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Radioiodination of 4-benzyl-1-(3-iodobenzylsulfonyl)piperidine, 4-(3-iodobenzyl)-1-(benzylsulfonyl)piperazine and their derivatives via isotopic and non-isotopic exchange reactions

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Abstract A mild and simple technique for preparing of 4-benzyl-1-(3-[^{125}I]iodobenzylsulfonyl)piperidine, 4-(3-[^{125}I] iodobenzyl)-1-(benzylsulfonyl)piperazine and their derivatives, as sigma-1 receptor ligands, with relatively high radiochemical yields via nucleophilic substitution reaction by means of isotopic and non-isotopic exchange reactions is described. Some factors affecting the radiochemical yield were commonly studied in presence of acidic medium at elevated temperature. Unfortunately, the radiochemical yields were weak. Some attempts were carried out in presence of polar aprotic solvents to enhance the radiochemical yield. *N*,*N*-Dimethylformamide was proved highly efficient for preparing of radioiodinated 4-benzyl-1-(3-iodobenzylsulfonyl)piperidine (4-B-[^{125}I]-IBSP, 70 ± 5.7 %) and 4-(3-iodobenzyl)-1-(benzylsulfonyl)piperazine (4-[^{125}I]-IBBSPz, 72 ± 6.0 %) at moderate temperature (100–105 °C) within 8 h. The specific activities of 4-B-[^{125}I]-IBSP and 4-[^{125}I]-IBBSPz (6,534.2 and 5,927.4 MBq/mmol) were obtained respectively.

Keywords Radioiodination · Isotopic and non-isotopic exchange · ^{125}I · 4-Benzyl-1-(3-iodobenzylsulfonyl) piperidine · 4-(3-Iodobenzyl)-1-(benzylsulfonyl) piperazine · Sigma-1 receptor ligands

Introduction

Nowadays, radioiodination of the biologically active compounds is used as a useful tool for diagnosis and treatment of a wide variety of diseases and cancers. Among them, radioiodination of the organic molecules is of particular importance. Achievement to this goal can be accomplished by a variety of techniques, depending on the structure of the compound to be labeled. Excellent reviews of radioiodination methods have recently been reported [1–3]. Although aromatic compounds possessing electron donating groups are easily radiolabeled by electrophilic iodination, radioiodination of deactivated aromatic rings suffer from some complexity. Despite the existence of a variety of methods for radioiodination of aromatic compounds such as radioiododethallation, radioiododestannylation, radioiododeboronation and radioiododehalogenation, there are still some structures need to more studies via their labeling, this is due to restrictions on their structural. The aromatic compounds with electron donating groups such as hydroxy, methoxy and amine substituents are radioiodinated by radioiododethallation method in presence of the thallium(III)-tris(trifluoroacetate) in trifluoroacetic acid medium and then by admixing of radioactive iodides [4, 5]. One of the most effective and convenient radioiodination methods represents the radioiododestannylation reaction. At the beginning, the bromo- or iodoaryl derivative intended for the labeling has to be stannylated. Most often the $(n\text{-Bu})_3$Sn group is used to replace the aryl halogen but Me_3Sn groups have also been applied [6, 7]. The oxidative cleavage of the boron–carbon bond with radioiodide/Chloramine-T has been shown to be useful for radioiodination of various organic compounds. After hydroboration, oxidation of radioiodide is performed with Chloramine-T forming HOI which then adds to the C–B bond. The reactivity of the C–B bonds depends on the position of boron which can either be formed from a terminal double bond or from an internal alkene [8, 9].

Radioiododehalogenation is the most common method for the introduction of radioiodine into organic molecules

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[10–14]. The iodide and bromide replacement induced by nucleophilic attack of radioiodide is an energy demanding process to produce radiopharmaceutical compounds [14]. The nucleophilic exchange reactions can occur with the aliphatic and aromatic compounds according to the nature of the leaving group. Mostly, nucleophilic substitution reactions occur slowly in case of the aromatic compounds comparing with the aliphatic compounds [12]. Moreover, the aromatic substrate must be activated by electron-withdrawing groups. To accelerate the exchange reactions in aromatic compounds, various metal-assisted reactions proved to be quite successful for nucleophilic radioiodinations of arenes [10, 13]. The radiochemical yields of all radioiodination reactions strongly depend on the amount of the starting material. Consequently, low specific activities must still be considered as the major drawback of this method [13].

Isotopic exchange reaction for aryl iodide is carried out by a wet method using different organic solvents like propylene glycol, at elevated temperatures (100–200 °C). Moreover, radioiodination is achieved in solid phase at high temperature and using in some cases the salts of Cu(I) and Cu(II) as catalysts or molten salts such as benzoic acid [15, 16], acetamide, ammonium sulfate, pivalic acid, citric acid and acetic acid, which have high dielectric constant to dissolve both of the substrate and radioiodine [10, 13, 17, 18]. In some cases the molten salts are not effective for radioiodination of some organic compounds. So, several explanations have been proposed to overcome the low radiochemical yield by studying the factors that affecting the labeling yield, such as the amount of substrate, temperature, reaction time and polar additives or by using different catalysts.

The sigma receptor was first described by Martin as a subtype of opioid receptors [19], but it is now known that the sigma receptor is a unique receptor, comprised of sigma-1 and sigma-2 sites [20]. Sigma receptors are involved in several biological processes, and sigma ligands might be promising as cancer treatment agents, cocaine abuse medicines, and valuable psychiatric drugs [21]. To date, a large number of ligands for both sigma subtypes have been explored [21]. Several radiolabeled sigma receptor ligands have been proposed for imaging the σ_1 receptor by single photon emission computed tomography [22, 23] and positron emission tomography [24, 25] as tumor imaging agents and/or sigma receptor imaging agents for investigating the CNS. Some of the halogenated 4-(phenoxymethyl)piperidine derivatives possessing moderate lipophilicity designed by Waterhouse et al. and Collier et al. [26–29] were reported not only as tumor imaging agents but also as sigma receptor imaging agents for investigating the CNS. In previous studies, we reported that most of 4,4-disubstituted arylalkyl/arylalkylsulfonyl

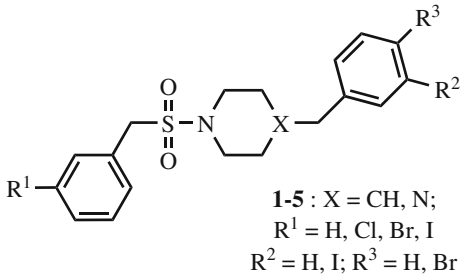


Fig. 1 General structural formula of radioiodinated sulfonamides **1–5**, substituents are listed in Table 3

piperazine and piperidine-based derivatives showed very high binding affinities for sigma receptors. Furthermore, 4-benzyl-1-(3-iodobenzylsulfonyl)piperidine and 4-(3-iodobenzyl)-1-(benzylsulfonyl)piperazine showed about 96 and 65 times higher binding affinities for the σ_1 (K_i = 0.96 ± 0.05 and K_i = 1.8 ± 0.3 nM) than the σ_2 receptor (K_i = 91.8 ± 8.1 and K_i = 117 ± 10 nM) respectively [30].

In current study, the authors endeavored to radioiodinate the compounds **1** and **4**, 4-benzyl-1-(3-iodobenzylsulfonyl) piperidine and 4-(3-iodobenzyl)-1-(benzylsulfonyl)piperazine (Fig. 1), including a high strained sulfonamide bond and possessing the relatively deactivated aromatic rings. These molecules are sigma-1 receptor ligands with high binding affinities and good σ_1/σ_2 selectivities [30]. On the basis of our literature survey, all of the reported radioiodination methods could not result in radiolabeled compounds with high radiochemical yield and desired specific activity. Therefore, we investigated the isotopic and non-isotopic exchange reaction by changing the physical and chemical conditions affecting the labeling process on these compounds with no-carrier-added $Na^{125}I$. Radiolabeling of the compounds **1** and **4** were performed with the view to further studies to its possible application as tumor imaging agents.

Materials and methods

All commercially available chemicals and reagents were used without further purification. The ^{125}I used was a no-carrier-added solution of $Na^{125}I$ (3,700 MBq (100 mCi)/0.2 mL) in reductant-free 0.04 N NaOH obtained from Institute of Isotopes Co. (IZOTOP). Radioactivity was quantified with a 600 B GAMMATEC γ-counter. *N,N*-Dimethylformamide (DMF) was dried by 4 Å molecular sieve prior to use. All radioiodination reactions were conducted inside a plexiglass glove box vented with an activated charcoal radioiodine trap. Thin layer chromatography (TLC) analyses were performed on Merck silica gel-60F254 aluminum-backed plates. The radiochemical yields of radioiodinated products were assessed using TLC by counting the cut sections in a gamma counter. Column

chromatography was performed on Merck silica gel-60 (230–400 mesh) eluted by ethyl acetate/*n*-hexane (2:3) as the solvent system in which the R_F of $Na^{125}I$ was from 0 to 0.05.

General procedure for preparation of 4-benzyl-1-(3-substituted benzyl)piperidines **1–3**

To a solution of arylmethanesulfonyl chloride (1 mmol) in dry CH_2Cl_2 (5 mL) was added 4-benzylpiperidines (1 mmol, 0.179 mL) followed by triethylamine (1 mmol, 0.14 mL) and the mixture was stirred for 2 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with H_2O and then with 2 N HCl. The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue was purified by short column chromatography over silica gel. Elution with ethyl acetate in hexane (2:3) furnished compounds **1–3** in good yields [30].

General procedure for preparation of 4-(substituted benzyl)-1-(benzylsulfonyl)piperazines **4** and **5**

These compounds were prepared from phenylmethanesulfonyl chloride and 4-(substituted benzyl)piperazines as described for compounds **1–3** [30]. In case of these compounds, after the completion of the reaction, the residue was diluted with CH_2Cl_2, washed with H_2O and then with saturated $NaHCO_3$.

Representative procedure for radioiodination of compounds **1–5**

Radioiodination of the compounds **1–5** were performed by a modified procedure previously described [12]. The method adopted for radiolabeling of 4-benzyl-1-(3-iodobenzylsulfonyl)piperidine (**1**) (4-B-IBSP) is described. Briefly, 37 MBq (1.0 mCi) of $Na^{125}I$ was transferred to a 5 mL U-shaped reactivial and the vial cap was fitted with inlet and venting needles, the latter fitted with activated carbon cartridges to trap any volatile radioactivity (radioiodine). The reaction vial was closed, the radioactivity was measured and then the solvent was evaporated to dryness under a stream of dry nitrogen. Anhydrous ethanol (100 μL) was added and re-evaporated to dryness under above mentioned condition. The radioactivity was measured again to determine loss of radioiodine during the drying procedure. Then 40 μL of a 165 mM solution of 4-B-IBSP in anhydrous DMF was added to the reactivial, sealed and placed in a heated oil bath. After heating at desired temperatures for certain times, the vial contents were cooled and the DMF removed under a stream of dry nitrogen. The solid residue was dissolved in 100 μL of dichloromethane and then was purified by passing it through a short column chromatography by silica gel eluted by mixture of the ethylacetate/*n*-hexane (2:3) as a mobile phase. The fractions containing the desired compound were pooled together and co-spotted on TLC along with authentic "cold" 4-B-IBSP and developed in EtOAc/n-Hex (2:3). The R_F of the cold compound and 4-B-[^{125}I]-IBSP were found to be 0.62 in the above solvent system. The radiochemical yield and the specific activity were obtained 70 ± 5.7 % and 6,534.2 MBq/mmol (176.6 mCi/mmol) respectively.

Results and discussion

The modified isotopic and non-isotopic exchange method reported here is one which was evolved during the development of 4-B-[^{125}I]-IBSP and 4-[^{125}I]-IBBSPz as sigma-1 receptor ligands [30]. These compounds have melting points of 136–137 °C and 151–153 °C respectively, and because of containing of a strained sulfonamide bonds, they are very unstable in high temperatures as well as nucleophilic conditions. All of our attempts for radioiodination of 4-B-IBSP and 4-IBBSPz with $Na^{125}I$ by commonly used methods such as radioiododethallation [4, 5], radioiododestannylation [6, 7] and radioiododeboronation [8, 9] reactions as well as ammonium salts or copper(I)- and copper(II)-assisted radioiodinations [10–14] were unsuccessful. Therefore, we focused on the isotopic and non-isotopic exchange reaction with some modifications.

The attempts for preparing of 4-B-[^{125}I]-IBSP via the direct isotopic exchange reaction under a variety of previously established conditions, which gave the low in radiochemical yield of 4-B-[^{125}I]-IBSP as shown in Table 1 [17, 31–33]. The results indicate that the exchange reaction does not occur by mixing of precursor and $Na^{125}I$ at elevated temperature (entry 1) only, but also in presence

Table 1 Isotopic exchange of 4-B-IBSP with $Na^{125}I$ under solid phase conditions

Entry	Additive[a]	Temperature (°C)	% free iodide (TLC)	% exchange (TLC)
1	None	110–115	92 ± 4.0	0
2	A	125–130	16 ± 2.0	0
3	B	110–115	52 ± 5.0	11 ± 3.0
4	C	110–115	45 ± 3.0	18 ± 2.0
5	D	120–125	33 ± 6.0	20 ± 4.0

Conditions 4-B-IBSP (1.0 mg), $Na^{125}I$ 37 MBq (1.0 mCi), additive, 30 min, under N_2 atmosphere

[a] *Additive* $A = (NH_4)_2SO_4$, B = 2,5-dihydroxybenzoic acid, citric acid, $SnSO_4$, $CuSO_4{\cdot}5H_2O$, C = benzoic acid, citric acid, $SnSO_4$, $CuSO_4$, under N_2 flow, D = benzoic acid

of ammonium sulfate (entry 2) as an agent increases the acidity of the reaction medium. The lack of exchange reaction may be due to the in situ formation of ammonia produced by thermal decomposition of ammonium sulfate and its nucleophilic attack. The cleavage of the strained sulfonamide bond was seen by TLC. Entries 3 and 4 shows the possibility of halogen exchange reactions by adding benzoic acid derivatives, citric acid, stannous sulfate and copper sulfate pent-hydrate for preparing of 4-B-[^{125}I]-IBSP. The radiochemical yield was slightly increased from 11 to 18 %. Attempts were made to develop and increase the radiochemical yield by failing add salts of Cu(I) as a catalyst at high temperature (entry 5) but to no avail because the RCY unchanged (20 %).

It seems probably that the formation and loss of volatile (molecular) radioiodine which occurs during the exchange process in presence of additive A, is a reflection of the existing oxidizing conditions and is in contrast to gradual increase in the acidity of the reaction medium. Limited success of the exchange reactions was observed in case of the additive B or C, accompanied by a reduction of the free radioiodine. The RCY is relatively low even in the absence of oxygen or in presence of a reducing agent under solid phase condition, it is attributed to the in situ formation of the nucleophilic side-products as a result of breaking of the sulfonamide bond of precursor.

The results of the effect of organic solvents, reaction temperature and reaction time as well as the amount of precursor on the RCY of 4-B-[^{125}I]-IBSP are shown in Table 2. Although it was used the polar solvents, such as alcohols but the RCY of 4-B-[^{125}I]-IBSP was not affected, whatever the reaction temperature and reaction time (entries 1 and 2). It is likely that the low RCYs were obtained because of the nucleophilic property of these solvents and relatively low dielectric constant. Although DMSO is non-nucleophilic solvent with high dielectric constant, but it gives low RCY of 4-B-[^{125}I]-IBSP at high temperature as shown in Table 2 (entries 3 and 4). The RCY of 4-B-[^{125}I]-IBSP was gradually increased by increasing the dielectric constant of solvents such as12.5, 18.3 and 36.7 for *t*-BuOH (entry 1), isopropyl alcohol (entry 2) and DMF (entry 5), respectively [34]. It seems that the lower percent of the labeled product, which was obtained in DMSO with more dielectric constant than that of DMF, caused the in situ formation of a nucleophilic intermediate in the basic medium. However, this problem was eventually overcome by changing the solvent at higher temperature (dry DMF, a non-nucleophilic polar solvent, instead of the above mentioned solvents) which afforded the radioiodinated product in 48 ± 5.0 % radiochemical yield (entry 6).

The influence of temperature on RCY is also shown in Table 2. The exchange reaction was performed with 40 μL of a 55 mM solution of 4-B-IBSP in anhydrous DMF and 2 μl of 37 MBq (1.0 mCi) Na^{125}I in 0.04 N NaOH solution. The data indicate a significant effect of temperature on the exchange reaction rate. A trace amount of the radiolabeled 4-B-[^{125}I]-IBSP was only formed in DMF at 85–90 °C. The RCY increased rapidly between 100 and 105 °C, at which point a RCY plateau of about 48 ± 5.0 % was reached. Due to thermal decomposition of precursor by raising the temperature up to 120 °C, so it is not effect on the RCY (entry 7). A temperature of 100–105 °C was selected for further optimization experiments, to insure that the reactions were performed in an optimum temperature range. Moreover, optimum reaction time was obtained 8 h by conducting the reaction mixture at different reaction times (entries 8 and 9).

A similar phenomenon to organic synthesis, in which the reaction rate is proportional to the amount of substrate, is noticed in labeling reactions. With higher amounts of

Table 2 The modified conditions for radiolabeling of 4-B-3-IBSP with iodine-125

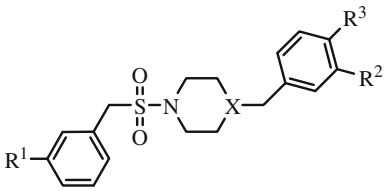
Entry	Solvent[a]	Sample (mg)	Temperature (°C)	Time (h)	% exchange (TLC)	RCY (%)[b]
1	*t*-BuOH	1	85–90	6	17 ± 3.0	–
2	Isopropyl alcohol	1	85–90	6	19 ± 3.0	–
3	DMSO	1	85–90	6	Trace	–
4	DMSO	1	115–120	6	16 ± 2.5	–
5	DMF	1	85–90	6	28 ± 4.0	–
6	DMF	1	100–105	6	57 ± 4.8	48 ± 5.0
7	DMF	1	125–130	6	43 ± 5.0	–
8	DMF	1	100–105	8	65 ± 7.0	59 ± 3.8
9	DMF	1	100–105	11	67 ± 4.0	58 ± 4.0
10	DMF	2	100–105	8	70 ± 5.5	63 ± 6.0
11	**DMF**	**3**	**100–105**	**8**	**81 ± 4.0**	**70 ± 5.7**
12	DMF	5	100–105	8	78 ± 6.0	–

[a] The dried solvents should be used

[b] The percentage of RCYs were obtained after purification by column chromatography

Bold value indicates the best optimized conditions for radioiodination of 4-B-3-IBSP

Table 3 Isotopic and non-isotopic exchange reactions of some of 4,4-disubstituted arylalkyl/arsulfonyl piperazine and piperidine-based derivatives



Compounds	R^1	R^2	R^3	X	% exchange (TLC)	RCY (%)[a]
4-Benzyl-l-(3-iodobenzylsulfonyl)piperidine (**1**)	I	H	H	CH	81 ± 4.0	70 ± 5.7
4-Benzyl-1-(3-bromobenzylsulfonyl)piperidine (**2**)	Br	H	H	CH	34 ± 3.0	–
4-Benzyl-1-(3-chlorobenzylsulfonyl)piperidine (**3**)	Cl	H	H	CH	0	–
4-(3-Iodobenzyl)-1-(benzylsulfonyl)piperazine (**4**)	H	I	H	N	85 ± 7.0	72 ± 6.0
4-(4-Bromobenzyl)-1-(benzylsulfonyl)piperazine (**5**)	H	H	Br	N	89 ± 6.0	77 ± 4.0

Conditions 40 µl of a 165 mM solution of the markers in anhydrous DMF, $Na^{125}I$ 37 MBq (1.0 mCi), under N2 atmosphere, 100–105 °C, 8 h

[a] The percentage of RCYs were obtained after purification by column chromatography

precursor, higher labeling yields are obtained (entries 10 and 11). At fixed temperature (100–105 °C) and optimized reaction time (8 h), the RCY increased rapidly and reached a plateau (70 ± 5.7 % RCY) of about 0.007 mmol (3 mg) of 4-B-IBSP (entry 11). Therefore, a precursor weight of 3 mg was chosen to insure that the reactions were performed in an optimum range of precursor concentration.

To further the study of the scope of the reaction, we subjected some of the analogues of compound **1** via these radioiodination conditions as shown in Table 3. Obviously, the replacement of chlorine and bromine with iodine reduces the RCYs of the labeled products. However, there is a close relation between the percent of exchange and the nature of the leaving group (R^1 = Cl, Br, I). Moreover, since aromatic compounds with halogen substitution at *meta* position are not very active towards nucleophilic substitution and are more stable than *para* or *ortho* forms in aqueous solutions [35], compound **5** with bromine substitution at *para* position shows higher RCY than compounds **1**–**4** in this methodology.

Optimization conditions for labeling of compounds **1**, **2**, **4** and **5** with $Na^{125}I$

Radioiodination of the compound **1**, was carried out by the following procedures. Evaporating 2 µL of $Na^{125}I$ (37 MBq (1.0 mCi)) to dryness and then adding 100 µL ethanol, re-evaporating. After that, 40 µL of 4-B-IBSP (165 mM) in anhydrous DMF was added into the reaction vial (U-shape), then closed and placed it in an oil bath at a temperature of 100–105 °C within 8 h to obtain the radiochemical yield of 70 ± 5.7 % with 6,534.2 MBq/mmol (176.6 mCi/mmol) specific activity. In case of the compound **2**, the same procedures were carried out as similar to that was done for the compound **1**. It gives the lower radiochemical yield (34 ± 3.0 %) than that was obtained with the compound **1**. The R_F values 0.64 and 0.59 were obtained for the radiolabeled of 4-benzyl-1-(3-bromobenzylsulfonyl)piperidine (compound **2**) and unlabeled compound, respectively. All efforts for the radioiodination of 4-benzyl-1-(3-chlorobenzylsulfonyl) piperidine (compound **3**) without success to form the radioiodinated product. Radioiodination of the compounds **4** or **5** was carried out by a similar method. In case of radioiodination of 4-(3-iodobenzyl)-1-(benzylsulfonyl)piperazine (compound **4**), R_F values for the radiolabeled and unlabeled compound were obtained to be 0.63. While, the R_F values 0.60 and 0.53 were obtained for radiolabeled of 4-(4-bromobenzyl)-1-(benzylsulfonyl)piperazine (compound **5**) and unlabeled compound, respectively. The radiochemical yields were equal to 72 ± 6.0 or 77 ± 4.0 % with the specific activity 5,927.4 or 6,752.5 MBq/mmol (160.2 or 182.5 mCi/mmol), respectively.

Discussion of the mechanism of the isotopic and non-isotopic exchange reactions as well as of the nature of the reactive radioiodine species responsible is complicated by the nonclassical behavior of iodide in very small quantities (37 MBq (1.0 mCi) of $Na^{125}I$ = 0.46 nmol). For example, several oxidation products of iodide, which are quite unstable in macroquantities, such as HIO or HIO_2 are easily formed in no-carrier-added solutions of radioiodide and can exist for long periods of time in such solutions [36, 37]. Nevertheless, iodide reacts as anion in nucleophilic substitution reaction of deactivated aromatic compounds with or without copper catalysts. This reaction is difficult because the π electron cloud of the aromatic

system rejects the electron-rich nucleophile and the delocalization, and therefore, stabilization of the negative charge during the reaction is not possible. These effects can be compensated by using Cu(I) to aid to replacement of radioiodide on aromatic rings. However, in this study, the iodide exchange reaction could proceed through a nucleophilic substitution type transition state facilitate formed at polar media in which the radioiodide is positioned in the side of the departing iodide. Nevertheless, the mechanism of the exchange process under the condition utilized for this study is not completely clear.

The major advantage of this modified isotopic exchange reaction lies in the purification. As the exchange employs no metals or solvents incompatible with human use and yields a single product of known structure, purification requires minimal and fort. The reaction mixture is dissolved in dichloromethane and is passed through a short column to remove free radioiodine. After evaporation of the solvents by reduced pressure, the solution is now ready for formulation for the human use.

Conclusion

A labeling procedure was therefore developed for radioiodination of sigma-1 receptor ligands and optimized with regard to temperature, selecting of the appropriate solvent, amount of precursor and reaction time. With these modifications, the synthesized compounds containing a high strained sulfonamide bond and possessing the deactivated aromatic rings radioiodinated successfully with RCYs > 70 % by a semi molten condition in DMF medium with an 8 h reaction time at 100–105 °C. Using the reagent concentrations (37 MBq (1.0 mCi) of $Na^{125}I$; 165 mM of markers) developed for these optimization studies, nominal specific activities ranged from 5,927.4 MBq/mmol (160.2 mCi/mmol) to 6,752.5 MBq/mmol (182.5 mCi/mmol) were obtained. However, we studied the effects of increasing the amount of precursor, the dielectric constant of the solvent, the reaction time as well as the reaction temperature on RCY of the ^{125}I-labeled 4-B-IBSP. Although, aromatic compounds with halogen substitution at *meta* position are not very active towards nucleophilic substitution, but it is likely that the high dielectric constant of the solvent promoted the replacement of iodide at transition state. The exchange of radiolabeling of the compounds **1** and **4** were performed with the view to further studies to its possible application as tumor imaging agents.

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