Journal of Pharmaceutical Research International

33(44B): 147-154, 2021; Article no.JPRI.74190
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Synthesis and Evaluation of Anticonvulsant Activity of Some Quinazoline Analogues

Surajmal G. Malpani[1*], Pradeepkumar Mohanty[1] and Janki Prasad Rai[1]

[1]School of Pharmacy, LNCT University, Bhopal-462042, Madhya Pradesh, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i44B32659
Editor(s):
(1) Dr. S. Prabhu, Sri Venkateswara College of Engineering, India.
(2) Dr. Ana Cláudia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.
Reviewers:
(1) Soroush Soltani, Universiti Putra Malaysia, Malaysia.
(2) Yohanes Firmansyah, Tarumanagara University, Indonesia.
Complete Peer review History: https://www.sdiarticle4.com/review-history/74190

Original Research Article

Received 15 July 2021
Accepted 20 September 2021
Published 22 September 2021

ABSTRACT

Aim: A new series of Quinazoline 4(3H)-one derivative were prepared by reacting quinazoline 4(3H)-one hydrazide with substituted aromatic aldehydes. Quinazoline is used as a potent pharmacological agent with various biological activities such as antimicrobial, antiviral, antitumor, convulsion, anxiety, anti-inflammatory, and analgesic. In this background, we have synthesized a series of Quinazoline 4(3H)-one derivatives (**4a-4f**) and screened for their anticonvulsant activity.
Methods: In this work, Schiff bases were prepared by treating quinazoline 4(3H)-one hydrazide with aromatic aldehydes. Six compounds (**4a-4f**) were screened for anticonvulsant activity by Isoniazid (INH) and Pentylenetetrazole (PTZ) induced convulsions in mice.
Results: All the compounds were given satisfactory reaction yields that representing the efficiency of the employed synthetic route. In INH induced convulsion model, delayed the onset of convulsion significantly 4a, 4b, 4d, 4e, 4f when compared to an induction control group. Whereas delayed onset of convulsion was non-significant for 4c. In PTZ induced convulsion model, delayed the onset of convulsion significantly 4a, 4d, 4e, 4f when compared to induction control group. Whereas delayed onset of convulsion was non-significant for 4b and 4c.
Conclusion: This indicates the anticonvulsant activity to these derivatives which might be due to potentiating GABA activity in the CNS. This anticonvulsant activity was due to presence of electron-donating group like OH, NH2, OCH3 and electron-withdrawing group like CF3 at 2nd and 4th position of aromatic ring attached to hydrazide.

**Corresponding author: E-mail: shethaji@gmail.com;*

Keywords: Quinazoline; convulsion; Isoniazid; PTZ; GABA.

1. INTRODUCTION

Epilepsy is the most common neurological disorder that causes unprovoked, recurrent seizures and affects all ages of people. About 65 million people are suffering from epilepsy in worldwide. It arises somewhat more in males than in females. Epilepsy is a non-curable disorder, but the disorder can be managed with antiepileptic drugs that will be prescribed on severity of symptoms, health and how well ketogenic diet Brain surgery respond to therapy as well as various strategies like vagus nerve stimulator [1]. Antiepileptic agents are neither curative nor preventive and are active exclusively as a means of controlling the symptoms of epilepsy. They can directly acts on ion channels or indirectly impact on synthesis, metabolism, or function of neurotransmitters or receptors that control channel opening and closing. Antiepileptic drugs are exhibited their action by various mechanism such as gamma aminobutyric acid (GABA) enhancers, sodium channel blockers, glutamate blockers, calcium channel inhibitors. These drugs are effectively reducing the seizures, whereas their therapeutic efficacy is overcome by some unwanted side effects such as drowsiness, megaloblastic anemia, ataxia, gastrointestinal disturbance, etc. [2]. Despite the broad and growing array of antiepileptic drugs available for treatment, approximately 30% of epileptic patients have inadequate seizure control and a further 25% suffer from significant adverse effects. Thus there is an ongoing need to develop more antiepileptic drugs that are effective and endowed with improved safety profiles.

Nitrogen containing heterocycles are amongst the most advantaged molecular scaffolds of pharmaceuticals, in which quinazoline is significant landmark that is present in a total of 9 U.S. FDA approved pharmaceuticals [3]. Quinazoline derivatives are the most active organic compounds that have a varied biological activities. They are widely utilized in pharmacy and agrochemicals, such as, fluquinconazole fungicide which is used for the control of agriculture diseases [4]. Numerous articles have been reported about the biological activity of quinazoline derivatives, including their antibactericidal, and anti-tumor activities [5,6]. 4(3H)-quinazolinone has a skeleton consisting of two fused rings in which two nitrogen atoms are attached to a carbon and a carbonyl group linked to one of the nitrogen [7]. This skeleton is found in the structure of some natural products and a number of drugs that were used to treat certain diseases [8,9]; therefore, their synthesis was specially targeted by chemists and pharmacists [10]. Literature survey reveals that natural quinazolinones and their synthetic analogues possess a variety of pharmacological activities including central nervous system (CNS) related disorders such as convulsion, anxiety [11-15], anti-inflammatory, analgesic [16-19], antiviral [20], antitumor [21-23] and antimicrobial [24].

2. MATERIALS AND METHODS

2.1 Chemistry

All of the compounds were characterized by IR, 1H, and 13C NMR spectra recorded with Bruker WM- 300 in deuterated DMSO at 400 and 100 MHz, respectively using tetra methyl silane (TMS) as the internal standard. All chemical shifts are described on the δ scale. Thin- layer chromatography (TLC) was carried out using Merck silica gel 60 F-254 plates (layer thickness: 0.25 mm) and a UV lamp and all solvents were distilled before use.

2.2 Synthesis

A mixture of 2-propyl-4*H*-3, 1-benzoxazinone, and ammonium acetate is irradiated in a MW bath reactor at 100 W and 120°C for 2–5 min. The resulting crude is filtered off, washed with cold water and recrystallized from petrol ether to give compound **1**.

To a solution of quinazolinone, **1** in DMF K_2CO_3 was added. The reaction mixture is stirred at 60°C for 30 min, then KI is added and the formed mixture is stirred for another 15 min. Solution of respective alkylating agents in DMF is dropped slowly into the mixture. After 4 h at 60 °C, the mixture is allowed to cool down and then is poured into ice-cold water. The solid that formed is scrubbed with water, filtered and crystallized using the suitable solvent to give the respective compounds **2.**

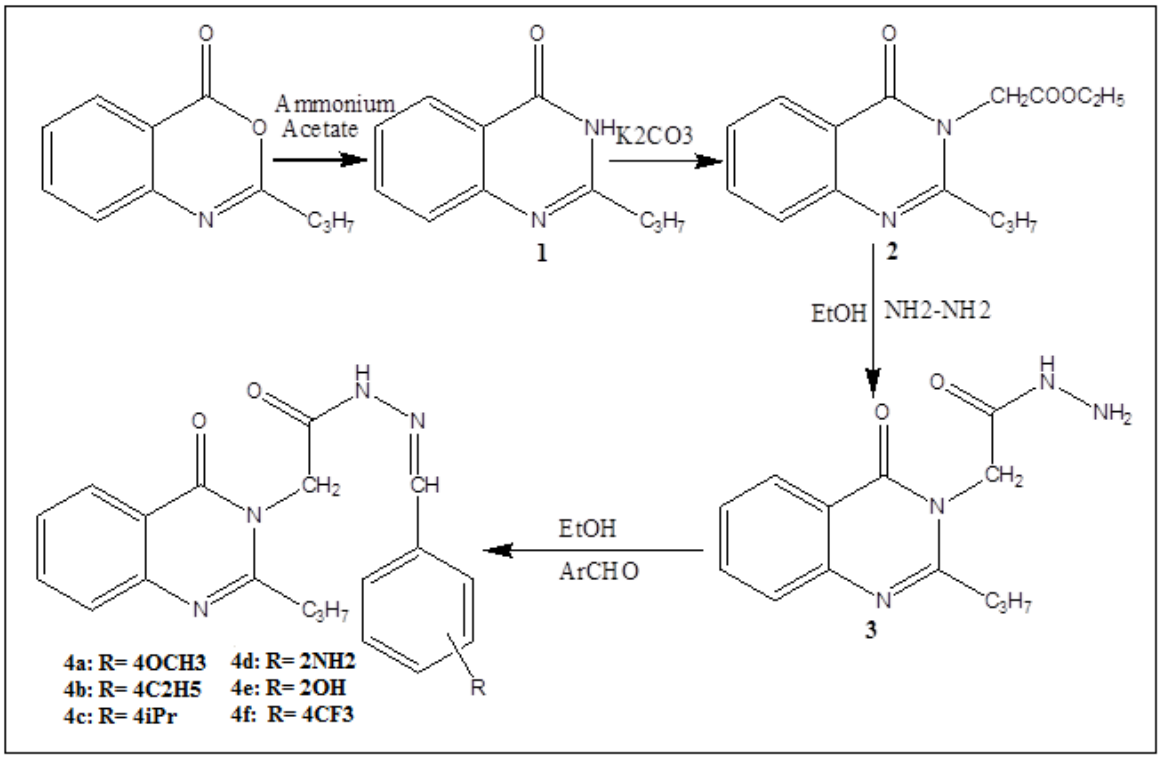


Fig. 1. Synthesis of Quinazoline 4(3H)-one derivatives

A suspension of the ester of 2 and hydrazine hydrate in absolute ethanol was refluxed for 3 h. The reaction mixture was concentrated and then cooled down to RT. The formed solid was filtered and recrystallized from EtOH to give acetohydrazide **3.**

An equimolar mixture of acetohydrazide **3** and aromatic aldehyde in 30 mL absolute EtOH was refluxed for 3 h. The reaction mixture was left overnight and the separated solid was filtered off and recrystallized from EtOH to give compound **4a-f**.

2.3 Anticonvulsant Activity

2.3.1 Isoniazid (INH) induced convulsions in mice

In the present study, 48 mice (18-30g) were divided into eight groups. Each group consisting of six (n=6) animals. Test compounds 4a, 4b, 4c, 4d, 4e and 4f 100 mg/kg i.p. were suspended in carboxy methyl cellulose (CMC). Diazepam 10 mg/kg i.p. used as a reference standard. After 60 minute of dose administration, isoniazid (200 mg/kg, i.p.) was administered to all mice to induce convulsions. Immediately after INH injection, each mice was kept in a separate cage and observed for the convulsions. Onset of convulsions and percentage protection (i.e. number of mice survived after 60 minutes of INH induced convulsion) were recorded in each group and compared against control group. All results statistically analysed by one way ANOVA followed by Turkey-Kramer multiple comparison test [25].

2.3.2 Pentylenetetrazole (PTZ) induced convulsions in mice

In PTZ induced convulsion model, 48 mice (18-30g) were divided into eight groups. Test compounds 4a, 4b, 4c, 4d, 4e and 4f 100 mg/kg i.p. were suspended in CMC solution. Diazepam 10 mg/kg i.p. used as a standard. After 60 minutes of dose administration, pentylenetetrazole (80 mg/kg) was administered to all mice to induce convulsions. Immediately after PTZ injection, each mice was kept in a separate cage and observed for convulsions. The onset of convulsions and percentage protection were recorded in each group and compared against a control group. All results were statistically analyzed by one way ANOVA followed by Turkey-Kramer multiple comparison test [26].

3. RESULTS AND DISCUSSION

3.1 Physicochemical Characterization of Quinazoline 4(3H)-One Derivatives

The table below shows the physicochemical characterization of the compounds estimated in this study (Table 1). All the compounds were given satisfactory reaction yields and properly separated from the reaction mixture, that representing the efficiency of the employed synthetic route.

The Characterization of synthesized derivatives were carried out by using Infrared spectroscopy (IR), Proton NMR (H1 NMR) and Carbon NMR (C13 NMR) for structure elucidation.

4a: IR (KBr, cm-1): IR (KBr, cm^{-1}): 1608 (C=N), 1680 (C=O), 3211 (NH), 2852 (OCH_3).

NMR 1H 400 MHz (DMSO-*d*6): 0.98 (t, 3H, CH3), 1.92 (h, 2H, CH2), 2.74 (t, 2H, CH2), 4.12 (s, 2H, CH2), 7.08 (d, 2H, Ar-H), 7.35 (t, 1H, Ar-H), 7.62-7.79 (m, 4H, Ar-H), 8.16 (d, 1H, Ar-H), 8.36 (s,1H, =CH), 12.65 (brs, 1H, NH), 3.68 (s,3H,OCH_3).

NMR 13C (100 MHz, DMSO*d6*): 36.8; 114.4, 122.4, 127.4, 128.8, 130.2, 133.5 (8; Ar-CH) 120.9, 126.1, 147.1, 163.0 (4; Ar-C), 143, 154.4 (2; Imine), 161.8,173 (2; amide), 14.9, 27.7, 48.9 (3; Aliphatic CH_2), 13.9, 55.9 (2; Aliphatic CH_3).

4b: IR (KBr, cm-1): 1612 (C=N), 1675 (C=O), 3218 (NH), 1205(C-C).

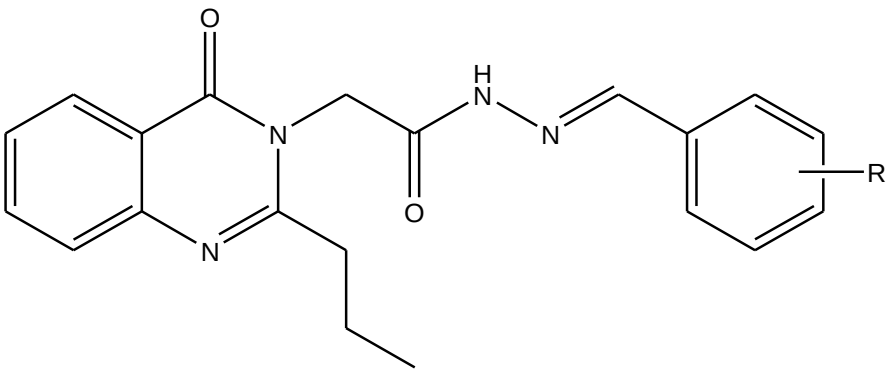
NMR 1H 400 MHz (DMSO-*d*6): 0.99 (t, 3H, CH3), 1.24 (t,3H, CH3),1.90 (h, 2H, CH2), 2.59(q, 2H, CH2), 2.75 (t, 2H, CH2), 4.16(s, 2H, CH2), 7.12 (d, 2H, Ar-H), 7.34 (t, 1H, Ar-H), 7.65-7.80 (m, 4H, Ar-H), 8.15 (d, 1H, Ar-H), 8.38 (s,1H, =CH), 12.67 (brs, 1H, NH).

NMR 13C (100 MHz, DMSO*d6*): 37.3; 122.4, 127.4, 127.9, 128.8, 129.1, 133.5 (8; Ar-CH) 120.9, 131.0, 141.8, 147.1, 163 (4; Ar-C), 143, 154.4 (2; Imine), 161.8,173 (2; amide), 14.9, 27.7, 32.4, 48.9 (4; Aliphatic CH_2), 13.9, 14.6 (2; Aliphatic CH_3).

4c IR (KBr, cm-1): 1609 (C=N), 1679(C=O), 3215 (NH), 1218(C-C).

NMR 1H 400 MHz (DMSO-*d*6): 0.98 (t, 3H, CH3), 1.24 (m,6H, 2CH3),1.91 (h, 2H, CH2), 2.57(q, 2H, CH2), 2.76 (t, 2H, CH2), 4.20(s, 2H, CH2), 7.25 (d, 2H, Ar-H), 7.39 (t, 1H, Ar-H), 7.66-7.89 (m, 4H, Ar-H), 8.09 (d, 1H, Ar-H), 8.40 (s,1H, =CH), 12.59 (brs, 1H, NH).

Table 1. Physicochemical characteristics of Quinazoline 4(3H)-one derivatives



Compound	R	Yield (%)	Rf *	Melting Point (^oC)
4a	4-OCH	64	0.60	178-180
4b	4-C_2H_5	61	0.58	244-245
4c	4-iPr	67	0.64	215-217
4d	2-NH_2	59	0.67	165-166
4e	2-OH	68	0.55	173-175
4f	4-CF_3	65	0.51	261-262

Rf Solvent system used for TLC was Chloroform: Methanol (40:60)*

NMR 13C (100 MHz, DMSO*d6*): 37.6, 122.4, 126.3, 127.4, 128.8, 128.9, 133.5 (8; Ar-CH) 120.9, 131.0, 147.1, 150.9 (4; Ar-C), 143.0, 154.4 (2; Imine), 161.8, 173.0 (2; amide), 14.9, 27.7, 48.9 (3; Aliphatic CH_2), 13.9, 23.4 (2; Aliphatic CH_3).

4d IR (KBr, cm-1): IR (KBr, cm^{-1}): 1607 (C=N), 1675 (C=O), 3216 (NH), 1340 (Ar-NH2).

NMR 1H 400 MHz (DMSO-*d*6): 0.98 (t, 3H, CH3), 1.90 (h, 2H, CH2), 2.73 (t, 2H, CH2), 4.15 (s, 2H, CH2), 7.10 (d, 2H, Ar-H), 7.34 (t, 1H, Ar-H), 7.62-7.86 (m, 4H, Ar-H), 8.15 (d, 1H, Ar-H), 8.34 (s,1H, =CH), 12.62 (brs, 1H, NH), 4.89 (s, 2H, NH2).

NMR 13C (100 MHz, DMSO*d6*): 36.9, 116.4, 118.9, 122.4, 127.4, 128.8, 130.0, 131.9, 133.5 (8; Ar-CH) 114.3, 120.9, 147.1, 150.1 (4; Ar-C), 143.0, 154.4 (2; Imine), 161.8, 173.0 (2; amide), 14.9, 27.7, 48.2 (3; Aliphatic CH_2), 13.9 (1; Aliphatic CH_3).

4e IR (KBr, cm^{-1}): 1605 (C=N), 1674 (C=O), 3218 (NH), 3364 (OH).

NMR 1H 400 MHz (DMSO-*d*6): 0.98 (t, 3H, CH3), 1.89 (h, 2H, CH2), 2.69 (t, 2H, CH2), 4.09 (s, 2H, CH2), 7.05 (d, 2H, Ar-H), 7.27 (t, 1H, Ar-H), 7.57-7.82 (m, 4H, Ar-H), 8.07 (d, 1H, Ar-H), 8.29 (s,1H, =CH), 12.54 (brs, 1H, NH), 13.05 (brs, 1H, OH).

NMR 13C (100 MHz, DMSO*d6*): 37.2, 116.0, 121.5, 122.4, 127.4, 128.8, 130.6, 132.5, 133.5 (8; Ar-CH) 118.5, 120.9, 147.1, 161.1 (4; Ar-C), 143.0, 154.4 (2; Imine), 161.8, 173.0 (2; amide), 14.9, 27.7, 48.2 (3; Aliphatic CH_2), 13.9 (1; Aliphatic CH_3).

4f IR (KBr, cm^{-1}): 1609 (C=N), 1668 (C=O), 3215 (NH), 1332 (CF3).

NMR 1H 400 MHz (DMSO-*d*6): 0.98 (t, 3H, CH3), 1.92 (h, 2H, CH2), 2.70 (t, 2H, CH2), 4.11 (s, 2H, CH2), 7.08 (d, 2H, Ar-H), 7.34 (t, 1H, Ar-H), 7.62-7.85 (m, 4H, Ar-H), 8.10 (d, 1H, Ar-H), 8.34 (s,1H, =CH), 12.52 (brs, 1H, NH).

NMR 13C (100 MHz, DMSO*d6*): 37.1, 122.4, 125.3, 127.4, 128.8, 129.5, 133.5 (8; Ar-CH) 120.9, 133.3, 137.1, 147.1 (4; Ar-C), 143.0, 154.4 (2; Imine), 161.8, 173.0 (2; amide), 14.9, 27.7, 48.2 (3; Aliphatic CH_2), 13.9 (1; Aliphatic CH_3).

3.2 Anticonvulsant Activity

3.2.1 Isoniazid (INH) induced convulsions in mice

In the Isoniazid induced convulsions, Isoniazid at 200 mg/kg, i.p., exhibited a mean onset of convulsions at 1203 seconds in induction control group animals. In test groups, one hour prior intraperitoneal administration of Quinazoline 4(3H)-one derivatives (i.e. 4a, 4b, 4c, 4d, 4e, 4f) at 100mg.kg to INH, delayed the onset of convulsion significantly ($p<0.05$) for 4a, 4b, ($p<0.01$) for 4f, ($P<0.001$) for 4d, 4e when compared to induction control group. Whereas delayed onset of convulsion was non-significant for 4c.

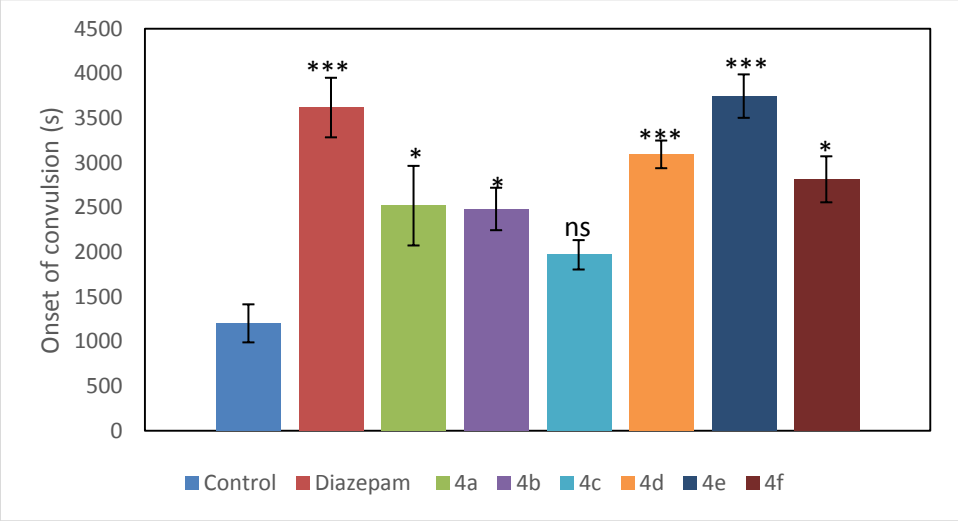


Fig. 2. Effect of Quinazoline 4(3H)-one derivatives in Isoniazide induced convulsions in mice
*Test drugs: significant from normal control, * P < 0.05; ** P < 0.001*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

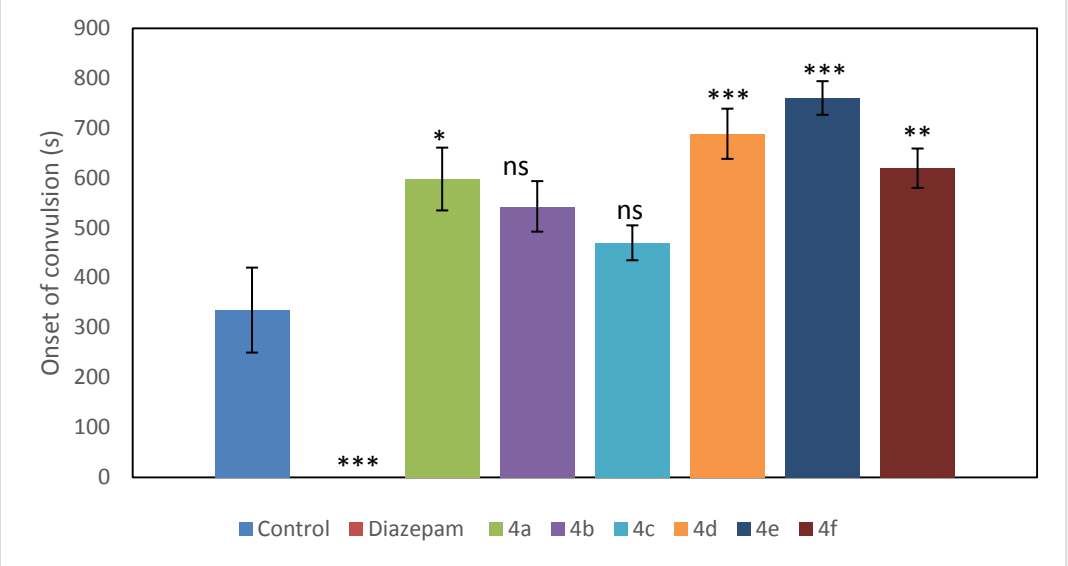


Fig. 3. Effect of Quinazoline 4(3H)-one derivatives in PTZ induced convulsions in mice
*Test drugs: significant from normal control, * P < 0.05; ** P < 0.001*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

3.2.2 Pentylenetetrazole (PTZ) induced convulsions in mice

The mean onset of convulsions in the Pentylenetetrazole (80 mg/kg i.p.) induction control group was observed at 335 seconds. In test groups, one hour prior intraperitoneal administration of Quinazoline 4(3H)-one derivatives (i.e. 4a, 4b, 4c, 4d, 4e, 4f) at 100mg.kg to PTZ delayed the onset of convulsion significantly ($p<0.05$) for 4a, ($P<0.001$) for 4d, 4e, 4f when compared to induction control group. Whereas delayed onset of convulsion was non-significant for 4b and 4c.

Quinazoline 4(3H)-one derivatives showed anticonvulsant effect in Isoniazid and PTZ induced convulsions in mice.

4. CONCLUSION

Convulsions being an important symptom of epilepsy precipitates either due to enhanced activity of excitatory neurotransmitters like Glutamate or depletion of inhibitory neurotransmitters like GABA in the CNS. Current pharmacotherapy for convulsions reported limited therapeutic outcomes and are associated with many deleterious side effects [27,28]. This indicates the need to develop new drugs for the treatment of convulsions with improved therapeutic outcome. Hence in the present study, preclinical trials for different derivatives of Quinozoline compounds were carried out for anticonvulsant activity in chemical (Isoniazid and PTZ) induced convulsions in mice.

INH was reported to inhibit GABA synthesis and glutamic acid decarboxylase by inhibiting pyridoxine phosphokinase and thereby depleting GABA concentration in the CNS [27,28,29] and precipitate the convulsions [30]. In present study derivatives 4a, 4b, 4c, 4d, 4e, 4f at 100 mg/kg,i.p, significantly delayed the mean onset of convulsion when compared to induction control group. This indicates the anticonvulsant activity to these derivatives which might be due to antagonizing the INH effect on GABA synthesis.

PTZ induced convulsions are a well-established animal model for absence seizure. PTZ is GABA antagonists that leads to CNS stimulation which produces convulsion in mice [30,31]. Quinazoline derivatives 4a, 4d, 4e, 4f prolonged mean onset of convulsions significantly when compared to induction control group. This indicates the anticonvulsant activity to these derivatives which might be due to potentiating GABA activity in the CNS. This anticonvulsant activity was due to presence of electron donating group like OH, NH2, OCH3 and electron withdrawing group like CF3 at 2^{nd} and 4^{th} position of aromatic ring attached to hydrazide.

On the basis of result, it can be concluded that Quinazoline 4(3H)-one derivatives exhibited anticonvulsant activity. All synthetic compounds of Quinazoline 4(3H)-one derivatives showed

prolonged the onset of convulsions and protecting maximum animals suggesting increase level of GABA by its potentiation or prevention of its depletion.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

The present study did not involve Patients.

ETHICAL APPROVAL

This project was approved by the Animal Ethics Committee from Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune (DYPCOP/IAEC/ 2020/04).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Al-Salem SA, Hegazy GH, El-Taher EH, El-Messery SM, Al-Obaid AM, El-Subbagh HI. Synthesis, Anticonvulsant Activity and Molecular Modeling Study of Some New Hydrazinecarbothioamide, Benzenesulfonohydrazide, and Phenacylacetohydrazide Analogues of 4(3*H*)-quinazolinone. Bioorg Med Chem Lett. 2015;25(7):1490-1499.
2. Boshta NM, El-Essawy FA, Ammar RM, Ismail AE Wahba NE. Synthesis of some new quinazolin-4(3H)-one derivatives and evaluation of their anticonvulsant activity. Monatsh Chem. 2016;1-12
3. Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem. 2014;57:10257-10274.
4. Xu GF, Song BA, Bhadury PS, Yang S, Zhang PQ, Jin LH et. al. Synthesis and antifungal activity of novel s-substituted 6-fluoro-4-alkyl (aryl) thioquinazoline derivatives. Bioorg. Med. Chem. 2007;15:3768–3774.
5. Van Horn KS, Burda WN, Fleeman R, Shaw LN, Manetsch R. Antibacterial Activity of a Series of N^2,N^4-Disubstituted Quinazoline-2,4-diamines. J. Med. Chem. 2014;57(7):3075–3093
6. Noolvi MN, Patel HM, Bhardwaj V, Chauhan A. Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: Search for anticancer agent. European Journal of Medicinal Chemistry. 2011;46(6):2327-2346.
7. Selvam TP, Kumar PV. Quinazoline Marketed drugs – A Review. Res. Pharm. 2011; 1: 1–21.
8. Rajput R, Mishra A P, A Review on Biological Activity of Quinazolinones. Int. J. Pharm. Pharm. Sci. 2012;4:66–70.
9. Mohammad A., Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. Int. J. Med. Chem. 2014;1–27.
10. Panneerselvam P, Rather BA, Reddy DRS and Kumar NR. Synthesis and anti-microbial screening of some Schiff bases of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones. European Journal of Medicinal Chemistry. 2009;44(5):2328–2333.
11. Alagarsamy V, Saravanan G. Synthesis and anticonvulsant activity of novel quinazolin-4(3H)-one derived pyrazole analogs. Medicinal Chemistry Research. 2013;22:1711–1722.
12. Amir M, Ali I, Hassan MZ. Design and synthesis of some new quinazolin-4-(3H)-ones as anticonvulsant and antidepressant agents. Archives of Pharmacal Research. 2013;36:61–68.
13. Ibrahim MK, El-Adl K, Al-Karmalawy AA. Design, synthesis, molecular docking and anticonvulsant evaluation of novel 6-iodo-2-phenyl-3-substituted-quinazolin-4(3H)-ones. Bulletin of Faculty of Pharmacy, Cairo University. 2015;53(2):101-116.
14. Dash B, Dash S, Laloo D. Design and synthesis of 4-substituted quinazoline derivatives for their anticonvulsant and CNS depressant activities. International Journal of Pharmacy and Pharmaceutical Sciences. 2017;9(1):165-172.

15. Kashaw SK, Kashaw V, Mishra P, Jain NK and Stables JP. Design, synthesis, and potential CNS activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2-methyl-4H-quinazolin-3-yl)-urea. Medicinal Chemistry Research. 2011;20:738–745.
16. Saravanan G, Alagarsamy V, Prakash CR. Synthesis, analgesic, anti-inflammatory, and in vitro antimicrobial activities of some novel quinazolin-4(3H)-one derivatives. Medicinal Chemistry Research. 2013;22:340–350.
17. Peddakonda R, Doddaga S, Rao DS, Kuntrapakam H, Donka R and Chamarthi NR. An efficient and economic synthesis of new quinazolin-4-(3H)-one derivatives and their anti-inflammatory activity. Scholars Research Library Der Pharmacia Lettre, 2012;4(5):1344-1351
18. Kumar S, Aghara JC, Alex AT, Aranjani JM, Joesph A. Novel Quinolone Substituted Quinazolin-4(3H)-Ones as Anti-Inflammatory, Anticancer Agents: Synthesis and Biological Screening. Indian Journal of Pharmaceutical Education and Research. 2018;52(4s [Suppl 2]):S268-S276.
19. Ghodge B, Kshirsagar A and Navghare V. Synthesis, characterization, and investigation of the anti-inflammatory effect of 2, 3-disubstituted quinazoline4 (1H)-one. Beni-Suef University Journal of Basic and Applied Sciences. 2020;9:30:1-12.
20. Krishnan SK, Ganguly S, Veerasamy R, Jan B, Synthesis, antiviral and cytotoxic investigation of 2-phenyl-3-substituted quinazolin-4(3H)-ones. European Review for Medical and Pharmacological Sciences. 2011;15:673-681.
21. Safavi M, Ashtari A, Khalili F. Novel quinazolin-4(3H)-one linked to 1,2,3-triazoles: Synthesis and anticancer activity. Chem Biol Drug Des. 2018;92(1):1373-1381.
22. Al-Suwaidan IA, Abdel-Aziz AM, Shawer TZ, Ayyad RR, Alanazi AM, El-Morsy AM. Synthesis, antitumor activity and molecular docking study of some novel 3-benzyl-4(3H) quinazolinone analogues. J Enzyme Inhib Med Chem. 2016;31(1):78–89
23. Jiajing S, Likai Z, Guanhai T, Shuai L, Shuxia W, Hua C, Xiaoliu L. Synthesis and Anti-tumor Activity of Novel Quinazolin-4-one Derivatives. Chin. J. Org. Chem. 2017;37(2):455-461.
24. Gatadi S, Lakshmi VT, Nanduri S. 4(3H)-Quinazolinone derivatives: Promising antibacterial drug leads. Eur J Med Chem. 2019;170:157-172.
25. Georgey H, Abdel-Gawad N, Abbas S. Synthesis and Anticonvulsant Activity of Some Quinazolin-4- (3H)-one Derivatives, Molecules. 2008;13:2557-2569.
26. Chimbalkar AD, Vyawahare NS. Evaluation of anticonvulsant activity of P*remnaherbacea* (roxb.) Root extracts in isoniazid and strychnine-induced convulsions. Asian J Pharm Clin Res. 2018;11(12):433-436.
27. Ramdhave AS, Badole SL, Bodhankar SL. Anticonvulsant activity of stem bark of *Pongamia pinnata*. Biomed Aging Pathol. 2011;1:147-157.
28. Carta M, Murru L, Barabino E, Talani G, Sanna E, Biggio G. Isoniazid‐induced reduction in GABAergic neurotransmission alters the function of the cerebellar cortical circuit. Neuroscience. 2008;154: 710-719.
29. L'Amoreaux WJ, Marsillo A, El Idrissi A. Pharmacological characterization of GABAA receptors in taurine‐fed mice. J Biomed Sci. 2010;17(Suppl 1):S14.
30. 30.Anwar F, Rajbala S, Harikesh M, Imran K,Muhammad A, Garima K, Gaurav G, Prashant K. Pharmacological role of *Alstonia scholaris* Leaves for its anticonvulsant and sedative action. American Journal of Phytomedicine and Clinical Theraupeticx. 2013;1:6478-6490.
31. Löscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. Seizure 2011;20: 359-368.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/74190