A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2021**, part x, 164-182

Synthesis of Florbetapir aza-analogues using chemistry of pyridinium *N*-aminides

Elena Gala[a,b], Javier Recio[a], Julio Alvarez-Builla[a]* and M Luisa Izquierdo[a]*

[a]*Departamento de Química Orgánica y Química Inorgánica, Universidad de Alcalá, Campus Científico-Tecnológico, 28805 Alcalá de Henares (Madrid), Spain*

[b]*Departamento de Tecnología Química y Ambiental, Universidad Rey Juan Carlos, 28933 Móstoles (Madrid), Spain*

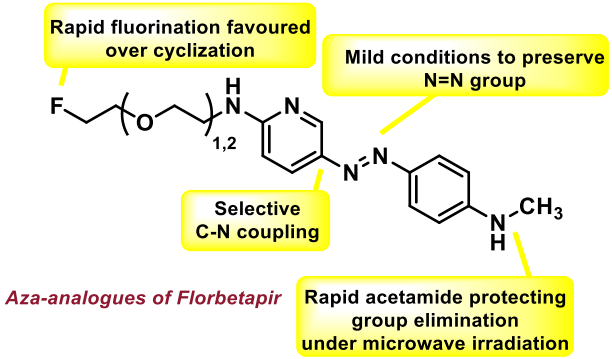
Email: julio.alvarez@uah.es mluisa.izquierdo@uah.es

Dedicated to Prof. Carolina Burgos

Received 10-29-2021 **Accepted Manuscript** 12-17-2021 **Published on line** 01-02-2022

Abstract

Neuroimaging of β-amyloid (Aβ) plaques in brain, employing Positron Emission Tomography (PET) has enabled early diagnosis of Alzheimer's Disease and, although different ^{18}F radiolabeled markers as Florbetapir and Florbetaben are already in the market, new molecules with better affinity and selectivity to Aβ plaques should be explored. In this article, two aza-analogues of Florbetapir have been synthesized from Pyridinium *N*-aminides. The new aza-analogues were prepared following straightforward synthetic routes under mild conditions. Although the products have been obtained using stable ^{19}F, the methods are compatible with the future use of ^{18}F, to generate products to be tested in the development of new PET reagents.



Keywords: Pyridinium *N*-aminides, florbetapir, heterocycles

Introduction

Alzheimer's disease (AD) is the most common dementia among the population, with a marked increase in the number of cases being expected in the future, due to the increase in life expectancy. There is currently no cure for AD, it is an irreversible illness and current therapies only slow its process, therefore early diagnosis is essential for an effective treatment.[1] Unfortunately, the diagnosis of a possible case of AD, based exclusively on the patient's medical history, can only be made once the cognitive decline is severe, as the initial symptoms of the illness are difficult to differentiate from other dementias. As such, it is still important to develop new strategies that allow AD to be diagnosed at an early stage.[1–3]

The pathogenesis of AD is complex and characterised by an abnormal β-amyloid metabolism, hyperphosphorylation of tau protein and other pathological processes in the central nervous system.[4,5] According to the amyloid hypothesis, there is a presymptomatic state of AD which begins with an imbalance between the production and clearance of β-amyloid protein (Aβ) in the brain, thus resulting in the accumulation and aggregation of Aβ, in the form of plaques, in the grey matter that triggers the neurodegenerative cascade seen in AD.[5–11] These plaques are absent in other types of dementias, and in the diagnosis of AD it is estimated that their progressive accumulation begins between 20 and 30 years before the symptomatic phase, thus meaning that Aβ plaques are excellent biomarkers for an early diagnosis.[7]

Aβ plaques were described by Alois Alzheimer in 1906, and their *post-mortem* staining with azo-dyes, such as Congo Red or Chrisamine G, was for many years the only way to detect them.[2] Fortunately, the development of positron emission tomography (PET), a non-invasive technique, now allows their presence to be detected *in vivo* when used with approved radiotracers such as Florbetapir, Florbetaben and Flutemetamol (Figure 1).[2,12–14]

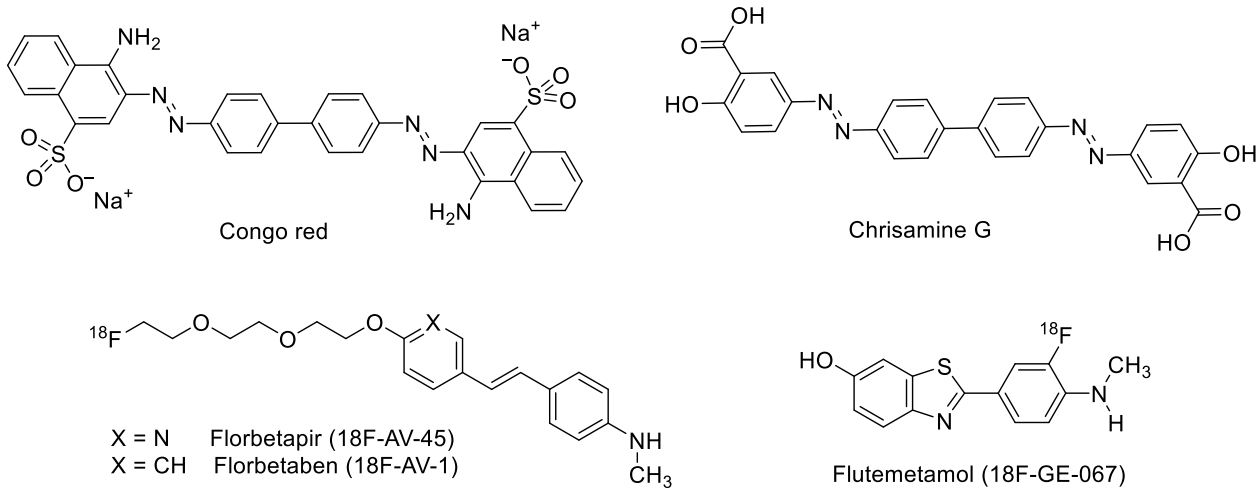


Figure 1. Structures of Congo Red, Chrisamine, Florbetapir, Florbetaben and Flutemetamol.

Although this first generation of PET markers is still used, there is a growing interest in the development of new radiotracers whose properties may allow the detection of Aβ plaques with better selectivity and sensitivity, with styrylbenzene derivatives,[15–18] benzoheterocycles,[6,19–24] and metallic complexes[20,25,26] being important in this regard. One of the strategies adopted to enhance the selective delivery of the PET marker to the grey matter involves the design of less lipophilic molecules.[3,6] Given this, we planned on the structure of Florbetapir, to prepare aza-analogues **1**, with azo groups similar to those present in Congo red and Chrisamine G, for evaluation as PET radiotracers. Calculated log P (ClogP) values have been taken as an orientation of the relative lipophilicity (Florbetapir ClogP 3.11), both the presence of an azo group and a 2-aminopyridine moiety would slightly decrease the lipophilicity of these new potential radioligands and favour the affinity of **1** with the Aβ-plaques (Figure 2).

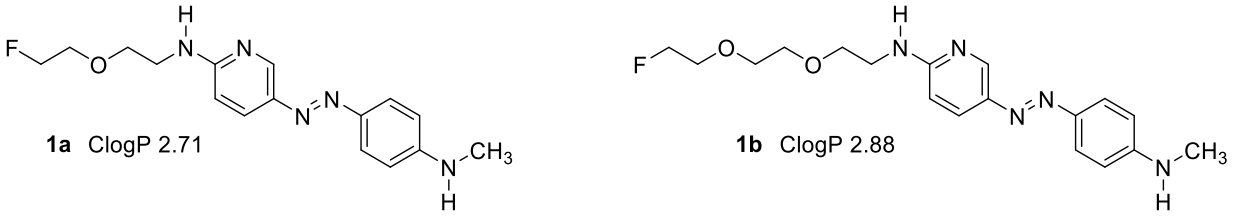
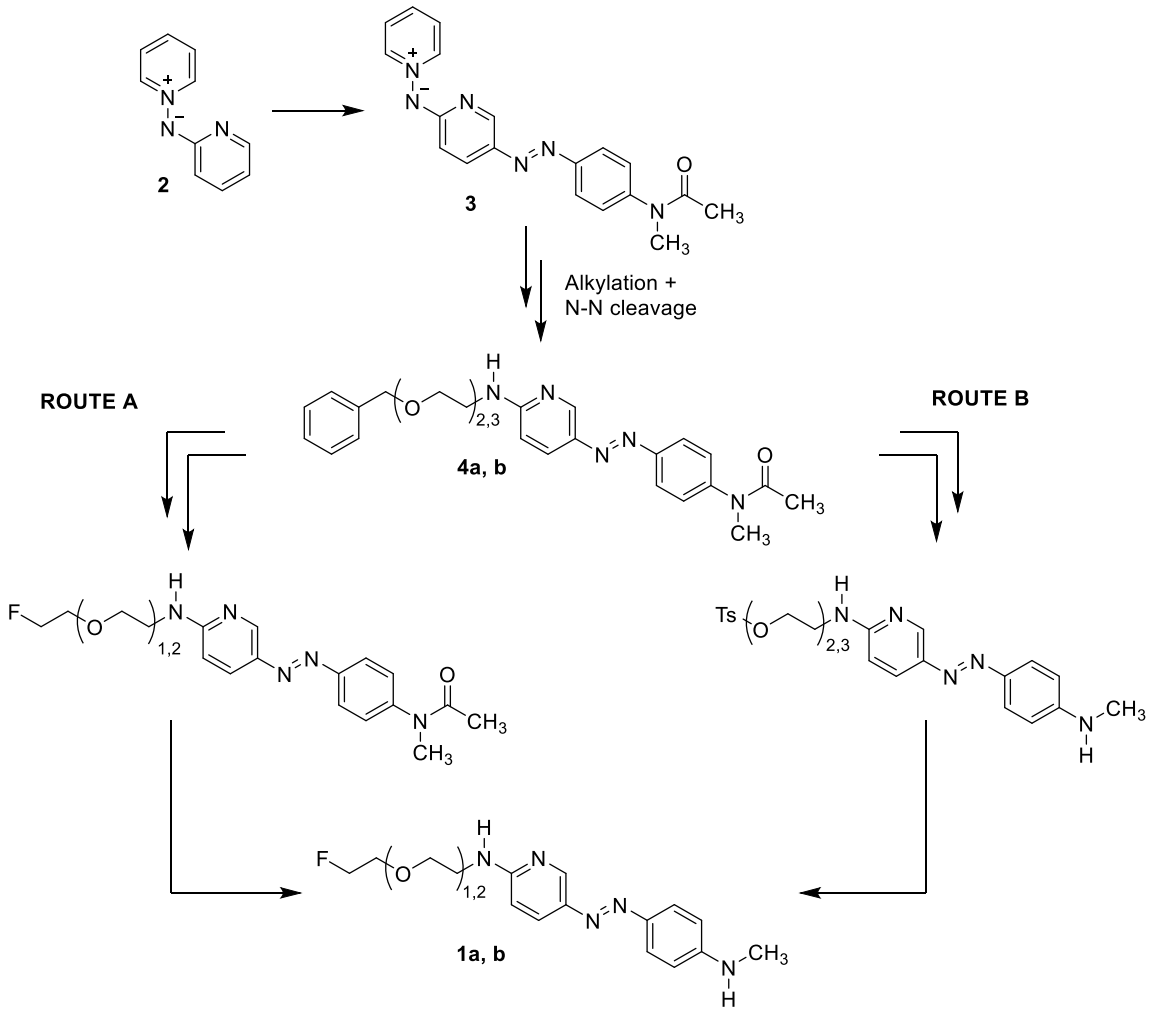


Figure 2. ClogP of aza-analogues **1**.

The synthesis of Florbetapir aza-analogues **1** was planned using acetamides **4** as key intermediates. These compounds were obtained, according to a previously published methodology which involves the regioselective C-N coupling of pyridinium aminide **2**[27] with a diazonium salt, and transformation of the resulting ylide **3** into **4**, by N-exo alkylation and subsequent N-N cleavage under reducing conditions (Scheme 1).[28] Two pathways were planned in order to obtain the final products **1** from **4**. Thus, whereas in route A aniline-type amino group is protected until the fluorine atom has been introduced into the molecule, in order to avoid possible side reactions, thus requiring a final step of hydrolysis of the amide, in the route B fluorination is the last step in the synthesis, thereby avoiding the need of an additional deprotection of the amino group, after the fluorine label has been introduced into the molecule (Scheme 1). Both schemes are suitable to be used in the preparation of PET reagents.

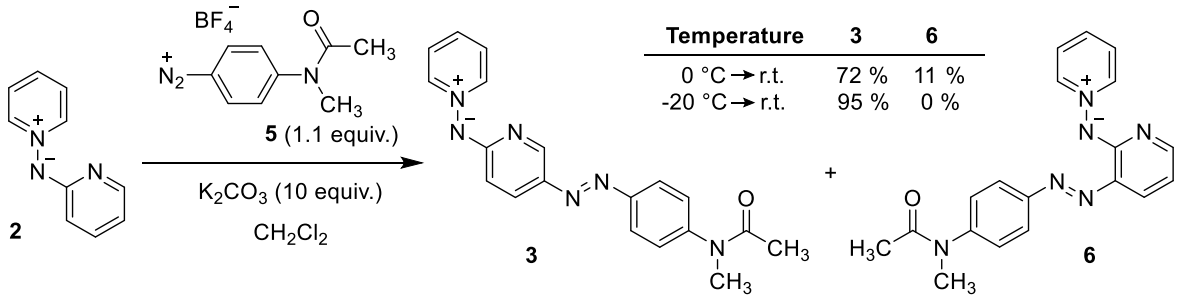


Scheme 1. Synthetic schemes of products **1**.

Results and Discussion

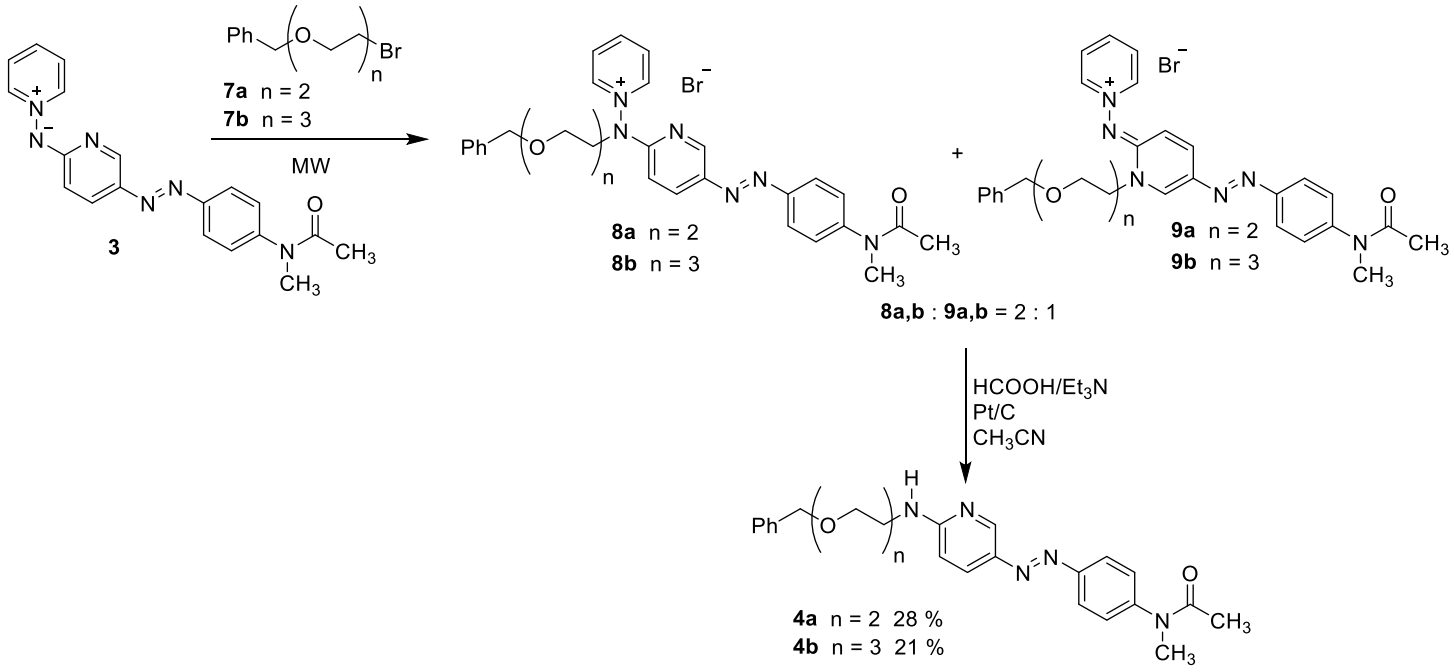
1. Synthesis of acetamides 4

As already noted, synthesis of acetamides **4** was planned employing the pyridinium *N*-(pyridin-2-yl)aminide **2** as starting material,[27] in a three step procedure that starts with the preparation of arylazo derivative **3** (Scheme 2).[28] Addition of the freshly prepared diazonium salt **5** to a solution of aminide **2**, containing the base at 0 °C yielded the desired aminide **3** in 72% yield, together with its minor isomer **6** (11%). Regioselectivity of the process is increased by reducing the temperature to -20 °C, and then **3** was the only product isolated (95% yield, Scheme 2).



Scheme 2. Synthesis of aminide **3**.

Alkylation of aminide **3** proved to be challenging because of the relatively low reactivity of both alkyl bromides **7**.[28] However, reaction was achieved by MW irradiation of the mixture in the absence of solvent, obtaining a mixture of salts **8** and **9**, produced by alkylation at each exocyclic and endocyclic nitrogen of the aminide (Scheme 3). Both temperature and reaction time were explored in order to improve regioselectivity and the best results are indicated (see Suppl. Table 1). As attempts to purify the reaction mixture proved unsuccessful, conversions and *exo/endo* ratios were deduced by ^{1}H NMR spectroscopy, with salt **8** being the major product in all cases.

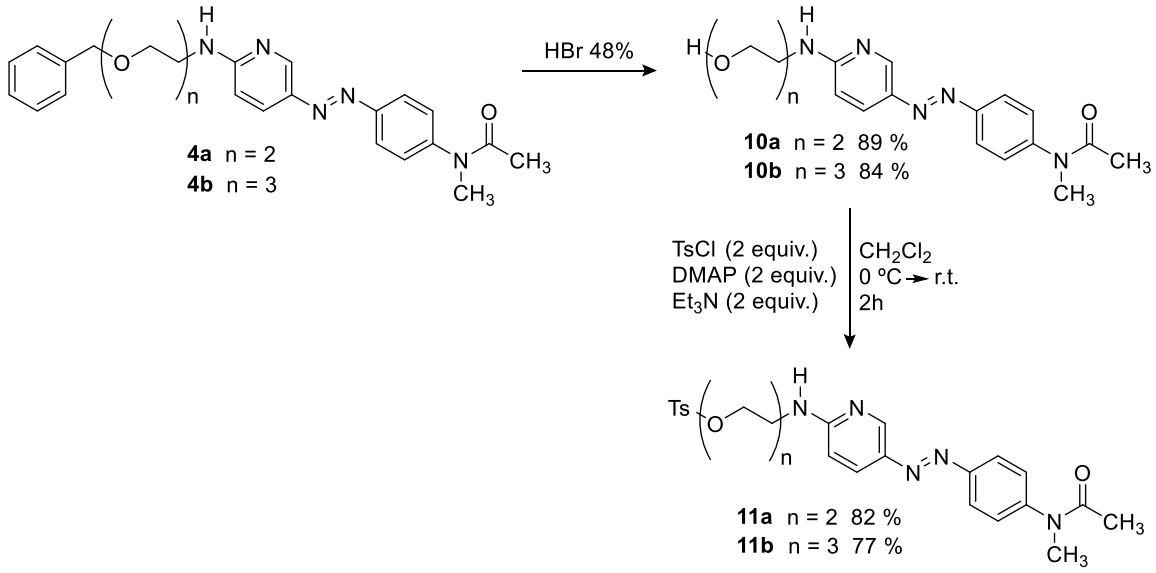


Scheme 3. Synthesis of acetamides **4** from aminide **3**.

The mixtures **8**/**9**, in which conversion was complete, were treated with the reducing system HCOOH/Et_3N in the presence of Pt/C as catalyst, to yield aminopyridines **4** (Scheme 3) as only the N-N bond easily cleaves under reduction. Product **4a** was obtained using a 5% Pt/C catalyst,[28] (28% yield), while **4b** required the use of 1% Pt/C, (21% yield). In both cases, compound **9** resulted stable in the reduction step.

2. Route A

This route began with elimination of the protecting benzyl group from acetamides **4,** by treatment with 48% hydrobromic acid (Scheme 4). Compounds **10** were obtained in good yields after reaction for 16 h at room temperature (Table 1). Decomposition was observed when higher temperatures were employed, in an attempt to accelerate the process. However, the reaction time was drastically reduced when the process was performed at 40 °C under microwave irradiation, giving similar slightly lower yields of **10** in 30 minutes (Table 1). The hydroxy group of both compounds was activated by reaction with tosyl chloride in the presence of triethylamine and DMAP, leading to tosylates **11** after reaction at room temperature for 2 h (Scheme 4).



Scheme 4. Synthesis of tosylates **11**.

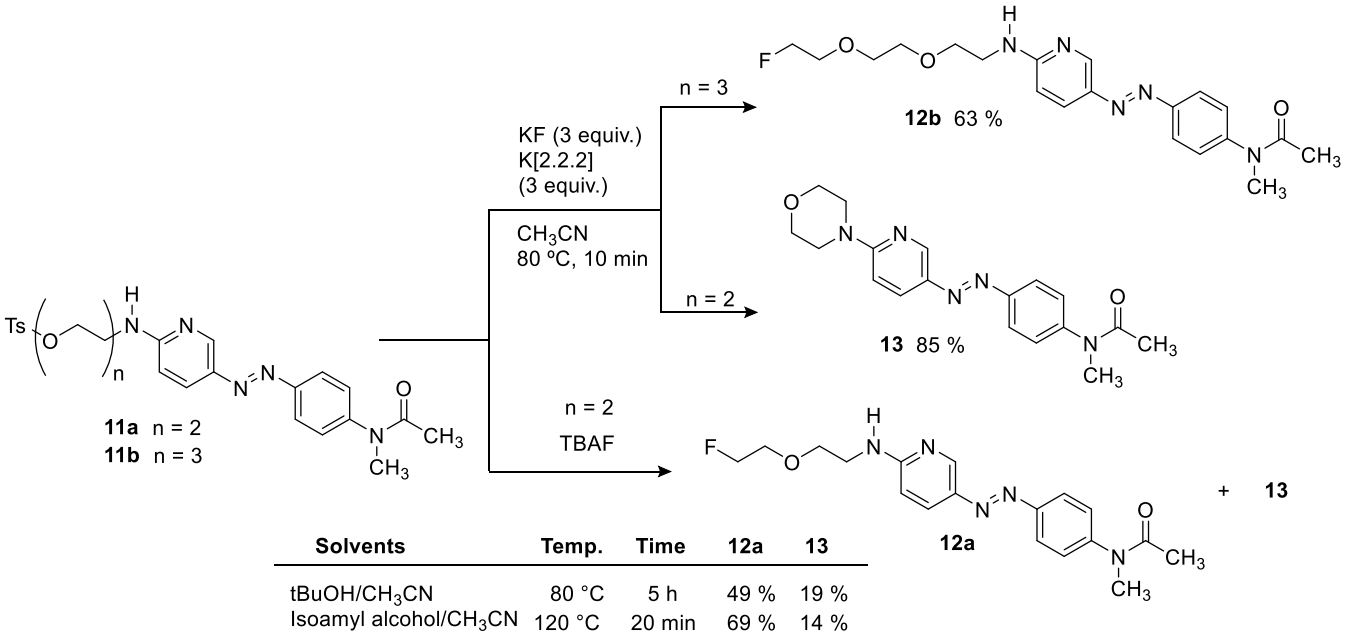
Table 1. Debenzylation of acetamides **4**

Compound	n	MW	Temp.	Time	Yield (%)
10a	2	No	r.t.	16 h	89
		Yes	40 °C	30 min	79
10b	3	No	r.t.	16 h	84
		Yes	40 °C	30 min	72

Initial attempts to fluorinate **11** were performed using KF and kryptofix [2.2.2] (K[2.2.2]) in acetonitrile, at 80 °C for 10 minutes (Scheme 5). However, while derivative **12b** was obtained in 63% yield, under the same reaction conditions, tosylate **11a** (n = 2) was transformed into the morpholine derivative **13**, due to an intramolecular nucleophilic substitution (Scheme 5).

Given this result, we became interested in finding conditions that favour the fluorination of **11a** over cyclization. In general, fluoride ions, either associated to kryptofix [2.2.2] or not, are known to act as a base. Experiments were performed with longer times, and when the same mixture was left to react for longer, up to 21 h, again tosylate **11a** was transformed into the morpholine derivative **13**, but the desired fluorinated product **12a** was detected (~3-5%) for the first time. Also, **11a** was treated with KF in the absence of cryptand, at 80 °C for 10 minutes, with only starting material being recovered. Alternatively, the treatment of **11a** with an excess of TBAF (3 equiv.) in *t*BuOH/CH_3CN, at 80 °C for 5 h, yielded the fluorinated compound **12a** as the major product

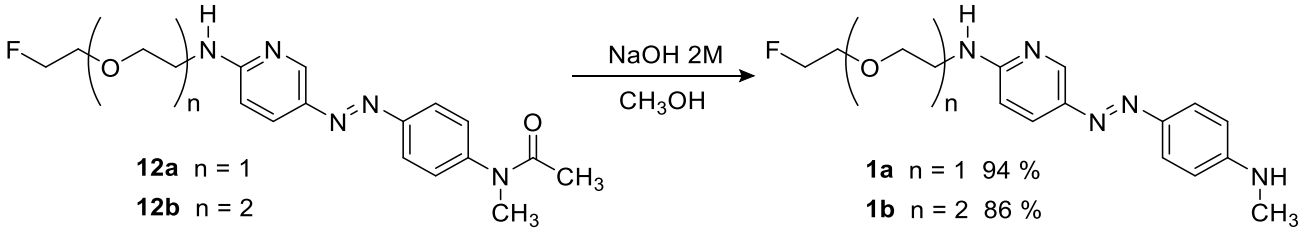
(49%), together with 19% of **13** (Scheme 5). The reaction time was reduced to 20 min when the same reaction was carried out at 120 °C using isoamyl alcohol/CH_3CN as solvents, and **12a** (69%) and **13** (14%) were obtained (Scheme 5).



Solvents	Temp.	Time	12a	13
tBuOH/CH_3CN	80 °C	5 h	49 %	19 %
Isoamyl alcohol/CH_3CN	120 °C	20 min	69 %	14 %

Scheme 5. Fluorination of tosylates **11**.

Having obtained the fluoro derivatives **12**, to convert them in compounds **1**, it was necessary the final acetamide deprotection. Deacylation under acid conditions was discarded because azo-derivatives could decompose in acid media. Alternatively, deprotection in basic media requires longer reaction times. In our case, refluxing acetamide **12b** with 2 M NaOH in methanol for 5 h, gave **1b** (79%) along with unreacted starting material (Scheme 6). However, the use of microwaves allowed deprotection under overheating conditions, thus showing that the reaction was significantly accelerated, giving **1** in 15 minutes, with excellent yields either for **1a** or for **1b** (Scheme 6 and Table 2).



Scheme 6. Synthesis of compounds **1**.

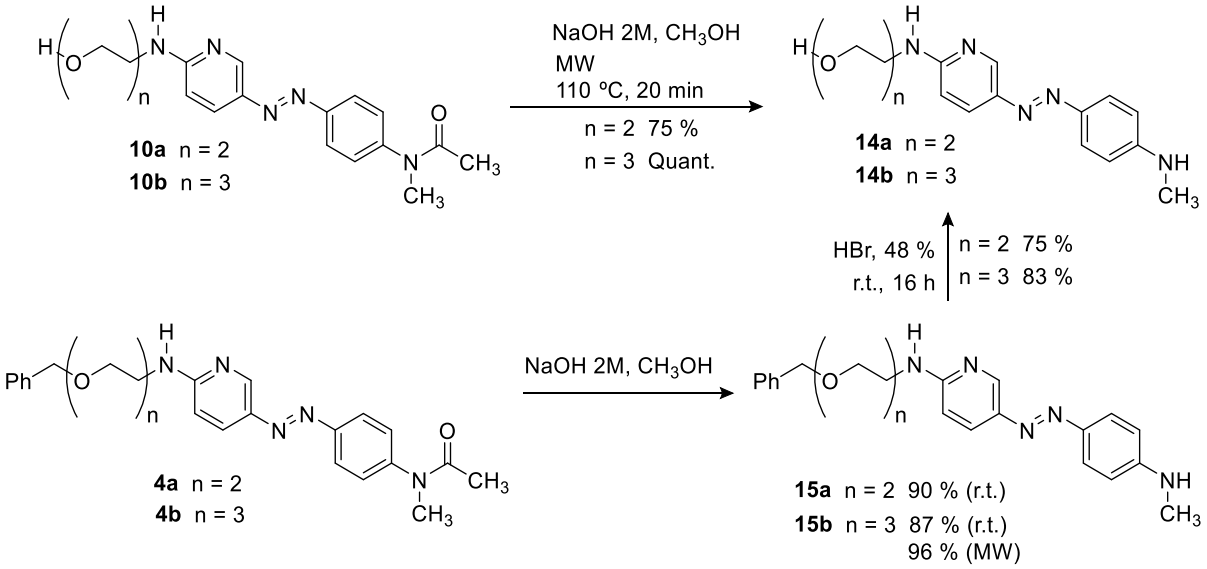
Table 2. Deacetylation of compounds **12**

Compound	n	MW	Temp.	Time	Yield (%)
1a	1	Yes	110 °C	15 min	94
1b	2	No	Reflux	5 h	79
		Yes	110 °C	15 min	86

3. Route B

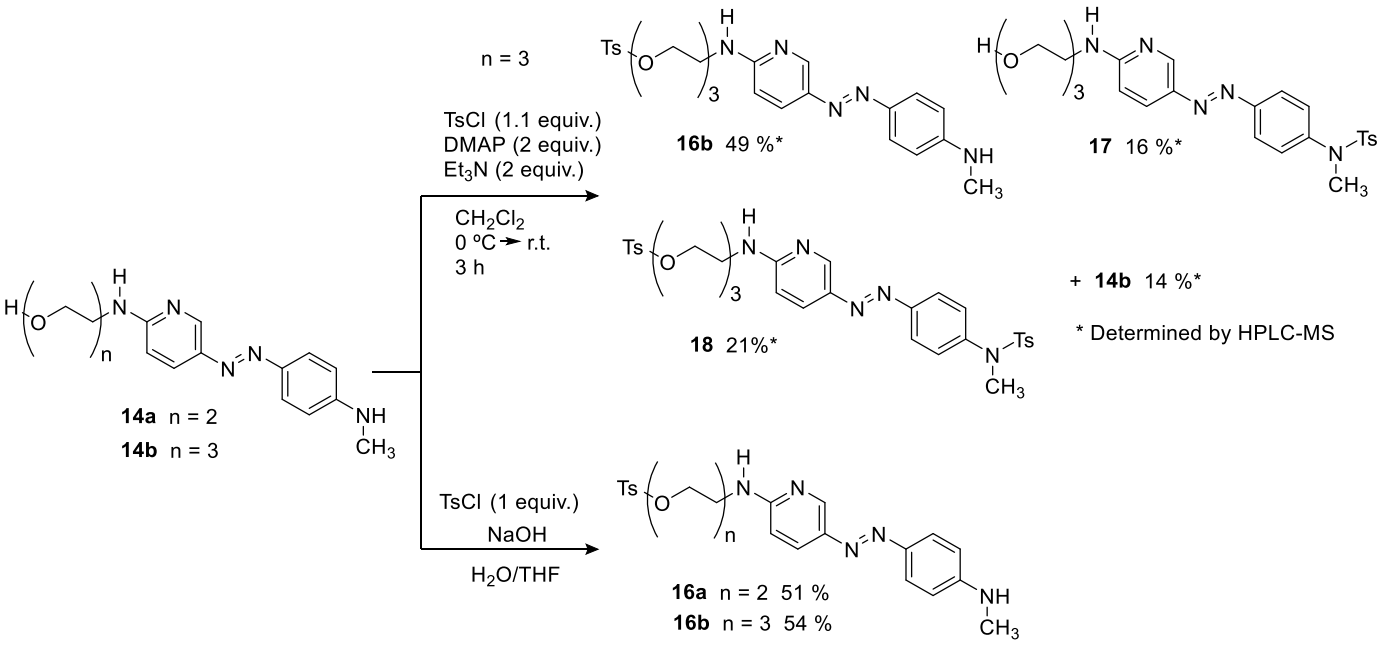
Although "cold" Florbetapir aza-analogues **1** could be obtained following route A, in the synthesis of any PET radiotracers, to make additional reaction steps after fluorination is undesirable because of the short half-life of the ^{18}F isotope. For this reason, and in order to avoid additional steps after fluorination, the alternative synthetic pathway B was tested.

Synthesis of alcohols **14** was achieved by treating compounds **10** (route A) with 2 M NaOH in methanol under microwave irradiation, giving the products **14** in excellent yields (Scheme 7). Alternatively, compounds **14** were also obtained from **4** via amines **15** (Scheme 7). In both cases, when the amide deacetylation was performed either before or after removal of the benzyl group, both schemes took place satisfactorily, thus allowing us to conclude that the order of the two deprotection steps has little effect on the overall synthetic yield. However, from our point of view, it is more convenient to deprotect the hydroxy group first because the synthesis of **10** is common to route A and the yields obtained are slightly higher.



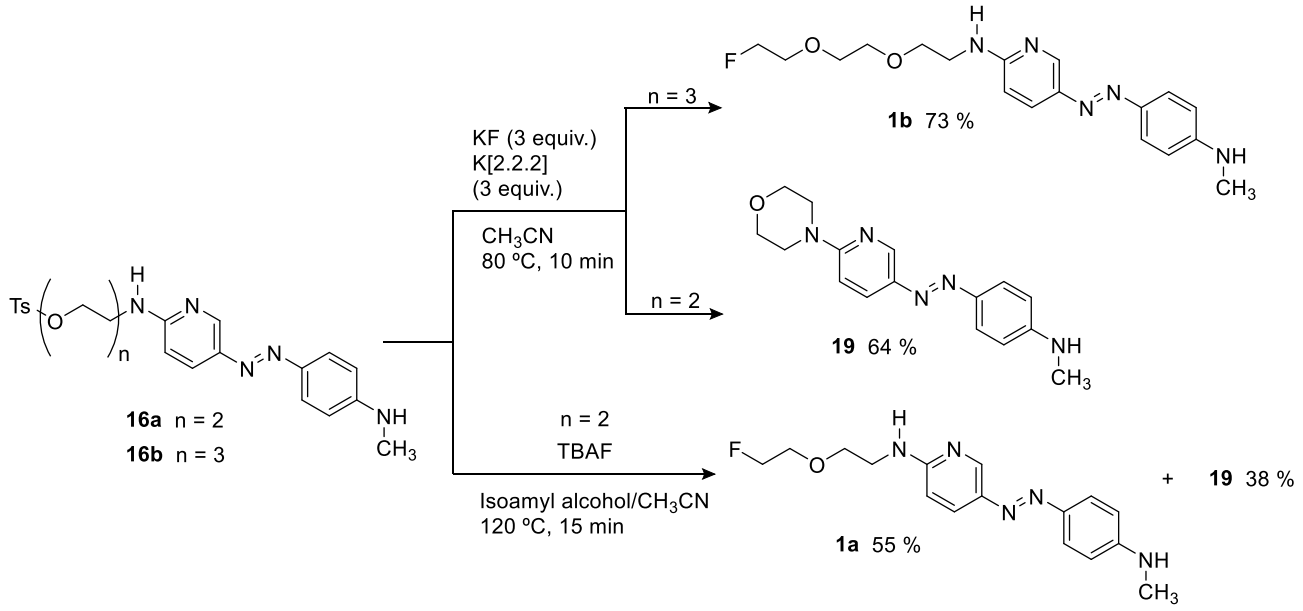
Scheme 7. Synthesis of alcohols **14**.

Initial attempts to tosylate **14b** using tosyl chloride, Et_3N and DMAP in dichloromethane yielded a mixture of compounds **16**, **17** and **18** along with unreacted starting material, thus indicating a non-selective reaction (Scheme 8). Alternatively, activation of products **14** resulted in better yields when using NaOH in aqueous media, which allowed the required tosylation on the hydroxy group (Scheme 8). Although the yields obtained were not as good as expected, the advantage of this process is that unreacted **14** was almost completely recovered and the formation of side products **17** and **18** was reduced to traces.



Scheme 8. Tosylation of compounds **14**.

As in route A, fluorination of tosylate **16b**, which contains the longer polyethoxy chain, was achieved using KF and kryptofix[2.2.2] in only a few minutes, whereas the same treatment of compound **16a** yielded the morpholine derivative **19** (Scheme 9). Although the undesirable cyclization process was not completely avoided, rapid fluorination of **16a** was achieved using TBAF in isoamyl alcohol/acetonitrile, thus giving **1a** in 55% yield (Scheme 9).



Scheme 9. Fluorination of tosylates **16**.

Conclusions

Two Florbetapir aza-analogues, bearing diazo groups have been synthesised following simple and straightforward processes, starting from pyridinium *N*-aminides, by reaction with diazonium salts. With the bottleneck of the lack of selectivity of the alkylation of the exocyclic nitrogen of the 2-aminopyridine moiety, two routes have been studied as different approaches to generate Florbetapir analogues labelled with F. From both approaches studied, the route B, with fluorination in the last step, and the compound **1b**, which prevents the intramolecular cyclisation, seems to be the best choice. The synthesis described would be tested in a program to develop new PET-radiotracers for brain imaging of β-amyloid plaques. In addition, synthetic efforts have resulted in the optimization of some common reactions in organic synthesis, as the microwave-assisted selective deprotection of alcohols and amines, and the fluorination of alkyl chains where a cyclization process is a competing reaction.

Experimental Section

General. ClogP values were estimated using the MarvinSketch 18.2 program. Melting points were determined in open capillary tubes using a Stuart Scientific SMP3 melting point apparatus. IR spectra were obtained using a Perkin-Elmer FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using Varian Unity 300/500 MHz or Varian Mercury VX-300 systems at room temperature. Chemical shifts are given in ppm (δ) downfield from TMS. Chemical shifts in ^{19}F NMR spectra are reported in ppm (δ) with $PhCF_3$ as internal standard ($PhCF_3$: -63.46 ppm). Coupling constants (*J*) are in Hertz (Hz) and signals are described as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; app, apparent; br, broad. The numbering employed in NMR analysis is described in the Supporting Information. Low resolution mass spectra (MS) were recorded using a Thermo Scientific ITQ900 system with Electronic Impact (EI), and high-resolution analysis (TOF) was performed using an Agilent 6210 time-of-flight LCMS system with Electro Spray Ionization (ESI). All reagents were obtained from commercial sources and were used without further purification. TLC analyses were performed on silica gel (DCFertigfolien ALUGRAM Xtra Sil G/UV254, Macherey-Nagel) and spots were visualised under UV light. Column chromatography was carried out on silica gel 60 (40-63 mm, Silicycle) columns using the eluent reported in each case. Microwave experiments were performed using a Biotage Initiator and sealed 2 or 5 mL Biotage vials. This is a single-mode operating system, working at 2.45 GHz, with a programmable power level from 0–400 W. Stirring was performed at 400 rpm with the magnetic stirrer included in the apparatus and Temperature was measured using an external surface sensor.

Pyridinium *N*-{5-[4-(*N*-methylacetamido)phenylazo]pyridin-2-yl} aminide (3). 4-(*N*-Methylacetamido)-benzenediazonium tetrafluoroborate (1.16 g, 4.8 mmol) in 120 mL of CH_2Cl_2 was added dropwise to a stirred solution of pyridinium *N*-(pyridin-2-yl)aminide **2** (684 mg, 4 mmol) and K_2CO_3 (5.52 g, 40 mmol) in CH_2Cl_2 (40 mL) cooled to -20 °C. After reaction for 30 minutes, the solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/CH_3OH, 95:5) to give **3** as a dark red solid (1.32 g, 95%, 3.8 mmol, CH_2Cl_2:Et_2O) m.p. 210 – 212 °C. ^{1}H NMR (500 MHz, CD_3OD): δ 8.80 (dd, *J* 6.9 and 1.3 Hz, 2H, *H*2(6)), 8.31 (d, *J* 2.6 Hz, 1H, *H*6'), 8.26 (tt, *J* 7.7 and 1.3 Hz, 1H, *H*4), 8.00 (app t, *J* 6.9 Hz, 2H, *H*3(5)), 7.97 (dd, *J* 9.2 and 2.6 Hz, 1H, *H*4'), 7.88 (d, *J* 8.7 Hz, 2H, *H*2''(6'')), 7.43 (d, *J* 8.7 Hz, 2H, *H*3''(5'')), 6.62 (d, *J* 9.2 Hz, 1H, *H*3'), 3.31 (s, 3H, NCH_3), 1.95 (br s, 3H, C(O)CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ 172.9 (*C*O), 167.5 (*C*2'), 153.8 (*C*1''), 153.1 (*C*6'), 145.9 (*C*4''), 145.6 (*C*2(6)), 141.4 (*C*5'), 140.5 (*C*4), 129.0 (*C*3(5)), 128.8 (*C*3''(5'')), 127.0 (*C*4'), 124.3 (*C*2''(6'')), 113.3 (*C*3'), 37.6

(N*C*H$_3$), 30.8 (C(O)*C*H$_3$) ppm. IR (KBr): ν_{max} 1599, 1498, 1473, 1238, 835, 771 cm^{-1}. MS (EI): *m/z* (%) 346 (100) [M$^{+\bullet}$], 345 (81), 290 (13), 170 (11), 120 (10), 81 (25), 79 (21). HRMS (ESI-TOF, CH$_3$OH) calculated for $C_{19}H_{19}N_6O$ [M + H]$^+$ 347.1615, found 347.1610.

When the reaction was performed at 0 °C, aminide **3** was obtained in a lower yield (993 mg, 72%, 2.88 mmol) along with **pyridinium *N*-{3-[4-(*N*-methylacetamido)phenylazo]pyridin-2-yl} aminide (6)** as a dark red solid (152 mg, 11%, 0.44 mmol) m.p. 122 – 124 °C. ^{1}H NMR (500 MHz, CD$_3$OD): δ 8.96 (d, *J* 5.8 Hz, 2H, *H*2(6)), 8.43 (t, *J* 7.9 Hz, 1H, *H*4), 8.14 (d, *J* 8.8 Hz, 2H, *H*2''(6'')), 8.08 (app t, *J* 7.3 Hz, 2H, *H*3(5)), 8.00 (dd, *J* 7.5 and 1.8 Hz, 1H, *H*4'), 7.98 (dd, *J* 4.9 and 1.8 Hz, 1H, *H*6'), 7.51 (d, *J* 8.8 Hz, 2H, *H*3''(5'')), 6.76 (dd, *J* 7.5 and 4.9 Hz, 1H, *H*5'), 3.33 (solvent overlapped, NC*H*$_3$), 1.97 (br s, 3H, C(O)C*H*$_3$) ppm. ^{13}C NMR (125 MHz, CD$_3$OD): δ 172.8 (*C*O), 159.7 (*C*2'), 153.6 (*C*1''), 152.2 (*C*6'), 147.4 (two overlapped signals) (*C*2(6) and *C*4''), 142.5 (*C*4), 135.3 (*C*3'), 129.2 (*C*3(5)), 128.9 (*C*3''(5'')), 127.0 (*C*4'), 125.4 (*C*2''(6'')), 114.7 (*C*5'), 37.6 (N*C*H$_3$), 22.4 (C(O)*C*H$_3$) ppm. IR (KBr): ν_{max} 1651, 1595, 1471, 1366, 1235, 1187, 1113, 760, 667 cm^{-1}. MS (EI): *m/z* (%) 267 (68) [M$^{+\bullet}$ – pyr], 225 (100), 224 (31), 191 (33), 182 (53), 79 (41), 56 (37). HRMS (ESI-TOF, CH$_3$OH) calculated for $C_{19}H_{19}N_6O$ [M + H]$^+$ 347.1615, found 347.1608.

Synthesis of *N*-[6-aminopyridin-3-ylazo)phenyl]-*N*-methylacetamides 4

General procedure. Aminide **3** (242.2 mg, 0.7 mmol) and the corresponding alkylating agent **7** (3.5 mmol) were placed in a Biotage Initiator system. The reaction mixture was stirred and irradiated with MW under the conditions indicated in each case. The residue obtained was dissolved in CH$_3$CN (9 mL) at 0 °C and platinum on charcoal (152 mg) was added to the solution, as described for every reaction. Formic acid (98%, 3 mL) in CH$_3$CN (5 mL) and triethylamine (7 mL) in the same solvent (10 mL) were then added dropwise. The reaction mixture was stirred at low temperature for the time indicated in each case, and the resulting suspension was then filtered through Celite. The filtrate was evaporated, made basic with saturated aqueous K_2CO_3 solution and extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) and identified.

***N*-(4-{6-[2-(2-Benzyloxyethoxy)ethylamino]pyridin-3-ylazo}phenyl)-*N*-methylacetamide (4a)**. A mixture of salts **8a** and **9a** in a 2:1 ratio (determined by ^{1}H NMR), together with the alkylating agent **7a**, was obtained after irradiation at 90 °C for 2 h. Reduction of the reaction mixture by adding Pt/C 5% and stirring for 15 min gave acetamide **4a** as a yellow oil [87.7 mg, 28% (global yield from **3**), 0.196 mmol]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, *J* 2.3 Hz, 1H, *H*2), 7.93 (dd, *J* 9.1 and 2.3 Hz, 1H, *H*4), 7.85 (d, *J* 8.4 Hz, 2H, *H*3'(5')), 7.29 (m, 7H, *H*2'(6'), *H*2''(6''), *H*3''(5'') and *H*4''), 6.36 (d, *J* 9.1 Hz, 1H, *H*5), 5.68 (br t, *J* 5.3 Hz, 1H, N*H*), 4.55 (s, 2H, C*H*$_2$Ph), 3.67 (m, 8H, C*H*$_2$A, C*H*$_2$B, C*H*$_2$C and C*H*$_2$D), 3.28 (s, 3H, NC*H*$_3$), 1.91 (br s, 3H, OC-C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (*C*O), 160.1 (*C*6), 151.7 (*C*4'), 151.1 (*C*2), 145.4 (*C*1'), 141.0 (*C*3), 128.3, 127.8, 127.7, 127.6, 127.5 and 126.5 (*C*4, *C*2'(6'), *C*1'', *C*2''(6'') *C*3''(5'') and *C*4''), 123.4 (*C*3'(5')), 108.5 (*C*5), 73.2 (*C*H$_2$Ph), 70.2, 69.5 and 69.3 (*C*H$_2$B, *C*H$_2$C and *C*H$_2$D), 41.4 (*C*H$_2$A), 37.0 (N-*C*H$_3$), 22.4 (OC-*C*H$_3$) ppm. IR (NaCl): ν_{max} 3427, 3060, 2860, 1660, 1607, 1520, 1380, 1136, 852, 830, 740 cm^{-1}. MS (EI): *m/z* (%) 447 (67) [M$^{+\bullet}$], 295 (31), 282 (79), 269 (100), 227 (47), 91 (41), 56 (62). HRMS (ESI-TOF, CH$_3$OH) calculated for $C_{25}H_{30}N_5O_3$ [M + H]$^+$ 448.2343, found 448.2330.

***N*-[4-(6-{2-[2-(2-Benzyloxyethoxy)ethoxy]ethylamino}pyridin-3-ylazo)phenyl]-*N*-methylacetamide (4b)**. A mixture of salts **8b** and **9b** in a 2:1 ratio (deduced by ^{1}H NMR), together with the alkylating agent **7b**, was obtained after irradiation at 110 °C for 30 min. The ^{1}H NMR signals or both salts were deduced and assigned as shown below.

(*N*-{2-[2-(2-Benzyloxyethoxy)ethoxy]ethyl}-*N*-{5-[4-(*N*-methylacetamido)phenylazo]pyridin-2-yl}amino) pyridinium bromide (8b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (d, *J* 5.4 Hz, 2H, *H*2(6)), 8.69 (m, 2H, *H*4 and *H*6'), 8.28 (dd, *J* 8.7 and 2.2 Hz, 1H, *H*4'), 8.24 (app t, *J* 7.0 Hz, 2H, *H*3(5)), 7.99 (d, *J* 8.3 Hz, 2H, *H*2''(6'')), 7.49 (d, *J* 8.3 Hz, 2H, *H*3''(5'')), 7.29 (m, 5H, *H*2'''(6'''), *H*3'''(5''') and *H*4'''), 7.13 (d, *J* 8.7 Hz, 1H, *H*3'), 4.50 (m, 4H, C*H*$_2$A and

C*H*$_2$Ph), 3.88 (t, *J* 4.9 Hz, 2H, C*H*$_2$B), 3.70-3.50 (m, 8H, C*H*$_2$C, C*H*$_2$D, C*H*$_2$E, and C*H*$_2$F), 3.32 (s, 3H, NC*H*$_3$), 1.96 (br s, 3H, OC-C*H*$_3$) ppm.

1-[*N*-(1-{2-[2-(2-Benzyloxyethoxy)ethoxy]ethyl}-5-[4-(*N*-methylacetamido)phenylazo]pyridin-2-yl)imino]pyridinium bromide (9b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, *J* 6.8 Hz, 2H, *H*2(6)), 8.66 (d, *J* 1.5 Hz, 1H, *H*6'), 8.49 (t, *J* 7.8 Hz, 1H, *H*4), 8.14 (app t, *J* 6.9 Hz, 2H, *H*3(5)), 8.06 (dd, *J* 9.8 and 1.5 Hz, 1H, *H*4'), 7.91 (d, *J* 8.3 Hz, 2H, *H*2''(6'')), 7.43 (d, *J* 8.3 Hz, 2H, *H*3''(5'')), 7.29 (m, 5H, *H*2'''(6'''), *H*3'''(5''') and *H*4'''), 6.24 (d, *J* 9.8 Hz, 1H, *H*3'), 4.58 (m, 2H, C*H*$_2$A), 4.43 (s, 2H, C*H*$_2$Ph), 4.07 (t, *J* 4.7 Hz, 2H, C*H*$_2$B), 3.70-3.50 (m, 8H, C*H*$_2$C, C*H*$_2$D, C*H*$_2$E and C*H*$_2$F), 3.29 (s, 3H, NC*H*$_3$), 1.96 (br s, 3H, OC-C*H*$_3$) ppm.

Acetamide **4b** was prepared by reducing the mixture of salts **8b** and **9b** with Pt/C 1% and stirring the reaction mixture for 30 minutes.

***N*-[4-(6-{2-[2-(2-Benzyloxyethoxy)ethoxy]ethylamino}pyridin-3-ylazo)phenyl]-*N*-methylacetamide (4b)**. Orange oil [72.2 mg, 21% (global yield from **3**), 0.147 mmol]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* 2.5 Hz, 1H, *H*2), 7.95 (dd, *J* 9.2 and 2.5 Hz, 1H, *H*4), 7.87 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 7.32 (m, 7H, *H*2'(6'), *H*2''(6''), *H*3''(5'') and *H*4''), 6.47 (d, *J* 9.2 Hz, 1H, *H*5), 5.75 (br s, 1H, N*H*), 4.57 (s, 2H, C*H*$_2$Ph), 3.73 (t, *J* 4.8 Hz, 2H, C*H*$_2$A), 3.68 (m, 10H, C*H*$_2$B, C*H*$_2$C, C*H*$_2$D, C*H*$_2$E and C*H*$_2$F), 3.30 (s, 3H, NC*H*$_3$), 1.93 (br s, 3H, OC-C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*O), 159.8 (*C*6), 151.6 (*C*4'), 150.5 (*C*2), 145.4 (*C*1'), 140.9 (*C*3), 137.9 (*C*1''), 128.2 (*C*2'(6')), 127.6 and 127.5 (*C*2''(6'') and *C*3''(5'')), 127.4 (*C*4''), 126.8 (*C*4), 123.4 (*C*3'(5')), 108.7 (*C*5), 73.2 (*C*H$_2$Ph), 70.6 (two overlapped signals) 70.3, 69.6 and 69.3 (*C*H$_2$B, *C*H$_2$C, *C*H$_2$D, *C*H$_2$E and *C*H$_2$F), 41.6 (*C*H$_2$A), 37.2 (N-*C*H$_3$), 22.6 (OC-*C*H$_3$) ppm. IR (NaCl): ν_{max} 3349, 2917, 2866, 1658, 1607, 1520, 1100, 740, 699 cm^{-1}. MS (EI): *m/z* (%) 491 (100) [M$^{+\bullet}$], 385 (74), 282 (67), 269(52), 227 (32), 91 (39), 56 (29). HRMS (ESI-TOF, CH_3OH) calculated for $C_{27}H_{34}N_5O_4$ [M + H]$^+$ 492.2605, found 492.2603.

Synthesis of Florbetapir aza-analogues. General procedures

Method A. The corresponding benzylated product **4** or **15** (0.3 mmol) was dissolved in commercial HBr and stirred at room temperature for 16 h. The solution was then basified with saturated aqueous K_2CO_3 solution (to pH > 10) and extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvents evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate/methanol 9:1) and identified.

Method B. The corresponding benzylated product **4** (0.5 mmol) and 5 mL of commercial HBr were placed in a Biotage Initiator system. The reaction mixture was stirred and irradiated with MW at 40 °C for 30 min. Workup of this reaction was carried out as described in method A.

Method C. NaOH (2 M, 3 mL) was added to a solution of the acetylated product **4** (0.3 mmol) in methanol (3 mL) and the mixture refluxed for 4 h. The solution was then cooled, water (15 mL) was added and the mixture extracted three times with ethyl acetate (3 x 25 mL). The layers were then separated. The combined organic phases were dried with $MgSO_4$, filtered and the solvents evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) and identified.

Method D. The corresponding acetylated product **4b**, **10 or 12**, methanol and 2 M NaOH were placed in a Biotage Initiator system. The reaction mixture was stirred and irradiated with MW at 110 °C for 20 min. Workup of this reaction was carried out as described in method C.

Method E. Et_3N (0.03 Ml, 0.21 mmol) and DMAP (55.7 mg, 0.40 mmol) were added to a solution of hydroxyl derivative **10** or **14b** (0.20 mmol) in dry CH_2Cl_2 (1 mL) and the resulting solution was cooled to 0 °C. A solution of tosyl chloride (41.9 mg, 0.22 mmol) in dry CH_2Cl_2 (0.2 mL) was then added dropwise and the mixture allowed to react at room temperature for 2 h. After washing with 1 M HCl, then with a saturated aqueous solution of $NaHCO_3$, and finally with brine, the organic layer was dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) and identified.

Method F. A solution of tosyl chloride (38.1 mg, 0.20 mmol) in THF (0.2 mL) was added dropwise to a solution of hydroxyl derivative **14** (0.20 mmol) in THF (0.2 mL) and NaOH (16 mg, 0.4 mmol) in water (0.2 mL) at 0 °C. The mixture was then stirred at room temperature for the time indicated in each case. Once the reaction had finished, 5 mL of water was added and the solution extracted three times with CH_2Cl_2 (3 x 25 mL). The organic layer was then dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) and identified

Method G. KF (26.1 mg, 0.45 mmol) and Kryptofix 2.2.2 (169.4 mg, 0.45 mmol) were added to a solution of the tosyl derivative **11** or **16** (0.15 mmol) in dry CH_3CN and the reaction mixture stirred at 80 °C for 10 minutes. The solvent was then evaporated and the resulting residue purified by flash chromatography (ethyl acetate) and identified.

Method H. TBAF·$3H_2O$ (141.9 mg, 0.45 mmol) was added to a solution of tosylated compound **11a** or **16a** (0.15 mmol) in 0.5 mL of isoamyl alcohol and 0.05 mL of CH_3CN and the reaction mixture stirred at 120 °C for 30 minutes. The solvent was then evaporated and the resulting residue purified by flash chromatography (ethyl acetate/hexane 9:1) and identified.

Synthesis of precursors 12 for the preparation of Florbetapir aza-analogues (Route A)

***N*-(4-{6-[2-(2-Hydroxyethoxy)ethylamino]pyridin-3-ylazo}phenyl)-*N*-methylacetamide (10a)**. Following method A, product **10a** was obtained from derivative **4a** (134 mg) as an orange oil (95.3 mg, 89%, 0.267 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* 2.4 Hz, 1H, *H*2), 7.97 (dd, *J* 8.8 and 2.4 Hz, 1H, *H*4), 7.84 (d, *J* 8.6 Hz, 2H, *H*3'(5')), 7.26 (d, *J* 8.6 Hz, 2H, *H*2'(6')), 6.47 (d, *J* 8.8 Hz, 1H, *H*5), 5.74 (br t, *J* 5.1 Hz, 1H, N*H*), 3.76 (m, 2H, CH_2D), 3.73 (m, 2H, CH_2B), 3.65 (m, 4H, CH_2A and CH_2C), 3.27 (s, 3H, NCH_3), 1.91 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (*C*O), 160.1 (*C*6), 151.8 (*C*4'), 150.8 (*C*2), 145.5 (*C*1'), 141.2 (*C*3), 127.6 (*C*2'(6')), 127.1 (*C*4), 123.5 (*C*3'(5')), 108.3 (*C*5), 72.4 (*C*H_2C), 69.7 (*C*H_2B), 61.7 (*C*H_2D), 41.7 (*C*H_2A), 37.1 (N-*C*H_3), 22.5 (OC-*C*H_3) ppm. IR (NaCl): ν_{max} 3218, 2960, 2919, 1651, 1528, 1380, 1106, 801, 667 cm^{-1}. MS (EI): *m/z* (%) 357 (100) [M$^{+\bullet}$], 282 (82), 269 (71), 227 (38), 56 (21). HRMS (ESI-TOF, CH_3OH) calculated for $C_{18}H_{24}N_5O_3$ [M + H]$^+$ 358.1874, found 358.1882. When method B was used, **10a** was obtained with a 79% yield (84.7 mg, 0.395 mmol).

***N*-[4-(6-{2-[2-(2-Hydroxyethoxy)ethoxy]ethylamino}pyridin-3-ylazo)phenyl]-*N*-methylacetamide (10b)**. Following method A, product **10b** was obtained from derivative **4b** (148 mg) as an orange oil (102 mg, 84%, 0.252 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* 2.5 Hz, 1H, *H*2), 8.00 (dd, *J* 9.2 and 2.5 Hz, 1H, *H*4), 7.84 (d, *J* 8.5 Hz, 2H, *H*3'(5')), 7.26 (d, *J* 8.5 Hz, 2H, *H*2'(6')), 6.48 (d, *J* 9.2 Hz, 1H, *H*5), 6.15 (br s, 1H, N*H*), 3.76 (m, 4H, CH_2B and CH_2F), 3.68 (m, 4H, CH_2C and CH_2D), 3.62 (m, 2H, CH_2E), 3.55 (br q, *J* 5.2 Hz, 2H, CH_2A), 3.27 (s, 3H, NCH_3), 1.90 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (*C*O), 160.2 (*C*6), 151.8 (*C*4'), 150.5 (*C*2), 145.4 (*C*1'), 141.1 (*C*3), 127.6 (two overlapped signals) (*C*4 and *C*2'(6')), 123.5 (*C*3'(5')), 107.3 (*C*5), 73.1 (*C*H_2E), 70.5 (two overlapped signals) (*C*H_2C and *C*H_2D), 69.4 (*C*H_2B), 61.4 (*C*H_2F), 41.9 (*C*H_2A), 37.1 (N-*C*H_3), 22.5 (OC-*C*H_3) ppm. IR (NaCl): ν_{max} 3350, 2916, 2866, 1659, 1607, 1524, 1380, 1099, 851, 740, 699 cm^{-1}. MS (EI): *m/z* (%) 401 (100) [M$^{+\bullet}$], 340 (27), 282 (94), 269(64), 227 (39), 56 (30). HRMS (ESI-TOF, CH_3OH) calculated for $C_{20}H_{28}N_5O_4$ [M + H]$^+$ 402.2136, found 402.2127. When method B was used, **10b** was obtained with a 72% yield (86.7 mg, 0.360 mmol).

2-[2-({5-[4-(*N*-Methylacetamido)phenylazo]pyridin-2-yl}amino)ethoxy]ethyl 4-methylbenzenesulfonate (11a). Following method E, product **11a** was obtained from derivative **10a** (71.4 mg) as an orange oil (84.0 mg, 82%, 0.164 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* 2.4 Hz, 1H, *H*6), 8.01 (dd, *J* 8.8 and 2.5 Hz, 1H, *H*4), 7.87 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 7.79 (d, *J* 8.3 Hz, 2H, *H*2''(6'')), 7.32 (d, *J* 8.3 Hz, 2H, *H*3''(5'')), 7.28 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.56 (d, *J* 8.8 Hz, 1H, *H*3), 5.84 (br s, 1H, N*H*), 4.20 (app t, *J* 4.4 Hz, 2H, CH_2D), 3.69 (app t, *J* 4.4 Hz, 2H, CH_2C), 3.67 (app t, *J* 4.9 Hz, 2H, CH_2B), 3.62 (app q, *J* 4.9 Hz, 2H, CH_2A), 3.29 (s, 3H, NCH_3), 2.41 (s, 3H, ArCH_3), 1.92 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*O), 159.4 (*C*2), 151.6 (*C*1'), 149.5 (*C*6), 145.6

(*C*4'), 144.9 (*C*4''), 141.0 (*C*5), 132.9 (*C*1''), 129.8 (*C*3''(5'')), 127.8 (*C*2''(6'')), 127.5 (*C*3'(5')), 127.4 (*C*4), 123.5 (*C*2'(6')), 109.1 (*C*3), 69.8 (*C*H_2B), 69.1 (*C*H_2D), 68.6 (*C*H_2C), 41.6 (*C*H_2A), 37.2 (N-*C*H_3), 22.6 (OC-*C*H_3), 21.7 (Ar-*C*H_3) ppm. IR (NaCl): ν_{max} 3402, 3324, 2923, 2873, 1659, 1607, 1353, 1176, 1097, 1012, 816, 664 cm^{-1}. MS (EI): *m/z* (%) 339 (100), 308 (16), 294 (11), 282 (14), 148 (9). HRMS (ESI-TOF, CH_3OH) calculated for $C_{25}H_{30}N_5O_5S$ $[M + H]^+$ 512.1962, found 512.1967.

2-{2-[2-({5-[4-(*N*-Methylacetamido)phenylazo]pyridin-2-yl}amino)ethoxy]ethoxy}ethyl 4-methylbenzenesulfonate (11b). Following method E, product **11b** was obtained from derivative **10b** (81.6 mg) as an orange oil (85.6 mg, 77%, 0.154 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* 2.4 Hz, 1H, *H*6), 7.96 (dd, *J* 8.8 and 2.4 Hz, 1H, *H*4), 7.85 (d, *J* 8.7 Hz, 2H, *H*2'(6')), 7.78 (d, *J* 8.3 Hz, 2H, *H*2''(6'')), 7.31 (d, *J* 8.3 Hz, 2H, *H*3''(5'')), 7.27 (d, *J* 8.7 Hz, 2H, *H*3'(5')), 6.48 (d, *J* 8.8 Hz, 1H, *H*3), 5.55 (br t, *J* 4.9 Hz, 1H, N*H*), 4.17 (m, 2H, CH_2F), 3.69 (m, 4H, CH_2B and CH_2E), 3.65 (m, 2H, CH_2A), 3.63 (app s, 4H, CH_2C and CH_2D), 3.28 (s, 3H, NCH_3), 2.40 (s, 3H, ArCH_3), 1.91 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (*C*O), 160.1 (*C*2), 151.9 (*C*1'), 151.0 (*C*6), 145.6 (*C*4'), 144.9 (*C*4''), 141.3 (*C*5), 132.9 (*C*1''), 129.8 (*C*3''(5'')), 127.9 (*C*2''(6'')), 127.6 (*C*3'(5')), 126.8 (*C*4), 123.5 (*C*2'(6')), 108.6 (*C*3), 70.7 and 70.3 (*C*H_2C and *C*H_2D), 69.7 (*C*H_2B), 69.2 (*C*H_2F), 68.7 (*C*H_2E), 41.6 (*C*H_2A), 37.1 (N-*C*H_3), 22.5 (OC-*C*H_3), 21.6 (Ar-*C*H_3) ppm. IR (NaCl): ν_{max} 3323, 2920, 1654, 1608, 1525, 1354, 1176, 1096, 1012, 921, 817, 555 cm^{-1}. MS (EI): *m/z* (%) 292 (100), 277 (91), 190 (34), 134(33), 77 (27). HRMS (ESI-TOF, CH_3OH) calculated for $C_{27}H_{34}N_5O_6S$ $[M + H]^+$ 556.2224, found 556.2224.

***N*-(4-{6-[2-(2-Fluoroethoxy)ethylamino]pyridin-3-ylazo}phenyl)-*N*-methylacetamide (12a)**. Following method H, product **12a** was obtained from derivative **11a** (76.3 mg) as an orange oil (37.2 mg, 69%, 0.104 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* 2.5 Hz, 1H, *H*2), 7.99 (dd, *J* 9.0 and 2.5 Hz, 1H, *H*4), 7.86 (d, *J* 8.7 Hz, 2H, *H*3'(5')), 7.28 (d, *J* 8.7 Hz, 2H, *H*2'(6')), 6.49 (d, *J* 9.0 Hz, 1H, *H*5), 5.39 (br t, *J* 5.9 Hz, 1H, N*H*), 4.57 (app dt, $^2J_{HF}$ 47 Hz, $^3J_{HH}$ 3.9 Hz, 2H, CH_2D), 3.83-3.66 (m, 6H, CH_2A, CH_2B and CH_2C), 3.29 (s, 3H, NCH_3), 1.92 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*O), 159.8 (*C*6), 151.7 (*C*4'), 150.5 (*C*2), 145.5 (*C*1'), 141.2 (*C*3), 127.5 (*C*2'(6')), 127.0 (*C*4), 123.5 (*C*3'(5')), 108.5 (*C*5), 83.0 (d, $^1J_{CF}$ 168.9 Hz, *C*H_2D), 70.2 (d, $^1J_{CF}$ 19.5 Hz, *C*H_2C), 69.9 (*C*H_2B), 41.7 (*C*H_2A), 37.3 (N-*C*H_3), 22.6 (OC-*C*H_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -223.9 (tt, J_{FH} 47.2 and 29.0 Hz, CH_2F) ppm. IR (NaCl): ν_{max} 3323, 2922, 2854, 1661, 1607, 1122, 1047, 853 cm^{-1}. MS (EI): *m/z* (%) 359 (100) $[M^{+\bullet}]$, 339 (15), 282 (62), 269 (56), 227 (28), 56 (16). HRMS (ESI-TOF, CH_3OH) calculated for $C_{18}H_{23}FN_5O_2$ $[M + H]^+$ 360.1830, found 360.1831.

***N*-Methyl-*N*-{4-[6-(morpholin-4-yl)pyridin-3-ylazo]phenyl}acetamide 13** was isolated as a secondary product. Yellow solid (7.1 mg, 14%, 21 µmol). m.p. 137 – 139 °C. ^{1}H NMR (500 MHz, CD_3OD): δ 8.79 (d, *J* 2.5 Hz, 1H, *H*2), 8.03 (dd, *J* 9.4 and 2.5 Hz, 1H, *H*4), 7.87 (d, *J* 8.5 Hz, 2H, *H*3'(5')), 7.28 (d, *J* 8.5 Hz, 2H, *H*2'(6')), 6.68 (d, *J* 9.4 Hz, 1H, *H*5), 3.83 (app t, *J* 4.8 Hz, 4H, OCH_2), 3.66 (app t, *J* 4.8 Hz, 4H, NCH_2), 3.30 (s, 3H, NCH_3), 1.93 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ 170.3 (*C*O), 160.1 (*C*6), 151.8 (*C*4'), 150.0 (*C*2), 145.7 (*C*1'), 141.0 (*C*3), 127.6 (*C*4), 127.2 (*C*2'(6')), 123.5 (*C*3'(5')), 106.4 (*C*5), 66.6 (O*C*H_2), 45.2 (N*C*H_2), 37.1 (N-*C*H_3), 22.5 (CO-*C*H_3) ppm. IR (KBr): ν_{max} 2961, 2921, 2853, 1661, 1598, 1500, 1399, 1377, 1233, 1114, 944 cm^{-1}. MS (EI): *m/z* (%) 339 (100) $[M^{+\bullet}]$, 308 (13). HRMS (ESI-TOF, CH_3OH) calculated for $C_{18}H_{22}N_5O_2$ $[M + H]^+$ 340.1768, found 340.1778. Following method G, compound **13** was obtained as the only reaction product (43.3 mg, 85%, 0.128 mmol).

***N*-[4-(6-{2-[2-(2-Fluoroethoxy)ethoxy]ethylamino}pyridin-3-ylazo)phenyl]-*N*-methylacetamide (12b)**. Following method G, product **12b** was obtained from derivative **11b** (93.3 mg) as an orange oil (38.1 mg, 63%, 94.5 µmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* 2.4 Hz, 1H, *H*2), 7.98 (dd, *J* 9.3 and 2.4 Hz, 1H, *H*4), 7.85 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 7.27 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 6.48 (d, *J* 9.3 Hz, 1H, *H*5), 5.49 (br t, *J* 5.4 Hz, 1H, N*H*), 4.57 (app dt, $^2J_{HF}$ 47 Hz, $^3J_{HH}$ 4.1 Hz, 2H, CH_2F), 3.79-3.64 (m, 10H, CH_2A, CH_2B, CH_2C, CH_2D and CH_2E), 3.30 (s, 3H, NCH_3), 1.92 (br s, 3H, OC-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (*C*O), 160.2 (*C*6), 151.9 (*C*4'), 151.1 (*C*2), 145.6 (*C*1'), 141.3 (*C*3), 127.6 (*C*2'(6')), 126.8 (*C*4), 123.5 (*C*3'(5')), 108.6 (*C*5), 83.1 (d, $^1J_{CF}$ 168.8 Hz, *C*H_2F), 70.4 (d, $^1J_{CF}$

19.1 Hz, *C*H_2E), 70.7, 70.6 and 69.7 (*C*H_2B, *C*H_2C and *C*H_2D), 41.5 (*C*H_2A), 37.1 (N-*C*H_3), 22.5 (OC-*C*H_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -223.6 (tt, J_{FH} 47.3 and 29.0 Hz, CH_2F) ppm. IR (NaCl): ν_{max} 3342, 2918, 1660, 1607, 1525, 1379, 1261, 1101, 1038, 822, 802 cm^{-1}. MS (EI): *m/z* (%) 403 (100) [M$^{+\bullet}$], 282 (72), 269 (97), 227 (38), 106 (18), 78 (15), 56 (41). HRMS (ESI-TOF, CH_3OH) calculated for $C_{20}H_{27}FN_5O_3$ [M + H]$^+$ 404.2092, found 404.2080.

Synthesis of precursors 16 for the preparation of Florbetapir aza-analogues (Route B)

***N*-{2-[2-(Benzyloxy)ethoxy]ethyl}-*N*-{5-[4-(methylamino)phenylazo]pyridin-2-yl}amine (15a)**. Following method C, product **15a** was obtained from derivative **4a** (134 mg) as an orange oil (109 mg, 90%, 0.270 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* 2.5 Hz, 1H, *H*6), 7.93 (dd, *J* 9.3 and 2.4 Hz, 1H, *H*4), 7.77 (d, *J* 9.0 Hz, 2H, *H*2'(6')), 7.36-7.28 (m, 5H, *H*2''(6''), *H*3''(5'') and *H*4''), 6.65 (d, *J* 9.0 Hz, 2H, *H*3'(5')), 6.38 (d, *J* 9.3 Hz, 1H, *H*3), 5.29 (br t, J 5.4 Hz, 1H, Pyr-N*H*), 4.58 (s, 2H, CH_2Ph), 3.73 (app t, *J* 5.2 Hz, 2H, CH_2B), 3.70 (m, 2H, CH_2C or CH_2D), 3.65 (m, 2H, CH_2C or CH_2D), 3.63 (app q, *J* 5.2 Hz, 2H, CH_2A), 2.92 (s, 3H, N-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (*C*2), 151.1 (*C*4'), 148.7 (*C*6), 144.9 (*C*1'), 141.6 (*C*5), 138.1 (*C*1''), 128.4, 127.8 and 127.7 (*C*2''(6'') *C*3''(5'') and *C*4''), 127.0 (*C*4), 124.5 (*C*2'(6')), 111.9 (*C*3'(5')), 108.2 (*C*3), 73.3 (*C*H_2Ph), 70.4, 69.8 and 69.4 (*C*H_2B, *C*H_2C and *C*H_2D), 41.7 (*C*H_2A), 30.5 (N-*C*H_3) ppm. IR (NaCl): ν_{max} 3419, 3369, 3027, 2857, 1599, 1520, 1087, 1027, 829 cm^{-1}. MS (EI): *m/z* (%) 405 (100) [M$^{+\bullet}$], 253 (14), 240 (53), 227 (82), 134 (28), 107 (19), 106 (34), 91 (14), 79 (15). HRMS (ESI-TOF, CH_3OH) calculated for $C_{23}H_{28}N_5O_2$ [M + H]$^+$ 406.2238, found 406.2240.

***N*-(2-{2-[2-(Benzyloxy)ethoxy]ethoxy}ethyl)-*N*-{5-[4-methylamino]phenylazo)pyridin-2-yl}amine (15b)**. Following method D, product **15b** was obtained from derivative **4b** (148 mg, 0.33 mmol), employing 2.5 mL of methanol and 2.5 mL of 2 M NaOH, as an orange oil (129 mg, 96%, 0.317 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* 2.4 Hz, 1H, *H*6), 7.91 (dd, *J* 8.3 and 2.4 Hz, 1H, *H*4), 7.75 (d, *J* 9.0 Hz, 2H, *H*2'(6')), 7.32-7.24 (m, 5H, *H*2''(6''), *H*3''(5'') and *H*4''), 6.62 (d, *J* 9.0 Hz, 2H, *H*3'(5')), 6.42 (d, *J* 8.3 Hz, 1H, *H*3), 5.36 (br t, J 5.4 Hz, 1H, Pyr-N*H*), 4.55 (s, 2H, CH_2Ph), 4.15 (br s, 1H, Me-N*H*), 3.70 (app t, *J* 5.4 Hz, 2H, CH_2B), 3.64 (m, 8H, CH_2C, CH_2D, CH_2E and CH_2F), 3.59 (app q, *J* 5.4 Hz, 2H, CH_2A), 2.88 (s, 3H, N-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2 (*C*2), 151.1 (*C*4'), 148.7 (*C*6), 144.8 (*C*1'), 141.5 (*C*5), 138.1 (*C*1''), 128.3 and 127.7 (*C*2''(6'') and *C*3''(5'')), 127.6 (*C*4''), 126.9 (*C*4), 124.4 (*C*2'(6')), 111.9 (*C*3'(5')), 108.2 (*C*3), 73.2 (*C*H_2Ph), 70.6, 70.6, 70.3, 69.8 and 69.4 (*C*H_2B, *C*H_2C, *C*H_2D, *C*H_2E, and *C*H_2F), 41.6 (*C*H_2A), 30.4 (N-*C*H_3) ppm. IR (NaCl): ν_{max} 3417, 3367, 2918, 2861, 1598, 1521, 1336, 1277, 1240, 1142, 1100, 829, 739, 699 cm^{-1}. MS (EI): *m/z* (%) 449 (100) [M$^{+\bullet}$], 240 (74), 227 (90), 134 (33), 106 (42), 91 (46), 79 (25). HRMS (ESI-TOF, CH_3OH) calculated for $C_{25}H_{32}N_5O_3$ [M + H]$^+$ 450.2463, found 450.2464. Product **15b** was obtained in 87% yield (117 mg, 0.261 mmol) when prepared from compound **4b** (148 mg) following method C.

2-[2-({5-[4-(Methylamino)phenylazo]pyridin-2-yl}amino)ethoxy]ethanol (14a). Following method D, product **14a** was obtained from derivative **10a** (107 mg), employing 2.5 mL of methanol and 2.5 mL of 2 M NaOH, as an orange solid (70.9 mg, 75%, 0.254 mmol). m.p. 157 – 159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* 2.4 Hz, 1H, *H*6), 7.98 (dd, *J* 8.8 and 2.4 Hz, 1H, *H*4), 7.77 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 6.65 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.48 (d, *J* 8.8 Hz, 1H, *H*3), 5.23 (br t, J 5.3 Hz, 1H, Pyr-N*H*), 3.78 (m, 2H, CH_2B or CH_2D), 3.74 (m, 2H, CH_2B or CH_2D), 3.63 (m, 4H, CH_2A and CH_2C), 2.92 (s, 3H, N-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (*C*2), 151.0 (*C*4'), 148.3 (*C*6), 144.7 (*C*1'), 141.5 (*C*5), 127.2 (*C*4), 124.4 (*C*2'(6')), 111.8 (*C*3'(5')), 107.8 (*C*3), 72.3 (*C*H_2B), 69.8 (*C*H_2C), 61.9 (*C*H_2D), 41.9 (*C*H_2A), 30.0 (N-*C*H_3) ppm. IR (KBr): ν_{max} 3416, 3346, 1603, 1558, 1517, 1334, 1145, 1126 cm^{-1}. MS (EI): *m/z* (%) 315 (100) [M$^{+\bullet}$], 240 (55), 227 (45), 134 (14), 107 (14), 106 (23), 79 (13). HRMS (ESI-TOF, CH_3OH) calculated for $C_{16}H_{22}N_5O_2$ [M + H]$^+$ 316.1775, found 316.1774.

Product **14a** was obtained in 75% yield (70.9 mg, 0.225 mmol) when prepared from amine **15a** (121 mg) following method A.

2-{2-[2-({5-[4-(Methylamino)phenylazo]pyridin-2-yl}amino)ethoxy]ethoxy}ethanol (14b). Following method D, product **14b** was obtained from derivative **10b** (120 mg), employing 2.5 mL of methanol and 2.5 mL of 2 M

NaOH, as an orange solid (108 mg, Quantitative, 0.3 mmol). m.p. 94 – 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* 2.5 Hz, 1H, *H*6), 7.96 (dd, *J* 8.8 and 2.5 Hz, 1H, *H*4), 7.74 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 6.60 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.44 (d, *J* 8.8 Hz, 1H, *H*3), 5.94 (br s, 1H, Pyr-N*H*), 3.75 (m, 4H, CH_2B and CH_2F), 3.69 (m, 2H, CH_2C or CH_2D), 3.65 (m, 2H, CH_2C or CH_2D), 3.61 (m, 2H, CH_2E), 3.50 (app q, *J* 5.4 Hz, 2H, CH_2A), 2.88 (s, 3H, N-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (*C*2), 151.2 (*C*4'), 148.0 (*C*6), 144.7 (*C*1'), 141.4 (*C*5), 127.8 (*C*4), 124.5 (*C*2'(6')), 111.9 (*C*3'(5')), 106.9 (*C*3), 73.1 (*C*H_2E), 70.5 and 70.4 (*C*H_2C and *C*H_2D), 69.5 (*C*H_2B), 61.4 (*C*H_2F), 42.0 (*C*H_2A), 30.4 (N-*C*H_3) ppm. IR (KBr): ν_{max} 3418, 2918, 2870, 1601, 1520, 1277, 1239, 1143, 1100, 830 cm^{-1}. MS (EI): *m/z* (%) 359 (100) [$M^{+\bullet}$], 240 (66), 227 (62), 134 (23), 107 (24), 106 (36), 79 (24). HRMS (ESI-TOF, CH_3OH) calculated for $C_{18}H_{26}N_5O_3$ $[M + H]^+$ 360.2030, found 360.2026.

Product **14b** was obtained in 83% yield (89.6 mg, 0.249 mmol) when prepared from amine **15b** (134.9 mg) following method A.

2-[2-({5-[4-(Methylamino)phenylazo]pyridin-2-yl}amino)ethoxy]ethyl 4-methylbenzenesulfonate (16a). Following method F, product **16a** was obtained from derivative **14a** (63.1 mg), after 24 h or reaction at room temperature, as an orange oil (47.9 mg, 51%, 0.102 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* 1.4 Hz, 1H, *H*6), 7.97 (dd, *J* 9.3 and 1.4 Hz, 1H, *H*4), 7.80 (d, *J* 7.8 Hz, 2H, *H*2''(6'')), 7.77 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 7.32 (d, *J* 7.8 Hz, 2H, *H*3''(5'')), 6.64 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.48 (d, *J* 9.3 Hz, 1H, *H*3), 5.38 (br s, 1H, Pyr-N*H*), 4.20 (m, 2H, CH_2D), 3.69 (m, 2H, CH_2C), 3.65 (app t, *J* 5.1 Hz, 2H, CH_2B), 3.56 (app q, *J* 5.1 Hz, 2H, CH_2A), 2.91 (s, 3H, NCH_3), 2.42 (s, 3H, ArCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (*C*2), 151.2 (*C*4'), 147.9 (*C*6), 144.9 and 144.8 (*C*1' and *C*4''), 141.6 (*C*5), 133.0 (*C*1''), 129.8 (*C*3''(5'')), 127.9 (*C*2''(6'')), 127.4 (*C*4), 124.5 (*C*2'(6')), 111.1 (*C*3'(5')), 108.4 (*C*3), 69.9 (*C*H_2B), 69.1 (*C*H_2D), 68.5 (*C*H_2C), 41.5 (*C*H_2A), 30.4 (N-*C*H_3), 21.6 (Ar-*C*H_3) ppm. IR (NaCl): ν_{max} 3417, 3289, 2961, 2917, 2874, 1614, 1175, 1120, 1011, 923, 832, 736, 666 cm^{-1}. MS (EI): *m/z* (%) 470 (100) [$M+H^+$], 454 (16), 413 (38), 391 (27). HRMS (ESI-TOF, CH_3OH) calculated for $C_{23}H_{28}N_5O_4S$ $[M + H]^+$ 470.1857, found 470.1901.

2-{2-[2-({5-[4-(Methylamino)phenylazo]pyiridin-2-yl}-amino)ethoxy]ethoxy}ethyl 4-methylbenzenesulfonate (16b). Following method F, product **16b** was obtained from derivative **14b** (71.9 mg), after 3 days or reaction at 50 °C, as an orange oil (55.5 mg, 54%, 0.108 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, *J* 2.5 Hz, 1H, *H*6), 7.93 (dd, *J* 9.3 and 2.5 Hz, 1H, *H*4), 7.78 (d, *J* 8.4 Hz, 2H, *H*2''(6'')), 7.75 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 7.30 (d, *J* 8.4 Hz, 2H, *H*3''(5'')), 6.63 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.45 (d, *J* 9.3 Hz, 1H, *H*3), 5.37 (br t, *J* 4.6 Hz, 1H, Pyr-N*H*), 4.16 (app t, *J* 4.9 Hz, 2H, CH_2F), 3.68 (m, 4H, CH_2B and CH_2E), 3.60 (m, 6H, CH_2A, CH_2C and CH_2D), 2.90 (s, 3H, NCH_3), 2.41 (s, 3H, ArCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (*C*2), 151.1 (*C*4'), 148.4 (*C*6), 144.9 and 144.8 (*C*1' and *C*4''), 141.6 (*C*5), 133.0 (*C*1''), 129.8 (*C*3''(5'')), 127.9 (*C*2''(6'')), 127.2 (*C*4), 124.5 (*C*2'(6')), 111.9 (*C*3'(5')), 108.1 (*C*3), 70.8, 70.3, 69.8 and 68.7 (*C*H_2B, *C*H_2C, *C*H_2D and *C*H_2E), 69.2 (*C*H_2F), 41.7 (*C*H_2A), 30.5 (N-*C*H_3), 21.6 (Ar-*C*H_3) ppm. IR (NaCl): ν_{max} 3417, 3366, 2921, 1599, 1521, 1349, 1176, 1143, 1018, 817, 644 cm^{-1}. MS (EI): *m/z* (%) 341 (100), 315 (34), 284 (41), 252 (40), 240 (52), 227 (82), 121 (82), 107 (55), 106 (43), 79 (55), 55 (80). HRMS (ESI-TOF, CH_3OH) calculated for $C_{25}H_{32}N_5O_5S$ $[M + H]^+$ 514.2119, found 514.2123. When the reaction was performed using method E, product **16b** was obtained with a lower yield (38.0 mg, 37%, 74 μmol), along with **2-{2-[2-({5-[4-[*N*,4-(dimethylphenylsulfonamido)phenylazo]pyridin-2-yl}amino)ethoxy]ethoxy}ethyl 4-methylbenzenesulfonate (18)** as secondary product as an orange oil (22.7 mg, 17%, 34 μmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, *J* 2.5 Hz, 1H, *H*6), 7.95 (dd, *J* 9.3 and 2.5 Hz, 1H, *H*4), 7.78 (d, *J* 8.3 Hz, 2H, *H*2''(6'')), 7.75 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 7.42 (d, *J* 8.3 Hz, 2H, *H*2'''(6''')), 7.31 (d, *J* 8.3 Hz, 2H, *H*3''(5'')), 7.21 (m, 4H, *H*3'(5') and *H*3'''(5''')), 6.48 (d, *J* 9.3 Hz, 1H, *H*3), 5.47 (br t, *J* 5.2 Hz, 1H, Pyr-N*H*), 4.18 (app t, *J* 4.9 Hz, 2H, CH_2F), 3.70 (m, 4H, CH_2B and CH_2E), 3.61 (m, 6H, CH_2A, CH_2C and CH_2D), 3.18 (s, 3H, NCH_3), 2.41 (s, 3H, Ar''CH_3), 2.39 (s, 3H, Ar'''CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1 (*C*2), 151.3 (*C*1'), 150.8 (*C*6), 144.9 (*C*4''), 143.7 (*C*4'''), 142.8 (*C*4'), 141.3 (*C*5), 133.3 (*C*1'''), 133.0 (*C*1''), 129.8 (*C*3''(5'')), 129.4 (*C*3'''(5''')), 127.9 (*C*2''(6'')), 127.9 (*C*2'''(6''')), 126.9 (*C*4),

126.7 (*C*3'(5')), 122.7 (*C*2'(6')), 108.6 (*C*3), 70.8 and 70.3 (*C*H_2C and *C*H_2D), 69.7 and 68.8 (*C*H_2B and *C*H_2E), 69.2 (*C*H_2F), 41.6 (*C*H_2A), 37.9 (N-*C*H_3), 21.6 (Ar''-*C*H_3), 21.5 (Ar'''-*C*H_3) ppm. IR (NaCl): ν_{max} 3405, 2919, 1606, 1521, 1350, 1175, 1097, 923, 815, 663 cm^{-1}. MS (EI): *m/z* (%) 648 (19), 292 (30), 277 (35), 167 (37), 149 (79), 81 (59), 67 (67), 57 (70), 55 (100). HRMS (ESI-TOF, CH_3OH) calculated for $C_{32}H_{38}N_5O_7S_2$ $[M + H]^+$ 668.2207, found 668.2206.

Together with tosylates **16b** and **18**, product **17** was identified by HPLC-MS and could not be isolated as a pure compound.

Synthesis of Florbetapir aza-analogues 1

***N*-[2-(2-Fluoroethoxy)ethyl]-*N*-{5-[4-(methylamino)phenylazo]pyridin-2-yl}amine (1a)**. Following method D, product **1a** was obtained from acetamide **12a** (35.9 mg, 0.1 mmol), employing 1.0 mL of methanol and 1.0 mL of 2 M NaOH, as an orange oil (29.5 mg, 94%, 94 µmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* 2.4 Hz, 1H, *H*6), 7.96 (dd, *J* 9.3 and 2.4 Hz, 1H, *H*4), 7.75 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 6.62 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.47 (d, *J* 9.3 Hz, 1H, *H*3), 5.19 (br s, 1H, Pyr-N*H*), 4.56 (app dt, $^2J_{HF}$ 48 Hz, $^3J_{HH}$ 4.2 Hz, 2H, CH_2D), 4.10 (br s, 1H, Me-N*H*), 3.78-3.70 (m, 4H, CH_2B and CH_2C), 3.64 (app q, *J* 5.4 Hz, 2H, CH_2A), 2.90 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (*C*2), 151.2 (*C*4'), 148.5 (*C*6), 144.8 (*C*1'), 141.7 (*C*5), 127.2 (*C*4), 124.5 (*C*2'(6')), 111.9 (*C*3'(5')), 108.2 (*C*3), 83.5 (d, $^1J_{CF}$ 168.8 Hz, *C*H_2D), 70.2 (d, $^1J_{CF}$ 20.0 Hz, *C*H_2C), 70.0 (*C*H_2B), 41.7 (*C*H_2A), 30.5 (*C*H_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -224.1 (tt, J_{FH} 48.0 and 20.0 Hz, CH_2F) ppm. IR (NaCl): ν_{max} 3417, 3364, 2957, 2922, 2852, 1598, 1520, 1336, 1239, 1142, 1046, 829 cm^{-1}. MS (EI): *m/z* (%) 317 (100) $[M^{+\bullet}]$, 284 (41), 240 (43), 227 (59), 185 (39), 171 (28), 106 (27), 87 (74), 79 (32), 73 (30). HRMS (ESI-TOF, CH_3OH) calculated for $C_{16}H_{21}FN_5O$ $[M + H]^+$ 318.1725, found 318.1727. When 77.0 mg of product **16a** was treated with KF and K[2.2.2] in CH_3CN, as described in method G, ***N*-Methyl-4-[6-(morpholin-4-yl)pyridin-3-ylazo]aniline 19** was the only reaction product obtained. Orange solid (28.5 mg, 64%, 96 µmol). m.p. 139 – 141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* 2.4 Hz, 1H, *H*2), 8.04 (dd, *J* 9.3 and 2.4 Hz, 1H, *H*4), 7.81 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.71 (d, *J* 9.3 Hz, 1H, *H*5), 6.67 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 4.16 (br s, 1H, N*H*), 3.86 (app t, *J* 4.9 Hz, 4H, OCH_2), 3.66 (app t, *J* 4.9 Hz, 4H, NCH_2), 2.95 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (*C*6), 151.3 (*C*1'), 147.9 (*C*2), 144.9 (*C*4'), 141.6 (*C*3), 127.3 (*C*4), 124.6 (*C*3'(5')), 111.9 (*C*2'(6')), 106.6 (*C*5), 66.7 (OCH_2), 45.5 (NCH_2), 30.4 (*C*H_3) ppm. IR (KBr): ν_{max} 3387, 2917, 2849, 1601, 1260, 1242, 1109, 942, 827 cm^{-1}. MS (EI): *m/z* (%) 297 (100) $[M^{+\bullet}]$, 296 (13), 266 (13), 252 (13), 239 (12), 106 (15), 79 (11). HRMS (ESI-TOF, CH_3OH) calculated for $C_{16}H_{20}N_5O$ $[M + H]^+$ 298.1662, found 298.1658.

Fluorination of the tosylate **16a** using method H yielded 26.2 mg of the final product ***N*-[2-(2-Fluoroethoxy)ethyl]-*N*-{5-[4-(methylamino)phenylazo]pyridin-2-yl}amine (1a)** (55%) and 16.9 mg of ***N*-Methyl-4-[6-(morpholin-4-yl)pyridin-3-ylazo]aniline 19** (38%).

***N*-{2-[2-(2-Fluoroethoxy)ethyl]ethyl}-*N*-{5-[4-(methylamino)phenylazo]pyridin-2-yl}amine (1b)**. Following method D, product **1b** was obtained from acetamide **12b** (40.3 mg, 0.1 mmol), employing 1.0 mL of methanol and 1.0 mL of 2 M NaOH, as an orange oil (31.0 mg, 86%, 0.86 µmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* 2.4 Hz, 1H, *H*6), 7.94 (dd, *J* 9.3 and 2.4 Hz, 1H, *H*4), 7.75 (d, *J* 8.8 Hz, 2H, *H*2'(6')), 6.62 (d, *J* 8.8 Hz, 2H, *H*3'(5')), 6.45 (d, *J* 9.3 Hz, 1H, *H*3), 5.31 (br t, *J* 5.4 Hz, 1H, Pyr-N*H*), 4.56 (app dt, $^2J_{HF}$ 47 Hz, $^3J_{HH}$ 4.2 Hz, 2H, CH_2F), 3.78-3.58 (m, 10H, CH_2A, CH_2B, CH_2C, CH_2D and CH_2E), 2.89 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2 (*C*2), 151.1 (*C*4'), 148.6 (*C*6), 144.8 (*C*1'), 141.6 (*C*5), 127.1 (*C*4), 124.5 (*C*2'(6')), 111.9 (*C*3'(5')), 108.1 (*C*3), 83.1 (d, $^1J_{CF}$ 168.8 Hz, *C*H_2F), 70.4 (d, $^1J_{CF}$ 19.1 Hz, *C*H_2E), 70.7, 70.3 and 69.8 (*C*H_2B, *C*H_2C and *C*H_2D), 41.6 (*C*H_2A), 30.4 (*C*H_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -222.7 (tt, J_{FH} 47.3 and 29.0 Hz, CH_2F) ppm. IR (NaCl): ν_{max} 3398, 3366, 2955, 2919, 2851, 1598, 1519, 1237, 1142, 1101, 827 cm^{-1}. MS (EI): *m/z* (%) 361 (100) $[M^{+\bullet}]$, 240 (46), 227 (59), 134 (21), 106 (33), 79 (18). HRMS (ESI-TOF, CH_3OH) calculated for $C_{18}H_{25}FN_5O_2$ $[M + H]^+$ 362.1987, found 362.1991. Fluorination of 77 mg of tosylate **16b** using method G yielded 39.6 mg of the Florbetapir aza-analogue **1b** (73%).

Supplementary Material

Synthesis of alkylating agents, numbering employed in NMR analysis and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra for new compounds described are provided as supplementary material in the online version of the text.

Acknowledgements

The authors thank the Comunidad de Madrid (CAM, project B2017/BMD-3688 MULTI-TARGET&VIEW-CM FEDER FUNDS and Instituto de Salud Carlos III (FEDER funds, ISCIII RETIC REDINREN, RD 16/0009/0015) for financial support. E.G. and J.R. are grateful to the UAH for a pre-doctoral research grant.

References

1. Breijyeh, Z.; Karaman, R. *Molecules* **2020**, *25* (24), 5789. https://doi.org/10.3390/molecules25245789
2. Vallabhajosula, S. *Semin. Nucl. Med.* **2011**, *41* (4), 283–299. https://doi.org/10.1053/j.semnuclmed.2011.02.005
3. van Oostveen, W. M.; de Lange, E. C. M. *Int. J. Mol. Sci.* **2021**, *22* (4), 1–34. https://doi.org/10.3390/ijms22042110
4. Wang, J.; Gu, B. J.; Masters, C. L.; Wang, Y.-J. *Nat. Rev. Neurol.* **2017**, *13* (10), 612–623. https://doi.org/10.1038/nrneurol.2017.111
5. van der Kant, R.; Goldstein, L. S. B.; Ossenkoppele, R. *Nat. Rev. Neurosci.* **2020**, *21* (1), 21–35. https://doi.org/10.1038/s41583-019-0240-3
6. Yu, P.; Cui, M.; Wang, X.; Zhang, X.; Li, Z.; Yang, Y.; Jia, J.; Zhang, J.; Ono, M.; Saji, H.; Jia, H.; Liu, B. *Eur. J. Med. Chem.* **2012**, *57*, 51–58. https://doi.org/10.1016/j.ejmech.2012.08.031
7. Selkoe, D. J.; Hardy, J. *EMBO Mol. Med.* **2016**, *8*, 595–608. https://doi.org/10.15252/emmm.201606210
8. Mathis, C. A.; Lopresti, B. J.; Klunk, W. E. *Nucl. Med. Biol.* **2007**, *34* (7), 809–822. https://doi.org/10.1016/j.nucmedbio.2007.06.015
9. Panza, F.; Lozupone, M.; Logroscino, G.; Imbimbo, B. P. *Nat. Rev. Neurol.* **2019**, *15* (2), 73–88. https://doi.org/10.1038/s41582-018-0116-6
10. Uzuegbunam, B. C.; Librizzi, D.; Yousefi, B. H. *PET Radiopharmaceuticals for Alzheimer's Disease and Parkinson's Disease Diagnosis, the Current and Future Landscape*; 2020; Vol. 25. https://doi.org/10.3390/molecules25040977
11. Koychev, I.; Hofer, M.; Friedman, N. *J. Nucl. Med.* **2020**, *61* (10), 1413–1418. https://doi.org/10.2967/jnumed.119.230458
12. Mathis, C. A.; Lopresti, B. J.; Ikonomovic, M. D.; Klunk, W. E. *Semin. Nucl. Med.* **2017**, *47* (5), 553–575. https://doi.org/10.1053/j.semnuclmed.2017.06.003
13. Cistaro, A.; Alongi, P.; Caobelli, F.; Cassalia, L. *Curr. Med. Chem.* **2018**, *25* (26), 3131–3140. https://doi.org/10.2174/0929867325666180117094704
14. Chen, X. Q.; Mobley, W. C. *Front. Neurosci.* **2019**, *13* (JUN), 1–21.

https://doi.org/10.3389/fnins.2019.00659
15. Nakazono, M.; Obayashi, K.; Sasamoto, K.; Tomiyoshi, K.; Suenaga, G.; Ando, Y. *Clin. Chim. Acta* **2014**, *436*, 27–34. https://doi.org/10.1016/j.cca.2014.04.028
16. Cui, M.; Tang, R.; Zhang, J.; Zhang, X.; Li, Z.; Jia, H.; Liu, B. *Radiochim. Acta* **2014**, *102* (1–2), 185–192. https://doi.org/10.1515/ract-2014-2087
17. Chauhan, K.; Tiwari, A. K.; Chadha, N.; Kaul, A.; Singh, A. K.; Datta, A. *Mol. Pharm.* **2018**, *15* (4), 1515–1525. https://doi.org/10.1021/acs.molpharmaceut.7b01070
18. Kaide, S.; Ono, M.; Watanabe, H.; Shimizu, Y.; Nakamoto, Y.; Togashi, K.; Yamaguchi, A.; Hanaoka, H.; Saji, H. *Bioorg. Med. Chem.* **2018**, *26* (12), 3352–3358. https://doi.org/10.1016/j.bmc.2018.05.001
19. Yousefi, B. H.; Drzezga, A.; von Reutern, B.; Manook, A.; Schwaiger, M.; Wester, H.-J.; Henriksen, G. *ACS Med. Chem. Lett.* **2011**, *2* (9), 673–677. https://doi.org/10.1021/ml200123w
20. Yang, Y.; Cui, M. *Eur. J. Med. Chem.* **2014**, *87*, 703–721. https://doi.org/10.1016/j.ejmech.2014.10.012
21. Sundaram, G. S. M.; Dhavale, D. D.; Prior, J. L.; Yan, P.; Cirrito, J.; Rath, N. P.; Laforest, R.; Cairns, N. J.; Lee, J.-M.; Kotzbauer, P. T.; Sharma, V. *Sci. Rep.* **2016**, *6* (1), 35636. https://doi.org/10.1038/srep35636
22. Cheng, Y.; Ono, M.; Kimura, H.; Kagawa, S.; Nishii, R.; Kawashima, H.; Saji, H. *ACS Med. Chem. Lett.* **2010**, *1* (7), 321–325. https://doi.org/10.1021/ml100082x
23. Lee, J. H.; Byeon, S. R.; Kim, Y.; Lim, S. J.; Oh, S. J.; Moon, D. H.; Yoo, K. H.; Chung, B. Y.; Kim, D. J. *Bioorg. Med. Chem. Lett.* **2008**, *18* (20), 5701–5704. https://doi.org/10.1016/j.bmcl.2008.05.019
24. Honer, M.; Gobbi, L.; Knust, H.; Kuwabara, H.; Muri, D.; Koerner, M.; Valentine, H.; Dannals, R. F.; Wong, D. F.; Borroni, E. *J. Nucl. Med.* **2018**, *59* (4), 675–681. https://doi.org/10.2967/jnumed.117.196741
25. Bandara, N.; Sharma, A. K.; Krieger, S.; Schultz, J. W.; Han, B. H.; Rogers, B. E.; Mirica, L. M. *J. Am. Chem. Soc.* **2017**, *139* (36), 12550–12558. https://doi.org/10.1021/jacs.7b05937
26. Zhen, W.; Han, H.; Anguiano, M.; Lemere, C. A.; Cho, C.-G.; Lansbury, P. T. *J. Med. Chem.* **1999**, *42* (15), 2805–2815. https://doi.org/10.1021/jm990103w
27. Cordoba, M.; Abet, V.; Moron, M.; Castillo, R. R.; Burgos, C.; Izquierdo, M. L. *Arkivoc* **2011**, *2011* (3), 156–165. https://doi.org/10.3998/ark.5550190.0012.312
28. Gala, E.; Reyes, M. J.; Alvarez-Builla, J.; Izquierdo, M. L. *European J. Org. Chem.* **2016**, *2016* (12), 2145–2156. https://doi.org/10.1002/ejoc.201600059