

## **Supplemental Figures**

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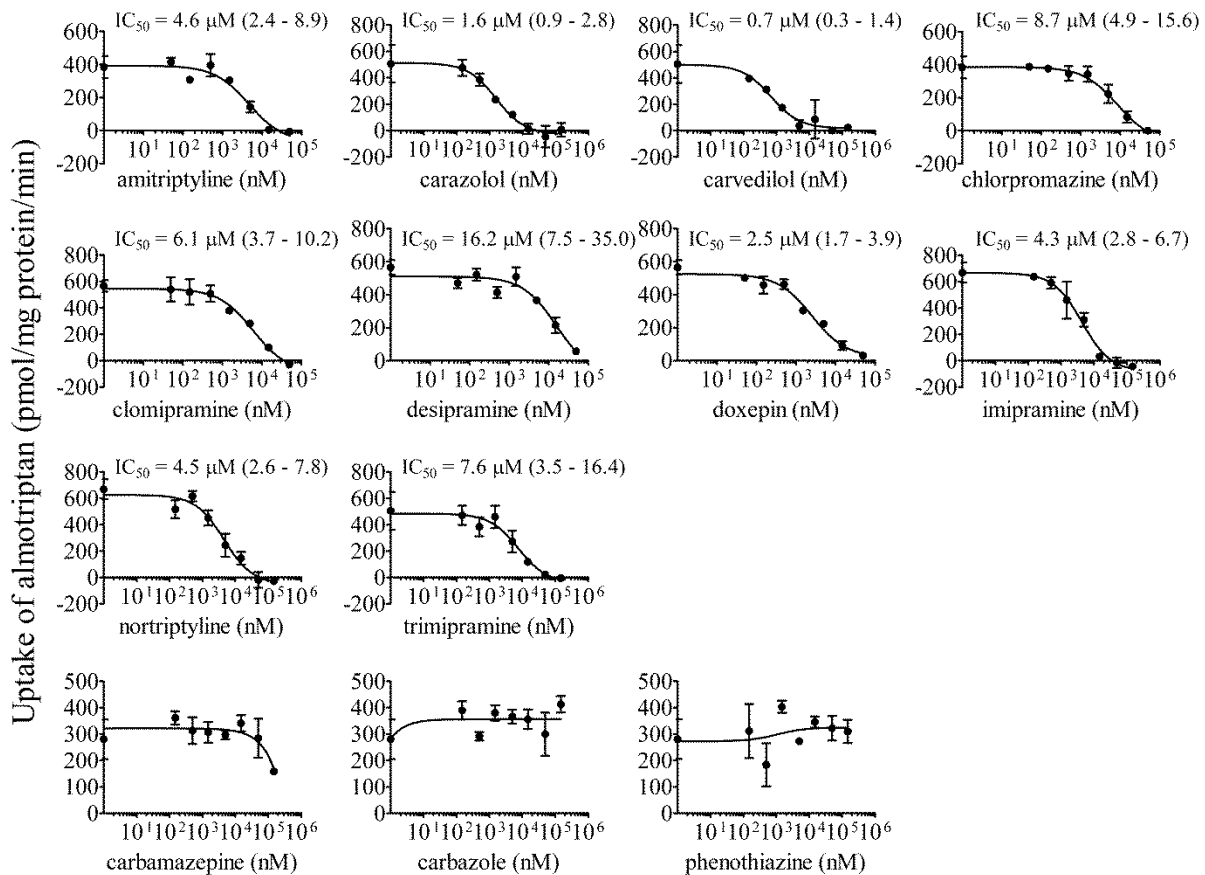
**Effects of tricyclic compounds on the transport of anti-migraine triptans  
through human organic anion transporting polypeptide 1A2 (OATP1A2)**

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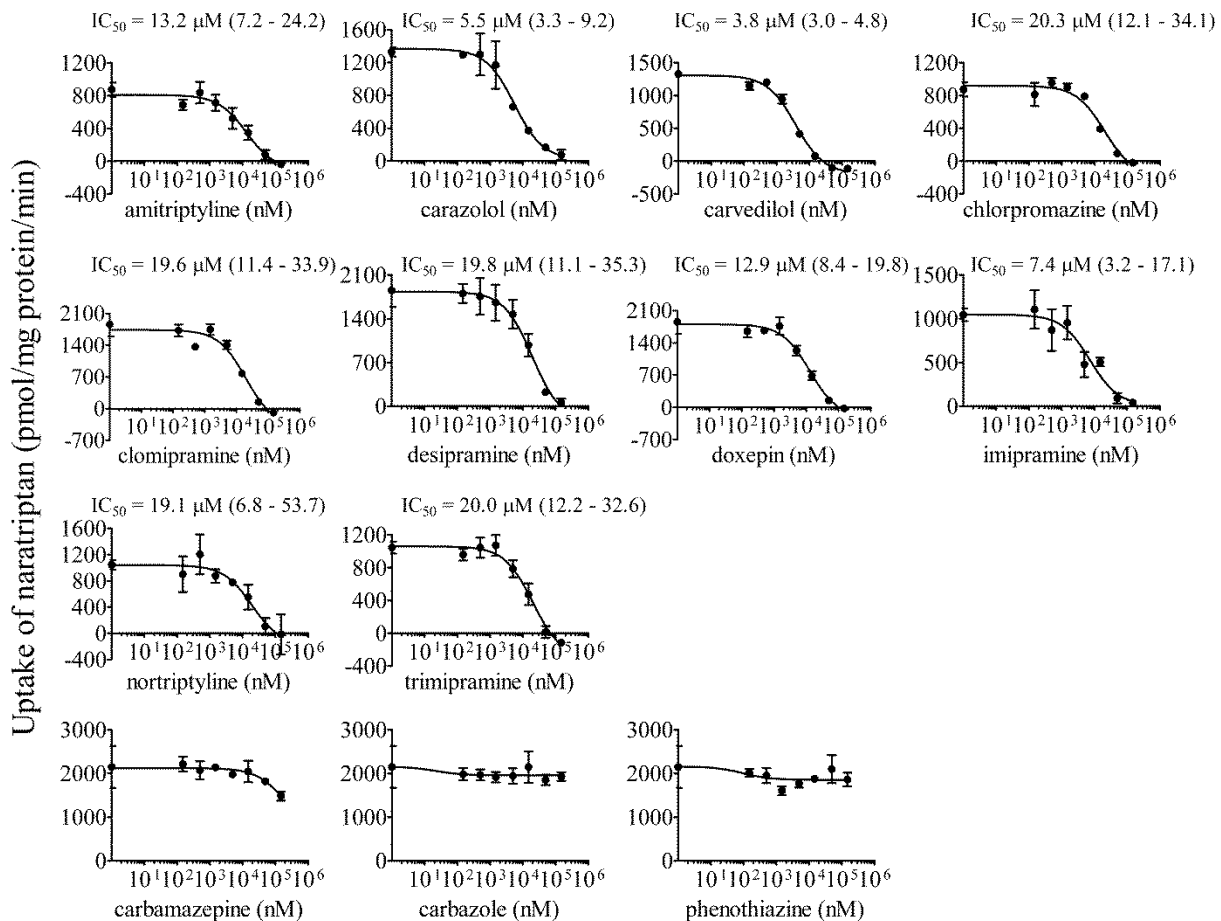
**Supplemental Table 1: Validation of LC-MS/MS quantification methods of triptans**

| Compound     | Concentration<br>(pg/mL) | Intra (n=3)          |           |                | Inter (n=9)          |           |                |
|--------------|--------------------------|----------------------|-----------|----------------|----------------------|-----------|----------------|
|              |                          | Mean ± SD<br>(pg/mL) | CV<br>(%) | Nominal<br>(%) | Mean ± SD<br>(pg/mL) | CV<br>(%) | Nominal<br>(%) |
| Almotriptan  | 75.0                     | 72.4 ± 3.7           | 5.1       | -3.5           | 76.2 ± 9.9           | 13.0      | 1.5            |
|              | 1250                     | 1203 ± 28            | 2.3       | -3.8           | 1189 ± 32            | 2.7       | -4.9           |
|              | 15000                    | 15424 ± 382          | 2.5       | 2.8            | 15013 ± 470          | 3.1       | 0.1            |
| Zolmitriptan | 300                      | 275 ± 2.9            | 1.1       | -8.4           | 282.8 ± 11.3         | 4.0       | -5.7           |
|              | 5000                     | 4633 ± 234           | 5.1       | -7.3           | 4814 ± 225           | 4.7       | -3.7           |
|              | 20000                    | 19322 ± 57           | 0.3       | -3.4           | 20045 ± 790          | 3.9       | 0.2            |

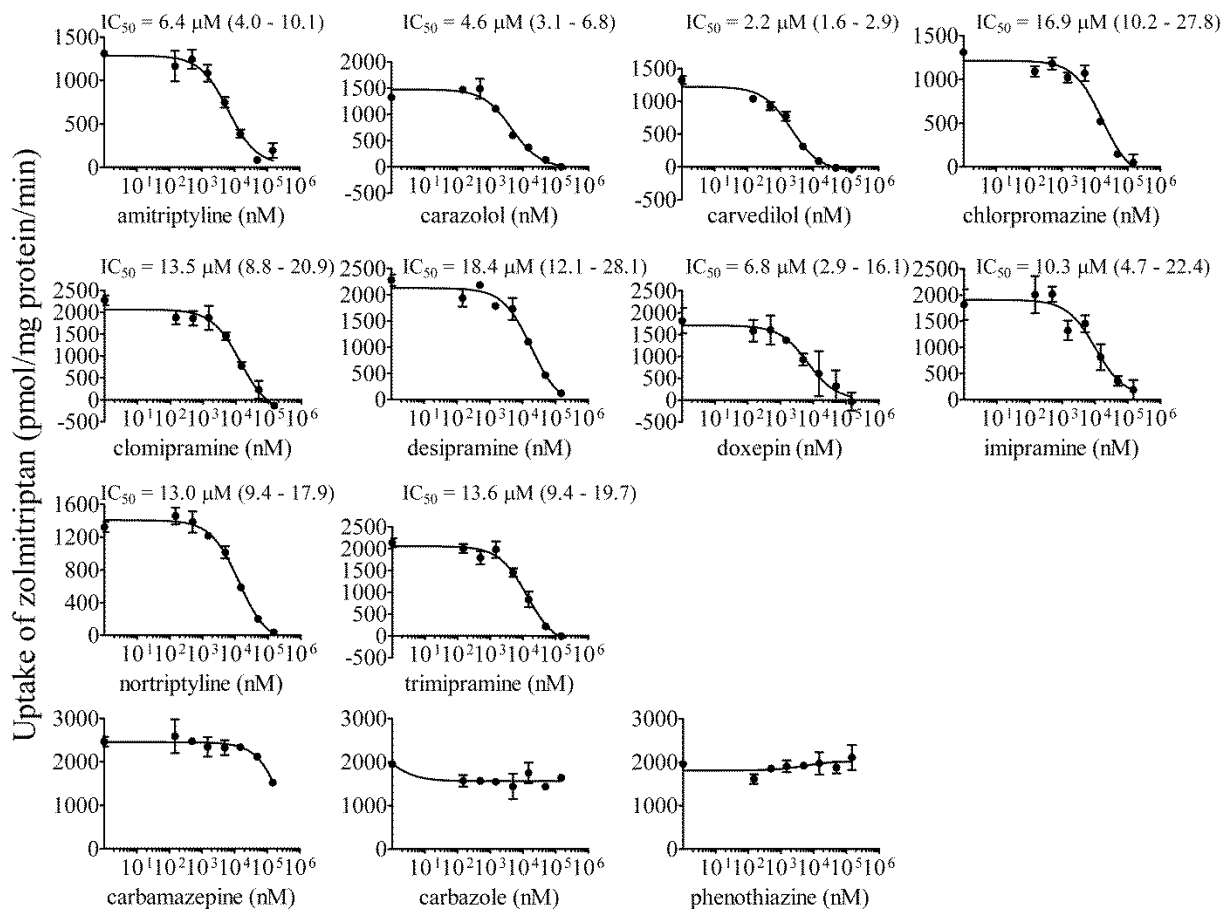
SD: standard deviation; CV: coefficient of variation



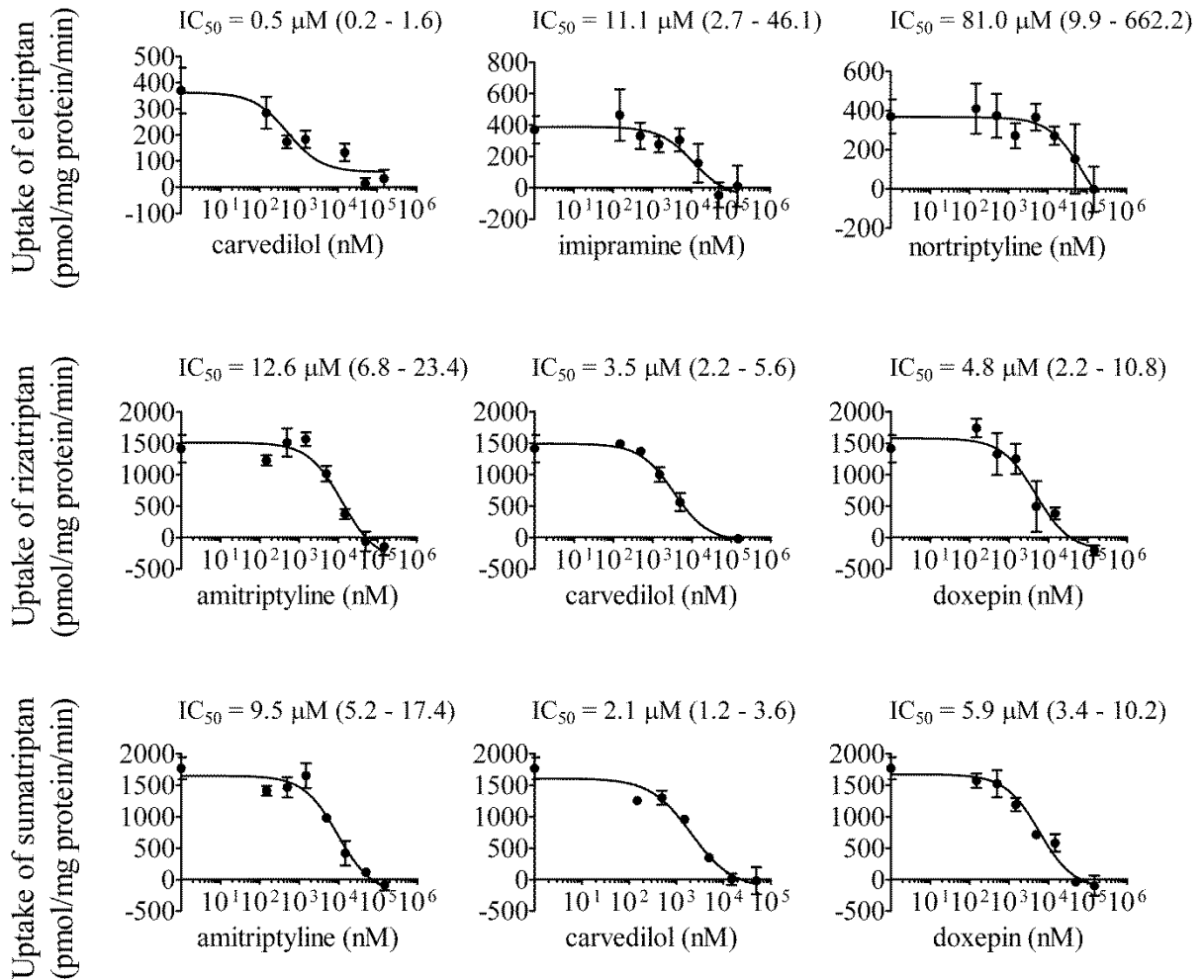
**Supplemental Figure 1. Inhibition of OATP1A2-mediated transport of almotriptan by different tricyclic compounds.** HEK293-OATP1A2 and HEK293-VC cells were coincubated with almotriptan (15  $\mu$ M) and different tricyclic compounds (150 nM – 150  $\mu$ M) for 2 min at 37°C. The quantity of intracellular almotriptan was normalized to protein content. To obtain the net transport, values measured in the VC cells were subtracted from the values measured in OATP1A2-expressed cells. IC<sub>50</sub> values were calculated by fitting the data to the log(inhibitor) vs. response equation in GraphPad Prism. Each point represents the mean  $\pm$  S.D. of triplicate from a single experiment. The values in parentheses represent the 95% confidence interval.



**Supplemental Figure 2. Inhibition of OATP1A2-mediated transport of naratriptan by different tricyclic compounds.** HEK293-OATP1A2 and HEK293-VC cells were coincubated with naratriptan (60  $\mu\text{M}$ ) and different tricyclic compounds (150 nM – 150  $\mu\text{M}$ ) for 2 min at 37°C. The quantity of intracellular naratriptan was normalized to protein content. To obtain the net transport, values measured in the VC cells were subtracted from the values measured in OATP1A2-expressed cells.  $\text{IC}_{50}$  values were calculated by fitting the data to the log(inhibitor) vs. response equation in GraphPad Prism. Each point represents the mean  $\pm$  S.D. of triplicate from a single experiment. The values in parentheses represent the 95% confidence interval.



**Supplemental Figure 3. Inhibition of OATP1A2-mediated transport of zolmitriptan by different tricyclic compounds.** HEK293-OATP1A2 and HEK293-VC cells were coincubated with zolmitriptan (65  $\mu\text{M}$ ) and different tricyclic compounds (150 nM – 150  $\mu\text{M}$ ) for 2 min at 37°C. The quantity of intracellular zolmitriptan was normalized to protein content. To obtain the net transport, values measured in the VC cells were subtracted from the values measured in OATP1A2-expressed cells.  $\text{IC}_{50}$  values were calculated by fitting the data to the log(inhibitor) vs. response equation in GraphPad Prism. Each point represents the mean  $\pm$  S.D. of triplicate from a single experiment. The values in parentheses represent the 95% confidence interval.



**Supplemental Figure 4. Inhibition of OATP1A2-mediated transport of eletriptan, rizatriptan and sumatriptan by different tricyclic compounds.** HEK293-OATP1A2 and HEK293-VC cells were coincubated with eletriptan (3  $\mu M$ ), rizatriptan (130  $\mu M$ ) or sumatriptan (300  $\mu M$ ) and different tricyclic compounds (150 nM – 150  $\mu M$ ). The incubation time for eletriptan was 1 min; whereas, rizatriptan and sumatriptan were incubated for 2 min at 37°C. The quantity of intracellular triptan was normalized to protein content. To obtain the net transport, values measured in the VC cells were subtracted from the values measured in OATP1A2-expressed cells.  $IC_{50}$  values were calculated by fitting the data to the log(inhibitor) vs. response

equation in GraphPad Prism. Each point represents the mean  $\pm$  S.D. of triplicate from a single experiment. The values in parentheses represent the 95% confidence interval.