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Statistical analysis on a series of glycine antagonists

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Abstract

Quantitative structure–activity relationships of two series of glycine antagonists, pyrido[2,3-*b*]pyrazines and pyrido[2,3-*b*]pyrazine *N*-oxides, was performed using PLS (Projection on Latent Variables) and traditional physico-chemical and topological descriptors. The effect of substitution on the heteroaromatic ring was investigated with the aim of further improving the affinity (expressed as pK_i) of these derivatives towards the strychnine-insensitive glycine binding site associated with the NMDA receptor. A significant model was obtained for both series of compounds. Structure–activity implications are discussed.

Keywords: QSAR; Statistical analysis; PLS; Glycine; NMDA; Pyrido[2,3-*b*]pyrazines; Pyrido[2,3-*b*]pyrazine *N*-oxides

Over-activation of the *N*-methyl-D-aspartate (NMDA) receptor has been involved in several neurodegenerative disorders such as stroke, epilepsy and Alzheimer's disease [1]. Over stimulation of this receptor leads to a massive influx of calcium ions into post-synaptic neurones. The resulting cell swelling, together with the activation of a series of neurotoxic cascades, finally leads to cell death [2].

In 1987, Johnson and Ascher [3] discovered the stimulatory action of glycine on the NMDA receptor. Glycine acts as co-agonist of glutamate, and being a modulator has raised a huge interest as a therapeutic site of intervention with respect to other competitive and non competitive NMDA receptor antagonists.

Since then, a large number of glycine antagonists have been described in the literature [4–6]: in particular, our computational studies focused on the quinoxaline [7] derivatives reported in Fig. 1.

Quinoxaline-2,3-diones like CNQX (**1**, R6 = NO_2, R7 = CN, Fig. 1) and DNQX (**1**, R6, R7 = NO_2, Fig. 1) were firstly introduced as antagonists of the AMPA subtype of non-NMDA excitatory amino acids receptor, and have then shown comparable affinities for the glycine site. Since then considerable efforts have been made to improve the glycine versus AMPA selectivity of this class of molecules. Recently, the newly synthesised classes of pyrido[2,3-*b*]pyrazine (**2**, Fig. 1) and pyrido[2,3-*b*]pyrazine *N*-oxide (**3**, Fig. 1) were reported [8,9]. These compounds are selective glycine antagonists endowed with in vivo activity in animal models of ischemia.

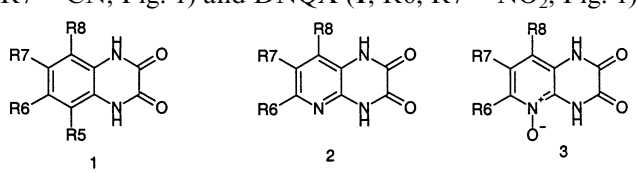

Fig. 1.

For both classes of compounds, the effect of substitution on the heteroaromatic ring was investigated with the aim of further improving the affinity (expressed as pK_i) of these derivatives towards the strychnine-insensitive glycine binding site associated with the NMDA receptor.

Data handling and parametrisation were performed with the programs TSAR 3.2 [10] and DAYLIGHT v4.51 [11]. Statistical analysis was carried out using PLS (Projections on Latent Variables) [12] as implemented in the program GOLPE [13]. Molecules used in the statistical analysis are reported in Table 1.

1. Statistical analysis on pyrido[2,3-*b*]pyrazine series (2, Fig. 1), Table 1

According to the Hansch approach, substituents in positions 6, 7 and 8 of the heteroaromatic ring (R6, R7

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Table 1
Pyrido[2,3-*b*]pyrazines (**2**, Fig. 1) and pyrido[2,3-*b*]pyrazine *N*-oxides (**3**, Fig. 1) used in the statistical analysis (C5 = *n*-pentyl, C3 = *n*-propyl)

Pyrido[2,3-*b*]pyrazines (**2**)					Pyrido[2,3-*b*]pyrazine *N*-oxides (**3**)				
	R6	R7	R8	pK_i		R6	R7	R8	pK_i
2a	Cl	H	H	5.21	**3a**	Cl	H	H	5.33
2b	Cl	Cl	H	6.73	**3b**	Cl	Cl	H	6.95
2c	H	Cl	H	5.5	**3c**	H	Cl	H	6.29
2d	H	CH_3	H	4.68	**3d**	H	H	CH_3	5.11
2e	CH_3	H	H	4.36	**3e**	H	CH_3	H	5.85
2f	Cl	Cl	C5	5.72	**3f**	CH_3	H	H	4.84
2g	Cl	Br	H	6.84	**3g**	H	Cl	C5	4.7
2h	Cl	Cl	Cl	6.96	**3h**	Cl	Br	H	6.95
2i	H	Br	CH_3	5.8	**3i**	Cl	Cl	C5	5.08
2j	C5	Cl	H	5.45	**3j**	H	Br	CH_3	6.27
2k	Cl	Br	CH_3	6.55	**3k**	C5	Cl	H	5.6
2l	H	Cl	CH_3	5.54	**3l**	Cl	Br	CH_3	5.52
2m	Cl	Cl	CH_3	6.72	**3m**	H	Cl	CH_3	6.43
2n	C3	Cl	H	5.82	**3n**	Cl	Cl	CH_3	5.5
2o	OCH_3	Cl	H	5.1	**3o**	C5	Cl	Cl	5.01
2p	C3	Cl	CH_3	5.56	**3p**	H	CF_3	H	6.37
2q	H	CF_3	H	6.3	**3q**	Cl	CF_3	H	6.29
2r	Cl	CF_3	H	6.37	**3r**	C3	Cl	H	6.34
2s	H	I	H	5.56	**3s**	H	I	H	6.13
2t	Cl	I	H	6.69	**3t**	H	CF_3	Cl	5.43
2u	H	CF_3	Cl	5.8	**3u**	Cl	I	H	6.68
2v	H	I	CH_3	5.75	**3v**	H	I	CH_3	6.04
2w	CH_3	Cl	CH_3	6.09	**3w**	CH_3	I	H	6.65
2x	CH_3	I	CH_3	5.52					
2y	CH_3	I	H	6.33					

and R8, respectively, **2**, Fig. 1) were parametrised using physico-chemical descriptors, such as Swain and Lupton's F and R [14,15], σ_{meta} and σ_{para} [15,16] (electronic effects); Verloop steric parameters L, B1 and B5 [17]; molar refractivity [18] (bulk); π [18] (lipophilicity). In addition, a series of physico–chemical and topological whole molecule descriptors was utilised: ClogP [18] (lipophilicity), CMR [18] (bulk), Kier's ChiV0-ChiV3, Chiv4 [19] (connectivity); Kier's kα1–kα3 [19] (shape); Kier's Φ (shape flexibility index) [19].

A fixing/excluding variable selection procedure [13] was applied to exclude from the calculations descriptors that have a detrimental effect on the predictive ability of the model. A two component model explaining 84% (R^2 0.84) of the activity variance was finally chosen as the best among other statistically significant equations.

The predictive power of the model is good with a R^2cv(LOO) of 0.73, and a R^2cv (three groups, 200 randomisations) of 0.67. The model obtained shows that field electron-withdrawing substituents in position 6 and 7 of the heteroaromatic ring increase pK_i. A parabolic trend of affinity with the global lipophilicity of substituents on the heteroaromatic ring can also be observed. Other contributions are assigned in the model to the bulk/shape of substituents and to topological properties related to the molecular connectivity.

2. Statistical analysis on pyrido[2,3-*b*]pyrazine *N*-oxide series (3, Fig. 1, Table 1)

The same physico-chemical and topological descriptors used for pyrido[2,3-*b*]pyrazines (see above) were also used for this series of derivatives.

As before, a fixing/excluding variable selection procedure [13] was applied. A two component model explaining 78% (R^2 0.78) of the activity variance was finally chosen as the best among other statistically significant equations.

The predictive power of the model is good with a R^2cv (LOO) of 0.67, and a R^2cv (three groups, 200 randomisations) of 0.52.

The model shows that while field electron-withdrawing, bulky substituents in R7 increase the pK_i, bulky, field electron-withdrawing substituents in R8 have a detrimental effect on the affinity. An increase in the global lipophilicity of substituents on the heteroaromatic ring also reduces the affinity. This trend corresponds to the descending arm of the parabola in the previous model.

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