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Triphenylamine-based receptor for selective recognition of dicarboxylates

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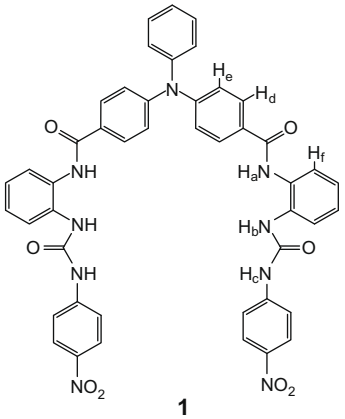
ABSTRACT

A new triphenylamine-based receptor **1** has been designed and synthesized for the recognition of aliphatic dicarboxylates of various chain lengths. This receptor has been designed to utilize an amide–urea conjugate for binding dicarboxylates. The receptor **1** is found to bind the dicarboxylates with moderate binding strength under a semi rigid, propeller shaped, fluorescent triphenylamine spacer. The binding behavior was studied in CH_3CN using ^1H NMR, fluorescence and UV–vis spectroscopic methods. The conformational behavior of **1** and its complexation modes have been investigated using classical and quantum mechanical theoretical methods. The receptor is found to be selective for long chain suberate.

Much attention has been paid recently to the development of synthetic molecular receptors for anions because of the fundamental role these anions play in a wide range of chemical, environmental, and biological processes.[1–3] The design and synthesis of artificial receptors that are capable of affecting the selective and sensitive binding of anionic species through visible, electrochemical, and optical responses has been the focus of numerous reports in recent times.[4] Dicarboxylates are important target anions for recognition and sensing owing to their critical role in numerous metabolic processes.[5,6] During the last decade, dicarboxylate anion binding by various hydrogen bonding receptors was demonstrated. In general, most of these receptors consist of urea/thiourea,[7,8] imidazolium cation,[9] guanidinium ion[10,11] ,etc., as the hydrogen bonding synthons placed onto various fluorophores. Gunnalangsson[12] et al. reported a neutral and fluorescent PET sensor for glutarate while He and co-workers[13] developed fluorescent sensors for adipate. Mei and Wu reported the sensitive detection of pimelate using a naphthalene-containing sensor molecule.[14] Liu and co-workers have reported cholic acid-based fluorescent sensors for glutarate and long chain suberate and sebacate.[15] A related recent report on dinuclear Eu(III) bismacrocyclic sensors for malonate is interesting due to the unique properties of lanthanides.[16] We have also recently reported the selective sensing of 1,4-phenyldiacetate as well as glutarate by anthracene-based ureidopyridyl[17] and *trans*-pyridylcinnamide receptors,[18] respectively. Thus, although significant progress in dicarboxylate anion recognition has been made, there is a continued interest in making new fluorescent receptors for dicarboxylates. Triphenylamine is a propeller-shaped fluorescent probe, which has been proven previously by us to be effective in reporting recognition events.[19] Using the fluorescence properties of triphenylamine we have recently designed and synthesized receptors with conformationally well-defined V-shape geometries for size-selective recognition of dicarboxylic acids[20] and dicarboxylates.[21]

We wish to report here the further design and synthesis of a new triphenylamine-based receptor **1** using an *o*-phenylenediamine binding site, composed of an amide–urea conjugate, for selective recognition of aliphatic dicarboxylates of various chain lengths. *ortho*-Phenylenediame is a well-established motif in anion recognition.[22]



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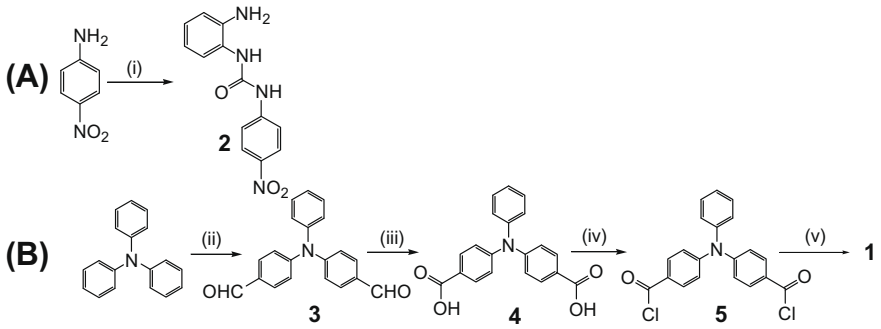

Scheme 1. Reagents and conditions: (A) (i) (a) triphosgene, Et_3N/dry DCM, 30 min; (b) excess *o*-phenylenediamine, dry DCM, 3 h, 53% yield; (B) (ii) $POCl_3$, DMF, reflux, 8 h, 56% yield; (iii) (a) $KMnO_4$, acetone–water, 4 h; (b) dil HCl, 72% yield; (iv) oxalyl chloride, DMF, dry DCM, 15 h, 95% yield; (v) **2**, Et_3N/dry THF–DMF, 4 h, 49% yield.

Receptor **1** was synthesized according to Scheme 1. Reaction of *o*-phenylenediamine with *p*-nitrophenyl isocyanate, which was obtained from the reaction between *p*-nitroaniline and triphosgene in the presence of Et_3N in dry CH_2Cl_2, gave the compound **2**. Subsequent coupling of **2** with triphenylamine diacid chloride **5** (obtained from the reaction of diacid **4** with oxalyl chloride in dry CH_2Cl_2 in the presence of catalytic amount of DMF) in dry THF and DMF mixture solvent yielded the desired receptor **1** in 49% yield as light yellow solid. Triphenylamine diacid **4** was accomplished from triphenylamine via formylation[23] followed by oxidation using $KMnO_4$. All the compounds were characterized by ^1H NMR, ^{13}C, FTIR, mass, and UV–vis spectroscopic techniques.

The dicarboxylate anion binding study of the receptor **1** was performed by ^1H NMR, fluorescence, and UV titration experiments. The binding ability of **1** was initially established by ^1H NMR. To the receptor solution of **1** in $CDCl_3$ containing 0.8% CD_3CN, aliphatic dicarboxylates of various chain lengths were added as their tetrabutylammonium salts in 1:1 stoichiometries. In the presence of the dicarboxylates, the amide proton H_a and urea protons H_b and H_c underwent downfield shift ($\Delta\delta_{NHa}$ = 1.07–2.73, $\Delta\delta_{NHb}$ = 0.76–2.88, $\Delta\delta_{NHc}$ = 1.79–2.24). Note that in the presence of malonate, the more basic of the dicarboxylates studied, deprotonation of the acidic urea proton H_a occurred resulting in the disappearance of the corresponding peak. Figure 1 demonstrates the change in ^1H NMR of **1** in the presence of an equivalent amount of malonate, glutarate, and suberate. The large downfield shift of the amide and urea protons in **1** demonstrated the involvement of the *o*-phenylenediamine-based receptor sites in complexation.

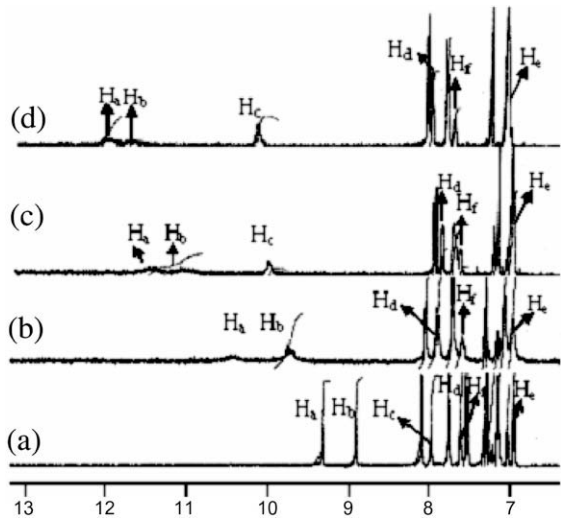

Figure 1. (a) Partial ^1H NMR (400 MHz, $CDCl_3$ containing 0.8% CD_3CN) of **1** ($c = 1.88 \times 10^{-3}$ M), in the presence of equivalent amount of (b) malonate, (c) glutarate, and (d) suberate (for identification of the labeled protons see structure **1**).

To ascertain the sensitivity and selectivity, we studied the fluorescence and UV–vis behaviors of **1** in CH_3CN containing 0.4% DMSO in the absence and presence of tetrabutylammonium dicarboxylate salts of malonate, succinate, glutarate, adipate, pimelate, and suberate. Receptor **1,** ($c = 6.55 \times 10^{-5}$ M) when excited at 350 nm in CH_3CN containing 0.4% DMSO, showed an emission band at 438 nm likely corresponding to excitation and emission of the triphenylamine moiety. Upon gradual addition of the dicarboxylate anions, the fluorescence emission decreased steadily up to a 1:1 stoichiometry and then increased gradually thereafter. These findings were more pronounced in case of adipate, glutarate, pimelate, and suberate and were least pronounced in case of malonate and succinate, the short chain analogs (see Supplementary data). Figure 2a and b shows the change in the emission spectra of **1** in the presence of malonate and suberate, respectively. Figure 2c represents the change in emission of **1** with guest concentration. At this time we are uncertain as to the nature of the fluorescence increase in the presence of excess nonflourescent anions; however we presume this may be due to subtle changes in receptor conformation. Theoretical studies are planned to probe this effect further.

Figure 3 displays the titration curves for **1** with the various dicarboxylates, and the break of the curves at [G]/[H] = 1 confirms a 1:1 host–guest stoichiometry of the complexes. The anion-induced decrease in the emission of **1** may be attributable to the activation of a PET process occurring during binding; theoretical studies are currently underway to explore this possibility.

Simultaneous UV–vis titration experiments of the receptor **1** with the same guests as mentioned above were carried out in the same solvent under controlled conditions. The absorption at 342 nm was gradually decreased resulting in a small red shift ($\Delta\lambda$ = 7–9 nm) as titration progressed. This was found to be true for all the dicarboxylates irrespective of their chain lengths (see Supplementary data). For instance, Figure 4 illustrates the titration spectra of **1** upon gradual increase in the concentration of suberate. The isosbestic points at 266 and 340 nm (see the inset of Fig. 4) in the UV–vis spectra indicate host–guest complexation. The red shift of the absorption peak of **1** at 342 nm upon increase in guest concentration signifies an increasing noncovalent interaction of **1** with the carboxylate motif of the guest.

The driving force for this interaction is most likely the acidity of the urea protons and the flexibility of the binding arms of **1**. The sharp nonlinear nature of the titration curves and the break at [G]/[H] = 1 also corroborate the 1:1 stoichiometry of the complexes (Fig. 5). This is also shown in the Job plots[24] in Figure 6. In this regard, the suggested mode of host–guest interaction is illustrated in Figure 7.

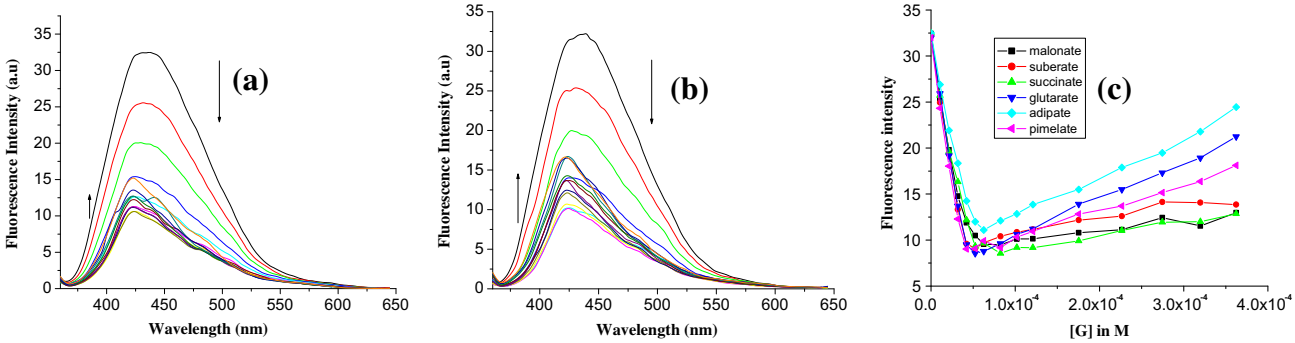

Figure 2. Change in fluorescence intensity of **1** ($c = 6.55 \times 10^{-5}$ M in CH_3CN containing 0.4% DMSO) with (a) malonate, (b) suberate (as tetrabutylammonium salt) at 438 nm, and also (c) the change in emission of **1** with guest concentration.

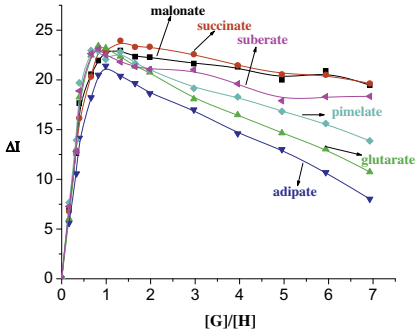

Figure 3. Titration curve of receptor **1** ($c = 6.55 \times 10^{-5}$ M in CH_3CN containing 0.4% DMSO) from fluorescence study (measured at 438 nm).

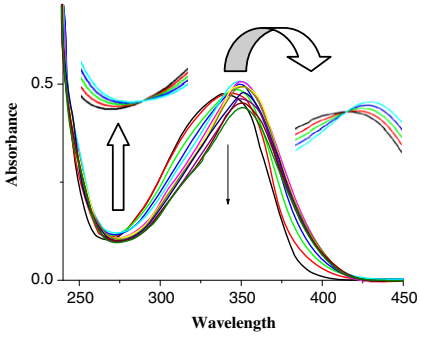

Figure 4. Change in absorbance of **1** ($c = 1.31 \times 10^{-5}$ M in CH_3CN containing 0.4% DMSO) upon gradual addition of tetrabutylammonium salt of suberic acid.

Interestingly, a gradual increase in the concentration of dicarboxylate anions (malonate, succinate, glutarate, adipate, pimelate, and suberate) produced no color change of the acetonitrile solution (containing 0.4% DMSO) of receptor **1**. However, when high concentrations ($c = 2.83 \times 10^{-3}$ M) of dicarboxylates of different chain lengths were added to a DMSO solution of **1**, the color of the solution changed dramatically. In the presence of an equivalent (1:1) amount of the guests, the color of the solution of receptor **1** was light in nature (Fig. 8a). However, when an excess of guest was added (4 equiv) to the solution of **1**, the color intensified. Particularly in the presence of excess malonate, the color of the solution of **1** changed from light yellow to deep yellow and finally to red, which could be observed by the naked eye (Fig. 8b). It is possible that the origin of the color change in the receptor solution upon complexation could be ascribed to a charge-transfer interaction between the electron rich amide–urea (donor unit) and the electron deficient *p*-nitrophenyl moiety.[25] We hypothesize that complexa-

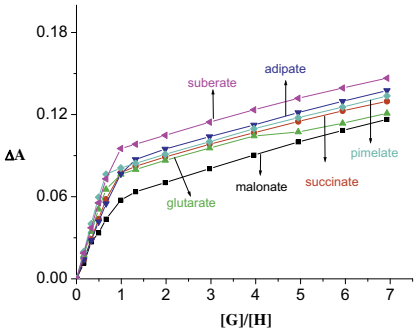

Figure 5. Titration curves of receptor **1** ($c = 1.31 \times 10^{-5}$ M in CH_3CN containing 0.4% DMSO from UV–vis titration (measured at 320 nm) upon addition of tetrabutylammonium salts of the dicarboxylates.

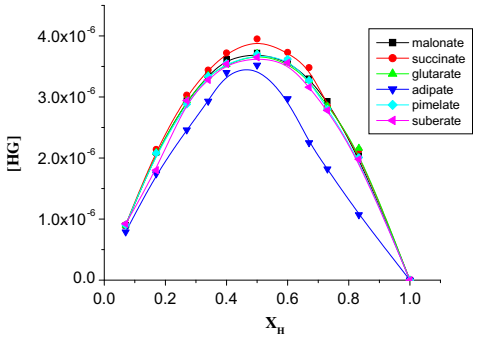

Figure 6. Job plot of receptor **1** with the dicarboxylates.

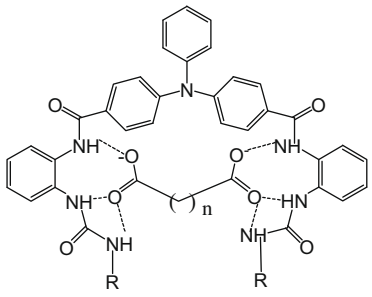

Figure 7. Suggested hydrogen bonding structure of **1** with dicarboxylates.

Table 1
Binding constant values of **1** with the guests in CH_3CN containing 0.4% DMSO

Guests[a]	Log K[b]	
Malonate	5.20 ± 0.2438	R = 0.9939
Succinate	6.60 ± 0.7209	R = 0.9728
Glutarate	6.53 ± 0.4245	R = 0.9939
Adipate	6.6 1 ± 0.3270	R = 0.9902
Pimelate	6.87 ± 0.4917	R = 0.9869
Suberate	7.62 ± 0.4287	R = 0.9903

[a] Tetrabutylammonium salts were taken.
[b] Binding constants measured at 320 nm.

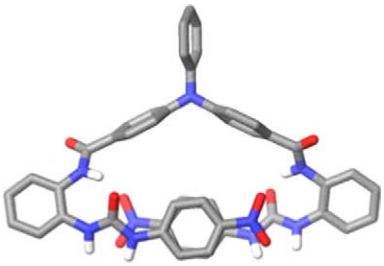

Figure 9. Lowest energy structures and hydrogen bonding patterns found for **1** in GBSA (chloroform) using the OPLS2005 force field.

tion with the electron-rich dicarboxylates increases the electron density around the amide–urea binding site and this facilitates intramolecular charge transfer. Particularly, in the presence of excess malonate, the most basic of all the dicarboxylates included in this study, deprotonation of the urea proton H_c in **1** (likely) occurs (vida supra) enhancing such charge transfer and resulting in the sharpest, most intense color change. Such anion-triggered deprotonation of neutral NH hydrogen bond donor groups in anion receptors in organic solution is well documented.[26] However, upon addition of methanol to the individual solutions of **1** containing dicarboxylate anions in DMSO, the color of the solution discharged immediately and returned to the initial color of the receptor solution. This indicated the reversible nature of the complexation.

In order to realize the binding selectivity of the open cleft of **1** we determined the binding constant values[27] by UV method (Table 1). We did not use fluorescence titration data for determination of binding constant values due to decrease followed by an increase in emission of **1** upon titration. As can be seen from Table 1, the receptor **1** shows higher binding for long chain dicarboxylates and the cleft is selective for suberate in the present study.

A conformational analysis of **1** was performed using the LM:MC method on the OPLS2005/GBSA($CHCl_3$) potential energy surface (see Supplementary data).[28] A 3.0 kcal/mol energetic cut off was chosen in order to focus on those conformations most likely to be populated at room temperature. The ensemble of low energy structures is well represented by the global minimum energy structure (Fig. 9). These results suggest that conformers of **1** adopt triangular shapes containing well-defined binding pockets that can accommodate the dicarboxylate guests for which they are intended. Similarly, full conformational searches of **1** in the presence of each dicarboxylate guest were also performed. To verify the molecular mechanics result, we also subjected the global minimum energy conformer of each complex to unrestrained quantum mechanical (QM) minimization using the B3LYP/6-31G*/SCRF-PB(chloroform) methodological treatment.[29] Receptor **1** was originally designed to hydrogen bond to the guests and the quantum-minimized structures reveal that the host is indeed interacting strongly with the guests and is flexible enough to accommodate the guests even as the guests grow in size. All guests bind to **1** in the trans conformation with significant hydrogen bonding interactions between the carboxyl end groups of the guests and the amides of each host. Upon complexation, the guest can bring the two receptor arms closer together creating a tighter binding cavity. As can be seen in Figure 10, one of the nitrophenyl arms twists back to the other side of the molecule forming a Z-shaped structure but with hydrogen bonding still connecting the guest to the arm. For **1** with suberate, the arm wraps back around to form a U-shaped structure again with extensive hydrogen bonding keeping the guest bound to the receptor.

Assuming a 1:1 stoichiometry theoretical binding enthalpies were computed and shown to vary depending on the solvent type used (Table 2). In vacuum, all complexes of **1** displayed favorable binding interactions and showed a strong trend that as the guests increase in size, binding energy decreases in a relatively linear fashion. Computations in chloroform were in the best agreement with the experimental binding energies shown in Table 1. Within the binding energies of **1** in chloroform with various guests, there is a slight preference for binding to suberate and this is reflected in the experimental data as well. Calculations in water showed no definitive trends of any kind, with binding affinities taking on both favorable and unfavorable values, scattering about zero kcal/mol.

In conclusion, we have designed, synthesized, and studied hydrogen bonding interactions of a new triphenylamine-based receptor **1** with aliphatic dicarboxylates of different chain lengths. The receptor binds dicarboxylates at the charge neutral sites with concomitant decrease in emission and shows selectivity for long chain suberate in CH_3CN. Complexation induces a color change in the DMSO receptor solution that is observable with the naked eye, particularly for malonate and suberate guests. A conformational analysis shows that the receptor adopts a triangular shape with a well-defined binding pocket. The quantum-minimized structures reveal that the receptor is indeed interacting strongly with the guests and are flexible enough to accommodate the dicarboxylates even as they grow in size. All guests bind to the receptor with significant hydrogen bonding interactions between the

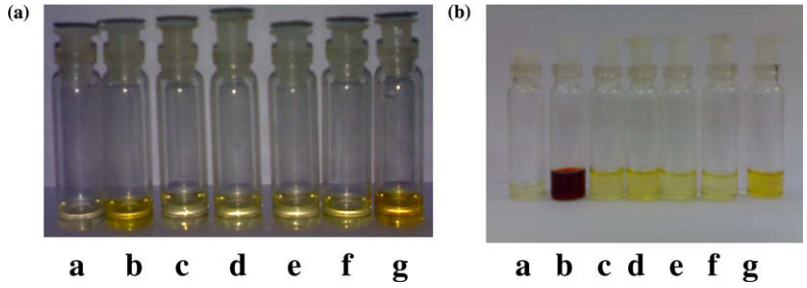

Figure 8. Change in color of the receptor solution of **1** ($c = 2.83 \times 10^{-3}$ M) in the presence of equivalent amount of dicarboxylates (a) and 4 equiv amounts of dicarboxylates (b) [a: receptor **1**, b: with malonate, c: with succinate, d: with glutarate, e: with adipate, f: with pimelate, and g: with suberate].

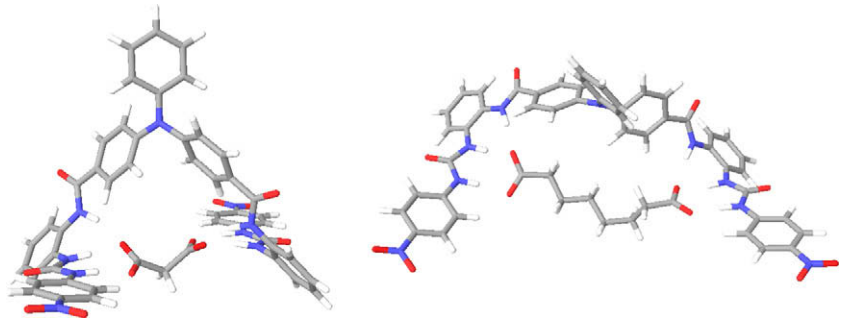

Figure 10. Representative B3LYP/6-31G* geometry optimized structures of **1** in chloroform. Solvent effects were included in the optimization using the self-consistent reaction field (SCRF) model and the Poisson–Boltzmann (PB) solver.

Table 2
B3LYP/6-31G* binding enthalpies (kcal/mol) for receptor **1**

	ΔH(vacuum)	ΔH($CHCl_3$)	ΔH(H_2O)
Malonate	−154.3	−55.5	−8.2
Succinate	−124.5	−49.5	−0.1
Glutarate	−125.1	−50.6	7.5
Adipate	−88.9	−45.9	3.8
Pimelate	−88.9	−40.1	4.8
Suberate	−144.7	−58.4	−16.4

Solvent effects were included in the optimization using the self-consistent reaction field (SCRF) model and the Poisson–Boltzmann (PB) solver.

carboxyl end groups of the guests and the *o*-phenylenediamine of the receptor. Theoretical binding energies are in good agreement with experimental data and suggest that receptor **1** binds the dicarboxylates most strongly and shows a slight preference for long chain suberate.

Acknowledgments

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Supplementary data

UV and fluorescence titration results, compound characterization data, binding constant curve, LM:MC conformational search results on the OPLS2005/GBSA(water) surface of 1 in vacuum, GBSA(water) and GBSA(chloroform) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.021.

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