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Research Article

The synthesis of dopaminergic radioligands labelled with tritium and iodine-125

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Abstract: The preparation of dopaminergic ligands radiolabelled with either tritium or iodine-125 has been an extremely important undertaking to advance understanding of this critical receptor class and the topic is reviewed from 1976 through 2006. Although not an exhaustive compilation of references, the cited examples highlight the many methods employed to prepare these useful reagents. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: dopaminergic; tritium; iodine-125

Introduction

Dopamine plays a critical neurotransmitter role in numerous mammalian physiological functions. As the dominant catechol neurochemical, it exerts its exquisite multiple effects by means of transmembrane G protein-coupled receptors. Based on biochemical evidence, this receptor family has been further divided into subtypes referred to as the D1, D2, D3, D4 and D5 receptors and some of these may exist in both high- and low-affinity states. However, even after decades of study, a complete understanding of the functional roles for all these individual receptor classes still appears incomplete. Abnormalities in the activity of dopamine receptors are thought to be in part responsible for such terrible diseases as schizophrenia, Parkinson's disease, attention deficit disorder and drug abuse among others. Therefore, the identification of potent dopaminergic agonists and antagonists has proven crucial to the discovery of safe and effective drugs in this area.[1] Clearly, the synthesis and characterization of radiolabelled dopaminergic ligands with tritium and iodine-125 have played a significant role in this important drug development process. This review will explore the successful techniques to label the structurally diverse collection of dopaminergic radioligands with tritium and iodine-125. It is not intended to be an exhaustive coverage of the voluminous literature in this field, but will showcase representative examples of synthetic strategy while spanning the momentous time period of 1976 to the end of 2006.

Tritiated dopaminergic radioligands

As a timely summary of the many methods to label compounds with tritium, the review by Saljoughian is recommended.[2] The methods related in this discussion for dopaminergic radioligands are essentially placed in the order of increasing specific activity outcome.

Tritium exchange reactions

Although rarely utilized because of the attendant low specific activity, tritium exchange reactions either with tritium gas or tritiated water and with or without catalyst have occasionally been used to prepare tritiated dopaminergic radioligands. Muccino and coworkers described the first tritium labelling of the antipsychotic haloperidol at very low specific activity using tritiated water[3] and a similar procedure was used to label (*R*)-(−)-apomorphine and (*R*)-(−)-*N*-propylnorapomorphine.[4] Recently, the low specific activity exchange tritiation of dopamine itself was reported as well.[5]

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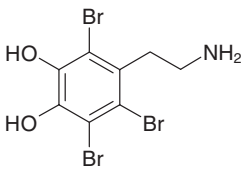
Catalytic tritium dehalogenation

Because many dopaminergic compounds contain electron-rich aromatic rings which can be readily halogenated by various methods, catalytic tritium dehalogenation has remained a useful method of choice for tritiation of these ligands at reasonably high specific activity. We were surprised to learn that the preparation of tribromodopamine (**1**) had never been described, but it proved to be easily synthesized and a very convenient precursor to afford [ring-^{3}H] dopamine at 44 Ci/mmol by catalytic (5% Pd/C) tritium debromination.[6] In this same report we described the tritiation of several fluorinated congeners as well. Using a similar approach with precursor **2**, we also obtained [8,9-^{3}H] (*R*)-(−)-apomorphine.[7] We employed a catalytic tritium dehalogenation scheme for the preparation of the irreversible agonist [8,9-^{3}H] (*R*)-(−)-*N*-chloroethylnorapomorphine[8] and [5,8-^{3}H] (+/−)-6,7-ADTN[9] too. In all of these cases, proton-decoupled tritium NMR was utilized to characterize the products.



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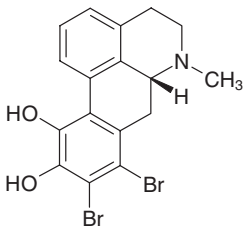

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The 2,3,4,5-tetrahydro-1H-3-benzazepine class of compounds, decorated with a variety of diverse functionality, has been a rich source of valuable dopaminergic ligands, especially D1 receptor antagonists. As a member of this class, (+/−)-SCH 23390 contains both a chlorine and hydroxyl group in the 7 and 8 positions, respectively, and was the subject of a tritiation study.[10] Hoping to exploit the presence of the large cyclic tertiary amine, a Leonard oxidation[11] of it to the enamine was first attempted. This approach had been used in the past with great success in the tritiation of such morphinan ring systems as [15,16-^{3}H] buprenorphine.[12] However, attempts at using mercuric oxide to create an enamine analogue of (+/−)-SCH 23390 inexplicably failed and the authors turned to a catalytic tritium dehalogenation approach. Bromination of (+/−)-SCH 23390 afforded the monobromo analogue in modest yield with halogenation occurring as expected only *ortho* to the phenol. Catalytic tritium dehalogenation for a short time using 5% Pd/C was selective enough to effect exclusive debromination and provide the desired product in modest yield and specific activity. In another report, two other compounds structurally related to (+/−)-SCH 23390 were also successfully tritiated.[13] (*R*,*S*)-SKF 82526 containing multiple hydroxyl groups was solely monobrominated in the 4-hydroxyphenyl ring and subsequently catalytically tritium debrominated to give [^{3}H] (*R*,*S*)-SKF 82526 at 15–23 Ci/mmol. In an attempt to elevate its specific activity and enhance receptor-binding performance, the *R* enantiomer alone of this compound was also diiodinated on the 4-hydroxyphenyl ring with ICl and tritiated in analogous manner to obtain [^{3}H] (*R*)-SKF 82526. However, both forms of [^{3}H] SKF 82526 were found to be rather unstable and storage solvent studies were conducted to minimize decomposition. The potential racemization of its benzylic chiral center during the tritiation was arguably ruled out by demonstrating that the chiral integrity was maintained during a parallel catalytic hydrogen dehalogenation. In the same paper an identical strategy was also used to prepare structurally related [^{3}H] SKF 38393.

The benzamide class of drugs has been another productive area to identify useful dopaminergic ligands. Sulpiride, a member of this group, was first successfully tritiated by a catalytic tritium debromination method at moderate specific activity.[14] Interestingly, conventional bromination conditions for sulpiride failed, but it could be successfully brominated with a mixture of hydrogen bromide and hydrogen peroxide. A similar method was also employed by these same authors to prepare the related drug [^{3}H] sultopride. Other benzamide dopaminergics that have been radiolabelled by catalytic tritium dehalogenation include NCQ 115[15] and a selective D4 receptor agonist by Abbott radiochemists.[16] In this last example, catalytic tritium dehalogenation of a tetrabromo precursor afforded the desired product at a high specific activity of 88 Ci/mmol.

Bromine and iodine have not been the only halogens to serve as valuable precursor functionality for catalytic tritium dehalogenation. Under certain circumstances even chlorine has been employed. For instance, the dopamine reuptake inhibitor mazindol has been tritiated by catalytic tritium dechlorination.[17] Also, we prepared and characterized [benzoyl-3,4-^{3}H] cocaine (**3**), utilizing a convenient dichlorophenyl precursor. Its proton-decoupled tritium NMR demonstrating exclusive aromatic tritium labelling is shown in Figure 1. Thurkauf reported the synthesis of the selective D4 receptor radioligand [^{3}H] NGD 94-1 (**4**) at a specific activity of 57 Ci/mmol using a multiple bromo dichloro iodo precursor.[18] The goal of this project was the development of a radioligand that could be used to explore the role of the D4 receptor in

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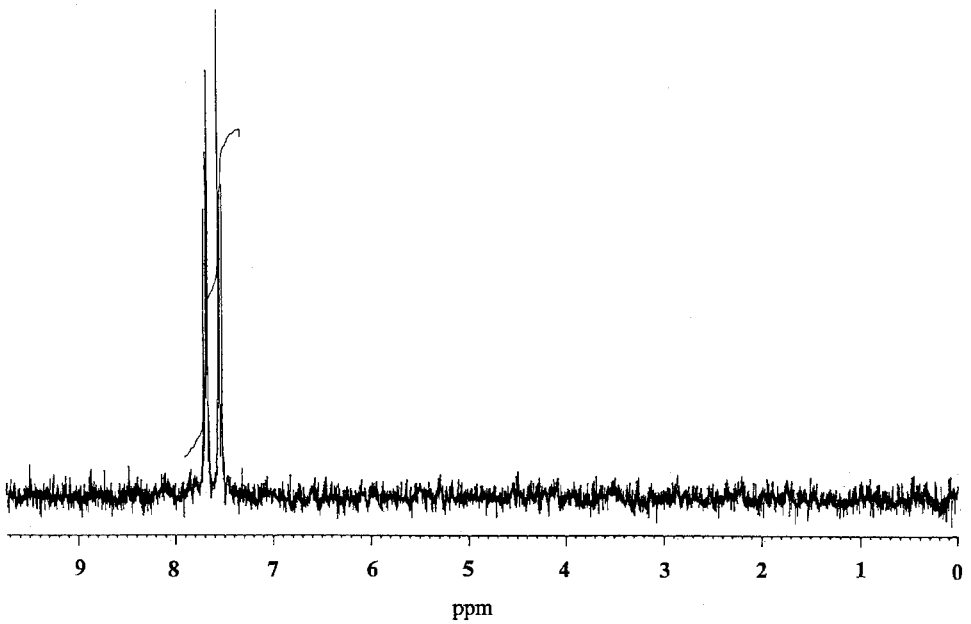
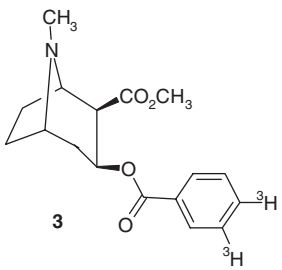


Figure 1 Proton decoupled tritium NMR (CD_3OD) of 3.

schizophrenia and other neurological diseases but with greater D4 receptor selectivity than [^{3}H] clozapine.



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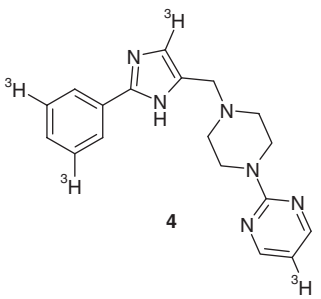

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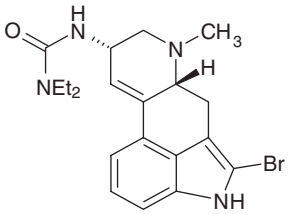
The strategy of catalytic tritium dehalogenation raises the intriguing issue of possible chemoselectivity in the process; namely, selective tritium dehalogenation without reduction of other accompanying functionality such as olefins, nitro and cyano groups or other halogens. The selective catalytic tritiation of an aryl bromide or iodide precursor also containing an aryl chlorine has already been described above for 5% Pd/C[10] and Lindlar catalyst ($Pd/CaCO_3$).[13] Also, the catalytic tritium polydebromination of a nitrile containing precursor has been reported.[16] Pfizer investigators also utilized Rosenmund catalyst ($Pd/BaSO_4$) to accomplish a selective catalytic tritium debromination in the presence of an aryl chlorine at 40–50 psi.[19] Demonstrating the chemoselectivity of a catalytic tritium debromination in the presence of an olefin, we also employed Lindlar catalyst on precursor **5** to obtain [2-^{3}H] (–)-lisuride (**6**), a D2 receptor agonist.[20] Again, proton-decoupled tritium NMR provided conclusive evidence of the exclusive 2-position tritium labelling of **6**. Other recently published reports[21–23] using sodium borotritide in conjunction with certain transition metal catalysts should also provide a valuable tool to effect such chemoselective tritium dehalogenations as they are required in this and other radioligand areas.



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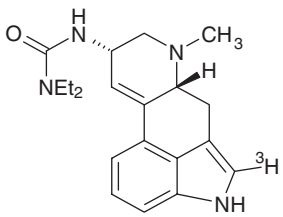

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Catalytic tritiation of unsaturated positions

The catalytic tritiation of various unsaturated precursors has also been an effective method to prepare many dopaminergic radioligands. Several benzamide class dopaminergics were tritiated at higher specific activity by means of a general and efficient approach as reported in publications from the Astra Lakemedel laboratory.[24–26] Taking advantage of the fact that a chiral pyrrolidine moiety is prevalent in many compounds of this group, these

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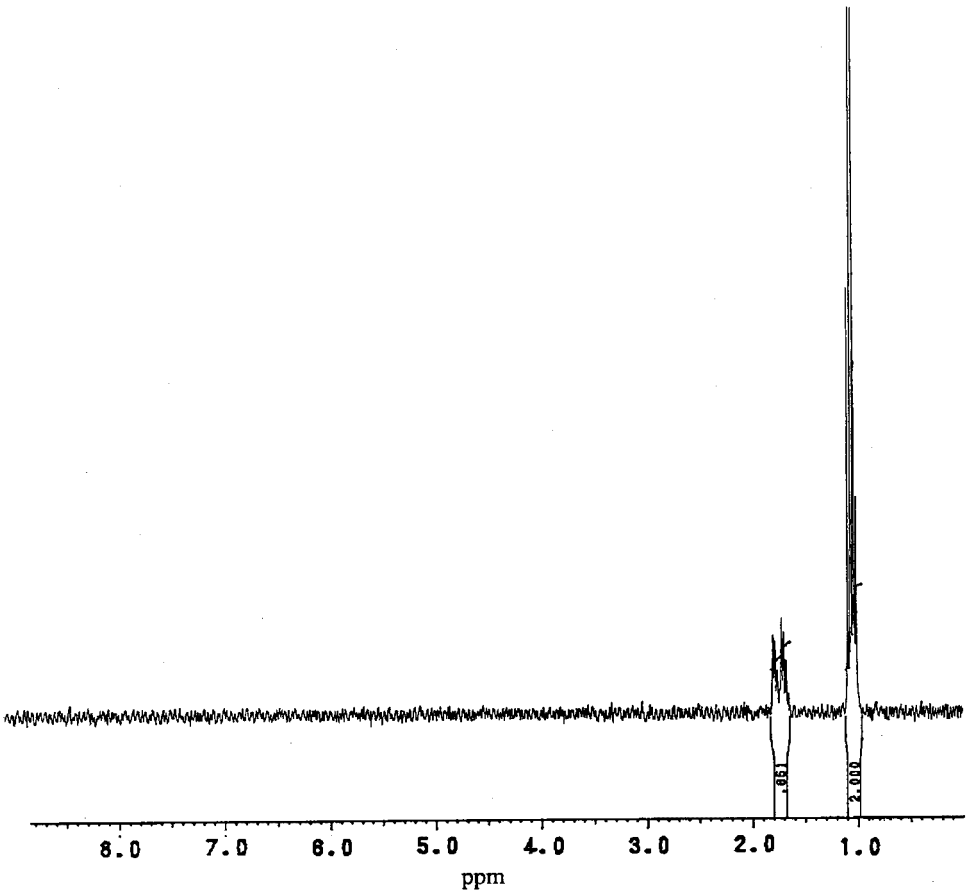

Figure 2 Proton decoupled tritium NMR (CD_3OD) of 8.

workers prepared a common precursor, (*S*)-*N*-acetyl-3, 4-dehydroprolinamide and catalytically tritiated it to the corresponding [3,4-pyrrolidine-^{3}H] (*S*)-2-(amino-methyl)-1-ethylpyrrolidine. This intermediate was then condensed with various functionalized benzoic acid derivatives to obtain an ensemble of interesting products. In this way, tritiated versions of such compounds as raclopride, eticlopride and remoxipride with specific activities as high as 58 Ci/mmol were prepared. In the case of [3,4-pyrrolidine-^{3}H] remoxipride, the location of tritium labelling was clearly elucidated by proton-decoupled tritium NMR and the observed tritium–tritium coupling constant of 10.3 Hz was consistent with the assigned doubly labelled structure. Also, the integrity of the chiral center was inferred by demonstrating the lack of racemization in a corresponding catalytic hydrogenation.

A tritiated photoaffinity analogue of the benzamide dopaminergic sulpride was also prepared by a related but slightly different strategy; namely, the conversion of an allyl group to a tritiated propyl group.[27] The use of an appended allyl group has been a convenient entry to other valuable tritiated dopaminergic radioligands. We employed this method both in the preparation of [*N*-propyl-^{3}H] (−)-*N*-propylnorapomorphine (**7**) [28] as well as [*N*-propyl-^{3}H] quinpirole (**8**), a radioligand with high affinity for the D2 receptor subclass.[29] For product **7**, proton-decoupled tritium NMR also corroborated the exclusive tritium labelling of the propyl group. A very similar tritium NMR for radioligand **8** is shown in Figure 2. This same allyl tritiation methodology was further utilized in the labelling of D2 agonists U-91356 and U-86170,[30,31] the latter containing two tritiated propyl groups. We were also able to introduce two tritiated *N*-propyl pendants in the synthesis and characterization of the selective D3 receptor agonist [^{3}H] (+/−)-7-hydroxy DPAT.[32] In our case the concomitant tritiation of a cyclic enamine conferred even higher specific activity on the product. Other tritiations that have exercised this strategy were the radiolabelling of the dopamine agonist pergolide by Wheeler and co-workers at Eli Lilly[33] and the D2 receptor agonist (+)-PHNO by

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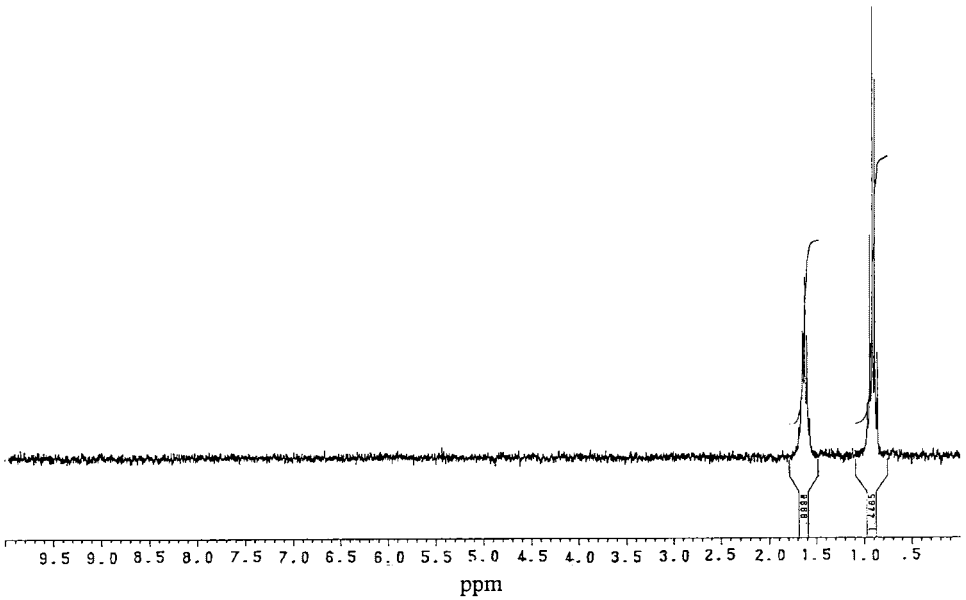
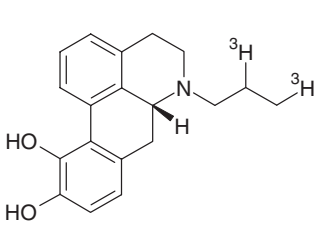


Figure 3 Proton decoupled tritium NMR (CD_3OD) of [*N*-propyl-^{3}H] (+)-3-PPP.

Seeman and colleagues at the University of Toronto.[34] Besides the allyl group, the propargyl functionality has also facilitated the installation of tritiated propyl groups at even higher specific activity. This methodology was used to tritiate the D3 receptor agonist PD 128907[35] and the D2 receptor agonist N-0437 as a racemic mixture.[36] We later employed a chiral *N*-propargyl analogue of N-0923 to prepare [*N*-propyl-^{3}H] N-0923, the (–) enantiomer of N-0437 with the most potent D2 receptor activity.[37] Again, its proton-decoupled tritium NMR documented the strictly propyl radiolabelling. Although the dopamine autoreceptor agonist (–)-3-PPP had been previously tritiated at modest specific activity by means of a ring olefin analogue,[38] we were able to prepare its other enantiomer [*N*-propyl-^{3}H] (+)-3-PPP, a sigma receptor radioligand, at greater than 80 Ci/mmol using an *N*-propargyl precursor. Its proton-decoupled tritium NMR is shown in Figure 3. This same strategy in principle could be employed to tritiate (–)-3-PPP at high specific activity.



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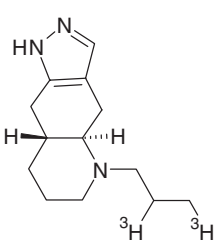

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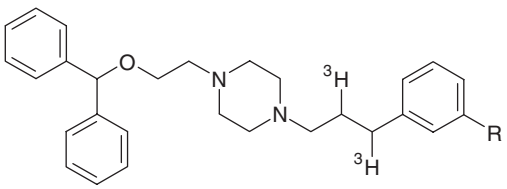
Because of its connection to the growing problem of cocaine abuse, the dopamine reuptake (or transporter) complex and compounds interacting with it have been very actively investigated. Such radioligands have been prepared by catalytic tritiation of olefin precursors and these include BTCP,[39] fourphit,[40] NNC 12-0781,[41] as well as our tritium labelling of O-972.[42] Workers at the NIMH also adopted this labelling strategy to prepare one of the most potent dopamine reuptake blockers, [^{3}H] GBR-12935 (**9**),[43] as well as a tritiated azido photoaffinity analogue (**10**) of it.[44] These latter radioligands have been exceptionally valuable since they do not bind to the norepinephrine or serotonin transporter complexes like other structurally related compounds.



9 R = H

10 R = N_3

Installation of the C^3H_3 group

Many dopaminergic radioligands, including some of those already mentioned, have pendant methyl groups incorporated in their structures, often attached to nitrogen or as methyl esters and ethers. This convenient structural circumstance has presented an outstanding opportunity to prepare tritiated methyl

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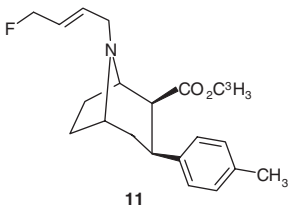
versions of these compounds by various means. Often these groups have been added by an electrophilic reaction using the reagent tritiated methyl iodide. However, Pounds has recently introduced a valuable alternative reagent, [^{3}H] methyl nosylate,[45,46] which has demonstrated even more advantages for such labelling, especially on a small scale where stoichiometry is often crucial.

The benzazepine SCH 23390 has been labelled as an N–C^{3}H$_3$ analogue with tritiated methyl iodide.[47] Also, Mailman and colleagues later improved upon the specific activity of this radioligand by first catalytic tritium debromination of a desmethyl precursor followed by N-methylation with tritiated methyl iodide to achieve an enhanced specific activity of 93.8 Ci/mmol.[48] Other dopaminergics labelled as N–C^{3}H$_3$ derivatives include clozapine,[49] U-101958,[50] WIN 35,065-2,[51] and our labelling of WIN 35,428 for study of the dopamine reuptake site.[52,53] There have also been several reports of dopaminergics radiolabelled with O–C^{3}H$_3$ groups and these include the methyl ester labelling of dopamine transport ligands [methyl ester-^{3}H] beta-CIT and fluoro analogues,[54] [methyl ester-^{3}H] LTB-999 (**11**)[55] the benzamide [methoxy-^{3}H] raclopride[56] along with our own synthesis of [methoxy-^{3}H] (−)-sulpiride (**12**).



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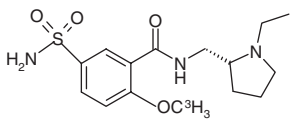

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Iodine-125-labelled dopaminergic radioligands

Over the past 30 years, along with their tritiated counterparts, numerous dopaminergic radioligands labelled with iodine-125 have also made a significant contribution in this area. Several useful reviews of the various methods to introduce radioiodine into organic molecules have been published[57,58] along with the comprehensive paper by Bolton on all radiohalogenation techniques with a significant section on radioiodination.[59] Because of the relatively smaller molecular size of dopaminergic compounds, bulky prosthetic groups like the classic Bolton–Hunter reagent are rarely used and it is often a single ^{125}I itself that is introduced into the parent structure. However, having said that, it is rather surprising that the attachment of such a large atom like iodine to an established dopaminergic compound scaffold could still result in the creation of a useful and effective radioligand.

Electrophilic iodine-125 radiolabelling

There are numerous instances of the direct radioiodination of dopaminergic ligands with iodine-125, employing some oxidation process on [^{125}I] sodium iodide. Early work at then SmithKline & French laboratories in the preparation of [^{125}I] iodospiroperidol is an excellent case study of the thoughtful planning and exacting experimental design that often accompanies such radiolabelling.[60] Encouraged by the report that [^{77}Br] *p*-bromospiroperidol was successfully synthesized at Argonne National Laboratory and utilized for *in vivo* imaging with its distribution much like that of [^{3}H] spiroperidol itself,[61–63] Landvatter explored the preparation of [^{125}I] iodospiroperidol for both *in vivo* as well as *in vitro* applications. He found that the oxidation conditions required for its radiolabelling were very pH sensitive, requiring careful control of the buffer environment. When phosphate buffer was substituted for potassium acetate buffer, no reaction occurred and pH ranges that varied from the optimum 3.85 gave sharply reduced yields. When the oxidant chloramine-T (CAT) was substituted for hydrogen peroxide, the side product *p*-chlorospiroperidol was formed. The paper further described an efficient single HPLC purification procedure to afford pure product at high specific activity.

Conveniently, the compound SCH 23982, a member of the benzazepine class of dopaminergics, already contains an iodine atom. It had previously been radiolabelled with ^{123}I[64,65] and ^{125}I[66] for use as a high-affinity D1 receptor antagonist. However, Mailman's group further improved the radioiodination process by a detailed and robust experimental protocol with increased yields and a simpler purification method.[67] They also unequivocally characterized the radioiodinated product by demonstrating that its diode array detected UV spectrum was completely superimposable on that of authentic unlabelled SCH 23982. As in the previous case of spiroperidiol, when the authors employed CAT as the oxidant for the [^{125}I] sodium iodide, they noted that a side product in the synthesis was the unlabelled chloro isomer SCH 23390. In this same receptor area and compound class there have been several reports of radioiodinated azido photoaffinity ligands for the D1 receptor emerging from the collaboration of the Neumeyer and Seeman groups along with our technical assistance.[68,69]

Other examples of dopaminergic ligands that have been directly radioiodinated are BZM,[70,71] NCQ 298[72]

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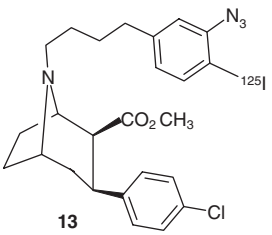
and both alpha and beta-CIT.[73] As mentioned, there have been many oxidants employed in direct radioiodination and in the case of BZM the authors examined a number of them including CAT, hydrogen peroxide, sodium persulphate, *meta*-chloroperoxybenzoic acid and peracetic acid. The latter was found to be a superior oxidant with a higher yield, reduced reaction time and enhanced radiochemical purity.[71] These authors found this method advantageous for iodine-123 labelling as well. Other examples using direct radioiodination in this way include the irreversible compounds for the dopamine transporter complex, photoaffinity ligands [^{125}I] RTI-82[74] and [^{125}I] MFZ-2-24 (**13**) as well as the alkylating agent [^{125}I] MFZ-3-37 (**14**).[75] In the case of these latter two radioligands, a common aniline derivative served as the branch point intermediate which was first radioiodinated and then converted into either the azide or isothiocyanate functionalized product. Very recently these same NIDA workers also reported the radioiodination of another cocaine analogue containing a biphenyl azide at the 3-beta position.[76] The strategy behind this effort was to vary the position of the azido group on the cocaine structure scaffold, possibly allowing radioligand attachment points on the dopamine transporter to be identified as an aid in novel drug design.



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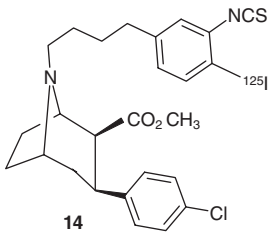

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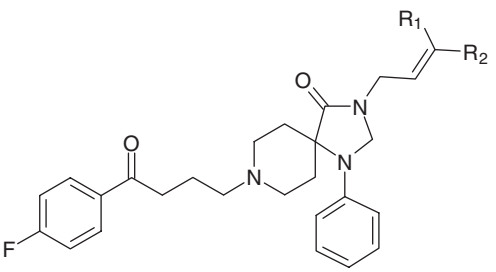
The previous literature citations all dealt with direct radioiodination of a particular dopaminergic ligand substrate and, more often than not, an aromatic group. Another popular strategy used in electrophilic radioiodination is destannylation; that is, the activation of an aromatic group as an organotin derivative prior to radiolabelling. Organotin compounds are easily prepared by a number of efficient organometallic reactions and radioiododestannylation has proved to be a robust and reliable synthetic method.[77] Several benzazepine D1 receptor ligands were radioiodinated in this way by the Kung group[78,79] as well as the dopamine transporter ligands beta-CIT,[54] RTI-121[80] and structurally related RTI-229.[81] Also, several benzamide class dopaminergics have been radioiodinated using this versatile methodology as well.[82–86]

Although early in this discussion it was mentioned that the relatively small size of dopaminergic substrates usually ruled out the use of most added bulky radiolabelled appendages like the Bolton–Hunter reagent, one prosthetic group that has been successfully employed for radioiodinations is the vinylstannyl group. This labelling option has been exceptionally valuable in preparing target compounds that required radioiodination in positions other than aromatic rings. In large part Hanson and colleagues working jointly at Northeastern University and the Harvard Medical School pioneered the early introduction of the vinylstannyl group for radioiodination via nucleophilic additions to carbonyl compounds.[87,88] In complimentary fashion, Lever and co-workers at Johns Hopkins later introduced electrophilic *cis* and *trans* vinylstannyl tosylate derivatives followed by radioiodination to label spiroperidol analogues **15** and **16**, respectively.[89,90] These radioiodinations occurred under mild conditions and with retention of the stannyl regio and steric configurations. The authors also examined whether their radioiodinated products might be contaminated by any unlabelled side products. For that reason both *E* and *Z* chloro analogues of compounds **15** and **16** were separately prepared (since they could have resulted from a CAT promoted chlorodestannylation), but these side products were not observed by HPLC. However, the allyl derivative (R1 = R2 = H) resulting from the protodestannylation was also synthesized and found to be present in the crude radioiodinated mixture. Fortunately, this allyl side product was well resolved from both compounds **15** and **16** and could be easily removed by reverse-phase HPLC purification. This electrophilic installation of vinylstannyl precursors has also been successfully employed in the radioiodination of several dopamine transporter ligands.[91,92] Finally, another successful method to introduce the vinylstannyl group has been a radical catalyzed addition of a tin reagent to a preexisting alkyne group as exploited by the Kung laboratory.[93–96]



15 R1 = ^{125}I, R2 = H

16 R1 = H, R2 = ^{125}I

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Nucleophilic iodine-125 radiolabelling

A second general method that has been useful to radioiodinate dopaminergic compounds has been by nucleophilic means and usually employing [^{125}I] sodium iodide. In this way the Nakatsuka group at Sumitomo utilized a radioiodine exchange to produce [2-^{125}I] 2-iodospiroperidol and the radioligand showed promise for both *in vitro* and *in vivo* dopamine receptor study.[97–101] Also, several benzamide dopaminergics[102,103] as well as mazindol[104] were radioiodinated in like fashion. Sulpride was radioiodinated by [^{125}I] sodium iodide displacement of a diazotized aniline precursor.[105] Finally, [^{125}I] iodoethylspiroperidol was prepared by [^{125}I] sodium iodide displacement of a tosylate group.[106,107]

Conclusion

Although dopaminergic ligands have been tagged with other stable and radioactive isotopes, this review has focused only on those radiolabelled with tritium and iodine-125 during the past 30 years, a significant time period for dopaminergic receptor binding assay development. Many of the radioligands discussed here each have scores of published papers on their use and application in biological assays, but the citations included in this review were selected for their relevance in highlighting the synthetic strategy for this structurally diverse ensemble of compounds. It is hoped that this coverage will not only provide an interesting historical perspective but also a useful guide for future radiosynthetic progress in this important receptor area.

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