

Multipurpose applications of coumarin derivatives with special emphasis on the fluorescent probes

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Abstract : The literature on the use of coumarin derivatives is very rich and highly significant. They have been widely used as fluorescent probes developed for detection and estimation of various cations, anions, amines and amino acids, biothiols, pH, chemical warfare agents, proteins, hydrogen peroxide, hydroxyl radicals and many more. Various pharmacological activities of coumarin derivatives have made them suitable for use as anti-oxidant and anti-inflammatory drugs. They have also exhibited anti-microbial, anti-hepatitis, anti-cancerous, anti-pyretic and analgesic activities.

Keywords : Coumarin derivatives, fluorescent probes, cations, anions, amino acids, small molecules, biomolecules, anti-microbial activity, trace level determination.

Introduction

Coumarin, a heterocyclic compound having oxygen as hetero atom occurs in many plants, notably in high concentration in tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass. Coumarins comprise a group of natural compounds originating from the shikimate pathway and widely distributed in plants and essential oils¹. It is a member of the benzopyrone family, which are subdivided into the benzo-*a*-pyrones and benzo-*g*-pyrones. Coumarin belongs to benzo-*a*-pyrones while principal members of flavonoids are benzo-*g*-pyrones. The basic structure of coumarin consists of a phenyl group fused with an oxazole ring; both rings are susceptible to functionalization. However, functional group addition in phenyl group has more attractive and chemically accessible.

Literature survey reveals that coumarins behave as effective anti-coagulants², antibacterial agents³⁻⁷, antifungal agents⁸⁻¹⁰, biological inhibitors¹¹, chemotherapeutics^{12,13} and also as bio-analytical reagents¹⁴. Some of the coumarin derivatives have been found to possess antitumour activity¹⁵⁻¹⁷, cytotoxicity^{18,19} and antioxidant activity²⁰⁻²². There are instances where coumarin ana-

logs have been described as inhibitors of cyclooxygenase, a key enzyme involved in inflammation process²³. Interestingly, coumarins have an inhibitory effect on DNA gyrase and have been shown to be linked to antihuman immunodeficiency virus (HIV) activity¹. Coumarin nucleus and related derivatives²⁴ have exhibited antithrombotic and vasodilatory activities^{24,25}, antimutagenic activity²⁶, lipoxygenase and cyclooxygenase inhibition^{27,28}, scavenger of reactive oxygen species²⁹ and anti-tumourigenic behaviour^{30,31}. Coumarins have been used in the treatment of lymphedema³². Various other medicinal applications of metal complexes of coumarins^{33,34} have been reported. In fact, the biological activities of some coumarin derivatives have been shown to be enhanced significantly due to binding with metal ions^{35,36}.

Recently, the fluorescent method of detection has become very popular in the fields of biological, clinical diagnosis and environmental research due to its operational simplicity, high selectivity, sensitivity, rapidity, non-destructive methodology and direct visual perception. Moreover, coumarin derivatives are frequently encountered as signaling units in sensors and in sophisticated photo-physical systems⁸. It was reported that this area of application has related to the molecular electronic structure of coumarins³⁷ accordingly the electronic structure

of a large number of coumarin derivatives have been investigated by combination of experimental and theoretical methods³⁸ including UV photoelectron spectra (UPS), UV-Vis spectroscopy and semi-empirical MO calculations. The main conclusions of these studies indicated that the excited electronic states of coumarins, which are responsible for luminescent properties have high density in the vicinity of S¹. In addition, the propensity for inter-system crossing to T² or T³ states further complicates analysis of fluorescent behavior and that the positions of absorption maxima are affected by the nature and position of substituents. Electronic releasing substituents (amino, methoxy) in 3- or 7-position induce not only bathochromic shifts of the longest wavelength absorption maxima, but also enhance band intensity (in absorption and fluorescence). The opposite is true for substituents in 6- or 8-position. The π -electron charge densities in the ground and excited states were also investigated³⁹. The consensus was that in the X state there is an increase in charge density on carbonyl oxygen with concurrent depletion of the same at the ring oxygen. In 7-substituted derivatives an enhancement of charge density within the benzene ring occurred, while the carbonyl oxygen experienced no net effect. In the first state a noticeable π -density transfer from the carbonyl oxygen to the pyranone ring appeared. In the second state, the π -density transfer took place from the benzene to the pyranone ring with negligible change at the CO group. The fluorescent properties of coumarins would naturally suggest the use of higher resolution fluorescence spectroscopy for studying details of the important excited states⁸. Coumarins, with the structure of benzopyrone, have many advantages including high fluorescence quantum yield, large Stokes shift, excellent light stability and less toxicity. Therefore coumarins have been widely used in the fields of biology, medicine, perfumes, cosmetics and fluorescent dyes. Coumarin derivatives have been used as cation/anion sensor⁴⁰, phosgene probe⁴¹ and possess interesting luminescent properties⁴². They have also been used for monitoring the polarity and microviscosity of the environment in various simple, mixed or ionic solvents^{43,44}.

Coumarins are an important class of oxygen heterocycles, widespread in the plant kingdom⁴⁵. Possession of their diverse pharmacological properties⁴⁶ has created a lot of interest in recent times. 4-Methyl coumarin derivatives have been found to possess choleric, analgesic,

anti-spermatogenic, anti-tubercular and diuretic properties^{47,48}. Coumarin Schiff bases are known as antioxidant and anti-inflammatory agents, being scavengers of reactive oxygen species (ROS). The *o*-dihydroxy substituted coumarins have been proved to be excellent radical scavengers⁴⁹. Aminocoumarins like clorobiocin and novobiocin, due to their antibiotic properties, have clinical use (Albamycin; Pharmacia-Upjohn) and are used for the treatment of infections with multi-resistant Gram-positive bacteria, e.g. *Staphylococcus aureus*. Studies on the structure activity relationships have revealed that the presence of substituted thiocarbonylmercaptoacetyl amino derivatives is the cause of their pharmacological activities. Synthesis of coumarin and their derivatives have attracted considerable attention from organic and medicinal chemists for many years, as a large number of natural products contain this heterocyclic nucleus. They are important in many fields of everyday life. Coumarins are used as active components in the formation of pesticides, additives in food, cosmetics, and pharmaceuticals⁵⁰, optical brighteners⁵¹, and dispersed fluorescent and laser dyes⁵². They are also used as sweetener, fixative of perfumes, enhancer of natural oils, odour stabilizer in tobacco and an odour masker in paints and rubber. Coumarins have been synthesized by several routes including Pechmann, Perkin, Knoevenagel, Reformatsky⁵³ and Wittig⁵⁴ reactions.

Coumarin is rapidly absorbed by the body following administration, either orally or topically⁵⁵. In humans and baboons, cytochrome P450 isoenzyme CYP2A6 forms 7-hydroxycoumarin (umbelliferone), via catalysis of coumarin⁵⁶. Coumarin, a weakly fluorescent molecule, turns into highly fluorescent 7-hydroxycoumarin in the presence of aqueous OH radicals⁵⁷.

Three classes of coumarin derivatives, namely aminocoumarins, hydroxycoumarins and aldehyd-coumarins have been commonly used in the design and syntheses of functionalized coumarins. Aminocoumarins and hydroxycoumarins being highly fluorescent; are used as optical brighteners and fluorescent probes^{58,59}. 7-Aminocoumarins have been widely used as blue laser dyes⁶⁰ and fluorescence probes in many chemical and physicochemical studies⁶¹. Since the early seventies of the last century, coumarins have been used as medicinal drugs for the treatment of different diseases (e.g. edema, cancer, infections, chronic fatigue syndrome).

In the present review, an exhaustive study on the literature of coumarins (Fig. 1) and their derivatives has been made in terms of their multipurpose activities, with

special emphasis on their applications as fluorescent sensors for cations, anions, amines and amino acids, biothiols, pH, chemical warfare agents, proteins, hydrogen peroxide, hydroxyl radicals, polymerization and polymeric micelles, enzymes, DNA and RNA.

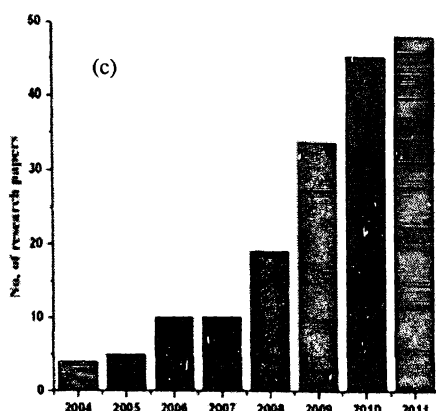
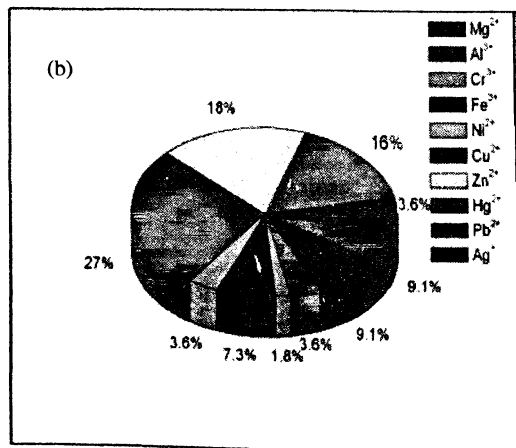
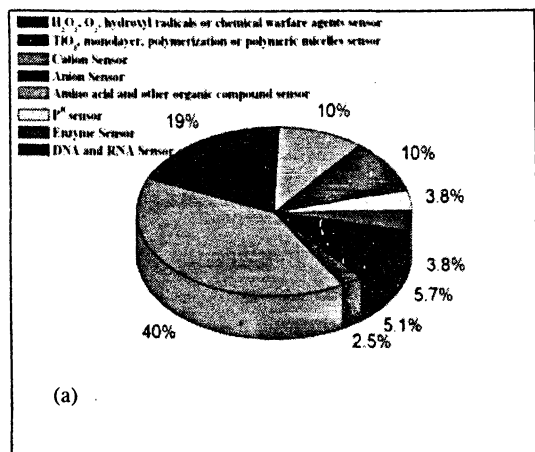


Fig. 1. (a) Relative number of reports (%) on coumarin derivatives during the time period from ~2004 to 2011 as (a) fluorescent probes, (b) cation sensors and (c) number of research articles published each year on the application of coumarin derivatives.

Coumarin derivatives as fluorescent sensors

Fluorescent chemosensors are usually made up of three components viz. receptor; fluorophore and a spacer to link them together (Fig. 2). A typical fluorescent chemosensors contains a receptor (the recognition site) linked to a fluorophore (the signal source) which translates the recognition event into the fluorescence signal. An ideal fluorescent chemosensor must meet two basic requirements firstly, the receptor must have the strongest affinity with the relevant target (binding-selectivity); secondly, the fluorescence signal should avoid environmental interference (signal-selectivity), such as photobleaching, sensor molecule concentration, and stability under illumination. The signal of a fluorescent chemosensor is usually measured as a change in fluorescence intensity, fluorescence lifetime, or a shift of fluorescence wavelength. Chemosensors of photoinduced electron transfer (PET) and intermolecular charge transfer (ICT) mechanisms have been used frequently. For a PET chemosensor, a fluorophore is usually connected via a spacer to a receptor containing a relatively high-energy non-bonding electron pair, such as nitrogen atom, which can transfer an electron to the excited fluorophore and as a result quench the fluorescence, giving rise to a turn off fluorescence sensor. When the electron pair is bound by coordination of a cation, anion, amino acid and other organic molecules, the redox potential of the receptor is raised so that the HOMO of the receptor becomes lower in energy than that of the fluorophore. Thus, the PET process from the receptor to the fluorophore is blocked and the fluorescence is switched on, giving rise to a turn on sensor. Ratiometric measurements, i.e. the observation of changes in the ratio of the intensity of the absorption or the emission at two wavelengths, have also been used to increase the signal-selectivity. The ICT mechanism has been widely used in the design of ratiometric fluorescent chemosensors. When a fluorophore, without a spacer, is directly connected to a receptor (usually an amino group) to form a π -electron conjugation system with electron rich and elec-

tron poor terminals, then ICT from the electron donor to receptor would be enhanced upon excitation by light.

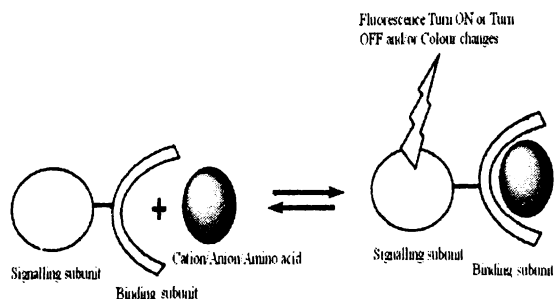


Fig. 2. Chemosensors based on the binding site-signaling subunit approach.

The following sections of this article illustrate the immense variety of coumarin based fluoroionophores that have been designed for cation, anion, amino acid and other organic molecules, recognition. The terms, 'turn on' and 'turn off' fluorescent sensors have been employed according to the nature of the photoinduced processes, photoinduced electron transfer like as photoinduced charge transfer, excimer formation or disappearance.

Coumarin derivatives as cation sensors

Fig. 3 shows coumarin derivatives as cation sensors. The fluorescent chemosensors have served as useful tools in sensing metal ions in various biologically important species. Probe (1) contains an aza-thio macrocycle ring as the chelating unit, which has great affinity for soft metal ions, whereas (2) is a parent species without macrocyclic unit. Both are highly selective toward cations of Ag^+ , Pd^{2+} , and Ni^{2+} ion⁶². Two coordination patterns involving one or both carbonyl groups were proposed for the coordination of hard metal ions (e.g. Li^+ , Na^+ , K^+ , Ca^{2+} or Mg^{2+}) with an analogous coumarin-bearing macrocycle.

Na^+ , K^+ and Li^+ sensor :

Kele *et al.* have synthesized cryptand-based PET sensors (5) and (6) by interaction of an aza-crown with a methylene spacer of 4-coumaryl group⁶³. The cavity of these probes fitted well for K^+ and Na^+ , enabling easy detection by fluorescence enhancement method in methanol. Coumaryl PET sensors were able to detect saxitoxin (a marine toxin produced by dinoflagellates and several blue-green algae species) in water, selectively over so-

dium and potassium ions; where as other metal ions had no effect. Another fluorescent macrocyclic compound synthesized by Blackburn *et al.* consisted of monoaza-12-crown-4, attached with nitrogen to the 7-position of a coumarin ring (7). The sensor effectively detected Li^+ by showing large hypsochromic shift in acetonitrile giving rise to turn on fluorescence⁶⁴ and exhibited 0.04 quantum yield.

Ca^{2+} and Mg^{2+} sensor :

The C=N isomerization was the predominant decay process of the excited states for compounds with an unbridged C=N structure so that those compounds were often nonfluorescent. In contrast, the fluorescence of its analogues with a covalently bridged C=N structure increased dramatically due to the suppression of C=N isomerization in the excited states. Therefore the C=N isomerization was applied in the design of chemosensors for metal ions. The binding of metal ions by the C=N group would stop the isomerization, and a significant fluorescence enhancement has achieved.

Following this strategy, Ray *et al.* designed a coumarin derivative (8) where, interaction of the nonfluorescent probe with Mg^{2+} , stopped the C=N isomerization resulting in strong red high-intensity 550-fold fluorescence emission⁶⁵. Mg^{2+} was highly selective over other alkali metals in acetonitrile solvent. The probe exhibited high fluorescence quantum yield (0.176). Taziaux *et al.* reported that the probe (9) and (10) has shown the rigidification of the complexing cavity of by incorporation of benzo groups greatly improved the selectivity of detection of the alkaline-earth cations versus Li^+ . Addition of benzo groups to the complexing cavity also increased the gap between the absorption maxima of the Mg^{2+} and Ca^{2+} complexes⁶⁶.

Two coumarin salen-based sensors (11) and (12) synthesized by condensation of *o*-phenylenediamine and (*R,R*)-1,2-diaminocyclohexane with 8-formyl-7-hydroxyl-4-methyl-coumarin via a nucleophilic addition elimination reaction. Which are exhibited 36-fold and 111-fold fluorescence enhancements respectively toward detection of Mg^{2+} ion under Na^+ triggered synergistic effect⁶⁷. The color of probe (11) was bright green instead of weak yellow after the addition of Mg^{2+} and Na^+ together, which are easily detected by the naked eye. They have been used to

develop AND and INHIBIT logic gates. Coumarin-based two-photon probe (**13**) is developed for the detection of free Mg^{2+} ions in living cells and living tissues. The probe is excited by 880 nm laser photons, emits strong two photon excited fluorescence in response to Mg^{2+} ions⁶⁸. Another Schiff base (**14**), without two-photon activity in the wavelength range 760–860 nm, exhibited large two photon absorption as well as emission in the presence of Mg^{2+} ⁶⁹. Whereas coumarin based another chromoionophore (**15**) implemented in a transparent membrane has used as an optical one-shot sensor for Mg^{2+} ⁷⁰. Moreover, coumarin-derived fluorescent molecular probes (**16**) and (**17**) are used for highly selective detection of Mg^{2+} versus Ca^{2+} by means of monitoring the absorption and fluorescence spectral change⁷¹.

A coumarin-based signaling unit was coupled directly to amine functionality with ONO-donor set having pendant ester functionality to prepared diethyl-2,2'-(3-nitro-2-oxochroman-4-ylazanediyl)diacetate (**18**). This probe showed significant turn on fluorescence upon binding to Ca^{2+} and Mg^{2+} ions in acetonitrile solution⁷². Other alkali/alkaline earth/lanthanide and certain transition metal ions have no effect. Involvements of both ICT and PET processes were responsible for this turn on effect.

Al^{3+} sensor :

Boc deprotected pyrrolidinyl-triazolyl-bipyridine moiety coupled with coumarin-3-carboxylic acid produced an Al^{3+} sensor (**19**), where the cation coordinating sites of the triazole ring together with the bipyridyl moiety served as an ionophore⁷³. Fluorescence enhancement occurred due to photoinduced electron transfer (PET) suppression with high sensitivity in the presence of Al^{3+} (1 : 1 stoichiometric complexation) binding to the bipyridyl-triazolyl moiety. The coumarin-bipyridyl chemosensor exhibited a high association constant with submicromolar detection for the aluminum ion. Arduini *et al.* reported a FRET based Al^{3+} sensor (**20**), synthesized by the interaction of coumarin 343 and 3,5-bis(*o*-hydroxyphenyl)-1,2,4-triazole substituted with benzoic acid via an ethylene spacer⁷⁴. This chemosensor operates with an innovative FRET-based amplification and chelation enhanced fluorescence (CHEF) mechanism and was able to recognise high affinity, selectivity, nanomolar detection of Al^{3+} ion.

Cr^{3+} sensor :

Recently, our group reported, a facile synthesis of an efficient fluorescent probe (**21**) for trace level selective determination of Cr^{3+} in acetonitrile solution⁷⁵. Probe is exhibited strong binding affinity towards Cr^{3+} and was almost free from interferences of common accompanying common alkali, alkaline earth and transition metal ions. Speciation studies have been performed in a very lucid and fast way. Finally, probe is used as detect trace level Cr^{3+} in living cells under fluorescence microscope.

Fe^{3+} sensor :

Squarate hydroxamate-coumarin conjugate (**22**) is designed as a CHEF-type sensor for Fe^{3+} . Due to a PET process, probe possesses a low fluorescence yield but upon exposure to Fe^{3+} , an irreversible 9-fold fluorescence intensity increase is observed as the result of an oxidation/hydrolysis reaction⁷⁶. Coumarin derivative (**23**) exhibited high selectivity for Fe^{3+} and the selectivity has not affected by the presence of representative alkali metals, alkali earth metals and other transition metal salts⁷⁷. Mugineic acid coumarin derivative (**24**) was synthesized by click chemistry acts as a fluorescent probe for Fe^{3+} ⁷⁸. Coumarin-based hexadentate fluorescent probes for selective quantification of Fe^{3+} have also been designed and synthesized⁷⁹. Two novel fluorescent probes, (**25**) and (**26**) developed by Liu *et al.*, were quenched at 380 nm to a greater extent by Fe^{3+} compared to Mn^{2+} , Co^{2+} , Zn^{2+} , Ca^{2+} , Mg^{2+} , Cu^{2+} , Na^{+} and K^{+} . These probes are highly selective for tribasic cations and will not suffer interference from physiological levels of dibasic cations such as Zn^{2+} , Mg^{2+} and Ca^{2+} . Quantum yields of the compounds were 0.036 and 0.182 respectively⁸⁰.

Ni^{2+} sensor :

Chattopadhyay *et al.* reported that a new coumarin based fluorophore 7-hydroxy-4-methyl-8-(4'-methyl-piperazin-1'-yl)methylcoumarin (**27**), an interesting intramolecular photoinduced proton transfer (PET) phenomenon and chelation-enhanced fluorescence (CHEF) for sensing Zn^{2+} and Ni^{2+} in water under neutral pH⁸¹. Solvatochromic shift in the fluorescence spectrum revealed an increase in the dipole moment in the lowest excited singlet state compared to that in the ground state. Fluorescence intensities increased to 10-fold and 7-fold upon

binding of this probe with Zn^{2+} and Ni^{2+} respectively.

Cu^{2+} sensor :

Coumarin bearing dihydrazones derivative acts as a turn-on fluorescent probe (28) for Cu^{2+} ⁸². Biscoumarin (29) linked by a C=N double bond is highly sensitive and selective to Cu^{2+} and the fluorescent sensing mechanism is based on C=N isomerization⁸³. Nonfluorescent coumarin derivative (30) was synthesized as an efficient turn-on fluorescent chemodosimeter for Cu^{2+} in water. Mechanism studies suggest that the sensor forms a complex with Cu^{2+} in a 1 : 2 metal-to-ligand ratio, and a 50-fold fluorescence enhancement was observed when the complex simultaneously undergoes Cu^{2+} -promoted hydrolysis⁸⁴. Probe (31) was a highly effective turn-on fluorescent sensor that was catalytically hydrolyzed by Cu^{2+} leading to a large increase in the fluorescence intensity⁸⁵. Another sensor (32) was highly selective for Cu^{2+} over biologically relevant alkali metals, alkaline earth metals and the first row transition metals⁸⁶. Sensor (33) relies on a coumarin-tagged ligand that selectively binds Cu^{2+} over other biometals to induce fluorescence quenching, which is subsequently relieved upon UV irradiation to provide the turn-on response⁸⁷. Studies on interaction of phosphorus-supported multidentate coumarin-containing fluorescent sensors (34) and (35) with various transition metal ions reveal substantial fluorescence enhancement upon interaction with Cu^{2+} enabling a selective detection mechanism for Cu^{2+} ⁸⁸. Due to complexation with Cu^{2+} isomerization of both compounds were completely hindered and lone pairs on imino nitrogen were engaged to metal ion coordination. Fluorescent biscoumarin (36) linked by a piperazine unit shows high selectivity towards Cu^{2+} ⁸⁹. For chemosensor (37) the mechanism of fluorescence is based on ICT, which is modified by the introduction of an electron-donating diethylamino group making it chromogenic and increasing the binding affinity⁹⁰. Rationally designed iminocoumarin fluorescent sensor (38) displays high selectivity for Cu^{2+} over a variety of competing metal ions in aqueous solution with a significant fluorescence increase⁹¹. The 'turn-on' fluorescence originated due to hindrance of the electron transfer reaction (PET) of the nitrogen lone pair upon complexation with Cu^{2+} and restricted C=N isomerization process. Another sensor (39) appending 2-picolyamide enables effi-

cient tridentate complexation for Cu^{2+} in preference to a variety of other common heavy and toxic metal ions⁹².

Kim *et al.* introduced coumarin 334 and hydrazones derivative as a highly effective turn-on fluorescent sensor (40) with strong fluorescence enhancement in the presence of paramagnetic Cu^{2+} ions in aqueous solutions⁹³. It was catalytically hydrolyzed by Cu^{2+} , and the catalytic process induced a large increase in the fluorescence intensity, due to amplification of the fluorescence signal. The detection limit was 100 nM in aqueous solution.

Sheng *et al.* developed a coumarin-based colorimetric chemosensor (41), which was synthesized by coupling coumarin aldehyde with diaminomaleonitrile to form a Schiff base structure⁹⁴. The enhanced intramolecular charge transfer of the probe was responsible for good sensitivity and selectivity and naked eye detection for the Cu^{2+} ion over other transition cations, alkali and alkaline earth metal cations both in aqueous solutions and on paper-made test kits. A fluorometric sensor of coumarin-appended calixarene in aqueous medium was reported by Quang *et al.*, where two nitrogen atoms and two of four oxygen atoms at the lower rim of calixarene of the probe (42) formed square planar complex with Cu^{2+} ⁹⁵. Quenching of fluorescence was explained either by an electron transfer (eT) or an electronic energy transfer (ET) from coumarin moieties in the excited state to these metal ions.

Cavitand (43) was synthesized from the tetrachloride of tetrahydroxy cavitand with coumarin 2 and NaI in acetonitrile⁹⁶. In acetonitrile-chloroform (4 : 1, v/v) excitation of the coumarin fluorophore at 357 nm caused an emission change of 200-fold for Cu^{2+} .

Zn^{2+} sensor :

Owing to the important role of zinc, the second most abundant transition metal in the human body, more and more attention has been paid to development of Zn^{2+} specific chemosensors including coumarin-derived fluorescent chemosensors for Zn^{2+} ions. Study on the sensory capabilities of two novel di(2-picoly)amine (DPA)-substituted coumarins (44) and (45) shows that the variation of the point of attachment of the DPA group to the coumarin framework. The 4-substituted system (44) is a chelation-enhanced fluorescence (CHEF)-type sensor which shows a significant increase in fluorescence inten-

sity upon Zn^{2+} binding, whereas the 3-substituted coumarin (**45**) is a ratiometric sensor⁹⁷. Coumarin Schiff base (**46**) acts as a turn-on fluorescent chemosensor for Zn^{2+} ions⁹⁸. Another probe (**47**) exhibited large two-photon absorption as well as emission in the same wavelength range⁶⁵ in the presence of Zn^{2+} . In coumarin Schiff base (**48**) the fluorescence quenching is dominant because of the nitrogen lone pair orbital contribution to the excitation. Upon Zn^{2+} coordination this probe shows a significant fluorescence enhancement due to the blocking of the nitrogen lone pair orbital by metal coordination⁹⁹. A series of coumarin-based fluorescent probes (**49-52**) for detecting Zn^{2+} with high affinities show the ratiometric fluorescent properties¹⁰⁰. Fluorescence emission was enhanced due to presence of 7-hydroxy groups at the coumarin moieties and 8-positions were blocked by the dipicolilic amine (DPA) derivative. Turn on properties increased when substituents were incorporated at 6- and/or 3-position. Another series of coumarin-derived chemosensors (**53-56**) belong to the CHEF-type and have been showed to be competent for detecting zinc pools in cultured rat pituitary (GH3) and hepatoma (H4IIE) cell lines¹⁰¹. Another coumarin Schiff base (**57**) is a highly sensitive and selective fluorescent probe for Zn^{2+} in tetrahydrofuran (THF)¹⁰². Coumarin (**58**) is a fluorescent sensor for Zn^{2+} and exhibited lower background fluorescence due to intramolecular PET but upon mixing with Zn^{2+} in aqueous ethanol, a turn-on fluorescence emission is observed¹⁰³. Recently it was reported that a biscoumarin linked by bi-thiazole acted as a colorimetric receptor selectively for Zn^{2+} ¹⁰⁴.

Wu *et al.* designed a nonfluorescent coumarin derivative (**59**). This probe has shown isomerization of the C=N double bond in the excited state¹⁰⁵. However, the CH_3CN solution of this probe showed about a 200-fold increase of fluorescence quantum yield upon addition of Zn^{2+} leading to a red-shift in emission from 500 to 522 nm ($\lambda_{ex} = 450$ nm).

(F-S)₃-R configuration (where F is fluorophore, S is CH_2 spacer and R is receptor unit) of the Tris-methoxy coumarin derivative of a cryptand¹⁰⁶ showed intramolecular PET from the receptor nitrogen atoms of the cryptand moiety to the coumarin units, thus reducing the fluorescence quantum yield and lifetime of coumarin in

the ligand (**60**). Turn on fluorescence was observed in presence of protons and Zn^{2+} ion in dry THF medium, while Cu^{II} and Co^{II} quenched the fluorescence. PET effect due to the presence of protons induced a greater enhancement of emission intensity. Interestingly this ligand exhibited room temperature phosphorescence (RTP) apart from exhibiting PET.

Cd^{2+} sensor :

Recently, Taki *et al.* reported a coumarin-120 derivative as a water-soluble and ratiometric fluorescent chemosensor (**61**) for Cd^{2+} based on the 7-amino-4-methyl-1,2-benzopyrone with derivative of *N,N,N',N'*-tetrakis (2-pyridylmethyl)ethylenediamine (TPEN) receptor¹⁰⁷. Upon addition of Cd^{2+} , a decrease in the absorbance band and a concomitant increase a new band at 333 nm were observed with a distinct isosbestic point at 340 nm. A significant hypsochromic shift of 23 nm of the absorption wavelength indicates coordination of the 7-amino group to Cd^{2+} to form the nonplanar structure. The absorption bands at 356 and 333 nm linearly decreased and increased, respectively, up to 1 : 1 stoichiometry. The binding of Cd^{2+} resulted in a bathochromic shift of the emission maximum of only 4 nm; this wavelength shift is much less than that observed in the absorption titration. The quantum yields of the free ligand and its Cd^{2+} complexes were 0.59 and 0.70 respectively. The probe could be applied for the detection of trace level Cd^{2+} in living mammalian cells.

Pb^{2+} sensor :

A coumarin based fluorescent photoinduced electron transfer cation sensor 4-[(bis(pyridin-2-ylmethyl)amino)methyl]-7-methoxychromen-2-one (**62**) was capable of indicating the presence of Zn^{2+} , Cd^{2+} and Pb^{2+} ions by turn on fluorescence¹⁰⁸. The extinction coefficients (ϵ) of Zn^{2+} , Cd^{2+} and Pb^{2+} complexes were found to be 9434, 9832, 11977 $cm^{-1} M^{-1}$ respectively.

Another fluorescent chemosensor (**63**) was based on a coumarin-crown ether conjugate exhibited a high affinity and selectivity for Pb^{2+} ¹⁰⁹. Other hand, coumarin dyes (**64-66**) seem to fulfill most of the criteria required for intracellular lead indicators, as they exhibited high selectivity for Pb^{2+} ¹¹⁰. Ion competition studies and fluorescence experiments show that a fullerene-coumarin dyad was selective for Pb^{2+} complexation¹¹¹.

Ag⁺ sensor :

Tsukamoto *et al.* developed a coumarin based probe (67) with an *N'*-acetylthioureido group as a novel fluorescence switch for detection of Hg²⁺ and Ag⁺ ¹¹². A hydrogen bond was formed between the *N*-hydrogen and the acetyl O atom markedly increases the susceptibility of the probe toward desulfurization by Hg²⁺ and Ag⁺. Fluorescent probe (67) for Hg²⁺ and Ag⁺ have ppb-levels detection limits, a high selectivity over other metal ions, a high miscibility of the DMSO stock solution in aqueous media, a wide working pH range, and a feasible preparation.

8-Alkyl thiourido-7-ethoxy-4-methyl coumarin derivatives were synthesized by Al-Kady *et al.* ¹¹³. The probe (68) exhibited about 5–12 fold turn-on fluorescence upon complexation with Hg²⁺, Ag⁺, and Ag nanoparticles by chelation enhanced fluorescence or (CHEF). Activation energy of the Ag⁺ complexes was twice of the Hg²⁺ complexes. It was quite selective for both Hg²⁺ and Ag⁺ ions, others metal ion like Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺, La³⁺, and Ce³⁺ did not interfere. The probe has induced by silver nanoparticles in the picomolar (pM) concentration ranges.

A highly sensitive and selective fluorescent chemosensor (69) for Ag⁺ based on a coumarin-Se₂N chelating conjugate is developed. Due to inhibiting a PET quenching pathway, a fluorescent enhancement of 4-fold was observed under the binding of the Ag⁺ with a detection limit down to the 10⁻⁸ M range ¹¹⁴. Coumarin (70) and (71) were highly silver ion selective fluorescence ionophores ¹¹⁵. By a microwave-assisted dual click reaction, fluorogenic 3-azidocoumarin has rapidly introduced onto a 3,4-dipropargylglucosyl galactosyl scaffold with restored fluorescence. Subsequent desilylation leads to water soluble sugar-bis-triazolocoumarin conjugates which are applicable toward selective Ag⁺ detection in aqueous media via fluorescence spectroscopy ¹¹⁶.

Hg²⁺ sensor :

Recently, our group reported, a Hg²⁺ sensitive turn-on fluorescent sensor (72) by blending vanillin with coumarin ¹¹⁷. Quantum yield of the probe and its mercury complexes were 0.162 and 0.372 respectively and detection limit of the sensor was 1.25 × 10⁻⁶ M in aqueous

methanol solution. Mercuration assisted restricted rotation of the vanillin moiety and inhibited photoinduced electron transfer from the O, N-donor sites to the coumarin unit are responsible for the enhancement of fluorescence upon mercuration of sensor. It was used for imaging the accumulation of Hg²⁺ ions in *Candida albicans* cells.

Voutsadaki was developed a water soluble, fluorescent ion probe (73) with high selectivity for Hg²⁺ ions was designed and synthesized via a short and high yield synthetic procedure. This sensor showed a twenty nine fold fluorescent enhancement on binding to Hg²⁺ ¹¹⁸. Quantum yield of the free and Hg²⁺ complexes were 0.015 and 0.43 respectively. Here Hg²⁺ ion coordinate with the sulfur atom with elements of the macrocycle system. This spatial arrangement prevents the Hg²⁺ ion from coordinating with the aminocoumarin nitrogen, therefore depleting the PCT effect and initiating the PET process. This fluorescent probe behaves as a potential tool for the detection and quantification of mercury in environmental and biological samples.

The recognition mechanisms of these chemosensors mainly involve photoinduced electron transfer (PET), intramolecular charge transfer (ICT), fluorescence resonance energy transfer (FRET), coordination, and desulfurization. For instance, the fluorescence detection of (74) upon Hg²⁺ addition is promoted by a Hg²⁺ induced desulfurization of the thiourea moiety, leading to a decrease in an ICT character of the excited-state coumarin moiety ¹¹⁹. Coumarin-thiazolobenzo-crown ether based chemosensor (75) has been developed for Hg²⁺ ions that utilizes the strong coordination of Hg²⁺ ions on the crown oxygen and thiazole nitrogen. The complexation of Hg²⁺ disrupts the ICT from the oxygen donor to the coumarin fluorophore resulting in blue-shift in absorption and quenching of the fluorescence ¹²⁰. The fluorescent ratiometric Hg²⁺ ion sensor (76), based on a coumarin platform coupled with a tetraamide receptor, can specifically detect Hg²⁺ ions through the ICT mechanism ¹²¹. Fluorescein-coumarin chemodosimeter (77) for signaling Hg²⁺ ions are designed based on FRET arising from the interaction between a pair of fluorophores ¹²². Rhodamine-coumarin conjugate (78) was developed as a probe for

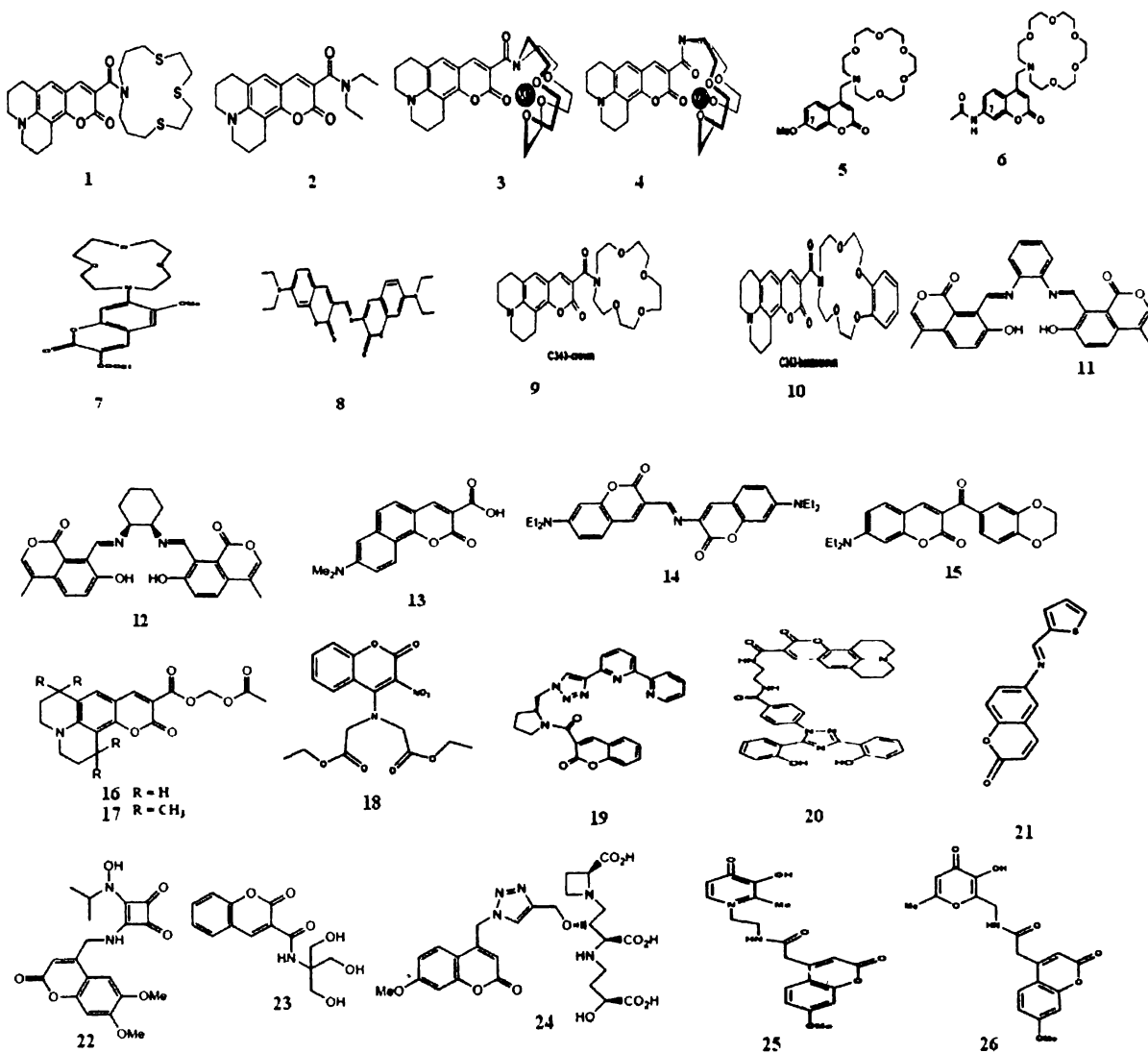
Hg²⁺ ions. The fluorescence response to Hg²⁺ ions is attributed to the 1 : 1 complex formation between probe (79) and Hg²⁺¹²³. Lee *et al.* developed another fluorescent coumarinylalkyne probe (80) for the selective detection of Hg²⁺ ion in water. Chemosensor (81) based on the coumarin thiosemicarbazide displays a selective fluorescence enhancement for Hg²⁺, which is attributed to the transformation of thiosemicarbazide unit to 1,3,4-oxadiazoles via Hg²⁺-induced desulfurization reaction in aqueous media¹²⁴. Coumarinyldithiane (82) and thiocoumarin (83) selectively sense Hg²⁺ also due to the Hg²⁺-induced desulfurization reaction¹²⁵. Another two Hg²⁺-selective chromogenic and fluorogenic chemodosimeter (84) based on thiocoumarins¹²⁶ and

iminocoumarin-based¹²⁷ Hg²⁺ ion probe (85) was reported. Probe (86) belongs to the turn-on class of sensors, functioning via a PET process¹²⁸.

Coumarin derivatives as anion sensors (Fig. 4)

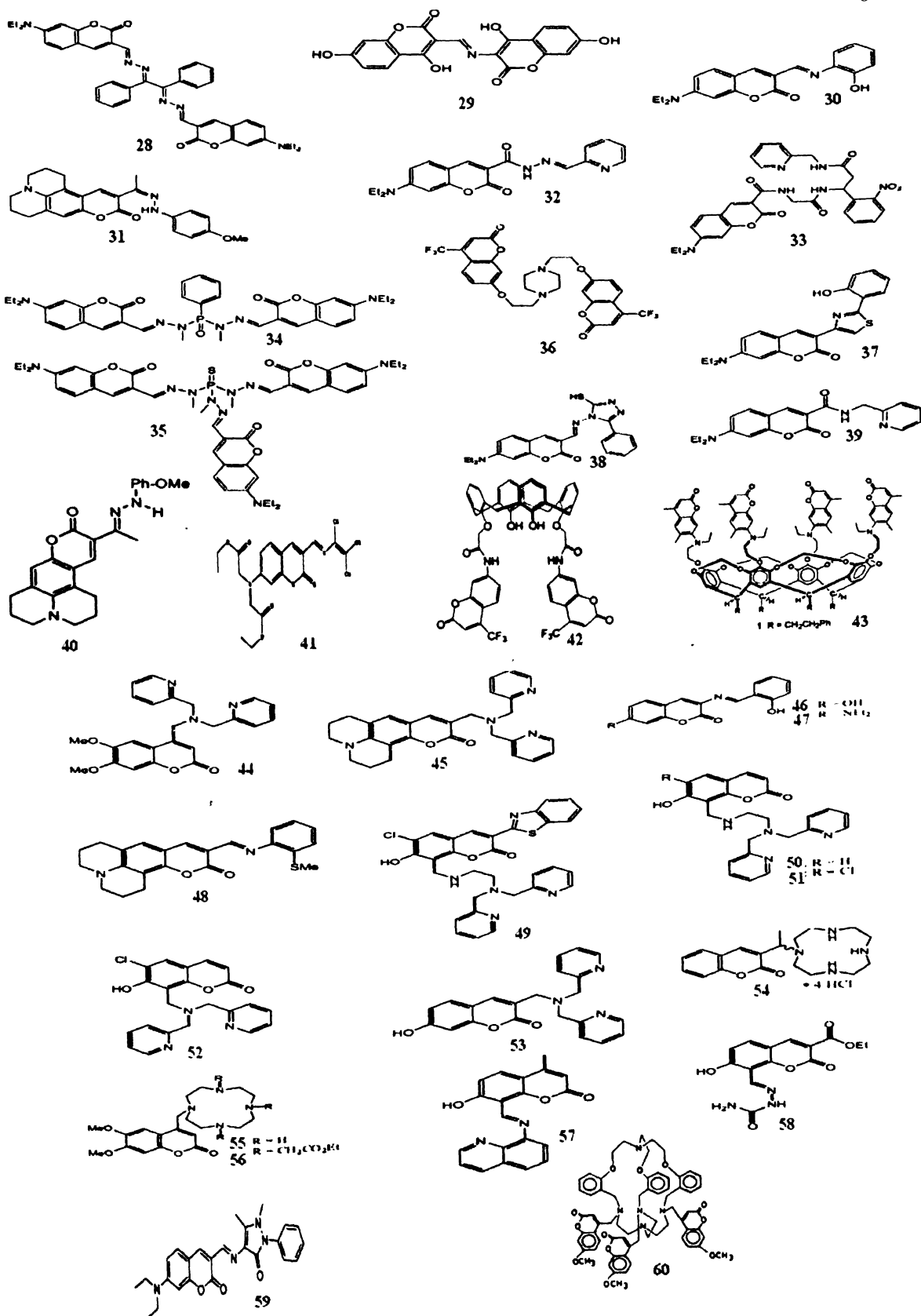
Pyrophosphate and citrate anion sensor :

A single reference on the pyrophosphate and citrate sensitive sensors of coumarin was reported by Mizukami *et al.* where the Cd²⁺ complex of the receptor (87), detected the anions in aqueous neutral solutions (pH 7.4)¹²⁹. Cd²⁺ was coordinated by the four nitrogen atoms of cyclen and the aromatic amino group of coumarin. When anions were added to solutions of Cd-complexes, the aromatic amino group of coumarin was displaced causing changes



Contd.

Fig. 3 (contd.)



Contd.

Fig. 3 (contd.)

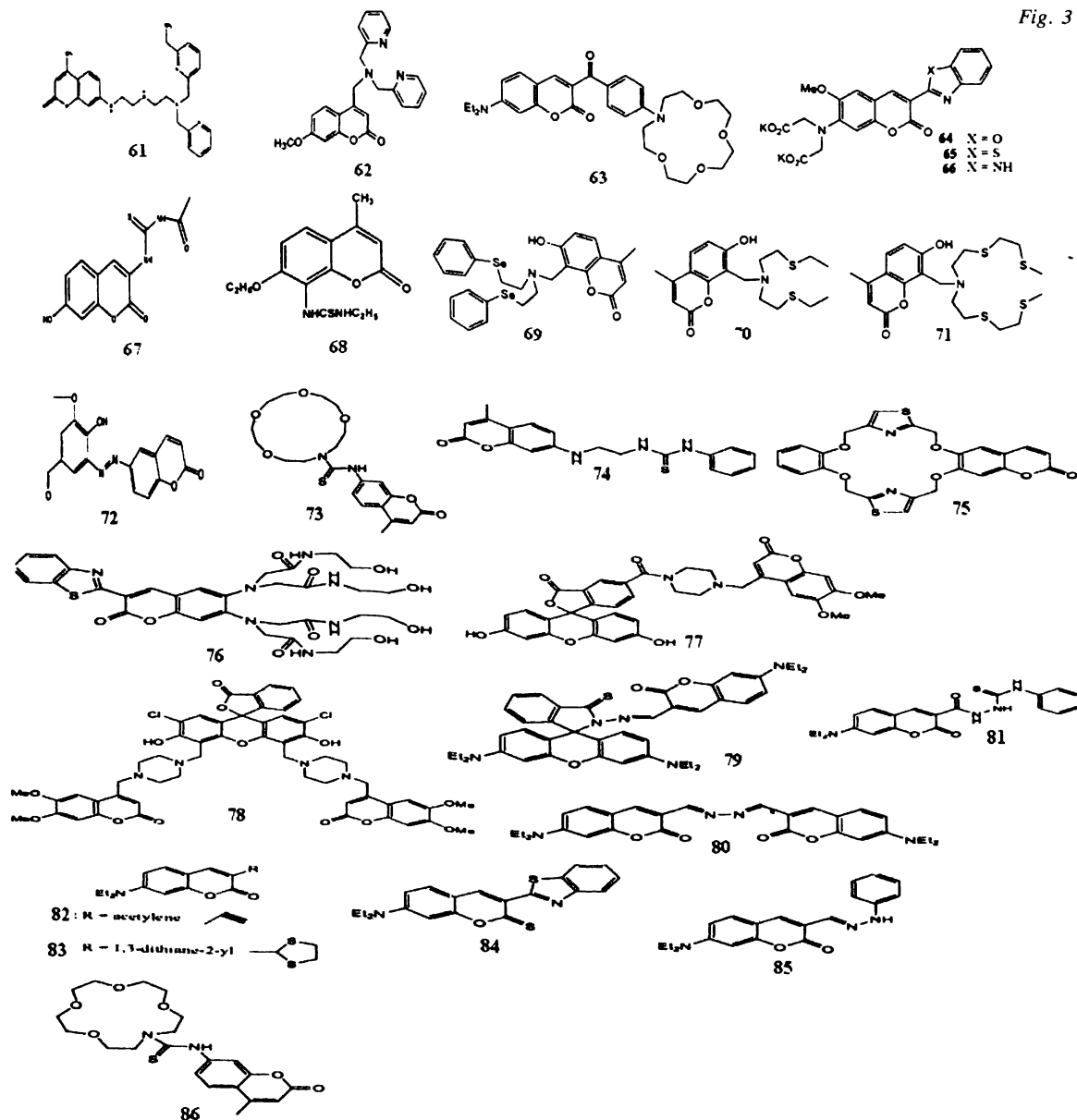


Fig. 3. Coumarin derivatives as cation sensor.

in its fluorescence spectrum. Pyrophosphate and citrate anions were detected with high sensitivity, while fluoride and perchlorate had no significant response. Four nucleotide monophosphates, AMP, GMP, CMP, and UMP, were added to solutions of Cd-complexes. GMP caused fluorescence quenching due to PET effect, whereas the other nucleotides caused red shift of the fluorescence band. On the basis of the fact that addition of cyclic AMP scarcely changed the fluorescence spectrum of Cd-complexes. This

phosphodiesterase catalyzes the conversion of cyclic AMP to AMP. The activity of phosphodiesterase cleaved cyclic nucleotide and monitored in real-time.

Cl⁻ sensor :

Miyaji *et al.* introduced a Cl^- and Na^+ sensitive sensor, where the strapped calix[4]pyrrole (88) was attached with the coumarin moiety¹³⁰. In the presence of an excess of NaPF_6 , the cation (Na^+) interacted with the lone

pair of the oxygen atoms present in the coumarin moiety causing an enhancement of fluorescence intensity in dry acetonitrile. It inhibited the PET quenching process and served to increase the fluorescence intensity in accord with the switching model. Fluorescence intensity was controlled by the dual "input parameters" of cation and anion; the added cation (Na^+) "switches on" the signal, generating a high intensity state, whereas the anion (Cl^-) "switches off" the signal, producing a low intensity state.

CN^- sensor :

Lee *et al.* designed Co^{2+} -salen based fluorescent sensor (**89**) which recognized CN^- by turn on fluorescence¹³¹. This probe displayed fluorescence enhancement upon the addition of cyanide owing to the interruption of photoinduced electron transfer from the coumarin fluorophore to the Co^{2+} ion. Addition of cyanide anions caused an alteration in HOMO and LUMO energy levels leading to a significant change in the fluorescence intensity of the complex by blocking the photoinduced electron transfer pathway. Micromolar dissociation constants were estimated.

Coumarin-spiropyran conjugate (**90**) is a highly sensitive chemosensor for CN^- and shows a CN^- selective fluorescence enhancement under UV irradiation¹³². An indole conjugated coumarin (**91**) for KCN chemodosimeter displays considerable dual changes in both absorption (blue-shift) and emission (turn-on) bands exclusively for KCN. The fluorescence enhancement of the cyanide-complex is mainly due to blocking of the ICT process¹³³. Doubly activated coumarin (**92**) acts as a colorimetric and fluorescent chemodosimeter for cyanide has been done by Kim *et al.*¹³⁴. A simple aldehyde-functionalized coumarin (**93**) has been utilized as a doubly activated Michael acceptor for cyanide¹³⁵. Coumarin-based fluorescent chemodosimeter (**94**) with a salicylaldehyde functionality as a binding site has shown selectivity for cyanide anions over other anions in water at biological pH¹³⁶.

F^- sensor :

Lee *et al.* designed a new F^- selective fluorescence chemosensor, i.e. calix[4]triazacrown-5 (**95**) which was prepared by the interaction of two pyrene amide groups and one coumarin amine group¹³⁷. This sensor excited at 343 nm, displayed the exciplex fluorescence at 425 nm. The probe displayed fluorescence enhancement due to H-

bonding between the azacrown unit and the two pyrene amide groups. Complexation of F^- with the probe quenched the fluorescence causing a decrease in exciplex emission at 425 nm as a result of PET effect and conformational change. The coumarin amine group together with an azacrown unit was responsible for behaving as a selective F^- sensor. Two coumarin signaling units and two amido groups interacted to form a novel PCT (photoinduced charge transfer) chemosensor calix[4]arene-based anion sensor (**96**), which was applied for selective detection of F^- ion¹³⁸. Fluorescence emission of this probe was due to H-bonding followed by deprotonation of NH-amide groups. Interference from other anions (e.g. Cl^- , Br^- , I^- , HSO_4^- , CH_3CO_2^- , H_2PO_4^-) is almost negligible. So, it was considered as a potential fluorescent chemosensor for F^- .

Recognition and detection of fluoride, the smallest anion with unique chemical properties of growing interest. Coumarin derivative (**97**) has been developed as a fluorescent probe for detection of F^- ion in water and bioimaging in A549 human lung carcinoma cells¹³⁹. A simple, highly selective, and sensitive fluoride chemosensor (**98**) based on the specific affinity of fluoride anion to silicon in organic and aqueous media¹⁴⁰. Coumarin-derived chemosensor (**99**) showed an obvious color change from yellow to blue upon addition of F^- ion with a large red shift of 145 nm in acetonitrile¹⁴¹. Coumarin-based hydrazone (**100**) showed as an ICT probe for fluoride ion in aqueous medium¹⁴². Coumarin-based system (**101**) has been developed as a novel turn-on fluorescent and colorimetric sensor for fluoride anions¹⁴³.

NO_2^- sensor :

Trace level analysis of nitrites was discussed by Diallo¹⁴⁴, where nitrite ions were diazotized in acidic medium forming a heteroaromatic primary amine of 4-methyl-7-aminocoumarin (Coumarin 120) (**102**). The diazonium salt was stable at room temperature and was selectively isolated in the aqueous layer by extraction with excess of unreacted Coumarin 120 with ethyl acetate. When the probe was excited at 380 nm and 100 °C, hydrolysis of the diazonium salt yielded a fluorescent product, 4-methyl-7-hydroxycoumarin (4-methylumbelliferone) at 380 nm. By these procedure levels of nitrites in water samples as low as $10 \mu\text{g L}^{-1}$ has easily quantified.

Peroxyoxalate sensor :

Shamsipur *et al.* group reported bis-(2,4,6-trichlorophenyl)-oxalate-hydrogen peroxide system in the presence of 7-amino-4-trifluoromethylcoumarin (**103**) has shown quenching effect¹⁴⁵. From Stern-Volmer plot k_Q of the probe was $1.07 \times 10^{-3} \text{ M}^{-1}$ in the quencher concentration range of $1.52 \times 10^{-4} - 1.36 \times 10^{-3} \text{ M}$. There was investigated the linear correlation between the decay rate constant of the resulting chemiluminescence and the quencher concentration.

Coumarin-based fluorescent probes (**104-107**) with salicylaldehyde functionality as recognition unit have been developed for selective detection of bisulfite anions in water¹⁴⁶. Another highly selective and sensitive turn-on Schiff base fluorogenic probe (**108**) used for detection of HSO_4^- ions in aqueous solution¹⁴⁷. Coumarin-based hydrazone (**109**) acts as an ICT probe for detection of acetate, benzoate, and dihydrogenphosphate¹⁴⁸. Another coumarin-based hydrazone (**110**) has been utilized as both a colorimetric and ratiometric chemosensor for acetate

and a selective fluorescence turn-on probe for iodide¹⁴⁹. A colorimetric and fluorescence anion sensor (**111**) exhibited as signal unit with the urea group as binding site and the coumarin moiety. This sensor displayed significant fluorescence enhancement response to anions such as acetate, because of complex formation¹⁵⁰. Coumarin-derived fluorescent chemosensors have also been used for detection of pyrophosphate¹⁵¹, H_2PO_4^- and PhPO_3H^- ¹⁵², and multiple anions including pyrophosphate, citrate, ATP and ADP¹⁵³. A new Zn^{2+} -2,2': 6',2''-terpyridine complex, derivatized with a coumarin moiety, acts as a fluorescent chemosensor for different biologically important phosphates like PPI, AMP and ADP in mixed aqueous media¹⁵⁴. A strapped calix[4]pyrrole-coumarin conjugate has been developed as a fluorogenic anions (Cl^- , Br^- and AcO^-) receptor modulated by cation and anion binding¹⁵⁵.

HSO₄⁻ sensor :

Acetonitrile-water 1 : 1 v/v solutions of coumarin-

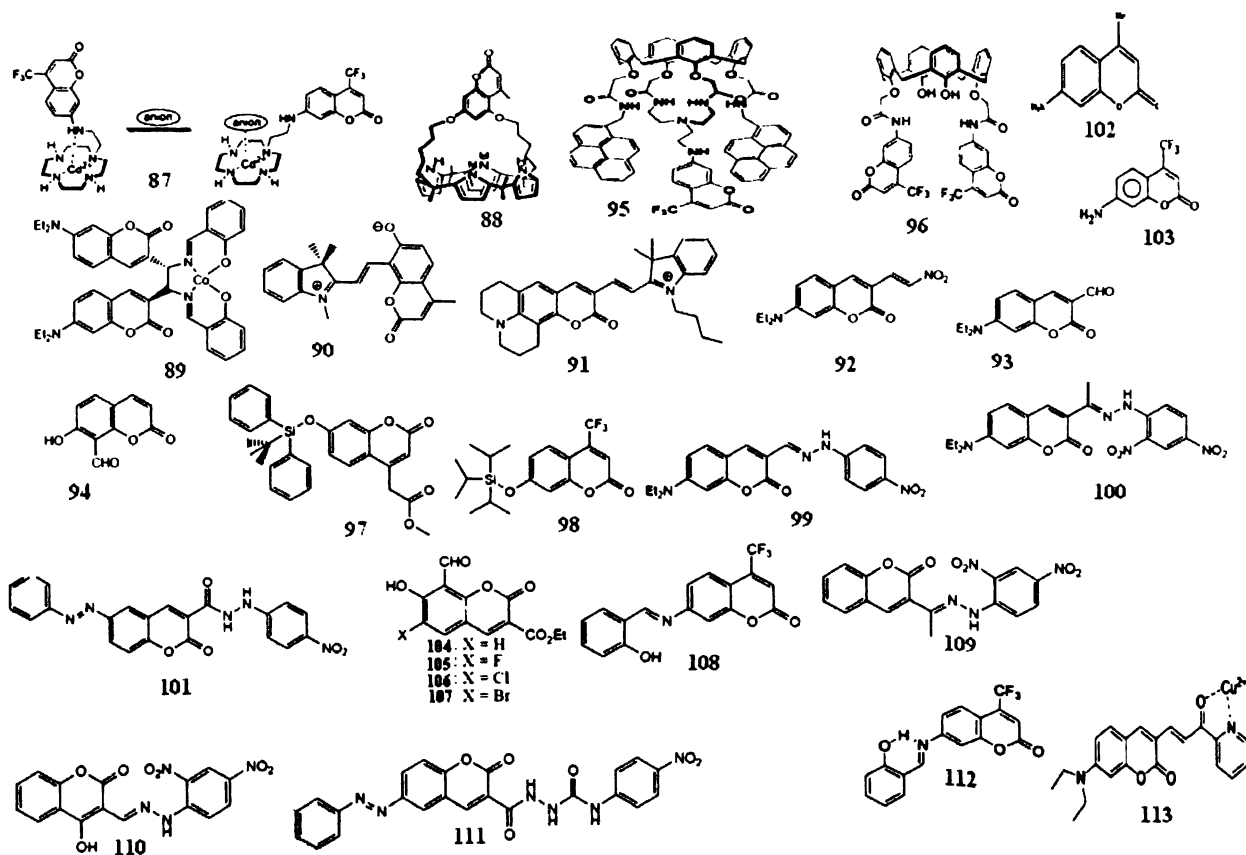


Fig. 4. Coumarin derivatives as anion sensors.

based receptor (**112**) showed a weak fluorescence band at 485 nm due to the existence of a PET process involving the lone electron pair of the imine nitrogen and the photo-excited coumarin fluorophore¹⁵⁶. Addition of the HSO_4^- anion to acetonitrile-water 1 : 1 v/v solutions of this probe induced a 13-fold emission enhancement at the same wavelength that was assigned to a suppression of the PET by the formation of hydrogen bonding interactions between the anion and the phenolic hydroxyl and the imine nitrogen of the receptor. This emission enhancement was selective and the addition of F^- , Cl^- , Br^- , I^- , AcO^- , H_2PO_4^- , NO_3^- and OH^- anions induced no changes in the emission profile.

I⁻ sensor :

A fluorescence turn-on probe, (**113**) for I^- based on the redox reaction between the cupric cation and I^- was reported¹⁵⁷. The authors reported that this probe resulted in a large red-shift, from 463 to 585 nm, in the UV-Vis spectrum while the fluorescence emission was strongly quenched. Addition of increasing quantities of I^- to the probe ensemble resulted in the rupture of the complex and the solution immediately turned yellow. The system exhibited also a drastic fluorescent enhancement at 551 nm in the presence of I^- . The selectivity of the probe to I^- was evaluated by studying the effect of other anions such as F^- , SO_3^{2-} , SO_4^{2-} , CO_3^{2-} , HCO_3^- , HPO_4^{2-} , BF_4^- , ClO_3^- or NO_3^- . Although Br^- and Cl^- elicit a small fluorescence-enhanced response, they did not interfere with fluorescence detection of I^- .

Coumarin derived fluorescent chemosensors for amines, amino acids or other organic compounds (Fig. 5)

Homocysteine and cysteine sensor :

Kim *et al.* designed a chemosensor (**114**) which had shown a selective response to homocysteine and cysteine over other amino acids via a ring formation of thiazinane or thiazolidine¹⁵⁸. This selectivity could be easily observed in a naked eye using a fluorescence microscope. The fluorescent intensity was completely quenched through photo-induced electron transfer when homocysteine and cysteine were added. The probe showed high sensitivity even at sub-millimolar concentrations.

Cystein sensor :

Jung *et al.* designed a new coumarin-based

chemodosimeter (**115**) which effectively recognized thiols by a Michael type reaction¹⁵⁹. This probe showed turn on fluorescence for cysteine in preference over other biological materials including homocysteine and glutathione. Another sensitive and selective reversible fluorescence probe (**116**) of coumarin-derived complex, Hg_2L_2 was developed by Wu *et al.*, which was applied for detection of mercapto biomolecules in aqueous solution¹⁶⁰. A fluorescence OFF-ON circle could be repeated at least 10 times by the alternative addition of cysteine and Hg^{2+} to the solution of Hg_2L_2 , indicating its use as a convertible and reversible probe for the detection of cysteine. Other competitive amino acids without a thiol group did not interfere, implying that Hg_2L_2 was selectively determining mercapto biomolecules. Confocal fluorescence imaging in the SYS5 cells revealed that $\text{L}/\text{Hg}_2\text{L}_2$ was applied to monitor the intracellular self-detoxification process to avoid toxic intracellular uptake.

Probe (**117**) consists of a *N,N*-diethylaminocoumarin fluorophore linked, through an α,β -unsaturated ketone, to a pyridine ring¹⁶¹. The low emission of this probe was explained by the formation of a non-emissive ICT state due to electron-donor *N,N*-diethylaminocoumarin to the electron-acceptor pyridine moiety. However, addition of Cys induced the appearance of a strong emission at 496 nm (211-fold of enhancement). This was assigned to a 1,4-addition reaction between the thiol moiety of the Cys and the α,β -unsaturated ketone. As a consequence of this reaction the intramolecular charge transfer was interrupted and the fluorescence of the coumarin restored. Nearly the same results, namely enhancement in the emission intensity at 496 nm, were obtained with homocysteine (180-fold) and with glutathione (35-fold) whereas no noticeable changes were found in the presence of other amino acids, metal ions, reactive oxygen species, reducing agents, nucleosides or glucose.

Coumarin-derived fluorescent chemosensors for other amino acids :

Feuster *et al.* reported butyl-substituted coumarin aldehyde (**118**) has an excellent chemosensor for detection of amines and unprotected amino acids in aqueous conditions by formation of highly fluorescent iminium ions¹⁶². Boronic acid-containing coumarin aldehyde (**119**) binds to primary catecholamines with good affinity and acts as

an effective colorimetric sensor for dopamine and norepinephrine with excellent selectivity over epinephrine, amino acids, and glucose. In the fluorescence manifold, this sensor responds differentially to catechol amines over simple amines, giving a fluorescence decrease in response to catechol-containing compounds and a fluorescence increase with other amines¹⁶³. Coumarin-based fluorescent functional monomers containing carboxylic acid functionality, (120) and (121) have been synthesized, which allow for the preparation of fluorescent imprinted polymer sensors for chiral amines¹⁶⁴. Coumarin aldehyde (66) has utilized as not only a doubly activated Michael acceptor for cyanide but also a highly selective and sensitive fluorescence turn-on probe for proline¹⁶⁵. Coumarin-azacrown ether conjugate (122) has been developed as a fluorescent probe for identifying melamine¹⁶⁶. Thiocoumarin (123) has efficiently desulfurized to its corresponding coumarin by the reaction with mCPBA, and results in a pronounced fluorescence turn-on type signaling. The conversion also provides a significant change in absorption behavior which allows a ratiometric analysis, providing a convenient detection method for mCPBA in aqueous environment¹⁶⁷. Polymers containing 4,8-dimethylcoumarin have been developed for detection of 2,4-dinitrotoluene (DNT) and 2,4,6-trinitrotoluene (TNT). The fluorescence quenching of these copolymers in solution has attributed to the collisional quenching. The response of these polymeric sensors is promising and can easily detect DNT and TNT at few parts per billion levels¹⁶⁸. A novel kind of luminescent vesicular chemosensors for the recognition of biologically important ions and molecules such as imidazoles has been developed by the self-assembly of lipids, amphiphilic binding sites, and fluorescent coumarin reporter dyes that are sensitive to their environment¹⁶⁹. Two hybrid compounds (124) and (125), linked via an ester-bond between the 7-hydroxyl residue of an umbelliferone and a carboxylic acid residue of two nitroxide radicals, act as fluorescence and spin-label probes. The ESR intensities of these probes were proportionally reduced after the addition of ascorbic acid sodium salt, and their fluorescence intensities are increased maximally by eight- and nine-fold, respectively¹⁷⁰.

Acetone sensor :

Sharma *et al.* reported a novel sensor 3-methyl-7-hy-

droxyl coumarin (126), which could be applied for the detection of acetone in vapour or solution¹⁷¹. Stern-Volmer constant was found to be 46.3 M⁻¹. The lifetime of the dye was reported as 3.5 ns. The reversible dynamic quenching was occurred due to S₀←S₂ (or other higher transitions).

NO/HNO sensor :

A selective and specific turn-on fluorescent probe for nitroxyl (HNO) was prepared by Zhou *et al.*, which included a coumarin chromophore and a tripodal dipicolylamine receptor attached by a triazole bridge¹⁷². When Cu²⁺ was added to compound (127) in aqueous solution, a dramatic fluorescence quenching was observed (23.6-fold) due to the photoinduced electron transfer (PET) from the coumarin fluorophore to the chelated Cu²⁺ at 499 nm. Under physiological conditions, upon the addition of Angeli's salt Na₂N₂O₃, chelated Cu²⁺ coumarin was reduced and the Cu⁺ coumarin complex was formed, which induced a 17.2-fold increase in the fluorescence intensity compared to the blank [HNO]. The probe was applied to bioimaging in human malignant melanoma A375 cells.

Alkaline phosphatase sensors :

A single step condensation reaction of 3-nitro-4-chloro coumarin and 2,2'-dipicolylamine (DPA) led to a coumarin derivative (128). A bathochromic shift was observed at 31 nm and 28 nm for turn-on luminescence response for Zn²⁺ and Cd²⁺ respectively in aqueous medium of pH 7.4¹⁷³. The fluorescence intensity of the complex in the presence of Zn²⁺ and Cd²⁺ remained unchanged in the presence of other metal ions, like Pb²⁺, Hg²⁺, Ni²⁺, Co³⁺, Cr³⁺, Fe²⁺, Fe³⁺ and Cu²⁺ in an aqueous buffer medium which indicate that a negligible binding of any of these metal ions to the DPA-based receptor in an aqueous environment. In the presence of Cd²⁺ and Zn²⁺, both turn-on and turn-off assays for the enzymatic activity of alkaline phosphatase was observed under physiological condition.

Indole acetic acid sensor :

Jiao *et al.* synthesized a fluorescence carrier, 4-allyloxy-7-aminocoumarin (AAC) (129) which had terminal double bonds for preparing an optical chemical sensor¹⁷⁴. The AAC based sensor was applied for indole-

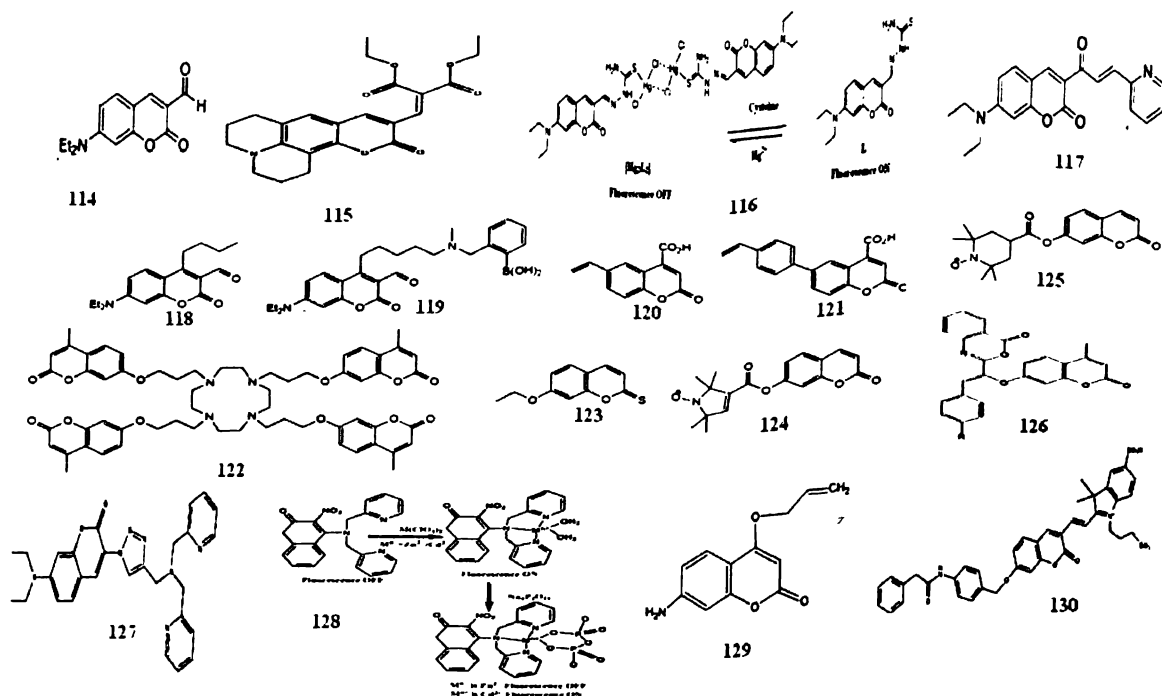


Fig. 5. Coumarin derived fluorescent probes for amines, amino acids and other organic compounds.

3-acetic acid (IAA) assay by fluorescence quenching. The AAC sensor showed a linear response toward IAA in the concentration range of 1.0×10^{-6} to 1.0×10^{-3} mol L⁻¹ with a detection limit of 9.0×10^{-7} mol L⁻¹ at pH 7.0.

Penicillin G acylase (PGA) sensor :

A novel class of water-soluble far-red emitting phenol-based NIR fluorophores were prepared by coupling a polysulfonated (benzo) indolium unit to the 3-formyl (or the 3-cinnamyl) derivative of umbelliferone¹⁷⁵. The probe (**130**) showed negative solvatochromism and excited-state intramolecular charge transfer (ICT) between the phenolate group (donor) and the indolium moiety (acceptor) due to hydrogen-bonding interaction between the solvent and the dye molecule. This hemicyanine-coumarin hybrid probe displayed high apparent Stokes shift (ranging from 60 to 140 nm) and fluorescence emission maxima between 620 and 720 nm in physiological conditions. The sensor has applied for the detection of Penicillin G acylase (PGA).

Thiol sensor

Study on fluorescent and colorimetric probes for detection of thiols has received much attention and many

coumarin-derived fluorescent chemosensors for detection of thiols have been reported. Generally detection of thiols by optical probes is based on two features of thiols; one is nucleophilicity which is strong and other is high binding affinity toward metal ions. Accordingly, most of the fluorescent probes for thiols are in fact chemodosimeters, which involve specific reactions between probes and thiols, such as Michael addition, cyclization with aldehyde (or ketone), cleavage of disulfide by thiols, 'metal complexes-displace coordination, demetalization from Cu-complex, thiolysis of dinitrophenyl ether, and Staudinger ligation. Fig. 6 showed thiol sensor of coumarin derivatives. A highly selective and sensitive ratiometric probe (**131**) for thiols was synthesized by tetrakis(4-hydroxyphenyl)porphyrin and coumarin scaffold¹⁷⁶. This probe has low detection limit, simple visual inspection and a large fluorescence dynamic range. A very weak emission showed at 465 nm in aqueous (TRIS, pH 7.4) sol of chemodosimeter (**132**) containing a coumarin fluorophore and a maleimide group¹⁷⁷. This weak fluorescence was ascribed to a photo-electron transfer process from the double bond of the maleimide moiety to the coumarin fluorophore. In addition of glutathione and

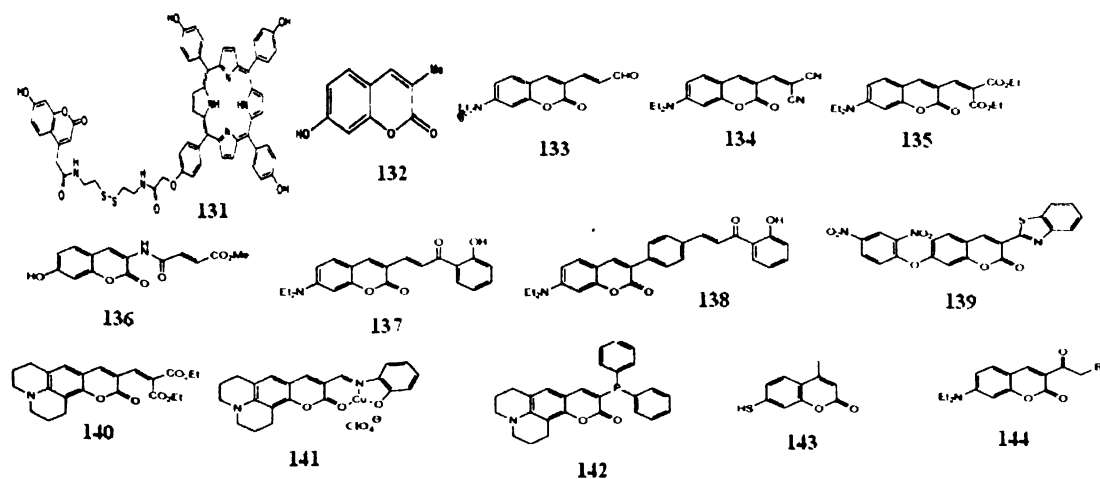


Fig. 6. Structures of coumarin derived chemosensors for detection of thiols.

Cys induced a dramatic turn-on fluorescent response (470-fold emission enhancement with glutathione) due to a Michael addition reaction between the thiol groups and the *cis* double bond in the maleimide subunit that results in an inhibition of the PET process. This glutathione reductase enzyme has used for selective thiol-containing amino acids.

Probe (133) has a ratiometric fluorescent probe for specific detection of Cys over Hcy and GSH based on the drastic distinction in the kinetic profiles¹⁷⁸. Nonfluorescent coumarin-malonitrile conjugate (134) which has transformed into a strongly fluorescent molecule through the Michael addition and thus exhibited a highly selective fluorescence response toward biothiols including Cys, Hcy and GSH with micromolar sensitivity¹⁷⁹. Similarly, non-fluorescent (135) displays a highly selective fluorescence enhancement with thiols and which has been successfully applied to thiols determination in intracellular, in human urine and blood samples¹⁸⁰. Probe (136) which has been developed as a water-soluble, fast-response, highly sensitive and selective fluorescence thiol quantification probe¹⁸¹. Compound (137)¹⁸² and (138)¹⁸³ with a hydrogen bond act as highly selective ratiometric fluorescence turn-on probes for GSH. Structure (139) which has been judiciously designed and synthesized as a new type of selective benzenethiol fluorescent probe based on the thiolysis of dinitrophenyl ether¹⁸⁴. Jung *et al.* reported that coumarin-based chemodosimeter (140) effectively and selectively recognizes thiols based on a Michael type reac-

tion, showing a preference for Cys over other biological materials including Hcy and GSH¹⁸⁵. Iminocoumarin-Cu²⁺ ensemble-based chemodosimeter (141) sensitively senses thiols followed by hydrolysis to give a marked fluorescence enhancement over other amino acids based on demetalization from Cu-complex¹⁸⁶. Nonfluorescent coumarin phosphine dye (142) which reacts with *S*-nitrosothiols (RSNOs) to create a fluorescent coumarin derivative and thus has used as a tool in the detection of RSNOs. The reaction mechanism is similar to the well-known Staudinger ligation¹⁸⁷. 7-Mercapto-4-methylcoumarin (143) is a reporter of thiol binding to the CdSe quantum dot surface¹⁸⁸. A simple coumarin derivative (144) which is the first fluorescence turn-on probe for thioureas by the double functional group transformation strategy. The probe has shown high sensitivity and selectivity for thioureas over other structurally and chemically related species including urea and thiophenol¹⁸⁹. Another simple probe (94) for not only cyanide anions but also Hcy and Cys in water has reported by Lee *et al.*¹⁹⁰. A new coumarin which contain zinc complex has been developed as a colorimetric turn-on and fluorescence turn-off sensor which shown high selectivity for hydrogen sulfide in the presence of additional thiols like Cys or GSH¹⁹¹.

pH and viscosity sensors

Fig. 7 showed the structures of coumarin derived fluorescent chemosensors for sensing pH. Wagner¹⁹² reported

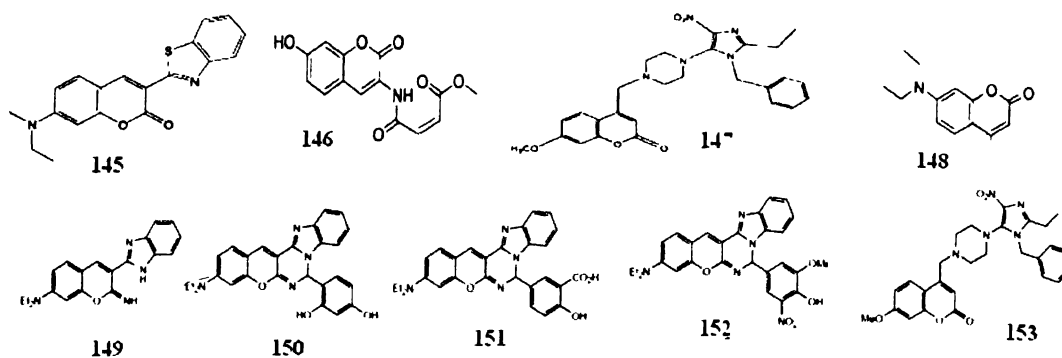


Fig. 7. Structures of coumarin derived fluorescent pH sensors.

the chemical structures of some commonly-used pairs of specifically-designed viscosity-dependent coumarin fluorescent probes (**145**) ($R = \text{OH}$ or CO_2CH_3) and dipolar coumarin fluorescent probes C6 (**146**). The fluorescence of these probes was strongly dependent on the polarity, hydrogen bonding ability, pH and microviscosity or rotational hindrance of their local environments. 7-Aminocoumarins have been showed highest fluorescence intensity in non-polar media, whereas 7-alkoxy has been showed highest fluorescence intensity in polar media. This opposing polarity dependence implied that a specific coumarin probe could be chosen to show a desired fluorescence change e.g. “switch on” (increased fluorescence) and “switch off” (decreased fluorescence) behavior upon inclusion in a specific cavity or region of a heterogeneous system via two photophysical non-radiative decay pathways, i.e. TICT and ISC. Sensor (**146**) was applied as pH-sensitive probe with vastly different fluorescence emission properties in its neutral and protonated forms. Saleh *et al.* utilized a coumarin derivative (**147**) as pH sensor¹⁹³ while Haidekker *et al.* utilized another coumarin derivative (**148**) as fluorescent molecular rotors or fluorescent viscosity sensors¹⁹⁴.

Several iminocoumarin (**149**) derivatives (**150-152**) have been synthesized as a new type of fluorescent pH indicator. The indicators possess moderate to high brightness, excellent photostability and compatibility with light-emitting diodes. The indicators has covalently immobilized on the surface of amino-modified polymer microbeads which in turn are incorporated into a hydrogel matrix to afford novel pH-sensitive materials. When a mixture of two different microbeads is used, the membranes are ca-

pable of optical pH sensing over a very wide range comparable to the dynamic range of the glass electrode (pH 1–11)¹⁹⁵. Another fluorescence probe (**153**) which contained piperazine and imidazole moieties has been developed as a fluorophore for hydrogen ions sensing. The fluorescence enhancement of the sensor with an increase in hydrogen ions concentration was based on the hindering of PET from the piperazinyl amine and the imidazolyl amine to the coumarin fluorophore by protonation. The sensor (**153**) has a novel molecular structure design of fluorophore-spacer-receptor (1)-receptor (2) format and therefore has proposed to sense two range of pH from 2.5 to 5.5 and from 10 to 12 instead of sensing one pH range¹⁹⁶. By applying rational molecular design, two molecular functions, the transport by vesicular monoamine transporter (VMAT) and ratiometric optical pH sensing, have been integrated to develop ratiometric pH-responsive fluorescent false neurotransmitter (FFN) probes¹⁹⁷. A FRET sensor with a donor and an acceptor attached to each end of pH-sensitive polysulfoamides exhibited an instantaneous conformation change from coil to globule at a specific pH, which results in the rastic on-and-off FRET efficiency. To detect a specific pH region, sulfadimethoxine and sulfamethizole are selected among various sulfonamides since their pK_a values are in the physiological pH. For tuning the emission color arising from FRET, 7-hydroxy-4-bromomethylcoumarin and Coumarin 343 are used as a FRET donor and an acceptor, respectively, for a blue-to-green FRET sensor¹⁹⁸.

Coumarin derived fluorescent chemosensors for H_2O_2 , O_2 , hydroxyl radicals or chemical warfare agents

Structures of coumarin derived fluorescent chemo-

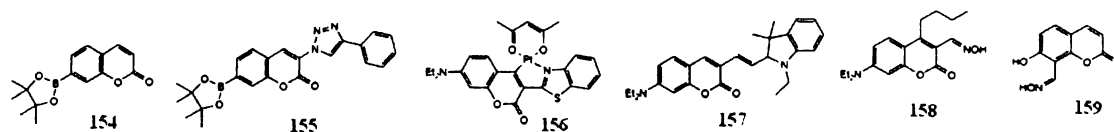


Fig. 8. Structures of coumarin derived fluorescent sensors for H₂O₂, O₂, hydroxyl radicals or chemical warfare agents.

sensors for hydrogen peroxide, oxygen, hydroxyl radicals or chemical warfare agents are shown in Fig. 8. Water-soluble umbelliferone-based fluorescent probe (**154**) showed very large increase (up to 100-fold) in fluorescent intensity upon reaction with hydrogen peroxide, and good selectivity over other reactive oxygen species¹⁹⁹. Other water-soluble fluorescent hydrogen peroxide probe (**155**) based on a ‘click’ modified coumarin fluorophore shows significant intensity increases (up to five-fold) in near-green fluorescence upon reaction with H₂O₂, and good selectivity over other reactive oxygen species²⁰⁰. More recently a simple and highly sensitive fluorometric method was proposed for the determination of H₂O₂ in milk samples. By this method, nonfluorescent coumarin was oxidized to highly fluorescent 7-hydroxycoumarin by hydroxyl radicals generated in a Fenton reaction, and the oxidation product had strong fluorescence with a maximum intensity at 456 nm and has used as a fluorescent probe for H₂O₂²⁰¹. Thiazo-coumarin ligand directly cyclometallated Pt²⁺ complex (**156**) for luminescent O₂ sensing was reported by Wu *et al.*²⁰². First ratiometric fluorescent probe for the detection of intracellular hydroxyl radicals developed by a hybrid coumarin-cyanine platform (**157**)²⁰³. The ratiometric fluorescence signal between 7-hydroxy coumarin 3-carboxylic acid and neutral red dyes was developed for detection of hydroxyl radical based on coumarin-neutral red (CONER) nanoprobe. Biocompatible poly lactide-*co*-glycolide nanoparticles containing encapsulated neutral red were produced using a coumarin 3-carboxylic acid conjugated poly(sodium *N*-undecylenyl-*Nε*-lysinate) as moiety reactive to hydroxyl radicals. The response of the CONER nanoprobe was dependent on various parameters such as reaction time and nanoparticle concentration. The probe was selective for hydroxyl radicals as compared with other reactive oxygen species including O₂^{•-}, H₂O₂, ¹O₂ and OCl⁻²⁰⁴. Recent rise in international concern over criminal terrorist attacks using chemical warfare agents has

brought about the need for reliable and affordable detection methods of toxic gases. Fluorogenic chemosensors for the specific detection of nerve agents was reported Royo *et al.*²⁰⁵. A coumarin oximate (**158**) has been developed for detection of chemical warfare simulants based on the PET mechanism that gives an “off-on” fluorescent response with a half-time of approximately 50 ms upon phosphorylation of reactive oximate functionality²⁰⁶. Coumarin-derived hydroxy oxime (**159**) serves as a nerve agent sensor based on the reaction of β-hydroxy oxime with organophosphorus agent mimics²⁰⁷.

Coumarin derived fluorescent sensors for TiO₂, monolayer, polymerization or polymeric micelles

Structures of coumarin-derived fluorescent chemosensors for detection of TiO₂, monolayer, or photopolymerization are shown in Fig. 9. A novel acac-coumarin chromophore linker (**160**) for robust sensitization of TiO₂ has been developed to find molecular chromophores with suitable properties for solar energy conversion. This probe improved sensitization to solar light and provides robust attachment to TiO₂ even in aqueous conditions²⁰⁸. A new amphiphilic coumarin dye, 7-aminocoumarin-4-acetic acid octadecylamide (**161**) has utilized as an efficient fluorescent probe for monolayer studies between air-water interfaces²⁰⁹. The performance of amidocoumarins (**162-164**) investigated by fluorescence probe technology for monitoring of cationic photopolymerization of monomers. 7-Diethylamino-4-methylcoumarin (**162**) has used for monitoring cationic photopolymerization of monomers using the fluorescence intensity ratio as an indicator of the polymerization process. The replacement of diethylamino group in (**162**) with benzamido or acetamido groups eliminates the effect of the probe protonation on kinetics of cationic photopolymerization. 7-Benzamido-4-methylcoumarin (**163**) and 7-acetamido-4-methylcoumarin (**164**) has used as fluorescent probes for monitoring progress of cationic polymerization of vinyl ethers under stationary

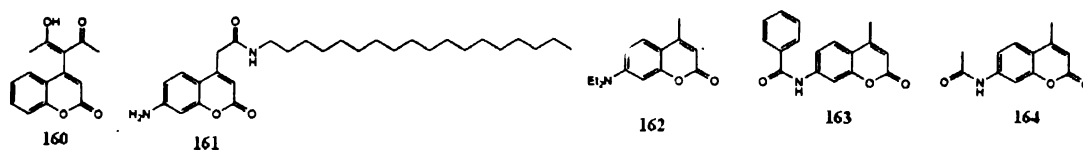


Fig. 9. Structures of coumarin-derived fluorescent sensors for detection of TiO_2 , monolayer, or photopolymerization.

measurement conditions, using normalized fluorescence intensity as an indicator of the polymerization progress²¹⁰. Coumarin 153 has been used as a fluorescent probe molecule to monitor the possible micellization of several amphiphilic block copolymers²¹¹.

Coumarin derived fluorescent sensors for enzymes

Structures of coumarin-derived fluorescent chemosensors for enzymes are shown in Fig. 10. Hemicyanine-coumarin hybrid (**165**) represents a new class of far-red emitting fluorogenic dyes whose fluorescence has unveiled through an enzyme-initiated domino reaction and thus acts as a fluorogenic probe for penicillin G acylase²¹². Similarly novel selfimmolative spacer systems (**166**) and (**167**) have been developed and are utilized as fluorogenic probes for sensing penicillin amidase²¹³. A library of 6-arylcoumarins has been developed as candidate fluorescent sensors (**168**), whose quantum yield has similar to that of ethyl 7-diethylaminocoumarin-3-carboxylate. The transformation of the methoxy group (**169**) to a

hydroxyl group (**170**) induces a change of fluorescence intensity, which suggests that (**169**) may be useful as a fluorescent sensor for dealkylating enzymes such as glycosidase. Probe (**171**) used as a fluorescent sensor for nitric oxide²¹⁴. It shows 50% decrease of the fluorescence intensity at pH 8.0 compared with that at pH 6.0 and this decrease has derived from the deprotonation of the triazole ring. Histone deacetylases are intimately involved in epigenetic regulation and, thus, are one of the key therapeutic targets for cancer. Coumarin suberoylanilide hydroxamic acid (**172**) was a fluorescent probe for determining binding affinities and off-rates of histone deacetylase inhibitors²¹⁵. A quinonemethide rearrangement reaction as the off-on optical switch has designed of the first long-wavelength latent fluorogenic substrate (**173**). It has a sensitive fluorimetric indicator for analyte determination in salicylate hydroxylase-coupled dehydrogenase assay²¹⁶. Another switch-on long-wavelength latent fluorogenic substrate (**174**) is reported as a fluorescent probe for nitroreductase²¹⁷.

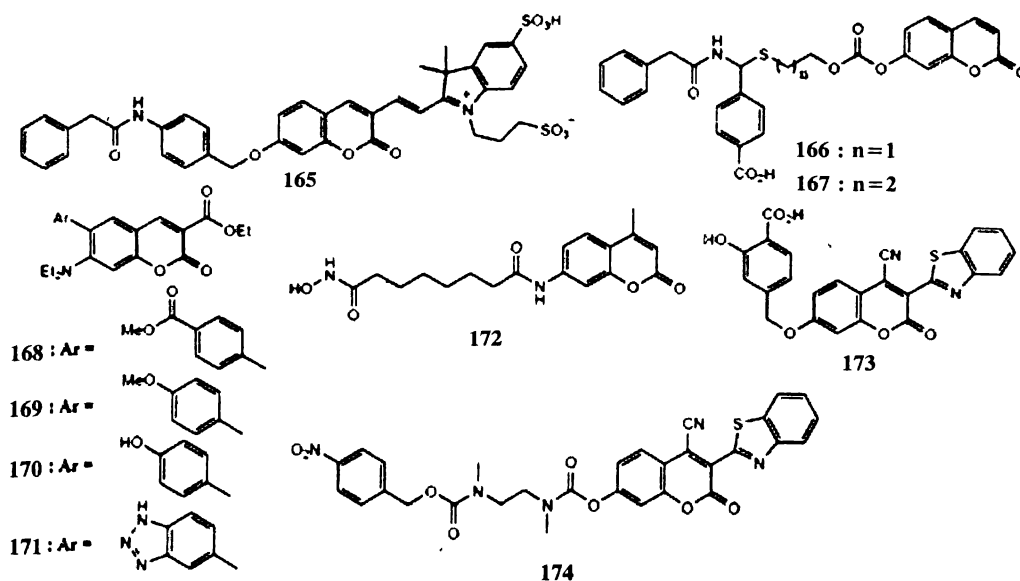


Fig. 10. Structures of coumarin-derived fluorescent chemosensors for enzymes.

Coumarin derived fluorescent chemosensors for proteins, DNA, RNA and other uses

Structures of coumarin-derived fluorescent chemosensors for DNA, RNA, nitroxyl and proteins are shown in Fig. 11. A novel coumarin C-riboside (**175**) has designed and synthesized based on the well-known photoprobe Coumarin 102 and has been used to probe ultrafast dynamics of duplex DNA using time-resolved Stokes shift methods²¹⁸. Coumarin-triazole (**176**) reacts with CuCl₂ to form a chelated Cu-complex which shows highly selective turn-on type fluorogenic behavior upon addition of Angeli's salt (Na₂N₂O₃) and has used for detection of nitroxyl in living cells²¹⁹. An acceptor used a simple coumarin derivative 7-diethylaminocoumarin-3-carboxylic acid (**177**) to construct a useful and effective FRET system for detection of RNA-small molecule binding²²⁰.

These sensors demonstrate that binding-induced modulation of spectral overlap has a powerful strategy for the rational design of FRET-based chemosensors²²⁶.

Properties and applications of coumarin derivatives (Fig. 12)

Photophysical properties

The studies of photophysical properties were carried out by Ranjith *et al.*²²⁷ by incorporating electron donating or withdrawing substituents at different positions of the coumarin scaffold (**180-182**). An electron-donating substituent at position 3 of the coumarin ring increased the fluorescence while an electron withdrawing group decreased the fluorescence. An electron-donating acetoxy group at position 7 and a methyl group at position 4 significantly enhanced the quantum efficiency of coumarin derivatives.

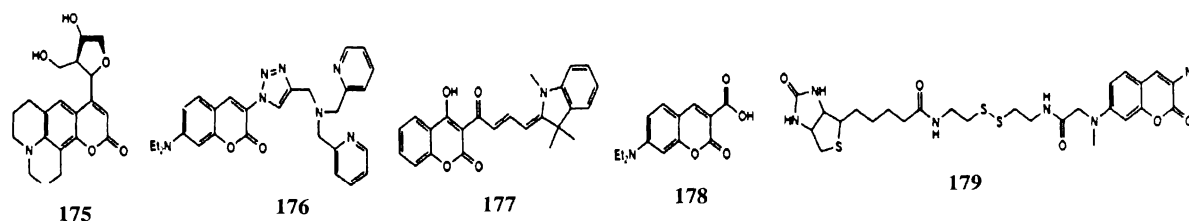


Fig. 11. Structures of coumarin derived fluorescent sensors for DNA, RNA, nitroxyl and proteins.

Coumarin dye bearing an indolenine substituent (**178**) displays high emission and bright fluorescence and offers promise as a fluorescent chemosensor for protein detection²²¹. Coumarin-containing trifunctional probe (**179**), assembled using a cleavable linker, has useful for efficient enrichment and detection of glycoproteins²²². Coumarin 6 has been used as a fluorescent probe to monitor protein aggregation and can distinguish between both amorphous and fibrillar aggregates²²³. An aromatic substitution reaction-triggered fluorescence probe has developed using a new fluorogenic compound derivatized from 7-aminocoumarin for oligonucleotides detection²²⁴. Coumarin C343 has been conjugated to silica nanoparticles and entrapped in a sol-gel matrix to produce a nanosensor capable of monitoring lipid peroxidation²²⁵. Coumarin-containing dual-emission chemosensors for nucleoside polyphosphates have been developed based on a new mechanism involving binding-induced recovery of FRET.

Surface plasmon resonance properties

Lacy *et al.* reported that the surface plasmon resonance inhibition assay and liquid chromatographic protocols were commonly used for the detection of warfarin 3-(α -acetylbenzyl)-4-hydroxycoumarin (**183**) in human plasma²²⁸. Probe (**183**) can accurately and quantitatively detect subpicogram quantities for food quality and environmental studies.

Antioxidants and free radical scavengers

There are several instances where coumarins have worked as effective antioxidants and free radical scavengers. Zhang *et al.* discussed the scavenging effect of 7-hydroxy-3-methyl-8-nitro coumarin (**184**) on Mn²⁺, Ni²⁺, Zn²⁺, Co²⁺, Cu²⁺ and Cd²⁺²²⁹. Kancheva *et al.* reported that chain-breaking antioxidants and free radicals scavengers activity of *o*-dihydroxycoumarins (**185**) were much higher than that of the *m*-dihydroxycoumarins (**186**).

However, substitution at C-3 position did not significantly change the antioxidant and antiradical capacities of the studied 7,8-dihydroxycoumarins (**187**) and 7,8-diacetoxy-4-methylcoumarins (**188**)²³⁰.

Coumarin derivatives (**189** and **190**), synthesized by Morabito *et al.* showed good antioxidant properties due to their lower mean scavenger concentration (SC50) or mean inhibitory concentration (IC50) and a confidence limit of 95%²³¹.

Substituted hydroxycoumarins and 7- or 8-hydroxybenzo[*f*]coumarins were prepared by the treatment of phenols and naphthalenediols, respectively, with malic acid and H₂SO₄ under microwave irradiation. Symeonidis *et al.* suggested that hydroxybenzocoumarins (**191**) having the phenolic hydroxyl group (6-, 7- or 8-) showed antioxidant activity but the effect on the activity was independent of the position of the hydroxyl group. Benzo derivative compound (**192**) has more potent than any of the cyclohexyl derivatives and shows higher antioxidant activity among various hydroxybenzocoumarins being synthesized²³².

Hamdi *et al.* reported that different substituted 3,3'-arylidenebis-4-hydroxycoumarins and tetrakis-4-hydroxycoumarin derivative (**193**) were synthesized by 4-hydroxycoumarin and aromatic aldehydes containing different groups in *ortho*, *meta* or *para* positions and condensing them in boiling ethanol or acetic acid. Dicoumarins (**193**) also showed antioxidant activities due to the presence of intermolecular hydrogen bonds capable of uncoupling and inhibiting mitochondrial oxidative phosphorylation²³³.

Anti-Candida activity

The most active Cu²⁺ complexes (**194**, **195** and **196**) of Schiff base ligands with electron withdrawing substituents such as -Cl, -Br, or -I, at the R₁ and R₃ positions of the salicylaldehyde moiety had greater anti-Candida activity (lower MIC50 μM value) than ligands with electron-donating substituents. Complexes (**194**, **195** and **196**) exhibited anti-Candida activity comparable to that of the commercially available antifungal drugs, ketoconazole and Amphotericin B²³⁴.

Antitumor activity

The series of novel 3-arylcoumarins of (**197**, **198** and

199) acetoxyated and hydroxylated 3-arylcoumarins, exhibited anti-tumor, anti-cancer and cytotoxic activities *in vitro*²³⁵. Particularly, compound (**197**) (i.e. acetoxyated derivative of 3-arylcoumarins) showed the most potent activity with an IC₅₀ value of 5.18 mol/L against KB cell lines. 8-(Benzylidiny)amino-3-bromo-7-methoxy-4-methyl coumarin (**200**) was another coumarin based molecule that showed remarkable antitumor activity²³⁶.

Anti-inflammatory activity

A novel series of coumarin-based carbamates (**201**) were synthesized, which exhibited potent inhibitory activity of TNF-α (Tumor necrosis factor). It has a proinflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. Cheng *et al.* observed that halogen substitution at C-6 position of the coumarin ring had the most influence on TNF-α (Tumor necrosis factor) inhibitory activity²³⁷. Khan *et al.* reported that an array of angularly fused polycyclic heterocycles with coumarin, benzofuran and pyridine rings by N-C-C3 annealation, were synthesized from 4-bromomethylcoumarins and salicylonitrile. These derivatives have wider applicability to create new fused heterocyclic systems for their anti-inflammatory activity. Among the compounds tested, probe (**202**) showed significant inhibition of inflammation at various doses, and it has been summarized that in this angularly fused system substitutions of electron donating groups are preferential for inflammatory inhibitions²³⁸.

Ortho-substituent effect

According to Chen *et al.*, newly synthesized arylamino-substituted coumarins showed enhanced blue and bright fluorescence both in solutions and in solid films²³⁹. The probe (**203**) exhibited pure blue electroluminescence with 2.7% of external quantum efficiency due to *ortho*-substituent effect.

Anti-cancer activity

7-Diethylaminocoumarin compounds were synthesized by Lee *et al.* and the cytotoxicities were tested against human umbilical vein endothelial cell (HUVEC) and some cancer cells. The introduction of benzothiazolyl and analogous groups at 3-position of the probe (**204**) improved

the overall inhibition activity and introducing a cyano group at the fourth position afforded the selectivity towards HUVEC²⁴⁰.

Analgesic and anti-pyretic activity

Rangappa *et al.* reported that a certain series of 4-[4-(6-phenyl-pyrimidin-4-yl)-phenoxy methyl]-chromen-2-ones (**205** and **206**) showed *in vivo* analgesic and anti-pyretic activities²⁴¹. The compounds exhibited significant analgesic activity comparable to standard drugs like Analgin and significant anti-pyretic activities comparable to standard drugs like aspirin. Thus it was concluded that among the tested compounds, those containing -NH₂ functional group at 2-position of pyrimidine ring increased their analgesic and anti-pyretic activities.

Anti-Helicobacter pylori activity

N-Substituted-2-oxo-2*H*-1-benzopyran-3-carboxamides (coumarin-3-carboxamides) were used as anti-*Helicobacter pylori* agents. Chimenti synthesized coumarin based compounds (**207**) showed no activity against different species of Gram-positive and Gram-negative bacteria of clinical relevance and against various strains of pathogenic fungi²⁴². Among these compounds those with a 4-acyl-phenyl group have shown the best performance against *H. pylori* metronidazole resistant strains in the 0.25–1 µg/ml MIC range.

Anti-bacterial activity

Kong *et al.* observed that 7-hydroxy-5-*O*-methyl-8-(3-methyl-2-butylene)-4-phenyl-9,10-dihydro-benzopyran-2-one (cajanuslactone) (**208**) possessed good antibacterial activity against *Staphylococcus aureus*, and the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were 0.031 and 0.125 mg/ml respectively²⁴³. It was a potential anti-bacterial agent against Gram-positive microorganisms.

According to Bagihalli *et al.*, Co²⁺, Ni²⁺ and Cu²⁺ complexes of 3-substituted-4-amino-5-mercapto-1,2,4-triazole (**209**) and 8-formyl-7-hydroxy-4-methylcoumarin showed antibacterial properties with microorganisms like *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Salmonella typhi*²⁴⁴. They showed antifungal activities with *Aspergillus*

niger, *Aspergillus flavus* and *Cladosporium* in DMF and DMSO by MIC method.

Cu²⁺, Co²⁺ and Ni²⁺ complexes of (1*E*)-1-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) thiosemicarbazide (OCET) (**210**) and (1*E*)-1-(1-(6-bromo-2-oxo-2*H*-chromen-3-yl)ethylidene) thiosemicarbazide (BOCET) (**211**) were screened for their antibacterial activity against bacterial species, *E. coli*, *P. aeruginosa* as Gram-negative, *B. subtilis* and *S. aureus* and were found to be Gram-positive. Coumarin-3-yl thiosemicarbazone derivatives behave as a bidentate ligand through both thione sulphur and azomethine nitrogen with 1 : 2 (metal : ligand) stoichiometry²⁴⁵.

Antileucemic activity

Kotali *et al.* synthesized 7-hydroxy-8-acetylcoumarin benzoylhydrazone (**212**) which showed antileucemic activity. The probe (**212**) has interesting producing survival time of drug-treated animals (T) versus corn-oil control animals (C) rates of 147% and 138% when the single and intermitted (days 1, 4, 7) treatment schedules, respectively, were used²⁴⁶.

Antiviral activity and antihypertensive activity

Pandey *et al.* prepared coumarin derivative (**213**) which showed antiviral activity and antihypertensive activity²⁴⁷.

Anticoagulant activity

8-Acetyl-7-hydroxy-4-methyl coumarin (**214**) azomethine derivatives of Cu²⁺, Ni²⁺ complexes showed anticoagulant activity²⁴⁸.

Cytotoxic activity

Kostova *et al.* reported that La³⁺ with bis-coumarins of 3,3'-benzylidene-bis(4-hydroxy-2*H*-1-benzopyran-2-one) (**215**) and bis(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-(1*H*-pyrazol-3-yl)-methane (**216**) showed cytotoxic-effects using human tumor cell lines²⁴⁹.

Antifungal and DNA cleavage activity

La³⁺, Th⁴⁺ and VO⁴⁺ complexes of 8-formyl-7-hydroxy-4-methylcoumarin (**217**) and *o*-phenylenediamine/ethylenediamine (**218**) showed antibacterial properties with *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi* and antifungal activities

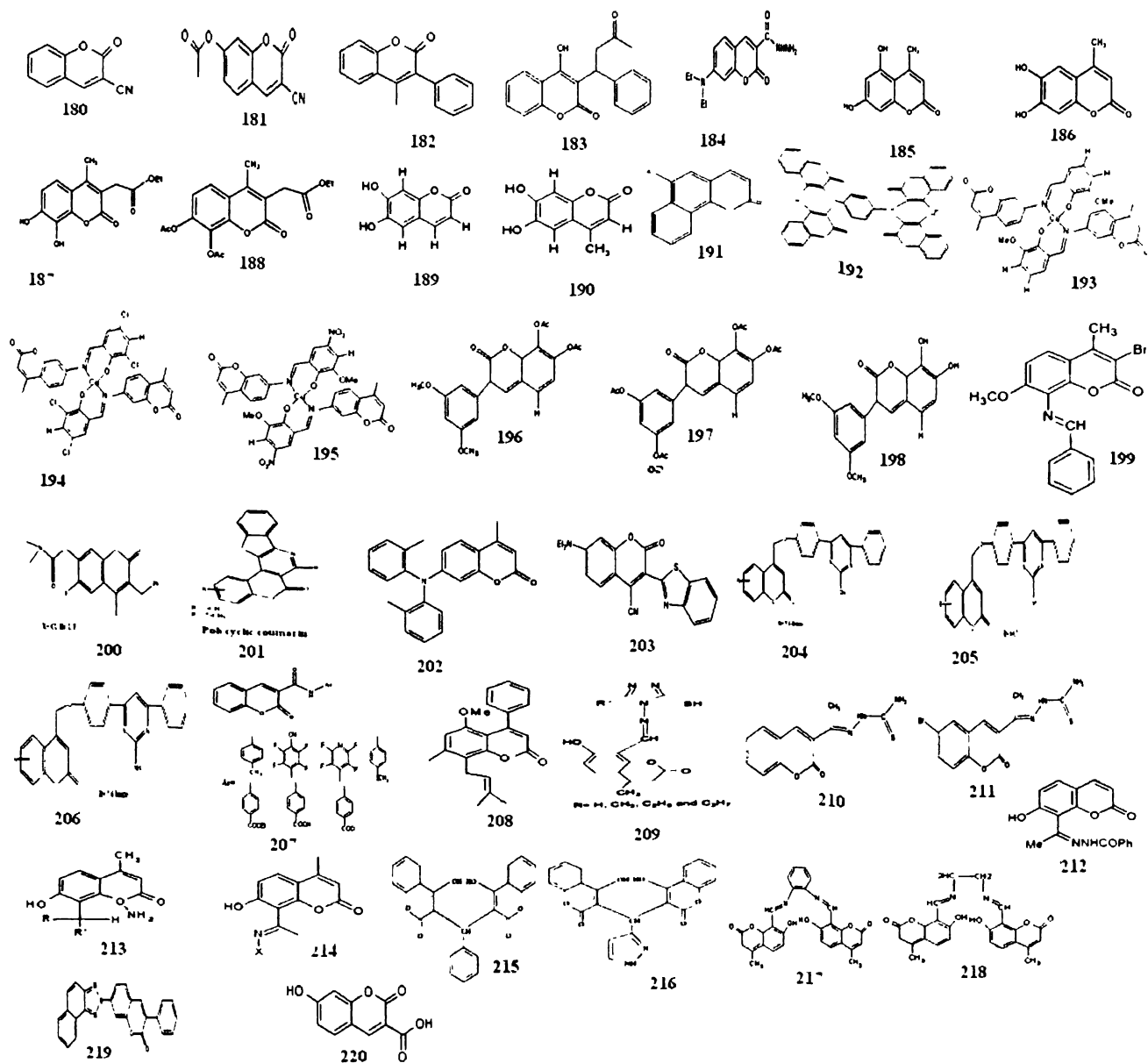


Fig. 12. Structures of various coumarin derivatives used as pharmaceutical compounds.

with *Aspergillus niger*, *Aspergillus flavus* and *Cladosporium* by minimum inhibitory concentration method in DMF and DMSO solution²⁵⁰.

Fluorescent whitening agent or optical brightener

Ballard and Betowski reported that 7-(2*H*-naphtho[1,2-*d*]triazol-2-yl)-3-phenylcoumarin (FB 236) (**219**) could be used as fluorescent whitening agent or optical brightener²⁵¹.

Cell analysis

Abrams *et al.* reported 3-carboxy-6-chloro-7-hydroxycoumarin (**220**) which was highly fluorescent, water-soluble violet-excitable dye for cell analysis. It had a high quantum yield (0.98), and human leucocyte-specific monoclonal antibodies (CD3, CD4, and CD45) conjugated with this dye which could be measured by flow cytometry assays²⁵².

Conclusion

This review describes different derivatives of coumarin which are synthesized by various researchers. Coumarin derived fluorescent chemosensors have been extensively applied in a variety of fields. There has been tremendous interest in detecting coumarin probes due to its multipurpose importance. These sensors are effective for detection of many species like metal ions, anions, amines and amino acids, biothiols, pH, chemical warfare agents, proteins, hydrogen peroxide, hydroxyl radicals, polymerization and polymeric micelles, enzymes, DNA and RNA, oxygen, titania. Moreover, coumarin derivatives have served as good chemosensors of anions including cyanide, fluoride, pyrophosphate, acetate, benzoate, and dihydrogen phosphate as well as various metal ions comprised of Hg^{2+} , Cu^{2+} , Zn^{2+} , Ni^{2+} , Ca^{2+} , Pb^{2+} , Mg^{2+} , Fe^{3+} , Al^{3+} , Cr^{3+} , and Ag^+ . Continuous efforts have been devoted for their application in environmental chemistry, analytical chemistry, and bio-medical science as anti-oxidant, anti-inflammatory, anti-microbial activity, anti-hepatitis, anti-cancerous, anti-pyretic, analgesic activity.

References

- 1 R D H Murray, I Mendez and S A Brawn, (1983) the Natural Coumarins, Wiley, New York, eds U Matern, P Luer, D Kreusch, D Barton, *et al.*, 'Comprehensive Natural Products Chemistry', Vol I, Elsevier Science Ltd , Oxford, 1999, p 623
- 2 J W Suttie, *Clin Cardiol* , 1990, **13**, 16
- 3 B Musicki, A -M Periers, P Laurin, D Ferroud, Y Benedetti, S Lachaud, F Chateaux, J -L Haesslein, A Iltis, C Fierre, J Khider, N Tessot, M Airault, J Demasse, C D Hamelin, P Lassaigne, A Bonnefoy, P Vicat and M Klich , *Bioorg Med Chem Lett* , 2000, **10**, 1695
- 4 P Laurin, M Klich, C Dupis-Hamelin, P Mauvais, P Lassaigne, A Bonnefoy and B Musicki, *Bioorg Med Chem Lett* , 1999, **9**, 2079
- 5 A A A Abu-Hussein, *J Coord Chem* , 2006, **59**, 157
- 6 M S Karthikeyan, D J Prasad, B Poojary and K S Bhat, *Bioorg Med Chem* , 2006, **14**, 7482
- 7 K Singh, M S Barwa and P Tyagi, *Eur J Med Chem* , 2006, **41**, 147
- 8 T Patonay, G Litkei, R Bogнар, J Eredi and C Miszti, *Pharmazie*, 1984, **39**, 86
- 9 S K Sridhar, M Saravan and A Ramesh, *Eur J Med Chem* , 2001, **36**, 615
- 10 S N Pandeya, D Sriram, G Nath and E De clerq, *Eur J Pharm Sci* , 1999, **9**, 25
- 11 C Gnerre, M Catto, F Leonetti, P Weber, P A Carrupt, C Altomare, A Carotti and B J Testa, *Med Chem* , 2000, **43**, 4747
- 12 D A Egan, P James, D Cooke and R O'Kennedy, *Cancer Lett* , 1997, **118**, 201
- 13 E Budzisz, B K Keppler, G Giester, M Wozniczka, A Kufelnicki and B Nawrot, *J Inorg Chem* , 2004, **22**, 4412
- 14 M Jiménez, J J Mateo and R Mateo, *J Chrom (A)*, 2000, **870**, 473
- 15 D Egan, R O'Kennedy, E Moran, D Cox, E Prosser and R D Thornes, *Drug Metab Rev* , 1990, **22**, 503
- 16 Y A Al-Soud, H H Al-Sa'doni, H A S Amajaour, K S M Salih, M S Mubarak, N A Al-Masoudi and I H Jaber, *Naturforsch* , 2008, **63**, 83
- 17 J N Modranka, E Nawrot and J Graczyk, *Eur J Med Chem* , 2006, **41**, 1301
- 18 R G Harvey, C Cortez, T P Ananthanarayan and S Schmolka, *J Org Chem* , 1988, **53**, 3936
- 19 G Feuer, J A Kellen and K Kovacs, *Oncology*, 1976, **33**, 35
- 20 A Kumar, B K Singh and R Tyagi, *Bioorg Med Chem* , 2005, **13**, 4300
- 21 K C Fylaktakidou, D J Hadjipavliou-Litina, K E Litinas and D N Nicolaides, *Curr Pharma Des* , 2004, **10**, 3813
- 22 R N Gacche, D S Gond, N A Dhole and B S Dawane, *J Enz Inhib Medic Chem* , 2006, **21**, 157
- 23 Y Kimura, H Okuda, S Arichi, K Baba and M Kozawa, *Biochim Biophys Acta*, 1985, **834**, 224
- 24 F A Jimenez-Orozco, J A Molina-Guarneros, N Mendoza-Patino, F Leon-Cedeno, B Flores-Perez, E Santos-Santos and J J Mandoki, *Melanoma Res* , 1999, **9**, 243
- 25 R J S Hoult and M Paya, *Gen Pharmacol* , 1996, **27**, 713
- 26 S P Pillai, S P Menon, L A Mitscher, C A Pillai and D A Shankel, *J Nat Prod* , 1999, **62**, 1358
- 27 N Kitamura, T Fukagawa, S Kohtani and R Nakagaki, *J Photochem Photobiol A Chem* , 2007, **188**, 378
- 28 J Hoffmanova, A Kozubik, L Dusek and J Pachernik, *Eur J Pharmacol* , 1998, **350**, 273
- 29 M Payá, B Halliwell and J R S Hoult, *Biochemical Pharmacology*, 1992, **44**, 205
- 30 G J Finn, B S Creaven and D A Egan, *Cancer Lett* , 2004, **214**, 43

31. G. J. Finn, B. S. Creaven and D. A. Egan, *Eur. J. Pharm. Sci.*, 2005, **26**, 16.
32. I. Kostova, I. Manolov, I. Nicolova and N. Danchev, *Il Farmaco*, 2001, **56**, 707.
33. I. Kostova, I. Manolov, I. Nicolova, S. Konstantinov and M. Karaivanova, *Eur. J. Med. Chem.*, 2001, **36**, 339.
34. I. Kostova, I. Manolov, S. Konstantinov and M. Karaivanova, *Eur. J. Med. Chem.*, 1999, **34**, 63.
35. K. B. Gudasi, R. V. Shenoy, R. S. Vadavi, M. S. Patil and S. A. Patil, *Chem. Pharm. Bull.*, 2005, **53**, 1077.
36. I. Kostova, G. Momekov, M. Zaharieva and M. Karaivanova, *Eur. J. Med. Chem.*, 2005, **40**, 542.
37. I. Kostova, I. Manolov and M. Karaivanova, *Arch. Pharm. Med. Chem.*, 2001, **334**, 157.
38. S. H. Lee, H. J. Kim, Y. O. Lee, J. Vicens and J. S. Kim, *Tetrahedron Lett.*, 2006, **47**, 4373.
39. M. T. Alonso, E. Brunet, C. Hernandez and J. C. Rodríguez-Ubis, *Tetrahedron Lett.*, 1993, **34**, 7465.
40. H. Zhang and D. M. Rudkevich, *Chem. Commun.*, 2007, 1238.
41. M. C. DeRosa, D. J. Hodgson, G. D. Enright, B. Dawson, C. E. B. Evans and R. J. Crutchley, *J. Am. Chem. Soc.*, 2004, **126**, 7619.
42. J. Otsuki, K. Sato, M. Tsujino, N. Okuda, K. Araki and M. Seno, *Chem. Lett.*, 1996, **25**, 847.
43. M. L. Horng, J. A. Gardeski, A. Papazyan and M. Maroncelli, *J. Phys. Chem.*, 1995, **99**, 17311.
44. F. Morlet-Savary, C. Ley, P. Jacques and J. P. Fouasier, *J. Phys. Chem. (A)*, 2001, **105**, 11026.
45. F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.*, 2005, **12**, 887.
46. J. R. Hoult and M. Payd, *Gen. Pharmacol.*, 1996, **27**, 713.
47. A. Goel, A. K. Prasad, V. S. Parmar, B. S. Ghosh and N. Saini, *FEBS Lett.*, 2007, **581**, 2447.
48. J. Z. Pedersen, C. Oliveira, S. Incerpi, V. Kumar, A. M. Fiore, P. De Vito, A. K. Prasad, S. V. Malhotra, V. S. Parmar and L. Saso, *J. Pharm. Pharmacol.*, 2007, **59**, 1721.
49. A. Kumar, B. K. Singh, R. Tyagi, S. K. Jain, S. K. Sharma, A. K. Prasad, H. G. Raj, R. C. Rastogi, A. C. Watterson and V. S. Parmar, *Bioorg. Med. Chem.*, 2005, **13**, 4300.
50. R. O'Kennedy and R. D. Thornes, "Coumarins Biology, Applications and Mode of Action", John Wiley & Sons, Chichester, 1997, p. 303.
51. M. Zabradnik, "The Production and Application of Fluorescent Brightening Agents", John Wiley & Sons, New York, 1992.
52. G. Jones II and M. A. Rahman, *J. Phys. Chem.*, 1994, **98**, 13028.
53. G. Brafolo, F. Fringuelli, O. Piermatti and F. Pizzo, *Heterocycles*, 1996, **43**, 1257.
54. R. L. Shringer, "Organic Reactions", Wiley, New York, 1942, **1**, 1.
55. G. Jones II, W. R. Jackson and A. M. Halpern, *Chem. Phys. Lett.*, 1980, **72**, 391.
56. B. Saadali, D. Boriky, M. Blaghen, M. Vanhaelen and M. Talbi, *Phytochemistry*, 2001, **58**, 1083.
57. L. Rahalison, M. Benathan, M. Monod, E. Frenk, M. P. Gupta, P. N. Solis, N. Fuzzati and K. Hostettmann, *Planta Med.*, 1995, **61**, 360.
58. R. Nakagaki, N. Kitamura I. Aoyama and H. Ohtsubo, *J. Photochem. Photobiol. A : Chem.*, 1994, **80**, 113.
59. R. H. Flatman, A. Eustaquio, S.-M. Li, L. Heide and L. Maxwell, *Antimicrob. Agents Chemotherapy*, 2006, **50**, 1136.
60. R. L. Atkins and D. E. Bliss, *J. Org. Chem.*, 1978, **43**, 1975.
61. G. Jones II, W. R. Jackson, Ch.-yoo Choi and W. R. Bergmark, *J. Phys. Chem.*, 1985, **89**, 294.
62. H. M. Santos, B. Pedras, A. Tamayo, J. Casabó, L. E. B. Covelo, J. L. Capelo and C. Lodeiro, *Inorg. Chem. Commun.*, 2009, **12**, 1128.
63. P. Kele, J. Orbulescu, T. L. Calhoun, R. E. Gawley and R. M. Leblanc, *Tetrahedron Lett.*, 2002, **43**, 4413.
64. C. Blackburn, M. Bai, K. A. LeCompte and M. E. Langmuir, *Tetrahedron Lett.*, 1994, **35**, 7915.
65. D. Ray and P. K. Bharadwaj, *Inorg. Chem.*, 2008, **47**, 2252.
66. D. Taziaux, J.-Ph. Soumillion and J.-L. Habib Jiwan, *J. Photochem. Photobiol. A : Chem.*, 2004, **162**, 599.
67. Y. Dong, J. Li, X. Jiang, F. Song, Y. Cheng and C. Zhu, *Org. Lett.*, 2011, **13**, 2252.
68. H. M. Kim, P. R. Yang, M. S. Seo, J.-S. Yi, J. H. Hong, S.-J. Jeon, Y.-G. Ko, K. J. Lee and B. R. Cho, *J. Org. Chem.*, 2007, **72**, 2088.
69. D. Ray, A. Nag, A. Jana, D. Goswami and P. K. Bharadwaj, *Inorg. Chim. Acta*, 2010, **12**, 2824.
70. L. F. Capitán-Vallvey, M. D. Fernández-Ramos, A. Lapresta-Fernández, E. Brunet, J. C. Rodríguez-Ubis and O. Juanes, *Talanta*, 2006, **68**, 1663.
71. Y. Suzuki, H. Komatsu, T. Ikeda, N. Saito, S. Araki, D. Citterio, H. Hisamoto, Y. Kitamura, T. Kubota, J. Nakagawa, K. Oka and K. Suzuki, *Anal. Chem.*, 2002, **74**, 1423.
72. M. Suresh and A. Das, *Tetrahedron Lett.*, 2009, **50**, 5808.
73. D. Maity and T. Govindaraju, *Inorg. Chem.*, 2010,

- 49, 7229.
74. M. Arduini, F. Felluga, F. Mancin, P. Rossi, P. Tecilla, U. Tonellato and N. Valentinuzzi, *Chem. Commun.*, 2003, 1606.
 75. S. Guha, S. Lohar, A. Sahana, A. Banerjee and D. Das, *Talanta*, 2012, **91**, 18.
 76. N. C. Lim, S. V. Pavlova and C. Brückner, *Inorg. Chem.*, 2009, **48**, 1173.
 77. J. Yao, W. Dou, W. Qin and W. Liu, *Inorg. Chem. Commun.*, 2009, **12**, 116.
 78. K. Namba, K. Kobayashi, Y. Murata, H. Hirakawa, T. Yamagaki, T. Iwashita, M. Nishizawa, S. Kusumoto and K. Tanino, *Angew. Chem. Int. Ed.*, 2010, **49**, 9956.
 79. Y. M. Ma and R. C. Hider, *Bioorg. Med. Chem.*, 2009, **17**, 8093.
 80. W. Luo, Y. M. Ma, P. J. Quinn, R. C. Hider and Z. D. Liu, *J. Pharm. Pharmacol.*, 2004, **56**, 529.
 81. N. Chattopadhyay, A. Mallick and S. Sengupta, *J. Photochem. Photobiol. A : Chem.*, 2006, **177**, 55.
 82. G. He, X. Zhao, X. Zhang, H. Fan, S. Wu, H. Li, C. He and C. Duan, *New J. Chem.*, 2010, **34**, 1055.
 83. J. R. Sheng, F. Feng, Y. Qiang, F. G. Liang, L. Sen and F.-H. Wei, *Anal. Lett.*, 2008, **41**, 2203.
 84. N. Li, Y. Xiang and A. Tong, *Chem. Commun.*, 2010, **46**, 3363.
 85. M. H. Kim, H. H. Jang, S. Yi, S.-K. Chang and M. S. Han, *Chem. Commun.*, 2009, 4838.
 86. X. Zhao, Y. Zhang, G. He and P. Zhou, *Chin. J. Lumin.*, 2010, **31**, 433.
 87. K. L. Ciesienki, L. M. Hyman, S. Derisavifard and K. J. Franz, *Inorg. Chem.*, 2010, **49**, 6808.
 88. V. Chandrasekhar, P. Bag and M. D. Pandey, *Tetrahedron*, 2009, **47**, 9876.
 89. X. Chen, H. Xi, X. Sun, T. Zhao, Q. Meng and Y. Jiang, *Chin. J. Org. Chem.*, 2011, **31**, 544.
 90. A. Helal, M. H. Q. Rashid, C.-H. Choi and H.-S. Kim, *Tetrahedron*, 2011, **67**, 2794.
 91. K. C. Ko, J.-S. Wu, H. J. Kim, P. S. Kwon, J. W. Kim, R. A. Bartsch, J. Y. Lee and J. S. Kim, *Chem. Commun.*, 2011, **47**, 3165.
 92. H. S. Jung, P. S. Kwon, J. W. Lee, J. I. Kim, C. S. Hong, J. W. Kim, S. Yan, J. Y. Lee, J. H. Lee, T. Joo and J. S. Kim, *J. Am. Chem. Soc.*, 2009, **131**, 2008.
 93. M. H. Kim, H. H. Jang, S. Yi, S.-K. Chang and M. S. Han, *Chem. Commun.*, 2009, 4838.
 94. R. Sheng, P. Wang, Y. Gao, Y. Wu, W. Liu, J. Ma, H. Li and S. Wu, *Org. Lett.*, 2008, **10**, 5015.
 95. D. T. Quang, H. S. Jung, J. H. Yoon, S. Y. Lee and J. S. Kim, *Bull. Korean Chem. Soc.*, 2007, **28**, 682.
 96. Y. J. Jang, B.-S. Moon, M. S. Park, B.-G. Kang, J. Y. Kwon, J. S. J. Hong, Y. J. Yoon, K. D. Lee and J. Yoon, *Tetrahedron Lett.*, 2006, **47**, 2707.
 97. N. C. Lim and C. Brückner, *Chem. Commun.*, 2004, 1094.
 98. H. Li, S. Gao and Z. Xi, *Inorg. Chem. Commun.*, 2009, **12**, 300.
 99. H. S. Jung, K. C. Ko, J. H. Lee, S. H. Kim, S. Bhuniya, J. Y. Lee, Y. Kim, S. J. Kim and J. S. Kim, *Inorg. Chem.*, 2010, **49**, 8552.
 100. S. Mizukami, S. Okada, S. Kimura and K. Kikuchi, *Inorg. Chem.*, 2009, **48**, 7630.
 101. N. C. Lim, J. V. Schuster, M. C. Porto, M. A. Tanudra, L. Yao, H. C. Freake and C. Brückner, *Inorg. Chem.*, 2005, **44**, 2018.
 102. M. Yan, T. Li and Z. Yang, *Inorg. Chem. Commun.*, 2011, **14**, 463.
 103. Z. Su, K. Chen, Y. Guo, H. Qi, X.-F. Yang and M. Zhao, *J. Fluoresc.*, 2010, **20**, 851.
 104. K. K. Upadhyay and R. K. Mishra, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 1211.
 105. J.-S. Wu, W.-M. Liu, X.-Q. Zhuang, F. Wang, P.-F. Wang, S.-L. Tao, X.-H. Zhang, S.-K. Wu and S.-T. Lee, *Org. Lett.*, 2007, **9**, 33.
 106. M. Chatterjee, S. Chatterjee, M. B. Roy, S. Ghosh, P. Bandyopadhyay and P. K. Bharadwaj, *J. Lumin.*, 2002, **99**, 175.
 107. M. Taki, M. Desaki, A. Ojida, S. Iyoshi, T. Hirayama, I. Hamachi and Y. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 12564.
 108. C. P. Kulatilleke, S. A. de Silva and Y. Eliav, *Polyhedron*, 2006, **25**, 2593.
 109. C.-T. Chen and W.-P. Huang, *J. Am. Chem. Soc.*, 2002, **124**, 6246.
 110. E. Roussakis, S. A. Pergantis and H. E. Katerinopoulos, *Chem. Commun.*, 2008, 6221.
 111. G. Pagona, S. P. Economopoulos, G. K. Tsikalas, H. E. Katerionopoulos and N. Tagmatarchis, *Chem. Eur. J.*, 2010, **16**, 11969.
 112. K. Tsukamoto, Y. Shinohara, S. Iwasaki and H. Maeda, *Chem. Commun.*, 2011, **47**, 5073.
 113. A. S. A. Kady, M. Gaber, M. M. Hussein, E. Zeiny and M. Ebeid, *J. Phys. Chem. (A)*, 2009, **113**, 9474.
 114. S. Huang, S. He, Y. Lu, F. Wei, X. Zeng and L. Zhao, *Chem. Commun.*, 2011, **47**, 2408.
 115. H. Sakamoto, J. Ishikawa, H. Osuga, K. Doi and H. Wada, *Analyst*, 2010, **135**, 550.
 116. X.-P. He, Z. Song, Z.-Z. Wang, X.-X. Shi and K. Chen, *Tetrahedron*, 2011, **67**, 3343.
 117. S. Guha, S. Lohar, I. Hauli, S. K. Mukhopadhyay and D. Das, *Talanta*, 2011, **85**, 1658.

118. S. Voutsadaki, G. K. Tsikalas, E. Klontzas, G. E. Froudakis and H. E. Katerinopoulos, *Chem. Commun.*, 2010, **46**, 3292.
119. Y. Shiraishi, S. Sumiya and T. Hirai, *Org. Biomol. Chem.*, 2010, **8**, 1310.
120. S. H. Lee, A. Helal and H.-S. Kim, *Bull. Korean Chem. Soc.*, 2010, **31**, 615.
121. J. Wang, X. Qian and J. Cui, *J. Org. Chem.*, 2006, **71**, 4308.
122. D. H. Ryu, J. H. Noh and S.-K. Chang, *Bull. Korean Chem. Soc.*, 2010, **31**, 246.
123. Q.-J. Ma, X.-B. Zhang, X.-H. Zhao, Z. Jin, G.-J. Mao, G.-L. Shen and R.-Q. Yu, *Anal. Chim. Acta*, 2010, **663**, 85.
124. W. Ma, Q. Xu, J. Du, B. Song, X. Peng, Z. Wang, G. Li and X. Wang, *Spectrochim. Acta (A)*, 2010, **76**, 1386.
125. D.-N. Lee, G.-J. Kim and H.-J. Kim, *Tetrahedron Lett.*, 2009, **50**, 4766.
126. M. G. Choi, Y. H. Kim, J. E. Namgoong and S.-K. Chang, *Chem. Commun.*, 2009, **24**, 3560.
127. H. J. Kim, J. E. Park, M. G. Choi, S. Ahn and S.-K. Chang, *Dyes Pigments*, 2009, **84**, 54.
128. S. Voutsadaki, G. K. Tsikalas, E. Klontzas, G. E. Froudakis and H. E. Katerinopoulos, *Chem. Commun.*, 2010, **46**, 3292.
129. S. Mizukami, S. Okada, S. Kimura and K. Kikuchi, *Inorg. Chem.*, 2009, **48**, 7630.
130. H. Miyaji, H.-K. Kim, E.-K. Sim, C.-K. Lee, W.-S. Cho, J. L. Sessler and C.-H. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 12510.
131. J. H. Lee, A. R. Jeong, I.-S. Shin, H.-J. Kim and J.-I. Hong, *Org. Lett.*, 2010, **12**, 764.
132. Y. Shiraishi, S. Sumiya and T. Hirai, *Chem. Commun.*, 2011, **47**, 4953.
133. H. J. Kim, K. C. Ko, J. H. Lee, J. Y. Lee and J. S. Kim, *Chem. Commun.*, 2011, **47**, 2886.
134. G.-J. Kim and H.-J. Kim, *Tetrahedron Lett.*, 2010, **51**, 185.
135. G.-J. Kim and H.-J. Kim, *Tetrahedron Lett.*, 2010, **51**, 2914.
136. K.-S. Lee, H.-J. Kim, G.-H. Kim, I. Shin and J.-I. Hong, *Org. Lett.*, 2008, **10**, 49.
137. Y. O. Lee, J. Y. Lee, D. T. Quang, M. H. Lee and J. S. Kim, *Bull. Korean Chem. Soc.*, 2006, **27**, 1469.
138. S. H. Lee, H. J. Kim, Y. O. Lee, J. Vicens and J. S. Kim, *Tetrahedron Lett.*, 2006, **47**, 4373.
139. S. Y. Kim, J. Park, M. Koh, S. B. Park and J.-I. Hong, *Chem. Commun.*, 2009, 4735.
140. P. Sakkalingam and C.-H. Lee, *J. Org. Chem.*, 2011, **76**, 3820.
141. X. Zhuang, W. Liu, J. Wu, H. Zhang and P. Wang, *Spectrochim. Acta (A)*, 2011, **79**, 1352.
142. K. K. Upadhyay, R. K. Mishra, V. Kumar and P. K. R. Chowdhury, *Talanta*, 2010, **82**, 312.
143. J. Li, H. Lin, Z. Cai and H. Lin, *J. Lumin.*, 2009, **129**, 501.
144. S. Diallo, P. Bastard, P. Prognon, C. Dauphin and M. Hamon, *Talanta*, 1996, **43**, 359.
145. M. Shamsipur and M. J. Chaichi, *Spectrochim. Acta (A)*, 2001, **57**, 2355.
146. K. Chen, Y. Guo, Z. Lu, B. Yang and Z. Shi, *Chin. J. Chem.*, 2010, **28**, 55.
147. H. J. Kim, S. Bhuniya, R. K. Mahajan, R. Puri, H. Liu, K. C. Ko, J. Y. Lee and J. S. Kim, *Chem. Commun.*, 2009, 7128.
148. K. K. Upadhyay, R. K. Mishra, A. Kumar, J. Zhao and R. Prasad, *J. Mol. Struct.*, 2010, **963**, 228.
149. A. K. Mahapatra, G. Hazra, J. Roy and P. Sahoo, *J. Lumin.*, 2011, **131**, 1255.
150. J. Shao, *Dyes Pigments*, 2010, **87**, 272.
151. S. K. Kim, D. H. Lee, J.-I. Hong and J. Yoon, *Acc. Chem. Res.*, 2009, **42**, 23.
152. K. Choi and A. D. Hamilton, *Angew. Chem. Int. Ed.*, 2001, **40**, 3912.
153. S. Mizukami, T. Nagano, Y. Urano, A. Odani and K. Kikuchi, *J. Am. Chem. Soc.*, 2002, **124**, 3920.
154. P. Das, A. Ghosh, M. K. Kesharwani, V. Ramu, B. Ganguly and A. Das, *Eur. J. Inorg. Chem.*, 2011, 3050.
155. H. Miyaji, H.-K. Kim, E.-K. Sim, C.-K. Lee, W.-S. Cho, J. L. Sessler and C.-H. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 12510.
156. H. J. Kim, S. Bhuniya, R. K. Mahajan, R. Puri, H. Liu, K. C. Ko, J. Y. Lee and J. S. Kim, *Chem. Commun.*, 2009, 7128.
157. W. Lin, L. Yuan, X. Cao, B. Chen and Y. Feng, *Sens. Actuators (B)*, 2009, **138**, 637.
158. T.-K. Kim, D.-N. Lee and H.-J. Kim, *Tetrahedron Lett.*, 2008, **49**, 4879.
159. H. S. Jung, K. C. Ko, G.-H. Kim, A.-R. Lee, Y.-C. Na, C. Kang, J. Y. Lee and J. S. Kim, *Org. Lett.*, 2011, **13**, 1498.
160. J. Wu, R. Sheng, W. Liu, P. Wang, J. Ma, H. Zhang and X. Zhuang, *Inorg. Chem.*, 2011, **50**, 6543.
161. W. Lin, L. Yuan, Z. Cao, Y. Feng and L. Long, *Chem.-Eur. J.*, 2009, **15**, 5096.
162. E. K. Feuster and T. E. Glass, *J. Am. Chem. Soc.*, 2003, **125**, 16174.
163. K. E. Secor and T. E. Glass, *Org. Lett.*, 2004, **6**, 3727.
164. T. H. Nguyen and R. J. Ansell, *Org. Biomol. Chem.*,

- 2009, **7**, 1211.
165. G.-J. Kim and H.-J. Kim, *Tetrahedron Lett.*, 2010, **51**, 4670.
166. M. Xiong, H. Xi, Y. Fu and X. Sun, *J. Org. Chem.*, 2010, **30**, 908.
167. S. Cha, J. Hwang, M. G. Choi and S.-K. Chang, *Tetrahedron Lett.*, 2010, **51**, 6663.
168. A. Kumar, M. K. Pandey, R. Anandakathir, R. Mosurkal, V. S. Parmar, A. C. Watterson and J. Kumar, *Sens. Actuators (B)*, 2010, **47**, 105.
169. B. Gruber, S. Stadlbauer, A. Späth, S. Weiss, M. Kalinina and B. König, *Angew. Chem. Int. Ed.*, 2010, **49**, 7125.
170. S. Sato, M. Suzuki, T. Soma and M. Tsunoda, *Spectrochim. Acta (A)*, 2008, **70**, 799.
171. J.-A. Richard, M. Massonneau, P.-Y. Renard and A. Romieu, *Org. Lett.*, 2008, **10**, 4175.
172. Y. Zhou, K. Liu, J.-Y. Li, Y. Fang, T.-C. Zhao and C. Yao, *Org. Lett.*, 2011, **13**, 1290.
173. P. Das, S. Bhattacharya, S. Mishra and A. Das, *Chem. Commun.*, 2011, **47**, 8118.
174. C.-X. Jiao, C.-G. Niu, L.-X. Chen, G.-L. Shen and R.-Q. Yu, *Sens. Actuators (B)*, 2003, **94**, 176.
175. J.-A. Richard, M. Massonneau, P.-Y. Renard and A. Romieu, *Org. Lett.*, 2008, **10**, 4175.
176. X. Cao, W. Lin and Q. Yu, *J. Org. Chem.*, 2001, **76**, 7423.
177. Q. Zhang, J. J. Zhai, Y. R. Zhang, Y. M. Liu, L. F. Wang, S. B. Li, D. Z. Liao and G. L. Wang, *Trans. Met. Chem.*, 2000, **25**, 93.
178. L. Yuan, W. Lin and Y. Yang, *Chem. Commun.*, 2011, **47**, 6275.
179. H. Kwon, K. Lee and H.-J. Kim, *Chem. Commun.*, 2011, **47**, 1773.
180. Q.-P. Zuo, B. Li, Q. Pei, Z. Li and S.-K. Liu, *J. Fluoresc.*, 2010, **20**, 1307.
181. L. Yi, H. Li, L. Sun, L. Liu, C. Zhang and Z. Xi, *Angew. Chem. Int. Ed.*, 2009, **48**, 4034.
182. G.-J. Kim, K. Lee, H. Kwon and H.-J. Kim, *Org. Lett.*, 2011, **13**, 2799.
183. S.-Y. Lim, S. Lee, S. B. Park and H.-J. Kim, *Tetrahedron Lett.*, 2011, **52**, 3902.
184. W. Lin, L. Long and W. Tan, *Chem. Commun.*, 2010, **46**, 1503.
185. H. S. Jung, K. C. Ko, G.-H. Kim, A.-R. Lee, Y.-C. Na, C. Kang, J. Y. Lee and J. S. Kim, *Org. Lett.*, 2011, **13**, 1498.
186. H. S. Jung, J. H. Han, Y. Habata, C. Kang and J. S. Kim, *Chem. Commun.*, 2011, **47**, 5142.
187. J. Pan, J. A. Downing, J. L. McHale and M. Xian, *Mol. Biosyst.*, 2009, **5**, 918.
188. M. González-Béjar, M. Frenette, L. Jorge and J. C. Scaiano, *Chem. Commun.*, 2009, 3204.
189. W. Lin, X. Cao, L. Yuan and Y. Ding, *Chem. Eur. J.*, 2010, **16**, 6454.
190. K.-S. Lee, T.-K. Kim, J. H. Lee, H.-J. Kim and J.-I. Hong, *Chem. Commun.*, 2008, 6173.
191. E. Galardon, A. Tomas, P. Roussel and I. Artaud, *Dalton Trans.*, 2009, 9126.
192. B. D. Wagner, *Molecules*, 2009, **14**, 210.
193. N. Saleh, Y. A. Al-Soud and W. M. Nau, *Spectrochim. Acta (A)*, 2008, **71**, 818.
194. M. A. Haidekker, T. P. Brady, D. Lichlyter and E. A. Theodorakis, *Bioorg. Chem.*, 2005, **33**, 415.
195. A. S. Vasylevska, A. A. Karasyov, S. M. Borisov and C. Krause, *Anal. Bioanal. Chem.*, 2007, **387**, 2131.
196. N. Saleh, Y. A. Al-Soud and W. M. Nau, *Spectrochim. Acta (A)*, 2008, 818.
197. M. Lee, N. G. Gubernator, D. Sulzer and D. Sames, *J. Am. Chem. Soc.*, 2010, **132**, 8828.
198. S. W. Hong and W. H. Jo, *Polymer*, 2008, **49**, 4180.
199. L. Du, M. Li, S. Zheng and B. Wang, *Tetrahedron Lett.*, 2008, **49**, 3045.
200. L. Du Y, N. Ni Y, M. Li and B. Wang, *Tetrahedron Lett.*, 2010, **51**, 1152.
201. M. E. Abbas, W. Luo, L. Zhu, J. Zou and H. Tang, *Food Chem.*, 2010, **120**, 327.
202. W. Wu, W. Wu, S. Ji, H. Guo and J. Zhao, *Dalton Trans.*, 2011, **40**, 5953.
203. L. Yuan, W. Lin and J. Song, *Chem. Commun.*, 2010, **46**, 7930.
204. G. M. Ganea, P. E. Kolic, B. El-Zahab and I. M. Warner, *Anal. Chem.*, 2011, **83**, 2576.
205. S. Royo, R. Martínez-Mañez, F. Sancenón, A. M. Costero, M. Parra and S. Gil, *Chem. Commun.*, 2007, 4839.
206. K. J. Wallace, R. I. Fagbemi, F. J. Folmer-Andersen, J. Morey, V. M. Lynth and E. V. Anslyn, *Chem. Commun.*, 2006, 3886.
207. T. J. Dale and J. Rebek (Jr.), *Angew. Chem. Int. Ed.*, 2009, **48**, 7850.
208. D. Xiao, L. A. Martini, R. C. Snoberger III, R. H. Crabtree and V. S. Batista, *J. Am. Chem. Soc.*, 2011, **133**, 9014.
209. P. Kele, J. Orbulescu, S. V. Mello, M. Mabrouki and R. M. Leblanc, *Langmuir*, 2001, **17**, 7286.
210. J. Ortyl, K. Sawicz and R. Popielarz, *J. Polym. Sci. (A)*, 2010, **48**, 4522.
211. S. Basu, D. P. Chatterjee, U. Chatterjee, S. Mondal and D. Mandal, *Colloids Surf. (A)*, 2009, **341**, 13.
212. J.-A. Richard, M. Massonneau, P.-Y. Renard and A.

- Romieu, *Org. Lett.*, 2008, **10**, 4175.
213. Y. Meyer, J.-A. Richard, M. Massonneau, P.-Y. Renard and A. Romieu, *Org. Lett.*, 2008, **10**, 1517.
214. T. Hirano, K. Hiromoto and H. Kagechika, *Org. Lett.*, 2007, **9**, 1315.
215. R. K. Singh, T. Mandal, N. Balasubramanian, G. Cook and D. K. Srivastava, *Anal. Biochem.*, 2011, **408**, 309.
216. S.-T. Huang, C.-J. Teng, Y.-H. Lee, J.-Y. Wu, K.-L. Wang and C.-M. Lin, *Anal. Chem.*, 2010, **82**, 7329.
217. H.-C. Huang, K.-L. Wang, S.-T. Huang, H.-Y. Lin and C.-M. Lin, *Biosensors Bioelectronics*, 2011, **26**, 3511.
218. R. S. Coleman, M. A. Berg and C. J. Murphy, *Tetrahedron*, 2007, **63**, 3450.
219. Y. Zhou, K. Liu, J.-Y. Li, Y. Fang, T.-C. Zhao and C. Yao, *Org. Lett.*, 2011, **13**, 1290.
220. Y. Xie, A. V. Dix and Y. Tor, *J. Am. Chem. Soc.*, 2009, **131**, 17605.
221. V. B. Kovalska, K. D. Volkova, A. V. Manaev, M. Y. Losytskyy, I. N. Okhrimenko, V. F. Traven and S. M. Yarmoluk, *Dyes Pigments*, 2010, **84**, 159.
222. C.-S. Tsai, P.-Y. Liu, H.-Y. Yen, T.-L. Hsu and C.-H. Wong, *Chem. Commun.*, 2010, **46**, 5575.
223. P. K. Makwana, P. N. Jethva and I. Roy, *Analyst*, 2011, **136**, 2161.
224. A. Shibata, H. Abe, M. Ito, Y. Kondo, S. Shimizu, K. Aikawa and Y. Ito, *Chem. Commun.*, 2009, 6586.
225. N. Baker, G. M. Greenway, R. A. Wheatley and C. Wiles, *Analyst*, 2007, **132**, 104.
226. Y. Kurishita, T. Kohira, A. Ojida and I. Hamachi, *J. Am. Chem. Soc.*, 2010, **38**, 13290.
227. C. Ranjith, K. K. Vijayan, V. K. Praveen and N. S. S. Kumar, *Spectrochim. Acta (A)*, 2010, **75**, 1610.
228. A. Lacy, L. Dunne, B. Fitzpatrick, S. Daly and G. Keating, *J. AOAC Int.*, 2006, **89**, 884.
229. Q. Zhang, J. J. Zhai, Y. R. Zhang, Y. M. Liu, L. F. Wang, S. B. Li, D. Z. Liao and G. L. Wang, *Trans. Met. Chem.*, 2000, **25**, 93.
230. V. D. Kancheva, L. Saso, P. V. Boranova, A. Khan, M. K. Saroj, M. K. Pandey, S. Malhotra, J. Z. Nechev, S. K. Sharma, A. K. Prasad, M. B. Georgieva, C. Joseph, A. L. DePass, R. C. Rastogi and V. S. Parmar, *Biochimie*, 2010, **92**, 1089.
231. G. Morabito, D. Trombetta, K. S. Brajendra, K. P. Ashok, S. P. Virinder, C. Naccari, F. Mancari, A. Saija, M. Cristani, O. Firuzi and L. Saso, *Biochimie*, 2010, **92**, 1101.
232. T. Symeonidis, M. Chamilos, D. J. Hadjipavlou-Litina, M. Kallitsakis and K. E. Litinas, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1139.
233. N. Hamdi, M. C. Puerta and P. Valerga, *Eur. J. Med. Chem.*, 2008, **43**, 2541.
234. B. S. Creaven, M. Devereux, D. Karcz, A. Kellett, M. McCann, A. Noble and M. Walsh, *J. Inorg. Biochem.*, 2009, **103**, 1196.
235. C. F. Xiao, L. Y. Tao, H. Y. Sun, W. Wei, Y. Chen, L. W. Fu and Y. Zou, *Chin. Chem. Lett.*, 2010, **21**, 1235.
236. Z. M. Nofal, M. I. El-Zahar and S. S. Abd El-Karim, *Molecules*, 2000, **5**, 99.
237. J.-F. Cheng, M. Chen, D. Wallace, S. Tith, T. Arrhenius, H. Kashiwagi, Y. Ono, A. Ishikawa, H. Sato, T. Kozono, H. Sato and A. M. Nadzan, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2411.
238. I. A. Khan, M. V. Kulkarni, M. Gopal, M. S. Shahabuddin and C. M. Sun, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3584.
239. C. T. Chen, C. L. Chiang, Y. C. Lin, L. H. Chan, C. H. Huang, Z. W. Tsai and C. T. Chen, *Org. Lett.*, 2003, **5**, 1261.
240. S. Lee, K. Sivakumar, W. S. Shin, F. Xie and Q. Wang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4506.
241. S. K. Rangappa, M. H. Kallappa, V. S. Ramya and H. H. Mallinath, *Eur. J. Med. Chem.*, 2010, **45**, 2597.
242. F. Chimenti, B. Bizzarri, A. Bolasco, D. Seed, P. Chimenti, S. Carradori, A. Granese, D. Rivanera, D. Lilli, M. M. Scaltrito and M. I. Brenciaglia, *Eur. J. Med. Chem.*, 2006, **41**, 208.
243. Y. Kong, Y. J. Fu, Y. G. Zu, F. R. Chang, Y. H. Chen, X. L. Liu, J. Stelten and H. M. Schiebel, *Food Chem.*, 2010, **121**, 1150.
244. G. B. Bagihalli, P. G. Avaji, S. A. Patil and P. S. Badami, *Eur. J. Med. Chem.*, 2008, **43**, 2639.
245. M. S. Refat, I. M. El-Deen, Z. M. Anwer and S. El-Ghol, *J. Mol. Struct.*, 2009, **920**, 149.
246. A. Kotali, I. S. Lafazanis and A. Papageorgiou, *Molbank M*, 2008, 574.
247. V. K. Pandey, S. Tusi and Z. Tusi, *Acta Pharm.*, 2004, **54**, 1.
248. B. C. Raju, *Phytopathology*, 1982, **72**, 1460.
249. I. Kostova, G. Momekov, T. Tzanova and M. Karaivanova, *Bioinorg. Chem. Appl.*, 2006, **25651**, 1.
250. A. Kulkarni, S. A. Patil and P. S. Badami, *Eur. J. Med. Chem.*, 2009, **44**, 2904.
251. J. M. Ballard and L. D. Betowski, *Org. Mass Spec.*, 1986, **21**, 575.
252. B. Abrams, Z. Diwu, O. Guryev, S. Aleshkov, R. Hingorani, M. Edinger, R. Lee, J. Link and T. Dubrovsky, *Anal. Biochem.*, 2009, **386**, 262.