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A new multi-gram synthetic route to labeling precursors for the D_{2/3} PET agent ¹⁸F-fallypride

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Abstract

This Letter describes a new multi-gram synthetic protocol for the preparation of the classic tosylate labeling precursor for the D_{2/3} PET agent [¹⁸F]fallypride. In the course of our studies, we also discovered two novel labeling precursors, the previously undescribed mesylate and chloro congeners of fallypride.

Dysfunction in dopaminergic neurotransmission has been implicated in a number of neuropsychiatric disorders including Parkinson's disease, Alzheimer's disease, schizophrenia and Huntington's disease.^{1–4} The discovery and development of small molecule ligands that can selectively target dopamine receptors (D₁–D₄), transport and synthesis is central to the development of therapeutic agents for the treatment of these complex diseases.^{1–4} The D₂ receptor antagonists fallypride (FP) **1** and desmethoxy fallypride (DFP) **2** stand out due to their selectivity, affinity and reversibility (Figure 1).^{5,6}

The corresponding [¹⁸F] and [¹¹C]-labeled analogs of **1** have found utility as positron emission tomography (PET) agents.^{7–13} In particular, [¹⁸F]FP has been employed to study D_{2/3} receptor occupancy and density in neuropsychiatric disorders and aging in both preclinical species and in humans.^{7–15}

The Vanderbilt Institute of Chemical Biology (VICB) established a Synthesis Core to provide synthetic and medicinal chemistry resources to the biomedical research community across the Vanderbilt campus, including the Vanderbilt Imaging Center. On one occasion, a request was made for a multi-gram synthesis of a labeling precursor for [¹⁸F]fallypride **4**, classically accessed by ¹⁸F displacement of the corresponding tosylate **3** (Scheme 1).^{7–15} Upon examination of the literature, we were dismayed to see that the classical published synthetic routes to **3** were performed on milligram quantities of material, employed preparative TLC for purification and afforded 30–50% yields for every step.^{8,9} In 2007 Rosch and co-workers reported a large scale synthesis utilizing a mixed anhydride coupling between the corresponding substituted benzoic acid **5** and proline-derived amine **6** to afford **7** in an unspecified yield (Scheme 2).¹⁶ Earlier de Paulis reported hydroboration-oxidation of allyl benzamide **8** to give alcohol **9** and following deprotection and *N*-allylation provide alcohol **7**.¹⁷ In examining these synthetic routes we became concerned with functional group

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Supplementary Data Experimental procedures and analytical data for compounds **1**, **11–17** are provided. This material is available free of charge via the Internet at <http://www.sciencedirect.com/science/journal/0960894X>.

compatibility under these reaction conditions and therefore turned our attention to developing a new synthetic route employing a protected derivative of benzoic acid **5** as a coupling partner.

To this end alcohol **5** was derived from commercially available methyl benzoate **10** in three steps starting with O-methylation to afford benzoate **11** in 95% yield (Scheme 3). Hydroboration of **11** followed by treatment with basic peroxide then gave alcohol **12**. Following ester hydrolysis (92%) benzoic acid **5** was treated with TBSCl and imidazole in DMF to provide TBS protected alcohol **13** in good overall yield. Next the coupling of **13** with amine **6** (derived in two-steps from L-prolineamide) was examined. Optimal conditions employed EDCI in combination with HOBT and *i*-Pr₂NEt as base to provide **14**. Under these conditions the coupled product was obtained in yields ranging from 45 to 64%. Finally, removal of the TBS group with TBAF delivered alcohol **7**. Standard conditions then provided the tosylate **15**, the immediate precursor to [¹⁸F]fallypride **4** in seven steps with an overall yield of 11%.¹⁸ Importantly, all the steps leading to **14** were conducted on multi-gram scales with standard column chromatographic purification, while the final deprotection and tosylation steps were run on 1-2 gram scales (See Supporting Information).

The silyl protection of **5** and subsequent deprotection steps were a necessity for the multi-gram synthesis of **15**. All attempts to perform the amide coupling of **5** and **6**, with multiple peptide coupling reagents (EDCI, HATU, TFFH, etc...) afforded poor results (yields less than 20%) and isolation of the extremely polar **7** proved difficult. Standard normal phase chromatography was insufficient on large scale to deliver pure **7** for the tosylation step. Thus, we were required to pursue preparative reverse phase chromatography with multiple injections, resulting in large volumes of CH₃CN/H₂O/TFA solutions to dry down with longer turn-around. While the protection/deprotection sequence adds two chemical steps, the overall yields and efficiency to access pure **15** are markedly improved.

The major problematic step in the synthesis was the amide coupling between the electron-rich, hindered benzoic acid **13** and amine **6** – a historically problematic reaction. We evaluated a number of coupling reagents (PyBop, BOP, TFFH), but none afforded advantages over EDCI. One attempted coupling that led to a new entity involved the treatment of benzoic acid **13** with thionyl chloride (Scheme 4). Reaction of the intermediate acid chloride with amine **6** led to the isolation of previously unknown chloride **16**, the result of substitution of the TBS ether for a chloro group, a variation of the Silyl-Durst chlorination.^{18,19} This new entity **16** (ClFP) was evaluated as a D₂ antagonist, and afforded an IC₅₀ of 17.1 nM. With **16** in hand, we then evaluated its ability to serve as a labeling precursor in route to [¹⁸F]fallypride **4**. Exposure of **16** to TBAF in THF provided a 55% yield of **1**, indicating that this new ClFP congener **16** is a viable labeling precursor for [¹⁸F]fallypride **4**. Activity at the D₂ receptor was also confirmed for our synthetic **1** with an IC₅₀ of 5.0 nM, a value in agreement with literature reports.

Based on these results, we examined the literature further, and were surprised to find that the corresponding mesylate analog **17** (MsFP) had never been prepared. To evaluate this potential labeling precursor, we intercepted alcohol **7** from the deprotection of **14** and treated it with MsCl in DCM and generated **17** (MsFP); however, this material was labile and proved difficult to isolate. Therefore, we generated **17** (MsFP) *in situ* and immediately treated the reaction mixture with TBAF in *t*-BuOH at 85°C to afford a 40% yield of **1** (Scheme 5), suggesting that **17** (MsFP) could also serve as a viable labeling precursor for the preparation of [¹⁸F]fallypride **4**.¹⁸

In summary, we have developed an improved, high yielding and scalable synthetic route to the classical labeling precursor **15** for [¹⁸F]fallypride **4**. During the course of this work, we

discovered **16** (ClFP), a novel D₂ antagonist and viable labeling precursor for [¹⁸F]fallypride **4**. This work also prepared and evaluated the previously unknown mesylate congener, **17** (MsFP), as a labeling precursor, and found that it too was viable. Further studies in this arena are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

1. Stoof JC, Kebabian JW. Life Sci. 1984; 35(23):2281–2296. [PubMed: 6390056]
2. Carbon M, Ghilardi MF, Fukuda M, Silvestri G, Mentis MJ, Ghez C, Moeller JR, Eidelberg D. Hum. Brain Mapp. 2003; 19(3):197–211. [PubMed: 12811735]
3. Chesselet MF, Delf JM. Trends Neurosci. 1996; 19(10):417–422. [PubMed: 8888518]
4. Seeman P, Bzowej NH, Guan HC, Bergeron C, Reynolds GP, Bird ED, Riederer P, Jellinger K, Tourtellotte WW. Neuropsychopharmacology. 1987; 1(1):5–15. [PubMed: 2908095]
5. Grunder G, Siessmeier T, Piel M, Vernaleken I, Buchholz HG, Zhou Y, Hiemke C, Wong DF, Rosch F, Bartenstein P. J. Nuc. Med. 2003; 44:109–116.
6. Siessmeier T, Zhou Y, Buchholz H-G, Landvogt C, Vernaleken I, Piel M, Schirmacher R, Rosch F, Schreckenberger M, Wong DF, Cummings P, Grunder G, Bartenstein P. J. Nuc. Med. 2005; 46:964–972.
7. Grunder G, Landvogt C, Vernaleken I, Buchholz HG, Ondraeck J, Siessmeier T, Hartter S, Schreckenberger M, Stoeter P, Hiemke C, Rosch F, Wong DF, Bartenstein P. Neuropsychopharmacology. 2006; 31:1027–1035. [PubMed: 16237387]
8. Mukherjee J, Shi BZ, Christian BT, Chattopadhyay S, Narayanan TK. Bioorg. Med. Chem. 2004; 12:95–102. [PubMed: 14697774]
9. Mukherjee J, Yang Z-Y, Das MK, Brown T. Nuc. Med. Biol. 1995; 22(3):283–296.
10. Mukherjee J. J. Fluorine Chem. 1990; 49:151–154.
- 11(a). Mukherjee J. Int. J. Appl. Radiat. Isotopes. 1991; 42:713–721.(b) Mukherjee J, Yang Z-Y, Copper M. Eur. J. Pharmacol. 1992; 175:363–364. [PubMed: 2323353]
12. Mathis CA, Bishop JE, Gerdes JM, Whitney JM, Brennan KM, Jagust WJ. Nuc. Med. Biol. 1992; 19:571–588.
- 13(a). Kessler RM, Mason NS, de Paulis T, Ansari MS, Schmidt D, Manning RG, Votaw JR. J. Nuc. Med. 1992; 33:847.(b) Kessler RM, de Paulis T, Ansari MS, Schmidt D, Manning RG, Votaw JR. J. Nuc. Med. 1993; 34:202P.
14. Mukherjee J, Christian BT, Narayanan TK, Shi B, Collins D. Brain Res. 2005; 1032:77–84. [PubMed: 15680944]
15. Riccardi PR, Li MS, Ansari D, Zald S, Park B, Dawant S, Anderson M, Doop N, Woddward E, Schoenberg D, Schmidt R, Baldwin R, Kessler R. Neuropsychopharmacology. 2006; 31:1016–1026. [PubMed: 16237395]
16. Stark D, Piel M, Hubner H, Gmeiner P, Grunder G, Rosch F. Bioorganic & Medicinal Chemistry. 2007; 15:6819–6829. [PubMed: 17765546]
17. de Paulis T. Current Pharmaceutical Design. 2003; 9:673–696. [PubMed: 12570798]
18. For full experimental details, see the Supplementary Data.
19. Odon G, Ugen U. Tetrahedron Lett. 1997; 25:4407–4410.

Figure 1.
Structures of the $D_{2/3}$ antagonists fallypride (FP), **1**, and desmethoxy fallypride (DFP), **2**.

Scheme 1.

Synthesis of [¹⁸F]fallypride **4**. Reagents: (a) ¹⁸F, Kryptofix, K₂CO₃, CH₃CN.

Scheme 2.

Existing routes to alcohol **7**. Reagents: (a) ClCO_2Et , Et_3N ; 9-BBN, H_2O_2 , NaOH ; (c) TFA, DCM; (d) allyl bromide, K_2CO_3 , DMF.

Scheme 3.

Improved synthetic route to **15**. Reagents: (a) MeI, K₂CO₃, Me₂CO, 95%; (b) (i) 9-BBN, THF, (ii) NaOH, H₂O₂, 92%; (c) NaOH, THF (aq.), 92%; (d) TBSCl, ImH, DMF, 75%; (e) **6**, EDCI, HOBT, *i*-Pr₂NEt, 45-64%; (f) TBAF, THF, 71%; (g) TsCl, DCM, pyridine, 44%.

Scheme 4.

Synthesis of a novel labeling precursor CIFP **16** and fallypride **1**. Reagents: (a) (i) SOCl₂, toluene, cat. DMF, (ii), **6**, 31%; (b) TBAF, THF, reflux, 55%.

Scheme 5.

Synthesis of a novel labeling precursor MsFP **17** and fallypride **1**. Reagents: (a) (i) MsCl, DCM, Et₃N; (b) TBAF, *t*-BuOH, reflux, 40% over two steps.