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Synthesis of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde: application to the synthesis of potent adenosine A_{2A} and A_3 receptor agonist

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ABSTRACT

Synthesis of potent adenosine A_{2A} and A_3 receptor agonist from the modification of adenosine-5′-*N*-ethylcarboxamide (NECA) has been reported. Diastereoisomer possessing an (*R*)-3,4-dihydro-2*H*-pyranyl (DHP) moiety exhibited the highest affinity at the A_{2A} and A_3 receptors. The key steps involve the synthesis of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde (**7**), which was obtained through the enzyme-catalyzed kinetic resolution of (±)-2-acetoxymethyl-3,4-dihydro-2*H*-pyran (**5**).

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The metabolite adenosine plays a critical role in the regulation of cell function in many tissues. It mediates its actions via four subtypes of G protein-coupled receptors named A_1, A_{2A}, A_{2B}, and A_3.[1] Based on adenosine's profound actions on the heart, kidney, brain, and the immune system, numerous potential therapeutic options have been discussed for adenosine receptor agonists and antagonists with selectivity for the known receptor subtypes.[2]

It has been demonstrated that a lipophilic linker in the N^6 position is necessary to gain high affinity for the A_3 receptor, and a polar linker possessing an additional lipophilic group in the C-2 position is necessary to gain high affinity for the A_{2A} receptor.[2] Thus, the major efforts in the discovery of new adenosine A_{2A} and A_3 agonists have been made with the introduction of appropriate substituents at the C-2 or N^6 position in combination with the modification of the 5′ position of the nucleoside scaffold via various linkers.[2,3]

The stimulation of both A_{2A} and A_3 receptor subtypes has been shown to mediate antiinflammatory actions,[4] generating interest in such compounds. Our interest in the synthesis of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde [(*R*)-acrolein dimer] arose from the investigation of one of our potent adenosine A_{2A} and A_3 receptor agonists **2**, which possesses a (*R*)-3,4-dihydro-2*H*-pyran (DHP) moiety.[5] During our structure–activity relationships study of 2-hydrazone-NECA derivatives, we discovered that compound **2** exhibits an interesting pharmacological profile. In a radioligand binding assay, it showed high affinity at both the A_{2A} and A_3 receptors. Compound **2** was initially prepared from racemic aldehyde **7** and 2-hydrazino-NECA **1** (Scheme 1). Due to the interesting properties of **2**, diastereomeric separation of isomers **3** and **4** from **2** was then performed via preparative HPLC using reverse phase C-8 or C-18 columns. After the resolution of diastereomers, we found that the molecule possessing the (*R*)-DHP ring (**3**) is more potent than the (*S*)-DHP analogue (**4**). The R-isomer (**3**) was also the more selective of the two diastereomers (Table 1).

In order to make compound **3**, we required the acrolein dimer (*R*)-**7** on a large scale. However, the lack of a literature method for the synthesis of enantiomers of acrolein dimer led us to investigate a convenient synthetic route for acrolein dimer (*R*)-**7**. The racemic aldehyde has been synthesized from acrolein under high pressure[6] or microwave-assisted[7] dimerization (Fig. 1). There is no report on the enantioselective synthesis of acrolein dimer.

Pederson et al.[8] have reported the parallel kinetic resolution of (±)-acrolein dimer by reacting with chiral phosphonates using asymmetric Horner–Wadsworth–Emmons reaction. Although resolution of the corresponding diastereoisomeric adducts with chiral auxiliaries has been completed, their conversion to pure enatiomers of (*R*) and (*S*)-aldehydes remains to be achieved. Herein, we report the convenient synthesis of (*R*)-**7** and its application in the synthesis of potent adenosine agonist **3** (Schemes 1 and 2).

There are several syntheses[9] and synthetic applications[10,11] of the precursor 3,4-dihydro-2*H*-pyran-2-methanol (**6**) reported in the literature. We decided to follow the method reported by Kang et al.[12] and Ley et al.[11a] for the source of (*R*)-**5** and (*R*)-**6** (Scheme 2), which describes the enzymatic hydrolysis of (±)-**5**. Kang et al.[12] performed enzymatic hydrolysis of (±)-**5** using porcine pancreatic lipase (PPL), 0.01 M phosphate buffer, and acetone that provided (*S*)-alcohol **3** in >99% ee. However, the process reported by Kang et al.[12] produced our desired product (*R*)-**5** only in 48% ee Ley et al.[11a] modified the above method[12] but it requires an additional enzymatic hydrolysis and two purification steps.

In an attempt to simplify the above reported methods,[11a,12] we performed the enzyme-catalyzed kinetic resolution on (±)-**5** by extending reaction time to 4 days as well as repeating the addition

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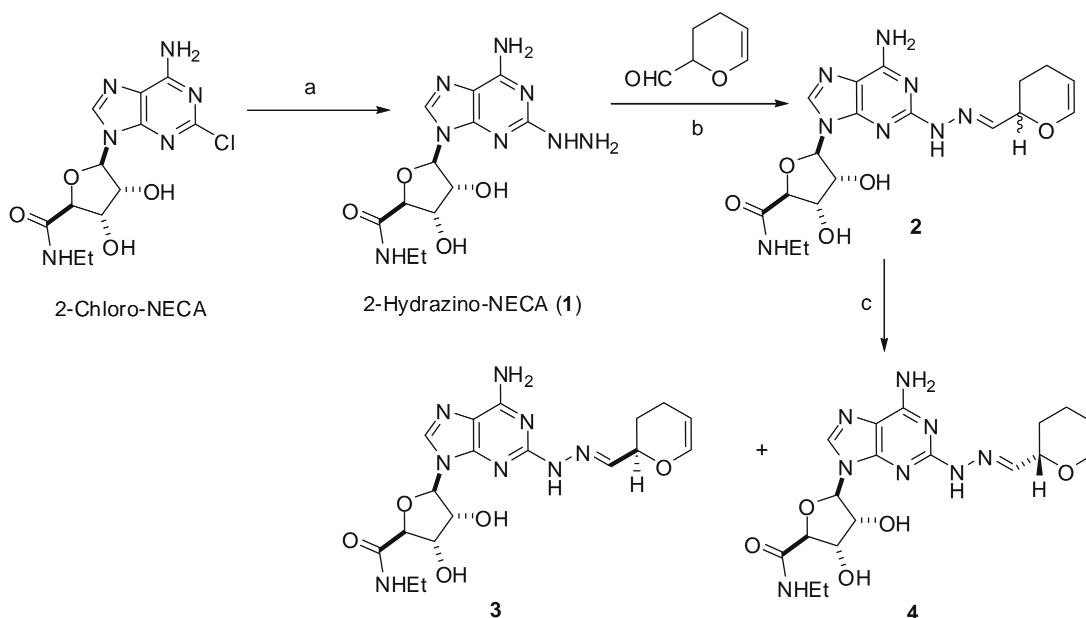


Scheme 1. (a) Hydrazine hydrate, neat, rt, 7 h, 99%; (b) MeOH, 50 °C, 78%; (c) HPLC purification on C-8 or C-18 column.

of PPL after the first 24 hours.[13] These modifications pleasingly lead us to (*R*)-acetate **5** in >99% ee in one step instead of (*S*)-alcohol-enriched product as reported by Kang et al.[12] The (*R*)-acetate was then hydrolyzed to the corresponding (*R*)-alcohol **5** in the presence of 0.3 equiv of 1.0 N potassium hydroxide.[14]

In order to make compound (±)-**7**, oxidation of commercially available racemic alcohol **6** was first carried out using various reagents. These results are summarized in Table 2. Our initial attempt of a Swern oxidation reaction[15] of (±)-**6** produced (±)-**7** in poor yield. Several other oxidation reactions were attempted, which did not result in any trace of the desired product (±)-**7**: (1) Tetrapropylammonium perruthenate (TPAP), 4-methylmorpholine N-oxide (NMO), CH_2Cl_2; (2) MnO_2, acetone; (3) Pyridini-

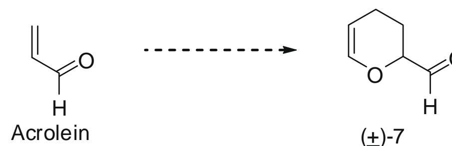
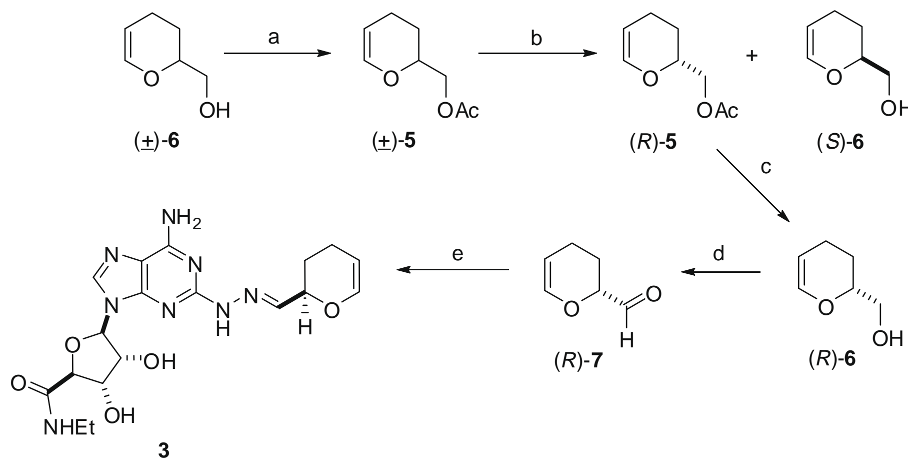


Figure 1.

Table 1
Affinities of the adenosine analogues **2**, **3**, and **4** in radioligand binding assays at human A_1, A_{2A}, and A_3 adenosine receptors

Linker at C-2 position of NECA and compound number	A_1 K_i[a] (nM)	A_{2A} K_i[b] (nM)	A_{2B} EC_{50}[d] (nM)	A_3 K_i[c] (nM)	A_1/A_{2a}	A_1/A_3
2	34.6	6.64	17,400	6.32	5.2	5.47
3	46.5	3.76	13,200	4.51	12.36	10.31
4	76.4	23.3	31,000	16.0	3.27	4.85
CGS-21680[e]	290	27	89,000	67	10.7	4.3

[a] Displacement of specific [³H]CCPA binding in CHO cells stably transfected with human recombinant A_1 adenosine receptor, expressed as K_i (nM).
[b] Displacement of specific [³H]NECA binding in CHO cells stably transfected with human recombinant A_{2A} adenosine receptor, expressed as K_i (nM).
[c] Displacement of specific [³H]NECA binding in CHO cells stably transfected with human recombinant A_3 adenosine receptor, expressed as K_i (nM).
[d] Activation of adenylyl cyclase in membranes forms CHO cells with stably transfected human A_{2B} receptors.
[e] Data from Ref. 1.



Scheme 2. (a) Ac_2O, pyridine, rt, 8 h, 75%; (b) 0.01 M phosphate buffer, acetone, NaOH, PPL, 4 days, *R*-(−)-acetate 31%; (c) MeOH, KOH (1 N, 0.3 equiv), 0 °C–rt, 1 h, 82%; (d) BAIB, TEMPO, CH_2Cl_2, 5 h, 54%; (e) **1**, MeOH, rt, 3 h, 93%.

Table 2
Oxidation of alcohol **6**

Entry	Conditions	Yield (%)
1	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	30
2	DMSO, SO_3–pyridine, Et_3N, CH_2Cl_2	22
3	TPAP, NMO, CH_2Cl_2	0
4	MnO_2, acetone	0
5	PCC, ether or PCC, CH_2Cl_2	0
6	Dess–Martin periodinane, CH_2Cl_2	25
7	BAIB, TEMPO, CH_2Cl_2	54

um chlorochromate (PCC), ether; (4) Pyridinium dichromate (PDC), CH_2Cl_2.

The reaction of (±)-**6** in the presence of Dess–Martin periodinane[16] in CH_2Cl_2 provided aldehyde **7** as the major product but the separation of **7** from impurities was complicated. Further attempts to oxidize (±)-**6** using iodobenzene diacetate (BAIB) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in CH_2Cl_2 provided (±)-**7** in better yield.[17] Under similar conditions, the enantiomer (*R*)-**7** was then prepared from (*R*)-**6**.[18] (*R*)-Aldehyde was separated from the crude reaction mixture by column chromatography. Of the various oxidizing reagents studied, the method with BAIB and TEMPO was found to be efficient and clean.

Treatment of (*R*)-**7** with 2-hydrazino-NECA (**1**) produced the diastereoisomer **3** enriched with (*R*)-3,4-dihydro-2*H*-pyranyl (DHP) side chain.[19] The (*R*)-DHP analogue **3** showed highest affinity for both A_{2A} and A_3 receptors [$K_i(A_{2A}) = 3.76$ and $K_i(A_3) = 4.51$ nM]. Compound **3** is sevenfold better than reference compound CGS 21680, binds with a $K_i(A_{2A})$ value of 3.76 nM, and is 12-fold selective versus A_1. Compound **3** also showed 10-fold A_3 selectivity versus the A_1 subtype, which is slightly better than the selectivity of CGS21680 as one of the most potent and selective A_{2A} agonists known (Table 1). The adenylyl cyclase functional assay[1] has shown that it is a full agonist at A_{2A} and A_3 receptors (data not shown).

In summary, a synthesis of potent and selective adenosine A_{2A} and A_3 receptor agonist **3** has been accomplished from the coupling reaction of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde (**7**) and 2-hydrazino-NECA (**1**). The enantiopure (*R*)-2-acetoxymethyl-3,4-dihydro-2*H*-pyran (**5**) was prepared on multi-gram scale by modifying the earlier PPL catalyzed resolution methods.[11a,12] A method for the synthesis of aldehyde (*R*)-**7** from alcohol (*R*)-**6** has been discussed. The results from in vivo studies will be published elsewhere.

Acknowledgments

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13. *Typical procedure for the enzymatic hydrolysis of 2-acetoxymethyl-3,4-dihydro-2H-pyran* (**5**): To the mixture of phosphate buffer (4.2 l, 0.01 M, pH 7.6) was added (±)-**5** (29.5 g, 189.1 mmol) in acetone (145 ml) at rt and stirred for 5 min. Then it was treated with PPL (Sigma, 2.8 g) and the reaction mixture was stirred at rt. During the reaction pH was constantly adjusted to 7.6 with NaOH (3 N). Additional PPL (0.7 g) was added after 24 h. Progress of the reaction was

monitored by HPLC using chiral column as shown below. After 4 days, the reaction mixture was extracted with EtOAc (4 × 700 ml) and organic layer was dried on Na_2SO_4. It was filtered and concentrated on rotavaporator and purified on the neutral aluminum oxide using 25% EtOAc–hexane to give (*R*)-**5** (8.1 g, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6–2.2 (m, 4H), 2.1 (s, 3H), 4.2 (m, 3H), 4.8 (m, 1H), 6.4 (m, 1H). $[\alpha]^{25}$ −76.67 (*c* 2.58 in $CHCl_3$). Following this method (*R*)-**5** was prepared on multi-gram scale (200 g). The enantiomeric excess was determined by HPLC using Chiralpak AD-RH column from Daicel. Conditions: Isocratic using 45% MeOH, 5% MeCN in H_2O for 35 min, flow rate 0.7 ml/min, and detected at 215 nM. The retention time of the (*R*) and the (*S*) isomers was 16.28 and 18.28 min, respectively.

14. (*R*)-3,4-dihydro-2*H*-pyran-2-methanol (**6**): $[\alpha]^{25}$ −74.61 (*c* 2.52 in $CHCl_3$).
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18. *Typical procedure for the oxidation of (R)-3,4-dihydro-2H-pyran-2-methanol* (**6**): A mixture of (*R*)-alcohol **6** (14.0 g, 122.8 mmol) and BAIB (59.13 g, 184.2 mmol) in CH_2Cl_2 (105 ml) was stirred at rt for 30 min, and then treated with TEMPO (1.92 g, 12.28 mmol). The reaction mixture was stirred at room temperature for 5 h. Progress of reaction was monitored by tlc (silica gel, 30% EtOAc–hexane, R_f = approx. 0.65). The reaction mixture was then diluted with CH_2Cl_2 (100 ml) and treated with saturated solution of $Na_2S_2O_3$ (100 ml) and NaCl (2 × 50 ml). The biphasic mixture was then treated with dilute solution of Na_2CO_3 (to adjust pH of mixture to 6 and 7). The organic layer was separated and the aqueous layer was extracted in CH_2Cl_2 (8 × 20 ml). The combined organic solution was dried over Na_2SO_4 (10 g) and filtered. Then it was concentrated on rotavaporator at 30 °C under vacuum. Purification of crude material on the silica gel column by eluting first with 100% CH_2Cl_2 followed by the mixture of CH_2Cl_2/MeOH (20:1) furnished aldehyde (*R*)-**7** (7.5 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–2.07 (m, 4H), 4.29–4.32 (dd, *J* = 5.4 and 7.5 Hz, 1H), 4.77–4.79 (m, 1H), 6.49 (d, *J* = 6.3 Hz, 1H), 9.71 (s, 1H). Compound (*R*)-**7** was found to be unstable if exposed to heat and light. It was stored in a refrigerator using the dark vials.
19. The HPLC analysis of the final product obtained from (*R*)-aldehyde and 2-hydrazino-NECA showed (*R*)-DHP-enriched diastereomer **3** as the major product (98.4%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, *J* = 6.6 Hz, 3H), 1.89–2.08 (m, 4H), 3.15–3.20 (m, 3H), 4.22–4.24 (m, 1H), 4.36 (d, *J* = 3.6 Hz, 1H), 4.55–4.61 (m, 2H), 4.80 (d, *J* = 5.4 Hz, 1H), 5.69 (s, 2H), 5.91 (d, *J* = 6.3 Hz, 1H), 6.49 (d, *J* = 6.3 Hz, 1H), 7.56 (d, *J* = 5.4 Hz, 1H), 8.25 (t, *J* = 5.1 Hz, 1H), 8.59 (s, 1H).