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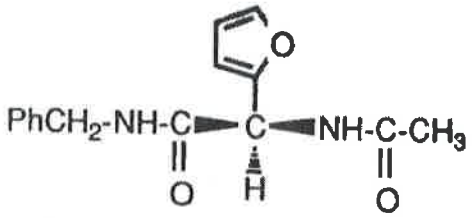
February 16, 1990

Dr. J. David Leander
Senior Research Scientist
M607
Lilly Research Labs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dave:

I would like to request that continued support be provided by the E. I. Lilly Company for our investigations on the development of new chemotherapeutic agents for treatment of central nervous systems disorders. Our rationale is clear and is *solely* based on our *recent* achievements.

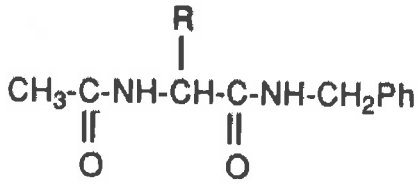
We in Houston, with the help and contributions of researchers at Lilly, have uncovered a novel class of functionalized amino acids that have pronounced anticonvulsant activities. Several of these compounds displayed superior activities in animal screens when compared to the benchmark drug, dilantin. Moreover, *unlike* any other medicinal agent in this area the drug candidate(s) exhibited chiral specificity. That is to say, only one of the two possible enantiomeric forms, was active. The source of this phenomenon has now been elucidated. Extensive pharmacological studies at Indianapolis and in vitro tests performed in England have confirmed that the observed pharmacological enantiomeric differentiation is due to a site-specific interaction process. The importance of this finding is immense since it paves the way for location of the active site within the brain for the control of epileptic seizures, as well as dramatically enhances Lilly's efforts to advance a member of this series of compounds to market. Our composite accomplishments have resulted in Lilly's promotion of L274959 to *Project Team Status*.

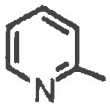


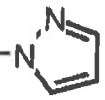
D - L 274959

With the discovery of L274959, we have intensified our efforts to fully discern the structure activity relationship of these unnatural amino acids. Well over 125 analogues have been prepared and evaluated. Two outstanding results obtained in the *Fall of 1989* support our continued investigations.

First, several new compounds have been prepared possessing comparable MES activity to L274959, and one derivative, L247602, exhibited superior activity (L247602: ED_{50} ~8.5mg/kg for *racemate*, L274959: ED_{50} ~11 mg/kg for *racemate*). Accordingly, we expect that the pure D-stereoisomer of L247602 will possess excellent anticonvulsant activity.



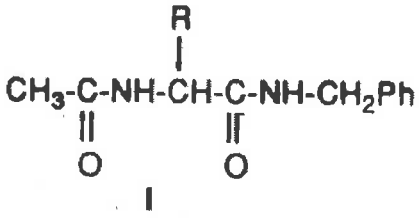
R=  (racemate) L 247602 ED_{50} 8.5 mg/ kg

R=  (racemate) L 202851 ED_{50} 10.6 mg/ kg

R= – $NH(OCH_3)$ (racemate) L 246385 ED_{50} < 10 mg/ kg

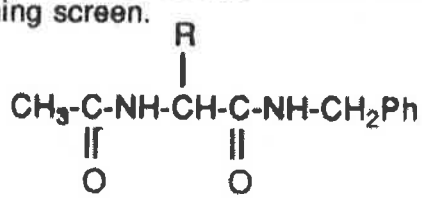
The structure of activity profile permits us to suggest future drug candidates. The SAR data demands that compounds of general structure I be evaluated for their MES activity. The synthetic challenges for the preparation of I are neither trivial nor insurmountable. A primary focus for the proposed funding period is the preparation and evaluation of analogues possessing a small *carbon*-substituted heteroaromatic ring substituent at the α-position. If the pharmacological results obtained in this series is as expected then, each of the corresponding enantiomeric forms of the drug candidate will be prepared and evaluated.

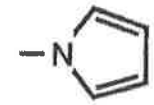
Dear Dave:

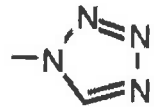


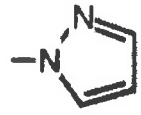
R= thiazole, isothiazole, oxazole, isoxazole,
imidazole,pyrazole, 3-pyridyl, 2-pyrimidyl

Second, recently a new and important pharmacological property has been discovered for our class of unnatural amino acid derivatives. α-Azasubstituted adducts displayed potent activity in a writhing assay conducted at Lilly. Significantly, several candidates exhibited preferential activity in the writhing screen versus the corresponding MES assay. This differentiation in activities suggests that the α-aza adducts do not readily penetrate the blood-brain barrier and, furthermore indicates that these compounds may prove beneficial for the control of peripheral pain disease states. Initial tests have confirmed that the unique chiral specificity observed for this class of compounds in the MES test is paralleled in the writhing screen.



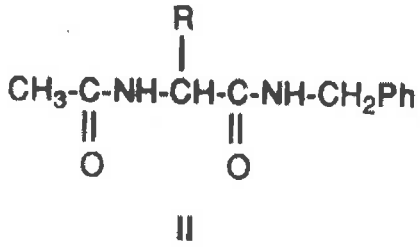
R=  (racemate) L 247201 ED_{50} (writhing) 12.7 mg/ kg;
ED_{50} (MES) > 30 < 100 mg/ kg

R=  (racemate) L 202875 ED_{50} (writhing) <10 mg/ kg;
ED_{50} (MES) >100 mg/ kg

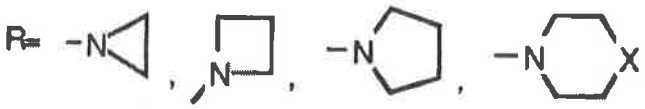
R=  (racemate) L 202851 ED_{50} (writhing) 27.6 mg/ kg;
ED_{50} (MES) 10.6 mg/ kg

These preliminary studies have provided us with a clear objective. We plan to elucidate the SAR for this subclass of compounds. Variation of the α-substituent both in size and the heteroatom substitution pattern should permit us to rapidly

discern the extent of activity within this class of compounds, and advance a candidate to Project Team Status. The synthetic protocols which permit the preparation of these derivatives have been already developed in our laboratory.



R= -NHR', -NR'$_2$, where R'= alkyl



An enclosed budget for the proposed study is provided. The funds are primarily earmarked for an experienced postdoctoral fellow and supplies. Dr. Kailash Sawhney has been instrumental in nearly every phase of the current project. He has made many outstanding contributions both in the development of new synthetic protocols to prepare key compounds and their chiral resolution. No support is requested for my own efforts or any publication costs. These will be absorbed by existing grants. If any additional information is needed please do not hesitate to request it. As is always the case, we in Houston, very much appreciate your input, help, and support.

With best wishes.

Sincerely,

Harold Kohn
Professor of Chemistry

cc: Dr. David Robertson
Dr. Dennis Zimmerman

HK:psl

Proposed Budget for November 1, 1990-October 31, 1991

Dr. Kailash Sawhney	$21,983.00
Expendable Supplies	8,017.00
	$30,000.00