Supporting Information

Resolution of co-eluting isomers of anti-inflammatory drugs conjugated to carbonic anhydrase inhibitors from plasma in liquid chromatography by energy-resolved tandem mass spectrometry

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ST1: Chromatographic peak parameters obtained for ISTD and the studied analytes using the conditions reported in 2.5 section.

|       | Rt (min) | ± 2 SD (min) | Width (min) | N (plates) | k  | α  | R   |
|-------|----------|--------------|-------------|------------|----|----|-----|
| ISTD  | 2.79     | 0.03         | 0.05        | 16435      | 3.99 |    |     |
| 1A    | 4.31     | 0.03         | 0.06        | 31100      | 6.69 | 1.01| 0.4 |
| 1B    | 4.26     | 0.02         | 0.06        | 31341      | 6.61 |    |     |
| 2A    | 3.53     | 0.02         | 0.05        | 24750      | 5.30 | 1.01| 0.2 |
| 2B    | 3.51     | 0.02         | 0.05        | 25257      | 5.26 |    |     |
| 3A    | 3.81     | 0.03         | 0.06        | 22928      | 5.80 | 1.01| 0.3 |
| 3B    | 3.77     | 0.02         | 0.06        | 23360      | 5.73 |    |     |
| 4A    | 4.44     | 0.01         | 0.06        | 31436      | 6.92 | 1.01| 0.4 |
| 4B    | 4.39     | 0.01         | 0.06        | 32273      | 6.84 |    |     |
| 5A    | 4.62     | 0.03         | 0.08        | 17767      | 7.26 | 1.01| 0.3 |
| 5B    | 4.58     | 0.02         | 0.08        | 20099      | 7.19 |    |     |
| 6A    | 4.15     | 0.02         | 0.06        | 24850      | 6.41 | 1.01| 0.3 |
| 6B    | 4.10     | 0.02         | 0.07        | 21538      | 6.33 |    |     |
| 7A    | 3.63     | 0.02         | 0.05        | 25394      | 5.48 | 1.01| 0.3 |
| 7B    | 3.60     | 0.01         | 0.06        | 22543      | 5.42 |    |     |
| 8A    | 3.79     | 0.02         | 0.05        | 30078      | 5.76 | 1.01| 0.3 |
| 8B    | 3.76     | 0.03         | 0.05        | 26624      | 5.71 |    |     |

Rt: Retention time
SD: Standard Deviation
Width: Peak width
N: Efficiency
k: Retention factor
α: Selectivity
R: Resolution
SF1: Breakdown curves for 1a-1b isomer pairs.

SF2: Breakdown curves for 2a-2b isomer pairs.
SF3: Breakdown curves for 3a-3b isomer pairs.

SF4: Breakdown curves for 4a-4b isomer pairs.
SF5: Breakdown curves for 5a-5b isomer pairs.

SF6: Breakdown curves for 6a-6b isomer pairs.
SF7: Breakdown curves for 7a-7b isomer pairs.

SF8: Breakdown curves for 8a-8b isomer pairs.
y = -0.0073x + 0.0256
R^2 = 0.991

SF9: Degradation plot of KEE in human plasma samples.

y = -0.031x + 0.0046
R^2 = 0.9958

SF10: degradation plot of Enalapril in rat plasma samples.
ST2: Half life of references and studied compounds.

|      | PBS T 1/2 (min) | Human plasma T 1/2 (min) | Rat plasma T 1/2 (min) |
|------|-----------------|---------------------------|------------------------|
| KEE  | n.d.            | 95                        | n.d.                   |
| Enalapril | n.d.          | n.d                        | 22                     |
| 1A   | >240            | >240                       | >240                   |
| 1B   | >240            | >240                       | >240                   |
| 2A   | >240            | >240                       | >240                   |
| 2B   | >240            | >240                       | >240                   |
| 3A   | >240            | >240                       | >240                   |
| 3B   | >240            | >240                       | >240                   |
| 4A   | >240            | >240                       | >240                   |
| 4B   | >240            | >240                       | >240                   |
| 5A   | >240            | >240                       | >240                   |
| 5B   | >240            | >240                       | >240                   |
| 6A   | >240            | >240                       | >240                   |
| 6B   | >240            | >240                       | >240                   |
| 7A   | >240            | >240                       | >240                   |
| 7B   | >240            | >240                       | >240                   |
| 8A   | >240            | >240                       | >240                   |
| 8B   | >240            | >240                       | >240                   |

n.d.: not determined
SF11: degradation plot of compound 1a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF12: degradation plot of compound 1b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF13: degradation plot of compound 2a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF14: degradation plot of compound 2b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF15: degradation plot of compound 3a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF16: degradation plot of compound 3b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF17: degradation plot of compound 4a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF18: degradation plot of compound 4b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF19: degradation plot of compound 5a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF20: degradation plot of compound 5b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF21: degradation plot of compound 6a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF22: degradation plot of compound 6b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF23: degradation plot of compound 7a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF24: degradation plot of compound 7b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF25: degradation plot of compound 8a in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.
SF26: degradation plot of compound 8b in phosphate buffer solution (PBS), human (H-Plasma) and rat (R-Plasma) plasma samples.