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An efficient route to pyridine and 2,2′-bipyridine macrocycles incorporating a triethylenetetraminetetraacetic acid core as ligand for lanthanide ions

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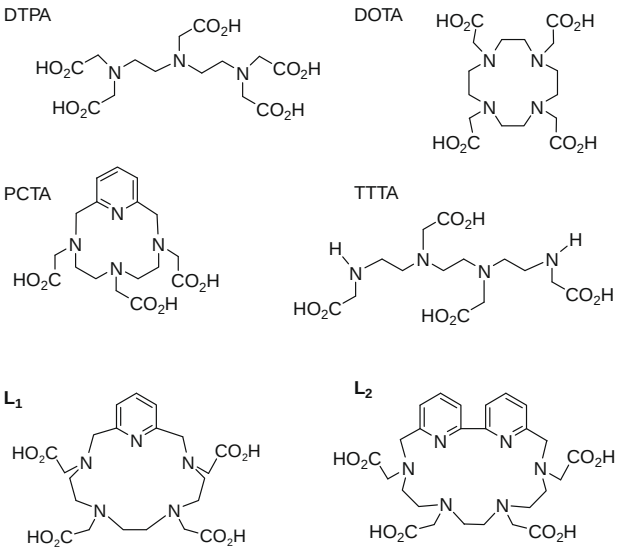
ABSTRACT

Two novel macrocyclic chelators $\mathbf{L_1}$ and $\mathbf{L_2}$ incorporating an intracyclic pyridine or 2,2′-bipyridine unit and a triethylenetetraminetetraacetic acid core (TTTA) were synthesized with the aim of forming lanthanide complexes suitable as efficient long-lived luminophores. For this goal, an efficient methodology for the preparation of TTTA derivatives using prealkylated precursors is described. Starting from commercially available compounds, the target ligands were obtained in seven ($\mathbf{L_1}$) and nine ($\mathbf{L_2}$) steps in 40% and 20% overall yields, respectively. Stable Tb(III) complexes were prepared and displayed interesting luminescence properties.

Some of the most widely used ligands in chemistry for the construction of metal complexes in aqueous solutions are ligands that possess both amino and carboxylate groups as metal-binding sites. From fundamental studies in coordination chemistry to the present day, this family of chelating agents has played a central role. In particular, they have found broad applications in pharmaceutical industry for diagnostic and therapeutic purposes. Thus, complexes combining lanthanide(III) and related ions with these ligands have been widely employed in magnetic resonance imaging (contrast agents based on Gd^{3+}),[1] in radiodiagnosis and radiotherapy (radiopharmaceuticals using metal radionuclides such as $^{86,90}Y$, ^{111}In, ^{153}Sm, ^{177}Lu, etc.),[2] or more recently, in fluorescence imaging (luminophores based on Eu^{3+} and Tb^{3+}).[3] A general advantage of these luminophores based on Ln^{3+} over conventional dyes is that their long-emission lifetimes (μs–ms range) permit easier distinction from the shorter-lived (ns range) endogenous fluorescence present in most biological matrices.[4] For these numerous applications in the biomedical domains, open-chain and macrocyclic polyazapolycarboxylate ligands DTPA, DOTA, and PCTA [12] are the main representative examples (Scheme 1).

In the domain of time-resolved fluorescence Ln(III) bioprobes, we and others have shown that macrocyclic lanthanide chelates comprising an intracyclic chromophoric unit and a diethylenetriaminetriacetic acid (DTTA) core (such as PCAT [12]) exhibit promising chemical and photophysical properties.[5] The macrocyclic structure provides high chelate stability and the chromophore-to-cation sensitization step (antenna effect)[6] occurs between partners in a rigid conformation that can improve the energy-transfer



Scheme 1. Ligands for lanthanide ions based on polyazapolycarboxylate cores.

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rates. However, as a coordination number of 9 is very common for lanthanide complexes in aqueous solutions, the introduction of a monodentate (pyridine) or bidentate (2,2′-bipyridine, *N,C*-pyrazolylpyridine) chromophoric unit in such macrocyclic DTTA systems allows two or one water molecules to coordinate the metal center, respectively. When solvents containing OH groups are coordinated to Eu(III) and Tb(III) ions, efficient nonradiative deactivation of the metal emissive states takes place via weak vibronic coupling between f electronic states of the central ion and vibrational states of high-frequency O–H oscillators.[7] The result is a partial quenching of the metal fluorescence.

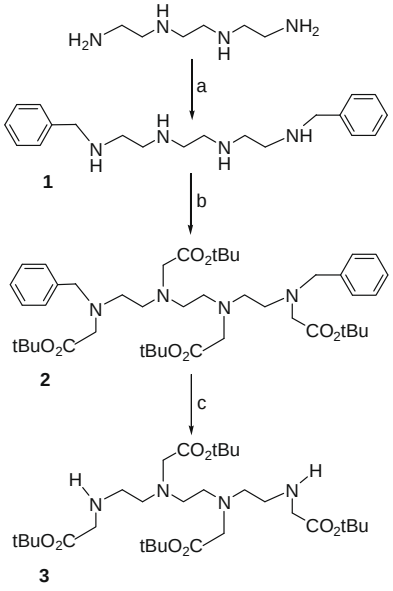
In order to overcome this drawback and in the course of our previous work on the synthesis of macrocyclic 2,2′-bipyridine-DTTA derivatives,[8] we have planned to introduce an octadentate host, a triethylenetetraminetetraacetic acid (TTTA) core in the macrocyclic framework. The use of a TTTA core in the field of chelating agents is less extensive than one might expect. To the best of our knowledge, there are no reports in the academic literature involving TTTA ligand (Scheme 1). On the other hand, four patents claimed its potential use but no data were reported.[9]

We report here a convergent synthetic route to two novel macrocycles (**L_1**, **L_2**, Scheme 1) based on pyridine and 2,2′-bipyridine chromophores and a TTTA backbone. In this synthetic pathway, the macrocyclization step involves tetra-*N*-alkylated tetramine block incorporating masked acetate arms (compound **3**, Scheme 2). This functionalized polyamine is a useful building block for the construction of macrocyclic structures, since it contains two secondary amine functions at the ends which can be connected by various heterocyclic cross-linkers. In addition, some preliminary luminescence properties of the **L_1Tb** and **L_2Tb** complexes are presented.

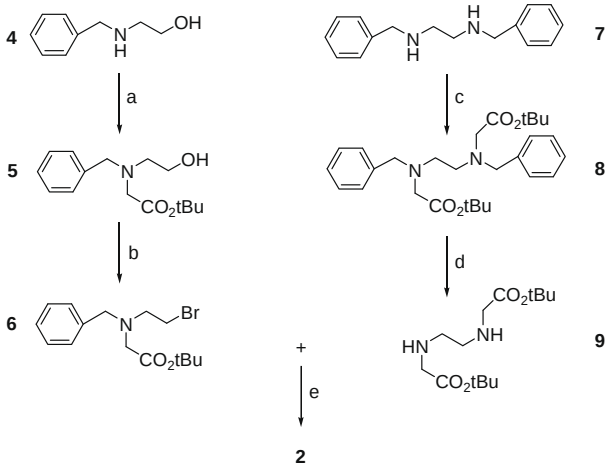
The preparation of the key compound **3** was firstly carried out following our previously reported procedure for the preparation of the corresponding diethylenetriamine skeleton.[10] This route is depicted in Scheme 2 and involves a three-step sequence: (i) reductive amination of commercially available triethylenetetramine with benzaldehyde, according to literature procedures,[11] (ii) tetra-alkylation on the resulting secondary tetramine with *tert*-butyl bromoacetate, (iii) removal of the benzyl-protecting groups by catalytic hydrogenation with Pd/C. This strategy allowed us to obtain the target compound (9% overall yield),[12] but, clearly, was hampered by the poor yield resulting from the per-alkylation reaction in the 2nd steps. As a matter of fact, when the four secondary amine groups of **1** were alkylated with *tert*-butyl bromoacetate, the tertiary compound **2** was isolated in 19% yield, at best, after extensive column chromatography. In fact, chromatographic purification of **2** was complicated due to the formation of polyalkylated by-products which are very difficult to differentiate from the desired product by TLC. Attempts to direct the reaction towards exclusive formation of **2**, mainly by varying mole ratios of the reagents and reaction time always yielded complex mixtures of alkylation products. This brings us to consider another way to have access to the key synthon **3**.

In order to minimize the formation of overalkylated by-products, an alternative method for the synthesis of **2** consists in the use of prealkylated precursor molecules. In this direction, the coupling reaction of *N,N′*-dialkylated ethylenediamine derivative **9** and two equivalents of *N*-Bn-protected monoalkylated bromide **6** was expected to provide the target compound **2** while simplifying the purification process (Scheme 3). These two precursor molecules were prepared in two steps from commercially available compounds **4** and **7**. Alkylation at the amine group of *N*-benzyl ethanolamine was performed with *tert*-butyl bromoacetate in the presence of *N,N*-diisopropylethyl amine (DIPEA) as a base, providing **5** in a quantitative yield. Note that the use of this hindered organic base, instead of K_2CO_3,[13] prevents a lactonization side reaction forming 4-benzyl-morpholin-2-one. Under these conditions, methyl ester and benzyl ester analogs of the *tert*-butyl ester compound **5** can be obtained in excellent yields (90–100%). The hydroxyl group of **5** was then replaced by bromine group by reaction with NBS/PPh_3 using standard methodology, yielding **6** in 82% yield. Starting from *N,N′*-benzyl ethylenediamine, a combination of alkylation with *tert*-butyl bromoacetate followed by a deprotection step under mild hydrogenolysis conditions produced the second precursor molecule **9** in 100% yield for the two steps.[14] Finally, the K_2CO_3-promoted coupling reaction of **9** and **6** (2 equiv) in CH_3CN successfully provided the tetra-*tert* butyl ester **2** in high yield (92%) after a simple column chromatography. The total yield of this reaction sequence was 75% in compound **2**.

We investigated the synthetic flexibility of this approach, studying the possibility (i) to mix the nature of carboxyl-protective groups of the four acid groups in the TTTA core, a feature which



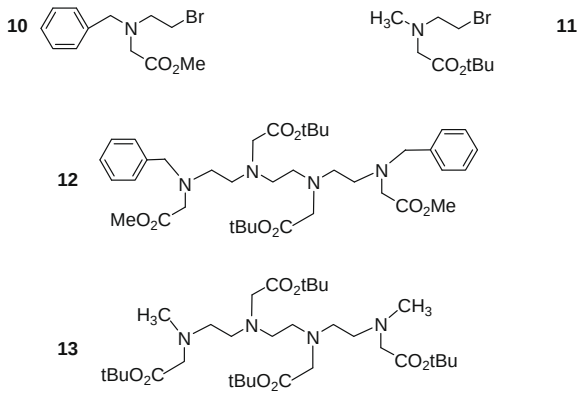
Scheme 2. Conventional synthesis of key compounds **2** and **3**. Reagents and conditions. (a) PhCHO, $NaBH_4$, $CHCl_3$, 48%; (b) $BrCH_2COOtBu$ (5 equiv), iPr_2NEt, DMF, rt, 48 h, 19%; and (c) Pd/C (10%), H_2 (2 bar), MeOH, rt, 12 h, 100%.



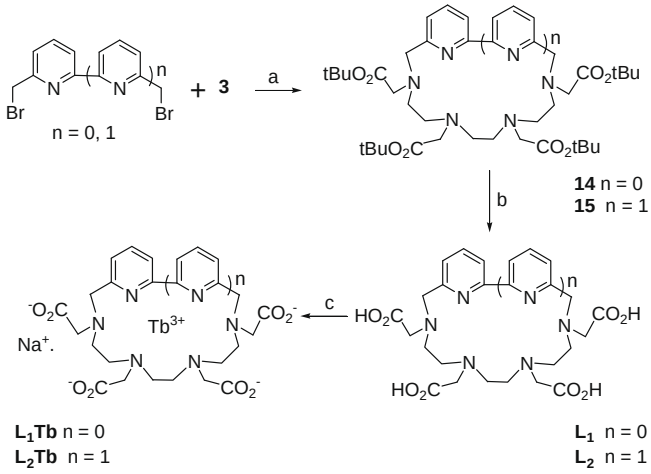
Scheme 3. Improved synthesis of compound **2**. Reagents and conditions: (a) $BrCH_2COOtBu$, iPr_2NEt, DMF, rt, 24 h, 100%; (b) NBS/PPh_3, CH_2Cl_2, rt, 82%; (c) $BrCH_2CO_2tBu$ (2 equiv), K_2CO_3, CH_3CN, reflux, 24 h, 100%; (d) Pd/C (10%), H_2 (2 bar), MeOH, rt, 12 h, 100%; and (e) **6** (2 equiv), K_2CO_3, CH_3CN, reflux, 24 h, 92%.

opens the way to further selective modifications and (ii) to prepare a precursor of an acyclic analog of DOTA (**12** and **13**, Scheme 4). Starting from *N*-benzyl ethanolamine and *N*-methyl ethanolamine, the bromo compounds **10** and **11** were prepared in two steps according to the procedure described above (70% and 65% overall yield, respectively). Subjecting the dialkylated material **9** to further dialkylation with bromo derivative **10** affords mixed tetraester **12** in 50% isolated yield in which the terminal and central carboxyl groups are differentiated as methyl and *tert*-butyl esters.[12] Similarly, proceeding with secondary diamine **9** and bromo derivative **11**, tetraester **13** was obtained in 65% yield after chromatographic purification.[12]

Having established a reliable synthetic route to **3**, we next investigated the use of this building block for the assembly of macrocyclic structures. Actually, reaction of **3** with 2,6-bis-(bromomethyl)-pyridine and 6,6′-bis (bromomethyl)-2,2′-bipyridine[15] gave the 15-membered and 18-membered macrocycles **14** and **15**, respectively (Scheme 5). The synthesis was carried out in refluxing CH_3CN for 24 h, in the presence of Na_2CO_3 as the base and without the use of high dilution techniques. ^1H, ^{13}C NMR and MS analyses of the crude mixtures evidenced the presence of a major species, characterized as the sodium monomeric complex. In both cases, attempted purification of the sodium complex by chromatography led to isolation of the mixtures of sodium complex and free ligand, as a result of alumina-mediated decomplexation. However, when the crude mixture was treated with a saturated EDTA solution (to remove sodium species) the free macrocycles **14** and **15** were readily obtained after chromatography on alumina in 54% and 58% yield, respectively. Finally, desired chelators $\mathbf{L_1}$ and $\mathbf{L_2}$ were obtained quantitatively by the treatment of the corresponding tetra-*tert*-butyl esters in a mixture of dichloromethane and trifluoroacetic acid (1:1) at room temperature.[12]



Scheme 4. TTA derivatives **12**, **13** and their precursors **10**, **11**.



Scheme 5. Synthesis of new macrocyclic ligands $\mathbf{L_1}$, $\mathbf{L_2}$ and their corresponding Tb(III) complexes. Reagents and conditions: (a) Na_2CO_3, CH_3CN, reflux, 24 h, [reactants] = 2.7×10^{-3} M, 54% (**14**) and 58% (**15**); (b) HCOOH, 60 °C, 24 h, 100% ($\mathbf{L_1}$ and $\mathbf{L_2}$); and (c) $TbCl_3.6H_2O$, rt, H_2O, pH 7.4.

The Tb^{3+} complexes of ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ were prepared by the addition of $TbCl_3 \cdot 6H_2O$ to the aqueous solutions of ligands.[16] Photoexcitation of the complexes (1×10^{-5} M in Tris buffer, pH 7.4) from the lowest energy absorption band of the pyridine or bipyridine moiety (268 and 310 nm, respectively) gave rise to a bright and long-lived green luminescence, indicating that these chromophoric moieties are able to transfer the excitation light to the luminescent f–f excited states of the metal ion. The measured excited state lifetimes are respectively of 1.54 and 2.18 ms for $\mathbf{L_1Tb}$ and $\mathbf{L_2Tb}$ in water with quantum yields of 11% and 26%,[17] respectively, improving the data previously observed for open chain and macrocyclic analogs.[5a,d,18] Comparison of the lifetimes obtained in H_2O and D_2O at 298 K allowed an assessment of the hydration state of these terbium complexes. By using the well-established method of Parker and co-workers,[19] these analyses indicate that there is one metal-bound water molecule in $\mathbf{L_1Tb}$ and no bound water molecule in $\mathbf{L_2Tb}$. Thus, the introduction of a TTTA moiety (vs DTTA) in these macrocyclic systems displaces one water molecule from the first coordination sphere of the lanthanide ion. A full study of the photophysical properties of terbium and other lanthanide complexes derived from these ligands is currently in progress.

As a conclusion, an efficient synthetic approach to macrocylic ligands for lanthanide complexation based on a triethylenetetraaminetetraacetic acid (TTTA) backbone and pyridine or bipyridine heterocycles is described. The key steps were (i) the formation of functionalized polyamine **2** which was achieved in high yield and in high purity by the use of prealkylated precursors, (ii) the macrocyclization reaction which gave azamacrocycles **14** and **15** in satisfying yields as a result of a sodium template-mediated cyclization. Presumably, the present procedures are quite useful for convenient synthesis of numerous open-chain and macrocyclic derivatives of TTTA. The terbium complexes derived from these ligands are stable in aqueous solutions and display attractive luminescence properties, as a result of a high degree of shielding of the metal.

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12. *Compound* **2**: ^{1}H NMR (300 Mz, $CDCl_3$): δ = 1.43 (s,18H), 1.45 (s, 18H), 2.68 (m, 4H), 2.75 (m, 8H), 3.23 (s, 4H), 3.29 (s, 4H), 3.78 (s, 4H), 7.28–7.31 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 28.20 (CH_3), 28.23 (CH_3), 52.1 (CH_2), 52.6 (CH_2), 52.9 (CH_2), 55.2 (CH_2), 56.1 (CH_2), 58.4 (CH_2), 80.62 (Cq), 80.67 (Cq), 127.0 (CH), 128.3 (CH), 128.9 (CH), 139.2 (Cq), 170.87 (Cq), 170.98 (Cq). LRMS (ES^+) calcd for $C_{44}H_{70}N_4O_8$+H^+, 783.5; found, 783.7 (100%); calcd for $C_{44}H_{70}N_4O_8$+2H^+, 392.3; found, 392.6 (97%). *Compound* **3**: ^{1}H NMR (300 Mz, $CDCl_3$): δ = 1.44 (s,18H), 1.46 (s, 18H), 2.81 (m, 4H), 3.01 (m, 8H), 3.40 (s, 4H), 3.59 (s, 4H). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 28.2 (CH_3), 28.3 (CH_3), 45.5 (CH_2), 49.0 (CH_2), 50.2 (CH_2), 51.3 (CH_2), 55.3 (CH_2), 81.0 (Cq), 82.5 (Cq), 168.5 (Cq), 171.2 (Cq). LRMS (ES^+) calcd for $C_{30}H_{58}N_4O_8$+H^+, 603.4; found, 603.5 (100%). *Compound* **12**: ^{1}H NMR (300 Mz, $CDCl_3$): δ = 1.42 (s, 18H), 2.70–2.95 (m, 12H), 3.37 (s, 4H), 3.42 (s, 4H), 3.66 (s, 6H), 3.79 (s, 4H), 7.20–7.35 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 28.06 (CH_3), 28.14 (CH_3), 47.0 (CH_2), 50.1 (CH_2), 51.3 (CH_3), 51.6 (CH_2), 52.4 (CH_2), 52.5 (CH_2), 54.1 (CH_2), 55.8 (CH_2), 58.5 (CH_2), 81.3 (Cq), 82.7 (Cq), 127.2 (CH), 128.3 (CH), 129.1 (CH), 138.4 (Cq), 169.8 (Cq), 170.4 (Cq), 171.9 (Cq). LRMS (ES^+) calcd for $C_{38}H_{59}N_4O_8$+H^+, 699.4; found, 699.7 (100%). *Compound* **13**: ^{1}H NMR (300 Mz, $CDCl_3$): δ = 1.42 (s, 18H), 1.43 (18H), 2.34 (s, 6H), 2.57–2.62 (m, 4H), 2.72 (s, 4H), 2.72–2.77 (m, 4H), 3.15 (s, 4H), 3.30 (s, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 28.17 (CH_3), 28.20 (CH_3), 42.4 (CH_3), 52.3 (CH_2), 53.0 (CH_2), 55.0 (CH_2), 56.2 (CH_2), 59.5 (CH_2), 80.7 (Cq), 80.8 (Cq), 170.3 (Cq), 170.9 (Cq). LRMS (ES^+) calcd for $C_{32}H_{62}N_4O_8$+H^+, 631.5; found 631.7 (100%). *Compound* $\mathbf{L_1}$: ^{1}H NMR (300 Mz, D_2O): δ = 3.42 (m, 4H), 3.55–3.66 (m, 8H), 3.71 (s, 4H), 3.87 (s, 4H), 4.67 (s, 4H), 7.59 (d, J = 7.8 Hz, 2H), 8.05(t, J = 7.8 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O): δ = 51.0 (CH_2), 51.6 (CH_2), 53.0 (CH_2), 54.8 (CH_2), 56.7 (CH_2), 58.1 (CH_2), 124.7 (CH), 140.6 (CH), 150.4 (Cq), 170.3 (Cq), 172.3 (Cq). HRMS (ES^+) calcd for $C_{21}H_{31}N_5O_8$+H^+, 482.2251, found, 482.2244 (100%); calcd for $C_{21}H_{31}N_5O_8$+Na^+, 504.2070, found, 504.2075 (96%). *Compound* $\mathbf{L_2}$: ^{1}H NMR (300 Mz, D_2O): δ = 3.20–3.40 (m, 8H), 3.49–3.60 (m, 4H), 3.63 (s, 4H), 3.67 (s, 4H), 4.63 (s, 4H), 7.88 (d, J = 7.4 Hz, 2H), 8.41(t, J = 7.4 Hz, 2H), 8.49 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75.4 MHz, D_2O): δ = 51.0 (CH_2), 51.2 (CH_2), 51.9 (CH_2), 54.5 (CH_2), 55.6 (CH_2), 57.1 (CH_2), 123.7 (CH), 128.0 (CH), 147.9 (Cq), 151.4 (Cq), 172.6 (Cq). HRMS (ES^+) calcd for $C_{26}H_{34}N_6O_8$+K^+, 597.2075, found, 597.2070 (100%).
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15. 6,6′-Bis (bromomethyl)-2,2′-bipyridine was obtained in two steps starting from 6,6′-dimethyl–2,2′-bipyridine. The latter compound was treated with mCPBA to form the corresponding di (*N*-oxide) derivative in 90% yield. Subsequent treatment in acetic anhydride, then in hydrobromic acid, and 40% in acetic acid, gave the desired compound in 52% isolated yield.
16. A water solution of $TbCl_3$ (1 equiv) was added dropwise while maintaining the pH at 7.4. The resulting mixture was then stirred during 24 h at room temperature and passed through chelex-100 to trap the eventual free Tb^{3+}, and the Tb^{3+}-loaded complex was recovered. The solvent was removed, the resulting solid was dissolved in a minimum of MeOH, and Et_2O was added to precipitate the desired complex, which was isolated by centrifugation and dried under vacuum. The absence of free Tb^{3+} ions was verified using the Arsenazo test and no peak ascribable to the free ligand was observed in the mass spectra of the isolated complexes. $\mathbf{L_1Tb}$: 80% yield. LRMS (ES^-) calcd for $C_{21}H_{28}N_5O_8Tb-H^-$, 636.1, found, 636.1 (100%). Luminescence (Tris buffer pH 7.4, λ_{exc} = 268 nm): λ_{em} (relative intensity, corrected spectrum), 488 (41), 544 (100), 584 (32), 620 (26) nm. $\mathbf{L_2Tb}$: 86% yield. LRMS (ES^-) calcd for $C_{26}H_{31}N_6O_8Tb-H^+$, 713.1, found, 713.1 (100%). Luminescence (Tris buffer pH 7.4, λ_{exc} = 310 nm): λ_{em} (relative intensity, corrected spectrum), 490 (40), 545 (100), 585 (33), 621 (24) nm.
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