^{11}C-Labeled rifampicin

[^{11}C]RIF

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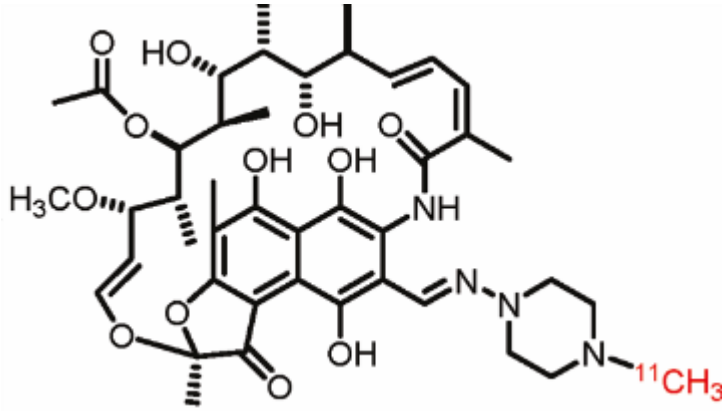
Chemical name:	^{11}C-Labeled rifampicin
Abbreviated name:	[^{11}C]RIF
Synonym:	^{11}C-Labeled rifampin
Agent Category:	Compounds
Target:	DNA-dependent RNA polymerase in bacterial cells
Target Category:	Enzymes (bacteria)
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



Structure of [^{11}C]RIF by Liu et al (1). Click on the PubChem for additional information.

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Background

[PubMed]

Rifampicin (RIF) (or rifampin) is a rifamycin derivative with a clinically effective group of 4-methyl-1-piperazinaminyl. RIF is typically used to treat *Mycobacterium* infections, including tuberculosis (TB) (1, 2). By binding the β subunit, RIF inhibits the DNA-dependent RNA polymerase and thus prevents RNA and protein synthesis in bacterial cells (2, 3). RIF labeled with ^{11}C ([^{11}C]RIF) has been generated by Liu et al. for *in vivo* and real-time analysis of the RIF pharmacokinetics (PK) and biodistribution with positron emission tomography (PET) (1). The half-life of ^{11}C is 20.4 min.

The PK and biodistribution of a novel drug are traditionally determined with blood and tissue sampling and/or autoradiography. Despite high workload and huge investment in drug development, only 8% of the drugs entering clinical trials today reach the market as estimated by the U.S. Food and Drug Administration. One main reason for this attrition is insufficient exploration of the *in vivo* drug-target interaction (1). Traditional methods are inadequate to answer questions such as whether a drug reaches the target, how the drug interacts with its targets, and how the drug modifies the diseases. Because of the high resolution and sensitivity of newly developed imaging techniques, investigators have become increasingly interested in addressing these issues (4, 5). In the case of PET imaging, most small molecules can now be efficiently labeled with ^{11}C or with ^{18}F at >37 GBq/μmol (1 Ci/μmol), and they can be detected with PET in the nanomolar to picomolar concentration range (6-8). Consequently, a sufficient signal for imaging can be obtained even though the total amount of a radiotracer administered systemically is extremely low (known as microdosing, typically <1 μg for humans). Microdosing is particularly valuable for evaluating tissue exposure in the early phase of drug development when the full-range toxicology is not yet available (9, 10). Increasing evidence has demonstrated the efficiency of PET imaging in: obtaining quantitative information on drug PK and distribution in various tissues including brain; confirming drug binding with targets and elucidating the relationship between occupancy and target expression/function *in vivo*; assessing drug passage across the blood–brain barrier (BBB) and ensuring sufficient exposure to brain for central nervous system drugs; and dissecting the modifying effects of drugs on diseases (4, 6, 7).

The current treatment regime for drug-sensitive TB involves the use of RIF, isoniazid (INH), pyrazinamide (PZA), and ethambutol or streptomycin for two months, followed by four months of continued dosing with INH and RIF (2, 3). This regime is primarily based on PK studies in serum and efficacy of treatment. The efficacy of each drug for different types of TB such as brain TB and the drug distribution in each compartment of an organ are not well understood. To provide direct insights into these drugs, Liu et al. labeled INH, RIF, and PZA with ^{11}C and investigated their PK and biodistribution in baboons with PET (1). Liu et al. found that the organ distribution and BBB penetration of each drug differed greatly. For [^{11}C]RIF, its ability to penetrate the BBB was lower than that of PZA and INH (PZA > INH). The RIF concentrations in the lungs and brain were

10 times and 3–4 times higher, respectively, than the RIF minimum inhibitory concentration (MIC) value against TB, supporting the use of RIF for treating TB infections in the lungs and the central nervous system. This chapter summarizes the data of [^{11}C]RIF obtained by Liu et al. The data obtained with [^{11}C]INH and [^{11}C]PZA were described in the MICAD chapters on [^{11}C]INH and [^{11}C]PZA, respectively.

Related Resource Links:

- Challenge and Opportunity on the Critical Path to New Medical Products, FDA
- Rifamycin derivatives in PubChem Substance
- Clinical trials for diagnosis and treatment of tuberculosis in ClinicalTrials.gov
- MICAD chapters on [^{11}C]INH and [^{11}C]PZA

Synthesis

[PubMed]

Liu et al. first synthesized the demethyl RIF (RIF precursor) and generated the [^{11}C]CH_3I from [^{11}C]CO_2 (1). Radiolabeling of the RIF piperazine moiety with [^{11}C]CH_3I was then accomplished with potassium carbonate and the combination of dimethyl sulfoxide and MeCN. The labeled product was subsequently purified, and ascorbic acid was added to prevent oxidation. The average decay-corrected yield of [^{11}C]RIF, calculated from [^{11}C]CH_3I, was 15–25% with a total synthesis time of 50 min. [^{11}C]RIF was >99% radiochemically pure with a specific activity of 21.46 GBq/μmol (580 mCi/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The lipophilicity (logD) of [^{11}C]RIF was measured on the basis of octanol–water partitioning. The plasma protein binding (% of free fraction in plasma) of [^{11}C]RIF was determined after incubation with baboon plasma for 10 min at room temperature. The logD was 1.67 and the plasma protein binding was 27.32%, which are similar to literature values reported elsewhere (1).

Animal Studies

Rodents

[PubMed]

No references are currently available.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

Liu et al. studied the biodistribution of [^{11}C]RIF in healthy baboons (n = 4) with PET imaging (1). The RIF concentrations in the brain and other organs were estimated on the basis of the weight of the baboon (17 kg), a standard drug dose (20 mg/kg), and the assumption that the positron signal derives primarily from the intact drug. Studies showed that the penetrating ability of [^{11}C]RIF and/or its radiolabeled metabolites through the BBB was weaker than that of PZA and INH. The RIF concentration in the brain tissue was higher than in the cerebrospinal fluid. The concentration in the whole brain was 0.000642% injected dose per cubic centimeter (ID/cc) (1.09 μg/ml) at 30 min, 0.000536% ID/cc (0.912 μg/ml) at 60 min, and 0.000710% ID/cc (1.21 μg/ml) at 90 min after injection, which was three to four times higher than its MIC against TB. The detailed data about the [^{11}C]RIF distribution in other organs were presented in table 2 in the paper published by Liu et al. In general, [^{11}C]RIF showed a moderate distribution in the heart, lungs, and kidneys, and was then concentrated in the liver and gallbladder. In most organs, the RIF concentration exceeded that observed in plasma over the 90-min period except for the cortex of kidney at 60 min. The RIF concentration in the lungs was >10 times higher than its MIC. Liu et al. concluded that the RIF concentrations determined by imaging the distribution of [^{11}C]RIF in healthy baboons were similar to those observed previously in mice, monkeys, and human, while PET imaging provided dynamic data from 0 min to 90 min. The PET imaging results supported the use of RIF for treating TB infections in the lungs and brain (1).

Human Studies

[PubMed]

No references are currently available.

References

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