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Original article

Synthesis, anticonvulsant and CNS depressant activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea

Sushil K. Kashaw [a,*], Varsha Kashaw [a], Pradeep Mishra [a], N.K. Jain [a], J.P. Stables [b]

[a] *Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, Dr. H.S. Gour University, Sagar 470003, India*
[b] *Preclinical Pharmacology Section, Epilepsy Branch, National Institutes of Health, Bethesda, MD 20892-9020, USA*

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ABSTRACT

Several new 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea were synthesized and screened for anticonvulsant, CNS depressant and sedative-hypnotic activity in the mice. After i.p. injection to mice at doses of 30, 100, and 300 mg/kg body weight synthesized compounds 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. Compounds **E1**, **E6**, **E9**, **E12**, **P3**, **P4** and **P6** were found to be active in the MES screen whereas **E1**, **P4**, **P6** and **P11** were found to be active in the scPTZ screen. All except **E6**, **E11** and **P6** showed more than 50% decrease in locomotor activity at 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. All the compounds were found to exhibit potent CNS depressants activity as indicated by increased immobility time. It can be concluded that newly synthesized compounds possessed promising CNS activities.

1. Introduction

Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities like anti-tumor [1], anti-inflammatory [2], CNS depressant [3], stimulant [4], anthelmentic [5], muscle relaxant [6], hypoglycemic [7] and anti-microbial activities [8]. 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. First was inspired from the pharmacophore hypothesis suggested by the Dommick et al. [9] and other scientists for aryl semicarbazones [10–12]. The hypothesis suggests the presence of an aryl hydrophobic binding site (A), a hydrogen bonding domain, an electron donor group and another hydrophobic–hydrophilic site (R) controlling the pharmacokinetic properties of the anticonvulsant. Fig. 1A shows the comparative pictorial representation of this hypothesis (aryl semicarbazones), *N*-desmethyl diazepam, phenytoin and our designed compounds. Second hypothesis was based on 4(3*H*)-quinazolinone nucleus containing well known sedative-hypnotic and anticonvulsant methaqualone (2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone). Chemical modifications at second and third position of this agent had lead to the generation of many CNS active agents. Among the few reports in the literature our attention was drawn to the earlier discovery by Boltz et al. [13] and Wolfe et al. [14] that $-CH_3$ at second position of 4(3*H*)-quinazolinone is not always necessary for the CNS activity and other groups when placed at this position can also lead to potent CNS active agents. Fig. 1B represents the similarities between methaqualone and our designed compounds. Third hypothesis was based upon the results and interpretations of our previous study on CNS activity of 2,3-disubstituted 4(3*H*)-quinazolinones in which we discovered more potent sedative-hypnotic and CNS depressant compounds as compared to anticonvulsant [15,16] (Fig. 1C). With all the mentioned hypothesis as background the present work was focused on three objectives: (i) the first objective was the synthesis of the hybrid compounds possessing mentioned molecular

* Corresponding author. Tel.: +91 7582 240757(R)/265457; fax: +91 7582 265457.
E-mail address: sushilkashaw@gmail.com (S.K. Kashaw).

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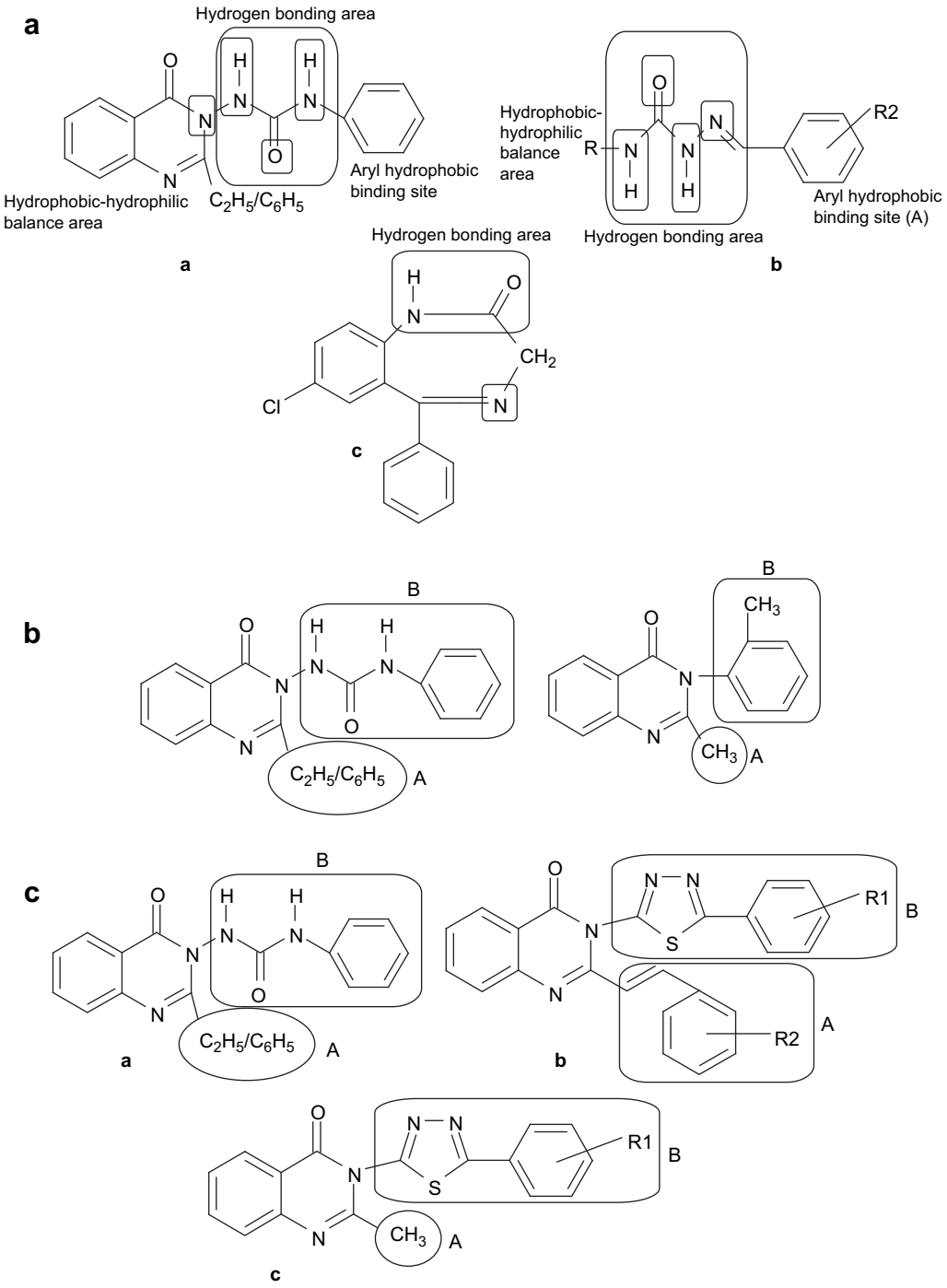


Fig. 1. (A) Comparative pictorial representation of the proposed hypothesis (a), previously reported hypothesis (b) (aryl semicarbazones) and *N*-desmethyl diazepam (c). (B) Comparative pictorial representation of the proposed hypothesis and methaqualone. (C) Comparative pictorial representation of the proposed hypothesis (a) and previously reported compounds by same group (b and c).

features; (ii) the second objective was anticonvulsant screening of the synthesized compounds by MES and scPTZ methods and (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 $-C_2H_5$ and $-C_6H_5$), the present paper reports on the synthesis, anticonvulsant, neurotoxicity, CNS depressant and behavioral study of 24 2,3-disubstituted-quinazolin-4(3*H*)-one.

2. Chemistry

The synthesis of the target compounds was accomplished as shown in Fig. 2. Synthesis of 2-ethylbenzoxazin-4-one (**8**), 2-phenyl benzoxazin-4-one (**6**) and substituted aryl semicarbazides (**3a**–**3L**) were carried out according to the procedure mentioned in the literature. Syntheses of 2-ethylbenzoxazone and 2-phenyl benzoxazin-4-one is based on the earlier reported methods. Anthranilic acid (**4**) (0.1 mol) was reacted with benzoyl chloride to get *N*-phenyl anthranilic acid, which was further refluxed with acetic anhydride for 2 h to get 2-phenyl benzoxazin-4-one (**6**). For the

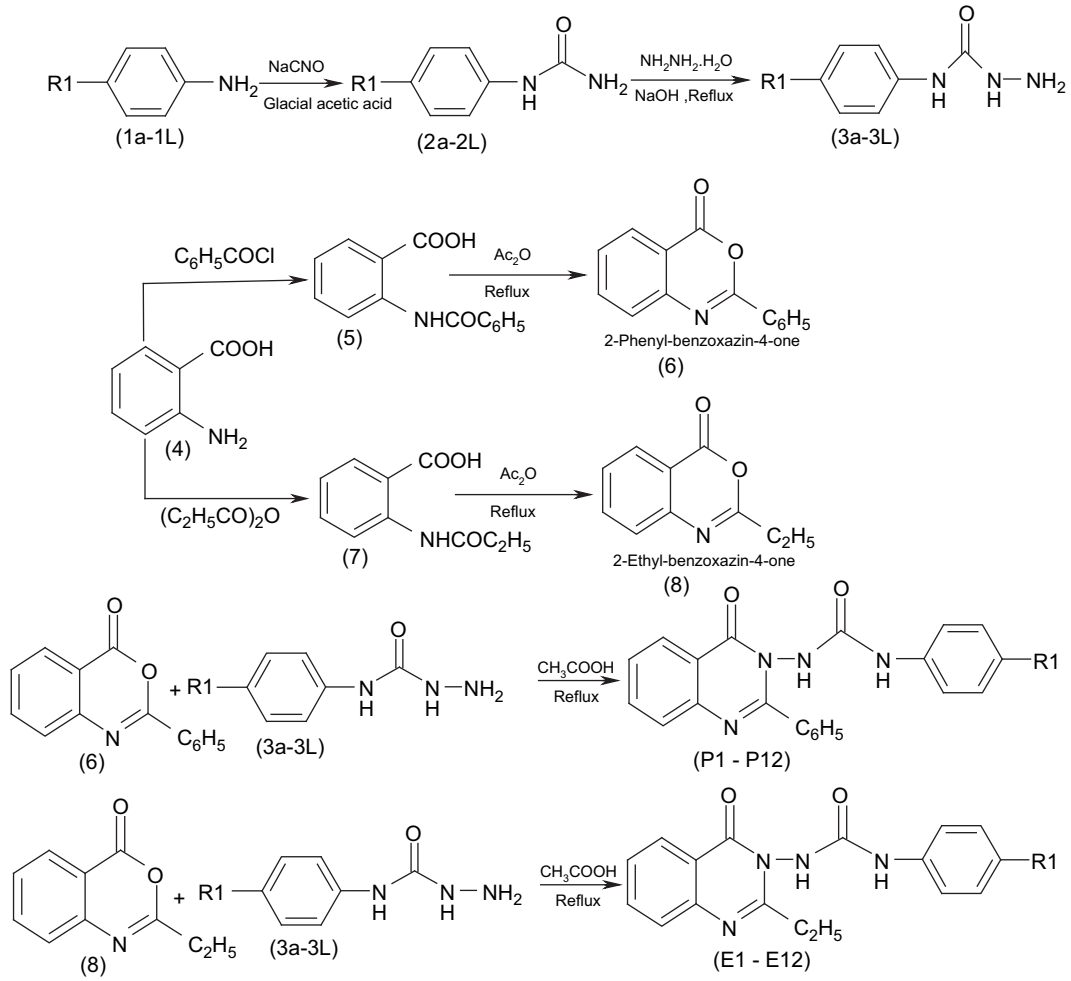


Fig. 2. Scheme for the synthesis of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea (**E1**–**E12** and **P1**–**P12**).

synthesis of 2-ethylbenzoxazone, anthranilic acid (**4**) was refluxed with propionic anhydride for 2 h to get *N*-ethyl anthranilic acid (**7**), which was cyclised under reflux with acetic anhydride to get 2-ethylbenzoxazone (**8**). 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 [17] to yield substituted phenyl urea (**2**), which 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. 2. Different substituted semicarbazides were refluxed in the presence of glacial acetic acid with 2-ethyl-benzoxazone and 2-phenyl benzoxazin-4-one to yield **H1**–**H12** and **M1**–**M12**, respectively. The ^{13}C NMR depicted spectrum at 163 (C-2), 166 (C-4), 112 (C-11) and 154 (C_z). ^{1}H NMR (300 MHz, δ) showed peaks at 7.3–7.8 for 4H of 4(3*H*)-quinazolinone and at 6.1 for 2H of –NH–CO–NH–. Compounds **E2**, **E3**, **E4**, **E5**, **P2**, **P3**, **P4** and **P5**, apart from IR and ^{13}C NMR, were well recognized by the help of mass spectroscopy. These mentioned compounds contained halogen in their structure and were confirmed with the help of characteristic isotopic peaks, in addition to molecular ion peak (MI). Compound **E3**, 1-(4-chloro-phenyl)-3-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-urea, showed intense MI peak (due to the presence of ^{35}Cl) at 343 and isotopic peak (less intense as compared to MI) at *m*/*z* 345 (due to the presence of ^{37}Cl isotope). Compound **E4** showed MI peak at 388 and isotopic peak at *m*/*z* value 390. In this compound intensity of both the MI and isotopic peak was almost equal. Similarly **P3** and **P4** observed MI peak at 391 and 436, respectively. Isotopic peak for **P3** was at 392 (lower intensity than MI) and for **P4** at 438 with an almost equal intensity to MI peak. Compounds **E5** and **P5** showed peaks at *m*/*z* 127 due to the presence of iodonium ion, I^{+} in the structure. Thin layer chromatography (TLC) was run throughout the reaction to optimize the reaction for purity and completion.

3. Pharmacology

The new derivatives obtained from the reaction sequence were injected intraperitoneally into mice and evaluated in the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and neurotoxicity screens, using doses of 30, 100 and 300 mg/kg at two different time intervals. All the experiments were carried out according to protocols approved by the Institutional Animal Ethical Committee (Ref. no.09, p.07/247, dated 03/11/07). 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 and phenobarbitone induced hypnosis potentiation in rats. The data of the pharmacological studies are reported in Tables 1 and 2.

Table 1
Anticonvulsant activity, minimal motor impairment and behavioral study of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea (**E1**–**E12** and **P1**–**P12**).

Code[a]	Intraperitoneal injection in mice						Activity score		% Inhibition of locomotor activity
	MES screen		scPTZ screen		Neurotoxicity screen		Control (24 h prior)	Post treatment	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h			
E1	100	–	300–	–	300		422.13 ± 1.04	227.20 ± 0.52	54
E2	–	–	–	–	–	–	469.23 ± 0.82	230.14 ± 0.34	51
E3	–	–	–	–	–		315.55 ± 0.74	151.35 ± 0.96	52
E4	–	–			300	–	421.61 ± 1.14	194.20 ± 0.52	54
E5	–	–		–	–	–	447.23 ± 0.52	201.42 ± 0.46	55
E6	300	–	–	–	100	–	354.12 ± 0.63	209.72 ± 0.79	41
E7	–	–	–	–	–	–	436.28 ± 0.91	206.24 ± 1.11	54
E8	–	–	–	–	–	–	363.12 ± 0.74	171.23 ± 1.18	53
E9	100	300	–	–	300	–	381.32 ± 0.78	172.14 ± 0.13	55
E10	–	–	–	–	–	–	351.29 ± 2.00	148.21 ± 0.34	58
E11	–	–	–	–	300		341.43 ± 0.48	177.32 ± 1.14	48
E12	300	–	–	–	300	300	361.45 ± 0.88	181.23 ± 1.35	50
P1	–	–	–	–	300	–	362.13 ± 0.74	159.32 ± 0.16	56
P2	–	–	–	–	–	–	506.45 ± 0.33	231.13 ± 0.93	54
P3	300	–		–	300	–	450.46 ± 0.82	203.15 ± 0.83	55
P4	100	300	300	–	300	–	476.53 ± 0.85	200.13 ± 0.21	58
P5	–	–			300–	–	493.52 ± 1.26	197.24 ± 1.12	60
P6	300	–	300	–	–300	–	321.40 ± 0.63	186.23 ± 1.24	42
P7	–	–	–	–	–	–	379.25 ± 0.85	159.12 ± 0.15	59
P8	–	–	–	–	–	–	516.45 ± 0.92	212.74 ± 0.81	59
P9	–	–	–	–	300	–	412.62 ± 1.11	190.24 ± 0.18	54
P10	–	–	–	–	–	–	430.43 ± 1.16	168.32 ± 1.10	61
P11	–	–	300	–	300	–	525.57 ± 0.73	262.41 ± 1.24	52
P12	–	–	–	–	100	–	374.47 ± 0.34	176.32 ± 0.42	53
Phenytoin	30	100	100	300	100	300	342.44 ± 14.16	107.12 ± 13.01	69
Carbamazepine	–	–	300	–	–	–			
Sodium valproate	100	30	30	300	100	300			
Phenobarbital	–	–	300	–	–	–			

[a] Doses of 30, 100 and 300 mg/kg were administered. The figures in the table indicate 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).

4. Results and discussion

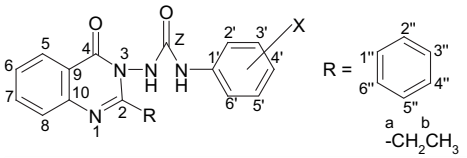
Initial anticonvulsant activity and neurotoxicity data for the quinazolinone analogs are reported in Table 1, along with the data on phenytoin, carbamazapine, sodium valproate and phenobarbital. All the quinazolinone analogs showed potent sedative-hypnotic and CNS depressant activity than anticonvulsant activity. In the prepared series **E1**, **E6**, **E9**, **E12**, **P3**, **P4** and **P6** were found to be active in the MES screen at 0.5 h, whereas **E9** and **P4** showed anticonvulsant activity at 4 h. Out of all the active compounds only two compounds namely **E9** and **P4** exhibited activity at 100 mg/kg body weight whereas rest of the compounds were active at 300 mg/kg. Except **E1**, **P4**, **P6** and **P11** all the remaining compounds were inactive in the scPTZ screen at 0.5 h. None of the compounds showed activity at 4 h interval time suggesting their long duration of activity. Synthesized compounds exhibited NT at 100 and 300 mg/kg. Compounds **E1**, **E4**, **E6**, **E9**, **E11**, **E12**, **P1**, **P3**, **P4**, **P5**, **P6**, **P9**, **P11** and **P12** showed NT lasting at 0.5 h. The NT of the compounds as indicated by their inability to grasp the rotating rot for sufficient time may be due to the increased BBB penetration and accumulation at neuroprotein sites. All the compounds were also screened for behavior study and CNS depressant activity. In the behavioral study using actophotometer scoring technique, the entire series of synthesized compounds showed decrease in locomotor activity where 41% was the lowest and 61% was the maximal decrease in locomotor activity when compared to phenytoin as reported in Table 1. All the compounds except **E6**, **E11** and **P6** showed more than 50% decrease in locomotor activity ($p < 0.05$) at 1 h of compound administration. Compound **E6** was the least potent compound and **P10** was the most potent compound in the prepared series with 41% and 61% decrease in locomotor activity, respectively. In a similar study with forced swim pool test, the immobility time after administration of the test compounds were compared with carbamazepine (Table 2). Readings of control groups were taken individually for each compound 24 h prior to compound administration. Biological activity was also ascertained for PEG because it was used as a vehicle for the synthesized compounds. All the tested compounds were found to exhibit potent CNS depressants activity ($p < 0.05$) as indicated by significantly increased immobility time. Experimental results indicate that our compound exhibited better sedative-hypnotic and CNS depressant as compared to anticonvulsant activity. Bulkier compounds are more lipophilic and can cross blood brain barrier to exert their effect at CNS. 2-Phenyl substituted compounds (**P1**–**P12**) possessed better CNS activity as compared to 2-ethyl substituted (**E1**–**E12**). Present study explored that substitution of substituted phenyl urea at third position and $-C_2H_5$ and $-C_6H_5$ moiety at second position of 4(3*H*)-quinazolinone leads to the development of new chemical entities with potent CNS activity.

5. Experimental protocol

5.1. Chemistry

Melting points were determined in one end open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. Infrared (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 (ppm) using tetramethylsilane (TMS) as an internal

Table 2
CNS depressant study on 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea (**E1**–**E12** and **P1**–**P12**) by forced swim pool test.



Compound[a]	X	Immobility time[b](s)	
		Control (24 h prior)	Post treatment (60 min after)
PEG		150.17 ± 10.72	152 .53 ± 10.33
E1	–H	120.11 ± 2.41	170.10 ± 12.45
E2	–F	196.12 ± 2.41	248.32 ± 11.67
E3	–Cl	127.13 ± 3.74	180.30 ±13.17
E4	–Br	182.16 ± 4.12	222.20 ± 12.04
E5	–I	135.21 ± 5.32	274.40 ± 14.36
E6	$-NO_2$	170.32 ± 312	212.72 ± 17.66
E7	*o*-CH_3(c)	140.11 ± 9.45	186.30 ± 18.37
E8	*m*-CH_3(c)	125.52 ± 7.32	165.63 ± 12.17
E9	*p*-CH_3(c)	204.61 ± 15.45	243.42 ± 13.58
E10	–CH_2(c)–CH_3(d)	176.32 ± 17.10	227.54 ± 14.27
E11	–OCH_3(c)	89.88 ± 13.12	141.17 ± 12.37
E12	–O CH_2(c)–CH_3(d)	110.27 ± 13.12	161.43 ± 10.14
P1	–H	132.32 ± 11.50	186.46 ± 11.35
P2	–F	156.47 ± 13.12	211.14 ± 12.23
P3	–Cl	162.51 ± 14.36	218.50 ± 11.19
P4	–Br	168.23 ± 13.45	228.53 ± 12.45
P5	–I	116.42 ± 15.15	181.15 ± 13.16
P6	$-NO_2$	137.45 ± 13.38	199.19 ± 12.84
P7	*o*-CH_3(a)	98.76 ± 12.15	162.13 ± 14.23
P8	*m*-CH_3(a)	102.42 ± 12.95	171.24 ± 12.27
P9	*p*-CH_3(a)	144.87 ± 13.16	205.22 ± 13.18
P10	–CH_2(a)–CH_3(b)	149.57 ± 17.34	213.13 ± 11.99
P11	–OCH_3(a)	159.67 ± 13.63	229.15 ± 13.94
P12	–OCH_2(a)–CH_3(b)	221.57 ± 8.23	273.22 ± 16.01
Carbamazapine[c]		168.32 ± 6.03	258.31 ± 14.13

[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 $p < 0.05$ (student's *t* test).
[c] Tested at 30 mg/kg (i.p.).

standard. Elemental analysis (C & N) was undertaken with Elemental vario EL III Carlo Erba 1108 analyzer. The purity of the compounds was confirmed by thin layer chromatography 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 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea (**E1**–**E12** and **P1**–**P12**) were performed by following steps.

5.2. 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) in 50 mL of warm water was added with constant stirring. Solution was allowed to stand for 60 min, cooled in ice and filtered with suction and dried. Physico-chemical data and melting point of the synthesized products were in agreement with that reported in the literature [18].

5.2.1. 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. Compounds exhibited IR (KBr) ν_{max} 3450, 1650, 3269, 840 cm^{-1}. ^1H NMR δ 7.2–7.5 (m, 4H, Ar–H), 8.26 (s, 1H, Ar–NH).

5.2.2. Synthesis of 2-phenyl benzoxazin-4-one (*6*) and 2-ethylbenzoxazin-4-one (*8*)

Anthranilic acid (**4**) (0.1 mol) was reacted with benzoyl chloride to get *N*-phenyl anthranilic acid, which was further refluxed with acetic anhydride for 2 h to get 2-phenyl benzoxazin-4-one (**6**). For the synthesis of 2-ethylbenzoxazone, anthranilic acid (**4**) was refluxed with propionic anhydride for 2 h to get *N*-ethyl anthranilic acid (**7**), which was cyclised under reflux with acetic anhydride to get 2-ethylbenzoxazone (**8**).

5.2.3. Synthesis of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea (*E1*–*E12* and *P1*–*P12*)

The title compounds were synthesized following procedure reported earlier by Jatav et al. [19]. Briefly solution of 2-phenyl benzoxazin-4-one, 2-ethylbenzoxazin-4-one (0.01 M), and 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 reported in Table 3.

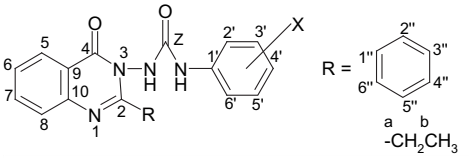
Compound **E1**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-phenyl urea; IR (cm^{-1}): 1690 (C=O str. of 4(3*H*)-quinazolinone ring), 1660 (C=O str. of phenyl urea), 1576 (C=N str.), 3048 (Ar–CH str.), 3421 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 166 (C-4), 163 (C-2), 110 (C-11), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 147.8 (C_9 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 154 (C_Z of phenyl urea); ^1H NMR (300 MHz, δ): 7.3–7.8 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.1–7.64 (m, 5H, Ar–H of phenyl urea), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$), 6.1 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 309.

Compound **E2**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-(4-fluoro-phenyl)-urea; IR (cm^{-1}): 1683 (C=O str. of 4(3*H*)-quinazolinone ring), 1650 (C=O str. of phenyl urea), 1580 (C=N str.), 3045 (Ar–CH str.), 3423 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 165 (C-4), 162 (C-2), 112 (C-11), 157.7 (C'_4), 122 (C_8 of 4(3*H*)-quinazolinone ring), 126 (C_{10} of 4(3*H*)-quinazolinone ring), 127.2 (C_6 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 147.3 (C_9 of 4(3*H*)-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 (3*H*)-quinazolinone ring), 6.94–7.61 (m, 4H, Ar–H of phenyl urea), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 327.

Compound **E3**: 1-(4-chloro-phenyl)-3-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1695 (C=O str. of 4(3*H*)-quinazolinone ring), 1660 (C=O str. of phenyl urea), 1590 (C=N str.), 3041 (Ar–CH str.), 3420 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 166 (C-4), 163 (C-2), 113 (C-11), 123 (C_8 of 4(3*H*)-quinazolinone ring), 127 (C_{10} of 4(3*H*)-quinazolinone ring), 128.2 (C_6 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 148.3 (C_9 of 4(3*H*)-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 (3*H*)-quinazolinone ring), 7.15–7.52 (m, 4H, Ar–H of phenyl urea), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$), 6.2 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 343.

Compound **E4**: 1-(4-bromo-phenyl)-3-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1683 (C=O str. of 4(3*H*)-quinazolinone ring), 1662 (C=O str. of phenyl urea), 1576 (C=N str.), 3040 (Ar–CH str.), 3426 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 165 (C-4), 164 (C-2), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone

Table 3
Physical data of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4*H*-quinazolin-3-yl)-urea (**E1–E12** and **P1–P12**).



Code No.	X	Yield (%)	M.p.[b] (°C)	Mol. formula	Elemental analyses[a] (calculated %/found %)
E1	–H	66	216	$C_{17}H_{16}N_4O_2$	N (18.17/18.15); C (66.22/66.20)
E2	–F	68	242	$C_{17}H_{15}FN_4O_2$	N (17.17/17.15); C (62.57/62.56)
E 3	–Cl	55	240	$C_{17}H_{15}ClN_4O_2$	N (16.34/16.32); C (59.57/59.56)
E4	–Br	50	>300b	$C_{17}H_{15}BrN_4O_2$	N (14.47/14.45); C (52.73/52.70)
E5	–I	45	237	$C_{17}H_{15}IN_4O_2$	N (12.90/12.88); C (47.02/47.01)
E6	$-NO_2$	60	231	$C_{17}H_{15}N_5O_4$	N (19.82/19.80); C (57.79/57.77)
E7	*o*-CH_3(c)	70	235	$C_{18}H_{18}N_4O_2$	N (17.38/17.35); C (67.07/67.05)
E8	*m*-CH_3(c)	65	231	$C_{18}H_{18}N_4O_2$	N (17.38/17.35); C (67.07/67.05)
E9	*p*-CH_3(c)	75	236	$C_{18}H_{18}N_4O_2$	N (17.38/17.35); C (67.07/67.05)
E10	–CH_2(c)–CH_3(d)	53	234	$C_{19}H_{20}N_4O_2$	N (16.66/16.64); C (67.84/67.83)
E11	–OCH_3(c)	59	285	$C_{18}H_{18}N_4O_3$	N (16.56/16.55); C (63.89/63.88)
E12	–OCH_2(c)–CH_3(d)	60	>300b	$C_{19}H_{20}N_4O_3$	N (15.90/15.89); C (64.76/64.75)
P1	–H	67	220	$C_{21}H_{16}N_4O_2$	N (15.72/15.70); C (70.77/70.75)
P2	–F	78	285	$C_{21}H_{15}FN_4O_2$	N (14.97/14.96); C (67.37/67.36)
P3	–Cl	61	252	$C_{21}H_{15}ClN_4O_2$	N (14.34/14.33); C (64.54/64.53)
P4	–Br	57	296	$C_{21}H_{15}BrN_4O_2$	N (12.87/12.85); C (57.95/57.94)
P5	–I	49	260	$C_{21}H_{15}IN_4O_2$	N (11.62/11.61); C (52.30/52.30)
P6	$-NO_2$	50	244	$C_{21}H_{15}N_5O_4$	N (17.45/17.44); C (62.84/62.82)
P7	*o*-CH_3(a)	59	272	$C_{22}H_{18}N_4O_2$	N (15.13/15.12); C (71.34/71.32)
P8	*m*-CH_3(a)	62	280	$C_{22}H_{18}N_4O_2$	N (15.13/15.13); C (71.34/71.33)
P9	*p*-CH_3(a)	71	288	$C_{22}H_{18}N_4O_2$	N (15.13/15.12); C (71.34/71.32)
P10	–CH_2(a)–CH_3(b)	63	239	$C_{23}H_{20}N_4O_2$	N (14.57/14.55); C (71.86/71.85)
P11	–OCH_3(a)	58	258	$C_{22}H_{18}N_4O_3$	N (14.50/14.48); C (68.38/68.36)
P12	–OCH_2(a)–CH_3(b)	62	291	$C_{23}H_{20}N_4O_3$	N (13.99/13.96); C (68.99/68.96)

[a] Elemental analyses for C and N were within ±0.4% of the theoretical value.
[b] Melting point of the compound at their decomposition.

ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 146.8 (C_9 of 4(3*H*)-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 (3*H*)-quinazolinone ring), 7.41–7.52 (m, 4H, Ar–H of phenyl urea), 1.4 (m, 2H, –CH_2), 0.9 (m, 3H, –CH_3), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 388.

Compound **E5**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-(4-iodo-phenyl)-urea; IR (cm^{-1}): 1685 (C=O str. of 4(3*H*)-quinazolinone ring), 1664 (C=O str. of phenyl urea), 1576 (C=N), 3044 (Ar–CH str.), 3430 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 165 (C-4), 164 (C-2), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 146.8 (C_9 of 4(3*H*)-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 (3*H*)-quinazolinone ring), 7.12–7.40 (m, 4H, Ar–H of phenyl urea), 1.4 (m, 2H, –CH_2), 0.9 (m, 3H, –CH_3), 6.3 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 435.

Compound **E6**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-(4-nitro-phenyl)-urea; IR (cm^{-1}): 1686 (C=O str. of 4(3*H*)-quinazolinone ring), 1666 (C=O str. of phenyl urea), 1570 (C=N str.), 3048 (Ar–CH str.), 3422 (secondary amide NH str.); ^{13}C NMR (300 MHz, δ): 165 (C-4), 164 (C-2), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-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 (3*H*)-quinazolinone ring), 7.92–8.14 (m, 4H, Ar–H of phenyl urea), 1.4 (m, 2H, –CH_2), 0.9 (m, 3H, –CH_3), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 354.

Compound **E7**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-*o*-tolyl urea; IR (cm^{-1}): 1690 (C=O str. of 4(3*H*)-quinazolinone ring), 1668 (C=O str. of phenyl urea), 1594 (C=N str.), 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), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 11.7 (C_c), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 129.6 ($C'2$); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 2.35 (s, 3H, –CH_3), 1.4 (m, 2H, –CH_2), 0.9 (m, 3H, –CH_3 present at C2 of 4(3*H*)-quinazolinone ring), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 323.

Compound **E8**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-*m*-tolyl urea; IR (cm^{-1}): 1686 (C=O str. of 4(3*H*)-quinazolinone ring), 1656 (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), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 20.9 (C_c), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 124.6 ($C'3$); ^{1}H NMR (300 MHz, δ): 7.1–7.6 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.84–7.50 (m, 4H, Ar–H of phenyl urea), 2.34 (s, 3*H*, –CH_3), 1.4 (m, 2H, –CH_2), 0.9 (m, 3H, –CH_3 present at C2 of 4(3*H*)-quinazolinone ring), 6.1 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 323.

Compound **E9**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-*p*-tolyl urea; IR (cm^{-1}): 1697 (C=O str. of 4(3*H*)-quinazolinone ring), 1658 (C=O str. of phenyl urea), 1590 (C=N), 3041 (Ar–CH str.), 3421 (secondary amide NH str.), 2970 (C–H str.); ^{13}C NMR (300 MHz, δ): 165 (C-4), 164 (C-2), 133.3 (C'_4), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 20.9 (C_c), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 133 ($C'4$); ^{1}H NMR (300 MHz, δ): 7.0–7.6 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 2.34 (s, 3*H*, –CH_3), 1.4

(m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$ present at C2 of 4(3*H*)-quinazolinone ring), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 323.

Compound **E10**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-(4-ethyl-phenyl)-urea; IR (cm^{-1}): 1696 (C=O str. of 4(3*H*)-quinazolinone ring), 1668 (C=O str. of phenyl urea), 1580 (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), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 28.6 (C_c), 16.1 (C_d), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 133 (C′4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.88–7.52 (m, 4H, Ar–H of phenyl urea), 1.24–2.59 (m, 5H, $-CH_2CH_3$), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$ present at C2 of 4(3*H*)-quinazolinone ring), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 337.

Compound **E11**: 1-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-3-(4-methoxy-phenyl)-urea; IR (cm^{-1}): 1686 (C=O str. of 4(3*H*)-quinazolinone ring), 1670 (C=O str. of phenyl urea), 1590 (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), 109 (C-11), 121.15(C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 56.0 (C_c), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 157 (C′4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.74–7.53 (m, 4H, Ar–H of phenyl urea), 3.73 (s, 3*H*, $-CH_3$), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$ present at C2 of 4(3*H*)-quinazolinone ring), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 339.

Compound **E12**: 1-(4-ethoxy-phenyl)-3-(2-ethyl-4-oxo-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1680 (C=O str. of 4(3*H*)-quinazolinone ring), 1665 (C=O str. of phenyl urea), 1582 (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), 109 (C-11), 121.1 (C_8 of 4(3*H*)-quinazolinone ring), 21.7 (C_a), 5.3 (C_b), 65.1 (C_c), 14.3 (C_d), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 157 (C′4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 6.75–7.53 (m, 4H, Ar–H of phenyl urea), 1.33–3.98 (m, 5H, $-CH_2CH_3$), 1.4 (m, 2H, $-CH_2$), 0.9 (m, 3H, $-CH_3$ present at C2 of 4(3*H*)-quinazolinone ring), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 353.

Compound **P1**: 1-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-3-phenyl urea; IR (cm^{-1}): 1682 (C=O str. of 4(3*H*)-quinazolinone ring), 1672 (C=O str. of phenyl urea), 1598 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154.3 (C_Z of phenyl urea), 138.2 (C'_1), 124.1 (C'_4), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 357.

Compound **P2**: 1-(4-fluoro-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1698 (C=O str. of 4(3*H*)-quinazolinone ring), 1656 (C=O str. of phenyl urea), 1581 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154.3 (C_Z of phenyl urea), 133 (C'_1), 157.7 (C'_4), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 4H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 375.

Compound **P3**: 1-(4-chloro-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1683 (C=O str. of 4(3*H*)-quinazolinone ring), 1669 (C=O str. of phenyl urea), 1582 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154.3 (C_Z of phenyl urea), 133 (C'_1), 129.4 (C'_4), 136.3 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 4H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 391.

Compound **P4**: 1-(4-bromo-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1698 (C=O str. of 4(3*H*)-quinazolinone ring), 1660 (C=O str. of phenyl urea), 1584 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 137.2 (C'_1), 118.7 (C'_4), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 4H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 436.

Compound **P5**: 1-(4-iodo-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1697 (C=O str. of 4(3*H*)-quinazolinone ring), 1668 (C=O str. of phenyl urea), 1578 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 137.1 (C'_1), 92.9 (C'_4), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 4H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 383.

Compound **P6**: 1-(4-nitro-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1681 (C=O str. of 4(3*H*)-quinazolinone ring), 1666 (C=O str. of phenyl urea), 1586 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 144.3 (C'_1), 144.0 (C'_4), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 4H, Ar–H of phenyl urea), 7.29–7.62 (m, 5H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 402.

Compound **P7**: 1-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-3-*o*-tolyl urea; IR (cm^{-1}): 1689 (C=O str. of 4(3*H*)-quinazolinone ring), 1665 (C=O str. of phenyl urea), 1588 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 138 (C'_1), 129.6 (C'_2), 124.0 (C'_4), 11.8 (Ca), 132.9 (C''_1), 129.9 (C''_4); ^1H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 371.

Compound **P8**: 1-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-3-*m*-tolyl urea; IR (cm^{-1}): 1679 (C=O str. of 4(3*H*)-quinazolinone ring), 1664 (C=O str. of phenyl urea), 1592 (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(3*H*)-quinazolinone

ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 138.1 (C'_1), 137.9 (C'_3), 124.8 (C'_4), 20.9 (Ca), 132.9 (C''_1), 129.9 (C''_4); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 371.

Compound **P9**: 1-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-3-*p*-tolyl urea; IR (cm^{-1}): 1686 (C=O str. of 4(3*H*)-quinazolinone ring), 1669 (C=O str. of phenyl urea), 1594 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 135.1 (C'_1), 129.9 (C'_3), 133.3 (C'_4), 20.9 (Ca), 132.9 (C''_1), 129.9 (C''_4); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 371.

Compound **P10**: 1-(4-ethyl-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1683 (C=O str. of 4(3*H*)-quinazolinone ring), 1674 (C=O str. of phenyl urea), 1590 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 135.4 (C'_1), 128.1 (C'_3), 135.3 (C'_4), 28.6 (Ca), 16.1 (C_b), 132.9 (C''_1), 129.9 (C''_4); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 1.24–2.59 (m, 5H, –CH_2CH_3), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 385.

Compound **P11**: 1-(4-methoxy-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1693 (C=O str. of 4(3*H*)-quinazolinone ring), 1671 (C=O str. of phenyl urea), 1596 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 130.5 (C'_1), 157.5 (C'_4), 56.1 (Ca), 132.9 (C''_1), 129.9 (C''_4); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 3.73 (s, 3H of –OCH_3), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 387.

Compound **P12**: 1-(4-ethoxy-phenyl)-3-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)-urea; IR (cm^{-1}): 1692 (C=O str. of 4(3*H*)-quinazolinone ring), 1664 (C=O str. of phenyl urea), 1585 (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(3*H*)-quinazolinone ring), 125.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.1 (C_6 of 4(3*H*)-quinazolinone ring), 146.8 (C_9 of 4(3*H*)-quinazolinone ring), 154 (C_Z of phenyl urea), 129.8 (C'_1), 154.5 (C'_4), 56.1 (Ca), 14.3 (C_b), 132.9 (C''_1), 129.9 (C''_4); ^{1}H NMR (300 MHz, δ): 7.4–7.9 (m, 4H, Ar–H of (3*H*)-quinazolinone ring), 7.0–7.64 (m, 5H, Ar–H of phenyl urea), 7.29–7.62 (m, 4H, Ar–H of phenyl ring at C2), 1.33–3.98 (m, 5H of –OCH_2CH_3), 6.0 (s, 2H of –NH–CO–NH–); MI *m*/*z* peak at 401.

5.3. Pharmacology

The anticonvulsant evaluation was undertaken using reported procedure [20–22]. Male albino mice (CF-1 strain or swiss, 18–25 g) and rats (Sprague–Dawley, 100–150 g, four animals per group) were used as experimental animals. The tested compounds were suspended in polyethylene glycol 400.

5.3.1. 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 1–4 animals. Activity was established using the MES and scPTZ test and these data are presented in Table 1.

5.3.2. Neurotoxicity screening

Minimal motor impairment [23] 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.

5.3.3. Behavioral testing

The title compounds (100 mg/kg) were screened for their behavioral effect using actophotometer [24] 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 percentage decrease in locomotor activity. The control group animals were administered PEG 400. The observations are tabulated in Table 1.

5.3.4. CNS depressant activity

The forced swim pool method described earlier [25] 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 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 were necessary to keep its head above the surface of water) during the 5 min test period were measured. The results are presented in Table 2.

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