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Design, Synthesis, and Development of Novel Caprolactam Anticonvulsants

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Abstract—Epilepsy afflicts 1–2% of the world's population and often goes untreated; nearly 70% of those with a form of epilepsy fail to receive proper treatment. Therefore, there is great demand for the design of novel, effective anticonvulsants to combat epilepsy in its numerous forms. Previously, α-hydroxy-α-phenylcaprolactam was found to have rather potent antiepileptic activity [anti-maximal electroshock (MES) $ED_{50} = 63$ mg/kg and anti-subcutaneous Metrazol (scMet) $ED_{50} = 74$ mg/kg] when administered intraperitoneally in mice. We focused our attention on the development of this compound through traditional medicinal chemistry techniques—including the Topliss approach, isosteric replacement, methylene insertion, and rigid analogue approach—in the hopes of determining the effect of caprolactam α-substitution and other structural modifications on anticonvulsant activity. A number of the desired targets were successfully synthesized and submitted to the Anticonvulsant Screening Program of the National Institute of Neurological Disorders and Stroke (NINDS). Phase I results were quite promising for at least three of the compounds: α-ethynyl-α-hydroxycaprolactam (**10**), α-benzyl-α-hydroxycaprolactam (**11**), and α-hydroxy-α-(phenylethynyl)caprolactam (**13**). Phase II results for **11** strongly suggested it as a new structural class for further development, as it exhibited an anti-MES T.I. in excess of 4.0. Further, the potent activity of **13** in all models also pointed to the substituted alkynylcaprolactams as a new anticonvulsant structural class.

Introduction

Of the countless neurological diseases and disorders that have been identified, few are as pervasive and common as epilepsy. Afflicting 1–2% of the world's population, it often goes untreated. The drugs that do exist to combat epilepsy are far from perfect, as modern clinical anticonvulsants are effective in reducing the severity and number of seizures in less than 80% of treated epileptics.[1] The side effects that accompany the use of these drugs are also quite significant in some cases. Therefore, there is a great demand for the design of new, novel, effective anticonvulsants that extend therapy to the millions suffering from epilepsy.

The anticonvulsants that serve to control the seizures associated with epilepsy have previously been categorized into a number of distinct classes on the basis of the molecular mechanisms through which they function.[2] Class I anticonvulsants bind to the neuronal voltage-dependent sodium channel (NVSC), a heterotrimeric transmembrane protein complex.[3] The NVSC from a typical mammalian brain consists of one α subunit and two β subunits and is instrumental in the mediation of action potentials in neurons and other electrically excitable cells. It is chiefly responsible for the change in ion permeability of cell membranes and allows for the voltage-stimulated depolarization of cells through the rapid influx of sodium ions.[3] Anticonvulsants belonging to class II act on γ-aminobutyric acid (GABA) receptors. GABA itself is believed to be a central inhibitory neurohormonal modulator,[1] with the receptor being responsible for local changes in ion conductance at chemical synapses.[3] The class III anticonvulsants function through undetermined mechanisms. A more recently disclosed class includes those anticonvulsants that bind to excitatory amino acid receptors, such as those for *N*-methyl-D-aspartate (NMDA).

Anti-Bredt bicyclic imides like **1** remain a class of compounds that possess significant anticonvulsant activity.

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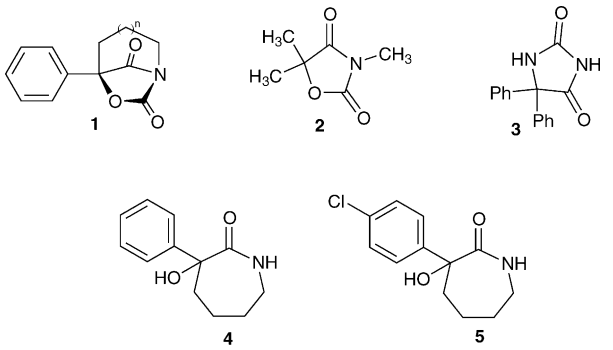


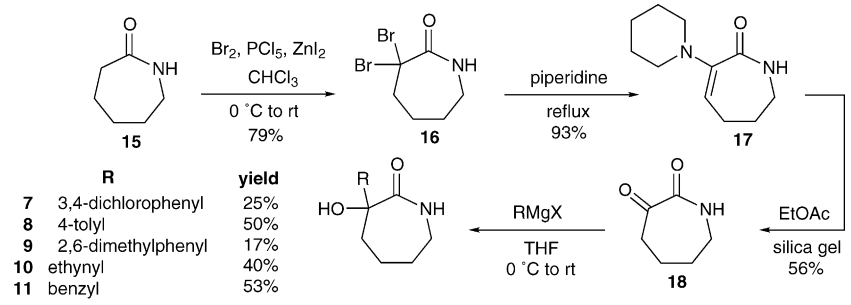
Figure 1. Smissmanones and related structures.

These compounds were originally proposed by Edward E. Smissman[4]—one of the fathers of modern medicinal chemistry—and are referred to as 'smissmanones.' After these unique compounds were first synthesized in the late 1980s, they were tested for anticonvulsant activity and found to be effective sodium channel binders (i.e., class I anticonvulsants).[2] Interestingly enough, the structurally related trimethadione (3,3,5-trimethyl-2,4-oxazolidinedione, **2**) has no effect on the NVSC and is considered a class III anticonvulsant, whereas phenytoin (diphenylhydantoin, **3**) is a class I anticonvulsant with rather strong binding to the neuronal voltage-dependent sodium channel (Fig. 1).[5]

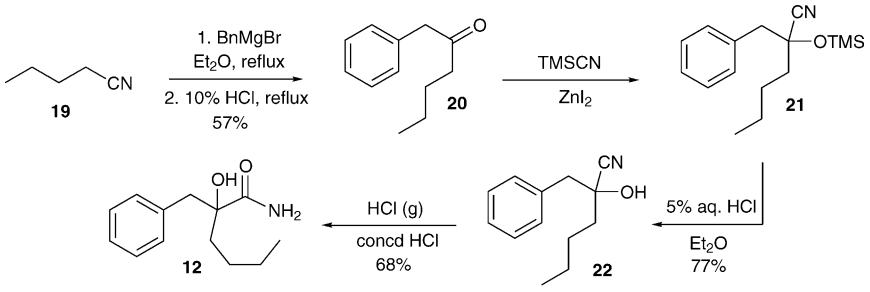
In an attempt to determine what structural features impart NVSC binding ability to the smissmanones, a number of partial structures were synthesized and evaluated for anti-epileptic activity.[2] One of the compounds—α-hydroxy-α-phenylcaprolactam (**4**)—was particularly interesting. The lactam exhibited weak NVSC binding with an $IC_{50} > 800\,\mu M$; IC_{50} is the concentration of anticonvulsant needed to inhibit 50% of the binding of [^{3}H]-batrachotoxinin A 20-α-benzoate ([^{3}H]BTX-B) to the sodium channel.[2] However, ip administration of **4** in mice resulted in potent anticonvulsant protection in both anticonvulsant models tested (scMet and MES induced convulsions), exhibiting an anti-MES $ED_{50} = 63\,mg/kg$ and an anti-scMet $ED_{50} = 74\,mg/kg$. These results encouraged a further investigation[6] into the possible anticonvulsant activity of analogues of the lactam. After testing analogues with *ortho*, *meta*, and *para* α-phenyl substitutions, one compound was found to be particularly active: α-hydroxy-α-4-chlorophenylcaprolactam (**5**). This lactam exhibited an anti-MES effective dose of 21.8 mg/kg. Amazingly, the toxic dose of this compound exceeded 250 mg/kg. This corresponded to a therapeutic index (the ratio of toxic dose to effective dose) greater than 11.5, implicating the lactam as a potential clinical agent.

With this in mind, we proposed the synthesis of compounds **7**–**14** (see Schemes 1–3) to further explore the effect of various substitutions (on the phenyl ring and otherwise) on the anti-epileptic effects of **4**. A number of these targets were selected through the use of traditional medicinal chemistry optimization techniques (Fig. 2).

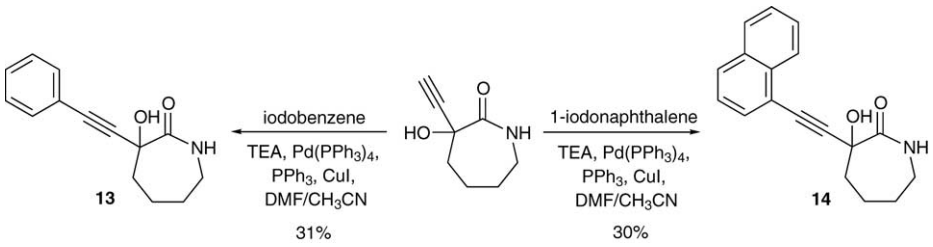
The Topliss series (begun with **4**, the unsubstituted compound, and **5**, the 4-chloro species) was completed with the synthesis of **7** (3,4-dichloro) and **8** (4-methyl). The 4-methoxy derivative, the final component of the Topliss series, was synthesized previously.[6] Target **11** was the product of a methylene insertion, whereas **9** was the rigid analogue (di-*ortho* substitution). Isosteric replacement of the phenyl ring with the characteristically similar ethynyl group yielded **10**. Initial anticonvulsant results concerning the activities of **10** and **11** (see Results and Discussion) prompted the inclusion of further targets, including the acyclic amide analogue **12**.



Scheme 1. Synthesis of α-substituted caprolactams.



Scheme 2. Synthetic route to acyclic amide analogue of **11**.



Scheme 3. Sonogashira couplings involving **10**.

Of particular interest was the alkyne moiety of **10** and the potential for coupling any number of different structures at this position. Compounds **13** and **14** were therefore targeted via traditional Sonogashira cross-coupling reactions.

Biology

The successfully synthesized compounds were screened for anticonvulsant activity through the Anticonvulsant Screening Program (ASP) of the National Institute of Neurological Disorders and Stroke (NINDS). The ASP consists of seven phases that thoroughly quantify the anticonvulsant activity of the compound in question. Phase I activity for each compound is reported as the number of protected animals per group at concentration mg/kg of drug measured over the duration of the anticonvulsant activity in mice (ip administration only) and in rats (oral administration only). The maximal electroshock (MES) model involves the induction of seizures through the application of an alternating current to corneal electrodes in the eyes of a rodent, whereas the subcutaneous pentylenetetrazol (PTZ, also known as Metrazol) seizures are generated chemically by the injection of PTZ. Neurotoxicity (at administered dose) is reported in the Rotorod model by loss of the righting reflex of the animal when placed on a rotating rod. Other toxicities are also reported as observed. Further evaluation of active compounds in Phase II provides quantification of activity as an ED_{50} (the effective dose needed to protect 50% of the mice or rats) in the MES or scMet model and a TD_{50} (the dose required to reach toxicity in 50% of the animals) in the Rotorod toxicity model. The results of these evaluations revealed new, active structural classes for the design of further targets. The discovery of a number of active leads may also help, in the future, to elucidate the mechanism of action of this broad class of anticonvulsants.

Chemistry

Of the eight target compounds, seven are produced through various reactions involving α-oxocaprolactam (**18**). The synthesis of this compound has been well-documented[7] and is shown in Scheme 1. The first step involves a bromination of the readily available ε-caprolactam (**15**) to yield the dibrominated lactam **16**. Refluxing this compound in piperidine affords the enamine, **17**, that is then cleaved when flash chromatographed on silica gel to yield α-oxocaprolactam (**18**). This novel step allows for the simultaneous formation and purification of the desired lactam.

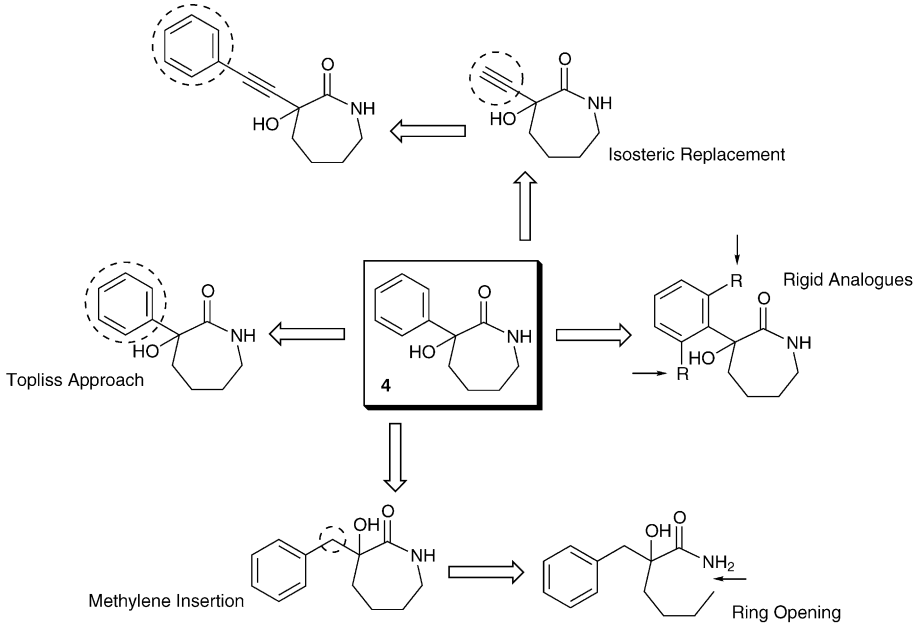


Figure 2. Optimization techniques.

Scheme 1 also details the synthesis of the targets derived directly from α-oxocaprolactam. The appropriate Grignard reagents (e.g., 3,4-dichlorophenyl magnesium bromide) are used to produce, through selective alkylation of the α-keto group, the α-phenyl, α-benzyl, and α-ethynyl derivatives (**7**–**11**).

The synthesis of the acyclic amide **12** (Scheme 2) is accomplished by first reacting valeronitrile with benzylmagnesium bromide in a Grignard reaction. The resulting ketone is then converted to the cyanohydrin through the use of trimethylsilyl cyanide and an aqueous acid workup. Subsequent hydrolysis with HCl gas yields the desired hydroxyamide. The substituted alkynes **13** and **14** are afforded via traditional Sonogashira couplings of the suitable aryl iodides (iodobenzene, 1-iodonaphthalene) and α-ethynyl-α-hydroxycaprolactam (**10**) in the presence of an appropriate palladium source [i.e., $Pd(PPh_3)_4$].[8] A summary of important synthetic and analytical results are listed in Table 1.

Results and Discussion

The first group of targets, lactams **7**–**11**, were obtained through Grignard reactions of α-oxocaprolactam. Unfortunately, it was quickly found that these reactions consistently gave low yields; significant amounts of the starting material were required to produce samples of the targets sufficient for biological testing (250–400 mg). The especially low yield (<20%) of the 2,6-dimethyl derivative was attributed to the steric hindrance of the Grignard reagent. Nonetheless, 250 mg of each compounds was synthesized and submitted to NINDS to determine their anticonvulsant activity.

Phase I results for both mice (ip administration) and rats (oral administration) have been obtained for these compounds and best activities are listed in Table 2 along with the log P values of the targets (as predicted by Crippen's fragmentation).[9] We note here that only those compounds showing promising activity in Phase I were evaluated in rats (Phase II) and listed in Table 3.

Little separation between activity and toxicity was seen in the *para*-methyl analogue **8**, where anti-MES activity was only seen in mice at a dose approaching 300 mg/kg. Compounds **7**, **9**, and **11** provided more promising results. For all three, anti-MES activity was seen at 100 mg/kg in mice; Rotorod toxicity was not seen until the dose reached 300 mg/kg. All three were only mildly active against the Metrazol-induced seizures (300 mg/kg). These three targets were also active in the anti-MES model when administered orally to rats. Analogues **7** and **9** were active over a longer duration than **11**, and the benzyl analogue appeared to be more potent and effective (4/4 rats protected) than the 3,4-dichloro and 2,6-dimethyl lactams. These results suggested **11** for further investigation, prompting the inclusion of the acyclic amide **12** in this study. The potent activity of **11** when administered orally also implicated this compound as a potential clinical anticonvulsant. The Phase I results for **10** were also quite promising. The compound was not active against MES-induced seizures in mice and showed no toxicity at or below 300 mg/kg. However, the acetylene analogue was active in the mice anti-scMet model at 300 mg/kg. This suggested α-ethynyl-α-hydroxycaprolactam (**10**) as a selective inhibitor of petite mal seizures. The initial identification of **10** as a promising, active compound encouraged immediate optimization and development. Alkynes **13** and **14** were targeted for this reason; their syntheses exploited the synthetically rich terminal alkyne moiety and are discussed below.

The two active α-substituted caprolactams **10** and **11** moved on to Phase II of the Anticonvulsant Screening Program, and those results (oral activity in rats) are listed in Table 3. Compound **11** (α-benzyl-α-hydroxycaprolactam) displayed significant activity, with an anti-MES $ED_{50} = 86$ mg/kg and an anti-scMet $ED_{50} < 83$ mg/kg. Given that the Rotorod TD_{50} was greater than 330 mg/kg, this particular lactam exhibited therapeutic indices exceeding 3.9 (MES) and 4.0 (scMet). These results showed that α-benzyl-α-hydroxycaprolactam was effective in halting seizures, although the effectiveness of this lactam appeared to be lower than that of **5** (anti-MES $ED_{50} = 22$ mg/kg, T.I. >11.5). However, because toxicity was not tested beyond 300 mg/kg (at which dose there was still no toxicity), the actual T.I. values may be higher than calculated.

More surprising were the results seen for **10**, where little separation between activity and toxicity was seen. The alkyne exhibited an anti-MES $ED_{50} > 120$ mg/kg and a Rotorod $TD_{50} > 120$ mg/kg (Table 3). This compound was ineffective at preventing MES-induced seizures at a non-toxic dose, further emphasizing the importance of the aryl moiety in the prevention of those seizures mimicked by the MES model.

The synthesis of the acyclic amide (**12**), inspired by the initially surprising activity of **11**, was also completed. The only major pitfall in the synthesis occurred early in the synthetic scheme. The first intermediate is benzyl butyl ketone; the initial attempt to synthesize this compound involved a Grignard reaction between phenylacetonitrile and butylmagnesium bromide. This consistently failed to provide the desired ketone; the starting material was isolated in every instance. It was concluded that the reaction failed because the Grignard reagent was deprotonating phenylacetonitrile at the benzyl position, producing a highly resonance-stabilized species that yielded the starting material upon acidification of the reaction mixture. The logical solution to this problem was a synthon switch to valeronitrile and benzylmagnesium bromide. This new reaction was more successful, affording the desired ketone in a 57% yield. The ketone was carried on without difficulty to the amide, which was promptly submitted to NINDS for anticonvulsant screening. Unfortunately, this particular compound showed little activity in both the MES and scMet models when administered to mice (Table 2); mild activity was seen at 100 mg/kg in less than 50% of the rats in both models. Furthermore, the compound

Table 1. Summary of synthetic results and product characterization

Compd	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	MS (APCI, M + 1)
7	25	134—136	7.50–7.41 (m, 2H, Ph), 7.23–7.16 (m, 1H, Ph), 6.92 (bs, 1H, NH), 5.02 (bs, 1H, OH), 3.21–3.05 (m, 1H, CH), 2.93–2.78 (m, 1H, CH), 2.60–2.48 (m, 1H, CH), 2.05–1.87 (m, 2H, CH), 1.77–1.64 (m, 1H, CH), 1.61–1.40 (m, 2H, CH)	178.2, 140.7, 133.8, 132.9, 131.7, 131.5, 129.1, 126.3, 42.9, 36.0, 29.0, 25.5	273.9
8	50	164—166	7.30–7.17 (m, 4H, Ph), 6.99 (bs, 1H, NH), 4.83 (bs, 1H, OH), 3.12–2.99 (m, 1H, CH), 2.94–2.80 (m, 1H, CH), 2.69–2.56 (m, 1H, CH), 2.35 (s, 3H, CH_3), 2.02–1.84 (m, 2H, CH), 1.71–1.37 (m, 3H, CH)	179.5, 138.4, 137.2, 130.2, 126.7, 42.9, 36.0, 29.2, 25.7, 21.6	220.0
9	17	132–134	7.10–6.94 (m, 3H, Ph), 6.62 (bs, 1H, NH), 4.94 (bs, 1H, OH), 3.08–2.77 (m, 3H, CH), 2.48 (s, 6H, CH_3), 2.02–1.31 (m, 5H, CH)	182.2, 138.0, 131.4, 127.7, 42.1, 38.8, 28.8, 25.4, 23.3	216.1 (M−OH)
10	53	159–161	6.91 (bs, 1H, NH), 5.02 (bs, 1H, OH), 3.78–3.60 (m, 1H, CH), 3.28–3.14 (m, 1H, CH), 2.71 (s, 1H, H–C=C), 2.20–1.79 (m, 4H, CH), 1.75–1.59 (m, 1H, CH), 1.50–1.32 (m, 1H, CH)	175.0, 81.6, 76.6, 70.5, 43.0, 37.9, 29.4, 26.1	154.1
11	53	121–122	7.33–7.18 (m, 5H, Ph), 6.63 (bs, 1H, NH), 4.16 (bs, 1H, OH), 3.54–3.40 (td, 1H, CH), 3.31–3.18 (m, 2H, CH), 2.89–2.81 (d, 1H, CH), 2.10–1.35 (m, 6H, CH)	179.3, 136.3, 130.9, 128.5, 127.2, 43.3, 42.1, 36.6, 29.6, 24.9	220.1
12	68	99–101	7.38–7.20 (m, 5H, Ph), 6.46 (bs, 2H, NH_2), 5.46 (bs, 1H, OH), 3.34–3.24 (d, 1H, CHPh), 2.86–2.76 (d, 1H, CHPh), 2.10–1.86 (m, 2H, CH), 1.63–1.20 (m, 4H, CH), 0.94–0.82 (t, 3H, CH_3)	177.9, 136.0, 130.9, 129.1, 127.7, 79.2, 45.6, 39.1, 26.2, 23.4, 14.5	222.1
13	31	116–118	7.56–7.22 (m, 5H, Ph), 6.92 (bs, 1H, NH), 5.10 (bs, 1H, OH), 3.87–3.67 (m, 1H, CH), 3.34–3.15 (m, 1H, CH), 2.29–1.67 (m, 5H, CH), 1.53–1.35 (m, 1H, CH)	175.6, 132.3, 129.3, 128.9, 122.6, 88.4, 86.8, 71.0, 43.2, 38.2, 29.5, 26.3	230.1
14	30	195–197	8.34–8.25 (m, Ph, 1H), 7.90–7.37 (m, 7H, Ph), 6.62 (bs, 1H, NH), 4.98 (bs, 1H, OH), 3.94–3.76 (m, 1H, CH), 3.33–3.18 (m, 1H, CH), 2.45–1.38 (m, 6H, CH)	175.7, 133.8, 133.6, 131.4, 129.8, 128.9, 127.6, 127.0, 126.4, 125.6, 120.2, 91.7, 86.6, 71.4, 43.2, 38.4, 29.6, 26.5	280.2
16	79	162–164	6.84 (bs, 1H, NH), 3.43–3.33 (q, 2H, CH_2), 2.79–2.70 (m, 2H, CH_2), 2.04–1.63 (m, 4H, CH_2)	169.0, 70.0, 46.5, 43.1, 28.9, 28.8	270.3, 272.2, 274.2
17	93	139–144	7.20 (bs, 1H, NH), 5.07–4.98 (t, 1H, CH), 3.23–3.14 (q, 2H, CH_2), 2.78–2.70 (t, 4H, CH_2), 2.17–2.06 (q, 2H, CH_2), 1.79–1.41 (m, 8H, CH_2)	172.1, 147.9, 105.8, 50.4, 47.0, 39.7, 30.6, 26.3, 25.8, 24.8, 21.8	195.4
18	56	60–64	7.71 (bs, 1H, NH), 3.30–3.22 (q, 2H, CH_2), 2.60–2.53 (m, 2H, CH_2), 1.97–1.68 (m, 4H, CH_2)	204.2, 170.3, 40.0, 27.9, 23.4	128.1
20	57	—	7.40–7.14 (m, 5H, Ph), 3.67 (s, 2H, CH_2), 2.51–2.39 (t, 2H, CH_2), 1.62–1.48 (quint, 2H, CH_2), 1.36–1.21 (m, 2H, CH_2), 0.96–0.83 (t, 3H, CH_3)	208.8, 135.0, 129.9, 129.2, 127.4, 20.6, 42.2, 26.3, 22.7, 14.3	177.2 (CI)
22	77	—	7.32–7.18 (m, 5H, Ph), 6.38 (bs, 1H, OH), 2.94 (s, 2H, CH_2), 1.69–1.14 (m, 6H, CH), 0.88–0.78 (t, 3H, CH_3) (DMSO)	134.1, 131.4, 131.1, 129.4, 128.7, 128.4, 121.4, 72.7, 46.8, 40.2, 26.7, 23.1, 14.4	177.1 (M−CN)

was noticeably toxic in the Rotorod model at 100 mg/kg in 75% (6 out of 8) of the mice receiving the compound by ip injection. When these results were compared to those obtained for **11**, it was clear that the ring opening decreased the efficacy of the compound and increased its toxicity. Removing the rigidity of the caprolactam ring was not effective in improving the anticonvulsant activity of **11**; the conformationally restricted seven-membered ring may play some role in site binding. Further study is necessary to determine precisely how it is relevant. Given the poor activity, it is unlikely we will further develop the class of compounds typified by **12**.

As another set of 'second generation' analogues, the substituted alkynes shown in Scheme 3 were successfully synthesized through Sonogashira couplings of **10** and the appropriate aryl iodides. Employing a palladium source of $Pd(PPh_3)_4$ as the catalyst, the reactions consistently afforded the desired products in modest yields (~30%). Both **13** and **14** were submitted to NINDS for evaluation of anticonvulsant activity, and Phase I results for both (Tables 2 and 3) are reported. Target **13** exhibited strong anti-MES and anti-scMet activity in mice at 100 mg/kg. Rotorod toxicity was noted at 300 mg/kg in 4/4 mice. Similarly, rats receiving **13** were

Table 2. NINDS anti-epileptic drug development program results, Phase 1: best activity in mice (ip administration)

Compd	Log P	Phase I: best activity in mice (ip admin)			Phase I: best activity in rats (oral admin)	
		MES (duration)	scMet (duration)	Rotorod (duration)	MES (duration)	Rotorod (duration)
4[a]	1.25	100 mg/kg (0.25 h)	300 mg/kg (0.25 h)	300 mg/kg (0.25 h)	No data	No data
5[a]	1.81	2/3 mice protected at 100 mg/kg (0.25 h)	3/5 mice protected at 300 mg/kg (0.25 h)	4/4 mice toxic at 300 mg/kg (0.25 h)	4/4 rats protected at 30 mg/kg (2 h)	No toxicity at 30 mg/kg
6[a]	1.13	1/3 mice protected at 100 mg/kg (0.25 h)	No activity at 100 mg/kg	No toxicity at 100 mg/kg	No data	No data
7	2.37	2/3 mice protected at 100 mg/kg (0.5 h)	1/1 mice protected at 300 mg/kg (0.5 h)	4/4 mice toxic at 300 mg/kg (0.5 h)	3/4 rats at 30 mg/kg (1 h)	No toxicity at 30 mg/kg
8	1.74	1/1 mice protected at 300 mg/kg (1 h)	No activity at 300 mg/kg	1/4 mice toxic at 300 mg/kg (0.5 h)	No data	No data
9	2.23	3/3 mice protected at 100 mg/kg (0.5 h)	No activity at 300 mg/kg	3/4 mice toxic at 300 mg/kg (0.5 h)	2/4 rats at 30 mg/kg (1 h)	No toxicity at 30 mg/kg
10	−0.27	No activity at 300 mg/kg	4/5 mice protected at 300 mg/kg (0.5 h)	No toxicity at 300 mg/kg	2/4 rats at 30 mg/kg (4 h)	No toxicity at 30 mg/kg
11	1.53	2/3 mice protected at 100 mg/kg (0.25, 1 h)	1/1 mice protected at 300 mg/kg (1 h)	4/4 mice toxic at 300 mg/kg (0.5 h)	4/4 rats at 30 mg/kg (0.25 h)	No toxicity at 30 mg/kg
12	2.22	1/3 mice protected at 100 mg/kg (0.25 h)	1/5 mice protected at 100 mg/kg (0.25 h)	6/8 mice toxic at 100 mg/kg (0.5 h)	No data	No data
13	1.52	3/3 mice protected at 100 mg/kg (0.5 h)	5/5 mice protected at 100 mg/kg (0.25 h)	4/4 mice toxic at 300 mg/kg (0.5 h)	4/4 rats protected at 30 mg/kg (1 h)	No toxicity at 30 mg/kg
14	2.52	No activity at 300 mg/kg	No activity at 300 mg/kg	No toxicity at 300 mg/kg	No data	No data

Table 3. NINDS anti-epileptic drug development program results, Phase II: best activity in rats (oral administration)

Compd	Log P	Phase II: Quantification in rats (oral administration)				
		MES ED_{50}	scMet ED_{50}	Rotorod TD_{50}	MES T.I.	scMet T.I.
10	1.81	> 120 mg/kg	No data	> 120 mg/kg	N/A	N/A
11	1.25	85.71 mg/kg	< 82.5 mg/kg	> 330 mg/kg	> 3.85	> 4.00

protected against MES-induced seizures at 30 mg/kg; no toxicity was noted. The difference in activity between **10** and **13** was postulated to result, at least partly, from the significant change in log P from the unsubstituted terminal alkyne (−0.27) to the phenyl-substituted alkyne (1.52). Unfortunately, the other alkyne, **14**, displayed no activity (nor toxicity) in any model in rats or mice. The large naphthyl group most likely interfered sterically in the activity of this compound relative to that of **13**.

Conclusion

The synthesis of a series of caprolactams derived from α-hydroxy-α-phenylcaprolactam (**4**) was completed, and the compounds were submitted to the NINDS Anticonvulsant Screening Program. Phase I results for a number of the targets were promising; the product of isosteric replacement, α-ethynyl-α-phenylcaprolactam (**10**), appeared to be selective for petit mal seizures. The benzyl derivative **11** exhibited strong activity when administered orally in rats, and when further evaluated in Phase II, was sufficiently active to suggest further development of its structural class. The activity of **10** prompted the inclusion of more targets, including the Sonogashira coupling products **13** and **14**. The phenyl-substituted alkyne **13** demonstrated extremely promising anti-epileptic activity in rats and mice in Phase I and will also be further developed in the future.

Experimental

Melting points were recorded on an Electrothermal capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a QE 300 MHz FT NMR spectrometer at ambient temperature and with an internal standard of tetramethylsilane (TMS). IR spectra were recorded on an FT-IR Impact 400D. Mass spectra were recorded on a Finnagan LCQ Classic (APCI+ unless otherwise noted). Elemental analyses were performed by Atlantic Microlabs in Norcross, GA, USA. See Table 1 for characterizations of products.

α-Hydroxy-α-3,4-dichlorophenylcaprolactam (7). Ground magnesium turnings (0.49 g, 0.020 mol) were placed in the bottom of a dry 100-mL two-neck round-bottom flask with a few crystals of iodine. A small amount of 4-bromo-1,2-dichlorobenzene (0.5 mL, 0.004 mol) was added to the flask; the remainder (1.8 mL, 0.014 mol) was dissolved in dry THF (20 mL) and added slowly. After the reaction cooled to room temperature, it was cooled in an ice bath while adding **18** (0.75 g, 0.006 mol) in dry THF (15 mL). The solution was then allowed to stir at room temperature under nitrogen for 48 h. The Grignard was then quenched with 5% HCl (75 mL) before extracting with Et_2O (3 × 100 mL). The ether layers were combined, dried over sodium sulfate, and concentrated in vacuo to yield a yellow oil. Addition of isopropanol and hexane (1:1) precipitated a solid that was collected by vacuum filtration, producing 0.40 g (25%) of **7** as a white powder. C, H, N analysis: calcd C, 52.27; H, 4.78; N, 5.11; found C, 52.79; H, 4.87; N, 5.13.

α-Hydroxy-α-*p*-tolylcaprolactam (8). To a dry 100-mL two-neck round-bottom flask was added ground magnesium turnings (0.97 g, 0.040 mol) and iodine (a few crystals). After melting 4-bromotoluene over a steam bath, a small amount (0.5 mL, 0.004 mol) was added to the flask. The remainder (3.2 mL, 0.026 mol) was dissolved in dry THF (30 mL) and added over 20 min. The solution was then allowed to cool to room temperature before cooling it in an ice bath and slowly adding **18** (1.27 g, 0.010 mol) in dry THF (20 mL). The ice bath was removed and the reaction was allowed to stir at room temperature under nitrogen for 96 h. The Grignard was quenched by the addition of 5% HCl (60 mL) before extracting with Et_2O (3 × 125 mL). The combined ether layers were dried over sodium sulfate and concentrated in vacuo to yield a yellow powder. The solid was recrystallized from $CHCl_3$/hexanes to collect 1.08 g (50%) of off-white crystals. C, H, N analysis: calcd C, 71.21; H, 7.81; N, 6.39; found C, 71.03; H, 7.73; N, 6.29.

α-Hydroxy-α-2,6-dimethylphenylcaprolactam (9). After placing ground magnesium turnings (1.46 g, 0.060 mol) and iodine (a few crystals) in a dry 250-mL two-neck round-bottom flask, 2-bromo-*m*-xylene (1.00 mL, 0.008 mol) was added. The remainder of the 2-bromo-*m*-xylene (5.00 mL, 0.037 mol) was dissolved in dry THF (40 mL) and added over a 30-min period. The solution was allowed to cool to room temperature. After cooling the reaction further in an ice bath, **18** (1.90 g, 0.015 mol) in dry THF (40 mL) was added slowly. The solution was then stirred under nitrogen at room temperature for 72 h. The reaction was quenched with 5% HCl (150 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to yield a yellow oil. The yellow oil was placed on the HPLC (hexane/isopropanol, 0–100% isopropanol, gradient time = 30 min, λ = 254 nm, flow rate = 3 mL/min) and eluted for 35 min. The fraction containing the compound eluting at 10 min was concentrated in vacuo to produce a clear oil that crystallized upon standing, yielding 0.58 g (17%) of **9** as colorless crystals. C, H, N analysis: calcd C, 72.07; H, 8.21; N, 6.00; found C, 71.83; H, 8.09; N, 5.92.

α-Ethynyl-α-hydroxycaprolactam (10). After placing ethynylmagnesium bromide in THF (0.5 M, 120.0 mL) in a dry 500-mL one-neck round-bottom flask, the solution was cooled in an ice bath before adding **18** (2.50 g, 0.020 mol) in dry THF (30.0 mL) over 30 min. The ice bath was removed, and the solution was stirred at room temperature under nitrogen for 72 h. The reaction was quenched by the gradual addition of 5% HCl (100 mL). After extracting with Et_2O (3 × 120 mL), the ether layer was dried over magnesium sulfate. Removal of the solvent on the rotary evaporatory yielded a brown solid. Flash chromatography on silica gel (5 × 20 cm) with 50% ethyl acetate/hexanes afford 1.61 g (53%)

of **10** as a white power (R_f 0.40, 2:1 ethyl acetate/hexanes, permanganate stain). C, H, N analysis: calcd C, 62.73; H, 7.24; N, 9.14; found C, 62.83; H, 7.17; N, 9.04.

α-Benzyl-α-hydroxycaprolactam (11). Under dry conditions, benzylmagnesium chloride in THF (2.0 M, 32.0 mL) was placed in a 250-mL three-neck round-bottom flask. After cooling the solution in an ice bath, **18** (2.00 g, 0.016 mol) in dry THF (40.0 mL) was added slowly over 1 h. The solution was stirred at room temperature under nitrogen for 72 h before quenching the Grignard with 5% HCl (75 mL). The mixture was extracted with Et_2O (3 × 150 mL); the combined ether layers were dried over magnesium sulfate and concentrated in vacuo to produce a yellow oil that crystallized on standing. The solid was recrystallized from hot EtOAc to yield 1.87 g (53%) of a white powder. C, H, N analysis: calcd C, 71.21; H, 7.81; N, 6.39; found C, 71.07; H, 7.79; N, 6.33.

2-Benzyl-2-hydroxyhexanoic acid amide (12). The cyanohydrin **22** (1.00 g, 0.005 mol) was placed in a 25-mL one-neck round-bottom flask. Concentrated HCl (37%, 1.00 mL) was added, and the reaction was stirred for 1 h at 0 °C while bubbling HCl gas through the solution. The HCl gas line was removed, and the solution was allowed to sit at room temperature overnight. The resulting semisolid was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). After drying the combined organics over magnesium sulfate, the solvent was removed to yield a yellow oil. Flash chromatography on silica gel (3 × 25 cm) with 2:1 hexanes/ethyl acetate yielded a yellow oil (R_f 0.15, 2:1 hexanes/ethyl acetate) that crystallized under vacuum to afford 0.75 g (68%) of an off-white powder. C, H, N analysis: calcd C, 70.56; H, 8.65; N, 6.33; found C, 70.26; H, 8.72; N, 6.23.

α-Hydroxy-α-(phenylethynyl)caprolactam (13). Iodobenzene (1.45 g, 0.007 mol) and **10** (0.80 g, 0.005 mol) were added to a solution of DMF (0.50 mL) and CH_3CN (1.00 mL) in a 25-mL one-neck round-bottom flask. To the stirring solution were added triethylamine (8.88 g, 0.088 mol), PPh_3 (0.21 g, 0.0008 mol), $Pd(PPh_3)_4$ (0.92 g, 0.0008 mol), and copper(I)iodide (0.15 g, 0.0008 mol). The mixture was stirred under nitrogen at 60 °C for 20 h. The solvent was removed under vacuum to yield a viscous brown oil that was purified by flash chromatography on silica gel (5 × 30 cm) with a gradient of 10% ethyl acetate/hexanes to 50% ethyl acetate/hexanes. Fractions with a component of R_f 0.50 (2:1 ethyl acetate/hexanes) were combined and evaporated to afford a yellow solid. The solid, slightly impure by ^1H NMR, was recrystallized from hot ethyl acetate to give the product as 0.36 g (31%) of off-white crystals. C, H, N analysis: calcd C, 73.34; H, 6.59; N, 6.11; found C, 73.01; H, 6.51; N, 6.05.

α-Hydroxy-α-(naphthalen-1-ylethynyl)caprolactam (14). To a mixture of **10** (0.80 g, 0.005 mol), 1-iodonaphthalene (1.80 g, 0.007 mol), DMF (0.50 mL), and CH_3CN (1.00 mL) in a 25-mL one-neck round-bottom flask were added triethylamine (8.88 g, 0.088 mol), PPh_3 (0.21 g, 0.0008 mol), $Pd(PPh_3)_4$ (0.92 g, 0.0008 mol), and copper(I)iodide (0.15 g, 0.0008 mol). The mixture was stirred for 20 h at 60 °C under nitrogen. After removing the solvent under vacuum, the resulting brown semisolid was placed on a silica gel column (5 × 30 cm) and eluted with a steady gradient of 10% ethyl acetate/hexanes to 60% ethyl acetate/hexanes. A single component (R_f 0.55, 2:1 ethyl acetate/hexanes) was collected. Evaporation of the solvent yielded a white solid that was recrystallized from hot ethyl acetate, giving 0.43 g (30%) of white crystals. C, H, N analysis: calcd C, 77.40; H, 6.13; N, 5.01; found C, 77.20; H, 6.12; N, 5.04.

3,3-Dibromo-azepan-2-one (16). To a stirring solution of chloroform (400 mL) in a 1000-mL three-neck round-bottom flask was added ε-caprolactam (**15**, 15.00 g, 0.133 mol). The solution was cooled to 0–5 °C through the use of an ice bath and phosphorus pentachloride (55.20 g, 0.265 mol) was added over a 30-min period. Zinc iodide (1.53 g, 0.0048 mol) was then added. The solution was removed from the ice bath and allowed to reach room temperature as bromine (42.35 g, 0.265 mol) was slowly added over the course of 30 min. After the mixture was stirred at room temperature for 6 h, the resulting orange solution was combined with ice water (300 mL). The chloroform layer was washed with water (1 × 200 mL) and 0.50 M sodium bisulfite (3 × 200 mL), dried over sodium sulfate, and concentrated in vacuo to yield a yellow solid. The solid was suspended in water, filtered, and washed with water and Et_2O to give 28.23 g (79%) of a fluffy, white solid.

3-Piperidin-1-yl-1,5,6,7-tetrahydro-azepin-2-one (17). A solution of **16** (20.00 g, 0.074 mol) in piperidine (175.0 mL) was stirred and heated at reflux for 4.5 h in a 500-mL two-neck round-bottom flask. After removing the heat, the solution was allowed to reach room temperature before being combined with 0.50 M sodium bisulfite (150.0 mL). The mixture was extracted with chloroform (3 × 75 mL). The combined organic layer was dried over sodium sulfate and concentrated in vacuo to yield a brown, oily solid that crystallized upon standing. The resulting solid was suspended in water, filtered, and washed with water and Et_2O to provide 13.31 g (93%) of **17** as a yellow-white, powdery solid.

α-Oxocaprolactam (18). The enamine **17** (12.00 g, 0.006 mol) was dissolved in chloroform (40.0 mL) and placed on an 8 × 24 cm silica gel column. The sample was eluted with ethyl acetate (4 L) and 30-mL fractions were collected. The fractions were monitored with TLC (40% Et_2O/chloroform); those fractions containing a material with R_f 0.12 were combined and concentrated in vacuo to provide a clear oil that crystallized on standing. The solid was suspended in 1:1 Et_2O/hexanes, filtered, and washed with hexanes to yield the product as a white solid (4.37 g, 56%).

Benzyl butyl ketone (20). Crushed magnesium turnings (1.94 g, 0.025 mol) and a few crystals of iodine were placed in a dry 250-mL two-neck round-bottom flask. Benzyl bromide (1.0 mL, 0.008 mol) was added. Additional benzyl bromide (7.9 mL, 0.066 mol) was dissolved in dry ether (40.0 mL) and added dropwise. Valeroni-

trile (**19**, 2.6 mL, 0.025 mol) was similarly dissolved in dry ether (15.0 mL) and slowly added over 15 min. The reaction was stirred at reflux under nitrogen for 8 h. After removing the oil bath, the mixture was stirred overnight at room temperature. The reaction was quenched by the slow addition of 5% H_2SO_4 (75.0 mL) and stirred at reflux for 90 min. After extracting with ether (3 × 100 mL) and drying the combined organic layers over magnesium sulfate, the solvent was removed to afford a dark yellow oil. Flash chromatography on silica gel (8 cm × 25 cm) with 5% ethyl acetate/hexanes yielded 2.52 g (57%) of the desired product as a yellow oil (R_f 0.38, 10% ethyl acetate/hexanes).

2-Benzyl-2-hydroxyhexanenitrile (22). In a dry 10-mL one-neck round-bottom flask were combined **20** (1.23 g, 0.007 mol), trimethylsilyl cyanide (1.87 mL, 0.014 mol), and a few crystals of zinc iodide. The reaction was stirred under nitrogen at room temperature for 24 h; the reaction was monitored by IR for the disappearance of the C=O stretch. The TMS ether (**21**) was not isolated but was instead converted directly to the cyanohydrin by combining the solution with 15% aq HCl (15.0 mL) and ether (15.0 mL). After stirring vigorously for 4 h at room temperature, the mixture was extracted with ether (3 × 50 mL). Evaporation of the solvent yielded 1.10 g (77%) of **22** as a red oil that was carried on without further purification.

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