Tetramethylcyclopropyl Analogue of a Leading Antiepileptic Drug, Valproic Acid. Synthesis and Evaluation of Anticonvulsant Activity of Its Amide Derivatives

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Although valproic acid (VPA) is an extensively used antiepileptic drug for treatment of various kinds of epilepsies, it has been proven to possess two life-threatening side effects: hepatotoxicity and teratogenicity. Amide and urea derivatives of 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMCA) were prepared to discover lead compounds with clinical potential. In the amide and alkylamide series of TMCA derivatives, ***N***-methoxy-2,2,3,3-tetramethylcyclopropanecarboxamide (**21**) was one of the most active compounds, having the subcutaneous metrazol test (scMet) ED_{50} values of 35 mg/kg in rats and 74 mg/kg in mice. In the maximal electroshock-induced seizure test (MES), this compound had ED_{50} values of 108 mg/kg in rats and 115 mg/kg in mice. Compound **21** was 18.5 and 4.5 times more potent than VPA in the corresponding rat tests. The most active compound in the series of urea derivatives was 2,2,3,3-tetramethylcyclopropanecarbonylurea (**25**), possessing MES ED_{50} values of 29 mg/kg in rats and 90 mg/kg in mice. In the scMet test this compound had ED_{50} values of 92 mg/kg in rats and 125 mg/kg in mice. The median toxic dose (TD_{50}) in rats was 538 mg/kg, providing compound **25** with a wide safety margin and a protective index (TD_{50}/ED_{50}) of 18.5 in the MES test, which is about 12 times greater than that of VPA. Compounds **21** and **25** have the potential for development as novel potent and safe central nervous system active drugs with a broad spectrum of antiepileptic activity.

Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population and characterized by recurrent seizure attacks.[1] Valproic acid (VPA, **1**, Figure 1) is one of the leading antiepileptic drugs (AEDs), which is also effective in migraine prophylaxis and treatment of bipolar disorders.[2−4] VPA is also currently undergoing clinical trials as an antineoplastic drug.[5] Despite its broad spectrum of antiepileptic activity, the clinical use of VPA is restricted by its two rare but potentially life-threatening side effects: teratogenicity and hepatotoxicity.[6−8] While VPA-induced hepatotoxicity (microvesicular steatosis) is associated with the formation of the metabolites with a terminal double bond, 4-ene-VPA (**2**) and 2,4-diene-VPA (**3**) (Figure 1),[9−12] VPA-induced teratogenicity is caused by the parent compound.[13] It was shown on various valproic acid derivatives and analogues that teratogenicity of these compounds is structure-dependent.[13]

Many analogues and derivatives of VPA were synthesized in an attempt to find a superior compound that would retain the anticonvulsant activity correlated with the basic structure of VPA but would not cause the adverse effects associated with VPA use.[14] Nonbranched small-chain fatty acids (butyric, pentanoic, hexanoic, and octanoic acids) were found to be active in anticonvulsant tests.[15−17] Numerous cyclic analogues of VPA have been synthesized to evaluate the role of the ring

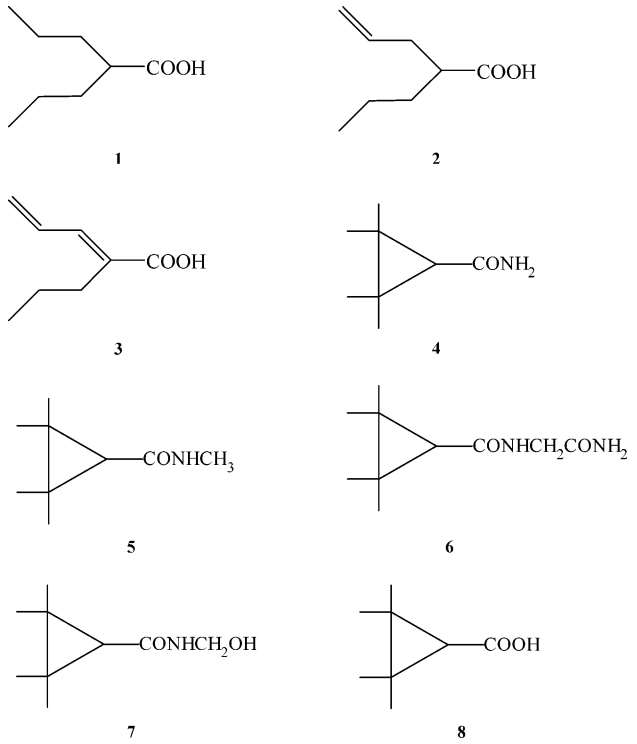

Figure 1.

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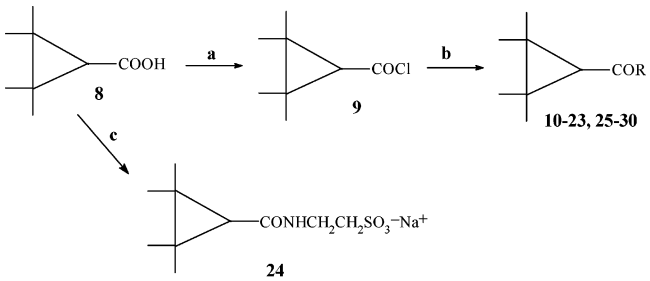
size for anticonvulsant activity. Cycloalkylcarboxylic acids with three to seven carbons in their ring were prepared and evaluated for anticonvulsant activity.[15,18−22] The rigid analogues of VPA, (*E*)-2,3-diethylcyclopropanecarboxylic acid and 2,2-dicyclopropylcarboxylic acid, were as active as VPA,[19] and spiro[4.6]undecane-2-carboxylic acid was more active than VPA in the pentylenetetrazol-induced seizures in mice.[20,21] 1-Methylcyclohexanecarboxylic acid was found to be more potent than VPA in pentylenetetrazol-induced seizures in rats.[15] In the analysis of cyclic VPA analogues with an increasing number of carbons in the cyclic portion of the molecule and a double bond in the α-position to the carboxyl group, it was demonstrated that cyclooctylideneacetic acid exhibits a much greater anticonvulsant potency than VPA.[23] Further branching of VPA by the addition of a methyl group in the α-position to the carboxyl group or to one of its side chains reduced the teratogenic effect of these VPA analogues without decreasing their anticonvulsant activity.[24] Propylisopropylacetic acid, diisopropylacetic acid, and valnoctic acid, structural isomers of VPA, were relatively inactive as anticonvulsants.[25,26] Substitution of the hydrogen adjacent to the α-carbon to the carboxyl group by a fluorine atom produced an α-fluoro-VPA, a compound with significantly reduced hepatotoxicity and only slightly reduced anticonvulsant activity compared to VPA.[27−29] Some of the unsaturated VPA analogues have been synthesized and evaluated for their antiepileptic activity.[30] Introduction of a double bond at C-2 (2-ene-VPA) led to improved anticonvulsant activity.[31] In addition to the modifications of the aliphatic moiety of VPA, several valproic acid ester derivatives have been tested.[32] These compounds were found to be prodrugs of VPA in dogs.[32] Recently, several ester derivatives of VPA with sugar alcohols have been synthesized and some were found to be active as anticonvulsants.[33] In addition, a large number of valproylamides have been examined. Valpromide (VPD), a primary amide of VPA, is more potent than the parent acid in animal models. However, VPD in humans is a prodrug of VPA and therefore has no clinical value.[34,35] Propylisopropylacetamide, diisopropylacetamide, and valnoctamide were found to be metabolically stable and active isomers of VPD.[36] Since the primary amide of VPA was much more potent in animal models, N-alkylated amides and urea derivatives of VPA have been extensively explored.[37−43] A series of prodrugs of VPA with amino acids were prepared, and their stability in the gastrointestinal tract was reported without stating the antiepileptic activity.[44] Conjugation of VPA with glycinamide yielded a very active compound with a broad spectrum of antiepileptic activity.[45,46]

Several years ago in our ongoing research to develop more active and less toxic antiepileptic drugs (AEDs), we synthesized 2,2,3,3-tetramethylcyclopropanecarboxamide (TMCD, **4)**, its *N*-methyl derivative (MTMCD, **5**), *N*-2,2,3,3-tetramethylcyclopropanecarbonylglycinamide (TMC-glycinamide, **6**),[37] and later *N*-hydroxymethyl TMCD (OH-MTMCD, **7**) (Figure 1).[47] 2,2,3,3-Tetramethylcyclopropanecarboxylic acid (TMCA, **8**, Figure 1), serving as a starting material in the syntheses of these cyclic analogues of VPA, possesses two tertiary carbons in the β-position to the carboxyl group and therefore cannot be biotransformed to metabolites with a terminal

Scheme 1[a]



10 R = $NHCH_2CH_3$
11 R = NH—(cyclopropyl)
12 R = $N(CH_3)_2$
13 R = $NHCH_2CH_2F$
14 R = $NHCH_2CH_2OH$
15 R = $N(CH_3)CH_2CH_2OH$
16 R = $N(C_2H_5)CH_2CH_2OH$
17 R = $NHCH(CH_3)CH_2OH$
18 R = $NHCH(C_2H_5)CH_2OH$
19 R = $NHCH_2CH(OH)CH_3$
20 R = NHOH
21 R = $NHOCH_3$
22 R = $NHNH_2$
23 R = NHNHCO—(cyclopropyl)
25 R = $NHCONH_2$
26 R = $NHCONHCH_3$
27 R = $NHCON(CH_3)_2$
28 R = $N(CH_3)CONHCH_3$
29 R = $NHCSNH_2$
30 R = $NHC(NH)NH_2$

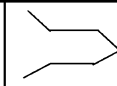
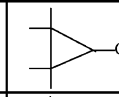
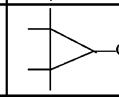
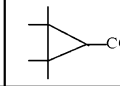
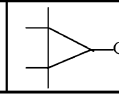
[a] Reagents and conditions: (a) $SOCl_2$, dichloromethane, room temperature, 24 h; (b) For compounds **10**−**23**, suitable amine, Et_3N, dichloromethane, room temperature, 2−24 h; for compounds **25**−**29**, suitable urea or thiourea, acetonitrile, reflux, 2−4 h; for compound **30**, guanidine·HCl, aqueous NaOH (2 N), acetonitrile, 0 °C, 2−24 h; (c) for compound **24**, taurine, aqueous NaOH (2 N), dichloromethane, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, 40 °C, 24 h.

double bond, analogous to hepatotoxic 4-ene-VPA and 2,4-diene-VPA. Unlike TMCA that does not possess anticonvulsant activity in animal models, its amide derivatives, TMCD and especially MTMCD, were found to be nonteratogenic, broad-spectrum anticonvulsants.[37,42] Consequently, the aim of the current study was to design more potent and safe VPA analogues with a broad spectrum of anticonvulsant activity. We synthesized numerous tetramethylcyclopropane carboxamides and evaluated their anticonvulsant activity and toxicity in well-established animal models.

Chemistry

The starting material in all the reactions was 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMCA, **8**, Scheme 1). It was converted by $SOCl_2$ to the corresponding acid chloride (TMC-Cl, **9**, Scheme 1) by a method described in the literature.[48] Compounds **10**−**23** were synthesized by coupling reactions of TMC-Cl (**9**) with suitable amines in the presence of triethylamine (route b of Scheme 1), using dry acetonitrile or dichloromethane. Compounds **25**−**29** were synthesized by coupling TMC-Cl with urea or suitable urea derivatives (route b of Scheme 1) under reflux conditions. Compound **30** was prepared as shown in Scheme 1, using 2 N NaOH as a base. Compound **24** was synthesized from TMCA and taurine, using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) as a coupling agent (route c of Scheme 1).[49] The synthesized products were purified by crystallization. ^{1}H NMR spectra of the synthesized compounds were measured using TMS as the internal standard. Elemental analyses were performed for all the synthesized compounds and were within ±0.4% of the theoretical values.

Table 1. Anticonvulsant Activity and Toxicity of Compounds **1** and **4**−**7** Administered Intraperitoneally to Mice As Reported in the Literature

Compd	Structure	MES[a] (ED_{50},mg/kg)	scMet[b] (ED_{50},mg/kg)	Tox[c] (TD_{50},mg/kg)	PI (MES)[d]	PI (scMet)[e]
1		263 (237-282)[f]	220 (177-268)	398 (356-445)[56]	1.5	1.8
4		>120	57 (39-76)	98 (85-109)[42]	–	1.7
5		98 (88-109)	39 (31-44)	153 (136-158)[42]	1.6	3.9
6		173 (149-202)	115 (65-164)	259 (200-313)[37]	1.5	2.3
7		>220	120 (108-133)	146 (127-177)[47]	–	1.2

[a] Maximal electroshock test. [b] Subcutaneous metrazol test. [c] Toxicity. [d] Protective index (TD_{50}/ED_{50} ratio) in the MES test. [e] Protective index in the scMet test. [f] The interval in parentheses stands for 95% confidence interval.

Table 2. Anticonvulsant Activity and Toxicity of Compounds **1** and **4**−**7** Administered Orally to Rats As Reported in the Literature

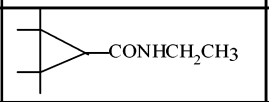
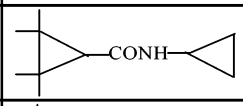
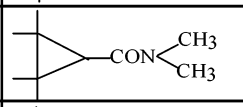
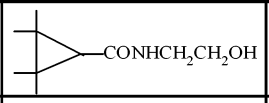
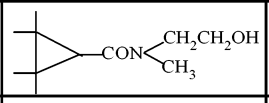
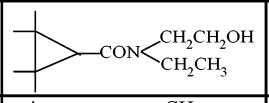
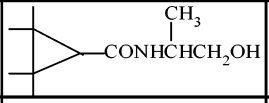
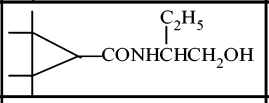
Compd	MES[a] (ED_{50},mg/kg)	scMet[b] (ED_{50},mg/kg)	Tox[c] (TD_{50},mg/kg)	PI (MES)[d]	PI (scMet)[e]
1	485 (324-677)[f]	646 (466-869)	784 (503-1176)[56]	1.6	1.2
4	>250	52 (42-63)	381 (355-418)[42]	–	7.3
5	82 (64-102)	45 (31-55)	163 (138-179)[42]	2.0	3.6
6	82 (61-103)	>250	>500[37]	>6.1	~ 2
7	NT[g]	NT	NT[47]	NT	NT

[a] Maximal electroshock test. [b] Subcutaneous metrazol test. [c] Toxicity. [d] Protective index (TD_{50}/ED_{50} ratio) in the MES test. [e] Protective index in the scMet test. [f] The interval in parentheses stands for 95% confidence interval. [g] Not tested.

Results and Discussion

Multiple mechanisms of action of existing antiepileptic drugs and the lack of well-identified and characterized binding sites on target macromolecules compel us to develop better anticonvulsant drugs utilizing the structure−activity relationship (SAR) approach. Recently in our laboratory four central nervous system (CNS) active derivatives of TMCA (TMCD, MTMCD, TMC-glycinamide, and OH-MTMCD) were synthesized and evaluated for their anticonvulsant activity.[37,47] Tables 1 and 2 present the anticonvulsant activity of these compounds in the maximal electroshock-induced seizure test (MES test) and subcutaneous metrazol seizure threshold test (scMet test) in mice and rats. Compounds **4**−**7** showed better anticonvulsant potency than VPA, but their protective indexes (toxic dose (TD_{50}) to effective dose (ED_{50}) ratio) still remained at the same magnitude as VPA's.[37,42,47] To improve the anticonvulsant potency and to optimize the efficacy−toxicity profile, we synthesized a series of new TMCA derivatives with various modifications in the amide moiety (compounds **10**−**30**, Scheme 1). Tables 3−5 present the anticonvulsant activity and toxicity of compounds **10**−**24** in mice and rats. The results obtained showed no significant differentiation between efficacy and toxicity of these compounds, with the exception of *N*-methoxy TMCD (**21**), in which the hydrogen atom of the $-NH_2$ group of TMCD was substituted by a methoxy group. This compound showed significant anticonvulsant activity in mice and rats. With ED_{50} values of 35 mg/kg in the rat scMet test and 108 mg/kg in the rat MES test, this TMCD derivative is 18.5 and 4.5 times, respectively, more potent than VPA in the corresponding tests (Tables 2 and 10). *N*-Methoxy TMCD had no toxic effects

Table 3. Anticonvulsant Activity and Toxicity of Compounds **10**−**24** Administered Intraperitoneally to Mice

Compd	Structure	Dose (mg/kg)	MES[a] 0.5 h[d]	MES[a] 4 h	scMet[b] 0.5 h	scMet[b] 4 h	Tox[c] 0.5 h	Tox[c] 4 h
10		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	1/1	0/1	4/4	2/2
11		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	1/4
		300	1/1	0/1	0/1	0/1	4/4	0/2
12		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	0/1	0/1	0/1	4/4	1/2
13		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	0/1	1/1	0/1	4/4	1/2
14		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	0/1	1/1	0/1	4/4	0/2
15		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	1/8	1/4
		300	0/1	0/1	0/1	0/1	2/4	0/2
16		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	7/8	1/4
		300	0/1	0/1	0/1	0/1	4/4	0/2
17		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	1/8	0/4
		300	0/1	0/1	0/1	0/1	4/4	0/2
18		30	0/1	0/1	0/1	0/1	0/4	0/2
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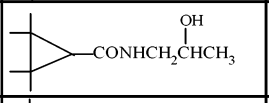
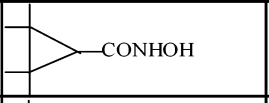
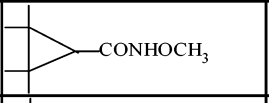
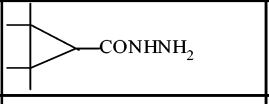
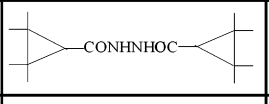
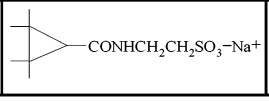
		300	0/1	0/1	0/1	0/1	4/4	0/2
19		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	0/1	0/1	0/1	3/4	0/2
20		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	0/1	0/1	0/1	1/4	0/2
21		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	2/3	0/3	5/5	0/1	0/8	0/4
		300	1/1	0/1	1/1	1/1	4/4	1/2
22		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	1/4
		300	1/1	1/1	0/1	0/1	2/4	0/2
23		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	0/1	0/1	0/1	0/4	0/2
24		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	0/1	0/1	0/1	0/4	0/2

[a] Maximal electroshock test (number of animals protected/number of animals tested). [b] Subcutaneous metrazol test (number of animals protected/number of animals tested). [c] Toxicity (number of animals exhibiting toxicity/number of animals tested). [d] Time after drug administration.

up to 333 mg/kg in rats, providing it a protective index of 9.5 in the scMet test, which is 8 times greater than the protective index of VPA in the same test. All the other compounds presented in Table 3, except for **23** and **24**, were toxic in mice at 300 mg/kg. The lack of toxicity of compound **24** is probably derived from its relatively high polarity and consequent inability to penetrate the blood−brain barrier. Substitution of hydrogens in the amide moiety of TMCD by alkyl (**10**), cyclic alkyl (**11**), dialkyl (**12**), fluoroalkyl (**13**), hydroxyalkyl (**14**), alkylhydroxyalkyl (**15**, **16**), and hydroxyisoalkyl (**17**−**19**) groups caused a significant decrease in anticonvulsant activity. Compound **11** was partially active in the rat MES test at 50 mg/kg (Table 4). Being the homologue of OH-MTMCD, compound **14** showed significant anticonvulsant activity in the rat scMet test at 50 mg/kg

Table 4. Anticonvulsant [Anti-MES] Activity and Toxicity of Compounds **10**−**24** Administered Orally to Rats[a]

Compd	Dose (mg/kg)	Times after drug administration					Tox[b]
		15 min	30 min	1 h	2 h	4 h	
10	30	−	−	−	−	+	−
11	50	−	+	+	++	+	−
12	100	−	+	−	−	−	−
13	30	+	−	−	−	+	−
14	30	−	+	−	−	−	−
15	100	−	−	−	−	−	−
16	100	−	−	−	−	−	+
17	100	−	+	+	−	−	−
18	100	−	−	−	−	+	−
19	30	+	−	+	−	−	−
20	30	−	−	−	−	−	−
21	30	−	++	++	−	−	−
22	30	−	−	−	−	+	−
23	50	−	+	−	−	−	−
24	100	−	−	−	+	−	−

[a] Symbols are as follows: ++++, 100% of the animals were protected; +++, 75% of the animals were protected; ++, 50% of the animals were protected; +, 25% of the animals were protected; −, no protection. In case of toxicity: ++++, 100% of the animals exhibited toxicity; +++, 75% of the animals exhibited toxicity; ++, 50% of the animals exhibited toxicity; +, 25% of the animals exhibited toxicity; −, no toxicity. [b] Toxicity.

Table 5. Anticonvulsant [Anti-scMet] Activity and Toxicity of Compounds **10**−**24** Administered Orally to Rats[a]

Compd	Dose (mg/kg)	Times after drug administration					Tox[b]
		15 min	30 min	1 h	2 h	4 h	
10	223	NT[c]	NT	++++	NT	NT	++
11	50	−	+	−	−	−	−
12	100	−	++	−	−	−	−
13	NT	NT	NT	NT	NT	NT	NT
14	50	+++	++	−	−	−	−
15	100	−	−	+	−	−	−
16	100	NT	++	+	−	+	+
17	NT	NT	NT	NT	NT	NT	NT
18	100	−	−	+	+	+	−
19	50	−	−	−	−	−	−
20	50	−	−	−	−	−	−
21	50	++++	+++	+	−	−	−
22	50	−	−	−	−	−	−
23	50	−	−	−	−	−	−
24	100	−	+++	+	++	+	−

[a] Symbols are as follows: ++++, 100% of the animals were protected; +++, 75% of the animals were protected; ++, 50% of the animals were protected; +, 25% of the animals were protected; −, no protection. In case of toxicity: ++++, 100% of the animals exhibited toxicity; +++, 75% of the animals exhibited toxicity; ++, 50% of the animals exhibited toxicity; +, 25% of the animals exhibited toxicity; −, no toxicity. [b] Toxicity. [c] Not tested.

(Table 5). Substitution of the $-NH_2$ hydrogen in TMCD by a hydroxyl group (**20**) or amino group (**22**) significantly reduced its anticonvulsant potential. Substitution of $-NH_2$ hydrogen in tetramethylcyclopropane hydrazide by tetramethylcyclopropane carbonyl (**23**) led to the formation of an absolutely inactive TMCD dimer. The final outcome of the SAR study with compounds **10**−**24** showed that only compound **21** was able to improve significantly the activity−toxicity profile of VPA.

Since taurine serves as an inhibitory amino acid in the brain, we decided to utilize the tetramethylcyclopropyl ring as a lipophilic carrier for the insertion of a taurine pharmacophore into the brain (compound **24**). Unfortunately, this compound had no anticonvulsant effect in the MES test in mice and rats (Tables 3 and 4) and was only active in the rat scMet test at 100 mg/kg (Table 5). This compound has a ClogP value of −0.88, the lowest value among the compounds **10**−**30** (Table 11), and circulates in the bloodstream in an ionized form. In contrast to VPA, which is also ionized in the blood, compound **24** probably does not have specific brain transporters and therefore is unable to penetrate the blood−brain barrier. Recently Isoherranen et al. examined the anticonvulsant activity of valproyltaurine and its amide derivatives.[50] Valproyltaurine did not

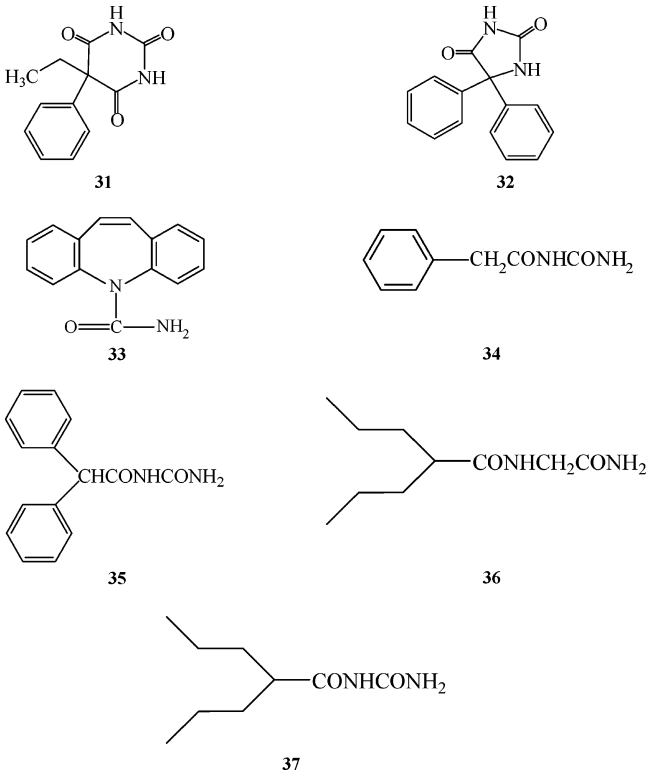


Figure 2.

show any anticonvulsant activity, whereas its monoamide, dimethylamide, and isopropylamide derivatives showed activity only in Frings audiogenic seizure susceptible mice. [50]

Urea is an integral part of the heterocyclic chemical structures of three leading AEDs: phenobarbital (**31**), phenytoin (**32**), and carbamazepine (**33**) (Figure 2). These drugs consist of two major parts: lipophilic moiety, delineated by phenylalkyl in phenobarbital, diphenyl in phenytoin, and dibenzazepine in carbamazepine; and a hydrophilic moiety, containing a ring fused urea molecule. The presence of urea in all these drugs implies that it plays an important role in the anticonvulsant pharmacophore. In 1948 Spielman et al. synthesized a series of acetylurea derivatives from which phenylacetylurea (**34**, Figure 2) emerged as the most potent anticonvulsant compound effective in grand mal and petit mal epilepsies as well as in psychomotor seizures.[51−53] However, the clinical use of this drug was limited because of the number of side effects, including hepatotoxicity and blood dyscrasias.[54,55] It is noteworthy that diphenylacetylurea (**35**, Figure 2) was so insoluble in aqueous media that it was impossible to reach effective therapeutic levels needed for a reasonable anticonvulsant effect in man,[53] while phenytoin (**32**, Figure 2), a cyclic form of diphenylacetylurea, has a satisfactory solubility and a very strong anticonvulsant effect.[56]

Zirvi et al. published data on the anticonvulsant activity of an additional group of urea derivatives in metrazol-induced seizures in mice.[18,57−59] In these studies cyclopropanecarbonylurea was not active at all and cyclobutanecarbonylurea had only marginal activity presumably because of insufficient lipophilicity of these molecules. N-alkylation on the urea moiety by propyl, *tert*-butyl, and phenyl groups increases their lipophilicity with a subsequent improvement in brain penetration and anticonvulsant activity. [18,57−59]

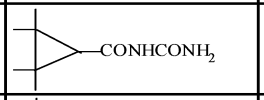
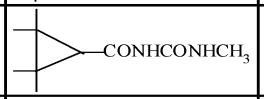
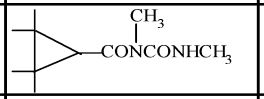
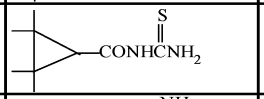
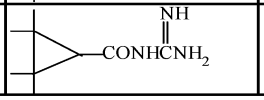
The optimal balance between lipophilic and hydrophilic moieties (optimal log *P*) is a very important issue in designing novel antiepileptic drugs. A log *P* that is too low will prevent satisfactory brain penetration, whereas one that is too high will lead to reduced absorption of the drug from the gastrointestinal tract, increased brain extraction by P-glycoproteins, and neurotoxicity.[23,30,60−62] In a survey of 257 marketed CNS drugs, it was found that for the overall beneficial behavior of these drugs an optimum log *P* value between 1 and 2 is required.[63]

In the current study several coupling products of TMCA (**8**) with urea and its derivatives (Scheme 1) were synthesized and evaluated for their anticonvulsant activity. The results of the anticonvulsant activity and toxicity of this group of compounds (**25**−**30**) are presented in Tables 6−8. Compound **25** (TMC-urea) showed excellent anticonvulsant activity in mice and rats in both MES and scMet tests. Having an ED_{50} of 29 mg/kg in the rat MES test and 92 mg/kg in the rat scMet test (Table 10), this compound was 17 and 7 times, respectively, more potent than VPA (Table 2).[56] TMC-urea had no toxic effects up to 538 mg/kg in rats, providing it a protective index of 18.5 in the MES test, which is about 12 times greater than the protective index of VPA in this test. In mice MES and scMet tests, TMC-urea was 3 and 2 times more potent than VPA,[56] respectively (Tables 1 and 9). Addition of methyl groups in TMC-urea at positions 1 and 1,3 (compounds **26**, **28**) and a dimethyl group at position 1 (compound **27**) significantly reduced its anticonvulsant activity. Compounds **26**−**28** were inactive in the mice scMet test and had only partial activity in the mice MES test. In the rat MES and scMet tests these compounds were less active than TMC-urea. The addition of a methyl group to the urea moiety may interrupt the correct spatial configuration of the anticonvulsant pharmacophore and therefore may lead to a significant reduction of anticonvulsant activity.[64]

Substitution of the carbonyl oxygen in the urea moiety in TMC-urea by a sulfur atom leads to a thiourea derivative of TMCA (**29**) with a reduction in the anticonvulsant activity and an increase in toxicity (Tables 6−8). Substitution of the carbonyl oxygen atom in the TMC-urea by the NH group produces TMC-imino urea (**30**), a highly toxic compound with only slight anticonvulsant activity in mice (Table 6).

A comparison of the antiepileptic potencies in mice and rats (Tables 6−8) obtained with TMC-urea (**25**), containing the tetramethylcyclopropane ring in its structure, versus reported activities of cyclopropane- and cyclobutanecarbonylureas[18,57−59] emphasizes the importance of the right degree of lipophilicity (among other factors) for better anticonvulsant activity. TMC-urea has a much better anticonvulsant profile than TMC-glycinamide (**6**, Figure 1), in which a methylene group of the glycine moiety increases the intramolecular distance between two carbonyl oxygens. The same pattern is also observed in a comparison of anticonvulsant activities between valproylglycinamide (**36**, Figure 2)[46] and valproylurea (**37**, Figure 2).[38] Having a shorter side chain, **37** possesses better anticonvulsant activity

Table 6. Anticonvulsant Activity and Toxicity of Compounds **25**−**30** Administered Intraperitoneally to Mice

Compd	Structure	Dose (mg/kg)	MES[a] 0.5 h[d]	MES[a] 4 h	scMet[b] 0.5 h	scMet[b] 4 h	Tox[c] 0.5 h	Tox[c] 4 h
25		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	3/5	0/4	1/2
26		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	1/1	0/1	0/1	4/4	0/2
27		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	3/4	0/2
28		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	0/1	0/1	0/1	3/4	0/2
29		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	2/3	3/3	0/1	0/1	0/8	3/4
		300	1/1	1/1	0/1	0/1	4/4	2/2
30		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	NT[e]	NT	7/8	4/4
		300	1/1	1/1	NT	NT	4/4	2/2

[a] Maximal electroshock test (number of animals protected/number of animals tested). [b] Subcutaneous metrazol test (number of animals protected/number of animals tested). [c] Toxicity (number of animals exhibiting toxicity/number of animals tested). [d] Time after drug administration. [e] Not tested.

Table 7. Anticonvulsant [Anti-MES] Activity and Toxicity of Compounds **25**−**30** Administered Orally to Rats[a]

Compd	Dose (mg/kg)	Times after drug administration 15 min	30 min	1 h	2 h	4 h	Tox[b]
25	30	+	++	+++	++++	+	−
26	50	++	+	−	++	+	−
27	50	−	++	+	+++	−	−
28	80	+	−	+	+	+	−
29	30	+	−	+	+	−	−
30	NT[c]	NT	NT	NT	NT	NT	NT

[a] Symbols are as follows: ++++, 100% of the animals were protected; +++, 75% of the animals were protected; ++, 50% of the animals were protected; +, 25% of the animals were protected; −, no protection. In case of toxicity: ++++, 100% of the animals exhibited toxicity; +++, 75% of the animals exhibited toxicity; ++, 50% of the animals exhibited toxicity; +, 25% of the animals exhibited toxicity; −, no toxicity. [b] Toxicity. [c] Not tested.

Table 8. Anticonvulsant [Anti-scMet] Activity and Toxicity of Compounds **25**−**30** Administered Orally to Rats[a]

Compd	Dose (mg/kg)	Times after drug administration 15 min	30 min	1 h	2 h	4 h	Tox[b]
25	50	+++	++	−	−	−	−
26	100	+	−	+	+	−	−
27	125	NT[c]	++	NT	NT	NT	−
28	100	−	−	NT	NT	NT	−
29	100	−	++	−	++	−	++++
30	NT	NT	NT	NT	NT	NT	NT

[a] Symbols are as follows: ++++, 100% of the animals were protected; +++, 75% of the animals were protected; ++, 50% of the animals were protected; +, 25% of the animals were protected; −, no protection. In case of toxicity: ++++, 100% of the animals exhibited toxicity; +++, 75% of the animals exhibited toxicity; ++, 50% of the animals exhibited toxicity; +, 25% of the animals exhibited toxicity; −, no toxicity. [b] Toxicity. [c] Not tested.

than **36** in both MES and scMet tests in mice, which is associated with greater protective indexes.

Conclusions

We have reported here on a novel class of anticonvulsant amides obtained by attaching the tetramethylcyclopropanecarbonyl ring to alkylamino, hydroxyalkylamino, hydroxylamino, hydrazino groups, and urea and its derivatives and analogues. In the amide and alkylamide series, *N*-methoxy TMCD (**21**) was the most active compound with an anticonvulsant potency 18.5 times greater than that of VPA in the rat scMet test. The most active compound in the series of urea derivatives was TMC-urea (**25**) with a protective index of 18.5

Table 9. Quantitative Anticonvulsant Data in Mice Dosed Intraperitoneally

Compd	MES[a] (ED_{50},mg/kg)	scMet[b] (ED_{50},mg/kg)	Tox[c] (TD_{50},mg/kg)	PI (MES)[d]	PI (scMet)[e]
21	115 (103-126)[f]	74 (64-83)	166 (152-183)	1.4	2.2
25	90 (83-96)	125 (93-175)	168 (146-202)	1.9	1.6

[a] Maximal electroshock test. [b] Subcutaneous metrazol test. [c] Toxicity. [d] Protective index (TD_{50}/ED_{50} ratio) in the MES test. [e] Protective index in the scMet test. [f] The interval in parentheses stands for 95% confidence interval.

Table 10. Quantitative Anticonvulsant Data in Rats Dosed Orally

Compd	MES[a] (ED_{50},mg/kg)	scMet[b] (ED_{50},mg/kg)	Tox[c] (TD_{50},mg/kg)	PI (MES)[d]	PI (scMet)[e]
21	108 (90-131)[f]	35 (16-54)	333 (290-424)	3.1	9.5
25	29 (18-47)	92 (50-151)	538 (437-664)	18.5	5.9

[a] Maximal electroshock test. [b] Subcutaneous metrazol test. [c] Toxicity. [d] Protective index (TD_{50}/ED_{50} ratio) in the MES test. [e] Protective index in the scMet test. [f] The interval in parentheses stands for 95% confidence interval.

Table 11. Lipophilicity Data (ClogP) of the Investigated Compounds

Compound	ClogP	Compound	ClogP
1	2.75	18	1.78
4	1.38	19	1.29
5	1.84	20	1.25
6	0.38	21	2.08
7	0.55	22	1.01
8	2.63	23	3.49
10	2.33	24	-0.88
11	2.64	25	1.53
12	2.05	26	2.00
13	2.27	27	2.21
14	0.87	28	2.21
15	1.08	29	1.85
16	1.57	30	0.85
17	1.29		

in the rat MES test, which is about 12 times greater than that of VPA (Table 2).[56] In these potent CNS-active VPA analogues, the tetramethylcyclopropyl moiety possesses two tertiary carbons in the β-position to the carbonyl group, avoiding the formation of metabolites with the terminal double bond analogous to hepatotoxic 4-ene-VPA and 2,4-diene-VPA.[10−13] *N*-Methoxy TMCD (**21**) and TMC-urea (**25**) are much more potent compounds with a much wider safety margin than VPA. Since existing AEDs cause a series of severe side effects and fail to control seizures in about 30% of epileptic patients, the advantages offered by *N*-methoxy TMCD and TMC-urea make these compounds potential candidates to become new, vitally needed, potent, and safe antiepileptic drugs.

Experimental Section

Chemicals, Materials, and Methods. All reagents were purchased from Sigma-Aldrich with the exception of TMC-Cl, which was prepared from TMCA by a method described in the literature.[48] Product formation follow-up was performed by means of GC/MS and TLC techniques. TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F_{254}, Merck). Gas chromatography−mass spectroscopy assay was performed on an HP5890 series II GC equipped with a Hewlett-Packard MS engine (HP5989A) single quadrupole MS spectrometer, HP7673 autosampler, HP MS-DOS Chemstation, and HP-5MS capillary column (0.25 μm × 15 m × 0.25 mm). The temperature program was as follows: injector temperature, 180 °C; initial temperature, 60 °C for 3 min; gradient of 20 °C/min until 140 °C; gradient of 10 °C until 190 °C; hold time, 3 min. The MS parameters were set as follows: source temperature, 180 °C; transfer line, 280 °C; positive ion monitoring, EI-MS (70 eV). The molecular ion and five most pronounced ions with their relative abundances are provided.

The chemical structure and purity of the newly synthesized compounds were assessed by TLC, GC/MS, NMR, and elemental analysis. Melting points were determined on a Buchi 530 capillary melting point apparatus. ^{1}H NMR spectra were recorded on a Varian Mercury series NMR 300 spectrometer. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the indicated reference. Coupling constants (J values) are given in hertz (Hz). Elemental analyses were performed on a 2400-2 Perkin-Elmer C, H, N analyzer. C, H, N analyses of all newly synthesized compounds had satisfactory results (within ±0.4 of theoretical values).

General Procedure for the Synthesis of Compounds 10−23. TMC-Cl **9** (3 g, 19 mmol) dissolved in dry dichloromethane (30 mL) was slowly added to a stirred cooled solution of suitable amine (23 mmol) and triethylamine (3.8 g, 38 mmol) in dry dichloromethane (100 mL). After addition, the reaction mixture was stirred for 3 h at room temperature. Then the organic solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (100 mL) and washed three times with 10 mL of distilled water. The organic fraction was dried over $MgSO_4$, filtered, and evaporated.

The obtained products were purified by crystallization using an ethyl acetate/petroleum ether mixture (1:3) or chloroform/hexane mixture (1:3). The reactions yields were around 90%.

***N*-Ethyl-2,2,3,3-tetramethylcyclopropane Carboxamide (10).** White needles. Mp 81−82 °C. MS-EI, *m*/*z* (%): 169 (M^+, 5), 154 (88), 111 (21), 97(56), 83 (65), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.81 (s, 1H), 1.10 (t, J = 7.2, 9H), 1.26 (s, 6H), 3.23−3.32 (m, 2H), 5.33 (br s, 1H). 5.78 (br s, 1H). Anal. ($C_{10}H_{19}NO$) C, H, N.

***N*-Cyclopropyl-2,2,3,3-tetramethylcyclopropane Carboxamide (11).** White needles. Mp 96 °C. MS-EI, *m*/*z* (%): 181 (M^+, 4), 166 (23), 125 (100), 97(21), 83 (23), 55 (82). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.46 (br s, 2H), 0.72−0.75

(dd, $J_1 = 1.8$, $J_2 = 2.1$, 3H), 1.13 (s, 6H), 1.25 (s, 6H), 2.64−2.69 (m, 1H), 5.53 (br s, 1H). Anal. ($C_{11}H_{19}NO$) C, H, N.

***N,N*-Dimethyl-2,2,3,3-tetramethylcyclopropane Carboxamide (12).** Oil. MS-EI, *m/z* (%): 169 (M^+, 3), 154 (100), 96 (80), 83 (28), 72 (55), 55 (53). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.05 (s, 1H), 1.15 (s, 12H), 2.91 (s, 3H), 3.02 (s, 3H). Anal. ($C_{10}H_{19}NO$) C, H, N.

***N*-(2-Fluoroethyl)-2,2,3,3-tetramethylcyclopropane Carboxamide (13).** White needles. Mp 58 °C. MS-EI, *m/z* (%): 187 (M^+, 5), 129 (34), 97 (63), 83 (55), 69 (22), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.87 (s, 1H), 1.17 (s, 6H), 1.26 (s, 6H), 3.48−3.53 (q, $J = 5.7$, 1H), 3.58−3.63 (q, $J = 5.1$, 1H), 4.41 (t, $J = 5.1$, 1H), 4.56 (t, $J = 4.5$, 1H), 5.78 (br s, 1H). Anal. ($C_{10}H_{18}NOF$) C, H, N.

***N*-(2-Hydroxyethyl)-2,2,3,3-tetramethylcyclopropane Carboxamide (14).** White crystals. Mp 94 °C. MS-EI, *m/z* (%): 185 (M^+, 4), 170 (59), 125 (16), 97 (59), 83 (82), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.88 (s, 1H), 1.16 (s, 6H), 1.26 (s, 6H), 2.87 (br s, 1H), 3.38−3.43 (m, 2H), 3.70 (t, $J = 6$, 2H), 3.89 (br s, 1H), 5.91 (br s, 1H). Anal. ($C_{10}H_{19}NO_2$) C, H, N.

***N*-Methyl-*N*-2-hydroxyethyl-2,2,3,3-tetramethylcyclopropane Carboxamide (15).** White crystals. Mp 50 °C. MS-EI, *m/z* (%): 199 (M^+, 1), 184 (100), 125 (41), 96 (55), 83 (67), 55 (90). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.10 (s, 1H), 1.80 (d, $J = 4.5$, 12H), 3.08 (s, 3H), 3.39 (br s, 1H), 3.53 (t, $J = 3.6$, 2H), 3.73−3.77 (q, $J = 4.8$, 2H). Anal. ($C_{11}H_{21}NO_2$) C, H, N.

***N*-Ethyl-*N*-2-hydroxyethyl-2,2,3,3-tetramethylcyclopropane Carboxamide (16):** White crystals. Mp 30−31 °C. MS-EI, *m/z* (%): 213 (M^+, 2), 198 (100), 125 (59), 97 (24), 83 (69), 55 (87). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.08 (s, 1H), 1.18 (br s, 15H), 3.39−3.45 (q, $J = 7.2$, 2H), 3.49 (t, $J = 6.0$, 2H), 3.73 (t, $J = 5.1$, 2H), 3.96 (br s, 1H). Anal. ($C_{12}H_{23}NO_2$) C, H, N.

***N*-(2-Hydroxy-1-methylethyl)-2,2,3,3-tetramethylcyclopropane Carboxamide (17).** White crystals. Mp 110−111 °C. MS-EI, *m/z* (%): 199 (M^+, 2), 184 (37), 125 (30), 97 (45), 83 (78), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.86 (s, 1H), 1.17 (t, $J = 3.6$, 9H), 1.25 (s, 6H), 3.16 (s, 1H), 3.46−3.53 (m, 1H), 3.63−3.67 (t, $J = 6.0$, 1H), 4.02−4.10 (m, 1H), 5.55 (br s, 1H). Anal. ($C_{11}H_{21}NO_2$) C, H, N.

***N*-(1-Hydroxymethyl)propyl-2,2,3,3-tetramethylcyclopropane Carboxamide (18).** White needles. Mp 94 °C. MS-EI, *m/z* (%): 213 (M^+, 2), 198 (27), 125 (30), 97 (34), 83 (58), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.89 (s, 1H), 0.96 (t, $J = 7.5$, 3H), 1.16 (s, 6H), 1.25 (s, 6H), 1.41−1.58 (m, 2H), 2.86−2.89 (q, $J = 4.8$, 1H), 3.52−3.59 (m, 1H), 3.66−3.72 (m, 1H), 3.82−3.88 (m, 1H), 5.52 (br s, 1H). Anal. ($C_{12}H_{23}NO_2$) C, H, N.

***N*-(2-Hydroxypropyl)-2,2,3,3-tetramethylcyclopropane Carboxamide (19).** White crystals. Mp 81−82 °C. MS-EI, *m/z* (%): 199 (M^+, 4), 184 (46), 125 (30), 97 (66), 83 (84), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.16 (br d, $J =$ 28, 15H), 1.59 (s, 1H), 3.06−3.15 (m, 1H), 3.37−3.45 (m, 1H), 3.89 (br s, 1H), 5.91 (br s, 1H). Anal. ($C_{11}H_{21}NO_2$) C, H, N.

2,2,3,3-Tetramethylcyclopropanecarbonylhydroxamic Acid (20). White crystals. Mp 110 °C. MS-EI, *m/z* (%): 157 (M^+, 0.4), 125 (61), 108 (28), 97(18), 83 (25), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.87 (s, 1H), 1.17−1.27 (d, J = 28, 12H), 7.97 (br s, 2H). Anal. ($C_8H_{15}NO_2$) C, H, N.

***N*-Methoxy-2,2,3,3-tetramethylcyclopropane Carboxamide (21).** White wool-like material. Mp 78 °C. MS-EI, *m/z* (%): 171 (M^+, 0.6), 156 (21), 125 (98), 97(17), 83 (22), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.18 (s, 6H), 1.28 (s, 7H), 3,74 (s, 3H), 7.84 (br s, 1H). Anal. ($C_9H_{17}NO_2$) C, H, N.

2,2,3,3-Tetramethylcyclopropanecarboxylic Acid Hydrazide (22). White needles. Mp 102−104 °C. MS-EI, *m/z* (%): 156 (M^+, 1), 125 (90), 97 (12), 83 (14), 69 (22), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.78 (s, 1H), 1.16 (s, 6H), 1.27 (s, 6H), 3.85 (s, 2H), 6.64 (br s, 1H). Anal. ($C_8H_{16}N_2O$) C, H, N.

***N,N*-Di-2,2,3,3-tetramethylcyclopropanecarboxylic Acid Hydrazide (23).** For the synthesis of this compound, double quantity of **9** was utilized. White needles. Mp 248 °C. MS-EI, *m/z* (%): 280 (M^+, 1), 125 (100), 97 (8), 83 (8), 69 (7), 55 (33). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.89 (s, 2H), 1.16 (s, 11H), 1.26 (s, 11H), 1.56 (s, 2H), 8.08 (br s, 2H). Anal. ($C_{16}H_{28}N_2O_2$) C, H, N.

Synthesis of 2,2,3,3-Tetramethylcyclopropanecarbonyltaurine (24). 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ, 2.4 g, 9.8 mmol) was added to a stirred ethanol solution (100 mL) of TMCA **8**. After 30 min, taurine (880 mg, 7 mmol) dissolved in aqueous NaOH (1:1) was added in one portion. The reaction mixture was stirred for 24 h at 40 °C. At the end of the reaction, ethanol was evaporated under vacuum and the residue was dissolved in water and extracted several times with ethyl acetate. The aqueous fraction evaporated, and the residue was crystallized from methanol/diethyl ether (1:3) or ethanol/diethyl ether (1:3) mixtures. White crystals. Yield: 35%. Mp 270−271 °C. ^{1}H NMR (300 MHz, δ D_2O): 0.99 (s, 13H), 2.90 (t, $J = 6.9$, 2H), 3.39 (t, $J = 6.9$, 2H). Anal. ($C_{10}H_{18}NO_4SNa$) C, H, N.

General Procedure for the Synthesis of Compounds 25−29. TMC-Cl **9** (3 g, 19 mmol) dissolved in dry acetonitrile (30 mL) was slowly added to the dry, stirred, boiling acetonitrile (100 mL) solution of the suitable urea derivative (47.5 mmol). After addition, the reaction mixture was refluxed for 2 h. Then the organic solvent was evaporated under vacuum and the products were dissolved in ethyl acetate (100 mL) and washed three times with 10 mL of distilled water. The organic fraction was dried over $MgSO_4$, filtered, and evaporated. The products were purified by crystallization using an ethyl acetate/petroleum ether mixture (1:3).

2,2,3,3-Tetramethylcyclopropanecarbonylurea (25). White crystals. Yield: 92%. Mp 194 °C. MS-EI, *m/z* (%): 184 (M^+, 2), 126 (40), 97 (57), 82 (48), 69 (19), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.21−1.27 (d, $J = 18$, 12H), 1,57 (s, 1H), 5.16 (br s, 1H), 8.23 (br s, 2H). Anal. ($C_9H_{16}N_2O_2$) C, H, N.

1-*N*-Methyl-2,2,3,3-tetramethylcyclopropanecarbonylurea (26). White crystals. Yield: 85%. Mp 92 °C. MS-EI, *m/z* (%): 184 ($M^+ - 14$, 2), 140 (58), 114 (69), 96 (86), 83 (35), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.21 (s, 12H), 1.28 (s, 1H), 3.26−3.31 (m, 3H), 5.18 (br s, 1H), 8.89 (br s, 1H). Anal. ($C_{10}H_{18}N_2O_2$) C, H, N.

***N,N*-(1,1-Dimethyl)-2,2,3,3-tetramethylcyclopropanecarbonylurea (27).** White crystals. Yield: 95%. Mp 105 °C. MS-EI, *m/z* (%): 213 ($M^+ + 1$, 3), 125 (32), 109 (41), 96 (70), 82 (68), 55 (100). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.22 (d, $J = 13.5$, 12H), 1.81 (s, 1H), 2.97 (s, 6H), 7.56 (br s, 1H). Anal. ($C_{11}H_{20}N_2O_2$) C, H, N.

***N,N*-(1,3-Dimethyl)-2,2,3,3-tetramethylcyclopropanecarbonylurea (28).** White crystals. Yield: 92%. Mp 55−56 °C. MS-EI, *m/z* (%): 212 (M^+, 0.2), 128 (59), 96 (100), 83 (20), 69 (12), 55 (63). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.20 (d, $J = 7.5$, 12H), 1.28 (s, 1H), 2.83−2.87 (m, 3H), 3.29 (q, $J =$ 0.6, 3H), 9.13 (br s, 1H). Anal. ($C_{11}H_{20}N_2O_2$) C, H, N.

2,2,3,3-Tetramethylcyclopropanecarbonylthiourea (29). White crystals. Yield: 93%. Mp 158 °C. MS-EI, *m/z* (%): 200 (M^+, 5), 125 (30), 116 (100), 97 (11), 83 (16), 55 (68). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.22 (d, $J = 11.5$, 12H), 1.55 (s, 1H), 6.87 (br s, 1H), 8.59 (br s, 1H), 9.90 (br s, 1H). Anal. ($C_9H_{16}N_2O_2S$) C, H, N.

Synthesis of 2,2,3,3-Tetramethylcyclopropanecarbonylguanidine (30). TMC-Cl **9** (4 g, 25 mmol) dissolved in dry acetonitrile (120 mL) was slowly added to stirred, cooled acetonitrile solution (150 mL) of guanidine hydrochloride (2.6 g, 27.5 mmol) and aqueous 2 N NaOH (27.5 mL, 55 mmol). After addition, the reaction mixture was stirred for 2 h at room temperature. The acetonitrile fraction was separated by filtration and evaporated to dryness under vacuum. The residue was dissolved in ethyl acetate (100 mL), dried over $MgSO_4$, filtered, and evaporated. The product was purified by crystallization from ethyl acetate/petroleum ether mixture (1:3). White crystals. Yield: 52%. Mp 178 °C. MS-EI, *m/z* (%): 183 (M^+, 0.5), 100 (44), 86 (100), 69 (18), 58 (19), 55 (24). ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.02−1.09 (br t, $J = 10.8$, 13H), 4.06 (br s, 4H). Anal. ($C_9H_{17}N_3O$) C, H, N.

Biological Testing. The evaluation of anticonvulsant activity in the maximal electroshock seizure test (MES) and subcutaneous metrazol seizure threshold test (scMet) and the determination of toxicity in the rotorod test, positional sense test, and others were performed at the NIH Epilepsy Branch as a part of Anticonvulsant Drug Development Program according to the protocols described in the ref 56.

Preparation of the Compounds for Testing. Regardless of their water solubility, all compounds were either dissolved or suspended in 0.5% methylcellulose. The tested compounds were given in a concentration that permits optimal accuracy of dosage without the volume contributing excessively to total body fluid. Thus, the volume used in mice was 0.01 mL per gram of body weight, and in rats, it was 0.04 mL per 10 g of body weight.

Calculation of ClogP. ClogP was calculated by means of EPI Suite V3.11 software provided on-line by Syracuse Research Corporation.

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Supporting Information Available: Elemental analysis results for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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