2-Substituted-2-acetamido-N-benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties

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A Thesis

Presented to

the Faculty of the Department of Chemistry

University of Houston-University Park

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

By

Philippe Le Gall

December, 1987

2-Substituted-2-acetamido-N-benzylacetamides.
Synthesis, Spectroscopic and Anticonvulsant Properties

Philippe Le Gall

APPROVED:

Dr. Harold L. Kohn

Dr. Douglas F. Dyckes

Dr. Thomas L. Lemke

Dr. Bernard M. Pettitt

Dr. Joseph P. Street

Roy Weinstein

Dean, College of Natural Sciences and Mathematics

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ABSTRACT

Select functionalized amino acid derivatives of the potent anticonvulsant agent α-acetamido-N-benzylphenylacetamide (68b) and 2-acetamido-N-benzylpropionamide (68a) have been prepared and evaluated. Attention has been focused on the replacement of the α-phenyl and α-methyl groups in 68a and 68b by five-membered ring hetereoaromatic moieties, benzo-fused heteroaromatic groups, and simple polar substituents.

The synthetic and pharmacological studies revealed several notable findings. First, the use of amidoalkylation procedures using boron trifluoride etherate provided a straightforward and reliable method to introduce an electron-rich heteroaromatic substituent at the α-carbon in the amino acid derivatives. This technology permitted the incorporation of acid sensitive, unsubstituted heteroaromatic compounds (i.e., pyrrole (74), indole (72) and benzofuran (75)) within the molecule. Second, all the five-membered ring heteroaromatic analogues of α-acetamido-N-benzylphenylacetamide proved highly active in the MES seizure test. In particular, α-acetamido-N-benzyl-2-furanacetamide (69a) and α-acetamido-N-benzyl-2-pyrroleacetamide (69b) exhibited activities similar to phenytoin and diazepam. Third, the α-alkoxy derivatives, 2-acetamido-N-benzyl-2-methoxyacetamide (86a) and 2-acetamido-N-benzyl-2-ethoxyacetamide, exhibited significant activity in the MES seizure test.

Fourth, neither the benzo-fused heteroaromatic derivatives nor the compounds bearing an electron-withdrawing substituent at the α-carbon had significant activity. Fifth, the composite pharmacological data suggested that small substituents are required at the α-carbon of the 2-acetamido-N-benzylglycine derivative for maximal activity in the MES test and that this activity is enhanced by the presence of electron-donating groups at this site.

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INTRODUCTION

Epilepsy is a major neurological disorder. It affects at least 0.5 percent of the world population[1,2] and its symptoms generally appear early in life.[1,3] If the origin of the disease is unknown, it is termed idiopathic. Correspondingly, when the epilepsy is of a known origin, the disease is referred to as symptomatic.[3] In the latter situation, prenatal and postnatal trauma, brain tumor, and vascular disorders are the major etiologies associated with the disease.[1,3] The occurrence of seizures is the manisfestation of epilepsy. Seizures may be of different types and may have sensory, motor and autonomic components.

Historically, epilepsy has been referred to as the "dread disease", the "Sacred Disease", the "falling sickness" or "St. John's disease". It was mentioned in the babylonian civil code of Hammurabi (2080 B.C.) and early akkadian and hebrew texts. Hippocrates (ca. 400 B.C.) wrote the first monograph on the affliction and first anticipated its brain origin.[3,4]

Despite the early recognition of this disease, significant activity directed towards the treatment and the understanding of epilepsies began in earnest in the mid-nineteenth century.[1,3,5] In 1870, H.J. Jackson described epilepsy as "an occasional and abnormally intense disorderly discharge of nervous tissue" of which the seizures are the symptom.[3] This statement is still accepted today. Our knowledge of the brain malfunction has not permitted a more detailed definition. It is generally accepted that epilepsy is reserved for those diseases

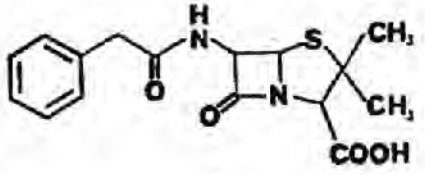
manisfesting themselves by a chronic occurrence of seizures. Accordingly, seizures elicited by punctual factors, such as alcohol and drug intoxication or withdrawal are not considered to be a form of this disease.

I. Biogenesis of the Epileptic Seizures.

Although the neurophysiology of the central nervous system and the biochemical processes associated with neuronal activity are now fairly well established[6-8], the key events leading to epileptic activity have not been determined. It was early recognized that epilepsy may affect only a part of the brain at the onset. Subsequently, the existence of epileptic foci were revealed.[7] In 1975, Ebersole and Levine[9] demonstrated that Enhanced Physiological Response (EPR) of neurons submitted to an epileptogenic application of penicillin (1) could lead to Paroxysmal Depolarization Shifts (PDS). The PDSs are characterized by abnormally large, prolonged and repetitive excitatory post-synaptic potential and are believed to participate in the spread of electrical discharge during the seizure.[10,11] The origins of EPRs are considered the key step in the epileptogenesis.[10]

These observations have led to a six stage model for the generation of epileptic seizures: (a) the initiation of the EPR; (b) the generation of PDSs; (c) the recruitment of normal neurons; (d) the intervention of control mechanisms that limit the spread of the epileptic discharges or promote selective routes of spread; (e) the establishment

of satellite and independent epileptic foci; and (f) the engagement of the brain stem and of the spinal motor neuron pools.[10]



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Both the generation of the EPR and the recruitment of normal neurons in the epileptic seizure have been extensively examined. The EPR has sometimes been related to local deterioration of neurons by extraneuronal factors. In 1880, Sommer observed an extensive loss of neural mass in the hippocampal area of one third of the epileptic patients examined. Shortly after, Alzheimer and Chaslin independently reported an associated abnormal proliferation of glial cells in the same area.[7] Gliosis has been related to seizures in three ways. First, this process may be a biological response to a decrease in neural matter.[7] Second, abnormal proliferation of glial cells may mechanically irritate the neurons and initiate the EPR-mediated processes[7]. Third, glial cells are known to participate in the regulation of the potassium ion concentration in the brain and in the metabolism of γ - amino

butyric acid (2). These substances may influence the seizure processes.[10] Finally, De Moor and Westrum noticed dendritic alterations adjacent to epileptic foci in human cortices and experimentally generated epileptic centers, respectively.[7,12]

2

Other factors which may be responsible for the generation of the EPR are associated with the blood-brain barrier. Scheibel[7] observed that neurons in epileptic foci were often altered in regions nearby damaged capillaries. He attributed the generation of epileptic neurons to exogenic factors such as viruses and toxins.

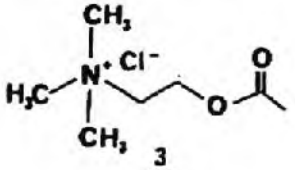
Despite these important initiation processes, the majority of researchers consider metabolic disorders existent in the epileptic patient to be the primary cause of the disease.[3,10] Most substances involved in the normal neuronal activity as well as their associated metabolic cycles have been claimed to participate in the EPR generation.[10,13] Extensive experimental evidence exists which demonstrate the involvement both of potassium ion[8,10,14-15] and the neuronal sodium-potassium pump[10] in the first step of the

seizure. Other ions (i.e., Cl^-, Ca^{++}, NH_4^+) may also be involved in abnormal membrane depolarization processes.[8] Disorders in the metabolic cycles of all the substances regulating the concentration and the transport of these ions across the membrane of the neuron, as well as structural disorders in the neuron membrane can ultimately be responsible for the EPR generation.

Several explanations have been offered for the mechanism involved in the recruitment of normal neurons in the seizure. Variations in the proteinic constitution of the synapses have been invoked to explain the propagation of the epileptic discharge by selective neuronal circuits. The same explanation has been suggested for the creation of secondary epileptic foci.[10] Extensive documentation does exist in support of various other phenomena. These include the enhancement of the excitatory neurotransmissions induced by substances such as acetylcholine (3), aspartic acid (4), glutamic acid (5) and some neuropeptides as well as the decrease in inhibitory regulation promoted by substances such as norepinephrine (6), dopamine (7), serotonin (8) and γ - aminobutyric acid (GABA) (2).[8, 17-20] Finally, transient modifications of the membrane of the normal neuron and anomalies in the dendritic and axon structures are also believed to participate in the epileptic discharge propagation.[10,19,21]

II. Symptomatology and Classification of Epileptic Seizures.

The part of the brain affected by the epileptic discharges has



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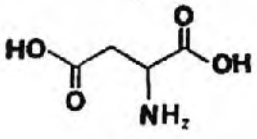

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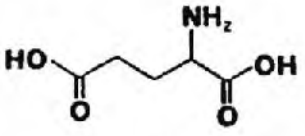

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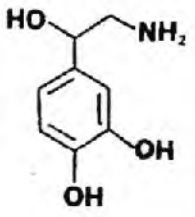

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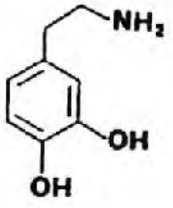

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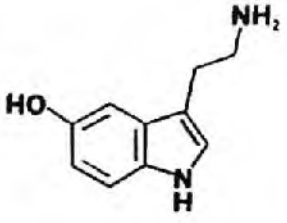

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direct bearing on the clinical manisfestation of the disease. In some cases, careful monitoring of the patient can permit the physician to follow the spread of the abnormal brain electrical activity. The observed clinical symptoms serve as a basis for the currently employed classifications of the various seizure states.

The first widely accepted classification of the epileptic seizures (Table 1) was established by the International League Against Epilepsy in 1969.[1,22] This classification attempted to correlate the symptoms and electroencephalographic (EEG) data to the anatomic substrate, the etiology, and the age of the patient. This system differentiated seizures which had a focal onset and evolved into generalized seizures, from those which are generalized from the beginning.[1] A revised classification (Table 2) appeared in 1981. This new classification was fostered by the development of better methods to analyze the seizures . (i.e., telemetered EEG, videotaping) The major changes incorporated in the new system were the exclusive use of the clinical and electroencephalographic data to determine the seizure type, and the restructuring of the partial seizures into simple partial seizures and complex partial seizures depending on whether or not consciousness is altered at the onset or in the further evolution of the seizure.[1]

Although, a clinical discussion of the various types of seizures is beyond the scope of this thesis a brief review of the major forms of the disease follows.

Table 1. The International Classification of Epileptic Seizures.[1]

I. Partial seizures (seizures beginning locally)
   A. Partial seizures with elementary symptomatology (generally without impairment of consciousness)
      1. With motor symptoms (includes Jacksonian seizures)
      2. With special sensory or somatosensory symptoms
      3. With automatic symptoms
      4. Compound forms
   B. Partial seizures with complex symptomatology (generally with impairment of consciousness) (temporal lobe or psychomotor seizures)
      1. With impairment of consciousness only
      2. With cognitive symptomatology
      3. With affective symptomatology
      4. With "psychosensory" symptomatology
      5. With "psychomotor" symptomatology (automatisms)
      6. Compound forms
   C. Partial seizures secondarily generalized

II. Generalized seizures (bilaterally symmetrical and without local onset)
   A. Absence (petit mal)
   B. Bilateral massive epileptic myoclonus
   C. Infantile spasms
   D. Clonic features
   E. Tonic features
   F. Tonic-clonic seizures (grand mal)
   G. Atonic seizures
   H. Akinetic seizures

III. Unilateral seizures (or predominately)

IV. Unclassified epileptic seizures (due to incomplete data)

Table 2. The Revised Classification of Epileptic Seizures.[1]

I. Simple partial seizures (consciousness not impaired)
   A. With motor signs
      1. Focal motor without march
      2. Focal motor with march (Jacksonian)
      3. Versive
      4. Postural
      5. Phonatory (vocalization or arrest of speech)
   B. With somatosensory or special-sensory symptoms (simple hallucinations, e.g., tingling, light flashes, buzzing)
      1. Somatosensory
      2. Visual
      3. Auditory
      4. Olfactory
      5. Gustatory
      6. Vertiginous
   C. With automatic symptoms or signs
   D. With psychic symptoms (disturbance of higher cortical function)
      1. Dysphasic
      2. Dysnesmic (e.g., deja vu)
      3. Cognitive (e.g., forced thinking)
      4. Affective (e.g., fear, anger)
      5. Illusions (e.g., macropsia)
      6. Structured hallucinations (e.g., music, scenes)

II. Complex partial seizures (generally with impairment of consciousness; may sometimes begin with simple symptomatology)
   A. Simple partial onset followed by impairment of consciousness
      1. With simple partial features (A-D) and impaired consciousness
      2. With automatisms
   B. With impairment of consciousness at onset
      1. With impairment of consciousness only
      2. With automatisms

III. Partial seizures evolving to generalized tonic-clonic (GTC) seizures (GTC with partial or focal onset)
   A. Simple partial seizures (I) evolving to GTC
   B. Complex partial seizures (II) evolving to GTC
   C. Simple partial seizures evolving to complex partial seizures evolving to GTC

Table 2 con't.

IV. Generalized seizures (bilaterally symmetrical and without local onset)
   A. Absence (petit mal)
   B. Bilateral massive epileptic myoclonus
   C. Infantile spasms
   D. Clonic features
   E. Tonic features
   F. Tonic-clonic seizures (grand mal)
   G. Atonic seizures

V. Unilateral seizures (or predominately)

VI. Unclassified epileptic seizures (due to incomplete data)

Simple partial seizures affect any part of the body depending on the origin of the discharge in the motor strip. The clinical observations are characterized by tonic contraction of the activated muscles followed by a clonus. Generally, one muscle or a group of muscles are involved in the seizure, resulting in involuntary movements, involuntary actions (i.e., vocalization) or posture change. The step by step spread of the electrical disorder from strictly focal to adjacent areas produce sequential involvement of body parts and is referred to as the epileptic march or Jacksonian seizure.[1,5] These muscular disorders find their origin in the part of the cortex responsible for motor activity. Likewise, epileptic discharges originating or spreading in the part of the cortex responsible for automatic functions result in manisfestations such as vomiting, incontinence, pupil dilatation and pallor.[1] Involvement of the cortex area subversing somatosensory and psychic functions lead to additional seizure manifestations within this general class of seizures (Table 2). In all instances, partial seizures are not associated with consciousness impairment.

Complex partial seizures are characterized by partial seizure symptoms with accompanying impairment of consciousness. This often results in automatisms (i.e., verbal, ambulatory, gestural, masticatory), and sometimes results in confusion.[1,23] This disease state is always associated with various degrees of amnesia.[5]

Generalized seizures which are non-convulsive are referred

to as absence (petit mal) seizures. Absence seizures affect children before puberty and are characterized by frequent (5 - 100 per day) attacks of impaired consciousness lasting usually less than 20 seconds. Interruption of ongoing activities, staring, occasional eyes movements, arm jerks and modification of the postural tone are manisfestations of this type of seizure. The associated EEG is characterized by a regular three per second spike and wave pattern.

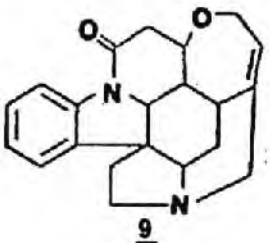
The classification of generalized seizures, involving convulsions has been subdivided according to the characteristics of the convulsive episodes. Bilateral massive epileptic myoclonus and infantile spasms (West's syndrome) are manisfested by sudden contractions of major muscle groups. The latter seizure type occur before the age of four and involves legs, arms and trunk muscles. It is often related to phenylketonuria, lipidosis and the metabolism of piridoxine. The EEG shows high voltage slow waves and spikes. Both of these seizure types involve the right and left brains.[1,5] Clonic seizures occur especially in childhood and are manisfested by a succession of shock-like spasms affecting one or both sides of the body and are associated with consciousness impairment. Tonic seizures are characterized by tonic contractions of long duration (up to one minute) of the trunkal and limbs musculatures, and are associated with autonomic activity. The EEG shows high voltage activity. Tonic-clonic seizures (grand mal) are a succession of tonic and clonic episodes with

loss of consciousness and autonomic hyperactivity. This form of epilepsy can occur in both children and adults. Grand mal is the most common type of epilepsy and the most disrupting in the life of the patient. The chronicity of the seizures varies from one or more a day to intervals of months between the seizure episodes.[1,5]

III. Evaluation of Anticonvulsant Agents.

Many procedures have been designed and evaluated for the screening of potential anticonvulsant drugs.[24] Current protocols can be divided into four general categories: (a) the employment of a chemical convulsant to induce the artifical seizures in animals; (b) the use of electrically induced seizures in animals; (c) the employment of genetically predisposed animal strains; (d) the use of nervous tissues in in vitro experiments.[17]

Many chemical convulsants have been utilized to generate artificial seizures.[17,24,25] The most widely used chemical convulsants are: strychnine (9), picrotoxin (10), bicuculline (11) and pentylenetetrazol (Metrazol) (12). All these subtances are subcutaneously injected in the test animals after the administration of the compound to be evaluated for anticonvulsant properties.[26] The augmentation of the seizure threshold reveals the anticonvulsant activity of the drug. The pentylenetetrazol (scMet) seizure threshold test[27-29] is of particular interest in the evaluation of new compounds. It is widely recognized that substances active



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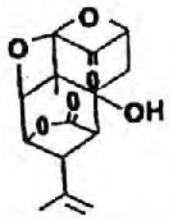

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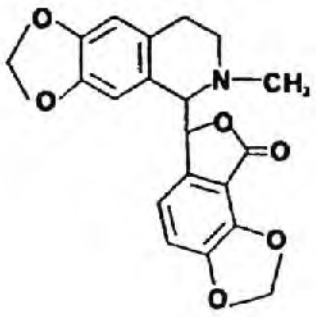

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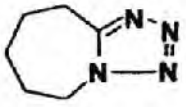

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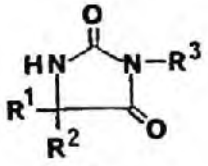

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a: R^1 = Ph, R^2 = Ph, R^3 = H

b: R^1 = Ph, R^2 = Et, R^3 = Me

c: R^1 = Ph, R^2 = H, R^3 = Et

in this test are likely to be effective in the treatment of petit mal seizures provided threshold doses of pentylenetetrazol are employed to produce clonic seizures.

The use of electrically induced seizures was introduced in the mid-1800s after the pioneering studies of Fritsch, Hitzig and Albertoni.[26] The systematic use of electrically induced seizures in cats eventually led Putnam and Merritt[30] to discover the anticonvulsant properties of 5,5-diphenylhydantoin (phenytoin, Dilantin) (13a). This medicinal agent is the most extensively used drug today for the treatment of grand mal epilepsy. Subsequently, Goodman and his colleagues standardized the technique which is now named the Maximal Electroshock Seizure (MES) test.[27-29,31] This test is believed to identify substances that will be useful in the treatment of partial and generalized tonic-clonic seizures.[3] In this technique a 60-cycle alternating current is applied for 0.1 or 0.3 seconds to mice and rats by means of corneal electrodes. Many other useful electrically induced seizure tests have also been described.[24,27-29,31,32] More recently, kindling procedures have been introduced in the hopes of identifying new drugs specific for partial seizures.[17] The kindling process refers to an experimental protocol where subthreshold stimuli are repeatedly applied to the animal until they become convulsant stimuli. This method requires the implantation of electrodes in the brain area where the epileptic discharge is to be generated.

Genetically predisposed animal strains have been employed

in the anticonvulsant testing of new substances. Among these, three species have found extensive use. They are the DBA/2 (Dilute Brown Agouti) strain of house mouse, in which seizures are elicited by audiogenic stimuli such as a door bell,[33] the Wistar strain of rat, in which seizures appear to be similar to petit mal;[34] and the baboon Papio papio, in which responses to anticonvulsant drugs are similar to that observed in human.[24,35,36] In this last strain of animal, the seizure is induced by flickering light.

Various in vitro test systems have been developed for the evaluation of anticonvulsant properties of drug candidates.[17] These procedures were originally developed to study the biogenesis of the epilepsies.[24] Hippocampal slices of rats and guinea-pigs as well as neuronal cultures have been employed in the experimental protocols. In the first case, burst firing are generated by altering the extracellular ionic concentration or by the application of convulsant agents such as bicuculline (3) or penicillin (6). In the second case, intracellular electrodes are used to deliver a current pulse that generates the epileptic activity. In these tests, the anticonvulsant properties of the substances are determined by their ability to limit the spread of the epileptic electrical phenomena to non-stimulated areas.[17]

None of the currently available test procedures independently provides a definitive method for the recognition of anticonvulsant drugs. Each procedure can give false-positive and

false-negative responses.[17,26] Meldrum has urged the use of as many tests as possible in order to increase the chance of identifying new antiepileptic drugs.[17] In addition to these protocols, the potential toxicity of new drugs must also be evaluated, and several general[36] and specific[26] tests have been described. Of these, the most common are the rotarod ataxia and the Horizontal screen (HS) tests which evaluate the neurotoxicity of test substances in mice. In the first of these tests, the ability of the animal to maintain its equilibrium on a rotating (6 rpm) knurled rod for more than one minute is determined after the intraperitoneal administration of the drug [29a]. In the horizontal screen test the animal is placed on top of a square (13 x 13 cm) wire screen mounted on a rod, and the ability of animal to return on top of the screen when the rod is rotated 180^{o} is determined.[29b]

Recently, the U.S. National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) through the Antiepileptic Drug Development Program (ADD) established a fixed sequence for the preclinical evaluation of novel anticonvulsant agents. This protocol is given in Table 3.[17]

IV. Antiepileptic Drugs.

The first two drugs widely used for the treatment of epilepsy were potassium bromide (14), introduced in 1857 by Locock, and phenobarbital (Luminal) (15a), introduced in 1912 by

Table 3. Sequential Test Phases Utilized for the Anticonvulsant Screening Project of the Antiepileptic Drug Development Program.[17]

Phase 1: Anticonvulsant indentification to determine the level of activity [active (<100 mg/kg to inactive (>300 mg/kg)] (mice, i.p.)
1. Maximal electro-shock (MES) test — seizure spread
2. Subcutaneous pentylenetetrazol (scMet) test—seizure threshold
3. Rotarod ataxia test—neurotoxicity

Phase 2: Anticonvulsant quantification to determine the level of activity at the ED_{50}, TD_{50}, and protective index (TD_{50}/ED_{50}) (mice, i.p.)
1. Maximal electro-shock (MES) test—seizure spread
2. Subcutaneous pentylenetetrazol (scMet) test—seizure threshold
3. Rotarod ataxia test—neurotoxicity

Phase 3: Toxicity profile to assess general behaviour and selected pharmacologic response at toxic doses (mice, i.p.)
1. Median lethal dose (LD_{50})
2. Median hypnotic dose (HD_{50})

Phase 4: Anticonvulsant quantification to measure activity by the usual clinical route of administration and indicate the adsorption and metabolic characteristics of the compound (mice, i.p.)
1. Maximal electro-shock (MES) test—seizure spread
2. Subcutaneous pentylenetetrazol (scMet) test—seizure threshold
3. Rotarod ataxia test—neurotoxicity

Phase 5: Antiepileptic drug differentiation and comparison with known effective drugs to help determine the mechanism of action (mice, i.p.)
1. Pentylenetetrazol seizure threshold test
2. Picrotoxin seizure threshold test
3. Bicuculline seizure threshold test
4. Strychnine seizure threshold test
5. Special in vitro receptor binding studies on selected candidate compounds

Table 3 con't.

Phase 6: Anticonvulsant quantification to measure activity in another species at the ED_{50}, TD_{50}, and protective index (TD_{50}/ED_{50}) (rats, p.o.)

1. Maximal electro-shock (MES) test—seizure spread
2. Subcutaneous pentylenetetrazol (scMet) test—seizure threshold
3. Positional sense test—neurotoxicity
4. Gait and stance test—neurotoxicity

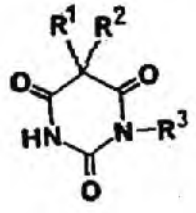
Phase 7: Estimation of minimal lethal dose (LD_3) and effect of prolonged administration on anticonvulsant activity (rats, p.o.)

1. Estimated LD_3 in male and female rats following administration once a day for 5 days
2. Administration for 5 days — tolerance
3. Hexobarbital sleep time test — tolerance
4. Microsomal enzyme studies in vitro — tolerance

Hauptmann.[4] Both agents were discovered by serependity while these drugs were being administered for sedative purposes. The bromides are now used only in intractable seizure disorders due to their low therapeutic ratios and their sedative and psychic side-effects. Phenobarbital (15a)[37] and the related barbiturates, mephobarbital (Mebaral) (15b)[26] and metharbital (Gemonil) (15c), are still currently prescribed for the treatment of epilepsy.[1,26] They all possess sedative side-effects.

It is with the pioneering studies of Putnam and Merritt in 1937 that a new era of antiepileptic research commenced.[5] Their research led to the discovery of the potent anticonvulsant properties of the hydantoins (13) and prompted an intense search for other compounds possessing different clinical properties. Most compounds subsequently evaluated during this period of time contained a 5- or 6-membered ring with an embedded amide and/or carbamide (CO-NH-CO) function. Among these were the succinimides (16),[38] the oxazolidinediones (17),[39-41] and the glutarimides (18).[5] Likewise, two other compounds introduced were structurally related. Phenacemide (19)[1] possessed a linear ureide structural unit, while primidone (20)[42,43] was a deoxybarbiturate analogue of phenobarbital (15a). The only three substances discovered that were not related to this general pattern were acetazolamide (21),[1,26] methazolamide (22),[26] and benzchlorpropamide (23)[5].

The inability to find new classes of antiepileptic drugs as

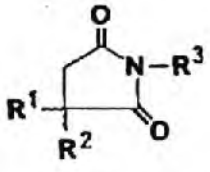


15

a: R^1 = Ph, R^2 = Et, R^3 = H

b: R^1 = Ph, R^2 = Et, R^3 = Me

c: R^1 = Et, R^2 = Et, R^3 = Me

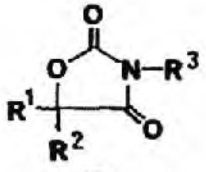


16

a: R^1 = Ph, R^2 = H, R^3 = Me

b: R^1 = Ph, R^2 = Me, R^3 = Me

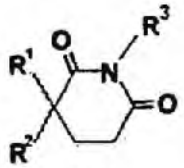
c: R^1 = Et, R^2 = Me, R^3 = H



17

a: R^1 = Me, R^2 = Me, R^3 = Me

b: R^1 = Me, R^2 = Et, R^3 = Me



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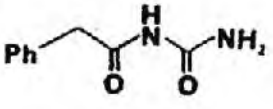

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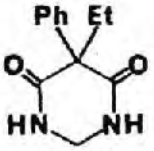

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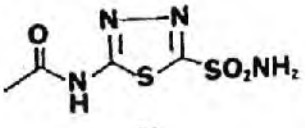

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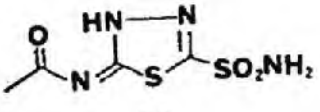

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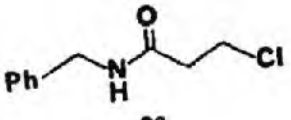
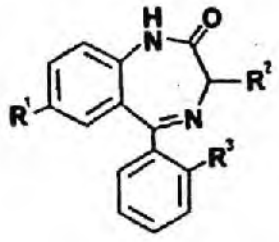


23

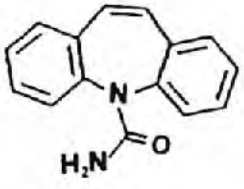
well as the need for new drugs for the treatment of intractable seizures led the National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) to create the Epilepsy Branch and the Epilepsy Advisory Committee in 1965.[44] These programs helped support controlled clinical trials of drugs that needed proof of efficacy for marketing approval and facilitated the screening of many potentially new anticonvulsant agents. Subsequently, three new drugs were introduced. All three possessed novel structures. They were clonazepam (24a),[45] carbamazepine (25)[46] and valproic acid (26)[47].

In 1975, a second program, the Anticonvulsant Screening Project (ASP), was established to help foster the search in the identification of new classes of antiepileptic agents.[5,26] Since then, thousands of compounds have been submitted for testing and many new structures have been shown to have anticonvulsant activity in the animal studies. Several of them are currently being evaluated in man.[17] Two of these compounds contain an imidazole group. They are denzimol (27)[48] and nafimidone (28)[49]. A number of other substances of current clinical interest are related to γ-aminobutyric acid (GABA) (2) and glycine (29a). Among these are 2-amino-7-phosphonoheptanoic acid (30)[50], γ-vinylGABA (vigitabrin) (31),[51] 1-(aminomethyl)cyclohexaneacetic acid (gabapentin) (32),[17] and 2-n-pentylaminoacetamide (milacetamide) (33)[17]. Additional active compounds discovered in recent years include the carbethoxyaminobenzylaminopyridine maleate (flurpirtine maleate)



24

a: $R^1=NO_2$, $R^2=H$, $R^3=Cl$
b: $R^1=Cl$, $R^2=COO^-K^+.KOH$, $R^3=H$
c: $R^1=Cl$, $R^2=R^3=H$



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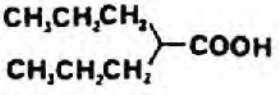

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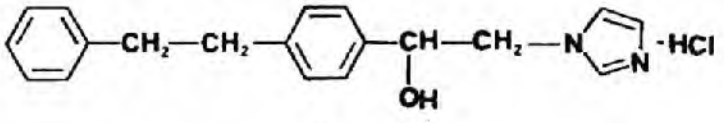

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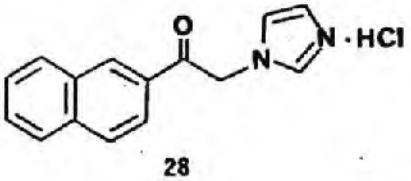
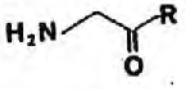


28

(34)[17], the phenyltriazene derivative 35 (lamotrigine),[17] the aminobenzobicyclononene adduct 36,[17] the benzisoxazole derivative 37 (zonisamide),[52-54] pyrazoloquinoline 38,[55] the two β - carbolines 39a and 39b,[56-58] thiazolidinone 40 (ralitoline),[17] two piperiodo-pyridazine derivatives 41a and 41b,[59] piperazine derivative 42 (flunarizine),[60] fructofuranose sulfamate 43,[61] azetidine carboxamide 44,[61] and the dicarbamate derivative 45 (felbamate)[17].

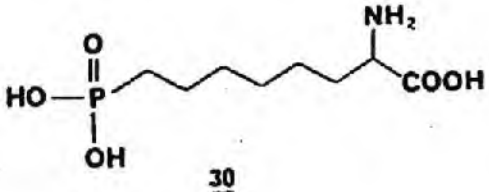
v. Clinical Applications.

Eighteen drugs are currently employed for the treatment of epilepsy. These are listed in Table 4 in the order of their introduction for clinical use in the United States. Historically, the practical use of antiepileptic drugs has often been related to the pharmacological profile observed in animal tests. For example, phenytoin (13a) and phenobarbital (15a) are both active in the MES seizure test and are employed for the control of generalized tonic-clonic seizures (grand mal). Significantly, these drugs are not active against absence seizures, and in fact have been observed to induce them. Correspondingly, the oxazolidinediones (i.e., trimethadione (Tridione) (17a), paramethadione (Paradione) (17b))[41] increase the seizure threshold in the scMet test and are currently used for the treatment of absence seizures. These agents are not active in MES seizure test and have not found clincial use in the treatment of tonic-clonic seizures.[3]
Some medicinal agents are active in both the MES and the



29

a: R = OH
b: R = NH_2



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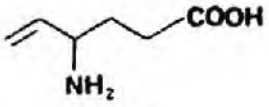

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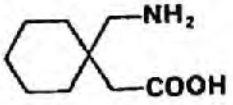

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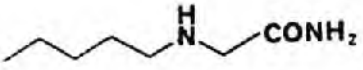

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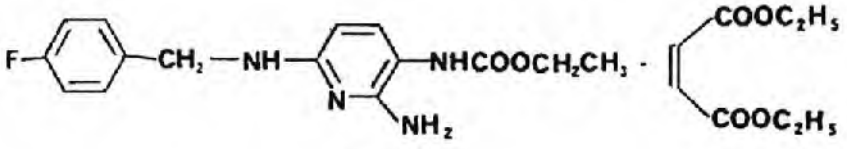

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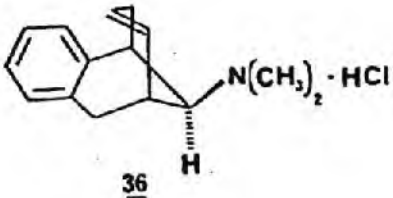

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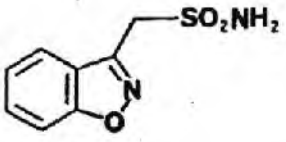

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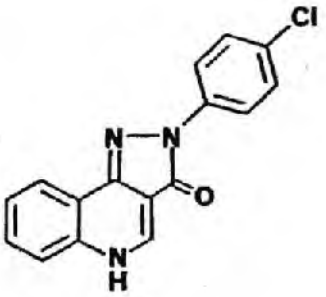

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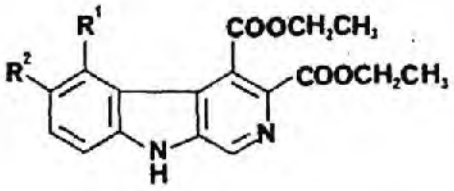

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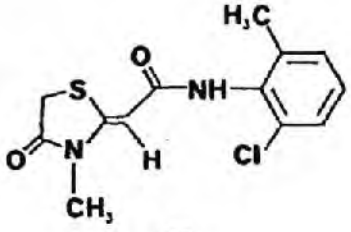
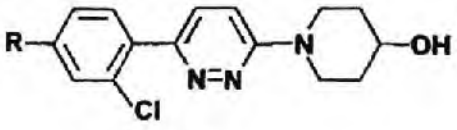


40

a: $R^1 = OCH_2Ph$, $R^2 = H$

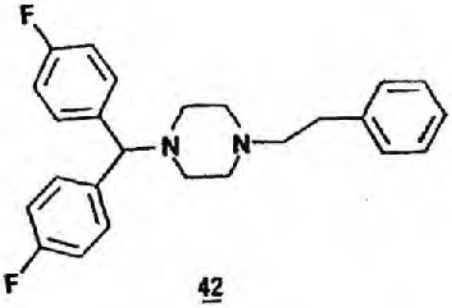
b: $R^1 = H$, $R^2 = OCH_2Ph$



41

a: R = H

b: R = Cl



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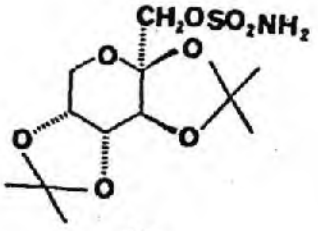

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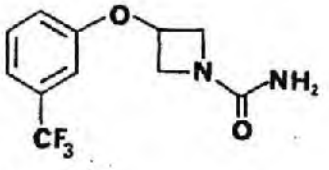

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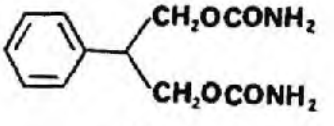

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Table 4. Antiepileptic Drugs Marketed in the United States.[1]

Year Introduced	International Nonproprietary Name	U.S. Trade Name	Company
1912	Phenobarbital	Luminal	Winthrop
1935	Mephobarbital	Mebaral	Winthrop
1938	Phenytoin	Dilantin	Parke-Davis
1946	Trimethadione	Tridione	Abbott
1947	Mephenytoin	Mesantoin	Sandoz
1949	Paramethadione	Paradione	Abbott
1950	Phethenylate[a]	Thiantoin	Lilly
1951	Phenacemide	Phenurone	Abbott
1952	Metharbital	Gemonil	Abbott
1952	Benzchlorpropamide[b]	Hibicon	Lederle
1953	Phensuximide	Milontin	Parke-Davis
1954	Primidone	Mysoline	Ayerst
1957	Methsuximide	Celontin	Parke-Davis
1957	Ethotoin	Peganone	Abbott
1960	Aminoglutethimide[c]	Elipten	Ciba
1960	Ethosuximide	Zarontin	Parke-Davis
1968	Diazepam[d]	Valium	Roche
1974	Carbamazepine	Tegretol	Geigy
1975	Clonazepam	Clonopin	Roche
1978	Valproic acid	Depakene	Abbott
1981	Clorazepate dipotassium[d]	Tranxene	Abbott

[a]Withdrawn in 1952.
[b]Withdrawn in 1955.
[c]Withdrawn in 1966.
[d]Approved by the FDA as an adjunct.

scMET seizure tests. In these cases, the broad activity scope observed in the animal tests may not necessarily correspond to their clinical use. For example, the barbiturates (15), carbamazepine (25) and methotoin (13c) which increase the seizure threshold in both tests but are not used for the treatment of absence seizures.[1,5,26] On the other hand, methsuximide (16b), the benzodiazepines (i.e., clonazepam (Clonopin) (24a), chlorazepate dipotassium (Tranxene) (24b), diazepam (Valium) (24c)) and valproic acid (Depakene) (26) are employed for a wide-range of epilepsies.[1,5,26] However, due to their strong hypnotic effects both diazepam (24c) and chlorazepate dipotassium (24b) are only authorized as adjuncts. Several drugs in Table 4 are usually reserved for the treatment of refractory forms of epilepsies. Among these are phenacemide (Phenurone) (19), primidone (Mysoline) (20), acetazolamide (Diamox) (21) and the bromides (14).

Most of the commercial drugs possess serious side effects.[1,3,26] Valproic acid (26) is the only substance with negligible toxicity.[26] This factor coupled with the wide array of seizure types has contributed to the current statistic that only fifty percent of all epileptic patients are satisfactorily treated.[26]

VI. Mechanism of Drug Action.

Any complete description of the mechanism of action of an antiepileptic drug requires a full understanding of the physiopathological mechanisms of epilepsy and how the drug prevents the

seizure. Since the physiopathological mechanism of epilepsy is poorly understood, any mechanism of drug action is speculative.[26]

A drug can produce an anticonvulsant effect by two general mechanisms: direct modification of the neuron membrane function and/or direct or indirect alteration of chemically-induced neurotransmission.[26]

Direct modification of the neuron membrane can be specific or non-specific. Specific action at the receptor sites or on adenosine triphosphatase can affect the sodium-potassium pump so as to enhance the ionic conductance in chloride or potassium ions, or decrease the calcium ion conductance. All these actions ultimately decrease the spread of electrical stimuli in the neuron. Non-specific interaction with the membrane results in disruption of the ionic channels and can have the same consequences. The anticonvulsant activities of the hydantoins (13), carbamazepine (25), primidone (20), trimethadione (17a) and the succinimides (16) are all believed to be derived in part from their involvement in one of these processes.[26]

Modification of the neurotransmission involves direct interaction at the receptor sites of the neurotransmitters or interaction with the metabolism of the neurotransmitters, and can have two types of consequences. First, the excitatory neurotransmission can be dimished. The modes of action of phenytoin (13a) and valproic acid (26) are believed to be involved in this process.[62] Second, the effect of the inhibitory neurotransmission can be en-

hanced. In this general type of mechanism considerable attention has been focused on the action of drugs on the GABAergic system.[73] The seizure activity in animals has been shown to be directly proportional to the brain concentration of GABA, and the administration of valproic acid (26) was reported to increase this concentration by as much as sixty percent.[63] This last compound is believed to act by inhibition of GABA transaminase and succinic aldehyde dehydrogenase. These two enzymes are involved in GABA metabolism.[62] Other proven anticonvulsant agents (i.e., benzodiazepines (24),[65] phenobarbital (15a),[64] ethosuximide (16c)[74]) are believed to interact with specific receptors which elicit inhibitory neurotransmission. Several drug candidates now in clinical trials have also been observed to interact with this system. These include the β-carboline derivatives 39a and 39b and the GABA derivatives 30 and 31.[17]

VII. Structure-activity Relationships.

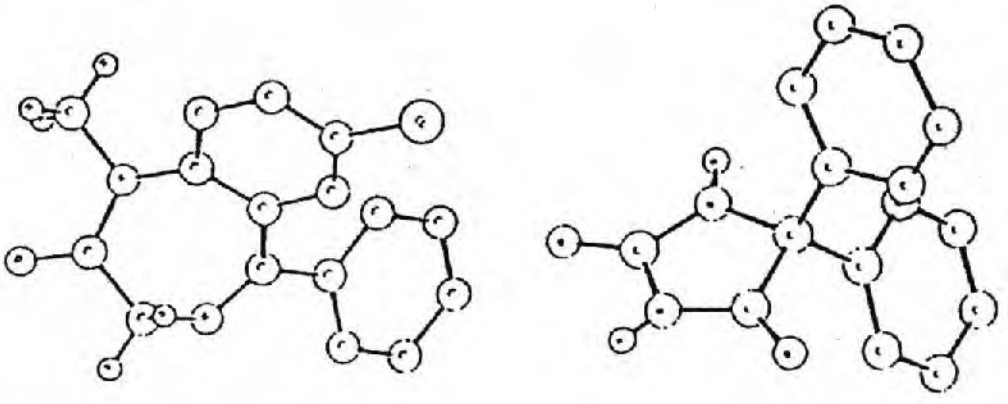
The structure-activity relationship of various classes of anticonvulsant drugs have been evaluated[5], and several general trends have been noted. In the carbamide series (i.e., barbiturates (15), hydantoins (13), primidone (20)) at least one phenyl or comparable aromatic group is needed at the tetrahedral ring carbon for the medicinal agent to be active against partial and tonic-clonic seizures.[5] Correspondingly, small alkyl groups are necessary at the tetrahedral ring carbon atom in both oxazolidine-

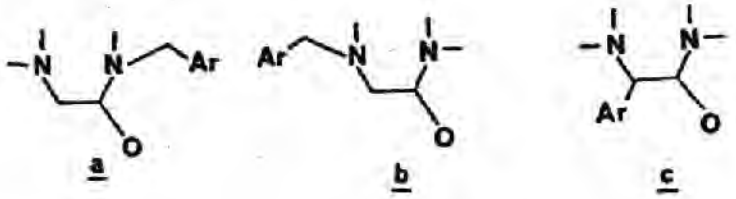
diones (17) and succinimides (16) for antiabsence activity.[5,26]

More recently, Camerman and Camerman[66,67] uncovered several interesting patterns when comparing the molecular structure of phenytoin (13a) with the benzodiazepines (24) (Figure 1). The investigators observed that both sets of compounds contained two bulky hydrophobic moieties (i.e., aromatic groups) and two hetero-atoms (i.e., the two carbonyl oxygens in phenytoin (13a) and the carbonyl oxygen and one nitrogen atom in the benzodiazepines (24)) with similar orientations in space. Futhermore, they also have demonstrated that a striking structural correspondence existed among the barbiturates (15), the benzodiazepines (24), phenytoin (13a), phenacemide (19). In all these types of compounds, the distance (4.06 - 4.23 Å) from the center of one aromatic ring to one heteroatom was comparable.[67]

In 1987, Conley and Kohn[68] pointed out that another structural pattern existed in many antiepileptic drugs. Inspection of a wide array of CNS-active agents indicated that many of these compounds contained a vicinal diamine linkage, an oxygen atom on the ethylene unit bridging the two amino groups, and an aromatic ring one carbon removed from an amino residue (46). The structure-activity relationships noted by various research groups have raised the intriging question of whether there exist both common as well as specific receptor sites responsible for the drug activity.[73]

Figure 1. Perspective Drawing of the Three-dimensional Conformations of Phenytoin (13a) (Right) and Diazepam (24c) (Left).[67]





a b c

46

VIII. Anticonvulsant Amino Acids and Amino Acid Derivatives.

Until recently amino acids and their derivatives have not had a significant impact in the development of new agents for the treatment of epilepsy. This lack of interest in amino acid compounds stems from the notion that these polar compounds do not readily penetrate the blood-brain barrier.[69] Nonetheless, many amino acids are involved in both the excitatory and the inhibitory regulatory processes of the brain. Furthermore, many receptor sites for amino acids have been identified.[70-73] The dicarboxylic acids, aspartic acid (4) and glutamic acid (5), as well as their sulfinic and sulfonic analogues are among the most potent excitatory neurotransmitters identified in the central nervous system.[70] Conversely, glycine (29a) and GABA (2) are two notable amino acids involved in the inhibitory processes.

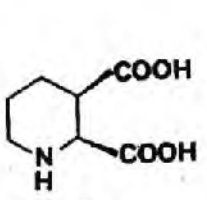
In light of these findings, it is not surprising that recent investigations have demonstrated that non-natural amino acids and amino acid derivatives also possess anticonvulsant properties. Evidence has been presented that the cis-piperidine dicarboxylic acid (47),[75,76] β - kainic acid (48)[77] kynurenic acid (49)[78,79]

2-amino-7-phosphonoheptanoic acid (30), and the dipeptides, γ-D-glutamylglycine (50) and β-D-aspartylaminomethylphosphonic acid (51)[80,81] (Figure 2), all specifically interact with excitatory amino acid receptor sites. Of these compounds, 30 is currently undergoing clinical evaluation. Moreover, with the exception of 49 in which there is no asymmetric center present in the molecule, all these substances show enhanced activity for specific stereoisomers.[75,76,72-86] In particular, the (-)-enantiomer of 30 is ten times more active than the corresponding (+)-enantiomer when administered intracerebroventricularly to sound sensitive mice.

Furthermore, several stereoisomers of 47 and 48 have convulsant properties.[75,77] Several non-natural amino acids and amino acid derivatives have been observed to interact with the inhibitory neurotransmission processes. These compounds can be classified according to whether they interact with biological processes involving glycine (29a) or GABA (2). One potent anticonvulsant substance, milacemide (33), has been reported to mimic glycine neurotransmission.[17,87] Compounds acting in the GABAergic system can be further subdivided according to whether they: 1) are GABA prodrugs; 2) interact with the GABA uptake; 3) interact with the enzymes responsible for the metabolism of GABA; and 4) act directly with specific GABA receptors.

Among the GABA prodrugs are compounds 52 - 56 (Figure 3). Each of these agents contains a protecting group(s) at the amine and/or carboxylic acid moieties. These groups permit

Figure 2. Amino Acids and Amino Acid Derivatives Interacting with Excitatory Neurotransmission.



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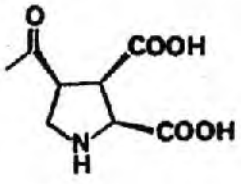

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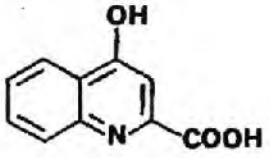

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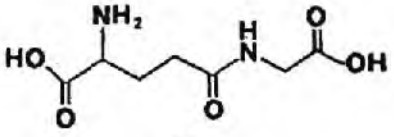

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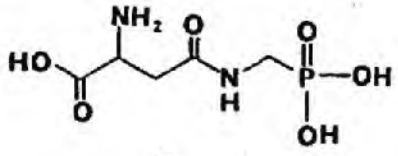

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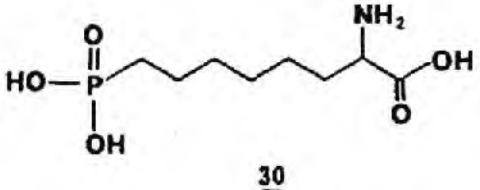


30

the prodrugs to penetrate the blood-brain barrier before they are metabolized to GABA or GABA-like compounds.[88-90]

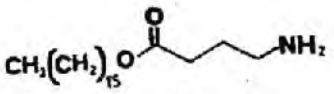
Examples of amino acids which decrease the GABA uptake (i.e., metabolism) in neuronal cells are nipecotic acid (57a), the corresponding phenyl esters 57b, as well as the related analogues 58 - 62 (Figure 4). Pharmacological evaluation of the individual enantiomers of 57a revealed that (-) - nipecotic acid was six times more active than the (+) - stereoisomer when tested in vitro in the isolated cerebellar cortex of cats.[91] Furthermore, examination of the anticonvulsant properties of the regioisomers 61 and 63 of 57a showed that the α - amino acid analogue 61 had the same type of action as 57a,[92] whereas the pharmacological properties of the γ - amino acid analogue 63 was different.[93] Similarly, α - aminoisobutyric acid (64) is believed to exert its activity by decreasing the GABA uptake by glial cells.[94]

Among the amino acids capable of decreasing the enzymatic metabolism of GABA are the two δ-unsaturated GABA analogues: γ - acetylenic GABA (65) and γ - vinyl GABA (31).[17,95-97]

Finally, several amino derivatives have been found to mimic GABA action at presynaptic or postsynaptic receptor sites. These include: isonipecotic acid (63), δ - aminolaevulinic acid (66) and trans-4-aminocrotonic acid (67) (Figure 5).[93,98,99]

During the past two decades there have been several reports describing the antiepileptic activity of select functionalized amino acid derivatives. The first two articles appeared in the

Figure 3. Amino Acids and Amino Acid Derivatives Interacting with the GABAergic System: GABA Prodrugs.



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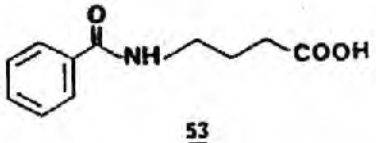

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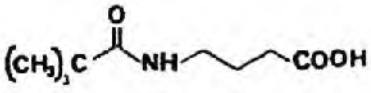

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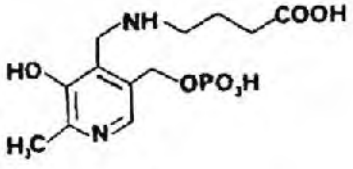

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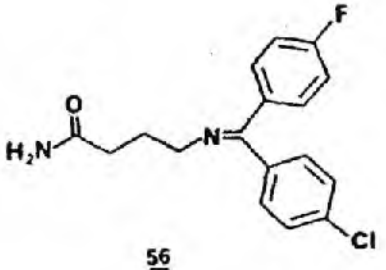

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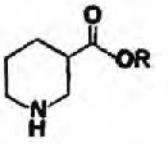
Figure 4. Amino Acids and Amino Acid Derivatives Interacting with the GABAergic System: Compounds Limiting GABA Uptake.



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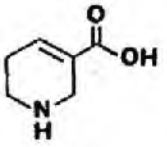

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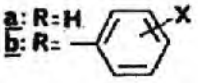

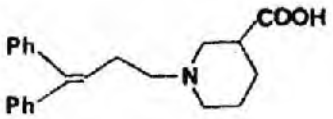

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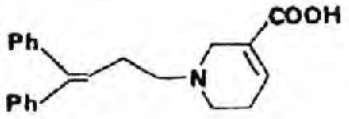

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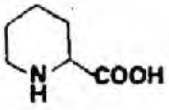

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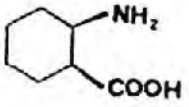

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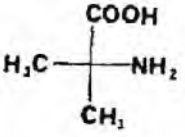

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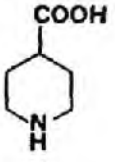

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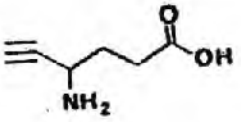

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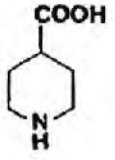
Figure 5. Amino Acids and Amino Acid Derivatives Interacting with the GABAergic System: GABA Receptor Agonists.



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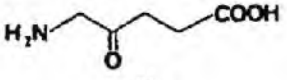

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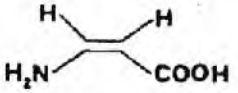
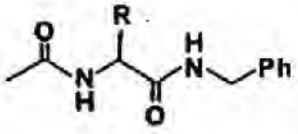


67

patent literature and focused on glycylderivatives[100] and N-benzoyl substituted amino acids[101]. Recently, Kohn and co-workers[68,102,103] described the anticonvulsant properties of several N-benzyl amino acids. Compounds 68 contained many of the structural elements (i.e. 46b, 46c) present in phenytoin (13a) and the benzodiazepines (24). Recent evidence has indicated that these compounds possess an unique mode of action, suggesting that, they may be a new class of anticonvulsant drugs.[68] Interestingly, the D-enantiomer of 68a was thirteen times more active than the L-isomer when tested orally in mice in the MES seizure test. A comparable difference in activity was also noted for the two stereoisomers of 68b. This information coupled with the stringent structure-activity relationship observed for this class of compounds[68] has led to the speculation that the anticonvulsant properties of these compounds may be related to interactions with specific receptor sites.



68

a: R=CH_3
b: R=Ph
c: R=$CH_2CH_2SCH_3$
d: R=$CH(CH_3)_2$
e: R=H

In an effort to further delineate the structure-activity relationship of this novel class of antiepileptic compounds, we have prepared and tested several select analogues of 68a and 68b. These substrates were designed to provide information concerning the importance of electronic effects at the α-carbon site in modulating the pharmacological properties of these drug candidates. In the first set of compounds prepared, the phenyl group of 68b was replaced by various heteroaromatic moieties; while in the second series synthesized, the methyl group of 68a was replaced by either polar and/or unsaturated substituents. The synthesis, spectral properties, and anticonvulsant activity of these two sets of compounds are presented in the Chapters I and II, respectively.

CHAPTER I

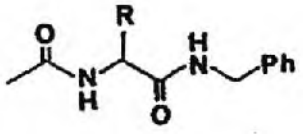
SYNTHESIS, SPECTROSCOPIC AND ANTICONVULSANT PROPERTIES OF STRUCTURAL ANALOGUES OF 2-ACETAMIDO-N-BENZYLPHENYL-ACETAMIDE AND 2-ACETAMIDO-N-BENZYL-2-ALKOXYACETAMIDE.

I. Introduction.

The potential list of heteroaromatic candidates to replace the phenyl group in α-acetamino-N-benzylphenylacetamide (68b) is large. In an effort to limit our initial choice of drug candidates, heterocycles containing only a single heteroatom were selected (Tables 5a and 5b). The first series of compounds (Table 5a) chosen consisted of the simple monocyclic adducts of furan (69a), pyrrole (69b), and thiophene (69c, 69d). The second set of compounds (Table 5b) comprised the corresponding benzoanalogues 69e - 69h. In both sets, no effort was made to control the site of substitution on the heterocycle. Of these seven heterocyclic compounds, two of the adducts (69c, 69d) were independently prepared in this laboratory.[104] We have also included in both lists the corresponding parent aromatic compounds 68b[68,103] and 69e[104]. These compounds serve as suitable reference substrates for the remaining adducts.

Several factors contributed to our selection of these functionalized amino acid derivatives. First, furan (70a), thiophene (71) and indole (72) have been previously substituted for a phenyl group in both hydantoins (13) and succinimides (16) possessing

Table 5a. Monocyclic Heteroaromatic Analogues 69 of 2-Acetamido-N-benzylphenylacetamide (68b).



69

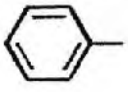
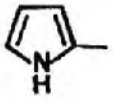
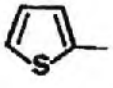
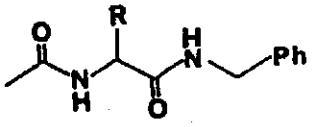
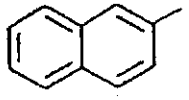
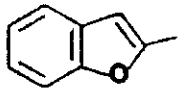
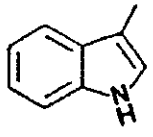
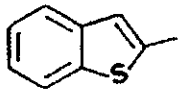
No	R
68b	
69a	
69b	
69c	
69d	

Table 5b. Benzofused Heteroaromatic Analogues 69 of 2-Acetamido-N-benzylphenylacetamide (68b).



69

No	R
69e	
69f	
69g	
69h	

anticonvulsant properties. The resulting heterocyclic analogues synthesized also exhibited pronounced biological activity.[105-107] Second, many heterocycles possessing side chains of varying length and polarities have been reported to be active in anticonvulsant animal screens.[5]

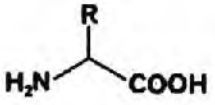
II. Results and Discussion.

1. Synthesis.

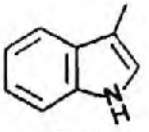
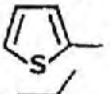
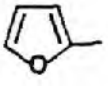
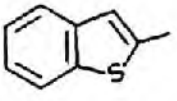
Surprisingly, only a few α-amino acids having a heterocycle directly bonded to the α-carbon have been reported. These include the 3-indolyl (73a), the 2-(73b) and 3-(73c) thienyl, the 2-furyl (73d) and the 2-benzo[b]thienyl (73e) glycine derivatives (Table 6). Of these, only the thienyl compounds 73b and 73c are commercially available.[108]

In our study, we chose to prepare the racemic amino acid derivatives rather than the individual enantiomers so as to provide a meaningful comparison with previous results obtained in this laboratory[68,102]. We anticipated that the use of amidoalkylation procedures employing the parent heterocycle and an appropriate amino acid derivative would provide a convenient route to the desired functionalized amino acid racemates. Several factors supported our selection of this general methodology. First, this general technique has been widely utilized for the alkylation of nucleophiles.[114-118] Second, substituted amino acids have been

Table 6. Examples of Amino Acids with an α-Heterocyclic Substituent.



73

No	R	Ref.
73a		109
73b		110
73c		111
73d		112
73e		113

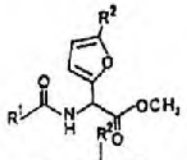
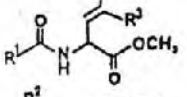
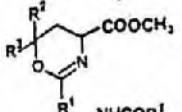
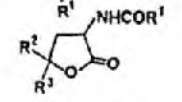
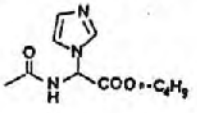
synthesized by this procedure. In these cases, the amidoalkylating species was usually a glycine derivative bearing a leaving group at the α-position. Table 7 lists various examples of this reaction. Third, previous examples of amidoalkylation transformations employing heteroaromatic substrates have been reported. Representative reactions are listed in Tables 8 - 12 for furan (70a), pyrrole (74), indole (72), thiophene (71) and various other heteroaromatic substrates, respectively. In all these reactions, alkylation on the heterocycle occurs preferentially at the most electron rich site. Significantly, only in the cases of furans and thiophenes were the parent heterocycles frequently employed. Amidoalkylation reactions involving benzofurans (i.e. 75) and benzo[b]thiophenes (i.e. 76) have not been reported.

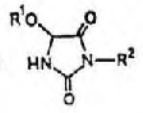
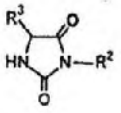
The desired compounds 69 a,b,f-h were synthesized by two general routes both utilizing an amidoalkylation step. The yields were not optimized.

In method A (Scheme 1), the initial targets were the 2-substituted-2-acetamidoacetic acids 82a-e. It was anticipated that these compounds would readily undergo condensation with benzylamine (83) using the mixed anhydride coupling method[144,145] to yield the desired products 69. Our projected synthesis of 82a-e was patterned after the procedure described by Chouteeten and co-workers[121]. These investigators prepared α-acetamido-2-thio-

Table 7. Synthesis of Amino Acid Derivatives by the Amidoalkylation Technique.

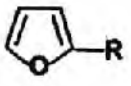
	Amidoalkylating Agent	Substrate	Conditions	Amino Acid Derivative	Ref.
a	$R^1CONHCH(OH)COOH$	ArH	H_2SO_4.HCl, H_2SO_4/CH_3COOH, H_3PO_4	$R^1CONHCH(Ar)COOH$	119-121
b	$R^1CONHCH(OH)COOH$	$ArCH_2R^2$	CH_3SO_3H	$R^1CONHCH(ArCH_2R^2)COOH$	122
c	$R^1CONHCH(OH)COOH$	R^2SH	H_2SO_4/CH_3COOH	$R^1CONHCH(SR^2)COOH$	123
d	$R^1CONHCH(OH)COOH$	$R^2COCH_2COR^3$	H_2SO_4	$R^1CONHCH(CH_2COR^2(3))COOH$	124-126
e	$R^1CONHCH(OH)COOH$	$R^2COCH_2COR^3$	CH_3SO_3H, H_2SO_4, H_2SO_4/CH_3COOH	$R^1CONHCH(CH_2COR^2(3)COOH$	125, 126

f	$R^1CONHCH(OCH_3)COOCH_3$		$BF_3 \cdot OEt_2$		127
g	$R^1CONHCH(OCH_3)COOCH_3$		NSA[a]		128
h	$R^1CONHCH(OCH_3)COOCH_3$		$BF_3.OEt_2$		128
i	$R^1CONHCH(OCH_3)COOCH_3$		H_2SO_4/dioxane		128
j	$R^1CONHCH(OCH_3)COOCH_3$	R^2SH	NSA[a]	$R^1CONHCH(SR^2)COOCH_3$	123
k	$R^1CONHCH(OCH_3)COOCH_3$	$R^2COCH_2COR^3$	$BF_3.OEt_2$	$R^1CONHCH(CH(COR^2)(COR^3))COOCH_3$	124, 126
l	$CH_3CONHCH(Cl)COOn\text{-}C_4H_9$		Et_3N		129

m	$CH_3CONHC(OCH_3)(CH_2R^1)COOCH_2CH_3$	R^2H(ArH, R^3SH)	$SnCl_4$	$CH_3CONHC(R^2)(CH_2R^1)COOCH_2CH_3$	130
n		R^3H(ArH, 	$BF_3 \cdot OEt_2$, H_2SO_4		129,131, 132

[a] b-Naphtalenesulfonic acid.

Table 8. Amidoalkylation Reactions Involving Furan (70a) and 2-Methyl furan (70b).



70

a: R = H
b: R = CH_3

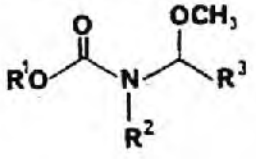
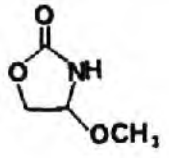
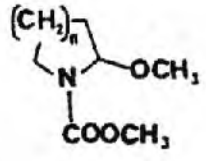
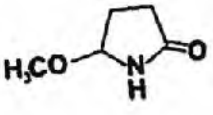
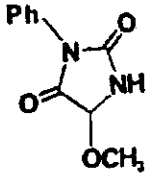
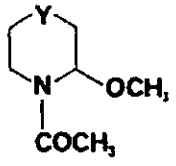
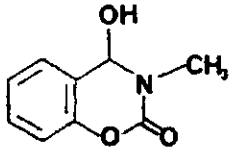
amidoalkylating agent	condition	yield	Ref.
a 	PTSA[a], BF_3OEt_2	66 - 84	127,133
b 	PTSA[a]	71	133
c 	PTSA[a]	72 - 89	133
d 	PTSA[a]	67	133

Table 8 con't.

amidoalkylating agent		condition	yield	Ref.
e		$BF_3 \cdot OEt_2$	-	134
f		$SnCl_4$	70	135
g		PTSA[a,b]	90 - 94	136

[a]p-Toluenesulphonic Acid. [b] PTSA was used as a catalyst and water was removed by azeotropic distillation.

Table 9. Amidoalkylation Reactions Involving Pyrrole (74) and Substituted Pyrroles.

74

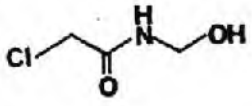
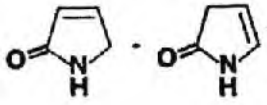
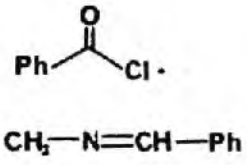
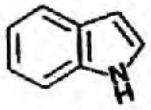
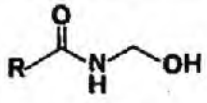
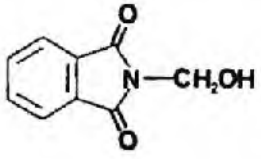
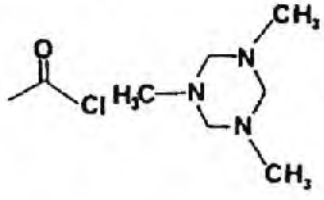
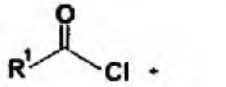
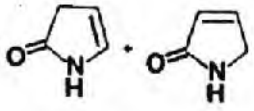
	amidoalkylating agent	conditions	yield(%)	ref.
a		HCl	31 - 35	137
b		CH_3COOH or reflux	62 - 80	138
c		Et_3N	60 - 64	118

Table 10. Amidoakylation Reactions Involving Indole (72) and Substituted Indoles.



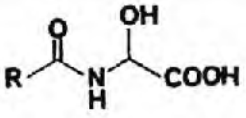
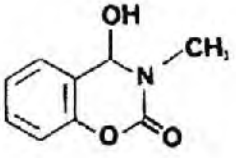
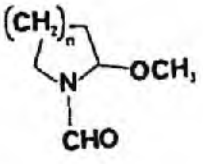
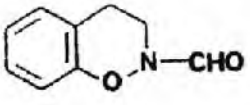
72

Amidoalkylating agent	condition	yield(%)	Ref.
a 	H_2SO_4	35 - 90	118, 139
b 	H_2SO_4	50 - 83	118,139
c 	a	52	140
d  	Et_3N	30 - 80	118
e 	CH_3COOH	75 - 83	118,140

[a] No catalyst was required.

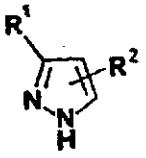
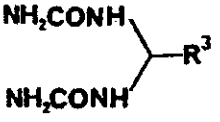
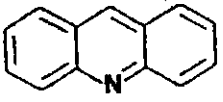
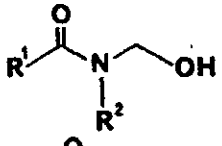
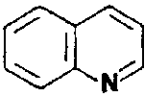
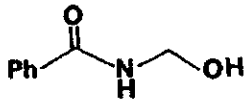
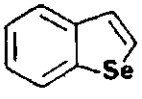
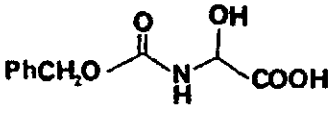
Table 11. Amidoalkylation Reactions Involving Thiophene (71).

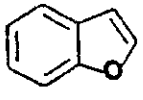
71

amidoalkylating agent		conditions	yield(%)	Ref.
a		H_2SO_4	45 - 92	121,127
b		PTSA[a,b]	82	136
c		$BF_3 \cdot OEt_2$	46 - 68	141
d		$BF_3 \cdot OEt_2$	73	141

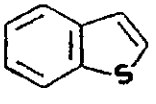
[a] p-Toluenesulphonic Acid. [b] Only a catalytic amount of PTSA was required and water was removed by azeotropic distillation.

Table 12. Amidoalkylation Reactions Involving Other Heterocycles.

heterocycle	amidoalkylating agent	conditions	yield(%)	Ref.
a 		CH_3COOH	15-42	118
b 		H_2SO_4	29-59	142
c 		H_2SO_4	41	118
d 		H_2SO_4/ CH_3COOH	63	143

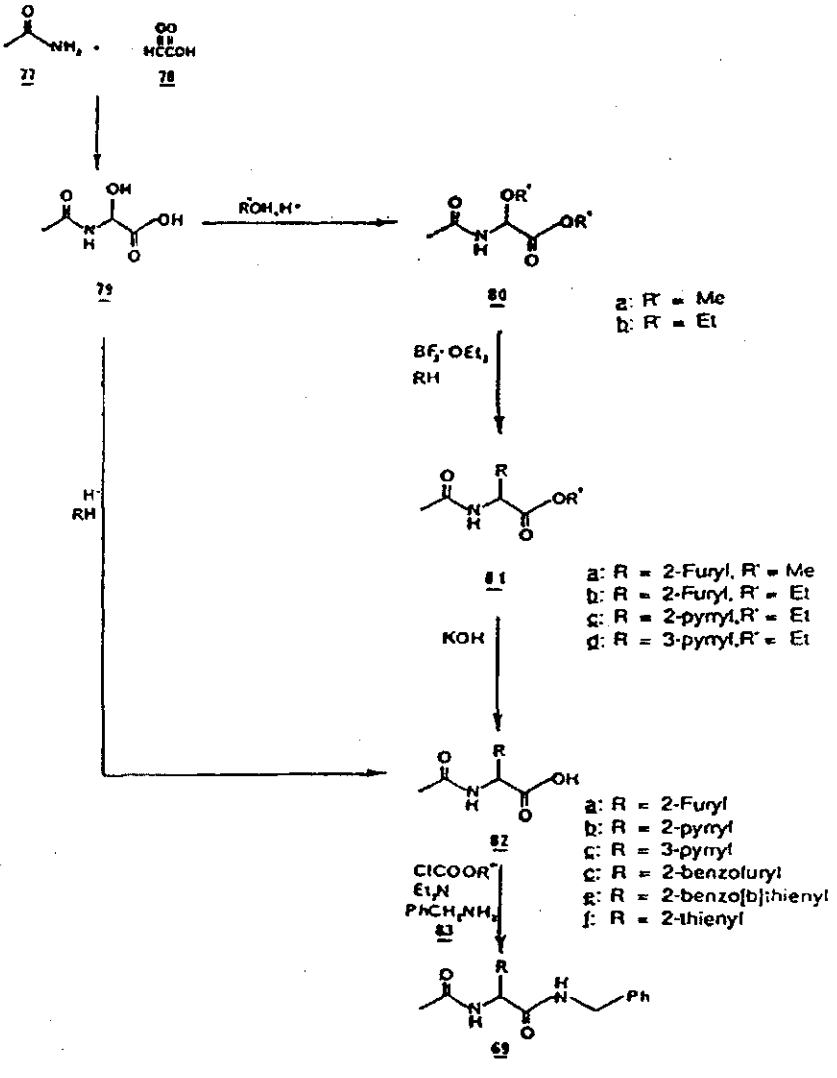


75



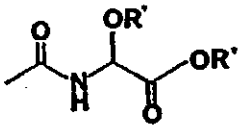
76

Scheme 1. Synthesis of 2-Substituted-2-acetamido-N-benzylacetamides (69a,b,f,h) by Method A.



pheneacetic acid (82f) by the treatment of 2-acetamido-2-hydroxyacetic acid (79) with thiophene (71) in the presence of phosphoric acid. Compound 79 was readily prepared in quantitative yield from acetamide (77) and glyoxylic acid (78)[121]. Replacement of furan (70a) for thiophene (71) in this approach furnished 82a in 14 % yield. The corresponding reactions using benzofuran (75), pyrrole (74) and indole (72) gave intractable mixtures of polymeric materials. Substitution of other acids (i.e., sulfuric acid, methanesulfonic acid) for phosphoric acid also proved unsuccessful. Fortunately, use of a 1:1 mixture of methanesulfonic acid and acetic acid permitted the synthesis of the benzofuran derivative 82d in modest yield (20%). The difficulty encountered in these transformations prompted our inspection of the procedure employed by Ben-Ishai, Sataty and Bernstein[127] for the synthesis of the furan derivative 84. Application of this method required the initial conversion of 2-acetamido-2-hydroxyacetic acid (79) to the corresponding alkyl 2-acetamido-2-alkoxyacetates 80a and b (Table 13). This was readily accomplished in moderate yields by treatment of the appropriate alcoholic solution containing 79 with sulfuric acid. These ethers were then reacted with either furan (70a) or pyrrole (74) in the presence of boron trifluoride etherate in ether to give the corresponding 2-substituted-2-acetamidoacetates (81a-d) (Table 14). Hydrolysis of these esters 81a-d with aqueous alcoholic potassium hydroxide gave the required

Table 13. Selected Physical and Spectral Data for Alkyl 2-Acetamido-2-alkoxyacetates (80).



80

No.	R	yield[a]	mp[b]	IR[c]	M^+/e[d]
80a	CH_3	32	44 - 46	1735,1090	162 (1)[e]
80b	CH_2CH_3	55	35 - 36	1735,1085(br)	190 (5)[e]

[a]Purified yield (%) from 2-acetamido-2-hydroxyacetic acid (79). [b]Melting points (°C) are uncorrected. [c] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrum was obtained at an ionizing voltage of 70 eV. The number in parentheses indicates the intensity of this ion relative to the base peak in the spectrum. [e] Protonated 80.

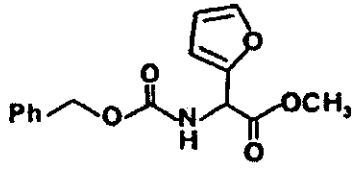


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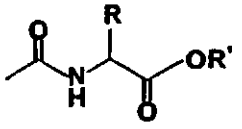
Table 14. Selected Physical and Spectral Data for α-Substituted Alkyl 2-Acetamidoacetates (81).



81

No.	R	R'	Yield[a]	mp[b]	IR[c]	M+/e[d]
81a	2-Furyl	CH_3	62	80 - 81	1740,1530(br),890	197 (14)[e]
81b	2-Furyl	CH_2CH_3	51	69 - 70	1750,1530,900	211 (8)[e]
81c	2-Pyrryl	CH_2CH_3	41	104 - 106	1715,1515 (br)	210 (22)[e]
81d	3-Pyrryl	CH_2CH_3	12	92 - 93	1720,1640 (br)	210 (12)[e]

[a]Purified yields (%) from the alkyl 2-acetamido-2-alkoxyacetates (80). [b]Melting points (°C) are uncorrected. [c] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrum was obtained at an ionizing voltage of 70 eV. The number in parentheses indicates the intensity of this ion relative to the base peak in the spectrum. [e] The M+ 1 ion peak was also observed.

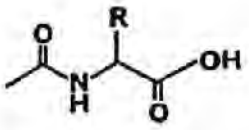
acids 82a-c (Table 15) needed for the mixed anhydride coupling reaction.

Several important observations were made for these amidoalkylation reactions. First, although slightly higher yields were obtained for the methyl ester 80a than for the corresponding ethyl ester 80b (Table 14), the ease of purification of 80b made this derivative the reagent of choice in this transformation. Second, the site of amidoalkylation on the heterocycle was similar to that previously observed in other electrophilic aromatic substitution reactions. Accordingly, a 1:3.4 ratio was observed for the alkylation of pyrrole (74) at the 3- and 2-positions, respectively; while furan (70a) was alkylated only at the 2-position. Third, the reactivity of the furan (70a) and pyrrole (74) were comparable. Similar observations have been previously noted.[146]

The benzo[b]thiophene acetic acid derivative 82e listed in Table 15 was independently prepared from the corresponding amino acid 73e by acetylation with acetic anhydride (85) in basic medium 73e by acetylation with acetic anhydride (85) in basic medium (Scheme 2). A sample of compound 73e was generously provided by the Eli Lilly Research Laboratories.

The final step in Method A required the coupling of the unnatural amino acids 82 with benzylamine (83). In our hands, use of the mixed anhydride method[144,145] proved unsatisfactory,

Table 15. Selected Physical and Spectral Data for α-Substituted 2-Acetamidoacetic Acids (82).

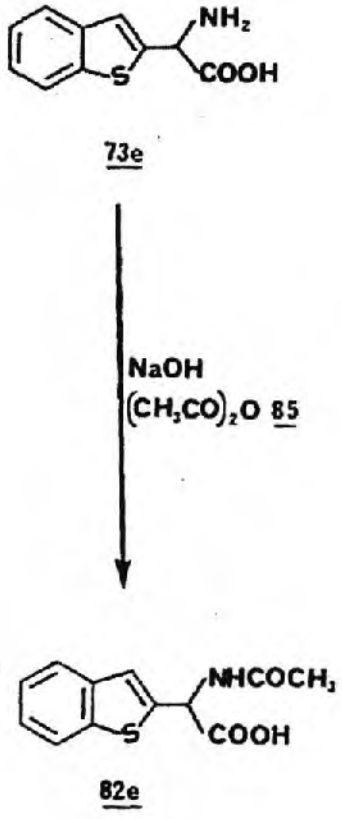


82

No.	R	yield[a]	mp[b]	IR[c]	M+/e[d]
82a	2-Furyl	51 (14)[e]	171 - 172	1705,1580 (br),900	183 (2)
82b	2-Pyrryl	29	112 - 114	1720,1530 (br)	182 (1)
82c	3-Pyrryl	38	135 - 138	1700,1530 (br)	182 (4)
82d	2-Benzofuryl	20[f]	203 -204	1720,1535 (br)	233 (12)[g]
82e	2-Benzo[b]thienyl	83[h]	224 - 226	1710,1520 (br)	249 (22)[g]

[a]Purified yields (%) from the corresponding α - substituted alkyl 2-acetamidoacetates (81) by saponification (KOH, EtOH/H_2O) unless otherwise indicated. [b] Melting points (°C) are uncorrected. [c] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrometer was obtained at a ionizing voltage of 70 eV. The number in parentheses indicates the intensity of this ion relative to the base peak in the spectrum. [e] From 2-acetamido-2-hydroxyacetic acid (79) in the presence of H_3PO_4. [f] From 2-acetamido-2-hydroxyacetic acid (79) in the presence of methanesulfonic acid. [g] The M + 1 ion peak was observed. [h] From acetylation of α-aminobenzo[b]thiopheneacetic acid (73e).

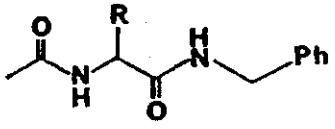
Scheme 2. Preparation of α-Acetamido-2-benzo[b]thiopheneacetic Acid (82e).



furnishing low amounts (6 - 16%) of the desired products (Table 16). All efforts to improve the yield of the reaction by varying the temperature, the alkylchloroformate and the concentration of the reagent were not successful. Other coupling reactions were also tried. These included the direct condensation of esters 81b and c with benzylamine (83), and the use of dicyclohexylcarbodiimide[147] in conjunction with acid 82a and 83. No significant improvement in product yields were noted for these modifications.

In an effort to circumvent this problem, we examined the synthetic pathway outlined in Scheme 3 (Method B). In this procedure, the coupling reaction was conducted prior to the amidoalkylation transformation. Treatment of alkyl 2-acetamido-2-alkoxyacetates 80a and b with benzylamine (83) in alcoholic solution produced the corresponding 2-acetamido-N-benzyl-2-alkoxyacetamides 86a and b, respectively (Table 17). Higher yields and cleaner product mixtures were noted for the synthesis of ethoxy adduct 86b versus the methoxy derivative 86a. Compound 86b was then converted to the final desired products 69 using the amidoalkylation procedure previously described in Method A. This synthetic route permitted the preparation of compounds 69a,b,f-h. Moderate yields for this step were observed for furan (70a), pyrrole (74), indole (72) and benzofuran (75) (28 - 58 %), while only a four percent yield was obtained for benzo[b]thiophene (76) (Table 16). In this last case,

Table 16. Selected Physical and Spectral Data for α-Substituted 2-Acetamido-N-benzylacetamides (69).



69

No.	R	yield[a]	mp[b]	IR[c]	M+/e[d]
69a	2-Furyl	58 (13)[e]	178 - 179	1625,1525	273 (1)[f]
69b	2-Pyrryl	35	174 -1 75	1570 (br)	271 (12)[f]
69c[g]	2-Thienyl	37	167 - 169	-	289 (2)
69f	2-Benzofuryl	33 (13)[e]	195 - 196	1625 - 1520	322 (5)[f]
69g	3-Indolyl	28	213 - 214	1610 - 1515	321 (5)[f]
69h	2-Benzo[b]thienyl	4 (16)[e]	226 - 227	1610 - 1510	338 (8)[f]

[a]Purified yields (%) from the 2-acetamido-N-benzyl-2-ethoxyacetamide (86b) unless otherwise indicated. [b] Melting (°C) points are uncorrected. [c]Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrum was obtained at an ionizing voltage of 70 eV. The number in parentheses indicates the relative intensity of this ion relative to the base peak in the spectrum. [e] From the corresponding α-substituted-2-acetamidoacetic acid 82 (mixed anhydride route, Method A). [f] The M + 1 ion peak was observed. [g] Ref. 104.

Scheme 3. Synthesis of 2-Substituted-2-acetamido-N-benzylacetamides (69a,b,f-h) by Method B.

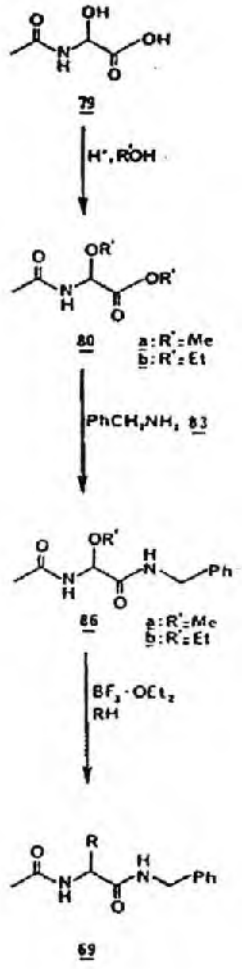
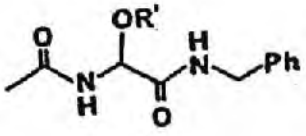


Table 17. Selected Physical and Spectral Data for 2-Acetamido-N-benzyl-2-alkoxyacetamides (86).



86

No.	R'	yield[a]	mp[b]	IR[c]	M+/e[d]
86a	CH_3	32	145 - 146	1550,1060	237 (1)
86b	CH_2CH_3	70	153 - 155	1550 (sh),1060	251 (4)

[a]Purified yield (%) from the corresponding alkyl 2-acetamido-2-alkoxy-acetates (80). [b] Melting points (°C) are uncorrected. [c]Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrum was not observed at an ionizing potential of 70 eV, instead the M + 1 ion peak was detected. The number in parentheses indicates the relative intensity of this ion relative to the base peak in the spectrum.

a large amount of unreacted starting material was recovered.

Several interesting observations were noted concerning these amidoalkylation transformations. In the reaction of pyrrole (74) with 86b, only a minute amount of the 3-substituted product was detected (TLC analysis). A much larger percentage of the corresponding adduct was observed when ester 80b was employed as the starting material. In the case of indole (72), the 3-substituted derivative 69g was the only product detected. This result is typical for electrophilic substitution of 72.[146] On the other hand, treatment of 80b with benzofuran (75) in the presence of boron trifluoride furnished only the 2-substituted derivative 69f, despite the known tendency of this heterocycle to undergo alkylation at both the 2- and 3-positions.[148] In the benzo[b]thiophene (76) reaction, only the 2-substituted product 69h was observed. This result was surprising since this heterocycle is reported to react at the 3-position with most electrophiles.[148] The low yield of this transformation, however, did not permit us to conjecture on the factors responsible for this inversion in site selectivity. The reactivity of furan (70a), pyrrole (74) and thiophene (71)[104] were comparable in this amidoalkylation transformation and the yields ranged between 35 - 38 %. The relatively high conversion rate observed for 71 versus 70a and 74 is surprising, since thiophene (71) is usually less reactive than furan (70a) and pyrrole (74).[146]

In the case of the annelated heteroaromatic substrates 72, 75 and 76 higher yields were noted for 72 and 75. Previous results concerning the ease of substitution of these substrates have produced widely varying results.[148] Finally, during the purification of the product mixture obtained from the synthesis of α-acetamido-N-benzyl-3-indoleacetamide (69g), a compound possessing a molecular weight of 351 (electron impact mass spectrometry) was isolated and identified as the indole trimer 87. Indole (72) is known to undergo trimerization in the presence of both mineral and Lewis acids.[149-151] A mechanism for this polymerization has been previously proposed[149] and is depicted in Scheme 4.

Table 18 summarizes our initial results for the various amidoalkylation transformations conducted using the heterocycles 70a, 71, 72 and 74 - 76. Many alternate procedures are conceivable but have not been examined. In general, we observed higher yields and cleaner product mixtures when boron trifluoride etherate was employed as the acid source with both alkyl 2-acetamido-2-alkoxyacetates 80a,b and 2-acetamido-N-benzyl-2-ethoxyacetamide 86b. Correspondingly, the use of mineral acids in the amidoalkylation transformations gave unpredictable results and always gave rise to polymeric-type materials.

Scheme 4. Acid Catalyzed Trimerization of Indole (76).[149]

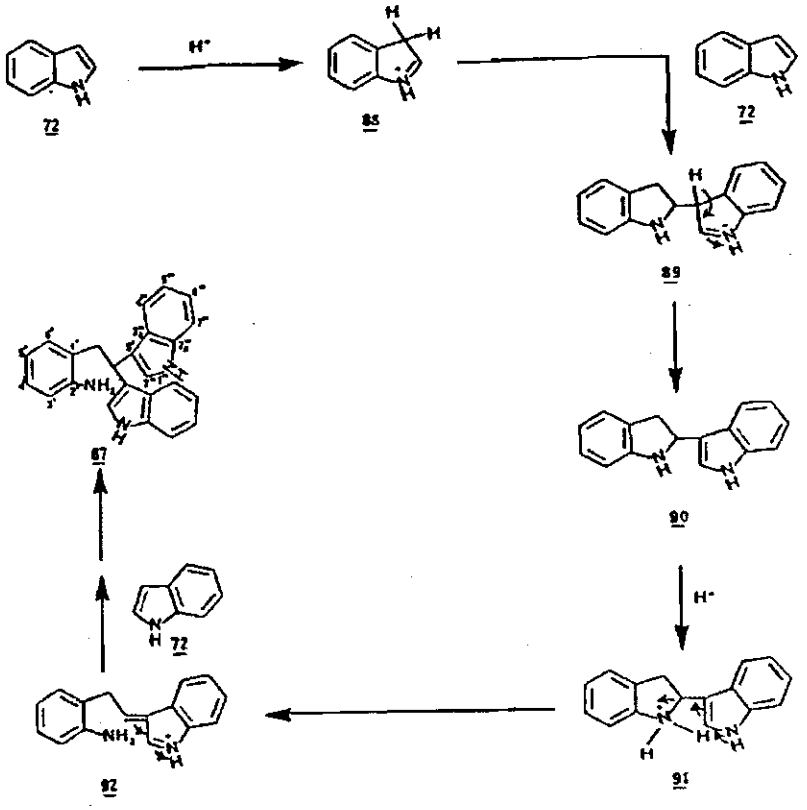
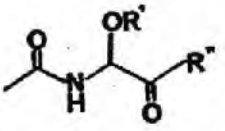


Table 18. Comparison of Several Amidoalkylation Reactions Involving Furan (70a), Pyrrole (74), Thiophene (71), Indole (72), Benzofuran (75) and Benzo[b]thiophene (76) Beginning with Either 80, 82a and b or 86b.[a]



	R' = H R" = OH H_3PO_4/ CH_3COOH[b]	R' = H R" = OH CH_3SO_3H/ CH_3COOH	R' = Me R" = OMe $BF_3 \cdot OEt_2$[c]	R' = Et R" = OEt $BF_3 \cdot OEt_2$[c]	R' = Et R"=$NHCH_2Ph$ $BF_3 \cdot OEt_2$[c]
Furan (70)	15[2]	d	62[2]	51[2]	58[2]
Pyrrole (74)	0	d	d	41[2],12[3]	35[2][e]
Thiophene(71)[f]	d	d	d	d	37[2]
Benzofuran (75)	0	39[2]	d	d	33[2]
Indole (72)	0	0	d	d	28[3]
Benzo[b]thiophene(76)	d	d	d	d	4[2]

[a] The number in each entry is the purified yield (%). The number in brackets indicates the position of alkylation on the heterocycle. [b] Ref. 121. [c] Ref. 127. [d] The reaction was not performed. [e] A trace amount of the 3-substituted derivative was observed by thin-layer chromatography. [f] Ref. 104.

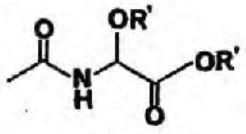
2. Spectral Evaluation.

a. Infrared Spectra.

Characteristic absorption bands were observed in the infrared spectra for the alkyl 2-acetamido-2-alkoxyacetates 80, the alkyl 2-substituted-2-acetamidoacetates 81, the corresponding acids 82 and the functionalized amino acid derivatives 69 and 86 and are listed in Tables 19 - 22, respectively. In particular, the absorption bands for the secondary amide groups were readily distinguished in all these compounds. This group typically shows three absorption bands corresponding to the NH stretching mode (3320 - 3270 cm^{-1}), a carbonyl stretching mode (amide I band, 1680 - 1630 cm^{-1}), and a NH bending mode (amide II band, 1570 - 1515 cm^{-1}).[152] These absorption bands were observed between 3200 - 3290, 1610 - 1655, and 1500 - 1535 cm^{-1}, respectively, in N-benzylamides 69 and 86 and esters 80 and 81 (Tables 19, 20, 22). In acids 82 the NH and CO stretching modes were slightly shifted from these values and were detected between 3305 - 3340 and 1585 - 1590 cm^{-1}, respectively (Table 21).

A consistent set of absorption bands in the infrared spectra for the phenyl group of the 2-substituted-2-acetamido-N-benzylacetamides 69 and 86 were observed. The CC stretching mode of the phenyl group appeared between 1610 - 1630 cm^{-1} and always overlapped the carbonyl stretching absorption. The in-plane bending mode for the phenyl group was observed between 1095 - 1090 cm^{-1}, while the most characteristic out-of-plane bending modes

Table 19. Selected Infrared Spectral Data for Alkyl 2-Acetamido-2-alkoxyacetates (80)[a].

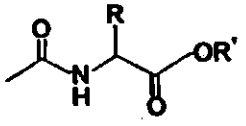


80

No.	R'	NH stretching	CO(COOR') stretching	CO(NHCO) stretching	NH bending	OR'	COOR'
80a	CH_3	3270	1735	1650	1505	1090[b]	1205,1010[c]
80b	CH_2CH_3	3400	1735	1655	1510	1085[b]	1200,1010[c]

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene. [b] COC antisymmetric stretch. [c] CO stretches.

Table 20. Selected Infrared Spectral Data for Alkyl 2-Substituted-2-acetamidoacetates (81)[a].

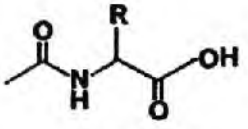


81

No.	R	R'	NH stretching	CO(COOR') stretching	CO(NHCO) stretching	NH bending	R'[b]	R[b]
81a	2-Furyl	CH_3	3200	1740	1620	1530	1205,1020[c]	890[d]
81b	2-Furyl	CH_2CH_3	3200	1750	1635	1530	1205,1020[c]	890[d]
81c	2-Pyrryl	CH_2CH_3	3200	1715	1635	1515	1220,1010[c]	3310[e]
81d	3-Pyrryl	CH_2CH_3	3240	1720	1640	1510	1210,1010[c]	3320[e]

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystrene. [b] Characteristic bands for R and R'. [c] CO stretches. [d] Furan ring deformation. [e]NH stretch.

Table 21. Selected Infrared Spectral Data for 2-Substituted-2-acetamidoacetic Acids (82)[a].

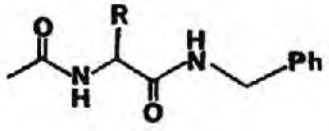


82

No.	R	NH stretching	CO(COOH) stretching	CO(CONH) stretching	NH bending	OH bending	R
82a	2-Furyl	3320	1705	1580	1530	1210	890[b]
82b	2-Pyrryl	3300	1710	1590	1530	1220	3340[c]
82c	3-Pyrryl	3300	1700	1585	1525	1240	3340[c]
82d	2-Benzofuryl	3340	1720	1590	1535	1200	890[d]
82e	2-Benzo[b]thienyl	3305	1710	1580	1520	1200	-

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band of polystyrene. [b] Furan ring deformation. [c] NH stretch. [d] Benzofuran ring deformation.

Table 22. Selected Infrared Spectral Data for 2-Substituted-2-acetamido-N-benzylacetamides (69, 86)[a].



69, 86

No.	R	NH stretching	CO, CC (Ph) stretching	NH bending	Ph ip,oop bending[b]	R
69a	2-Furyl	3230	1625	1525	1090,740,690	890[d]
69b	2-Pyrryl	3230	1610	1500	1070,740,685	e
69f	2-Benzofuryl	3230	1625	1520	1090,735,690	890[f]
69g	3-Indolyl	3260	1610	1515	1095,735,695	3400[g]
69h	2-Benzo[b]thienyl	3240	1610	1510	1085,730,685	-
86a	OCH_3	3260	1625	1505	1065,740,690	1120[h]
86b	OCH_2CH_3	3260	1630	1505	1060,740,690	1115[h]

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band of polystyrene. [b] In-plane and out-of-plane bendings. [c] Characteristic absorption bands for R. [d] Furan ring deformation. [e] No stretching absorption band was observed for this compound. [f] Benzofuran ring deformation. [g] NH stretch. [h] COC antisymmetric stretch.

for the monosubstituted phenyl moiety were detected between 730 - 740 and 685 - 695 cm^{-1} (Table 19). These absorptions fit well with values obtained for similar compounds.[153]

Characteristic absorption bands were also observed for the furan, pyrrole, benzofuran and indole moieties. The sharp ring deformation bands of the furan and benzofuran rings were detected at 890 cm^{-1}.[153,154] In the pyrrole and indole series, the NH stretching mode was readily observed between 3310 - 3340 and 3400 cm^{-1}, respectively. These bands appeared at higher frequencies than normally observed.[153]

b. Mass Spectral Data.

All the α-substituted-2-acetamidoacetic acid derivatives 69, 81 and 82 exhibited a discernable parent ion peak in the electron impact mass spectra (Tables 14 - 16). Interestingly, the M + 1 ion rather than the parent ion peak was detected for the 2-acetamido-2-alkoxyacetic acid derivatives 80 and 86. (Tables 13 and 17). This observation is attributed to the tendency of ethers to undergo protonation in the mass spectrometer at moderately high sample pressures.[155,156] The same behavior has been described for amides.[155,156] In agreement with this observation, we detected a M + 1 ion for most of the derivatives 69, 81 and 82.

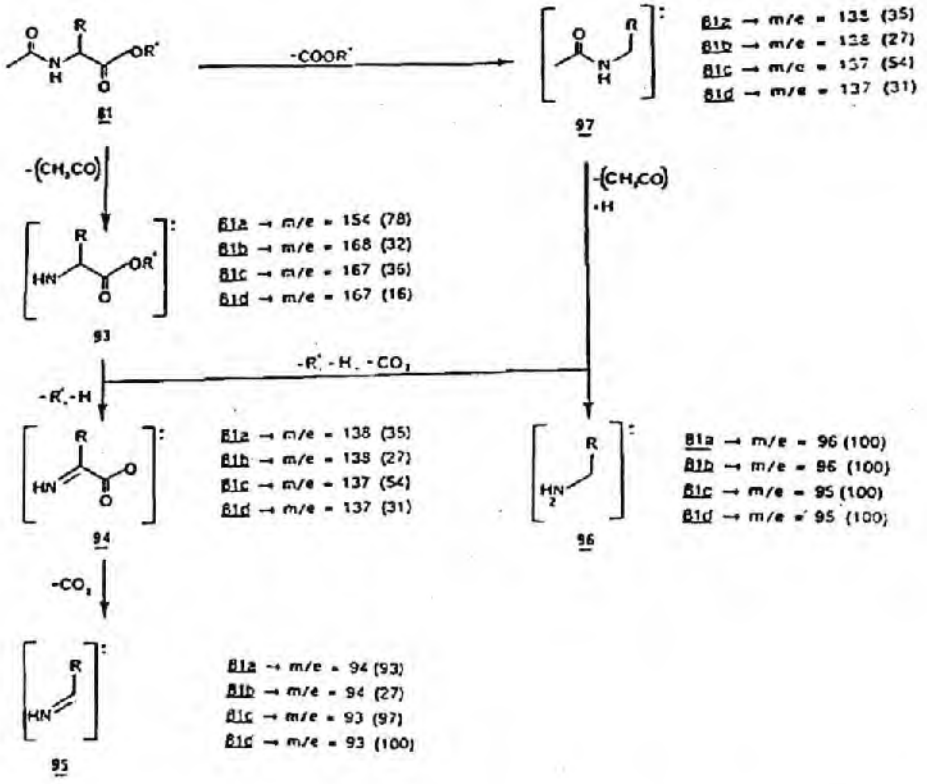
Distinct fragmentation patterns were found in the electron impact mass spectra for compounds 69, 81-82 and 86. Rational cleavage patterns could be assigned for each adduct consistent with

the proposed structural assignment and are presented in Schemes 5 - 8. No studies were conducted to verify the proposed assignments. Similar fragmentations were noted for both alkyl 2-substituted 2-acetamidoacetates 81 (Scheme 5) and 2-substituted-2-acetamido-N-benzylacetamides 69 and 86 (Scheme 6). In each case, the major cleavage patterns were the loss of either the N-benzylcarbamyl ($PhCH_2NHCO$) or the acetyl (CH_3CO) moieties. The mass spectral fragmentation patterns observed for alkyl 2-acetamido-2-alkoxyacetates (80) (Scheme 7) and the 2-substituted-2-acetamidoacetic acids (82) (Scheme 8) was somewhat similar to that of 69, 81 and 86. In several cases, however, fragmentation of the ester function, was observed in addition to the cleavage of the acetyl moiety. This pattern has been previously observed for this functional group.[156] Interestingly, in the spectra of the esters 80 (Scheme 7) ion 102 was observed, whereas this ion was not detected in the spectra of esters 81 (Scheme 5). In all the compounds examined a major peak was noted corresponding to ion 96 or the related species 101. The alkyl 2-substituted-2-acetamidoacetates (81) and the 2-substituted-2-acetamidoacetic acids (82) also exhibited a peak two mass unit smaller than 96. This latter fragment has been tentatively assigned to the ion 95.

c. ^1H NMR Spectral Data.

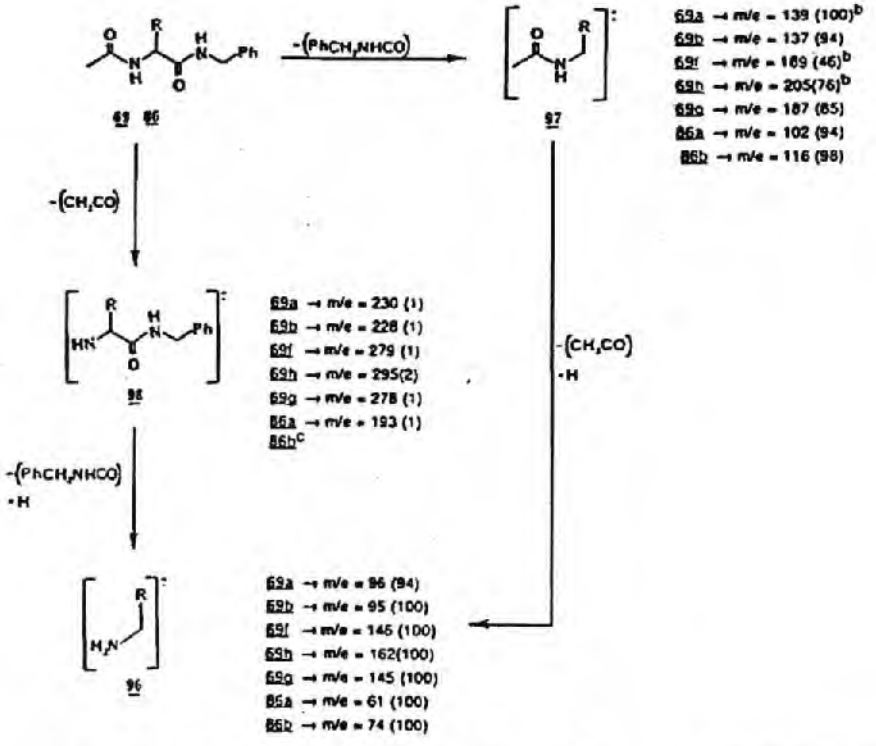
The ^1H NMR spectral data for the alkyl 2-acetamido-2-alkoxyacetates 80, the alkyl 2-substituted-2-acetamido-

Scheme 5. Selected Mass Spectral Patterns Observed for Alkyl 2-substituted-2-acetamidoacetates (81).[a]



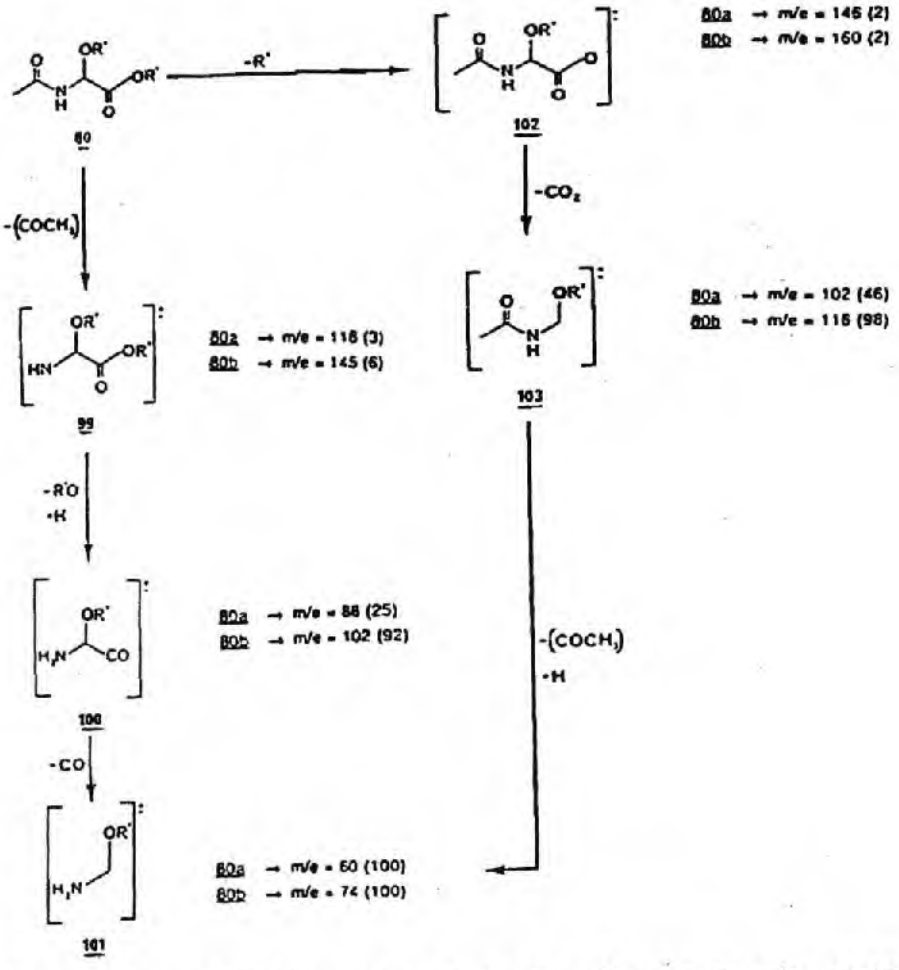
[a] Electron impact, ionizing potential: 70 eV. The number in parenthesis indicates the intensity of the ion relative to the base peak in the spectrum.

Scheme 6. Selected Mass Spectral Clevage Patterns. Observed for 2-Substituted-2-acetamido-N-benzylacetamides (69, 86)[a].



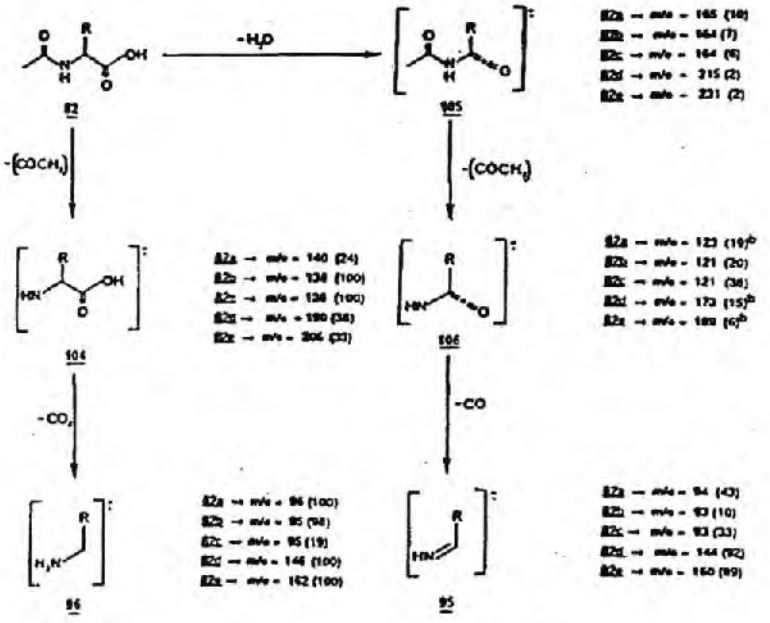
[a]Electron impact, ionizing potential: 70 eV. The number in parentheses indicates the intensity of the ion relative to the base peak in the spectrum. [b] This fragment shows a m/e one mass unit larger than expected in this scheme. This difference may be due to protonation in the mass spectrometer. [c] The ion was not observed.

Scheme 7. Selected Mass Spectral Cleavage Patterns Observed for Alkyl 2-Acetamido-2-alkoxyacetates (80)[a].



[a] Electron impact, ionizing potential: 70 eV. The number in parentheses indicates the intensity of the ion relative to the base peak in the spectrum.

Scheme 8. Selected Mass Spectral Patterns Observed for Alkyl 2-substituted -2-acetamidoacetates (82).[a]



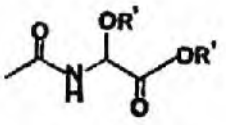
[a] Electron impact, ionizing potential: 70 eV. The number in parenthesis indicates the intensity of the ion relative to the base peak in the spectrum. [b] This fragment shows a m/e one mass unit larger than unexpected in this scheme. This difference may be due to protonation in the mass spectrometer.

acetates 81, the corresponding acids 82 and the 2-substituted-2-acetamido-N-benzylacetamides 67 and 93 are listed in Tables 23 - 26, respectively. The chemical shifts observed for the various protons present in these adducts were consistent with previously reported values for similar compounds.[68]

The proton on the α-carbon ranged from δ 5.05 - 5.86. This signal appeared consistently upfield (0.16 - 0.61 ppm) in the pyrrole derivatives versus all the other heteroaromatic substituted adducts. Several of the methylene protons in compounds 81 and 86 were disastereotopic due to the presence of the asymmetric center within the molecule. These were readily distinguished in the ^{1}H NMR spectra of these adducts and are indicated in Tables 24 and 25. This effect was most notable in the 2-acetamido-N-benzyl-2-alkoxyacetamides 86 and the pyrrole and furan derivatives 81b-d. In ethyl 2-acetamido-N-benzyl-2-ethoxy-acetamide (86b) both the ethyl ether and the benzylamide methylene protons were diastereotopic.

Characteristic signals were observed for the heteroaromatic moieties in derivatives 69, 81, 82 and 86.[157] Strong support for the proposed site of heteroaromatic substitution in compounds 69, 81, 82 and 86 was secured from the analysis of the proton chemical shift data in the aromatic region. In each case, the chemical shift values were in excellent agreement with previously reported compounds of comparable substitution patterns.[157] For example, in

Table 23. ^1H NMR Spectral Properties for Alkyl 2-Acetamido-2-alkoxy-acetates (80)[a].

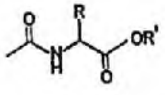


80

No.	R'	CH_3	NH	CH	OR'	COOR'
80a	CH_3	2.08(s)	6.70 - 6.80 (br d)	5.54(d,9.3)	3.46(s)	3.81(s)
80b	CH_2CH_3	2.08(s)	6.96(br d, 9.6)	5.60(d,9.6)	1.23[b](t,7.3) 3.70 (q,7.3)	1.32[b](t,7.3) 4.25 (q,7.3)

[a] The ^1H NMR spectra were taken in $CDCl_3$. The number in each entry is the chemical shift value (δ) observed in parts per million relative to TMS. The information in parentheses is the multiplicity of the signal, followed by the coupling constant *(J)* in Hertz.
[b] These peaks may be interchangeable.

Table 24. ^1H NMR Spectral Properties for Alkyl 2-Substituted-2-acetamidoacetates (81).[a]



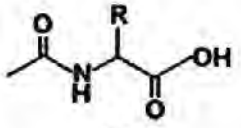
81

No.	R	R'	CH_3	NH	CH	R	R'
81a		CH_3	2.03(s)	7.02(d,7.8)	5.77 (d, 7.8)	6.35- 6.36(m, C_3-H,C_4-H) 7.36 (br s, C_5-H)	3.75 (s)
81b		CH_2CH_3	2.04(s)	6.35 - 6.54 (d,8.1)	5.75 (d, 8.1)	6.34- 6.35 (m,C_3-H,C_4-H) 7.35 - 7.36 (m,C_5-H)	1.24 (t,7.2,CH_3) 4.14 - 4.32 (m,CH_2)[b]
81c[c]		CH_2CH_3	1.88(s)	8.48 (d,6.9)	5.33 (d,6.9)	5.96 - 5.99 (m,C_3-H,C_4-H) 6.69 - 6.72 (m,C_5-H) 10.80- 10.99 (br s,NH)	1.16 (t,7.2, CH_3) 4.01 - 4.16 (m,CH_2)[b]

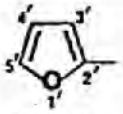
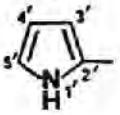
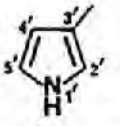
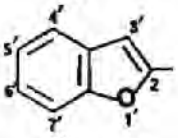
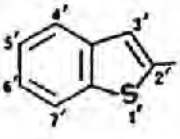
81d		CH_2CH_3	2.02(s)	6.25 (d,7.2)	5.53 (d,7.2)	6.17-6.30(m,C_4-H) 6.70-6.75 (m,C_5'H) 6.78-6.80 (m,C_2H) 8.45-8.60 (br s, NH)	1.25 (t,6.9,CH_3) 4.10 -4.30 (m,CH_2)[b]

[a] The ^{1}H NMR spectra were taken in $CDCl_3$ unless otherwise indicated. The number in each entry is the multiplicity of the signal, followed by the coupling constant (J) in Hertz, and in select cases the proposed assignment. [b] The methylene protons were diastereotopic. [c] The ^{1}H NMR spectrum was taken in DMSO-d_6.

Table 25. ^{1}H NMR Spectral Properties for 2-Substituted-2-acetamido-acetic Acids (82)[a].

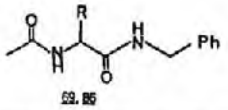


82

No.	R	CH_3	NH	CH	OH	R
82a		1.88(s)	8.69 (d,7.8)	5.45 (d,7.8)	b	6.39 - 6.45 (m,C_3-H,C_4-H) 7.65 (s, C_5-H)
82b		1.87(s)	8.40 (d,7.2)	5.31 (d,7.2)	b	5.96 (s, C_3-H) 5.97 (s, C_4-H) 6.87 (s, C_5-H) 10.79-10.85 (br s,NH)
82c		1.85(s)	8.23 (d,7.0)	5.05 (d,7.0)	b	6.04 (s, C_4-H) 6.69 (s, C_2-H) 6.76 (s, C_5-H) 10.68-10.86 (br s,NH)
82d		1.91(s)	8.85 (d,7.8)	5.66 (d,7.8)	b	6.90 (s, C_3-H) 7.23-7.35 (m,C_5-H,C_6-H) 7.55-7.65 (m,C_4-H,C_7-H)
82e[c]		2.08(s)	b	b	b	7.36-7.45(m,C_3-H,C_6-H,C_7-H) 7.81-7.84(m,C_4-H or C_5-H) 7.88-7.92 (m,C_4-H or C_5-H)

[a] The ^{1}H NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to TMS. The information in parentheses is the multiplicity of the signal, followed by the coupling constant (J) in Hertz and, in select cases the proposed assignment. [b] Signals not observed under the employed experimental conditions. [c] The ^{1}H NMR spectrum was taken in D_2O/NaOD.

Table 26. ^1H NMR Spectral Properties for 2-Substituted-2-acetamido-N-benzylacetamides (69 , 86).[a]



69, 86

No.	R	CH_3	NHCH	CH	$NHCH_2$	CH_2	Ph	R
69b[b]	Ph	1.91(s)	8.38 - 8.96 (m)	5.50(d,7.9)	8.38-8.86(m)	4.27 (d,5.6)	7.36 (s)	7.36(m,Ph)
69a		1.90(s)	8.57 (d, 8.1)	5.58 (d,8.1)	8.73 (t, 6.0)	4.31 (d,6.0)	7.20-7.36(m)	6.27-6.33 (m,C_3-H) 6.40-6.44 (m,C_4-H) 7.60-7.64 (m,C_5-H)
69b[c]		1.93(s)	7.04 (d,6.9)	5.42 (d,6.9)	7.17 (t,6.0)	4.35 (d,6.0)	7.10-7.47 (m)	6.00-6.18 (m,C_3-H,C_4-H) 6.68- 6.72 (m,C_5-H) 9.25 - 9.35 (br s, NH)
69b[d]		1.91(s)	8.64 (d, 7.9)	5.74 (d, 7.9)	8.85 (t, 6.0)	4.31 (d, 6.0)	6.99-7.44 (m)	6.99 - 7.44 (m)
69d[d]		1.91(s)	8.55 (d, 7.9)	5.61 (d, 7.9)	8.74 (t,5.2)	4.29 (d,5.2)	7.15-7.50 (m)	7.15 - 7.50 (m)

69g[d]		1.94(s)	8.63 (d, 7.9)	5.68 (d, 7.9)	8.83 (t, 5.2)	4.30 (d,5.2)	7.15-7.91 (m)	7.15 - 7.91 (m)
69f		1.94(s)	8.74 (d, 8.1)	5.77 (d, 8.1)	8.86 (t,5.7)	4.34 (d,5.7)	7.24-7.32 (m)	7.24 - 7.32 (m,C_3-H,C_5-H,C_6-H) 7.54 (d, 7.0, C_4-H or C_7-H) 7.62 (d, 7.0, C_4-H or C_7-H)
69n		1.90(s)	7.88 (d, 7.2)	5.72 (d, 7.2)	8.13 (t,6.0)	4.36 (d, 6.0)	6.90-7.37 (m)	6.90 - 7.37 (m, C_2-H) 7.02 (dd, 7.5, 7.5, C_5-H or C_6-H) 7.12 (dd, 7.5, 7.5, C_5-H or C_6-H) 7.39 (d, 7.5, C_4-H or C_7-H) 7.85 (d,7.5, C_4-H or C_7-H) 10.30 - 10.60 (br s, NH)
69h		1.94(s)	8.76 (d, 8.1)	5.86 (d, 8.1)	8.97 (t,5.7)	4.34 (d, 5.7)	7.20-7.38 (m)	7.20 - 7.38 (m, C_3-H,C_6-H,C_7-H) 7.77 - 7.80 (m, C_4-H or C_5-H) 7.89 - 7.93 (m, C_4-H or C_5-H)
86a[e]	OCH_3	2.06(s)	7.12 (d, 8.7)	5.52 (d, 8.7)	t	4.40-4.35 (m)[g]	7.20-7.40(m)	3.39 (s, CH_3)
86b[e]	OCH_2CH_3	2.07(s)	6.63 (d, 8.7)	5.60 (d, 8.7)	7.00 (br s)	4.40 - 4.54 (m)[g]	7.26 - 7.36 (m)	1.20 (t, 7.0, CH_3) 3.60 - 3.76 (m, CH_2)[g]

[a] The ^1H NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to TMS. The information in parentheses is the multiplicity of the signal, followed by the coupling constant (J in Hertz and in selected cases by the proposed assignment. [b] Ref. 68. [c] The ^1H NMR spectrum was taken in CD_3CN. [d] Ref. 104. [e] The ^1H NMR spectra were taken in $CDCl_3$. [f] This signal was not detected and may have overlapped with the aromatic protons of the phenyl group. [g] The methylene protons were diastereotopic.

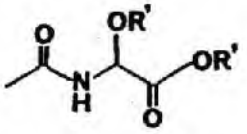
the 2-pyrryl adducts 69b, 81c,d and 82b two upfield signals close to 6 ppm (the β-CH's) and one downfield signal near 7 ppm (the α-CH) were observed whereas, in the 3-pyrryl derivatives 81d and 82b the opposite pattern was obtained.

d. ^{13}C NMR Spectral Data.

The ^{13}C NMR spectral data for the alkyl 2-acetamido-2-alkoxyacetates 80, the alkyl 2-substituted-2-acetamidoacetates 81, the corresponding acids 82, and the 2-substituted -2-acetamido-N-benzylacetamides 69 and 86 are listed in Tables 27 - 30, respectively. The chemical shift values for the various carbon atoms present in these compounds agreed with expectations.[58,158 - 160]

Analysis of the composite set of data revealed a consistent set of resonances for the different carbon atoms present in the functionalized amino acid derivatives. Only in the case of 2-acetamido-2-benzo[b]thiopheneacetic acid (82e) were the resonances shifted downfield (4.0 - 9.3 ppm) from the expected values. This perturbation may be attributed to the unusual nature of the solvent system (D_2O/NaOD) employed for 82e. The most diagnostic signal observed for the amino acid derivatives was the methine carbon atom. This signal always appeared between 49.98 - 52.88 ppm for 69, 81, 82 and 86. In the alkoxy derivatives 80 and 86, the corresponding signal appeared downfield (ca. 28 ppm) from this value. This shift is in agreement with the known electronic effect exerted by oxygen substituents.[160]

Table 27. ^{13}C Spectral Properties for Alkyl 2-Acetamido-2-alkoxyacetates (80).[a]

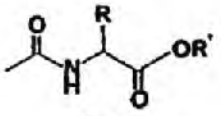


80

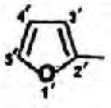
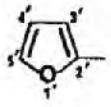
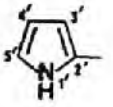
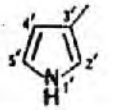
No.	R'	CH_3	CH_3CO	CH	COO	OR'	COOR'
80a	CH_3	22.98	168.49	78.16	170.67	56.48	52.69
80b	CH_2CH_3	22.91	168.25	76.85	170.48	13.78[b]	14.75[b]
						64.72	61.74

a ^{13}C NMR spectra were taken in $CDCl_3$. The number in each entry is the chemical shift value observed in parts per million relative to TMS. [b] These peaks may be interchangeable.

Table 28. ^{13}C NMR Spectral Properties for Alkyl 2-Substitued-2-acetamidoacetates (81).[a]

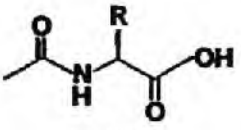


81

No	R	R'	CH_3	CH_3CO	CH	COO	R	R'
81a		CH_3	22.69	169.57	52.88	169.96	108.72($C_{3'}$) 110.78 ($C_{4'}$) 142.84 ($C_{5'}$) 148.89 ($C_{2'}$)	50.43(CH_3)
81b		CH_2CH_3	22.81	168.89	50.33	169.43	108.49($C_{3'}$) 110.62($C_{4'}$) 142.64($C_{5'}$) 148.85($C_{2'}$)	13.91(CH_3) 62.08(CH_2)
81c		CH_2CH_3	22.79	169.24	50.73	170.11	106.35($C_{3'}$) 107.52($C_{4'}$) 118.07($C_{5'}$) 125.28($C_{2'}$)	13.93(CH_3) 61.38(CH_2)
81d		CH_2CH_3	22.79	169.79	50.73	171.76	106.78($C_{4'}$) 116.56($C_{2'}$) 118.25($C_{3'}$) 118.63($C_{5'}$)	13.93(CH_3) 61.38(CH_2)

a ^{13}C NMR spectra were taken in $CDCl_3$. The number in each entry is the chemical shift value observed in parts per million relative to TMS. The information in parentheses in select cases is the proposed assignment.

Table 29. ^{13}C NMR Spectral Properties for 2-Substituted-2-acetamido-acetic Acids (82).[a]



82

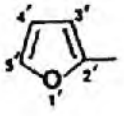
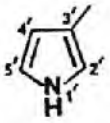
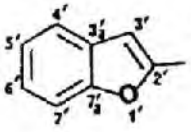
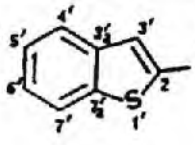
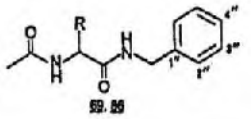
No.	R	CH_3	$COCH_3$	CH	COOH	R
82a		22.10	169.21[b]	50.16	170.01[b]	108.17 ($C_{3'}$) 110.66 ($C_{4'}$) 142.83 ($C_{5'}$) 149.75 ($C_{2'}$)
82b		22.16	169.15	50.45	171.56	106.21 ($C_{3'}$) 107.45 ($C_{4'}$) 117.83 ($C_{5'}$) 126.11 ($C_{2'}$)
82c		22.18	169.13[b]	50.57	173.00[b]	106.98 ($C_{4'}$) 116.28 ($C_{2'}$) 117.83 ($C_{3'}$,$C_{5'}$)
82d		22.11	169.20[b]	50.51	169.62[b]	104.93 ($C_{3'}$) 111.06 ($C_{7'}$) 121.22 ($C_{4'}$) 123.02 ($C_{5'}$) 124.51 ($C_{6'}$) 127.65 ($C_{3a'}$) 152.92 ($C_{7a'}$) 154.10 ($C_{2'}$)

Table 29 con't

No.	R	CH_3	$COCH_3$	CH	COOH	R
82e[c]		26.33	177.65	59.56[d] 59.85 60.14	179.62	126.86 ($C_{4'}$ or $C_{7'}$) 127.18 ($C_{4'}$ or $C_{7'}$) 128.12 ($C_{3'}$) 129.08 ($C_{5'}$ or $C_{6'}$) 129.09($C_{5'}$ or $C_{6'}$) 143.66($C_{3'a}$ or $C_{7'a}$) 143.71 ($C_{3'a}$ or $C_{7'a}$) 146.03 ($C_{2'}$)

[a] The ^{13}C NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value observed in parts per million relative to TMS. [b] These sets of peaks may be interchangeable. [c] The ^{13}C NMR spectrum was taken in D_2O/NaOD. The chemical shift values are relative to DSS. [d] The methine α-carbon is assumed to have undergone C - H → C - D exchange, giving rise to a triplet pattern for this signal.

Table 30. ^{13}C NMR Spectral Properties of 2-Substituted-2-acetamido-N-benzylacetamides (69 , 86).[a]



69, 86

No.	R	CH_3	$COCH_3$	CH	COCH	CH_2	$C_{1'}$	$C_{2''}$,$C_{3''}$	$C_{4''}$	R
68b[b]		22.30	168.90[c]	56.30	169.90[c]	42.00	139.00[d]	127.40[e,f] 128.10[e,f]	127.00[g]	126.00[e,f] ($C_{2'}$ or $C_{3'}$) 127.10[e,f] ($C_{2'}$ or $C_{3'}$) 128.10[g] ($C_{4'}$) 138.90[d] ($C_{1'}$)
69a		22.35	168.02[c]	50.95	169.30[c]	42.27	139.05	126.82[f,h] 127.08[f,h]	128.27	107.60($C_{3'}$) 110.55 ($C_{4'}$) 142.58 ($C_{5'}$) 151.16 ($C_{2'}$)

69b		22.02	170.94[c]	52.85	171.21[c]	43.83	140.01	128.01[f,h] 128.09[f,h]	129.49	107.57 (C_3') 108.85 (C_4') 119.33 (C_5') 127.96 (C_2')
69c[j]		22.40	169.20[c]	52.20	169.30[c]	42.30	139.00	127.30[f,h] 128.30[f,h]	126.90	125.60 (C_3' or C_4') 125.80 (C_3' or C_4') 126.60 (C_5') 141.40 (C_2')
69d[j]		22.50	169.00[c]	52.50	169.80[c]	42.00	139.00	127.00[f,h] 128.20[f,h]	127.00	122.40 (C_4') 126.10 (C_2' or C_5') 126.70 (C_2' or C_5') 139.20 (C_3')
69e[j]		22.50	169.20[c]	56.60	170.00[c]	42.20	139.10	127.10[d] 128.40[d]	]	[

59l		22.27	167.40	51.22	169.26	42.30	138.87	127.01[f,h] 127.69[f,h]	126.14	104.34 (C_3') 110.90 (C_7') 121.05 (C_4') 122.90 (C_5') 124.28 (C_6') 126.73 ($C_{3'a}$) 154.10 ($C_{7'a}$) 154.30 (C_2')
59o		22.32	169.13[c]	49.98	170.81[c]	42.23	139.44	127.33[f,h] 128.18[f,h]	126.71	111.51 (C_7') 112.08 (C_3') 116.76 (C_4' or C_6') 119.24 (C_4' or C_6') 121.37 (C_5') 123.94 (C_2') 128.58 ($C_{3'a}$) 136.38 ($C_{7'a}$)

69b		22.34	168.43[c]	52.70	169.12[c]	42.38	142.58	127.27[f,h] 128.27[f,h]	126.89	122.15 ($C_{4'}$ or $C_{7'}$) 122.32 ($C_{4'}$ or $C_{7'}$) 123.45 ($C_{3'}$) 124.37 ($C_{5'}$ or $C_{6'}$) 124.41 ($C_{5'}$ or $C_{6'}$) 138.84 ($C_{3'a}$ or $C_{7'a}$) 138.95 ($C_{3'a}$ or $C_{7'a}$) 142.58 ($C_{2'}$)
86a[k]	OCH_3	23.03	167.91	76.94	171.57	43.51	137.45	127.70[f,h] 128.70[f,h]	127.62	55.84 (CH_3)
86b[k]	OCH_2CH_3	23.25	168.13	77.43	171.29	43.60	137.57	127.69[h,l] 128.79[f,h]	127.69[l]	15.06 (CH_3) 64.51 (CH_2)

[a] The ^{13}C NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value in parts per million relative to TMS. The number in parentheses in select cases is the proposed assignment. [b] Ref. 68. [c,d,e] These sets of peaks may be interchangeable. [f] The peak had approximately twice the intensity of nearby peaks. [g] These peaks may be interchangeable. [h] The close proximity of the two peaks did not permit the assignment of these resonances. [i] Ref. 104. [j] The remaining aromatic carbon signals (125.50, 126.00, 126.10, 126.30, 126.80, 127.50, 127.70, 127.90, 132.40, 132.80, 136.50) were not assigned due to their similar chemical shift values. [k] The 13 C NMR spectra were taken in $CDCl_3$. [l] The peak had approximately three time the intensity of nearby peaks.

The chemical shifts values observed for the heterocyclic carbon atoms provided strong support for the proposed substitution site in this portion of the molecule. In all cases, the chemical shift value for the substituted aromatic carbons was downfield (6.0 - 20.0 ppm) versus the corresponding signal in the unsubstituted heterocycle. This trend was consistent with previous observations.[158]

3. Pharmacological Evaluation.

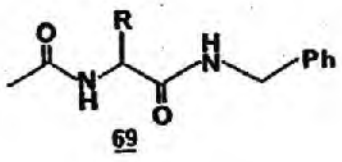
The 2-substituted-2-acetamido-N-benzylacetamides 69 and 86 prepared in this study were submitted to the Eli Lilly Corporation, Indianapolis, Indiana, for evaluation of their anticonvulsant activity. The previous results obtained by Kohn and co-workers[68,102], for related compounds suggested that these substances would be most active in the MES seizure test. Accordingly, only this anticonvulsant screening procedure was conducted. Each of the substances were administered intraperitoneally at three doses (300, 100 and 30 mg/kg) to groups of four mice (male albino, CF-1 strain). Those compounds which were found to be effective in the protection of seizures induced by electrical stimulation were further tested with better monitoring of dosages in groups of twelve mice. This procedure permitted the determination of the Effective Dose (ED) 50 value for the drug candidate. This value is the dose which is effective in protecting 50 % of the animals tested against seizures. In addition to this test, the neurologic toxicity (TOX) of some of the biologically active compounds was evaluated by means of the

horizontal screen test using the same conditions (dosages, number of animals tested) employed in the ED 50 determination. This procedure permitted the calculation of the Toxic Dose (TD) 50 value which corresponds to the dose that leads to toxic manisfestations in 50 % of the animals screened. Tables 31 - 34 summarize the pharmacological results observed for compounds 69, 86 and some clinically used anticonvulsant agents.

For the purpose of the discussion of the results, several assumptions have been made. First, it is assumed that each substrate is influenced to the same degree by the many processes (i.e., absorption, distribution, metabolism, elimination) which affect a drug's action from the time it is administered to the time the biological response occurs. Second, it is assumed that the active agent is the substrate itself and not a metabolite of the compound. No tests were conducted to verify the validity of these assumptions.

The 2-acetamido-N-benzylacetamides bearing a five membered ring heteroaromatic at the α-carbon (69 a-d) (Table 31) all displayed outstanding anticonvulsant properties in the MES seizure test. Within this series, the 2-furyl (69a) and the 2-pyrryl (69) derivatives were more potent than the parent aromatic substrate 68b, while the 2-thienyl (69c) and 3-thienyl (69d) adducts were less active than 68b. Of particular note, 69a and 69b exhibited activity similar to phenytoin (13a) and diazepam (24c) (Table 34) under comparable conditions. Of these two medicinal agents,

Table 31. Pharmacological Evaluation of 2-Substituted-2-acetamido-N-benzylacetamides (69) Containing a Monocyclic Heterocyclic Moiety.[a]

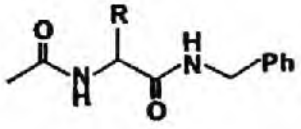


69

No.	R	MES[b], ED50	Tox[c], TD50
68b[d]	Phenyl	32.1 (27.5 - 40.2)	> 40[e]
69a	2-Furyl	10.3 (9.1 - 11.6)	~ 40
69b	2-Pyrryl	16.1 (13.2-19.9)	30 - 100
69c[f]	2-Thienyl	44.8 (38.9-51.4)	30 - 100
69d[f]	3-Thienyl	87.8 (69.9 - 150.0)	> 100

[a] The compounds were administered intraperitoneally. ED50 and TD50 are in mg/kg. The number in parentheses are the 95 % confidence intervals. [b] Maximal electroshock seizure test. [c] Horizontal screen test (neurotoxicity) unless otherwise indicated. [d] Ref. 162. [e]Rotarod ataxia test. [f] Ref. 104.

Table 32. Pharmacological Evaluation of 2-Substituted-2-acetamido-N-benzylacetamide (69) Containing a Benzo-fused Heteroaromatic Moiety.[a]

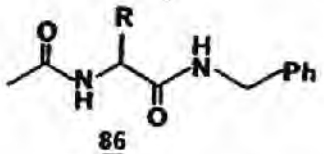


69

No.	R	MES[b], ED50	Tox[c], TD50
69e[d]	β-Naphtyl	> 300	> 300
69f	2-Benzofuryl	> 100, < 300	> 100, < 300
69g	3-Indolyl	> 300	< 300
69h	2-Benzo[b]thienyl	> 100, < 300	> 100, < 300

[a]The compounds were administered intraperitoneally. ED50 and TD50 are in mg/kg. [b] Maximal electroshock seizure test. [c] Horizontal screen test (neurotoxicity). [d] Ref. 104.

Table 33. Pharmacological Evaluation of 2-Alkoxy-2-acetamido-N-benzylacetamide (86).[a]



86

No.	R	MES[b], ED50	Tox[c], TD50
68a[d]	CH_3	51.0 (46.6 - 58.6)	> 100[e]
68c[f]	$CH_2CH_2SCH_3$	> 100, < 300	g
68d[f]	$CH(CH_3)_2$	> 100, < 300	g
86a	OCH_3	98.3	< 300
86b	OCH_2CH_3	62.0(51.1 - 78.4)	> 112

[a]The compounds were administered intraperitoneally. ED50 and TD50 are in mg/kg. The numbers in parentheses are the 95 % confidence intervals. [b] Maximal electroshock seizure test. [c] Horizontal screen test (neurotoxicity) unless otherwise indicated. [d] Ref. 104. [e] Rotarod ataxia test. [f] Ref. 68. [g] These values were not determined.

Table 34. Pharmacological Activity of Some Proven Anticonvulsants.[a]

No.	Name	MES[b], ED50	Tox[c], TD50
13a[d]	Phenytoin	14.0	86
24c[d]	Diazepam	18.7	57
13b[e]	Metphenytoin	61.0	154
15a[e]	Phenobarbital	20.1	97
26[e]	Valproic Acid	664.8	1264

[a]The compounds were administered intraperitoneally. ED50 and TD50 are in mg/kg. [b] Maximal electroshock seizure test. [c] Rotarod ataxia test (neurotoxity). [d] Ref. 162. [e] Ref. 163.

phenytoin (13a) is the most widely prescribed drug today for the treatment of epilepsies. Examination of the TD 50 values for the monocyclic heteroaromatic adducts 69 indicated that neurologic toxicity closely paralleled their activity in the MES seizure test. The TD 50 value for the most active compound, the furyl derivative 69a, was approximately 40 mg/kg. The observed data permitted several tentative conclusions. First, compounds 69 a-d like 68b all contain an electron rich π-aromatic system. Second, all of the heteroaromatic substituents at the α-carbon were relatively small. Moreover, within this series of five compounds the smallest analogues (69a, 69b) were the most active.

All of the fused ring heteroaromatic compounds 69 f-h, as well as the parent naphtyl adduct 69e (Table 32) were considerably less active than their monocyclic counterparts (Table 31). None displayed significant activity at dosages below 100 mg/kg. Of these compounds, the 2-benzofuryl (69f) and the 2-benzo[b]thienyl (69h) derivatives were the most potent agents. The dramatic decrease in biological activity versus their monocyclic counterparts suggested that stringent steric requirements may exist for maximal biological activity.

The 2-acetamido-N-benzyl-2-alkoxyacetamides 86 intermediates utilized in the synthesis of many of the heteroaromatic functionalized amino acids derivatives (Method B) were also submitted for pharmacological testing (Table 33). Included in this table are several alkyl and substituted alkyl analogues which

serve as suitable reference compounds. Both the 2-methoxy (86a) and the 2-ethoxy (86b) derivatives exhibited notable activity in the MES seizure test. The pharmacological activity of 86b was comparable to metphenytoin (13b) under similar conditions. The limited results secured from this series of compounds do not permit us to make any tentative conclusions concerning the role of the oxygen atom in modulating the biological activity of these derivatives.

The composite set of data (Tables 31 - 33) suggests that stringent steric constraints exist at the receptor site for drug binding. Moreover, among the four monocyclic heteroaromatic compounds, the pharmacological activity increased with decreasing resonance stability of the aromatic moiety. This trend suggests that the biological activity is modulated by the ability of the drug candidate to bind with an electrophilic site at the receptor.

III. **Experimental Section. General Methods. Syntheses.** Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Perkin-Elmer 1330 spectrophotometer and calibrated against the 1601 cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were taken on a Nicolet NT-300 instrument. Chemical shifts are in parts per million (δ values) relative to tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) and coupling constants (*J*

values) are in Hertz. Mass spectra were performed at the Eli Lilly Corporation, Indianapolis, Indiana ,or by Dr. John Chinn at the Department of Chemistry, University of Texas at Austin. Elemental analysis was conducted at the Eli Lilly Corporation, Indianapolis, Indiana. Furan (70a), pyrrole (74), ethyl chloroformate, isobutyl chloroformate, benzylamine (83), methanesulfonic acid, boron trifluoride etherate, benzo[b]thiophene (76), indole (72) and triethylamine were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin; ethyl acetamidocyanoacetate and $NaBH_4$ were obtained from Sigma Chemical Company, St. Louis, Missouri; benzofuran (75) was obtained from Chemicals Procurement Laboratories Inc., College Point, New York; and benzothienylglycine (73e) was provided by Eli Lilly Corporation, Indianapolis, Indiana. Acetonitrile and triethylamine were distilled from CaH_2 and tetrahydrofuran and ethyl ether were distilled from Na/benzophenone. Furan (70a), pyrrole (74), benzofuran (75), acetic anhydride (85), ethyl chloroformate, isobutyl chloroformate and methanesulfonic acid were fractionally distilled prior to use. All other chemicals were of the highest grade available and were used without further purification. The mixed anhydride reactions and the amidoalkylation transformations using boron trifluoride etherate were run under anhydrous conditions. In these cases, all glassware was flame-dried under N_2, the solid starting materials were dried in vacuo immediately prior to use, and the reactions were conducted under a positive pressure of N_2. Preparative flash column chromatography was run using Merck silica gel, grade 60, 230-240 mesh, 60 Å from Aldrich Chemical Company, Milwaukee, Wisconsin.

Method A.

Preparation of Methyl 2-Acetamido-2-methoxyacetate (80a). Sulfuric acid (95%, 4 mL, 70 mmol) was added to a methanolic solution (230 mL) of 2-acetamido-2-hydroxyacetic acid (79) (13.30 g, 100 mmol). The solution was stirred at room temperature (48 h), neutralized with solid $NaHCO_3$, filtered, and then the methanol was removed in vacuo. The pink oil was distilled under vacuum (70-120 °C, 0.6 torr) to give a colorless oil which was recrystallized from petroleum ether (35-60 °C) to yield 5.20 g (32%) of the desired product: R_f 0.52 (98:2 chloroform/methanol); mp 44-46 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, CH_3CO), 3.46 (s, OCH_3), 3.81 (s, $COOCH_3$), 5,54 (d, J = 9.3 Hz, CH), 6.70-6.80 (br d, NH) ; ^{13}C NMR (75 MHz, $CDCl_3$) 22.98 (CH_3CO), 52.69 ($COOCH_3$), 56.48 (CH_3O), 78.16 (CH), 168.49 (CH_3CO), 170.67 ($COOCH_3$) ppm; IR (KBr) 3270, 2820, 1735, 1650 (br), 1505, 1205, 1110, 1090, 1010, 930, 900 cm^{-1}; mass spectrum, m/e (relative intensity) 162 (1), 146 (2), 131 (3), 118 (3), 102 (46), 88 (25), 60 (100).

Anal. Calcd for $C_6H_{11}NO_4$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.46; H, 7.14; N, 8.72.

Preparation of Ethyl 2-Acetamido-2-ethoxyacetate (80b). Sulfuric acid (95%, 4 mL, 70 mmol) was added to an ethanolic solution (250 mL) of 2-acetamido-2-hydroxyacetic acid (79) (13.30 g, 100 mmol). The solution was stirred at room temperature (48 h) and then poured into a chilled saturated aqueous solution of $NaHCO_3$ (250 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried ($MgSO_4$) and

evaporated to dryness in vacuo. The oily residue was purified by distillation under vacuum (70-95 °C, 0.3-0.8 torr) to give 10.52 g (55%) of a white waxy solid: R_f 0.53 (98:2 chloroform/methanol): mp 35-36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, OCH_2CH_3), 1.32 (t, J = 7.3 Hz, OCH_2CH_3), 2.08 (s, CH_3CO), 3.70 (q, J = 7.3 Hz, OCH_2CH_3), 4.25 (q, J = 7.3 Hz, $COOCH_2CH_3$), 5.60 (d, J = 9.6 Hz, CH), 6.96 (br d, J = 9.6 Hz, NH) ; ^{13}C NMR (75 MHz, $CDCl_3$) 13.78 (OCH_2CH_3), 14.75 (OCH_2CH_3), 22.91 (CH_3CO), 61.74 ($COOCH_2CH_3$), 64.72 (OCH_2CH_3), 76.85 (CH), 168.25 (CH_3CO), 170.48 ($COOCH_2CH_3$) ppm; IR (KBr) 3400 (br), 1735, 1655 (br), 1200, 1085 (br), 1010, 930, 890 cm^{-1}; mass spectrum, m/e (relative intensity) 190 (5), 160 (2), 144 (38), 116 (98), 102 (92), 74 (100); high resolution mass spectrum, calcd for $C_8H_{16}NO_4$ 190.1079, found 190.1087.

Preparation of Alkyl 2-Substituted-2-acetamidoacetates (81).General Procedure. The alkyl 2-acetamido-2-alkoxyacetate (80) (1 equiv) was suspended in anhydrous ethyl ether (60 mL/10 mmol), and then boron trifluoride etherate (1.6 equiv) was added in one portion followed by the heterocycle (4 equiv). The solution was stirred at room temperature (72 h) and then poured into an ice-cold saturated aqueous solution (50 mL) of $NaHCO_3$, stirred at ice temperature (20 min), and then extracted with ethyl acetate (3 x 40 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to dryness in vacuo. The resulting oil was purified by flash chromatography or recrystallization.

Preparation of Methyl α-Acetamido-2-furanacetate (81a). The preceeding procedure was employed using methyl 2-acetamido-2-

methoxyacetate (80a) (1.68 g, 10.4 mmol), boron trifluoride etherate (2.71 g, 2.35 mL, 16.6 mmol) and furan (70a) (2.81 g, 3 mL, 41.6 mmol) to produce a black oil which was purified by flash chromatography (99:1 chloroform/ methanol) to give1.28 g (62%) of the desired product as a beige solid: R_f 0.32 (99:1 chloroform/methanol); mp 80-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, CH_3CO), 3.75 (s, $COOCH_3$), 5.77 (d, J = 7.8 Hz, CH), 6.35-6.36 (m, C_3-H, C_4-H), 7.02 (d, J = 7.8 Hz, NH), 7.36 (br s, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.69 (CH_3CO), 50.43 ($COOCH_3$), 52.88 (CH), 108.72 ($C_{3'}$),110.78 ($C_{4'}$), 142.84 ($C_{5'}$), 148.89 ($C_{2'}$), 169.57 (CH_3CO), 169.96 ($COOCH_2CH_3$) ppm; IR (KBr) 3200, 1740, 1620 (br), 1530 (br), 1205, 1090, 1020, 900 , 890 cm^{-1}; mass spectrum, m/e (relative intensity) 197 (14), 165 (35), 154 (78), 138 (36), 96 (100), 94 (93), 69 (16).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.96; H, 5.40; N, 7.27.

Preparation of Ethyl α-Acetamido-2-furanacetate (81b). The preceeding procedure was employed using ethyl 2-acetamido-2-ethoxyacetate (80b) (3.72 g, 19.7 mmol), boron trifluoride etherate (3.75 g, 3.25 mL, 26.4 mmol) and furan (70a) (5.35 g, 5.70 mL, 78.6 mmol) to produce a black oil which was purified by two successive flash chromatographies ((a) 100% chloroform, (b) 70:30 ethyl ether/pentane ,then 97:3 chloroform/ methanol) to give 2.11 g (51%) of the desired product as a white solid: R_f 0.17 (100% chloroform); mp 69-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, $COOCH_2CH_3$), 2.04 (s, CH_3CO), 4.14 - 4.32 (m, $COOCH_2CH_3$), 5.75 (d, J = 8.1 Hz, CH), 6.34-6.35 (m, C_3-H, C_4-H), 6.35-6.54 (br d, J = 8.1 Hz, NH), 7.35-7.36 (m, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.91

($COOCH_2CH_3$), 22.81 (CH_3CO), 50.33 (CH), 62.08 ($COOCH_2CH_3$), 108.49 ($C_{3'}$), 110.62 ($C_{4'}$), 142.64 ($C_{5'}$), 148.85 ($C_{2'}$), 168.89 (CH_3CO), 169.43 ($COOCH_2CH_3$) ppm; IR (KBr) 3200, 1750, 1635 (br), 1530, 1380, 1335, 1205, 1180, 1020, 890, 745, 595 cm^{-1};mass spectrum,m/e(relative intensity) 211 (8),168 (32), 138 (27), 96 (100), 94 (27).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.98; H, 6.19; N, 6.83.

Preparation of Ethyl α-Acetamido-2-pyrroleacetate (81c) and α-Acetamido-3-pyrroleacetate (81d) .The preceeding procedure was employed using ethyl 2-acetamido-2-ethoxyacetate (80b) (3.78 g, 20 mmol), boron trifluoride etherate (4.53 g, 4.84 mL, 32 mmol) and pyrrole (74) (5.36 g, 5.54 mL, 80 mmol) to produce a black oil. TLC analysis indicated the presence of two major compounds (R_f 0.33 and R_f 0.19, 98:2 chloroform/methanol) which were isolated by flash chromatography (98:2 chloroform/methanol).

The initial fraction (R_f 0.33, 98:2 chloroform/methanol) was further purified by another flash chromatography (97:3 dichloromethane/methanol) to produce 1.74 g (41%) of the desired product as a light brown solid: mp 104-106 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.16 (t, J =7.2 Hz, CH_2CH_3), 1.88 (s, CH_3CO), 4.01-4.16 (m, CH_2CH_3), 5.33 (d, J = 6.9 Hz, CH), 5.96-5.99 (m, $C_{3'}H$, $C_{4'}H$), 6.69-6.72 (m, $C_{5'}H$), 8.48 (d, J =6.9 Hz, CONH), 10.80-10.99 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 13.93 (CH_2CH_3) 22.79 (CH_3CO), 50.73 (CH), 61.38 (CH_2CH_3), 106.35 ($C_{3'}$), 107.52 ($C_{4'}$), 118.07 ($C_{5'}$), 125.28 ($C_{2'}$), 169.24 (CH_3CO), 170.11 ($COOCH_2CH_3$) ppm; IR (KBr) 3310, 3200, 1715, 1635 (br), 1515 (br), 1220, 1180, 1085, 1010, 890 cm^{-1};

mass spectrum, m/e (relative intensity) 210 (22), 167 (36), 137 (54), 121 (7), 106 (7), 95 (100), 93 (97), 79 (5), 68 (53).

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.20; H, 6.55; N, 13.13.

The second fraction (R_f 0.19, 98:2 chloroform/methanol) was further purified by a second flash chromatography (95:5 dichloromethane/ methanol) to give 0.52 g (12%) of the desired product as a beige solid: mp 92-93 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.25 (t, J =6.9 Hz, CH_2CH_3), 2.02 (s, CH_3CO), 4.10-4.30 (m, CH_2CH_3), 5.53 (d, J =7.2 Hz, CH), 6.17-6.30 (m, C_4·H), 6.25 (d, J = 7.2 Hz, CONH), 6.70-6.75 (m, C_5·H), 6.78-6.80 (m, C_2·H), 8.45-8.60 (brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$), 13.93 (CH_2CH_3), 22.79 (CH_3CO), 50.73 (CH), 61.38 (CH_2CH_3), 106.78 (C_4·), 116.56 (C_2·), 118.25 (C_3·), 118.63 (C_5·), 169.79 ($COCH_3$), 171.76 ($COOCH_2CH_3$) ppm; IR (kBr) 3320, 3240, 1720, 1640 (br), 1510, 1400 (br), 1210, 1180, 1010, 890 cm^{-1}; mass spectrum, m/e (relative intensity) 210 (12), 167 (16), 152 (5), 137 (31), 121 (3), 95 (100), 93 (100), 80 (5), 68 (71); high resolution mass spectrum, calcd for $C_{10}H_{14}N_2O_3$ 210.1004, found 210.1015.

Preparation of 2-Substituted 2-Acetamidoacetic Acids (82). Preparation of α-Acetamido-2-furanacetic Acid (82a). Ethyl α-acetamido-2-furanacetate (81b) (2.93 g, 13.8 mmol) was dissolved in 90:10 ethanol/water (110 mL), and KOH (0.85 g, 15.2 mmol) was added and the solution was stirred at room temperature (48 h). The solution was concentrated in vacuo and the residue diluted with H_2O (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The aqueous layer was then acidified with 8.5% H_3PO_4 (25 mL) and extracted with ethyl acetate (3 x 200

mL). The organic layers were combined, dried (Na_2SO_4) and then evaporated to dryness in vacuo to produce a beige solid (2.00 g) which was recrystallized (acetonitrile) to yield 1.31 g (51%) of the desired product as beige crystals: R_f 0.37 (8:1:1 isopropanol/NH_4OH/H_2O); mp 171-172 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.88 (s, CH_3), 5.45 (d, J = 7.8 Hz, CH), 6.39-6.45 (m, C_3·H, C_4·H), 7.65 (s, C_5·H), 8.69 (d, J = 7.8 Hz, NH). [The carboxyl proton was not detected.]. ^{13}C NMR (75 MHz, DMSO- d_6) 22.10 (CH_3), 50.16 (CH), 108.17 (C_3·), 110.66 (C_4·), 142.83 (C_5·), 149.75 (C_2·) 169.21 (CH_3CO), 170.01 (COOH) ppm; IR (KBr) 3320, 3100, 1705, 1580 (br), 1530, 1410, 1360, 1320, 1280, 1270, 1225, 1210, 1145, 1100, 1010, 890, 640, 660, 610, 570, 400 cm^{-1}; mass spectrum, m/e (relative intensity) 183 (2), 165 (10), 140 (24), 123 (19), 109 (1), 96 (100), 94 (43), 80 (2), 69 (8).

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.61; H, 4.93; N, 7.94.

Preparation of α-Acetamido-2-pyrroleacetic Acid (82b). Ethyl α-acetamido-2-pyrroleacetate (81c) (2.11 g, 10 mmol) was dissolved in 90:10 ethanol/water (88 mL), and then KOH (0.61 g, 11 mmol) was added and the resulting solution stirred at room temperature (48 h). The solution was concentrated in vacuo and the residue diluted with H_2O (80 mL) and washed with ethyl ether (3 x 80 mL). The aqueous layer was then made acidic with 8.5% H_3PO_4 (20 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated in vacuo to give a brown solid which was successively triturated with ethyl acetate (50mL) and petroleum ether (35-60 °C) (650 mL), and then recrystallized (chloroform/methanol/ hexanes) to give 0.53 g (29%) of the

desired product as beige crystals: R_f 0.55 (8:1:1 isopropanol/NH_4OH/H_2O); mp 112-114 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.87 (CH_3), 5.31 (d, J = 7.2 Hz, CH), 5.96 (s, C_3·H), 5.97 (s, C_4·H), 6.87 (s, C_5·H), 8.40 (d, J = 7.2 Hz, CONH), 10.79-10.85 (br s, NH). [The carboxyl proton was not detected.]. ^{13}C NMR (75 MHz, DMSO-d_6) 22.16 (CH_3), 50.45 (CH), 106.21 (C_3·), 107.45 (C_4·), 117.83 (C_5·), 126.11 (C_2·), 169.13 (CH_3CO), 171.56 (COOH) ppm; IR (KBr) 3340, 3300,1710, 1590 (br), 1530 (br), 1220, 1080, 885, 725 cm^{-1};mass spectrum, m/e (relative intensity)182 (1), 164 (7), 151 (45), 138 (100), 137 (25), 121 (2), 95 (98), 93 (10), 91 (46).

Preparation of α-Acetamido-3-pyrroleacetic Acid (82c).

Ethyl α-acetamido-3-pyrroleacetate (81d) (0.81 g, 3.85 mmol) was dissolved in 90:10 ethanol/water (33 mL), and then KOH (0.24 g, 4.2 mmol) was added and the resulting solution stirred at room temperature (48 h). The solution was concentrated in vacuo and the residue diluted with water (30 mL), and then washed with ethyl ether (3 x 30 mL). The aqueous layer was then made acidic with 8.5% H_3PO_4 (8 mL) and extracted with ethyl acetate (4 x 30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated in vacuo. The resulting beige solid was recrystallized (chloroform/methanol/hexanes) to give 0.27 g (38%) of the desired product as beige crystals: R_f 0.28 (8:1:1 isopropanol/NH_4OH/H_2O); mp 135-138 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, CH_3), 5.05 (d, J = 7.0 Hz, CH), 6.04 (s, C_4·H), 6.69 (s, C_2·H), 6.76 (s, C_5·H), 8.23 (d, J = 7.0 Hz, CONH), 10.68-10.86 (br s, NH). [the carboxyl proton was not detected]. ^{13}C NMR (75 MHz, DMSO-d_6) 22.18 (CH_3), 50.57 (CH), 106.98 (C_4·), 116.28 (C_2·),

117.83 ($C_{3'}$ and $C_{5'}$), 169.13 (CH_3CO), 173.00 (COOH) ppm; IR (KBr) 3340, 3300, 1700, 1585 (br), 1525 (br), 1240 (br), 920, 895 cm^{-1}; mass spectrum, m/e (relative intensity) 182 (4), 164 (6), 157 (1), 138 (100), 124 (3), 121 (38), 95 (19), 93 (33), 80 (94), 68 (91); high resolution mass spectrum, calcd for $C_8H_{10}N_2O_3$ 182.0691, found 182.0688.

Preparation of α-Acetamido-2-benzofuranacetic Acid (82d). 2-Acetamido-2-hydroxyacetic acid (79) (6.65 g, 50 mmol) was dissolved in glacial acetic acid (12 mL) and the resulting yellow solution was chilled in an ice bath, benzofuran (75) (11.80 g, 11 mL, 100 mmol) was then added in one portion, followed by the rapid dropwise addition of methanesulfonic acid. The orange solution was stirred at room temperature (16 h) and the solution was poured into an ice-water mixture (100 mL) and then triturated. The resulting semi-solid was separated from the aqueous layer and recrystallized from petroleum ether (35-60 °C) and then triturated with ethyl acetate. The product was further purified by recrystallization (acetonitrile) and then dissolved in a 5% aqueous NaOH solution, washed with ethyl acetate, and then made acidic (pH 1) with 10% aqueous HCl and filtered to give 2.38 g (20%) of the desired product as white crystals: R_f 0.62 (8:1:1 isopropanol/NH_4OH/H_2O); mp 203-204 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.91 (s, CH_3), 5.66 (d, J = 7.8 Hz, CH), 6.90 (s, C_3'H), 7.23-7.35 (m, C_5'H, C_6'H), 7.55-7.65 (m, C_4'H, C_7'H), 8.85 (d, J = 7.8 Hz, NH). [The carboxyl proton was not detected]. ^{13}C NMR (75 MHz, DMSO-d_6) 22.11 (CH_3), 50.51 (CH), 104.93 ($C_{3'}$), 111.06 ($C_{7'}$), 121.22 ($C_{4'}$), 123.02 ($C_{5'}$), 124.51 ($C_{6'}$), 127.65 ($C_{3'a}$), 152.92 ($C_{7'a}$), 154.10 ($C_{2'}$), 169.20 ($COCH_3$),

169.62 (COOH) ppm; IR (kBr) 3340, 3090, 1720, 1590 (br), 1535 (br), 1240, 1200, 1090, 890, 750 cm^{-1}; mass spectrum, m/e (relative intensity) 233 (12), 215 (2), 190 (38), 173 (15), 146 (100), 144 (92), 130 (14), 91 (32).

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.55; H, 4.76; N, 5.77.

Preparation of α-Acetamido-2-benzo[b]thiopheneacetic Acid (82e). α-Amino-2-benzo[b]thiopheneacetic acid (73e) (5.18 g, 25 mmol) was suspended in H_2O (60 mL), and then NaOH (1.50 g, 37 mmol) was added and the suspension stirred until a homogeneous solution was obtained. The aqueous solution was cooled to 5 °C, and then acetic anhydride (85) (5.08 g, 4.70 mL, 50 mmol) was added slowly so as to maintain the temperature of the solution below 7 °C. The solution was stirred an additional 5 min and then an aqueous NaOH (2.50 g, 63 mmol) solution (15 mL) was added and the solution stirred 30 min. The reaction was then made acidic (pH 1) with 10% aqueous HCl and the resulting precipitate (5.93 g) was filtered and washed with H_2O (2 x 15 mL). The beige crystals were dissolved in an aqueous NaOH (1.00 g, 25 mmol) solution (100 mL) and the solution was extracted with ethyl acetate (2 x 50 mL) and then the aqueous solution was made acidic with 10% aqueous HCl. The precipitate which formed was washed with H_2O to yield 5.23 g (83%) of the desired product as beige crystals: mp 224-226 °C; ^1H NMR (300 MHz, NaOD/D_2O) δ 2.08 (s, CH_3), 7.36-7.45 (m, C_3-H, C_6'H, C_7-H), 7.81- 7.84 (m, C_4-H or C_5-H) 7.88-7.92 (m, C_4'H or C_5-H) ppm. [The α-proton was not observed in the employed NMR solvent and is presumed to have undergone C-H to C-D exchange.]. ^{13}C NMR (75 MHz, NaOD/D_2O) 26.33 (CH_3),59.85 (t, CH),

126.86 ($C_{4'}$ or $C_{7'}$), 127.18 ($C_{4'}$ or $C_{7'}$), 128.12 ($C_{3'}$), 129.08 ($C_{5'}$ or $C_{6'}$), 129.09 ($C_{5'}$ or $C_{6'}$), 143.66 ($C_{3'a}$ or $C_{7'a}$), 143.71 ($C_{3'a}$ or $C_{7'a}$), 146.03 ($C_{2'}$); IR (KBr) 3305, 1710, 1580 (br), 1525 (br), 1275, 1200, 1090, 890cm^{-1}; mass spectrum, m/e (relative intensity) 249 (22), 231 (20),206 (33), 189 (6), 162 (100),160 (89), 135 (38), 89 (26).

Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.55; H, 4.38; N, 5.35.

Preparation of 2-Substituted-2-acetamido-N-benzyl-acetamides (69, 86). Preparation of α-Acetamido-N-benzyl-2-furaacetamide (69a). α-Acetamido-2-furanacetic acid (82a) (0.47 g, 2.56 mmol) was combined with acetonitrile (10 mL) and cooled to -5 °C (ice/salt water bath). Triethylamine (0.26 g, 0.36 mL, 2.56 mmol) was then rapidly added and the mixture stirred at -5 °C (3 min). Ethyl chloroformate (0.28 g, 0.25 mL, 2.56 mmol) was added dropwise between -4 and -3 °C, and the resulting suspension was stirred at -4 °C (20 min), and then an acetonitrile solution (2 mL) of benzylamine (83) (0.30 g, 0.31 mL, 2.82 mmol) was carefully added. During the addition of benzylamine the temperature of the solution did not go above 0 °C. The mixture was stirred at -5 °C (1 h) and at room temperature (18 h), and then concentrated in vacuo. The residue was then triturated with hot tetrahydrofuran (5 mL), cooled at -16 °C (3 h), and the resulting white precipitate was filtered and identified as triethylamine hydrochloride (^{1}H NMR (60 MHz, DMSO-d_6) δ 1.00 (t, J = 7.5 Hz, CH_3), 2.82 (q, J = 7.5 Hz, CH_2), 3.83 (s, NH))[164]. The filtrate was evaporated to dryness in vacuo and the resulting oil purified by flash chromatography (98:2

chloroform/methanol) to give 0.09 g (13%) of the desired product as a white solid: R_f 0.30 (98:2 chloroform/methanol); mp 178-179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (s, CH_3), 4.31 (d, J = 6.0 Hz, CH_2), 5.58 (d, J = 8.1 Hz, CH), 6.27-6.33 (m, C_3'H), 6.40-6.44 (m, C_4'H), 7.20-7.36 (m, Ph), 7.60-7.64 (m, C_5'H), 8.58 (d, J = 8.1 Hz, NH), 8.73 (t, J = 6.0 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 22.35 (CH_3), 42.27 (CH_2), 50.95 (CH), 107.60 (C_3'), 110.55 (C_4'), 126.82 (2C_2'' or 2C_3''), 127.08 (2C_2'' or 2C_3''), 128.27 (C_4''), 139.05 (C_1''), 142.58 (C_5'), 151.16 (C_2'), 168.02 (CH_3CO), 169.30 (NHCO) ppm; IR (KBr) 3230, 1625 (br), 1525 (br), 1375 (br), 1230, 1090, 890, 740, 690 cm^{-1}; mass spectrum, m/e (relative intensity) 273 (1), 230 (1), 139 (100), 96 (94), 91 (51), 65 (9).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.83; N, 10.29. Found: C, 65.92; H, 5.83; N, 10.15.

Preparation of α-Acetamido-N-benzyl-2-benzofuranacetamide(69f). α-Acetamido-2-benzofuranacetic acid (82d) (2.38 g, 10.2 mmol) was combined with acetonitrile (100 mL) and then triethylamine (1.01 g, 1.39 mL, 10.2 mmol) was added. The mixture was stirred at room temperature (20 min) and then cooled to -5 °C (ice/salt water bath) and isobutyl chloroformate (1.37 g, 1.30 mL, 10.2 mmol) was added rapidly. The mixture was stirred between -5 and -8 °C (20 min) and then an acetonitrile solution (5 mL) of benzylamine (83) (1.18 g, 1.19 mL, 11.0 mmol) was added dropwise. The resulting suspension was stirred at -5 °C (1 h) and at room temperature (17 h). The mixture was then concentrated in vacuo and the yellowish residue triturated with tetrahydrofuran (150 mL) and cooled at -16 °C (4 h). The resulting precipitate was filtered and identified as triethylamine hydrochloride

(^{1}H NMR (60 MHz, DMSO-d_6) δ 1.00 (t, J = 7.5 Hz, CH_3), 2.82 (q, J 7.5 Hz, CH_2), 3.83 (s, NH))[164]. The remaining filtrate was concentrated to (~ 5 mL) in vacuo and refrigerated (-16 °C) resulting in the formation of a precipitate which was filtered and purified by flash chromatography (98:2 chloroform/methanol) to give 0.42 g (13%) of the desired product as a white solid: R_f 0.30 (98:2 chloroform/methanol); mp 195-196 °C; ^{1}H NMR (300 MHz; DMSO-D_6) δ 1.94 (s, CH_3), 4.34 (d, J = 5.7 Hz, CH_2), 5.77 (d, J = 8.1 Hz, CH), 7.24-7.32 (m, C_3'H, C_5'H, C_6'H, Ph), 7.54 (d, J = 7.0 Hz, C_4'H or C_7'H), 7.62 (d, J = 7.0 Hz, C_4'H or C_7'H), 8.74 (d, J = 8.1 Hz, NH), 8.86 (t, J = 5.7 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 22.27 (CH_3), 42.30 (CH_2), 51.22 (CH), 104.34 (C_3'), 110.90 (C_7'), 121.05 (C_4'), 122.90 (C_5'), 124.28 (C_6'), 126.73 ($C_{3'a}$), 127.01 (2 C_2'' or 2 C_3''), 127.69 (2C_2'' or 2C_3''), 128.14 (C_4''), 138.87 (C_1''), 154.10 ($C_{7'a}$),154.30 (C_2'), 167.40 (CH_3CO), 169.26 (NHCO) ppm; IR (KBr) 3230, 1625 (br), 1520 (br), 1440, 1090, 1085, 890, 735, 690 cm^{-1}; mass spectrum, m/e (relative intensity) 322 (5), 189 (46), 146 (100), 130 (10), 91 (93), 65 (17); mass spectrum, m/e (relative intensity) 322 (5), 279 (1), 264 (1), 234 (1), 215 (5), 189 (45), 146 (100), 130 (11), 118 (7), 91 (87), 65 (16); high resolution mass spectrum, calcd for $C_{19}H_{18}N_2O_3$ 322.1317, found 322.1318.

Preparation of α-Acetamido-N-benzyl-2-benzo[b]thiopheneacetamide (69h). α-Acetamido-2-benzo[b]thiopheneacetic acid (82e) (1.38 g, 5.5 mmol) was combined with acetonitrile (35 mL), and then triethylamine (0.56 g, 0.77 mL, 5.5 mmol) was added dropwise. The mixture was cooled to -5 °C (ice salt/water bath), and ethyl chloroformate (0.60 g, 0.53 mL, 5.5 mmol) was added slowly so as to maintain the temperature below 0

°C. Benzylamine (83) (0.65 g, 0.66 mL, 6.0 mmol) in acetonitrile (2 mL) was then added between -9 and -6 °C and the mixture stirred at -5 °C (1 h), and then at room temperature (24 h). The reaction mixture was evaporated in vacuo and the residue combined with tetrahydrofuran (75 mL) and cooled at -16 °C (3 h), resulting in the formation of a white precipitate which was filtered and identified as triethylamine hydrochloride (^{1}H NMR (60 MHz, DMSO-d_6) δ 1.00 (t, J = 7.5 Hz, CH_3), 2.82 (q, J = 7.5 Hz, CH_2), 3.83 (s, NH))[164] . The filtrate was concentrated in vacuo (~5 mL) and refrigerated (-16 °C), resulting in the formation of a precipitate which was filtered and then purified by flash chromatography (98.5:1.5 chloroform/methanol). The solid obtained from the column was dissolved in hot tetrahydrofuran (5 mL) and then treated with decolorizing charcoal. The mixture was cooled, filtered, and then the filtrate evaporated in vacuo to yield 0.29 g (16%) of the desired product as a white solid: R_f 0.32 (99:1 chloroform/methanol); mp 226-227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.94 (s,CH_3), 4.34 (d, J = 5.7 Hz, CH_2), 5.86 (d, J = 8.1 Hz, CH), 7.20-7.38 (m, C_3'H, C_6'H, C_7'H, Ph), 7.77-7.80 (m, C_4'H or C_5'H), 7.89-7.93 (m, C_4'H or C_5'H), 8.76 (d, J = 8.1 Hz, NH), 8.97 (t, J = 5.7 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 22.34 (CH_3), 42.38 (CH_2), 52.70 (CH), 122.15 (C_4' or C_7'), 122.32 (C_4' or C_7'), 123.45 (C_3'), 124.37 (C_5' or C_6'), 124.41 (C_5' or C_6'), 126.89 (C_4''), 127.27 (2C_2'' or 2C_3''), 128.27 (2C_2'' or 2 C_3''), 138.84 ($C_{3'a}$ or $C_{7'a}$), 138.95 ($C_{3'a}$ or $C_{7'a}$), 142.58 (C_1'), 168.648 (CH_3CO), 169.12 (CONH) ppm. [A distinct signal for the C_2' carbon was not detected and is presumed to coincide with the C_1' carbon at 142.58 ppm]. IR (KBr) 3240, 1610 (br), 1510 (br), 1420, 1360, 1215, 1085, 885, 730, 710, 685 cm^{-1}; mass spectrum, m/e (relative intensity) 338 (8), 295

(2), 205 (76), 162 (100), 135 (22), 108 (12), 91 (59).

Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.21; H, 5.37; N, 8.12.

Method B.

Preparation of 2-Acetamido-N-benzyl-2-methoxyacetamide (86a). To a methanolic solution (180 mL) of methyl 2-acetamido -2-methoxyacetate (80a) (8.73 g, 54 mmol) was rapidly added benzylamine (83) (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50 °C (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2 x) to give 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95 : 5 chloroform/methanol) ; mp 145 - 146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, CH_3CO), 3.39 (s, CH_3O), 4.40 - 4.35 (m, CH_2), 5.52 (d, J = 8.7 Hz, CH), 7.12 (d, 8.7 Hz, NH), 7.20- 7.40 (m, Ph, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 23.03 (CH_3CO), 43.51 (CH_2), 55.84 (CH_3O), 78.94 (CH), 127.62 ($C_{4''}$), 127.70 ($2C_{2''}$ or $2C_{3''}$), 128.70 ($2C_{2''}$ or $2C_{3''}$), 137.45 ($C_{1''}$), 167.91 ($COCH_3$), 171.57 (CONH) ppm; IR (KBr) 3260, 1625 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1060, 935, 890, 740, 690 cm^{-1}; mass spectrum, m/e (relative intensity) 237(1), 205(2), 193 (1), 177(2), 163(4), 146(1), 134(1), 121(2), 106(26), 102(94), 91(95), 77(13), 61(100).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.91; H, 6.85; N, 11.66.

Preparation of 2-Acetamido-N-benzyl-2-ethoxyacetamide (86b). An ethanolic solution (420 mL) of ethyl 2-acetamido-2- ethoxyacetate

(80b) (27.92 g, 147 mmol) and benzylamine (83) (23.70 g, 24 mL, 221 mmol) was stirred at 40-45 °C for 3 days. The reaction mixture was evaporated *in vacuo* and the residue recrystallized (1:3.5 tetrahydrofuran/hexanes [650 mL]) to yield 25.80 g (70%) of the desired product as beige crystals: R_f 0.59 (95:5 chloroform/methanol); mp 153-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, CH_3), 2.07 (s, CH_3), 3.60-3.76 (m, CH_2CH_3), 4.40-4.54 (m, CH_2NH), 5.60 (d, J = 8.7 Hz, CH), 6.63 (d, J = 8.7 Hz, NH), 7.00 (br s, NH), 7.26-7.36 (m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) 15.06 (CH_3CH_2), 23.25 (CH_3CO), 43.60 (CH_2NH), 64.51 (CH_2CH_3), 77.43 (CH), 127.69 ($2C_{2''}$ or $2C_{3''}$, $C_{4''}$), 128.79 ($2C_{2''}$ or $2C_{3''}$), 137.57 ($C_{1''}$), 168.13 ($COCH_3$), 171.29 (CONH) ppm; IR (KBr) 3260, 1630 (br), 1550 (sh), 1505 (br), 1380, 1360, 1230, 1115, 1065, 1015, 890, 740, 690 cm^{-1}; mass spectrum, m/e (relative intensity) 251 (4), 163 (9), 116 (98), 106 (34), 91 (98), 74 (100).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.49; H, 7.27; N, 11.24.

Preparation of α-Acetamido-*N*-benzyl-2-furanacetamide (69a). 2-Acetamido-*N*-benzyl-2-ethoxyacetamide (86b) (1.00 g, 1 mmol) was suspended in anhydrous ethyl ether (30 mL), and then boron trifluoride etherate (0.91 g, 0.79 mL, 6.3 mmol) was added rapidly and the resulting solution was stirred for 10 min. Furan (70) (1.09 g, 1.16 mL, 16 mmol) was then added in one portion and the solution was stirred at room temperature (26 h). The reaction mixture was poured into an ice-cold saturated aqueous solution (50 mL) of $NaHCO_3$,and then stirred at 0 °C for 20 min, and then the mixture was extracted with ethyl acetate (3 x 40 mL). The organic layers

were combined, dried (Na_2SO_4), and evaporated to dryness in vacuo to give 0.93 g of a beige solid. The product was further purified by flash chromatography (70:30 benzene/acetone) to yield 0.63 g (58%) of the title compound as white crystals: Rf 0.30 (98:2 chloroform/methanol); mp 178-179 °C, mixed melting point with sample prepared by mixed anhydride method, mp 178-179 °C.

Preparation of α-Acetamido-N-benzyl-2-pyrroleacetamide (69b). 2-Acetamido-N-benzyl-2-ethoxyacetamide (86b) (2.00 g, 8.00 mmol) was suspended in anhydrous ethyl ether (60 mL), and then boron trifluoride etherate (1.82 g, 1.57 mL, 12.8 mmol) was added in one portion and the resulting solution was stirred (15 min), the pyrrole (74) (2.14 g, 2.22 mL, 32 mmol) was then added in one portion and the solution was stirred at room temperature (48 h) during which time a precipitate formed. Hexanes (80 mL) were then added to the suspension, and the mixture was filtered and the brown semi-solid was triturated with 95:5 chloroform/methanol (30 mL) to furnish a green solid. This material was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.94 g (35%) of the desired product as a white solid: R_f 0.29 (96:4 chloroform/methanol); mp 174-175 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 1.93 (s, CH_3), 4.35 (d, J = 6.0 Hz, CH_2), 5.42 (d, J = 6.9 Hz, CH), 6.00-6.18 (m, C_3'H, C_4'H), 6.68-6.72 (m, C_5'H), 7.04 (d, J = 6.9 Hz, NH), 7.17 (t, J = 6.0 Hz, NH), 7.10-7.47 (m, Ph), 9.25-9.35 (br s, NH); ^{13}C NMR (75 MHz, CD_3CN) 22.02 (CH_3), 43.83 (CH_2), 52.65 (CH), 107.57 (C_3'), 108.85 (C_4'), 119.33 (C_5'), 127.96 (C_2'), 128.01 ($2C_2$'' or $2C_3$''), 128.09 ($2C_2$'' or $2C_3$''), 129.49 (C_4''), 140.01 (C_1''), 170.94 ($COCH_3$),

171.21 (CONH) ppm; IR (KBr) 3230, 1610 (br), 1500, 1470 (br), 1330, 1230, 1070, 950, 890, 860, 740, 710, 685, 655 cm^{-1}; mass spectrum, m/e (relative intensity) 271 (12), 228 (1), 213 (1), 180 (2), 164 (9), 137 (94), 108 (20), 95 (100), 91 (38), 82 (35), 68 (15); high resolution mass spectrum, calcd for $C_{15}H_{17}N_3O_2$: 271.13208, Found 271.13144.

Preparation of α-Acetamido-N-benzyl-2-benzofuranacetamide (69f). 2-Acetamido-N-benzyl-2-ethoxyacetamide (86b) (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (30 mL), and then boron trifluoride etherate (0.91 g, 0.79 mL, 6.3 mmol) was added rapidly and the resulting solution was stirred (15 min). Benzofuran (75) (1.89 g, 1.76 mL, 16 mmol) was then added in one portion and the solution was stirred at room temperature for an additional 72 h during which time a white precipitate appeared. The reaction mixture was then poured into an ice-cold saturated aqueous solution (35 mL) of $NaHCO_3$, and then the mixture was maintained at this temperature for an additional 15 min. The mixture was extracted with ethyl acetate (2 x 35 mL), and the organic layers were combined, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (100% chloroform, then 99:1 chloroform/methanol) to yield 0.43 g (33%) of the desired product: Rf 0.30 (98:2 chloroform/methanol); mp 195-196 °C, mixed melting point with sample prepared by mixed anhydride method, mp 195-196 °C.

Preparation of α-Acetamido-N-benzyl-3-indoleacetamide (69g). 2-Acetamido-N-benzyl-2-ethoxyacetamide (86b) (0.69 g, 2.75 mmol)

was suspended in anhydrous ethyl ether (20 mL) and then boron trifluoride etherate (0.63 g, 0.54 mL, 4.40 mmol) was added rapidly and the resulting solution was stirred (15 min) at room temperature. Indole (72) (1.30 g, 11.00 mmol) was then added in one portion and the solution was stirred at room temperature for an additional 22 h. Petroleum ether (35-60 °C) (50 mL) was then added to the reaction, and the resulting semisolid material (1.20 g) filtered, and washed with petroleum ether (35-60 °C) (25 mL). Purification of the reaction mixture was accomplished by flash chromatography (98:2 chloroform/methanol) to produce 0.25 g (28%) of the desired product as a white solid: R_f 0.14 (95:5 chloroform/methanol);mp 213-214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (s, CH_3), 4.36 (d, J =6.0 Hz, CH_2), 5.72 (d, J = 7.2 Hz, CH), 6.90-7.37 (m, Ph, C_2·H), 7.02 (dd, J = 7.5 Hz, J = 7.5 Hz, C_5·H or C_6·H), 7.12 (dd, J = 7.5 Hz, J = 7.5 Hz, C_5·H or C_6·H), 7.39 (d, J = 7.5 Hz, C_4·H or C_7·H), 7.65 (d, J = 7.5 Hz, C_4·H or C_7·H), 7.86 (d, J = 7.2 Hz, NHCH), 8.13 (t, J = 6.0 Hz, $NHCH_2$), 10.30-10.80 (br s, NH); ^{13}C (75 MHz, DMSO-d_6) 22.32 (CH_3), 42.23 (CH_2), 49.98 (CH), 111.51 ($C_{7'}$), 112.08 ($C_{3'}$), 118.76 ($C_{4'}$ or $C_{6'}$), 119.24 ($C_{4'}$ or $C_{6'}$), 121.37 ($C_{5'}$), 123.94 ($C_{2'}$), 126.58 ($C_{3'a}$), 126.71 ($C_{4''}$), 127.33 ($2C_{2''}$ or $2C_{3''}$), 128.18 ($2C_{2''}$ or $2C_{3''}$), 136.28 ($C_{7'a}$), 139.44 ($C_{1''}$), 169.13 ($COCH_3$), 170.81 (CONH) ppm; IR (KBr) 3260, 1610 (br), 1515 (br), 1450, 1420, 1370, 1350, 1235, 1095, 895, 735, 715, 695, 600 cm^{-1}; mass spectrum, m/e (relative intensity) 321 (5), 278 (1), 264 (1), 233 (1), 214 (6), 187 (85), 171 (3), 145 (100), 118 (18), 91 (39).

Anal. calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.06. Found: C, 70.87; H, 6.15; N, 12.78.

During the purification of 69g a fraction (R_f 0.48; 95:5 chloroforom/methanol) was isolated and further purified by recrystallization from benzene to yield 0.10 g (11%) of the indole trimer 87: mp 150-152 °C (lit.[151] mp 169.5-170 °C); ^{1}H NMR (300 MHz, DMSO-D_6) δ 3.32-3.36 (m, CH_2), 4.79-4.86 (m, CH), 6.34 (dd, J = 7.5 Hz, J = 7.5 Hz, C_5'H), 6.57 (d, J = 7.5 Hz, C_6'H), 6.78 (dd, J = 7.5 Hz, J = 7.5 Hz, C_4'H) 6.82 (d, J = 7.5 Hz, C_3'H), 6.86 (dd, J = 7.8 Hz, J = 7.8 Hz, C_5"H or C_6"H), 6.97 (dd, J = 7.8 Hz, J = 7.8 Hz, C_5"H or C_6"H), 7.24 (s, C_2"H), 7.26 (d, J = 7.8 Hz, C_7"H or C_4"H), 7.51 (d, J = 7.8 Hz, C_7"H or C_4"H), 10.58 (s, NH). [The signal for the NH_2 protons were not detected and may have overlapped with the aromatic protons]. ^{13}C NMR (75 MHz, DMSO-d_6) 32.57 (CH), 36.01 (CH_2), 111.45 (C_6"), 114,91 (C_3' or C_3"), 116.43 (C_3' or C_3"), 117.76 (C_2"), 118.63 (C_5'), 118.93 (C_4" or C_7"), 120.44 (C_4" or C_7"), 122.12 (C_5"), 124.88 ($C_{3"a}$), 125.99 (C_4' or C_6') 126.66 (C_4' or C_6'), 129.24 (C_1'), 136.42 ($C_{7"a}$), 145.71 (C_2') ppm; IR (KBr) 3380, 1605, (br), 1085, 1040, 1000, 890, 735 cm^{-1}; mass spectrum, m/e (relative intensity) 351 (100), 145 (2), 106 (2).

Preparation of α-Acetamido-N-benzyl-2-benzo[b]thiopheneacetamide (69h). 2-Acetamido-N-benzyl-ethoxyacetamide (86b) (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (15 mL), and then boron trifluoride etherate (0.91 g, 0.79 mL, 6.3 mmol) was added rapidly and the resulting solution was stirred 15 min. A solution of benzo[b]thiophene (76) (2.14 g, 16 mmol) in ether (30 mL) was then rapidly (1 min) introduced in the reaction, and the solution was stirred at room temperature (72 h). The

solution was poured into an ice-cold saturated aqueous solution (35 mL) of $NaHCO_3$, and then stirred for 15 min at 0 °C. The mixture was extracted with ethyl acetate (2 x 35 mL), and the organic layers were combined, dried (Na_2SO_4) and evaporated in vacuo to give an orange oil (2.87 g). The oil was triturated with ethyl ether to give a crystalline product which was filtered and further purified by flash chromatography (99:1 chloroform/methanol) to yield 0.06 g (4%) of the desired product: Rf 0.32 (99:1 chloroform/methanol); mp 226-227 °C, mixed melting point with sample prepared by mixed anhydride method, mp 226-227 °C.

Pharmacology. The compounds prepared in this study were tested for anticonvulsant activity using male albino mice (CF-1 strain, 18-25 g, Charles River, Wilmington, MA).The drug candidates were intraperitoneally administered to the animals in 30% polyethylene glycol 400 or 5% acacia/water prior to the tests. Maximal electroshock seizures (MES) were elicited with a 60-cycle alternating current of 50 mA intensity (approximately 6 times that was necessary to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9%saline solution was instilled in the eyes of the animal prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. In this initial test, the compound to be evaluated was administered at three dosages (300, 100, 30 mg/kg), with four mice at a dose and, maximal electroshock seizures were elicited at 0.5, 1, 2, 3 and 4 hr post-treatment to determine the approximate time of peak effect (TPE). Compounds demonstrating significant

anticonvulsant activity were then retested at the estimated TPE using at least four doses, with twelve mice at a dose, and the ED 50 was calculated. The neurologic toxicity was evaluated by the horizontal screen (HS) test. Previously trained mice were dosed with the compounds and placed individually on top of a square (13 x13 cm) wire screen (No. 4 mesh) which was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within one minute was determined. This measurement was performed at the estimated TPE, using at least four doses, with twelve mice at a dose, and the TD 50 was calculated.

CHAPTER II

Synthesis, Spectroscopic and Anticonvulsant Properties of Polar Analogues of 2-Acetamido-N-benzylpropionamide.

I. Introduction.

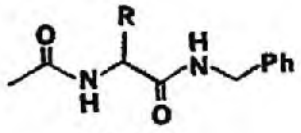
Compounds 107a-e were selected as polar analogues of the potent anticonvulsant agent, 2-acetamido-N-benzylpropionamide (68a) (Table 35). Several of the compounds within this set (107a-c) contained a site of unsaturation as well as a polar substituent at the α-position. Significantly, the serine derivatives 107d and 107e were isomeric with the 2-acetamido-N-benzyl-2-alkoxyacetamides 86a and 86b, respectively. Of the five compounds chosen for evaluation, only 107a was previously known.[165] This compound is an antifungal agent.

II. Results and Discussion.

1. Synthesis.

A common precursor (107a) was employed for the preparation of the five compounds in this set of substrates. Our selection of the general pathway depicted in Scheme 9 was spurred by our finding that 2-acetamido-2-cyanoacetate (108) reacted in moderate yield (64 %) with benzylamine (83) in ethanol to give 2-acetamido-N-benzyl-2-cyanoacetamide (107a). This strategy (Scheme 9) obviated the need to utilize the individual free amino acids 109a-e.

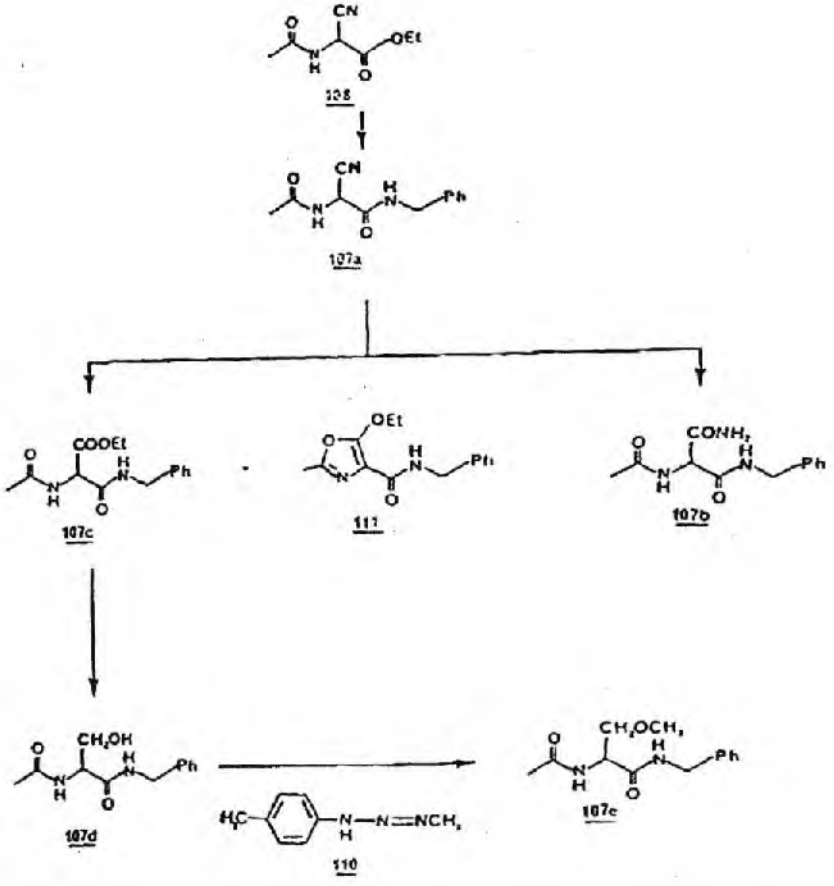
Table 35. 2-Acetamido-N-benzylpropionamide Analogues 107.



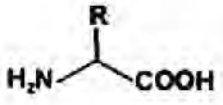
107

No.	R
68a	CH_3
107a	CN
107b	$CONH_2$
107c	$COOCH_2CH_3$
107d	CH_2OH
107e	CH_2OCH_3

Scheme 9. Preparation of the Polar Analogues 107a-e of 2-Acetamido-N-benzylpropionamide (68a).



In each case, the functionalized amino acid racemate was prepared rather than the individual enantiomers. This tack permitted the direct comparison of the observed biological data with that previously generated in this study.



109

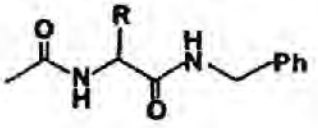
a: R = CN
b: R = $CONH_2$
c: R = $COOCH_2CH_3$
d: R = CH_2OH
e: R = CH_2OCH_3

All the reactions in Scheme 9 were patterned after procedures described in the literature. The synthesis of 2-acetamido-N-benzylmalonamide (107b) was accomplished in 55% yield by hydrolysis of nitrile 107a using aqueous 35 % hydrochloric acid. This reaction was comparable to the protocol employed for the conversion of benzyl cyanide to phenylacetamide.[167] The preparation of ethyl 2-acetamido-N-benzylmalonamate (107c) from 107a was similar to the method reported by James and Bryan.[168] These investigators synthesized several aliphatic esters by treatment of the corresponding nitrile with the appropriate alcohol in the presence of p-toluenesulfonic acid monohydrate. The carbethoxy

derivative 107c obtained by this procedure was readily reduced to 2-acetamido-N-benzylhydracrylamide (107d) with lithium chloride - sodium borohydride (1:1, 2 equivalents) in ethanol-tetrahydrofuran.[169] Selective O-methylation of 107d was accomplished in 4 % purified yield by treatment of the serine derivative with 1-methyl-3-p-tolyltriazene (110).[170] Selected physical and spectral data for compounds 107a-e are listed in Table 36.

During the purification of the carbethoxy derivative 107c a small amount (4 %) of a by-product was isolated. This compound was identified as 5-ethoxy-2-methyloxazole-4-carboxylic acid N-benzylamide (111) (Scheme 9) by comparison of the observed spectral properties with ethyl 5-ethoxy-2-methyloxazole-4-carboxylate (112)[171], and by elemental analysis. Compound 112 was prepared by the Robinson-Gabriel oxazole synthesis[173,174] using diethyl 2-acetamidomalonate (113) and phosphorus pentoxide (Scheme 10). Oxazole derivative 111 is a cyclic analogue of 107c and can be viewed as a prototype of a rigid functionalized amino acid derivative bearing a polar substituent at the α-position. Consequently, it was of interest to evaluate the biological activity of this material. This rationale prompted our efforts to provide a more efficient synthesis of 111. This was achieved in 97 % yield by utilizing the Robinson-Gabriel procedure beginning with 107c and phosphorus pentoxide (Scheme 10). An alternative route involving the direct condensation of 112 with benzylamine (83) proved unsuccessful.

Table 36. Selected Physical and Spectral Properties for the Polar Analogues (107a-e) of 2-Acetamido-N-benzylpropionamide (68a).

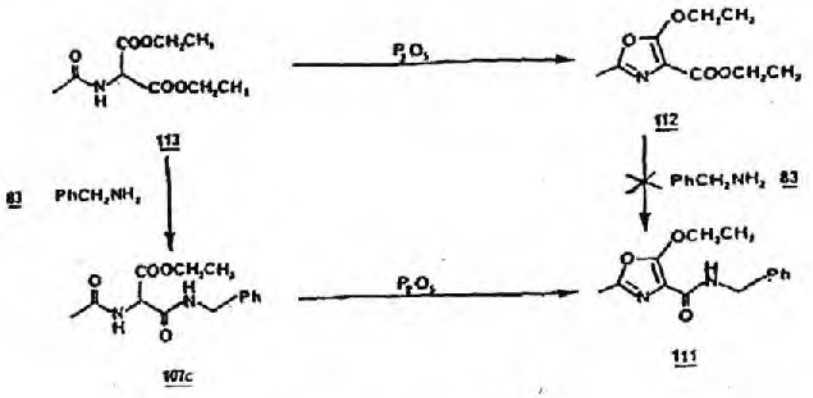


107

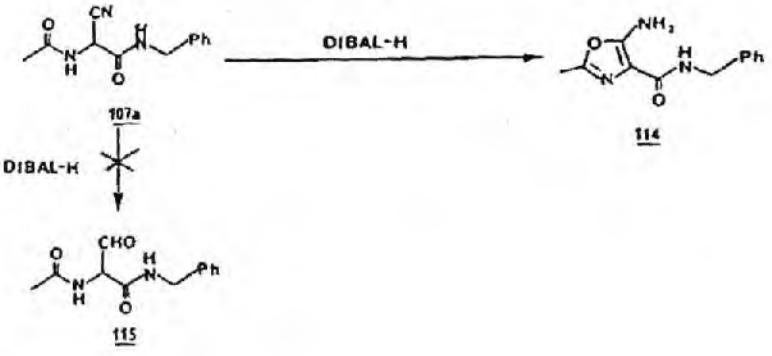
No.	R	yield[a]	mp[b]	IR[c]	M+/e[d]
107a	CN	64	179 - 180	1620,1505	231 (4)[e]
107c	$CONH_2$	55	191 - 192	1665, 1635, 1520	249 (6)[e]
107b	COOEt	45	142 - 143	1740, 1625, 1525	278 (6)[e]
107d	CH_2OH	66	201 - 203	1605, 1530	237 (48)
107e	CH_2OCH_3	4	109-112	1610, 1525	f

[a] Purified yields (%) for the final synthetic step (Scheme 9). [b] Melting points (^oC) are uncorrected. [c] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [d] The molecular ion peak in the mass spectrum were obtained at an ionizing voltage of 70 eV. The number in parentheses indicates the intensity of this ion relative to the base peak in the spectrum. [e] The M + 1 ion peak was also observed. [f] This information has not been received.

Scheme 10. Preparation of 5-Ethoxy-2-methyloxazole-4-carboxylic Acid N-Benzylamide (111).



Scheme 11. Preparation of 5-Amino-2-methyloxazole-4-carboxylic Acid N-benzylamide (114).



Another oxazole derivative, 5-amino-2-methyloxazole-4-carboxylic acid N-benzylamide (114) (Scheme 11) was isolated during the attempted synthesis of aldehyde 115.[174] Treatment of 107a with diisobutylaluminum hydride furnished 114 in 37 % yield. A potential mechanism for this conversion is depicted in Scheme 12 in which diisobutylaluminum hydride acts as a base rather than a reducing agent. Selected physical and spectral data for oxazole derivatives 111 and 114 are listed in Table 37.

2. Spectral Evaluation.

a. Infrared Spectra.

Characteristic absorption bands were observed in the infrared spectra of compounds 107a-e for the secondary amide groups and the α-carbon substituent (Table 38), as well as for the benzylamide phenyl moiety in compounds 107a-e (Table 38) and in compounds 111 and 114 (Table 39). The observed values were in excellent agreement with the proposed structures for the amino acid derivatives. Only the NH stretching absorption for 2-acetamido-N-benzylmalonamide (107b) was found at lower frequency (40 - 90 cm^{-1}) than expected with respect with other compounds in this series. Interestingly, the CN antisymmetric stretch (2000 - 2300 cm^{1}) was not observed for the cyano derivatives 107a and 108.[153]

Scheme 12. Proposed Mechanism for the Conversion of Compound 107a to the Oxazole Derivative 114.

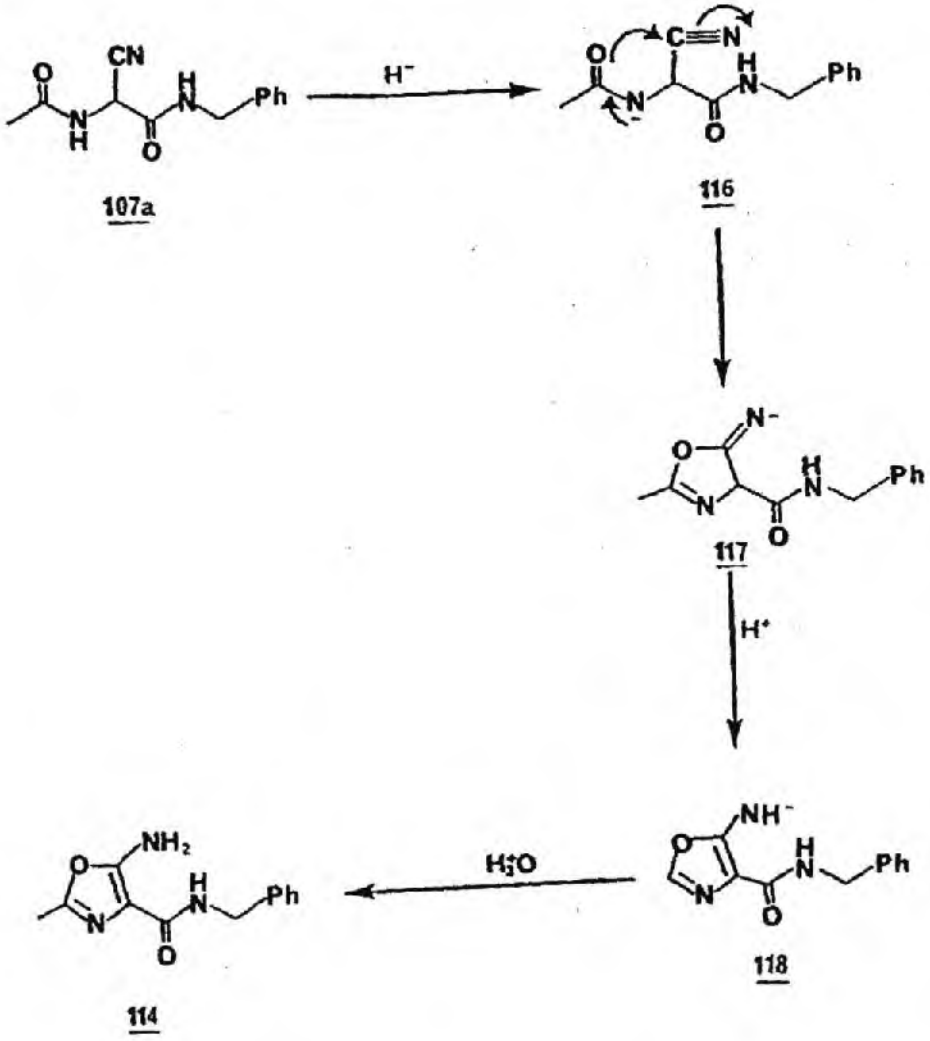
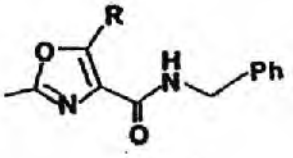


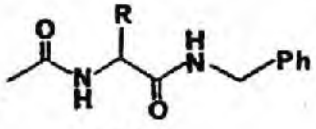
Table 37. Selected Physical and Spectral Data for Oxazole Derivatives 111 and 114.



No.	R	yield	mp[a]	IR[b]	M+/e[c]
111	OCH_2CH_3	97[d]	111 - 113	1620, 1540	260 (48)
114	NH_2	37[e]	108 - 110	1605, 1510	231 (21)[f]

[a] Melting points (°C) are uncorrected. [b] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 band in polystyrene, and were taken in KBr disks. [c] The molecular ion peak in the mass spectrum was obtained at a ionizing voltage of 70 eV. The number in parentheses indicates the intensity of this ion relative to the base peak in the spectrum. [d] Purified yield (%) from 107c. [e] Purified yield from 107a. [f] The M + 1 ion peak was also observed for this compound.

Table 38. Selected Infrared Spectral Data for the Polar Analogues 107a-e of 2-Acetamido-N-benzylpropionamide (68a).[a]



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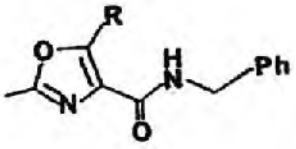
No.	R	NH stretching	COCH(Ph) stretching	NH bending	Ph ip,oop,bending[b]	R[c]
107a	CN	3200	1620	1505	1030,725,690	d
107b	$CONH_2$	3160	1635	1520	1050,730,690	3370[e],3300[e],1665[f]
107c	COOEt	3250	1625	1525	1080,730,680	1750[g]
107d	CH_2OH	3220	1605	1530	1045,725,690	-
107e	CH_2OCH_3	3240	1610	1525	1080,680	1150[h]

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [b] In-plane and out-of-plane bendings. [c] Characteristic absorption for R. [d] The antisymmetric stretching bend[153] between 2000 - 2300 cm^{-1} was not observed for this compound. [e] NH stretch. [f] CO stretch. [g] CO Stretch. [h] COC antisymmetric stretch.

Table 39. Selected Infrared Spectral Data for the Oxazole Derivatives 111 and 114.[a]



No.	R	NH stretching	CO,CH(Ph) stretching	NH bending	Ph ip,oop bending[b]	R[c]
111	OCH_2CH_3	3280	1620	1540	1085,720,695	1085[d]
114	NH2	3230	1605	1510	1090,730,690	3360[e]

[a] Infrared peak positions are recorded in reciprocal centimeters (cm^{-1}) vs. the 1601 cm^{-1} band in polystyrene and were taken in KBr disks. [b] In-plane and out-of-plane bendings. [c] Characteristic absorptions for R. [d] COC antisymmetric bending. [e] NH stretch.

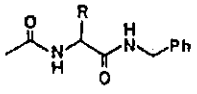
b) Mass Spectral Data.

The functionalized amino acid derivatives 107a-d as well as the oxazole derivatives 110 and 112 exhibited a discernible molecular ion peak and a M + 1 ion peak in their mass spectra (electron impact) (Tables 36 and 37). The M + 1 ion peak is attributed once again to the tendency of amides to undergo protonation in the mass spectrometer at moderately high sample pressures.[152] Compounds 107a-d exhibited fragmentation patterns similar to that detected for the structurally related derivatives 69 and 86 (Scheme 6). Accordingly, the loss of the N-benzylcarbamyl ($PhCH_2NHCO$) and the acetyl (CH_3CO) moieties were noted in the mass spectra for 107a-d. In this series of compounds, however, the relative intensities of the peaks corresponding to fragment ions 96 and 98 versus the base peak in the spectra were smaller than in the α-substituted heteroaromatic derivatives 69. The fragmentation pattern observed in the mass spectra of oxazole derivative was relatively simple. The loss of both the N-benzylcarbamyl ($PhCH_2NHCO$) and the carbon-5 substituent were noted.

c. ^1H NMR Spectral Data

The ^1H NMR spectral data for the functionalized amino acid derivatives 107a-e are listed in Table 40. The chemical shifts observed for the various protons present in these adducts were consistent with previously reported values[68,102] and support

Table 40. ^1H NMR Spectral Properties for the Polar Analogues 107a-e of 2Acetamido-N-benzylpropionamide (68a).[a]



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No.	R	CH_3	NHCH	CH	$NHCH_2$	CH_2	Ph	R
107a	CN	1.94 (s)	9.09 (d, 8.1)	5.59 (d, 8.1)	8.86 (t, 6.0)	4.33 (d, 6.0)	7.20 - 7.36 (m)	-
107b	$CONH_2$	1.92 (s)	8.10 (d, 7.8)	4.92 (d, 7.8)	8.60 (t, 5.7)	4.31 (d, 5.7)	7.20 - 7.34 (m)	7.36 (s, NHH') 7.50 (s, NHH')
107c[b]	$COOCH_2CH_3$	2.02 (s)	7.01 (d, 7.2)	5.18 (d,7.2)	c	4.35 (dd,5.4, 14.7) 4.50 (dd, 6.3, 14.7)	7.20 - 7.33 (m)	1.22 (t, 7.2, CH_3) 4.21 (q, 7.2, CH_2)
107d	CH_2OH	1.86 (s)	7.94 (d, 8.1)	4.19 - 4.35 (m)	8.38 (t, 5.7)	4.19 - 4.35 (m)	7.10 -7.40(m)	3.59 (dd,5.7,5.7,CH_2) 4.92 (t, 5.7, OH)

107e[b]	CH_2OCH_3	2.02 (s)	6.46 - 6.56 (brd)	4.46 (dt, 4.2, 7.2)5.80 - 6.90 (brs)	4.39 - 4.42 (m)[d]	7.20 - 7.36 (m)	3.31 (s, CH_3) 3.37 (m, CHH') 3.73 (m,CHH')

[a] The ^1H NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to TMS. The information in parentheses is the multiplicity of the signal, followed by the coupling constant (J) in hertz, and in select cases the proposed assignment. [b] The ^1H NMR spectra were taken in $CDCl_3$. [c] This signal was not observed and may overlap with the signal from the phenyl protons. [d] The methylene protons were diastereotopic.

the assigned structures. An interesting difference existed in the ^{1}H NMR spectra of 107d and its methylated derivative 107e. In the latter case the methylene protons of the α-substituent were diastereotopic. This was not the case for 107d.

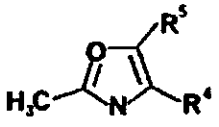
In the two oxazole derivatives 111 and 114, the resonances for the N-benzylamide methylene protons appeared at values similar to those detected for 69a-h and 86a,b. (Table 41) The most diagnostic signal in the NMR spectra for these adducts was the resonance observed for the carbon-2 methyl protons. This resonance appeared downfield (0.3 - 0.4 ppm) from the corresponding acetyl methyl signal. Comparable chemical shift values (~ δ 2.38) were noted for the acetyl methyl group in 112[171] and 119a.[176]

d. ^{13}C NMR Spectral Data.

The ^{13}C NMR spectral data for the functionalized amino acids 107a-e are reported in Table 42 and were as expected. The considerable variation (44.22 - 57.28 ppm) observed for the α-carbon chemical shift values agreed with the predicted values based on empirical substituent effects previously observed in branched alkanes.[161]

A characteristic set of signals were detected for the ring carbon atoms of oxazole derivatives 111 and 114. Comparison of these values with those previously reported for oxazole (119b) (Table 43) revealed an interesting trend. Substitution of the hydro-

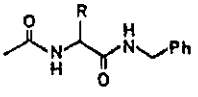
Table 41. ^{1}H NMR Spectral Properties for the Oxazole Derivatives 111 and 114.[a]



No.	R^4	R^5	CH_3	R^4	R^5
119a[b]	H	H	2.37 (s)	6.82 (s)	7.41 (s)
112	$COOCH_2CH_3$	OCH_2CH_3	2.38 (s)	1.47 (t, 6.9, CH_3) 4.47 (q, 6.9, CH_2)	1.37 (t, 6.9, CH_3) 4.35 (q, 6.9, CH_2)
111[c]	$CONHCH_2Ph$	OCH_2CH_3	2.33 (s)	4.50 (d, 6.9, CH_2) 7.15 - 7.35 (m, Ph)[d]	1.33 (t, 8.3, CH_3) 4.25 (q, 8.3, CH_2)
114	$CONHCH_2Ph$	NH_2	2.28 (s)	4.54 (d, 5.0, CH_2) 6.60 - 6.80 (br s, NH) 7.20 - 7.50 (m, Ph)	5.20 - 5.35 (br s, NH_2)

[a] The ^{1}H NMR spectra were taken in $CDCl_3$, unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to TMS. The information in parentheses is the multiplicity of the signal, followed by the coupling constant (J) in hertz, and in select cases the proposed assignment. [b] Ref. 175. The ^{1}H NMR spectrum was taken in CCl_4. [c] The ^{1}H NMR spectrum was taken in DMSO-d_6. [d] The NH signal was not observed and may overlap with the signal for the phenyl protons.

Table 42. ^{13}C NMR Spectral Properties for the Polar Analogues 107a-e of 2-Acetamido-N-benzylpropionamide (68a).[a]



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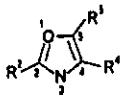
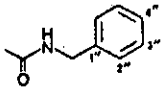
No.	R	CH_3	$COCH_3$	CH	COCH	CH_2	$C_{1''}$	$C_{2''}$-$C_{3''}$	$C_{4''}$	R
68a[b]	H	22.50	169.00[c]	42.50	169.60[c]	42.00	139.30	126.10[d,e] 128.10[d,e]	126.50	-
68a[b]	CH_3	22.50	169.5	42.00	174.3	42.10	139.70	127.10[d,e] 128.30[d,e]	126.70	15.80
107a[f]	CN	22.07	162.81	44.22	169.69	42.64	138.38	126.90[d,e] 127.11[d,e]	126.23	116.45
107b	$CONH_2$	22.48	168.53[c]	57.26	169.41[c]	42.22	138.99	127.02[d,e] 128.19[d,e]	126.73	166.87

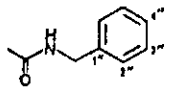
107c	$COOCH_2CH_3$	22.50	167.41	58.81	170.42	43.67	137.45	127.39[d,g] 128.50[d,e]	127.39[g]	13.81 (CH_3) 62.29 (CH_2) 165.19 (CO)
107d	CH_2OH	22.19	169.86[c]	54.87	169.08[c]	41.58	138.90	126.63[d,e] 127.71[d,e]	126.15	61.30
107e[f]	CH_2OCH_3	23.19	169.96[c]	52.40	169.96[c]	43.55	h	127.44[d,e] 128.70[d,e]	127.49	59.06 (CH_3) 71.65 (CH_2)

[a]The ^{13}C NMR spectra were taken in DMSO-d_6 unless otherwise indicated. The number in each entry is the chemical shift value observed in parts per million relative to TMS. The information in parentheses in select cases is the proposed assignment. [b]Ref. 103. [c] This set of resonances may be interchangeable. [d] The close proximity of these two peaks did not permit the assignment of these resonances. [e] This peak had approximately twice the intensity of nearby peaks. [f] The ^{13}C NMR spectrum was taken in $CDCl_3$. [g] This peak had approximately three times the intensity of nearby peaks. [h] A discrete signal for this carbon resonance was not observed.

Table 43. ^{13}C NMR Spectral Properties for Oxazole Derivatives 111 and 114.[a]



No.	R_2	R_4	R_5	C_2	C_4	C_5	R_2	R_4	R_5
119b	H	H	H	150.60	125.40	138.10	-	-	-
112	CH_3	$COOCH_2CH_3$	OCH_2CH_3	161.53[b]	107.30	151.01	13.90	14.48 (CH_3) 60.38 (CH_2) 161.48[b] (CO)	15.00(CH_3) 69.11(CH_2)
111[c]	CH_3 		OCH_2CH_3	159.42[b]	104.55	141.74	13.94	41.69 (CH_2) 126.68 (C_4') 126.94 (C_2'' or C_3'') 128.28[d], (C_2'' or C_3'') 139.96 (C_1'') 154.50[b](CO)	14.83(CH_3) 64.44(CH_2)

114	CH_3		NH_2	163.40[b]	106.37	149.40	13.29	42.51 (CH_2) 127.10 ($C_{4''}$) 127.44[d,e] ($C_{2''}$ or $C_{3''}$) 128.45[d,e] ($C_{2''}$ or $C_{3''}$) 138.50 ($C_{1''}$) 156.65[b] (CO)

[a] The ^{13}C NMR spectra were taken in $CDCl_3$ unless otherwise indicated. The number in each entry is the chemical shift value in parts per million relative to TMS. [b] This set of resonances may be interchangeable. [c] The ^{13}C NMR spectra was taken in DMSO-d_6. [d] This set of resonances may be interchangeable. [e] This peak had approximately twice the intensity of nearby peaks.

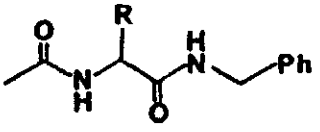
gen atoms at carbons -4 and -5 by an electron - withdrawing and a electron-donating groups, respectively, led to a pronounced shift in the resonances of the corresponding carbon atoms. The carbon-4 signal moved upfield (19.03 - 20.85 ppm) from 119b, while the resonance for the carbon-5 atom was shifted downfield (11.30 - 13.64 ppm) from that observed in 119b. This perturbation in the ^{13}C NMR spectra for 111, 112 and 114 is attributed to the push-pull resonance effects exerted by the carbon-5 and carbon-4 substituents.

3. Pharmacological Evaluation.

The 2-substituted-2-acetamido-N-benzylacetamides 107a-d and the oxazole derivative 111 prepared in this study were submitted to the Eli Lilly Corporation, Indianapolis, Indiana, for evaluation of their anticonvulsant activity. They were tested using the same protocols described in Chapter I. Pharmacological data for these functionalized amino acids are listed in Table 44.

Compounds 107a-c did not exhibit significant activity in the MES seizure test. The lack of anticonvulsant properties of these adducts was interesting in light of the pronounced activity of the methyl analogue 68a. A tentative explanation for this dichotomy of results can be offered. In a first approximation compounds 68a and 107a-c all contain relatively small substituents. The primary difference between the two sets of compounds is the presence of an electron-donating (68a) or an electron-withdrawing (107a-c) moiety at the α-carbon. Our previous studies have indicated that

Table 44. Pharmacological Evaluation of the Polar Analogues of 2-Acetamido-N-benzylpropionamide (68a).[a]



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No.	R	MES,ED50[b]	TOX, TD50[c]
68a[d]	CH_3	51 (46.6 - 58.6)	> 100[e]
107a	CN	> 300	> 300
107b	$CONH_2$	> 300	> 300
107c	COOEt	> 300	< 300
107d	CH_2OH	> 100, < 300	< 300

[a]The compounds were administered intraperitoneally. ED50 and TD50 values are in mg/kg. The number in parentheses is the 95 % confidence interval. [b] Maximal electroshock seizure test. [c]Horizontal screen test (neurotoxicity), unless otherwise indicated. [d] Ref. 104. [e]Rotarod ataxia test.

the activity of the drug candidate in the MES seizure test is enhanced by the presence of electron-donating groups at the α-carbon. The negligible activity of 107a,b and c is in agreement with this trend.

The serine derivative 107d exhibited only slight anticonvulsant activity in the MES seizure test. The activity of this compound was considerably diminished from the corresponding isomeric methoxy ether 86a (Table 33). This result may reflect the inability of 107d to readily pass through the blood-brain barrier. The more lipophilic methoxy ether 107e has not been evaluated yet. The close structural analogy of this compound with 86b suggest that this adduct may have good anticonvulsant activity.

No activity in the MES seizure test was observed for the oxazole derivative 111. The absence of other pharmacological data in this series prohibits any definitive statement concerning the significance of this observation.

Experimental Section .GeneralMethods.Syntheses. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Perkin-Elmer 1330 spectrophotometer and are calibrated against the 1605 cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton nuclear magnetic resonances (^{1}H NMR) and carbon nuclear magnetic resonances (^{13}C NMR) spectra were taken on a Nicolet NT-300 instrument or

a General Electric QE-300 instrument. Chemical shift are in parts per million (δ values) relative to tetramethylsilane (TMS) and coupling constant (*J* Values) are in hertz. Mass spectra were performed at the Eli Lilly Corporation, Indianapolis, Indiana, or by Dr. John Chinn at the Department of Chemistry, University of Texas at Austin. Elemental analysis was conducted at the Eli Lilly Corporation, Indianapolis, Indiana. p-Toluenesulfonic acid, diethyl 2-acetamidomalonate and diisobutylaluminum hydride were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin; phosphorus pentoxide and lithium chloride were obtained from Fisher Scientific, Pittsburg, Pennsylvania. Tetrahydrofuran was distilled from Na/benzophenone. All other chemicals were of the highest grade available and were used without further purification. The reaction with diisobutylaluminum hydride was run under anhydrous conditions. In this case all glassware was flame dried under N_2, the solid starting material was dried in vacuo immediately prior to use, and the reaction was conducted under positive pressure of N_2. Preparative flash column chromatographies were run using Merck silica gel, grade 60, 230-240 mesh, 60Å from Aldrich Chemical Company, Milwaukee, Wisconsin.

Preparation of 2-Acetamido-N-benzyl-2-cyanoacetamide (107a). Benzylamine (83) (4.72 g, 4.78 mL, 44.0 mmol) was added in one portion to a suspension of ethyl acetamidocyanoacetate (108) (4.90 g, 28.8 mmol) in ethanol (75 mL). The mixture was stirred at room temperature (18 h) and the resulting suspension was evaporated in vacuo. The residue was recrystallized (tetrahydrofuran/petroleum ether (35-60 °C)) to give 4.26 g (64%) of the desired product as white crystals: R_f 0.25 (95:5

chloroform/methanol); mp: 179-180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.94 (s, CH_3), 4.33 (d, J = 6.0 Hz, CH_2), 5.59 (d, J = 8.1 Hz, CH), 7.20-7.36 (m, Ph), 8.86 (t, J = 6.0 Hz, NH), 9.09 (d, J = 8.1 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 22.07 (CH_3), 42.64 (CH_2), 44.22 (CH), 116.45 (CN), 126.90 ($2C_{2''}$ or $2C_{3''}$), 127.11 ($2C_{2''}$ or $2C_{3''}$), 128.23 ($C_{4''}$), 138.38 ($C_{1''}$), 162.81 (CH_3CO), 169.69 (NHCO) ppm; IR (KBr) 3200, 3040, 1620 (br), 1565 (br), 1505 (br), 1360, 1280, 1210, 1030, 990 (br), 890, 725, 690, 580 cm^{-1}; mass spectrum, m/e (relative intensity) 231 (4), 215 (1), 204 (2), 190 (4), 172 (17), 148 (1), 129 (6), 106 (20), 98 (42), 91 (100), 77 (19), 65 (29).

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C,62.33; H 5. 67; N, 18.17. Found: C, 62.60; H, 5.65; N, 17.99.

Preparation of 2-Acetamido-N-benzylmalonamide (107b). 2-Acetamido-N-benzyl-2-cyanoacetamide (107a) (2.00 g, 8.65 mmol) and concentrated aqueous HCl (4.20 g, 4 mL, 34.6 mmol) were combined and stirred at 40 °C (15 min). The resulting suspension was filtered and the white solid was triturated with chloroform (20 mL, 5 min), filtered, and then dissolved in 4:1 n-butanol/H_2O (150 mL). The organic phase was concentrated to a small volume in vacuo, and then hexanes were added and the resulting solution was refrigerated (-16 °C) overnight to yield after filtration 1.20 g (55%) of the desired compound as a white solid: R_f 0.18 (95:5 chloroform/methanol); mp 191-192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (s, CH_3), 4.31 (d, J = 5.7 Hz, CH_2), 4.92 (d, J = 7.8 Hz, CH), 7.20-7.34 (m, Ph), 7.36 (s, NHH'), 7.50 (s, NHH'), 8.10 (d, J = 7.8 Hz, NH), 8.60 (t, J =5.7 Hz, NH); ^{13}C (75 MHz, DMSO-d_6) 22.48 (CH_3), 42.22 (CH_2), 57.28 (CH), 126.73 ($C_{4''}$), 127.02 ($2C_{2''}$ or $2C_{3''}$), 128.19 ($2C_{2''}$ or $2C_{3''}$), 138.99

($C_{1''}$), 166.87 ($CONH_2$), 168.53 ($COCH_3$), 169.41 (CONH) ppm; IR (KBr) 3370, 3300, 3160, 2905, 1665 (br), 1635 (br), 1520, 1480, 1390, 1260, 1050, 730, 690, 665, 600 cm^{-1}; mass spectrum, m/e (relative intensity) 249 (6), 232 (3), 206 (5), 190 (13), 163 (6), 146 (8), 116 (70), 99 (92), 91 (100), 73 (95), 66 (46); high resolution mass spectrum, calcd for $C_{12}H_{15}N_3O_2$ 249.11134, found 249.11101.

Preparation of Ethyl 2-Acetamido-N-benzylmalonamate (107c). To an ethanolic suspension(400mL) of 2-acetamido-N-benzyl-2-benzyl-2-cyanoacetamide (107a) (4.00 g, 17.2 mmol), was added p-toluenesulfonic acid (3.26 g, 17.2 mmol). The mixture was heated to reflux (9 h) and then stirred at room temperature (12 h). The resulting suspension was concentrated in vacuo and the residue dissolved in a 2:1 mixture of ethyl acetate and H_2O (300 mL), the organic layer was separated and the aqueous layer extracted with ethyl acetate (200 mL). The organic layers were combined, washed with aqueous 10% $NaHCO_3$ (100 mL), dried (Na_2SO_4) and evaporated in vacuo. The white residue was recrystallized (75:25 ethanol/H_2O) to yield 1.34 g (45%) of the desired product as slightly beige crystals: R_f 0.43 (95:5 chloroform/methanol); mp 142-143 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.2 Hz, CH_3CH_2), 2.02 (s, CH_3), 4.21 (q, J = 7.2 Hz, CH_3CH_2), 4.35 (dd, J = 5.4 Hz, J =14.7 Hz, NHCHH'), 4.50 (dd, J = 6.3 Hz, J = 14.7 Hz, NHCHH'), 5.18 (d, J = 7.2 Hz, CH), 7.01 (d, J = 7.2 Hz, NH), 7.20-7.33 (m, Ph, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 13.81 (CH_3CH_2), 22.50 (CH_3CO), 43.67 (CH_2NH), 56.81 (CH), 62.29 (CH_3CH_2), 127.39 ($2C_{2''}$ or $2C_{3''}$, $C_{4''}$), 128.50 ($2C_{2''}$ or $2C_{3''}$), 137.45 ($C_{1''}$), 165.19 ($COCH_3$), 167.41 ($COOCH_3$), 170.42 (CONH) ppm; IR (KBr) 3250, 1750, 1625 (br),

1525 (br), 1365, 1300, 1230, 1180, 1140, 1080, 1010, 895, 730, 680, 600 cm^{-1}; mass spectrum, m/e (relative intensity) 278 (6), 259 (8), 219 (5), 163 (12), 145 (93), 117 (5), 104 (77), 99 (100), 74 (53), 66 (44).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.64; H, 6.48; N, 10.19.

Preparation of 2-acetamido-N-benzylhydracrylamide (107d). Ethyl 2-acetamido-N-benzylmalonamate (107c) (2 17 g, 7.8 mL) was dissolved in anhydrous tetrahydrofuran (50 mL). To this solution dry LiCl (0.66 g, 15.6 mmol), $NaBH_4$ (0.59 g, 15.6 mmol) and ethyl alcohol (30 mL) were successively added. The mixture was stirred at room temperature (15 h), cooled (0 °C) and then made acidic (pH 4) by the addition of a 5% aqueous solution of citric acid (ca. 14 mL). The suspension was concentrated in vacuo, and then H_2O (20 mL) was added, and the resulting solution was extracted with ethyl acetate (3 x 25 mL). The organic layers were combined, dried ($NaSO_4$), and evaporated in vacuo to give a colorless oil (1.52 g) which was crystallized with hexanes. The desired product was further purified by recrystallization from acetonitrile to yield 1.21 g (66%) of 107d as white crytals: Rf 0.20 (95:5 chloroform/ethanol); mp 201-203 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.88 (s, CH_3), 3.59 (dd, J = 5.7 Hz, J = 5.7 Hz, CH_2O), 4.19-4.35 (m, CH_2NH, CH), 4.92 (t, J= 5.7 Hz, OH), 7.10-7.40 (m, Ph), 7.94 (d, J = 5.7 Hz, NHCH), 8.38 (t, J = 5.7 Hz, $NHCH_2$); ^{13}C NMR (75 MHz, DMSO-d_6) 22.19 (CH_3), 41.58 (CH_2NH), 54.87 (CH), 61.30 (CH_2OH), 126.15 ($C_{4''}$), 126.53 (2 $C_{2''}$ or 2 $C_{3''}$), 127.71 (2 $C_{2''}$ or 2 $C_{3''}$), 138.90 ($C_{1''}$), 169.08 (CH_3CO), 169.86 (CHCO) ppm; IR (KBr) 3220 (br), 1605 (sh), 1530 (br), 1375, 1280, 1230, 1045, 895, 725, 690, 570 cm^{-1}; mass spectrum,

m/e (relative intensity) 237 (48), 219 (4), 206 (10), 193 (5), 177 (37), 163 (21), 146 (11), 130 (76), 106 (100), 91 (100).

Anal. Calcd for $C_{12}H_{15}N_2O_3$: C, 61.26; H, 6.43; N, 11.91. Found: C, 61.06; H, 6.72; N, 11.78.

Preparation of 2-Acetamido-N-benzyl-3-methoxypropionamide (107e). To a tetrahydrofuran (ca. 20 mL) suspension of 2-acetamido- N-benzylhydracrylamide (107d) (150 mg, 0.63 mmol) was added 3-methyl-p-tolyltriazene (110) (210 mg, 1.41 mmol), and the resulting mixture was stirred at reflux (4 d). The suspension was then filtered and the filtrate evaporated in vacuo. The residue was purified by column chromatography (100% chloroform, then 97:3 chloroform/methanol) to give 7 mg (4%) of the desired product as a light yellow solid: Rf 0.30 (97:3 chloroform/methanol); mp 109-112 ^{o}C; ^{1}NMR (300 MHz, $CDCl_3$) δ 2.02 (s,CH_3), 3.31 (s, CH_3O), 3.30-3.45 (m, CHH'O),3.70-3.85 (m, CHH'O), 4.39-4.42 (m, CH_2NH), 4.48 (dt, J =4.2 Hz, J =7.2 Hz, CH), 6.46-6.56 (br d, J =4.2 Hz, NHCH), 6.80-6.90 (br s, $NHCH_2$), 7.20-7.36 (m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) 23.19 (CH_3CO), 43.55 (CH_2NH), 52.40 (CH), 59.06 (CH_3O), 71.65 (CH_2O), 127.44 (2 $C_{2"}$ or 2 $C_{3"}$), 127.49 ($C_{4"}$), 128.70 (2 $C_{2"}$ or 2 $C_{3"}$), 169.96 ($COCH_3$, CONH) ppm. [The C1" was not detected]. IR (KBr) 3240, 1610, 1525, 1150, 1085, 720, 690 cm^{-1}.

Preparation of 5-Ethoxy-2-methyloxazole-4-carboxylic Acid N-benzylamide (111). To a solution of 2-acetamido-N-benzylmalonamate (107c) (1.35 g, 4.85 mmol) in chloroform (15 mL) was added P_2O_5 (6.88 g, 48.5 mmol) and the resulting suspension was heated to reflux (8 h). The reaction mixture was carefully neutralized (10% aqueous

KOH) and then extracted with dichloromethane (4 x 100 mL). The organic fractions were combined, dried (Na_2SO_4) and concentrated in vacuo to yield a beige residue which was recrystallized (4:2 tetrahydrofuran/hexanes) to give 1.22 g (97%) of the desired product as white crystals: R_f 0.85 (95 : 5 chloroform/methanol); mp 111 - 113 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.33 (t, J = 8.3 Hz, CH_3CH_2), 2.33 (s, CH_3), 4.25 (q, J = 8.3 Hz, CH_2CH_3), 4.50 (d, J = 6.9 H, CH_2Ph), 7.15-7.35 (m, **Ph**, 2NH); ^{13}C NMR (75 MHz, DMSO-d_6) 13.94 (CH_3), 14.83 (CH_3CH_2), 41.69 (CH_2Ph), 64.44 (CH_2CH_3), 104.55 (C_4), 126.68 ($C_{4''}$), 126.94 ($2C_{2''}$ or $2C_{3''}$), 128.28 ($2C_{2''}$ or $2C_{3''}$), 139.96 ($C_{1''}$), 141.74 (C_5), 154.50 (C_2 or CONH), 159.42 (C_2 or CONH) ppm; IR (KBr) 3300, 2900, 1620 (br), 1585, 1570, 1540, 1430 (br), 1380, 1350, 1300, 1175, 1085, 900, 720 cm^{-1}; mass spectrum, m/e (relative intensity) 260 (48), 215 (12), 173 (7), 126 (6), 106 (6), 91 (100).

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.38; H, 6.74; N, 10.76.

Preparation of 5-Amino-2-methyloxazole-4-carboxylic Acid N-benzylamide (114). To a chilled solution (-5 °C) of 2-acetamido-N- benzyl-2-cyanoacetamide (107a) (0.50 g, 2.16 mmol) in anhydrous tetrahydrofuran (40 mL) was slowly added (7 min) a 25% solution of diisobutylaluminum hydride (0.92 g, 6.48 mmol) in toluene . The solution was stirred at -5 to 0 °C for 15 min, and then at room temperature (50 h), and finally at reflux (96 h). A saturated aqueous solution of NH_4Cl (50 mL) was then added to the reaction, followed by a 5% aqueous solution of H_2SO_4 (20 mL). The mixture was then extracted with ethyl acetate (3 x 60 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to dryness in

vacuo. The residue was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.20 g (37%) of the product as a pale yellow solid: R_f 0.58 (95:5 chloroform/methanol); mp 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, CH_3), 4.54 (d, J = 5.0 Hz, CH_2), 5.20-5.35 (br s, NH_2), 6.60-6.80 (br s, NH), 7.20-7.50 (m, Ph); ^{13}C NMR (75 MHz, DMSO-d_6) 13.29 (CH_3), 42.51 (CH_2), 106.37 (C_4), 127.10 ($C_{4''}$), 127.44 ($2C_{2''}$ or $2C_{3''}$), 128.45 ($2C_{2''}$ or $2C_{3''}$), 138.50 ($C_{1''}$), 149.40 (C_2), 156.65 (CO), 163.40 (C_5) ppm; IR (KBr) 3360, 3240, 3230, 1605 (br), 1510 (br), 1220, 1210, 1090, 890, 730, 690 cm^{-1}; mass spectrum, m/e (relative intensity) 231 (21), 106 (63), 98 (18), 91 (100); high resolution mass spectrum, calcd for$C_{12}H_{13}N_3O_2$ 231.10078, found 231.10107.

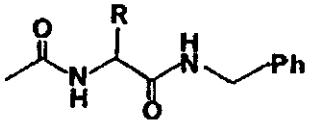
Pharmacology. The compounds prepared in this study were tested for anticonvulsant activity using male albino mice (CF-1 strain, 18-25 g, Charles River, Wilmington, MA).The drug candidates were intraperitoneally administered to the animals in 30% polyethylene glycol 400 or 5% acacia/water prior to the tests. Maximal electroshock seizures (MES) were elicited with a 60-cycle alternating current of 50 mA intensity (approximately 6 times that was necessary to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9%saline solution was instilled in the eyes of the animal prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. In this initial test, the compound to be evaluated was administered at three dosages (300, 100, 30 mg/kg), with four mice at a dose, and maximal electroshock seizures were elicited at 0.5, 1, 2, 3 and 4 hr post-treatment to determine the approximate

time of peak effect (TPE). Compounds demonstrating significant anticonvulsant activity were then retested at the estimated TPE using at least four doses, with twelve mice at a dose, and the ED 50 was calculated. The neurologic toxicity was evaluated by the horizontal screen (HS) test. Previously trained mice were dosed with the compounds and placed individually on top of a square (13 x13 cm) wire screen (No. 4 mesh) which was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within one minute was determined. This measurement was performed at the estimated TPE, using at least four doses, with twelve mice at a dose, and the TD 50 was calculated.

GENERAL CONCLUSIONS

The synthesis and pharmacological properties of the new functionalized amino acids analogues of α-acetamido-N-benzylphenylacetamide (68b) and 2-acetamido-N-benzylpropionamide (68a) revealed several notable findings. First, the use of amidoalkylation procedures provided a straightforward and reliable method to introduce an electron rich heteroaromatic substituent at the α-carbon in the amino acid derivatives. In particular, the employed conditions (boron trifluoride etherate, ether) permitted the synthesis of both 2-acetamido-N-benzyl-2-pyrroleacetamide (69b), 2-acetamido-N-benzyl-3-indoleacetamide (69g) and 2-acetamido- N-benzyl-2-benzofuranacetamide (69f). We are unaware of any previous results in which the acid sensitive unsubstituted heterocycles, pyrrole (74), benzofuran (75) and Indole (72), have been successfully employed in amidoalkylation transformations. We suspect that optimization of the general reaction conditions will not only provide higher yields but permit the use of less reactive heteroaromatic compounds in this procedure. Second, all five-membered ring heteroaromatic analogues of 68b proved highly active in the MES seizure test. Significantly, the furan-(69a) and pyrrole-(69b) adducts exhibited activities similar to those of phenytoin (13a) and diazepam (24c) under comparable conditions. The recent finding that the D-enantiomers of 68a and 68b were more active and less toxic than the corresponding racemates[68] suggests that the D-enantiomer

of each of these compounds (69a and 69b) may display even improved pharmacological properties. Third, the composite biological data suggests that stringent electronic and steric requirements exist for maximal activities. Moreover this study supports the notion that the α-carbon substituent interacts with an electrophilic site on the receptor. This scenario for biological activity can be tested. We suggest that replacement of the ring hydrogen atoms in the furan (69a) and pyrrole (69b) adducts by small electron-donating groups may be accompanied by an increase in anticonvulsant activity in the MES seizure test. Furthermore, we speculate that the O-vinyl and O-ethynyl adducts (120a-d) may be active in this biological screen. Fourth, the importance of the location of the heteroatom on the α-substituent in the monocyclic derivatives 69a and 69b has not been adequately addressed. This information should be accessible by comparing the biological data of 120e-g with those already obtained for the furan derivative 69a , the pyrrole adduct 69b and the two thienyl compounds 69c and 69d.

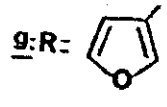


120

a: R = $OCH{=}CH_2$
b: R = $CH_2OCH{=}CH_2$
c: R = $OC{\equiv}CH$
d: R = $CH_2OC{\equiv}CH$

e: R =

f: R =



g: R =

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