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ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 6297–6305
Bioorganic & Medicinal Chemistry

Synthesis and anticonvulsant activity of aromatic tetramethylcyclopropanecarboxamide derivatives

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Received 22 November 2007; revised 12 March 2008; accepted 20 March 2008
Available online 23 March 2008

Abstract—As part of our ongoing research on potential new antiepileptic drugs (AEDs), a series of tetramethylcyclopropanecarboxamide derivatives containing benzene ring were designed, synthesized, and evaluated for anticonvulsant activities in the murine maximal electroshock (MES) and subcutaneous pentylenetetrazole (scMet) seizure tests. The most potent compound emerging from this study was *N*-(2,2,3,3-tetramethylcyclopropanecarboxamide)-*p*-phenyl-sulfonamide (**21**), possessing an ED_{50} value of 26 mg/kg in the rat-MES test and a remarkable PI (PI = TD_{50}/ED_{50}) value above 19. The better anticonvulsant potency of compound **21** and its wider safety margin compared to valproic acid (VPA) and zonisamide make it a potential candidate to become a new AED second-generation to VPA.

1. Introduction

Epilepsy is one of the most common neurological conditions, occurring in about 1% of the global population.[1] Valproic acid (VPA, Fig. 1) is a major antiepileptic drug (AED) in the treatment of epilepsy and is also approved for the treatment of bipolar disorder, migraine prophylaxis, and neuropathic pain.[1–4] Nevertheless, VPA's clinical use is limited by two life-threatening side effects: teratogenicity and hepatotoxicity.[5–9] Since several of the currently available AEDs have been associated with severe side effects and fail to control seizures in about 30% of epileptic patients, there is a substantial need for the development of new, more effective and less toxic AEDs.[10]

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

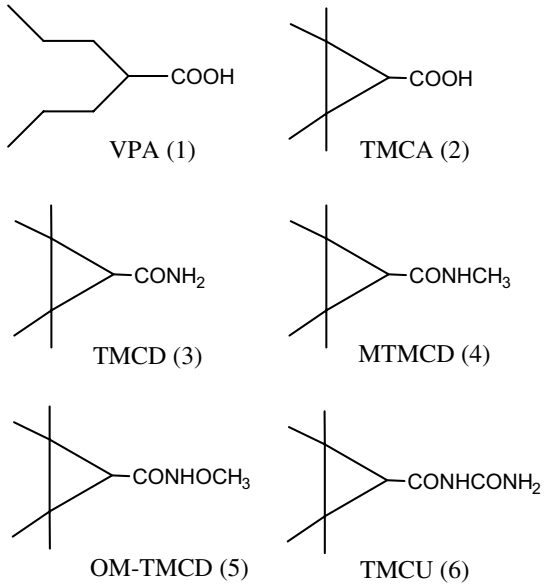

Figure 1. Chemical structures of VPA, TMCA, TMCD, MTMCD, OM-TMCD, and TMCU.

Keywords: 2,2,3,3-Tetramethylcyclopropanecarboxylic acid; Valproic acid; Phenyl-alkyl-amines; Sulfonamides; Anticonvulsants; Structure–activity relationships; Maximal electroshock seizure test; Subcutaneous pentylenetetrazole seizure test.
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0968-0896/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2008.03.051

adverse effects associated with VPA use.[11,12] 2,2,3,3-Tetramethylcyclopropanecarboxylic acid (TMCA, **2**, Fig. 1) is a cyclic analogue of VPA displaying weak anticonvulsant activity. Unlike VPA, the presence of two quaternary carbons in the TMCA structure at the β-position to the carbonyl group prevents the formation of hepatotoxic metabolites with a terminal double bond, analogous to 4-ene-VPA.[8,9] As part of our ongoing research program we have synthesized and evaluated the anticonvulsant activity of several coupling products of TMCA with urea and its *N*-alkyl derivatives as well as thiourea and iminourea.[13] The most active compound in this series was 2,2,3,3-tetramethylcyclopropanecarbonylurea (TMCU, **6**, Fig. 1), being 17 and 7 times more potent than VPA in the rat maximal electroshock seizure (MES) and the subcutaneous pentylenetetrazole seizure (scMet) tests, respectively.

In the early seventies, Bentoit-Guyod et al., studied the anticonvulsant structure–activity relationship (SAR) of a large series of aromatic VPA amide derivatives.[14,15] Some of the compounds (e.g., di-*n*-propylacetyl-(2-chloro-5-trifluoromethyl)-anilide), demonstrated remarkable antipyretic and analgesic properties, although none of them showed superior anticonvulsant activity and safety margin compared to VPA. Recently, Netzeva et al. showed that an improvement of VPA's pharmacological profile can be achieved by coupling VPA to certain aromatic amino alkanes.[16] An extensive SAR of various aromatic and heteroaromatic sulfonamide derivatives of VPA demonstrated the influence of the sulfonamide group on the anticonvulsant activity of these VPA derivatives.[17] Zonisamide and acetazolamide are currently used AEDs, containing a sulfonamide group in their structure.[1]

In the current study, we explored the anticonvulsant activity and safety margin of a series of TMCD derivatives containing benzene ring in their structure, in the MES and scMet tests, in order to investigate if some of these compounds might become new AED candidates.[18,19]

2. Results and discussion

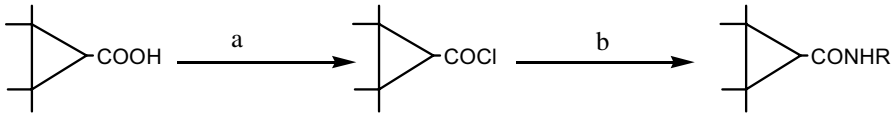
2.1. Synthesis

TMCA served as the starting material for the synthesis of all aromatic tetramethylcyclopropanecarboxamide derivatives (**2**, Scheme 1). It was converted by thionylchloride to the corresponding acyl chloride (TMC-Cl) by a method described in the literature.[20] The compounds presented in Table 1, except **21**–**23**, were synthesized by coupling at room temperature of TMC-Cl with the suitable amines in dichloromethane.[21] The products were purified by crystallization from ethylacetate/petroleum ether. Their structures were identified by ^{1}H NMR and their purity established by thin-layer chromatography and elemental analyses.

Compounds **21**–**23** were prepared by coupling at room temperature TMC-Cl with the suitable para amino sulfanylamides in acetone. Subsequently, the product was purified and identified as described above.

2.2. Pharmacology

Since VPA has multiple mechanisms of action and the specific mechanism primarily responsible for the antiepileptic activity in patients is still unknown, a mechanistic approach to develop new second-generation VPA drugs



2 **7-23**

7 R= C_6H_5

8 R= $CH_2C_6H_5$

9 R= $CH_2CH_2C_6H_5$

10 R= $CH_2CH_2CH_2C_6H_5$

11 R= $CH(CH_3)C_6H_5$

12 R= $CH_2CH(CH_3)C_6H_5$

13 R= N-$(CH_3)CH(CH_3)CH(OH)C_6H_5$

14 R= $CH(CH_3)CH_2OC_6H_3$(1,5-dimethyl)

15 R= C_6H_4(4-acetyl)

16 R= $CH_2C_6H_4$(2-Cl)

17 R= $CH_2C_6H_4$(4-F)

18 R= $CONHC_6H_5$

19 R= CH_2CH_2(1H-indole)

20 R= C_6H_2(3-chloro,4,6- SO_2NH_2)

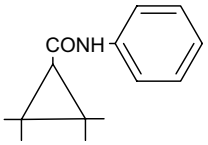
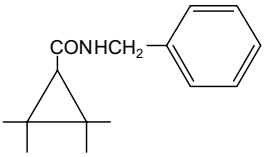
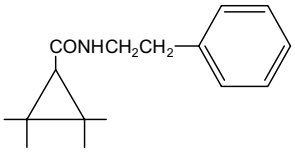
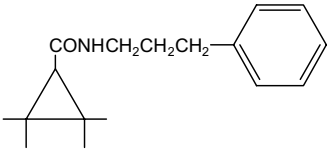
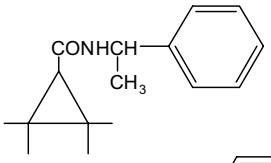
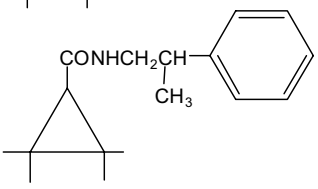
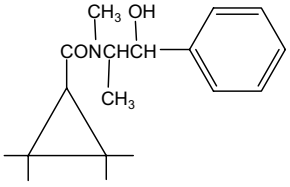
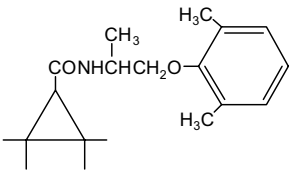
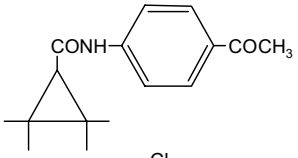
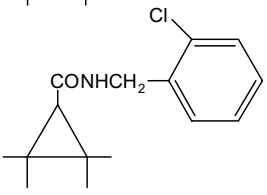
21 R= C_6H_4(4-SO_2NH_2)

22 R= $CH_2C_6H_4$(4-SO_2NH_2)

23 R= $CH_2CH_2C_6H_4$(4-SO_2NH_2)

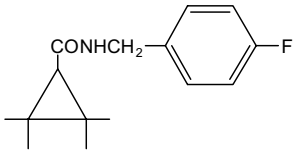
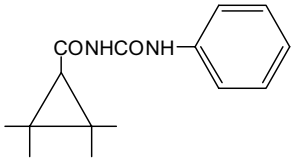
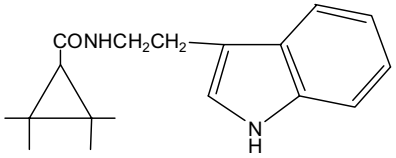
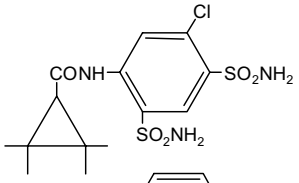
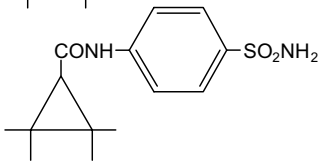
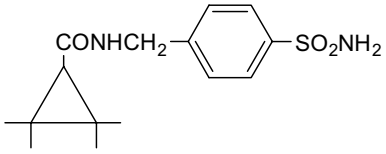
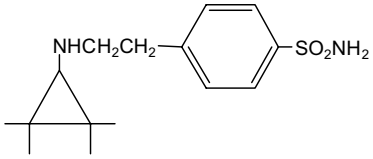
Scheme 1. Synthetic route for aromatic TMCD derivatives. Reagents and conditions: (a) $SOCl_2$, dichloromethane, rt, 8 h; (b) for compounds **7**–**21** and **23**, dichloromethane, suitable amines, triethylamine, rt, 2–12 h; for compound **22**, acetone, benzenesulfonamide, pyridine, rt, 12 h.

Table 1. Anticonvulsant activity and neurotoxicity of compounds **7**–**23** in the MES model following ip administration to mice[a]

Compound		Dose (mg/kg)	Times after drug administration			Tox.[b]
			0.5 h	2 h	4 h	
7		300	—[c]	NT[d]	—	3/4
8		300	1/1	NT	—	3/4
9		300	—	NT	—	1/4
10		300	—	NT	—	—
11		300	—	NT	—	3/4
12		300	—	NT	—	2/4
13		300	—	NT	—	3/4
14		300	—	NT	—	—
15		300	—	NT	1/1	—
16		300	—	NT	—	—

(*continued on next page*)

Table 1 (*continued*)

Compound		Dose (mg/kg)	Times after drug administration			Tox.[b]
			0.5 h	2 h	4 h	
17		300	—	NT	—	—
18		300	—	NT	—	—
19		300	—	NT	—	—
20		300	—	NT	—	—
21		100	—	3/3	2/3	—
22		100	—	1/3	1/3	—
23		300	—	NT	—	—

[a] Anticonvulsant activity expressed as the ratio between the number of animals protected and the number of animals tested.
[b] Toxicity.
[c] Not active.
[d] Not tested.

might be impracticable. Current development of new CNS-active VPA derivatives and analogues is based on pharmacokinetic- or pharmacodynamic-based structural modifications of the VPA molecule utilizing anticonvulsant animal models that have gained a reputation for their predictability since the discovery of phenytoin.[22,23] Rational design of second-generation to VPA molecules is applicable to the development of non-teratogenic and non-hepatotoxic follow-up compounds to VPA. The amide derivatives of TMCA are attractive lead compounds for the development of non-teratogenic and non-hepatotoxic second-generation to VPA CNS drugs, since no terminal double bond could be formed during the metabolism of these molecules. Recently, four new potent anticonvulsant amide derivatives of TMCA, namely 2,2,3,3-tetramethylcyclopropanecarboxamide (TMCD, **3**), *N*-methyl-TMCD (MTMCD, **4**), *N*-methoxy-TMCD (OM-TMCD, **5**), and TMCU (**6**) have been synthesized in our laboratory (Fig. 1).[13,21] TMCD was active only in the scMet test, while, MTMCD, OM-TMCD, and TMCU showed better anticonvulsant potency than VPA in the MES and scMet animal models tested along with improved protective indexes.[13,21] In rats, TMCU emerged as the most potent compound in the MES test (ED_{50} = 29 mg/kg) with a protective-index (PI = TD_{50}/ED_{50}) 12 times larger than that of VPA. In the scMet test OM-TMCD exhibited the highest potency and safety margin (ED_{50} = 35 mg/kg and PI = 10).[13]

In this study, we synthesized a series of TMCD aromatic derivatives with various branched and non-branched alkyl and alkoxy groups attached to a phenyl ring with various substituents (Scheme 1 and Table 1).

As shown in Table 1, 2,2,3,3-tetramethylcyclopropanecarbonylbenzylamide (**8**) and 2,2,3,3-tetramethylcyclopropanecarbonyl-(4-acetylphenyl)-amide (**15**) were active in the mice MES test only at the highest dose tested (300 mg/kg). In the mice scMet test compound **8** and 2,2,3,3-tetramethylcyclopropanecarbonylphenylethylamide (**9**) provided full protection against the clonic seizures only at 300 mg/kg (Table 2). Netzeva et al. showed that the VPA analogues of both compounds **15** and **9** displayed remarkable anticonvulsant activity in the mice scMet test.[16] Thus, replacing the VPA moiety with TMCA in these derivatives, resulted in a loss of activity in the scMet test (Table 2). Similarly, valproylbenzylamide, the VPA analogue of **8**, previously synthesized in our laboratory, displayed excellent anticonvulsant activity in the scMet test with 50% of the animals protected at 100 mg/kg, whereas compound **8** demonstrated a significant drop in the anticonvulsant activity in the scMet test (Table 2). The same phenomenon was also observed for 2,2,3,3-tetramethylcyclopropanecarbonyl-(2-methyl-2-phenylethyl)-amide (**12**), in which the replacement of the VPA moiety with TMCA, resulted in a diminished anticonvulsant activity in the scMet test (Table 2).[16]

Branching or increasing of the number of carbon atoms beyond two in the alkyl chain connecting the phenyl with the amine group (e.g. Compounds **10**–**13**) resulted in lack of activity in the MES test (Table 1). However, the corresponding VPA analogues reported by Netzeva, showed enhanced anticonvulsant activity in the scMet test.[16]

Some commercially available drugs that possess anticonvulsant activity in the MES and scMet tests, are utilized clinically outside of epilepsy.[24,25] Mexiletine, 1-(2,6-dimethylphenoxy)-2-propanolamine used in the treatment of arrhythmias, showed potent anticonvulsant activity in the mice MES test (ED_{50} = 10 mg/kg).[25] However, coupling mexiletine with TMCA leads to an amide (**14**) with a significantly reduced anticonvulsant activity (Tables 1 and 2). Although, TMCU is very active in the MES and scMet tests,[13] the coupling product between phenylurea and TMCA (compound **18**) failed to yield a potent TMCD aromatic derivative (Tables 1 and 2). Ortho-chloro and para-fluoro derivatives of compound **8**, yielded compounds **16** and **17** that exhibited reduced anticonvulsant activity compared to **8** (Tables 1 and 2).

Several currently available AEDs (e.g., acetazolamide, zonisamide, and topiramate) contain sulfonamide or sulfamate groups in their chemical structures (Fig. 2).[17] Masereel et al. extensively explored the SAR of numerous aromatic and heterocyclic sulfonamide derivatives of the corresponding amide of VPA, valpromide (VPD), aiming to develop new VPA analogous and derivatives with improved anticonvulsant profile.[17] They found that 5-valproylamide-1,3,4-thiadiazole-2-sulfonamide, displayed excellent anticonvulsant activity in the mice MES test with improved PI-index in comparison to VPA.[17] Another aromatic sulfonamide derivative of VPD, 4-(valproylamide)-benzyl sulfonamide (the VPA analogue of compound **22**) has been found to be a potent anticonvulsant in mice (MES-ED_{50} = 16 mg/kg, PI > 19).[26]

The compound *N*-(2,2,3,3-tetramethylcyclopropanecarboxamide)-*p*-phenylsulfonamide (**21**) displayed excellent anticonvulsant activity in the MES test at 100 mg/kg and a wide safety margin (Table 1), however no anti-

Table 2. Anticonvulsant activity and neurotoxicity of compounds **7**–**23** in the scMet model following ip administration to mice[a]

Compound	Dose (mg/kg)	Times after drug administration		Tox.[b]
		0.5 h	4 h	
7	300	—[c]	—	—
8	300	1/1	—	3/4
9	300	1/1	—	1/4
10	300	—	—	—
11	300	—	—	3/4
12	300	—	—	2/4
13	300	—	—	3/4
14	300	—	—	—
15	300	—	—	—
16	300	—	—	—
17	300	—	—	—
18	300	—	—	—
19	300	—	—	—
20	300	—	—	—
21	300	—	—	—
22	300	—	—	—
23	300	—	—	—

[a] Anticonvulsant activity expressed as the ratio between the number of animals protected and the number of animals tested.
[b] Toxicity.
[c] Not active.

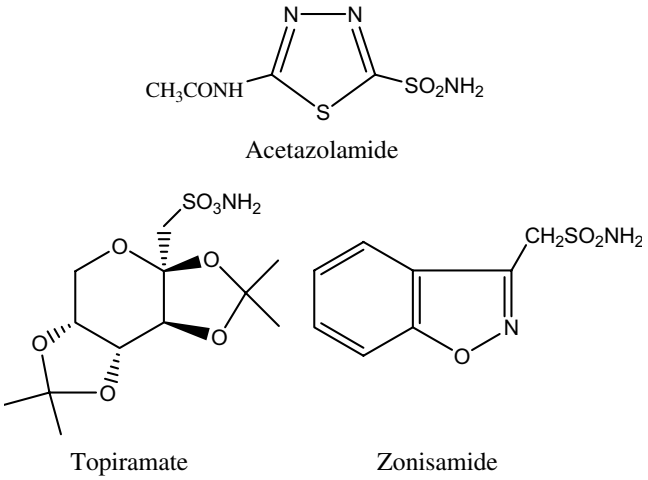


Figure 2. Chemical structures of clinically approved AEDs containing sulfonamide (acetazolamide and zonisamide) and sulfamate (topiramate) in their molecule.

convulsant activity was observed in the scMet test (Table 2). This pharmacological profile of compound **21**, namely potent anticonvulsant activity in the MES test and lack of activity in the scMet test, is shared by zonisamide (ZNS) and topiramate (TPM), two widely used AEDs containing sulfonamide (ZNS) and sulfamate (TPM) in their chemical structure (Fig. 2).[22,27] The insertion of a spacer methylene (compound **22**) or an ethylene group (compound **23**) between the amine and the phenyl ring of **21** reduced the anticonvulsant activity in the MES test. Consequently, in the series of TMCD alkylamine-*p*-phenylsulfonamide derivatives the length and the characteristics of the alkyl chain linking the phenyl ring with the amine group might have a crucial influence on the anticonvulsant activity. An addition of sulfonamide group at ortho and chlorine-atom at the meta-position to the phenyl ring of **21**, yielded compound **20**, which lacked the anticonvulsant activity in the MES test (Table 1).

We have found that compound **21**, the most potent aromatic sulfonamide derivative of TMCD in the mice-MES model (Table 1) was also very potent and non-toxic in the rat-MES test (ED_{50} = 26 mg/kg, PI > 19) (Table 3). However in the rat-scMet test, it was inactive up to 100 mg/kg (Table 3). Compound **21** is far less toxic than zonisamide with a PI value greater than 19, compared to zonisamide's PI value of 9 (Table 3).[22] Consequently, the higher anticonvulsant activity of compound **21** in the MES test as compared to VPA and its substantially wider safety margin than VPA and zonisamide, makes this aromatic sulfonamide derivative of the cyclic analogue of VPA a potential candidate to become a new AED.

3. Conclusions

We have designed a series of TMCD aromatic derivatives and evaluated their anticonvulsant profile in the traditional animal models for anticonvulsant activity, the MES and scMet models.[23] In the MES model compounds **8** and **15** were active at 300 mg/kg, whereas in the scMet test only compounds **8** and **9** displayed anticonvulsant activity at 300 mg/kg (Table 2).

The most potent compound in the MES test emerging from this study was **21** (Tables 1–3). The one carbon spacer in the side chain of compound **22** led to a decreased anticonvulsant activity compared to compound **21**. Additional carbon in the spacer (compound **23**) caused remarkable drop in the activity compared to **21**.

The anticonvulsant profile of compound **21** resembles that of zonisamide, an AED with a sulfonamide group in its structure. Compound **21** possesses a similar MES-ED_{50} value to that of zonisamide, however its PI value is two times larger than that of zonisamide.[22] Thus, the better anticonvulsant potency of compound **21**, compared to VPA, one of the most widely used AEDs, coupled with its wider safety margin make it a potential candidate to become a new AED that is a second-generation drug to VPA.

4. Experimental

4.1. Materials and methods

All reagents were purchased from Sigma–Aldrich. Product formation follow-up was performed by means of TLC techniques. TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F_{254}, Merck).

Chemical structure and purity of the newly synthesized compounds were assessed by TLC, 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).

4.2. General procedure A for the synthesis of aromatic 2,2,3,3-tetramethylcyclopropylcarboxamide derivatives (7–19)

2,2,3,3-Tetramethylcyclopropanecarbonyl chloride (TMC-Cl) (3 g, 9 mmol) dissolved in dry dichloromethane (30 mL) was slowly added to a stirred cooled solution of suitable amine (23 mmol) and triethylamine

Table 3. Anticonvulsant activity and toxicity of *N*-2,2,3,3-tetramethylcyclopropanecarboxamide)-*p*-phenylsulfonamide (**21**), VPA and zonisamide following oral administration to rats

Compound	MES[a] (ED_{50}, mg/kg)	scMet[b] (ED_{50}, mg/kg)	Tox.[c] (TD_{50}, mg/kg)	PI(MES)[d]	PI(scMet)
VPA[e]	485 (324–677)	646 (466–869)	784 (503–1176)	1.6	1.2
Zonisamide[e]	21 (18–25)	>300	192 (155–242)	9.1	—
21	26 (14–42)	>100	>500	>19	—

Values in parentheses are 95% confidence intervals determined by probit analysis.
[a] Maximal electroshock test.
[b] Subcutaneous pentylenetetrazol test.
[c] Toxicity.
[d] Protective index (TD_{50}/ED_{50}).
[e] Data taken from reference.[25]

(3.8 g, 38 mmol) in dry dichloromethane (100 mL). After addition, the reaction mixture was stirred for 3 h at room temperature. The organic solvent was then evaporated under vacuum and the residue 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 ethylacetate/petroleum ether mixture (1:3).

4.2.1. 2,2,3,3-Tetramethylcyclopropanecarbonyl phenyl amide (7). This compound was obtained as solid in 75% yield, mp 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.994 (s, 1H: CH), 1.211–1.323 (d, $J = 0.112$, 12H: CH_3), 7.06–7.492 (m, 5H: H-Ar), 7.201 (s, 1H: NH). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.26; H, 9.05; N, 6.44.

4.2.2. 2,2,3,3-Tetramethylcyclopropanecarbonyl benzyl amide (8). This compound was obtained as solid in 89% yield, mp 88–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.841 (s, 1H: CH), 1.137–1.274 (d, $J = 0.137$, 12H: CH_3), 4.416–4.397 (d, 2H: CH_2), 5.674 (s, 1H: NH), 7.228–7.345 (m, 5H: H-Ar). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.14; N, 6.05. Found: C, 78.02; H, 9.16; N, 6.16.

4.2.3. 2,2,3,3-Tetramethylcyclopropanecarbonyl phenylethylamide (9). This compound was obtained as solid in 84% yield, mp 81–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.757 (s, 1H: CH), 1.123–1.241 (d, $J = 0.118$, 12H: CH_3), 2.78–2.826 (t, 2H: CH_2), 3.463–3.529 (t, 2H: CH_2), 5.405 (s, 1H: NH), 7.188–7.334 (m, 5H). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.45; N, 5.71. Found: C, 78.38; H, 9.6; N, 5.72.

4.2.4. 2,2,3,3-Tetramethylcyclopropanecarbonyl phenylpropylamide (10). This compound was obtained as solid in 86% yield, mp 72–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.773 (s, 1H: CH), 1.139–1.25 (d, $J = 0.111$, 12H: CH_3), 1.799–1.847 (m, 2H: CH_2), 2.622–2.673 (t, $J = 0.026$, 2H: CH_2), 3.238–3.306 (q, $J = 0.02$, 2H: CH_2), 5.23 (s, 1H: NH), 7.163–7.281 (m, 5H). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.39. Found: C, 78.44; H, 9.80; N, 5.37.

4.2.5. 2,2,3,3-Tetramethylcyclopropanecarbonyl (1-methyl-benzyl)-amide (11). This compound was obtained as solid in 79% yield, mp 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.843 (s, 1H: CH), 1.135–1.27 (dd, $J = 0.022$, $J' = 0.046$, 12H: CH_3), 1.464–1.487 (d, $J = 0.023$, 3H: CH_3), 5.11–5.18 (m, 1H: CH), 5.610 (s, 1H: NH), 7.233–7.341 (m, 5H: H-Ar). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.45; N, 5.71. Found: C, 78.29; H, 9.53; N, 5.69.

4.2.6. 2,2,3,3-Tetramethylcyclopropanecarbonyl (2-methyl-2-phenylethyl)-amide (12). This compound was obtained as solid in 82% yield, mp 55–56 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.707 (s, 1H: CH), 1.086–1.218 (dd, $J = 0.038$, $J' = 0.049$, 12H: CH_3), 1.246–1.273 (d, $J = 0.027$, 3H: CH_3), 2.911–2.962 (m, 1H: CH_2), 3.141–3.235 (m, 1H: CH_2), 3.581–3.672 (m, 1H: CH), 5.26 (s, 1H: NH), 7.197–7.356 (m, 5H: H-Ar). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.39. Found: C, 78.75; H, 9.82; N, 5.43.

4.2.7. 2,2,3,3-Tetramethylcyclopropanecarbonyl (2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methylamide (13). This compound was obtained as solid in 89% yield, mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.005 (s, 1H: CH), 1.104–1.213 (m, 15H: CH_3), 2.669 (s, 3H: CH_3), 4.443 (s, 1H: CH), 4.835 (s, 1H: CH), 7.247–7.381 (m, 5H: H-Ar). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.68; H, 9.41; N, 4.84. Found: C, 74.85; H, 9.67; N, 4.85.

4.2.8. 2,2,3,3-Tetramethylcyclopropanecarbonyl-1-methyl-2-(2,6-dimethyl-phenoxy)-ethylamide (14). This compound was obtained as solid in 78% yield, mp 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.870 (s, 1H: CH), 1.165–1.294 (dd, $J = 0.008$, $J' = 0.03$, 12H: CH_3), 1.385–1.408 (d, $J = 0.023$, 3H: CH_3), 2.27 (s, 6H: CH_3), 3.677–3.788 (dd, $J = 0.01$, $J' = 0.013$, 2H: CH_2), 4.35 (m, 1H: CH), 5.833–5.859 (d, $J = 0.026$, 1H: NH), 6.897–7.017 (m, 3H: H-Ar). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.25; H, 9.56; N, 4.70.

4.2.9. 2,2,3,3-Tetramethylcyclopropanecarbonyl-(4-acetyl-phenyl)-amide (15). This compound was obtained as solid in 79% yield, mp 194–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.012 (s, 1H: CH), 1.222–1.324 (d, $J = 0.102$, 12H: CH_3), 2.565 (s, 3H: CH_3), 7.426 (s, 1H: NH), 7.577–7.606 (d, $J = 0.029$, 2H: H-Ar), 7.892–7.921 (d, $J = 0.029$, 2H: H-Ar). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.36; H, 8.33; N, 5.45.

4.2.10. 2,2,3,3-Tetramethylcyclopropanecarbonyl-2-chloro-benzylamide (16). This compound was obtained as solid in 81% yield, mp 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.856 (s, 1H: CH), 1.139–1.241 (d, $J = 0.102$, 12H: CH_3), 4.509–4.489 (d, $J = 0.02$, 2H: CH_2), 5.821 (s, 1H: NH), 7.189–7.388 (m, 4H: H-Ar). Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.79; H, 7.57; N, 5.27; Cl, 13.30. Found: C, 67.89; H, 7.50; N, 5.40; Cl, 13.13.

4.2.11. 2,2,3,3-Tetramethylcyclopropanecarbonyl-4-fluoro-benzylamide (17). This compound was obtained as solid in 75% yield, mp 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 0.851 (s, 1H: CH), 1.154–1.281 (d, $J = 0.127$, 12H: CH_3), 4.377–4.396 (d, $J = 0.019$, 2H: CH_2), 5.728 (s, 1H: NH), 7.009–7.260 (m, 4H: H-Ar). Anal. Calcd for $C_{15}H_{20}NOF$: C, 72.26; H, 8.08; N, 5.61; F, 7.61. Found: C, 72.08; H, 8.08; N, 5.94; F, 7.08.

4.2.12. 1-Phenyl-3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-urea (18). This compound was obtained as solid in 77% yield, mp 195–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS): 1.214 (s, 1H: CH), 1.243–1.316 (d, $J = 0.073$, 12H: CH_3), 7.057–7.11 (d, $J = 0.053$, 1H: H-Ar), 7.259–7.316 (m, 2H: H-Ar), 7.523–7.555 (d, $J = 0.032$, 2H: H-Ar), 9.612 (s, 1H: NH), 10.679 (s,

1H: NH). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N: 10.76. Found: C, 69.43; H, 7.88; N, 10.47.

4.2.13. 2,2,3,3-Tetramethylcyclopropanecarbonyl-(1*H*-indol-3-ethyl)-amide (19). This compound was obtained as solid in 92% yield, mp 109–110 °C. ^{1}H NMR (300 MHz, CD_3OD δ TMS): 1.001 (s, 1H: CH), 1.139–1.216 (d, $J = 0.077$, 12H: CH_3), 2.883–2.931 (t, $J = 0.022$, 2H: CH_2), 3.404–3.453 (t, 2H: CH_2), 6.981–7.070 (m, 4H: H-Ar), 7.126 (d, $J = 0.028$, 1H: CH), 7.296–7.322 (d, $J = 0.026$, 1H: NH), 7.537–7.563 (d, $J = 0.026$, 1H: NH). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.99; H, 8.61; N, 9.87.

4.3. General procedure B for the synthesis of aromatic sulfonamide 2,2,3,3-tetramethylcyclopropyl carboxamide derivatives (20–23)

TMC-Cl (3 g, 9 mmol) dissolved in dry acetone (20 mL) was slowly added to stirred solution of suitable sulfonamide (9.2 mmol) and pyridine (9.1 mmol) in dry acetone (50 mL). After addition, the reaction mixture was stirred for 12 h at room temperature. The organic solvent was then evaporated under vacuum and the residue dissolved in ethyl acetate (100 mL) and washed three times with 20 mL of distilled water. The organic fraction was dried over $MgSO_4$, filtered, and evaporated.

The obtained products were purified by crystallization using ethylacetate/petroleum ether mixture (1:3).

4.3.1. 2,2,3,3-Tetramethylcyclopropanecarbonyl-(2,4-disulfamoyl-5-chloro-phenyl)-amide (20). This compound was obtained as solid in 52% yield, mp 230–232 °C. ^{1}H NMR (300 MHz, CD_3COCD_3 δ TMS): 0.961 (s, 1H: CH), 1.248–1.306 (d, $J = 0.058$, 12H: CH_3), 6.376 (s, 1H: NH), 6.556 (s, 2H: SO_2NH_2), 6.801 (s, 2H: SO_2NH_2), 7.074 (s, 1H: H-Ar), 8.305 (s, 1H: H-Ar). Anal. Calcd for $C_{14}H_{20}N_3O_5ClS_2$: C, 41.02; H, 4.92; N, 10.25; Cl, 8.65; S, 15.64. Found: C, 41.22; H, 4.99; N, 10.16; Cl, 8.51; S, 15.17.

4.3.2. *N*-(2,2,3,3-Tetramethylcyclopropanecarboxamide)-*p*-phenylsulfonamide (21). This compound was obtained as solid in 61% yield, mp 208–209 °C. ^{1}H NMR (300 MHz, CD_3SOCD_3 δ): 1.171–1.224 (d, $J = 0.053$, 12H: CH_3), 1.302 (s, 1H: CH), 7.197 (s, 2H: SO_2NH_2), 7.694 (m, 4H: H-Ar), 10.219 (s, 1H: NH). Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45; S, 10.82. Found: C, 57.00; H, 6.75; N, 9.66; S, 10.57.

4.3.3. 2,2,3,3-Tetramethylcyclopropanecarbonyl-(4-sulfamoyl-benzyl)-amide (22). This compound was obtained as solid in 75% yield, mp 207–208 °C. ^{1}H NMR (300 MHz, CD_3SOCD_3 δ): 1.102–1.162 (d, $J = 0.06$, 12H: CH_3), 1.232 (s, 1H: CH), 4.257–4.277 (d, $J = 0.02$, 2H: CH_2), 7.269 (s, 2H: SO_2NH_2), 7.359–7.387 (d, $J = 0.028$, 2H: H-Ar), 7.725–7.752 (d, $J = 0.027$, 2H: H-Ar), 8.317 (t, $J = 0.019$, 1H: NH). Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.14; N, 9.02; S, 10.33. Found: C, 57.91; H, 7.07; N, 9.11; S, 10.45.

4.3.4. 2,2,3,3-Tetramethylcyclopropanecarbonyl-(4-sulfamoyl-phenylethyl)-amide (23). This compound was obtained as solid in 87% yield, mp 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$ TMS δ): 0.765 (s, 1H: CH), 1.138–1.244 (d, $J = 0.106$, 12H: CH_3), 2.869–2.917 (t, $J = 0.024$, 2H: CH_2), 3.474–3.534 (q, $J = 0.02$, 2H: CH_2), 4.753 (s, 2H: SO_2NH_2), 5.45 (s, 1H: NH), 7.344–7.370 (d, $J = 0.026$, 2H: H-Ar), 7.855–7.881 (d, $J = 0.026$, 2H: H-Ar). Anal. Calcd for $C_{16}H_{24}N_2O_3S$: C, 59.23; H, 7.45; N, 8.63; S, 9.88. Found: C, 59.01; H, 7.37; N, 8.86; S, 9.53.

4.4. Biological testing

The evaluation of anticonvulsant activity in the maximal electroshock (MES), subcutaneous pentylenetetrazole (scMet) tests as well as the determination of toxicity in the rotorod test and positional stence tests were performed at the NIH-Epilepsy Branch as a part of the Anticonvulsant Drug Development Program according to the protocols described in reference.[22] All compounds for testing were prepared either by dissolving or suspending 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 body weight, and in rats, 0.04 mL per 10 g body weight.

4.5. Determination of the median effective dose (ED_{50}) and the median neurotoxic dose (TD_{50})

For the determination of the ED_{50} by the respective anticonvulsant procedures, doses of the titled compounds were varied until at least four points were established between the dose level of no protection and 100% protection. These data were then subjected to probit analysis and the ED_{50} and 95% confidence intervals were calculated.

The TD_{50} was determined by varying the dose of the studied compounds until four points were established between the dose level that induced no signs of minimal motor impairment in any of the animals, and the dose at which all the animals were considered impaired. The TD_{50} and the 95% confidence intervals were then calculated by probit analysis. The protective index was calculated by dividing the TD_{50} by ED_{50}.

Acknowledgments

This work is abstracted from the Ph.D. thesis of Mr. Jakob A. Shimshoni in partial fulfillment of the Ph.D. degree requirements for The Hebrew University of Jerusalem. The authors thank Mr. James P. Stables, Director of the NIH-NINDS-Anticonvulsant Screening Program (ASP), for testing the compounds.

References and notes

1. (a) McNamara, J. O. In *The Pharmacological Basis of Therapeutics*; Brunton, L. L., Lazo, J. S., Parker, K. L., Eds., 11th ed.; McGraw-Hill: New York, 2006; pp 501–525; (b) Jackson, E. K. In *The Pharmacological Basis of Therapeutics*; Brunton, L. L., Lazo, J. S., Parker, K. L., Eds., 11th ed.; McGraw-Hill: New York, 2006; pp 743–745.
2. Bourgeois, F. D. B. In *Antiepileptic Drugs*; Levy, R. H., Mattson, R. H., Meldrum, B. S., Perucca, E., Eds., 5th ed.; Lippincott Williams & Wilkins Publishers: New York, 2002; pp 808–817.
3. Silberstein, D. S. In *Antiepileptic Drugs*; Levy, R. H., Mattson, R. H., Meldrum, B. S., Perucca, E., Eds., 5th ed.; Lippincott Williams & Wilkins Publishers: New York, 2002; pp 818–827.
4. Swann, C. A. In *Antiepileptic Drugs*; Levy, R. H., Mattson, R. H., Meldrum, B. S., Perucca, E., Eds., 5th ed.; Lippincott Williams & Wilkins Publishers: New York, 2002; pp 828–836.
5. Koenig, S. A.; Buesing, D.; Longin, E.; Oehring, R.; Häussermann, P.; Kluger, G.; Lindmayer, F.; Hanusch, R.; Degen, I.; Kuhn, H.; Samii, K.; Jungck, A.; Brückner, R.; Seitz, R.; Boxtermann, W.; Weber, Y.; Knapp, R.; Richard, H. H.; Weidner, B.; Kasper, J. M.; Haensch, C. A.; Fitzek, S.; Hartmann, M.; Borusiak, P.; Müller-Deile, A.; Degenhardt, V.; Korenke, G. C.; Hoppen, T.; Specht, U.; Gerstner, T. *Epilepsia* **2006**, *47*, 2027.
6. Tomson, T.; Battino, D. *Curr. Opin. Neurol.* **2005**, *18*, 135.
7. Vajda, F. J.; O'Brien, T. J.; Hitchcock, A.; Graham, J.; Cook, M.; Lander, C.; Eadie, M. J. *J. Clin. Neurol.* **2004**, *11*, 854.
8. Sussman, N. M.; McLean, L. W., Jr. *JAMA* **1979**, *242*, 1173.
9. Zimmerman, H. J.; Ishak, K. G. *Hepatology* **1982**, 591.
10. Smith, M.; Wilcox, K. S.; White, H. S. *Neurotherapeutics* **2007**, *4*, 12.
11. Isoherranen, N.; Yagen, B.; Bialer, M. *Curr. Opin. Neurol.* **2003**, *16*, 203.
12. Bialer, M.; Yagen, B. *Neurotherapeutics* **2007**, *4*, 130.
13. Sobol, E.; Bialer, M.; Yagen, B. *J. Med. Chem.* **2004**, *47*, 4316.
14. Bentoid-Guyod, M.; Boucherle, A.; Eymard, P.; Carraz, G.; Meunier, H. *Chim. Ther.* **1968**, *1*, 17.
15. Bentoid-Guyod, J. L.; Boucherle, A.; Bentoid-Guyod, M.; Dardas, A.; Rupp, R.; Eymard, P.; Carraz, G.; Boitard, M.; Lebreton, S.; Beriel, H.; Meunier, H. *Chim. Ther.* **1968**, *5*, 336.
16. Netzeva, T.; Astroug, H.; Behar, E.; Koprivlenska, C. *Pharmacia (UAPMEИЯ)* **1999**, *4*, 3.
17. Masereel, B.; Rolin, S.; Abbate, F.; Scozzafava, A.; Supran, C. T. *J. Med. Chem.* **2002**, *45*, 312.
18. Schmidt, D.; Rogawski, M. A. *Epilpesy Res.* **2002**, *50*, 71.
19. Rogawski, M. A. *Epilpesy Res.* **2006**, *69*, 273.
20. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Prentice Hall: New York, 1989, pp 720–723.
21. Sobol, E.; Yagen, B.; Lamb, J. G.; White, H. S.; Wlodarczyk, B.; Finnell, R. H.; Bialer, M. *Epilepsy Res.* **2007**, *73*, 75.
22. White, H. S.; Woodhead, J. H.; Wilcox, K. S.; Stables, J. P.; Kupferberg, H. J.; Wolf, H. H. In *Antiepileptic Drugs*; Levy, R. H., Mattson, R. H., Meldrum, B. S., Perucca, E., Eds., 5th ed.; Lippincott Williams & Wilkins Publishers: New York, 2002; pp 36–48.
23. Perucca, E.; French, J.; Bialer, M. *Lancet Neurol.* **2007**, *6*, 743.
24. Krall, R. L.; Penry, J. K.; White, H. S.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *51*, 1657.
25. Meldrum, B. S. In *New Anticonvulsant Drugs*; Meldrum, B. S., Porter, R. J., Eds.; John Libbey: London, 1986; pp 31–48.
26. Tasso, M. S.; Moon, C. S.; Bruno-Blanch, E. L.; Estiu, L. *Bioorg. Med. Chem.* **2004**, *12*, 3857.
27. Gavernt, L.; Barrios, I. A.; Sella Cravero, M.; Bruno-Blanch, L. E. *Bioorg. Med. Chem.* **2007**, *15*, 5604.