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Synthesis, anticonvulsant activity, and neuropathic pain-attenuating activity of *N*-benzyl 2-amino-2-(hetero)aromatic acetamides

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ABSTRACT

N-Benzyl 2-acetamido-2-substituted acetamides, where the 2-substituent is a (hetero)aromatic moiety, are potent anticonvulsants. We report the synthesis and whole animal pharmacological evaluation of 16 analogues where the terminal 2-acetyl group was removed to give the corresponding primary amino acid derivatives (PAADs). Conversion to the PAAD structure led to a substantial drop in seizure protection in animal tests, demonstrating the importance of the *N*-acetyl moiety for anticonvulsant activity. However, several of the PAADs displayed notable pain-attenuating activities in a mouse model.

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1. Introduction

Up to 1% of the world's population, including more than 2 million Americans, are affected by epilepsy, a disorder characterized by reoccurring, unprovoked seizures that result from neuronal hyperexcitability and hypersynchronous neuronal firing.[1,2] Newer generation antiepileptic drugs (AEDs[a]) have improved patient care but still 30% of patients are pharmacoresistant (non-responder to two first-line AEDs)[3] and nearly 40% of patients experience adverse drug side effects (e.g., drowsiness, dizziness, nausea).[4] Therefore, the need remains for new AEDs with novel mechanisms to overcome these limitations.

We have advanced a class of anticonvulsant compounds termed functionalized amino acids (FAAs, Fig. 1, e.g., **1**).[5–16] The FAAs exhibited pronounced activities in the maximal electroshock seizure[17] (MES) and the 6 Hz psychomotor seizure[18] tests. Our studies culminated in the discovery of (*R*)-*N*-benzyl 2-acetamido-3-methoxypropionamide (lacosamide, (*R*)-**2**),[14] a first-in-class AED for the adjuvant treatment of partial-onset seizures in adults.[19]

Pharmacological and clinical studies have documented the pathophysiological similarities in epilepsy and neuropathic pain models.[20] Neuropathic pain results from excessive neuronal activity due to damaged or dysfunctioning neuronal pathways within the peripheral and central nervous sysems.[20,21] Thus, it is not surprising that we see antiepileptic agents used to manage neuropathic pain.[20,21] For example, the FAA (*R*)-**2** demonstrated excellent protection in several animal neuropathic pain models, including diabetic neuropathy,[22] neuropathic pain of spinal cord,[23] trigeminal nerve injury,[23] osteoarthritis pain,[24] and chronic inflammatory pain.[25]

Recently, we showed that N-deacetylated analogues of FAAs, the primary amino acid derivatives (PAADs, e.g., **3**), also exhibited excellent anticonvulsant and pain-attenuating properties.[26–29] The most active PAADs in the MES test were C(2)-hydrocarbon PAADs, such as (*R*)-**4**.[27] The pharmacological activity for (*R*)-**4** was unexpected since the corresponding FAA (*R*)-**5** showed little anticonvulsant activity in the MES test.[27] Equally surprising was the modest loss

Abbreviations: AED, antiepileptic drug; ASP, Anticonvulsant Screening Program; B:P, brain-to-plasma; Cbz, carboxybenzyl; DBU, 1,8-diazabicycloundec-7-ene; DIPEA, *N,N*-diisopropylethylamine; DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; ED_{50}, effective dose (50%); FAA, functionalized amino acid; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate; ip, intraperitoneally; MAC, mixed anhydride coupling; MES, maximal electroshock seizure; MAD, minimal active dose; MTD, maximal tolerated dose; NINDS, National Institute of Neurological Disorders and Stroke; PAAD, primary amino acid derivative; PI, protective index; SAR, structure–activity relationship; TBTU, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate; TD_{50}, neurological impairment (toxicity 50%); TFA, trifluoroacetic acid.

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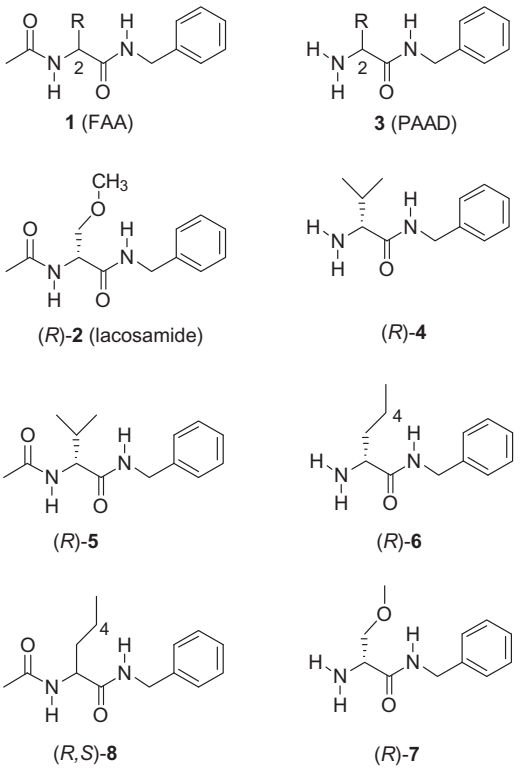


Figure 1. Functionalized amino acids (FAAs) and primary amino acid derivatives (PAADs).

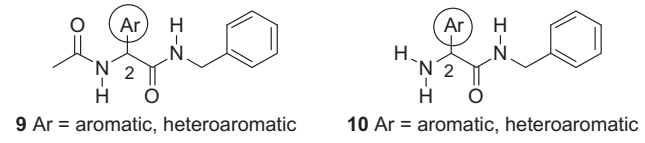


Figure 2. General structure of C(2)-aromatic (heteroaromatic) FAAs **9** and PAADs **10**.

of anticonvulsant activity when the C(4)-methylene group in PAAD (*R*)-**6** was substituted with an oxygen to give PAAD (*R*)-**7**. This result was opposite to the structure-activity relationship (SAR) of **1**, where incorporation of a substituted heteroatom one atom from the C(2) center improved activity.[9–12,14] Using (*R,S*)-**8** as an example, replacement of the C(4)-methylene group by oxygen gave (*R,S*)-**2** and a ~4-fold increase in potency. These collective findings questioned whether FAAs and PAADs functioned by similar pathways despite their structural similarity.[27–29] In agreement with this speculation, we and others have recently demonstrated that the FAA (*R*)-**2** potently transitioned Na^+ channels into the slow inactivated state,[30–32] while the C(2)-hydrocarbon PAAD (*R*)-**4** did not (data not shown).

The FAA SAR revealed that select C(2)-aromatic and C(2)-heteroaromatic FAAs **9** (Fig. 2) exhibited outstanding anticonvulsant activities[9,11,12] that were comparable to or exceeded the value reported for phenytoin.[33] Seizure protection increased with placement of a heteroatom one atom removed from the C(2) center, consistent with the SAR of **1**. We found that both electron-rich and electron-poor heteroaromatic FAAs **9** were active[9,11,12] but that the expansion of the size of the (hetero)aromatic unit from a 6-π to a benzannulated 10-π system led to a sharp loss in activity.[9] In light of the different structural patterns for PAADs and FAAs, we asked whether C(2)-(hetero)aromatic PAADs **10** exhibited anticonvulsant activity. The C(2)-(hetero)aromatic PAADs were also evaluated in the formalin model for neuropathic pain[34,35] because both PAAD (*R*)-**4** and FAA (*R*)-**2** exhibited pain-attenuating activities in this test.[25,27] In this report, we show that the C(2)-(hetero)aromatic PAADs **10** do not exhibit notable activity in the seizure models but several compounds did display appreciable activity in the formalin pain model.

2. Results and discussion

2.1. Choice of compounds

Sixteen C(2)-(hetero)aromatic PAADs were selected for study. We prepared 10 PAADs where the C(2)-substituent was either a six-membered or a benzannulated six-membered (hetero)aromatic moiety (Table 1 and **11**–**20**) and 6 PAADs where the C(2)-attached ring was either a five-membered or benzannulated five-membered heteroaromatic moiety (Table 2 and **21**–**26**). Of the 16 compounds, 7 possessed a C(2)-benzannulated substituent (i.e., **16**–**20**, **23**, **26**). All 16 compounds were prepared as their racemates to facilitate their synthesis and to remove concerns of possible racemization of an optically pure PAAD or intermediates due to the ease of ionization of the C(2) proton.

Several factors entered into selection of the candidate PAADs. First, we wanted to determine if FAA activity[9,11,12] was predictive of 2-(hetero)aromatic substituted PAAD activity. Thus, PAADs **11**, **12**, **15**, **21**, **22**, **24**, and **25** were prepared. Second, PAADs were synthesized to test the hallmarks of the FAA SAR. Accordingly, PAADs **11**–**14** evaluated the importance of a heteroatom for anticonvulsant activity and its proximity to the C(2) center.[9–12,14] For the C(2)-(hetero)aromatic FAAs, anticonvulsant activity markedly increased with inclusion of a substituted heteroatom that was one atom removed from this carbon. C(2)-Benzannulated (hetero)aromatic PAADs **16**–**20**, **23**, and **26** were prepared to assess the effect of the C(2)-substituent size on pharmacological activity. For FAAs, anticonvulsant activity dramatically decreased when the aromatic system was expanded from 6-π to 10-π by benzannulation.[9]

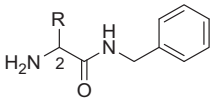
2.2. Chemistry

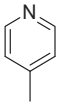
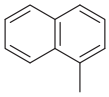
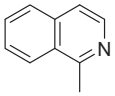
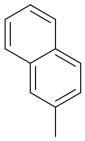
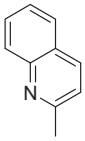
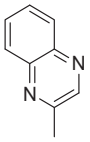
Different protocols (Schemes 1–8) were needed to prepare PAADs **11**–**26**. In the Experimental Section, we detail the final step (synthetic procedure and characterization) for all compounds evaluated in the animal models. In the Supplementary data section, we provide the procedures for each step and the complete physical, spectral, and analytical properties for all intermediates and final products.

PAAD **11**[26] was synthesized using a method previously described to prepare C(2)-hydrocarbon PAADs.[27,28] Thus, carboxybenzyloxy (Cbz)-protection of the commercial amino acid **27** was followed by mixed anhydride coupling[36] (MAC) with benzylamine to give amide **29**, which upon deprotection (10% Pd–C/H_2) gave PAAD **11** (Scheme 1).

The C(2)-amino group in PAADs **12**, **17**, **19**, and **20** was introduced by Zn-mediated reduction of the corresponding C(2)-oxime (Scheme 2) using Zn dust and ammonium formate[37] or Zn dust and formic acid.[38,39] PAAD **17** was isolated as the free amine, while PAADs **12**, **19**, and **20** were isolated as the corresponding salt. For PAAD **12**, ethyl ester **30** was converted to the free acid and then immediately coupled with benzylamine, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU), and *N,N*-diisopropylethylamine (DIPEA) to afford amide **34**. Treatment of **34** with sodium nitrite in acetic acid provided the oxime **38** as a mixture of syn- and anti-isomers, which

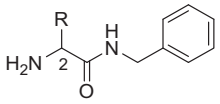
Table 1
Pharmacological activities of C(2)-six-membered aromatic and heteroaromatic *N*-benzylamide PAADs in mice (mg/kg)

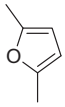
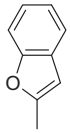
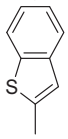


Compd No.	R	Mice (ip)[a]						
		MES,[b] ED_{50}	6 Hz,[c] ED_{50}	Formalin, ED_{50}	Tox,[d] TD_{50}	Comments[e]	PI,[f] MES	PI,[f] Form
11		>30	>43	24[g] (37%)	51	77 (C), 140 (MT)	>1.7	>1.2
12		100 (MAD)[h]	>100	33	180 (MTD)[i]			
13		120 (MAD)[h]	>210	74	ND[j]			
14		210 (MAD)[h]	>120	67	ND[j]			
15		85	28 (MAD)[h]	>160	>160		>1.9	>1.0
16		>69	>59	>33	ND[j]	105 (C, MT)		
17		>52	>93	29	ND[j]			
18		45	>110	<110 (Inactive) 110[g] (100%)	110 (MTD)[i]	59 (T, W) 110 (C, M)	<2.4	
19		>41	>130	54	ND[j]	130 (W, C)		
20		>120	>120	42	ND[j]			
(*R*)-**2**[k]		3.3	10	15	19		5.8	1.3
Phenytoin[l]		9.5 [2.0] (8.1–10)			66 [0.5] (53–72)		6.9	
Phenobarbital[l]		22 [1.0] (15–23)			69 [0.5] (63–73)		3.1	
Valproate[l]		270 [0.25] (250–340)			430 [0.25] (370–450)		1.6	

[a] The compounds were administered intraperitoneally to adult male NMRI mice under the auspices of UCB. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration.
[b] MES = maximal electroshock seizure test.
[c] 6 Hz test = psychomotor seizure model (44 mA).
[d] Tox = neurological toxicity. TD_{50} value determined from the rotorod test.
[e] Dose in mg/kg is followed by whole animal pharmacological observation (T = tremors, C = convulsions, MT = mortality, W = writing).
[f] PI = protective index (TD_{50}/ED_{50}).
[g] Single dose experiments where the mg/kg used is followed by the percentage protected in parenthesis.
[h] MAD = minimal active dose.
[i] ND = not determined.
[j] MTD = maximal tolerated dose.
[k] Ref. 14.
[l] Ref. 33.

Table 2
Pharmacological activities of C(2)-five-membered heteroaromatic *N*-benzylamide PAADs in mice (mg/kg)



Compd No.	R	Mice (ip)[a]						
		MES,[b] ED_{50}	6 Hz,[c] ED_{50}	Formalin, ED_{50}	Tox,[d] TD_{50}	Comments[e]	PI,[f] MES	PI,[f] Form
21		85	>150	29	>150		>1.8	>5.1
22		100 (MAD)[g] 140[h] (100%)	>140	>78	ND[i]	100 (IG, T)		
23		90	>120	90[h] (31%)	ND[i]	90 (T)		
24		68 (MAD)[g]	>91	48	51 (MTD)[j]	160 (C)	<0.8	<1.1
25		67	>140	45	140 (MTD)[j]		<2.1	<3.1
26		120	>170	66	ND[i]			

[a] The compounds were administered intraperitoneally to adult male NMRI mice under the auspices of UCB. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration.
[b] MES = maximal electroshock seizure test.
[c] 6 Hz test = psychomotor seizure model (44 mA).
[d] Tox = neurological toxicity. TD_{50} value determined from the rotorod test.
[e] Dose in mg/kg is followed by whole animal pharmacological observation (T = tremors, C = convulsions, IG = impaired gait).
[f] PI = protective index (TD_{50}/ED_{50}).
[g] MAD = minimal active dose.
[h] Single dose experiments where the mg/kg used is followed by the percentage protected in parenthesis.
[i] ND = not determined.
[j] MTD = maximal tolerated dose.

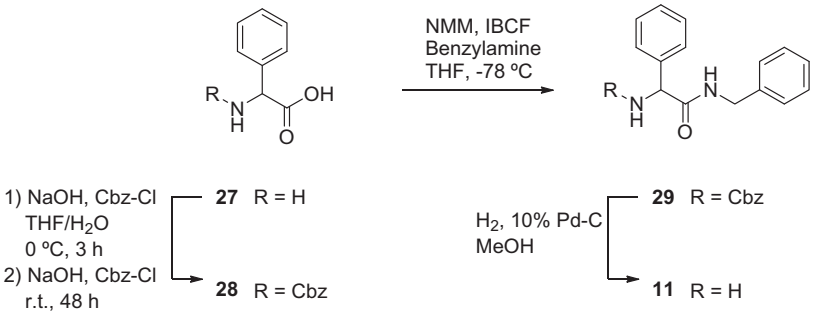
were then reduced to the C(2) amine **12**. Similar procedures were employed to prepare **17**, **19**, and **20**, beginning with the 2-substituted acetic esters **31**–**33** (Fig. 3), respectively. For **17**, methyl ester **31**[39] was generated by reacting N-oxide **42** with **43** and benzoyl chloride (**44**) to give **45**, followed by acid treatment. A similar N-oxide pathway was used for PAAD **19** starting with methyl ester **32**.[39,40] Thus, addition of methyl acetoacetate (**47**) to quinoline N-oxide (**46**) in acetic anhydride gave **48**, which upon acid treatment provided methyl ester **32**. Ethyl 2-(2-quinoxaline)acetic ester (**33**),[41] a synthetic precursor to PAAD **20**, was obtained by treatment of *ortho*-phenylenediamine (**49**) with ethyl 4-chloroacetoacetate (**50**).

An oxime-mediated pathway similar to Scheme 2 was used to prepare PAADs **13**, **14**, and **18** (Scheme 3) but the oxime was introduced at an earlier stage in the synthesis. Thus, ethyl 2-((hetero)aryl)acetoacetic acids **51**–**53** were esterified to give **54**–**56** and then converted to the oximes **57**–**59**[42,43] with *t*-butylnitrite and base. The oxime ethyl esters were reduced to the amines[42] and protected using *t*-Boc anhydride to give **60**–**62**.[44,45] Hydrolysis of esters **60**–**62** to the corresponding acids, followed by coupling with benzylamine using either *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) or 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and removal of the protecting group with acid, gave PAADs **13**, **14**, and **18** that were isolated as salts.

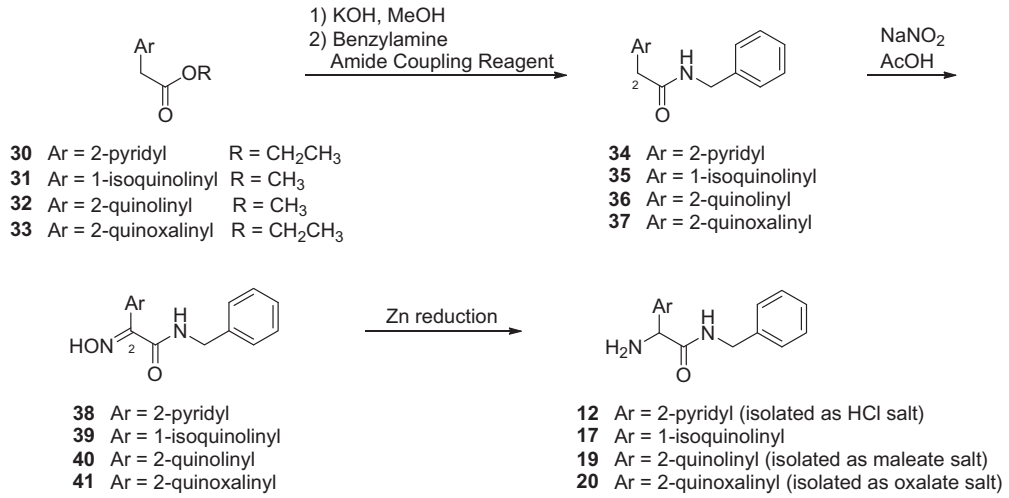
An oxime route was also employed to prepare benzothiophene PAAD **26** (Scheme 4). Here, diethyl oxalate (**66**) was added to the 2-lithio salt of benzothiophene (**67**) at −78 °C to give α-ketoester **68**.[46] Treatment of **68** with benzylamine provided amide **69**, which was converted to oxime **70** (syn- and anti-isomers) with hydroxylamine. Reduction of oxime **70** (Zn, ammonium formate) gave PAAD **26**.

The 2-pyrazin-2-yl PAAD **15** was prepared using a procedure similar to the route reported for the corresponding FAA derivative.[12] Commercially available ethyl *N*-(diphenylmethylene)-glycinate (**71**) was treated with solid potassium carbonate, tetra-*n*-butylammonium bromide and 2-chloropyrazine (**72**) in 1-methyl-2-pyrrolidinone to afford pyrazin-2-yl **73** (Scheme 5). Acid hydrolysis of **73** liberated the ethyl ester **74**, which was protected as the Cbz-derivative **75**. Treatment of **75** with benzylamine gave amide **76**. The Cbz unit was removed (Pd–C/H_2) to give PAAD **15** and then converted to the HCl salt.

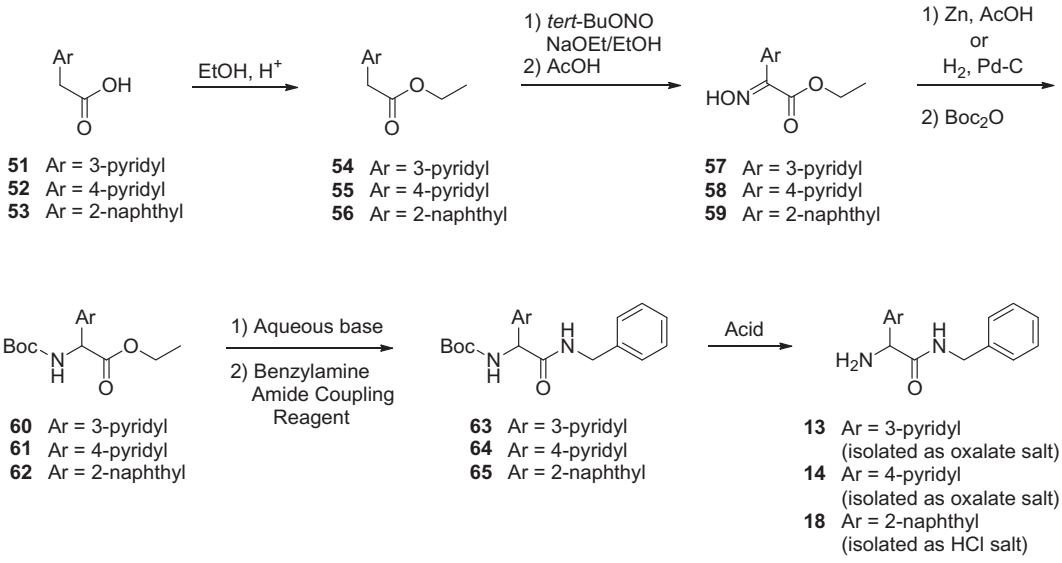
A diazo route was used to prepare the 1-naphthyl PAAD **16** (Scheme 6). Treatment of methyl 2-(1-naphthyl)acetic acid (**77**) with tosyl azide (**78**) and 1,8-diazabicycloundec-7-ene (DBU) gave diazo **79**,[47] which was transformed to the *t*-butyl carbamate **81**



Scheme 1. Synthesis of PAAD **11**.



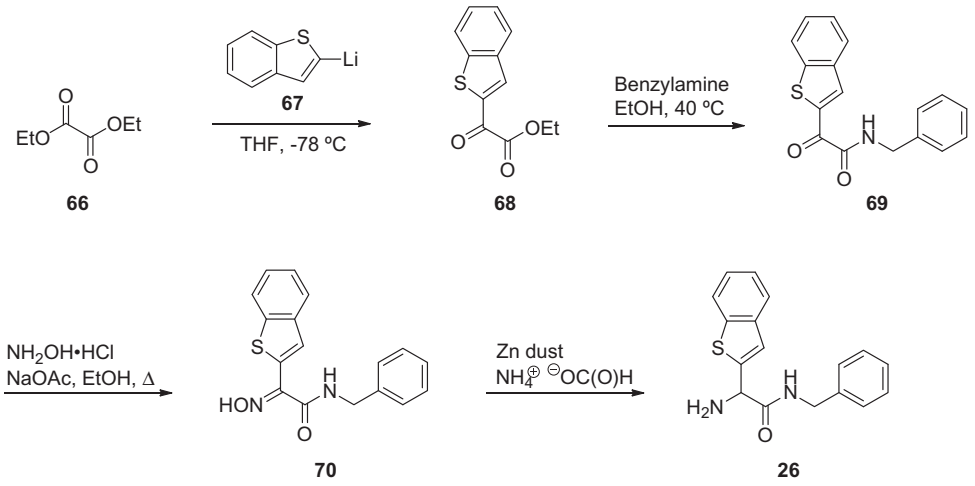
Scheme 2. Synthesis of PAADs **12**, **17**, **19**, and **20**.



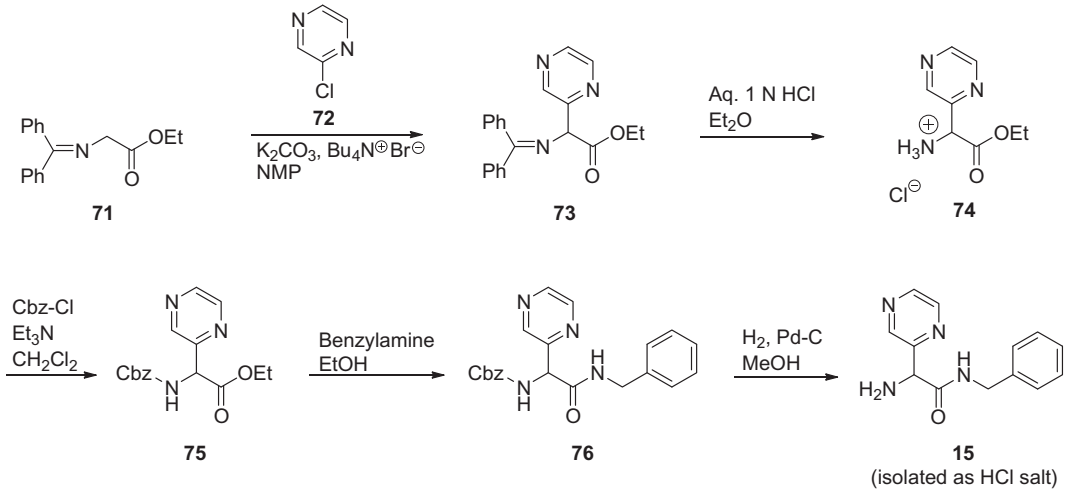
Scheme 3. Synthesis of PAADs **13**, **14**, and **18**.

with $RuCl_2$(*para*-cymene)$_2$ and *t*-butyl carbamate (**80**). LiOH-mediated ester hydrolysis of **81** followed by benzylamine coupling (TBTU, DIPEA) gave amide **83**. Trifluoroacetic acid (TFA) deprotection of the *t*-Boc group in **83** provided PAAD **16** as the hydrochloride salt.

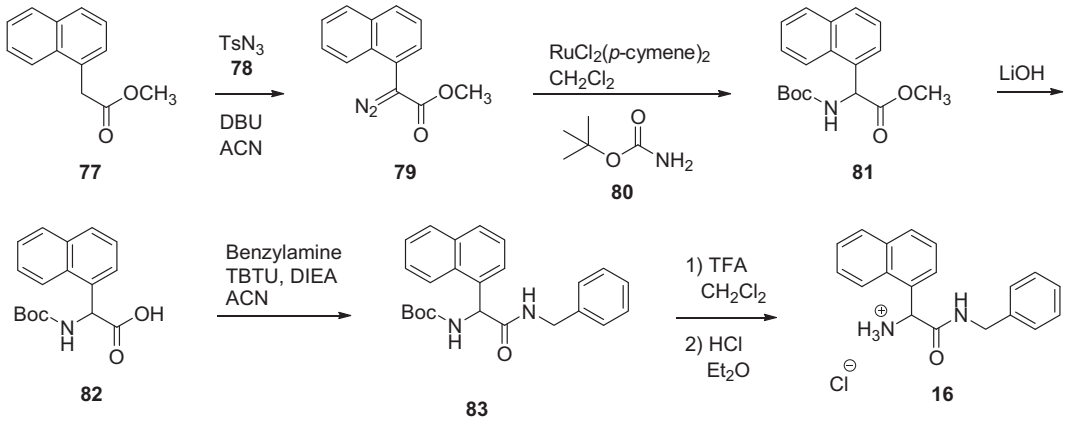
PAADs **21**–**24** were prepared by an amidoalkylation method using intermediate **87** (Scheme 7). Treatment of benzyl carbamate (**84**) with glyoxylic acid (**85**) afforded the addition product **86**,[48–50] which was converted to **87**[49,50] in acidic MeOH. Addition of the electron-rich heteroaromatic compounds (e.g., furan, 5-methylfuran,



Scheme 4. Synthesis of PAAD **26**.



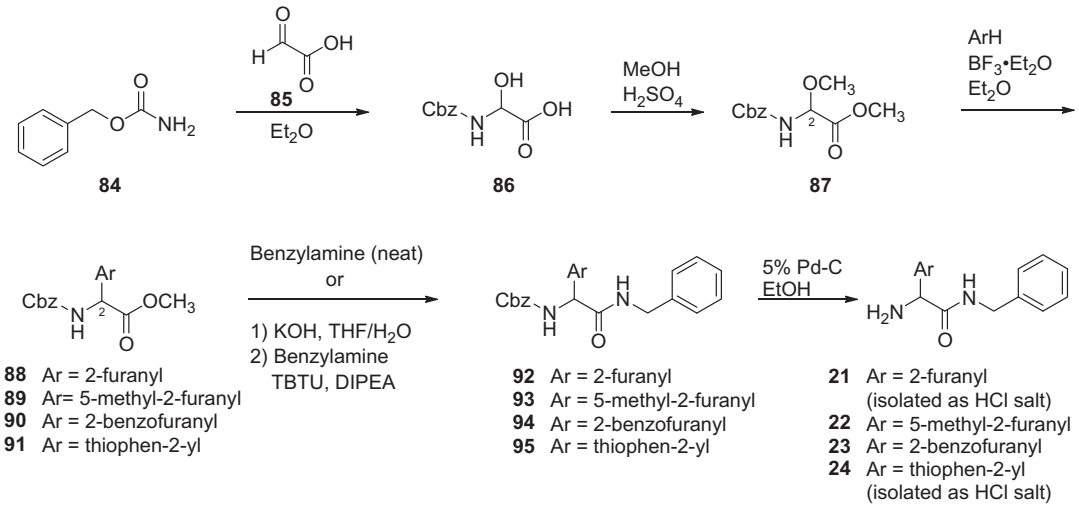
Scheme 5. Synthesis of PAAD **15**.



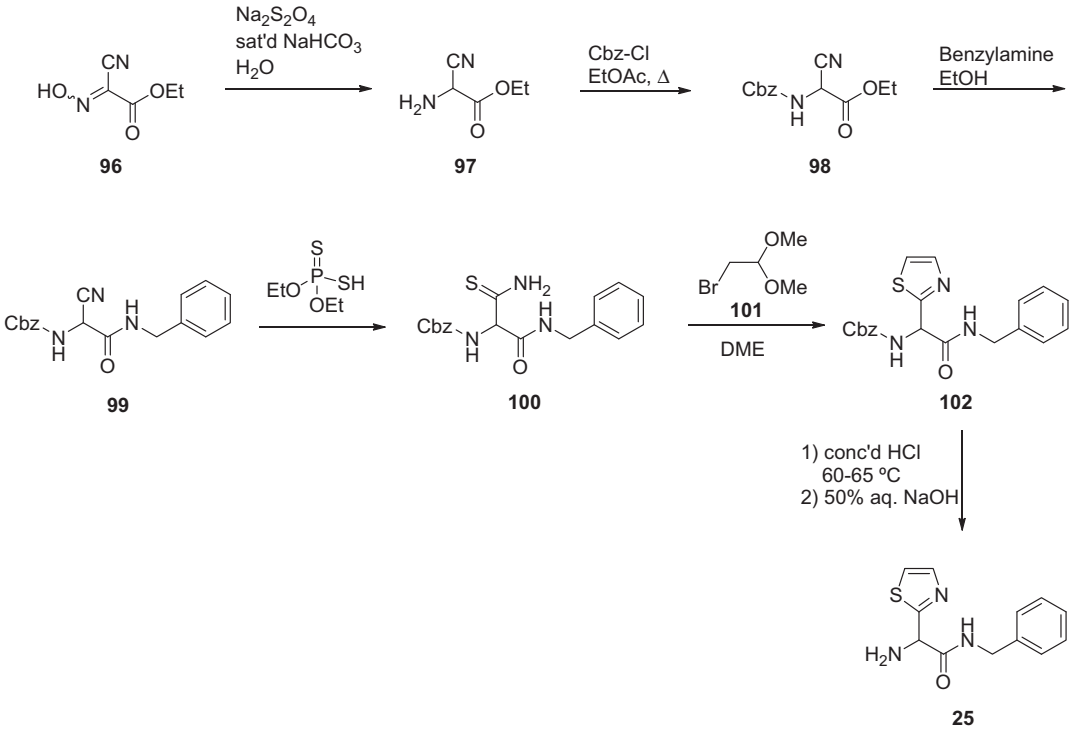
Scheme 6. Synthesis of PAAD **16**.

benzofuran, thiophene) in the presence of $BF_3{\cdot}Et_2O$ led to heteroaromatic incorporation at the C(2) site to give **88**–**91**,[51] respectively. Methyl esters **88**–**91** were either treated with benzylamine or first hydrolyzed to the free acid and then coupled with benzylamine (TBTU, DIPEA) to give amides **92**–**95**. Catalytic removal (Pd–C/H_2) of the Cbz-protecting group provided PAADs **21**–**24** that were either isolated as the free amine or their corresponding HCl salt.

The final PAAD in this study was the C(2)-thiazol-2-yl derivative **25**. Sodium dithionite reduction of commercially available ethyl



Scheme 7. Synthesis of PAADs **21**–**24**.



Scheme 8. Synthesis of PAAD **25**.

(hydroxyimino)cyanoacetate (**96**) gave the amine **97**,[52] which was protected as the Cbz-derivative **98**[53] and then converted to amide **99** with benzylamine (Scheme 8). Treatment of **99** with *O,O'*-diethyl dithiophosphate produced thioamide **100**, permitting condensation with excess bromoacetaldehyde dimethyl acetal (**101**) in dimethoxyethane to give the thiazole **102**. Removal of the Cbz-protecting group (concentrated aqueous HCl, 65 °C) followed by neutralization provided PAAD **25**.

2.3. Pharmacological evaluation

PAADs **11**–**26** were evaluated for anticonvulsant activity at UCB Pharma using the MES test,[17] following the procedure described by Klitgaard,[54] and the 6 Hz test (44 mA),[18] following the protocol described by Kaminski and co-workers.[55] The PAADs were also evaluated using the formalin test,[34,35] which is an effective tool to prescreen compounds for pain-attenuating properties.[27,28,56] All compounds were administered intraperitoneally (ip) to mice. The pharmacological data for **11**–**26** in the MES, 6 Hz, and formalin tests are summarized in Tables 1 and 2. The MES activities of PAADs are compared with the MES activities of their corresponding FAAs in Table 3. The tables list the results obtained from qualitative (dose range) or quantitative (effective dose (50%), ED_{50}) testing in mice (ip). We also include qualitative (dose range) or median neurological impairing dose (toxicity (50%), TD_{50}) values in mice (ip) using the rotorod test[57] in mice. The protective indices (PI = TD_{50}/ED_{50}) are provided, when applicable.

Early evaluation of **12** revealed a 2.7:1 brain-to-plasma (B:P) ratio in mice (data not shown), a value higher than reported for other PAADs.[58] The high B:P ratio for this PAAD indicated that this

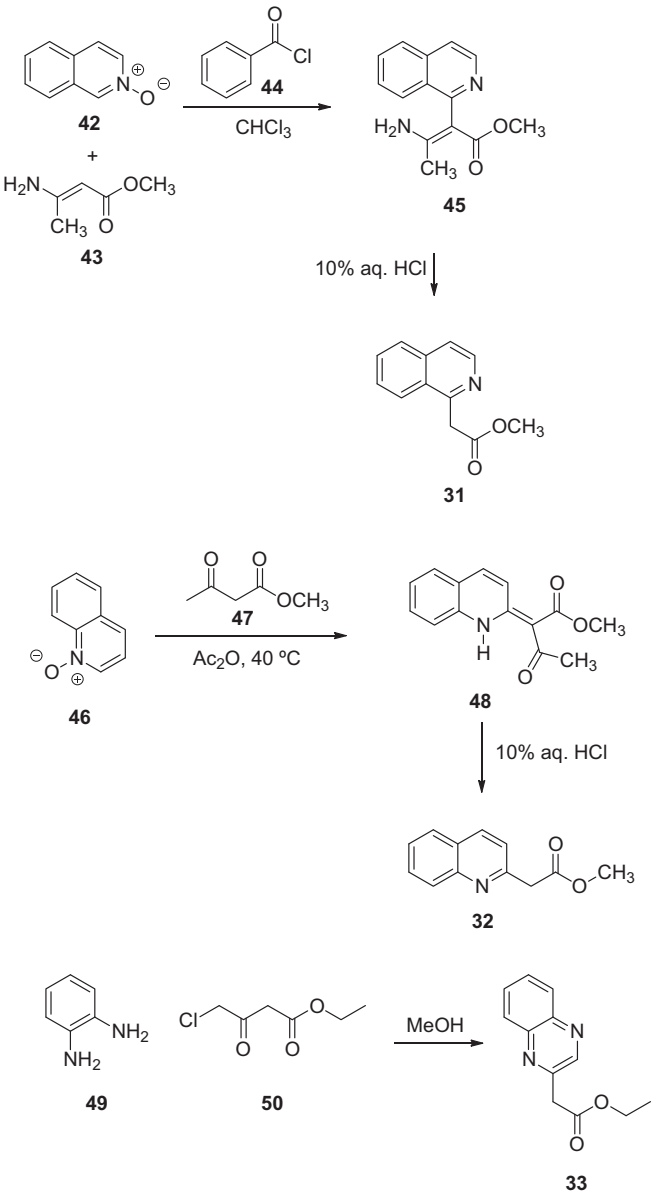


Figure 3. Synthesis of 2-substituted acetic esters **31**–**33**.

compound was able to penetrate the blood brain barrier, and thus capable of exerting a neurological effect in either the absence or presence of a stimulus (e.g., electrical, chemical).

The pharmacological activities in mice for C(2)-six-membered and C(2)-benzannulated six-membered (hetero)aromatic PAADs **11**–**20** are listed in Table 1. The composite data set showed the effect of heteroatom substitution, the site of heteroatom substitution, and the size of the (hetero)aromatic unit on PAAD anticonvulsant activity. Distinctive patterns for all three structural factors were previously reported that defined the SAR for FAAs.[9,11,12] The PAADs exhibited minimal activities in the MES (>30 mg/kg) and 6 Hz (>30 mg/kg) seizure models in mice. Moreover, unlike the FAA SAR,[9,11,12] there was no improvement in activity upon either inclusion of a heteroatom within the aromatic ring (i.e., MES ED_{50} (mg/kg): **11**, >30; **12**, 100 (minimal active dose (MAD)) or positioning the heteroatom one atom removed from the C(2) center (i.e., MES ED_{50} (mg/kg): **12**, 100 (MAD); **13**, 120 (MAD)). We observed notable activity in the formalin test for the six-membered heteroaromatic PAADs **12**–**14**, **17**, **19**, and **20** (ED_{50} (mg/kg): **12**, 33; **13**, 74; **14**, 67; **17**, 29; **19**, 54; **20**, 42) demonstrating that these compounds were more effective in this pain-attenuating model compared with the anticonvulsant tests. The formalin ED_{50} values for PAADs **12**, **14**, and **20** were ~3-fold lower (more potent) than the corresponding values in the MES test. This finding differed from the PAADs containing a C(2)-acyclic moiety (i.e., CH_2OR, CH_2NR, CH_2CH_2R), where we consistently observed lower activity in the formalin test compared with the MES seizure model.[27] Within the C(2)-pyridyl series **12**–**14**, **12** showed the greatest protection in the formalin test and protection slightly improved upon benzannulation (ED_{50} (mg/kg): **12**, 33; **17**, 29). Similarly, benzannulation of **15** to give **20** also resulted in an increase in activity in the formalin test (ED_{50} (mg/kg): **15**, >160 mg/kg; **20**, 42 mg/kg). These findings differed from patterns observed for the anticonvulsant activities of FAAs, where placement of a benzannulated system at the C(2) site led to a sharp loss in seizure protection[9] (see Table 3).

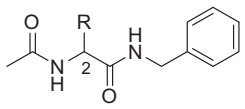
PAADs that contained either a C(2)-five-membered or a C(2)-benzannulated five-membered substituent were also evaluated (Table 2). The five-membered heteroaromatic PAADs **21**–**26** displayed modest anticonvulsant activity in the MES test (ED_{50} = >67, <120 mg/kg), with 2-thiazole **25** exhibiting the most activity (ED_{50} = 67 mg/kg). PAADs **21**–**26** were insensitive to the 6 Hz test (ED_{50} = >90 mg/kg). The most active PAAD in the formalin model was the 2-furan derivative **21** (ED_{50} = 29 mg/kg), followed by the 2-thiazole **25** (ED_{50} = 45 mg/kg) and the 2-thiophene **24** (ED_{50} = 48 mg/kg) derivatives. Unlike the six-membered heteroaromatic series, benzannulation of both **21** and **24** to give **23** and **26**, respectively, decreased pain attenuation (ED_{50} (mg/kg): **21**, 29; **23**, 90 (31% reduction); **24**, 48; **26**, 66). Collectively, the C(2)-five-membered and C(2)-benzannulated five-membered heteroaromatic PAADs attenuated pain in the formalin test and were 1.5- to 3-fold more selective for neuropathic pain protection in the formalin model over anticonvulsant activity in the MES test.

The MES activities of heteroaromatic PAADs **11**, **12**, **15**, **18**, and **21–26** were compared with their corresponding FAAs **103**–**112**.[6,9,11,12] With the exception of **18** and **23**, there was up to a 10-fold drop in activity in going from FAA to PAAD, demonstrating the importance of the *N*-acetyl moiety in the FAA for maximal seizure protection (Table 3). These findings were similar to those reported for the C(2)-acyclic PAAD derivatives containing a C(2)-CH_2XR substituent, where X is a heteroatom and R is an alkyl moiety.[27] We were unable to conduct a similar comparison of the formalin activity in PAADs and their corresponding FAAs since extensive formalin data in the FAA series is not available.

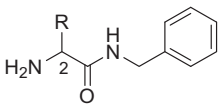
3. Conclusions

We have developed the PAAD SAR from the pharmacological evaluation of more than 80 compounds in whole animal models of epilepsy and neuropathic pain.[26–29] We examined the effect of select substituents at the C(2)-site (i.e., CH_2OR, $CH_2N(R)R'$, CH_2CH_2XR [X = heteroatom, R = alkyl moiety], five- and six-membered (hetero)aromatic, five- and six-membered benzannulated (hetero)aromatic, hydrocarbon) to test the hallmarks of the FAA SAR for maximal activity, including the requirement for a heteroatom one atom removed from the C(2) center, the need for heteroatom substitution, and the stereochemical preference at the C(2) position corresponding to the D-amino acid. The anticonvulsant SARs for the FAAs and PAADs revealed significant differences. The PAAD SAR suggested that anticonvulsant activity, unlike FAAs, does not improve with the inclusion of a substituted heteroatom one atom removed from the C(2) center (e.g., (*R*)-**6** versus (*R*)-**7**).[27] The most active PAADs discovered were the C(2)-hydrocarbon PAADs (e.g., (*R*)-**4**),[27,28] where activity exceeded that reported for

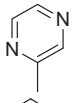
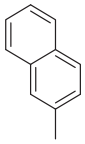
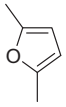
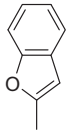
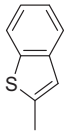
Table 3
Comparison of the pharmacological activities of C(2)-six-membered and five-membered aromatic and heteroaromatic FAAs and their PAAD counterparts in mice (mg/kg)



FAA



PAAD

R	FAA compd no.	FAA test site	Mice (ip)[a]		PAAD compd no.	PAAD test site	Mice (ip)[a]	
			FAA MES,[b] ED_{50}	FAA Tox,[c] TD_{50}			PAAD MES,[b] ED_{50}	PAAD Tox,[c] TD_{50}
	**103**[d]	Lilly	32 [0.5] (28–40)	>40	**11**	UCB	>30	51
	**104**[e]	NINDS	11 [0.5] (9–12)	>25, <100	**12**	UCB	100 (MAD)[f]	180 (MTD)[g]
	**105**[e]	NINDS	15 [0.5] (13–17)	58 [0.5] (46–73)	**15**	UCB	85	>160
	**106**[i]	NINDS	>300	>300	**18**	UCB	45	110 (MTD)[g]
	**107**[h]	NINDS	10 [0.5] (9–12)	~40 [0.5]	**21**	UCB	85	>150
	**108**[h]	NINDS	19 [0.5] (16–24)	75 [0.5]	**22**	UCB	100 (MAD)[g]	ND[i]
	**109**[h]	NINDS	>100, <300	>100, <300	**23**	UCB	90	ND[i]
	**110**[h]	NINDS	45 [0.5] (39–51)	>30, <100	**24**	UCB	68 (MAD)[f]	51 (MTD)[g]
	**111**[e]	NINDS	12 [0.5] (10–15)	69 [0.5] (62–79)	**25**	UCB	67	140 (MTD)[g]
	**112**[h]	NINDS	>100, <300	>100, <300	**26**	UCB	120	ND[i]

[a] The compounds were administered either intraperitoneally to adult male NMRI mice under the auspices of UCB or administered intraperitoneally to adult male albino CF-1 mice under the auspices of the NINDS ASP or Lilly Research Laboratories. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration (UCB) or a dose–response curve was generated for all compounds that displayed sufficient activity and the dose-effect data for these compounds was obtained at the 'time of peak effect' (indicated in hours in the brackets) (NINDS ASP and Lilly Research Laboratories). Numbers in parentheses are 95% confidence intervals.
[b] MES = maximal electroshock seizure test.
[c] Tox = neurological toxicity. TD_{50} value determined from the rotorod test (UCB and NINDS) or the horizontal screen test (Lilly Research Laboratories).
[d] Ref. 6.
[e] Ref. 12.
[f] MAD = minimal active dose.
[g] MTD = maximal tolerated dose.
[h] Ref. 9.
[i] ND = not determined.

phenobarbital in the MES test.[33] Moreover, when we compared the C(2)-(hetero)aromatic and C(2)-benzannulated C(2)-(hetero)aromatic PAADs and FAAs (Table 3), we found that benzannulation in the PAADs resulted in anticonvulsant activities that either remained the same or improved, while in the FAAs, benzannulation led to a precipitous drop in anticonvulsant activity.[9] Overall, we observed that other than for the C(2)-hydrocarbon and the C(2)-benzannulated PAADs, the PAADs were approximately 5- to 10-fold less sensitive in the MES test compared with their corresponding FAAs. Thus, an important finding of these studies was the demonstration that N-acetylation of PAADs containing a substituted heteroatom one atom removed from the C(2) center

to give the FAAs is important for maximal anticonvulsant activity. Correspondingly, the unexpected excellent activity for C(2)-hydrocarbon PAADs and the loss of anticonvulsant activity upon N-acetylation for these compounds[27] suggests that these agents function by different pathways despite their close structural correspondence to the active FAA class.

Several racemic C(2)-six-membered, C(2)-five-membered (hetero)aromatic, and benzannulated (hetero)aromatic PAADs displayed significant activity in the formalin test (ED_{50} (mg/kg): **12**, 33; **17**, 29; **20**, 42; **21**, 29). These PAADs were 1.5- to 3-fold selective for pain attenuation over anticonvulsant activity (MES ED_{50} (mg/kg), formalin ED_{50} (mg/kg): **12**, 100 (MAD), 33; **17**, >52, 29; **20**, >120, 42; **21**, 85, 29). Thus, while the non-benzannulated C(2)-six-membered and C(2)-five-membered (hetero)aromatic PAADs did not provide any significant advantage for the prevention of seizures compared with their structurally related FAAs, they displayed notable activity as pain attenuating agents that may increase with further optimization (e.g., at the N-benzylamide site[29]).

4. Experimental section

4.1. Chemistry: general

Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were recorded at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C) using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from TMS. Low-resolution mass spectra (LRMS) were recorded with a BioToF-II-Bruker Daltonics spectrometer by Drs. M. Crowe and S. Habibi at the University of North Carolina Department of Chemistry. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex-Q 12 Telsa FTICR spectrometer by Drs. M. Crowe and S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, Catalog No. Z12272-6, or Dynamic Adsorbents Inc., Catalog No. 84111) and analyzed with 254 nm light. The reaction mixtures were purified by medium pressure liquid chromatography (MPLC, CombiFlash *Rf*) with self-packed columns (silica gel from Dynamic Adsorbents Inc., Catalog No. 02826-25) or by flash column chromatography using silica gel (Dynamic Adsorbents Inc., Catalog No. 02826-25). All chemicals and solvents were reagent grade and used directly from commercial sources without further purification. THF was distilled from blue sodium benzophenone ketyl. Yields reported are for purified products and were not optimized. All compounds were checked by TLC, ^1H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within ±0.40% of the theoretical value. The TLC, NMR, and analytical data confirmed the purity of the products was $\geqslant$95%.

4.1.1. (*R,S*)-*N*-Benzyl 2-amino-2-phenylacetamide (11)[26]

(*R,S*)-*N*-Benzyl 2-*N*-(benzyloxycarbonyl)amino-2-phenylacetamide (**29**) (2.00 g, 5.35 mmol) was treated with 10% Pd–C (250 mg) and H_2 (1 atm) in MeOH (100 mL) (18 h), and then the reaction mixture was filtered through a bed of Celite® to give the crude product that was purified by flash column chromatography (SiO_2; 1:10 MeOH/$CHCl_3$). The oil was dissolved in CH_2Cl_2 (20 mL) and was extracted with aqueous 0.1 N HCl (3 × 20 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 × 60 mL). The aqueous layer was basified to pH 10–12 with aqueous 0.1 N NaOH and then extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give the desired product (1.07 g, 83%) as a waxy solid. Mp 67–68 °C. R_f 0.52 (1:20 MeOH/$CHCl_3$). IR (nujol mull) 3361, 2856 (br), 1646, 1459, 699 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 2H), 4.27 (d, J = 5.9 Hz, 2H), 4.40 (s, 1H), 7.17–7.43 (m, 10H), 8.57 (t, J = 5.9 Hz, 1H). HRMS (ESI) 241.1342 [M+H$^+$] (calcd for $C_{15}H_{16}N_2OH^+$ 241.1341). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.74; H, 6.76; N, 11.61.

4.1.2. (*R,S*)-*N*-Benzyl 2-amino-2-(pyridin-2-yl)acetamide (12)

To a solution of (*R,S*)-*N*-benzyl 2-(hydroxyimino)-2-(pyridin-2-yl)acetamide (**38**) (1.50 g, 4.3 mmol) in MeOH (25 mL) was added $HC(O)ONH_4$ (1.10 g, 17.4 mmol) as a solid and then the reaction was stirred (5 min). Zn dust (1.14 g, 17.4 mmol)[37] was added and the reaction heated at reflux (6 h). The reaction was cooled and filtered through Celite®. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with saturated aqueous brine solution (2 × 40 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography (SiO_2; 3:97 MeOH/$CHCl_3$) to give the desired product (0.79 g, 56%) as a yellow oil. R_f 0.38 (0.1:1:9 Et_3N/MeOH/$CHCl_3$). IR (nujol) 3302, 3055, 2860, 1663, 1585, 1520, 1459, 1373, 1264, 1155, 1083, 922, 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.20–2.40 (br s, 2H), 4.34–4.53 (m, 2H), 4.65 (s, 1H), 7.18–7.32 (m, 6H), 7.59–7.71 (m, 2H), 7.96–8.16 (br s, 1H), 8.53 (d, J = 6.0 Hz, 1H). HRMS (ESI) 242.1295 [M+H$^+$] (calcd for $C_{14}H_{15}N_3OH^+$ 242.1293), 264.1115 [M+Na]$^+$ (calcd for $C_{14}H_{15}N_3ONa^+$ 264.1113), 280.0855 [M+K]$^+$ (calcd for $C_{14}H_{15}N_3OK^+$ 280.0852).

4.1.3. (*R,S*)-*N*-Benzyl 2-amino-2-(pyridin-2-yl)acetamide hydrochloride (12·HCl)

To a precooled methanolic 1.25 M HCl solution (12.5 mL, 15.66 mmol) was slowly added a solution of (*R,S*)-**12** (1.26 g, 5.22 mmol). The reaction mixture was stirred at room temperature (1 h) and the MeOH was removed in vacuo and the residue was recrystallized from a mixture of MeOH and Et_2O to give the desired product (1.20 g, 73%) as a white solid. Mp 196–197 °C. IR (nujol) 3221, 3176, 2863, 1990, 1700, 1621, 1547, 1545, 1374, 1302, 1249, 1165, 1077, 1024, 727 cm^{-1}. ^1H NMR (CD_3OD) δ 4.33–4.43 (m, 2H), 5.33–5.36 (m, 1H), 7.20–7.30 (m, 6H), 7.67–7.71 (m, 1H), 7.81–7.84 (m, 1H), 8.13–8.18 (m, 1H), 8.76–8.78 (m, 1H); ^1H NMR (DMSO-d_6) δ 4.30–4.33 (m, 2H), 5.29–5.33 (m, 1H), 7.19–7.31 (m, 5H), 7.45–7.50 (m, 1H), 7.86–7.97 (m, 2H), 8.63–8.64 (m, 1H), 8.82 (br s, 3H), 9.59 (br t, 1H). HRMS (ESI) 242.1295 [M+H$^+$] (calcd for $C_{14}H_{15}N_3OH^+$ 242.1293). Anal. Calcd for $C_{14}H_{17}Cl_2N_3O$: C, 53.52; H, 5.45; Cl, 22.57; N, 13.37. Found: C, 53.54; H, 5.33; Cl, 22.69; N, 13.25.

4.1.4. (*R,S*)-*N*-Benzyl 2-amino-2-(pyridin-3-yl)acetamide oxalate (13·oxalic acid)

A suspension of (*R,S*)-*N*-benzyl 2-*N*-(*t*-butoxycarbonyl)amino-2-(pyridin-3-yl)acetamide (**63**) (3.87 g, 11.35 mmol) in 1 M HCl in Et_2O (150 mL) was stirred at room temperature (20 h). The solvent was removed in vacuo and the residue dissolved in H_2O (30 mL). The solution was basified with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were washed with a saturated aqueous brine solution (2 × 100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue dissolved in THF (20 mL). A solution of oxalic acid (4.09 g, 45.40 mmol) in THF (10 mL) was added and the reaction was allowed to stand at room temperature (1 h). The precipitate was filtered and washed with THF (100 mL) to give

the desired product (3.09 g, 82%) as a white solid. Mp 153–155 °C. IR (nujol) 3222, 1695, 1635, 1458, 1375, 1212, 701 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.24–4.39 (m, 2H), 5.16 (s, 1H), 7.15–7.30 (m, 5H), 7.45–7.51 (m, 1H), 7.93–7.96 (m, 1H), 8.61–8.75 (m, 2H), 9.18–9.37 (m, 1H), 10.00–11.60 (br s, 3H). HRMS (ESI) 242.1294 $[C_{14}H_{15}N_3OH]^+$ (calcd for $C_{14}H_{15}N_3OH^+$ 242.1293).

4.1.5. (*R,S*)-*N*-Benzyl 2-amino-2-(pyridin-4-yl)acetamide oxalate (14·oxalic acid)

A suspension of (*R,S*)-*N*-benzyl 2-*N*-(*t*-butoxycarbonyl)amino-2-(pyridin-4-yl)acetamide (**64**) (0.80 g, 2.34 mmol) in 1 M HCl in Et_2O (30 mL) was stirred at room temperature (20 h). The solvent was removed in vacuo and the residue dissolved in H_2O (30 mL). The solution was basified with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 layers were washed with a saturated aqueous brine solution (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue dissolved in THF (15 mL). A solution of oxalic acid (0.84 g, 9.38 mmol) in THF (5 mL) was added and the reaction was allowed to stand at room temperature (1 h). The precipitate was filtered and washed with THF (20 mL) to give the desired product (0.63 g) as an ash colored solid. The product was further triturated with MeOH to give the desired product (0.58 g, 75%) as an off-white solid. Mp 200–201 °C. IR (nujol) 3403, 3188, 3143, 1694, 1589, 1458, 1373, 1233, 1073, 717 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.23–4.40 (m, 2H), 5.12 (s, 1H), 7.15–7.28 (m, 5H), 7.57–7.59 (2H), 8.65–8.67 (m, 2H), 9.31 (br s, 1H), 9.90–11.15 (br s, 3H). HRMS (ESI) 242.1294 [M+H$^+$] (calcd for $C_{14}H_{15}N_3OH^+$ 242.1293).

4.1.6. (*R,S*)-*N*-Benzyl 2-amino-2-(pyrazin-2-yl)acetamide (15)

(*R,S*)-*N*-Benzyl *N*-(benzyloxycarbonyl)-2-amino-2-(pyrazin-2-yl)acetamide (**76**) (2.70 g, 0.80 mmol) was treated with 10% Pd–C (30 mg) and H_2 (1 atm) (18 h). The reaction mixture was filtered through Celite® and the crude product was purified by flash column chromatography (SiO_2; 3:97 MeOH/$CHCl_3$) to give the desired product (0.90 g, 52%) as a yellow paste. R_f 0.63 (0.1:1:9 Et_3N/MeOH/$CHCl_3$). IR (nujol) 3304, 3037, 2860, 1662, 1518, 1459, 1403, 1256, 1137, 1020, 915, 838, 735, 670 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.60 (s, 2H), 4.36–4.53 (m, 2H), 4.74 (s, 1H), 7.24–7.35 (m, 5H), 8.00–8.18 (br s, 1H), 8.40–8.60 (m, 2H), 8.92 (s, 1H). HRMS (ESI) 243.1248 [M+H$^+$] (calcd for $C_{13}H_{14}N_4OH^+$ 243.1246), 265.1068 [M+Na$^+$] (calcd for $C_{13}H_{14}N_4ONa^+$ 265.1065), 281.0807 [M+K$^+$] (calcd for $C_{13}H_{14}N_4OK^+$ 281.0805).

4.1.7. (*R,S*)-*N*-Benzyl 2-amino-2-(pyrazin-2-yl)acetamide hydrochloride (15·HCl)

To a precooled methanolic 1.25 M HCl solution (3.3 mL, 4.2 mmol) was slowly added a solution of **15** (0.50 g, 2.1 mmol). The reaction mixture was stirred (1 h) and the MeOH was removed in vacuo. The crude residue was dissolved in MeOH and then precipitated with Et_2O to give the desired product (0.47 g, 82%) as a light brown solid. Mp 212–213 °C. IR (nujol) 3217, 3167, 1698, 1613, 1459, 1375, 1244, 1179, 1048, 878, 702 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.25–4.34 (m, 2H), 5.47 (s, 1H), 7.20–7.32 (m, 5H), 8.73–8.75 (m, 2H), 8.80–9.10 (br s, 3H), 9.13–9.14 (m, 1H), 9.60–9.73 (m, 1H). HRMS (ESI) 243.1243 [M+H$^+$] (calcd for $C_{13}H_{14}N_4OH^+$ 243.1246), 265.1062 [M+Na$^+$] (calcd for $C_{13}H_{14}N_4ONa^+$). Anal. Calcd for $C_{13}H_{15}ClN_4O$: C, 56.02; H, 5.42; Cl, 12.72; N, 20.10. Found: C, 56.06; H, 5.57; Cl, 12.73; N, 19.95.

4.1.8. (*R,S*)-*N*-Benzyl 2-amino-2-(naphthalen-1-yl)acetamide hydrochloride (16·HCl)

TFA (1.18 mL, 15.4 mmol) was added at 0 °C to a CH_2Cl_2 (15 mL) solution of (*R,S*)-*N*-benzyl 2-(*t*-butoxycarbonylamino)-2-(naphthalen-1-yl)acetamide (**83**) (600 mg, 1.5 mmol). The reaction was stirred at room temperature (2 h) and then a saturated aqueous Na_2CO_3 solution was added until pH ~9. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, concentrated in vacuo, and the residue purified by flash column chromatography (SiO_2; 10:0–9.5:0.5 EtOAc/Et_3N) to give the desired product as a colorless oil. Et_2O was added followed by 1 M HCl in Et_2O at 0 °C. The precipitate was filtered to give the desired product (240 mg, 48%) as a white solid. Mp 210 °C (decomp). IR (nujol) 2919, 2866, 1727, 1625, 1458, 1378, 1297, 1228, 1174, 1098, 1024, 858, 772 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.32 (d, J = 5.7 Hz, 2H), 5.76–5.83 (br s, 1H), 7.14–7.28 (m, 5H), 7.57–7.70 (m, 4H), 7.71–8.02 (m, 2H), 8.37 (d, J = 8.1 Hz, 1H), 8.72–8.84 (br s, 3H), 9.01 (t, J = 5.7 Hz, 1H). Anal. Calcd for $C_{19}H_{19}ClN_2O{\cdot}0.08H_2O$: C, 69.54; H, 5.88; Cl, 10.80; N, 8.54. Found: C, 69.15; H, 5.97; Cl, 11.04; N, 8.46.

4.1.9. (*R,S*)-*N*-Benzyl 2-amino-2-(isoquinolin-1-yl)acetamide (17)

To a suspension of (*R,S*)-*N*-benzyl 2-(hydroxyimino)-2-(isoquinolin-1-yl)acetamide (**39**) (0.20 g, 0.66 mmol), in MeOH was added $HC(O)ONH_4$ (0.13 g, 2.94 mmol) and Zn dust (0.12 g, 2.94 mmol)[37] and the reaction heated to reflux (6 h). The reaction mixture was filtered through Celite®. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2. The organic layer was washed with H_2O (2 × 50 mL) and saturated aqueous brine solution (2 × 50 mL). The CH_2Cl_2 layer was dried (Na_2SO_4), concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2; 4:96 MeOH/$CHCl_3$) to give the desired product (0.04 g, 21%) as a pale yellow solid. Mp 115–116 °C. R_f 0.67 (0.1:0.8:9.1 Et_3N/MeOH/$CHCl_3$). IR (nujol) 3403, 3241, 1651, 1510, 1457, 1374, 1244, 1121, 1084, 960, 818, 703 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.20-2.60 (br s, 2H), 4.30–4.53 (m, 2H), 5.42 (s, 1H), 7.22–7.34 (m, 5H), 7.59–7.72 (m, 3H), 7.81–7.84 (m, 1H), 8.14–8.24 (br s, 1H), 8.45–8.47 (m, 2H). HRMS (ESI) 292.1450 [M+H$^+$] (calcd for $C_{18}H_{17}N_3OH^+$ 292.1450), 314.1270 [M+Na$^+$] (calcd for $C_{18}H_{17}N_3O$-Na$^+$ 314.1269). Anal. Calcd for $C_{18}H_{17}N_3O{\cdot}0.02\ CH_2Cl_2$: C, 73.85; H, 5.86; N; 14.34. Found: C, 73.60; H, 5.80; N, 14.04.

4.1.10. (*R,S*)-*N*-Benzyl 2-amino-2-(naphthalen-2-yl)acetamide hydrochloride (18·HCl)

A solution of (*R,S*)-*N*-benzyl 2-*N*-(*t*-butoxycarbonyl)amino-2-(naphthalene-2-yl)acetamide (**65**) (2.79 g, 7.15 mmol) was dissolved in a 1 M HCl in Et_2O solution (174 mL) and stirred at room temperature (20 h). The reaction mixture was filtered and the precipitate washed with dry Et_2O to give the desired product (2.18 g, 93%) as a white solid. Mp 214–216 °C. IR (nujol) 3391, 3274, 1689, 1593, 1526, 1458, 1374, 1247, 742 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.28–4.40 (m, 2H), 5.21 (s, 1H), 7.16–7.26 (m, 5H), 7.58–7.71 (m, 3H), 7.91–8.09 (m, 4H), 8.65–9.01 (br s, 3H), 9.23 (t, J = 5.9 Hz, 1H). HRMS (ESI) 291.1496 [M+H$^+$] (calcd for $C_{19}H_{18}N_2OH^+$ 291.1497). Anal. Calcd for $C_{19}H_{19}ClN_2O{\cdot}0.15\ H_2O$: C, 69.15; H, 5.91; Cl, 10.74; N, 8.49. Found: C, 68.78; H, 5.87; Cl, 10.65; N, 8.57.

4.1.11. (*R,S*)-*N*-Benzyl 2-amino-2-(quinolin-2-yl)acetamide (19)

Employing the procedure for **17** and using (*R,S*)-*N*-benzyl 2-(hydroxyimino)-2-(quinolin-2-yl)acetamide (**40**) (0.95 g, 3.11 mmol), MeOH (70 mL), $HC(O)ONH_4$ (0.61 g, 9.34 mmol, 3 equiv) and Zn dust (0.59 g, 9.34 mmol)[37] gave the crude product that was purified by flash column chromatography (4:96 MeOH/$CHCl_3$) to give the desired product (0.56 g, 62%) as a red flocculent solid. R_f 0.57 (0.1:0.8:9.1 Et_3N/MeOH/$CHCl_3$). HRMS (ESI) 292.1451 [M+H$^+$] (calcd for $C_{18}H_{17}N_3OH^+$ 292.1450).

4.1.12. (*R,S*)-*N*-Benzyl 2-amino-2-(quinolin-2-yl)acetamide maleate salt (19·maleic acid)

To a solution of **19** (0.62 g, 2.13 mmol) in THF (20 mL) was added a solution of maleic acid (0.62 g, 5.32 mmol) in Et_2O

(50 mL). The reaction was allowed to stand overnight at room temperature and then the precipitated solid was filtered and washed with Et_2O (3 × 20 mL) to give the desired product (0.62 g) as a pale orange solid. The solid was further recrystallized from a mixture of THF and ether to give the desired product (0.38 g, 44%) as a pale orange solid. Mp 162–163 °C. IR (nujol) 3413, 1672, 1554, 1497, 1372, 1186, 1065, 863, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.36-4.38 (m, 2H), 5.34–5.36 (1H), 6.03–6.05 (m, 2H), 7.23–7.32 (m, 5H), 7.68–7.90 (m, 3H), 8.05–8.10 (m, 2H), 8.54 (d, J = 8.4 Hz, 1H), 8.56–9.20 (br s, 3H), 9.26–9.28 (m, 1H). HRMS (ESI) 292.1451 [M+H$^+$] (calcd for $C_{18}H_{17}N_3OH^+$ 292.1450). Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.88; H, 5.15; N, 10.34.

4.1.13. (*R,S*)-*N*-Benzyl 2-amino-2-(quinoxalin-2-yl)acetamide (20)

Method A: To a suspension of (*R,S*)-*N*-benzyl 2-(hydroxyimino)-2-(quinoxalin-2-yl)acetamide (**41**) (0.30 g, 0.98 mmol) in 88% HCO_2H (2.30 mL), H_2O (0.8 mL) and MeOH (4 mL) was added Zn dust (0.16 g, 2.45 mmol)[38,39] portion wise and the mixture stirred at room temperature (18 h). The mixture was filtered through Celite® and basified with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL) and the CH_2Cl_2 layer washed with saturated aqueous brine solution (2 × 40 mL). The crude product was purified by flash column chromatography (SiO_2; 1:20 MeOH/CH_2Cl_2) to give the desired product (0.14 g, 73%) as a brown solid with small amounts of impurities: R_f 0.50 (1:10 MeOH/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.25–2.50 (br s, 2H), 4.34–4.55 (m, 2H), 4.94 (s, 1H), 7.23–7.34 (m, 5H), 7.73–7.79 (m, 2H), 8.03–8.37 (3H), 9.27 (s, 1H).

Method B: To a suspension of (*R,S*)-**41** (0.07 g, 0.23 mmol) and $HC(O)ONH_4$ (0.4 g, 0.69 mmol) in MeOH (3 mL) was added Zn dust (0.04 g, 0.69 mmol)[37] and the reaction heated to reflux (4 h). The reaction mixture was filtered through Celite® and MeOH removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic layer washed with H_2O (2 × 50 mL) and saturated aqueous brine solution (2 × 50 mL). The crude product was purified by flash column chromatography (SiO_2; 1:20 MeOH/CH_2Cl_2) to give the desired product (0.02 g, 30%) as a brown solid along with small amounts of impurities. R_f 0.50 (1:10 MeOH/$CHCl_3$). IR (nujol) 3303, 3132, 3055, 1663, 1520, 1459, 1376, 909, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.10–2.60 (br s, 2H), 4.34–4.55 (m, 2H), 4.94 (s, 1H), 7.19–7.34 (m, 5H), 7.73–7.79 (m, 2H), 8.03–8.35 (3H), 9.27 (s, 1H). HRMS (ESI) 293.1399 [M+H$^+$] (calcd for $C_{17}H_{16}N_4OH^+$ 293.1402), 315.1221 [M+Na$^+$] (calcd for $C_{17}H_{16}N_4ONa^+$ 315.1222).

4.1.14. (*R,S*)-*N*-Benzyl 2-amino-2-(quinoxalin-2-yl)acetamide oxalate salt (20·oxalic acid)

To a solution of (*R,S*)-**20** (0.49 g, 1.68 mmol) in CH_2Cl_2 (10 mL) was added a solution of oxalic acid (0.45 g, 5.03 mmol) in Et_2O (40 mL) and allowed to stand at room temperature (2 h) leading to the precipitation of an off white solid. The solid was filtered and washed with a 1:4 mixture of CH_2Cl_2 and Et_2O (30 mL). The solid was dissolved in MeOH (20 mL) and reprecipitated with Et_2O to give the desired product (0.51 g, 80%) as an off white solid. Mp 172–173 °C (became dark red on melting). IR (nujol) 3420, 3221, 1851, 1691, 1601, 1549, 1458, 1375, 1185, 977, 773, 703 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.35 (d, J = 6.0 Hz, 2H), 5.46 (s, 1H), 7.25–7.30 (m, 5H), 7.91–7.98 (m, 2H), 8.11–8.18 (m, 2H), 8.18–9.05 (br s, 3H), 9.20 (s, 1H), 9.30–9.50 (m, 1H). HRMS (ESI) 293.1391 [M+H]$^+$ (calcd for $C_{17}H_{16}N_4OH^+$ 293.1402). Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.48; H, 4.75; N, 14.66.

4.1.15. (*R,S*)-*N*-Benzyl 2-amino-2-(furan-2-yl)acetamide (21)

(*R,S*)-*N*-Benzyl *N*′-(benzyloxycarbonylamino)-2-(2-furanyl)acetamide (**92**) (1.35 g, 3.73 mmol) was added to EtOH (30 mL) followed by addition of 5% Pd–C (67.5 mg). The system was evacuated, purged with H_2, and stirred at room temperature (4 h). The reaction was filtered through Celite® and evaporated in vacuo. The crude mixture was purified by flash column chromatography (SiO_2; 3:97 MeOH/CH_2Cl_2) to give the desired product (853 mg, 83%) as a light yellow oil. R_f 0.41 (1:20 MeOH/CH_2Cl_2). IR (nujol) 3448, 3211, 3061, 2925, 1665, 1526, 1453, 1360, 1248, 1149, 1073, 1011, 917, 809 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.89 (s, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.61 (s, 1H), 6.26–6.34 (m, 2H), 7.26–7.36 (m, 6H), 7.40–7.57 (br s, 1H). HRMS (ESI) 253.0953 [M+Na$^+$] (calcd for $C_{13}H_{14}N_2O_2Na^+$ 253.0953). Anal. Calcd for $C_{13}H_{14}N_2O_2$: 0.04CH_2Cl_2: C, 67.00; H, 6.07; N, 11.98. Found: C, 67.03; H, 6.22; N, 11.94.

4.1.16. (*R,S*)-*N*-Benzyl 2-(furan-2-yl)acetamide-2-ammonium chloride (21·HCl)

A 1.0 M HCl/Et_2O solution (3.48 mL, 3.48 mmol) was added dropwise to an Et_2O solution (3.5 mL) of (*R,S*)-**21** (801 mg, 3.48 mmol). The reaction was stirred (5 min) at room temperature and then the solid was filtered and washed with Et_2O (2 × 10 mL) to give the desired product (928 mg, 100%) as a hygroscopic white solid. IR (nujol) 3474, 3033, 1679, 1558, 1464, 1371, 1250, 1148, 1066, 1012, 925, 816, 741 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.34 (d, J = 6.0 Hz, 2H), 5.04 (s, 1H), 6.52 (s, 2H), 7.21–7.34 (m, 5H), 7.76 (s, 1H), 7.80–7.98 (br s, 3H), 8.92–9.01 (br t, 1H). HRMS (ESI) 231.1132 [M+H$^+$] (calcd for $C_{13}H_{14}N_2O_2H^+$ 231.1134).

4.1.17. (*R,S*)-*N*-Benzyl 2-amino-2-(5-methylfuran-2-yl)acetamide (22)

(*R,S*)-*N*-Benzyl *N*′-(benzyloxycarbonylamino)-2-(5-methylfuran-2-yl)acetamide (**93**) (48.9 mg, 0.129 mmol) was added to EtOH (2 mL) followed by addition of 10% Pd–C (4.9 mg). The reaction was evacuated, purged with H_2, and stirred at room temperature (2 h). The crude mixture was filtered through Celite®, concentrated in vacuo, and purified by flash column chromatography (SiO_2; 3:97 MeOH/CH_2Cl_2) to give the desired product (21 mg, 66%) as a clear oil. R_f 0.19 (3:97 CH_2Cl_2/hexanes). IR (nujol) 3307, 2922, 1665, 1523, 1450, 1221, 1080, 1021, 958, 788, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.80–1.90 (br s, 2H), 2.26 (s, 3H), 4.48 (d, J = 5.7 Hz, 2H), 4.56 (s, 1H), 5.89–5.91 (br s, 1H), 6.15–6.20 (br s, 1H), 7.26–7.36 (m, 6H). HRMS (ESI) 267.1110 [M+Na$^+$] (calcd for $C_{14}H_{16}N_2O_2Na^+$ 267.1109). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.03; H, 6.67; N, 11.47.

4.1.18. (*R,S*)-*N*-Benzyl 2-amino-2-(benzofuran-2-yl)acetamide (23)

(*R,S*)-*N*-Benzyl *N*′-(benzyloxycarbonylamino)-2-(benzofuran-2-yl)acetamide (**94**) (50 mg, 0.121 mmol) was added to EtOH (2 mL) followed by addition of 10% Pd–C (5.0 mg). The reaction was evacuated, purged with H_2, and stirred at room temperature (4 h). The crude mixture was filtered through Celite®, concentrated in vacuo, and purified by flash column chromatography (SiO_2; 3:100 MeOH/CH_2Cl_2) to give the desired product (20 mg, 58%) as a white solid. Mp 74–75 °C. R_f 0.16 (3:97 MeOH/CH_2Cl_2). IR (nujol) 3058, 2924, 1666, 1522, 1453, 1250, 1173, 943, 810, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82–2.02 (br s, 2H), 4.49 (d, J = 6.0 Hz, 2H), 4.72 (s, 1H), 6.70 (s, 1H), 7.18–7.60 (m, 10H). HRMS (ESI) 281.1291 [M+H$^+$] (calcd for $C_{17}H_{16}N_2O_2H^+$ 281.1290). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.75; N, 9.90.

4.1.19. (*R,S*)-*N*-Benzyl 2-amino-2-(thiophen-2-yl)acetamide (24)

(*R,S*)-*N*-Benzyl *N*′-(benzyloxycarbonylamino)-2-(thiophen-2-yl)acetamide (**95**) (200 mg, 0.526 mmol) was added to concentrated HCl (3 mL) and then heated between 60–70 °C (6 h). The reaction solution was cooled to room temperature, basified to pH ~10 with aqueous 50% NaOH, and extracted with CH_2Cl_2

(3 × 25 mL). The organic layers were combined and dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (SiO_2; 3:97 MeOH/CH_2Cl_2) to give the desired product (67 mg, 52%) as a light yellow oil. R_f 0.21 (3:97 MeOH/ CH_2Cl_2). IR (nujol) 3296, 3067, 2922, 2864, 1662, 1524, 1450, 1360, 1244, 1079, 1029, 908, 847, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.93 (s, 2H), 4.30–4.46 (m, 2H), 4.80 (s, 1H), 6.29–6.96 (m, 1H), 7.05 (d, J = 3.6 Hz, 1H), 7.19–7.37 (m, 6H), 7.23–7.51 (br s, 1H). HRMS (ESI) 269.0726 [M+Na^+] (calcd for $C_{13}H_{14}N_2OSNa^+$ 269.0725).

4.1.20. (*R,S*)-*N*-Benzyl 2-amino-2-(thiophen-2-yl)acetamide hydrochloride (24·HCl)

HCl in Et_2O (0.60 mL, 0.0603 mmol) was cooled to 0 °C followed by drop wise addition of (*R,S*)-**24** (135 mg, 0.0548 mmol). The mixture was warmed to room temperature, stirred for 20 min, and then filtered. The solid was washed with anhydrous Et_2O (2 × 10 mL) and dried in vacuo to give the desired product (110 mg, 71%) as a light yellow solid. IR (nujol) 3208, 3059, 2904, 1678, 1563, 1460, 1373, 1250, 1112, 1032, 852, 708, 609, 502 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.33 (d, J = 5.7 Hz, 2H), 5.38 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.23–7.32 (m, 6H), 7.62 (dd, J = 3.6, 3.6 Hz, 1H), 8.67–9.01 (br s, 3H), 9.32 (t, J = 5.7 Hz, 1H). HRMS (ESI) 269.0726 [M+Na^+] (calcd for $C_{13}H_{14}N_2OSNa^+$ 269.0725). Anal. Calcd for $C_{13}H_{14}ClN_2OS$: 0.08H_2O: C, 54.73; H, 5.33; Cl, 12.43; N, 9.82; S, 11.24. Found: C, 54.77; H, 5.48; Cl, 12.37; N, 9.52; S, 11.04.

4.1.21. (*R,S*)-*N*-Benzyl 2-amino-2-(thiazol-2-yl)acetamide (25)

(*R,S*)-*N*-Benzyl *N*′-(benzyloxycarbonylamino)-2-(thiazol-2-yl) acetamide (**102**) (183 mg, 0.480 mmol) was added to concentrated aqueous HCl (3 mL) and heated between 65–70 °C (6.5 h). The reaction mixture was cooled to room temperature, basified to pH ~10 with aqueous 50% NaOH, and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were concentrated in vacuo and purified by flash column chromatography (SiO_2; 3:97 MeOH/CH_2Cl_2) to give the desired product (73 mg, 62%) as a light yellow solid. Mp 83–84 °C. R_f 0.18 (3:97 MeOH/CH_2Cl_2). IR (nujol) 3468, 3157, 2957, 1652, 1563, 1456, 1374, 1311, 1237, 1182, 1092, 938, 703 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.67 (s, 2H), 4.30–4.46 (m, 2H), 4.76 (s, 1H), 7.21–7.32 (m, 5H), 7.62 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 8.73–8.77 (br t, 1H). HRMS (ESI) 270.0678 [M+Na^+] (calcd for $C_{12}H_{13}N_3OSNa^+$ 270.0677). Anal. Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 58.43; H, 5.29; N, 16.77; S, 12.92.

4.1.22. (*R,S*)-*N*-Benzyl 2-amino-2-(benzo[b]thiophen-2-yl)acetamide (26)

(*R,S*)-*N*-Benzyl 2-(benzo[b]thiophen-2-yl)-2-(hydroxyimino) acetamide (**70**) (206 mg, 0.664 mmol) was added to MeOH (3 mL) followed by the addition of Zn dust (174 mg, 2.66 mmol) and $HC(O)ONH_4$ (167 mg, 2.65 mmol). The mixture was heated at 70 °C (2–3 h). The reaction mixture was filtered hot and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2; 3:97 MeOH/CH_2Cl_2) to give the desired product (100 mg, 51%) as a white solid. Mp 100–101 °C. R_f 0.29 (3:97 MeOH/CH_2Cl_2). IR (nujol) 3188, 2954, 2842, 1654, 1523, 1373, 1299, 1229, 1073, 939, 824, 738, 591 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.49 (s, 2H), 4.36 (d, J = 6.0 Hz, 2H), 4.76 (s, 1H), 7.22–7.36 (m, 8H), 7.73 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 8.63–8.79 (br t, 1H). HRMS (ESI) 297.1062 [M+H^+] (calcd for $C_{17}H_{17}N_2OS^+$ 297.1062). Anal. Calcd for $C_{17}H_{16}N_2OS$: 0.06H_2O: C, 68.40; H, 5.42; N, 9.38; S, 10.74. Found: C, 68.42; H, 5.44; N, 9.34; S, 10.69.

4.2. Pharmacological evaluation

Compounds were screened under the auspices of UCB Pharma (Braine L'Alleud, Belgium). Housing, handling, and feeding were in full accordance with recommendations contained in the Guide for the Care and Use of Laboratory Animals.[59] Pharmacological evaluation by UCB Pharma consisted of four assays using male NMRI mice (ip): the MES test[54] and the 6 Hz test[55] to assess anticonvulsant activity, the formalin test[35] to assess neuropathic pain attenuation, and the rotorod test[57] to assess neurological toxicity.

The compounds were administered ip. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration. In cases where the ED_{50} could not be determined, the lowest dose that elicited activity (minimally active dose) or the percent reduction in activity from a single dose was given (see Tables 1 and 2 for doses employed).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.04.002.

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