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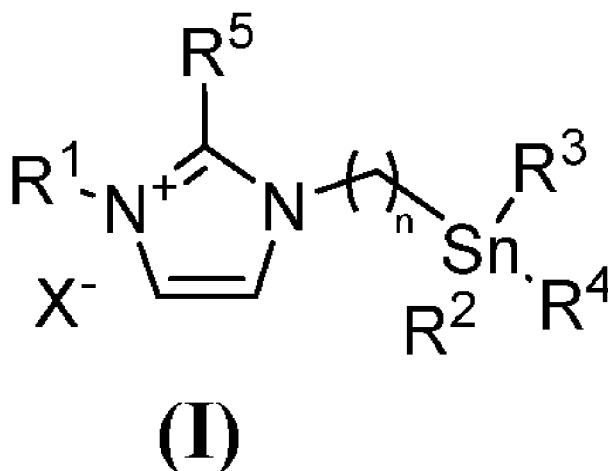
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(54) Title: IONIC LIQUID SUPPORTED ORGANOTIN REAGENTS FOR THE MANUFACTURING OF RADIOPHARMACEUTICALS COMPOUNDS



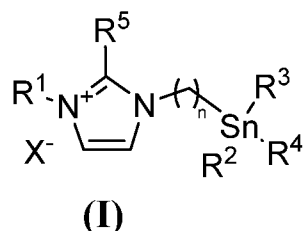
(57) Abstract: The present invention relates to an ionic liquid supported organotin reagent of formula (I). The invention further relates to a process for manufacturing the ionic liquid supported organotin reagent of formula (I) and to a process for manufacturing an halogenated or radio-halogenated compound using compound of formula (I). The invention also relates to a device for implementing the halogenating process of the invention and to a kit comprising the compound of formula (I).



IONIC LIQUID SUPPORTED ORGANOTIN REAGENTS FOR THE MANUFACTURING OF RADIOPHARMACEUTICALS COMPOUNDS

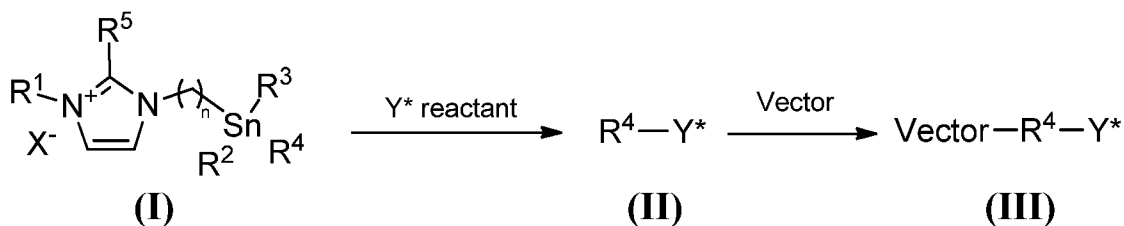
FIELD OF INVENTION

5 The present invention relates to ionic liquid supported organotin reagents of formula (I)



wherein X^- , n , R^1 , R^2 , R^3 , R^4 and R^5 are as defined below. Especially, R^4 represents an aryl or heteroaryl group, said group having vector properties or said group being substituted by at least one reactive function able to react with a vector or said group being substituted by at least one substituent having vector properties.

The invention further relates to a process for manufacturing ionic liquid supported organotin reagents of formula (I). The invention also relates to a labeling process for manufacturing halogenated compounds (II), comprising the use of ionic liquid supported organotin reagents of formula (I):



wherein Y^* represents a halogen, preferably a radiohalogen

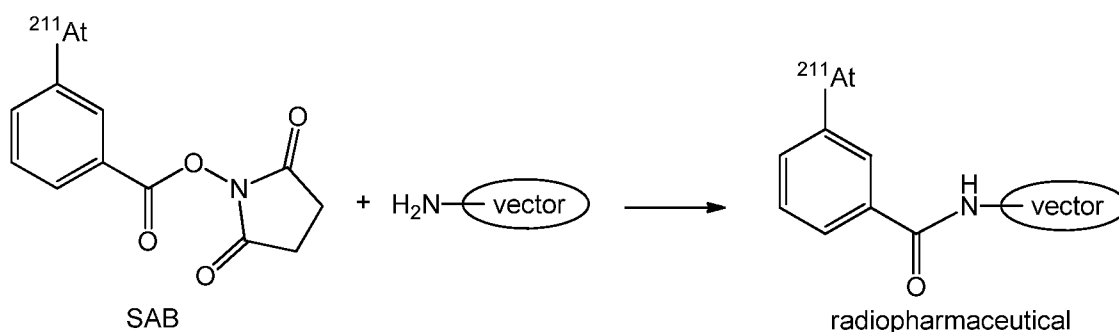
Preferably, the halogen of compounds (II) is a radiohalogen, leading to a radiolabeled compound (II). Radiolabeled compounds (II) obtained by the labeling process of the invention may be used to label vectors, leading to radiopharmaceuticals (III). Another aspect of the invention is a device to implement the labeling process of the invention.

BACKGROUND OF INVENTION

Cancer diseases are among the most important causes of mortality. Radiolabeled drugs, also called radiopharmaceuticals, play an important role in the diagnosis and therapy of cancers. Especially, nuclear medicine is opening new perspectives for diagnostic and functional imaging of tumors, for their characterization (phenotype, proliferation, response to treatment) and that of their environment (vascularization, hypoxia, inflammation, immune response). This characterization of tumors leads to individualized therapeutic strategies. Radiopharmaceuticals are also used in therapy, wherein the vectorization and targeting of radionuclides emitting alpha or beta radiations enables locoregional or systemic therapy.

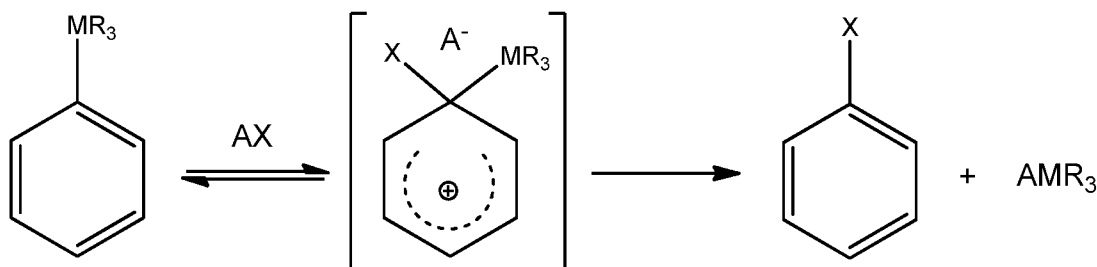
Radiopharmaceuticals are constituted by two entities: the vector and the radionuclide. Vectors may be peptides, antibodies or organic molecules targeting tumors. Various radionuclides may be used, especially radioactive isotopes of halogens (i.e. radiohalogens), such as for example ^{125}I or ^{211}At . Astatine-211, due to its decay properties (half-life: 7.2 hours; E_{α} : 5.9-7.5 MeV (100%); multiple X-ray emissions 76-92 keV) is considered as one of the most promising radionuclides for the development of targeted alpha-radionuclide therapy.

The labeling of a vector by a radionuclide to form a radiopharmaceutical may be performed either directly or using a labeled precursor comprising a reactive function able to react with a reactive function of the vector. A commonly used labeled precursor for ^{211}At -labeling of vectors is succinimidyl astatobenzoate (SAB) (scheme 1):



Scheme 1. ^{211}At -labeling of vectors using succinimidyl astatobenzoate (SAB).

Among methods enabling the introduction of a radiohalogen, especially ^{211}At , halodemetalation reaction of an organometallic compound with an electrophilic species is commonly used (scheme 2):

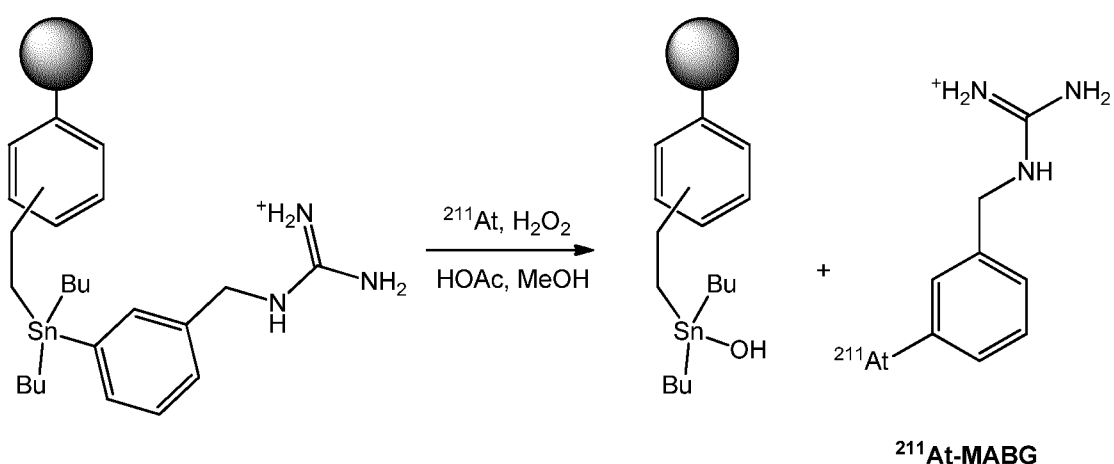


5 **Scheme 2.** Halodemetalation reaction of an organometallic compound.

Due to the high reactivity of the carbon-metal bond, the halodemetalation reaction occurs quickly in mild conditions. The rapidity of the reaction enables radiolabeling compounds with radionuclides having short half-lives while providing high specific activities.

- 10 Among organometallic compounds suitable for halodemetalation reaction, organotin derivatives are the most interesting due to the weakness of the carbon-tin bond, making of the tin group a good leaving group. Moreover, tin precursors are easily accessible by conventional synthesis methods from a broad variety of compounds. Especially, commonly used processes of labeling with radiohalogens involve tin(IV) derivatives
- 15 such as tributyl tin or trimethyl tin (Garg et al., Nucl. Med. Biol., 1995, 22(4), 467-473; Vaidyanathan et al., J. Label. Compd Radiopharm., 2007, 50, 177-182). However, the use of this kind of tin derivatives releases by-products difficult to separate from products of interest leading to low chemical and radiochemical purities and decrease of coupling yields.
- 20 Moreover, organotin compounds are known to have an important cellular toxicity. Therefore, any contamination by stannic by-products should be avoided when compounds are dedicated to pharmaceutical or veterinary applications. For these reasons, procedures involving usual tin derivatives are excluded in industrial synthesis of pharmaceutical compounds, despite their synthetic interest.

Solid supported tin reagents have been developed to easily eliminate tin reagents excess from the product of interest and to overcome tin contamination (WO99/18053; Gifford et al., *Bioconj. Chem.*, 2011, 22, 406-412). To the knowledge of the Applicant, the sole example of radiolabeling with ^{211}At using a solid supported organotin reagent was reported by Vaidyanathan et al. for the synthesis of ^{211}At -MABG (meta- ^{211}At]Astatobenzylguanidine) (Vaidyanathan et al., *Bioorg. Med. Chem.*, 2007, 15, 3430-3436):



Scheme 3. ^{211}At -radiolabeling using a solid supported organotin reagent.

The synthesis of ^{211}At -MABG was achieved with acceptable yields and good purity (<1 ppm of tin). However, the duration of reaction was quite long and reactivity on solid support was not optimum. Moreover, when using solid supported reagents, it is difficult to automatize the process of synthesis, whereas it is of common practice in radiolabeling processes. Indeed, automatization enables manipulators protection from radiations. Moreover, it accelerates the handling and thus provides higher specific activities and is well-suited to GMP process.

Other attempts have been done recently to overcome tin contamination problems, leading for example to the use of phosphonium grafted organotin (Poupon, et al. *Org. Lett.* 2007, 9, 3591) and other modified organotin reagents (Olofsson et al. *J. Org. Chem.* 1999, 64, 4539; Fouquet et al. *J. Org. Chem.* 1997, 62, 5242; Fouquet et al. *J. Chem. Soc. Chem. Comm.* 1995, 2387).

There is thus a need for new organotin reagents suitable for halodemallation reaction to provide radiolabeled compounds with high specific activities and with limited, if any, tin contamination.

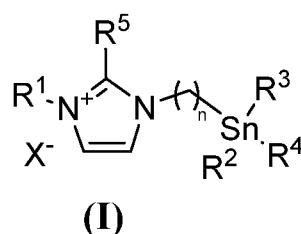
In the field of supported reagents, ionic liquids were proposed to replace solid supports. Ionic liquids are onium salts, constituted by the association of an anion and a cation, at least one of which being organic, said onium salts having a melting point below 100°C. The more commonly used ionic liquids have a cation structure centered on nitrogen (tetraalkylammonium, alkylpyridinium, alkylimidazolium), phosphorus (phosphonium), sulfur (sulfonium), 1,4-diazoniabicyclo[2.2.2]octane, sulfethanammonium, prolinium, pyrrolidinium. A large diversity of anions may be used, such as for example halide, acetate, trifluoroacetate, triflate, alkylsulfate, sulfonate, tetrafluoroborate, tetraarylborate, hexafluorophosphate, nitrate, hexafluoroantimonate, proline, hydroxide, hydrogen sulfate, tetrachloroferrate, aluminum tetrachloride, perfluorobutylsulfonate, p-toluenesulfonate, formate, dihydrogen phosphate. The simplest method to exchange the anion of an ionic liquid is ionic metathesis.

As for solid-supported reagents, ionic liquid supported reagents enable simple separation and purification at the end of the reaction, such as for example by filtration on silica, by distillation or by extraction. As for non-supported reagents, ionic liquid supported reagents enable conducting reactions in homogeneous conditions and therefore improve reactivity. Therefore, ionic liquid supported reagents have the advantage to play a dual role of support and solvent. Moreover, in the particular case of a halodemallation reaction wherein an electrophilic radiohalogen species should be used, the ionic liquid can act as a catalyst for its formation or can enhance its reactivity (Pavlinac et al., *Tetrahedron* 2009, 65, 5625–5662; Yadav et al., *Adv. Synth. Catal.* 2004, 346, 77–82).

The Applicant proved the interest of ionic liquid supported organotin reagents for Stille cross coupling reaction, catalytic free radical reduction of alkyl halides and for solvent-free reductive amination (Vitz et al., *Green Chem.*, 2007, 9, 431-433; Louaisil et al., *Eur. J. Org. Chem.*, 2011, 143-149; Pham et al., *Chem. Comm.*, 2009, 6207-6209; Pham et al., *Tet. Lett.*, 2009, 3780-3782). However, to the knowledge of the Applicant, ionic

liquid supported organotin reagents have never been used in halodemallation reaction and even less using radiohalogens.

Considering the potential advantages of ionic liquid supported organotin reagents, the Applicant focused on providing ionic liquid supported organotin reagents suitable for halogenation reaction, especially for the synthesis of “tin free” radiohalogenated compounds. Especially, the Applicant intended providing ionic liquid supported organotin reagents of following formula (I):



wherein X^- , n , R^1 , R^2 , R^3 , R^4 and R^5 are as defined below. Especially, R^4 represents an aryl or heteroaryl group, said group having vector properties, or said group being substituted by at least one reactive function able to react with a vector or said group being substituted by at least one substituent having vector properties.

Moreover, it was intended to provide a method of manufacturing of such ionic liquid supported organotin reagents being a reproducible method and a versatile method, adaptable to a large variety of substrates with various reactive functions or vector properties.

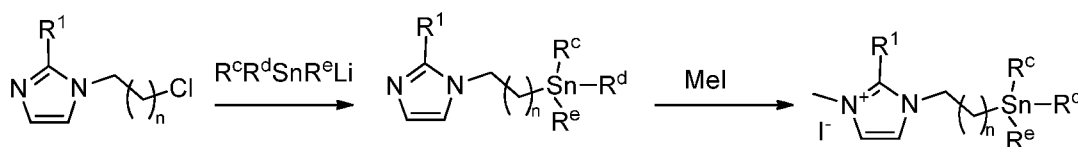
A method described in the prior art to prepare ionic liquid supported organotin reagents involves a reaction between the stannylchloride function in the side chain of an ionic liquid with a Grignard reagent (Scheme 4 - Louaisil et al., Eur. J. Org. Chem., 2011, 143-149):



Scheme 4. Substitution reaction by a Grignard reagent.

In the case of ionic liquid supported organotin reagents of formula (I) wherein R^4 is substituted by at least one substituent having vector properties, such bioactive substituents are sensible to degradation. Therefore, harsh Grignard conditions are not suitable for such case.

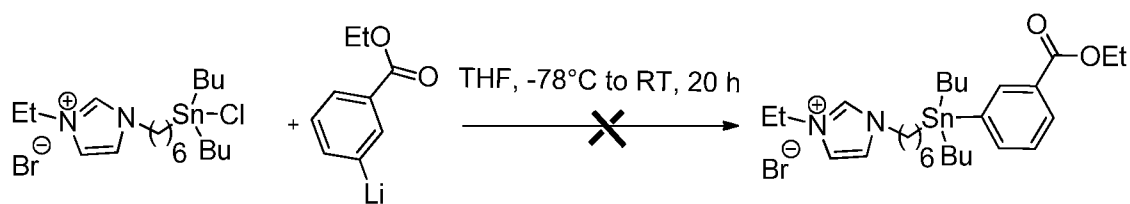
- 5 Another method described in the prior art to prepare ionic liquid supported organotin reagents involves a substitution reaction of a halogen atom in the side chain of a precursor of an ionic liquid, by a stannylithium derivative (Scheme 5 - Vitz et al., Green Chem., 2007, 9, 431-433).



10 **Scheme 5.** Substitution reaction by a stannylithium derivative.

Despite various attempts, above method did not enabled to obtain ionic liquid supported organotin reagents of formula (I) comprising a reactive function. Moreover, the use of very reactive lithium derivatives is not compatible in the case of ionic liquid supported organotin reagents comprising bioactive substituents, which are sensible to degradation.

- 15 The Applicant also attempted to adapt method of scheme 5 to prepare ionic liquid supported organotin reagents bearing a reactive function by substituting the halogen atom on an stannylchloride ionic liquid by an aryllithium reactant (Scheme 6).



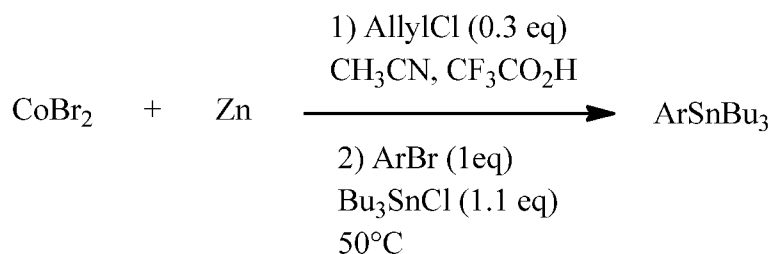
Scheme 6. Ineffective substitution reaction by an aryllithium.

- 20 However, the Applicant showed that the substitution by an aryllithium of a stannylchloride derivative of ionic liquid does not provide an ionic liquid supported organotin reagent comprising a reactive function. Especially, this was evidenced with

the reaction reported in scheme 6, wherein none of the expected compound was obtained, while unreactive ionic liquid only was recovered after purification.

Therefore, mere transposition of what was known with ionic liquid as support of organotin reagents is not sufficient to provide ionic liquid supported organotin reagents comprising a reactive function.

Gosmini et al. described a cobalt-catalyzed preparation of non-supported functionalized arylstannanes (Gosmini et Périchon, *Org. Biomol. Chem.*, 2005, 3, 216-217). Especially, the following reaction was described:



Ar = aryl group comprising a reactive functional substituent

Scheme 7. Cobalt-catalyzed preparation of non-supported functionalized arylstannanes.

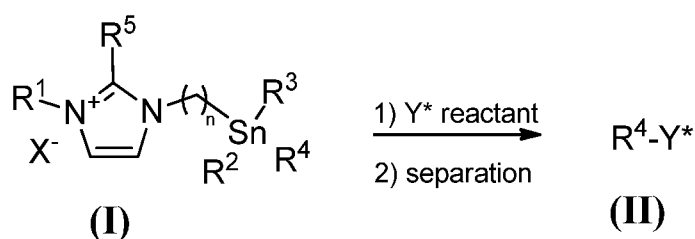
Gosmini conditions comprise a first step of activation of zinc dust and cobalt bromide in presence of allylchloride and trifluoroacetic acid in acetonitrile. Then, arylstannane derivatives are obtained in a one-pot reaction from arylbromides or iodide, in presence of tributylstannylchloride, through the passage to the arylzinc derivative.

- The mere transposition of above conditions of Gosmini to stannyl chloride ionic liquid did not enable to obtain expected compounds, even less ionic liquid supported organotin reagents comprising a reactive function. Even with some modifications of the conditions, such as varying the number of equivalents or the temperature of reaction, expected compounds have not been isolated.
- An important research work was thus conducted to systematically explore all the parameters of the reaction. Especially, it enabled highlighting that very fine zinc dust should be used and carefully activated before use. Besides, the Applicant evidenced that

conducting the reaction in presence of dibromoethane enabled to obtain expected compounds in a reproducible manner, even for ionic liquid comprising a reactive function.

Therefore, the present invention provides ionic liquid supported reagents of formula (I) and a reproducible and versatile process for their preparation.

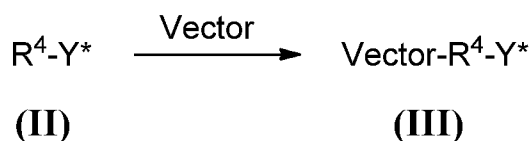
Reagents of formula (I) of the invention may be used in a halodemetallation reaction, leading to halogenated compounds (II), preferably radiohalogenated compounds, as described in scheme 8.



wherein Y* represents a halogen, preferably a radiohalogen

Scheme 8. General scheme for halodemetallation reaction on reagent (I) leading to halogenated compound (II).

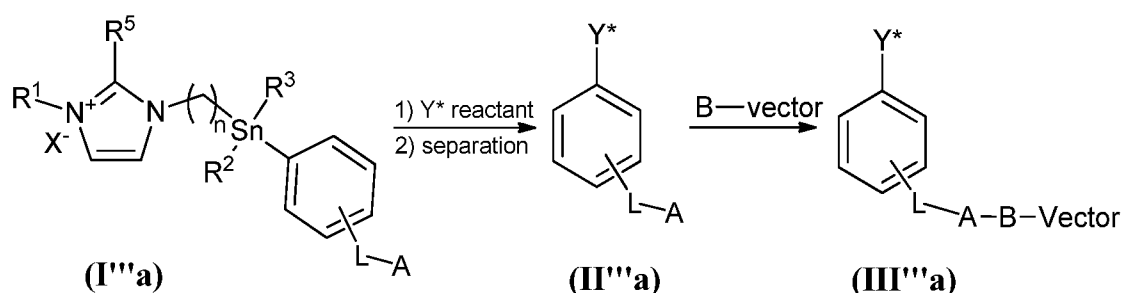
In one embodiment, in compound (II) Y* is preferably a radiohalogen, and compound (II) may react with a biological vector, such as for example an antibody, a peptide or an organic molecule, to provide a radiopharmaceutical (III) useful in nuclear medicine (scheme 9).



Scheme 9. General synthesis of radiopharmaceutical (III) using compound (II).

In a specific embodiment, compounds (I) of the invention are of formula (I''a) and react according to scheme 10 to afford intermediate compound (II''a) bearing a

reactive function A able to react with the reactive function B of a vector, leading to radiopharmaceutical of formula (III''a).



Scheme 10. Halo-labeling using the ionic liquid supported organotin reagent (I''a),

wherein A and B represent reactive functions and L represents a linker.

Conditions of radiolabeling with radiohalogen described in the art did not provided expected results. Therefore, an important research work was necessary to determine suitable radiolabeling conditions. The invention thus further relates to a radiolabeling process comprising the reaction of the ionic liquid supported organotin reagent of the invention with a radiohalogen.

The labeled compound (II) may be a radiolabeled vector or can react with a vector, such as an antibody, a peptide or an organic molecule, to provide a radiopharmaceutical (III) useful in nuclear medicine (scheme 9). Reactive function A of the labeled compound (II) and reactive function B of the vector are reactive functions compatible together to form a bound between the labeled compound (II) and the vector, such as for example amine and carboxylic functions leading to an amide bound.

Thanks to the use of the ionic liquid supported reagents of the invention, the purification of the labeled compound (II) may be easily performed in good yields, for example by a filtration on silica gel, distillation or extraction.

Radiolabeling processes are usually performed on automated devices to avoid manipulators irradiation and/or contamination. Moreover, automated devices enable to reduce the time of manufacturing to obtain more important specific activities. Syntheses using ionic liquid supported reagents are performed in homogeneous conditions and

with purification methods which present the advantage to be compatible with automated devices. Reactions using non-supported reagents can be automated but require complex, time-consuming and costly systems wherein chromatographic purification unit must be included. Reactions using solid supported reagents require batch process to change the
5 solid substrate.

The Applicant demonstrated that the covalent binding of organotin derivatives on the ionic liquid supported reagents (I) of the invention enables limiting, if any, toxic release of tin when these reagents are used in halodemallation reactions. Especially, the residual quantity of tin is inferior to 6 ppm, preferably inferior to 3 ppm, in the
10 halogenated compounds obtained using reagents (I) of the invention. Consequently, the tin contamination rate of halogenated products is compatible with pharmaceutical or veterinary applications without further purification as the amount of tin therein is very low. Moreover, as release of tin is avoided, it reduces the environmental impact of the process.

15 The use of ionic liquid as support instead of solid support also enables to increase the rate of reaction, especially due to a better reactivity in homogeneous medium compared to heterogeneous medium. Increasing the rate of reaction was preponderant more particularly for short half-life radionuclides and leads advantageously to higher specific activities for radiolabeled compounds. Moreover, the use of reagents supported
20 on ionic liquids also opens the possibility to combine effective and fast purifications to innovative automation systems including microfluidic devices.

Therefore, with the ionic liquid supported organotin reagents (I) of the present invention, reactions occur quickly and purification is performed by simple filtration. Radiolabeled compounds with a higher specific activity may thus be obtained. This
25 rapidity of synthesis and purification is all the more important with radionuclides with short half-lives, especially for the 7.2 hours of ^{211}At .

The ionic liquid supported organotin reagents of the invention display the following further advantages:

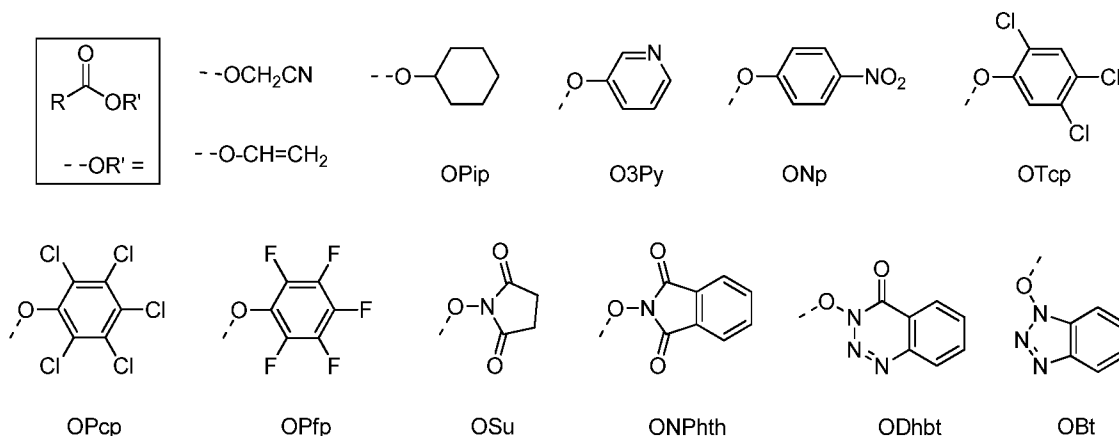
- residual derivatives obtained after halogenation reaction and isolation of compounds (II) may be recycled;
- 5 - ionic liquid supported organotin reagents (I) and residual derivatives obtained after halogenation reaction and isolation of compounds (II) are odorless and stable at room temperature.

Therefore, the use of the ionic liquid supported organotin reagents (I) of the invention in the halogenation process of the invention enables the manufacturing of radiolabeled
10 compounds (II) and (III) having a high specific activity, without contamination by tin, for preclinical and/or clinical applications, either in pharmaceutical or veterinary uses.

DEFINITIONS

In the present invention, the following terms have the following meanings:

- 15 - “**Activated ester**” refers to esters in which the alkoxy group is an electron-withdrawing group, preferably OCH_2CN , $\text{OCH}=\text{CH}_2$, OPip, O3Py, ONp, OTcp, OPcp, O-tetrafluorophenyl, OPfp, O-nitrophenyl, OSu (succinimidyl), sulfosuccinimidyl, ONPhth, ODhbt, OBt. These groups are represented in the scheme below:



- **“alkenyl”** refers to any linear or branched hydrocarbon chain having at least one double bond, of 2 to 12 carbon atoms, and preferably 2 to 6 carbon atoms.
- **“alkyl”** refers to any saturated linear, cyclic or branched hydrocarbon chain, with 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms, and more preferably methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.
- **“alkynyl”** refers to any linear or branched hydrocarbon chain having at least one triple bond, of 2 to 12 carbon atoms, and preferably 2 to 6 carbon atoms. Non limiting examples of alkynyl groups are ethynyl, 2- propynyl, 2-butylnyl, 3-butylnyl, 2-pentylnyl and its isomers, 2-hexynyl and its isomers-and the like.
- **“amine”** or **“primary amine”** refers to the group -NH₂. **“secondary amine”** refers to the group -NHR wherein R is different from H, preferably an alkyl group; **“tertiary amine”** refers to the group -NRR' wherein R and R' are different from H, preferably represent alkyl groups.
- **“antibody”** (Ab) as used herein includes monoclonal antibodies (mAb), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments, so long as they exhibit the desired biological activity. An “antibody fragment” comprises a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Pat. No. 5,641,870; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules, especially single-chain variable fragment (scFv); and multispecific antibodies formed from antibody fragments.
- **“aryl”** refers to a mono- or polycyclic system of 5 to 20, and preferably 6 to 12, carbon atoms having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphthyl) or linked covalently, wherein at least one ring is aromatic. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto. Non- limiting examples of aryl comprise phenyl, biphenyl, biphenylenyl, naphthalen-1- or -2-yl, binaphthyl, indenyl, acenaphthylenyl, acenaphthenyl, phenanthryl, pentalenyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyrenyl. The aryl group can be substituted by

- one or more substituents chosen independently of one another, among a hydroxyl group; a linear, cyclic or branched alkyl group comprising 1, 2, 3, 4, 5 or 6 carbon atoms, in particular methyl, ethyl, propyl, butyl; an alkoxy group; a halogen atom, in particular bromine, chlorine and iodine; a nitro group; a cyano group; an azido group; an aldehyde group; a boronato group; a phenyl; CF₃; methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl; a second aryl group which may be substituted as recited above.
- 10 - **“azidoalkyl”** refers to the general term of alkyl, comprising cycloalkyl and heterocyclyl groups as herein defined, bearing the azido function, commonly represented as R-N₃.
- **“azidoaryl”** refers to the general term of aryl, comprising heteroaryl groups, as herein defined, bearing the azido function, commonly represented as Ar-N₃.
- 15 - **“bioactive group”** or **“vector”** refers to a molecule being able to recognize a biological target tissue (depending on the pathology to be treated or detected). Preferably, “bioactive group” or “vector” refers to biomolecules, organic compounds or nanocarriers. By “biomolecules”, it is understood an antibody or fragments thereof or any antibody construct (like minibodies or diabodies, resulting from antibody engineering) as well as recombinant proteins or synthetic peptides selected to bind target cells (e.g., but not limited to, affibodies). By “organic compounds” it is referred to organic compounds binding cells, or organic compounds transported by transporters expressed by cells (e.g., but not limited to, glucose, amino-acids, biogenic amines), peptides binding specific receptors (e.g. but not limited to somatostatine, cholecystokinin, neurotensine receptors), aptamers, haptens, drugs. In a specific embodiment, “vector” refers to a small organic molecule. Especially, this term may refer, but is not limited to biotin, benzylguanidine, dihydroxyphenylalanine and theirs derivatives. By “nanocarrier” it is referred to compound able to recognize the target cells such as a nanocapsule, a
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liposome, a dendrimer or a carbon nanotube. These nanocarriers may be linked if necessary to tumor specific ligands.

Bioactive groups and biological targets of interest are illustrated by the non-limiting examples below:

Bioactive group type	Biological target	Bioactive group family	Examples of bioactive group
mAb	protein CAIX	Anti CAIX	Cg250
mAb	CTLA-4	Anti CTLA-4	Ipilimumab
saccharide	TRL4		LPS (lipopolysaccharide)
peptide	alphavbeta3 integrin	RGD peptides	Cyclo-RGD (GAERTNER, Eur. J. Nucl. Med, 2012), RGD tetramer (CHENG, Eur J. Nucl. Med, 2011)
Ab	TNF- α	anti-TNF- α antibody	
peptide	somatostatin receptors	somatostatin analogs	OCTREOTIDE, octreotate, 1-Nal ³ -octreotide (NOC), lanreotide, p-Cl-Phe-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)D-Tyr-NH ₂ (LM3), p-NO ₂ -Phe-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)D-Tyr-NH ₂ (JR10), Cpa-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)D-Tyr-NH ₂ , pansomatostatin
peptide	gastrin-releasing peptide (GRP) receptors	Bombesin, derivatives and analogs of bombesin	PEG4-Bombesin (D. WILD, Canc. Res., 2011; S. DäPP, Eur J Nucl Med, 2012), Bombesin, -[D-Tyr ⁶ , β Ala ¹¹ ,Thi ¹³ ,Nle ¹⁴]bombesin, PEG ₂ -[D-Tyr ⁶ , β Ala ¹¹ ,Thi ¹³ ,Nle ¹⁴]bombesin, -4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH ₂ , D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH ₂ , RGD-BBN
peptide	neuropeptide Y receptors	neuropeptide Y and analogs	

peptide	vasoactive intestinal peptide receptor (VPAC-1)	vasoactive intestinal and analogs	
peptide	cholecystokinin 2 receptors (CCK)	CCK analogs	CCK-8, minigastrin
peptide	neurokinin-1 receptor	Neurokinin-1 analogs	
peptide	melanocortin-1 receptor	α -MSH analogs	Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val (H. Guo, J. Nucl Med, 2010)
small molecules	melanocortin-1 receptor	α -MSH analogs	benzamides derivatives (A. Maisson, J Med Chem, 2011, Eur J Med Chem, 2013)
peptide	chemokine receptor 4 (CXCR4)	Chemokine analogs	Gourni; J. Nucl. Med, 2011,52,1803: SDF1-alpha, FC131 and analogues, T140 and analogs
peptide	neurotensin (NT) receptor	Neurotensin, and analogs	
small molecule	neurotensin (NT) receptor	neurotensin and analogs	
peptide		insulin and analogs	(M. Contino et al., Advances in Alzheimer's Disease 2 (2013) 13-30)
Monobody	IGF-R	Anti-IGF-R	
mAb	IGF-R	Anti-IGF-R	R1507
peptide	P-gp	P-gp ligands	
mAb	CD20	Anti CD20	Tositumomab (BEXXAR), ibritumumab tiuxetan (Zevalin) Rituximab, Ofatumumab
mAb	CD22	Anti-CD22	epratuzumab
mAb	CD33	Anti-CD33	gemtuzumab
mAb	CD52	Anti-CD52	Alemtuzumab
mAb	CD44-v6	Anti- CD44-v6	U36
mAb	CD105	Anti-CD105	TCR105
mAb	CD30	Anti-CD30	Brentuximab vedotin (Adcetris)
peptide	$\alpha 2\beta 1$ integrin		Asp-Gly-Glu-Ala (DGEA) peptide
steroid	estrogen receptor	estrogen analogs	Estradiol radiolabelling (Academic Radiology, 14, 9, 2007, 1050)
mAb	CD164	Anti-CD164	103B2/9E10, N6B6, 67D2, 105A5 (doi: 10.4049/jimmunol.165.2.840);

steroid	progesterone receptors	progestin analogs	16alpha,17alpha- dioxolane progestin analogs (J Med Chem. 2006 Jul 27;49(15):4737-44.)
mAb	Beta-amyloid	Anti- Beta-amyloid	11- 1F4; WO2014/089500, Aducanumab (imaging) (coupe)
peptide	Beta-amyloid	Beta-amyloid binding	ANA-1, ANA-5 and analogs
mAb	FCGR2A	Anti-FCGR2A (Anti-CD32)	3E8;
Small molecule	Porphyrin (biosynthesis precursor of)	Porphyrin precursor	5 -aminolevulinic acid hydrochloride
Small molecule	beta-sheet proteins	derivatives of thioflavin-T (ThT)	benzothiazole derivatives (WO2010/053218)
mAb	GPA33	Anti-GPA33	A33, KRN330 (Investigational New Drugs, August 2014, Volume 32, Issue 4, pp 682-690)
Small molecule	neuronal nicotinic acetylcholine receptor (nAChR)	alpha-7 nicotinic receptor binding ligands	A-84543 (3-[(1-methyl-2(S)-pyrrolidinyl)methoxy]pyridine), AFDB-02 (Synthesis and Evaluation of New Analogs of A-84543 as Nicotinic Acetylcholine Receptor Ligands by <i>Ogunjirin, Adebawale E.</i> , Ph.D., HOWARD UNIVERSITY, 2011, 112 pages; 3460685), 2-pyrrolidinylloxy-substituted pyridines, Nicotin, epibatidine, RJR-2403, SIB-1508Y, ABT-418, A85380 and derivatives (WO2005/000806); azetidinylmethoxypyridine derivatives
affibody	HER-2	Anti-HER-2	ZHER2:342 (J Nucl Med 2009; 50:417–425), ZHER2:2891, ZHER2:2395, ZHER2:2891-ABD035 and derivatives (J Nucl Med. 2010;51:1131-1138; J Nucl Med. 2013 Jun;54(6):961-8.), ABY-025, ABY-028 and derivatives
mAb	HER-2	Anti-HER-2	Trastuzumab
Small molecules		piperidines	N-methylpiperidin-4-yl acetate, N-methylpiperidin-4-yl propionate
Small	Cholinesterase	anticholinester	Galantamine; molecules in Mol.

molecules	(inhibitor)	ase	BioSyst., 2013,9, 792-805
Small molecules	c-Met (tyrosine-kinase receptor)	Tyrosine kinase inhibitor (TK)	AH113804
Small molecules		Tyrosine kinase inhibitor (TKI)	Erlotinib, sorafenib, Imatinib, dasatinib, nilotinib, pazopanib, vandetanin, vemurafenib, crizotinib
mAb	cMet	Anti-cMet	DN30
mAb	vegf	Anti-vegf antibodies	Bevacizumab WO2005/000900
Monobodies (adnectin)	vegfr	Vegfr2 antagonist	pegdinetanib
hormon		androgen receptor modulators	
mAb	egfr	anti-egfr	Cetuximab, panitumumab, L19-SIP,
monobody	egfr	anti-egfr	
protein	Annexin A2	Annexin A2 ligands	
protein	Annexin V	Annexin ligand	Annexin V (The scientific World Journal, 2014, Kazuma Ogawa)
scFV	ED-B-fibronectin	anti-ED-B-fibronectin	
mAb	ED-B-fibronectin	anti-ED-B-fibronectin	L19-SIP
minibody	PSMA	Anti-PSMA	HuJ591 minibody
mAb	PSMA	Anti-PSMA	J591, WO2011/069019, 7E11
diabodies	PSMA	Anti-PSMA	WO2011/069019
Small molecule	psma	Psmaligand	2-(3-{1-carboxy-5-[(6-[F]fluoropyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, 2-(3-{1-carboxy-5-[pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid
mAb	MCSP	antimelanoma antibodies	
Small molecule	folate receptor	Folate receptor ligand	Folate and folate derivatives
mAb	folate receptor alpha	Anti-folate receptor alpha	FARLETUZUMAB (MORAb-003)
Small molecule	Bones	Bone mineralisation	Phosphonates family
Small molecule	PD1	PD1 receptor	PD1 ligand

mAb	PD1	PD1 receptor	PD1 ligand (Onco target and therapy, M. Lagreca, 2014,p 1115)
mAb, Fab'	CEA	Anti-CEA	IMMU-4, arcitumomab, M5A, T84, 2A3, 2A3-mFc, 9A6 (Journal of Controlled Release, 05/2012; 161(1):18-24.); WO 2012/040824
scFv	CEACAM1	Anti-CEACAM1	DIATHIS1
mAb	endosialin		ONTUXIZUMAB (MORAb-004)
chimeric IgG ₁ antibody	mesothelin	Anti-mesothelin	AMATUXIMAB (MORAb-009)
mAb	GM3	Anti- GM3	MORAb-050
mAb	GD3	Anti-GD3	
mAb	Tissue Factor	Anti-TF	MORAb-066
Small molecule	Endothelin receptor	Endothelin receptor ligand (antagonist)	Atrasentan
Small molecule	Amyloid beta	Amyloid beta binding	AZD- 2995; AZD-2184; AZD-4694, AZPET
mAb	LewisY carbohydrate antigen	Anti- Lewis Y carbohydrate antigen	B3
oligonucleotide	CDK	antisense oligonucleotide CDK inhibitor	
mAb or fragments	tau	Human anti-tau antibodies)	WO2014/100600
Ab	notch3	Anti-notch3 antibodies	WO2014/100435
Small molecule		Lenalidomide and analogs	lenalidomide
mAb	CD38	Anti-CD38 Antibodies	
mAb	CD138	Anti-CD138 Antibodies	BB4, 9E7
haptan		haptan	In-DTPA, peptide or heteropeptide containing the "Histidyl-succinimidyl-glycyl" sequence
Biotin	Biotin	Biotin	biotin

Multispecific and/or multivalents antibodies			defined and obtained as described in WO03/057829, WO2013/005194, WO 2011/069104, WO2013/005194, WO2010/108127, WO 2014/081954, WO2014/144280, CN103694354, US2014/213771, WO2011/131746, US2009/182127, WO2014/082179
Multispecific complexes			such as described in WO2014/144600, WO2014/096015

- “**cycloalkyl**” refers to a cyclic or polycyclic alkyl group, optionally branched, such as for cyclopropyle, cyclopentyle or cyclohexyle.
 - “**cycloalkenyl**” refers to a cyclic or polycyclic alkenyl group, optionally branched.
 - “**cycloalkynyl**” refers to a cyclic or polycyclic alkynyl group, optionally branched.
- 5 - “**heteroaryl**” refers to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 2 rings which are fused together or linked covalently, typically containing 5 to 6 atoms; at least one of which is aromatic in which one or more carbon atoms in one or more of these rings can be replaced by oxygen, nitrogen or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized
- 10 and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl,
- 15 oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2- b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indoliziny, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1- benzisoxazolyl, 1,3-
- 20 benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-

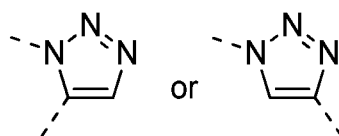
- pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl. The heteroaryl group can be substituted by one or more substituents chosen independently of one another, among a hydroxyl group; a linear, cyclic or branched alkyl group comprising 1, 2, 3, 4, 5 or 6 carbon atoms, in particular methyl, ethyl, propyl, butyl; an alkoxy group; a halogen atom, in particular bromine, chlorine and iodine; a nitro group; a cyano group; an azido group; an aldehyde group; a boronate group; a phenyl; CF₃; methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.
- **“heterocyclyl”** refers to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 7 member monocyclic, 7 to 11 member bicyclic, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. Non limiting exemplary heterocyclic groups include aziridinyl, oxiranyl, thiiranyl, piperidinyl, azetidiny, 2-imidazolinyl, pyrazolidinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, succinimidyl, 3H-indolyl, indolyl, isoindolyl, 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 4H-quinolizinyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, tetrahydro-2H-pyranyl, 2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, indolyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydroquinolinyl, tetrahydroisoquinolin-1-yl, tetrahydroisoquinolin-2-yl, tetrahydroisoquinolin-3-yl, tetrahydroisoquinolin-4-yl, thiomorpholin-4-yl, thiomorpholin-4-ylsulfoxide, thiomorpholin-4-ylsulfone, 1, 3-

dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 1H-pyrroliziny, tetrahydro-1,1-dioxothiophenyl, N- formylpiperaziny, and morpholin-4-yl.

- **“heteropeptide”** refers to a peptide comprising at least one amino acid and at least one building block which is not an amino acid. The term “amino acid” includes both L- and D-isomers of the naturally occurring amino acids and non-naturally-occurring amino acids. Examples of naturally-occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine. Other amino acids include for example norleucine, norvaline, biphenyl alanine or substituted phenyl alanine. . Non limited exemplary non-amino acid part of the heteropeptide include beta-glutamic acid, beat-alanine, amino benzoic acid, succinic acid, oxalic acid or ethylenediamine.
- **“linker”** refers to a single covalent bond or a moiety comprising series of stable covalent bonds, the moiety often incorporating 1-40 plural valent atoms selected from the group consisting of C, N, O, S and P, that covalently attach a reactive function or bioactive group to the aryl or heteroaryl group of the ionic liquid supported organotin reagent (I) or of compounds (II) or (III) of the invention. The number of plural valent atoms in a linker may be, for example, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 25, 30 or a larger number up to 40 or more. A linker may be linear or non-linear; some linkers have pendant side chains or pendant functional groups (or both). Examples of such pendant moieties are hydrophilicity modifiers, for example solubilising groups like, e.g. sulfo ($-\text{SO}_3\text{H}$ or $-\text{SO}_3^-$). In one embodiment, the “linker” is composed of any combination of single, double, triple or aromatic carbon-carbon bonds, carbon-nitrogen bonds, nitrogen-nitrogen bonds, carbon-oxygen bonds and carbon-sulfur bonds. Linkers may by way of example consist of a combination of moieties selected from alkyl, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})\text{n}-$ where n is 0, 1 or 2; $-\text{O}-$; 5- or 6- membered monocyclic rings and optional pendant functional groups, for example sulfo, hydroxy and carboxy.

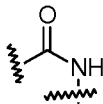
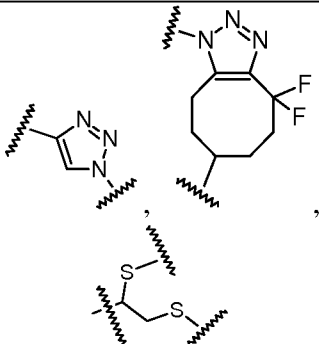
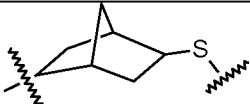
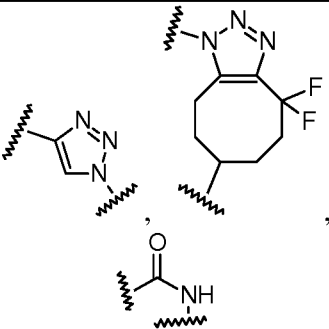
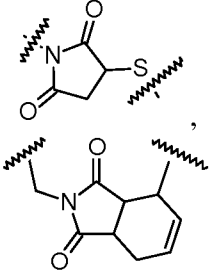
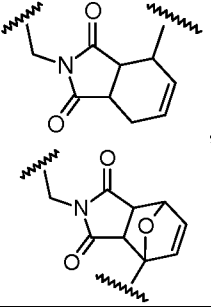
In the case wherein the linker is bonded to a reactive group, the reactive group may be reacted with a substance reactive therewith, whereby the linker becomes bonded to a bioactive group. In this case, the linker typically contains a residue of the

reactive group (such as for example the carbonyl group of an ester or a triazolo group resulting from a click reaction between an azide and an alkyne). By “triazolo group” it is referred to the following moiety:

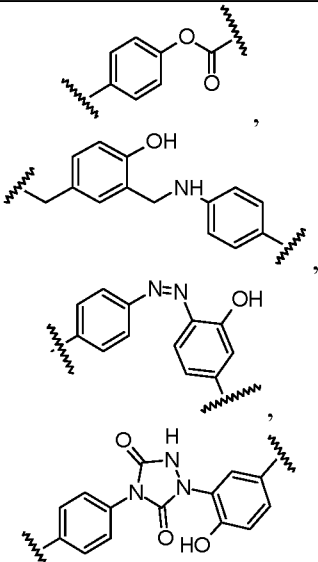
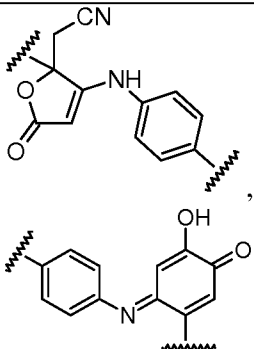
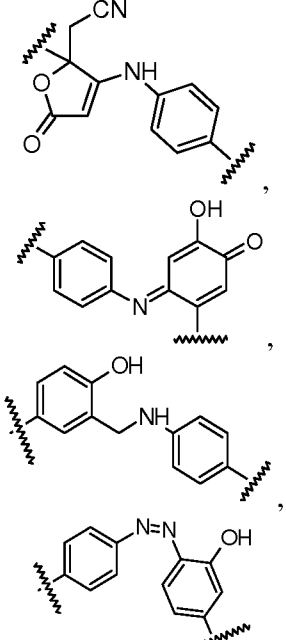


- 5 Other examples of residues of coupling residues resulting from coupling between reactive functions are the following:

reactive function A	reactive function B	coupling residue	examples of coupling residue
carboxylic acid	amine hydroxyl sulfhydryl, hydrazine	amide, ester, thioester, hydrazide :	
activated ester	amine, hydroxyl, sulfhydryl hydrazine	amide, ester, thioester, hydrazide	
aldehyde	amine, alkoxyamine, hydrazine, hydrazide	amine, oxime hydrazone	
ketone	amine, alkoxyamine, hydrazide, hydrazine	amine, oxime, hydrazone	

thioester	azide	amide (through traceless Staudinger ligation)	
alkyne	azide, thiol	triazolyl thioether,	
alkene	thiol	thioether	
azide	alkyne, phosphine, thioester	triazole, amide (through traceless Staudinger ligation)	
maleimide	sulfhydryl, diene	thioether, cyclic alkene	
diene	maleimide	cyclic alkene	
hydroxyl	carboxylic acid, activated ester, tosylate ester	ester, ether	

thiol	alkene, alkyne, maleimide, carboxylic acid, activated ester, tosylate ester, vinyl sulfone	thioether, thioester	
amine	aldehyde, ketone, hydroxyl (oxydation), tosylate ester, carboxylic acid, activated ester, isothiocyanate, isocyanate, alkylphosphate, ester carbonate	amine, amide, phosphoramida te, thiourea, urea, carbamate	
phosphine	azide	amide	
isothiocyanate	amine	thiourea	
isocyanate	amine	urea	
alkoxyamine	aldehyde, ketone	oxime	
hydrazide	aldehyde, ketone,	hydrazone	
hydrazine	aldehyde, ketone, carboxylic acid, ctivated ester	hydrazone, hydrazide	

phenol	carboxylic acid, aniline, PTAD derivatives	ester, substituted phenol, azo compounds	
2-aminophenol	aniline		
aniline	carboxylic acid, 2-aminophenol, phenol	anilide, substituted phenol, azo compounds,	

tosylate ester	amine, hydroxyle, sulfhydryle,	alkylated amine, thioether, ether	
vinyl sulfone	sulfhydryle		
carbonate ester	amine	carbamate	
PTAD derivatives	phenol		
alkyl phosphate	amine	phosphoramida te	

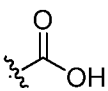
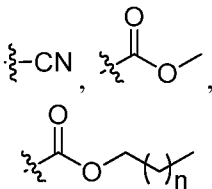
- “**neurotransmitter**” refers to endogenous chemicals that transmit signals across a synapse from one neuron (brain cell) to another 'target' neuron. Examples of neurotransmitters are: amino acids such as for example glutamate, aspartate, D-serine, γ -aminobutyric acid (GABA) or glycine; monoamines such as for example dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine or serotonin (SER, 5-HT); trace amines such as for example phenethylamine, N-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine or tryptamine; peptides such as for example somatostatin, substance P, cocaine and amphetamine regulated transcript or opioid peptides; gasotransmitters such as for example nitric oxide (NO), carbon monoxide (CO) or hydrogen sulfide (H₂S); acetylcholine (ACh), adenosine, anandamide. “**Sympatomimetic drug**” refers to compounds which mimic the effects of neurotransmitter substances of the sympathetic nervous system such as catecholamines, epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine, etc. Examples of sympathomimetic drugs can be direct-acting drugs, such as α -adrenergic agonists, β -adrenergic agonists (such as for example salbutamol, phenylephrine, isoproterenol, dobutamine), and dopaminergic agonists (such as for example fenoldopam); or

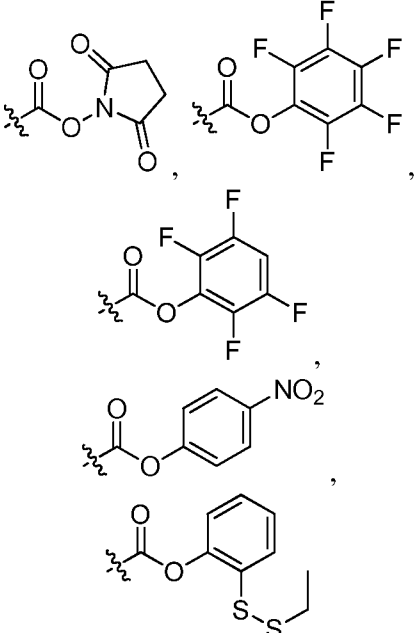
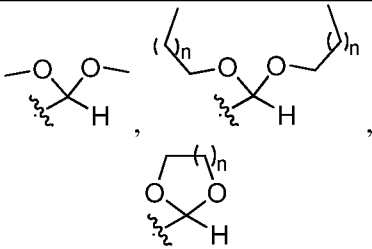
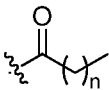
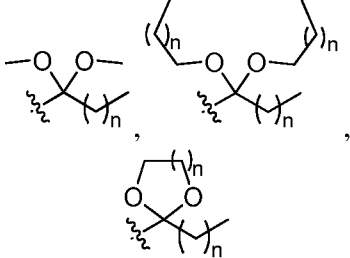
indirect-acting drugs, such as MAOIs, COMT inhibitors, release stimulants, and reuptake inhibitors that increase the levels of endogenous catecholamines, norepinephrine and dopamine transporter blockade (such as for example amphetamines, including MDMA; ephedrine; cocaine).

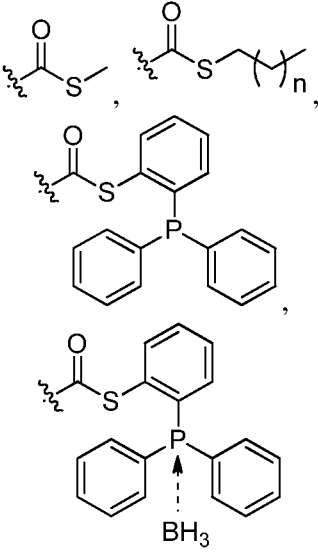
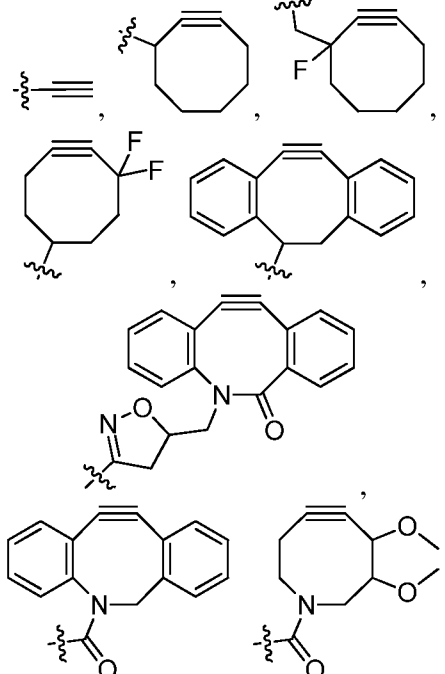
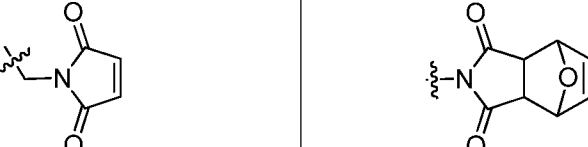
- 5 - **“PEG chain”** or “polyethylene glycol chain” refers to an oligomer or polymer of ethylene oxide, with a molecular mass below 20,000 g/mol.
- **“protected phosphine”** refers to a phosphine group $-PR^1R^2R^3$, wherein R^1 , R^2 and R^3 are selected from H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl or even a phosphorus atom (diphosphine) in
10 which the lone pair (valence electron pair) of the phosphorus atom is in a dative bond, disabling the nucleophilicity of the phosphorus atom, and therefore its reactivity towards electrophilic functional group; the dative bond being cleavable in specific conditions. Examples of protected phosphines are phosphine-boranes.
- **“protected thiol”** refers to a thiol group -SH in which the hydrogen is substituted by
15 a protecting group selected for its ability to be cleavable in specific conditions (acidic conditions for example), disabling the nucleophilicity of the sulfur atom, and therefore its reactivity towards electrophilic functional groups or the formation of disulfide bond. Examples of protected thiols are thioacetate or disulfide such as for example 2-pyridyldithio group.
- 20 - **“reactive function”** refers to a group capable of reacting with another chemical group to form a covalent bond, i.e. is covalently reactive under suitable reaction conditions, and generally represents a point of attachment for another substance. The reactive group is a moiety on the compounds of the present invention that is capable of chemically reacting with a functional group on a different compound to
25 form a covalent linkage. Reactive groups generally include nucleophiles, electrophiles and photoactivable groups. In a preferred embodiment, “reactive function” refers to any chemical group which is reactive towards the chemical functions of a vector (i.e. bioactive group) and thus allows the formation of a stable chemical bond between the vector and the radiolabelled precursor. The formation of
30 the stable bond between the vector and the reactive function of the radiolabelled

precursor can occur in one step or in a multi-step synthesis. According to a first embodiment, the reactive group may be under deprotected form, and may thus directly be used to react with the reactive group of the vector. According to a second embodiment, the reactive group may be under protected form and should thus be deprotected before being reacted with the reactive group of the vector. According to one embodiment, “reactive function” may refer, but is not limited to protected or unprotected reactive functions selected from carboxylic acid, nitriles, esters (e.g but not limited to ethyl and methyl esters), activated ester (e.g. but not limited to, succinimidyl, sulfosuccinimidyl, tetrafluorophenyl, pentafluorophenyl, nitrophenyl esters), aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, alcohol (i.e. hydroxyl), ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione (PTAD), sulphide, azidoalkyl and azidoaryl.

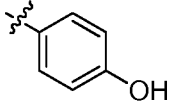
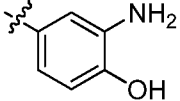
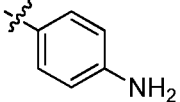
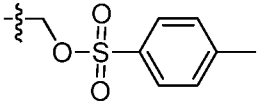
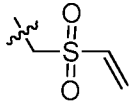
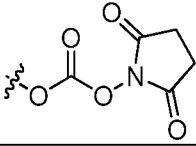
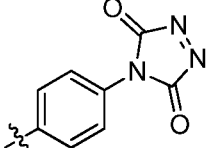
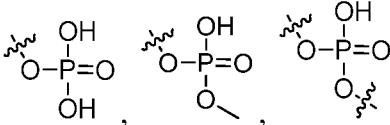
Illustrative examples of such reactive functions are the following:

Type of reactive function	examples of reactive function	
	unprotected form	protected form
carboxylic acid		 wherein n represents an integer ranging from 0 to 10

activated ester	 (see also the definition of activated esters above)	
aldehyde		 wherein n represents an integer ranging from 0 to 10
ketone	 wherein n represents an integer ranging from 0 to 10	 wherein n represents an integer ranging from 0 to 10

thioester	 wherein n represents an integer ranging from 0 to 10	
alkyne		
alkene		
azide		
maleimide		

diene		
hydroxyl	---OH	wherein n represents an integer ranging from 0 to 10
thiol	---SH	, thiosulfonates
amine	---NH_2 , ---NH--- , $\text{---NH---(CH}_2\text{)}_n\text{---}$ wherein n represents an integer ranging from 0 to 10	
phosphine		
isothiocyanate	---NCS ,	
isocyanate	---NCO	
alkoxyamine	---O---NH_2	---O---NH-Boc
hydrazide		
hydrazine	---NH---NH_2	---NH---NH-Boc

phenol		
2-aminophenol		
aniline		
tosylate ester		
vinyl sulfone		
carbonate ester		
PTAD derivatives		
alkyl phosphate		

- “**radiohalogen**” refers to a radioactive isotope of a halogen atom, preferably ^{123}I , ^{125}I , ^{131}I , ^{124}I , ^{211}At , ^{76}Br , ^{18}F , more preferably ^{125}I , ^{211}At or ^{18}F , more preferably ^{211}At or ^{18}F .

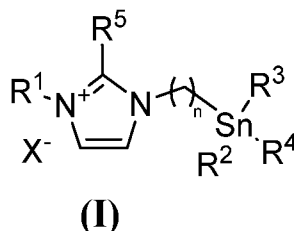
- **Y*** represents a halogen atom, preferably a radiohalogen atom. According to a specific embodiment, **Y*** represents ^{125}I . According to another specific embodiment, **Y*** represents ^{211}At . According to another specific embodiment, **Y*** represents ^{18}F .

Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyl" refers to the group (aryl)-(alkyl)-.

DETAILED DESCRIPTION

Ionic liquid supported organotin reagent (I)

The present invention relates to an ionic liquid supported organotin reagent of formula (I)



wherein:

X^- represents an anion, preferably X^- represents an anion selected from the group comprising halide, acetate, trifluoroacetate, triflate (Tf), NTf_2^- , alkylsulfate, sulfonate, tetrafluoroborate (BF_4^-), tetraarylborate, hexafluorophosphate (PF_6^-), NO_3^- , SbF_6^- , proline, hydroxide, hydrogen sulfate, tetrachloroferrate, aluminum tetrachloride, perfluorobutylsulfonate, p-toluenesulfonate, formate and dihydrogen phosphate; more preferably X^- represents BF_4^- , PF_6^- , Cl^- , Br^- , I^- , NTf_2^- , even more preferably X^- represents BF_4^- , PF_6^- or Br^- ;

n represents an integer ranging from 3 to 10, preferably n represents 4, 5, 6, 7 or 8, more preferably n represents 6;

R^1 represents an alkyl group, a PEG chain, preferably R^1 represents methyl, ethyl, n -butyl;

R^2 and R^3 each independently represent an alkyl group, preferably R^2 and R^3 are both n -butyl;

R^5 represents H, alkyl or aryl, preferably H, methyl or phenyl;

R^4 represents:

- an aryl vector; or
- a group selected from aryl and heteroaryl substituted by one or more substituents $-\text{L}-\text{M}$ wherein:

L represents a single bound or a linker selected from aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl or a combination thereof;

5 said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, imino, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate, halogen;

10 said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

optionally **L** additionally comprises a residue of a reactive group through which **L** is bounded to **M**;

M represents:

15 a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, 20 hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl; or

25 a bioactive group selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate,

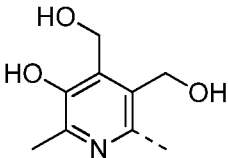
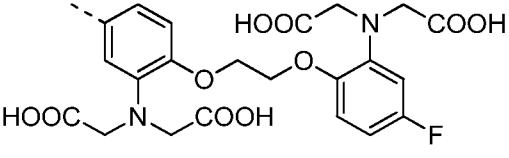
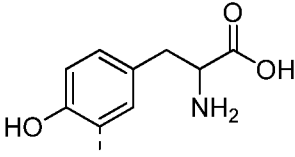
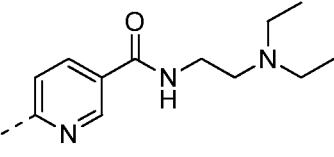
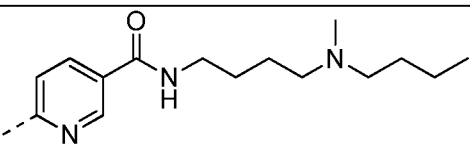
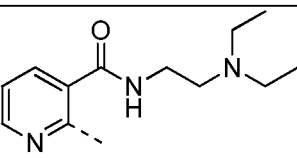
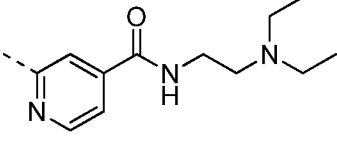
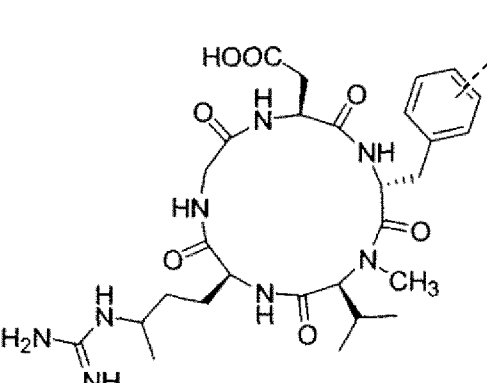
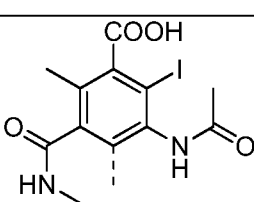
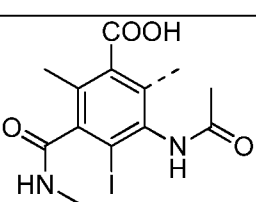
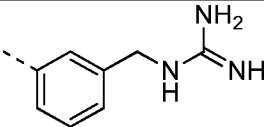
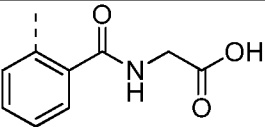
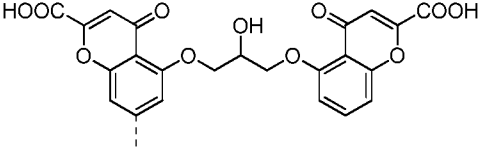
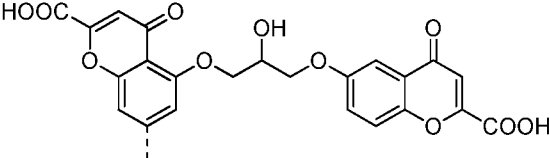
nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube and combinations thereof;

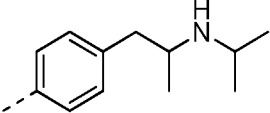
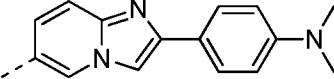
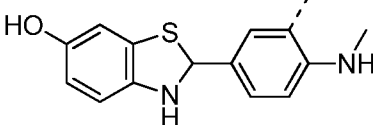
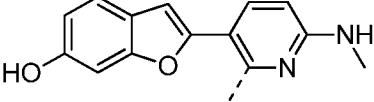
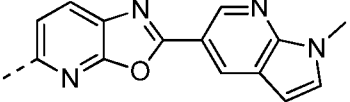
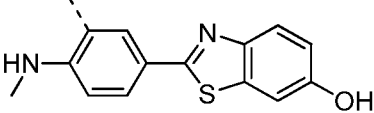
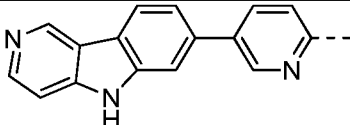
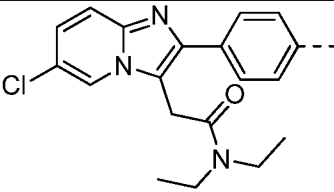
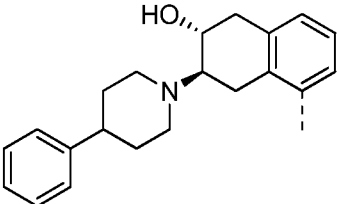
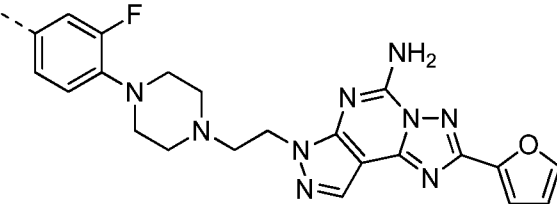
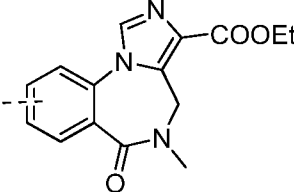
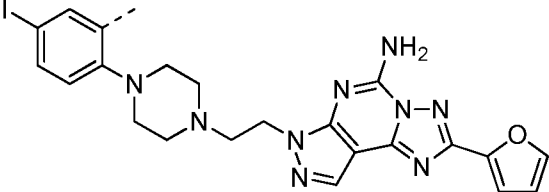
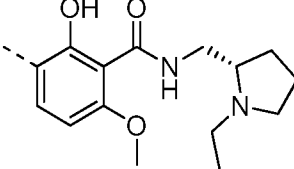
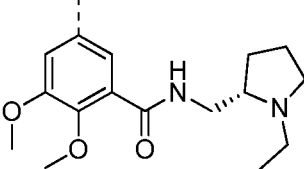
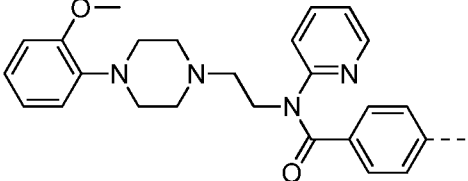
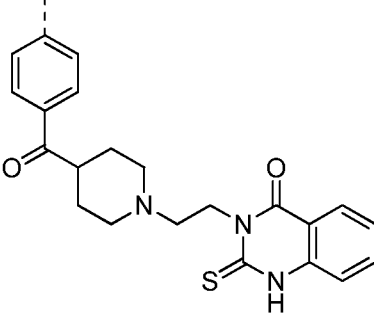
said aryl or heteroaryl being optionally further substituted by one or more substituents selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF₃; -CH(OH)(CF₃); -CH(OCH₂OCH₃)(CF₃); methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR, CONRR', NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.

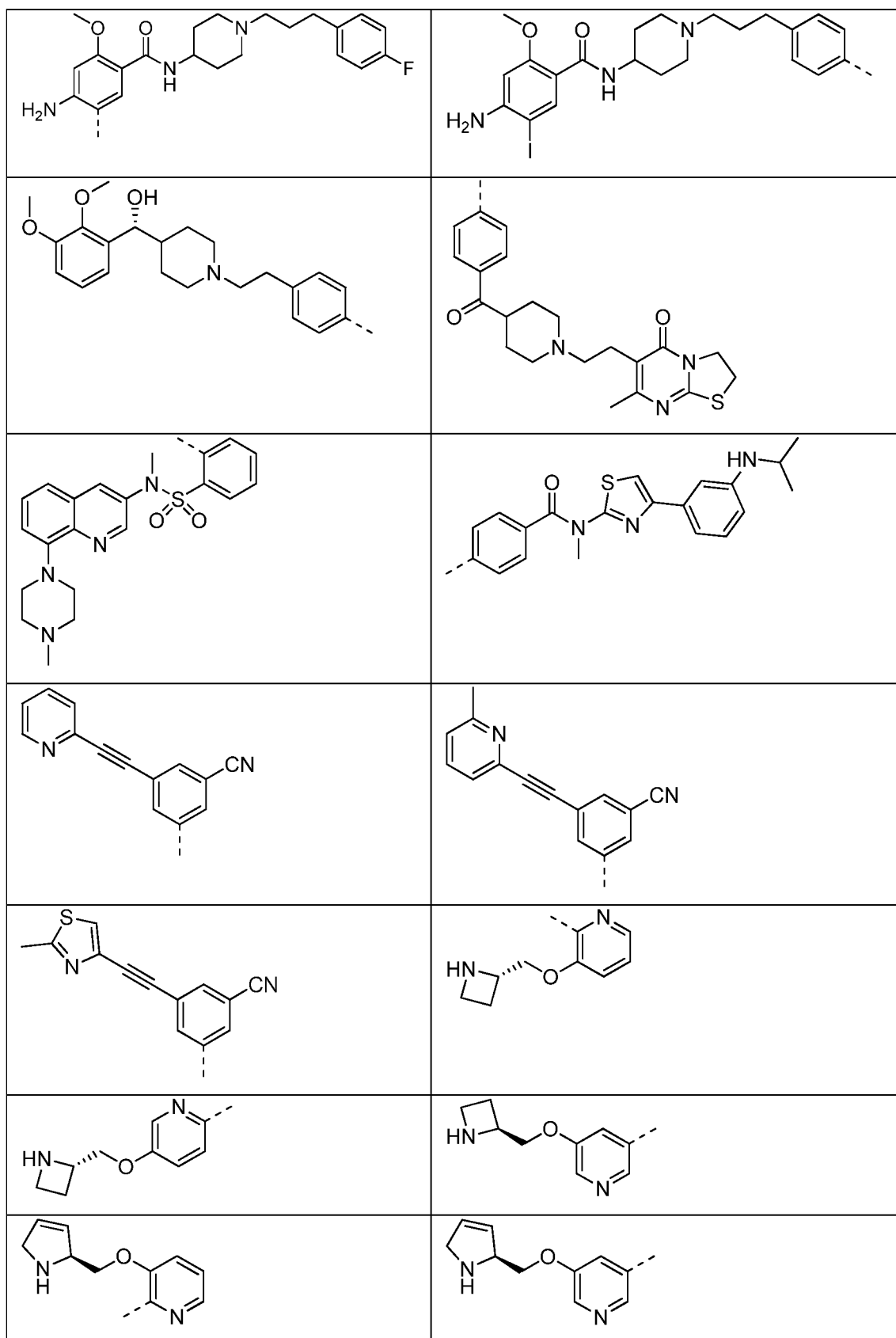
According to one embodiment, compound (I) is such that:

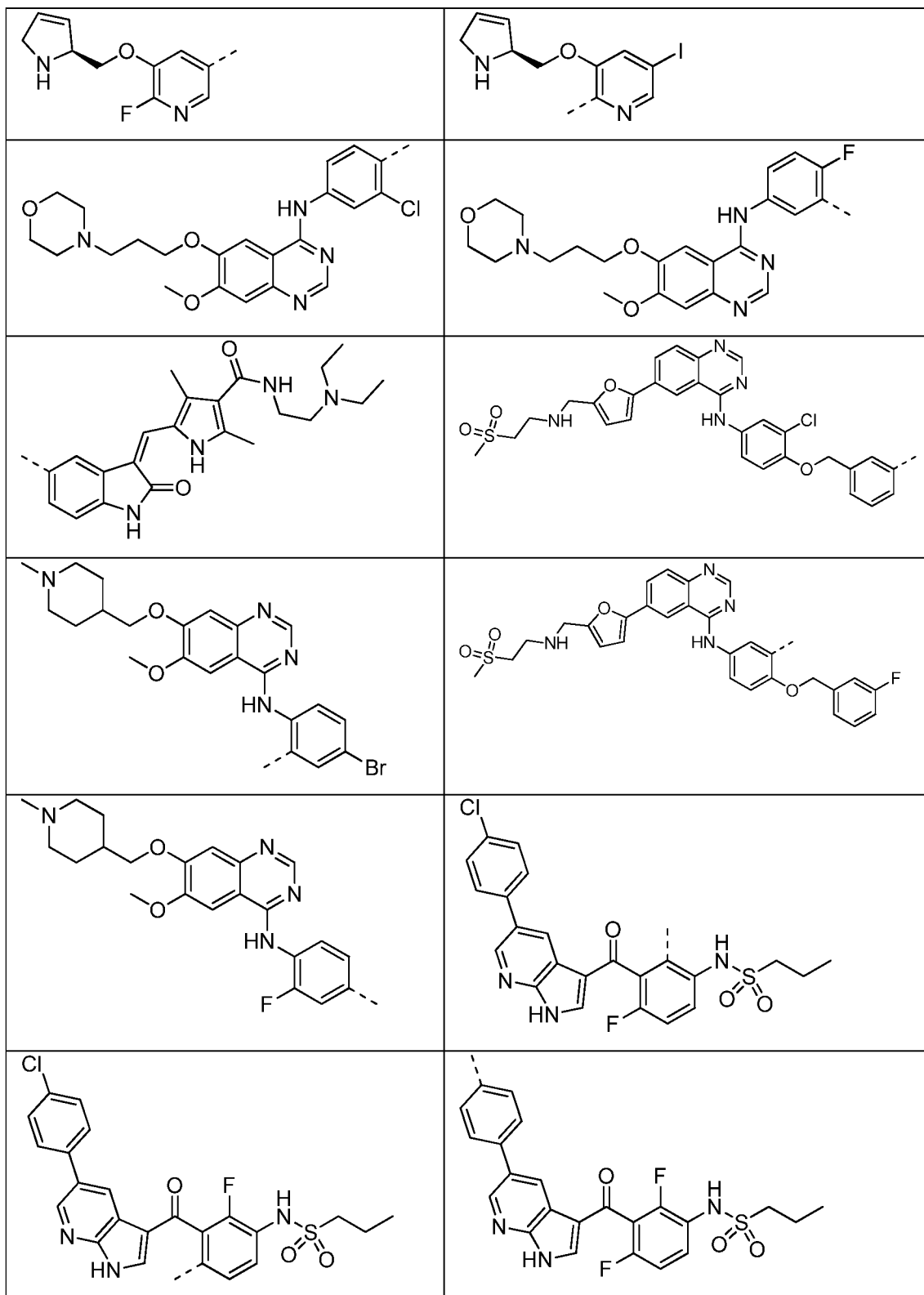
- when **n** is equal to 6, **X**⁻ is I, **R**¹ is methyl, **R**² and **R**³ are both *n*-butyl and **R**⁵ is H, then **R**⁴ is not phenyl;
- when **n** is equal to 6, **X**⁻ is Br⁻, **R**¹ is ethyl, **R**² and **R**³ are both *n*-butyl and **R**⁵ is H, then **R**⁴ is not phenyl, 4-methoxyphenyl, 4-fluorophenyl or thiophen-2-yl;
- when **n** is equal to 3, **X**⁻ is BF₄⁻, **R**¹ is methyl, **R**² and **R**³ are both *n*-butyl and **R**⁵ is H or methyl, then **R**⁴ is not phenyl;
- when **n** is equal to 3, **X**⁻ is I, **R**¹ is methyl, **R**² and **R**³ are both *n*-butyl and **R**⁵ is H or methyl or phenyl, then **R**⁴ is not phenyl;
- when **n** is equal to 6, **X**⁻ is I, **R**¹ is methyl, **R**² and **R**³ are both *n*-butyl and **R**⁵ is H, then **R**⁴ is not phenyl.

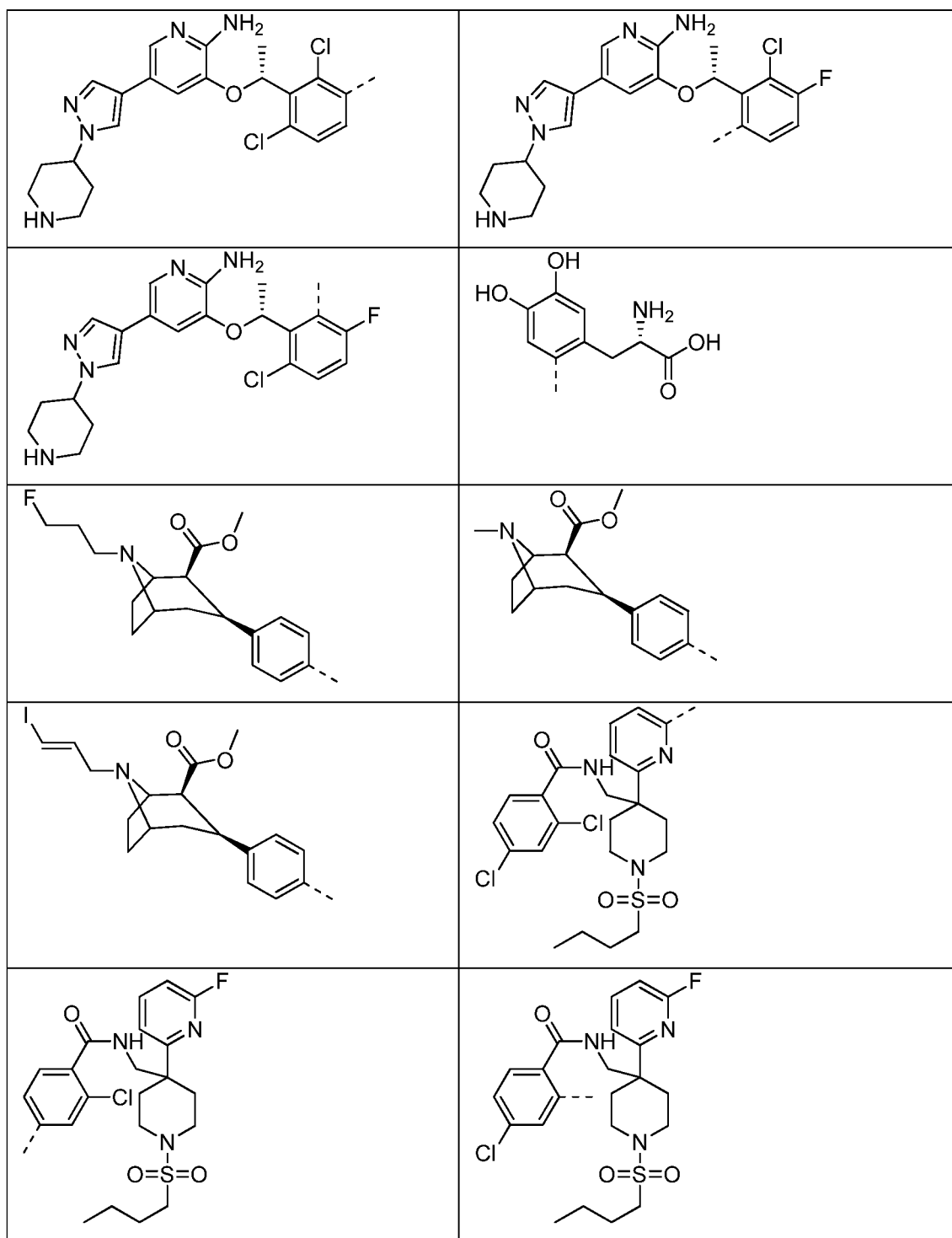
According to one embodiment, when R^4 is an aryl vector, R^4 is:







Above aryl vectors correspond to compounds which upon labeling by a radiohalogen atom lead to radiopharmaceuticals enabling nuclear imaging and/or therapy.

According to one embodiment, the ionic liquid supported organotin reagent of formula (I) is such that

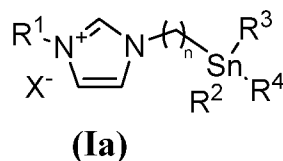
- X⁻** represents an anion, preferably an anion selected from the group comprising halide, acetate, trifluoroacetate, triflate (Tf), alkylsulfate, sulfonate, tetrafluoroborate (BF₄⁻), tetraarylborate, hexafluorophosphate (PF₆⁻), NO₃⁻, SbF₆⁻ and derivatives thereof, more preferably BF₄⁻, PF₆⁻, Cl⁻, Br⁻, I⁻, NTf₂⁻, more preferably BF₄⁻, PF₆⁻ or Br⁻;
- n** represents an integer ranging from 3 to 10, preferably **n** is 4, 5, 6, 7 or 8, more preferably **n** is 6;
- R¹** represents an alkyl group, a PEG chain, preferably methyl, ethyl, *n*-butyl;
- R²** and **R³** each independently represent an alkyl group, preferably **R²** and **R³** are both *n*-butyl;
- R⁴** represents a group selected from aryl and heteroaryl, substituted by one or more substituents **-L-M** wherein:
- L** represents a linker selected from single bond or a group selected from aryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl;
- said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate;
- said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and
- optionally additionally comprising a residue of a reactive group through which L is bounded to M;
- M** represents:
- a hydrogen atom;
- a reactive function selected from carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester such as for example ethyl or methyl ester, activated ester; alkyne,

alcohol, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and azidoaryl;

a bioactive group selected from amino acid, biogenic amine, peptide, affibody, protein, antibody or fragment thereof, antibody construct such as a for example minibody or, diabody, saccharide, polysaccharide, benzylguanine, biotine, dihydroxyphenylalanine, nucleotide, oligonucleotide, hapten, ligand, enzyme substrate, nanocarrier such as for example nanocapsule, liposome, dendrimer or carbon nanotube and derivatives and combinations thereof;

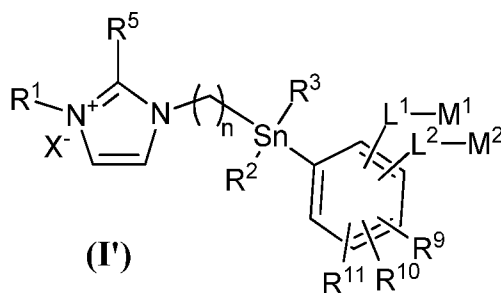
R^5 represents H, alkyl or aryl, preferably H, methyl or phenyl.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (Ia)



wherein X^- , n , R^1 , R^2 , R^3 , R^4 are as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I')



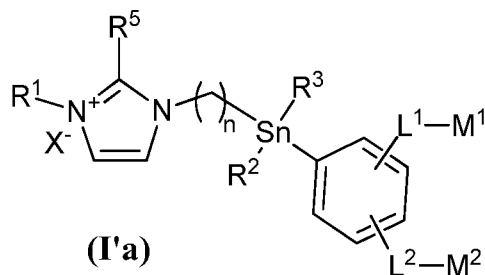
wherein

X^- , n , R^1 , R^2 , R^3 and R^5 are as defined above;

$-L^1-M^1$ and $-L^2-M^2$ represent each independently $-L-M$, wherein $-L-M$ is as defined above; and

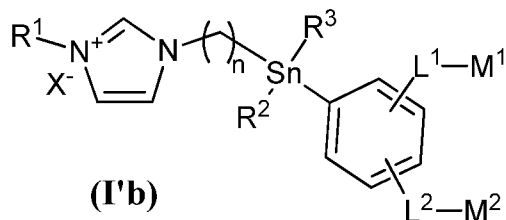
R^9 , R^{10} and R^{11} represent each independently independently a group selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF_3 ; $-CH(OH)(CF_3)$; $-CH(OCH_2OCH_3)(CF_3)$; methylenedioxy; ethylenedioxy; SO_2NRR' , NRR' , $COOR$, $CONRR'$, $NRCOR'$ wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'a)



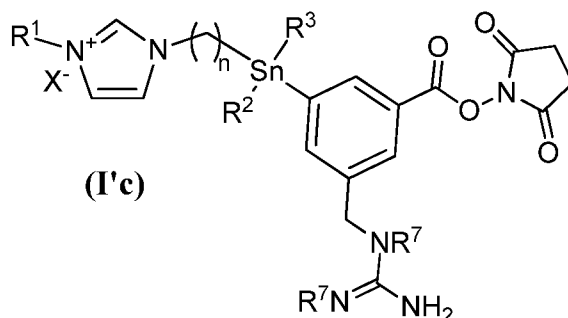
wherein X^- , n , R^1 , R^2 , R^3 and R^5 are as defined above, $-L^1-M^1$ and $-L^2-M^2$ represent each independently $-L-M$, wherein $-L-M$ is as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'b)



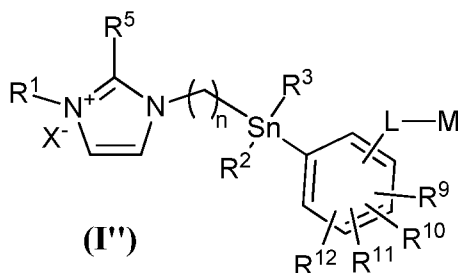
wherein X^- , n , R^1 , R^2 and R^3 are as defined above, $-L^1-M^1$ and $-L^2-M^2$ represent each independently $-L-M$, wherein $-L-M$ is as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'c)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above, and R^7 represent Boc or H.

- 5 In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'')

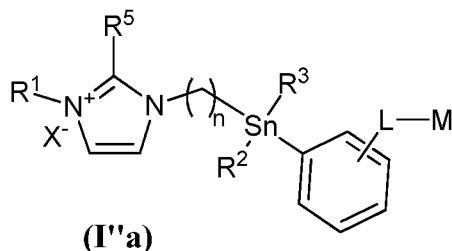


wherein

X^- , n , R^1 , R^2 , R^3 , R^5 and $-L-M$ are as defined above, and

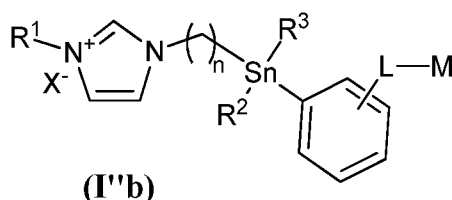
- 10 R^9 , R^{10} , R^{11} and R^{12} represent each independently a group selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF_3 ; $-CH(OH)(CF_3)$; $-CH(OCH_2OCH_3)(CF_3)$; methylenedioxy; ethylenedioxy; SO_2NRR' , NRR' ,
 15 $COOR$, $CONRR'$, $NRCOR'$ wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I''a)



wherein X^- , n , R^1 , R^2 , R^3 , R^5 and $-L-M$ are as defined above.

- 5 In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I''b)



wherein X^- , n , R^1 , R^2 , R^3 and $-L-M$ are as defined above.

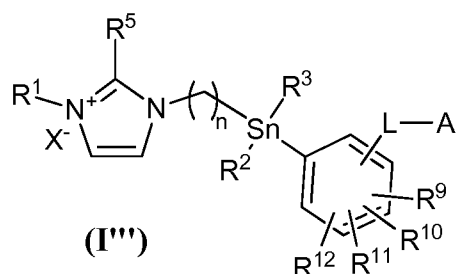
- In one embodiment, R^4 is an aryl or heteroaryl group substituted by one or more substituents $-L-M$ wherein M represents a reactive function A selected from carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester such as for example ethyl or methyl ester, activated ester such as for example succinimidyl, sulfosuccinimidyl, tetrafluorophenyl, pentafluorophenyl or nitrophenyl ester; alkyne, hydroxyl, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and azidoaryl.
- 10
15

- In one embodiment, R^4 is an aryl or heteroaryl group substituted by one or more substituents $-L-M$ wherein M represents a reactive function A selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates,
- 20

isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl.

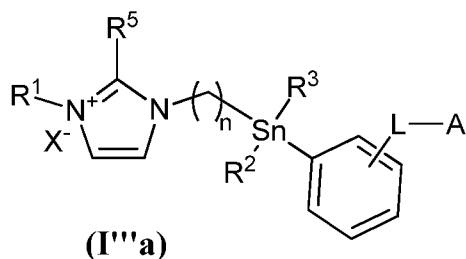
In a preferred embodiment, R^4 is an aryl group substituted by one or more substituents $-L-A$, wherein A is as defined above. In another preferred embodiment, R^4 is an aryl group substituted by one substituent $-L-A$, wherein A is as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I''')



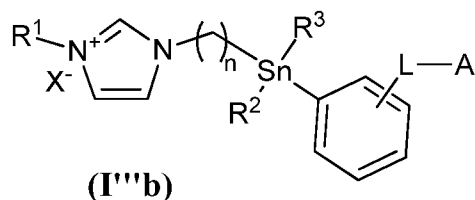
wherein X^- , n , R^1 , R^2 , R^3 , R^5 , $-L-A$, R^9 , R^{10} , R^{11} and R^{12} are as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'''a)



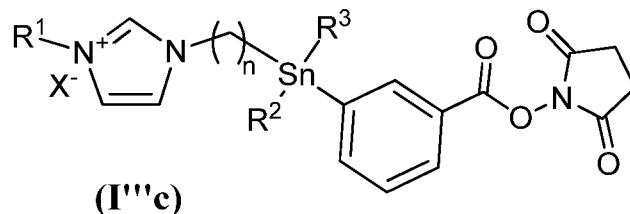
wherein X^- , n , R^1 , R^2 , R^3 , R^5 and $-L-A$ are as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'''b)



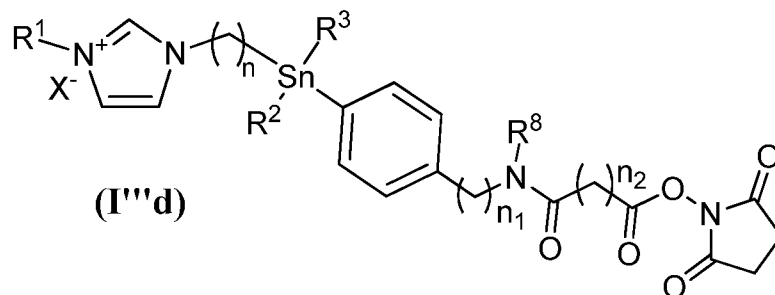
wherein X^- , n , R^1 , R^2 , R^3 and $-L-A$ are as defined above.

In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'''c)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above.

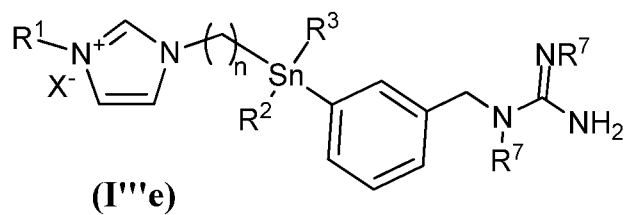
- 5 In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'''d)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above; R^8 represents H or alkyl, preferably H or methyl; n_1 and n_2 represent each independently 1, 2, 3, or 4 preferably 2.

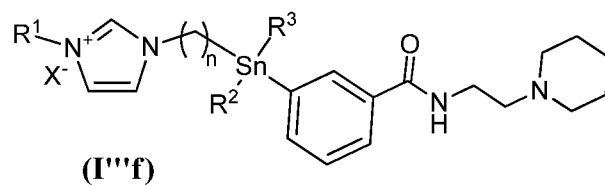
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In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I'''e)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above and R^7 represent Boc or H.

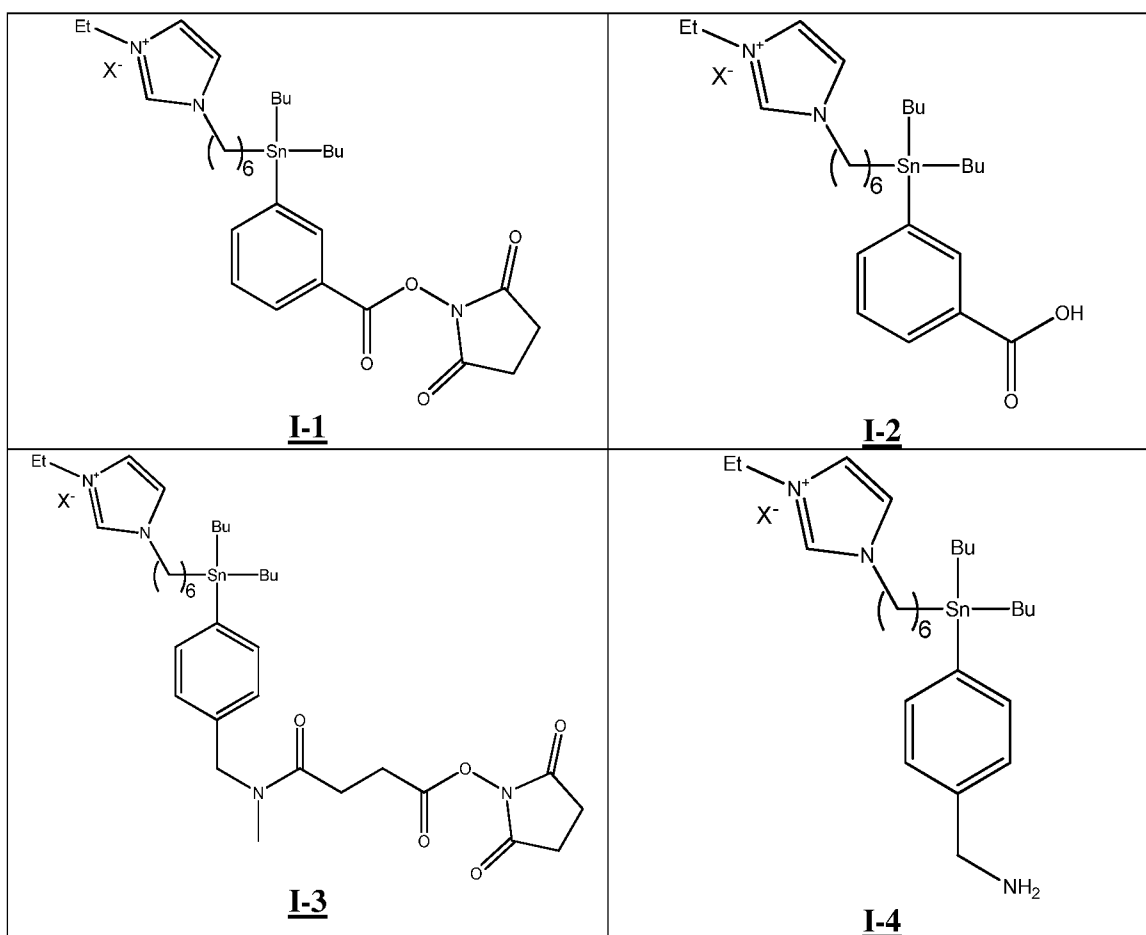
In one embodiment, the ionic liquid supported organotin reagent of the invention is of formula (I''f)

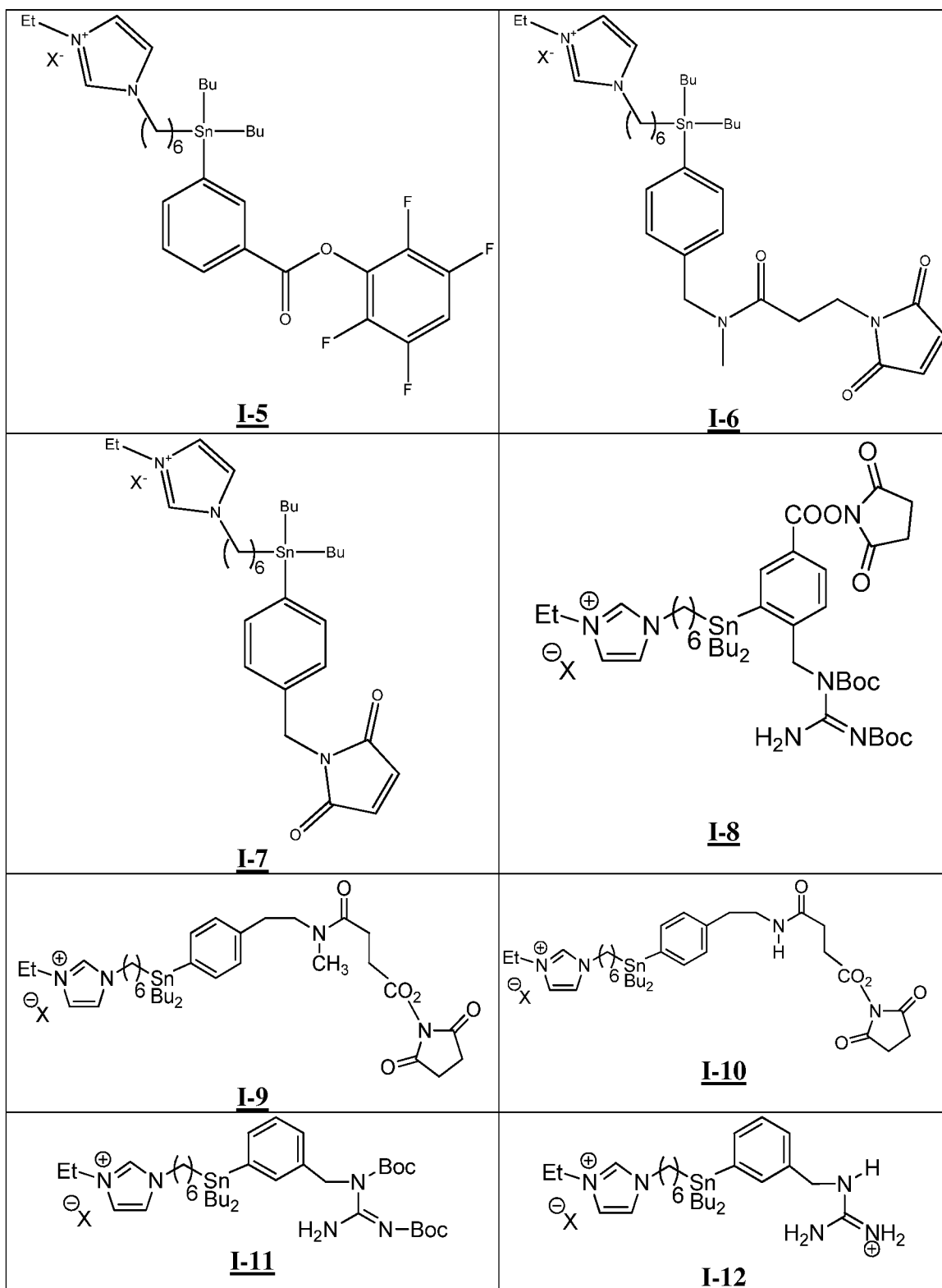


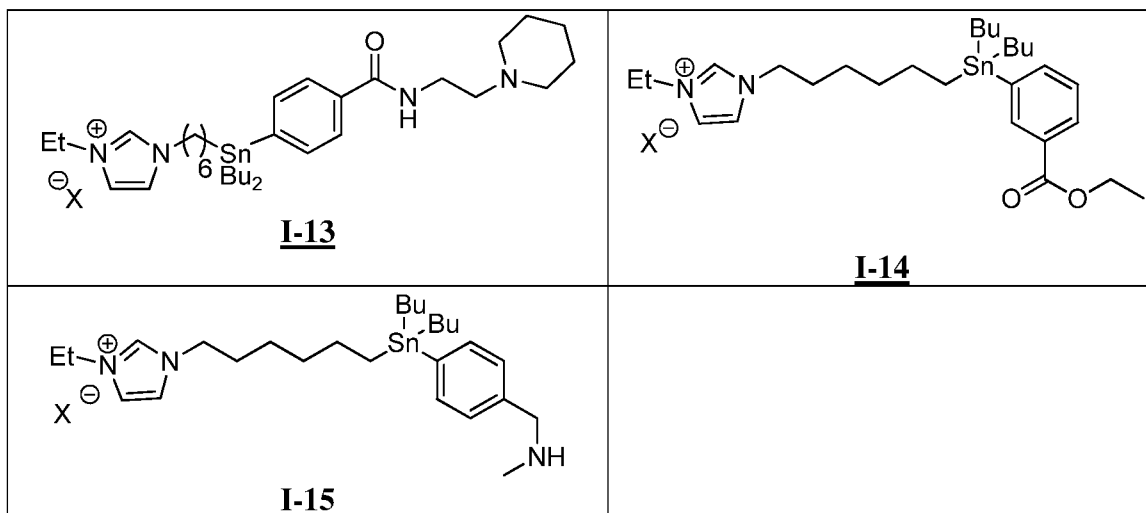
wherein X^- , n , R^1 , R^2 and R^3 are as defined above.

- 5 In a preferred embodiment n is equal to 6, R^1 is ethyl and R^2 and R^3 are both n -butyl.

In an embodiment, the ionic liquid supported organotin reagent of the invention is one of the following compounds:





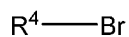


wherein X^- represents Br^- , BF_4^- or PF_6^- .

Process for manufacturing the ionic liquid supported organotin reagent (I)

The present invention further relates to a process for manufacturing an ionic liquid supported organotin agent (I) as defined above comprising:

- 5 1) reacting an activated mixture of zinc and $CoBr_2$ with a compound of formula (IV)



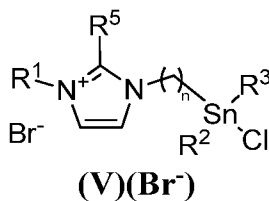
(IV)

wherein R^4 is as defined above;

in presence of dibromoethane,

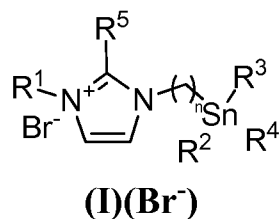
to afford the corresponding zinc derivative;

- 10 2) reacting the zinc derivative prepared in step 1) with ionic liquid (V)(Br^-),



wherein n , R^1 , R^2 , R^3 and R^5 are as defined above;

to form compound of formula (I)(Br⁻)



wherein **n**, **R¹**, **R²**, **R³**, **R⁴** and **R⁵** are as defined above;

- 3) optionally, a metathesis step to exchange Br⁻ to another counterion X⁻ as defined
5 above, to afford compound of formula (I).

According to one embodiment, the process for manufacturing of the invention is for manufacturing an ionic liquid supported organotin agent (I) wherein:

X⁻ represents an anion, preferably an anion selected from the group comprising halide, acetate, trifluoroacetate, triflate (Tf), alkylsulfate, sulfonate,
10 tetrafluoroborate (BF₄⁻), tetraarylborate, hexafluorophosphate (PF₆⁻), NO₃⁻, SbF₆⁻ and derivatives thereof, more preferably BF₄⁻, PF₆⁻, Cl⁻, Br⁻, I⁻, NTf₂⁻, more preferably BF₄⁻, PF₆⁻ or Br⁻;

n represents an integer ranging from 3 to 10, preferably **n** is 4, 5, 6, 7 or 8, more preferably **n** is 6;

15 **R¹** represents an alkyl group, a PEG chain, preferably methyl, ethyl, *n*-butyl;

R² and **R³** each independently represent an alkyl group, preferably **R²** and **R³** are both *n*-butyl;

R⁴ represents a group selected from aryl and heteroaryl substituted by one or more substituents **-L-M** wherein:

20 **L** represents a linker selected from single bond or a group selected from aryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl;

said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl,
25 amine, amide, guanidine, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate;

said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

optionally additionally comprising a residue of a reactive group through which L is bounded to M;

5 **M** represents:

a hydrogen atom;

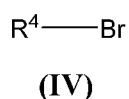
a reactive function selected from carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester such as for example ethyl or methyl ester, activated ester; alkyne, 10 alcohol, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and azidoaryl;

a bioactive group selected from amino acid, biogenic amine, peptide, affibody, protein, antibody or fragment thereof, antibody construct 15 such as a for example minibody or, diabody, saccharide, polysaccharide, benzylguanine, biotine, dihydroxyphenylalanine, nucleotide, oligonucleotide, hapten, ligand, enzyme substrate, nanocarrier such as for example nanocapsule, liposome, dendrimer or carbon nanotube and derivatives and combinations thereof;

20 **R**⁵ represents H, alkyl or aryl, preferably H, methyl or phenyl;

and comprises:

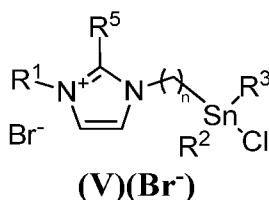
1) reacting an activated mixture of zinc and CoBr₂ with a compound of formula (IV)



wherein **R**⁴ is as defined above;

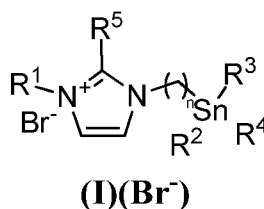
25 to afford the corresponding zinc derivative;

2) reacting the zinc derivative prepared in step 1) with ionic liquid (V)(Br⁻),



wherein **n**, **R¹**, **R²**, **R³** and **R⁵** are as defined above;

to form compound of formula (I)(Br⁻)



5

wherein **n**, **R¹**, **R²**, **R³**, **R⁴** and **R⁵** are as defined above;

3) optionally, a metathesis step to exchange Br⁻ to another counterion X⁻ as defined above, to afford compound of formula (I).

According to one embodiment, zinc used in the process of the invention is under the form of zinc dust. According to a specific embodiment, zinc dust has a particle size equal or lower than 50 μm, preferably equal or lower than 30 μm, more preferably equal or lower than 10 μm.

According to one embodiment, activation of zinc and CoBr₂ is performed by heating a mixture of zinc and CoBr₂ under vacuum at a temperature ranging from 150°C to 250 °C, preferably at about 200°C. Preferably activation is performed for a period of time ranging from 1 hour to 24 hours, preferably about 12 hours. Preferably, activation is performed under argon atmosphere.

According to one embodiment, formation of the zinc derivative (step 1) is performed in presence of dibromoethane, preferably in presence of 0.05 to 0.15 equivalents of dibromoethane. According to a preferred embodiment, step 1 is performed in acetonitrile.

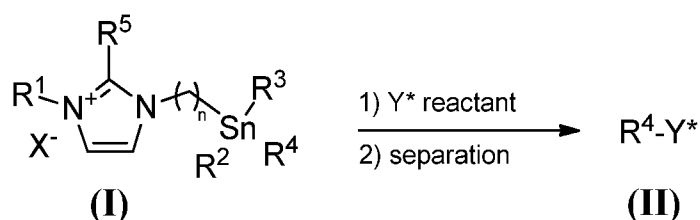
According to one embodiment, the reaction between the zinc derivative and the ionic liquid of formula (V)(Br⁻) (step 2) is performed for a period of time ranging from 1 hour to 24 hours, preferably for 18 hours, at a temperature ranging from room temperature to 100°C, preferably at room temperature.

- 5 According to one embodiment, the reaction between the zinc derivative and the ionic liquid (V)(Br⁻) (step 2) is performed in an organic solvent, preferably the organic solvent is selected in the group comprising acetonitrile, THF, DMF. According to a preferred embodiment the reaction between the zinc derivative and the ionic liquid (V)(Br⁻) is performed in anhydrous THF and/or acetonitrile.
- 10 According to one embodiment, step 1 and/or step 2 are performed in acidic conditions, such as for example in presence of trifluoroacetic acid.

According to one embodiment, the formation of the zinc derivative (step 1) is performed using zinc dust, preferably activated zinc dust.

Radiolabeling processes

- 15 1) Halodemetallation reaction in presence of ionic liquid supported organotin reagent (I) of the invention



- 20 The ionic liquid supported organotin reagent (I) of the present invention may be used in a halodemetallation reaction in presence of an electrophilic reactant comprising the halogen atom, preferably a radioactive halogen atom, more preferably ²¹¹At, ¹²⁵I, ¹³¹I, ¹²⁴I, ¹²³I, ⁷⁶Br, ¹⁸F. The radioactive halogen may be used isotopically pure or as a carrier-added i.e. in a mixture with stable isotope(s).

According to one embodiment, the organotin reagent (I) of the invention is used for the synthesis of halogenated compounds, preferably for the synthesis of radiohalogenated compounds.

The invention thus relates to a labeling process for the manufacturing of a compound of
5 formula (II):



wherein

Y* represents a halogen atom, preferably a radiohalogen atom;

R⁴ represents:

- 10 - an aryl vector; or
- a group selected from aryl and heteroaryl substituted by one or more substituents **-L-M** wherein:

L represents a single bound or a linker selected from aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl or a combination
15 thereof;

 said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, imino, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate, halogen;
20 said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

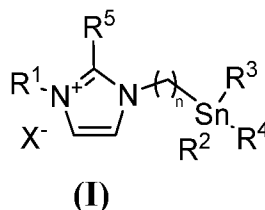
 optionally **L** additionally comprises a residue of a reactive group through which L is bounded to M;
25

M represents:

 a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-

- aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl; or
- a bioactive group selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate, nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube and combinations thereof;
- said aryl or heteroaryl being optionally further substituted by one or more substituents selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF_3 ; $-\text{CH}(\text{OH})(\text{CF}_3)$; $-\text{CH}(\text{OCH}_2\text{OCH}_3)(\text{CF}_3)$; methylenedioxy; ethylenedioxy; $\text{SO}_2\text{NRR}'$, NRR' , COOR , CONRR' , NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl;
- said process comprising performing a halodemallation by reacting an electrophilic reactant comprising halogen Y^* , with an ionic liquid supported organotin reagent (I) according to the invention.

According to one embodiment, the labeling process of the invention comprises reacting a halogen **Y*** with an ionic liquid supported organotin reagent (I)



wherein:

5 **X⁻** represents an anion, preferably an anion selected from the group comprising halide, acetate, trifluoroacetate, triflate (Tf), alkylsulfate, sulfonate, tetrafluoroborate (BF₄⁻), tetraarylborate, hexafluorophosphate (PF₆⁻), NO₃⁻, SbF₆⁻ and derivatives thereof, more preferably BF₄⁻, PF₆⁻, Cl⁻, Br⁻, I⁻, NTf₂⁻, more preferably BF₄⁻, PF₆⁻ or Br⁻;

10 **n** represents an integer ranging from 3 to 10, preferably **n** is 4, 5, 6, 7 or 8, more preferably **n** is 6;

R¹ represents an alkyl group, a PEG chain, preferably methyl, ethyl, *n*-butyl;

R² and **R³** each independently represent an alkyl group, preferably **R²** and **R³** are both *n*-butyl;

15 **R⁴** represents a group selected from aryl and heteroaryl substituted by one or more substituents **-L-M** wherein:

L represents a linker selected from single bond or a group selected from aryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl;

20 said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate;

25 said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

optionally additionally comprising a residue of a reactive group through which **L** is bounded to **M**;

M represents:

a hydrogen atom;

a reactive function selected from carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester
5 such as for example ethyl or methyl ester, activated ester; alkyne, alcohol, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and azidoaryl;

a bioactive group selected from amino acid, biogenic amine, peptide,
10 affibody, protein, antibody or fragment thereof, antibody construct such as a for example minibody or, diabody, saccharide, polysaccharide, benzylguanine, biotine, dihydroxyphenylalanine, nucleotide, oligonucleotide, hapten, ligand, enzyme substrate, nanocarrier such as for example nanocapsule, liposome, dendrimer or
15 carbon nanotube and derivatives and combinations thereof;

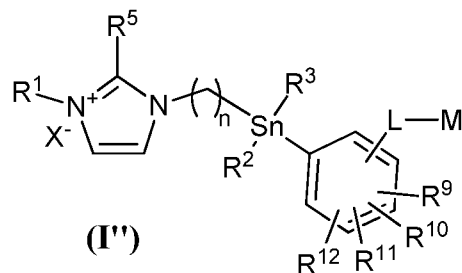
R⁵ represents H, alkyl or aryl, preferably H, methyl or phenyl;

to form compound of formula (II) **R**⁴-**Y***, wherein **R**⁴ is as described above.

In one embodiment, the halogen **Y*** is a radiohalogen, preferably **Y*** is a radiohalogen selected from the group comprising ¹²⁵I, ¹²³I, ¹³¹I, ¹²⁴I, ²¹¹At, ⁷⁶Br, ¹⁸F, more preferably
20 **Y*** is ²¹¹At or ¹⁸F.

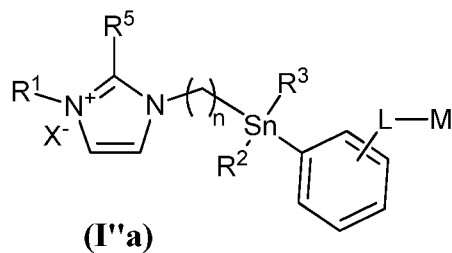
In one embodiment, the halogen **Y*** is a radiohalogen, preferably **Y*** is a radiohalogen selected from the group comprising ¹²⁵I, ¹³¹I, ¹²⁴I, ²¹¹At, ¹⁸F, more preferably **Y*** is ²¹¹At.

In one embodiment, the ionic liquid supported organotin reagent used in the labeling process of the invention is of formula (I'')



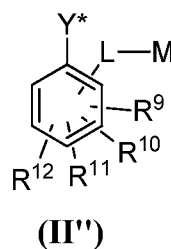
wherein X^- , n , R^1 , R^2 , R^3 , R^5 , $-L-M$, R^9 , R^{10} , R^{11} and R^{12} are as defined above.

- 5 In one embodiment, the ionic liquid supported organotin reagent used in the labeling process of the invention is of formula (I''a)



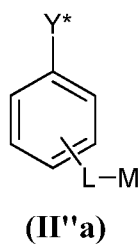
wherein X^- , n , R^1 , R^2 , R^3 , R^5 and $-L-M$ are as defined above.

In one embodiment, compound R^4-Y^* is of formula (II'')



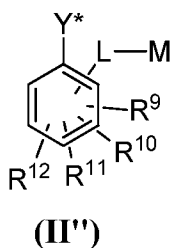
wherein Y^* , $-L-M$, R^9 , R^{10} , R^{11} and R^{12} are as defined above.

In one embodiment, compound **R⁴-Y*** is of formula (II''a)



wherein **Y*** and **-L-M** are as defined above.

The invention thus relates to a process for the synthesis of a compound of formula (II'')

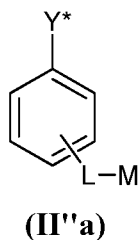


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wherein **Y***, **-L-M**, **R⁹**, **R¹⁰**, **R¹¹** and **R¹²** are as defined above

said process comprising performing a halodemallation by reacting an electrophilic reactant comprising halogen **Y***, with an ionic liquid supported organotin reagent (I'') to form compound of formula (II'').

- 10 According to one embodiment, the invention also relates to a process for the synthesis of a compound of formula (II''a)



wherein:

Y* represents a halogen, preferably a radiohalogen;

15

L represents a linker selected from single bond or a group selected from aryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl;

said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate;

said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

optionally additionally comprising a residue of a reactive group through which L is bounded to M;

M represents:

a hydrogen atom;

a reactive function selected from carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester such as for example ethyl or methyl ester, activated ester; alkyne, alcohol, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and azidoaryl;

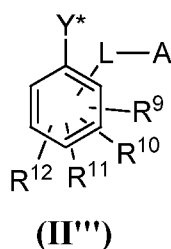
a bioactive group selected from amino acid, biogenic amine, peptide, affibody, protein, antibody or fragment thereof, antibody construct such as a for example minibody or, diabody, saccharide, polysaccharide, benzylguanine, biotine, dihydroxyphenylalanine, nucleotide, oligonucleotide, hapten, ligand, enzyme substrate, nanocarrier such as for example nanocapsule, liposome, dendrimer or carbon nanotube and derivatives and combinations thereof.

comprising:

reacting a halogen Y* with compound as defined above, to form compound of formula (II' a).

According to a preferred embodiment, in compound (II), M represents a reactive function, and the process further comprises a subsequent step of reacting compound (II)

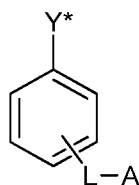
- with a vector selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate, nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube; said vector comprising at least one reactive function **B**; said reactive function **B** being able to react with the reactive function of compound (II), leading to the labeled vector (III).
- 10 According to a preferred embodiment, in compound (II), M represents a reactive function, and the process further comprises a subsequent step of reacting compound (II) with a vector selected from amino acid, biogenic amine, peptide, affibody, protein, antibody or fragment thereof, antibody construct such as a for example minibody or, diabody, saccharide, polysaccharide, benzylguanine, biotine, dihydroxyphenylalanine, nucleotide, oligonucleotide, hapten, ligand, enzyme substrate, nanocarrier such as for example nanocapsule, liposome, dendrimer or carbon nanotube and derivatives and combinations thereof; said vector comprising at least one reactive function **B**; said reactive function **B** being able to react with the reactive function of compound (II), leading to the labeled vector (III).
- 15
- 20 In one embodiment, compound **R⁴-Y*** is of formula (II''')



- wherein **Y***, **L**, **R⁹**, **R¹⁰**, **R¹¹** and **R¹²** are as defined above and **A** represents a reactive function selected from a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline,
- 25

amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl.

In one embodiment, compound **R⁴-Y*** is of formula (II''a)



(II''a)

5

wherein **Y*** and **L** are as defined above and **A** represents a reactive function selected from a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, 10 thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl.

According to a specific embodiment, **A** represents a reactive function selected from 15 carboxylic acid, primary amine, secondary amine, tertiary amine, carbamate, amide, maleimide, ester such as for example ethyl or methyl ester, activated ester such as for example succinimidyl, sulfosuccinimidyl, tetrafluorophenyl, pentafluorophenyl or nitrophenyl ester; alkyne, alcohol, aldehyde, nitrile, isocyanate, isothiocyanate, phosphine, protected phosphine, thiol, protected thiol, azide, sulphide, azidoalkyl and 20 azidoaryl.

*Electrophilic reactant for halodemallation by Y**

The labeling process of the invention comprises performing a halodemallation reaction by reacting an electrophilic reactant comprising halogen **Y*** with the ionic liquid of the invention.

In one embodiment, the electrophilic reactant involved in the halodemallation reaction is generated *in situ* in the reaction medium from a “starting reactant” comprising halogen Y*.

According to one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably a radiohalogen selected from the group comprising ^{18}F , ^{76}Br , ^{125}I , ^{131}I , ^{124}I , ^{123}I , ^{211}At , more preferably Y* is ^{211}At . When Y* is a radiohalogen, the “starting reactant” and/or the “electrophilic reactant” is radioactive and may be produced by irradiation and further treatments such as liquid or solid phase extraction, distillation, thermal diffusion potentially combined to recovery in a solvent or recovery in a solvent then treatment to obtain a dry residue and/or other purification method.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably ^{76}Br , ^{125}I , ^{131}I , ^{124}I , ^{211}At and the labeling process of the invention need the help of a catalyst selected in, but not limited to, the group of onium salts.

According to one embodiment, when Y* is bromine, preferably ^{76}Br , the electrophilic reactant may be Br_2 , (i.e. Br^+Br^- wherein half reacts).

According to another embodiment, when Y* is bromine, preferably ^{76}Br , the electrophilic reactant may be a species comprising $\text{Br}(+\text{I})$, such as for example BrCl .

According to another embodiment, when Y* is bromine, preferably ^{76}Br , the electrophilic reactant may be a species comprising $\text{Br}(+\text{I})$, such as for example BrCl , obtained by oxidation of a “starting reactant” which may be:

- a species comprising $\text{Br}(-\text{I})$, such as for example NH_4Br or HBr ; or
- a species comprising $\text{Br}(0)$, such as for example Br_2 ; or
- a mixture thereof.

According to one embodiment, the oxidation of the “starting reactant” is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, terbutylhydroperoxyde; in presence or not of a catalyst.

According to one embodiment, when Y* is Bromine, preferably ^{76}Br , the labeling process of the invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from, but not limited to
5 sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably ^{76}Br , and the labeling process of the invention is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T,
10 hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably ^{76}Br , and the labeling process of the invention is performed in presence or not of a catalyst.

15 According to one embodiment, when Y* is iodine, preferably ^{125}I , ^{131}I , ^{124}I or ^{123}I , the electrophilic reactant may be I_2 , (i.e. I^+T wherein half reacts).

According to another embodiment, when Y* is iodine, preferably ^{125}I , ^{131}I , ^{124}I or ^{123}I , the electrophilic reactant may be a species comprising $\text{I}(+\text{I})$, such as for example ICl . According to another embodiment, when Y* is iodine, preferably ^{125}I , ^{131}I , ^{124}I or
20 ^{123}I , the electrophilic reactant may be a species comprising $\text{I}(+\text{I})$, such as for example ICl , obtained by oxidation of a “starting reactant” which may be:

- a species comprising $\text{I}(-\text{I})$, such as for example NaI ; or
- a species comprising $\text{I}(0)$, such as for example I_2 ; or
- a mixture thereof.

25 According to one embodiment, the oxidation of the “starting reactant” is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

According to one embodiment, when Y* is iodine, preferably ^{125}I , ^{131}I , ^{124}I or ^{123}I , the labeling process of the invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from, but not
5 limited to sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably ^{125}I , and the labeling process of the invention is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide,
10 sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y* is a radiohalogen, preferably ^{125}I , and the labeling process of the invention is performed in presence or not of a catalyst.

In one embodiment, Y* is a radiohalogen, , preferably ^{125}I , the labeling process of the
15 invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the
20 invention, Y* is a radiohalogen, preferably ^{131}I , and the labeling process of the invention is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the
25 invention, Y* is a radiohalogen, preferably ^{131}I , and the labeling process of the invention is performed in presence or not of a catalyst.

In one embodiment, Y* is a radiohalogen, preferably ^{131}I , the labeling process of the invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be

performed in presence of a reducing agent selected from sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{124}I , and the labeling process of the invention
5 is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{124}I , and the labeling process of the invention
10 is performed in presence or not of a catalyst.

In one embodiment, Y^* is a radiohalogen, , preferably ^{124}I , the labeling process of the invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from sodium metabisulfite, sodium
15 sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{123}I , and the labeling process of the invention is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide,
20 sodium hypochlorite, tertbutylhydroperoxyde; in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{123}I , and the labeling process of the invention is performed in presence or not of a catalyst.

In one embodiment, Y^* is a radiohalogen, preferably ^{123}I , the labeling process of the invention may comprise a step of reduction after the substitution with tin supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from sodium metabisulfite, sodium
25 sulfite, cysteine or dithiothreitol.

Relative to astatine, it should be noted that the form of the species comprising ^{211}At is not well known in the art. It may be At^- , $\text{At}(0)$ (but it is not determined if it is under the form of molecular At or At_2), At^+ , AtO^- , AtO^+ or a complex formed by these species with solvent, or a mixture thereof. Compositions and proportions of such mixtures
 5 depend from experimental conditions used to produce ^{211}At , such as for example the method of extraction, solvents, additives, contaminants present in the solvent, moisture content, radiolysis rate. These species are disclosed in Champion J et al, J Phys Chem A. 2013;117(9):1983-90; A. Serov et al., Radiochimica Acta 2011, 99 (9) , 593; C. Alliot et al., Radiochim. Acta 2009, 97, 161; O. R. Pozzi et al., J Nucl Med July 2007,
 10 48, 1190; O. R. Pozzi et al., J Nucl Med 2005, 46, 1393; Visser, G. W., Radiochim. Acta 47, 97 (1989); Visser, G. W., Diemer, E. L.: Radiochim. Acta 1983, 33, 145; J. Champion et al., J. Phys. Chem. A 2009, 114, 576.

The formation of complexes between astatine species and solvent as described in Visser, G. W.: Radiochim. Acta 47, 97 (1989); Visser, G. W., Diemer, E. L.:
 15 Radiochim. Acta 1983, 33, 145; C. Alliot et al., Radiochim. Acta 2009, 97, 161.

According to one embodiment, when Y^* is astatine, preferably ^{211}At , the electrophilic reactant may be At_2 , (i.e. At^+At^-) wherein half reacts).

According to one embodiment, when Y^* is astatine, preferably ^{211}At , the electrophilic reactant may be a species comprising $\text{At}(+\text{X})$, wherein X may be equal to 1 (At^+) or
 20 equal to 3 (AtO^+), such as for example AtCl , AtI , AtBr , AtNO_3 , AtClO_4 , AtSO_4Na , AtSO_4K , AtOH , AtOCl , AtOBr , AtOI , or complexes formed by these species with solvent.

According to an embodiment, when Y^* is astatine, preferably ^{211}At , the electrophilic reactant may be a species comprising $\text{At}(+\text{I})$, such as for example AtCl or AtI , obtained
 25 by oxidation of a “starting reactant” which may be:

- a species comprising $\text{At}(-\text{I})$, such as for example AtNa , AtK or complexes formed by these species with solvent; or
- a species comprising $\text{At}(0)$, such as for example molecular $\text{At}(0)$, At_2 or complexes formed by these species with solvent; or
- 30 - a mixture thereof.

According to another embodiment, when Y^* is astatine, preferably ^{211}At , the electrophilic reactant may be a species comprising $\text{At}(+\text{III})$ AtOCl AtOBr , AtOI , or complexes formed by these species with solvent.

Such electrophilic reactants may be obtained from “starting reactants” which may be:

- 5 - a species comprising $\text{At}(-\text{I})$, such as for example AtNa , AtK or complexes formed by these species with solvent; or
- a species comprising $\text{At}(0)$, such as for example $\text{At}(0)$, At_2 or complexes formed by these species with solvent; or
- a species comprising $\text{At}(+\text{I})$ such as for example AtCl , AtI , AtBr , AtNO_3 ,
10 AtClO_4 , AtSO_4Na , AtSO_4K , AtCl_2Na , AtBr_2Na , AtI_2Na , AtONa , AtOK , AtOH ,
 or complexes formed by these species with solvent; or
- a mixture thereof.

According to one embodiment, the oxidation of the “starting reactant” is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-
15 iodosuccinimide (NIS), N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; potassium dichromate in presence or not of a catalyst.

According to one embodiment, when Y^* is astatine, preferably ^{211}At , the labeling process of the invention may comprise a step of reduction after the substitution with tin
20 supported by the ionic liquid of the invention. According to one embodiment, reduction may be performed in presence of a reducing agent selected from, but not limited to sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{211}At , and the labeling process of the
25 invention is performed in presence of an oxidizing agent selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde; potassium dichromate in presence or not of a catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{211}At , and the labeling process of the invention is performed in presence or not of a catalyst.

According to one embodiment, when Y^* is fluorine, preferably ^{18}F , the electrophilic reactant may be a species comprising $\text{F}(+\text{I})$, such as for example FOAc or F18-selectfluor and its derivatives.

Such electrophilic reactants may be obtained from a “starting reactant” which may be:

- a species comprising $\text{F}(-\text{I})$, such as for example KF ; or
- a species comprising $\text{F}(0)$, such as for example F_2 ; or
- a mixture thereof.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{18}F and the labeling process of the invention need the help of a catalyst selected in, but not limited to, the group of copper, nickel, palladium and silver complexes.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{18}F , and the labeling process of the invention is performed with or without catalyst and any chemical species including $[\text{}^{18}\text{F}]\text{F}(+\text{I})$ in their structure such species are described in, but not limited to, Nyffeler, et al., *Angew. Chem. Int. Ed.*, 2005, 44, 192 – 212; Yingda et al., *JACS*, 2013, 135(12), 4648-4651; Stenhagen et al., *Chem. Comm.*, 2013, 49(14), 1386; Eskola et al., *Eur. J. Nucl. Med. Mol. Im.*, 2012, 39, (5), 800-810; Furuya et al., *JACS*, 2009, 131(5), 1662-1663; Eskola et al., *Nucl. Med. Biol.*, 2004, 31(1), 103-110; Fischer et al., *Forschungszentrum Rossendorf e.V., [Bericht]*, 1997, 200, 174-176; Namavari et al., *Appl. Rad. Isotopes*, 1993, 44(3), 527-536; Tius et al., *Synth. Comm.*, 1992, 22(10), 1461-1471; Bryce, Martin et al., *Bulletin de la Société Chimique de France*, 1986, 939-932 ; Adam et al., *J. Fluorine Chem.*, 1984, 25 (3), 329-337; US 5510522; WO 2010059943; WO 2001027122; DE 19928911.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{18}F , and the labeling process of the invention is performed with $[\text{}^{18}\text{F}]\text{F}_2$; with or without catalyst.

In one embodiment, in the electrophilic reactant used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{18}F , and the labeling process of the invention is performed with $[^{18}F]F^-$ in the presence of an oxidizing agent selected in, but not limited to, the group of hypervalent iodine species, with or without catalyst such as
5 described in Geary et al., Chem. Comm., 2013, 49, 9263-9265; Lee et al., JACS., 2012, 134, 17456-17458 ; Lee et al., Science 2011, 334, 639-642.

In one embodiment, in the electrophilic reactant comprising halogen Y^* used in the labeling process of the invention, Y^* is a radiohalogen, preferably ^{18}F , and the labeling process of the invention is performed with $[^{18}F]F_2$ in presence of, but not limited to,
10 acetate, perchlorate, triflate salts, Selectfluor salts and their derivatives; with or without catalyst. Selectfluor refers to 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

In another embodiment, the labeling process of the invention is performed without adding an oxidizing agent and in presence of a catalyst. In an alternative embodiment,
15 the labeling process of the invention is performed without adding an oxidizing agent and in the absence of catalyst.

In another embodiment, a reducing agent is added at the end of the reaction. The reducing step is performed in the presence of, but not limited to, sodium sulfite, sodium metabisulfite, cysteine or dithiothreitol. In another embodiment, the labeling process is
20 performed without using a reducing agent.

According to one embodiment, compound (II) obtained by the labeling process of the invention is easily separated from the reaction medium by filtration on a silica cartridge, preferably on normal phase silica cartridge.

According to another embodiment, compound (II) obtained by the labeling process of
25 the invention is easily separated from the reaction medium by filtration on a silica cartridge, preferably on C18 grafted silica cartridge.

According to one embodiment, compound (II) obtained by the labeling process of the invention is easily separated from the reaction medium by liquid/liquid extraction and recovered in the aqueous phase.

5 According to one embodiment, compound (II) obtained by the labeling process of the invention is easily separated from the reaction medium by liquid/liquid extraction and recovered in the organic phase.

In one embodiment, the labeling process of the invention comprises the following steps:

- adding the ionic liquid supported organotin reagent (I) of the invention solubilized in a solvent;
- 10 - adding an oxidizing agent solubilized in a solvent; and
- adding the Y^* reactant solubilized in a solvent.

In another embodiment, the labeling process of the invention comprises the following steps:

- adding the ionic liquid supported organotin reagent (I) of the invention solubilized in a solvent; and
- 15 - adding the Y^* reactant solubilized in a solvent.

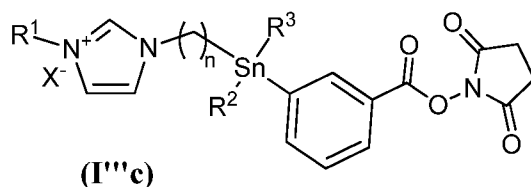
In an embodiment, the solvent used in the labeling process of the invention is selected from methanol, ethanol, acetonitrile, diisopropyl ether, diethyl ether, dimethylformamide, dimethylsulfoxide, ethyl acetate, dichloromethane, dichloroethane, chloroform, aqueous solutions, acetic acid, a ionic liquid or a mixture of these solvents.

20 In an embodiment, the solvent used in the labeling process of the invention is selected from methanol, acetonitrile, diisopropyl ether, dichloromethane, chloroform, aqueous solutions, acetic acid or a mixture of these solvents.

25 In another embodiment, the labeling process of the invention comprises adding the ionic liquid supported organotin reagent (I) of the invention solubilized in a solvent and an oxidizing agent solubilized in a solvent to the Y^* reactant (dry residue).

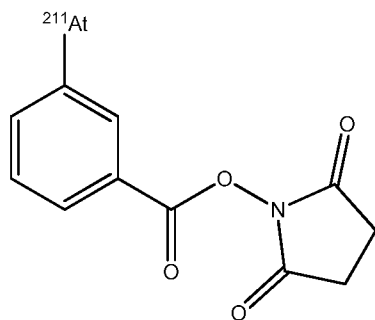
In another embodiment, the labeling process of the invention comprises adding the ionic liquid supported organotin reagent (I) of the invention solubilized in a solvent to the **Y*** reactant (dry residue).

In a preferred embodiment, the labeling process of the invention comprises reacting an
 5 electrophilic reactant comprising ^{211}At , with an ionic liquid supported organotin reagent (**I'''c**)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above;

to form radiolabeled succinimidyl astatobenzoate (SAB) of formula [^{211}At]-II-1



10

In a specific embodiment, the labeling process of the invention comprises the following steps:

- adding a starting reactant comprising astatine-211 solubilized in methanol;
- adding N-chlorosuccinimide (NCS) solubilized in Methanol/Acetic Acid (95:5); and
- 15 - adding the ionic liquid supported organotin reagent (I) of the invention solubilized in Methanol/Acetic Acid (95:5).

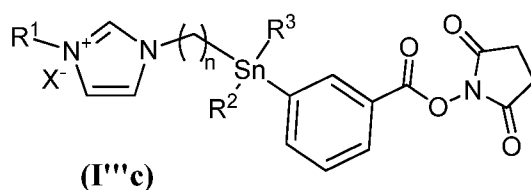
In this embodiment, the starting reactant comprising astatine-211 is oxidized by NCS to form the electrophilic reactant comprising astatine-211.

In a specific embodiment, the labeling process of the invention comprises the following steps:

- adding the ionic liquid supported organotin reagent (I) of the invention solubilized in Methanol/Acetic Acid (95:5); and
- 5 - adding the electrophilic reactant comprising astatine-211 solubilized in methanol.

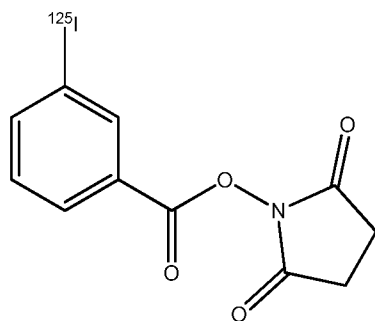
According to one embodiment the labeling reaction is performed at a temperature ranging from 15°C to 100°C, preferably at room temperature, for a period of time ranging from 1 to 90 minutes, preferably for 30 minutes.

- 10 In a preferred embodiment, the labeling process of the invention comprises reacting an electrophilic reactant comprising ^{125}I with an ionic liquid supported organotin reagent (I''c)



wherein X^- , n , R^1 , R^2 and R^3 are as defined above;

to form radiolabeled succinimidyl iodobenzoate (SIB) of formula [^{125}I]-II-1



15

In a specific embodiment, the labeling process of the invention comprises the following steps:

- adding a starting reactant comprising Iodine-125 solubilized in aqueous sodium hydroxide (pH 7 to 13);
- 20 - adding N-chlorosuccinimide NCS solubilized in Methanol/Acetic Acid (95:5); and

- adding the ionic liquid supported organotin reagent (I) of the invention solubilized in Methanol/Acetic Acid (95:5).

In this embodiment, the starting reactant comprising iodine-125 is oxidized by NCS to form the electrophilic reactant comprising iodine-125.

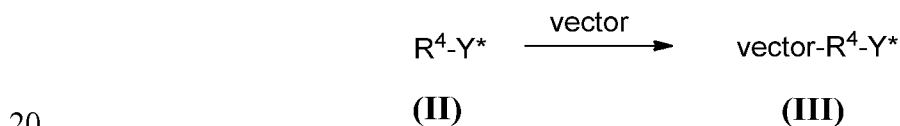
5 In another particular embodiment, the labeling process of the invention comprises the following steps:

- adding the ionic liquid supported organotin reagent (I) of the invention solubilized in Methanol/Acetic Acid (95:5); and
- adding the electrophilic reactant comprising Iodine-125 solubilized in aqueous
10 sodium hydroxide (pH 7 to 13).

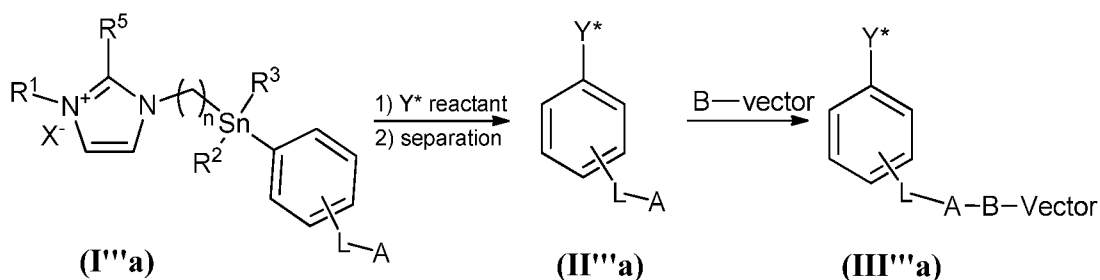
2) Labeling of a vector to form a radiopharmaceutical

When compounds of formula (II) (R^4-Y^*) obtained by the labeling process of the invention comprise a radiohalogen and at least one functional group having targeting properties, they are directly considered as radiopharmaceuticals. This is especially the
15 case when R^4 is substituted by $-L-M$ wherein M is a bioactive group.

When compounds of formula (II) (R^4-Y^*) obtained by the labeling process of the invention comprise a radiohalogen and at least one reactive function, they may be considered as radiolabeled precursors and they may be used as reactant to label a vector to form a radiopharmaceutical (III) as schematically represented below:



According to a specific embodiment, the ionic liquid reagent is of formula (I''a), leading to compound (II''a) comprising a reactive function, enabling the coupling with a vector (i.e. bioactive group), through the reaction with a reactive function **B** of said vector:



5

wherein A and B represent reactive functions

According to one embodiment, in radiopharmaceutical (III''a), -A-B- represents the residue of coupling between reactive function A and reactive function B.

In one embodiment, the present invention relates to the radiolabelling of a compound of formula (I) to form a compound of formula (II) bearing one reactive function and coupling the resulting compound to a vector to form a radiopharmaceutical (III).

In another embodiment, the present invention relates to the radiolabelling of a compound of formula (I) to form a compound of formula (II) bearing one protected reactive function and, after deprotection of said reactive function, coupling the resulting compound to a vector to form a radiopharmaceutical (III).

In another embodiment, the present invention relates to the radiolabelling of a compound of formula (I) to form a compound of formula (II) bearing one reactive function and, after activation of said reactive function, coupling the resulting compound to a vector to form a radiopharmaceutical (III).

Coupling of compound (II) to the vector may be performed methods well known by one skilled in the art, and are for example described in: Wong et al., CRC press 2011 (NY), 604; Benoiton et al. WORKBENCH EDITION; Basle et al., Chemistry & Biology (2010), Volume 17, Issue 3, 213-227; Sletten et al., Angew. Chem. Int. Ed. (2009), 48, 6974-6998; Liu et al. Advanced Drug Delivery Reviews (2008), 60 (12), 1347-1370;

Wu et al. Nat Biotechnol 2005, 23:1137-1146; Fritzberg et al., Pharmaceutical Research (1988), 5 (6), 325-334.

Automated device

The present invention further relates to a device for implementing the labeling process of the invention comprising at least one automaton of synthesis comprising at least:

- controlling means;
- a vacuum system;
- one reaction vessel;
- a purification cartridge;
- 10 - at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising ionic liquid organotin reagent (I) of the invention;
- at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel containing an electrophilic reactant comprising
15 halogen Y^* , or directly connected at the other end to an arrival of an electrophilic reactant comprising halogen Y^* or a precursor thereof (distillation apparatus or production line);
- optionally at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising an oxidizing agent;
- 20 - at least one line connected at one end to the reaction vessel and at the other end to the top of the purification cartridge;
- at least one output line connected at one end to the bottom end of the purification cartridge, the other end enabling to recover compound (II) of the invention;
- optionally a line connected to an inert gas arrival.

25 According to one embodiment, the device for implementing the labeling process of the invention further optionally comprises a heater and/or an inert gas arrival.

In one embodiment, the device for implementing the labeling process of the invention further optionally comprises a second automaton including at least:

- controlling means;

- a vacuum system;
- one reaction vessel;
- a purification cartridge;
- at least one input line connected at one end to the output line of the first automaton
5 and at the other end to the reaction vessel to introduce compound (II) of the invention in the second automaton;
- at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising the vector;
- at least one line connected at one end to the reaction vessel and at the other end to a
10 storage vessel, said storage vessel comprising an aqueous solvent;
- at least one line connected at one end to the reaction vessel and at the other end to the top of the purification cartridge;
- at least one line connected at one end to the bottom end of the purification cartridge, the other end enabling to recover compound (III) of the invention;
- 15 - optionally a line connected to an inert gas arrival.

According to one embodiment, the second automaton further optionally comprises a heater and/or an inert gas arrival.

A device comprising two automatons according to the invention is represented in Figure 1.

- 20 In an embodiment, lines and connections are compatible with the use of organic solvent, preferably ethyl acetate, heptane, hexane, cyclohexane, acetone, methanol, acetonitrile, diisopropyl ether, dichloromethane, chloroform, acetic acid, or a mixture thereof.

Kit of parts

- 25 The present invention further relates to a kit comprising an ionic liquid supported organotin reagent (I) of the invention.

According to one embodiment, the kit of the invention comprises an ionic liquid supported organotin reagent (I) of the invention and an oxidizing agent. In one

embodiment, the oxidizing agent is selected from the group comprising N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde, potassium dichromate more preferably N-chlorosuccinimide.

- 5 According to one embodiment, the kit of the invention comprises an ionic liquid supported organotin reagent (I) of the invention and an oxidizing agent. In one embodiment, the oxidizing agent is selected from the group comprising N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, tertbutylhydroperoxyde, more preferably N-chlorosuccinimide.
- 10 chlorosuccinimide.

According to one embodiment, the kit of the invention further comprises a selectfluor, acetate or triflate salt, more preferably selectfluor salt.

According to one embodiment, the kit of the invention further comprises a metallic catalyst.

- 15 According to one embodiment, the kit of the invention further comprises a selectfluor, acetate or triflate salt and a metallic catalyst.

According to one embodiment, the kit of the invention further comprises a reducing agent. In one embodiment, the reducing agent is selected from sodium sulfite, sodium metabisulfite, cysteine and dithiothreitol.

20

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a scheme representing a synthesis device comprising two automatons to implement the labeling process of the invention.

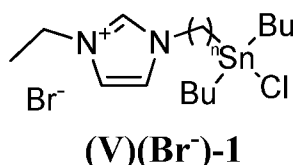
25 EXAMPLES

The present invention is further illustrated by the following examples.

Material

Commercially available reagents and solvents were purified and dried, when necessary, by standard methods prior to use. ^1H (300 MHz), ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300 spectrometer or on a Bruker Avance 400 spectrometer. The compounds studied were measured in CDCl_3 and ^1H and ^{13}C chemical shifts, reported in ppm, were referred to the central signal of the solvent. ^{13}C NMR spectra were recorded with complete proton decoupling. The ^{119}Sn NMR spectra were recorded on a Bruker Avance 400 spectrometer (149 MHz) and chemical shifts were referred to external tetramethylstannane. High resolution mass spectra measurements were recorded on Waters-Micromass GCT Premier spectrometers. Analytical thin layer chromatography was performed on pre-coated silica gel 60-F254 plates.

I. Synthesis of ionic liquid



The synthesis of the ionic liquid **(V)(Br⁻)-1** is described in Louaisil et al. Eur. J. Org. Chem. 2011, 143-149.

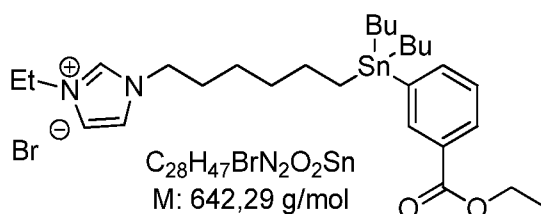
II. Synthesis of ionic liquid supported organotin reagents (I)

General method

A dried Schlenk tube is flushed with argon and charged with zinc dust (Aldrich Zinc dust <10 μm , 1.36 g, 20.8 mmol, 5 eq) and cobalt(II) bromide (0.095 g, 0.416 mmol, 0.1 eq). The mixture is activated under vacuum at 200°C during 12 h. Acetonitrile (3 mL) is added to the cooled mixture under argon atmosphere then 1,2-dibromoethane (0.10 mL) is added and the resulting solution is stirred for additional 15 minutes (gas evolution and an increase of temperature are observed). Then arylbromide (6.36 mmol, 6.3 eq) is introduced to the mixture which is stirred at room temperature for 12 h. The

resulting solution of arylzinc reagent is introduced dropwise to the ionic liquid (V)(Br⁻)-1 (529 mg, 1.0 mmol, 1 eq) in solution in THF (6 mL). After 18 h of stirring 10 at room temperature, the resulting mixture is filtered through a short pad of silica gel then extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers are dried over
5 MgSO₄ and concentrated under reduced pressure. The crude product is purified by silica gel chromatography.

1-(6-(dibutyl(3-(ethoxycarbonyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide I-14(Br⁻)

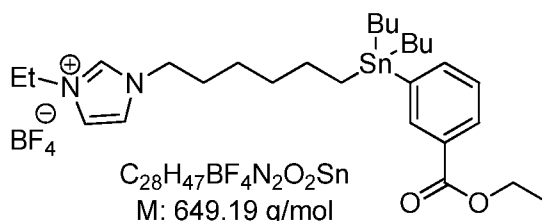


10 Compound **I-14(Br⁻)** was obtained using general method described above, using ethyl 3-bromobenzoate as arylbromide.

Alternatively, the following conditions were also used. A dried 50 mL Schlenk tube was flushed with argon and charged with zinc dust (1.36 g, 20.8 mmol, 5 eq) and cobalt(II) bromide (0.095 g, 0.419 mmol, 0.1 eq). The mixture was activated under vacuum at
15 150°C during 4 h. Acetonitrile (5 mL) was added to the cooled mixture then trifluoroacetic acid (0.15 mL) and 1,2-dibromoethane (0.1 mL) were added and the resulting solution stirred for additional 15 minutes (an increase of temperature was observed). Then ethyl 3-bromobenzoate (1.46 g, 6.36 mmol, 6.3 eq) was introduced to the mixture which was stirred at room temperature for 12 h. The resulting solution of
20 arylzinc reagent was introduced dropwise to the ionic liquid (V)(Br⁻)-1 (529 mg, 1.0 mmol, 1 eq) in solution in THF (6 mL). After 18 h of stirring at room temperature, the resulting mixture was filtered through a short pad of silica gel then extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica gel
25 chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) to afford compound **I-14(Br⁻)** as viscous yellow oil (450 mg, 70 %).

¹H NMR (CDCl₃): δ 10.17 (s, 1H), 8.14 (bs, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.39 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H), 7.30 (bs, 1H), 7.23 (bs, 1H), 4.48-4.33 (m, 4H), 4.32 (t, 2H, J = 7.2 Hz), 1.89-1.78 (m, 2H), 1.61-1.47 (m, 9H), 1.42-1.24 (m, 11H), 1.13-1.00 (m, 6H), 0.87 (t, J = 7.2 Hz, 6H). ¹³C NMR 75 MHz (CDCl₃) δ (ppm): 166.8, 141.9, 140.6, 136.9, 135.9, 129.4, 128.8, 127.5, 122.0, 121.8, 60.6, 49.8, 45.1, 33.4, 30.0, 28.7, 27.0, 26.3, 25.5, 15.5, 14.4, 13.4, 9.4, 9.3. HRMS (FAB) calcd. for C₂₈H₄₇N₂O₂Sn 563.2654 [M-Br]⁺; found 563.2675.

1-(6-(dibutyl(3-(ethoxycarbonyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium tetrafluoroborate I-14(BF₄⁻)



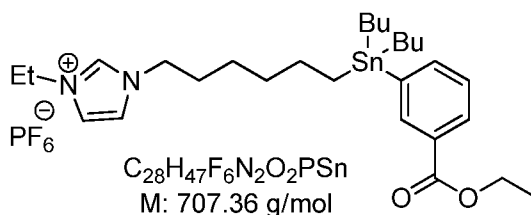
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Compound **I-14(Br⁻)** (50 mg, 0.078 mmol, 1eq) was dissolved in acetone (4 ml) and stirred with NaBF₄ (17 mg, 0.155 mmol, 2 eq) at room temperature for 24 h to exchange the anion. The reaction mixture was filtered off to remove precipitated NaBr and excess of NaBF₄ and the acetone was evaporated under reduced pressure. The crude product was purified by silica gel chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 95:05 to 90:10 to) to afford compound **I-14(BF₄⁻)** as viscous yellow oil (42 mg, 83%).

¹H NMR (CDCl₃): δ 9.26 (s, 1H), 8.14 (bs, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.42 (dd, J = 7.2 Hz, J = 7.2 Hz, 1H), 7.35 (bs, 1H), 7.28 (bs, 1H), 4.44-4.30 (m, 4H), 4.21 (t, J = 7.4 Hz, 2H), 1.93-1.80 (m, 2H), 1.75-1.65 (m, 2H), 1.63-1.49 (m, 7H), 1.45-1.28 (m, 13H), 1.15-1.03 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). ¹³C NMR 75 MHz (CDCl₃) δ (ppm): 167.3, 142.3, 141.0, 137.3, 136.3, 129.7, 129.2, 127.8, 121.9, 121.6, 60.9, 50.2, 45.4, 33.6, 30.1, 29.1, 27.4, 26.6, 25.7, 15.3, 14.4, 13.7, 9.6 (2C). HRMS (FAB) calcd. for C₂₈H₄₇N₂O₂Sn 563.2654 [M-BF₄]⁺; found 563.2655.

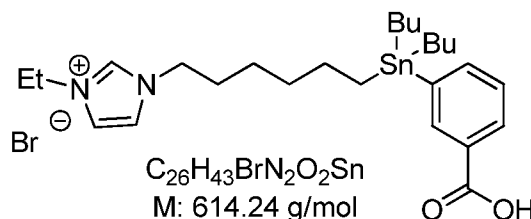
20

1-(6-(dibutyl(3-(ethoxycarbonyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium hexafluorophosphate I-14(PF₆⁻)



- Compound **I-14(Br⁻)** (150 mg, 0.233 mmol, 1eq) was dissolved in acetone (4 ml) and stirred with NaPF₆ (78 mg, 0.464 mmol, 2 eq) at room temperature for 24 h to exchange the anion. The reaction mixture was filtered and the acetone was evaporated under reduced pressure. The crude product was purified by silica gel chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) to afford compound **I-14(PF₆⁻)** as viscous yellow oil (156 mg, 94%).
- ¹H NMR (CDCl₃): δ 9.51 (bs, 1H), 8.15 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.42 (dd, J = 7.2 Hz, J = 7.2 Hz, 1H), 7.26 (bs, 1H), 7.22 (bs, 1H), 4.51-4.31 (m, 6H), 1.95-1.77 (m, 4H), 1.62-1.50 (m, 8H), 1.45-1.28 (m, 12H), 1.14-1.06 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). ¹³C NMR 75 MHz (CDCl₃) δ (ppm): 167.3, 142.3, 141.0, 137.3, 136.5, 129.7, 129.1, 127.9, 121.8, 121.4, 61.0, 50.4, 45.6, 33.7, 30.2, 29.1, 27.4, 26.6, 25.8, 15.6, 14.4, 13.8, 9.7, 9.6. HRMS (FAB) calcd. for C₂₈H₄₇N₂O₂Sn 563.2654 [M-PF₆]⁺; found 563.2655.

1-(6-(dibutyl(3-carboxyphenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide I-2(Br⁻)

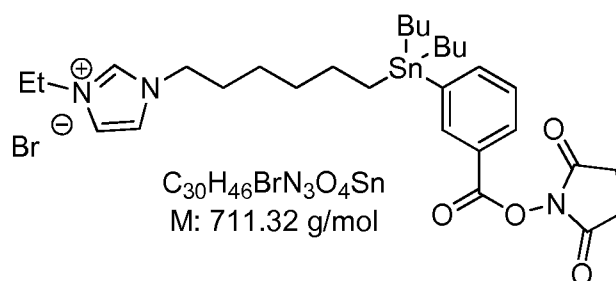


- To a solution of 600 mg of compound **I-14(Br⁻)** (0.934 mmol, 1 eq) in ethanol (5 mL) were added 0.97 mL of an aqueous solution of NaOH (15% w/w). The resulting mixture

was stirred for 20 min at room temperature, then refluxed 2 h and the ethanol was removed under reduced pressure. The residue was acidified with 3 mL of HCl 1M, and then extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product **I-2(Br⁻)** was used
 5 without purification in the next step (520 mg, 90%).

HRMS (FAB) calcd. for C₂₆H₄₃N₂O₂Sn 535.2341 [M-Br]⁺; found 535.2336.

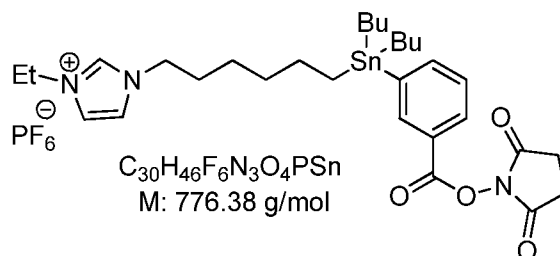
1-(6-(dibutyl(3-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide I-1(Br⁻)



10 A mixture of compound **I-14(Br⁻)** (510 mg, 0.83 mmol, 1 eq), N-hydroxysuccinimide (105 mg, 0.913 mol, 1.1 eq.) and DCC (188 mg, 0.913 mol, 1.1 eq) in dry THF (10 mL) was stirred for 12h at room temperature under argon. The reaction mixture was filtered and the residue was concentrated under reduced pressure. The corresponding product **I-1(Br⁻)** was purified by silica gel chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 98:02 to
 15 90:10) to afford yellow oil (371 mg, 63%).

¹H NMR (CDCl₃): δ 9.83 (s, 1H), 8.20 (bs, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, J = 7.5 Hz, 1H), 7.36 (bs, 1H), 7.22 (bs, 1H), 4.48-4.26 (m, 4H), 2.96 (s, 4H), 1.75-1.62 (m, 2H), 1.58-1.44 (m, 7H), 1.38-1.23 (m, 12H), 1.13-1.04 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). ¹³C NMR 75 MHz
 20 (CDCl₃) δ (ppm): 169.7, 162.5, 143.5, 143.1, 138.0, 136.6, 130.1, 128.3, 124.4, 122.2, 121.8, 50.1, 45.4, 33.6, 29.0, 28.2, 27.3, 26.9, 25.9, 20.4, 15.7, 13.8, 13.7, 9.7, 9.6.
 HRMS (FAB) calcd. for C₃₀H₄₆N₃O₄Sn 632.2505 [M-Br]⁺; found 632.2522.

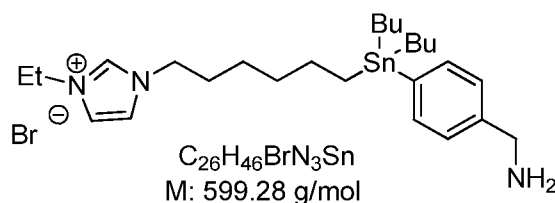
1-(6-(dibutyl(3-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium hexafluorophosphate I-1(PF₆⁻)



Compound **I-1(Br⁻)** (110 mg, 0.154 mmol, 1eq) was dissolved in acetone (4 ml) and stirred with NaPF₆ (52 mg, 0.308 mmol, 2 eq) at room temperature for 24 h to exchange the anion. The reaction mixture was filtered and the acetone was evaporated under reduced pressure. The crude product was purified by silica gel chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) to afford compound **I-1(PF₆⁻)** as viscous yellow oil (81 mg, 67%).

¹H NMR (CDCl₃): δ 8.59 (bs, 1H), 8.18 (bs, 1H), 8.03 (dm, J = 7.8 Hz, 1H), 7.77 (dm, J = 7.2 Hz, 1H), 7.47 (dd, J = 7.2 Hz, J = 7.2 Hz, 1H), 7.27 (bs, 1H), 7.17 (bs, 1H), 4.26 (q, J = 7.5 Hz, 2H), 4.11 (t, J = 7.5 Hz, 2H), 2.97 (s, 4H), 1.82-1.46 (m, 10H), 1.43-1.28 (m, 11H), 1.17-1.07 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H). HRMS (FAB) calcd. for C₃₀H₄₆N₃O₄Sn 632.2505 [M-PF₆]⁺; found 632.2484.

1-(6-((4-(aminomethyl)phenyl)dibutylstannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide I-4(Br⁻)

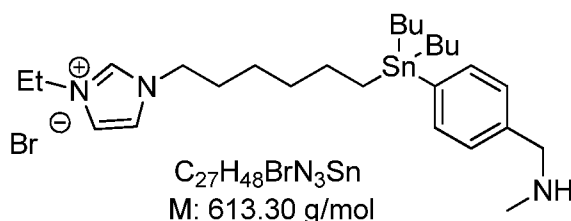


Compound **I-4(Br⁻)** was obtained using general method described above, using 4-bromophenyl)methanamine as arylbromide.

Alternatively, compound **I-4(Br⁻)** was obtained according to the procedure of the synthesis of compound **I-14(Br⁻)** and starting from (4-bromophenyl)methanamine (513 mg, 2.76 mmol, 4.9 eq) and ionic liquid **(V)(Br⁻)-1** (300 mg, 0.568 mmol, 1 eq) in dry THF (4 mL). The crude product was filtered and solvent was removed under reduced pressure. The residue was extracted with Et₂O to remove the excess then CH₂Cl₂ to afford crude compound **I-4(Br⁻)** as viscous yellow oil (490 mg).

¹H NMR (CDCl₃): δ 9.89 (s, 1H), 8.26-8.04 (m, 2H), 7.63-7.56 (m, 2H), 7.44-7.30 (m, 2H), 7.2 (bs, 1H), 7.19 (bs, 1H), 4.41 (q, J = 7.5 Hz, 2H), 4.32 (t, J = 7.2 Hz, 2H), 4.25-4.12 (m, 2H), 1.92-1.75 (m, 2H), 1.62-1.39 (m, 8H), 1.37-1.20 (m, 10H), 0.88 (t, J = 7.2 Hz, 6H), 0.83-0.71 (m, 5H). MALDI calcd. for C₃₂H₅₄N₃Sn 520.27 [M-Br]⁺; found 520.50.

1-(6-(dibutyl(4-((methylamino)methyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium bromide I-15(Br⁻)



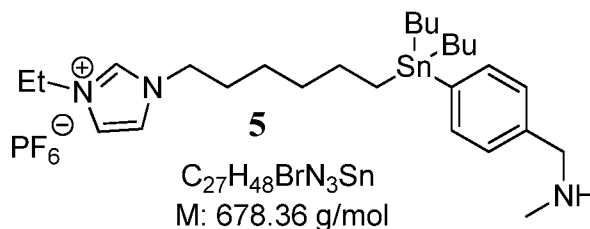
Compound **I-15(Br⁻)** was obtained using general method described above, using 1-(4-bromophenyl)-N-methylmethanamine as arylbromide.

Alternatively, compound **I-15(Br⁻)** was obtained According to the procedure of the synthesis of compound **I-14(Br⁻)** and starting from 1-(4-bromophenyl)-N-methylmethanamine (350 mg, 1.75 mmol, 3.1 eq) and ionic liquid **(V)(Br⁻)-1** (300 mg, 0.568 mmol, 1 eq).in dry THF (4 mL). The crude product was filtered and solvent was removed under reduced pressure. The residue was extracted with Et₂O to remove the excess then CH₂Cl₂ to afford compound **I-15(Br⁻)** as viscous yellow oil (350mg, 92%).

¹H NMR (CDCl₃): δ 9.62 (s, 1H), 7.48-7.42 (m, 2H), 7.39-7.33 (m, 2H), 7.24-7.20 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.21 (t, J = 7.2 Hz, 2H), 4.05-3.87 (m, 2H), 2.52 (s, 3H),

1.83-1.70 (m, 2H), 1.61-1.47 (m, 8H), 1.38-1.22 (m, 10H), 1.07-0.96 (m, 5H), 0.87 (t, J = 7.2 Hz, 6H). ^{13}C NMR 75 MHz (CDCl_3) δ (ppm): 136.7, 136.4, 131.6, 130.2, 128.9, 121.8, 121.5, 54.7, 50.2, 45.5, 34.7, 33.1, 30.1, 29.0, 27.3, 26.4, 25.7, 15.5, 13.7, 9.6, 9.5. HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{48}\text{N}_3\text{Sn}$ 534.2865 $[\text{M}-\text{Br}]^+$; found 534.2846.

5 ***1-(6-(dibutyl(4-((methylamino)methyl)phenyl)stannyl)hexyl)-3-ethyl-1H-imidazol-3-ium hexafluorophosphate I-15(PF₆⁻)***



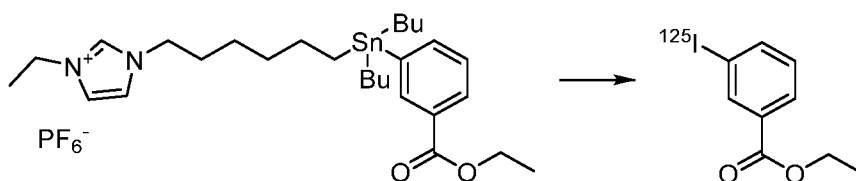
Compound **I-15(Br⁻)** (320 mg, 0.522 mmol, 1 eq) was dissolved in acetone (5 ml) and stirred with NaPF_6 (175 mg, 1.04 mmol, 2 eq) at room temperature for 24 h to exchange the anion. The reaction mixture was filtered; the acetone was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 to afford crude compound **I-15(PF₆⁻)** as viscous yellow oil (325mg).

HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{48}\text{N}_3\text{Sn}$ 534.2865 $[\text{M}-\text{PF}_6]^+$; found 534.2874.

III. Halodemetallation reaction

15 ***125-Iodide***

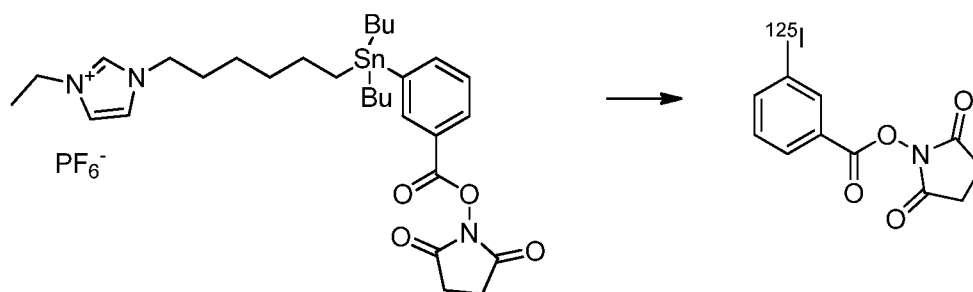
Synthesis of ethyl 3-[I-125]iodobenzoate [I-125]-II-2



To NaI (1 μl , 26 nmol. including 1.2 pmol (100 kBq) of $[\text{I}-125]\text{NaI}$) in NaOH 0.048 M was added NCS (8.7 μl , 130 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 21°C. **I-14(PF₆⁻)** (20 μl , 130 nmol) in MeOH/AcOH (95/5) was then added.

After 5 minutes stirring, the radioiodinated ethyl iodobenzoate [^{125}I]-II-2 was obtained (93% radiochemical yield (RCY)). The solution was evaporated to dryness and the crude product was recovered in 400 μl of Diethyl ether. After filtration using a silica gel cartridge and Diethyl ether as eluant, the product [^{125}I]-II-2 was obtained with a good radiochemical purity.

Synthesis of succinimidyl 3-[I-125]iodobenzoate [¹²⁵I]-II-1



To NaI (1 μ l, 46.2 pmol (3,5 MBq) of [I-125]NaI) in NaOH 0.048 M was added NCS (8 μ l, 130 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 21°C. **I-1(PF₆⁻)** (20 μ l, 26 nmol) in MeOH/AcOH (95/5) was then added. After 30 minutes stirring, the radioiodinated succinimidyl iodobenzoate was obtained (67 % radiochemical yield (RCY)). The solution was evaporated to dryness and the crude product was recovered in 400 μ l of Diethyl ether. After filtration using a silica gel cartridge and Diethyl ether as eluant, the product was obtained with a good radiochemical purity. Volatiles were evaporated under argon and the purified [¹²⁵I]-II-1 (commonly named SIB) was obtained as a dry residue ready for the coupling to the vector.

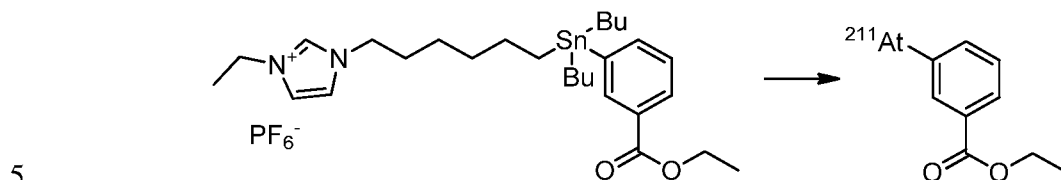
Synthesis of Di-HSGL-BSA-SIB

Bovine serum albumin (40 μ l,) modified with about 50 Di-HSGL residues per BSA (1,5 mg/ml of BSA in Borate buffer pH 8.6 300 mM) was added to the dry SIB previously obtained ($[^{125}\text{I}]\text{-II-1}$). The solution was stirred 30 min at 21°C. The radiolabelled BSA was obtained in 54% yield. The radiolabelled BSA was purified on

NAP-5 cartridge in a very good radiochemical purity (> 90%). and the immunoreactivity of the Di-HSGL residues for IgG 679 was controlled (80%).

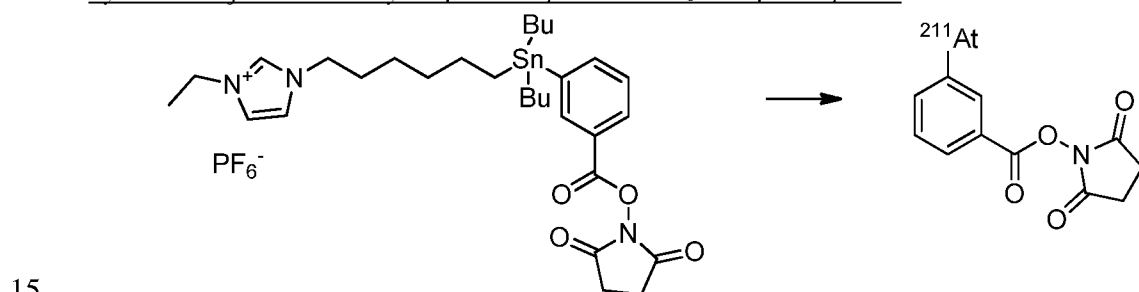
211-Astatine

Synthesis of ethyl 3-[At-211]astatobenzoate [²¹¹At]-II-2



To astatine (50 μ l, 1.5 MBq) in methanol was added NCS (2 μ l, 30 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 21°C. **I-14(PF₆⁻)** (20 μ l, 130 nmol) in MeOH/AcOH (95/5) was added. After 30 minutes stirring, 2 μ l of an aqueous solution of sodium metabisulfite (20 mg/ml) was added. The ethyl
 10 astatobenzoate [²¹¹At]-II-2 was obtained (87% RCY). The solution was evaporated to dryness and the crude product recovered in 400 μ l of diethyl ether. After filtration using a silica gel cartridge and diethyl ether as eluant, the product [²¹¹At]-II-2 was obtained with a good radiochemical purity.

Synthesis of succinimidyl 3-[At-211]astatobenzoate [²¹¹At]-II-1



To astatine (50 μ l, 4.2 MBq) in methanol was added to NCS (2 μ l, 6 nmol.) in MeOH/AcOH (95/5). The solution was stirred 30 s at 21°C. **I-1(PF₆⁻)** (20 μ l, 650 nmol) in MeOH/AcOH (95/5) was then added. After 30 minutes stirring, 2 μ l of an aqueous solution of sodium metabisulfite (20 mg/ml) was added. The succinimidyl m-
 20 astatobenzoate [²¹¹At]-II-1 was obtained (78% RCY). The solution was evaporated to

dryness and recovered in 400 µl of diethyl ether. After filtration using a silica gel cartridge and as eluant, the product [^{211}At]-II-1 (commonly named SAB) was obtained with a good radiochemical purity. Volatiles were evaporated under argon and the purified SAB was obtained as a dry residue ready for the coupling to the vector.

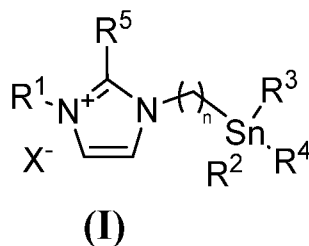
5 Synthesis of 9E7-SAB

The mAb 9E7 (50 µl, 3.35 mg/ml of 9E7 in Borate buffer pH 8.6 300 mM) was added to the dry SAB previously obtained [^{211}At]-II-1. The solution was stirred 30 min at 21°C. The radiolabelled 9E7 was obtained in 76% yield. The radiolabelled 9E7 was purified on NAP-5 cartridge and was obtained in a very good radiochemical purity (> 90%).

10

CLAIMS

1. Compound of formula (I)



wherein:

- 5 **X⁻** represents an anion, preferably **X⁻** represents an anion selected from the group comprising halide, acetate, trifluoroacetate, triflate (Tf), NTf₂⁻, alkylsulfate, sulfonate, tetrafluoroborate (BF₄⁻), tetraarylborate, hexafluorophosphate (PF₆⁻), NO₃⁻, SbF₆⁻, proline, hydroxide, hydrogen sulfate, tetrachloroferrate, aluminum tetrachloride, perfluorobutylsulfonate, p-toluenesulfonate, formate and
- 10 dihydrogen phosphate; more preferably **X⁻** represents BF₄⁻, PF₆⁻, Cl⁻, Br⁻, I⁻, NTf₂⁻, even more preferably **X⁻** represents BF₄⁻, PF₆⁻ or Br⁻;
- n** represents an integer ranging from 3 to 10, preferably **n** represents 4, 5, 6, 7 or 8, more preferably **n** represents 6;
- R¹** represents an alkyl group, a PEG chain, preferably **R¹** represents methyl, ethyl,
- 15 *n*-butyl;
- R²** and **R³** each independently represent an alkyl group, preferably **R²** and **R³** are both *n*-butyl;
- R⁵** represents H, alkyl or aryl, preferably H, methyl or phenyl;
- R⁴** represents:
- 20 - an aryl vector; or
- a group selected from aryl and heteroaryl substituted by one or more substituents **-L-M** wherein:
- L** represents a single bond or a linker selected from aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl or a combination
- 25 thereof;

5 said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, imino, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate, halogen;

said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and optionally L additionally comprises a residue of a reactive group through which L is bounded to M;

M represents:

15 a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl; or

20 a bioactive group selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, 25 enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate, nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube and combinations thereof;

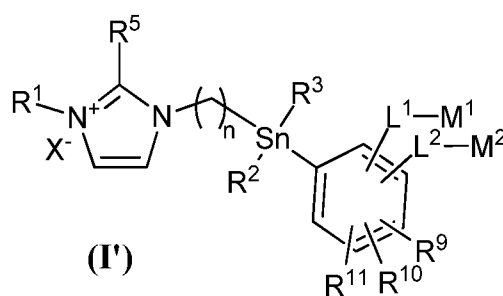
30 said aryl or heteroaryl being optionally further substituted by one or more substituents selected from hydroxyl; linear, cyclic or branched alkyl

comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF_3 ; $-\text{CH}(\text{OH})(\text{CF}_3)$; $-\text{CH}(\text{OCH}_2\text{OCH}_3)(\text{CF}_3)$; methylenedioxy; ethylenedioxy; $\text{SO}_2\text{NRR}'$, NRR' , COOR , CONRR' , NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl;

provided that

- when n is equal to 6, X^- is I^- , R^1 is methyl, R^2 and R^3 are both *n*-butyl and R^5 is H, then R^4 is not phenyl;
- when n is equal to 6, X^- is Br^- , R^1 is ethyl, R^2 and R^3 are both *n*-butyl and R^5 is H, then R^4 is not phenyl, 4-methoxyphenyl, 4-fluorophenyl or thiophen-2-yl;
- when n is equal to 3, X^- is BF_4^- , R^1 is methyl, R^2 and R^3 are both *n*-butyl and R^5 is H or methyl, then R^4 is not phenyl;
- when n is equal to 3, X^- is I^- , R^1 is methyl, R^2 and R^3 are both *n*-butyl and R^5 is H or methyl or phenyl, then R^4 is not phenyl;
- when n is equal to 6, X^- is I^- , R^1 is methyl, R^2 and R^3 are both *n*-butyl and R^5 is H, then R^4 is not phenyl.

2. Compound according to claim 1, of formula (I')



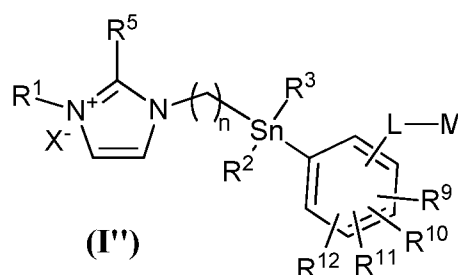
wherein

X^- , n , R^1 , R^2 , R^3 and R^5 are as defined in claim 1,

$-\text{L}^1-\text{M}^1$ and $-\text{L}^2-\text{M}^2$ represent each independently $-\text{L}-\text{M}$, wherein $-\text{L}-\text{M}$ is as defined in claim 1; and

R⁹, **R¹⁰** and **R¹¹** represent each independently a group selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF₃; -CH(OH)(CF₃); -CH(OCH₂OCH₃)(CF₃); methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR, CONRR', NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.

3. Compound according to claim 1 or claim 2, of formula (I'')

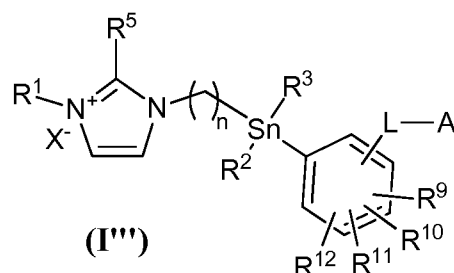


10 wherein

X⁻, **n**, **R¹**, **R²**, **R³**, **R⁵** and **-L-M** are as defined in claim 1; and

R⁹, **R¹⁰**, **R¹¹** and **R¹²** represent each independently a group selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato; phenyl; CF₃; -CH(OH)(CF₃); -CH(OCH₂OCH₃)(CF₃); methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR, CONRR', NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl.

4. Compound according to anyone of claims 1 to 3, of formula (I''')



wherein

X^- , n , R^1 , R^2 , R^3 , R^5 and L are as defined in claim 1;

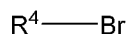
- 5 R^9 , R^{10} , R^{11} and R^{12} are as defined in claim 3; and

A represents a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl.

- 15 5. Process for manufacturing a compound of formula (I) according to anyone of claims 1 to 4,

comprising:

- 1) reacting an activated mixture of zinc and $CoBr_2$ with a compound of formula (IV)

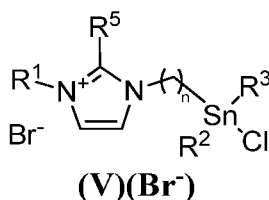


(IV)

wherein R^4 is as defined in claim 1;

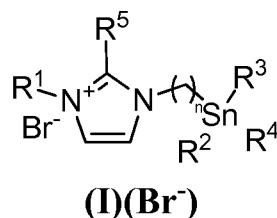
- 20 in presence of dibromoethane,
to afford the corresponding zinc derivative;

2) reacting the zinc derivative prepared in step 1) with ionic liquid (V)(Br⁻),



wherein **n**, **R¹**, **R²**, **R³** and **R⁵** are as defined in claim 1;

to form compound of formula (I)(Br⁻)



5

wherein **n**, **R¹**, **R²**, **R³**, **R⁴** and **R⁵** are as defined in claim 1;

3) optionally, a methatesis step to exchange Br⁻ to another counterion X⁻ as defined in claim 1, to afford compound of formula (I).

6. Process for the synthesis of a compound of formula (II)

10



wherein

Y* represents a halogen, preferably a radiohalogen; and

R⁴ represents:

- an aryl vector; or
- a group selected from aryl and heteroaryl substituted by one or more substituents **-L-M** wherein:
L represents a single bound or a linker selected from aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl or a combination thereof;

20

said groups being optionally substituted by at least one group selected from oxo, thioxo, hydroxyl, ether, carboxylic acid, ester, alkyl,

cycloalkyl, alkenyl, cycloalkenyl, heterocyclyl, alkynyl, cycloalkynyl, amine, amide, guanidine, imino, nitro, nitrile, azide, sulfhydryl, sulfide, thioester, thioether, sulfite, sulfate, phosphine, phosphite, phosphate, halogen;

5 said groups being optionally interrupted or terminated by -O-, -S-, -NR⁶- wherein R⁶ is H or alkyl, or a combination thereof; and

optionally L additionally comprises a residue of a reactive group through which L is bounded to M;

M represents:

10 a reactive function selected from carboxylic acid, nitrile, ester, activated ester, aldehyde, acetal, ketone, ketal, alkyne, azide, alkene, diene, maleimide, protected maleimide, hydroxyl, ether, phenol, 2-aminophenol, thiol, thioester, thioether, thiosulfonate, primary amine, secondary amine, tertiary amine, alkoxyamine, aniline, amide, 15 phosphine, alkyl phosphate, isocyanates, isothiocyanates, hydrazide, hydrazine, tosylate ester, vinyl sulfone, carbamate, carbonate ester, 4-phenyl-1,2,4-triazole-3,5-dione, sulphide, azidoalkyl and azidoaryl; or

a bioactive group selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, 20 affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate, 25 nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube and combinations thereof;

said aryl or heteroaryl being optionally further substituted by one or more substituents selected from hydroxyl; linear, cyclic or branched alkyl comprising 1, 2, 3, 4, 5 or 6 carbon atoms; aryl; heteroaryl; heterocyclyl; 30 arylheterocyclyl; alkoxy; halogen; nitro; cyano; azido; aldehyde; boronato;

phenyl; CF₃; -CH(OH)(CF₃); -CH(OCH₂OCH₃)(CF₃); methylenedioxy; ethylenedioxy; SO₂NRR', NRR', COOR, CONRR', NRCOR' wherein R and R' are each independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl and aryl;

5 said process comprising:

performing a halodemallation by reacting an electrophilic reactant comprising halogen Y*, with a compound of formula (I) according to anyone of claims 1 to 4, to form compound of formula (II).

7. Process according to claim 6, wherein the halogen Y* is a radiohalogen, preferably a radiohalogen selected from the group comprising ¹²⁵I, ¹³¹I, ¹²⁴I, ¹²³I, ²¹¹At, ⁷⁶Br, ¹⁸F, more preferably Y* is ²¹¹At or ¹⁸F.

8. Process according to claim 6 or claim 7, wherein in compound (II), M represents a reactive function, comprising a subsequent step of reacting compound (II) with a vector selected from amino acid, biogenic amine, peptide, heteropeptide, protein, antibody or fragment thereof, monobody, affibody, antibody construct such as a for example minibody or diabody, saccharide, polysaccharide, benzylguanine, biotin, avidin, nucleotide, oligonucleotide, microRNA, hapten, aptamer, ligand, enzyme, enzyme substrate, steroid, hormone, porphyrin, neurotransmitters, sympatomimetic drug, vitamin, phosphonate, nanocarrier such as for example nanocapsule, liposome, dendrimer, carbon nanotube; said vector comprising at least one reactive function B; said reactive function B being able to react with the reactive function of compound (II), leading to the labeled vector (III).

9. Device for implementing the labeling process according to anyone of claims 6 to 8, comprising at least one automaton of synthesis comprising:

- 25 - controlling means;
- a vacuum system;
- one reaction vessel;
- a purification cartridge;

- at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising a compound of formula (I) according to anyone of claims **1** to **4** ;
 - at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel containing an electrophilic reactant comprising halogen **Y***, or directly connected at the other end to an arrival of an electrophilic reactant comprising halogen **Y*** or a precursor thereof (distillation apparatus or production line);
 - optionally at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising an oxidizing agent;
 - at least one line connected at one end to the reaction vessel and at the other end to the top of the purification cartridge;
 - at least one output line connected at one end to the bottom end of the purification cartridge, the other end enabling to recover compound (II) as defined in claim **6**;
 - optionally a line connected to an inert gas arrival.
- 10.** Device according to claim **9**, further comprising a second automaton comprising:
- controlling means;
 - a vacuum system;
 - one reaction vessel;
 - a purification cartridge;
 - at least one input line connected at one end to the output line of the first automaton and at the other end to the reaction vessel to introduce compound (II) as defined in claim **6**, in the second automaton;
 - at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising a vector as defined in claim **8**;
 - at least one line connected at one end to the reaction vessel and at the other end to a storage vessel, said storage vessel comprising an aqueous solvent;

- at least one line connected at one end to the reaction vessel and at the other end to the top of the purification cartridge;
 - at least one line connected at one end to the bottom end of the purification cartridge, the other end enabling to recover compound (III'') as defined in claim 8;
 - optionally a line connected to an inert gas arrival.
- 5
- 11.** Kit comprising a compound of formula (I) according to anyone of claims 1 to 4.
- 12.** Kit according to claim 11, further comprising an oxidizing agent, preferably selected from N-chlorosuccinimide (NCS), N-iodosuccinimide, N-Bromosuccinimide, Chloramine-T, hydrogen peroxide, sodium hypochlorite, 10 terbutylhydroperoxyde, potassium dichromate, more preferably N-chlorosuccinimide.
- 13.** Kit according to claim 11 or claim 12, further comprising a selectfluor, acetate or triflate salt, preferably selectfluor salt.
- 15 **14.** Kit according to anyone of claims 11 to 13, further comprising a metallic catalyst.
- 15.** Kit according to anyone of claims 11 to 14, further comprising a reducing agent, preferably selected from sodium metabisulfite, sodium sulfite, cysteine or dithiothreitol.
- 20 **16.** Use of a compound of formula (I) according to anyone of claims 1 to 4 for the synthesis of halogenated compounds.

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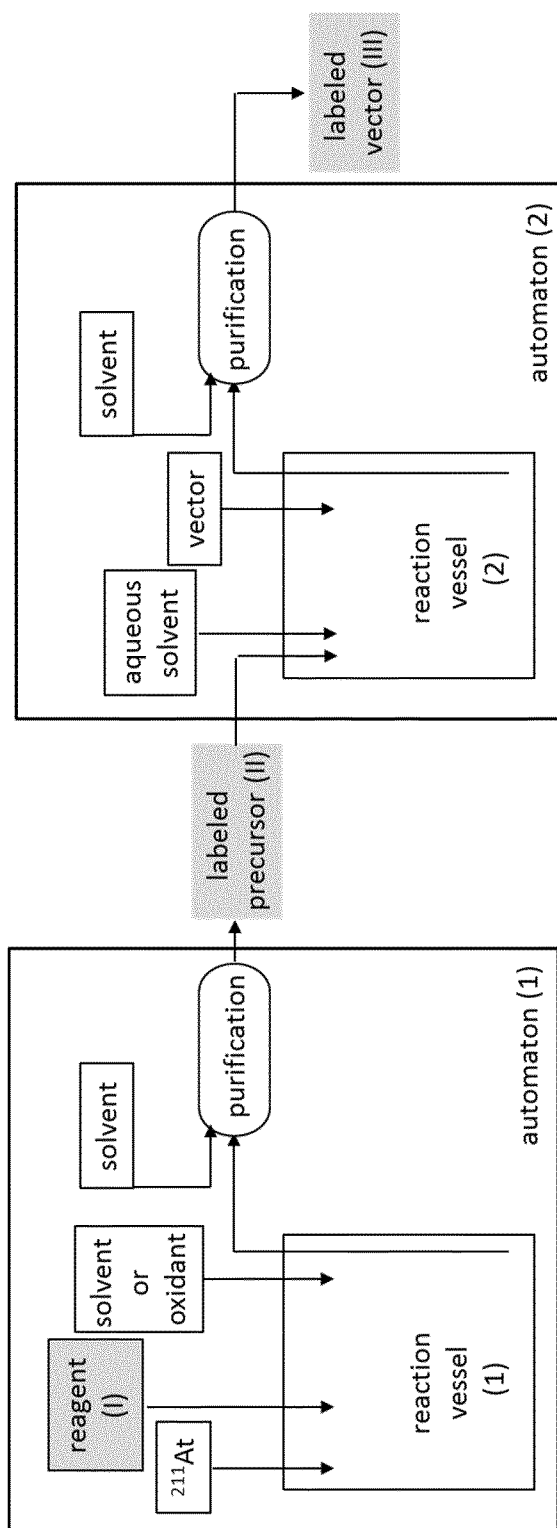


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/050180

A. CLASSIFICATION OF SUBJECT MATTER INV. C07F7/22 C07B59/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07F C07B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAS LOUAISIL ET AL: "Ionic Liquid Supported Organotin Reagents: Green Tools for Stille Cross-Coupling Reactions with Brominated Substrates", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2011, no. 1, 24 January 2011 (2011-01-24), pages 143-149, XP055113453, ISSN: 1434-193X, DOI: 10.1002/ejoc.201001195 cited in the application compounds 2, 3, 30-32 scheme 2; page 145 page 144; table 2 ----- -/--	1-16
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
20 March 2015		31/03/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Duval, Eric

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/050180

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PHUOC DIEN PHAM ET AL: "Stille Cross-Coupling Reactions with Tin Reagents Supported on Ionic Liquids", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2009, no. 19, 1 July 2009 (2009-07-01), pages 3249-3257, XP055034461, ISSN: 1434-193X, DOI: 10.1002/ejoc.200900177 cited in the application compounds 8a-8d, 9a, 9c -----	1-16
Y	CORINNE GOSMINI ET AL: "New and simple one-step cobalt-catalyzed preparation of functionalized arylstannanes from the corresponding aryl bromides or iodides", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 3, no. 2, 1 January 2005 (2005-01-01), page 216, XP055113466, ISSN: 1477-0520, DOI: 10.1039/b417326k cited in the application the whole document -----	5
Y	WO 99/18053 A1 (UNIV WESTERN ONTARIO [CA]; HUNTER DUNCAN H [CA]; ZHU XIZHEN [CA]) 15 April 1999 (1999-04-15) cited in the application claim 1 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/050180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9918053	A1	15-04-1999	CA 2345710 A1	15-04-1999
			WO 9918053 A1	15-04-1999
