

Figures

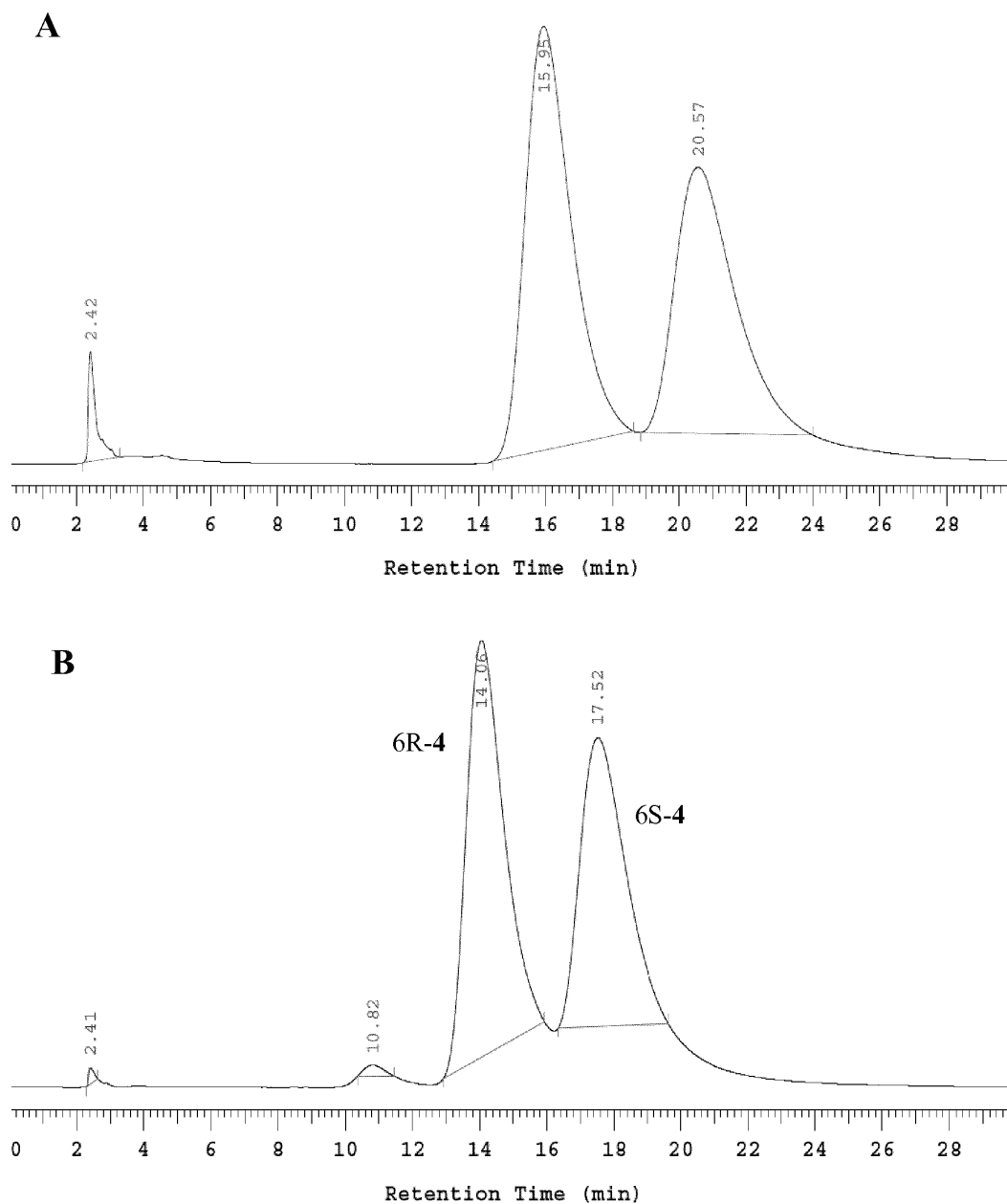


Figure 1. Chiral HPLC chromatograms of the precursor N^2 -acetyl-3'-aza-2'-chloro-5-methyltetrahydrofolate-di-*tert*-butylester 6S-3 and 6R-3 (A) and the protected reference N^2 -acetyl-3'-aza-2'-fluoro-5-methyltetrahydrofolate-di-*tert*-butylester 6S-2 and 6R-2 (B).

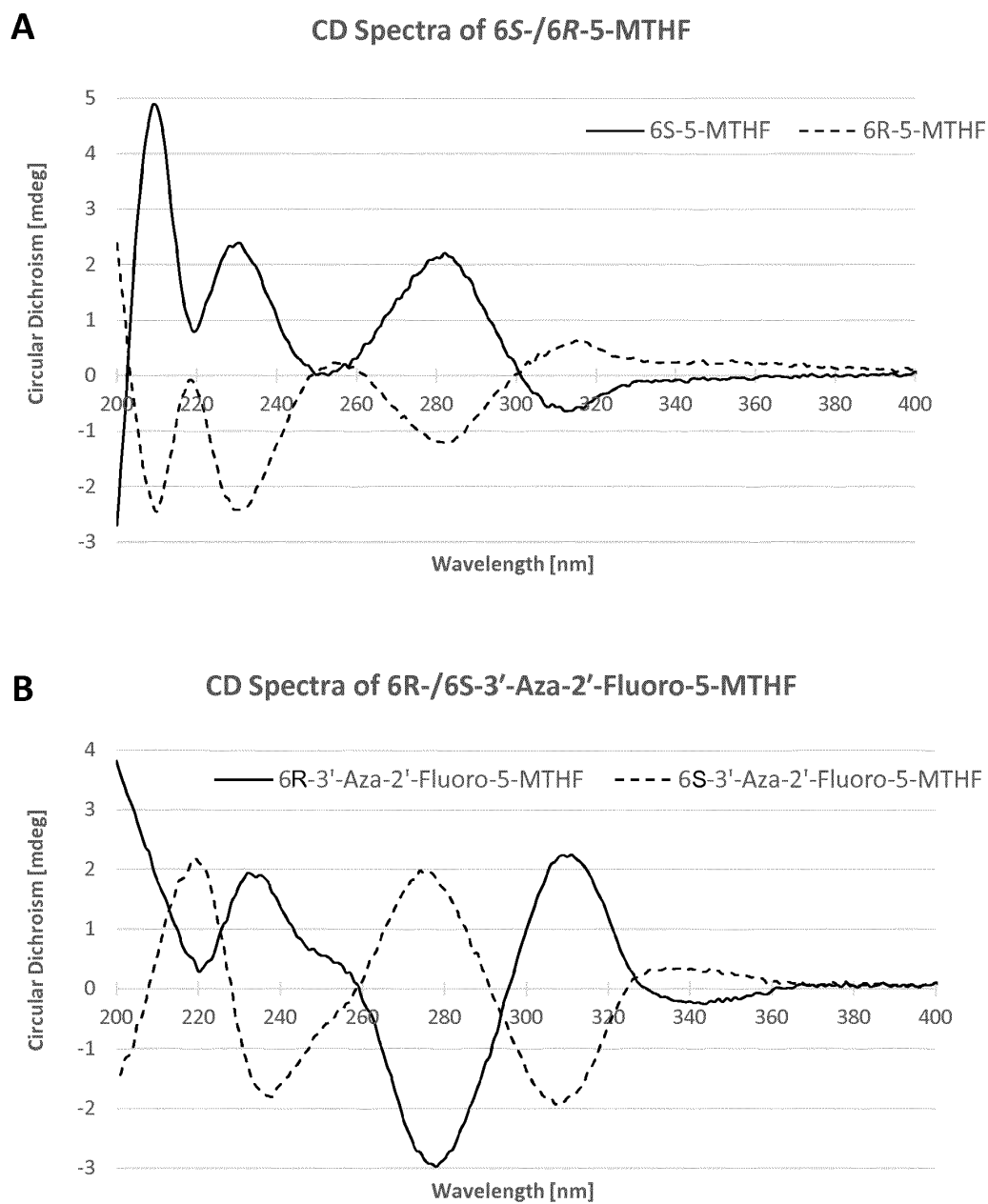


Figure 2. CD spectra of 6S- and 6R-5-MTHF (A) and 6R-1 and 6S-1 (B) measuring from 400 nm to 200 nm.

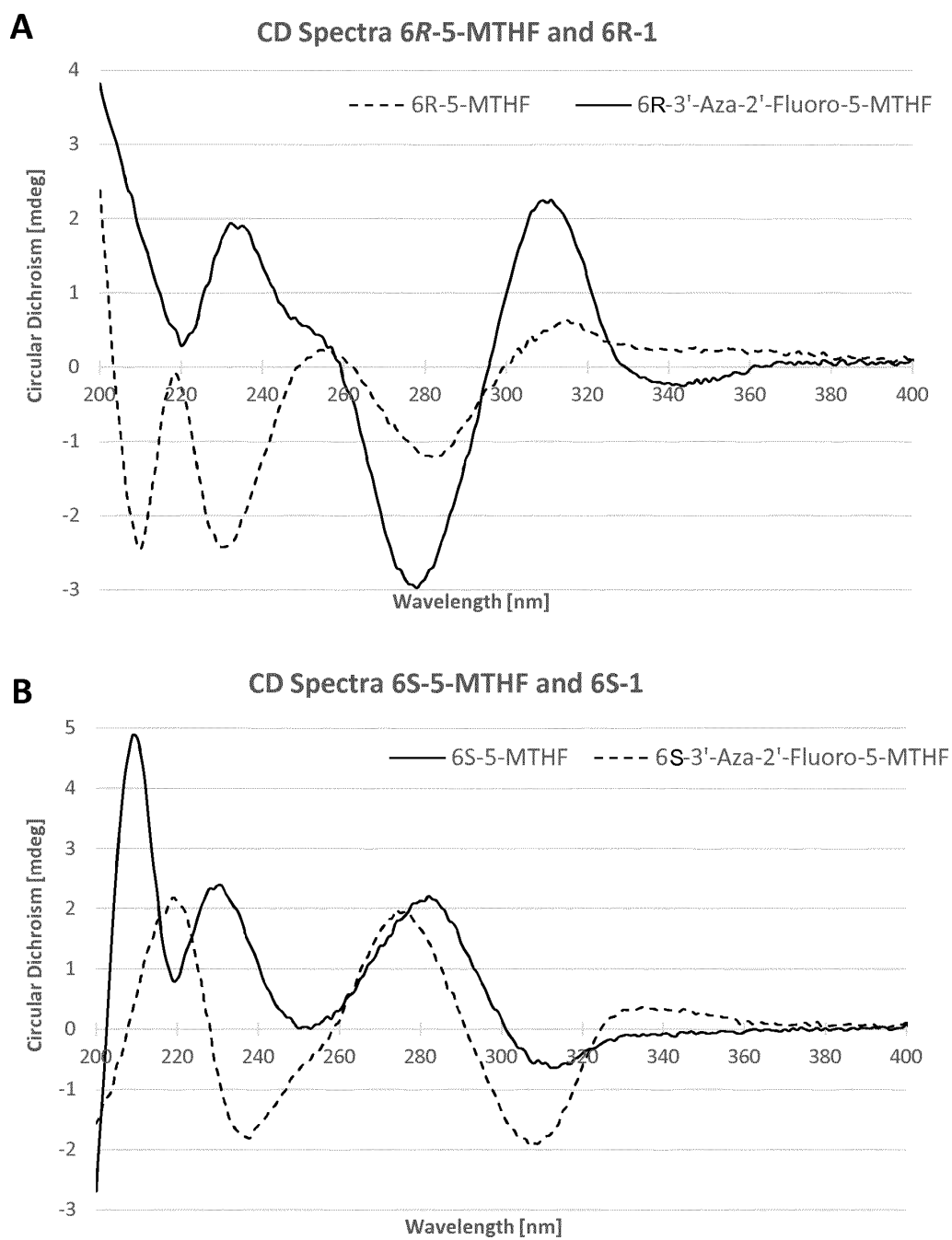


Figure 3. Overlay of the CD spectra of 6R-5-MTHF and 6R-3'-aza-2'-fluoro-5-MTHF (A) and 6S-5-MTHF and 6S-3'-aza-2'-fluoro-5-MTHF (B).

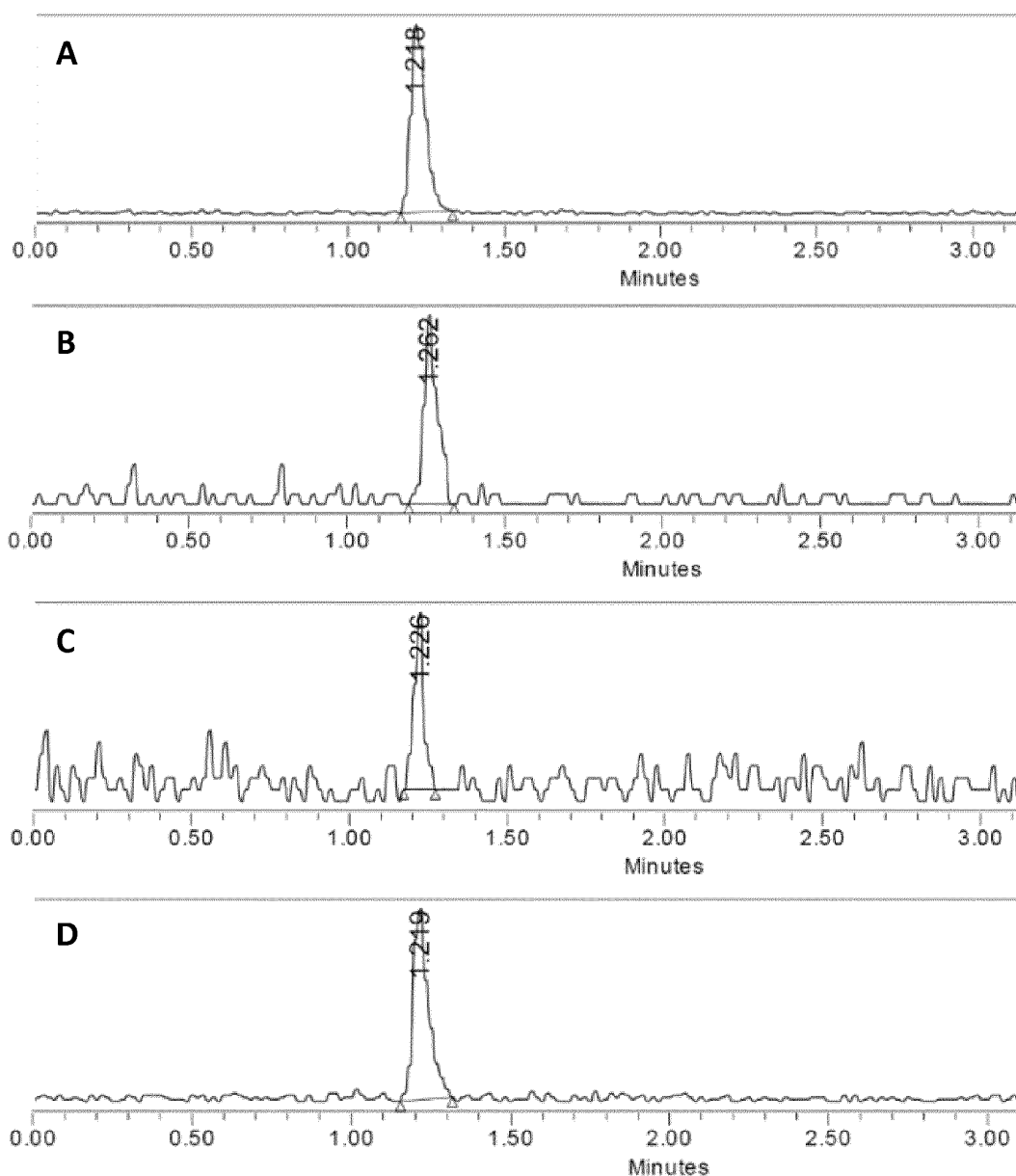


Figure 4. Radio-UPLC chromatograms of reference radiotracer 6S/6R-[¹⁸F]1 (A), liver sample (B), blood plasma (C) and urine sample (D) 60 min after injection of 6S/6R-[¹⁸F]1. Retention time is indicated above the peak.

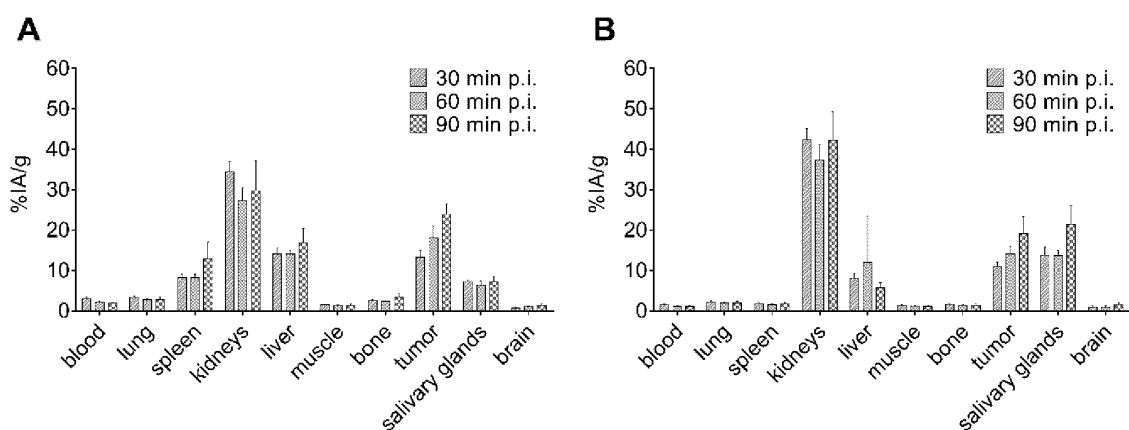


Figure 5. Radioactivity accumulation of 6R-3'-aza-2'-[^{18}F]fluoro-5-MTHF (A) and 6S-3'-aza-2'-[^{18}F]fluoro-5-MTHF (B) in some selected tissues at 30, 60 and 90 min p.i..

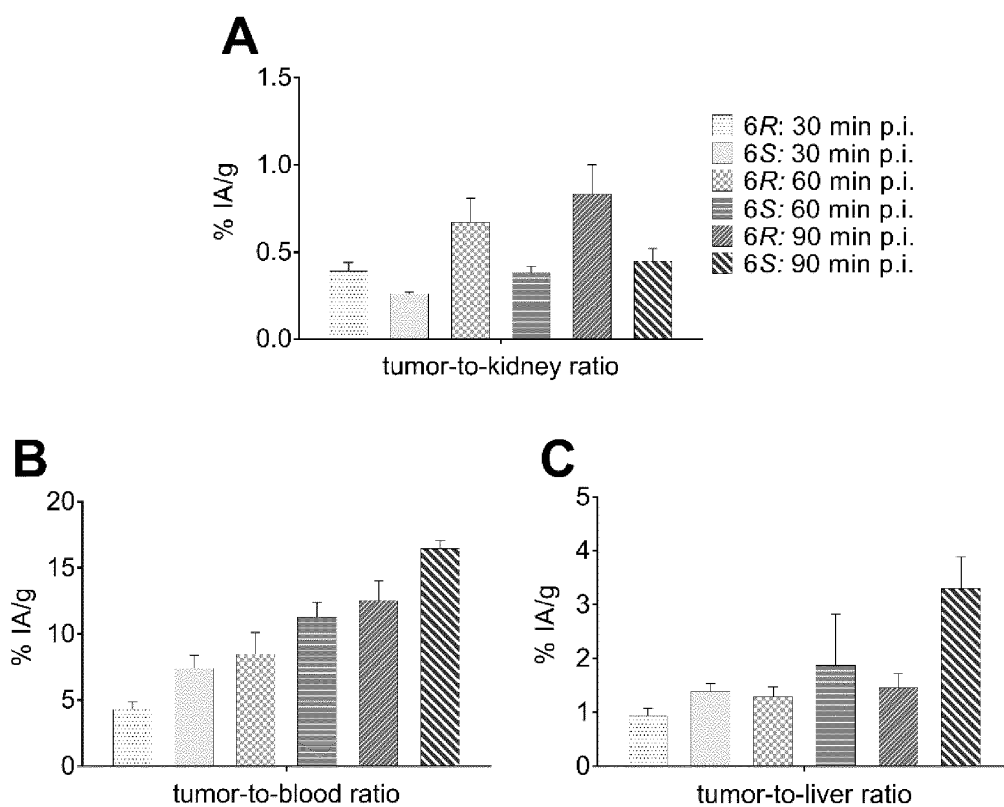


Figure 6. Comparison of the tumor-to-kidney (A), tumor-to-blood (B) and tumor-to-liver (C) ratios of 6R-[^{18}F]1 and 6S-[^{18}F]1.

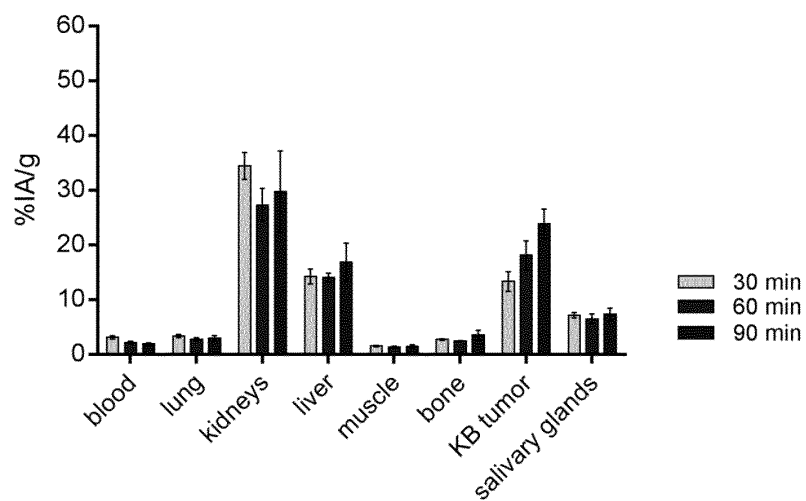


Figure 7. Tissue distribution profile at 30, 60 and 90 min after injection of ^{18}F -6R-5Me-AzaTHF.

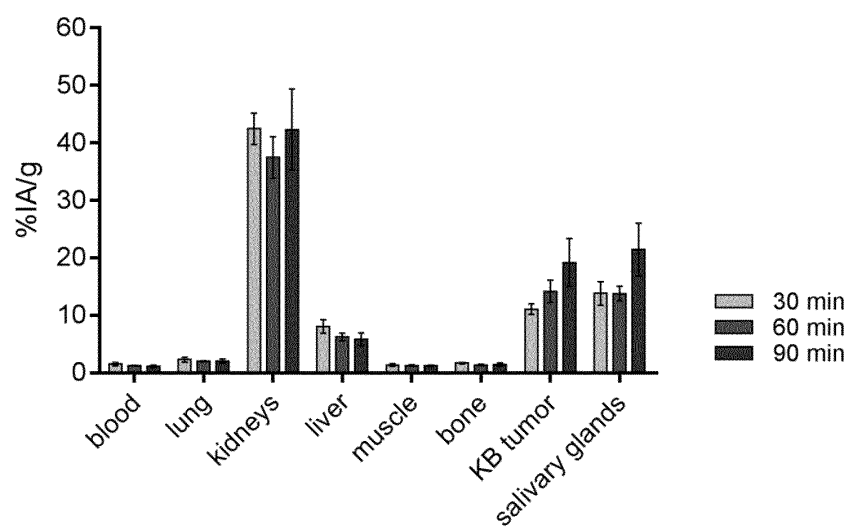


Figure 8. Tissue distribution profile at 30, 60 and 90 min after injection of ^{18}F -6S-5Me-AzaTHF.

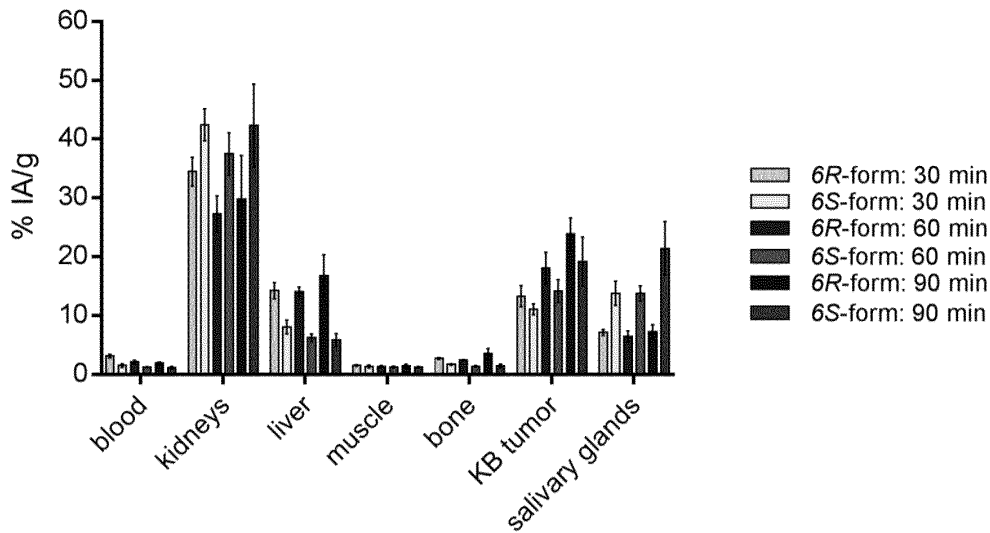


Figure 9. Comparison of the tissue distribution profile of ^{18}F -6R-5Me-AzaTHF (6R-form) and the ^{18}F -6S-5Me-AzaTHF (6S-form).

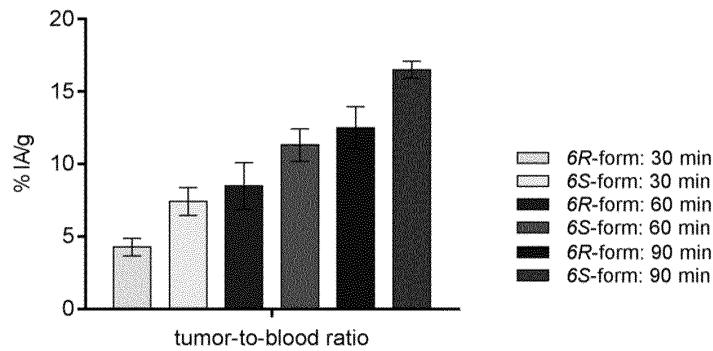


Figure 10. Comparison of the tumor-to-blood ratios of ^{18}F -6R-5Me-AzaTHF (6R-form) and the ^{18}F -6S-5Me-AzaTHF (6S-form).

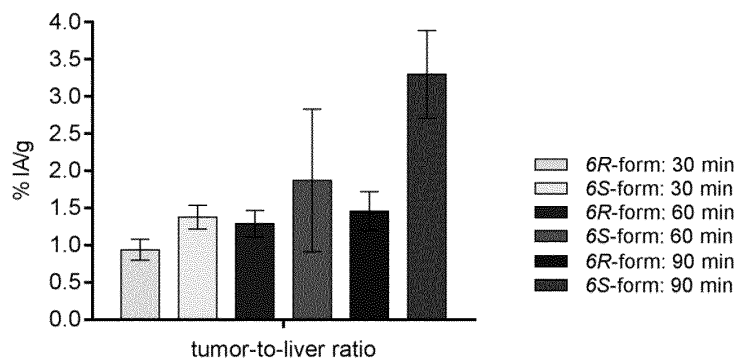


Figure 11. Comparison of the tumor-to-liver ratios of ^{18}F -6R-5Me-AzaTHF (6R-form) and the ^{18}F -6S-5Me-AzaTHF (6S-form).

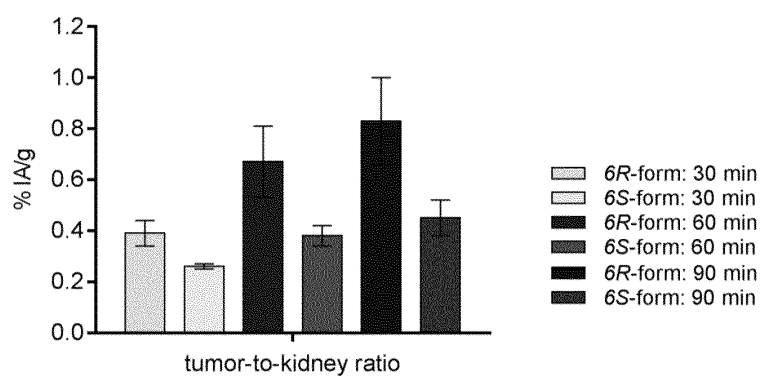


Figure 12. Comparison of the tumor-to-kidney ratios of ^{18}F -6R-5Me-AzaTHF (6R-form) and the ^{18}F -6S-5Me-AzaTHF (6S-form).

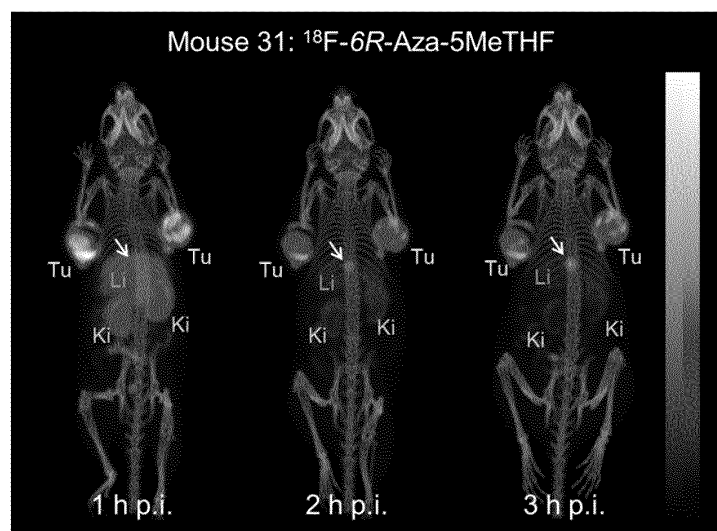


Figure 13. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of ^{18}F -6R-Aza-5MeTHF. (Tu = tumor xenografts, Li = liver, Ki = kidney, white arrow = gall bladder).

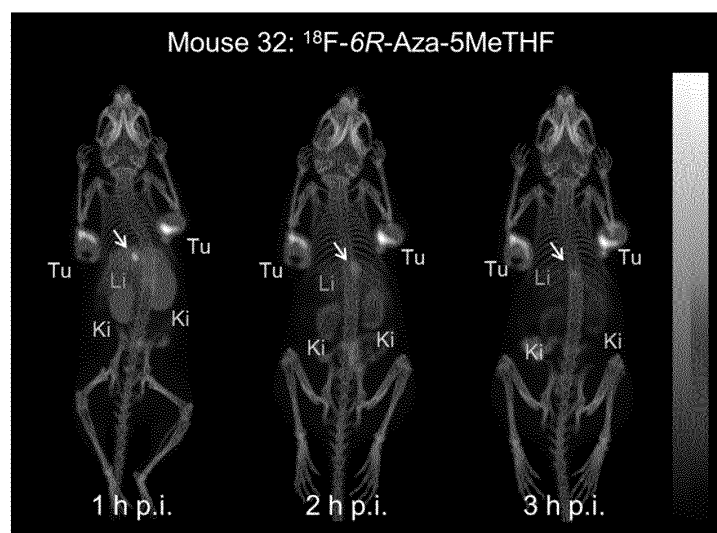


Figure 14. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of ^{18}F -6R-Aza-5MeTHF. (Tu = tumor xenografts, Li = liver, Ki = kidney, white arrow = gall bladder).



Figure 15. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of excess folic acid prior to ^{18}F -6R-Aza-5MeTHF. (Li = liver, white arrow = gall bladder).



Figure 16. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of ^{18}F -6S-Aza-5MeTHF. (Tu = tumor xenografts, Ki = kidney, SG = salivary glands, white arrow = gall bladder, green arrow = choroid plexus).

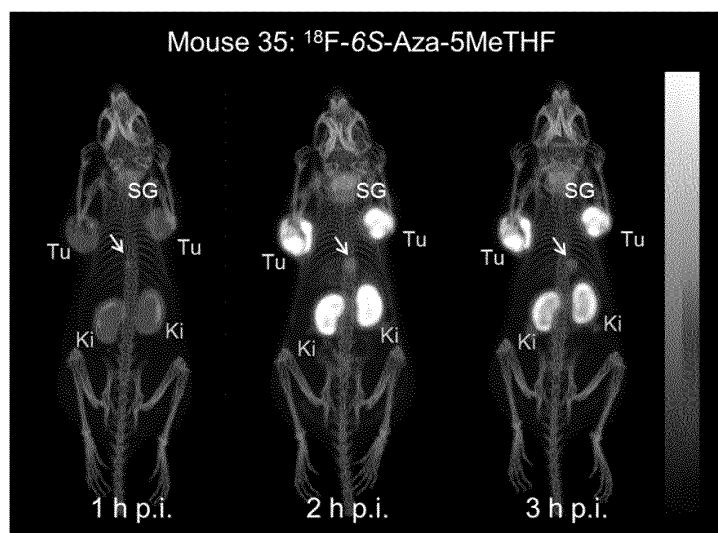


Figure 17. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of ^{18}F -6S-Aza-5MeTHF. (Tu = tumor xenografts, Ki = kidney, SG = salivary glands, white arrow = gall bladder, green arrow = choroid plexus).

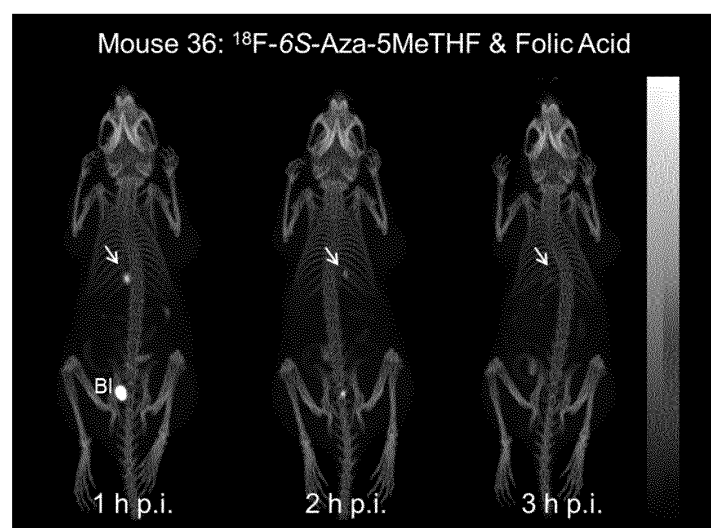


Figure 18. PET/CT scans of a KB tumor-bearing mouse 1 h, 2 h and 3 h after injection of excess folic acid prior to ^{18}F -6S-Aza-5MeTHF. (Bl = urinary bladder, white arrow = gall bladder).

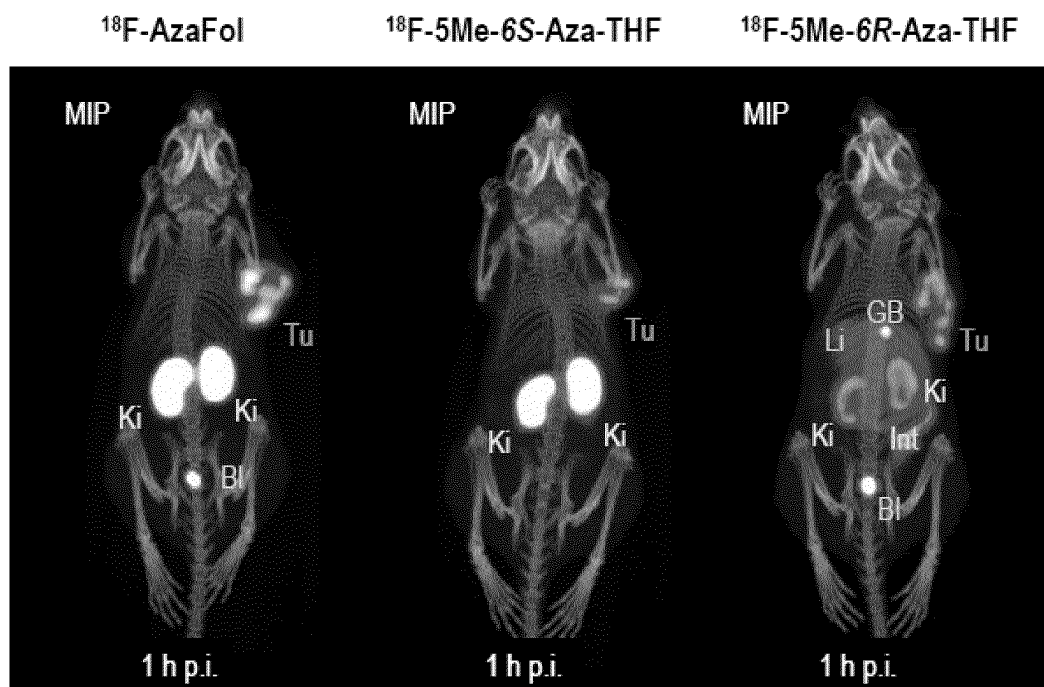


Figure 19. PET/CT scans of a IGROV-1 (human ovarian carcinoma cell line) tumor-bearing mouse 1 h after injection of ^{18}F -AzaFol, ^{18}F -5Me-6S-Aza-THF and ^{18}F -5Me-6R-Aza-THF (Tu = tumor xenografts, Ki = kidney, SG = salivary glands, white arrow = gall bladder, green arrow = choroid plexus).

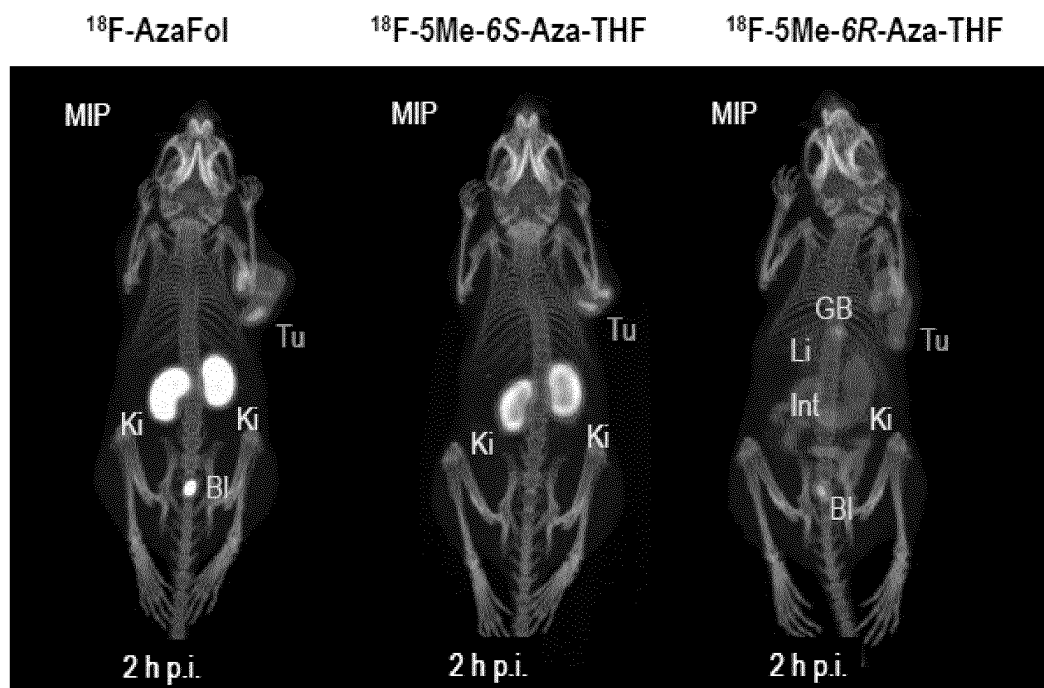


Figure 20. PET/CT scans of a IGROV-1 (human ovarian carcinoma cell line) tumor-bearing mouse 2 h after injection of ^{18}F -AzaFol, ^{18}F -5Me-6S-Aza-THF and ^{18}F -5Me-6R-Aza-THF (Tu = tumor xenografts, Ki = kidney, SG = salivary glands, white arrow = gall bladder, green arrow = choroid plexus).

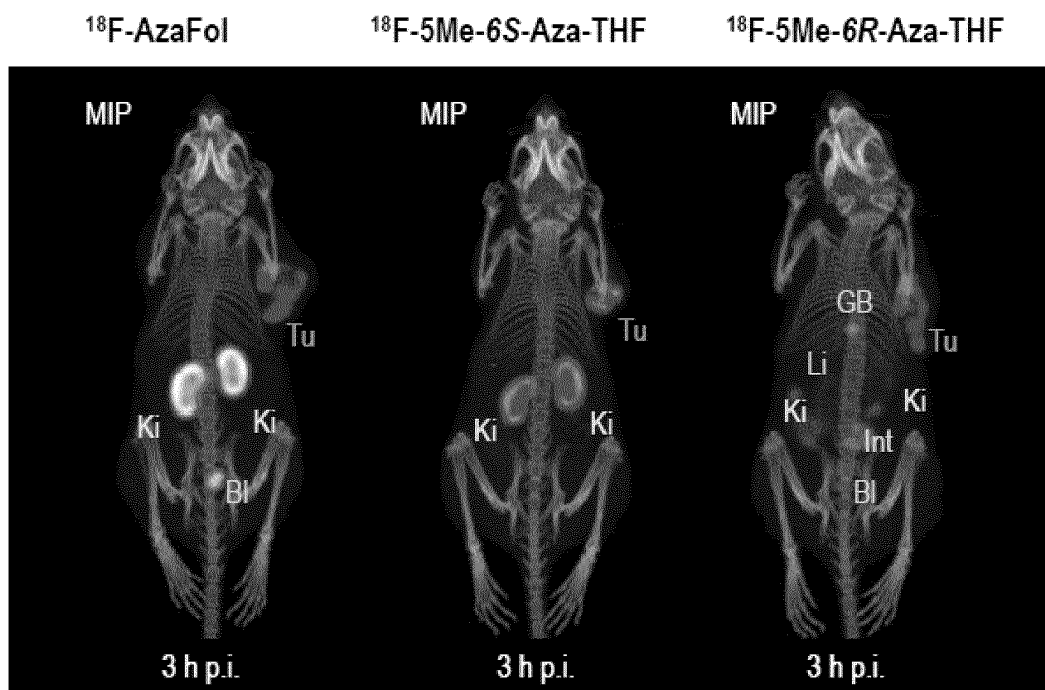


Figure 21. PET/CT scans of a IGROV-1 (human ovarian carcinoma cell line) tumor-bearing mouse 3 h after injection of ¹⁸F-AzaFol, ¹⁸F-5Me-6S-Aza-THF and ¹⁸F-5Me-6R-Aza-THF (Tu = tumor xenografts, Ki = kidney, SG = salivary glands, white arrow = gall bladder, green arrow = choroid plexus).

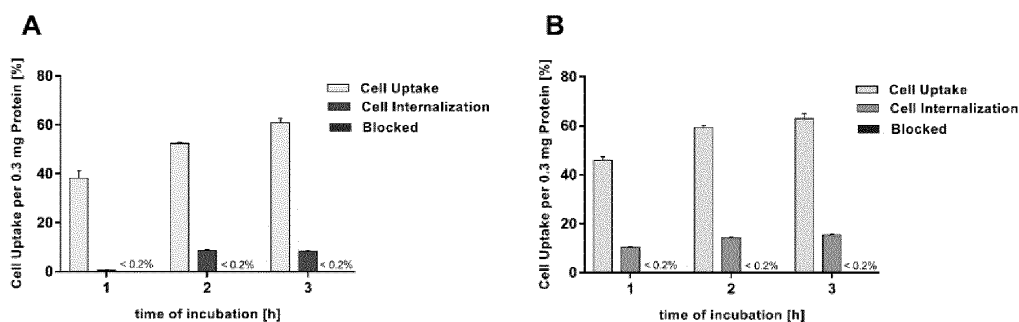


Figure 22. Uptake and internalization of $6R$ -[^{18}F]1 (A) or $6S$ -[^{18}F]1 (B) with FR-positive KB cells incubating at 37 °C for 1, 2, or 3 h. Blocking studies were performed using an excess of folic acid.

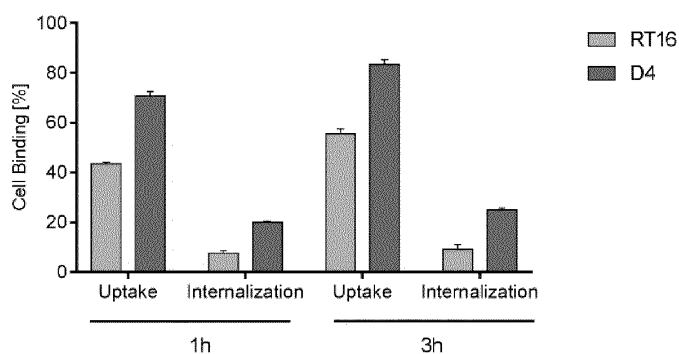


Figure 23. Total uptake and internalization of ^{18}F -AzaFol, using RT16 (FR- α) and D4 (FR- β) cell lines.

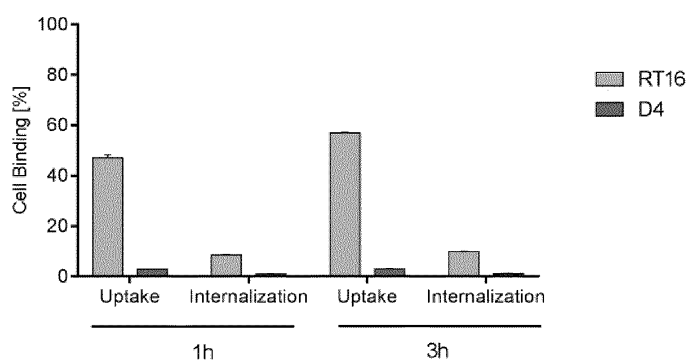


Figure 24. Total uptake and internalization of 6R-3-aza-2-¹⁸F-5-MTHF using RT16 (FR-α) and D4 (FR-β) cell lines.

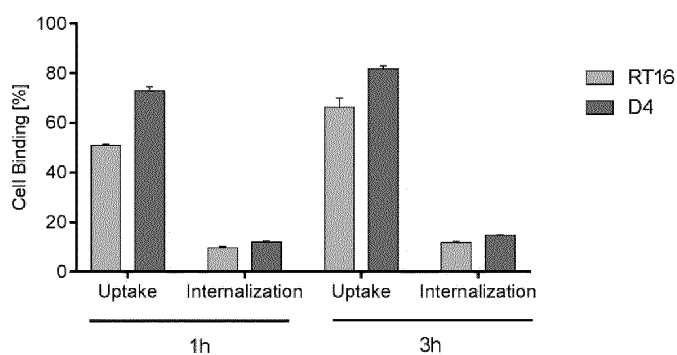


Figure 25. Total uptake and internalization of 6S-3-aza-2-¹⁸F-5-MTHF using RT16 (FR-α) and D4 (FR-β) cell lines.

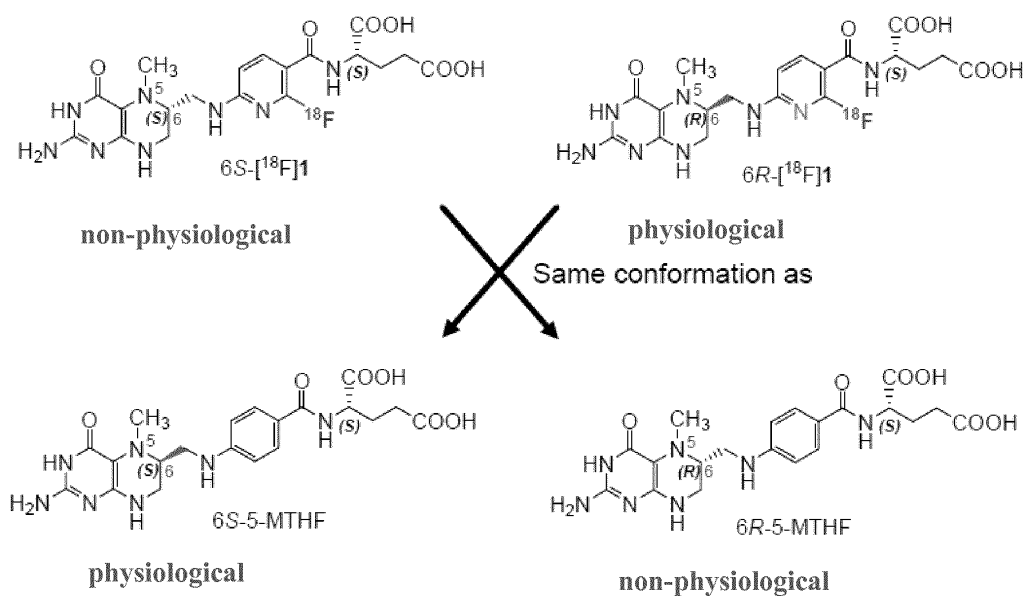


Figure 26. Structure and stereochemical denomination of reduced ^{18}F -folates and unfluorinated isomers.