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Research Article

Design, Synthesis and Evaluation of CNS Depressant Activity of 2-(Substituted Aryl)- Piperazine -3-Phenyl -4(*3H*)-Quinazolinone

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ABSTRACT

Anxiety is characterized by excessive fear that persists and interferes with a person's daily activities. In this study, a new class of 16 derivatives of 2-(Substituted Aryl)-piperazine-3-phenyl-4(3H)-quinazolinones were synthesized, and all of the derivatives were tested for their ability to reduce anxiety using the hole-board test and the elevated plus maize test, administered intraperitoneally to mice at doses of 10 mg/kg body weight. Test compounds 3-phenyl-2-(4-(3-methylphenyl) piperazin-1-yl)quinazolin-4(3H)-one (SD-05), 2-(4-(2-fluorophenyl) piperazin-1-yl)-3-phenylquinazolin-4(3H)-one (SD-06), 3-phenyl-2-(4-(4-methoxyphenyl) piperazin-1-yl)-quinazolin-4(3H)-one (SD-10) showed an increased number of head pocking (56 ± 3.5 to 70 ± 1) as compare to control group number of head pocking (27 ± 3) and increased duration of pocking (50 ± 12 ns) as compare to control group duration of pocking (25 ± 2) in hole board test and increased time spent in open arm (35.5 ± 1.5) and a number of entries in open arm (12.5 ± 0.50) as compare to control group. Test compounds SD-05, SD-06, SD-10 showed significant antianxiety activity.

Introduction

Anxiety is an unpleasant emotional condition that includes jittery behavior, somatic anxiety, and despises its consequences. Anxiety can cause actual or imagined fear. Anxiety is a disorder in which the patient is restless all the time from fear.[1] With changes in people's social-economic conditions and cultural aspirations, the prevalence of anxiety-like disorders is increasing day by day in the modern era. Antianxiety medications are available to treat such conditions, but the majorities of available treatments are highly non-specific in nature and have debilitating side effects. Therefore, there is a dire need to develop newer and safer anxiolytic agents.[2,3]

Quinazolinone has been found to have good GABA binding potential; hence, an attempt was made to target the GABA receptor by synthesizing new quinazolinone derivatives as antianxiety agents.

Naturally, quinazolinone alkaloids form the basic core of febrifugine and isofebrifugine, which were found to have immense antimalarial activity and are extracted from traditional Chinese medicine. Chemically, quinazolin constitutes an important class of fused heterocycles with six members (benzene and pyrimidine rings). Two conjoined aromatic rings react with two nitrogen atoms, and one of the carbons is oxidised with keto oxygen.The structure is also known as quinazolindiones, and it is chemically known as quinazolin-4(3*H*)-one.[4]

Materials and Methods

The purity of the compounds and the progress of the reaction were monitored using thin layer chromatography on silica gel coated glass plates using solvent system A [Benzene: ethyl acetate (4:1)], with the spots being

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located under iodine vapours and UV light. Melting points were determined using the open tube capillary method. The FTIR spectra were captured using an infrared spectrophotometer, the Shimadzu Affinity-1. Using TMS as the internal standard, NMR spectra were captured using a Bruker Advance II 400 spectrometer.

Synthetic Procedure

Synthesis of 1-(4-substituted phenyl)piperazine hydrochloride (A)

An equimolar mixture of the p-chloroaniline and bis (β-chloroethyl)amine hydrochloride in 1-butanol was refluxed for24 hours, the reaction mixture was cooled and powdered anhydrous K_2CO_3 was added and refluxing continues for another 48 hours.

The progress of reaction was checked with help of TLC solvent system A After completion of the reaction mixture was filtered while hot, the filtrate was cooled, and the 1-(4-chlorophenyl) piperazine hydrochloride which separated were filtered and washed successively with 1–butanol and ether (Fig. 1).

Synthesis of 3-phenyl 2, 4(3H) Quinazolindione (B)

An equimolar mixture of isatoic anhydride and substituted aniline were taken in a 500 mL round bottom flask refluxed for about 12 hours in ethyl alcohol in presence of few drops of acetic acid. The progress of the reaction was monitored by TLC using solvent system A. The content was then poured into crushed ice and solid obtained was collected, re-crystallized from ethanol, water.

Synthesis of 3-phenyl-2-choro-4(3H) Quinazolinone (C)

An equimolar mixture of 3-phenyl 2, 4(3H) quinazolindione phosphorus pentachloride and phosphorus oxychloride were taken in 500 mL round bottom flask in refluxed for 14 hours. The progress of the reaction was monitored by TLC using solvent system A. The contents were then poured into crushed ice and solid obtained was collected. re-crystallized from ethanol.

Synthesis of 2-(Substituted aryl)Piperazine -3-Phenyl-4(3H)-Quinazolinone (D)

An equimolar concentration of 2-chloro-3-phenyl-4-*(3H)*-quinazolinone and substituted aryl piperazine and sodium carbonate in DMF were taken in 100 mL round bottom flask and refluxed for 30 hours. The progress of the reaction was monitored by TLC using solvent system A. The contents were then poured into crushed ice and solid obtained was collected. Re-crystallized from ethanol (Fig. 2).

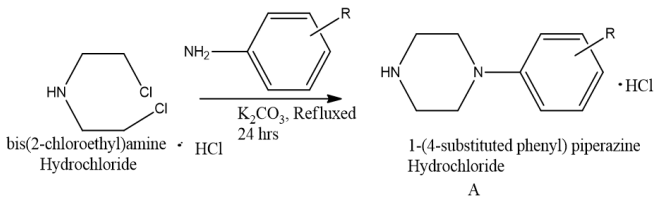

Fig. 1: Synthesis of 1-(4-substituted phenyl)piperazine hydrochloride

Pharmacological Screening

All of the processes and protocols used in the animal experiments were reviewed and approved by the Institutional Animal Ethical Committee (IAEC), which was established under the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environments and Forests, Government of India (IAEC/2013/06).

Acute Toxicity Studies of Synthesized Compounds

OECD recommendations (no. 425) were followed when determining the median lethal dose (LD_{50}) for acute toxicity tests in mice. Each animal was carefully monitored for toxicity symptoms and mortality in the first 30 minutes following dosage, as well as periodically for a further 4 hours, and then every day after that for a period of 14 days. It was recorded how many mice died over a 48 hour period.

Determination of LD_{50} (Acute Toxicity Study)

LD_{50} was calculated by using the software AOT425 StatPgm as 1000 mg/kg. The exact doses used to assess the activity of the synthesized compounds were dose I, which was 10 mg/kg (about $1/10^{th}$ of the LD_{50}).

Hole-Board Test

Placing a mouse is on the hole board apparatus, elevated to 25 cm from table, induces anxiety as it is exposed to a new environment. The anxiogenic agents reduce the number of nose pocking, where as the anxiolytic agents increase the number of head pocking.

Animals were divided into group 1 - Vehicle treated group, group 2 - Diazepam (1-mg/kg, i.p), group 3 - Test compound 10 mg/kg (I.P).

Test compounds 3-phenyl-2-(4-(3-methylphenyl) piperazin-1-yl)quinazolin-4(3H)-one (SD-05), 2-(4-(2-fluorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3H)-one (SD-06), 3-phenyl-2-(4-(4-methoxyphenyl) piperazin-1-yl)- quinazolin-4(3H)-one (SD-10) showed significant antianxiety.

Elevated Plus Maze Test

An animal's exploratory behavior changes when it is placed in an unfamiliar situation or environment because of anxiety. A mouse likes to stay in the enclosed arm when placed on the elevated plus maze. The amount of time the animal spends in the enclosed arm increases, as do the frequency of entries into the open arm. If a medication has anxiolytic effects, the mouse will spend longer in the open arm and more entrances into the open arm overall.

Animals were divided into the following groups and given treatment group 1**:** vehicle-treated group group 2**:**

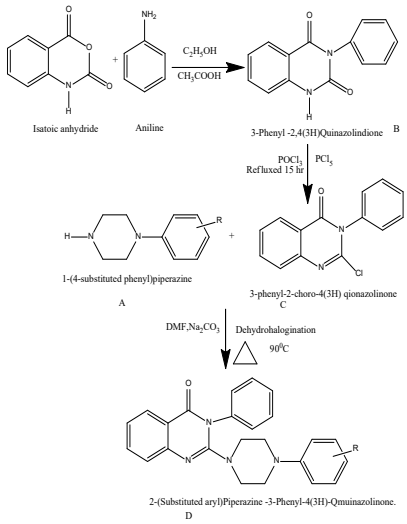

Fig. 2: Synthesis of 2-(Substituted aryl)Piperazine -3-Phenyl-4(3H)-Quinazolinone

diazepam (1-mg/kg, ip) group 3: Test compound 10 mg/kg (i.p). Group 1= Vehicle treated, Group 2=[standard, (Diazepam) 1-mg/kg ,i.p], group 3= group 3- Test compound 10 mg/kg (I.P).Test compounds SD-01 to Test SD-16[(synthesized compounds) 10 mg/kg i.p]

Results and Discussion

(SD 01) 3-phenyl-2-(4-(p-tolyl)piperazin-1-yl)quinazolin-4(3*H*)-one:Yellow white in 82% 4.28 g, IR (cm^{-1}): 1731 (C=O), 3304 (N-H), 2921 (C-H);^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 7.91-7.45 (d,13 H, Aromatic),2.92-2.92 (s,4H,, N-CH_2),3.21-3.21 (t,4H, N-CH_2).

(SD 02) 2-(4-(3-fluorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one:White crystalline solid in 42% 5.32 g , IR (cm^{-1}): 1731(C=O),3344(N-H),2851(C-H),1018 (C-F);^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 7.83-7.53(q,13 H, Aromatic),2.82-2.26 (s,4H,N-CH_2), 3.3141-3.1212 (t,4H,N-CH_2).

(SD 03) 2-(4-(2-chlorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one:White crystalline solid in 65% 3.23 g, IR (cm^{-1}): 1731(C=O), 3344(N-H), 3060((Ar C-H),2851(C-H),754 (C-Cl); ^{1}H-NMR (400MHz, δ ppm,DMSO-d_6): 7.92-7.45 (d,13 H, ArH),2.83-2.83 (s,4H,N-CH_2), 3.2541-3.2322 (t,4H,N-CH_2).

(SD 04) 2-(4-(3-chlorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: Yellow white crystalline solid in 60% 4.28 g, IR (cm^{-1}): 1731(C=O), 3348(N-H), 3082(Ar C-H), 2921(C-H), 754(C-Cl); ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 7.92-7.45 (d,13 H, ArH),2.81-2.83 (s,4H,N-CH_2),3.2541-3.2322 (t,4H ,N-CH_2).

(SD 05) 2-(4-(4-chlorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: Yellow white crystalline solid in 35% 3.28 g, IR (cm^{-1}): 1731(C=O), 3348(N-H), 3082(Ar C-H),2921(C-H),754(C-Cl); ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 7.92-7.45 (d,13 H, ArH),2.81-2.83 (s,4H,N-CH_2),3.2541-3.2322 (t,4H ,N-CH_2).

(SD 06) 3-phenyl-2-(4-phenylpiperazin-1-yl)quinazolin-4(3*H*)-one: white crystalline solid in 75% 3.28 g, IR (cm^{-1}): 1731 (C=O), 3348(N-H),), 3060(C-H Ar), 1018(C-F), 2921(C-H); ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 7.53-7.83 (d,13 H,ArH,), 2.82-2.26 (s,4H,N-CH_2), 3.31-3.12 (t,4H,N-CH_2).

(SD 07) 2-(4-(4-methoxyphenyl) piperazin-1-yl)-3-phenylquinazolin-4 (3*H*)-one: white crystalline solid in 70% 4.28g, IR (cm^{-1}): 1730(C=O), 3058 (N-H), 3060 (Ar C-H), 2921.96 (C-H) 1670 (C=C); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.91-7.45 (d,13 H, ArH), 2.92-2.92 (s,4H, N-CH_2), 3.21-3.21 (t,4H, N-CH_2).

(SD 08) 2-(4-(4-hydroxyphenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: white crystalline solid in 80% 5.25g, IR (cm^{-1}): 1730 (C=O), 3058 (N-H), 3060 (Ar C-H), 2921.96 (C-H) 1670 (C=C); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.91-7.45 (d,13 H, ArH), 2.92-2.92 (s,4H, N-CH_2), 3.21-3.21 (t,4H, N-CH_2).

(SD 09) 2-(4-(2-methoxyphenyl) piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: white crystalline solid in 80% 3.25g, IR (cm^{-1}): 1730(C=O), 3348 (N-H), 3082 (C-H Ar), 2921 (C-H); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.81-7.55 (q,13 H, ArH), 2.92-2.92 (s,4H, N-CH_2), 3.21-3.21 (t,4H, N-CH_2), 3.83-3.87 (t,3H,O-CH_3).

(SD 10) 2-(4-(4-methoxyphenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one:yellow white crystalline solid in 52% 4.25g, IR (cm^{-1}): 1731.96 (C=O), 3348 (N-H), 3082(C-H Ar), 2854 (C-H.; ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.81-7.55 (q,13 H, ArH), 2.92-2.92 (s,4H ,N-CH_2), 3.2141-3.2122 (t,4H ,N-CH_2), 3.834 - 3.8791 (t,3H,O-CH_3).

(SD 11) 3-phenyl-2-(4-(o-tolyl) piperazin-1-yl) quinazolin-4(3*H*)-one: yellow white crystalline solid in 50% 3.25g, IR (cm^{-1}): 1731 (C=O), 3344 (N-H), 3060 (C-H Ar); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.8143-7.551 (m,13 H, ArH), 2.8241-2.721 (s,4H, N-CH_2), 3.2141-3.2122 (t,4H, N-CH_2).

(SD 12) 2-(4-(2-hydroxyphenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: yellow white crystalline solid in 70% 3.25g, IR (cm^{-1}): 1731(C=O), 3344 (N-H), 3060 (C-H Ar); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.8143-7.551 (m,13 H, ArH), 2.8241-2.721 (s,4H, N-CH_2), 3.2141-3.2122 (t,4H, N-CH_2) .

(SD 13) 2-(4-(4-chlorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: yellow white crystalline solid in 75 % 4.25g, IR (cm^{-1}): 1731 (C=O), 3348 (N-H), 3082 (C-H Ar), 2921 (C-H); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.92-7.45 (d,13 H, ArH), 2.82-2.83 (s,4H, N-CH_2), 3.25 - 3.23 (t,4H, N-CH_2).

(SD 14) 2-(4-(2-hydroxyphenyl) piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: yellow white crystalline solid in 45% 3.25 g, IR (cm^{-1}): 1731 (C=O), 3344(N-H), 3060 (Ar CH), 2851 (CH), 1018 (C-F): ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.83-7.53 (q,13 H, ArH), 2.82-2.26 (s,4H, N-CH_2), 3.31-3.12 (t,4H, N-CH_2).

(SD 15) 2-(4-(3-methoxyphenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: yellow white crystalline solid in 65% 5.25g, IR (cm^{-1}): 1731(C=O),3344(N-H),

3060 (Ar CH), 2851 (CH), 1018 (C-F): ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.8143-7.551 (q,13 H, ArH), 2.9241-2.921 (s,4H, N-CH_2),3.2141-3.2122 (t,4H, N-CH_2), 3.834-3.8791 (t,3H,O-CH_3) .

(SD 16) 2-(4-(2-hydroxyphenyl)piperazin-1-yl)-3-phenylquinazolin-4(3*H*)-one: yellow white crystalline solid in 65% 5.25g, IR (cm-1): 1730 (C=O), 3058 (N-H), 3060 (Ar C-H), 2921.96 (C-H) 1670 (C=C); ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 7.91-7.45 (d,13 H, ArH), 2.92-2.92 (s,4H, N-CH_2), 3.21-3.21 (t,4H ,N-CH_2).

A synthesis of 16 derivatives of 2(Substituted Aryl) piperazine -3-phenyl -4(3*H*)-quinazolinone and expected to have antianxiety activity. The process for creating the novel molecule involved synthesis of synthesis of 1-(4-chlorophenyl) piperazine hydrochloride and Synthesis of 3-phenyl 2, 4(3*H*) quinazolindione then chlorination of 3-phenyl 2, 4(3*H*) quinazolindione using phosphorus oxychloride, and condensation of 3-phenyl 2, 4(3*H*) Quinazolindione and of 3-phenyl-2-choro-4(3H) quinazolinone by dehydrohalogenation to produce 2-(Substituted aryl) piperazine-3-phenyl-4(3H)-quinazolinone.

The synthesized compounds were confirmed on the basis of IR, ^{1}H-NMR . The pharmacological screening of the synthesized compounds showed antianxiety out of 16 compounds only 3-phenyl-2-(4-(3-methylphenyl)piperazin-1-yl)quinazolin-4(3H)-one, 2-(4-(2-fluorophenyl)piperazin-1-yl)-3-phenylquinazolin-4(3H)-one, 3-phenyl-2-(4-(4-methoxyphenyl)piperazin-1-yl)- quinazolin-4(3H)-one showed significant antianxiety activity.

Anxiety disorders are due to GABAergic, serotonergic involvement in the nerve fibres. Benzodiazepines have extensively used for the last 40 years to treat several forms of anxiety, but due to unwanted side effects, alternative treatment strategies with favorable side effect profiles. Compounds with quinazoline derivatives have very good neuropharmacological activity profile as cited in various literature. So the present study of discussion of antianxiety activity is based upon the results obtained by different experimental models. The antianxiety activity of the synthesized compounds was evaluated by elevated plus maze test and hole board apparatus in mice. Elevated plus maze test is used to evaluate mice's psychomotor performance and emotional aspects. In elevated plus maze test the tested compounds showed antianxiety activity (Table 1). All the compounds showed significant activity as compounds to control. In hole board test, the mice were tested for evaluating different parameters i.e the number of head dipping and number of line crossing. Test compounds 3-phenyl-2-(4-(3-methylphenyl)piperazin-1-yl)quinazolin-4(*3H*)-one (SD-05), 2-(4-(2-fluorophenyl) piperazin-1-yl)-3-phenylquinazolin-4(*3H*)-one (SD-06), 3-phenyl-2-(4-(4-methoxyphenyl)piperazin-1-yl)-quinazolin-4(*3H*)-one (SD-10) showed significant antianxiety activity (Table 2).

Group I= Vehicle treated, group II=[standard, (Diazepam) 1 mg/kg ,i.p], Group III Test compounds SD-01 to test SD-16[(synthesized compounds) 100 mg/kg p.o]. Values are expressed as mean ± S.E.M Group.

Table 1: Evaluation of anxiolytic activity of 2-(Substituted Aryl)- piperazine -3-phenyl -4(3H)-quinazolinone in albino mice by using elevated plus maize

Sr. No	*Treatments*	*Time spent (s)*		*No. of entries*
		Open arm	*Close arm*	*Open arm*
1	Control	32.8 ± 6.4	241.0 ± 4.1	8.4 ± 0.2
2	Stand. (Diazepam) 1-mg/kg ,i.p	121.8 ± 1.81*	160 ± 1.1*	14 ± 2^{ns}
3	SD 01 (100 mg/kg)	30 ± 0.0	128 ± 7.0*	1.5 ± 0.50*
4	SD 02 (100 mg/kg)	26 ±4	38 ± 2.5**	2 ± 0*
5	SD 03 (100 mg/kg)	65.4 ± 0.50^{ns}	40.5 ± 5.3**	13 ± 1 ^{ns}
6	SD 04 (100 mg/kg)	35 ± 1.5 ^{ns}	15 ± 2.5**	9.4 ± 2.5^{ns}
7	SD 05 (100 mg/kg)	38.5 ±0.0*	134.5 ± 23.5^{ns}	10 ± 0^{ns}
8	SD 06 (100 mg/kg)	30.5 ± 6*	148.5 ±15*	12 ±0*
9	SD 07 (100 mg/kg)	26 ± 2.5^{ns}	38 ± 2.5 **	1.5 ± 0.5^{ns}
10	SD 08 (100 mg/kg)	35 ± 1.5 ^{ns}	15 ± 2.5**	13 ± 1^{ns}
11	SD 09 (100 mg/kg)	10 ± 65 ^{ns}	70 ± 43^{ns}	2 ± 1^{ns}
12	SD 10 (100 mg/kg)	35.5 ± 1.5*	129.5 ± 0.5*	12.5 ± 0.50*
13	SD 11 (100 mg/kg)	43 ± 2.5^{ns}	45 ± 0*	1 ± 0*
14	SD 12 (100 mg/kg)	45 ± 15^{ns}	56 ± 6.5*	2 ± 0*
15	SD 13 (100 mg/kg)	43±2.5^{ns}	45±0*	1±0*
16	SD 14 (100 mg/kg)	43 ± 2.5^{ns}	10 ± 20 ^{ns}	2 ± 0*
17	SD 15 (100 mg/kg)	43 ±2.5^{ns}	65 ±5**	4 ± 0*
18	SD 16 (100 mg/kg)	45 ±15^{ns}	12 ±21^{ns}	2.5 ±0.50

Table 2: Evaluation of anxiolytic activity of 2-(Substituted Aryl)-piperazine -3-phenyl -4(*3H*)-quinazolinone in albino mice by using hole board

Sr. No	*Treatments*	*No. of pocking*	*Duration of pocking (s)*
1	Control	27 ± 3	25 ± 2
2	Std (Diazepam 1mg/kg)	73 ± 2.342**	70 ± 5*
3	SD 01 (10 mg/kg)	9 ± 1.5^{ns}	36 ± 8.5 ^{ns}
4	SD 02 (10 mg/kg)	3 ± 0.5 ^{ns}	11 ± 1.0*
5	SD 03 (10 mg/kg)	6 ± 2 ^{ns}	70 ± 2*
6	SD 04 (10 mg/kg)	9 ± 1 ^{ns}	75 ± 4 ^{ns}
7	SD 05 (10 mg/kg)	56 ± 3.5*	59 ± 6 ^{ns}
8	SD 06 (10 mg/kg)	45 ± 1*	26 ± 7.5^{ns}
9	SD 07 (10 mg/kg)	5 ± 1.0 ^{ns}	65 ± 2.0 ^{ns}
10	SD 08 (10 mg/kg)	6 ± 3.5^{ns}	50 ± 14 ^{ns}
11	SD 09 (10 mg/kg)	10 ± 1.2^{ns}	68 ± 38 ^{ns}
12	SD 10 (10 mg/kg)	70 ± 1.5 *	75 ± 11 ^{ns}
13	SD 11 (10 mg/kg)	5 ±3.6 ^{ns}	50 ± 12^{ns}
14	SD 12 (10 mg/kg)	4 ± 0 ^{ns}	23 ± 7 ^{ns}
15	SD 13 (10 mg/kg)	12 ± 1^{ns}	38 ± 13^{ns}
16	SD 14 (10 mg/kg)	10 ± 0.50 ^{ns}	18 ± 2.5 ^{ns}
17	SD 15 (10 mg/kg)	15 ± 1.0 ^{ns}	20 ± 10 ^{ns}
18	SD 16 (10 mg/kg)	9 ± 1.5 ^{ns}	36 ± 9 ^{ns}

Values are expressed as mean ± S.E.M

* p < 0.05, ** p < 0.01, *** p < 0.001, ns-Non-significant.Group I= Vehicle treated, Group II= Standard, (Diazepam) 1 mg/kg, i.p, Group III = Test SD 01 to Test SD 16 [(Synthesized compounds) 10 mg/kg i.p]. Group II compared to group I. Groups III to groups XVIII compared to Group I. (One-way ANOVA followed by Dunnett' s test).[5-9]

Conclusion

All the synthesized compounds were characterized by IR, Mass and ^{1}H-NMR spectroscopy. In this Experimental work, new class of 2–substituted-aryl-piperazine-3-phenyl-4(*3H*) quinazolinone derivatives were synthesized and evaluated for CNS depressant activity.

The compounds with test compounds 3-phenyl-2-(4-(3-methylphenyl)piperazin-1-yl)quinazolin-4(*3H*)-one (SD-05), 2-(4-(2-fluorophenyl) piperazin-1-yl)-3-phenylquinazolin-4(*3H*)-one (SD-06), 3-phenyl-2-(4-(4-methoxyphenyl) piperazin-1-yl)-quinazolin-4(*3H*)-one (SD-10) showed increased number of head pocking (56 ± 3.5 to 70 ±1) as compare to control group number of head pocking(27 ± 3) and increased duration of pocking (50 ± 12^{ns}) as compare to control group duration of pocking (25 ± 2) in hole board test and increased time spent in open arm (35.5 ± 1.5) and number of entries in open arm (12.5 ± 0.50) as compare to control group. Test compounds SD05, SD-06 and SD-10 .showed significant antianxiety activity.

References

1. Jagdale AS, Amrutkar S V. Substituted Quinazoline A Potential Drug Candidate: An Overview. World Journal of Pharmaceutical Research2017;6(15):281-295.doi.10.20959/wjpr201715-10086.
2. Kashaw SK, Kashaw, V, Mishra P, Jain NK. Design, synthesis and potential CNS activity of some novel 1-(4-substituted-phenyl)-3-(4-oxo-2-propyl-4H-quinazolin-3-yl)-urea. Archive for Organic Chemistry 2008; xiv: 17-26.
3. Ilangovan P, Ganguly S, Pandi P, Stables JP. Design and Synthesis of Novel Quinazolinone derivatives as Broad Spectrum Anticonvulsants. Der Pharmacia Lettre 2010; 2(1):13-21.
4. Koleva V, Yotova I, Dragoeva A , Enchev D. Synthesis, cytotoxicity, and promising anticancer potential of novel β-amino- and β-iminophosphonates. Journal of Applied Pharmaceutical Science 2021; 11(07): 080-088.doi. 10.7324/JAPS.2021.110708
5. Kadri A, Aoudai K. In vitro antimicrobial and α-glucosidase inhibitory potential of enantiopure cycloalkylglycine derivatives: Insights into their in silico pharmacokinetic, druglikeness, and medicinal chemistry properties. Journal of Applied Pharmaceutical Science 2012; 10(06):107-115.doi. 10.7324/JAPS.2020.10614
6. Zala SP, Badmanaban R, Sen DJ, Patel CN. Synthesis and biological evaluation of 2,4,5-triphenyl-1H-imidazole-1-yl Derivatives. Journal of Applied Pharmaceutical Science 2012; 02(07): 202- 208.doi. 10.7324/JAPS.2012.2732
7. Dutta A, Sarma D. Recent advances in the synthesis of Quinazoline analogues as Anti-TB agents. Tuberculosis 2020; 124.doi.org/10.1016/j.tube.2020.101986
8. Ram K, Agrawal P, Sinha M, Mahatao N. Recent Advances on Quinazoline Derivatives: A Potential Bioactive Scaffold in Medicinal Chemistry. Chemengineering 2021; 5(4):73.doi.org./10.3390/chemengineering5040073
9. Farshid H, Hojjat S, Elham J, Azadeh S, Nasim D. Synthesis and cytotoxic evaluation of some quinazolinone-5-(4-chlorophenyl) 1, 3, 4-oxadiazole conjugates". Research in Pharmaceutical Science2019;14(5):408–413. Doi.10.4103/1735-5362.268201

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