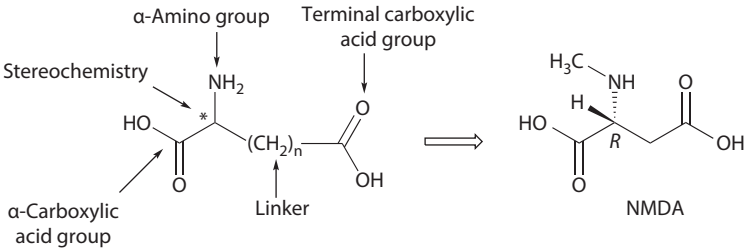


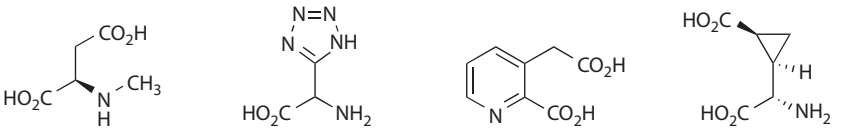
FIGURE 3.6 Structure–activity relationship study noting the effect of a number of structural changes to aspartate (n = 1) and glutamate (n = 2) that led to the identification of *N*-methyl-D-aspartate.

In this study, the effect of changing the structure of glutamate and aspartate on agonist activity was investigated as follows: (1) role of stereochemistry, (2) nature of alpha and terminal acidic groups, (3) chain length of linker connecting amino acid moiety and terminal acidic group, and (4) substitution of the α-amino group with an alkyl group (Figure 3.6). This study led to the identification of NMDA as a potent agonist for glutamate receptors. It was later found to be highly selective for a subtype of glutamate receptor that was eponymously named the NMDAR.

A number of conclusions regarding structural requirements for optimal agonist activity for the NMDAR were made following this SAR study:

1. For simple open-chain glutamate analogs, *S* stereochemistry is preferred, whereas for some aspartate analogs such as NMDA, *R* stereochemistry is preferred.
2. An alpha and terminal acidic group is required. Replacement of the α-CO_2H group with a phosphonate group lowers NMDAR affinity. With regard to the terminal acidic group, the rank order of affinity for the NMDAR is CO_2H and $SO_2H > SO_3H > PO_3H_2$ for *R* or *S* aspartate analogs and for (*S*)-glutamate analogs is $CO_2H > SO_2H$ and $SO_3H \gg PO_3H_2$. An analog of glycine with a tetrazole substituent on the α-carbon, (*RS*)-TetGly (Figure 3.7), has a high affinity for the NMDAR and is among the most potent agonists tested to date. Due to the delocalization of the negative charge in the deprotonated tetrazole ring, it probably represents an isosteric replacement of CH_2COO^-,and therefore, (*RS*)-TetGly is an aspartate analog.
3. The optimal number of CH_2 groups in the linker is either 1 or 2.
4. With the exception of NMDA, *N*-alkyl substitution of the amino group is detrimental for aspartate and glutamate, and NMDAR affinity becomes lower with increasing size of the alkyl chain.

Conformational restriction of glutamate has led to some potent agonists such as homoquinolinic acid and (2*S*,3*R*,4*S*)-CCG, the latter being one of the most potent NMDAR agonists described to date (Figure 3.7).



NMDA (11 μM, [^{3}H]AP5) | (*RS*)-TetGly (0.098 μM, [^{3}H]CGS19755) | Homoquinolinic acid (7 μM, [^{3}H]AP5) | (2*S*,3*R*,4*S*)-CCG (0.019 μM, [^{3}H]CPP)

FIGURE 3.7 Structures of *N*-methyl-D-aspartate receptor agonists identified in structure–activity relationship studies. K_i values obtained from competition binding assays using rat brain membranes are given in parenthesis together with the radioligand used.