N.C.A. ^{18}F-FLUOROALKYLATION OF H-ACIDIC COMPOUNDS

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SUMMARY

The fluoroalkylation of H-acidic compounds in the presence of the aminopolyether 2.2.2./potassium carbonate complex was systematically studied. With acetonitrile as solvent nucleophilic fluorination and subsequent fluoroalkylation can be carried out in a one-pot mode. Using the bifunctional fluoroalkanes $^{18}F(CH_2)_nX$ (n = 1-3, X = Br, OMes, OTos) the best n.c.a. labelling yields were obtained with tosylates. Fluoroethylation and fluoropropylation of phenol gave rise to radiochemical yields of $\geq$ 90% under optimized conditions within 10 min. The fluoroethyl moiety is the smallest generally applicable fluoroalkylation agent. In a series of H-acidic compounds a strong influence of their pK_a value on the fluoroethylation reaction was observed. Besides H-acidic compounds all Lewis bases are principally potential substrates for n.c.a. ^{18}F-fluoroalkylation.

Key words: n.c.a. ^{18}F-fluorination, ^{18}F-fluoroalkylation, bifunctional [^{18}F]fluoroalkanes, aminopolyether 2.2.2.

INTRODUCTION

Fluoroalkylation represents an alternative method for no-carrier-added (n.c.a.) radiofluorination with the positron emitting fluorine-18 ($T_{1/2}$ = 110 min), the most useful nuclide for positron emission tomography (PET) besides carbon-11

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($T_{1/2}$ = 20 min). The major advantage over ^{11}C-alkylation, one of the most common ^{11}C-labelling methods, is the longer half-life, thus making it compatible with extended pharmacokinetic in-vivo studies with PET. Also higher specific activities can more easily be obtained with [^{18}F]fluoride as starting material than with $^{11}CO_2$.

In addition to direct nucleophilic substitution, labelling with ^{18}F-fluoroalkyl moieties as prosthetic groups widely extends the spectrum of biomolecules which can be labelled. Direct nucleophilic substitution, for example, cannot be applied to H-acidic compounds due to the high proton affinity of the fluoride ion unless protecting groups have been introduced before. Further, compounds with several nucleofugic groups render positional selective labelling difficult. Suitable precursor molecules for direct nucleophilic fluorination are frequently not easy to obtain while fluoroalkylation can often be performed with the original unprotected compounds. The reaction conditions in the fluoroalkylation are not as restricting as those required in the direct fluorination where they often lead to a destruction of the precursor molecule. Direct exchange with [^{18}F]fluoride in butyrophenones may exemplify this problem (1-3). Since our first report on the effective preparation of n.c.a. [^{18}F]bromofluoromethane (4) various groups have also used bifunctional [^{18}F]fluoroalkanes and applied it to the n.c.a. labelling of receptor ligands, in particular spiperone (5-8). Most of them used 1-fluoro-n-haloalkanes as alkylating agents, while we found the 1-fluoro-n-tosyloxyalkanes which are easy to prepare from the disubstituted precursors more suitable (9). One practical advantage is their relatively lower volatility, particularly in the case of the ethane moiety.

In this study we report on the optimization of the fluoroalkylation of simple H-acidic compounds with respect to the

influence of the leaving group, reaction time, substrate concentration and basicity as well as product stability. Special emphasis was placed on the development of a method which uses the same basic system, namely aminopolyether 2.2.2./K_2CO_3, for the preceding fluorination (9) and the condensation step, thus allowing a one-pot synthesis which lends itself to an easy automation.

RESULTS AND DISCUSSION

^{18}F-Fluoroalkylation of phenol in various solvents.

Strongly acidic substrates are often poorly soluble in dipolar aprotic solvents but fortunately alkylation reactions are possible even in polar protic solvents. Although it was the goal to develop a fluoroalkylation reaction which can be performed in a one-pot mode, the effect of solvents other than acetonitrile on the fluoroalkylation was of interest with respect to the correlation of solvent properties and radiochemical yields.

Phenol was used as a model substrate for fluoroethylation (eq. 1) with an equimolar amount of the aminopolyether 2.2.2./K_2CO_3 complex for its transformation into the reactive anionic form.

$$^{18}FCH_2CH_2OTos + C_6H_5OH \xrightarrow{[2.2.2./K]_2CO_3} {}^{18}FCH_2CH_2OC_6H_5 \quad (1)$$

To accelerate the condensation, K_2CO_3 was chosen as a non nucleophilic base with rather low basicity in dipolar aprotic solvents ($pK_a \leq 19$) (10,11). The non-volatile [^{18}F]fluorotosyloxyethane was selected as fluoroalkylation agent in view of its high yield of production and its stability (9). The 2.2.2.-potassium phenolate preformed in the desired solvent was added to the reaction mixture of the preceding nucleophilic fluorination step after evaporation of acetonitrile without removing the excess of bistosyloxyethane.

The radiochemical yields of the fluoroethylation of phenol in various solvents obtained at reflux temperature and at 30 °C are listed in Table 1. At reflux temperature the radiochemical

Table 1: Radiochemical yield of the n.c.a. ^{18}F-fluoroethylation of phenol in various organic solvents

Solvent	Radiochemical yield (%)		pK_a of solvent
	Reflux	30 °C	
acetonitrile	49.9 ± 2	2.5	25.0 (12)
tetrahydrofurane	76.1 ± 1	3.3	> 35 (13)
1.4-dioxane	79.5 ± 4	2.4	> 35 (13)
dichloromethane	49.9 ± 3	13.7	> 25 (14)
acetone	37.8 ± 4	1.0	20.0 (15)
ethanol	32.0 ± 5	2.2	16.0 (16)

Reaction conditions: 0.005 M phenol, APE [2.2.2./K]$_2CO_3$; 0.05 M bistosyloxyethane; 10 min

yields obtained in THF and dioxane are very high, amounting to about 80%. High yields are also obtained in acetonitrile and methylene chloride (about 50%). Lower yields are found in acetone and the polar protic solvent ethanol. The reaction at 30 °C as a standard temperature only,yielded notable product yields in CH_2Cl_2. The pK_a values which are also listed in Table 1 have to be higher than those of the substrate to be alkylated in order to avoid competing deprotonation reactions. However, the excess of 2.2.2./K_2CO_3 from the fluorination step can also lead to side reactions in solvents with a low pK_a value (acetone, ethanol).

The fluoroalkylation of phenol is an S_N2 reaction. The expected decrease of substitution yields with increasing polarity of the solvent is surprisingly not observed. Obviously the nucleo-

philicity of the organic anion (phenolate) and its solubility exhibit different individual interactions with various solvents. Another implication of the S_N2 substitution on the tosyloxyethanes is the preferential reaction of fluorotosyloxyethane in the presence of the excess of bistosyloxyethane from the preceding fluorination step. Considering the high excess of bistosyloxyethane over phenolate and especially the extremely low concentration of the n.c.a. fluoroalkylation agent, the high substrate specificity can only be explained by sterical hindrance of the ß-substituent in a bimolecular reaction.

Furthermore, the observed sequence of solvent effects cannot be transfered to other substrates. The choice of a suitable solvent has to be substrate specific. Fortunately, alkylation can be carried out in polar protic solvents which may help to obtain homogeneous reaction solutions. Acetonitrile, which is the best solvent for the preceding fluorination step (9), is also known as a good solvent for alkylation (17). It was therefore chosen for further evaluation of other reaction parameters.

Dependence of ^{18}F-fluoroalkylation of phenol on reaction time.

The anion activating effect of the aminopolyether (2.2.2.) on the nucleophilic n.c.a. ^{18}F-fluorination (9,18), which leads to a completion of the labelling reaction within 10 min, was also observed in the fluoroalkylation of phenol as shown in Figure 1. With both bifunctional alkylation agents examined, 1-fluoro-2-tosyloxyethane and 1-fluoro-3-tosyloxypropane, maximum radiochemical yields of 45 and 55%, respectively are obtained after 10 to 15 min under non-optimized reaction conditions. With respect to the half life of fluorine-18 the short reaction times are very convenient. The decrease in yield with extended reaction times can only be due to the decomposition of the ether formed and the destabilizing effect of the fluorine

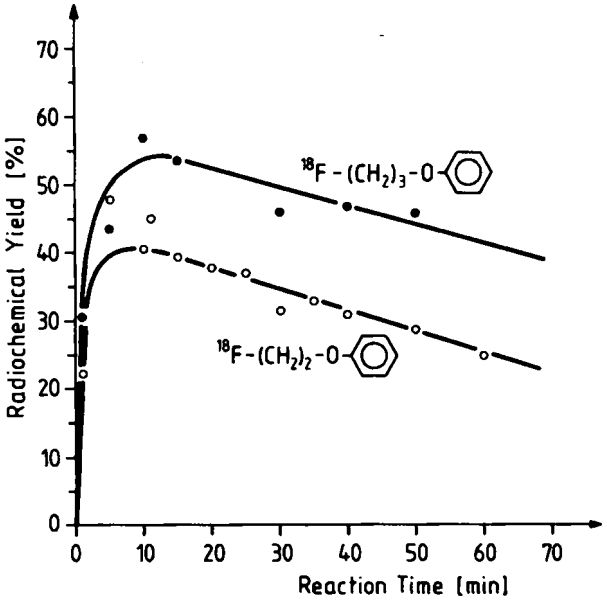

Fig. 1: Dependence of ^{18}F-fluoroethylation and ^{18}F-fluoropropylation of phenol on reaction time. Reaction condition: 0.005 mmol phenol and 0.025 mmol [2.2.2./K]$_2CO_3$ in 1 ml acetonitrile, 82 °C.

substituent, especially in the ethyl derivative. The destruction of the ether is probably due to the excess of base originating from the preceding F^--exchange step (see above).

Correspondingly, decreasing yields are found with increasing APE 2.2.2./K_2CO_3 concentrations exceeding 50 mM. Also use of bases with higher basicity in dipolar aprotic solvents such as KOH or KH ($pK_a \geq 30$) (19) already leads to decomposition of bifunctional alkanes and products, and to deprotonation with some of the solvents examined (cf. Table 1).

Effect of leaving group on ^{18}F-fluoroalkylation.

The electronic and small sterical effect of the fluorine atom is almost identical for the leaving groups examined (bromide, tosylate and mesylate), and the reactivity should only depend on their nucleofugicity. Fluoromethyl-, fluoroethyl- and fluoro-

propyl-derivatives were used for the fluoroalkylation of phenols as model substrates. However, the alkyl chain length should have a strong influence on the stability of fluoroalkylated compounds (20). Fluoromethylated compounds are only stable if the heteroatom in α-position to fluorine cannot promote the formation of carbenes by dehydrofluorination (21,22). Therefore p-chlorophenol with a strong electron withdrawing effect was used as substrate for the fluoromethylation.

The radiochemical yields obtained under standardized but non-optimized conditions are summarized in Table 2. Most striking are the low yields obtained with the mesyloxy compound for all three alkanes, indicating the reactivity sequence OMes < Br < OTos. This is probably due to the higher instability of the intermediate fluoromesyloxyalkanes. Similar to the fluorination reaction (9), tosyloxy compounds are also the most favourable for the fluoroalkylation procedure as indicated by the high radiochemical yields. In the case of the fluoromethylation, the tosylate is the only reagent leading to notable yields. With the mono-

Table 2: Chain length (n) and substituent (X) effect on the ^{18}F-fluoroalkylation of phenols

Substrate	n	X	Radiochemical yield (%)
p-chlorophenol	1	-Br	< 0.1
		-OTos	22.8 ± 3
		-OMes	1 ± 0.5
phenol	2	-Br	22.5 ± 8
		-OTos	51.3 ± 1
		-OMes	7.1 ± 1
phenol	3	-Br	43.5 ± 2
		-OTos	56.2 ± 1
		-OMes	39 ± 2

Reaction condition: 0.005 mmol phenol or 0.38 mmol p-chlorophenol in 1 ml acetonitrile; 82 °C; 10 min

fluorinated bifunctional propyl compounds the leaving group effect is only small and comparable yields with different substituents indicate an equalization of nucleofugicities. This is advantageous for labelling purposes since commercially obtainable dibromoalkanes ($n \geq 3$) can be used as suitable precursors for fluoroalkylation (see ref. 8).

Dependence of ^{18}F-fluoroalkylation on substrate concentration .

In order to identify the influence of the various parameters on the reactivity of the fluoroalkylation the experiments were performed at extremely low substrate concentrations. The effect of substrate concentration is shown in Figure 2 for the fluoro-

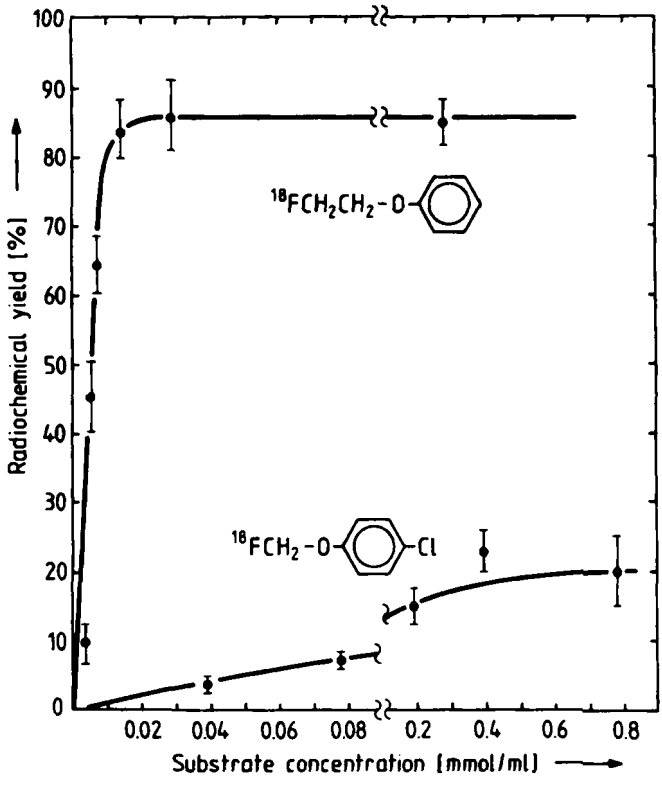

Fig. 2: Effect of substrate concentration on ^{18}F-fluoroethylation of phenol and ^{18}F-fluoromethylation of p-chlorophenol.
Reaction condition: 0.06 mmol bistosyloxyethane, 0.24 mmol bistosyloxymethane in 1 ml acetonitrile; 82 ^{o}C; 10 min.

ethylation of phenol and the fluoromethylation of p-chlorophenol. In both the cases the tosyloxy derivatives and equimolar amounts of substrate and APE 2.2.2./K_2CO_3 were used. While fluoroethylation reaches a maximum radiochemical yield already at 10 to 20 mM solutions, fluoromethylation barely exceeds values of 20% at 0.8 M concentrations. This is in spite of a fourfold higher concentration of bistosyloxymethane compared to bistosyloxyethane. This finding is in agreement with the low stability of fluoromethylated compounds as discussed above.

The nucleophilicity of the anion formed from the substrate in the presence of a base, however, is another important yield-determining factor, and optimization of concentration is necessary for each individual substrate.

Effect of substrate pK_a on ^{18}F-fluoroalkylation.

Fluoroethyltosylate appears to be the smallest generally applicable fluoroalkylation agent and was therefore chosen to study the influence of substrate acidity in a standard reaction. This was performed in a one-pot mode by adding an equimolar mixture of substrate and APE 2.2.2./K_2CO_3 to the unseparated mixture of the bifunctional alkane after fluorination. Thus, the same base is used for fluoride activation and the condensation reaction. The yields obtained with various compounds in acetonitrile as solvent are listed in Table 3.

At low substrate concentrations high yields of 35 to 48% are obtained with p-chlorophenol, phenol, and spiperone (at the lactam position). With optimized substrate concentrations higher radiochemical yields are obtainable as shown for phenol (see above) and spiperone (5,27). The very low radiochemical yields with benzylalcohol and benzamide must be due to their high pK_a value which is similar to or exceeds that of 2.2.2./K_2CO_3 in acetonitrile with $pK_a \leq 19$ (10,11). Efficient deprotonation

Table 3: Radiochemical yields of the ^{18}F-fluoroethylation of H-acidic compounds in the presence of APE 2.2.2./K_2CO_3

Substrate	pK_a	Radiochemical yield (%)
p-chlorophenol	10	47.9 ± 0.4
phenol	11	45.5 ± 5
spiperone		35.4 ± 4
nitromethane	11	7.4 ± 3
phthalimide	11	6.0 ± 4
benzylalcohol	19	2.7 ± 1
benzamide	25	0.1

Reaction condition: 0.005 mmol phenol and p-chlorophenol, 0.025 mmol other substrates in 1 ml acetonitrile; 82 °C; 10 min.

with these substrates is not possible with K_2CO_3. With KOH or KH as bases, the fluoroethylation yields increase but also lead to many side products. These deprotonation agents do not lend themselves to application with base labile substrates.

Nitromethane and phthalimide having a pK_a value of 11 also exhibit a low reactivity. In the case of nitromethane this should be due to its instability and polymerisation under basic conditions. Phthalimide, on the other hand, is poorly soluble and 0.025 mmol did not dissolve in 1 ml of acetonitrile. The compounds used (Table 3), however, indicate that fluoroalkylation is generally possible and should be applicable to other H-acidic compounds containing -SH, -PH, and -C-H acidic groups. The fluoroalkylation proceeds very easily with phenol on -OH groups, however, careful choice of the base and solvent will allow efficient ^{18}F-labelling of a whole spectrum of substrates. Phase transfer catalysts in combination with suitable bases proved to be very useful for alkylation of various compounds (23-25).

CONCLUSION

When labelling with fluorine-18 via prosthetic groups such as fluoroalkyl moieties, only small steric and electronic changes will be caused in the parent molecule, thus this technique is a useful approach to analogue tracers. With respect to stability of the reagent and the fluoroalkylated product, the fluoroethyl moiety is the smallest prosthetic group generally applicable. A direct counterpart to [^{11}C]methyl, i.e. fluoromethyl, is therefore missing. However, the change of lipophilicity introduced by a fluoroethyl moiety is similar to that of a methyl substituent with ΔlogP of 0.54 and 0.70, respectively (26). [^{18}F]Fluorotosyloxy alkanes seem to be the most suitable small fluoroalkylation reagents with respect to their stability, high boiling points and high reactivity. With longer alkyl chain the fluoroalkylation is facilitated and the leaving group is of minor importance. While fluoropropyl bromides are almost as effective as the tosylate, the latter is superior for fluoroethylation and essential for fluoromethylation, due to stability reasons.

The highest yields are found with phenols but a great variety of other substrates can be fluoroalkylated, in principle any Lewis base, such as amines, H-acidic or organometallic compounds. In each case an optimal solvent and base due to different substrate pK_a should be selected. However, the aminopolyether 2.2.2. and K_2CO_3 in acetonitrile can be used for both the n.c.a. nucleophilic ^{18}F-labelling and subsequent n.c.a. fluoroalkylation step in a one-pot reaction. This greatly facilitates automation for routine labelling procedures.

The [^{18}F]fluoroalkylation agents are more sensitive to different pK_a values than the naked ^{18}F-anion is towards the nucleofugicity of leaving groups. Fluoroalkylation is therefore

more selective than direct nucleophilic fluorination and the selectivity can be influenced by bases with appropriate pK_a values. This is even more important since there are more potential precursors for fluoroalkylation available than those with exchangable nucleofugic groups.

The availability of precursors is also an advantage for the fluoroalkylation method when compared to direct fluorine exchange in the corresponding ω-substituted alkyl derivatives. Their macroscopic preparation often demands complicated synthetic and purification procedures. Furthermore, the direct n.c.a. exchange on these precursors meets the same problems as discussed above, although introduction of the label in the very last step is generally desirable whenever possible. ^{18}F-fluoroalkylation, however, offers the possibility to obtain n.c.a. labelled analogue tracers starting from the original compound.

EXPERIMENTAL

Materials.

The aminopolyether Kryptofix® 2.2.2. (4,7,13,16,21,24-hexaoxa-1,10-diazobicyclo-8,8,8-hexacosan) and the other reagents and solvents were purchased from Merck (Darmstadt, FRG). The solvents which were used for n.c.a. radiofluorination reactions were appropriately dried. The preparation of disubstituted and bifunctional alkanes is described elsewhere (9).

Except for N-(2-fluoroethyl)benzamide the cold fluoroalkylated compounds were prepared as follows: 1 mmol of the substrate to be alkylated was dissolved in absolute acetonitrile and 5 mmol K_2CO_3, 1 mmol APE 2.2.2., and 1 mmol fluorotosyloxyalkane. After 8 hours of reflux the reaction mixture was concentrated and the products separated by preparative thin layer chromatography (PSC silicagel plates from Merck) using ether-hexane mixtures as eluant. The yields ranged from 5 to 10% for the fluoroethylation of

benzylalcohol and nitromethane, while all phenols and phthalimide gave rise to fluoroalkylation yields of 70 to 75%.

Benzamide was fluoroethylated analogous to a procedure given in the literature (24). Each 1 mmol benzamide and fluorotosyloxyethane and 0.1 mmol tetraethylammonium iodide were dissolved in 5 ml of toluene. 5 mmol of NaOH in 1 ml water was added under vigorous stirring to form an emulsion and subsequently heated at reflux for 10 hours. 10 ml water was then added and the mixture extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in $CHCl_3$ and also separated on PSC-plates. The yield was 4% of the theory.

The identity of the prepared compounds was confirmed by comparison with ^{1}H-NMR data. Those for the new compounds are in $CDCl_3$: N-2-fluoroethylbenzamide: δ(ppm) = 7.25-7.5 (5H); 4.17 (2H, d. of t. 47 Hz); 3.45 (2H, d. of t. 27 Hz); 2-fluoroethylbenzylether: δ(ppm) = 7.25 (5H); 4.52 (2H, s); 4.37 (2H, d. of t. 44.3 Hz); 3.74 (2H, d. of t. 25.4 Hz), and 1-fluoro-3-nitropropane: δ(ppm) = 4.58 (2H, d. of t. 47.3 Hz); 4.52 (2H, t); 2.25 (2H, d. of m. 24 Hz).

N.c.a. ^{18}F-fluoroalkylation and analysis.

The preparation of [^{18}F]fluoride and the bifunctional fluoroalkanes have been described by us in an earlier paper (9). The desired amount of a H-acidic compound was mixed with an equimolar amount of APE 2.2.2. and K_2CO_3 in typically 1 ml of acetonitrile and heated to 50 °C for 10 min to prepare the potassium salt of the substrate to be fluoroalkylated. This solution was added to the freshly prepared bifunctional [^{18}F]fluoroalkane without removing the excess of disubstituted alkane. This mixture was then heated to reflux for further 10 min under vigorous stirring. In experiments where the solvent for the alkylation was different, the acetonitrile was evaporated in a stream of helium after the

[^{18}F]fluoride exchange and the APE 2.2.2./K-substrate complex was added to the dry residue in the desired solvent. In the kinetic experiments aliquots were taken at given time intervals via septum and syringes. After cooling, aliquots were taken to determine the total radioactivity in the solution and for analysis via high performance liquid chromatography (HPLC, see Table 4).

Table 4: HPLC conditions and k'-values of fluoroalkylated compounds

Compound	Eluant	Column Material	k'-Value
α-fluoro-p-chloroanisol	MeOH:H_2O 6:4 0.1% HAc	RP-18	12.0
ß-fluoroethylphenylether	MeOH:H_2O 4:6 0.1% TEA	RP-18	3.0
ß-fluoroethylbenzylether	MeOH:H_2O 4:6 0.1% TEA	RP-18	4.1
ß-fluoroethyl-p-chloro-phenylether	MeOH:H_2O 4:6 0.1% TEA	RP-18	5.3
N-ß-fluoroethylspiperone	MeOH:H_2O 7:3 0.1% TEA	RP-18	4.5
ß-fluoroethylphthalimide	hexane 1.2 - dichloroethane 2:1	Si60	9.0
1-fluoro-3-nitropropane	MeOH:H_2O 1:4 0.1% TEA	RP-18	5.1
γ-fluoropropylphenylether	MeOH:H_2O 1:1 0.1% TEA	RP-18	7.7
N-ß-fluoroethylbenzamide	MeOH:H_2O 1:1 0.1% TEA	RP-18	4.4

MeOH = methanol; HAc = acetic acid; TEA = triethylamine

The radiochemical yields of fluoroalkylated products were calculated by comparison of the activity of discontinuously taken eluant fractions of the HPLC (containing the compound of interest) with that of the original solution. The radioactive samples were

measured in a Packard Auto-Gamma scintillation counter. The separation of the individual n.c.a. [^{18}F]fluoroalkylated products were performed on 250 x 4 mm LiChorsorb Si60 or RP-18 columns from Merck. The identity of expected products was ensured by comparison with k'-values of the cold reference compounds which are listed together with the corresponding eluants in Table 4.

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