**Supplementary Information**

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Are Δ9-tetrahydrocannabinol and its major metabolites substrates or inhibitors of placental or human hepatic drug solute-carrier transporters?

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**Supplementary Table S1**: Mass spectrometer conditions

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **Parent/Daughter (m/z)** | **Cone (V)** | **Collision (eV)** |
| THC | 315.2900/123.0800 | 30 | 22 |
| THC-D3 | 318.2900/123.3000 | 31 | 20 |
| 11-OH-THC | 331.2872/193.1584 | 30 | 26 |
| 11-OH-THC-D3 | 334.2872/196.2826 | 30 | 26 |
| THC-COOH | 345.2872/299.2664 | 30 | 20 |
| THC-COOH-D3 | 348.2872/302.2859 | 30 | 20 |

The mass spectrometer was operated in the positive atmospheric pressure chemical ionization mode.

**Supplementary Table S2**: LC-MS/MS gradient

|  |  |
| --- | --- |
| **Time (min)** | **Gradient A%** |
| 0.0 | 90 |
| 0.5 | 90 |
| 5.0 | 5 |
| 6.0 | 5 |
| 6.1 | 90 |
| 8.0 | 90 |

The aqueous (solvent A) and organic (solvent B) phase used were water and acetonitrile containing 0.2% (v/v) acetic acid, respectively. The flow rate was 0.3 mL/min.

**Supplementary Table S3: Coefficient of variation (CV% of triplicate determinations) of the uptake of the cannabinoids by placental or hepatic transporters in the absence (DMSO) and presence of their respective inhibitor**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **OATP2B1** | **CV%** | **DMSO** | | | **10 μM erlotinib** | | |
| **THC** | 2.9 | 22.2 | 12.4 | 2.2 | 24.2 | 7.8 |
| **11-OH-THC** | 30.4 | 11.5 | 11.4 | 10.0 | 11.3 | 4.7 |
| **THC-COOH** | 13.3 | 9.7 | 6.5 | 8.9 | 8.1 | 6.3 |
|  | | | | | | | |
| **OCT3** | **CV%** | **DMSO** | | | **100 μM corticosterone** | | |
| **THC** | 31.7 | 9.3 | 12.3 | 8.1 | 5.7 | 13.9 |
| **11-OH-THC** | 11.8 | 17.8 | 28.1 | 22.9 | 11.5 | 9.5 |
| **THC-COOH** | 13.1 | 8.6 | 18.7 | 5.5 | 6.1 | 8.4 |
|  | | | | | | | |
| **OAT4** | **CV%** | **DMSO** | | | **200 μM bromsulphthalein** | | |
| **THC** | 29.0 | 15.2 | 5.6 | 23.0 | 2.2 | 2.3 |
| **11-OH-THC** | 21.8 | 30.0 | 10.8 | 12.7 | 18.4 | 8.3 |
| **THC-COOH** | 12.3 | 6.8 | 3.7 | 4.9 | 7.3 | 4.4 |
|  | | | | | | | |
| **OATP1B1** | **CV%** | **DMSO** | | | **500 μM rifampin** | | |
| **THC** | 21.9 | 20.1 | 6.7 | 5.1 | 11.9 | 14.7 |
| **11-OH-THC** | 76.9 | 57.8 | 57.1 | 23.3 | 45.5 | 100.0 |
| **THC-COOH** | 7.9 | 7.3 | 17.8 | 4.9 | 7.6 | 4.4 |
|  | | | | | | | |
| **OATP1B3** | **CV%** | **DMSO** | | | **500 μM rifampin** | | |
| **THC** | 7.8 | 8.5 | 79.8 | 4.3 | 2.5 | 80.0 |
| **11-OH-THC** | 23.1 | 15.8 | 26.7 | 23.1 | 20.0 | 23.1 |
| **THC-COOH** | 4.1 | 8.1 | 15.1 | 8.4 | 24.0 | 17.6 |
|  | | | | | | | |
| **OCT1** | **CV%** | **DMSO** | | | **100 μM quinidine** | | |
| **THC** | 19.5 | 26.1 | 10.3 | 50.5 | 9.4 | 13.0 |
| **11-OH-THC** | 20.0 | 28.6 | 14.3 | 18.8 | 30.8 | 18.8 |
| **THC-COOH** | 13.8 | 10.9 | 6.6 | 37.0 | 14.7 | 16.9 |
|  | | | | | | | |
| **OAT2** | **CV%** | **DMSO** | | | **200 μM ketoprofen** | | |
| **THC** | 7.5 | 17.1 | 7.6 | 41.9 | 29.2 | 9.7 |
| **11-OH-THC** | 14.3 | 15.4 | 14.8 | 18.4 | 21.4 | 13.0 |
| **THC-COOH** | 11.6 | 21.3 | 6.0 | 19.0 | 32.8 | 3.3 |
|  | | | | | | | |
| **NTCP** | **CV%** | **DMSO** | | | **1 μM bulevirtide** | | |
| **THC** | 3.3 | 8.2 | 10.7 | 5.3 | 9.8 | 4.5 |
| **11-OH-THC** | 23.5 | 14.8 | 33.3 | 20.6 | 12.8 | 21.4 |
| **THC-COOH** | 5.6 | 18.0 | 10.3 | 5.3 | 6.2 | 23.8 |

**Supplementary Table S4: Coefficient of variation (CV% of triplicate determinations) of the uptake of the prototypic substrates of the placental or hepatic transporters in the absence and presence of their respective prototypic inhibitor (see Table 1) or cannabinoids**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **CV%** | **DMSO** | **Prototypic inhibitor** | **5 μM**  **THC** | **0.3 μM**  **11-OH-THC** | **2.5 μM**  **THC-COOH** |
| **OAPTP2B1** | 42.4 | 3.8 | 27.6 | 8.5 | 13.4 |
| 2.7 | 7.1 | 20.2 | 6.2 | 30.6 |
| 37.3 | 3.4 | 10.9 | 21.2 | 29.5 |
| **OCT3** | 13.4 | 47.4 | 61.8 | 2.1 | 4.5 |
| 57.1 | 95.1 | 4.4 | 12.2 | 5.7 |
| 6.0 | 13.8 | 12.5 | 13.5 | 15.5 |
| **OAT4** | 68.0 | 6.8 | 72.6 | 15.2 | 114.0 |
| 15.7 | 12.7 | 35.5 | 13.8 | 11.9 |
| 2.9 | 18.5 | 9.1 | 21.7 | 10.0 |
| **OATP1B1** | 3.2 | 90.5 | 18.2 | 9.2 | 11.4 |
| 16.6 | 69.1 | 25.2 | 30.2 | 15.0 |
| 3.3 | 15.3 | 4.7 | 12.9 | 9.3 |
| **OATP1B3** | 3.9 | 26.5 | 15.9 | 4.1 | 4.1 |
| 3.2 | 33.1 | 13.2 | 4.2 | 23.5 |
| 12.0 | 12.5 | 30.5 | 14.2 | 15.8 |
| **OCT1** | 7.9 | 1.2 | 12.4 | 1.6 | 3.8 |
| 10.7 | 9.8 | 20.9 | 4.5 | 32.6 |
| 8.9 | 1.1 | 43.1 | 43.9 | 35.7 |
| **OAT2** | 24.1 | 5.3 | 37.1 | 9.0 | 8.3 |
| 20.2 | 8.3 | 6.3 | 15.4 | 3.6 |
| 7.8 | 3.1 | 8.8 | 27.2 | 16.0 |
| **NTCP** | 7.0 | 17.6 | 8.1 | 12.7 | 14.4 |
| 9.5 | 11.1 | 12.9 | 3.2 | 4.7 |
| 10.2 | 4.9 | 34.1 | 42.3 | 7.6 |