



Design and synthesis of europium luminescent bio-probes featuring sulfobetaine moieties



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ABSTRACT

Herein we report the straightforward preparation of chromophore-functionalized TACN ligand via Cu-free cross-coupling reactions using a common halogenated platform. This versatile methodology allows the preparation of original macrocyclic ligand featuring both optimized antenna for the sensitization of europium luminescence and sulfobetaine zwitterionic groups to ensure water solubility of the complex. In addition preliminary two-photon excited microscopy imaging experiments of fixed cells reveal that sulfobetaine groups are able to limit undesirable non specific interactions with biological surrounding.

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The peculiar photophysical properties of f-block elements make them attractive candidates for the design of lanthanide luminescence bioprobes (LLB) for biological imaging or sensing applications.¹ An optimized LLB must fulfill a set of requirements namely (i) solubility and stability in water, and (ii) optimized chromophore antenna (Chrom) to ensure efficient sensitization. In this context, triazacyclonane macrocycle has become a platform of choice for the design of LLB for the following reasons: (i) its tris N-alkylation by pyridine carboxylate or phosphinate leads to the formation of a nonadentate ligand which can saturate the coordination sphere of lanthanide ion and form a stable complex in aqueous solutions.² (ii) In addition, following pioneering works of Takalo,³ functionalization of the *para* position of the pyridine by chromophore antenna (Fig. 1, Chrom = aromatics, *p*-substituted aryl-ethynyl) enhances the absorption in the visible, while making it possible to tune its position. Recently, this strategy led to the preparation of Yb-bioprobes for thick tissue biphotonic microscopy imaging⁴ and Eu-bioprobes with optimized brightness for one photon imaging⁵ and sensing applications.⁶ In each case, the ligand's synthesis proceeds according to the same convergent procedure (Fig 1A), involving the preparation of a Chrom-substituted picolinic arm followed by alkylation of the TACN moieties. This last step requires the use of excess Chrom-picolinic arm, which multi-

step synthesis requires lots of efforts, and which is hard to recover during purification.

In this Letter we describe an alternative versatile synthesis of various chromophore-functionalized triazacyclonane ligand $L^n(\text{COOMe})$, ($n = 1-3$) using a divergent approach (Fig. 1B) involving the key synthon $L^3(\text{COOMe})$. The versatile character of the new synthetic methodology is first illustrated by the preparation of $L^{1,2}(\text{COOMe})$ featuring methoxy donor groups, via Suzuki–Miyaura and copper-free Sonogashira cross-coupling reaction. In a second time, this procedure is applied for the design of the advanced ligand $L^3(\text{COOMe})$ containing sulfobetaine end-groups. This zwitterionic fragment has been widely used for the hydrosolubilization of quantum dots or magnetic nanoparticles for bio-imaging applications⁷ and it has been reported that the covering of the surface nanoparticles by sulfobetaine moieties presents the additional advantage of limiting the non specific interactions with the lipophilic biological surrounding compared to other neutral (poly-ethylene glycol) or charge (sulfonate, carboxylate, or ammonium) hydrosolubilizing functions.^{7,8} This issue is crucial for any practical biological applications (imaging, sensing, and bioconjugation...) but has rarely been addressed for molecular probes. In this context, sulfobetaine groups are only present as polar fragments in the now commercially available amphiphilic membrane chromophore di-4-ANEPPS,⁹ and have been recently introduced as hydrosolubilizing moieties in functional BODIPY dyes by Ziesel, Ulrich and co-workers.¹⁰ To the best of our knowledge, this zwitterionic function has never been used in combination with lan-

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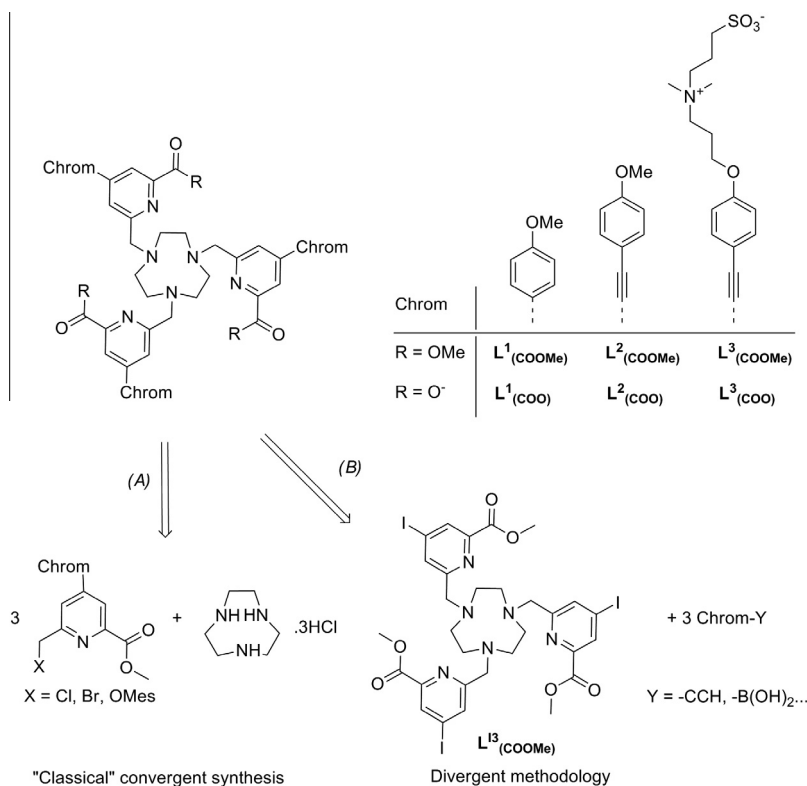


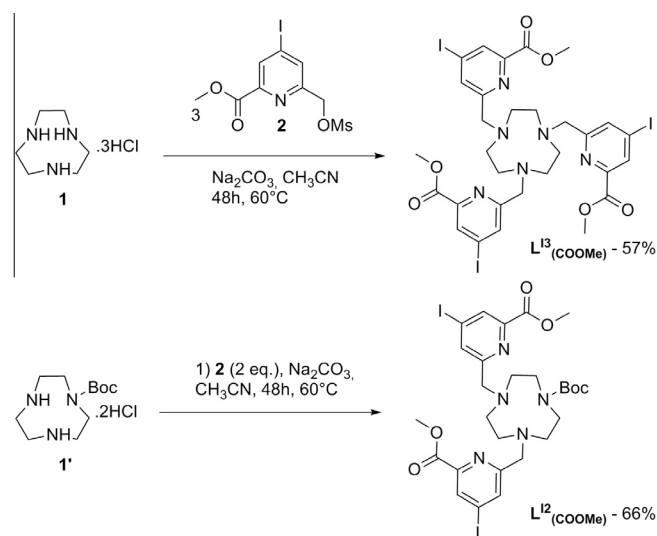
Figure 1. Retro-synthetic scheme for the preparation of target chromophore-TACN ligands.

thanide complexes. Here we described the design of [Eu·L³(COO)], a LLB featuring sulfobetaine moieties enabling both hydrosolubilization and limitation of undesirable non-specific interactions with bio-molecules or lipophilic part of cells. The photophysical properties of the complex and preliminary two-photon bio-imaging experiments¹¹ are reported.

The 'classical' convergent synthesis illustrated in **Figure 1**, involving the alkylation of the TACN macrocycle in the last step, is not compatible with the presence of the dimethylamino peripheral moieties precursor of the sulfobetaine. Therefore an alternative synthetic pathway has been envisaged to tackle this issue, using the L¹³(COOMe) ligand as a key functional platform. Moreover, this intermediate is an excellent starting point for a divergent and versatile one step preparation of various chromophore-ligands combinations via cross-coupling reaction with different Chrom-Y (Y is cross-coupling compatible function, typically terminal alkyne, boronic or stannane groups). This new synthetic pathway allows performing a systematic study of the influence of the antenna on the luminescence of the related Ln(III) complexes.

This L¹³(COOMe) scaffold was obtained via a classical synthetic strategy, involving the alkylation of triazacyclononane trihydrochloride **1** by the mesylated derivative **2** in dry acetonitrile in the presence of sodium carbonate (**Scheme 1**). The synthesis was optimized and scaled-up to ca. 1.5 g (57%) after purification by simple precipitation in ethyl acetate.¹² This procedure was further extended to the preparation of the related dissymmetric L¹²(COOMe) platform starting from the mono-boc protected TACN macrocycle, **1'**.^{5b,6a}

The L¹³(COOMe) platform was first engaged in model cross coupling reactions to check its reactivity. Two kinds of cross-coupling reactions were envisioned, namely a Suzuki–Miyaura and a Sonogashira coupling to introduce the chromophore onto the triiodo ligand (**Scheme 3**). The Suzuki–Miyaura coupling with the commercially available anisole boronic acid (**3**) under classical conditions (Pd(PPh₃)₄, Na₂CO₃, DMF, 90 °C) led to the formation



Scheme 1. Synthesis of the iodo containing platform.

of the expected L¹(COOMe) ligand in 40% yield after column chromatography.¹³ On the other hand, Sonogashira coupling with anisole acetylene (**4**) under classical conditions (PdCl₂(PPh₃)₂, CuI, THF–NEt₃) was not successful. However, alternative conditions with PdCl₂(PPh₃)₂ as the catalyst in the absence of Cu(I) gave the expected L²(COOMe) ligand in 40% yield (**Scheme 3**). This result can be explained by the parasitic complexation of Cu(I) in the macrocyclic precursor. The apparently modest 40% yield is in fact the average of three coupling reactions in each picolinic moiety of the ligand and the effective yield of each coupling is around 75% which is classical for this type of ligands.¹⁴ After optimization of the reaction conditions, we applied this synthetic procedure to

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