Research Article

Design, synthesis and evaluation of novel 2, 3-disubstituted-4-(3*H*) quinazolinone derivatives

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Abstract

Objective: The aim of the present work was to synthesize some new bioactive 1-(4-substituted-phenyl-3-(4-oxo-2-styryl-4*H*-quinazolin-3-yl)-urea and to evaluate them for anticonvulsant activity. **Materials and methods:** A series of novel 2,3 disubstituted-4-(3*H*)quinazolinone derivatives (RKJ17-48) were synthesized by anthranilic acid using sodium cyanate, substituted anilines and different benzaldehydes. Structures of compounds synthesized were confirmed by IR, ^{13}C NMR and Mass spectroscopic analysis. All synthesized compounds were screened for anti-convulsant activity. The anti-convulsant activity of synthesized compounds was performed against maximal electroshock-induced seizures and PTZ-induced clonic seizures using phenytoin and carbamazepine as standard drug respectively. Same compounds were studied for their Neurotoxicity screens and CNS behavioral activity in mice using rotorod test and actophotometer respectively. **Results:** Several synthesized compounds have shown anti-convulsant activity as compared to standard drug phenytoin and carbamazepine. Compounds RKJ-46 and RKJ-47 have shown very good anti-convulsant activity. **Conclusion:** Present study explored that substitution of 4(3*H*)-quinazolinone at second and third position of 4(3*H*)-quinazolinone leads to the development of new chemical entities with potent anticonvulsant activity.

Keywords: 4(3H)-Quinazolinones; MES; Pentylenetetrazole, seizure, anticonvulsant

Introduction

One of the most frequently encountered heterocyclic molecules in medicinal chemistry is 4(3H) quinazolinone with wide applications including anticonvulsant (Georgey et al., 2008; Ilangovan et al., 2010; Bhandari et al., 2008; Jatav et al., 2008, 2008a, 2008b, 2008c, 2008d, 2008e, 2010; Kashaw et al., 2008, 2009, 2009a, 2010), bactericide (Shi et al., 2007), fungicide (Isloor et al., 2009), antimicrobial (Vijesh et al., 2013; Patel et al., 2009; Havaldar et al. 2008; Siddappa et al., 2009; Rajasekaran et al., 2012; Mistry et al., 2006), anti-inflammatory (Mohamed et al., 2009; Dravyakar et al., 2012; Laddha et al., 2006), antitumor (Kandu et al., 2008), anticancer (Cipak et al., 2007), sedative-hypnotic (Alagarsamy et al., 2006), diuretic (Zyl et al., 2001; Shetty et al., 1974), antiviral (Gao et al., 2007), anti-hypertensive (Campbell et al., 1987) and antitubercular (Mosaad et al., 2004; Chandra et al., 2009) activities. Several 2,3-disubstituted Quinazolinone derivatives were synthesized and tested for different biological activities. These reports showed that aryl substitution at 2nd and 3rd position enhances biological activities. Efforts towards the development and identification of new molecules for anti-convulsion activities with minimal side effects have extended implication in the recent past during which the quinazolinones came into the scenario.

An increase in its anti-convulsant activity by substituting different quinazolinone heterocyclic ring at the third position is also well documented in the literature. 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 activity (Jackman et al., 1960). Modification of methyl group by some other (-CH_2=CH_2-C_6H_5, -CH_2=CH_2-C_6H_4 (*p*-OCH_3), -CH_2=CH_2-C_6H_4(*p*-Cl) etc.) also showed anticonvulsant activity. The increased anti-convulsant activity obtained by placing a styryl moiety at the second position has also been reported. In our research we found that

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quinazolines itself possessed anti-convulsant activity. In an effort to observe the synergistic effect of both of these effects we have pointed a hypotheses (Figure 1) that have been situated into view by prior workers in this area. A few of them are:

1. An aryl hydrophobic binding site (A) with substituents at aryl ring.
2. A hydrogen bonding domain (HBD)
3. An electron donor system (D) and
4. Another hydrophobic–hydrophilic site (C) controlling the pharmacokinetic properties were essential for the aryl semicarbazones, they reported as anticonvulsants.

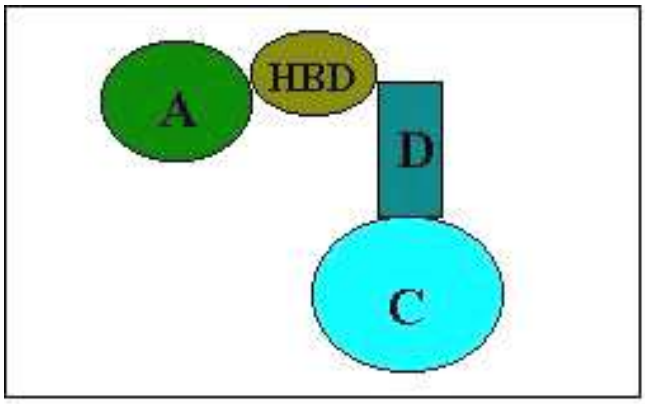
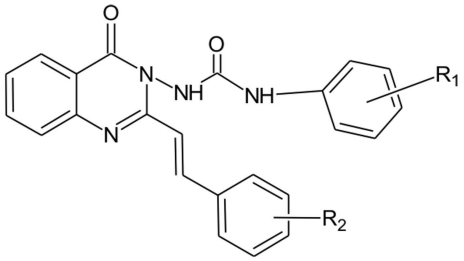


Figure 1. Pharmacophore model for anticonvulsant activity

We synthesized new 4(3H)-qunazolinone analogues incorporating the styryl moiety and substituted anilines at the second and third position, respectively. With the exposure of discovering the assorted pharmacological nature of 4(3H)-qunazolinone derivatives, it was considered to synthesize some substituted 4(3H)-qunazolinone analogues incorporating the styryl moiety and substituted anilines at the second and third position, respectively having general structure of figure 2 as potential anti-convulsion agents.



Where R_1 is 4-Cl, 4-F, *p*-CH_3, 2,5-Cl and R_2 is –H, 4-Br, 4-Cl, 4-CH_3

Figure 2. Proposed pictorial representation of the proposed hypothesis

Material and Methods

Substituted anilines (4-Cl, 4-F, 4-CH_3, 2,5-Cl, 2,4-F, 2,4-CH_3, 2,3,4- F, 2,4,6- CH_3), Sodium cyanate, hydrazine hydrate, sodium hydroxide, glacial acetic acid, benzoyl chloride, pyridine, substituted benzaldehydes (4-Br, 4-Cl, 4-NO_2, 4-CH_3) was purchased from CDH (Chemical Drug House), New Delhi, India. The chemical used for experimental work were synthetic grade. The chemical used for experimental work were synthetic grade. The melting points of the synthesized compounds were determined in open glass capillaries. IR spectra were recorded on ALPHA (Bruker) FTIR Spectrometer. Elemental analysis was performed and found values were within 0.4% of theoretical values. ^{13}C NMR spectra were recorded on BrukerAvance 400 spectrophotometer at 400 MHz, 5 mm multi-nuclear inverse probe head, low and high-temperature facility and HRMAS accessory. Mass Spectra were recorded using Mass Spectrometers Jeol SX-102 (FAB) by ESI.

The synthesis of 1-(4-substituted-phenyl-3-(4-oxo-2-methyl/phenyl-4H-quinazolin-3-yl)-urea is accompanied in figure 3 and comprises the following steps

I. Synthesis of substituted phenyl semicarbazides
II. Synthesis of 2-substituted benzoxazin-4-one
III. Synthesis of the title compounds

Synthesis of Substituted Phenyl Semicarbazides

Step1: Synthesis of substituted phenyl urea

p-Substituted aniline (0.1 mol) (1) was dissolved in 10-50 ml of glacial acetic acid and volume was made upto 100 ml with water. To this sodium cyanate (0.1 mol) in 50 ml of warm water was added with constant stirring. Solution was allowed to stand for 60 min. then cooled in ice and filtered with suction and dried. The substituted phenyl urea (2) thus obtained was used in the next step without further purification.

Step 2: Synthesis of substituted phenyl semicarbazides

Equimolar quantity of substituted phenyl urea (0.1 mol) (2) and hydrazine hydrate (0.1 mol) in ethanol under alkaline condition (NaOH) were refluxed for 4-10 h with stirring. Excess of ethanol was distilled off under vacuum and then poured into ice. The obtained product was filtered and recrystallized from 90% aqueous ethanol. Generally compounds exhibited IR (KBr) ν_{max} 3450, 1650, 3269, 844 cm-1. 1H NMR δ 7.2-7.5 (m, 4H, Ar-H), 8.26 (s, 1H, Ar-NH).

Synthesis of 2-Substituted benzoxazin-4-one

Anthranilic acid, 4 (0.1 mol) was refluxed with benzoylchloride/ acetic anhydride for 2 h. Excess of anhydride was distilled off by vacuum distillation to obtain the precipitate of N-phenyl anthranilic acid (5)/N-acetyl

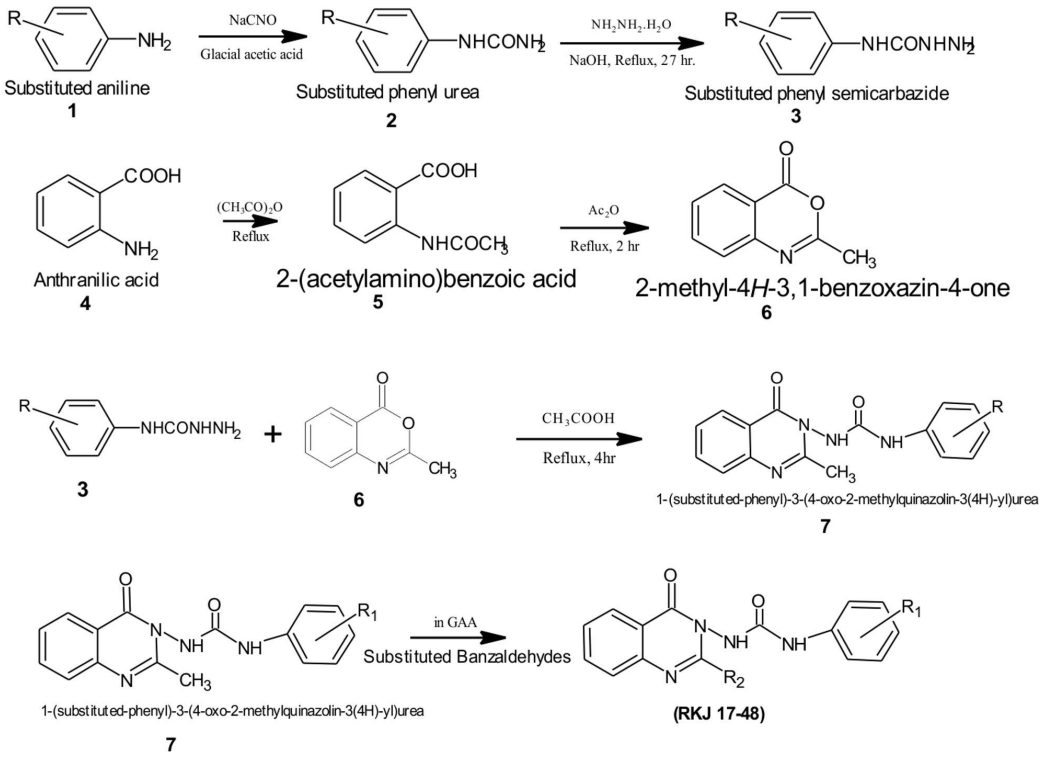


Figure 3. Scheme for synthesis

anthranilic acid (7) which was further refluxed with acetic anhydride for 2 h to get 2-phenyl benzoxazin-4-one (6)/ 2-methyl benzoxazin-4-one (8).

Synthesis of title compound

Scheme I: Synthesis of Quinazolinones

The title compounds were synthesized following procedure reported earlier. To a solution of 2-phenyl benzoxazin-4-one/2-methyl benzoxazin-4-one (6/8) (0.01 M), substituted phenyl semicarbazides (0.01M) 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 with cold distilled water, dried and recrystallized from hot ethanol.

Scheme II: Synthesis of 2-styrylquinazolinone

A mixture of quinazolinone (0.01M), respective aldehyde (0.01M) and anhydrous zinc chloride was fused at 130-140°C for 2 hr. After cooling, the reaction mixture was treated with cold water to dissolve zinc chloride. The residue left after filtration was washed with cold ethanol. Purification of the synthesized compounds was done by dissolving the compounds in minimum quantity of dimethylformamide (DMF) and then added the solution to distilled water.

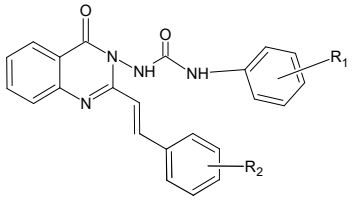
Characterization

Melting points were determined in one end open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected (Table 1). Infrared (IR) and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded for the compounds on Perkin Elmer Spectrum RXI Spectrophotometer in KBr pellets and ^{13}C Advance Bruker (300 MHz) instrument, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis (C, N and S) was undertaken with Elemental Vario EL III Carlo Erba 1108 analyzer (Table 2). The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates and a solvent system of benzene:ethanol (8:2). The spots were developed in iodine chamber and visualized under ultraviolet lamp.

RKJ17: 1-(4-chlorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl) urea

Molecular Formula: $C_{23}H_{17}ClN_4O_2$; Molecular weight: 416.86; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 129.0 C_{26} and C_{28}, 120.8 C_{25} and C_{29} 137.5, 133.3 C_{24} and C_{27} of phenyl ring of substituted urea at C_1 of 4(3*H*)-quinazolinone ring, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5, C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring

Table 1. List of synthesized compounds

Code	Compounds		
RKJ17	1-(4-chlorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	-Cl
RKJ18	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-chlorophenyl)urea	4-Br	-Cl
RKJ19	1-(4-chlorophenyl)-3-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-Cl	-Cl
RKJ20	1-(4-chlorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	-Cl
RKJ21	1-(4-fluorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	-F
RKJ22	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-fluorophenyl)urea	4-Br	-F
RKJ23	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-fluorophenyl)urea	4-Cl	-F
RKJ24	1-(4-fluorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	-F
RKJ25	1-(4-oxo-2-styrylquinazolin-3(4H)-yl)-3-(p-tolyl)urea	-H	*p*-CH_3
RKJ26	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea	4-Br	*p*-CH_3
RKJ27	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea	4-Cl	*p*-CH_3
RKJ28	1-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea	4-CH_3	*p*-CH_3
RKJ29	1-(2,5-dichlorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	2,5-Cl
RKJ30	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,5-dichlorophenyl)urea	4-Br	2,5-Cl
RKJ31	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,5-dichlorophenyl)urea	4-Cl	2,5-Cl
RKJ32	1-(2,5-dichlorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	2,5-Cl
RKJ33	1-(2,4-difluorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	2,4-F
RKJ34	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-difluorophenyl)urea	4-Br	2,4-F
RKJ35	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-difluorophenyl)urea	4-Cl	2,4-F
RKJ36	1-(2,4-difluorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	2,4-F
RKJ37	1-(2,4-dimethylphenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	2,4-CH_3
RKJ38	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-dimethylphenyl)urea	4-Br	2,4-CH_3
RKJ39	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-dimethylphenyl)urea	4-Cl	2,4-CH_3
RKJ40	1-(2,4-dimethylphenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	2,4-CH_3
RKJ41	1-(4-oxo-2-styrylquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea	-H	2,3,4- F
RKJ42	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea	4-Br	2,3,4- F
RKJ43	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea	4-Cl	2,3,4- F
RKJ44	1-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea	4-CH_3	2,3,4- F
RKJ45	1-(2,4,6-trimethylphenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea	-H	2,4,6- CH_3
RKJ46	1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4,6-trimethylphenyl)urea	4-Br	2,4,6- CH_3
RKJ47	1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4,6-trimethylphenyl)urea	4-Cl	2,4,6- CH_3
RKJ48	1-(2,4,6-trimethylphenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea	4-CH_3	2,4,6- CH_3

at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 3120 C-H str aromatic ring, 1655 C=O str, carbonyl group (quinazolinone ring), 1570 C=C str aromatic ring, 1650 C=O str Phenyl urea, 1220 C-N str quinazolinone ring, 1580 C=N str quinazolinone ring, 3320 N-H str Phenyl urea, 1090 C-Clstr (Aryl C-Cl), 1650 C=C str Alkene group, 730 C-H wag ; Mass (m/z): 416.10

RKJ18: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-chlorophenyl)urea

Molecular Formula: $C_{23}H_{16}BrClN_4O_2$; Molecular weight: 495.76; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1090 C-Clstr (Aryl C-Cl , C-Br str) 810 C-H wag ; Mass (m/z): 496.01

RKJ19: 1-(4-chlorophenyl)-3-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{23}H_{16}Cl_2N_4O_2$; Molecular weight: 451.3; 13C NMR (DMSO-d6, d ppm): 129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-

quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 848 C-H wag ; Mass (m/z): 450.07

RKJ20: 1-(4-chlorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{24}H_{19}ClN_4O_2$; Molecular weight: 430.89; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2902 C-H str (Alkyl group), 852 C-H wag ; Mass (m/z): 430.12

RKJ21: 1-(4-fluorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{23}H_{17}FN_4O_2$; Molecular weight: 400.41; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 119.3 C_{26} and C_{28}, 115.7 C_{25} and C_{29},135.0, 162.9 C_{24} and C_{27} of phenyl ring of substituted urea at C_1 of 4(3*H*)-quinazolinone ring, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring 127.3, C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and $C_{27}$of the phenyl ring, 113.3 $C_{15}$of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 1178 C-F str (Aryl C-F), 1645 C=C str Alkene group , 760 C-H wag ; Mass (m/z): 400.13

RKJ22: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-fluorophenyl)urea

Molecular Formula: $C_{23}H_{16}BrFN_4O_2$; Molecular weight: 479.30; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 121.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1175 C-F str, 1010 C-Br str, 810 C-H wag ; Mass (m/z): 478.04

RKJ23: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(4-fluorophenyl)urea

Molecular Formula: $C_{23}H_{16}ClFN_4O_2$; Molecular weight: 434.85; 13C NMR (DMSO-d6, d ppm):129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1170 C-F str, 1100 C-Clstr, 750 C-H wag ; Mass (m/z): 434.09

RKJ24: 1-(4-fluorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{24}H_{19}FN_4O_2$; Molecular weight: 414.43; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2860 C-H str (Alkyl group), 1178 C-F str, 800 C-H wag ; Mass (m/z): 414.15

RKJ25: 1-(4-oxo-2-styrylquinazolin-3(4H)-yl)-3-(p-tolyl)urea

Molecular Formula: $C_{24}H_{20}N_4O_2$; Molecular weight: 396.44; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 129.2 C_{26} and C_{28}, 121.5 C_{25} and C_{29}, 136.4, 136.6, C_{24} and C_{27}, 21.6 Methyl of phenyl ring of substituted urea at C_1 of 4(3*H*)-quinazolinone ring, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and $C_{27}$of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2910 C-H str (Alkyl group), 810, 740 C-H wag; Mass (m/z): 396.16

RKJ26: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea

Molecular Formula: $C_{24}H_{19}BrN_4O_2$; Molecular weight: 475.34; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 121.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1160 C-Br str (Alkyl group), 802 C-H wag ; Mass (m/z): 474.07

RKJ27: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea

Molecular Formula: $C_{24}H_{19}ClN_4O_2$; Molecular weight:

430.89; 13C NMR (DMSO-d6, d ppm): 129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1138 C-Br str (Alkyl group), 778 C-H wag ; Mass (m/z): 430.12

RKJ28: 1-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)-3-(p-tolyl)urea

Molecular Formula: $C_{25}H_{22}N_4O_2$; Molecular weight: 410.47; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2950 C-H str (Alkyl group), 830 C-H wag ; Mass (m/z): 410.17

RKJ29: 1-(2,5-dichlorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{23}H_{16}Cl_2N_4O_2$; Molecular weight: 451.30; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 132.8C_{24}, 128.9 C_{25}, 130.6 C_{26}, 131.3 C_{27}, 121.0 C_{28}, 127.9 C_{29}, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 1155 C-Clstr, 758, 890 C-H wag ; Mass (m/z): 450

RKJ30: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,5-dichlorophenyl)urea

Molecular Formula: $C_{23}H_{15}BrCl_2N_4O_2$; Molecular weight: 530.20; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1158 C-Br str (Alkyl group), 780, 872 C-H wag ; Mass (m/z): 529.97

RKJ31: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,5-dichlorophenyl)urea

Molecular Formula: $C_{23}H_{15}Cl_3N_4O_2$; Molecular weight: 485.75; 13C NMR (DMSO-d6, d ppm): 129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1120 C-Clstr, 780, 878 C-H wag ; Mass (m/z): 484.03

RKJ32: 1-(2,5-dichlorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{24}H_{18}Cl_2N_4O_2$; Molecular weight: 465.33; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2950 C-H str (Alkyl group), 1128 C-Clstr, 789, 870 C-H wag ; Mass (m/z): 464.08

RKJ33: 1-(2,4-difluorophenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{23}H_{16}F_2N_4O_2$; Molecular weight: 418.4; 13C NMR (DMSO-d6, d ppm):153.8 C_{12} of phenyl urea, 114.7 $C_{24,}$ 164.4 C_{25}, 104.9 C_{26}, 160.3 C_{27},111.3 C_{28}, 124.8 C_{29}, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr):1175 C-F str, 758, 890 C-H wag ; Mass (m/z): 418.12

RKJ34: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-difluorophenyl)urea

Molecular Formula: $C_{23}H_{15}BrF_2N_4O_2$; Molecular weight: 497.29; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr):1160 C-F str, C-Br str, 760, 892 C-H wag ; Mass (m/z): 496.03

RKJ35: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-

yl)-3-(2,4-difluorophenyl)urea

Molecular Formula: $C_{23}H_{15}ClF_2N_4O_2$; Molecular weight: 452.84; 13C NMR (DMSO-d6, d ppm): 129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1156 C-F str, C-Cl str, 780, 878 C-H wag ; Mass (m/z): 452.09

RKJ36: 1-(2,4-difluorophenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{24}H_{18}F_2N_4O_2$; Molecular weight: 432.42; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and $_{21}$ of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2958 C-H str (Alkyl group), 1169 C-F str, 780, 878 C-H wag ; Mass (m/z): 432.14

RKJ37: 1-(2,4-dimethylphenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{25}H_{22}N_4O_2$; Molecular weight: 410.47; 13C NMR (DMSO-d6, d ppm):153.8 C_{12} of phenyl urea, 131.7 C_{24}, 134.2 C_{25}, 131.1 C_{26}, 143.4 C_{27}, 126.2 C_{28}, 114.7 C_{29}, 17.6 and 21.6 C_{30} and C_{31}, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2946 C-H str (Alkyl group), 780, 878 C-H wag; Mass (m/z): 410.17

RKJ38: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-dimethylphenyl)urea

Molecular Formula: $C_{25}H_{21}BrN_4O_2$; Molecular weight: 489.36; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 2980 C-H str (Alkyl group), 1108 C-Br str, 772, 874 C-H wag ; Mass (m/z): 488.08

RKJ39: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4-dimethylphenyl)urea

Molecular Formula: $C_{25}H_{21}ClN_4O_2$; Molecular weight: 444.91; 13C NMR (DMSO-d6, d ppm):129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 2988 C-H str (Alkyl group), 1123 C-Cl str, 776, 860 C-H wag ; Mass (m/z): 444.14

RKJ40: 1-(2,4-dimethylphenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{26}H_{24}N_4O_2$; Molecular weight: 424.49; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2968 C-H str (Alkyl group), 796, 890 C-H wag ; Mass (m/z): 424

RKJ41: 1-(4-oxo-2-styrylquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea

Molecular Formula: $C_{23}H_{15}F_3N_4O_2$; Molecular weight: 436.39; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 116.3 C_{24}, 153.9 C_{25}, 137.2 C_{26}, 146.7 C_{27}, 110.4 C_{28}, 120.4 C_{29}, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr):1180 C-F str, 754, 806 C-H wag ; Mass (m/z): 436.11

RKJ42: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea

Molecular Formula: $C_{23}H_{14}BrF_3N_4O_2$; Molecular weight: 515.28; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1172 C-F str, C-Br str, 764, 829 C-H wag ; Mass (m/z): 514.03

RKJ43: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-

yl)-3-(2,3,4-trifluorophenyl)urea

Molecular Formula: $C_{23}H_{14}ClF_3N_4O_2$, Molecular weight: 470.83; 13C NMR (DMSO-d6, d ppm): 129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 1172 C-F str, C-Clstr, 767, 840 C-H wag ; Mass (m/z): 470.08

RKJ44: 1-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,3,4-trifluorophenyl)urea

Molecular Formula: $C_{24}H_{17}F_3N_4O_2$; Molecular weight: 450.41; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2920 Alkyl C-H str, 1172 C-F str, C-Br str, 764, 829 C-H wag ; Mass (m/z): 451

RKJ45: 1-(2,4,6-trimethylphenyl)-3-(4-oxo-2-styrylquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{26}H_{24}N_4O_2$; Molecular weight: 424.49; 13C NMR (DMSO-d6, d ppm): 153.8 C_{12} of phenyl urea, 131.5 C_{24}, 134.1 C_{25}, 128.1 C_{26}, 136.4 C_{27}, 128.1 C_{28}, 134.1 C_{29}, 17.9 and 21.6 C_{30},C_{32} and C_{31}, 160.6 C_2 of 4(3*H*)-quinazolinone ring, 145.5 C_4 of 4(3*H*)-quinazolinone ring, 158.9 C_6 of 4(3*H*)-quinazolinone ring, 126.6 C_7 and C_{10} of 4(3*H*)-quinazolinone ring, 127.3 C_8 of 4(3*H*)-quinazolinone ring, 133.4 C_9 of 4(3*H*)-quinazolinone ring and C_{27} of the phenyl ring, 113.3 C_{15} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 138.1 C_{16} of the styryl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.6 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 135.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 127.9 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr): 2978 Alkyl C-H str, 720, 860 C-H wag ; Mass (m/z): 424.19

RKJ46: 1-(2-(4-bromostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4,6-trimethylphenyl)urea

Molecular Formula: $C_{26}H_{23}BrN_4O_2$; Molecular weight: 503.39; 13C NMR (DMSO-d6, d ppm): 128.6 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 131.5 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 134.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 122.3 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 2980 Alkyl C-H str, 1148 C-Br str, 729, 864 C-H wag ; Mass (m/z): 502.10

RKJ47: 1-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4H)-yl)-3-(2,4,6-trimethylphenyl)urea

Molecular Formula: $C_{26}H_{23}ClN_4O_2$; Molecular weight: 458.94; 13C NMR (DMSO-d6, d ppm):129 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.7 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.3 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 133.5 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring; IR (cm-1, KBr): 2971 Alkyl C-H str, 1148 C-Clstr, 729, 864 C-H wag ; Mass (m/z): 458.15

RKJ48: 1-(2,4,6-trimethylphenyl)-3-(2-(4-methylstyryl)-4-oxoquinazolin-3(4H)-yl)urea

Molecular Formula: $C_{27}H_{26}N_4O_2$; Molecular weight: 438.52; 13C NMR (DMSO-d6, d ppm): 128.5 C_{18} and C_{22} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 128.9 C_{19} and C_{21} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 132.2 C_{17} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 137.6 C_{20} of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring, 21.3 Methyl at of the phenyl ring at C-6 of 4(3*H*)-quinazolinone ring ; IR (cm-1, KBr):2987 Alkyl C-H str, 862 C-H wag ; Mass (m/z): 438.21

Table 2. Physical properties of the synthesized title compounds

Code	Mol. Formula	Molecular weight	Elemental data
RKJ17	$C_{23}H_{17}ClN_4O_2$	416.86	C, 66.27; H, 4.11; N, 13.44
RKJ18	$C_{23}H_{16}BrClN_4O_2$	495.76	C, 55.72; H, 3.25; N, 11.30
RKJ19	$C_{23}H_{16}Cl_2N_4O_2$	451.3	C, 61.21; H, 3.57; N, 12.41
RKJ20	$C_{24}H_{19}ClN_4O_2$	430.89	C, 66.90; H, 4.44; N, 13.00
RKJ21	$C_{23}H_{17}FN_4O_2$	400.41	C, 68.99; H, 4.28; N, 13.99
RKJ22	$C_{23}H_{16}BrFN_4O_2$	479.30	C, 57.64; H, 3.36; N, 11.69
RKJ23	$C_{23}H_{16}ClFN_4O_2$	434.85	C, 63.53; H, 3.71; N, 12.88
RKJ24	$C_{24}H_{19}FN_4O_2$	414.43	C, 69.55; H, 4.62; N, 13.52
RKJ25	$C_{24}H_{20}N_4O_2$	396.44	C, 72.71; H, 5.08; N, 14.13
RKJ26	$C_{24}H_{19}BrN_4O_2$	475.34	C, 60.64; H, 4.03; N, 11.79
RKJ27	$C_{24}H_{19}ClN_4O_2$	430.89	C, 66.90; H, 4.44; N, 13.00
RKJ28	$C_{25}H_{22}N_4O2$	410.47	C, 73.15; H, 5.40; N, 13.65
RKJ29	$C_{23}H_{16}Cl_2N_4O_2$	451.30	C, 61.21; H, 3.57; N, 12.41
RKJ30	$C_{23}H_{15}BrCl_2N_4O_2$	530.20	C, 52.10; H, 2.85; N, 10.57
RKJ31	$C_{23}H_{15}Cl_3N_4O_2$	485.75	C, 56.87; H, 3.11; N, 11.53
RKJ32	$C_{24}H_{18}Cl_2N_4O_2$	465.33	C, 61.95; H, 3.90; N, 12.04
RKJ33	$C_{23}H_{16}F_2N_4O_2$	418.4	C, 66.03; H, 3.85; N, 13.39
RKJ34	$C_{23}H_{15}BrF_2N_4O_2$	497.29	C, 55.55; H, 3.04; N, 11.27
RKJ35	$C_{23}H_{15}ClF_2N_4O_2$	452.84	C, 61.00; H, 3.34; N, 12.37
RKJ36	$C_{24}H_{18}F_2N_4O_2$	432.42	C, 66.66; H, 4.20; N, 12.96
RKJ37	$C_{25}H_{22}N_4O_2$	410.47	C, 73.15; H, 5.40; N, 13.65
RKJ38	$C_{25}H_{21}BrN_4O_2$	489.36	C, 61.36; H, 4.33; N, 11.45
RKJ39	$C_{25}H_{21}ClN_4O_2$	444.91	C, 67.49; H, 4.76; N, 12.59
RKJ40	$C_{26}H_{24}N_4O_2$	424.49	C, 73.56; H, 5.70; N, 13.20
RKJ41	$C_{23}H_{15}F_3N_4O_2$	436.39	C, 63.30; H, 3.46; N, 12.84
RKJ42	$C_{23}H_{14}BrF_3N_4O_2$	515.28	C, 53.61; H, 2.74; N, 10.87
RKJ43	$C_{23}H_{14}ClF_3N_4O_2$	470.83	C, 58.67; H, 3.00; N, 11.90
RKJ44	$C_{24}H_{17}F_3N_4O_2$	450.41	C, 64.00; H, 3.80; N, 12.44
RKJ45	$C_{26}H_{24}N_4O_2$	424.49	C, 73.56; H, 5.70; N, 13.20
RKJ46	$C_{26}H_{23}BrN_4O_2$	503.39	C, 62.03; H, 4.61; N, 11.13
RKJ47	$C_{26}H_{23}ClN_4O_2$	458.94	C, 68.04; H, 5.05; N, 12.21
RKJ48	$C_{27}H_{26}N_4O_2$	438.52	C, 73.95; H, 5.98; N, 12.78

Evaluation of Anticonvulsant activity

Animals

Albino mice of either sex (20-30 g) were used as experimental animals for anticonvulsant. Animals were kept in wire-mesh cages in a restricted-access room for one week before the experiments. Twelve days wash period was allowed prior to start of next study. The animals were fed with standard lab pellets and purified water *ad libitum*. Prior to the experiments animals were fasted for 12 h. All the test compounds were suspended in 0.5% w/v methyl cellulose. In each of the experiment a control group was made which received the vehicle (0.5% w/v methyl cellulose). All the experiments were carried out according to protocols approved by the Institutional Animal Ethical Committee, Sagar Institute of Pharmaceutical Sciences, Sagar (Committee registration number 1387/a/10/CPCSEA and letter reference number is Animal Ethical Committee SIPS/EC/2015/68 dated 17-10-16).

Anticonvulsant activity of synthesized compounds

Antiseizure or anticonvulsive pharmacology of novel test substances was done by the anticonvulsant drug development (ADD) program protocol (Krall et al., 1978; Pester et al., 1984). The profile of anticonvulsant activity was established after *i.p.* injection by the MES pattern test and the subcutaneous pentylenetetrazole (scPTZ) seizure threshold test (65 mg/kg). Minimal motor impairment was measured by the rotorod (neurotoxicity, NT) test using doses of 30, 100 and 300 mg/kg at two different time intervals. Same compounds were studied for their CNS behavioral activity in mice using actophotometer. Using these basic tests, we can identify and differentiate the anticonvulsant pharmacology of novel compounds. Standard drugs used for both the above studies were phenytoin and carbamazepine.

Electroshock method

Albino mice were used for this experiment. Food was withdrawn 6 h before the commencement of the experiments, while water was withdrawn immediately before the experiment. Maximum seizures were induced by applications of electrical current across the brain via corneal electrodes primed with normal saline (0.9 % NaCl). Place mice together in the transparent plastic holding cage as they are dosed. Set an electroshock apparatus to deliver a 50-mA stimulus, with 0.4 sec duration, a pulse width of 0.5 msec and a frequency of 60 pulses/sec. After applying shock mice were observed for the type of convulsion produced and the hind limb extensor response was taken as the end point. Animals showing positive hind limb extensor response were used for testing drug substance.

The animals were divided into groups of three animals each. Select mice, record their weight, and place a unique identifying mark on each animal with a permanent-ink black marker. Place the group in a transparent plastic holding cage to await dosing. The test compounds were suspended in 0.5% methyl cellulose in concentrations. Administer the test substance intra-peritoneally in the dose of 30, 100, 300 mg/kg, reference compound, or vehicle to each mouse. Stagger the administration (1- to 5-min intervals) to maintain the same time between dosing and testing for each animal. After 30 min and 4 h of drug administration electrical shock was given through corneal electrodes. Disappearance of the hind limb extensor component of convulsion if any was used as positive criteria.

Subcutaneous Pentylenetetrazole method (scPTZ)

Mice of either sex were divided in groups of three animals each. The test compounds were administrated *i.p.* to all animals in a group in dose of 30, 100, 300 mg/kg. Pentylenetetrazole (65 mg/kg) was injected intra-peritoneally, 30 min and 4 h after the administration of the drugs. The absence or presence of an episode of clonic convulsion was taken as the end point.

Neurotoxicity screening

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that rotates 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 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. Percentage decrease in locomotor activity is calculated with the help of activity score of control (24 h prior) and score after 1 h of drug treatment. Mean values were taken for the calculations. The control group animal was administered with PEG 400. The observations are tabulated in table 5.

Statistical analysis

The effect of phenytoin and carbamazepine.in different doses on MES and PTZ models of seizure induction were expressed. Percentage inhibition of seizure was calculated respectively. Data was analysed using one-way-ANOVA followed by Bonferroni's multiple comparison tests. p-values <0.05 were considered significant.

Results

Chemistry

The Synthesis of the intermediate and target compounds

was accomplished according to the stepsdepicted in the scheme of synthesis (Figure 3). Substituted phenyl urea (2) was obtained from thereaction of substituted aniline (1) with sodium cyanate. Which on treatment with hydrazine hydrate in basic medium (NaOH) converted into respective substituted semicarbazide(3). On the other hand anthranilic acid (4) refluxed with acetic anhydride in the presence of pyridine yields benzoxazine-4-one (6) via 2-acetylamino benzoic acid as intermediate. Substituted Quinazolines (7) were synthesized by the reaction of 3 with benzoxazine-4-one which again reacts with four different benzaldehyde resulting in the formation of title compounds (RKJ17-48). The elemental analysis data of synthesizedcompounds are given in table 2. Synthesized compounds were characterized by IR, ^{13}CNMR, LC-MS (FAB) and elemental analysis.

Anticonvulsant activity

Antiseizure or anticonvulsive pharmacology of selected test substances (RKJ17-48) was characterized using the variations of two basic test methods in mice: blockade of electroshock-induced convulsive seizures and blockade of chemical-induced convulsive seizures. In the maximal electroshock (MES) test, convulsive seizures are induced by applying a sufficiently strong electric current to the brain to initiate a seizure event that spreads throughout the CNS. Four of the most effective drugs that control partial and generalized tonic-clonic seizures in human epilepsy are phenytoin, carbamazepine, valproic acid, and phenobarbital. These drugs block MES seizures in mice, and thus MES seizures are considered an animal model of human clonic and/or tonic generalized seizures. The most frequently used chemical

Table 3. Lipophilic behavior of synthesized compounds

Sr. No.	Code	logP
1.	RKJ17	4.81
2.	RKJ18	5.64
3.	RKJ19	5.37
4.	RKJ20	5.29
5.	RKJ21	4.41
6.	RKJ22	5.24
7.	RKJ23	4.97
8.	RKJ24	4.89
9.	RKJ25	4.74
10.	RKJ26	5.56
11.	RKJ27	5.29
12.	RKJ28	5.22
13.	RKJ29	5.37
14.	RKJ30	6.19
15.	RKJ31	5.92
16.	RKJ32	5.85
17.	RKJ33	4.57
18.	RKJ34	5.39
19.	RKJ35	5.12
20.	RKJ36	5.05
21.	RKJ37	5.22
22.	RKJ38	6.05
23.	RKJ39	5.78
24.	RKJ40	5.71
25.	RKJ41	4.72
26.	RKJ42	5.55
27.	RKJ43	5.28
28.	RKJ44	5.21
29.	RKJ45	5.71
30.	RKJ46	6.54
31.	RKJ47	6.27
32.	RKJ48	6.2

Table 4. Anticonvulsant activity of selected 25 compounds

Compounds	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
RKJ18	-	300	300	-	-	-
RKJ19	-	-	-	-	-	-
RKJ20	-	-	-	-	300	-
RKJ22	-	-	-	-	-	-
RKJ26	-	300	-	-	-	-
RKJ27	-	-	-	-	-	-
RKJ28	-	-	-	-	300	-
RKJ29	-	-	-	-	-	-
RKJ30	100	300	300	300[b]	-	-
RKJ31	-	300	-	-	-	-
RKJ32	-	100	-	-	-	-
RKJ34	-	-	-	-	100	-
RKJ35	-	-	-	-	-	-
RKJ36	-	-	-	-	-	-
RKJ37	-	-	-	-	100	-
RKJ38	-	100	-	-	300	-
RKJ39	-	100	-	-	-	-
RKJ40	-	300	-	-	-	-
RKJ42	-	300	-	-	-	-
RKJ43	-	-	-	-	-	-
RKJ44	-	-	-	-	-	-
RKJ45	-	300[b]	-	-	-	-
RKJ46	100	300	300	300	100	-
RKJ47	100	300	300	300	300	-
RKJ48	100	300	300	-	-	-
Phenytoin[c]	30	30	-	-	100	100
Carbamazepine[c]	30	100	100	300	100	300

[a]Doses of 30, 100 and 300 mg/kg were administered. The values in the tableindicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after the injections were made; the symbol (-) indicates the absence of activity at maximum dose administered (300 mg/kg); [b]Died during test at 300 mg/kg without seizure; [c]Data from Refs

convulsant is pentylenetetrazol (PTZ). In mice, PTZ is administered subcutaneously at a dose of 65 mg/kg to induce mostly clonic convulsions. PTZ seizures are blocked by ethosuximide, valproic acid, phenobarbital, and diazepam, drugs that are used in controlling generalized absence seizures and/or myoclonic seizures (shock like contractions of muscles) in epilepsy. PTZ-induced clonic seizures are therefore considered a model of myoclonic/generalized absence epilepsy. Using these basic tests, we can identify and differentiate the anticonvulsant pharmacology of novel compounds. Therefore, out of the 32 synthesized compounds total 25 compounds were screened for the anticonvulsant activity (Table 4) on the basis of their lipophilic behavior (Table 3) (logP> 5.0).

The anticonvulsant potential of these compounds was investigated by both PTZ, MES tests and neurotoxicity data for the quinazolinone analogs are reported in table 4.

In the earlier reports it was highlighted that the presence of electron rich atom/group attached at the para position of the aryl ring showed increased potency in the MES screen. Compounds RKJ (18, 26, 30-32, 38-42, 45-48) were found to exhibit anticonvulsant activity in MES screen, however, compound RKJ48 showed potency near to standard drug (phenytoin, carbamazepine) without any neurotoxicity. Most of the synthesized compounds were active in MES screen for a long duration of time (after 4 h). Compound RKJ30, RKJ46-48 displayed activity in the MES screen after 0.5 h (100 mg/kg) and 4 h (300 mg/kg) while it was active at both 0.5 h (300 mg/kg) and 4 h (300 mg/kg) in the scPTZ test. This compound exhibited rapid onset of action and long duration of activity. Compounds RKJ (19, 22, 27, 29, 35-36, 43) and RKJ44 did not show any activity in MES as well as in scPTZ after 0.5 h. Compounds RKJ (20, 28, 34, 37, 38, 46) and RKJ47 showed neurotoxicity after 0.5 h at 300 mg/kg body weight. The most active compound in the scPTZ test, a test used to identify compound that elevates seizure threshold, were RKJ46 and RKJ47. All the compounds were screened for behavior study. In the behavioral study using actophotometer scoring technique, compounds showed decrease in locomotor activity between 18% and 71% where 18% was the lowest and 71% was the maximal decrease in locomotor activity when compared to phenytoin as reported in table 5.

Table 5. Behavioral study of synthesized Compounds

Compounds	Activity score			% Inhibition
	Control (24 h prior)	Post treatment		
		0.5 h After	1 h After	
RKJ18	589.32 ± 20.48	472.31 ± 26.78	239.45 ± 11.69	59
RKJ19	446.04 ± 12.26	381.82 ± 9.69	276.36 ± 11.89	38
RKJ20	497.63 ± 8.89	419.24 ± 6.12	250.24 ± 12.62	50
RKJ22	448.10 ± 9.97	250.62 ± 10.30	232.04 ± 12.16	48
RKJ26	484.16 ± 10.62	319.57 ± 9.66	265.52 ± 12.70	45
RKJ27	484.72 ± 20.52	372.87 ± 2.21	289.92 ± 11.63	40
RKJ28	428.46 ± 26.18	315.46 ± 4.56	142.19 ± 13.28	67
RKJ29	482.82 ± 21.24	308.13 ± 7.25	280.30 ± 12.05	42
RKJ30	472.24 ± 10.72	531.00 ± 17.22NS	287.00 ± 21.11NS	39
RKJ31	358.16 ± 22.94	291.39 ± 1.02	292.20 ± 34.91	18
RKJ32	498.62 ± 17.38	362.37 ± 11.02	298.32 ± 26.72	40
RKJ34	354.76 ± 37.79	292.39 ± 29.87	110.45 ± 11.25	69
RKJ35	450.86 ± 39.25	353.52 ± 6.77	265.15 ± 31.79	41
RKJ36	427.92 ± 13.83	272.19 ± 2.11	287.19 ± 32.84	33
RKJ37	440.52 ± 10.60	306.98 ± 21.13	155.31 ± 17.30	65
RKJ38	465.72 ± 32.68	373.56 ± 2.35	253.08 ± 10.90	46
RKJ39	344.76 ± 22.72	292.39 ± 29.87	110.45 ± 11.25	68
RKJ40	442.82 ± 11.24	308.13 ± 7.25	180.30 ± 12.05	59
RKJ42	388.46 ± 16.18	315.46 ± 4.56	142.19 ± 13.28	63
RKJ43	400.52 ± 14.62	306.98 ± 21.13	155.31 ± 17.30	61
RKJ44	447.63 ± 18.90	419.24 ± 6.12	310.24 ± 12.62	31
RKJ45	448.62 ± 20.33	362.37 ± 11.02	208.32 ± 26.72	54
RKJ46	410.86 ± 25.27	353.52 ± 6.77	185.15 ± 31.79	55
RKJ47	387.92 ± 15.84	272.19 ± 2.11	137.19 ± 32.84	65
RKJ48	318.16 ± 12.92	291.39 ± 1.02	92.20 ± 34.91	71
Phenytoin	546.40 ± 31.12	251.02 ± 12.32	164.10 ± 30.11	70

The compounds were tested at a dose of 100 mg/kg i.p.; Each score represents the means ± SEM of six mice significantly different from the control score at $p < 0.05$ and NS at $p > 0.05$ denotes not significant (Student's t-test)

Conclusion

The anticonvulsant drug design was based on the presumption that the activity in maximal electroshock (MES) evaluation requires at least one phenyl or similar aromatic group in close proximity to two electron donor atoms and the activity in the pentylenetetrazole (PTZ) evaluation requires an alkyl group substituted close to two electron donor atoms. It has been hypothesized that, ureas displaying anticonvulsant activity interact at locations on the recognized binding site designated as aryl binding site, hydrogen bonding domain and an auxiliary aryl or other hydrophobic binding site. Derivatives of 4(3H)-quinazolinone were found to be more potent due to their ability to form strong hydrogen bonds and their hydrophobic nature. Furthermore, the derivatives of RKJ46 and RKJ47 were much more potent than the other in PTZ test because of the bulkiness they own and their lipophilicity. These data may be useful for future molecular modifications leading to compounds with greater favorable pharmacological properties.

Conflicts of interest: None

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