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Design, synthesis and evaluation of new colourimetric chemosensors containing quinazolinones moiety for some cations detection in an aqueous medium and biological sample

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The current project deals with designing and synthesizing of colourimetric chemosensors to detect the cations in the aqueous medium and biological sample. To achieve this goal a new series of quinazolinone derivatives have been synthesized *via* reaction of the novel 6-nitro-2-propyl-4*H*-benzo[*d*][1,3]oxazin-4-one **3** with selected nitrogen nucleophiles, namely, formamide, hydrazine hydrate, hydroxylamine hydrochloride, *o*-phenylendiamine, *o*-aminophenol and *o*-aminothiophenol, urea and/or thiourea. Structures of the new compounds have been investigated depending on their spectral data (IR, ^{1}H and ^{13}C NMR and MS) and elemental analyses. Some of the newly synthesized products exhibit significant response as chemosensors for a few cations detection.

Keywords: Chemosensor, quinazolinone, copper, cadmium, mercury

Currently, synthesis of colourimetric sensors for detecting of cations and anions is one of the researcher's targets in the organic synthesis fieldbecause of the prospect implementation of these chemosensors as diagnostic tools in medical, physiological and environmental applications[1]. Copper cation is the most abundant ion in the human body and several proteins utilize Cu^{2+} as a cofactor for the transfer of electrons in redox reactions. Biologically, excess Cu^{2+} in cells can stimulate the creation of reactive oxygen species and can harm lipids, DNA and RNA and cause some of the dangerous diseases, such as Dementia's disorder, Prion, Wilson and Menkes disease, which are directly related to the copper toxicity[2]. Also, Cd^{2+} is extremely poisonous to the living organism and its compounds pass in the environment from human activities or geological. Cadmium and its salts are classified as blacklist compounds because high exposure level of Cd^{2+} is associated to raise cardiovascular risks diseases, cancer, liver diseases and kidney disorder[3]. On the other hand, mercury is considered as the greatest harmful pollutant, which affects directly on human and environmental health, so assay of mercury ions in the environment is a significant target reference[4]. The most reports of sensing Hg^{2+} based on using atomic absorption spectrometry, Raman spectroscopy, inductively coupled plasma mass spectrometry, which is expensive and needs long time pre-treatment[5]. Various techniques such as electrochemical, atomic absorption, inductively coupled plasma atomic emission and piezoelectric quartz crystals[6], have been used for notifying of metal ions but their utilization is limited due to its expensive equipment, laboratories and time consuming procedures. Lin *et al*. have applied a ratiometric fluorescent probe for Cu^{2+} determination[7]. Kato *et al*. used isotope dilution inductively coupled plasma mass spectrometry for the detection of silver copper, zinc, nickel, lead and cadmium in seawater[8]. Colourimetric techniques are the most favorable methods to their low cost, lack of equipment, rapid and we can detect it by naked eye[9]. Thus, development of colourimetric chemosensors depend on changing in absorption accompanied by sensible colour changes, for heavy metal ions has produced as an active area of valuable importance. Kim *et al*. showed a colourimetric sensor for the

determination of Cd, Hg and Pb ions[10]. Li *et al*. utilized a turn-on fluorescent sensor for assay of Cd^{2+}, Hg^{2+} and Zn^{2+} in water[11]. Fegade *et al*, showed selectivity of dualchannel chemosensor for copper in semiaqueous media[12]. In the last decade, several heterocyclic chemosensors were synthesized for the recognition of different ions[13]. Synthesized azo dye-based heterocyclic chemosensors designed to produce fluorescent sensors for the detection of zinc without interference with cadmium[14]. Lu *et al*.[15], designed a sensor containing naphthalimide as the fluorophore, which by undergoing two reverse ICT processes in sensing Zn^{2+} and Cd^{2+} distinguished between this ion pair proficiently.

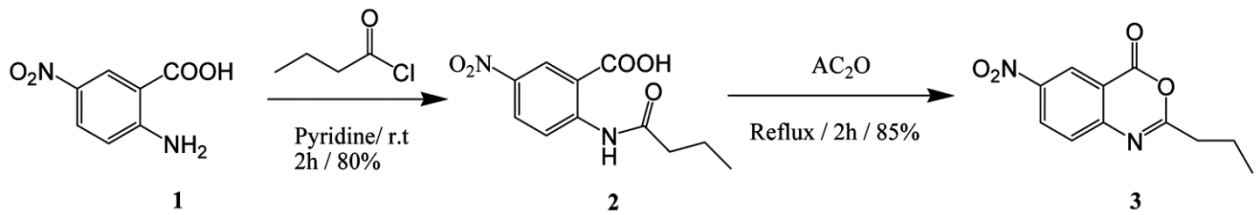
Quinazolinones have attracted notable interest in organic and medicinal chemistry due to their therapeutic potential such as anticancer, antibacterial, antidiabetic, hypnotic, sedative, analgesic, anticonvulsant, antitussive, anti-inflammatory activities[16]. Few reports were performed for checking the sensor activity of quinazolinone derivatives. Ailin Yuan *et al*, synthesized novel quinazolinone compound as a fluorescence sensor for the ferric ion[17]. Quinazolinonebased sensors for amine vapors and Cu^{2+} ion[18] have been developed. As an extension of our awareness in synthesis of quinazolinone heterocyclic, we report that some quinazolin-4(3*H*)-ones can be used as a simple and efficient 'turn-on' fluorescent chemosensor for a highly selective and sensitive detection of some cations, Cu^{2+}, Hg^{2+} and Cd^{2+} in aqueous medium and biological sample.

Results and Discussion

As part of our concern in the organic synthesis of quinazolinone derivatives[19] we produced a new chemosensor carrying quinazolinone moiety. As displayed in (Scheme I), 2-amino-5-nitrobenzoic acid **1** was reacted with butyryl chloride, in dry pyridine, to yield 2-(butyramido)-5-nitrobenzoic acid **2**. Microanalytical and spectral data were used for structure elucidation of the anilide **2**. IR spectrum showed absorption bands at ν 1730 and 1640 cm^{-1} which are characteristic for both C=O carboxylic acid and amide functions stretching vibration, respectively. ^{1}H NMR spectrum of the anilide **2** exposed two deuterium- exchangeable, protons at δ 8.95 and 11.80 related to N–H and CO_2H. Mass spectrum showedthe molecular ion peak at *m/z* 252 which is coincident with the prospective anilide formula.

Using acetic anhydride,intramolecular cyclization for of the anilide **2** was performed leading to our target 6-nitro-2-propyl-4*H*-benzo[*d*][1,3]oxazin-4-one **3** as a dynamic benzoxazinone moiety with electronically unsaturated character[20]. IR spectra of compound **3**was very good indication for absence of both carboxylic and amide functions. On the other hand, a characteristic absorption band was observed at ν 1750 cm^{-1} signifying C=O function of 3,1-benzoxazin-4-ones. Mass spectrum gave a molecular ion peak at *m/z* 234 which is matching with the predictable molecular formula acquired through loosing of one molecule of water from the anilide **2**. These results are deemed confirmatory for the postulation that cyclization process implicated both carboxylic and amidic functions (Scheme I).

Reaction of 6-nitro-2-propyl-4*H*-benzo[*d*][1,3] oxazin-4-one **3** with some selected nitrogen nucleophiles, namely, formamide, hydrazine hydrate, hydroxylamine hydrochloride, *o*-phenylendiamine, *o*-aminophenol, *o*-aminothiophenol, urea and/or thiourea furnished a variety of 4(3*H*)-quinazolinones **4-14** *via* aminolysis at position **3** (Scheme II). It is expectant that the reactions managed through nucleophilic ring opening ring closure (RORC) process accompanied by ring oxygen replacing with nitrogen. Oxazinone ring splitting takes place by the attack of nitrogen nucleophile followed by cyclization on the highly electrophilic sp^2 hybridized carbonyl carbon of the intermediate to give our coveted quinazolinones[21].



1 2 3

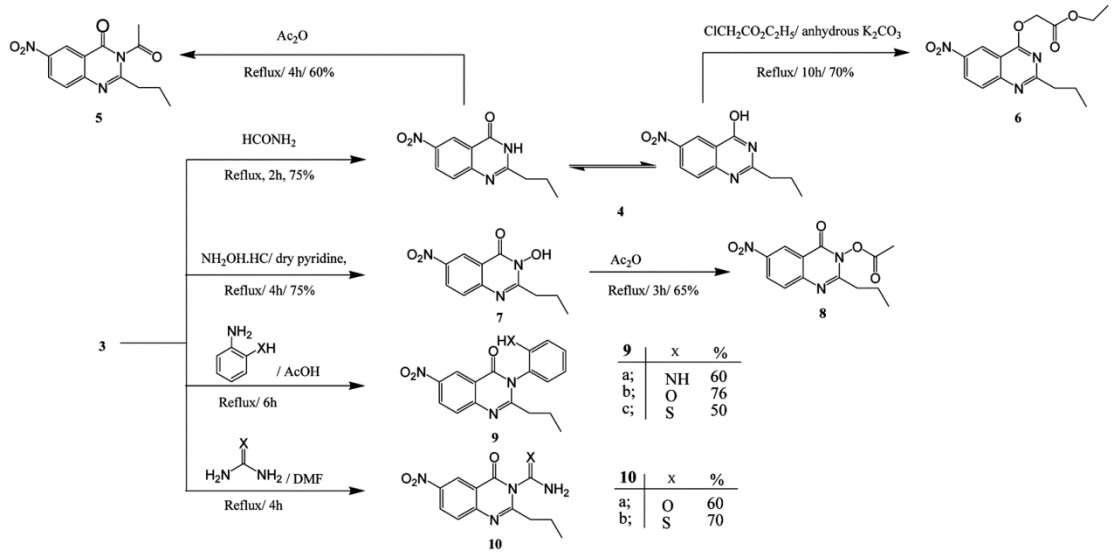
Scheme I — 6-Nitro-2-propyl-4*H*-benzo[*d*][1,3]oxazin-4-one **3**

Fusion of the benzoxazinone **3** with extra amount of formamide afforded 6-nitro-2-propylquinazolin-4(3*H*)-one **4**. Structure of compound **4** was elucidated from its correct elemental analysis together with its IR spectrum which showed strong absorption bands at ν 3280, 3150, 1670 and 1622 cm^{-1} related to NH (bonded and non-bonded), C=O and C=N, respectively. Quinazolinone **4** showed, in solution, lactam–lactim dynamic equilibrium. In polar solvents, the lactam form is more predominant than the lactim one, hence with decreasing the solvent polarity, the lactim form becomes more predominant[22].

The existence of compound **4** in the lactam-lactim tautomeric equilibrium was demonstrated *via* its reaction with acetic anhydride where it undergoes *N*-acetylation (through the lactam form) to yield compound 3-acetyl-6-nitro-2-propylquinazolin-4(3*H*)-one **5**, but, it upon alkylation with ethyl chloroacetate the ester ethyl 2-(6-nitro-2-propylquinazolin-4-yloxy)acetate **6** was produced (through the lactim form) (Scheme II). The ^{1}H NMR spectra of compounds **5** and **6** afforded signals at δ 2.10 ppm for three protons related to compound **5** acetyl group (CH_3-C=O) in addition to δ 1.20-1.30 and 4.00-4.10 which proved the exitance of the ester group protons in compound **6** (3H, CH_3-CH_2-), (2H, -OCH_2CH_3.

Aiming to expand the synthetic efficiency of our newly synthesized benzoxazinone **3**, reaction with hydroxylamine hydrochloride was studied as convenient route to the synthesis of 3-hydroxy-6-nitro-2-propylquinazolin-4(3*H*)-one **7**. Structure of compound **7** was proved from its IR spectrum which showed strong absorption bands at ν 3530 and 1680 cm^{-1} due to both (OH and C=O) groups, respectively. The ^{1}H NMR spectrum showed the D_2O exchangeable proton for the OH group at 11.50 ppm. Reactions of the ultimate compound **7** with acetic anhydride yielded 3-(acetyloxy)-6-nitro-2-propylquinazolin-4(3*H*)-one **8** which is a convenient intermediate for various organic synthesis. Structure of compound **8** was proved from its IR spectrum which showed a notable absorption bands at υ 1614, 1670 and 1725 due to C=N, C=O (amide) and C=O (ester) groups, respectively with the lake of υ OH band. Mass spectrum of both compounds **7** and **8** exhibited their proposed molecular ion peaks at *m/z* 249, 291 respectively as base peaks.

The aforementioned findings prompted us to carry out the reaction of **3** with some additional *N*-nucleophiles. So, reaction of compound 3 with an equimolar quantities of 1,4-*N*,*N*, 1,4-*N*,*O* and 1,4-*N*,*S*-nucleophiles, namely, *o*-phenylendiamine, *o*-aminophenol and *o*-aminothiophenol, furnished the corresponding 3-substituted aminoquinazolinones **9a-c**. ^{1}H NMR spectra of products **9a-c** exhibited the integral count of seven aromatic protons at their characteristic chemical shift area. ^{13}C NMR spectra of both compounds **9a-c** confirmed the proposed structures exhibiting the expected count of carbon atoms. The mass spectrometry was an outstanding tool to demonstrate the suggested structures for compounds **9a-c** showing their molecular ion peaks in agreement with their proposed molecular formulas.



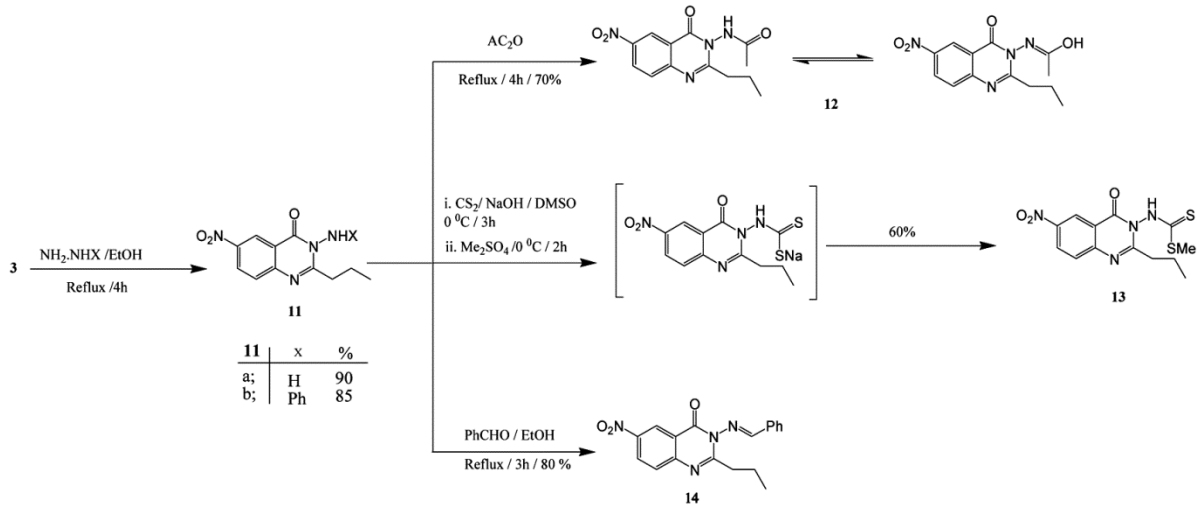
Scheme II — Formation of quinazolinones **3 - 10**

In the same sense, equimolar remediation of compound **3** with 1,3-binnucleophiles such as urea and thiourea in boiling DMF furnished smoothly the anticipated quinazolinone derivatives **10a,b**. Analytical and spectral data of these products were found in similarity with the proposed formula. IR spectra of both **10a,b** compounds showed the C=O stretching vibrations at 1671, 1675 cm^{-1} and the C=S stretching vibrations at 1220-1050 cm^{-1} in addition to NH_2 stretching vibrations at 3330, 3270 cm^{-1}.The ^1H NMR spectra of compounds **10a,b** demonstrated the appearance of the emergence of new singlet signals assigned to the characteristic NH_2 groups protons at 6.2 and 6.5 ppm for both **10a** and **10b**, respectively. ^1H NMR spectral data displayed a characteristic signal at δ 177.1 and 178.2 ppm attributed to both C=O and C=S carbons, respectively. In addition, mass spectrum represents a good guide to **10a,b** structure and showed the molecular ion peak at *m/z* 276 and 292 which corresponds to the suggested molecular formulas.

Benzoxazinone **3** was reacted with hydrazine hydrate and /or phenyl hydrazine in boiling ethanol, 3-amino-6-nitro-2-propylquinazolin-4(3*H*)-one **11a** and 6-nitro-3-(phenylamino)-2-propylquinazolin-4(3*H*)-one **11b** were produced in a respective yield. 3-Aminoquinazolinone **11a** used as many-sided constructing bulk in synthetic heterocyclic chemistry. IR spectrum of the amine **11** exhibited a specific stretching bands at ν 3309 and 3212 cm^{-1} related to symmetric and asymmetric vibrations of NH_2 group. The absorption bands due to C=O group, for ideal quinazolin-4-ones, was observed at ν 1673cm^{-1}. These outcomes are in accordance with ^1H NMR spectral data of compounds **11** which showed a broad singlets chemical shifts at δ 5.50 due to deuterium-exchangeable protons of NH_2. In addition, the mass spectra of compound **11a** revealed its molecular ion peak at *m/z* 248 as base peak. All spectral data of 6-nitro-3-(phenylamino)-2-propylquinazolin-4(3*H*)-one **11b** were fully consistent with its suggested formula (Scheme III).

N-(6-nitro-4-oxo-2-propylquinazolin-3(4*H*)-yl)acetamide **12** was obtained on refluxing of quinazolinone **11a** with acetic anhydride. The IR spectrum of compound **12** revealed strong absorption bands assigned to C=N, two C=O group, NH and OH, respectively. ^1H NMR spectrum of compound **12** revealed that it exists in solution in a keto-enol tautomerism of an amide functionality, as it showed two singlet signals at δ 6.50 and 8.90 attributable to NH and OH of the keto and the enol forms, respectively.

The carbothioamides **13** was targeted because of its expected biological activity[23]. Consequently, reacting of the amine **11a** with carbon disulfide, in existence of sodium hydroxide as base catalyst and *in situ* methylation of the non-separable sodium dithiocarbamide salt, with the use of dimethyl sulfate, yielded Methyl(6-nitro-4-oxo-2-propylquinazolin-3(4*H*)-yl)carbamodithioate **13**. Structure of compound **13** was elucidated from its IR spectrum which showed a strong absorption bands at 1450 and 1670 related to υ max C=S and C=O respectively and freed from the NH_2 band. ^1H NMR spectrum of the product showed a characteristic singlet chemical shift at δ 2.54 due three



Scheme III — Synthesis of quinazolinones **11-14**

protons of SCH_3. Mass spectrum exhibited a molecular ion peak at *m/z* 338, confirming the proposed molecular formula.The amine **11$_a$**was condensed with benzaldehyde to give the corresponding Schiff 's bases **14** (Scheme III) which could be utilized as multilateral building bulk in a variety of heterocyclic synthesis. It will be of interest in our future project to discuss the behavior of azomethine **14** which includes an activated azomethine group (–N=CH)[24]. Spectral data of the product pointed to the disappearance of NH_2 function, indicating its embodiment in the condensation reaction. IR spectra of compounds **14** showed a strong absorption bands at 1610, 1676; related to υ C=N and υ C=O, respectively in addition of lacking any absorption band due to NH_2. ^{1}H NMR spectrum of the trio gave specific chemical shift signals of azomethine proton (N=C–H) observed at δ 8.80. Mass spectrum exhibited a molecular ion peak at *m/z* 336 as base peak, confirming the proposed structure.

The FT-IR comparison of some of our newly synthesized chemosensor **7, 10b** and **11a,b** *versus* their related complexs **15**, **16**, **17** and **18** were identified as shown in the Table I. The FT-IR spectrum changes of our produced complexs confirm that our primary amine, carbonyl groups, thiocarbonyl and hydroxyl group are sharing in the binding with our targeted metal cations.

Colourimetric Study

The colourimetric study was applied for 2.5×10^{-5} M of all the synthesized compounds, which were prepared in DMF- water (1:10). As can be seen from (Table II), Compounds **3**, **9b,c**, **10a**, **12**, **13** and **14** did not give any changes of colour after adding all metals. The chemosensor **10b** and **7** showed the colour change from colourless to yellow when adding Cd^{2+} ion and the intensity of colour was increased with the addition of Cd^{2+} ions. The chemosensors **11a,b** exhibited notable colour change from pale yellow to green when adding Cu^{2+} ion which gets more colour intensity on further addition of Cu^{2+} cation. The same chemosensor exhibited a remarkable colour change to rose on interacting with $Hg^{2+}$and the intensity of colour also increased with further addition of Hg^{2+}ion cation. This important colour change of complex **7**, **10b** and **11a,b** can be easily applied for detection Cu^{2+}, Cd^{2+} and Hg^{2+} ions in an aqueous mediums and biological samples.

UV-vis absorption spectroscopy study

The absorption response of complexes **15**, **16**, **17** and **18** were examined in the presence of different solvents, for instance, ethanol, dimethylformamide, acetonitrile and. The chemosensor **7**, **10b**, **11a,b** displayed good absorption intensity in the dimethylformamide solution contrast to other solvents and so we used dimethylformamide as a solvent for all UV-Vis spectral studies because it showed good absorbance shift and absorption intenisty[25]. Metal ions were prepared as aqueous solutions of 0.02 M nitrate salts in distilled water. Chemosensor stock solutions of **7**, **10b**, **11a,b** (0.02 M) were dissolved in dimethylformamide. By using a micropipette, we prepared and diluted various concentrations of metal

Table I — FT-IR variation between chemosensors and formed complexes

Functional group	Chemosensor number	Stretching vibration chemosensor (cm^{-1})	Complex	Stretching vibration complex (cm^{-1})
(C=O)	**7**	1680	15	1609
(OH)		3530		3403
(C=O)	**10b**	1671	16	1620
(NH_2)		3330 and 3270		3000 and 3100
(C=O)	**11a**	1673	17	1615
(NH_2)		3309 and 3212		3290 and 3190
(C=O)	**11b**	1675	18	1630
(NH)		3360		3265

Table II — Colourimetric responses of selected chemosensors toward various cations

Chemosensor	Detected cation	Colourimetric Responses
7	Cd	Colourless to yellow
10b	Cd	Colourless to yellow
11a	Cu	Pale yellow to green
	Hg	Pale yellow to rose
11b	Cu	Pale yellow to green
	Hg	Pale yellow to rose
9b,c, 10a, 12, 13, 14	All cations	No response

ions to 2.5×10^{-5} M with the same solution. The diluted chemosensors were added to various concentrations of metal ions. The complex **17**-Cu^{2+} showed the main absorption peak (λ max) at 345 nm. The complex **17**-Hg^{2+} showed λ max at 495 nm. The complex **18**-Cu^{2+} showed λ max at 360 nm. The complex **18**-Hg^{2+} λ max at 505 nm. The complex **15**-Cd^{2+} showed λ max at 362 nm, the complex **16**-Cd^{2+}displayed λ max at 425 nm. The calibration curves established standard concentrations of ions and specific absorbance for each one (Figure 1).

Suggested Mechanism

According to UV-Vis absorption analysis and the FT-IR spectrum of compounds **7**, **10b** and **11a,b** towards their complexes **15**, **16**, **17** and **18** respectively, the binding positions were labeled in chemosensor **7**, **10b** and **11a,b**. Some predictable observations can be inferred. The variations in the FT-IR frequencies of **17** and **18** suggest the primary or secondary amine and carbonyl groups are participating in the binding with metal ions and an established binding mechanism is shown in Table III. In the aqueous medium, the nucleophile chemosensors **11a,b** attacked cations by lone pairs of electrons from amino and carbonyl groups to form five-membered ring which have high stability and a low amount of ring strained[26,27]. The change of the FT-IR frequencies of complex **16** indicates that Cd^{2+} coordinated with oxygen atom of carbonyl group and C=S group which inform binding mechanism was presented in Table III. Complex **15** have clearly observed shifts of FT-IR spectrum Table I, which indicated the formation of a binding mechanism, is shown in Table III. The nucleophile chemosensor **7** attacked cations by lone pairs of electrons from OH and C=O groups to form a five-member ring[26].

Application of chemosensor in biological and environmental water samples

The main purpose of the current study was to detect ions traces in a biological sample, so samples were collected from the medical laboratory in Al-zulfi hospital. The relationship between absorption and concentration was obtained by the calibration curve and a linear relationship was established to the determination of the concentration of Cu^{2+}, Cd^{2+} and Hg^{2+} ions in the various blood samples. All blood samples were also further assayed by Atomic Absorption Spectroscopy (AAS) to show the chemosensor sensitivity. The synthesized chemosensors **7**, **10b** and **11a,b** were carried as strip paper and added one drop of ion analyte to the chemosensor strip which directly detects the concentration of cation.

Experimental Section

Melting points were measured on an Optimelt automated melting point system and are uncorrected.

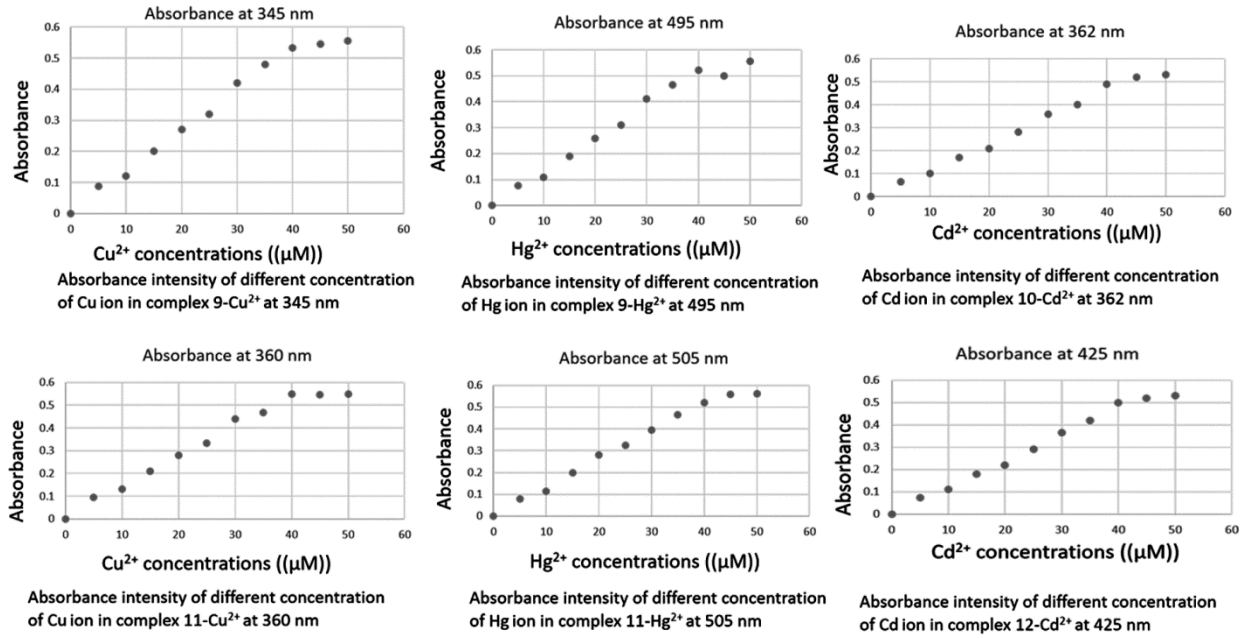
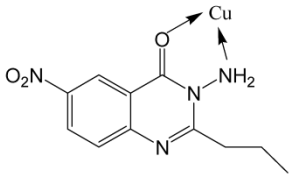
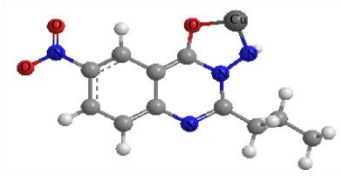
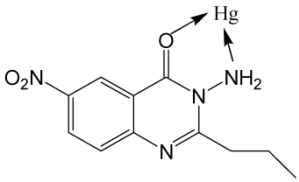
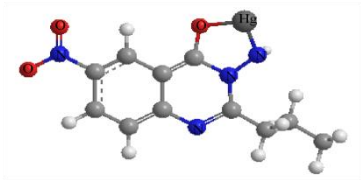
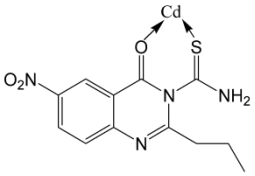
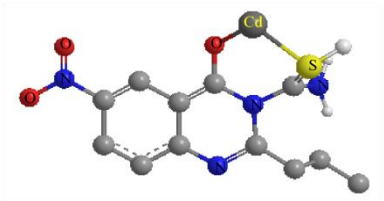
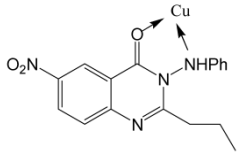
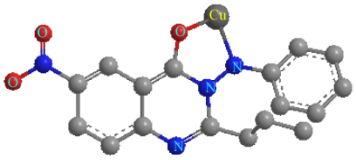
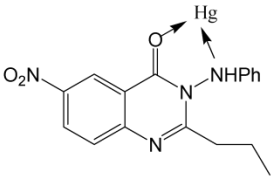
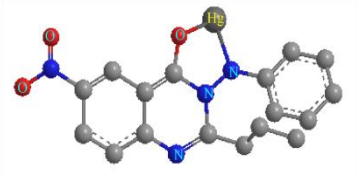
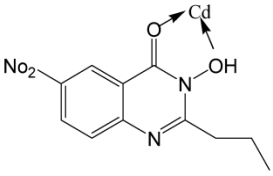
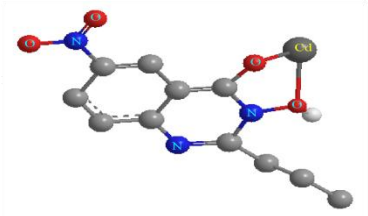


Figure 1 — Calibration curves of absorbance intensity of different concentrations of ions

Table III — Proposed binding mechanism of different chemosensors

Chemosensor	λ max	Complex structure	Suggested binding mechanism
18-Cu^{2+}	345 nm		
18-Hg^{2+}	495 nm		
16-Cd	362 nm		
17-Cu^{2+}	360 nm		
17-Hg^{2+}	505 nm		
15-Cd^{2+}	425 nm		

The IR spectra were recorded on a Perkin−Elmer 1800 Series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in base-filtered DMSO-d_6 on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. Elemental microanalyses were recorded on a Perkin−Elmer series II CHNS analyzer 2400. Mass spectra were obtained using GCMS (QP-1000EX) Shimadzu gas chromatography instrument mass spectrometer (70 eV).

2-(Butyramido)-5-nitrobenzoic acid, 2

Butyryl chloride (1.06 g, 10 mmol) was portion-wise added to a stirred solution of 2-amino-5-nitrobenzoic acid (1.8 g, 10 mmol), in dry pyridine (30 mL) during 30 min. The mixture was stirred at RT for 2 h then poured into ice-cold water (200 mL),

acidified with hydrochloric acid (2N) up to complete precipitation. The crude solid product was filtered off, washed thoroughly with cold water and crystallized from benzene to give compound **2** (2 g, 80%), yellow crystals, m.p.130-135°C. IR (KBr): 3300 (O–H, N–H), 3010 (C–H_{arom}), 2975, 2985 (C–H_{aliph}), 1730 (C=$O_{carboxylic}$), 1640 (C=O_{amidic}), 1615 cm^{-1} (bending N–H); ^{1}H NMR ($CDCl_3$): δ 1.90 (t, 2H, -CH_2-CH_2-CH_3), 1.50 (m, 2H, -CH_2Me) and 1.20 (t, 3H, -CH_3), 7.20-8.70 (m, 3H, H_{arom}), 8.95 (bs, 1H exchangeable with D_2O, NH), 11.80 (bs, 1H exchangeable with D_2O, OH); ^{13}C NMR (100 MH_Z): δ 143.3 (C-1), 115.15(C-2), 129.7 (C-3), 122.4(C-4), 132.98(C-5), 121.52 (C-6), 168.1 (C-7_{COOH}), 170.2 (C-$8_{NHC=O}$), 35.1 (C-9), 19.0 (C-10), 13.2 (C-11); MS: *m/z* 252(M^+,70),253 (M+1,80). Anal. Calcd for $C_{11}H_{12}N_2O_5$ (252): C, 52.38; H, 4.80; N, 11.11; O, 31.72. Found: C, 52.50; H, 4.95; N, 31.94%.

6-Nitro-2-propyl-4*H*-benzo[*d*][1,3]oxazin-4-one, 3

The dry solid anthranilide (2.52g, 10 mmol) **2** was treated with freshly distilled acetic anhydride until being pasted and then heated over water bath for 2 h before lifting to cool. The separated out solid was filtered off and recrystallized from light petroleum ether 40/60 affording the benzoxazinone **3** (2 g,85%), pale yellow crystals, m.p.185°C. IR (KBr): 3050 (C-$H_{aromatic}$), 2971, 2929,2881 (C-$H_{aliphatic}$),1710(C=O), 1617(C=N),1159 cm^{-1} (C-O-C); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.10(2H, -CH_2-CH_2-CH_3), 1.60 (m, 2H, -CH_2Me) and 1.10 (t, 3H, -CH_3), 7.3-8.2 (m, 3H, Ar-H);^{13}C NMR (100 MH_Z): δ 155.2 (C-$1_{C=N}$), 159.1 (C-$2_{C=O}$), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11); MS: *m/z* 234 (M^+,20), 235(M+1,18). Anal. Calcd for $C_{11}H_{10}N_2O_4$ (234): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.50; H, 4.47; N, 11.99%.

6-Nitro-2-propylquinazolin-4(3*H*)-one, 4

A solution of benzooxazinone derivative 3 (2.34 g, 10 mmol,) in formamide (15 mL) was refluxed for 2 h, left to cool, then poured into ice. The crude solid product was collected by filtration, dried and recrystallised from ethanol to give **4** (1.75g,75%), yellow crystals, m.p. > 300°C. IR (KBr): 3372, 3280 (NH), 1670(C=O), 1622 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.30(2H, -CH_2-CH_2-CH_3), 1.80 (m, 2H, -CH_2Me) and 1.22 (t, 3H, -CH_3), 7.82-8.90 (m, 3H, Ar-H), 9.40 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MH_Z): δ 155.2 (C-1), 164 (C-2), 123 (C-3), 130.5 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 148.8 (C-8), 25.4 (C-9), 14.6 (C-10), 13.7 (C-11); MS: *m/z* 233(M^+,30), 234(M+1,23). Anal. Calcd for $C_{11}H_{11}N_3O_3$ (233): C, 56.65; H, 4.75; N, 18.02. Found: C, 56.80; H, 4.90; N, 18.40%.

3-Acetyl-6-nitro-2-propylquinazolin-4(3*H*)-one, 5

A solution of **4** (2.33 g, 10 mmol) in 20 mL acetic anhydride was refluxed for 4 h. The reaction mixture was then allowed to stand at RT for 2 h. The separated solid product was washed with water (2×100 mL), dried and crystallized from ethanol to afford compound **5** (1.65 g, 60%), pale-yellow crystals, m.p.135-7°C. IR (KBr): 1663 (C=O_{Acetyl}), 1675 (C=$O_{Quinazolinone}$), 1622 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.40 (s, 3H, CH_3-C=O), 2.00 (2H, -CH_2-CH_2-CH_3), 1.85 (m, 2H, -CH_2Me), 1.10 (t, 3H, -CH_3), 7.55- 7.83 (m, 3H, Ar-H); ^{13}C NMR (100 MH_Z): δ 163.1 (C-1), 166.9 (C-2), 129.2 (C-3), 131.8 (C-4), 121.5 (C-5), 136.1 (C-6), 124.0 (C-7), 146.2 (C-8), 23.1 (C-9), 13.4 (C-10), 13.4 (C-11), 175.1 (C-$12_{C=O\ acetyl}$), 20.3 (C-13CH_{3CO}); MS: *m/z* 275 (M^+,10), 276 (M+1,33). Anal. Calcd for $C_{13}H_{13}N_3O_4$ (275): C, 56.72; H, 4.76; N, 15.27. Found: C, 53.85; H, 4.90; N, 15.40%.

Ethyl 2-(6-nitro-2-propylquinazolin-4-yloxy)acetate, 6

To a mixture of **4** (2.33 g, 10 mmol) and ethyl chloroacetate (1.22 g, 10 mol) in dry acetone (20 mL), anhydrous potassium carbonate (1.4 g, 10 mol) was added and refluxed on a water-bath for 10 h. The reaction mixture was washed with water (3×100 mL). The organic material was extracted with ether (2×100 mL) and left to be evaporated slowly. The solid obtained was crystallized from ethanol to furnish **6** (2.23g, 70%), pale-yellow crystals, m.p.165-167°C. IR (KBr): 2900, 2920, 2880 (C-$H_{aliphatic}$),1659 (C=O_{ester}), 1615 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 1.25-1.34 (m, 6H, 2CH_3-CH_2-), 1.90(2H, -CH_2-CH_2-CH_3), 1.75 (m, 2H, -CH_2Me),4.27 (q, 2H, -OCH_2CH_3), 4.78 (s, 2H, O-CH_2-C=O), 8.19, 8.38 (m, 3H, Ar-H); ^{13}C NMR (100 MH_Z): δ 164 (C-1), 160 (C-2), 120.9 (C-3), 128.8 (C-4), 127.4 (C-5), 133.5 (C-6), 122.4(C-7), 147.1(C-8), 25.6(C-9), 14.6(C-10), 13.9 (C-11), 65.5(C-12, OCH_2), 170 (C-$13_{C=O\ ester}$), 28.2(C-14), 15.5 (C-15); MS: *m/z* 319 (M^+,22), 320 (M+1,38). Anal. Calcd for $C_{15}H_{17}N_3O_5$ (319): C, 56.42; H, 5.37; N, 13.16. Found: C, 56.80; H, 5.80; N, 1350.80%.

3-Hydroxy-6-nitro-2-propylquinazolin-4(3*H*)-one, 7

An equimolar mixture of benzoxazinone **3** (2.34 g, 10 mmol) and hydroxylamine hydrochloride (6.9 g,

10 mmol) in 20 mL of dry pyridine was heated under reflux for 4 h, left to cool and then poured into cold water with constant stirring. The solid product that separated out was filtered off, thoroughly washed with water, dried and then recrystallized from benzene to give compound **7** (1.86, 75%), white crystals, m.p.230-231°C. IR (KBr): 3530 (OH),1680 (C=O), 1615 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.20(2H, -CH_2-CH_2-CH_3), 1.80 (m, 2H, -CH_2Me), 1.15 (t, 3H, -CH_3), 11.20 (bs, 1H exchangeable with D_2O, O–H), 7.80, 8.10 (m, 3H, Ar-H, quinazolone); ^{13}C NMR (100 MH_Z): δ 164.2 (C-1), 162.3 (C-2), 131.1 (C-3), 130.7 (C-4), 123.5 (C-5), 139.4 (C-6), 118.7 (C-7), 149.8 (C-8), 23.0 (C-9), 13.4 (C-10), 11.6 (C-11); MS: *m/z* 249 (M^+,100),250 (M+1,12). Anal. Calcd for $C_{11}H_{11}N_3O_4$ (249): C, 53.01; H, 4.45; N, 16.86. Found: C, 53.30; H, 4.80; N, 16.90%.

3-(Acetyloxy)-6-nitro-2-propylquinazolin-4(3*H*)-one, 8

1 mol of compound **7** (2.49g, 10 mmol) was heated under reflux in 30 mL of freshly distilled acetic anhydride for 3 h. The reaction solution was left to cool and the solid that deposited was filtered off, washed several times with light petroleum, dried and recrystallized from ethanol to afford the desired product **8** (1.9g, 65%), white crystals, m.p.175-177°C. IR (KBr): 1669 ($C=O_{quinazolinone}$), 1725 ($C=O_{ester}$), 1614 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.02 (2H, -CH_2-CH_2-CH_3), 1.68 (m, 2H, -CH_2Me), 1.28 (t, 3H, -CH_3), 7.9 (s, 3H, $COCH_3$), 7.80-8.10 (m, 3H, Ar-H); ^{13}C NMR (100 MH_Z): δ 155.2 (C-1), 161 (C-2), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11), 169.3 (C-12), 18.5 (C-13); MS: *m/z* 291 (M^+,100), 292 (M+1,12). Anal. Calcd for $C_{13}H_{13}N_3O_5$ (291): C, 53.61; H, 4.50; N, 14.43. Found: C, 53.70; H, 4.80; N, 14.90%.

General procedure for formation of synthesis of compounds 9a-c

A magnetically stirred solution of benzoxazinone **3** (2.34 g, 10 mmol) in glacial acetic acid (20 mL) maintained at 100°C was treated with each of *o*-phenylendiamine (1.08 g, 10 mmol), *o*-aminophenol (1.09 g, 10 mmol) *o*-aminothiophenol (1.46 mL, 10 mmol). The resulting solution was stirred at 100°C for additional 4 h before being cooled, poured into water (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The solid obtained were crystallized from AcOH to give compounds **9a-c**.

3-(2-Aminophenyl)-6-nitro-2-propylquinazolin-4(3*H*)-one, 9a: 1.94 g, 60%, pale-yellow crystals, m.p.164-165°C. IR (KBr): 3360, 3280 (NH_2), 3051 ($C–H_{aromatic}$), 2920 ($C–H_{aliphatic}$), 1675 ($C=O_{quinazolinone}$), 1620 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.00 (2H, -CH_2-CH_2-CH_3), 1.70 (m, 2H, -CH_2Me), 1.02 (t, 3H, -CH_3), 5.2(s, 2H, D_2O-exchangeable, NH_2), 7.21-7.34 (m, 7H, Ar-H); ^{13}C NMR (100MHz): δ 164.0 (C-1), 164.8 (C-3), 133.0 (C-3), 131.0 (C-4), 124.1 (C-5), 135.1 (C-6), 117.5 (C-7), 148.5 (C-8), 22.1 (C-9), 13.9 (C-10), 11.8 (C-11),, 127.5 (C-12), 136.8 (C-13), 116.9 (C- 14), 125.9 (C-15), 119.0 (C-16), 120.0 (C-17); MS: *m/z* 324 (M^+,100), 325 (M^++1,12). Anal. Calcd for $C_{17}H_{16}N_4O_3$ (324): C, 62.95; H, 4.97; N, 17.27. Found: C, 63.20; H, 5.10; N, 17.40%.

3-(2-Hydroxyphenyl)-6-nitro-2-propylquinazolin-4(3*H*)-one, 9b: 2.5 g, 76%, orange crystals, m.p.170-172°C. IR (KBr): 3360 (OH), 3040 ($C–H_{aromatic}$), 2929 ($C–H_{aliphatic}$), 1680 ($C=O_{quinazolinone}$), 1625 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.20 (2H, -CH_2-CH_2-CH_3), 1.85 (m, 2H, -CH_2Me), 1.12 (t, 3H, -CH_3), 7.22-7.85 (m, 7H, Ar-H), 11.81 (s, 1H, OH exchangeable with D_2O); ^{13}C NMR (100MHz): δ 163.0 (C-1), 164.7 (C-3), 132.4 (C-3), 130.4 (C-4), 123.3 (C-5), 137.1 (C-6), 118.1 (C-7), 149.5 (C-8), 23.1 (C-9), 13.4 (C-10), 13.4 (C-11), 127.3 (C-12), 138.4 (C-13), 115.1 (C- 14), 124.6 (C-15), 118.5 (C-16), 121.1 (C-17); MS: *m/z* 325 (M^+,60), 326 (M^+ + 1,22). Anal. Calcd for $C_{17}H_{15}N_3O_4$ (325): C, 62.76; H, 4.65; N, 12.92%. Found: C, 62.90; H, 4.80; N, 13.01%.

3-(2-Mercaptophenyl)-6-nitro-2-propylquinazolin-4(3*H*)-one, 9c: (1.7 g, 50%), orange crystals, m.p. 210-211°C. IR (KBr): 3400 (SH), 3030 ($C–H_{aromatic}$), 2910 ($C–H_{aliphatic}$), 1670 ($C=O_{quinazolinone}$), 1618 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.10 (2H, -CH_2-CH_2-CH_3), 1.75 (m, 2H, -CH_2Me), 1.10 (t, 3H, -CH_3), 7.52-7.95 (m, 7H, Ar-H), 12.51 (s, 1H, SH exchangeable with D_2O; ^{13}C NMR(100MHz): δ 163.2 (C-1), 164.1 (C-3), 132.0 (C-3), 130.0 (C-4), 123.1 (C-5), 136.1 (C-6), 118.5 (C-7), 149.0 (C-8), 22.9 (C-9), 13.2 (C-10), 11.4 (C-11),, 127.1 (C-12), 136.4 (C-13), 116.1 (C- 14), 125.6 (C-15), 119.5 (C-16), 120.1 (C-17); MS: *m/z* 341 (M^+,18),342 (M^+ + 1,20). Anal. Calcd for $C_{17}H_{15}N_3O_3S$ (341): C, 59.81; H, 4.43; N, 12.31. Found: C, 60.00; H, 4.61; N, 12.44%.

General procedure for formation of synthesis of compounds 10a,b

A mixture of benzoxazinone **3** (2.342 g, 10 mmol) and the appropriate urea derivatives, urea (0.60g, 10 mmol) and/or thiourea (0.76 g, 10 mmol), in DMF (20 mL) was refluxed for 4 h. After the completion of reaction, the reaction mixture was poured into ice water to give a precipitate that was filtered off and recrystallized from ethanol to give **10a,b**.

6-Nitro-4-oxo-2-propylquinazoline-3(4*H*)-carboxamide 10a: 1.66 g, 60%, pale-yellow crystals, m.p.180-182°C. IR (KBr): 3300-3240 (NH_2), 3050 (C–H_{arom}atic), 2950 (C–$H_{aliphatic}$), 1675 (C=$O_{quinazolinone}$), 1640 (C=O), 1618 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 1.90 (2H, -CH_2-CH_2-CH_3), 1.72 (m, 2H, -CH_2Me), 1.15 (t, 3H, -CH_3), 4.5 (s, 2H, D_2O-exchangeable, NH_2), 7.50-7.70 (m, 3H, Ar-H); ^{13}C NMR (100MHz): δ 164 (C-1), 160 (C-2), 120.9 (C-3), 128.8 (C-4), 127.4 (C-5), 133.5 (C-6), 122.4(C-7), 147.1(C-8), 25.6(C-9), 14.6(C-10), 13.9 (C-11), 168(C-$12_{C=ONH2}$); MS: *m/z* 276 (M^+,100), 277 (M^+ + 1,12). Anal. Calcd for $C_{12}H_{12}N_4O_4$ (276): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.20; H, 4.60; N, 20.65%.

6-Nitro-4-oxo-2-propylquinazoline-3(4*H*)-carbothioamide10b: 2g, 70%, white crystals, m.p.200-201°C. IR (KBr): 3320, 3270 (NH_2), 3000 (C–$H_{aromatic}$), 2900 (C–$H_{aliphatic}$), 1671 (C=$O_{quinazolinone}$), 1621 (C=N), 1240 cm^{-1} (C=S); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.10 (2H, -CH_2-CH_2-CH_3), 1.82 (m, 2H, -CH_2Me), 1.10 (t, 3H, -CH_3), 5.4 (s, 2H, D_2O-exchangeable, NH_2), 7.90-8.50 (m, 7H, Ar-H); ^{13}C NMR (100MHz): δ 162 (C-1), 161 (C-2), 121.9 (C-3), 127.5 (C-4), 126.2 (C-5), 131.5 (C-6), 120.4(C-7), 146.2(C-8), 24.6(C-9), 13.6(C-10), 11.9 (C-11), 172(C-$12_{C=S}$); MS: *m/z* 292 (M^+,32),293 (M^+ + 1,18). Anal. Calcd for $C_{12}H_{12}N_4O_3S$ (292): C, 49.31; H, 4.14; N, 19.17. Found: C, 49.70; H, 14.30; N, 19.40%.

General procedure for formation of synthesis of compounds 11a,b

An equimolar mixture of benzoxazinone **3** (2.34 g, 10 mmol) and hydrazine hydrate (0.75 g, 10 mmol) and/or phenylhydrazine (1.08 g, 10 mmol), in ethanol was heated at refluxing temperature for 4 h. The solid that settled down on cooling was filtered off and crystallized from light petroleum 60/80 to give **11a,b**.

3-Amino-6-nitro-2-propylquinazolin-4(3*H*)-one, 11a: 2.23g, 90%, pale-yellow crystals, m.p.133-134°C. IR (KBr): 3309, 3212 (NH_2), 3010 (C–$H_{aromatic}$), 2930 (C–$H_{aliphatic}$), 1673 (C=$O_{quinazolinone}$), 1620 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.20 (2H, -CH_2-CH_2-CH_3), 1.80 (m, 2H, -CH_2Me), 1.15 (t, 3H, -CH_3), 5.50 (s, 2H, D_2O-exchangeable, NH_2), 7.20-7.80 (m, 3H, Ar-H); ^{13}C NMR (100MHz): δ 163.5 (C-1), 167.1 (C-2), 129.2 (C-3), 131.7 (C-4), 121.5 (C-5), 136.7 (C-6), 124.3 (C-7), 146.4 (C-8), 23.0 (C-9), 13.4 (C-10), 12.6 (C-11); MS: *m/z* 248 (M^+,100), 249 (M^+ + 1,12). Anal. Calcd for $C_{11}H_{12}N_4O_3$ (248): C, 53.22; H, 4.87; N, 22.57. Found: C, 53.55; H, 4.95; N, 22.90%.

6-Nitro-3-(phenylamino)-2-propylquinazolin-4(3*H*)-one, 11b: 2.75g, 85%, pale-yellow crystals, m.p.192-193°C. IR (KBr): 3385 (NH), 3000 (C–$H_{aromatic}$), 2910 (C–$H_{aliphatic}$), 1675 (C=$O_{quinazolinone}$), 1622 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.10 (2H, -CH_2-CH_2-CH_3), 1.70 (m, 2H, -CH_2Me), 1.10 (t, 3H, -CH_3), 8.90 (bs, 1H exchangeable with D_2O, N–H), 7.50-8.80 (m, 8H, Ar-H); ^{13}C NMR (100MHz): δ 163.1 (C-1), 166.9 (C-2), 129.2 (C-3), 131.8 (C-4), 121.5 (C-5), 136.1 (C-6), 124.0 (C-7), 146.2 (C-8), 23.1 (C-9), 13.4 (C-10), 12.3 (C-11), 136.0 (C-12), 130.1 (C- 13), 128.4 (C-14), 132.1 (C-15), 128.4 (C-16), 130.1 (C-17); MS: *m/z* 324 (M^+,100), 325 (M^+ + 1,12). Anal. Calcd for $C_{17}H_{16}N_4O_3$ (324): C, 62.95; H, 4.97; N, 17.27. Found: C, 62.02; H, 5.10; N, 17.90%.

N-(6-Nitro-4-oxo-2-propylquinazolin-3(4*H*)-yl) acetamide, 12

A solution of **11** (2.48 g, 10 mmol) and acetic anhydride (20 mmol) in glacial acetic acid (30 mL) was heated at refluxing temperature for 4 h. When the reaction mixture was left to cool and diluted with cold water, the solid which separated out was filtered off and recrystallized from ethanol to afford **12** (2 g, 70%), yellow crystals, m.p.170-172°C. IR (KBr): 3487 (OH), 3280 (NH), 3080 (C–H_{arom}), 2910 (C–H_{aliph}), 1673 (C=$O_{quinazolinone}$), 1635 (C=O_{amidic}) 1610 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.30 (2H, -CH_2-CH_2-CH_3), 2.00 (2, 3H, CH_3-C=O), 1.70 (m, 2H, -CH_2Me), 1.30 (t, 3H, -CH_3), 8.00-7.85 (m, 3H, Ar-H), 6.50 (bs, 1H exchangeable with D_2O, NH), 8.90 (bs, 1H exchangeable with D_2O, OH); ^{13}C NMR (100 MHz): δ 155.2 (C-1), 161 (C-2), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11), 173.0 (C-12 $_{NHCO}$), 12.0 (C-$13_{CO}CH_3$); MS: *m/z* 290 (M^+,100), 291 (M^+ +

1, 12). Anal. Calcd for $C_{13}H_{14}N_4O_4$ (290): C, 53.79; H, 4.86; N, 19.30. Found: C, 53.90; H, 4.95; N, 19.90%.

Methyl (6-nitro-4-oxo-2-propylquinazolin-3(4*H*)-yl)carbamodithioate, 13

An aqueous solution of sodium hydroxide (12 mL, 24 mmol, 2 N) was drop-wise added to a stirred mixture of the amine **11** (2.48 g, 10 mmol) and carbon disulfide (1.5 mL, 24 mmol), in DMSO (20 mL), in an ice bath, over a period of 30 min. Then the reaction mixture was stirred for additional 3 h. Afterwards, dimethyl sulphate (1.9 mL, 20 mmol) was gradually added with continuous stirring in 2 h. Then the reaction mixture was diluted with ice-cold water (40 mL) to give solid deposits which were filtered, washed with water, dried and crystallized from acetonitrile to yield compound **13** (2 g, 60%), yellow crystals, m.p.145-146°C. IR (KBr): 3280, 3150 (N–H), 3060 (C– $H_{aromatic}$), 2980, 2900, 2870 (C–$H_{aliphatic}$), 1670 (C=O), 1610 (C=N, N–H), 1450 cm^{-1} (C=S); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.50 (s, 3H, SCH_3), 2.10 (2H, -CH_2-CH_2-CH_3), 1.65 (m, 2H, -CH_2Me), 1.15 (t, 3H, -CH_3), 7.20-7.80 (m, 3H, Ar-H), 9.95 (bs, 1H exchangeable with D_2O, N–H); ^{13}C NMR (100 MHz): δ 155.2 (C-1), 161 (C-2), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11), 179.3 (C-12_{CS}), 12.2 (C-13 SCH_3); MS: *m/z* 338 (M^+,100), 339 (M^+ + 1, 12). Anal. Calcd for $C_{13}H_{14}N_4O_3S_2$ (338): C, 46.14; H, 4.17; N, 16.56. Found: C, 46.30; H, 4.25; N, 16.90%.

3-(Benzylideneamino)-6-nitro-2-propylquinazolin-4(3*H*)-one, 14

A mixture of **11** (2.48 g, 10mol) and benzaldehyde (0.01 mol) in 60 mL of ethanol, containing a few drops of piperidine as a catalyst, was refluxed for 4h. The solid separated out upon cooling was filtered off and recrystallized from benzene to produce compound **14** (2.7g, 80%), white crystals, m.p.180-181°C. IR (KBr): 3020 (C– $H_{aromatic}$),2900(C–$H_{aliphatic}$), 161676 (C=O), 1610 cm^{-1} (C=N); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 2.20 (2H, -CH_2-CH_2-CH_3), 1.85 (m, 2H, -CH_2Me), 1.10 (t, 3H, -CH_3), 7.40-8.20 (m, 8H, Ar-H), 8.80 (s, 1H, N=CH); ^{13}C NMR (100 MHz): δ 163.1 (C-1), 166.9 (C-2), 129.2 (C-3), 131.8 (C-4), 121.5 (C-5), 136.1 (C-6), 124.0 (C-7), 146.2 (C-8), 23.1 (C-9), 13.4 (C-10), 13.4 (C-11), 164.5(C-$12_{C=N}$), 136.0 (C-13), 130.1 (C- 14), 128.4 (C-15), 132.1 (C-16), 128.4 (C-17), 130.1 (C-18); MS: *m/z* 336 (M^+,100), 337 (M^+ +1,18). Anal. Calcd for $C_{18}H_{16}N_4O_3$ (336): C, 64.28; H, 4.79; N, 16.66. Found: C, 64.30; H, 4.90; N, 16.90%.

Conclusion

The current study established new chemosensors quinazolinones **9a** and **11** for the quantitative determination of Cu^{2+}, Cd^{2+} at exact wavelengths in an aqueous medium and in blood samples. Similarly, chemosensors **10b** and **7** have been synthesized for determination of Hg^{2+} ion in an aqueous medium and the environmental samples like water samples. Hence, we designed a paper strip carrying chemosensor, so the determination of Cu^{2+}, Cd^{2+} and Hg^{2+} will become easy and inexpensive.

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References

1 (a) Xu Z, Chen X, Kim H N & Yoon J, *Chem Soc Rev*, 39 (2010) 127; (b) Yoon J, Kim S K, Singh N J & Kim K S, *Chem Soc Rev*, 35 (2006) 355; (c) Kundu A, Hariharan P S & Prabakaran K, *Sen Actuators*, 206 (2015) 524; (d) Lee H N, Xu Z, Kim S K, Swamy K M K, Kim Y, Kim S J & Yoon J, *J Am Chem Soc*, 129 (2007) 3828; (e) Chen C F & Chen Q Y, *New J Chem*, 30 (2006) 143; (f) Ghosh S, Choudhury A R, Guru Row T N & Maitra U, *Org Lett*, 7 (2005) 1441.

2 (a) Barnham K J & Masters C L, *Nat Rev Drug Discov*, 3 (2004) 205; (b) Brown D R, *Brain Res Bull*, 55 (2001) 165; (c) Waggoner D J, Bartnikas T B & Gitlin J D, *Neurobiol Dis*, 6 (1999) 221.

3 Lauwerys R R, Bernard A M, Roels H A & Buchet J P, *Clin Chem*, 40 (1994) 1391.

4 Rahim M, Ullah I, Khan A & Haris M R H M, *J Chem Soc Pak*, vol. 38 (2016) 177.

5 Ivan S, Irina K, Trajce S & Juli J, *Microchemical Journal*, 89 (2008) 42.

6 (a) Butler O T, Cook J M, Harrington C F, Hill S J, Rieuwerts J & Miles D L, *J Anal Atom Spectrom*, 21 (2006) 217; (b) Li Y, Chen C, Li B, Sun J, Wang J, Gao Y, Zhao Y & Chai Z, *J Anal Atom Spectrom*, 21 (2006) 94; (c) Leermakers M, Baeyens W, Quevauviller P & Horvat M, *Trends Anal Chem*, 24 (2005) 383.

7 Lin W, Yuan L, Tan W, Feng J & Long L, *Chemistry*, 15 (2009) 1030.

8 Kato T, Nakamura S & Morita M, *Anal Sci*, 6 (1990) 623

9 (a) Cho E J, Ryu B J, Lee Y J & Nam K C, *Org Lett*, 7 (2005) 2607; (b) Duke R M, Veale E B, Pfeffer F M, Kruger P E & Gunnlaugsson T, *Chem Soc Rev*, 39 (2010) 3936; (c) Kaur P & Sareen D, *Dyes Pigm*, 88 (2011) 296.

10 Kim H N, Ren W X, Kim J S & Yoon J, *Chem Soc Rev*, 41 (2012) 3210.

11 Li M, Lu H Y, Liu R L, Chen J D & Chen C F, *J Org Chem*, 77 (2012) 3670.

12 Fegade U, Saini A, Sahoo S K, Singh N, Bendre R & Kuwar A, *RSC Adv*, 4 (2014) 39639.

13 (a) Razi S S, Ali R, Srivastava P, Shahid M & Misra A, *RSC Adv*, 4 (2014) 16999; (b) Mahapatra A K, Manna S K & Sahoo P, *Talanta*, 85 (2011) 2673; (c) Velmathi S, Reena V, Suganya S & Anandan S, *J Fluoresc*, 22 (2012) 155; Isaad J & El-Achari A, *Tetrahedron*, 67 (2011) 4939.

14 Bai X, Ren J, Zhou J & Song Z, *Heterocycl Commun*, 24 (2018) 135.

15 Lu C, Xu Z, Cui J, Zhang R & Qian X, *J Org Chem*, 72 (2007) 3554.

16 (a) Azab M E, Kassab E A, El-Hashash M A & Ali R S, *Phosphorus Sulfur Silicon Relat Elem*, 184 (2009) 610; (b) Giri R S, Thaker H M, Giordano T, Williams J & Rogers D, *Eur J Med Chem*, 44 (2009) 2184; (c) El-Hashash M A, Guirguis D B & El-Badry Y A, *Der Pharma Chem*, 3 (2011) 147; (d) El-Hashash M A, Darwish K M, Rizk S A & El-Bassiouny F A, *Pharmaceutical*, 4 (2011) 1032; (e) Jessy E M, Sambanthan A T, Alex J, Sridevi C H & Srinivasan K K, *Indian J Pharm Sci*, 69 (2007) 476; (f) Jatav V, Mishra P & Kashaw S, *Eur J Med Chem*, 43 (2008) 1945; (g) Kadi A A, Azab A S, Alafeefy A M & Abdel S G, *J Pharm Sci*, 34 (2006) 147; (h) Alagarsamy V, Thangathiruppathy A, Mandal S C & Rajasekaran S, *Indian J Pharm Sci*, 68 (2006) 108; (i) Cao S L, Feng Y P, Jiang Y Y, Liu S Y & Ding G Y, *Bioorg Med Chem Lett*, 15 (2005) 1915; (j) Xia Y, Yang Z Y, Hour M J, Kuo S C & Xia P, *Bioorg Med Chem Lett*, 11 (2001) 1193.

17 (a) Yuan A, Zheng C, Zhang Z, Lu-Yang L C & Wang H, *J Fluoresc*, 24 (2014) 557; (b) Gao M, Li S-W, Lin Y-H, Geng Y, Ling X & Wang X, *ACS Sens*, 1 (2016) 179.

18 Borase P N, Thale P B & Shankarling G S, *Dyes Pigments*, 134 (2016) 276.

19 (a) Algohary A M, Hassan M & Abass M, *Der Pharmacol Chem*, 3 (2011) 1; (b) Eissa A M F, El-Metwally A M & El-Hashash M A, *J Korean Chem Soc*, 3 (2008) 328; (c) El-Hashash M A, Azab M E, Morsy J M & Mahmoud N, *J Heterocyclic Chem*, 92 (2016) 316.

20 El-Hashash M A, Azab M E & Morsy J M, *J Heterocyclic Chem*, 53 (2016) 95.

21 Ghorab M M & Hassan A Y, *Phosphorus Sulfur Silicon Relat Elem*, 141 (1998) 251.

22 Joule J A & Smith G F, *Heterocyclic Chemistry* (Van Nostrand Reinhold, London), 61 (1972).

23 (a) Pilátová M, Sarisský M, Kutschy P, Mirossay A, Mezencev R, Curillová Z, Suchý M, Monde K, Mirossay L & Mojzis J, *Leuk Res*, 29 (2005) 415; (b) Csomós P, Zupkó I, Réthy B, Fodor L, Falkay G & Bernáth G, *Bioorg Med Chem Lett*, 16 (2006) 6273; (c) Hou X, Ge Z, Wang T, Guo W, Cui J, Cheng T, Lai C & Li R, *Bioorg Med Chem Lett*, 16 (2006) 4214; (d) Zahran M A-H, Salem T A-R, Samaka R M, Agwa H S & Awad A R, *Bioorg Med Chem*, 16 (2008) 9708; (e) Gaspari P, Banerjee T, Malachowski W P, Muller A J, Prendergast G C, DuHadaway J, Bennett S & Donovan A M, *J Med Chem*, 49 (2006) 684.

24 (a) Kumar A & Rajput C S, *Eur J Med Chem*, 44 (2009) 83; (b) Alafeefy A M, El-Azab A S, Mohamed M A, Bakhat M A & Abdel-Hamid S G, *J Saudi Chem Soc*, 15 (2011) 319.

25 Venkatadri T, Darshak R & Trivedi A, *Analytica Chimica Acta*, 972 (2017) 81.

26 Wiberg K B, Lampman G M, Ciula R P, Connor D S, Schertler P & Lavanish J, *Tetrahedron*, 21 (1965) 2749.