Determination and Imaging of Small Biomolecules and Ions Using Ruthenium(II) Complex-Based Chemosensors

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Received: 30 September 2021 / Accepted: 27 May 2022 / Published online: 13 June 2022
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Abstract

Luminescence chemosensors are one of the most useful tools for the determination and imaging of small biomolecules and ions in situ in real time. Based on the unique photo-physical/-chemical properties of ruthenium(II) (Ru(II)) complexes, the development of Ru(II) complex-based chemosensors has attracted increasing attention in recent years, and thus many Ru(II) complexes have been designed and synthesized for the detection of ions and small biomolecules in biological and environmental samples. In this work, we summarize the research advances in the development of Ru(II) complex-based chemosensors for the determination of ions and small biomolecules, including anions, metal ions, reactive biomolecules and amino acids, with a particular focus on binding/reaction-based chemosensors for the investigation of intracellular analytes’ evolution through luminescence analysis and imaging. The advances, challenges and future research directions in the development of Ru(II) complex-based chemosensors are also discussed.

Keywords Ru(II) complexes · Chemosensors · Luminescent imaging · Ions · Small biomolecules detection

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This article is part of the Topical Collection “Metal Legand Chromophores for Bioassays,” edited by Kenneth Kam-Wing Lo and Peter Kam-Keung Leung.

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Abbreviations

Ru(II) Ruthenium(II)
HPLC High-performance liquid chromatography
ICP-OES/MS Inductively coupled plasma-optical emission spectroscopy/mass spectrometry
bpy 2,2′-Bipyridine
CT Computerized tomography
MRI Magnetic resonance imaging
PET Positron emission tomography
CA Contrast agent
LoD Limit of detection
ϕ Quantum yields
TGL Time-gated luminescence
Ir(III) Iridium(III)
Pt(II) Platinum(II)
Au(I) Gold(I)
Re(I) Rhenium(I)
Os(II) Osmium(II)
MLCT Metal-to-ligand charge transfer
ILCT Intraligand charge transfer
LLCT Ligand-to-ligand charge transfer
MMLCT Metal–metal-to-ligand charge transfer
LMCT Ligand-to-metal charge transfer
MLLCT Metal-to-ligand-metal charge transfer
LMMCT Ligand-to-metal–metal charge transfer
MC Metal centered
LC Ligand centered
FRET Förster resonance energy transfer
PeT Photo-induced electron transfer
dppz Dipyridophenazine
ROS Reactive oxygen species
RNS Reactive nitrogen species
RCS Reactive carbonyl species
RSS Reactive sulfur species
F− Fluoride
CH3COO− Acetate
CN− Cyanide
H2PO4− Phosphate
Cl− Chloride
Br− Bromide
CH3CN Acetonitrile
DMSO Dimethyl sulfoxide
SCN− Thiocyanate
Cys Cysteine
Hcy Homocysteine
GSH Glutathione
HSO$_3^-$ Hydrogen sulfite
S$^2^-$ Sulfide
PPi Pyrophosphate
DPA Di(2-picolyl)amine
ATP Adenosine triphosphate
UCNP Upconversion nanoparticle
UCL Upconversion luminescence
NO Nitric oxide
ONOO$^-$ Peroxynitrite
HNO Nitroxy1
O$_2^•^-$ Superoxide
Cy5 Cyanine 5
•OH Hydroxyl radicals
H$_2$O$_2$ Hydrogen peroxide
$^1$O$_2$ Singlet oxygen
HOCI Hypochlorous acid
DNP 2,4-Dinitrophenyl
BFO Benzofurazan-1-oxide
GO Glyoxal
CO Carbon monoxide
MGO Methylglyoxal
FA Formaldehyde
CBS Cystathionine β-synthase
CSE Cystathionine γ-lyase
H$_2$S Hydrogen sulfide
NBD 7-Nitro-2,1,3-benzoxadiazoles
His Histidine
S/N Signal-to-noise

1 Introduction

Small biomolecules and ions are building blocks of living organisms and play indispensible roles in all biological processes, such as enzymatic reactions, metabolism, growth, adaptation, and various disease developments and progressions [1, 2]. Determination and monitoring of the levels of these biomolecules and ions in situ are essential for better understanding their biological roles in biomedical systems, thus contributing to early diagnosis and treatment assessment of various diseases [3–5]. The most common and typical methods, such as high-performance liquid chromatography (HPLC) and inductively coupled plasma-optical emission spectros-copy/mass spectrometry (ICP-OES/MS), have been developed for the determination of small biomolecules and ions in vitro [6–8]. Onsite determination of these analytes in situ and in vivo, using these techniques, is not possible because the sample preparation in solution is an essential step to ensure performing successful analysis [9]. Imaging technologies, such as computerized tomography (CT) [10], magnetic resonance imaging (MRI) [11] and positron emission tomography (PET), have been
widely used in clinical diagnosis [12], while these technologies cannot be directly used for the determination of the concentration and/or activity of these analytes in biological samples [13, 14]. This is mainly because the contrast agents (CAs) used in these technologies are generally nonspecific; more importantly, these CAs hardly respond to small biomolecules and ions at the molecular level because of their resolution and sensitivity limitations [15]. Other approaches to optical detection, such as fluorescence and phosphorescence measurements, have also been successfully developed and adopted in biomedical research and clinical diagnosis [16]. In contrast to conventional bioassay and imaging technologies, luminescence bioassay and imaging using advanced optical spectroscopic and imaging instruments are featured with high sensitivity and selectivity, fast response time and low cost, enabling their use in biological and biomedical investigations involving in vitro bioassay and in vivo luminescence bioimaging [17–20].

Chemosensors are one of the most important tools for luminescence bioassay and imaging of small biomolecules and ions in situ in real time [21–23]. Luminescent chemosensors are normally designed as chemical compounds that can respond to targeted analytes through a unique binding/reaction (Fig. 1) [24, 25]. Generally, the chemosensors with reaction-based sensing mechanisms have higher selectivity, and the chemosensors with binding-based sensing mechanisms feature excellent reversibility for monitoring the targeted analyte in situ. As a result of these response processes, the luminescence signals can be switched “ON” (Fig. 1A) or “OFF” (Fig. 1B). Of the luminescence switch “OFF” and “ON” responses, the emission switch “ON” chemosensors are preferable for imaging analysis because

![Fig. 1 Design of chemosensors for the determination of analytes through the response mechanisms of binding and reaction, resulting in “OFF–ON” (A), “ON–OFF” (B), and ratiometric (C) luminescence response to analytes](image-url)
the enhancement of the luminescence intensity can be easily observed by microscopy. The emission wavelengths of the chemosensors can also be shifted after the response processes (Fig. 1C) [25–27], allowing ratiometric luminescence detection and imaging of targeted analytes with the potential for precise and quantitative analyses. The changes of emission signals generally correspond to the concentrations of the targeted analyte and thus can be recorded for the analyte’s determination of abundance by luminescence spectrosopes and/or microscopes. Because of the unique advantages of luminescence bioassays and imaging, enormous efforts have been devoted to the development of luminescent chemosensors for the detection of a variety of analytes in complicated biological and environmental systems in the past few decades.

As shown in Fig. 1, luminescence chemosensors generally consist of three parts, including the luminophore, response unit and spacer, which links the luminophore and response unit. Of all luminophores that are being used for the development of chemosensors, fluorescent organic dyes are most widely investigated because of their high quantum yields (ϕ) and easy modification of chemical structures [28]. Lanthanide chelates are another family of luminophores that have been successfully employed in the development of chemosensors [29, 30]. Compared with fluorescent organic dyes, lanthanide chelate luminescence has high photostability, large Stokes shift and unique line-like emissions [29]. The prolonged lifetime of lanthanide chelates (microseconds to milliseconds) enables a background-free bioassay and imaging of targeted analytes through time-gated luminescence (TGL) measurement [28, 31]. Transition metal complexes, particularly the luminescent ruthenium(II) (Ru(II)) [32], iridium(III) (Ir(III)) [33], platinum(II) (Pt(II)), gold(I) (Au(I)) [34], rhenium(I) (Re(I)) [35] and osmium(II) (Os(II)) complexes with d6, d8 and d10 electron structures, have also been studied when developing chemosensors for biomolecule and ion detection and imaging [36–40]. Different from the fluorescent organic dyes that emit from excited singlet state, phosphorescence of transition metal complexes is derived from excited triplet states [41]. The excited states of these transition metal complexes are more complicated than those of fluorescent dyes and mainly include metal-to-ligand charge transfer (MLCT), intraligand charge transfer (ILCT), ligand-to-metal charge transfer (LMCT), metal–metal-to-ligand charge transfer (MMLCT), ligand-to-metal–metal charge transfer (LMMCT) and ligand-to-metal–ligand charge transfer (LMLCT) [41–43]. The excited state-mediated emission properties of transition metal complexes are varied upon the changes of the metal center, local environment and particularly chemical structure of ligands, enabling transition metal complexes to be designed as the chemosensors through modulating these parameters [43].

Of all transition metal complex-based luminophores, Ru(II) polypyridine complex, particularly the prototype of the Ru complex ([Ru(bpy)3]2+ (bpy: 2,2'-bipyridine)) (Fig. 2A), has been one of the most popular molecules and widely investigated in the past few decades [44]. Ru(II) polypyridine complexes have octahedral symmetry with three kinds of electronic transitions, including metal centered (MC), ligand centered (LC) and MLCT [41]. As shown in Fig. 2B, in this octahedral symmetry of Ru(II) complex, MC excited states are obtained for an electron transition from πM to σ*M orbitals, LC excited states are formed through an
electron transition from $\pi_L$ to $\pi^*_L$, and MLCT excited states are produced by promotion of an electron from $\pi_M$ metal orbital to $\pi^*_L$ ligand orbitals [45]. The lowest excited state MC can decay to the ground state through a fast radiationless process. In contrast, the lowest excited states LC and MLCT undergo radiative deactivation to the ground state, thus exhibiting intense luminescence at room temperature in a rigid matrix and fluid solution, respectively [41]. Consequently, the lowest excited state is $^3$MLCT for most luminescent Ru(II) polypyridine complexes in solution. Upon the excitation at about 450 nm (spin-allowed $^1$MLCT), the lowest spin-forbidden $^3$MLCT excited state is obtained after a fast intersystem crossing process and then emits orange to near infrared emission [46]. The $^3$MLCT-based emission of Ru(II) polypyridine complexes displays unique photochemical and photophysical properties, including large Stokes shift (about 150 nm), prolonged luminescence lifetime (hundreds of nanoseconds to microseconds level), high photostability and brightness by visible light excitation [41, 47].

The emission of Ru(II) complexes, including luminescence intensity and lifetime, can be fine-modulated by modifying the chemical structure of ligands, allowing the Ru(II) complexes to be used for the development of chemosensors for biomolecule and ion detection. As described in early review articles [42, 43, 48, 49], the response mechanisms of luminescent Ru(II) complex chemosensors for target analytes mainly include (1) photo-induced electron transfer (PeT), in which the Ru(II) polypyridine complexes are ideal electron donors and acceptors, (2) Förster resonance energy transfer (FRET), in which the Ru(II) complexes can serve as the energy donor and acceptor [50–53] for the energy transfer (ET), (3) distortion of ligand and the octahedral symmetry after binding/reaction with the target analyte and (4) changes of the local environment upon the analyte’s binding. In addition to the luminescence response of Ru(II) complex-based chemosensors to the analyte [40, 54, 55], other prerequisites for this family of chemosensors to be applied in bioassay and imaging include (1) capability of analyte determination in aqueous solution, (2) high sensitivity and selectivity, which allow the chemosensors to be used for targeted analyte detection even at extremely low concentration without non-specific binding of

Fig. 2 Molecular structure of [Ru(bpy)$_3$]$^{2+}$ prototype complex (A). Ru(II) polypyridine complexes’ molecular orbital diagram and the corresponding LC, MC and MLCT electronic transitions (B)
interference species, (3) low cytotoxicity, enabling targeted analyte determination and imaging with minimum perturbation to the native micro-environment and (4) high cell membrane permeability to ensure the chemosensors are easily internalized into biological tissues.

The last few years have witnessed a huge leap forward in the development of Ru(II) complexes as the chemosensors for the detection of various analytes. Based on the above-described response mechanisms, hundreds of Ru(II) complex chemosensors for colorimetric and luminescent determination of anions, metal ions, small biomolecules and biomacromolecule have been available [42, 43]. For example, the triplet nature of the emission state with long lifetime of Ru(II) complexes allows them to be used for oxygen sensing by monitoring the changes of their luminescence intensity and lifetime [56–58]. Some of the Ru(II) complexes have also been revealed to be nucleic acid sensitive [59, 60], thus serving as a “light switch” for DNA detection [61]. The Ru(II) complexes with dipyridophenazine (dppz) ligands (e.g., complex 1 ([Ru(phen)2(dppz)]2+) are particularly interesting (Fig. 3A) [61]. These complexes are non-luminescent (undetectably small quantum yield) in water, while the emission intensity is significantly increased when bound to DNA [62, 63], which allows the Ru(II) complexes (e.g., complex 2) to be used for imaging of DNA structure and related mitosis progression (Fig. 3A). Subsequent research has also revealed that Ru(II) complexes (e.g., complex 3) can be used for the determination of DNA mismatches and RNA (Fig. 3B) [64–67]. Since the investigation of cellular uptake and imaging of the Ru(II) complex by Barton’s group [68, 69], the application of Ru(II) complex chemosensors for sensing and imaging of intracellular biomolecules and ions has increasingly attracted interest in recent years.

In this chapter, we wish to summarize recent examples of Ru(II) complex chemosensors for the detection of small biomolecules and ions in aqueous solution, with a particular focus on binding/reaction-based chemosensors for the investigation of intracellular analytes’ evolution through luminescence imaging. Specifically, the chemosensors for the determination of reactive oxygen/nitrogen/carbonyl species (ROS/RNS/RCS), biothiols, amino acids, pH, metal ions and anions are summarized, followed by the discussion of these chemosensors for luminescence bioimaging. The advances, challenges and future research directions in the development of Ru(II) complex-based chemosensors will also be discussed.

2 Ru(II) Complex Chemosensors for Anions

In various chemical and biological processes, anions play important roles in the body, such as blood pressure stabilization, blood purification, sugar level reduction, respiration and fatigue recovery. For anion sensing, the development of Ru(II) complex-based chemosensors has attracted enormous attention in the past few decades [70–72]. By virtue of their abundant photo-physical and chemical properties, hundreds of Ru(II) complexes have been designed and synthesized for the detection of various anions, such as fluoride (F−) [73–76], acetate (CH3COO−) [77], cyanide (CN−)[78], phosphate (H2PO4−) [79–81], chloride (Cl−) and bromide (Br−). Similar to the design of other anion receptors [82], most Ru(II) complex-based
chemosensors are designed using the following three response mechanisms, including (1) the binding of the Ru(II) complex’s recognition unit with anions via hydrogen bonding and deprotonation [83], electrostatic and Lewis acid–base interactions [84], (2) specific reactions of the Ru(II) complex’s recognition unit with anions [85] and (3) displacement of metal ions from heterobimetallic Ru(II) complex [86]. In the following section, the Ru(II) complex-based chemosensors for anions will be discussed according to their different response mechanisms.

### 2.1 Response Based on Hydrogen Bonding, Electrostatic and Lewis Acid–Base Interactions

Although most Ru(II) complex-based anion chemosensors are developed through the mechanism of hydrogen bonding and electrostatic and Lewis acid-base interactions, the colorimetric and luminescent response of these Ru(II) complexes to anions can only be obtained in organic solvents, including acetonitrile (CH$_3$CN) and dimethyl sulfoxide (DMSO) [87, 88]. This is mainly because the hydrogen bonding, electrostatic and Lewis acid-base interactions are significantly inhibited by the water molecules and other anions in the buffer solution [89]. This sub-section will discuss some examples of Ru(II) complex chemosensors for determination of anions in aqueous solution [90–92].
Through modification of the [Ru(bpy)$_3$]$^{2+}$ with amide containing a calix-arene moiety (binding site), Maity et al. reported a Ru(II) complex (4) for CN$^-$ and CH$_3$COO$^-$ determination (Fig. 4) [93]. Titration of complex 4 with CN$^-$ and CH$_3$COO$^-$ in H$_2$O–CH$_3$CN (95:5) resulted in a remarkable luminescence quenching and enhancement, respectively. The different response mechanisms of complex 4 to CN$^-$ and CH$_3$COO$^-$ were investigated by $^1$H NMR spectra. The CN$^-$ can bind to each amide N–H and leads to the deprotonation to form HCN. The electron density on the bpy ligand increased, and thus the intramolecular quenching was enhanced. In contrast, the weak interaction of bidentate CH$_3$COO$^-$ with two N–H protons led to the formation of electron delocalization, in which the CH$_3$COO$^-$ pulls the electron density to itself and thus decreases the intramolecular quenching. The luminescence response of complex 4 to CN$^-$ showed a LoD of 70 ppb.

Mardanya and co-workers described a Ru(II) complex (5) with pyrene-biimidazole ligand as a chemosensor for highly selective CN$^-$ detection in both CH$_3$CN and aqueous media (Fig. 5) [94]. The imidazole N–H protons of the coordinated ligand were found to be highly acidic with $pK_{a1} = 5.09$ and $pK_{a2} = 8.95$. Deprotonation of these two N–Hs was found through hydrogen bonding interaction with CN$^-$, leading to the increase of electron density of the metal center. As a result, red shift of absorption and quenching of emission were obtained for complex 5 after CN$^-$ binding. Detection limit of complex 5 to CN$^-$ was determined to be $5.24 \times 10^{-9}$ and $4.67 \times 10^{-9}$ M for colorimetric and luminescent analyses, respectively. A similar hydrogen bonding-based interaction has been employed for the development of Ru(II) complex 6 for selective detection of thiocyanate (SCN$^-$) (Fig. 5) [95]. In complex 6, the SCN$^-$ interacts with N–H through a 1:1 binding mode, which hinders the photo-induced electron transfer (PeT) between the long pair electron of the

![Fig. 4 Molecular structure of Ru(II) complex 4 and its response mechanism to CN$^-$ and CH$_3$COO$^-$](image-url)
N atom and the Ru(II) complex. The increase of luminescence intensity was thus recorded for SCN⁻ detection in CH₃CN-HEPES buffer solution (1:1, v/v, pH = 7.2).

In an early study, Lin et al. reported a Ru(II) complex (7) for highly selective detection of F⁻ in water by naked eye and luminescence (Fig. 6) [96]. Complex 7 was developed by incorporating a Schiff-base ligand with two bpy ligands. In the presence of F⁻, the conversion of quinonehydrazone moiety to azophenol could occur, resulting in a remarkable red shift of absorption spectra from 475 to 580 nm and a solution color change from orange to blue-violet. The binding of F⁻ also led

![Molecular structures of Ru(II) complexes 5 and 6 as the chemosensors for CN⁻ and SCN⁻, respectively](image)

**Fig. 5** Molecular structures of Ru(II) complexes 5 and 6 as the chemosensors for CN⁻ and SCN⁻, respectively

![Molecular structure of Ru(II) complexes 7 and 8 as chemosensors for F⁻](image)

**Fig. 6** Molecular structure of Ru(II) complexes 7 and 8 as chemosensors for F⁻. The test paper prepared by complex 7 was then used for F⁻ detection in aqueous solution. Adapted with permission from Ref. [96]. Copyright 2006 Royal Society of Chemistry

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to the increase of luminescence intensity at 630 nm. Although the spectrometric responses were measured in CH$_3$CN, the test paper prepared by staining of complex 7 also showed color changes in aqueous solution. In a later study, the same group modified the 1,10-phenanthroline-5,6-dione ligand to produce complex 8 for F$^-$ detection (Fig. 6) [97]. In the presence of F$^-$, a similar red shift of absorption spectra (from 467 to 580 nm), color change (from yellow to magenta) and luminescence enhancement were obtained, which were attributed to the F$^-$-mediated hydrogen bonding and deprotonation of N–H. The test papers were also prepared for F$^-$ detection in aqueous solution with ten times higher sensitivity (LoD = 1 ppm) than complex 7.

2.2 Response Based on Specific Reactions

Compared with the above-discussed response mechanism of hydrogen bonding and Lewis acid-base interactions, the chemosensors developed by the mechanism of chemical reaction have high sensitivity and selectivity [78, 98, 99]. The interference from water is also minimized because specific chemical reactions are involved in the sensing mechanism of these chemosensors. Aldehyde is a strong electron-withdrawing group that can quench the MLCT emission of Ru(II) complex. In a previous study, a Ru(II) complex ([Ru(CHO-bpy)$_3$]$^{2+}$) with three aldehyde functionalized bpy ligands was designed and synthesized by Zhang et al. as the chemosensor for biothiol (cysteine-Cys and homocysteine-Hcy) detection in DMSO-HEPES buffer [100]. In a later study, Zhang et al. found that the nucleophilic addition of aldehyde can also be triggered by hydrogen sulfite (HSO$_3^-$) in acidic buffer [24],

![Molecular structures of Ru(II) complexes 9 and 10 and their reactions with HSO$_3^-$ and CN$^-$, respectively](image-url)
thus allowing complex 9 to be used as a chemosensor for HSO$_3^-$ detection in phosphate-buffered saline (PBS) buffer (50 mM, pH = 5) (Fig. 7) [101]. The reaction of HSO$_3^-$ and complex 9 led to the formation of 9-SO$_2^-$, accompanied by an increase of luminescence at 620 nm. The result of HSO$_3^-$ detection in wine and sugar samples showed that complex 9 has good precision and accuracy for HSO$_3^-$ in food samples.

Using 5-formyl-2,2'-bipyridine as the ligand, Zhu et al. prepared a Ru(II) complex (10) as the luminescence chemosensor for CN$^-$ detection (Fig. 7) [102]. Similar to [Ru(CHO-bpy)$_3$]$_2^{2+}$, complex 10 in CH$_3$CN-H$_2$O (6:4) showed weak emission at 700 nm. The nucleophilic attack by CN$^-$ led to the formation of 10-CN$^-$, accompanied by a blue shift and increase of emission at 618 nm. Complex 10 with a detection limit of 0.75 μM was then used for the preparation of a test paper for naked eye CN$^-$ detection.

In addition to aldehyde, nucleophilic addition between the azo (N=N) group and HSO$_3^-$ has recently been exploited for the development of chemosensors for HSO$_3^-$ detection (Fig. 8A) [24, 85]. Owing to the PeT from the Ru(II) center to the attached azo-2,4-dinitrobenzene (DNB), Ru(II) complex 11 (Ru-azo) exhibited weak emission in 25 mM PBS buffer of pH 7.4. The HSO$_3^-$ triggered reaction with the azo group led to the formation of 11-SO$_3$ (Ru-SO$_3$), accompanied by an enhancement in luminescence at 635 nm. More interestingly, complex 11 has a long emission lifetime of 258 ns, which enabled its use for background-free luminescence detection.

**Fig. 8** Molecular structure of Ru(II) complex 11 and its reaction with HSO$_3^-$ (A). Detection of HSO$_3^-$ in rhodamine (RhB)-contaminated wine samples by steady-state luminescence (B) and TGL (C) analyses. Adapted with permission from Ref. [85]. Copyright 2020 Royal Society of Chemistry.
of HSO$_3^-$ through a TGL mode. In a wine sample containing rhodamine (spiked as the artificial background signal), steady-state luminescence analysis of HSO$_3^-$ failed (Fig. 8B). TGL analysis eliminated the background signals and allowed for HSO$_3^-$ detection with high accuracy and precision (Fig. 8C).

2.3 Response Based on Displacement of Metal Ions

By modifying the ligands with additional coordination sites, the produced Ru(II) complexes are capable of binding to other metal ions, such as Cu$^{2+}$, Co$^{2+}$, Zn$^{2+}$ and Hg$^{2+}$, to form heterobimetallic complexes. The heterobimetallic Ru(II) complexes thus can be used as chemosensors for anion sensing through a displacement approach. Different from the hydrogen bonding-based anion sensing approach, the displacement-based response mechanism also allowed the chemosensors to be used for anion detection in water because the water molecules are not involved in the displacement processes. Among various heterobimetallic Ru(II) complexes, the one with Cu$^{2+}$ (Ru(II)–Cu(II)) has been widely studied because Ru(II) complex luminescence can be quenched by Cu$^{2+}$ binding through electron and energy transfers. Then, Cu$^{2+}$ can be displaced in the presence of several anions, including sulfide (S$^{2-}$), CN$^-$ and pyrophosphate (PPi) (Fig. 9A).

By coupling di(2-picolyl)amine (DPA) to one bpy ligand, Zhang et al. synthesized a Ru(II) complex (12) and then demonstrated the corresponding heterobimetallic Ru(II)–Cu(II) complex as the chemosensor for S$^{2-}$ detection (Fig. 9B) [86]. Complex 12 showed high luminescence (ϕ = 3.07%) in HEPES buffer (pH 7.2), while the luminescence was completely quenched upon binding to Cu$^{2+}$ through a 1:1 coordination stoichiometry. In the presence of S$^{2-}$, Cu$^{2+}$ was then displaced to form the original complex 12, which was accompanied by the recovery of luminescence. This heterobimetallic Ru(II)–Cu(II) complex showed high sensitivity to S$^{2-}$ (LoD = 20.7 nM), allowing its use for S$^{2-}$ detection in three wastewater samples. In a similar work, Li et al. modified the bpy ligand with a Cu$^{2+}$ receptor, 1,4,7,10-tetraazacyclododecane (cyclen), and then demonstrated the Ru(II) complex (13) for sequential Cu$^{2+}$ and S$^{2-}$ detection (Fig. 9B) [103]. Compared with complex 12, complex 13 has better selectivity to Cu$^{2+}$ binding, while the formed 13-Cu is not as sensitive as 12-Cu for S$^{2-}$ sensing.

The displacement approach has also been employed for the development of Ru(II) complex chemosensors for CN$^-$. In 2017, two Ru(II) complexes (14 and 15) were synthesized by Zheng and co-workers, and the corresponding heterobimetallic Ru(II)–Cu(II) complexes were used for CN$^-$ detection in 20 mM HEPES buffer (pH 7.2) (Fig. 9B) [104]. A recovery of luminescence was observed after the displacement of Cu$^{2+}$ from 14-Cu to 15-Cu to form [Cu(CN$^-$)X]$^{n-}$ and complexes 14 and 15. The LoD for CN$^-$ was then determined to be 0.36 and 0.87 μM using 14-Cu and 15-Cu as the chemosensors, respectively. Similarly, Zhang et al. reported a Ru(II) complex (16) for PPi detection in 2018 (Fig. 9B) [105], in which one Cu$^{2+}$ from the 16-Cu was displaced by the addition of two PPi. The chemosensor 16-Cu showed high sensitivity (LoD=0.58 nM) for PPi detection in 10 mM HEPES buffer (pH 7.4).
Ru(II) Complex Chemosensors for pH

Similar to most pH sensors, Ru(II) complex chemosensors for pH have mainly been developed through the mechanism of protonation and deprotonation of several functional groups, such as imidazole [106, 107], hydroxyl (–OH) [108–110], carboxyl (–COOH) [111], pyridine [112, 113] and others [114]. As a result of the protonation-deprotonation process, the molecular structures and the electron density distribution of Ru(II) complex are changed, leading to the variations of absorption and emission intensity/wavelength. In this section, the progress in the development of Ru(II) complex chemosensors for pH will be briefly discussed.

As described above, deprotonation of N–H of Ru(II) complex 5's 2,2'-biimidazole ligand occurs under basic conditions or binding with CN⁻ [94]. In 2020, Tormo et al. also reported the use of imidazole-based ligand for the development of Ru(II) complex chemosensors for pH [115]. In later research, deprotonation of

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Fig. 9 The principle of displacement-based Ru(II) complex chemo sensors for anion detection (A) and the molecular structures of Ru(II) complexes 12–16

3 Ru(II) Complex Chemosensors for pH

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imidazole N–H under neutral and basic conditions was exploited by Yu et al. for the development of Ru(II) complex 17 ([Ru(bim)2(pip)]2+) for pH sensing and imaging (Fig. 10A) [116]. The increase of pH led to the deprotonation of all imidazole N–H from both bim and pip ligands, resulting in red shift of absorption spectra and decrease of MLCT emission. Complex 17 has a pKa of 4.49 and low cytotoxicity, enabling lysosome imaging in U251 cells. Luminescence images of U251 cells with complex 17 and LysoTracker Red showed good co-localization (Fig. 10B), and then the application of complex 17 in monitoring of intracellular pH changes was demonstrated by treating the U251 cells with lysosomal acidification inhibitor (bafilomycin A1).

In 2015, Zheng and coworkers synthesized two Ru(II) complexes (18 and 19) and investigated their absorption and luminescence responses to pH (Fig. 11A) [112]. Protonation-deprotonation process occurs on the imidazole N–H and both imidazole N–H and pyridine for complexes 18 and 19, respectively. The two-step protonation-deprotonation processes resulted in complex 18 with pKa1 = 0.98 ± 0.04 and pKa2 = 8.34 ± 0.03, while the three-step protonation-deprotonation processes of complex 19 exhibited pKa1 = 1.86 ± 0.02, pKa2 = 3.43 ± 0.04 and pKa3 = 9.07 ± 0.08. Coordination of the terpyridine (tpy) ligand of complex 19 with Re(I), a heterobimetallic Ru(II)–Re(I) complex 20, was developed by Zheng et al. in 2014 (Fig. 11A) [113]. The coordination of the tpy ligand blocked the protonation-deprotonation of one pyridine; thus, a two-step protonation-deprotonation process was obtained. The pKa1 and pKa2 value of complex 20 was 1.38 ± 0.03 and 6.84 ± 0.04, respectively. Interestingly, the coordination with Re(I) significantly improved the biocompatibility, allowing complex 20 to be used for luminescence imaging in HeLa cells.

Dinuclear Ru(II) complex 21 was then synthesized by Meng and co-workers in 2017 (Fig. 11A) [117]. Ru(II) complex 21 showed NIR emission at 760 nm with a large Stokes shift of 254 nm and lifetime (τ) 108.3 ± 0.4 ns. Different from complex 20, a three-step protonation-deprotonation process was observed on imidazole N–H at the second ligand. pKa values of complex 21 changed to pKa1 = 1.36 ± 0.02, pKa2 = 5.76 ± 0.05 and pKa3 = 9.01 ± 0.14. Through modification of the second ligand, the same group recently reported a Ru(II) complex (22) as a chemosensor for pH imaging and cancer cell discrimination (Fig. 11A) [118]. Compared with complex 20, similar photophysical properties, including intense NIR emission (~ 700 nm) and large Stokes shift (~ 200 nm) were obtained for complex 22.

![Fig. 10](https://example.com/fig10.png) Molecular structure of pH-sensitive Ru(II) complex 17 (A). Luminescence co-localization imaging of U251 cells stained with complex 17 and DYPI and LysoTracker Red (B). Adapted with permission from Ref. [116]. Copyright 2017 Elsevier
Importantly, the pKa2 value of complex 22 was determined to be 7.87, which is closer to the physiological value (i.e., 7.0–7.4). This allowed complex 22 to be used for luminescence imaging of intracellular pH in lysosomes (Fig. 11B). Moreover, imaging of HeLa cells showed about 13-fold higher intensity than HEK293 cells (Fig. 11C), demonstrating the “distinguishing” ability of complex 22 to identify the tumor and healthy cells.

4 Ru(II) Complex Chemosensors for Metal Ions

In addition to the anions, metal ions also play important roles in biological and environmental systems. Some metal ions, such as Cu2+, Fe3+ and Zn2+, are essential elements in the human body, while the metal ions, such as Hg2+, Cd2+ and Cr3+, are highly toxic, causing several problems for biological and environmental systems [119]. To detect these metal ions in biological and environmental systems, a number of Ru(II) complex chemosensors have been developed in the past few decades. In
this section, the progress in the development of chemosensors for Cu\textsuperscript{2+}, Hg\textsuperscript{2+} \cite{120} and others will be discussed according to the types of ions.

4.1 Ru(II) Complex Chemosensors for Cu\textsuperscript{2+}

As described above, the binding of Ru(II) complexes with Cu\textsuperscript{2+} could lead to the quenching of their luminescence through an excited-state electron transfer or energy transfer mechanism \cite{86, 104, 105}. By virtue of this mechanism, a series of Ru(II) complexes have been developed as luminescence “ON–OFF” chemosensors for Cu\textsuperscript{2+} determination and imaging (Fig. 12). Complex 17 with biimidazole ligands showed good performance in pH sensing with the protonation-deprotonation mechanism \cite{116}. In a recent study, the biimidazole-coupled phen ligand was employed as the binding site for the development of Ru(II) complex chemosensor (23) for Cu\textsuperscript{2+} detection by Li and co-workers \cite{121}. The coordination (1:1 bonding ratio) of Cu\textsuperscript{2+} with complex 23’s biimidazole led to the formation of a stable cyclic structure. The quenched emission of complex 23 showed a linearity with Cu\textsuperscript{2+} concentration in the range of 0.25–12 μM, and the LoD was 83.3 nM. The application of complex 23 was then demonstrated by Cu\textsuperscript{2+} detection in tap and lake water samples and imaging in A549 cells. For simple modification of imidazole to pyrazol, Cu\textsuperscript{2+} “ON–OFF” Ru(II) complex 24 was then reported by Xia and colleagues \cite{122}. Different from complex 23, complex 24 coordinated with Cu\textsuperscript{2+} through a 1:2 stoichiometry. This complex showed higher sensitivity to Cu\textsuperscript{2+} (LoD = 17.8 nM) compared with complex 23. The test paper was then prepared for Cu\textsuperscript{2+} detection in river water samples. Interestingly, complex 25 with quinoline substitution showed a 1:1 stoichiometry when binding to Cu\textsuperscript{2+} in HEPES buffer (LoD = 50.67 nM) \cite{123}. The test paper was also prepared using complex 25 as the chemosensor for Cu\textsuperscript{2+} detection. In another study, Zhang et al. reported a Ru(II) complex 26 for Cu\textsuperscript{2+} detection in aqueous solution and imaging in live pea aphids (LoD = 244 nM) \cite{124}. Complex 26 was developed through coordination with two phen ligands and one 2-(2-hydroxyphenyl) imidazo[4,5-f][1,10]phenanthroline. The Cu\textsuperscript{2+} binding with 2-hydroxyphenyl imidazo through a 1:1 stoichiometry quenched complex 26’s emission. Similar to Cu\textsuperscript{2+}-coordinated complexes 23 and 25, the Cu\textsuperscript{2+} can be displaced by the addition of

![Fig. 12 Molecular structure of Ru(II) complexes 23–27 as the chemosensors for Cu\textsuperscript{2+}](image-url)
EDTA (ethylene diamine tetraacetic acid), which allows the reset of the chemosensors for further detection of Cu²⁺.

In addition to imidazole, some other groups, such as DPA [86, 125–128], 1,8-naphthyridine [129], 1,3-benzothiazole [130], carboxyl [131] and others [132], have also been utilized as the response units for the development of Ru(II) complex chemosensors for Cu²⁺. For example, complex 27 reported by Ramachandran and colleagues was capable of detecting phosphate anions through C–H-anion interaction and Cu²⁺ through coordination with triazole, benzothiazole and the “O” linker, respectively [130] (Fig. 12). The application of this chemosensor (27) for Cu²⁺ detection (LoD = 700 nM) and imaging was also demonstrated by luminescence Cu²⁺ imaging in MCF-7 cells.

Similar to complex 15, the pyridine “linker” of dinuclear Ru(II) complex 28 has also been developed as the chemosensor for Cu²⁺ detection in H₂O/CH₃CN (1:1, v/v) [133], in HEPES buffer solution (10 mM, pH 7.4) (Fig. 13A) [134]. Complex 28 showed high luminescence (ϕ = 0.06) at 600 nm, while the Ru(II) complex’s MLCT emission was quenched after coordination of Cu²⁺ with imidazole and pyridine. This chemosensor showed high sensitivity (LoD = 33.3 nM) and selectivity, reversibility (in the presence of EDTA) and good biocompatibility and cell membrane permeability, enabling it to be used for luminescence imaging. In addition, the Ru(II) complex’s large two-photon absorption (TPA) cross-section enabled complex 28 to be used for TP imaging of Cu²⁺ in HeLa cells and zebrafish (Fig. 13B).

Although “OFF–ON” luminescence response chemosensors feature high sensitivity and selectivity, and excellent performance in luminescent bioimaging, the development of turn “ON” response chemosensors remains a challenge due to the intrinsic luminescence quenching property of Cu²⁺. In 2009, a phenothiazine-coupled Ru(II) complex 29 was developed by Ajayakumar as the luminescence turn

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**Fig. 13** Molecular structure of Ru(II) complex 28 and its response mechanism to Cu²⁺ (A). One-photon microscopy (OPM) and two-photon microscopy (TPM) imaging of Cu²⁺ in cells and zebrafish (B). Adapted with permission from Ref. [134]. Copyright 2013 Wiley
“ON” chemosensor for Cu\(^{2+}\) detection (Fig. 14A) [135]. Complex 29 was almost non-luminescent (\(\phi = 0.0035\) in CH\(_3\)CN) because of the PeT from electron-rich phenothiazine to the Ru(II) center. In the presence of Cu\(^{2+}\), the oxidation of phenothiazine to phenothiazine-5-oxide inhibited the PeT process, and thus the emission of complex 29 was switched “ON.” In another research, Zhang et al. reported a Ru(II) complex “OFF–ON” luminescence chemosensor 30 for Cu\(^{2+}\) detection and imaging (Fig. 14A) [136]. Complex 30 with an o-(phenylazo)aniline structure showed weak luminescence in HEPES buffer solution (20 mM, pH 7.4). Cu\(^{2+}\)-mediated oxidative cyclization led to > 80-fold enhancement in luminescence at 599 nm. The large enhancement in luminescence allowed complex 30 for highly sensitive (LoD = 4.42 nM) and selective detection of Cu\(^{2+}\) in buffer and imaging of Cu\(^{2+}\) in pea aphids (Fig. 14B).

Despite the quenching of most Ru(II) complexes’ emission by Cu\(^{2+}\) binding, the heterobimetallic Ru(II)–Cu(II) complexes provided an excellent platform for further development of “OFF–ON” response chemosensors for the detection of various analytes, such as anions [137], adenosine triphosphate (ATP) [138], amino acids [139, 140], redox biology [128] and other metal ions [141]. For example, in 2012, Wang et al. reported a Ru(II) complex for sequential detection of Cu\(^{2+}\) and Cr\(^{3+}\) in aqueous solution [141]. The coordination of a complex with Cu\(^{2+}\) produced the non-luminescent Ru(II)–Cu(II) complex, and this heterobimetallic complex showed high selectivity to Cr\(^{3+}\) in NaOAc-HOAc buffer (pH 5.6). A high sensitivity of this chemosensor to Cr\(^{3+}\) was also obtained with a LoD 66 nM.

### 4.2 Ru(II) Complex Chemosensors for Hg\(^{2+}\)

Because of the high binding affinity of S atom with Hg\(^{2+}\), a series of S atom-bearing Ru(II) complexes have been developed as the chemosensors for Hg\(^{2+}\) detection. Previous research has revealed the colorimetric response of N-719 to Hg\(^{2+}\), in which the absorption spectra of N-719 were blue-shifted after binding of Hg\(^{2+}\) [142, 143]. The N-719 functionalized upconversion nanoparticles (UCNPs) were then prepared,

![Fig. 14 Molecular structure of Ru(II) complexes 29, 30 and their response reaction with Cu\(^{2+}\) (A). The application of Ru(II) complex 30 for Cu\(^{2+}\) imaging in pea aphids. Adapted with permission from Ref. [136]. Copyright 2015 Springer Nature](image-url)

 Springer
and the application of the ratiometric upconversion luminescence (UCL) nanosensor for Hg\textsuperscript{2+} detection and imaging was also demonstrated [142]. In 2015, the N-719 derivative Ru(II) complex \textit{31} was prepared by Fan and co-workers for colorimetric and luminescent determination of Hg\textsuperscript{2+} [144]. Similar to N-719, the response of complex \textit{31} to Hg\textsuperscript{2+} was ascribed to the binding of electron-deficient Hg\textsuperscript{2+} to the electron-rich sulfur atom of NCS (thiocyanate) groups. A 40-nm blue shift (from 525 to 485 nm) of absorption and a remarkable increase of luminescence at 720 nm were observed upon binding of complex \textit{31} to Hg\textsuperscript{2+}. In another study, Li et al. reported that a cyclometallated Ru(II) complex \textit{32} was then produced as the chemosensor for Hg\textsuperscript{2+} colorimetric analysis [146]. The Hg\textsuperscript{2+}-initialized conversion of coordination from C to S atom led to a remarkable absorption and solution color change from dark red to light yellow. In a subsequent study, the same group modified sulfonate to carboxyl to prepare a polymer membrane for colorimetric detection of Hg\textsuperscript{2+} [147].

The binding of S atom to Hg\textsuperscript{2+} has also been exploited for the development of Ru(II) complexes \textit{33} and \textit{34} for Hg\textsuperscript{2+} detection. For complex \textit{33}, oxathiacrown ether is able to bind Hg\textsuperscript{2+}, resulting in a 30 nm blue shift of absorption spectra and color change from red-orange to yellow [148]. For complex \textit{34}, Hg\textsuperscript{2+} can bind to four benzothiazole S atoms from two complex \textit{34}s through a 1:2 binding stoichiometry [149]. The response of Hg\textsuperscript{2+} was accompanied by a significant increase of complex \textit{34}'s emission at 656 nm. Nevertheless, complex \textit{34} showed poor selectivity to Hg\textsuperscript{2+}, as luminescence enhancement at 630 nm was observed in the presence of Ag\textsuperscript{+}. The response of complex \textit{34} to Ag\textsuperscript{+} was due to the binding of Ag\textsuperscript{+} to benzothiazoles’ S atoms through a 1:1 stoichiometry (Fig. 15).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{complexes.png}
\caption{Molecular structure of Ru(II) complexes \textit{31–34} for Hg\textsuperscript{2+} detection}
\end{figure}
Based on the Hg$^{2+}$-mediated desulfation and intramolecular cyclic guanylation of thiourea reaction, Ru et al. developed Ru(II) complex 35 as an “OFF–ON” luminescence response chemosensor for Hg$^{2+}$ (Fig. 16A) [150]. Complex 35 showed weak luminescence ($\phi = 0.4\%$), while the emission significantly increased upon reacting with Hg$^{2+}$ ($\phi = 2.2\%$). This reaction-based chemosensor (35) showed high selectivity and sensitivity (LoD = 8 nM) for Hg$^{2+}$ detection. More importantly, the long lifetime emission of Ru(II) complex ($\tau_{35} = 215$ ns, $\tau_{35-Hg^{2+}} = 785$ ns) enabled the background-free TGL analysis of Hg$^{2+}$. With this Ru(II) complex 35, luminescence imaging of Hg$^{2+}$ in SMMC-7721 cells was then demonstrated (Fig. 16B). Using the same response reaction, the same research group then developed a phen ligand-based Ru(II) complex 36 for Hg$^{2+}$ detection (Fig. 16A) [151]. Compared with complex 35, complex 36 has higher sensitivity with a detection limit down to 5.4 nM. Similarly, the applications of this chemosensor for TGL Hg$^{2+}$ detection and luminescence imaging of Hg$^{2+}$ in SMMC-7721 cells were also demonstrated.

### 4.3 Ru(II) Complex Chemosensors for Other Metal Ions

Ru(II) complex-based chemosensors have also been developed for the detection of other metal ions [152], such as Fe$^{3+}$ [153], Fe$^{2+}$ [77], Na$^+$ [154], Ag$^+$ [149], Co$^{2+}$ [155], Ba$^{2+}$ [156] and Zn$^{2+}$ [157]. For example, the 1,8-naphthyridine linked dinuclear Ru(II) complex has been reported for both Cu$^{2+}$ and Fe$^{3+}$ detection [153], and the azacrown ether coupled Ru(II) complex was found to respond to Ba$^{2+}$ ion.
[156]. The high binding affinity of the tpy ligand with Fe²⁺ allowed Zheng et al. to use Ru(II) complex 18 for Fe²⁺ detection [158]. The coordination of Fe²⁺ with complex 18 through a 1:2 binding stoichiometry was accompanied by the quenching of Ru(II) complex’s emission at 608 nm. In 2014, Kumar and colleagues developed Ru(II) complex 37 for the detection of Pd²⁺ (Fig. 17) [159]. In the presence of Pd²⁺, a 16-nm blue shift of the MLCT absorption band and the emerging of a new absorption at 565 nm were observed, which was accompanied by a solution color change from orange to dark red. The emission at 670 nm of complex 37 (ϕ = 3.5\%) was about 12-fold decreased (ϕ = 0.12\%) because of the paramagnetic properties of Pd²⁺ ions. Recently, Xie and colleagues reported a Ru(II) complex 38 as the chemosensor for gold(III) (Au³⁺) detection (Fig. 17) [160]. Complex 38 showed high luminescence in PBS buffer (pH 7.2), while its emission was remarkably quenched after binding with Au³⁺. Complex 38 showed high sensitivity (LoD = 135 nM) and selectivity to Au³⁺, and low cytotoxicity, allowing its use for Au³⁺ imaging in living cells and zebrafish. The application of this chemosensor for Au⁺ drug release in anti-inflammation drugs was then demonstrated in inflamed microphage cells and LPS-induced zebrafish.

5 Ru(II) Complex Chemosensors for Reactive Biomolecules

Ru(II) complexes have also been designed and synthesized as the chemosensors for the determination of small reactive biomolecules, including reactive nitrogen/oxygen/sulfur/carbonyl species (RNS/ROS/RSS/RCS) and amino acids. These biomolecules play very important roles in biological systems [25, 27, 161]. For example, ROS/RNS are important signaling molecules in the body, while high levels of ROS/RNS lead to oxidative stress, causing damage to the cell membrane, protein and nucleic acids [162]. It has been reported that the overexpression of ROS/RNS is implicated in pathological processes in inflammation, cancer, cardiovascular disease, Alzheimer’s disease (AD) and aging [162, 163]. Nevertheless, determination and monitoring their levels in situ remain a challenge due to (1) the limited numbers of robust chemosensors and (2) their high reactivity and the short lifetime of

![Molecular structures of Ru(II) complexes 37 and 38 for Pd²⁺ and Au³⁺ detection, respectively](image-url)
most species, particularly the ROS/RNS [99, 164–166]. This section will outline the contributions of Ru(II) complex chemosensors to the determination and imaging of these small biomolecules.

5.1 Ru(II) Complex Chemosensors for RNS

RNS, mainly nitric oxide (NO), peroxynitrite (ONOO⁻) and nitroxyl (HNO), are endogenous biomolecules that play essential roles in various biological processes [167]. Of these RNS, NO is produced by conversion of arginine through nitric oxide synthase-mediated oxidation [167]. NO has been found to be associated with blood vessel health and signaling pathways [168]. The reaction of NO with superoxide (O₂•⁻) forms ONOO⁻, a highly reactive biomolecule, contributing to signaling transduction in living systems [169]. In 2010, Zhang et al. pioneered the use of Ru(II) complexes for reactive biomolecule detection and demonstrated the first Ru(II) complex chemosensor for NO detection [170]. This Ru(II) complex (39) was simply designed by coupling of NO response unit, 3,4-diaminophenoxy, to Ru(II)-bpy luminophore (Fig. 18A). After reacting with NO, the electron density of the triazolephenoxy product was reduced, thus inhibiting the PeT process and turning “ON” the MLCT emission. Ru(II) complex 39 has high sensitivity and selectivity, and fast response to NO, allowing its further use for NO determination and imaging in animal and plant cells [170, 171]. Later research showed that complex 39 has better performance in endothelial NO detection compared with the DAF-FM (Fig. 18B), demonstrating the usefulness of complex 39 as a promising chemosensor.

![Fig. 18](image-url) Molecular structure of Ru(II) complexes 39 and 40 and their response reaction with NO (A) and ONOO⁻ (C), respectively. Comparison of sensitivity of complex 39 with DAF-FM in cell-free media (B). Adapted with permission from Ref. [172]. Copyright 2019 Springer Nature. Luminescence ratio-metric imaging of ONOO⁻ in HeLa cells by complex 40 (D). Adapted with permission from Ref. [177]. Copyright 2018 Royal Society of Chemistry
for NO clinical investigations [172]. Further efforts have also been devoted to modifying complex 39 for the development of other chemosensors for NO detection [173–175].

To determine the levels of ONOO− in living cells [176], Zhang et al. developed a Ru(II) complex 40 by coupling of Ru(II) complex with a cyanine 5 (Cy5) dyes (Fig. 18C) [177]. In this FRET-based chemosensor, the Ru(II) complex served as the energy donor, and Cy5 served as the energy acceptor. In the presence of ONOO−, the oxidation-cleavage led to the corruption of the electron transfer (ET) process [178], accompanied by the decrease of Cy5’s emission and increase of Ru(II) complex’s luminescence. Complex 40 also showed fast response, high sensitivity and selectivity to ONOO−, and low cytotoxicity, facilitating its application in ratiometric detection and imaging of mitochondrial ONOO− in living HeLa cells (Fig. 18D).

5.2 Ru(II) Complex Chemosensors for ROS

ROS is a group of reactive biomolecules and free radicals derived from molecular oxygen [162, 164, 179]. Generally, ROS include O₂−, hydroxyl radicals (•OH), hydrogen peroxide (H₂O₂), singlet oxygen (¹O₂) and hypochlorous acid (HOCl) [164]. These short-lived species display high reactivity, causing oxidation of other biomolecules, such as DNA, lipids and proteins [162]. In the past years, a number of Ru(II) complex chemosensors have been developed for the detection and imaging of ¹O₂ and HOCl [180], which will be discussed in this section.

Coupling with anthracene [181], pyrene [182] and 1,8-naphthalimide [183], early research revealed that Ru(II) complexes’ emissions can be quenched by the energy transfer mechanism. The triplet states of pyrene and 1,8-naphthalimide have similar energy levels to 3MLCT of Ru(II) complexes [46]; the energy transfer between these triplet states enables a longer emission lifetime with lower quantum yields compared with [Ru(bpy)₃]²⁺ prototype complex [182–184]. Different from pyrene and 1,8-naphthalimide, the energy of anthracene’s triplet state lies 1460 cm⁻¹ below the Ru(II) complexes’ 3MLCT [185], which leads to the quenching of 3MLCT states as the energy transfer from Ru(II) complexes’ 3MLCT to anthracene’s triplet state [181]. Upon specific oxidation of anthracene with ¹O₂, the corresponding endoperoxide is produced; thus, the quenching of 3MLCT is inhibited [186]. Inspired by this mechanism, Zhang et al. designed three Ru(II) complexes (41a, b, c) for ¹O₂ detection in buffer (Fig. 19) [187]. All three complexes showed high selectivity to ¹O₂ over other ROS and RNS, and the LoD was 0.17 μM, using 41a as the chemosensor.

For the determination of HOCl, Ru(II) complex chemosensors have been developed by exploiting different response reactions, including (1) oxidation of S atom [188, 189], (2) amines (including dibenzoylhydrazine) [190, 191] and (3) oxime derivatives and others [192, 193]. In 2013, Zhang et al. reported a Ru(II) complex chemosensor 42 for HOCl detection and imaging [188]. Complex 42 was developed by conjugating a Ru(II) complex luminophore and 2,4-dinitrophenyl (DNP) quencher through an S linker (Fig. 20). The specific oxidation of the S linker with HOCl led to the cleavage of electron transfer acceptor (DNP quencher), accompanied by an increase of MLCT emission at 626 nm. The applications of complex 42...
for imaging of exogenous HOCl in HeLa and endogenous HOCl in RAW 264.7 cells were then demonstrated. HOCl-mediated oxidation of phenothiazine’s “S” has also been exploited for developing Ru(II) complexes for HOCl detection in biological [194] and environmental samples [189]. For example, in 2014, Liu et al. reported a Ru(II) complex 43 as the reversible chemosensor for HOCl determination and imaging (Fig. 20) [194]. An early study found that the Ru(II) complex emissions can be quenched by phenothiazine through a PeT mechanism, and the oxidation of

Fig. 19 Molecular structures of Ru(II) complexes 41a, b, c for \( ^1 \text{O}_2 \) detection

Fig. 20 Molecular structure of Ru(II) complexes 42 and 43 and the oxidations with HOCl
“S” by Cu²⁺ resulted in the “OFF–ON” luminescent response of complex 29 for Cu²⁺ detection [135]. The oxidation of phenothiazine’s “S” can also be triggered by HOCl, enabling complex 43 to be used for HOCl detection by recording the emission changes at 605 nm. More interestingly, the sulfoxide oxidation product can be reduced by H₂S, resulting in a reversible chemosensor for HOCl detection.

In 2013, HOCl-mediated oxidation of amide was exploited by Zhang et al. for the development of Ru(II) complex chemosensor 44 for HOCl detection (Fig. 21) [195]. The emission of Ru(II) complex luminophore was quenched by the PtT from Ru(II) center to DNP quencher. In the presence of HOCl, fast oxidation-cleavage of DNP allowed the production of the luminescent Ru(II) complex. More than 1100-fold enhancement in luminescence at 626 nm was obtained immediately after the reaction of complex 44 with HOCl. The application of complex 44 for imaging of phagocytosis-induced HOCl production in RAW 264.7 macrophage cells was then successfully demonstrated. The decrease and blue shift of an absorption band at about 450 nm allowed further development of complex 44-loaded UCNPs for background-free luminescent detection of HOCl [53]. In a subsequent study, Zhang et al. reported Ru(II) complex 45 for HOCl detection and lysosomal imaging (Fig. 21) [191]. Complex 45 was developed by coupling of the Ru(II) complex and ferrocenyl moiety through a HOCl-responsive hydrazine linker. Complex 45 can be internalized through a caveolae-mediated endocytosis process. The lysosomal accumulation of complex 45 allowed its use for imaging of lysosomal HOCl. The application of complex 45 in imaging of HOCl in vivo, including in flea and zebrafish, was then demonstrated.

O-nitroaniline can react specifically with HOCl to form a benzofurazan-1-oxide (BFO) in aqueous solution. Based on this reaction, Zhang et al. developed Ru(II) complex 46 as a chemosensor for HOCl detection (Fig. 22) [196]. The MLCT emission was quenched because of the PtT mechanism, while the
products of complex 46 reacting with HOCl showed intense emission in borate buffer. Complex 46 was then applied to imaging of exogenous HOCl in HeLa and endogenous HOCl in neutrophils. In a subsequent study, Shi et al. modified complex 46 with a Gd-DOTA contrast agent to produce the heterobimetallic Ru(II)–Gd(III) complex 47 for bimodal (luminescence and magnetic resonance imaging (MRI)) determination and imaging of HOCl (Fig. 22) [197]. Upon reacting with HOCl, both luminescence and MR signals were increased. The increase of luminescence was attributed to the corruption of PeT between o-nitroaniline and Ru(II) complex, and the increase of MR signal was ascribed to the increased number of inner-water molecules. Then, complex 47 was applied to luminescence and MRI detection of HOCl in drug-induced acute liver and kidney injury in a mouse. Following the development of complex 30 for Cu$^{2+}$ detection [136], the same group found that the dinuclear Ru(II) complex 48 can also be used for HOCl detection (Fig. 22) [198]. The oxidation-cyclization of the azo and amino group in complex 48 produced a triazole derivative, accompanied by > 50-fold enhancement of MLCT emission at 600 nm. Moreover, this oxidation-cyclization showed high selectivity to HOCl over other ROS and Cu$^{2+}$. Complex 48 was then applied to luminescence imaging of HOCl in mouse.
5.3 Ru(II) Complex Chemosensors for RCS

RCS is a family of small and transient carbon-based metabolites that are implicated in several biological processes [199]. These species can react with proteins through covalent bonds. As a result, the functions of proteins are changed, and thus the biological processes of these proteins are affected. In living organisms, the RCS mainly include glyoxal (GO), carbon monoxide (CO), formaldehyde (FA) and methylglyoxal (MGO). Although Ru(II) complexes have been widely investigated in developing chemosensors for ions and ROS/RNS, only a few complexes have been reported for RCS detection and imaging, which will be outlined in this section.

Ru(II) complex with 4,5-diamino-1,10-phenanthroline ligand has been previously employed as the chemosensor for NO detection [173]. Recent research found that the Ru(II) complexes’ 4,5-diamino-1,10-phenanthroline ligand can respond to RCS [200], particularly the MGO to form 2-methylpyrazino-1,10-phenanthroline ligand coordinated products [201]. Based on this reaction, Zhang et al. investigated the capability of the Ru(II) complex chemosensor for MGO determination and imaging in RAW 264.7 macrophages and flea. Recently, Zhang et al. reported a “dual-key-and-lock” Ru(II) complex chemosensor 49 for lysosomal FA determination in cancer cells and tumors (Fig. 23A) [202]. Complex 49 was designed by coupling of Ru(II) complex with a DNP quencher through an FA-responsive linker. Interestingly, the response reaction of complex 49 can only take place in the presence of FA (first “key”) under acidic conditions (second “key”), which allow FA detection specifically in lysosomes. Complex 49 has a long lifetime (τ = 330.4 ns), which facilitates the application of background-free TGL analysis in human serum samples and mouse organs. Luminescence imaging results clearly showed that complex 49 could be used for lysosomal FA detection in HeLa cells (Fig. 23B). With this FA-responsive Ru(II) complex, in vivo and ex vivo imaging results confirmed the much higher FA levels in tumor cells and tissues (Fig. 23C).

Fig. 23 Molecular structure of Ru(II) complex 49 and its response reaction with FA (A). The luminescence imaging of intracellular FA in lysosomes (B) and ex vivo imaging of FA in different mouse organs (C). Adapted with permission from Ref. [202]. Copyright 2019 American Chemical Society
5.4 Ru(II) Complex Chemosensors for RSS

Hydrogen sulfide (H₂S) is one of the major RSS in the human body and is involved in various biological processes. This endogenous gaseous molecule is produced by CBS (cystathionine β-synthase) and CSE (cystathionine γ-lyase) catalyzed reaction with thiol-containing biomolecules [203]. Recent research has also revealed that the H₂S is a gasotransmitter and a regulator of critical biological processes [204, 205]. The metabolites of H₂S, such as polysulfides and persulfides, are also important RSS that may have similar or divergent regulatory roles in living systems [206, 207]. Recently, by exploiting the response mechanisms of sulfoxide reduction [194], displacement of Cu²⁺ [137], cleavage of 7-nitro-2,1,3-benzoxadiazoles (NBD) [208] and DNP [209], a few Ru(II) complexes have been developed as chemosensors for RSS detection [194], and these RSS-responsive Ru(II) complexes will be discussed in this section.

In 2018, coupling of Ru(II) luminophore and DNP quencher with a H₂S-responsive linker, Du et al. reported Ru(II) complex 50 as the chemosensor for H₂S (Fig. 24A) [209]. Complex 50 was weakly luminescent because of the PeT from the Ru(II) center to DNP. In the presence of H₂S, the cleavage of the linker led to more than 86-fold enhancement in emission intensity at 612 nm. The long lifetime (> 300 ns) of both complex 50 and the products facilitated the TGL assay of H₂S in human blood serum samples and mouse organs without any background signals. The H₂S concentration was 47.70 ± 4.50 μM and < 1.2 μmol/g in sera and mouse organs, respectively. Luminescent imaging results showed that complex 50 accumulated in lysosomes, thus allowing lysosomal H₂S to be detected. By exploiting the H₂S-triggered thiolysis of NBD, Ru(II) complex 51 was recently developed by Liu et al. for the detection of H₂S in PBS buffer and in living organisms (Fig. 24B) [208]. Similar to complex 50, the emission quenching of complex 51 was attributed to the PeT from the Ru(II) center to DNB. The thiolysis of complex 51 showed high effectiveness for H₂S detection.

![Fig. 24](https://example.com/fig24.png)

**Fig. 24** Molecular structures of complex 50 (A) and 51 (B) and the application of complex 50, 51 for H₂S imaging in cells and zebrafish. Adapted with permission from Ref. [208, 209]. Copyright 2018 Wiley and 2021 Elsevier
sensitivity (LoD = 177.3 nM) and selectivity to H₂S over other biothiols, including Cys, Hcy and glutathione (GSH). Complex 51 was then applied to visualize the H₂S in living HeLa cells and zebrafish.

6 Ru(II) Complex Chemosensors for Amino Acids

Amino acids are building blocks of proteins and play critical roles in living organisms [210]. In living organisms, the amino acids are involved in synthesis of proteins and other nitrogen-containing species, such as hormones, enzymes, creatine and some neurotransmitters. In the past few years, luminescent Ru(II) complexes have contributed significantly to the development of chemosensors for various amino acids, such as biothiols (Cys, Hcy, and GSH), histidine (His) and others, which will be discussed in this section.

6.1 Ru(II) Complex Chemosensors for Biothiols

GSH is one of the most abundant biothiols in the human body with intracellular concentrations ranging from 1 to 10 mM and about 1 mM in blood [161]. The intracellular Cys concentration is in the range of 30–200 μM and about 250 μM in blood [161]. Different from GSH and Cys, Hcy has a much lower concentration in the body, i.e., 5–15 μM in cells and about 10 μM in blood [211]. Recent studies have also revealed that the concentration of biothiols is implicated in different conditions, such as inflammation, cardiovascular diseases, HIV infection and cancers [161]. To detect biothiols in the body, a series of Ru(II) complex chemosensors have been developed through the following response mechanisms, (1) nucleophilic substitution and cleavage of the sulfonamide or sulfonate ester bond [212–214], (2) cyclization of aldehyde group with amino and thiol groups [100, 215, 216] and (3) others [217], such as reaction with azo group [218] and α,β-unsaturated ketone [219], cleavage of NBD and displacement of metal ions [139, 220].

Through coupling of 2,4-dinitrobenzenesulfonyl to the amine of phen ligand, Ru(II) complex 52 was developed for biothiols determination by Ji and co-workers in 2010 (Fig. 25) [221]. Upon the reaction with biothiols, cleavage of the DNP electron acceptor led to a 90-fold enhancement of MLCT emission at 598 nm. Imaging of biothiols in NCI-H446 cells was then demonstrated using complex 52 as chemosensor. In a prior study, Zhang et al. found that the Ru(II) complexes with two response units could have higher “OFF-to-ON” ratios for thiophenol detection [222]. In 2017, Gao et al. reported on Ru(II) complex 53 for luminescence detection of biothiols (Fig. 25) [223]. In this Ru(II) complex, two DNP quenchers were linked to two bpy ligands through a sulfonate ester bond, which enabled the quenching of MLCT emission and the “OFF–ON” response to biothiols. A morpholine moiety was conjugated to the third bpy ligand, allowing complex 53 with lysosome
targeting ability. The capability of complex 53 for background-free TGL detection of biothiols was also demonstrated.

Although a number of biothiol-sensitive chemosensors have been reported, the measurement of total biothiols and determination the level of each one remains a challenge. In 2020, Liu et al. reported a “Two Birds with One Stone” Ru(II) complex 54 for the detection and discrimination of biothiols in vitro and in vivo (Fig. 26A) [224]. Complex 54 was developed through coupling of two different signaling units (Ru(II) complex and NBD) through a “luminophore-responsive linker-luminophore” approach. In the presence of GSH, the cleavage of “O” ether bond led to the formation of a luminescent Ru(II) complex and non-fluorescent NBD-SR1. In contrast, the reaction of complex 54 with Cys and Hcy led to the formation of a red-emitting Ru(II) complex and NBD-SR2 that can further undergo a five- or six-member cyclic intermediate-associated rearrangement to form corresponding green-emitting NBD-NR. This allowed for discrimination of GSH from Cys and Hcy under steady-state luminescence measurements. Moreover, under the TGL measurement model, the total biothiol concentration was obtained as elimination of the emission from NBD-NR. The GSH and Cys/Hcy concentrations were thus determined by measuring the same sample with both steady-state and TGL models. The time-gated luminescence imaging of
intracellular biothiols was then demonstrated, showing that the NBD emission was eliminated after a 4-ns delay ($\tau_{\text{NBD-NR}} = 0.8$ ns) (Fig. 26B).

### 6.2 Ru(II) Complex Chemosensors for Other Amino Acids

Ru(II) complexes have also been developed for the detection of other amino acids, such as methionine (Met) and histidine (His), through the response mechanism of amino acid-dominated binding of metal ions (e.g., Cu$^{2+}$ and Ni$^{2+}$) [140, 220, 225]. For example, Gao et al. developed Ru(II) complex 55 in 2015 and then used the heterobimetallic Ru(II)–Ni(II) complex as the chemosensor for His detection (Fig. 27) [226]. Complex 55 showed intense luminescence in EtOH/HEPES buffer (50 mM, pH 7.2, 2:3, v/v), and its emission was quenched upon binding to Ni$^{2+}$.
In the presence of His, the displacement of Ni$^{2+}$ led to the recovery of Ru(II) complex’s emission at 603 nm. The LoD was 265 nM at this test condition. Imaging of His in HeLa cells, zebrafish and flea was then performed using complex 55 as the chemosensor.

### 7 Conclusions

The past few decades have witnessed rapid progress in the development of chemosensors for biological investigations and environmental sample determinations. Of various chemosensors, the ones using Ru(II) complex-based luminophores are particularly interesting because of their abundant photo-physical/-chemical properties. Consequently, a series of Ru(II) complex chemosensors have been developed for the detection of ions and small biomolecules in recent years. In this review, the progress in the development of Ru(II) complex chemosensors for the detection of anions, metal ions, reactive biomolecules (ROS, RNS, RSS, and RCS) and amino acids was summarized, particularly focused on those chemosensors that can be used for target analyte detection in aqueous solution and imaging in living systems.

By carefully surveying the reported Ru(II) complex chemosensors, it is clear that the Ru(II) complex has been a useful platform for the determination of various analyte levels in vitro and in vivo. Nevertheless, there is still some room for further development of Ru(II) complex chemosensors in future studies. As it has been confirmed that the photo-physical/-chemical properties of Ru(II) complexes are varied by changes of the coordination ligands [227–230], the toxicity, particularly the photo-toxicity, could be one of the key considerations in developing Ru(II) complex chemosensors in the future. Generally, low cytotoxicity is one of the essential criteria for a chemosensor to be applied in biological studies. Moreover, the triplet nature of the emission state of Ru(II) complexes with long phosphorescence lifetime is easily quenched by oxygen [56]. Therefore, development of the Ru(II) complex chemosensors with minimal quenching from the surrounding environments, particularly the levels of oxygen, is also demanded. With intense background autofluorescence in biological systems limiting the use of other probes, recent research has confirmed that Indeed Ru(II) complexes with prolonged emission lifetime can be used for TGL

![Molecular structure of Ru(II) complex 55 and heterobimetallic Ru(II)–Ni(II) complex for His detection](image-url)
bioassays and imaging [28, 31, 202]. Such a background-free bioassay and imaging approach allow the determination of target analytes in living cells with higher sensitivity and signal-to-noise (S/N) ratio, which can be further investigated for biomolecule detection in vivo in future studies.

In summary, taking together with the unique photo-physical/-chemical properties of Ru(II) complexes and the potential applications of chemosensors, ongoing research is expected to develop robust Ru(II) complex chemosensors for the determination and imaging of ions and biomolecules in the future. We hope that this review will provide a knowledge base for the Ru(II) complex chemosensor area and inspire the readers to contribute to this promising research field in the future.

Acknowledgements The authors gratefully acknowledge the financial support from Australian Research Council (DE170100092) and National Health and Medical Research Council (APP1175808).

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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