Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ritter reaction-mediated syntheses of 2-oxaadamantan-5-amine, a novel amantadine analog

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ARTICLE INFO

Article history:
Received 24 December 2014
Revised 21 January 2015
Accepted 26 January 2015
Available online xxxx

Keywords:
Adamantane
Amantadine
NMDA receptor antagonist
M2 channel
Ritter reaction

ABSTRACT

Two alternative syntheses of 2-oxaadamantan-5-amine, a novel analog of the clinically approved drug amantadine, are reported. The compound has been tested as an anti-influenza A virus agent and as an NMDA receptor antagonist. While the compound was not antivirally active, it displayed moderate activity as an NMDA receptor antagonist.

Introduction

The highly symmetrical structure of adamantane is a very common building block in organic chemistry. Among the several applications of adamantane derivatives, two are of the highest interest. First, the adamantane scaffold is used as a sterically demanding group in the synthesis of ligands for transition metal catalysts. Currently there are several adamantane-derived phosphines, such as Me-DalPhos®, Mor-DalPhos®, AdBrettPhos®, cataCXium® A, that are commercially available (Fig. 1).[1] Of note, the use of heteroadamantanes in catalysis has been less studied. The nitroxyl radical AZADO, a highly active catalyst for alcohol oxidation with superior catalytic proficiency to the well-known TEMPO, is a remarkable exception (Fig. 1).[2]

On the other hand, adamantane is of great interest in medicinal chemistry. The first clinically approved adamantane derivative, amantadine, was already introduced in the clinic in 1966.[3] Since then, thousands of adamantane derivatives have been pharmacologically evaluated and, so far, seven of them have been approved for clinical use (Fig. 2). Many more are in development as potential therapeutics against a plethora of targets.[4]

Although there are thousands of adamantyl derivatives that have been tested for biological activity, the number of heteroadamantanes that have been used in medicinal chemistry is only very small. Indeed, several oxaadamantanes, and azaadamantanes have been synthesized and pharmacologically tested, but no derivative has reached clinical trials so far. Some examples from either academic laboratories or the pharmaceutical industry are presented in Figure 3.[5]

Some time ago, we reported the synthesis and pharmacological evaluation of several 2-oxaadamantan-1-amines as analogs of amantadine (Fig. 4). Taking into account that amantadine shows NMDA receptor antagonist and anti-influenza A virus activities, we evaluated the 2-oxaanalogs for these two activities. We found that although all the compounds were devoid of antiviral activity, several of them displayed NMDA receptor antagonism, with some having lower IC_{50} values than amantadine.[6]

In order to further explore the biological interest of heteroadamantanes, in this Letter we report the synthesis of a novel scaffold, 2-oxaadamantan-5-amine, **11**, of potential interest in medicinal chemistry. We have found that **11** is devoid of any inhibitory activity against the M2 channel of influenza A virus, but displays activity as an NMDA receptor antagonist, albeit being less active than amantadine.

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http://dx.doi.org/10.1016/j.tetlet.2015.01.160
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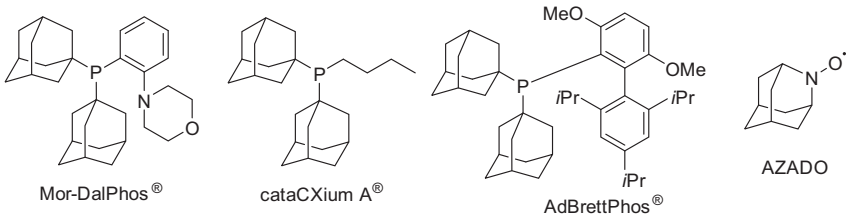

Figure 1. Structures of selected adamantyl- and heteroadamantyl-based compounds of interest in catalysis.

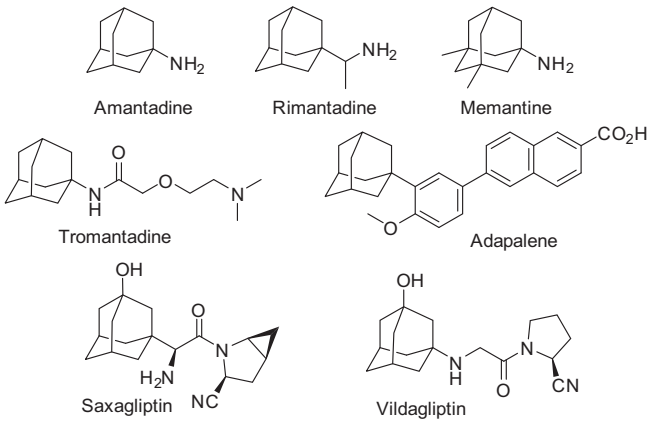

Figure 2. Structures of adamantyl-based compounds in clinical use.

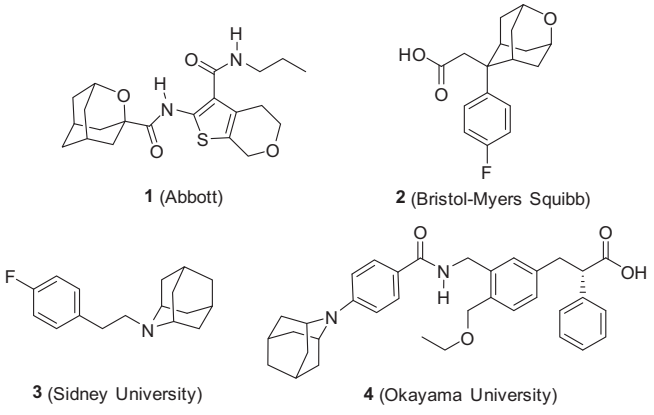

Figure 3. Selected heteroadamantyl-based compounds. **1** is a cannabinoid receptor 2 agonist; **2** an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1); **3** a low nanomolar inhibitor of σ receptors; and **4** a nanomolar agonist of the human peroxisome proliferator activated receptor-γ.[5]

Results and discussion

In order to synthesize the novel amantadine analog **11**, we envisaged chloroacetamide **9** as a key intermediate. In turn **9**, may be accessible from two already known 2-oxaadamantane derivatives, namely **8** and **12**.[7,8] When we applied the Jirgensons' modification of the classical Ritter reaction to **8**,[9] we recovered most of the starting material, along with an unseparable mixture of the expected chloroacetamide **9** and the corresponding bromoacetamide, **10**, as evidenced by GC/MS analysis. As it is known that alcohols behave better in the Ritter reaction, we attempted to obtain **11** from the known alcohol **12**.[8] To our satisfaction, reaction of **12** with chloroacetonitrile in acidic medium proceeded uneventfully to furnish **9** in high yield. Finally, cleavage of the

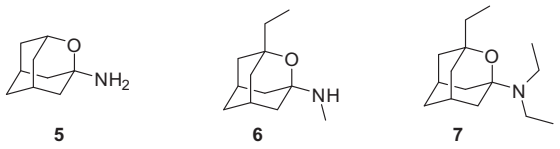

Figure 4. Selected 2-oxaadamantylamines previously reported by our group. NMDA receptor antagonist activities (IC_{50}) are: >200 μM for **5**; 32 ± 9 μM for **6**, 14 ± 3 μM for **7**, and 92 ± 29 μM for amantadine.

haloacetamide group by using thiourea, either from pure **9** or from a mixture of **9** and **10**, furnished 2-oxaadamantane-5-amine, **11**, in good yield. Amine **11** was fully characterized as its corresponding hydrochloride (Scheme 1).

Amine **11** was tested for antiviral activity. However, it did not display activity against the influenza viruses A/H1N1, A/H3N2 or B. Also, it was found to be inactive against the enveloped DNA viruses herpes simplex virus (type 1 or type 2) or vaccinia virus; the enveloped RNA viruses HIV-1, HIV-2, feline coronavirus, parainfluenza-3 virus, respiratory syncytial virus, vesicular stomatitis virus, sindbis virus or Punta Toro virus; or the non-enveloped RNA viruses Coxsackievirus B4 and Reovirus-1. Of interest, **11** did not show cytotoxicity (CC_{50} >100 μM) in the human MT4 lymphoblast cells; human embryonic lung (HEL) fibroblast cells; HeLa cervix carcinoma cells; or African green monkey Vero cells.

Previously, we had found that although **5** did not show any anti-influenza virus activity,[6] it was able to inhibit the wild-type (wt) M2 channel of influenza A virus, the target for the antiviral action of amantadine.[10] In order to assess if **11** was an inhibitor of the M2 protein, its inhibitory activity was tested on A/M2 channels expressed in *Xenopus* oocytes using the two-electrode voltage clamp (TEV) technique. At 100 μM, amantadine was able to inhibit 91% of the activity of the wt A/M2 channel (IC_{50} = 16.0 ± 1.2 μM) and oxaamantadine **5** showed similar activity (IC_{50} = 29.2 ± 1.2 - μM). On the other hand, the novel oxaamantadine **11**, at 100 μM, produced only 18.9% inhibition of the activity of the wt M2 channel, and similar values were obtained when the compound was evaluated against the amantadine-resistant V27A (8.8% inhibition) and S31N (21.4% inhibition) M2 mutant channels.

Overall, taking into account the aforementioned pharmacological results, it seems that the introduction of the oxygen atom in the adamantane scaffold is much more deleterious for the anti-influenza A virus activity in **11** than in **5**.

Finally, we measured the effect of **11** on the increase in intracellular calcium evoked by NMDA (at a concentration of 100 μM and in the presence of 10 μM of glycine) on cultured rat cerebellar granule neurons. Although we indeed found some antagonistic activity, amine **11** was 2.5 fold less potent (IC_{50} = 258 ± 93 μM, n = 3) than amantadine (IC_{50} = 92 ± 29 μM, n = 3).[11]

Conclusions

In conclusion, we have synthesized a novel heteroanalog of amantadine. Although **11** does not behave as a bioisostere of