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5-AMINOMETHYLQUINOXALINE-2,3-DIONES. PART II: N-ARYL DERIVATIVES AS NOVEL NMDA/GLYCINE AND AMPA ANTAGONISTS.

Yves P. Auberson*, Pierre Acklin, Hans Allgeier, Michel Biollaz, Serge Bischoff, Silvio Ofner, Siem J. Veenstra

Novartis Pharma AG, Klybeckstrasse 141, 4002 Basel, Switzerland.

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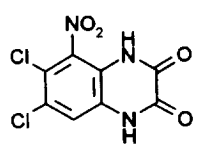
Abstract: Potent antagonists at the glycine-binding site of NMDA receptors, as well as dual antagonists acting also at AMPA receptors have been identified in a series of 5-arylaminomethylquinoxaline-2,3-diones. A study of the structure-activity relationship of these compounds is reported here.

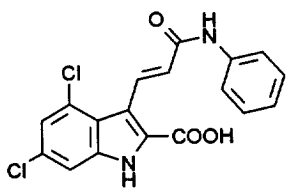
L-glutamate is the main excitatory neurotransmitter in the brain, acting both at ionotropic and at metabotropic receptors. The overexcitation of several of these receptors has been shown to be involved in the neurodegeneration occuring after cerebral ischemia[1a], and to play a role in triggering seizures associated with epilepsy[1b]. Compounds preventing this excessive stimulation are expected to be of therapeutic interest. Quinoxaline-2,3-diones are well-known antagonists at the glycine-binding site of NMDA receptors[2], and as such show considerable potential as neuroprotective agents after stroke[3], traumatic brain injury, or for the treatment of epilepsy[4]. Most of the *in vitro* potent antagonists described in the literature[2,5] are poorly water-soluble and, except for the quinoxaline-2,3-dione ACEA 1021[6] and possibly GV150526[7], not active in preclinical models of stroke. As a result, very few glycine antagonists have proceeded into clinical development[8].

During a study of quinoxaline-2,3-diones[9], **1a** was found to be active *in vivo* as a mixed antagonist at AMPA receptors and at the glycine-binding site of NMDA receptors. The structure-activity relationship of further 5-aminomethylquinoxaline-2,3-diones will be described in this article (series **1-3**, R = aryl or cyclohexyl).

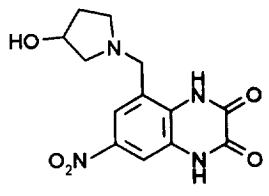
Figure 1:



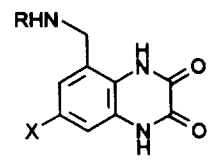
ACEA-1021
[^{3}H]DCKA: 10 nM



GV150526
[^{3}H]DCKA: 7 nM



1a
[^{3}H]DCKA: 280 nM
[^{3}H]AMPA: 330 nM



1b-u X = NO_2
2a-c X = Br
3a,b X = Cl

* Fax: (41) 61 696 8676, e-mail: yves.auberson@pharma.novartis.com

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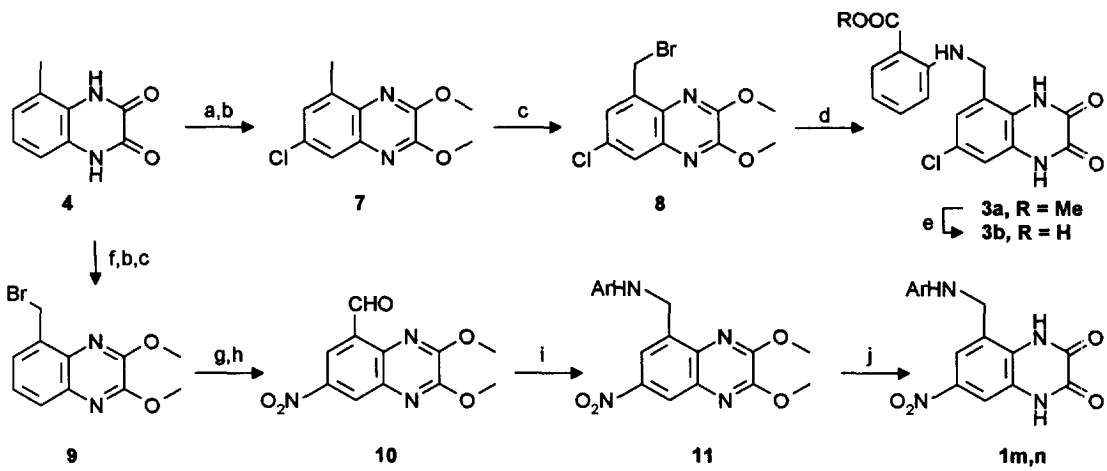
Chemistry

5-Methylquinoxaline-2,3-dione **4**[10] was chlorinated on the aromatic ring and protected as its dimethoxy derivative **7** by treatment with PCl_5 and sodium methanolate. Benzylic bromination with NBS, followed by alkylation of methyl anthranilate and hydrolysis gave the desired compounds (**3a,b**) with good yields. Further derivatives were obtained in a similar manner from the 7-bromo and 7-nitro analogues of **8**[9]. Carboxylic acids were prepared as their methyl or ethyl ester, which were hydrolyzed by treatment with refluxing 4N HCl. When the ester was desired, the quinoxaline-2,3-dione moiety was selectively deprotected with HBr in acetic acid.

Aldehyde **10** was obtained by bromination of **4**, oxidation to the aldehyde and nitration. **10** was then coupled to 2- and 3-aminopyridine by reductive amination, and the desired products (**1m,n**) obtained after deprotection under acidic conditions.

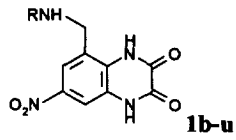


Reagents and conditions: a) PCl_5, neat, 160°C, 2h, 60%; b) MeOH, MeONa, reflux, 18h, 98%; c) NBS, AIBN, CCl_4, reflux, 24h, 80-87%; d) i: methyl anthranilate, $(i\text{-Pr})_2NEt$, MeCN, reflux, 38%; ii: HBr/AcOH, 16h, 80°C, 99%; e) MeOH, 2N aq. NaOH, 80°C, 31%; f) $POCl_3$, reflux, 18h, 96% g) 2-nitropropane, EtONa, 81% h) HNO_3, H_2SO_4, CF_3COOH, $(CF_3CO)_2O$, 0°C, 75%; i) aminopyridine, $NaBH_3CN$, MeOH, 30-37%; j) HBr in AcOH, 50°C, 18h, 73-91%.

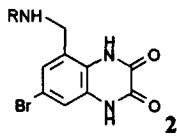
Results and discussion

The parent N-aryl derivative **1b** showed moderate affinity for the glycine-binding site of NMDA receptors, and was unselective with regard to binding at AMPA receptors. Introduction of a fluorine atom on the aromatic ring had little influence on these affinities (**1c-e**). In contrast, functionalization by a carboxylate group in the ortho position of the phenyl ring had a pronounced effect: **1f** displayed dramatically greater affinities for both binding sites. The meta and para derivatives **1g** and **1h** were much weaker. Reduction of the aromatic ring to a cyclohexyl group strongly decreased potency of the ortho (**1i**) but not meta derivatives (**1k**). Derivatization of the carboxylic acid to an amide (**1j**) or to an ester (**1l**) had no beneficial effect.

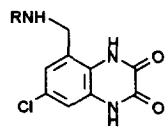
Table 1: *In vitro* potencies[11] of 5-arylaminomethylquinoxaline-2,3-diones and related structures



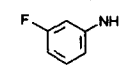
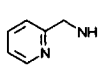
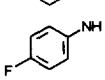
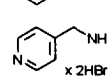
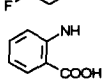
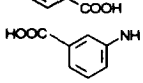
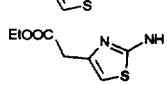
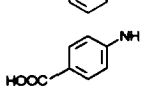
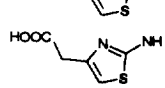
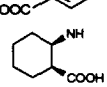
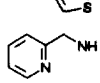
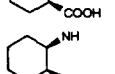
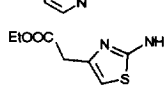
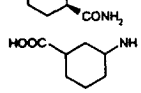
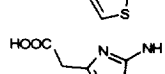
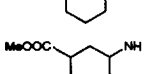
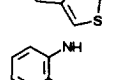
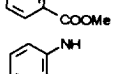
1b-u



2a-c



3a,b

	RNH	NMDA[a] (glycine)[b]	AMPA[a]		RNH	NMDA[a] (glycine)[b]	AMPA[a]
1b[c]		1.4	1.5	1o[c]		12%	0.38 ± 0.1
1c[c]		0.50 ± 0.17	1.4	1p[c]		59%	0.22 ± 0.14
1d[c]		0.72 ± 0.08	1.4	1q[c]		40%	3.1
1e[c]		0.75 ± 0.24	1.2	1r		36%	1.4
1f		0.05 ± 0.02	0.05 ± 0.01	1s[c]		41%	0.19 ± 0.03
1g[c]		0%	0.9 ± 0.06	1t[c]		0.41 ± 0.3	1.8
1h[d]		10%	1.6	1u[d]		0.12 ± 0.02	0.18 ± 0.09
1i[c]		25%	0.67 ± 0.09	2a		40%	12
1j[c]		25%	0.65 ± 0.06	2b[c]		0.34 ± 0.09	17%
1k[d]		21%	0.78 ± 0.22	2c		0.12 ± 0.03	1.45
1l		30%	1.3	3a		25%	0%
1m[c]		0%	0.50 ± 0.21	3b		0.03 ± 0.001	2
1n[c]		12%	0.97 ± 0.05				

a: IC_{50} ± SEM in μM or % inhibition at 1 μM; average of at least two triplicate experiments; b) [^{3}H]-(Z)-2-carboxy-4,6-dichloroindole-3-(2'-phenyl-2'-carboxy)-ene (MDL-105519) or [^{3}H]-DCKA binding assay; c) HBr salt; d) HCl salt.

Additional structural variations were obtained by replacement of the phenyl group with heteroaromatic rings. The 2- and 3-aminopyridine (**1m,n**), 2-aminopyrimidine (**1o**) and 2-aminopyrazine (**1p**) derivatives bound to AMPA receptors, but had little or no affinity for the glycine site of NMDA receptors. Compounds possessing a methylene linker between the aromatic ring and the nitrogen atom, as exemplified by **1q** and **1r**, were weaker.

In a separate series, the phenyl ring was replaced by a thiazole: **1s** was more potent at AMPA receptors. A satisfactory affinity at the glycine-binding site of NMDA receptors was achieved by addition of an acetic acid side-chain (**1u**). The selectivity for the glycine-binding site could be further improved by replacing the 7-nitro substituent on the quinoxaline-2,3-dione nucleus with a bromine atom (**2c**), although affinity did not increase. The highest potency was observed with the 7-chloro derivative **3b**, which displayed a strong affinity for the glycine binding site of NMDA receptors, while thirty-fold weaker at AMPA receptors. Interestingly, the corresponding ester (**3a**) was inactive in both assays.

In conclusion, the study of the 5-arylaminomethylquinoxaline-2,3-diones reported here reveals the potential of these molecules to bind selectively to the glycine-binding site of NMDA receptors or to AMPA receptors. The best affinities were obtained with anthranilic acid as a side-chain (e.g. **1f**), and selectivity for the glycine-binding site of NMDA receptors achieved when the 7-nitro group was replaced by a chlorine atom (**3b**).

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References and notes:

1. a) Choi, D.W.; Rothman, S.M. *Annual Rev. Neurol.* **1990** *13* 171; b) Bradford, H.F. *Progress in Neurobiology* **1995** *47* 477.
2. a) Keana, J.F.W.; Kher, S.M.; Cai, S.X.; Dinsmore, C.M.; Glenn, A.G.; Guastella, J.; Huang, J.-C.; Ilyin, V.; Lü, Y.; Mouser, P.L; Woodward, R.M.; Weber, E. *J. Med. Chem.* **1995** *38* 4367; b) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. *J. Med. Chem.* **1994** *37* 3956; c) Epperson, J.R.; Hewawasam, P.; Meanwell, N.A.; Boissard, C.G.; Gribkoff, V.K.; Post-Munson, D. *Bioorg. and Med. Chem. Lett.* **1993** *3* 2801.
3. Leeson, P.D.; Iversen, L.L. *J. Med. Chem.* **1994** *37* 4053.
4. McCulloch, J.; Bullock, R.; Teasdale, G.M. In *Excitatory Amino Acid Antagonists*; Meldrum, B., Ed.; Blackwell Scientific Publications: Oxford **1991** 287.
5. a) Mignani, S., Aloup, J.-C., Barreau, M.; Birraux, G.; Blanchard, J.-C.; Böhme, A.; Boireau, A.; Damour, D.; Doble, A.; Jimonet, P.; Malgouris, C.; Mary, V.; Randle, J.C.R.; Rataud, J.; Stutzman, J.-M. *Drugs of the Future* **1995** *20* 1133. b) Kulagowski, J.J.; Baker, R.; Curtis, N.R.; Leeson, P.D.; Mawer, I.M.; Moseley, A.M.; Ridgill, M.P.; Rowley, M.; Stansfield, I.; Foster, A.C.; Grimwood, S.; Hill, R.G.; Kemp, J.A.; Marshall, G.R.; Syawell, K.L.; Trickelbank, M.D. *J. Med. Chem.* **1994** *37* 1402, and ref. cited therein.
6. a) Woodward, R.M.; Huettner, J.E.; Guastella, J.; Keana, J.F.W.; Weber, E. *Mol. Pharmacol.* **1995** *47* 568. b) Warner, D.S.; Martin, H.; Ludwig , P.; McAllister, A.; Keana, J.F.W.; Weber, E. *J. Cereb. Blood Flow Metab.* **1995** *15* 188.
7. Di Fabio, R.; Capelli, A.; Conti, N.; Cugola, A.; Donati, D.; Feriani, A.; Gastaldi, P.; Gaviraghi, G.; Hewkin, C.T.; Micheli, F.; Missio, A.; Mugnaini, M.; Pecunioso, A.; Quaglia, A.M.; Ratti, E.; Rossi, L.; Tedesco, G.; Trist, D.G.; Reggiani, A. *J. Med. Chem.* **1997** *40* 841.
8. Kulagowski, J.J.; Leeson, P.D. *Exp. Opin. Ther. Patents* **1995** *5* 1061.
9. Auberson, Y.P.; Bischoff, S.; Moretti, R.; Schmutz, M.; Veenstra, S.J. *Bioorg. and Med. Chem. Letters*, preceeding article.
10. a) St. Clair, R.L.; Thibault, T.D. *US Patent # 3992378* **1976** (CA 86:89890m).
11. a) Honoré, T.; Lauridsen, J.; Krogsgaard-Larsen, P. *J. Neurochem.* **1982** *38* 173; b) Baron, B.M., Siegel, B.W., Harrison, B.L., Gross, R.S., Hawes, C. and Towers, P. *J. Pharmacol. Exp. Ther.* **1996** *279* 62-68.