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Research Article

Synthesis and anti-convulsant screening of novel Schiff bases of 3-amino-2-methyl quinazolin-4-(3H)-one

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ABSTRACT

In the present study, a novel schiff bases were synthesized by condensation of 3-amino-2-methyl quinazolin-4-(3H)-ones with different aromatic aldehyde. The 3-amino-2-methyl quinazolin-4-(3H)-one was synthesized from anthranilic acid via 2-methyl benzoxazin-4-one. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral and elemental analysis. These compounds were screened for anti-convulsant activity by MES method in mice. All the compounds exhibited significant anti-convulsant activity. Entire title compounds exhibit more effect on extensor phase than flexion phase. 3-(4-methyl benzylideneamino)-2-methyl quinazolin-4(3H)-one **(4f)** exhibited highest activity among the series. Compound **4d** and **4e** exhibited moderate activity.

Keywords: 3-Amino-2-methyl quinazolin-4-(3H)-one; Schiff base; anti-convulsant.

INTRODUCTION

Epilepsy, a ubiquitous disease characterized by recurrent seizures, inflicts more than 60 million people worldwide according to epidemiological studies (Wolfgang Loscher, 1998). For epilepsy treatment, nearly 95% of clinically available drugs were approved before 1985 and they could provide satisfactory seizure control for 60–70% of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia, and even life threatening conditions (Perucca E, 1996 and Zhaiwei Lin et. al., 1997). Research to find more effective and safer antiepileptic drugs are, therefore, imperative and challenging in medicinal chemistry. Among the important pharmacophores responsible for anticonvulsant activity, the quinazolinone scaffold is still considered a viable lead structure for the synthesis of more efficacious anticonvulsant activity. Quinazolin-4(3H)-one was reported to possess sedative-hypnotic and/or anticonvulsant activities (Archana et. al., 2002 and Alagarsamy V. et. al., 2006) apart from other pharmacological properties (Kant P, 2006 and Pattan S.R. et. al., 2006). These observation led to the conception that a novel series of schiff bases of 3-amino-2-methyl quinazolin-4-(3H)-ones **(4a-4l)** were synthesized using different aromatic aldehydes by condensation and their chemical structure were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral and elemental analysis. These compounds were screened for their anti-convulsant activities by MES method.

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MATERIALS AND METHODS

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ^{1}H (300 MHz) and ^{13}C-NMR (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were obtained with an elemental Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E Merk) using ethyl acetate: n-hexane (20:80) and visualized in UV chamber. IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

GENERAL PROCEDURE

In the present study anthranilic acid **(1)** was treated with acetic anhydride to form 2-methyl benzoxazin-4-one **(2)** which further reacted with hydrazine hydrate resulted into 3-amino-2-methyl quinazolin-4-(3H)-ones **(3)**. The compound **3** was subjected to react with various aromatic aldehydes in presence of ethanol as a solvent to form schiff bases **(4a-4l)** are summarized in scheme.

The 3-amino 2-methyl quinazolin-4(3H)-one **(3)** was prepared according to reported literature (Alagarsamy V. et. al., 2005) and characterized. Yield: 73%; m.p.141-143 °C; IR (KBr, cm^{-1}): 3030 (Ar-CH), 2927 (CH in CH_3), 1716 (C=O), 1464 (C=C), 1332 (N-H). ^{1}H-NMR ($CDCl_3$) δ: 7.41-7.82 (m, 4H;C_5,C_6,C_7,C_8,Ar-H), 1.94 (s, 2H; -NH_2), 0.97 (s, 3H; -CH_3). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 161.7 (C_4), 133.6 (C_7), 128.2 (C_5), 127.6 (C_6), 122.3 (C_8), 18.9 (-$\underline{C}H_3$). EI-MS m/z (M+): 175 (Calcd for $C_9H_9N_3O$; 175.18). Anal. Calcd for $C_9H_9N_3O$; C, 61.70; H, 5.18; N, 23.99. Found: C, 61.65; H, 5.18; N, 23.88. Equimolar quantities (0.01 mol) of 3-amino 2-methyl quinazolin 4-(3H)-one **(3)** and aromatic aldehyde were dissolved in 20 ml of ethanol and refluxed for 8 h then kept aside for 3 days, the product **(4a-4l)** which separated out was filtered, dried and recrystallised from absolute ethanol.

3-(benzylideneamino)-2-methyl quinazolin-4-(3H)-one (4a)

Pale yellow crystal; Yield: 80%; m.p. 153-155 °C; IR (KBr, cm^{-1}): 3018 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1510 (C=N), 1460 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.05 (s, 1H; -N=C$\underline{H}$-), 7.19-7.88 (m, 9H;C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{4'}$,$C_{5'}$, $C_{6'}$,Ar-H), 0.86 (s, 3H; C_2, -CH_3). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.1 (C_4), 143.3 (-N=$\underline{C}$H-), 133.3 (C_7), 131.4 ($C_{4'}$), 129.4 ($C_{2'}$ & $C_{6'}$), 128.9 ($C_{3'}$ & $C_{5'}$), 128.6 (C_5), 127.1 (C_6), 19.8 (-$\underline{C}H_3$). EI-MS m/z (M+): 263 (Calcd for $C_{16}H_{13}N_3O$; 263.29). Anal. Calcd for $C_{16}H_{13}N_3O$; C, 72.99; H, 4.98; N, 15.96. Found: C, 72.95; H, 4.96; N, 15.92.

3-(4-methoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4b)

Cream solid; Yield: 72%; m.p. 191-194 °C; IR (KBr, cm^{-1}): 3046 (Ar-CH), 2912 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1462 (C=C), 1124 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.07 (s, 1H; -N=C$\underline{H}$-), 6.81-7.92 (m, 8H; C_5,C_6,C_7,C_8,$C_{2'}$, $C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 3.70 (s, 3H; -OC$\underline{H}_3$), 0.79 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.9 (C_2), 160.2 (C_4), 143.2 (-N=$\underline{C}$H-), 133.2 (C_7), 163.1 ($C_{4'}$), 130.1 ($C_{2'}$ & $C_{6'}$), 128.6 (C_5), 127.3 (C_6), 126.2 ($C_{1'}$), 122.2 (C_8), 114.3 ($C_{3'}$ &$C_{5'}$), 55.6 (-O$\underline{C}H_3$), 20.2 (-$\underline{C}H_3$). EI-MS m/z (M+): 293 (Calcd for $C_{17}H_{15}N_3O_2$; 293.31). Anal. Calcd for $C_{17}H_{15}N_3O_2$; C, 69.61; H, 5.15; N, 14.33. Found: C, 69.58; H, 5.14; N, 14.28.

3-(2-hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4c)

Pale yellow solid; Yield: 66%; m.p. 173-175 °C; IR (KBr, cm^{-1}): 3040 (Ar-CH), 2915 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1457 (C=C) 1350,1205 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C$\underline{H}$-), 6.78-7.88 (m, 8H; C_5,C_6,C_7, C_8,$C_{3'}$,$C_{4'}$,$C_{5'}$,$C_{6'}$,Ar-H), 5.41 (s, 1H; Ar-O$\underline{H}$), 0.82 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 164.5 ($C_{2'}$) 160.6 (C_4), 142.9 (-N=$\underline{C}$H-), 133.7 (C_7), 132.2 ($C_{4'}$), 130.3 ($C_{6'}$), 128.6 (C_5), 127.4 (C_6), 122.1 (C_8), 121.3 ($C_{5'}$), 118.2 ($C_{1'}$), 116.2 ($C_{3'}$), 20.1 (-$\underline{C}H_3$). EI-MS m/z (M+): 279 (Calcd for $C_{16}H_{13}N_3O_2$; 279.29). Anal. Calcd for $C_{16}H_{13}N_3O_2$; C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.61; N, 15.01.

3-(4-N, N-dimethylamino benzylideneamino)-2-methyl quinazolin-4-(3H)-one (4d)

Bright yellow crystal; Yield: 68%; m.p. 187-190 °C; IR (KBr, cm^{-1}): 3032 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1518 (C=N), 1453 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.02 (s, 1H; -N=C$\underline{H}$-), 6.75-7.89 (m, 8H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 2.86 (s, 6H; -N-($C\underline{H}_3$)$_2$), 0.82 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 159.2 (C_4) 151.2 ($C_{4'}$), 142.2 (-N=$\underline{C}$H-), 133.6 (C_7), 130.3 ($C_{2'}$ &$C_{6'}$), 128.6 (C_5), 127.6 (C_6), 123.2 ($C_{1'}$), 122.3 (C_8), 113.8 ($C_{3'}$ & $C_{5'}$), 55.6 (-O$\underline{C}H_3$), 20.1 (-$\underline{C}H_3$). EI-MS m/z (M+): 306 (Calcd for $C_{18}H_{18}N_4O$; 306.36). Anal. Calcd for $C_{18}H_{18}N_4O$; C, 70.57; H, 5.92; N, 18.29. Found: C, 70.48; H, 5.94; N, 18.31.

3-(3-nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4e)

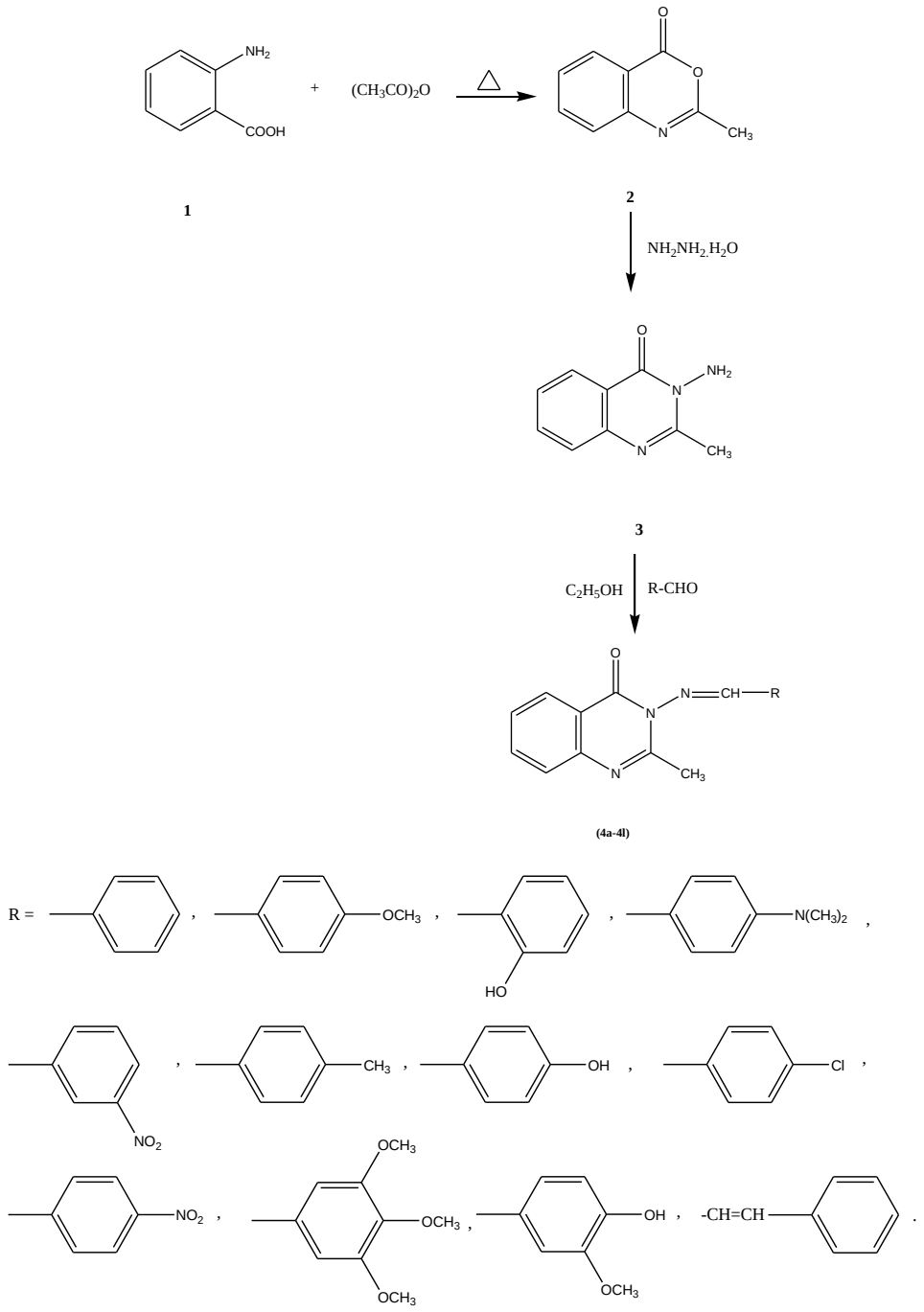
Cream solid; Yield: 65%; m.p. 190-194 °C; IR (KBr, cm^{-1}): 3017 (Ar-CH), 2922 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1522 and 1335 (N=O), 1450 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.09 (s, 1H; -N=C$\underline{H}$-), 7.41-7.92(m, 7H; C_5,C_6,C_7,C_8,$C_{4'}$,$C_{5'}$,$C_{6'}$,Ar-H), 0.92 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.9 (C_2), 159.8 (C_4), 148.6 ($C_{3'}$), 143.1 (-N=$\underline{C}$H-), 134.3 ($C_{1'}$), 135.3 ($C_{6'}$), 133.6 (C_7), 129.8 ($C_{5'}$), 128.8 (C_5), 127.4 (C_6), 124.2 ($C_{2'}$), 123.2 ($C_{4'}$), 122.4 (C_5), 20.3 (-$\underline{C}H_3$). EI-MS m/z (M+): 308 (Calcd for $C_{16}H_{12}N_4O_3$; 308.29). Anal. Calcd for $C_{16}H_{12}N_4O_3$; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.31; H, 3.83; N, 18.14.

3-(4-methylbenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4f)

Cream crystal; Yield: 76%; m.p. 164-166 °C; IR (KBr, cm^{-1}): 3041 (Ar-CH), 2926 (CH in CH_3) 1718 (C=O), 1522 (C=N), 1448 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C$\underline{H}$-), 7.09-7.81 (m, 8H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 2.36 (s, 3H; -C$\underline{H}_3$), 0.92 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.3 (C_4), 143.1 (-N=$\underline{C}$H-), 133.8 (C_7), 130.8 ($C_{1'}$), 129.4 ($C_{3'}$ & $C_{5'}$), 129.1 ($C_{2'}$ & $C_{6'}$), 128.6 (C_5), 127.4 (C_6), 122.6 (C_8), 24.3 (-$\underline{C}H_3$), 20.3 ($\underline{C}H_3$). EI-MS m/z (M+): 277 (Calcd for $C_{17}H_{15}N_3O$; 277.32). Anal. Calcd for $C_{17}H_{15}N_3O$; C, 73.63; H, 5.45; N, 15.15. Found: C, 73.53; H, 5.41; N, 15.14.

3-(4-hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4g)

Pale yellow crystal; Yield: 77%; m.p. 210-214 °C; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2924 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1454 (C=C), 1355 and 1208 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C$\underline{H}$-), 6.82-7.88 (m, 8H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 5.44 (s, 1H; Ar-O$\underline{H}$), 0.88 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.1 (C_2), 160.4 ($C_{4'}$), 159.2 (C_4), 144.2 (-N=$\underline{C}$H-), 134.2 (C_7), 130.5 ($C_{2'}$ & $C_{6'}$), 129.2 (C_5), 127.4 (C_6), 122.8 (C_8), 115.6 ($C_{3'}$ & $C_{5'}$), 20.1 (-$\underline{C}H_3$). EI-MS m/z (M+): 279 (Calcd for $C_{16}H_{13}N_3O_2$; 279.29). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.64; N, 15.07.



Scheme 1: Synthesis of Schiff bases of 3-amino-2-methyl quinazolin-4(3H)-one

3-(4-chlorobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4h)

Pale yellow powder; Yield: 74%; m.p. 259-263 °C; IR (KBr, cm^{-1}): 3036 (Ar-CH), 2932 (CH in CH_3), 1726 (C=O), 1520 (C=N), 1446 (C=C), 729 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 6.91-7.82 (m, 8H; C_5,C_6,C_7, C_8,$C_{2'}$,$C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 160.8 (C_4), 144.2 (-N=<u>C</u>H-), 136.2 ($C_{4'}$), 133.4 (C_7), 132.5 ($C_{1'}$), 130.8 ($C_{2'}$ & $C_{6'}$), 129.2 ($C_{3'}$ & $C_{5'}$), 128.6 (C_5), 126.9 (C_6), 122.4 (C_8), 19.8 (-<u>C</u>H$_3$). EI-MS m/z (M+): 297 (Calcd for $C_{16}H_{12}ClN_3O$; 297.73). Anal. Calcd for $C_{16}H_{12}ClN_3O$; C, 64.54; H, 4.06; N, 14.91. Found: C, 64.50; H, 4.01; N, 14.81.

3-(4-nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4i)

Yellow crystal; Yield: 75%; m.p. 222-225 °C; IR (KBr, cm^{-1}): 3048 (Ar-CH), 2926 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1518 and 1342 (N=O), 1452(C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 7.35-7.99 (m, 8H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{5'}$,$C_{6'}$,Ar-H), 0.82 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.2 (C_2), 161.2 (C_4), 150.2 ($C_{4'}$), 143.2 (-N=<u>C</u>H-), 140.1 ($C_{1'}$), 134.0 (C_7), 129.4 ($C_{2'}$ & $C_{6'}$), 128.9(C_5), 127.6 (C_6), 122.6 (C_8), 121.2 ($C_{3'}$ & $C_{5'}$), 0.92 (-<u>C</u>H$_3$). EI-MS m/z (M+): 308 (Calcd for $C_{16}H_{12}N_4O_3$; 308.29). Anal. Calcd for $C_{16}H_{12}N_4O_3$; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.22; H, 3.94; N, 18.21.

Table 1: Anti-convulsant activity of the title compounds (4a-4l)

COMPOUNDS	DOSE (mg/kg)	FLEXION PHASE		EXTENSOR PHASE	
		MEAN±SEM	% PROTECTION	MEAN±SEM	% PROTECTION
4a	100	5.62±0.33*	21.62	6.33±0.49*	57.32
4b	100	5.33±0.33*	25.66	6.00±0.58*	59.54
4c	100	5.83±0.31*	18.69	6.17±0.40*	58.40
4d	100	5.00±0.37*	30.26	4.83±0.40**	67.43
4e	100	5.17±0.48*	27.89	5.67±0.35**	61.77
4f	100	5.17±0.48*	27.89	4.33±0.33**	70.82
4g	100	5.33±0.42*	25.66	5.50±0.43**	62.91
4h	100	5.50±0.43*	23.29	5.83±0.31*	60.69
4i	100	5.17±0.31*	27.89	5.67±0.33**	61.77
4j	100	5.67±0.42*	20.92	5.50±0.43**	62.91
4k	100	5.67±0.42*	20.92	5.83±0.48*	60.69
4l	100	5.33±0.42*	25.66	6.33±0.33*	57.32
Phenytoin	25	4.00±0.37**	44.21	0.00±0.00**	100.00
Control	-	7.17±0.48	-	14.83±0.31	-

The results are expressed as mean±SEM (n=6). Significance was calculated by using one-way ANOVA with Dunnet's t-test. The difference in results was considered significant when *P< 0.05, **P<0.01. NS (Non significant).

3-(3,4,5,-trimethoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4j)

Bright yellow powder; Yield: 70%; m.p. 261-264 °C; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2922 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1463 (C=C), 1132 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.10 (s, 1H; -N=C<u>H</u>-), 7.38-7.92 (m, 4H; C_5,C_6,C_7,C_8,Ar-H), 6.61 (s, 1H; $C_{2'}$,Ar-H), 6.64 (s, 1H; $C_{6'}$,Ar-H), 3.82 (s, 9H; [OC<u>H</u>$_3$]$_3$), 0.91 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.5 (C_2), 160.2 (C_4), 150.8 ($C_{3'}$ & $C_{5'}$), 143.3 (-N=<u>C</u>H-), 141.9 ($C_{4'}$), 135.2 (C_7), 129.9 (C_5), 128.2($C_{1'}$), 127.6 (C_6), 122.6 (C_8), 107.1 ($C_{2'}$ & $C_{6'}$), 56.5 (-O<u>C</u>H$_3$), 21.2 (-<u>C</u>H$_3$). EI-MS m/z (M+): 353 (Calcd for $C_{19}H_{19}N_3O_4$; 353.37). Anal. Calcd for $C_{19}H_{19}N_3O_4$; C, 64.58; H, 5.42; N, 11.89. Found: C, 64.49; H, 5.38; N, 11.85.

3-(4-hydroxy-3-methoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4k)

Cream solid; Yield: 65%; m.p. 122-124 °C; IR (KBr, cm^{-1}): 3032 (Ar-CH), 2925 (CH in CH_3), 1722 (C=O), 1518 (C=N), 1455 (C=C), 1352 and 1208 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.92 (s, 1H; -N=C<u>H</u>-), 7.42-7.82 (m, 4H; C_5,C_6,C_7,C_8,Ar-H), 7.10 (s, 1H; Ar-H), 6.66-6.69 (d, J=6.7 Hz; $C_{5'}$, Ar-H), 7.01-7.05 (d, J=5.8 Hz; $C_{6'}$, Ar-H), 5.12 (s, 1H; Ar-OH), 3.90 (s, 3H; -OC<u>H</u>$_3$), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.1 (C_2), 161.0 (C_4), 151.2 ($C_{3'}$), 148.2 ($C_{4'}$), 143.4 (-N=<u>C</u>H-), 133.6 (C_7), 128.6 (C_5), 127.6 (C_6), 127.4($C_{1'}$), 122.9 ($C_{6'}$), 122.6 (C_8), 56.2 (-O<u>C</u>H$_3$), 20.2 (-<u>C</u>H$_3$). EI-MS m/z (M+): 309 (Calcd for $C_{17}H_{15}N_3O_3$; 309.31). Anal. Calcd for $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.89; N, 13.58. Found: C, 66.06; H, 4.78; N, 13.62.

3-(3-phenylallylideneamino)-2-methyl quinazolin-4-(3H)-one (4l)

Lemon yellow crystal; Yield: 75%; m.p. 155-157 °C; IR (KBr, cm^{-1}): 3019 (Ar-CH), 2916 (CH in CH_3), 1728 (C=O), 1512 (C=N), 1458 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 7.61 (s, 1H; -N=C<u>H</u>-), 7.14-7.88 (m, 9H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{4'}$, $C_{5'}$,$C_{6'}$ Ar-H), 6.59-6.62 (d, 1H; J=7.2 Hz; C_6H_5-C<u>H</u>=CH-), 5.61-5.63 (d, 1H; J=6.5 Hz; C_6H_5-CH=C<u>H</u>-), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.6 (C_4), 139.2 (C_6H_5-<u>C</u>H=CH-) 137.6 (-N=<u>C</u>H-), 135.2 ($C_{1'}$), 134.6 (C_7), 128.8 (C_5), 128.6 ($C_{3'}$ &$C_{5'}$), 128.1 ($C_{4'}$), 127.6 (C_6), 126.6 (C2' & C6'), 126.3 (C_6H_5-CH=<u>C</u>H-), 20.2 (-<u>C</u>H$_3$). EI-MS m/z (M+): 289(Calcd for $C_{18}H_{15}N_3O$; 289.33). Anal. Calcd for $C_{18}H_{15}N_3O$; C, 74.72; H, 5.23; N, 14.52. Found: C, 74.36; H, 5.08; N, 14.38.

PHARMACOLOGICAL EVALUATION

Animals

The animals used in the present study such as swiss albino mice weighing 20-25 gm were procured from C.L.Baid Metha College of Pharmacy, Chennai, India. Animals were maintained in colony cages at 25±2^{0}C, relative humidity of 45-55%, maintained under 12 h light and dark cycle and were fed with standard animal feed and water *ad libitum*. Animals were maintained under standard conditions in an animal house approved by committee for the purpose of control and supervision on experiments on animals (CPCSEA). Institutional Animal Ethics Committee approved the experimental protocol. The entire animals were acclimatized for a week before use.

Acute toxicity

The acute toxicity[10] test was carried out according to the Organization for Economic Co-operation and Development (OECD) guidelines to establish the effective dose of test compounds after obtaining ethical clearance from Animal Ethics Committee of C.L. Baid Metha College of Pharmacy, Chennai-600 096, Tamil Nadu, India. Albino mice of either sex weighing between 20 and 25 g were grouped starved for 24 h with water *ad*

libitum prior to test. On the day of the experiment, animals were administered with different compounds to different groups in an increasing dose of 10, 20, 100, 200, 1000 and 2000 mg/kg body weight orally. The animals were then observed continuously for 3 h for general behavioral, neurological, autonomic profiles and then every 30 min for next 3 h and finally for next 24 h or till death.

Anti-convulsant activity (MES method in mice)

In the present study anti-convulsant activity of the synthesized compounds were screened by MES (Maximal electrical shock) method (Kulkarini S.K., 1987). Swiss mice (n=6) of either sex selected by random sampling technique was used for the study. Phenytoin at the dose of 25 mg/kg, i.p. was administered as standard drugs for comparison. The test compounds at 100 mg/kg) were administrated orally. The animals were held in suitable position and the corneal electrodes was placed on the cornea of the mice and applied 50mA current for 0.2 sec after half an hour administration of test compounds. Then the time spent by animal in each phase of convulsion was recorded. The reduction in time or abolition of tonic extensor phases was recorded. Animals in which extensor response was abolished were taken as protected mice. The percentage protection was calculated by using the following formula and the results were depicted in table 1.

$$\% \text{ protection} = [(\text{Control-Test})/\text{Control}] \times 100$$

RESULTS AND DISCUSSION

From the preliminary toxicity studies, it was observed that, all the test compounds have revealed good safety profile till the uppermost dose (2000 mg/kg, b.w.). No mortality of animals observed even after 24 h but there were few changes in the behavioral response like alertness, touch response and restlessness. Therefore, $1/20^{th}$ of the maximum tolerated dose i.e. 100 mg/kg, b.w. was chosen as a dose for evaluating its anti-convulsant potency.

MES method was used to study the anti-convulsant activity of the synthesized compounds (100 mg/kg, p.o) when compared with phenytoin (25 mg/kg, i.p) as standard drug. The effect of drug on tonic flexion and tonic extensor phase was recorded. All the compounds exhibited significant anti-convulsant activity. All compounds exhibit more action on extensor phase than flexion phase. 3-(4-methyl benzylideneamino)-2-methyl quinazolin-4(3H)-one **(4f)** exhibited highest activity among the series. Compound **4d** and **4e** exhibited moderate activity. Synthesized compound **4a** and **4l** shows lesser activity among the series of compounds. From the data it reveals that compounds having substituent in the phenyl ring (electron donating or electron withdrawing groups) exhibited better anti-convulsant activity than the unsubstituted one.

CONCLUSION

In conclusion, the present study highlights the importance of aromatic imino substitution at 3^{rd} position of the quinazolin-4(3H)-one ring features responsible for the anti-convulsant activity and therefore may serves as a lead molecule to obtain clinically useful novel entities in the new millennium.

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