J Radioanal Nucl Chem (2016) 309:859–889
DOI 10.1007/s10967-015-4679-z

Critical analysis of radioiodination techniques for micro and macro organic molecules

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Received: 22 October 2015 / Published online: 13 January 2016

Abstract A variety of radioiodination methods is available in the literature depending upon the nature of organic compound to be labeled, however only few can completely fulfill manufacturing requirements.Ideally a selected method should be one which offers maximum benefits like regioselectivity, minimum reaction steps, minimum reaction time, high radiochemical yield and high specific activity. In this review radioiodination techniques were critically analyzed. Advantages, drawbacks, possible mode of action and special reaction conditions required to get high radiochemical yield were taken into account. The influence of iodine introduction on physicochemical properties, in vivo or in vitro pharmacological properties of pharmaceutical due to increase of lipophilicity were discussed along with examples.

Keywords Radioiodination Chloramine-T · Iodogen · *N*-halosuccinimides · Radioiodo-desilylation

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Introduction

Radiolabeled pharmaceuticals being used in clinical oncology are emerging agents for the diagnoses and treatment of cancer and many other abnormalities like neurological or heart disorders, gastrointestinal or endocrine disorders etc. [3]. This pharmacodynamics causes dramatic changes in cell cycle that hampers the rapid division of malignant and myeloid cells by depriving them of synthesis of DNA, RNA, thymidylates and proteins or chemically irreversible reactions leading to the absence or repair, to cell death etc. [3, 4].

Depending on the variety of gamma and positron emitting radionuclides, a wide range of radio pharmaceuticals have been developed. Among these, radioisotopes of iodine confirmed their worth with specific half-lives and decay modes that projected their use as therapeutic agent (I^{123}, I^{125}) [9, 15], single photon emission tomography (SPECT) imaging agent (I^{123}, I^{125}, I^{131}) [9, 10, 18] and as positron emission tomography (PET) imaging agent (I^{124}) [47]. More than thirty artificial radioisotopes of iodine have been recognized, with only one stable, naturally occurring i.e. iodine-127 (I^{127}), properties of some important isotope have been summarized in Table 1.

Radioiodination of pharmacologically/biologically active compounds via classical iodination approach can be done by considering several important parameters including half-life of isotope, concentrations used, in vitro stability, binding of the radiolabeled drug with plasma protein and biodistribution in living systems, etc. [162]. It is reported that radioiodine pharmaceutical coalition can impart remarkable alterations in physicochemical and in vivo or in vitro pharmacological properties of precursors because of increased lipophilic efficiency. Therefore, to avoid said effects, position of the radioiodine on target

Table 1 Nuclear properties and uses of important radioiodine

Isotope	Decay mode %	Half life	Applications	Ref.
^{120}I	β^+(56), EC (44)	1.35 h	PET imaging	[30]
^{122}I	β^+(77), EC (23)	3.6 min	PET imaging	[33]
^{123}I	EC (100)	13.2 h	SPECT imaging	[15, 18]
^{124}I	β^+(22), EC (78)	4.8 days	PET imaging	[47, 63]
^{125}I	EC(100)	60 days	Radiotherapy	[9]
			SPECT imaging	
^{131}I	β^- (90), EC(10)	8.04 days	Radiotherapy	[10]
			SPECT and PET imaging	

β^+ positron emission, *EC* electron capture, β^- electron emission, *PET* positron emission tomography, *SPECT* single photon emission tomography

pharmaceutical should be taken into account. Hence it is always recommended to introduce the radioiodine as far as possible from pharmacophore [55, 72]. Besides pharmacological properties it is important to investigate toxicological properties of iodinated compound.

The selection of labeling site purely depends upon the chemical, biological and structural properties of precursors to be labeled. Structural motifs particularly steric and electronic attributes of the precursors usually suggest the electrophilic or nucleophilic attack to delineate the directing effect of the incoming radioiodine. That gives rise to the formation of strong carbon-iodine bond with high in vivo stability e.g. electrophilic or nucleophilic substitution of radioiodine on vinylic or aromatic compounds [162].

Electrophilic substitution reaction

Chloramine-T method

In electrophilic radioiodination, use of sodium salts of *N*-chlorosulphonic acid amides (Fig. 1) such as *N*-chloro-*p*-toluenesulphonic acid (Chloramine-T), *N*-chloro-benzenesulphonic acid (Chloramine-B) and *N*-dichloro-*p*-toluenesulphonic acid (Dichloramine-T) is prominent.

Chloramine-T is strong oxidizing agent in both basic and acidic media. Nature of active oxidizing species depends upon the reaction conditions specially pH of the media. In 2013, M.E. Moustafa et al. suggested that in neutral or weakly acidic media possible oxidizing species are $ArSO_2NHCl$ ($Ar=CH_3C_6H_4$) and HOCl (Scheme 1) [2].

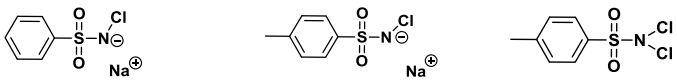
Hypochlorous acid, with high oxidizing power will react with iodide forming iodonium ion H_2OI^+. However in strong acidic medium inter halogen species are formed which are not favorable for electrophlic substitution [1, 2, 22]

In weakly basic media HOCl do not exist, predominating species are $ArSO_2NHCl$ ($Ar=CH_3C_6H_4$) and hypochlorite ion. Hypochlorite ion reacts with iodide to form HOI which is actually takes a part in electrophilic substitution reaction (Scheme 2).

HOI rapidly disproportionate to give iodate and iodide (pH > 8). Hence strong basic media will favor the conversion of IO^- to IO_3^- and these species are not favorable for iodination of organic compounds [2, 22, 26].

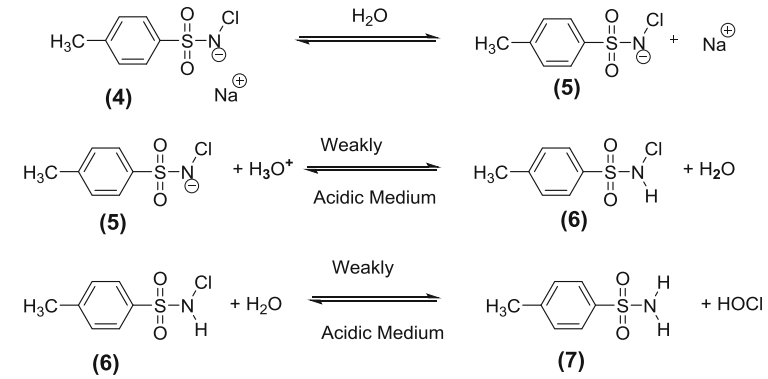
Successful radioiodination and high chemical yield depends upon various factors like pH, temperature, reaction time and concentration of Chloramine-T. Usually Chloramine-T works well to generate the iodonium ions around pH 7 [5, 11, 12]. If compound to be labeled contains phenyl ring, then at pH 7 the protonation of gives H^+ and substitution by radiochemical iodonium ion I^+ becomes very easy [20, 23, 26]. For substrate (**10**, **22**, **24**, **28**, **30**, **48**) Table 2, maximum radiochemical yield was obtained at pH 7. Temperature of reaction mixture is critical factor as in case of electrophilic substitution reaction some energy is required for H^+ ion to set free by breaking carbon hydrogen bond and to introduce radioactive iodonium ion into the ring. Maximum radiochemical yield is obtained when reactions proceed above room temperature giving rise to stable labeled compound [12, 14, 16]. Radioiodination of precursors (**28**, **30**, **34**, **38**, **46**, **48**) Table 2, high radiochemical yield was obtained at very high temperatures

Fig. 1 Structural formulas of *N*-chloroamides

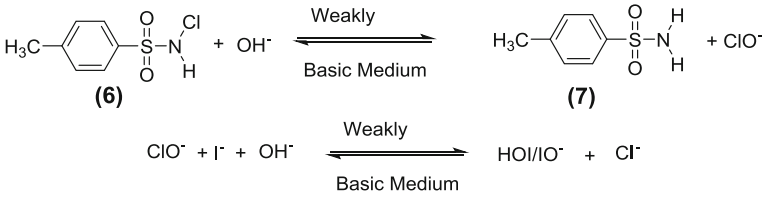


Chloramine B **(1)** Chloramine T **(2)** Dichloramine T **(3)**

Scheme 1 Oxidation reaction of Chloramine T in acidic media [2]



Scheme 2 Oxidation reaction of Chloramine T in weakly basic media [1]



ranging from 50 to 80 °C. Usually 3–5 min were required for completion of reaction. Longer reaction time can affect radiochemical yield that is because of harsh oxidizing nature of Chloramine-T [10–17].

Chloramine-T (CAT) is strong oxidizing agent hence small concentration of CAT is recommended as large concentration may decrease radiochemical yield due oxidative side reaction such as polymerization, chlorination and denaturation of the substrate (**5**, **9**, **19**, **29**). i.e. oxidation of thiol groups and cleavage of tryptophanyl peptide bonds [9, 12]. Chloramine-T method is not suitable for proteins as it causes oxidative damage to proteins. Radioiodination by using Chloramine-T also lacks site selectivity. However in some cases regioselective iodination is possible where organometallic precursor are used [28] (Scheme 3).

Iodogen method

Iodogen is trade name of 1,3,4,6- tetrachloro-3α, 6α-diphenylglycouril (Fig. 2), an oxidizing agent, which gives similar or lower radiochemical yield as that of Chloramine-T, but causes minimum oxidative damages to proteins, peptides and cell membranes to be labeled [31, 43]. Iodogen is insoluble in aqueous phase, but dissolves in some volatile organic solvents like dichloromethane or chloroform and transferred to the reaction vessel. A thin layer of oxidizing agent is obtained by evaporating organic solvent [39, 45]. In a reaction vessel, an aqueous solution of compound to be labeled along with radioiodine is allowed to interact with oxidizing agent [38], followed by the removal of aqueous mixture. This oxidizing agent is suitable for compounds that contain activated aromatic groups [39, 42] Few selected examples are given in Table 4.

Iodogen is mild oxidizing agent hence chances of oxidative side reactions are quite minimum [45]. Concentration of Iodogen plays a key role in radioiodination reaction as higher concentration can decrease radiochemical yield since iodogen forms precipitates on the walls of reaction vessel [31, 32, 39, 43, 52]. The exact oxidation mechanism of Iodogen is not clear [32, 41] however attached two carbonyl groups may involve in the process (Scheme 4).

In 2008, Keti Wang et al. [44] suggested that radioiodination yield was very low when water insoluble substrates were radioiodinated by using aqueous medium. To improve the efficiency polar aprotic solvent dimethyl sulfoxide (DMSO) was used as medium. Dimethyl sulfoxide increased the radiochemical yield of water soluble as well as water insoluble precursors. Radiochemical yield increases up to 95–100 % when DMSO is used as solvent, important results are given in Table 3 [44].

pH of reaction also plays important role to get high radiochemical yield [40]. In 2011, Biber Muftuler et al. [36] reported that high radiochemical yield of (**107**) was obtained at pH 8 due to the presence of activated aromatic ether group. In case of substrates (**80**, **88**, **99**, **100**, **106**, **114**, **125**, **133**) Table 4, high radiochemical yield was obtained at pH 7. Sobal et al. [59] performed radioiodination of compound (**117**) Table 4, by using iodine monochloride, Chloramine-T and Iodogen as oxidizing agent, among all, Iodogen proved to be the best with maximum radiochemical yield. Reason is that, Chloramine-T iodinate under

Table 2 Compounds labeled by using chloramine-T method

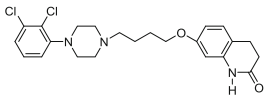
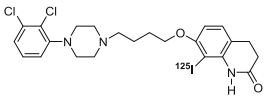
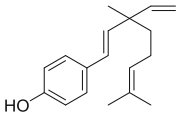
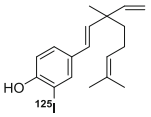
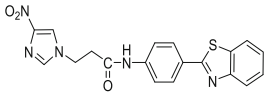
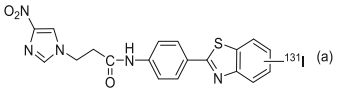
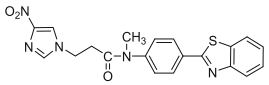
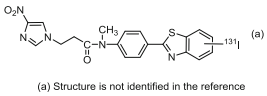
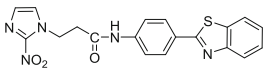
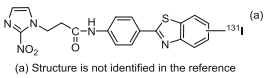
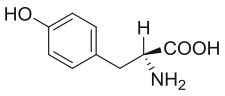
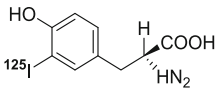
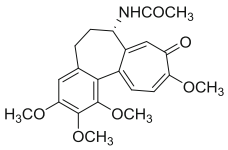
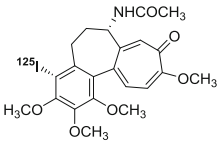
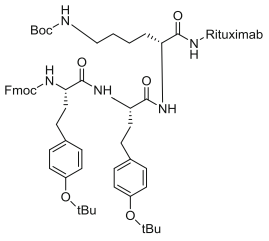
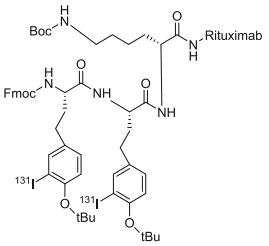
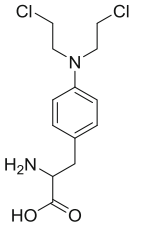
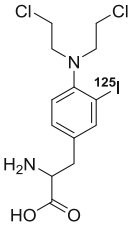
Organic compound	Product	Ref.
 **(8)**	 **(9)**	[1]
 **(10)**	 **(11)**	[5]
 **(12)**	 (a) Structure is not identified in the reference **(13)**	[6]
 **(14)**	 (a) Structure is not identified in the reference **(15)**	
 **(16)**	 (a) Structure is not identified in the reference **(17)**	
$VEGF_{121}$ (**18**) and $VEGF_{165}$ (**20**)	^{125}I-$VEGF_{121}$ (**19**) and ^{125}I- $VEGF_{165}$ (**21**)	[7]
 **(22)**	 **(23)**	[8]
 **(24)**	 **(25)**	[9]
Streptokinase (SK) thrombolytic agent (**26**)	^{131}I-SKA (**27**)	[10]
 **(28)**	 **(29)**	[11]
 **(30)**	 **(31)**	[12]

Table 2 continued

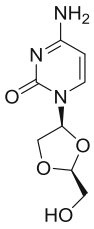
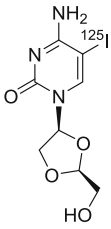
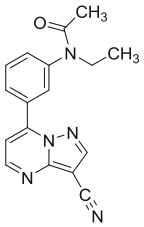
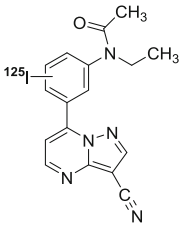
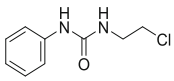
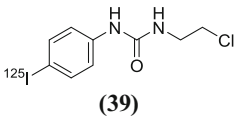
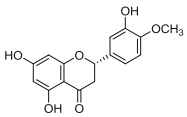
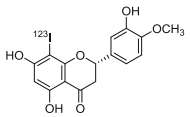
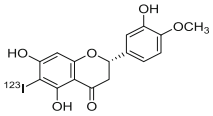
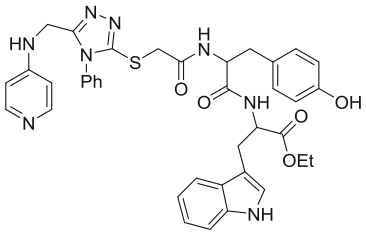
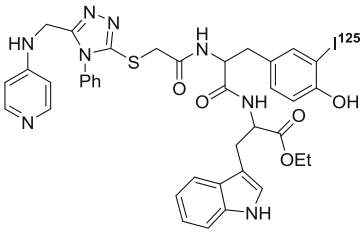
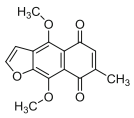
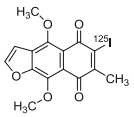
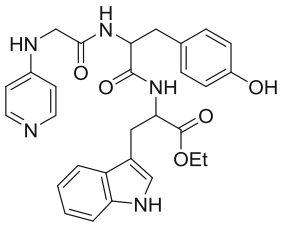
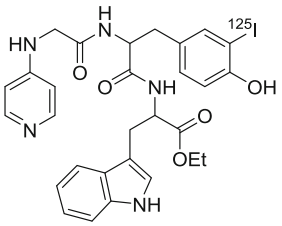
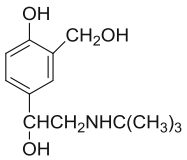
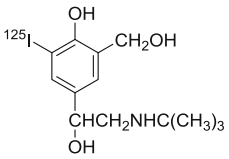
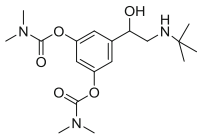
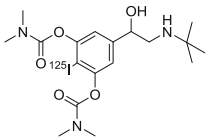
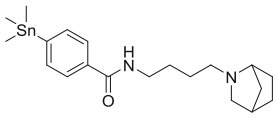
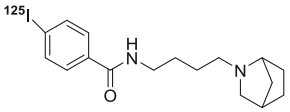
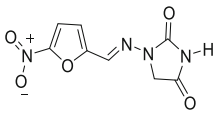
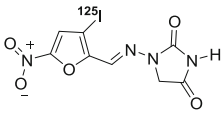
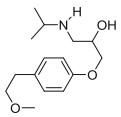
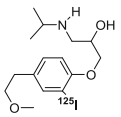
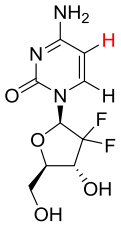
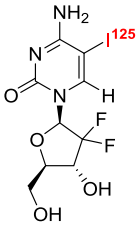
Organic compound	Product	Ref.
 **(32)**	 **(33)**	[13]
 **(34)**	 **(35)**	[14]
Monoclonal antibody(MAb) Anti-CD20 (**36**)	^{131}I-anti-CD20 (**37**)	[15]
 **(38)**	 **(39)**	[16]
 **(40)**	 **(41)**  **(42)**	[17]
Monoclonal antibody TU-20 (**43**)	^{125}I-TU-20 (44) & ^{123}I-TU-20 (**45**)	[18]
 **(46)**	 **(47)**	[19]
 **(48)**	 **(49)**	[20]

Table 2 continued

Organic compound	Product	Ref.
(2-Benzyl-1-oxo-1,2-dihydropyrido[4,3-b]quinoxaline 5,10-dioxide) NBNPQD (**50**)	^{125}I-NBNPQD (**51**)	[21]
 **(52)**	 **(53)**	[22]
 **(54)**	 **(55)**	[23]
 **(56)**	 **(57)**	[24]
 **(58)**	 **(59)**	[25]
 **(60)**	 **(61)**	[26]
 **(62)**	 **(63)**	[27]
 **(64)**	 **(65)**	[29]

such stringent conditions may alter the physicochemical structure of compound to be labeled [39]. On the other hand Iodogen is hydrophobic in nature, hence active only at aqueous interface, it is thus less destructive as compare to Chloramine-T [34]. Although chemical action of Chloramine-T and Iodogen is similar but immobilization of Iodogen on walls of iodination tube reduces chances of structural damage [36, 37].

Scheme 3 Radioiodination of 15-(4-Iodophenyl)pentadecanoic acid [28]

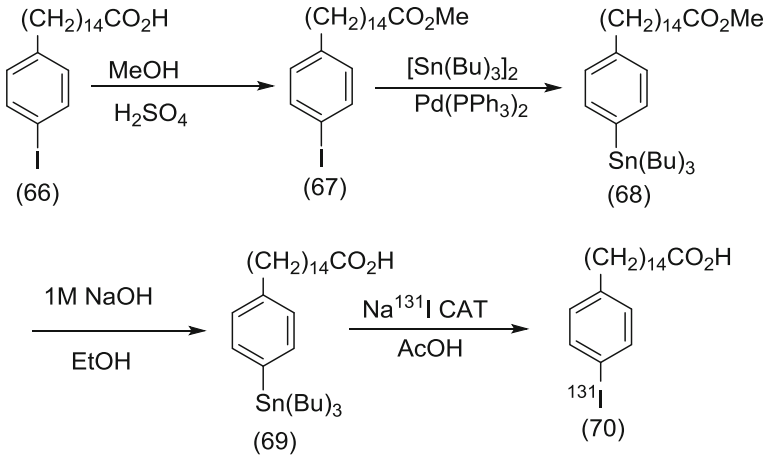
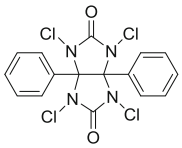


Fig. 2 Structural formula of Iodogen



(71)

Iodobead method

A variety of oxidizing agents have been used for the labeling of protein such as Chloramine-T, Iodogen, and Iodobead etc. [65]. It was found that Chloramine-T and Iodogen are not suitable for very sensitive molecules [67].

In 2005, Efimova et al. [64] used Chloramine-T, Iodogen and Iodobead reagent for the radiolabeling of substrates (**150**) and (**152**) and reported that although the efficiency of three methods was same but CD spectroscopy showed that Chloramine-T caused secondary structural changes in proteins, while enzyme activity test revealed that Iodogen caused decrease in the biological activity of (**152**). Iodobead reagent proved its worth with no structural or biological changes to said proteins.

Iodobead reagent is modified version of Cholramine-T, that is, an immobilize Chloramine-T on polystyrene beads (Fig. 3). These beads constitute great advances over others as easy to use, store, long shelf life, shorter contact time and ability to retard liberation of oxidizing species at low concentration [69, 70]. Moreover iodobead materials can easily be separated from solution mixture by an inexpensive filtration, without using expensive reducing agent [65].

Since the monochloro-sulphonamides are insoluble in organic solvents so their use is restricted to aqueous media only, on the other hand Iodobead can be used in aqueous as well as organic media [66]. The oxidation strength and labeling efficiency of Iodobead is far better as compare to Chloramine-T [66, 68, 73]. Selected examples of compound labeled by Iodobead method are given in Table 5.

Eventually, Iodobead method disclosed its exquisite insights in protein iodination i.e. having least reaction time (only 2–15 min in some cases), wide pH range (5.5–8.5), reaction temperature of 4 °C to room temperature, no enzymatic or biological alteration and presence or absence of detergents, azide and Urea [64]. So this is a reliable substitute for Chloramine-T and iodogen methods for radioiodination of proteins in trace quantities [65].

N-Halosuccinimides

N-Halosuccinimides such as *N*-chloro-tetra-fluorosuccinimide (NCTFS), *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) are very good radioiodinating reagents where transformation can be modulated under

Scheme 4 Oxidation reaction of Iodogen

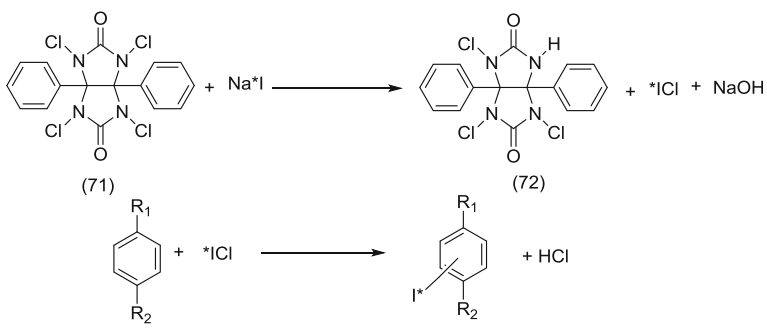


Table 3 Solvent effect on Radioiodination via Iodogen [44]

Compound	Solvent used	Reaction volume (mL)	Buffer/pH	Oxidant	Yield (%)
^{125}IUdR	DMSO	12	PBS/7.4	Iodogen	99.87 ± 0.2
(**73**)	Methanol	12	-do-	Iodogen	90.57 ± 1.2
	Dichloromethane	11	-do-	Iodogen	82.17 ± 3.2
	Water	12	-do-	Iodogen	18.97 ± 5.5
$^{125}IQ_{2\text{-}p}$	DMSO	13	PBS/7.4	Iodogen	99.37 ± 0.5
(**74**)	Methanol	13	-do-	Iodogen	11.67 ± 4.8
	Water	13	-do-	Iodogen	18.87 ± 5.3
^{125}I-Rhod	DMSO	25	$CuCl_4$/4.0	CAT	97.67 ± 1.5
(**75**)	Methanol	25	$CuCl_4$/4.0	CAT	29.97 ± 4.5
	Water	25	$CuCl_4$/4.0	CAT	27.17 ± 5.2
^{125}I-Acr	DMSO	13	PBS/7.4	CAT	98.0 ± 1.2
(**76**)	Methanol	13	-do-	CAT	79.7 ± 3.5
	Water	13	-do-	CAT	40.1 ± 3.7
^{125}I-BH	DMSO	12	PBS/7.4	Iodogen	97.3 ± 1.6
(**77**)	Methanol	12	-do-	Iodogen	66.3 ± 3.6
	Dichloromethane	11	-do-	Iodogen	86.37 ± 2.5
^{125}I-lgG	DMSO	25	PBS/7.4	Iodogen	99.7 ± 0.3
(**78**)	Water	25	-do-	Iodogen	49.5 ± 2.6
^{125}I-B72.3	DMSO	15	PBS/7.4	Iodogen	99.97 ± 0.1
(**79**)	Water	15	-do-	Iodogen	99.97 ± 0.1

various reaction conditions like catalyst, solvents and mediator. These reagents are attributed by their easy access, relative stability (compared to other *N*-Halo reagents) and formation of reactive intermediates i.e. halogen cations, anions or radicals depending upon the conditions. In 2005, Stefani et al. synthesized 4-halo-3,5-dimethyl pyrazoles in very good yield by using 3,5-dimethyl pyrazoles and *N*-halosuccinimides under ultrasound irradiation without adding any catalyst [76]. In 2010, Takuya Yamamoto et al. suggested that regioselective iodination of electron rich aromatic compounds is possible using *N*-chlorosuccinimide and sodium iodide in acetic acid (AcOH) with less reaction time and high chemical yield Possible mechanism of iodonation is given in following Scheme 5 [78].

In 2005, Amartey et al. [79] reported the synthesis and radiolabeling of IL-8 (**175**) Table 6, by using SIPC prosthetic group. For the radioiodination of *N*-succinimidyl-5-iodopyridine-3-carboxylate *N*-chlorosuccinimide (NCS), Iodogen and Iodobead method were used maximum radiochemical yield obtained with NCS.

N-chlorosuccinimide and sodium iodide along with trifluoromethanesulphonic acid can be used for direct electrophilic radioiodination of non-activated and strongly deactivated arenes, isoxazoles and pyrazoles [77, 85]. The only condition is the stability of compound in triflic acid. In 2004, Surya Prakash et al. explored that BF_3–H_2O is more economical than triflic acid, easier to prepare and credits high radiochemical yield [85]. Chlorinated by products can be formed when N-chlorosuccinimide is used as an oxidizing agent, which can be suppressed by using acidic medium [75].

N-Iodosuccinimide has long been known as iodinating agent. It is effective towards a wide spectrum of substrate from phenols to anilines to nitrobenzene which are deactivated towards electrophilic substitution. It is also reported that *N*-iodosuccinimide exhibits highest/greatest activity in strong acidic medium like triflic acid or sulfuric acid. This method is also applicable to non benzenoid aromatic or heteroaromatic compounds. *N*-bromosuccinimide as oxidizing agent gives very small radiochemical yield, simultaneously radical side reactions are observed.

N-chlorosuccinimide can be used for the radioiodination of proteins followed by conjugation technique. In 1994, Yasushi Arano et al. used *N*-iodosuccinimide for radiolabeling of protein (Scheme 6). Maleimidoethyl 3-(tri-*n*-butylstannyl) hippurate (HIM) (**192**), was first radioiodinated by *N*-iodosuccinimide and prior to conjugation with either NGA or mAb (OST7), sodium metabisulfite was added to quench excess NCS. This is because neutralization of excess NCS with sodium metabisulfite prevents the protein from exposure to the oxidant [86].

Peracids as oxidizing agent

Radioiodination with organic peracids is usually accomplished in homogeneous solution and often proceeds rapidly under mild reaction conditions with minimum by-

Table 4 Compounds labeled by use of iodogen method

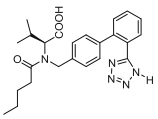
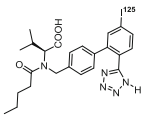
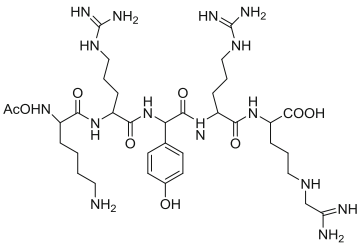
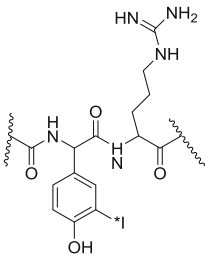
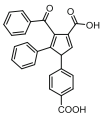
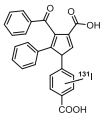
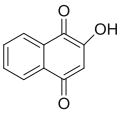
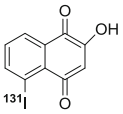
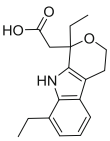
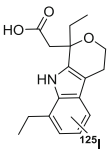
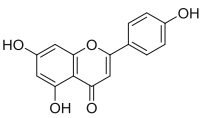
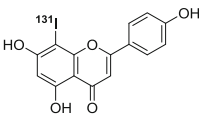
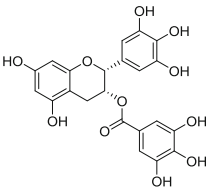
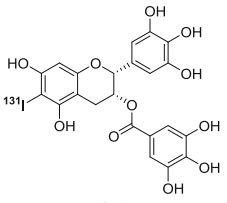
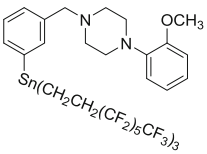
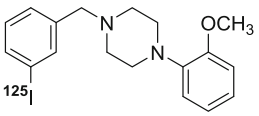
Organic compound	Product	Ref.
 **(80)**	 **(81)**	[31]
 **(82)**	 **(83)**	[37]
 **(84)**	 **(85)**	[51]
 **(86)**	 **(87)**	[53]
 **(88)**	 **(89)**	[39]
 **(90)**	 **(91)**	[41]
(Fe_3O_4–8OHQ) (**92**)	^{131}I-labeled MTC (Magnetic Targeting Carrier) (Fe_3O_4-8OHQ)-^{131}I (**93**)	[42]
 **(94)**	 **(95)**	[55]
 **(96)**	 **(97)**	[57]

Table 4 continued

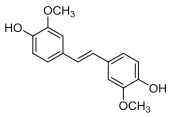
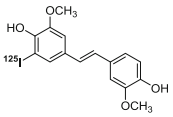
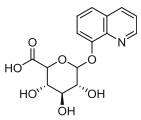
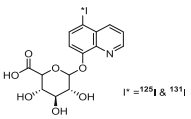
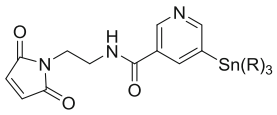
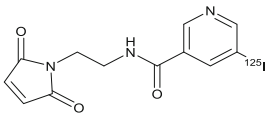
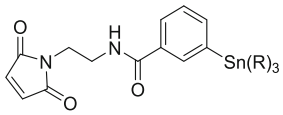
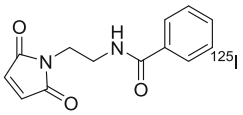
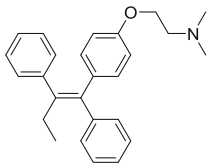
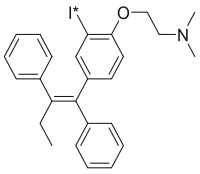
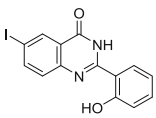
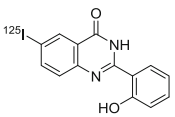
Organic compound	Product	Ref.
 **(98)**	 **(99)**	[60]
 **(100)**	 **(101)**	[43]
 **(102)**	 **(103)**	[61]
 **(104)**	 **(105)**	[61]
 **(106)**	 **(107)**	[62]
Anti-Thomsen–Friedenreich antigen (TF-Ag) mAb (**108**)	^{124}I-TFA (**109**)	[63]
O-methyl-L-α-methyltyrosine (MT) (**110**)	^{123}I-MT & ^{131}I-MT (**111**)	[45]
[mag-poly(HEMA–MAPA)] (**112**)	^{131}I-[mag-poly(HEMA–MAPA)] (**113**)	[32]
Annexin V (**114**)	^{123}I-Annexin (**115**) & ^{125}I-Annexin (**116**)	[58]
Low-density lipoproteins (LDL) (**117**)	^{125}I-LDL (**118**)	[59]
5-(2-Amimo-4-styryl pyrimidine-4-yl)-4-methoxy benzofuran-6-ol (SPBF) (**119**)	^{125}I-ASPMBF (**120**)	[56]
Bleomycins; BLM (**121**)	^{131}I-BLM (**122**)	[40]
 **(123)**	 **(124)**	[46]
ChiB_E144Q (**125**) (ChiB=chitinase B)	^{123}I-[ChiB_E144Q] (**126**)	[34]
Monoclonal antibody MN-14 (**127**)	^{131}I-MN-14 (**128**)	[35]
Tamoxifen [TAM; ([Z]-2-[4-(1,2-diphenyl-1-di-butenyl)-phenoxy]-N,N-dimethylethanamine) (**129**)	^{131}I-TAM-G (**130**)	[36]

Table 4 continued

Organic compound	Product	Ref.
anti-HER2 diabody C6.5 (**131**)	^{124}I-[anti-HER2 diabody C6.5] (**132**)	[47]
anti-CEA monoclonal antibody CL58 (**133**)	^{125}I-CL58 (**134**)	[48]
Mtr-TOCA (**135**) & Gluc-S-TOCA (**137**)	[^{125}I] Mtr-TOCA (**136**) & [^{125}I] Gluc-S-TOCA (**138**)	[49]
Ibuprofen {2-[4-(2-methylpropyl)phenyl] propanoic acid} (**139**)	^{125}I-Ibuprofen (**140**)	[38]
Hypericin (HYP) (**141**)	^{131}I-HYP (**142**)	[50]
mag-poly(-HEMA–APH) (**143**)	^{131}I-mag-poly(-HEMA–APH) (**144**)	[52]
Diethylstilbestrol glucuronide (DESG) (**145**)	^{131}I-[DESG] (**146**) &^{125}I-[DESG] (**147**)	[54]

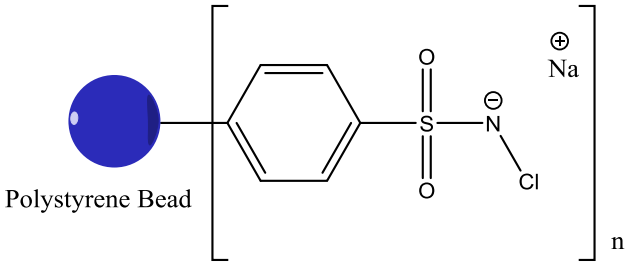


Fig. 3 Iodobead oxidizing agent

products formation. Aliphatic peracids such as performic acid, peracetic acid and carboxylic acids and their corresponding analogues are soluble in aqueous as well as organic media; hence offer a wide choice of solvent & solvent mixtures. In case of peracids the most important oxidizing agent is hydrogen peroxide. Hydrogen peroxide has low equivalent weight and its reduction product is water. For effective utilization of oxidizing capacity its active oxygen is converted into peracid form. In 2011, Xu et al. [87] used H_2O_2 along with HCl for radiolabeling of substrate (**197**) Table 7.

In 2014, Annukka et al. [91] tried radiolabeling of stannane precursors of substrate (**229**) and (**231**) by using Iodogen, Chloramine-T and peracetic acid. It was found that radiochemical yield was very low in case of mild oxidizing agent like Iodogen, while many chlorinated side products were formed when Chloramine-T was used. Peracetic acid gave 99 % radiochemical yield with 99 % purity. Thus Peracids can be used for the radioiodination of some especially sensitive substrates [91]. Peracids are generated by the use of hydrogen peroxide along with an organic acid such as formic or acetic acid, therefore concentration of oxidant is kept lower.

Demetallation techniques

In this method organometallic compounds like trialkylstannyl, trialkylsilyl or boronic acid derivatives etc. are used as precursors for the electrophilic radioiodination as shown in Table 8. Under mild oxidative conditions regioselective radioiodination of arenes with electron withdrawing or electron donating substituents is possible. Regioselectivity by using organometallic compounds

Table 5 Compounds labeled by use of iodobead method

Organic Compound	Product	Ref.
Human alpha-fetoprotein (h-AFP) (**148**)	^{125}I-h-AFP (**149**)	[65]
Bovine serum albumin (BSA) (**150**)	^{125}I-BSA (**151**)	[64]
lysozyme (LSZ) (**152**)	^{125}I-LSZ (**153**)	[64]
N-succinimidyl 3-iodobenzoate (**154**)	*N*-succinimidyl 3- [^{124}I]iodobenzoate (**155**)	[70]
N-succinimidyl 4-iodobenzoate (**156**)	*N*-succinimidyl 4- [^{124}I]iodobenzoate (**157**)	
Recombinant v-H-*ras* protein (**158**)	^{125}I-ras protein (**159**)	[71]
2′-Deoxyuridine (**160**)	5-[^{123}I]iodo-2′-deoxyuridine (**161**)	[72]
I-MEX2 (**162**)	^{125}I-MEX2 (**163**)	[73]

Scheme 5 Mechanism of iodination of aromatic compounds by *N*-chlorosuccinimide NCS/sodium iodide (NaI) activated acetic acid

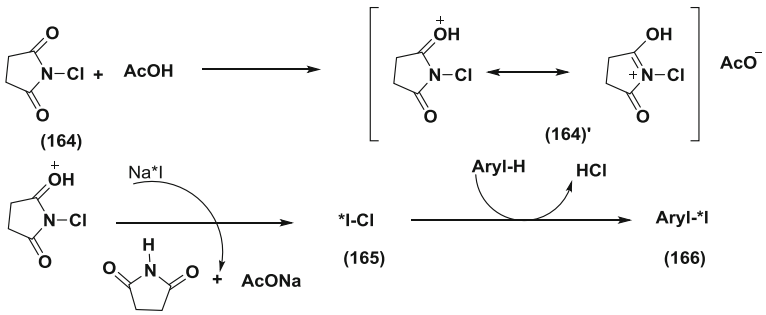
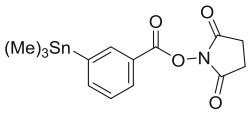
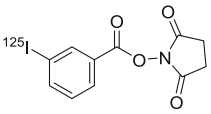
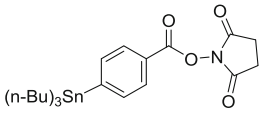
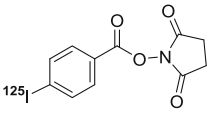
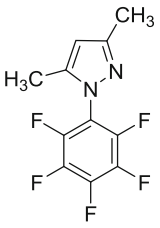
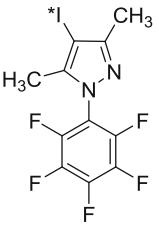
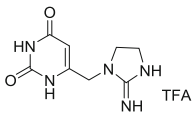
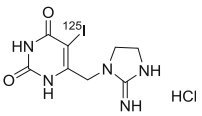
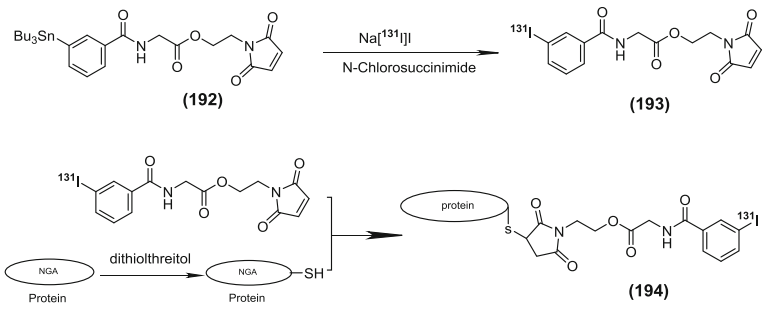


Table 6 Compounds labeled by use of *N*-halosuccinimides

Organic Compound	Product	Ref.
Meta-iodobenzylguanidine (MIBG) (**167**)	^{131}I-MIBG(**168**)	[74]
 **(169)**	 **(170)**	[75]
 **(171)**	 **(172)**	[75]
 **(173)**	 **(174)**	[76]
Interleukin-8 (IL-8) (**175**)	^{123}I-IL-8 (176) &^{131}I-IL-8 (**177**)	[79]
Nido-1-succinylamido-carborane (**178**)	Nido-1-succinylamido-[^{131}I]carborane (**179**)	[80]
Closo-1-succinylamido-carboranes (**180**)	Closo-1-succinylamido-[^{125}I]carboranes (**181**)	
AHP7 peptide (**182**)	^{125}I-AHP7 (**183**)	[81]
 **(184)**	 **(185)**	[82]
Anti-EGFRvIII mAb L8A4 (**186**)	^{125}I-L8A4 (187) &^{131}I-L8A4 (**188**)	[83]
Maleimidoethyl 3-(tri-*n*-butylstanny1)hippurate (MIH) (**189**) & Osteogenic sarcoma (OST7) (**190**)	[^{131}I]MIH-OST7 (**191**)	[84]

generally reduces the formation side products specially positional isomers which are difficult to separate. Due to electropositive character of metals, the polarization of carbon metal bond is higher than carbon-hydrogen bond, hence minimum energy is required to cleave carbon to metal bond as compare to carbon to hydrogen bond. Presence of alkyl group attached to the metal increases electron density at aromatic or vinylic carbon directly



Scheme 6 Radioiodination of maleimidoethyl 3-(tri-nbutylstanny1)hippurate by NCS and conjugation with NGA protein [84]

bound to the metal. Hence availability of carbon–metal bond increases the feasibility of electrophilic attack. For the radioiodination of organometallic precursors, Chloramine-T or other oxidizing agents can be used. Peracids are given preference to suppress formation of chlorinated by-product.

Among all available organometallic reagents, organoboranes are notably being acknowledged due to their high reactivity and variety of attached functional groups. In 2009, Kabalka et al. used organoborane intermediate of substrate (**233**) for high radiochemical yield of (**234**) Table 8, and confirmed that carbon to boron bond has high bond energy and is hardly polar but still empty 2p orbital of boron facilitate electrophilic attack. Furthermore small covalent radius of boron causes large steric influence of the attached ligands. The availability of functionalized boronic acids as starting materials, and non-toxic nature of boron intended researchers to explore its applications in overwhelming realm of radiolabeling. The reaction proceeds readily at non carrier added level and tolerate variety of functional groups. The reaction between electrophilic iodospecies and organoboranes is regioselective as well as stereoselective. The speed of reaction is directly proportional to the number of alkyl substitute attached to the boron atom [92].

In case of organotin compounds, tin-carbon bond is weak bond is readily available for substitution reaction. Presence of alkyl groups on metal increases electron density at aromatic or vinyl carbon directly attached the metal and hence facilitate the electrophilic attack. Radioiodinated compounds (**276**, **280**, **282**, **286**, **288**, **290**, **294**, **296**, **310**, **316**, **320** and **322**) Table 8, were obtained from their corresponding iodo precursors in a palladium catalyzed iodo to tributyltin exchange reaction. Each tributyltin precursor was then treated with peracid in the presence of Na*I to get desired product. An efficient way to obtained functionally substituted vinyltin is the addition of tin hydride across carbon to carbom triple bond as in case of substrate (**277**, **305** and **307**) [90, 106].

Radioiodo-desilylation is another way to get radioiodinated compounds. In case of activated aryl rings protic solvents, acidic condition and room temperature is required for radioiodo-desilylation reaction. Aryltrialkylsilane an important precursor is prepared by the reaction trialkylchlorosilane with an aromatic Grignard reagent or sometimes organolithium derivatives. Another efficient method is reaction of hexaalkyldisilane with ArX in the presence of palladium catalyst.

Miscellaneous oxidizing agents

Standard reduction potential data reveals that potassium iodate and sodium iodate are stronger oxidising agents than iodine. Iodate method is used for the radiolabelling of very sensitive proteins as iodate is mild oxidizing agent. The reaction between potassium iodate or sodium iodate and reducing agent Na*I takes place in the presence of hydrochloric acid. Results shows that high radiochemical yield and high specific activity can be obtained although this is not carrier free method [114, 117].

Enzymatic radiolabelling is used for the radiolabelling of proteins and peptides [45, 115]. The oxidation of radioiodide is performed with the help of enzyme called peroxidases in the presence of H_2O_2. Histidines can also be radioiodinated by this method. Radioiodination is pH dependent so pH 5-6 is used to get maximum radiochemical yield. As compare to chemical oxidants, enzymatic radioiodination is milder alternative technique, hence immunological and biological properties of molecule are maintained [116, 117].

Radioiodine monohalides can also be used to label small molecules possess a site feasible for electrophilic attack. This kind of radioiodine monohalides can be prepared either by treating monochloride with solution of radioactive sodium iodide or oxidizing radioactive sodium iodide with elemental halogen. Drawback of radioiodine monochloride is its high oxidation potential and carrier iodide, but still can be used for the radioiodination of weakly activated arenes [162].

Electrolytic cell can be used for the radiolabelling of proteins, histidine and tyrosine containing compounds. The main advantage of this method is negligible side product formation under mild conditions. Electrolytic method requires high cost technical equipment with lot of expertise

Table 7 Compounds labeled by use of peracids

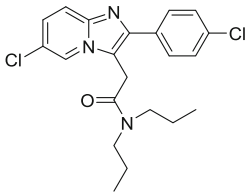
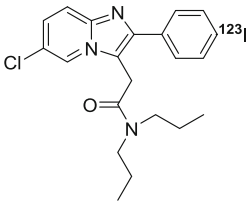
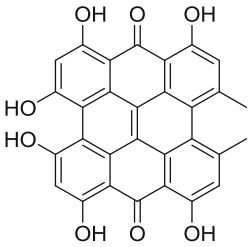
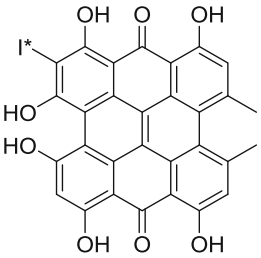
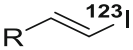
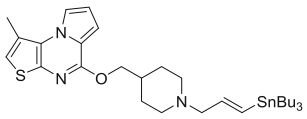
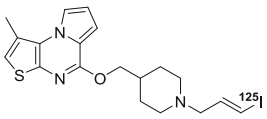
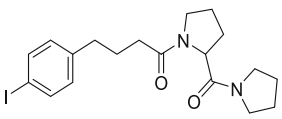
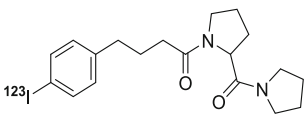
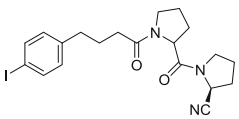
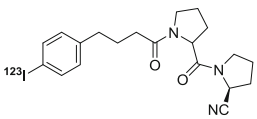
Organic compound	Product	Ref.
 **(195)**	 **(196)**	[86]
3b-hydroxy-lup-20(29)-en-28-oic acid (**197**)	^{131}I-AB (**198**)	[87]
 **(199)**	 **(200)**	[88]
R–BF_3K	^{123}I-R	[89]
R=Phenyl (**201**)	R=Phenyl (**202**)	
R=2,4-Dimethylphenyl (**203**)	R=2,4-Dimethylphenyl (**204**)	
R=4-Methoxyphenyl (**205**)	R=4-Methoxyphenyl (**206**)	
R=4-Chlorophenyl (**207**)	R=4-Chlorophenyl (**208**)	
R=4-Acetylphenyl (**209**)	R=4-Acetylphenyl (**210**)	
R=3-Nitrophenyl9 (**211**)	R=3-Nitrophenyl (**212**)	
R=1-Naphthalenyl (**213**)	R=1-Naphthalenyl (**214**)	
R=3-Thienyl (**215**)	R=3-Thienyl (**216**)	
R–CH_2=CH_2–BF_3K		[89]
R=Phenyl (Trans) (**217**)	R=Phenyl (Trans) (**218**)	
R=Phenyl (Cis) (**219**)	R=Phenyl (Cis) (**220**)	
R=4-Methylphenyl (**221**)	R=4-Methylphenyl (**222**)	
R=4-Chlorophenyl (**223**)	R=4-Chlorophenyl (**224**)	
R=Heptyl (**225**)	R=Heptyl (**226**)	
 **(227)**	 **(228)**	[90]
 **(229)**	 **(230)**	[91]
 **(231)**	 **(232)**	[91]

Table 8 Compounds labeled by use of organometallic compounds

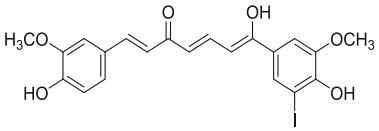
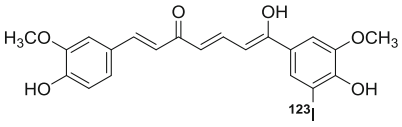
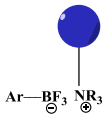
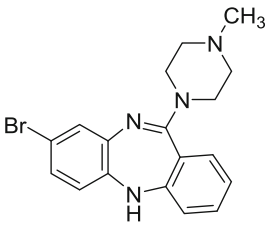
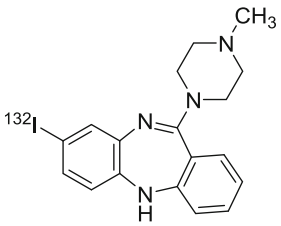
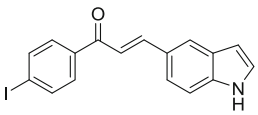
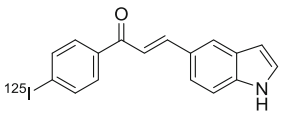
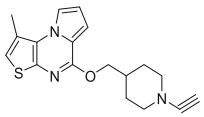
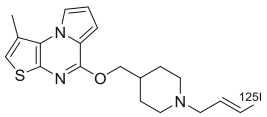
Organic compound	Product	Organometallic compound	Ref.
 **(233)**	 **(234)**	Organoboranes	[92]
R–C ≡ C-BF_3K R=Phenyl (**235**) R=4-Methylphenyl (**237**) R==1-Cyclohexenyl (**239**) R=1-Chloropropyl (**241**) R=Hexyl (**243**) R=tert-Butyl (**245**) R=4-Methoxyphenyl (**247**) R=4-Cyanophenyl (**249**) R=1-Hydroxybutyl (**251**) R=t-Butyldimethylsilyloxybutyl (**253**)	R-C ≡ C-^{123}I R=Phenyl (**236**) R=4-Methylphenyl (**238**) R=1-Cyclohexenyl (**240**) R=1-Chloropropyl (**242**) R=Hexyl (**244**) R=tert-Butyl (**246**) R=4-Methoxyphenyl (**248**) R=4-Cyanophenyl (**250**) R==Hydroxybutyl (**252**) R=t-Butyldimethylsilyloxybutyl (**254**)	Organoboranes	[93]
Dowex-supportedorganotrifluoroborate reagents  Ar=Phenyl (**255**) Ar=2-Naphthelenyl (**257**) Ar=4-Ph-phenyl (**259**) Ar=4-tBu-phenyl (**261**) Ar=3,5-Dimethyphenyl (**263**) Ar=3,4,5-Trimethoxyphenyl (**265**) Ar=4-NO_2-phenyl (**267**) Ar=(E)-2-(Phenyl)vinyl (**269**) Ar=(E)-2-(4-CF3-phenyl)vinyl (**271**)	^{123}I-Ar Ar=Phenyl (**256**) Ar=2-Naphthelenyl (**258**) Ar=4-Ph-phenyl (**260**) Ar=4-tBu-phenyl (**262**) Ar=3,5-Dimethyphenyl (**264**) Ar=3,4,5-Trimethoxyphenyl (**266**) Ar=4-NO_2-phenyl (**268**) Ar=(E)-2-(Phenyl)vinyl (**270**) Ar=(E)-2-(4-CF3-phenyl)vinyl (**272**)	Organoboranes	[94]
 **(273)**	 **(274)**	Organotin	[95]
 **(275)**	 **(276)**	Organotin	[96]
 **(277)**	 **(278)**	Organotin	[90]

Table 8 continued

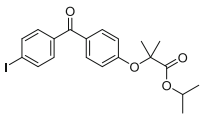
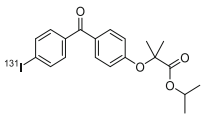
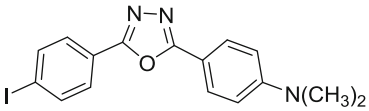
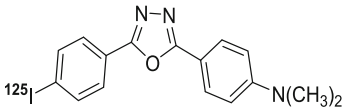
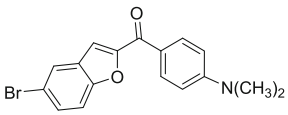
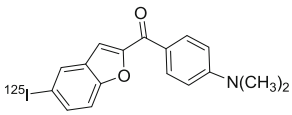
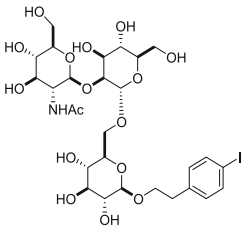
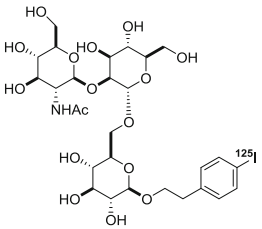
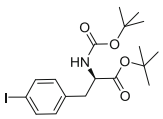
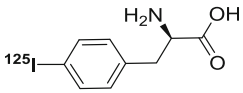
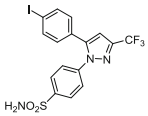
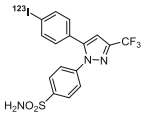
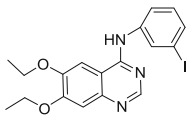
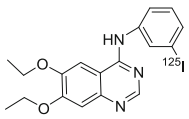
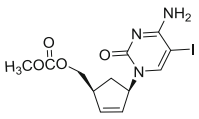
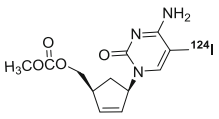
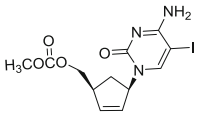
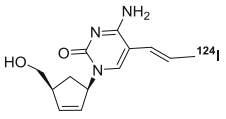
Organic compound	Product	Organometallic compound	Ref.
 **(279)**	 **(280)**	Organotin	[97]
 **(281)**	 **(282)**	Organotin	[98]
 **(283)**	 **(284)**	Organotin	[98]
 **(285)**	 **(286)**	Organotin	[99]
 **(287)**	 **(288)**	Organotin	[100]
 **(289)**	 **(290)**	Organotin	[101]
IMBA (N-(2-diethylaminoethyl)-3-iodo-4-metoxybenzamide) (**291**)	^{131}I-IMBA (**292**)	Organotin	[102]
 **(293)**	 **(294)**	Organotin	[103]
 **(295)**	 **(296)**	Organotin	[104]
 **(297)**	 **(298)**	Trimethylsilyl	[104]

Table 8 continued

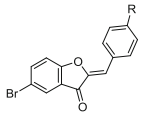
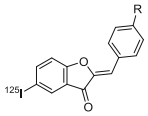
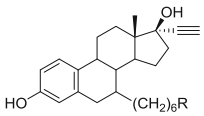
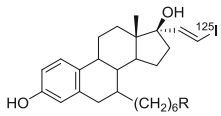
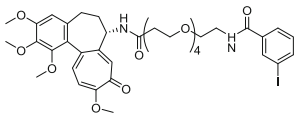
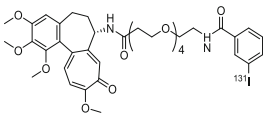
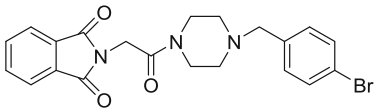
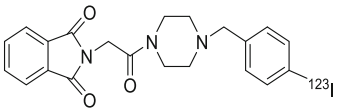
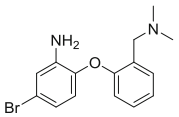
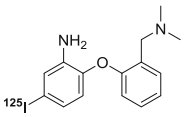
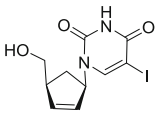
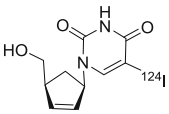
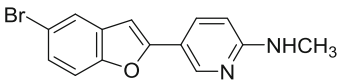
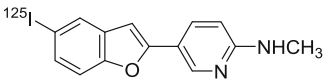
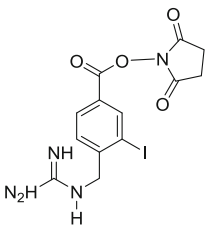
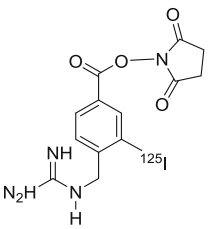
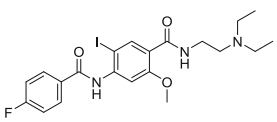
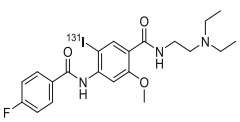
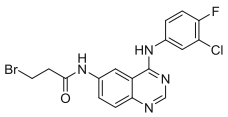
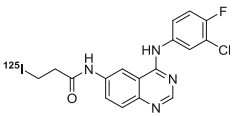
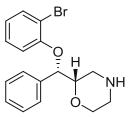
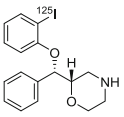
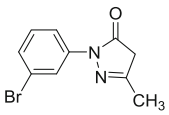
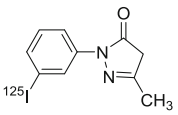
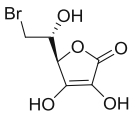
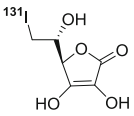
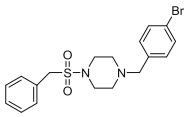
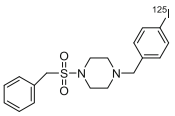
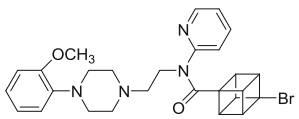
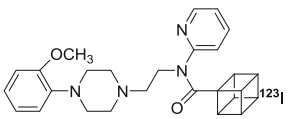
Organic compound	Product	Organometallic compound	Ref.
 R=OCH_3 **(299)** R=OH**(301)** R=$(OCH_2CH_2)_3OH$**(303)**	 R=OCH_3 **(300)** R=OH**(302)** R=$(OCH_2CH_2)_3OH$**(304)**	Organotin	[105]
 R=$CONH_2$**(305)** R=CN**(307)**	 R=$CONH_2$**(306)** R=CN**(308)**	Organotin	[106]
 **(309)**	 **(310)**	Organotin	[107]
 **(311)**	 **(312)**	Organotin	[108]
 **(313)**	 **(314)**	Organotin	[109]
 **(315)**	 **(316)**	Organotin	[110]
 **(317)**	 **(318)**	Organotin	[111]
 **(319)**	 **(320)**	Organotin	[112]
 **(321)**	 **(322)**	Organothallium (Tl)	[113]

Table 9 Compounds labeled by use halogen exchange method

Organic Compound	Product	Ref.
 **(323)**	 **(324)**	[118]
5-(4-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole **(325)**	5-(4-[^{125}I]iodophenyl)-1-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole **(326)**	[119]
5-(4-bromophenyl)-1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole **(327)**	5-(4-[^{125}I]iodophenyl)-1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole **(328)**	[119]
 **(329)**	 **(330)**	[120]
 **(331)**	 **(332)**	[121]
 **(333)**	 **(334)**	[122]
 **(335)**	 **(336)**	[123]
 **(337)**	 **(338)**	[124]

to operate. As radiochemical yield obtained by this method is small as compare to other reported techniques so its uses are very limited.

Nucleophilic Substitution Reaction

Halogen (bromine/chlorine) exchange method

In this type of radioiodination reaction bromine or chlorine atom in compound to be labeled is replaced by radioiodine. Reactions usually take place under drastic conditions, i.e. at elevated temperature and long reaction time although radiochemical yield is usually very small. For example in 2006, Yuji Kugea et al. radiolabeled substrate (**325** and **327**) Table 9 at temperature 140 °C for 2 h with 42 % and 35 % radiochemical yield respectively [119]. Similarly 65 % radiochemical yield was obtained for substrate (**330**) Table 9, in 45 min at 130 °C [120]. Hence it is proved that rate of nucleophilic substitution reaction is slow in case of aromatic compounds as compare to aliphatic compounds. Moreover it is better if aromatic substrate contains some electron withdrawing groups. Radiolabeled compound with high specific activity can be obtained from its brominated or chlorinated precursor. Radioiodine can best replace bromine than chlorine possibly due to the larger size and decreasing electronegativity of bromine.

Table 10 Compounds labeled by isotopic exchange method

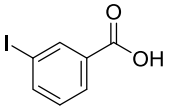
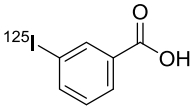
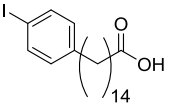
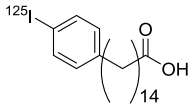
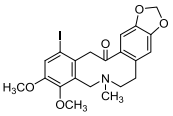
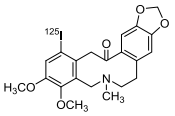
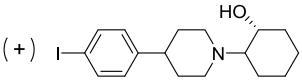
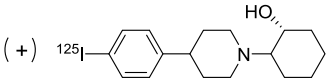
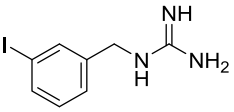
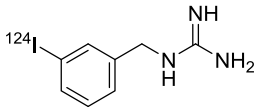
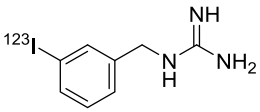
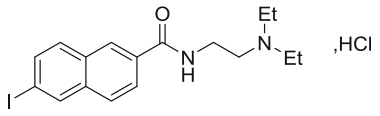
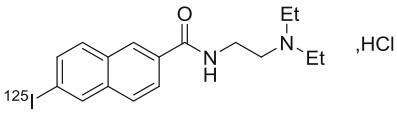
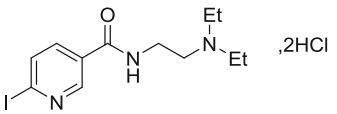
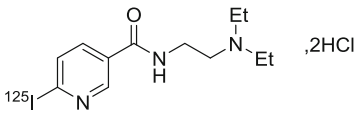
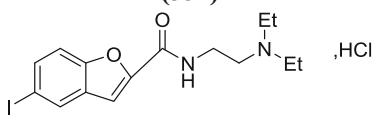
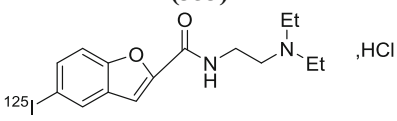
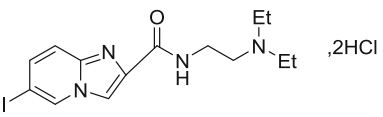
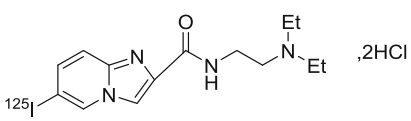
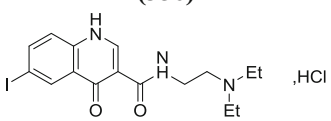
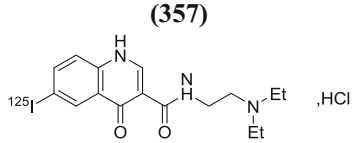
Organic Compound	Product	Ref.
 **(339)**	 **(340)**	[125]
 **(341)**	 **(342)**	
 **(343)**	 **(344)**	[126]
 **(345)**	 **(346)**	[127]
 **(347)**	 **(348)**	[128]
	 **(349)**	
 **(350)**	 **(351)**	[129]
 **(352)**	 **(353)**	
 **(354)**	 **(355)**	
 **(356)**	 **(357)**	
 **(358)**	 **(359)**	

Table 11 Compounds labeled by use of copper as catalyst

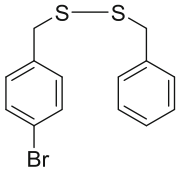
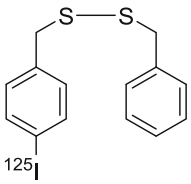
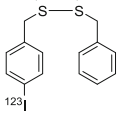
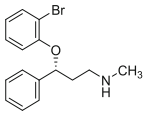
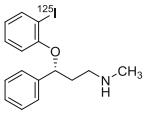
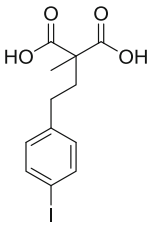
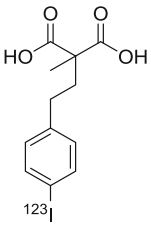
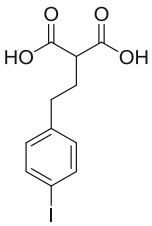
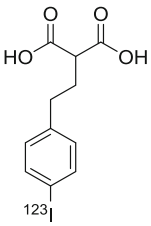
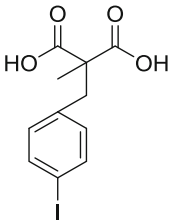
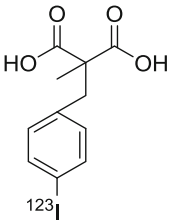
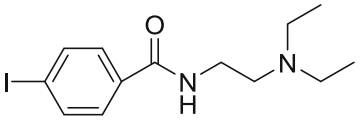
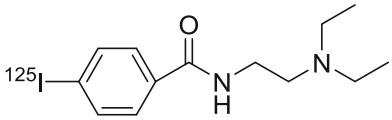
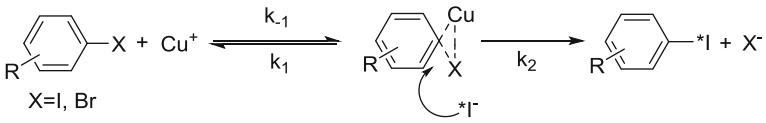
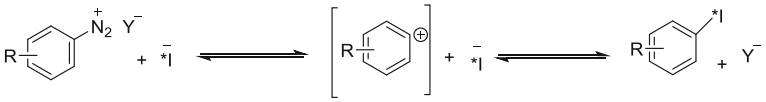
Organic compound	Product	Ref.
[D-Ala^2,4́-I-Phe^8]α-neoendorphin (**360**)	^{131}I-[D-Ala^2,4́-I-Phe^8]α-neoendorphin (**361**)	[130]
 **(362)**	 **(363)**  **(364)**	[131]
meta-iodobenzylguanidine (MIBG) (**365**)	^{123}I-MIBG (**366**)	[132]
Bromo-CGS 27023A (**367**)	[^{123}I]I-CGS 27023 A (**368**) [^{125}I]I-CGS 27023 A (**369**)	[133]
 **(370)**	 **(371)**	[134]
15-(4-iodophenyl)-9-methylpentadecanoic acid (**372**)	15-(4-[^{123}I]iodophenyl)-9-methylpentadecanoic acid (**373**)	[135]
 **(374)**	 **(375)**	[137]
 **(376)**	 **(377)**	
 **(378)**	 **(379)**	

Table 11 continued

Organic compound	Product	Ref.
 **(380)**	 **(381)**	[138]

Scheme 7 Copper assisted nucleophilic radioiodination reaction [136]





Scheme 8 Aromatic SN1 mechanism of iodo-dediazonisation [162]

Isotopic exchange method

The best and simplest method to prepare radioiodinated compound is to replace already present iodine atom of biologically active compound with radioiodine. The supremacy of the technique over others is proved by its ease of synthesis, characterization, handling and separation procedures. Usually isotopic exchange with sodium radioiodide is conducted in refluxing solvents such as acetone, dichloromethane, acetonitrile, water, ethanol or methyl ethyl ketone. In 2005, Wei et al. [126] labeled substrate (**343**) Table 10, by using isotopic exchange method. For many aromatic compounds, isotopic exchange with Na*I in solvent under reflux conditions gives very low radiochemical yield. In 2005, Nasima Akhtar et al. [127] prepared radioiodinated compound (**346**) Table 10, by solid-phase exchange reaction of (**345**) with ^{125}I NaI in the presence of ammonium sulfate and got high radiochemical yield.

Copper-assisted halogen exchange

In nucleophilic radioiodination of arenes the use of copper catalyst along with some reducing agents like Tin(II)Sulfate ($SnSO_4$), gentisic acid, sodium sulfite ($NaSO_3$) or ascorbinic acid etc. is characterized by high chemical yield [132]. Copper catalyzed nucleophilic radioiodination can be accomplished via non isotopic or isotopic exchange in water or mix aqueous organic solution. Selection of suitable solvent along with reducing agent is very important. Dimethylsulfoxide, acetic acid, Acetonitrile, water or their mixture with ethanol are promising solvent systems. In case of water soluble compounds use of Cu^{+2} along with Sn(II) is recommended. While for lipophilic compounds, ethanol:water and for basic lipophilic compounds aqueous solution of acetic acid is recommended [162]. Selected examples of compounds labeled by using copper as catalyst are given in Table 11.

In 2011, Eersels et al. discussed mechanism of copper assisted radioiodination via Cu^{+}-arylhalogen complex, (Scheme 7) & suggested that this intermediate complex facilitate the nucleophilic attack of radioiodine on carbon-halogen bond to give single pure radioiodinated product [136]. In 2010, Eersels did radiolabeling of MIBG (**365**) Table 11, and suggested that standard pH 2.3 can be extended to range of 1–4.4 by using gentisic acid to get good labeling yield. It was suggested that addition of acid with oxidative properties should be avoided however acid with redox neutral or reducing nature is suitable [132].

Radioiodo-dediazonisation

Diazonium compounds or diazonium salts are group of organic compounds s comprises of R - $N_2^+X^-$ where R can be alkyl or aryl and X may be an inorganic or organic anion or halogen [140]. One of the most frequently used method for the radioiodination of aromatic compounds is substitution of diazonium ion by radioiodine. The process of diazotization is carried out with sodium nitrite at low temperatures in aqueous solution of hydrochloric or sulfuric acid, and then treated with sodium radioiodide to label corresponding compound [139]. The radioiodo-dediazonisation follows aromatic SN_1 mechanism (Scheme 8).

Table 12 Compounds labeled by use of prosthetic group

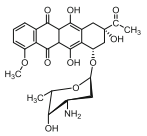
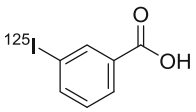
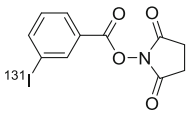
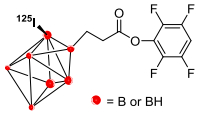
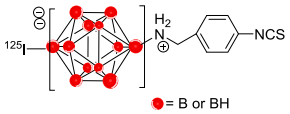
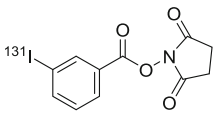
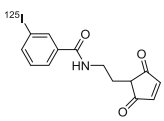
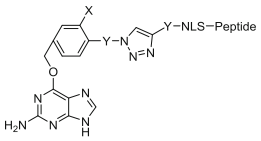
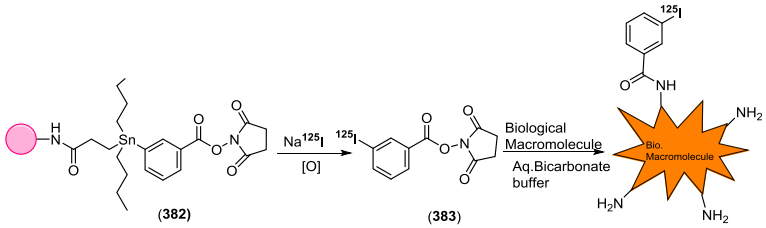
Organic compound	Prosthetic group	Ref.
 **(384)**	 **(385)**	[148]
Hexapeptide *N*-formyl-Nle-Leu-Phe-Nle-Tyr-Lys (**386**)	 **(387)**	[149]
Bovine serum albumin (BSA) (**388**)	 **(389)**	[150]
Trastuzumab (**390**)	 **(391)**	[151]
Insulin (**392**)	 **(393)**	[152]
Bovine serum albumin (BSA) (**388**)	*N*-succinimidyl 3-[^{125}I]iodobenzoate (**394**)	[153]
Goat IgG (**395**)	*N*-succinimidyl 3-[^{125}I]iodobenzoate (**396**)	[153]
Bovine serum albumin (BSA) (**388**)	Unactivated 3-[^{125}I]Iodobenzoic acid (**397**)	[153]
anti-PSMA Fab́(107-1A4 Fab́) (**398**)	Radioiodinated maleimido-closo-decaborate(2) derivatives	[154]
Monoclonal antibodies (**399**)	3-Iodophenyl isothiocyanate (**400**)	[155]
Monoclonal antibodies (**399**)	(Radioiodophenyl)-α-bromoacetamide (**401**)	[156]
Monoclonal antibodies (**399**)	α-Iodoacetyl derivatised tyramine (**402**)	[157]
Rabbit immunoglobin G (IgG) (**403**)	*N*-(m-[^{125}I]iodophenyl) maleimide (**404**)	[158]
Bovine serum albumin (BSA) (**388**)		
F3-Cys peptide (**405**)	 **(406)**	[159]

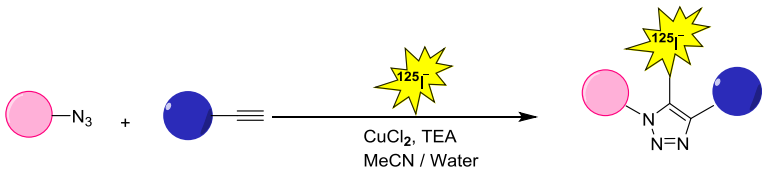
Table 12 continued

Organic compound	Prosthetic group	Ref.
Pure AGT protein (**407**)	 **(408)**	[160]

Scheme 9 Polymer supported organotin reagent for prosthetic labeling of macromolecules [153]



Scheme 10 Synthesis of 5 ^{125}I iodo-1,2,3-triazoles by Click reaction 466



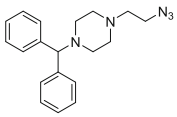
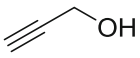
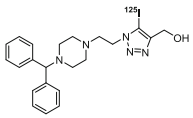
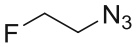
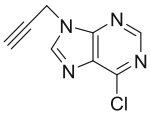
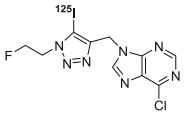
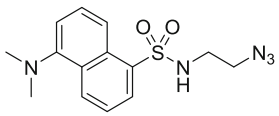
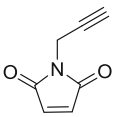
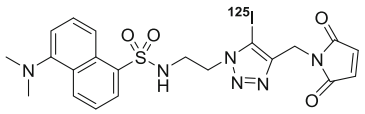
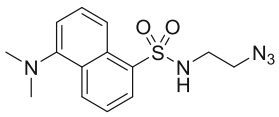
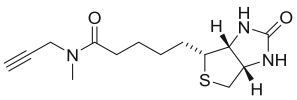
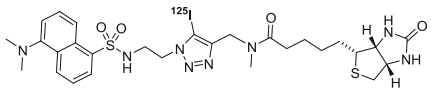
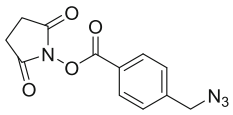
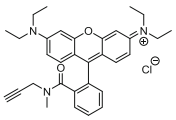
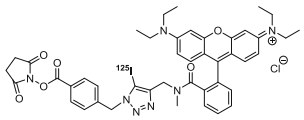
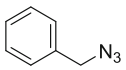
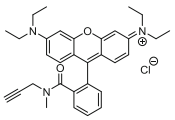
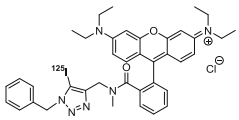
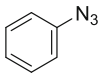
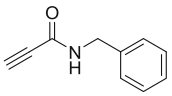
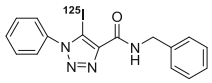
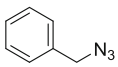
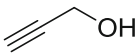
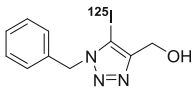
The main disadvantage of the process is the formation of intermediate aryl cation or aryl radicals that are capable to react with free electrons in vicinity to form side products. To suppress the issue high concentration of diazonium salts is used. The method can be used to synthesized radioiodinated derivatives of spiperone and various benzamides. Success of the reaction relies on the availability of appropriate aniline and other functional groups to react with alkyl nitrite or nitrous acid to form diazonium salt. Gattermann reaction is another form of standard iodo-dediazonization procedure which uses copper-bronze as catalyst [140]. Wallach reaction is also acknowledged in this regard, where diazotized amine can be trapped by the formation of triazene with secondary amine, these triazenes when react with inorganic halides under acidic condition give corresponding radiopharmaceutical [162].

Radioiodination by conjugate method

Direct radioiodination of proteins, MAbs and similar macromolecule is not feasible if molecules do not possess active functional group (or attaching sites) or may be unapproachable to iodinating agent or radioiodinated pharmaceutical thus prepared undergo deiodination in vivo). It is also possible that desired compound is not stable to harsh oxidizing conditions [150]. To cope with such issues, indirect radioiodination technique is used. It involves radioiodination of prosthetic group before or after conjugation with macromolecules. As whole if extra baggage of prosthetic and in some cases connecting bridge do not effect the binding properties, than the labeled compound will behave like parent compound [142, 149]. The important functional groups on proteins that can be used for conjugation are sulfhydryls, amines and oxidised sugars etc. In 2009, Rushan Lin et al. reported TCP (**389**) Table 12 as new potential bifunctional linker to copulate proteins and peptides. It was used for radioiodination of BSA (**388**) giving 75 % radiochemical yield and 99.8 % radiochemical purity [150]. In another study Pozzi et al. used prosthetic group (**387**) Table 12 to investigate the behavior of small peptides [149].

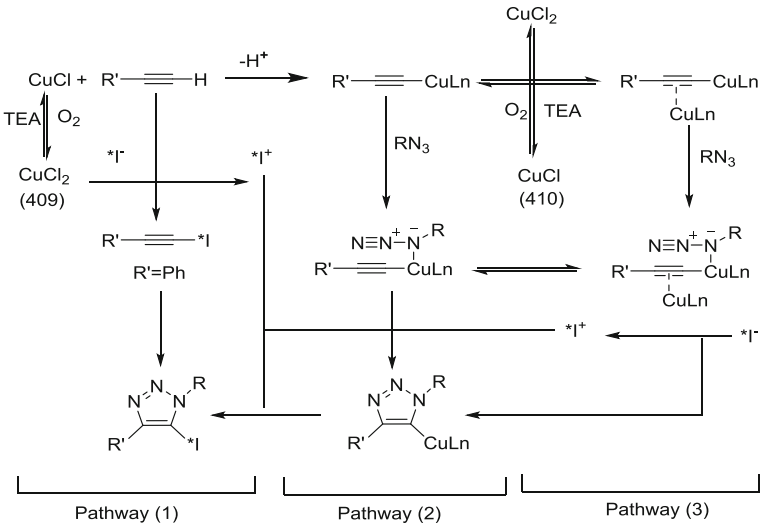
Coupling of protein amines with esters through amide linkage provides small stable molecule. The most commonly used ester is Bolton Hunter reagent (*N*-succinimidyl-3-(4-hydroxy5-[I*]iodophenyl)-propionate).The Bolton Hinter reagent however falls short with respect to in vivo enzymatic deiodination by deiodinases. In order to achieve stable labeled groups,3- and 4- radioiodinated phenylalkyl carboxylic acid esters and benzoic acid ere used for conjugation [143–146]. Among radioiodinated

Table 13 Compounds synthesized using click reaction

Azide	Alkyne	Product
 **(411)**	 **(412)**	 **(413)**
 **(414)**	 **(415)**	 **(416)**
 **(417)**	 **(418)**	 **(419)**
 **(420)**	 **(421)**	 **(422)**
 **(423)**	 **(424)**	 **(425)**
 **(426)**	 **(427)**	 **(428)**
 **(429)**	 **(430)**	 **(431)**
 **(432)**	 **(433)**	 **(434)**

prosthetic groups, *N*-succinimidyl-5-[I^{131}]iodo-3-pyridine carboxylate [147] and *N*-succinimidyl-3-(tri-*n*-butylstannyl radioiodo) benzoate are found to be very stable towards in vivo deiodination. In 2011, Gifford et al. tried to synthesized radiolabeled prosthetic group by using poly-mer-bound precursor for biological macro molecules conjugation (Scheme 9) [153]. Substrate (**388** and **395**) Table 12 was radiolabeled by same prosthetic group.

Imidate esters are also used as prosthetic groups that when co-reacted with protein yields stable amidine bonds e.g. imidate ester of phenol, which is also called Wood reagent. In addition aldehydes have been used for peptide conjugation to form stable radiolabeled molecule. This technique has been proposed for radioiodination of multimeric cyclic RGD peptides [141]. Some more examples are given in Table 12.



Scheme 11 Potential mechanistic pathways for the formation of 5 ^{125}I iodo-1,2,3-triazoles by Click reaction

Radioiodination by click chemistry

In 2012, Ran Yan et al. designed novel radioiodination route, in which copper(II) assisted reaction of azides, alkynes and [^{125}I] iodide gives 5 ^{125}I iodo-1,2,3-triazoles (Scheme 10). This method proved to be very straight forward, versatile and high yielding that provides access to many pharmacologically attractive tracers [161].

Variety of radioiodinated compounds (Table 13) are prepared by this method using 1.0 μM of azides and alkynes in the presence of equivalent copper(II) chloride (1.0 μM) and triethylamine (1.5 equivalent) at room temperature at 60 °C for 90 min. Mostly acetonitrile and water was used as solvent. Three possible mechanistic path ways (Scheme 11) were proposed for the formation of 5 ^{125}I iodo-1,2,3-triazoles however none of them fully explained the reported experimental data.

In order to confirm potential applications of 5- ^{125}I iodo-1,2,3-triazzoles for in vivo imaging and to assess the metabolic stability substrate (**422**, **425** and **428**) Table 13, were subjected to preliminary biological evaluation. Initial results showed that 5- ^{125}I iodo-1,2,3-triazzoles are resistant to in vivo deiodination because of smaller molecular probe and antibody conjugation. Hence flexibility of trisubstituted triazoles, and their metabolic stability has confirmed them as potential candidates for being radioiodinated pharmaceuticals in biomedical imaging with substantially highest therapeutic applications [161].

Conclusions

Nuclear perspectives of different radioiodine isotope make it exceptionally unique in the development of radioiodinated pharmaceuticals that are used in in vitro or in vivo assay screening, as long-lived low energy gamma emitter (^{125}I), for diagnosis (^{123}I, ^{124}I) and for radiotherapy (^{131}I).

Electrophilic or nucleophilic substitution of radioiodine is found to be satisfactory to obtain high radiochemical yield and specific activity regardless to few limitations. Actually choice of a particular reaction path way depends on structural and steric aspects of compounds to be labeled that suggest the feasibility of orientation and reactivity, reliability in terms of high radiochemical yield and specific activity. The presence of electron donating group accelerates electrophilic substitution. Here the choice of best oxidizing agent becomes priority. These oxidizing agents upon reaction with labeled sodium iodide produce electrophilic iodine specie that react with aromatic moiety to give respective radioiodinated compound. Drawbacks of this reaction is there may be either structural damage of compound to be labeled or possibility of side reactions due to harsh oxidizing conditions. These issues can be resolved by the use of mild oxidizing agent or some solid phase oxidizing agent.

Electron withdrawing groups promote nucleophilic substitution mechanism. Nuccleophilic aromatic radioiodination reactions are often carried out by diazonium salts, the issue of unstable intermediates can be overcome by starting with shelf stable triazenes. However not looking suitable synthesis of modified precursor, the critical reaction conditions and use of large amount of precursor made this method unpopular. Thus the method of choice in nucleophilic radioiodination is copper catalyzed halogen exchange reaction in an acidic or aqueous medium. In the absence of suitable activated aromatic moiety prosthetic groups are used to achieve the goal. Prosthetic group is first attached to the compound to be labeled and then radioiodinated by some suitable oxidizing agent. If compound is sensitive towards oxidizing agent then radiolabeling of

prosthetic group is done followed by the attachment to target compound.

Another approach is the attachment of an appropriate leaving group to that of desired molecule with subsequent replacement by radioiodine. Non-radioactive iodine, bromine, fluorine, diazotized aniline and organometallic compounds of boron, silicon, tin, thallium, mercury etc. can be used as leaving groups. Problem associated with this approach is the separation of radioiodinated compounds from unlabeled starting material, however high performance liquid chromatography is used to deal with this issue.

Acknowledgments This work was supported by the National Research Foundation of Korea grant funded by the Korean Government (Grant Nos. 2012M2B2B1055245 and 2012M2A2A6011335) and Korean Atomic Energy Research Institute. Authors also highly acknowledge Higher Education Commission of Pakistan for the award of PhD Fellowship under "PhD Fellowship for 5000 Scholars" (Indigenous) Scheme, Batch-VI, 2010 (17-5-6(Ps6-135)/HEC/Sch/2010).

Compliance with ethical standard

Conflicts of Interest Authors have no conflict of interest

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