**Supplementary Figures and Tables**

**Identification and preclinical development of kinetin as a safe error-prone SARS-CoV-2 antiviral and anti-inflammatory therapy**

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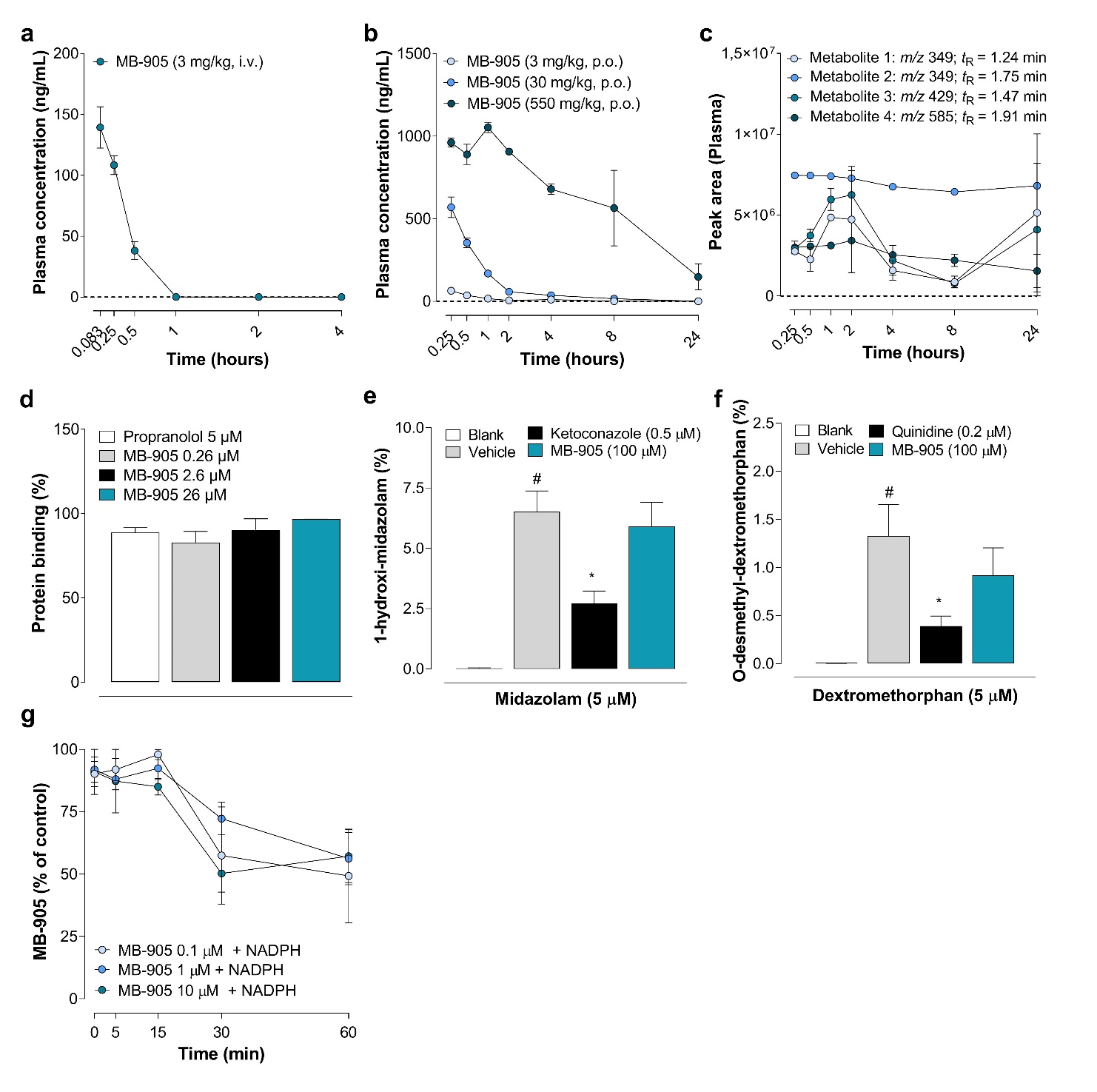
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**Supplementary Figure 1: Pharmacokinetics in mice, protein binding, CYP inhibition and metabolites. a**, Single intravenous dose (3 mg/kg bodyweight) pharmacokinetics properties of MB-905 in mouse plasma (n = 6); **b**, Single oral doses (3, 30 and 550 mg/kg bodyweight) pharmacokinetics properties of MB-905 in mouse plasma (n = 2-6); **c,** Plasma putative metabolites after treatment with MB-905 (550 mg/kg, p.o.) (n=3); **d,** Evaluation of *in vitro* protein binding percentage of MB-905 (0.26 – 26 µM) in mouse plasma (n = 3); **e,** MB-905 (100 µM) or ketoconazole (0.5 µM- an inhibitor of CYP3A4) were incubated with recombinant human CYP3A4 and midazolam and evaluated the production of 1-hydroxy-midazolam (n = 3); **f,** MB-905 or quinidine (0.2 µM- an inhibitor of CYP2D6) were incubated with recombinant human CYP2D6 and dextromethorphan and evaluated the production of O-demethyl-dextromethorphan (n = 3); **g,** MB-905 (0.1, 1 and 10 µM) was incubated with human liver microssome (HLM) in the presence and in the absence of NADPH following analysis of MB-905 concentrations at 0, 5, 15, 30 and 60 minutes after NADPH (n = 2-3). Data were expressed as mean ± SEM (Standard Error of the Mean). (**e**, **f**) #p<0.05 significantly different from the negative control (blank); \*p<0.05 significantly different from the vehicle. One-way ANOVA followed by the Tukey Test were performed. Noncompartmental data analysis was performed using Phoenix WinNonlin®.

**Supplementary Table 1:**  Pharmacokinetic parameters for MB-905 in mice.

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| --- | --- | --- | --- |
| Compound | MB-905 | | |
| Dose and Route | 3 mg/kg (i.v.) | 30 mg/kg (p.o.) | 550 mg/kg (p.o.) |
| Cmax (ng/mL) | 155.16 | 569.97 | 1053.37 |
| Tmax (h) | 0.083 | 0.083 | 0.5 |
| T1/2 (h) | 0.22 | 1.11 | 2.72 |
| CL (mL/min/kg) | 918.38 | 1060.15 | 1843.18 |
| Vz (L/kg) | 19.04 | 102.21 | 434.2 |
| AUClast (h\*ng/mL) | 55.48 | 355.63 | 4392.27 |
| AUCall (h\*ng/mL) | 66.41 | 355.63 | 4392.27 |
| Ke (1/h) | 3.09 | 0.62 | 0.25 |
| F(%) | 100% | 53.50% | 36.10% |

Cmax: Peak concentration; Tmax: Time to reach Cmax; T1/2: Half-life; CL: Clearance; Vz: Volume of distribution; AUClast: Area under de curve (last); AUCall area under de curve (all); Ke: elimination rate constant; F: bioavailability. Noncompartmental data analysis was performed using Phoenix WinNonlin®. Data represents the mean values of 3-6 animals per group.

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**Supplementary Figure 2: Pharmacokinetic and putative metabolites of MB-905 in rats. a**, Single intravenous dose (1 mg/kg bodyweight) pharmacokinetics properties of MB-905 in rat plasma (n = 6); **b**, Single oral dose (30 mg/kg bodyweight) pharmacokinetics properties of MB-905 in rat plasma (n = 5); **c**, Plasma metabolites (5 metabolites) after treatment with MB-905 (30 mg/kg, p.o.) (n = 3); **d,** Single oral dose (30 mg/kg bodyweight) pharmacokinetics properties of MB-905 in lung plasma (n = 3); **e,** Lung metabolites (5 metabolites) after treatment with MB-905 (30 mg/kg, p.o.) (n = 3); **f,** Single oral dose (30 mg/kg bodyweight) pharmacokinetics properties of MB-905 in rat urine (n = 3); **g,** Urine metabolites (5 metabolites) after treatment with MB-905 (30 mg/kg, p.o.) (n = 3). Data were expressed as mean ± SEM (Standard Error of the Mean). Noncompartmental data analysis was performed using Phoenix WinNonlin®.

**Supplementary Table 2:**  Pharmacokinetic parameters for MB-905 in rats.

|  |  |  |
| --- | --- | --- |
| Compound | MB-905 | |
| Dose and Route | 1 mg/kg (i.v.) | 30 mg/kg (p.o.) |
| Cmax (ng/mL) | 123.61 | 370.47 |
| Tmax (h) | 0.083 | 0.25 |
| T1/2 (h) | 0.56 | 3.81 |
| CL (mL/min/kg) | 213.63 | 330.53 |
| Vz (L/kg) | 10.4 | 109.18 |
| AUClast (h\*ng/mL) | 77.12 | 1498.08 |
| AUCall (h\*ng/mL) | 77.12 | 1498.08 |
| Ke (1/h) | 1.23 | 0.18 |
| F(%) | 100% | 64.70% |

Cmax: Peak concentration; Tmax:Time to reach Cmax; T1/2: Half-life; CL: Clearance; Vz: Volume of distribution; AUClast: Area under de curve (last); AUCall: area under de curve (all); Ke: elimination rate constant; F: bioavailability. Noncompartmental data analysis was performed using Phoenix WinNonlin®. Data represents the mean values of 5-6 animals per group.

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**Supplementary Figure 3. hERG channel assay *in vitro*** **and** **cardiovascular safety pharmacology in *vivo***. **a**, Concentration-response curve of MB-905 on the hERG channel inhibition assay (% of hERG relative inhibition). Data are expressed as mean ± SEM (n=3) through non-linear regression; **b**, Systolic Blood Pressure in millimeter of mercury (mmHg); **c**, Diastolic Blood Pressure in mmHg; **d**, Heart Rate expressed as beats per minute (bpm); **e**, QT-interval in millisecond (ms) in rats treated with vehicle (5 ml/Kg, p.o.) or MB-905 (50 or 250 mg/Kg, p.o.) administered orally once a day for 7 consecutive days. Data were expressed as mean ± SEM (n= 4-6). **c-f**: statistical analyses were performed using mixed effects model followed by the Dunnet’s test.



**Supplementary Figure 4** – **Kinetin-ribose-5’-monophosphate as a substrate for 5’-nucleotidase.** Liver extracts from untreated Swiss webster mice, 20-week old, were incubated with MB-711 (Kinetin-ribose-5’-monophosphoramidate) or AMP as a substrate for a commercial reaction to detect 5’-nucletidase activity. Liver extracts enzymes cathepsin A or carboxylesterase 1 and histidine triad nucleotide-binding protein 1 (HINT1) released nucleotide monophosphate from MB-711, to be further used by 5’-nucleotidase (#ab235945 from [www.abcam.com](http://www.abcam.com)). Each column represents the means ± SEM of three independent experiments.