# Synthesis and Structure-Activity Relationships of 2,3-Benzodiazepines as AMPA Receptor Antagonists

M. Zappalà,[a] S. Grasso,[a]* N. Micale,[a] S. Polimeni[a] and C. De Micheli[b]

[a]*Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 Messina, Italy,* [b]*Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20121 Milano, Italy*

**Abstract -** There is increasing evidence of the potential therapeutic utility of glutamate receptor antagonists in the treatment of several neurodegenerative disorders, including stroke and epilepsy. In the last few years noncompetitive AMPA receptor antagonists have received considerable attention due to their therapeutic potentiality. The discovery of GYKI 52466, the prototype of noncompetitive AMPA receptor antagonists endowed with anticonvulsant and neuroprotective properties, induced growing interest on 2,3-benzodiazepine derivatives. This review covers the chemistry and pharmacology of this important class of AMPA receptor antagonists.

## INTRODUCTION

Glutamate (Glu) is the main amino acid mediator of the excitatory neurotransmission of the central nervous system (CNS) and is believed to be implicated in many physiological conditions, such as cognitive functions and neuronal plasticity, and in neurodegenerative pathological processes [1]. An over-activation of the glutamatergic pathways causes acute neurological disorders such as cerebral ischaemia and epilepsy as well as chronic neurodegenerative pathologies, i.e. Parkinson's and Alzheimer's diseases, Huntington's chorea, and amyotrophic lateral sclerosis [2, 3].

Two main classes of Glu receptors have been characterized: the metabotropic (mGluRs) and ionotropic (iGluRs) receptors. The mGluRs regulate the activity of ion channels or enzymes by producing second messengers via GTP-coupled proteins [4]. The iGluRs are ligand-gated ion channels directly responsible for the fast depolarization of postsynaptic cells. The iGluRs are classified into three heterogeneous types based on their pharmacology and functional properties: the *N*-methyl-D-aspartic acid (NMDA) receptor and two non-NMDA receptors named (*R,S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) and kainic acid (KA) receptors [5, 6]. On the basis of sequence identities, the iGluRs subunits can be divided in at least six groups. The first group, containing the GluR1-GluR4, subunits generates the AMPA receptor complex. The low affinity KA receptor subunits, GluR5-GluR7, along with the high affinity KA receptor subunits, KA1 and KA2, form the family of the KA receptors, whereas the NMDA receptor complex is composed by three groups of subunits: NR1, NR2A-NR2D and NR3A. Against initial expectations, all iGluR subunits proved to possess only three transmenbrane domains (M1, M3 and M4) plus a re-entrant membrane loop (M2) on the cytoplasmic side. The N terminus is located extracellularly and the C terminus intracellularly [7]. Early evidence favored a pentameric structure for iGluRs [8, 9], but recent studies suggest that the functional receptor complex may be composed of four subunits similarly to the potassium ion channels [10, 11].

Considerable interest has been focused on the molecular mechanism underlying GluR-mediated neuronal death. Glu induces neuronal death by eliciting a rise in intracellular free $Ca^{2+}$, which activates a number of proteases, phospholipases and endonucleases, through the generation of free radicals that destroy cellular membranes by lipid peroxidation and by inducing an apoptotic process. A conceivable mechanism by which Glu could elicit a rise in intracellular $Ca^{2+}$ includes the activation of $Ca^{2+}$-permeable AMPA receptors. In fact, AMPA receptors from combinations of GluR1, GluR3 and/or GluR4 are permeable to $Ca^{2+}$ whereas the presence of edited GluR2 subunit greatly reduces $Ca^{2+}$ permeability. Thus, a change in the level of GluR2 expression would be expected to have significant physiological and pathological consequences [12].

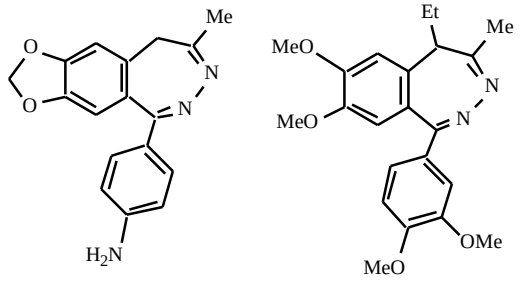
The acute neurological disorders and chronic neurodegenerative pathologies, involving excessive stimulation of iGluRs, have stimulated research programs on the identification of competitive and noncompetitive antagonists of these receptors that could have great potential therapeutic utility [13-15]. In the early 1990s, a number of NMDA receptor antagonists were subjected to preliminary clinical trials for stroke [14] but the results of these studies were not encouraging since serious unwanted effects such as psychotomimetic action [16, 17] and impairment of learning and memory [18] hampered their clinical development. On the contrary, AMPA/KA receptor antagonists appear to be relatively well tolerated and devoid of psychostimulant effects [19]. Therefore, interest in this area seems now to be focused on antagonists acting selectively on AMPA and KA receptors due to their effectiveness in the treatment of epilepsy [20, 21] and cerebral ischaemia [22, 23].

An important group of noncompetitive AMPA receptor antagonists, represented by 2,3-benzodiazepines, has been

*Address correspondence to this author at the Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 Messina, Italy

1389-5575/01 $20.00+.00 

described and will be the topic of the present review. The 2,3-benzodiazepine derivatives, in contrast to their 1,4-analogues, have no affinity for the γ-aminobutyric acid receptor ($GABA_A$) but block both native and recombinant AMPA receptors [24-26] and, in addition, they show a high degree of selectivity for AMPA receptors over kainate receptors [25, 27]. The prototype of these noncompetitive AMPA receptor antagonists is GYKI 52466 (**1**), (Fig. **1**), whereas, it is worthy of note that the structurally-related Tofisopam (**2**) possesses anxiolytic and antipsychotic properties.




**1**, GYKI 52466 **2**, Tofisopam

**Fig. (1).** Structure of compounds **1-2**.

In order to define the structure-activity relationship of 2,3-benzodiazepines and to project new derivatives with a more favorable pharmacological profile, an intense chemical and pharmacological research was started in the 1990s by different research teams. This paper is aimed at providing a summary of the chemistry and structure-activity relationships of 2,3-benzodiazepine-related compounds.

## CHEMISTRY

### Synthesis of 1-Aryl-5*H*-2,3-Benzodiazepines

Tofisopam (**2**) (Grandaxin®), (Fig. **1**), the first 2,3-benzodiazepine derivative reported in literature, was synthesized in 1966 [28] but its correct structure was assigned only in 1974 [29, 30]. This compound was introduced into therapy as a psychovegetative regulator in 1975 [31]. Following the discovery of tofisopam, a number of 2,3-benzodiazepines was synthesized and tested for biological activity.

Usually the key step in the synthesis of 1-aryl-5*H*-2,3-benzodiazepines **10** is represented by the preparation of 1,5-diketone derivatives **8** (Scheme 1) which by a treatment with hydrazine hydrate yield final derivatives **10**. The sequence commonly used to prepare intermediates **8** is the acid-catalyzed reaction of arylisopropanols **3** with a suitable aromatic aldehyde to afford 1-arylisochromans **4** followed by a chromium trioxide oxidation [32]. Diketones **8** were also obtained through a pyridinium chlorochromate oxidation of alcohols **3** to ketones **5** which were then submitted to a Friedel-Crafts acylation with an appropriate carboxylic acid [33].

Alternatively, the synthesis of diketones **8** could be achieved via a chromium trioxide oxidation of indene derivatives **7** [29], in turn prepared by condensing indanones **6** with an appropriate Grignard reagent.

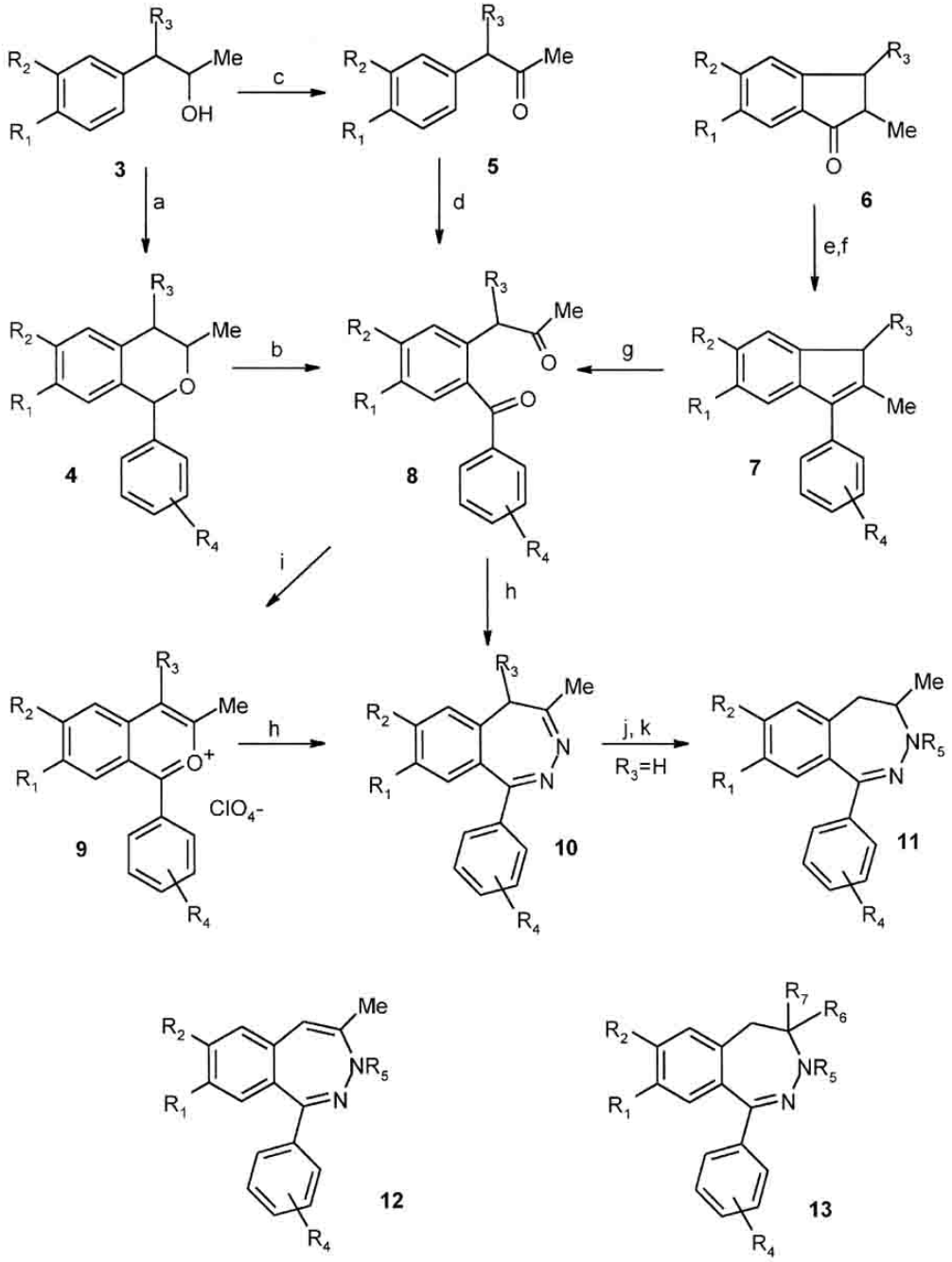
Final derivatives 1-aryl-5*H*-2,3-benzodiazepines **10** were obtained by reacting a slight excess of hydrazine either with intermediates **8** or after their conversion into easily crystallizable 2-benzopyrylium perchlorates **9** [29, 32, 33]. In order to study the relationship between the structure of 2,3-benzodiazepines **10** and their pharmacological profile, a series of analogues, i.e. **11**, **12** and **13** have been prepared and tested.

An alternative route to the 5*H*-2,3-benzodiazepine system has been developed and applied to the synthesis of GYKI 52466 (**1**), (Scheme 2). This approach starts from commercially available piperonal (**14**) [34] which was reduced and then dibrominated to provide 5-bromo-6-bromomethylbenzo[1,3]dioxole (**15**). The acetyl group was introduced into **15** through the transformation of the bromine atom at the benzylic position into a low order cuprate followed by condensation with ethyl vinyl ether. The arylacetone derivative **16** was transformed into the corresponding dimethyl ketal **17**, then treated with butyl lithium to generate an anion which reacted with the Weinreb amide **18** to yield intermediate **19**. Upon treatment of **19** with hydrazine, deprotection of the dimethyl ketal group and cyclization occurred simultaneously to give GYKI 52466 (**1**).

From a pharmacological point of view *N*-3-substituted 3,4-dihydro-5*H*-2,3-benzodiazepines **11** are quite interesting (Scheme 1). Their synthesis was accomplished in a two-step procedure using 5*H*-2,3-benzodiazepines **10** as the starting material. The 3,4-double bond of derivatives **10** was reduced with sodium borohydride and the emerging NH group was acylated in different experimental conditions [35, 36]. The preparation of a number of new 2,3-benzodiazepine derivatives **12** and **13** has been disclosed in recent patents [37, 38]. The new derivatives proved to be potent blockers of the AMPA/kainate receptor complexes.

The synthesis of the enantiomers of homochiral 2,3-benzodiazepines, i.e. **22** and **23** (Scheme 3) has also been the goal of detailed investigations [39-44]. The synthesis of both the enantiomers of the potent noncompetitive AMPA/kainate receptor antagonists **22** and **23** was achieved with different methodologies [39-41]. In this way it was possible to demonstrate that the ability of GYKI 53405 (**22**) to block electroshock and chemically-induced seizures in mice resides in its levorotatory enantiomer GYKI 53773 (LY 300164) (**22a**) [41]. The enantioselective reduction of the 3,4 double bond of **20** was accomplished with different chiral borane reagents [39, 40]. In terms of enantiomeric excess, the most effective borane reducing agent contained an enantiomer of 2-amino-3-methyl-1,1-diphenylpentan-1-ol as the chiral ligand.

A homochiral synthesis of (4*R*)-3-acetyl-1-(4-amino-phenyl)-3,5-dihydro-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (**22a**) (Scheme 4) has also been reported [41]. The same strategy was subsequently used to prepare a

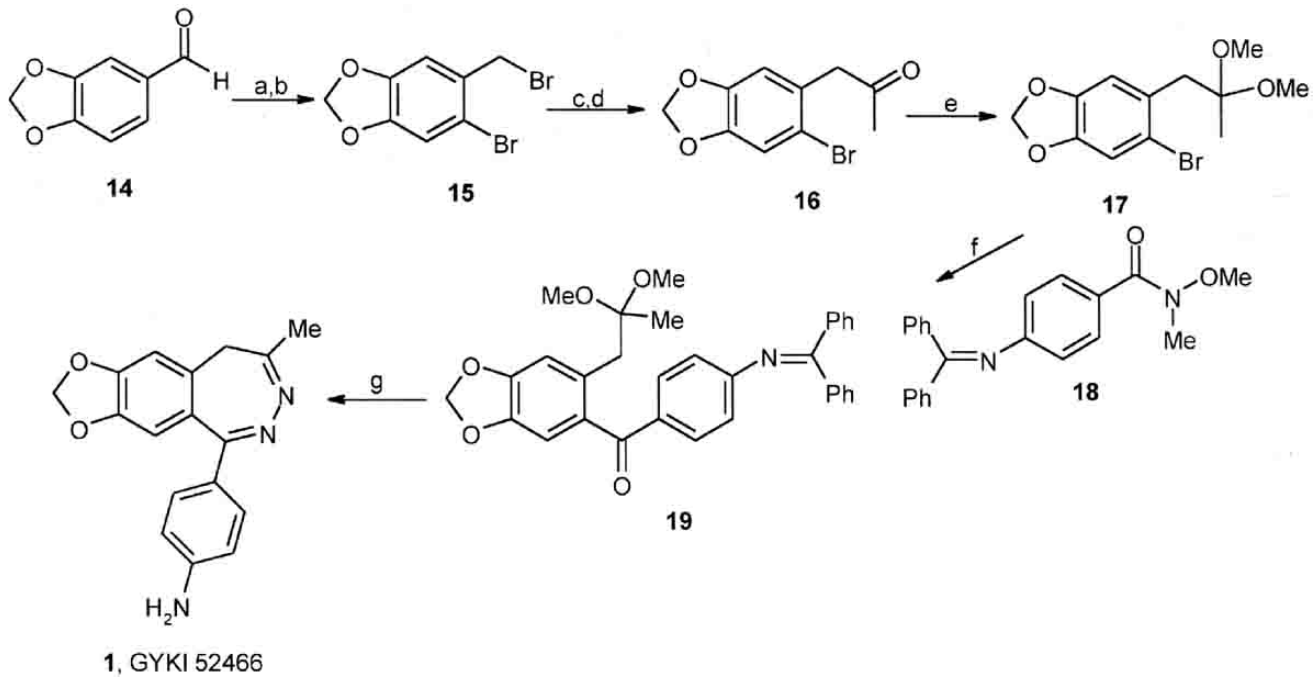


**Scheme 1.** (a) ArCHO, HCl, dioxane; (b) $CrO_3$, $H_2SO_4$, $H_2O$, 5°C; (c) PCC, $CH_2Cl_2$, rt; (d) ArCOOH, $P_2O_5$, $CH_2Cl_2$, rt; (e) ArMgBr; (f) 5N $H_2SO_4$; (g) $CrO_3$, MeCOOH; (h) $NH_2NH_2.H_2O$, EtOH, Δ; (i) $HClO_4$; (j) $NaBH_4$, MeOH, rt; (k) $(MeCO)_2O$ or RNCO, $Et_3N$, $CH_2Cl_2$, rt.

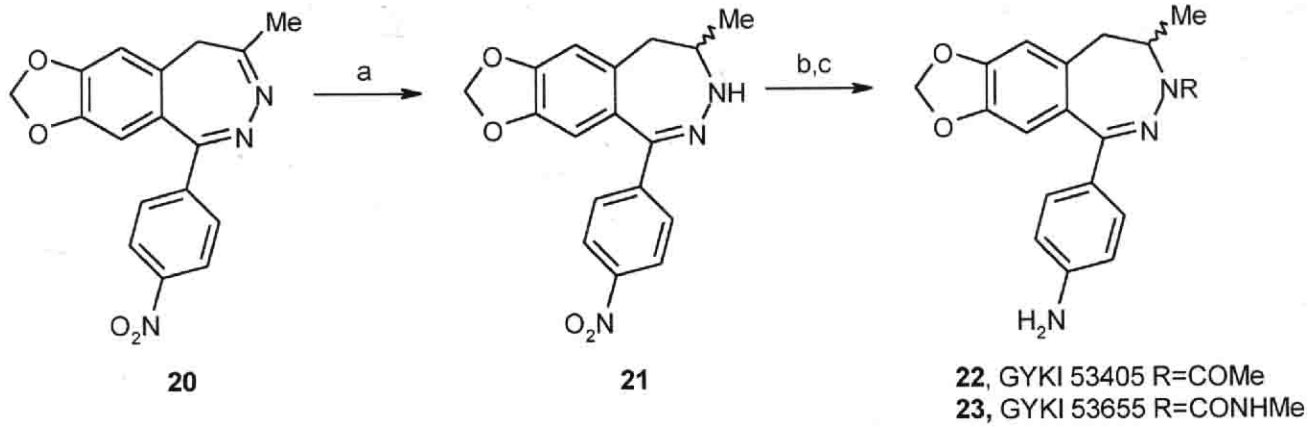
number of chiral analogues [42-44]. As shown in Scheme 4, the 5*H*-2,3-benzodiazepine nucleus of **22** was assembled through an intramolecular hydrazone alkylation which gave a clean inversion of configuration at the chiral center. The alkylation step was performed either by applying the Mitsunobu methodology or via the nucleophilic displacement of a suitable leaving group i.e. a mesylate group. The required chiral precursor **25** was obtained with the highly effective biocatalytic reduction of 3-(3,4-methylene-dioxyphenyl)propanone (**24**) with commercially available *Zygosaccharomyces rouxii* yeast.

## Synthesis of 1-Aryl-3,5-Dihydro-4*H*-2,3-Benzodiazepin-4-ones

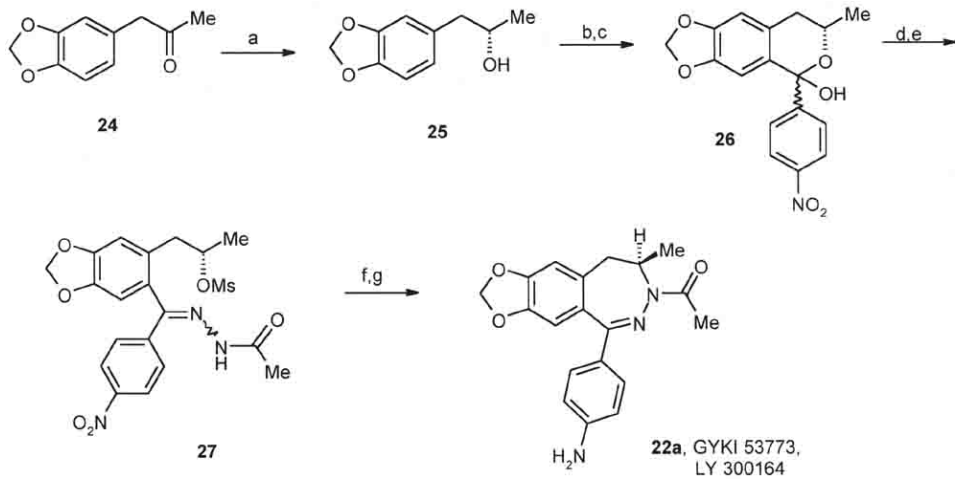
1-Aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones **34** have been synthesized through different procedures as outlined in (Scheme 5). Similarly to a strategy previously described for 2,3-benzodiazepines **10** (Scheme 1), Jones oxidation of isochromans **29**, in turn obtained by a condensation-cyclization reaction of arylethanol derivatives **28** with aromatic aldehydes, yielded ketocarboxylic acids **30**. When reacted with an excess of hydrazine hydrate in ethanol, these intermediates gave either 2,3-benzodiazepin-4-



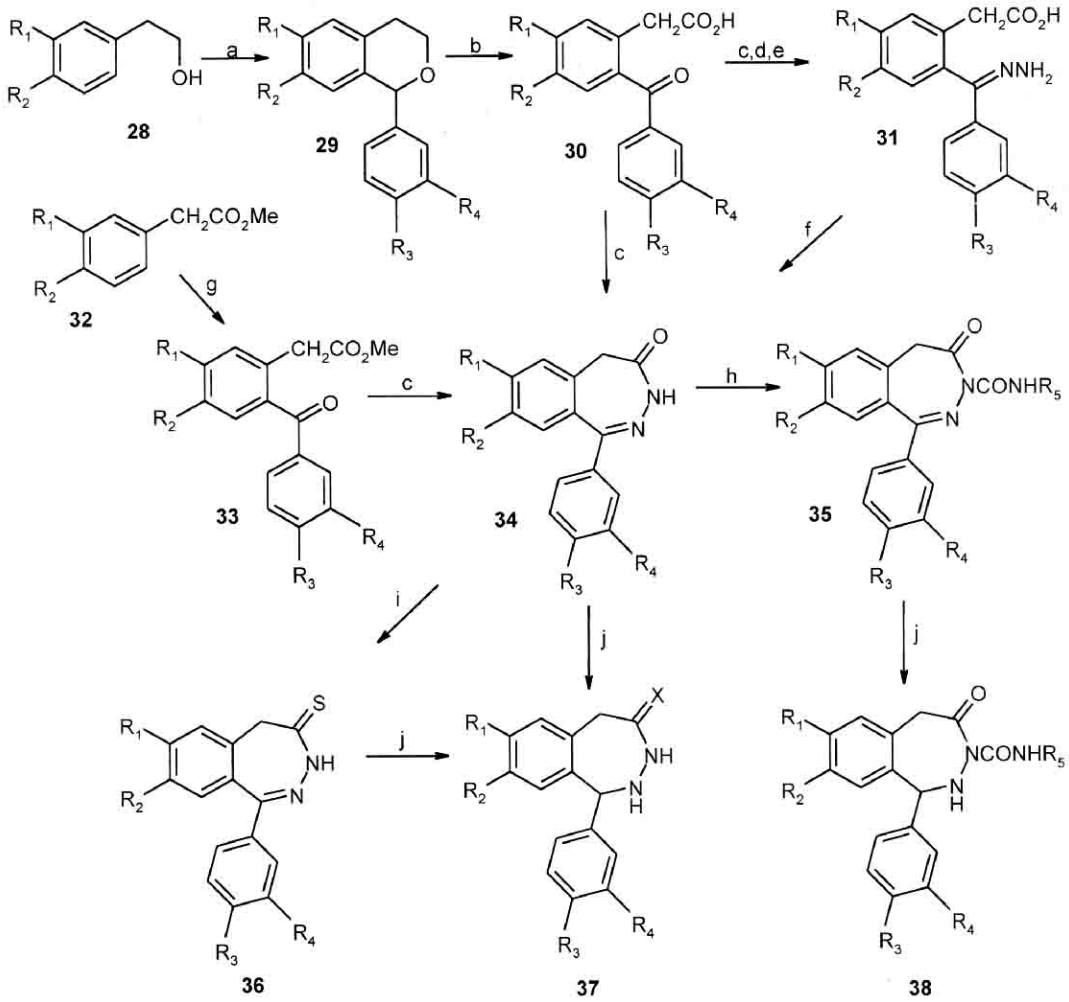

**Scheme 2.** (a) $NaBH_4$, EtOH; (b) $Br_2$, MeCOOH; (c) $(EVE)_2CuLi$; (d) $H_3O^+$; (e) $(MeO)_3CH$, TsOH; (f) BuLi, THF, -78°C; (g) $NH_2NH_2$, MeOH, HCl.




**Scheme 3.** (a) (*S*)-(-)- or (*R*)-(+)-2-amino-3-methyl-1,1-diphenylpentan-1-ol, $BH_3$.THF, $CH_2Cl_2$, -65→25°C; (b) $(MeCO)_2O$ or MeNCO, $CH_2Cl_2$, rt; (c) $NH_2NH_2.H_2O$, Raney-Ni, MeOH, rt.




**Scheme 4.** (a) *Z. Rouxii*, XAD-7 resin; (b) *p*-$NO_2$PhCHO, HCl, toluene; (c) 50% NaOH, air, DMSO/DMF; (d) $NH_2NHCOMe$, EtOH, cat. HCl; (e) $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$; (f) *t*-BuOLi, THF; (g) Pd/C, $H_2$, EtOH.




$R_1$=H, Cl, MeO; $R_2$=Br, Cl, MeO; $R_1R_2$=$OCH_2O$
$R_3$=H, $NH_2$, NHCOR, $N(COMe)_2$, Br, Cl, F, CN, OH, Me, MeO, $NO_2$
$R_4$=H, $NH_2$, MeO, $NO_2$; $R_5$=Me, Et, Pr, Bu

**Scheme 5.** (a) ArCHO, HCl, benzene; (b) $CrO_3$, $H_2SO_4$, $H_2O$, 5°C; (c) $NH_2NH_2.H_2O$, EtOH, Δ; (d) $OH^-$; (e) MeCOOH; (f) DCC, $CH_2Cl_2$; (g) $ArCO_2H$, $P_2O_5$, $CH_2Cl_2$, rt; (h) $R_5NCO$, $Et_3N$, $CH_2Cl_2$, rt; (i) Lawesson's reagent, toluene, Δ; (j) $NaBH_3CN$, MeOH/2N HCl, rt.

ones **34** [32, 45, 46] or hydrazones **31** [47]. Hydrazones **31** were then cyclized to final derivatives **34** by a treatment with dicyclohexylcarbodiimide.

Alternatively derivatives **34** have been prepared via a Friedel-Crafts acylation of methyl arylacetate **32** followed by the cyclocondensation of intermediate ketoesters **33** with an excess of hydrazine hydrate [48-50].

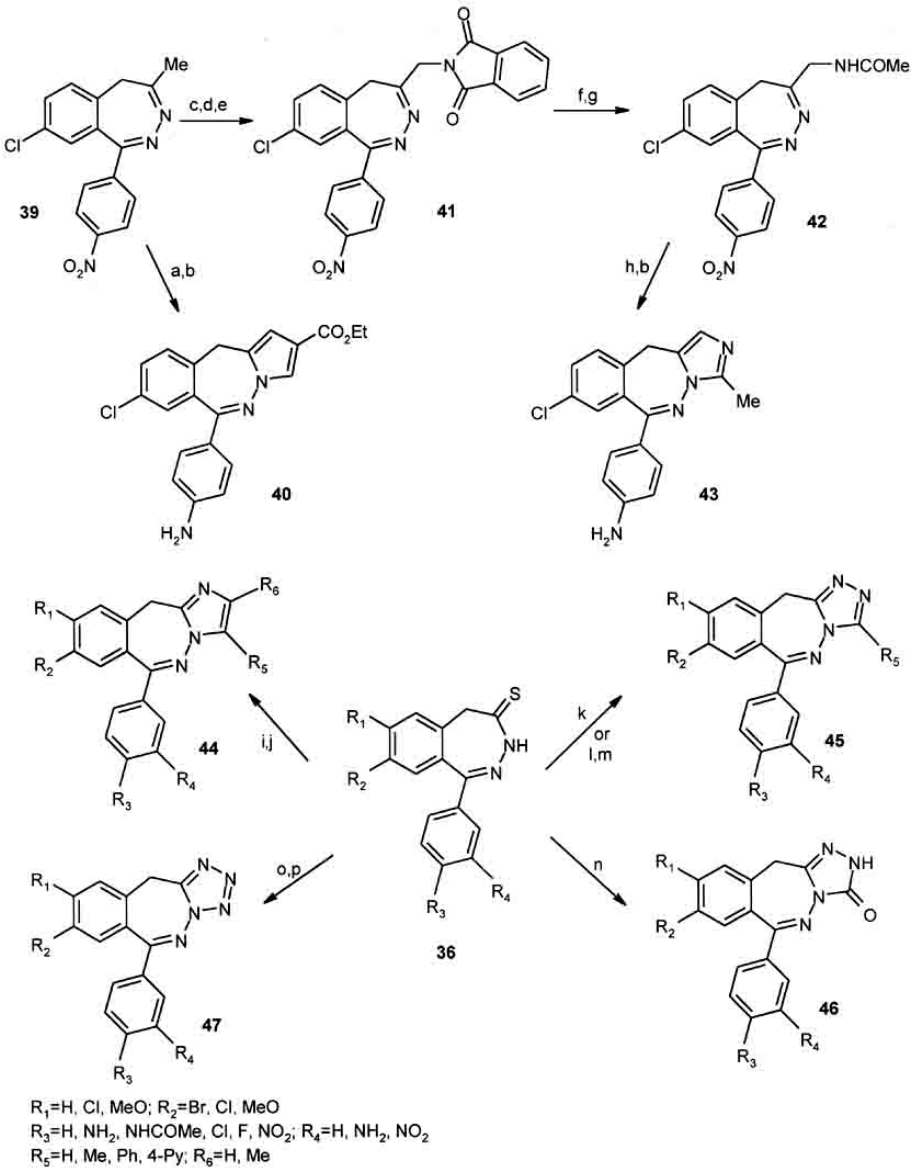
Compounds **34** were further converted into both the thiocarbonyl analogues **36** by a treatment with Lawesson's reagent [51, 52] and into the 3-*N*-alkylcarbamoyl derivatives **35** by reaction with an excess of alkyl isocyanates [52].

Tetrahydro derivatives **37-38** were prepared by reducing 2,3-benzodiazepines **34-36** with sodium cyanoborohydride in methanol at room temperature [53].

## Annelated 2,3-Benzodiazepines

Recently, a number of approaches towards the synthesis of tricyclic derivatives in which nitrogen-containing five-membered heterocycles are fused to the "c" edge of the diazepine skeleton have been reported (Scheme 6).

The pyrrolo derivative **40** was prepared from 8-chloro-4-methyl-1-(4-nitrophenyl)-5*H*-2,3-benzodiazepine (**39**) by




**Scheme 6.** (a) $BrCH_2COCO_2Et$, EtOH, Δ; (b) $MeOH/CH_2Cl_2$, Raney-Ni, $NH_2NH_2.H_2O$; (c) $SeO_2$, dioxane; (d) $NaBH_4$, THF- $H_2O$; (e) $Ph_3P$, phthalimide, DEAD, THF; (f) $NH_2NH_2.H_2O$, MeOH; (g) $(MeCO)_2O$; (h) $POCl_3$, $(CH_2Cl)_2$ ,Δ; (i) red HgO, 2-methoxyethanol, Δ; (j) HCl, Δ; (k) $R_4CONHNH_2$, *n*-BuOH, Δ; (l) MeI, $K_2CO_3$; (m) $R_4CONHNH_2$, cat. HCl, DMF; (n) $NH_2NHCO_2Et$, *n*-BuOH, Δ; (o) $NH_2NH_2.H_2O$, THF, rt; (p) $NaNO_2$/HCl, rt.

using a combined alkylation-condensation procedure with bromopyruvate [54].

To build up the 11*H*-imidazo[3,4-*c*][2,3]benzodiazepine ring system of **43**, the methyl group of **39** was oxidized to the corresponding aldehyde with selenium dioxide, then reduced to alcohol by a treatment with sodium borohydride and finally transformed into phthalimide **41** under Mitsunobu conditions. Hydrazinolysis of **41** followed by acetylation under standard conditions gave **42**. The side chain of **42** was cyclized to the corresponding imidazo derivative by a reaction with $POCl_3$ and the intermediate compound was transformed into final derivative **43** by a hydrazine/Raney-Nickel reduction of its nitro group [54].

The synthesis of imidazo- (**44**), triazolo- (**45** and **46**), and tetrazolo- (**47**) 2,3-benzodiazepines was accomplished by using thiocarbonyl derivatives **35** as the starting material in order to enhance the reactivity towards the cyclocondensation process.

The reaction of **35** with a number of aminoacetals, in the presence of red mercury oxide as the sulfur binding agent, afforded 11*H*-imidazo[2,1-*c*][2,3]benzodiazepines **44** in high yield [54]. The triazole ring of **45** was set up by reacting suitable acylhydrazides either directly with thiocarbonyl derivatives **35** [55] or through a preliminary transformation into the corresponding methylthio analogues [54]. The reaction of ethyl carbazate with **35** led to the synthesis of 11*H*-triazolo[4,5-*c*][2,3]benzodiazepin-3(2*H*)-ones **46** [56]. Finally, the tetrazole ring of **47** was built up through the preparation of 2,3-benzodiazepin-4-yl-hydrazines followed by a treatment with sodium nitrite in an acidic medium [57].

## STRUCTURE-ACTIVITY RELATIONSHIPS

The 2,3-benzodiazepines represent a class of compounds which behave as selective noncompetitive AMPA-receptor antagonists. Their mode of action has been thoroughly investigated and it is now quite clear that the blockade of the AMPA receptor complex is due to the binding to a specific allosteric site [24, 58].

GYKI 52466 (**1**), (Fig. **2**), the prototype of this class of allosteric modulators, was initially studied as a muscle relaxant [59]. Subsequent experiments demonstrated that GYKI 52466 possesses anticonvulsant properties in various seizure models [60-63] but, contrary to the classical 1,4-benzodiazepines, it is devoid of any sedative and anxiolytic activity and it does not bind to the benzodiazepine site of the $GABA_A$ receptor complex. Furthermore, it behaves as an effective neuroprotective agent in both focal [64] and global ischaemias [65].

Structure-activity relationship studies revealed that several structural features are important to maintain and/or to potentiate the pharmacological properties of GYKI 52466. Indeed, by analyzing the pharmacological profile of a series of analogues of GYKI 52466 (**1**), so far reported in literature, it is possible to deduce the following observations.

The presence of a 4-aminophenyl group in position 1 of the benzodiazepine ring is of utmost importance for the antiepileptic effect of this class of compounds. The replacement of the amino group with an halogen atom eliminates all the antiepileptic effects [66]. The presence of an acyl group on the aromatic amine moiety is always detrimental to the *in vitro* activity but it is sometimes advantageous for the *in vivo* potency [35]. In addition, the replacement of the aryl ring with other heterocycles as well as its replacement with an arylvinyl group [67, 68] affords derivatives marginally active.

The substitution of the 7,8-methylenedioxy moiety with two methoxy groups yields derivatives i.e. Nerisopam (**48**), (Fig. **2**), which, at variance with GYKI 52466, do not show any anticonvulsant effect but are endowed with remarkable anxiolytic and antipsychotic activities [47]. As a matter of fact, Tofisopam (**2**), the parent compound of Nerisopam, was approved as an anxiolytic drug. Studies on the mode of action of these 2,3-benzodiazepines indicate a possible involvement of the opioid signal transduction. A conceivable biochemical target is the alteration in the phosphorylation of proteins important in the process of the signal transduction [47].

Saturation of the 3,4-double bond of GYKI 52466 (**1**) afforded GYKI 52895 (**49**), a derivative characterized by a different mechanism of action. GYKI 52895 is in fact a selective dopamine uptake inhibitor endowed with antidepressive and antiparkinsonian properties [69]. Interestingly, the presence of substituents at position 3 transforms GYKI 52895 from a dopamine uptake inhibitor into noncompetitive AMPA antagonists, in some cases considerably more potent and selective than GYKI 52466. Among the series of 3-acylsubstituted analogues, acetyl and propionyl derivatives proved to be the most effective ones. Furthermore, racemic GYKI 53405 (**22**), **(**Fig. **2**), was resolved into its enantiomers and the 4-*R* isomer GYKI 53773 (**22a**) (LY 300164, Talampanel) proved to be the eutomer. Among this set of noncompetitive AMPA antagonists, LY 300164 is the sole agent submitted to clinical trials due to its selectivity and oral bioavailability [41, 42]. The introduction of a cyano group in position 4 led to EGIS 8332 (**50**), which is endowed with remarkable anticonvulsant and neuroprotective properties [70]. A significant improvement in the pharmacological profile of GYKI 52466 was also obtained by appending an alkylcarbamoyl group at *N*-3 of the benzodiazepine ring [35]. The 3-*N*-methylcarbamoyl derivative **23** (GYKI 53655, LY 300168) emerged as the most potent compound among this series of derivatives [35, 63]. Its $ED_{50}$ value against KA-induced seizures as well as in the maximal electroshock seizure test is 2-3-fold higher than that of **1**, the lead compound. In addition **23** proved to be 5-8-fold more potent than **1**, when tested as a blocker of the AMPA and KA currents. The shift of the 4-methyl group of **22**, **23** and **49** to the 5-position is non-productive [71].

Quite interestingly, the replacement of the iminohydrazone portion of GYKI 52466 by an

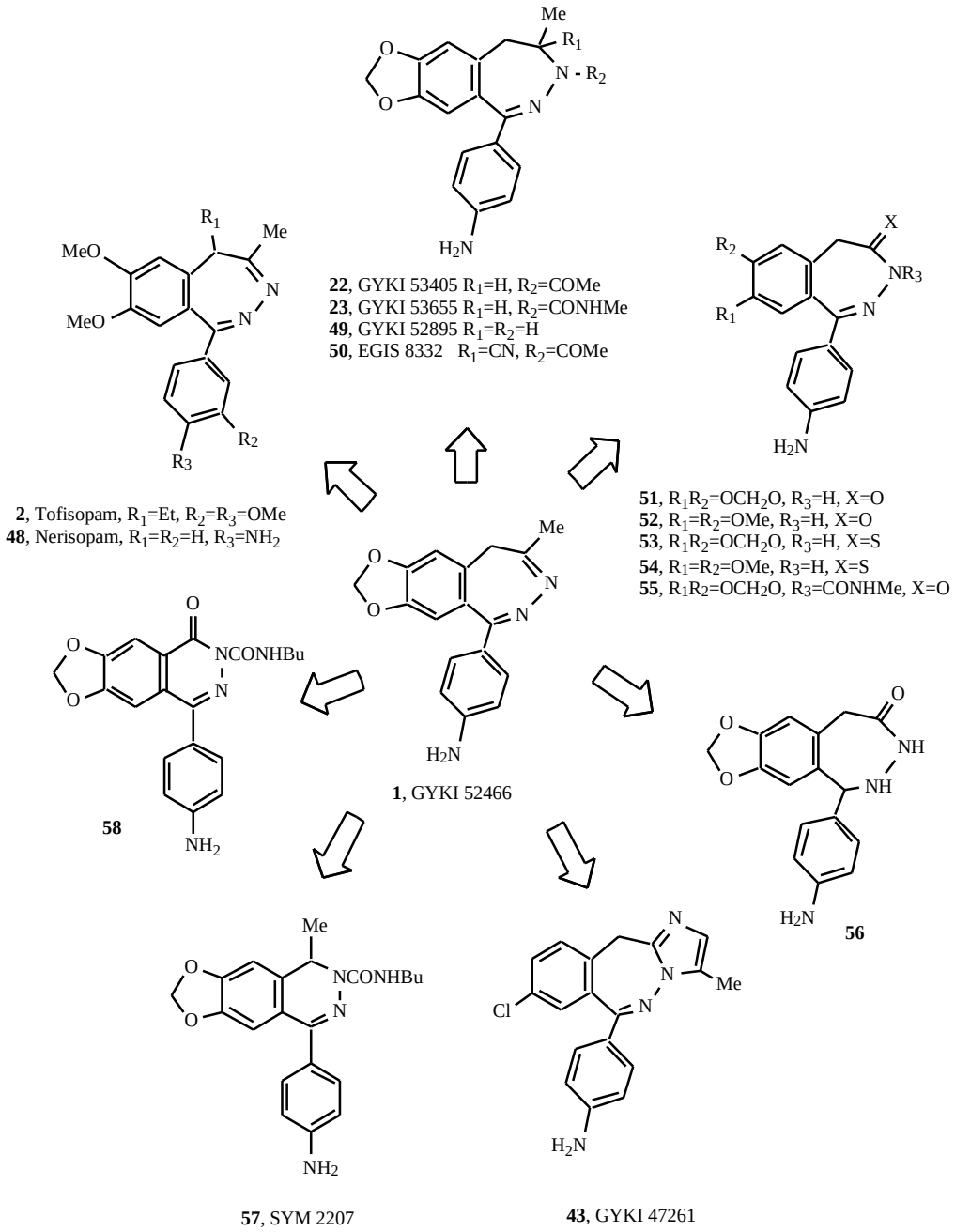



**Fig. (2).** Main structure-activity relationships of 2,3-benzodiazepine derivatives.

iminohydrazide moiety i.e. **51** [48-50], brought about a significant increase in the anticonvulsant activity with respect to the reference compound. The same trend was also observed in the 7,8-dimethoxy substituted derivatives i.e. **52** [46]. Furthemore, the bioisosteric replacement of oxygen by sulfur in the carbonyl group of derivatives **51-52** ameliorated the pharmacological profile of compounds **53-54**, presumably owing to a more favorable diffusion across the blood-brain barrier [51, 52]. As previously observed for GYKI 53655 (**23**), the introduction of a methylcarbamoyl group at *N*-3 (i.e. **55**) [52] is a productive structural modification. Recently, we observed [53] that the reduction of the 1,2-azomethine functionality of **51** does not significantly affect the *in vivo* anticonvulsant activity. As a matter of fact, compound **56** is endowed with a remarkable antiseizure activity and its effects are longer-lasting. Compounds **51-56** are also characterized by a toxicity lower than that of GYKI 52466.

Surprisingly enough, a recent report shows that an unsubstituted phenyl ring at C-1 of 3-alkyl-3,5-dihydro-7,8-methylenedioxy-4*H*-2,3-benzodiazepin-4-ones gives rise to compounds which potentiate rather than inhibit the effect of AMPA [72, 73].

The cyclofunctionalization of the 3,4 position with an imidazole nucleus and, at the same time, the replacement of the methylenedioxy moiety with a chlorine atom produced a new class of imidazobenzodiazepines endowed with anticonvulsant and neuroprotective properties that found their lead compound in GYKI 47261 (**43**) [74].

The reduction in size of the seven-membered ring of 2,3-benzodiazepines was also studied. Dihydrophthazines, such as the 3-*N*-butylcarbamoyl derivative SYM 2207 (**57**) [75] showed selective and noncompetitive inhibitory properties at the AMPA receptor complex. The same structural modification, applied to derivatives in which the lactam functionality was present, led to the identification of a compound, namely 4-(4-aminophenyl)-2-*N*-butylcarbamoyl-6,7-methylenedioxyphthalazin-1(2*H*)-one (**58**), which displayed an anticonvulsant potency 11-fold higher than that of GYKI 52466 [76].

## CONCLUSIONS

Since glutamatergic neurotransmission via ionotropic receptors, i.e. NMDA, AMPA, and KA receptors, is the predominant source of fast excitatory signalling in the mammalian brain, an over-activation of these channels can be regarded as the major trigger of neurodegeneration via both necrosis and apoptosis. The 2,3-benzodiazepine derivatives, reviewed in the present paper, constitute a class of negative allosteric modulators of the synaptic glutamatergic transmission. This class of compounds acts as selective, non-competitive antagonists of the AMPA receptors. As a consequence 2,3-benzodiazepines could find clinical applications as anticonvulsants, neuroprotective agents in acute ischaemic insults as well as in chronic neurodegenerative pathologies. Nevertheless, their pharmacological profile needs to be optimized in order to remove or reduce a number of serious side-effects which prevent their development as a drug. In fact, most of the compounds cause motor impairment, ataxia and sedation. Cognitive disorders are also caused by the administration of AMPA antagonists. In some instances, due to their poor solubility, the pharmacokinetic properties and the bioavailability of the compounds cause their precipitation in the kidneys inducing necrosis. In conclusion, even if the structure-activity relationships of 2,3-benzodiazepines have been thoroughly investigated and well defined, the pharmacological profile of the most promising derivatives needs to be significantly improved before clinical trials can be performed.

## REFERENCES

[1] Hicks, T.P. In *CNS Neurotransmitters and Neuromodulators: Glutamate*, Stone, T.W. Ed.; CRC Press: New York, **1995**; pp. 201-215.

[2] Ikonomidou, C.; Turski, L. In *CNS Neurotransmitters and Neuromodulators: Glutamate*, Stone, T.W. Ed.; CRC Press: New York, **1995**; pp. 253-266.

[3] Danysz, W.; Parsons, C.G.; Bresink, I.; Quack, G. *Drug News Perspect*., **1995,** *8*, 261.

[4] Conn, P.J; Pin, J.-P. *Annu. Rev. Pharmacol. Toxicol.*, **1997**, *37*, 205.

[5] Krogsgaard-Larsen, P.; Hansen, J.J. Eds., In *Excitatory Amino Acid Receptors: Design of Agonists and Antagonists*, Ellis Horwood: Chichester, **1992**.

[6] Monaghan, D.T.; Wenthold R.J., Eds., In *The Ionotropic Glutamate Receptors*, Humana Press: New Jersey, **1997**.

[7] Dingledine, R.; Borges, K.; Bowie, D.; Traynelis, S.F. *Pharmacological Reviews*, **1999**, *51*, 7.

[8] Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci*., **1994**, *17*, 31.

[9] Wenthold R.J.; Yokotani, N.; Doi, K.; Wada, K., *J. Biol. Chem*., **1992**, *267*, 501.

[10] Rosenmund, C.; Stern-Bach, Y.; Stevens, C.F. *Science*, **1998**, *280*, 1596.

[11] Mano, I.; Teichberg, V.I. *Neuroreport*, **1998**, *9*. 327.

[12] Tanaka, H.; Grooms, S.Y.; Bennett, M.V.L.; Zukin, R.S. *Brain Res*., **2000**, *886*, 190.

[13] Gill, R.; Lodge, D. *Int. Rev. Neurobiol.*, **1997**, *40*, 197.

[14] Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E.; Krogsgaard-Larsen, P. *J. Med. Chem.*, **2000**, *43*, 2609.

[15] Lees, G.J., *Drugs*, **2000**, *59*, 33.

[16] Koek, W.; Woods, J.H.; Winger, G.D. *J. Pharmacol. Exp. Ther*., **1988**, *245*, 969.

[17] Herting, R.L. *J. Neurochem.*, **1993,** *61 (Suppl.)*, S283C.

[18] Morris, R.G.; Anderson, E.; Lynch, G.S.; Baudry, M. *Nature*, **1986,** *319*, 774.

[19] Umemura, K.; Kondo, K., Ikeda, Y.; Teraya, Y.; Yoshida, H.; Homma, M.; Uematsu, T.; Nakashima, M. *J. Clin. Pharmacol*., **1997**, *37*, 719.

[20] Desos, P.; Lepagnol, J.M.: Morain, P.; Lestage, P.; Cordi, A.A. *J. Med. Chem.*, **1996**, *39*, 197.

[21] Lin, Z.; Kadaba, P.K. *Med. Res. Rev.*, **1997**, *17*, 537.

[22] Sheardown, M.J.; Nielsen, E.O.; Hansen, A.J.; Jacobsen, P.; Honore, T. *Science*, **1990**, *247*, 571.

[23] Buchan, A.M.; Lesiuk, H.; Barnes, K.A.; Li, H.; Huang, Z.G.; Smith, K.E.; Xue, D. *Stroke*, **1993,** *24* (*suppl. I)*, 1148.

[24] Donevan, S.D.; Rogawski, M.A. *Neuron*, **1993,** *10*, 51.

[25] Wilding, T. J.; Huettner, J. E. *Mol. Pharmacol*., **1995**, *47*, 582.

[26] Bleackman, D.; Ballyk, B. A.; Schoepp, D. D.; Palmer, A. J.; Bath, C. P.; Sharpe E. F.; Woolley, M. L.; Bufton, H. R.; Kamboj, R. K.; Tarnawa, I.; Lodge, D. *Neuropharmacology*, **1996**, 35, 1689.

[27] Paternain, A.V.; Morales, M.; Lerma, J. *Neuron*, **1995**, *14*, 185.

[28] Körösi, J.; Láng, T.; Komlos E.; Erdelyi-Petócz, L. Hungarian Patent 155,572, *Chem. Abs.*, **1969**, *70*, 115026a.

[29] Körösi, J.; Láng, T. *Chem. Ber*., **1974**, *107*, 3883.

[30] Neszmélyi, A.; Gács-Baitz, E.; Horváth, G.; Láng, T.; Körösi, J. *Chem. Ber*., **1974**, *107*, 3894.

[31] Petócz, L.; Kosóczky, I. *Therapia Hungarica*, **1975**, *23*, 134.

[32] Gatta, F.; Piazza, D.; Del Giudice, M. R.; Massotti, M. *Il Farmaco Ed. Sc.*, **1985**, *40*, 942.

[33] Zappalà, M.; Grasso, S.; Micale, N.; Polimeni, S.; De Micheli, C. *Synth. Commun.*, **2001**, in press.

[34] Chenard, B.L.; Butler, T.W.; Menniti, F.S.; Prochniak, M.A.; Richter, K.E.G. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1991.

[35] Tarnawa, I.; Berzsenyi, P.; Andrási, F.; Botka, P.; Hámori, T.; Ling, I.; Körösi, J. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 99.

[36] Andrási, F.; Berzsenyi, P.; Botka, P.; Farkas, S.; Goldschmidt, K.; Hámori, T.; Körösi, J.; Moravcsik, I.; Tarnawa, I. US Patent 5,639,751 (*Chem. Abs*., **1997**, *127*, 108948v).

[37] Ratkai, Z.; Barkoczy, J.; Schneider, G.; Cselenyak, J.; Simig, G.; Balazs, L.; Doman, I.; Greff, Z.; Kotay, N.P.; Seres, P.; Szabo, G.; Gacsalyi, I.; Gigler, G.; Gyertyan, I.; Levai, G.; Kovacs, A.; Simo, A.; Szabados, T.; Egyed, A.; Vegh, M.; Tihanyi, K. WO 99 07,707 (*Chem. Abs.*, **1999**, *130*, 196674t).

[38] Barkoczy, J.; Cselenyak, J.; Ratkai, Z.; Simig, G.; Balazs, L.; Doman, I.; Kotay, N.P.; Greff, Z.; Seres, P.; Szabo, G.; Gacsalyi, I.; Gigler, G.; Gyertyan, I.; Levai, G.; Kovacs, A.; Simo, A.; Szabados, T.; Egyed, A.; Vegh, M.; Tihanyi, K. WO 99 07,708 (*Chem. Abs.*, **1999**, *130*, 196675u).

[39] Ling, I.; Podányi, B.; Hámori, T.; Sólyom, S. *J. Chem. Soc. Perkin Trans I*, **1995**, 1423.

[40] Ling, I.; Hámori, T.; Botka, P.; Sólyom, S.; Simay, A.; Moravcsik, I. WO 95 01,357 (*Chem. Abs.*, **1995**, *122*, 214111y).

[41] Anderson, B.A.; Hansen, M.M.; Harkness, A.R.; Henry, C.L.; Vincenzi, J.T.; Zmijewski, M.J. *J. Am. Chem. Soc.*, **1995**, *117*, 12358.

[42] Anderson, B.A.; Harn N.K.; Hansen, M.M.; Harkness, A.R.; Lodge, D.; Leander, J.D. *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1953.

[43] Anderson, B.A.; Hansen, M.M.; Vicenzi, J.T.; Varie, D.L.; Zmijewski, M.J. EP 699,677. (*Chem. Abs.*, **1996**, *125*, 33693f).

[44] Anderson, B.A.; Hansen, M.M.; Harn N.K. US 5,795,886. (*Chem. Abs.*, **1998**, *129*, 189346p).

[45] De Sarro, G.; Chimirri, A.; De Sarro, A.; Gitto, R.; Grasso, S.; Giusti, P.; Chapman, A. G. *Eur. J. Pharmacol.*, **1995**, *294*, 411.

[46] Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Grasso, S.; Quartarone, S.; Zappalà, M.; Giusti, P.; Libri,V.; Constanti, A.; Chapman, A. G. *J. Med. Chem.*, **1997**, *40*, 1258.

[47] Horváth, E. J.; Horváth, K.; Hámori, T.; Fekete, M.I.K.; Sólyom, S.; Palkovits, M. *Progress in Neurobiology*, **2000,** *60*, 309**.**

[48] De Sarro, A.; De Sarro, G.; Gitto, R.; Grasso, S.; Micale, N.; Quartarone, S.; Zappalà M. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 971.

[49] Wang, Y.; Konkoy, C.S.; Ilyin, V.I.; Vanover, K.E.; Carter, R.B.; Weber, E.; Keana, J.F.W.; Woodward, R.M.; Cai, S.X. *J. Med. Chem.*, **1998**, *41*, 2621.

[50] De Sarro, A.; De Sarro, G.; Gitto, R.; Grasso, S.; Micale, N.; Zappalà M. *Il Farmaco*, **1999**, *54*, 179.

[51] Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Quartarone, S.; Zappalà, M.; Constanti, A.; Libri,V. *J. Med. Chem.*, **1998**, *41*, 3409.

[52] Grasso, S.; De Sarro, G.; De Sarro, A.; Micale, N.; Zappalà, M.; Puia, G.; Baraldi, M.; De Micheli, C. *J. Med. Chem.*, **1999**, *42*, 4414.

[53] Grasso, S.; De Sarro, G.; De Sarro, A.; Micale, N.; Polimeni, S.; Zappalà, M.; Puia, G.; Baraldi, M.; De Micheli, C. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 463.

[54] Ábrahám, G.; Sólyom, S.; Csuzdi, E.; Berzsenyi, P.; Ling, I.; Tarnawa, I.; Hámori, T.; Pallagi, I.; Horváth, K.; Andrasi, F.; Kapus G.; Harsing Jr. L.G.; Király, I.; Patthy M.; Horváth, G. *Bioorg. Med. Chem. Lett.*, **2000**, *8*, 2127.

[55] Chimirri, A.; Bevacqua, F.; Gitto, R.; Quartarone, S.; Zappalà, M.; De Sarro, A.; Maciocco, L.; Biggio G.; De Sarro, G. *Med. Chem. Res.*, **1999**, *9*, 203.

[56] Zappalà, M.; Gitto, R.; Bevacqua, F.; Quartarone, S.; Chimirri, A.; Rizzo, M.; De Sarro, G.; De Sarro, A. *J. Med. Chem.*, **2000**, *43*, 4834.

[57] Chimirri, A.; Zappalà, M.; Gitto, R.; Quartarone, S.; Bevacqua, F. *Heterocycles*, **1999**, *51*, 1303.

[58] Rogawski, M.A. *Trends Pharmacol. Sci.*, **1993,** *14*, 325.

[59] Tarnawa, I.; Farkas, S.; Berzsenyi, P.; Patfalusi, M.; Andrasi, F. *Acta Physiol. Hung.*, **1990**, *75*, 277.

[60] Chapman, A.G.; Smith, S.E.; Meldrum, B.S. *Epilepsy Res.*, **1991**, *9*, 92.

[61] Smith, S.E.; Durmuller, N.; Meldrum, B.S. *Eur. J. Pharmacol.*, **1991,** *201*, 179.

[62] Chapman, A.G.; Al-Zubaidy, Z.; Meldrum, B.S. *Eur. J. Pharmacol.*, **1993,** *231*, 301.

[63] Donevan, S.D.; Yamaguchi, S.I.; Rogawski, M.A. *J. Pharmac. Exp. Ther.*, **1994,** *271*, 25

[64] Smith, S. E.; Meldrum, B. S. *Stroke*, **1992**, *23*, 861.

[65] Le Peillet, P.; Arvin, B.; Moncada, C.; Meldrum, B.S. *Brain Research*,**1992**, *571*, 115.

[66] Marinelli, S.; Gatta, F.; Sagratella, S. *Eur. J. Pharmacol.*, **2000**, *391*, 75.

[67] Vago, P.; Reiter, J.; Gyertyan, I.; Gigler, G.; Andrasi, F.; Bakonyi, A.; Berzsenyi, P.; Botka, P.; Birkas, Faigl, E. et al. *Eur. Pat. Appl.*, EP 726,256 (*Chem. Abs.*, **1996**, *125*, 195698p).

[68] Vago, P.; Reiter, J.; Gyertyan, I.; Gacalyi, I.; Bilkei-gorzo, A.; Egyed, A.; Andrasi, F.; Bakonyi, A.; Berzsenyi, P. *Eur. Pat. Appl*., EP 726,257 (*Chem. Abs.*, **1996**, *125*, 221885u).

[69] Horváth, K.; Szabo, H.; Patfalusi, M.; Berzsenyi, P.; Andrasi, F. *Eur. J. Pharmac.*, **1990**, *183*, 1416.

[70] Lévay, G. *Fundam. Clin. Pharmacol.*, **1999**, *13* (Suppl.1), 58.

[71] Hámori, T.; Sólyom, S.; Berzsenyi, P.; Andrási, F.; Tarnawa, I.; *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 899.

[72] Menniti, F. S.; Chenard, B. L.; Collins, M. B.; Ducat, M. F.; Elliott, M. L.; Ewing F. E.; Huang, J. I.; Kelly, K. A.; Lazzaro, J. T.; Pagnozzi, M. J.; Weeks, J. L.; Welch, W. M.; White, W. F. *Mol. Pharmacol*., **2000**, *58*, 1310.

[73] Konkoy, C.S.; Ilyin, V.I.; Xia, H.J.; Whittemore, R., Society for Neuroscience 28th Annual Meeting, **1998**, *24*, 99.

[74] Ábrahám, G.; Csuzdi, E.; Sólyom, S.; Berzsenyi, P.; Tarnawa, I.; Andrasi, F.; Ling, I.; Hámori, T.; Horváth, K.; Pallagi, I.;. Moravcsik, I.; Simay, A.; WO 9906408 (*Chem. Abs*., **1999**, *130*, 168401h).

[75] Pelletier, J. C.; Hesson, D. P.; Jones, K. A.; Costa, A. M. *J. Med. Chem.*, **1996**, *39*, 343

[76] Grasso, S.; De Sarro, G., De Sarro, A.; Micale, N.; Zappalà, M.; Puia, G.; Baraldi, M.; De Micheli, C. *J. Med. Chem.*, **2000**, *43*, 2851.