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1,2,4-Triazine method of bipyridine ligand synthesis for the preparation of new luminescent Eu(III) complexes

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ABSTRACT

The 'triazine' methodology for the synthesis of functionalized bipyridine ligands proved to be a convenient method for the preparation of luminescent Eu(III) complexes. The approach allows flexible construction of chromophore and coordination sphere with control of photophysical properties. Europium (III) complexes [**Eu1**]–[**Eu5**] prepared in this way exhibit intense long-life metal-centered luminescence in aqueous media. The aromatic substituent in the position 5 of bipyridine has a significant influence on luminescence parameters and is used to introduce functionality for bioconjugation. The complexes [**Eu4**] and [**Eu5**] bearing primary amine groups are ready-to-go luminescent 'tags' for peptide labeling.

1. Introduction

Luminescent complexes of trivalent lanthanide cations are of great interest because of their applications as molecular probes in biomedical,[1] sensing[2] or imaging areas,[3] as light emitting devices.[4] In particular, Eu(III) complexes, possessing long-life (milliseconds) intense luminescence in aqueous solutions, have been widely used as luminescent labels for time-resolved immunoassays.[5] In this case, the structure of a ligand plays a key role since the Eu(III) cation itself cannot be effectively excited by light in the visible or long-wave UV region (e.g., at 395 nm, generated by cheap LED lasers) and cannot be attached to a biomolecular substrate. The synthesis of such a polyfunctionalized ligand is not a trivial task: the ligand has to form a stable complex with Eu(III) in aqueous media; nine coordination sites of the metal should be occupied by a multidentate ligand to exclude water coordination resulting in non-radiative decay of the excited state, and the ligand should bear appropriate linker for bioconjugation.[6] The choice of a chromophore, that is, capable of transferring its excited state energy to the encapsulated Eu(III) ion, is a very important step in the ligand design. The energy transfer from ligand to metal is most efficient when the chromophore is integrated into the coordination sphere and directly participates in metal ion binding.[7] From this point of view, oligopyridines (bi- and ter-pyridines, phenanthroline) are the most suitable bases for desired ligands.

The '1,2,4-triazine' methodology for the synthesis of pyridines[8] has proved to be an effective approach toward various functionalized polypyridine ligands.[9–11] This method includes the synthesis of properly substituted 1,2,4-triazines followed by their transformation to the targeted substituted pyridines in reactions with dienophiles (enamines, enols, 2,5-norbornadiene, substituted acetylene, allylcarborane).[12–17] The main advantage of this strategy is the control of particular properties of metal complexes through structural variety of ligands: from photophysical to liquid crystal properties.[18–22] Herein we describe the design and synthesis of new luminescent Eu(III) complexes, which can potentially be used as luminescent labels for bioassays.

2. Results and discussion

2.1. Ligand design and synthesis

The design of ligands is the crucial point in the preparation of luminescent europium labels.[7] The correct choice of a chromophore, connected with appropriate construction of the coordination sphere, provides desired chemical and photophysical properties of the target complex. We chose 5-aryl-2,2′-bipyridines as chromophore units for our systems. This is because bipyridines were successfully used previously for the creation of luminescent europium(III) complexes and proved an efficient sensitization and energy transfer to the emitting metal center.[23] Introduction of aromatic substituents at position 5 of bipyridine is an effective tool

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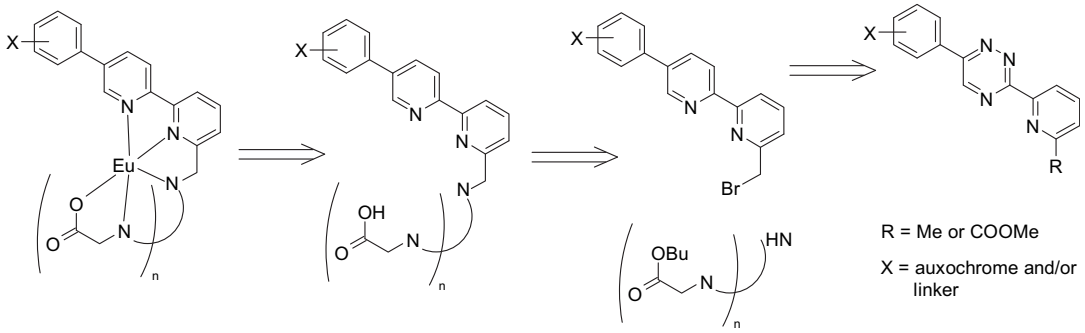
for fine-tuning of photophysical properties of the chromophore: decreasing the energy of the excited state (red-shift of absorption and emission maxima) and increasing the extinction coefficient.[24,25] In addition, the aryl ring allows the introduction of functionalities to expedite binding to biological targets and acts as a linker keeping the emissive center away from the biomolecular substrate. We exemplify it here by introducing an amino group, which can further be transformed into isothiocyanate to provide amino reactive luminescent dye.

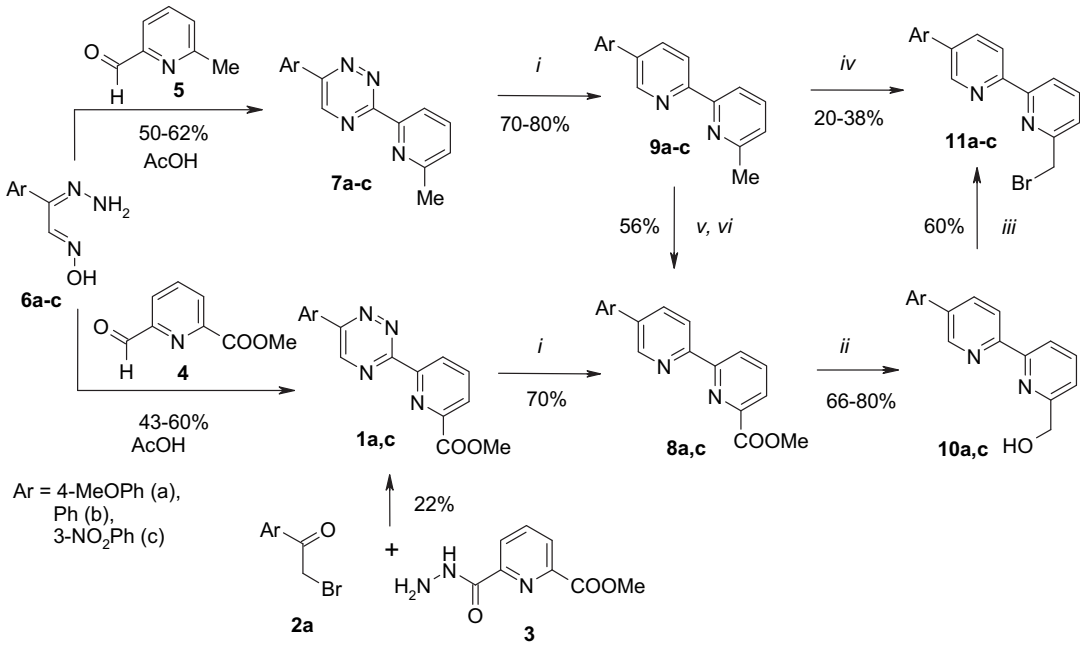
In order to strongly bind the Eu(III) ion we chose three types of widely used poly(aminoacetate) moieties: (1) 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacylodecane (DO3A), attached to position 6′ of 2,2′-bipyridine; (2) diethylenetriamine *N*,*N*,*N*″*N*″-tetraacetate (DTTA), attached the same way; (3) two iminodiacetates (IDA) in the 6 and 6′ positions of 2,2′-bipyridine. In this way, poly(aminoacetate) connected to bipyridine at the α-positions to the nitrogen atoms through methylene bridges binds the Eu(III) ion strongly and includes bipyridine into the coordination sphere, which is important in achieving effective energy transfer from the light-absorbing bipyridine chromophore to the emissive metal center.

Scheme 1 illustrates the retrosynthetic path toward the target Eu-complexes. The key step is the synthesis of 3-pyridyl-1,2,4-triazine, which contains aryl as well as a methyl or ester group at desired positions. The following Diels–Alder reaction of 1,2,4-triazines with 2,5-norbornadiene gives corresponding 2,2′-bipyridines and the methyl or ester group are transformed into bromomethyl group. The later is then used in alkylation of the polyiminoacetate and gives the desired ligand.

Among the various possible pathways[26] for formation of the 1,2,4-triazine ring only the three following could give the desired configuration of the substituents. Two methods involve cyclization of isonitrosoacetophenone hydrazone with aldehyde to give 1,2,4-triazines[22] or 1,2,4-triazine 4-oxides[27] depending on conditions. The third method is the cyclization of α-bromoacetophenone with aromatic hydrazide.[28] The last one was found to be ineffective for the synthesis of pyridyltriazinecarboxylate **1** (Scheme 2). The cyclization of 2-bromo-4′-methoxyacetophenone **2a** with monohydrazide of 2,6-pyridinedicarboxylic acid **3** gave methoxyphenyltriazine **1a** in low (22%) yield and needed a double excess of not easily accessible monohydrazide **3**. On the contrary, the reaction of readily available methyl 6-formylpyridine-2-carboxylate **4** or 6-methylpyridine-2-carboxaldehyde **5** with hydrazones of isonitrosoacetophenones **6** afforded desired methoxycarbonyl(methyl)pyridyltriazines **1** or **7** in 43–62% yields (Scheme 2). Reflux of triazines **1** and **7** with 2,5-norbornadiene in xylene gave methoxycarbonyl(methyl)-2,2′-bipyridines **8** and **9** in 70–90% yields. Reduction of the ester group of **8** gave hydroxymethylbipyridine **10**, which was transformed to bromomethylbipyridine **11**. At the same time, direct bromination of the methyl group of **9** was not so successful and afforded **11** only in 20–38% yield. An alternative pathway from methylbipyridine **9** to



Scheme 1. Retrosynthetic path for synthesis of new Eu-complexes.

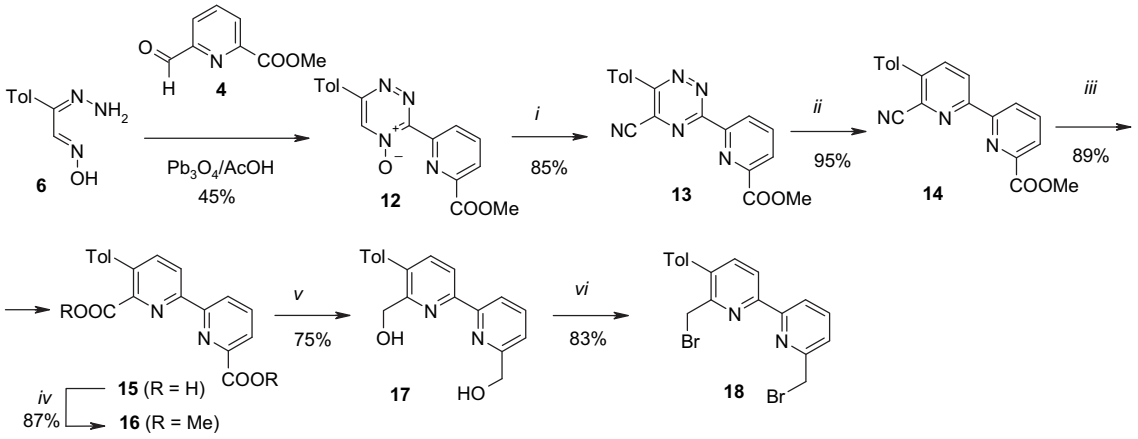


Scheme 2. Reagents and conditions: (i) 2,5-norbornadiene, *o*-xylene, reflux, 24 h; (ii) $NaBH_4$, EtOH, 20–78 °C, 4 h; (iii) PBr_3, CH_2Cl_2, 40 °C, 5 h; (iv) NBS, CCl_4, 77 °C, 7 h; (v) SeO_2, pyridine, 115 °C, 20 h; (vi) $SOCl_2$, 76 °C, 6 h, then MeOH, 65 °C, 1 h.

bromomethylbipyridine **11** was the synthesis through ester **8** (oxidation of the methyl group with SeO_2 and esterification). However, the overall yield for the three steps proved to be nearly the same.

1,2,4-Triazine methodology allows introduction of two bromomethyl groups in both rings of 2,2′-bipyridine. In this case, the starting heterocyclic system, pyridyl-1,2,4-triazine 4-oxide **12**, was obtained by oxidative cyclization of hydrazone **6** and aldehyde **4** (Scheme 3). The presence of the *N*-oxide group provides easy access

Bipyridine bearing two bromomethyl groups has advantages over monosubstituted bipyridine, since two small and readily available aminoacetate fragments, such as iminodiacetate (IDA), can be used for chelating system formation. Indeed, reaction of bis(bromomethyl)bipyridine **18** with IDA dimethyl ester resulted in the formation of bipyridinetetraacetate **29** (Scheme 6). Consecutive nitration of **29**, Pd/C-catalyzed hydrogenation of the nitroester **30**, and basic hydrolysis of the

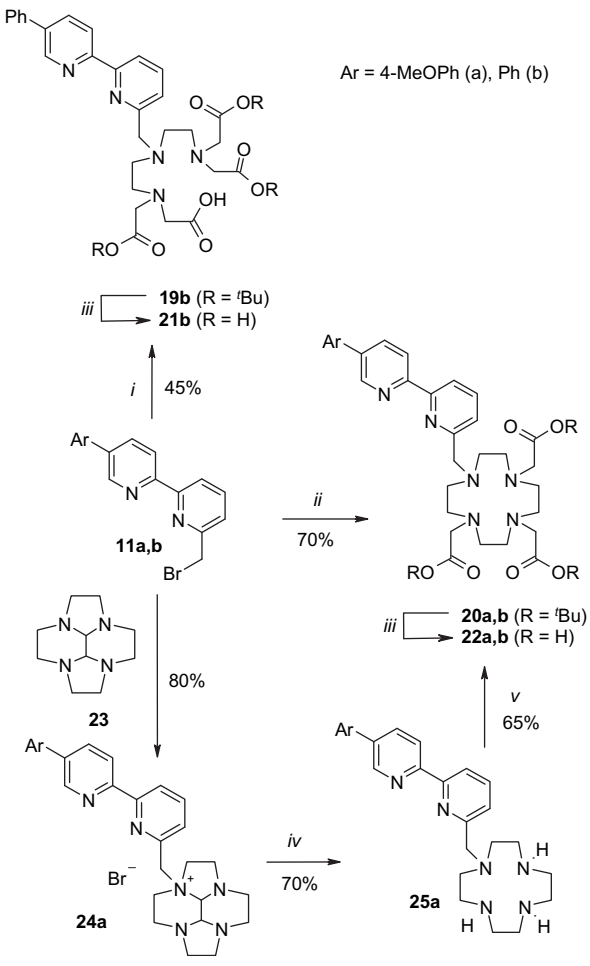


Scheme 3. (i) acetone cyanohydrin, NEt_3, rt; (ii) 2,5-norbornadiene, toluene, reflux, 6 h; (iii) H_2SO_4 (50%), 120 °C, 15 h; (iv) $SOCl_2$, reflux, 1 h, then MeOH, reflux, 1 h; (v) $NaBH_4$, EtOH, rt, 20 h; (vi) PBr_3, CH_2Cl_2, 40 °C, 2 h.

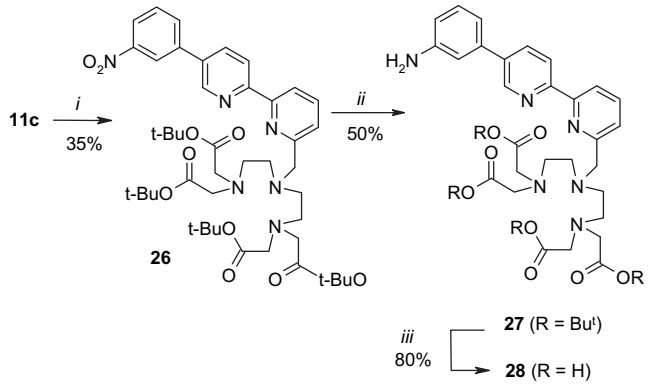
to corresponding 5-cyano-1,2,4-triazines by direct substitution of hydrogen under mild conditions.[27] Thus, the reaction of **12** with acetone cyanohydrin in the presence of a weak base (triethylamine) gave pyridyltriazine **13** bearing ester and nitrile groups. Further reaction of cyanotriazine **13** with 2,5-norbornadiene is facilitated by the presence of electron withdrawing cyano group and proceeded smoothly to give cyanobipyridine **14** (Scheme 3). The nitrile and ester groups were then easily transformed to bromomethyl groups by standard methods to provide strategically important bis (bromomethyl)arylbipyridine **18** (Scheme 3).

The next part of the synthesis was the construction of the coordination sphere by combining bromomethyl building blocks with the poly(aminoacetates). Reaction of bromomethylbipyridines **11** with tetra-*tert*-butyl ester or tri-*tert*-butyl ester in the presence of K_2CO_3 led, respectively, to the esters **19** and **20**, which gave, after a further acidic hydrolysis, the new ligands **21** and **22** as hydrochloride salts (Scheme 4). The acetate arms of **20** could also be grafted to the cyclic ligand by in an alternative way, starting from bis-aminal protected cyclen **23**.[29] This compound **23** was easily prepared as previously described and was then alkylated to give the quaternary salt **24**, which was deprotected in hydrazine hydrate[30] with formation of monoalkylated cyclen **25**. Alkylation of the cyclic pro-ligand **25** by bromoacetate afforded ester **20** in 36% total yield for the three steps. In practice, this way is much more appropriate when compared with the direct alkylation of tri-*tert*-butyl ester because of the complicated synthesis of the latter.

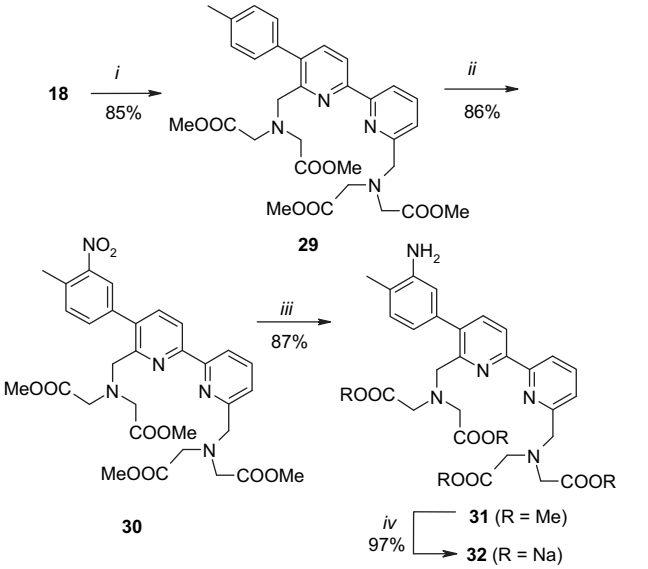
The suggested method for synthesis of the bipyridine chromophore allows variation of the aromatic substituents. This helps to form linker for proteins binding by introducing special groups in the early steps. One of them is the amino group, which can be used in several protocols for protein labeling.[31] Here we illustrate this using nitroacetophenone as starting material. Nitrophenylbipyridine building block **11c**, obtained as described above, was involved in the reaction with tetra-*tert*-butyl ester to give nitroester **26** (Scheme 5). The nitro group was reduced by Pd/C-catalyzed hydrogenation, while hydrolysis of the resulting aminoester **27** gave ligand **28** bearing the amino group at the appropriate position.



Scheme 4. Construction of coordination site. Reagents and conditions: (i) DTTA tetra-*tert*-butyl ester, K_2CO_3, CH_3CN, 82 °C; (ii)DO3A tri-*tert*-butyl ester, K_2CO_3, CH_3CN, 82 °C; (iii) HCl (5 M), 20 °C; (iv) N_2H_4, H_2O, 100 °C; (v) $BrCH_2COO^tBu$, K_2CO_3, MeCN.



Scheme 5. (i) DTTA tetra-*tert*-butyl ester, K_2CO_3, CH_3CN, 82 °C; (ii) H_2, Pd/C, MeOH, 20 °C, 6 h; (iii) HCl, 20 °C, 12 h.

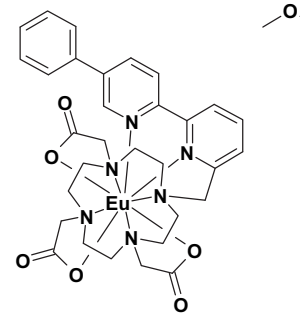


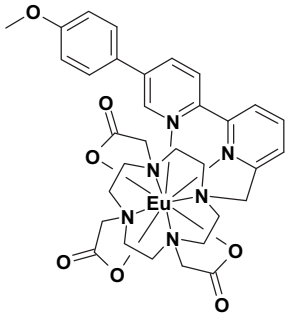
Scheme 6. Construction of coordination site. Reagents and conditions: (i) IDA dimethyl ester, K_2CO_3, CH_3CN, 82 °C; (ii) 65% HNO_3, 30 min, 0 °C; (iii) H_2, Pd/C, EtOH, 60 h, 15 atm; (iv) NaOH (1 equiv)/water.

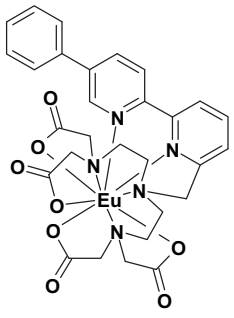
aminoester **31** gave the octadentate amino-ligand **32** for synthesis of potential Eu-label.

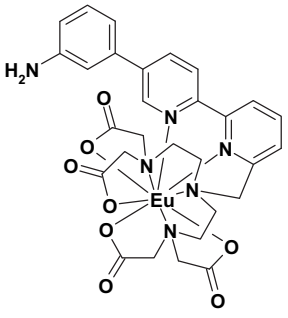
Finally, we prepared three types of ligands: nonadentate **22** bearing triple negative ionic charge (macrocyclic DO3A derivatives); nonadentate **21** and **28** with quadruple negative ionic charge (open-chain DTTA derivatives); and octadentate **32** with quadruple ionic charge (open-chain bis-IDA).

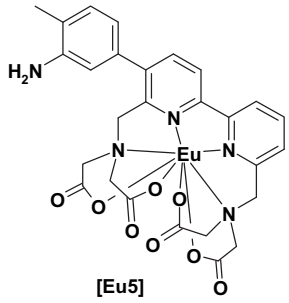
2.2. Complex preparation and photophysical properties











Eu(III) complexes [**Eu1**]–[**Eu5**] were prepared according to a standard procedure upon treatment of corresponding sodium salts of ligands **22b**, **22a**, **21b**, **28**, **32** with 1 equiv of europium chloride (III). All complexes were formed with ligand to metal ratio as 1:1. Complexes [**Eu1**]–[**Eu4**] have nine-coordinated Eu(III) ions, and [**Eu5**] has an eight-coordinated one with one unoccupied coordination site open to interaction with water molecules. The complexes [**Eu1**] and [**Eu2**] are neutral, while [**Eu3**], [**Eu4**], and [**Eu5**] are mononegatively charged and have a Na^+ ion as counterion.

All complexes were isolated and the structures proved by microanalysis and ESI mass-spectroscopy. A single crystal was grown and X-ray structure was obtained for the complex [**Eu2**] (Fig. 1). The structure proved that the metal cation is nine-coordinated by the two nitrogen atoms of the bipyridine, the four nitrogen atoms and the three carboxylic groups of the macrocycle. The distances between nitrogen atoms of bipyridine and europium center are 2.65 and 2.58 Å, and this is nearly the same distances as between europium and nitrogen atoms of macrocycle. The structure indicates that the bipyridine moiety is strongly distorted from planarity: the torsion between pyridine rings is 8° and that between pyridine and aromatic substituent is 19°. Moreover, the lateral pyridine ring is distorted from planarity itself and the nitrogen atom is out of the ring plane, obviously, because of strains related to metal coordination. The nitrogen atoms and the oxygen atoms form N_4 and

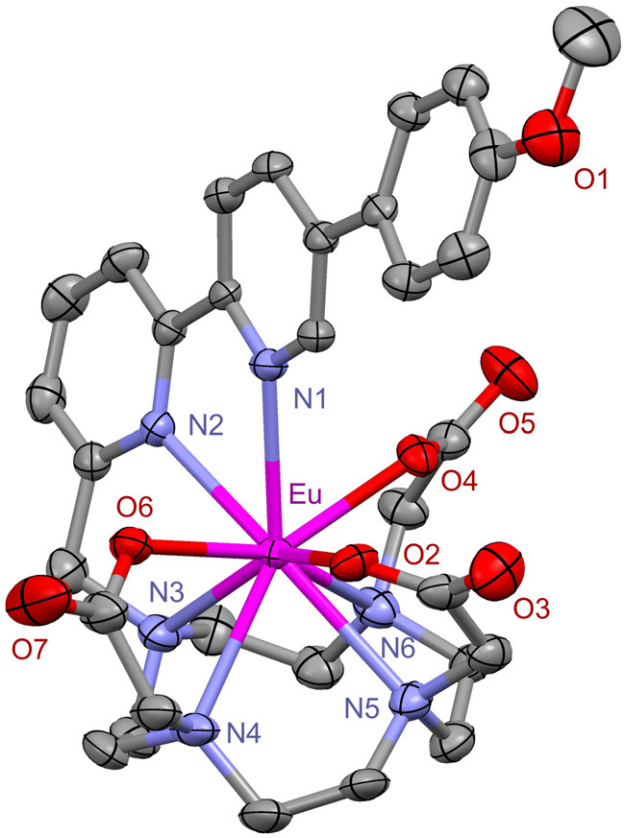


Fig. 1. Molecular structure of [**Eu2**].

O_3 bases that are planar and nearly parallel. The angle between the planes is less than 1°. The europium ion lies between these planes, but is closer to the O_3 base. The twist angles of the bases around the local fourfold axis (as counted for nonequivalent pendant arms) is between 23° and 30°. Thus, the arrangement should be termed as a twisted-square antiprism, so the DO3A complex is present in the solid state as the twisted square-antiprismatic (TSAP) isomer.

The absorption spectra of the complexes [**Eu1**]–[**Eu4**] in water solution are shown in Fig. 2 and the wavelengths and extinction coefficients are given in Table 1. The two peaks in the UV region at 270 and 330 nm are assigned to the ligand-centered transition of the 5-aryl-2,2′-bipyridine system. The 4-methoxy derivative

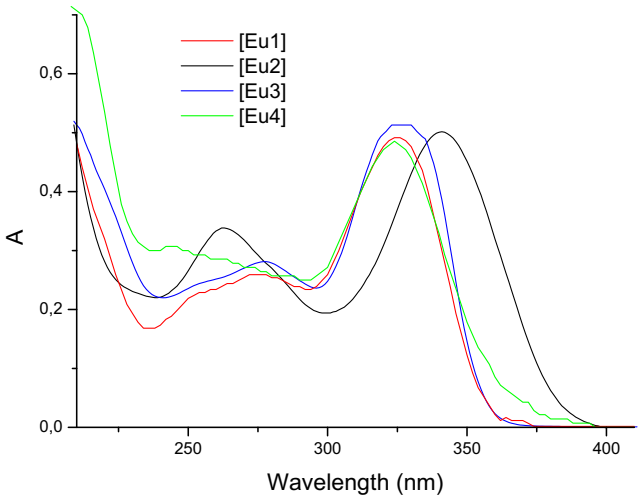


Fig. 2. The absorption spectra of [**Eu1**]–[**Eu4**].

Table 1
Photophysical parameters of [**Eu1**]–[**Eu5**]

	λ_{abs} (nm)	ϵ ($dm^3 mol^{-1} cm^{-1}$)	Φ_{EM}	τ_{H2O}, ms	τ_{D2O}, ms	q
[**Eu1**]	325	7505	0.073	1.00	1.10	−0.19
[**Eu2**]	341	8091	0.011	0.27	0.30	0.15
[**Eu3**]	327	12,015	0.093	0.80	1.30	0.27
[**Eu4**]	325	10,080	0.006	0.60	0.70	−0.01
[**Eu5**]	328	9012	0.002	0.17	0.21	1.05

exhibits the most red-shifted absorption (341 nm) because of the electron-donating effect of the methoxy group reducing the energy gap between ligand ground and single exited states. The absorption bands of the complexes are 30–40 nm red-shifted in comparison with free 5-aryl-2,2′-bipyridines,[22] confirming direct coordination of bipyridine nitrogen atoms to the Eu^{3+} cation.

Upon excitation into low energy absorbance bands, the europium complexes displayed the luminescence typical for Eu-complexes as a series of sharp emission bands due to transitions from the $^5D_0$ excited state of Eu(III) ion. The emission spectra of all complexes [**Eu1**]–[**Eu5**] are quite similar (Fig. 3). Some differences were observed for the bands at 680–710 nm, which correspond to $^5D_0 \rightarrow {}^7F_4$ transition. The structure and intensity of this band is known to be very sensitive to ligand environment. Indeed, we can see the complexes [**Eu1**] and [**Eu2**] with the same coordination sphere have the similar band profiles. The same is true for the pair [**Eu3**] and [**Eu4**]. As we can see, chromophore type has a slight influence on the profile of emission spectrum. On the other hand, acting as 'antenna' chromophore strongly enhance the overall emission efficiency, which depends on the efficiencies of ISC and ET processes of the ligand.

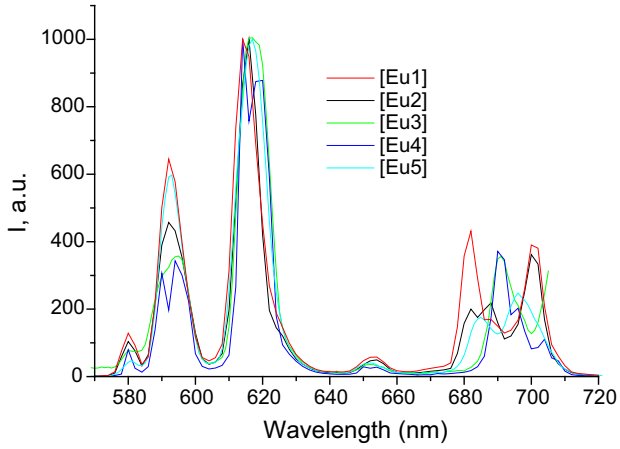


Fig. 3. The emission spectra of [**Eu1**]–[**Eu5**].

The overall quantum yields of luminescence of new complexes in water solution are given in Table 1. The highest efficiency was observed for [**Eu1**] and [**Eu3**] with the same chromophore unit, 5-phenyl-2,2′-bipyridine. For other complexes, which are bearing electron-donating group on aromatic substituent the quantum yields are lower. This can be explained by dependence of ligand-to-metal energy transfer (ET) efficiency on the energy gap ΔE between ligand triple state and europium emissive state $^5D_0$. The higher ΔE, the greater the ET efficiency or, in other words, lower energy of ligand triplet state causes less effective luminescence. Electron-donating groups of the ligand **22b**, **28**, **32** decrease the triplet state energy decreasing the quantum yields of the complexes [**Eu2**], [**Eu4**], and [**Eu3**]. In the case of amino-substituted derivatives, photo-induced electron transfer can also be responsible for low quantum yields of the complexes.

As was shown, for the complexes [**Eu1**]–[**Eu4**] with nine-coordinated Eu(III) ion, the luminescence efficiency depends mostly on aromatic system and is rather independent of the binding poly(aminoacetate) structure. This is not true for [**Eu5**] with eight-coordinated metal ion, where an unprotected coordination site is accessible for interaction with water molecules. Interaction with OH oscillators result in excited state non-radiative deactivation and luminescence quenching. In this regard, comparison of luminescence lifetimes obtained in water and deuterated water solutions allows the assessment of water binding to Eu(III) center.[32] This can be done by using the following equations where q is the number of coordinated water molecules (uncertainty ±0.5) and lifetimes (τ) are in ms.

$$q = 1.2\left(1/\tau_{H_2O} - 1/\tau_{D_2O} - 0.25\right) \quad (1)$$

The obtained lifetimes and calculated numbers of water molecules in the Eu(III) inner coordination sphere are given in Table 1. As expected, q ~0 for [**Eu1**]–[**Eu4**] where the metal ion is nine-coordinated and q=1 for eight-coordinated [**Eu5**]. So, we can say that binding poly(aminoacetate) is responsible only for complex stability and luminescence quenching protection.

3. Conclusions

In conclusion, the proposed '1,2,4-triazine' method for bipyridine ligands synthesis is a useful tool for the preparation of luminescent Eu(III) complexes. The approach makes possible an aromatic chromophore design for tuning photophysical properties, it allows a flexible construction of a coordination sphere for Eu(III) binding and provides the possibility to introduce suitable functionality for binding to biomolecules. Here we described five new luminescent europium complexes, and two of them [**Eu4**] and [**Eu5**] with primary amine group are 'ready-to-go' luminescent labels. They exhibit intense long-life luminescence, can be excited with available 337 nm laser light, are water-soluble, and can be used for further conjugation to peptides. The other three complexes [**Eu1**]–[**Eu3**] are 'model' compounds and designed to show an influence of aromatics and coordinating poly(aminoacetate) on photophysical properties.

4. Experimental

4.1. General methods

Manipulations were performed under an atmosphere of dry argon using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. Commercially available chemicals were reagent grade and were used without further purification. The following compounds were prepared as described in the literature: **3**,[33] **4**,[34] **6**,[27] **23**,[29] tetra-*tert*-butyl diethylenetriamine *N*,*N*,*N*″*N*″-tetraacetate (tetra-*tert*-butyl DTTA).[35] Thin-layer chromatography was performed on Merck silica plates with a fluorescence indicator. TLC spots were visualised by irradiation with UV light or by exposure to iodine vapors (R_f values refer to relative mobilities on TLC plates). Column chromatography was carried out on silica gel (Merck, 60–200 mm, porosity 60 Å). Melting points are uncorrected. Magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at 400 MHz on a Bruker Avance 400 MHz spectrometer. Elemental analyses were carried out by the Elemental Analysis Group in Postovsky Institute of Organic Synthesis (Ekaterinburg) on Perkin–Elmer 2400 elemental analyzer. Absorption measurements were done with a Perkin–Elmer Lambda 45 spectrophotometer. The Eu(III) luminescence emission and luminescence lifetimes were recoded and calculated using a Varian Cary Eclip spectrofluorimeter. The luminescence quantum yields were determined by the described method,[32] using as standard $[Ru(bpy)_3]_2$ in aerated water and corrected for the refractive index of the solvent.

4.2. Methyl 6-(6-aryl-1,2,4-triazin-3-yl)picolinates (1)

4.2.1. Via cyclization of 2-bromoacetophenone with hydrazide. 2-Bromo-4′-methoxyacetophenone **2a** (12.85 g, 56.11 mmol), monohydrazide **3** (21.89 g, 112.25 mmol), and sodium acetate (5.06 g, 61.7 mmol) were stirred at 50 °C in mixture ethanol/acetic acid (4:1) (280 mL) during 15 h. Solids were filtered off, solvents removed in vacuum. Ethanol was added to residue, after 3 h crystals of **1a** were filtered off, washed with water and ethanol, dried and then passed for the next step without further purification.

4.2.2. Via cyclization of isonitrosoacetophenone hydrazone with aldehyde. Mixture of corresponding hydrazone **1** (33.65 mmol) and monoaldehyde **4** (5.55 g, 33.65 mmol) was solved in ethanol (150 mL). Reaction mass was kept at rt for 8 h. The resulting precipitate was filtered off and suspended in acetic acid (100 mL). Suspension was heated to reflux two times. Solvent was removed in vacuum. Residue was treated by ethanol. Crystals of **1** were filtered off, washed by ethanol, dried and then passed for the next step without further purification.

*4.2.3. Methyl 6-(6-phenyl-1,2,4-triazin-3-yl)picolinates (**1a**).* Yield 3.94 g (12.2 mmol, 22%) via path 4.2.1. and 6.14 g (19.00 mmol, 56%) via path 4.2.2. Mp: 222–224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.89 (s, 3H, OMe), 3.96 (s, 3H, COOMe), 7.21 (m, 2H, C–H$_{arom}$), 8.24–8.32 (m, 4H, C–H$_{arom}$, H-4′,5′), 8.70 (d, 1H, J=7.8 Hz, H-3′), 9.56 (s, 1H, H-5).

*4.2.4. Methyl 6-(6-(3-nitrophenyl)-1,2,4-triazin-3-yl)picolinates (**1c**).* Yield 6.24 g (18.51 mmol, 55%) via path 4.2.2. Mp: 244–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.97 (s, 3H, COOMe), 7.97 (dd, 1H, J=8.2, 8.0 Hz, H-5″), 8.25–8.35 (m, 2H, H-4′,5′), 8.49 (m, 1H, H-6″), 8.76 (m, 2H, H-3′,4″), 9.12 (d, 1H, J=2.0 Hz, H-2″), 9.77 (s, 1H, H-5).

4.3. 6-Aryl-3-(6-methylpyridine-2-yl)-1,2,4-triazines (7)

A corresponding hydrazone **6** (20 mmol) and 6-methylpyridine-2-carbaldehyde **5** (2.42 g, 20 mmol) were solved in ethanol (50 mL). Reaction mass was kept for 5 h at rt. Solids were filtered and suspended in glacial acetic acid (50 mL). Mixture was heated at 90 °C in 30 min, and allowed to cool to rt. Solvent was removed in vacuum, residue was treated with ethanol. Crystals of **7** were filtered, washed with ethanol and dried.

*4.3.1. 6-(4-Methoxyphenyl)-3-(6-methylpyridine-2-yl)-1,2,4-triazine (**7a**).* Yield 3.45 g (12.4 mmol, 62%). Mp: 188–190 °C (from ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.64 (s, 3H, Me), 3.89 (s, 3H, OMe), 7.12 (m, 2H, C–H$_{arom}$), 7.40 (d, 1H, J=7.5 Hz, H-5′), 7.87 (d, 1H, J=7.5 Hz, H-4′), 8.23–8.27 (m, 3H, C–H$_{arom}$, H-3′), 9.39 (s, 1H, H-5). Anal. Calcd for $C_{16}H_{14}N_4O$: C 69.05, H 5.07, N 20.13. Found: C 68.67, H 5.03, N 20.29.

*4.3.2. 6-Phenyl-3-(6-methylpyridine-2-yl)-1,2,4-triazine (**7b**).* Yield 2.48 g (10 mmol, 50%). Mp: 175–177 °C (from ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.66 (s, 3H, Me), 7.40 (d, 1H, J=7.0 Hz, H-5′), 7.59 (m, 3H, Ph), 7.88 (dd, 1H, J=7.0, 6.8 Hz, H-4′), 8.29 (m, 3H, Ph, H-3′), 9.43 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{12}N_4$: C 72.56, H 4.87, N 22.57. Found: C 72.31, H 4.81, N 22.70.

*4.3.3. 6-(3-Nitrophenyl)-3-(6-methylpyridine-2-yl)-1,2,4-triazine (**7c**).* Yield 3.28 g (11.2 mmol, 56%). Mp: 206–208 °C (from ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.67 (s, 3H, Me), 7.44 (d, 1H, J=7.6 Hz, H-5′), 7.91 (m, 2H, H-4′,5″), 8.35 (d, 1H, J=7.6 Hz, H-3′), 8.43 (m, 1H, H-4″), 8.75 (m, 1H, H-6″), 9.14 (d, 1H, J=2.0 Hz, H-2″),

9.67 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{11}N_5O_2$: C 61.43, H 3.78, N 23.88. Found: C 61.18, H 3.59, N 23.71.

4.4. 5-Aryl-6′-methoxycarbonyl-2,2′-bipyridines (8)

*4.4.1. Starting from corresponding 1,2,4-triazine **1**.* A corresponding 1,2,4-triazine **1** (5 mmol) was suspended in *o*-xylene (50 mL), 2,5-norbornadiene (2.55 mL, 25 mmol) was added and the mixture was refluxed during 24 h with addition of 2,5-norbornadiene (1.53 mL, 15 mmol) every 5 h. The solvent was removed in vacuum, and the residue was treated by methanol. The resulting crystals of **8** were filtered, washed with methanol and dried.

*4.4.2. Starting from 6′-methyl-2,2′-bipyridines **9**.* Mixture of 6′-methyl-2,2′-bipyridines **9a** (1.28 g, 4.63 mmol) and SeO_2 (2.06 g, 18.53 mmol) was refluxed in dry pyridine (25 mL) for 2 days. Solids were filtered off, and solvent was removed in vacuum. The residue was treated with water solution of NaOH (1 M) and heated to 80 °C. Solids were filtered off, and HCl (11 M) was added to adjust pH=2. The precipitate of 6-(4-methoxyphenyl)-2,2′-bipyridine-2′-carboxylic acid was filtered off, washed by water and dried. Then it was suspended in $SOCl_2$ (25 mL) and stirred under reflux for 6 h. Solvent was removed, methanol (20 mL) was added and the mixture was reflux for 1 h. Solvent was removed in vacuum, and the residue was treated by methanol. The resulting precipitate of **8a** was filtered off, washed with methanol, and dried.

*4.4.3. 5-(4-Methoxyphenyl)-6′-methoxycarbonyl-2,2′-bipyridine (**8a**).* Yield 1.12 g (3.5 mmol, 70%) via path 4.4.1. and 0.81 g (2.53 mmol, 81%) via path 4.4.2. Mp: 142–144 °C (from methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 3H, OMe), 3.96 (s, 3H, COOMe), 7.10 (m, 2H, C–H_{arom}), 7.79 (m, 2H, C–H_{arom}), 8.11 (d, 1H, J=8.0 Hz, H-3′), 8.17 (dd, 1H, J=8.0, 7.8 Hz, H-4′), 8.26 (dd, 1H, J=8.0, 2.4 Hz, H-4), 8.47 (d, 1H, J=8.0 Hz, H-3), 8.63 (d, 1H, J=8.0 Hz, H-5′), 9.02 (d, 1H, J=2.4 Hz, H-6). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C 71.24, H 5.03, N 8.74. Found: C 71.01, H 4.88, N 8.49.

*4.4.4. 5-(3-Nitrophenyl)-6′-methoxycarbonyl-2,2′-bipyridine (**8c**).* Yield 1.17 g (12.59 mmol, 70%). Mp: 187–189 °C (from methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.97 (s, 3H, COOMe), 7.85 (dd, 1H, J=8.2, 8.0 Hz, H-5″), 8.15 (d, 1H, J=7.6 Hz, H-3′), 8.20 (dd, 1H, J=7.6, 7.6 Hz, H-4′), 8.32 (m, 2H, H-4″,6″), 8.46 (dd, 1H, J=8.4, 2.4 Hz, H-4), 8.55 (d, 1H, J=8.4 Hz, H-3), 8.63 (dd, 1H, J=2.0 Hz, H-2″), 8.67 (d,1H, J=7.6 Hz, H-5′), 9.17 (d, 1H, J=2.4 Hz, H-6). Anal. Calcd for $C_{18}H_{13}N_3O_4$: C 64.48, H 3.91, N 12.53. Found: C 64.31, H 3.80, N 12.32.

4.5. 5-Aryl-6′-methyl-2,2′-bipyridine (9)

A corresponding 1,2,4-triazine **7** (25 mmol) was suspended in *o*-xylene (100 mL). 2,5-Norbornadien (7.58 mL, 75 mmol) was added and the mixture was refluxed during 24 h with addition of 2,5-norbornadien (7.58 mL, 75 mmol) after 9 h. Solvent was removed in vacuum, and the residue was treated by methanol. The resulting crystals of **9** were filtered off, washed with methanol, and dried.

*4.5.1. 5-(4-Methoxyphenyl)-6′-methyl-2,2′-bipyridine (**9a**).* Yield 5.73 g (20.8 mmol, 83%). Mp: 132–134 °C (from methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.58 (s, 3H, Me), 3.83 (s, 3H, OMe), 7.10 (m, 2H, C–H_{arom}), 7.32 (d, 1H, J=7.6 Hz, H-5′), 7.76 (m, 2H, C–H_{arom}), 7.84 (dd, 1H, J=7.6, 7.6 Hz, H-4′), 8.19 (m, 2H, H-3′,4), 8.43 (d, 1H, J=8.3 Hz, H-3), 8.97 (d, 1H, J=1.8 Hz, H-6). Anal. Calcd for $C_{18}H_{16}N_2O$: C 78.24, H 5.84, N 10.14. Found: C 77.81, H 5.70, N 10.28.

*4.5.2. 5-Phenyl-6′-methyl-2,2′-bipyridine (**9b**).* Yield 4.49 g (18.3 mmol, 73%). Mp: 92–94 °C (from methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.60 (s, 3H, Me), 7.23 (d, 1H, J=7.8 Hz, H-5′), 7.35–7.56 (m, 3H, Ph), 7.65–7.80 (m, 3H, Ph, H-4′), 8.10 (dd, 1H, J=8.3, 2.3 Hz, H-4), 8.23 (d, 1H, J=7.8 Hz, H-3′), 8.49 (d, 1H, J=8.3 Hz, H-3), 8.90 (d, 1H, J=2.3 Hz, H-6). Anal. Calcd for $C_{17}H_{14}N_2$: C 82.90, H 5.73, N 11.37. Found: C 82.55, H 5.74, N 11.37.

*4.5.3. 5-(3-Nitrophenyl)-6′-methyl-2,2′-bipyridine (**9c**).* Yield 5.46 g (18.75 mmol, 75%). Mp: 152–154 °C (from methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.61 (s, 3H, Me), 7.25 (d, 1H, J=7.6 Hz, H-5′), 7.79 (m, 2H, H-4′,5″), 8.21 (m, 1H, H-4″), 8.26 (m, 3H, H-4,3′,6′), 8.50–8.69 (m, 2H, H-3,2″), 9.00 (d, 1H, J=7.6 Hz, H-6). Anal. Calcd for $C_{17}H_{13}N_3O_2$: C 70.09, H 4.50, N 14.42. Found: C 69.81, H 4.34, N 14.40.

4.6. 5-(4-Methoxyphenyl)-6′-hydroxymethyl-2,2′-bipyridine (10a)

The ester **8a** (1 g, 3.13 mmol) was suspended in ethanol (100 mL), $NaBH_4$ (480 mg, 12.52 mmol) was added and the mixture was refluxed during 2 h. An additional portion of $NaBH_4$ (240 mg, 6.26 mmol) was added and the mixture was refluxed for another 2 h. Water (200 mL) was added and the product was extracted with methylene chloride (3×50 mL). The extract was dried on anhydrous sodium sulfate, and the solvent was removed in vacuum to give a crude **10a**, which was used for next step without further purification. Yield 0.73 g (2.5 mmol, 80%). Mp: 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.83 (s, 3H, OMe), 4.68 (d, 2H, J=5.6 Hz, CH_2OH), 5.51 (t, 1H, J=5.6 Hz, CH$_2$OH), 7.09 (m, 2H, C–H_{arom}), 7.53 (d, 1H, J=7.6 Hz, H-5′), 7.77 (m, 2H, C–H_{arom}), 7.95 (dd, 1H, J=7.8, 7.6 Hz, H-4′), 8.18 (dd, 1H, J=8.4, 2.4 Hz, H-4), 8.27 (d, 1H, J=7.8, 7.6 Hz, H-3′), 8.43 (d, 1H, J=8.4 Hz, H-3), 8.97 (d, 1H, J=2.4 Hz, H-6).

4.7. 5-(3-Nitrophenyl)-6′-hydroxymethyl-2,2′-bipyridine (10c)

The ester **8c** (2 g, 5.97 mmol) was dissolved in ethanol (150 mL), $NaBH_4$ (680 mg, 17.91 mmol) was added and the mixture was stirred at rt with cooling in water bath for 2 h. An additional portion of $NaBH_4$ (450 mg, 11.94 mmol) was added and the mixture was stirred for another 2 h. Water (200 mL) was added and the product was extracted by methylene chloride (3×70 mL). The extract was dried on anhydrous sodium sulfate, and the solvent was removed in vacuum to give a crude **10c**, which was used for next step without further purification. Yield 1.21 g (3.94 mmol, 66%). Mp: 126–128 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.68 (d, 2H, J=5.2 Hz, CH_2OH), 5.31 (t, 1H, J=5.2 Hz, OH), 7.54 (d, 1H, J=8.0 Hz, H-5′), 7.79 (dd, 1H, J=8.0, 7.8 Hz, H-5″), 7.89 (dd, 1H, J=8.0, 7.8 Hz, H-4′), 8.20 (dd, 1H, J=8.0, 2.0 Hz, H-4), 8.25 (m, 2H, H-4″,6″), 8.30 (d, 1H, J=8.0 Hz, H-3′), 8.47–8.62 (m, 2H, H-3,2″), 9.00 (d, 1H, J=2.0 Hz, H-6).

4.8. 5-Aryl-6′-bromomethyl-2,2′-bipyridines (11)

*4.8.1. Starting from hydroxymethyl derivative **10**.* A corresponding hydroxymethyl derivative **10** (5 mmol) was dissolved in methylene chloride (150 mL), and PBr_3 (0.94 mL, 10 mmol) was added. The resulting mixture was stirred for 3 h at rt, and then for another 5 h under reflux. The reaction mixture was washed with an aqueous solution of sodium carbonate, and the product was extracted with methylene chloride (3×100 mL). The organic layer was dried on anhydrous sodium sulfate, and solvent was removed in vacuum to give **11** as white solids.

*4.8.2. Starting from 6′-methyl-2,2′-bipyridines **9**.* A mixture of 6′-methylbipyridine **9** (4 mmol), NBS (710 mg, 4 mmol), and benzoic peroxide (in catalytic quantity) was refluxed in dry CCl_4 (100 mL) during 7 h under light radiation. Solids were filtered off, and solvent was removed in vacuum. The product was isolated by column

chromatography and passed for the next step without further purification.

*4.8.3. 5-(4-Methoxyphenyl)-6′-bromomethyl-2,2′-bipyridine (**11a**).* Yield 0.91 g (2.55 mmol, 51%) via path 4.8.1. and 500 mg (1.4 mmol, 35%) via path 4.8.2. Mp: 166–168 °C (from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 4.66 (s, 2H, CH_2Br), 7.05 (m, 2H, C–H_{arom}), 7.48 (d, 1H, J=8.0 Hz, H-5′), 7.61 (m, 2H, C–H_{arom}), 7.84 (dd, 1H, J=8.0, 7.8 Hz, H-4′), 7.99 (dd, 1H, J=8.4, 2.4 Hz, H-4), 8.36 (d, 1H, J=7.8 Hz, H-3′), 8.51 (d, 1H, J=8.4 Hz, H-3), 8.90 (d, 1H, J=2.4 Hz, H-6).

*4.8.4. 5-Phenyl-6′-bromomethyl-2,2′-bipyridine (**11b**).* Yield 490 mg (1.52 mmol, 38%) via path 4.8.2. Mp: 132–134 °C (from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.66 (s, 2H, CH_2Br), 7.40–7.55 (m, 4H, Ph, H-5′), 7.66 (m, 2H, Ph), 7.84 (dd, 1H, J=8.0, 7.8 Hz, H-4′), 8.03 (dd, 1H, J=8.4, 2.4 Hz, H-4), 8.36 (d, 1H, J=7.8 Hz, H-3′), 8.54 (d, 1H, J=8.4 Hz, H-3), 8.92 (d, 1H, J=2.4 Hz, H-6).

*4.8.5. 5-(3-Nitrophenyl)-6′-bromomethyl-2,2′-bipyridine (**11c**).* Yield 1.11 g (3 mmol, 60%) via path 4.8.1. and 300 mg (0.8 mmol, 20%). Mp: 133–135 °C (from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.67 (s, 2H, CH_2Br), 7.53 (d, 1H, J=7.6 Hz, H-5′), 7.72 (dd, 1H, J=7.6, 7.6 Hz, H-4′), 7.89 (dd, 1H, J=8.0 Hz, H-5″), 8.00 (d, 1H, J=7.6 Hz, H-3′), 8.12 (dd, 1H, J=8.2, 2.6 Hz, H-4), 8.31 (m, 1H, H-6″), 8.43 (m, 1H, H-4″), 8.53 (dd, 1H, J=2.0 Hz, H-5′), 8.64 (d, 1H, J=8.2 Hz, H-3), 8.98 (d, 1H, J=2.6 Hz, H-6).

4.9. 3-(6-Methoxycarbonyl-pyrid-2-yl)-6-(4-methylphenyl)-1,2,4-triazine-4-oxide (12)

A solution of the hydrazone **6** (2.58 g, 14.6 mmol) in acetic acid (20 mL) was added to solution of the aldehyde **4** (2.41 g, 14.6 mmol) in acetic acid (20 mL) at 0 °C, and the mixture was stirred at rt overnight. Then powder of red lead oxide Pb_3O_4 (10 g, 14.6 mmol) was added as five separate portions of 2 g at 30 min intervals. After Pb_3O_4 had been dissolved, water (80 mL) was added, and resulting precipitate of crude **12** was separated by filtration and washed with ethanol. The product was purified by recrystallization from DMF to give colorless crystals of **12**. Yield 2.1 g (7.14 mmol) 45%. Mp: 167–168 °C (from DMF). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.93 (s, 3H), 7.43 (d, 2H, J=8.0 Hz), 8.15 (d, 2H, J=8.0 Hz), 8.24–8.29 (m, 3H), 9.41 (s, 1H). ^{13}C (100 MHz, $CDCl_3$) δ: 20.93, 52.53, 126.14, 127.16, 128.93, 129.05, 129.78, 132.36, 138.16, 141.74, 147.53, 148.28, 155.11, 156.92, 164.62. Anal. Calcd for $C_{17}H_{14}N_4O_3$: C 63.35, H 4.38, N 17.38. Found: C 63.03, H 4.70, N 17.61.

4.10. 5-Cyano-(6-methoxycarbonyl-pyrid-2-yl)-6-(4-methylphenyl)-3-1,2,4-triazine (13)

Acetone cyanohydrin (1.095 mL, 12 mmol) and triethylamine (0.84 mL, 6 mmol) were added to solution of 1,2,4-triazine-4-oxide **12** (1.76 g, 6 mmol) in DCM (30 mL) and the mixture was stirred under reflux for 30 min. Then solvent was removed and diethyl ether (10 mL) was added to the residue to form a yellow precipitate of 5-cyano-1,2,4-triazine **13**, which was filtered off and washed with another portion of diethyl ether. Yield 1.51 g (5.1 mmol, 85%). Mp: 113–114 °C (from 2-propanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 3.97 (s, 3H), 7.53 (d, 2H, ^3J=8.0 Hz), 8.02 (d, 2H, ^3J=8.0 Hz), 8.33 (d, 1H, ^3J=4.4 Hz), 8.33 (d, 1H, ^3J=4.9 Hz), 8.77 (dd, 1H, J=4.9, 4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.00, 52.62, 115.33, 126.97, 127.20, 128.78, 129.07, 129.63, 133.91, 139.37, 141.84, 146.30, 151.14, 156.92, 159.56, 164.76. Anal. Calcd for $C_{18}H_{13}N_5O_2$: C 65.25, H 3.95, N 21.14. Found: C 65.21, H 4.17, N 21.36.

4.11. 6-Cyano-5-(4-methylphenyl)-6′-methoxycarbonyl-2,2′-bipyridine (14)

5-Cyano-1,2,4-triazine **13** (1.51g, 5.1 mmol) and bicyclo[2.2.1]hepta-2,5-diene (2.19 mL, 20.4 mmol) in toluene (20 mL) were stirred under reflux for 6 h. Then solvent was removed and the residue was recrystallized from ethanol to give colorless crystals of **14**. Yield 1.45 g (4.9 mmol, 95%). Mp: 123–125 °C (from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 7.42 (d, 2H, J=8.0 Hz), 7.64 (d, 2H, J=8.0 Hz), 8.17 (dd, 1H, ^3J=7.7Hz, ^4J=2.2 Hz), 8.21 (dd, 1H, ^3J=7.7, 6.9 Hz), 8.30 (d, 1H, ^3J=8.5 Hz), 8.60 (dd, 1H, ^3J=6.9 Hz, ^4J=2.2 Hz), 8.86 (d, 1H, ^3J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.76, 117.22, 123.82, 124.60, 125.57, 128.70, 129.46, 130.31, 131.81, 139.18, 139.29, 139.49, 141.57, 148.14, 152.99, 154.27, 165.64. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.59, N 12.76. Found: C 72.63, H 4.17, N 12.39.

4.12. 5-(4-Methylphenyl)- 2,2′-bipyridine-6,6′-dicarboxylic acid (15)

A solution of compound **14** (1.45 g, 4.9 mmol) in the mixture of ethanol (10 mL), 1 M NaOH (50 mL), and THF (20 mL) was stirred under reflux for 2 h. Then solvent was removed and the resulting residue of sodium salt of monocarboxylic acid was dissolved in 50% H_2SO_4 (15 mL). The resulted mixture was stirred at 120 °C for 15 h. Then water (30 mL) was added to give a precipitate of **15**, which was separated by filtration and washed with water. Then the product was passed for the next step without further purification. Yield 1.46 g (4.36 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 7.31 (d, 2H, J=8.0 Hz), 7.41 (d, 2H, J=8.0 Hz), 8.10 (d, 1H, ^3J=8.2 Hz), 8.13 (dd, 1H, ^3J=7.9 Hz, ^4J=1.9 Hz), 8.18 (dd, 1H, ^3J=7.9, 7.1 Hz), 8.61 (dd, 1H, ^3J=7.1 Hz, ^4J=1.9 Hz), 8.69 (d, 1H, ^3J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.66, 121.90, 123.68, 125.03, 128.00, 129.19, 134.20, 134.83, 137.70, 138.86, 139.34, 148.03, 150.08, 152.20, 154.08, 165.82, 168.27.

4.13. Dimethyl 5-(4-methylphenyl)-2,2′-bipyridine-6,6′-dicarboxylate (16)

Dicarboxylic acid **15** (1.46g, 4.36 mmol) was stirred under reflux in $SOCl_2$ (20 mL) for 1 h until a clear solution was obtained. Then excess of $SOCl_2$ was removed in vacuum to reduce the reaction mixture volume to 3 mL. This was added dropwise to 50 mL of methanol and then stirred under reflux for 1 h. Solids were filtered off and resulted solution was condensed in vacuum to give crude **16**, which was purified by crystallization from methanol. Yield 1.37 g, (3.8 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.74 (s, 3H), 3.95 (s, 3H), 7.31 (d, 2H, J=8.0 Hz), 7.33 (d, 2H, J=8.0 Hz), 8.15 (dd, 1H, ^3J=7.8 Hz, ^4J=2.1 Hz), 8.16 (d, 1H, ^3J=8.2 Hz), 8.18 (dd, 1H, ^3J=7.8, 7.0 Hz), 8.58 (dd, 1H, ^3J=7.0 Hz, ^4J=2.1 Hz), 8.59 (d, 1H, ^3J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.66, 52.36, 52.52, 122.22, 123.92, 125.36, 127.79, 129.35, 133.80, 135.59, 137.89, 138.96, 139.58, 147.26, 148.51, 152.39, 154.06, 164.90, 167.16.

4.14. 6,6′-Di(hydroxymethyl)-5-(4-methylphenyl)- 2,2′-bipyridine (17)

Compound **17** (1 g, 2.76 mmol) was suspended in ethanol (50 mL) and $NaBH_4$ (250 mg, 6.7 mmol) was added. The mixture was stirred for 20 h at rt. The solvent was removed, water (5 mL) was added, and mixture was heated to boil for 5 min. Then the solution was cooled and extracted with chloroform (5×100 mL), the organic layer was separated and dried with anhydrous potassium sulfate. The solvent was removed and boiling ethanol (20 mL) was added to the residue. The hot solution was separated from solids and the solvent was removed to give product **17**, which was passed for the next step without further purification. Yield 0.63 g (2.07 mmol, 75%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 4.57 (d, 2H, ^3J=5.5 Hz), 4.68 (d, 2H, ^3J=5.5 Hz), 5.23 (t, 1H, ^3J=5.5 Hz), 5.53 (t, 1H, ^3J=5.5 Hz), 7.30 (d, 2H, ^3J=8.0 Hz), 7.43 (d, 2H, ^3J=8.0 Hz), 7.55 (d, 1H, ^3J=6.9 Hz), 7.83 (d, 1H, ^3J=8.1 Hz), 7.97 (dd, 1H, ^3J=6.9, 7.4 Hz), 8.36 (d, 1H, ^3J=8.1 Hz), 8.43 (d, 1H, ^3J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.67, 62.51, 64.33, 118.77, 119.10, 120.45, 128.79, 128.96, 135.09, 135.84, 137.09, 137.56, 138.59, 147.26, 153.13, 156.13, 151.58.

4.15. 6,6′-Di(bromomethyl)-5-(4-methylphenyl)- 2,2′-bipyridine (18)

Compound **17** (0.49 g, 1.6 mmol) was mixed with DCM (25 mL) and phosphorus tribromide (0.5 mL, 4.8 mmol) was added at −10 °C. The mixture was stirred under reflux for 2 h. Then an aqueous solution of 5% $NaHCO_3$ (50 mL) was added and the mixture was extracted with chloroform (2×50 mL). The organic layer was separated and evaporated to give colorless solid of **18**. Yield 0.57 g (1.33 mmol, 83%). Mp: 143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 4.69 (s, 2H), 4.81 (s, 2H), 7.35 (d, 2H, ^3J=8.1 Hz), 7.44 (d, 2H, ^3J=8.1 Hz), 7.66 (dd, 1H, ^3J=7.5 Hz, ^4J=1.0 Hz), 7.87 (d, 1H, ^3J=8.2 Hz), 8.02 (dd, 1H, ^3J=7.5, 7.5 Hz), 8.35 (dd, 1H, ^3J=7.5 Hz, ^4J=1.0 Hz), 8.38 (d, 1H, ^3J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.71, 33.72, 34.78, 119.89, 120.29, 124.16, 128.45, 129.25, 134.83, 137.11, 137.56, 138.56, 139.58, 152.91, 153.57, 154.28, 156.49. Anal. Calcd for $C_{19}H_{16}Br_2N_2$: C 52.81, H 3.73, N 6.48. Found: C 52.66, H 3.41, N 6.30.

4.16. Compounds 19b and 26

Compound **11b** or **11c** (2 mmol) correspondingly, DTTA tetra-*tert*-butyl ester (1.18 g, 2.1 mmol), and anhydrous potassium carbonate (1.38 g, 10 mmol) were mixed in dry acetonitrile (90 mL). The mixture was stirred under reflux for 48 h under argon atmosphere. Then solvent was removed in vacuum and water (30 mL) was added, the product was extracted by chloroform (2×35 mL). The chloroform extract was dried with anhydrous sodium sulfate and solvent was removed in vacuum. The product (**19b** or **26** correspondingly) was isolated by column chromatography (eluent—acetonitrile, R_f=0.2) as a yellow oil and passed for next step without further purification.

*4.16.1. Compound **19b**.* Yield 0.72 g (0.9 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 36H, ^{t}Bu), 2.75 (t, 4H, J=7.0 Hz, bipy-$CH_2NCH_2CH_2$), 2.92 (t, 4H, J=7.0 Hz, bipy-$CH_2NCH_2CH_2$), 3.45 (s, 8H, CH_2COO^tBu), 3.93 (s, 2H, bipy-CH_2), 7.42 (m, 1H, Ph), 7.51 (m, 3H, Ph, H-5′), 7.66 (m, 2H, Ph), 7.77 (dd, 1H, J=8.0, 7.8 Hz, H-4′), 8.00 (dd, 1H, J=8.2, 2.2 Hz, H-4), 8.28 (d, 1H, J=7.8 Hz, H-3′), 8.51 (d, 1H, J=8.4 Hz, H-3), 8.91 (d, 1H, J=2.4 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.16, 52.17, 53.27, 56.16, 60.63, 80.82, 119.07, 121.18, 122.98, 127.08, 128.12, 129.12, 135.17, 136.25, 137.24, 137.80, 147.52, 150.53, 154.92, 160.36, 170.72. ESI-MS, m/z: found 804.4811 $(M+H)^+$, calcd 804.4833.

*4.16.2. Compound **26**.* Yield 0.59 g (0.7 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 36H, ^{t}Bu), 2.76 (t, 4H, J=7.0 Hz, bipy-$CH_2NCH_2CH_2$), 2.92 (t, 4H, J=7.0 Hz, bipy-$CH_2NCH_2CH_2$), 3.45 (s, 8H, CH_2COO^tBu), 3.94 (s, 2H, bipy-CH_2), 7.54 (d, 1H, J=8.0 Hz, H-5′), 7.70 (dd, 1H, J=8.0, 8.0 Hz, H-4′), 7.79 (dd, 1H, J=7.4, 7.2 Hz, H-5″), 7.98 (d, 1H, J=8.0 Hz, H-3′), 8.06 (dd, 1H, J=8.2, 2.4 Hz, H-4), 8.30 (m, 2H, H-4″,6″), 8.52 (d, 1H, J=1.8 Hz, H-2″), 8.59 (d, 1H, J=8.2 Hz, H-3), 8.94 (d, 1H, J=2.4 Hz, H-6).ESI-MS, m/z: found 849.4667 $(M+H)^+$, calcd 849.4684.

4.17. Compound 20b

Compound **11b** (136 mg, 0.42 mmol) and tri-*tert*-butyl ester (216 mg, 0.42 mmol) were dissolved in dry acetonitrile (20 mL) at 60 °C and potassium carbonate (230 mg, 1.70 mmol) was added. The mixture was refluxed for 2 days. Then solids were filtered off and washed with MeCN. Combined filtrates were condensed in vacuo to dryness to give brown oil of crude product. It was dissolved in boiling hexane (40 mL), insoluble impurities were filtered off. Hexane solution was evaporated to dryness and the residue was again recrystallized from hexane to give pure product as white crystals. Yield 220 mg (0.29 mmol, 70%). Mp 70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 18H, ^{t}Bu), 1.46 (s, 9H, ^{t}Bu), 2.74 (m, 4H, CH_2), 2.87 (m, 12H, CH_2), 3.24 (s, 4H, CH_2), 3.34 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.50 (m, 3H, Ph), 7.66 (m, 3H, Ph+Py), 7.79 (dd, 1H, J=7.8, 7.8 Hz, Py), 8.00 (dd, 1H, J=8.2, 1.8 Hz, Py), 8.26 (d, 1H, J=8.2 Hz, Py), 8.48 (d, 1H, J=7.8 Hz, Py), 8.91 (d, 1H, J=1.8 Hz, Py). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 28.19, 51.94, 52.36, 52.71, 52.84, 55.42, 56.56, 61.60, 80.66, 118.90, 119.12, 121.00, 127.05, 128.10, 129.09, 135.15, 136.21, 137.70, 147.54, 154.84, 155.26, 159.70, 159.80, 171.05.ESI-MS, m/z: found 759.4800 $(M+H)^+$, calcd 759.4809.

4.18. Compound 24a

Compound **11a** (1 mmol, 355 mg) and cyclene/glyoxal **23** (1 mmol, 194 mg) were mixed in 20 mL of acetonitrile and stirred at 60 °C for 24 h. During the reaction, a precipitate was formed. The reaction mixture was evaporated to dryness and the residue was treated with THF (20 mL). The resulting salt **24a** was filtered off as a white solid, and then passed for the next step without further purification. Yield 440 mg (0.80 mmol, 80%). ^{1}H NMR (400 MHz, D_2O) δ: 2.50 (m, 2H), 2.81 (m, 2H), 2.98 (m, 2H), 3.10–3.22 (m, 4H), 3.50 (m, 6H), 3.59 (s, 3H, Me), 3.68 (br s, 1H), 4.08 (br s, 1H), 4.35 (m, 1H), 4.60 (m, 1H), 6.63 (m, 2H, Ph), 7.17 (m, 2H, Ph), 7.49 (d, 1H, J=8.0 Hz, Py), 7.59 (dd, 1H, J=8.0, 8.0 Hz, Py), 7.75 (d, 1H, J=8.0 Hz, Py), (m, 2H, Py), 8.22 (d, 1H, J=2.0 Hz, Py). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.11, 48.50, 48.53, 49.24, 52.17, 55.45 (2C), 59.26, 60.50, 62.17, 72.35, 82.74, 114.73, 120.77, 122.09, 128.20, 129.57, 134.80, 136.77, 139.02, 143.00, 147.50, 148.55, 153.02, 156.34, 160.10.

4.19. Compound 25a

Compound **24a** (440 mg, 0.80 mmol) was suspended in 30 mL of hydrazine hydrate and stirred at 120 °C overnight. A precipitate was formed. The mixture was cooled down and white crystals of product **25a** were filtered off and washed with water. The product was passed for the next step without further purification. Yield 250 mg (0.56 mmol, 70%). Mp 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32–3.00 (br s, 3H, NH), 2.57 (m, 4H), 2.71 (m, 8H), 2.81 (m, 4H), 3.86 (s, 3H, CH_3), 3.88 (s, 2H, CH_2). 7.03 (d, 2H, Ph), 7.40 (d, 1H, J=7.8 Hz, Py), 7.57 (d, 2H, Ph), 7.78 (dd, 1H, J=7.8, 7.8 Hz, Py), 7.93 (dd, 1H, J=7.8, 2.0 Hz, Py), 8.26 (d, 1H, J=7.8 Hz, Py), 8.50 (d, 1H, J=7.8 Hz, Py), 8.86 (d, 1H, J=2.0 Hz, Py). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 45.18, 46.47, 47.17, 51.57, 55.42, 60.77, 114.61, 119.20, 121.15, 122.86, 128.18, 130.17, 134.51, 135.91, 137.39, 147.17, 154.50, 155.30, 158.92, 159.84.

4.20. Compound 20a

Compound **25a** (250 mg, 0.56 mmol) was dissolved in dry acetonitrile (20 mL) and potassium carbonate (2.24 mmol) and *tert*-butyl bromoacetate (1.85 mmol) were added. The mixture was refluxed for 2 days. Then solids were filtered off and washed with MeCN. Combined filtrates were condensed in vacuo to dryness to give a brown oil of crude product. It was dissolved in boiling hexane (40 mL), insoluble impurities were filtered off. Hexane solution was evaporated to dryness and the residue was again recrystallized from hexane to give pure product as white crystals. Yield 265 mg (0.37 mmol, 65%). Mp 79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 18H, ^{t}Bu), 1.45 (s, 9H, ^{t}Bu), 2.62–2.80 (m, 4H, CH_2), 2.82–2.90 (m, 12H, CH_2), 3.23 (s, 4H, CH_2), 3.33 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.86 (s, 3H,

CH_3), 7.01 (m, 2H, Ph), 7.60 (m, 2H, Ph), 7.67 (d, 1H, J=7.8 Hz, Py), 7.77 (dd, 1H, J=7.8, 7.8 Hz, Py), 7.94 (dd, 1H, J=8.2, 1.8 Hz, Py), 8.25 (d, 1H, J=8.2 Hz, Py), 8.46 (d, 1H, J=7.8 Hz, Py), 8.86 (d, 1H, J=1.8 Hz, Py). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.24, 52.17, 52.49, 52.59, 52.84, 55.42, 56.61, 61.79, 80.64, 114.61, 118.93, 121.08, 123.27, 129.06, 130.19, 134.62, 135.85, 137.22, 147.19, 154.84, 154.93, 159.74, 159.83, 171.17.ESI-MS, m/z: found 799.4967 $(M+H)^+$, calcd 789.4915.

4.21. Compound 27

Compound **26** (440 mg, 0.52 mmol) and Pd/C (10%) (138 mg) in absolute ethanol (50 mL) were stirred at rt in hydrogen atmosphere (P=3.5 atm) for 6 h. Then the catalyst was filtered off, solvent was removed in vacuum. The product **27** was isolated by column chromatography. Yield 200 mg (0.24 mmol, 48%). ^{1}H NMR (400 MHz, CDCl3) δ: 1.42 (s, 36H, ^{t}Bu), 2.75 (t, 4H, J=7.0 Hz, bipy-CH_2NCH_2CH_2), 2.91 (t, 4H, J=7.0 Hz, bipy-CH_2NCH_2CH_2), 3.44 (s, 8H, CH_2COO^{t}Bu), 3.81 (br s., 2H, NH_2), 3.92 (s, 2H, bipy-CH_2), 6.74 (m, 1H, H-6″), 6.95 (dd, 1H, J=2.0 Hz, H-2″), 7.04 (m, 1H, H-4″), 7.28 (dd, 1H, J=8.0, 7.8 Hz, H-5″), 7.50 (d, 1H, J=8.0 Hz, H-5′), 7.77 (dd, 1H, ^3J=8.0, 8.0 Hz, H-4′), 7.97 (dd, 1H, J=8.2, 2.4 Hz, H-4), 8.26 (d, 1H, J=8.0 Hz, H-3′), 8.47 (d, 1H, J=8.2 Hz, H-3), 8.87 (d, 1H, J=2.4 Hz, H-6). ESI-MS, m/z: found 819.5047 $(M+H)^+$, calcd 819.5020.

4.22. Ligand 21b

The *tert*-butyl ester **19b** (120 mg, 0.15 mmol) was dissolved and stirred in 6 M water solution of HCl (40 mL) at rt overnight. Then acid was evaporated to dryness, and residue was treated with dry acetonitrile to give yellow crystals of **21b** in form of pentahydrochloride trihydrate. Yield 100 mg (0.12 mmol, 82%). Anal. Calcd for $C_{29}H_{44}Cl_5N_5O_{11}$: C 42.69, H 5.44, N 8.58. Found: C 42.34, H 5.11, N 8.61.

4.23. Ligand 22a

The *tert*-butyl ester **20a** (265 mg, 0.33 mmol) was dissolved and stirred in 6 M water solution of HCl (40 mL) at rt overnight. Then acid was evaporated to dryness, and residue was treated with dry acetonitrile to give yellow crystals of **22a** in form of tetrahydrochloride trihydrate. Yield 245 mg, 90%. Anal. Calcd for $C_{32}H_{50}Cl_4N_6O_{10}$: C 46.84, H 6.14, N 10.24. Found: C 46.63, H 6.28, N 10.12.

4.24. Ligand 22b

The *tert*-butyl ester **20b** (200 mg, 0.26 mmol) was dissolved and stirred in 6 M water solution of HCl (20 mL) at rt overnight. Then acid was evaporated to dryness, and residue was treated with dry acetonitrile to give yellow crystals of **22b** in form of tetrahydrochloride trihydrate. Yield 165 mg, 79%. Anal. Calcd for $C_{31}H_{48}Cl_4N_6O_9$: C 47.10, H 6.12, N 10.63. Found: C 46.91, H 6.05, N 10.47.

4.25. Ligand 28

The *tert*-butyl ester **27** (120 mg, 0.15 mmol) was dissolved and stirred in 6 M water solution of HCl (40 mL) at rt overnight. Then acid was evaporated to dryness, and residue was treated with dry acetonitrile to give yellow crystals of **21b** in form of pentahydrochloride trihydrate. Yield 98 mg (0.12 mmol, 80%). Anal. Calcd for $C_{29}H_{44}N_5O_{11}Cl_5$: C 42.38, H 5.51, N 10.23, Cl 20.28. Found: C 42.06, H 5.42, N 11.12, Cl 20.45.

4.26. Compound 29

Compound **18** (200 mg, 0.46 mmol), dimethyl iminodiacetate (IDA dimethyl ester) (198 mg, 1 mmol), and potassium carbonate (634 mg, 4.6 mmol) were mixed in dry acetonitrile (25 mL) and stirred under reflux for 24 h. Then water (100 mL) was added and product was extracted with DCM (3×25 mL). Solvent was removed to give product **29** as a white solid. The product was passed for the next step without further purification. Yield 231 mg (0.39 mmol, 85%). Mp 89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.49 (s, 6H), 3.61 (s, 6H), 3.62 (s, 4H), 3.64 (s, 4H), 3.95 (s, 2H), 4.06 (s, 2H), 7.29 (d, 2H, ^3J=8.0 Hz), 7.51 (d, 2H, ^3J=8.0 Hz), 7.57 (dd, 1H, ^3J=7.5 Hz, ^4J=0.8 Hz),7.82 (d, 1H, ^3J=8.1 Hz), 7.97 (dd, 1H, ^3J=7.5, 7.1 Hz), 8.24 (dd, 1H, ^3J=7.1 Hz, ^4J=0.8 Hz), 8.30 (d, 1H, ^3J=8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.68, 50.91, 51.10, 54.10, 54.13, 56.68, 59.15, 118.67, 118.93, 122.95, 128.79, 129.06, 135.66, 136.90, 137.60, 137.71, 138.86, 152.79, 153.96, 154.11, 158.26, 170.97, 171.08.

4.27. Compound 30

A concentrated sulfuric acid (5 mL) was added to compound **29** (190 mg, 0.32 mmol) at 0 °C and stirred until solution became clear. Then 65% nitric acid (0.025 mL, 0.35 mmol) was added. The mixture was stirred at rt for 30 min and poured on ice. The mixture was neutralised with saturated solution of potassium hydrocarbonate and extracted with DCM (3×25 mL). Solvent was removed to give product **30** as a brown solid. The product was passed for the next step without further purification. Yield 179 mg (0.28 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (s, 3H), 3.50 (s, 6H), 3.64 (s, 6H), 3.67 (s, 4H), 3.69 (s, 4H), 3.99 (s, 2H), 4.11 (s, 2H), 7.59 (d, 1H, ^3J=6.5 Hz), 7.61 (d, 1H, ^3J=8.0 Hz), 7.90 (dd, 1H, ^3J=6.5 Hz, ^4J=1.6 Hz), 7.96 (d, 1H, ^3J=8.0 Hz), 8.01 (dd, 1H, ^3J=8.0, 7.4 Hz), 8.29 (d, 1H, ^3J=7.4), 8.37 (d, 1H, ^3J=8.0 Hz), 8.41 (d, 1H, ^4J=1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.07, 50.91, 51.12, 54.02, 54.13, 57.27, 59.07, 118.90, 119.24, 123.23, 124.83, 131.85, 132.62, 133.77, 135.65, 137.52, 137.75, 139.19, 148.86, 153.33, 153.66, 153.87, 158.23, 170.87, 171.03.

4.28. Compound 31

Compound **30** (150 mg, 0.24 mmol) and Pd/C (10%) (100 mg) in absolute ethanol (30 mL) were stirred at rt in hydrogen atmosphere (P=15 atm) for 60 h. Catalyst was filtered off, solvent was removed in vacuum to give product **31**. Yield 128 mg (0.21 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 3.61 (s, 6H), 3.66 (s, 6H), 3.68 (s, 4H), 3.69 (s, 4H), 4.04 (s, 2H), 4.11 (s, 2H), 6.77 (dd, 1H, ^3J=7.5 Hz, ^4J=1.6 Hz), 7.03 (d, 1H, ^4J=1.6 Hz), 7.10 (d, 1H, ^3J=7.5 Hz), 7.53 (d, 1H, ^3J=8.5 Hz), 7.72 (d, 1H, ^3J=8.0 Hz), 7.82 (dd, 1H, ^3J=8.5, 8.5), 8.30 (d, 1H, ^3J=8.5 Hz), 8.33 (d, 1H, ^3J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.30, 51.66, 51.82, 54.60, 55.07, 57.82, 60.42, 116.28, 119.54, 119.70, 122.06, 123.42, 130.62, 137.80, 138.25, 139.16, 145.37, 153.96, 154.68, 155.66, 158.62, 171.97, 172.22.ESI-MS, m/z: found 608.2790 $(M+H)^+$, calcd 608.2720.

4.29. Ligand 32

Compound **31** (100 mg, 0.165 mmol) was dissolved in methanol (50 mL) and 1 N NaOH water solution (0.66 mL, 0.66 mmol) was added. The mixture was stirred for 2 h at rt. Then solvent was removed and the residue was dissolved in water (10 mL). Insolubles were filtered off and ethanol was added to the clear solution. The precipitate of sodium salt of ligand **32** was filtered off and dried in vacuum. Yield 87 mg (0.16 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 3.66 (s, 8H), 4.49 (s, 4H), 6.62 (dd, 1H, ^3J=7.3 Hz, ^4J=1.6 Hz), 6.66 (d, 1H, ^4J=1.6 Hz), 7.06 (d, 1H, ^3J=7.3 Hz), 7.39 (d, 1H, ^3J=7.5 Hz), 7.80 (d, 1H, ^3J=8.0 Hz), 7.95 (dd, 1H, ^3J=7.5, 7.5 Hz), 8.39 (d, 1H, ^3J=7.5 Hz), 8.46 (d, 1H, ^3J=8.0 Hz). Anal. Calcd for $C_{27}H_{25}N_5Na_4O_8$: C 50.71, H 3.94, N 10.95. Found: C 50.55, H 3.71, N 10.66.

4.30. Complex [Eu1]

1 M NaOH aqueous solution (0.5 mL, 0.5 mmol) was added to a solution of ligand **22b** tetrahydrochloride trihydrate (60 mg, 0.072 mmol) in water (10 mL) and then a solution of $EuCl_3 \cdot 6H_2O$ (26.50 mg, 0.072 mmol) in water (10 mL) was added. Then mixture was stirred under reflux for 10 min. Solvent was removed and methanol (10 mL) was added. Insolubles were filtered off and solvent was removed to give a white powder of the complex [**Eu1**]. Yield 50 mg (0.065 mmol, 91%). Anal. Calcd for $C_{32}H_{37}EuN_6O_7$: C, 46.03; H, 3.49; N, 9.73%. Found: C, 46.36; H, 3.60; N, 10.01%. *Crystallography data*: A single crystal of [**Eu1**] polyhydrate was obtained by slow evaporation of a saturated water solution of [**Eu1**]. $C_{32}H_{49}EuN_6O_{13}$, FW=865.64, monoclinic, a=15.1841(8), b=15.4329 (18), c=17.1105(18) Å, α=90.00°, β=98.146(7)°, γ=90.00°, V=3969.1 (7) Å^3, T=295(2) K, space group $P2(1)/c$, Z=4, 7719 reflections measured, 43,894 unique (R_{int}=0.0467), which were used in all calculations. R_1=0.0414, wR_2=0.1062. Crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication number CCDC 791942. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.au.uk/data_request/cif.

4.31. Complex [Eu2]

1 N NaOH aqueous solution (0.44 mL, 0.44 mmol) was added to a solution of ligand **22a** tetrahydrochloride trihydrate (50 mg, 0.063 mmol) in water (10 mL) and then a solution of $EuCl_3 \cdot 6H_2O$ (23.20 mg, 0.063 mmol) in water (10 mL) was added. Then mixture was stirred under reflux for 10 min. Solvent was removed and methanol (10 mL) was added. Insolubles were filtered off and solvent was removed to give a white powder of the complex [**Eu2**]. Yield 40 mg (0.054 mmol, 86%). Anal. Calcd for $C_{31}H_{35}EuN_6O_6$: C, 50.34; H, 4.77; N, 11.36. Found: C, 50.08; H, 4.80; N, 11.32.

4.32. Complex [Eu3]

NaOH (1 N) aqueous solution (0.37 mL, 0.37 mmol) was added to a solution of ligand **21b** pentahydrochloride trihydrate (43 mg, 0.053 mmol) in water (10 mL) and then a solution of $EuCl_3 \cdot 6H_2O$ (19.31 mg, 0.063 mmol) in water (10 mL) was added. Then mixture was stirred under reflux for 10 min. Solvent was removed and methanol (10 mL) was added. Insolubles were filtered off and solvent was removed to give a white powder of the complex [**Eu3**]. Yield 31 mg (0.043 mmol, 78%). Anal. Calcd for $C_{29}H_{29}EuN_5O_8Na$: C, 46.41; H, 3.89; N, 9.33%. Found: C, 46.08; H, 3.75; N, 9.38%. ESI-MS, m/z (I_{rel} (%)). Found: 741.13 (87), 742.13 (28), 743.13 (100), 744.13 (34), 745.14 (7.5) $(M-Na)^-$; calcd: 741.13 (85.8), 742.13 (29.4), 743.13 (100), 744.14 (33.1), 745.14 (7).

4.33. Complex [Eu4]

NaOH (1 N) aqueous solution (0.84 mL, 0.84 mmol) was added to a solution of ligand **28** pentahydrochloride trihydrate (98 mg, 0.12 mmol) in water (10 mL) and then a solution of $EuCl_3 \cdot 6H_2O$ (43.92 mg, 0.12 mmol) in water (10 mL) was added. Then mixture was stirred under reflux for 10 min. Solvent was removed and methanol (10 mL) was added. Insolubles were filtered off and solvent was removed to give a white powder of the complex [**Eu4**] as trihydrate. Yield 71 mg (0.091 mmol, 76%). Anal. Calcd for $C_{29}H_{29}EuN_5O_8Na$: 42.96, H 4.52, N 10.01. Found: 42.50, H 4.43, N 10.25. ESI-MS, m/z (I_{rel} (%)). Found: 726.12 (87.5), 727.12 (30), 728.12 (100), 729.12 (34.1), 730.13 (7.7) $(M-Na)^-$; calcd: 726.12 (85.9), 727.12 (29.09), 728.12 (100), 729.13 (32.74), 730.13 (6.88).

4.34. Complex [Eu5]

A solution of $EuCl_3 \cdot 6H_2O$ (28.55 mg, 0.078 mmol) in water (10 mLL) was added to a solution of ligand **32** sodium salt (50 mg, 0.078 mmol) in water (10 mL). Then the mixture was stirred under reflux for 10 min. Solvent was removed and methanol (10 mL) was added. Insolubles were filtered off and solvent was removed to give white powder of the complex [**Eu2**]. Yield 50 mg (0.069 mmol, 89%). Anal. Calcd for $C_{27}H_{25}EuN_5O_8Na$: C 44.89, H 3.49, N 9.69. Found: C 44.56, H 3.60, N 9.51.

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References and notes

1. Richardson, F. S. *Chem. Rev.* **1982**, *82*, 541–552.
2. Parker, D.; Yu, J. *Chem. Commun.* **2005**, 3141–3143.
3. Weibel, N.; Charbonnière, L. J.; Guardigli, M.; Roda, A.; Ziessel, R. *J. Am. Chem. Soc.* **2004**, *126*, 4888–4896.
4. Bakker, B. H.; Goes, M.; Hoebe, N.; Van Ramesdonk, H. J.; Verhoeven, J. W.; Werts, M. H. V.; Hofstaat, J. W. *Coord. Chem. Rev.* **2000**, *208*, 3–16.
5. Diamandis, E. P. *The Analyst* **1992**, *117*, 1879–1884.
6. Pandya, S.; Yu, J.; Parker, D. *Dalton Trans.* **2006**, 2757–2766.
7. Armelao, L.; Quici, S.; Barigelletti, F.; Accorsi, G.; Bottaro, G.; Cavazzini, M.; Tondello, E. *Coord. Chem. Rev.* **2010**, *254*, 487–505.
8. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000, Chapter 5.15.
9. Pabst, G. R.; Pfüller, O. C.; Sauer, J. *Tetrahedron* **1999**, *55*, 8045–8064.
10. Pabst, G. R.; Schmid, K.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 6691–6694.
11. Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111–6113.
12. Sauer, J.; Heldmann, D. K.; Pabst, G. R. *Eur. J. Org. Chem.* **1999**, 313–321.
13. Bromley, W. J.; Gibson, M.; Lang, S.; Raw, S. A.; Whitwood, A. C.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 6004–6014.
14. Prokhorov, A. M.; Slepukhin, P. A.; Rusinov, V. L.; Kalinin, V. N.; Kozhevnikov, D. N. *Tetrahedron Lett.* **2008**, *49*, 3785–3789.
15. Ławecka, J.; Olender, E.; Piszcz, P.; Rykowski, A. *Tetrahedron Lett.* **2008**, *49*, 723–725.
16. Diring, S.; Retailleau, P.; Ziessel, R. *J. Org. Chem.* **2007**, *72*, 10181–10193.
17. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2002**, *43*, 6015–6017.
18. Kozhevnikov, V. N.; Ustinova, M. M.; Slepukhin, P. A.; Santoro, A.; Bruce, D. W.; Kozhevnikov, D. N. *Tetrahedron Lett.* **2008**, *49*, 4096–4098.
19. Lu, W.; Chan, M. C. W.; Zhu, N.; Che, C.-M.; Li, C.; Hui, Z. *J. Am. Chem. Soc.* **2004**, *126*, 7639–7651.
20. Kozhevnikov, V.; Donnio, B.; Bruce, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6286–6289.
21. Kozhevnikov, D. N.; Kozhevnikov, V. N.; Ustinova, M. M.; Santoro, A.; Bruce, D. W.; Koenig, B.; Czerwieniec, R.; Fischer, T.; Zabel, M.; Yersin, H. *Inorg. Chem.* **2009**, *48*, 4179–4189.
22. Kozhevnikov, D. N.; Shabunina, O. V.; Kopchuk, D. S.; Slepukhin, P. A.; Kozhevnikov, V. N. *Tetrahedron Lett.* **2006**, *47*, 7025–7029.
23. Cross, J. P.; Dadabhoy, A.; Sammes, P. G. *J. Lumin.* **2004**, *110*, 113–124.
24. Loren, J. C.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 754–757.
25. Kozhevnikov, V. N.; Shabunina, O. V.; Kopchuk, D. S.; Ustinova, M. M.; Koenig, B.; Kozhevnikov, D. N. *Tetrahedron* **2008**, *64*, 8963–8973.
26. Neunhoeffer, H. In *Comp. Heterocycl. Chem. II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, pp 50–574.
27. Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; Koenig, B. *J. Org. Chem.* **2003**, *68*, 2882–2888.
28. Saraswathi, T. V.; Srinivasan, V. R. *Tetrahedron Lett.* **1971**, *12*, 2315–2316.
29. Baker, W. C.; Choi, M. J.; Hill, D. C.; Thompson, J. L.; Petillo, P. A. *J. Org. Chem.* **1999**, *64*, 2683–2689.
30. Le Baccon, M.; Chuburu, F.; Toupet, L.; Handel, H.; Soibinet, M.; Déchamp-Olivier, I.; Barbier, J. P.; Aplincourt, M. *New J. Chem.* **2001**, *25*, 1168–1174.
31. Miyadera, T.; Kosower, E. M. *J. Med. Chem.* **1972**, *15*, 534–537.
32. Beeby, A.; Clarkson, I. M.; Dickins, R. S.; Faulkner, S.; Parker, D.; Royle, L.; de Sousa, A. S.; Williams, G.; Woods, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 493–503.
33. Xu, Z.; Thompson, L. K.; Miller, D. O. *Dalton Trans.* **2002**, *12*, 2462–2466.
34. Platas-Iglesias, C.; Mato-Iglesias, M.; Djanashvili, K.; Muller, R. N.; Vander Elst, L.; Peters, J. A.; De Blas, A.; Rodriguez-Blas, T. *Chem.—Eur. J.* **2004**, *10*, 3579–3590.
35. Bryson, J. M.; Chu, W.-J.; Lee, J.-H.; Reineke, T. M. *Bioconjugate Chem.* **2008**, *19*, 1505–1509.