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Synthesis of some noval qunazolinone derivatives for their anticonvulsant activity

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ABSTRACT

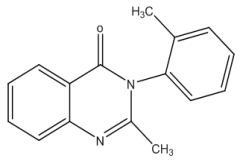
The quinoline family comprises an appealing group of heterocyclic compounds, with quinazolinones and their synthetic analogs being of particular interest. To synthesize 3- amino 2-phenyl quinazolinones, anthranilic acid and its substituted derivatives were employed as initial materials. The MES method was utilized to evaluate the anticonvulsant activity of the developed substances on albino mice, with phenytoin serving as a benchmark anticonvulsant medication.The synthesized compounds demonstrated noteworthy anticonvulsant activity, comparable to that of established prescription medications. Among these compounds, Compound A-1 exhibited the highest level of activity. This indicates the potential of these synthetic analogs as effective anticonvulsants, with Compound A-1 standing out as particularly promising in this regard. Preliminary results indicate that certain quinazolinone derivatives exhibited promising anticonvulsant effects in the MES test. Further investigation into the mechanism of action and safety profile of these compounds is underway. The structure-activity relationships deduced from this study may guide the design of future anticonvulsant agents based on the quinazolinone scaffold.This research contributes to the ongoing efforts to discover new therapeutic options for epilepsy and provides valuable insights into the potential of quinazolinone derivatives as anticonvulsant agents. The findings underscore the importance of exploring diverse chemical structures in the quest for improved treatments for neurological disorders.

Keywords: An anticonvulsant, Maximal Electroshock (MES), Quinazolinone and Synthesis.

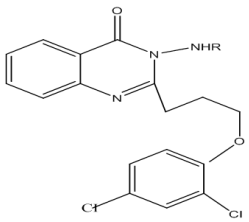
INTRODUCTION

Quinazolinone derivatives have emerged as a class of compounds with versatile biological activities, drawing considerable interest in medicinal chemistry. The broad spectrum of biological properties associated with quinazolinones, coupled with their structural diversity, has positioned them as promising candidates for drug development[1-3]. In particular, quinazolinone derivatives have exhibited a myriad of pharmacological effects, including anticancer[4], antimicrobial[5], antifungal[6], antiviral[7], antitumer[8], antimalarial[9], muscle relaxant[10], anti-inflammatory[11], anti-tubercular[12], and anticonvulsant[13] activities, among others. The focus of this study is the synthesis of novel quinazolinone derivatives designed

with the specific aim of evaluating their potential anticonvulsant activity. Epilepsy, a neurological disorder characterized by recurrent seizures, remains a significant global health concern. Despite advancements in treatment options, there is a continuous need for the discovery of new and more effective anticonvulsant agents[14-17]. This research contributes to the ongoing efforts in medicinal chemistry to explore diverse chemical structures for their therapeutic potential. By synthesizing and evaluating novel quinazolinone derivatives, we aim to expand the understanding of their anticonvulsant properties, paving the way for the development of new drugs to address the challenges associated with epilepsy. The investigation involves not only the synthesis of these compounds but also their comprehensive characterization and evaluation using established preclinical models, such as the Maximal Electroshock (MES) method. The outcomes of this research hold the promise of advancing our knowledge in the pursuit of innovative treatments for neurological disorders, with a particular focus on anticonvulsant interventions.



I



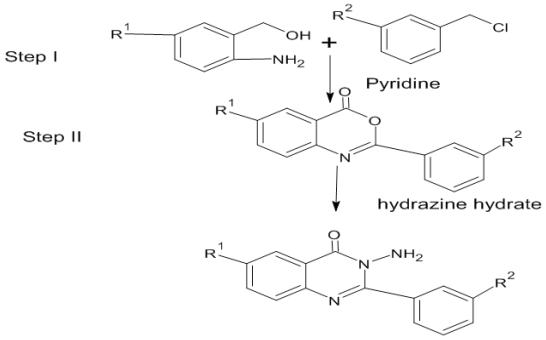
II

II a R=4 (2-Chlolophenyl)-piperazin-1- ylmethyl amno carbonyl

II b R= H

Method and Scheme

Quinazolines were studied using the synthetic method.[18]



Step-I Synthesis

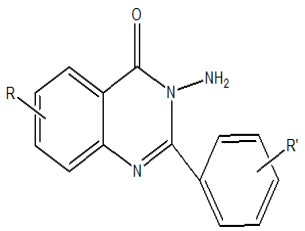
Anthranillic acid or substituted anthranillic acid (0.1M) was dissolved in 60 mL pyridine and then added benzoyl chloride (0.05M) drop wised and stirring the product half an hour and neutralize the product with $NaHCo_3$, recrystallized with ethanol. 'Tempo' melting point equipment was used to determine the melting point, and the results were uncorrected. There were also melting points.144^{0}C, 135^{0}C, 141^{0}C, 178^{0}C, 98^{0}C, 194-198^{0}C, 184-188^{0}C, 147^{0}C, 118^{0}C, 178^{0}C, 144^{0}C and 118^{0}C and Percentage yield were 78, 64.5, 56, 43, 45, 54, 40, 64.6, 68.4, 64.9, 43, 45, and 38 . IR of KBr (in cm^{-1}): 3076 (C-H, ArH Str), 1758 (C=O Str),1681Cycle C=0 Str, 1616 (C=N Str), 1512 (C=C Str), 1456, (C-N Starching) 839, ^{1}HNMR(ppm) $CDCl_3$, 4.531 (s, 3H, -SCH_3); 7.483-8.091 (m, 8H, Ar-H). 3.78 (Methoxy proton),1.7 (Methylene Proton). 4.07(3H, CH_3),11.32(s1H,NH).

Physical characteristics of synthesized compounds (I)

Step-II, Synthesis

A 0.05 Molar concentration of product (I) and hydrazine hydrate in ethanol was refluxed for three hours after that cooled. Ethanol was used to recrystallize the isolated solid (S). The melting points were. 148^{0}C, 145^{0}C, 179^{0}C, 158^{0}C, 179^{0}C, 144^{0}C, 148^{0}C, 140^{0}C, 148^{0}C, 143^{0}C,140^{0}C and 176^{0}C and yield were Compounds with 76%, 75%, 50, 56%, 54%, 50%, 65%, 71%, 64%, 44.9%, 43%, 44%, and 36% IIa-l, accordingly. "The values are IR (KBr in cm^{-1})" 3068 (C-H, ArHStr), 3305 (N-H Str), 1664 (cyclic C=0 Str), 1598 (C=N Str), 1514 (C=C Str), 1450 (C-N Str), and 839 (C-H deflaction). ^{1}HNMR (ppm) ($CDCl_3$), 4.530 (s, 3H, -SCH_3), 7.484-8.090 (m, 8H, Ar-H), 3.78 (Methoxy proton),1.7 (Methylene Proton).4.07(3H, CH_3) 11.32(s1H,NH).

The physical characteristics of synthesized final compounds



(b)

Table : 1

S. No	R Substituent	R' Quantity	Substituent	Quantity	CODE	Yield (%)	Color	m.p. (0C)	Rf
1	H	13.7g	H	7.03g	1a	78	Pale yellow	124	0.8
2	H	13.7g	Cl	8.70g	1b	62.5	Pale yellow	135	0.12
3	H	13.7g	NO_2	9.20g	1c	56	Pale yellow	141	0.51
4	H	13.7g	OCH_3	8.55g	1d	42	Ash grey	178	0.38
5	H	13.7g	F	7.92g	1e	54	Ash grey	98	0.53
6	H	13.7g	Br	12.3g	1f	40	Ash grey	194-198	0.42
7	Br	21.7g	H	7.03g	1g.	62.6	Yellow	184-188	0.54
8	Br	21.7g	Cl	8.70g	1h	68.4	Yellow	127	0.24
9	Br	21.7g	NO_2	9.20g	1i	62.9	Yellow	118	0.37
10	Br	21.7g	OCH_3	8.55g	1j	43	Yellow	178	0.46
11	Br	21.7g	F	7.92g	1k	45	Ash grey	122	0.43
12	Br	21.7g	Br	12.3g	1l	38	Ash grey	118	0.47

Table: 2

S. No	Code	Name of the compound	Quantity	Yield (%)	Color	m.p. (^{0}C)	Rf
1	2a	3-aminoTwo-phenyl quinazolin-4(3H)-one	2.38g	26	Grayish	147-150	0.59
2	2b	three Amino Two-(4-chlorophenyl) quinazolin-4(3H)-one	2.72g	70	Grayish	144-148	0.12
3	2c	three Amino Two-(4-nitrophenyl) quinazolin-4(3H)-one	2.83g	28	Yellow	178-182	0.2
4	2d	three Amino Two-(4-methoxy phenyl) quinazolin-4(3H)-one	2.68g	56	Grayish	156-164	0.37
5	2e	three Amino Two-(4-flurophenyl) quinazolin-4(3H)-one	2.55g	52	Grayish	177-180	0.44
6	2f	three Amino Two-(4-bromophenyl) quinazolin-4(3H)-one	3.17g	38	Grayish	182	0.36
7	2g	6- bromo, 3-aminoTwo-phenyl quinazolin-4(3H)-one	3.17g	65	Yellow	148	0.46
8	2h	6- bromo, three Amino Two-(4-chlorophenyl) quinazolin-4(3H)-one	3.82g	71	Grayish	120	0.32
9	2i	6- bromo, three Amino Two-(4-nitrophenyl) quinazolin-4(3H)-one	3.62g	64	Yellow	148	0.38
10	2j	6- bromo, three Amino Two-(4-methoxy phenyl) quinazolin-4(3H)-one	3.48g	42	Grayish	137-146	0.26
11	2k	6- bromo, three Amino Two-(4-flurophenyl) quinazolin-4(3H)-one	3.35g	39	Grayish	120	0.38
12	2l	6- bromo, three Amino Two-(4-bromophenyl) quinazolin-4(3H)-one	3.97g	36	Grayish	176	0.34

Anticonvulsant activity determination

Using the MES (maximal electroshock) method, we conducted assessments on the anti-convulsant activity of all synthesized compounds. Swiss albino mice, weighing between 20 and 35 g and sourced from Bhubaneshwar, were employed in the study. The animal facility maintained a 12:12 h light/dark cycle, a room temperature of 24°C, humidity levels between 45% and 55%, and adhered to stringent hygiene standards for water supply. Prior to experimentation, the Institutional Animal Ethical Committee (IAEC) of SOA University Bhubaneswar granted approval in accordance with the ethical guidelines outlined by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), registration number 1171/c/08/ (CPCSEA). Methodology involved the formation of three groups of male albino mice, each weighing 20–30 g, with six animals in each group. The groups received different treatments: a control group (3% saline), a standard medicine group (phenytoin 25 mg/kg), and a group administered with the synthesized substance. For the experimental technique, mice were subjected to a 0.2-second electrical stimulus via small alligator clips attached to the cornea. A rectangular plastic cage with an open top was used for housing mice during the test session, allowing the recording of various parameters and full visibility of the animal's motor reactions to seizures. During the 30-min testing period, parameters such as clonus convulsions, tonic flexion, tonic extension, stupor, and the percentage of protection were recorded. Mean SEM values were calculated from the results of six animals. Statistical analysis involved ANOVA and Dunnett's t-test to determine any significant differences between the groups, with a significance level set at $P<0.05$.19,20

Results are shown in (Table)

Anticonvulsant characteristics of a synthesized compound

Table: 3

Treatment	Dose	Mean SD of the tonic hind limb extension time in seconds	% Convulsion Inhibition	Recovery
Control (saline)	2. ml/kg	16.84 +/- 1.83	00.00%	YES
Standard (Phenytoin)	25 mg/kg	6.32 +/- 1.76*	63.5%	YES
A-1	50 mg/kg.	7.54 +/- 1.73*	55.5%	YES
A-2	50 mg/kg.	14.26+/- 1.72	16.7%	YES
A-3	50 mg/kg.	15.76 +/- 1.34	6.96%	YES
A-4	50 mg/kg.	10.26+/- 0.99*	38.7%	YES
A-5	50 mg/kg.	14.34+/- 0.98	15.9%	YES
A-6	50 mg/kg.	11.34+/- 1.50*	33.7%	YES
B-1	50 mg/kg.	14.7+/- 2.64	12.8%	YES
B-2	50 mg/kg.	11.26+/- 0.99*	33.6%	YES
B-3	50 mg/kg.	16.26+/- 1.74	9.9%	YES
B-4	50 mg/kg.	16.43+/- 1.52	2.9%	YES
B-5	50 mg/kg.	11.2+/- 0.99*	33.6	YES
B-6	50 mg/kg.	12.53 +/- 0.33*	25.6%	YES

RESULT AND DISCUSSION

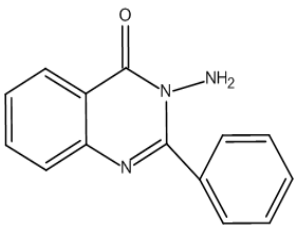
The synthesis of novel quinazolinone derivatives was achieved through a systematic multi-step process, involving the condensation of appropriate precursors. The structures of the synthesized compounds were confirmed through comprehensive spectroscopic characterization, including NMR and mass spectrometry. The successful synthesis of these compounds provided a solid foundation for further investigation into their pharmacological activities. The anticonvulsant potential of the synthesized quinazolinone derivatives was assessed using the Maximal Electroshock (MES) method, a standard preclinical model for screening antiepileptic drugs. Rodent models subjected to maximal electroshock-induced seizures were administered with various doses of the synthesized compounds, and their effects on seizure activity were meticulously observed.[21-24]

A glance at the table, which lists the anti-seizure activity and associated structures, reveals that almost all of the drugs are active. “The values are IR (KBr in cm^{-1})" 3068 (C-H, ArHStr), 3305 (N-H Str), 1664 (cyclic C=0 Str), 1598 (C=N Str), 1514 (C=C Str), 1450 (C-N Str), and 839 (C-H deflaction). ^{1}HNMR (ppm) ($CDCl_3$), 4.530 (s, 3H, -SCH_3), 7.484-8.090 (m, 8H, Ar-H) 3.78 (Methoxy proton),1.7 (Methylene Proton).4.07 (3H, CH_3) 11.32(s1H,NH), The analytical calculation of Compounds A-1(Carbon 66.46%), (Hydrogen 5.99%), (Nitrogen 15.05%), A-3(Carbon 67.57%), (Hydrogen 7.88%), (Nitrogen 10.37%), B -4(Carbon 63.88 %), (Hydrogen 5.64%), (Nitrogen 12.78 %), Mass Spectra of A-1, A-3 and B-4 m/z: 238, 282 and 397 respectively.[25-27]

The compounds B-4 and A-3, which were the least active, had the following chemical structures.

B-4 → R=Br
R’=OCH_3
A-3→R=H
R’=NO_2

If we compare the structures of the produced compounds to their activities, we observe that the R' group of the =C6H5- R' should be substituted at position -4 of the ring. The activity is at its highest when the substitution is R=H, R'=H relative to other substituent’s.



The compound's structure which gave the best activity is A-1

A-1→ R=H
R’=H

The unsubstituted compound showed the maximum activity then substituted compounds.

CONCLUSION

In conclusion, the synthesis and evaluation of novel quinazolinone derivatives for their anticonvulsant activity have yielded

significant insights into their potential therapeutic applications. The diverse biological properties historically associated with quinazolinones have been further extended by the discovery of promising anticonvulsant effects in our study. The Maximal Electroshock (MES) method served as a robust preclinical model to assess the efficacy of the synthesized compounds in mitigating seizures. The observed anticonvulsant activity of select quinazolinone derivatives underscores their potential as candidates for further development in the treatment of epilepsy. The structure-activity relationships deduced from this research provide a foundation for future medicinal chemistry endeavors. Understanding the specific structural features that contribute to anticonvulsant effects is crucial for the rational design of more potent and selective compounds. Additionally, further studies exploring the mechanisms of action, pharmacokinetics, and safety profiles of these derivatives will be essential for their progression toward clinical applications.

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Conflects of interest

There are no financial or other conflicts of interest that the authors of this work have disclosed.

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