Med Chem Res (2011) 20:738–745
DOI 10.1007/s00044-010-9362-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and potential CNS activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea

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Received: 10 August 2009 / Accepted: 3 May 2010 / Published online: 1 July 2010

Abstract Twelve new 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea were synthesized and screened for anticonvulsant, CNS depressant, and sedative-hypnotic activity. After i.p. injection to mice at doses of 30, 100, and 300 mg/kg body weight 2,3-Disubstituted-quinazolin-4(3H)-one were examined in the maximal electroshock-induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. Spectroscopic data and elemental analysis were consistent with the newly synthesized compounds. The neurotoxicity was assessed using the rotorod method. M3, M4, and M10 were found to be active in both MES screen and scPTZ screen at 0.5 h. All except M11 showed more than 44% decrease in locomotor activity after 1 h of compound administration via actophotometer screen. CNS-depressant activity screened with the help of the forced swim method resulted into some potent compounds. Except for M6 and M11 other tested compounds were found to exhibit potent CNS depressants activity as indicated by increased immobility time. It can be concluded that newly synthesized compounds possessed sedative-hypnotic and CNS depressant activities.

Keywords 4(3H)-quinazolinone · Anticonvulsant · Sedative-hypnotic

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Introduction

Epilepsy is one of the most common diseases of the brain affecting at least 50 million persons worldwide. There is currently a need for improved agents for the treatment of seizures. Polytherapy with antiepileptic drugs is necessary in clinical practice because of the limited efficacy of monotherapy. In recent years many new chemical entities (NCE) have been designed that were structurally dissimilar from many common anticonvulsant containing dicarboximide function (CONRCO), which contributes to toxic side effects. 4(3*H*)-Quinazolinones and related quinazolines are classes of fused heterocyclic that are of considerable interest. Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities like anti-tumor, anti-inflammatory, central nervous system depressant, stimulant, anthelmintic, muscle relaxant, hypoglycemic, and anti-microbial activities (Armarego, 1963; Chaurasia and Sharma, 1982; Gupta *et al.*, 2008; Kumar *et al.*, 1983; Misra *et al.*, 1982, 2006; Mukerji *et al.*, 1980; Saxena *et al.*, 1992). Literature survey revealed that presence of substituted aromatic ring at position 3 and methyl group at position 2 are necessary requirement for the central nervous system (CNS) depression and anticonvulsant activities. Modification of methyl group by some other chemical moiety yielded structural analogues with anticonvulsant activity. Various hypotheses were analyzed before we undertook chemical syntheses of the compounds synthesis (Boltze *et al.*, 1963; Wolfe *et al.*, 1990; Jatav *et al.*, 2008a, b; Dimmock *et al.*, 1995a, b; Kashaw *et al.*, 2008, 2009). The present work was carried out on three objectives: (i) The first objective was the synthesis of the hybrid compounds possessing mentioned molecular features; (ii) the second objective was anticonvulsant screening

of the synthesized compounds by MES and subcutaneous pentylenetetrazole (scPTZ) methods; (iii) the third objective was the sedative-hypnotic, CNS depressant, and phenobarbitone induced hypnosis potentiation screening of the synthesized compounds. In hope of getting synergistic response of 4(3*H*)-quinazolinone nucleus itself, placement of substitution semicarbazides at third position and chemically modifying second position of 4(3*H*)-quinazolinone (substituting $-CH_3$), this article reports on the synthesis, anticonvulsant, neurotoxicity, CNS depressant, and behavioral study of twelve 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea.

Chemistry

The synthesis of the target compounds was accomplished as shown in Fig. 1. Synthesis of 2-methyl benzoxazin-4-one is based on the earlier reported methods (Mishra *et al.*, 2006; Smith *et al.*, 1996). Anthranilic acid **(4)** was refluxed under standard conditions with acetic anhydride to yield 2-methyl benzoxazin-4-one. Various substituted aryl semicarbazides were synthesized according to the procedure mentioned in the literature. Substituted aniline **(1)** was treated with sodium cyanate in the presence of glacial acetic acid according to the known urea method to yield substituted phenyl urea **(2)**. These substituted phenyl urea derivatives on condensation with hydrazine hydrate in ethanol under alkaline conditions provided substituted aryl semicarbazides **(3)**. Synthesis of the target compounds was carried out according to the scheme presented in Fig. 1. Different substituted semicarbazides were refluxed in the presence of glacial acetic acid with 2-methyl benzoxazin-4-one to yield M1–M12, respectively. The infrared (IR) spectra showed the C=O str. at 1670 cm^{-1}, C=N stretching of quinazolinone ring at 1590 cm^{-1}. The ^{13}C NMR depicted spectrum at (C-2) 163, (C-4) 166, (C-11) 112, and (Cz) 146. Thin layer chromatography (TLC) was run throughout the reaction to optimize the reaction for purity and completion.

Results and discussion

Initial anticonvulsant activity and neurotoxicity data for the quinazolinone analogs are reported in Table 1, along with the literature data on Phenytoin, Carbamazapine, Sodium valproate, Phenobarbital, and Ethosuximide. All the quinazolinone analogs showed potent sedative-hypnotic and CNS-depressant activity than anticonvulsant activity. In the prepared series M3, M4, and M10 were found to be active in the MES screen at 0.5 h, whereas M10 showed anticonvulsant activity at 4 h. All the compounds exhibited activity at 300 mg/kg body weight. Except M3, M4, and M10, all the remaining compounds were inactive in the scPTZ screen at 0.5 h. Only M10 observed activity at both 0.5 and 4 h interval time which indicate their rapid action and long duration of activity. Synthesized compounds exhibited NT at only 300 mg/kg. M3 and M12 showed extend NT lasting up to 4 h. The NT of the compounds as indicated by their unableness to grasp the rotating rot for sufficient time may be due to the increase BBB penetration and accumulation at neuroprotein sites and then binding to unwanted receptor sites. All the compounds were also screened for behavior study and CNS-depressant activity. In the behavioral study using actophotometer scoring technique, the entire synthesized compounds showed decrease in locomotor activity where 42% was the lowest and 53% was the maximal decrease in locomotor activity when compared to phenytoin as reported in Table 2. All the compounds except M11 showed more than 44% decrease in locomotor activity ($P < 0.05$) after 1 h of compound administration. In a

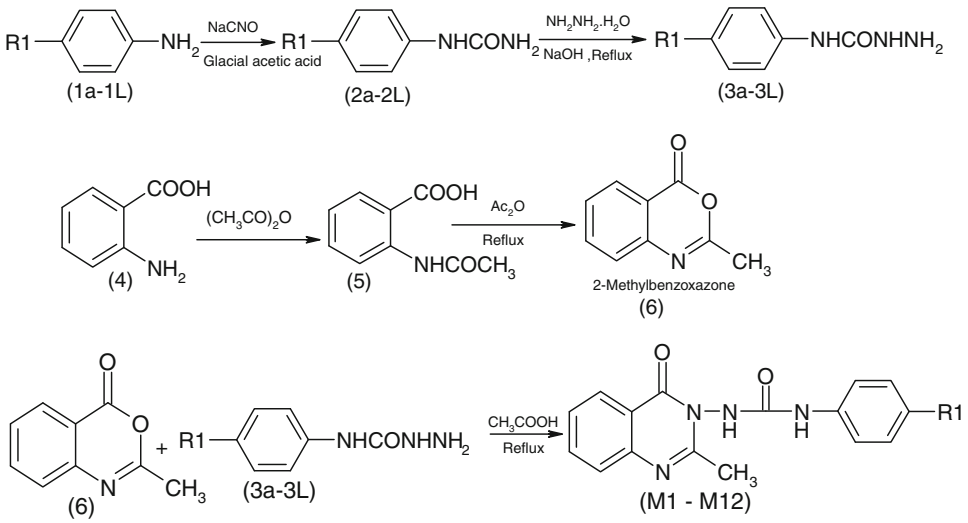


Fig. 1 Scheme for the synthesis of substituted phenyl semicarbazides (3a–3L), 2-methyl benzoxazin-4-one (6), and 1-(4-substituted-phenyl)-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-urea (M1–M12)

Table 1 Anticonvulsant activity and minimal motor impairment of 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea (M1–M12)

Code no.	Intraperitoneal injection in mice[a]					
	MES screen		scPTZ screen		Neurotoxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
M1	–	–	–	–	300	–
M2	–	–	–	–	–	–
M3	300	–	300	–	300	300
M4	300	–	300	–	300	–
M5	–	–	–	–	–	–
M6	–	–	–	–	–	–
M7	–	–	–	–	–	–
M8	–	–	–	–	–	–
M9	–	–	–	–	–	–
M10	300	300	300	–	–	–
M11	–	–	–	–	–	–
M12	–	–	–	–	300	300
Phenytoin	30	30	–	–	100	100
Carbamazepine	30	100	100	300	100	300
Sodium valproate	–	–	300	–	–	–
Phenobarbitals	100	30	30	300	100	300
Ethosuximide	–	–	300	–	–	–

[a] Doses of 30, 100, and 300 mg/kg were administered. The figure in the table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after injections. – indicates an absence of activity at maximum dose administered (300 mg/kg)

similar study with forced swim pool test, the immobility time after administration of the test compounds was compared with carbamazepine (Table 3). Readings of control groups were taken individually for each compound 24 h prior to compound administration. Experimental results indicate that our compound exhibited better sedative hypnotic and CNS-depressant activity as compare to anticonvulsant activity. Biological activity was also ascertained for PEG because it was used as a vehicle for the synthesized compounds. Except for M6 and M11 other tested compounds were found to exhibit potent CNS-depressants activity as indicated by increased immobility time. Bulkier compounds are more lipophilic and can cross blood brain barrier to exert their effect at CNS. 2-Methyl substituted compounds (M1–M12) possessed better CNS activity as compared to unsubstituted compounds (H1–H12). Among M7–M9 *para* phenyl substituted compounds showed better activity may be due to proper spatial orientation of –CH3 toward receptor site. This study explored that substitution of aryl semicarbazides at third position and $-CH_3$ moiety at second position of 4(3H)-quinazolinone leads to the development of NCE with potent CNS activity.

Conclusion

Based upon the experimental results it may be concluded that the synthesized NCE showed potent sedative-hypnotic

Table 2 Behavioral study of 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea (M1–M12)

Compound[a]	Activity score[b]			% Inhibition
	Control (24 h prior)	Post-treatment		
		0.5 h after	1 h after	
M1	484.32 ± 0.72	289.19 ± 0.77	242.24 ± 0.18	50
M2	485.56 ± 0.32	322.56 ± 1.29	262.36 ± 0.82	45
M3	324.76 ± 0.84	312.32 ± 0.82	120.45 ± 0.86	48
M4	515.54 ± 0.82	298.73 ± 0.48	251.10 ± 0.19	51
M5	476.62 ± 1.26	273.55 ± 0.99	220.30 ± 1.20	53
M6	416.50 ± 0.65	391.76 ± 1.29	209.48 ± 1.36	40
M7	530.54 ± 0.82	298.73 ± 0.48	266.10 ± 0.19	51
M8	400.62 ± 0.98	282.13 ± 0.76	187.78 ± 0.99	51
M9	520.71 ± 1.21	326.28 ± 2.20	249.41 ± 0.28	52
M10	480.62 ± 1.26	273.55 ± 0.99	223.30 ± 1.20	53
M11	490.67 ± 0.78	342.82 ± 1.14	285.42 ± 1.24	42
M12	495.56 ± 0.32	322.56 ± 1.29	272.36 ± 0.82	45
Phenytoin[c]	646.40 ± 31.12	251.02 ± 12.32	194.10 ± 30.11	70

[a] The compounds were tested at a dose of 100 mg/kg (i.p.)

[b] Each score represents the mean ± SEM of six mice, significantly different from the control score at <0.02 and NS indicate not significant at $P > 0.02$ (student's *t*-test)

[c] Tested at 25 mg/kg i.p

Table 3 CNS study on 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea (M1–M12)

Compound[a]	Immobility time[b](s)	
	Control (24 h prior)	Post-treatment (60 min after)
PEG	174.67 ± 10.72	178 .53 ± 14.23 NS
M1	73.32 ± 18.50	130.56 ± 11.25
M2	120.47 ± 17.12	188.16 ± 12.67
M3	130.58 ± 18.36	204.70 ± 12.59
M4	45.60 ± 19.45	70.63 ± 14.63
M5	130.73 ± 15.15	194.05 ± 13.16
M6	176.87 ± 17.78	190.29 ± 12.84 NS
M7	180.97 ± 14.15	226.29 ± 16.76
M8	172.47 ± 17.95	218.29 ± 20.27
M9	174.57 ± 13.15	210.29 ± 19.28
M10	162.67 ± 17.58	208.29 ± 20.99
M11	177.77 ± 18.49	202.29 ± 12.95 NS
M12	152.87 ± 8.37	198.29 ± 15.97
Carbamazepine[c]	138.12 ± 15.03	240.30 ± 14.18

[a] The compounds were tested at a dose of 100 mg/kg (i.p.)

[b] Each value represent the mean ± SEM of six rats significantly different from the control at $P < 0.05$ and NS denotes not significant at $P < 0.05$ (student's *t*-test)

[c] Tested at 30 mg/kg (i.p.)

and CNS-depressant activity as compared to anticonvulsant activity.

Experimental

Chemistry

Melting point was determined in one end open capillary tubes on a Buchi 530 melting point apparatus and is uncorrected. IR spectra were recorded for the compounds on Perkin Elmer Spectrum RXI Spectrophotometer in KBr. ^{13}C nuclear magnetic resonance (^{13}C NMR) and ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds on Advance bruker (300 MHz) instrument. Chemical shifts are reported in parts per million using tetramethylsilane as an internal standard. Elemental analysis (C & N) was undertaken with Elemental vario EL III Carlo Erba 1108 analyzer. The purity of the compounds was confirmed by TLC using silica gel glass plates and a solvent system of benzene: ethanol (9:1). The spots were developed in iodine chamber and visualized under ultra violet lamp.

Synthesis of substituted phenyl urea (2a–2L)

p-Substituted aniline (1a–1L; 0.1 mol) was dissolved in 10–50 ml of glacial acetic acid and volume was made up to 100 ml with water. To this sodium cyanate (6.5 g, 0.1 mol), 50 ml of warm water was added with constant stirring. Solution was allowed to stand for 60 min than cooled in ice and filtered with suction and dried. Physico-chemical data and m.p. of the synthesized products was in agreement with the data reported in the literature.

Synthesis of substituted phenyl semicarbazides (3a–3L)

Equimolar quantity of substituted phenyl urea (0.1 mol) and hydrazine hydrate (0.1 mol; 5 ml) in ethanol under alkaline condition (NaOH, 4 g) were refluxed for 4–10 h with stirring. Excess ethanol was distilled off under vaccum and then poured into ice. The product was filtered and recrystallized from 90% aqueous ethanol. In general, compounds exhibited IR (KBr) ν_{max} 3450, 1650, 3269, 840 cm^{-1}. ^{1}H NMR δ 7.2–7.5 (m, 4H, Ar–H), 8.26 (s, 1H, Ar–NH).

Synthesis of 2-methyl benzoxazin-4-one (7)

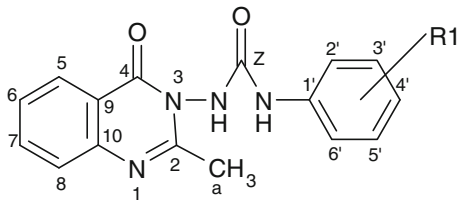
Anthranilic acid (4) (0.1 mol) was refluxed with acetic anhydride for 2 h to get *N*-acetyl anthranilic acid (6), which was cyclized under reflux with acetic anhydride. Excess of acetic anhydride was distilled off under vaccum and recrystallized with petroleum ether to get 2-methyl-benzoxazone (7). Physico-chemical data and m.p. of the 6 and 7 was in agreement with the data reported in the literature.

Synthesis of title compounds (M1–M12)

The title compounds were synthesized following procedure reported earlier. To a solution of 6 (0.01 M), substituted phenyl semicarbazides (3a–3L; 0.01 M) in glacial acetic acid was added and refluxed for 4 h. Obtained reaction mixture was poured into crushed ice and left overnight. The solid which separated out was filtered, washed thoroughly with cold distilled water, dried, and recrystallized from hot ethanol. The yield, melting point, and other physical properties of synthesized compound are recorded in Table 4.

M1 IR (cm^{-1}) 1680 (C=O str. of (*3H*)-quinazolinone ring), 1696 (C=O str. of phenyl urea), 1573 (C=N), 3048 (Ar–CH str.), 3420 (secondary amide NH str.): ^{13}C NMR (300 MHz, δ) ^{13}C NMR (300 MHz, δ) 166 (C-4), 164 (C-2), 122.1 (C_8 of 4(*3H*)-quinazolinone ring), 126.9 (C_{10} of 4(*3H*)-quinazolinone ring), 127.1 (C_6 of 4(*3H*)-quinazolinone ring), 147.8 (C_9 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 124.3 (C'_4 of phenyl urea), 154 (C_Z of phenyl urea): ^{1}H NMR (300 MHz, δ) 7.3–7.8 (m, 4H, Ar–H of (*3H*)-

Table 4 Physical data of 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-*4H*-quinazolin-3-yl)-urea (M1–M12)



Code no.	R1	Yield (%)	m.p. (°C)	Mol. formula	R_f	Element[b] (found % calculated %)
M1	–H	66	210	$C_{16}H_{14}N_4O_2$	7.1	N (19.04/19.01)
						C (65.30/65.28)
M2	–F	63	275	$C_{16}H_{13}FN_4O_2$	7.3	N (17.94/17.92)
						C (61.53/61.50)
M3	–Cl	69	242	$C_{16}H_{13}ClN_4O_2$	5.2	N (17.04/17.02)
						C (58.45/58.43)
M4	–Br	57	>300[a]	$C_{16}H_{13}BrN_4O_2$	5.5	N (15.01/15.0)
						C (51.49/51.46)
M5	–I	50	250	$C_{16}H_{13}IN_4O_2$	5.0	N (13.33/13.30)
						C (45.73/45.71)
M6	$–NO_2$	49	234	$C_{16}H_{13}N_5O_4$	5.3	N (20.64/20.63)
						C (56.64/56.62)
M7	*o*-CH_3(b)	59	262	$C_{17}H_{16}N_4O_2$	6.5	N (18.17/18.15)
						C (66.22/66.20)
M8	*m*-CH_3(b)	62	270	$C_{17}H_{16}N_4O_2$	6.0	N (18.17/18.15)
						C (66.22/66.20)
M9	*p*-CH_3(b)	71	278	$C_{17}H_{16}N_4O_2$	5.7	N (18.17/18.15)
						C (66.22/66.20)
M10	$–CH_2$(b)–CH_3(c)	64	229	$C_{18}H_{18}N_4O_2$	6.1	N (17.38/17.37)
						C (67.07/67.03)
M11	$–OCH_3$(b)	68	248	$C_{17}H_{16}N_4O_3$	5.6	N (17.27/17.25)
						C (62.95/62.93)
M12	$–OCH_2$(b)–CH_3(c)	58	>300[a]	$C_{18}H_{18}N_4O_3$	6.3	N (16.56/16.54)
						C (63.89/63.88)

[a] Melting point of the compound at their decomposition

[b] Elemental analyses for C and N were within ±0.4% of the theoretical value

quinazolinone ring), 7.1–7.64 (m, 5H, Ar–H of phenyl urea), 2.34 (s, *3H*, $–CH_3$), 6.1 (s, 2H of –NH–CO–NH–).

M2 IR (cm^{-1}) 1682 (C=O str. of (*3H*)-quinazolinone ring), 1695 (C=O str. of phenyl urea), 1585 (C=N), 3045 (Ar–CH str.), 3423 (secondary amide NH str.): ^{13}C NMR (300 MHz, δ) 165 (C-4), 162 (C-2), 122 (C_8 of 4(*3H*)-quinazolinone ring), 126 (C_{10} of 4(*3H*)-quinazolinone ring), 127.2 (C_6 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 147.3 (C_9 of 4(*3H*)-quinazolinone ring), 155 (C_Z of phenyl urea), 157.7 (C_4'): ^1H NMR (300 MHz, δ) 7.3–7.8 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.94–7.61 (m, 4H, Ar–H of phenyl urea), 6.0 (s, 2H of –NH–CO–NH–).

M3 IR (cm^{-1}) 1690 (C=O str. of (*3H*)-quinazolinone ring), 1696 (C=O str. of phenyl urea), 1570 (C=N), 3045 (Ar–CH str.), 3420 (secondary amide NH str.): ^{13}C NMR (300 MHz, δ) 166 (C-4), 163 (C-2), 123 (C_8 of 4(*3H*)-quinazolinone ring), 127 (C_{10} of 4(*3H*)-quinazolinone ring), 128.2 (C_6 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 148.3 (C_9 of 4(*3H*)-quinazolinone ring), 156 (C_Z of phenyl urea), 129.4 (C_4'): ^1H NMR (300 MHz, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 7.15–7.52 (m, 4H, Ar–H of phenyl urea), 6.2 (s, 2H of –NH–CO–NH–).

M4 IR (cm^{-1}) 1685 (C=O str. of (*3H*)-quinazolinone ring), 1692 (C=O str. of phenyl urea), 1588 (C=N), 3040 (Ar–CH str.), 3426 (secondary amide NH

str.): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 118.4 (C'_4): ^{1}H NMR (300 MHz, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 7.41–7.52 (m, 4H, Ar–H of phenyl urea), 6.0 (s, 2H of –NH–CO–NH–).

M5 IR (cm^{-1}) 1679 (C=O str. of (*3H*)-quinazolinone ring), 1690 (C=O str. of phenyl urea), 1571 (C=N), 3044 (Ar–CH str.), 3431 (secondary amide NH str.): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 92.9 (C'_4): ^{1}H NMR (300 MHz, δ) 7.4–7.7 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 7.12–7.40 (m, 4H, Ar–H of phenyl urea), 6.3 (s, 2H of –NH–CO–NH–).

M6 IR (cm^{-1}) 1680 (C=O str. of (*3H*)-quinazolinone ring), 1690 (C=O str. of phenyl urea), 1590 (C=N), 3048 (Ar–CH str.), 3421 (secondary amide NH str.): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 114 (C'_4): ^{1}H NMR (300 MHz, δ) 7.2–7.8 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 7.92–8.14 (m, 4H, Ar–H of phenyl urea), 6.0 (s, 2H of –NH–CO–NH–).

M7 IR (cm^{-1}) 1670 (C=O str. of (*3H*)-quinazolinone ring), 1690 (C=O str. of phenyl urea), 1576 (C=N), 3041 (Ar–CH str.), 3430 (secondary amide NH str.), 2971 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 129.6 (C'_2), 11.8 (C_b): ^{1}H NMR (300 MHz, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 2.35 (s, *3H*, $-CH_3$), 6.0 (s, 2H of –NH–CO–NH–).

M8 IR (cm^{-1}) 1670 (C=O str. of (*3H*)-quinazolinone ring), 1698 (C=O str. of phenyl urea), 1570 (C=N), 3041 (Ar–CH str.), 3430 (secondary amide NH str.), 2970 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 124.6 (C'_3), 11.8 (C_b): ^{1}H NMR (300 MHz, δ) 7.1–7.6 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.84–7.50 (m, 4H, Ar–H of phenyl urea), 2.34 (s, *3H*, $-CH_3$), 6.1 (s, 2H of –NH–CO–NH–).

M9 IR (cm^{-1}) 1678 (C=O str. of (*3H*)-quinazolinone ring), 1694 (C=O str. of phenyl urea), 1563 (C=N), 3041 (Ar–CH str.), 3420 (secondary amide NH str.), 2970 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 133 (C'_4), 11.8 (C_b): ^{1}H NMR (300 MHz, δ) 7.0–7.6 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 2.35 (s, *3H*, $-CH_3$), 6.0 (s, 2H of –NH–CO–NH–).

M10 IR (cm^{-1}) 1692 (C=O str. of (*3H*)-quinazolinone ring), 1698 (C=O str. of phenyl urea), 1595 (C=N), 3041 (Ar–CH str.), 3422 (secondary amide NH str.), 2970 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 133 (C'_4), 28.8 (C_b), 16.1 (C_c): ^{1}H NMR (300 MHz, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 1.24–2.59 (m, 5H, $-CH_2CH_3$), 6.0 (s, 2H of –NH–CO–NH–).

M11 IR (cm^{-1}) 1680 (C=O str. of (*3H*)-quinazolinone ring), 1692 (C=O str. of phenyl urea), 1580 (C=N), 3042 (Ar–CH str.), 3423 (secondary amide NH str.), 2970 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.15 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 157 (C'_4), 28.6 (C_b): ^{1}H NMR (300 MHz, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-quinazolinone ring), 6.74–7.53 (m, 4H, Ar–H of phenyl urea), 3.73 (s, *3H*, $-CH_3$), 6.0 (s, 2H of –NH–CO–NH–).

M12 IR (cm^{-1}) 1689 (C=O str. of (*3H*)-quinazolinone ring), 1695 (C=O str. of phenyl urea), 1580 (C=N), 3045 (Ar–CH str.), 3420 (secondary amide NH str.), 2970 (C–H str): ^{13}C NMR (300 MHz, δ) 165 (C-4), 164 (C-2), 121.1 (C_8 of 4(*3H*)-quinazolinone ring), 14.0 (C_a), 125.9 (C_{10} of 4(*3H*)-quinazolinone ring), 126.1 (C_6 of 4(*3H*)-quinazolinone ring), 146.8 (C_9 of 4(*3H*)-quinazolinone ring), 154 (C_Z of phenyl urea): 157 (C'_2), 65.1 (C_b), 14.1 (C_c): ^{1}H NMR (300 MH_z, δ) 7.4–7.9 (m, 4H, Ar–H of (*3H*)-

quinazolinone ring), 6.75–7.53 (m, 4H, Ar–H of phenyl urea), 1.33–3.98 (m, 5H, $–CH_2CH_3$), 6.0 (s, 2H of –NH–CO–NH–).

Pharmacology

The new derivatives obtained from the reaction sequence were injected intraperitoneally into mice and evaluated in the MES, scPTZ, and neurotoxicity screens, using doses of 30, 100, and 300 mg/kg at two different time intervals. These data are presented in Table 1. These compounds were also screened for their CNS behavioral activity in mice using actophotometer, CNS-depressant activity with the help of the forced swim method. The data of the pharmacological studies are reported in Tables 1–3.

Anticonvulsant screening

Initially all the compounds were administered i.p. in a volume of 0.01 ml/g body weight for mice and 0.004 ml/g body weight for rats at doses of 30, 100, 300 mg/kg to one to four animals. Activity was established using the MES and scPTZ test and these data are presented in Table 1.

Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that rotated at six revolutions per minute. The rod diameter was 3.2 cm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials.

Behavioral testing

The titled compounds (100 mg/kg) were screened for their behavioral effect using actophotometer (Boissoer and Simon, 1965) at 30 min and 1 h after drug administration. The behavior of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioral activity. The activity of the compounds was at maximum at 1 h; therefore, the activity values at 1 h were used to calculate % decrease in locomotor activity. The control group animals were administered PEG 400. The observations are tabulated in Table 2.

CNS-depressant activity

The forced swim pool method described earlier (Porsolt *et al.*, 1978) was followed. Wistar rats were placed in chamber (diameter 45 cm, height 20 cm) containing water up to a height of 15 cm at 25 ± 2°C. Two swim sessions were conducted an initial 15 min pre test, followed by a 5-min test session 24 h later. The animals were drug administrated (100 mg/kg) the test compound i.p. 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period was measured. The results are presented in Table 3.

Acknowledgment The authors acknowledge the assistance of the Antiepileptic Drug Development Program, Epilepsy Branch, Preclinical Pharmacology Section, NIH, USA.

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