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Recent trends in coumarin based neutral synthetic receptors for naked eye sensing of anions

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Abstract: Coumarin moiety is increasingly employed for the construction of artificial neutral receptors and sensors for effectively binding anions of various sizes and geometries. A lion's share of these receptors have been documented and developed for the detection of highly basic fluoride ion because of its deleterious effects. This review showcases the development of coumarin as artificial neutral receptors for binding and sensing anions by colour change detectable by naked eye, which are useful for at-site analysis without resorting to expensive instruments, covering literature references from the year 2010 till date.

Introduction

Nature's fundamental biological processes involving receptor-guest interactions or enzyme-substrate are regulated *via* ions' concentration; wherein anions are selectively detected and complexed through the intricate binding sites of proteins [1]. Most widely found are the two basic pyrrole containing macrocycles, haeme protein and porphyrin, which bind Fe^{+2} and Mg^{+2} ions for conducting vital functions in human body and plants [2]. This has encouraged the innovation in chemical sensor technology and development of abiotic host molecular systems capable of imitating the ionic recognition found in biological systems [3-7].

Anion receptors can be broadly categorized into cationic and neutral receptors [8]. Cationic anion receptors are positively charged receptors which establishes electrostatic interactions with anions. These receptors marked the beginning of anion recognition chemistry, with the earliest artificial receptor being reported in 1968 which was a macrocyclic compound consisting of two bridgehead ammonium units, capable

of encapsulating halide ions [9]. Moieties, guanidinium, quaternary ammonium groups, isothiouronium, polyamines, porphyrins etc. have been largely employed for the formulation of cationic receptors to achieve electrostatic binding with anions [10-17]. Although, larger binding constants could be achieved with positively charged receptors, they lack directional and selective nature of hydrogen bonding. Moreover, associated counter-anion with charged hosts creates competition for desired anion.

In contrast to this, neutral receptors rely on hydrogen bonding, which possess higher degree of directionality and strength than columbic forces and is arguably the most common forces utilized in crafting anion receptors [18-20]. Urea/thiourea, secondary amide, sulphonamides [21-24] possess acidic N-H, which can build hydrogen bond with negatively charged species and thus have found their use in creating anion receptors. Moreover these moieties offer several advantages which enabled their extensive exploitation in composing putative anion receptors. Synthetic accessibility of urea and thiourea has enabled their incorporation in a wide variety of putative anion receptors [25-29]. They possess two acidic hydrogen bonds and have been extensively utilized for developing receptors for binding carboxylates and phosphates [30].

Anions play several significant roles in biological as well as in environment, this demands continuous research for the development of techniques to quantify them [31-34]. Amongst them, host molecules that can recognize and sense anions selectively through visible, electrochemical and optical responses are of particular interest [35-37]. Color change, which can be detected *via* naked eye is highly appreciated being a low cost and does not require any spectroscopic instrument and requisite in terms of practical purpose [38-

40]. There are three popular approaches for designing chemosensors (**Figure 1**) [41]:

- **Binding – signalling unit approach,**
- **Displacement approach**
- **Chemodosimeter approach**

In the first approach, receptor consists of chromophoric units, covalently attached to binding unit [42]. Receptor binds the anion and brings about a change in the photophysical properties of chromophore attached with an optical response as the output.

Chromophoric groups become coloured by absorbing light in visible region (400-700 nm). These consist of a system of conjugated bonds that brings down the energy gap between HOMO and LUMO to visible region. Appropriate anchoring of electron donor and acceptor groups to this system generates a charge transfer band, corresponding to transition of electrons from donor to acceptor group *via* conjugated system, upon excitation with light [43].

In the displacement approach, binding and signalling units form a coordination complex. In solution, anion displaces the signalling unit from the complex, which comes into its non-coordinated spectroscopic behaviour [44].

Both of the above approaches are reversible in nature, while the last, the chemodosimeter approach, is irreversible in nature [45]. Here, anion induces a specific reaction on binding and generates a naked eye response. This anion induced approach is highly selective and is directly related to anion concentration
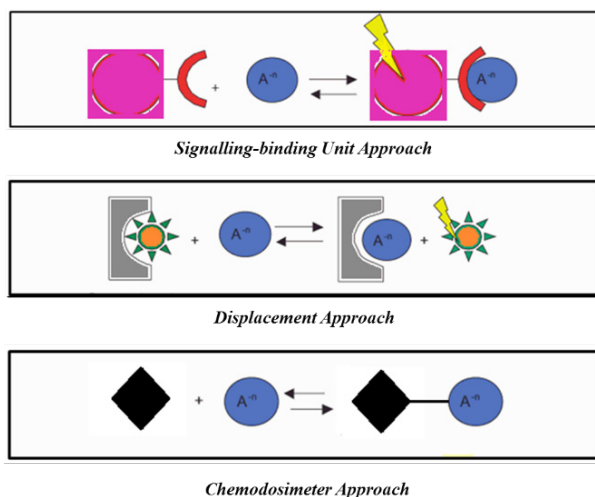
Figure 1 Design approaches for chemosensors [46]

Various non-covalent interactions, mainly coulombic [47-48], anion- pi interactions [49], metal based [50] have been exploited for trapping anions. A large share of receptors utilizes polarized N-H that behaves as hydrogen bond donor to bind anions [51-54]. The acidity of these protons can be modulated by electronic and substituents effects [55]. Insertion of electron withdrawing groups such as nitro, trifluoromethyl groups etc. onto the framework of molecular structures of receptors has enhanced the binding capabilities which has often been accompanied by visible colour change in case of deprotonation [56]. Fluoride, amongst the anionic species, is undoubtly the most investigated individual of the vast family of anions [57]. Being the most electronegative atom, it rightfully establishes the strongest hydrogen bond interactions with an unmatched selectivity [58]. It is well noted observation that the colorimetric receptors show moderate or slight changes in presence of other anions, however with fluoride, receptors exhibit drastic colour changes. Beautiful and interesting colour changes with fluoride have been reported usually with anion receptors capable of donating one or more hydrogen bonds. The negative charge brought by the anion modifies the dipole associated to the charge transfer spectrum and thus a colour change is obtained. [59].

Coumarin, with the structure of benzo-α-pyrones has been extensively investigated for electronic and photonic applications such as fluorescence probes, charge transfer agents, solar energy collectors and non linear optical properties due to their inherent photochemical characteristics, reasonable stability, good solubility and their relative ease of synthesis [60-61]. A great number of receptors for metal ions have been developed in recent years, however anion sensors derived from coumarins are scarcely reported [62-70]. This review comprehensively describes the employment of coumarin and sensing abilities for anions in organic solvents or in aqueous media covering literature references from 2010 to recent development till date.
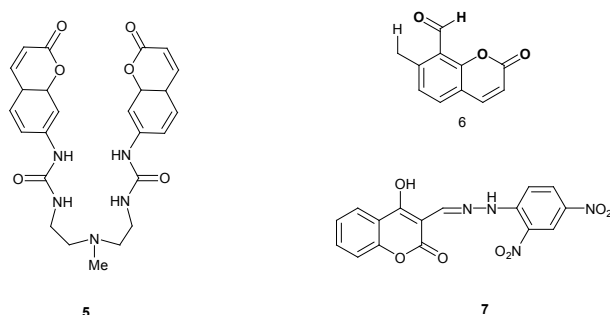
Naked eye coumarin based anion receptors
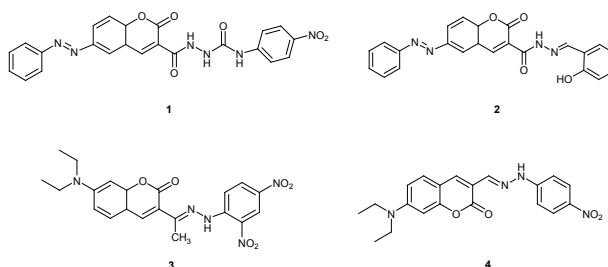
Figure 2 Coumarin based naked eye receptors, **1-4**

Shao *et. al.* reported colorimetric and fluorescent receptor **1** based on coumarin moiety as chromogenic and fluorescent unit and urea as anion binding site. It exhibited high selectivity for acetate ion over fluoride and dihydrogen phosphate due to multiple hydrogen binding interaction in DMSO. Fluorescent spectrum of receptor with acetate ion showed hypsochromic shift with significant increase in florescence intensity. The fluorescence in emission spectrum was observed due to anion induced conformation restriction [71]. Shao in 2011,

reported analogue of above, a coumarinschiffs base derivative **2**, which in the presence of acetate ion, exhibited "turn-on" fluorescence; resulting from binding induced conformational restriction. Colorimetric response for fluoride, acetate and dihydrogen phosphate was observed from yellow to red (**Figure 2**) [72].

Among the entire range of biologically important anions, fluoride is particularly useful, owing to its role in preventing dental caries and treatment of osteoporosis [73-82]. The biggest bottleneck in naked eye detection of fluoride is interference by acetate and other anion of comparative basicity [83-85]. In 2010, Coumarin based phenylhydrazone receptor **3** was synthesized and reported by Upadhyay *et. al.* that selectively detected fluoride over acetate in DMSO solution. Addition of 1 eq of fluoride to receptor solution (5×10^{-5}M) produced change from yellow to red, while similar addition of acetate ion produced faint pink color. Receptor differentiated the two anions not only visually, but in the terms of maxima by a margin of 30 nm which is a rare observation in UV spectrum (**Figure 2**) [86].

Liu *et. al.* reported fluoride receptor based on coumarin7-(diethylamino)-2-oxo-2H-chromene-3-carbaldehyde **4**, which bound fluoride *via* hydrogen bonding in acetonitrile. The receptor exhibited a large red shift of 145 nm along with change in the colour from yellow to blue upon addition of fluoride ion in acetonitrile and without interference of other anions such as Cl^-, Br^-, I^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, and AcO^-. The ^{1}H NMR spectrum titration established that F^- first formed a hydrogen bonding interaction with receptor **4** and then, excess of fluoride induced deprotonation (**Figure 2**) [87].


Figure 3 Coumarin based naked eye receptors, **5-7**

An off-on fluoride ion fluorosensor, 1,11-bis(4-methylcoumarin-7-yl)-6-methyl-1,3,6,9,11-pentaazaundeca-2,10-dione **5**, containing two coumarin-urea units attached by a flexible diethylenetriamine fragment has been designed and developed by Fusi and Zappia. Anion binding tendencies was investigated in both DMSO as well as CH_3CN solvents. Fluorescence emission of receptor in visible range (400 nm) was demonstrated to be quenched by the presence of acetate, chloride and pyrophosphate ions, while fluoride ion enhanced the emission, which proved the selectivity of receptor for fluoride ion (**Figure 3**) [88].

A fluorescent chemodosimeter **6** for cyanide ion with coumarin as signal unit and salicyaldehyde functionality as recognition unit has been synthesized by Kim and Hong group. It showed a higher selectivity for cyanide ion over other anions in water as demonstrated in fluorescence spectroscopy titration; wherein emission intensity of dosimeter at $\lambda = 450$ nm was enhanced to about 190 folds on addition of cyanide. The affinity and selectivity of chemodosimeter for cyanide was due to the nucleophilicity of cyanide as indicated by ^{1}H-NMR titration where aldehyde proton shifted upfield due to formation of cynohydrin, from δ 10.1 to 6.1 ppm (**Scheme 1**). In-vivo selectivity was also examined with living cells at pH 7.4 by using fluorescence microplate reader where only cyanide treated P19 cells showed enhancement

in fluorescent intensity in living cells (**Figure 3**) [89].
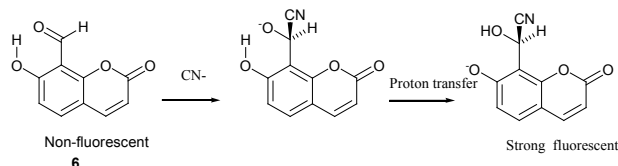
**Scheme 1** Fluorescentchemodosimeter for selective detection of cyanide in water

Receptors bearing phenylhydrazone-coumarin moieties, **7** was rationally designed for chemosensing acetate ion as well as fluorescence turn-on probe for iodide ion**.** It produced dramatic colour change from yellow to purple upon addition of acetate ion, with bathochromic shift from 411 to 573 nm in UV-visible spectra. Exploiting novel strategy based on the redox reaction between Cu^{+2} and iodide, which is a notorious fluorescence quencher due to heavy atom effect, receptor has been developed as fluorescence amplifier probe for iodide (**Figure 3**) [90].

Coumarin as signaling unit and acetamidothiophene ring as hydrogen donor, colorimetric and fluorimetriccoumarinthiophene based chemosensor, **8** for cyanide, fluoride and acetate was developed by Dede and Seferoglu *et. al*., which showed naked eye colour change from light yellow to dark yellow as well as emission quenching in fluorescence spectrum. Other anions failed to induce any spectral changes. Anion binding properties carried out with spectrophotometric and H NMR techniques showed that receptor exhibited more affinity towards cynide ion (**Figure 4**) [91].
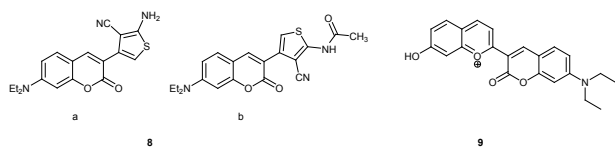
**Figure 4**Coumarin based naked eye receptors, **8-9**

2-(7-diethylamino-2-oxo-2H-1-benzopyran-3-yl)-7-hydroxyl-1- benzopyrylium, a ratiometric fluorescent probe, **9** constructed by hybridizing coumarin and benzopyrylium moieties for sensing sulphite ion. Nucleophilic addition of sulphite to electronically positive benzopyrylium moiety alters the π conjugation of receptor and thus ratiomatric sensing is realized. A fluorescent emission peak centered at 640 nm blue shifted to 485 nm upon addition of sulphite ion. Preliminary study conducted by authors showed that receptor is cell permeable and can be used for detecting cellular sulphite (**Figure 4**)[92].
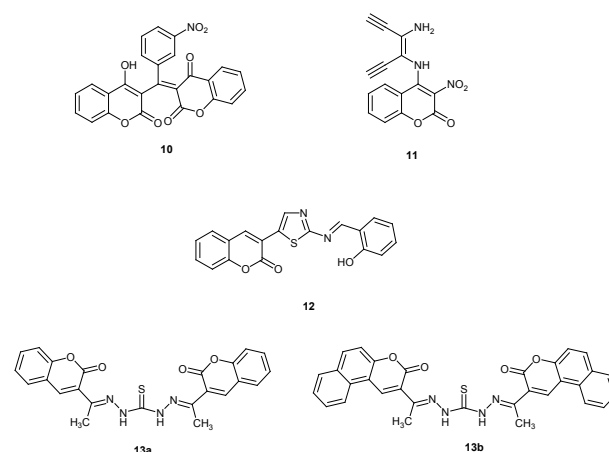

Figure 5 Coumarin based naked eye receptors, **10-13**

Mahapatra *et. al.* designed and synthesized turn-on fluorescent and colorimetric sensor, **10** based on oxidized bis(coumarin)methane, 3,3'-(3-nitrophenylmethylene)-bis-(4-hydroxycoumarin) (**Figure 5**) for fluoride ion detection in organic media, acetonitrile (Scheme 2). Authors found that biscoumarin containing oxidizable H atom, was unstable and spontaneously oxidize to conjugated product. The conjugated product can act as colour reporting group as well as binding affinity group containing acidic H donor moiety. They conducted anion binding studies by UV-visible, fluorescence and NMR titrations to show selective nature of receptor towards fluoride ion

over other anionic species. Receptor exhibited absorbance band at 261 and 319 nm in UV-visible spectra. Upon addition of fluoride ion, a new absorbance band at 349 nm appeared, which was accompanied by naked eye colour change of receptor solution from colourless to yellow. Authors found that no other anions could trigger similar naked eye and spectral change upon addition to receptor solution. The stoichiometry between receptor and fluoride ion was found to be 1:2 from Jobs plot. Fluorescence enhancement was observed at 394 nm, when excited at 287 nm, upon addition of fluoride ion into receptor solution in acetonitrile. ^{1}H NMR spectra of receptor showed peak at 9.5 ppm due to O-H proton, which shifted downfield and disappeared at 1.5 equivalents of fluoride ion. Fluoride ion established hydrogen bonding with receptor initially, followed by proton transfer, which gave rise to drastic colour change (**Scheme 3**) [93].
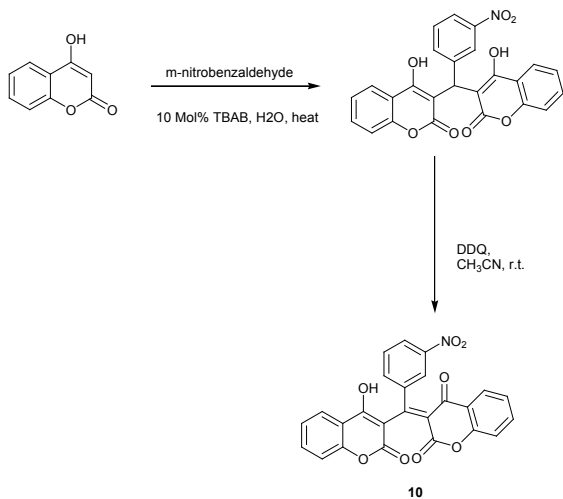
Scheme 2 Synthesis of 3,3'-(3-nitrophenylmethylene)-bis-(4-hydroxycoumarin), **10**
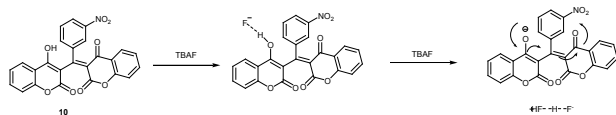
Scheme 3 Proposed binding mechanism of receptor **10**

A new chromogenic multifunctional chemosensor, **11**, (2-(3-nitro-2-oxo-2H-chromen-4-ylamino)-3-aminomaleonitrile) was synthesized and documented for the detection of Al^{3+} and F^{-} by Kim *et. al.* (**Figure 5**) [94]. Receptor was synthesized in a single step by coupling 2,3-diaminomaleonitrile with 4-chloro-3-nitrocoumarin in methanol. The preferential selectivity of receptor as fluoride ion naked eye receptor has been studied by authors in presence of various competing anions, chloride, bromide, iodide, acetate, benzoate, dihydrogen phosphate and cyanide, where no interference was observed. The fluoride recognition property of receptor was studied by UV-visible titrations, in which absorption bands at 338 and 441 nm disappeared, with simultaneous appearance of absorbance band at 510 nm. 1:1 stoichiometry between receptor and fluoride ion was proved by Jobs plot and ESI mass spectroscopy. In ^{1}H NMR spectra of receptor, peaks at 9.96 and 8.07 ppm due to NH and NH_2 disappeared upon addition of 1 equivalent of fluoride ion (TBA salt). Authors concluded that colorimetric response was obtained due to the decrease in the intramolecular charge transfer band by a deprotonation process.

Mishra and coworkers synthesized coumarin-thiazole based molecular scaffolds, out of which probe **12** exhibited fluorescence quenching on interaction with Cu^{+2} ion, while remaining silent towards anions (**Figure 5**) [95]. When this **12**-Cu^{+2} ensemble was tested for detection of anions, only fluoride ion enabled copper displacement as CuF_2 and led to fluorescent enhancement. Authors reported that this naked eye sensitive "*On-Off-On*" sensing behavior of probe could mimic the function of sequential logic circuit at molecular level. Paper strips have been developed by dipping the pieces of small cellolose paper into receptor solution and were then dried. They showed the analytical application of probe by detecting Cu^{+2}/F^{-} ions on paper strips and real contaminated water

samples.Paper strips changed its colour from fluorescent blue-green to deep blue (under UV light at 365 nm) upon addition of Cu^{+2} ions. Interestingly, when this strip was dipped into the solution of fluoride ion, the naked-eye sensitive color of the paper strip was regained from a deep blue to a fluorescent blue-green (under UV light at 365 nm). Limit of detection was found to be 1.60 ppb and 2.12 ppb for Cu^{+2} and F^- ions, respectively.

Two thiocarbonohydrazone receptors functionalized with coumarin derivatives, **13a-b** have been designed, synthesized and investigated for selective detection of fluoride ions by Sahu*et. al.* in 2016(**Figure 5**) [96]. Receptor **13a** displayed distinct colour change from colourless to pink and 20-fold fluorescent enhancement upon addition of fluoride ion. Receptor **13b** exhibited colour change from colourless to deep red and 5-folds fluorescence enhancement upon interaction with fluoride ion. Receptor **13a** and **b** showed absorption band at 342 and 379 nm, which decreased in intensity with simultaneous appearance of new bands at 546 and 542, respectively on interaction with fluoride ion. At lower concentrations of fluoride ion, 1:1 stoichiometry was observed, while at higher concentration, 1:2 binding was seen between receptor and fluoride ion. Authors provided insight into the nature of interaction by NMR titrations. Receptor **13a** demonstrated broadening and subsequent collapse of two NH signals at 9.76 and 10.41 ppm to a single broad peak at 10.17 ppm, which disappeared on addition of excess of fluoride ion (5 equivalents). This observation could be ascribed to initial hydrogen bonding formation, followed by deprotonation. Characteristic triplet at 16 ppm corresponding to the formation of HF_2^- ion through deprotonation was observed by authors.

Yeap*et. al.* synthesized chalcone based probe, **14**, containing coumarin and naphthol at both ends *via* aldol condensation [97] (**Scheme 4**).

Receptor, with coumarin unit as signalling unit and naphthol as binding unit, displayed high selectivity and sensitivity towards fluoride ion in acetonitrile. Authors studied anion binding properties by fluorescence spectroscopic titrations at excitation wavelength of 420 nm. Receptor exhibited an emission band at 524 nm, which upon addition of fluoride ion, showed enhancement in fluorescence intensity. Authors ascribed this interaction to internal charge transfer developed by deprotonation of OH from naphthol unit and formation of HF_2^- complex (**Scheme 5**).
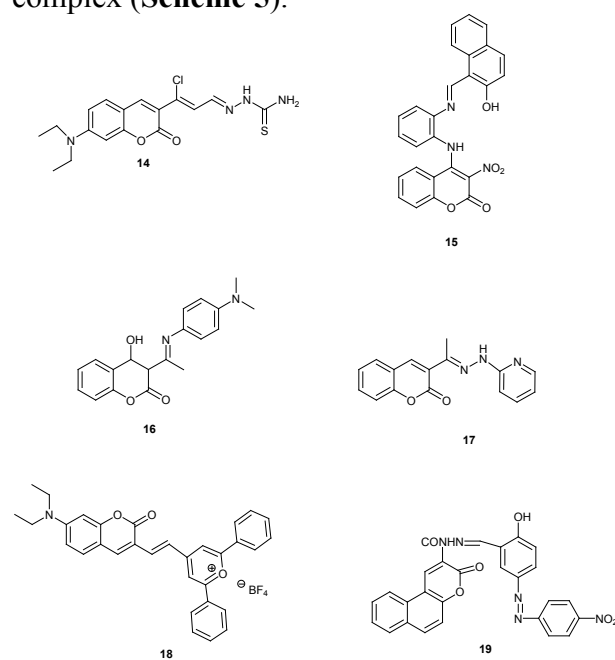
**Figure 6** Coumarin based naked eye receptors, **14-19**
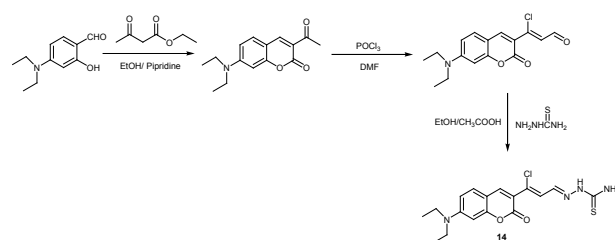
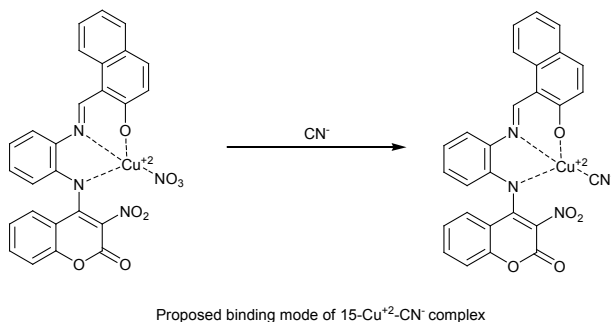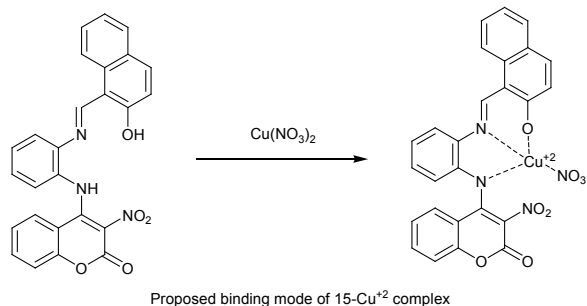**Scheme 4** Chalcone based probe, **14**
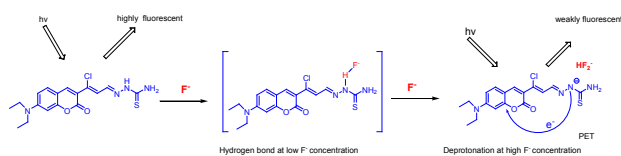
Scheme 5 Proposed binding model of 14 with fluoride ion

Kim *et. al.* designed assymetric coumarin-conjugated naphthol based chemosensor, **15** for sequential sensing of Cu^{+2} and CN^- ions in aqueous media (**Figure 6**) [98]. Chemosensor, (E)-4-((2-((2-hydroxynaphthalen-1-yl) methylene)amino)phenylamino)-3-nitro-2H-chromen-2-one, was synthesized by coupling of 4-((2-aminophenyl)amino)-3-nitro-2H-chromen-2-one and 2-hydroxy-1-naphthaldehyde with a 58% yield in absolute methanol (**Scheme 6**). Receptor exhibited naked eye colour change from orange to yellow in presence of Cu^{+2} ion. The receptor- Cu^{+2} could sense cyanide ion *via* naked eye colour change (**Scheme 7**) and in-depth UV-visible study was carried out by authors, where other anions, OAc^-, F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, N_3^- and SCN^- demonstrated almost no change in both UV-visible spectra and color of receptor- Cu^{+2} under the identical conditions. 1:1 stoichiometry between receptor-Cu^{+2} and CN^- was observed from Jobs plot and ESI-mass spectrometry analysis.
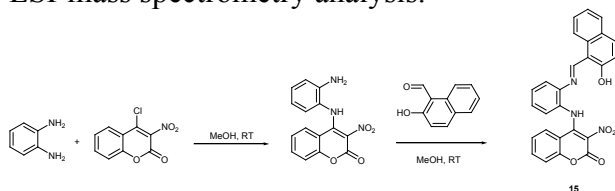
Scheme 6 Synthesis of chemosensor, (E)-4-((2-((2-hydroxynaphthalen-1-yl)methylene)amino) phenylamino)- 3-nitro-2H-chromen-2-one, **15**

Proposed binding mode of 15-Cu^{+2} complex


Proposed binding mode of 15-Cu^{+2}-CN^- complex

Scheme 7 Proposed binding mechanism of receptor **15**

Mondal *et. al.* developed coumarin based fluorescent turn-on chemosensor, **16** for HSO_4^- ions by economically cheap method involving Schiff base condensation of 3-acetyl-4-hydroxycoumarin and N,N'-dimethyl-p-phenylenediamine in 1:1 molar ratio in methanolic medium [99]. UV-visible spectra of receptor revealed absorbance bands at 321 and 369 nm. Upon gradual addition of HSO_4^- ions, absorbance band at 321 red shifted to 330 nm and band at 369 nm disappeared resulting in two distinct isosbestic points at 307 nm and 357 nm. Other anionic species could not trigger any spectral response upon addition. In the absence of external analyte, emission spectrum of receptor displayed weak band at 422 nm, when excited at 370 nm. Fluorescence intensity increased 17 folds and emission maxima blue shifted by 46 nm to yield new maxima centred at 376 nm. Jobs plot indicated 1:1 stoichiometry between receptor and HSO_4^-. This receptor also

showed fluorescence turn-on behaviour towards Zn^{+2} ions.

Mukherjee *et. al*. documented coumarin based luminescent chemosensor, **17** for Cu^{+2} and CN$^-$ ions in 2016 [100]. Receptor was prepared in a single step 1:1 condensation of 2- hydrazinopyridine with 3-acetylcoumarin (**Scheme 8**) and characterized by ^{1}H NMR, ^{13}C NMR, FTIR and Mass spectroscopic studies. Receptor worked for selective fluorescent recognition of Cu^{+2} inMeOH/H$_2$O (4:1, v/v at pH = 7.2 aqueous solution) medium with 1:1 binding stoichiometry. The in-situ Cu^{+2} complex thus prepared, showed high selectivity towards CN$^-$*via* Cu^{+2} displacement approach with detection limit in the micro molar range (Scheme 9).
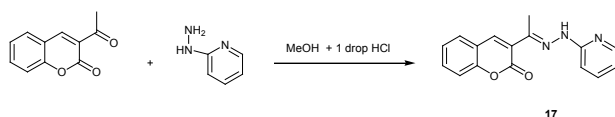

**Scheme 8** Synthesis of coumarin based luminescent chemosensor, **17**
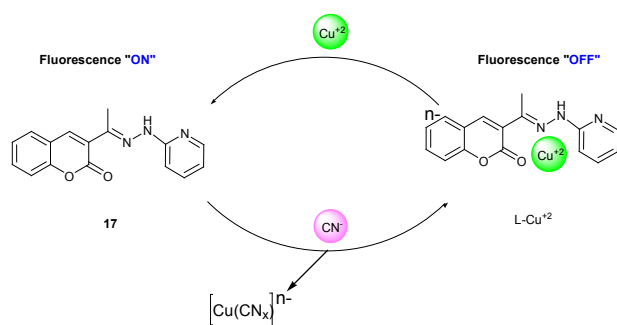
Scheme 9 Proposed binding model for fluorescence response of **17**-Cu^{+2} with fluoride ion

A pyrylium–coumarin dyad, **18** was synthesized and reported by Shiraishi *et. al*. in 2016 for ratiometric colorimetric sensing of cyanide ion in aqueous media (9:1 acetonitrile-water) (**Scheme 10**) [101]. Receptor displayed long-wavelength absorption band at 643 nm

in UV-visible spectrum due to the strong intramolecular charge transfer (ICT) from the diethylaminocoumarin to pyrylium moiety. Addition of cyanide ion into receptor solution triggered ring cleavage within 8 minutes, which suppressed the ICT phenomenon (Scheme 11). This resulted in the appearance of new band at 472 nm assigned to π to π* transition of the diethylaminocoumarin moiety itself, with decrease in intensity of band at 643 nm. Limit of detection of receptor for cyanide ion was found as low as 8 µM by authors.
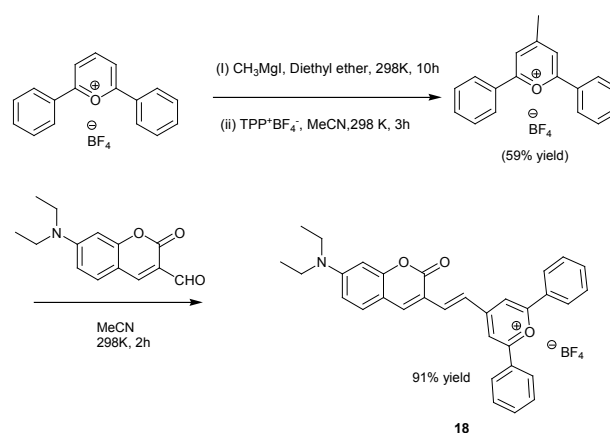

Scheme 10. Synthesis of pyrylium–coumarin dyad, **18**
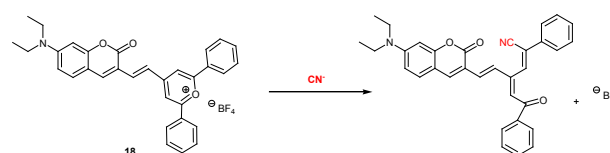
Scheme 11 Proposed mechanism of nucleophilic addition to receptor **18**

Zhao *et. al*. synthesized coumarin based receptor, **19** by using phenprocoumon containing acyl hydrazine and p-nitro azo salicyladehyde(**Scheme 12**) [102]. Authors designed receptor with nitro moiety as signaling group and phenolic hydroxyl moiety as anion binding site. They carried out anion recognition properties in the presence of OAc$^-$, F$^-$, OH$^-$, Cl$^-$, Br$^-$, I$^-$ and H$_2$PO$_4^-$. Addition of OAc$^-$, F$^-$, OH$^-$ and H$_2$PO$_4^-$ in DMSO into the receptor solution caused change in colour of

receptor from yellow to blue. In UV-visible spectrum, receptor displayed absorbance band at 383 nm, which upon addition of OAc^-, F^-, OH^- and $H_2PO_4^-$ showed a red shift in maxima and a new absorbance band centred at 598 nm was formed. An isobestic point at 439 nm was observed by authors indicative of formation of fixed stoichiometry between receptor and anion. Selectivity of receptor for anions followed order: $OAc^- > F^- > OH^- > H_2PO_4^-$, which authors attributed to guest basicity and shape complementarity between host and anionic guests (**Scheme 13**). Fluorescence emission spectrum of receptor displayed two weak emission bands at 413 and 663 nm. Upon addition of these anions, intensity of band at 413 nm increased and intensity of band at 663 nm decreased and gradually disappeared. Authors concluded that addition of these anions elicited visible decrease in fluorescence intensity due to quenching PET process from –OH or –NH group to –NO_2 group.
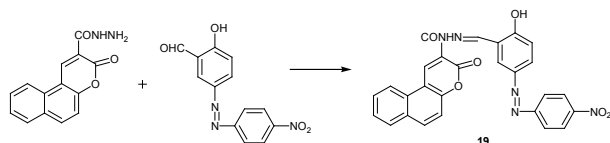
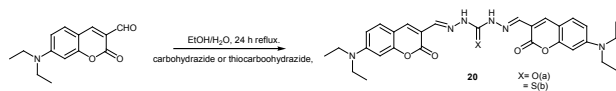**Scheme 12** Synthesis of coumarin based receptor **19**
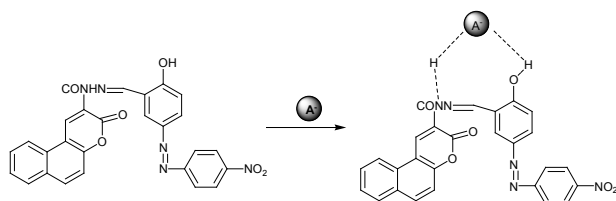
**Scheme. 13** Proposed binding model of **19** with anions
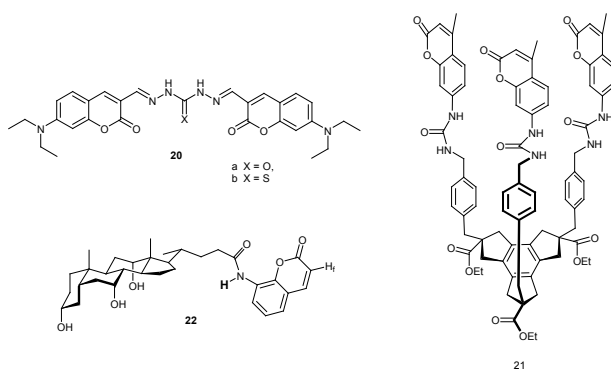
Figure 7 Coumarin based naked eye receptors, **20-22**

Coumarinthiocarbohydrazone (**20a**) and coumarincarbohydrazone(**20b**) were developed and reported by Singh *et. al* in 2016 for fluoride ion detection in $CH_3CN/DMSO$ media(**Scheme 14**) [103]. Receptor **20a** exhibited specific selectivity and sensitivity for fluoride ion over other anions *via* naked eye colour change and fluorescence ON-OFF-ON fluorescence response. Authors carried out UV-visible spectroscopic titrations in CH_3CN containing 0.25 % DMSO. Receptor **20a** showed absorption band at 448 nm, corroponding to n-π* transition and at 278 nm, corresponding to π-π* transition. Receptor **20b** showed absorbance bands at 446 and 275 nm. Fluoride ion produced light brown colour in both receptors, while other anionic species failed to induce any response. In UV-visible spectra of receptor a, addition of fluoride ion induced decrease in intensity of 448 nm and maxima shifted slightly towards longer wavelength. Fluorescence spectra of receptor **20a** consisted of emission maxima centred at 516 nm, when excited at 450 nm. Addition of fluoride ion caused quenching in emission intensity by 70% (switched off). Authors attributed the quenching phenomenon to the formation of hydrogen bonding between receptor and fluoride ion. Further addition of fluoride ion, emission band slightly blue shifted by 20 nm and intensity of new band increased (switched on), which occurred due to formation

of deprotonation species (**Scheme 15**). Detection limit was found to be 9.2 µM. In case of receptor **20b**, fluorescence intensity decreased by only 18% upon addition of fluoride ion. Both receptors established 1:1 stoichiometric ratio with fluoride ion, as observed by authors from Jobs plot.

**Scheme 14** Synthesis of Coumarinthiocarbohydrazone, **20a** and coumarincarbohydrazone, **20b**
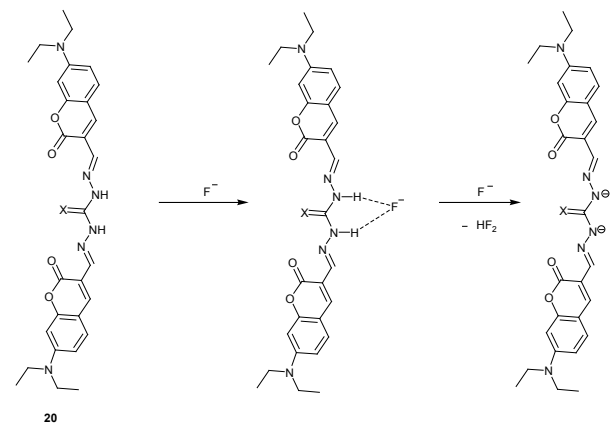
Scheme 15 Proposed binding mechanism of receptor **20** with fluoride ion

Choi and coworkers developed C_3V-symmetric tris(coumarin-urea) anion receptor, **21** from trindane based tripodal scaffold for detection of $H_2PO_4^-$ and F^- ions (**Figure 7**) [104]. Receptor with urea group as recognition unit and coumarin as signaling unit naked-eye detectable turn-on fluorescence selectively in the presence of $H_2PO_4^-$ and F^- ions in CH_3CN. The colourless solution of receptor displayed maxima at 332 nm, which was red shifted by 5 nm, upon addition of anions, to form a new band at 337 nm. Addition of anions resulted in red shift of emission maxima of receptor into visible region 415 nm, naked eye detectable under UV lamp (365 nm). ^{1}H NMR titration experiments indicated towards the formation of a hydrogen bonded 1:1 caviplex receptor-$H_2PO_4^-$, whereas

F^- ion, being more basic anion, induced the deprotonation of urea-NH protons.

Neutral cholic acid-coumarin conjugate, **22** was synthesized and reported by Li *et. al.* in 2015 for anion recognition by cooperative coumarin C-H and adjoining amide N-H fragments (**Figure 7, 8**) [105]. Receptor was synthesized by reaction of monomers cholic acid and 7-amino-coumarin with N-hydroxybenzotriazole (HOBt), o-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (HBTU) and N,N'-diisopropylethylamine (DIEA) in dry DMF at room temperature in a yield of 78%. UV-visible spectra of receptor consisted of absorption band centred at 345 nm, which decresed slightly in intensity upon addition of anions ($H_2PO_4^-$, F^-, Cl^-, Br^-), with red shift in band towards 356 nm. Fluorescence emission spectra of receptor showed maxima at 380-510 nm upon excitation at wavelength 345 nm. Addition of $H_2PO_4^-$ resulted in enhanced fluorescence emission at 452 nm. Authors claimed that excellent biocompatibility of receptor makes it an efficient and non-destructive probe for anion detection in living cells.
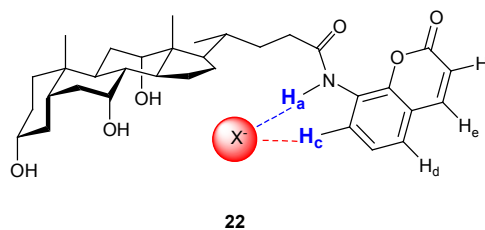
Figure 8 Binding model cholic acid-coumarin conjugate, **21** with anions

Conclusion

The review sums up the coumarin derivatives as naked eye receptors documented so far, rely on signaling-binding unit approach, which exhibited colour changes on deprotonation by highly basic anions. Naked eye sensing is commendable with respect to real-life application. The remarkable progress has been

achieved in developing coumarin derivatives as naked eye receptors. Use of coumarin also imparted interesting photophysical properties to receptor systems to achieve naked eye sensing.The incorporation of hydrogen binding moieties, urea/thiourea and amide have been attempted to create hybrids. However, the key issues appeared are interference amongst related basic anions and receptor functioning in aqueous media, which are pre-requisites for practical purpose. It remains a challenge to develop receptors in 100% aqueous media i.e. water.

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