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Triazole-based chromogenic and non-chromogenic receptors for halides

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ABSTRACT

We designed and synthesized a series of triazole-based receptors for anion recognition. Our studies demonstrated that an amide-linked triazole unit is a promising moiety for anion recognition. We synthesized various chromogenic and non-chromogenic receptors based on this moiety. Receptor **11** binds very strongly ($K = 102{,}750\ M^{-1}$) to fluoride. Receptor **18** changes color from faint yellow to orange upon binding to fluoride.

The design of anion receptors is an area of intense research interest, owing to their biological, medical, and chemical applications. Anions and cations are important players in living systems and therefore their transport across the cell membrane has high therapeutic significance.[1] Synthetic ligands with cation-binding properties are common, but less effort has been devoted to the design and synthesis of anion receptors, in spite of their significance and potential applications.[2] For example, a defect in chloride ion transport leads to cystic fibrosis; synthesized anion receptors could contribute to a cure for this disease.[3] Fluoride ions are commercially used in toothpaste industries; excess fluoride in the body can lead to fluorosis.[4] Chemists are interested in the design of anion receptors and have produced novel receptors with many intricate structures.[5] These receptor molecules display good binding ability and selectivity for anions.[6]

There are several positively charged synthetic anion receptors. Their binding efficacy is mainly due to Coulomb interactions that contribute to the attractive force.[7] Neutral receptors bind anions through interactions weaker than Coulomb interactions. Therefore, preorganization and the introduction of several binding sites are the salient features of neutral anion receptor design. The use of non-conventional H-bonding moieties is an additional advantage in the design of anion receptors. The crystallographic evidence of CH···X (X = N, O) hydrogen bonds was first proposed by Taylor and Kennard in 1982.[8] A number of studies later demonstrated their existence, after notable developments in crystal engineering.[9] In recent years, the design of receptors that use non-conventional hydrogen bonding interactions has gained importance. CH···X hydrogen bonding is an additional attractive interaction that chemists can employ in isolation or with other attractive interactions in the design of receptors.

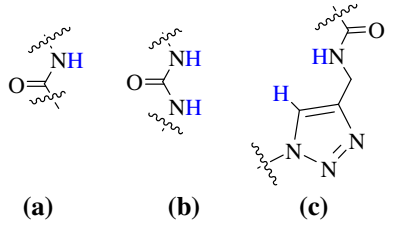

Figure 1. Comparison of anion binding motifs (a) amide; (b) urea and; (c) amide-linked triazole unit. The colored protons are the potential hydrogen bond donors.

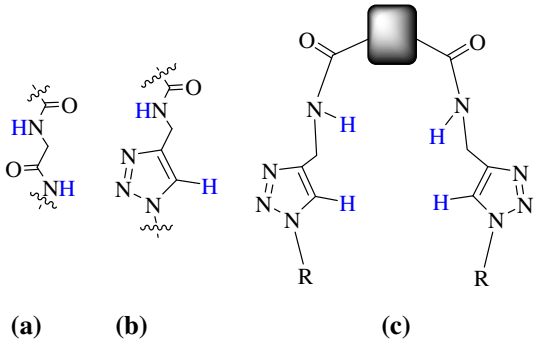

Figure 2. Comparison of two peptide linkages with an amide-linked triazole. The trans arrangement of hydrogen bond donors (a and b). Co-facially oriented amide-linked triazole on a scaffold (c).

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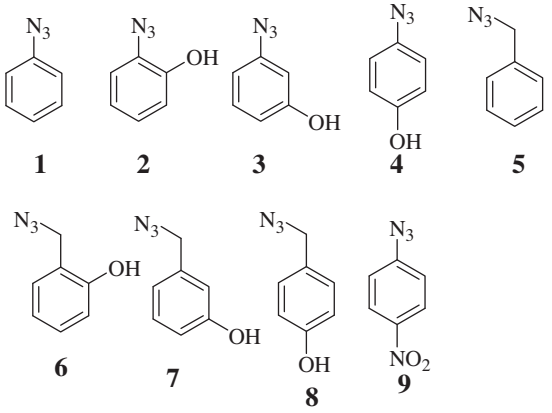
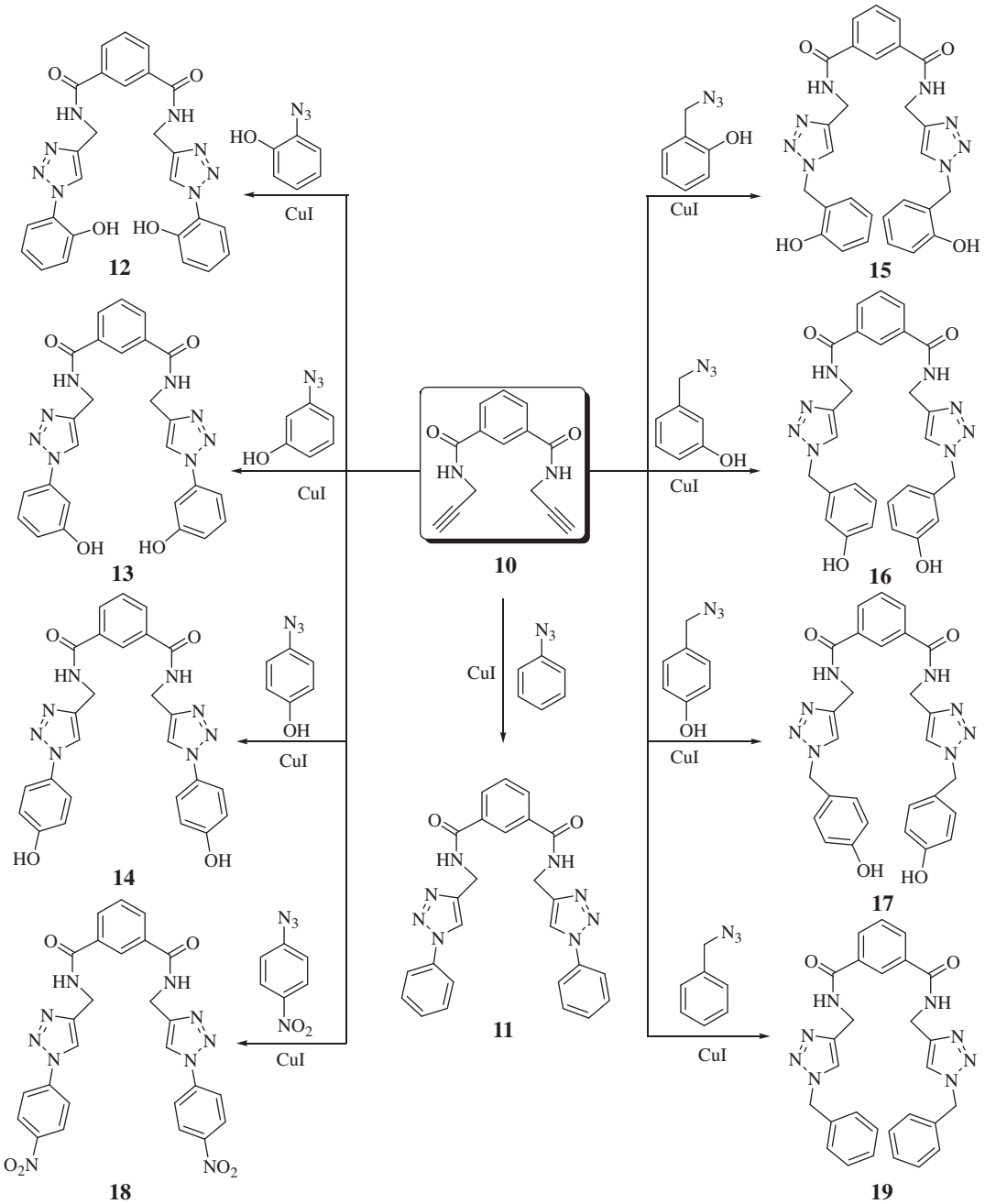


Figure 3. Structure of various azides.

Herein, we report the design and synthesis of anion receptors with remarkable selectivity and binding affinity. Receptors with selectivity for spherical anions like halides are mainly based on cavity size. A cavity decorated with a variety of H-bond donors may show selectivity. Conventional hydrogen bond donors (e.g., amide NHs and urea NHs) are used in typical receptor designs.[10] Urea moieties bind anions, but in most cases fluoride binding involves proton transfer.[11] The use of triazole in the design introduced rigid geometry, as well as an acidic CH capable of H-bonding.[12] Triazole is an excellent amide bond mimic; therefore, we hypothesized that a triazole-amide link would be similar to two consecutive peptide linkages (Fig. 1). Co-facially oriented amide-linked triazole places the H-bond donors on one face and thus is ideal for anion binding (Fig. 1c). A scaffold that can arrange two co-facially orientated amide-linked triazole moieties so that they face each other will favor better binding (Fig. 2).



Scheme 1. Synthesis of triazole-based receptors **11**–**19**.

We envisioned that a rigid phenyl ring with a 1,3-substitution could accommodate spherical anions. The cavity generated as a result of functionalization at the 1,3-positions could be further decorated with H-bond donors. The amide-linked triazole moiety on the 1,3-positions of the phenyl ring could thus serve as an ideal motif for anion recognition.

The dialkyne **10** was synthesized by reacting isophthaloyl chloride and propargyl amine. It was further reacted with a series of azides **1–9** (Fig. 3) to provide the amide-linked triazole receptors **11–19** (Scheme 1). Azides **6–8** were synthesized by reacting the corresponding benzyl alcohol with triphenyl phosphine and sodium azide.[13] The aryl azides **1–4** and **9** were synthesized from the corresponding amino compound by reacting with $NaNO_2$/HCl, by the formation of diazonium salt as the intermediate. The diazonium group was displaced with an azide nucleophile by the reaction with sodium azide.[14] This was completed in a single step and the yields were ~75–90%. These azides were reacted with dialkyne **10** to provide good yields (~80–90%) of the final triazole-based receptors **11–19**.

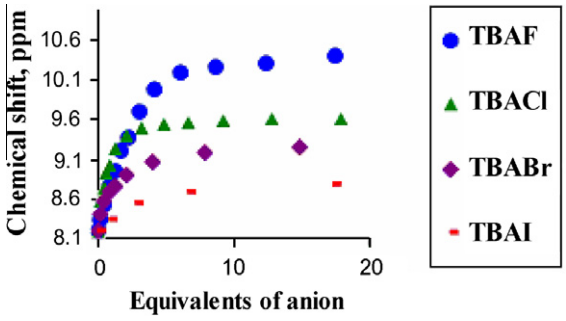


Figure 4. Chemical shift changes of the aromatic proton in the ^{1}H NMR spectrum (300 MHz, DMSO-d_6 + $CDCl_3$) of **18** as a result of addition of TBAX.

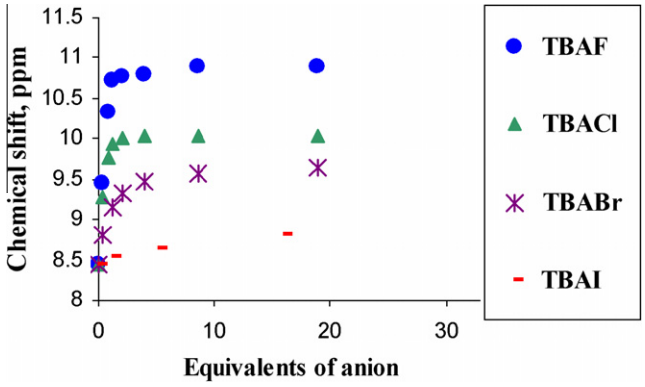


Figure 5. Chemical shift changes of the aromatic proton in the ^{1}H NMR spectrum (300 MHz, acetone-d_6) of **11** as a result of addition of TBAX.

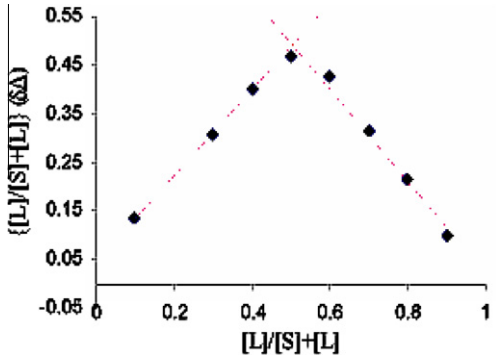


Figure 6. Job's plot for **11** with TBAF.

Table 1
Binding constant of various receptors determined using ^{1}H NMR

Anion salts	K_a (M^{-1}) (**11**)	K_a (M^{-1}) (**12**)	K_a (M^{-1}) (**15**)	K_a (M^{-1}) (**17**)	K_a (M^{-1}) (**18**)
F^-	102,750	1285	6568	742	798
Cl^-	56,515	492	502	1616	5001
Br^-	2124	177	223	257	1203
I^-	60	[a]	31	[a]	595

[a] Indicating very low binding constant value.

We performed systematic experiments to determine the binding abilities of these receptors **11–18** toward tetrabutylammonium halides. The binding studies of halide ions were conducted using ^{1}H NMR studies (Figs. 4 and 5). Tetrabutylammonium halide (TBAX) was added to the receptor; amide NHs, triazole CHs, and Ar-C2Hs were monitored for the ^{1}H NMR chemical shifts. The affinity of the receptor toward anions was analyzed by NMR titration, followed by WinEQ NMR analysis.[15] To quantify the complexation between halides and the receptor, a Job's plot was done using ^{1}H NMR by varying the concentrations of both TBAX and the receptor. The maximum point appears at the mole fraction of 0.5, consistent with a 1:1 stoichiometry (Fig. 6).

A comparison of binding constants showed that phenyl-substituted triazole **11** is superior to the benzyl-substituted receptor **19** (Table 1, Fig. 7). Receptor **11** showed an exceptionally high binding constant ($K \sim 10^5$ M^{-1}) for fluoride. This is attributed to the –I effect of the phenyl group. We envisioned that placing a hydroxyl group on the phenyl ring would further enhance binding via additional hydrogen bonds with the guest molecule. Moreover, the two hydroxyl groups in the receptors **12–17** can make intramolecular hydrogen bonds and thus can preorganize the receptors. However, another aspect of the hydroxyl groups is that the activation of the benzene ring decreases the hydrogen bond donor ability of the triazole CH.

Analysis of the ^{1}H NMR binding studies showed that the initial addition of TBAF to phenolic receptors **12–17** resulted in the disappearance of hydroxyl protons in the ^{1}H NMR spectrum, indicating a deprotonation event. Subsequent addition of TBAF showed binding to amide NHs and aromatic C2H. This sequence of events indicates the possibility that the initial step might be the proton exchange between the fluoride and –OH. In the next step; the fluoride binds to the amide-linked triazole moiety. To unconditionally prove such an unusual binding mechanism, requires a detailed structural analysis using X-ray crystallography. In order to investigate the role of the position of the hydroxyl group in anion binding, we placed the –OH group on a different position on the terminal phenyl ring. The ^{1}H NMR titration studies indicated that, in all cases, the hydrogen of phenolic –OH disappeared instantly upon the addition of TBAF. This observation suggests that the phenolic –OH as such is not augmenting the binding of fluoride to the amide-linked triazole moiety; instead the fluoride independently removes the hydroxyl proton. This finding is supported by a control experiment in which phenolic azides **2–4**, **6–8** treated with TBAF displayed an instantaneous exchange of –OH protons. Of all the phenolic receptors **12–17**, hydroxylated ortho-receptors **12, 15** have the higher binding constant (1285, 6568 M^{-1}) for fluoride. Interestingly, the ortho hydroxybenzyl substituted receptor **15** showed higher binding toward fluoride than the unsubstituted receptor **19**. The higher binding of the fluoride to the amide-linked triazole moiety of **15** compared to **19** might be due to the presence of two ortho-phenolate groups. These ortho-phenolates might arrange in such a way that repulsion is minimized, resulting in higher binding. The order of binding of receptor **17** toward halide is: $Cl^- > F^- > Br^- > I^-$.

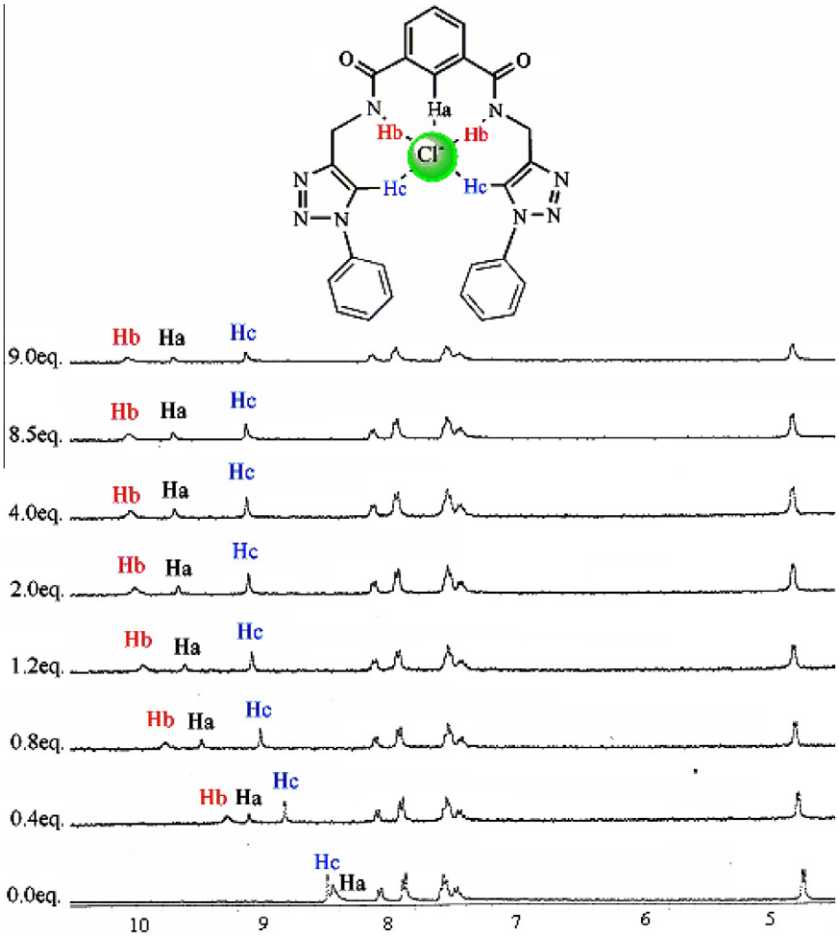


Figure 7. Changes in the ^{1}H NMR spectrum (300 MHz, acetone-d_6) of receptor **11** with the addition of varying amounts of TBACl.

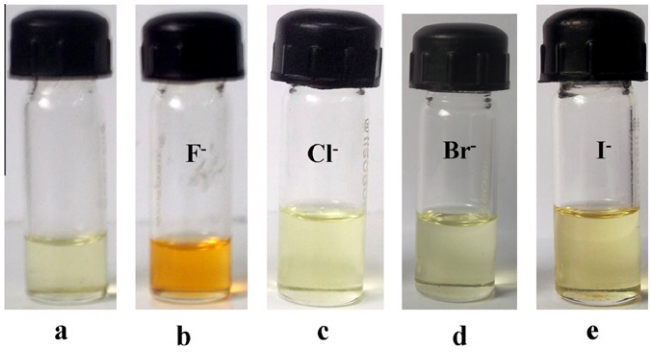


Figure 8. Photograph of (a) (4.3 mM) solution of receptor **18** in (2% DMSO in $CHCl_3$); (b) after addition of 0.5 equiv of F^-; (c) 30 equiv of Cl^-; (d) 30 equiv of Br^-; (e) 30 equiv of I^-.

The fine-tuning of the p*K*a value of triazole CH enhances the binding, as evidenced by the change of the benzyl to phenyl ring. Activating groups such as –OH decreases the binding affinity. Therefore, to further test this hypothesis, we used a *p*-nitrophenyl unit on the N-1 position of the triazole unit. The receptor **18**, with a nitro group on the terminal phenyl ring, was synthesized. This receptor showed insolubility in acetone-d_6 and $CDCl_3$; therefore, the binding studies were performed in (2% DMSO-d_6 in $CDCl_3$). It should be noted that DMSO, being a very polar solvent, will result in reduced receptor binding. The binding constant of **18** for chloride, bromide, and iodide was higher than that of **11** in (2% DMSO-d_6 in $CDCl_3$). Receptor **18** binds the anion in the order: $Cl^- > Br^- > F^- > I^-$. The *p*-nitro substituted receptor **18** changes color from faint yellow to orange on binding to fluoride ions (Fig. 8) and thus is an excellent chromogenic receptor for fluoride detection. Addition of TBAF to **18** showed changes in the chemical shift of triazole CHs, amide NHs, and aromatic C2H (gradual down field shift of triazole CHs, amide NHs, and aromatic C2H. See supplementary data, page S-17). This indicates a co-operative binding phenomenon, wherein all hydrogen bond donors of the receptor take part at the same time for binding to fluoride.[16] The addition of other halides did not result in a visible color change even after adding 30 equiv. Receptor **18** is therefore useful for detecting fluoride in the presence of other halides. The addition of water changes the color from orange to colorless. Since water binds strongly to anions, thereby releasing them from the receptor, this indicates that the orange color is caused by the fluoride complex of **18**. This also indicates the complex formation between the receptor and the anion is reversible.

In this communication, we demonstrated a design strategy for anion binding that illustrated the use of amide-linked triazole on an aromatic scaffold. The substituent at the N1 position on the triazole has a profound influence on anion binding. By fine-tuning the electronic nature of the substituent at N1, we can influence the acidity of triazole CH to ensure enhanced binding to guest molecules. This is primarily due to the enhanced hydrogen bonding nature of triazole CH. In conclusion, we have demonstrated that the amide-linked triazole is an excellent motif for anion recognition. It can be considered a mimic of constrained dipeptide linkage and could be used efficiently for binding guest molecules. We also

designed and synthesized a triazole-based receptor that can change color upon binding, providing a useful tool for the visual detection of anions.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedure and data for all new compounds. All the spectral details and the details of binding studies) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.066.

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