Paper C1

CAN WE PREDICT REACTIVITY FOR AROMATIC NUCLEOPHILIC SUBSTITUTION WITH [^{18}F]FLUORIDE?

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Nucleophilic aromatic substitution using NCA [^{18}F]fluoride ion has become a widespread method for the synthesis of high specific activity fluorine-18 radiotracers. As [^{18}F]fluoride has become easier to use, this labeling reaction has been applied to ever more complex molecules, and could be potentially applied to the radiolabeling of very many drug molecules. In this regard, it would be helpful to be able to predict reactivity of substrates towards [^{18}F]fluoride ion substitution. Recently, the electron density of an aromatic ring carbon as indicated by the ^{13}C-NMR chemical shift has been shown to correlate with radiochemical yields of [^{18}F]fluoride ion substitution in various nitrobenzaldehydes with electron-donating substituents (Ding et al 1990). However, not all compounds were found to fit that correlation line; low reactivity of certain anisaldehydes has also been noted by others (Lemaire et al 1991).

In examining various substrates to be used for synthesis of [^{18}F]fluorophenols and [^{18}F]fluorocatechols (Chakraborty and Kilbourn 1991a,b), we had also observed unexpected low reactivity of certain substitution patterns in benzaldehydes. In an attempt to understand this behaviour, and to further examine the predictability of [^{18}F]fluorinations based on ^{13}C-NMR chemical shifts, we have re-examined this question in some detail, with particular attention to the effects of other leaving groups and different ring substituents.

A series of tri- and tetra-substituted aromatic compounds were examined for [^{18}F]fluoride ion incorporation under carefully controlled conditions (identical concentrations of fluoride and substrate, reaction time and temperature, source of [^{18}F]fluoride), with yields ranging from17 to 85%. All values reported in Fig. 1 are mean $\pm$ SD of 6-18 determinations. ^{13}C-NMR values were obtained from the literature, calculated from known additivity relationships , or obtained in our laboratories; the values reported are for the ring carbon bearing the leaving group in the aromatic substitution reaction.

The correlation between radiochemical yield and ^{13}C-NMR chemical shift is shown in Fig. 1, with the correlation line drawn for only compounds **1 - 8**. Within this series the correlation is excellent ($r^2 = 0.90$). These results confirm and extend the original observations of Ding et al. (1990). Three compounds (#**9**,**10**, and **11**) do not fit the correlation line; these are the trimethylammonium and methyl substituted benzaldehydes. The trimethylammonium salt **9** provided a much higher than would be predicted radiochemical yield; the kinetics of the reaction of [^{18}F]fluoride ion with the charged substrate **9** were subsequently examined and found to be very much faster than the other compounds, consistent with the literature experience with trimethylammonium leaving groups (Miller 1968). The results obtained with the methyl substituted anisaldehydes are somewhat puzzling. Methyl groups have little projected impact on ring electron densities as suggested by ^{13}C-NMR data, and thus would not be expected to be a negative influence on the [^{18}F]fluorination reaction. In preliminary kinetic experiments, however, these compounds are reacting very slowly. The possibilities of impurities which rapidly consume [^{18}F]fluoride ion could be considered; however, competition studies using mixtures of the methyl derivatives with compound **9** showed no effect of the methyl derivatives or any possible impurity on the reactivity of **9** towards the [^{18}F]fluoride ion. Methyl groups are not always detrimental, as good yields (60-70%) have been obtained with 2-methoxy-4-fluoro-5-methylbenzaldehyde substitution by [^{18}F]fluoride ion (3). The difficulties with methyl substituted anisaldehydes remains unresolved, but would be important in the design of synthetic strategies for complex drug structures.

In conclusion, our work supports the use of ^{13}C-NMR as a means to predict reactivity in nitro-substituted alkoxybenzaldehydes, but the extension to other leaving groups and other ring subtituents is not straightforward and requires additional study.

Ackowledgements. This work was supported by DOE grant DE-FG02-88ER60639.

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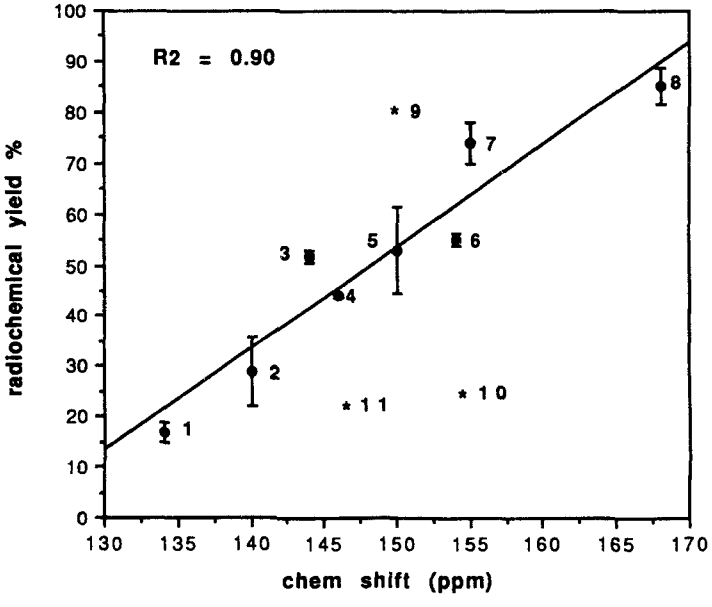

#	Compound	Radiochemical yield
1	3-methoxy-2-nitrobenzaldehyde	16.8 ±1.9
2	3-methoxy-4-nitrobenzaldehyde	29 ±6.9
3	6-nitroveratraldehyde	52 ± 1.2
4	6-nitropiperonaldehyde	44 ± .35
5	2-nitrobenzaldehyde	53 ± 8.6
6	4-nitrobenzaldehyde	55 ± 1.2
7	2-methoxy-4-nitrobenzaldehyde	74 ± 4.1
8	4-fluorobenzaldehyde	85 ± 3.6
9	4-trimethylammoniobenzaldehyde	82 ± 5.0
10	3-methyl-4-nitrobenzaldehyde	25 ± 2.8
11	2-nitro-5-methylbenzaldehyde	23 ± 4.8

Fig. 1. Correlation of radiochemical yields with carbon-13 NMR chemical shift values for various substituted benzaldehydes.

Paper C2

PRODUCTION OPTIMIZATION OF A BIFUNCTIONAL FLUORINE-18 LABELLED RADIOPHARMACEUTICAL INTERMEDIATE: FLUORINE-18 FLUOROACETOPHENONE.

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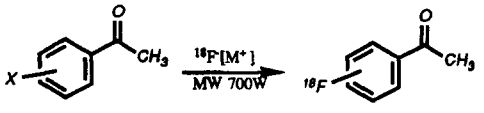
As the demand for novel positron emitting radiopharmaceutical agents grows, the number of labelled intermediates available to the radiopharmaceutical chemist also needs to increase. Since the nucleophilic aromatic substitution of NCA [^{18}F]fluoride for activated nitro group was reported (1), several useful fluorine-18 labelled synthetic intermediates have evolved (2,3,4) which include [^{18}F]fluoroacetophenone ([^{18}F]FAP) (5). Due to its two reactive sites, namely the electrophilic carbonyl and the acidic α-protons, we have have become actively interested in the chemistry of this useful precursor. There exist a number of potential radiopharmaceutical agents which carry the "phenethyl" fragment which need to be investigated. Hwang et al. (5) utilized [^{18}F]FAP for the production of [^{18}F]fluorofentanol; however, they utilized the multi-step production of the key reagent starting from nitrobenzonitrile (5). We report a yield optimization study of [^{18}F]FAP produced directly from activated acetophenones such as niroacetophenone (NAP) (Scheme 1). Additionally, we will present some of the synthetic reactions envisioned as useful to the radiopharmaceutical laboratory.

Since it is expected that this labelled reagent will find widespread applications at our institution, we initially focused on the optimization of [^{18}F]FAP in detail in order to obtain the highest possible consistent radiochemical yield with a maximum effective specific activity. Parameters studied included a) effect of nucleofuge on substrate reactivity; NO_2 vs I vs Me_3N^+, b) effect of base; K_2CO_3/kryptofix 2.2.2 vs TBAOH, c) effect of base concentration, d) effect of substrate concentration (Figure 1), e) effect of substrate/base ratio (Figure 1), and f) effect of heating time (Table 1).

SCHEME 1



X=NO_2, I, Me_3N^+ [^{18}F]FAP

The procedures is as follows. Aqueous [^{18}F]fluoride was azeotroped dry with the appropriate base using CH_3CN and N_2 at 110°C. The appropriate substrate and solvent were introduced, the vials were sealed and heated (700 W microwave) for a set time interval. The vessel was cooled, and the contents were diluted with H_2O. The aqueous fraction was transfered to a test tube, the vessel was rinsed with Et_2O, and the rinse was added to the aqueous phase with vigorous agitation. The layers were separated, the ether dried over Na_2SO_4, and the radioactivity distribution assayed. Aliquots for analysis by tlc and/or HPLC were taken as a check on the extraction efficiency (typically > 94%). Alternatively, a C18 sep pak workup could be utilized with equal efficiency. Thus far the labelling precursor of choice is NAP, giving decay corrected and reproducible yields as high as 64% with reaction times as short as 2.5 min. The effects of substrate concentration and substrate to base ratio on the radiochemical yields was summarized in Figure 1. Thus far the best ratio was obtained using 32 μmol of NAP and 7.25 μmol K_2CO_3.

Concurrent to these on going optimization studies, we are investigating a silica gel separation of the nitro-precursor, in addition to the use of the trimethylammonium moiety as a leaving group which should enhance the effective specific activity of tracers derived from this intermediate. We will also present methods towards simplifying the α–bromination of [^{18}F]FAP to give [^{18}F]fluorophenacyl bromides, which have already been shown to be useful labelling intermediates (6,7).

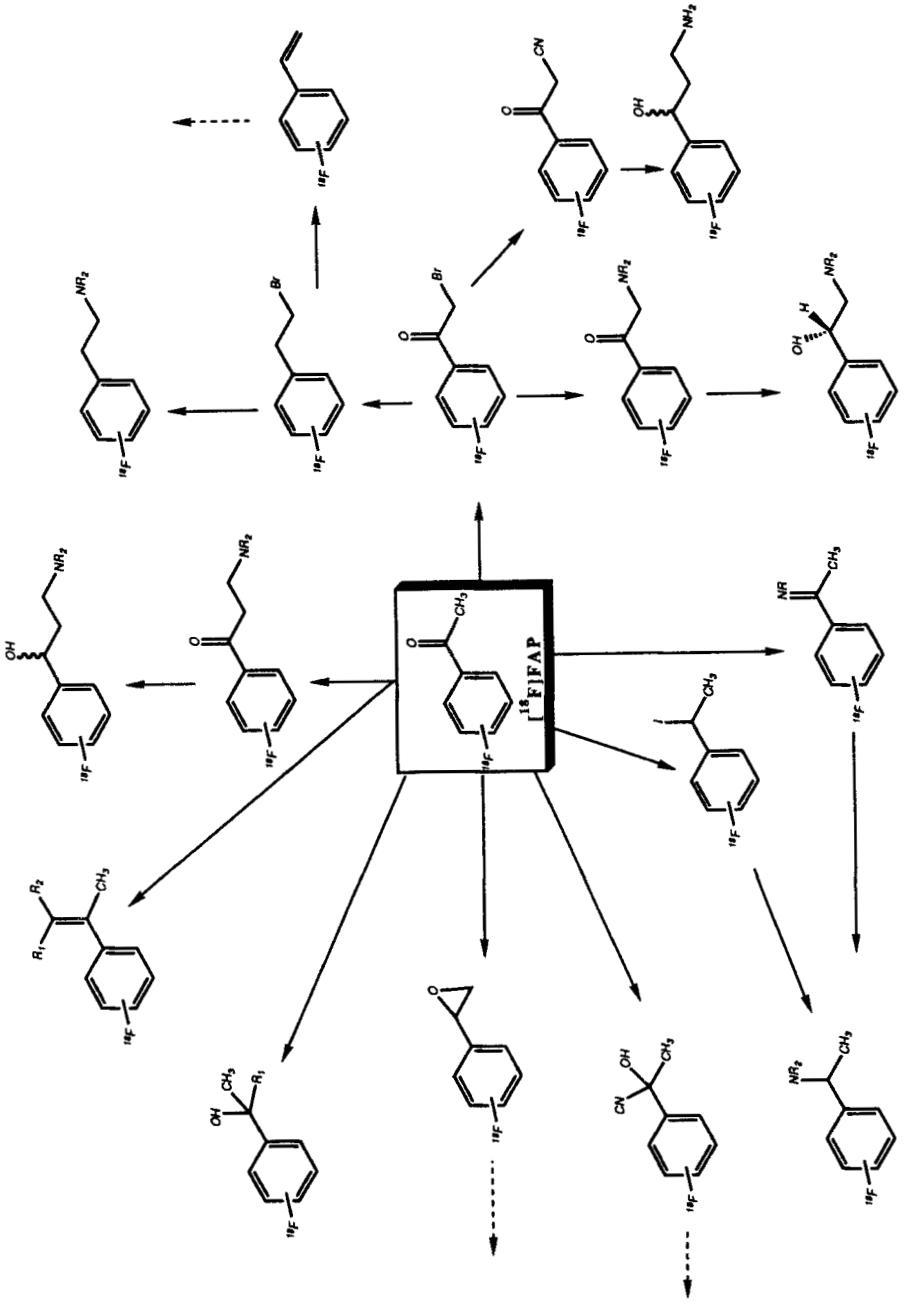


Figure 2. Potential Reaction Pathways Envisioned from [^{18}F]FAP

Table 1. Effect of Reaction Time

TIME (min)	% YIELD
1.0	23.3±16.6; n=3
2.5	63.5±3.4; n=4
5.0	59.8±1.8; n=3
8.0	43.7+10.2; n=3

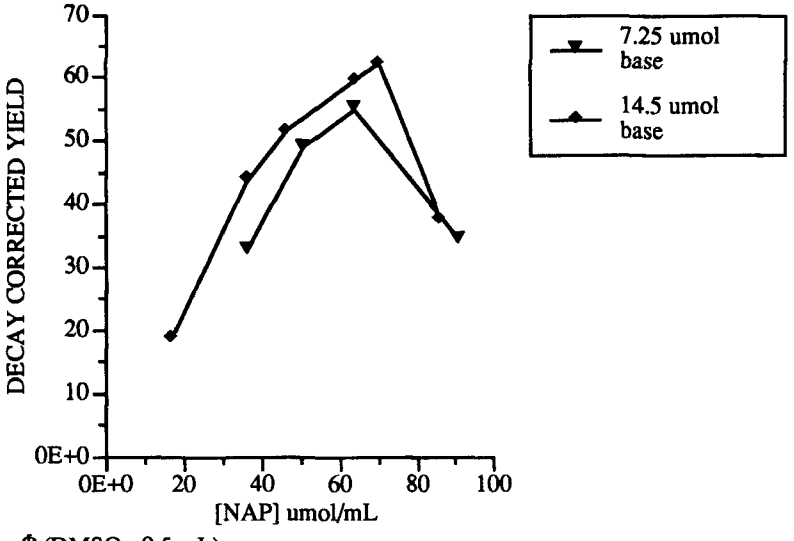
p-nitroacetophenone (5.3 mg, 32 µmol), 0.5 mL DMSO, 7.25 µmol K2CO3, 13.3 µmol APE 2.2.2

Table 2. Effect of Substrate

X	% YIELD
NO_2	44.1±9.2; n=3
I	3.6±3.3; n=2: 3.2 n=1*
$^+NMe_3$	

18.5 µmol substrate/0.5 mL DMSO/MW 5.0 min 7.25 µmol K2CO3, 13.3 µmol APE 2.2.2; * TBAOH used as base.

Figure 1.Φ



Φ (DMSO =0.5 mL)

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We wish to thank Kettering Medical Center for its generous financial support.

[^{18}F]FLUORINATION OF 3-PYRROLIDINOL. A COMPARISON OF RELATIVE [^{18}F]FLUORINATION RATE OF SULFONIC ESTERS OF 3-PYRROLIDINOL AND THE UNEXPECTED [^{18}F]LABELING OF TRESYLATE.

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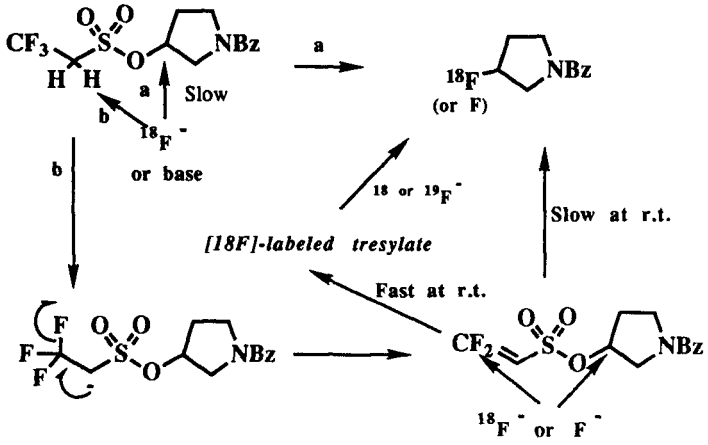
Recently, we have evaluated a general method for the preparation of [^{18}F]-labeled derivatives of U-50488, a specific kappa opioid ligand, for imaging kappa receptor by PET (1). Our synthetic strategy involved the fluorination of 2-pyrrolidinol to give the fluorinated derivatives. Initial attempt to prepare the [^{18}F]-labeled compound via the [^{18}F]fluoride displacement of a tosylate has revealed the low reactivity of the tosylate as well as the instability of the substrate under the examined reaction conditions.

In an attempt to find a reactive yet stable precursor suitable for [^{18}F]-labeling of 2-pyrrolidinol, a series of sulfonic esters of 1-benzyl-3-pyrrolidinol, which included the p-toluenesulfonate (tosylate), methanesulfonate (mesylate), 2,2,2-trifluoroethanesulfonate (tresylate), and trifluoromethanesulfonate (triflate), were prepared, and their reactions with K[^{18}F]/Kryptofix222 in MeCN were evaluated. The results were summarized in Table 1. Our findings clearly indicate the reactivity of these sulfonates (except the tresylate) towards [^{18}F]fluoride parallel the reported solvolysis rates of various sulfonates: i.e. triflate >> mesylate > tosylate (2). However, the instability of the triflate caused the inconsistent yield of the fluorinated pyrrolidine and hence limited its use for the preparation of [^{18}F]fluoropyrrolidine. The most surprising finding was the isolation of [^{18}F]-labeled starting tresylate under the same fluorination conditions at room temperature. A radiochemical yield as high as 30% was obtained with a reaction time of 30 min. It was of interest to find that, upon heating, the amount of labeled tresylate decreased in a rate faster than the formation of the [^{18}F]fluorinated pyrrolidine.

Facile ^{18}F-for-^{19}F isotopic exchange reactions have been reported recently, but all reactions were observed at elevated reaction temperatures (3). Satter et al proposed a mechanism which involved the addition of [^{18}F]fluoride to a difluoroethene formed via an anion intermediate (3). A similar anion-difluoroethene mechanism, as outlined in scheme 1, was proposed to explain our results.

Scheme 1



In our tresylate there are two reactive sites : a) the carbon atom bearing the secondary sulfonic ester group and b) the acidic α-methylene protons which are activated by the sulfonyl group. Because of the low reactivity of the secondary tresylate towards the fluoride at room temperature, the acidic methylene protons became the primary reactive site. The base, either K_2CO_3 or K[^{18}F], reacts with the activated proton to form an anion which then loses fluorine anion from the adjacent carbon

to form the ethene. Since the sulfonyl group activates the beta carbon of the ethene intermediate towards nucleophilic reactions, the [^{18}F]fluoride can attack the beta carbon to yield an anion which in turn yields the labeled tresylate. Although the tresylate can be converted into the [^{18}F]-labeled product upon heating, the isotopic exchange reaction has resulted in serious isotope dilution which drastically decreases the specific activity of the final labeled product.

Our results clearly demonstrate that the relative reactivity of sulfonates towards [^{18}F]fluoride paralleled to that observed from hydrolysis studies: triflate >> mesylate > tosylate. The unexpected [^{18}F]-labeling of tresylate suggests the presence of a facile isotopic exchange reaction which is expected to reduce the specific activity of the final [^{18}F]-labeled product. Our results suggest that tresylate should not be employed as precursor for [^{18}F]-labeling of radiopharmaceuticals when high specific activity is desired.

The authors would like to thank the financial support of Kettering Medical Center.

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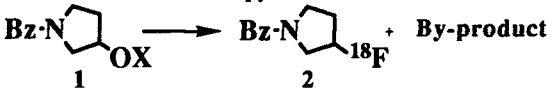
Table 1.Fluorination yields of sulfonic esters of pyrrolidinol



X	Reaction§ (ºC)	(min)	Yields (%)¶ 2	By-product
Me-Ph-SO_2-	r.t.	30	0	0
	110	15	15	0
Me-SO_2-	r.t.	30	0	0
	110	15	25	0
	110	30	45	0
CF_3-CH_2-SO_2-	r.t. 30		2	16*
	110	15	6	8*
CF_3-SO_2-†	r.t.	15	16	

§ All reactions were carried out using 2 mg of sulfonate.
¶ All yields were determined by radio-TLC (silica gel, EtOAc/hexane 3/1).
* The by-product was identified as the [F-18]-labeled starting tresylate.
† The triflate was extremely unstable. In one occasion the triflate was isolated along with excess of starting triflic anhydride and all [^{18}F]fluoride was converted into a nonpolar by-product (98%, Rf=0.7, silica gel, EtOAc/ hexane = 2/1) with a reaction time of 10 min at room temperature.

Paper C4

A NOVEL, METABOLICALLY STABLE SITE FOR FLUORINE-18 LABELING OF PROGESTINS, USEFUL IN THE DEVELOPMENT OF IMAGING AGENTS FOR PROGESTERONE RECEPTOR-POSITIVE BREAST TUMORS.

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Imaging agents for receptor-positive breast tumors are useful in providing an in situ assay of tumor receptor content and in delineating the metastatic spread of the disease. We have been successful in imaging both primary and metastatic tumors in humans,[1,2] using fluorine-18 labeled estrogens; however, there might be significant advantages for imaging breast tumors based on their content of progesterone receptor (PgR): PgR content is often greater than estrogen receptor (ER), and in patients on hormonal therapy (tamoxifen), PgR would not become occupied (as is ER), and might even be induced.[3,4] While we have been successful in preparing fluorine substituted progestins with high affinity for PgR that show good target tissue uptake in the rat,[5] the best of these compounds, 21-fluoro-16α-ethyl-19-norprogesterone (FENP) has not proved to be very useful as an imaging agent in humans.[6] The major problems appear to be high liver uptake and defluorination from the C-21 site of labeling. In this report, we describe the synthesis of a progesterone ketal derivative (**1**) whose structure provides additional sites for altering lipophilicity and that bears fluorine-18 on an aromatic ring, a site that is stable to metabolic defluorination.

Ketals of 16α,17α-dihydroxyprogesterone (**6**) were prepared a number of years ago and shown to be potent progestins.[7] We have prepared a number of derivatives of the acetophenone ketal and demonstrated in competitive binding assays that they have good affinity for PgR (Table 1). In particular, the p-fluoroacetophenone ketal has an affinity 3 times that of progesterone. While fluoro-for-nitro substitution on the corresponding nitroacetophenone ketal (**7**) does not proceed, we have prepared **1** in fluorine-18 labeled form by the two-step process involving fluoride ion displacement on p-nitroacetophenone, followed by a rapid ketalization step (Scheme 1). This material can be prepared in high radiochemical purity, and distribution studies in rats show that only ca. 6% of the injected dose (ID) is deposited in the bone after 3 hours, compared with the 30% uptake seen for FENP. While there is modest evidence of receptor mediated uptake by the uterus, fat uptake of 2.5% ID/g is quite high. We anticipate that less lipophilic analogs of **1** will show more favorable distribution while retaining this metabolic inertness to defluorination.

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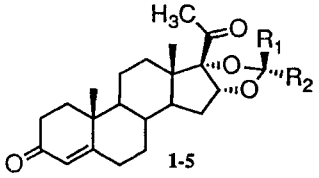

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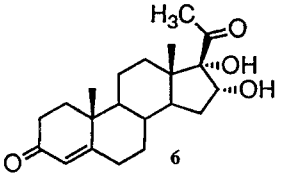

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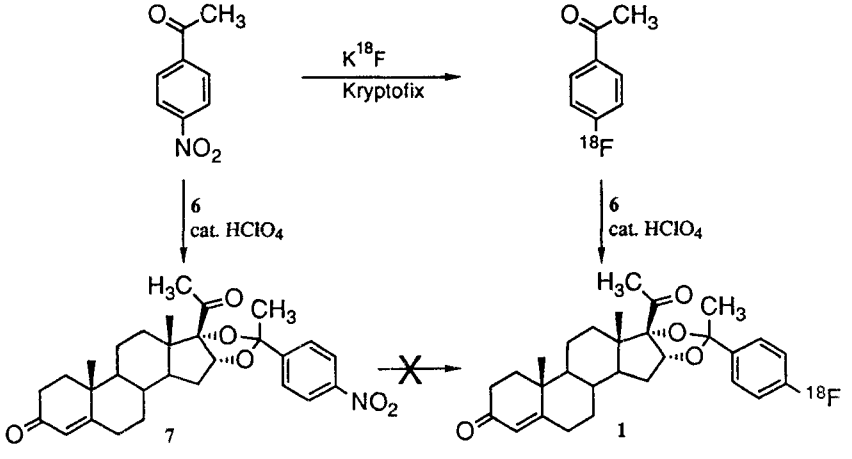
Table 1

Compound	R_1	R_2	RBA(PgR)[a]
1	CH_3	C_6H_4F	55
2	CH_3	C_6H_4I	20
3	CH_3	C_6H_5	20
4	CH_3	C_6F_5	28
5	H	C_6H_5	18
6	--	--	0.01

a Relative binding affinity for the progesterone receptor determined by competitive binding assay using [3H]R5020 as a tracer. The RBA of R5020 is 100 and progesterone is 15.



Scheme 1

[^{18}F]FLUOROACETIC ACID AND [2-^{18}F]FLUOROPROPIONIC ACID DERIVATIVES AS REACTIVE FLUOROACYLATION AGENTS

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For labelling of proteins with fluorine-18 (T½ = 110 min) various prosthetic groups were applied, however, so far with limited success (1-4). In order to obtain sterically small prosthetic acylation groups suitable for radiofluorination of peptides as well as monomeric components with acidic hydrogen, preparation and reactivity of fluoropropionic and acetic acid derivatives were further investigated.

First attempts to obtain activated fluoroacylation agents by direct nucleophilic substitution (5,6) proved to be limited to rather unreactive alkyl esters. These react only with strongly basic amines at molar concentration. In continuation of earlier experiments (1), condensation of the free [^{18}F]fluoropropionic acid with amines by activation with carbodiimides was possible at millimolar educt concentration as shown for butylamine and DCC in Fig. 1. Acylation yields, however, are limited due to the formation of N-acetylated urea and the fact that the activated form of the fluoropropionic acid cannot be isolated. The following highly reactive fluoroacylation agents, however, could be prepared and isolated with high radiochemical yields according to the synthetic scheme outlined in Fig. 2.: [^{18}F]fluoroacetic acid and [2-^{18}F]fluoropropionic acid p-nitrophenylester, [2-^{18}F]fluoropropionic acid N-hydroxysuccinimidester and -imidazolide.

After aminopolyether (2.2.2) activated nucleophilic substitution with n.c.a. ^{18}F$^-$ on corresponding bromoacetic and 2-bromopropionic acid esters the [^{18}F]fluoroacids are isolated and hydrolyzed with 90% radiochemical yield. Subsequent reaction with di-(4-nitrophenyl)carbonate, di-(N-succinimidyl)carbonate, or carbonyldiimidazole, respectively, give rise to the highly activated acid derivatives in almost quantitative yield. Their potential for fluoroacylation under mild reaction conditions is demonstrated for various amines of different basicity and steric hindrance (Tab. 1). The high labelling yields, especially for phenylalanine ethylester, are promising for fluoroacylation of peptides and proteins.

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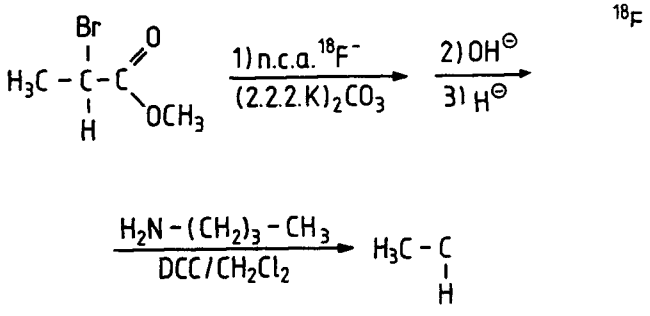

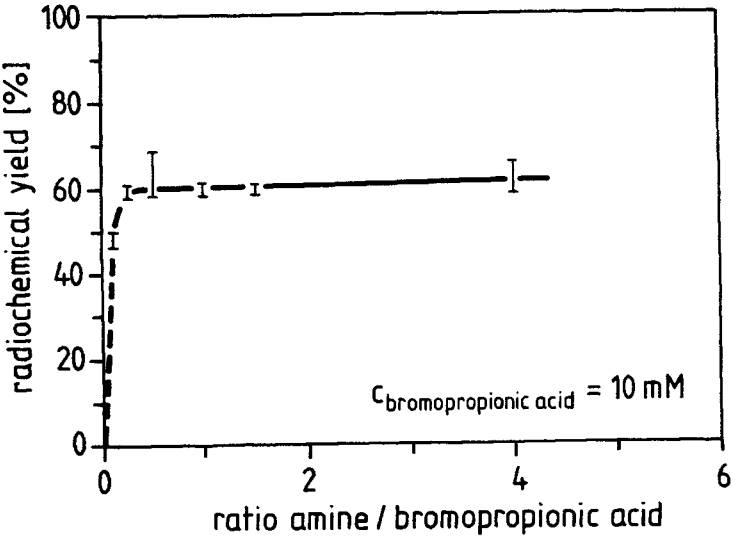

Fig. 1 Dependence of ^{18}F-fluoroacylation yield of n-butylamine with dicyclohexyl-carbodiimide on amine concentration

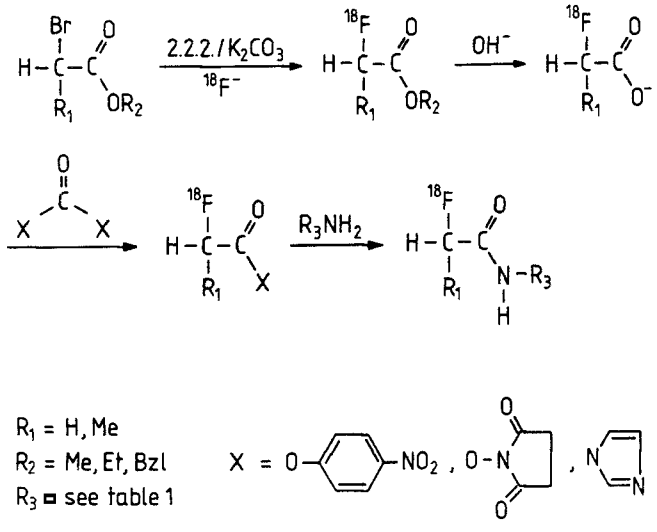

Fig. 2 Preparation of n.c.a. [2-^{18}F]fluorocarboxylic acid derivatives and fluoroacylation of amines in CH_3CN or DMF

TABLE 1 Comparison of n.c.a. fluoroacylation of different amines with activated [2-^{18}F]fluoropropionic acid derivatives (% RCY)

AMINE	ACYLATION AGENT [2-^{18}F]fluoropropionic acid			
	p-nitrophenyl-ester	N-hydroxysuc-cinimideester	imidazolide	methyl-ester*
Homoveratryl-amine	93 ± 2	-	-	70 ± 2
Benzoylhydra-zide	90 ± 3	-	88 ± 3	-
Biotinhydra-zide**	58 ± 5	-	53 ± 5	-
n-Butylamine	-	92 ± 3	-	88 ± 4
2-Butylamine	-	90 ± 3	-	7 ± 2
Phenylalanine-ethylester	90 ± 3	92 ± 2	-	0

25°C, CH_3CN, C_{Amin} 0.1 M; *64°C, MeOH, C_{Amin} 4M; **90°C, DMF, C_{Amin} 0.1 M

Paper C6

N.C.A.- [18F] - Fluorination of Aromatic Compounds by Fluorodediazonisation

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The most common labelling technique using Fluorine-18 is the Aminopolyether-supported nucleophilic substitution of aliphatic compounds, the so called Kryptofix® -method.

For the ^{18}F- labelling of aromatic compounds a procedure with comparable potential is not known. The direct nucleophilic substitution of aromates is limited to compounds with strongly electron-drawing substituents in o and p-position respectively.

A more commonly usable procedure could be the electrophilic aromatic substitution. But up to now, in this field there is only known the fluorination using ^{18}F- [F_2] as precursor, giving low yields of compounds, containing inactive carrier.

We therefore studied the potential of dediazonisationreactions for the ^{18}F-labelling of aromatic compounds on the n.c.a. level. We started with the so called Baltz-Schiemann-decomposition of different aromatic diazoniumsalts in the presence of F^-.

The best corresponding anion in this field was 2,4,6 - Triisopropylbenzenesulfonate. Diazoniumsalts, containing this anion are thermic stable, low sensitive for light and good soluble in unpolar solvents. Inactive studies showed, that the best conditions for the fluorodediazonisation are given in an acidic environment under conditions stimulating an ionic mechanism of the dediazonisation.

In contrast all conditions stimulating a radicalic mechanism are lowering the yield of the fluorodediazonisation.

For bringing reactive F^- in the unpolar solvents of the reactionssystem, different phase-transfer catalysts were studied. Best results were achieved in the presence of 15-crown-5, using NaF as fluorideprecursor, giving in the case of ^{18}F-Fluorotoluene E.O.B.-yields of 39% under n.c.a.-conditions.

Optimal conditions of this procedure could be transferred without any further variations to the syntheses of ^{18}F-L-p-Fluorophenylalanine and ^{18}F-Haloperidole, giving E.O.B.-yields of 15% and 18% respectively on the n.c.a.-level.

PREPARATION OF NO-CARRIER-ADDED N-([^{18}F] 4-FLUOROPHENYL)PIPERAZINE

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Many compounds of pharmaceutical interest possess a piperazine ring (1). Access to a number of these containing the 4-fluorophenyl analogue should be possible *via* the title compound, and thus made available for human *in vivo* study by positron emission tomography (2).

Introduction of fluoride by direct nucleophilic aromatic substitution is not practicable due to the absence of a strong electron-withdrawing group *ortho* or *para* to the position of interest (3). An alternative approach involving a classic piperazine ring formation, for example the condensation between aniline and diethanolamine (4) or *bis*-(2-chloroethyl)amine (5), has the inherent disadvantages of long reaction time and/or low yield.

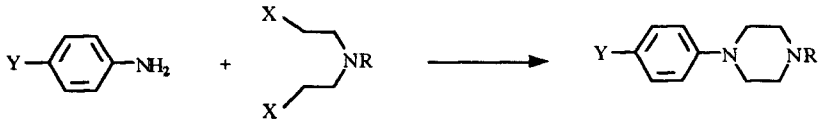
We describe here (table 1) a synthesis of the required piperazine in satisfactory yield, and in a reaction time compatible with fluorine-18 chemistry (β^+, $t_{1/2}$ =110 min) (scheme 1) facilitated by choosing an appropriate solvent and suitable system for cyclisation (6, 7).

The reaction was successfully carried out using the readily available [^{18}F]4-fluoroaniline (8), the better results being obtained in polar protic solvents. A selection of the reactions carried out are shown in table 1, including that of the *bis*-(2-bromoethyl)compound 2a which did not transfer successfully to the conditions under which the radiochemistry was carried out.

Detosylation of piperazine 3c [HBr/phenol, reflux, 30 min, 40-45% (9)] gave N-([^{18}F] 4-fluorophenyl)piperazine 3d which was purified by Sep-Pak (silica gel) or HPLC (normal phase). Identification was made by Rf (radio-TLC) and retention time (HPLC) comparison with authentic fluorine-19 analogue. Typically 16.3 MBq (0.47 mCi, EOS) of 3d was obtained in 2 steps from 148.1 MBq (4.27 mCi) of [^{18}F] 4-fluoroaniline (in 87-120 min from [^{18}F]fluoroaniline), and overall in 151-184 min from 603.1 MBq (16.8 mCi) of [^{18}F] fluoride.

Work is at present being carried out in the optimisation of the above reaction, and also towards the direct formation of the piperazine ring on the molecule of interest.

Scheme 1: Preparation of Piperazines 3



	1a	1b		2a	2b		3a	3b	3c	3d
Y	F	^{18}F	X	Br,	OTS	Y	F	F	^{18}F	^{18}F
			R	COOEt	Ts	R	COOEt	Ts	Ts	H

Table 1 : Reaction Conditions for the Preparation of 3a-c.

reagents[a]	1a + 2a	1a + 2b	1b + 2b				
solvent	HMPA[b]	HMPA[b]	HMPA[b]	*n*-butanol			*n*-octanol
temperature (°C)	130	130	130	130	150-170	180 to dryness	180
time (min)	15	30	30	30	30-40	7	40
yield (%)	15-20	50-60	no reaction	27-35	42-62	35	57

(a) all the reactions were carried out in the presence of $NaHCO_3$;
(b) HMPA : hexamethylphosphoramide

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Paper C8

Non-Activated ^{18}F-Fluorinated Aromatic Compounds Through Nucleophilic Substitution and Decarbonylation Reactions Using $RhCl[P(C_6H_5)_3]_3$

A. Plenevaux, C. Lemaire, A.J. Palmer, P. Damhaut and D. Comar.
Cyclotron Research Center, Liège University, B-4000 Liège, Belgium.

Nucleophilic displacement by [^{18}F]fluoride of a nitro group activated by electron withdrawing groups is currently the method of choice for the preparation of no-carrier-added (n.c.a.) ^{18}F-labeled aromatic compounds. Among activating groups the aldehyde function has been one of the most extensively employed owing to the wide scope it offers for subsequent chemical syntheses (1).

Although a new procedure for labeling alkylbenzenes with [^{18}F]fluoride has appeared recently (2), synthesis of n.c.a. [^{18}F]labeled aromatic rings without electron withdrawing groups remains a challenge to radiochemistry. Therefore, selection of an appropriate precursor bearing an aldehyde group in an activating position, followed by decarbonylation of the ^{18}F-labeled product appears to offer an attractive solution to this problem. Decarbonylation is a well documented reaction (3), and a preliminary report of the application of reductive decarbonylation to ^{18}F-chemistry using Pd/C as catalyst has recently appeared (4).

In this paper, the synthesis of n.c.a. 3-[^{18}F]fluoroanisole, 2-[^{18}F]fluoroanisole, [^{18}F]fluorobenzene and 4-[^{18}F]fluoroveratrole are reported. The strategy consists of amino-polyether supported nucleophilic substitution with [^{18}F]F^- on activated nitro aromatic aldehyde precursors followed by decarbonylation using tris(triphenylphosphine)rhodium (I) chloride (Wilkinson's catalyst). The experimental parameters for this reaction (solvent, temperature, amount of catalyst and time) have been studied and optimized. The decarbonylation yields obtained were 84 ± 5% (corrected for decay) within 15 minutes at 150°C in 1,4-dioxan for the four compounds studied. The results are summarized in Table 1.

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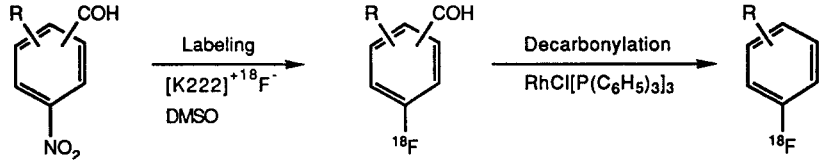
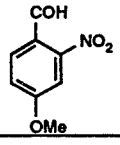
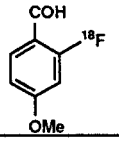
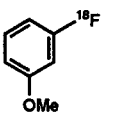
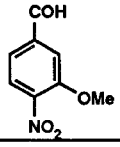
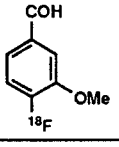
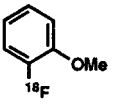
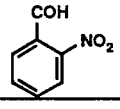
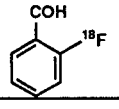
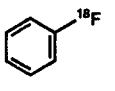
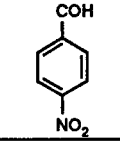
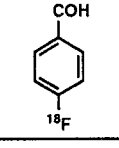
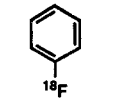
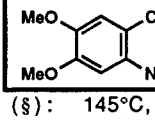
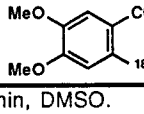
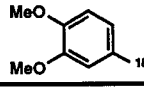
Table 1: Radiochemical yields obtained for the aromatic nucleophilic substitution on nitrobenzaldehydes with $[K222]^{+}{}^{18}F^{-}$ by using classical heating and microwave heating, and for the decarbonylation of ^{18}F-labeled aromatic aldehydes with $RhCl[P(C_6H_5)_3]_3$.



Labeling reactions				Decarbonylation reactions	
Precursors	Products	Classical heating (§) (yield)	Microwave heating (◊) (yield)	Products	Decarbonylation yield (¥)
		75 %	75 %		85 ± 5 %
		55 %	55 %		84 ± 5 %
		65 %	65 %		83 ± 5 %
		65 %	65 %		84 ± 5 %
		50 %	50 %		85 ± 4 %

(§): 145°C, 20 min, DMSO.
(◊): 300W, 2 min, DMSO.
(¥): n.c.a. [^{18}F]aldehyde, 1.5 mg of the corresponding nitro precursor, 15 mg of catalyst, 150°C, 15 min in 1,4-dioxan (1 mL).

Synthesis and Evaluation of 2-Deoxy-2-[^{18}F]-Fluoro- β-Mannosyl Fluoride as a Mechanism-based Imaging Probe for Glycosidase Enzymes

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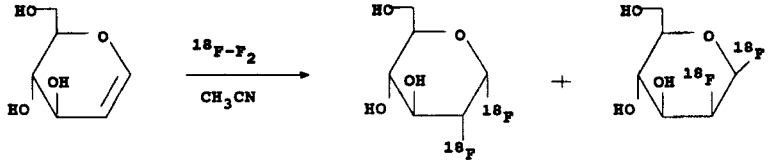
Recently, a novel class of covalent, mechanism-based glycosidase inhibitors, using 2-deoxy-2-fluoroglycosides, was developed by Withers and co-workers (1,2). There are many diseases which are associated with specific deficiencies in cerebral glycosidases (3). We undertook this project to label some of these inhibitors with ^{18}F for use as potential agents to image glycosidase activity in the brain with PET.

We labelled 2-deoxy-2-fluoro-β-mannosyl fluoride, in a 12% radiochemical yield, with ^{18}F-F_2 in acetonitrile as shown in the scheme below.



The β mannose derivative was separated from the gluco-isomer using a silica column with moist ether as the eluant. The manno/gluco isomer ratio before separation was 1:2. The mannosyl fraction was evaporated to dryness and the residue dissolved in buffer. A portion of the buffer solution was added to a solution of *Agrobacter* β-glucosidase and the mixture incubated for 15 minutes at 37°C. This mixture was then injected into a gel permeation HPLC column and the labelled enzyme separated from the excess mannose sugar. The radiochromatogram showed that the fluorinated mannose sugar had bound to the enzyme. The release of the inhibitor from the enzyme was then monitored by following hydrolysis of the covalent glycosyl-enzyme complex in buffer and transglycosylation with glucosyl benzene (197 mM). It was shown that the inhibitor was released from the enzyme faster by transglycosylation when compared to hydrolysis.

In summary we have demonstrated for the first time that one can incorporate a [^{18}F]-fluorinated carbohydrate inhibitor into a glycosidase and that the release of the inhibitor can be easily monitored by following the loss of radioactivity from the enzyme.

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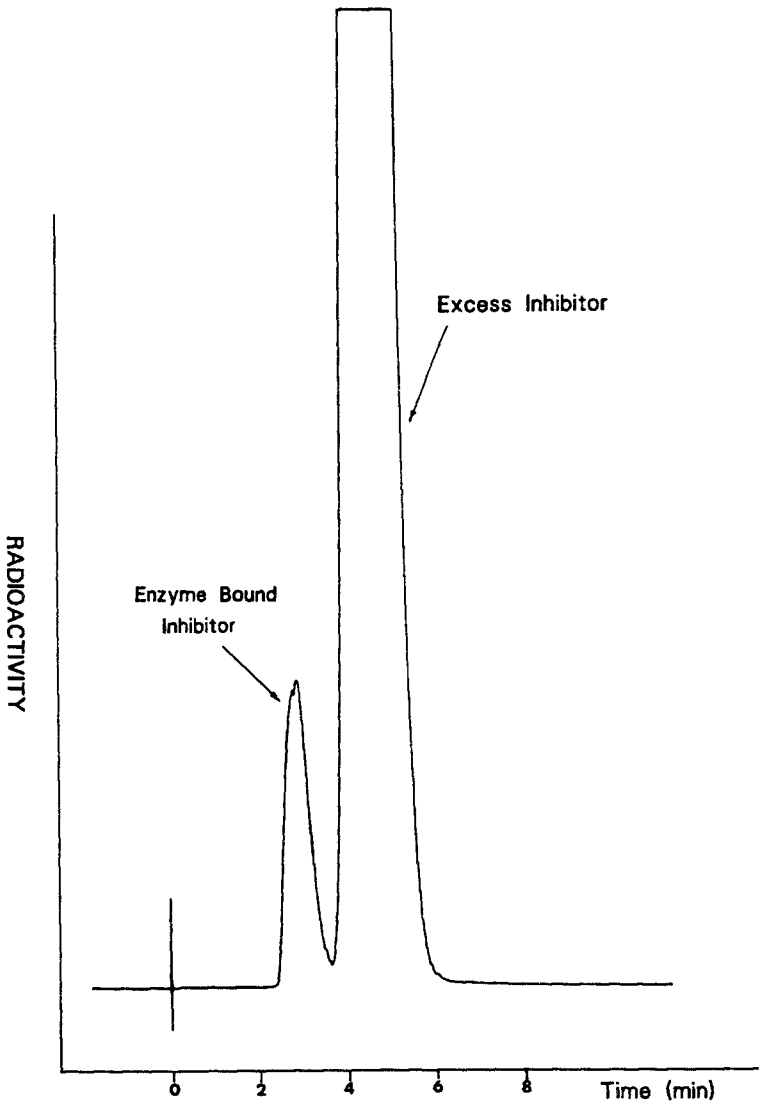

Fig 1. Radiochromatogram on gel permeation column of incubated mixture of 2-fluoro-mannosyl fluoride and glucosidase.

Paper C10

Selective Recovery of Usable Quantities of [^{18}F]Fluoride and [^{13}N]Nitrate/Nitrite for FDG and Ammonia Synthesis From a Single Irradiation of Low-Enriched [^{18}O]Water.

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Brookhaven National Laboratory, Department of Chemistry, Upton, New York, USA 11973.

Myocardial imaging in clinical PET using [^{13}N]NH_3 to measure blood flow followed in series with [^{18}F]FDG to assess tissue uptake, is finding increased use for diagnosing myocardial disease (Schelbert, *et al.* 1986). Studies of this nature can impose enormous time constraints on both cyclotron and hot lab operations to produce and deliver these radiotracers in rapid succession. This action can lead to unnecessary radiation exposure to personnel, particularly if production targets are mounted by hand, to excessive cyclotron usage, and ultimately to longer radiotracer delivery times. A method has been developed that allows for quantitative extraction and selective recovery of usable quantitites of [^{18}F]F^- and [^{13}N]NO_3^-/NO_2^- for radiotracer synthesis for a single patient scan, from a single irradiation of low-enriched [^{18}O]H_2O (20-30%). The method uses an anion exchange resin (Dowex AG1-X8 carbonate form, 7mm x 2mm i.d. column packed with 200-400 mesh) for simultaneous extraction of [^{18}F]F^- and [^{13}N]NO_3^-/NO_2^- anions from the target water after irradiation (Schlyer, *et al.* 1990). Selective and near quantitative recovery of these radionuclides is achieved by rinsing the resin in series with 1.5 mL of 0.01 M K_2CO_3 to recover 99% of the bound ^{18}F-activity at 99% radionuclidic purity, and with 1.5 mL of 1 N HCL to recover 94% of the bound ^{13}N-activity at 99% radionuclidic purity. Rapid and quantitative conversion of the released ^{13}N-activity can be accomplished over DeVarda's alloy provided the acid solution is first made basic. The above method is amenable to automated processing of these radionuclides in the cyclotron vault. The key benefit seen by this is that it should be possible to effect simultaneous transfer of both [^{18}F]F^- to the hot lab and [^{13}N]NH_3 gas directly to the PET thus streamlining radiotracer delivery times, and minimizing personnel exposure to radiation. This research was carried out under contract DE-ACO2-76CH00016 with USDOE and supported by its OHER.

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Schlyer, D.J., Bastos, M.A.V., Alexoff, D. and Wolf, A.P. (1990) Separation of [^{18}F]fluoride from [^{18}O]water using anion exchange resin. *Appl. Radiat. Isot.*, **41**, 531.

Table 1

Effect of the Nature and Strength of Extraction Reagent on Recovery Efficiency[a]

Extraction Reagent	Reagent Strength		% ^{13}N Recovered From AG1-X8 Resin
K_2CO_3	0.01	M	< 1
Cs_2CO_3	0.005	M	< 1
NaOH	1.0	N	5
NaOH	10.0	N	12
Sodium Citrate	0.1	M	7
Sodium Citrate	0.5	M	19
Sodium Citrate	0.045	M	24
Saline	0.9%		23
H_2SO_4	1.0	N	43
HCl	0.1	N	16
HCl	0.5	N	53
HCl	1.0	N	82
HCl	2.5	N	89

a. All tests were carried out using 1 mL of the appropriate reagent.

Table 2

Results From Studies on ^{18}F and ^{13}N Separation Using AG1-X8 Anion Exchange Columns

% Enrichment of $H_2{}^{18}O$	Recovered Target Activity as ^{18}F and ^{13}N (mCi at EOB)	% Radionuclidic Distribution		% Resin Recovery		% Radionuclidic Purity in Extracted Fractions	
		^{18}F	^{13}N	^{18}F	^{13}N	^{18}F	^{13}N
50	195	45	55	>99	80	98.8	99.2
30	214	35	65	>99	81	99.4	98.4
20	163	23	77	>99	94[b]	98.9	99.3

a. ^{18}F was recovered from resin using 1.5 mL of 0.01 M K_2CO_3. ^{13}N was recovered from resin, after ^{18}F extraction, using 1mL of 1N HCl.

b. ^{13}N was recovered from resin in this case using 1.5 mL of 1N HCl.

Paper C11

Fluorine-18 Derivatives of 7-Chloro-8-Hydroxy-3-Methyl-1-(3'-Aminophenyl)-2,3,4,5-Tetrahydro-1H-3-Benzazepine (SCH 38548): Selective and High Affinity Fluorinated Radioligands for Dopamine D-1 Receptors

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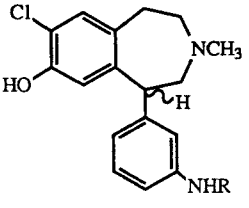
Efforts are being made to study dopamine D-1 receptors non-invasively by PET (1). These studies have not been as extensive as those for D-2 receptors primarily due to the lack of suitable specific radioligands. The only radioligand used, until recently, to image D-1 receptors by PET was [C-11]SCH 23390 (2). This radiotracer suffers from (i) a short physical half-life (due to labeling with carbon-11, $t_{1/2}$ 20.4 min); (ii) short biological half-life and; (iii) poor selectivity due to affinity for 5-HT_2 receptors. Recently, SCH 39166, a compound based on benzonaphthazepines has been described as a more selective antagonist for the D-1 receptor (3).

Development of [F-18]fluorinated derivatives of benzazepines as radioligands for imaging of the D-1 receptor by PET has attracted attention due to the advantages of fluorine-18. N-Fluoroalkyl derivatives of SCH 24518 have been reported, but they show decreased affinity for the receptor-site (4, 5). We have therefore investigated N-alkyl, N-aryl, N-fluoroalkyl and N-fluoroaryl derivatives of 7-chloro-8-hydroxy-3-methyl-1-(3'-aminophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH 38548) as high affinity ligands for the D-1 receptor. Here we report syntheses of the derivatives of SCH 38548, their in vitro binding affinities for the D-1 receptor-sites and radiosyntheses.

Synthesis of SCH 38548 was carried out by modifications of the reported procedure (6) (see supporting data). In vitro binding studies in rat striatal tissue indicated high affinity for all the compounds studied. Shown below are IC_{50}'s of the fluorinated derivatives. Amongst the four derivatives, p-fluorobenzoyl showed higher affinity comparable to that of SCH 38548.



Compd. (R)	IC_{50} nM ([^{3}H]SCH 23390)
H	0.20
CH_2CH_2F	2.54
$CH_2CH_2CH_2F$	2.28
COC_6H_4F (para)	0.31
$CH_2C_6H_4F$ (para)	0.96

For purposes of [^{18}F]fluoroalkylation, [^{18}F]fluoroethyl bromide, [^{18}F]fluoropropyl bromide and [^{18}F]fluoropropyl iodide were produced by reacting nca [^{18}F]fluoride/kryptofix/ K_2CO_3 with dibromoethane, dibromopropane and diiodopropane respectively, in CH_3CN at 75°C. Two approaches were used: 1) radiolabeling the *O*-methylated SCH 38548 derivative followed by deprotection (BBr_3) of the methyl group; 2) direct radiolabeling of SCH 38548 with the [^{18}F]fluoroalkyl halide. [^{18}F]fluoroalkylation was carried out in dimethylformamide at 110°C with and without added base (K_2CO_3). For the two-step reaction, decay corrected yields of both the reactions (fluoroethyl and fluoropropyl with added base) were found to be ~ 9-11% in 120 min. EOB. For the one-step reaction, without base the yield was poor (~ 3% EOB), whereas with base a mixture of *O*-and *N*-[^{18}F]fluoroalkylated derivatives was obtained from which the *N*-[^{18}F]fluoroalkylated products were separated using HPLC in 12-15% yields. Purifications (RP-HPLC) of *N*-[^{18}F]fluoroethyl and *N*-[^{18}F]fluoropropyl SCH 38548 provided specific activities of 700-1400 Ci/mmol.

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Supporting Data :

Figure-1: Synthesis of SCH 38548

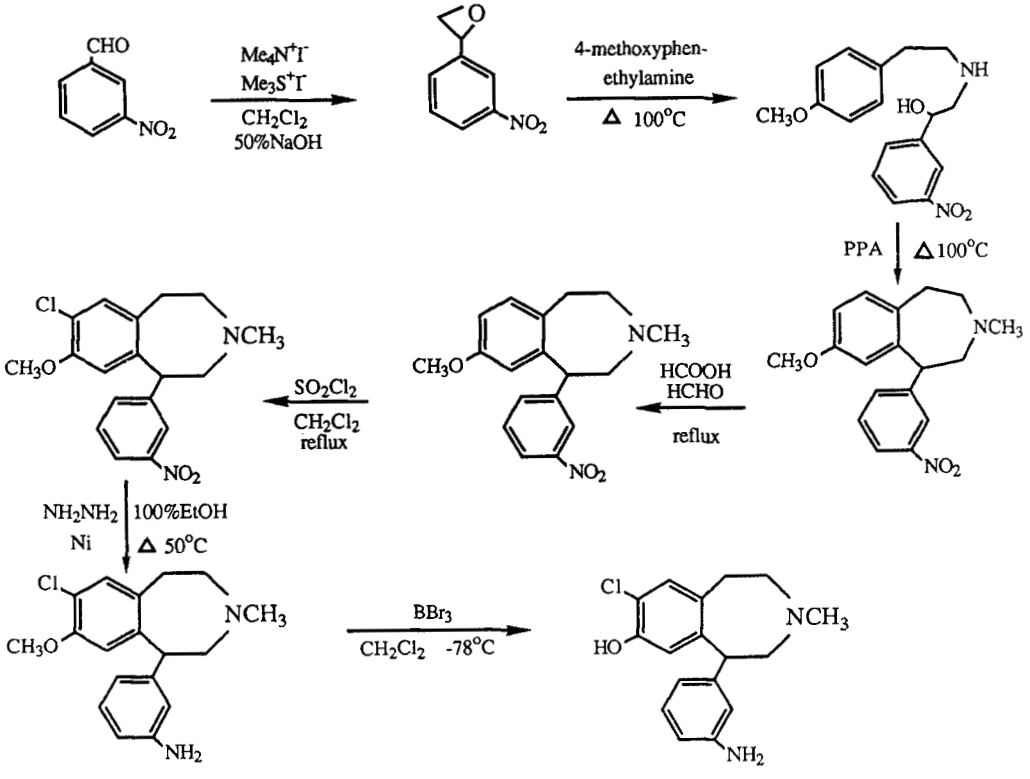


Figure-2: Syntheses of Fluorinated and Non-fluorinated Derivatives of SCH 38548.

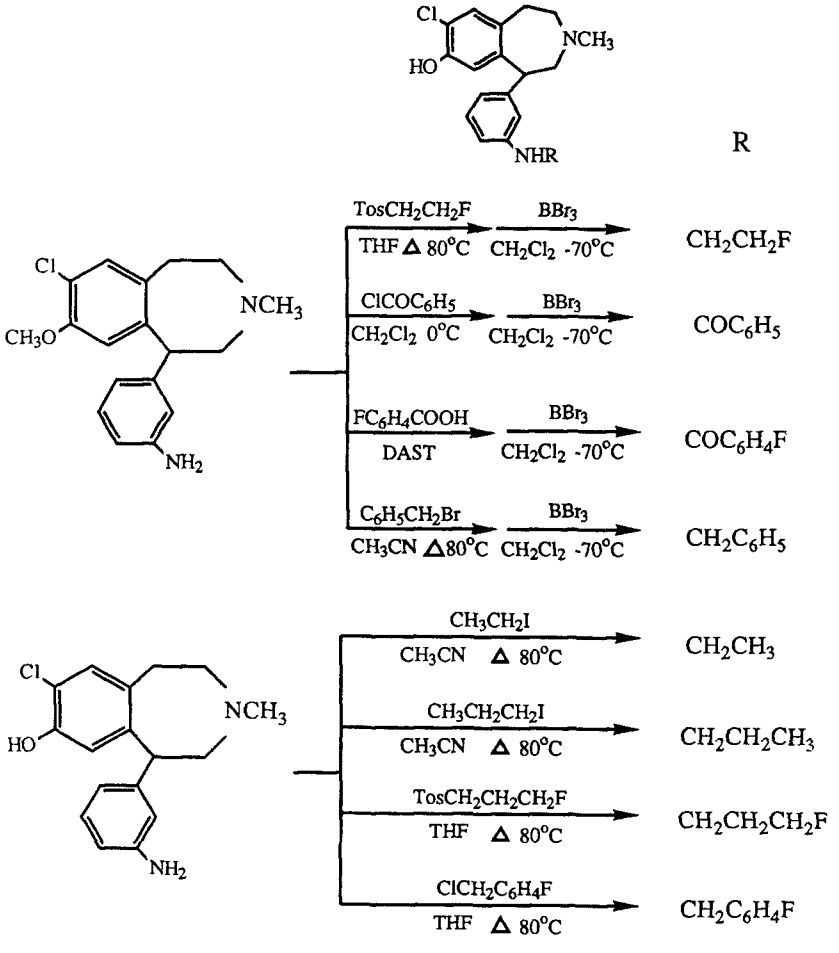
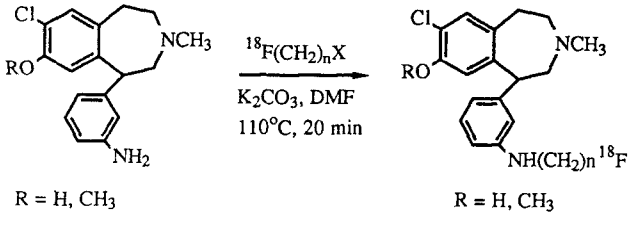


Figure-3: Radiosyntheses



R = H, CH_3 R = H, CH_3

Paper C12

Synthesis of 2-[^{18}F]FDG using Microwave Radiation

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Synthesis of ^{18}F-labelled radiopharmaceuticals designed for *in vivo* studies requires optimization of reaction conditions so that all reactions occur as efficiently and as quickly as possible. Gedye *et al.*[1] have demonstrated the use of microwave for the rapid synthesis of organic compounds. Recently microwave heating has been employed for radiolabelling reactions.[2,3] We now report the results from our preliminary studies on the use of commercial microwave oven for the synthesis of 2-[^{18}F]FDG and the results are compared with conventional heating method.

Radio-TLC analysis of the reaction mixture, obtained during the reaction between ^{18}F-fluoride (containing 10^{-13} mole of [^{19}F]KF) and 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethane-sulphonyl-β-D-mannopyranose (0.02 mmol) (**1**) in CH_3CN (HPLC grade), shows that the radiochemical yield of [^{18}F]2-fluoro-2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-gluocopyranose (**2**) is 73 and 54 %, respectively, using microwave and conventional heating methods. Unlike the conventional method, where three unidentified fluorine-containing side products are produced during the reaction (Fig. 1A), no ^{18}F-containing side products are produced when microwave heating is employed (Fig. 1B). Fluorine-19 NMR spectra of both dry KF/crypt/K_2CO_3 (0.02 mmol of F^-) and the reaction mixture (Table 1) showed impurities at -147.7 ppm (HF_2^-)[4] and at -159.2 ppm (unknown)[5] when conventional heat is used for the reaction. It was also observed that the hydrolysis of the four acetate groups of fluorinated intermediate is complete in 5 min. using the microwave (at 20% power) compared to 15 min. reflux at 100 ^{o}C used in the conventional synthesis.

The radiochemical yield of 2-[^{18}F]FDG at the end of synthesis (60 min. synthesis time) is 33% while the conventional heating method produced 25% 2-[^{18}F]FDG at the end of 80 min. synthesis time.

References:

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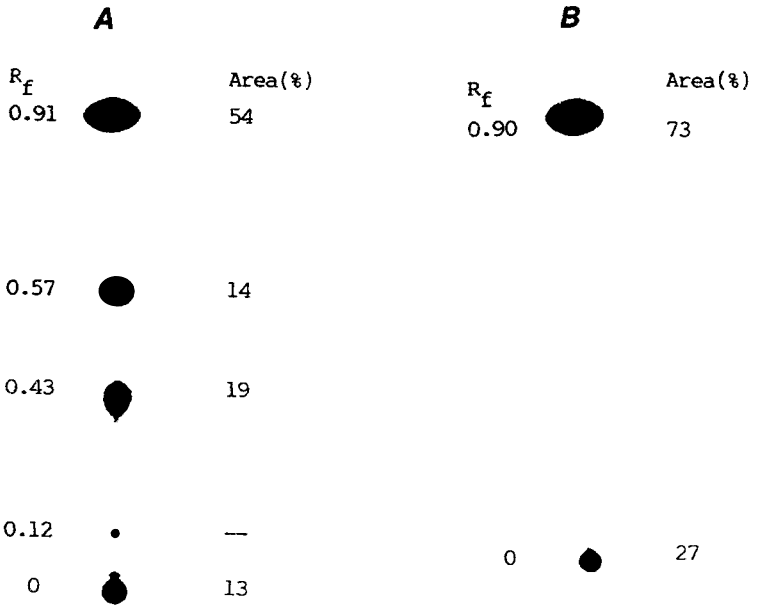
Table 1. Fluorine-19 chemical shifts (δ ppm from $CFCl_3$) of the dry KF/2,2,2-crypt/K_2CO_3 and the reaction mixture in CH_3CN obtained after microwave heating and conventional heating

Microwave Heat		Conventional Heat		Tentative Assignment
Dry F^-	Rx. Mix	Dry F^-	Rx. Mix	
-	-74.5	-	-74.5	Triflate (1)
-	-78.5	-	-78.5	$CF_3SO_3^-$
-109.13	-	-102.7	-	KF/crypt/K_2CO_3
-147.7	-147.7*	-147.7	-	HF_2^- ($^1J_{HF}$ = 127.1 Hz)
-	-	-159.2	-159.2*	Unknown
-	-201.5*	-	-201.5	Intermediate (2) $^3J_{H3\text{-}F}$ = 15.27 Hz $^2J_{H2\text{-}F}$ = 50.86 Hz

*only trace amounts observed.

Figure 1. Radio-TLC (stationary phase: Kieselgel 60 (BDH), mobile phase: CH_3CN : H_2O = 95 : 5) of the reaction mixture: (A) using conventional heat and (B) using microwave heat



The Effect of Acetonitrile and Inert Atmosphere on ^{18}F-fluoride Ion Exchange Reaction.

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ABSTRACT

^{18}F-Fluoride exchange with nitro and/or trimethylamine groups on aromatic ring has become one of the most useful method for production of different ^{18}F labeled radiopharmaceuticals. This reaction is typically is carried out in DMSO at temperatures ranging between 70-180. We have tried this reaction on a number of substrates for producing ^{18}F-L-Dopa, and ^{18}F-NCQ-115. Two important points were noted which would greatly facilitate these reactions including 1. The effect of acetonitrile, and 2. The effect of inert atmosphere. The radiolabeling exchange of different substrates such as 4-Nitrobenzaldehyde(A), 4-Trimethylaminobenzaldehyde trifluoromethansulphonate(B), 6-Nitroveratraldehyde(C), and Ethyl 6-Trimetylamino-3,4-dimethoxy benzoate trifluoromethansulphonate(D) are summarized below:

Precursor	Yields of reaction under different conditions at 120C, for 30 minutes.			
	DMSO	CH_3CN	DMSO+CH_3CN	DMSO/N_2
A	7	35	37	30
B	10	75	60	72
C	2	10	9	12
D	4	15	14	16

Table I. The results of radiofluorination exchanged reaction under different conditions.

A possible explanation for this phenomenon is discussed.

EXPERIMENTAL

^{18}F-Fluoride was produced by ^{18}O(p,n)^{18}F reaction on ^{18}O-Water (95-97% enrichment, Isotec) in all silver target. All reagents were obtained from Aldrich Chemicals except for Ethyl-6-amino-3,4-dimethoxybenzoate which were purchased from Lancaster Chemical.

Synthesis of Ethyl-6-Trimetylamino-3,4-dimethoxy benzoate trifluoromethansulphonate.

A solution of ethyl-6-amino-3,4-dimethoxybenzoate (1.0g, 4.4mmoles), and methyl trifluormethansulphonate (2.6g,17.6mmoles) in toluene (25mL) was heated with stirring to reflux under nitrogen for two hours. The mixture was then cooled down to room temperature for complete precipitation of the product. The precipitates were filtered, and washed with toluene before drying with a stream of nitrogen at room temperature. MS (C.I.)(NH_3) m/e:268(M^+), 253(M^+-15).

General radiofluorine exchange method.

The appropriate amounts of ^{18}F-Fluoride (usually about 2mCi) in ^{18}O-Water was added to a mixture of kryptofix 222 (15-20mg), and potassium carbonate (2mg). This mixture was held under a stream of nitrogen and heated in an oil bath. Acetonitrile (1mL) was then added and the solution was evaporated to dryness. The evaporation of acetonitrile was repeated twice for complete removal of water. A solution of the appropriate precursor (2mg) in appropriate solvent was then added to the residue. The mixture was then capped (except for the reactions that were carried out under nitrogen) and heated in an oil bath at 120C for 30 minutes. The reactions that were carried out under nitrogen were also heated in the oil bath

for 30 minutes, but they were not capped; instead they were carried out under a slow stream of nitrogen.

RESULTS AND DISCUSSIONS

The results of our radiofluorination exchanged reactions are summarized in table I. We were quite surprised by these findings due to relative mass amounts of fluoride ion present in the reaction and therefore the possibility of undesired effects from the generated nitrite ion in the reaction mixture. The most likely explanation for this phenomenon is the capability of both acetonitrile and nitrogen to remove the generated nitrite ion rapidly from the reaction mixture. This would favor not only the radiofluorination exchanged equilibrium, but also eliminate any possibility of destruction of the product as reported recently[1].

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Paper C14

Preparation and In Vitro Evaluation of ^{18}F Labeled Biotin.

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ABSTRACT

Radiolabeled Monoclonal Antibodies (MoAb's) with various radioisotopes have been used for radioimmunoimaging and radioimmunotherapy. Although this method has been somewhat successful, one of the major problems which remains is the background radioactivity in normal tissue which causes problems in imaging and even more serious problems in treatment. Recently a method has been described using avidin biotin binding[1] capability to improve targeting of the tumor tissue. In this method, a specific MoAb is coupled to avidin and is injected intravenously to animals or subjects. After a week (or a sufficient time for the MoAb to localized in the tumor and for the tissue background to be reduced to a minimum) radiolabeled biotin is injected. We have now prepared ^{18}F labeled Biotin where the radiolabel is bound to an aromatic moiety and therefore quite stable "in vivo". This has been done by preparation of ^{18}F-Flurobenzylaldehyde or ^{18}F-Fluorobenzylbromide and their reaction with Biotin hydrazide. Radiolabeled biotin using both precursors are shown to bind to Avidin "in vitro", and therefore retains its biological integrity. We are presently investigating the utility of this radiotracers for "in vivo" imaging of tumors in nude mice.

EXPERIMENTAL

Snthesis:

An aliquot of the ^{18}F-Fluoride solution prepared by irradiation of ^{18}O-water in an all-silver cyclotron target was added to a reaction vial containing potassium carbonate (2mg) and Kryptofix 2.2.2 (20mg). Water was removed azeotropically with acetonitrile (3 X 1mL) under a stream of nitrogen in an oil bath at 130C. A solution of trimethylamine benzaldehyde trifluoromethylsuphonate (1mg) in dimethylsulphoxide (DMSO) (1ml) was added to the dry residue. The reaction vial was heated in an oil bath at 100C for 30 minutes under slow stream of nitrogen. This yielded ^{18}F-Flourobenzaldehyde (~50%) (Rf=0.85 using Silica gel plates and a %50 solution of ether:pet ether as eluate). The ^{18}F-Fluorobenzaldehyde was then purified by using a sep-Pack column eluting the product with a solution of 50% ether:pet ether. The isolated solution of ^{18}F-Fluorobenzaldehyde was then reacted with Biotin Hydrazide (1mg) in a solution of water:ethanol (5:1). This yeilded ^{18}F-Fluorobenzylated Biotin Hydrazide quantitatively (Rf=0.15 using Silica gel plates and a %50 solution of ether:pet ether as eluate).

In another experiment a similar exchanged reaction was performed. In this case, the mixture was reduced using a solution of LAH in tetrahydrfuran at room temperature before purification of ^{18}F-Flourobenzaldehyde. This yeilded ^{18}F-Fluorobenzylalcohol which was purified using a sep-Pack column. The product was then reacted with thionyl bromide in ether to yield ^{18}F-Fluorobenzylbromide which was purified using a alumina column, and reacted with Biotin Hydrazide (1mg) in a solution of water:ethanol (5:1).The product was shown to

be ^{18}F-Fluorobenzylated Biotin Hydrazide by TLC chromatography.

Determination of Biotin biological integrity

^{18}F labeled biotin was added to a suspension of avidin (1:1 molar ratio) conjugated agarose beads. After a 45-min incubation the suspension was centrifuged, and the ratio of radioactivity bound to the beads against the supernatant was measured. A control study was also performed where the avidin conjugated beads were incubated with an excess of unlabeled biotin before incubation with radiolabeled biotin. This suspension was also centrifuged as before, and the ratio of radioactivity bound to the beads was measured to calculate the nonspecific binding.

RESULTS AND DISCUSSION

The radiofluorine exchange on teimethylaminebenzaldehyde trifluoromethylsulphonate (TBTS) has been reported before. We have done now this exchange successfully at 100C for 15 minuets, and had yields of over %50 routinely, but only when the TBTS is freshly prepared. This is probably due to the fact that TBTS is extremely hydroscopic, and even trace amount of water inhibit the exchange. The reaction of fluorobenzaldehye with Biotin hydrazide was fast, and quantitative as expected. This is despite the fact that very small amount of Biotin hydrazide was used. Therefore high specific activity product was generated. This is very important since there will be minimal avidin sights available in the tumor tissue following injection of avidin bound MoAb.

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Paper C15

OBSERVATIONS AND STRATEGIES TO REDUCE GASEOUS EMISSIONS DURING 2-[^{18}F]FLUORO-2-DEOXYGLUCOSE SYNTHESIS

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Loss of [^{18}F]fluoride during synthesis of 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) by the method of Hamacher et al. (1) has been observed by many groups, though not widely publicized. The form of this lost activity has been conjectured to be an extremely volatile material, [^{18}F]CF_3SO_2F, produced during "triflate" displacement [Tewson,(2)]. Kleck et al. (3) have also observed releases during the triflate reaction and a gradual release of a material that plates out on the exhaust stack during the subsequent acid hydrolysis. Further, volatile short-lived radioactive materials, probably containing [^{13}N], have been observed on releasing the target contents, notably at the end of beam bombardment (EOB). These observations could have serious repercussions for new groups, especially those specializing only in "clinical" studies, that will be located close to highly populated areas in hospitals. Many of these groups will be using vendor-supplied systems such as the one described by Kleck et al. (3), the CTI/Siemens "black box" [Padgett et al., (4)], or the Scanditronix/GEMS robotic system as used in our laboratory. The containment, or preferably elimination, of these volatile materials is not only desirable, but is likely to be mandated in the current environment of stricter regulatory control.

The location of our cyclotron/radiochemical laboratories in the heart of a major hospital, the Iowa State NRC mandate for containment and monitoring of stack emissions, and the requirement to practise ALARA (as low as reasonably achievable) approaches to radiation exposure has put us in an ideal situation to document, evaluate, and implement corrective measures to curb the releases of these radioactive materials and fulfill ALARA requirements.

In our vendor supplied set-up for [^{18}F]FDG production, the target water containing [^{18}F]fluoride is dispensed into an open 5 mL vial containing K_2CO_3/"Kryptofix" which is then capped. During this process we have observed volatile releases that appear to be inversely related to time of release after EOB. The material eludes trapping by charcoal/HEPA filters present in the hot-cell exhaust stack. This source of release was rectified by modifying the receiving station so that target water was dispensed into a sealed vial which was vented back to a delay tank in the vault prior to release to the environment. This simple ploy also circumvents situations where the robot mishandles the vial or fails to cap, circumstances that could result in study termination or result in excessive radiation exposure to the radiochemist attempting manual corrective action.

During the preparation of "naked" fluoride by multiple azeotropic distillations of the [^{18}O]water with CH_3CN at 130°C we have also observed up to 3% loss of radioactivity. This loss could be almost eliminated by use of a heavy duty 10/90 mil teflon/silicone septa [TSS](Alltech) rather than the recommended 10/50 mil red teflon/rubber septa [TRS] (Sun Brokers). With the thinner TRS septa we have often heard hissing emissions of vapors during septum penetration on CH_3CN additions. Simple pressure tests bear out our contention that these TRS septa are not likely to withstand the pressures generated when 1.5 mL of CH_3CN (82°C b.p.) solvent is rapidly dispensed into a 5 mL volume at 130°C and that they do not reseal adequately after penetration. Although the very low vapor pressure of the fluoride anion precludes its distillation under these conditions, we postulate that the rapid emission of "gases" actually includes a contribution of aerosolized fluoride which can plate out on the hot-cell or the exhaust stack prior to being trapped by the charcoal filter. The superior resealing qualities of the TSS septa essentially eliminates these emissions.

The most serious source of emissions is clearly related to a competing reaction occurring during displacement of the triflate group by fluoride. A chemical solution to this problem could also result in an improved yield of desired [^{18}F]FDG at the expense of the undesired competing volatile product. But, as noted by Tewson (2), for many groups the loss of yield is not considered a major issue, since the nuclear reaction is relatively efficient and the actual amount of material obtainable is sufficient to conduct several clinical studies. However this fails to take into account the increased longevity of the target foils and less target activation by running at a lower beam current or shorter irradiation times while still achieving comparable yields, and avoiding the increased radiation exposure to personnel and emissions to the general public from the by-product. As in the case of the evaporation step we have found that the TRS septa were unable to contain the volatile activity. Use of the thicker TSS septa resulted in a major reduction in the volatile releases by containing the activity within the vial until the volatile effluent was diverted to the delay tank for decay. The charcoal filters were able to effectively remove the major portion of the volatile release and contain it within the radiochemical laboratories, leaving only minor stack emissions. Further major improvements have been achieved by installing charcoal filters at the exit ports of the hot cells, thus containing the activity within a well-shielded environment. With these preventative devices installed we have redirected our efforts to pursue a chemical solution. Serendipitously, during one run we noted an unusually large emission of volatile materials which we were able to trace back to a broken micro-switch operating a cooling fan for the heater block. This resulted in the triflate displacement reaction taking place at a temperature higher than the 90°C routinely used. Preliminary studies indicate that maintaining the temperature of the displacement reaction at or below 90°C is critical in reducing the contribution of the volatile contaminant. Losses in excess of 20-30% are easily achieved above 100°C, suggesting the thermal decomposition of the precursor triflate to a product which can effectively compete for the available fluoride. Given the variability of heating devices to transfer/dissipate heat to/from the reaction vessel, it would seem advisable to determine the actual temperature in the vessel, say with a microprobe thermocouple.

Thus our preliminary findings are that volatile stack emissions during [^{18}F]FDG synthesis can be essentially reduced to zero by carefully monitoring reaction temperature during the triflate displacement reaction, use of appropriate septa to contain volatile products during needle penetration, and judicious choice and location of charcoal filters. Changing needles regularly, thus avoiding blunt or burred points, should also be considered in preventing septum penetration leakage. To maintain ALARA levels it would seem appropriate to situate charcoal stack filters as close as possible to the hot-cell/radiochemistry hood and locate the filter in a well-shielded yet accessible area such as a part of a vault, even better locate within hot-cell.

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Paper C16

OPTIMIZATION STUDIES CONCERNING THE DIRECT NUCLEOPHILIC FLUORINATION OF BUTYROPHENONE NEUROLEPTICS

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In order to investigate the pharmacokinetic properties of different butyrophenone neuroleptics with PET it was our aim to synthesize n.c.a. ^{18}F-labelled benperidol, haloperidol, droperidol and fluanison via a simple, one step method.

Based on the direct nucleophilic aromatic fluorination described earlier for the synthesis of [^{18}F]N-methylspiperone (1) fluorine-18 labelled butyrophenones were prepared via nucleophilic displacement of the 4'-nitro group of the corresponding aromatic nitro precursors (Scheme 1). In the presence of the cryptand kryptofix 2.2.2, potassium oxalate and a small amount of potassium carbonate, kinetic studies of the n.c.a. fluorination were performed in dimethylsulfoxide, dimethylformamide or dimethylacetamide. The optimum reaction conditions for all butyrophenones investigated were found to lie in the range of 140 to 160°C within a reaction time of 5 to 30 min (Fig. 1). In all cases the radiochemical yields ranged from 30 to 45 % and showed only small differences for DMSO, DMF and dimethylacetamide. Nevertheless, the decomposition products were found to depend strongly on the solvent, offering a higher chemical stability of the nitro-precursors in DMF and dimethylacetamide. This is quite significant since a decrease in the amount of precursor decomposition allows the use of much smaller quantities of the nitro percursor without any loss in the overall yield and reaction time. In addition, the absence of decomposition products also provides a more efficient HPLC separation eliminating the need of a two step HPLC purification as described earlier (1). The relatively high radiochemical yields achieved via the simple displacement reaction and the radiochemical purities of 99 % indicate that the moderate basic oxalate/carbonate cryptate is suitable for the direct n.c.a. nucleophilic fluorination of the base sensitive butyrophenone neuroleptics.

1. Hamacher K., Nebeling B., Coenen H.H., Stöcklin G. -
J. Label. Compds. Radiopharm. 30: 353 (1991)

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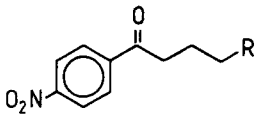
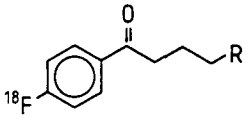
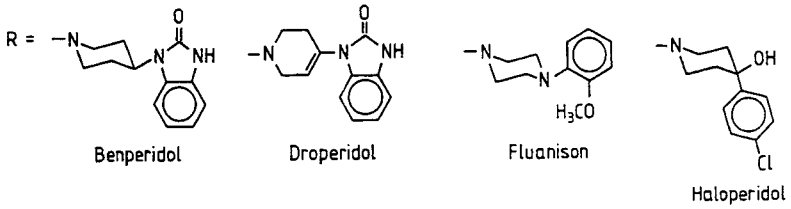
SCHEME 1



$^{18}F^-$ | $[K^{\oplus}\subset(2.2.2.)]\,C_2O_4^{2-}$; CO_3^{2-}
DMSO, DMF or dimethylacetamide
140...160 °C, 5...30 min



Radiochemical yield 30...45 %



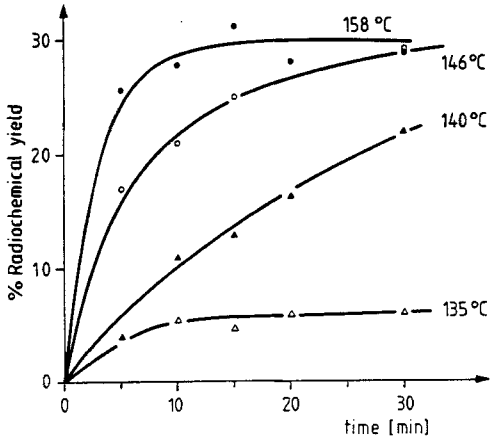


Fig. 1 Dependence of the radiochemical yield of [^{18}F]fluanison on time and temperature. Experimental conditions: Cryptate: Kryptofix 2.2.2 (35-44 μmol), potassium oxalate (2 mg, 12 μmol), potassium carbonate (30 μg, 0,21 μmol). Educt: 9-10 μmol nitro precursor / 1 ml dry distilled solvent.

Paper C17

RAPID SYNTHESIS OF FLUORINE-18 LABELLED BENZHYDROLS, HIGH SPECIFIC ACTIVITY INTERMEDIATES FOR USE IN SYNTHESES OF [^{18}F]-1,4-BENZODIAZEPINE-2-ONES

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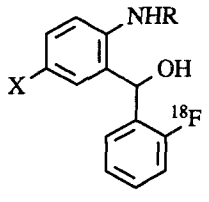
The *in vivo* quantification of the distribution of radiotracers in PET can sometimes be complicated by the appearance of radioactive metabolites during the investigation period. Development of new labelling methods for introducing the radionuclide in different positions in the tracer molecule can be an useful tool in charting the metabolic fate of different parts of the molecule.

We present here a general method for synthesizing ^{18}F-labelled benzhydrols, which can be used as building blocks in the syntheses of [^{18}F]-5-(2-fluorophenyl)-1,4-benzodiazepine-2-on es with high specific activity. The method is based on Sugasawas method (1) using anilino-chloroboranes as a specific ortho-coupling reagent. Four different anilinochloroboranes have been synthesized and their use in coupling with [^{18}F]-2-fluorobenzaldehyde has been studied showing the versatility of this reaction. Radiochemical yields are on the order of 70-90% after 10 minutes. We have recently demonstrated the use of a ^{18}F-labelled benzhydrol in 3 subsequent transformations to rapidly synthesize the corresponding [^{18}F]-1,4-benzodiazepine-2-one (2).



The authors would like to thank Dr. T. Sugasawa for valuable discussions concerning the coupling reaction, W. Pulka for technical assistance with the synthesis of reference substances and G. Printz for the radionuclide production.

1. T. Sugasawa et al., *J. Am. Chem. Soc.*, 100:4842 (1978).
2. P. Johnström et al., Proceedings, Synthesis and Applications of Isotopically Labelled Compounds, Toronto Sep. 3-7, 1991.

Paper C18

DRUG SUBSTANCE DETERMINATION IN 2-DEOXY-2-[^{18}F]FLUORO-D-GLUCOSE PREPARATIONS. COMMENTS ON THE PURITY OF ^{18}F-LABELLED 2-DEOXY-2-FLUORO-D-GLUCOSE.

Franz Oberdorfer, Klaus Weber, Uwe Haberkorn, Klaus Gottschall*) and Wolfgang Maier-Borst, Deutsches Krebsforschungszentrum, Institut für Radiologie und Pathophysiologie, im Neuenheimer Feld 280, D-6900 Heidelberg, F.R.G. *) EUROCHROM Dr. Ing. H. Knauer GmbH, Am Schlangengraben 16, D-1000 Berlin 20, F.R.G.

Final 2-deoxy-2[^{18}F]fluoro-D-glucose formulations originating from three major radiosynthethic procedures were examined with regard to the drug proper beneath a variety of additional ingredients. Based on these results comments are made on the chemical and radiochemical purity of the drug product. The difficult problem of quantifying 2-deoxy-2-[^{18}F]fluoro-D-glucose in a formulated preparation is discussed. Aspects concerning the need of a high quality product are critically evaluated. An attempt has been made to describe an injectable solution of 2-deoxy-2[^{18}F]fluoro-D-glucose giving information about all of the substances in the parenteral drug product.

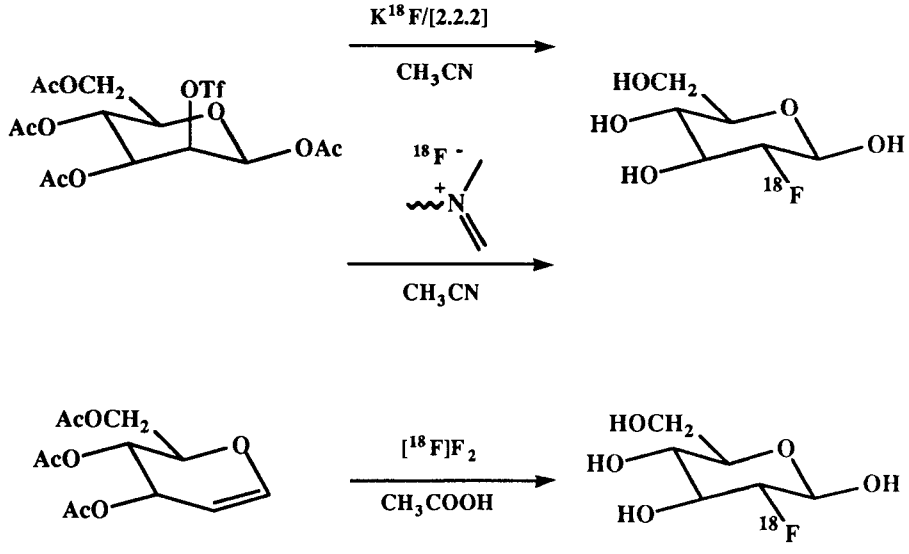


Figure 1: Procedures evaluated with regard to the drug proper by quantitative HPLC

The decision which of the contaminants should, and which of them have not to be removed for a given experiment seems more to be a matter of the function to be traced than a pharmaceutical problem. In any case, all of the chemical and radiochemical contaminants found are certainly far below toxicity, even pharmacological effects may be excluded.

Ion-chromatographic procedures at high [1] and low [2] pH will be evaluated and compared with regard to their reliability. The sensitivity of k' of 2-deoxy-2-[^{18}F]fluoro-D-glucose versus various NaOH concentrations will be discussed in anionic applications. Different HPLC-patterns were observed when comparing the solid phase supported nucleophilic exchange reaction introduced by Toorongian and Mulholland et al. [3] with the more convenient "kryptofix" method of Hamacher [4].

We suspect, under certain conditions, either retention of configuration at C-2 or rearrangement reactions during the solid phase supported nucleophilic exchange procedure. This is evidenced by appearance of a labelled fluorocarbohydrate with a retention time similar to 2-deoxy-2-fluoro-D-mannose. The NMR-data of that contaminant from a carrier added synthesis compare with our previous results [5] suggesting the mannose analog. However the corresponding rearrangement product 3-deoxy-3-fluoro-D-glucose could not be ruled out clearly until now.

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[3] Toorongian S. A., Mulholland G.K., Jewett D.M., Bachelor M.A. and Kilbourn M.L., Nucl. Med. Biol. Int. J. Radiat. Appl. Instrum. Part B 17: 273 (1990).

[4] Hamacher K., Coenen H.H. andStöcklin G., J. Nucl. Med. 27: 235 (1986).

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SYNTHESIS OF $[^{18}F]F_2$ FROM $[^{18}F]F^-$(aq)

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Electrophilic fluorination of organic molecules with $[^{18}F]F_2$ or its derivatives is a very useful route in preparation of PET radiochemicals. Two factors limit however the more widespread use of these ; the specific radioactivities are low, normally in the order of 1-5 Ci/mmol and the difficulties attached to the production of this precursor with a cyclotron.

We have studied a method were ^{18}F is produced with a normal water target (1) and is transformed into $[^{18}F]F_2$ in post-irradiation synthesis. The aim of this work is to develope methods were a low-energy proton cyclotron can be used to produce large amounts $[^{18}F]F_2$ with high specific radioactivity (100 - 500 Ci/mmol).

Aqueous ^{18}F (specific radioactivity > 10^5 Ci/mmol (1)) is first used in synthesis of $[^{18}F]CH_3F$ (azeotropic destillation of ^{18}F(aq) and Kryptofix 2.2.2/K_2CO_3 in CH_3CN (2), the residue is reacted with CH_3I/CH_3CN). The synthesis of $[^{18}F]CH_3F$ is ready in 6 minutes and the yield is better than 90 %.

In a second step the $[^{18}F]CH_3F$ is reacted with carrier F_2-gas (1-10 umol) in a quartz reaction vessel. During the reaction of these two gases several labelled products are formed, namelly $[^{18}F]CH_2F_2$, $[^{18}F]CHF_3$, $[^{18}F]CF_4$ and $[^{18}F]F_2$. At room temperature the exchange of ^{18}F for F proceeds slowly. The reaction rate can be enhanced by irradiating the gas mixture with UV-light or by heating the reaction vessel. The F_2 molecule has an UV absorbtion maximum at 310 nm. The relative amounts of the labelled fluoromethanes seem to behave as predicted by a model we have developed through computer simulation using a Monte Carlo routine, see figure 1. In the model $[^{18}F]F_2$ is formed efficiently if the molecular ratio of CH_3F/F_2 is <0.01 and no other reaction channels are available.

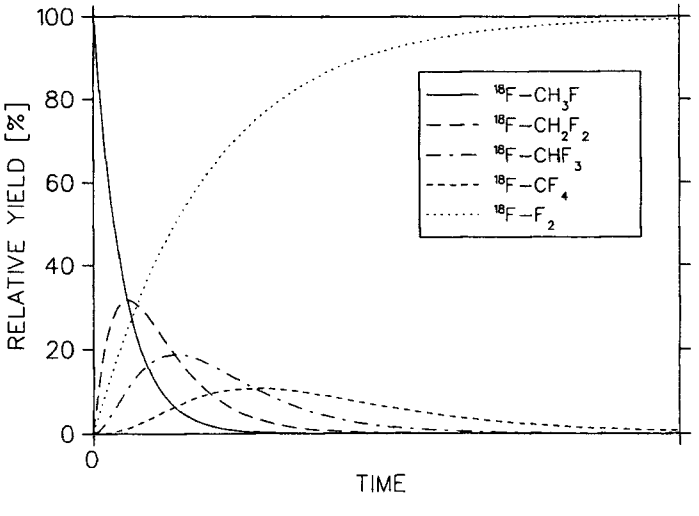

Figure 1. Monte Carlo model for reaction of F_2 with $[^{18}F]CH_3F$.

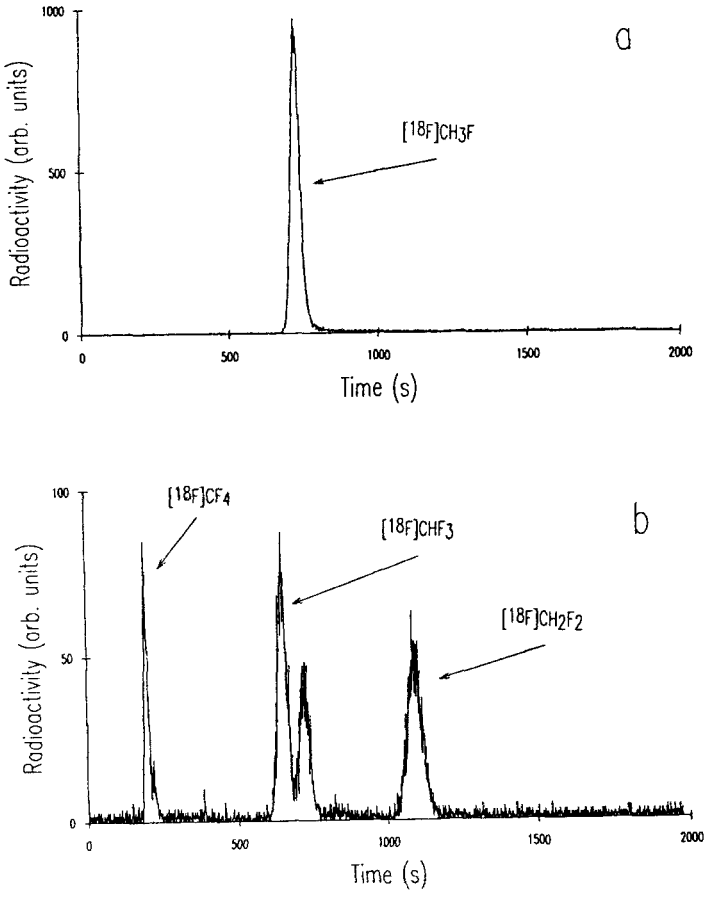

Figure 2. Radiogas chromatograms of a) $[^{18}F]CH_3F$ and
b) sample from gas reaction vessel during reaction of F_2 and $[^{18}F]CH_3F$.

We have followed the reaction as a function of UV dose and heating by using gas cromatography (Porapak Q 60-80 mesh, column ID 2 mm, length 3 m, He-carrier, 50 C, TC- and radioactivity detectors) for the determination of the fluoromethanes, see figure 2 a,b. The $[^{18}F]F_2$ is identified by its incorporation into tri-O-acetylglucal (TAG), after conversion to $[^{18}F]CH_3COOF$ (3).

Uptil now the results show a maximum yield of about 20 % in the conversion of $[^{18}F]CH_3F$ to $[^{18}F]F_2$ as measured from the incorporation of radioactivity into TAG. The results from the gas chromatography indicate higher incorporation yields, the main problems uptil now have been in the handling of small amounts of very reactive F_2.

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2. Hamacher K., Coenen H.H. and Stöcklin G. - J. Nucl. Med. 27: 235(1986)
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Paper C20

NCA Asymmetric Synthesis of 2-[^{18}F]Fluoro-L-Tyrosine

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2-[^{18}F]Fluoro-L-tyrosine has been proposed for probing cerebral protein synthesis by Positron Emission Tomography (1). The methods reported to date for the synthesis of this radiopharmaceutical are based on the electrophilic fluorination of protected or unprotected tyrosine using reagents such as [^{18}F]F_2 or acetyl [^{18}F]hypofluorite (2). These methods involve the addition of carrier and have been reported to produce regioisomeric mixtures leading to low yields of 2-[^{18}F]fluoro-L-tyrosine after chromatographic purification.

As an alternative to these electrophilic procedures, a regioselective and enantioselective synthesis of this compound using $^{18}F^-$ produced from enriched ^{18}O-water has been developed. The synthetic pathway described in the present work consists of the alkylation of the same inductor of chirality, (S)-(-)1-Boc-2-*tert*-butyl-3-methyl-4-imidazolidinone (compound A) previously used for the preparation of [β-^{11}C]amino acids (3), 6-[^{18}F]fluoro-L-dopa and 4-[^{18}F]fluoro-L-m-tyrosine (4).

The first step of this synthesis requires ^{18}F-fluorination of either 4-methoxy-2-nitro-benzaldehyde or the corresponding trimethylammonium trifluoromethanesulfonate (B) (Scheme 1). These starting precursors are prepared from 4-methyl-3-nitroanisole and 3-fluoro-4-methylaniline respectively as described previously (5). In the presence of diiodosilane (DIS), the ^{18}F-fluorinated benzaldehyde (C) (Radiochemical Yield: 65-70 %) was rapidly reduced to the corresponding benzyl iodide (D) which was easily purified by column chromatography (Silica gel: dichloromethane). After evaporation of the solvent, the alkylating agent was added to the lithium enolate of Boc-BMI which had been previously generated by treatment with lithium diisopropylamide (LDA) (Scheme 2). After reaction (-78°C, 10 min), hydrolysis (HI, 200°C, 25 min) and preparative reverse phase HPLC purification, the [^{18}F]fluoro-L-amino acid (E) was obtained with an overall yield of 10-20% and an enantiomeric excess ≥ 98%.

The final n.c.a. amino acid and intermediate products were identified by comparison with cold authentic samples synthesized according to the same procedure and identified by ^{1}H NMR and MS.

This synthesis starting from ^{18}F-fluoride will greatly simplify laboratory procedures as well as making available higher activities of this radiopharmaceutical and other amino acids in the n.c.a. state.

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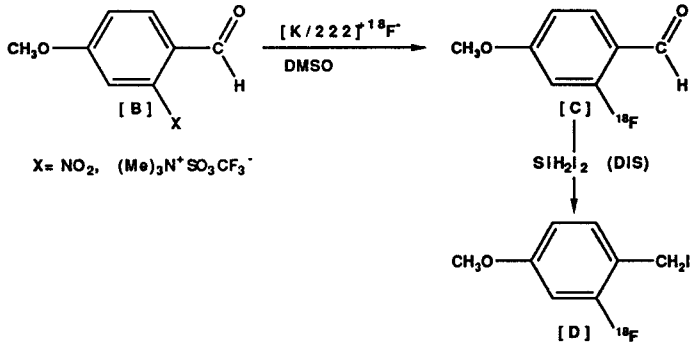
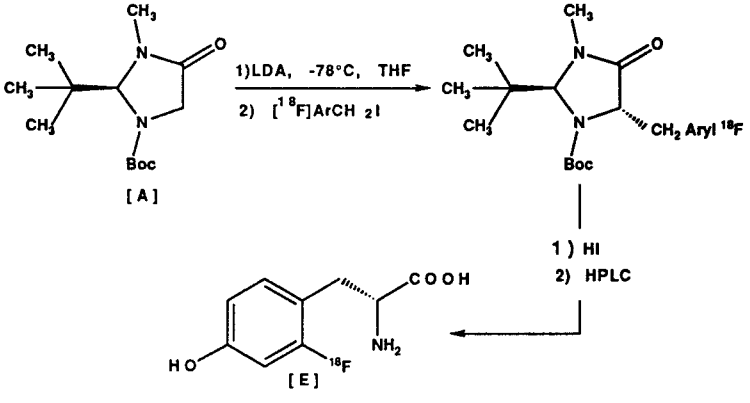
4. Lemaire C, Damhaut P., Plenevaux A., Cantineau R, Christiaens L., and Guillaume M. - J. Nucl. Med. 32, 935 (1991).

5. Lemaire C, Damhaut P., Plenevaux A., Cantineau R, Christiaens L., and Guillaume M. - Appl Radiat. Isot. (1991) in press



Scheme 1.

General labelling reaction for 2-[^{18}F]fluoro-4-methoxybenzaldehyde and 2-[^{18}F]fluoro-4-methoxybenzyl iodide



Scheme 2.

Asymmetric synthesis of n.c.a. 2-[^{18}F]fluoro-L-tyrosine starting from (1S)-Boc-BMI

Paper C21

1-[^{18}F]Fluoro-2-propanol *p*-Toluenesulfonate: a Synthon for the Preparation of N-([^{18}F]Fluoroisopropyl)amines

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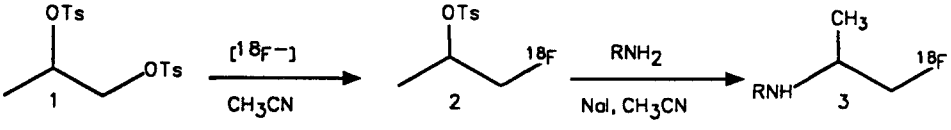
The $ß_1$-adrenergic receptors are involved in the regulation of the rate and the contractile force of the myocardium. Several forms of heart failure are related to the $ß_1$-receptor density in the heart. In this respect, a suitable procedure for the visualisation and quantification of myocardial $ß_1$-receptors by PET would be of great clinical interest. In this abstract, we present the synthesis of [^{18}F]fluoroisopropyl tosylate **2**, prepared from 1,2-ditosyloxypropane **1** in CH_3CN (110 °C, 20 min) in 45% radiochemical yield (corrected for decay), as a new versatile radiolabelling agent for the synthesis of N-([^{18}F]fluoroisopropyl)-analogues of $ß_1$-receptor binding ligands. In order to investigate the scope of this compound, the [^{18}F]fluoroisopropyl-alkylated derivatives of benzylamine and



RNH_2 = benzylamine or norephedrine

norephedrine **3** were prepared from **2** with a yield of 7 and 2% respectively (after HPLC purification and corrected for decay, synthesis time 90 min). These last two reactions were carried out in acetonitrile at 125 °C for 1 hr, in the presence of a Kryptofix/K_2CO_3/NaI mixture. We conclude that this alkylation reaction gives a good perspective for the preparation of [^{18}F]fluoro-labelled analogues of $ß_1$-adrenergic receptor binding ligands for PET.

Acknowledgement.- This study was supported by a grant from the Jan Kornelis de Cock stichting.

SYNTHESIS AND EVALUATION OF ^{18}F-LABELLED BIOTIN DERIVATIVES FOR TUMOR LOCALIZATION WITH PET

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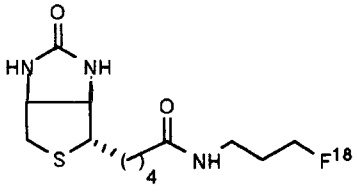
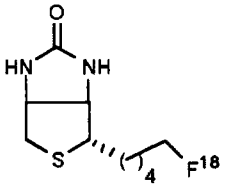
MASSACHUSETTS GENERAL HOSPITAL , BOSTOM , MA 02114 USA

High contrast in imaging of tumors can be achieved by allowing a nonradiolabelled specific antibody to localize and clear from circulation prior to the administration of a low molecular weight radiolabelled moiety with high affinity to the pretargeted antiboby. One such method is the avidin-biotin system.[1] The very high affinity of biotin for avidin indicates that biotin can be a useful carrier for targeting radionuclides to avidin-conjugated antibodies previously localized on tumors.[2,3] We wish to report the synthesis of two ^{18}F-labelled biotin derivatives that may be useful imaging agents in this regard.



1



2

The synthesis of [^{18}F]-propylbiotinylamide **1** and [^{18}F]-pentylbiotin **2** was accomplished by treating their corresponding trifLates with $^{18}F^-$ in the presence of Kriptofix (Scheme 1). Yields of the labelled biotin derivatives were 8% in preliminary conditions. The distribution of the ^{18}F-biotin derivatives in infected and tumor bearing animals pretreated with avidin will be reported.

This work was supported by DOE grant DE-FG02-86ER60460.

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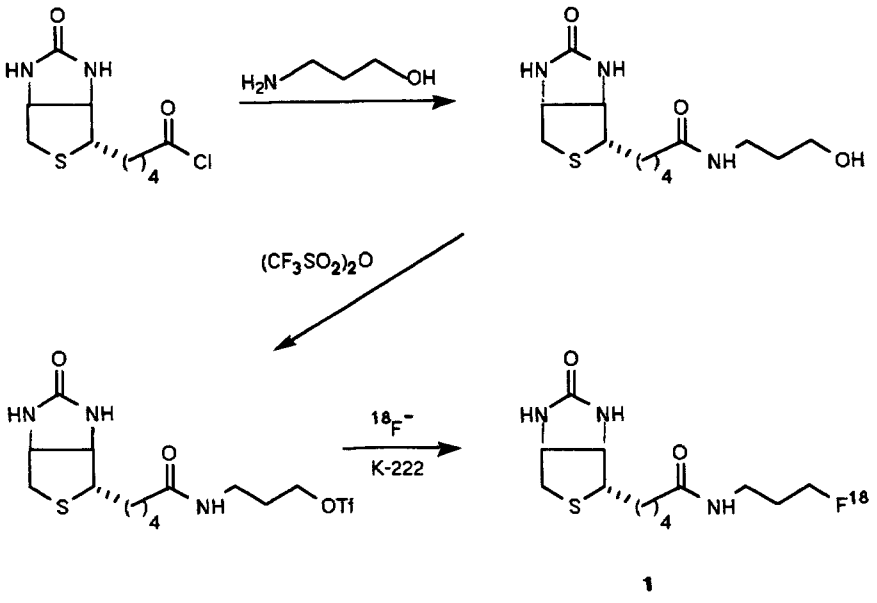
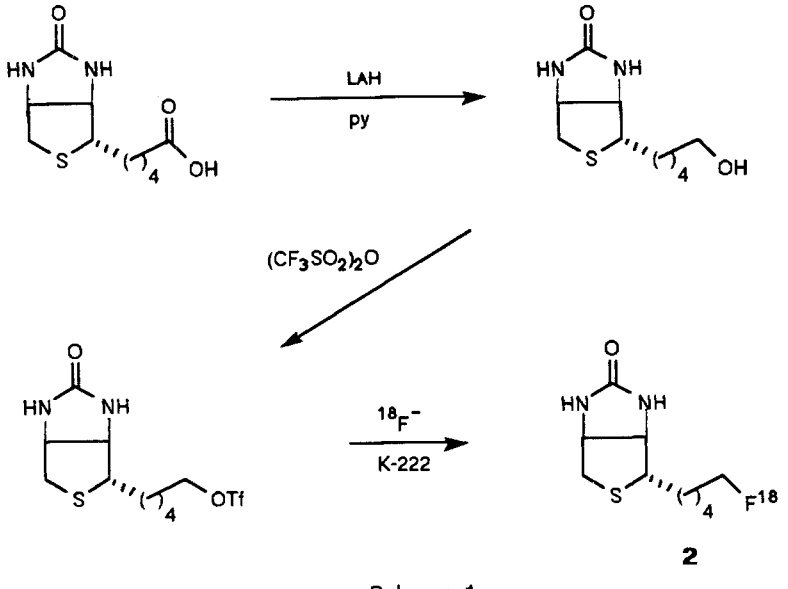
2. Kalofonos, H. P.; Rusckowski,M.; Siebecker, D. A. *J. Nucl. Med.* **1990**, *31* ,1791.
3. Garlick, R.K.; Giese, R.W. *J. Biol. Chem.* **1988**, *263*, 210.


HN
NH
O
S
Cl
H_2N
OH
NH
$(CF_3SO_2)_2O$
OTf
$^{18}F^-$
K-222
F^{18}

1


HN
NH
O
S
OH
LAH
py
$(CF_3SO_2)_2O$
OTf
$^{18}F^-$
K-222
F^{18}

2

Scheme 1

EXPERIENCES WITH THE SOLID PHASE SUPPORTED NUCLEOPHILIC SUBSTITUTION APPROACH IN THE PREPARATION OF 2-DEOXY-2-[^{18}F]FLUORO-D-GLUCOSE USING A COMPUTER ASSISTED REMOTE CONTROLLED SYSTEM

Stefan Dietrich-Wolber, Helmut Knigge, Willi J. Obers, Franz Oberdorfer and Wolfgang Maier-Borst. Deutsches Krebsforschungszentrum, Institut für Radiologie und Pathophysiologie, im Neuenheimer Feld 280, D-6900 Heidelberg, F.R.G.

A remote operated apparatus for the synthesis 2-deoxy-2[^{18}F]fluoro-D-glucose has been developed. The system is based on the procedure (Fig.1) described by Toorongian and Mulholland [1]. The phase transfer catalyst is covalently bound to a resin and acts in so far as an immobilized quaternary ammonium salt.

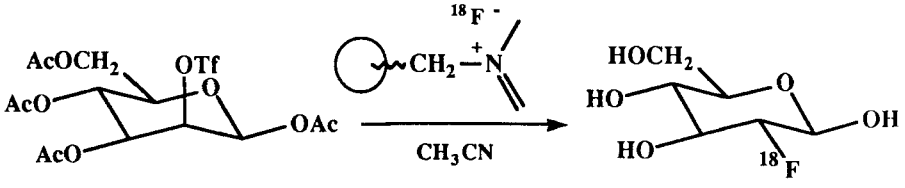


Figure 1: Procedure for the solid phase supported synthesis of [^{18}F]FDG.

This procedure has certain evident advantages in addition to the easiness of its technical realization by a remote operated radiochemistry device. The extraction of the fluoride anion from the aqueous phase by the bound quaternary ammonium cation has a high efficiency. The so formed ion pairs are distributed over a large surface. This in turn calls for an efficient and rapid step in the subsequent nucleophilic displacement reaction. The complete set-up works as a closed system. Mechanical movements are not necessary.

Experiences in running routine productions with that system are not yet sufficient to validate the reliability of the apparatus. This contribution will demonstrate circumstances under which productions worked but also often failed. Problems of decomposing or poisoning the catalyst are discussed.

[1] Toorongian S. A., Mulholland G.K., Jewett D.M., Bachelor M.A. and Kilbourn M.L., Nucl. Med. Biol. Int. J. Radiat. Appl. Instrum. Part B 17: 273 (1990).

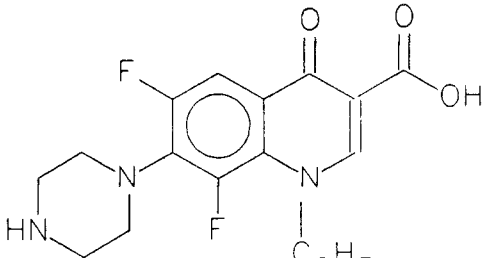
Paper C24

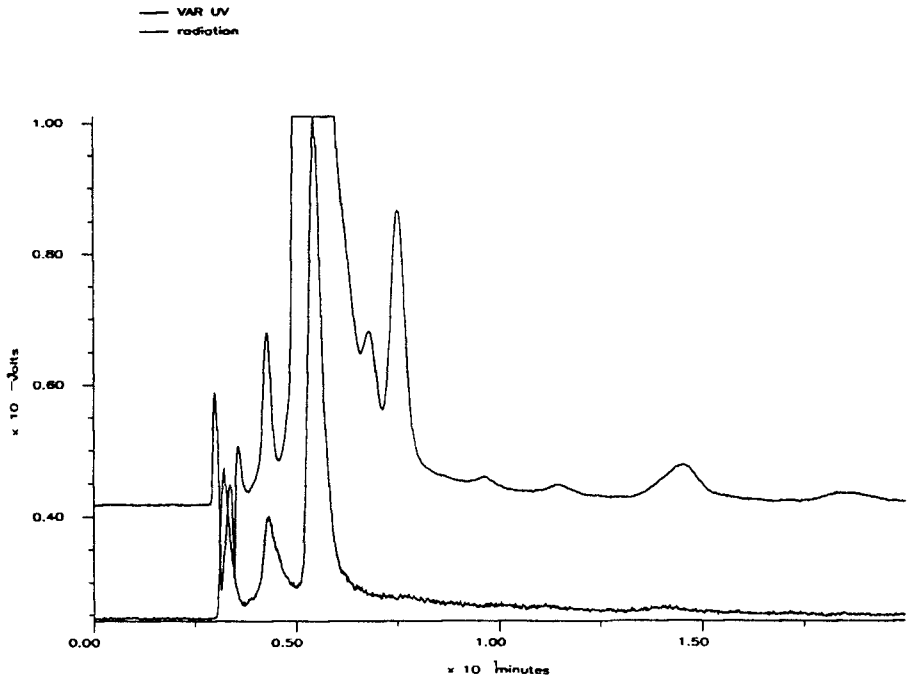
Synthesis of Fluorine-18 Lomefloxacin, A Fluorinated Quinoline Antibiotic.

T.J.Tewson. Cyclotron Facility, University of Texas Health Science Center at Houston, 6431 Fanin, Houston, Texas, 77030, USA.

Lomefloxacin, a fluorinated quinoline antibiotic of the structure shown is required labelled with fluorine-18 for biodistribution studies in humans using PET. The material is not required at high specific activity, indeed just the opposite as the labelled material must be administered at the pharmacologically active dose of 200 mgs, and so an exchange reaction of fluorine-18 for fluorine-19 would appear to be the obvious method of synthesis. However at first this compound would appear to be a poor substrate for the exchange reaction as it has two electron donating nitrogen substituents and only one electron withdrawing carbonyl group. Generally the aromatic exchange reaction only works well when the aromatic ring contains electron withdrawing groups to facilitate the reaction. Re-examination suggests that the outlook may not be that gloomy. The 3-methylpiperazine substitution is an amine but the quinoline ring structure could be regarded as a vinylogous amide with two carbonyl groups on the ß end of the double bond. This system is strongly electron withdrawing and would counteract the electron donating characteristics of the amine.

With this in mind the exchange reaction on Lomefloxacin was performed using potassium fluoride/Kryptofix as the source of fluorine-18 in DMSO at a variety of temperatures. At 130°C the exchange occurred, albeit somewhat slowly, but as the temperature was raised to 160°C the exchange occurred more rapidly and was essentially complete after 15 minutes.





HPLC Conditions: Phenyl Fatty Acid Column,
Solvent 60% 1 M Ammonium Acetate pH 3.3 40% Methanol, Flow rate 1 ml/min
UV 286 nm