QSAR Study of Anticonvulsant Negative Allosteric Modulators of the AMPA Receptor

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A quantitative structure−activity relationship (QSAR) study was performed on a set of 49 negative allosteric modulators of AMPA receptor, acting as anticonvulsant agents, using multiple linear regression. The predictive ability of the resulting model was evaluated against a set of 12 compounds; the results showed good statistics in regression and revealed high correlation between anticonvulsant activity and some electrotopological descriptors.

Introduction

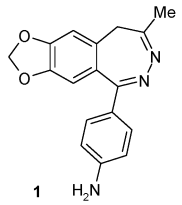
Glutamate (L-Glu) activates both metabotropic (mGluRs) and ionotropic receptors (iGluRs).[1,2] iGluRs comprise the α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor (AMPAR) subtype which mediates fast glutamatergic synaptic transmission. On route to the discovery of novel neuroprotective drugs, an intensive effort has been made toward the design and synthesis of anticonvulsant selective noncompetitive AMPAR antagonists[3] such as the prototype 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466, **1**),[4] some 2,3-benzodiazepin-4-(thi)ones (**2**−**35**),[5,6] cyclofunctionalized 2,3-benzodiazepines (**36**−**45**),[7] 1,2-phthalazines (**46**−**56**),[8] and isoquinolines (**57**−**61**).[9] Despite the considerable interest toward noncompetitive AMPAR antagonists, no quantitative structure−activity relationship (QSAR) data have been reported to date.

To gain insights into the structural and molecular requirements influencing the anticonvulsant activity, we herein describe the QSAR analysis of a large set of different classes of negative allosteric modulators, for which it is conceivable to make the assumption that they interact with AMPAR in the same allosteric binding site.[10]

Methods

Tables 1−3 show the chemical structures and anticonvulsant activity of selected noncompetitive AMPAR antagonists (**1**−**61**) collected from literature or synthesized by us.[5−9] In particular, 49 antagonists were included in the training set (TS) while an additional set of 12 derivatives was selected as a test set to validate the predictive power of the generated model. Although in vitro data are available for all the studied compounds, they derive from different methods and cannot be considered homogeneous enough for QSAR analysis. In vivo anticonvulsant activity was therefore considered as the median effective dose (ED_{50}) required to prevent clonic and tonic phases of seizures in DBA/2 mice.[5] The TS included molecules spanning from nearly inactive to highly potent anticonvulsants (see Supporting Information). Since the activities versus the clonic and tonic phases are highly correlated ($r^2 = 0.926$), we chose to use the activity in the clonic phase of seizures, expressed as the natural logarithm of the inverse of the median effective dose (log $1/ED_{50}$), to define the dependent variable.

Table 1. 2,3-Benzodiazepines



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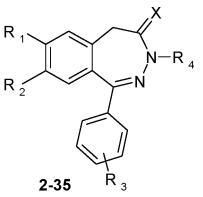

2-35

	R_1	R_2	R_3	R_4	X	ED_{50}, μmol clonus	ED_{50}, μmol tonus
1						35.8	25.3
2	MeO	H	H	H	O	75.5	64.8
3	MeO	H	H	Me	O	117	99.1
4	MeO	MeO	H	H	O	33.9	31.8
5	MeO	MeO	H	Me	O	37.8	26.7
6	MeO	MeO	H	Ac	O	101	72.1
7	-OCH_2O-		H	H	O	43.3	40.6
8	-OCH_2O-		H	Me	O	82.5	70.4
9	-OCH_2O-		H	H	S	23.8	18.8
10	MeO	MeO	H	H	S	19.7	15.0
11	MeO	MeO	H	Me	S	30.6	24.7
12	MeO	MeO	4-F	H	O	78.0	57.2
13	-OCH_2O-		4-F	H	O	89.8	63.8
14	MeO	MeO	4-Cl	H	O	102	75.3
15	MeO	MeO	4-Cl	Me	O	41.2	38.6
16	MeO	MeO	4-Cl	H	S	82.4	55.0
17	MeO	MeO	4-Br	H	O	110	82.5
18	MeO	MeO	4-Br	Me	O	63.0	38.0
19	MeO	MeO	4-Br	H	S	52.1	33.3
20	MeO	MeO	4-Br	Me	S	105	60.4
21	-OCH_2O-		4-OH	H	O	52.3	49.6
22	MeO	MeO	3-NH_2	H	O	19.3	18.3
23	MeO	MeO	3-NH_2	Me	O	36.8	30.6
24	MeO	MeO	3-NH_2	H	S	18.8	9.10
25	-OCH_2O-		3-NH_2	H	O	18.0	12.7
26	MeO	MeO	4-NH_2	H	O	15.0	12.6
27	MeO	MeO	4-NH_2	Me	O	50.2	43.7
28	MeO	MeO	4-NH_2	H	S	6.30	3.30
29	MeO	MeO	4-NH_2	Me	S	29.8	20.3
30	-OCH_2O-		4-NH_2	H	O	15.4	10.9
31	-OCH_2O-		4-NH_2	Me	O	41.1	29.5
32	-OCH_2O-		4-NH_2	CONHMe	O	12.4	8.70
33	MeO	MeO	4-NO_2	H	S	93.4	69.8
34	MeO	MeO	4-NO_2	Me	S	103	81.5
35	MeO	MeO	4-NAc_2	Ac	O	56.8	43.9

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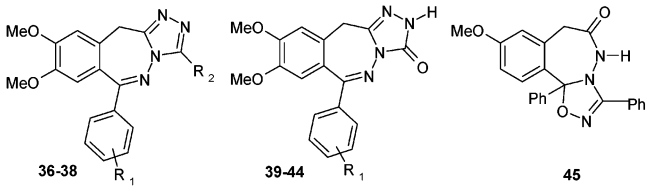
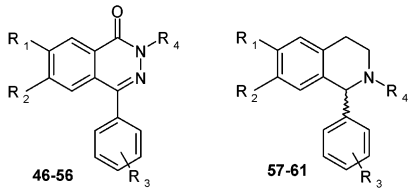
Table 2. Annelated 2,3-Benzodiazepines



			ED$_{50}$, μmol				ED$_{50}$, μmol	
	R_1	R_2	clonus	tonus		R_1	clonus	tonus
36	4-NH_2	H	57.3	48.3	**41**	3-NH_2	20.1	13.1
37	4-NH_2	Me	59.9	44.7	**42**	4-NH_2	16.1	10.2
38	4-NO_2	Me	66.7	59.3	**43**	3-NO_2	56.4	43.2
39	H	−	44.6	27.5	**44**	4-NO_2	74.1	58.3
40	4-F	−	32.1	21.8	**45**	−	119	100

Table 3. 1,2-Phthalazines and Tetrahydroisoquinolines



					ED$_{50}$, μmol	
	R_1	R_2	R_3	R_4	clonus	tonus
46	-OCH_2O-		H	H	36.7	31.3
47	MeO	MeO	3-NH_2	H	68.3	59.9
48	MeO	MeO	3-NH_2	Me	63.7	55.2
49	-OCH_2O-		3-NH_2	H	23.3	15.7
50	MeO	MeO	4-NH_2	H	60.5	52.0
51	-OCH_2O-		4-NH_2	H	21.2	7.56
52	-OCH_2O-		4-NH_2	CONHMe	23.4	16.8
53	-OCH_2O-		4-NH_2	CONHnPr	15.8	6.82
54	MeO	MeO	4-NHAc	H	62.0	48.8
55	MeO	MeO	3-NO_2	H	81.7	75.5
56	MeO	MeO	3-NO_2	Me	110	80.3
57	MeO	MeO	4-Cl	H	20.1	19.3
58	MeO	MeO	4-Br	H	30.6	12.5
59	MeO	MeO	3-NO_2	H	19.3	7.19
60	MeO	MeO	4-NO_2	H	100	56.1
61	MeO	MeO	3-NO_2	Ac	37.2	12.7

All the compounds studied were constructed starting from fragment dictionary and their geometries optimized using the UNIVERSAL force field[11] with the Smart Minimizer protocol of Open Force Field. Partial atomic charges were computed by the semiempirical MOPAC/AM1 method. QSAR analysis was performed using the QSAR+ module of Cerius-2.[12] Thirty molecular descriptors were selected from the Cerius-2 library. In particular, these independent variables belong to the following descriptors: quantum mechanical (lowest and highest occupied molecular orbital energy, dipole moment), structural (number of H-bond acceptors and donors, and rotatable bonds), thermodynamic (hydrophobic/hydrophilic balance, desolvation free energy for water and octanol), topological descriptors (Zagreb index, Wiener index and Hosoya index), and electrotopological state indices (18 E_state indices). E-state indices have been used in QSAR models to derive structural features significantly related to the dependent variable. The electrotopological state index of an atom encodes information about both the topological environment of that atom and the electronic interactions due to all other atoms in the molecule. Topological indices are 2D descriptors based on graph theory concepts. These indices (Zagreb index, Wiener index, and Hosoya index) have been widely used in QSPR and in QSAR studies.[13] They help to differentiate the molecules mostly according to their size, degree of branching, flexibility, and overall shape. These parameters aid the description of important features of the molecules such as their solubility and absorption.

Table 4. QSAR Equation. log(1/ED$_{50}$) = *a* (HOMO) + *b* (Hbond donor) + *c* (AlogP) + *d* (I_ssCH2) + *e* (I_dsN) + *f* (Zagreb) + Intercept

	coefficient	corr coefficient	standard error	stat t	P value
intercept	−5.811		0.781	−7.443	3.403×10^{-9}
(*a*) HOMO	−0.125	1.015	0.066	−1.895	0.065
(*b*) Hb donor	0.371	0.560	0.054	6.867	2.251×10^{-8}
(*c*) AlogP	−0.124	−0.331	0.072	−1.720	0.093
(*d*) I_ssCH2	0.661	0.594	0.189	3.496	0.001
(*e*) I_dsN	−0.762	−0.716	0.216	−3.529	0.001
(*f*) Zagreb	0.483	0.937	0.218	2.221	0.032

The test set containing 12 compounds was constructed including the most active derivative(**28**) and selecting the remaining 11 objects based on the results of a principal component analysis (PCA). Briefly, the full set of molecules (61 objects) and descriptors (30 variables) was analyzed by means of a PCA. The first and second resulting components were used to plot the 61 objects in a two-dimensional space (see Supporting Information).

Eleven objects were randomly selected in such a way as to cover all the space occupied by the 61 objects. The correlation between the pool of 30 descriptors and the anticonvulsant activity of the TS was quantitatively studied by means of partial least-squares (PLS) and multiple linear regression analyses (MLR), which were performed on autoscaled variables. Cross-validation protocol was used to determine the statistical significance of the equations.

Results

PLS analysis was carried out to optimize the selection of those variables highly correlated with the biological activity. Thus, several PLS runs were carried out removing at each run the descriptor with the lowest PLS loading in a conditional way. The optimal selection of descriptors was achieved when the cross-validated r^2 (q^2) did not improve. The PLS optimization yielded a final model having training and cross validation coefficients of $r^2 = 0.747$ and $q^2 = 0.700$, respectively. The model was described by two principal components and contained six independent variables: HOMO energy; number of H-bond donors; the octanol/water partition coefficient (AlogP); Zagreb index; two E_state indices (I_ssCH2 and I_dsN). The final system, consisting of 49 objects and 6 selected independent variables, was submitted to MLR analysis and used to derive a new model for predicting the anticonvulsant activity of the external test set of compounds. The choice of using MLR analysis instead of PLS to produce the final QSAR equation was dictated by the fact that MLR is quick and easy to interpret. Furthermore, in this specific case it is reliable since we have a number of objects (49) significantly larger than the number of independent variables (six) . The selected descriptors are reported in Supporting Information, along with the observed and the calculated activities expressed as log(1/ED$_{50}$). The MLR analysis yielded a final correlation equation (Table 4) where the training and cross validation coefficients were $r^2 = 0.757$ and $q^2 = 0.704$, respectively with the *F*-test = 21.837. The plot of experimental versus calculated log(1/ED$_{50}$) for the TS is shown in Figure 1. The standard error of estimation (SEE) was 0.332. For the statistics of the model and the intercorrelation matrix for the six variables employed in the final QSAR

Table 5. External Set Used to Validate the Predictivity of the Model

	Log(1/ED_{50})	predicted	residual	HOMO	Hb donor	AlogP	I_ssCH2	I_dsN	Zagreb
17	−4.700	−4.059	−0.641	−7.353	1	3.144	1	1	2
60	−4.611	−3.011	−1.600	−8.931	1	2.849	1	0	2
13	−4.497	−3.790	−0.707	−8.543	1	2.681	1	1	2
16	−4.411	−3.923	−0.488	−8.730	1	3.604	1	1	2
54	−4.127	−3.892	−0.235	−8.718	2	1.268	0	1	2
43	−4.032	−3.734	−0.298	−9.095	1	2.856	1	1	2
31	−3.716	−3.358	−0.358	−8.507	2	2.005	1	1	2
5	−3.632	−4.026	0.394	−8.976	0	2.598	1	1	2
61	−3.617	−3.274	−0.343	−8.913	0	2.514	1	0	2
10	−2.980	−3.837	0.857	−8.693	1	3.086	1	1	2
9	−3.169	−3.857	0.688	−8.780	1	3.276	1	1	2
28	−1.840	−3.212	1.372	−7.740	3	2.303	1	1	2

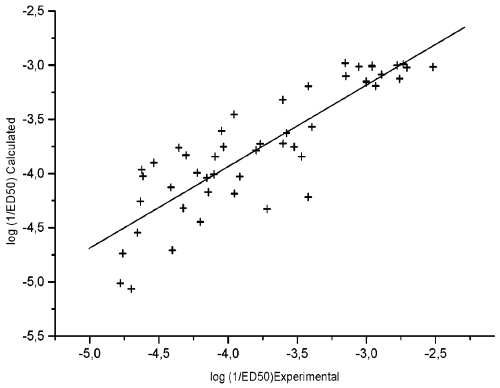


Figure 1. Plot of estimated log(1/ED_{50}) versus predicted log(1/ED_{50}).

equation, see Supporting Information. The largest pairwise correlation is between AlogP and I_ssCH2 with $r^2 = 0.306$. The selected variables can therefore be considered largely independent. As a further and stronger predictive criterion, the obtained model (Table 4) was evaluated for its ability to predict the activity of an external test set of 12 compounds (Table 5). The standard error of prediction (SEP) was 0.809. The analysis of the residuals showed that only 2 out of the 12 test compounds were not optimally predicted: **28** (residual = 1.372) and **60** (residual = −1.600). Compound **28**, the most active derivative, was assigned to the test set to valuate the performance of the model in predicting compounds with a range of activities outside the domain of activities of the TS. Although poorly predicted (residual = 1.372), our QSAR model successfully predicts **28** among the most active ones, the residual being 0.232 from the predicted most active molecule (**52**) and the residual being 0.694 from the estimated most active molecule (**32**) of the TS. Furthermore, metabolic biotransformation cannot be ruled out.[5] The overprediction for tetrahydroisoquinoline **60** could be due to a bad estimation of the effect of the 4-nitro group. Indeed, if compared to the 3-substituted analogue (**59**, log 1/ED_{50} = −3.420), **60** loses much more potency (log 1/ED_{50} = −4.611) than the analogous substitution in the 2,3-benzodiazepines (**43**, log 1/ED_{50} = −4.032; **44**, log 1/ED_{50} = −4.305). This effect cannot be ascribed to a sterically forbidden region around the 4-position of the aromatic ring because this drastic fall of potency is not observed in other 4-substituted tetrahydroisoquinolines (**57** and **58**), indicating that the origin of the poor in vivo activity of **60** might be due to other factors.

Discussion

A QSAR model has been obtained for a quite large set of noncompetitive AMPAR antagonists. The relevance of the model for the design of novel derivatives should be assessed not only in terms of predictivity, either internal or external, but also in terms of its ability to provide a chemical and structural explanation of their binding interactions. According to the regression coefficients of the model (Table 4), corrected to the magnitudes of the descriptor to which they apply, the following comments can be made about the importance of pharmacodynamic- or pharmacokinetic-related parameters in describing the anticonvulsant data.

Pharmacodynamic-Related Parameters. The descriptors connected to the pharmacodynamics of the compounds are I_ssCH2, I_dsN and HOMO. I_ssCH2 and I_dsN describe the structure of a molecule on the basis of its atoms and encode information about both the topological environment of a specific atom and the electronic interactions due to all other atoms in the molecule. Since this information may reflect the conformation and configuration properties of a molecule and its interaction with a given target, I_ssCH2 and I_dsN were assigned to the pharmacodynamic-related parameters. The HOMO is localized onto the phenyl moiety of the compounds. Its energy describes the ability of the aromatic ring to make $\pi-\pi$ or π-cation interactions, respectively, with aromatic or basic residues of a protein target. So, it is conceivable to assign the HOMO energy descriptor to the class of pharmacodynamic-related parameters. In agreement with the recently reported pharmacophoric study of noncompetitive AMPAR antagonists,[9b] the HOMO energy has the highest favorable effect on the anticonvulsant activity.

The electrotopological state indices I_ssCH2 and I_dsN encode for the presence/absence (0/1), respectively, of a carbon atom bound to two hydrogens and two single bonds, and a nitrogen atom with a single bond and a double bond. The carbon atom type described by I_ssCH2 is present in all the compounds studied with the exception of the phthalazine derivatives **47**-**48**, **50**, and **54**−**56**. In particular, since this descriptor encodes the presence/absence of methylene groups in the selected compounds, it is referred to the positive influence on the activity of both the carbon atoms in the methylenedioxy moiety and the methylene carbon atom in the diazepine ring. This might explain the higher anticonvulsant effects of 7,8-methylenedioxy-1,2-phthalazines compared to the corresponding 7,8-dimethoxy analogues and 7,8-dimethoxy-2,3-benzodiazepines in comparison with 7,8-dimethoxyphthalazines. In par-

ticular, **23** and **26** are more active than **48** and **50**, respectively. The influence of this descriptor also explains the higher activity demonstrated by **49** and **51** compared to the corresponding **47** and **50**. As can be observed in the final QSAR equation (Table 4), the occurrence of I_dsN-like atoms negatively affects the biological activity. Indeed, this atom type is not present in the tetrahydroisoquinolines (**57**−**61**), which are more potent than the corresponding halo- and nitro-substituted benzodiazepine and phthalazine derivatives.

Pharmacokinetic Descriptors. The descriptors coupled to the pharmacokinetic moment of the compounds are the Zagreb index, the number of H-bond donors, and the AlogP. Although some of these parameters can also describe hydrophobic or H-bond interactions with a target protein and be classified as pharmacodynamic-related, we arbitrarily assigned them to the class of pharmacokinetic descriptors. Indeed, both the size, degree of branching, and flexibility of a molecule (described by the Zagreb index) or the number of donating H-bonds and the octanol/water partition coefficient affect the ability of a given molecule to pass physiological barriers such as the blood−brain barrier, or its solubility and absorption into the haematic flux.

Among the pharmacokinetic descriptors, the Zagreb descriptor shows the highest value of correlation (Zagreb = 0.937). In particular, the positive influence of the Zagreb descriptor is related to the occurrence of substituents on the benzene-fused ring of the studied compounds.

We observed that the introduction of two methoxy groups or the dioxole ring optimizes the pharmacological effects, as proved by the higher activity of **4** in comparison with **2**.

The number of H-bond donating groups and the AlogP represent the effect on the activity of the degree of solubility of the molecules. In particular, the positive sign of the H-bond descriptor coupled to the negative sign of the AlogP indicates a slightly positive effect of the hydrophilicity in determining an optimal pharmacological profile for noncompetitive AMPAR antagonists. Nevertheless, if we consider that these compounds should cross the blood−brain barrier to exert their action, the slight effect on the activity of the H-bond descriptor should be explained by its influence on the pharmacodynamic rather than on the pharmacokinetic phase.

The observation that N-unsubstituted derivatives are generally more active than the *N*-methyl analogues supports this suggestion. This trend occurs in all compounds with the exception of **4** and **5** which show similar potency. However, HPLC studies carried out on rat plasma following administration of the tested compounds[14] suggested that metabolic N-dealkylation process occurs in **5**, thus explaining why this compound shares a similar activity with the N-unsubstituted analogue **4**.

Conclusion

The present study was focused on developing and validating the first predictive six-parameter QSAR model for noncompetitive AMPAR antagonists acting as anticonvulsant agents. The tools used were quantum mechanical, topological, structural, and thermodynamic descriptors and electrotopological state indices. The evaluation of the regression model confirmed that the presence of some structural moieties positively influences the anticonvulsant properties. In particular, H-bond donor functions, a methylene bridge, and two methoxy substituents on the benzene-fused ring are important for the anticonvulsant activity, whereas the occurrence of an imine nitrogen atom seems to be detrimental. These results could be particularly useful to further develop new noncompetitive AMPAR antagonists.

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Supporting Information Available: More complete data about our studies are available free of charge via Internet at http://pubs.acs.org

References

(1) Lees, G. J. Therapeutic Potential of AMPA/Kainate Receptor Ligands and their Therapeutic Potential in Neurological Disorders. *Drugs* **2000**, *59*, 33−78.
(2) Pellicciari, R.; Costantino, G. Metabotropic G-protein-coupled glutamate receptors as therapeutic targets. *Curr. Opin. Chem. Biol.* **1999**, *3*, 433−440.
(3) Chimirri, A.; Gitto, R.; Zappalà, M. AMPA Receptor Antagonists. *Exp. Opin. Ther. Pat.* **1999**, *9*, 557−570.
(4) Donevan, S. D.; Rogawski, M. GYKI 52466, a 2,3-Benzodiazepine, is a Highly Selective, Noncompetitive Antagonist of AMPA/Kainate Receptor Responses *Neuron* **1993**, *10*, 51−59.
(5) 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. 1-Aryl-3,5-dihydro-4H-2,3-benzodiazepin-4-ones: Novel AMPA Receptor Antagonists. *J. Med. Chem.* **1997**, *40*, 1258−1269. (b) Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Quartarone, S.; Zappalà, M.; Constanti, A.; Libri, V. 3,5-Dihydro-4H-2,3-benzodiazepine-4-thiones: a New Class of AMPA Receptor Antagonists. *J. Med. Chem.* **1998**, *41*, 3409−3416.
(6) Grasso, S.; De Sarro, G.; De Sarro, A.; Micale, N.; Zappalà, M. Puja, G.; Baraldi, M.; De Micheli, C. Synthesis and Anticonvulsant Activity of Novel and Potent 2,3-Benzodiazepine AMPA/Kainate Receptor Antagonists. *J. Med. Chem.* **1999**, *42*, 4414−4421.
(7) Chimirri, A.; Bevacqua, F.; Gitto, R.; Quartarone, S.; Zappalà, M.; De Sarro, A.; Maciocco, L.; Biggio, G.; De Sarro, G. Synthesis and Anticonvulsant Activity of New 11H-triazolo[4,5-*c*][2,3]-benzodiazepines. *Med. Chem. Res.* **1999**, *9*, 203-212. (b) Zappalà, M.; Gitto, R.; Bevacqua, F.; Quartarone, S.; Chimirri, A.; Rizzo, M.; De Sarro, G.; De Sarro A. Synthesis and Evaluation of Pharmacological and Pharmacokinetic Properties of 11H-Triazolo[4,5-*c*][2,3]benzodiazepin-3(2*H*)-ones *J. Med. Chem.* **2000**, *43*, 4834−4839.
(8) Gitto, R.; Chimirri, A.; Zappalà, M.; De Sarro, G. Synthesis and pharmacological evaluation of 4-aryl-6,7-dimethoxyphthalazines as anticonvulsant agents. *Med. Chem. Res*, **2000**, *10*, 1−10. (b) Grasso, S.; De Sarro, G.; De Sarro, A.; Micale, N.; Zappala, M.; Puja, G.; Baraldi, M.; De Micheli, C. Synthesis and Anticonvulsant Activity of Novel and Potent 6,7-Methylenedioxyphthalazin-1(2*H*)-ones**.** *J. Med. Chem.* **2000**, *43*, 2851−2859.
(9) Gitto, R.; Barreca, M. L.; De Sarro, G.; Quartarone, S.; Orlando, V.; De Luca, L.; Russo, E.; Chimirri, A. Discovery of a New Class of AMPA Receptor Antagonists Containing a Tetrahydroisoquinoline Skeleton. *Drugs Future* **2002**, *27 (Suppl. A)*, 252. (b) Barreca, M. L.; Gitto, R.; Quartarone, S.; De Luca, L.; De Sarro, G.; Chimirri, A.; Pharmacophore Modeling as an Efficient Tool in the Discovery of Novel Noncompetitive AMPA Receptor Antagonists. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 651−655.
(10) De Luca, L.; Macchiarulo, A.; Costantino, G.; Barreca, M. L.; Gitto, R.; Chimirri, A.; Pellicciari, R. Binding Modes of Noncompetitive AMPA Antagonists: a Computational Approach. *Il Farmaco* **2003**, *58*, 107−113.
(11) Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard W. A.; Skiff, W. M.; UFF, a Full Periodic Table Force Field for Molecular Mechanics and Molecular Dynamics Simulations. *J. Am. Chem. Soc.* 1**992**, *114*, 10024−10035
(12) Cerius-2 and Insight-II distributed by Accelrys, San Diego, CA.
(13) Katritzky, A. R., Gordeeva, E. V.; Traditional Topological Indices vs Electronic, Geometrical, and Combined Molecular Descriptors in QSAR/QSPR Research. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 835−857.
(14) Rizzo, M.; Sinopoli, V. A.; Gitto, R.; Zappala', M.; De Sarro, G.; Chimirri, A. High-Performance Liquid Chromatographic Determination of New 2,3-Benzodiazepines *J. Chromatogr. B.* **1998**, *705*, 149−153.

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