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Exogenous Fluorescent Agents for the Determination of Glomerular Filtration Rate

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1. Introduction

Glomerular filtration rate (GFR) is now widely accepted as the best indicator of renal function in the state of health and illness.^{1,2} Current clinical guidelines advocate its use in the staging of chronic kidney disease as well as in assessing the risk of kidney failure under acute clinical, physiological, and pathological conditions.³⁻⁶ Acute renal failure (ARF) is a major cause of complications in the post-surgical and post-intervention vascular and cardiac procedure patient populations. ARF is also a major public health issue because it may lead to chronic renal failure. Real-time, continuous monitoring of GFR in patients at the bedside is particularly important in the case of critically ill or injured patients, and those undergoing organ transplantation because most of these patients face the risk of multiple organ failure (MOF) resulting in death.⁷⁻¹⁰ MOF is a sequential failing of lung, liver, and kidneys and is incited by one or more severe causes such as acute lung injury (ALI), adult respiratory distress syndrome (ARDS), hypermetabolism, hypotension, persistent inflammation, or sepsis. The transition from early stages of trauma to clinical MOF is marked by the extent of liver and renal failure and a change in mortality risk from about 30% to about 50%.¹⁰ Accurate determination of GFR is also necessary for monitoring patients undergoing cancer chemotherapy with nephrotoxic anticancer drugs,¹¹ or those at risk for contrast media induced nephropathy (CIN).¹² Finally, GFR measurement is also useful for patients with chronic illness such as diabetes, hypertension, obesity, hyperthyroidism, cystic fibrosis, etc. who are at risk for renal impairment.¹³⁻¹⁵

2. Current GFR markers

In order to assess the status and to follow the progress of renal disease, there is a need to develop a simple, accurate, and continuous method for the determination of renal function by non-invasive procedures. At present, endogenous serum creatinine (**1**) (Fig. 1) concentration measured at frequent intervals over a 24-hour period has been the most common method of assessing renal function despite the well known serious limitations.¹⁶⁻¹⁸ The results from this analysis are frequently misleading since the value is affected by age, state of hydration, renal perfusion, muscle mass, dietary intake, and many other anthropometric and clinical variables. Theoretical methods for estimating GFR (eGFR)¹⁹⁻²¹ from body cell mass and plasma creatinine concentration have also been developed, but these methods also rely on the above anthropomorphic variables. Moreover, creatinine is

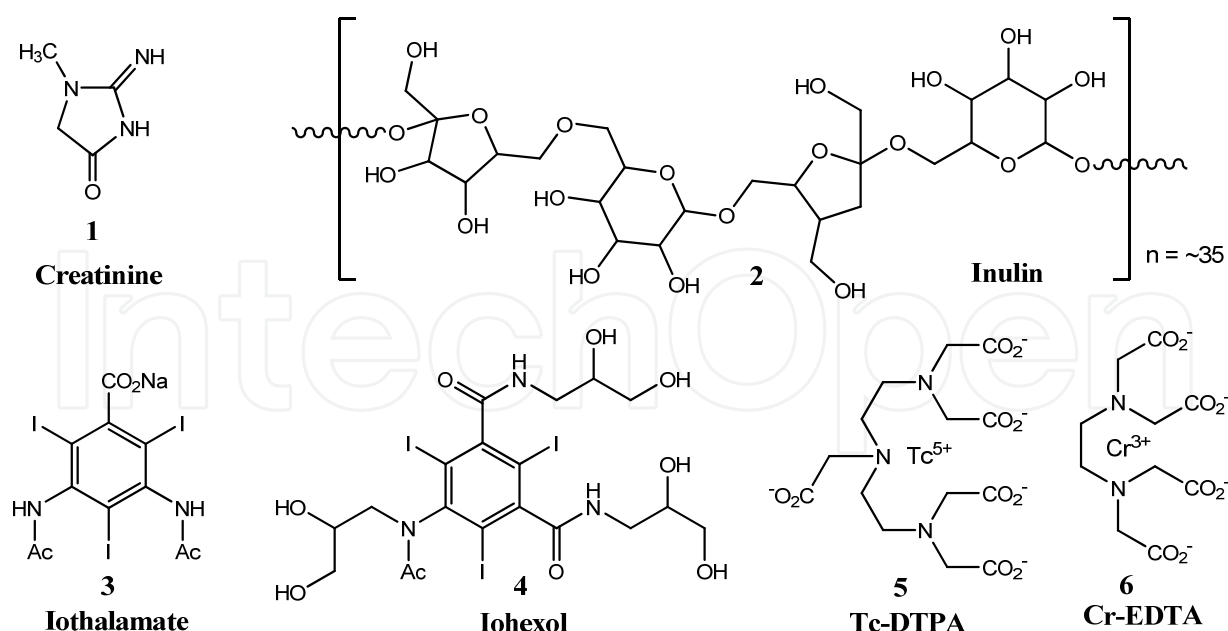


Fig. 1. Structures of Currently Known Exogenous GFR Markers.

partially cleared by tubular secretion along with glomerular filtration, and, as Diskin¹⁷ recently remarked, “Creatinine clearance is not and has never been synonymous with GFR, and all of the regression analysis will not make it so because the serum creatinine depends upon many factors other than filtration.” More recently, endogenous cystatin-C has been suggested as an improvement over creatinine,^{15,20} but this marker also suffers from the same limitations as creatinine, and thus it remains questionable whether it is really an improvement.

In the past several decades, exogenous tracers such as inulin (2), iothalamate (3), iohexol (4), ^{99m}Tc-DTPA (diethylenetriaminepentaacetate) (5), and ⁵¹Cr-EDTA (ethylenediaminetetraacetate) (6) (Fig.1), have been developed to determine GFR, but all of them require either radiometric, HPLC (high performance liquid chromatography), or X-ray fluorescence methods for detection and quantification.²²⁻²⁹ Unfortunately, all of these markers suffer from various undesirable properties including the use of radioactivity, ionizing radiation, and the laborious ex-vivo handling of blood and urine samples, and the use of HPLC method that render them unsuitable for continuous monitoring of renal function in the clinical setting. Furthermore, inulin as well as other polysaccharides are polydisperse polymers, and availability of these substances in a reliable, uniform batches is a serious limiting factor for their use as GFR markers. Currently, iothalamate and iohexol are the accepted standard for the assessment of GFR. However, iothalamate requires the collection of blood samples and requires HPLC method, which is not well suited for continuous monitoring. Continuous monitoring of GFR has been accomplished via radiometric¹² and magnetic resonance imaging³⁰ techniques, but these are not suitable at the bedside. Hence, the availability of an exogenous marker for the measurement of GFR under specific yet changing circumstances would represent a substantial improvement over any currently available or widely practiced method. Moreover, a method that depends solely on the renal elimination of an exogenous chemical entity would provide an absolute and continuous pharmacokinetic measurement requiring less subjective interpretation based upon age, muscle mass, blood pressure, etc.

3. Development of fluorescent tracer agents

Accordingly, there has been some effort on developing exogenous GFR tracer agents that absorb and emit in the visible or near infrared (NIR) region, which includes small molecules as well as macromolecular bioconjugates such as FITC (fluorescein isothiocyanate)-inulin and FITC- and Texas Red-dextran.³¹⁻³⁷ The key requirements for an ideal fluorescent tracer agent are: (a) must be excited at and emit in the visible region ($\lambda \geq \sim 425$ nm); (b) must be highly hydrophilic; (c) must be either neutral or anionic; (d) must have very low or no plasma protein binding; (e) must not be metabolized in vivo, and (f) must clear exclusively via glomerular filtration as demonstrated by equality of plasma clearance with and without a tubular secretion inhibitor such as probenecid.³⁸ The selection of the lead clinical candidate(s) may be based on secondary considerations such as the ease of synthesis, lack of toxicity, and stability. The secondary screening criteria should further take into account the tissue optics properties and the degree of extracellular distribution of the fluorescent tracers. Volume of distribution is an important parameter in the assessment of hydration state of the patient, whereas the absorption/emission properties provide essential information for the design of the probe.

This chapter focuses on the most recent development on luminescent tracers for GFR measurement. There are basically two principal pathways for the design of fluorescent tracers for GFR determination. The first method involves enhancing the fluorescence of known renal agents that are intrinsically poor emitters such as lanthanide metal complexes; and the second involves transforming highly fluorescent dyes (which are intrinsically lipophilic) into hydrophilic, anionic species to force them to clear via the kidneys.³² In the first approach, several europium-DTPA complexes endowed with various molecular 'antenna' to induce ligand-to-metal fluorescence resonance energy transfer (FRET) were prepared and tested.³² Some of metal complexes (e.g. compound **7** exhibited high (c.a. 2000-fold) enhancement of europium fluorescence and underwent clearance exclusively through the kidneys, but whether they cleared exclusively via glomerular filtration remains uncertain. Moreover, the excitation maxima of these complexes remained in the violet or UV-A region.

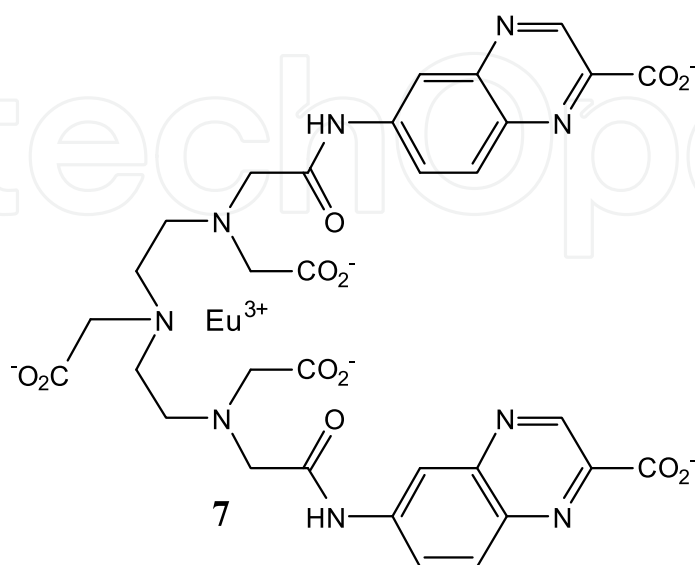


Fig. 2. Eu-DTPA-Quinoline Complex.

Pyrazines (Fig. 3) are one the very few classes of photostable small molecules having highly desirable properties for various biomedical and non-medical optical applications.³⁹⁻⁴¹ Pyrazine derivatives **8** containing electron donating groups (EDG) in the 2,5 positions and electron withdrawing groups (EWG) in the 3,6 positions such as compounds **9-11** are shown to absorb and emit in the visible region with a large Stokes shift on the order of ~ 100 nm and with fluorescence quantum yields of about 0.4.^{39,40} For example, conversion of the carboxyl group in **8** to the secondary amide derivatives **9** produces a bathochromic (red) shift of about 40 nm, and alkylation of the amino group in **9** produces further red shift of about 40 nm. Thus, the pyrazine nucleus offers considerable opportunity to ‘tune’ the electronic properties by even simple modifications. Furthermore, the relative small size of pyrazine renders it an ideal scaffold to introduce hydrophilic substituents to bring about renal clearance.

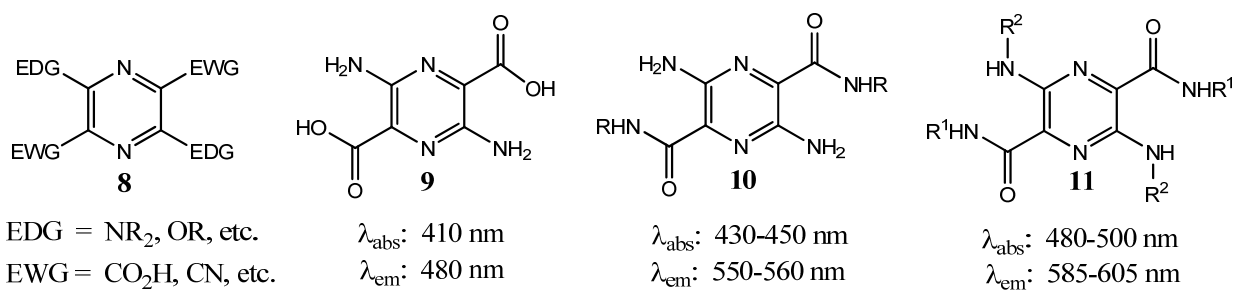


Fig. 3. Pyrazine Derivatives.

Based on the structure and properties of known GFR tracer agents, and on the primary and secondary considerations stated earlier, the set of GFR tracer agents can be divided into our categories as outlined in Table 1. The upper and lower quadrants address the tissue optics differences, and the left and right quadrants address volume of distribution (V_d) differences. (V_d) is important not only in affecting clearance rates, but also in the assessment of hydration state of a patient. Tissue optics parameters are important in instrument design in that the longer the wavelength of light, the deeper the penetration into the tissue. Recently, low and high molecular weight hydrophilic pyrazine derivatives **12-15** (Fig. 4) bearing neutral and anionic side chains such as alcohols, carboxylic acids, and polyethylene glycol (PEG) units were reported.⁴¹ The structures of the candidates from each of the four quadrants above are shown in Fig. 2. Unlike inulin, dextran, and other polymers, compounds **13** and **15** are monodisperse. The photophysical and biological properties of these compounds are given in Table 2. Both plasma protein binding and urinary clearance properties are superior to iothalamate, which is a currently used ‘gold standard’ for clinical GFR measurement. Furthermore, all four compounds displayed insignificant biodegradation.

Tissue Optics	Volume of Distribution	
	Short Wavelength Low Molecular Weight	Short Wavelength High Molecular Weight
	Long Wavelength Low Molecular Weight	Long Wavelength High Molecular Weight

Table 1. Design of Exogenous Fluorescent GFR Tracers.

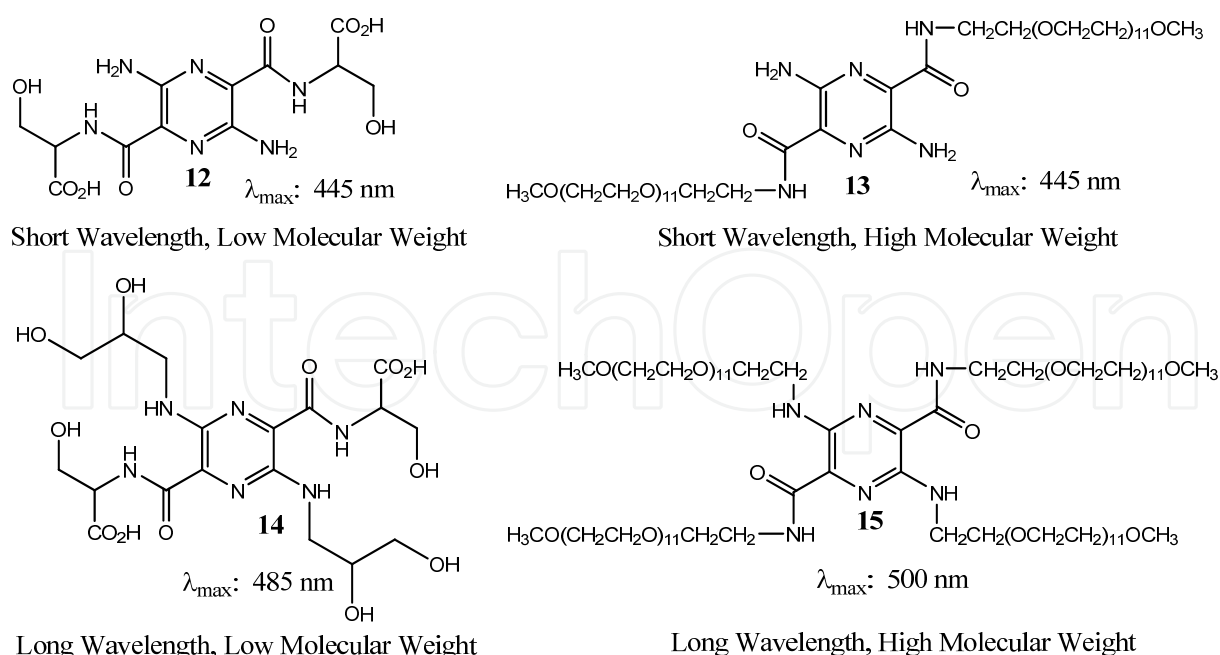


Fig. 4. Hydrophilic Pyrazine Derivatives.

	12	13	14	15	Iothalamate
Absorption Maxima, (λ_{\max} , nm)	435	437	488	499	NA
Emission Maxima, (λ_{\max} , nm)	557	558	597	604	NA
Plasma Protein Binding (%)	0	0	0	3	10
Plasma Clearance Half-Life (min)	29	25	20	19	32
Injected Dose Recovered in Urine at 6 Hrs (%)	90	71	88	97	80
Clearance – No probenecid (mL/min)	2.5	NA	3.0	3.1	2.5
Clearance – Probenecid, 70 mg/kg (mL/min)	2.6	NA	2.4	3.3	2.2

Table 2. Physicochemical and Pharmacokinetic Properties of Pyrazine Tracers.

An in vivo fluorescence image of the renal clearance of compound **13** is shown in Fig. 5. The panel contains images of three mice. The mouse in the middle was administered 300 μ L of a 2 mM solution in phosphate-buffered saline (PBS) of compound **13**. The other mice served as controls where the mice received only PBS. Compound **13** distributed throughout the body and then concentrated in one spot in the abdomen. Surgery after the 60 minute time point verified that this highly fluorescent spot in the abdomen was the bladder. Thus, this observation of fluorescence only appearing at the bladder is a visual demonstration of the high percent of injected dose recovered in urine given in Table 2.

4. Real-time monitoring of renal clearance

In vivo noninvasive real-time monitoring of renal clearance, with eventual translation to commercial development, has been demonstrated in the rodent model. A schematic of an apparatus is shown in Fig. 6. A 445 nm solid state laser was directed into one leg of a silica

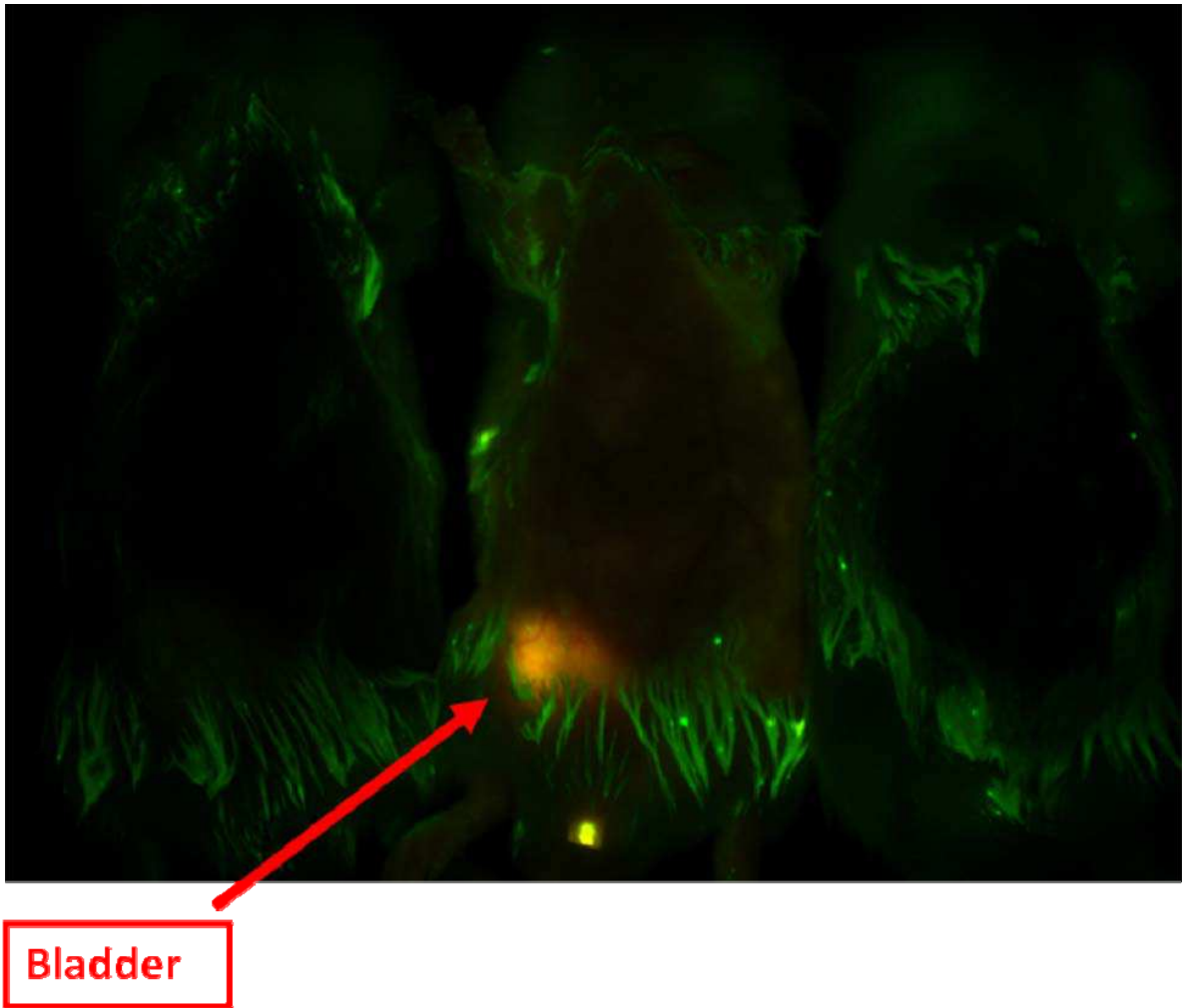


Fig. 5. Optical Image of Pyrazine 13 at 1 Hour Post Administration.

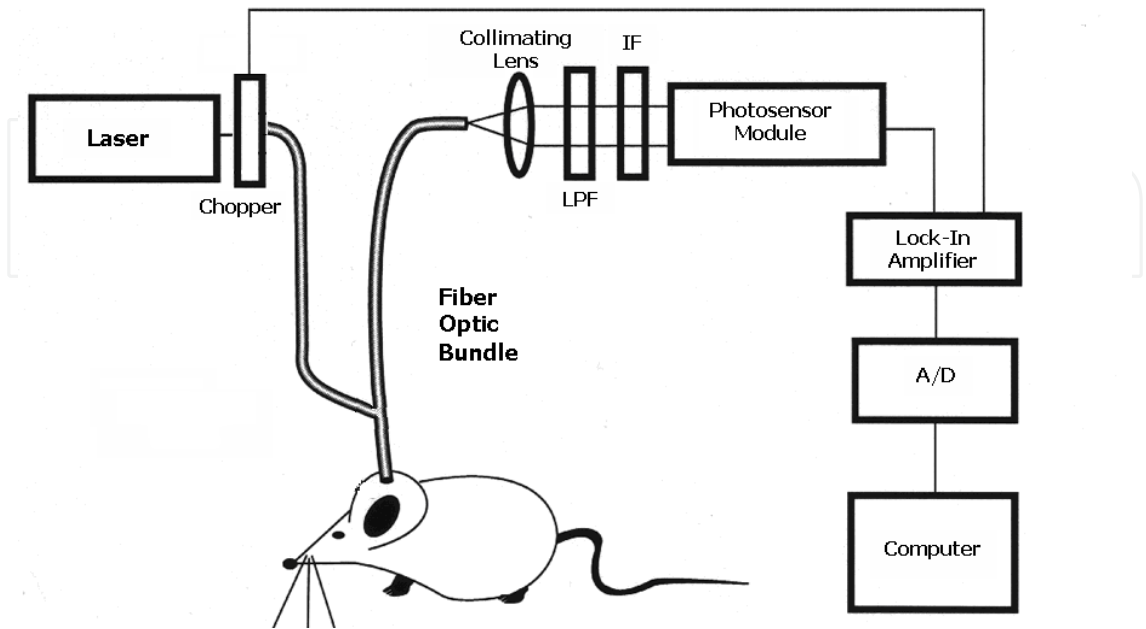


Fig. 6. Apparatus for non-invasive in vivo detection of fluorescence.

bifurcated fiber optic bundle, with the common end of this bifurcated bundle placed approximately 2 mm from the rat ear. The second leg of the bifurcated fiber optic bundle was fitted with a collimating beam probe. A long pass filter and narrow band interference filter were placed in front of a photosensor module. A chopper was placed after the laser and before the launch into the bifurcated cable. The output of the photosensor was connected to a lock-in amplifier. The lock-in output was digitized and the digitized data was acquired by computer using data acquisition software.

Anesthetized Sprague-Dawley rats of weight ~ 400 g were used. A volume of 1 mL of a 0.4 mg/mL concentration in PBS of compound **12** was administered to a rat with normal functioning kidneys and to a rat with a recent bi-lateral nephrectomy. The continuously monitored fluorescent signal is shown in Figure 5. An increase in fluorescence at the ear is immediately seen in both rats. In the normal rat, the fluorescence decreases back to baseline as the kidney removes compound **12** from the body. In the ligated rat, the fluorescence remains elevated with time as the body is unable to remove compound with the kidneys not functioning.

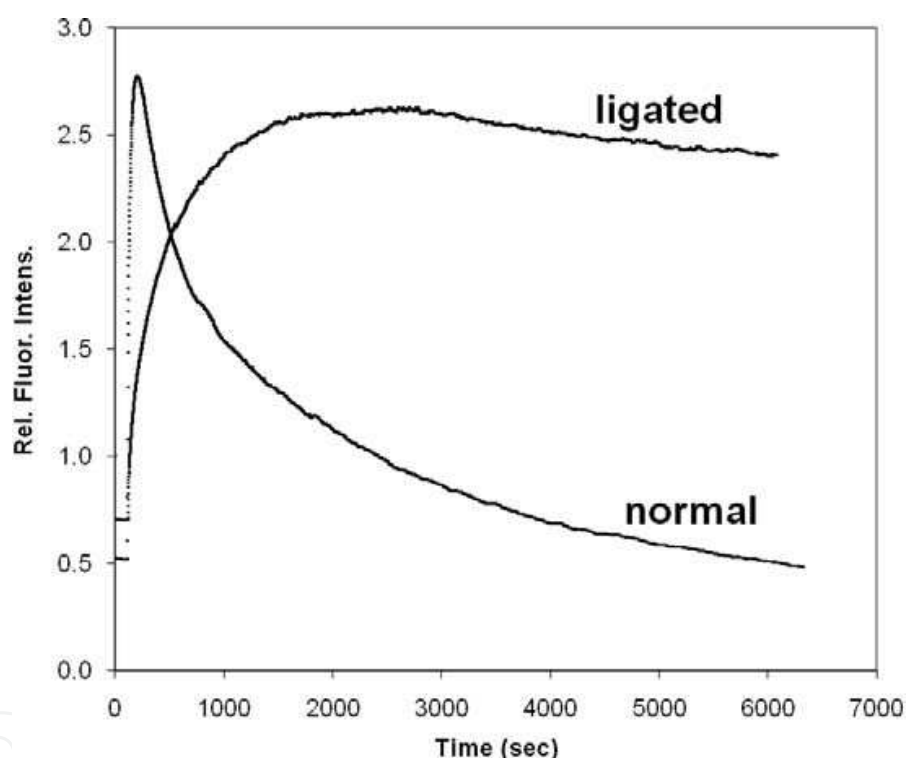


Fig. 7. Continuous Monitoring of Pyrazine **12** in Normal and Partially Nephrectomized Rats.

5. Conclusions

On the basis of the fluorescence properties, plasma protein binding data, the injected dose recovered in urine, the plasma clearance data, and the renal tubular secretion studies, the pyrazine derivatives **12-15** are promising candidates as exogenous fluorescent tracer agents for the determination of GFR under both chronic and acute settings. In the rat model, these compounds display superior properties compared to iothalamate, which is currently an accepted standard for the measurement of GFR.

A prototype instrument for clinical trials has been developed based on the apparatus in Figure 4. A clinical trial with one of the pyrazine compounds is currently being planned.

The clinical trial will test the safety and efficacy of the tracer agent, as well as refine the instrumentation. Optimization parameters for the instrument include incident light power and power density, light delivery and collection fiber optics, light source and detector, placement of detector on body, and the data acquisition and analysis algorithm.

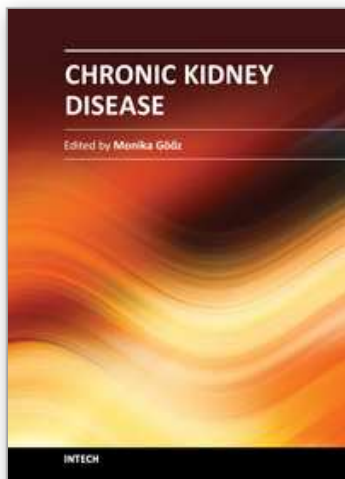
The addition of a fluorescent GFR tracer agent would be a major addition to the armament of fluorescent compounds in clinical use today. Indocyanine green (ICG) is FDA-approved for use in angiography, cardiac output, and liver function.⁴² Currently, there are on-going clinical trials for lymph node mapping and melanoma imaging using ICG.⁴³ Fluorescein is the only other FDA approved fluorescent agent, used for angiography.⁴² A near-infrared dye for attachment to targeting vectors for optical imaging has been studied for safety and pharmacology, and may soon be ready for human clinical trials too.⁴⁴

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Chronic Kidney Disease

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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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