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## Methanocarba ring as a ribose modification in ligands of G protein-coupled purine and pyrimidine receptors: synthetic approaches

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### Abstract

Adenosine receptors (ARs) and P2Y receptors for purine and pyrimidine nucleotides have widespread distribution and regulate countless physiological processes. Various synthetic ligands are in clinical trials for treatment of inflammatory diseases, pain, cancer, thrombosis, ischemia, and other conditions. The methanocarba (bicyclo[3.1.0]hexane) ring system as a rigid substitution for ribose, which maintains either a North (N) or South (S) conformation, tends to preserve or enhance the potency and/or selectivity for certain receptor subtypes. This review summarizes recent developments in the synthetic approaches to these biologically important nucleoside and nucleotide analogues.

### Introduction

G protein-coupled receptors (GPCRs) serve as the mechanistic target of a large fraction of the pharmaceuticals in current use. Among the numerous members of this superfamily, *i.e.* corresponding to ~800 human genes including olfactory receptors, are two families consisting of a total of twelve GPCR subtypes that are activated by endogenous nucleosides and nucleotides present in the extracellular medium.<sup>1,2</sup> These include four subtypes of adenosine receptors (ARs) and the eight subtypes of P2Y receptors (P2YRs) for purine and pyrimidine nucleotides. The production and release of these small molecule modulators that contain D-ribose, such as adenosine, ATP and UTP, are widespread in the body and involved in countless physiological processes. Numerous studies of the structure activity relationships (SARs) at these receptors have been performed, and in many cases agonists and/or antagonists that are selective for a given subtype have been reported.<sup>2–5</sup> At ARs, the subtype selectivity is largely determined by the substitution at the adenine *N*<sup>6</sup> and C2 positions and at ribose. Some of these ligands are currently in clinical trials or preclinical testing for the treatment of inflammatory diseases, pain, cancer, thrombosis, ischemia, and other conditions.<sup>1</sup>

A general approach to restricting the recognition of these nucleoside and nucleotide derivatives by specific receptor subtypes, as a means of enhancing selectivity, is to rigidify the ribose ring in the form of a bicyclo[3.1.0]hexane (also known as “methanocarba”), which is designed to maintain a receptor-preferred conformation of the ribose ring. The methanocarba ring system can maintain either a North (N) or South (S) conformation, depending on the position of fusion of the cyclopentane and cyclopropane rings. This approach to rigidify the normally flexible ribose moiety was introduced and first applied to antiviral agents by Marquez and coworkers.<sup>6a</sup> Fig. 1 shows the (N) and (S)-envelope conformations of methanocarba ring systems ( $P = -12^\circ$  or  $192^\circ$ , respectively) on the pseudorotational cycle, in relation to the pure (N) and (S)-conformations of  $P = 0^\circ$  or  $180^\circ$ , respectively.<sup>7</sup> Conformationally locked methanocarba nucleosides and nucleotides have applicability to probing structure–function of nucleic acids in general, as well the specific focus on GPCRs. This substitution has produced great selectivity in substrates and inhibitors of various enzymes, such as polymerases, DNA methyltransferase, and HIV-RT, and when incorporated into DNA.<sup>6a</sup> Other constrained ring systems, such as locked nucleic acids (LNAs), have been utilized for this purpose,<sup>8</sup> but the methanocarba ring system has displayed a generally higher success rate in preserving or enhancing the potency at a given receptor subtype.

Nucleoside and nucleotide analogues containing a novel methanocarba ring system in place of ribose ring have been systematically explored as ligands for the ARs and P2YRs. In general, the (N)-methanocarba modification enhances affinity of adenosine derivatives at the  $A_3$  subtype of ARs and of adenine nucleotide derivatives at the  $P2Y_1$  subtype of P2YRs. The  $A_3$ AR (activated by endogenous adenosine and inosine) is coupled to inhibition of adenylate cyclase, and the  $P2Y_1$ R (activated by ADP) is coupled to stimulation of phospholipase C. At the  $A_{2A}$ AR and  $A_{2B}$ AR, which are coupled to stimulation of adenylate cyclase, and certain other P2YRs, the introduction of (N)- methanocarba tends to reduce affinity. Therefore, this modification has led to agonist and antagonists of exceptionally high selectivity at the  $A_3$  and  $P2Y_1$  subtypes. At the  $A_1$ AR,  $P2Y_2$ R and  $P2Y_4$ R, the (N)-methanocarba-substituted analogues are similar in potency to the native ligands. The only receptor within these families found to prefer the (S) conformation using a methanocarba substitution is the  $P2Y_6$ R, at which the (N)-methanocarba analogue of the native ligand (UDP) is inactive. At all three of the P2YR subtypes of the  $P2Y_{12}$ -like family, which are coupled to inhibition of adenylate cyclase, we have not yet identified the preferred conformation of ribose. Modification of the native ligands in each case with either (N)-methanocarba or (S)-methanocarba rings greatly reduces the potency. Thus, the use of this pair of bicyclic modifications of nucleosides and nucleotides has been effective in the design of selective receptor ligands. This review summarizes recent developments in the synthetic approaches to methanocarba derivatives in the context of their use as definitive pharmacological probes of various ARs and P2Ys.

## Synthetic approaches to methanocarba nucleosides

General synthetic methods for the preparation of carbanucleosides, including methanocarba ribonucleosides and 2'-deoxyribonucleosides have been reviewed.<sup>6</sup>

### a (N)-Methanocarba derivatives

The first methanocarba nucleoside was designed<sup>7,9</sup> as a 2',3'-dideoxy nucleoside for conformational comparison with the more planar antiviral agent neplanocin C.<sup>10</sup> Marquez and coworker reported a simple method for the synthesis of a series of racemic (N)-methanocarba dideoxynucleosides.<sup>7,9</sup> A hydroxyl-directed cyclopropanation of benzyloxy cyclopentenol **1** *via* a samarium(II) carbenoid intermediate provided the pseudosugar **2** (Scheme 1). Nucleobases were incorporated *via* a Mitsunobu coupling reaction, following a convergent strategy. Mitsunobu coupling of **2** with 6-chloropurine afforded a mixture of N9–N7 isomers in a 3 : 1 ratio favoring the N9 isomer **4**. The pyrimidine derivatives **6** were obtained using the same Mitsunobu conditions. With *N*-benzoylthymine, a separable 1 : 1 mixture of *N*- and *O*-alkylated products **6** and **7** (R=CH<sub>3</sub>) was obtained, while in the case of *N*-benzoyluracil (R=H) no *O*-alkylated product was detected. Compound **4** was transformed into an adenosine derivative by heating with methanolic ammonia followed by catalytic debenzoylation to give racemic compound **5**. Treatment of compound **6** with BCl<sub>3</sub> resulted in removal of the benzyl and benzoyl groups to give racemic pyrimidine derivatives of (N)-methanocarba nucleosides **8**.

Marquez *et al.* also reported<sup>11,12</sup> an enantioselective route for the synthesis of (N)-methanocarba-riboadenosine analogues (Scheme 2). Treatment of (–)-5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone **9** with lithium dimethyl methylphosphonate in THF provided hemiketal **10**. Subsequently, the hemiketal group was opened with sodium methoxide, which upon oxidation with a modified Collins reagent provided the diketo phosphonate **11**. Intramolecular cyclization of compound **11** in the presence of potassium carbonate and 18-crown-6 ether afforded the desired cyclopentenone **12**. A synthesis of intermediate **12** was reported by Chu and coworkers,<sup>13a</sup> and a later synthesis of the same intermediate by Jeong and coworkers was based on a ring closing metathesis reaction.<sup>13b,c</sup> Treatment of compound **12** with sodium borohydride in the presence of cerium(III) chloride yielded a cyclopentenol derivative, which underwent a stereoselective Simmon–Smith cyclopropanation to give the key precursor **13**. Mesylation of alcohol **13** followed by adenine condensation and deprotection of benzyl and isopropylidene groups provided the enantiomerically pure (N)-methanocarba-adenine derivative **14**. (N)-Methanocarba-adenosine derivatives, including those with 3'-amino substitution, were also synthesized from D-ribose using ring closing metathesis.<sup>14,15</sup> The most efficient synthesis currently of (N)-methanocarba-ribonucleosides involves ring closing metathesis, as described by the groups of Jeong and Strazewski.<sup>13,15</sup>

A novel intramolecular cyclopropanation approach for the synthesis of (N)-methanocarba-adenosine analogues was explored in several laboratories.<sup>16,17</sup> L-Ribose **15a** was converted to an isopropylidene derivative, which upon treatment with iodine in the presence of triphenylphosphine and imidazole provided the iodo derivative **15b** (Scheme 3a). The reductive elimination of iodine of compound **15b** in the presence of zinc and acetic acid generated the unstable aldehyde **15c**, which was immediately treated with ethyl diazoacetate in the presence of tin(II) chloride to give compound **15d**. The ketoester **15d** was reacted with tosyl azide to afford the diazo derivative **15e**, which underwent a thermally induced intramolecular cyclopropanation reaction to give the bicyclo[3.1.0]hexane derivatives **16a**

and **16b** in a 4 : 1 ratio. After chromatographic separation, the reduction of compound **16a** with sodium borohydride followed by isomerization of alcohol **17a** in the presence of trifluoromethane sulfonic acid afforded the glycosyl donor **17b**. After isolation by crystallization, compound **17b** was subjected to a Mitsunobu condensation with 2,6-dichloropurine to give the nucleoside derivative **18**. This intermediate was aminated with 3-chlorobenzylamine followed by 5'-amidation and isopropylidene deprotection to provide the enantiomerically pure (N)-methanocarba-adenine derivative **19**.

Our group has recently reported a novel class of (N)-methanocarba derivatives having a phenylacetylene moiety at the C2 position that are highly potent and selective agonists of the A<sub>3</sub>AR.<sup>18</sup> This class of compounds was synthesized by using an extension of the methodology shown in Scheme 3a. Compound **20a** was derived from (N)-methanocarba sugar **17b** through a Mitsunobu condensation with 6-chloro-2-iodo-purine. Treatment of compound **20a** with 3-chlorobenzylamine followed by amination of the resulting intermediate gave the amide derivative **20b** (Scheme 3b). A Sonogashira coupling of **20b** with phenylacetylene and subsequent acid hydrolysis of the resulting compound afforded the C2-phenylacetylene methanocarba derivative **21**.

Truncation of adenosine derivatives at the ribose C4' has variable effects on the pharmacological properties of potency and efficacy at the ARs, and the SAR of truncated methanocarba nucleosides has been explored.<sup>21</sup> Extensive modification of this class of molecules provided various lead molecules to achieve selectivity for either the A<sub>1</sub>AR or the A<sub>3</sub>AR.<sup>19,20</sup> The cyclopentone derivative **22b** was synthesized from D-ribose **22a** in six steps (Scheme 3c),<sup>22a</sup> and the glycosyl sugar **22c** was formed upon the stereoselective reduction of **22b** by sodium borohydride in the presence of cerium(III) chloride followed by a Simmons–Smith cyclopropanation of the resulting alcohol. An alternate synthesis of intermediate **22b** involving ring closing metathesis reaction and starting with D-isoascorbic acid had a lower yield and a volatile intermediate.<sup>22b</sup> Mitsunobu condensation of the compound **22c** with various purine bases gave the intermediates of the general formula **23**, which upon amination with various amines at the N<sup>6</sup> position, and subsequent acid hydrolysis provided truncated methanocarba nucleosides **24**.<sup>19,20</sup> Alternately, group R of **24** was an arylethynyl substitution, which despite its steric bulk was recognized at the A<sub>3</sub>AR, especially with small R<sup>1</sup> groups.<sup>19</sup>

Lowary and Li devised a novel synthetic route for the synthesis of (N)-methanocarba equivalents of β-arabinofuranosyl and α-galactofuranosyl amino sugar intermediates (Scheme 4).<sup>23</sup> The key step of the synthetic strategy was the base-promoted ring contraction of an epoxy ketone. Thus, the ketal–allylic alcohol **25** was hydrolysed with oxalic acid followed by protection of the hydroxyl group as a methoxymethyl (MOM) ether, and subsequent epoxidation provided the keto epoxy compound **26**. The epoxy ketone **26** underwent a ring contraction in the presence of sodium hydroxide, which afforded the methanocarba derivative **27** along with the undesired isomer. Compound **27** was then converted to enone derivative **28** by sequential benzylation, α-selenation and selenoxide elimination. Enone derivative **28** was epoxidised in the presence of alkaline hydrogen peroxide to give compound **29**, which was elaborated to compound **31** by a sequence of

reactions. Treatment of compound **31** with *O*-acetyl-(*S*)-mandelic acid followed by hydrolysis of the ketal gave the easily separable diastereomers **32a** and **32b**. Periodate cleavage of the diol, subsequent ester hydrolysis and reduction provided the (N)-methanocarba  $\beta$ -arabinofuranosyl **33a** and  $\alpha$ -galactofuranosyl **33b** amino sugars.

(N)-Methanocarba-2'-deoxy purine analogue **40** was synthesized by a convergent approach from compound **34** (derived from **12**) as depicted in Scheme 5.<sup>24</sup> Regioselective opening of the isopropylidene group in the presence of trimethylaluminum and selective silylation of the allylic alcohol gave compound **35**. Treatment of compound **35** with carbon disulfide in the presence of sodium hydride gave xanthate ester **36**, which underwent deoxygenation in the presence of TBTH and AIBN under Barton's condition and subsequent desilylation to provide the precursor **37**. The unmasked hydroxyl derivative **37** was cyclopropanated in the presence of Sm-HgCl<sub>2</sub> and chloro-iodo-methane to give the glycosyl donor **38**, which was directly coupled with 6-chloropurine under Mitsunobu conditions to afford the protected nucleoside intermediate **39**. Ammonolysis of compound **39** and simultaneous removal of benzyl and *tert*-butyl groups provided the (N)-methanocarba-2'-deoxy adenine derivative **40**.

Marquez and coworkers have also developed another simple and efficient route for the synthesis of (N)-methanocarba-2'-deoxy nucleoside derivatives<sup>25</sup> from an inexpensive starting material, ethyl acetoacetate (Scheme 6), with intramolecular olefin-ketocarbene cycloaddition and lipase-catalysed resolution as the key steps. Thus, compound **41** was treated with LDA in the presence of acrolein, and the resulting alcohol was silylated with TBDPSCI to give silyl derivative **42**. Treatment of compound **42** with *p*-toluenesulfonyl azide provided the carbene precursor **43**. Intramolecular cyclopropanation of **43**, which presumably proceeds *via* a copper-carbenoid intermediate under thermolysis, generated a chromatographically separable mixture of compounds ( $\pm$ )-**44** and ( $\pm$ )-**45**. Sequential reduction of compound **45** with sodium borohydride followed by lithium aluminium hydride afforded compound **46**. Surprisingly, the simultaneous reduction of both keto and ester groups of compound **45** with diisobutyl aluminium hydride (DIBAL) resulted a mixture of epimeric alcohols. Treatment of compound ( $\pm$ )-**46** with a commercially available Lipase PS-C "Amano" I from *Pseudomonas cepacia*, in the presence of a large excess of vinyl acetate was able to resolve the two enantiomers giving ( $-$ )-**47** as a monoacetate and ( $+$ )-**48** as a diacetate. Deblocking of the silyl group of compound ( $+$ )-**48** with (NH<sub>4</sub>)HF<sub>2</sub> gave ( $+$ )-**49** having high optical purity (99% *e.e.*). A Mitsunobu condensation under standard conditions of compound ( $+$ )-**49** with 2-acetamido-6-chloropurine afforded ( $+$ )-**50**, which was converted to a (N)-methanocarba-2'-deoxyguanosine derivative ( $+$ )-**51** by heating with 2 N HCl at 80 °C. Chiral resolution of (N)-methanocarba-2'-deoxy pyrimidine nucleosides was also accomplished using the same synthetic strategy.

### b (S)-Methanocarba derivatives

The synthesis of (S)-methanocarba nucleosides is more challenging than (N)-methanocarba because the nucleobase has to be attached directly to a tertiary carbon of the bicyclo[3.1.0]hexane moiety. This structural template ruled out a convergent strategy, and the synthesis must proceed from an appropriately protected bicyclic amine. Altmann and coworkers have reported<sup>26</sup> the first synthesis of a (S)-methanocarba nucleoside, which was a

(S)-methanocarba-2'-deoxythymidine **57**. Thus, the chiral bicyclic lactone **52** was opened to give the  $\gamma$ -bromo ester in the presence of TMSBr, and subsequent protection as a TBDMS ether gave compound **53** (Scheme 7). Treatment of compound **53** with potassium *tert*-butoxide in *tert*-butanol created the cyclopropane ring derivative **54**, which gave the acid derivative **55** upon saponification. Compound **55** underwent a one-pot three-step procedure involving formation of a carboxylic acid azide. This consisted of an *in situ* Curtius rearrangement followed by quenching of the ensuing isocyanate with benzyl alcohol, to provide a benzyloxycarbonyl-protected amine, which was hydrogenated in the presence of palladium-carbon to afford the key amino sugar derivative **56**. Construction of the thymine nucleobase was accomplished by reaction of **56** with  $\beta$ -methoxy  $\alpha$ -methacryloyl-isocyanate and subsequent cyclization of the resulting acryloyl-urea and deprotection of the silyl group simultaneously under acidic condition to furnish (S)-methanocarba-2'-deoxythymidine **57**.

Marquez and coworkers utilized an intramolecular olefinketocarbene cycloaddition strategy for the synthesis of an (S)-methanocarba-riboadenosine analogue<sup>27</sup> as shown in Scheme 8. Esterification of (*E*)-butanol **58** and *p*-methoxybenzyloxyacetic acid in the presence of DCC gave the glycolate ester **59**, which underwent an enolate Claisen-Ireland rearrangement in the presence of LDA and TMSCl to afford the desired  $\gamma,\delta$ -unsaturated acid diastereomer **60** mixed with its isomer in a 95 : 5 ratio. The favorable outcome was explained in term of a chair-like transition state that was controlled by the *trans*-geometry of the starting olefin and the local geometry of the enolate induced by the coordinated metal. A Dieckmann condensation of methyl 2-lithioacetate with the carbonyldiimidazole-activated acid **60**, produced the  $\beta$ -ketoester **61**, which upon diazo transfer with tosyl azide in the presence of triethylamine gave the diazo derivative **62**. Copper acetylacetonate-catalysed thermolysis of compound **62** resulted in an intramolecular olefin keto-carbene cycloaddition and provided a separable mixture of bicyclo[3.1.0]hexane derivatives **63** and **64** in a 2 : 1 ratio. Sodium borohydride reduction of compound **64** gave exclusively the alcohol **65**, which upon the simultaneous deprotection of the PMB group and protection of the diol as an acetonide in the presence of copper(II) sulfate and a catalytic amount of sulfuric acid afforded the precursor **66**. Saponification of the ester of **66** and a one-pot three-step Curtius rearrangement as in Scheme 7 gave the amine derivative **67**, which was elaborated to the racemic (S)-methanocarba riboadenosine derivative **68** by a sequence of reactions.<sup>27</sup>

In collaboration with the Marquez group, we recently reported a synthesis of enantiomerically pure (S)-methanocarba-uridine and its nucleotide derivatives (Scheme 9).<sup>28</sup> The intermediate **70** was synthesized from D-ribose **69** in seven steps, following the same method as for its enantiomer **17b** from L-ribose **15a** as presented in Scheme 3a. Treatment of compound **70** with trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) in the presence of pyridine gave the triflate derivative **71**, which was immediately converted to a cyano analogue **72** by an S<sub>N</sub>2 reaction with LiCN. A controlled catalytic hydrogenation of the nitrile in the presence of palladium in aqueous acetic acid provided the unstable aldehyde **73**, which immediately underwent a sodium borohydride reduction and subsequent silyl protection of the resulting alcohol to afford silyl ether **74**. Compound **74** was transformed to the key amine derivative **75**, which was further elaborated to (S)-methanocarba-uridine **76** following the same method as in Scheme 7.

## Application of methanocarba templates to AR and P2YR ligands

Ring-constrained nucleosides have been used to define conformational preferences of adenine nucleosides at the ARs and adenine and uracil nucleotides at the P2YRs. Medicinal chemists frequently utilize the approach of conformationally constraining otherwise flexible molecules to probe the active conformation and to increase ligand affinity by overcoming the energy barriers needed to attain this preferred conformation. The focus on conformational factors of the ribose or ribose-like moiety allows the introduction of general modifications that lead to enhanced potency and selectivity at certain subtypes of these receptors.

Jacobson and coworkers were the first to report<sup>29</sup> that a methanocarba modification of the ribose moiety to incorporate ring constraints is a general approach to the design of AR agonists having favorable pharmacodynamic properties. While simple carbocyclic substitution of adenosine derivatives often diminishes potency at ARs, methanocarba-adenosine analogues have preserved or enhanced pharmacological properties as agonists at two AR subtypes. In such methanocarba analogues, the fused cyclopropane moiety constrains the pseudosugar ring of nucleoside to either a Northern (N)- or Southern (S)-conformation, which helps to define the role of sugar puckering in stabilizing the active AR-bound conformation, and thereby allows identification of a favoured isomer.

In the binding assays at A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub>ARs, (N)-methanocarba-adenosine had a higher affinity than the (S)-analogue, particularly at human A<sub>3</sub>AR [(N)/(S)—affinity ratio of 150]. (N)-methanocarba analogues of various N<sup>6</sup> substituted adenosine derivatives, including N<sup>6</sup>-cyclopentyl and N<sup>6</sup>-(3-iodobenzyl), in which parent compounds are potent agonists at either A<sub>1</sub> or A<sub>3</sub>ARs, respectively, were synthesized (Fig. 2). The N<sup>6</sup>-cyclopentyl derivatives were A<sub>1</sub>AR selective and maintained high efficacy at recombinant human, but not rat brain A<sub>1</sub>ARs, indicated in a functional assay based on stimulation of binding of [<sup>35</sup>S]GTP-γ-S. The 2-chloro analogue **80** (MRS 1761), was a selective full agonist at the human A<sub>1</sub>AR. (N)-Methanocarba-N<sup>6</sup>-(3-iodobenzyl) adenosine **81** and its 2-chloro derivative **82** (MRS1760) had equilibrium inhibition constant (K<sub>i</sub>) values of 4.1 and 2.2 nM at the A<sub>3</sub>AR, respectively, and were highly selective partial agonists. Partial agonism combined with high functional potency at A<sub>3</sub>ARs (EC<sub>50</sub> < 1 nM) may lead to tissue selectivity.

After finding the enhancement of potency and selectivity in ligand binding to ARs by a substitution of the ribose ring with a methanocarba moiety, a series of new (N)-methanocarba nucleoside was designed and synthesized<sup>30</sup> by modifying the 5'-position of the methanocarba sugar along with N<sup>6</sup> position of the purine as shown in Fig. 3. The N<sup>6</sup>-methyl derivatives **83** and **84** having 4'-hydroxymethyl were selective in binding to the A<sub>3</sub>AR in comparison to the A<sub>1</sub> by 12- and 39-fold, respectively, while compound **85** having a 5'-uronamide displayed 4-fold increased A<sub>3</sub>AR affinity over compound **84** and consequently 130-fold selectivity in comparison to the A<sub>1</sub>AR. The 5'-uronamide modified N<sup>6</sup>-(3-halobenzyl) analogues **19** (MRS3558), **89** (MRS1898) and **91** maintained the approximate affinities associated with the corresponding 9-ribosides at A<sub>1</sub> and A<sub>3</sub>ARs and therefore selectivity for the A<sub>3</sub>AR. The corresponding 5'-truncated N<sup>6</sup>-(3-halobenzyl) analogues **88** and **90** (general formula **24**) maintained affinity at the A<sub>3</sub>AR but had reduced

efficacy. The 3-bromo derivatives **90** (MRS5147) and **91** (MRS3581) were reported as [<sup>87</sup>Br]-labeled ligands for *in vivo* imaging of the A<sub>3</sub>AR.<sup>31</sup> The 2'-deoxynucleosides derivatives **92** and **93** having an N<sup>6</sup>-cyclopentyl group bound weakly to ARs and were nonselective, while compounds **86** (MRS3630) and **87** having a 5'-uronamide and a N<sup>6</sup>-cyclopentyl or bicycloalkyl group had mixed A<sub>1</sub> and A<sub>3</sub>AR selectivity.<sup>32</sup> This clearly indicated that a 2'-hydroxy group or 5'-uronamide are important for receptor recognition, and 2'-deoxy analogues tend to be partial A<sub>3</sub>AR agonists. All of the N<sup>6</sup>-modified (N)-methanocarba-adenosine-5'-uronamide derivatives had full A<sub>3</sub>AR agonist efficacy.

The (N)-methanocarba modification was introduced into known purine receptor ligands containing a 6-oxo substitution and studied further at the ARs by Jacobson and coworkers.<sup>30</sup> The (N)-methanocarba purine nucleosides **94–98** (Fig. 4) and nucleotides **103–108** (Fig. 5) containing alternate nucleobases to adenine were synthesized by conventional methods. While inosine itself displayed a measurable affinity at the A<sub>3</sub>AR and was even suggested to be an endogenous ligand for this AR, the corresponding (N)-methanocarba analogue **94** bound weakly. However introduction of a 5'-methyluronamide group **95** slightly increased the affinity. The truncated (N)-methanocarba purine analogues **99** (MRS5474) and **100** (MRS5719) showed selectivity as A<sub>1</sub>AR full agonist and partial agonist, respectively.<sup>20</sup> The 2-phenylalkynyl derivative **21** in the truncated series showed selectivity as an A<sub>3</sub>AR antagonist,<sup>19,21</sup> and the related 5'-methyluronamides **101** (MRS5697) and **102** (MRS5698) were highly selective agonists at both human and mouse A<sub>3</sub>ARs.<sup>18</sup>

Fig. 5 shows various nucleotides that have increased potency and or selectivity, either at P<sub>2</sub>YRs or at ARs, based on the presence of a (N) or (S) methanocarba ring. The inosine-5'-monophosphate derivative **103** was completely inactive at the A<sub>3</sub>AR, while the dinucleotide **105** displayed binding at A<sub>3</sub>AR with a K<sub>i</sub> value of 22 μM.<sup>33</sup> Dimerization of an inactive ligand might increase the affinity by bridging two sites on a receptor. It is unusual for such a highly anionic molecule to bind to an AR, which may be the result of an enhancing effect of the (N)-methanocarba ring on A<sub>3</sub>AR affinity. The (N)-methanocarbaguanosine analogue **96** bound very weakly at the A<sub>3</sub>AR, and its corresponding triphosphate derivative **106** was completely inactive. The 1,3-dibutylxanthine-7-riboside **97** was equipotent at A<sub>1</sub> and A<sub>3</sub> AR and inactive at A<sub>2A</sub>AR, whereas introduction of 5'-methyluronamide **98** decreased A<sub>1</sub>AR affinity by 8-fold and increased A<sub>3</sub>AR affinity by 2-fold. The xanthine-7-riboside-5'-triphosphate analogue **107** was inactive at the A<sub>3</sub>AR. (N)-Methanocarba nucleotide derivatives provide high selectivity for P<sub>2</sub>Y<sub>1</sub>Rs, as in antagonists **109** (MRS2279) and **110** (MRS2500) or agonist **111** (MRS2365), and maintain affinity at certain other P<sub>2</sub>YRs, such as P<sub>2</sub>Y<sub>2</sub>, while a South (S) conformation of UDP and its analogues increases potency with respect to the native riboside at the P<sub>2</sub>Y<sub>6</sub>R (as in potent agonist MRS2795 **112**).<sup>34</sup>

## Conclusions

ARs and P<sub>2</sub>YRs have become important pharmaceutical targets for treating diverse chronic and acute diseases. The methanocarba (bicyclo[3.1.0]hexane) ring system, as a substitution for ribose, may maintain a receptor-preferred conformation, and thereby preserve or enhance the potency and/or selectivity for certain receptor subtypes. North (N) methanocarba derivatives provide selectivity for the A<sub>3</sub> and P<sub>2</sub>Y<sub>1</sub>Rs and maintain affinity at the A<sub>1</sub>AR,



while a South (S) conformation is highly preferred at the P2Y<sub>6</sub>R. No receptor ligands that are methanocarba analogues are yet in clinical trials, but some analogues are widely used as pharmacological probes. Although the synthetic approaches to these important nucleoside and nucleotide analogues require many steps, methods are being developed to make these feasible for drug development.

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## Abbreviations

<b>AIBN</b>	Azobisisobutyronitrile
<b>AR</b>	Adenosine receptor
<b>DCC</b>	Dicyclohexylcarbodiimide
<b>DIBAL</b>	Diisobutyl aluminium hydride
<b>DPPA</b>	Diphenylphosphoryl azide
<b>GPCR</b>	G protein-coupled receptor
<b>LDA</b>	Lithium diisopropylamide
<b>MOM</b>	Methoxymethyl
<b>MRS1760</b>	(1' <i>S</i> ,2' <i>R</i> ,3' <i>S</i> ,4' <i>R</i> ,5' <i>S</i> )-4'-{2-Chloro-6-[(3-iodophenylmethyl)amino]purin-9-yl}-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol
<b>MRS1761</b>	2-Chloro-(N)-methanocarba- <i>N</i> <sup>6</sup> -(cyclopentyl) adenosine
<b>MRS2279</b>	(1' <i>R</i> ,2' <i>S</i> ,4' <i>S</i> ,5' <i>S</i> )-4-(2-Chloro-6-methylaminopurin-9-yl)-1-[(phosphato)methyl]-2-(phosphato)-bicyclo[3.1.0]hexane
<b>MRS2500</b>	(1' <i>R</i> ,2' <i>S</i> ,4' <i>S</i> ,5' <i>S</i> )-4-(2-Iodo-6-methylaminopurin-9-yl)-1-[(phosphato)methyl]-2-(phosphato)-bicyclo[3.1.0]hexane
<b>MRS3558</b>	(1' <i>S</i> ,2' <i>R</i> ,3' <i>S</i> ,4' <i>R</i> ,5' <i>S</i> )-4'-{2-Chloro-6-[(3-chlorophenylmethyl)amino]purin-9-yl}-1-(methylaminocarbonyl)bicyclo[3.1.0]hexane-2,3-diol
<b>P2YR</b>	P2Y receptor
<b>PMB</b>	<i>p</i> -Methoxybenzyl
<b>TBTH</b>	tri- <i>n</i> -butyltin hydride
<b>TBDPS</b>	<i>tert</i> -Butyldiphenylsilyl
<b>THF</b>	tetrahydrofuran
<b>TBDMS</b>	<i>tert</i> -Butyldimethylsilyl
<b>TMS</b>	Trimethylsilyl

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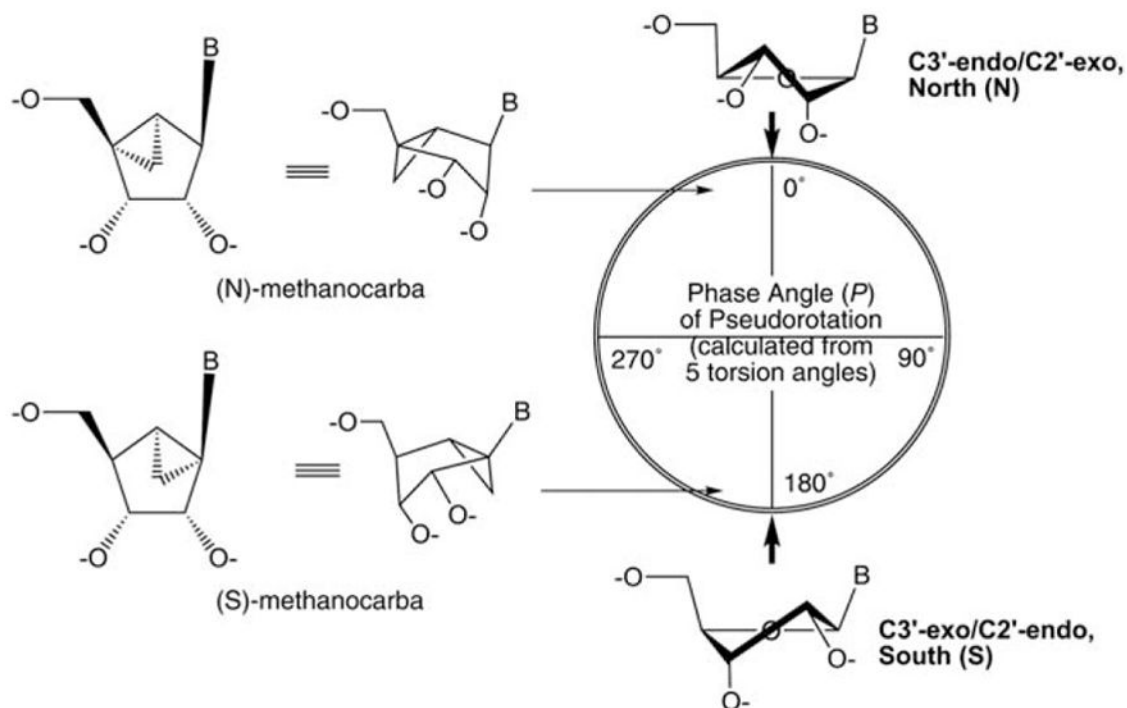
## Biographies



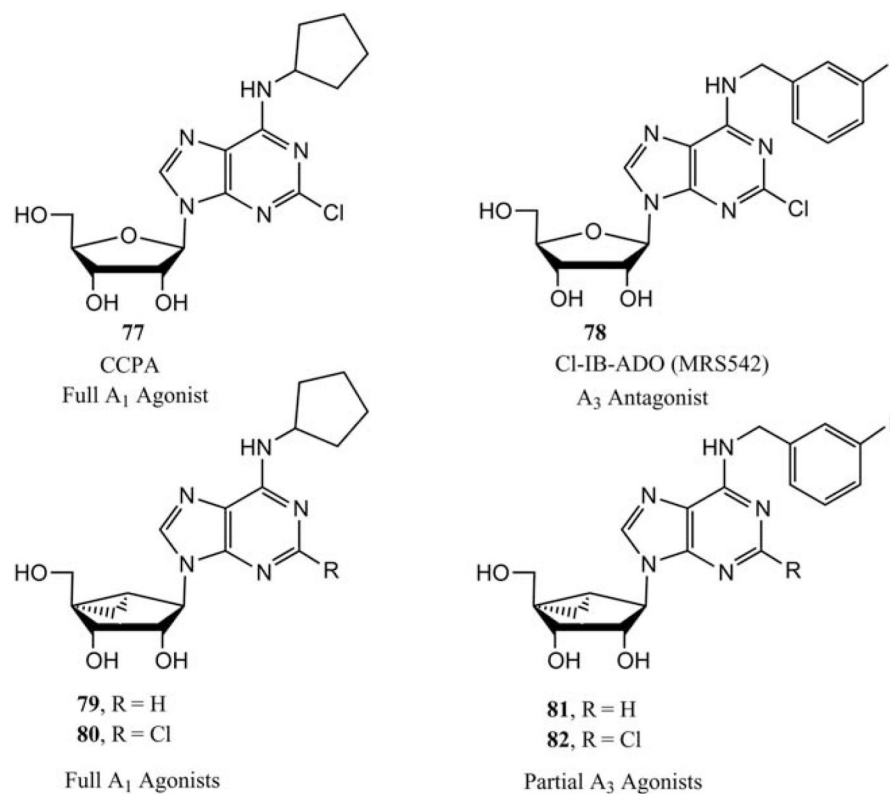
Dilip K. Tosh, Ph.D. is a Visiting Fellow at the Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, NIH in Bethesda, Maryland, USA. He received his Ph.D. in Organic Chemistry from the Indian Institute of Technology, Bombay, under the supervision of Prof. V. K. Singh. Subsequently he joined as a postdoc in the laboratory of Prof. Lak Shin Jeong, at Ewha Womans University, Seoul, Korea, where he worked on Medicinal Chemistry and discovery employing nucleoside chemistry. Currently he works on drug discovery based on G protein-coupled receptors (GPCRs), in particular for adenosine and P2Y receptors under the direction of Dr Kenneth A. Jacobson.



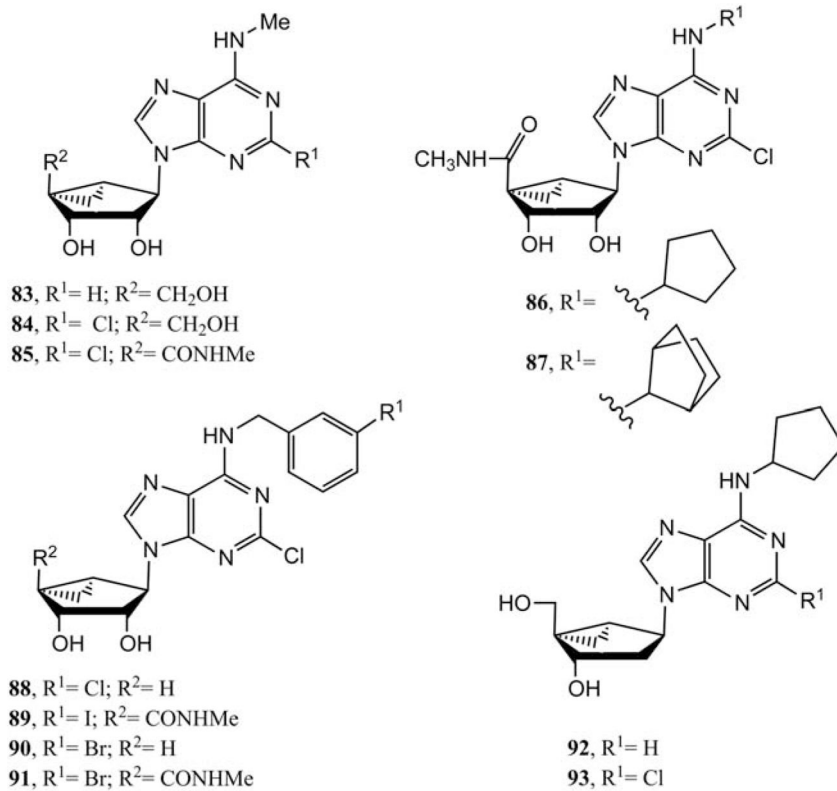
Kenneth A. Jacobson, Ph.D. is Chief of the Laboratory of Bioorganic Chemistry and the Molecular Recognition Section at the National Institute of Diabetes and Digestive and Kidney Diseases, NIH in Bethesda, Maryland, USA. He is a medicinal chemist with interests in the structure and pharmacology of G protein-coupled receptors (GPCRs), in particular receptors for adenosine and for purine and pyrimidine nucleotides. He was inducted into the Medicinal Chemistry Hall of Fame of the American Chemical Society in 2009. Several adenosine agonists from his laboratory are in advanced clinical trials for autoimmune inflammatory diseases and cancer.



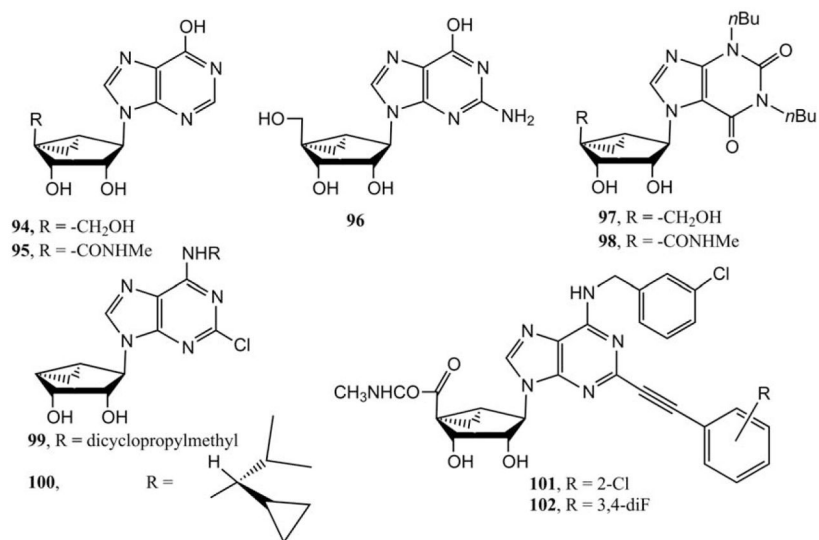
**Fig. 1.** Relationship between the (N)- and (S)-envelope conformations that are maintained in the methanocarba nucleosides and nucleotides and the possible conformations of the ribose ring. The pseudorotational cycle is a mathematical construct derived from all of the torsion angles of ribose to describe the full range of ring twist conformations. The degree of deviation from planarity of the 5-membered ring corresponds to the distance from the center of the cycle. In nature, the observed ribose conformations cluster around the (N) and (S) poles. Thus, the two methanocarba ring systems approximately mimic the favored natural states of ribose. B = nucleobase.



**Fig. 2.** *N*<sup>6</sup> and C2 substituted adenosine derivatives that act as prototypical AR ligands in the ribose (**77**, **78**) and (N)-methanocarba (**79–82**) series.

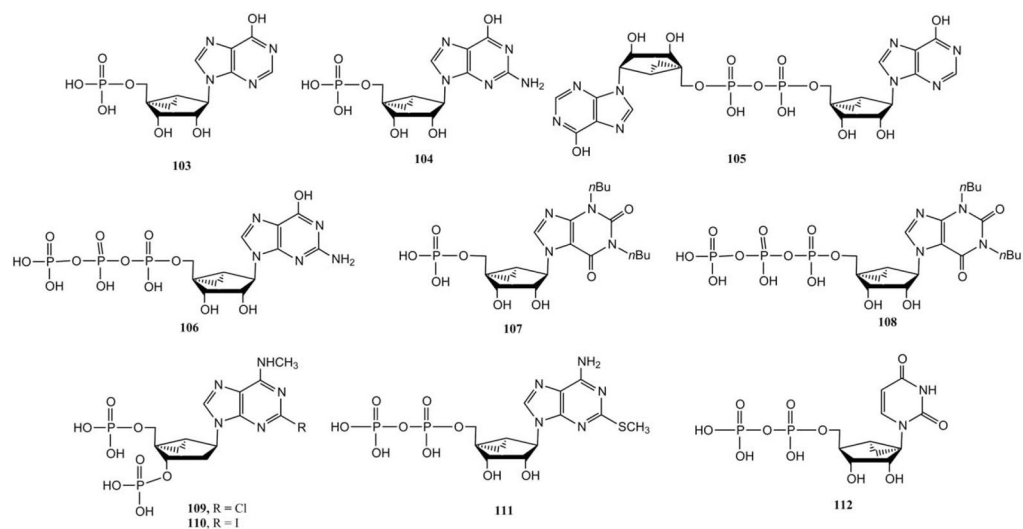


**Fig. 3.** Second-generation adenosine derivatives in the (N)-methanocarpa series that were explored as AR ligands.

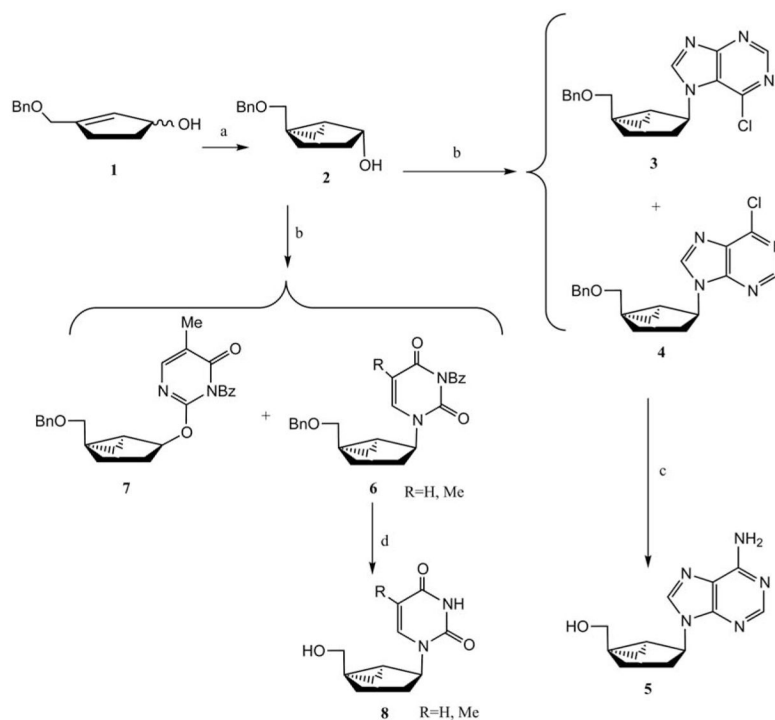


**Fig. 4.** Purine nucleoside derivatives in the (N)-methanocarba series that were explored as AR ligands. Both nonadenosine (**94–98**) and adenosine derivatives (**99–102**) are shown.

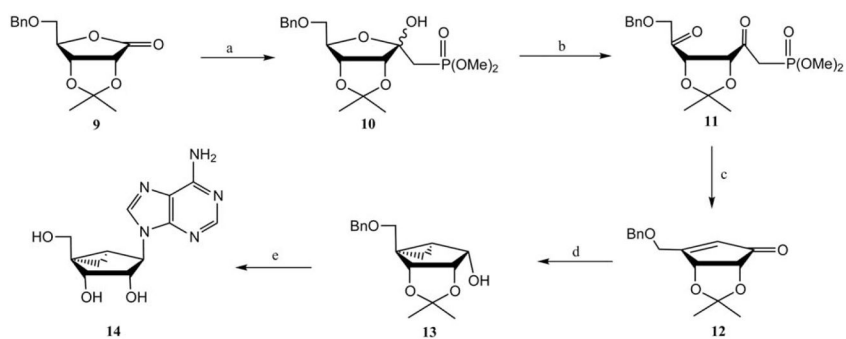




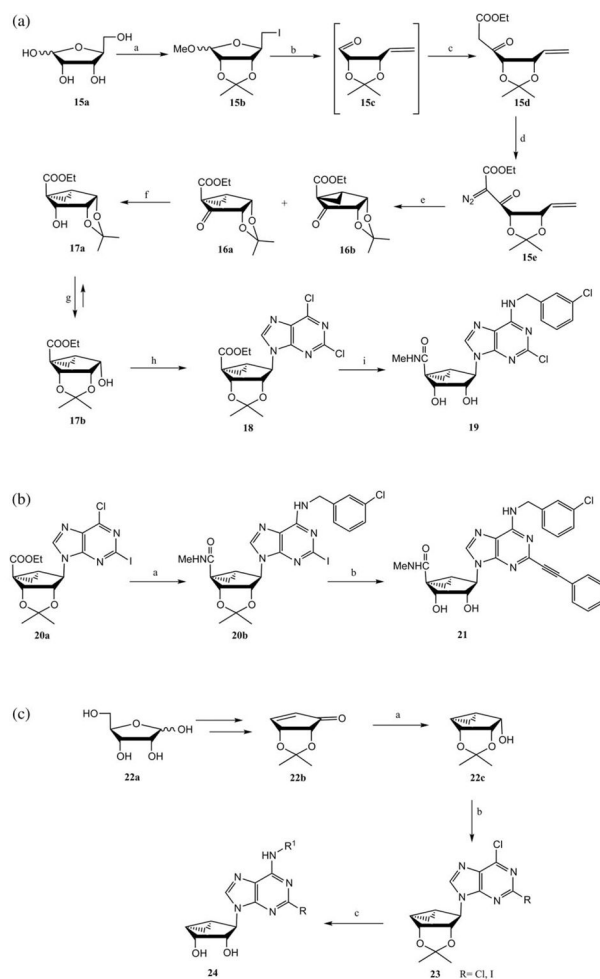
**Fig. 5.** Purine nucleotide derivatives in the (N)-methanocarba series that were explored as AR and P2YR ligands. Nonadenine purines (**103–98**), adenine derivatives (**109–111**) and a uracil derivative **112** are shown.

**Scheme 1.**

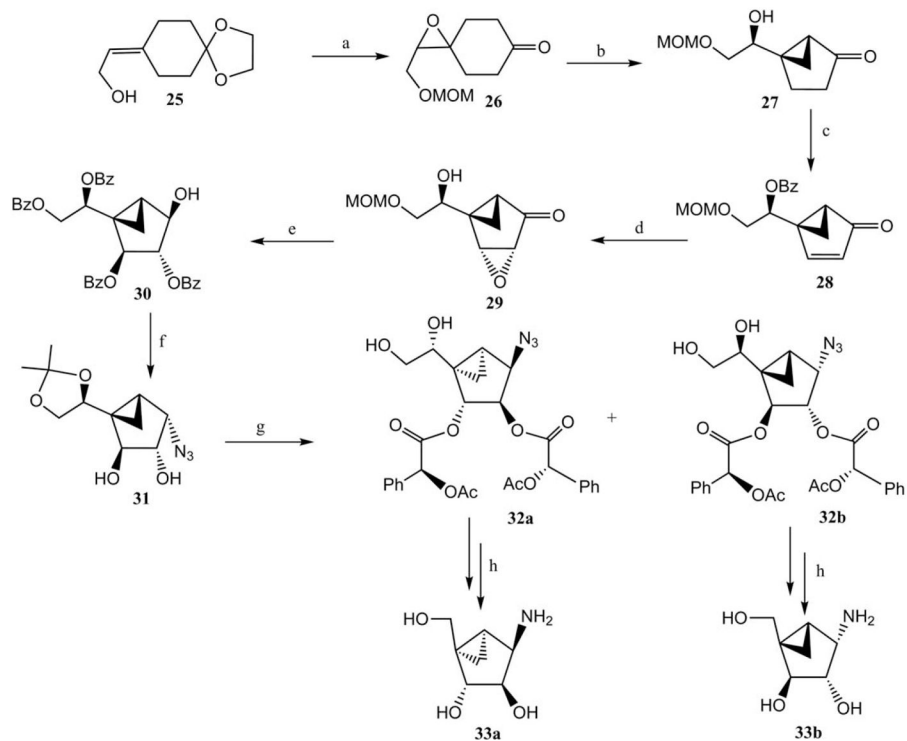
Earliest reported synthesis of methanocarba nucleosides (2',3'-dideoxy), from cyclopentenol **1** by Marquez and coworkers.<sup>7,9</sup> *Reagents and conditions:* (a) CH<sub>2</sub>ICl, Sm, HgCl<sub>2</sub>, THF; (b) 6-chloropurine or *N*-benzoyluracil, Ph<sub>3</sub>P, DEAD; (c) (i) NH<sub>3</sub>/MeOH; (ii) NH<sub>4</sub>COOH, Pd/C, MeOH; (d) BCL<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

**Scheme 2.**

Earliest reported synthesis of (N)-methanocarpa-adenosine, from a D-ribose derivative **9**.<sup>7,9</sup> *Reagents and conditions:* (a)  $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$ ; (b), (i)  $\text{NaOMe}$ ,  $\text{MeOH}$ ; (ii)  $\text{CrO}_3$ , pyridine; (c)  $\text{K}_2\text{CO}_3$ , 18-crown-6; (d), (i)  $\text{NaBH}_4$ ,  $\text{CeCl}_3$ ; (ii)  $\text{Et}_2\text{Zn}$ ,  $\text{CH}_2\text{I}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; (iii)  $\text{MsCl}$ , pyridine; (e), (i) adenine,  $\text{K}_2\text{CO}_3$ , 18-crown-6,  $\text{DMF}$ ; (ii)  $\text{Pd black}$ ,  $\text{HCOOH}$ ,  $\text{MeOH}$ .

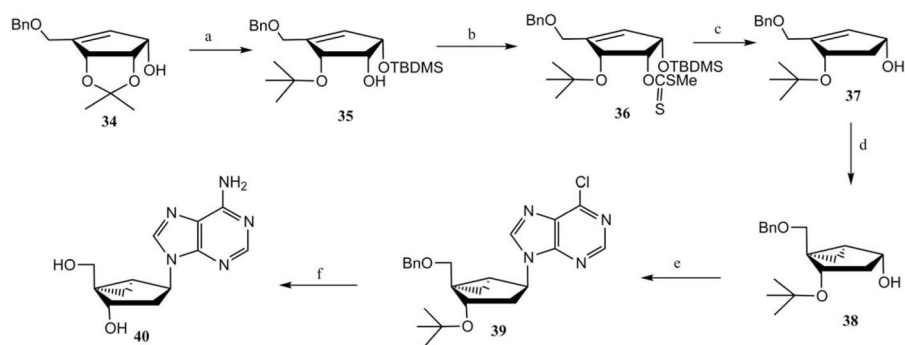
**Scheme 3.**

(a) Synthesis starting from L-ribose of a (N)-methanocarba-adenosine analogue **19** that was optimized for binding to the A<sub>3</sub>AR.<sup>16,17</sup> *Reagents and conditions:* (a) (i) acetone, MeOH; (ii) Ph<sub>3</sub>P, I<sub>2</sub>, imidazole (b) Zn, AcOH; (c) N<sub>2</sub>CHCOOEt, SnCl<sub>2</sub> CH<sub>2</sub>Cl<sub>2</sub> (d) TsN<sub>3</sub>, Et<sub>3</sub>N, MeCN; (e) CuI, toluene; (f) NaBH<sub>4</sub>, MeOH; (g) TfOH, CH<sub>2</sub>Cl<sub>2</sub>; (h) 2,6-dichloropurine, Ph<sub>3</sub>P, DIAD; (i) (i) 3-Cl-BnNH<sub>2</sub>, Et<sub>3</sub>N; (ii) MeNH<sub>2</sub>, MeOH; (iii) TFA–H<sub>2</sub>O, MeOH. (b) Introduction of a 2-arylethynyl substituent, which further increased for binding selectivity at the A<sub>3</sub>AR.<sup>18</sup> *Reagents and conditions:* (a) (i) 3-Cl-BnNH<sub>2</sub>, Et<sub>3</sub>N; (ii) MeNH<sub>2</sub>, MeOH (b) (i) phenylacetylene, PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub>, CuI, Et<sub>3</sub>N; (ii) 10%TFA, MeOH. (c) Synthesis starting from D-ribose of 5'-truncated analogues of the (N)-methanocarba-adenosine derivatives that were selective for the A<sub>3</sub>AR. This modification tended to decrease efficacy of receptor activation, but not binding affinity at this subtype.<sup>19</sup> *Reagents and conditions:* (a) (i) NaBH<sub>4</sub>, Ce(III)Cl<sub>3</sub>·7H<sub>2</sub>O; (ii) Et<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>; (b) purine derivatives, DIAD, Ph<sub>3</sub>P; (c) (i) R<sup>1</sup>NH<sub>2</sub>, Et<sub>3</sub>N; (ii) TFA–H<sub>2</sub>O.



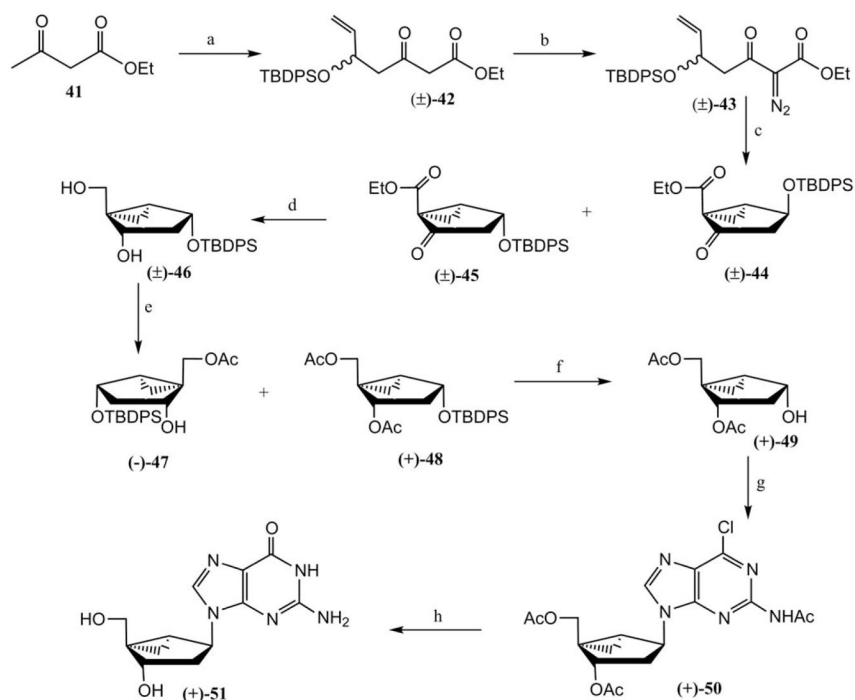
**Scheme 4.**

Novel synthetic route to the (N)-methanocarba equivalents of  $\beta$ -arabinofuranosyl and  $\alpha$ -galactofuranosyl 1-amino sugars.<sup>23</sup> *Reagents and conditions:* (a) (i) oxalic acid, acetone–H<sub>2</sub>O; (ii) (MeO)<sub>2</sub>CH<sub>2</sub>, LiBr, *p*-TsOH; (iii) *m*-CPBA; (b) NaOH, EtOH; (c) (i) BzOH, Ph<sub>3</sub>P, DIAD; (ii) PhSeCl, HCl; (iii) NaIO<sub>4</sub>; (d) H<sub>2</sub>O<sub>2</sub>, NaOH; (e) (i) H<sub>2</sub>SO<sub>4</sub>, (ii) BzCl, pyridine; (iii) NaBH<sub>4</sub>; (f) (i) (PhO)<sub>2</sub>PON<sub>3</sub>, Ph<sub>3</sub>P, DIAD; (ii) MeONa, MeOH; (iii) (MeO)<sub>2</sub>CMe<sub>2</sub>, *p*-TsOH; (g) (i) *O*-acetyl-(*S*)-mandelic acid, DCC, DMP; (ii) AcOH–H<sub>2</sub>O; (h) (i) NaIO<sub>4</sub>; (ii) MeONa; (iii) NaBH<sub>4</sub>; (iv) H<sub>2</sub>, Pd/C.

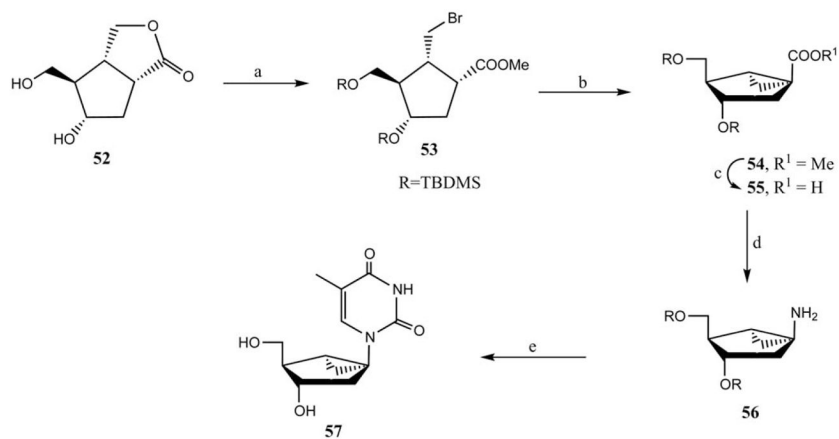
**Scheme 5.**

A convergent approach to the synthesis of (N)-methanocarpa-2'-deoxyadenosine.<sup>24</sup>

*Reagents and conditions:* (a) (i)  $\text{AlMe}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (ii) TBDMSCl, imidazole; (b)  $\text{CS}_2$ , NaH, MeI; (c) (i) TBTH, AIBN; (ii) TBAF; (d) Sm,  $\text{HgCl}_2$ ,  $\text{CH}_2\text{I}_2$ ; (e) 6-chloropurine,  $\text{Ph}_3\text{P}$ , DEAD; (f) (i)  $\text{NH}_4\text{OH}$ , dioxane; (ii)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ .

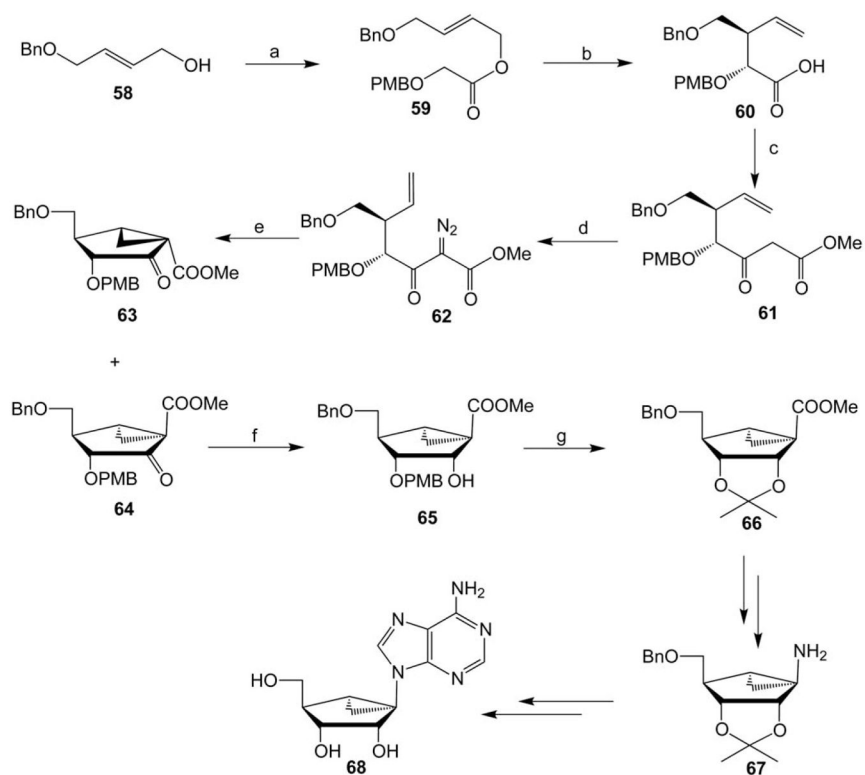
**Scheme 6.**

Synthesis from ethyl acetoacetate **41** of enantiomerically pure (N)-methanocarpa-2'-deoxyguanosine **51** using an enzymatic resolution.<sup>25</sup> *Reagents and conditions:* (a) (i) acrolein, LDA; (ii) TBDPSCl, imidazole; (b) TsN<sub>3</sub>, Et<sub>3</sub>N; (c) CuSO<sub>4</sub>, cyclohexane; (i) NaBH<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH; (ii) LiAlH<sub>4</sub>, Et<sub>2</sub>O (e) vinyl acetate, Lipase PS-C; (f) (NH<sub>4</sub>)HF<sub>2</sub>, DMF-H<sub>2</sub>O; (g) 2-acetamide-6-chloropurine, Ph<sub>3</sub>P, DEAD; (h) 2N HCl, THF, 80 °C.

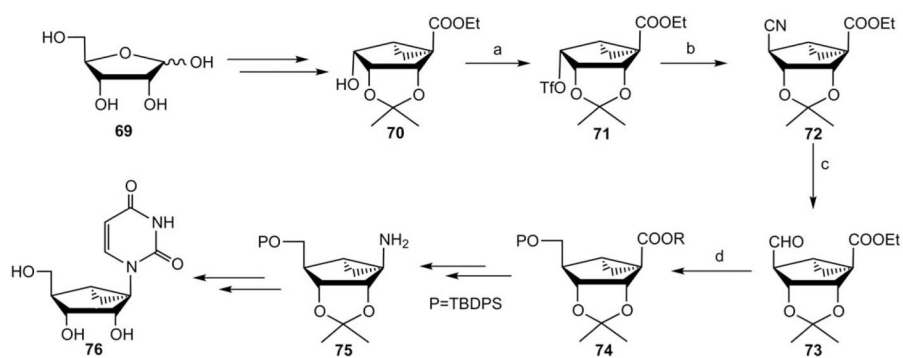
**Scheme 7.**

Synthesis of (*S*)-methanocarba-2'-deoxythymidine **57**, which has been utilized for enzymatic, nonreceptor targets.<sup>26</sup> *Reagents and conditions:* (a) (i) TMSBr, ZnBr<sub>2</sub>, MeOH; (ii) N-TBDMS, N-methylacetamide, DMF; (b) <sup>t</sup>BuOK, <sup>t</sup>BuOH; (c) KOH, EtOH; (d) (i) DPPA, Et<sub>3</sub>N, toluene, heat; (ii) BnOH, heat; (iii) H<sub>2</sub>, Pd/C, toluene; (e) (i) MeOCH=C(Me)C(O)NCO, CH<sub>2</sub>Cl<sub>2</sub>; (ii) 0.2N HCl/EtOH-H<sub>2</sub>O.



**Scheme 8.**

Synthesis from a *trans*-1,4-butenediol derivative **58** of racemic (*S*)-methanocarba-adenosine **67**.<sup>27</sup> *Reagents and conditions:* (a) PMBOCH<sub>2</sub>COOH, DCC, DMAP; (b) (i) LDA, THF; (ii) TMSCl, Et<sub>3</sub>N; (c) (i) carbonyldiimidazole, THF; (ii) LiCH<sub>2</sub>COOMe, THF; (d) TsN<sub>3</sub>, Et<sub>3</sub>N; (e) Cu(AcAc)<sub>2</sub>, cyclohexane; (f) NaBH<sub>4</sub>, MeOH-CH<sub>2</sub>Cl<sub>2</sub>; (g) CuSO<sub>4</sub>, cat. H<sub>2</sub>SO<sub>4</sub>, acetone.

**Scheme 9.**

Synthesis from a D-ribose **69** of enantiomerically pure (S)-methanocarpa-uridine **76**.<sup>28</sup>

*Reagents and conditions:* (a)  $\text{Tf}_2\text{O}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ; (b)  $\text{LiCN}$ , DMF; (c)  $\text{H}_2/\text{Pd}$ ,  $\text{H}_2\text{O}$ - $\text{AcOH}$ ; (d) (i)  $\text{NaBH}_4$ , MeOH; (ii)  $\text{TBDPSCl}$ , imidazole, DMF.