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**Short communication**

# Synthesis and anticonvulsant activity of a series of benzamides

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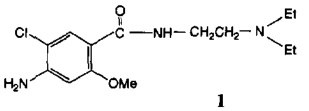
**Summary** — A series of benzamides containing *N,N*,2-trimethyl-1,2-propane diamine as the amide moiety was synthesized. The compounds were evaluated in the maximal electroshock (MES) and pentylenetetrazol (metrazole, MET) screens for anticonvulsant activity. The 3,5-trifluoromethyl, 3,5-dichloro, and 3-bromo analogues proved to be either equipotent with or more potent than phenytoin.

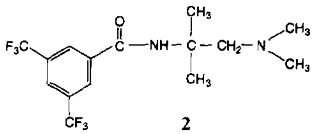
***N*-(2-(dimethylamino)-1,1-dimethylethyl)benzamide / anticonvulsant activity**

## Introduction

The benzamides are reported to possess a wide range of biological activity, including muscle relaxant [1], antiarrhythmic, antiemetic, and antipsychotic properties [2] and anticonvulsant activity [3–7]. Figure 1 illustrates a variety of benzamides reported to possess anticonvulsant activity in a number of animal models used to predict potential anticonvulsant activity in man. Compounds **I** [3], **II** [4], **IV** [6], and **V** [7] respectively have $ED_{50}$'s of 59, 18, 61.8, and 35 mg/kg ip in mice in the maximal electroshock (MES) assay indicative of activity against grand mal seizures in man. Compound **III** [5] has an $ED_{50}$ of 1.7 mg/kg po in mice in preventing electroshock-induced seizures. During our investigations of compounds closely related to metoclopramide **1**, we found an interesting series with potential anticonvulsant activity against grand mal seizures. Compounds in our series differ structurally from **1** in that *N,N*,2-trimethyl-1,2-propanediamine replaces *N,N*-diethylethylenediamine. Application of the topliss tree [8] approach to analogue selection resulted in the discovery of **2**,



**1**



**2**

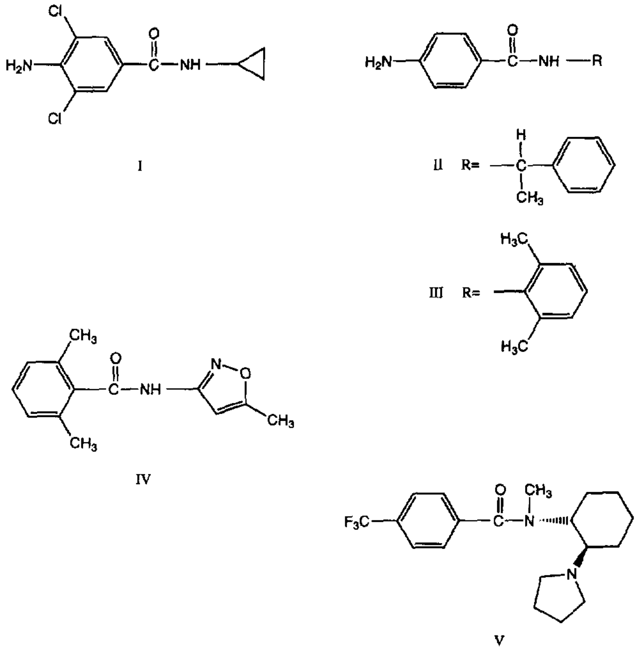


**Fig 1.** Benzamides reported to possess anticonvulsant activity.

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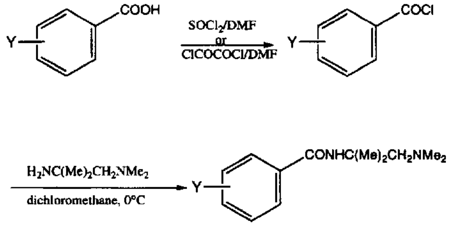
*N*-(2-(dimethylamino)-1,1-dimethylethyl)-3,5-bis(trifluoromethyl)benzamide. This paper describes the synthesis and structure–activity relationships for a number of derivatives of **2**.

## Chemistry

The benzamides were prepared by reaction of the corresponding benzoyl chlorides with two equivalents of *N*,*N*,2-trimethyl-1,2-propanediamine in dichloromethane, as shown in scheme 1. The benzoyl chlorides were either commercially available or prepared from the corresponding benzoic acids by reaction with oxalyl chloride or thionyl chloride in the presence of dimethylformamide. The benzoic acids were commercially available.

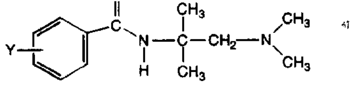


**Scheme 1.** General synthesis; see table I for substituents Y.

## Pharmacological results and discussion

The structure–activity relationship study was based on the Topliss Tree [8] approach to analogue selection. The nitrogen moiety for all of the analogues was *N*,*N*,2-trimethyl-1,2-propanediamine. Compounds were evaluated for potential anticonvulsant activity against grand mal and petit mal seizures as determined by the maximal electroshock (MES) and metrazol (MET) assays respectively. The unsubstituted derivative **3** had an $ED_{50}$ of 10.5 mg/kg ip rat in the MES screen and was inactive at 25 mg/kg ip in the MET screen. Incorporating a 4-chloro substituent as in **4** caused no change in activity. Because **4** was equipotent with **3**, the 4-methyl derivative **6** was evaluated; it gave only 33% protection against seizures at 25 mg/kg. These findings led us to prepare the 3-chloro analogue **8**. This compound was more active than **6** and equipotent with **3**. The 3-bromo derivative **9** was equipotent with **8**. Compound **10**, the 3,5-dichloro derivative, showed a modest increase in activity as compared to **8** and **3**; it gave an $ED_{50}$ of 6.0 mg/kg ip rat. Comparison of **10** with the 3,5-bis(trifluoromethyl) derivative **2** indicated that the latter was one of the most active compounds in the series; the $ED_{50}$ was 2.3 mg/kg. This compares favorably with the $ED_{50}$ in the MES screen for phenytoin, 9.6 mg/kg [9]. Other analogues that were evaluated were the 4-methoxy derivative **5**, which was inactive, and the 3,4-dichloro analogue **7**, which was equipotent with **3**. As table I indicates, this series of compounds is active and selective for grand mal seizures in animal models used to predict activity against seizures in humans.

**Table I.** Structure–anticonvulsant activity relationship.



| *Compound* | *Y* | *Anticonvulsant activity*<br>*Maximal electroshock*<br>*$ED_{50}$ mg/kg ip rat* | <br>*Metrazole*<br>*$ED_{50}$ mg/kg ip rat* |
|---|---|---|---|
| **2** | 3,5-$(CF_3)_2$ | 2.3 ± 6.1[a] | IA at 50 |
| **3** | H | 10.5 ± 1.5 | IA at 25 |
| **4** | 4-Cl | 14.5 ± 2.8 | |
| **5** | 4-OMe | IA at 25 | |
| **6** | 4-Me | 33% at 25 | |
| **7** | 3,4-$Cl_2$ | 11.1 ± 1.8 | IA at 25 |
| **8** | 3-Cl | 10.6 ± 0.8 | IA at 25 |
| **9** | 3-Br | 9.2 ± 0.8 | |
| **10** | 3,5-$Cl_2$ | 6.0[b] ± 0.8 | |
| Phenytoin | | 9.6[c] | |

[a]$ED_{50}$ mg/kg ip mouse is 9.4; [b]$ED_{50}$ mg/kg ip mouse is 17.7; [c]see reference [9].

**Table II.** Physicochemical properties.

| *Compound* | *Yield (%)* | *Mp (°C)* | *Formula* |
|---|---|---|---|
| **2** | 52[a] | 72–74 | $C_{15}H_{18}F_6N_2O$ |
| **3** | 21[b] | 56–58 | $C_{13}H_{20}N_2O$ |
| **4** | 77[c] | 90–93 | $C_{13}H_{19}ClN_2O$ |
| **5** | 29[b] | 84–85 | $C_{14}H_{22}N_2O_2$ |
| **6** | 38[d] | 69–72 | $C_{14}H_{22}N_2O$ |
| **7** | 78[c] | 63–66 | $C_{13}H_{18}Cl_2N_2O$ |
| **8** | 40[e] | 30–32 | $C_{13}H_{19}ClN_2O$ |
| **9** | 82[f] | Oil | $C_{13}H_{19}BrN_2O$ |
| **10** | 60[c] | 88–90 | $C_{13}H_{18}Cl_2N_2O$ |

[a]Recrystallized from pentane; [b]recrystallized from petroleum ether; [c]recrystallized from ethanol/water; [d]distilled on Kugelrohr apparatus, bp 110–120 °C, 0.3 mmHg; [e]distilled on Kugelrohr apparatus, bp 120–125 °C, 0.3 mmHg; [f]distilled on Kugelrohr apparatus, bp 42–90 °C, 0.1 mmHg.

## Experimental protocols

### *Chemistry*

Melting points were determined in a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab Inc, or Galbraith Laboratories Inc, and C, H, N values are within ±0.4% of the theoretical values. The NMR spectra were recorded on a Varian XL100, Varian XL300, Gemini 200 or a CFT-20 spectrometer using tetramethylsilane as the standard. Spectroscopic data are consistent with the assigned structures. The benzoic acid, 4-methoxybenzoic acid, 4-methylbenzoic acid, 3-chlorobenzoic acid, 3-bromobenzoic acid, 3,5-dichlorobenzoic acid, and 3,5-bis(trifluoromethyl)benzoyl chloride were purchased from Aldrich Chemical Co. The 4-chlorobenzoic acid was purchased from Matheson, Coleman and Bell, and the 3,4-dichlorobenzoic acid was purchased from Eastman Chemical Co. The *N*,*N*,2-trimethyl-1,2-propanediamine was a gift from Angus Chemical Co.

*N-(2-(Dimethylamino)-1,1-dimethylethyl)benzamide* **3**

To a mixture of benzoic acid (9.8 g, 0.08 mol) and dimethylformamide (2 drops) at ambient temperature under a nitrogen atmosphere was added oxalyl chloride (25 mL). After stirring for 48 h, the excess oxalyl chloride was removed by distillation and toluene was added to the residue. The toluene was removed by distillation and the residue was dissolved in dichloromethane (100 mL), then added dropwise to a solution of *N*,*N*,2-trimethyl-1,2-propanediamine (19.8 g, 0.17 mol) in dichloromethane (150 mL) at ambient temperature. After stirring for 18 h, the mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The aqueous phase was made basic with potassium carbonate and extracted with ethyl acetate. The combined organic extracts were dried over potassium carbonate, then filtered and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (Kugelrohr) to obtain a white solid at 120 °C and 0.3 mmHg. The solid was crystallized from petroleum ether to give 3.7 g (21%) of **3** as a white solid: mp 56–58 °C. $^1$H-NMR ($CDCl_3$) δ: 1.47 (s, 6H, $CH_3$), 2.37 (s, 6H, $CH_3$), 2.49 (s, 2H, $CH_2$), 7.05 (br s, 1H, NH), 7.37–7.47 (m, 3H, ArH), 7.72–7.77 (m, 2H, ArH).

*4-Chloro-N-(2-(dimethylamino)-1,1-dimethylethyl)benzamide* **4**

To a mixture of 4-chlorobenzoic acid (5.0 g, 0.03 mol) and dimethylformamide (2 drops) at ambient temperature under a nitrogen atmosphere was added thionyl chloride (30 mL). After stirring for 3 h, the mixture was concentrated in vacuo. Toluene was added to the residue and the mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (50 mL) and the solution was added dropwise to a solution of *N*,*N*,2-trimethyl-1,2-propanediamine (7.4 g, 0.06 mol) in dichloromethane (50 mL) at ice-bath temperature. After stirring at ambient temperature for 3.5 h, the mixture was concentrated in vacuo and the residue was partitioned between water and diethyl ether. The aqueous phase was made basic with potassium carbonate and extracted with diethyl ether. The combined organic extracts were dried over potassium carbonate, then filtered and concentrated in vacuo. Recrystallization of the residue from ethanol/water mixtures gave 6.28 g (77%) of **4** as a white solid: mp 90–93 °C. $^1$H-NMR (DMSO-$d_6$) δ: 1.30 (s, 6H, $CH_3$), 2.20 (s, 6H, $CH_3$), 2.57 (s, 2H, $CH_2$), 7.46–7.51 (m, 2H, ArH), 7.68 (br s, 1H, NH), 7.74–7.81 (m, 2H, ArH).

Preparation of compounds **5** and **7–10** was as described for compound **3**, using oxalyl chloride. Compound **6** was prepared as described for compound **4** using thionyl chloride. The acid chloride for preparation of compound **2** was commercially available.

### *Pharmacology*

The test compounds were evaluated in two standard screens, the MES [10] and the pentylenetetazol (MET) convulsion [11] screens. The rat was the preferred animal in both tests, and saline-treated animals were used as controls. Phenytoin was used as the reference drug.

*Procedure for induction of maximum electroshock (MES) seizures*

Male Wistar rats (weight range 150–250 g) or male CD-1 mice (weight range 16–30 g) were obtained from Charles River Labs and group-housed with access to food and water ad libitum. Test compounds were dissolved in distilled water or microsuspended in 0.5% methyl cellulose, and a range of doses was administered to groups of animals ($N$ = 6) orally (po) by gavage or intraperitoneally (ip) by injection. One hour after oral administration, or half an hour after ip injection, the animals were tested for protection against seizures. An animal was considered protected if the hind limb extensor component of the seizure was abolished. Seizures were induced using a Wahlquist Instrument Co electroshock generator, as described by Woodbury and Davenport [10]. The eyes of each rat were wetted with a lidocaine/saline solution and a current of 150 mA and 0.2 s duration was delivered via corneal electrodes. The same procedure was employed for mice using reduced stimulus intensity (50 mA, 0.2 s duration). In both species the stimulus was sufficient to induce a maximal seizure in 100% of control animals. The number of animals protected in each group was expressed as a percentage, and an $ED_{50}$ value was calculated by probit analysis.

*Procedure for induction of pentylenetetrazol (metrazol) seizures (MET)*

Male Wistar rats (weight range 150–250 g) or male CD-1 mice (weight range 16–30 g) were obtained from Charles River Labs and group housed with access to food and water ad libitum. Test compounds were dissolved in distilled water or microsuspended in 0.5% methyl cellulose, and a range of doses was administered to groups of animals ($N$ = 6) orally (po) by gavage or intraperitoneally (ip) by injection. One hour after oral administration, or half an hour after ip injection, the animals were challenged with a dose of pentylenetetrazol (90 or 100 mg/kg sc rats and mice respectively) and observed individually in Plexiglas cages for seizure activity as described by Swinyard [11]. An animal was considered protected if the tonic-clonic seizure accompanied by loss of righting was abolished. The number of animals protected in each group was expressed as a percentage, and an $ED_{50}$ value was calculated by probit analysis.

## Acknowledgments

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