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Methaqualone Derivatives are Potent Noncompetitive AMPA Receptor Antagonists

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Abstract—Quinazolin-4-one derivatives of methaqualone substituted at C-2 define a new class of noncompetitive antagonists at AMPA receptors.

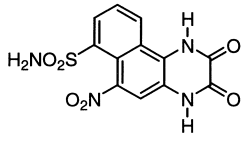
Introduction

The 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionate (AMPA) receptor mediates fast glutamatergic synaptic transmission in the central nervous system. Overactivation of AMPA receptors may play a role in epileptogenesis and glutamate-induced neuronal death.[1] Thus there is considerable interest in discovery of AMPA receptor antagonists and several classes of compounds have been identified.[2] These include compounds that competitively displace glutamate binding, represented by structures **1**–**3**. Issues relating to solubility and brain penetration have been a hindrance to the rapid development of these compounds. Noncompetitive inhibitors such as **4** have also been identified but have only modest potency.

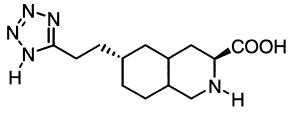
In the course of our search for new compounds which inhibit AMPA receptor function, we discovered that the known anticonvulsant compound **5**,[3] effectively blocks AMPA receptor mediated responses in primary neuron cultures in a manner not competitive with glutamate-site agonists.[4] Herein we describe our initial structure activity studies which focus largely on modifications to the pyridine ring of **5**.

Chemistry

The synthetic route is outlined in Scheme 1. Briefly, the acetamides **7** of anthranilic or 5-fluoroanthranilic acid were condensed with 2-chloroaniline in the presence of



1
NBQX



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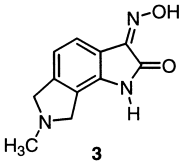
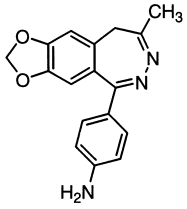
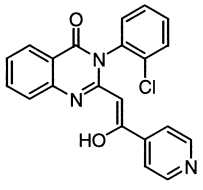
LY 293558



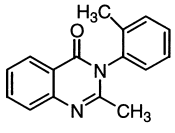
3
NS-257



4
GYKI 52466



5



6
Methaqualone

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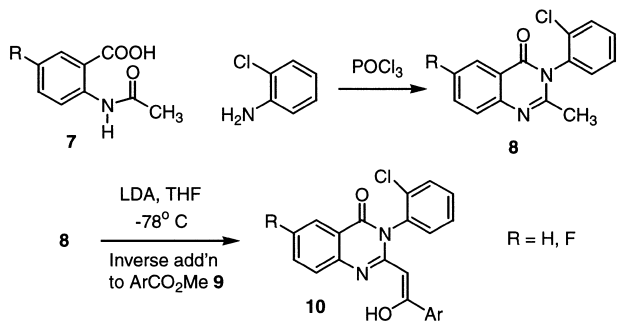

Scheme. 1. Synthesis of quinazolin-4-ones.

$POCl_3$ to generate the quinazolin-4-one templates **8**.[5] Deprotonation of **8** with LDA or NaH as previously described and quenching with various esters **9** produced vanishingly small amounts of the desired products **10**.[6] After some experimentation, we found it necessary to generate the wine red anions at −78 °C and add them to solutions containing two equivalents of the ester. The best yields were obtained when the cannula anion transfer was performed rapidly (less than 1 min). A sharp one proton singlet in the NMR spectrum generally in the 5.5–6.0 ppm range provided convincing evidence that the products exist exclusively in the enol tautomeric form—presumably due to the combination of extended conjugation and the internal hydrogen bond between N-1 and the enolic hydroxyl group.

Results and Discussion

Antagonist potency at AMPA receptors was determined against a functional AMPA receptor mediated response, kainate-induced $^{45}Ca^{+2}$ uptake in rat cerebellar granule neurons in primary culture.[4] Results are summarized in Table 1. The initial lead structure **5** containing the pyrid-4-yl ring was a modestly potent AMPA receptor antagonist ($IC_{50} = 0.37\,\mu M$) as measured in the functional assay. Nonetheless, the potency of **5** is significantly greater than the prototype competitive AMPA antagonist NBQX (**1**, $IC_{50} = 2.4\,\mu M$) and the prototype noncompetitive compound GYKI 52466 (**4**, $IC_{50} = 22\,\mu M$). The potency of NBQX is considerably lower than its reported displacement binding affinity ($K_i = 0.060\,\mu M$) since in this functional assay, NBQX must compete with a high concentration of agonist for access to the binding site.[7]

Quinazolin-4-ones such as **5** are structurally related to methaqualone (**6**).[8] However methaqualone and related structures such as **8** containing only the C-2 methyl group did not block AMPA receptor function at 10 μM. This indicates that the C-2 enol side chain is essential for inhibitory activity.

Movement of the pyridine ring nitrogen of **5** from the 4 to the 2 position (**10a**) results in a small loss of potency. However, introduction of a fluorine atom at C-6 (**10b**) increases the potency to 0.25 μM. Replacement of the pyridine ring with substituted phenyl rings gives mixed results. In the case of the 2-fluorophenyl analogue **10c**, all activity is lost. In contrast the 2-cyanophenyl compound **10d** is more potent than any of the previously tested pyridine analogues (0.13 μM). A convincing explanation for the lost activity of **10c** is currently lacking but might relate to the difference in Hammett sigma values ($\sigma_p = 0.06$ and 0.66 for F and CN, respectively).[9] It is also possible that the fluorine atom in **10c** may have an electrostatic interaction with the enol hydroxyl group which could disrupt the hydrogen bond previously suggested to occur with N-1.[6] Such an F–OH interaction could result in a loss of planarity necessitated by the enol-N-1 hydrogen bond and the concomitant loss of antagonist potency (Fig. 1).

The potency boost afforded by the cyano group in **10d** was magnified 10-fold by returning to the pyrid-2-yl ring system. Thus **10e** blocked AMPA receptor function with an IC_{50} of 0.014 μM. A simple methyl substituent at C-6 on the pyridine ring (**10f**) reduced activity to 5.5 μM. However, the combination of the cyano and methyl substituents (**10g**) afforded the most potent AMPA receptor antagonist from the series ($IC_{50} = 0.0093\,\mu M$).

A growing body of literature supports the potential therapeutic utility for compounds which attenuate AMPA receptor function.[10] However, there are relatively few known structural classes of such compounds and many of these suffer from either poor solubility and/or only modest potency. The quinazolin-4-one compounds described here represent a new class of non-competitive

Table. 1. AMPA antagonist activity of reference and quinazolin-4-one compounds

Entry	R	Ar	Blockade of $^{45}Ca^{+2}$ influx (IC_{50}, μM ± SEM)[a]
NBQX (**1**)	—	—	2.4±0.7
GYKI 52466 (**4**)	—	—	22±3
5	H	Pyrid-4-yl	0.37±0.4
Methaqualone (**6**)	—	—	>10
8	H	—	>10
10a	H	Pyrid-2-yl	0.49±0.05
10b	F	Pyrid-2-yl	0.25±0.02
10c	F	2-Fluorophenyl	>30
10d	F	2-Cyanophenyl	0.13±0.01
10e	F	3-Cyanopyrid-2-yl	0.014±0.002
10f	F	6-Methylpyrid-2-yl	5.5
10g	F	3-Cyano-6-methylpyrid-2-yl	0.0093±0.002

[a]Average of at least two triplicate experiments.

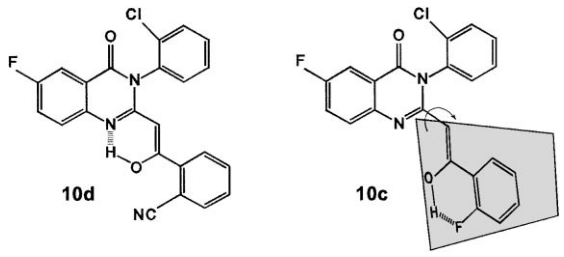

Figure 1. Disruption of H-bonding pattern and geometry change to rationalize biological activity.

AMPA receptor antagonists. As such, they offer the medicinal chemist a new entry point from which to explore the function of this important CNS receptor.

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