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In Vivo and *in Vitro* Metabolic Fate and Urinary Detectability of Five Deschloroketamine Derivatives Studied by Means of Hyphenated Mass Spectrometry

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Keywords: new psychoactive substance; deschloroketamine; deschloro-*N*-ethyl-ketamine; deschloro-*N*-isopropyl-ketamine; deschloro-*N*-cyclopropyl-ketamine; deschloro-*N*-propyl-ketamine; metabolism; *in vivo*; *in vitro*; LC-HRMS/MS;

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Fable S1. List of *in vivo* phase I and II metabolites of 2-oxo-PCcP, identified in rat urine samples and *in vitro* phase I metabolites identified in incubations using pooled human liver microsomes (pHLM), including the respective metabolite ID, metabolic reaction, masses of the precursor ion (PI) and characteristic fragment ions (FI) detected in MS², calculated exact masses, elemental composition, calculated mass errors in parts per million (ppm), retention times (RT) in minutes, and system in which metabolites were identified. The metabolites are sorted by their mass and RT. pHLM, identified in pHLM incubations; rat, identified in rat urine samples

| Metabolite ID | Metabolic | Characteristic Ions Calculated Exac | | t Elemental | Error, ppm | RT, min | Identified in |
|---------------|-----------------|--------------------------------------|---------------|---------------------------------|------------|---------|---------------|
| | Reaction | Measured Accurate | Masses, m/z | Composition | | , | |
| | | Masses | | 1 | | | |
| 2-Oxo-PCcP | Parent | PI at <i>m</i> / <i>z</i> 230.1537 | 230.1539 | C15H20ON | -0.91 | 5.70 | pHLM and rat |
| | compound | FI at <i>m/z</i> 212.1430 | 212.1434 | C15H18N | -1.68 | | |
| | 1 | FI at <i>m/z</i> 173.0958 | 173.0961 | C12H13O | -1.63 | | |
| | | FI at <i>m/z</i> 155.0849 | 155.0855 | C12H11 | -4.04 | | |
| | | FI at <i>m/z</i> 145.1009 | 145.1012 | C11H13 | -1.76 | | |
| | | FI at <i>m/z</i> 129.0697 | 129.0699 | C10H9 | -1.12 | | |
| | | FI at <i>m/z</i> 117.0698 | 117.0699 | C9H9 | -0.78 | | |
| | | FI at <i>m/z</i> 91.0546 | 91.0542 | C7H7 | 3.72 | | |
| | | FI at <i>m</i> / <i>z</i> 58.0659 | 58.0651 | C ₃ H ₈ N | 13.0 | | |
| CM1 | N-Dealkylation | PI at <i>m</i> / <i>z</i> 190.1222 | 190.1226 | C12H16ON | -2.52 | 5.06 | pHLM and rat |
| | - | FI at <i>m/z</i> 173.0961 | 173.0961 | C12H13O | -0.05 | | - |
| | | FI at <i>m</i> / <i>z</i> 155.0854 | 155.0855 | C12H11 | -0.94 | | |
| | | FI at <i>m/z</i> 145.1011 | 145.1012 | C11H13 | -0.37 | | |
| | | FI at <i>m/z</i> 129.0700 | 129.0699 | C10H9 | 0.89 | | |
| | | FI at <i>m/z</i> 117.0702 | 117.0699 | C9H9 | 2.74 | | |
| | | FI at <i>m/z</i> 91.0548 | 91.0542 | C7H7 | 6.10 | | |
| | | FI at <i>m</i> / <i>z</i> 67.0550 | 67.0542 | C5H7 | 12.0 | | |
| CM2 | N-Dealkylation | + PI at <i>m</i> / <i>z</i> 232.1330 | 232.1332 | $C_{14}H_{18}O_2N$ | -0.90 | 6.81 | rat |
| | acetylation | FI at <i>m/z</i> 173.0959 | 173.0961 | C12H13O | -1.19 | | |
| | - | FI at <i>m</i> / <i>z</i> 145.1015 | 145.1012 | C11H13 | 2.34 | | |
| | | FI at <i>m/z</i> 129.0968 | 129.0699 | C10H9 | -0.41 | | |
| | | FI at <i>m/z</i> 91.0547 | 91.0542 | C7H7 | 5.47 | | |
| | | FI at <i>m</i> / <i>z</i> 67.0549 | 67.0542 | C5H7 | 10.6 | | |
| CM3 | Hydroxylation | PI at <i>m</i> / <i>z</i> 246.1486 | 246.1489 | C15H20O2N | -0.95 | 4.56 | pHLM and rat |
| | isomer 1 | FI at <i>m/z</i> 189.0907 | 189.0910 | $C_{12}H_{13}O_2$ | -1.55 | | |
| | | FI at <i>m/z</i> 171.0804 | 171.0804 | C12H11O | -0.43 | | |
| | | FI at <i>m</i> / <i>z</i> 143.0856 | 143.0855 | C11H11 | 0.31 | | |
| | | FI at <i>m/z</i> 91.0547 | 91.0542 | C7H7 | 4.89 | | |
| | | FI at <i>m</i> / <i>z</i> 58.0660 | 58.0651 | C ₃ H ₈ N | 15.0 | | |
| CM4 | Hydroxylation | PI at <i>m</i> / <i>z</i> 246.1490 | 246.1489 | $C_{15}H_{20}O_2N$ | 0.78 | 4.85 | pHLM and rat |
| | isomer 2 | FI at <i>m/z</i> 189.0912 | 189.0910 | $C_{12}H_{13}O_2$ | 0.95 | | |
| | | FI at <i>m</i> / <i>z</i> 161.0962 | 161.0961 | C11H13O | 0.43 | | |
| | | FI at <i>m</i> / <i>z</i> 107.0496 | 107.0491 | C7H7O | 3.98 | | |
| | | FI at <i>m</i> / <i>z</i> 58.0660 | 58.6051 | C ₃ H ₈ N | 15.2 | | |
| CM5 | N-Dealkylation | + PI at <i>m/z</i> 366.1552 | 366.1547 | C18H24O7N | 1.15 | 5.35 | rat |
| | glucuronidation | FI at <i>m</i> / <i>z</i> 348.1449 | 348.1442 | C18H22O6N | -1.73 | | |
| | | FI at <i>m</i> / <i>z</i> 330.1336 | 330.1336 | $C_{18}H_{20}O_5N$ | -0.77 | | |
| | | FI at <i>m</i> / <i>z</i> 173.0964 | 173.0961 | C12H13O | 1.72 | | |
| | | FI at <i>m</i> / <i>z</i> 145.1014 | 145.1012 | C11H13 | 1.29 | | |
| | | FI at <i>m</i> / <i>z</i> 129.0701 | 129.0699 | C10H9 | 1.60 | | |
| | | FI at <i>m</i> / <i>z</i> 91.0548 | 91.0542 | C7H7 | 6.73 | | |
| | | FI at <i>m</i> / <i>z</i> 67.0551 | 67.0542 | C5H7 | 13.4 | | |

Fable S2. List of *in vivo* phase I and II metabolites of 2-oxo-PCE, identified in rat urine samples and *in vitro* phase I metabolites identified in incubations using pooled human liver microsomes (pHLM), including the respective metabolite ID, metabolic reaction, masses of the precursor ion (PI) and characteristic fragment ions (FI) detected in MS², calculated exact masses, elemental composition, calculated mass errors in parts per million (ppm), retention times (RT) in minutes, and system in which metabolites were identified. The metabolites are sorted by their mass and RT. pHLM, identified in pHLM incubations; rat, identified in rat urine samples

| ReactionMeasesy | Metabolite ID | Metabolic | Characteristic Ions | Calculated Exact | Elemental | Error, ppm | RT, min | Identified in |
|--|---------------|------------------|------------------------------------|------------------|--------------------|------------|---------|---------------|
| Jacobs PCE Parent Pl at m/z 218,1540 218,1359 Cut-fac0N -2.21 5.44 pHLM and rat 2-Oxor-PCE compound Fl at m/z 173,0957 173,0961 CuH alo -2.31 - | | Reaction | Measured Accurate | Masses, m/z | Composition | | | |
| 20-OPCE Function P14 mer 2018.19 P14130 P141300 P141300 P141300 | | | Masses | | | | | |
| compound H at m/z 120.1429 200.1434 CuHaN -2.54 H at m/z 173.0957 173.0961 CuHa -3.66 H at m/z 145.0087 173.0999 CuHa -2.18 H at m/z 112.04697 120.0999 CuHa -2.18 H at m/z 117.0699 117.0699 CuHa -2.18 H at m/z 117.0699 117.0699 CuHa -0.12 H at m/z 100.1225 190.1226 CuHa 9.37 EM1 N-Dealkylation P1 at m/z 100.1225 190.1226 CuHa 0.60 H at m/z 105.0854 155.0855 CuHa 0.60 | 2-Oxo-PCE | Parent | PI at <i>m/z</i> 218.1540 | 218.1539 | C14H20ON | -2.21 | 5.44 | pHLM and rat |
| Fi at m/2 173.0967 I73.0961 CarhaO -1.98 Fi at m/2 155.0851 155.0855 Carha -3.06 Fi at m/2 125.0097 129.0999 Carha -3.06 Fi at m/2 120.097 129.0999 Carha -1.12 Fi at m/2 120.097 129.0990 Carha -1.2 Fi at m/2 10.0545 91.0542 CArh 3.38 Fi at m/2 10.0545 91.0542 CArh 3.38 Fi at m/2 10.0545 91.0542 CArh 0.70 5.04 pHLM and rat Fi at m/2 10.0545 173.0961 CarhaO 0.03 | | compound | FI at <i>m</i> / <i>z</i> 200.1429 | 200.1434 | $C_{14}H_{18}N$ | -2.54 | | - |
| Fi at m/2 155.0851155.0855Carha-3.06Fi at m/2 145.002Fi at m/2 120.0697Carha-2.18Fi at m/2 120.0697120.0699CuHa-1.12Fi at m/2 117.0699117.0699CuHa-0.12Fi at m/2 100.05459.0522CHa-0.12Fi at m/2 100.1226190.1226CuHa9.37EM1N-DealkylationPl at m/2 10.1226CuHa-0.60Fi at m/2 105.0854155.0855CuHu-0.60 | | - | FI at <i>m</i> / <i>z</i> 173.0957 | 173.0961 | C12H13O | -1.98 | | |
| First arms'n 145 1009 145 1012 Curlis -2.18 First arms'n 129.0699 Col-b -1.12 First arms'n 129.0699 Ci-b -0.12 First arms'n 129.0699 Ci-b -0.12 First arms'n 129.0699 Ci-b 3.38 EM1 N-Dealkylation Plat arms'n 107.0961 Carluo 0 0.14 First arms'n 129.0025 190.1226 Carluo 0 0.14 - EM1 N-Dealkylation Plat arms'n 155.0085 Carluo 0 0.14 - First arms'n 155.0085 155.0085 Carluo 0 0.05 - - First arms'n 107.0701 117.0699 Carlu 0 0.05 - - First arms'n 107.0701 117.0699 Carlu 0 0.61 4.75 rat EM2 Hydroxylation + Plat arms'n 201.333 221.332 Carluo 0 0.61 4.75 rat EM3 Hydroxylation to a Flat arms'n 10.41491 241.4149 241.4100 1.61 - - EM3 Hydroxyl | | | FI at <i>m</i> / <i>z</i> 155.0851 | 155.0855 | C12H11 | -3.06 | | |
| Fit at m/2 120,099 129,099 CuHs -1.12 Fit at m/2 17,0099 117,0699 CuHs -0.12 Fit at m/2 17,0099 170,0699 CuHs 3.38 EMI N-Dealkylation P1 at m/2 17,0961 CuHsON -0.78 5.04 pHLM and rat Fit at m/2 17,001 173,0961 CuHsON -0.78 5.04 pHLM and rat Fit at m/2 173,0961 173,0961 CuHsON -0.60 - - Fit at m/2 129,0700 129,0699 CuHs 0.03 - - Fit at m/2 129,0700 129,0699 CuHs 0.89 - - Fit at m/2 129,0700 129,0699 CuHs 0.89 - - Fit at m/2 19,0751 187,0754 CuHsON 0.61 4.75 rat eX14 PI at m/2 19,0754 187,0754 CuHsON 0.61 4.75 rat eX14 PI at m/2 129,0701 123,0142 CuHsON 0.11 - - eX14 161,093 161,085< | | | FI at <i>m</i> / <i>z</i> 145.1009 | 145.1012 | C11H13 | -2.18 | | |
| Fi at m/c 117,0699 Ci-H- -0.12 Fi at m/c 10,0549 67,0542 C:H- 9.37 EM1 N-Dealkylation Pl at m/c 190,1225 190,1226 C:H-IO 0.78 5.04 pHLM and rat Fl at m/c 17,05061 173,0961 173,0961 C:aHi-O 0.60 - - Fl at m/c 175,0585 G:De909 C:aHi-O 0.60 - - - Fl at m/c 170,0701 120,0700 120,0999 C:aHi-O 0.60 - - - Fl at m/c 170,0701 120,0700 120,0999 C:aHi-O 0.61 - - - EM2 Fl at m/c 170,0505 67,0542 C:Hi-O 0.28 - - - EM2 Hydroxylation + Pl at m/c 123,0305 159,0084 C:uHao-O:N 0.61 4.75 rat EM3 Hydroxylation Pl at m/c 121,0805 159,0084 C:uHao-O:N 1.16 - - EM3 Hydroxylation Pl at m/c 121,0805 157 - - <td></td> <td></td> <td>FI at <i>m/z</i> 129.0697</td> <td>129.0699</td> <td>C10H9</td> <td>-1.12</td> <td></td> <td></td> | | | FI at <i>m/z</i> 129.0697 | 129.0699 | C10H9 | -1.12 | | |
| | | | FI at <i>m/z</i> 117.0699 | 117.0699 | C9H9 | -0.12 | | |
| Hat m/z 67.0542 Ceht/z 9.37 EM1 N-Dealkylation PI at m/z 190.1225 190.1226 CuHuON -0.78 5.04 pHLM and rat H at m/z 153.0961 CuHuO 0.14 - </td <td></td> <td></td> <td>FI at <i>m/z</i> 91.0545</td> <td>91.0542</td> <td>C7H7</td> <td>3.38</td> <td></td> <td></td> | | | FI at <i>m/z</i> 91.0545 | 91.0542 | C7H7 | 3.38 | | |
| EM1N-DealkylationPI at m/z 190.1226Ord-BON-0.785.04PILM and ratF1 at m/z 173.0961173.0961CriHuO0.14-0.60F1 at m/z 155.0854155.0855CuHu-0.60F1 at m/z 155.0854155.0857CuHu0.33F1 at m/z 129.0700129.0699CuHu0.89F1 at m/z 129.0700170.099CuHu0.89F1 at m/z 19.035491.0542CHu1.6EM2Hydroxylation + PI at m/z 21.313321.332CuHuON0.614.75KotonF1 at m/z 187.0754187.0754CuHuON0.614.75EM3Hydroxylation + PI at m/z 187.0754187.0754CuHuON0.11F1 at m/z 190.081190.084CuHuON0.111.11F1 at m/z 190.081190.084CuHuON2.961.11EM3HydroxylationF1 at m/z 161.080CuHuON0.371.11F1 at m/z 110.080110.081CuHuON0.371.11F1 at m/z 110.080160.081CuHuON0.371.11F1 at m/z 110.080160.081CuHuON0.371.11F1 at m/z 110.080160.081CuHuON0.611.57F1 at m/z 110.080170.804CuHuON0.634.62PHLM and ratF1 at m/z 120.0701120.0699CuHuO0.634.62PHLM and ratF1 at m/z 120.0701120.0699CuHuO0.634.62PHLM and ratF1 at m/z 110.081161.0961CuHuO0.23 | | | FI at <i>m</i> / <i>z</i> 67.0549 | 67.0542 | C5H7 | 9.37 | | |
| FI at m/z 173.0961 173.0961 CuHuO 0.14 FI at m/z 155.0854 155.0855 CuHu -0.60 FI at m/z 125.0021 125.0855 CuHu -0.60 FI at m/z 129.0700 129.0699 CuHu 0.03 FI at m/z 129.0701 117.06699 CuHu 0.89 FI at m/z 10.0710 117.06699 CuHu 0.61 4.75 FI at m/z 91.0547 91.0542 CuHu 11.6 | EM1 | N-Dealkylation | PI at <i>m</i> / <i>z</i> 190.1225 | 190.1226 | C12H16ON | -0.78 | 5.04 | pHLM and rat |
| Fi at m/2 155.0854 155.0855 Cn/Hn 0.60 Fi at m/2 145.1012 145.1012 Cn/Hn 0.03 Fi at m/2 129.0700 129.0699 CaHe 0.89 Fi at m/2 191.0547 91.0542 CHe 5.65 Fi at m/2 91.0547 91.0542 CHe 5.65 EM2 Hydroxylation + P1 at m/2 232.1333 232.1332 CuHaON 0.61 4.75 rat EM2 Hydroxylation + P1 at m/2 187.0754 187.0754 CuHaON 0.61 4.75 rat EM3 Hydroxylation P P1 at m/2 19.0547 91.0542 CuHaON 0.11 110 110 Fi at m/2 19.0547 91.0542 CuHaON 0.21 4.11 pHLM and rat isomer 1 F1 at m/2 19.0910 159.0804 CuHaON 2.37 110 111 F1 at m/2 19.0910 159.0804 CuHaON 2.21 4.11 pHLM and rat isomer 1 F1 at m/2 19.0910 120.049 CuHaON 0.37 111 111 111 111 F1 at m/2 19.0514 1120.0690 CuHaO 0.37< | | - | FI at <i>m/z</i> 173.0961 | 173.0961 | C12H13O | 0.14 | | - |
| Fi at m/z 145.1012 145.1012 Cn/Hn 0.03 Fi at m/z 129.0700 129.0699 Ca/Hs 0.89 Fi at m/z 117.0701 117.0699 Ca/Hs 2.29 Fi at m/z 19.0547 91.0542 CA/Hs 5.65 EM2 Hydroxylation + P1 at m/z 137 232.1332 Ca/Hs 11.6 EM2 oxidation to a F1 at m/z 187.0754 Ca/Hs 0.11 rat EM3 F1 at m/z 19.0547 19.0542 CA/Hs 0.11 rat EM3 Hydroxylation or F1 at m/z 19.0547 19.0542 CA/Hs 0.11 F1 at m/z 19.0547 19.0542 CA/Hs 0.11 pHLM and rat 19.0542 EM3 Hydroxylation P1 at m/z 241.149 241.1492 Cu/Hs 0.37 F1 at m/z 17.0805 171.0804 Cu/Hs 0.37 F1 at m/z 19.0791 19.0692 F1 at m/z 19.0791 129.0699 Cu/Hs 0.43 4.62 pHLM and rat isomer 1 F1 at m/z 19.0711 129.0699 Cu/Hs <td< td=""><td></td><td></td><td>FI at <i>m</i>/<i>z</i> 155.0854</td><td>155.0855</td><td>C12H11</td><td>-0.60</td><td></td><td></td></td<> | | | FI at <i>m</i> / <i>z</i> 155.0854 | 155.0855 | C12H11 | -0.60 | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | FI at <i>m</i> / <i>z</i> 145.1012 | 145.1012 | C11H13 | 0.03 | | |
| Fl at m/z 117.0701 117.0699 CaHs 2.29 Fl at m/z 91.0547 91.0542 CrH 5.65 Fl at m/z 97.0550 67.0542 CrH 11.6 EM2 Hydroxylation + P1 at m/z 123.133 232.132 CuHsO:N 0.61 4.75 rat coxidation to a ketone Fl at m/z 187.0754 187.0754 CuHsO:N 0.61 4.75 rat EM3 Hydroxylation P1 at m/z 234.1491 234.1489 CuHsO:N 1.21 4.11 pHLM and rat isomer 1 F1 at m/z 161.0389 216.1383 CuHsO:N 2.96 | | | FI at <i>m</i> / <i>z</i> 129.0700 | 129.0699 | C10H9 | 0.89 | | |
| $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$ | | | FI at <i>m</i> / <i>z</i> 117.0701 | 117.0699 | C9H9 | 2.29 | | |
| H at m/z 67.0550 67.0542 CaHz 11.6 EM2 Hydroxylation + PI at m/z 232.1332 CuHaO2N 0.61 4.75 rat exidation to a FI at m/z 187.0754 187.0754 CnHuO0 0.11 EM3 Hydroxylation PI at m/z 19.0547 91.0542 CrHz 5.48 EM3 Hydroxylation PI at m/z 24.1499 CuHuON 1.21 4.11 pHLM and rat isomer 1 FI at m/z 16.1389 216.1383 CuHuON 2.64 -0.01 FI at m/z 171.0805 171.0804 CuHuO 0.37 - - FI at m/z 120.0901 189.0910 CuHuO 0.37 - - FI at m/z 120.0701 129.0699 CuHuO 1.57 - - EM4 Hydroxylation PI at m/z 120.1831 CuHuO1 0.84 - - isomer 2 FI at m/z 143.0855 CuHuO 0.63 4.62 | | | FI at <i>m</i> / <i>z</i> 91.0547 | 91.0542 | C7H7 | 5.65 | | |
| EM2 Hydroxylation + Pl at m/z 232.1333 232.1332 CuHsO:N 0.61 4.75 rat exidation to a Fl at m/z 187.0754 187.0754 CuHuO: 0.28 0.28 ketone Fl at m/z 195.0805 159.0804 CuHuO: 0.28 0.28 EM3 Hydroxylation Pl at m/z 10.9147 91.0542 CH+ 5.48 EM3 Hydroxylation Pl at m/z 12.16.1389 CuHaO2:N 1.21 4.11 pHLM and rat isomer 1 Fl at m/z 110.0805 171.0804 CuHuO 0.37 1.57 Fl at m/z 12.0051 171.0804 CuHuO 0.37 1.84 1.84 H at m/z 12.0701 129.0699 CuHuO 0.63 4.62 pHLM and rat isomer 2 Fl at m/z 12.04.189 CuHuO2:N 0.63 4.62 pHLM and rat isomer 2 Fl at m/z 10.0845 143.0855 CuHu 0.43 4.62 pHLM and rat isomer 2 Fl at m/z 10.0845 143.0855 CuHu 0.28 1.12 1.12 EM4 Hydroxylation Pl at m/z 12.04.189 CuHaO2:N 0.63 </td <td></td> <td></td> <td>FI at <i>m</i>/<i>z</i> 67.0550</td> <td>67.0542</td> <td>C5H7</td> <td>11.6</td> <td></td> <td></td> | | | FI at <i>m</i> / <i>z</i> 67.0550 | 67.0542 | C5H7 | 11.6 | | |
| oxidation to a ketone FI at m/z 187.0754 187.0754 Cu2HuOz 0.28 ketone FI at m/z 159.0805 159.0804 CuHuO 0.11 FI at m/z 190.0805 159.0804 CuHuO 0.11 FI at m/z 190.0805 159.0804 CuHuO 0.11 EM3 Hydroxylation PI at m/z 216.1389 CuHuOz 1.21 4.11 pHLM and rat isomer 1 FI at m/z 189.0910 189.0910 CuHuOz -0.01 | EM2 | Hydroxylation + | PI at <i>m</i> / <i>z</i> 232.1333 | 232.1332 | $C_{14}H_{18}O_2N$ | 0.61 | 4.75 | rat |
| ketoneFl at m/z 159.0803159.0804Cn HuO0.11Fl at m/z 91.0542Cr.Hz5.48EM3HydroxylationPI at m/z 234.149Cl.HzoON1.214.11pHLM and ratisomer 1Fl at m/z 161.0383Cl.HtaON2.96Fl at m/z 161.0365171.0804Cl.HtaO0.37Fl at m/z 161.0965161.0961Cl.HtaO0.37Fl at m/z 1161.0963161.0961Cl.HtaO1.57Fl at m/z 120.0701129.0699CuHo0.84Fl at m/z 19.054891.0542Cr.Hz6.23EM4HydroxylationPI at m/z 234.1490234.1489Cu.HzoOxN0.634.62EM4HydroxylationPI at m/z 243.1490234.1489Cu.HzoOxN0.634.62EM4HydroxylationPI at m/z 234.1490234.1489Cu.HzoOxN0.634.62EM4HydroxylationPI at m/z 243.1490234.1489Cu.HzoOxN0.634.62pHLM and ratisomer 2Fl at m/z 161.081161.0961Cu.HzoOxN0.634.62pHLM and ratisomer 4H at m/z 180.0910Cu.HzoOxN0.634.62pHLM and ratisomer 5FI at m/z 180.0911Cu.HzoOxN0.634.62pHLM and ratisomer 6FI at m/z 161.0961Cu.HzoOxN0.634.62pHLM and ratisomer 7FI at m/z 161.0961Cu.HzoOxN0.634.62pHLM and ratisomer 7FI at m/z 161.0961Cu.HzoOxN0 | | oxidation to a | FI at <i>m/z</i> 187.0754 | 187.0754 | C12H11O2 | 0.28 | | |
| Fi at m/z 91.0547 91.0542 CrHz 5.48 EM3 Hydroxylation PI at m/z 234.1491 234.1489 CuHaoOxN 1.21 4.11 pHLM and rat isomer 1 FI at m/z 1216.1389 216.1383 CuHaoOxN 2.96 1.21 4.11 pHLM and rat Isomer 1 FI at m/z 1210.0309 120.0380 CuHaoOx 0.37 1.21 1.2 | | ketone | FI at <i>m/z</i> 159.0805 | 159.0804 | C11H11O | 0.11 | | |
| EM3 Hydroxylation PI at m/z 234.1491 234.1489 CuHzOrN 1.21 4.11 pHLM and rat isomer 1 FI at m/z 216.1389 216.1383 CuHzOrN 2.96 FI at m/z 171.0805 171.0804 CuHizON 2.96 FI at m/z 171.0805 171.0804 CuHizO 1.57 FI at m/z 129.0701 129.0699 CuHz 1.84 FI at m/z 129.0701 129.0699 CuHz 1.84 EM4 Hydroxylation PI at m/z 234.1489 216.1383 CuHzOrN 0.63 4.62 pHLM and rat isomer 2 FI at m/z 161.1381 216.1383 CuHzOrN 0.63 FI at m/z 129.0701 129.0699 CuHz 0.44 FI at m/z 129.0701 129.0699 CuHz 0.45 EM4 Hydroxylation FI at m/z 216.1381 216.1383 CuHzOrN 0.63 4.62 pHLM and rat isomer 2 FI at m/z 189.0910 CuHzOrN 0.63 FI at m/z 189.0912 189.0910 CuHzOrN 0.28 FI at m/z 129.0701 129.0699 CuHz 1.12 FI at m/z 129.0701 129.0699 CuHz 0.28 FI at m/z 129.0701 129.0694 CuHuO 0.28 FI at m/z 129.0701 129.0695 CuHz 0.23 FI at m/z 129.0701 129.0699 CuHz 0.24 FI at m/z 129.0701 129.0699 CuHz 0.24 FI at m/z 129.0701 129.0699 CuHz 0.24 FI at m/z 129.0703 129.0699 CuHz 0.24 FI at m/z 127.0963 173.0961 CuHzON 0.26 FI at m/z 127.0963 173.0961 CuHzON 0.93 FI at m/z 127.09703 129.0699 CuHz 3.14 FI at m/z 127.09703 12 | | | FI at <i>m/z</i> 91.0547 | 91.0542 | C7H7 | 5.48 | | |
| isomer 1 F at $m/2$ 216.1389 216.1383 C ₁₄ H ₁₈ ON 2.96 F1 at $m/2$ 189.0910 189.0910 C ₁₂ H ₁₃ O ₂ -0.01 F1 at $m/2$ 117.0805 171.0804 C ₁₂ H ₁₃ O 0.37 F1 at $m/2$ 117.0805 171.0804 C ₁₂ H ₁₃ O 0.37 F1 at $m/2$ 117.0805 171.0804 C ₁₂ H ₁₃ O 1.57 F1 at $m/2$ 129.0701 129.0699 C ₁₀ H ₂ 1.84 F1 at $m/2$ 129.0701 129.0699 C ₁₀ H ₂ 0.63 4.62 pHLM and rat isomer 2 F1 at $m/2$ 234.1490 234.1489 C ₁₄ H ₂₃ O ₂₁ N 0.63 4.62 pHLM and rat isomer 2 F1 at $m/2$ 129.0701 129.0690 C ₁₀ H ₂₃ O ₂₁ N 0.63 4.62 pHLM and rat H at $m/2$ 129.0701 129.0690 C ₁₀ H ₂₃ O ₂₁ N 0.63 4.62 pHLM and rat isomer 2 F1 at $m/2$ 216.1381 216.1383 C ₁₄ H ₂₃ O ₂₁ N 0.63 4.62 pHLM and rat H at $m/2$ 110.0911 160.091 C ₁₂ H ₁₃ O 0.28 F1 at $m/2$ 117.0805 171.0804 C ₁₂ H ₁₃ O 0.228 F1 at $m/2$ 129.0701 129.0699 C ₁₀ H ₃ 1.47 F1 at $m/2$ 129.0701 129.0699 C ₁₀ H ₃ 1.47 F1 at $m/2$ 19.0548 91.0542 C ₇ H ₇ 6.57 EM5 N-Dealkylation + P1 at $m/2$ 366.1346 366.1547 C ₁₈ H ₂₄ O _{2N} 0.661 F1 at $m/2$ 130.1329 330.1336 C ₁₆ H ₂₄ O _N 0.61 F1 at $m/2$ 130.1329 330.1336 C ₁₆ H ₂₄ O _N 0.61 F1 at $m/2$ 130.903 173.0961 C ₁₂ H ₁₃ O 0.93 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 129.0703 129.0699 C ₁₀ H ₃ 3.14 F1 at $m/2$ 10.548 91.0542 C ₇ H ₇ 6.32 F1 at $m/2$ 10.548 91.0542 C ₇ H ₇ 11.9 | EM3 | Hydroxylation | PI at <i>m/z</i> 234.1491 | 234.1489 | C14H20O2N | 1.21 | 4.11 | pHLM and rat |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | isomer 1 | FI at <i>m</i> / <i>z</i> 216.1389 | 216.1383 | C14H18ON | 2.96 | | 1 |
| FI at m/z 171.0805 171.0804 CuHnO 0.37 FI at m/z 161.0963 161.0961 CuHuSO 1.57 FI at m/z 143.0856 143.0855 CuHu 0.84 FI at m/z 129.0701 129.0699 CuHs 1.84 EM4 Hydroxylation PI at m/z 124.149 234.1489 CuHsON -6.23 EM4 Hydroxylation PI at m/z 161.081 216.1383 CuHsON -0.84 isomer 2 FI at m/z 171.0805 171.0804 CuHuSON -0.84 FI at m/z 171.0805 171.0804 CuHuSO 1.12 FI at m/z 171.0805 171.0804 CuHuSO -0.23 FI at m/z 171.0805 171.0804 CuHuSO -0.23 FI at m/z 129.0701 129.0699 CuHsO -0.23 FI at m/z 129.0701 129.0699 CuHsO -0.26 FI at m/z 129.0701 129.0699 CuHsO -0.26 FI at m/z 130.055 GuHsON -0.26 5.20 rat EM5 N-Dealkylation + PI at m/z 348.1444 348.1442 CuHsON -0.26 5.20 rat glucuronidation | | | FI at <i>m/z</i> 189.0910 | 189.0910 | C12H13O2 | -0.01 | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | FI at <i>m/z</i> 171.0805 | 171.0804 | C12H11O | 0.37 | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | FI at <i>m/z</i> 161.0963 | 161.0961 | C11H13O | 1.57 | | |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | | | FI at <i>m/z</i> 143.0856 | 143.0855 | C11H11 | 0.84 | | |
| FI at m/z 91.0548 91.0542 CrHz 6.23 EM4 Hydroxylation isomer 2 PI at m/z 234.1490 234.1489 Ci4HasO2N 0.63 4.62 pHLM and rat isomer 2 FI at m/z 216.1381 216.1383 Ci4HisON -0.84 - - FI at m/z 189.0912 189.0910 Ci2HisO2 112 - - - FI at m/z 171.0805 171.0804 Ci2HisO - - - - FI at m/z 161.0961 161.0961 Ci1HisO -0.23 - - - - FI at m/z 129.0701 129.0699 CioHa 1.47 - </td <td></td> <td></td> <td>FI at <i>m/z</i> 129.0701</td> <td>129.0699</td> <td>C10H9</td> <td>1.84</td> <td></td> <td></td> | | | FI at <i>m/z</i> 129.0701 | 129.0699 | C10H9 | 1.84 | | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | | FI at <i>m/z</i> 91.0548 | 91.0542 | C7H7 | 6.23 | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | EM4 | Hydroxylation | PI at <i>m/z</i> 234.1490 | 234.1489 | C14H20O2N | 0.63 | 4.62 | pHLM and rat |
| FI at m/z 189.0912 189.0910 C12H13O2 1.12 FI at m/z 171.0805 171.0804 C12H11O 0.28 FI at m/z 161.0961 161.0961 C11H13O -0.23 FI at m/z 129.0701 129.0699 C10H9 1.47 FI at m/z 91.0548 91.0542 C/H7 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 130.033 173.0961 C12H13O 0.93 - - FI at m/z 129.0703 129.0699 C10H9 3.14 - - - EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat EM5 N-Dealkylation + FI at m/z 348.1444 348.1442 C18H24O5N -2.01 - - FI at m/z 173.0963 173.0961 C12H13O 0.93 - </td <td></td> <td>isomer 2</td> <td>FI at <i>m/z</i> 216.1381</td> <td>216.1383</td> <td>C14H18ON</td> <td>-0.84</td> <td></td> <td>1</td> | | isomer 2 | FI at <i>m/z</i> 216.1381 | 216.1383 | C14H18ON | -0.84 | | 1 |
| FI at m/z 171.0805 171.0804 C12H10 0.28 FI at m/z 161.0961 161.0961 C11H13O -0.23 FI at m/z 143.0856 143.0855 C11H11 0.84 FI at m/z 129.0701 129.0699 C10H9 1.47 FI at m/z 91.0548 91.0542 C7H7 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 330.1329 330.1336 C18H24O7N -0.26 5.20 rat FI at m/z 173.0963 173.0961 C12H13O 0.61 | | | FI at <i>m/z</i> 189.0912 | 189.0910 | C12H13O2 | 112 | | |
| FI at m/z 161.0961 161.0961 C11H13O -0.23 FI at m/z 143.0856 143.0855 C11H11 0.84 FI at m/z 129.0701 129.0699 C10H9 1.47 FI at m/z 91.0548 91.0542 C7H7 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 330.1329 330.1336 C18H22O6N 0.61 | | | FI at <i>m/z</i> 171.0805 | 171.0804 | C12H11O | 0.28 | | |
| FI at m/z 143.0856 143.0855 C11H11 0.84 FI at m/z 129.0701 129.0699 C10H9 1.47 FI at m/z 91.0548 91.0542 C7H7 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 348.1444 348.1442 C18H22O6N 0.61 | | | FI at <i>m/z</i> 161.0961 | 161.0961 | C11H13O | -0.23 | | |
| FI at m/z 129.0701 129.0699 C10H9 1.47 FI at m/z 91.0548 91.0542 C7H7 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 348.1444 348.1442 C18H22O6N 0.61 | | | FI at <i>m/z</i> 143.0856 | 143.0855 | C11H11 | 0.84 | | |
| FI at m/z 91.0548 91.0542 CrHz 6.57 EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C18H24O7N -0.26 5.20 rat glucuronidation FI at m/z 348.1444 348.1442 C18H22O6N 0.61 -2.01 -2.01 FI at m/z 173.0963 173.0961 C12H13O 0.93 -2.01 <td< td=""><td></td><td></td><td>FI at <i>m/z</i> 129.0701</td><td>129.0699</td><td>C10H9</td><td>1.47</td><td></td><td></td></td<> | | | FI at <i>m/z</i> 129.0701 | 129.0699 | C10H9 | 1.47 | | |
| EM5 N-Dealkylation + PI at m/z 366.1546 366.1547 C ₁₈ H ₂₄ O ₇ N -0.26 5.20 rat glucuronidation FI at m/z 348.1444 348.1442 C ₁₈ H ₂₂ O ₆ N 0.61 FI at m/z 330.1329 330.1336 C ₁₈ H ₂₀ O ₅ N -2.01 FI at m/z 173.0963 173.0961 C ₁₂ H ₁₃ O 0.93 FI at m/z 145.1012 145.1012 C ₁₁ H ₁₃ 0.45 FI at m/z 129.0703 129.0699 C ₁₀ H ₉ 3.14 FI at m/z 91.0548 91.0542 C ₇ H ₇ 6.32 FI at m/z 67.0550 67.0542 C ₅ H ₇ 11.9 | | | FI at <i>m/z</i> 91.0548 | 91.0542 | C7H7 | 6.57 | | |
| glucuronidationFI at m/z 348.1444348.1442C18H22O6N0.61FI at m/z 330.1329330.1336C18H20O5N-2.01FI at m/z 173.0963173.0961C12H13O0.93FI at m/z 145.1012145.1012C11H130.45FI at m/z 129.0703129.0699C10H93.14FI at m/z 91.054891.0542C7H76.32FI at m/z 67.055067.0542C5H711.9 | EM5 | N-Dealkylation + | PI at <i>m/z</i> 366.1546 | 366.1547 | C18H24O7N | -0.26 | 5.20 | rat |
| FI at m/z 330.1329 330.1336 C18H20O5N -2.01 FI at m/z 173.0963 173.0961 C12H13O 0.93 FI at m/z 145.1012 145.1012 C11H13 0.45 FI at m/z 129.0703 129.0699 C10H9 3.14 FI at m/z 91.0548 91.0542 C7H7 6.32 FI at m/z 67.0550 67.0542 C5H7 11.9 | | glucuronidation | FI at <i>m</i> / <i>z</i> 348.1444 | 348.1442 | C18H22O6N | 0.61 | | |
| FI at m/z 173.0963173.0961C12H13O0.93FI at m/z 145.1012145.1012C11H130.45FI at m/z 129.0703129.0699C10H93.14FI at m/z 91.054891.0542C7H76.32FI at m/z 67.055067.0542C5H711.9 | | 0 | FI at <i>m</i> / <i>z</i> 330.1329 | 330.1336 | C18H20O5N | -2.01 | | |
| FI at m/z 145.1012145.1012C11H130.45FI at m/z 129.0703129.0699C10H93.14FI at m/z 91.054891.0542C7H76.32FI at m/z 67.055067.0542C5H711.9 | | | FI at <i>m</i> / <i>z</i> 173.0963 | 173.0961 | C12H13O | 0.93 | | |
| FI at m/z 129.0703 129.0699 C10H9 3.14 FI at m/z 91.0548 91.0542 C7H7 6.32 FI at m/z 67.0550 67.0542 C5H7 11.9 | | | FI at <i>m</i> / <i>z</i> 145.1012 | 145.1012 | C11H13 | 0.45 | | |
| FI at <i>m/z</i> 91.0548 91.0542 C ₇ H ₇ 6.32 FI at <i>m/z</i> 67.0550 67.0542 C ₅ H ₇ 11.9 | | | FI at m/z 129.0703 | 129.0699 | C10H9 | 3.14 | | |
| FL at m/z 67.0550 67.0542 C ₅ H ₇ 11.9 | | | FI at <i>m</i> / <i>z</i> 91.0548 | 91.0542 | C7H7 | 6.32 | | |
| | | | FI at m/z 67.0550 | 67.0542 | C5H7 | 11.9 | | |

Table S3. List of *in vivo* phase I and II metabolites of 2-oxo-PCiP, identified in rat urine samples and *in vitro* phase I metabolites identified in incubations using pooled human liver microsomes (pHLM), including the respective metabolite ID, metabolic reaction, masses of the precursor ion (PI) and characteristic fragment ions (FI) detected in MS², calculated exact masses, elemental composition, calculated mass errors in parts per million (ppm), retention times (RT) in minutes, and system in which metabolites were identified. The metabolites are sorted by their mass and RT. pHLM, identified in pHLM incubations; rat, identified in rat urine samples

| Metabolite ID | Metabolic | Characteristic Ions | Calculated Exact | t Elemental | Error, ppm | RT, min | Identified in |
|---------------|------------------|------------------------------------|------------------|--------------------|------------|---------|---------------|
| | Reaction | Measured Accurate | Masses, m/z | Composition | , 11 | , | |
| | | Masses | , | 1 | | | |
| 2-Oxo-PCiP | Parent | PI at <i>m</i> / <i>z</i> 232.1690 | 232.1696 | C15H22ON | -2.71 | 5.95 | pHLM and rat |
| | compound | FI at m/z 214.1596 | 214.1590 | C15H20N | 2.50 | | 1 |
| | 1 | FI at <i>m</i> / <i>z</i> 173.0958 | 173.0961 | C12H13O | -1.54 | | |
| | | FI at <i>m</i> / <i>z</i> 155.0852 | 155.0855 | C12H11 | -2.17 | | |
| | | FI at <i>m</i> / <i>z</i> 145.1009 | 145.1012 | C11H13 | -2.08 | | |
| | | FI at <i>m</i> / <i>z</i> 129.0697 | 129.0699 | C10H9 | -1.00 | | |
| | | FI at <i>m</i> / <i>z</i> 117.0700 | 117.0699 | C9H9 | 0.66 | | |
| | | FI at <i>m</i> / <i>z</i> 91.0546 | 91.0542 | C7H7 | 3.72 | | |
| | | FI at <i>m</i> / <i>z</i> 60.0815 | 60.0808 | $C_3H_{10}N$ | 12.1 | | |
| IM1 | N-Dealkylation | PI at <i>m</i> / <i>z</i> 190.1229 | 190.1226 | C12H16ON | 1.49 | 5.03 | pHLM and rat |
| | - | FI at <i>m</i> / <i>z</i> 173.0962 | 173.0961 | C12H13O | 0.66 | | - |
| | | FI at <i>m</i> / <i>z</i> 155.0856 | 155.0855 | C12H11 | 0.29 | | |
| | | FI at <i>m</i> / <i>z</i> 145.1012 | 145.1012 | C11H13 | 0.45 | | |
| | | FI at <i>m</i> / <i>z</i> 129.0701 | 129.0699 | C10H9 | 1.48 | | |
| | | FI at <i>m</i> / <i>z</i> 117.0702 | 117.0699 | C9H9 | 2.42 | | |
| | | FI at <i>m</i> / <i>z</i> 91.0548 | 91.0542 | C7H7 | 6.07 | | |
| | | FI at <i>m</i> / <i>z</i> 67.0550 | 67.0542 | C5H7 | 12.1 | | |
| IM2 | N-Dealkylation - | + PI at <i>m/z</i> 206.1175 | 206.1176 | $C_{12}H_{16}O_2N$ | -0.38 | 4.78 | pHLM and rat |
| | hydroxylation | FI at <i>m</i> / <i>z</i> 189.0910 | 189.0910 | $C_{12}H_{13}O_2$ | -0.01 | | |
| | | FI at <i>m</i> / <i>z</i> 171.0804 | 171.0804 | C12H11O | 0.02 | | |
| | | FI at <i>m</i> / <i>z</i> 161.0961 | 161.0961 | C11H13O | -0.04 | | |
| | | FI at <i>m</i> / <i>z</i> 143.0856 | 143.0855 | C11H11 | 0.31 | | |
| | | FI at <i>m</i> / <i>z</i> 129.0701 | 129.0699 | C10H9 | 1.37 | | |
| | | FI at <i>m</i> / <i>z</i> 91.0547 | 91.0542 | C7H7 | 5.64 | | |
| IM3 | Hydroxylation | PI at <i>m</i> / <i>z</i> 246.1490 | 246.1489 | $C_{15}H_{20}O_2N$ | 0.66 | 5.22 | rat |
| | isomer 1 + | FI at <i>m</i> / <i>z</i> 187.0755 | 187.0754 | $C_{12}H_{11}O_2$ | 0.77 | | |
| | oxidation to a | FI at <i>m</i> / <i>z</i> 159.0805 | 159.0804 | $C_{11}H_{11}O$ | 0.40 | | |
| | ketone | FI at <i>m</i> / <i>z</i> 91.0547 | 91.0542 | C7H7 | 5.48 | | |
| | | FI at <i>m</i> / <i>z</i> 60.0817 | 60.0808 | C3H10N | 14.6 | | |
| IM4 | Hydroxylation | PI at <i>m</i> / <i>z</i> 248.1644 | 248.1645 | $C_{12}H_{22}O_2N$ | -0.61 | 4.75 | pHLM and rat |
| | isomer 1 | FI at <i>m</i> / <i>z</i> 230.1541 | 230.1539 | $C_{12}H_{20}ON$ | 0.81 | | |
| | | FI at <i>m</i> / <i>z</i> 189.0912 | 189.0910 | $C_{12}H_{13}O_2$ | 0.87 | | |
| | | FI at <i>m</i> / <i>z</i> 171.0805 | 171.0804 | C12H11O | 0.28 | | |
| | | FI at <i>m</i> / <i>z</i> 143.0856 | 143.0855 | C11H11 | 0.84 | | |
| | | FI at <i>m</i> / <i>z</i> 91.0548 | 91.0542 | C7H7 | 6.15 | | |
| | | FI at <i>m</i> / <i>z</i> 60.0817 | 60.0808 | C3H10N | 15.1 | | |
| IM5 | Hydroxylation | PI at <i>m</i> / <i>z</i> 248.1645 | 248.1645 | $C_{15}H_{22}O_2N$ | 0.23 | 5.04 | pHLM and rat |
| | isomer 2 | FI at <i>m</i> / <i>z</i> 189.0910 | 189.0910 | C12H13O | -0.18 | | |
| | | FI at <i>m</i> / <i>z</i> 161.0961 | 161.0961 | C11H13O | -0.09 | | |
| | | FI at <i>m</i> / <i>z</i> 107.0496 | 107.0491 | C7H7O | 4.30 | | |
| | | FI at <i>m</i> / <i>z</i> 60.0816 | 60.0808 | $C_3H_{10}N$ | 14.2 | | |

| IM6 | Hydrovylation | PL at m/z 248 1646 | 248 1645 | $C_{15}H_{22}O_{2}N$ | 0.55 | 5 58 | nHI M and rat |
|-------|------------------|--|----------------------|-----------------------------------|---------|------|------------------|
| 11110 | isomer 3 | FL at m/z 230 1541 | 230 1539 | C15H22O2I | 0.69 | 0.00 | printivi and rat |
| | isonier b | FI at $m/z = 200.1011$ FI at $m/z = 173.0963$ | 173 0961 | $C_{12}H_{13}O$ | 1.02 | | |
| | | FL at m/z 1/5.0000 | 145 1012 | C11H12 | 0.66 | | |
| | | FL at m/z 149.1019 | 129.0699 | | 1 13 | | |
| | | FL at m/z 91 05/8 | 91.0542 | C ₇ H ₇ | 6.23 | | |
| | | FL at m/z 76 0764 | 76.0757 | C2H10ON | 9.24 | | |
| | | FI at m/z 58 0660 | 58.0651 | C3H9N | 15.4 | | |
| IM7 | Dibudrovulation | PI at m/z 264 1593 | 264 1645 | C15H22O2N | -0.45 | 4.61 | rat |
| 11017 | Diffydroxylation | FL at m/z 246 1490 | 204.1049 | $C_{15}H_{22}O_{3}N$ | -0.45 | 4.01 | Iat |
| | | FL at m/z 2240.1490 | 228 1383 | C15H120O2IV | -0.07 | | |
| | | FL at m/z 189 0908 | 189 0910 | | -1 14 | | |
| | | FL at $m/z = 171.0905$ | 171 0804 | $C_{12}H_{13}O_2$ | 0.37 | | |
| | | FI at $m/z = 1/1.0005$ | 143 0855 | C11H11 | 0.63 | | |
| | | FI at m/z 76.0764 | 76.0757 | C ₂ H ₁₀ ON | 9.94 | | |
| | | FI at m/z 58 0660 | 58 0651 | C3H8N | 15.4 | | |
| 11/10 | N Dealladation | \downarrow DI at m/z 266 1542 | 266 1547 | CulturO-N | 1 1 1 2 | 5.22 | rat |
| 1110 | N-DealKylation | F I I at III/2 300.1343 | 249 1442 | C18I I24O/IN | -1.18 | 5.22 | Idi |
| | glucuronidation | FI at $11/2 \ 546.1441$ | 340.1442 220.1226 | $C_{18}\Pi_{22}O_{61}N$ | -0.06 | | |
| | | FI at $m/2 330.1340$ | 330.1330 | $C_{18}H_{20}O_{51}N$ | 1.17 | | |
| | | FI at m/z 1/3.0962 | 173.0961 | C12H13U | 0.47 | | |
| | | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.14 | | |
| | | FI at m/z 129.0/01 | 129.0699 | C10H9 | 1.58 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.58 | | |
| IM9 | Hydroxylation | PI at m/z 424.1966 | 424.1966 | $C_{21}H_{30}O_8N$ | 0.00 | 5.24 | rat |
| | isomer 3 + | FI at m/z 230.1537 | 230.1539 | C15H20ON | -0.85 | | |
| | glucuronidation | FI at m/z 173.0963 | 173.0961 | $C_{12}H_{13}O$ | 1.28 | | |
| | | FI at m/z 145.1013 | 145.1012 | C12H13O | 0.72 | | |
| | | FI at m/z 129.0703 | 129.0699 | C10H9 | 3.06 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.62 | | |
| | | FI at m/z 76.0764 | 76.0757 | C ₃ H ₁₀ ON | 8.90 | | |

Table S4. List of *in vivo* phase I and II metabolites of 2-oxo-PCMe, identified in rat urine samples and *in vitro* phase I metabolites identified in incubations using pooled human liver microsomes (pHLM), including the respective metabolite ID, metabolic reaction, masses of the precursor ion (PI) and characteristic fragment ions (FI) detected in MS², calculated exact masses, elemental composition, calculated mass errors in parts per million (ppm), retention times (RT) in minutes, and system in which metabolites were identified. The metabolites are sorted by their mass and RT. pHLM, identified in pHLM incubations; rat, identified in rat urine samples

| Reaction Measured Accurate Masses Masses Composition Masses 2-Oxo-PCMe Parentt If at mt/2 201-383 204.1383 CaFlacON 0.15 5.10 pHIM and rat 2-Oxo-PCMe Parentt If at mt/2 201-380 204.1383 CaFlacON 0.15 5.10 pHIM and rat 2-Oxo-PCMe Pat mt/2 150055 1550855 CaFlacON 0.03 - <th>Metabolite ID</th> <th>Metabolic</th> <th>Characteristic Ions</th> <th>Calculated Exac</th> <th>t Elemental</th> <th>Error, ppm</th> <th>RT, min</th> <th>Identified in</th> | Metabolite ID | Metabolic | Characteristic Ions | Calculated Exac | t Elemental | Error, ppm | RT, min | Identified in |
|--|---------------|------------------|----------------------|-----------------|--------------------|---------------|---------|---------------|
| Masses Curry Data Parent Pl at m/2 201.383 CuFHsON 0.15 5.10 pHLM and rat 2-Oxo-PCMe Parent Pl at m/2 185.0327 186.1277 CuFHsON 0.15 5.10 pHLM and rat 2-Oxo-PCMe Parent/17.03062 173.0961 C-0FHsO 0.75 FI at m/2 155.055 155.0855 C-MHs 0.015 FI at m/2 150.012 117.0990 C-dHs 0.45 FI at m/2 145.1012 145.1012 CuHs 0.45 FI at m/2 150.05 FI at m/2 150.07 FI at m/2 150.07 <th></th> <th>Reaction</th> <th>Measured Accurate</th> <th>Masses. m/z</th> <th>Composition</th> <th>2.1.01, PP.1.</th> <th></th> <th></th> | | Reaction | Measured Accurate | Masses. m/z | Composition | 2.1.01, PP.1. | | |
| 240xo-PCMe Parent compound PI at m/z 204.1383 PI at m/z 120.022 204.1383 C.JHAON 0.15 5.10 pHLM and rat compound P1 at m/z 120.022 P1 at m/z 120.022 173.0961 C.uHLO 0.035 5.10 pHLM and rat P1 at m/z 120.0700 120.0699 C.uHLO 0.045 1.13 pH at m/z 120.0700 120.0699 C.uHL 0.045 P1 at m/z 120.0700 120.0699 C.uHL 0.045 2.87 pHLM and rat P1 at m/z 10.0548 91.0542 C.HL 6.07 pHLM and rat P1 at m/z 10.0548 91.0542 C.HL 0.84 pHLM and rat P1 at m/z 10.0546 150.0555 C.MH 0.84 pHLM and rat P1 at m/z 10.0545 150.0555 C.MH 0.84 pHLM and rat P1 at m/z 10.0542 C.HH 0.33 pHLM and rat pHLM and rat P1 at m/z 10.0555 67.0542 C.HH 0.33 pHLM and rat P1 at m/z 10.0551 71.0804 C.HH-O 0.55 pHLM and rat P1 at m/z 10.0551 | | | Masses | | | | | |
| compound Fl at m/r 18,127 Ref.1277 CaFlaN 0.03 Fl at m/r 18,0127 Fl at m/r 17,0962 73,0961 CoHnO 0.75 Fl at m/r 18,0102 145,1012 CoHnO 0.45 | 2-Oxo-PCMe | Parent | PI at m/z 204.1383 | 204.1383 | C13H18ON | 0.15 | 5.10 | pHLM and rat |
| n Fl at m/r 173.0962 173.0961 CoFHo 0.075 Fl at m/r 153.0855 155.0855 CaFho 0.01 Fl at m/r 121.002 115.0025 CaFho 0.01 Fl at m/r 121.0070 117.0099 CaHs 1.13 Fl at m/r 121.0070 117.0099 CaHs 2.37 MM1 N-Dealkylation Pl at m/r 120.052 70.1522 CaFho 0.84 Fl at m/r 173.0962 CaFho 0.84 5.00 pHI.M and rat Fl at m/r 173.0962 173.0961 CaFho 0.84 1.13 MM1 N-Dealkylation Pl at m/r 173.0962 CaFho 0.84 1.13 Fl at m/r 173.091 170.099 CaHs 3.23 1.14 1.14 Fl at m/r 173.091 129.099 CaHs 3.23 1.14 1.14 Fl at m/r 173.091 129.099 CaHs 3.23 1.14 1.14 MM2 N-Dealkylation + Pl at m/r 120.0118 20.1176 CaHs-0 0.55 1.14 1.14 1.14 1.14 | | compound | FI at m/z 186.1277 | 186.1277 | C13H16N | 0.03 | | 1 |
| Fit at m/z155.0855155.0855CaHa-0.01Fit at m/z145.1012CaHa0.45Fit at m/z117.0090CaHa1.13Fit at m/z117.0090CaHa2.87Fit at m/z117.0092CAHa2.87MM1N-DealkylationP1 at m/z109.1226CaHa0.48Fit at m/z155.0855CaHa0.481Fit at m/z155.0856CaHa0.481Fit at m/z155.0856CaHa0.481Fit at m/z155.0856CaHa0.481Fit at m/z155.0856CaHa0.481Fit at m/z117.0090CaHa0.481Fit at m/z117.0090CaHa0.481Fit at m/z117.0090CAHa0.331Fit at m/z117.0090CAHa0.351Fit at m/z117.0091117.0090CAHa0.55Fit at m/z117.0092CAHa0.551Fit at m/z117.0091CaHaO0.551Fit at m/z117.0092CAHa0.551Fit at m/z117.0092CaHaO0.551Fit at m/z117.0092CAHa0.551Fit at m/z117.0092CAHaO0.551Fit at m/z117.0094CAHaO0.551Fit at m/z117.0094CAHaO0.585.61Fit at m/z117.0095CAHaO0.585.61 <t< td=""><td></td><td>1</td><td>FI at m/z 173.0962</td><td>173.0961</td><td>C12H13O</td><td>0.75</td><td></td><td></td></t<> | | 1 | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.75 | | |
| Fl at m/z 145.1012 145.1012 CuHa 0.45 Fl at m/z 117.0702 117.0699 CuHa 1.13 Fl at m/z 117.0702 117.0699 CuHa 0.054 Fl at m/z 19.0548 91.0542 CHa 0.27 MMI N-Dealkylation Pl at m/z 170.072 170.0695 CuHaON -2.28 5.00 pHLM and rat Fl at m/z 173.0962 173.0965 CuHaON -2.28 5.00 pHLM and rat Fl at m/z 173.0962 173.0965 CuHaON -2.28 5.00 pHLM and rat Fl at m/z 145.1013 145.1012 CuHa 0.69 - | | | FI at m/z 155.0855 | 155.0855 | C12H11 | -0.01 | | |
| Flat m/z 129.0700 129.0699 CaHb 1.13 Flat m/z 117.0702 117.0699 CaHb 2.87 Flat m/z Flat m/z 67.0542 C.Hb 6.07 Hat m/z 191.1222 190.1226 C.Hb 0.84 MMI N-Dealkylation Flat m/z 190.1220 190.1226 C.Hb 0.84 Flat m/z 113.013 145.0121 CaHb 0.69 172 Flat m/z 112.00548 9.10542 C.Hb 0.33 172 Flat m/z 112.00548 10.542 C.Hb 6.23 172 Flat m/z Flat m/z 147.0703 17.0699 CaHo 0.87 MM2 N-Dealkylation + Plat m/z 147.0149.0912 189.0912 189.0910 CaHo 0.87 Flat m/z 161.0962 161.0961 CaHuO 0.55 171.084 140.085 140.085 Flat m/z 172.0901 129.0699 CaHuO 0.51 140.114.141.114.114.114.114.114.114.114. | | | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.45 | | |
| Fit at m/z 117,0702 117,0709 CiFa 2,87 Hat m/z 91,0548 91,0542 CiH 617 MM1 N-Dealkylation Plat m/z 70,0542 CaHa 2.3 MM1 N-Dealkylation Flat m/z 173,0962 173,0961 CaHaO 0.48 Flat m/z 173,0962 173,0960 CaHa 0.48 | | | FI at m/z 129.0700 | 129.0699 | C10H9 | 1.13 | | |
| Hat m/2 91.0582 CH2 CH2 CH2 L MM1 N-Dealkylation Pl at m/2 67.0551 67.052 CdH2 12.3 MM1 N-Dealkylation Pl at m/2 173.0961 CdHa/O 0.84 5.00 pHLM and rat Fi at m/2 155.0856 155.0855 CdHa 0.69 1.72 1.70 Fi at m/2 155.0856 150.099 CdH4 1.72 1.70 1.70 Fi at m/2 157.0131 145.1012 CdH4 6.23 1.70 1.70 Fi at m/2 10.7013 117.0703 117.0703 17.0891 CdH-0 0.87 1.70 MM2 N-Dealkylation + Pl at m/2 26.01181 200.0176 CdH-0 0.55 1.70 1.70 Fi at m/2 17.0805 17.0804 CdH-0 0.57 1.70 1.70 1.70 1.70 Fi at m/2 17.0805 17.0804 CdH-0 0.51 1.70 1.70 1.70 1.70 Fi at m/2 17.0805 17.0804 CdH-0 0.51 1.70 1.70 1.70 | | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.87 | | |
| Fl at m/z 67.0551 67.0542 CdHz 12.3 MMI N-Dealkylation Pl at m/z 190.1222 190.1226 CuHaON -2.28 5.00 pHLM and rat H at m/z 17.03062 17.3061 CuHaO 0.84 | | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.07 | | |
| MMI N-Dealkylation PI at m/z 190.1222 190.1226 Ca/HaON -2.28 5.00 pHLM and rat H at m/z 173.0961 Ca/HaO 0.84 0.48 Fi at m/z 117.007 173.0961 Ca/HaO 0.44 Fi at m/z 1150.085 55.0855 Ca/Ha 0.48 Fi at m/z 117.007 Fi at m/z 117.007 170.0699 Ca/Ha 0.72 Fi at m/z 117.0703 Fi at m/z 170.0699 Ca/Ha 3.33 Fi at m/z 170.073 Fi at m/z 170.073 Fi at m/z 170.073 Fi at m/z 170.074 Ca/Ha 6.23 MM2 N-Dealkylation F1 at m/z 160.012 180.010 Ca/Ha-Oz 0.87 Fi at m/z 170.009 Ca/Ha 0.87 Fi at m/z 170.020 Fi at m/z 170.021 | | | FI at m/z 67.0551 | 67.0542 | C5H7 | 12.3 | | |
| Fi at m/z 173.0962 173.0961 CnHnO 0.84 Fi at m/z 155.0856 155.0855 CuHn 0.48 Fi at m/z 155.0856 155.0855 CuHn 0.48 Fi at m/z 129.0701 129.0699 CuHn 0.49 Fi at m/z 117.005 177.0690 CuHs 1.72 Fi at m/z 107.051 67.0542 CuHs 6.23 Fi at m/z 47.0551 67.0542 CuHs 0.87 MM2 N-Dealkylation +P1 at m/z 108.0112 206.1176 CuHsO: 0.87 Fi at m/z 171.0805 171.0804 CuHsO: 0.37 4.82 pHLM and rat hydroxylation Fi at m/z 170.0802 161.0961 CuHsO: 0.71 110.001 Fi at m/z 170.0807 170.809 CuHsO: 0.71 110.001 110.001 Fi at m/z 10.012 189.0101 CuHsO: 0.71 110.001 110.001 Fi at m/z 10.012 190.0542 CuHsO: 0.53 110.011 110.011 Fi at m/z 10.021 120.0590 CuHsO: 0.51 110.011 110.011 110.011 110.011 110.011 110.0 | MM1 | N-Dealkylation | PI at m/z 190.1222 | 190.1226 | C12H16ON | -2.28 | 5.00 | pHLM and rat |
| Fi at m/z 155.0856 155.0855 CnHn 0.48 Fi at m/z 145.1012 CnHn 0.69 Fi at m/z 129.0701 129.0699 CuHs 3.33 Fi at m/z 710.584 91.0542 CH 3.33 Fi at m/z 70.0551 67.0521 CH 3.33 MM2 N-Dealkylation + P1 at m/z 70.05181 206.176 CuHsO2N 2.73 4.82 pHLM and rat hydroxylation Fi at m/z 16.09021 189.0910 CuHsO2N 0.87 5.61 7.61 Fi at m/z 161.0982 161.0961 CuHsO2N 0.71 5.61 7.61 7.61 Fi at m/z 161.0982 161.0961 CuHsO2N 0.71 5.61 7.61 7.61 Fi at m/z 170.0803 Fi at M/z 170.0804 CuHsO 0.71 7.7 4.82 PHLM and rat hydroxylation Fi at m/z 180.0971 129.0699 CuHsO 0.71 7.7 4.82 PHLM and rat hydroxylation Fi at m/z 180.0971 129.0699 CuHsO 0.51 7.7 7.7 Hat m/z 170.020 170.0590 CuHsO 0.51 7.61 | | 5 | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.84 | | 1 |
| Fl at m/z 145.1013 145.1012 CnHis 0.69 Fl at m/z 129.0701 129.0699 CnHs 1.72 Fl at m/z 117.0703 117.0699 CnHs 1.72 Fl at m/z 91.0548 91.0542 CnHs 6.23 MM2 N-Dealkylation + Pl at m/z 60.6118 206.1176 CaHs 0.27 8.82 pHLM and rat hydroxylation Fl at m/z 17.0703 170.0690 CaHs 0.27 0.87 9 MM2 N-Dealkylation + Pl at m/z 206.1181 206.1176 CaHs 0.20 0.87 9 Hard m/z 17.0703 170.0690 CaHs 0.20 0.87 143.0857 143.0857 Fl at m/z 13.0857 143.0857 CnHs 0.95 14 145 Fl at m/z 17.0701 129.0690 CaHs 1.48 145 145 Fl at m/z 17.0702 117.0699 CaHs 8.69 141 145 MM3 N-Dealkylation + Pl at m/z 180.1071 206.1176 CaHs/0.N 0.51 rat Fl at m/z 173.0962 173.0961 CaHs/0.N 0.51 <td></td> <td></td> <td>FI at m/z 155.0856</td> <td>155.0855</td> <td>C12H11</td> <td>0.48</td> <td></td> <td></td> | | | FI at m/z 155.0856 | 155.0855 | C12H11 | 0.48 | | |
| Fl at m/2 129.0701 129.0699 CaHo 1.72 H at m/2 117.0703 117.0699 CiHo 3.33 Hat m/2 91.0543 67.0542 CiHo 6.23 MM2 N-Dealkylation + Pl at m/2 20.1818 206.176 CaHo 2.73 4.82 pHLM and rat hydroxylation Fl at m/2 170.0801 180.0910 CaHo 0.55 | | | FI at m/z 145.1013 | 145.1012 | C11H13 | 0.69 | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.72 | | |
| $ \begin{array}{ c c c c c c } Fl at m/z \ 17.0548 & 91.0542 & Ci Hz & 6.23 \\ Fl at m/z \ 7.0551 & 67.0542 & Ci Hz & 12.5 \\ \hline \mbox{MM2} & N-Dealkylation + Pl at m/z \ 206.1176 & Ci Hu Oz & 2.73 & 4.82 & pHLM and rat \\ \mbox{hydroxylation} & Fl at m/z \ 189.0910 & Ci Hu Oz & 0.87 \\ \hline \mbox{Fl at m/z \ 189.0912 & 189.0910 & Ci Hu Oz & 0.55 \\ \mbox{Fl at m/z \ 160.062 & 10.062 & 0.71 \\ \mbox{Fl at m/z \ 160.062 & 10.062 & 0.71 \\ \mbox{Fl at m/z \ 160.062 & 10.062 & 0.71 \\ \mbox{Fl at m/z \ 120.0658 & 143.0855 & Ci Hu 1 & 0.95 \\ \mbox{Fl at m/z \ 120.0659 & Ci Hs & 1.48 \\ \mbox{Fl at m/z \ 120.0701 & 120.0699 & Ci Hs & 1.48 \\ \mbox{Fl at m/z \ 110.0702 & 117.0699 & Ci Hs & 2.87 \\ \mbox{Fl at m/z \ 170.0702 & 117.0699 & Ci Hs & 6.69 \\ \mbox{MM3} & N-Dealkylation + Pl at m/z \ 206.1177 & 206.1176 & Ci Hu Oz & 0.58 \\ Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 6.69 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.51 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.51 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.51 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0702 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.13 \\ \mbox{Fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.13 \\ \mbox{fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.13 \\ \mbox{fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.13 \\ \mbox{fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.13 \\ \mbox{fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0703 & 170.0699 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0704 & 170.0699 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0704 & 170.0690 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0705 & 170.060 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0705 & 170.060 & Ci Hs & 0.14 \\ \mbox{fl at m/z \ 170.0705$ | | | FI at m/z 117.0703 | 117.0699 | C9H9 | 3.33 | | |
| Fl at m/z 67.0551 67.0542 CaHz 12.5 MM2 N-Dealkylation + Pl at m/z 206.118 06.1176 CnHaO2N 2.73 4.82 pHLM and rat hydroxylation Fl at m/z 17.0050 171.080 CnHuO2 0.87 4.82 pHLM and rat hydroxylation Fl at m/z 171.0805 171.080 CnHuO 0.55 4.82 pHLM and rat H at m/z 110.0962 161.0961 CnHuO 0.55 4.82 FL 4.82 FL Fl at m/z 110.0962 161.0961 CnHuO 0.55 5.61 5.61 5.61 7.61 H at m/z 107.072 117.0699 CAHz 8.69 7.61 | | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.23 | | |
| MM2 N-Dealkylation + PI at m/z 206.1181 206.1176 Cn:HisO2N 2.73 4.82 pHLM and rat hydroxylation FI at m/z 189.0912 189.0910 Cn:HisO2 0.87 0.87 FI at m/z 1190.0912 189.0910 Cn:HisO2 0.87 0.87 0.87 FI at m/z 110.0805 F1 at m/z 10.0961 Cn:HisO 0.71 0.71 0.95 0.71 FI at m/z 110.0805 F1 at m/z 10.0962 Co:HisO 0.87 0.87 0.87 FI at m/z 117.0702 117.0699 CoHs 1.48 0.95 0.71 0.95 0.71 FI at m/z 10.0548 91.0542 C1Hr 6.32 0.71 0.88 5.61 rat MM3 N-Dealkylation + PI at m/z 206.1177 206.1176 Cn:HisON 0.51 0.58 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.14 0.13 0.14 0.13 0.13 0.14 <td></td> <td></td> <td>FI at m/z 67.0551</td> <td>67.0542</td> <td>C5H7</td> <td>12.5</td> <td></td> <td></td> | | | FI at m/z 67.0551 | 67.0542 | C5H7 | 12.5 | | |
| hydroxylation FI at m/z 189.0912 189.0910 CnHnO 0.87 FI at m/z 171.0805 F71.0804 CnHnO 0.55 FI at m/z 140.092 161.0961 CnHnO 0.55 FI at m/z 140.855 H3.0855 CnHnO 0.95 FI at m/z 140.855 H3.0855 CnHn 0.95 FI at m/z 129.0701 129.0699 CnHs 1.48 FI at m/z 19.0548 91.0542 CrHr 6.32 FI at m/z 219.0701 129.0699 CnHs 8.69 MM3 N-Dealkylation + PI at m/z 206.1177 206.1176 CnHsON 0.51 FI at m/z 173.0962 173.0961 CnHsON 0.51 FI at m/z 19.0701 129.0699 CnHsON 1.37 FI at m/z 19.0701 129.0699 CnHsON 1.48 MM4 Hydroxylation FI at m/z 187.0751 <td rowspan="3">MM2</td> <td>N-Dealkylation -</td> <td>+ PI at m/z 206.1181</td> <td>206.1176</td> <td>$C_{12}H_{16}O_2N$</td> <td>2.73</td> <td>4.82</td> <td>pHLM and rat</td> | MM2 | N-Dealkylation - | + PI at m/z 206.1181 | 206.1176 | $C_{12}H_{16}O_2N$ | 2.73 | 4.82 | pHLM and rat |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | hydroxylation | FI at m/z 189.0912 | 189.0910 | $C_{12}H_{13}O_2$ | 0.87 | | 1 |
| Fl at m/z 161.0962 161.0961 CnHaO 0.71 Fl at m/z 143.0857 143.0855 CnHn 0.95 Fl at m/z 129.0701 129.0699 CoH9 1.48 Fl at m/z 191.0548 91.0542 CHr 6.32 MM3 N-Dealkylation + Pl at m/z 206.1177 206.1176 CaHaOX 0.88 5.61 rat hydroxylamine Fl at m/z 178.0702 173.0961 CnHaOX 0.51 | | 5 5 | FI at m/z 171.0805 | 171.0804 | C12H11O | 0.55 | | |
| Fl at m/z 143.0857 143.0855 CnHn 0.95 Fl at m/z 129.0701 129.0699 CnHs 1.48 Fl at m/z 17.0702 117.0699 CoHs 2.87 Fl at m/z 70.548 67.0542 C4Hr 8.69 MM3 N-Dealkylation + Pl at m/z 206.1177 206.1176 CnHnON 0.51 hydroxylamine Fl at m/z 173.0962 173.0961 CnHaON 0.51 Fl at m/z 171.0702 117.0699 CnHaON 0.51 | | | FI at m/z 161.0962 | 161.0961 | C11H13O | 0.71 | | |
| Fi at m/z 129.0701 129.0699 Cn/H9 1.48 Fi at m/z 117.0702 117.0699 Cn/H9 2.87 Fi at m/z 91.0548 91.0542 C/H7 6.32 MM3 N-Dealkylation + PI at m/z 206.1177 206.1176 Cn/H1xeON 0.88 5.61 rat MM3 N-Dealkylation + PI at m/z 106.1177 206.1176 Cn/H1xeON 0.51 - - Hydroxylamine FI at m/z 188.1071 188.1070 Cn/H1xeON 0.58 - - - FI at m/z 129.0701 129.0699 Cn/H2 0.13 - | | | FI at m/z 143.0857 | 143.0855 | C11H11 | 0.95 | | |
| FI at m/z 117.0702 117.0699 CsH ₉ 2.87 FI at m/z 91.0542 C:H7 6.32 FI at m/z 67.0548 67.0542 C:H7 8.69 MM3 N-Dealkylation + PI at m/z 206.117 206.1176 CuHuoN 0.88 5.61 rat hydroxylamin FI at m/z 173.0962 173.0961 CuHuoN 0.51 - - FI at m/z 173.0962 173.0961 CuHuON 0.58 - <td< td=""><td></td><td></td><td>FI at m/z 129.0701</td><td>129.0699</td><td>C10H9</td><td>1.48</td><td></td><td></td></td<> | | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.48 | | |
| $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$ | | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.87 | | |
| Fl at m/z 67.0548 67.0542 CsH7 8.69 MM3 N-Dealkylation + Pl at m/z 206.1177 206.1176 Cu2HisO2N 0.88 5.61 rat hydroxylamine Fl at m/z 188.1071 188.1070 Cu2HisON 0.51 | | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.32 | | |
| MM3 N-Dealkylation + PI at m/z 206.1177 206.1176 C12HisO2N 0.88 5.61 rat hydroxylamine FI at m/z 188.1071 188.1070 C12HisON 0.51 1 FI at m/z 173.0962 173.0961 C12HisO 0.58 1 1 FI at m/z 145.1012 145.1012 C11His 0.13 1 1 FI at m/z 129.0701 129.0699 C10H9 1.37 1 1 FI at m/z 191.0548 91.0542 CH7 5.81 1 rat MM4 Hydroxylation PI at m/z 218.1172 218.1176 C13HisO2N -1.48 4.61 rat MM4 Hydroxylation PI at m/z 187.0751 187.0754 C12HisO2N -1.48 4.61 rat isomer 1 + FI at m/z 187.0751 187.0754 C12HisO2N -1.48 4.61 rat MM5 Hydroxylation oa FI at m/z 189.002 159.0804 C1HinO -1.23 1 MM5 Hydroxylation oa FI at m/z 201.332 C20.1322 C1HaisO2N -0.88 4.49 PHLM and rat isomer 1 F | | | FI at m/z 67.0548 | 67.0542 | C5H7 | 8.69 | | |
| hydroxylamine FI at m/z 188.1071 188.1071 188.1070 C12H14ON 0.51 FI at m/z 173.0962 173.0961 C12H13O 0.58 1 <td< td=""><td>MM3</td><td>N-Dealkylation +</td><td>+ PI at m/z 206.1177</td><td>206.1176</td><td>$C_{12}H_{16}O_2N$</td><td>0.88</td><td>5.61</td><td>rat</td></td<> | MM3 | N-Dealkylation + | + PI at m/z 206.1177 | 206.1176 | $C_{12}H_{16}O_2N$ | 0.88 | 5.61 | rat |
| FI at m/z 173.0962 173.0961 C12H13O 0.58 FI at m/z 145.1012 145.1012 C11H13 0.13 FI at m/z 129.0701 129.0699 Cu0H9 1.37 FI at m/z 117.0702 117.0699 C9H9 2.35 FI at m/z 91.0548 91.0542 C7H7 5.81 FI at m/z 67.0550 67.0542 C3H7 12.0 MM4 Hydroxylation PI at m/z 18.1172 218.1176 C13H16O2N -1.48 4.61 rat xisomer 1 + FI at m/z 187.0751 187.0754 C12H11O2 -1.27 -1.27 MM5 Hydroxylation PI at m/z 129.0130 220.1332 C1H11O -1.23 -1.23 MM5 Hydroxylation PI at m/z 202.1223 202.1226 C1H7 4.56 -1.48 4.49 pHLM and rat isomer 1 FI at m/z 19.0910 189.0910 C12H13O2 -0.01 -1.61 -1.61 FI at m/z 117.0804 171.0804 C12H13O2 -0.01 -1.61 -1.61 -1.61 -1.61 FI at m/z 199.0910 189.0910 C12H13O2 -0.01 -1.61 | | hydroxylamine | FI at m/z 188.1071 | 188.1070 | C12H14ON | 0.51 | | |
| FI at m/z 145.1012 145.1012 C11H13 0.13 FI at m/z 129.0701 129.0699 C10H9 1.37 FI at m/z 117.0702 117.0699 C9H9 2.35 FI at m/z 91.0548 91.0542 C7H7 5.81 MM4 Hydroxylation PI at m/z 187.0751 67.0542 CsH7 12.0 MM4 Hydroxylation PI at m/z 187.0751 187.0754 C12H10O2 -1.27 oxidation to a FI at m/z 159.0802 159.0804 C1H1x0 -1.23 MM5 Hydroxylation PI at m/z 20.1330 220.1332 C1Hx0N -0.88 4.49 PHLM and rat isomer 1 FI at m/z 189.0910 189.0910 C12H1x02 -0.01 | | 5 5 | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.58 | | |
| FI at m/z 129.0701 129.0699 CtoH9 1.37 FI at m/z 117.0702 117.0699 C9H9 2.35 FI at m/z 91.0548 91.0542 C7H7 5.81 FI at m/z 67.0550 67.0542 CsH7 12.0 MM4 Hydroxylation PI at m/z 218.1172 218.1176 CtaHnO2 -1.48 4.61 rat isomer 1 + FI at m/z 187.0751 187.0754 CtaHnO2 -1.27 -1.23 -1.23 wtotation to a FI at m/z 19.0802 159.0804 CtnHnO -1.23 -1.24 -1.24 MM5 Hydroxylation PI at m/z 20.1330 220.1332 CtaHtsO2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 189.0910 189.0910 CtaHtsO2N -1.61 -1.61 isomer 1 FI at m/z 189.0910 189.0910 CtaHtsO2N -0.01 -1.61 FI at m/z 171.0804 171.0804 CtaHtsO2N -0.01 -1.61 -1.61 FI at m/z 189.0910 189.0910 CtaHtsO2N -0.01 -1.61 -1.61 FI at m/z 171.0804 171.0804 CtaHtsO2N | | | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.13 | | |
| FI at m/z 117.0702 117.0699 C9H9 2.35 FI at m/z 91.0548 91.0542 C7H7 5.81 MM4 Hydroxylation PI at m/z 218.1172 218.1176 CsH7 12.0 MM4 Hydroxylation PI at m/z 187.0751 187.0754 C13H16O2N -1.48 4.61 rat isomer 1 + FI at m/z 159.0802 159.0804 C11H11O -1.27 - - MM5 Hydroxylation FI at m/z 19.0546 91.0542 C7H7 4.56 - - MM5 Hydroxylation FI at m/z 202.1230 220.1332 C13H16O2N -1.61 - - MM5 Hydroxylation FI at m/z 202.1233 220.1332 C13H16O2N -0.088 4.49 pHLM and rat isomer 1 FI at m/z 189.0910 189.0910 C12H11O2 -0.01 - - - HM5 Hydroxylation FI at m/z 143.0856 143.0855 C1H10 -0.07 - - - HM5 Hydroxylation FI at m/z 143.0856 143.0855 C1H10 -0.07 - - - | | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.37 | | |
| FI at m/z 91.0548 91.0542 C7H7 5.81 MM4 Hydroxylation PI at m/z 67.0550 67.0542 C3H7 12.0 MM4 Hydroxylation PI at m/z 218.1172 218.1176 C13H16O2N -1.48 4.61 rat isomer 1 + FI at m/z 187.0751 187.0754 C12H11O2 -1.27 -1.27 oxidation to a FI at m/z 159.0802 159.0804 C11H11O -1.23 -1.23 MM5 Hydroxylation PI at m/z 220.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 202.1223 202.1226 C13H16ON -1.61 | | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.35 | | |
| FI at m/z 67.0550 67.0542 C ₅ H7 12.0 MM4 Hydroxylation PI at m/z 218.1172 218.1176 C13H16O2N -1.48 4.61 rat isomer 1 + FI at m/z 187.0751 187.0754 C12H11O2 -1.27 -1.27 -1.23 oxidation to a FI at m/z 159.0802 159.0804 C11H11O -1.23 -1.23 -1.27 MM5 Hydroxylation PI at m/z 91.0546 91.0542 C7H7 4.56 -1.23 MM5 Hydroxylation PI at m/z 202.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 189.0910 189.0910 C12H13O2 -0.01 -1.61 -1.61 FI at m/z 171.0804 171.0804 C12H13O2 -0.01 -1.61 -1.61 -1.61 FI at m/z 171.0804 171.0804 C12H13O2 -0.01 -1.61< | | | FI at m/z 91.0548 | 91.0542 | C7H7 | 5.81 | | |
| MM4 Hydroxylation PI at m/z 218.1172 218.1176 C13H16O2N -1.48 4.61 rat isomer 1 + FI at m/z 187.0751 187.0754 C12H11O2 -1.27 -1.23 oxidation to a FI at m/z 159.0802 159.0804 C11H11O -1.23 | | | FI at m/z 67.0550 | 67.0542 | C5H7 | 12.0 | | |
| isomer 1 + FI at m/z 187.0751 187.0754 C12H11O2 -1.27 oxidation to a FI at m/z 159.0802 159.0804 C11H11O -1.23 ketone FI at m/z 91.0546 91.0542 C7H7 4.56 MM5 Hydroxylation PI at m/z 220.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 202.1223 202.1226 C13H18O2N -1.61 FI at m/z 189.0910 189.0910 C12H13O2 -0.01 FI at m/z 171.0804 171.0804 C12H11O -0.07 FI at m/z 143.0856 143.0855 C11H11 0.52 FI at m/z 91.0548 91.0542 C7H7 5.98 | MM4 | Hydroxylation | PI at m/z 218.1172 | 218.1176 | $C_{13}H_{16}O_2N$ | -1.48 | 4.61 | rat |
| oxidation to a ketone FI at m/z 159.0802 159.0804 C11H11O -1.23 MM5 FI at m/z 91.0546 91.0542 C7H7 4.56 MM5 Hydroxylation PI at m/z 220.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 202.1223 202.1226 C13H16ON -1.61 -1.61 FI at m/z 189.0910 189.0910 C12H13O2 -0.01 -1.61 -1.61 FI at m/z 171.0804 171.0804 C12H13O2 -0.01 -1.61 -1.61 FI at m/z 171.0804 171.0804 C12H11O -0.07 -1.61 -1.61 FI at m/z 143.0856 143.0855 C11H11 0.52 -1.61 -1.61 | | isomer 1 + | FI at m/z 187.0751 | 187.0754 | $C_{12}H_{11}O_2$ | -1.27 | | |
| ketone FI at m/z 91.0546 91.0542 C7H7 4.56 MM5 Hydroxylation PI at m/z 220.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat isomer 1 FI at m/z 202.1223 202.1226 C13H16ON -1.61 -1.61 FI at m/z 189.0910 189.0910 C12H13O2 -0.01 -0.07 -0.07 FI at m/z 171.0804 171.0804 C12H11O -0.07 -0.07 -0.01 FI at m/z 143.0856 143.0855 C11H11 0.52 -0.01 -0.07 FI at m/z 91.0548 91.0542 C7H7 5.98 -0.01 -0.07 | | oxidation to a | FI at m/z 159.0802 | 159.0804 | C11H11O | -1.23 | | |
| MM5 Hydroxylation isomer 1 PI at m/z 220.1330 220.1332 C13H18O2N -0.88 4.49 pHLM and rat ISOmer 1 FI at m/z 202.1223 202.1226 C13H16ON -1.61 -0.01 -1.61 <td></td> <td>ketone</td> <td>FI at m/z 91.0546</td> <td>91.0542</td> <td>C7H7</td> <td>4.56</td> <td></td> <td></td> | | ketone | FI at m/z 91.0546 | 91.0542 | C7H7 | 4.56 | | |
| isomer 1 FI at m/z 202.1223 202.1226 C13H16ON -1.61 FI at m/z 189.0910 189.0910 C12H13O2 -0.01 FI at m/z 171.0804 171.0804 C12H11O -0.07 FI at m/z 143.0856 143.0855 C11H11 0.52 FI at m/z 91.0548 91.0542 C7H7 5.98 | MM5 | Hydroxylation | PI at m/z 220.1330 | 220.1332 | $C_{13}H_{18}O_2N$ | -0.88 | 4.49 | pHLM and rat |
| FI at m/z 189.0910189.0910C12H13O2-0.01FI at m/z 171.0804171.0804C12H11O-0.07FI at m/z 143.0856143.0855C11H110.52FI at m/z 91.054891.0542C7H75.98 | | isomer 1 | FI at m/z 202.1223 | 202.1226 | C13H16ON | -1.61 | | - |
| FI at m/z 171.0804171.0804C12H11O-0.07FI at m/z 143.0856143.0855C11H110.52FI at m/z 91.054891.0542C7H75.98 | | | FI at m/z 189.0910 | 189.0910 | $C_{12}H_{13}O_2$ | -0.01 | | |
| FI at m/z 143.0856143.0855C11H110.52FI at m/z 91.054891.0542C7H75.98 | | | FI at m/z 171.0804 | 171.0804 | C12H11O | -0.07 | | |
| FI at m/z 91.0548 91.0542 C7H7 5.98 | | | FI at m/z 143.0856 | 143.0855 | C11H11 | 0.52 | | |
| | | | FI at m/z 91.0548 | 91.0542 | C7H7 | 5.98 | | |

| MM6 | Hydroxylation | PI at m/z 220.1335 | 220.1332 | C13H18O2N | 1.27 | 4.70 | pHLM and rat |
|-----|-----------------|----------------------|----------|--------------------|-------|------|--------------|
| | isomer 2 | FI at m/z 189.0911 | 189.0910 | $C_{12}H_{13}O_2$ | 0.55 | | Ĩ |
| | | FI at m/z 161.0961 | 161.0961 | C11H13O | 0.34 | | |
| | | FI at m/z 107.0496 | 107.0491 | C7H7O | 4.13 | | |
| | | FI at m/z 67.0551 | 67.0542 | C5H7 | 12.4 | | |
| MM7 | N-Dealkylation | + PI at m/z 232.1341 | 232.1332 | $C_{14}H_{18}O_2N$ | 3.83 | 6.90 | rat |
| | acetylation | FI at m/z 190.1231 | 190.1226 | $C_{12}H_{16}ON$ | 2.62 | | |
| | | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.75 | | |
| | | FI at m/z 155.0853 | 155.0855 | $C_{12}H_{11}$ | -1.58 | | |
| | | FI at m/z 145.1013 | 145.1012 | C11H13 | 0.66 | | |
| | | FI at m/z 129.0697 | 129.0699 | C10H9 | -1.00 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.23 | | |
| | | FI at m/z 67.0550 | 67.0542 | C5H7 | 12.0 | | |
| MM8 | N-Dealkylation | + PI at m/z 366.1552 | 366.1547 | C18H24O7N | 1.15 | 5.25 | rat |
| | glucuronidatior | n FI at m/z 348.1444 | 348.1442 | C18H22O6N | 0.70 | | |
| | | FI at m/z 330.1332 | 330.1336 | C18H20O5N | -1.28 | | |
| | | FI at m/z 173.0963 | 173.0961 | C12H13O | 1.11 | | |
| | | FI at m/z 155.0856 | 155.0855 | $C_{12}H_{11}$ | 0.19 | | |
| | | FI at m/z 145.1013 | 145.1012 | C11H13 | 0.76 | | |
| | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.37 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.57 | | |
| | | FI at m/z 67.0551 | 67.0542 | C5H7 | 12.9 | | |
| MM9 | N-Dealkylation | + PI at m/z 382.1491 | 382.1469 | $C_{18}H_{24}O_8N$ | -1.52 | 4.37 | rat |
| | hydroxylation | FI at m/z 364.1381 | 364.1391 | C18H22O7N | -2.59 | | |
| | glucuronidatior | n FI at m/z 171.0803 | 171.0804 | $C_{12}H_{11}O$ | -0.91 | | |
| | | FI at m/z 161.0960 | 161.0961 | C11H13O | -0.79 | | |
| | | FI at m/z 143.0856 | 143.0855 | $C_{11}H_{11}$ | 0.29 | | |
| | | FI at m/z 91.0553 | 91.0542 | C7H7 | 11.5 | | |

Table S5. List of *in vivo* phase I and II metabolites of 2-oxo-PCPr, identified in rat urine samples and *in vitro* phase I metabolites identified in incubations using pooled human liver microsomes (pHLM), including the respective metabolite ID, metabolic reaction, masses of the precursor ion (PI) and characteristic fragment ions (FI) detected in MS², calculated exact masses, elemental composition, calculated mass errors in parts per million (ppm), retention times (RT) in minutes, and system in which metabolites were identified. The metabolites are sorted by their mass and RT. pHLM, identified in pHLM incubations; rat, identified in rat urine samples

| Metabolite ID | Metabolic Reaction | Characteristic Ions Measured Accurate | Calculated Exact Masses, m/z | Elemental Composition | Error, ppm | RT, min | Identified in |
|---------------|-----------------------|--|--------------------------------|--------------------------|------------|---------|---------------|
| | | Masses | | | | | |
| 2-Oxo-PCPr | Parent | PI at m/z 232.1690 | 232.1696 | C15H22ON | -2.39 | 5.96 | pHLM and rat |
| | compound | FI at m/z 214.1587 | 214.1590 | C15H20N | -1.71 | | |
| | | FI at m/z 173.0958 | 173.0961 | C12H13O | -1.54 | | |
| | | FI at m/z 155.0851 | 155.0855 | $C_{12}H_{11}$ | -2.47 | | |
| | | FI at m/z 145.1009 | 145.1012 | C11H13 | -1.87 | | |
| | | FI at m/z 129.0697 | 129.0699 | C10H9 | -1.71 | | |
| | | FI at m/z 117.0700 | 117.0699 | C9H9 | 1.31 | | |
| | | FI at m/z 91.0546 | 91.0542 | C7H7 | 3.89 | | |
| | | FI at m/z 60.0815 | 60.0808 | C3H10N | 12.4 | | |
| PM1 | N-Dealkylation | PI at m/z 190.1223 | 190.1226 | C12H16ON | -1.82 | 5.05 | pHLM and rat |
| | | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.63 | | |
| | | FI at m/z 155.0854 | 155.0855 | C12H11 | -1.05 | | |
| | | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.17 | | |
| | | FI at m/z 129.0700 | 129.0699 | C10H9 | 0.80 | | |
| | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.35 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 5.99 | | |
| | | FI at m/z 67.0550 | 67.0542 | C5H7 | 11.5 | | |
| PM2 | Hydroxylation | PI at m/z 246.1490 | 246.1489 | $C_{15}H_{20}O_2N$ | 0.66 | 5.37 | rat |
| | isomer 1 + | FI at m/z 228.1380 | 228.1383 | C15H18ON | -1.07 | | |
| | oxidation to a | FI at m/z 187.0753 | 187.0754 | $C_{12}H_{11}O_2$ | -0.53 | | |
| | ketone | FI at m/z 159.0804 | 159.0804 | C11H11O | -0.46 | | |
| | | FI at m/z 141.0698 | 141.0699 | C11H9 | -0.48 | | |
| | | FI at m/z 91.0546 | 91.0542 | C7H7 | 4.14 | | |
| | | FI at m/z 60.0816 | 60.0808 | C3H10N | 14.2 | | |
| PM3 | Hydroxylation | PI at m/z 248.1639 | 248.1645 | C15H22O2N | -2.52 | 4.75 | pHLM and rat |
| | isomer 1 | FI at m/z 230.1540 | 230.1539 | C15H20ON | 0.15 | | |
| | | FI at m/z 189.0912 | 189.0910 | $C_{12}H_{13}O_2$ | 0.87 | | |
| | | FI at m/z 171.0805 | 171.0804 | C12H11O | 0.28 | | |
| | | FI at m/z 143.0857 | 143.0855 | C11H11 | 0.95 | | |
| | | FI at m/z 60.0817 | 60.0808 | C3H10N | 17.8 | | |
| PM4 | Hydroxylation | PI at m/z 248.1649 | 248.1645 | C15H22O2N | 1.41 | 5.31 | pHLM and rat |
| | isomer 2 | FI at m/z 230.1537 | 230.1539 | C15H20ON | -0.91 | | - |
| | | FI at m/z 173.0963 | 173.0961 | C12H13O | 1.02 | | |
| | | FI at m/z 155.0854 | 155.0855 | C12H11 | -0.50 | | |
| | | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.34 | | |
| | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.96 | | |
| | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.94 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.07 | | |
| | | FI at m/z 76.0764 | 76.0757 | C3H10ON | 9.44 | | |
| | | FI at m/z 67.0550 | 67.0542 | C5H7 | 12.2 | | |

| PM5 | Hydroxylamine | PI at m/z 248.1648 | 248.1645 | $C_{15}H_{22}O_2N$ | 1.29 | 6.21 | pHLM and rat |
|---------|------------------|--|----------------------|-----------------------------------|--------------|------|--------------|
| | | FI at m/z 230.1541 | 230.1539 | C15H20ON | 0.55 | | - |
| | | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.40 | | |
| | | FI at m/z 155.0860 | 155.0855 | C12H11 | 3.04 | | |
| | | FI at m/z 145.1013 | 145.1012 | C11H13 | 0.69 | | |
| | | FI at m/z 129.0701 | 129.0699 | C10H9 | 1.72 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 6.65 | | |
| | | FI at m/z 67.0550 | 67.0542 | C5H7 | 11.3 | | |
| PM6 | Dihydroxylation | PI at m/z 262.1438 | 262.1438 | C15H20O3N | 0.11 | 4.85 | rat |
| | isomer 1 + | FI at m/z 244.1321 | 244.1332 | $C_{15}H_{18}O_2N$ | -4.61 | | |
| | monooxoidation | FI at m/z 187.0754 | 187.0754 | $C_{12}H_{11}O_2$ | 0.28 | | |
| | to a ketone | FI at m/z 159.0805 | 159.0804 | C11H11O | 0.21 | | |
| | | FI at m/z 76.0764 | 76.0757 | C ₃ H ₁₀ ON | 9.64 | | |
| PM7 | Hydroxylation | PI at m/z 262.1440 | 262.1438 | C15H20O3N | 0.69 | 5.31 | rat |
| | isomer 2 + | FI at m/z 244.1338 | 244.1332 | C15H18O2N | 2.33 | | |
| | oxidation to | FI at m/z 173.0962 | 173.0961 | C12H13O | 0.58 | | |
| | carboxylic acid | FI at m/z 155.0855 | 155.0855 | C12H11 | -0.11 | | |
| | 5 | FI at m/z 145.1012 | 145.1012 | C11H13 | 0.45 | | |
| | | FI at m/z 129.0700 | 129.0699 | C10H9 | 0.77 | | |
| | | FI at m/z 117.0702 | 117.0699 | C9H9 | 2.87 | | |
| | | FI at m/z 91.0548 | 91.0542 | C7H7 | 5.98 | | |
| | | FI at m/z 67.0660 | 67.0542 | C5H7 | 12.2 | | |
| PM8 | Dihvdroxvlation | PI at m/z 264.1596 | 264.1594 | C15H22O3N | 0.82 | 4.61 | rat |
| 1 1110 | isomer 1 | FL at m/z 246.1490 | 246.1489 | $C_{15}H_{20}O_2N$ | 0.72 | 101 | 140 |
| | | FI at m/z 228.1382 | 228.1383 | $C_{15}H_{18}ON$ | -0.60 | | |
| | | FI at m/z 189 0911 | 189 0910 | $C_{12}H_{13}O_2$ | 0.31 | | |
| | | FL at m/z 171.0805 | 171.0804 | $C_{12}H_{11}O$ | 0.55 | | |
| | | FI at m/z 143 0857 | 143 0855 | C11H11 | 1.06 | | |
| | | FL at m/z 76 0764 | 76.0757 | C3H10ON | 9.94 | | |
| PM9 | Dihydroxylation | PL at m/z 264 1595 | 264 1594 | $C_{15}H_{22}O_{3}N$ | 0.36 | 5.09 | rat |
| 1 1012 | isomer ? | FL at $m/z 201.1090$ | 201.1091 | $C_{15}H_{22}O_{2}N$ | 0.72 | 0.07 | iut |
| | 15011101 2 | FL at m/z 189 0910 | 189 0910 | $C_{12}H_{13}O_2$ | -0.01 | | |
| | | FI at m/z 161 0961 | 161.0961 | C11H12O | 0.15 | | |
| | | FL at m/z 107 0495 | 107.0491 | C7H7O | 3.77 | | |
| | | FL at m/z 76 0764 | 76.0757 | | 9.45 | | |
| PM10 | N-Dealkylation + | - PL at m/z 366 1547 | 366 1547 | C18H24O7N | -0.01 | 5 29 | rat |
| 1 10110 | glucuronidation | FI at m/z 348 1437 | 348 1442 | C18H22O4N | -1 22 | 0.2 | iut |
| | gracaronitation | FL at m/z 330 1341 | 330 1336 | $C_{18}H_{22}O_{5}N$ | 1.22 | | |
| | | FL at $m/z = 0.0000000000000000000000000000000000$ | 173 0961 | C12H120 | 0.66 | | |
| | | FL at $m/z = 1/5.0002$ | 1/5 1012 | C11H12 | 0.66 | | |
| | | FL at m/z 129 0701 | 129 0699 | CioHo | 1.72 | | |
| | | FL at m/z 91 05/8 | 91 0542 | C-H- | 6.23 | | |
| PM11 | Hydroxylation | PL at m/z 424 1964 | 124 1966 | CatHaoOeN | -0.36 | 5.24 | rət |
| 1 1/111 | isomer 2 ± | EL at m/z 248 1640 | 424.1900 248 1645 | C1-HanOnN | -0.30 | 5.24 | Iat |
| | ducuronidation | FI at m/z 240.1040 | 240.1043 | $C_{15}H_{22}O_{21}N$ | -1.85 | | |
| | giucuronitation | FI at $m/z = 230.1009$ | 230.1339 | CulturO | -0.31 | | |
| | | FI at $m/2 = 1/5.0905$ EL at $m/2 = 1/5 = 1012$ | 1/5.0901 | $C_{12}H_{13}$ | 0.34 | | |
| | | FI at m/z 140.1012 EL at m/z 120.0702 | 140.1012 | | 0.04 0.10 | | |
| | | FI at $m/2$ 129.0/02 EL at $m/2$ 01 0549 | 127.0077 01.0547 | | 2.17 6 72 | | |
| | | F1 at $\frac{11}{2}$ 71.0040 | 71.0342 | | 0.23 | | |
| | | F1 at m/z 76.0764 | /6.0/5/ | C3H10UN | 9.73 | | |

| Table S6. Parent compounds and metabolites of five deschloroketamine derivatives detected by GC-MS |
|--|
| including masses of precursor ions (PI), elemental composition, and masses of characteristic fragment ions |
| (FI). AC, acetylated. |

| Parent compound or metabolite | PI mass, <i>m</i> /z | RI | Elemental composition | Characteristic FI |
|-------------------------------|-------------------------|------|-----------------------|--|
| 2-Oxo-PCcP | 229 | 1760 | C15H19NO | 200, 172, 145, 104, 91 |
| 2-Oxo-PCE | 217 | 1635 | C14H19NO | 189, 160, 146, 132, 117, 104, 91 |
| 2-Oxo-PCiP | 231 | 1648 | $C_{15}H_{21}NO$ | 203, 174, 160, 132, 117, 104, 91 |
| 2-Oxo-PCMe AC | 245 | 1990 | C15H19NO2 | 217, 174, 160, 144, 132, 118, 104, 91 |
| 2-Oxo-PCPr | 231 | 1747 | C15H21NO | 203, 174, 160, 132, 117, 104, 91 |
| 2-Oxo-PCPr AC | 273 | 2038 | C15H21NO | 245, 203, 174, 160, 144, 132, 117, 104, 91 |
| N-Dealkylation AC | 231 | 1874 | C14H17NO2 | 188, 174, 144, 132, 104, 91 |

Table S7. 2-Oxo-PCcP and its metabolites detected in rat urine after oral administration using different sample preparations in combination with LC-HRMS/MS (*) or GC-MS (*). Metabolite IDs correspond to Tables S1. CM, 2-oxo-PCcP metabolite; UPP, urine precipitation; UGLUC, urine after glucuronidase/arylsulfatase cleavage; LLE, liquid-liquid extraction; SPE, solid-phase extraction; UHyAc, partial urine hydrolysis followed by LLE and acetylation

| Match alter ID | Sample preparation performed | | | | | | | | | |
|----------------|------------------------------|-------------------------------|------------------|--------------|--------------|--|--|--|--|--|
| Metabolite ID | UPP# | UGLUC LLE [#] | SPE [#] | UGLUC SPE# | UHyAC* | | | | | |
| 2-oxo-PCcP | not detected | not detected | detected | detected | not detected | | | | | |
| CM1 | detected | detected | detected | detected | detected | | | | | |
| CM2 | not detected | not detected | detected | not detected | not detected | | | | | |
| CM3 | not detected | detected | detected | detected | not detected | | | | | |
| CM4 | not detected | detected | detected | detected | not detected | | | | | |
| CM5 | detected | not detected | detected | not detected | not detected | | | | | |
| Summary | 2 of 6 | 3 of 6 | 6 of 6 | 4 of 6 | 1 of 6 | | | | | |

Table S8. 2-Oxo-PCE and its metabolites detected in rat urine after oral administration using different sample preparations in combination with LC-HRMS/MS (*) or GC-MS (*). Metabolite IDs correspond to Table S2. EM, 2-oxo-PCE metabolite; UPP, urine precipitation; UGLUC, urine after glucuronidase/arylsulfatase cleavage; LLE, liquid-liquid extraction; SPE, solid-phase extraction; UHyAc, partial urine hydrolysis followed by LLE and acetylation

| | Sample preparation performed | | | | | | | | | |
|---------------|------------------------------|-------------------------------|------------------|--------------|--------------|--|--|--|--|--|
| Metabolite ID | UPP# | UGLUC LLE [#] | SPE [#] | UGLUC SPE# | UHyAC* | | | | | |
| 2-Oxo-PCE | detected | detected | detected | detected | not detected | | | | | |
| EM1 | detected | detected | detected | detected | detected | | | | | |
| EM2 | detected | detected | detected | detected | not detected | | | | | |
| EM3 | detected | detected | detected | detected | not detected | | | | | |
| EM4 | detected | detected | detected | detected | not detected | | | | | |
| EM5 | detected | not detected | detected | not detected | not detected | | | | | |
| Summary | 6 of 6 | 5 of 6 | 6 of 6 | 5 of 6 | 1 of 6 | | | | | |

Table S9. 2-Oxo-PCiP and its metabolites detected in rat urine after oral administration using different sample preparations in combination with LC-HRMS/MS (*) or GC-MS (*). Metabolite IDs correspond to Table S3. IM, 2-oxo-PCiP metabolite; UPP, urine precipitation; UGLUC, urine after glucuronidase/arylsulfatase cleavage; LLE, liquid-liquid extraction; SPE, solid-phase extraction; UHyAc, partial urine hydrolysis followed by LLE and acetylation

| Metabolite ID | Sample preparation performed | | | | | | |
|---------------|------------------------------|------------------------------|------------------|------------------------------|--------------|--|--|
| | UPP# | UGLUC LLE[#] | SPE [#] | UGLUC SPE[#] | UHyAC* | | |
| 2-Oxo-PCiP | not detected | detected | detected | detected | not detected | | |
| IM1 | detected | detected | detected | detected | detected | | |
| IM2 | not detected | detected | detected | detected | not detected | | |
| IM3 | not detected | not detected | detected | not detected | not detected | | |
| IM4 | detected | detected | detected | detected | not detected | | |
| IM5 | not detected | detected | not detected | detected | not detected | | |
| IM6 | not detected | detected | not detected | detected | not detected | | |
| IM7 | not detected | not detected | detected | not detected | not detected | | |
| IM8 | detected | not detected | detected | not detected | not detected | | |
| IM9 | detected | not detected | detected | not detected | not detected | | |
| Summary | 4 of 10 | 6 of 10 | 8 of 10 | 6 of 10 | 1 of 10 | | |

Table S10. 2-Oxo-PCMe and its metabolites detected in rat urine after oral administration using different sample preparations in combination with LC-HRMS/MS (*) or GC-MS (*). Metabolite IDs correspond to Table S4. MM, 2-oxo-PCMe metabolite; UPP, urine precipitation; UGLUC, urine after glucuronidase/arylsulfatase cleavage; LLE, liquid-liquid extraction; SPE, solid-phase extraction; UHyAc, partial urine hydrolysis followed by LLE and acetylation

| Metabolite ID | Sample preparation performed | | | | | |
|---------------|------------------------------|-------------------------------|------------------|------------------------|--------------|--|
| | UPP [#] | UGLUC LLE [#] | SPE [#] | UGLUC SPE [#] | UHyAC* | |
| 2-Oxo-PCMe | detected | detected | detected | detected | not detected | |
| MM1 | detected | detected | detected | detected | detected | |
| MM2 | detected | detected | detected | detected | not detected | |
| MM3 | detected | detected | detected | detected | not detected | |
| MM4 | detected | detected | detected | detected | not detected | |
| MM5 | detected | detected | detected | detected | not detected | |
| MM6 | not detected | detected | detected | detected | not detected | |
| MM7 | not detected | not detected | detected | not detected | not detected | |
| MM8 | detected | not detected | detected | not detected | not detected | |
| MM9 | not detected | not detected | detected | not detected | not detected | |
| Summary | 7 of 10 | 7 of 10 | 10 of 10 | 7 of 10 | 1 of 10 | |

Table S11. 2-Oxo-PCPr and its metabolites detected in rat urine after oral administration using different sample preparations in combination with LC-HRMS/MS (*) or GC-MS (*). Metabolite IDs correspond to Table S5. PM, 2-oxo-PCPr metabolite; UPP, urine precipitation; UGLUC, urine after glucuronidase/arylsulfatase cleavage; LLE, liquid-liquid extraction; SPE, solid-phase extraction; UHyAc, partial urine hydrolysis followed by LLE and acetylation

| Metabolite ID | Sample preparation performed | | | | | |
|---------------|------------------------------|-------------------------------|------------------|------------------------------|--------------|--|
| | UPP [#] | UGLUC LLE [#] | SPE [#] | UGLUC SPE[#] | UHyAC* | |
| 2-Oxo-PCPr | detected | detected | detected | detected | not detected | |
| PM1 | detected | detected | detected | detected | detected | |
| PM2 | detected | detected | detected | detected | not detected | |
| PM3 | detected | detected | detected | detected | not detected | |
| PM4 | detected | detected | detected | detected | not detected | |
| PM5 | detected | detected | detected | detected | not detected | |
| PM6 | detected | detected | detected | detected | not detected | |
| PM7 | detected | detected | detected | detected | not detected | |
| PM8 | not detected | detected | detected | detected | not detected | |
| PM9 | detected | detected | detected | detected | not detected | |
| PM10 | detected | not detected | detected | not detected | not detected | |
| PM11 | not detected | not detected | detected | not detected | not detected | |
| Summary | 10 of 12 | 10 of 12 | 12 of 12 | 10 of 12 | 1 of 12 | |



Figure S1. HRMS² spectra of 2-oxo-PCcP and its metabolites detected in rat urine after oral administration. Metabolite IDs correspond to Table S1. CM, 2-oxo-PCcP metabolite; RT, retention time



Figure S2. HRMS² spectra of 2-oxo-PCE and its metabolites detected in rat urine after oral administration. Metabolite IDs correspond to Table S2. EM, 2-oxo-PCE metabolite; RT, retention time



Figure S3. HRMS² spectra of 2-oxo-PCiP and its metabolites detected in rat urine after oral administration. Metabolite IDs correspond to Table S3. IM, 2-oxo-PCiP metabolite; RT, retention time



MS^c of IM9 (Hvdroxvlation isomer 3 + dlucuronidation, at *m*/z 424.1966, R1 5.24 min. pos Figure S3. continued



Figure S4. HRMS² spectra of 2-oxo-PCMe and its metabolites detected in rat urine after oral administration. Metabolite IDs correspond to Table S4. MM, 2-oxo-PCMe metabolite; RT, retention time



MS² of MM9 (*N*-Dealkylation + hydroxylation + glucuronidation, at $\overline{m/z}$ 382.1469, RT 4.37 min, pos Figure S4. continued



Figure S5. HRMS² spectra of 2-oxo-PCPr and its metabolites detected in rat urine after oral administration. Metabolite IDs correspond to Table S5. PM, 2-oxo-PCPr metabolite; RT, retention time



Figure S5. continued



Figure S6. EI-MS spectra of 2-oxo-PCCP, 2-oxo-PCE, 2-oxo-PCiP, 2-oxo-PCMe AC, 2-oxo-PCPr, and acetylated *N*-dealkylation metabolites. Metabolite IDs correspond to Tables S1-S5. RI: retention index.



EI-MS of acetylated N-dealkylation metabolites CM1, EM1, IM1, MM1, and PM1, at m/z 231, RI: 1874 Figure S6. continued



Figure S7. In vivo metabolic pathways of 2-oxo-PCE, ID corresponding to Table S2. EM, 2-oxo-PCE metabolite.



Figure S8. In vivo metabolic pathways of 2-oxo-PCMe, ID corresponding to Table S4. MM, 2-oxo-PCMe metabolite.