

Supplemental Material for:

Facile aromatic radiofluorination of [^{18}F]flumazenil from diaryliodonium salts with evaluation of their stability and selectivity

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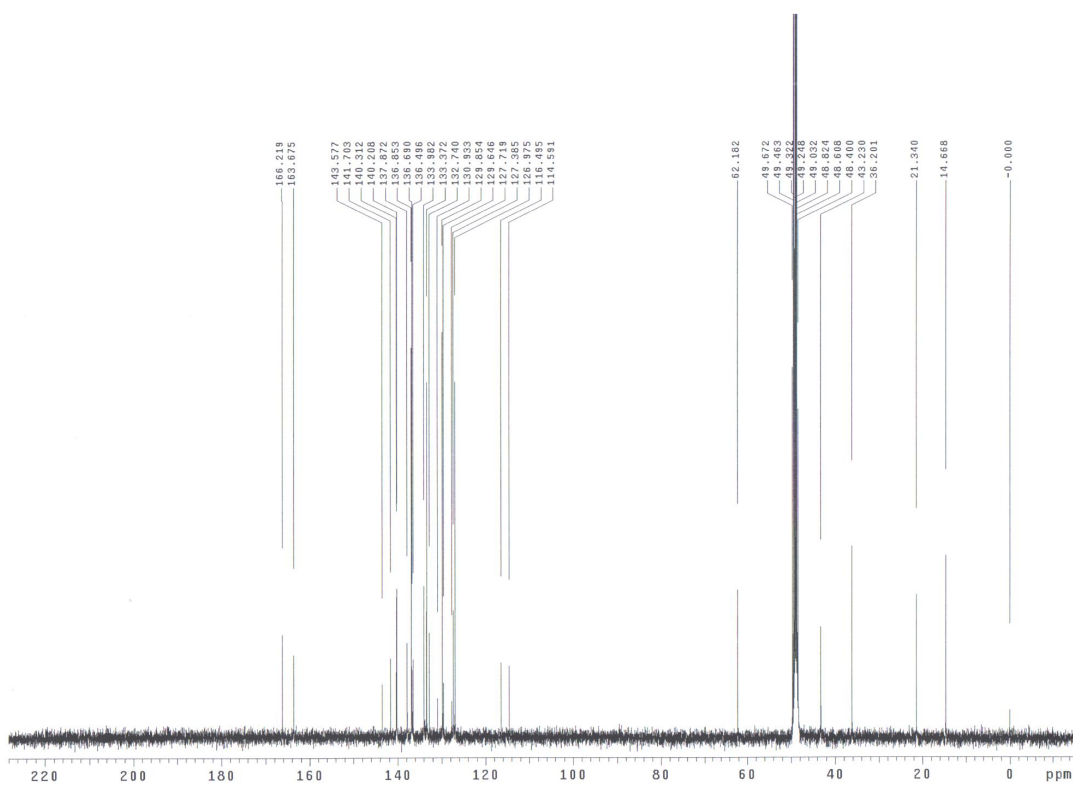
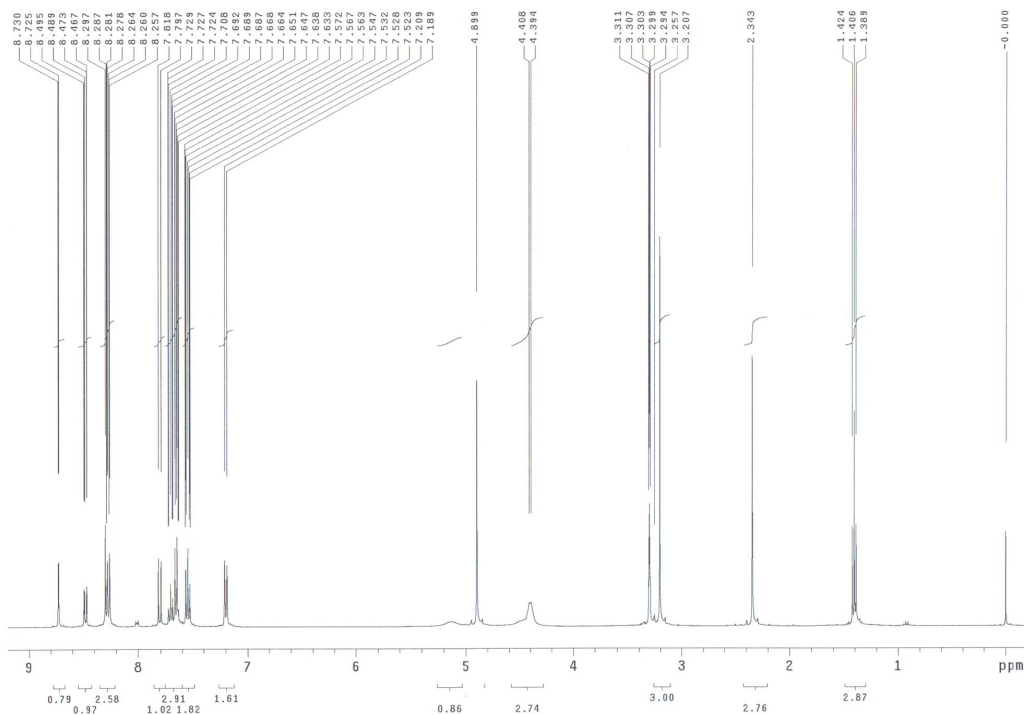
Supporting Information

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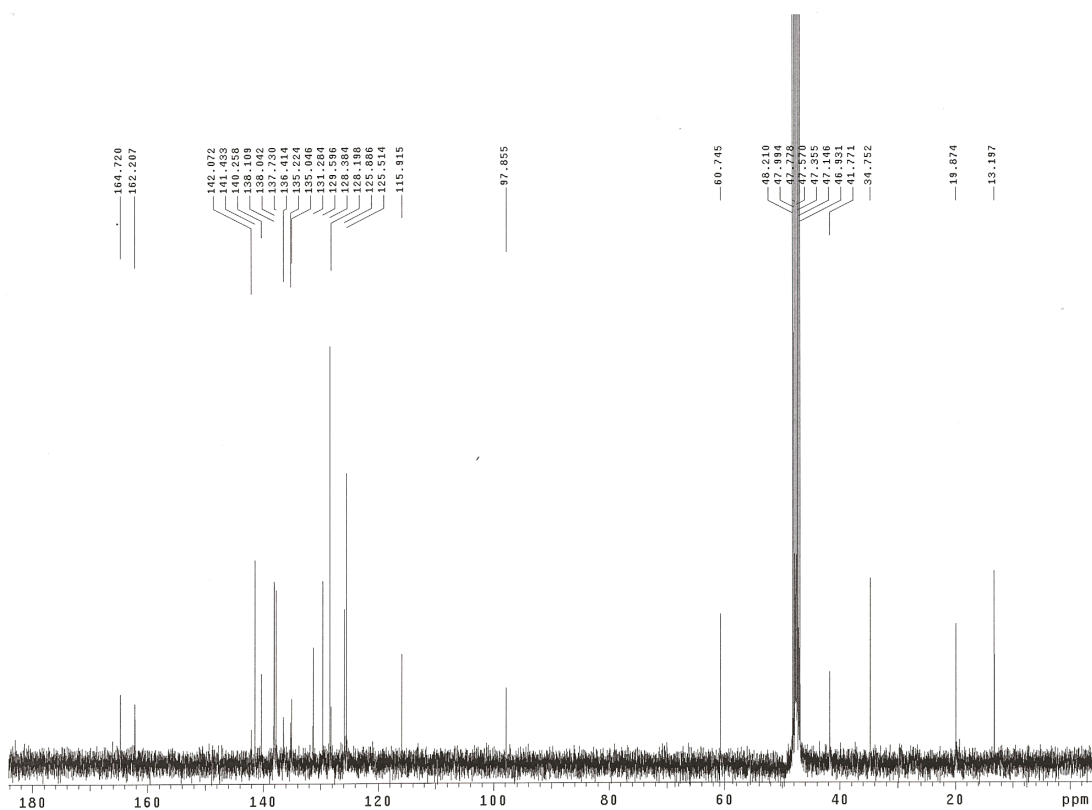
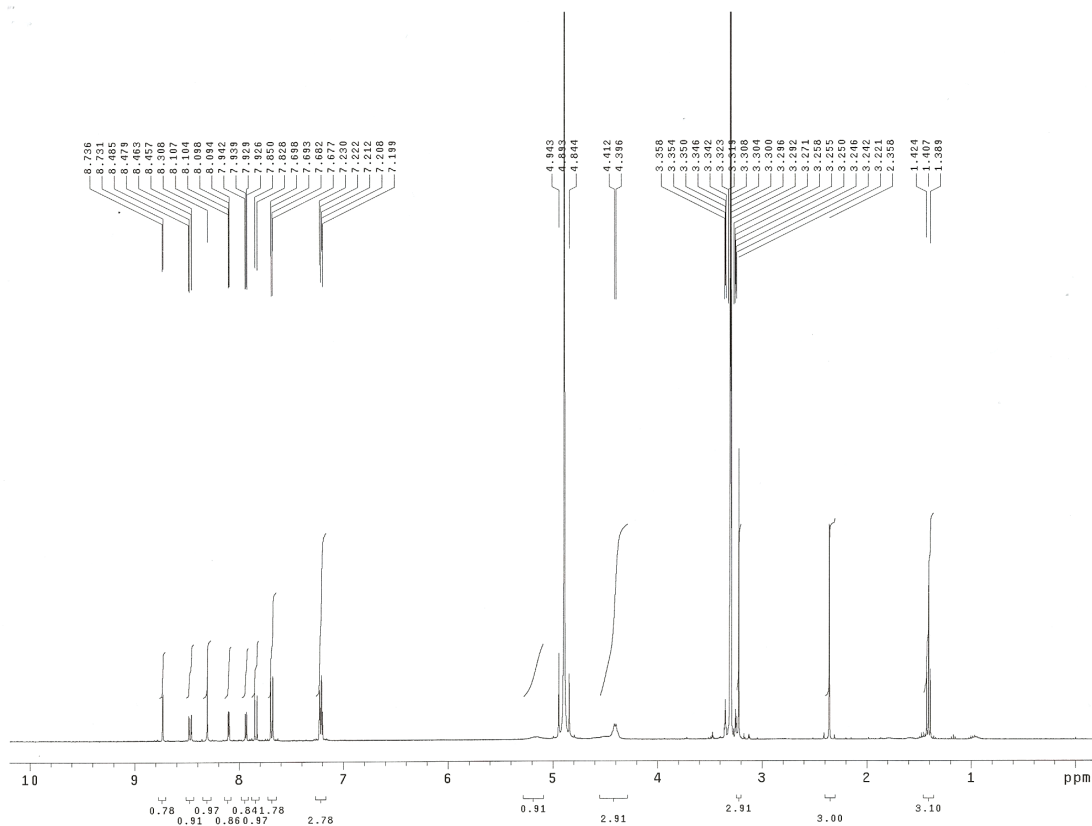
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1. NMR (¹H NMR & ¹³C NMR) of compounds (5a-f)

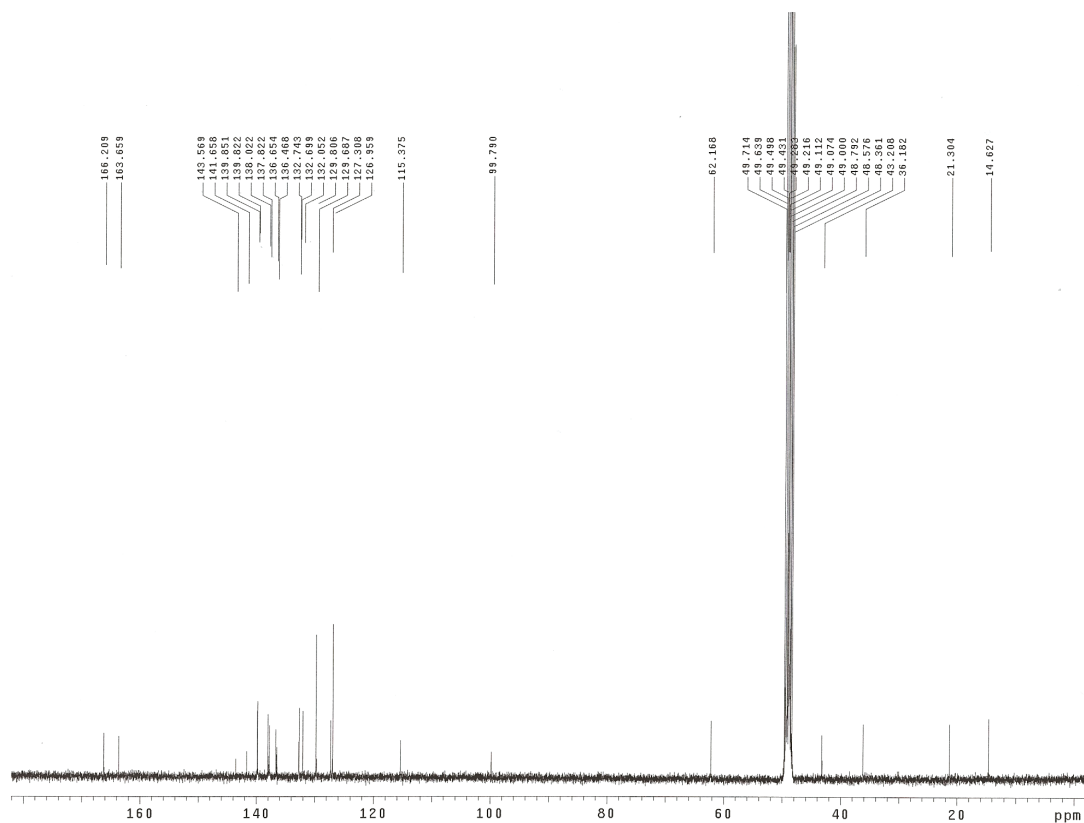
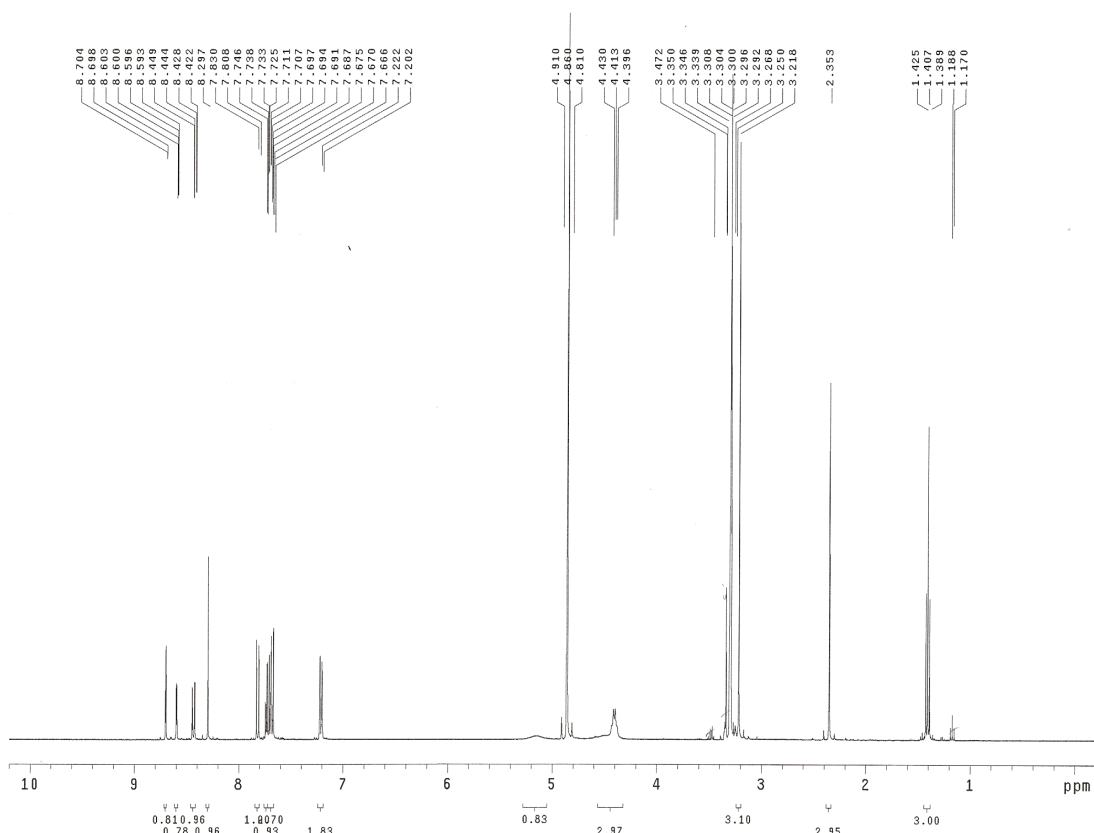
Ethyl 8-phenyl(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5a)



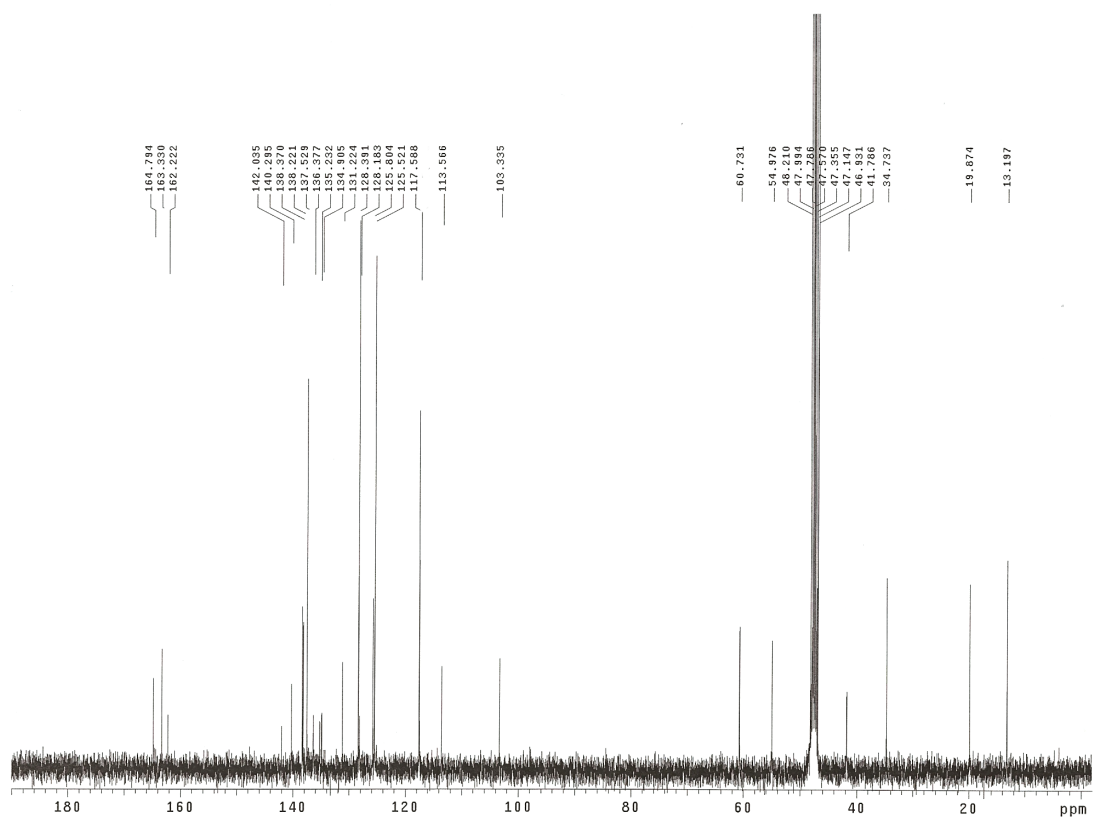
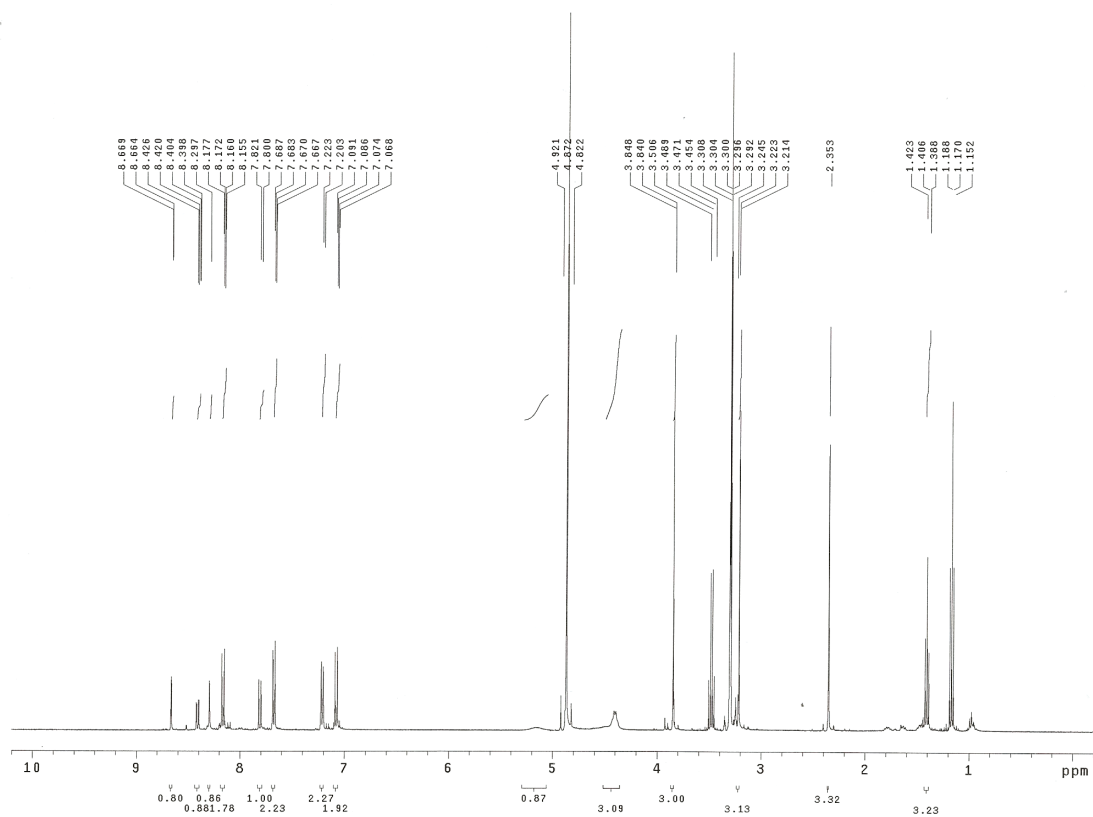
Ethyl 8-(2-thiophenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5b)



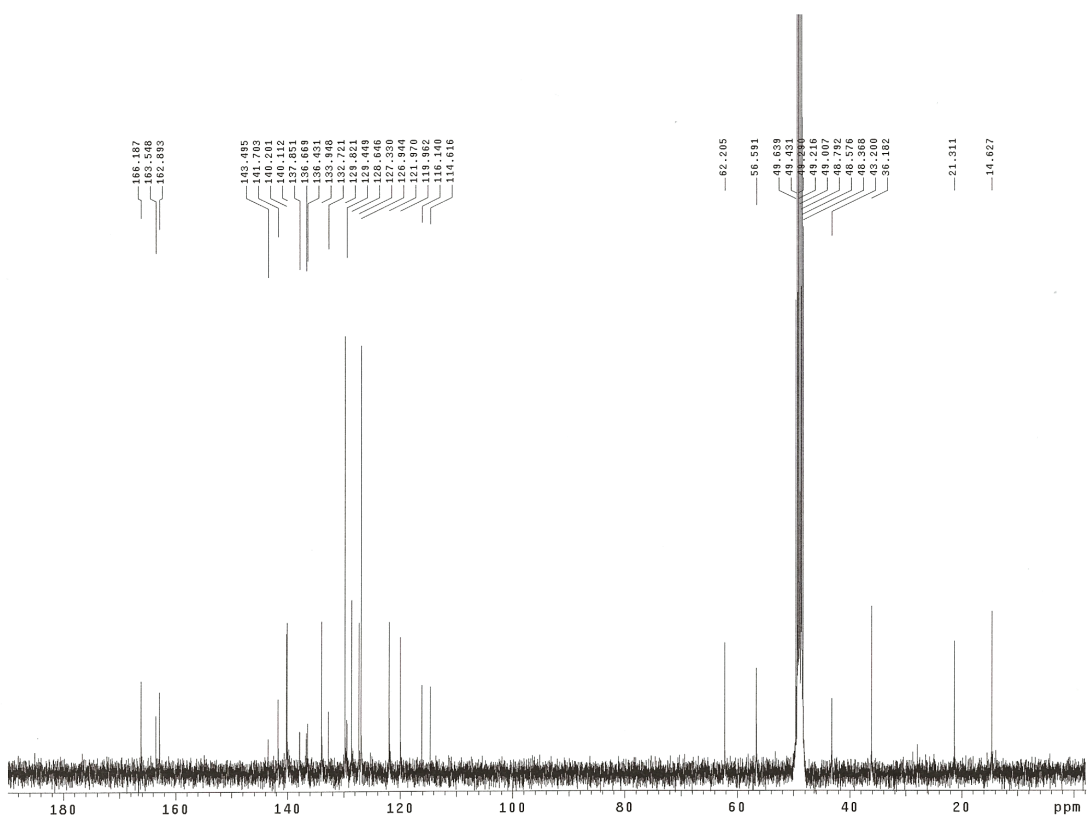
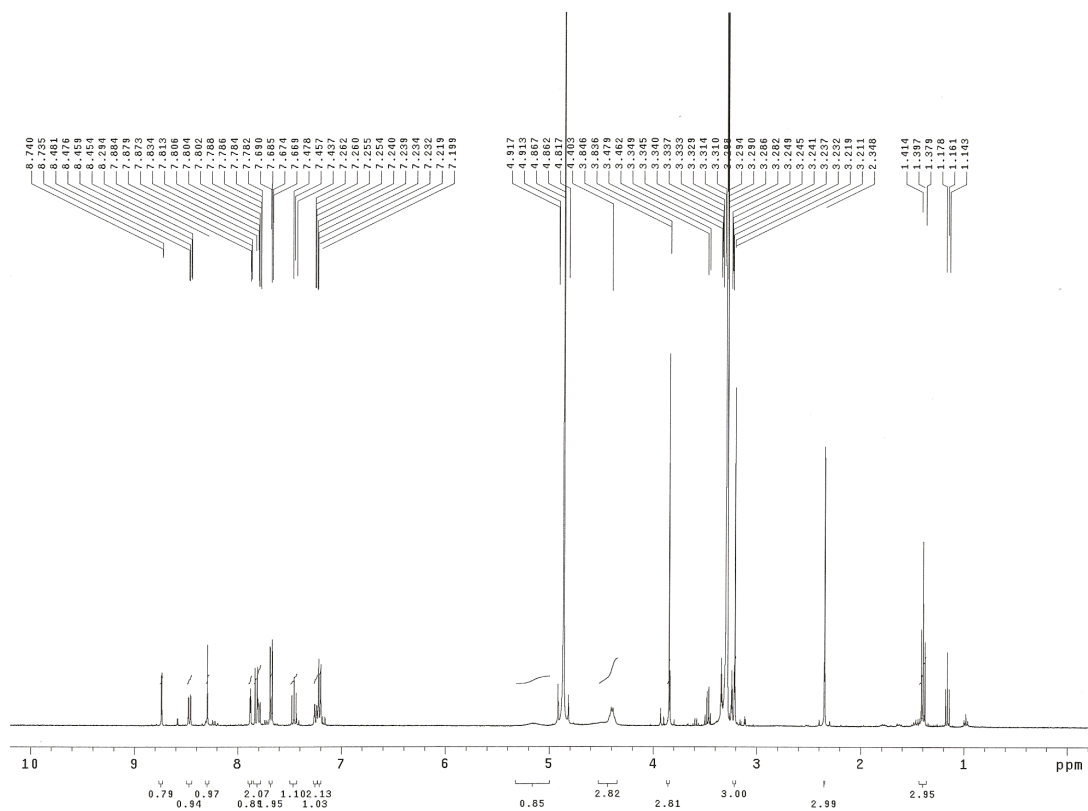
Ethyl 8-(3-thiophenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5c)



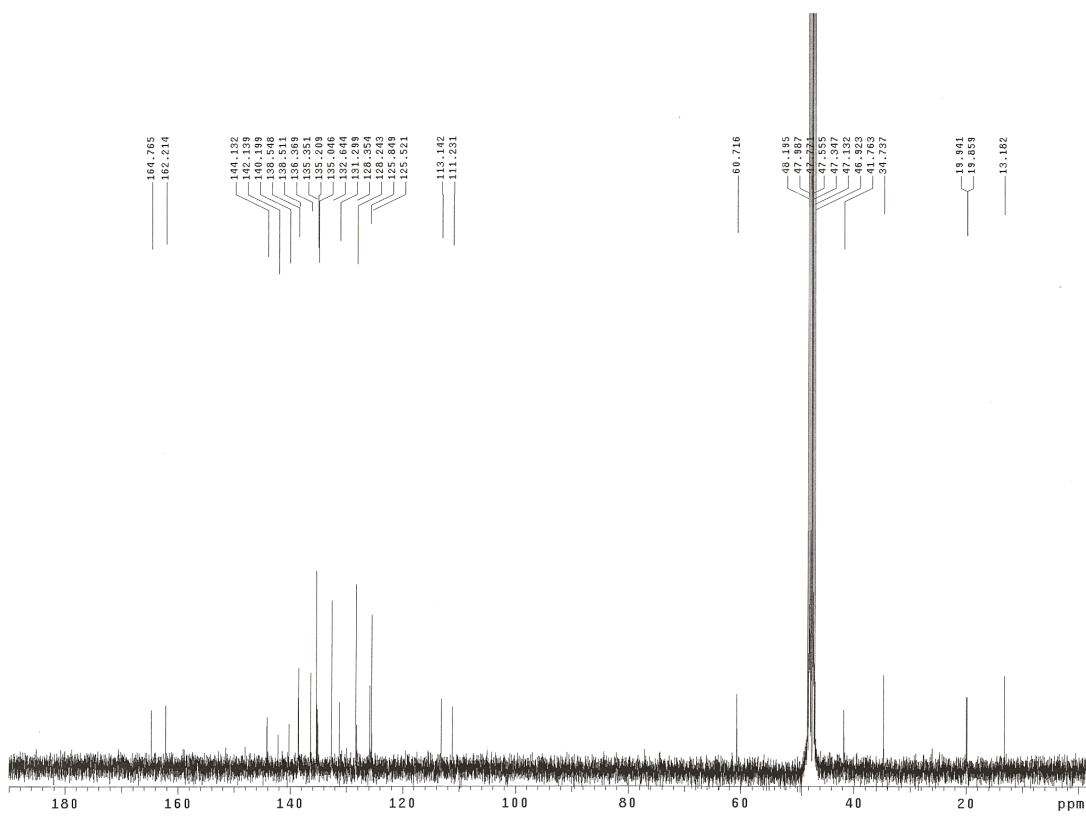
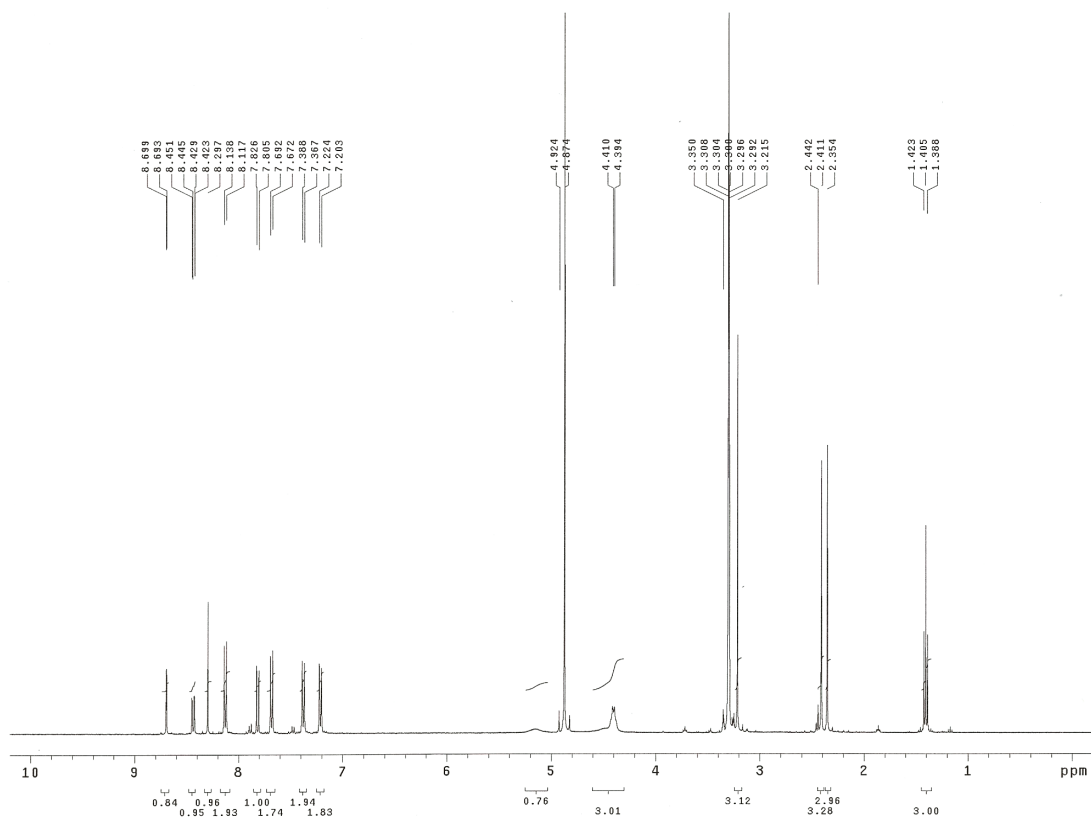
Ethyl 8-(4-methoxyphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5d)



Ethyl 8-(3-methoxyphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5e)



Ethyl 8-(4-methylphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (5f)



2. HPLC chromatogram of 5a-f for purity

HPLC Condition:

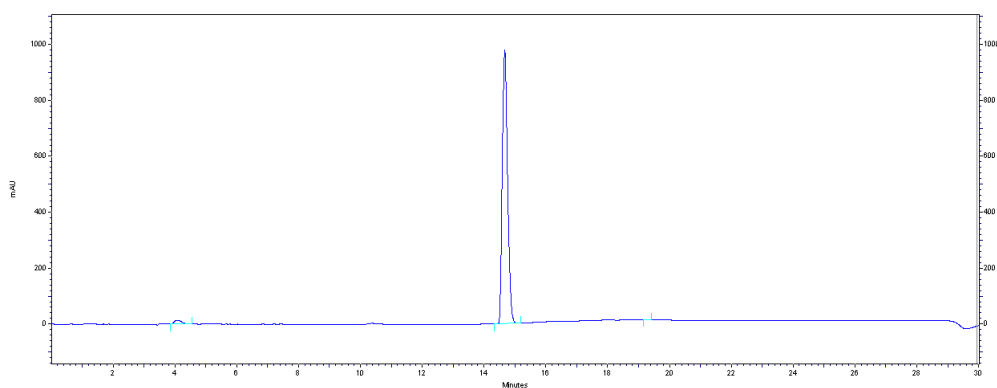
System: Thermo Separation Products System (Fremont, U.S.) with UV-2000 (254 nm)

Column: Thermo, Hypersil gold C18; 4.6 x 250 mm, 5 μ

Eluent: 0 min: 10% MeOH/H₂O/0.1% TFA; 5 min: 10% MeOH/H₂O/0.1% TFA; 15 min: 90% MeOH/H₂O/0.1% TFA; 25 min: 90% MeOH/H₂O/0.1% TFA

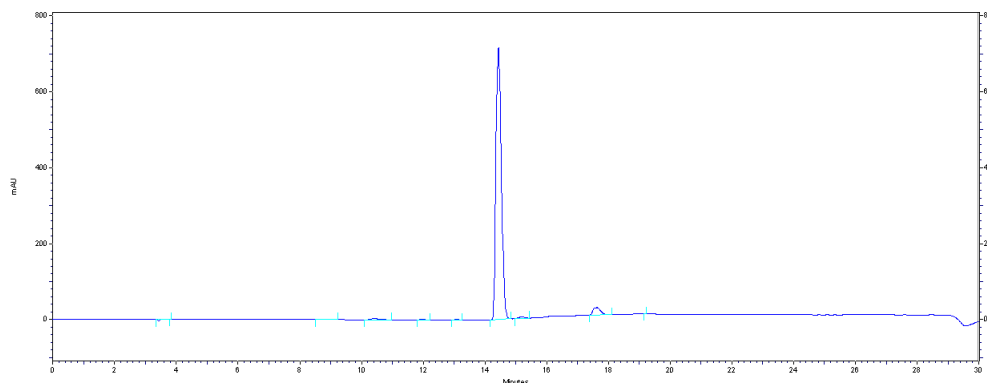
Flow rate: 1 mL/min

Ethyl 8-phenyl(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5a): 98.06%



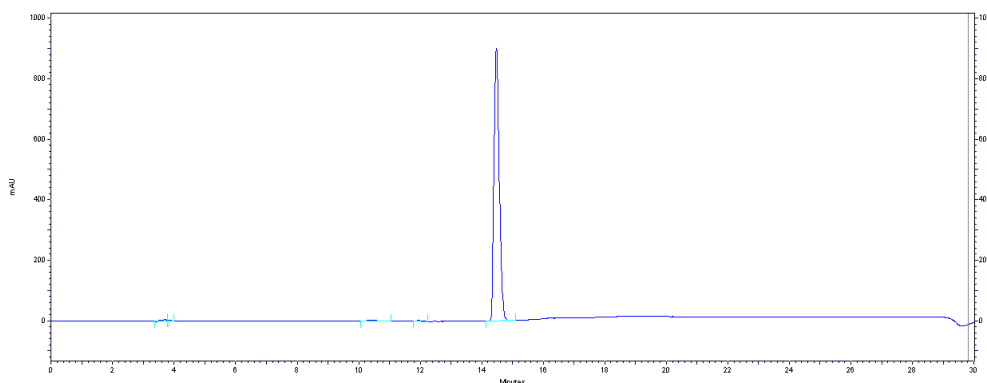
Retention Time	Area	Area %
4.080	235050	1.94
14.672	11902810	98.06
19.150	803	0.01
Totals	12138663	100.00

Ethyl 8-(2-thiophenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5b): 94.57%



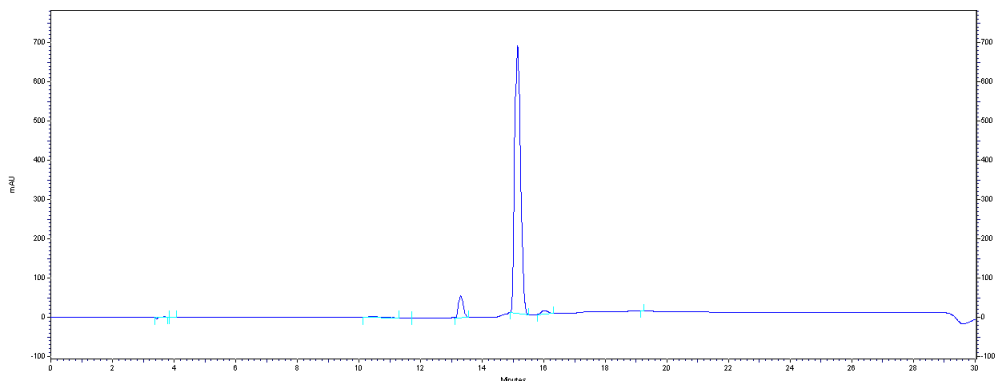
Retention Time	Area	Area %
3.680	382	0.00
3.790	268	0.00
8.500	2485	0.03
10.413	70731	0.76
11.962	31305	0.34
13.093	14033	0.15
14.437	8751347	94.57
15.197	64173	0.69
17.633	319257	3.45
19.150	70	0.00
Totals	9254051	100.00

Ethyl 8-(3-thiophenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5c): 98.60%



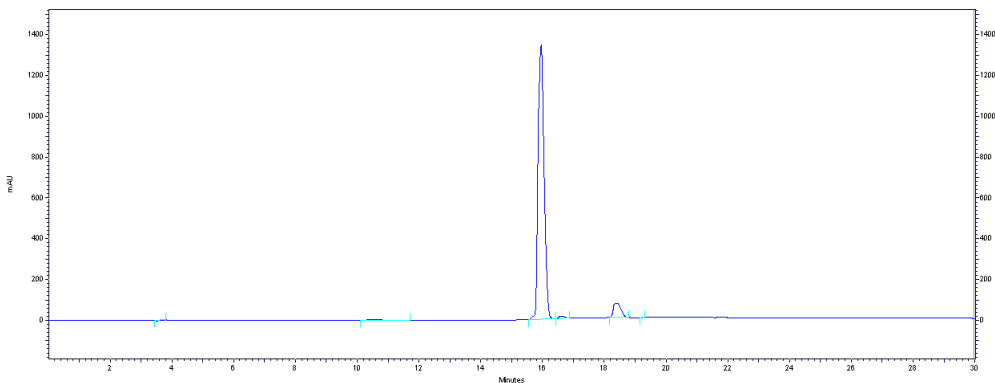
Retention Time	Area	Area %
3.697	33855	0.31
3.790	485	0.00
3.830	7271	0.07
10.415	79527	0.73
11.948	32194	0.29
14.477	10767618	98.60
Totals	10920950	100.00

Ethyl 8-(4-methoxyphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5d): 92.46%



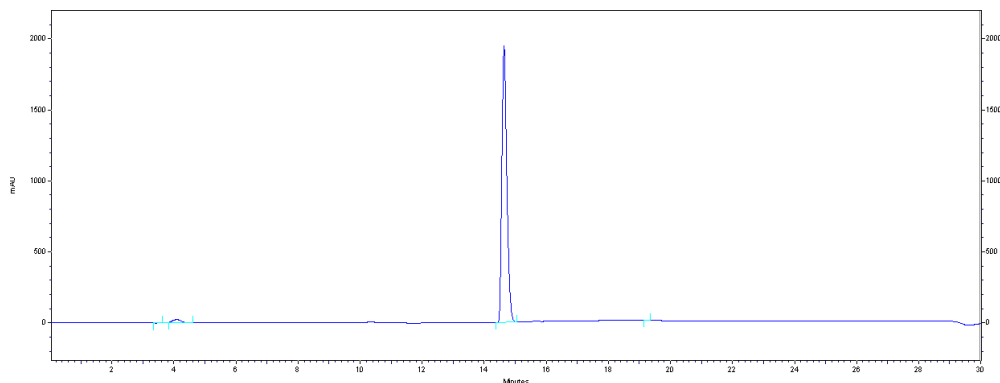
Retention Time	Area	Area %
3.683	7867	0.07
3.790	1101	0.01
3.830	914	0.01
10.423	94129	0.84
11.700	0	0.00
13.305	608247	5.44
15.153	10332698	92.46
16.057	129611	1.16
19.160	201	0.00
Totals	11174768	100.00

Ethyl 8-(3-methoxyphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5e): 92.61%



Retention Time	Area	Area %
3.618	32550	0.16
11.700	185302	0.88
15.953	19430588	92.61
16.625	153391	0.73
18.352	1177334	5.61
19.150	283	0.00
Totals	20979448	100.00

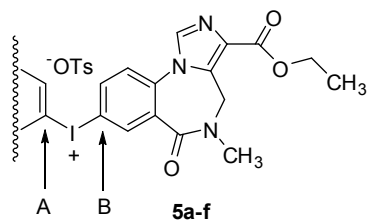
Ethyl 8-(4-methylphenyl)(iodonium tosylate)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-
a][1,4]benzodiazepine-3-carboxylate (5f): 97.94%



Retention Time	Area	Area %
3.497	8072	0.04
4.083	457289	2.02
14.640	22116723	97.94
19.150	784	0.00
Totals	22582868	100.00

3. The Electron density of 5a-f from observed ^{13}C NMR

Electron density (compound #, ppm): phenyl- (**5a**, 114.59) \approx 3-methoxyphenyl- (**5e**, 114.62) < 4-methylphenyl- (**5f**, 111.23) < 4-methoxyphenyl- (**5d**, 103.34) < 3-thiophenyl- (**5c**, 99.79) < 2-thiophenyl-mazenil (**5b**, 97.86). (from observed ^{13}C NMR).



Precursors	A carbon (ppm)	B carbon (ppm)
5a	114.59	116.50
5b	97.86	115.92
5c	99.79	115.38
5d	103.34	113.57
5e	114.62	116.14
5f	111.23	113.14

4. HPLC chromatogram of [¹⁸F]flumazenil production by TracerLab FX-FN (automation)

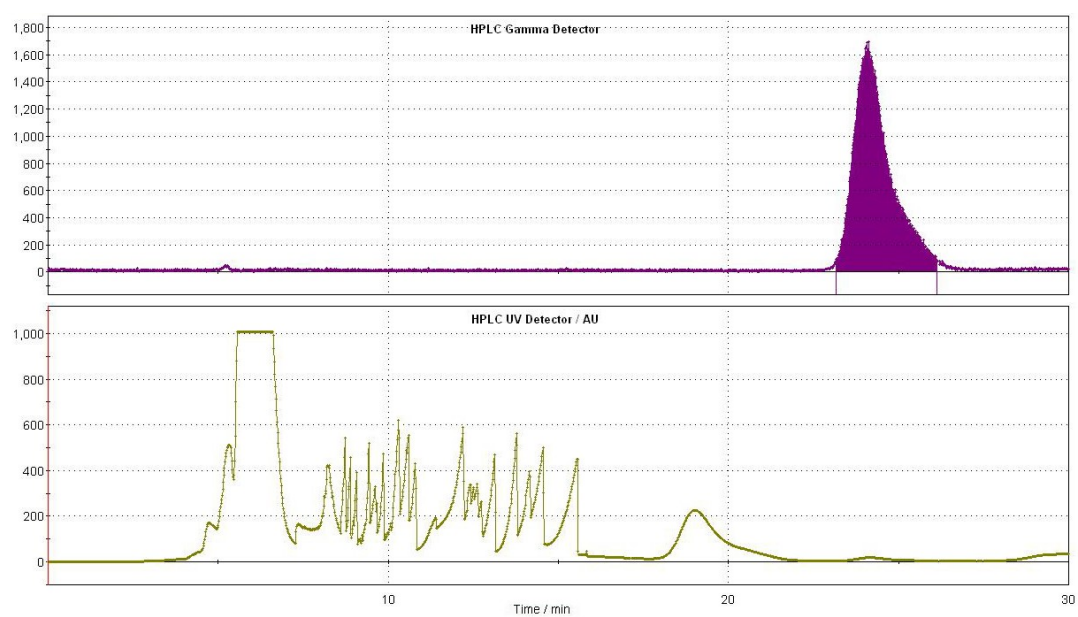
HPLC Condition:

System: TracerLab FX-FN (GE Healthcare, U.S.) (UV-254 nm)

Column: Waters, semi-Preparative Xterra RP-18, 7.9 × 250 mm, 5 μ

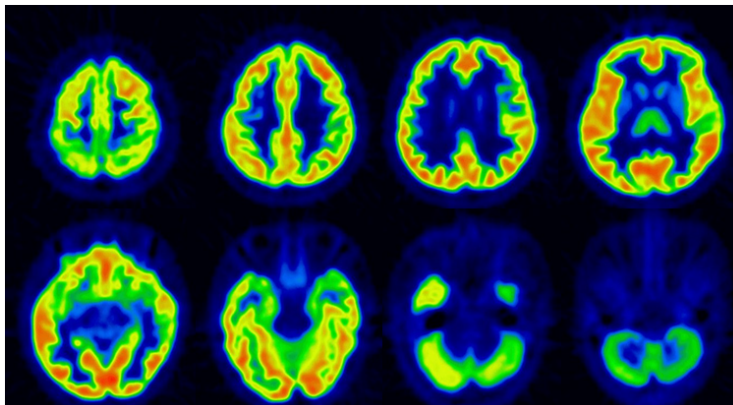
Eluent: 20% CH₃CN/H₂O

Flow rate: 4.5 mL/min



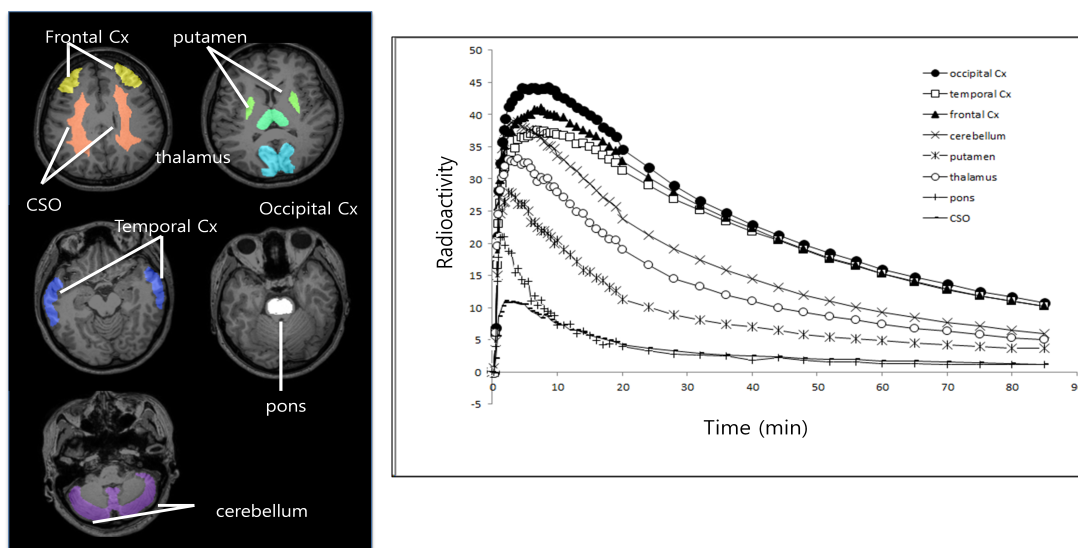
5. PET/CT image and time activity curve of [¹⁸F]flumazenil in healthy human subject

5-1. PET image of [¹⁸F]flumazenil in healthy human subject (0 to 90 min sum)



Female aged 38 y, Injection dose: ~220 MBq

5-2. Time activity curve of [¹⁸F]flumazenil in healthy human subject



5-3. Time activity curve of [¹¹C]flumazenil (Ref. 15)