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Synthesis of novel azanorbornylpurine derivatives

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ABSTRACT

Azanorbornylpurine derivatives were prepared by Mitsunobu reaction of appropriate hydroxyazanorbornane derivative with 6-chloropurine or construction of purine base at azanorbornylamines. The prepared target compounds were evaluated for antiviral activity and effect on neuronal and muscle nicotinic acetylcholine receptors.

1. Introduction

Human enteroviruses (HEV) belong to the Enterovirus (EV) genus of the family of the Picornaviridae. They are single stranded, positive sense non-envelop RNA virus with more than 80 serotypes. The genus can be subdivided into HEV-A, HEV-B, HEV-C, HEV-D. Coxsackieviruses B are representative members of the genus.[1] Although mild and self-limiting diseases are the major clinical features of CVB infection, CVB is a common etiological agent of myocarditis and aseptic meningitis.[2,3] Moreover, epidemiological data strongly suggest that enteroviruses, such as Coxsackievirus B4, are associated with type 1 diabetes.[4] Fatalities are often associated with neonatal myocarditis or hepatitis.[5,6] There are no drugs available for the treatment of infections with enteroviruses.[7] Such drugs are urgently needed for the treatment HEV infections.

Recently, we reported on the syntheses of novel potential Coxsackievirus inhibitors based on 6-chlorpurines substituted at position 9 with variously modified bicyclic scaffolds.[8] The impact of various substitutions of the purine moiety on the antiviral activity was also studied.[9] The most active compounds of these series were analogues **1** (EC_{50} 0.81±0.20 μM, CC_{50}>50 μM) and **2** (0.66±0.35 μM, CC_{50}>50 μM) (Fig. 1).[8a]

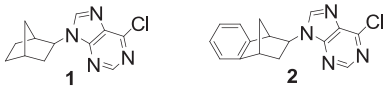

Fig. 1. Structure of compounds **1** and **2**.

This current study concerns the synthesis and antiviral evaluation of novel racemic purine analogues substituted at position 9 with 2-azanorbornane, 7-azanorbornane, and 7-azabenzonorbornane. These compounds exhibit a certain structural analogy to a very potent non-opioid analgesic—epibatidine (**3**, Fig. 2).

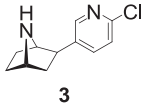

Fig. 2. Structure of epibatidine.

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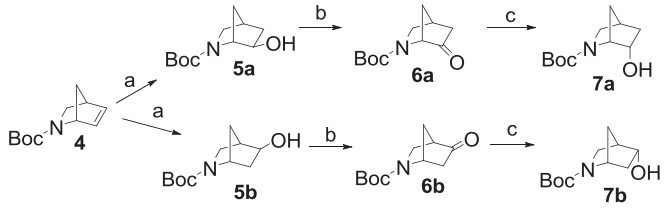
Epibatidine was isolated from the skin of the Ecuadorian frog *Epipedobates tricolor*,[10] and shortly afterward it was shown that its analgesic potency is about 200-fold higher than that of morphine. Epibatidine is a highly potent nicotinic acetylcholine receptor agonist.[11] Therefore, evaluation of this biological phenomenon of the target compounds is also subject of the paper.

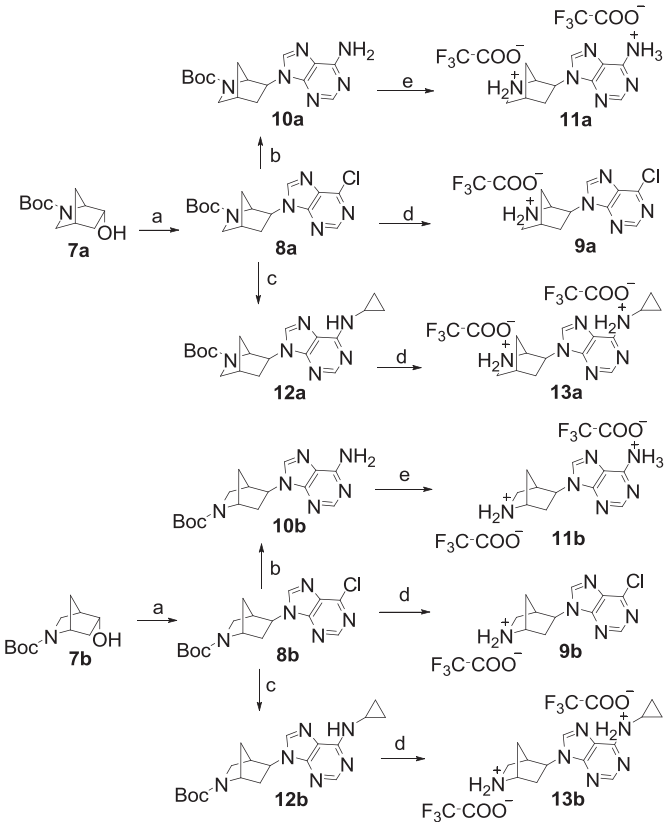
2. Results and discussion

Synthesis of the 2-azanorbornane derivatives started from protected 2-azanorbornene **4**[12] (Scheme 1). Hydroboration of **4** afforded a mixture of hydroxy derivatives **5a** and **5b** in moderate yields (18.5% and 24%, respectively). These alcohols were converted to ketones **6a** and **6b** with pyridinium dichromate in 49% and 92% yield, respectively. The key intermediates, alcohols **7a** and **7b**, were prepared by reduction of ketones **6a** and **6b** with sodium borohydride.



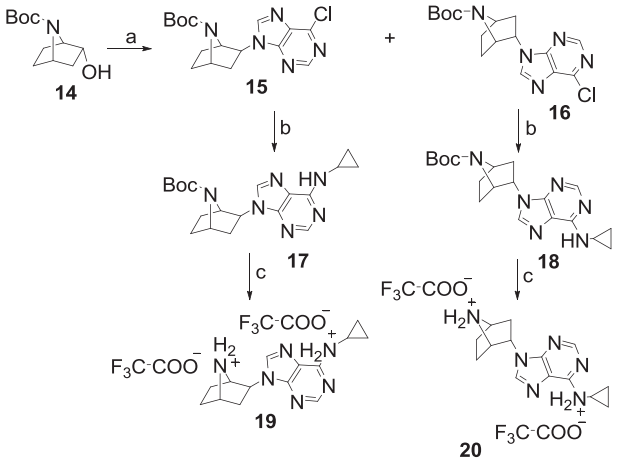
Scheme 1. Reagents and conditions: (a) 1. BH_3/THF, THF, 0 °C, 3 h, 2. $NaBO_3$, H_2O/THF, rt, overnight, 18.5% of **5a**, 24% of **5b**; (b) PDC, molecular sieves, CH_2Cl_2, rt, 96 h, 49% of **6a**, 92% of **6b**; (c) $NaBH_4$, CH_3OH, 0 °C, 40 min, 85% of **7a**, 98% of **7b**.

The Mitsunobu reaction[13] of **7a** and **7b** with 6-chloro-9*H*-purine afforded 6-chloropurine derivatives **8a** (72%) and **8b** (38%), respectively (Scheme 2). Ammonolysis of **8a** and **8b** with liquid ammonia at 75 °C gave adenine derivatives **10a** (91%) and **10b** (93%), respectively. Reaction of **8a** and **8b** with cyclopropylamine led to cyclopropylamine derivatives **12a** (89%) and **12b** (87%), respectively. Trifluoroacetic acid salts **9a**, **9b**, **11a**, **11b**, **13a**, and **13b** were obtained by treatment of *tert*-butylcarbonyl derivatives **8a**, **8b**, **10a**, **10b**, **12a**, and **12b**, respectively, with trifluoroacetic acid.



Scheme 2. Reagents and conditions: (a) 6-chloropurine, PPh_3, DIAD, THF, rt to reflux, 72% of **8a**, 38% of **8b**; (b) liquid NH_3, 70 °C, 48 h, 91% of **10a**, 93% of **10b**; (c) cyclopropylamine, rt, overnight, 89% of **12a**, 87% of **12b**; (d) TFA, CH_2Cl_2, rt, 3 h, 71% of **9a**, 77% of **9b**, 86% of **13a**, 86% of **13b**; (e) TFA, rt, 3 h, 88% of **11a**, 73% of **11b**.

Similarly, we tried to prepare of the 7-aza analogues by Mitsunobu reaction from alcohol **14**[14,15](Scheme 3). Unfortunately, this reaction led to an inseparable mixture of *exo* and *endo*-isomers **15** and **16**, probably due to the steric effect of the *tert*-butoxycarbonyl group. The mixture was treated with cyclopropylamine giving a mixture of cyclopropylamino derivatives **17** (21%) and **18** (23%), which were easily separated by chromatography on silica gel.



Scheme 3. Reagents and conditions: (a) 6-chloropurine, PPh_3, DIAD, THF, rt to reflux, 52.5% of the mixture **15** and **16**; (b) cyclopropylamine, rt, overnight, 21% of **17**, 23% of **18**; (c) TFA, CH_2Cl_2, rt, 3 h, 74% of **19**, 82% of **20**.

Since the Mitsunobu reaction of alcohol **14** led to a mixture of isomers, it was necessary to find a new route leading unambiguously to the target analogues with the *exo*-oriented purine base. We chose the mercuryazidation[16] of protected 7-azanorbornene **21**[17] for the introduction of the *exo*-amino function. Sodium borohydride reduction of the adduct of 7-azanorbornene **21** and mercuric azide gave azide **22** (85%), which was converted to amine **23** by hydrogenation using $Pd(OH)_2$ on activated charcoal as catalyst. The 6-chloropurine base was then constructed by a coupling of the amine **23** with 4,6-dichloropyrimidine-5-amine,[18] and the subsequent ring closure of the obtained pyrimidine derivative **24a** with diethoxymethyl acetate[19] (Scheme 4). This reagent was used in place of the commonly used triethyl orthoformate and mineral acid to avoid deprotection and side reactions. Ammonolysis of chloropurine analogue **15** furnished adenine derivative **25** (86%). Treatment of the *tert*-butylcarbonyl derivatives **15**, **17**, **18**, **24a**, and **25** with trifluoroacetic acid afforded salts of free bases **26**, **19**, **20**, **24b**, and **27**, respectively.

We recently found[8a] that compound **2**, with an annelated benzene ring, exhibits more pronounced antiviral activity then the norbornane analogue **1**, we decided to synthesize 7-azanorbornane analogues with an annelated benzene ring. The synthesis started from the easily accessible benzo derivative **28**[20] as shown in Scheme 5.

Hydroboration of **28** gave hydroxy derivative **29** (78.5%). Treatment of this compound with pyridinium dichromate furnished lactam **30**. This unexpected reaction could be explained by oxidation of the compound **29** in the bridgehead position, which proceeds simultaneously with oxidation of the hydroxy group. Nevertheless, Swern oxidation[21] of **29** gave ketone **31** (90%), which was treated with sodium borohydride affording *endo*-hydroxy derivative **32** (91%). Mitsunobu reaction of **32** with 6-chlorpurine led only to *exo*-isomer **33**, but in the very low yield (13%).