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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF VARIOUS THIADIAZOLYLPYRIDINYL/INDOLYLISOXAZOLYL QUINAZOLINONE-4-ONES

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ABSTRACT

A series of 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(un/substituted hetetocyclic/aryl) -4,5-dihydroisoxazol-3-yl)hydrazinyl)methyl)quinazolin-4(3H)-ones **6a-i** have been synthesized by the reaction of 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(un/substituted heterocyclic/ arylchalconyl)-hydrazinyl)methyl)-substitutedquinazolin-4(3H)-one **5a-5i** with hydroxyl amine hydrochloride in presence of 2% NaOH. All the newly synthesized compounds were screened for their antipsychotic and anticonvulsant activities. Structures of all the compounds were established by elemental and spectral (IR, ^{1}H NMR and Mass) analysis.

KEYWORDS

Thiadiazolylquinazolinones, Pyridiny/Indolyllquinazolinones, isoxazolylquinazolinones, antipsychotic activity, anticonvulsant activity, toxicity study.

INTRODUCTION

Psychotic disorders refers to the major mental illness like schizophrenia and manic depression in which (a) insight is said to be lost: and (b) patient's experience e.g. hallucinations, outside the normal range of human experience. Antipsychotic drugs are those which cause the blockade mainly of postsynaptic dopaminergic (D_2) receptors and to smaller extent 5-HT receptor. Moreover, epilepsy is very often associated with CNS psychiatric disorders, a drug with both antipsychotic as well as antiepileptic activity will be more beneficial. Therefore, the need for more effective and less toxic antipsychotic drugs still exists.Quinazoline-4-one is. Based on these findings, we attempted to synthesize the title versatile pharmacophore which exhibits a wide variety of biological activities like antipsychotic [1], CNS depressant [2] and anticonvulsant [3]. Moreover, thiadiazole derivatives have been reported to possess antipsychotic [4] and anticonvulsant activities [5]. Furthermore, various derivatives of pyridine, indole and isoxazole have also been reported to exhibit antipsychotic [6-8] and anticonvulsant [9-11] activities compounds presuming that the incorporation of thiadiazole, pyridine, indole and isoxazole in quinazolinone may impart prominent antipsychotic

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and anticonvulsant activities. The newly synthesized compounds were screened for their antipsychotic as well as their anticonvulsant activity with the hope to get better antipsychotic and anticonvulsant agents.

MATERIAL AND METHODS

Antipsychotic activity

All the newly synthesized compounds (i.e. compounds **5a-i** and **6a-i)** have been evaluated for their antipsychotic activity according to following parameters

(a) Effect on amphetamine induced stereotyped behaviour (SB):

It was done by the method of Castall and Naylor[12]. Before the administration of drugs, the animals were fasted for 12 h and were deprived of food during experiment. Amphetamine (4mg/kg, i.p.) was used to induce the stereotyped behaviour (SB) in albino rats. The intensity of SB was assessed for 60 min after test compounds treatment, using the following scoring system. Periodic sniffing = 1 Score, continuous sniffing = 2 Score, periodic biting, gnawing or licking = 3 Score and continuous biting, gnawing or licking = 4 Score. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group. Chlorpromazine (4mg/kg, i.p.) was used as standard and was injected 30 min. before the challenge, while propylene glycol (0.5 mL i.p.) or test compounds was given 20 min prior to the injection of amphetamine.

Induction of catalepsy

It was performed according to the method of Castall and Naylor [12]. According this method, the front limbs of the rat were placed over the wooden block of 8 cm high and measure the time the animal maintained the imposed posture. Animals maintaining the imposed posture for more than 10 sec were considered to be cataleptic. Animals were tested for catalepsy by using the scoring system to maintain the impose posture 0-10 sec = 0 score, 11-30 sec = 1 score, 31-60 sec = 2 score, 61-120 = 3 score, after injecting propylene glycol (0.5 mL, i.p.) or test compounds or haloperidol (0.5mg/kg, i.p.) as standard.

Anticonvulsant activity

Maximum electroshock seizure (MES) test

This activity was performed by method the of Toman et al [13] on albino rats of the Charles foster strain of either sex, weighing, between 100-120 g. Rats were divided into the groups of 10 animals each and pregnancy was excluded in female rats. The rats were treated with the test drugs 40 mg/kg and phenytoin sodium 30 mg/kg i.p. After 1 hour they were subjected to the shock of 150 mA by convulsiometer through ear electrodes for 0.2 sec. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animals protected/ number of animals tested.

Acute toxicity study

The compounds were investigated for this acute toxicity (ALD_{50}) in albino mice by following the method of smith [14]. Test compounds were administered orally in one group and the same volume of normal saline in another group of animals consisting six mice each in graded doses. During the study, the animals were allowed to take water and food adlibidum. After 24 h of drug administration percent mortality in each group was observed. From the data obtained ALD_{50} was calculated.

EXPERIMENTAL

Synthesis of 2-Amino-5-(2-fluorophenyl)-1,3,4-thiadiazole

Thiosemicarbzone (1.0 mole) was suspended in 500 ml warm water, $FeCl_3$ (3.0 mole) in 500 ml water was added quantitatively, slowly with constant

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stirring. The contents were heated at 80-90 ^{0}C for 45 minutes. Solution was filtered hot and then citric acid (2 mole) and sodium citrate (1.0 ml) was added. The resulting mixture was divided into 4 parts and each part was neutralized separately with ammonia (10%). The required amine separated out, filtered with suction, dried and recrystallized with appropriate solvent.

2-methyl-substituted-4H-benzo[d]oxazin-4-ones

These compounds were prepared according to the method of bogert & sciel [15]. A mixture of substituted anthranilic acid (1.0 mol) and acetic anhydride (100 ml) to the solution of compound 2 in acetic acid (50 ml). The reaction mixture was poured onto crushed ice then left overnight at room temp. The precipitate thus obtained was filtered washed dried and recrystallized with appropriate solvents to obtain compounds 2-methyl-substituted-4H-benzo[d]oxazin-4-ones.

2-Methyl-4H-benzo[d]oxazin-4-one

Yield 80% (Methanol); m.p. 80 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1680 (C=O), 1615 (C⋯C of aromatic ring), 1580 (C=N), 1294 (N-N), 692 (C-S-C). ^{1}H-NMR (DMSOd_6) □δ in ppm: 7.90-6.92 (m, 4H, Ar-H), 2.30 (s, 3H, CH_3). MS: $[M]^+$ at *m/z* 161.16. Anal. calcd. for $C_9H_7NO_2$: C,67.07; H, 4.38; N, 8.69: Found : C,67.09; H, 4.40; N,8.70: %

6-Bromo-2-methyl-4H-benzo[d]oxazin-4-one

Yield 89% (Acetone); m.p. 85 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1688 (C=O), 1618 (C⋯C of aromatic ring), 1586 (C=N), 1290 (N-N), 696 (C-S-C), 612 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 7.89-6.90 (m, 3H, Ar-H), 2.35 (s, 3H, CH_3). MS: $[M]^+$ at *m/z* 240.05; Anal. calcd. for $C_9H_6BrNO_2$: C,45.03; H, 2.52; N, 5.83: Found : C, 45.04; H, 2.58; N, 5.85: %

6,8-Dibromo-2-methyl-4H-benzo[d]oxazin-4-one

Yield 80% (Methanol); m.p. 90 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1680 (C=O), 1617 (C⋯C of aromatic ring), 1580 (C=N), 1294 (N-N), 692 (C-S-C), 611 (C-Br). ^{1}H-NMR (DMSOd_6) □δ in ppm: 7.95-6.82 (m, 2H, Ar-H), 2.38 (s, 3H, CH_3). MS: $[M]^+$ at *m/z* 318.95; Anal. calcd. for $C_9H_5Br_2NO_2$: C, 33.89; H,1.58; N, 4.39: Found : C, 33.90; H,1.60; N,4.40%

2-Methyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)substituted quinazolin-4(3H)-ones **(1a-1c)**

To a solution of 2-methyl-substituted-4H-benzo[d]oxazin-4-ones add 2-Amino-5-(2-fluorophenyl)-1,3,4-thiadiazole (1.0 mol) was heated on a free flame for 10-20 minutes in a conical flask. After the disappearance of water droplets in a conical flask it was kept at room temperature. On cooling a jelly like mass obtained which was dissolved in ethanol were refluxed and poured in to water. The solid thus obtained was filtered, dried and finally recrystallized appropriate solvent to obtained compounds 1a-1c.

2-Methyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(1a)** Yield 83% (Ethanol); m.p. 167 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1683 (C=O), 1616 (C⋯C of aromatic ring), 1585 (C=N), 1293 (N-N), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 7.80-6.82 (m, 8H, Ar-H), 2.28 (s, 3H, CH_3),. MS: $[M]^+$ at *m/z* 338.36. Anal. calcd. for $C_{17}H_{11}FN_4OS$: C, 60.34; H, 3.28; N, 16.56: Found : C, 60.36; H, 3.24; N, 16.59%

6-Bromo-2-methyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one *(***1b)** Yield 80% (DMF-Water); m.p. 172 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1688 (C=O), 1614 (C⋯C of aromatic ring), 1589 (C=N), 1291 (N-N), 696 (C-S-C), 611 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 7.95-6.71 (m, 7H, Ar-H), 2.35 (s, 3H, CH_3),. MS: $[M]^+$ at *m/z* 417.25. Anal.

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calcd. for $C_{17}H_{10}BrFN_4OS$: C, 48.53; H, 2.42; N, 13.43: Found : C, 48.57; H, 2.40; N, 13.46%

6,8-Dibromo-2-methyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(1c)** Yield 84% (Methanol); m.p. 186 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1683 (C=O), 1619 (C⋯C of aromatic ring), 1587 (C=N), 1292 (N-N), 698 (C-S-C), 614 (C-Br). ^{1}H-NMR ($DMSOd_6$) □δ in ppm: 7.80-6.82 (m, 6H, Ar-H), 2.28 (s, 3H, CH_3). MS: $[M]^+$ at *m/z* 496.15. Anal. calcd. for $C_{17}H_{10}Br_2N_6OS$: C, 41.15; H, 1.83; N, 11.29: Found : C, 41.14; H, 1.80; N, 11.30%

2-Bromomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)substitutedquinazolin-4(3H)-ones **(2a-2c)**

Bromine (0.6 mol) in acetic acid was added drop wise to the solution of compound 1a-1c in acetic acid (50 ml). The reaction mixture was poured onto crushed ice then left overnight at room temperature. The precipitate thus obtained was filtrated washed with suitable solvents to furnish compounds **2a-2c**.

2-(Bromomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(2a)** Yield 77% (Acetone); m.p. 190 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1693 (C=O), 1621 (C⋯C of aromatic ring), 1590 (C=N), 1292 (N-N), 695 (C-S-C). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 7.84-6.79 (m, 8H, Ar-H), 1.38 (s, 2H, CH_2-Br). MS: $[M]^+$ at m/z 417.25. Anal. calcd. for $C_{17}H_{10}BrFN_4OS$: C, 48.93; H, 2.42; N, 13.43: Found : C, 48.95; H, 2.41; N, 13.47%

6-bromo-2-(Bromomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(2b)** Yield 75% (Methanol); m.p. 178 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1692 (C=O), 1619 (C⋯C of aromatic ring), 1593 (C=N), 1294 (N-N), 694 (C-S-C), 615 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 7.94-6.70 (m, 7H, Ar-H), 1.35 (s, 2H, CH_2-Br). MS: $[M]^+$ at m/z 496.15; Anal. calcd. for $C_{17}H_9Br_2FN_4OS$: C, 41.15; H, 1.83; N, 11.29: Found : C, 41.16; H, 1.80; N, 11.29%

6,8-Dibromo-2-(bromomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(2c)** Yield 75% (Acetone); m.p. 188 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 1693 (C=O), 1615 (C⋯C of aromatic ring), 1597 (C=N), 1293 (N-N), 693 (C-S-C), 613 (C-Br). ^{1}H-NMR ($DMSOd_6$) □δ in ppm: 7.86-6.83 (m, 6H, Ar-H), 1.28 (s, 2H, CH_2-Br). MS: $[M]^+$ at m/z 575.05; Anal. calcd. for $C_{17}H_8Br_3FN_4OS$: C, 35.51; H, 1.40 ; N, 9.74: Found : C, 35.55; H, 1.42; N, 9.72%

2-Hydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)substitutedquinazolin-4(3H)-ones **(3a-3c)**

A compound 2a-2c (0.1 mole) and hydrazine hydrate (0.1 mole) in methanol was refluxed for 10 hours. The excess of solvent was distilled off and the reaction mixture was poured on to ice. The solid thus obtained was filtered washed with water dried and recrystallized from appropriate solvents to yielded compounds **3a-3c**.

2-Hydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(3a)** Yield 73% (Methanol); m.p. 245 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3342 (NH), 1690 (C=O), 1620 (C⋯C of aromatic ring), 1587 (C=N), 1291 (N-N), 693 (C-S-C). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.80 (brs, 1H, NH), 8.49 (brs, 2H, NH_2), 7.94-6.69 (m, 8H, Ar-H), 3.38 (d, 2H, CH_2). MS: $[M]^+$ at m/z 368.39. Anal. calcd. for $C_{17}H_{13}FN_6OS$: C, 55.43; H, 3.56; N, 22.81: Found : C, 55.46; H, 3.55; N, 22.78%

6-Bromo-2-hydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(3b)**

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Yield 77% (Methanol); m.p. 254 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3348 (NH), 1696 (C=O), 1615 (C⋯C of aromatic ring), 1589 (C=N), 1292 (N-N), 694 (C-S-C), 612 (C-Br). ^{1}H-NMR (DMSOd_6) □δ in ppm: 8.80 (brs, 1H, NH), 8.47 (brs, 2H, NH_2), 7.95-6.71 (m, 7H, Ar-H), 2.35 (d, 2H, CH_2). MS: $[M]^+$ at m/z 447.28. Anal. calcd. for $C_{17}H_{12}BrFN_6OS$: C, 45.65; H, 2.70; N, 18.79: Found : C, 45.68; H, 2.68; N, 18.76%

6,8-Dibromo-2-hydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(3c)** Yield 74% (Ethanol); m.p. 258 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3354 (NH), 1692 (C=O), 1616 (C⋯C of aromatic ring), 1590 (C=N), 1294 (N-N), 698 (C-S-C), 615 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.80 (brs, 1H, NH), 8.48 (brs, 2H, NH_2), 7.80-6.82 (m, 6H, Ar-H), 2.28 (d, 2H, CH_2). MS: $[M]^+$ at m/z 526.18. Anal. calcd. for $C_{17}H_{11}Br_2FN_6OS$: C, 38.80; H, 2.11; N, 15.97: Found : C, C, 38.80; H, 2.15; N, 15.92%

2-Acetylhydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)substitutedquinazolin-4(3H)-ones **(4a-4c)**

A mixture of compounds **3a-3c** (0.14 mole) and freshly distilled acetic anhydride (100 ml) was heated to 110-120^{0}C for 4 hours and after removal of acetic anhydride from the reaction mixture with the help of rotary vaccum evaporator, a solid mass was obtained which was recrystallized from suitable solvents to give compounds **4a-4c**.

2-Acetylhydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(4a)**

Yield 76% (Methanol); m.p. 270 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3355 (NH), 1700, 1692 (C=O), 1622 (C⋯C of aromatic ring), 1592 (C=N), 1292 (N-N), 690 (C-S-C). ^{1}H-NMR (DMSOd_6) □δ in ppm: 8.84 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.90-6.79 (m, 8H, Ar-H), 4.32 (s, 3H, CH_3), 3.38 (d, 2H, CH_2). MS: $[M]^+$ at m/z 410.42. Anal. calcd. for $C_{19}H_{15}FN_6O_2S$: C, 55.60; H, 3.68; N, 20.48: Found : C, 55.65; H, 3.65; N, 20.47%

6-Bromo-2-Acetylhydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(4b)** Yield 78% (Methanol); m.p. 280 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3356 (NH), 1698, 1680 (C=O), 1625 (C⋯C of aromatic ring), 1590 (C=N), 1290 (N-N), 696 (C-S-C), 611 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.87 (brs, 1H, NH), 8.48 (brs, 1H, NH), 7.85-6.77 (m, 7H, Ar-H), 4.31 (s, 3H, CH_3), 2.32 (d, 2H, CH_2),. MS: $[M]^+$ at m/z 488.01. Anal. calcd. for $C_{19}H_{14}BrFN_6O_2S$: C, 46.64; H, 2.88; N, 17.17: Found : C, 41.21; H, 3.91; N, 25.63%

6,8-Dibromo-2-Acetylhydrazinomethyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(4c)** Yield 79% (Ethanol); m.p. 276 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3352, (NH), 1692, 1684 (C=O), 1618 (C⋯C of aromatic ring), 1594 (C=N), 1293 (N-N), 699 (C-S-C), 614 (C-Br). ^{1}H-NMR (DMSOd_6) □δ in ppm: 8.83 (brs, 1H, NH), 8.43 (brs, 1H, NH), 7.83-6.83 (m, 6H, Ar-H), 4.37 (s, 3H, CH_3), 2.28 (d, 2H, CH_2). MS: $[M]^+$ at m/z 568.22; Anal. calcd. for $C_{19}H_{13}Br_2FN_6O_2S$: C, 4.16; H, 2.31; N, 14.79: Found : C, 4.14; H, 2.30; N, 14.82%

3-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(un/substituted hetetocyclic/arylchalconyl)-hydrazinyl)methyl)-substitutedquinazolin-4(3H)-one **(5a-5i)**

A solution of compound **4a-4c** (0.1 mole) in absolute ethanol (100 ml) in 2% NaOH and various aromatic aldehydes (0.1 mole) was refluxed for 8-12 hours, concentrated, cooled and poured onto ice. The solid thus obtained was filtered, washed with water and recrystallised from appropriate solvent to obtained

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compound **5a-5i**.

2-(Pyridinylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin -4(3H)-one **(5a)**
Yield 77% (Methanol); m.p. 290 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3355 (NH), 1696, 1682 (C=O), 1627 (CH=CHAr), 1622 (C⋯C of aromatic ring), 1592 (C=N), 1292 (N-N), 690 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ in ppm: 8.84 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.90-6.79 (m, 12H, Ar-H), 7.71 (d, 1H, CH=CHAr), 6.71 (d, 1H, COCH=CHAr), 3.38 (d, 2H, CH_2). MS: $[M]^+$ at m/z 499.52; Anal. calcd. for $C_{25}H_{18}FN_7O_2S$: C, 60.11; H, 3.63; N, 19.63: Found : C, 60.15; H, 3.60; N, 19.60%

6-Bromo-2-(pyridinylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5b)** Yield 71% (Ethanol); m.p. 296 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3356 (NH), 1699, 1680 (C=O), 1632 (CH=CHAr), 1625 (C⋯C of aromatic ring), 1590 (C=N), 1290 (N-N), 696 (C-S-C), 611 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm: 8.87 (brs, 1H, NH), 8.48 (brs, 1H, NH), 7.85-6.77 (m, 11H, Ar-H), 7.71 (d, 1H, CH=CHAr), 6.71 (d, 1H, COCH=CHAr), 2.32 (d, 2H, CH_2). MS: $[M]^+$ at m/z 578.42. Anal. calcd. for $C_{25}H_{17}BrFN_7O_2S$: C, 51.91; H, 2.96; N, 16.95: Found : C, 51.98; H, 2.93; N, 16.96%

6,8-Dibromo-2-(pyridinylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol -2-yl)quinazolin-4(3H)-one **(5c)** Yield 70% (Methanol); m.p. 288 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3359 (NH), 1693, 1684 (C=O), 1625 (CH=CHAr), 1618 (C⋯C of aromatic ring), 1594 (C=N), 1293 (N-N), 699 (C-S-C), 614 (C-Br). ^{1}H-NMR ($DMSOd_6$) δ in ppm: 8.83 (brs, 1H, NH), 8.43 (brs, 1H, NH), 7.83-6.83 (m, 10H, Ar-H), 7.74 (d, 1H, CH=CHAr), 6.73 (d, 1H, COCH=CHAr), 2.28 (d, 2H, CH_2). MS: $[M]^+$ at m/z 657.31 ; Anal. calcd. for $C_{25}H_{16}Br_2FN_7O_2S$: C, 45.68; H, 2.45; N, 14.92: Found : C, 45.64; H, 2.48; N, 14.90%

2-(4-Methoxybenzylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5d)** Yield 77% (Methanol); m.p. 283 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3348 (NH), 1700, 1681 (C=O), 1627 (CH=CHAr), 1620 (C⋯C of aromatic ring), 1590 (C=N), 1294 (N-N), 694 (C-S-C), 1225 (OCH_3). ^{1}H-NMR ($CDCl_3$) δ in ppm: 8.84 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.90-6.79 (m, 12H, Ar-H), 7.71 (d, 1H, CH=CHAr), 6.72 (d, 1H, COCH=CH), 3.52 (s, 3H, OCH_3), 2.33 (d, 2H, CH_2). MS: $[M]^+$ at m/z 528.56. Anal. calcd. for $C_{27}H_{21}FN_6O_3S$: C, 61.35; H, 4.00; N, 15.90: Found : C, 61.32; H, 4.03; N, 15.93%

6-Bromo-2-(4-methoxybenzylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5e)** Yield 76% (Methanol); m.p. 288 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3338 (NH), 1699, 1683 (C=O), 1629 (CH=CHAr), 1615 (C⋯C of aromatic ring), 1596 (C=N), 1291 (N-N), 695 (C-S-C), 615 (C-Br), 1224 (OCH_3). ^{1}H-NMR ($DMSOd_6$) δ in ppm: 8.82 (brs, 1H, NH), 8.47 (brs, 1H, NH), 7.95-6.78 (m, 11H, Ar-H), 7.73 (d, 1H, CH=CHAr), 6.75 (d, 1H, COCH=CH), 3.45 (s, 3H, OCH_3), 2.34 (d, 2H, CH_2). MS: $[M]^+$ at m/z 607.45. Anal. calcd. for $C_{27}H_{20}BrFN_6O_3S$: C, 53.38; H, 3.32; N, 13.83: Found : C, 53.37; H, 3.33; N, 13.80%

6,8-Dibromo-2-(4-methoxybenzylidenechalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5f)** Yield 70% (Methanol); m.p. 284 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3356 (NH), 1702, 1681 (C=O), 1626 (CH=CHAr),

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1614 (C⋯C of aromatic ring), 1592 (C=N), 1294 (N-N), 698 (C-S-C), 611 (C-Br), 1226 (OCH_3). ^{1}H-NMR ($DMSOd_6$) □δ in ppm: 8.87 (brs, 1H, NH), 8.45 (brs, 1H, NH), 7.93-6.84 (m, 10H, Ar-H), 7.72 (d, 1H, CH=CHAr), 6.72 (d, 1H, COCH=CH), 3.48 (s, 3H, OCH_3), 2.28 (d, 2H, CH_2). MS: $[M]^+$ at m/z 686.35; Anal. calcd. for $C_{27}H_{19}BrFN_6O_3S$: C, 47.25; H, 2.79; N, 12.24: Found : C, 47.28; H, 2.80; N, 12.23%

2-(4-Methoxyindolidenylchalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5g)** Yield 72% (Ethanol); m.p. 289 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3348 (NH), 1706, 1686 (C=O), 1631 (CH=CHAr), 1621 (C⋯C of aromatic ring), 1592 (C=N), 1290 (N-N), 693 (C-S-C), 1225 (OCH_3). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 9.55 (brs, 1H, NH of indole exchangeable), 8.84 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.90-6.79 (m, 12H, Ar-H), 7.71 (d, 1H, CH=CHAr), 6.71 (d, 1H, COCH=CH), 3.45 (s, 3H, OCH_3), 2.38 (d, 2H, CH_2). MS: $[M]^+$ at m/z 567.59; Anal. calcd. for $C_{29}H_{22}FN_7O_3S$: C, 61.37; H, 3.91; N, 17.27: Found : C, 61.35; H, 3.94; N, 17.27%

6-Bromo-2-(4-methoxyindolidenylchalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5h)** Yield 70% (Methanol); m.p. 287 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3358 (NH), 1697, 1683 (C=O), 1629 (CH=CHAr), 1626 (C⋯C of aromatic ring), 1595 (C=N), 1291 (N-N), 693 (C-S-C), 613 (C-Br), 1227 (OCH_3). ^{1}H-NMR ($CDCl_3$+DMSOd6) □δ in ppm: 9.45 (brs, 1H, NH of indole exchangeable), 8.89 (brs, 1H, NH), 8.42 (brs, 1H, NH), 7.88-6.67 (m, 11H, Ar-H), 7.75 (d, 1H, CH=CHAr), 6.70 (d, 1H, COCH=CH), 3.44 (s, 3H,OCH_3), 2.35 (d, 2H, CH_2). MS: $[M]^+$ at m/z 646.49. Anal. calcd. for $C_{29}H_{21}BrFN_7O_3S$: C, 53.88; H, 3.27; N, 15.17: Found : C, C, 53.90; H, 3.23; N, 15.19%

6-Bromo-2-(4-methoxyindolidenylchalconyl)-hydrazino)methyl)-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one **(5i)** Yield 79% (Methanol); m.p. 290 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3333 (NH), 1695, 1682 (C=O), 1631 (CH=CHAr), 1624 (C⋯C of aromatic ring), 1598 (C=N), 1292 (N-N), 696 (C-S-C), 612 (C-Br), 1224 (OCH_3). ^{1}H-NMR ($CDCl_3$+DMSOd6) □δ in ppm: 9.47 (brs, 1H, NH of indole exchangeable), 8.93 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.86-6.82 (m, 10H, Ar-H), 7.74 (d, 1H, CH=CHAr), 6.70 (d, 1H, COCH=CH), 3.46 (s, 3H, OCH_3), 2.22 (d, 2H, CH_2). MS: $[M]^+$ at m/z 725.39. Anal. calcd. for $C_{29}H_{20}BrFN_7O_3S$: C, 48.02; H, 2.78; N, 13.52: Found : C, 48.00; H, 2.79; N, 13.50%

3-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(un/substituted heterocyclic/aryl)-4,5-dihydro isoxazol-2-yl-yl)hydrazinyl)methyl)substitutedquinazolin-4(3H)-one **(6a-i)**

To a solution of **5a-5h** (0.04 mol) in methanol (100 ml), hydroxyl amine hydrochloride (0.04 mol) was added. The reaction mixture was refluxed for 10 hours in presence of 2% NaOH solution. The resulting mixtures were concentrated and poured onto ice. The completion of reaction was monitored by TLC. The solid thus obtained were filtered, washed and recrystallized with appropriate solvents to furnish compounds **6a-6i**.

3-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(pyridinyl)-4,5-dihydroisoxazol-2-yl) hydrazinyl)methyl)quinazolin-4(3H)-one **(6a)** Yield 74% (Methanol); m.p. 241 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3353 (NH), 1699,1682 (C=O), 1623 (C⋯C of aromatic ring), 1610 (C=N), 1295 (N-N), 1238 (C-O-N), 690 (C-S-C). ^{1}H-NMR ($CDCl_3$+DMSOd6) □δ in ppm: 8.89 (brs, 1H, NH), 8.48 (brs, 2H, NH), 7.99-6.89 (m, 12H, Ar-H), 7.69 (t, 1H, CH-Ar), 3.33 (d,

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2H, CH_2 of isoxazole ring), 2.20 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 514.53. Anal. calcd. for $C_{25}H_{19}FN_8O_2S$: C, 58.36; H, 3.72; N, 21.78: Found : C, 58.39; H, 3.74; N, 21.80%

6-Bromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(pyridin-2-yl)-4,5-dihydroisoxazol-2-yl) hydrazinyl)methyl)quinazolin-4(3H)-one **(6b)** Yield 78% (Acetone); m.p. 257 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3357 (NH), 1696, 1680 (C=O), 1624 (C⋯C of aromatic ring), 1608 (C=N), 1292 (N-N), 1235 (C-O-N), 696 (C-S-C), 611 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.87 (brs, 1H, NH), 8.50 (brs, 1H, NH), 7.85-6.77 (m, 11H, Ar-H), 7.71 (t, 1H, CH-Ar), 3.32 (d, 2H, CH_2 of isoxazole ring), 2.21 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 593.43. Anal. calcd. for $C_{25}H_{18}FN_8BrO_2S$: C, 50.60; H, 3.06; N, 18.88: Found : C, 50.65; H, 3.07; N, 18.86%

6,8-Dibromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(pyridin-2-yl)-4,5-dihydro- isoxazol-2-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6c)** Yield 77% (Methanol); m.p. 240 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3354 (NH), 1693, 1683 (C=O), 1628 (C⋯C of aromatic ring), 1604 (C=N), 1290 (N-N), 1233 (C-O-N), 699 (C-S-C), 614 (C-Br). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.83 (brs, 1H, NH), 853 (brs, 1H, NH), 7.93-6.93 (m, 10H, Ar-H), 7.74 (t, 1H, CH-Ar), 3.28 (d, 2H, CH_2 of isoxazole ring), 2.23 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 672.33. Anal. calcd. for $C_{25}H_{17}FN_8Br_2O_2S$: C, 44.66; H, 2.55; N, 16.67: Found : C, 44.69; H, 2.50; N, 16.69%

3-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol-2-yl-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6d)** Yield 69% (Methanol); m.p. 260 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3335 (NH), 1702, 1684 (C=O), 1623 (C⋯C of aromatic ring), 1612 (C=N), 1292 (N-N), 1231 (C-O-N), 694 (C-S-C), 1225 (OCH_3). ^{1}H-NMR ($CDCl_3$+DMSOd6) □δ in ppm: 8.84 (brs, 1H, NH), 8.56 (brs, 1H, NH), 7.92-6.80 (m, 12H, Ar-H), 7.71 (t, 1H, CH-Ar), 3.47 (s, 3H, OCH_3), 3.38 (d, 2H, CH_2 of isoxazole ring), 2.21 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 543.15. Anal. calcd. for $C_{27}H_{22}FN_7O_3S$: C, 59.66; H, 4.08; N, 18.04: Found : C, 59.62; H, 4.09; N, 18.00%

6-Bromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol -2-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6e)** Yield 71% (Ethanol); m.p. 256 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3346 (NH), 1699, 1685 (C=O), 1625 (C⋯C of aromatic ring), 1611 (C=N), 1291 (N-N), 1234 (C-O-N), 695 (C-S-C), 615 (C-Br), 1224 (OCH_3). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.87 (brs, 1H, NH), 8.50 (brs, 1H, NH), 7.89-6.75 (m, 11H, Ar-H), 7.76 (t, 1H, CH-Ar), 2.31 (d, 2H, CH_2NH), 3.43 (s, 3H, OCH_3), 3.32 (d, 2H, CH_2 of isoxazole ring). MS: $[M]^+$ at m/z 622.47. Anal. calcd. for $C_{27}H_{21}FN_7BrO_3S$: C, 52.10; H, 3.40; N, 15.75: Found : C, 52.11; H, 3.39; N, 15.79%

6,8-Dibromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyphenyl)-4,5-dihydro-isoxazol-2-yl-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6f)** Yield 79% (Methanol); m.p.262 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3357 (NH), 1706, 1683 (C=O), 1624 (C⋯C of aromatic ring), 1612 (C=N), 1292 (N-N), 1235 (C-O-N), 698 (C-S-C), 611 (C-Br), 1226 (OCH_3). ^{1}H-NMR ($CDCl_3$) □δ in ppm: 8.83 (brs, 1H, NH), 8.48 (brs, 1H, NH), 7.93-6.93 (m, 10H, Ar-H), 7.72 (t, 1H, CH-Ar), 3.48 (s, 3H, OCH_3), 3.38 (d, 2H, CH_2 of isoxazole ring), 2.23 (d, 2H, CH_2NH),. MS: $[M]^+$ at m/z 701.36. Anal. calcd. for $C_{27}H_{20}FN_7Br_2O_3S$: C, 46.24; H, 2.87; N, 13.98: Found : C, 46.20; H, 2.85; N, 13.96%

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3-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyindol-3-yl)-4,5-dihydroisoxazol-2-yl-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6g)** Yield 77% (Acetone); m.p. 246 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3355, 3345 (NH), 1700, 1683 (C=O), 1620 (C⋯C of aromatic ring), 1616 (C=N), 1291 (N-N), 1228 (C-O-N), 693 (C-S-C), 1225 (OCH_3). ^{1}H-NMR ($CDCl_3$+DMSOd6) δ in ppm: 9.41 (brs, 1H, NH of indole exchangeable), 8.84 (brs, 1H, NH), 8.46 (brs, 1H, NH), 7.90-6.75 (m, 12H, Ar-H), 7.75 (t, 1H, CH-Ar), 3.38 (s, 3H, OCH_3), 3.38 (d, 2H, CH_2 of isoxazole ring), 2.11 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 582.61. Anal. calcd. for $C_{29}H_{23}FN_8O_3S$: C, 59.78; H, 3.98; N, 19.23: Found : C, 59.80; H, 3.99; N, 19.30

6-Bromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyindol-3-yl)-4,5-dihydro isoxazol-2-yl-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6h)** Yield 75% (Ethanol); m.p. 252 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3352, 3338 (NH), 1693, 1682 (C=O), 1621 (C⋯C of aromatic ring), 1618 (C=N), 1293 (N-N), 1232 (C-O-N), 695 (C-S-C), 612 (C-Br), 1225 (OCH_3). ^{1}H-NMR ($CDCl_3$) δ in ppm: 9.45 (brs, 1H, NH of indole exchangeable), 8.87 (brs, 1H, NH), 8.45 (brs, 1H, NH), 7.85-6.89 (m, 11H, Ar-H), 7.75 (t, 1H, CH-Ar), 3.30 (d, 2H, CH_2 of isoxazole ring), 3.40 (s, 3H, OCH_3), 2.13 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 661.50. Anal. calcd. for $C_{29}H_{22}FN_8BrO_3S$: C, 52.65; H, 3.35; N, 16.94: Found : C, 52.69; H, 3.34; N, 16.93%

6,8-Dibromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(4-methoxyindol-3-yl)-4,5-dihydroisoxazol-2-yl-yl)hydrazinyl)methyl)quinazolin-4(3H)-one **(6i)** Yield 72% (Methanol); m.p.270 ^{0}C. IR (KBr, ν_{max} in cm^{-1}): 3356, 3343 (NH), 1695, 1682 (C=O), 1624 (C⋯C of aromatic ring), 1598 (C=N), 1292 (N-N), 696 (C-S-C), 612 (C-Br), 1224 (OCH_3). ^{1}H-NMR ($CDCl_3$) δ in ppm: 9.43 (brs, 1H, NH of indole exchangeable), 8.83 (brs, 1H, NH), 8.49 (brs, 1H, NH), 7.98-6.92 (m, 10H, Ar-H), 7.70 (t, 1H, CH-Ar), 3.45 (s, 3H, OCH_3), 3.27 (d, 2H, CH_2 of isoxazole ring), 2.10 (d, 2H, CH_2NH). MS: $[M]^+$ at m/z 740.40. Anal. calcd. for $C_{29}H_{21}FN_8Br_2O_3S$: C, 44.40; H, 3.59; N, 19.18: Found : C, 44.44; H, 3.60; N, 19.14%

RESULTS AND DISCUSSION

Compounds **5a-5i** and **6a-6i** were screened for their antipsychotic and anticonvulsant activities at a dose of 40 mg/kg i.p. and pharmacological data of these compounds have been reported in Table 1.

Antipsychotic activity

Amphetamine induced stereotyped behaviour

It was observed that compounds **5a-5i** (having different chalconyl moieties at 2nd position of quinazolinone ring) exhibited significant results. The compounds **5c, 5f, 5h** and **5i** showed good response (0.4-0.6 score) against amphetamine induced stereotyped behaviour. In the next step, i.e. compounds **6a-6i** (having isoxazole moiety at 2nd position of quinazolinone ring) showed different results (0.0-0.8). Among the compounds **6a-6i**, compounds **6b, 6d, 6f** and **6h** exhibited potent response (i.e. 0.2 score). Moreover, compounds **6c** and **6i** (having pyridine and 4-methoxyindole moieties respectively at 6, 8-dibromoquinazolinone ring) showed most potent results, because these compounds completely antagonized the amphetamine induced stereotyped behaviour.

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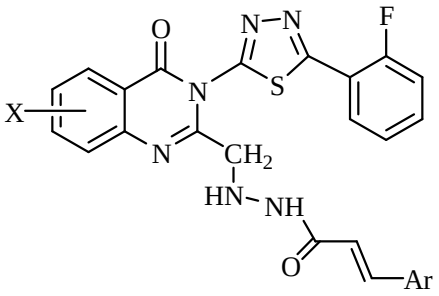
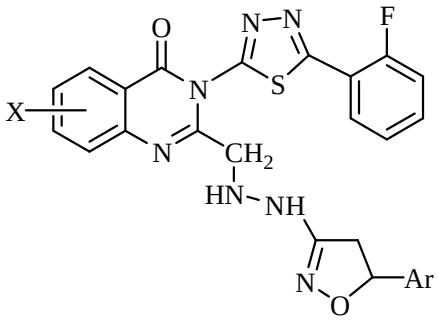
Table 1

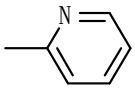
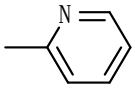
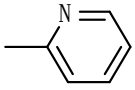
Antipsychotic and anticonvulsant activities of compounds synthesized **5a-5i** and **6a-6i**.



(5a-5i)



(6a-6i)

Com. No	X	Ar	Dose mg/kg i.p.	Amphetamine induced SB (Mean Score) [c]	Catalepsy Scored [d]	MES % seizures Protection	ALD_{50} [f]
P.G. [a]	-	-	0.5 ml	3.8	0	0	
CPZ [a]	-	-	4.0	0.0	0.0	-	
HPL [b]	-	-	0.5 ml	0	1.8	0	
P.S. [b]	-	-	30	-	-	80	
5a	H		40	1.2 ± 0.12*	1.8 ± 0.38	50*	>1000
5b	6-Br		40	0.8 ± 0.23*	1.2± 0.28*	60**	>1000
5c	6,8-Br		40	0.4 ± 0.14**	1.0 ± 0.18*	70***	>1000

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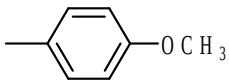
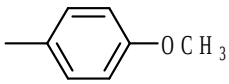
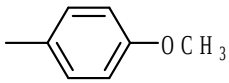
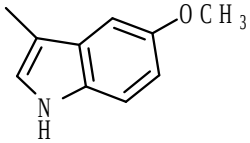
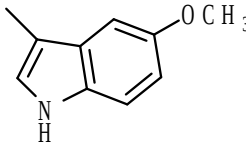
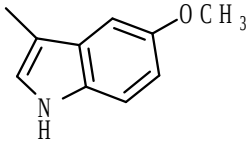
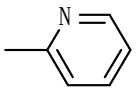
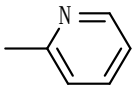
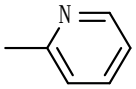
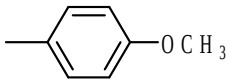
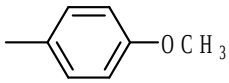
5d	H		40	1.0 ± 0.30*	2.0 ± 0.26*	30	>1000
5e	6-Br		40	1.0 ± 0.35*	2.0 ± 0.25	40	>1000
5f.	6,8-Br		40	0.6 ± 0.24**	1.8 ± 0.19	50*	>1000
5g	H		40	0.8 ±0.20*	1.2 ± 0.30*	40	>1000
5h	6-Br		40	0.6 ± 0.20**	1.8 ± 0.34	50*	>1000
5i	6,8-Br		40	0.4 ± 0.15**	1.4 ± 0.30	60**	>1000
6a	H		40	0.4 ± 0.27**	1.0 ± 0.27*	60**	>1000
6b	6-Br		40	0.2± 0.10**	0.2 ± 0.18**	70***	>1000
6c	6,8-Br		40	0.0± 0.0***	0.0 ± 0.0***	90***	>1600
6d	H		40	0.2 ± 0.17**	0.8 ± 0.22*	50*	>1000
6e	6-Br		40	0.8 ± 0.13*	0.6 ± 0.23**	60**	>1000

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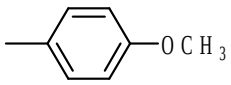
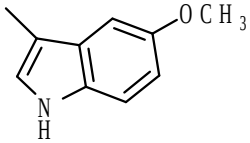
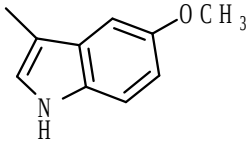
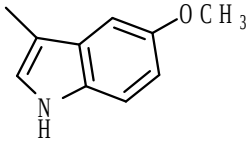
6f	6,8-Br		40	0.2 ± 0.15**	0.4 ± 0.28**	50*	>1000
6g	H		40	0.6 ± 0.30**	0.6 ± 0.20**	60**	>1000
6h	6-Br		40	0.2 ± 0.32**	0.4 ± 0.30**	70***	>1000
6i	6,8-Br		40	0.0 ± 0.0***	0.2 ± 0.10**	80***	>1000

**P < .05, **P < .01, ***P < .001*

[a] *P.G. = Propylene glycol, CPZ = Chlorpromazine,* [b] *HPL = Haloperidol , P.S. = Phenytoin sodium.*

[c] *Protection against amphetamine (4mg/kg) induced stereotyped bahaviour (SB).*

[d] *Score of cataleptic behaviour with reference to propylene glycol treated group of rats; Haloperidol (0.5 ml i.p.)induced group 1.8 with reference to control group.*

[e] *Percentage protection against convulsions in Maximal Electroshock Seizure test.*

[f] *ALD_{50} of the compounds **5a-5i** and **6a-6i.***

Cataleptic behaviour

In compounds **5a-5i**, compounds **5a, 5d, 5e, 5f** and **5h** showed moderate response against cataleptic behaviour, while compounds **5b, 5c 5g** and **5i** exhibited significant results (as shown in table 1). Further in next step, i.e. compounds **6a-6i** showed potent (0.0-1.0 score) response against cataleptic behaviour. Moreover, compound **6c** did not produce any cataleptic behaviour which prove that this compound have shown maximum response against cataleptic behaviour.

Anticonvulsant activity

Among the compounds **5a-5i** compounds **5a, 5b, 5f, 5h** and **5i** exhibited good anticonvulsant activity varying from 50% to 60%. Among the Compounds **5a-5i** compound **5c** (pyridine moiety at 6, 8-dibromo quinazolinone ring) was the most potent compound of this step. This compound showed 70% seizure protection in MES test. In the next step, compounds **6a-6i** showed varying degree (50-90%) of anticonvulsant activity. The compounds **6a, 6b, 6e, 6g** and **6h** exhibited interesting anticonvulsant response (i.e. 60-70%). However, compound **6c** namely 6,8-dibromo-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl)hydrazinyl) methyl)quinazolin-4(3H)-one have shown maximum anticonvulsant activity (90%) which was more potent than reference drug phenytoin sodium (30 mg/kg i.p.). Furthermore, compound **6i**

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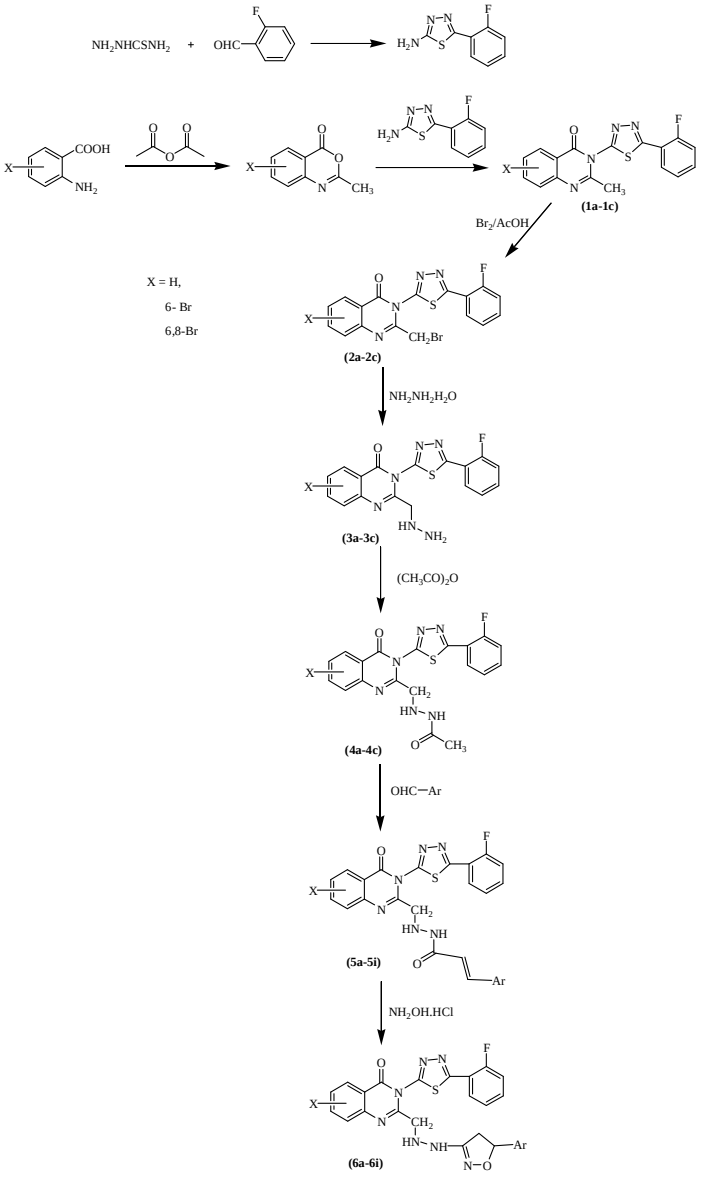
showed 80% anticonvulsant activity equipotent to the reference drug phenytoin sodium.

The newly synthesized compounds were also tested for approximate lethal dose ALD_{50} and were found to exhibit a higher value of ALD_{50} i.e. more than 1000 mg/kg i.p. except compound **6c** which exhibited ALD_{50} of more than 1600 mg/kg i.p. (maximum dose tested). As these compounds have shown high value of ALD_{50} thus indicating good safety margin.



Scheme 1: Synthetic route of quinazolinone derivatives

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CONCLUSION

While considering all the newly synthesized compounds of this series we may concluded that:

1. Compounds having 6, 8-dibromoquinazolinone moiety show the better antipsychotic and anticonvulsant activities than the compounds having unsubstituted or monosubstituted quinazolinone moiety.
2. Substitution by pyridine and 5-methoxyindole moiety at 2nd position of substitutedquinazolinone ring in general beneficial for biological activities.

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