Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2173–2176

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS OF HETEROCYCLIC ENOL ETHERS AND THEIR USE AS GROUP 2 METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

Sabine Kolczewski,* Geo Adam, Heinz Stadler, Vincent Mutel,

Jürgen Wichmann and Thomas Woltering

Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., CH-4070 Basel

Received 12 May 1999; accepted 17 June 1999

Abstract

Heterocyclic enol ethers of type **1** were studied with respect to the inhibition of 1S,3R-ACPD (10μM)-stimulated GTP γ^{35}S binding on rat mGluR2 transfected cell membranes. The structure activity relationship with regard to the substitution pattern of the phenyl ring, the oxygen substituent and the nature of the heterocycle is discussed.

Introduction

L-Glutamate is the major excitatory amino acid neurotransmitter in the central nervous system and binds to and activates several classes of receptors which are divided into two groups termed ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors.[1] G-protein coupled metabotropic glutamate receptors comprise a family of at least eight subtypes, grouped according to pharmacology and second messanger coupling.[2] The primary transduction mechanism of group I receptors (mGluR1 and mGluR5) is the stimulation of phosphoinositide (PI) hydrolysis, whereas group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) receptors evoke an inhibition of forskolin-stimulated cyclic AMP accumulation.[3] Here we report on the synthesis and structure-activity relationship of heterocyclic enol ethers of type **1** which were discovered by random screening for group II selective mGluR antagonists.

Chemistry

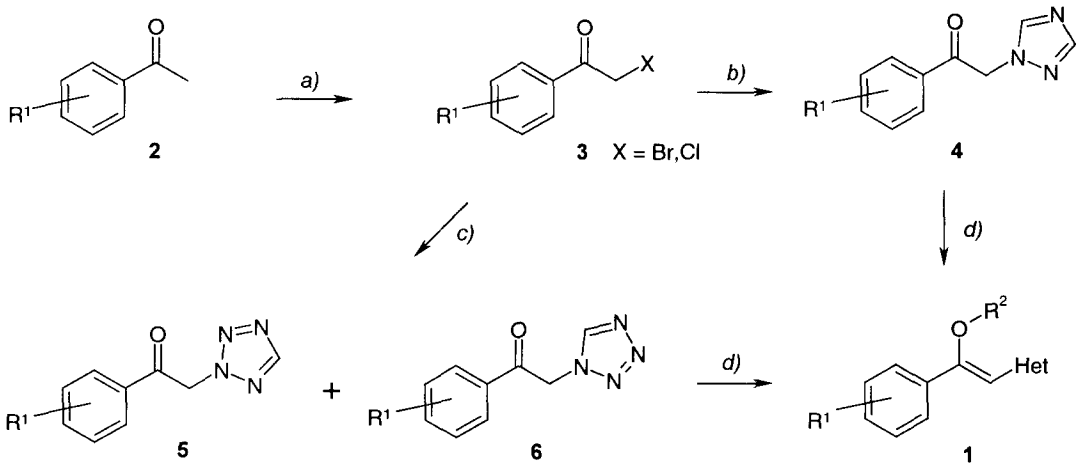
Enol ethers of the general structure **1** were synthesized starting from commercially available α-bromo or α-chloro ketones **3**. In cases where these starting materials were not available, α-bromoketones were synthesized by bromination of acetophenones **2** with bromine in acetic acid. Selective formation of 1-substituted 1,2,4-triazoles **4** was achieved using the 2-step procedure reported by Keay.[4] Reaction of α-bromo or α-chloro ketones **3** with tetrazole in DMF gave a 1:1 mixture of 2-alkylated (**5**) and 1-alkylated (**6**) products which could be easily separated by column chromatography. Because enol ether formation via thermolysis of the

*Fax:+41-61-688 87 14 E-mail: sabine.kolczewski@roche.com

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00346-7

corresponding ketals was reported to give mixtures of *E* and *Z* products[5] we investigated various alkylation procedures for the β-keto azoles **4-6**. Exclusive *Z*-enol ether formation was achieved by deprotonation with sodium hydride in a 1:3 mixture of DMPU and THF and subsequent quenching with excess alkyltriflate.[6] When alkylbromides or alkylchlorides were used in the alkylation step undesired *C*-alkylated by-products were obtained which were difficult to separate.

Scheme 1. Synthesis of Heterocyclic Enol Ethers



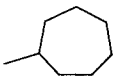
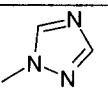
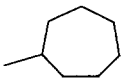
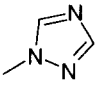
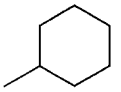
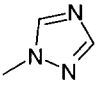
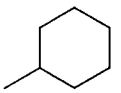
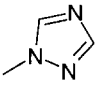
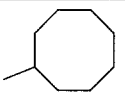
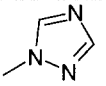
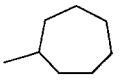
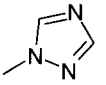
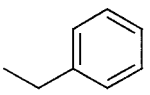
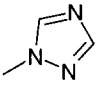
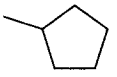
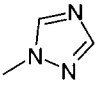
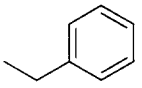
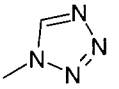
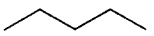
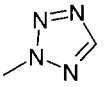
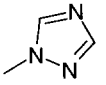
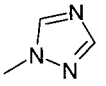
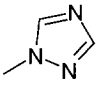
a) Br_2, HOAc, X = Br *b)* 1. 4-Amino-1,2,4-triazole, Isopropanol, 2. $NaNO_2$, HCl
c) Tetrazole, DMF *d)* 1. NaH, THF, DMPU, 2. R^2OTf

Pharmacology

The activities of the compounds at rat mGluR2 receptors were assessed using the GTP $\gamma^{35}S$ binding model. The IC_{50} values for the inhibition of 1S,3R-ACPD (10μM)-stimulated GTP $\gamma^{35}S$ binding on transfected cell membranes from CHO cells permanently expressing rat mGlu2 receptors were determined as described[7] (table 1). The given IC_{50} values are the mean values obtained from three experiments performed in quadruplicate.

The most active compounds have at least one chlorine atom in the ortho-position of the phenyl ring. This led us to the initial hypothesis that a sterically demanding ortho substituent is needed to maximize the distortion angle between the planes of the phenyl ring and the double bond, thus leading to increased potency. However electronic parameters also seem to be important. Electron-deficient aryl groups lacking the sterically demanding ortho substituent, as in **1f** and **1j**, are still favored whereas electron-rich aryl groups (**1m**) lead to inactive compounds.

Table 1. IC_{50} values for the inhibition of 1S,3R-ACPD (10μM)-stimulated GTP $\gamma^{35}S$ binding on rat mGluR2 transfected cell membranes

Compound	R^1	R^2	Het	IC_{50} [μM] GTP$\gamma^{35}S$
1a	2,6-diCl			0.11
1b	2,4-diCl			0.47
1c	2,6-diCl			0.58
1d	2,4-diCl			1.05
1e	2,4-diCl			1.21
1f	4-CF_3			1.38
1g	2,6-diCl			2.00
1h	2,4-diCl			2.55
1i	2,4-diCl			2.68
1j	4-Cl			3.16
1k	2,4-diCl			11.5
1l	2,4-diF			75
1m	2,4-diOCH_3			>100

Variation of the oxygen substituent showed that maximum binding could be achieved with a cycloalkyl group, wherein cycloheptyl was optimum. The only heterocycles tolerated in this position were 1-substituted 1,2,4-triazole and 1- or 2-substituted tetrazole. Others, like 4-substituted 1,2,4-triazole, 1,2,3-triazole or imidazole (not shown), were inactive in this model.

The best compound (**1a**) was characterized in additional assays for selectivity. When tested as described[8] this compound was inactive up to 100 μM in inhibition of binding of [^{3}H]-Ro 48-8587, [^{3}H]-kainate and [^{3}H]-MK 801 to AMPA, kainate and NMDA receptors in rat brain membranes. It was also devoid of agonistic or antagonistic activity on rat mGluR4 using the GTP γ^{35}S binding model and rat mGluR1 and mGluR5 using intracellular Ca^{2+} measurement up to 100 μM. Interestingly this compound was able to inhibit concentration-dependently [^{3}H]-DCG IV binding on rat mGluR2[7] with an IC_{50} of 500 nM. According to these results, compound **1a** appeared to be a highly selective and potent mGluR2 antagonist.

Acknowledgment

We wish to thank R. Mossiere, P. Oberli and M. Vogler for their skillfull technical assistance.

References and Notes

1. Collingridge, G.L.; Lester, R.A.; *Pharmacol. Rev.* **1989**, *40*, 143-210.
2. Conn, P.J.; Pin, J.-P.; *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205-237.
3. Pin, J.-P.; Duvoisin, R., *Neuropharmacology* **1995**, *34*, 1-26.
4. Astleford, B.A.; Goe, G.L.; Keay, J.G.; Scriven, E.F.V.; *J. Org. Chem.* **1989**, *54*, 731-732.
5. Sturm, E.; *Eur. Pat. Appl.*, EP 79856, A1 830525.
6. Gompper, R.; Vogt, H.-H.; Chem. Ber. **1981**, *114*, 2866-2883.
7. Cartmell, J.; Adam, G.; Chaboz, S.; Henningsen, R.; Kemp, J. A.; Klingelschmidt, A.; Metzler, V.; Monsma, F.; Schaffhauser, H.; Wichmann, J.; Mutel, V.; *Br. J. Pharmacol.*, **1998**, *123*, 497-504.
8. Mutel, V.; Klingelschmidt, A.; Messer, J.; Bleuel, Z.; Clifford, M.M.; Ellis, G.J.; Richards, J.G.; *J. Neurochem.*, 1998, *71*, 418-426.