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

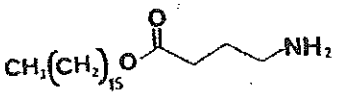
Examples of amino acids which decrease the GABA uptake (i.e., metabolism) in neuronal cells are nipecotic acid (57a), the corresponding phenyl esters 57b, as well as the related analogues 58 - 62 (Figure 4). Pharmacological evaluation of the individual enantiomers of 57a revealed that (-) - nipecotic 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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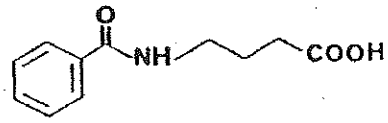

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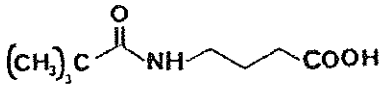

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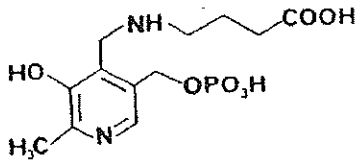

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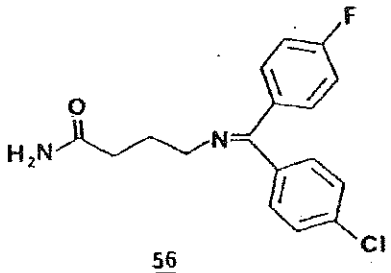

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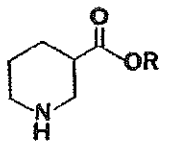
Figure 4. Amino Acids and Amino Acid Derivatives Interacting with the GABAergic System: Compounds Limiting GABA Uptake.



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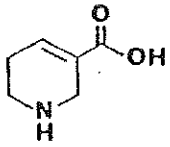

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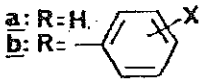

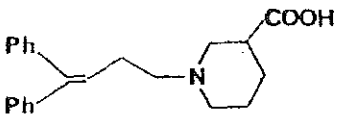

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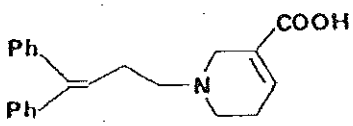

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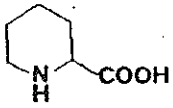

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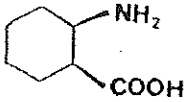

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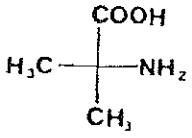

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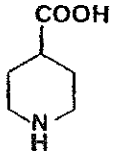

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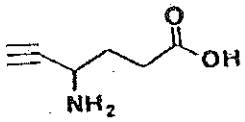

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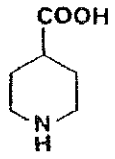
Figure 5. Amino Acids and Amino Acid Derivatives Interacting with the GABAergic System: GABA Receptor Agonists.



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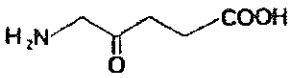

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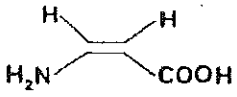
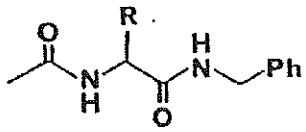


67

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

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