SYNTHESIS AND ANTIICONVULSANT ACTIVITY OF SUBSTITUTED QUINOLINE DERIVATIVES

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ABSTRACT
In the present study we report the synthesis and anticonvulsant evaluation of several new 3-[(2-4-(methylquinolin-2-yl)hydrazinyl)oxazol-2-yl]-2-substituted phenylthiazolinol-4-ones 9-12 and 3-[(2-4-(methylquinolin-2-yl)hydrazinyl)thiazol-2-yl]-2-substituted phenylthiazolinol-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, Quinolinylthiazoles, Quinolinylthiazolidinone, Anticonvulsant activity, Toxicity studies.

INTRODUCTION
Epilepsy is a neurological disorder characterized by unprovoked multiple drug therapy1-2. Therefore, the need for more effective and development of new anticonvulsant agents as it has not been 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 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 ±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 Brucker 300 FT-NMR instrument using CDCl3 as solvent and tetramethyl silane (TMS) as internal reference standard. Homogeneity of the NMR instrument using CDCl3 as solvent and tetramethyl silane 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 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, NH exchangeable with D2O). 6.40 (s,2H, NH exchangeable with D2O), 2.38 (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.

SYNTHESIS

2-Chloro-4-methylquinoline (1).
The starting compound 2-hydroxy-4-methyl quinoline was refluxed 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=C); 1H NMR (CDCl3) δ [ppm]: 7.90-7.75 (m, 5H, Ar-H), 2.35 (s, 3H, CH3) ; Anal. Calcd for C10H8ClN: C, 67.62; H, 4.54; N, 27.43 ; Found C, 67.55 ; H, 4.45; N, 27.70 %. MS: [M]+ at m/z 173.21.

2-Quinolinyloxazoles, Quinolinylthiazoles, Quinolinylthiazolidinone, Anticonvulsant activity, Toxicity studies.

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, NH 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, 24.24 %. MS: [M]+ at m/z 2180.

2-(2-Chloro-4-methyl)-4-phenylquinoline (3).
To the solution of 2-hydrazinyl-4-methylquinoline 2 (0.01 mol) in dry benzene and chloro acetyl chloride (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, NH exchangeable with D2O), 6.40 (s, 2H, NH exchangeable with D2O) 2.32 (s, 3H, CH3) ; Anal. Calcd for C12H12ClN3O: C, 67.49; H, 6.30; N, 24.40 %. MS: [M]+ at m/z 173.21.

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 acetonitrile (60 mL) was refluxed for 12 h. The completion of the reaction was monitored by TLC. It was then concentrated 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]: 7.84-7.72 (m, 6H, Ar-H), 7.36 (brs, 2H, NH exchangeable with D2O), 6.40 (s, 2H, NH exchangeable with D2O), 2.38 (s, 3H, CH3) ; Anal. Calcd for C13H13N5O: C, 57.54; H, 4.83; N, 25.61 %; 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) PCl₅/POCl₃; (b) NH₂NH₂.H₂O; (c) ClCOCH₂Cl; (d) NH₂CONH₂; (e) NH₂CSNH₂; (f) Ar (R)CHO; (g) gl CH₃COOH/ ZnCl₂ (h) Thioglycolic acid/ ZnCl₂; (i) Thioglycolic acid/ ZnCl₂

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'  

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<tr>
<th>Compound No.</th>
<th>R</th>
<th>Dose (mg/kg i.p.)</th>
<th>No. of animals exhibiting convulsions</th>
<th>% Seizure protection</th>
<th>ALDₕ₀ (mg/kg i.p.)</th>
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<td>70**</td>
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* P < 0.05 ** P < 0.01 *** P < 0.001 a. P.G.- Propylene glycol standard for control, b. Phenytin sodium reference standard drug for anticonvulsant activity, c. Supramaximal electroshock seizure pattern test.

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

Yield 65% (Methanol): m.p: 253°C; IR (KBr) [cm⁻¹]: 3395 (N-H), 2952 (C-H aliphatic), 1638 (C=O), 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, NHN exchangeable with D₂O), 8.20 (s, 1H, N=CH), 2.32 (s, 3H, CH₃); Anal. Calc'd for C₂₀H₁₇N₅O: C, 69.96; H, 4.99; N, 20.40; Found C, 68.37; H, 4.86; N, 19.67. MS: [M]+ at m/z 359.38.

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

Yield 60% (Acetone): m.p: 254°C; IR (KBr) [cm⁻¹]: 3485 (OH), 3394 (N-H), 2953 (C-H aliphatic), 1632 (C=O), 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, NHN exchangeable with D₂O), 8.25 (s, 1H, N=CH), 2.34 (s, 3H, CH₃); Anal. Calc'd for C₂₀H₁₇N₅O: C, 66.74; H, 4.86; N, 19.32. MS: [M]+ at m/z 359.38.

2-(4'-Hydroxybenzylidene)-amino oxazol-4-yl)-hydrazinyl)-4-methyl quinoline (7).

Yield 68% (Ethanol): m.p: 255°C; IR (KBr) [cm⁻¹]: 3482 (OH), 3390 (N-H), 2956 (C-H aliphatic), 1630 (C=O); 1550 (C=C of aromatic ring), 1272 (N-N), 1226 (C=C), 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, NHN exchangeable with D₂O), 8.27 (s, 1H, N=CH), 3.20 (s, 3H, OCH₃), 2.30 (s, 3H, OCH₃); Anal. Calc'd for C₂₁H₁₇N₅O₃: 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-(4'-N,N-Dimethyl benzylidene)-amino xazol-4-yl)-hydrazinyl)-4-methyl quinoline (8).

Yield 72% (DMF/Water): m.p: 258°C; IR (KBr) [cm⁻¹]: 3395 (N-H), 2952 (C-H aliphatic), 1625 (C=C), 1553 (C=C of aromatic ring), 1270 (N-N), 1224 (C=C), 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, NHN exchangeable with D₂O), 8.24 (s, 1H, N=CH), 2.36 (s, 3H, CH₃), 2.18 (s, 6H, 2X CH₃); Anal. Calc'd for C₂₂H₂₂N₆O₆: 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'-8') in methanol (80 mL), substituted benzaldehyde (0.001 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′-Benzildene amino thiazol-4-yl)-hydrazinyl)-4-methyl
quinoline (5). Yield 72% (Acetone): mp 2540°C; IR (KBr) [cm⁻¹]: 3396 (N-H),
2954 (C-H aliphatic), 1640 (C=N), 1552 (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, 10H Ar-H, 1H of thiazole), 7.35 (brs, 2H, NHH exchangeable with D2O, 8.20 (s, 1H, N=CH-Ar), 7.23 (s, 3H, CH3) ; Anal. Calc d C22H19NSO2S: 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): mp 2560°C; 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), 1224 (C=N),
1070 (C=O-C); 1H NMR (CDCl₃) δ [ppm]: 7.72-7.50 (m, 10H, 9H Ar-H, 1H of oxazole), 7.32 (brs, 2H, NHH exchangeable with D2O), 5.22 (s, 2H, CH2-CO), 5.91 (s, 1H, N=CH-Ar), 3.23 (s, 3H, CH3) ; Anal. Calc d C22H19NSO2S: 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-methylphenyl)-3-(4-(2-(4-methylquinolin-2-
yl)hydrazinyl)oxazol-2-yl)thiazolidin-4-one (11). Yield 72% (Methanol): mp 2700°C; IR (KBr) [cm⁻¹]: 3486 (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),
1079 (C=O-C); 1H NMR (CDCl₃) δ [ppm]: 7.72-7.61 (m, 9H, 8H Ar-H, 1H of oxazole), 7.37 (brs, 2H, NHH 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. Calc d C23H2N2O4S: C, 59.60; H, 4.57; N, 15.11 ; Found C, 59.76; H, 4.42; N, 15.23 %. MS: [M]+ at m/z 465.13.
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 anticonvulsant activity than standard drug phenytoin sodium at a doses of 7.5 and 15 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 thiazide 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

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