

Synthesis, Characterization, and Antitumour Activity of Isonicotinamido-4-bis(2-chloroethyl)aminobenzaldimine Complexes of Some Transition Metals

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Isonicotinamido-4-bis(2-chloroethyl)aminobenzaldimine (IBAB) was synthesized through multi-step reactions and characterized by spectral methods. The complexes $M(\text{IBAB})_2(\text{NO}_3)_2$ ($M = \text{copper(II)}$, nickel(II) , cobalt(II) , iron(III) , zinc(II) , and cadmium(II)) were isolated and characterized by elemental analysis, IR, UV VIS, and EPR spectra. The results show that IBAB binding to the metals is bidentate. In copper complex, IBAB is coordinated to the metal through carbonyl oxygen and azomethine nitrogen atoms. In the other complexes, which can form polymeric structure, IBAB is coordinated to the metal ions *via* amide nitrogen and pyridine nitrogen atom. The molar conductivity and spectral data suggest an octahedral geometry for the nickel(II), cobalt(II), and iron(III) complexes, a planar geometry for the copper(II) complex and a tetrahedral stereochemistry for the zinc(II) and cadmium(II) complexes. The data of antitumour activities indicate that the complexes have a definite cytotoxicity effect.

Cancer rates among the top three causes of death [1]. Although men have understood some character of its formation, division, and proliferation, much more information remains unknown. Many drugs have been used as antitumour agents in clinical practice, however, the toxic side-effects limit their applications. Many transition metal complexes have demonstrated cytotoxicity in cell cultures and/or antitumour activity in tumour-bearing animals [2, 3], but only complexes of platinum are currently in routine clinical applications [4, 5]. It is well known that nitrogen mustard (mechlorethamine) was first used for treating lymphosarcoma, which marked the beginning of chemotherapy. However, the patients were exposed to the toxic side-effects in application. In order to obtain high-effect low-toxic antitumour drugs, thousands of derivatives of it had been synthesized and some derivatives have been or are to be used as antitumour agents in clinical practice [6]. Schiff bases are also kinds of compounds with a good biological activity, some compounds have higher antitumour activity [7]. According to the structure-effect relation, if a molecule contains two active groups having antitumour activity, the

compound may have a novel biological feature. In view of significant roles of transition metal ions in life process, the formation of metal complexes may improve both biological activities of the organic compound through synergic effect and a favourably slow release of drug. On the basis of this idea, we synthesized the title compounds that contain alkylating and Schiff base groups. 4-Bis(2-chloroethyl)aminobenzaldehyde (BAB) and isonicotinic acid hydrazide (INH) were selected due to their good biological activity, the former having significant antitumour activity and the latter being well known for its highly specific antitubercular activity. In this paper, a modified method was used to prepare isonicotinamido-4-bis(2-chloroethyl)aminobenzaldimine (IBAB) [8–10] and its metal complexes that have not been reported in literature. The antitumour activities of all the compounds against SMMC-7721 and K₅₆₂ cell lines were also investigated.

EXPERIMENTAL

Nitrogen, carbon, and hydrogen were determined

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using an Elementary Vario EL analyzer. The analyses of the metals were carried out by the EDTA method. The IR spectra were recorded in the 200–4000 cm^{-1} region using KBr pellets and a Nicolet 170-SX FTIR spectrometer. Electronic spectra were taken on a Shimadzu UV-240 spectrophotometer in the region of 190–450 nm and 400–900 nm. Conductivity measurements were carried out with a DDS-11 type conductivity bridge in DMSO. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 400L instrument using $\text{DMSO}-d_6$ as solvent. The EPR spectra were obtained with a Bruker ER200D-SRC apparatus at room temperature and 125 K, magnetic field was varied in the interval 0–0.68 T. The Gouy method was employed to measure magnetic moment.

IBAB

A solution of BAB (2.46 g; 0.01 mol) in 30 cm^3 of absolute EtOH was added to solution of INH (1.37 g; 0.01 mol) in 20 cm^3 of absolute EtOH. The mixture was refluxed under the acid catalysis (one drop of acetic acid) for 0.5 h; a yellow precipitate formed was collected by filtration, washed with absolute EtOH and recrystallized from MeCN, yield 3.1 g, 85 %.

Complexes

In a typical preparation, a solution of hydrated copper(II) nitrate (48 mg; 0.2 mmol) in 5 cm^3 of THF was added dropwise to a solution of IBAB (146 mg; 0.4 mmol) in 10 cm^3 of THF with stirring; a yellow-green precipitate formed immediately. The mixture was continuously stirred for 8 h to assure complete precipitation, then the product was filtered off, washed with THF and dried *in vacuo*, yield 88 mg, 90 %.

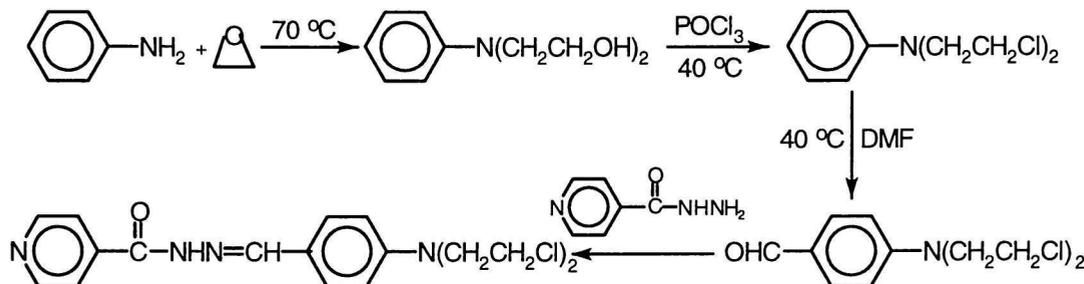
MTT Assay

SMMC-7721 human liver cancer cells were propagated continuously in culture and the cells were grown in Eagles MEM medium supplemented with 10 % inactivated fetal calf serum (FCS) and antibiotics. K₅₆₂ cells were grown in RPMI 1640 medium with 10 % inactivated FCS and antibiotics. Cells harvested from exponential phase were inoculated into 96 well plates and incubated for 24 h, then compounds studied were added in concentration gradient. The final concentrations were maintained at $c/(\mu\text{mol dm}^{-3})$ 125, 100, 75, and 50, respectively. The plates were maintained at 37°C in a humidified 5 % CO_2 – 90 % N_2 – 5 % O_2 atmosphere and incubated for 48 h, then MTT (3-(4,5-dimethyl(thiazol-2-yl))-2,5-diphenyltetrazolium bromide) solution was added, the following procedure referred to literature [11]. The measurements of absorption of the solution concerned with the number of live cells were performed on ELISA spectrophotometer at 570 nm. The metal nitrates were examined at the same conditions.

The survival ratio (SR) is expressed as $A/A_0 \times 100\%$, where A is average absorbance of the experimental wells and A_0 the average absorbance of the control wells. The logarithm of concentration numerical values of the compounds and SR were treated by linear regression analysis and IC_{50} values were obtained from the equations. IC_{50} was defined as drug concentration required for reducing the number of living cells by 50 %.

RESULTS AND DISCUSSION

The IBAB was obtained by condensing INH and BAB. The synthetic scheme is as follows



BAB was made by a three-step synthesis. In the first step, cold ethylene oxide (88 g; 2 mol) was added to cold solution ($< 5^\circ\text{C}$) of freshly distilled aniline (93 g; 1 mol) in 50 g of 1 % acetic acid aqueous solution, the mixture was heated slowly to 70°C during 2 h and kept at this temperature for 20 h. The white solid

product (N,N -bis(2-hydroxyethyl)aniline) was isolated under reduced pressure ($206\text{--}208^\circ\text{C}$, 1973.7 Pa), yield 162 g, 90 %. The next two reactions were carried out according to Refs. [8–10].

All complexes of IBAB with metals (Table 1) are stable in air and insoluble in ethanol, acetone, and

Table 1. The Data of Elemental Analysis and Molar Conductivity

Compound	Colour	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$				μ_{eff} B.M.	Λ S cm ² mol ⁻¹	Yield %
		M	C	N	H			
IBAB	Yellow		55.8 56.0	15.3 15.2	5.0 5.2			
[Cu(IBAB) ₂](NO ₃) ₂	Yellowish-green	6.9	44.5	15.3	4.0	1.89	74.1	90
[Ni(IBAB) ₂](NO ₃) ₂	Green	6.6 6.4	44.1 44.7	15.0 15.3	4.1 4.0		20.6	80
[Co(IBAB) ₂](NO ₃) ₂	Brown-red	6.7 6.5	44.5 44.7	15.0 15.3	4.1 4.0	3.46	22.3	74
[Fe(IBAB) ₂](NO ₃) ₂ NO ₃	Brown-red	6.8 5.7	44.3 42.0	15.0 15.8	4.1 3.9	5.50	36.7	63
[Zn(IBAB) ₂](NO ₃) ₂	Light-red	5.5 7.1	42.2 44.4	15.7 15.2	4.1 4.9		56.8	61
[Cd(IBAB) ₂](NO ₃) ₂	Yellow	6.8 11.6 11.5	44.8 42.2 44.2	15.0 14.5 14.2	4.3 3.8 4.0		63.2	78

Table 2. IR Spectra of Ligand and the Complexes ($\bar{\nu}/\text{cm}^{-1}$)

Compound	$\nu(\text{NH})$	$\nu(\text{C}=\text{O})$	Pyridine breathing	In-plane bending	Out-plane bending	$\nu(\text{M}-\text{O})/\nu(\text{M}-\text{N})$
IBAB	3184 m	1643 vs	967 w	625 w	429 w	
[Cu(IBAB) ₂](NO ₃) ₂	3065 w	1618 s	925	626 m	426 w	512/328
[Ni(IBAB) ₂](NO ₃) ₂	3220 w 3078 w	1674 s	1019	656 w	439 w	513/332
[Co(IBAB) ₂](NO ₃) ₂	3199 w 3068 w	1677 vs	1036	658 w	439 w	510/330
[Fe(IBAB) ₂](NO ₃) ₂ NO ₃	3232 m 3077 w	1677 vs	1020	658 w	444 w	510/334
[Zn(IBAB) ₂](NO ₃) ₂	3237 m 3077 w	1675 s	1024	660 w	440 w	366
[Cd(IBAB) ₂](NO ₃) ₂	3264 w 3166 m	1664 vs	1031	638 w	442 w	343

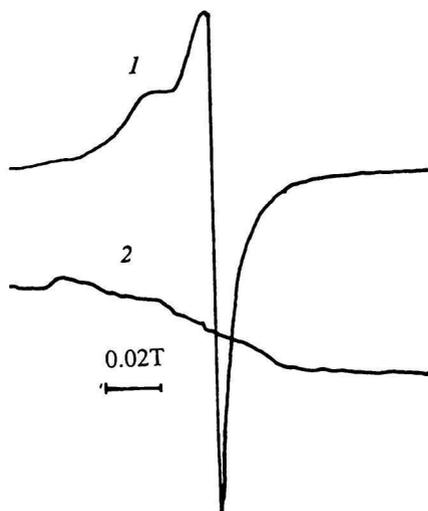
ether and soluble in DMF and DMSO. The molar conductivity data (of 10^{-3} mol dm⁻³) in DMSO solution of the complexes were measured to determine whether the anion was coordinated. The results suggest non-electrolyte nature for nickel(II) and cobalt(II) and 1 : 2 electrolyte for copper(II), iron(III), zinc(II), and cadmium(II) complexes [12]. The compounds decompose on heating in the temperature range 197–235 °C.

Some characteristic IR absorptions of IBAB and its complexes with assignments are given in Table 2. The vibration frequencies of IBAB at 1597 cm⁻¹, 1643 cm⁻¹, and 3184 cm⁻¹ can be assigned to $\nu(\text{N}-\text{H})$, $\nu(\text{C}=\text{O})$, and $\nu(\text{C}=\text{N})$ (azomethine), respectively, which differ from BAB and INH; in the spectrum of the latter, the $\nu(\text{C}=\text{O})$ appears at 1670–1680 cm⁻¹. The presence of $\nu(\text{C}=\text{N})$ is taken as an evidence for the hydrazone and indicative of the preferential presence of the keto form in solid state [13]. In the copper(II) complex, both $\nu(\text{C}=\text{O})$ and $\nu(\text{C}=\text{N})$ (azomethine) are shifted to lower frequencies, indicating the involvement of the carbonyl oxygen atom and azomethine nitrogen atom in coordination [14, 15]. In the

other complexes, however, the $\nu(\text{C}=\text{O})$ is shifted to a higher frequency, suggesting noninvolvement of the carbonyl oxygen in coordination [16]. The result is different from those in the other hydrazone metal complexes [13, 14], it might be related to the presence of alkylating group. The splitting bands of $\nu(\text{NH})$ occur in spectra of nickel(II), cobalt(II), iron(III), zinc(II), and cadmium(II) complexes, with separation of *ca.* 81–155 cm⁻¹ in comparison to free IBAB, suggesting involvement of amide nitrogen atom in coordination [17]. Compared to free IBAB, the $\nu(\text{C}=\text{N})$ (azomethine) bands (1591–1607 cm⁻¹) in the complexes are almost unchanged in frequency, suggesting that the azomethine nitrogen does not take part in coordination. The pyridine ring breathing, in-planar bending and out-planar bending vibrations shift to higher wavenumber, suggesting its involvement in coordination through pyridinic ring nitrogen [18]. The coordination modes of nitrate group can be explained by the separation in combination band at 1700–1800 cm⁻¹ [19–21]. In the cobalt(II), nickel(II), and iron(III) complexes, the splittings of the combination bands are

Table 3. ^1H and ^{13}C NMR Spectral Data and their Assignments

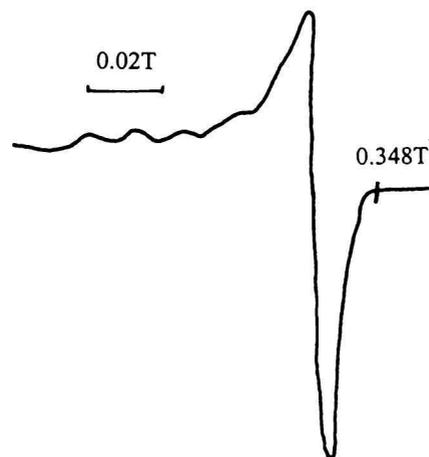
Protons/Carbons	δ	
	IBAB	$[\text{Cd}(\text{IBAB})_2](\text{NO}_3)_2$
—NH—	11.84	13.05
—CH=N—	8.30	8.24
—CH ₂ CH ₂ —	3.74—3.77	3.72—3.83
Phenyl protons	6.62—7.57	6.62—7.70
Pyridine protons	7.78—8.75	7.89—9.04
C=O	164.2	164.2
—CH=N—	151.1	151.1
C-1 (pyridine)	152.0	153.5
C-2 (pyridine)	142.7	142.8
C-3 (pyridine)	123.1	123.2
Phenyl carbons	123.8—150.2	123.9—150.3
—CH ₂ CH ₂ —	41.5—54.1	41.5—51.1

**Fig. 1.** The EPR spectra of the complexes in solid state. 1. Copper(II) complex; 2. cobalt(II) complex.

at 25 cm^{-1} , 20 cm^{-1} , and 22 cm^{-1} , respectively, indicating that the nitrate group binds to the metals in a unidentate manner.

The ^1H and ^{13}C NMR spectra of IBAB and cadmium(II) complex were recorded in DMSO- d_6 solution and the data along with their assignment are presented in Table 3. ^1H NMR spectrum of IBAB shows a low-field signal at $\delta = 11.84$ assigned to —NH— protons, indicating that IBAB exists predominately in the keto form in solution [22]. Compared to IBAB, the small downfield shift of NH and pyridine signals in the spectrum of cadmium(II) complex suggests that IBAB binding is through the amide and pyridine nitrogen atoms. The pyridine carbons showing a slight shift to lower field in ^{13}C NMR spectra support such a conclusion and it is consistent with their IR spectra.

The EPR spectra of the complexes in polycryst-

**Fig. 2.** The EPR spectrum of the copper(II) complex in frozen solution (at 125 K).

talline state (Fig. 1) at room temperature show anisotropic character for copper(II) complex, inactive for cobalt(II) complex. In order to get better resolution, the spectrum of the complex in DMSO was recorded. At ambient temperature, hyperfine line could not be resolved. Hence, EPR behaviour of the complex was examined further at 125 K (Fig. 2). Compared to EPR in the solid state, the peak shape of copper(II) complex was slightly changed and splitted, but the hyperfine line could not be resolved at room temperature. However, a four-weak-peak separation by A_{\parallel} in parallel hyperfine structure is exhibited in frozen solution. A considerable change in g values in the solid state and DMSO solution at 125 K is observed. The difference lies in two aspects: one is due to the inaccuracies of measurement of g values in the solid state and the other may be attributed to fluxional nature of geometry owing to tumbling effects. The situation was reported in literature [23]. The Hamilton parameters obtained from the spectrum are $g_{\parallel} = 2.3924$, $g_{\perp} = 2.0775$, $g_{\text{av}} = 2.182$, $A_{\parallel} = 130.68 \times 10^{-4}\text{ cm}^{-1}$, $A_{\perp} = 9.7 \times 10^{-4}\text{ cm}^{-1}$, $A_{\text{av}} = 50.0 \times 10^{-4}\text{ cm}^{-1}$, and $\alpha^2 = 0.83$. The $g_{\parallel} > g_{\perp} > 2.04$ indicates that the copper(II) ion in axial symmetry will have the principal axes parallelly aligned and that the unpaired electron is in a $d_{x^2-y^2}$ orbital [23]. The G factor (defined as $g_{\parallel} - 2/g_{\perp} - 2$) > 4 shows that a significant exchange coupling is present and the exchange interactions between copper(II) centres in solid state are not negligible [24]. No signal observed at half field may rule out the possibility of dimeric form [23]. From the line shape and Hamilton parameter, the square planar structure can be tentatively proposed [25].

The electronic spectrum shows that the cobalt(II) complex is EPR-inactive. The fact that cobalt(II) complex is not showing any EPR signal is expected for octahedral structure. As it is well documented, the high-spin octahedral cobalt(II) complexes are EPR-

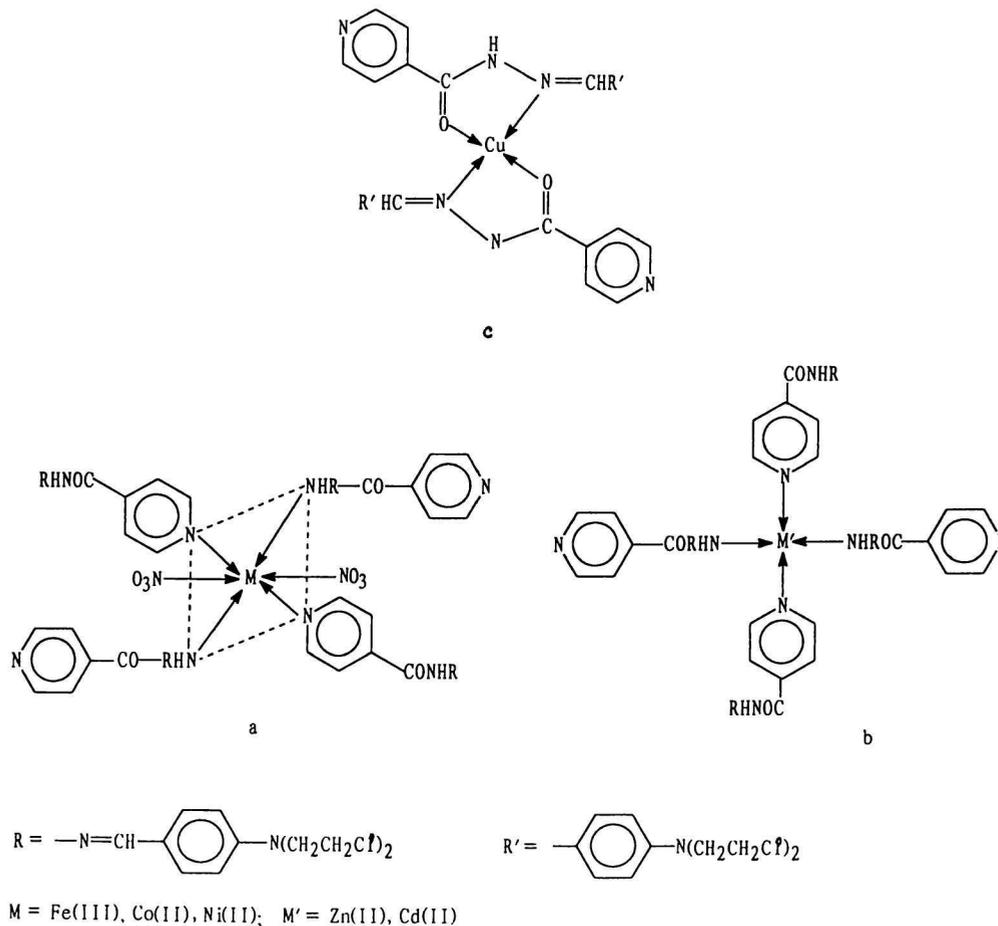


Fig. 3. The structures of the complexes tentatively proposed.

active only at low temperatures ($T < 20$ K), while the low-spin octahedral and square-planar cobalt(II) complexes are showing well defined EPR signals at ambient temperature as well [26]. At 125 K, the EPR signals of the cobalt(II) complex are not obtained in our experiment, which is consistent with literature. The datum of magnetic moment further supports this conclusion (Table 1).

The important electronic absorption bands of IBAB and the complexes were recorded in DMSO and in nujol mull, two absorption bands at 36360 cm^{-1} ($\epsilon = 1.3 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) and 28010 cm^{-1} ($\epsilon = 2.33 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) were seen in the UV region in spectrum of IBAB and were attributed to $\pi-\pi^*$ transition of C=N group in the side and pyridine ring in resonance with the C=O group, respectively [27]. In the spectra of the complexes, changes of absorption intensity occur (A_{357}/A_{275} for IBAB 1.79, for the complexes 0.39–4.8) and slightly red shifts were observed, which suggest the coordination of the IBAB to the metals [28]. The absorption bands of copper(II) complex in nujol mull observed at 19800 and 22220 cm^{-1} may be tentatively assigned to the envelopes of ${}^2B_{1g} \rightarrow {}^2A_{1g}$, ${}^2B_{1g} \rightarrow A^2B_{2g}$, and ${}^2B_{1g} \rightarrow A^2E_g$ transition, suggesting the square-planar geometry around

the copper(II) ion [29]. The electronic spectrum of cobalt(II) complex gave two bands corresponding to octahedral geometry of the cobalt(II) ion, the bands lie in the regions $20840\text{--}22220 \text{ cm}^{-1}$ and $19600\text{--}19880 \text{ cm}^{-1}$, which can be assigned to the ${}^4T_{1g}(F) \rightarrow A^4T_{1g}(P)$ and ${}^4T_{1g}(F) \rightarrow A^4A_{2g}(F)$ transitions, respectively. The electronic spectrum of nickel(II) complex exhibits three bands in the 11620 cm^{-1} and $19050\text{--}19600 \text{ cm}^{-1}$ and $23800\text{--}26300 \text{ cm}^{-1}$ regions which assign to ${}^3A_{2g} \rightarrow A^3T_{2g}(F)(V_1)$ and ${}^3A_{2g} \rightarrow A^3T_{1g}(F)(V_2)$ and ${}^3A_{2g} \rightarrow A^3T_{1g}(P)(V_3)$ transitions, respectively [30], indicating an octahedral geometry around the nickel(II) ion. The octahedral behaviour of the iron(III) complex was found to be due to the absorption bands at $13380\text{--}14700 \text{ cm}^{-1}$, $19410\text{--}20200 \text{ cm}^{-1}$, and $21740\text{--}23250 \text{ cm}^{-1}$, the first two bands correspond to the positions of the 4G state (T_{1g}) and 4G state (T_{2g}), respectively, but the band at $21740\text{--}23250 \text{ cm}^{-1}$ might be a forbidden charge-transfer band [30].

Based on the above-mentioned data, a polymeric octahedral geometry (a) for the cobalt(II), nickel(II), and iron(III) complexes, a polymeric tetrahedral geometry (b) for the zinc(II) and cadmium(II) complexes, and a square-planar structure (c) for the cop-

Table 4. Antitumour Activities of IBAB and its Complexes
IC₅₀/($\mu\text{mol dm}^{-3}$)

Compound	K ₅₆₂	SMMC-7721
IBAB	80	71.3
[Cu(IBAB) ₂](NO ₃) ₂	–	62.8
[Co(IBAB) ₂ (NO ₃) ₂]	28	65.7
[Ni(IBAB) ₂ (NO ₃) ₂]	–	68.2
[Zn(IBAB) ₂](NO ₃) ₂	–	70.1
[Cd(IBAB) ₂](NO ₃) ₂	31.1	75.4
[Fe(IBAB) ₂ (NO ₃) ₂ NO ₃]	none	35.3

per(II) complex may be tentatively proposed (Fig. 3).

As for the antitumour activity, MTT assay is a novel method for quantifying metabolically viable cells through their ability to reduce a soluble yellow tetrazolium salt to blue-purple formazan crystals. The crystals are thought to be produced by the mitochondrial enzyme succinate dehydrogenase [31]. The data of the biological activities of the compounds are given in Table 4. The concentration of DMSO was controlled under 1 % to assure not to affect the result [32]. The experimental data were treated with linear regression, the IC₅₀ values were obtained from the regression equations. The results show that all the complexes have a definite cytotoxicity effect. Although the parent metal nitrates have some cytotoxicity effect at high concentration, the effect is not evident at IC₅₀ dosage of the complexes (SR > 90 %). It is interesting that IBAB has good antitumour activities against both K₅₆₂ and SMMC-7721 cell lines, however, the iron(III) complex does not exhibit any activity for the K₅₆₂ cell line. Compared to IBAB, the synergic effect is evident for the cobalt(II) and cadmium(II) complexes for K₅₆₂. The effect perhaps is due to special mechanisms of them. For cobalt(II) complex, the non-electrolytic character may be helpful to pass the complex through cellular membrane, and then the complex proceeds to alkylated DNA. Although the IBAB is favourable to the membrane, it might react immediately with biomolecules on cellular surface due to its strong alkylation. The formation of complex might change the target molecule. The good antitumour activity of cadmium(II) complex might be related to special acceptor (or carrier) on cellular surface or other manner, such as phagolysis. Both IBAB and its metal complexes have a good antitumour activity for the SMMC-7721 cell line, but the synergic effect is not obvious. The difference in antitumour activities for different tumour cell lines may reflect respective action mechanisms or the difference of sensitivity for the complexes.

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