

Synthesis of Two Novel Aroyl Thioureas and Their Use as Anion Binding Receptors

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New aroyl thioureas; *N*-nicotinoyl-*N'*-(4-nitrophenyl) thiourea (**3a**) and *N*-nicotinoyl-*N'*-(2-nitrophenyl) thiourea (**3b**) were synthesized and studied as anion-binding receptors. Upon adding tetrabutyl ammonium halides (fluoride, chloride bromide and iodide), cyanide and hydroxide ions to their solutions in DMSO respectively, the colour of the solutions has shown striking changes from pale yellow to brilliant yellow or red. The binding effects of the anions were investigated by UV-VIS spectroscopic method and ¹H NMR titrations.

Key Words: *N*-Substituted thiourea, Anion coordination, UV-VIS and ¹H NMR titrations.

INTRODUCTION

Over the past few years, the recognition and sensing of various biologically and/or environmentally important anions such as F⁻, AcO⁻, H₂PO₄⁻, CN⁻, OH⁻, etc. have been a key research area of anion coordination known as anion binding chemistry¹⁻⁸. In this context, the coordination chemistry of anions is a relatively new area of research as opposed to that of cations⁹. Anion binding chemistry using neutral host molecules has been extensively studied as a result, anions play in various industrial processes, environmental sciences and enzymatic activity in organisms, clinical treatment of various disease states, etc.¹⁰.

Among the many inorganic anions, fluoride is drawing a special attention due to its beneficial (*e.g.* prevention of dental caries and treatment of osteoporosis) as well as detrimental (*e.g.* fluorosis) roles¹¹. Cyanide ion is a species of high toxicity found mostly in industrial effluents. Inorganic cyanide salts are often used in metallurgical industry activities such as metal surface treatment, but also in mining industry (*e.g.* for gold extraction)¹². Iodide is mainly associated with biological activities such as thyroid function and neurological activity¹³.

The anion binding mainly occurs through weak hydrogen bonding or electrostatic interactions, thus, is usually weaker than cation binding. Anion binding sites of receptors may contain neutral H-bond donor groups such as (thio)ureas¹⁴, calix[4]pyrroles, porphyrins or, activated amides as well as positively charged guanidinium or ammonium groups which bind anions based on electrostatic interactions. In particular, amide NH groups are well-known to be involved in anion binding

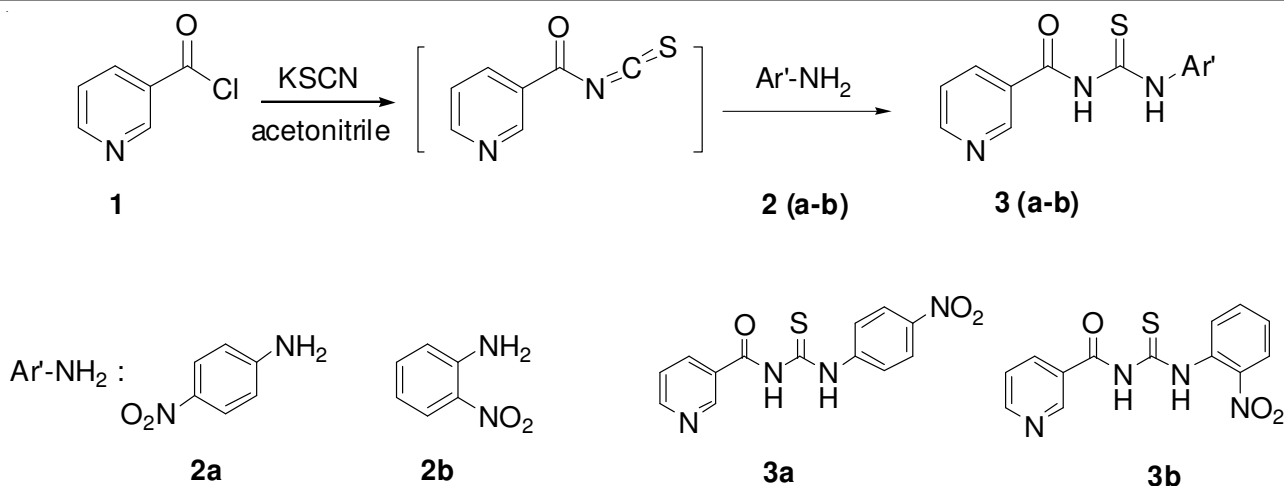
of proteins⁷ and they have been widely used in developing anion receptors and sensors.

Herein, we report two new aroyl thiourea receptors **3(a, b)**, given in **Scheme-I**, which are avid binders of cyanide, hydroxide ions and fluoride anion among halide anions such as chloride, bromide, iodide, as tetrabutylammonium salts. Structurally, compounds **3a** and **3b** are newly introduced receptor nicotinoylthioureas that are substituted with NH groups of *o*- and *p*-nitrophenylamines in their extended framework.

EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded on a resolution Fourier transform Bruker NMR spectrometer operating at 400 and 101.6 MHz. Infrared absorption spectra were obtained from a Perkin Elmer BX II spectrometer in KBr discs and were reported in cm⁻¹ units. The UV-VIS spectra were measured using Perkin-Elmer WinLab series spectrometer. MS spectra were recorded on an Agilent 5973 inert mass selective detector equipped with direct insertion probe. Melting points were measured on an electrothermal IA 9100 apparatus using a capillary tube. All reagents were purchased from Merck Chemical Co.

General synthesis of the aroyl thioureas (3a, b): A mixture of nicotinyl chloride hydrochloride (1.769 g, 10 mmol), KSCN (0.969 g, 10 mmol) and 20 mL of acetonitrile was refluxed with stirring for 1 h, then, a solution of 10 mmol of 2- or 4-nitroaniline in 20 mL acetonitrile was added dropwise to the nicotinoyl isothiocyanate hydrochloride for 0.5 h period at ambient temperature. When the solution was added completely, the resulting mixture was then refluxed for 4 h and the progress



Scheme-I: Synthesis of *N*-nicotinoyl-*N'*-(4-nitrophenyl)thiourea (**3a**) and *N*-nicotinoyl-*N'*-(2-nitrophenyl)thiourea (**3b**)

of reaction was controlled by TLC. After cooling, the solution was poured into a beaker containing ice-water mixture. The yellowish precipitate was altered off and washed with distilled water several times and then dried under vacuum. Recrystallization from acetone yielded 84 % and 87 % of the pure yellow products, respectively.

N-Nicotinoyl-*N'*-(4-nitrophenyl) thiourea (**3a**), $C_{13}H_{10}N_4O_5S$, was obtained as bright yellow crystals (87 %); m.p. 212-213 °C; IR (KBr, ν_{\max} , cm^{-1} pellet): 3005 (N-H), 1673 (C=O), 1518 (C(O)-N), 1283 (N-C(S), thioureido), 845 (C=S); 1H NMR (DMSO- d_6): δ = 12.61 (s, 1H, N-H), 11.95 (s, 1H, N-H), 8.992-7.47 (8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 179.5 (C=S); 170.2 (C=O); 146.1; 137.1; 134.7; 132.9; 131.8; 130.1; 130.0; 129.6; 128.2(Ar); MS: 302, 180, 138.

N-Nicotinoyl-*N'*-(2-nitrophenyl)thiourea (**3b**): $C_{13}H_{10}N_4O_5S$, was obtained as dark yellow crystals (84 %); m.p. 206-207 °C; IR (KBr, ν_{\max} , cm^{-1} pellet) : 3334.8 (N-H), 1674 (C=O), 1511 (carbonyl C-N), 1346 (N-C=S, thioureido), 860 (C=S); 1H NMR (DMSO- d_6), δ ppm: 12.65 (s, 1H, C=ONHC(S)), 12.17 (s, 1H, C=SNHC_{Ph}), 8.992-7.47 (8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 180.4 (C=S); 171.3 (C=O); 145.2; 137.3; 134.2; 132.5; 131.3; 130.6; 130.2; 129.4; 128.1 (C_{Ar}); MS: 302, 138.

RESULTS AND DISCUSSION

N-Nicotinoyl-*N'*-(4-nitrophenyl) thiourea (**3a**) and *N*-nicotinoyl-*N'*-(2-nitrophenyl) thiourea (**3b**) were easily synthesized by reacting the corresponding aryl isothiocyanates with commercially available 4- or 2-nitroaniline in 84 % and 87 % yield (Scheme-I).

In the IR spectra of thiourea derivatives (**3a** and **3b**), the N-H stretching vibrations were observed at 3005 and 3335 cm^{-1} ν (N-H), as intense broad bands, respectively. The strong ν (C=O) absorption bands appeared at 1673 and 1674 cm^{-1} , apparently decreasing in frequencies compared with the ordinary carbonyl absorption (1710 cm^{-1}). This was interpreted as a result of its conjugation with the nicotinoyl ring and formation of intra-molecular hydrogen bonding with N-H. In addition, the strong ν (C=S) absorptions band, appeared at 1283 and 1253 cm^{-1} . The bands corresponding to the C-C stretching vibrations of the nicotinoyl group were observed around 1423 and 1465 cm^{-1} for **3a** and **3b**, respectively. The bands at 1326

and 1347 cm^{-1} were assigned to the -N-C=S vibrations. Vibration bands at 845 and 860 cm^{-1} are known as the relatively high frequency values of the ν (C=S), indicated a strong double bond character of this group in aroylthioureas. Two singlet signals at 12.61 and 11.95 ppm for **3a**; 12.65 and 12.17 ppm for **3b** in 1H NMR spectrum ascribed to NH protons. Multiplet signals in the range 7.47-8.99 ppm were assigned to nicotinoyl and nitrophenyl aromatic protons. Bands at 179.5, 180.4 for C=S and 171.3, 170.2 for C=O ascribed carbon atoms with their ^{13}C NMR spectra for **3a** and **3b**, respectively. In addition, mass spectra of thiourea derivatives (**3a** and **3b**) were obtained to observe $[M]^+$ ions at 302.

Anion binding interaction studies: Upon addition of OH^- , CN^- , F^- , Cl^- , Br^- and I^- (as their tetrabutylammonium salts) in DMSO solutions, the bindings of these anions to host (**3a**, **b**) were investigated by monitoring the changes in the UV-VIS spectra and the colour changes were also observed by 'naked-eye' (Figs. 1-4). The spherical halides were investigated first. However, the additions of either I^- , Br^- or Cl^- afforded only minor changes in the UV-VIS absorbance spectra and we concluded that very weak, binding of these anions occurred, if any. In the case of F^- and CN^- , the addition of the anions into DMSO solutions of **3a** afforded major changes in the UV-VIS absorbance values (Figs. 1). However there was no significant change with **3b** (Fig. 2).

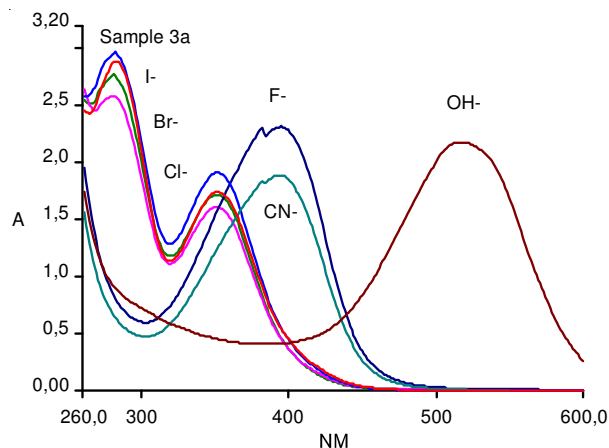


Fig. 1. UV-VIS absorption spectra of compound **3a** (5×10^{-5} M) upon addition of tetrabutylammonium fluoride, chloride, bromide, iodide, cyanide and hydroxide (5×10^{-5} M) in DMSO

TABLE-1
SPECTRAL PARAMETERS (λ_{\max}) OF THE NEW AROYLTHIOUREAS UPON THE ADDITION OF HYDROXIDE, CYANIDE AND HALIDES IONS IN DMSO SOLUTION

Sample	Only	OH ⁻	CN ⁻	F ⁻	Cl ⁻	Br ⁻	I ⁻
3a	352	516	394	393	351	351	350
	281				281	280	280
3b	415	516	416	416	416	416	416
	280		280	280	280	280	280

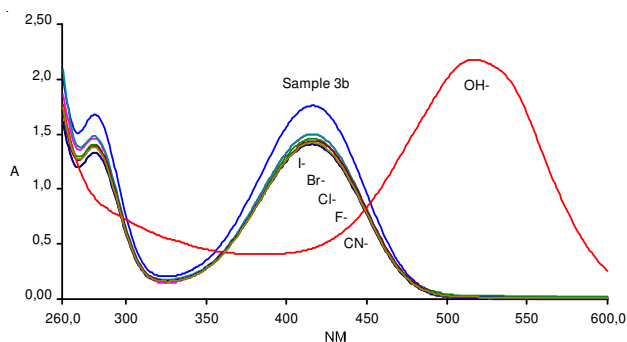


Fig. 2. UV-VIS absorption spectra of compound **3b** (5×10^{-5} M) upon addition of tetrabutylammonium fluoride, chloride, bromide, iodide, cyanide and hydroxide (5×10^{-5} M) in DMSO

A drastic change, thus, the highest λ_{\max} shift, was caused by OH⁻ ions. The successive addition of OH⁻ to DMSO solutions of **3a**, **b** resulted in quite significant changes in the absorbance spectra (Figs. 3 and 4). The results of absorbance changes due to H-bonding of various anions such as F⁻, OH⁻ (λ_{\max}) are shown in Table-1.

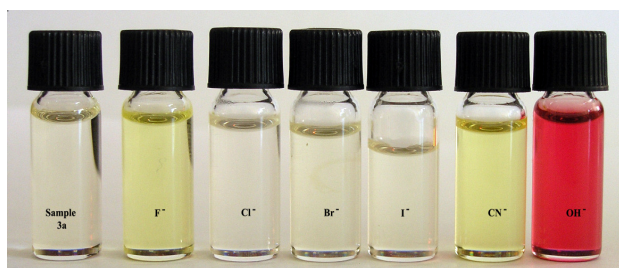


Fig. 3. Changes in the colour of 5×10^{-5} M DMSO solution of receptor **3a**. From left to right, in the absence of ions, in the presence of tetrabutylammonium anions; fluoride, chloride, bromide, iodide, cyanide and hydroxide



Fig. 4. Changes in the colour of 5×10^{-5} M DMSO solution of receptor **3b**. From left to right, in the absence of ions, in the presence of 1 equiv. of tetrabutyl-ammonium anions; fluoride, chloride, bromide, iodide, cyanide and hydroxide

Fig. 5 shows the UV-VIS spectral changes of **3a** during titration with fluoride. The original absorbance peaks appeared at λ_{\max} of 352 nm and 393 nm, *i.e.* the π - π^* transition bands of

the chromophore (nitrophenyl). Upon the addition of fluoride ions in increasing quantities, the peak at 352 nm first decreased but that at 393 nm increased, which was ascribed to the charge transfer (CT) between the anion bound-NH units and electron-deficient-NO₂ moiety at the *para* position, causing the sensor solution to change from light yellow to bright yellow. Obviously, there was one and only one well-defined isosbestic point at 345 nm, which indicated that there existed only one type of host-F⁻ complex. (Fig. 5). The addition of OH⁻ also led to spectral changes (Fig. 6). Similarly, there were two well-defined isosbestic points at 492 and 516 nm which indicated that there existed two types of host-OH⁻ complexes.

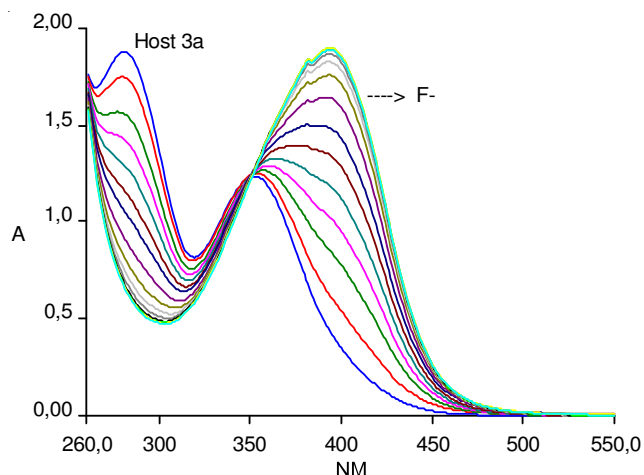


Fig. 5. UV-VIS spectral titration of **3a** with F⁻ (as its tetrabutylammonium salt) in DMSO, from which the association constant was determined¹⁵, $\log K = 4.3 \pm 0.13$

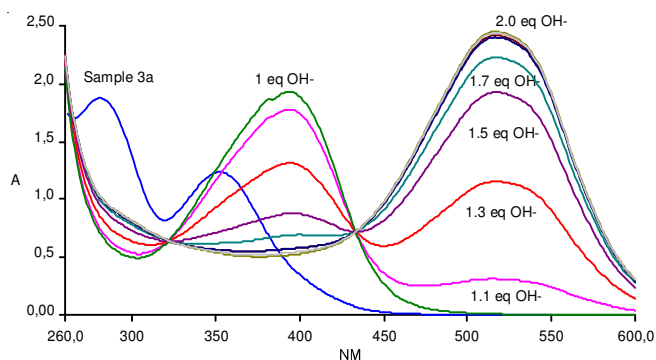


Fig. 6. UV-VIS spectral titration of **3a** with OH⁻ (as its tetrabutylammonium salt) in DMSO, from which the two association constants were determined¹⁵, $\log K_1 = 5.53 \pm 0.24$ and $\log K_2 = 4.24 \pm 0.18$

Secondly, to explore more about the applicability of **3b** as a sensor for F⁻ and OH⁻ anions, UV-VIS titrations were performed in DMSO. Upon the addition of hydroxide ion in increasing quantities, the colour of the sensor solution changed

from light yellow to red and the intensity of the peak at 415 nm decreased, but that at 516 nm increased, which was ascribed to the charge transfer (CT) between the anion bound -NH units and the electron-deficient-NO₂ moiety at the *ortho* position. In the presence of 1 equivalent amount of F⁻, no change in the absorbance values was observed (Figs. 7 and 8).

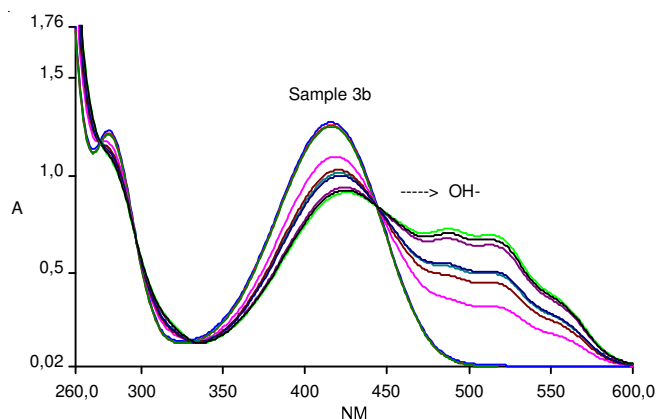


Fig. 7. UV-VIS spectral titration of **3b** with OH⁻ (as its tetrabutylammonium salt) in DMSO solution, from which the association constant was determined¹⁵, log K = 3.92 ± 0.21

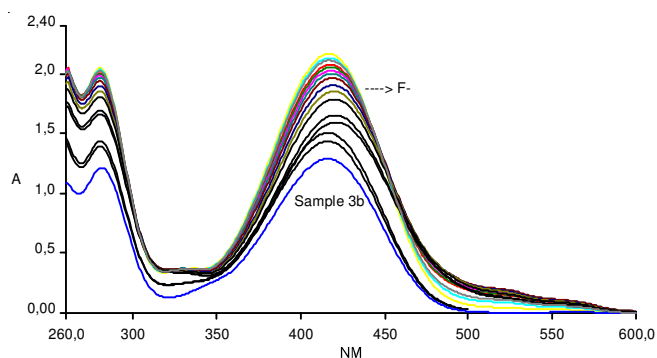


Fig. 8. UV-VIS spectral titration of **3b** with F⁻ (as its tetrabutylammonium salt) in DMSO solution

The bindings of host **3a** to F⁻ ion was investigated by monitoring the changes in the ¹H NMR spectra of DMSO-*d*₆ solutions of **3a** upon addition of F⁻. In the case of F⁻, the N-H signal of **3a** at 12.61 ppm completely disappeared while the other N-H signal at 11.95 ppm was significantly broadened after the addition of 1 equiv. of the anion (12.02 ppm) solution. Complete disappearance of both N-H signals was observed after the addition of 2 equiv. of the ion solution due to deprotonation of the thiourea moiety of the sensor, **3a** via hydrogen binding with the anion (Fig. 9).

In the qualitative experiments, the presence of F⁻ or CN⁻ or OH⁻ ions resulted in visible changes of solution of the sensor **3a** and **3b** from pale or light yellow to brilliant yellow and red which could be detected by naked-eye without resorting to any spectroscopic instruments (Figs. 3 and 4).

Conclusion

The two new *N*-aroylthiourea derivatives were synthesized as potential colorimetric chemosensors for fluoride, cyanide and hydroxide ions. *N*-aroylthiourea derivatives display hydrogen binding ability according to their ¹H NMR and UV-VIS spectra upon the addition of fluoride, cyanide and hydroxide

ions in DMSO. It was proven that there was a strong hydrogen binding interaction between fluoride anion and the two N-H groups of these aroylthioureas by means of ¹H NMR titration, UV-VIS spectra or with naked-eyed change results.

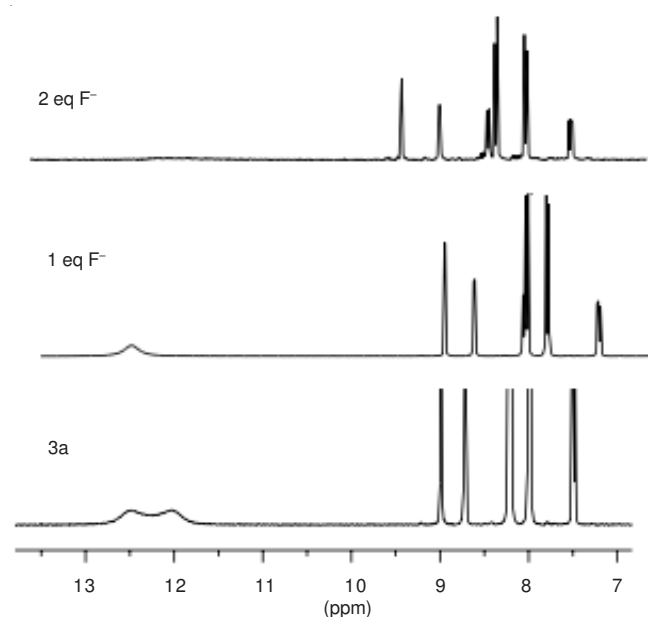


Fig. 9. Partial ¹H NMR (400 MHz) of **3a** (1 mM) in DMSO-*d*₆. Compound a only; 1+1 equiv of F⁻; 1+2 equiv of F⁻

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