



# Schiff base of 4*E*,10*E*-4-(2-(4-nitrophenyl)-*N*-((1*H*-indol-3-yl)methylene) benzenamine-based “turn-on” fluorescence chemosensor for highly selective detection of Ni<sup>2+</sup>, Fe<sup>3+</sup>, and Mg<sup>2+</sup> ions

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## Abstract

A Schiff base of 4*E*,10*E*-4-(2-(4-nitrophenyl)-*N*-((1*H*-indol-3-yl)methylene) benzenamine was synthesized and characterized by <sup>1</sup>H&<sup>13</sup>C-NMR, FT-IR, and ESI-MS spectroscopy. UV-visible and fluorescence studies were explored for chemosensor **ICPA** to detect Ni<sup>2+</sup>, Fe<sup>3+</sup>, and Mg<sup>2+</sup> by fluorescence chemosensor “turn-on” method in 10 mM HEPES buffer in EtOH/H<sub>2</sub>O (1:4, v/v) medium. Chemosensor **ICPA** binds with the selective heavy metal ions and could be proved in very low detection limits. Job’s plot demonstrates 1:1 stoichiometric complexes of **ICPA** + Ni<sup>2+</sup>, **ICPA** + Fe<sup>3+</sup>, and **ICPA** + Fe<sup>3+</sup> with the calculated mole fraction of 0.5 μM. Binding constant values calculated using the Benesi–Hildebrand method are found to be 3.45 × 10<sup>8</sup> M<sup>-2</sup>, 5.63 × 10<sup>4</sup> M<sup>-2</sup>, and 8.63 × 10<sup>3</sup> M<sup>-2</sup>, respectively. Competitive metal ions tests were also carried out with transition metal ions. Furthermore, HeLa cell activity at different concentrations added with ligand to perform inhibition capability of the probe was also carried out.

**Keywords** Synthesis · Fluorescent · Chemosensor · Nickel, iron, and magnesium · HeLa cells

## Introduction

Fluorescent chemosensors attracted a huge deal of interest due to their high simplicity, sensitivity, versatility, selectivity, and capabilities through the sensing of various chemical, biological, and environmental significance species, including metal ions and anions, between in vitro and also in vivo (Yiran et al. 2014), and, in addition, portability and the availability of a broad variety as indicator dyes. There is nothing to doubt fluorescent chemosensors with their different responsibilities against several analytes for cost-effective and instrumental practical applications (Sun et al. 2017). In earlier studies, small molecular-structured

fluorescent chemosensors are used as a monitoring agent over the analyte in a living system. These contained high selectivity and sensitivity with uncomplicated recognition procedures. Therefore, this decade has seen various experiments paying attention to the construction of sensitive and selective chemosensors using spectral techniques with both spectrofluorometric and spectrophotometric techniques for the recognition (Vijay et al. 2019). In general, chemosensors either enhance or reduce the emission and absorption band due to binding with metal ions (Nayab and Shkir 2017). The most benefit of fluorescence “turn-on” chemosensors related to “turn-off” chemosensors is for their low concentration compared to a “dark” background, which decreases the opportunity of wrong positive signals and enhances the sensitivity, as established by several studies. Moreover, colorimetric chemosensors got involved in much attention for allowed “naked-eye” recognition in a difficult and inexpensive method, to contribute qualitative and quantitative information (Li et al. 2014). Detection and sense of different metal ions have to befall a dynamic field of analysis due to its potential application in various fields including such as biomedicine, chemistry, and finally environmental studies (Hyvönen and Aksela 2010). The high content of transition and heavy metals in soil, air, drinking water, and plants is

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responsible for their accumulation in the human body, and this occurrence has been coupled to the tumors, insurgence of allergies, and other serious diseases above the genetic pathologies, particularly in children (Lvova et al. 2016). Among the different transition metals,  $\text{Ni}^{2+}$  ion is an essential nutrient for living organisms incorporating into the biological process lists such as biosynthesis, metabolism, and respiration (Prabhu et al. 2017). The  $\text{Ni}^{2+}$  ion, in particular at big doses, results in genotoxic and also mutagenic activity, and its genotoxicity might be aggravated by the generation of DNA-damaged ROS (reactive oxygen species) and inhibited of DNA (deoxyribonucleic acid) repairs (Inoue et al. 1997). The small amount of  $\text{Ni}^{2+}$  examined is very often investigated through diverse methods such as inductively coupled plasma-mass spectroscopy (Fujishiro et al. 1994) and atomic absorption spectroscopy (Miller et al. 2001; Lidén et al. 2008). Among different metal ions over  $\text{Fe}^{3+}$  ions being a vital element with the human body, it plays a much important role factor in the growth and improvement of living systems (Madhu and Sivakumar 2019a, b). Recent research shows that the  $\text{Fe}^{3+}$  participates in a few neurodegenerative diseases both of Parkinson's and Alzheimer's disease (Madhu and Sivakumar 2019a, b). And, either it is a deficiency or an excess in the body which had generally persuaded several disorders with iron smuggling and storage, and the balance being tightly uncomfortable in an organism (Zhang et al. 2018). Provided the paramagnetic nature of  $\text{Fe}^{3+}$ , fluorescent chemosensors were based on the fluorescence quenching mechanism (Wu et al. 2018). And also the most important is to maintain the redox balance of labile iron species which can generate iron catalysis reaction of oxygen species (ROS) (D'Autréaux et al. 2005; Galaris et al. 2008; Natarajan et al. 2019). Between inadequacy and excess of iron absorption in the human body cause cellular homeostasis and also cause different biological diseases (Haas and Brownlie 2001; Thum and Anker 2007; Zheng et al. 2005; Bonda et al. 2011; Pithadia and Lim 2012).  $\text{Mg}^{2+}$  ions are among the majority abundant divalent metal cations present in cells and play crucial roles in numerous cellular processes such as the proliferation of cells, stabilization of DNA conformation, and enzyme-driven biochemical reactions (Hariharan and Anthony 2014). A deficient and excessive amount of metal ions leads to several diseases. The main source is drinking water which gives magnesium in fair quantities. The standard technique for the determination of  $\text{Mg}^{2+}$  ions in drinking water is with EDTA complexometric titration (Li et al. 2016). A drug designed and synthesized as a chemosensor for  $\text{Mg}^{2+}$  recognition in an aprotic solvent with far above the ground selectivity is desired (Marimuthu and Ramu 2018). Schiff bases are unique classes among discovered and had drawn special attention by tempting to the chemists for their manufacture access, efficient chemical and physical properties, and easy isolation, and, in addition,

applications as the synthesis of coordination ligand, catalysis, molecular ion recognition, magnetic properties, and optical properties (Chowdhury et al. 2018) Schiff base compounds are called “privileged compounds” because they are shortly synthesized with the condensation of both aldehydes and amines, a well-known one. The strong ability of Schiff base–metal complexes enables their use across a different range of fields, to catalysis, from medicine, fluorescent sensors, and chemosensors (Abdel-Rahman et al. 2013, 2014, 2016, 2017, 2018; Abu-Dief and Nassr 2015; Abdel-Rahman et al. 2019a, b, 2020; Al-Saedi et al. 2018; Gao et al. 2018). There are different processes answerable for the photophysical reaction of these fluorophores for detection of  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$  and  $\text{Mg}^{2+}$  ion, such as photoinduced electron transfer (PET) (Banerjee et al. 2013; Sahana et al. 2013; Zhou et al. 2015), excited-state ES IPT (intramolecular proton transfer) (Dhineshkumar et al. 2018; Qin et al. 2015a, b, c; Hossain et al. 2015; Qin et al. 2015a, b, c), CHEF (chelation-enhanced fluorescence) (Ta et al. 2019; Dhineshkumar et al. 2020), ICT (internal charge transfer) (Dhineshkumar et al. 2019; Maity and Govindaraju 2012), FRET (fluorescence resonance energy transfer) (Qin et al. 2015a, b, c; Kim et al. 2008), and C=N isomerization (Kim et al. 2014). Water pollution is the contamination of bodies of water (such as groundwater, aquifers, rivers, lakes, seas, and oceans) typically caused by human activities. Water pollution is any change in water's physical, biological, or chemical properties that would be harmful to any living organism (Ali et al. 2005, 2013, 2016, 2017, 2018; Alharbi et al. 2018). Drinking water, also known as potable water, is the water considered safe enough for both animal and human use. This is water, usually used to wash, drink, eat, irrigate crops, etc. Chemicals, bacteria, and other pollutants affect even our drinking water these days (Basheer 2018a, b; Basheer and Ali 2018; Burakova et al. 2018).

In the part of this research, a Schiff base chemosensor has been synthesized and characterized by  $^1\text{H}$  &  $^{13}\text{C}$ -NMR, FT-IR, and ESI-MS spectroscopy. The chemosensor is studied by UV-visible and fluorescence measurement and found to recognize three metal ions such as  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  using 10 mM HEPES buffer in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH = 7.0) medium. Competitive metal ion studies and associated constant value are also predicted. In chemosensor sensing achieved by PET mechanism due to linked nitrogen atom by forming the metal complex, it is followed by a 1:1 ratio of stoichiometry.

## Experimental

### Chemicals and reagents

The essential materials used were high purity of Analar grade indole-3-carbaldehyde and substituted aldehydes purchased from (India) Sigma–Aldrich and used without further purification. To prepare the solutions of different metal ions, the nitrate or chlorate salts of  $\text{Cu}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{V}^{3+}$ , and  $\text{Ti}^{3+}$  were used in distilled water for this experiment. The compounds were confirmed and investigated by  $^1\text{H}$  &  $^{13}\text{C}$ -NMR, FT-IR, and ESI-MS spectroscopy. Interestingly, the  $^1\text{H}$  NMR spectrum was recorded on a Bruker-400 MHz and  $^{13}\text{C}$  NMR 100 MHz enhancement of the employed with TMS as an internal standard in  $\text{DMSO-}d_6$ , respectively. Infrared measurement was calculated at  $4000\text{--}400\text{ cm}^{-1}$  region on an Agilent Carry 630 FT-IR spectrometer. UV and fluorescence measurements were conducted on a PerkinElmer LS45 fluorescence spectrophotometer with a scan rate at 1200 nm at room temperature. For fluorescence measurements, the emission and excitation are at distanced enhancement value, respectively.

### Synthesis of the chemosensor ICPA

(4)-4-(phenyldiazenyl)aniline (0.34 g, 1 mmol) and indole-3-carbaldehyde (0.29 g, 1 mmol) were added with 20 mL absolute  $\text{CH}_3\text{CH}_2\text{OH}$  in a RB (round-bottom) flask and refluxed for 12 h. The solution was continuously cooled at room temperature and added with absolute distill water to form a yellow precipitate solution. The solution was filtered and washed with  $\text{H}_2\text{O}$  and then recrystallized from ethanol. As shown in Scheme 1 Yield: 0.5 g, 55%. M.p =  $197\text{ }^\circ\text{C}$ ; FT-IR (KBr,  $\text{cm}^{-1}$ ): 3429 ( $\nu\text{N-H}$ ), 2979 ( $\nu\text{Ar-C-H}$ ), 2927 ( $\nu\text{Al.C-H}$ ), 1628, 1605 ( $\nu\text{C=N}$ ), 1576, 1503, 1438 ( $\nu\text{C=C}$ ), 1389–1194 ( $\beta\text{C-H}$ ), 1120 ( $\beta\text{N-H}$ ), 1082–691 ( $\Gamma\text{C-H}$ ) shown in Fig S1; 400 MHz  $\text{DMSO-}d_6$  ( $^1\text{H}$  NMR) 9.9 (*s*, NH), 8.31–8.28 (*t*, 3H  $J=1.2$ ), 8.09–8.07 (*d*, 2H  $J=7.6$ ), 7.954–7.932 (*d*, 2H  $J=8.8$ ), 7.70 (*s*, 1H), 7.52–7.50 (*d*, 2H  $J=8.0$ ), 7.28–7.21 (7H  $J=2.6$ ), 7.73 (*s*, -ArH), 6.60–6.58 (*d*, -ArH  $J=8.8$ ) shown in Fig S2; 100 MHz,  $\text{DMSO-}d_6$ , ( $^{13}\text{C}$  NMR) ppm: 155.66, 153.91, 149.18, 138.43, 136.99, 135.57, 128.33, 126.36, 125.42, 124.06, 123.42, 122.09,

120.77, 118.11, 112.37, 112.33 shown in Fig S3: Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_4$ : 365.00 shown in Fig S4.

### UV-visible and fluorescence titration measurements

In this experiment, chemosensor ICPA (0.0032 mg, 0.001) was dissolved in absolute ethanol (10 mL) and different metal ions such as  $\text{Fe}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Sn}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{V}^{3+}$ ,  $\text{Sr}^{2+}$ , and  $\text{Ti}^{3+}$  (50  $\mu\text{M}$ ) were also dissolved in absolute distil water. The stock solutions were diluted with 10 mM HEPES buffer (pH = 7.0) to make the final concentration (50  $\mu\text{M}$ ). A variety of stock solutions (0.5 equiv) with the solution of metal ions including 0.5 equiv were makeup in  $\text{CH}_3\text{CH}_2\text{OH}/\text{H}_2\text{O}$  (1:4, *v/v*, pH = 7.0). Fluorescence and UV-Vis spectra were taken at room temperature.

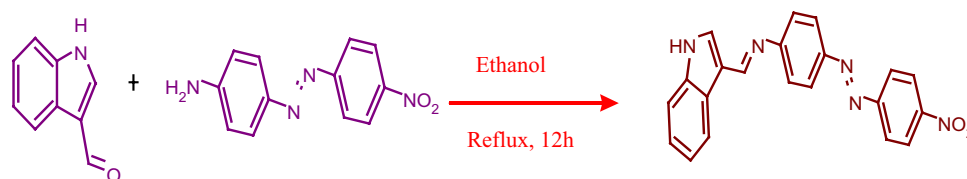
### Job's plot studies

The stock solutions of ICPA (0.0036 mg, 0.002 mmol) were diluted with 10 mM HEPES buffer in  $\text{EtOH}/\text{H}_2\text{O}$  (1:4, *v/v*) medium to make a concluding concentration of 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, and 0.5  $\mu\text{M}$  and transferred to quartz cells. For metal solutions, 0.5  $\mu\text{M}$  of the  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  solution (10 mM) were diluted to 10 mM HEPES buffer in  $\text{EtOH}/\text{H}_2\text{O}$  (1:4, *v/v*) medium with 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0  $\mu\text{M}$  with ICPA and fluorescence spectra were taken at room temperature.

### Cell culture and cytotoxicity assays

HeLa cells were grown in DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% FBS. All cells were supplemented with an (0.1  $\text{mg mL}^{-1}$  streptomycin, 0.25  $\text{mg mL}^{-1}$  amphotericin B and 100 units  $\text{mL}^{-1}$  penicillin) antibiotic antimycotic solution and grown-up at  $37\text{ }^\circ\text{C}$  in standard (5%  $\text{CO}_2$ , 95% humidity) cell culture conditions. HeLa cells were cultured in culture media (DMEM, High Glucose) in an atmosphere of 95% air and 5%  $\text{CO}_2$  at  $37\text{ }^\circ\text{C}$ . The cells were seeded into 96-well plates at a density of  $4 \times 10^3$  cells per well in culture media, and then (1) 0, (2) 7.8, (3) 15.6, (4) 31.2, (5) 62.5, (6) 125, (7) 250, (8) 500, (9) 1000, and (10) 2000  $\mu\text{M}$  (final concentration) compounds were added. The cells were an atmosphere of 95% air and 5%  $\text{CO}_2$  for 24 h then incubated at  $37\text{ }^\circ\text{C}$ . The absorbance of the cells was measured by ELISA.

**Scheme 1** Synthesis of compound ICPA



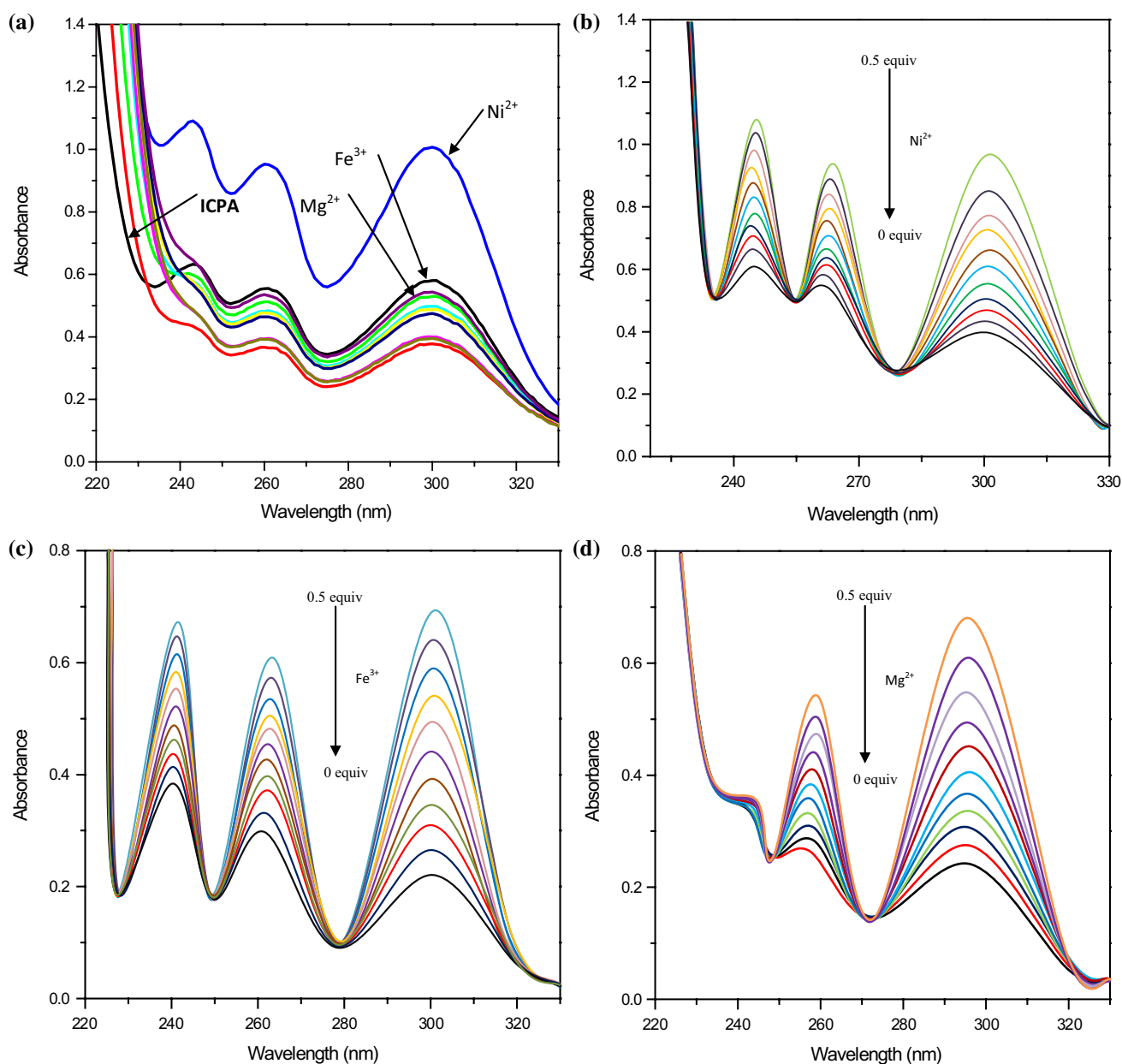
## Results and discussion

The chemosensor's response is often described by spectroscopic methods (Fluorescence and UV–Vis spectroscopy) with various cations such as detectable silent substances. The chemosensor **ICPA** shows that it is sensitive to certain metal cations. Addition of 1.0 equiv. of  $\text{Cu}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{V}^{3+}$ , and  $\text{Ti}^{3+}$  cations into the **ICPA** leads to the change of absorption and fluorescence spectra.

## UV–visible studies

Absorption spectrum behavior of chemosensor **ICPA** (10  $\mu\text{M}$ ) was investigated in EtOH/ $\text{H}_2\text{O}$  medium (1:4,  $v/v$ , and pH 7.0 and 10 mM buffer solution HEPES) at room temperature. The selectivity of different heavy metal ions such as  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Sn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{V}^{3+}$ , and  $\text{Ti}^{3+}$  (50  $\mu\text{M}$ ) was carried out by spectroscopic studies as shown in Fig. 1a.

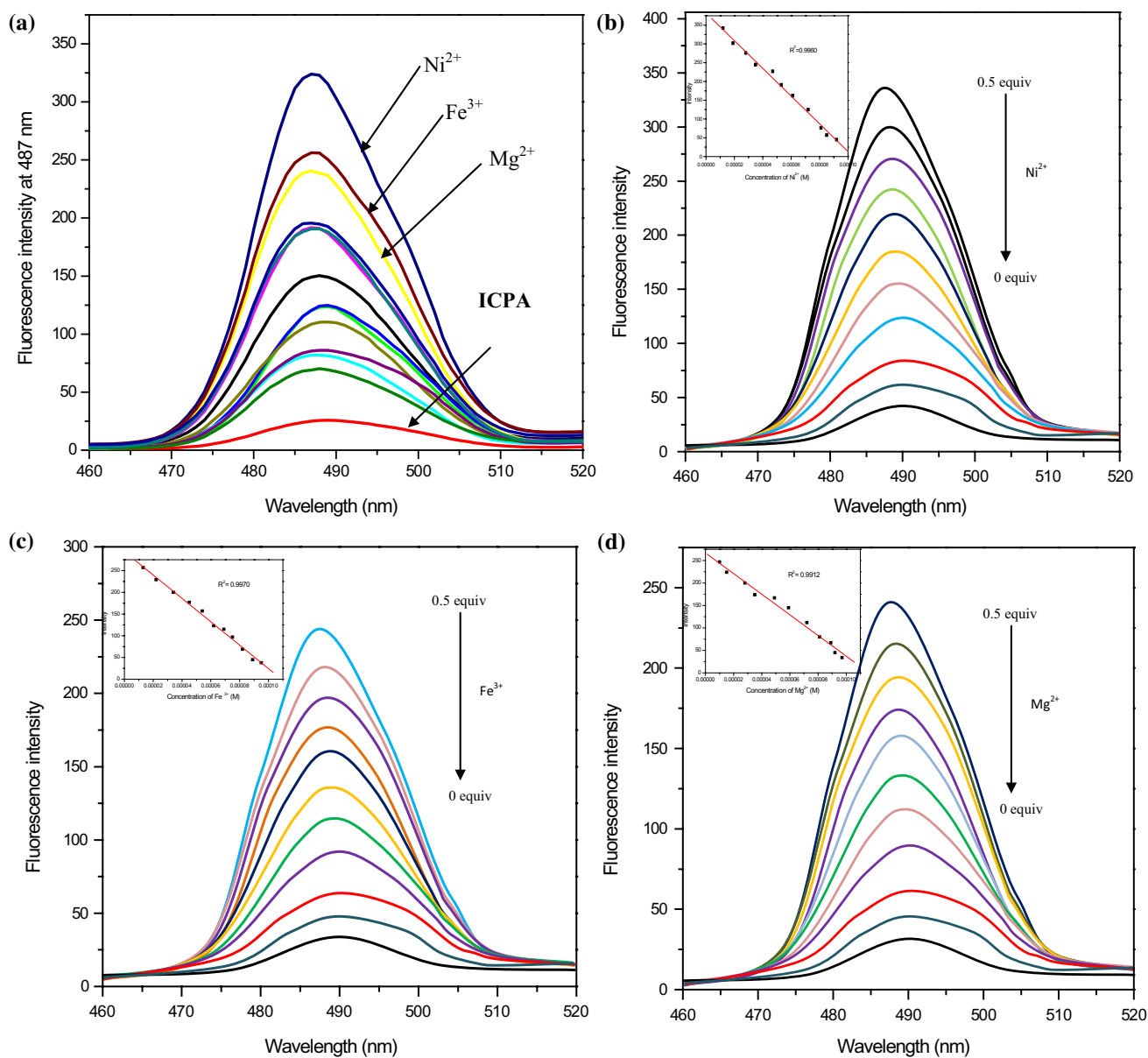
When added 0.5 equiv concentration of chemosensor **ICPA** in various metal ion (0.5 equiv) concentrations'



**Fig. 1** **a** Absorption spectrum of ICPA (10  $\mu\text{M}$ ) with 0.5 equiv of various metal ions used in EtOH/ $\text{H}_2\text{O}$  (1:4,  $v/v$ , pH 7.0) 10 mM HEPES buffer solution, **b** upon addition of  $\text{Ni}^{2+}$ , **c** upon addition of  $\text{Fe}^{3+}$ , **d** upon addition of  $\text{Mg}^{2+}$

absorption of three bands at 243, 260, and 299 nm appeared, while the mentioned peaks are for  $\text{Ni}^{2+}$  ion, also for the all transition metal ions. Chemosensor **ICPA** responsibility for another two metal ions  $\text{Fe}^{3+}$  and  $\text{Mg}^{2+}$  shows a slight increase from other metal ions, as two absorption band peaks at 260 nm and 299 nm appeared while initial absorption peak at 243 nm disappears. However, 0.5 equiv of  $\text{Ni}^{2+}$  ion addition increases gradually the binding of chemosensor **ICPA** to provide the three absorption bands one at 243 nm,

while new absorption band peaks at 260 and 299 nm normally decreased with concentration (Fig. 1b). Both binding formations of  $\text{Fe}^{3+}$  and  $\text{Mg}^{2+}$  (0.5 equiv) used with chemosensors **ICPA** show the first absorption band at 260 nm slightly decrease while concomitantly at 299 nm decreased (Fig. 1c and d).



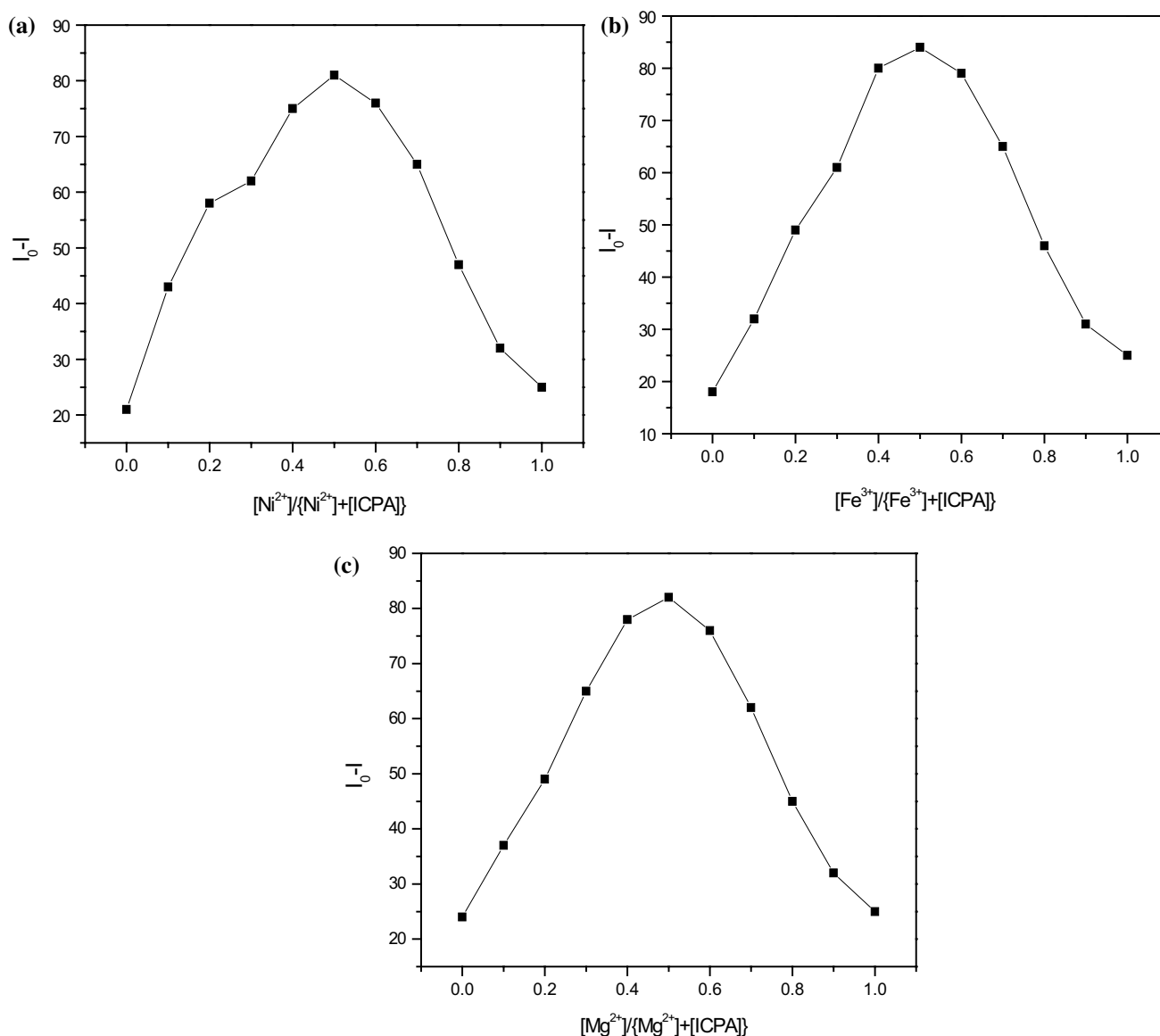
**Fig. 2** **a** Fluorescence spectra of **ICPA** (20  $\mu\text{M}$ ) in the presence 0.5 equiv of various metal ions in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution ( $\lambda_{\text{ex}} = 299$  nm). **b** Fluorescence titration spectra of receptor **ICPA** (10  $\mu\text{M}$ ) used in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution upon incremental addition of  $\text{Ni}^{2+}$  (0–5.0 equiv.). **c** Fluorescence titration spectra of receptor **ICPA**

(20  $\mu\text{M}$ ) in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution upon incremental addition of  $\text{Fe}^{3+}$  (0–2.4 equiv.). **d** Fluorescence titration spectra of receptor **ICPA** (20  $\mu\text{M}$ ) in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution upon incremental addition of  $\text{Mg}^{2+}$  (0–2.4 equiv.). Inset: ( $\lambda_{\text{ex}} = 299$  nm,  $\lambda_{\text{em}} = 487$  nm)

## Fluorescence studies

Fluorescence studies for chemosensor **ICPA** (20  $\mu\text{M}$ ) participated with different heavy metal ions such as  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Sn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{V}^{3+}$ , and  $\text{Ti}^{3+}$  (50  $\mu\text{M}$ ) carried out in EtOH/ $\text{H}_2\text{O}$  medium (1:4, v/v, and pH 7.0 and 10 mM HEPES buffer solution) at room temperature. Upon 0.5 equiv addition of different metal ions react with 0.5 equiv of chemosensor **ICPA**, the fluorescence intensity around at 487 nm appeared while excitation wavelength at 299 nm as shown in Fig. 2a. Therefore, fluorescence “turn-on” for selectively of three metal ions  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$ , which lead to a slight decrease or increase to all other the transition heavy metal

ions. The chemosensor **ICPA** is completely involved down-field below all metal ions. The presence of three metal ions  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  could be displayed in “Off–On” fluorescence behavior on the spectroscopic measurement experiment. Also the sensing of chemosensor **ICPA** behavior in different concentrations in EtOH/ $\text{H}_2\text{O}$  medium (1:4, v/v, pH 7.0) is provided by  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$ . Upon the addition of  $\text{Ni}^{2+}$  (0.5 equiv) increase, the (fluorescence) intensity at 487 gradually increased in Fig. 2b, and it was great that the linear relationship of emission intensity at 487 nm in that concentration  $\text{Ni}^{2+}$  (0–5.0 equiv) ( $R^2 = 0.9960$ ) could be seen in Fig. 2b. The intensity was evaluated through the limit of detection calculated at  $6.82 \times 10^{-7} \text{M}$ . Furthermore,



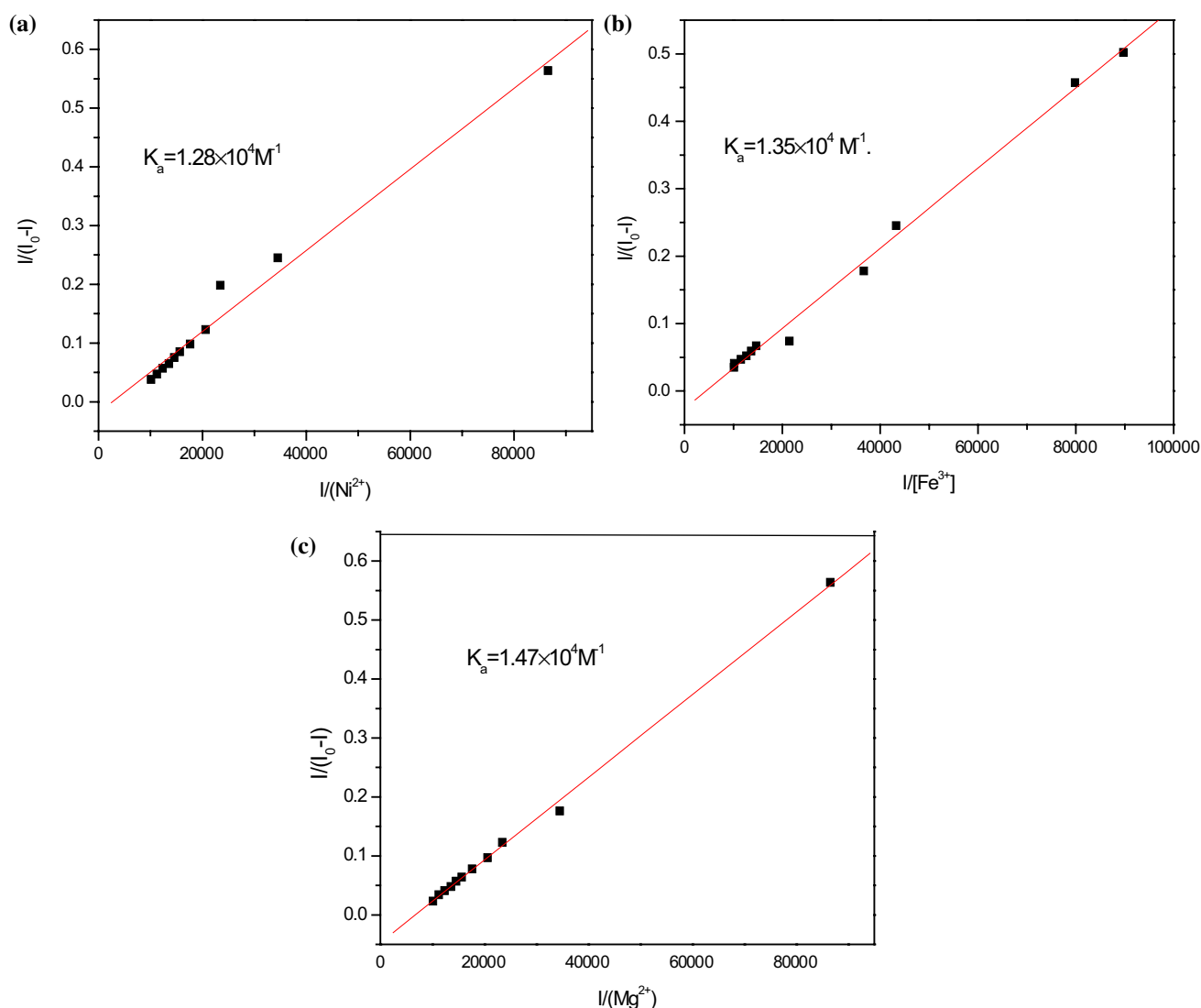
**Fig. 3** Job's plot of the **ICPA**- $\text{Ni}^{2+}$  complexes in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution, keeping the total concentration of **ICPA** (20  $\mu\text{M}$ ) and **a**  $\text{Ni}^{2+}$ , **b**  $\text{Fe}^{3+}$ , and **c**  $\text{Mg}^{2+}$  (0–5.0 equiv.) indicating 1:1 stoichiometry at intensity = 487 nm

with the gradual increase in  $\text{Fe}^{3+}$  (0.5 equiv), the 487 nm fluorescence intensity gradually increased in Fig. 2c.

The good linear relationship of the emission intensity at 487 nm predicted with the concentration of  $\text{Fe}^{3+}$  (0–20  $\mu\text{M}$ ) ( $R^2=0.9970$ ) could be seen (inset in Fig. 2c), and the result was evaluated by the limit of detection  $5.27 \times 10^{-7}$  M. Finally, with 0.5 equiv of  $\text{Mg}^{2+}$  ions gradually increasing with the fluorescence intensity at 487 nm (Fig. 2d), a linear relationship was assumed that the fluorescence intensity with different concentrations of selectivity for  $\text{Mg}^{2+}$  (0–20  $\mu\text{M}$ ) ( $R^2=0.9912$ ) could be seen (inset in Fig. 2d, with the detection limit calculated  $5.96 \times 10^{-7}$  M). Chemosensor **ICPA** binding affinity with the selectivity of  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  was examined by fluorescence experiments. A Job plot indicated that 1:1 stoichiometric complex of **ICPA** +  $\text{Ni}^{2+}$ ,

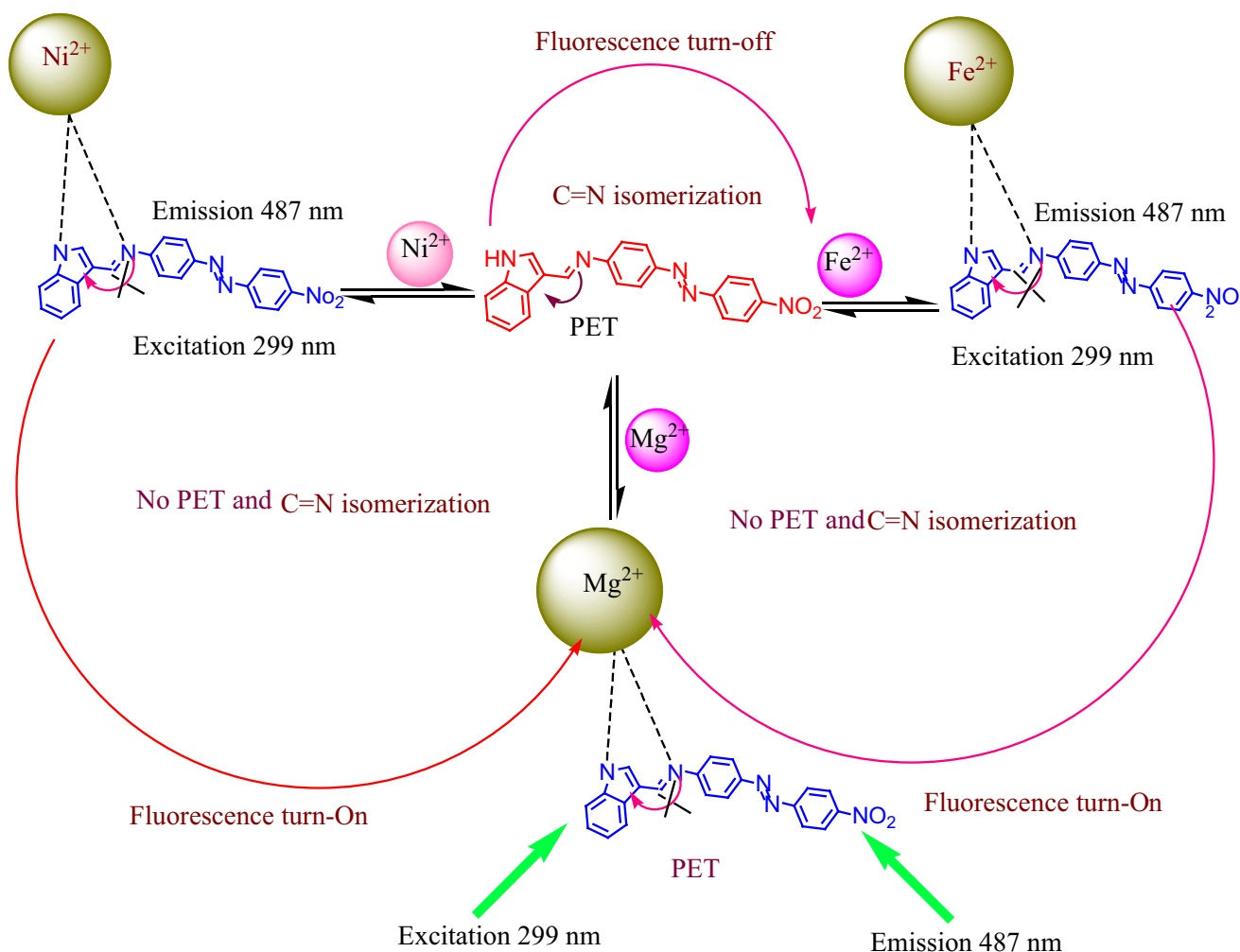
**ICPA** +  $\text{Fe}^{3+}$ , and **ICPA** +  $\text{Mg}^{2+}$  has been predicted different concentrations by each 0.5 equiv of  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$ .

These results confirmed by Job's plot with 1:1 stoichiometric complexes with chemosensor **ICPA** were detected to maximum at 0.5  $\mu\text{M}$  mole fraction determined through the binding addition of  $[\text{Ni}^{2+}]/\{[\text{Ni}^{2+}] + [\text{ICPA}]\}$ ,  $[\text{Fe}^{3+}]/\{[\text{Fe}^{3+}] + [\text{ICPA}]\}$  and  $[\text{Mg}^{2+}]/\{[\text{Mg}^{2+}] + [\text{ICPA}]\}$ , respectively (Fig. 3a–c). In combination with fluorescence titration in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 20 mM HEPES buffer solution, the association constants ( $K_a$ ) for **ICPA** +  $\text{Ni}^{2+}$ , **ICPA** +  $\text{Fe}^{3+}$  and **ICPA** +  $\text{Mg}^{2+}$  have been determined by Benesi–Hildebrand method and calculated as  $3.45 \times 10^8 \text{ M}^{-2}$  (Fig. 4a),  $5.63 \times 10^4 \text{ M}^{-2}$  (Fig. 4b) and  $8.63 \times 10^3 \text{ M}^{-2}$  (Fig. 4c), respectively.



**Fig. 4** a Benesi–Hildebrand plot of **ICPA** using 1:1 stoichiometry for the association between **ICPA** and  $\text{Ni}^{2+}$ . b Benesi–Hildebrand plot of **ICPA** using 1:1 stoichiometry for the association between **ICPA** and

$\text{Fe}^{3+}$ . c Benesi–Hildebrand plot of **ICPA** using 1:1 stoichiometry for the association between **ICPA** and  $\text{Mg}^{2+}$



**Scheme 2** Proposed binding mechanism of ICPA-Ni<sup>2+</sup>, ICPA-Fe<sup>3+</sup>, and ICPA-Mg<sup>2+</sup>

### Proposing the sensing mechanism

The FT-IR spectra recognized the binding mechanism of chemosensor ICPA-Ni<sup>2+</sup>, ICPA-Fe<sup>3+</sup> and ICPA-Mg<sup>2+</sup> together analyzed in this experiment (Fig. S5). Chemosensor ICPA showed FT-IR peaks at (C=N) group in 1628 cm<sup>-1</sup> and NH-group in 3429 cm<sup>-1</sup> obtained. Meantime, 0.5 equiv of Ni<sup>2+</sup> addition results in the functional group decrease from 1628 cm<sup>-1</sup> shifted to 1613 cm<sup>-1</sup> peaks as well as NH-group stretching vibration decrease from 3429 cm<sup>-1</sup> shifted to 3422 cm<sup>-1</sup> was obtained (Fig. S5).

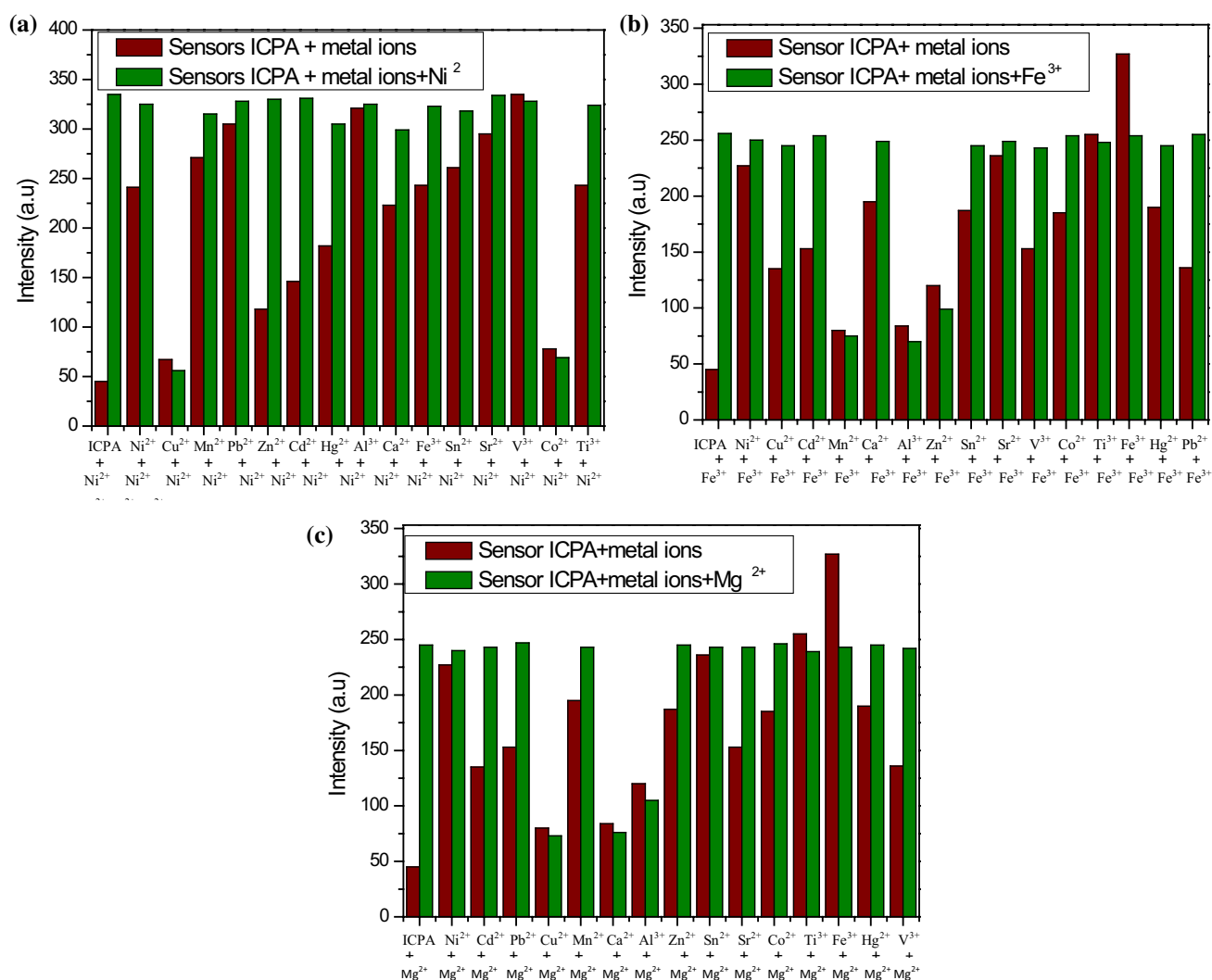
Furthermore, 0.5 equiv of Fe<sup>3+</sup> addition which results in a change from (C=N) 1628 to 1617 cm<sup>-1</sup>, while NH-group stretching vibration shifted to change from 3429 to 3391 cm<sup>-1</sup> (Fig. S6). Finally, 0.5 equiv of Mg<sup>2+</sup> addition with 1628 cm<sup>-1</sup> shifted to 1620 cm<sup>-1</sup> gradually decrease peaks observed; however, NH-group stretching vibration shifted to change from 3429 cm<sup>-1</sup> to 3401 cm<sup>-1</sup> (Fig. S7). As shown in Scheme 2, the fluorescence “turn-on” in the

presence of Ni<sup>2+</sup>, Fe<sup>3+</sup>, and Mg<sup>2+</sup> metal ions, by enhancing emission intensity of the excited state with intersystem crossing to electron and energy transfer mechanism in proposed for chemosensor ICPA, emission intensity increases around 487 nm selectively of three metal ions due to inhibition of PET (photoinduced electron transfer) and also >C=N isomerization methods. PET mechanism showed C=N isomerization of imine group “N” to the excited fluorescence indole-dye moiety with more profit of non-radiative decay with excited energy. In Chemosensor ICPA (fluorescence turn-on) binding modes with Ni<sup>2+</sup>, Fe<sup>3+</sup>, and Mg<sup>2+</sup> (fluorescence turn-off), these PET and >C=N isomerization method inhibitions caused effective complexation formation.

### Competitive metal studies

In this work, the competitive metal ions such as (1 × 10<sup>6</sup> M<sup>-1</sup>) Ni<sup>2+</sup>, Fe<sup>3+</sup>, Co<sup>2+</sup>, Hg<sup>2+</sup>, Al<sup>3+</sup>, Pb<sup>2+</sup>, Mn<sup>2+</sup>, Cd<sup>2+</sup>, Ca<sup>2+</sup>, Cu<sup>2+</sup>, Sn<sup>2+</sup>, Zn<sup>2+</sup>, Sr<sup>2+</sup>, V<sup>3+</sup>, and Ti<sup>3+</sup> (50 μM)





**Fig. 5** Fluorescence intensity at 487 nm of **ICPA** (20 μM) upon addition of various metal ions in EtOH/H<sub>2</sub>O (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution. Brown bars represent the fluorescence inten-

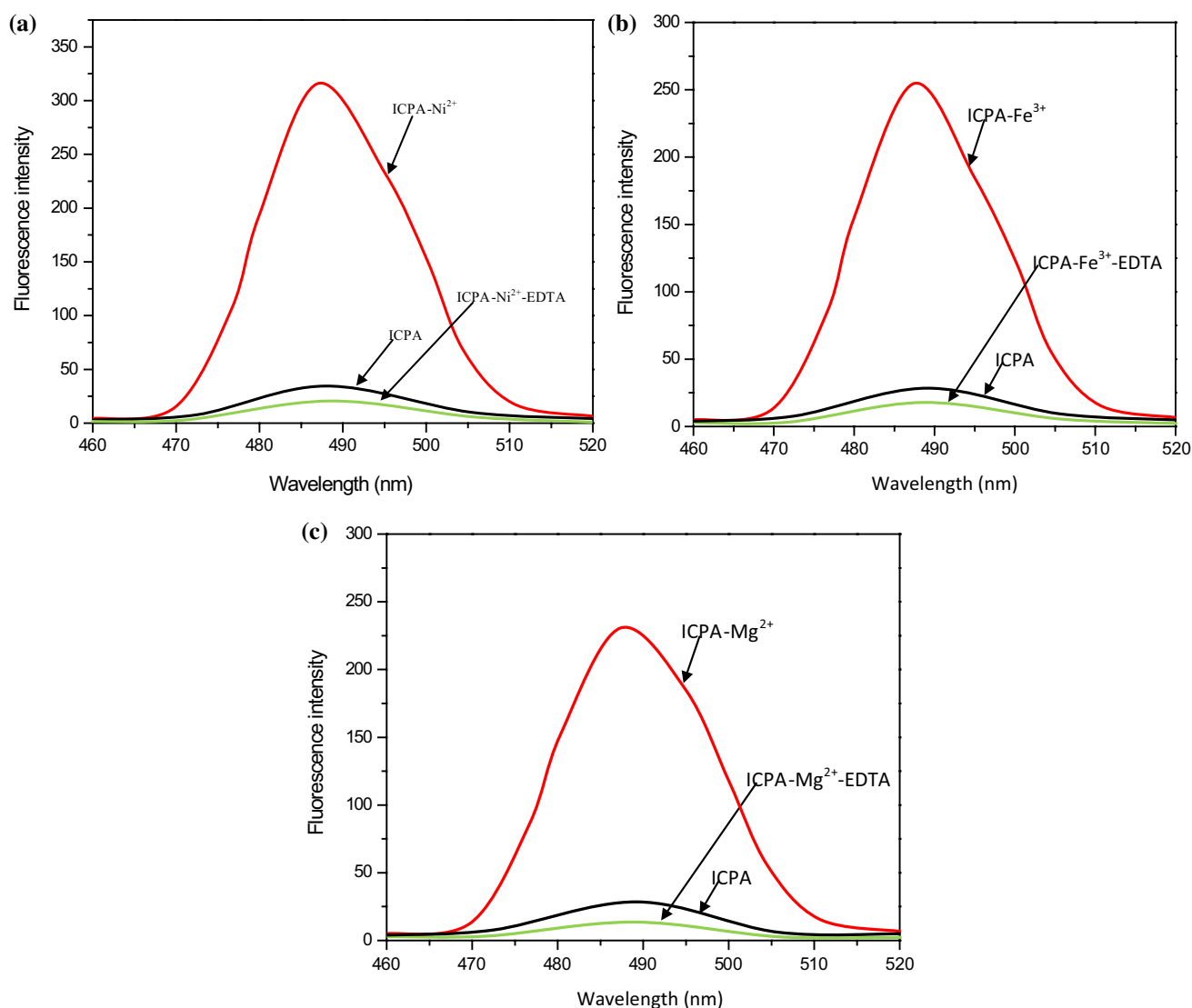
sity of **ICPA** in the presence of metal ion (20 μM). Green bars represent the fluorescence intensity in the presence of **a** Ni<sup>2+</sup>, **b** Fe<sup>3+</sup>, and **c** Mg<sup>2+</sup> (50 μM) after the addition of various metal ions

at concentrations mentioned at experimental section were used with the binding of chemosensor **ICPA** (20 μM) and the fluorescence spectra shown in Fig. 3. Addition of 0.5 equiv different metal ions and 0.5 equiv of Ni<sup>2+</sup> shows an increase in fluorescence intensity at 487 nm while excitation wavelength at 299 nm for Ni<sup>2+</sup> only. The spectrum revealed that Cu<sup>2+</sup> and Co<sup>2+</sup> decreased 100% and 90% by 0.5 equiv of Fe<sup>3+</sup> ion above the others transition metal ions; therefore, no change for other metal ions due to well-known paramagnetism is shown in Fig. 5a. Similarly, 0.5 equiv of Fe<sup>3+</sup> with chemosensor **ICPA** binding and 0.5 equiv various metal ions contain best binding interaction with Al<sup>3+</sup>, Zn<sup>2+</sup>, and Mn<sup>2+</sup> gradually decreased from 100%, 90%, and 80% except all metal ions due to which not only paramagnetism, as a result, enormous three metal ions in coordinated 2 + Fe<sup>3+</sup> compared with highly paramagnetic for **ICPA** + Ni<sup>2+</sup> as

shown in Fig. 5b. Finally, 0.5 equiv of Mg<sup>2+</sup> concentrating all metal ions contained to bind with chemosensor **ICPA** caused the interaction of transition metal ions Cu<sup>2+</sup>, Al<sup>3+</sup> and Ca<sup>2+</sup> having been decreased level of 100%, 70%, and 50%; consequently, in Cu<sup>2+</sup> paramagnetic, remaining Al<sup>3+</sup> and Ca<sup>2+</sup> are not paramagnetic, while it was great coordinated both sides binding of **ICPA** + Ni<sup>2+</sup> complexes formation as shown in Fig. 5c. Competitive metal ions completely involved or participated in surroundings.

### Reversibility test

This experiment proved that Schiff base chemosensor has been confirmed for practical application with reversibility. The studies of the reversibility experiment of **ICPA** with Ni<sup>2+</sup>, Fe<sup>3+</sup>, and Mg<sup>2+</sup> were carried out compared with

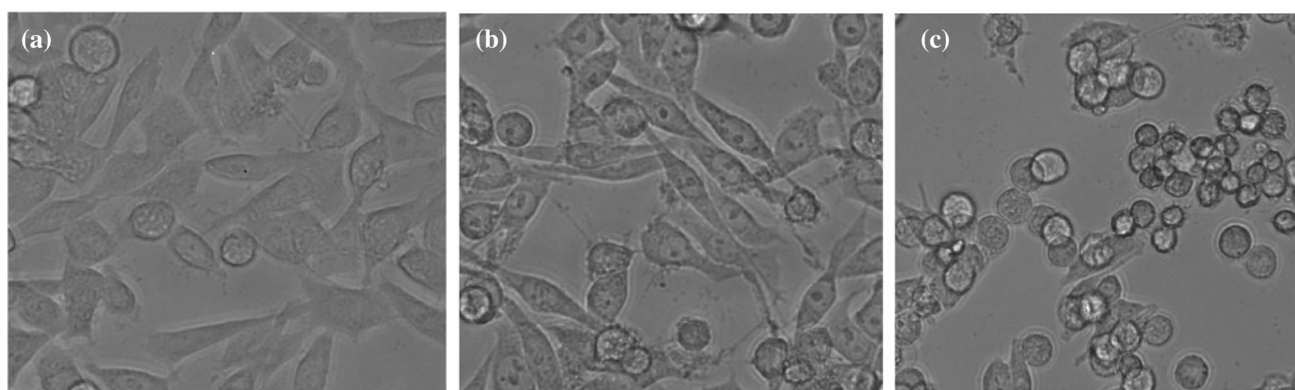


**Fig. 6** Fluorescence spectrum of **ICPA** (20  $\mu\text{M}$ ) with compared EDTA solution in the presence of **a**  $\text{Ni}^{2+}$ , **b**  $\text{Fe}^{3+}$  and **c**  $\text{Mg}^{2+}$  used in EtOH/ $\text{H}_2\text{O}$  (1:4, v/v, pH 7.0) 10 mM HEPES buffer solution

EDTA solution. The addition of EDTA solution to **ICPA**- $\text{Ni}^{2+}$  complex resulted in the complete quenching its fluorescence intensity; however, **ICPA** solution just showed over EDTA solution; afterward, the solution of **ICPA**- $\text{Ni}^{2+}$  complex increases the original fluorescence intensity again; and therefore, result was chemosensor **ICPA** completely reversible sensing for  $\text{Ni}^{2+}$  as shown in Fig. 6a. Simultaneously, another **ICPA**- $\text{Fe}^{3+}$  and **ICPA** +  $\text{Mg}^{2+}$  complex must be recognized by the same fluorescence intensity at 487 nm between up ( $\text{Fe}^{3+}$ ) and down ( $\text{Mg}^{2+}$ ) as a result of reversible chemosensor, although EDTA solution of both **ICPA**- $\text{Fe}^{3+}$  and **ICPA** +  $\text{Mg}^{2+}$  complexes it is completely quenching fluorescence intensity as shown in Fig. 6b and c. These synthesized chemosensors have been compared with the EDTA compound with this experiment.

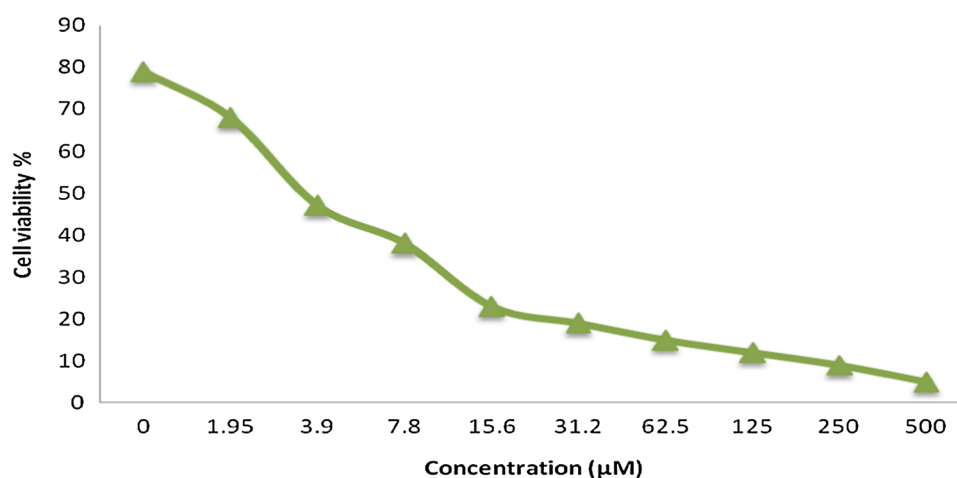
### The cytotoxicity effects

Cancer is a disease caused by an abnormal cell growth that leads to disturbance to other parts of the body, and it is now one of the most dangerous health issues. The combined number of deaths from AIDS, malaria, and tuberculosis is far smaller than those who die from cancer (Rain 2009; Reinberg 2008). The anticancer drugs available on the market have suffered from certain limitations, so the development of new drugs is essential for society (Singh et al. 2009). The indole and its analogs demonstrated a wide spectrum of anticancer activity. We synthesized 4E,10E-4-(2-(4-nitrophenyl)-*N*-((1H-indol-3-yl)methylene)benzenamine and investigated their anticancer activity across the human cancer cell line of HeLa. The cytotoxicity activity of probe



**Fig. 7** HeLa cells treatment with ligand **ICPA** in different concentrations **a** empty cell lines, **b** ligand added with cell lines inhibited for a long time, **c** ligand added with whole-cell line killed

**Fig. 8** The cells viability of HeLa cells different concentrations used with ligand **ICPA**



ligand was investigated in different cell lines. HeLa cell lines grown at 37 °C by the culture of different concentrations were prepared in an atmosphere of CO<sub>2</sub>-5% and air-95% for 24 h. Furthermore, the HeLa cell lines were applied in different concentrations of ligand and have been treated for many hours; it caused much time to kill cancer cells by ligand as exposed in Fig. 7a, in which the first empty plate of HeLa cells before the addition of ligand, the second plate is applied with ligand and cell lines for the time needed to cell death for half of the concentration shown in Fig. 7b.

Finally, the third plate shows the spread of ligand and cancer cells where the complete death of cancer cells within 2 h is exposed in Fig. 7c. The cell viability with an increased order of concentration with the ligand was calculated and detected at 4.7 μM as shown in Fig. 8. As well as, the IC<sub>50</sub> value also established at different concentrations of ligand shows decreased value due to applied various concentrations of cancer cell lines such as (1) 0, (2) 0.9, (3) 1.95, (4) 3.9, (5) 7.8, (6) 15.6, (7) 31.2, (8) 62.5, (9) 125, (10) 250, and (11) 500 μM in Table 1.

**Table 1** IC<sub>50</sub> values calculated different concentrations of HeLa cells

Hela cells Concentration (μM)	IC <sub>50</sub> values ICPA
0	100
0.9	79
1.95	68
3.9	47
7.8	38
15.6	23
31.2	19
62.5	15
125	12
250	9
500	5

## Conclusion

In this work, we have designed and synthesized a new Schiff base of 4*E*,10*E*-4-(2-(4-nitrophenyl)-*N*-((1*H*-indol-3-yl)

methylene)benzenamine **ICPA** fluorescent probe which has been evaluated as a sensor for  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  ions by fluorescence “turn-on” response using steady-state absorption and fluorescence spectroscopy. Based on Job’s plot, ESI-mass spectral analysis, and Benesi–Hildebrand relation, we propose the structure of ligand and its metal ion as 1:1 stoichiometry complex. This chemosensor exhibits a very good fluorescence sensing ability to  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  ions over a wide pH range. An efficient way for the regeneration of free ligand from the complex probe was achieved using EDTA as a coordinating ligand for  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Mg}^{2+}$  ions sensing. The MTT assay experiments further demonstrated the cytotoxic in vitro against the HeLa cell line. Thus, the chemosensor meets all the requirements to be an excellent fluorescent probe for wide applications in the field of biolabeling, biosensing, imaging, and so on. Moreover, this work provides a new approach with the economically cheap and less complicated synthetic route for selective, sensitive, and quantitative detection of these three most abundant and essential trace elements in the human body.

**Authors’ contribution** All authors read and sanctioned the final manuscript.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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