2,3-BENZODIAZEPINES: MULTIPLE PHARMACOLOGICAL ACTIONS AND STRUCTURE-ACTIVITY RELATIONSHIP

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2,3-Benzodiazepines (BZDs) are members of a series of chemical entities that have been synthesized by changing the position of nitrogen atoms in the classical structure of 1,4-BZDs. Investigation of 2,3-BZDs emerged in EGIS Pharmaceuticals and Institute for Drug Research Hungary led to the conclusion that these molecules exhibit extremely rich pharmacology. The first remarkable molecule of this series was tofisopam, a drug acting as anxiolytic, vegetative modulator and antiparkinsonian agent. 2,3-BZDs with anxiolytic and antipsychotic characteristics were found and minor structural changes led to development of novel dopamine transporter inhibitors [1]. Compounds with AMPA receptor antagonistic properties were also identified in this series [2]. It was shown that methylene- or ethylenedioxy groups in 7,8-position or chlorine in C8 position and amino group in para position at the phenyl ring are requirement for blocking AMPA receptors [3]. Substitution of 2,3-BZD with cyclopropyl-carbamoyl group in C3 position further increases AMPA receptor antagonistic properties. Additional substitution of the phenyl ring with a methyl group in meta position enhanced the time-course of AMPA receptor blocking action. Although a series of modification in the molecular structures of AMPA receptor antagonist BZDs resulted in increased efficacy, lack of correlation was found between in vivo and in vitro pharmacological potencies. 2,3-BZDs with AMPA receptor-blocking activity may have therapeutic value in a wide range of CNS disorders such as Parkinson's disease, stroke, epilepsy, multiple sclerosis or motoneuron disease. Furthermore, lengthening the spacer between the phenyl and BZD rings led to the discovery of 2,3-BZDs containing stryryl double bound [1]. These changes resulted in anxiolytic compounds that devoid of binding to AMPA receptors. Some styryl-BZDs may exert anxiolytic effect acting on $GABA_A$ receptor subunits, their effect; however differ from that of 1,4-BZDs. Thus, the stryryl-2,3-BZD EGIS-8858, which exhibits anxiolytic effects in the elevated plus maze and the Vogel test, is not sedative, does not induce dependency, or amnesia and is not anxiogenic upon withdrawal.

[1] Szenasi, G., Harsing, L. G.: Drug Discovery Today, 2004, 1, 69-76.
[2] Abraham, G., et al.: Bioorg. Med. Chem., 2000, 8, 2127-2143.
[3] Kapus, G., et al.: Pharmaceutical Res., 2004, 21, 317-323.