Synthesis and Anticonvulsant Activities of α-Heterocyclic α-Acetamido-*N*-benzylacetamide Derivatives

Harold Kohn,*,† Kailash N. Sawhney,† Patrick Bardel,† David W. Robertson,‡,§ and J. David Leander‡

Department of Chemistry, University of Houston, Houston, Texas 77204-5641, and Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Earlier studies showed that (R,S)-α-acetamido-*N*-benzylacetamides (2) containing a five- and six-membered aromatic or heteroaromatic group appended at the C(α) site displayed outstanding activity in the maximal electroshock-induced seizure (MES) test in mice. An expanded set of C(α)-heteroaromatic analogues of 2 have been prepared and evaluated. The observed findings extended the structure–activity relationships previously discerned for this novel class of anticonvulsants and have validated previous trends. The α-furan-2-yl (4), α-oxazol-2-yl (18), and α-thiazol-2-yl (19) α-acetamido-*N*-benzylacetamides afforded excellent protection against MES-induced seizures in mice. The ED_{50} and PI values for these adducts rivaled those reported for phenytoin. The outstanding properties provided by 4 led to an in-depth examination of the effect of structural modification at key sites within this compound on biological activity. The pharmacological data in this series indicated that stringent steric and electronic requirements existed for maximal activity and revealed the outstanding activity of (R)-(−)-α-acetamido-*N*-(4-fluorobenzyl)-α-(furan-2-yl)acetamide [(R)-30].

Non-naturally occurring amino acid derivatives constitute an increasing resource of new chemotherapeutic agents that include antibacterial and CNS agents and enzyme inhibitors.[1] In recent years, we have reported on the anticonvulsant properties of functionalized amino acid derivatives 1.[2-7] Our studies demonstrated that α-acetamido-*N*-benzylacetamides (2) containing a five- and six-membered aromatic or heteroaromatic group appended at the C(α)-site afforded excellent protection against maximal electroshock (MES)-induced seizures in mice (Table I).[3,6] For example, the ED_{50} values against MES seizures for the racemic α-phenyl (3) (32.1 mg/kg) and α-furan-2-yl (4) (10.3 mg/kg) derivatives[6] compared favorably with phenobarbital (21.8 mg/kg) and phenytoin (9.5 mg/kg).[8] Examination of the individual enantiomers of 3 and 4 demonstrated the importance of stereochemistry at the C(α) site in 2 on biological activity.[5,6] In both 3 and 4, the (R)-stereoisomer was 10 times more potent in the control of MES seizures than the (S)-enantiomer. This difference in activity is the greatest eudismic ratio reported to date for MES-selective anticonvulsant agents.
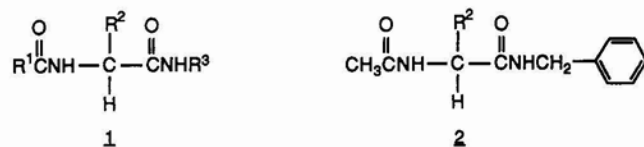
In the present study we report the synthesis and pharmacological activities of a carefully selected series of C(α)-heteroaromatic analogues of 2. Information is provided on the effect of type, number, and site of heteroatom substitution within the C(α)-substituent on anticonvulsant activity (Table I). The outstanding properties provided

by α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (4) against MES seizures led to an in-depth examination of the effect of structural modification at key sites in 4 on biological activity (Table II). Included in this study was also the preparation of several enantiopure congeners of (R)-4 to demonstrate that this absolute configuration afforded compounds with marked anticonvulsant activity.

Selection of Compounds

Our investigation proceeded in two stages. First, we determined the effect of the C(α)-heteroaromatic group in 2 on anticonvulsant activity (Table I). Amino acid derivatives 4-8[6] (Table I) served as the reference compounds for this investigation. The placement of additional heteroatoms within these derivatives or the preparation of isomeric adducts led to multiple effects. These included perturbations in the electron density of the aromatic ring, changes in the spatial orientation of the nonbonding electrons, and alterations in the basicity and bioavailability of the drug candidates. These multifaceted electronic, structural, and physical effects complicated the interpretation of the biological data. Nonetheless, the pronounced improvement in MES-induced seizure protection previously observed by the placement of an electron-rich aromatic ring at the C(α)-site in 2 (i.e., 3 (ED_{50} = 32.1 mg/kg) versus 4 (ED_{50} = 10.3 mg/kg); 7 (ED_{50} = 44.8 mg/kg) versus 5 (ED_{50} = 16.1 mg/kg) versus 4 (ED_{50} = 10.3 mg/kg)) prompted us to provide additional documentation for this trend. The compounds selected for synthesis and evaluation were grouped into three categories. The first set (i.e., 9–12) included aza analogues of 5 where the C(α)-heteroaromatic ring was appended by a carbon–carbon bond. Compounds in this series were α-imidazolyl (9 and 10), α-triazolyl (11), and α-tetrazolyl (12). The second category (i.e., 13–17) encompassed the isomeric C(α)-azaromatics where heteroaromatic attachment to the amino acid backbone occurred through a nitrogen–carbon bond. Compounds evaluated were α-pyrrolyl (13), α-pyra-zolyl (14), α-imidazolyl (15), α-triazolyl (16), and α-tet-
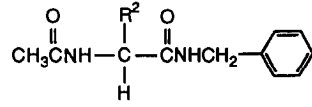

Table I. Physical and Pharmacological Data in Mice for C(α)-Heteroaromatic α-Acetamido-*N*-benzylacetamides[a]

$$\underset{H}{\overset{\overset{O}{\|}\ \ \ \ \ \overset{R^2}{|}\ \ \ \overset{O}{\|}}{CH_3CNH-C-CNHCH_2-C_6H_5}}$$

no.	R²	mp[b]	MES[c] ED$_{50}$	HS[d] TD$_{50}$	PI[e]
3[f]	phenyl	202–203	32.1 (27.5–40.2)	>40	
4[f]	furan-2-yl	178–179	10.3 (9.1–11.6)	~40	>3.9
5[f]	pyrrol-2-yl (NH)	174–175	16.1 (13.2–19.9)	>30, <100	
6[f]	pyrrol-2-yl (NCH₃)	179–181	~300	g	
7[f]	thien-2-yl	167–169	44.8 (38.9–51.4)	>30, <100	
8[f]	thien-3-yl	198–199	87.8 (69.9–150)	>100	
9	imidazolyl	228–230	>100	g	
10	imidazolyl	188–191 dec	>100	g	
11	triazolyl	205–207	>100	g	
12	tetrazolyl	236–238	>30, <100	g	
13	pyrrolyl (N-linked)	182–184	80.2 (66.6–100.6)	g	
14	pyrazolyl	158–160	16.5 (14.1–22.5)	g	
15	imidazolyl	146–148	>100	g	
16	triazolyl	146–148	>30, <100	g	
17	tetrazolyl	169–171	>300	g	
18	oxazolyl	164–166	10.4 (9.2–11.6)	38.6[h] (33.8–46.0)	3.7
19	thiazolyl	166–167	12.1 (9.5–14.5)	69.1[h] (61.6–78.6)	5.7
20	oxadiazolyl	164–166	>100, <300	g	
phenytoin[i]			9.5 (8.1–10.4)	65.5[h] (52.5–72.1)	6.9
phenobarbital[i]			21.8 (15.0–22.5)	69.0[h] (62.8–72.9)	3.2
valproate[i]			272 (247–338)	426[h] (369–450)	1.6

[a] The compounds were administered intraperitoneally. ED$_{50}$ and TD$_{50}$ values are in milligrams per kilogram. Number in parentheses are 95% confidence intervals. A dose–response curve was generated for all compounds that displayed sufficient activity. The dose effect data for these compounds was obtained at 0.5 h ("time of peak effect") except for compound 19, which was obtained at 0.25 h. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] HS TD$_{50}$ = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] PI = protective index (TD$_{50}$/ED$_{50}$). [f] Reference 6. [g] Not determined. [h] Neurologic toxicity determined using the rotorod test. [i] Reference 8.

20) contained C(α)-mixed heteroaromatic systems. The three compounds prepared were α-oxazolyl (18), α-thiazolyl (19), and α-1,2,4-oxadiazolyl (20) derivatives. In all cases, the functionalized amino acids were synthesized as the racemates.

The second phase of this study (Table II) focused on α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (4), the most active compound evaluated in the initial study. Structural modifications were conducted at key sites in 4, including the furan ring (i.e., 21), the C(α)-position (i.e.,

N-benzyl substituent (i.e., 25–29) to discern how these changes influenced biological activity. Moreover, because of the substantial eudismic ratio observed with enantiomers of 4, enantiopure (*R*)-isomers of several congeners in the present series were prepared (i.e., (*R*)-30–(*R*)-32) to demonstrate that this absolute configuration afforded compounds with marked anticonvulsant activity.

Chemistry

The novel α-heteroaromatic amino acid derivatives 9–20

Table II. Physical and Pharmacological Data in Mice for α-Acetoamido-*N*-benzyl-α-(furan-2-yl)acetamide (**4**) Derivatives[a]

$$\underset{\substack{|\\R_b}}{CH_3CNH - \overset{\substack{X\\\|}}{C} - \overset{\substack{R_a\ \ Y\\|\ \ \|}}{C} - NHR_c}$$

no.	R_a	R_b	R_c	X	Y	mp[b]	MES[c] ED$_{50}$	HS[d] TD$_{50}$	PI[e]
4[f]	(furan)	H	CH$_2$C$_6$H$_5$	O	O	178–179	10.3 (9.1–11.6)	~40	>3.9
(R)-4[f]	(furan)	H	CH$_2$C$_6$H$_5$	O	O	196–197	3.3 (2.8–3.9)	23.8	7.2
(S)-4[f]	(furan)	H	CH$_2$C$_6$H$_5$	O	O	196–197	>25	>200	
21a	(tetrahydrofuran)	H	CH$_2$C$_6$H$_5$	O	O	159–161	51.7 (44.4–59.9)	g	
21b	(tetrahydrofuran)	H	CH$_2$C$_6$H$_5$	O	O	130–132	89.8 (78.4–103.4)	g	
22	(furan)	CH$_3$	CH$_2$C$_6$H$_5$	O	O	—[h]	>300	g	
23	(furan)	H	CH$_2$C$_6$H$_5$	S	O	78–80	18.4 (15.9–22.0)	g	
24	(furan)	H	CH$_2$C$_6$H$_5$	S	S	99–101	>100	g	
25	(furan)	H	CH$_2$—(pyridine)	O	O	172–174	~30	g	
26	(furan)	H	CH$_2$—(pyridine)	O	O	168–170	>100	g	
27	(furan)	H	CH$_2$—(pyridine-O)	O	O	159–161	~30	g	
28	(furan)	H	CH$_2$—(pyridine N→O)	O	O	210–212	>100	g	
29	(furan)	H	NH—(pyrimidine)	O	O	226–228	>100	g	
30	(furan)	H	CH$_2$—(C$_6$H$_4$F)	O	O	188–190	12.7 (10.4–15.1)	144 (123–171)	11.3
(R)-30	(furan)	H	CH$_2$—(C$_6$H$_4$F)	O	O	205–207	3.5 (2.9–4.4)	14.4 (7.3–28.9)	4.1
(R)-31	(furan)	H	CH$_2$—(C$_6$H$_4$CH$_3$)	O	O	210–212	43.6 (26.1–143)	g	
(R)-32	(furan)	H	CH$_2$—(C$_6$H$_4$CF$_3$)	O	O	193–195	22.8 (15.9–33.4)	g	
phenytoin[i]							9.5 (8.1–10.4)	65.5[j] (52.5–72.1)	6.9
phenobarbital[i]							21.8 (15.0–22.5)	69.0[j] (62.8–72.9)	3.2
valproate[i]							272 (247–338)	426[j] (369–450)	1.6

[a] The compounds were administered intraperitoneally. ED$_{50}$ and TD$_{50}$ values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. A dose–response curve was generated for all compounds that displayed sufficient activity. The dose effect data for these compounds was obtained at 0.5 h ("time of peak effect") except for compound **27** which was obtained at 1 h. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. Compound was suspended in 30% PEG. [d] HS TD$_{50}$ = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] PI = protective index (TD$_{50}$/ED$_{50}$). [f] Reference 6. [g] Not determined. [h] Thick oil. [i] Reference 8. [j] Neurologic toxicity determined using the rotorod test.

moacetamide[7] (**33**) or α-acetamido-*N*-benzyl-α-cyanoacetamide[9] (**34**). Addition of a tetrahydrofuran solution of the C(2)-lithio salt of 1-(diethoxymethyl)imidazole[10] (**35**) to **33** prepared *in situ* afforded **9** after workup. Correspondingly, treatment of **33** with triethylamine followed by introduction of the lithio salt of 1-(*N*, *N*-dimethylsulfamoyl)imidazole[11] (**36**) gave **37**, which upon deprotection with acid furnished **10**. The structure of **37** has been tentatively assigned as the C(4)-imidazole-substituted derivative based on a comparison of the NMR chemical shift values for **37** versus the parent heterocycle **36**[11] and 1-(*N*,*N*-dimethylsulfamoyl)-4-methylimidazole (**38**) (Table III). Compound **38** was prepared by the addition of dimethylsulfamoyl chloride to 4-methylimidazole (**39**) in the presence of triethylamine. NMR and TLC analyses of the crude reaction mixture indicated the presence of only one major compound, and the structure was confirmed by X-ray crystallography (Figure 1, supplementary material). Select ¹H–¹³C NMR decoupling

Table III. NMR Assignments for Substituted Imidazoles[a]

compd no.	¹H NMR[b]		¹³C NMR[c]	
	H(4)	H(5)	C(4)	C(5)
imidazole	7.13	7.13	121.96	121.96
36	7.13	7.56	130.45	118.75
37		7.40	140.26	115.50
38		7.32	138.85	114.34
39		6.75	131.00	118.18
40[d]	7.09[e]	7.47	130.5[f]	115.9

[a] All spectra were recorded in DMSO-*d*$_6$ unless otherwise indicated. [b] The number in each entry is the chemical shift value (δ) observed in ppm relative to Me$_4$Si. ¹H NMR spectra were recorded at 300 MHz. [c] ¹³C NMR spectra were obtained at 75 MHz. [d] Spectra taken in CDCl$_3$. [e] Reference 12b. [f] Reference 12a.

III and permitted the assignments for the corresponding

Scheme I. Preparation of α-Acetamido-*N*-benzyl-α-methyl-α-(furan-2-yl)acetamide (**22**)
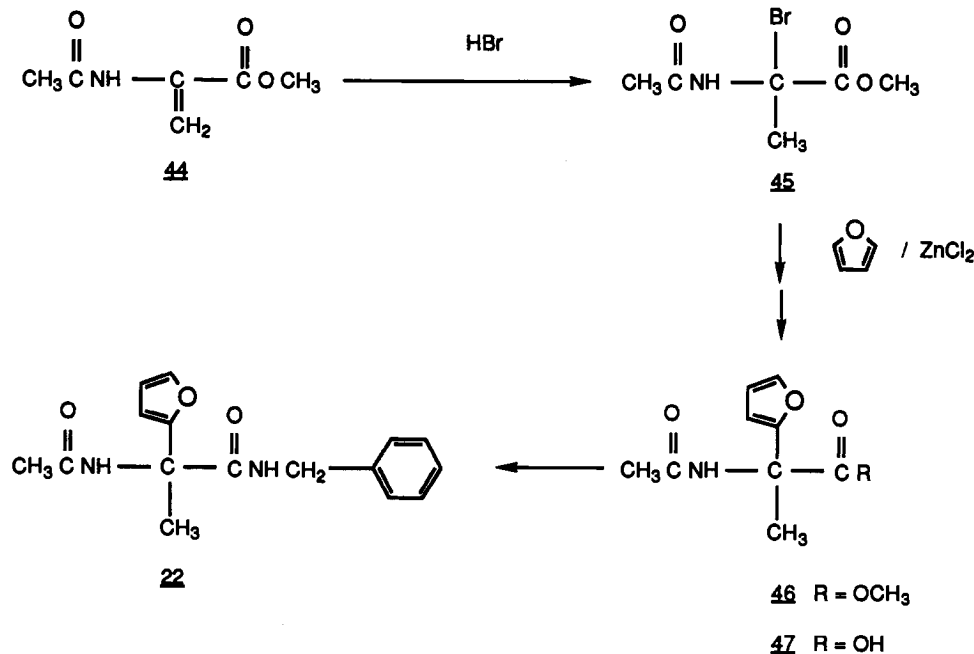
for **36** were in agreement with the values reported by Chadwick and Ngochindo[11] and follow the pattern cited by Begtrup and co-workers for *N*-acetylimidazole[12a] (**40**). Our NMR decoupling experiments on **36**, however, required a reversal of the previously proposed C(4) and C(5) proton assignments.[11] The revised values mirrored the ^{1}H NMR pattern reported for *N*-acetylimidazole[12b] (**40**). The origin for the formation of the C(4)-imidazole-substituted derivative **37** has not been determined. Previous studies have shown that treatment of the C(2)-lithio salt of **36** with alkyl halides furnished the C(2) substituted product, while addition of electrophiles to the C(2),C(5)-dilithio intermediate provided the C(5)-substituted adduct as a major product.[11]
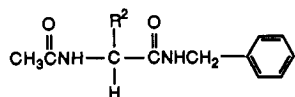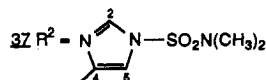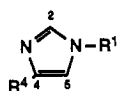
Comparable protocols were employed for the preparation of the *N*-substituted heteroaromatics **13–17** beginning with **33**. Addition of an excess amount of the preformed potassium salt of pyrrole to **33** in tetrahydrofuran yielded **13**, while **14–17** were synthesized by initial treatment of **33** with excess triethylamine at −78 °C followed by addition of the parent heterocycle.

α-Acetamido-*N*-benzyl-α-cyanoacetamide (**34**) served as the starting point for the synthesis of **11**, **12**, and **18–20**. Addition of formic hydrazide to **34** in basic ethanol gave

triethylamine hydrochloride in 1-methyl-2-pyrrolidinone afforded **12**.[13] α-Oxazol-2-yl (**18**) and α-thiazol-2-yl (**19**) derivatives were prepared by initial conversion of **34** to the α-amide[9b] (**41**) and α-thioamide (**42**) adducts, respectively, and then these compounds were condensed with excess bromoacetaldehyde dimethyl acetal[14] in dimethoxyethane. α-Oxadiazol-3-yl (**20**) derivative was generated in two steps from **34**.[15] Addition of NH$_2$OH·HCl to **34** in basic ethanol gave the α-carboxamide oxime derivative **43**. Treatment of **43** with trimethyl orthoformate and a catalytic amount of boron trifluoride etherate gave **20**.

Several synthetic protocols were utilized for the preparation of compounds **21–32**. Catalytic hydrogenation (H$_2$, Pd/C) of (*R,S*)-**4** gave the tetrahydrofuran-2-yl adduct **21**. Fractional recrystallization of the product mixture from ethyl acetate provided diastereomers **21a** and **21b**. Synthesis of the α-methyl analogue **22** was achieved by a four-step procedure (Scheme I) beginning with methyl 2-acetamidoacrylate[16] (**44**). Addition of HBr to **44** furnished **45**, which was directly treated with furan and ZnCl$_2$ to give the α-amidoalkylation adduct **46**.[6,17] Hydrolysis of **46** to the free acid **47**, followed by treatment of **47** with benzylamine using the mixed carbonic anhydride coupling procedure[6,18] (i.e., isobutyl chloroformate, 4-methylmorpholine), gave **22**.

The two thioamides **23** and **24** were prepared directly from **4** using Lawesson's reagent.[19] Treatment of **4** with this thiation reagent (0.5 molar equiv) at room temperature yielded the monothio derivative **23**. Elevation of the reaction temperature and the relative proportion of Lawesson's reagent (>1 molar equiv) to **4** gave the dithio product **24**.

Synthesis of **25**, **26**, and **29** was accomplished from racemic α-acetamido-α-(furan-2-yl)acetic acid (**48**), isobutyl chloroformate, 4-methylmorpholine, and the appropriate amine or hydrazine, while use of (*R*)-α-acetamido-α-(furan-2-yl)acetic acid[6] [(*R*)-**48**] in this protocol with 4-fluorobenzylamine, 4-methylbenzylamine, and 4-(trifluoromethyl)benzylamine furnished the three optically active *N*-benzylamides (*R*)-**30**–(*R*)-**32**, respectively. This coupling strategy previously provided enantiopure (*R*)-**4**

ceeded without racemization (<5%) was obtained by examining the ^{1}H NMR spectra (CDCl$_3$) of (*R,S*)-30 and (*R*)-30–(*R*)-32 both in the absence and the presence of saturating amounts of (*R*)-(–)-mandelic acid.[20] Addition of this chiral solvating reagent to (*R,S*)-30 led to the appearance of two acetyl methyl signals (~Δ ppm 0.02) of equal intensity,[21] while only a single acetyl methyl singlet was observed in the corresponding ^{1}H NMR spectra for (*R*)-30–(*R*)-32. Similar results were earlier secured for (*R*)-4, (*S*)-4, and (*R,S*)-4[6] (see the supplementary material for appropriate ^{1}H NMR spectra). Access to the starting material (*R*)-48 was readily achieved using the protocol advanced by Whitesides and co-workers.[22] Treatment of racemic 48 with acylase I led to the selective hydrolysis of the (*S*)-amino acid derivative providing (*R*)-48 in 75% yield. Previously, (*R*)-48 was obtained by fractional

48
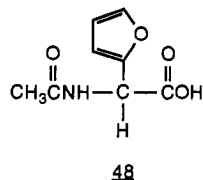
recrystallization of the corresponding diastereomeric salts formed with (*R*)-α-methylbenzylamine.[6] The two pyridine *N*-oxide adducts 27 and 28 were prepared by treating 25 and 26, respectively, with *m*-chloroperoxybenzoic acid.

Pharmacological Evaluation

The heteroaromatic amino acid derivatives 9–32 were tested for anticonvulsant activity using the procedures described by Krall and co-workers,[23] and these results were compared to the findings previously reported for 3–8.[6] All compounds were administered intraperitoneally (ip) to mice. Tables I and II list the ED$_{50}$ values required to prevent toxic extension of the hind limbs in mice in the MES test by 9–32. Included in these tables are the median neurologically impairing dose (TD$_{50}$) values using either the horizontal screen[24] (HS) or the rotorod test.[25] In most cases, the TD$_{50}$'s were only determined for those compounds that had good activity in the MES test. The protective index (PI = TD$_{50}$/ED$_{50}$) for these adducts, where appropriate, is also shown in Tables I and II.

Our previous studies indicated that placement of electron-rich five- and six-membered aromatic and heteroaromatic moieties at the α-site within functionalized amino acids 2 led to compounds providing excellent protection against MES-induced seizures in mice.[6] Moreover, we noted in this series that improved activity resulted by the positioning of a heteroatom two atoms removed from the C(α)-site. A similar result was observed in α-acyclic derivatives of 2.[7] The pharmacological data obtained in this study provided evidence in support of these two structure–activity themes.

Support for the beneficial value accrued by the placement of an electron-rich aromatic ring at the C(α)-position was obtained by the comparison of the ED$_{50}$ values in the MES-test for pyrrole 5 (ED$_{50}$ = 16.1 mg/kg) versus the azoles 9–12 (ED$_{50}$ > 30 mg/kg) (Table I). The data demonstrated that overall reduction of the electron excessive character of the C(α) π-aromatic system by heteroatom incorporation[26] led to decreased biological activity despite the fact that additional nitrogen incorporation often provided a substrate that contained two heteroatoms two atoms removed from the C(α)-site (i.e.,

Comparison of the pharmacological activities of the C-substituted azoles 5, 9–12 versus the N-substituted isomers 13–17 provided qualitative information concerning the importance of heteroatom substitution versus the C(α)-position. We observed a significant reduction in activity for 13 (ED$_{50}$ = 80.2 mg/kg) versus 5 (ED$_{50}$ = 16.1 mg/kg), and 17 (ED$_{50}$ > 300 mg/kg) versus 12 (ED$_{50}$ >30, <100 mg/kg). In compound 5 one heteroatom exists two atoms removed from the C(α)-site, while in 13 there is none. Similarly, in 12 there are two heteroatoms two atoms removed from the C(α)-site, while in 17 there is only one.

The delicate interplay of the π-electron character of the appended C(α)-heteroaromatic group, the site of the heteroatom incorporation, and the identity of the heteroatom on anticonvulsant activity was reinforced by comparison of the biological activities of the α-oxazol-2-yl (18), α-imidazol-2-yl (9), and α-thiazol-2-yl (19) derivatives. Of these three compounds, 18 was the most active (ED$_{50}$ = 10.4 mg/kg), displaying protection similar to that reported for phenytoin (ED$_{50}$ = 9.5 mg/kg).[8] The slight decrease in protection in the MES test afforded by 19 (ED$_{50}$ = 12.1 mg/kg) versus 18 paralleled the larger difference previously observed for α-furan-2-yl (4) (ED$_{50}$ = 10.3 mg/kg) and α-thien-2-yl (7) (ED$_{50}$ = 44.8 mg/kg) adducts.[6] Surprisingly, the α-imidazol-2-yl (9) derivative failed to protect the mice from MES-induced seizures at dosages of 100 mg/kg or less. Previously, we observed that the anticonvulsant activity of 2 decreased in proceeding from oxygen to nitrogen to sulfur containing C(α)-heteroaromatic derivatives.[6] The low potency of 9 may be a reflection in part of the increased basicity of this compound versus 18 and 19.[26]

The pyrazole derivative 14 provided protection in the MES test (ED$_{50}$ = 16.5 mg/kg) comparable to phenobarbital (ED$_{50}$ = 21.8 mg/kg),[8] and this compound was considerably more potent than the isomeric imidazoles 9, 10, and 15. Our results do not provide information concerning the underlying factors that contribute to this difference in activity. We do note that pyrazoles are substantially less basic than imidazoles.[26]

Inspection of the composite data set for analogues of α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (4) revealed that most structural changes at the α-carbon, amide carbonyl, and *N*-benzylamide site in 4 led to decreased potency of the compounds as anticonvulsants (Table II). This result is in agreement with previous findings demonstrating that stringent steric and electronic factors governed the anticonvulsant activities of this class of compounds.[3,4,6,7] Examination of the individual test results led to several important observations. First, reduction of the furan ring in 4 to the tetrahydrofuran analogues 21a and 21b led to a decrease, but not an abolition, of activity in the MES test (i.e., ED$_{50}$ < 90 mg/kg). The decreased activity of 21 versus 4 can be attributed to the loss of the aromatic ring at the α-carbon site, since previous findings have demonstrated that substantial improvement in activity accompanied the placement of a small aromatic group at this position.[6] The potency of 21a and 21b was greater than that observed for 49 (ED$_{50}$ > 100 mg/kg).[9b] This observation provided support for our suggestion that increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid α-carbon.[7] Second, replacement of the α-carbon proton in 4 by a methyl group led to a sharp decrease in anticonvulsant activity of the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.