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# Novel receptors with quinoline and amide moieties for the biologically important ions

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ABSTRACT

New chromogenic anion receptors **2** and **4** utilizing quinoline and nitrophenyl groups as signaling groups were synthesized. In these receptors, amide and amine groups made strong multiple hydrogen interactions with anions. The receptors **2** and **4** bind anions with a selectivity of $F^- > CN^- > CH_3CO_2^-$ and proved to be an efficient naked-eye detector for the fluoride and cyanide ion.



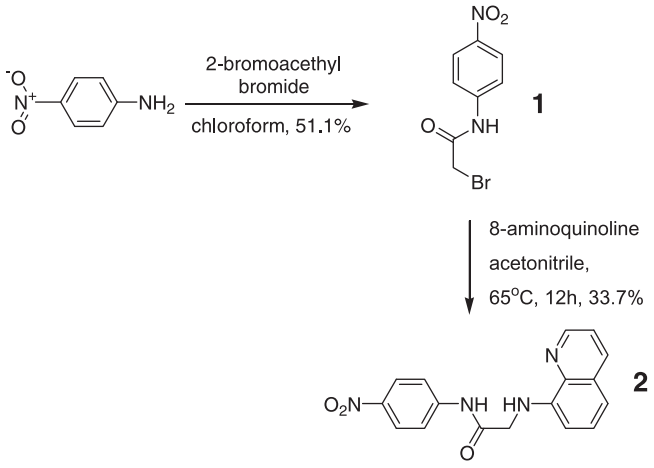
The design and synthesis of efficient receptors capable of binding biologically and environmentally important anionic species has received considerable interest in recent years.[1] Most of these sensors contain chromogenic or fluorogenic groups that are covalently or non-covalently linked to the receptor moiety, thus enabling the colorimetric and fluorimetric sensing of anions.[2]

Many chemical sensors follow the approach of the covalent attachment of signaling subunits and binding sites.[3] Hydrogen-bonding sites as binding sites typically used in chromogenic or fluorogenic chemsensors are ureas,[4] thioureas,[5,2b] calyx[4]pyrroles,[6] sapphyrins,[7] amines[8], and amides.[9] Usually a single hydrogen bond is weak and multiples of such interactions must be applied for efficient complexation of anions. Among the binding units mentioned above, amide and amines are the most biologically relevant groups. They are inspired by anion binding proteins that exploit the hydrogen bond donor properties of neutral amide N–H and amine $NH_2$ groups.[4a–e]

Previously, we reported on novel colorimetric receptors containing a nitrophenyl group or a benzophenone group as chromogenic signaling subunit and urea/thiourea as binding sites, which were selective for fluoride or acetate ion.[10] As an extension of our efforts, we have designed new simple receptors **2** and **4**, which have both a nitrophenyl group and a quinoline group as chromogenic signaling subunits. In these receptors, amide and amine groups are incorporated so that anions can make strong multiple interactions with the hydrogen atoms of these groups through hydrogen bonding.

These receptors were found to be an efficient detector for fluoride and cyanide. The anion recognition via hydrogen-bonding interactions could be easily monitored by anion-complexation induced changes in UV–vis absorption spectra and with the naked eye.

The receptors **2** and **4** were synthesized by the reaction of both 2- or 4-nitroaniline and 8-aminoquinoline group with a simple 2-bromoacetyl bromide (Schemes 1 and 2).[11] The X-ray structure




**Scheme 1.** The synthetic procedure for the anion receptor **2**.

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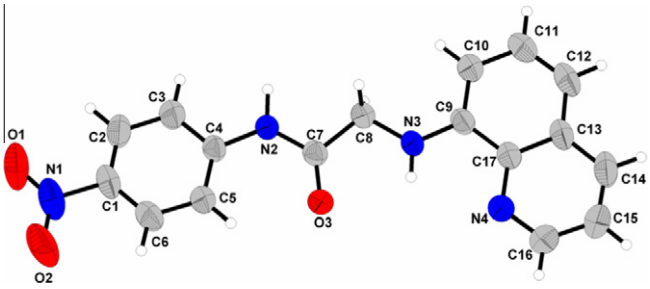
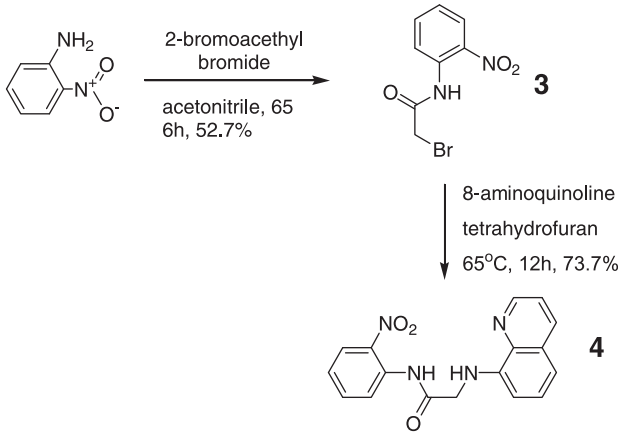



**Figure 1.** The structure of **2** showing the atom-labeling scheme. Displacement ellipsoids are shown at the 50% probability level.




**Scheme 2.** The synthetic procedure for the anion receptor **4**.

of **2** is shown in Figure 1. The crystallographic data, and the selected bond lengths and angles are given in Tables S1 and S2 (see Supplementary data).

The receptors **2** and **4** displayed strong absorption bands at 320 nm and 346 nm in acetonitrile, respectively. Figure 2 shows the family of spectra obtained over the course of the titration of solution **2** with tetrabutylammonium fluoride in acetonitrile. As fluoride ions were added to the 40 μM solution of **2**, $\lambda_{max}$ of **2** moved from 320 nm to 431 nm and the spectra showed the clear isosbestic point at 356 nm. In the case of **4** in acetonitrile solution at the same concentration, the intensity of the peak at 346 nm was decreased as fluoride ions were added and the spectra showed an isosbestic point at 369 nm (Fig. 2b). The presence of the sharp isosbestic point for both compounds indicates that only two species were present at equilibrium over the course of the titration experiment. From the titration experiments, it was found that both compounds **2** and **4** were deprotonated by the basic fluoride ion.[12] The deprotonation was confirmed through the titration experiments with tetrabutylammonium hydroxide ion (Fig. 2c and d). Assuming 1:1 stoichiometry, a Benesi–Hildebrand plot[13] by use of absorption intensity change at 320 nm and 346 nm gave equilibrium constants for deprotonation. From the experiments, the

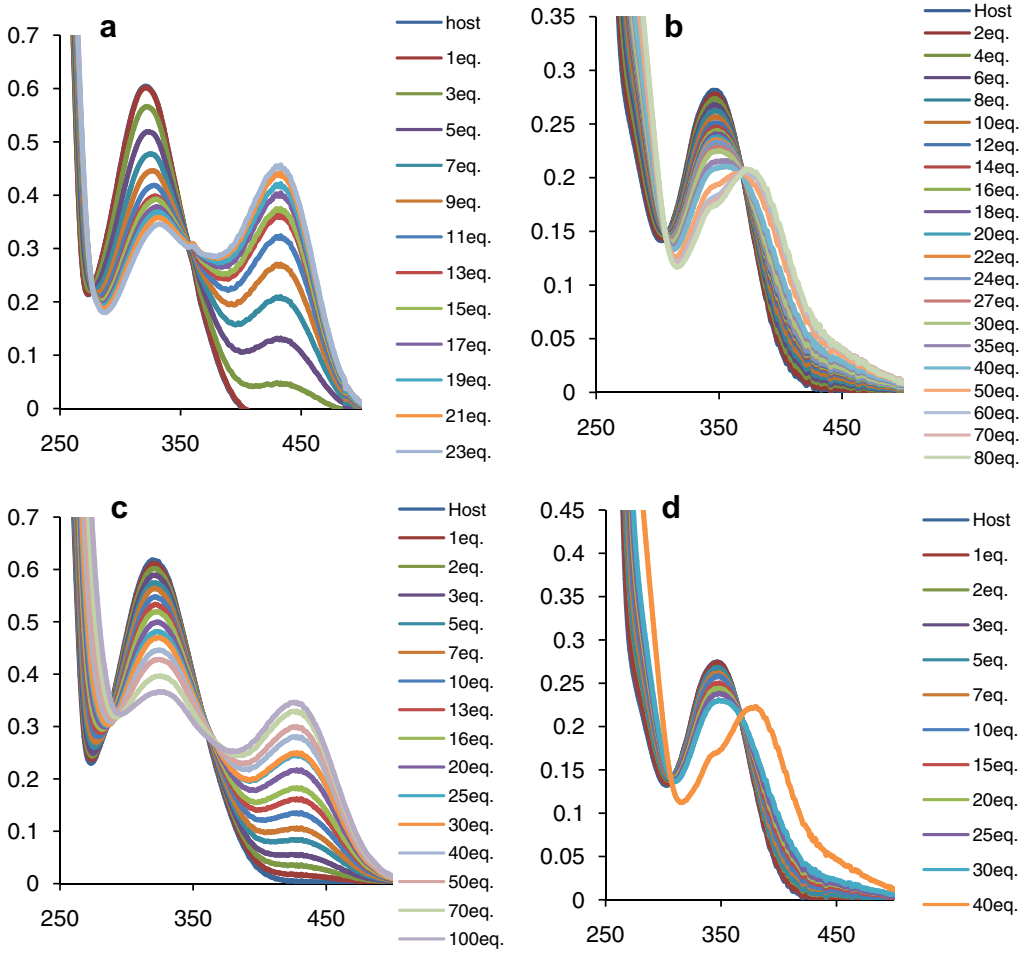



**Figure 2.** Family of spectra recorded over the course of titration of 40 μM acetonitrile solution of the receptors **2** (a) and **4** (b) with the standard solution tetrabutylammonium fluoride and **2** (c) and **4** (d) with the standard solution tetrabutylammonium hydroxide.

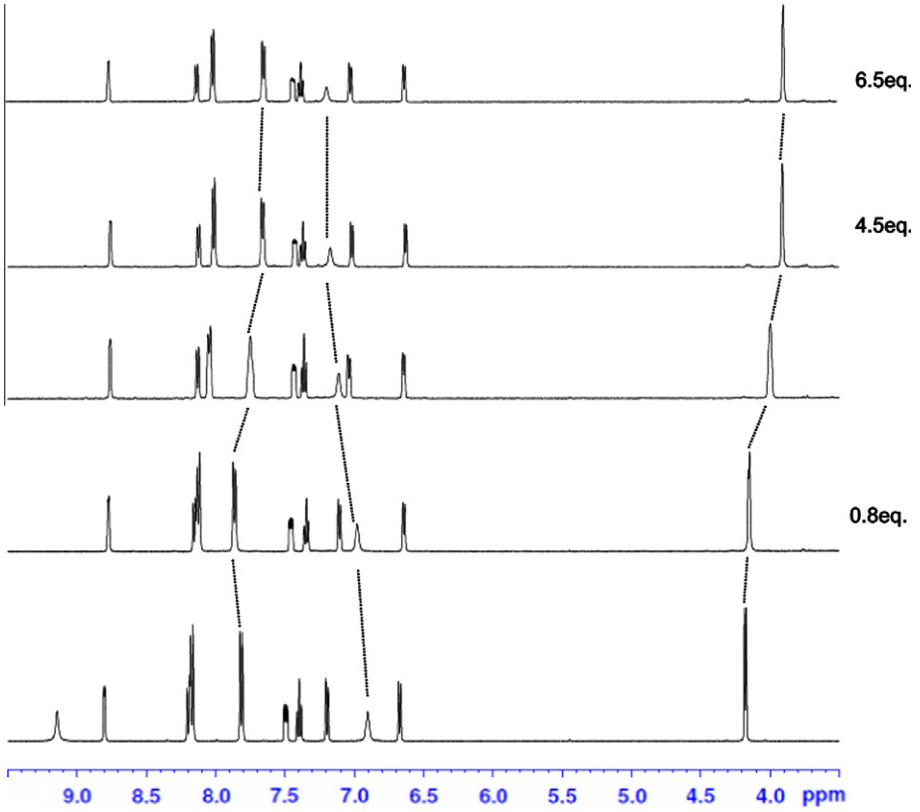



**Figure 3.** $^1$H NMR spectra of 2 mM of **2** with increased amounts of tetrabutylammonium fluoride (0–6.5 equiv) in $CD_3CN$.

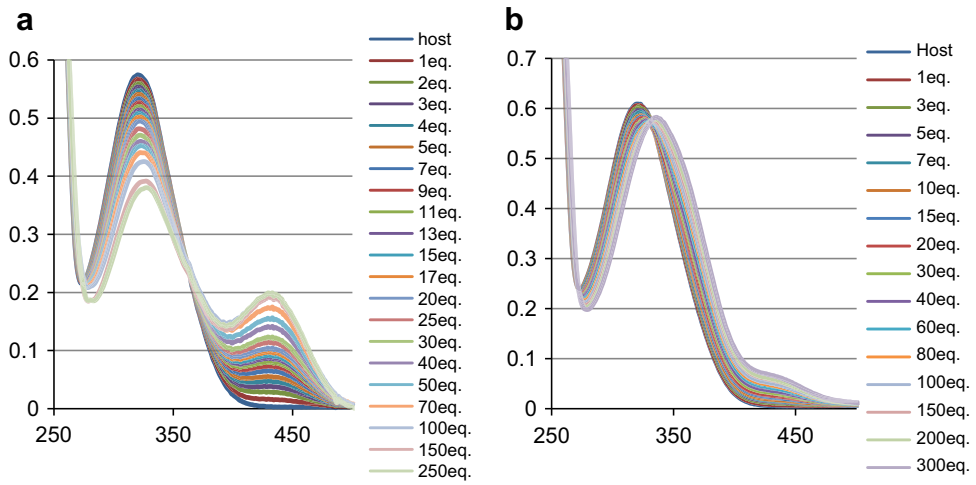



**Figure 4.** Family of spectra recorded over the course of titration of 40 μM acetonitrile solution of the receptor **2** with the standard solution tetrabutylammonium cyanide (a) and tetrabutylammonium aceatate (b).

equilibrium constants of the receptors **2** and **4** for fluoride were calculated as $1.7 \times 10^3$ and $8.3 \times 10^2$ $M^{-1}$, respectively.

This phenomenon could be confirmed by a $^1$H NMR titration. In $CD_3CN$, amide N–H hydrogen peaks of receptors **2** and **4** became invisible upon addition of fluoride ion. However, amine peaks of the compounds **2** and **4** showed downfield shifts. For example, the amine peak of the compound **2** which appeared about 6.90 ppm showed a downfield shift until 7.18 ppm, indicating that both amide and amine participate in the binding event (Fig. 3). These results suggest that both compounds **2** and **4** interact with fluoride through hydrogen bonds. Another evidence of deprotonation phenomenon of amide hydrogen was also observed from the chemical shift during titration. For example, in the case of compound **2**, the doublet at 7.8 ppm moved slightly downfield when the fluorides added are less than 1 equiv (Fig. 3), and then showed large upfield shifts when more than 2 equiv of fluoride added. However, when tetrabutylammonium hydroxide was added to the solution of compound **2**, the doublet at 7.8 ppm showed only upfield shifts (data not shown). Therefore, it is likely that the initial downfield shift arises from H-bonding to the anion, but the subsequent upfield shift could be explained by the deprotonation of amide hydrogen.

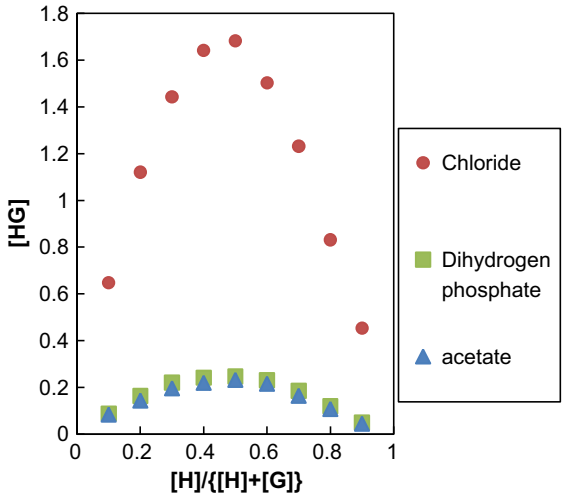



**Figure 5.** Job plots of the receptor **2** and various anions.

**Table 1**
The association constants ($M^{-1}$) of the receptors **2** and **4** with various anions in acetonitrile

| Anion | 2 | | 4 | |
|---|---|---|---|---|
| | UV ($K_a$) | NMR ($K_a$) | UV ($K_a$) | NMR ($K_a$) |
| $F^-$ | $1.7 \times 10^3$ | $1.6 \times 10^3$ | $8.3 \times 10^2$ | $5.0 \times 10^2$ |
| $CH_3CO_2^-$ | $8.8 \times 10^2$ | | $1.5 \times 10^2$ | |
| $CN^-$ | $1.6 \times 10^3$ | | $2.8 \times 10^2$ | |
| $C_6H_5CO_2^-$ | $4.1 \times 10^2$ | | $9.6 \times 10$ | |
| $H_2PO_4^-$ | $4.6 \times 10^2$ | | $1.4 \times 10$ | |
| $Cl^-$ | $8.4 \times 10$ | | – | |
| $Br^-$ | $4.1 \times 10$ | | – | |
| $I^-$ | $3.5 \times 10$ | | 9 | |
| $HSO_4^-$ | $1.1 \times 10$ | | – | |

For titration, $CH_2$ peak next to amide group or amine peak was used. For example, in the case of receptor **2**, $CH_2$ peak next to amide appeared at 4.17 ppm. This signal moved from 4.17 ppm to 3.89 ppm until 6.5 equivalents of fluoride ion were present and no more shifts were observed. In fact, two effects are expected as a result of hydrogen bond formation between the receptor subunit and the anion; (i) A through-bond propagation, which causes a shielding effect and promotes an upfield shift and (ii) A through-space effect, which causes deshielding and promotes a downfield shift. In this case, through-bond propagation dominates, and an upfield shift is observed.

Analysis of chemical shift utilizing EQNMR[14] gave equilibrium constants $1.6 \times 10^3$ and $5.0 \times 10^2\ M^{-1}$ for the receptors **2** and **4**, respectively, which are similar values obtained from UV–vis titration.

With cyanide, a similar phenomenon was observed. In UV–vis titration with cyanide, $\lambda_{max}$ of **2** was moved from 320 nm to 431 nm and spectra showed the clear isosbestic point at 356 nm again (Fig. 4). From the experiments, the equilibrium constants for cyanide were calculated as $1.6 \times 10^3$ and $2.8 \times 10^2\ M^{-1}$ for the receptors **2** and **4**, respectively. Fluoride and cyanide showed similar deprotonation equilibrium constants for the receptors **2** and **4**.

However, titration spectra of acetate were somewhat different with those of fluoride and cyanide. For example, as acetate ions were added to the 40 μM solution of **2**, the spectra shifted slightly to longer wavelength and showed a new isosbestic point at 326 nm (Fig. 4b). Spectra with the new isosbestic point at 326 nm without a $\lambda_{max}$ at 431 nm suggest that hydrogen bonding is a predominant interaction in the case of acetate at the concentration we investigated.

We also investigated association constants of other anions. Their binding stoichiometry was determined with the Job plot and 1: 1 binding was confirmed (Fig. 5). The results are summarized in Table 1. The receptors **2** and **4** interact with most of anions through hydrogen bonding at the concentration we investigated except fluoride and cyanide. In addition, the receptor **2** showed higher affinities than the receptor **4** for the all the anions investigated. These results could be explained by two possibilities: (1) one is that the inductive effect of 4-nitro group is stronger than that of 2-nitro group in the benzene ring and (2) the other is that 2-nitro group has an intra-molecular H-bonding to the hydrogen atom of the amide group, thus inhibiting the hydrogen bonding with anions.

Figure 6 shows the color change of the solutions of the receptors **2** and **4** upon additions of various anions in DMSO. It can be seen that the color changes from colorless to yellow in the presence of fluoride and cyanide with naked eye. As expected, the color change was more distinct in the receptor **2**. However, the receptor **4** showed more selective color change than the receptor **2**. Other anions did not induce any color changes even with excess amounts.

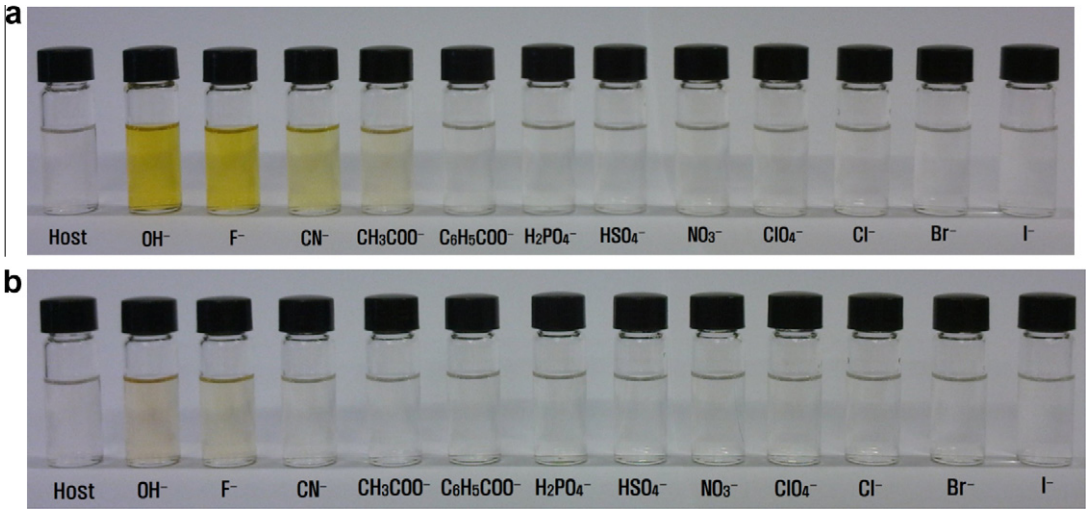



**Figure 6.** The color changes of the receptors **2** (a) and **4** (b) when 100 μM acetonitrile solutions of receptors were treated with 5 equiv of various anions.

In summary, we developed new chromogenic anion receptors **2** and **4** utilizing quinoline and nitrophenyl group as the signaling group. The receptors **2** and **4** bind anions via hydrogen bonds with a selectivity of $F^- > CN^- > CH_3CO_2^-$ and proved to be an efficient naked-eye detector for the fluoride and cyanide ion.

## Acknowledgments

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## Supplementary data

Supplementary data (X-ray crystallography, crystal data, and structure refinement for **2**, bond lengths [Å] and angles [°] for **2**, and crystal structure of intermolecular H-bonds between the molecule **2** and water molecules) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.058.

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11. *Synthesis of compound* **1**: **1** was immediately precipitated when 4-nitroaniline (1.67 g, 12.0 mmol) and 2-bromoacetyl bromide (0.89 mL, 10.0 mmol) were mixed together in chloroform (200 mL) at room temperature under nitrogen. The mixture was evaporated to produce crude residue, which was purified by chromatography (silica gel, methylene chloride). Yield 51.1%. Anal. Calcd for $C_8H_7BrN_2O_3$ (259.06): C, 37.09; H, 2.72; N, 10.81. Found: C, 37.23; H, 2.85; N, 10.73. $^1$H NMR (DMSO-$d_6$): 10.99 (s, 1H), 8.23 (d, 2H), 7.84 (d, 2H), 4.10 (s, 2H). IR (KBr): 3276 (N–H), 1684 (C=O), 1506 ($NO_2$) cm$^{-1}$. FAB MS $m/z$ ($M^+$): calcd, 259.06, found, 259.27.
*Synthesis of compound* **2**: To a mixture of **1** (1.30 g, 5.0 mmol) and 8-aminoquinoline (0.88 mL, 6.0 mmol) in acetonitrile (130 mL) was added *N*,*N*-diisopropylethylamine (0.54 mL, 6.0 mmol). The resulting solution was refluxed for 12 h and concentrated. The pure product was recrystallized in acetonitrile. Yield 33.7%. Anal. Calcd for $C_{17}H_{14}N_4O_3$ (322.32): C, 63.35; H, 4.38; N, 17.38; O, 14.89. Found: C, 63.54; H, 4.37; N, 17.08. $^1$H NMR (DMSO-$d_6$): 10.90 (s, 1H), 8.80 (d, 1H), 8.25 (m, 3H), 7.89 (d, 2H), 7.55 (t, 1H), 7.39 (t, 1H), 7.15 (d, 1H), 7.02 (t, 1H), 6.61 (d, 1H), 4.23 (s, 2H). IR (KBr): 3352 (N–H), 1715 (C=O), 1520 ($NO_2$) cm$^{-1}$. $^{13}$C NMR (DMSO-$d_6$, 300 MHz): $\delta$ 170.67, 148.01, 144.64, 140.51, 138.35, 136.69, 135.54, 132.72, 128.89, 128.28, 125.98, 125.35, 124.36, 122.57, 115.53, 105.84, 48.42. FAB MS $m/z$ ($M^+$): calcd, 322.32, found, 322.28.
*Synthesis of compound* **3**: A mixture of 2-bromoacethyl bromide (0.89 mL, 10.0 mmol) and 2-nitroaniline (1.13 g, 8.0 mmol) in acetonitrile (60 mL) was refluxed for 6 h. After cooling, the mixture was evaporated to produce crude residue, which was recrystallized from methanol/water, filtered, and dried. Yield 52.7%. Anal. Calcd for $C_8H_7BrN_2O_3$ (259.06): C, 37.09; H, 2.72; N, 10.81. Found: C, 37.11; H, 2.65; N, 10.85. $^1$H NMR (DMSO-$d_6$): 10.71 (s, 1H), 8.00 (d, 1H), 7.74 (m, 2H), 7.42 (t, 1H), 4,13 (s, 2H). IR (KBr): 3341 (N–H), 1686 (C=O), 1505 ($NO_2$) cm$^{-1}$. $^{13}$C NMR (DMSO-$d_6$, 300 MHz): $\delta$ 166.45, 145.36, 143.32, 125.73 (2C), 119.71 (2C), 30.84. FAB MS $m/z$ ($M^+$): calcd, 259.06, found, 259.23.
*Synthesis of compound* **4**: To a mixture of **3** (1.04 g, 4.0 mmol) and 8-aminoquinoline (1.03 g, 7.0 mmol) in tetrahydrofuran (40 mL) was added *N*,*N*-diisopropylethylamine (0.63 mL, 7.0 mmol). The resulting solution was refluxed for 12 h. The mixture was evaporated to produce crude residue, which was purified by chromatography (silica gel, methylene chloride/0–4% tetrahydrofuran), filtered, and dried. Yield 73.7%. Anal. Calcd for $C_{17}H_{14}N_4O_3$ (322.32): C, 63.35; H, 4.38; N, 17.38; O, 14.89. Found: C, 63.33; H, 4.45; N, 17.42. $^1$H NMR (DMSO-$d_6$): 10.83 (s, 1H), 8.83 (d, 1H), 8.28 (d, 1H), 8.15 (d, 1H), 8.03 (d, 1H), 7.75 (t, 1H), 7.56 (t, 1H), 7.38 (m, 2H), 7.23 (t, 1H), 7.19 (d, 1H), 6.63 (d, 1H), 4.16 (s, 2H). IR (KBr): 3435 (N–H), 1708 (C=O), 1501 ($NO_2$) cm$^{-1}$. $^{13}$C NMR (DMSO-$d_6$, 300 MHz): $\delta$ 170.43, 147.89, 145.66, 144.66, 142.94, 138.22, 136.66, 128.93, 128.36, 125.72 (2C), 122.53, 119.58 (2C), 114.86, 105.45, 47.63. FAB MS $m/z$ ($M^+$): calcd, 322.32, found, 322.50.
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