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# Fluoride selective colorimetric sensor based on cefetamet pivoxil drug

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ABSTRACT

A simple fluoride ion selective chemosensor was developed using cefetamet pivoxil (L) drug. In the presence of $F^-$ ions, the drug L selectively portrayed a naked-eye detectable color change from colorless to red with the appearance of a new charge transfer band at 500 nm. No significant color change was observed with other tested anions such as $Cl^-$, $Br^-$, $I^-$, $AcO^-$, $HSO_4^-$ and $H_2PO_4^-$. Further, the antimicrobial activity of L was screened in the absence and presence of $F^-$ by agar well diffusion method.


## 1. Introduction

Fluorine is the thirteenth most abundant element in the earth's crust and is the lightest member of the halogens. It is the most electronegative and reactive of all the elements and as a result, elemental fluorine does not occur in nature but is found as fluoride mineral complexes [1]. Fluoride is present in soil and rock formations: fluorapatite [$Ca_5(PO_4)_3F$], fluorspar ($CaF_2$), amphiboles [$Na(CaNa)Mg_5\ Si_8O_{22}F_2$], micas [$K(Fe,Mg)_3AlSi_3O_{10}(F,OH)_2$] [2–5]. The fluoride present in these soil/rock/minerals is substituted by hydroxide ions resulting in the release of fluoride ions to the circulating water [5]. Hence, the presence of high fluoride content in drinking water is a serious health hazard and found to cause arthritis, osteoporosis, hip fractures, cancer, infertility, Alzheimer's disease and brain damage [6,7]. Human body is also exposed to fluoride mainly through consumption of water and other edible products; for example, fluoride contents in drinking water is generally in the range of 0.5–1.5 mg/L, tea leaves containing 4–138 μg of fluoride per gram, toothpaste containing 53–338 μg of fluoride per gram and 16–306 μg per gram for pan masala with tobacco [8]. Besides its biological role, fluoride is also used as a potential catalyst in a number of inorganic and organic syntheses [9,10]. The importance of accurate determination of fluoride has been increased with the growth of the practice of fluoridation of water supplies as a public health measure. Taking into account of the importance of fluoride, an attempt has been made to design and develop a low cost sensor.

Fluoride ions mainly recognized through hydrogen-bonding interactions [11], electrostatic interactions [12] and coordination with metal ions [13]. Among various non-covalent interactions, hydrogen-bonding is particularly useful and effective in this respect [14]. Among the different types of chemosensors, the sensors based on colorimetric have many advantages due to the simplicity and high sensitivity. However, the development of anion sensor is challenging in compared to cations because anions are larger (lower charge to radius ratio), pH sensitive, highly solvated and they come in a wide range of different geometries: spherical, linear, trigonal, tetrahedral, octahedral, etc., [15,16]. Recently, numerous charged/neutral receptors containing binding groups such as imidazoles [17,18], pyrroles [19], calixpyrroles [20], amides [21,22], cabamides [23], phenols [24], ureas [25,26], thioureas [27,28] and amidoureas [29,30] have been studied for the selective sensing of target anions.

Cephalosporins are β-lactam antibiotics that differ from the penicillin's in that the β-ring is 6-membered dihydrothiazine ring (Fig. 1) [31]. Variations among the cephalosporins are made on either the acyl side chain at 7-position to change antibacterial activity or at the 3-position to alter the pharmaokinetic profile. Cephalosporin C was first isolated in 1948 by Dr. Abraham from a fungus, *Cephalosporium acremonium*, collected in seawater near a sewage outlet in Sardinia by Professor Guiseppe Brotzu in 1945.

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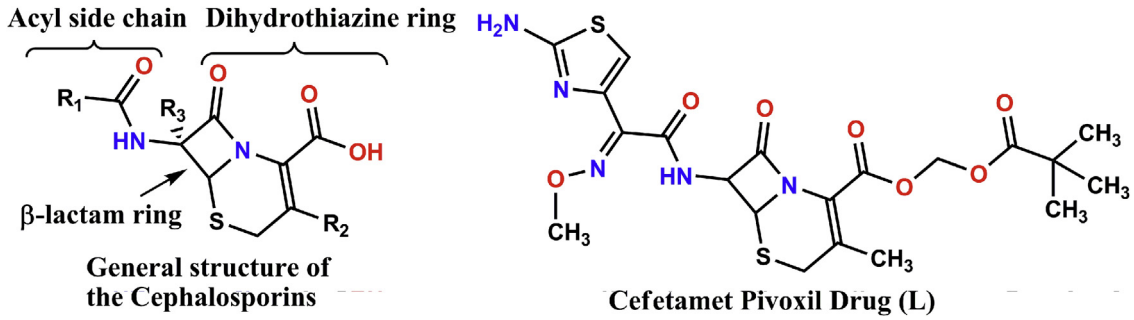


**Fig. 1.** General representation of cephalosporin and cefetamet drug (L).

Moreover, Cefetamet is classified as a third generation cephalosporin with excellent activity against many aerobic gram positive and gram negative organisms [32,33]. In this paper, we have investigated the colorimetric sensing ability of cefetamet pivoxil (L) drug toward different anions such as $F^-$, $Cl^-$, $Br^-$, $I^-$, AcO–, $HSO_4^-$ and $H_2PO_4^-$ by various experimental (naked-eye, UV–vis, $^1H$ NMR and FT-IR) and theoretical (B3LYP/6-31G(d,p)) methods. Also, the antimicrobial activity of L was screened in the absence and presence of $F^-$ by agar well diffusion method.

## 2. Experimental

### 2.1. Materials and methods

All chemicals of AR grade were purchased from Sigma–Aldrich, Alfa Aesar or Spectrochem based on their availability and used without further purification. All the solvents were procured from SD Fine, India of HPLC grade and used without further purification. The anions were added in the form of tetra-n-butyl ammonium (TBA) salts and were obtained commercially in the purest form. UV–vis spectra were recorded on a VARIAN CARY 50 spectrophotometer in the wavelength range of 250–700 nm with a quartz cuvette of 1 cm path length. All spectroscopic experiments were carried out at room temperature. Stock solutions of drug ($1.0 \times 10^{-3}$ M) and different anions ($1.0 \times 10^{-3}$ M) were prepared in $CH_3CN$ and stored in the dark chamber. $^1H$ NMR spectra were recorded on a Bruker AM 400 spectrometer with tetramethylsilane (TMS) as internal reference and DMSO-$d_6$ as solvent. The infrared spectrum (KBr pellet) was recorded using a Perkin-Elmer IR spectrophotometer in the range of 400–4000 $cm^{-1}$. The drug was collected from Orchid Pharma, Chennai, India and characterized by $^1H$ NMR (DMSO-$d_6$, $\delta$, ppm: 1.16 (s, 9H, $CH_3$), 2.03 (s, 3H, $CH_3$), 3.42 and 3.63 (two doublets, 2H, $CH_2$), 3.93 (s, 3H, $CH_3$), 5.16 (d, 1H, CH), 5.73 (dd, aH, CH), 5.78 and 5.89 (two doublets, 2H, $CH_2$), 6.92 (s, 1H, CH), 8.68 (sb, 2H, $NH_2$) and 9.77 (d. 1H, amide-NH).

### 2.2. Determination of antimicrobial activity

The materials Muller Hinton agar plates, Haemophilus test medium plates, sterile saline, densi-la-meter, cotton swabs, cefepime (30 μg) discs were used for the antimicrobial test. The cultures *E. coli* ATCC 25922 and *H. Influenzae* ATCC 33533 were used. Muller Hinton Agar plate and Haemophilus medium plate were inoculated with overnight grown cultures, previously adjusted to 0.5 McFarland standard turbidity and diluted to 1:10 using sterile saline solution, following the CLSI recommendations. Wells were made in the plates with a well puncture rod. Then, 10 μL of the drug (1 mM), fluoride and 20 μL (1 mM) of the mixture of drug and fluoride were added to the wells. Similarly, 30 μL of standard drug was added as a control. All plated were incubated overnight at 37 °C, and the zone of inhibition was measured to determine the antimicrobial activity.

### 2.3. Computational methods

The theoretical calculations were carried out with the Gaussian 09W computer code using the density functional theory (DFT) method [34]. The structural optimization of receptor L and the fluoride-L complex was performed without symmetry constraints by applying B3LYP/6-31G(d,p) method in the gas phase. Then, the harmonic vibrational frequency calculations were carried out to ascertain the presence of a local minimum.

## 3. Results and discussion

### 3.1. Anion sensing ability of L

The selective colorimetric sensing ability of L ($5 \times 10^{-4}$ M) toward different anions ($5 \times 10^{-4}$ M) were monitored by naked-eye observation and UV–vis absorption spectra in $CH_3CN$. The naked-eye test inferred that the colorless solution of L changed into red on selective interaction with one equivalent of $F^-$ (Fig. 2). However, the addition of other anions ($Cl^-$, $Br^-$, $I^-$, $AcO^-$, $H_2PO_4^-$ and $HSO_4^-$) did not result in obvious visual responses even in abundance. Simultaneously, the absorption spectra of L were recorded in the absence and presence of one equivalent of different anions to investigate the qualitative anion binding ability of the drug in $CH_3CN$ (Fig. 2). The colorless drug showed an absorption band at 275 nm can be assigned due to $\pi \rightarrow \pi^*$ transition. With the addition of $F^-$ ions to the drug solution resulted in the appearance of a new broad peak at ~500 nm which indicates the possible

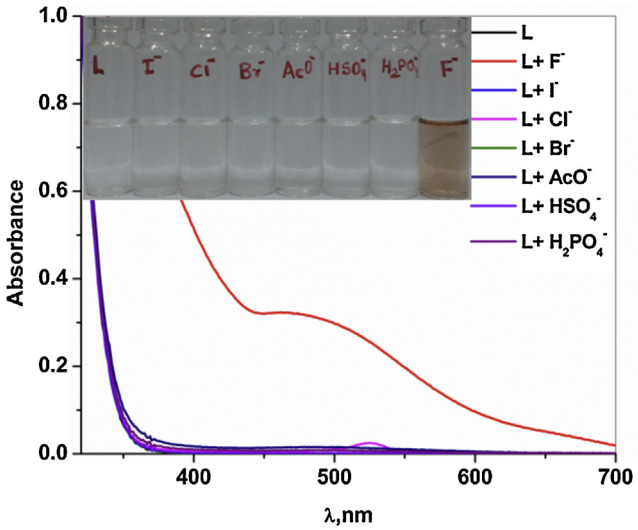


**Fig. 2.** UV–vis spectral changes of the receptor L ($5.0 \times 10^{-4}$ M) upon addition of equivalent of different anions in $CH_3CN$. Inset showing the color changes of the different vials.