# Pharmacokinetic Analysis and Antiepileptic Activity of Tetra-Methylcyclopropane Analogues of Valpromide

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***Purpose.*** The described structure pharmacokinetic pharmacodynamic relationships (SPPR) study explored the utilization of tetramethylcyclopropane analogues of valpromide (VPD), or tetramethylcyclopropane carboxamide derivatives of valproic acid (VPA) as new antiepileptics.

***Methods.*** The study was carried out by investigating the pharmacokinetics in dogs and pharmacodynamics (anticonvulsant activity and neurotoxicity) of the following three cyclopropane analogues of VPD: 2,2,3,3-tetramethylcyclopropane carboxamide (TMCD), N-methyl TMCD (M-TMCD) and N-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]-glycinamide (TMC-GLD).

***Results.*** The three investigated compounds showed a good anticonvulsant profile in mice and rats due to the fact that they were metabolically stable VPD analogues which were not biotransformed to their non-active acid, 2,2,3,3-tetramethylcyclopropane carboxylic acid (TMCA). M-TMCD was metabolized to TMCD and TMC-GLD underwent partial biotransformation to its glycine analogue N-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]-glycine (TMC-GLN). Unlike TMC-GLN, the above mentioned amides had low clearance and a relatively long half life.

***Conclusions.*** In contrast to VPD which is biotransformed to VPA, the aforementioned cyclopropane derivatives were found to be stable to amide-acid biotransformation. TMCD and M-TMCD show that cyclic analogues of VPD, like its aliphatic isomers, must have either two substitutions at the β position to the carbonyl, such as in the case of TMCD, or a substitution in the α and in the β positions like in the VPD isomer, valnoctamide (VCD). This paper discusses the antiepileptic potential of tetramethylcyclopropane analogues of VPD which are in animal models more potent than VPA and may be non-teratogenic and non-hepatotoxic.

**KEY WORDS:** valproic acid; valpromide; tetramethylcyclopropane derivatives; pharmacokinetics; antiepileptic activity; structural requirements.

## INTRODUCTION

Valpromide—VPD (I—Fig. 1) is the primary amide of valproic acid—VPA (II—Fig. 1), a major antiepileptic drug. In animal studies VPD was found to be more potent than VPA and non-teratogenic (1). However, the advantages of VPD over VPA in animals have no clinical implications as VPD serves as a prodrug of VPA in humans. Therefore, there is a substantial need to develop stable VPD analogues, which unlike VPD, will not undergo amide-acid biotransformation to their corresponding acid (2).

In previous studies we explored the structure pharmacokinetic pharmacodynamic (anticonvulsant activity and neurotoxicity) relationships (SPPR) of a series of aliphatic analogues of VPD (2–4). Our studies showed that, despite similarities in the chemical structure of the investigated VPD isomers and analogues, significant differences were discovered in the fraction of the amides biotransformed to their corresponding acids (fm). These differences in fm values may account for the observed differences in the extent of the anticonvulsant activity of the investigated amides. In this series of amides derived from short-branched fatty acids, the biotransformation of the amide to its corresponding acid appeared to depend upon the substitutions at the α and β positions of the carboxamide moiety of the molecule (2–4). A stable VPD isomer, which is not metabolized to its corresponding acid, was found to be more potent as an anticonvulsant, than an isomer which is able to undergo biotransformation to its corresponding acid (a biotransformed isomer) (2–4).

VPA is one of the major antiepileptic drugs which possess a wide spectrum of antiepileptic activity (5). However its anticonvulsant potency, shown in the classical animal (rodents) models for anticonvulsant screening, is less than the other three major antiepileptic drugs: phenobarbital, phenytoin and carbamazepine (6).

One of the severe side effects of VPA is teratogenicity (7). Structure teratogenicity relationship studies (in rodents) showed that the presence of a free carboxylic acid moiety in the VPA molecule is essential for teratogenicity. Unlike VPA, VPD is not teratogenic (7,8).

The second major side effect, associated with VPA therapy, is hepatotoxicity caused by $\Delta^4$-VPA, a metabolite with a terminal double bond at position 4 (9). So far, worldwide, 132 patients have died of VPA-associated liver failure and/or pancreatitis (10). An active VPA analogue, which structurally will not be able to be biotransformed to a metabolite with a terminal double bond, might not cause hepatotoxicity.

In the current study, the following three new tetramethylcyclopropane carboxamide derivatives of VPA (or cyclopropane analogues of VPD) were synthesized and evaluated (Fig. 1): 2,2,3,3-tetramethylcyclopropane carboxamide—TMCD (III), N-methyl TMCD—M-TMCD (IV) and N-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]-glycinamide—TMC-GLD (V). Compounds III-V are cyclic symmetrically disubstituted amides which cannot be biotransformed to a metabolite with a terminal double bond. Thus, methylene cyclopropane acetic acid, the active metabolite of hepatotoxin A, which produces a pattern of hepatic injury, similar to that of VPA, cannot be formed with compounds III-V (11,12).

The current pharmacokinetic (PK) study was designed in order to investigate the *in vivo* performance of compounds III-V (Fig. 1), and to assess whether these compounds undergo a metabolic hydrolysis to their corresponding acids 2,2,3,3-

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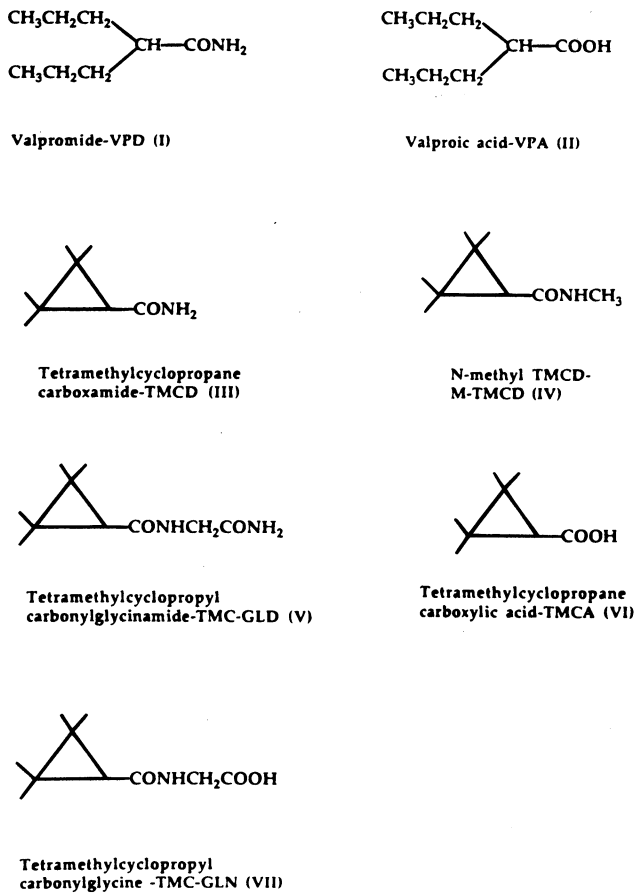


**Fig. 1.** The chemical structures of valpromide—VPD (I), valproic acid—VPA (II), 2,2,3,3-tetramethylcyclopropane carboxamide -TMCD (III), N-methyl TMCD—M-TMCD (IV), N-[(2,2,3,3-tetramethylcyclopropyl) carbonyl]-glycinamide-TMC-GLD (V), 2,2,3,3-tetramethylcyclopropane carboxylic acid—TMCA (VI) and N-[(2,2,3,3-tetramethylcyclopropyl) carbonyl]-glycine—TMC-GLN (VII).

tetramethylcyclopropane carboxylic acid—TMCA (VI) and N-[(2,2,3,3-tetramethylcyclopropyl) carbonyl]-glycine—TMC-GLN (VII). In addition, this study was designed to evaluate SPPR of the above mentioned three compounds. The pharmacodynamic (PD) evaluation was carried out in collaboration with the anticonvulsant screening project of the NIH Epilepsy Branch (13).

## MATERIALS AND METHODS

### Materials

TMCA (VI), methylamine, glycine and glycinamide were purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin. VPD was a gift from Sanofi, France, and VPA was a gift from Teva Pharmaceuticals, Israel. Compounds III-V were prepared according to the following methods:

### 2,2,3,3-Tetramethylcyclopropanecarboxamide—TMCD (III)

The compound was obtained from 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (16.05 g. 0.1 mol) and aqueous ammonia, by a procedure similar described for M-TMCD (IV). Crystallization ($CHCl_3$:hexane) afforded 7.05 g (50 mmole, 50%) of a crystalline white solid.

*Anal. calculated for* $C_8H_{15}NO$:

| | | | |
|---|---|---|---|
| Calculated: | C: 68.0% | H: 10.0% | N: 9.9% |
| Found: | C: 67.7% | H: 10.3% | N: 9.2% |

### N-Methyl-2,2,3,3-tetramethylcyclopropanecarboxamide—M-TMCD (IV).

A solution of 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (16.05 g, 0.1 mole) in THF (50 ml) was added slowly to 35% aqueous methylamine (200 ml). The reaction mixture was stirred for 24 hours at room temperature, and, after removal of THF under reduced pressure, was extracted with $CH_2Cl_2$ (2 × 50 ml). The $CH_2Cl_2$ extract was washed successively with $H_2O$ (2 × 100 ml), 0.3 N HCl (200 ml), 0.1 $NaHCO_3$ (100 ml) and saturated NaCl (150 ml), dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude product was treated with hexane (100 ml) at room temperature for 30 minutes, filtered and dried to afford 10.5 g (68 mmole, 68%) of a white solid, m.p.: 98°C.

*Anal. calculated for* $C_9H_{17}NO$:

| | | | |
|---|---|---|---|
| Calculated: | C: 69:62% | H: 11.04% | N: 9.03% |
| Found: | C: 68.90% | H: 10.89% | N: 9.72% |

$^1$H NMR δ($CDCl_3$): 5.55 (br s, 1H, NH), 2.78(d, 3H, NH*Me*), 1.27 (s, 6H, Me, 1.15 (s, 6H, Me), 0.83 (s, 1H, CH) ppm
MS: 156 ($MH^+$, 100).
IR(KBr): 3268, 1641, 1562, 1423, 1252, 1119 $cm^{-1}$.

### N-[(2,2,3,3-Tetramethylcyclopropyl)carbonyl]-glycinamide—TMC-GLD (V)

To a solution of TMCA (2.82 g, 20 mmole) in dry $CH_2Cl_2$ (150 ml) were added N-hydroxysuccinimide (2.3 g, 20 mmole) and DMAPE-carbodimide HCl (3.92 g, 20 mmole). The substance obtained was stirred for 15 hours at room temperature. To this mixture was added $(CH_3CH_2)_3N$ (4,5 ml), glycinamide HCl (2.2 g. 20 mmole) and dry DMF (100 ml), with stirring for 24 hours at room temperature. The solvents were removed under reduced pressure. The residue was purified by chromatography ($SiO_2$, $CHCl_3$:MeOH 97:3) followed by successive crystallization from $CH_2Cl_2$:hexane and EtOAc:hexane, to afford 1.1 g (5.6 mmole, 28%) of a white crystalline solid, m.p.: 176°C.

*Anal. calculated for* $C_{10}H_{18}N_2O_2$:

| | | | |
|---|---|---|---|
| Caluclated: | C: 60.0% | H: 9.1% | N: 14.0% |
| Found: | C: 60.4% | H: 8.9% | N. 14.1% |

$^1$H NMR δ($CDCl_3$): 6.2 (br. s, 2H, NH), 5.40 (br. s, 1H, NH), 3.93 (d, 2H, $CH_2$), 1.26 (s, 6H, Me), 1.17 (s, 6H, Me), 0.95 (s, 1H, CH) ppm.
MS: 199 ($MH^+$, 100).

**N-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]-glycine—TMC-GLN (VII).**

TMC-GLN (VII) was synthesized according to the same procedure as TMC-GLD (V) with a yield of 70%.

*Anal. calculated for* $C_{10}H_{17}NO_3$

| | | | |
|---|---|---|---|
| Calculated: | C: 60.3% | H: 8.54% | N: 7.04% |
| Found: | C: 59.9% | H: 8.35% | N: 6.95% |

## Animals

The experiments were carried out with three different groups of six dogs (mongrels), ranging in weight between 16 and 20 kg. In a parallel design, each dog was injected intravenously (TMCD 392 mg and TMC-GLD 550 mg dissolved in 1.5 ml 70% ethyl alcohol and 431 mg of M-TMCD dissolved in 1.5 ml of DMSO). The injected doses of the compounds III–V represented corresponding molar equivalents of 400 mg (2.8 mM) of VPA. As TMC-GLD (V) was partially biotransformed to TMC-GLN (VII), compound VII was also studied under the same conditions (553 mg-iv) in the 6 dogs which received TMC-GLD (V). Urine was collected systematically for 12 hours after dosing, by means of an indwelling catheter.

## Protocol

Venous blood samples (5 ml) were collected via an indwelling catheter (from the cephalic vein) at specified intervals following injection (0,5,10,15,20,30,40 and 50 min and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hr, respectively). The plasma was then immediately separated by centrifugation at 3000 g for 15 min and stored at −20°C. Plasma and urine levels of compounds V and VII were then assayed by a new HPLC assay previously reported by us for valproyl glycinamide and valproyl glycine (14). The plasma levels of TMCD (III) and M-TMCD (IV) were assayed by a GC assay previously reported by us for VPD and its isomer valnoctamide—VCD (15,16).

## Anticonvulsant activity

Compounds II–VII, VPA (II) and VPD (I) were screened in Carworth Farm #1 mice (ip) and Sprague-Dawley rats (po) for their anticonvulsant activity and neurotoxicity at the NIH Epilepsy Branch (13). The screening procedure involved the following: 1) the maximal electroshock (MES) test, which measures seizure spread; 2) the subcutaneous pentylenetetrazol test (sc Met test), which measures seizure threshold; and 3) the rotorod ataxia test, which assesses minimal neurotoxicity (13).

## Pharmacokinetic (PK) Analysis

The linear terminal slope (β) of log C (drug plasma concentration) versus t (time) was calculated by the method of least squares. The terminal half-life of the compound ($t_{1/2}\beta$) was calculated from the quotient 0.69/terminal slope. The AUC (area under the C versus t curve) was calculated by using the trapezoidal rule with extrapolation to infinity (17). The total body clearance (CL) of compounds III–V and VII, their volume of distribution (Vβ), their volume of distribution at steady state (Vss), the fraction excreted unchanged (fe) and their mean residence time (MRT) were calculated by classical methods assuming linear PK (17–20). The fraction metabolised (fm) of TMC-GLD (V) to TMC-GLN (VII) was calculated from the ratio of the fe obtained after iv administration of TMC-GLD (V) to the fe of its corresponding glycine metabolite—TMC-GLN (VII).

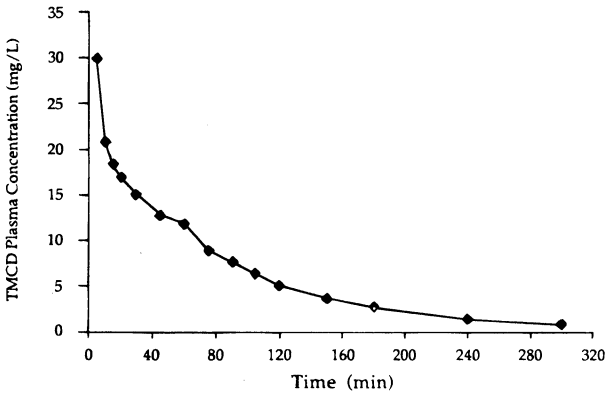


**Fig. 2.** Mean plasma levels of 2,2,3,3-tetramethylcyclopropane carboxamide TMCD (III) following its iv administration (392 mg) to six dogs.

## Stability Studies

A blood stability study of compounds II–VII was carried out as previously described for VPD and its analogues (3,4).

## RESULTS

Stability studies showed that compounds II–VII were stable in dog blood for 8 hr at physiological conditions.

The mean plasma levels of compounds II-V and VII are presented in Figs 2–4, respectively. Following the administration of TMCD or M-TMCD (IV), TMCA was not detected in either the plasma or urine. TMCD was found and quantified in the plasma as a metabolite of M-TMCD. TMC-GLN (VII)

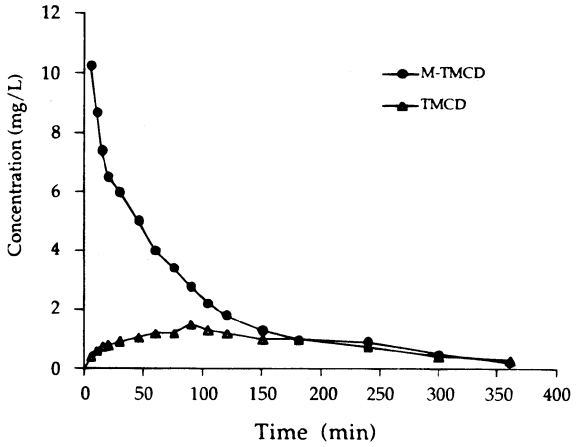


**Fig. 3.** Mean plasma levels of N-methyl 2,2,3,3-tetramethylcyclopropane carboxamide- M-TMCD (IV) and its metabolite 2,2,3,3-tetramethylcyclopropane carboxamide—TMCD (III) following iv administration (431 mg) of M-TMCD (IV) to six dogs.

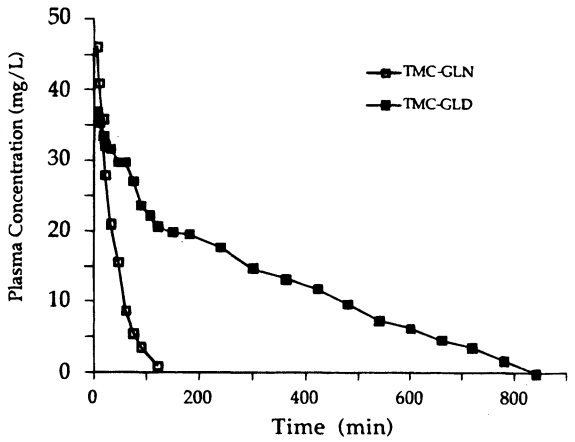


**Fig. 4.** Mean plasma levels of [(2,2,3,3-tetramethylcyclopropyl)carbonyl]-glycinamide—TMC-GLD (V) and 2,2,3,3-tetramethylcyclopropyl) carbonyl]-glycine-TMC-GLN (VII) following their iv administration (580 mg) to six dogs.

**Table II.** Anticonvulsant Activity and Neurotoxicity of the Investigated Compounds following IP Administration to Mice in Comparison to VPA and VPD[a]

| | TMCD | M-TMCD | TMC-GLD | VPA | VPD |
|---|---|---|---|---|---|
| MES, $ED_{50}$ (mg/kg) | >120 | 98 | 173 | 200 | 56 |
| sc Met, $ED_{50}$ (mg/kg) | 57 | 39 | 115 | 146 | 55 |
| Neurotoxicity, $TD_{50}$ (mg/kg) | 94 | 83 | 259 | 283 | 81 |
| PI, MES | — | 0.8 | 1.5 | 0.9 | 1.4 |
| PI, sc Met | 1.7 | 2.1 | 2.3 | 1.9 | 1.5 |

MES—Maximal electroshock.
sc Met—Chemically induced shock obtained following subcutaneous injection of metrazol.
$ED_{50}$—Effective dose in 50% of the animals.
$TD_{50}$—Neurotoxic dose in 50% of the test animals.
PI—Protective index—The ratio of the $TD_{50}$ to the $ED_{50}$.
[a] The data for VPA and VPD are taken from ref. 6.

was detected as a urinary metabolite and quantified following the administration of TMC-GLD (V). Table I summarizes the mean PK parameters of compounds III–V and VII obtained following their iv administration to dogs.

In phase I of the anticonvulsant screening project of the NIH Epilepsy Branch, TMCA (VI) and TMC-GLN (VII) were found to be inactive. Unlike these two acids, compounds III–V demonstrated qualitative anticonvulsant activity in mice. Subsequently, TMCD (III), M-TMCD (IV) and TMC-GLD (V) were tested in phases II (mice,ip) and VI (rats, po) of the NIH-anticonvulsant screening project, in order to determine their $ED_{50}$ and $TD_{50}$ values, as well as their protective indices—PI (the ratio between the $TD_{50}$ and $ED_{50}$ values). The PD (Anticonvulsant activity and neurotoxicity) results of these three active amides in comparison to VPD (I) and VPA (II) are shown in Tables II and III.

## DISCUSSION

PK analysis in dogs showed that TMC-GLD (V) had the lowest clearance value. Its clearance was one tenth of that of its TMC-GLN (VII) and 5% of the clearance value of M-TMCD (IV). This low clearance value led to the fact that TMC-GLD had a mean half life of 2.4 hours, which was about seven times longer than that of TMC-GLN. Urine analysis showed that 47% of TMC-GLD was biotransformed to its corresponding acid TMC-GLN, while 53% of TMC-GLN was excreted intact. No metabolic cleavage of TMC-GLD or TMC-GLN, to their two components (TMCA and the neuroinhibitory transmitter glycine or glycinamide) was observed in this study.

The pharmacokinetics and pharmacodynamics of TMC-GLD (V) were similar to valproyl glycinamide, previously reported by us (14). Neither compound was metabolically cleaved to its components. They were however partially biotransformed to their inactive corresponding glycine analogues, which appeared in dogs as urinary metabolites. Thus, TMC-GLD was active on its own and not as a chemical drug delivery system for glycine or glycinamide.

TMCD (III) and M-TMCD (IV) were likewise found to be stable amides, which did not biotransform to their corresponding acid, TMCA (VI). The only biotransformation observed was N-demethylation of M-TMCD to TMCD. Following the administration of M-TMCD the mean AUC of TMCD was about 40% of the AUC of the parent compound. Less than 1% of either TMCD or M-TMCD was excreted unchanged in the urine, indicating that both compounds are mainly eliminated by metabolism to unknown metabolites. Comparative PK analysis of M-TMCD and TMCD showed that the former had larger

**Table I.** Mean (± SD) Pharmacokinetic Parameters of TMCD (III), M-TMCD (IV), TMC-GLD (V) and TMC-GLN (VII) Obtained following their IV Administration (a dose Equivalent to 400 Mg VPA) to Six Dogs in Comparison to Valproic Acid (VPA) and Valpromide (VPD)[a]

| Pharmacokinetic Parameter | TMCD | M-TMCD | TMC-GLD | TMC-GLN | VPA | VPD |
|---|---|---|---|---|---|---|
| t 1/2β (hr) | 1.0 ± 0.4 | 1.0 ± 0.8 | 2.4 ± 0.4 | 0.36 ± 0.06 | 1.3 ± 0.3 | 2.8 ± 0.5 |
| AUC (mg/L hr) | 40 ± 21 | 12 ± 6 | 197 ± 62 | 28 ± 4 | 62 ± 10 | 103 ± 18 |
| CL (L/hr) | 15 ± 6 | 41 ± 20 | 2.2 ± 0.7 | 20 ± 2 | 3.2 ± 0.2 | 4.0 ± 1.8 |
| Vss (L) | 20 ± 7 | 56 ± 27 | 10 ± 2 | 12 ± 2 | — | — |
| Vβ (L) | 19 ± 8 | 48 ± 43 | 7 ± 2 | 10 ± 2 | 5.8 ± 2.2 | 16 ± 4 |
| MRT (hr) | 1.5 ± 0.5 | 1.5 ± 0.5 | 4.9 ± 0.9 | 0.6 ± 0.1 | | |
| fe (%) | <1 | 0.27 ± 0.08 | 0 | 53 ± 13 | | |
| fm (%) | 0 | 20 | 47 ± 17 | — | | |

[a] The data for VPA and VPD are taken from ref. 23.

**Table III.** Anticonvulsant Activity and Neurotoxicity of the Investigated Compounds following Oral Administration to Rats in Comparison to VPA and VPD[a]

| | TMCD | M-TMCD | TMC-GLD | VPA | VPD |
|---|---|---|---|---|---|
| MES, $ED_{50}$ (mg/kg) | >250 | 82 | 82 | 490 | 32 |
| sc Met, $ED_{50}$ (mg/kg) | 52 | 45 | >250 | 180 | 59 |
| Neurotoxicity, $TD_{50}$ (mg/kg) | 381 | 163 | >500 | 200 | 87 |
| PI, MES | — | 2.0 | >6.1 | 0.6 | 2.7 |
| PI, sc Met | 7.3 | 3.6 | — | 1.6 | 1.5 |

MES—Maximal electroshock.
sc Met—Chemically induced shock obtained following subcutaneous injection of metrazol.
$ED_{50}$—Effective dose in 50% of the animals.
$TD_{50}$—Neurotoxic dose in 50% of the test animals.
PI—Protective index—The ratio of the $TD_{50}$ to the $ED_{50}$.
[a] The data fro VPA and VPD are taken from ref. 6.

CL and V values and therefore the t1/2 and MRT values of these two analogues, were similar. M-TMCD had a higher clearance than TMC-GLD, but it had a larger volume of distribution than both TMC-GLD and TMCD.

Anticonvulsant testing showed that compounds III-V were more potent than VPA in mice and rats and showed a potency similar to VPD. The anticonvulsant profiles of TMCD and M-TMCD were different from that of VPA. TMCD was only active at the sc Met test while M-TMCD was more potent than VPA in both the MES and sc Met test. Both TMCD and M-TMCD had a better safety margin than VPA.

TMCD and M-TMCD were found to be stable analogues of VPD. The metabolic stability of these two compounds may contribute to their anticonvulsant activity and shows that stable cyclopropane analogues of VPD, like its aliphatic isomers (2–4, 6), must have two substitutions at the β position to the carbonyl. M-TMCD was found to be more potent and to have a wider antiepileptic spectrum of activity than TMCD. A comparative analysis of the parallel studies with TMCD and M-TMCD showed that the fraction metabolised (fm) of M-TMCD to TMCD was about 12%.

In the literature there are several reports regarding another cyclopropyl derivative of glycine—1-aminocyclopropane-1-carboxylic acid—ACC (21, 22). ACC mimics the effect of glycine on the NMDA receptor ion channel (21), and also exhibits antidepressant and anxiolytic actions in animal models (22).

The current study suggests a good PK-PD correlation in the case of compounds V and VII. The better pharmacokinetic profile of TMC-GLD (low CL, and long t1/2–2.4 hours) over TMC-GLN may explain its anticonvulsant activity. In spite of the difficulties in making PK-PD correlation across species, the dog is the best animal model for PK studies while mice and rats are the classical animal models for antiepileptic screening.

Out of the three novel compounds investigated in the current study, M-TMCD (IV) showed the best anticonvulsant activity. The pharmacokinetics of M-TMCD and its metabolic stability offers the following advantages over VPD or VPA:

a) As a stable VPD analogue it has the potential to act in humans as a drug on its own and not as a prodrug of its corresponding inactive acid.
b) As a stable VPD analogue it should not be teratogenic.
c) In contrast to the stable VPD analogue valnoctamide (6, 16), M-TMCD is not a chiral molecule.
d) As a cyclic VPD analogue, with four methyl substituents, it cannot form a metabolite with a terminal double bond and therefore has the potential to be a non-hepatotoxic compound.

Thus, M-TMCD has the potential to become an improved derivative of VPA, which will be more potent than VPA without the problems of hepatotoxicity and teratogenicity.

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