

## Review

# Excited-State Proton Transfer for Biomarker Detection

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**Abstract:** Biomarker detection is imperative in the realms of modern medicine, biology, and environmental science, owing to the numerous avenues for its application. The recent scientific upsurge in the development of molecules, materials, and mechanisms for such scientific development has garnered considerable attention among scientists. In this connection, excited-state intramolecular proton transfer (ESIPT) properties of photoluminescent compounds provide considerable insights into the designing, development, and detection of biomarkers. ESIPT molecules significantly show a Stokes-shifted emission due to their sensitive nature and unique photophysical properties. Leveraging this photophysical property and tunable nature, several fluorescent probes of this genre can be designed and synthesized for a plethora of application spheres. Schiff bases encompass one such category of functional molecules displaying ESIPT properties, which can be mitigated by adding several other functionalities and desired optical characteristics. The current review article spans the basics of ESIPT properties of certain photoluminescent molecules and also envisages biosensing applications of recently developed imine-functionalized Schiff base molecules with such properties as the *prima-foci*, along with other applications.

**Keywords:** proton transfer; excited state; sensor; biomarker; Schiff base; tautomer; fluorescence



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## 1. Introduction

Spectroscopy has been an intriguing methodology for scientists of various disciplines to study different molecules. The absorption of electromagnetic radiation by photoactive molecules is a fundamental phenomenon, and it can be applied for both qualitative and quantitative analytical purposes. The photoexcitation of molecules by electromagnetic radiation of suitable wavelengths in the ultraviolet and/or visible regions initiates various significant photophysical and photochemical processes in the molecules. Photophysical processes are those that bring the excited molecule intact down to the ground state, while photochemical processes lead to the formation of new products. All these photophysical processes occur within the natural radiative lifetime of the molecule. Radiative transitions occur by the emission of light quanta or photons. The emission of a photon results from two major phenomena depending on the spin multiplicity of the two states involved, namely, *Fluorescence* and *Phosphorescence* [1–4]. Fluorescence spectroscopy is one of the most coveted, cheap, sensitive, and simple techniques that offers a wealth of molecular information, widely used in medical diagnostics, biotechnology, genetic analysis, physiology, biology, pharmacology, DNA sequencing, forensics, and cellular and molecular imaging. They have extensive applications, such as being used as chemical sensors, fluorescent labels,

fluorescent dyes, biological detectors, fluorescent lamps, etc. [5–8]. *Chemosensors*, in many instances, extrapolate fluorescence properties for the detection of analytes. These fluorescent receptors establish a non-covalent reversible host–guest interaction with the analytes, thus aiding their detection [9–11]. Fluorescence imaging, owing to its sensitivity, finds common applicability in the medical domain to sense and detect analytes of biological importance [12–14].

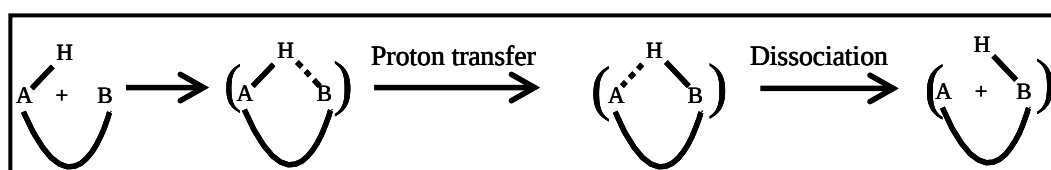
Photoexcitation of molecules in solution induces several changes in the geometrical and electronic structure/properties of molecules, which becomes significantly heightened in the excited electronic states, ultimately leading to various photophysical and photochemical processes within them [15,16]. Photochemistry delves into the emergence of several interesting phenomena, such as charge transfer (CT), proton transfer (PT), energy transfer (ET), etc., which are direct results of the charge redistribution on the different parts of a molecular system [17–20]. The acidic or basic properties of a photoactive molecule differ in the ground and excited states. The most interesting cases are those where acids and bases are stronger in the excited state than in the ground state since, in these cases, excitation may lead to the transfer of protons in the photoexcited state. PT, the simplest chemical reaction where an actual displacement of an atomic nucleus occurs, is a notable primary step in many chemical or biological reactions, especially in enzyme catalysis reactions. A PT reaction, being associated with a charge separation along with a mass transfer, gets remarkably modified in the excited state. Changes in dipole moment and molecular geometry can lead to large dielectric relaxation effects on the spectroscopy and transformation dynamics of the prototropic system [21–26]. Photoinduced proton transfer reactions can be classified as either (i) Excited-State Intermolecular Proton transfer (ESPT) or (ii) Excited-State Intramolecular Proton transfer (ESIPT), depending on the hydrogen bond formation, as will be discussed vividly in the upcoming section. Both ESPT and ESIPT have been of considerable interest and intrigue for scientists on account of their applications in photovoltaics, sensors, chemodosimeters, biological imagers, molecular switches, etc. Their applicability as suitable probes for biomarker detection is mainly due to their structural adjustability, sensitivity, and fast response time [27–33]. This review will primarily focus on the applicability of these photochemical proton transfer processes for biological marker detection and imaging.

### 1.1. Principles and Mechanism of ESPT and ESIPT

Proton transfer reactions are associated with charge separation, where mass transfer occurs within different atoms of the same molecule or between two different molecules having differential charge centers. This charge separation gets dramatically modified upon photoexcitation. For instance, a score of aromatic amines that are weakly basic in the ground state becomes acidic in the excited state. Such an excited-state acidic molecule can readily donate a proton to a proton-acceptor, thereby producing the corresponding anion in the excited state, and the substrate is termed a photo acid. Similarly, a photo base is one that displays pronounced basic properties in the photo-excited state relative to its ground state [34–36]. In an ESPT process, the proton is transferred from one molecule to another. The kinetics of the intermolecular ESPT process have been extensively studied over the years, complementing and sometimes permitting the correction of previously existing thermodynamic data or dissociation constants. Thermodynamic principles corroborate the above-mentioned ESPT mechanism [37,38]. The detailed knowledge of intermolecular ESPT involving  $O^-$  acids and  $N^-$  acids and their fast rates observed have stimulated the use of these atomic centers as probes of increasingly complex structures. The review work of Arnaut and Formosinho [39] focused on the thermodynamics and kinetics of intermolecular proton transfer occurring in the lowest excited singlet state of organic

compounds, followed by a discussion about the acidity constant ( $pK^*$ ), deprotonation, and protonation rates in this electronic state. In the case of ESPT, a logical question is whether the acid–base equilibrium is attained or not within the excited-state lifetime of the photoacid or the photobase. If the acid–base equilibrium is attained in the photoexcited state,  $pK_a$  and  $pK_b$  of the corresponding excited states are determined by steady state or time-resolved emission spectroscopy. The ESPT mechanism is mainly found to occur in p-conjugated organic flat heterocyclic moieties or molecules with biological relevance, viz., DNA bases, photosystem II, green fluorescence protein (GFP), and bacteriorhodopsin. Among these, the last two are invincible biomarkers in the realms of biotechnology, as is evident from the work of Hong et al., where they mainly highlighted the ESPT mechanism in a D- $\pi$ -A molecular architecture [40]. A biomarker or biological marker is defined as a measurable indicator of a biological state or condition, since biomarkers are critical kits in precision medicine, enabling personalized treatment options for individual patients with specific biological characteristics. Hence, their methods of detection through an array of methodologies have a significant impact on the scientific fraternity.

ESIPT, on the other hand, proceeds within the same molecule along a preformed hydrogen bond. ESIPT takes place in a molecule when the acidic or basic part of it becomes stronger in the excited state, which ultimately leads to the formation of a tautomer. This takes place via the formation of an intramolecular hydrogen bond between the two moieties that provide the doorway for the intramolecular proton transfer process, as shown in Scheme 1. The photo-tautomers are usually formed in the excited state and relax quickly to the ground state (non-emissive) or fluoresce with a large Stokes-shift (emissive). Generally, ESIPT reactions are followed by the rise and decay of the strong Stokes-shifted fluorescence of the tautomer produced through the ESIPT process [41–45].



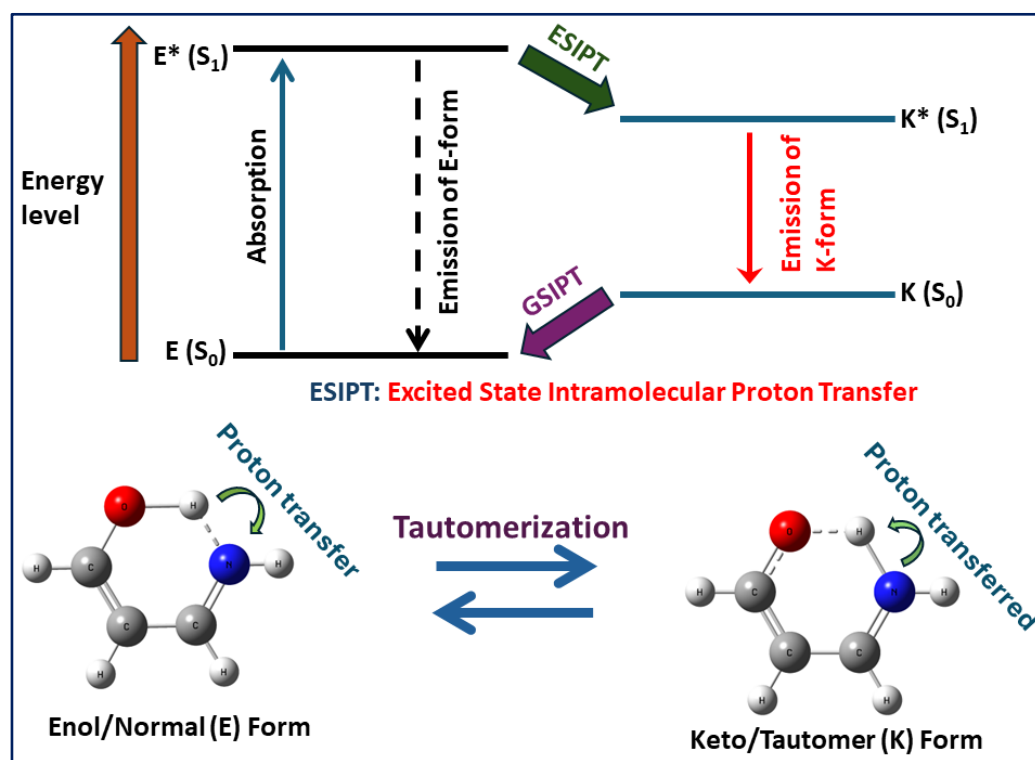
**Scheme 1.** A schematic showing the reaction mechanism of ESIPT.

The pioneering research on ESIPT was reported by Weber [46], Förster [47,48], and Weller [49–52], which have prompted the photochemists to study this phenomenon extensively. While classifying ESIPT reactions, Kasha distinguished four operative mechanisms: (i) those in which there is hydrogen bond between the H atom of the donor group and the acceptor (intrinsic intramolecular transfers), (ii) those in which the proton is far away from the acceptor and requires a mediator (concerted solvent assisted biprotonic transfer), (iii) static and dynamic catalysis of proton transfer involving strong catalysis in doubly H-bonded acetic acid complexes and (iv) proton relay transfer [53]. An extension of this classification had also been presented later by Heldt et al. [54]. The dynamics of the ESIPT process can be strongly dependent on the conformation of the molecule, temperature, pH, and the nature of the solvent, particularly with respect to the capacity for the formation of hydrogen bonds [55–58]. In the current scenario of fundamental and translational research, the ESIPT phenomenon has been a stimulating realm for scientists, especially due to its biological implications [59–64]. In the current study, we have decided to include relevant literary works on the ESIPT of Schiff-base compounds in several application verticals.

### 1.2. Concept of Dual Emission

ESIPT molecules can be fairly classified under ‘Dual-State Emission’ (DSE) molecules, with two different emitting forms, viz., normal and tautomer, where the tautomeric emis-

sion is largely Stokes-shifted compared to the normal. ESIPT evidently corresponds to a photoinduced tautomerization between the excited enol/normal (E) form and the keto/tautomer (K) form. The general mechanism of an ESIPT reaction depicting the dual emission is shown below in Scheme 2. The ESIPT reaction is a four-level photochemical process that induces a significant dynamicity to the excited state properties of a molecule [65–67]. This phenomenon prevents the  $\pi$ – $\pi$ -stacking processes, which in some instances might be unfavorable. ESIPT molecules generally show dual emission under the influence of solvation and some electronic effects. In such cases, E\*/K\* emissions are notably visible. Nitrogen-containing heterocycles are prospective candidates for showing such prototropic properties where an intramolecular hydrogen bond is seen with the formation of five/six/seven-membered ring structures. A strong reorganization of molecular geometry is noticed in these types of molecules in the excited state, which actually leads to the large Stokes-shifted (up to  $12,000\text{ cm}^{-1}$ ) tautomeric emission, thus ultimately limiting the other deactivation mechanisms such as reabsorption, inner filter effect, etc. [68–70]. In a recent study by Durgo-Maciag et al. [71], they clearly demarcated the plausible disagreements between ESIPT and DSE probes. They showed that the majority of DSE probes are non-ESIPT fluorophores owing to their semi-co-planarity, rigidity, and solubility.



**Scheme 2.** A scheme depicting the general mechanism of an ESIPT reaction showing the property of dual emission.

Recent literature reports ESIPT fluorophores with Near Infrared Radiation (NIR) emission due to large Stokes-shifted tautomeric emission, which paves the gateway towards intracellular sensing of heavy metal ions and fluorescence imaging [72–75]. Optical absorption/emission tuning in ESIPT active fluorophores serves as a colossal important methodology for addressing major applicative avenues. Biomedical research and the development of biomaterials constitute the major domains where these ESIPT-based functional compounds find their apt applications.

### 1.3. ESIPT Reaction in Schiff Bases

Schiff bases are specially designed imine-functionalized derivatives with an innumerable number of applications in the context of modern chemical, biological, and material research. These molecules present promising ESIPT properties with tunable luminescence. The proton transfer in these compounds is catered through the  $\text{—C=N}$  bond, which creates a charge difference within the molecule and thus makes it prone to IPT in the excited state. A significant number of such promising ESIPT-based Schiff bases are reported in the literature, and they have diverse application avenues. Several such luminescent ESIPT-based Schiff bases were reported by Bose et al., who reported that hydroxy-naphthaldehyde was the parent homolog [21,41,42]. In another article, Shang et al. discussed the effects of substituents on the photophysical properties of seven ESIPT-based Schiff bases with a 4-(Dimethylamino)salicylaldehyde core [76]. Salicylaldehyde hydrazone-based Schiff bases with ESIPT properties find promising applications as photoswitches, as studied by Zhang et al. [77]. In another article, Moraes et al. demonstrated white light generation from two ESIPT active Schiff bases, salicylidene-4,6-(dimethylamino)-pyridine and salicylidene-5-bromo-4,6-(dimethylamino)-pyridine. He, through the ESIPT mechanism, showed the influence of near-attack conformation, which ultimately forms the IMHB (Intramolecular Hydrogen Bond), conferring stability to the tautomer [78].

In the present context, 2-hydroxy-1-naphthaldehyde deserves special mention as the parent homolog of many ESIPT-based Schiff bases, which have been widely explored in various sensor and biological applications. The examples of such Schiff bases along with their application verticals are tabulated below in Table 1.

**Table 1.** Schiff bases with 2-hydroxy-1-naphthaldehyde backbone showing varied applications.

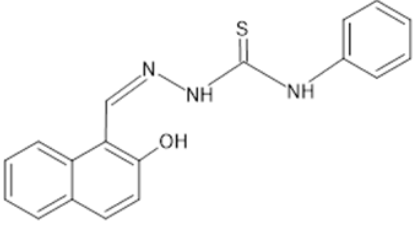
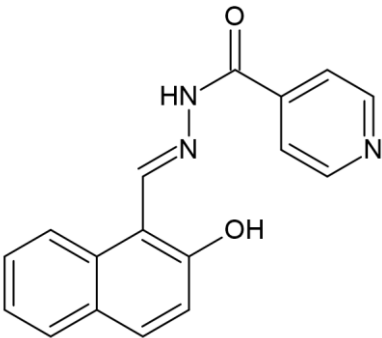
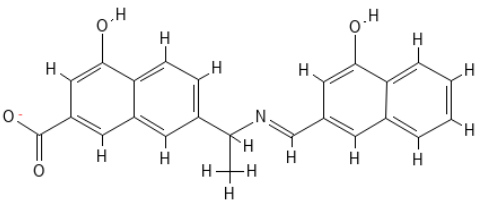
| Sl. No. | Name of the Schiff Base                                                 | Structure of the Schiff Base                                                        | Applications                                                  | Reference No. |
|---------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------|
| 1.      | N-Phenyl-2-(2-hydroxynaphthalen-1-ylmethylene) hydrazine carbothioamide |  | Fluorescent sensor for the determination of $\text{Fe}^{3+}$  | [79]          |
| 2.      | 2-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone                      |  | Colorimetric sensor for the determination of $\text{Al}^{3+}$ | [80]          |
| 3.      | bis-[N-(2-hydroxynaphthyl-1-methylimine)) carboxylate                   |  | Chemosensor for the determination of $\text{Zn}^{2+}$         | [81]          |

Table 1. Cont.

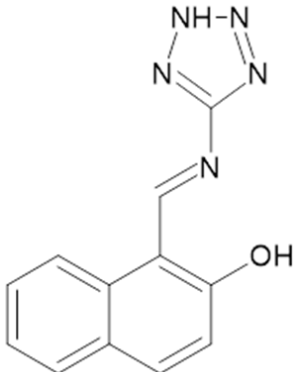
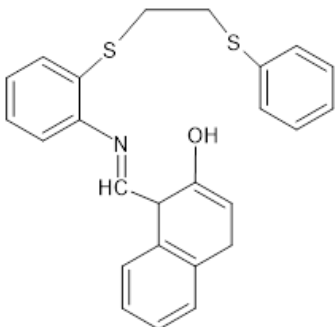
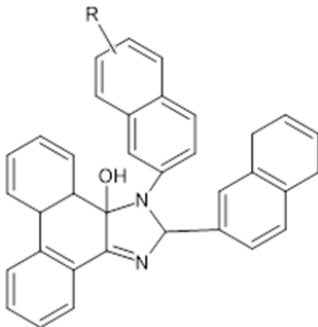
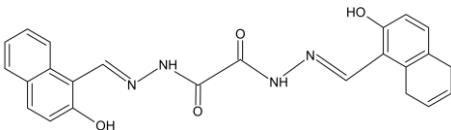
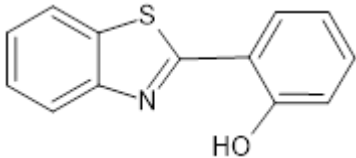
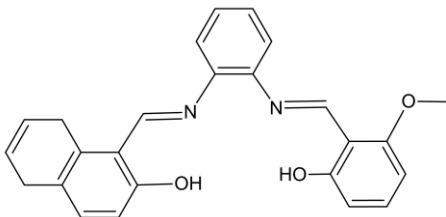
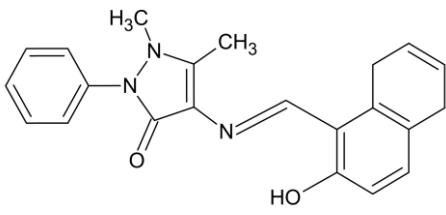
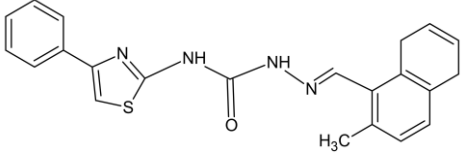
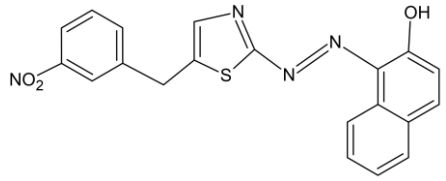
| Sl. No. | Name of the Schiff Base                                                                    | Structure of the Schiff Base                                                        | Applications                                               | Reference No. |
|---------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------|---------------|
| 4.      | 1-[(1H-tetrazol-5-ylimino)methyl]naphthalen-2-ol                                           |    | Fluorescent chemosensor for the determination of $Zn^{2+}$ | [82]          |
| 5.      | 1-((E)-(2-(2 (phenylthio) ethylthio) phenylimino) methyl)naphthalene -2-ol                 |   | Fluorescent sensor for the determination of $Al^{3+}$      | [83]          |
| 6.      | 1-(1-(p-tolyl)-1H-phenanthro[9,10-d]imidazol-2-yl)naphthalen-2-ol                          |  | Chemosensor for the determination of $Zn^{2+}$ and $F^{-}$ | [84]          |
| 7.      | N,N''-bis ((2-hydroxynaphthalen-1-yl) methylene) oxalohydrazide                            |  | Fluorescent sensor for the determination of $Al^{3+}$      | [85]          |
| 8.      | hydroxynaphthyl benzothiazole                                                              |  | Fluorescent sensor for the determination of $OAc^{-}$      | [86]          |
| 9.      | (Z)-1-(((2-((E)-(2-Hydroxy-6-methoxybenzylidene)amino)pher methylene) Naphthalen-2(1H)-one |  | Fluorescent probe showing antibacterial properties         | [87]          |

Table 1. Cont.

| Sl. No. | Name of the Schiff Base                                                              | Structure of the Schiff Base                                                      | Applications                                                | Reference No. |
|---------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------|---------------|
| 10.     | 2-hydroxy-1-naphthaldehyde-4-aminoantipyrine                                         |  | Fluorescent probe showing anticancer activity               | [88]          |
| 11.     | 2-((2-hydroxynaphthalen-1-yl)methylene)-N-(4-phenylthiazol-2-yl)hydrazinecarboxamide |  | Fluorescent probe having the property to cleave plasmid DNA | [89]          |
| 12.     | 1-[(5-(3-nitrobenzyl)-1,3-thiazol-2-yl)diazenyl]naphthalene-2-ol                     |  | Fluorescent probe showing anticancer activity               | [90]          |

## 2. Principle of Biosensing

A biosensor is a device combining a biological recognition element like nucleic acid, antibody, enzyme, etc., with a transducer to detect analytes through optical, electrochemical, or mechanical systems [91,92]. The recognition element interacts with the analyte, and the transducer converts this interaction into an electrical signal for further analysis. Biosensors serve as artificial receptors, similar to human sensory organs, detecting specific stimuli and transmitting signals. They are precise or highly specific, capable of sensing even low analyte concentrations, and have diverse applications, including DNA manipulation, drug development, security, clinical diagnostics, healthcare monitoring, food quality control, and environmental monitoring [93–95]. Selectivity is crucial for biosensors to detect target analytes in complex samples, minimizing false positives. Antibodies use binding domains, enzymes rely on specific pockets, and nucleic acids face reduced selectivity from electrostatic interactions, addressable with peptide nucleic acids. Biosensor sensitivity measures the signal response to changes in analyte concentration, with detection limits defining the range. High sensitivity allows responses to minor concentration fluctuations, often in the pico- to nanomolar range. The reproducibility of biosensors is the ability to consistently produce the same results for a sample, defined by precision and accuracy. Antibodies and enzymes, sensitive to pH and temperature, face reproducibility challenges, especially in low-resource settings. Aptamers, polymers, and some specific nanoformulations offer highly reproducible outcomes, benefiting from cost-effective and consistent chemical synthesis. The stability of biosensors, critical for continuous monitoring, depends on bioreceptor affinity and resistance to degradation over time [96,97]. The structure and construction of biosensors are shown below in Figure 1.

With reference to the categorization of biosensors, the optical biosensors or “Optopodes” is one of the simplest in terms of construction, working, and versatility. Optical biosensors, being hyphenated, integrate an optical technique with a biological element to identify the required chemical or biological species. Optical biosensors are mainly developed based on surface plasmon resonance and optical spectroscopy, such as luminescence, fluorescence, phosphorescence, etc. [98]. Fluorescence-based optical biosensors rely on different photo processes like CT, PT, ET, etc., for signal transduction. In this connection, it

is pertinent to state that biosensors based on changes in fluorescence intensity are the most accepted and universally used owing to their sensitivity, simplicity, and adaptability for different measurements [99]. One example is the transfer of energy through the routing of fluorescent signals from NADH to quantum dots (QDs), which has been a comprehensive subject of extensive research for Fluorescence Resonance Energy Transfer (FRET) -based applications. The dipolar interaction between CdTe QD and NADH may lead to an efficient energy transfer, enhancing the fluorescence intensity of the QD and the subsequent quenching of the fluorescence of tagged NADH [100]. The mechanistic procedure is shown in Figure 2.

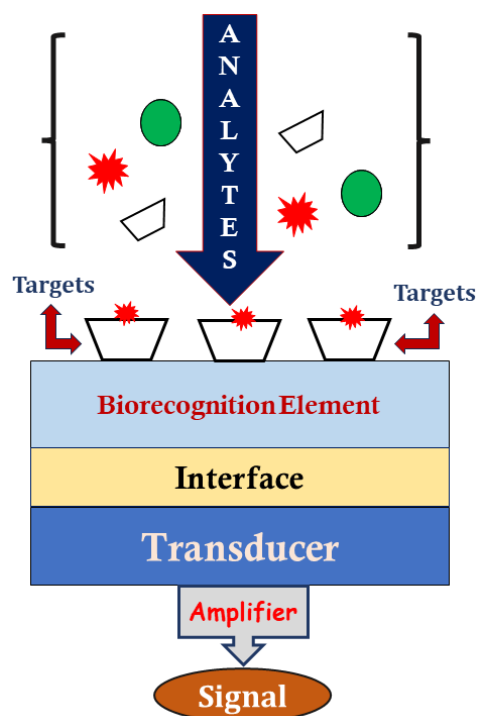


Figure 1. A schematic diagram of a model biosensor showing its prime components.

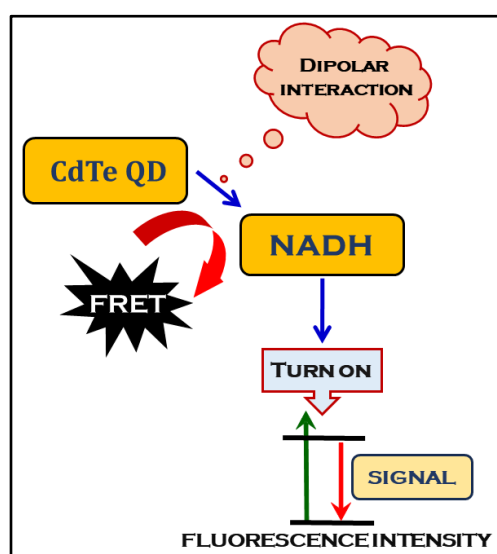


Figure 2. The mechanism of working of a FRET-based optical biosensor.

In context to the present review, ESIPT-based biosensors would be the primary point of consideration here. Many researchers across the globe ventured upon the biosensing mechanism, extrapolating ESIPT on account of its excellent characteristics and tunable properties.

### 2.1. Different Types of Sensing

Biosensors, with their reliable performance, convert analyte–receptor interactions into measurable signals through various transduction methods. Optical systems measure changes in luminescence, absorption, or surface plasmon resonance, utilizing techniques like fluorescence, Raman spectroscopy, and refractive angle measurement. Electrochemical systems detect impedance, current, or potential changes and can combine with optical methods for enhanced sensitivity, achieving detection limits comparable to fluorescent biosensors. Mass-based systems employ piezoelectric crystals, where oscillation frequency shifts due to analyte binding are measured electrically to evaluate mass changes. Each method offers unique advantages tailored to specific detection needs.

ESIPT probes offer a multitude of sensing applications across various domains. Nejadmansouri et al., in their review article, walked through five years of history and comprehensively explained the use of ESIPT-based biosensors to analyze antioxidants in food samples [101]. In this connection, mention might be made of electrochemical and optical biosensors with ESIPT probes serving as the prime components. These are the “Aptamers” in which biomolecules like DNA and RNA, etc., are used as receptors and are linked to the ESIPT probes for detecting and improving the sensing level [102]. Detection of progressive disease-causing analytes like carcinogens, mutagens, and allergens can also be aided using such biosensors [103,104]. The electrochemical assays and measurements like conductometry, amperometry, voltammetry, impedance measurement, etc., serve colossally important roles in ESIPT-based biosensors for point-of-care applications to diagnose critical diseases in patients suffering from COVID-19, Leukaemia, etc. [105]. Illustrations of the different structural forms of Schiff-base compounds displaying ESIPT, which is deployed in various instances of biomarker detection for certain disease types, can be summarized in Table 2.

**Table 2.** Different ESIPT-based Schiff bases deployed in biomarker detection for certain diseases.

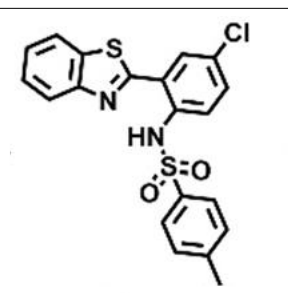
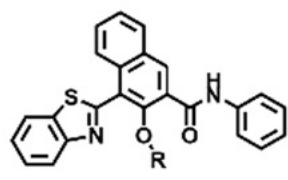
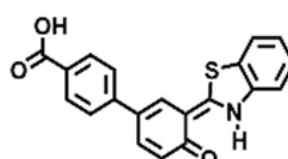
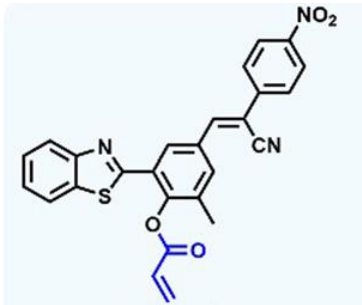
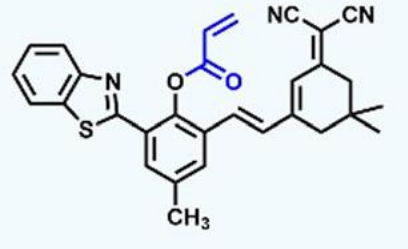
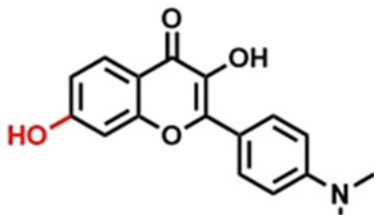
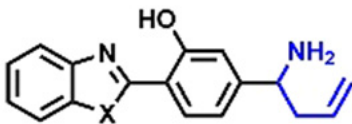
| Name of the Biomarkers | Abbreviation | Disease Type | Structure of Schiff Bases                                                                                                                                                                                                                                            | Reference No. |
|------------------------|--------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Acid and Base          | pH           | Cancer       | <br><br> | [106–108]     |

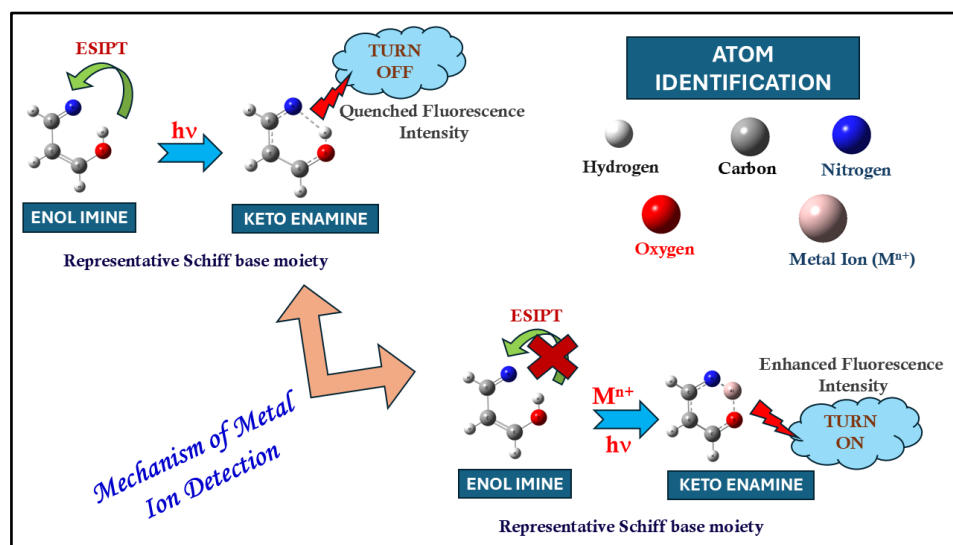
Table 2. Cont.

| Name of the Biomarkers | Abbreviation | Disease Type                  | Structure of Schiff Bases                                                            | Reference No. |
|------------------------|--------------|-------------------------------|--------------------------------------------------------------------------------------|---------------|
| Cysteine               | Cys          | Alzheimer's disease           |    | [109,110]     |
| Phosphatase            | ALP          | Diabetes                      |    | [111,112]     |
| Serum Albumin          | HSA          | Hypertension, Liver Cirrhosis |  | [113]         |
| Formaldehyde           | HCHO         | Neurodegenerative diseases    |  | [114]         |

### 2.1.1. ESIPT-Based Schiff-Bases in Heavy Metal Detection

Schiff bases with ESIPT characteristics present enhanced selectivity towards binding metal ions and establish themselves as excellent sensor materials for the detection of such metal ions. Metal detection approaches can broadly be classified into two types: 'recognition' and 'reactivity', as exemplified by Aron et al. [115]. The general mechanism

of identification/sensing metal ions by ESIPT-based Schiff bases can be represented by Scheme 3.



**Scheme 3.** A schematic representation showing the fluorescence ‘Turn On’ mechanism in ESIPT-based Schiff base molecules for heavy metal ion detection.

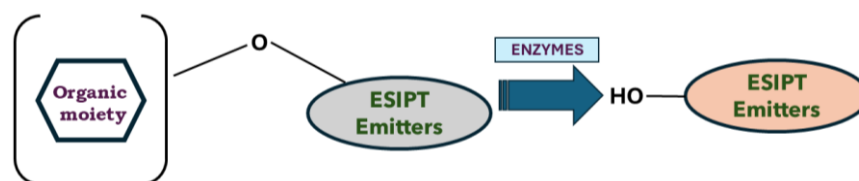
Zhao et al. synthesized a rare tri-responsive fluorescent probe with ESIPT characteristics, which successfully identified the presence of  $\text{Ag}^+$ ,  $\text{Pb}^{2+}$ , and  $\text{Fe}^{3+}$  in different solvent systems [104]. This same probe emerged to be an excellent bioimager of  $\text{Fe}^{3+}$  ions in Hela cells [104]. In another article, Yang et al. showed a Schiff base probe synthesized by linking rhodamine 6G with a pyrazole derivative to detect the toxic  $\text{Hg}^{2+}$  metal ion in an aqueous solution [115]. Though ESIPT renders this probe weakly fluorescent, binding to  $\text{Hg}^{2+}$  produced a new conjugated structure, leading to a turn-on reaction and a distinct color change from colorless to pink [116]. Wu et al. prepared a substituted ESIPT-based Schiff base benzothiazole for the turn-on detection of  $\text{Zn}^{2+}$  [117]. This ratiometric probe utilizes the benzothiazole moiety as the donor and the Schiff base moiety as the receptor. Kaur et al. reported the synthesis of a novel hydroxy benzothiazole-based fluorophore featuring ESIPT-coupled AIE characteristics for the selective detection of  $\text{Cu}^{2+}/\text{Cu}^+$  in aqueous media, real water samples, and live cells [118].

ESIPT is often conjoined with AIE or Aggregation-Induced Emission to produce sensors with a high Stokes’ shift and a selectivity towards analytes. Currently, AIE-assisted ESIPT probes are receiving considerable attention, owing to their enhanced fluorescence emission and applicability as sensors and bioimagers [119–121]. Hydroxyphenyl-Benzothiazole (HBT) derivatives, Tetraphenylethylene based ESIPT probes, Phenol-Pyridine derivatives, Cyanohydroxychalcone-based probes, Benzimidazole-Phenol derivatives, Boron Dipyrrromethene (BODIPY)-ESIPT probes, etc., can be tuned into effective sensors for heavy metal ion detection in conjugation with AIE assisted probes. ESIPT–AIE-based Schiff bases conjoined with fluorescent organic nanoparticles are also deployed to detect metal ions like  $\text{Al}^{3+}$ , forming a complex, which ultimately has applications in cell imaging [122].

Musikavanhu et al., through their comprehensive review of fluorescent Schiff bases showing ESIPT characteristics, suggested several strategies for enhancing their sensitivity towards heavy metal ion detection [123]. Through their article, structural modifications of the binding pockets of the molecules, along with augmented strategies to amplify the signals for detection, were suggested with several illustrations in the already existing literature [123]. ESIPT-based Schiff bases can be used as pH molecular switches to sense heavy metal ions using their ratiometric responses [124].

### 2.1.2. ESIPT-Based Schiff-Bases in Biomolecule Sensing

Schiff base molecules, owing to their dual emission characteristics and polarity-sensitive nature, offer numerous avenues for the detection of biomolecules both in vitro and in vivo. Schiff bases, through the aid of their photophysical ESIPT fluorescence properties, can sense proteins like serum albumins, enzymes, antibodies, etc., interact with nucleic acids (DNA/RNA) through intercalation, and help in their detection. Immense applications of ESIPT-based Schiff bases as biomolecule sensor molecules are significantly scattered in the literature. Jadhao et al. synthesized a plausible amyloid-targeted heterocyclic Schiff base molecule ((E)-2-((6-chlorobenzo[d]thiazol-2-ylimino)methyl)-5-(diethylamino)phenol (CBMDP)), which can potentially address Alzheimer's disease [125]. Yang et al. designed a ratiometric probe for ALP detection by deploying the ESIPT fluorophore N-(3-(benzo[d]thiazol-2-yl)-4-hydroxyphenyl) benzylamide [126]. Chen et al. introduced an acetoxymethyl ether on 2-(2'-hydroxyphenyl)-benzothiazole (HBT) as a recognition group to detect the enzyme esterase [127]. In a similar fashion, Leucine aminopeptidase (LAP) was detected by Zeng et al., who developed the first tetraarylimidazole-based AIE fluorophore by substituting different aryl groups of a Schiff base [128]. This probe, with the conjoined effects of ESIPT and AIE, traced the precise detection of LAP [128]. The generalized mechanism of working of such ESIPT probes to detect various enzymes may be represented as Scheme 4.



**Scheme 4.** General mechanism of enzyme detection with ESIPT-based Schiff bases.

### 2.1.3. ESIPT-Based Schiff-Bases in Imaging or Diagnosis

ESIPT-based Schiff bases can be selectively employed for staining cellular structures like mitochondria or nuclei owing to their enhanced contrast and deeper tissue penetration in bioimaging. The Schiff base compound synthesized by the condensation of 5-phenylsalicylaldehyde and 2-aminobenzohydrazide showed comprehensive selectivity and sensitivity towards Zn(II) ions [129]. The bioimaging studies of this probe with A549 cells containing Zn(II) ions were visualized through live-cell imaging [130]. The lipophilicity and surface charge characteristics of ESIPT-based Schiff bases prove them to be important candidates for visualizing mitochondria and lysosomes. The phenolic proton in these Schiff bases becomes acidic, which turns on their fluorescence, thus making them suitable for visualizing lysosomes whose environmental pH ranges between 4 and 5 [131]. A 2-(2'-hydroxyphenyl)benzothiazole (HBT)-based ESIPT fluorophore with a near-infrared enhanced emission at 836 nm and a large Stokes shift (286 nm) was applied to image SO<sub>2</sub> derivatives in mitochondrial cells in vivo [132]. ESIPT-based Schiff bases can also find extensive applications in theranostics. The Schiff base derivatives of 4-Hydroxybenzylidene, 2-Hydroxy-1-naphthaldehyde, and 4-(Diethylamino)salicylaldehyde are extensively used in Reactive Oxygen Species (ROS) detection and ultimately prove to benefit cancer/tumor therapy [133–135]. Pang et al. developed a lysosome tracker which is functional at pH 5 [135]. This ESIPT Schiff base probe exhibits a NIR tautomeric emission band at ~ 700 nm [135]. In Table 3 we present a list of ESIPT-based Schiff bases used in diagnosis.

Recent advancements in fluorescence mechanisms have integrated ESIPT with other systems, enhancing its benefits and addressing some of its drawbacks. AIE or aggregate-

induced emission works alongside ESIPT by boosting fluorescence during aggregation, which helps mitigate ESIPT's sensitivity to the environment. Combining ESIPT with FRET enables the development of probes for detecting longer wavelengths or near-infrared signals, which is beneficial for in vivo biological analysis. Photoinduced electron transfer-based fluorescent probes incorporating ESIPT provide improved sensitivity and selectivity, with fluorescence alterations in the presence of specific analytes. Additionally, ESIPT-based probes allow for ratiometric detection, providing direct measurement of analyte concentration without the need for calibration. However, ESIPT emission is highly sensitive to its surroundings, with polar or hydrogen-bonding solvents hindering the process and preventing keto-emission-throwing challenges.

**Table 3.** Different ESIPT-based Schiff bases used in diagnosis.

| Types of Schiff Bases                                      | Used In/As                                                  | Reference No. |
|------------------------------------------------------------|-------------------------------------------------------------|---------------|
| 2-(2'-Hydroxyphenyl)benzothiazole (HBT) based Schiff bases | Tracking CORM-3 in body fluids, living cells, and Zebrafish | [136]         |
| Salicylaldehyde-derived Schiff Bases                       | Binds to DNA possessing antimicrobial properties            | [137]         |
| Naphthalimide Schiff Bases                                 | Bioimaging of Fe <sup>3+</sup> cells                        | [138]         |
| Coumarin-based Schiff Bases                                | Theranostic agents for diagnosis and therapy                | [139]         |
| Hydroxyquinoline Schiff Bases                              | Anticancer activity                                         | [140]         |
| Benzimidazole Schiff Bases                                 | DNA binding and cleavage                                    | [141]         |
| Phenanthroline Schiff Bases                                | Anticancer and antimicrobial activity                       | [142,143]     |
| Pyrene Schiff Bases                                        | Antibacterial activity                                      | [144]         |
| Thiazole-based Schiff Bases                                | Antioxidant activity                                        | [145]         |
| Indole Schiff Bases                                        | Antimicrobial activity                                      | [146]         |

### 3. Conclusions

This current review comprehensively discusses the excited-state intramolecular proton transfer behavior in Schiff bases with applicative demonstrations across different biomarker detection methods. Investigations on the ESIPT properties of photoactive fluorophores have received enlivening interest from researchers working in varied fields. Tuning the photophysical properties of such ESIPT active imine-functionalized derivatives or Schiff bases has been quite intriguing for scientists in the past few years. These ESIPT-active Schiff-base compounds, owing to their polarity sensitive nature and large Stokes-shifted fluorescence, find extensive applications as sensors in chemical, biological, and material science domains. In this review, we closely monitored such illustrative applications in a number of Schiff-base compounds, such as heavy metal ion detectors, biomolecule sensors, bioimagers, therapeutic intervention, and diagnostics. Schiff bases with ESIPT characteristics augmented with other photophysical/photochemical processes, like FRET, PET, AIE, etc., are better instruments in their applications as chemosensors in biomedical applications and bioimaging.

### 4. Future Direction

The future perspective for studies about ESIPT-based Schiff bases for their potential applications to detect biomarkers is quite relevant and promising due to their unique photophysical properties and advancements in their design and application. ESIPT-based Schiff bases are increasingly being explored for their potential in theranostics, combining therapeutic and diagnostic capabilities in a single platform. Their large Stokes shifts, environmental sensitivity, and multi-channel fluorescence make them ideal for precise

and sensitive biomarker detection, even in complex biological systems, considering their plethora of application verticals. These Schiff bases, which leverage their ESIPT properties, can be tailored to detect individual and specific biomarkers that can play a critical role in precision diagnostics. The ESIPT properties of Schiff bases hyphenated with electrochemical measurements can be successfully augmented to produce portable point-of-care application devices that are expected to enable rapid, onsite biomarker detection, especially in resource-limited settings. Leveraging OMICS like Proteomics, Genomics, Metabolomics, and Lipidomics with the ESIPT properties of Schiff bases can be extrapolated to detect and revolutionize disease diagnosis and monitoring.

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