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Synthesis of Coumarin Based Chemo-Sensors for the Detection of CN^- Ions

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Abstract

In the modern day, chemistry governs the very essence of life on a sub-atomic level from simple toothpaste to life-saving drugs, we depend on the chemicals that constitute the very essence of existence itself. Therefore, the detection and study of these chemicals recognized as an absolute necessity because along with pros comes the cons, i.e., the toxicity & the notorious side effects of the very same chemicals. Thus, certain compounds called 'Chemo-sensors' specialise in trapping target chemical entities which could be separated later or create specific fluorescent lights, making them visible to the naked eye. One such type of 'fluorescent chemo-sensor is the family of chemicals called Coumarins. From the topic, we come across the family of Coumarins that can help detect the Cyanide ions (CN^-) following the mechanism involving nucleophilic addition and intermolecular charge transfer (ICT), resulting in high fluorescence.

Keywords: Coumarin, Cyanide, probe, ratiometric.

Introduction

In modern times where chemistry is applied to each and every sphere of life, various chemical compounds, despite having severe toxic traits are used in the important chemical reactions related to our daily life, thereby making procedures like molecular sensing, probing and imaging with luminophores, chromophores and other indicators a major topic of interest in the field of analytical as well as supramolecular chemistry. The very large family of compounds containing 1-benzopyran-2-one motif called the Coumarins (Perkin, 1868) have proven to be the best of these chemosensors, majorly due to its variety of unique biological and photophysical properties (Mantulin and Song, 1973). The high quantum yielding fluorescent properties have gained much attention due to the exceptional stability and biological compatibility they possess.

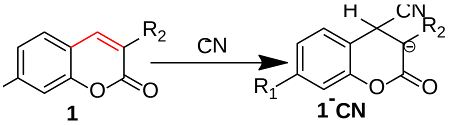

Fig. 1. The reaction of CN$^-$ with Coumarin.

Various cations and anions are responsible for the life of organisms, so much so that the slightest change in the ratio of these elements can lead to serious complications to the organism. Such a chemical compound is Cyanide ion (CN$^-$) with a permissible limit of 0.07 mg/l i.e., 2.7 µM in drinking water (Herschy, 2012). It is considered the most baleful compound, from electroplating, resin industries, metallurgy, and gold mining (Timofeyenko et al., 2007). Nevertheless, its highly toxic and harmful nature is not something to be taken lightly as it adversely affects both flora and fauna of the environment and is perhaps the most intriguing compound with an absolute necessity for detection (Xu et al., 2010). The stereochemical behaviour of a simple intramolecular charge transfer probe is primarily dependent on the nucleophilic addition of coumarins at specific locations (Kaushik et al., 2016) or displacement processes by Cu ions.

Fluorescent Coumarin based Chemosensors for Cyanide ion obtained via- Nucleophilic addition to 4-position of the Coumarin group

Because the 4-position of coumarin and its derivatives has a solid electronic partial charge, it acts as a good electrophile, resulting in a strong Michael type nucleophilic addition reaction with CN-. This causes a decrease in moity planarity and disrupts intra-molecular charge transfer (ICT) through the coumarin backbone, resulting in a spectral blue shift as well as a significant change in the moity. Few major examples are as follows:

Sun et al., synthesized compounds **2** and **3** which are doubly activated Michael acceptors purposed to sensitively select CN$^-$ (Sun et al., 2012).

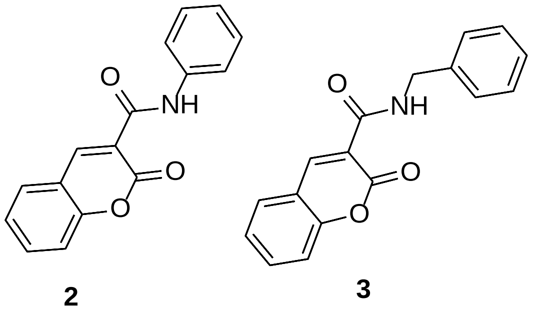

Fig. 2. Structure of the compounds proposed by Cao's group.

The following scheme provides the synthetic way of forming compounds 2 and 3 to finished products **2-CN** and **3-CN**. These can be easily prepared by reacting coumarin-3-carboxylic acid with the right amide and under mild circumstances (Barnes et al., 1978).

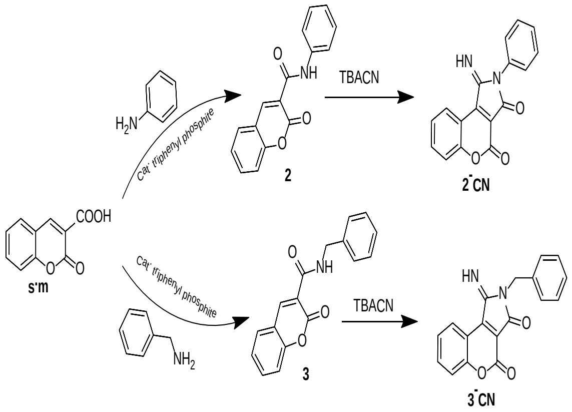

Fig. 3. The reaction mechanism of synthesis.

A plausible addition reaction of cyanide ion with the probe has been suggested as well (Hamilakis and Tsolomitis, 2003).

The ^{1}HNMR of the original compounds explains that they undergo nucleophilic addition with cyanide ion and then internal cyclization regaining aromaticity. The final intra-molecular cyclization occurs through a proton transfer, thus completing the reaction, which results in ratiometric absorbance (Demas and Crosby, 1971) and a blue-shift from 332 to 298 nm for compound **1** and 292 to 270 nm for compound **2** (Dong et al., 2012).

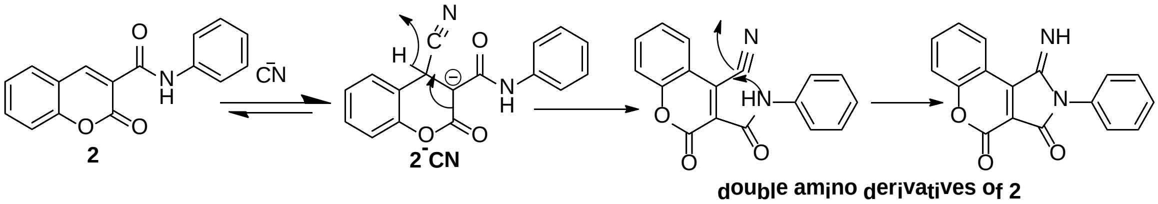

Fig. 4. A possible mechanism involving compound 2.

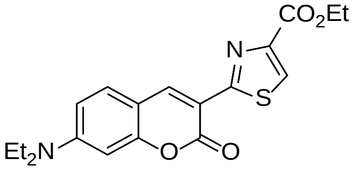

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Fig. 5. Structure of the coumarin-thiazole compound.

Kim's group discovered a coumarin-thiazole chemical 4 as a cyanide ion chemoreceptor with a similar mechanism.

As suggested by Kim's group (Park and Kim, 2012), compound **4** is prepared via the reaction of 3-cyano coumarin and sodium ethoxide in a dry ethanol medium at room temperature for later L-cystine ethyl ester hydrochloride was added and was refluxed overnight. After cooling down, the resulting ethanol solution was concentrated in vacuum and purified by flash chromatography (1 : 3 = acetone : hexane), resulting in an orange solid.

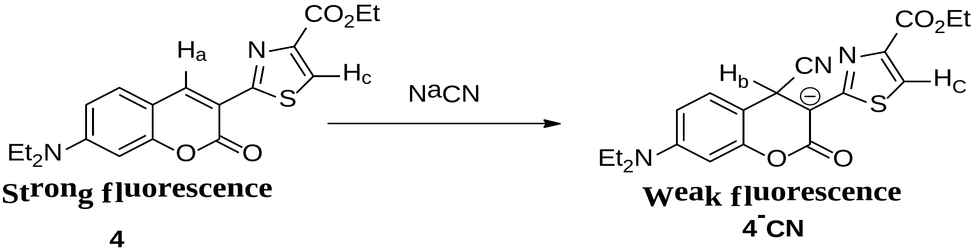


Fig. 6. The reaction of probe 4 with CN$^-$.

To prepare the cyanide derivative, sodium cyanide in heavy water was added to a solution of the probe in DMSO medium. The resulting clear solution was then subjected to

^{1}H NMR (Kim and Kim, 2010).

Long et al., reported two compounds **5 & 6** for the detection of endogenous cyanide with the help of similar transient 4-position coumarin intermediates. In addition, they exhibit little fluorescent due to ICT (Fukuhara, 2020) process occurring from coumarin ring to pyridyl vinyl ketone.

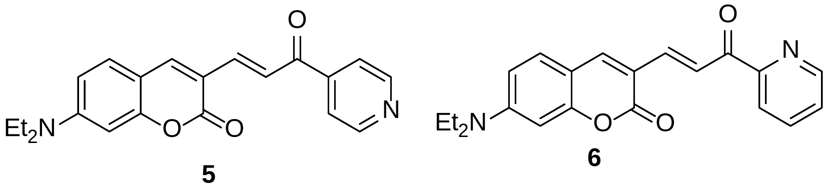


Fig.7. Structures of pyridyl vinyl ketone derivatives of coumarin.

A rational design of the probe has been suggested as well (Long et al., 2018). A (green coloured) 7-diethylamino coumarin dye was used as a fluorophore, while a (pink coloured) 1-mythelene pyrrolidinium is used as the reaction based recognition site for detection of endogenous HCN.

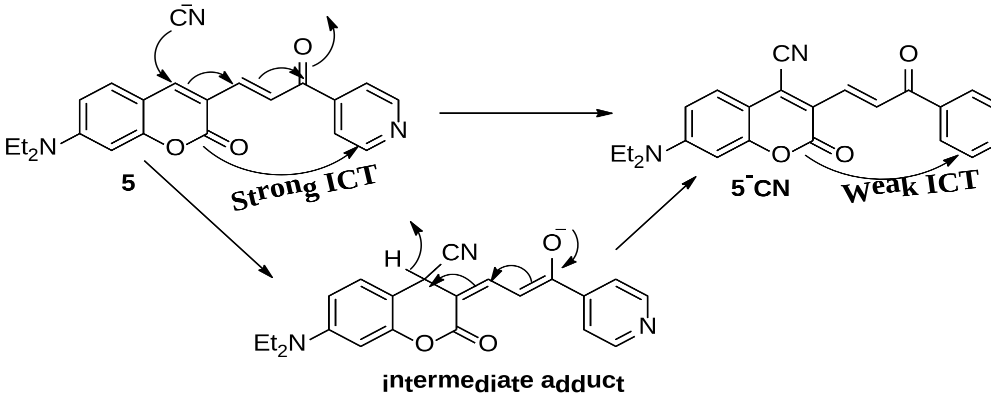
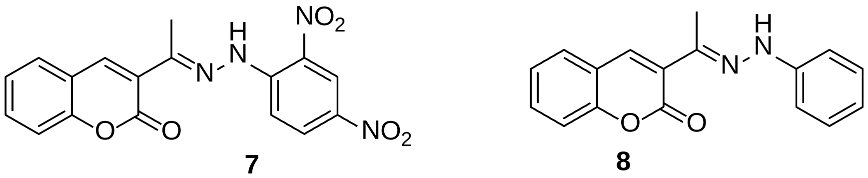


Fig. 8. A mechanism involving compound 5.

The phospho-fluroscent ability of the compounds are tested in potassium phosphate buffer/acetonitrile, where the initial emission at 599nm gradually decreased with the addition of HCN to 490 nm.

Razi and his group (Razi et al., 2014) introduced two new coumarin derivatives (compounds **7** & **8**) as a turn-on fluorescent probe to recognize cyanide ions in a fully aqueous medium. Although showing very low quantum fluorescent yield ($\Phi6=0.0023$, $\Phi7=0.0012$), after the addition of CN^- there is a substantial increase in fluorescent ($\Phi6\text{-}CN=0.022$, $\Phi7\text{-}CN=0.024$).



7 **8**

Fig.9. Structures of amino derivatives of coumarin probe by Long's group.

Here a planar intra-molecular structure is developed due to the Michael type addition of cyanide ion (CN$^-$) to 4-position of the coumarin group leading to an improvement in ICT.

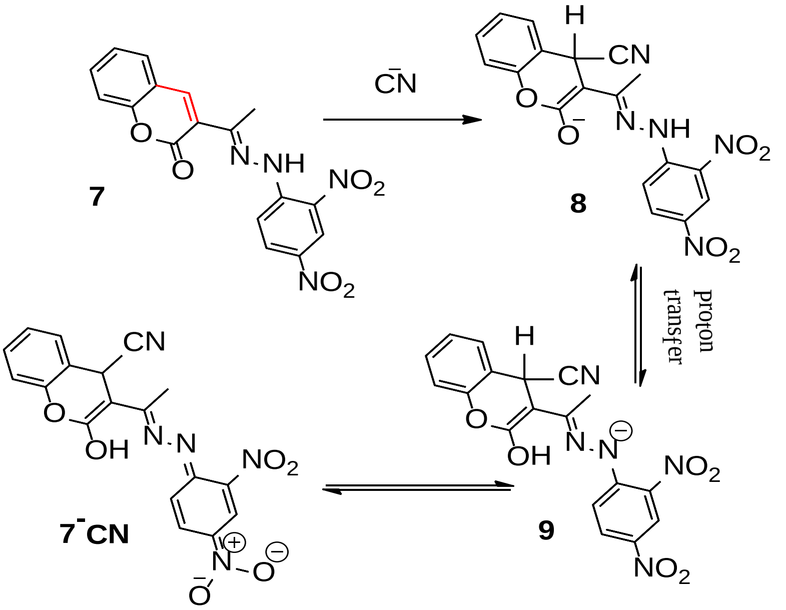


Fig. 10. Mechanism involving compound 7.

Nucleophilic addition of CN$^-$ to C=C/C=N in conjugated bridge

Coumarin derivatives possess a polarized C=C or C=N are highly susceptible to nucleophilic attacks, which may disrupt the elongated π-conjugations and thus letting the exhibits only show the core coumarin properties. The following examples are notable Li and coworkers developed a highly sensitive and selective chemodosimetric probe as a novel cyanide detecting site, a coumarin-malonitrile **compound 10.**

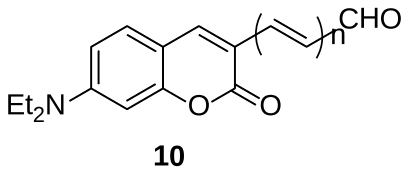


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Fig. 11. Structure of coumarin-malonitrile probe-10.

Cyanide derivative of **10** is prepared by the reaction of the said probe with Bu_4CN in acetonitrile, thereby giving almost 85% yield. The probe was previously prepared by condensation of coumarinyl aldehyde with Meldrum's acid (Dumas et al., 2007) in piperdium acetate giving about 78-80% yield.

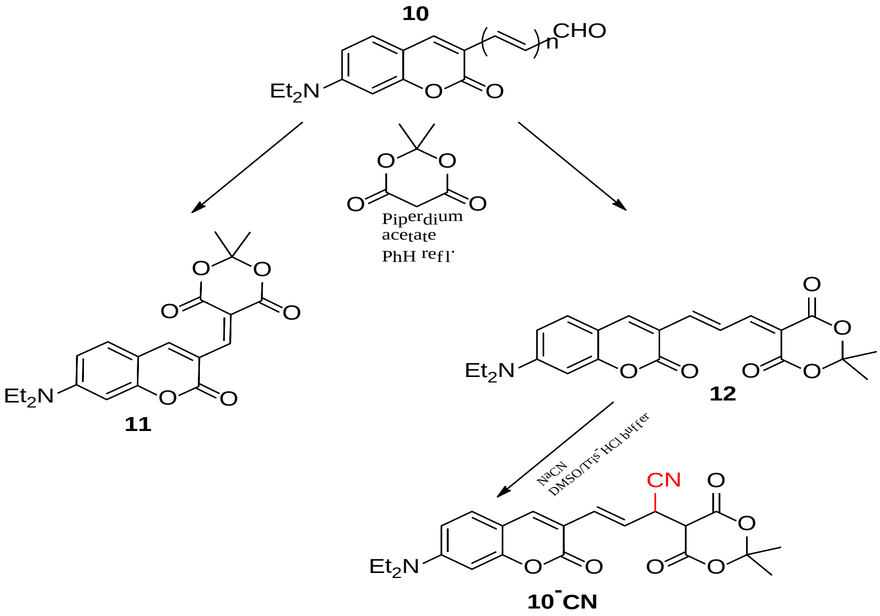

Fig. 12. Synthesis mechanism of 10-CN.

Probe shows photophysical properties wherein CN^- the fluorescence drops a significant amount gradually at 551 nm with a concomitant increase at 415 nm, inducing a sharp colour conversion from dark amaranth to pale yellow., which implies the demolition of huge conjugation.

Xiong's group (Xiong et al., 2015) independently discovered a similar coumarin-Meldrum derivative compound **13.**

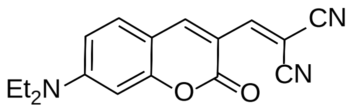

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Fig. 13. Structure of the coumarin-Meldrum probe.

This probe has three distinct sites for chemodosimetric selective detection of CN^-. 2-[(7-(Diethyl amino)-2-oxo-2H-chromen-3-yl)-methylene] malonitrileis prepared when under dry argon atmosphere by refluxing aldehyde-coumarin and malononitrile together in ethanol overnight with Et_3N as a catalyst. The experiment is conducted under room temperature and the removal of solvent was performed under reduced pressure and further purification was performed by silica gel chromatography petroleum ether.

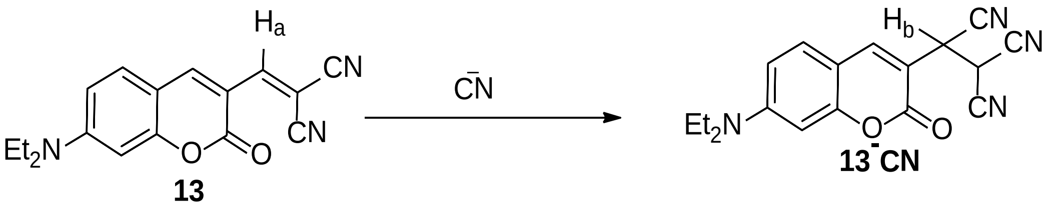

Fig. 14. Reaction of compound 13.

Fluorescent properties of compound **9** have high perseverance for cyanide ion and good aqueous solubility, where maximum excitation frequency was observed at 520 nm, which shifted to 415 nm due to the addition of excess CN ions. Zhang and coworkers (Zhang et al., year) discovered another coumarin derivative as a means of ratiometric cyanide detection.

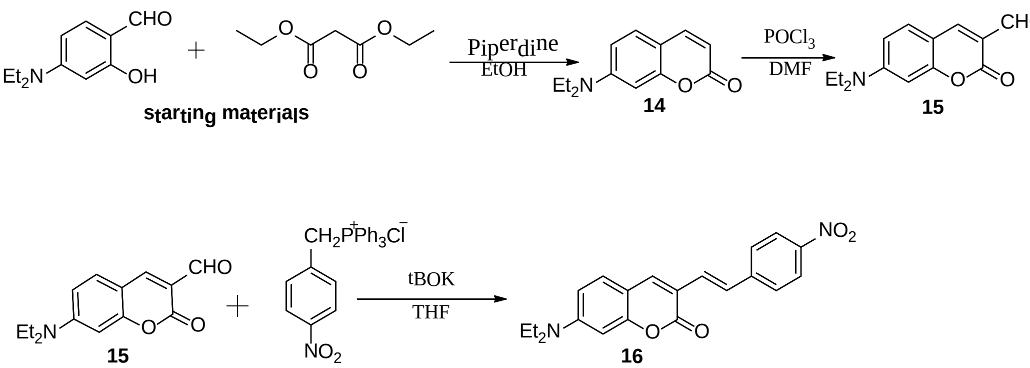

Fig. 15. Nitro based coumarin derivative compound and its synthesis mechanism.

Li et al., 2014 suggested the synthesis mechanism of coumarin compound **16** following the above mechanism.

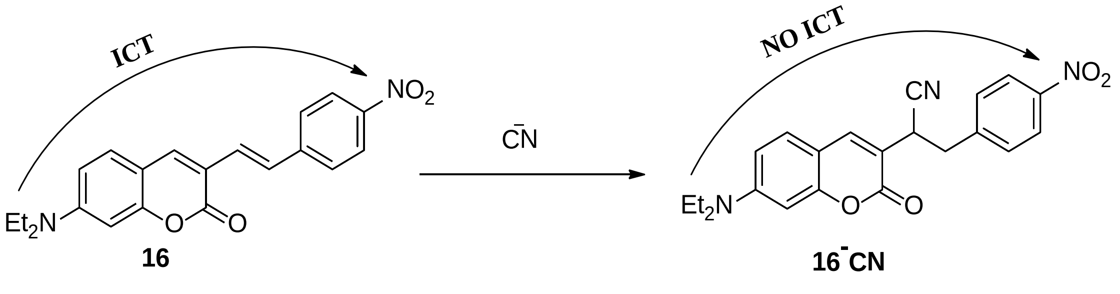

Fig. 16. Fluorescence change of compound 16 during reaction.

Similarly, Davis et al., 2014 proposed a coumarin-enamine scaffold for selective detection of CN^-.

Compound **17** exists as a blend of E & Z isomers independently in 1:3 ratios (Traven et al., 2010). Tautomeric transformations are also viable. However, E & Z isomers were the only ones observed in the solution. E isomer of compound **17** is prepared by heating a concentrated compound **17** in DMSO, and allowed to stand for several days. DMSO is, although considered to be a competitive solvent often hindering hydrogen bond formations, yet E-isomer of **17** consists of 2 sets of bifurcated C-H…O interactions.

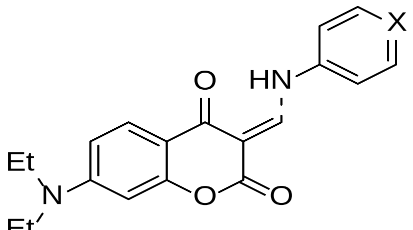

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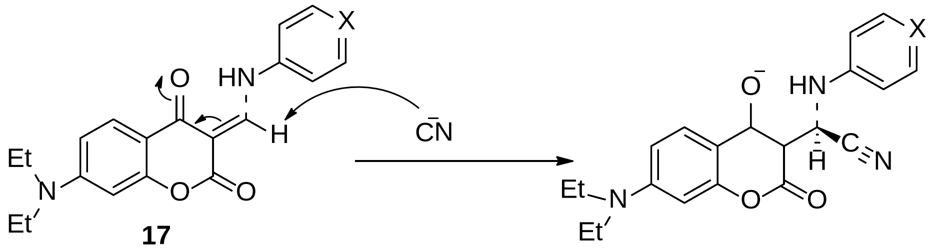
Fig. 17. Structure of the coumarin-enamine compound.

Relying on the polarity of the solvent, compound **17** gets influenced differently leading to a unique, abnormal photo-physical property (Nad and Pal, 2003 ; Cigáň et al., 2013).



17 **17^-CN**

Fig. 18. A mechanism involving compound 17.

Nucleophilic addition of CN^- to C=N/C-N bond of heterocyclic pendants conjugated to coumarin

The C=N/C-N bonds conjugated to the benzothiazole and in dolium (Aksungur et al., 2017) salts bear heavy positive partial charges and are rather susceptible to nucleophilic addition through Michael addition by CN^- ion. As a result, charged compounds' transformation to neutral compounds occurs, causing a blue shift due to ICT reduction.

Yang et al., 2012 developed a coumarin-hemicyanin probe for ratiometric and colourimetric detection of cyanide ion.

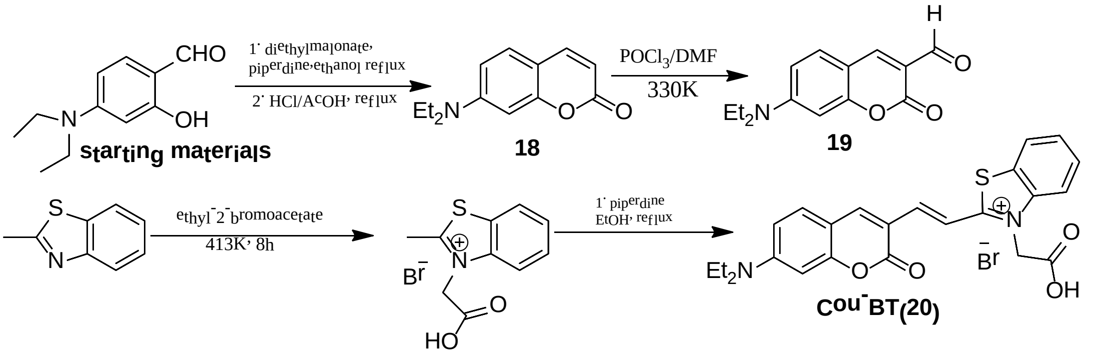


Fig. 19. Cou-BT and synthesis mechanism.

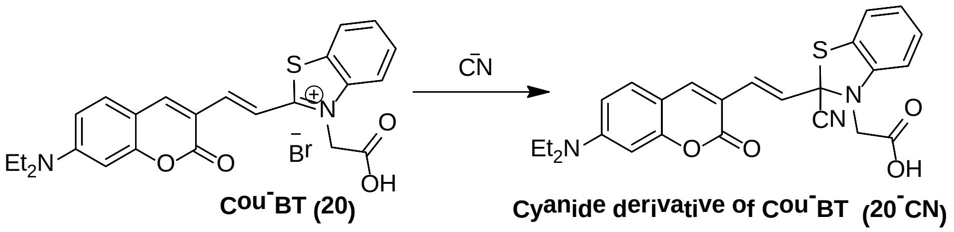


Fig. 20. Addition reaction of the probe.

The above diagrams are the suggested synthetic mechanism of Cou-BT and the addition reaction performed by the probe (Richard et al., 2008 ; Yuan et al., 2010).

Shiraishi et al., 2014 studied the varied influences of additional electron-withdrawing and electron-donating to the in dolium moiety of the coumarin-indolium complexes. Each showed a varied affinity for cyanide ion in basic medium with 30% ACN, as spirogyran (Shiraishi et al., 2011) derived dyes facilitate srulpulous and reactive flurometric identification of cyanide ion under UV irradiation.

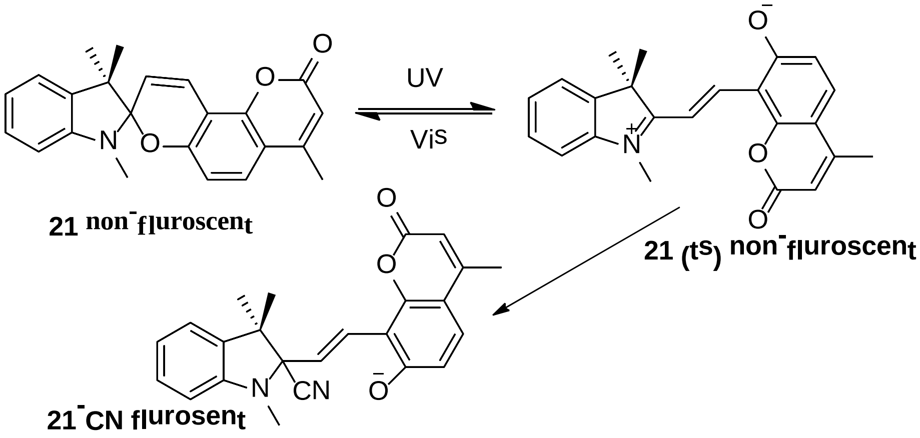


Fig. 21. Coumarin indolium compound and its addition reaction with cyanide.

Xiong et al., 2015 synthesized julolidine type analogues which shows identical photophysical behaviours as compound **22**.

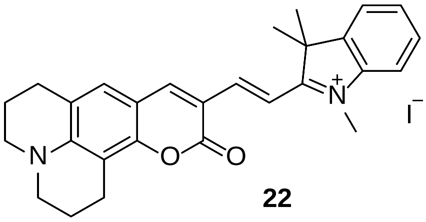


Fig. 22. Coumarin-julolidine compound.

The above compound was synthesized via the condensation of 1-methyl-2,3,3-trimethyl-3H-indolium (Isaad and El-Achari, 2011) and coumarin aldehyde in ethanol and refluxed for approximately 14 hours. The solid was accumulated and cleansed with anhydrous ethanol and dried to resultant bluish-violet solid.

For the concoction of the cyanide derivatives, the probe solution was made in methanol and also in de-ionized water. Cyanide solution was composed by dissolving KCN in de-ionized water. Fluoresce spectra was conducted with a slit of width 5nm (λ_{ex}=400nm); the spectra were calculated from 425-600 nm with an excitation at 400 nm in HEPES (pH=9.3) buffer/ CH_3OH (v/v 1:1). Various other halogens and anions were also tested although they triggered very minute changes but in the presence of 1 equivalent CN^- there was a tremendous increase in fluorescing with colour changing from blue to green (Martínez-Máñez and Sancenón, 2003).

Copper Complex displacement reaction:

Cyanide ion shows high binding affinity for transition metal complex like of Cu^{2+} (Noipa, Tuntulani, and Ngeontae 2013), which originally are non-emissive due to high PET effect. Therefore, by performing displacement reaction high fluorescence (Chen and Rosenzweig, 2002) can be observed which becomes the basis of several chemosensors.

Lee's group (Lim and Lee 2016) reported a coumarin fluorophore decorated peptoid (Maayan and Kirshenbaum 2009; Fowler and Blackwell, 2009; Holub et al., 2006) based Cu^{2+} complex probe which exhibits clear fluorescence dousing response to Cu^{2+} in aprotic solvents like DMSO and DMF and to a marginal level in methanol.

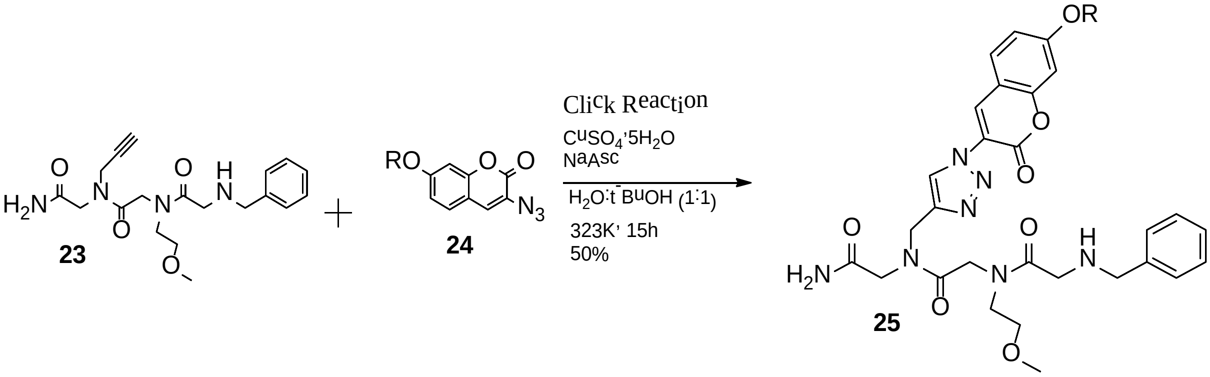


Fig. 23. Coumarin-peptoid based-compound and its synthesis mechanism.

Kaushik et al., 2016 implemented copper complex of natural product aesculetin (6, 7-dihydroxycoumarin) as a cyanide detector in DMSO (1% solution) as well as mouse serum. The probe showed high efficiency phospho fluorescence in presence of various cations like Zn^{2+}, Fe^{3+} and Pb^{2+}. But Cu^{2+} was the highest with 13-fold increase in fluorescence at 495 nm (Wang et al., 2014 ; 'Jeong et al., 2012 ; Cho and Sessler, 2009).

Additional sensing reactions

Kim et al., (Kim et al., 2016) proposed detection of cyanide ion via the use of CN^- catalysed 2-hydroxycinnamate to coumarin reaction in a 5% ACN buffer.

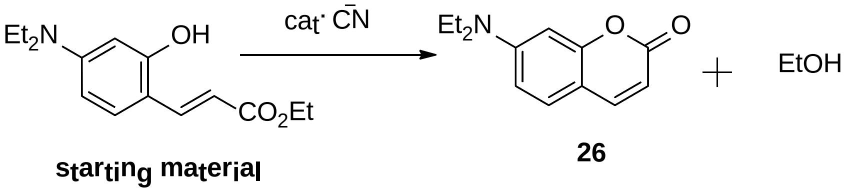


Fig. 24. A mechanism involving synthesis of the coumarin-hydroxy cinnamate compound.

A solution of **compound 26** and Bu_4NCN in CH_2Cl_2 and EtOH was stirred at room temperature for 8 h and monitored by TLC for completion, purification of the crude product was done via column chromatography on silica gel using ethyl acetate and CH_2Cl_2 (1:2, v/v) as an solvent, giving the required product.

The probe showed dramatic enhancement in fluorescence at 453 nm (Hong et al., 2009; Hong and Kim, 2013).

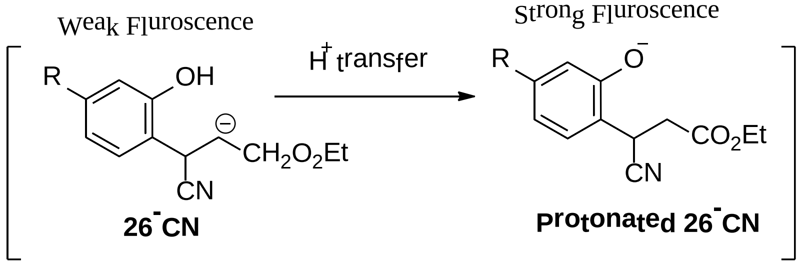


Fig. 25. Reason of fluorescence.

Tarafdar and coworkers (Tarafdar et al., 2017) reported three coumarin-based urea-amide scaffold compounds. Compound **29** shows bright yellow fluorescence turn-on retalliation to CN- with high electivity (Marcus, 1994). The mechanism put forward contains many deprotonation steps, followed by a nucleophilic addition and ring-opening of the coumarin lactone.

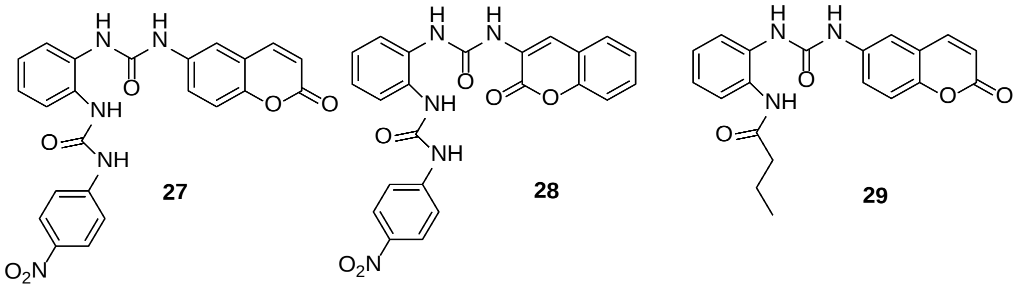


Fig. 26. Coumarin based urea-amide scaffold compounds were proposed by Tarafdar et al., 2017.

Synthesis of the above compounds provided by Tarafdar et al., 2017 as follows,

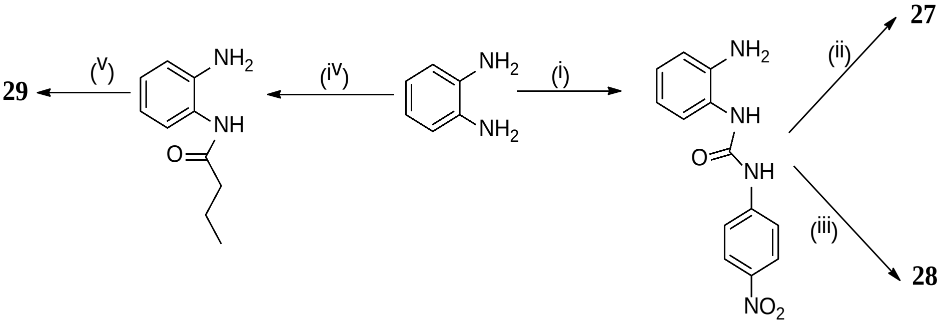


Fig. 27. Reagents used in the given mechanistic diagram: (i) *p*-nitroaniline, triphosgene, Et_3N, dry CH_2Cl_2 stirred for 7 h (ii) 6-amino-coumarin, triphosgene, Et_3N, dry CH_2Cl_2, stirred for 8 h (iii) 3-aminocoumarin, triphosgene, Et_3N, dry CH_2Cl_2, stirred for 10 h (iv) butyryl chloride, dry Et_3N, dry CH_2Cl_2, stirred for 6 h (v) 3-amino coumarin, triphosgene, Et_3N, dry CH_2Cl_2, stirred 8 h.

Conclusion

Coumarins have been widely used as chemosensors to detect various analytes, including inorganic anions, metal cations, reactive oxygen, sulphur, or nitrogen species, tiny physiologically active molecules, and fatal toxic cyanides, as discussed above. Most of the time, the coumarin serves as a fluorescent molecule linked to a recognition unit, however, there are a few instances of sensing mechanisms in which the coumarin skeleton plays a role in the reactivity or selectivity via different processes that are discussed in this study. Coumarin has developed as a powerful and versatile platform in recent years, and we anticipate a bright future for this fluoro-phore in the area of fluorescence sensing.

Acknowledgement

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