Figure S1. Comparison between the calibration curves of theophylline and paraxanthine when the two compounds were present in a mixture (blue) or were prepared separately (red). Calibrators were prepared in solvent between the range 1.8 – 360 ng/mL.

Figure S2. Homoscedasticity test for caffeine, paraxanthine, theobromine, and theophylline. Ten calibrators were analyzed for the lowest concentration and ten for the highest points of the calibration curves.
Figure S3. Percentage of relative error (%RE) versus concentration obtained for each calibration curve using the $1/x^2$ as weighting factor. The criteria of acceptance were for 1st calibrant $\leq 20\%$ and other calibrants $\leq 15\%$. 
Figure S4. Calibration curves for (A) caffeine, (B) theobromine, (C) theophylline and (D) paraxanthine prepared in solvent and plasma. For each molecule and matrix, peak areas and peak area ratios were plotted against concentration.
Table S1: Selection of the best weighting factor for the regression model. Calibration curves prepared in solvent were generated for each weighting factor and the sums of the relative errors (%RE) and coefficients of determination (R^2) were calculated for each regression model.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Caffeine</th>
<th>Theobromine</th>
<th>Theophylline</th>
<th>Paraxanthine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∑</td>
<td>%RE</td>
<td>Mean R^2</td>
<td>∑</td>
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<tr>
<td>1/x^0 (OLS)</td>
<td>859.3</td>
<td>0.9986</td>
<td>232.2</td>
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<tr>
<td>1/x (WLS)</td>
<td>152.4</td>
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<tr>
<td>1/x^2 (WLS)</td>
<td>86.0</td>
<td>0.9983</td>
<td>63.0</td>
<td>0.9990</td>
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<td>1/y (WLS)</td>
<td>156.8</td>
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<tr>
<td>1/y^2 (WLS)</td>
<td>88.7</td>
<td>0.9982</td>
<td>64.0</td>
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<tr>
<td>1/x^1/2 (WLS)</td>
<td>295.4</td>
<td>0.9988</td>
<td>103.6</td>
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<td>1/y^1/2 (WLS)</td>
<td>304.2</td>
<td>0.9988</td>
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<td>a+bx+cx^2 (Quad)</td>
<td>860.5</td>
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<td>261.6</td>
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Table S2: Selection of the best weighting factor for the regression model. Calibration curves prepared in plasma were generated for each weighting factor and the sums of the relative errors (%RE) and coefficients of determination (R^2) were calculated for each regression model.

<table>
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<tr>
<th>Concentration</th>
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<th>Theobromine</th>
<th>Theophylline</th>
<th>Paraxanthine</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>∑</td>
<td>%RE</td>
<td>Mean R^2</td>
<td>∑</td>
</tr>
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<td>500.4</td>
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Table S3: The ratio of the regressed concentrations in solvent and plasma calibration curves represented by the average, standard deviation (SD) and %CV.

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