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Synthesis and Anticonvulsant Activity of *N*-(Substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamides

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A series of new *N*-(substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamides were designed, synthesized, and evaluated for their anticonvulsant activity. Most of the synthesized compounds exhibited potent anticonvulsant activities in the maximal electroshock (MES) and pentylenetetrazol (PTZ) test. The most promising compound **4c** showed significant anticonvulsant activity with a protective index value of 3.58. The compounds **4a–c** were also found to have encouraging anticonvulsant activity in the MES and PTZ screen when compared with the standard drugs, valproate and methaqualone. The same compounds were found to exhibit advanced anticonvulsant activity as well as lower neurotoxicity than the reference drugs.

Keywords: Anticonvulsant / Glycosmicine / MES / Neurotoxicity / PTZ

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Introduction

Epilepsy is a chronic disorder of the brain characterized by recurrent unprovoked seizures that affects about 1% of the world's population [1, 2]. Despite the availability of many antiepileptic drugs (AEDs), there is still an urgent need for the development of more effective and safer AEDs, as about 30% of epileptic patients are not seizure-free with the existing AEDs [3, 4]. Moreover, their usage is associated with undesirable numerous side effects including drowsiness, ataxia, gastrointestinal disturbances, hirsutism, and megaloblastic anemia [5]. Thus, there is an enormous need for the development of novel AEDs with fewer side effects and more effectiveness.

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The structure–activity relationship (SAR) studies of clinically available AEDs and other anticonvulsant active compounds showed that most of these compounds included quinazolinone moiety in their molecules. Quinazolinones (methaqualone, quinethazone, albaconazole, febrifugine, afloqualone, fenquizone, raltitrexed, etc.) are considered to be an important chemical synthon of various physiological significance and pharmaceutical utility like anticonvulsant, sedative, tranquilizing, analgesic, antirheumatic, hypotensive, antiallergic, antidiabetic, diuretic, antimalarial, etc. Moreover, they continued to attract a widespread interest for a long time due to their diverse pharmacological activities [6]. As such, quinazoline-2,4(1*H*,3*H*)-dione derivatives have been widely used as key structures in the production of medicinal drugs [7].

In search of new anticonvulsant agents, the titled compounds (**4a–g**) possessed all the required pharmacophoric elements as the phenyl ring attached to the nitrogen moiety can be referred to the aryl ring (lipophilic aryl ring), the nitrogen of the amide group can act as a hydrogen bond donor and the amide keto group can act as a hydrogen bond acceptor (HBA). The proposed quinazolinone seems to

resemble better with standards. With this as background and in continuation of our research program on design and synthesis of new anticonvulsant agents [8–10], the present work highlights the importance of the synthesis of prototypes of *N*-(substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamides and efficacy of their anticonvulsant activity.

Result and discussion

Chemistry

Most target *N*-(substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamides (**4a–g**) reported herein were prepared according to Scheme 1. A variety of combinatorial approaches have been described by which pharmacophophoric groups were attached to such relatively rigid scaffold. The naturally occurring plant-derived 1-methylquinazoline-2,4(1*H*,3*H*)-dione (glycosmicine) **1** used to prepare target compounds was obtained from synthesized by published method [7]. The structures of the synthesized compounds were deduced on the basis of ^{1}H NMR, IR, and mass spectra. The composition of all the compounds was obtained by elemental analysis. The proton magnetic resonance spectra of synthesized compounds have been recorded in $CDCl_3$. In addition, the chemical shift and multiplicity patterns correlated well with the proposed structures. The elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values.

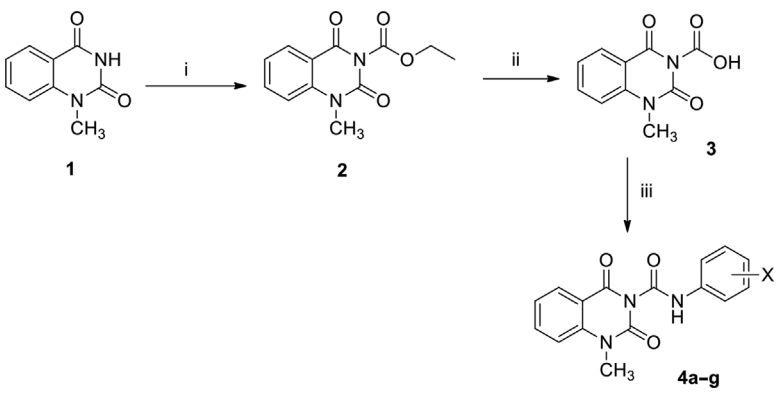
Amino function of compound **1** was reacted with ethyl chloroformate in dry benzene in the presence of triethylamine at room temperature to afford a quantitative yield of ethyl 1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxylate (**2**). Then compound **3** was obtained after hydrolysis using 1 N sodium hydroxide/ethanol solution at room temperature for 12 h. Further acid group in compound **3** was converted to their corresponding acid chlorides by reaction with an excess of thionyl chloride in dichloromethane and coupled to substituted anilines to give desired compounds **4a–g**.

Anticonvulsant activity

Maximal electroshock (MES), pentylenetetrazole (PTZ), and picrotoxin seizure threshold tests were well known to evaluate the potential anticonvulsant activity of compounds under investigation [11]. At the present time, there are three *in vivo* models that are routinely used by most AED discovery programs. They include the MES, PTZ, and picrotoxin model. The anticonvulsant activities of the newly synthesized compounds were evaluated by the use of standard technique. The preliminary screening was performed at 1.0 mmol/kg of all synthesized compounds **4a–g** by use of PTZ, MES, and picrotoxin models of seizures. The MES test is associated with the electrical induction of the seizure, whereas PTZ and picrotoxin methods involve a chemical induction to generate the convulsion [12]. The results are presented in Table 1.

The preliminary anticonvulsant screening showed that some of these compounds are less active; however, compounds **4a–c** and **4e** were active against MES, PTZ, and picrotoxin tests, among which compounds **4a** and **4c** presented 100% protection. The compounds **4b** and **4e** exhibited 100 and 50% protection, respectively, in MES test. The compounds (**4a–c** and **4e**) that exhibited significant activity were subsequently subjected to a quantitative determination of the pharmacological parameters, that is, median effective dose (ED_{50}) and toxic dose (TD_{50}) in mice. Results of the quantitative test for these compounds, along with the data on the current AEDs (methaqualone and valproate) are shown in Table 2.

The protective index (PI) (TD_{50}/ED_{50}) is considered to be an index representing the margin of safety and tolerability between anticonvulsant doses and doses of anticonvulsant drugs exerting acute adverse effects (e.g., sedation, motor coordination impairment, ataxia, or other neurotoxic manifestations) [13]. The compound **4e** showed a higher PI than all the standard drugs. The compound **4c** gave an ED_{50} of 0.24 mg/kg and a TD_{50} of 0.86 mg/kg, resulting in a high PI,



Scheme 1. Synthetic route to **4a–g**. Reagents and conditions: (i) ethyl chloroformate, TEA, benzene, 8 h; (ii) $SOCl_2$, EtOH, NaOH, 12 h; (iii) substituted phenylamine (**a–g**), $SOCl_2$, $CH2Cl_2$, reflux.

Table 1. Anticonvulsant activity of the new-synthesized compounds (1.0 mmol/kg), valproate (1.5 mmol/kg), and methaqualone (1.4 mmol/kg).

Compounds	MES[a] (% protection)	PTZ[b] (% protection)	Pictrotoxin (% protection)
4a	100	100	100
4b	100	70	50
4c	100	100	100
4d	0.0	25	0.0
4e	50	67	40
4f	33	66	10
4g	10	50	0.0
Methaqualone	100	100	50
Valproate	100	100	100
Control	–	–	–

Values are expressed as mean ± SE. n = 6 animals in each group.
[a]Maximal electroshock seizure test.
[b]Pentylenetetrazole test.

that is, TD_{50}/ED_{50}, of 3.58 when compared to phenobarbital and valproate. Almost all the PI values of the selected compounds (2.93, 2.07, 3.58, and 1.41) were higher than or equal to the reference drugs as compared to 1.14 for methaqualone and 2.0 for valproate.

In the present series of compounds, the active compounds possess all the requirements essential for anticonvulsant activity as proposed by Dimmock and Baker [14]. Thus, our new proposal for a pharmacophore model includes factors which are responsible for bioactivity. On correlating the structures of the synthesized compounds with their biological activity, it has been observed that compounds bearing the *para*-substituted halogens groups like chloro, bromo, and fluoro on phenyl ring possess high potency in MES, PTZ, and picrotoxin tests. Introduction of halogen on the phenyl ring changed (reduced or increased) the anticonvulsant activity at different levels. The bioevaluation led to an understanding of the importance of the position of the halogen at the phenyl. The compounds bearing *para*-substituted halogens groups on phenyl ring showed high potency in MES and PTZ tests. Whereas replacement of *para* position with halogens groups on phenyl ring has resulted in compounds with decrease in anticonvulsant activity. Compounds **4a–c** and **4e** show apparent activity in MES, PTZ, and picrotoxin screen, and which is considered to be the optimum lipophilicity for the congeners that act on the central nervous system. It may indicate the importance of lipophilicity as well as electronic properties of the substituents on the activity of these compounds.

SAR recommendations withdrawn from those findings revealed that (i) halogens like chloro, fluoro, and bromo groups connected to phenyl ring as in *para* position is essential for anticonvulsant activity; (ii) the removal of halogen substitution of *para* position will yield compounds with

Table 2. Comparison of the anticonvulsant activities (ED_{50}), acute neurotoxic effects (TD_{50}), median lethal doses (LD_{50}), therapeutic and protective indexes of the most promising anticonvulsant new-synthesized compounds and standards in mice.

Compound	ED_{50} (mg/kg)	TD_{50} (mg/kg)	LD_{50} (mg/kg)	Therapeutic index	Protective index
Valproate	4.8	9.6	11.9	2.48	2.0
Methaqualone	1.40	1.60	2.00	1.40	1.14
4a	0.31	0.91	1.13	3.64	2.93
4b	0.41	0.85	1.02	2.48	2.07
4c	0.24	0.86	1.18	4.91	3.58
4e	0.56	0.79	0.92	1.64	1.41

ED_{50}, median effective dose providing anticonvulsant protection in 50% of mice against pentylenetetrazole (PTZ)-induced seizures; TD_{50}, median toxic dose producing minimal neurological toxicity in 50% of mice subjected to the Chimney test; LD_{50}, median lethal dose that causes 50% mortality in mice; therapeutic index, LD_{50}/ED_{50}; protective index, TD_{50}/ED_{50}.

decrease in anticonvulsant activity; and (iii) lipophilicity manipulates the magnitude of anticonvulsant potency of such chemical synthons.

Conclusion

In the current study, a series of novel *N*-(substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamide derivatives (**4a–g**) were designed, synthesized, and evaluated for anticonvulsant activity. For anticonvulsant evaluation, three animal models were adopted, namely MES, PTZ, and picrotoxin (Pic)-induced convulsions. The most active was **4c** which showed a PI of 3.58. This compound showed greater PI to standard drugs. Additionally, compounds **4a** and **4b** showed advanced anticonvulsant activity as well as lower toxicity than methaqualone and valproate reference drugs. The obtained results showed that certain compounds could be useful as a template for future design, modification, and investigation to produce more active analogs.

Experimental

Materials

Elemental analysis (C, H, N) was determined using a Carlo-Erba 1160 elemental analyzer. IR spectra were recorded on a JASCO FTIR-8400 spectrophotometer using Nujol mulls. The ^{1}H NMR spectra were recorded on a Varian AC 400 spectrometer instrument in $CDCl_3$ using TMS as the internal standard. Low resolution ESI-MS spectra were obtained on a Varian 1200L model mass spectrometer (solvent: CH_3OH). Melting points were determined with a Buchi 530 melting point apparatus in open capillaries and are uncorrected. Compound purity was checked by thin layer chromatography (TLC) on precoated silica gel plates (Merck, Kieselgel 60 F254, layer thickness 0.25 mm).

The InChI codes and NMR spectra of the investigated compounds are provided as Supporting Information.

Synthesis

*Preparation of ethyl 1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxylate (**2**)*

Compound **1** (15 mmol) was refluxed with ethyl chloroformate (15.5 mmol) in dry benzene (30 mL) and in the presence of triethylamine. Then the reaction mixture was stirred at room temperature for about 8 h. After completion of the reaction (TLC), the reaction mixture was quenched in ice cold water and extracted with dichloromethane. The organic layer was washed with 5% $NaHCO_3$ and dried over Na_2SO_4 and concentrated *in vacuo* to give desired product. Yield: (96%), m.p.: 273°C. Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.01; H, 4.73; N, 11.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, 3H, $-CH_3$), 3.78 (s, 3H, N–CH_3), 4.26 (q, 2H, COO–CH_2), 7.35–7.90 (m, 4H, Ar–H). IR (Nujol, cm^{-1}): 3053–2829.5 (Ar C–H), 1708, 1675, 1635 (C=O). MS, *m/z*: 249 (M+1).

*Preparation of 1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxylic acid (**3**)*

To a solution of compound **2** (10.0 mmol) in EtOH was added sodium hydroxide (1 N, 10 mL), and the resulting mixture stirred at room temperature for 12 h. EtOH was removed under reduced pressure, water was added to the residue and the mixture was acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give product **3**. Yield: (92%), m.p.: 264°C. Anal. calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.35; H, 3.51; N, 12.83. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.78 (s, 3H, N–CH_3), 7.37–7.88 (m, 4H, Ar–H), 11.02 (s, 1H, COOH). IR (Nujol, cm^{-1}): 3053–2829.5 (Ar C–H), 2738 (COOH), 1708, 1676, 1635 (C=O). MS, *m/z*: 220 (M+1).

*General procedure for the synthesis of **4a–g***

To the acid (**3**, 2 mmol) in CH_2Cl_2 was added an freshly distilled thionyl chloride and refluxed for 1 h, excess of thionyl chloride was removed *in vacuo* and thereafter condensed with methylenechloride solution of substituted phenylamine (2 mmol) and stirred for 2 h. The organic layer was washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to give crude product and recrystallization from absolute ethanol gave desired compounds **4a–g**.

*N-(4-Chlorophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4a**)*

Yield: (81%), m.p.: 281°C. Anal. calcd. for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.25; H, 3.59; N, 12.83. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.69 (s, 3H, N–CH_3), 6.19 (s, 1H, NH), 6.78–7.79 (m, 8H, Ar–H). IR (Nujol, cm^{-1}): 3235 (N–H), 3051–2828 (Ar C–H), 1705, 1675, 1637 (C=O). MS, *m/z*: 330 (M+1).

*N-(4-Bromophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4b**)*

Yield: (78%), m.p.: 287°C. Anal. calcd. for $C_{16}H_{12}BrN_3O_3$: C, 51.36; H, 3.23; N, 11.23. Found: C, 51.26; H, 3.11; N, 11.39. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.66 (s, 3H, N–CH_3), 6.78–7.92 (m, 8H, Ar–H), 8.65 (s, 1H, NH). IR (Nujol, cm^{-1}): 3230 (N–H), 3052–2829 (Ar C–H), 1703, 1678, 1632 (C=O). MS, *m/z*: 374 (M+1).

*N-(4-Fluorophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4c**)*

Yield: (80%), m.p.: 277°C. Anal. calcd. for $C_{16}H_{12}FN_3O_3$: C, 61.34; H, 3.86; N, 13.41. Found: C, 61.21; H, 3.73; N, 13.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.72 (s, 3H, N–CH_3), 7.03–7.85 (m, 8H, Ar–H), 8.86 (s, 1H, NH). IR (Nujol, cm^{-1}): 3235 (N–H), 3051–2828 (Ar C–H), 1703, 1675, 1632 (C=O). MS, *m/z*: 314 (M+1).

*N-(3-Chlorophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4d**)*

Yield: (81%), m.p.: 280°C. Anal. calcd. for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.16; H, 3.54; N, 12.91. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.70 (s, 3H, N–CH_3), 7.01–7.88

(m, 8H, Ar–H), 8.75 (s, 1H, NH). IR (Nujol, cm^{-1}): 3238 (N–H), 3055–2830 (Ar C–H), 1704, 1671, 1632 (C=O). MS, *m/z*: 330 (M+1).

*N-(2,5-Difluorophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4e**)*
Yield: (80%), m.p.: 298°C. Anal. calcd. for $C_{16}H_{11}F_2N_3O_3$: C, 58.01; H, 3.35; N, 12.68. Found: C, 57.95; H, 3.23; N, 12.81. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.70 (s, 3H, N–CH_3), 5.63 (s, 1H, NH), 6.52–7.75 (m, 7H, Ar–H). IR (Nujol, cm^{-1}): 3235 (N–H), 3052–2828 (Ar C–H), 1705, 1671, 1632 (C=O). MS, *m/z*: 332 (M+1).

*N-(3,5-Difluorophenyl)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamide (**4f**)*
Yield: (78%), m.p.: 289°C. Anal. calcd. for $C_{16}H_{11}F_2N_3O_3$: C, 58.01; H, 3.35; N, 12.68. Found: C, 57.91; H, 3.27; N, 12.83. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.71 (s, 3H, N–CH_3), 6.95–7.84 (m, 7H, Ar–H), 8.73 (s, 1H, NH). IR (Nujol, cm^{-1}): 3235 (N–H), 3052–2828 (Ar C–H), 1705, 1671, 1632 (C=O). MS, *m/z*: 332 (M+1).

*1-Methyl-2,4-dioxo-N-(2,3,4-trifluorophenyl)-1,2-dihydroquinazoline-3(4H)-carboxamide (**4g**)*
Yield: (80%), m.p.: 291°C. Anal. calcd. for $C_{16}H_{10}F_3N_3O_3$: C, 55.02; H, 2.89; N, 12.03. Found: C, 54.95; H, 2.11; N, 12.15. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.77 (s, 3H, N–CH_3), 7.05–7.89 (m, 6H, Ar–H), 8.78 (s, 1H, NH). IR (Nujol, cm^{-1}): 3238 (N–H), 3050–2825 (Ar C–H), 1708, 1670, 1632 (C=O). MS, *m/z*: 350 (M+1).

Pharmacology

The anticonvulsant activity was evaluated by MES and PTZ tests. Mice (18–20 g) were procured from National Institute of Nutrition, Hyderabad. The animals were kept in individual cages for 1 week to acclimatize for laboratory conditions. They were allowed to free access of water and food. All the experimental procedures were carried out in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The study was reviewed and approved by the Institutional Animal Ethics Committee, G Pulla Reddy College of Pharmacy, Hyderabad, India.

Anticonvulsant activity
MES model was used in the current study to evaluate the anticonvulsant activity of the drugs on mice. Seizures were induced in mice by delivering electroshock of 150 mA for 0.2 s by means of a convulsiometer through a pair of ear clip electrodes. The test compounds were administered intraperitoneally (i.p.) at dose of 1.0 mmol/kg 30 min before the seizure induction. The animals were observed closely for 2 min. The percentage of inhibition of seizure relative to control was recorded and calculated [15]. Sodium valproate (200 mg/kg) and methaqualone (300 mg/kg) were used as reference drugs. The PTZ test was carried out by the i.p. injection of a convulsant dose of PTZ (100 mg/kg). As with PTZ, the chemoconvulsants picrotoxin was administered i.p. to mice in a dose eliciting convulsions in 100% of control mice of dose 8 mg/kg. Seizures and tonic-clonic convulsions, hypnosis, and death were recorded. Sodium valproate (200 mg/kg) and methaqualone (300 mg/kg) were used as reference drugs.

The neurological toxicity
The acute neurotoxicity of the selected compounds was performed according to a method described by Boissier et al. [16]. In this test, the animals had to climb backwards up the tube. Motor impairment was indicated by the inability of the animals to climb backward up the transparent tube within 30 s. The neurotoxic effects of the tested compounds were expressed as their median toxic doses (TD_{50} values), representing the doses at which the investigated compounds impaired motor coordination in 50% of the animals.

Quantification studies
Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}), that is, the dose of drug required to produce the biological responses in 50% of animals, neurotoxicity was expressed as the median toxic dose (TD_{50}). Groups of six mice each were given a range of i.p. doses of the selected drug until at least four points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity [17]. From the plot of these data, the respective ED_{50} and TD_{50} values, slope of the regression line, and standard error of the slope were calculated by means of a computer program based on the method described by Finney [18].

The authors have declared no conflicts of interest.

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