ISSN: 1410-8917
e-ISSN: 2597-9914

Jurnal Kimia Sains dan Aplikasi 25 (2) (2022): 63–70

Jurnal Kimia Sains dan Aplikasi
Journal of Scientific and Applied Chemistry

Journal homepage: http://ejournal.undip.ac.id/index.php/ksa

Synthesis of Dansyl Cyclen and Preliminary Study of Its Fluorescent Properties

La Ode Kadidae [a,*], Ruslin [b], Thamrin Azis [a], La Aba [c], Laode Abdul Kadir [a]

[a] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Halu Oleo University, Kendari, Indonesia
[b] Department of Pharmacy, Faculty of Pharmacy, Halu Oleo University, Kendari, Indonesia
[c] Department of Physics, Faculty of Mathematics and Natural Sciences, Halu Oleo University, Kendari, Indonesia

*Corresponding author: laode.kadidae@uho.ac.id

https://doi.org/10.14710/jksa.25.2.63-70

Article Info

Article history:

Received: 19th November 2021
Revised: 20th February 2022
Accepted: 24th February 2022
Online: 28th February 2022

Keywords:
Synthesis; dansyl cyclen; fluorophore; chemical sensor

Abstract

The synthesis of a dansyl cyclen-based compound as a potential chemical sensor has been carried out. The initial study of its fluorescent properties has also been conducted. This study aims to synthesize a cyclen-based compound comprising three identical pendant arms and another different arm carrying a dansyl fluorophore. Producing these heterogenous pendant arms, a-three pendant arm cyclen **9** was reacted with dansyl aziridine **10**. The synthesis products were characterized using ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. In addition, a Fluorescent Spectrophotometer has been used to assess the fluorescent intensity changes of the synthetic ligand in a range of pH 2–13 and when it was titrated with some metal ions. Based on the results of characterization with ^{13}C NMR for compound **2** and additional characterization with IR and elemental analysis for its hydrochloric form **11**, it is wisely said that the proposed compound has been successfully synthesized, giving 66% yield as viscous brown oil **2**. Moreover, the fluorescent property showed that the higher the pH employed, the higher the fluorescent intensity observed. Meanwhile, the addition of some cationic metals revealed that cadmium (II) gave the highest increase in the fluorescent intensities among other cationic metals.

1. Introduction

The development of chemical sensors has been quite remarkable during the last few decades. Many studies have been conducted and recently reported related to this field, for instance, Wahyuni *et al.*, who investigated uric acid sensor [1]. Nonetheless, the field of chemical sensor is very broad. Tetraazamacrocycles have been the subject of many research groups to study and design to create a class of molecular receptors [2]. Successful development of molecular receptor complexes, such as **1** by Smith [3], has enabled the evolution in the synthesis of a new generation of analogous cyclen-based receptor complexes. Evidence from **1** that four identical pendant arms N-bonded constructs it to the cyclen framework. Therefore, the methodology responsible for its synthesis is quite simple.

Meanwhile, synthesizing a new generation of four pendant-armed receptors incorporating three identical pendant arms and a different fourth pendant arm is quite challenging because a significant synthetic effort dealing with N-protection and deprotection steps is required. Bradbury [4] has reported that an anthracene moiety has been included to replace one of the pendant arms of the Smith [3] compound. In addition, Hodyl [5] has also reported a similar compound as Bradbury [4], but instead of using anthracene as the substituent, he attached a silica moiety. Inspired by Bradbury [4] and Hodyl [5], the current study also addresses this issue. The mainframe of the current study was to replace one of the pendant arms of **1** with a functional group bearing a fluorescent agent, in this case, a dansyl moiety, to produce a molecular ligand **2**, as depicted in Figure 1. Dansyl group has been commonly utilized as fluorescence signals in chemical sensors [6], Gu [7], Omer [8], and Kim [9].

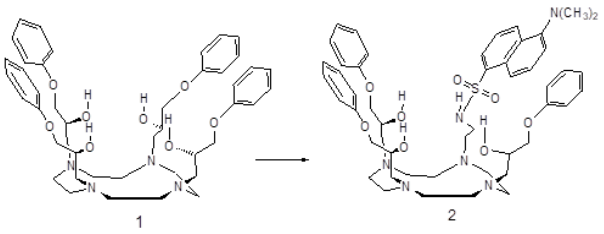

Figure 1. Molecular receptor ligands

Nonetheless, to the best of our knowledge, the synthesis of dansyl cyclen-based receptors and the study of their fluorescent properties have not been reported. Due to the presence of the dansyl group, it was expected that the synthesized compound would be the potential for being a molecular fluorescent sensor. This report focuses on the synthesis of the free receptor ligand **2**; secondly, the assessment of the fluorescence emission intensity of the free ligand against a range of pH and the fluorescent emission of the free ligand on its own and with the addition of metals.

This study proposed the schematic diagram to achieve the synthetic compound target, as shown in Figure 2. The synthesis would be initiated by using a cyclen **3** as the primary precursor in the reaction, after which protection and deprotection reactions would take place. Moreover, finally, a fluorescence ligand **2** would be attained by a reaction between a three-identical substituted arm of cyclen **9** with dansyl aziridine **10**.

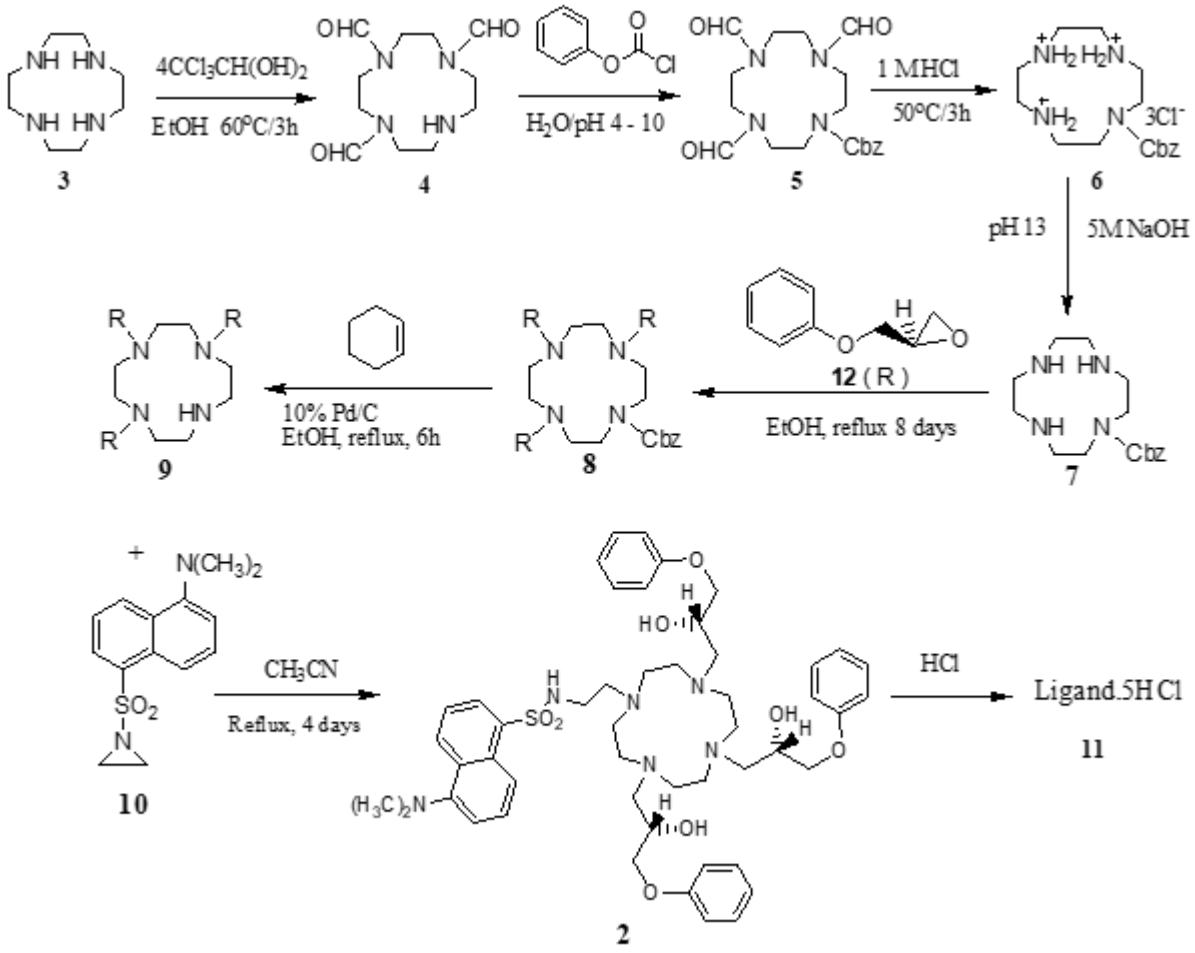

Figure 2. Schematic pathway of synthesis of dansyl cyclen ligand

2. Methodology

All reactions were conducted under a nitrogen atmosphere unless specified otherwise. Solvents were always purified prior to utilization by standard methods. Cyclen (98%) was purchased from Strem Chemicals, U.S.A. The stationary phase of column chromatography utilized Merck Silica gel 60 (230–400 mesh). The progress of a reaction or separation during the chromatographic process was monitored by thin-layer chromatography (TLC) No. 5554 (60 PF_{254}) from Merck, and N-Dansyl aziridine was purchased from Sigma-Aldrich.

Microanalysis was conducted at Campbell Microanalytical Laboratory Chemistry Department, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained using Varian Gemini 300 or Bruker 400 Avance spectrometers at Flinders University, Australia. ^{1}H spectra were collected at an operating frequency of 300.075 or 400.13 MHz. The ^{13}C spectra were recorded at 75.462 or 100.61 MHz, while ^{1}H NMR chemical shifts were referenced to $CDCl_3$ at δ 7.26 ppm and DMSO-d_6 at δ 2.50 ppm. Meanwhile, ^{13}C NMR spectra, chemical shifts were referenced to $CDCl_3$ at δ 77.00 pp; DMSO-d_6 at δ 39.52 ppm; CD_3CN at 1.39 ppm; CD_3OD at 49.00 ppm; and D_2O at

δ 67.19 ppm by the addition of 1,4-dioxane. In order to examine the functional groups of synthetic compounds, a HORIBA FT-720 FT-IR Spectrometer was used. The measurement of fluorescence emission spectra was conducted with a Varian Cary Eclipse Fluorescence Spectrophotometer using quartz cells with 1.0 cm path length, at a wavelength ranging from 400–650 nm at 0.15 nm intervals, with a scan rate of 40 nm/min. A blank solution was always run first at each measurement.

2.1. Preparation of the mono-protected cyclen

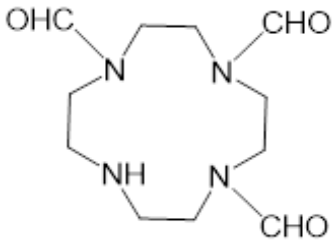

Figure 3. 1,4,7-triformyl-1,4,7,10-tetraazacyclododecane, **4**

Chloral hydrate (4.23 g, 25.54 mmol) was added to a stirred solution of cyclen, **3** (1.1 g, 6.39 mmol), in anhydrous ethanol (30 ml). The mixture was stirred at 60°C for 4 h under a nitrogen atmosphere, concentrated using a rotary evaporator to dry it, and then held under vacuum (0.75 mmHg) for about 2 days to produce a clear oil **4** (1.61 g). ^{1}H NMR ($CDCl_3$): δ 8.30–7.82 (3H, br, *H*C=O), 3.90–2.65 (17H, br, cyclen). ^{13}C ($CDCl_3$): δ 164.01–162.89 (3C, -*C*HO), 53.10–40.00 (8C, cyclen -CH_2). This data was in good agreement with the reference of Bradbury [4] and Hodyl [5].

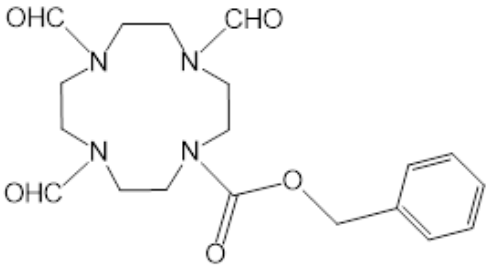

Figure 4. 1,4,7-triformyl-10-(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, 5

Benzyl chloroformate (710 mg, 4.15 mmol) was added to a solution of **4** (682 mg, 2.7 mmol, pH 9) dissolved in deionized water. The resultant mixture was then stirred for 1 h at room temperature after adjusting the pH from 4 to 10 using saturated Na_2CO_3 solution. A second aliquot of benzyl chloroformate (710 mg, 4.15 mmol) was added using an identical procedure as the first aliquot after the pH was again adjusted from 6 to 10 with saturated Na_2CO_3 solution. Then, the third aliquot of benzyl chloroformate (710 mg, 4.15 mmol) was added. The resultant mixture was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was extracted with dichloromethane (5 x 20 ml), and the combined organic layers were washed with saturated $NaHCO_3$ (1 x 10 ml), dried over $MgSO_4$, and concentrated *in vacuo* to obtain crude **5** as a yellow oil (583 mg) or 56% yield. It was used in the triformyl deprotection step without further purification [10].

This data was in good agreement with the reference of Bradbury [4] and Hodyl [5]. Purification was conducted by suspending the crude **5** in the cold (4°C) diethyl ether for 7 days. The white solid was obtained and filtered under nitrogen to produce **5** as a hygroscopic white powder in a 95% yield. ^{13}C NMR ($CDCl_3$): δ166.10 (1 C, C=O); 165.25 (1 C, C=O); 164.51 (1 C, C=O); 163.76 (1 C, C=O); 162.97 (1 C, Bn); 157.54 (1 C, Bn); 135.87 (2 C, Bn); 129.15–128.71 (2 C, Bn); 67.86–67.67 (1 C, Bn-CH_2); 52.56–43.29 (8 C, cyclen -CH_2). This data was in good agreement with Bradbury [4] and Hodyl [5].

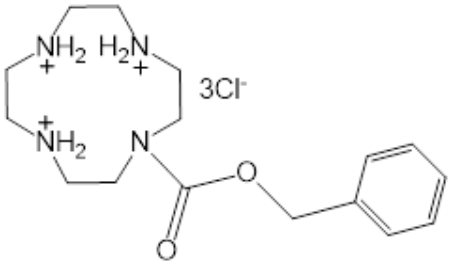

Figure 5. 1-(benzyloxycarbonyl)-1,4,7,10-tetraazadodecane·3HCl·1.5H_2O, **6**

A hydrolysis reaction with hydrochloric acid removed the tri-formyl protecting groups. A solution of **5** (504 mg, 1.38 mmol) was dissolved in HCl (1M, 35 ml, 35 mmol), and the resultant mixture was stirred at 50°C for 5 h. The solvent was obliterated using a rotary evaporator under reduced pressure at 60°C to yield a white solid. The crude product was suspended in ethanol (20 ml), refluxed for 1 h, cooled to room temperature, filtered, and dried in air to yield **6**: first crop 64 mg, 12%. The filtrate was treated with excess diethyl ether to result in the cloudiness of the solution after the white precipitate formed, filtered, and washed with diethyl ether (1 x 7.5 ml). Then, it was dried in air (room temperature) to give **6**: second crop 450 mg (84%). Both crops indicated equal purity and were combined each other to give an overall yield of 514 mg(96%). ^{1}H NMR (D_2O/1,4-dioxane): δ7.45 (5 H, br s, Bn-*H*); 5.21 (2 H, br s, Bn-CH_2); 3.72 (4 H, br s, cyclenCH_2); 3.20 (12 H, br s, cyclenCH_2). ^{13}C NMR (D_2O/1,4-dioxane): δ 158.98 (1 C, *C*=O); 136.34 (1 C, Bn, *ipso*); 129.52 (1 C, Bn, *para*); 129.40 (2 C, Bn, *meta*); 129.01 (2 C, Bn, *ortho*); 69.21 (1 C, Bn-CH_2); 47.17 (2 C, cyclen -CH_2); 45.88 (2 C, cyclen -CH_2); 45.16 (2 C, cyclen -*C*H_2); 43.49 (2 C, cyclen -CH_2). This data was in good agreement with the reference of Bradbury [4] and Hodyl [5].

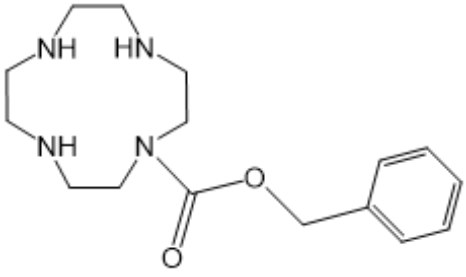

Figure 6. 1-(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, **7**

Chilled NaOH (10 M) was added, dropwise, to a stirred solution of **6** (514 mg 1.24 mmol), dissolved in deionized water (5 ml), adjusting the pH to 13. The solution was stirred for 2 h at room temperature and extracted with $CHCl_3$ (4 x 25 ml). The combined organic extracts were washed with cold NaOH (1.25 M, (1 x 10 ml), $NaHCO_3$ (1 x 5 ml), brine (1 x 5 ml), respectively. Then it was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator under reduced pressure to give the free base **7** as a yellow oil (98%). ^{1}H NMR ($CDCl_3$): δ 7.34 (5 H, br s, Bn); 5.08 (2 H, s, -C*H*$_2$-Bn); 3.61–3.56 (4 H, br m, cyclenC*H*$_2$); 3.31 (3 H, -N*H*-); 3.14–3.08 (12 H, br m, cyclenC*H*$_2$). ^{13}C NMR ($CDCl_3$): δ156.77 (1 C, C=O); 136.44 (1 C, Bn, *ipso*); 128.49 (1 C, Bn, *para*); 128.09 (2 C, Bn, *meta*); 127.98 (2 C, Bn, *ortho*); 67.26 (1 C, Bn-*C*H$_2$); 49.65 (2 C, cyclen -*C*H$_2$); 48.97 (2 C, cyclen -*C*H$_2$); 47.98 (2 C, cyclen -*C*H$_2$); 46.47 (2 C, cyclen -*C*H$_2$). This data was in good agreement with Bradbury [4] and Hodyl [5].

2.2. Preparation of the pendant arm epoxides

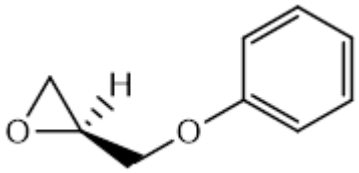

Figure 7. (2*S*)-(+)-3-phenoxy-1,2-epoxypropane, **12**

This compound was prepared to employ a procedure introduced by Smith [3]. To a sodium hydride (95%, 1.5 g, 62.50 mmol), which was suspended in dry DMF (15 ml), a solution of phenol (4.63 g, 49.20 mmol), also dissolved in dry DMF (10 ml), was added dropwise and stirred at room temperature for 1 h. A solution of (2*S*)-(+)-glycidyl tosylate (9.12 g, 40.00 mmol), dissolved in dry DMF (15 ml), was added, and the resultant mixture was stirred at room temperature for 20 h. The proceeding reaction was monitored using TLC on silica (10% hexane/DCM). After that, the reaction was quenched with NH_4Cl (10 ml), diluted with deionized water (1 x 150 ml), and extracted with diethyl ether (5 x 150 ml). The combined ether extracts were washed with ice-cold NaOH (0.1 M, 4 x 100 ml, deionized water (1 x 200 ml), brine (1 x 100 ml), dried over Na_2SO_4, and concentrated using an evaporator to yield a pale yellow oil. Purification by column chromatography over silica (eluent 10% hexane/DCM; rf: 0.37) afforded **12** as a clear oil: yield 4.5 g, 74%. ^{1}H NMR ($CDCl_3$): δ 7.34–7.29 (2 H, m, Ar-*H*); 7.02–6.93 (3 H, m, Ar-*H*); 4.22 (1 H, dd, *J* = 3.08, 11.04 Hz, -*H*CH-); 3.92 (1 H, dd, *J* = 5.8, 11.04 Hz, -HC*H*-); 3.36–3.33 (1 H, m, -C*H*O-); 2.88 (1 H, dd, *J* = 4.16, 4.96 Hz, -HC*H*O-); 2.74 (1 H, dd, *J* = 2.68, 4.98 Hz, -*H*CHO-). ^{13}C NMR ($CDCl_3$): δ158.34 (1 C, Ar, *ipso*); 129.35 (2 C, Ar, *meta*); 121.04 (1 C, Ar, *para*); 114.47 (2 C, Ar, *ortho*); 68.52 (1 C, -*C*H$_2$-); 49.96 (1 C, -*C*HO-); 44.46 (1 C, -*C*H$_2$O-). This data was in good agreement with the reference Hodyl [5].

2.3. Preparation of three-N-protected cyclen

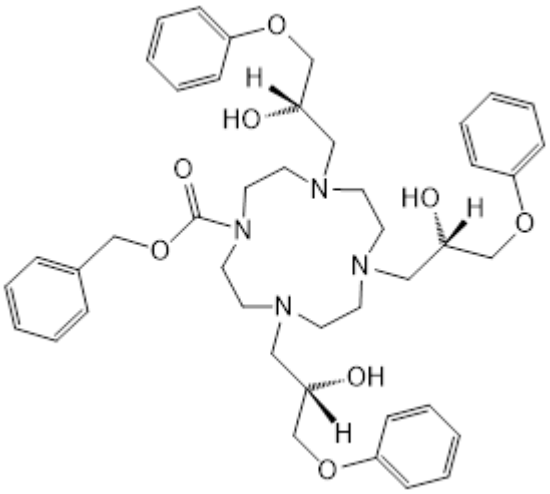

Figure 8. 1-(benzyloxycarbonyl)-4,7,10-*tris*-((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane, **8**

The compound was prepared by adapting a method introduced by Smith [3]. A solution of **12** (638 mg, 4.25 mmol), in dry ethanol (10 ml) was added (drop-wise) to a refluxing solution of **7** (424 mg, 1.40 mmol) that was dissolved in anhydrous ethanol (10 ml). The reaction was then traced for the disappearance of the starting epoxide using TLC on silica (eluent 10% hexane/DCM; rf: 0.39) which occurred after 9 days. Evaporation of the solvent gave **8** as a viscous yellow oil as much as 1.0 g (quantitative). ^{13}C NMR ($CDCl_3$): δ 158.48 (3 C, Ph, *ipso*); 156.35 (1 C, *C*=O); 136.45 (1 C, Bn, *ipso*); 129.28 (6 C, Ph); 129.25 (1 C, Bn); 128.34 (2 C, Bn); 127.88 (2 C, Bn); 120.72 (3 C, Ph); 114.38 (6 C, Ph); 69.62 (2 C, O*C*H$_2$); 68.82 (1 C, O*C*H$_2$); 67.10 (1 C, OCH$_2$Bn); 66.70 (2 C, *C*H); 65.93 (1 C, *C*H); 59.10 (2 C, *C*H$_2$N); 57.89 (1 C, *C*H$_2$N); 54.06 (2 C, cyclen -*C*H$_2$); 53.31 (2 C, cyclen -*C*H$_2$); 50.40 (2 C, cyclen -*C*H$_2$); 47.42 (2 C, cyclen -*C*H$_2$). This data was in a good agreement with the reference of Bradbury [4] and Hodyl [5].

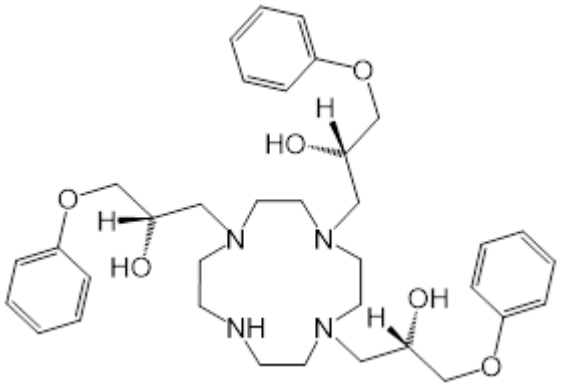

Figure 9. Preparation 1,4,7,tris-((2*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetrazacyclododecane

Cyclohexene (300 mg, 3.65 mmol) was added to a solution of **8** (523 mg, 0.69 mmol) dissolved in anhydrous ethanol (10 ml). The solution was stirred and then 10% Pd/C catalyst (500 mg) was added. The reaction mixture was refluxed at 80°C for 5 h, filtered through a small celite column and the filter cake was washed with absolute

ethanol (5 ml). The filtrate was concentrated using rotary evaporator under reduced pressure to give a deprotected **9** as a brown oil, yield 497 mg or 95%. ^{13}C NMR ($CDCl_3$): δ 158.67 (2 C, Ar, *ipso*); 158.60 (1 C, Ar, *ipso*); 129.29 (4 C, Ar); 129.23 (2 C, Ar); 120.72 (2 C, Ar); 120.60 (1 C, Ar); 114.45 (4 C, Ar); 114.40 (2 C, Ar); 69.91 (2 C, OCH_2); 69.28 (1 C, OCH_2); 66.43 (1 C, *C*H); 65.46 (2 C, *C*H); 60.2 (2 C, CH_2N); 58.04 (1 C, CH_2N); 52.51 (2 C, cyclen -CH_2); 51.41 (2 C, cyclen -CH_2); 50.41(2 C, cyclen -CH_2); 44.36 (2 C, cyclen -CH_2). This data was in a good agreement with the reference of Bradbury [4] and Hodyl [5].

2.4. Preparation of macrocyclic receptor ligand

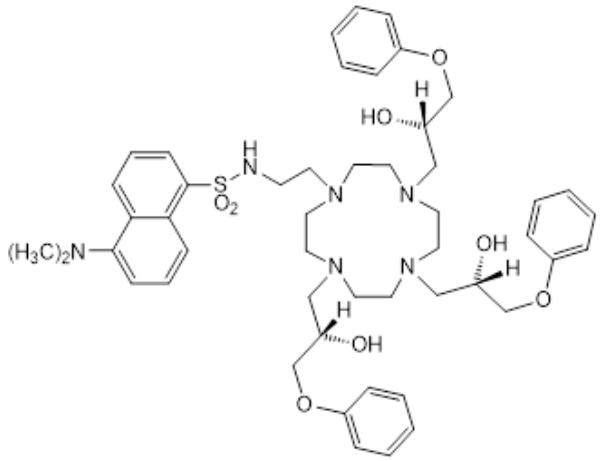

Figure 10. Synthesis of 1-[(5-(Dimethylamino)-naphthalene-1-sulfonyl-amino)ethyl]-4,7,10-[(2*S*)-2-hydroxy-3-phenoxypropyl) -1,4,7,10-tetraazacyclododecane, **2**

Modifying the method of Li [11] 1,4,7-tris-((2*S*)-2-hydroxy- 3- phenoxypropyl)- 1,4,7,10 tetraazacyclododecane, **9** (400 mg, 0.64 mmol) was dissolved in acetonitrile (20 ml) and then refluxed for 5 minutes. To the refluxing solution, a solution of dansylaziridine, **10** (216 mg, 0.78 mmol) in acetonitrile (12 ml) was added. The mixture was refluxed in the absence of light for 5 days whilst being monitored by TLC (acetone:triethylamine = 98:2 as eluent, R_f (dansylaziridine) = 0.62). The reaction was then cooled to room temperature and the solvent was removed using rotary evaporator under reduced pressure. The crude product was then purified by column chromatography (Ac:TEA = 98:2 as eluent, Rf **2** = 0.48) producing a brown oil (382 mg, 66%). ^{13}C NMR free base (75 MHz, $CDCl_3$): δ = 158.76 (3 C, Ph, *ipso*), 151.44 (1 C, Nap, *ipso*), 135.72 (1 C, Nap), 129.76 (1 C, Nap), 129.60 (1 C, Nap), 129.38 (1 C, Nap), 129.29 (4 C, Ph), 129.22 (2 C, Ph), 128.52 (1 C, Nap), 128.00 (1 C, Nap), 122.99 (1 C, Nap), 120.92 (1 C, Ph), 120.60 (2 C, Ph), 119.61 (1 C, Nap), 114.96 (1 C, Nap), 114.51 (2 C, Ph), 114.48 (4 C, Ph), 69.81 (2 C, PhO-C), 69.36 (1 C, PhO-C), 66.04 (2 C, C-OH), 65.81 (1 C, C-OH), 58.21 (2 C, CH_2N), 57.15 (1 C, CH_2N), 56.43 (1 C, CH_2N), 52.06 (2 C, cyclen), 51.62 (2 C, cyclen), 51.34(2 C, cyclen), 50.97 (2 C, cyclen), 45.31 (2 C, $(CH_3)_2$), 41.43 (1 C, CH_2-NHS).

In order to obtain an analytically pure sample, **2** was converted to its hydrochloride salt in the following way: **2** (200 mg, 0.22 mmol) was dissolved in methanol (5 ml) and the resulting solution was cooled to 0°C, and then HCl (32% aqueous, 0.3 ml, 3 mmol) was added dropwise precipitating the pentahydrochloride as brown oil. After decanting off the solvent, the oil was triturated with diethyl ether generating the pure product, **11**, as a brown powder (212 mg, 89 %). (Found C, 54.53; H, 6.87; N, 7.56%). $C_{49}H_{71}Cl_5N_6O_8S$ requires C, 54.42; H, 6.62; N, 7.77%). ^{13}C NMR Ligand pentahydrochloride (75 MHz, CD_3OD): δ = 159.89 (1 C, Ph, *ipso*), 159.71(1 C, Ph, *ipso*), 159.46 (1 C, Ph, *ipso*), 140.01 (1 C, Nap, *ipso*-N), 137.98 (1 C, Nap, *ipso*-S), 130.57 (7 C, 6C-PhC dan 1 C, Nap), 129.22 (1 C, Nap), 128.86 (1 C, Nap), 128.69 (1 C, Nap), 128.08 (1 C, Nap), 127.07 (1 C, Nap), 122.32 (3 C, Ph), 120.88 (1 C, Nap), 115.71 (5 C, 4C-Ph dan 1C, Nap), 115.38 (2 C, Ph), 71.14 (1 C, PhO-C), 70.88 (1 C, PhO-C), 70.45 (1 C, PhO-C), 66.87 (2 C, C-OH), 64.62 (1 C, C-OH), 57.32 (2 C, CH_2N), 56.98 (1 C, CH_2N), 54.25 (1 C, CH_2N), 52.44 (2 C, Cyclen), 51.85 (4 C, Cyclen), 51.09 (2C, Cyclen), 47.97 (2 C, $(CH_3)_2$), 40.13 (1 C, CH_2-NHS).

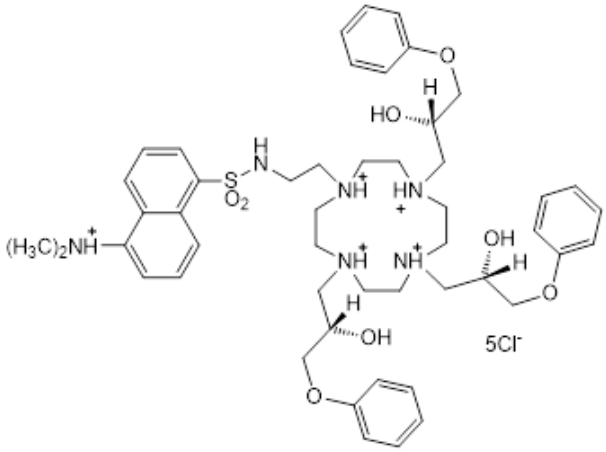

Figure 11. 1-[(5-(Dimethylamino)-naphthalene-1-sulfonyl-amino)ethyl]-4,7,10-[(2*S*)-2-hydroxy-3-phenoxypropyl) -1,4,7,10-tetraazacyclododecane.5HCl, **11**

2.5. pH Titration of Free Ligand

Solution of protonated ligand 34 (at 5 x 10^{-6} M) in 30% aqueous acetonitrile, at a constant ionic strength of I = 0.1 M, NEt_4ClO_4, was titrated with 0.1 M NEt_4OH with the range spectra was 400–650 nm. The range of pH applied was from 2 to 13, and it was indicated by using a combination glass electrode that was calibrated against an aqueous buffer solution for pH 2–12. While pH 13 was indicated using litmus paper.

2.6. Metal Titration of Free Ligand

The effect of the addition of metal ions on fluorescence emission of the ligand was studied by conducting a series of titrations using several cationic metals. Solution of the ligand was at 10^{-5} M buffered at pH 10.5 with CAPS in 30% aqueous acetonitrile and at a constant ionic strength of I = 0.1 M, NEt_4ClO_4 with the range of spectra was from 400 to 650 nm. The concentration of metal ions used were arranged to be at 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0 up to 10.0 equivalent to the concentration of the free ligand **2**. The metals used were Cd, Ca, Zn, Hg, $Pb(ClO_4)_2$, La, and Y(triflate).

3. Results and Discussion

All the synthetic precursor compounds ran according to procedures obtained from previous reports and gave results as expected. They were all in good agreement with the references. The results of the syntheses of 1-[(5-(Dimethylamino)-naphthalene-1-sulfonyl-amino)ethyl]-4,7,10-[(2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane and its protonated form were also successfully achieved. Due to a huge amount of hydrogen in the compound, using ^{1}H NMR to identify the resulting product's protons was not useful. The appearance of proton NMR was messy and noninformative. That is why the ^{13}C NMR was utilized instead of ^{1}H NMR to characterize the product.

3.1. Synthesis of Free Ligand

This reaction is based on the ring-opening of aziridine, which is similar in principle to epoxide ring-opening except that a nitrogen atom has replaced the oxygen atom. The synthetic approach employed in this reaction was adapted from Yang [12], as shown in Figure 12.

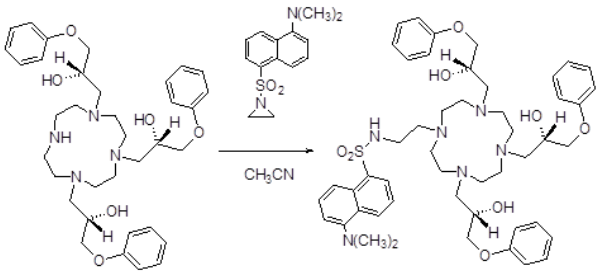

Figure 12. Synthesis of the fluorescent ligands

A mixture of dansyl aziridine **10** and compound **9** was refluxed in acetonitrile at 80°C for five days. Since the dansyl fluorophore is light-sensitive, the reaction apparatus was covered with aluminum foil to exclude light. Progress of the reaction was monitored by thin-layer chromatography to detect the disappearance of dansyl aziridine. The product was purified by column chromatography on silica gel using acetone/ triethylamine (95:5) eluent to obtain **2** in 66% yield. Besides the ^{13}C NMR spectrum of the synthetic product presented in the subheading 2.4, the ring-opening was confirmed by ^{13}C NMR spectroscopy due to the loss of resonances at about 28 ppm, originating from the aziridine carbon atoms was also crucial evidence that the compound target **2** was successfully achieved. In order to produce a sample suitable for microanalysis, which occurs as a viscous oil, **2** was converted to its pentahydrochloride salt form, **11,** by treatment with an excess of 32% hydrochloric acid [13]. It was found that C, 54.53; H, 6.87; N, 7.56% in which the proposed compound consisting of pentahydrogenchloride, $C_{49}H_{71}Cl_5N_6O_8S$, requires C, 54.42; H, 6.62; N, 7.77% [14]. This indicates that the proposed compound was achieved. The absorption peak at 1318 cm^{-1} represents the infrared frequency of the asymmetric SO_2 stretching frequency ($\upsilon_{as}SO_2$). This is in good agreement with Wang [15] and Xue [16].

3.2. Effect of pH on the fluorescent properties of the receptor-ligand

Several titration experiments were conducted to investigate the influence of the pH on the fluorescence properties of the receptor-ligand. The emission spectra of ligand **2** were recorded as a function of pH, as depicted in Figure 13. The pH values recorded between 2 and 13 were indicated by a pH meter employing a combination glass electrode calibrated against an aqueous buffer. For pH values above 12, indicator paper was used. In general, this involved the addition of aliquots of a solution tetraethylammonium hydroxide (NEt_4OH) to a dilute solution (10^{-5} M) of each protonated ligand (by treatment with perchloric acid) in 30% aqueous acetonitrile for ligand **2**. The existence of Net_4OH in the solution provides a constant ionic strength of I = 0.1 M and the measurement of the emission spectra (over 370–650 range) at each addition of the base. Acetonitrile is a polar, water-miscible organic solvent in which the ligands and their complexes are soluble at the concentrations required for physical studies.

The fluorescence emission curve against pH of ligand **2** provided an apparent increase with the increase of pH, as shown in Figure 13. This fact agrees with a report by Aoki *et al.*, [17] stating that cyclen moiety will deprotonate as the pH increases causing the emission intensity also increases.

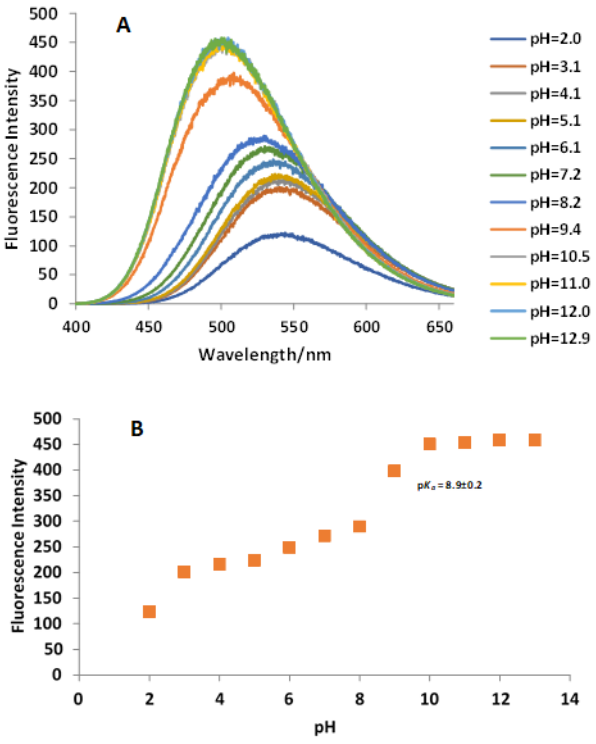

Figure 13. (A) Fluorescence emission spectra during protonated **2** (10^{-5} M) titration with NH_4OH in 30% aqueous acetonitrile (I = 0.1 M, Net_4ClO_4) at 298 K when excited at 337 nm. Emission maxima are at 500.3 at pH 13, 529.4 at pH 8.2 and 544.0 at pH 2.0. Maximum fluorescence emission intensity increases from pH 2.0 (blue curve) to pH 13 (green curve); (B) Fluorescence intensity of 27 at λmax plotted against pH, values derived from (A)

As shown from Figures 13 (A) and (B), there are groups of emission spectra having close to each other. For example, at pH 3–8 the emission spectrum is quite close to another, so that of pH 10–12, while in comparison, the fluorescence emission spectrum at pH 9 is relatively isolated. This titration curve indicates that pH around the pKa value is sensitive to the acid and base environment. It is also clearly shown from Figure 13 (B) that the quantum yield of fluorescence tended to increase while the pH of ligand solution increased.

3.3. The effect of metal complexation on fluorescence

In this study, the potentially eight-coordinating metal ions Cd(II), Zn(II), Hg(II), Pb(II), La(III), Y(III), and Ca(II) were investigated for their influence on the fluorescence properties of the ligand. The previous work showed that when the metal ions under consideration bind to ligands similar to **2**, they bound to all four nitrogen atoms in the macrocycle residue. If the pendant dansylamine did not coordinate with the metal atom, it could exist in the protonated or deprotonated form, depending on the prevailing pH.

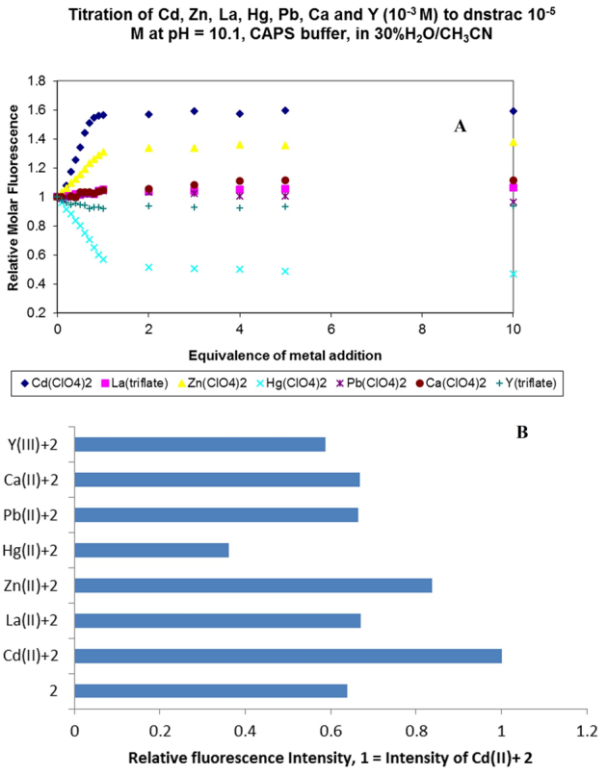

Figure 14. The fluorescence emission intensity of ligand **2** at its own and with the additional metals on at pH 10.5, CAPS buffer

The previous section showed obviously from fluorescence pH curves of titration that minor pH change around the pK_a value of the pendant dansylamine led to significant shifts in the fluorescence emission intensity of the ligand. Therefore, it was necessary to investigate the fluorescence of metal complexes of **2** to buffer the solution at working pH to avoid bias recorded fluorescence emission intensities due to metal hydrolysis. For this reason, it was decided to buffer the solutions at pH 10.5 using CAPS (*N*-cyclohexyl-3-aminopropanesulfonic acid). CAPS was preferred as it is known to be resistant to metal ion complexation and would then control the pH without interfering with the investigation [18, 19, 20]. The effect of metals on free ligand **2** can be seen in Figure 14.

From Figure 14(A), it is clear that the most significant increase in the intensity of fluorescence of the solution of ligand occurred when Cd(II) solution was added, followed by Zn(II). The former gained up to 150% compared to the free ligand, while the latter contributed 130%, as shown in Figures 14 (A) and (B). The presence of Y(III), Ca(II), Pb(II), and La(II), however, relatively did not change the intensity of the fluorescence. The fluorescence intensity quenched quite significantly while Hg(II) was added. Nonetheless, all the metal-ligand complexation followed the 1:1 ratio, as the titration curve indicated in Figure 14 (A). It was evident that the maximum point was achieved when the ligand and cationic metals ratio was identical at 1:1 [21, 22].

4. Conclusion

The synthesis of the dansyl cyclen-based receptor has been successfully achieved. The characterization results confirmed this synthetic product using ^{13}C NMR, IR spectrophotometer, and microanalysis. The physical properties, in particular, the fluorescent emission trend of the receptor-ligand against the pH tended to increase as the pH increased and it experienced a hypsochromic shift. From metal ions' titration, it revealed that Cd(II) ion had a significant impact on increasing the fluorescence of the ligand to almost two-fold, followed by Zn(II). Meanwhile, Hg(II) ion caused a significant decrease in the fluorescence intensity of the ligand. The synthetic receptor-ligand likely has a great potency to develop it as a chemical sensor.

Acknowledgment

We would like to thank Halu Oleo University for providing funds for conducting this research as it was granted in research contract number 1456e/UN29.20/PG/2021. We also would like to thank the Flinders University of South Australia for allowing us to do some sample preparations and NMR and IR analysis. Special thanks to Mr. Kevin P. Wainwright, who gave invaluable help during the sample preparations and spectrophotometer data analysis.

References

[1] Rudi Heryanto, Eti Rohaetia, Achmad Fauzi, Uric Acid Sensor Based on PEDOT: PSS Modified Screen-Printed Carbon Electrode Fabricated with a Simple Painting Technique, *Jurnal Kimia Sains dan Aplikasi*, 24, 2, (2021), 43-50 https://doi.org/10.14710/jksa.24.2.43-50

[2] Yinyan Chen, Yiban Wu, Yifan Zhu, Saiqi Tian, A fluorescent polyurethane foam based on rhodamine derivative as Fe (III) sensor in pure water, *Polymer International*, 71, 2, (2022), 169-174 https://doi.org/10.1002/pi.6296

[3] Christopher B. Smith, Mark A. Buntine, Stephen F. Lincoln, Kevin P. Wainwright, Metal ion-activated molecular receptors for aromatic anions with receptor cavities formed from 1-or 2-naphthyloxy moieties appended to cyclen, *Dalton Transactions*, 15,

(2003), 3028-3033 https://doi.org/10.1039/B305461F

[4] Adam J. Bradbury, Stephen F. Lincoln, Kevin P. Wainwright, Fluorescent signaling provides deeper insight into aromatic anion uptake by metal-ion activated molecular receptors, *New Journal of Chemistry*, 32, 9, (2008), 1500-1508 https://doi.org/10.1039/B719183A

[5] Jozef A. Z. Hodyl, Stephen F. Lincoln, Kevin P. Wainwright, Solvent induced selectivity switching in aromatic-anion binding molecular receptors, *Journal of Inclusion Phenomena Macrocyclic Chemistry*, 67, 3, (2010), 483-487 https://doi.org/10.1007/s10847-009-9725-4

[6] Qin-Peng Zhang, Tai-Bao Wei, Jun-Nian An, Yan-Yan Chen, Guan-Fei Gong, Qi Zhou, Hai-Long Yang, Hong Yao, You-Ming Zhang, Qi Lin, A simple chemosensor for ultrasensitive fluorescent "turn-on" detection of Fe^{3+} and alternant detection of CN, *Supramolecular Chemistry*, 31, 12, (2019), 745-755 https://doi.org/10.1080/10610278.2019.1690655

[7] Yun-Qiong Gu, Wen-Ying Shen, Yan Mi, Yan-Fang Jing, Jing-Mei Yuan, Peng Yu, Xiao-Min Zhu, Fei-Long Hu, Dual-response detection of Ni^{2+} and Cu^{2+} ions by a pyrazolopyrimidine-based fluorescent sensor and the application of this sensor in bioimaging, *RSC Advances*, 9, 61, (2019), 35671-35676 https://doi.org/10.1039/C9RA06227K

[8] Nahla Omer, Fayin Zhang, Gang Zhao, Shanyi Guang, Hongyao Xu, Highly selective chemosensor for repetitive detection of Fe^{3+} in pure water and bioimaging, *Analyst*, 144, 10, (2019), 3414-3421 https://doi.org/10.1039/c9an00070d

[9] Hyemi Kim, Kyung-Soo Moon, Soyoung Shim, Jinsung Tae, Cyclen-Conjugated Rhodamine Hydroxamate as Pd^{2+}-Specific Fluorescent Chemosensor, *Chemistry-An Asian Journal*, 6, 8, (2011), 1987-1991 https://doi.org/10.1002/asia.201100126

[10] Jesus L. Pablos, Fernando Catalina, Saturnino Ibeas, Teresa Corrales, Fluorescent imidazolium-based poly(ionic liquid)s for Fe^{3+} detection in aqueous medium, *Journal of Photochemistry Photobiology A: Chemistry*, 406, 113015, (2021), 1-9 https://doi.org/10.1016/j.jphotochem.2020.113015

[11] Honglin Li, Jiangli Fan, Fengling Song, Hao Zhu, Jianjun Du, Shiguo Sun, Xiaojun Peng, Fluorescent probes for Pd^{2+} detection by allylidene–hydrazone ligands with excellent selectivity and large fluorescence enhancement, *Chemistry–A European Journal*, 16, 41, (2010), 12349-12356 https://doi.org/10.1002/chem.201000796

[12] Yang Yang, Chao-Ying Gao, Tingting Li, Jing Chen, A Tetraphenylethene-Based Rhodamine Hydrazone Chemosensor for Colorimetric and Reversible Detection of Cu^{2+}, *ChemistrySelect*, 1, 15, (2016), 4577-4581 https://doi.org/10.1002/slct.201600883

[13] Mahesh P. Bhat, Madhuprasad Kigga, Harshith Govindappa, Pravin Patil, Ho-Young Jung, Jingxian Yu, Mahaveer Kurkuri, A reversible fluoride chemosensor for the development of multi-input molecular logic gates, *New Journal of Chemistry*, 43, 32, (2019), 12734-12743 https://doi.org/10.1039/C9NJ03399H

[14] Pavel B. Tsitovich, Timothy Y. Tittiris, Jordan M. Cox, Jason B. Benedict, Janet R. Morrow, Fe(II) and Co(II) *N*-methylated CYCLEN complexes as paraSHIFT agents with large temperature dependent shifts, *Dalton Transactions*, 47, 3, (2018), 916-924 https://doi.org/10.1039/C7DT03812G

[15] Dongxu Gu, Weiting Yang, Fuxiang Wang, Meiling Li, Lijuan Liu, Huihui Li, Qinhe Pan, A metal-organic gel-based fluorescent chemosensor for selective Al^{3+} detection, *Applied Organometallic Chemistry*, 33, 11, (2019), e5179 https://doi.org/10.1002/aoc.5179

[16] Shirui Xue, Peng Wang, Kai Chen, A novel fluorescent chemosensor for detection of mercury(II) ions based on dansyl-peptide and its application in real water samples and living LNcap cells, *Spectrochimica Acta Part A: Molecular Biomolecular Spectroscopy*, 226, 117616, (2020), 1-8 https://doi.org/10.1016/j.saa.2019.117616

[17] Shin Aoki, Hiroki Kawatani, Teruhiro Goto, Eiichi Kimura, Motoo Shiro, A Double-Functionalized Cyclen with Carbamoyl and Dansyl Groups (Cyclen = 1,4,7,10-Tetraazacyclododecane): A Selective Fluorescent Probe for Y^{3+} and La^{3+}, *Journal of the American Chemical Society*, 123, 6, (2001), 1123-1132 https://doi.org/10.1021/ja0033786

[18] Kazunori Matsuura, Koichi Hisamoto, Tomoya Tanaka, Ryota Sakamoto, Mizuki Okazaki, Hiroshi Inaba, Turn-On Fluorescent Probe Based on a Dansyl Triarginine Peptide for Ganglioside Imaging, *ACS Organic Inorganic Au*, 1, 2, (2021), 60-67 https://doi.org/10.1021/acsorginorgau.1c00013

[19] Jee Young Kim, Swarbhanu Sarkar, Kondapa Naidu Bobba, Phuong Tu Huynh, Abhinav Bhise, Jeongsoo Yoo, Development of dansyl based copper (II) complex to detect hydrogen sulfide in hypoxia, *Organic Biomolecular Chemistry*, 17, 29, (2019), 7088-7094 https://doi.org/10.1039/c9ob00948e

[20] Peng Wang, Dagang Zhou, Bo Chen, High selective and sensitive detection of Zn(II) using tetrapeptide-based dansyl fluorescent chemosensor and its application in cell imaging, *Spectrochimica Acta Part A: Molecular Biomolecular Spectroscopy*, 204, (2018), 735-742 https://doi.org/10.1016/j.saa.2018.07.001

[21] Peng Wang, Dagang Zhou, Bo Chen, A fluorescent dansyl-based peptide probe for highly selective and sensitive detect Cd^{2+} ions and its application in living cell imaging, *Spectrochimica Acta Part A: Molecular Biomolecular Spectroscopy*, 207, (2019), 276-283 https://doi.org/10.1016/j.saa.2018.09.029

[22] Lin-Bo Li, Shun-Jun Ji, Wei-Hong Lu, A novel highly selective fluorescent chemosensor for Zn^{2+} by terpyridyl based on naphthalimide fluorophore, *Chinese Journal of Chemistry*, 26, 3, (2008), 417-420 https://doi.org/10.1002/cjoc.200890079