Pharmacophore Modeling as an Efficient Tool in the Discovery of Novel Noncompetitive AMPA Receptor Antagonists

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A three-dimensional pharmacophore model for the binding of noncompetitive AMPA receptor antagonists was developed in order to map common structural features of highly active compounds. This hypothesis, which consists of two hydrophobic regions, one hydrogen bond acceptor and one aromatic region, was successfully used as framework for the design of a new class of allosteric modulators containing a tetrahydroisoquinoline skeleton and for *in silico* screening. The promising biological results suggested that the identified molecules might be useful "lead compounds" for future drug development.

INTRODUCTION

Glutamate (L-Glu) is considered the main excitatory neurotransmitter in the mammalian central nervous system (CNS), activating ionotropic (iGluRs) as well as metabotropic receptors (mGluRs). iGluRs are thought to play an important physiological role in learning and memory, whereas their excessive activation seems to be related to the neuronal death associated with stroke, global ischemia, and epilepsy.[1−3]

iGluRs are divided into three classes on the basis of sequence identity and pharmacological response to the agonists 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), kainic acid (KA), and *N*-methyl-D-aspartic acid (NMDA).[4]

Considering the pivotal role of AMPA receptor (AMPAR) in physiological and pathological CNS phenomena, significant effort has been focused toward the synthesis of specific ligands as a source of potential anticonvulsant and neuroprotective agents.[5,6]

The first AMPAR antagonists reported in the literature were the competitive inhibitors such as NBQX, heterocyclic-fused quinoxalinones, isatinoximes, etc. Later, the search for compounds able to interact with AMPAR resulted in the identification of several classes of modulators which proved to act via a noncompetitive mechanism of action.

For a long time 2,3-benzodiazepine derivatives were the only noncompetitive AMPAR antagonists available as pharmacological tools; within this class of compounds GYKI 52466 (**1**) was the prototypic anticonvulsant and neuroprotective agent in rodents.[7] Subsequently, talampanel (**2**) was identified, and clinical trials in patients with severe epilepsy not responsive to other drugs are now under way.[8]

Moreover, taking the 2,3-benzodiazepines as template, highly potent arylphthalazine derivatives (e.g. **3**, SYM-2207) have been synthesized.[9]

In the field of 2,3-benzodiazepine analogues, we reported chemical and biological studies of a large series of 7,8-dimethoxy-2,3-benzodiazepines (e.g. **4**, CFM-2) which have been shown to be specific noncompetitive AMPAR antagonists and potent anticonvulsant agents in various seizure models.[10−14]

Recently a new class of noncompetitive AMPAR antagonists has been identified by Pfizer scientists, who discovered CP-4650223 (**5**) as lead compound of this series of quinazolines.[15,16]

Despite the insightful interest for allosteric modulators of AMPAR and their crucial role in specific diseases, their mechanism has not been completely clarified to date, and a comprehensive study of the structural features affecting potency and selectivity is still lacking. Furthermore, no information is currently available about the location and composition of the AMPAR negative allosteric ligand binding region.

In the absence of such three-dimensional structure-based information, we attempted to identify the hypothetical 3-D ligand-based pharmacophore model by using the common features hypothesis generation approach (HipHop) implemented in the program Catalyst.[17] In particular, HipHop algorithm finds common feature pharmacophore models among a set of highly active compounds thus carrying out a "qualitative model" (without the use of activity data), which represents the essential 3D arrangement of functional groups common to a set of molecules for interacting with a specific biological target, i.e., AMPAR in the current study. This approach is the most appropriate for our ligands; in fact, the "quantitative" hypothesis generation method is not suitable considering that the available in vitro and in vivo biological data were evaluated through different experimental protocols and therefore these values are not homogeneous.

Thus, the main goal of this work was the deciphering of main three-dimensional structural requirements that are relevant in a molecule in order to noncompetitively interact with AMPAR.

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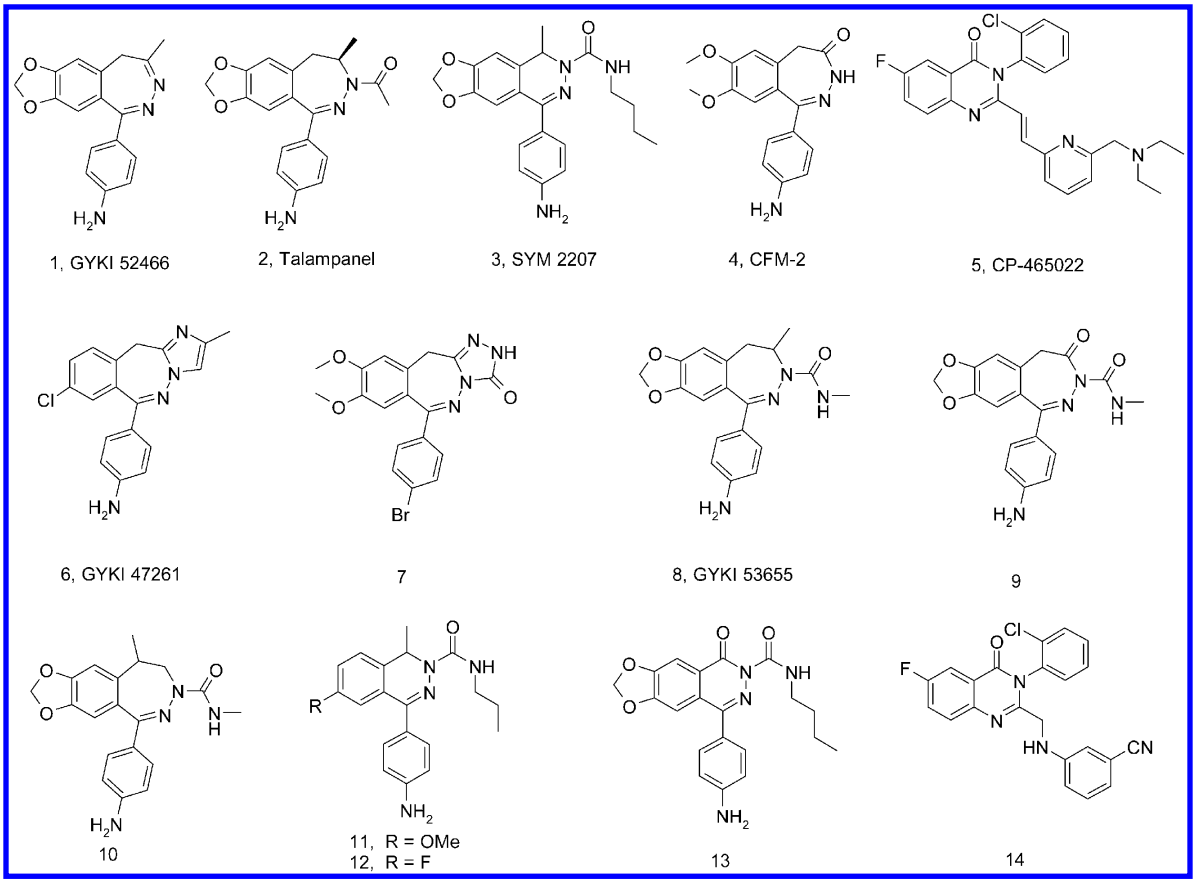

Figure 1. Chemical structures of noncompetitive AMPA receptor antagonists

The reliability of the postulated pharmacophore model was validated by directing the synthesis and the identification of new AMPAR negative noncompetitive modulators.

MATERIALS AND METHODS

Training Set. Fourteen molecules (**1**−**14**, Figure 1) were selected as the training set, representing the most interesting compounds within the three chemical classes of known noncompetitive AMPAR antagonists, i.e., 2,3-benzodiazepines, phthalazines, and quinazolines. These compounds are characterized by significant anticonvulsant effects in various experimental models of seizures, and their interaction with AMPAR was confirmed by in vitro biological tests.[7−9,11,14,16,18−22]

All structures were generated using 2D/3D editor sketcher in Catalyst 4.6 software package and were energy minimized to the closest local minimum using the CHARMM-like force field implemented in the program.[23]

The chirality of the asymmetric carbon atom in compound **2** (talampanel) was known and assigned as reported in the literature, that is *R*. On the contrary, regarding the asymmetric centers of compounds **3**, **8**, **10**, **11,** and **12**, as no experimental data on the biologically relevant conformations of these molecules are available, it was arbitrarily decided to assign "undefined" chirality, allowing the pharmacophore model generation procedure to choose which configuration of the asymmetric carbon atoms was the most appropriate.

To build conformational models of up to 250 conformers for each molecule,[24] the "best conformer generation" option and a 10 kcal/mol energy cutoff were chosen.

Pharmacophore Model Generation. Our pharmacophoric analysis was carried out using the Catalyst/HipHop procedure,[17] which consisted only of identification and overlay of common chemical features shared by negative noncompetitive modulators of AMPAR of the training set, without taking their biological data into account.

In the hypothesis generation, on the basis of the atom types in the molecules of the training set, the following chemical functions were selected in the feature dictionary of Catalyst: hydrogen bond acceptor, hydrogen bond donor, aromatic ring, positive ionizable and hydrophobic groups.

Ten hypotheses were obtained using the default parameters of Catalyst, and the first five models had the same chemical characteristics with the ranking scores ranging from 106.25 to 105.31 (Table 1). This small range of ranking score suggested that the four features are spatially arranged similarly in the five hypotheses (number 1−5), which can thus be considered equivalent.

Furthermore, when in Catalyst some models exibit the same value of ranking score, this means that their statistical relevance is identical and that the molecules in the training set have exactly the same probability to fit those hypotheses by a chance correlation. In our study, this occurred between models 1 and 2, 3 and 4 as also for the hypotheses 8, 9 and 10, which all mainly differ from each other in the direction of the projected point in the aromatic feature locating the proposed π-stacking interaction.

A 3D query of the Maybridge database using the highest scoring pharmacophore model was accomplished by means of Catalyst. The Maybridge 3D-coordinate database was obtained from Accelrys, Inc. with the Catalyst software.

Anticonvulsant Activity. The anticonvulsant properties of tested compounds were evaluated 30 min after intraperi-

Table 1. Summary of the Common Feature Hypothesis Run

no.[a]	composition[b]	ranking score[c]	direct hit mask[d]	partial hit mask[e]
1	RHHA	106.249	11111111111111	00000000000000
2	RHHA	106.249	11111111111111	00000000000000
3	RHHA	105.414	11111111111111	00000000000000
4	RHHA	105.414	11111111111111	00000000000000
5	RHHA	105.307	11111111111111	00000000000000
6	HHHA	96.668	11111111111111	00000000000000
7	HHHA	93.303	11111111111111	00000000000000
8	RRA	86.291	11111111111111	00000000000000
9	RRA	86.291	11111111111111	00000000000000
10	RRA	86.291	11111111111111	00000000000000

[a] Numbers for the hypothesis are consistent with the numeration as obtained by the hypothesis generation. [b] R: aromatic ring; H: hydrophobic group; A: hydrogen bond acceptor. [c] The higher the ranking score, the less likely it is that the molecules in the training set fit the hypothesis by a chance correlation. Best hypotheses have highest ranks. [d] Direct hit mask: a training set molecule mapped every feature in the hypothesis. 1 means yes and 0 means no. For our 10 hypotheses, all 14 compounds mapped all hypothesis features. [e] Partial hit mask: a training set molecule mapped all but one feature in the hypothesis. 1 means yes and 0 means no.

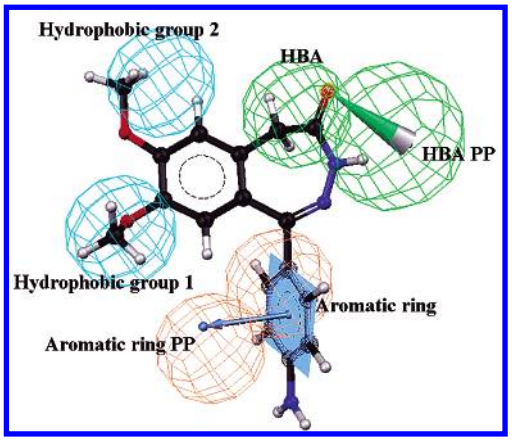

Figure 2. The highest-ranked four-point hypothesis for noncompetitive AMPAR antagonists derived using the Catalyst/HipHop program. Cyan: hydrophobic groups; green: hydrogen bond acceptor feature (HBA) with a vector in the direction of the putative hydrogen donor (HBA PP); orange: aromatic ring with proposed π-stacking interaction shown by an arrow (aromatic ring PP). The alignment of compound **4** with the pharmacophore is shown.

toneal administration against audiogenic seizures in DBA/2 mice, which has been considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs.[25] Further information about this method has previously been reported.[12] The biological activity of the ligands is expressed as ED_{50} (median effective dose values required to prevent clonic and tonic phases of sound-induced seizures).

RESULTS AND DISCUSSION

3D-Pharmacophore Description. The HipHop module of Catalyst was used for our hypothesis generation and the highest scoring (statistically best) pharmacophore was chosen as the model for this study.

The minimal structural requirements for AMPAR interaction were identified to be two hydrophobic groups, one aromatic region and one hydrogen bond acceptor in a specific three-dimensional arrangement (Figure 2). Table 2 summarizes the distances between the four chemical features.

Table 2. Distance Matrix (in Å) for the Chemical Features of the 3D-Pharmacophore Model

	aromatic ring	aromatic ring PP[b]	hydrophobic group 1	hydrophobic group 2	HBA[a]
aromatic ring					
aromatic ring PP	3.0				
hydrophobic group 1	5.5	4.6			
hydrophobic group 2	7.2	8.3	5.1		
HBA	5.3	7.7	6.6	4.3	
HBA PP	5.7	8.6	8.9	7.3	3.0

[a] HBA: hydrogen bond acceptor. [b] PP: projected point.

Table 3. Anticonvulsant Activity against Audiogenic Seizures in DBA/2 Mice

	ED_{50} μmol/kg[a]	
	clonic phase	tonic phase
CFM-2[b]	15.0 (9.01−24.0)	12.6 (8.01−19.0)
talampanel[c]	13.4 (10.1−17.8)	9.70 (7.00−13.4)
GYKI 52466[b]	35.8 (24.4−52.4)	25.3 (16.0−40.0)
15	32.1 (17.7−58.3)	21.1 (11.0−40.4)
DP 00595	47.8 (34.2−66.6)	42.5 (32.0−56.5)
DP 01855	85.0 (52.9−136)	68.7 (46.3−102)
KM 08780	>100	>100
PD 00735	19.7 (14.6−20.4)	16.3 (12.6−21.1)
RDR 01318	89.5 (52.2−153)	63.8 (45.1−90.2)
RH 01490	76.4 (45.4−128)	63.0 (41.9−94.7)
RJC 00552	75.3 (42.0−135)	50.1 (35.0−77.7)
SEW 01207	>100	>100

[a] All data were calculated according to the method of Litchfield and Wilcoxon. 95% confidence limits are given in parentheses. At least 32 animals were used to calculate each ED_{50}. [b] Reference 12. [c] Reference 26.

Figure 2 shows the alignment of compound CFM-2 (compound **4**) onto the putative four-feature hypothesis. This molecule has been selected as example because it represents our first lead compound and is ∼2-fold more active than **1**, the prototype of noncompetitive AMPAR antagonists (Table 3). The compound **4** mapped well onto the four chemical functionalities of the pharmacophore model: particularly, the carbonyl oxygen of the lactam moiety occupied the hydrogen bond acceptor region, the C-1 phenyl ring was disposed over the aromatic region, whereas the two methoxy substituents overlapped with the hydrophobic features.

The different alignments for the other molecules in the training set are provided as Supporting Information.

Rational Design of a New Class of Noncompetitive AMPAR Antagonists. The generated pharmacophore hypothesis suggested some structural modifications of our ligand CFM-2 that could lead to new selective negative allosteric AMPAR modulators.

In particular, the simple replacement of diazepine ring with tetrahydropyridine system directed the synthesis toward the 2-acetyl-1-(4′-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15**, Figure 3), which theoretically could have been the lead candidate of a novel series of ligands. We decided to keep the 4′-aminophenyl substituent and dimethoxybenzene moiety by analogy with CFM-2; furthermore, we chose to include the *N*-acetyl functional group in the compound to be synthesized in order to meet the hydrogen bond acceptor feature described in the 3D model, improving the chance of obtaining an active molecule.

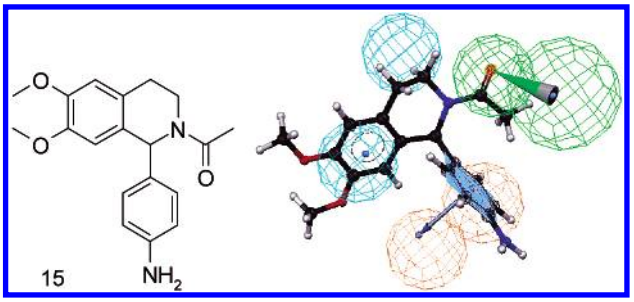

Figure 3. Mapping of compound **15** onto the best four-feature pharmacophore of noncompetitive AMPAR antagonists (cyan: hydrophobic groups; green: hydrogen bond acceptor; orange: aromatic ring).

In fact, the alignment between **15** and the 3D-hypothesis showed that the features of the proposed model are well matched by the chemical groups of the molecule, indicating a preference for the *S* enantiomer: the carbonyl oxygen group of the acetyl moiety could act as hydrogen bond acceptor, the aryl group occupied the aromatic region, and the benzene-fused ring and the ethylene bridge corresponded to the two hydrophobic regions (Figure 3). A similar mapping onto the pharmacophore model was observed for other members of the training set such as compounds **2** and **7** (Supporting Information).

Compound **15** was easily synthesized as a racemic mixture via Pictet−Spengler synthetic approach and, after confirming its interaction with AMPAR by in vitro studies, the anticonvulsant effect was evaluated.[26] The results of pharmacological screening put in evidence that this molecule was efficacious against sound-induced seizures, showing comparable activity to GYKI 52466 (Table 3).

Compound **15** can be thus considered the lead template of a new class of negative modulators of AMPAR and, even if it is ∼2-fold less active than talampanel (**2**) (Table 3), suitable chemical modifications could lead to more potent and selective ligands.

***In Silico* Screening.** The four-point pharmacophore hypothesis was directly used as a query for virtual screening, looking for additional candidates for biological testing among the molecules that contain the pharmacophore in their low-energy conformation.

The "fast flexible search" option in Catalyst was first selected to screen the Maybridge 3D-database and yielded a collection of about 14 000 compounds that shared, in some conformation, the same 3D representations of the functional groups.

A subset of these structures was created by removing all the molecules that did not satisfy the well-known Lipinski rules, describing properties of drug-like compounds.[27] The remaining molecules were overlaid with the 3D-pharmacophore by using the "Best Fit" option and, among the top 200 scored hits, eight compounds were selected for anticonvulsant testing on the basis of their fit value, chemical diversity, logP, cost, availability,[28] and our knowledge on AMPAR ligands. The 2D structures of the eight hits for noncompetitive AMPAR antagonists are reported in Figure 4.

The anticonvulsant efficacy of the selected compounds was evaluated as reported in the Method session, and the biological results are provided in Table 3. Some of these compounds demonstrated anticonvulsant effects, and it is worthwhile to note that the compound **PD 00735** retains higher activity with respect to GYKI 52466 (**1**). These results further confirmed the validity of our pharmacophore modeling approach.

The superimposition of compound **PD 00735** against the four-feature hypothesis (Figure 5) showed that the model predicted a stereochemical partiality for the *R,R* configuration, where the carbonyl group corresponded to the hydrogen bond acceptor site, the benzyl and phenyl substituents are positioned over the two hydrophobic areas, whereas the benzene-fused ring overlapped with the aromatic feature.

Structural modifications of these new ligands will be carried out with the general aims to obtain new noncompetitive antagonists with higher biological affinities toward AMPAR.

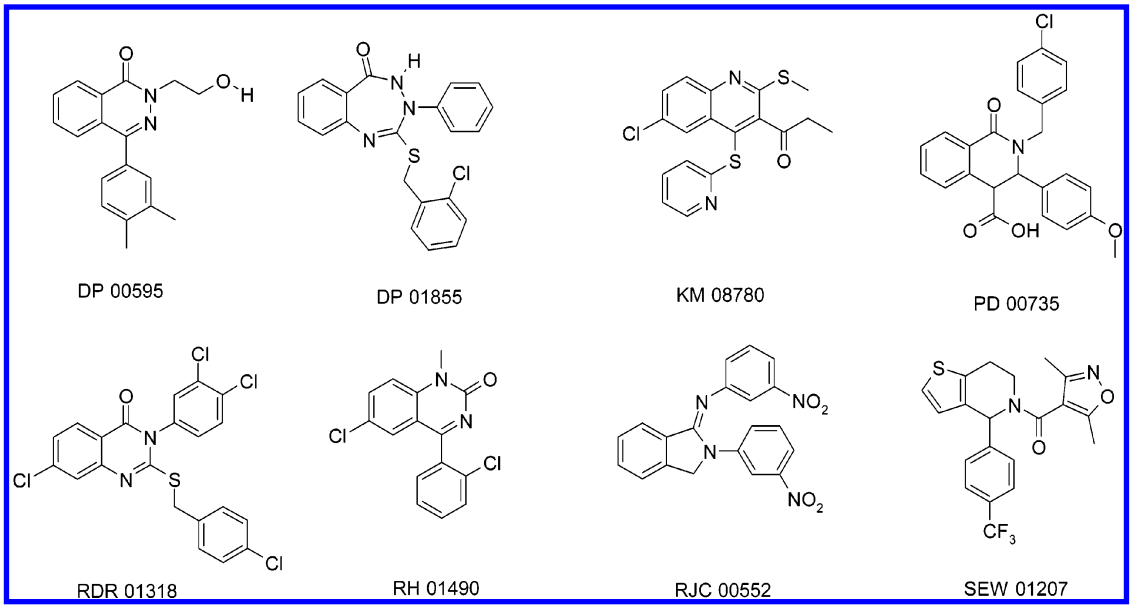

Figure 4. Compounds retrieved from the Maybridge 3D-database and chosen for experimental testing.

Figure 5. Alignment between **PD00735** and the proposed 3D-pharmacophore for noncompetitive AMPAR antagonism (cyan: hydrophobic groups; green: hydrogen bond acceptor; orange: aromatic ring).

CONCLUSION

We have herein reported the first three-dimensional pharmacophore for noncompetitive AMPAR antagonists, whose development was achieved by the HipHop/Catalyst software employing as the training set a series of highly potent in vivo and in vitro compounds, both collected from the literature and synthesized by us.

The model consisted of four features corresponding to one hydrogen bond acceptor, one aromatic ring and two hydrophobic groups, and enabled us to achieve the rational design of a new class of ligands containing a tetrahydroisoquinoline skeleton.

Moreover, three-dimensional structural database pharmacophore searching was performed on the Maybridge database and allowed the discovery of some molecules with anticonvulsant activity.

These results show the efficiency of the proposed 3D-pharmacophore model in aiding the discovery of novel compounds in the AMPAR field, directing the synthesis, and identifying potential ligands for further lead optimization processes.

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Supporting Information Available: Alignment of the 14 molecules of the training set onto the pharmacophore model. This material is available free of charge via the Internet at http://pubs.acs.org.

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