.88 (s, 1H, N-CH-Ar), 2.38 (s, 3H, CH₃) ; Anal. Calcd for C22H19N5O2S : C, 60.95 ; H, 4.42 ; N, 16.15 ; Found C, 60.84 ; H, 4.60 ; N, 16.32 %. MS : [M]⁺ at m/z 433.55.

2-(4-Hydroxyphenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl) thiazol -2-yl)thiazolidin-4-one (10').

Yield 704% (DMF/ Water): m.p 2700C ; IR (KBr) [cm-1]: 3490 (OH), 3396 (N-H), 2955 (C-H aliphatic), 1726 (C=O of quinoline ring), 1636 (C=N), 1556 (C=C of aromatic ring), 1275 (N-N), 1225 (C-N), 670 (C-S-C); 1H NMR (CDCl3) δ [ppm] : 11.12 (s, 1H, Ar-OH exchangeable), 7.83-7.56 (m, 10H, 9 H Ar-H, 1 H of thiazole), 7.34 (brs, 2H, NHHN exchangeable with D2O), 5.23 (s, 2H, CH₂-CO), 5.90 (s, 1H, N-CH-Ar), 2.35 (s, 3H, CH₃) ; Anal. Calcd for C22H19N5O2S₂ :

C, 58.78 ; H, 4.26 ; N, 15.58 ; Found C, 58.64 ; H, 4.16 ; N, 15.54 % . MS : [M]⁺ at m/z 449.55.

2-(4-Hydroxy-3-methoxyphenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)thiazol-2-yl)thiazolidin-4-one (11')

Yield 72 % (Methanol): m.p 2700C ; IR (KBr) [cm⁻¹]: 3484 (OH), 3398 (N-H), 2951 (C-H aliphatic), 1724 (C=O of quinoline ring), 1643 (C=N), 1560 (C=C of aromatic ring), 1281 (N-N), 1222 (C-N), 692 (C-S-C); ¹H NMR (CDCl₃) δ [ppm]: 11.16 (s, 1H, Ar-OH exchangeable), 7.77-7.54 (m, 9H, 8 H Ar-H, 1 H of thiazole), 7.31 (brs, 2H, NHHN exchangeable with D₂O), 5.26 (s, 2H, CH₂-CO), 5.94 (s, 1H, N-CH-Ar), 3.28 (s, 3H, OCH₃), 2.44 (s, 3H, CH₃) ; Anal. Calcd for C₂₃H₂₁N₅O₃S₂ : C, 57.60 ; H, 4.41 ; N, 14.60 ; Found C, 57.49 ; H, 4.32 ; N, 14.73 % . MS : [M]⁺ at m/z 479.57.

2-(4-(N,N-Dimethyl amino)phenyl)-3-(4-(2-(4-methylquinolin-2-yl)hydrazinyl)thiazol-2-yl)thiazolidin-4-one (12')

Yield 69 % (methanol): m.p 2650C ; IR (KBr) [cm⁻¹]: 3394 (N-H), 2952 (C-H aliphatic), 1720 (C=O of quinoline ring), 1630 (C=N), 1548 (C=C of aromatic ring), 1283 (N-N), 1221 (C-N), 694 (C-S-C); ¹H NMR (CDCl₃) δ [ppm] : 7.74-7.51 (m, 10H, 9 H Ar-H, 1 H of thiazole), 7.33 (brs, 2H, NHHN exchangeable with D₂O), 5.22 (s, 2H, CH₂-CO), 5.92 (s, 1H, N-CH-Ar), 2.44 (s, 3H, CH₃), 2.26 (s, 6H, 2 X CH₃) ; Anal. Calcd for C₂₄H₂₄N₆O₂S₂ : C, 60.48 ; H, 5.08 ; N, 17.23 ; Found C, 60.60 ; H, 5.18 ; N, 17.15 % . MS : [M]⁺ at m/z 476.62.

BIOLOGICAL ACTIVITY

Anticonvulsant activity

The anticonvulsant activity was performed according the method of Toman et al [12] on Charles foster rats of either sex weighing, between 90-150 g. Rats were divided into groups of ten animals each. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p. After 1 h they were subjected to a shock of 150 m.A by convulsimeter, through ear electrodes for 2 s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats. The compounds were also investigated for their acute toxicity ALD50 in mice by following the method of Smith [13]

Table 2: Anticonvulsant activity of compounds 1-4, 4', and 5-8, 5'-8', 9-12 and 9'-12'

S.No.	Formulations	R _i Values Hydrochloro-thiazide	Captopril
1.	Standard Drug	0.913	0.856
2.	Physical Mixtures (1:1)&(1:1.7) HCT - CAP	0.912	0.858
3.	Solid Dispersions (1:1) &(1:1.7) HCT - CAP	0.913	0.860

RESULTS AND DISCUSSION

All synthesized compounds were administered at the dose of 30 mg/kg and the results of all the compounds are mentioned in Table 1. The characteristic feature of this series is the substitution by the different moieties at second position of quinazolin ring. It was observed that compounds 1-4 and 4' showed mild anticonvulsant activity i.e. 30%, 40%, 30%, 40% and 40% respectively. It was also observed that compound 5 (substituted with phenyl group) exhibited 50% activity and compound 7 (having 3-methoxy, 4-hydroxy phenyl group) showed 70% activity. Moreover compounds

6 (having 4-hydroxy phenyl group) exhibited 60% activity, while compound 8 (substituted with N,N dimethyl phenyl group) showed 50% activity. However, compounds 5'-8' exhibited 50-70% protection against seizure. Compound 7' (substituted with 3-methoxy, 4-hydroxy phenyl group) showed 70% at 30 mg/ kg activity. Further the next step compounds 9, 10 and 12 exhibited good response against MES model i.e. 60%, 70%, and 50% respectively and compound 11 showed 80% inhibition of seizure at 30 mg/ kg which is equipotent to standard drug phenytoin sodium. The compounds 9'-12' have shown anticonvulsant activity in the range 50-90%. The compound 11' substituted with 3-methoxy,4-hydroxy phenyl group has been tested at 30 mg/ kg shown most potent activity of 90% against MES test which is more potent than standard drug phenytoin sodium. Considering the potentiality of compounds 11 and 11' these were tested at three graded doses and it is interesting to note that these compounds have shown better activity than standard drug phenytoin sodium at a doses of 30 mg/ kg, while these compounds at a doses of 7.5 and 15 mg/ kg, exhibited less activity than standard drug phenytoin sodium. The ALD50 values of these compounds indicate the safer nature of these compounds.

CONCLUSIONS

While considering all the newly synthesized compounds of this series together, we may conclude that:

- Presence of thiazol moiety has shown better anticonvulsant activity than the compounds having oxazol moiety.
- 3-Methoxy-4-hydroxy substitution at second position of quinoline ring showed more potent activity.

REFERENCES

1. WHO data obtained from <http://www.who.int/mediacentre/factsheets/fs16/en/>.
2. Schmidt D , Loscher W. Epilepsia.2005; 46, 858.
3. Guan LP, Jin QH, Tian GR, Chai KY, Quan ZS. J Pharm Pharmaceut Sci. 2007; 10 254.
4. Xie ZF, Chai KY, Piao HR, Kyung-Chell , Kwak KC , Quan ZS. Bioorganic and Med Chem. 2005; 15, 4803
5. Ping GL, Hao JQ , Feng WS, Nan, Shan QZ. Archiv der Pharmazie. 2008; 341, 774.
6. Garg N, Chandra T, Lata S, Saxana KK, Kumar A. Pak. J. Sci. Ind. Res. 2009; 52, 8.
7. Mikhalev AI, Kon'shin ME, Kolla VE, Nazmetdinov F Y, Vakhrin MI. Pharmaceutical Chemistry Journal. 1997; 31, 600.
8. Chia EW, Pearce AN, Berridge MV, Larsen LL, Perry NB, Sansom CE, Godfrey CA, Hanton LR, Lu GL, Walton M, Denny WA, Webb VL, Copp BR, Harper JL. Bioorganic and Med.Chem Letters. 2008; 16, 9432.
9. Sathi G, Gujrati VR, Sharma M, Nath C, Bhargava KP, Shanker K. Archiv der Pharmazie. 1983; 316, 767.
10. Kidwai M . Chem Edu. 1993; 4, 55.
11. Kidwai M , Kumar K, Goel Y , Srivastava KC. Bioorganic and Med Chem Letters. 1996; 6, 871.
12. Tomon JEP, Swinyard EA, Goodman LS. J. Neurophysio. 1946; 9 , 231.
13. Smith QE. Pharmacological Screening Test Progress in Medicinal Chemistry. Butterworth, London. 1960;1.