Pergamon

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Bioorganic & Medicinal Chemistry 11 (2003) 4275–4285

BIOORGANIC & MEDICINAL CHEMISTRY

Functionalized Amido Ketones: New Anticonvulsant Agents

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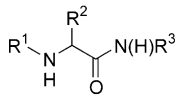
Received 22 January 2003; accepted 15 April 2003

Abstract—We have reported that functionalized amino acids (FAA) are potent anticonvulsants. Replacing the N-terminal amide group in FAA with phenethyl, styryl, and phenylethynyl units provided a series of functionalized amido ketones (FAK). We show that select FAK exhibit significant anticonvulsant activities thereby providing information about the structural requirements for FAA and FAK bioactivity.

Introduction

We, and others, have shown that functionalized amino acids (FAA, **1**) are potent anticonvulsants.[1–3] Evaluation of more than 250 FAA have provided 12 compounds with anticonvulsant activity in rodents that is equal to or greater than phenytoin[4] according to the MES-seizure test.[1e–h,j] The MES test is a proven method of generalized tonic-clonic seizures and identifies clinical candidates that prevent seizure spread.[5,6] FAA provided excellent protection against MES-induced seizures when R^1 was an *N*-acetyl unit, R^2 was either a small aromatic, a small heteroaromatic, or a substituted heteroatom one carbon removed from the asymmetric center, and R^3 was a benzylamide group. Distinguishing this class of compounds was our demonstration that the principal anticonvulsant activity resided in the (*R*)-stereoisomer.[1c–e,g,j,k] Preclinical studies have identified (*R*)-*N*-benzyl-2-acetamido-3-methoxypropionamide [(*R*)-**2**][1j] as the lead FAA, and (*R*)-**2** has entered Phase II clinical trials for the treatment of epilepsy and neuropathic pain under Schwarz Pharma sponsorship.



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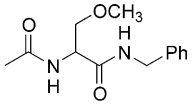

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We have recently studied whether or not conformationally restricted[7] and peptidomimetic[8] FAA derivatives can provide analogues with improved pharmacological properties. We tested whether altering the N-terminus[9] and the central α-carbon[1b,8] within FAA would provide compounds with efficacy in the MES-seizure test. We learned that both sites can be modified in select cases without appreciable losses in activities. Now, we examine whether functionalized amidoketones (FAK, **3**) display anticonvulsant activity when the C-terminal amide in the FAA has been replaced with a ketone unit. In our study, we chose to retain in the FAK other FAA structural components that provided MES-seizure protection.[1] The ketone for amide substitution eliminated a potential hydrogen bond donor interaction of the anticonvulsant with its receptor, altered the conformationally mobility of the test compound, and reduced the number of sites for amidase metabolism. We show herein that FAK exhibit significant anticonvulsant activities.

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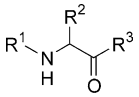
doi:10.1016/S0968-0896(03)00434-6



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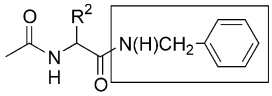
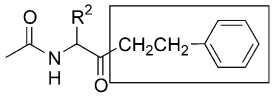
Results and Discussion

Choice of compounds and method of evaluation

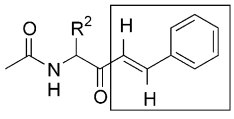
FAA **4**–**6** served as our reference compounds. In this study, we systematically modified two structural sites to provide the FAK **7**–**14**. The first was the R^3 group in which we successively replaced the terminal benzylamino ($N(H)CH_2Ph$) group in FAA with a phenethyl (CH_2CH_2Ph), a styryl (C(H)C(H)Ph), and a phenylethynyl (CCPh) unit. Next, we prepared FAK derivatives in which the R^2 moiety was either a methyl (CH_3), phenyl (C_6H_5), or methoxymethyl (CH_2OCH_3) unit. For FAA we found a significant improvement in anticonvulsant activities in the MES-induced seizure test in mice as we progressed from **4**[1b] to **5**[1b] to **6**.[1j] We elected to prepare the racemic FAK since we did not know if either isomer would exhibit preferential activity. This choice obviated the need to prepare optically pure FAK. For **7**, however, we synthesized both (*R*)-**7** and (*S*)-**7** to learn if the pharmacological properties of FAK, like FAA,[1c–e,g,j,k] was stereoselective.



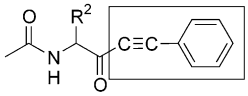
4 $R^2 = CH_3$
5 $R^2 = Ph$
6 $R^2 = CH_2OCH_3$



7 $R^2 = CH_3$
8 $R^2 = Ph$
9 $R^2 = CH_2OCH_3$



10 $R^2 = CH_3$
11 $R^2 = Ph$
12 $R^2 = CH_2OCH_3$

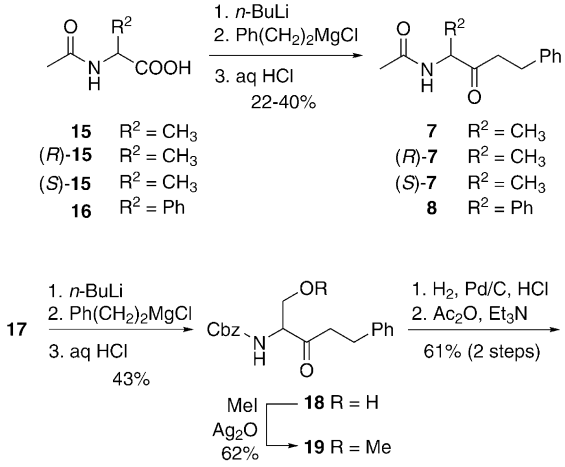


13 $R^2 = CH_3$
14 $R^2 = CH_2OCH_3$

The FAK were evaluated in rodents at the NIH Epilepsy Branch. In one test, the compound was administered to mice intraperitoneally (ip) and then the anticonvulsant properties determined using MES- and scMet-induced seizure models.[5,6] In the second test, the compound was administered to rats orally (po) and then evaluated in the MES-seizure model. The neurological toxicity (Tox) of the compound was evaluated in mice using the rotorod model[10] and in rats by the observation of motor impairment.

Synthesis

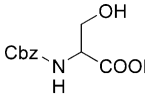
It was necessary to use different methods to prepare compounds **7**–**14**. For saturated compounds **7**–**9**, the method of Rapoport[11,12] was employed to introduce the ketone unit starting from either the *N*-acetyl or the *N*-Cbz-amino acid (Scheme 1). Treatment of **15**, (*R*)-**15**, (*S*)-**15**, **16** and **17** with *n*-BuLi (1 equiv) followed by phenethylmagnesium chloride (2–3 equiv) gave ketones **7**, (*R*)-**7**, (*S*)-**7**, **8**, and **18**, respectively, in 22–43% yields. Methylation of **18** with MeI and Ag_2O gave **19**, which was then converted to **9** by catalytic hydrogenation (H_2, Pd/C) followed by acetylation (Ac_2O, Et_3N).



15 $R^2 = CH_3$
(*R*)-**15** $R^2 = CH_3$
(*S*)-**15** $R^2 = CH_3$
16 $R^2 = Ph$

7 $R^2 = CH_3$
(*R*)-**7** $R^2 = CH_3$
(*S*)-**7** $R^2 = CH_3$
8 $R^2 = Ph$

Scheme 1. Synthesis of saturated functionalized amido ketones.



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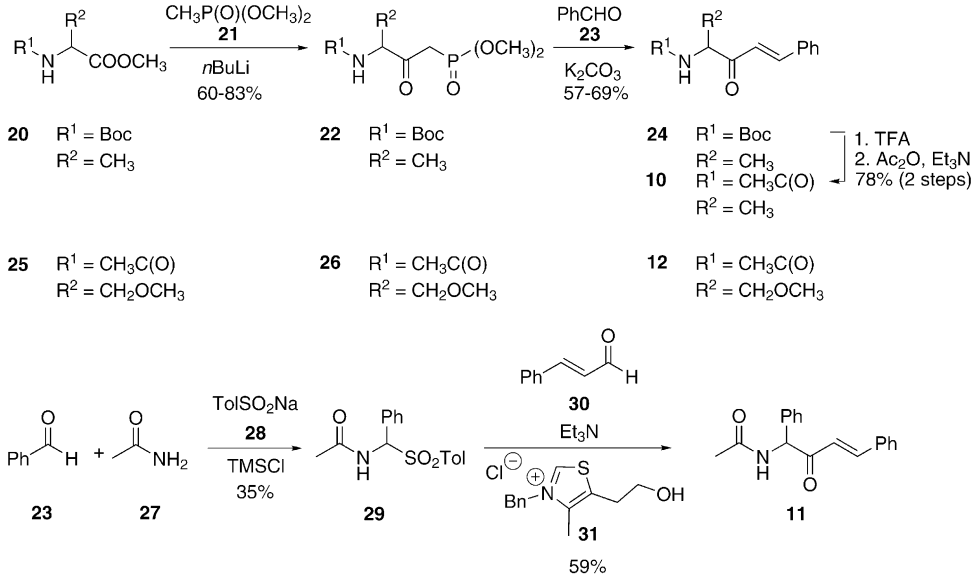
Two of the three vinylogous ketones (**10**, **12**) were prepared using a Horner–Emmons reaction (Scheme 2). Treatment of either *N*-*tert*-Boc-alanine methyl ester (**20**) or *N*-acetyl-*O*-methylserine methyl ester (**25**) with the lithium anion of dimethylmethanephosphonate[13,14] gave the corresponding dimethyl phosphonate esters **22** and **26**. Phosphonates **22** and **26** were readily converted to the *trans* vinylogous ketones **24** and **12**, respectively, upon reaction with benzaldehyde (**23**) and base.[15] Conversion of **24** to **10** was straightforward. Acid (TFA) removal of the *tert*-Boc protecting group in **24** followed by acetylation (Ac_2O, Et_3N) gave **10** in 78% yield. We utilized the thiazolium-catalyzed cross-coupling of aldehydes with acylimines described by Murry and Frantz[16] to prepare **11** (Scheme 2). Accordingly, benzaldehyde (**23**) and acetamide (**27**) were treated with toluenesulfinic acid sodium salt (**28**) and TMSCl to give **29**.[17] Subsequent addition of cinnamaldehyde (**30**) to a tosyl amide **29** and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**31**) suspension provided *trans*-**11** in 59% yield. Inspection of the ^1H NMR spectra[18] for vinylic FAK **10**–**12** documented that the predominant product was the *trans*-isomer. We determined that **10** existed as a 97:3 *trans*:*cis* mixture, **11** to be solely *trans*, and **12** to be a 98:2 *trans*:*cis* mixture.

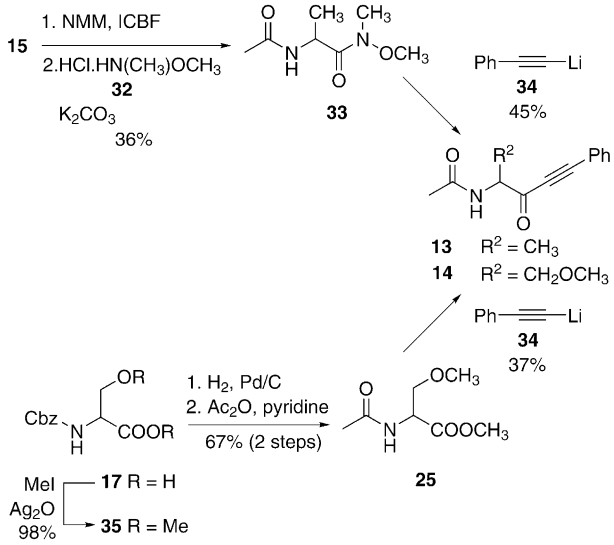
Lithium phenylacetylide[19] (**34**) served as the organometallic reagent for α,β-acetylenic ketones **13** and **14** (Scheme 3). For **13**, we coupled **34** with *N*-acetylalanine-*N*-methoxy-*N*′-methylamide[20] (**33**), which was prepared from *N*-acetylalanine (**15**) and *N*,*O*-dimethylhydroxylamine



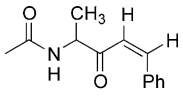
Scheme 2. Synthesis of (*E*)-vinylic amido ketones.

(**32**), using the mixed anhydride coupling method. Synthesis of **14** began with *N*-Cbz-serine (**17**). Conversion of **17** to **35** with CH_3I and Ag_2O followed by removal of the Cbz-protecting group (H_2, Pd/C) and acetylation (Ac_2O, pyridine) gave **25**.[21] Treatment of **25** with **34** provided **14** in 36% yield.

We wanted to compare the pharmacological properties of the *trans*-vinylogous ketone **10** with its *cis*-isomer **36**. Several reductive methods beginning with **13** were examined, but none proved satisfactory. We observed that catalytic reduction of **13** to **36** was accompanied by production of the *trans*-isomer **10** and the saturated ketone **7**. The use of $Pd/CaCO_3/Pb(OAc)_2$ and quinoline[22] (5 equiv) provided the highest amount of *cis*-**36** (73%) (Scheme 4). Attempts to separate the ternary mixture (PTLC, column chromatography) were unsatisfactory. Moreover, *cis*-**36** slowly isomerized to *trans*-**10** at room temperature (data not shown).[23]



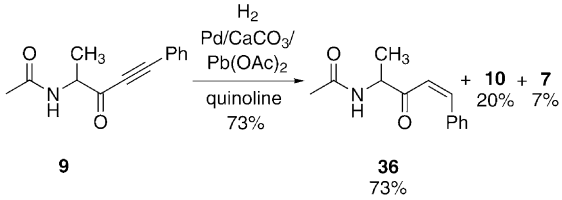
Scheme 3. Synthesis of acetylenic amido ketones.



FAK **7**–**14** gave satisfactory spectroscopic (IR, ^1H and ^{13}C NMR, MS) and elemental analyses in accordance with their proposed structures. We observed a diagnostic upfield shift in the ^{13}C NMR spectra for the terminal carbonyl carbon as it proceeded from the saturated FAK **7**–**9** (δ205.3–208.6) to the vinylic FAK **10**–**12** (δ194.4–198.0) and then to the acetylenic FAK **13** and **14** (δ184.1–186.3).[24]

Pharmacological evaluation

The FAK (Table 1) were tested for anticonvulsant activity using the procedure described by Stables and Kupferberg.[5] We wished to learn if their in vivo pharmacological profile followed the general profile previously observed for FAA.[1] Table 1 lists the results obtained from qualitative (MES, scMet) testing in mice (ip) along with quantitative (MES ED_{50}) mice (ip) and rat (po) evaluations. We include in this table the median neurologically impairing dose (TD_{50}) values using the rotorod test in mice[10] and motor impairment in rats. Finally, protective indices ($PI = TD_{50}/MES\ ED_{50}$) for these adducts, when appropriate, are shown.



Scheme 4. Synthesis of (*Z*)-vinylic amido ketones.

Table 1. Selected physical and pharmacological data for amidoketones

Compd	Mp[c]	Mice (ip)[a]				Rat (po)[b]		
		MES, ED_{50}	scMet, ED_{50}	Tox, TD_{50}	PI[d]	MES, ED_{50}	Tox, TD_{50}	PI[d]
Section A: FAA								
4	138–139	76 [1] (67–89)	>600	450 [0.5] (420–500)	5.9	48 [1] (32–72)	>1000	>21
5	202–203	20 [0.5] (17–25)	>120	97 [0.5] (80–120)	4.8	48 [4] (31–68)	>1000	>21
6	121–122	8.3 [0.5] (7.9–9.8)	>25	43 [0.25] (38–47)	5.2	3.8 [2] (2.9–5.5)	390 [1] (320–520)	102
Section B: Saturated FAK								
7	64–66	49 [0.25] (43–53)	>100, <300	94 [0.25] (84–120)	1.9	47 [0.25] (37–61)	120 [0.25] (100–140)	2.5
(*R*)-**7**	82–84	62 [0.25] (54–65)	>100, <300	160 [0.25] (130–180)	2.5	26 [0.25] (18–37)	>500	>19
(*S*)-**7**	79–81	>30, <100	>300	>100, <300	—	>30	>30	—
8	106–107	>30, <100	>100, <300	~100	—	23 [0.25] (18–26)	>500	>22
9	66–68	47 [0.25] (37–61)	>150, <300	120 [0.25] (100–140)	2.5	18 [0.25] (12–24)	>250	>14
Section C: Vinylic FAK								
10	109–110	96 [0.25] (83–110)	>350	190 [0.25] (140–240)	2.0	~30 [2]	>30	—
11	119–121	>100, <300	>100, <300	>100, <300	—	>30	>30	—
12	127–128	120 [0.25] (100–150)	>300	120 [0.25] (72–150)	1.0	—[e]	>130	—
Section D: Acetylenic FAK								
13	oil	>300	>300	>30, <100	—	—[f]	—[f]	—
14	96–99	>300	>300	>30, <100	—	—[f]	—[f]	—
Section E: Antiepileptic agents								
Phenytoin[g]	—	9.5 [2] (8.1–10)	—[h]	66 [2] (53–72)	6.9	30 [4] (22–39)	—[i]	>100
Phenobarbital[g]	—	22 [1] (15–23)	13 [1] (5.9–16)	69 [0.5] (63–73)	3.2	9.1 [5] (7.6–12)	61 [0.5] (44–96)	6.7
Valproate[g]	—	270 [0.25] (250–340)		430 [0.25] (370–450)	1.6	490 [0.5] (350–730)	280 [0.5] (190–350)	0.6

MES, maximal electroshock seizure test; scMet, subcutaneous metrazol; Tox, neurologic toxicity determined from rotorod test in mice and motor impairment in rats.

[a]The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the 'time of peak effect' (indicated in h in the square brackets).

[b]The compounds were administered orally.

[c]Melting points (°C) are uncorrected.

[d]PI, protective index (TD_{50}/ED_{50}).

[e]2/2 animals protected at 15 mg/kg after 2 h. The ED_{50} could not be determined because the response was not linear.

[f]Not determined.

[g]Ref 26.

[h]Not effective.

[i]No ataxia observed up to 3000 mg/kg.

Table 1A lists the prototypical FAA **4–6**, B gives the saturated FAK **7–9**, C are the vinylic FAK **10–12**, D are acetylenic FAK **13** and **14**, and E contains the antiepileptic agents, phenytoin, phenobarbital, and valporate.[25,26] For FAA **4–6** where R^3 is a benzylamino group ($N(H)CH_2Ph$), we observed an increase in anticonvulsant activity (MES-seizure test) in mice (ip) as we progressed from R^2 equal to methyl[1b] (**4**) to phenyl[1b] (**5**) to methoxymethyl[1j] (**6**). In rats, **4** and **5** show similar activity but **6** displayed increased activity. The ED_{50} values for **4** and **6** were lower in rats than in mice. We saw on the rotorod test that **4–6** exhibited low toxicity, which led to high PI values. None of the three FAA showed noticeable activity in the scMet test in mice.

The saturated FAK **7–9** displayed a comparable activity pattern when administered to rats (po). The ED_{50} values for **7**, **8**, and **9** were 47, 23, and 18 mg/kg, respectively. The ED_{50} values for **8** and **9** compared favorably with phenytoin ($ED_{50}=30$ mg/kg) and phenobarbital ($ED_{50}=9.1$ mg/kg),[26] and both **8** and **9** exhibited PI values that exceeded 14. When the (*R*)- and (*S*)-enantiomers of **7** were evaluated, (*R*)-**7** ($ED_{50}=26$ mg/kg) was found to be nearly 50% more potent than (*R,S*)-**7**

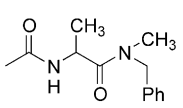
(ED_{50} = 47 mg/kg) and more active than the (*S*)-isomer (ED_{50} > 30 mg/kg). This trend mirrors the findings for FAA **4** in rats [ED_{50} values (mg/kg): (*R,S*)-**4**, 48; (*R*)-**4**, 28; (*S*)-**4**, 55].[1c,d] These patterns of activity were not evident when FAK **7–9** were administered to mice. Little difference in activity was observed as we modified the R^2 group (ED_{50} values (mg/kg): **7**, 49; **8**, 30–100; **9**, 47). Moreover, the ED_{50} value for (*R*)-**7** (62 mg/kg) exceeded that of the racemate (*R,S*)-**7** (49 mg/kg). It is unclear why the mouse data differed from rat data. For FAA, we generally observed increased anticonvulsant activity in the rat compared with the mice, but SAR trends were similar in both mice and rats. FAK **7–9** showed no appreciable scMet activity when administered to mice.

The profile for vinylic FAK **10–12** was similar to FAA **4–6** and FAK **7–9**. We observed that the ED_{50} values in the rat for **10–12** (ED_{50} values (mg/kg): **10**, ~30; **11**, >30; **12** est. 15) were comparable with **7–9** (ED_{50} mg/kg values: **7**, 47; **8**, 23; **9**, 18). When **10–12** were tested in mice we found that the anticonvulsant activities were less than those in rats, that the activities did not improve in proceeding from **10** to **12**, and that none of the compounds exhibited noticeable anticonvulsant activities in the scMet seizure test.

The remaining compounds were acetylenic FAK **13** and **14**. These amidoynones were only evaluated in mice because of their toxicity (>30, <100 mg/kg). We observed that both compounds exhibited low activity in the MES-seizure test (ED_{50} > 300 mg/kg).

The saturated FAK **7–9** and vinylic FAK **10–12** showed anticonvulsant activities in rats that matched FAA **4–6**. Inspection of activity in each of the three active sets of compounds (Table 1, Sections A–C) suggested that they all functioned by similar pathways. For the FAA, saturated FAK, and vinylic FAK series we observed a general increase in anticonvulsant activity in the MES-seizure test (rat) as we changed the R^2 group from methyl to methoxymethyl. For **4** and **7** we found that the (*R*)-enantiomer was more active than either the (*R,S*)-racemate or the (*S*)-isomer.

The near equal anticonvulsant activities of FAA **4–6**, saturated FAK **7–9** and the *trans*-vinylic FAK **10–12** suggested that the terminal substituent in the three active series ($N(H)CH_2Ph$, CH_2CH_2Ph, *trans*-C(H)C(H)Ph) adopted a similar conformation when eliciting drug function. Accordingly, the diminished anticonvulsant activities for the acetylenes **13** and **14** may be explained by the placement of a linear terminal group within the FAK. The pattern observed for FAK may explain an earlier finding.[7] We reported that placement of a *N*-methyl unit within **4** and **6** to give **37** and **38**, respectively, led to a loss in activity.[7] The MES ED_{50} values for **37** and **38** in mice were between 100 and 300 mg/kg, and in rats they exceeded 30 mg/kg. We were unsure whether the diminished activities for **37** and **38** resulted from the loss of a N(H) hydrogen bond interaction, the increased size of the FAA, or the adoption of an FAA conformation for the terminal unit that was unfavorable for seizure protection. Indeed, ^1H NMR analyses ($CDCl_3$) showed that both **37** and **38** existed as a 65:35 mixture of conformational isomers. Our finding that the activities of FAK **7–9** and **10–12** approached that of FAA **4–6** indicated that the C-terminal amide hydrogen within FAA **1** is not essential for anticonvulsant activity and that the conformation of this structural unit may be critical for drug function.



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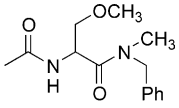

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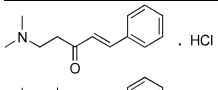
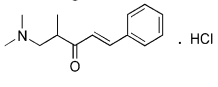
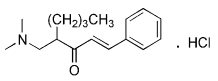
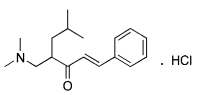
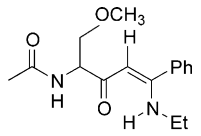
The rise in neurological toxicity for **13** and **14** was striking. This finding was reminiscent of an earlier structure–toxicity relationship study of alkanones, α,β-unsaturated alkenones and ynones in a static *Tetrahymena pyriformis* population growth assay.[27] Schultz and co-workers observed toxicity to increase in proceeding from the alkanones, to alkenones, to ynones[27] and discussed the proclivity of alkenones and ynones to undergo Michael addition.[28] Accordingly we asked if vinylic and acetylenic FAK readily underwent chemical modification. Both vinylic and acetylenic FAK contain an unsaturated unit in conjugation with a carbonyl group, and may undergo Michael addition with nucleophiles. Accordingly, we treated **12** and **14** with both EtSH (16 equiv) and $EtNH_2$ (16 equiv) in THF under Ar at room temperature for 18 h. We observed no reaction for **12** with either EtSH or $EtNH_2$. We further tested whether **12** underwent reversible conjugate addition with EtSH by repeating the experiment in a 1:2 CD_3OD–THF mixture. Isolation of **12** after 18 h showed no deuterium incorporation at the vinylic site (data not shown). When we treated acetylenic FAK **14** with EtSH we again observed no reaction. Correspondingly, reaction of **14** with $EtNH_2$ led to the full consumption of **14** (room temperature, 18 h) and the appearance of a single, major product (TLC analysis) that has been tentatively identified as **39**. We assigned **39** as the *trans*-product on the basis of NOESY analysis and a comparison of the ^1H NMR chemical shift (δ 10.69) for the N(H) enaminone proton with related compounds.[29]

Table 2. Vinylic aminoketones with anticonvulsant activities[a]

Compd	MES ED_{50} (mg/kg)[b]
	Inactive
	87.9
	53.9
	36.2

[a]All compounds were tested in mice.[30]
[b]MES, maximal electroshock seizure test, the compounds were administered intraperitoneally (ip).



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Vinylic aminoketones have been previously evaluated in seizure models.[30] Most ketones showed activity (Table 2). The compounds in our series differ from those in Table 2 in the nature of the R^1 and R^2 groups and the incorporation of a central α-amino acid moiety. Nonetheless, the anticonvulsant activities for our FAK with those previously reported document that this class of compounds deserve further investigation.

Conclusions

We have determined that FAK exhibit excellent anticonvulsant activities that approach those observed for their FAA counterparts in rats. The favorable activities for FAK have been attributed to the incorporation of key R^2 structural units within the FAK backbone and the conformation of the terminal ketone unit. The neurological toxicities of select FAK in rats exceeded that found for the corresponding FAA.

Experimental

General methods

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a ATI Mattson Genesis Series FTIR™ spectrometer. Absorption values are expressed in wave-numbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on a General Electric QE-300 NMR instrument. Chemical shifts (δ) are in parts per million (ppm) relative to tetramethylsilane and coupling constants (J values) are in Hertz. Low resolution mass spectra (CI+) were obtained with a Varian MAT CH-5 spectrometer by Dr. M. Moini at the University of Texas-Austin. The high-resolution chemical ionization mass spectrum was performed on a Finnigan MAT TSQ-70 by Dr. M. Moini at the University of Texas-Austin. Microanalysis were provided by Atlantic Microlab, Inc. (Norcross, GA). Thin layer chromatography was performed on a precoated silica gel GHLF microscope slides (2.5×10 cm; Analtech No. 21521).

Synthesis of saturated α-amidoketones. General procedure. *n*-BuLi (1 equiv) was added to a stirred N_2-blanketed solution of the *N*-acylamino acid (1 equiv) in dry THF at −78 °C. To the resulting suspension was slowly added phenethylmagnesium chloride (2–3 equiv) and the reaction was stirred at −78 °C (30 min) and then at room temperature (18 h). The mixture was poured into an equal volume of aqueous 1 N HCl and extracted with EtOAc (3×100–200 mL). The organic extracts were combined and washed successively with saturated aqueous $NaHCO_3$ (200–300 mL), and brine (200–300 mL), dried (Na_2SO_4), filtered and evaporated in vacuo. The resulting oily residue was triturated with Et_2O (100–200 mL) to obtain a white solid which upon filtration and drying afforded the desired product. Using this general procedure, the following compounds were prepared.

Synthesis of (*R*,*S*)-2-acetamido-5-phenyl-3-pentanone (7). Compound **7** (3.00 g, 40%) was prepared as a white crystalline solid from **15** (5.00 g, 38 mmol), *n*-BuLi (24 mL, 38 mmol), phenethylmagnesium chloride (96 mL, 96 mmol), THF (150 mL): mp 64–66 °C; R_f 0.42 (EtOAc); IR (KBr) 3313, 3074, 3030, 2936, 1717, 1634, 1546, 1442, 1374, 1296, 1073, 996, 750, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 7.2 Hz, CHC**H**$_3$), 1.99 (s, C**H**$_3$C(O)), 2.70–3.01 (m, C**H**$_2$C**H**$_2$Ph), 4.50–4.65 (m, C**H**CH$_3$), 6.30–6.35 (m, N**H**), 7.15–7.40 (m, Ph**H**), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of **7** did not lead to a separation of the NMR signals; ^{13}C NMR ($CDCl_3$) δ 17.7 (CH**C**H$_3$), 23.4 (**C**H$_3$C(O)), 29.7 (CH$_2$**C**H$_2$Ph), 41.1 (**C**H$_2$CH$_2$Ph), 54.3 (**C**HCH$_3$), 126.5 (**C**$_4'$), 128.5 (2**C**$_2'$ or 2**C**$_3'$), 128.8 (2**C**$_2'$ or 2**C**$_3'$), 140.7 (**C**$_1'$), 169.8 (**C**(O)NH), 208.6 (**C**(O)); MS (+CI) (rel intensity) 220 (M^+ + 1, 100), 178 (22); M_r (+CI) 220.133 93 [M^+ + 1] (calcd for $C_{13}H_{18}NO_2$ 220.133 75). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.23%; H, 7.76%; N, 6.39%. Found C, 71.31%; H, 7.86%; N, 6.34%.

Synthesis of (*S*)-2-acetamido-5-phenyl-3-pentanone [(*S*)-7]. Compound (*S*)-**7** (1.10 g, 22%) was prepared as a white crystalline solid from (*S*)-**15** (3.00 g, 22.9 mmol), *n*-BuLi (14.3 mL, 22.9 mmol), phenethylmagnesium chloride (46 mL, 46 mmol), THF (100 mL): mp 79–81 °C; $[\alpha]_D^{24} = -57.3°$ (*c* 0.8, MeOH); R_f 0.42 (EtOAc); IR (KBr) 3324, 3067, 3038, 2941, 1721, 1642, 1541, 1438, 1362, 1301, 1077, 989, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 7.5 Hz, CHC**H**$_3$), 1.98 (s, C**H**$_3$C(O)), 2.70–3.00 (m, C**H**$_2$C**H**$_2$Ph), 4.50–4.62 (m, C**H**CH$_3$), 6.40–6.50 (m, N**H**), 7.15–7.40 (m, Ph**H**); ^{13}C NMR ($CDCl_3$) δ 17.3 (CH**C**H$_3$), 23.3 (**C**H$_3$C(O)), 28.6 (CH$_2$**C**H$_2$Ph), 41.0 (**C**H$_2$CH$_2$Ph), 54.2 (**C**HCH$_3$), 126.4 (**C**$_4'$), 128.4 (2**C**$_2'$ or 2**C**$_3'$), 128.7 (2**C**$_2'$ or 2**C**$_3'$), 140.7 (**C**$_1'$), 169.8 (**C**(O)NH), 208.6 (**C**(O)); MS (+CI) (rel intensity) 220 (M^+ + 1, 100); M_r (+CI) 220.133 34 [M^+ + 1] (calcd for $C_{13}H_{18}NO_2$ 220.133 75). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.23%; H, 7.76%; N, 6.39%. Found C, 71.46%; H, 7.85%; N, 6.21%.

Synthesis of (*R*)-2-acetamido-5-phenyl-3-pentanone [(*R*)-7]. Compound (*R*)-**7** (1.80 g, 36%) was prepared as a white crystalline solid from (*R*)-**15** (3.00 g, 22.9 mmol), *n*-BuLi (14.3 mL, 22.9 mmol), phenethylmagnesium chloride (46 mL, 46 mmol), THF (100 mL): mp 82–84 °C; $[\alpha]_D^{24} = +58.7°$ (*c* 0.95, MeOH); R_f 0.42 (EtOAc); IR (KBr) 3328, 3072, 3033, 2945, 1718, 1650, 1544, 1435, 1366, 1296, 1079, 992, 752, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 7.2 Hz, CHC**H**$_3$), 1.99 (s, C**H**$_3$C(O)), 2.65–3.00 (m, C**H**$_2$C**H**$_2$Ph), 4.50–4.65 (m, C**H**CH$_3$), 6.30–6.40 (m, N**H**), 7.15–7.40 (m, Ph**H**); ^{13}C NMR ($CDCl_3$) δ 17.7 (CH**C**H$_3$), 23.4 (**C**H$_3$C(O)), 29.7 (CH$_2$**C**H$_2$Ph), 41.1 (**C**H$_2$CH$_2$Ph), 54.3 (**C**HCH$_3$), 126.5 (**C**$_4'$), 128.5 (2**C**$_2'$ or 2**C**$_3'$), 128.7 (2**C**$_2'$ or 2**C**$_3'$), 140.7

($\mathbf{C}_1'$), 169.8 (**C**(O)NH), 208.6 (**C**(O)); MS (+CI) (rel intensity) 220 ($M^+ + 1$); M_r (+CI) 220.133 11 [$M^+ + 1$] (calcd for $C_{13}H_{18}NO_2$ 220.133 75). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.23%; H, 7.76%; N, 6.39%. Found C, 71.47%; H, 7.94%; N, 6.22%.

Synthesis of (*R*,*S*)-1-acetamido-1,4-diphenyl-2-butanone (8). Compound **8** (2.00 g, 35%) was prepared as a white crystalline solid from **16** (4.00 g, 21 mmol), *n*-BuLi (13.2 mL, 21 mmol), phenethylmagnesium chloride (42 mL, 42 mmol), THF (100 mL): mp 106–107 °C; R_f 0.33 (EtOAc); IR (KBr) 3283, 3061, 3024, 1717, 1649, 1540, 1452, 1371, 1297, 1073, 1020, 751, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, C**H**$_3$C(O)), 2.62–2.93 (m, C**H**$_2$C**H**$_2$Ph), 5.54 (d, J = 6.0 Hz, C**H**Ph), 6.83 (d, J = 6.0 Hz, N**H**), 7.00–7.35 (m, 10 Ph**H**); ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H$_3$C(O)), 29.8 (CH$_2$**C**H$_2$Ph), 41.5 (**C**H$_2$CH$_2$Ph), 63.3 (**C**HPh), 126.4, 128.2, 128.4, 128.7, 128.8, 129.4, 136.4, 140.4 (2 **C**$_6$H$_5$), 169.5 (**C**(O)NH), 205.3 (**C**(O)); MS (+CI) (rel intensity) 282 ($M^+ + 1$); M_r (+CI) 282.148 62 [$M^+ + 1$] (calcd for $C_{18}H_{20}NO_2$ 282.149 40). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.87%; H, 6.76%; N, 4.98%. Found C, 76.99%; H, 6.87%; N, 4.95%.

Synthesis of (*R*,*S*)-2-(carbobenzyloxy)amino-1-hydroxy-5-phenyl-3-pentanone (18). Compound **18** (4.22 g, 43%) was prepared as a white crystalline solid from **17** (7.10 g, 29.7 mmol), *n*-BuLi (18.6 mL, 29.7 mmol), phenethylmagnesium chloride (90 mL, 90 mmol), THF (150 mL): mp 88–90 °C; R_f 0.39 (1:1, EtOAc/hexanes); IR (KBr) 3417, 3383, 2949, 1714, 1684, 1454, 1262, 1059, 742, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10–2.20 (m, O**H**), 2.80–3.00 (m, C**H**$_2$C**H**$_2$Ph), 3.80–4.00 (m, C**H**$_2$OH), 4.30–4.40 (m, C**H**), 5.12 (s, OC**H**$_2$Ph), 5.79–5.90 (m, N**H**), 7.10–7.40 (m, 10 Ph**H**); ^{13}C NMR ($CDCl_3$) δ 29.6 (CH$_2$**C**H$_2$Ph), 41.7 (**C**H$_2$CH$_2$Ph), 62.2 (**C**H or OCH$_2$Ph), 62.9 (**C**H or OCH$_2$Ph), 67.4 (**C**H$_2$O), 126.5, 128.3, 128.5, 128.8, 136.2, 140.7 (2 **C**$_6$H$_5$), 156.5 (O**C**(O)NH), 206.8 (**C**(O)), the remaining aromatic signals were not detected and are believed to overlap with nearby signals; MS (+CI) (rel intensity) 328 ($M^+ + 1$, 100), 310 (73), 298 (77), 284 (56), 266 (36), 254 (62); M_r (+CI) 328.154 02 [$M^+ + 1$] (calcd for $C_{19}H_{22}NO_4$ 328.154 88). Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.72%; H, 6.42%; N, 4.28%. Found C, 70.10%; H, 6.71%; N, 3.98%.

Synthesis of (*R*,*S*)-2-(carbobenzyloxy)amino-1-methoxy-5-phenyl-3-pentanone (19). To an acetonitrile (150 mL) solution of **18** (3.19 g, 9.8 mmol) was added successively Ag_2O (9.28 g, 40 mmol) and MeI (3.25 mL, 50 mmol) and the mixture was stirred at room temperature (4 days). The insoluble salts were removed by filtration and the filtrate was concentrated under reduced pressure to obtain an oily residue, which was purified by column chromatography (SiO_2, 1:4, EtOAc/hexanes) to afford pure **19** (2.05 g, 62%) as a viscous oil, which solidified upon standing: mp 47–49 °C; R_f 0.31 (1:4, EtOAc/hexanes); IR (KBr) 3420, 3372, 2956, 1722, 1687, 1551, 1456, 1270, 1059, 745, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75–3.00 (m, C**H**$_2$C**H**$_2$Ph), 3.27 (s, OC**H**$_3$), 3.57 (dd, J = 3.9, 9.6 Hz, C**H**H′OCH$_3$), 3.80 (dd, J = 3.2, 9.6 Hz, CH**H**′OCH$_3$), 4.35–4.45 (m, C**H**), 5.11 (s, OC**H**$_2$Ph), 5.76 (d, J = 7.2 Hz, N**H**), 7.15–7.46 (m, 10 Ph**H**); ^{13}C NMR ($CDCl_3$) δ 29.5 (CH$_2$**C**H$_2$Ph), 41.6 (**C**H$_2$CH$_2$Ph), 59.4 (CH$_2$O**C**H$_3$ or **C**HCH$_2$OCH$_3$), 60.5 (CH$_2$O**C**H$_3$ or **C**HCH$_2$OCH$_3$), 67.2 (O**C**H$_2$Ph), 72.2 (**C**H$_2$OCH$_3$), 126.4, 128.3, 128.5, 128.6, 128.7, 128.8, 136.4, 140.9 (2 **C**$_6$H$_5$), 156.2 (O**C**(O)NH), 206.5 (**C**(O)); MS (+CI) (rel intensity) 342 ($M^+ + 1$, 100), 298 (17); M_r (+CI) 342.169 72 [$M^+ + 1$] (calcd for $C_{20}H_{24}NO_4$ 342.170 53). Anal. calcd for $C_{20}H_{23}NO_4$: C, 70.38%; H, 6.74%; N, 4.11%. Found C, 70.20%; H, 6.83%; N, 4.16%.

Synthesis of (*R*,*S*)-2-acetamido-1-methoxy-5-phenyl-3-pentanone (9). A MeOH (250 mL) solution of **19** (4.04 g, 11.8 mmol) and aqueous 12 N HCl (1.1 mL, 13.2 mmol) was hydrogenated in the presence of 10% Pd/C (0.5 g) at room temperature (2 h). The catalyst was removed by filtration through Celite and the filtrate was evaporated in vacuo to obtain a solid residue. To a vigorously stirred CH_2Cl_2 (50 mL) suspension of the residue was added Ac_2O (1.13 mL, 12 mmol) followed by the slow addition of Et_3N (3.35 mL, 24 mmol). The mixture was stirred (1 h) and then concentrated in vacuo to obtain an oil, which was purified first by column chromatography (SiO_2, EtOAc), and then by recrystallization from Et_2O–hexanes to afford **9** (1.80 g, 61%): mp 66–68 °C; R_f 0.50 (EtOAc); IR (KBr) 3315, 2923, 1719, 1646, 1529, 1375, 1115, 748, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 2.65–3.11 (m, C**H**$_2$C**H**$_2$Ph), 3.27 (s, OC**H**$_3$), 3.58 (dd, J = 3.9, 9.6 Hz, C**H**H′OCH$_3$), 3.80 (dd, J = 3.3, 9.6 Hz, CH**H**′OCH$_3$), 4.60–4.70 (m, C**H**), 6.52 (d, J = 6.0 Hz, N**H**), 7.10–7.40 (m, Ph**H**); ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H$_3$C(O)), 29.5 (CH$_2$**C**H$_2$Ph), 41.6 (**C**H$_2$CH$_2$Ph), 59.0 (O**C**H$_3$ or **C**H), 59.4 (O**C**H$_3$ or **C**H), 72.0 (**C**H$_2$OCH$_3$), 126.4 ($\mathbf{C}_4'$), 128.5 (2$\mathbf{C}_2'$ or 2$\mathbf{C}_3'$), 128.7 (2$\mathbf{C}_2'$ or 2$\mathbf{C}_3'$), 140.8 ($\mathbf{C}_1'$), 170.2 (**C**(O)NH), 206.5 (**C**(O)); MS (+CI) (rel intensity) 250 ($M^+ + 1$, 100), 129 (18); M_r (+CI) 250.144 17 [$M^+ + 1$] (calcd for $C_{14}H_{20}NO_3$ 250.144 32). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.47%; H, 7.63%; N, 5.62%. Found C, 67.55%; H, 7.73%; N, 5.59%.

Synthesis of (*R*,*S*)-(3-*tert*-butoxycarbonylamino-2-oxobutyl)phosphonic acid dimethyl ester (22). To a THF (150 mL) solution of **21** (3.65 mL, 34.12 mmol) was added *n*-BuLi (2.5 M in hexanes, 13.6 mL) at −78 °C and the mixture was stirred (1 h). A THF (80 mL) solution of **20** (3.00 g, 14.8 mmol) was added dropwise to the lithium salt of **21** and the mixture was stirred at −78 °C (2 h) and then at −23 °C (1 h). Glacial acetic acid (0.5 mL) was added and the reaction mixture was poured into saturated aqueous $NaHCO_3$ (150 mL). The solution was extracted with EtOAc (2×100 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude was purified by flash column chromatography (SiO_2; 2:23, MeOH/$CHCl_3$) to obtain **22** (3.58 g, 83%) as a colorless oil: R_f 0.40 (1:9, MeOH/$CHCl_3$); IR (KBr) 3289 (br), 2974, 1710, 1521, 1455, 1369, 1253, 1172, 1036, 865, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 7.2 Hz, C**H**$_3$CH), 1.45 (s, (C**H**$_3$)$_3$C), 3.14 (dd, J = 22.2 Hz, J_{PH} = 14.1 Hz, C**H**H′P(O)), 3.32 (dd, J = 22.2 Hz, J_{PH} = 14.1 Hz, CH**H**′P(O)), 3.79 (d, J_{PH} = 11.1 Hz, P(O)(OC**H**$_3$)), 3.80

(d, $J_{PH}=11.4$ Hz, P(O)(OCH′$_3$)), 4.36 (dq, $J=7.2$, 7.2 Hz, CH), 5.46 (d, $J=7.2$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3CH), 28.0 ((CH_3)$_3$C), 37.7 (d, $J_{PC}=131.1$ Hz, $CH_2P(O)$), 52.7 (d, $J_{PC}=2.3$ Hz, P(O)(OCH$_3$)), 52.8 (d, $J_{PC}=2.9$ Hz, P(O)(OC′H$_3$)), 55.8 (CH), 79.6 ((CH_3)$_3$C), 155.1 (OC(O)NH), 201.6 (C(O)); MS (+CI) (rel intensity) 296 (18), 268 (10), 257 (17), 240 (100), 222 (21), 196 (76); M_r (+CI) 296.125 59 [$M^+ + 1$] (calcd for $C_{11}H_{23}NO_6P$ 296.126 30).

Synthesis of (*R*,*S*)-(1-methyl-2-oxo-4-phenyl-but-3-enyl)-carbamic acid *tert*-butyl ester[31] (24). Using the procedure of Koskinen and co-workers[15] compound **24** was prepared. To a MeCN (100 mL) solution of **22** (3.58 g, 14.14 mmol) was added dried (140 °C, 18 h) K_2CO_3 (3.35 g, 24.27 mmol) and **23** (1.67 mL, 24.17 mmol). The suspension was stirred at room temperature (24 h) and then the insoluble solids were filtered and the reaction solvent evaporated. The oily crude residue was purified by flash column chromatography (SiO_2; 1:9, EtOAc/hexanes) to obtain **24** (2.30 g, 69%) as an off-white solid: mp 71–72 °C; R_f 0.44 (1:4, EtOAc/hexanes); IR (KBr) 3352 (br), 2979, 2935, 1701, 1612, 1502, 1451, 1364, 1249, 1168, 1051, 864, 764, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, $J=7.2$ Hz, CH_3CH), 1.43 (s, (CH_3)$_3$C), 4.66 (dq, $J=7.2$, 7.2 Hz, CH), 5.48 (d, $J=7.2$ Hz, NH), 6.80 (d, $J=16.2$ Hz, CHC(O)), 7.33–7.38 (m, PhH, 3H), 7.52–7.55 (m, PhH, 2H), 7.69 (d, $J=16.2$ Hz, CHPh); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3CH), 28.3 ((CH_3)$_3$C), 53.7 (CH), 79.6 ((CH_3)$_3$C), 122.3 (CHC(O)), 128.4 (2C$_2$′ or 2C$_3$′), 128.9 (2C$_2$′ or 2C$_3$′), 130.7 (C$_4$′), 134.2 (C$_1$′), 144.3 (CHPh), 155.1 (OC(O)NH), 198.2 (C(O)); MS (+CI) (rel intensity) 276 ($M^+ + 1$, 14), 248 (13), 221 (14), 220 (100), 176 (43); M_r (+CI) 276.159 26 [$M^+ + 1$] (calcd for $C_{16}H_{22}NO_3$ 276.159 97). Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79%; H, 7.69%; N, 5.09%. Found C, 69.85%; H, 7.75%; N, 5.05%.

Synthesis of *trans*-(*R*,*S*)-2-acetamido-5-phenyl-4-penten-3-one (10).[32] To a cold (0 °C) CH_2Cl_2 (35 mL) solution of **24** (1.36 g, 4.95 mmol) was added TFA (7.6 mL, 98.65 mmol) dropwise and the mixture was stirred at 0 °C (1 h). The reaction solvent was evaporated in vacuo and the residue dissolved in THF and Ac_2O (4.7 mL, 49.81 mmol) and Et_3N (3.4 mL, 24.39 mmol) were successively added. The solution was stirred at room temperature (75 min), and then the solvent evaporated. The crude product was purified by flash column chromatography (SiO_2; 1:49, MeOH/$CHCl_3$) to obtain a yellow solid, which was further purified by crystallization (EtOAc) to give **10** (835 mg, 78%) as a crystalline solid: mp 109–110 °C; R_f 0.31 (1:49, MeOH/$CHCl_3$); IR (KBr) 3285 (br), 3061, 2983, 2935, 1745, 1653, 1611, 1540, 1450, 1375, 1304, 1205, 1152, 1071, 985, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (d, $J=6.9$ Hz, CH_3CH), 2.05 (s, $CH_3C(O)$), 4.94–5.03 (m, CH), 6.54 (br s, NH), 6.80 (d, $J=15.9$ Hz, CHC(O)), 7.38–7.59 (m, PhH), 7.74 (d, $J=15.9$ Hz, CHPh); ^{13}C NMR ($CDCl_3$) δ 18.6 (CH_3CH), 23.3 ($CH_3C(O)$), 52.5 (CH), 122.2 (CHC(O)), 128.5 (2C$_2$′ or 2C$_3$′), 129.0 (2C$_2$′ or 2C$_3$′), 131.0 (C$_4$′), 134.0 (C$_1$′), 144.9 (CHPh), 169.5 (C(O)NH), 198.0 (C(O)); MS (+CI) (rel intensity) 219 (15), 218 ($M^+ + 1$, 100); M_r (+CI) 218.117 96 [$M^+ + 1$] (calcd for $C_{13}H_{16}NO_2$ 218.118 10). Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.87%; H, 6.96%; N, 6.45%. Found C, 71.71%; H, 6.93%; N, 6.45%.

Synthesis of (*R*,*S*)-(3-acetamido-2-oxo-butyl-4-methoxy)-phosphonic acid dimethyl ester (26). To a THF (65 mL) solution of **21** (7.95 mL, 74.32 mmol) was added *n*-BuLi (1.6 M in hexanes, 46.1 mL) at −78 °C, and the mixture was stirred (1 h). A THF (45 mL) solution of **25** (1.98 g, 11.31 mmol) was added dropwise to the lithium salt of **21** and the mixture was stirred at −78 °C (1 h) and then at 0 °C (3 h). Glacial acetic acid (0.5 mL) was added and the reaction mixture was poured into saturated aqueous $NaHCO_3$ (70 mL). The solution was extracted with CH_2Cl_2 (4×70 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude was purified by flash column chromatography (SiO_2; 1:49, MeOH/$CHCl_3$) to obtain **26** (1.81 g, 60%) as a colorless oil: R_f 0.37 (1:49, MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.07 (s, $CH_3C(O)$), 3.13 (dd, $J=22.2$ Hz, $J_{PH}=14.1$ Hz, CHH′P(O)), 3.34 (s, OCH$_3$), 3.39 (dd, $J=22.2$ Hz, $J_{PH}=14.1$ Hz, CHH′P(O)), 3.60 (dd, $J=4.2$, 9.6 Hz, CHH′OCH$_3$), 3.79 (d, $J_{PH}=11.1$ Hz, P(O)(OCH$_3$)), 3.80 (d, $J_{PH}=11.4$ Hz, P(O)(OCH′$_3$)), 3.89 (dd, $J=3.9$, 9.6 Hz, CHH′OCH$_3$), 4.80–4.85 (m, CH), 6.67 (br s, NH); ^{13}C NMR ($CDCl_3$) δ 23.0 ($CH_3C(O)$), 38.6 (d, $J_{PC}=131.1$ Hz, $CH_2P(O)$), 53.1 (d, $J_{PC}=6.3$ Hz, P(O)(OCH$_3$)), 53.2 (d, $J_{PC}=6.9$ Hz, P(O)(OC′H$_3$)), 59.0 (OCH$_3$ or CH), 59.1 (OCH$_3$ or CH), 71.2 (CH_2OCH_3), 170.0 (C(O)NH), 199.0 (d, $J_{PC}=6.9$ Hz, C(O)).

Synthesis of *trans*-(*R*,*S*)-2-acetamido-1-methoxy-5-phenyl-4-penten-3-one (12). To a MeCN (50 mL) solution of **26** (1.75 g, 6.55 mmol) was added dried (140 °C, 18 h) K_2CO_3 (1.81 g, 13.10 mmol) and **23** (0.9 mL, 13.10 mmol). The suspension was stirred at room temperature (24 h) and the insoluble solids were filtered and the reaction solvent evaporated. The oily crude residue was purified by flash column chromatography (SiO_2; 1:49, MeOH/$CHCl_3$ to 1:24, MeOH/$CHCl_3$) and then crystallized (EtOAc) to obtain **12** (920 mg, 57%) as an off-white solid: mp 127–128 °C; R_f 0.47 (1:49, MeOH/$CHCl_3$); IR (KBr) 3362, 3056, 2901, 2822, 1654, 1616, 1508, 1378, 1117, 1072, 987, 748, 662, 589 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, $CH_3C(O)$), 3.33 (s, OCH$_3$), 3.72 (dd, $J=4.2$, 9.9 Hz, CHH′OCH$_3$), 3.87 (dd, $J=3.6$, 9.9 Hz, CHH′OCH$_3$), 5.03–5.08 (m, CH), 6.65 (d, $J=6.9$ Hz, NH), 6.90 (d, $J=15.9$ Hz, CHC(O)), 7.39–7.60 (m, PhH), 7.75 (d, $J=15.9$ Hz, CHPh); ^{13}C NMR ($CDCl_3$) δ 23.2 ($CH_3C(O)$), 57.4 (OCH$_3$ or CH), 59.4 (OCH$_3$ or CH), 72.1 (CH_2OCH_3), 122.1 (CHC(O)), 128.6 (2C$_2$′ or 2C$_3$′), 129.0 (2C$_2$′ or 2C$_3$′), 131.0 (C$_4$′), 134.1 (C$_1$′), 144.7 (CHPh), 169.9 (C(O)NH), 195.4 (C(O)); MS (+CI) (rel intensity) 249 (27), 248 ($M^+ + 1$, 100), 236 (41), 129 (11), 111 (13); M_r (+CI) 248.128 15 [$M^+ + 1$] (calcd for $C_{14}H_{18}NO_3$ 248.128 67). Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00%; H, 6.93%; N, 5.66%. Found C, 67.95%; H, 6.86%; N, 5.65%.

Synthesis of (*R*,*S*)-*N*-(toluylsulfonylphenylmethyl)acetamide[17] (29). Using the procedure of Murry and co-workers,[16] compound **29** was prepared. To a MeCN (250 mL) solution of **27** (710 mg, 12.02 mmol) and **28**

(2.14 g, 12.01 mmol) was added **23** (813 μL, 8.00 mmol). The mixture was cooled to 0 °C and TMSCl (2.0 mL, 15.21 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred (24 h). The reaction solvent was evaporated and the crude residue was triturated (1:9, MeOH/H_2O). The remaining white solid was purified by crystallization (2:1, EtOAc/hexanes) to give **29** (1.28 g, 35%) as a white solid: mp 140–141 °C; R_f 0.65 (1:9, MeOH/$CHCl_3$); IR (KBr) 3345, 2979, 1663, 1519, 1316, 1146, 1084, 703, 673, 584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, C**H**$_3$C(O)), 2.44 (s, C**H**$_3$Ph), 6.31 (d, J = 10.5 Hz, C**H**), 7.11 (d, J = 10.5 Hz, N**H**), 7.26–7.44 (m, Ph**H**, 7H), 7.72–7.75 (m, Ph**H**, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7 (**C**H$_3$C(O) or **C**H$_3$Ph), 22.9 (**C**H$_3$C(O) or **C**H$_3$Ph), 72.2 (**C**H), 128.7, 129.0, 129.3, 129.7, 129.8, 130.3, 133.5, 145.4 (2 **C**$_6$H$_5$), 168.9 (**C**(O)NH); MS (+CI) (rel intensity) 304 ($M^+ + 1$, 5), 157 (16), 149 (12), 148 (100), 106 (55); M_r (+CI) 304.100 02 [$M^+ + 1$] (calcd for $C_{16}H_{18}NO_3S$ 304.100 74). Anal. calcd for $C_{16}H_{17}NO_3S$: C, 63.34%; H, 5.65%; N, 4.62%. Found C, 63.05%; H, 5.65%; N, 4.57%.

Synthesis of *trans*-(*R*,*S*)-1-acetamido-1,4-diphenyl-3-penten-2-one (11). To a $ClCH_2CH_2Cl$ (100 mL) suspension of tosyl amide **29** (2.00 g, 6.60 mmol) and **31** (550 mg, 1.98 mmol) was added **30** (920 μL, 7.26 mmol). The mixture was warmed to 35 °C and then Et_3N (13.8 mL, 99.01 mmol) was added in one portion and the mixture was stirred at 35 °C (24 h). The solvent was evaporated and the crude residue was purified by flash column chromatography (SiO_2; 1:49, MeOH/$CHCl_3$), followed by crystallization (EtOH/iPr$_2$O, 1:9) to give **11** (1.08 g, 59%) as a pale yellow solid: mp 119–121 °C; R_f 0.41 (1:49, MeOH/$CHCl_3$); IR (KBr) 3351, 3058, 2914, 1656, 1607, 1516, 1448, 1336, 1076, 993, 730, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 5.88 (d, J = 6.5 Hz, C**H**), 6.69 (d, J = 15.9 Hz, C**H**C(O)), 6.99 (d, J = 6.5 Hz, N**H**), 7.26–7.44 (m, 10 Ph**H**), 7.72 (d, J = 15.9 Hz, C**H**Ph); ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H$_3$C(O)), 61.8 (**C**H), 122.4 (**C**HCHPh), 128.3, 128.5, 128.6, 128.9, 129.2, 131.0, 134.0, 136.7 (2 **C**$_6$H$_5$), 144.8 (CH**C**HPh), 169.2 (**C**(O)NH), 194.4 (**C**(O)); MS (+CI) (rel intensity) 281 (18), 280 ($M^+ + 1$, 100); M_r (+CI) 280.134 25 [$M^+ + 1$] (calcd for $C_{18}H_{18}NO_2$ 280.134 75). Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40%; H, 6.13%; N, 5.01%. Found C, 77.27%; H, 6.23%; N, 5.10%.

Synthesis of (*R*,*S*)-*N*-acetylalanine-*N*-methoxy-*N*-methylamide (33). Hydroxylamine **32** (1.79 g, 18.35 mmol) was dissolved in THF (20 mL) and H_2O (1 mL) and then anhydrous K_2CO_3 (5.04 g, 36.47 mmol) was added, and the mixture stirred at room temperature (2 h). In a separate flask **15** (2.00 g, 15.26 mmol) was dissolved in THF (70 mL) and the solution was cooled to −15 °C under Ar, and then *N*-methylmorpholine (1.7 mL, 15.26 mmol) was added, followed by isobutyl chloroformate (2.0 mL, 15.26 mmol). After 1 min, the **32** solution was added in one portion through a cannula. The mixture was stirred at −15 °C (1.5 h) and then H_2O (10 mL) was added. The solvents were evaporated leaving a clear oil and then aqueous 5% citric acid (30 mL) was added and the mixture was extracted with EtOAc (2×50 mL). The combined organic layers were washed with aqueous 5% citric acid (30 mL), saturated aqueous $NaHCO_3$ (2×30 mL), and then dried (Na_2SO_4) and evaporated to yield **33** (940 mg, 36%) as a white solid: mp 81–82 °C; R_f 0.18 (1:49, MeOH/$CHCl_3$); IR (KBr) 3300, 1645, 1551, 1457, 1377, 1298, 1184, 984, 621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 6.9 Hz, C**H**$_3$CH), 2.00 (s, C**H**$_3$C(O)), 3.22 (s, NC**H**$_3$), 3.78 (s, OC**H**$_3$), 4.93–5.02 (m, C**H**), 6.50 (br s, N**H**); ^{13}C NMR ($CDCl_3$) δ 18.4 (**C**H$_3$CH), 23.2 (**C**H$_3$C(O)), 32.0 (N**C**H$_3$), 45.4 (**C**H), 61.6 (O**C**H$_3$), 169.4 (**C**(O)N), 173.2 (**C**(O)NH); MS (+CI) (rel intensity) 175 ($M^+ + 1$, 13), 114 (100); M_r (+CI) 175.107 97 [$M^+ + 1$] (calcd for $C_7H_{15}N_2O_3$ 175.108 27). Anal. calcd for $C_7H_{14}N_2O_3$: C, 48.26%; H, 8.10%; N, 16.08%. Found C, 48.29%; H, 8.00%; N, 16.06%.

Synthesis of (*R*,*S*)-2-acetamido-5-phenyl-4-pentyn-3-one (13). To a cold (−78 °C) THF (50 mL) solution of **33** (920 mg, 5.29 mmol) was added **34** (1.0 M in THF, 18.5 mL) dropwise. The solution was warmed to −30 °C and then stirred (2 h). The reaction was then quenched with aqueous 1.0 M NaH_2PO_4 (30 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were successively washed with aqueous 1.0 M NaH_2PO_4 (30 mL), H_2O (30 mL) and brine (30 mL) and then dried (Na_2SO_4) and evaporated. The oily crude was purified by PTLC (thick plates, 1:49, MeOH/$CHCl_3$) to yield **13** (509 mg, 45%) as a yellow oil: R_f 0.45 (1:49, MeOH/$CHCl_3$); IR (neat) 3286, 3062, 2985, 2198, 1678, 1539, 1446, 1373, 1296, 1146, 1072, 1041, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (d, J = 6.6 Hz, C**H**$_3$CH), 2.05 (s, C**H**$_3$C(O)), 4.82 (dq, J = 6.6, 6.6 Hz, C**H**), 6.52 (d, J = 6.6 Hz, N**H**), 7.27–7.59 (m, Ph**H**); ^{13}C NMR ($CDCl_3$) δ 17.6 (**C**H$_3$CH), 23.0 (**C**H$_3$C(O)), 55.9 (**C**H), 85.8 (**C**CPh), 94.6 (C**C**Ph), 119.3 (**C**$_1'$), 128.6 (2**C**$_3'$), 131.1 (**C**$_4'$), 133.1 (2**C**$_2'$), 169.8 (**C**(O)NH), 186.3 (**C**(O)); MS (+CI) (rel intensity) 216 ($M^+ + 1$, 51), 174 (100), 114 (21); M_r (+CI) 216.102 58 [$M^+ + 1$] (calcd for $C_{13}H_{14}NO_2$ 216.102 45). Anal. calcd for $C_{13}H_{13}NO_2$: C, 71.35%; H, 6.17%; N, 6.40%. Found C, 71.48%; H, 6.19%; N, 6.39%.

Synthesis of (*R*,*S*)-2-acetamido-1-methoxy-5-phenyl-4-pentyn-3-one (14). (*R*,*S*)-2-Acetylamino-3-methoxypropionic acid methyl ester[31] (**25**) was prepared using the procedure of Andurkar and co-workers.[21] To a cold (−78 °C) THF (25 mL) solution of **25** (1.00 g, 5.71 mmol) was added **34** (1.0 M in THF, 11.4 mL) dropwise and the mixture was stirred at −78 °C (2 h). The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (2×25 mL). The combined organic layers were washed with brine (30 mL) and then dried (Na_2SO_4) and evaporated. The crude residue was crystallized in Et_2O (20 mL) to yield **14** (500 mg, 36%) as a yellow solid: mp 96–99 °C; R_f 0.62 (1:32, MeOH/$CHCl_3$); IR (KBr) 3356, 2997, 2935, 2198, 1678, 1520, 1446, 1369, 1284, 1250, 1165, 1057, 995, 760, 690, 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, C**H**$_3$C(O)), 3.37 (s, OC**H**$_3$), 3.76 (dd, J = 2.8, 9.9 Hz, CH**H**′OCH$_3$), 4.15 (dd, J = 3.2, 9.9 Hz, CH**H**′OCH$_3$), 4.90–4.95 (m, C**H**), 6.60 (d, J = 7.8 Hz, N**H**), 7.38–7.60 (m, Ph**H**); ^{13}C NMR ($CDCl_3$) δ 23.4 (**C**H$_3$C(O)), 59.7 (O**C**H$_3$ or **C**H), 60.5 (O**C**H$_3$ or **C**H), 71.8 (**C**H$_2$OCH$_3$), 86.1 (**C**CPh), 94.5 (C**C**Ph), 119.7

($\mathbf{C}_1'$), 128.9 ($2\mathbf{C}_3'$), 131.4 ($\mathbf{C}_4'$), 133.4 ($2\mathbf{C}_2'$), 170.2 (**C**(O)NH), 184.1 (**C**(O)); MS (+CI) (rel intensity) 246 ($M^+ + 1$, 38), 214 (11), 199 (16), 198 (100), 197 (15); M_r (+CI) 246.113 41 [$M^+ + 1$] (calcd for $C_{14}H_{16}NO_3$ 246.113 02). Anal. calcd for $C_{14}H_{15}NO_3 \cdot 0.2H_2O$: C, 67.56%; H, 6.24%; N, 5.63%. Found C, 67.54%; H, 6.24%; N, 5.67%.

Synthesis of *cis*-(36) and *trans*-(10)-2-acetamido-5-phenyl-4-penten-3-one. An EtOH (50 mL) solution **13** (440 mg, 2.05 mmol) was hydrogenated in the presence of Lindlar catalyst (30 mg) and quinoline (1.2 mL, 10.15 mmol) at room temperature (4 h). The catalyst was removed by filtration through a Celite pad and the reaction solvent was evaporated. The crude product was treated with an 1:1 Et_2O (30 mL) and aqueous 0.1 N HCl (30 mL) mixture. The aqueous layer was separated and extracted with Et_2O (3×30 mL) and the combined organic layers were successively washed with aqueous 0.1 N HCl (20 mL) and brine (20 mL), and dried (Na_2SO_4). The solution was concentrated in vacuo to give an oil (649 mg, 73%) that contained **36**, **10** and **7** in an approximate 11:3:1 ratio, respectively: R_f 0.31 (1:49, MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 7.2 Hz, C**H**$_3$CH (**7**)), 1.35 (d, J = 7.2 Hz, C**H**$_3$CH (**36**)), 1.40 (d, J = 7.2 Hz, C**H**$_3$CH (**10**)), 1.96 (s, CH_3C(O) (**7**)), 1.98 (s, CH_3C(O) (**36**)), 2.01 (s, CH_3C(O) (**10**)), 2.75–2.93 (m, C**H**$_2$C**H**$_2$Ph (**7**)), 4.50–4.60 (m, C**H** (**7**)), 4.66–4.76 (m, C**H** (**36**)), 4.92–5.02 (m, C**H** (**10**)), 6.26 (d, J = 12.6 Hz, C**H**C(O) (**36**)), 6.77 (br s, N**H** (**36**)), 6.82 (d, J = 16.2 Hz, C**H**C(O) (**10**)), 6.88 (br s, N**H** (**10**)), 6.92 (d, J = 12.6 Hz, C**H**Ph (**36**)), 7.31–7.64 (m, Ph**H** (**36**, **10**, **7**)), 7.72 (d, J = 16.2 Hz, C**H**Ph (**10**)); ^{13}C NMR δ ($CDCl_3$) 18.0 (**C**H_3CH (**36**)), 18.5 (**C**H_3CH (**10**)), 23.2 (**C**H_3C(O) (**36**)), 52.5 (**C**H (**10**)), 54.4 (**C**H (**36**)), 122.2 (**C**HC(O) (**10**)), 123.7, 128.1, 128.9 (**C**HC(O) and $2\mathbf{C}_2'$ and $2\mathbf{C}_3'$ (**36**)), 128.5 ($2\mathbf{C}_2'$ or $2\mathbf{C}_3'$ (**10**)), 129.0 ($2\mathbf{C}_2'$ or $2\mathbf{C}_3'$ (**10**)), 131.0 ($\mathbf{C}_4'$ (**10**)), 134.0 ($\mathbf{C}_1'$ (**10**)), 134.6, 136.0, 144.4 ($\mathbf{C}_1'$ and $\mathbf{C}_4'$ and **C**HPh (**36**)), 144.9 (**C**HPh (**10**)), 169.4 (**C**(O)NH (**36**)), 198.0 (**C**(O) (**10**)), 199.0 (**C**(O) (**36**)); MS (+CI) (rel intensity) 220 (17), 219 (15), 218 ($M^+ + 1$, 100), 114 (16); M_r (+CI) 218.118 15 [$M^+ + 1$] (calcd for $C_{13}H_{16}NO_2$ 218.118 10).

Chemical evaluation of 12 and 14. EtSH (46–54 μL, 0.63–0.73 mmol) or $EtNH_2$ (2.0 M in THF, 310–350 μL, 0.62–0.70 mmol) was added to a solution of either **12** or **14** (9.5–11.3 mg, 37–46 μmol) in THF (0.7–1.0 mL) and the reaction was stirred at room temperature (18 h) and then analyzed by TLC. For **12** no reaction was observed with EtSH and $EtNH_2$. For **14** no reaction was observed for EtSH and with $EtNH_2$ the starting material was consumed and a new product [R_f 0.23 (1:49, MeOH/$CHCl_3$)] was observed.

Chemical evaluation of 14 with $EtNH_2$. $EtNH_2$ (2.0 M in THF, 166 μL, 0.33 mmol) was added to a solution of **14** (10.2 mg, 42 μmol) in THF-d_8 (0.7 mL) and the reaction was stirred at room temperature (18 h) and then was analyzed by ^{1}H NMR and TLC. The reaction was concentrated to dryness, purified by PTLC (1:49, MeOH/$CHCl_3$) to give **39** (5.4 mg, 45%) as a pale yellow oil: R_f 0.23 (1:49, MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, CH_2C**H**$_3$), 2.04 (s, C**H**$_3$C(O)), 3.13–3.22 (m, C**H**$_2$$CH_3$), 3.33 (s, OC**H**$_3$), 3.63 (dd, J = 4.2, 9.6 Hz, C**H**H′OCH_3), 3.69 (dd, J = 3.9, 9.6 Hz, CH**H**′OCH_3), 4.62–4.67 (m, C**H**), 5.10 (s, C**H**CPh), 6.61 (d, J = 6.6 Hz, N**H**C(O)), 7.31–7.43 (m, 5 Ph**H**), 10.69 (br s, N(H)); ^{13}C NMR ($CDCl_3$) δ 15.8 (**C**$H_3$$CH_2$), 23.3 (**C**$H_3$C(O)), 39.7 (N(H)**C**$H_2$$CH_3$), 56.5 (O**C**$H_3$ or **C**H), 59.4 (O**C**H_3 or **C**H), 73.5 (**C**$H_2$$OCH_3$), 93.5 (**C**(H)C(O)), 127.4, 128.4, 129.9 ($2\mathbf{C}_2'$, $2\mathbf{C}_3'$, $\mathbf{C}_4'$), 135.0 ($\mathbf{C}_1'$), 166.7 (**C**(O)NH or **C**(Ph)(N(H)CH_2CH_3), 169.6 (**C**(O)NH or **C**(Ph)(N(H)CH_2CH_3), 191.5 (**C**(O)C(H)).

Pharmacology

Compounds were screened under the auspices of the National Institutes of Health's Anticonvulsant Screening Project. Experiments were performed in male rodents [albino Carworth Farms No. 1 mice (intraperitoneal route, ip), albino Sprague–Dawley rats (oral route, po)]. The mice weighed between 18 and 25 g while rats were between 100 and 150 g. All animals had free access to feed and water except during actual testing period. Housing, handling and feeding were all in accordance with recommendations contained in the 'Guide for the Care and Use of Laboratory Animals'. All of the test compounds were administrated in suspensions of 0.5% (w/v) of methylcellulose in water. The volumes administered were 0.01 mL/g of body weight for mice and 0.2 mL/10 g for rats. Anticonvulsant activity was established using the maximal electroshock (MES) test.[5,26] For the MES test, a drop of electrolyte solution with an anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was placed in the eyes of the animals prior to positioning the corneal electrodes and delivery of a non-lethal current. A 60-cycle alternating current was administered for 0.2 s in both species, utilizing 50 mA in mice and 150 mA in rats. Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure.[6] The subcutaneous pentylenetetrazole (Metrazol®) seizure threshold test (scMet) entailed administration of either 85 mg/kg of pentylenetetrazole in mice (Carworth Farms No. 1) or 70 mg/kg in rats (Sprague–Dawley) as a 0.5% solution subcutaneously in the posterior midline. This amount of pentylenetetrazole produces clonic seizures in 97% (CD_{97}) of animals tested. The animal is observed for 30 min. Protection is defined as the failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5-s duration). In mice, effects of compounds on forced spontaneous motor activity were determined using the rotorod test.[10,33] The inability of experimental mice to maintain their balance for 1 min on a 1-inch diameter knurled rod rotating at 6 rpm in three successive trials was interpreted as a demonstration of motor impairment or toxicity. Under these conditions, mice can normally maintain their balance indefinitely. Endpoints for motor impairment in rats also referred to as toxicity or neurological deficit was assessed by observing any overt evidence of ataxia, problems with the righting reflex, abnormal gait and stance, and/or loss of placing response and muscle tone. In the mouse identification screens all compounds were administered at three dose levels (30, 100, 300 mg/kg)

using two time periods (0.5 and 4 h). Typically, in the MES seizure test two animals were used at each of two time periods for doses of 30 and 300 mg/kg, and a total of six animals at 100 mg/kg (three per time period). In the rotorod toxicity test four animals were used at 30 and 300 mg/kg, and eight animals at 100 mg/kg (Table 1). Oral rat identification screening was performed using four animals per time point over five time points (1/4, 1/2, 1, 2, 4 h) at a fixed dose of 30 mg/kg for the MES tests. The quantitative determination of the median effective (ED_{50}) and toxic doses (TD_{50}) were conducted at previously calculated time of peak effect using ip route in mice and oral route in rats. Groups of at least eight animals were tested using different doses of test compound until at least two points were determined between 100 and 0% protection and minimal motor impairment. The dose of the candidate substance required to produce the desired endpoint (abolition of hindlimb tonic extensor component) in 50% of the animals in each test, and 95% confidence interval were calculated by a computer program based on methods described by Finney.[34]

Acknowledgements

The authors thank the NINDS and the Anticonvulsant Screening Project (ASP) at the National Institutes of Health, for kindly performing the pharmacological studies via the ASP's contract site at the University of Utah with Drs. H. Wolf, S. White, and Karen Wilcox.

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