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RESEARCH ARTICLE

Spectrophotometric Determinationof 6-(Trifluoro methyl)-furo[2, 3-b]pyridine-2-carbohydrazide Derivatives using Iodine in Water

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Abstract: New, rapid and accurate spectrophotometric procedure was developed, to determine the 6-(trifluoro methyl)furo[2, 3-b]pyridine-2-carbohydrazide analogues in pure form. The method was based on the reaction of these analogues as *n*-electron donors with the sigma-acceptor iodine. The obtained charge transfer complexes were measured at 370 nm for iodine in water. The obtained complexes were examined by using the UV, IR and ^{1}H NMR spectral analysis. A complete detailed investigation of the formed complex was made with respect to the association constant and free energy change. The association constants were calculated using iodine method and Rose-Dragoequation. The values of association constants show a strong donor-acceptor interactions, which help to study the possible site of interaction between the donors and the acceptors.

Keywords: Spectrophotometry, Charge transfer complexes, Fluoro-pyrine-2-carbohydrazides, Iodine

Introduction

6-(Trifluoro methyl) furo [2, 3-b] pyridine-2- carbohydrazides (FP2C) are chemical agents that exert their principle pharmacological and therapeutic effects by acting at peripheral sites to reduce the activity of components of the sympathetic division on autonomous nervous system[1]. Based on the importance of these compounds a series of novel trifluoromethyl substituted pyrido-pyrimidine derivatives were synthesized by our collaborative research group. All the compounds were screened for cytotoxic activity against breast carcinoma MDA-MB 231 (aggressive) cell lines at 10 μm concentration and promising compounds have been identified[2].

FP2C analogues are known to form electron donor acceptor complexes with a number of electron acceptors. Iodine is one of the good electron acceptor with electron affinity of 3.059eV[3].

Intermolecular charge-transfer (CT) complexes are formed when electron donor and electron acceptor interacts which is evident from Mulliken theory[4]. CT complexes have unique absorption bands in the ultraviolet-visible region[5]. Some of the charge transfer complexes containing I_2 as an acceptor have been reported they are Mesytelene-Iodine[6], Perylene-Iodine[7] *etc*.

The spectrophotometric methods based on these interactions are usually simple and convenient because of the rapid formation of the complexes. In present communication, spectrophotometric study provides an estimation method of therapeutic FP2C analogues via reaction with σ-acceptor in their common dosage forms irrespective of the presence of contaminants or additives.

Experimental

All the chemicals were used of analytical grade. Fischer certified Iodine was directly used and the FP2C analogues were collected from IICT, Hyderabad. Spectrophotometric analysis for optical density measurements were carried out on an ELICO-SL171 UV-Visible Mini Spectrometer having a fixed slit width 1 cm quartz cells**.**

Preparation of experimental solutions

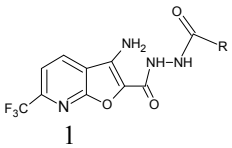
The concentration of iodine (reagent) was held constant at 3.58×10^{-4} M by dissolving the iodine in 2-3 drops of 0.1 M KI solution and 110 mL of distilled water quantitatively to obtain the suitable concentration. 10^{-4} M concentration of ascorbic acid was prepared by weighing the 1.7 mg of ascorbic acid (standard) accurately and by dissolving in 2 mL of ethanol. Ascorbic acid solution was added to the reagent solution. Ascorbic acid concentration is standard and by maintaining this standard concentration each time dilute solution of FP2C analogues were prepared.

General analytical procedure

Initially absorbance of the freshly prepared reagent solution was measured at the wave length of 370 nm by using spectrophotometer at room temperature, prepared standard solution of FP2C analogue was then added to 110 mL of reagent solution and the absorbance of this solution (test solution containing charge transfer complex) was measured at the same wave length at room temperature and after 10 minutes absorbance was recorded. Basic structures and structural skeleton of the FP2C analogues were shown in the Figure 1 and Table 1

Table 1. Structural skeleton of FP2C analogues

Compound	R	R'
1S1		
1S2		
1S3		
1S4		
1S5		
1S6		
2S1	CH_3	CH_3
2S2		
2S3		
2S4		
2S5		
2S6		



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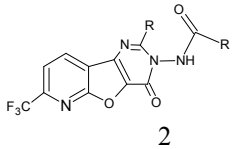

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Figure 1. Basic structures

Results and Discussion

FP2C analogues were basic nitrogen compounds, which act as *n*-donors and form charge transfer complexes with *σ*-acceptor iodine followed by tri- iodide ion pair. Donors were completely transparent to visible light while iodine absorbs at 370 nm to shorter wave length 247 nm (hypsochromic shift). Mixing of iodine solution to donors resulted in decrease in intensity of colour. As a consequence, absorption of iodine shifted to shorter wave length with a simultaneous appearance of blue shift iodine band which provide a significant, time saving method for the determination of donors from intensities of iodine band and BSB Origins. Formation of CT complexes is due to excitation of electrons from orbital of donor to orbital of acceptor. Charge transfer complex formation was confirmed by the formation of polymer with acrylo nitrile[8].

$$D + I_2 \Leftrightarrow D - I^+ I^- \Leftrightarrow \qquad [D - I^+] + I - \overset{+I_2}{\Leftrightarrow} I_3^-$$

Charge transfer complex Tri iodide ion pair

Optimum reaction conditions

It was found that the suitable wave length for carrying the assay is 370 nm (Figure 2) and the reaction time required for the formation of charge transfer complex is 10 minutes.

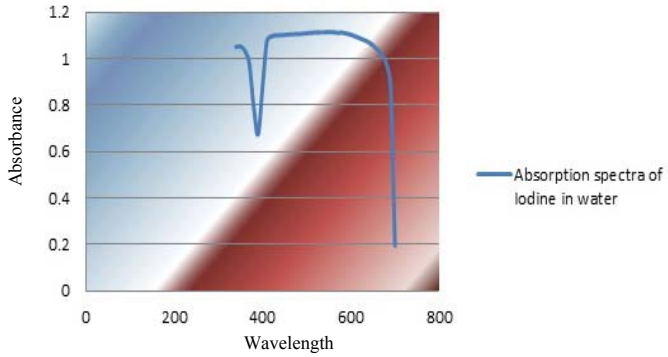

Figure 2. Absorption spectra of iodine in water

Association constants and standard free energy changes

The association constants were calculated for the interaction of each FPC2 analogue with iodine complex using Iodine method[9] and Rose -Dragoequation[10].

Iodine method

Association constants (K_c) of complexes were calculated from the following equation**.**

$$K_C = \frac{[C]}{([I_2] - [C])([N] - [C]}$$

Where, [C] = molar concentration of the complex, $[I_2]$ - [C] = molar concentration of the free iodine, [N] -[C] = molar concentration of the free donor.

Free energy change (ΔG) is obtained from K_C values using the following equation.

$$\Delta G = -2.303RT \log Kc$$

Where, K_C is the association constant of drug-acceptor complex.

Table 2. Association constants values from Iodine method

Compound	$K_C \times 10^3$ J/mol	ΔG kJ/mol
1S1	5.698	-21.56
1S2	5.810	-21.62
1S3	5.893	-21.65
1S4	5.893	-21.65
1S5	6.005	-21.70
1S6	5.837	-21.63
2S1	5.949	-21.67
2S2	5.530	-21.49
2S3	5.670	-21.55
2S4	5.418	-21.44
2S5	5.782	-21.60
2S6	5.642	-21.54

Rose-Drago method

Association constants (Kc) of complexes were calculated from the following equation**.** $K^{-1} = A/\varepsilon - ([A_0] + [D_0]) + [A_0D_0]\ \varepsilon/A$, Where ε = Molar extinction coefficient of the complex, A_0 = initial concentration of the acceptor, D_0 = initial concentration of the acceptor.

Table 3. Association constant values from Rose-Drago method

Compound	$\varepsilon \times 10^4$	$K_C \times 10^3$ J/mol	ΔG kJ/mol
1S1	0.426	2.635	-19.64
1S2	0.404	2.626	-19.62
1S3	0.381	2.626	-19.65
1S4	0.404	2.626	-19.65
1S5	0.415	2.620	-19.70
1S6	0.431	2.629	-19.63
2S1	0.443	2.623	-19.67
2S2	0.474	2.639	-19.49
2S3	0.462	2.636	-19.55
2S4	0.515	2.641	-19.44
2S5	0.417	2.631	-19.60
2S6	0.448	2.636	-19.54

High association constant and free energy change values which were obtained by iodine and Rose-Drago equation reveals the good binding affinity between *σ*-acceptor iodine and *n*-donor FP2C analogues. The high values of association constants are common in *n*-electron donors where the intermolecular overlap may be considerable[11].

Spectral analysis

From the data given in Table 5 it is clear that most of the fundamental frequencies of the electron-pair donor compound 1S1 show significant shifts, strongly supporting the formation of the 1S1-I_2 complex. Generally, υ (C=O) and υ (C-H) aliphatic bands of the free donors are shifted to lower frequencies on complex formation. This behavior is in accordance with the charge migration from donors to acceptors. Meanwhile, such small changes clearly indicate that these bonds in 1S1 are not involved in the complexation process with iodine. On the other hand, υ (N-H) of the 1S1 show the largest shifts upon complexation with iodine. These changes clearly show that, as expected[12], the nitrogen atoms as *n*-donors in 1S1 molecule are mainly involved in the complexation with iodine as an electron-accepting molecule.

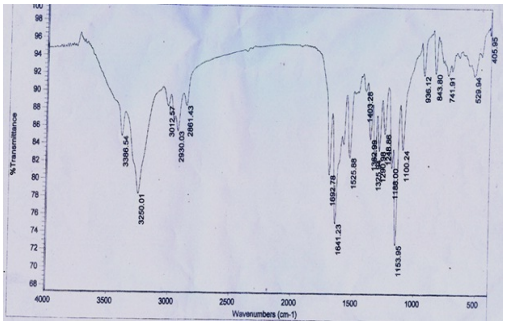

Figure 3. IR spectrum of 1S1 before the formation of complex

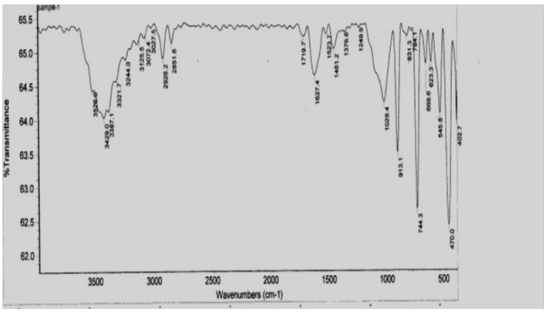

Figure 4. IR spectrum of 1S1 after the formation of complex

Table 5. Infrared frequencies (cm^{-1}) and tentative assignments for 1S1 and its charge transfer complex with iodine

Sample (1S1) Sample (S1)	Complex $(1S1i^{+})i_3^{-}$ Complex $(S1i^{+})i_3^{-}$	Assignment Assignment
3250.01	3429.01	υ(N-H)aromatic
3386.54	3526.0	υ(N-H)
3012.57	3072.4	υ(C-H)aromatic
2930.03	2926.2	υ(C-H)aliphatic
1403.28	1461.2	$\upsilon(-CH_2-)$
1692.78	1627.4	υ(C=O)
1188.00	1249.9	$\upsilon(CF_3)$

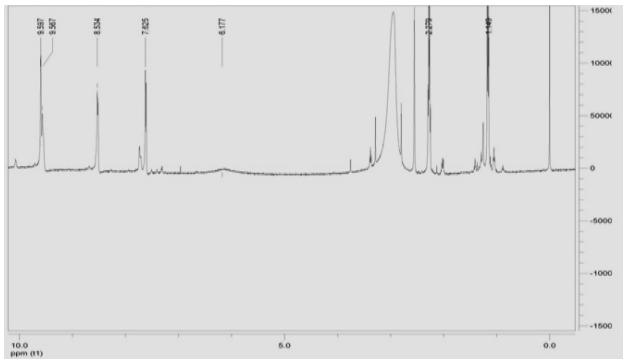

Figure 5. NMR spectra of S5 before the formation of complex

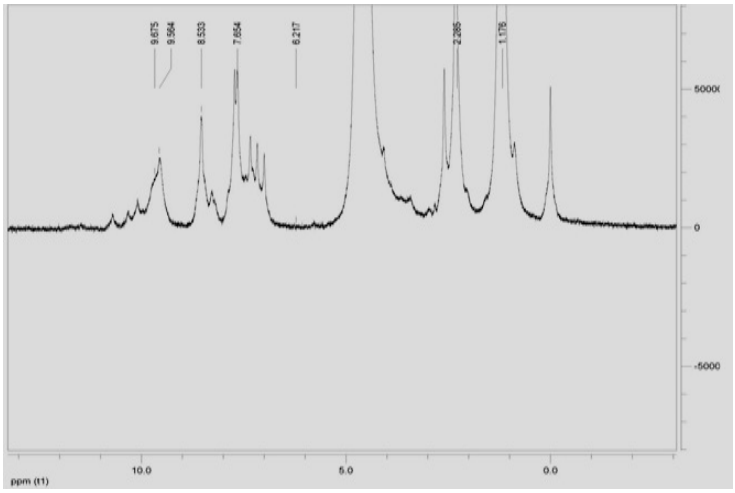

Figure 6. NMR spectra of 1S5 after the formation of complex

Table 6. [1]H NMR spectral data of 1S5 and its charge transfer complex with iodine

S5	6.17 (s, 2H) $-NH_2$	9.59 and 9.56 (s, 1H) -CONH	8.53 and 7.62 (d, 1H) Ar-H	2.27 (q, 2H) $-CH_2$	1.14 (t, 3H) $-CH_3$
S5-I_2	6.21	9.67 and 9.56	8.53 and 7.65	2.31	1.17

[1]H NMR spectrum of 1S5 showed 7 series of signals for different protons involved; these consisted of a singlet at 9.56 ppm for one of the amide proton, a singlet at 9.59 ppm for the other amide proton, a singlet at 6.17 for $-NH_2$ protons, triplet at 1.14 ppm for methyl protons, a quartlet at 2.27 ppm for CH_2 protons and doublets at 7.62 ppm and 8.53 ppm for aromatic protons. Meanwhile, all protons of the 1S5 show some pronounced shifts upon complexation with iodine, the shifts in both amine and amide -NH protons being larger than that of other 1S5 protons. In support of the IR results, the observed chemical shift behavior may reveal the transfer of charge from nitrogen atoms of the 1S5 to the acceptor molecule iodine, during the course of complexation reaction[13].

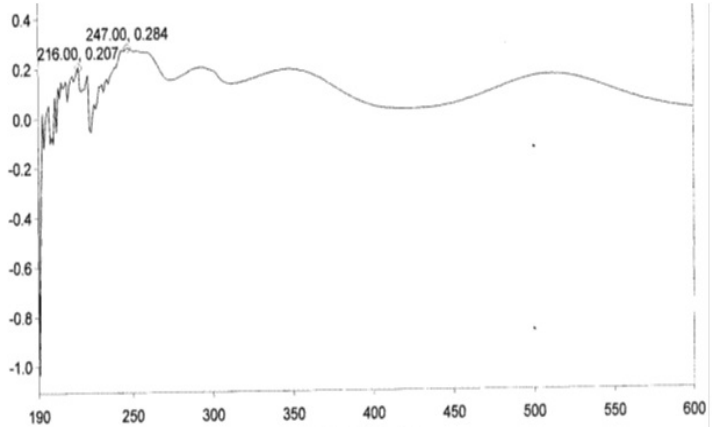

Figure 7. Absorption spectrum of 1S1 complex

In the UV spectrum of 1S1 and iodine complex electronic absorption bands are found shifted towards shorter wavelength upon complex formation *i.e.* from 370 nm to 247 nm, which confirms the formation of charge transfer complex[14].

Conclusion

The proposed method is simple and free from drastic experimental conditions such as heating. It is also accurate and precise enough to be successfully adopted as an alternative to the existing spectrophotometric methods. The present research work has demonstrated the feasibility of the use of UV Vis spectrophotometry, complexation reaction and the suitability of Iodine as electron acceptor, which is evident from association constant values and spectral data. On the other hand, in terms of simplicity and expense, the method could be considered superior in comparison with the chromatographic method and the previously reported methods, especially with those based on non-aqueous medium.

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