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New 2-aminoethylimidazole-based dicarboxylic acid receptor derived from cholestane

Jyoti Ramesh Jadhav, Md. Wasi Ahmad, Hong-Seok Kim *

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Republic of Korea

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ABSTRACT

A new facial amphiphile cholestane-based receptor **1** containing a 2-imidazolylethylamino moiety at the 3α and 7α positions of cholestane was synthesized. Recognition selectivity of the new receptor **1** with various dicarboxylic acids was assessed by ^{1}H NMR titration. Maleic acid showed the highest binding constant among all the tested acids ($K_a = 9.36 \times 10^4\ M^{-1}$).

During the last decade, many receptors for neutral molecules based on properly oriented hydrogen-bonding sites have been reported. In particular, numerous studies have been devoted to the design and synthesis of receptors to be used as sensing probes for dicarboxylic acids and dicarboxylate anions constituting important components of various metabolic, biological, and environmental processes.[1] To date, several receptors containing different functional groups for selective recognition of carboxylic and dicarboxylic acids have been reported.[2] More specifically, Hamilton and other research groups have designed and synthesized numerous receptors for dicarboxylic acids.[3,4] Receptors containing α-aminopyridine as a binding site and spacers, such as quinoline[5a] and triphenylamine[5b] have also been reported. In many of these receptors, the α-aminopyridine unit is located in a suitable position to bind the carboxylic acid. Challenging developments in this area have led to the development of a variety of host molecules for dicarboxylic acids, that are functionalized with various groups, for example, calix[4]arene,[6a] ferrocene,[6b] and thiourea-based[6c,d] systems. Thus, in designing a receptor for dicarboxylic acids, a number of valuable insights can be obtained from the vast related literature. First, the rigidity of the host molecule and the number of preferable binding sites for hydrogen-bonding interactions between the host and guest molecules have to be considered. Additionally, the distance between two binding sites within specific binding subunits needs to be considered.

Among the dicarboxylic acids, maleic acid is one of the most attractive targets owing to its central role in biology.[7a,b] Maleic acid, the *cis* isomer of fumaric acid, has long been known to be a potent inhibitor of enzyme systems in vitro: the inhibition of succinodehydrogenase and coenzyme activity of glutathione.[7c] It has also been used as an alternative method for bonding orthodontic brackets.[7d]

The design of a steroid-based receptor capable of selectively recognizing a variety of guests is of particular interest because of their rigid framework, facial amphiphilicity, and suitably oriented functional groups.[8] Recently, novel steroid-based receptors have been synthesized in this laboratory. These receptors contain urea and amide groups, recognized to act as pendant donors at different positions of bile acids and 5α-cholestane-based platforms for anions and have been evaluated by ^{1}H NMR titration.[9] Herein, a 5α-cholestane-based platform was chosen as a building block in the design of a receptor for dicarboxylic acids. This choice is based on the fact that this platform offers exactly the same bond length attachment of ligands at C3 and C7 in an axial manner, which is not possible using the same positions within the 5β-configuration.[10] The introduction of an axial amino group at C3 and C7 could be derivatized rapidly in and quantitatively by reductive amination of 3,7-diketosteroid.[9d] Thus a 5α-cholestane-based scaffold with a rigid structure, simple derivatization, and easy one-pot reductive amination at the 3 and 7 positions with various amino groups can be used as the building block for the construction of receptor molecules.

In this Letter, we report on the synthesis of a new 2-aminoethylimidazole receptor **1** bearing two binding imidazole units at the

* Corresponding author. Tel.: +82 53 9505588; fax: +82 53 9506594.
E-mail address: kimhs@knu.ac.kr (H.-S. Kim).

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C3 and C7 positions of 5α-cholestane; this receptor can be used for the recognition of dicarboxylic acids. To establish the role of both imidazole groups in the complex formation, an alternative 5α-cholestan-3α-imidazolylethylamino-7α-phenylamino receptor **2** (Fig. 1), in which one of the imidazole rings was replaced with a phenyl ring while keeping all the other groups fixed, is examined. The binding abilities of receptors **1** and **2** with various dicarboxylic acids were subsequently determined by ^{1}H NMR titration. In most of the receptors, the α-aminopyridine groups connected with different spacers were used as important hydrogen-binding sites for dicarboxylic acid recognition.[2–5] On the other hand, in the case of the imidazole receptor, its acidic H-2 proton was used for anion recognition.[11] The present study revealed that imidazole groups containing acidic H-2 protons and free –N atom (N-3) as binding sites were more suitable for the recognition of dicarboxylic acids. To the best of the authors' knowledge, this is the first synthetic receptor whose imidazole groups can be utilized for dicarboxylic acid recognition. This significant result was obtained owing to the better-defined substrate-binding sites, their reduced structural flexibility, and increased uniformity.

Imidazole receptor **1** was prepared by one-step reductive amination of 5α-cholestane-3,7-dione **3**[9d] with 1-(2-aminoethyl)imidazole[12] in the presence of NaBH(OEh)$_3$, whereas receptor **2** was synthesized by two-step reductive amination as shown in Scheme 1. The structure of receptors **1** and **2** were confirmed by ^{1}H and ^{13}C NMR and fast atom bombardment (FAB)-mass analysis.[13]

Owing to the poor solubility of dicarboxylic acids in $CDCl_3$, the binding properties of **1** with dicarboxylic acids were investigated by ^{1}H NMR titration in DMSO-d_6. In the ^{1}H NMR spectrum, we noted that the H-2 protons of both imidazoles had shifted considerably downfield from their original positions as compared to the other imidazole protons (H-4 and H-5). Significant downfield chemical shifts of all the imidazole protons of **1** clearly revealed the complexes formed with dicarboxylic acids. The ^{1}H NMR titration curves of **1** with various dicarboxylic acids are shown in Figure 2.

In the case of **1**, among the tested dicarboxylic acids that included oxalic, malonic, succinic, maleic, fumaric, phthalic, D- and L-tartaric acids, L-aspartic, and propionic acids, maleic acid showed the largest downfield shift of the imidazole H-2 protons (from δ 7.78 to 8.93 ppm ($\Delta\delta$ = 1.15 ppm)) upon the addition of 8 equiv proportions of maleic acid. The oxalic and malonic acids also caused significant downfield shifts of $\Delta\delta$ = 0.71 and 0.46 ppm, respectively, with respect to **1**. Furthermore, their association constant values were estimated to be comparable to that of other acids, as depicted in Table 1. However, all other acids were characterized by relatively small chemical shift changes ($\Delta\delta$ = 0.004–0.11 ppm) and association constant values were obtained by titration of **1**.

When **1** was titrated with fumaric acid, the chemical shift changes of the imidazole protons were negligible. Owing to the fact that a *trans*-ethene group was flanked by dicarboxylic acid groups that are *anti* to each other when dissolved in fumaric acid, the desirable free orientation of the carboxylic acid group toward the binding sites could not be achieved. However, *cis* geometry of

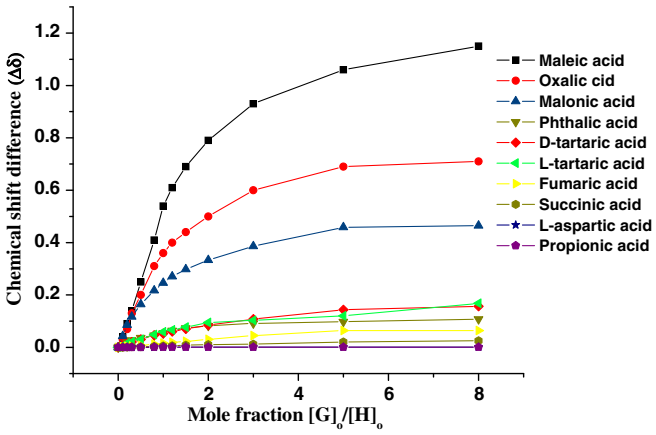


Figure 2. ^{1}H NMR titration curves of receptor **1** with various dicarboxylic acids dissolved in DMSO-d_6.

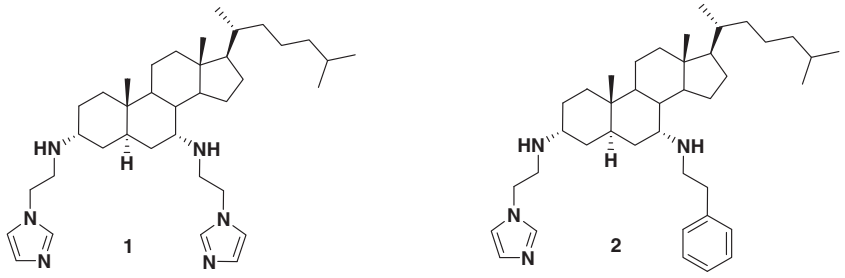
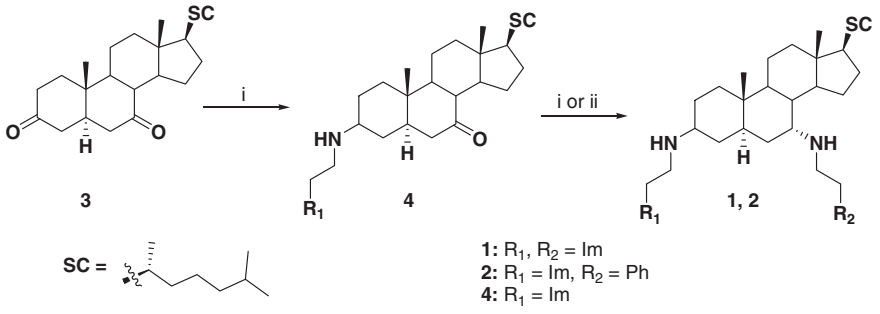


Figure 1. Structures of cholestane-based 2-aminoethylimidazole receptors **1** and **2**.



Scheme 1. (i) Amine, NaBH(OEh)$_3$, AcOH, THF, rt; (ii) amine, NaBH$_3$CN, AcOH, THF–MeOH 1:1, rt.

Table 1
Association constants (K_a) of receptor **1** with various dicarboxylic acids[a]

Carboxylic acid	Association constant (K_a)
Maleic acid	9.36×10^4
Oxalic acid	6.46×10^4
Malonic acid	2.46×10^4
L-Tartaric acid	2.56×10^4
D-Tartaric acid	2.63×10^4
Succinic acid	1.10×10^1
Phthalic acid	1.72×10^2
Fumaric acid	3.10×10^1
L-Aspartic acid	NC[b]
Propionic acid	NC

[a] Determined in a DMSO-d_6 at 298 K, [host] = 4.5×10^{-3} M, [guest] = 4.5×10^{-2} M. Errors were estimated to be ⩽10%.
[b] NC: not calculated.

the maleic acid makes it possible for the dicarboxylic acid groups to shift toward the binding sites of **1**. During the complexation of **1** with maleic acid, both acidic sharp H-2 protons of **1** gave rise to a broad peak with a comparatively large downfield shift, implying that both acidic imidazole protons contributed to the complex formation. Figure 3 shows the partial ^{1}H NMR spectra of **1** before and after the successive addition of maleic and fumaric acid. It is worth noting that **1** binds selectively to maleic acid rather than to isomeric fumaric acid. Oxalic acid and malonic acid also showed a comparatively large chemical shift difference with respect to other dicarboxylic acids owing to the strong binding of the dicarboxylic acid's –OH group with the N3 of both imidazole pendants. This comparison of the differences in the chemical shift and association constant of **1** with respect to a variety of dicarboxylic acids revealed that it is a suitable receptor for undersized dicarboxylic acids.

Studying the binding properties of **1** with phthalic and succinic acids led to a unique result. The spatial hindrance caused by the phenyl groups of phthalic acid seems to have been out of reach for the two pendants of **1** that interacted only with the carboxylic groups. Because of the increase observed in the bond length between the two methylene groups (1.52 Å) connecting the two carboxylic groups and the orientation of the hydrogens of the methylene group in succinic acid, the latter may not have been viable in terms of binding with the imidazole groups. The response of **1** to chiral dicarboxylic acids, such as D- and L-tartaric acids was also worth investigating, but a comparative study of these two acids did not offer distinguishable data. The chemical shift differences and binding constant values obtained for both stereoisomers are nearly the same, as depicted in Table 1. Lastly, the chemical shift differences obtained for aspartic and propionic acids were so small that it was not possible to calculate the corresponding binding constants ($\Delta\delta$ <0.01 ppm).

The role of both imidazole groups could be analyzed by titrating **2** with maleic acid. More specifically, receptor **2** titrated with maleic acid showed a very small chemical shift difference of the H-2 proton ($\Delta\delta$ = 0.05 ppm), which might have been due to one-side binding of dicarboxylic acid to the imidazole ring. On the other hand, negligible chemical shifts were observed in the case of the protons of the other arm of **2**. The comparison of **1** and **2** provided sufficient evidence that the two imidazole groups are essential for the selective binding of dicarboxylic acids. The changes observed in the partial ^{1}H NMR spectra of **2** after the addition of 1 equiv of maleic acid are shown in Figure S-1. The significantly lower association constant K_a value (1.22×10^2 M^{-1}) calculated for **2** with respect to the H-2 proton of imidazole was comparable to the value obtained in the case of binding maleic acid with **1**. Thus, the large downfield shifts of H-2 protons and the significant shifts of the H-4 and H-5 protons of both imidazole rings in **1** clearly show that both O–H and C=O oxygens of dicarboxylic acids participated in the binding process. The direct hydrogen binding of O–H in the carboxylic acid with the N-3, and C=O oxygen with the H-2 protons of imidazoles through =C–H···O=C and =N···H–O bonds could potentially clarify the shifting of all imidazole protons. This verifies that 5α-cholestane bearing axially two 2-aminoethylimidazole pendants at the 3 and 7 positions is a good receptor for dicarboxylic acid recognition. The association constants were calculated from the chemical shift changes of the H-2 protons of imidazoles by using the WinEQNMR2 software,[14] which suggested a 1:1 complex formation. The results are summarized in Table 1. The 1:1 stoichiometry of the maleic acid bound with **1** was further confirmed by its Job's plot (see Fig. S-2).

The selectivity of **1** toward dicarboxylic acids was also evaluated by treating **1** with F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, $CH_3CO_2^-$, and $HP_2O_7^{-3}$ (2 equiv) in the form of tetrabutylammonium salts, as **1** contains two acidic imidazole protons. None of these anions induced any changes in the chemical shift of the imidazole H-2 proton. This behavior could be attributed to the distance between the

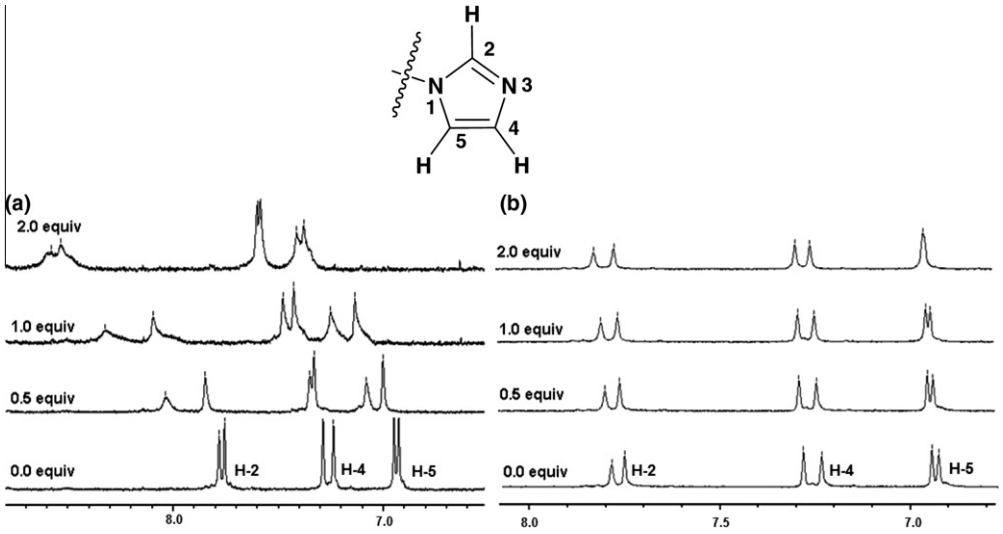


Figure 3. Partial ^{1}H NMR spectra of **1** after successive addition of (a) maleic acid and (b) fumaric acid in DMSO-d_6.

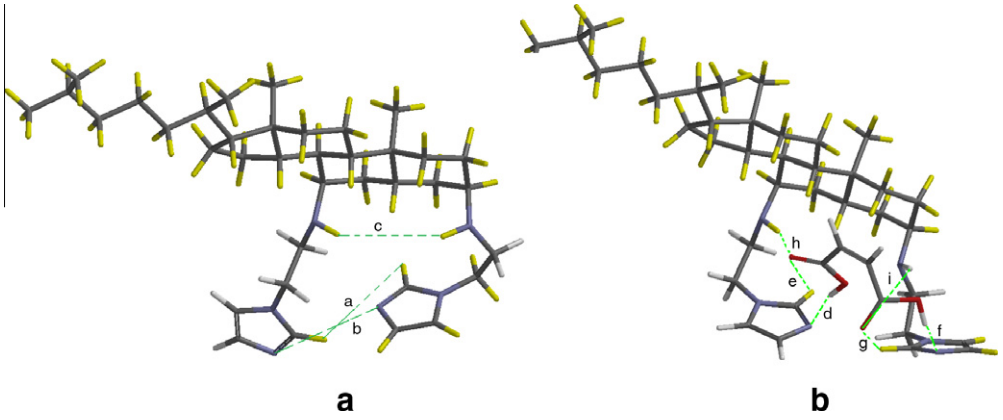


Figure 4. Energy-minimized structures of (a) **1** and (b) **1** treated with maleic acid.

two binding subunits and the orientation of the two imidazole pendants. In other words, comparing the response of **1** to all different acids and anions confirmed its relatively rigid structure and high binding affinity for dicarboxylic acids.

In order to better understand the nature as well as the binding mode of **1** with maleic acid, we calculated the energy-minimized structure. For this purpose, the geometries of all compounds involved were subjected to optimization at the Hartree-Fock 3-21G (*) level using Spartan 04 software.[15] It is evident from the optimized geometry of the complex of **1** shown in Figure 4 that the guest was bound strongly in the open cleft involving a large number of hydrogen-bonding interactions. The distances between the two H-2 and N-3 atoms of imidazole and 3,7-amino N–H in the uncomplexed structure were estimated to be equal to $a = 2.82$, $b = 4.98$, and $c = 3.62$ Å, as shown in Figure 4a. However, after complexation with maleic acid, these values changed to 6.90, 6.53, and 5.30 Å, respectively, thus providing an open cavity for the guest molecule.

The distances for the hydrogen bond interactions of **1** with maleic acid are indicated by the dotted lines in Figure 4b ($d = 1.78$, $e = 3.01$, $f = 1.69$, $g = 2.62$, $h = 2.10$, and $i = 3.18$ Å). As predicted by ^{1}H NMR titration both the O–H and the –C=O groups of dicarboxylic acid formed hydrogen bonds with the imidazole-binding sites as well as the 3,7-amino N–H protons. However, it was not possible to determine the chemical shift values by NMR titration because of the assimilation of N–H protons in the up field area. Nonetheless, similar to α-aminopyridine and urea group receptors, properly inclined 2-aminoethylimidazole groups are also attractive building blocks for dicarboxylic acids.

In conclusion, a new 5α-cholestane-based 2-aminoethylimidazole receptor **1** was synthesized in high yield. This new receptor showed, through hydrogen-bonding interactions, relatively high selectivity toward maleic acid. The key feature of **1** designed to bind with dicarboxylic acids is the two axially oriented 2-aminoethylimidazole pendants located at the C3 and C7 positions of cholestane that act both as spacers and as binding units.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.030.

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13. Compound **1**: $[\alpha]_D$ −17.42 (*c* 0.06), TLC R_f 0.68 (CH_2Cl_2–MeOH–NH_4OH 15:2:0.5); ^{1}H NMR ($CDCl_3$) δ 0.59 (s, 3H, 18-CH_3), 0.73 (s, 3H, 19-CH_3), 0.84 (d, $J = 6.8$ Hz, 3H, 26-CH_3), 0.85 (d, $J = 6.6$ Hz, 3H, 27-CH_3), 0.87 (d, $J = 6.8$ Hz, 3H, 21-CH_3), 2.51 (bs, 1H, 7β-H), 2.66 (m, 1H, 3β-H), 2.85 (bs, 1H, N–H), 2.95 (m, 4H), 4.01 (m, 2H), 4.15 (t, 2H, $J = 6.2$ Hz), 6.96 and 6.98 (s, 1H, Im H-5), 7.01

and 7.03 (s, 1H, Im H-4), 7.57 and 7.68 (s, 1H, Im H-2); ^{13}C NMR ($CDCl_3$) δ 11.2, 12.2, 19.0, 21.0, 22.9, 23.2, 24.0, 24.3, 24.9, 28.4, 32.2, 32.4, 32.5, 32.6, 36.2, 36.5, 36.7, 39.2, 39.7, 39.9, 43.0, 46.1, 46.4, 47.9, 48.6, 49.4, 51.0, 51.2, 54.4, 55.6, 56.5, 119.5, 119.7, 128.2, 129.6, 137.9, 138.7; FAB-mass Calcd for $C_{39}H_{67}N_6$: 591.5224. Found: m/z 591.5111 $(M+H)^+$. Compound **2**: $[\alpha]_D$ +14.30 (c 0.06), TLC R_f 0.67 (CH_2Cl_2–MeOH–NH_4OH 15:2:0.5); ^{1}H NMR ($CDCl_3$) δ 0.62 (s, 3H, 18-CH_3), 0.79 (s, 3H, 19-CH_3), 0.89 (d, J = 6.8 Hz, 3H, 26-CH_3), 0.90 (d, J = 6.6 Hz, 3H, 27-CH_3), 0.91 (d, J = 6.6 Hz, 3H, 21-CH_3), 2.64 (m, 2H), 2.88 (m, 4H), 3.01 (m, 1H, 7β-H), 3.04 (bs, 1H, N–H), 3.62 (m, 1H, 7β-H), 3.77 (m, 1H, 3β-H), 4.07 (m, 2H), 7.01 (s, 1H, Im H-4), 7.06 (s, 1H, Im H-5), 7.21 (bs, 1H, Ph H-3), 7.23 (d, 2H, J = 3.6 Hz, Ph H-1), 7.29 (m, 2H, Ph H-2), 7.59 (s, 1H, Im H-2); ^{13}C NMR ($CDCl_3$) δ 11,3, 12.1, 19.0, 21.1, 22.9, 23.2, 23.7, 24.2, 26.3, 28.4, 31.8, 32.7, 33.1, 36.1, 36.5, 36.9, 38.9, 39.2, 39.7, 43.2, 46.5, 47.8, 48.1, 49.5, 50.7, 52.6, 55.9, 56.4, 61.8, 73.0, 119.5, 126.7, 128.9, 129.2, 129.5, 137.8, 140.0; FAB-mass Calcd for $C_{39}H_{67}N_6$: 601.5083. Found: m/z 601.5088 $(M+H)^+$.

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15. Energy minimization was carried out using Spartan 04 for Windows (Wavefunction: Irvine, CA).