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Enaminones 9. Further studies on the anticonvulsant activity and potential type IV phosphodiesterase inhibitory activity of substituted vinylic benzamides

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Abstract—Structure–activity relationship studies were employed to synthesize a series of 3- and 3,4-substituted benzamides from 3-amino-2-cyclohexenones. An improved method for the synthesis of benzamides from 3-amino-2-cyclohexenones is presented which provided significantly higher yields (71–79%) for the reported compounds. NMR and X-ray structural analyses were undertaken to note the possible intra- and intermolecular interactions of the synthesized analogs. Molecular modeling studies were used to determine the minimized configuration and were compared to their X-ray structures for correlation. These new entities were evaluated as potential anticonvulsants and type IV phosphodiesterase inhibitors (PDE4).

1. Introduction

Cyclic nucleotides are soluble second messengers found in all tissues throughout the body. Many drugs, hormones, and other agents modify physiological processes by causing changes in the steady state levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in cells. Levels of these nucleotide second messengers can be controlled by altering the activity of the cyclic nucleotide phosphodiesterases (PDEs) that degrade them. PDE isoenzyme families have been classified on the basis of their substrate specificities (cAMP or cGMP), kinetic characteristics (K_m and V_{max}), and their regulation by specific inhibitors or activators.[1–6] In a wide range of immune and inflammatory cells, including neutrophils, T-lymphocytes, macrophages, and eosinophils, inhibition of cellular responses is associated with elevated levels of cAMP. It has been shown that among the 11 major families,[1,7] PDE4 (cAMP-specific) is the predominant PDE subtype in such cells. Inhibition of PDE4 in inflammatory cells influences several of the cell-specific responses. PDE4 activity, when localized in airways of the smooth muscle cells, is associated with several inflammatory states, for example, asthma, chronic obstructive and pulmonary disease. Thus, selective inhibition of PDE4 could potentially be a mechanism of treating these diseases.[7] Asthma is one of the most common chronic diseases[8] worldwide and antiasthma medications are widely prescribed. Asthma treatments account for 1–2% of the total health budget in industrialized countries.[9,10] The prototype agent was (*R*)-rolipram **1**[11] (Fig. 1). However, **1** exhibited several untoward side effects, such as emesis and nausea, which has precluded its clinical development. Ariflo, **2**[12] (Fig. 1) evolved from this initial research. Ariflo was a potent second-generation PDE4 inhibitor followed with a decreased potential for side effects. Additionally, it has been noted that a number of benzamide derivatives using the rolipram pharmacophore, **1** (Fig. 1) possessed selective inhibition of cyclic AMP-specific phosphodiesterase (PDE4) for use as antiasthmatics. The research of Ashton et al. led to a series of active benzamides **3** (Fig. 1).[13] We were intrigued with the similarity of the active amides **3** with the enaminone

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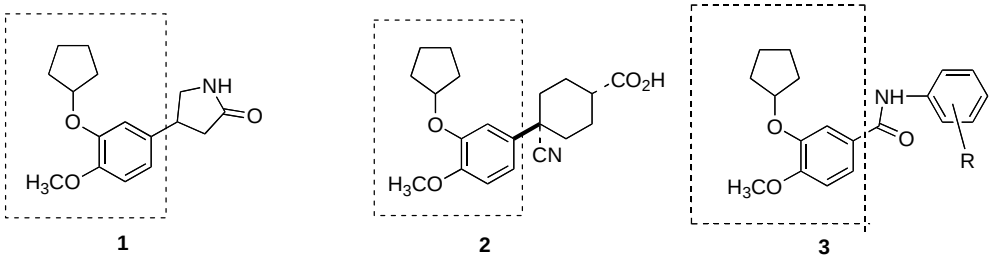


1 2 3

Figure 1. Structures of (*R*)-rolipram **1**, ariflo **2**, and an active pharmacophore (after Ashton[13]).

pharmacophore that we have studied (Fig. 2). The Ashton pharmacophore could be adapted to this area as well (Fig. 3). We herein report the results of our study as well as further studies of the vinylic benzamides as potential anticonvulsants.

2. Chemistry

The synthesis of the benzamides was previously reported from our laboratories.[17] This procedure (Scheme 1) involved amination of the respective β-diketones[25] followed by acylation with the respective benzoyl chlorides **15**, and using triethyl-amine as the acid scavenger to provide the target compound, **11**. Careful monitoring of this latter reaction minimized the possible α-acylation, **16**. The synthesis of vinylogous amides has been extensively reported,[25–32] however the base-catalyzed coupling of enaminones from cyclohexane-1,3-diones with substituted benzoyl chlorides has only recently been reported in our laboratories.[22]

Scheme 1 has been modified as shown in Scheme 2. 3-Aminocyclohex-2-enone, **10a**, 3-amino-5-methylcyclohex-2-enone, **10b**, or 3-amino-5,5-dimethylcyclohex-2-enone, **10c**, was prepared either by the method of Baraldi et al.[31] aminating the respective diketone precursor with ammonium acetate and acetic acid in benzene and collecting the water produced in a Dean–Stark trap, or by treatment with gaseous ammonia in benzene with the analogous water collection method used previously.[17] N-Acylation of enaminones producing **11** has been made use of by several laboratories as well;[27,28] however, these methods were limited in several areas: (1) the reported yields were moderately low, ranging from 6% to 32%; (2) the reaction conditions varied, with no single procedure being ideal; and (3) extensive purification techniques were needed to obtain the desired product. The factors contributing to the above include: (1) poor nucleophilicity of the cyclic enaminone system; (2) competing side reactions, that is, O, Cα, and N-acylation, in theory, can occur; and (3) the rapacious HCl by-product which, in theory, can consume an equivalent amount of unreacted enaminone **10**, thus cutting the theoretical yield by 50%. These obstacles make this method limited as an attractive candidate for parallel synthesis or other high throughput synthetic methods. Our current methodology involves the N-deprotonation of the enaminone system with 2 equiv of sodium hydride in tetrahydrofuran (THF) under a nitrogen atmosphere.[13] The subsequent reaction involved the addition of 1 equiv of the benzoyl chloride **15a–e** to **10a–c**, producing the amide salt intermediate **10d**. The reaction mixture was quenched with water and neutralized with HCl, which liberated the amide from its salt and destroyed the excess NaH to yield the crude enamides **11a–l** and **14a–c**. Table 1 provides the yields of the enamides after purification in this procedure in comparison to other methods.

The above procedure was subjected to solution-phase parallel synthesis in a Radley's Carousel reaction station to generate a 12-member library of desired benzamide derivatives, Table 2 provides data on the new benzamides generated by this method.

As noted in Table 2, the yields ranged from 63% to 90%, with the yields of the dimethoxy catechol ethers **11g–i** being the lowest of the series. The C log *P* values ranged from 1.21 (3,4-dimethoxy analog, **11g**) to 3.83 (3-butoxy-4-methoxy, **11l**).[33]

3. IR and NMR analysis

The amido and enaminone C=O stretching frequencies for all of the benzamides, as well as the N–H stretching frequency of each imide, were identified in the infrared (IR) spectra (see Section 9). The presence of the amido proton in the ^{1}H NMR spectra in each of the imides ranged from δ 8.10 to 9.81 ppm and verified the presumption that the reaction occurred as predicted. As reported previously,[17] the vinyl proton assignments were indicative of hydrogen bonding between it and the carbonyl oxygen of the amide group and were deshielded appearing downfield ranging from δ 6.76 to 6.82 ppm. The current study also verified this downfield tendency with the vinyl proton appearing at δ 6.50–6.82 ppm. The presence of the catechol ether moiety was also confirmed with ^{1}H NMR employing integration.

4. X-ray crystallography

X-ray analyses of the 3-chlorobenzamide, **11f**, and two catechol ethers **11g** and **i** were performed. The results are shown in Figures 1–3, respectively, and the atomic coordinates provided in Tables 5–7. In our original investigation,[17] the X-ray crystal structures of two benzamides that were determined {methyl 4-(4-methoxy-benzoylamino)-6-methyl-2-oxocyclohex-3-ene carboxylate (**11**,

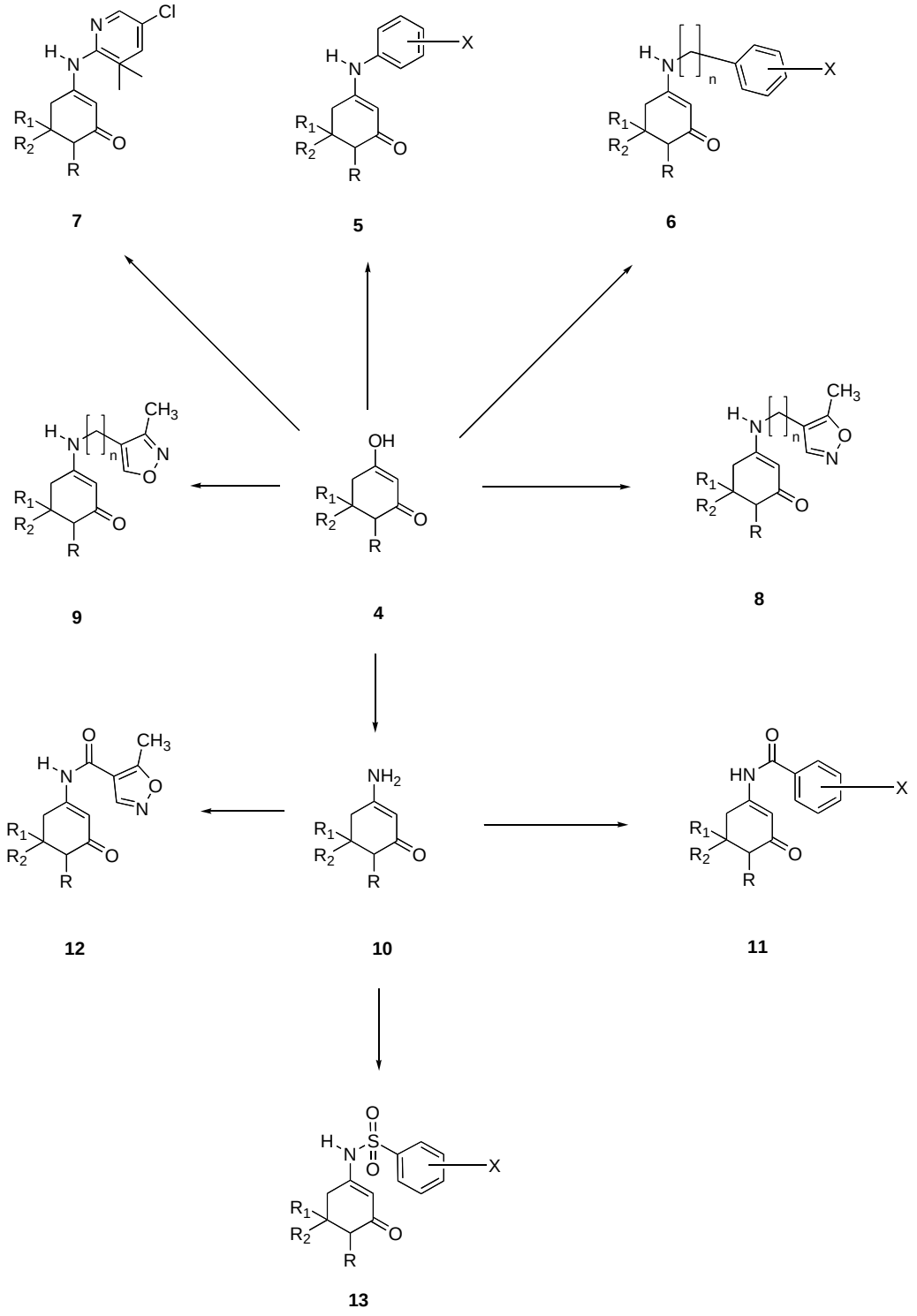


Figure 2. Enaminones and their analogs (after Scott et al.[14–24]).

R = CO_2CH_3; R_1 = CH_3; R_2 = H; X = 4-OCH_3) and 4-cyano-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (**11**, R = H; R_1 = CH_3; R_2 = H; X = 4-CN)}, demonstrated strong hydrogen bonding between the vinyl proton and the carbonyl oxygen of the amido group in each structure providing a pseudo-three-ring structure. By contrast, however, **11f**,**g**, and **i** displayed no such property. Instead, these latter compounds resembled benzylamines as shown by Kubicki and Codding[34] in which intermolecular, rather than intramolecular, hydrogen bonding was displayed. In compound **11f** (Fig. 4), intermolecular hydrogen bonding occurred between the carbonyl oxygen (O2A) and the hydrogen on the adjacent amido group; while in **11g** and **i**, bonding occurred between the aromatic hydrogen on C2 (Figs. 5 and 6), the N–H hydrogen of the amido group, and one of the hydrogens on C13 (Fig. 5) or C15 (Fig. 6), each with the adjacent carbonyl oxygen.

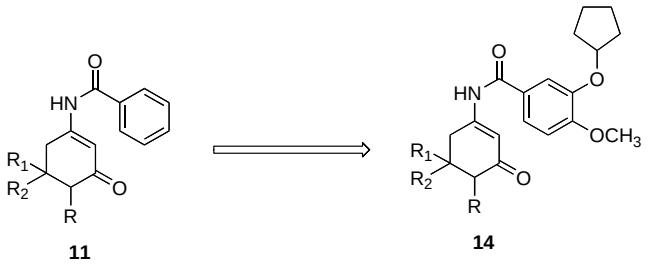
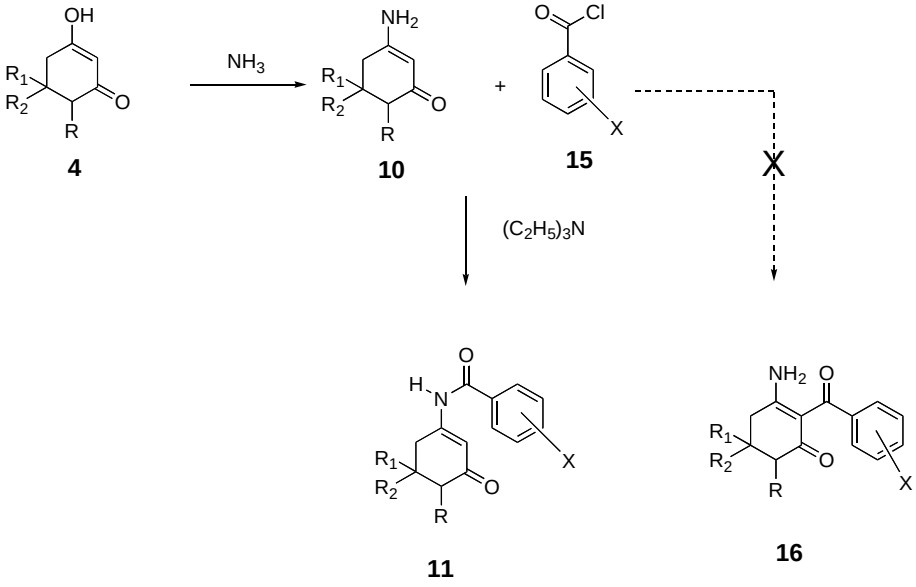


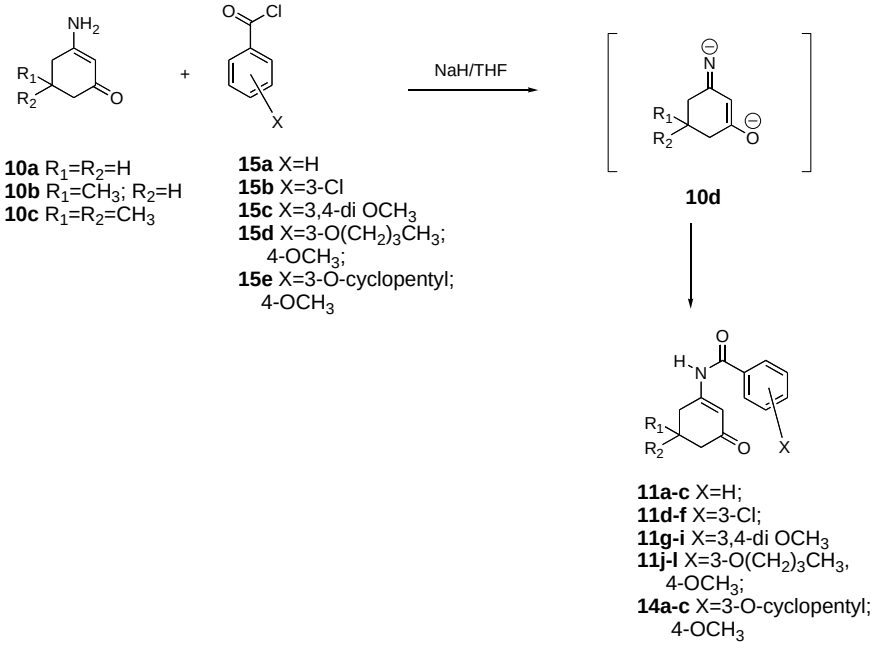
Figure 3. Potential PDE4 analogs.

5. Pharmacology

Pharmacological testing of the compounds listed in Table 2 has 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.[35–37] Phase I study involved three tests: maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (scPTZ), and neurologic toxicity (Tox). Intraperitoneal (ip) adminis-



Scheme 1.



Scheme 2.

Table 1. Yields of benzamides **11a–c** compared to reported values

Compound	R_1	R_2	Reaction time (min)	Mp (°C)	Mp (°C) (literature)	Yield (%)	Yield (%) (literature)
11a	H	H	40	177–178	178–179[28]	79	14.9[26]
11b	CH_3	H	40	135–137	136.5–138[8]	71	29.4[25]
11c	CH_3	CH_3	40	144–146	146–148[26]	76	25.0[27]

Table 2. Parallel solution-phase synthesis of benzamides **11d–l** and **14a–c**

Compound	R_1	R_2	Mp (°C)	Yield (%)	Clog P[a]
11d	H	H	138–139	79	2.25
11e	CH_3	H	128–129	84	2.77
11f	CH_3	CH_3	138.5–140	90	3.29
11g	H	H	187.5–189	63	1.21
11h	CH_3	H	152–154	71	1.73
11i	CH_3	CH_3	163–165	69	2.24
11j	H	H	120–121	80	2.79
11k	CH_3	H	160–161	82	3.31
11l	CH_3	CH_3	119–121	81	3.83
14a	H	H	171–172	85	2.68
14b	CH_3	H	128–129	84	3.20
14c	CH_3	CH_3	149–150	85	3.72

[a] Ref. 33.

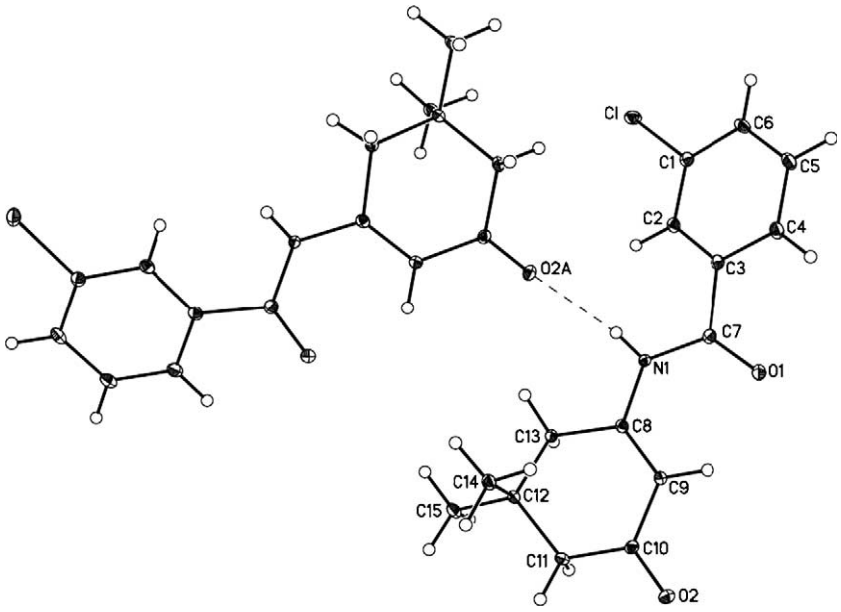


Figure 4. X-ray crystal structure of 3-chloro-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (**11f**). Note intramolecular hydrogen boding between O2A and the hydrogen on N1.

tration of the test compounds was carried out as a suspension in 0.5% methylcellulose. As previously reported,[14–24] active compounds in the phase I evaluation were subsequently tested either for an ED_{50} quantitation in mice (phase II) or qualitatively in rats (phase VIA). The anticonvulsant screening project (ASP) classifications are as follows: class 1 = activity at 100 mg kg^{-1} or less; class 2 = activity > 100 mg kg^{-1}, but less than 300 mg kg^{-1}; class 3 = no activity at doses up to and including 300 mg kg^{-1}. Further, to differentiate the results between distinct rodent species, several of the analogs were evaluated for oral (po) activity (phase VIA) in the rat. Data are summarized in Table 3. Several of the compounds (**11e** and **l**) were further evaluated by a 6 Hz test. It has recently been found that the above evaluative tests may miss novel antiepileptic drugs that may be useful for the treatment of therapy resistant partial seizures (e.g., levetiracetam). In contrast to the MES test, levetiracetam has been found to be highly effective ($ED_{50(mice)}$ 19 mg kg^{-1}) in the 6 Hz model originally described by Toman et al.[38] Thus, the ADD program has determined that selected moieties that were found to be inactive in either the MES or scPTZ tests will be screened for their ability to block seizure induced by a low-frequency (6 Hz), long-duration (3 s) stimulus delivered through corneal electrodes.

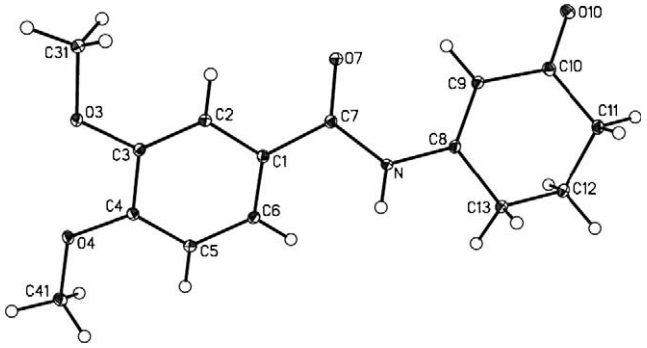


Figure 5. X-ray crystal structure of 3,4-dimethoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (**11g**).

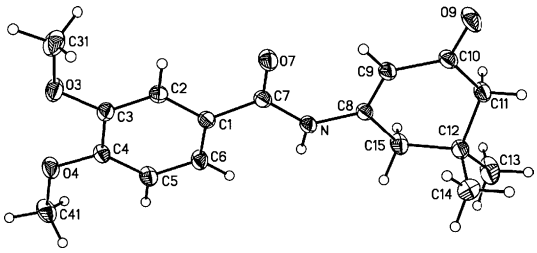


Figure 6. X-ray crystal structure of 3,4-dimethoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (**11i**).

6. PDE4 analysis

PDE4 inhibitory studies on **14a–c** were performed by MDS Pharma Services, Taipei, Taiwan, Republic of China employing standard assay procedures,[39,40] on human U937 cells with Ro 20-1724 as the reference compound (IC_{50} 1.22 μM). The results are summarized in Table 4. Significance criterion was ⩾50% of maximum inhibition.

Table 4. PDE4 evaluation

Compound	% Inhibition results (10 μM)[a]
14a	−7
14b	35
14c	6

[a] Negative values correspond to stimulation of binding or enzyme activity. Significance criteria = ⩾50% of maximum inhibition.

7. Results and discussion

7.1. Anticonvulsant evaluation

The current synthetic approach varied from our previous studies that utilized the Free–Wilson analysis[41] success-

Table 5. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx 2 \times 10^3$) for 3-chloro-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (**11f**)

	X	*Y*	*Z*	*U*(eq)
Cl	2154(1)	1219(1)	2580(1)	27(1)
O(1)	2562(2)	5613(1)	5095(1)	27(1)
O(2)	5667(2)	7013(1)	8706(1)	25(1)
N(1)	4135(2)	4256(2)	5876(2)	17(1)
C(1)	1519(3)	2401(2)	2970(2)	19(1)
C(2)	2477(2)	3012(2)	3835(2)	19(1)
C(3)	1963(3)	3949(2)	4167(2)	19(1)
C(4)	511(3)	4250(2)	3622(2)	23(1)
C(5)	−424(3)	3622(2)	2756(2)	25(1)
C(6)	75(3)	2688(2)	2414(2)	23(1)
C(7)	2903(3)	4691(2)	5080(2)	19(1)
C(8)	5095(2)	4744(2)	6871(2)	16(1)
C(9)	4887(2)	5716(2)	7257(2)	18(1)
C(10)	5922(3)	6161(2)	8314(2)	18(1)
C(11)	7318(2)	5572(2)	8901(2)	20(1)
C(12)	7144(2)	4370(2)	8810(2)	17(1)
C(13)	6413(2)	4080(2)	7495(2)	17(1)
C(14)	6202(3)	3979(2)	9555(2)	21(1)
C(15)	8653(3)	3854(2)	9260(2)	23(1)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

Table 3. Anticonvulsant evaluation

Compound	Anticonvulsant results[a]
3-Chloro analogs:	
11d	No activity or toxicity noted at 10–100 mg kg^{-1}
11e	Marginal toxicity at 100 mg kg^{-1}; no protection; 6 Hz screen: 2/4 animals protected at 100 mg kg^{-1}; neurotoxicity noted at that 100 mg kg^{-1} at 30 min and 1 h
11f	Class 3
3,4-Dimethoxy analogs:	
11g	Class 3
11h	Inactive in mice screen; inactive in oral rat screen
11i	Marginal toxicity at 100 mg kg^{-1}; no protection inactive in 6 Hz screen
3-n-Butoxy-4-methoxy analogs:	
11j	No protection; some toxicity at 100 mg kg^{-1}
11k	Toxic: 3/8[b] animals toxic at 100 mg kg^{-1}
11l	Class 3
3-Cyclopentyloxy-4-methoxy analogs:	
14a	Increased toxicity (3/8)[b] at 100 and at 300 mg kg^{-1} at 30 min and (1/2)[b] at 300 mg kg^{-1} at 4 h
14b	Increased toxicity (3/8)[b] at 100 and at 300 mg kg^{-1} at 30 min and (1/2)[b] at 300 mg kg^{-1}
14c	Increased toxicity (1/8)[b] at 100 mg kg^{-1}

[a] Phase I in mice activity—class 1 = activity at 100 mg kg^{-1} or <; class 2 = activity between 100 and 300 mg kg^{-1}; class 3 = no activity at 300 mg kg^{-1}.
[b] Data in parenthesis under toxicity indicate the number of animals exhibiting toxicity (numerator) over the number of animals tested (denominator).

Table 6. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx 2 \times 10^3$) for 3,4-dimethoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (**11g**)

	X	*Y*	*Z*	*U*(eq)
O(3)	4421(1)	643(1)	2485(1)	18(1)
O(4)	1717(1)	243(1)	−524(1)	17(1)
O(7)	9232(1)	−1042(1)	5099(1)	20(1)
O(10)	13441(1)	−2641(1)	7869(2)	28(1)
N	7274(1)	−1836(1)	4139(1)	16(1)
C(1)	6020(2)	−886(1)	2837(2)	14(1)
C(2)	6037(2)	−297(1)	3306(2)	15(1)
C(3)	4579(2)	68(1)	2165(2)	14(1)
C(31)	6006(2)	907(1)	4024(2)	18(1)
C(4)	3071(2)	−152(1)	493(2)	14(1)
C(41)	172(2)	45(1)	−2235(2)	19(1)
C(5)	3076(2)	−730(1)	12(2)	15(1)
C(6)	4551(2)	−1098(1)	1187(2)	15(1)
C(7)	7657(2)	−1249(1)	4129(2)	15(1)
C(8)	8566(2)	−2283(1)	5023(2)	15(1)
C(9)	10462(2)	−2213(1)	6082(2)	17(1)
C(10)	11707(2)	−2707(1)	6977(2)	18(1)
C(11)	10809(2)	−3293(1)	6818(2)	18(1)
C(12)	9031(2)	−3362(1)	4937(2)	22(1)
C(13)	7640(2)	−2872(1)	4664(2)	22(1)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

Table 7. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx 2 \times 10^3$) for 3,4-dimethoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (**11i**)

	X	*Y*	*Z*	*U*(eq)
N	3662(2)	1597(1)	4623(2)	45(1)
O(3)	2740(2)	−1467(1)	3211(2)	68(1)
O(4)	4875(1)	−1325(1)	1667(1)	61(1)
O(7)	1984(1)	863(1)	5431(1)	61(1)
O(9)	988(2)	2984(1)	7595(2)	77(1)
C(1)	3529(2)	392(1)	3818(2)	42(1)
C(2)	2851(2)	−255(1)	3902(2)	46(1)
C(3)	3313(2)	−814(1)	3177(2)	47(1)
C(31)	1581(3)	−1577(1)	4066(3)	81(1)
C(4)	4480(2)	−740(1)	2327(2)	46(1)
C(41)	6132(2)	−1287(1)	891(2)	70(1)
C(5)	5133(2)	−102(1)	2236(2)	53(1)
C(6)	4666(2)	460(1)	2976(2)	52(1)
C(7)	2980(2)	959(1)	4691(2)	43(1)
C(8)	3321(2)	2207(1)	5290(2)	41(1)
C(9)	2261(2)	2276(1)	6167(2)	47(1)
C(10)	1955(2)	2929(1)	6787(2)	49(1)
C(11)	2794(2)	3554(1)	6388(2)	53(1)
C(12)	4345(2)	3391(1)	6018(2)	54(1)
C(13)	4990(3)	4037(1)	5389(3)	100(1)
C(14)	5319(2)	3161(1)	7348(3)	85(1)
C(15)	4228(2)	2812(1)	4916(2)	58(1)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

fully employed by Craig.[42,43] However, in this study, our prior research[17] provided us with a different approach: that was used previously with an investigation of the imidooxy anticonvulsants,[44] employing the Topliss approach.[45,46] This was due to inactivity of the initial series with only 4-methoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (**11**, R = H; $R_1 = R_2 = CH_3$; X = 4-OCH_3) being modestly active [po MES $ED_{50(rat)}$ 183.5 mg kg^{-1}, $TD_{50} > 400$ mg kg^{-1} PI (PI = TD_{50}/ED_{50}) > 2.2]. Thus, a variety of disubstituted benzamides were prepared (Table 2). As noted in Table 3, phase I evaluation of the 3-chloro derivatives indicated that they were universally inactive. This paralleled the initial work by Foster et al., who synthesized comparable 4-chloro analogs.[17] 3,4-Dimethoxy compounds were also inactive, as were the 3-*n*-butoxy-4-methoxy series with increased toxicity. Disubstitution of 4-methoxy pharmacophore thus leads to inactive compounds. The 3-cyclopentyloxy-4-methoxy series proved the most toxic, with all analogs exhibiting significant toxicity at all doses tested. Although the 6 Hz test was employed, no viable candidates were noted.

7.2. PDE4 analysis

From Table 7, only **14b** provided modest inhibition (30%) that was not significant. Thus, the aromatic ring, in addition to the 3-cyclopentyloxy, 4-methoxy substitution, was deemed essential in PDE4 activity.

8. Conclusion

In conclusion, we have shown a rapid, versatile method for the preparation of vinylic benzamides readily adaptable to combinatorial synthesis. This method also provides higher yields than those previously reported. X-ray crystal analyses and NMR studies have indicated that the benzamides synthesized in this study are able to form intermolecular hydrogen bonds; however, they were devoid of anticonvulsant activity or PDE4 activity.

9. Experimental

9.1. Chemistry

Melting points were determined with Thomas–Hoover capillary melting point apparatus. The IR spectra were obtained on a Nicolet Magna-IR 560 spectrometer. The samplers were recorded as KBr pellets. The ^1H and ^{13}C NMR spectra were determined either on a Bruker 1 Ultra Shield-400 MHz NMR spectrometer or a General Electric QE 300 MHz NMR spectrometer. The samples were dissolved either in deuterated dimethylsulfoxide (DMSO-d_6) or chloroform ($CDCl_3$) containing 0.03% tetramethylsilane (TMS) as an internal reference. Elemental analyses (C, H, N, and Cl) were determined by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377, USA. The analytical results for the elements were within ±0.4% of the theoretical values. 3-Aminocyclohex-2-enone, **10a**,[28] 3-amino-5-methylcyclohex-2-enone, **10b**,[17] and 3-amino-5,5-dimethylcyclohex-2-enone, **10c**,[28] were prepared by the literature methods. All reagents were obtained from Aldrich Chemical Company, Milwaukee, WI, USA. Compounds **15d** and **e** were prepared by literature methods.[13]

9.2. General synthetic procedure

Employing a Radley's Carousel Reaction Station, comprised of twelve reaction tubes (24 × 150 mm), the appropriate amino ketones, **10a**–**c**, (0.75 g) and anhydrous tetrahydrofuran (THF, 35 mL) were added under a nitrogen atmosphere. Each reaction tube was then cautiously treated with NaH [(2.4 equiv), 60% dispersion in oil, previously washed with petroleum ether]. THF (<6 mL) was used to rinse the residual NaH into each reaction vessel. The reaction tubes were capped, magnetically stirred, and refluxed for 25 min. After cooling to room temperature, the appropriate benzoyl chloride, **15a**–**e** (1.05 equiv), in dry THF (10 mL), was carefully added to each tube. Each reaction vessel was capped and stirred for an additional 10 min, the reaction then quenched with 10 mL water. The mixtures of the individual reaction tubes were transferred to 250 mL Erlenmeyer flasks, neutralized with concentrated HCl (~5 mL), and transferred to a 250 mL separatory funnel containing dichloromethane (25 mL). After separation, the aqueous phase was discarded, the organic phase was washed successively with water (25 mL), 10% $NaHCO_3$ (25 mL), and again with water (25 mL). The organic phase was dried over sodium sulfate, evaporated in vacuo, and the resulting residue was washed twice with anhydrous ether (25 mL). The crude compounds that separated were recrystallized and characterized.

9.2.1. 3-Chloro-*N*-(3-oxocyclohex-1-enyl)benzamide (11d). Yield: 79%; pale yellow crystals from ethyl acetate (EtOAc), mp: 138–139 °C. ν_{max} 3339.41, 1685.35, 1618.78 cm^{-1}. δ ^1H ($CDCl_3$) 2.10 (2H, quint, J = 6.54 Hz, CH_2); 2.41 (2H, t, J = 6.78 Hz, CH_2); 2.74 (2H, t, J = 5.73 Hz, CH_2); 6.72 (1H, s, =CH); 7.28–7.81 (4H, m, aromatic ring); 8.10 (1H, s, NH). ^{13}C ($CDCl_3$) δ 21.68; 28.59; 36.73; 112.77; 125.61; 127.72; 130.15; 134.97; 135.64; 156.17; 165.08; 200.30. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; Cl, 14.20; N, 5.61. Found: C, 62.52; H, 4.67; Cl, 14.27; N, 5.59.

9.2.2. 3-Chloro-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (11e). Yield: 84%; white solid from EtOAc/MeOH, mp: 168–169 °C. ν_{max} 3350.34, 1688.51, 1617.51 cm^{-1}. δ ^1H (DMSO-d_6) 1.13 (3H, d, J = 6.52 Hz, CH_3); 2.07–2.79 (5H, cyclohexene ring); 6.71 (1H, s, =CH); 7.28–7.34 (4H, m aromatic ring); 8.18 (1H, s, NH). ^{13}C (DMSO-d_6) δ 21.00 (CH_2), 29.31; 36.77; 44.91; 112.39; 125.55; 127.68; 130.20; 132.58; 135.05; 135.59; 155.41; 164.92; 200.28. Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; Cl, 13.44; N, 5.31. Found: C, 63.74; H, 5.25; Cl, 13.55; N, 5.30.

9.2.3. 3-Chloro-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (11f). Yield: 90%; white solid from EtOAc, mp: 138.5–140 °C. ν_{max} 3288.19, 1690.47, 1639.26, 1618.78 cm^{-1}. δ ^1H (DMSO-d_6) 1.08 (6H, s, *gem* 2× CH_3); 2.19 (2H, s, CH_2); 2.56 (2H, s, CH_2); 6.82 (1H, s, =CH); 7.35–7.80 (4H, m aromatic ring); 8.88 (1H, s, NH). ^{13}C (DMSO-d_6) δ 28.24; 32.86; 42.28; 50.51; 111.50; 125.79; 127.85; 130.01; 132.40; 134.79; 135.64; 154.70; 165.60; 200.75. Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.87; H, 5.81; Cl, 12.76; N, 5.04. Found: C, 64.82; H, 5.60; Cl, 12.70; N, 4.87.

9.2.4. 3,4-Dimethoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (11g). Yield: 63%; yellow solid from EtOAc/MeOH, mp: 187.5–189 °C. ν_{max} 3267.71, 1680.23, 1634.40 cm^{-1}. δ ^1H (DMSO-d_6) 1.94 (2H, quint, J = 7.21 Hz CH_2); 2.26 (2H, t, J = 6.87 Hz, CH_2); 2.63 (2H, t, J = 5.62 Hz, CH_2); 3.83 (6H, s, 2× OCH_3); 6.76 (1H, s, =CH); 7.07 (1H, d, J = 8.52 Hz, aromatic H); 7.44 (1H, d, J = 2.08 Hz, aromatic H); 7.56 (1H, dd, J = 6.35 Hz, aromatic H); 9.32 (1H, s, NH). ^{13}C (DMSO-d_6) δ 21.82; 28.16; 28.23; 36.97; 56.08; 56.18; 111.27; 111.53; 111.59; 111.66; 122.12; 126.52; 126.57; 148.76; 152.66; 157.54; 157.68; 166.50; 166.58; 199.24. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.15; H, 6.05; N, 4.99.

9.2.5. 3.4-Dimethoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)-benzamide (11h). Yield: 84%; white solid from EtOAc/MeOH, mp: 168.5–169 °C. ν_{max} 3283.07, 1680.23, 1623.90 cm^{-1}. δ ^1H (DMSO-d_6) 1.03 (3H, d, J = 6.23 Hz CH_3); 2.03–2.73 (3H, m, cyclohexene ring); 3.84 (6H, s, 2× OCH_3); 6.76 (1H, s, =CH); 7.07 (1H, d, J = 8.44 Hz, aromatic H); 7.45 (1H, s, aromatic H); 7.57 (1H, d, J = 8.38 Hz, aromatic H); 9.32 (1H, s, NH). ^{13}C (DMSO-d_6) δ 21.20; 29.20; 36.28; 45.09; 56.07; 56.16; 111.18; 111.28; 111.63; 112.10; 122.10; 122.15; 123.11; 126.49; 148.76; 152.68; 152.99; 156.90; 166.52; 167.27; 199.34. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.43; H, 6.68; N, 4.66.

9.2.6. 3,4-Dimethoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (11i). Yield: 83%; light-yellow solid from EtOAc/MeOH, mp: 163–165 °C. ν_{max} 3359.89, 1690.47, 1613.66, 1608.31 cm^{-1}. δ ^1H (DMSO-d_6) 1.04 (6H, s, *gem* CH_3); 2.16 (2H, s, CH_2); 2.57 (2H, s, CH_2); 3.84 (6H, s, 2 × OCH_3); 6.79 (1H, s, =CH); 7.08 (1H, d, J = 8.44 Hz, aromatic H); 7.46 (1H, s, aromatic H); 7.58 (1H, d, J = 8.34 Hz, aromatic H); 9.77 (1H, s, NH). ^{13}C (DMSO-d_6) δ 28.32; 32.78; 41.81; 50.56; 56.10; 56.17; 110.44; 111.29; 111.63; 122.16; 126.45; 148.76; 152.69; 155.44; 166.59; 167.27; 199.21. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.05; H, 6.84; N, 4.63.

9.2.7. 3-*n*-Butoxy-4-methoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (11j). Yield: 80%; pale-white solid from EtOAc, mp: 120–121 °C. ν_{max} 3283.07, 1675.11, 1623.90 cm^{-1}. δ ^1H (DMSO-d_6) 0.94 (3H, d, J = 7.44 Hz CH_3); 1.45 (2H, quint, J = 7.35 Hz, CH_2); 1.72 (2H, t, J = 6.87 Hz, CH_2); 1.92 (2H, t, J = 5.98 Hz, CH_2); 2.25 (2H, t, J = 6.09 Hz, CH_2); 2.33 (2H, t, J = 5.54 Hz, CH_2); 3.84 (3H, s, OCH_3); 4.02 (2H, t, J = 6.44 Hz, OCH_2); 6.75 (1H, s, =CH); 7.07 (1H, d, J = 8.43 Hz, aromatic H); 7.43 (1H, s, aromatic H); 7.55 (1H, d, J = 8.95 Hz, aromatic H); 9.82 (1H, s, NH). ^{13}C (DMSO-d_6) δ 14.17; 19.23; 21.82; 28.23; 31.25; 36.97; 56.21; 68.49; 111.45; 111.58; 112.77; 122.11; 126.55; 148.16; 152.88; 157.70; 166.58; 199.25. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.85; H, 7.32; N, 4.35.

9.2.8. 3-*n*-Butoxy-4-methoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (11k). Yield: 82%; white solid from EtOAc/MeOH, mp: 160–161 °C. ν_{max} 3316.93, 1675.11, 1629.02, 1603.41 cm^{-1}. δ ^1H (DMSO-d_6) 0.94 (3H, d,

$J = 7.34$ Hz CH_3); 1.03 (3H, d, $J = 6.18$ Hz, CH_3); 1.43–1.56 (2H, quint, $J = 6.95$ Hz, CH_2); 1.69–1.76 (2H, m, CH_2); 2.01–2.72 (5H, m, cyclohexene ring); 3.84 (3H, s, OCH_3); 4.02 (2H, t, $J = 6.36$ Hz, OCH_2); 6.75 (1H, s, =CH); 7.07 (1H, d, $J = 8.45$ Hz, aromatic H); 7.43 (1H, s, aromatic H); 7.55 (1H, d, $J = 8.42$ Hz, aromatic H); 9.73 (1H, s, NH). ^{13}C (DMSO-d_6) δ 14.18; 19.23; 21.21; 29.19; 31.25; 36.27; 45.09; 56.21; 68.45; 111.16; 111.47; 112.73; 122.14; 126.47; 148.15; 152.89; 156.93; 166.55; 199.35. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.88; H, 7.60; N, 4.03.

9.2.9. 3-*n*-Butoxy-4-methoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (11l). Yield: 81%; light-tan solid from EtOAc/MeOH, mp: 119–121 °C. ν_{max} 3334.28, 1685.35, 1603.41, 1598.29 cm^{-1}. δ ^1H (DMSO-d_6) 0.94 (3H, d, $J = 7.34$ Hz CH_3); 1.03 (6H, s, $2 \times CH_3$); 1.40–1.50 (2H, m, CH_2); 1.67–1.76 (2H, quint, $J = 7.56$ Hz, CH_2); 2.15 (2H, s, CH_2); 2.56 (2H, s, CH_2); 3.84 (3H, s, OCH_3); 4.02 (2H, t, $J = 6.36$ Hz, OCH_2); 6.76 (1H, s, =CH); 7.06 (1H, d, $J = 8.50$ Hz, aromatic H); 7.45 (1H, s, aromatic H); 7.55 (1H, d, $J = 8.35$ Hz, aromatic H); 9.75 (1H, s, NH). ^{13}C (DMSO-d_6) δ 14.17; 19.24; 28.31; 31.26; 32.77; 41.80; 50.56; 56.19; 68.50; 110.42; 111.44; 112.15; 126.42; 148.16; 152.91; 155.46; 166.59; 199.21. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.61; H, 7.97; N, 4.05.

9.2.10. 3-Cyclopentyloxy-4-methoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (14a). Yield: 81%; pale-white solid from EtOAc, mp: 171–172 °C. ν_{max} 3271.00, 1675.98, 1621.70 cm^{-1}. δ ^1H (DMSO-d_6) 1.58–1.93 (10H, m, cyclopentyl Hs and CH_2); 2.22–2.38 (2H, m, CH_3); 2.63–2.69 (2H, m, CH_2); 3.35 (3H, s, OCH_3); 4.87 (1H, m, OCH); 6.50 (1H, s, =CH); 7.08 (1H, d, $J = 8.63$ Hz, aromatic H); 7.40 (1H, s, aromatic H); 7.53 (1H, d, $J = 8.41$ Hz, aromatic H); 9.81 (1H, s, NH). ^{13}C (DMSO-d_6) δ 21.83; 24.04; 28.22; 36.98; 56.21; 80.29; 111.60; 111.65; 114.65; 122.08; 126.56; 147.02; 153.61; 157.69; 166.59; 199.21. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.39; H, 7.02; N, 4.21.

9.2.11. 3-Cyclopentyloxy-4-methoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (14b). Yield: 84%; pale-yellow solid from EtOAc, mp: 128–129 °C. ν_{max} 3310.18, 1678.17, 1613.17, 1603.41 cm^{-1}. δ ^1H (DMSO-d_6) 1.03 (3H, d, $J = 6.10$ Hz, CH_3); 1.58–1.89 (8H, m, cyclopentyl); 2.25–2.86 (5H, m, cyclohexene); 3.83 (3H, s, OCH_3); 4.88 (1H, m, OCH–); 6.75 (1H, s, =CH); 7.06 (1H, d, $J = 8.47$ Hz, aromatic H); 7.42 (1H, s, aromatic H); 7.55 (1H, d, $J = 8.42$ Hz, aromatic H); 9.85 (1H, s, NH). ^{13}C (DMSO-d_6) δ 21.22; 24.05; 29.20; 32.68; 36.26; 45.11; 56.21; 80.27; 111.18; 111.66; 114.63; 122.13; 126.47; 147.00; 153.61; 156.99; 166.57; 199.33. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.78; H, 7.18; N, 4.00.

9.2.12. 3-Cyclopentyloxy-4-methoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (14c). Yield: 85%; pale-yellow solid from EtOAc, mp: 149–150 °C. ν_{max} 3359.89, 1685.35, 1608.31, 1598.29 cm^{-1}. δ ^1H (DMSO-d_6) 1.03 (6H, s, $2 \times CH_3$); 1.59–1.90 (8H, m, cyclopentyl); 2.15 (2H, s, CH_2); 2.56 (2H, s, CH_2); 3.83 (3H, s, OCH_3); 4.87 (1H, m, OCH–); 6.76 (1H, s, =CH); 7.07 (1H, d, $J = 8.47$ Hz, aromatic H); 7.42 (1H, s, aromatic H); 7.55 (1H, d, $J = 7.91$ Hz, aromatic H); 9.85 (1H, s, NH). ^{13}C (DMSO-d_6) δ 24.06; 28.33; 32.68; 32.78; 50.57; 56.21; 80.29; 110.40; 111.65; 114.64; 122.11; 126.46; 147.00; 153.63; 155.56; 166.64; 199.18. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.35; H, 7.64; N, 3.93.

9.3. X-ray analysis

3-Chloro-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide, **11f**, 3,4-dimethoxy-*N*-(3-oxocyclohex-1-enyl)benzamide, **11g**, and 3,4-dimethoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide, **11i**, were recrystallized from ethyl acetate. All experimental details related to the structural analysis are provided in Figures 1–3, Tables 5–7, and Supplementary material. The structure was solved by direct methods of the SHELXTLPC program and refined by the SHELXTL program.[47] The full crystallographic data were deposited at the Cambridge Crystallographic Data Center. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033, or email: deposit@ccdc.camac.uk.). Compounds **11f**,**g**, and **i** are designated CCD 226697, CCD 219084, and CCDC 219085, respectively.

9.4. Pharmacology

Initial evaluations for anticonvulsant activity were performed by the ADD Program, epilepsy branch, Neurological Disorders Program, NINDS. These evaluations included the phase I test which has been described.[35–37] These tests were performed in Carworth Farms no. 1 (CF1) mice (weighing 18–25 g). Phase I, a qualitative anticonvulsant ip evaluation in mice, included three tests: MES, scPTZ, and the rotorod test for Tox. Compounds were suspended in 30% poly(ethyleneglycol) 400 and were administered at four dosage levels (10, 20 200, and 300 mg kg^{-1}) with anticonvulsant activity and motor impairment noted 30 min and 4 h after administration. Phase VIA was a similar qualitative evaluation; however, the test drug was administered orally (po) in rats utilizing the three tests noted previously. The 6 Hz 'Psychomotor' seizure test is described. Twenty mice were pretreated ip with 200 mg kg^{-1} of the test analog (**11h**). At varying times (0.25, 0.5, 1, 2, and 4 h) after treatment, individual mice (four at each time point) were challenged with sufficient current (32 mA at 6 Hz for 3 s) delivered through corneal electrodes to elicit a psychomotor seizure. Typically, the seizure is characterized by a minimal clonic phase that is followed by stereotyped, automatistic behaviors described originally[38] as being similar to the aura of human patients with partial seizures. Animals not displaying this behavior were considered protected. Results were expressed as the number of animals protected over the number of animals tested over time. The results are listed in Table 3.

9.5. Phosphodiesterase inhibition

Phosphodiesterase inhibition studies on compounds **14a–c** were performed by MDS Pharma Services by a referenced procedure.[39,40] The data are provided in Table 4.

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Supplementary material

Supplementary data associated with this article (Tables 8–24) can be found, in the online version, at doi:10.1016/j.bmc.2005.09.023.

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