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Short communication

# Synthesis, characterization and biological activity of Schiff base analogues of indole-3-carboxaldehyde

Deepa Sinha [a,b], Anjani K. Tiwari [a], Sweta Singh [a], Gauri Shukla [a,b], Pushpa Mishra [a], Harish Chandra [b], Anil K. Mishra [a,*]

[a] *Division of Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, Brig. S. K. Mazumdar Road, Delhi 110054, India*
[b] *Department of Chemistry, University of Delhi, Delhi 110007, India*

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**Abstract**

Eight novel heterocyclic Schiff bases derived from the condensation reactions of indole 3-carboxaldehyde with different L-amino acids (histidine, glutamic acid, aspartic acid, leucine, valine) as well as with some aminophenols, have been synthesized and characterized by various spectroscopic methods (IR, MS, $^{1}$H NMR). Schiff base derivatives of indole 3-carboxaldehyde were labeled with $^{99m}$Tc and radiochemical purity was above 97% which is ascertained by instant thin layer chromatography using different solvent conditions. Stability studies of all the derivatives of indole 3-carboxaldehyde was determined under physiological conditions and were stable for more than 24 h. Blood clearance showed a quick wash out from the circulation and biological half life was found to be $t_{½}$(F) = 1 h 15 min; $t_{½}$(S) = 10 h 05 min. Excellent quality radioimages of tumor bearing mice were recorded showing rapid clearance of background activity, visualization of tumor at 3 h and clearance from kidneys of histidine analogue which was further evidenced in biodistribution studies. Antimicrobial activity of these Schiff base compounds was evaluated against *Bacillus subtilis*, *Pseudomonas fluorescence*, *Staphylococcus aureus*, *Aspergillus niger*, *Candida albicans* and *Trichophyton rubrum*.


*Keywords:* Heterocyclic; Schiff base; Spectroscopic; Biodistribution; Antimicrobial

## 1. Introduction

Compounds with the structure of −C═N− (azomethine group) are known as Schiff bases, which are usually synthesized from the condensation of primary amines and active carbonyl groups. Schiff bases are important class of compounds in medicinal and pharmaceutical field. They show biological applications including antibacterial [1–6], antifungal [3–6] and antitumor activity [7,8]. Similarly indole derivatives are prepared for a long time for a variety of biological activities such as CNS depressant, anticancerous, antibiotic, antihistaminic, anticonvulsants and many others.

Radiolabeled bio-molecules are potentially useful tools for cancer diagnosis and therapy. Radiometals such as $^{99m}$Tc(VII), have physical properties, that are well suited for tumor imaging with monoclonal antibodies, while $^{186}$Re(VII), $^{188}$Re(VII), have cytotoxic properties which can be exploited for therapy by antibody-directed tumor targeting. Many efforts have been made to develop diagnostic pharmaceuticals of $^{99m}$Tc-labelled small molecular complexes because of the superior medico-imaging characteristics (biological $t_{1/2}$, low energy content) and the availability of radionuclide [9]. Since the small size of the complex is very important for the retention of the bioactivity [10], one of the strategies in the investigation is to explore novel complexes with small size, multifunctional ligands that possess specific bioactivities. Amino acids, mono/disaccharides and vitamins are some good examples for these applications. Some applications of these Schiff bases with favorable

* Corresponding author. Tel.: +91 1123905117; fax: +91 1123919509.
*E-mail addresses:* mis_ak@rediffmail.com, akmishra@gmail.com (A.K. Mishra).

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cell membrane permeability have been exploited in cancer multidrug resistance [9].

Based on the mentioned properties of Schiff bases and indole analogues we report herein their synthesis, spectroscopic characterization as well as their efficacy for tumor imaging after labeling with $^{99m}$Tc. Antimicrobial activity of these biologically important unsymmetrical Schiff bases of indole 3-carboxaldehyde with different amino acids (histidine, glutamic acid, aspartic acid, valine, leucine) as well as some aminophenol analogues (2-aminophenol, 2-aminophenol-4-sulphonic acid, 1-amino-2-naphthol-4-sulfonic acid) are also mentioned.

In this work, we have used optically active amino acids and substituted aromatic amines to prepare Schiff base compounds as reported in literature [11–14]. Presence of −C═N− and other functional groups forms more stable complexes compared to Schiff bases having only −C═N− coordinating moiety. For nuclear medicine applications, novel derivatives, of indole 3-carboxaldehyde with amino acids or substituted aromatic amines have been synthesized. Their synthesis, radiolabeling, radioimaging and antimicrobial activity are described herein.

## 2. Experimental

### 2.1. Materials and methods

All chemicals used in the present study are of analytical grade purchased from Sigma, Aldrich and Merck chemical co. All the solvents were used after distillation. TLC was run on the silica coated aluminium sheets (silica gel 60 $F_{254}$, E Merck, Germany) and visualized in UV light. IR spectra were recorded on the FT-IR Perkin Elmer spectrum BX spectrophotometer. NMR spectra were obtained by using Brucker NMR instrument 300 MHz. The MS spectra were recorded from JEOL SX 102/DA-6000 spectrometer using *m*-nitrobenzyl alcohol as matrix. Elemental analysis was done on elemental analyzer system Gmbh variable system. Radiocomplexation and radiochemical purity were checked by instant strip chromatography (silica gel impregnated paper chromatography) with IILC-SG (Gelman Sciences, Ann arbor, MI, USA).

### 2.2. Preparation of Schiff base

The Schiff base used was prepared by mixing an ethanolic solution (25 ml) of 1.45 g (0.01 mol) of indole 3-carboxaldehyde with 0.01 mol of other moiety in the same volume of ethanol. The mixture was then refluxed with stirring for 2–6 h. The precipitate was collected by filtration through Buchner funnel, recrystallized from ethanol, and dried at room temperature with 60–85% yield.

The IR spectrum of the Schiff bases (Table 1) shows very strong intensity absorption band at 1450–1590 $cm^{-1}$ assigned to CN stretching mode. The presence of aromatic rings has been identified by their characteristic ring vibrations at 1450–1400, 1100–1090 and 760–720 $cm^{-1}$ regions. The absence of bands characteristic of $\nu$(CO), primary amine $\nu$(NH) confirms the formation of the proposed Schiff base framework. The infrared spectra of the complexes (Table 1) show a weak intensity absorption band in the frequency range 1530–1520 $cm^{-1}$ for the coordinated imine function $\nu$(CN).

### 2.3. Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Pseudomonas fluorescence* by disc diffusion method [15,16]. A standard inoculum ($1-2 \times 10^7$ c.f.u./ml 0.5 McFarland standards) was introduced onto the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.25 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were maintained. The plates were inverted and incubated for 24 h at 37 °C. Ciprofloxacin was used as a standard drug. The inhibition zone were measured and compared with the controls. The bacterial zone of inhibition values are given in Table 2. Minimum inhibitory concentration (MIC) was determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two-fold diluted amount of test compound and controls, was inoculated with approximately $5 \times 10^5$ c.f.u. of actively dividing bacterial cells. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition.

### 2.4. Antifungal studies

The newly prepared compounds were screened for their antifungal activity against *Aspergillus niger*, *Candida albicans* and *Trichophyton rubrum* in DMSO by serial plate dilution method [17,18]. Sabourand agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of corresponding species. Twenty milliliters of agar media was poured in each petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made into each well labelled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The fungal activity of each compound was compared with that of flucanozole as standard drug. The inhibition zones were measured and compared with controls. The fungal zone of inhibition values are given in Table 2. The nutrient broth, which contained logarithmic serially two-fold diluted amount of test compound and controls, was inoculated with approximately $1.6 \times 10^4 - 6 \times 10^4$ c.f.u./ml. The cultures were incubated for 48 h at 35 °C and the growth was monitored.

Table 1
Spectral analysis of Schiff bases

| Name of the compound | Spectral data |
|---|---|
| 3-(3*H*-Imidazol-4-yl)-2-[(1*H*-indol-3-ylmethylene)-amino]-propionic acid (**1**) | MP 112 °C; UV–vis: 280 nm; IR (KBr): 1423, 1576, 3258 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, $CH_2$), 6.8–7.6 (m, 7H, ArH), 7.3 (d, $J = 8.1$ Hz, 1H), 7.5 (s, 2H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$, ppm): 166 (C═N), 179.5, 69.2, 33.2; MS (EI): *m/z* (282), $M + 2Na^+$ (328); elemental analysis: $C_{15}H_{14}N_4O_2$ C (62.62%), H (5.1%), N (18.81%) |
| 2-[(1*H*-Indol-3-ylmethylene)-amino]-pentanedioic acid (**2**) | MP 128 °C; UV–vis: 235 nm; IR (KBr): 1123, 1390, 2695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 1.8, 2.3 (t, 2H, $CH_2$), 2.4 (t, 1H, CH), 7.2–7.7 (m, 5H, ArH), 7.2 (d, $J = 7.7$ Hz, 1H), 7.6 (s, 1H, CH); $^{13}C$ NMR (DMSO-$d_6$, ppm): 162.3 (C═N), 68.4, 180.1, 28.2; MS (EI): *m/z* (274), $M + 3Na^+$ (343); elemental analysis: $C_{14}H_{14}N_2O_4$ C (60.24%), H (4.94%), N (9.71%) |
| 2-[(1*H*-Indol-3-ylmethylene)-amino]-succinic acid (**3**) | MP 207 °C; UV–vis: 235 nm; IR (KBr): 1145, 1468, 3392 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 2.5 (d, 2H, $CH_2$), 2.7 (t, 1H, CH), 7.0–7.3 (d, $J = 8.1$ Hz, 1H), 7.4 (s, 1H, CH); $^{13}C$ NMR (DMSO-$d_6$, ppm): 169.2 (C═N), 180.0, 65.1, 38.5; MS (EI): *m/z* (260), $M + K^+$ (337); elemental analysis: $C_{13}H_{12}N_2O_4$ C (60.12%), H (4.12%), N (10.54%) |
| 2-[(1*H*-Indol-3-ylmethylene)-amino]-4-methyl-pentanoic acid (**4**) | MP 119 °C; UV–vis: 224 nm; IR (KBr): 915, 1156, 1480 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 1.2 (d, 6H, $CH_3$), 1.8 (m, 1H, CH), 7.1–7.7 (m, 5H, ArH), 7.3 (d, $J = 8.5$ Hz, 1H), 7.6 (s, 1H, CH); $^{13}C$ NMR (DMSO-$d_6$, ppm): 161.7 (C═N), 67.8, 42.6; MS (EI): *m/z* (258); elemental analysis: $C_{15}H_{18}N_2O_2$ C (68.71%), H (6.92%), N (9.82%) |
| 2-[(1*H*-Indol-3-ylmethylene)-amino]-3-methyl-butyric acid (**5**) | MP 161 °C; UV–vis: 248 nm; IR (KBr): 1396, 1592, 3286 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 1.5 (d, 6H, $CH_3$), 2.1 (d, 1H, CH), 2.2 (m, 1H, CH), 7.0–7.8 (m, 5H, ArH), 7.7 (s, 1H, CH), 7.2 (d, $J = 7.7$ Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, ppm): 166.9 (C═N), 77.3, 26.9; MS (EI): *m/z* (244); elemental analysis: $C_{14}H_{16}N_2O_2$ C (67.54%), H (5.94%), N (10.97%) |
| 2-[(1*H*-Indol-3-ylmethylene)-amino]-phenol (**6**) | MP 97 °C; UV–vis: 272, 348 nm; IR (KBr): 1245, 1495, 3421 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 6.2–7.7 (m, 9H, ArH), 7 (d, $J = 8.6$ Hz, 1H), 7.8 (s, 1H, CH); $^{13}C$ NMR (DMSO-$d_6$, ppm): 159.9 (C═N), 137.6, 72.3; MS (EI): *m/z* (236); elemental analysis: $C_{15}H_{12}N_2O$ C (74.21%), H (5.02%), N (10.92%) |
| 3-Hydroxy-4-[(1*H*-indol-3-ylmethylene)-amino]-naphthalene-1-sulfonic acid (**7**) | MP 214 °C; UV–vis: 258, 384 nm; IR (KBr): 1156, 1468, 3356 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 6.8–7.7 (m, 10H, ArH), 7.5 (s, 1H, CH), 7.6 (d, $J = 8.8$ Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, ppm): 168.1 (C═N), 132.7, 91.3; MS (EI): *m/z* (366); elemental analysis: $C_{19}H_{14}N_2O_4S$ C (61.20%), H (3.75%), N (7.56%) |
| 2-[(1*H*-indol-3-ylmethylene)-amino]-phenol-1-sulfonic acid (**8**) | MP 115 °C; UV–vis: 326 nm; IR (KBr): 1156, 1495, 3420 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ (ppm) 6.2–7.97 (m, 8H, ArH), 7.7 (d, $J = 8.6$ Hz, 1H), 7.8 (s, 1H, CH); $^{13}C$ NMR (DMSO-$d_6$, ppm): 159.6 (C═N), 137.6, 70.3; MS (EI): *m/z* (316); elemental analysis: $C_{15}H_{12}N_2SO_4$ C (56.21%), H (3.82%), N (8.92%) |

Table 2
Microbial activity of Schiff bases

| Minimum inhibitory concentrations (μg/ml) | | | | | | |
|---|---|---|---|---|---|---|
| Compound | *Bacillus subtilis* | *Pseudomonas fluorescence* | *Staphylococcus aureus* | *Aspergillus niger* | *Candida albicans* | *Trichophyton rubrum* |
| **1** | 35.1 | 3.8 | 3.4 | 47.5 | >50 | >50 |
| **2** | 48.2 | 5.7 | 19.2 | >50 | 12.5 | >50 |
| **3** | 11.3 | 19.3 | 18.5 | 17.8 | 11.9 | 16.2 |
| **4** | 12.1 | >50 | 35.3 | >50 | 19.9 | >50 |
| **5** | 42.5 | 38.1 | 16.8 | >50 | 26.8 | >50 |
| **6** | 18.4 | 15.8 | 35.9 | >50 | 28.4 | >50 |
| **7** | 15.5 | 21.6 | >50 | 21.3 | 15.2 | 21.9 |
| **8** | 13.5 | 11.3 | >50 | 25.6 | >50 | 19.4 |

### 2.5. Radiolabeling of the compounds with $^{99m}Tc$

Hundred microliters of 0.03 nM solution of the compounds were dissolved in DMSO and taken in a shielded vial and 60 μl of $1 \times 10^{-2}$ M $SnCl_2 \cdot 2H_2O$ (dissolved in $N_2$ purged 1 ml 10% acetic acid) was added followed by addition of (<1 h) freshly eluted saline solution of sodium pertechnetate ($NaTcO_4$) (74 MBq, 100 ml). The pH of the reaction mixture was adjusted to 6.5 with 0.1 M $NaHCO_3$ solution and shook to mix the contents. The vial was allowed to stand for 20–30 min at room temperature. Labeling of the compound, radiochemical purity as well as $R_f$ of the $^{99m}$Tc based complex was determined by ITLC-SG strips using 0.9% NaCl aqueous solution (saline) as developing solvent and simultaneously in acetone and PAW (pyridine, acetic acid and water in 3:5:1.5 ratio). Each ITLC was cut into 0.1 cm segments and counts of each segment were taken.

### 2.6. In vitro serum stability assay

The fresh human serum was prepared by allowing blood collected from healthy volunteers to clot for 1 h at 37 °C in a humidified incubator maintained at 5% carbon dioxide, 95% air. Then the sample was centrifuged at 400 rpm and the serum was filtered through 0.22 μm syringe filter into sterile plastic culture tubes. The above freshly prepared technetium radiocomplexes were incubated in fresh human serum at physiological conditions, i.e. at 30 °C at a concentration of 100 nM/ml and then analyzed by ITLC-SG at different time intervals to detect any dissociation of the complex. Percentage of free pertechnetate at a particular time point that was estimated using saline and acetone as mobile phases, represented percentage dissociation of the complex at that particular time point in serum.

### 2.7. Blood kinetics studies

The blood clearance study was performed in albino New Zealand rabbits weighing approximately 2.5–3.0 kg after administration of 10 MBq of the $^{99m}$Tc labeled compounds in 0.3 ml via the ear vein. At different time intervals about 0.5 ml blood samples were withdrawn from the dorsal vein of other ear and radioactivity was measured in the gamma counter. The data from the experiment were expressed as percentage of administered dose at each time interval in Fig. 1.

### 2.8. Biodistribution studies

Albino mice strain (A) was used for the tissue distribution studies. Animal handling and experimentation was carried out as per the guidelines of the Institutional Animal Ethics Committee.

An equal dose of 10 μCi of labeled test compound was injected in mice through tail vein of each animal. At different time intervals mice were sacrificed, blood was collected and different tissues and organs were dissected and analyzed in Table 3. The radioactivity was measured in a gamma counter.

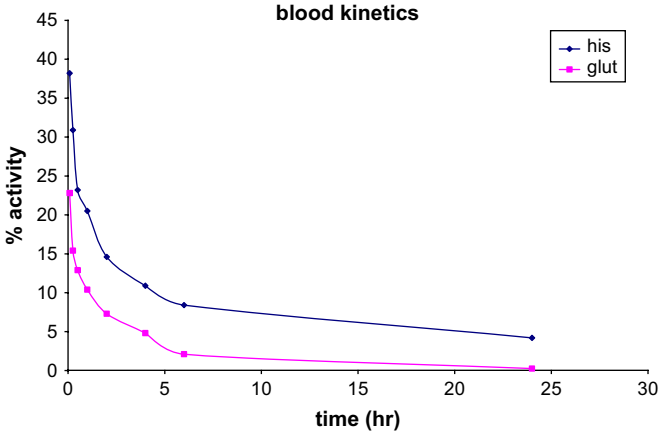


Fig. 1. Blood kinetics study in rabbit.

The actual amount of radioactivity administered to each animal was calculated by subtracting the activity left in the tail from the activity injected. Radioactivity accumulated in each organ was expressed as percentage administered dose per gram of tissue. Total volume of the blood was calculated as 7% of the body weight.

## 3. Results and discussion

Synthesis of Schiff bases have been achieved in high yields starting from the condensation reaction of indole 3-carboxaldehyde and L-amino acids such as histidine, aspartic acid, glutamic acid, valine, leucine (as all these are important in the metabolism and mechanism proposed for tumor as well as due to their strong affinity for donar sites in physiological reaction conditions) as well as some aminophenol analogues (2-aminophenol, 2 aminophenol-4-sulphonic acid, 1-amino-2-naphthol-4-sulphonic acid) as reported in literature

Table 3
Biodistribution study of histidine and glutamic acid analogues

| Organs | Uptake (% ID/g) | | | | |
|---|---|---|---|---|---|
| | After 1 h | After 2 h | After 4 h | After 6 h | After 8 h |
| Histidine | | | | | |
| Stomach | 1 | 2.5 | 3 | 3 | 3.0 |
| Intestine | 0.5 | 0.5 | 0.2 | 3 | 3 |
| Brain | 0 | 0.2 | 0.45 | 1 | 1 |
| Liver | 18 | 25 | 18 | 15 | 15 |
| Spleen | 10 | 15 | 14 | 12 | 11 |
| Kidney | 5 | 7 | 2 | 6 | 6 |
| Blood | 3 | 2 | 2 | 0.5 | 0.5 |
| Heart | 1 | 0.4 | 0.3 | 0.3 | 0.2 |
| Glutamic acid | | | | | |
| Stomach | 1 | 2.0 | 3 | 3 | 3.0 |
| Intestine | 0.5 | 0.5 | 0.2 | 1 | 1 |
| Brain | 0 | 0.2 | 0.45 | 1 | 1 |
| Liver | 16 | 23 | 14 | 15 | 15 |
| Spleen | 10 | 15 | 17 | 16 | 16 |
| Kidney | 5.5 | 6.0 | 7 | 4.5 | 4.5 |
| Blood | 2.5 | 2 | 2 | 2.5 | 2.5 |
| Heart | 0.8 | 0.5 | 0.2 | 0.1 | 0.2 |

[1–3,9–11]. The synthesized ligands were checked by comparing the TLC with the starting materials, which resulted in a single spot different from the starting materials. IR studies of each compound confirms the formation of −C═N− bonds as well as lack of −C═O− from original aldehydic compounds. $^{1}$H NMR spectra, respectively, confirm the proposed stoichiometry and structure for the Schiff bases. The signal of azomethine protons de-shielded in the spectra of Schiff bases was found to occur at lower ppm. Integral of NMR confirms the number of protons in Schiff bases as well as coupling constant which confirms the formation of −C═N− bonds.

The Schiff bases were tested for antimicrobial activity against *B. subtilis*, *P. fluorescence*, *S. aureus*, *A. niger*, *C. albicans* and *T. rubrum*. The microbial activity shows that compound **1** and compound **2** have very good activity against *P. fluorescence*, *S. aureus* while compound **3** shows good activity against all the species which is due to additional polarity in amino acid analogues. In the synthesized compounds, three amino acids having additional acidic/basic moieties showed good activity. Compound **7** which is a naphthalene derivative having higher aromaticity than other compounds showed good activity against *B. subtilis*, *P. fluorescence*, *S. aureus*.

The radiolabeling study under physiological conditions was done as reported in the literature [19–21]. Preliminary complexation of novel synthesized compounds with $^{99m}$Tc was found to give sufficiently stable complexes under physiological conditions. Complexes of indole 3-carboxaldehyde-histidine and indole 3-carboxaldehyde-aspartic acid showed very good tumor uptake, while remaining analogues showed poor uptake in tumor (indicating no potential of the complexes in tumor imaging). Good bone uptake of indole 3-carboxaldehyde-aspartic acid, and indole 3-carboxaldehyde-glutamic acid, high spleen accumulation of histidine, valine and leucine and non-specific biodistribution of indole 3-carboxaldehyde-aminophenol were observed. In vitro serum stability of the radiocomplexes is a necessary parameter meant to measure the effectiveness of chelating moiety to coordinate the radiometal. Generally there is transchelation of radiometal to serum proteins particularly albumin. In vitro serum stability of the complexes clearly indicates that initially there was fall in the stability of the complex but later on it shows a constant stability. Initial fall in the labeling efficiency after addition of fresh serum could be attributed to the transchelation that could have taken place in serum due to high affinity of plasma proteins for metal ions.

The retention of drug in the blood of the animal depends upon the pharmacological and physical properties of the drugs. Nearly all the Schiff bases show a very rapid fast clearance of

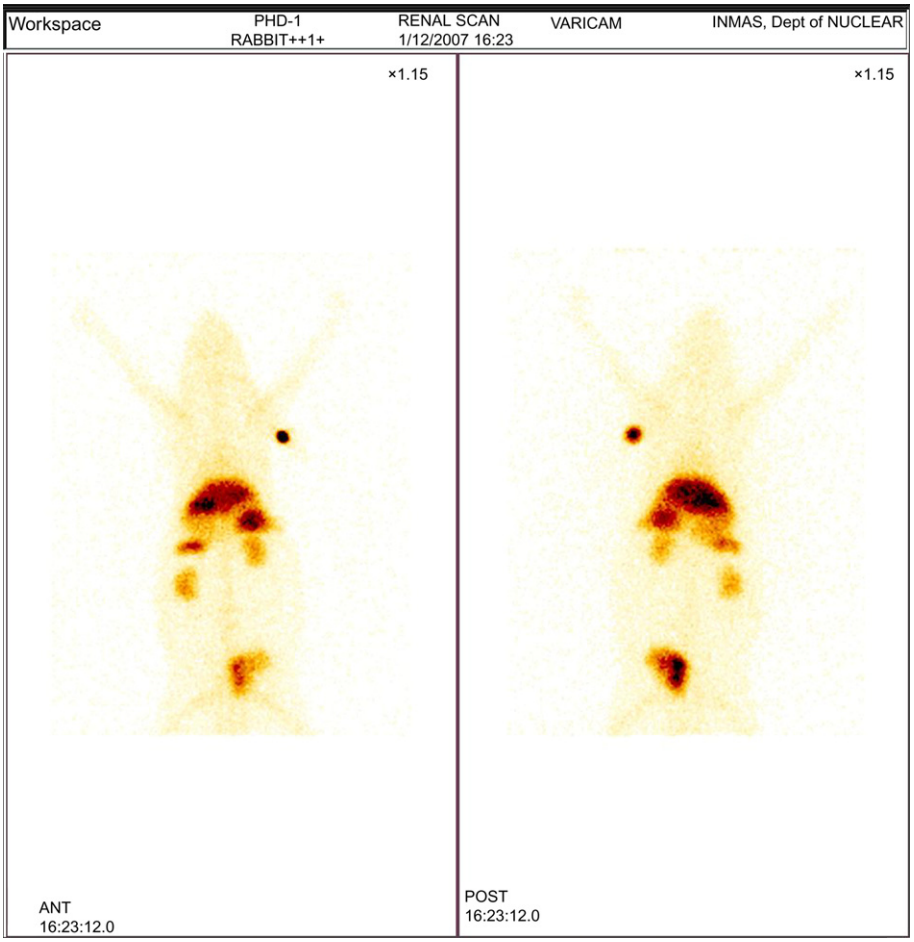


Fig. 2. Imaging of Schiff bases (histidine analogue) in rabbit.

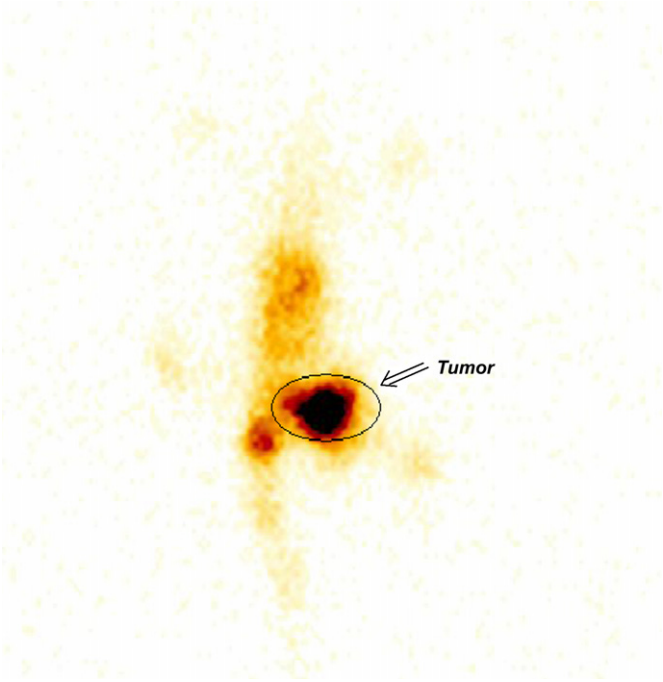


Fig. 3. Tumor imaging of histidine analogues in mice.

radioactivity from the blood. Approximately 55–65% of activity was removed within 1 h and more then 90% in 3 h. It shows fast kinetics which may be attributed to the hydrophilic nature of the drug radiometal complexes.

Biodistribution of the radiocomplexes is an important phenomenon to study because it gives an idea how the radiocomplex drugs distribute in vivo and how it excretes. Accumulation of low amount of radioactivity in the stomach precludes the presence of free pertechnetate going to stomach which indicates in vivo stability of preparation. The distribution in various organs of mice is shown as percentage of injected dose per organ or tissue at different time intervals. It seems that drug is localized in the liver and kidneys, with passage of time, the activity of kidney was increased in most of the compounds, while if it is in the intestine there was negligible increase in activity. This shows that major route of excretion of activity is through kidneys. This was supported by radioimages of tumor bearing mice (Fig. 3) as with passage of time, there was increased accumulation of activity in urinary bladder. Besides that the radioactivity remained in liver for very longer time, indicating that most probably the metabolism of drugs may be taking place in liver, but the excretion of drugs and metabolites is mainly through kidney. Accumulation of drugs in liver may also be because of protein binding nature of drugs. Very little accumulation in lungs, spleen and stomach was observed, negligible accumulation occurs in heart and brain. The best results of blood kinetics and imaging is given in Figs. 1–3.

## 4. Conclusion

The preliminary studies with these novel Schiff base ligands are encouraging to carry out further in vivo experiments for targeted imaging of human tumor. The therapeutic potential of these complexes can further extend by applying these in different animal models and cell lines.

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