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PAPER

A receptor incorporating OH, NH and CH binding motifs for a fluoride selective chemosensor†

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An anion receptor combined different types of hydrogen bond donors such as OH, NH and CH groups has been synthesized. By rotation of the sub methyl group, this receptor showed evident ^{1}H NMR response to both fluoride and sulfate, while colorimetric and fluorescent responses were only observed in the presence of fluoride.

Introduction

Anions play important roles in a wide range of chemical and biological processes. For example, the chloride anion is used by living systems in cellular tasks.[1] The fluoride anion shows beneficial effects in dental health and the treatment of osteoporosis,[2] however, it is accused of several human pathologies.[3] Therefore, the design of new types of anion receptors has attracted much attention recently.[4]

The common binding subunits for anion receptors include amide,[5] pyrrole,[6] urea,[7] thiourea,[8] azophenol,[9] and imidazolium.[10] In these motifs, O–H···X$^-$, N–H···X$^-$, (C–H)$^+$···X$^-$ and C–H···X$^-$ hydrogen bonding play very important roles for selective anion binding. The phenolic OH group is often introduced as a strong donor and color-reporting unit,[11] and it often undergoes deprotonation in the presence of basic anions such as fluoride, acetate, and dihydrogen phosphate. The amide NH group is less susceptible to deprotonation than hydroxyl group, and it is able to form strong hydrogen bonds. The (C–H)$^+$···X$^-$ type ionic hydrogen bond is stronger, due to the charge–charge electrostatic interaction.[12] Compared to the OH hydrogen bond donor and the NH hydrogen bond donor, the neutral CH hydrogen bond donor is rarely used in designing anion receptors, owing to its weak interactions.[13] Interestingly, the click reaction[14,15] assisted the driving of synthetic innovations in anion receptor design. The 1,2,3-triazole with a 5-debye dipole is a new motif which can result in multiple noncovalent interactions such as anion recognition[16] within flexible,[17] shape-persistent triazolophanes[13,18] and in foldamers[19] and they have the ability to facilitate self-assembly.[20] Highly sensitive and selective fluoride anion sensors have been constructed based on this motif.[21]

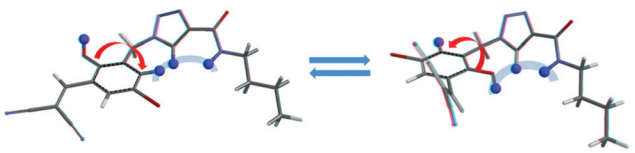

Fig. 1 Schematic interpretation of the cavity formed by molecule **1**.

Recently, we have developed a urea like anion recognizing motif, amidetriazole, which can be easily synthesized and derived. This molecular platform can be used extensively for the construction of numerous receptor systems with functional groups.[22] Here we designed compound **1** based on amidetriazole, in which different types of hydrogen bond donors such as OH, NH and CH groups were linked covalently together for understanding their interactions with various anionic guests by rotation of the sub methyl group (Fig. 1). The colorimetric and fluorometric dual-modal response of this molecule towards fluoride anion was also investigated. In this molecule, electron poor 2,2-dicyano-vinyl group was introduced to generate intramolecular charge transfer from the electron rich hydroxide upon the deprotonation of the OH group.

Results and discussion

The compound **1** was synthesized starting from (5-bromo-3-hydroxymethyl-2-methoxy-phenyl)-methanol **7**,[23] which was converted to azide **6** in one step using Reddy's procedure (Scheme 1). A click chemistry coupling of **6** with propynoic acid methyl ester gave **5** in 96% yield. Subsequent amination with butylamine gave 1-(5-bromo-3-hydroxymethyl-2-methoxy-benzyl)-1*H*-[1,2,3] triazole-4-carboxylic acid butylamide **4** in 94% yield. **2** was obtained through the oxidation of **4** with PCC

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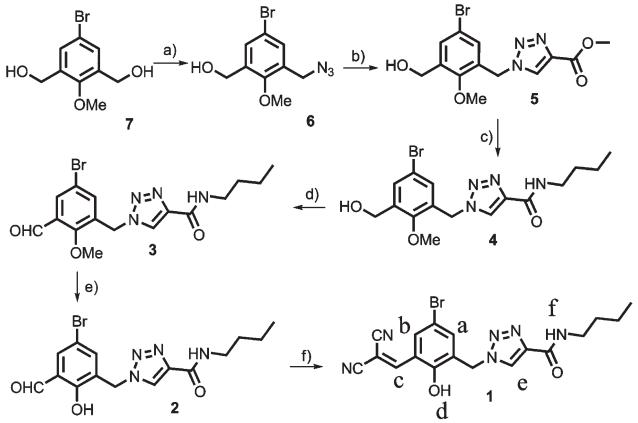

Scheme 1 Synthesis route for the receptor **1**. Conditions: (a) NaN_3, Ph_3P, DMF–CCl_4 (4 : 1), (b) propynoic acid methyl ester, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, EtOH–H_2O (1 : 1), (c) butylamine, (d) PCC, DCM, (e) BBr_3, (f) malononitrile.

(pyridinium chlorochromate) in DCM followed by the removal of methyl group with the aid of BBr_3. Coupling **2** with malononitrile in the presence of base gave **1** in 79% isolated yield.

The ^{1}H NMR titration of **1** with various anions provided structural information about the receptor and its complexes present in solution. ^{1}H NMR titration experiment in acetone-d_6 was performed to investigate the fluoride–**1** interactions, as shown in Fig. 2. The hydrogen bond donors exhibited two different resonance signals at 8.78 (triazole-H_e) and 7.70 (amido-H_f) ppm. The dicyanovinyl-H_c, the phenyl-H_b and phenyl-H_a showed signals at 8.44, 8.11 and 7.94 ppm, respectively. Fluoride has a high affinity to hydrogen and it could easily induce H–O bond cleavage. Upon addition of F^- as tetrabutylammonium salt, the signals of H_a and H_b on the phenyl ring gradually migrated to upfield owing to charge delocalization on the entire phenyl ring with the deprotonation of O–H. Upon addition of 2.0 equivalents of F^-, all of the signals associated with compound **1** completely vanished, which indicated that the OH group had been deprotonation completely. The relative protons showed signals at 8.50 (triazole-H_e), 7.65 (amido-H_f), 8.44 (dicyanovinyl-H_c), 7.31 (phenyl-H_b) and 7.14 (phenyl-H_a). With the continuous addition of F^-, more complicated ^{1}H NMR signal shifts were observed. It was the combination of the F^- anion binding process and the intramolecular hydrogen bonding between the deprotonated O^- anion and the dicyanovinyl-H_c proton or triazole C–H. The deprotonated O^- anion can form intramolecular hydrogen bond with the dicyanovinyl-H_c proton or triazole C–H_e. This may account for the reason why the signal of dicyanovinyl-H_c showed two sets of peaks upon addition of 4.0 equivalents of F^-. One signal showed at 8.60 ppm (c_1) which is related to the dicyanovinyl-$H_c\cdots O^-$ hydrogen bonded species **1F-1**, and the other signal showed at 6.95 ppm (c_2) which is due to the charge delocalization on the dicyanovinyl group conjugated to the phenyl ring with the deprotonation of O–H, while the deprotonated O^- anion formed intramolecular hydrogen bond with the triazole C–H_e (**1F-2**). The F^- anion binding based on these two species would lead to the splitting of the signal of amido-H_f. One signal shifted to 8.70 ppm (f_2) through the fluoride binding by triazole-H_e and amido-H_f in **1F-1**, and the other constant

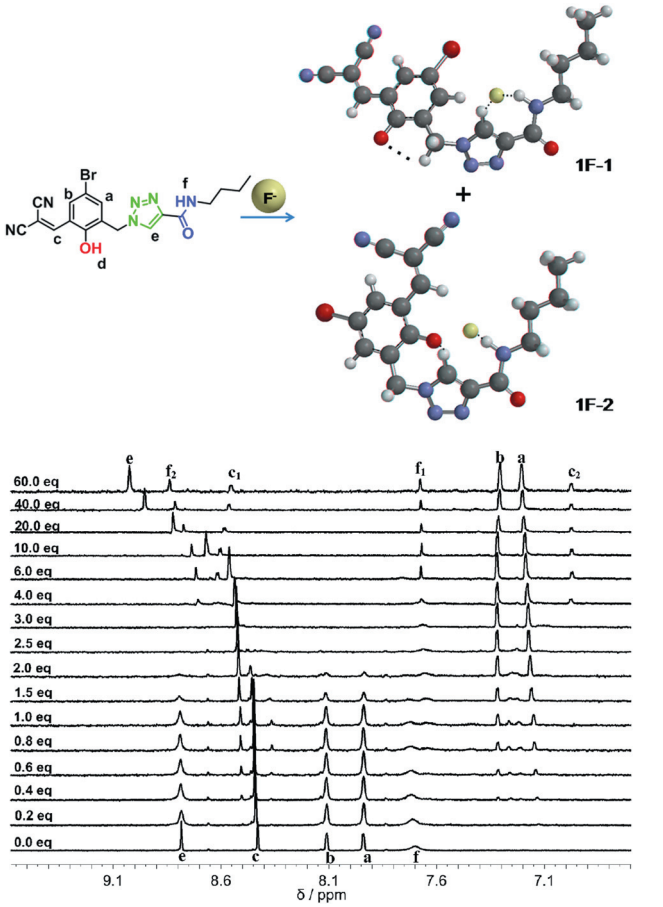

Fig. 2 Top: The models of the fluoride complex of **1** before and after the sub methyl group rotating. Bottom: Partial ^{1}H NMR titration of **1** with F^- ([d_6] acetone, 298 K).

signal at 7.65 ppm (f_1) which indicated that there is weak fluoride binding in **1F-2**.

As shown in Fig. 3, upon addition of 2.5 equivalents of SO_4^{2-} as tetrabutylammonium salt, the developments of the signals were similar with that of F^- titration, potentially indicating the occurrence of O–H deprotonation. Upon addition of more SO_4^{2-}, there generated two sets of signals, which probably accounted for the different chemical environments when binding with sulfate anion (as the binding models shown in Fig. 3), that is, the more negative charged sulfate binds with the proton H_a, triazole-H_e and amido-H_f (top) or triazole-H_e and amido-H_f (down). The triazole proton H_e preferred to bind with SO_4^{2-} rather than to the deprotonated O^- anion. The two set of peaks of H_e at 9.59 and 9.60 ppm, those of H_f split and shifted downfield to 8.08 and 9.10 ppm, respectively. The two sets of peaks of H_c shifted to the reversed directions, that is, one set of peak shifted upfield to 8.50 ppm, while the other set of peak shifted downfield to 8.90 ppm. One set of peak of H_b remained nearly unchanged, while the other set of peak of H_b shifted upfield from 7.30 ppm to 7.25 ppm. The two sets of peaks of H_a located at 7.05 and 6.95 ppm, respectively.

The Cl^- titration spectra exhibited totally different sets of signals compared to F^- and SO_4^{2-}. Upon addition of 0.2 to 60.0 equivalents of Cl^- (as tetrabutylammonium salt), the protons H_e,

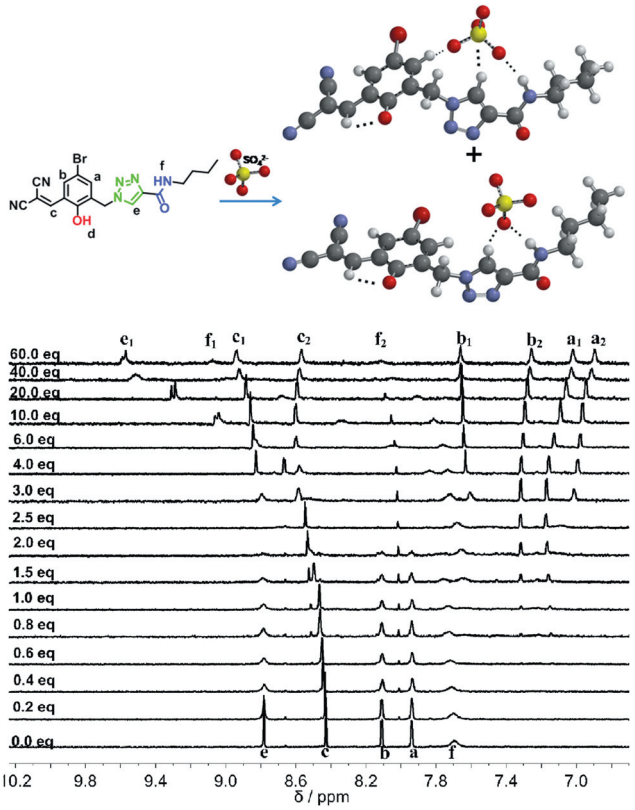

Fig. 3 Top: The models of the sulfate complex of **1** before and after the sub methyl group rotating. Bottom: Partial ^{1}H NMR titration of **1** with SO_4^{2-} ([d_6] acetone, 298 K).

H_c, H_b, H_a and H_f all shifted downfield, which indicated that no O–H deprotonation occurred and the protons formed moderate hydrogen bond interactions with Cl^-. The signals of the protons remained one set of peaks, potentially indicating that all the hydrogen donor protons directed to Cl^- and there is only one conformation (Fig. 4).

Color and fluorescence emission changes could be observed by mixing the receptor and anions as shown in Fig. 5. Only when fluoride ions were added, the color of the receptor solution turned from colorless to yellow and the fluorescence color became light green. However, a weak red color could be observed when acetate, dihydrogen phosphate, and sulfate ions were added, and a weak green color was observed for fluorescence color.

Fig. 6a and Fig. S5† showed the absorption and emission spectral of compound **1** in the presence of various anions (60 equiv.). Significant UV-vis absorption changes were observed only when F^- was added. Meanwhile only F^- caused a drastic increase to the original emission peak at 408 nm and induced a new strong emission peak at 580 nm. Only a slight increase for emission was observed when $H_2PO_4^-$ was added, which is followed by a weak charge transfer absorption band centered at 500 nm.

The interaction of **1** with fluoride anion was investigated in detail. Fig. 7a showed the absorption spectral changes of **1** with the increase of the F^- concentration in CH_2Cl_2 at room temperature. The UV-vis spectrum of **1** exhibited two absorption bands

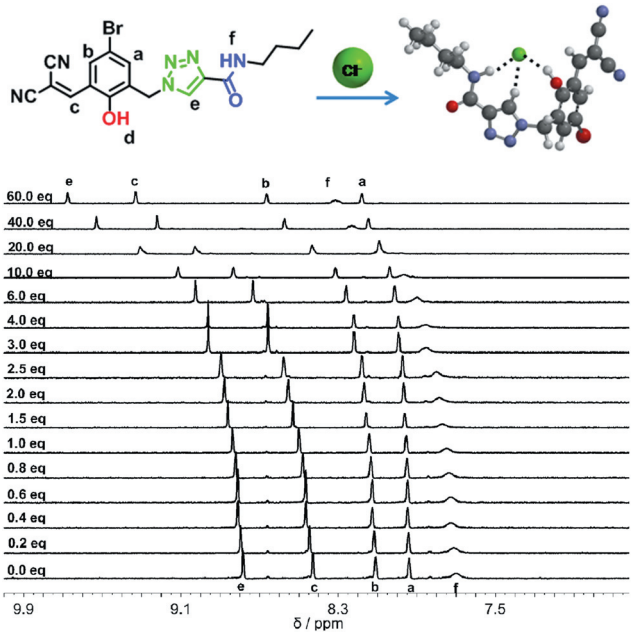

Fig. 4 Top: The models of the chloride complex of **1** before and after the sub methyl group rotating. Bottom: Partial ^{1}H NMR titration of **1** with Cl^- ([d_6] acetone, 298 K).

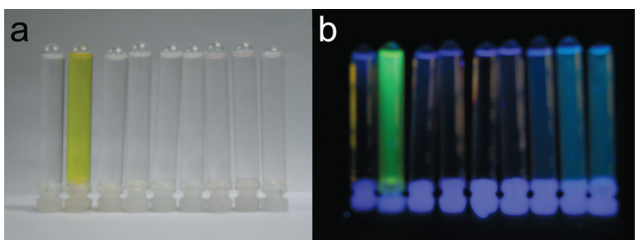

Fig. 5 Visible color (a) and visual fluorescence color (b) changes of **1** (0.05 mM) in CH_2Cl_2 after the addition of 60 equiv. of various anions (50 mM). From left to right: only **1**, F^-, Cl^-, Br^-, I^-, PF_6^-, AcO^-, $H_2PO_4^-$, SO_4^{2-} (TBA^+ salts). The visual fluorescence color was obtained with excitation at 365 nm using a hand-held UV lamp.

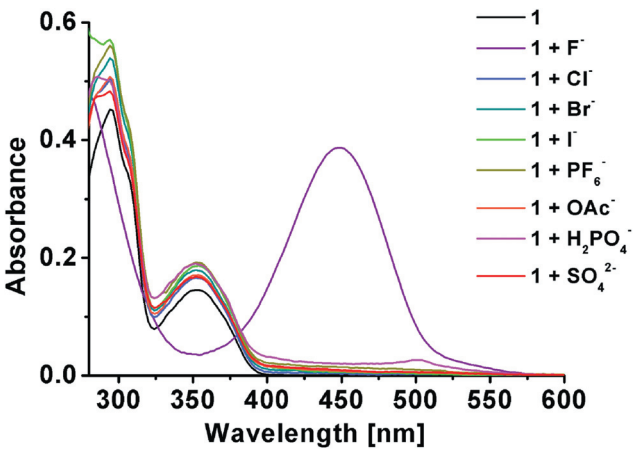

Fig. 6 Absorption spectra of compound **1** (5×10^{-5} M) upon addition of 60 equivalents of tetrabutylammonium fluoride, chloride, bromide, iodide, hexafluorophosphate, acetate, dihydrogen phosphate, and sulfate in CH_2Cl_2.

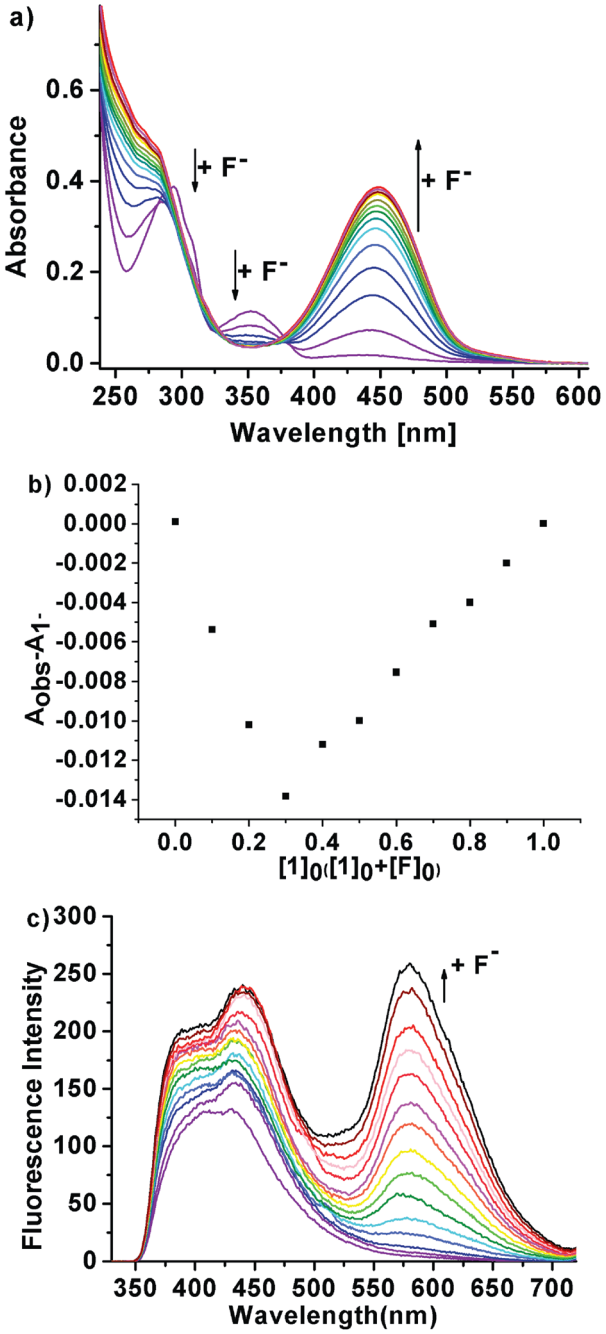

Fig. 7 (a) Changes in the UV-vis spectra of **1** (5×10^{-5} M in CH_2Cl_2) upon titration with *n*-Bu_4NF from 1 to 10, and 20, 30, 40, 50, 60 equiv. (b) Absorption changes at 352 nm *vs.* concentrations of F^-. Inset: Job's plot for fluoride–**1** interactions. (c) Emission spectra of 1 (1×10^{-5} M in CH_2Cl_2) upon titration with *n*-Bu_4NF from 1 to 10, and 20, 30, 40, 50, 60 equiv. Excitation wavelength was 320 nm with 10.0 nm slit widths.

in dichloromethane. One moderately strong absorption band appeared at 294 nm and the other relative weak absorption band appeared at 352 nm. With the deprotonation of O–H, the UV-vis spectra exhibited a red-shifted charge-transfer (CT) band from electron rich hydroxide to electron poor dinitrile side. Addition of tetrabutylammonium fluoride induced drastic color development from colorless to yellow, which is associated with

Table 1 Binding constants (K_1) determined by UV-vis titration[a] for the interaction of **1** with various anions[b]

Anion	F^-	Cl^-	Br^-	I^-	PF_6^-	OAc^-	$H_2PO_4^{2-}$	SO_4^{2-}
K_1	21 721	477	399	321	140	968	1193	1475

[a] The calculation is according to ref. 18. [b] Anions as tetrabutylammonium salts in CH_2Cl_2.

continuing decrease in the absorption band at 294 nm and 352 nm and simultaneous growth of a new strong absorption band at 448 nm. The binding stoichiometry of the **1**–fluoride interactions was confirmed to be 1 : 2 from the Job's plot (Fig. 7b). Fig. 7c showed the emission spectral changes of **1** with the increasing of the F^- concentration in CH_2Cl_2 at room temperature. The fluorescence responses of **1** with F^- were recorded with an excitation at the isosbestic point of 320 nm from UV-vis titration experiment. The emission spectra of **1** showed one band at 408 nm. Upon addition of fluoride anion, the emission band of **1** at 408 nm increased gradually and one new strong emission band at 580 nm simultaneously grew, which is ascribed to a twisted intramolecular charge-transfer (TICT) state as internal rotation of the dicyanovinyl group with respect to the benzene ring was limited upon the formation of the intramolecular hydrogen bonding between the deprotonated O^- anion and the dicyanovinyl-H_c proton or triazole C–H.

The receptor–anion stoichiometry was determined *via* a continuous variation method (Job's plots) and proved to be 1 : 2 for fluoride anions. The association constant K_1 between **1** and various anions was determined by nonlinear curve fitting of the titration curves obtained by plotting the absorbance changes at 352 nm (ΔA) against the concentration of anions added[18] (Table 1). In the anions studied, **1** showed great selectivity towards fluoride.

Conclusion

In summary, an anion receptor combining different types of hydrogen bond donors such as OH, NH and CH groups had been synthesized for the understanding of their interactions with various anionic guests. With the help of the free rotation of the sub methyl group, this receptor showed different binding behavior towards fluoride, sulfate and other halides. This receptor showed evident ^1H NMR response to both fluoride and sulfate, while colorimetric and fluorescent responses were only observed in the presence of fluoride.

Experimental

(3-Azidomethyl-5-bromo-2-methoxy-phenyl)-methanol, 6

Ph_3P (2 mmol, 268 mg) and NaN_3 (2.4 mmol, 160 mg) were added into a solution of **7**[23] (2 mmol, 492 mg), then 4 mL CCl_4 were added. After a few minutes, the reaction was heated at reflux with stirring for 6 hours, and then cooled to room temperature. The resulting solution was poured into 125 mL of water, and then extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried

over $MgSO_4$. Concentrated *in vacuo* and purified by flash chromatography (7 : 1 hexanes–EtOAc) gave **6** (287 mg, 53%). Mp 139–141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 7.53 (s, 1 H), 7.4 (s, 1 H), 4.68 (s, 2 H), 4.36 (s, 2 H), 3.79 (s, 3 H), 2.36 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 155.06, 136.47, 132.11, 132.01, 130.93, 117.38, 62.29, 59.85, 49.02. MS (EI) Calcd for $C_9H_{10}BrN_3O_2$ (M + H) 272.10; Found 272.2. Anal. Calcd for $C_9H_{10}BrN_3O_2$: C, 39.73; H, 3.70; N, 15.44. Found: C, 39.81; H, 3.74; N, 15.49.

1-(5-Bromo-3-hydroxymethyl-2-methoxy-benzyl)-1*H*-[1,2,3]-triazole-4-carboxylic acid methyl ester, 5

A solution of **6** (1 mmol, 127 mg), propynoic acid methyl ester (2.2 mmol, 222 mg), sodium ascorbate (0.2 mmol, 44.6 mg), and $CuSO_4$ (0.02 mmol, 5.6 mg) in a 1 : 1 mixture of EtOH–H_2O (14 mL) was stirred at room temperature for 24 h. After removal of the solvents *in vacuo*, the crude product was purified by column chromatography (CH_2Cl_2–MeOH, 3 : 1) to afford **5** (309 mg, 94%). Mp 191–193 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 8.10 (s, 1 H), 7.65 (s, 1 H), 7.29 (s, 1 H), 5.56 (s, 2 H), 4.75 (s, 2 H), 3.92 (s, 3 H), 3.76(s, 3 H), 2.75 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 160.92, 154.88, 140.11, 137.18, 133.21, 132.00, 128.94, 127.64, 117.68, 62.27, 59.40, 52.18, 48.71. MS (EI) Calcd for $C_{13}H_{14}BrN_3O_4$ (M + H) 356.17; Found 356.2. Anal. Calcd for $C_{13}H_{14}BrN_3O_4$: C, 43.84; H, 3.96; N, 11.80. Found: C, 43.88; H, 3.99; N, 11.74.

1-(5-Bromo-3-hydroxymethyl-2-methoxy-benzyl)-1*H*-[1,2,3]-triazole-4-carboxylic acid butylamide, 4

5 (1 mmol, 127 mg) in 4 mL butylamine was stirred at 70 °C for 4 h. After removal of butylamine *in vacuo*, the crude product was purified by column chromatography (CH_2Cl_2–MeOH, 3 : 1) to afford **4** (309 mg, 94%). Mp 187–189 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 8.05 (s, 1 H), 7.63 (s, 1 H), 7.27 (s, 1 H), 7.16 (s, 1 H), 5.52 (s, 2 H), 4.72 (s, 2 H), 3.75 (s, 3 H), 3.42 (q, 2 H, J = 7.2 Hz), 2.54 (s, 1 H), 1.58 (m, 2 H), 1.39 (m, 2 H), 0.93 (t, 3 H, J = 7.2 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 159.90, 154.93, 143.67, 137.15, 133.19, 132.07, 129.18, 125.41, 117.74, 62.30, 59.52, 48.69, 38.88, 31.58, 20.03, 13.70. MS (EI) Calcd for $C_{16}H_{21}BrN_4O_3$ (M + H) 397.27; Found 397.3. Anal. Calcd for $C_{16}H_{21}BrN_4O_3$: C, 48.37; H, 5.33; N, 14.10. Found: C, 48.41; H, 5.37; N, 14.06.

1-(5-Bromo-3-formyl-2-methoxy-benzyl)-1*H*-[1,2,3]triazole-4-carboxylic acid butylamide, 3

Pyridinium chlorochromate (1.5 mmol, 322 mg) was added to a solution of **4** (1 mmol, 396 mg) in CH_2Cl_2 under a nitrogen atmosphere, and the mixture was stirred at room temperature overnight. The crude product was purified by column chromatography (CH_2Cl_2) to afford **3** (355 mg, 90%). Mp 178–180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 10.26 (s, 1 H), 8.11 (s, 1 H), 7.97 (d, 1 H, J = 2.4 Hz), 7.60 (d, 1 H, J = 2.0 Hz), 7.12 (s, 1 H), 5.60 (s, 1 H), 3.92 (s, 1 H), 3.44 (q, 2 H, J = 6.8 Hz), 1.59 (m, 2 H), 1.41 (m, 2 H), 0.94 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 187.30, 159.80, 159.64, 143.91, 138.51, 133.40, 130.84, 130.77, 125.54, 118.11, 65.32, 47.95, 38.83, 31.55, 19.99, 13.66. MS (EI) Calcd for $C_{16}H_{19}BrN_4O_3$ (M + H) 395.25; Found 395.3. Anal. Calcd for $C_{16}H_{19}BrN_4O_3$: C, 48.62; H, 4.85; N, 14.18. Found: C, 48.69; H, 4.82; N, 14.22.

1-(5-Bromo-3-formyl-2-hydroxy-benzyl)-1*H*-[1,2,3]triazole-4-carboxylic acid butylamide, 2

BBr_3 (10 mmol, 10 mL, 1 M in DCM) was slowly added to a solution of **3** (1 mmol, 394 mg) in dichloromethane (20 mL) and the solution was stirred under argon at room temperature. After 4 hours, the mixture was poured slowly into a solution of saturated sodium bicarbonate (100 mL) to obtain a precipitation of a grey solid. After filtrated and washed with cold water and ether, the crude product was further purified by column chromatography (CH_2Cl_2–MeOH, 4 : 1) to yield **2** (304 mg, 80%) as an off-white solid. Mp 175–177 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 11.44 (s, 1 H), 9.87 (s, 1 H), 8.16 (s, 1 H), 7.73 (s, 1 H), 7.63 (s, 1 H), 7.11 (s, 1 H), 5.59 (s, 2 H), 3.44 (m, 2 H), 1.60 (m, 2 H), 1.40 (m, 2 H), 0.94 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 195.27, 159.77, 158.04, 143.65, 139.74, 136.54, 125.80, 125.06, 121.76, 111.59, 47.57, 38.77, 31.54, 19.95, 13.63. MS (EI) Calcd for $C_{15}H_{17}BrN_4O_3$ (M + H) 381.22; Found 381.3. Anal. Calcd for $C_{15}H_{17}BrN_4O_3$: C, 47.26; H, 4.49; N, 14.70. Found: C, 47.34; H, 4.53; N, 14.64.

1-[5-Bromo-3-(2,2-dicyano-vinyl)-2-hydroxy-benzyl]-1*H*-[1,2,3]-triazole-4-carboxylic acid butylamide, 1

Piperidine (0.025 mmol, 25 μL) was added to a mixture of **2** (0.5 mmol, 190 mg) and malononitrile (0.5 mmol, 33 mg) in ethanol (20 mL). The solution was stirred at room temperature overnight and the resulting precipitate was collected by filtration. The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 5 : 1) to yield compound **1** (169 mg, 79%) as a pale white solid. Mp 203–205 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ = 8.22 (s, 1 H), 8.18 (s, 1 H), 7.76 (s, 1 H), 7.62 (s, 1 H), 7.12 (s, 1 H), 5.79 (s, 2 H), 3.44 (d, 2 H, J = 8 Hz), 1.56 (t, 2 H, J = 4 Hz), 1.40 (m, 2H), 0.94 (t, 3 H, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 162.87, 162.40, 139.83, 136.07, 133.78, 133.60, 133.53, 129.48, 129.15, 124.80, 123.50, 122.92, 40.97, 30.27, 20.35, 13.91, 1.156. MS (EI) Calcd for $C_{18}H_{17}BrN_6O_2$ (M + H) 429.27; Found: 429.3. Anal. Calcd for $C_{18}H_{17}BrN_6O_2$: C, 50.36; H, 3.99; N, 19.58. Found: C, 50.46; H, 3.95; N, 19.49.

Acknowledgements

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