

# ABSTRACT

Chemical structures of CK-4021586 and its derivatives, labeled M1 through M37. The structures show various modifications to the core molecule, including different linker lengths, functional groups, and stereochemistry. A box highlights the CK-4021586 structure with a \*14C-label.

**CK-4021586**  
\*14C-label

**M1** (CK-4022235) **M2** (CK-4022473) **M3, M4** **M5-M8** **M11** **M12** (CK-4022534) **M15** (CK-4022533)

**M16** **M17, M19** **M18** **M20** **M21-24** **M25** **M26, M27** **M28, M29**

**M30** **M31, M32** **M33** **M34** **M35** **M36** **M37**

### Table 2. Major Components Detected in Plasma and Excreta

## METHODS

- Radioactivity derived from [<sup>14</sup>C]CK-4021586 was rapidly excreted after oral administration.
- Plasma C<sub>max</sub>, AUC<sub>0-inf</sub>, and elimination half-life values for total radioactivity were **7.22 µg eq/mL**, **42.8 µg eq·h/g**, and **5.5 h**, respectively.
- After oral administration to intact rats, means of **29.7%** and **63.3%** of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours.
- **50.5%** of radioactive dose was eliminated in bile after oral dosing, indicating biliary excretion was the major route of elimination. Based on the radioactivity excreted in urine and bile, a minimum of approximately **90.6%** of the orally administered dose was absorbed.
- [<sup>14</sup>C]CK-4021586-derived radioactivity was widely distributed to most tissues by 1 hour in LE male rats with highest distribution to liver, eye uvea, kidney cortex and Harderian and adrenal glands.
- Metabolite profiling and identification results indicated that [<sup>14</sup>C]CK-4021586 was eliminated in rats primarily *via* metabolism.
- Unchanged [<sup>14</sup>C]CK-4021586 was the major circulating component from intact rats and accounted for approximately **37.7%** of the total radioactivity exposure, followed by metabolite **M1 (36.3%)** and metabolite **M2 (9.9%)**.
- Metabolite **M15** was the major component in bile (**28% of dose**).
- Metabolite **M15** was the major component detected in feces from intact rats (**45.8% of dose**).