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Synthesis, Characterization and Anticonvulsant Activity of Enaminones. Part 6: Synthesis of Substituted Vinylic Benzamides as Potential Anticonvulsants

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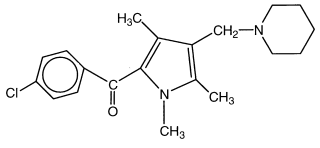
Abstract—A comparison of enaminones from various unsubstituted and *p*-substituted benzamides to the analogous benzylamines has been undertaken with the aim of elucidating the essential structural parameters necessary for anticonvulsant activity. Initial studies on methyl 4-*N*-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-oate, **3a**, 3-*N*-(benzylamino)cyclohex-2-en-1-one, **3p**, and 5,5-dimethyl-3-*N*-(benzylamino)-cyclohex-2-en-1-one, **3r** indicated that benzylamines possessed significant anti-maximal electroshock seizure (MES) activity. Evaluation of the analogous benzamides revealed significant differences in anticonvulsant activity, these differences were most probably related to the differences in their three-dimensional structures.

Introduction

Despite optimal use of available antiepileptic drugs marketed in the United States, many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients.[1] A new group of unique drugs have entered the antiepileptic armamentarium. These include felbamate, lamotrigine, oxacarbazine, dezinamide, gabapentin, topiramate, vigabatrin, and zonisamide.[2] In addition, a new series of compounds have been reported, most notably the aroyl(aminoacyl)pyrroles, **1**,[3] and the 3-aminopyrroles, **2**.[4] The most active compound in each series is shown below.



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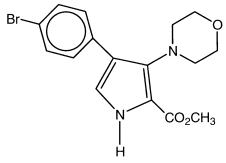

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Carson et al.[3] indicated in their report that the structural similarity of the aroyl(aminoacyl)-pyrroles to the *N*-benzyl enaminones, **3** (Table 1), synthesized in our laboratories[5–10] was pervasive in their synthetic efforts. Further, Carson indicated the extensive charge delocalizaton involving the nitrogen atom and the carbonyl oxygen was analogous in both the acyl pyrroles[11] and enaminones.[12] Further molecular modeling studies of **1** with **3a** (Fig. 1) by Carson et al. showed a congruent spatial relationship of the phenyl ring, nitrogen atoms and carbonyl groups, indicating RMS deviation = 0.38 Å; volume **1** = 320 Å; volume **3b** = 254 Å; common volume = 168 Å.[3]

Key words: Anticonvulsants; NMR; X-ray crystal structures; molecular modeling/mechanics.
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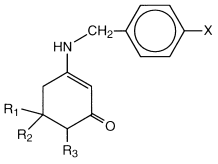
The Carson report provided an impetus to reinvestigate the *N*-benzylamine enaminone series and to synthesize the analogous benzamides, **4**, the latter functionality which had previously been shown to possess significant anticonvulsant activity in their own right in other laboratories.[13–16] We had reported an initial study of the enaminones of the benzylamines,[5,6] however, this series was considerably abbreviated due to significant activity shown with the aniline derivatives which engaged our synthetic efforts. Compound **3a** ($R_1 = CH_3$, $R_2 = H$, $R_3 = CO_2CH_3$, $X = H$) was the most potent in the series, displaying an intraperitoneal (ip) ED_{50} in mice of 64.7 mg/kg and a TD_{50} > 500 mg/kg and an oral (po) ED_{50} in rats of 26.8 mg/kg and no toxicity noted at dosages up to 500 mg/kg. In addition, in the corneal kindling model **3a** provided an ED_{50} of 78.3 mg/kg, compared to phenytoin, 48.3 mg/kg, under the same conditions.[5] A brief structure activity relationship was attempted. It was found in the same carbomethoxy series, *para* substitution led to less active or inactive compounds.[5] However, the *p*-fluoro compound ($R_1 = CH_3$, $R_2 = H$, $R_3 = CO_2CH_3$, $X = F$) was also active, providing an ip ED_{50} of 159 mg/kg in mice, and a po ED_{50} of 49.3 mg/kg and a TD_{50} > 230 mg/kg in rats.[5] We postulated that the activity of this analogue verified Topliss's findings that *p*-fluoro substitution produced a minimal change in σ and π effects compared to the unsubstituted compound.[5] In addition, the *p*-chloro ($R_1 = CH_3$, $R_2 = H$, $R_3 = CO_2CH_3$, $X = Cl$; $+\sigma$, $+\pi$) provided spurious results, probably due to solubility problems, while the *p*-tolyl ($R_1 = CH_3$, $R_2 = H$, $R_3 = CO_2CH_3$, $X = CH_3$; $-\sigma$, $+\pi$) and *p*-carboxy ($R_1 = CH_3$, $R_2 = H$, $R_3 = CO_2CH_3$, $X = CO_2H$; $+\sigma$, $-\pi$) analogues were inactive. Further, in the dimedone series, the unsubstituted benzylamine compound (**3r**, $R_1 = R_2 = CH_3$, $R_3 = H$, $X = H$), was active with an ED_{50} of 53 mg/kg and a TD_{50} of 148 mg/kg in mice,[5] while the comparable cyclohexene derivative (**3p**, $R_1 = R_2 = R_3 = H$, $X = H$) was less active.[6] Additionally, it was noted that replacing one of the benzylic protons with a methyl group, producing a chiral α-phenethyl side chain, yielded isomers both of which were inactive.[6] In contrast, the β-phenethyl side chain was highly active.[6] We herein report further studies on these benzylamino analogues and the comparable vinylic benzamides.

Table 1. Benzylamines



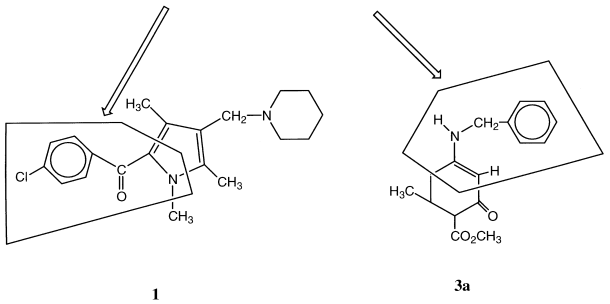
3

Compound	R_1	R_2	R_3	X	Yield	MP, °C	Clog P[a]
3a[b]	CH_3	H	CO_2CH_3	H	90	154–155[c]	2.79
3b[d]	CH_3	H	$CO_2C_2H_5$	H	77	134–135[f]	3.32
3c	CH_3	H	$CO_2C(CH_3)_3$	H	55	152–155[c]	4.03
3d[e]	CH_3	H	CO_2CH_3	Cl	64	173–174[g]	2.79
3e	CH_3	H	$CO_2C_2H_5$	Cl	69	169–172[h]	4.03
3f	CH_3	H	$CO_2C(CH_3)_3$	Cl	47	182–185[f]	4.74
3g[b]	CH_3	H	CO_2CH_3	CH_3	48	160–163[e]	3.29
3h	CH_3	H	$CO_2C_2H_5$	CH_3	76	134–135[e]	3.82
3i	CH_3	H	$CO_2C(CH_3)_3$	CH_3	58	123–126[e]	4.53
3j	CH_3	H	CO_2CH_3	OCH_3	77	168.5–172[e]	2.71
3k	CH_3	H	$CO_2C_2H_5$	OCH_3	74	154–157[e]	3.24
3l	CH_3	H	$CO_2C(CH_3)_3$	OCH_3	38	174–175[c]	3.95
3m	CH_3	H	CO_2CH_3	CN	44	204–208[c]	2.22
3n	CH_3	H	$CO_2C_2H_5$	CN	38	184–186[h]	2.75
3o	CH_3	H	$CO_2C(CH_3)_3$	CN	37	172–175[c]	3.46
3p[e]	H	H	H	H	25	125–127[f]	2.41
3q	CH_3	H	H	H	25	137.5–139[f]	2.93
3r[b]	CH_3	CH_3	H	H	15	124–127[f]	3.45
3s	H	H	H	Cl	48	170–172[h]	3.12
3t	CH_3	H	H	Cl	44	186–187[h]	3.64
3u	CH_3	CH_3	H	Cl	47	159–162[c]	4.16
3v	H	H	H	CH_3	39	153–155[c]	2.91
3w	CH_3	H	H	CH_3	32	146–148[f]	3.43
3x	CH_3	CH_3	H	CH_3	59	139–140[f]	3.95
3y	H	H	H	OCH_3	35	159–160[g]	2.33
3z	CH_3	H	H	OCH_3	68	160–162[h]	2.85
3aa	CH_3	CH_3	H	OCH_3	82	159–160[g]	3.37
3bb	H	H	H	CN	57	156–159[h]	1.84
3cc	CH_3	H	H	CN	34	168–171[i]	2.36
3dd	CH_3	CH_3	H	CN	43	215–217[j]	2.90

[a] CLog P calculated on the protonated form.
[b] Ref. 5.
[c] Ethyl acetate.
[d] Ref. 9.
[e] Ref. 6.
[f] Ethyl acetate-petroleum ether (bp 38–54°C).
[g] Methanol.
[h] 2-Propanol.
[i] Ethyl acetate–ethanol (95%).
[j] 2-Propanol–acetone.

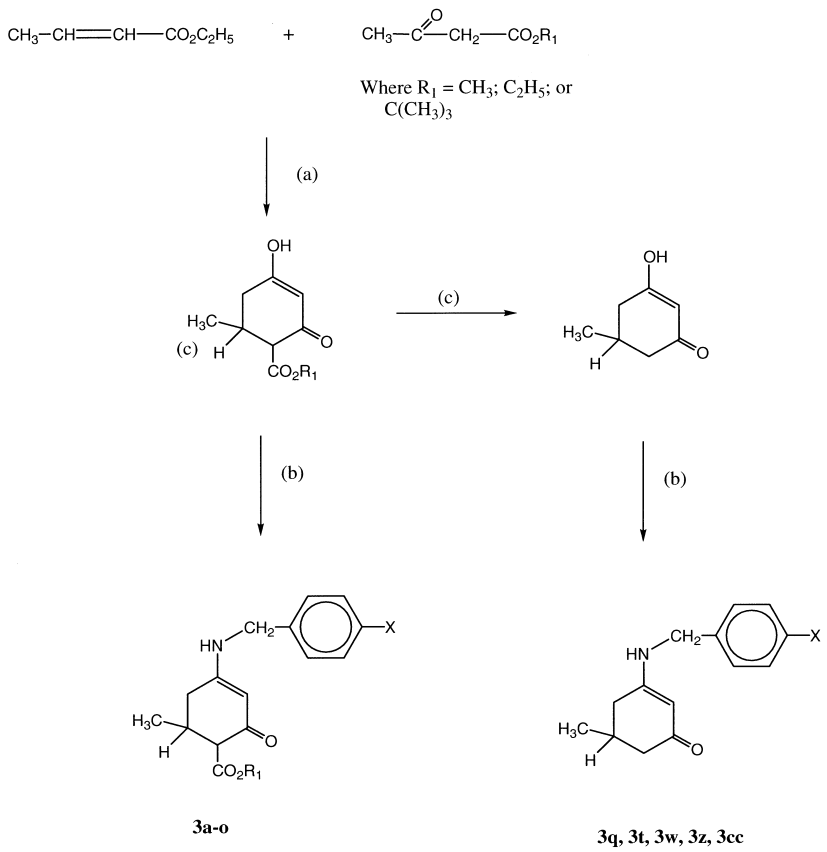
Chemistry

Cyclic enaminone esters of the benzylamine series, **3** (Table 1), were synthesized from β-hydroxy keto esters, as previously reported.[5–10] The synthetic pathway is shown in Scheme 1. The condensation reaction of ethyl crotonate with the respective acetoacetic ester was modified as reported by Friary and co-workers for the synthesis of the 4-carbo-*tert*-butoxy-5-methylcyclo-hexane-1,3-dione.[17] It was noted that in the synthesis of the methyl ester, if sodium ethoxide was employed as the base, a transesterification reaction occurred and the ethyl ester was obtained. 5-Methyl-1,3-cyclohexanedione was synthesized by the decarboxylation of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione as reported by Friary and co-workers.[17] The subsequent condensation of the β-keto esters with the appropriate benzylamine was varied to maximize overall yields.



1 **3a**

Figure 1. Sites of conguent spatial relationship (arrows) of the aroyl-(aminoacyl)pyrroles, **1** (ref 3) and methyl 4-*N*-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-oate, **3a** (ref 3).



Scheme 1. Synthesis of benzylamino enaminone esters and 5-methyl-cyclohexane analogues. Conditions: (a) NaOEt or NaOMe, Δ; (b) substituted benzylamine; (c) H_2SO_4, Δ (ref 17) (see Experimental).

Previous studies indicated that a 1:1 ratio of absolute ethanol:ethyl acetate was employed as the solvent mixture.[8] The benzamides, **4** (Table 2), were synthesized by amination of the respective β-diketones[18] followed by acylation with the corresponding benzoyl chlorides with triethylamine as the acid scavenger. Careful monitoring of this latter reaction was undertaken to minimize the β-acylation (**5**) side product.[12] However, the yields of benzamides **4** were lower when compared to the benzylamines. In view of the reported lability of the *tert*-butoxy group,[10] an excess of triethylamine was used in these reactions and the isolated product was not extracted with aqueous acid and base as indicated for the methyl and ethyl esters, but evaporated to dryness and chromatographed on a silica gel column. The synthetic pathway is shown in Scheme 2.

X-ray Crystallography

In view of our previous reports on the intramolecular hydrogen bonding of the vinyl hydrogen and the aromatic ring,[6,7] an X-ray diffraction study of two representative benzamides was performed. As noted in Fig. 2 of **4j** and Fig. 3 of **4cc**, strong hydrogen bonding occurred between the vinyl proton and the carbonyl oxygen of the amide group in each structure, providing a pseudo three-ring structure. This pseudo three-ring configuration was not observed with the comparable benzylamines. Codding et al.,[19] in the X-ray analysis of **3a** indicated intermolecular N-H...O bonding, providing an extended sofa conformation without intramolecular vinyl proton involvement. A summary of the atomic coordinates of **4j** and **4cc** are provided in Tables 3 and 4.

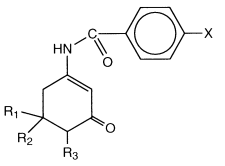
High Field NMR

To further establish a structural difference between the benzylamines and benzamides, a high field NMR study was performed. We had previously shown[6,7] that the vinyl proton was deshielded due to its hydrogen-bonding to the aromatic ring in the aniline series. In the benzamide series, we propose that the carbonyl oxygen forms a hydrogen bond with this proton. As was shown from X-ray analysis of benzylamine **3a**, however, hydrogen bonding of the vinyl proton, unlike that shown with the aniline series, does not occur. Table 5 displays a comparison of NMR data of the vinyl proton assignments in three individual sets of analogues. As noted, the benzamides were all deshielded and appeared downfield compared to the comparable benzylamines, thus further verifying these structural differences.

Molecular Modeling

Molecular modeling studies were performed on the active Carson's pyrrole, **1**,[3] the most active 3-amino-pyrrole, **2**[4] and the three active benzylamines (**3a, 3q** and

Table 2. Benzamides



4

Compound	R_1	R_2	R_3	X	Yield	MP, °C	Clog P
4a	CH_3	H	CO_2CH_3	H	32	178–179[a]	1.55
4b	CH_3	H	$CO_2C_2H_5$	H	32	161–163[a]	2.08
4c	CH_3	H	$CO_2C(CH_3)_3$	H	44	193–197[b]	2.78
4d	CH_3	H	CO_2CH_3	Cl	38	200–202[c]	2.46
4e	CH_3	H	$CO_2C_2H_5$	Cl	36	160–162[a]	2.99
4f	CH_3	H	$CO_2C(CH_3)_3$	Cl	14	166–168[a]	3.70
4g	CH_3	H	CO_2CH_3	CH_3	35	157–159[a]	2.05
4h	CH_3	H	$CO_2C_2H_5$	CH_3	27	125–127[a]	2.57
4i	CH_3	H	$CO_2C(CH_3)_3$	CH_3	11	136–139[a]	3.28
4j	CH_3	H	CO_2CH_3	OCH_3	21	166–168[a]	1.75
4k	CH_3	H	$CO_2C_2H_5$	OCH_3	43	126–128[a]	2.28
4l	CH_3	H	$CO_2C(CH_3)_3$	OCH_3	46	142–144[a]	2.98
4m	CH_3	H	CO_2CH_3	CN	33	233–237[d]	1.45
4n	CH_3	H	$CO_2C_2H_5$	CN	49	187–189[e]	1.98
4o	CH_3	H	$CO_2C(CH_3)_3$	CN	55	212–213[f]	2.68
4p	H	H	H	H	12	172–174[f]	1.16
4q	CH_3	H	H	H	25	137.5–139[a]	1.68
4r	CH_3	CH_3	H	H	13	146–148[g]	2.20
4s	H	H	H	Cl	28	196–199[g]	2.08
4t	CH_3	H	H	Cl	22	170–171.5[a]	2.60
4u	CH_3	CH_3	H	Cl	18	196–199[g]	3.12
4v	H	H	H	CH_3	20	197–200[a]	1.66
4w	CH_3	H	H	CH_3	28	174–176[a]	2.18
4x	CH_3	CH_3	H	CH_3	16	183–186[f]	2.70
4y	H	H	H	OCH_3	32	171–174[f]	1.36
4z	CH_3	H	H	OCH_3	20	166–167[a]	1.88
4aa	CH_3	CH_3	H	OCH_3	37	153–156[g]	2.40
4bb	H	H	H	CN	6	207–210[f]	1.31
4cc	CH_3	H	H	CN	15	219–221[a]	1.83
4dd	CH_3	CH_3	H	CN	15	238–241[f]	2.35

[a] 95% Ethanol–ether.
[b] Ethanol (abs.)-ligroine (bp 60–90°C).
[c] 2-Propanol.
[d] Methanol–EtOAc-acetone.
[e] 2-Propanol–EtOAc.
[f] EtOAc.
[g] Methylene chloride.

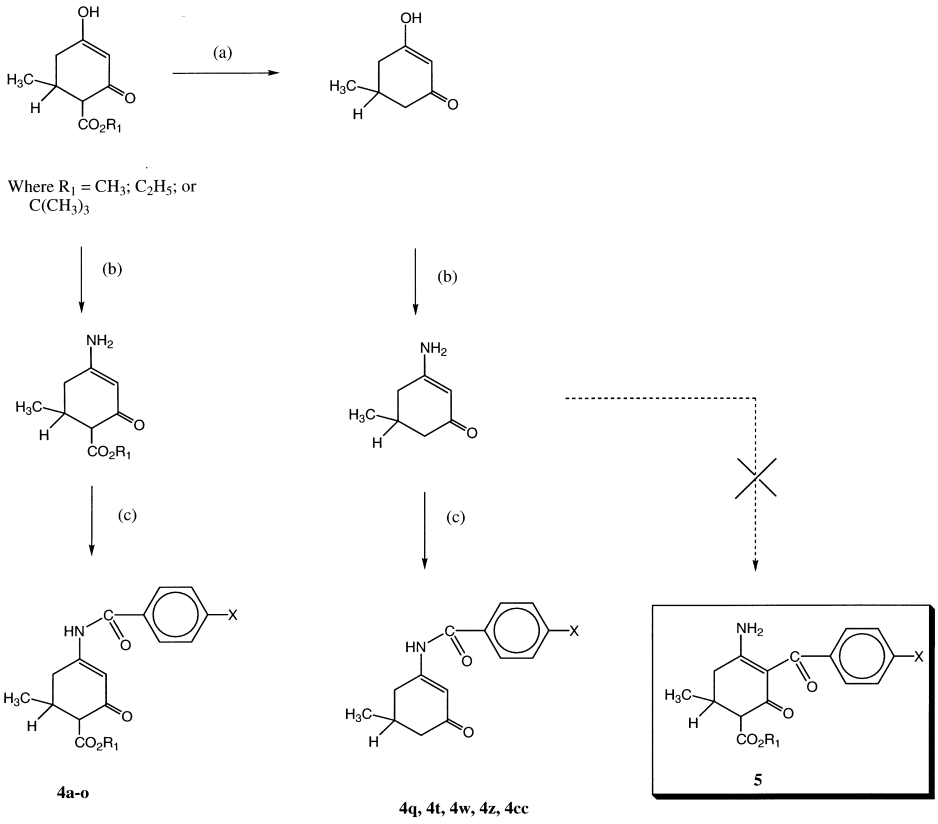
3r). The compounds were modeled and minimized by Spartan programs[20] using AM1 model with geometry optimization. These conformations were transferred to the SYBYL[21] program where they were superimposed via the MULTIFIT program. Each structure was constrained to superimpose the phenyl centroid, the pyrrole nitrogen (in **1** and **2**, or the benzylamine nitrogen in **3a, 3q** and **3r**), and the carbonyl oxygen. The RMS deviations from the templates of the two pyrroles were 0.77 Å for **1** and 0.78 Å for **2**, while the mean RMS deviation of the five molecules was the same in both cases: 0.595 Å. The results of the MULTIFIT program are shown in Figure 4.

Pharmacology

Pharmacological testing of the compounds listed in Tables 1 and 2 have been provided by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological Disorders and Stroke (NINDS). These testing procedures have been described.[22–24] Phase I evaluation of the reported benzylamines and benzamides involved three tests: maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (ScMet), and neurologic toxicity (Tox) in mice. Phase I data for the benzylamines and the comparable benzamides are shown in Table 6. As previously reported,[5,6,8] to differentiate the results between different rodent species, the most active class 1 analogues, were subsequently evaluated for oral (po) activity (Phase VIA) in the rat. Data are shown in Table 6. In several instances, the threshold tonic extension (TTE) test[25] was performed. This clinically nonselective, electroconvulsive seizure model has been described previously.[25] The test is similar to the MES test but uses a lower level of electrical current. The lower current makes the TTE test more sensitive, but less discriminate than the MES screen. If a compound was found to possess significant activity in the TTE test while still remaining inactive in the MES rescreen, it becomes a candidate for more advanced testing.

Results and Discussion

Consistent with the previous studies, our synthetic approach utilized the Free-Wilson analysis[26] successfully employed by Craig.[27,28] The *para* substitution pattern for this study involved: chloro ($+\pi$, $+\sigma$), cyano ($-\pi$, $+\sigma$), methoxy ($-\pi$, $-\sigma$), and methyl ($+\pi$, $-\sigma$) groups which were compared to the unsubstituted analogue (0 π, 0 σ). As noted in Tables 1 and 2, Clog P[29] measurements of the protonated benzylamines,which predominates at physiological pH, still provided more lipophilic compounds than the comparable benzamides. The Clog P range for the benzylamines was 1.84 for **3bb** to 4.74 for **3f** while the benzamides varied from 1.16 for **4p** to 3.70 for **4f**. In either series, the highly lipophilic compounds were inactive. Class 4 benzylamines in Table 6 which included **3s** (Clog P 3.12) and **3t** (3.64) were found to be soluble with difficulty and presented problems establishing a uniform dosage, thus accounting for erratic test results. These current results with the *p*-chloro benzylamine derivatives **3s** and **3t**, reaffirmed our initial observation with this substituent.[5] Further data analysis on **3d–f** and **3s–u** showed only marginal, class 2, activity (**3d, 3u**), while each comparable *p*-chloro aniline moiety was highly active.[5–7] Class 4 benzamides were more numerous and included **4f, 4i** (Clog P 3.70), **4m** (1.45), **4q** (1.68), **4aa** (2.40) and **4cc** (1.83). Paradoxically, **4aa** was the most active benzamide in the series in the rat, displaying an oral MES ED_{50} of 183.51 mg/kg and a TD_{50} of >400 mg/kg, providing a protective index (TD_{50}/ED_{50}) of >2.18. Analysis of the esters indicated that of the ten *tert*-butyl esters synthesized, only one, **3i**, possessed anticonvulsant activity. In addition to the lipophilicity of the *tert*-butyl group, a steric (E_s)[30] factor for this group must also be taken into consideration. E_s values for the esters shows a significant difference: -1.54 for *tert*-butyl; -0.07 for ethyl; and 0.00 for methyl. The role of the ester functionality



Scheme 2. Synthesis of vinylic benzamido compounds. Conditions: (a) H_2SO_4, $\triangle$ (ref. 17); (b) NH_3, $\triangle$; (c) substituted benzoyl chloride NEt_3 (see Experimental).

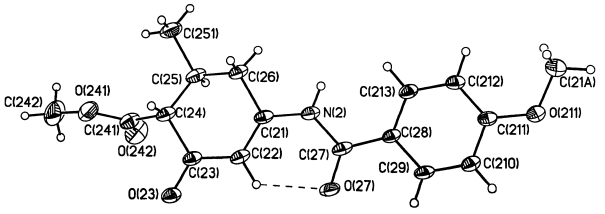


Figure 2. X-ray crystal structure of methyl 4-*N*-[(*p*-methoxy)-benzamido]-6-methyl-2-oxocyclohex-3-en-1-oate (**4j**).

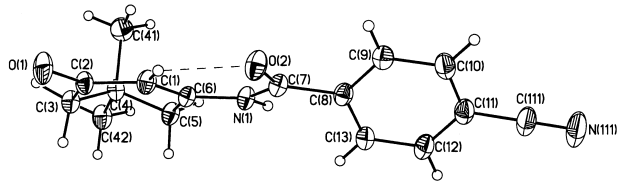


Figure 3. X-ray crystal structure of 3-*N*-{(*p*-cyano)benzamido]-5-methylcyclohex-2-en-1-one (**4cc**).

in contributing to anticonvulsant activity was most dramatically shown in the benzylamine series with prototype **3a** (Clog P 2.79). Changing the ester functionality to the ethyl ester **3b** (Clog P 3.32) or the *tert* butyl ester **3c** (Clog P 4.03) completely abolished activity. Further, in this series, only the unsubstituted compounds **3a, 3p 3q** and **3r** possessed significant anti MES activity reaffirming our initial conclusion[5] that a steric factor was most probably operating on the aromatic group as well. The lack of the -I effect in the benzylamines, was due to the presence of the methylene bridge which blocks this contribution, thus, comparison to the active *p*-substituted aniline derivatives was unsound.[5] ED_{50} analysis for **3p** and **3r** are currently underway and will be reported shortly.

In the benzamide series, none of the unsubstituted esters was active, while dimedone derivative **4r** was the most active analogue in this study. Of interest in this series was the significant anti-pentylenetetrazol activity shown by a number of analogues. *Para*-tolyl derivatives **4g** and **4h**, *p*-methoxy **4j** and **4z**, *p*-chloro **4s**, and unsubstituted **4p** all possessed significant anti-scMet activity which was not observed in the benzylamine series. The interpretation of this significant change in protection may be explained by analysis of the three dimensional behavior of these series. It was shown in X-ray crystal studies, high field NMR analysis and molecular modeling examination, that these two series are distinct. Thus, binding of an active benzylamine to a putative receptor would be different than that of the active benzamide. The fact that only the unsubstituted benzylamines are MES-active, while only **4r** of the unsubstituted benzamides protects the animals from electroshock seizures further verifies this hypothesis. Further, the lack of scMet activity in the benzylamines parallels that of the aniline derivatives,[5,6,8] and further differentiates them from the benzamides.

To further justify the pseudo three ring hypothesis, a search of the Cambridge Structural Database[31] for

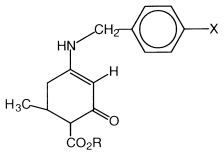
Table 3. Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [$Å^2 \times 10^3$] for methyl 4-*N*-[(*p*-methoxy)benzamido]-6-methyl-2-oxocyclohex-3-en-1-oate, **4j**. *U* (eq) is defined as one third of the orthogonalized U_{ij} tensor

	x	*y*	*z*	*U* (eq)
O (13)	3471 (5)	2620 (2)	1518 (2)	86 (1)
O (17)	2543 (5)	−1142 (2)	533 (2)	88 (1)
O (111)	235 (4)	90 (2)	−3682 (2)	77 (1)
O (141)	3181 (6)	1186 (4)	3824 (3)	122 (2)
O (142)	5696 (6)	1134 (3)	3313 (3)	90 (1)
O (23)	−2290 (4)	7260 (2)	1679 (2)	68 (1)
O (27)	1428 (5)	6597 (2)	−615 (2)	80 (1)
O (211)	6740 (4)	4279 (2)	−2771 (2)	75 (1)
O (241)	−3213 (5)	5662 (3)	3997 (3)	98 (1)
O (242)	−992 (6)	6237 (4)	3803 (3)	109 (2)
N (1)	2596 (5)	562 (3)	−25 (3)	60 (1)
N (2)	1876 (5)	4980 (3)	576 (2)	59 (1)
C (11)	3082 (5)	626 (3)	789 (3)	51 (1)
C (12)	3122 (6)	1574 (3)	745 (3)	59 (1)
C (13)	3497 (7)	1754 (4)	1537 (4)	71 (2)
C (14)	4053 (15)	773 (6)	2466 (5)	156 (5)
C (141)	4193 (10)	1096 (4)	3268 (4)	71 (2)
C (142)	6054 (13)	1410 (7)	4058 (5)	122 (3)
C (15)	3588 (34)	−93 (12)	2576 (6)	57 (5)
C (15A)	4478 (25)	−188 (10)	2418 (15)	65 (6)
C (151)	4580 (16)	−1133 (6)	3368 (5)	105 (3)
C (16)	3545 (9)	−336 (4)	1686 (3)	62 (2)
C (17)	2306 (6)	−284 (3)	−131 (3)	61 (1)
C (18)	1675 (5)	−103 (3)	−1073 (3)	52 (1)
C (110)	971 (6)	−878 (4)	−2066 (3)	65 (1)
C (11A)	120 (10)	1034 (5)	−4515 (4)	96 (2)
C (111)	693 (6)	79 (3)	−2843 (3)	57 (1)
C (112)	850 (6)	950 (4)	−2723 (3)	64 (1)
C (113)	1339 (6)	850 (3)	−1854 (3)	61 (1)
C (21)	780 (6)	5212 (3)	1235 (3)	54 (1)
C (22)	−166 (6)	6191 (4)	1138 (3)	60 (1)
C (23)	−1331 (6)	6382 (4)	1823 (3)	57 (1)
C (24)	−1453 (7)	5469 (3)	2756 (3)	64 (1)
C (241)	−1847 (8)	5843 (4)	3553 (3)	72 (2)
C (242)	−3528 (13)	5916 (8)	4865 (5)	134 (3)
C (25)	100 (7)	4550 (4)	2985 (3)	72 (2)
C (251)	−112 (10)	3577 (4)	3850 (4)	99 (2)
C (26)	646 (7)	4273 (3)	2123 (3)	62 (1)
C (27)	3457 (6)	5231 (3)	−887 (3)	50 (1)
C (28)	3457 (6)	5231 (3)	−887 (3)	50 (1)
C (29)	3904 (7)	5944 (4)	−1741 (3)	65 (1)
C (210)	5015 (6)	5602 (4)	−2334 (4)	68 (1)
C (21A)	7398 (9)	3188 (4)	−2612 (5)	93 (2)
C (211)	5698 (6)	4534 (3)	−2113 (3)	57 (1)
C (212)	5307 (6)	3823 (4)	−1261 (3)	60 (1)
C (213)	4209 (6)	4169 (3)	−662 (3)	59 (1)

Table 4. Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [$Å^2 \times 10^3$] for 3-*N*-[(*p*-cyano)benzamido]-5-methylcyclohex-2-en-1-one, **4c**. *U* (eq) is defined as one third of the orthogonalized U_{ij} tensor

	x	*y*	*z*	*U* (eq)
O (1)	−332 (1)	8647 (2)	5409 (2)	82 (1)
O (2)	−192 (1)	8829 (2)	2950 (2)	71 (1)
N (1)	829 (1)	9009 (2)	3311 (2)	54 (1)
N (111)	1149 (3)	9835 (4)	−567 (2)	118 (2)
C (1)	204 (2)	8817 (3)	4354 (2)	57 (1)
C (2)	181 (2)	8756 (3)	5104 (2)	56 (1)
C (3)	780 (2)	8849 (3)	5506 (2)	59 (1)
C (4)	1366 (2)	8516 (3)	5123 (2)	53 (1)
C (41)	1345 (2)	7455 (3)	5026 (2)	76 (1)
C (42)	1961 (2)	8793 (3)	5521 (2)	73 (1)
C (5)	1372 (2)	9006 (3)	4414 (2)	60 (1)
C (6)	758 (2)	8928 (2)	4026 (2)	49 (1)
C (7)	363 (2)	8989 (2)	2816 (2)	52 (1)
C (8)	574 (2)	9152 (3)	2086 (2)	54 (1)
C (9)	232 (2)	8724 (3)	1560 (2)	63 (1)
C (10)	396 (2)	8884 (3)	870 (2)	70 (1)
C (11)	886 (2)	9486 (3)	711 (2)	66 (1)
C (111)	1034 (2)	9678 (4)	1 (2)	84 (1)
C (12)	1225 (2)	9924 (3)	1234 (2)	68 (1)
C (13)	1073 (2)	9753 (3)	1921 (2)	59 (1)

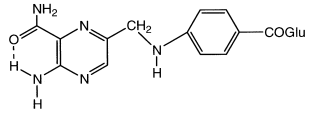
Table 5. Vinyl proton assignments



Compound	R	X	δ, ppm	Compound	R	X	δ, ppm
3a[a]	CH_3	H	4.98[b]	**4a**	CH_3	H	6.82[c]
3b[d]	C_2H_5	H	5.22[b]	**4b**	C_2H_5	H	6.82[c]
3f	$C(CH_3)_3$	Cl	5.17[b]	**4f**	$C(CH_3)_3$	Cl	6.76[c]

[a] Ref 5.
[b] Solvent: $CDCl_3$.
[c] Solvent: $(CD_3)_2SO$.
[d] Ref 6.

potential intermolecular or intramolecular hydrogen bonding interactions between vinyl protons as donors and oxygen atoms (selecting a screening H...O distance of between 1.8 and 2.5 Å) as acceptors gave a total of 11,241 hits. While some of these could be discarded as not being hydrogen bonding in character based on their small C-H...O angle, nevertheless the mean H....O distance was 2.448 Å. The distribution of C-H....O angles was bimodal with a minor cluster centered between 95 and 100° and a main cluster centered between 155 and 160°. These results clearly show that a hydrogen-bonding interaction between a vinylic proton and oxygen is a relatively common occurrence in the solid state. The pseudo ring hypothesis is not novel. Rososowsky[32] postulated a ''pseudo-ring'' system in explaining the activity of a 2-amino-3-carbamoylpyrazino folic acid analogue **6**, in which the ortho amino group was intramolecularly hydrogen bonded to the carboxamide oxygen.



6

Molecular modeling analysis of the active benzylamines and the active aroylpyrroles (Fig. 4) further substantiate the conclusion that these molecules are highly congruent in their three-dimensional conformation.

Conclusion

The anticonvulsant analysis of the benzylamines and benzamides reveal different activity profiles, due most probably to their three dimensional conformations. These conformational differences may influence the potential binding interactions in protecting against

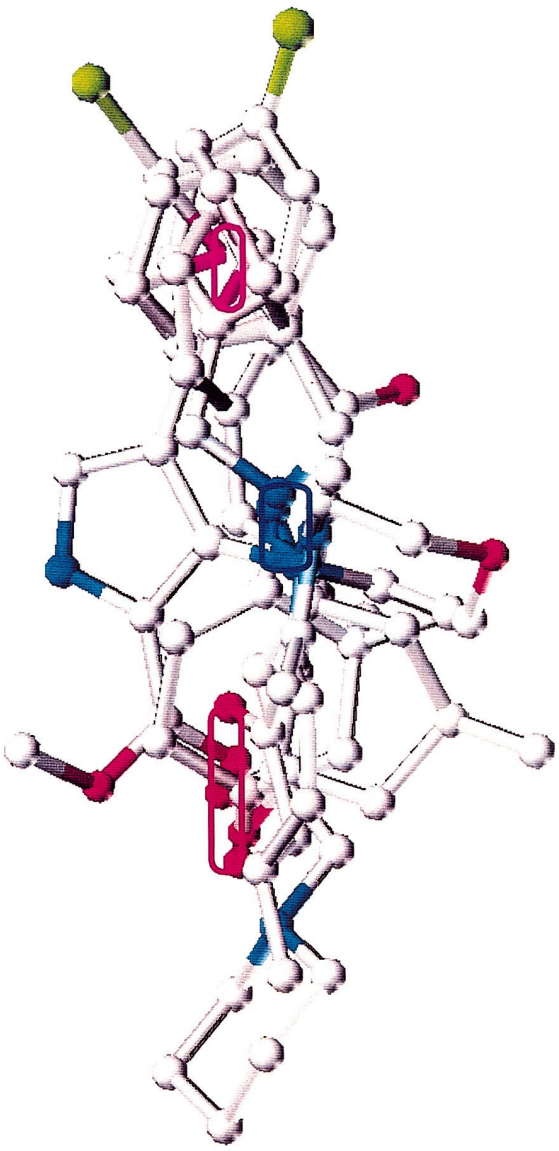


Figure 4. Multifit modeling of the five active anticonvulsants **1**, **2**, **3a**, **3q** and **3r** with the three atoms/centroid encircled. Colors: chlorine = green; oxygen = red; nitrogen = blue.

electroshock and/or pentylenetetrazol induced seizures. Further research in this area is continuing and will be reported shortly.

Experimental

Chemistry

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Observed boiling points were also uncorrected. Infrared spectra were recorded with samples in KBr, as diluted chloroform solutions in matched sodium chloride cells, or neat on a Perkin–Elmer 1660 series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a General Electric QE 300-MHz spectrometer in deuterated solvents using tetramethylsilane as an internal reference. TLC analysis employed ethyl acetate:cyclohexane (3:1) elution solvent mixture and 5-×10 cm and 5-×20 cm fluorescent plates (Whatman silica gel 60A). Elemental analyses (C, H, N, and halogen) were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377. X-ray crystal analysis was performed on a Nicolet P3 diffractometer. 4-Carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione,[8,17] 4-carbomethoxy-5-methylcyclohexane-1,3-dione,[5] 4-carbethoxy-5-methylcyclohexane-1,3-dione[5] and 5-methyl-1,3-cyclohexanedione[17] were prepared by literature methods. 1,4-Cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) were obtained from Aldrich Chemical Company and used without further purification.

Typical experiments illustrating the general procedures for the preparation of the benzylamines and benzamides are described below.

General procedure for the preparation of benzylamines

***tert*-Butyl 4-*N*-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-oate (3c).** Into a single-neck 100 mL round bottom flask fitted with a magnetic stirring bar containing 25 mL of absolute ethanol and 30 mL of ethyl acetate was added 1.80 g (8 mmol) of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione, and benzylamine (1.04 g, 9.7 mmol) and the mixture stirred and refluxed for 4 h. Removal of the ca. one-half of the solvent mixture and stirring overnight at room temperature produced the crude product which was recrystallized twice from ethyl acetate to provide **3c** in 55% yield, mp 152–155°C as white crystalline needles: ^{1}H NMR δ ($CDCl_3$): 1.08 (3H, d, J = 6.60 Hz, CH_3); 1.49 (9H, s, 3×CH_3); 1.45–3.21 (3H, m, C_1, C_5 of cyclohexene ring); 3.01 (1H, d, J = 11.00 Hz, C_6 of cyclohexene ring); 5.05 (1H, br s, NH split by CH_2); 5.23 (1H, s, =CH); 7.25–7.40 (5H, m, aromatic ring). Anal. calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found C, 72.54; H, 8.05; N, 4.68.

***tert*-Butyl 4-*N*-[(*p*-methyl)benzylamino]-6-methyl-2-oxocyclohex-3-en-1-oate (3i;).** Employing a similar procedure, 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione, and 4-methylbenzylamine produced an oil after stirring overnight and volume reduction. To the oil was added ca. 10 mL of anhydrous ether, while stirring and after 30 min, a crude solid was obtained, which after recrystallization twice from ethyl acetate gave **3i** in 58% yield, mp 123–126°C as a white crystalline powder: ^{1}H NMR δ ($(CD_3)_2SO$): 0.89 (3H, d, J = 5.88 Hz, CH_3); 1.97–3.25 (4H, m, cyclohexene ring); 3.47 (3H, s, CH_3); 3.70 (3H, s, OCH_3); 4.11 (2H, s, CH_2 of $NHCH_2$); 4.77 (1H, s, =CH); 6.80–7.30 (4H, m, aromatic ring); 7.64 (1H, s, NH). Anal. calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found C, 73.06; H, 8.06; N, 4.45.

Ethyl 4-*N*-[(*p*-methoxy)benzylamino]-6-methyl-2-oxocyclohex-3-en-1-oate (3k). Employing a similar procedure, 4-carbethoxy-5-methylcyclohexane-1,3-dione, and 4-methylbenzylamine produced crude solid after stirring overnight, which after recrystallization twice from ethyl acetate gave **3k** in 74% yield, mp 154–157°C as a white

Table 6. Anticonvulsant evaluation

Benzylamines		Benzamides	
Compound	Anticonvulsant results[a]	Compound	Anticonvulsant results[a]
3a	Phase I (mice): Class 1 (MES) Mice: ED_{50} 64.7 mg/kg; TD_{50} > 500 mg/kg; Rats: ED_{50} 26.8 mg/kg TD_{50} > 500 mg/kg	**4a**	Phase I (mice): Class 3
3b	Phase I (mice): Class 3	**4b**	Phase I (mice): Class 3
3c	Phase I (mice): Class 3	**4c**	Phase I (mice): Class 3
3d	Phase I (mice): Class 2 (MES)	**4d**	Phase I (mice): Class 3
3e	Phase I (mice): Class 3	**4e**	Phase I (mice): Class 3
3f	Phase I (mice): Class 3	**4f**	Phase I (mice): Class 4
3g	Phase I (mice): Class 3	**4g**	Phase I (mice): Class 1 (ScMet)
3h	Phase I (mice): Class 3	**4h**	Phase I (mice): Class 1 (ScMet)
3i	Phase I (mice): Class 1 (MES)	**4i**	Phase I (mice): Class 4
3j	Phase I (mice): Class 3	**4j**	Phase I (mice): Class 1 (MES/ScMet)
3k	Phase I (mice): Class 3	**4k**	Phase I (mice): Class 2 (MES)
3l	Phase I (mice): Class 3	**4l**	Phase I (mice): Class 3
3m	Phase I (mice): Class 3	**4m**	Phase I (mice): Class 4
3n	Phase I (mice): Class 3	**4n**	Phase I (mice): Class 3
3o	Phase I (mice): Class 3	**4o**	Phase I (mice): Class 3
3p	Phase I (mice): Class 1 (MES) Rat po identification: Active at 50 mg/kg (30 min–4 h) No toxicity at 50 mg/kg at all times	**4p**	Phase I (mice): Class 2 (ScMet) TTE[b] Active at 100 mg/kg MES Confirmation: 0/4 at all times at 100 mg/kg
3q	Phase I (mice): Class 1 (MES) Rats: ED_{50} 55.36 mg/kg TD_{50} > 500 mg/kg	**4q**	Phase I (mice): Class 4
3r	Phase I (mice): Class 1 (MES) Rat po identification: Active at 30 mg/kg (30 min–4 h) No toxicity at 50 mg/kg at all times 1/1 died at 4 h	**4r**	Phase I (mice): Class 1 (MES) Rat po identification: Active at 30 mg/kg (30 min–4 h) No toxicity at 30 mg/kg at all times
3s	Phase I (mice): Class 4	**4s**	Phase I (mice): Class 1 (MES/ScMet) Rat po identification: No protection at 30 mg/kg at all times
3t	Phase I (mice): Class 4	**4t**	Phase I (mice): Class 3
3u	Phase I (mice): Class 2 (MES)	**4u**	Phase I (mice): Class 1 (MES)
3v	Phase I (mice): Class 2 (MES)	**4v**	Phase I (mice): Class 3 TTE: Inactive at 100 mg/kg
3w	Phase I (mice): Class 3	**4w**	Phase I (mice): Class 3
3x	Phase I (mice): Class 3	**4x**	Phase I (mice): Class 3
3y	Phase I (mice): Class 2 (MES)	**4y**	Phase I (mice): Class 1 (MES)
3z	Phase I (mice): Class 3	**4z**	Phase I (mice): Class 1 (ScMet)
3aa	Phase I (mice): Class 3	**4aa**	Phase I (mice): Class 4 (MES) Rat: ED_{50} (MES) 183.51 mg/kg TD_{50} > 400 mg/kg
3bb	Phase I (mice): Class 2 (MES)	**4bb**	Phase I (mice): Class 1 (MES/ScMet)
3cc	Phase I (mice): Class 1 (MES) 8/8 Toxic at 100 mg/kg 4/4 Toxic at 300 mg/kg	**4cc**	Phase I (mice): Class 4 (MES/ScMet)
3dd	Phase I (mice): Class 3	**4dd**	Phase I (mice): Class 1 (MES)

[a] Phase I in mice activity-class 1 = activity at 100 mg/kg or <; class 2 = activity between 100 and 300 mg/kg; class 3 = no activity at 300 mg/kg; class 4 = activity was inconsistent.
[b] TTE = Threshold tonic extension test (see Experimental).

crystalline powder: ^{1}H NMR δ ($(CD_3)_2SO$): 0.89 (3H, d, J = 5.86 Hz, CH_3); 1.13 (3H, t, J = 7.33 Hz CH_3 of CH_2CH_3); 1.82–3.56 (4H, m, cyclohexene ring); 3.69 (3H, s, OCH_3); 4.04 (2H, q, J = 7.33 Hz, CH_2 of CH_2CH_3); 4.11 (2H, d, J = 7.26 Hz, CH_2); 4.77 (1H, s, =CH); 6.80–7.28 (4H, m, aromatic ring); 7.64 (1H, s, NH). Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found C, 68.22; H, 7.34; N, 4.68.

Methyl 4-*N*-[(*p*-cyano)benzylamino]-6-methyl-2-oxocyclohex-3-en-1-oate (3m). Employing a similar procedure, 4-carbomethoxy-5-methylcyclohexane-1,3-dione, and 4-aminobenzyl cyanide produced crude solid after stirring overnight, which after recrystallization twice from ethyl acetate provided **3m** in 44% yield, mp 204–208°C as a orange crystalline powder: ^{1}H NMR δ ($(CD_3)_2SO$): 0.95 (3H, d, J = 7.33 Hz, CH_3 on C_6); 1.97–3.24 (4H, m, cyclohexene ring); 3.61 (3H, s, CO_2CH_3); 3.99 (2H, s, CH_2); 5.25 (1H, s, =CH); 6.93–7.67 (4H, m, aromatic ring); 9.08 (1H, s, NH). Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found C, 68.49; H, 6.04; N, 9.44.

3-*N*-[(*p*-chloro)benzylamino]-5-methylcyclohex-3-enone (3t). Employing a similar procedure, 5-methylcyclohexane-1,3-dione, and 4-chlorobenzylamine produced crude solid after stirring overnight, which after recrystallization twice from 2-propanol gave **3t** in 44% yield, mp 186–187°C as fine yellow needles: ^{1}H NMR δ ($(CD_3)_2SO$): 1.03 (3H, d, J = 5.86 Hz, CH_3 or C_6); 2.88 (1H, d, J = 9.52 Hz, CH at C_6); 3.30 (2H, s, CH_2); 4.31 (2H, t, J = 3.67 Hz, CH_2 of $NHCH_2$); 4.88 (1H, s, =CH); 6.58 (1H, br s, NH); 7.37 (5H, m, aromatic ring). Anal. calcd for $C_{18}H_{20}ClNO_4$: C, 67.33; H, 6.46; Cl, 13.44; N, 5.31. Found C, 68.53; H, 6.94; Cl, 13.49; N, 6.55.

General procedure for the preparation of benzamides

***tert*-Butyl 4-*N*-(benzamido)-6-methyl-2-oxocyclohex-3-en-1-oate (4c).** Into a 1L three neck flask equipped with a magnetic stirrer, gas bubbler, Dean-Stark trap and condenser, was introduced 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (55.5 g, 0.25 mol) and 500 mL of benzene. After the mixture was heated to reflux, dry ammonia was introduced. Within 5 min, a thick amorphous precipitate of the crude 6-carbo-*tert*-butoxy-3-amino-5-methylcyclohex-2-enone formed. The mixture was refluxed an additional 1 h. On cooling, the slurry was filtered, washed with anhydrous ether and air dried. This crude product could be used as such for the subsequent reaction.

Into a 500 mL three neck flask fitted with a condenser, pressure-equalizing dropping funnel, a magnetic stirrer and a gas inlet tube, was added 6-carbo-*tert*-butoxy-3-amino-5-methyl-cyclohexanone, (11.25 g, 50 mmol) and triethylamine (10.11 g, 100 mmol) to 300 mL of dry acetone under a N_2 atmosphere. Upon reflux, benzoyl chloride (7.14 g, 51 mmol), dissolved in 50 mL of dry methylene chloride, was added. The reaction mixture was refluxed for 2.5 h. Once the reaction had cooled, the mixture was filtered to remove triethylamine hydrochloride. The solvent was evaporated in vacuo. The crude product was dissolved in 50 mL of methylene chloride and washed twice with an equivalent volume of saturated $KHCO_3$ and water and dried (Na_2SO_4). The organic layer was evaporated in vacuo at a temperature not exceeding 50°C, taken up with a minimum amount of methylene chloride and chromatographed on a silica gel column (10 g of silica gel per 1 g of product). The residue was recrystallized from absolute ethanol:ligroine (bp 60–90°C), to provide **4c** in a 44% yield which occurred as bright yellow plates, mp 193–197°C: ^{1}H NMR δ ($(CD_3)_2SO$): 1.06 (3H, d, $J=6.59$ Hz, C_6 CH_3); 1.18 (9H, s, $3\times CH_3$); 2.18–3.79 (4H, m, cyclohexene ring); 6.70 (1H, s, =CH); 7.44–8.28 (5H, m, aromatic ring); 9.99 (1H, s, NH). Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found C, 69.38; H, 7.09; N, 6.95.

Methyl 4-*N*-[(*p*-chloro)benzamido]-6-methyl-2-oxocyclohex-3-en-1-oate (4d). The amination reaction was modified using the above molar quantity of 4-carbomethoxy-5-methylcyclohexane-1,3-dione and 0.025 mol of *p*-toluenesulfonic acid as catalyst. 6-Carbomethoxy-3-amino-5-methylcyclohex-2-enone did not precipitate immediately. The benzene was decanted and the reddish-brown residue triturated with anhydrous ether until cloudy and the mixture refrigerated. After 14 days, a crystalline product was obtained. Seeding with this crystalline product readily converted subsequent runs into solids on overnight refrigeration. The acylation reaction proceeded as previously indicated to yield a residue which was washed with fresh methylene chloride and the oil that remained, after evaporation, was taken up with 100 mL of methylene chloride, washed successively with an equivalent volume of saturated $KHCO_3$ (twice), 1 N HCl, and water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure at a temperature not exceeding 50°C to yield a solid residue which was recrystallized from 2-propanol. Compound **4d** was produced in 38% yield and occurred as light yellow crystals, mp 200–202°C: ^{1}H NMR: δ ($(CD_3)_2SO$): 1.05 (3H, d, $J=7.33$ Hz, C_6 CH_3); 2.13–3.72 (4, m, cyclohexene ring); 3.47 (3H, s, OCH_3); 6.75 (1H, s, =CH); 7.76–8.27 (4H, m, aromatic ring); 10.11 (1H, s, NH). Anal. calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; Cl, 11.02; N, 4.35. Found C, 59.99; H, 4.94; Cl, 10.96; N, 4.38.

Ethyl 4-*N*-[(*p*-methoxy)benzamido]-6-methyl-2-oxocyclohex-3-en-1-oate (4k). The amination reaction was modified to include 4-carbethoxy-5-methyl-cyclohexane-1,3-dione and 0.025 mol of *p*-toluenesulfonic acid as catalyst. 6-Carbethoxy-3-amino-5-methyl-2-cyclohexenone did not precipitate immediately, but did so on trituration with anhydrous ether and hexane. The acylation reaction and workup proceeded as previously indicated for **4d** to yield **4k**, 43% as yellow needles, from ethanol-ether, mp 126–128°C: ^{1}H NMR: δ ($CDCl_3$): 1.00 (3H, d, $J=6.59$ Hz, CH_3); 1.20 (3H, t, $J=6.96$ Hz, CH_3 or CH_2CH_3); 2.28–2.85 (3H, m, cyclohexene ring); 3.19 (1H, d, $J=11.72$ Hz, C_1 *trans* H); 3.84 (3H, s, OCH_3); 4.13 (2H, q, $J=6.96$ Hz, CH_2 of CH_2CH_3); 6.78 (1H, s, =CH); 6.99–7.97 (4H, dd, $J=8.79$ Hz, aromatic ring); 9.99 (1H, s, NH). Anal. calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found C, 65.29; H, 6.44; N, 4.37.

3-*N*-[(*p*-methyl)benzamido]-5-methylcyclohex-3-enone (4v). Amination of 1,3-cyclohexanedione as in **4d** provided 3-aminocyclohex-2-enone as a brown, low melting solid. The acylation reaction and workup proceeded as previously indicated for **4d** to yield **4v**, 20%, as yellow needles, from ethanol-ether, mp 197–200°C: ^{1}H NMR: δ ($CDCl_3$): 1.99–2.16 (2H, m, CH_2); 2.26 (2H, t, CH_2); 2.48 (3H, s, CH_3); 2.61–2.86 (2H, t, CH_2); 6.60 (1H, s, =CH); 7.23–7.82 (4H, dd, aromatic ring); 7.90 (1H, S, NH). Anal. calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found C, 73.47; H, 6.49; N, 6.38.

3-*N*-[(*p*-cyano)benzamido]-5,5-dimethylcyclohex-3-enone (4dd). Amination of dimedone under similar conditions as in **4d** provided 3-amino-5,5-dimethyl-cyclohex-2-enone which did not precipitate immediately, but did so on trituration with anhydrous ether. The acylation reaction and work up proceeded as previously indicated for **4d** to yield **4dd**, 15% as a yellow crystalline powder, from ethyl acetate, mp 238–241°C: ^{1}H NMR: δ ($(CD_3)_2SO$): 1.00 (6H, s, $2\times CH_3$); 2.20 (2H, s, CH_2); 2.50 (2H, s, CH_2); 6.80 (1H, s, =CH); 8.00 (4H, m, aromatic ring); 10.10 (1H, s, NH). Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found C, 71.67; H, 6.34; N, 10.78.

X-ray crystal analysis

Methyl 4-*N*-[(*p*-methoxy)benzamido]-6-methyl-2-oxocyclohex-3-en-1-oate, **4j**, and 3-*N*-[(*p*-cyano)benzamido]-5-methylcyclohex-2-en-1-one, **4cc**, were recrystallized from an ethanol:water mixture. All experimental details related to the structural analysis are provided in Figs. 2 and 3 and Tables 3 and 4 and supplemental material. The structure was solved by direct methods of the

ShelXTLPC program and refined by the ShelXTL program.[33]

Molecular modeling

Initial computations on the benzamides and benzylamines were performed on a Silicon Graphics Personal Iris 4D/35 workstation running Molecular Simulations Quanta and CHARMM molecular mechanics software.[34] Each structure in Tables 1 and 2 was initially minimized employing steepest descents (100 minimization steps) and subsequently by adopted-basis Newton Raphson (ABNR, 1000 steps). These individual minima were saved for a conformational search, using torsion angles and restrictions previously reported.[6] The active analogues in each series were superimposed and their molecular volumes calculated and compared to the inactive analogues. There was no difference between the active and inactive analogues (union volume$_{(\text{inactive benzamides})}$ = 371.87 Å v. union volume$_{(\text{active benzamides})}$ = 385.14 Å).

Structures **1, 2, 3a, 3q** and **3r** were modeled with the Spartan programs[20] using the AM1 model with geometry optimization. These individual minima were transferred to the SYBYL[21] program where they were superimposed via the MULTIFIT program.[21] The structures were constrained to superimpose the phenyl centroid, the pyrrole nitrogen (in **1** and **2**, or the benzylamine nitrogen in **3a, 3q** and **3r**), and the carbonyl oxygen. The analysis did not employ a reference structure (i.e. phenytoin) to which the other molecules were fit. Quite the opposite, all molecules were allowed to fit each other simultaneously, resulting in a "consensus conformation" (multifit cluster).[35] The results of the MULTIFIT program are shown in Fig. 4.

Pharmacology

Initial evaluations for anticonvulsant activity were performed by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological Disorders and Stroke and included phases I, II, VIA and VIB test procedures which have been described.[22–24] These tests were performed in male Carworth Farms no. 1 (CF1) mice (Phases I and II) or male Sprague–Dawley rats (Phase VIA and VIB). Phase I and Phase VIA of the evaluation included three tests: maximal electroshock (MES), subcutaneous pentylenetetrazol (ScMet), and the rotorod test for neurological toxicity (Tox). Compounds were suspended in 0.5% aqueous methylcellulose and were administered at three dosage levels (30, 100 and 300 mg/kg) with anticonvulsant activity and motor impairment noted 30 min and 4 h after administration. Phase II and phase VIB testing quantitated the anticonvulsant activity and motor impairment observed for the most promising compounds in phase I. Phase II quantified data in CF1 mice by intraperitoneal (ip) administration, while phase VIB provided oral rat data comparable to phase II ip data in mice. Data for the respective evaluations are shown in Table 5. The TTE test[25] performed on **4p** and **4v** is described as follows. Twenty mice were pretreated with 100 mg/kg of the test compound. At several time intervals (15 min, 30 min, 1, 2 and 4 h) post treatment with the test compound, four mice at each time point were challenged with 12.5 mA of electrical current for 0.2 s via corneal electrodes. This stimulation produced a TTE seizure in the animals. For each time interval, results were expressed as a ratio of the number of animals protected over the number of animals tested.

Supplemental material

Additional X-ray crystal data are provided for **4j** (4 tables) and **4cc** (4 tables). Unit cells of **4j** and **4cc** and are available from the authors.

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