Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 65–70

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

5-AMINOMETHYLQUINOXALINE-2,3-DIONES. PART I: A NOVEL CLASS OF AMPA RECEPTOR ANTAGONISTS.

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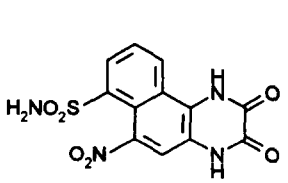
Received 18 August 1997; accepted 17 November 1997

Abstract: A series of 5-aminomethylquinoxaline-2,3-diones have been identified as potent and selective AMPA antagonists. Some of these compounds are also active at the glycine-binding site of the NMDA receptors. A number of these novel, water-soluble quinoxaline-2,3-dione derivatives display protective effects in the electroshock-induced convulsion model in mice.

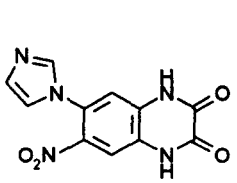
The neurodegeneration and cell death following cerebral ischemia have been linked to an excessive glutamate release, which initiates excitotoxic damage via overactivation of several ionotropic receptors[1]. This process is mediated by NMDA, AMPA and kainate-preferring glutamate receptors, and blocking their activation is expected to have a neuroprotective effect. AMPA antagonists are of particular interest, as they have been shown to be neuroprotective in animal models of focal[2] and global[3] cerebral ischemia, without the side-effects associated with NMDA receptors blockade. They can also prevent the excessive neuronal activation by glutamate receptors responsible for epileptic seizures[4].

The quinoxaline-2,3-diones represent a well-known class of AMPA receptors antagonists[5]. Except for the recently disclosed MPQX[5e], other published compounds (Fig. 1) suffer from a limited *in vivo* activity, due to a low bioavailability or a short duration of action.

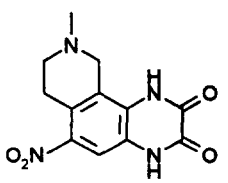
Figure 1: Most prominent AMPA antagonists of the quinoxaline-2,3-dione type.



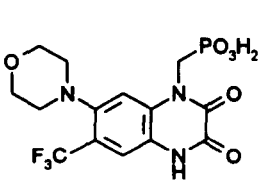
NBQX
[^{3}H]AMPA: 150 nM



YM90K
[^{3}H]AMPA: 220 nM



PNQX
[^{3}H]AMPA: 42 nM[5b]



MPQX
[^{3}H]AMPA: 105 nM

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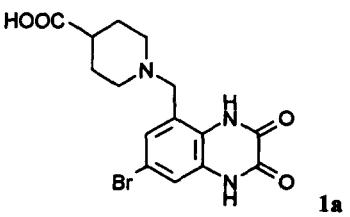
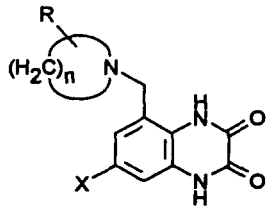
0960-894X/98/$19.00
PII: S0960-894X(97)10186-X

Screening of the in-house chemical collection allowed the identification of **1a**, a moderate, albeit selective AMPA antagonist with a good water solubility. As it has previously been shown that 7-nitro-, rather than 7-bromo-quinoxaline-2,3-diones are potent AMPA antagonists[5b,c], several analogs of **1a** with this substitution were synthesized. The structure-activity relationship of the resulting 5-aminomethylquinoxaline-2,3-diones bearing a cyclic amine (**2**) will be described in this article.

Figure 2



1a

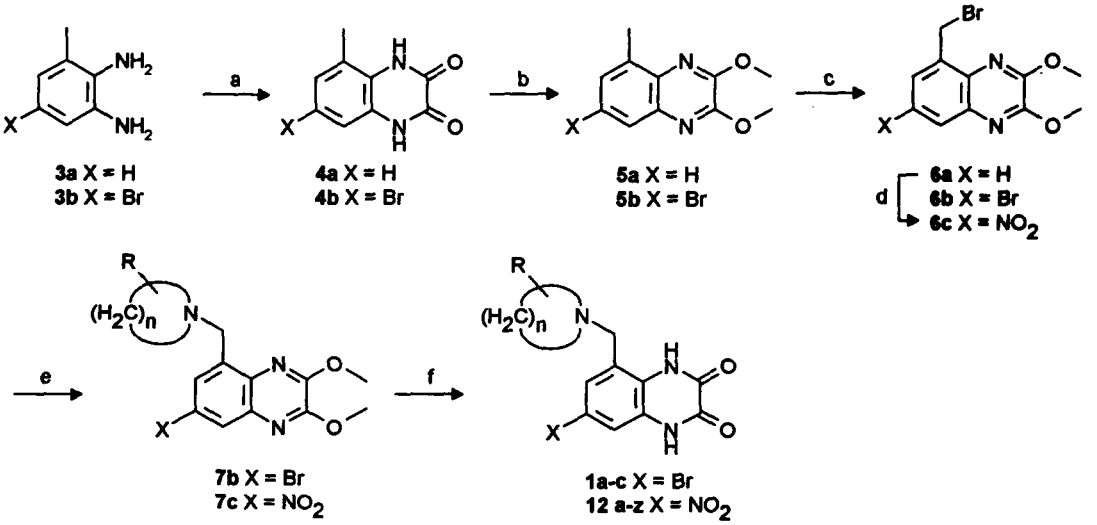


2, X = Br, NO_2

Chemistry

5-Methylquinoxaline-2,3-dione **4a**[6] was prepared from **3a** and oxalic acid, then protected as its dimethoxy derivative **5a** by treatment with $POCl_3$ followed by methanolysis. Benzylic bromination with NBS and nitration gave a mixture of 7- and 8-nitro isomers, from which **6c** was crystallized with a 38% yield. The 7-bromo derivative **6b** was obtained from **3a** via a similar procedure. Alkylation of cyclic secondary amines with **6b** or **6c**, followed by acid hydrolysis, gave the desired compounds with good yields (scheme 1).

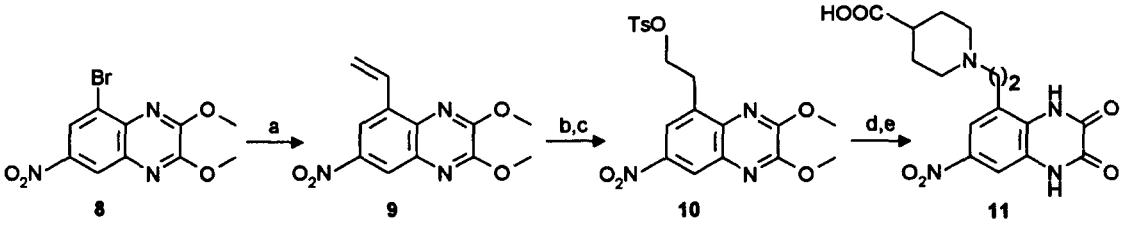
Scheme 1



Reagents and conditions: a) $(COOH)_2$, 2N HCl, reflux, 18h, 98% b) i: $POCl_3$, reflux, 18h. ii: MeOH, MeONa, reflux, 18h, 94%; c) NBS, AIBN, CCl_4, reflux, 24h, 80%; d) H_2SO_4, CF_3COOH, KNO_3, 38%; e) cyclic amine, $(i\text{-Pr})_2NEt$, MeCN, reflux, 82-98%, except 2-methyl-aziridine or azetidine, CH_2Cl_2, aq. 40% Bu_4NOH, 92% or 99%; f) 24% HBr/AcOH, 50°C, 4h or 2N HCl, reflux, 4-18h, 52-99%.

Tosylate **10** was obtained via the palladium-catalyzed coupling of **8** with vinylbutylstannene, followed by hydroboration with 9-BBN, oxidative work-up and tosylation. **10** reacted with ethyl piperidine-4-carboxylate to yield **11** after deprotection with refluxing 2N HCl.

Scheme 2:



a) $Bu_3SnCHCH_2$, $Pd(PPh_3)_4$, toluene, 110°C, 75%; b) 9-BBN, then H_2O_2, aq. Na_2CO_3, 59%; c) TsCl, pyridine, 30%; d) ethyl piperidine-4-carboxylate, 110°C, no solvent; e) 2N HCl, reflux, 8h, 14% from **10**.

Results and discussion

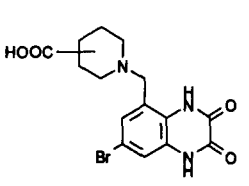
We first studied the influence of the carboxylic acid group in our lead compound (**1a**) through its displacement on the piperidine ring. The resulting structures (**1b,c**) have weaker affinities for AMPA receptors. The 7-bromo substituent was subsequently replaced by a nitro group to yield **12a**, which displayed the most potent *in vitro* activity within this series. Converting this compound to an ester (**12b**) or an amide (**12c**) diminished its affinity. Interestingly, the corresponding 7-bromo-8-nitro derivative **13**[7] is inactive.

Removal of the carboxylic acid group of **12a** affected its binding potency only to a limited extent (**12d**). Other substituents in this position did not improve the affinity for AMPA receptors (**12e-i**), although replacement of the carboxylate by a phenyl group (**12e**) showed that there are minimal steric constraints in this position. Piperidine derivatives with small groups on positions 4 (**12g-i**) or 3 (**12j-l**) maintained an almost constant affinity, regardless of the nature of the substituent.

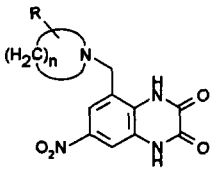
Through systematic variations of the ring size from 3 to 7 members (**12d, m-p**), it was shown that the best binding affinities could be obtained with the pyrrolidine and piperidine derivatives. The introduction of a double bond in these cycles had little influence (**12q-r**), whereas opening the piperidine ring decreased the potency slightly (**12s**). The insertion of a second heteroatom within the saturated ring decreased the affinity (**12t-v**), especially for piperazine. Pyrrolidine derivatives did not display better affinities for AMPA receptors (**12w-z**). Of interest is that the 3-hydroxy-pyrrolidine derivative **12z** binds strongly to the glycine-binding site of NMDA receptors, in contrast to the parent pyrrolidine **12o**.

Homologation of the linker between the piperidine ring and the quinoxaline-2,3-dione nucleus of **12a** decreased the affinity for AMPA receptors to 1.6 μM (compound **11**).

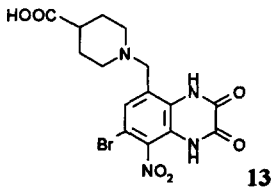
Table 1: Structures and *in vitro*[8] affinities of the cyclic 5-aminomethylquinoxaline-2,3-diones



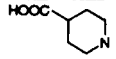
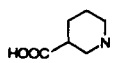
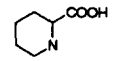
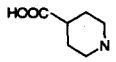
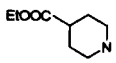
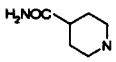
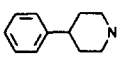
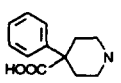
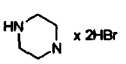
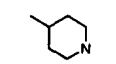
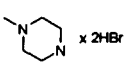
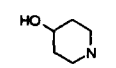
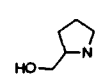
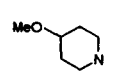
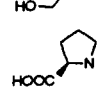
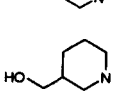
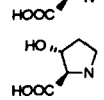
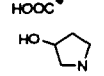
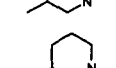
1a-c



12a-z



13

		AMPA[a]	NMDA (glycine)[a,b]			AMPA[a]	NMDA (glycine)[a,b]
1a		0.89 ± 0.12	0%	**12m**[c]		2.2	40%
1b		2.5	24%	**12n**[c]		1.5	3.8
1c		18%	0.84 ± 0.11	**12o**[c]		0.28 ± 0.13	0%
12a[c]		0.07 ± 0.02	3.9	**12p**[c]		0.58 ± 0.15	0%
12b[c]		0.35 ± 0.04	0.59 ± 0.01	**12q**[c]		0.49 ± 0.13	36%
12c[c]		0.76 ± 0.5	4%	**12r**[c]		0.36 ±0.12	40%
12d[c]		0.29 ± 0.09	41%	**12s**[c]		0.84 ±0.25	0%
12e[c]		0.43 ± 0.1	0.33 ± 0.06	**12t**[c]		0.66 ±0.09	32%
12f[d]		2.0	34%	**12u**		11	21%
12g[c]		0.37 ± 0.13	31%	**12v**		3.4	8%
12h[d]		0.31 ± 0.09	18%	**12w**[d]		0.70 ±0.11	24%
12i[d]		0.43 ± 0.29	45%	**12x**[c]		0.46 ±0.16	2
12j[d]		0.52 ± 0.15	14%	**12y**[d]		2.1	1.5
12k[c]		0.60 ± 0.19	3	**12z**[c]		0.33 ±0.02	0.28 ± 0.19
12l[c]		0.43 ± 0.14	4%	**13**[c]	-	15%	14%

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 ([^{3}H]MDL-105519) or [^{3}H]-DCKA binding assay c: HBr salt; d: HCl salt

The compounds with the best binding affinities were tested in the electroshock- and metrazole-induced convulsion assays in mice[9] (Table 2). Activities remained modest, with ataxia being the most frequently observed side-effect at doses close to the ED_{50}. Interestingly, **12g** also proved active after oral administration (1h pretreatment, ED_{50} = 54 mg/kg).

Table 2: compounds active in the anticonvulsion tests with an ED_{50} below 50 mg/kg:

	ED_{50} (mg/kg) or % protection at 50 mg/kg after 30' (i.p. administration)	
	electroshock	**metrazole**
12a[a]	44	n.t.
12g[a]	33	16
12o[a]	40%	26
12q[a]	60%	35
12z[a]	34	n.t.

a: HBr salt; n.t.: not tested

In summary, the optimization of our lead compound **1a** led to the identification of the nitro derivative **12a**, a potent, selective AMPA antagonist with a good water solubility (1.68 g/L at pH = 7.4). Broad variations of the piperidine ring could not improve the binding affinity any further. Although potencies were moderate, several of these compounds were shown to be active in the electroshock- or metrazole-induced convulsion models in mice. Further 5-aminomethylquinoxaline-2,3-diones containing an acidic function have been synthesized, and will be the subject of a separate publication.

Acknowledgment

The authors would like to thank P. Felber, M. Roggwiller and P. Schmid, whose technical assistance was essential for progress of this work. Thanks also to P. Martin and N. Reymann for running the radioligand binding assays, and to C. Portet for the anticonvulsion tests.

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e) Turski, L.; Huth, A.; Sheardown, M.J.; Jacobsen, P.; Ottow, E. *26th Annual Meeting of the Society for Neuroscience*, Washington D.C., November 16-21, 1996, poster 604.6.

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7. **13** was obtained by nitration of **6b** (H_2SO_4, CF_3COOH, KNO_3, 86%), followed by alkylation with ethyl 4-pipecolate and hydrolysis as exemplified in scheme 1 for e.g. **1a**.

8. a) [^{3}H]AMPA binding assay: Honoré, T.; Lauridsen, J.; Krogsgaard-Larsen, P. *J. Neurochem.* **1982** *38* 173.

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