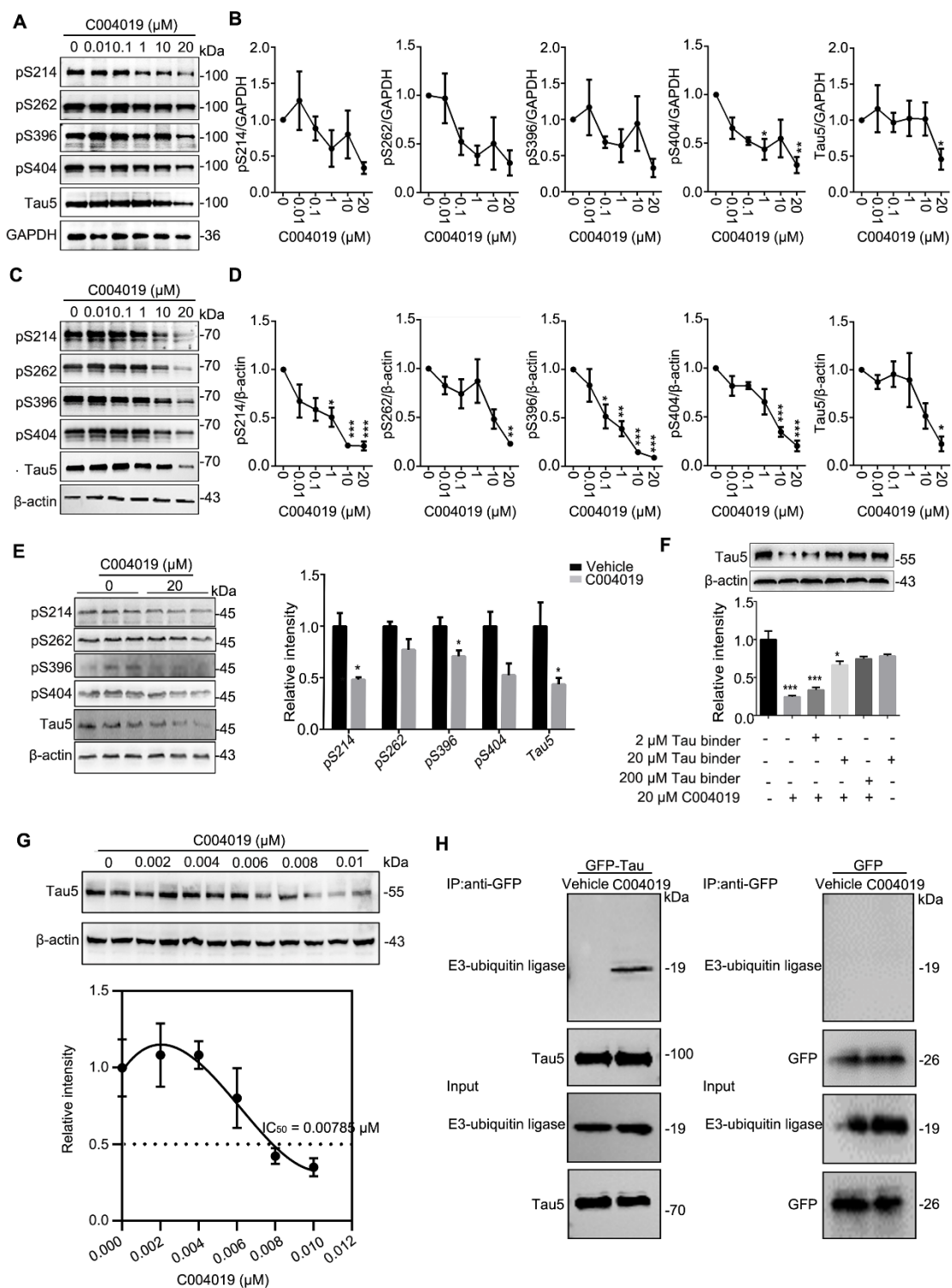


1 Supplementary Materials



2

3 **Figure S1 C004019 induces tau reduction in HEK293 cells with transient**
 4 **hTau expression in E3-ubiquitin-dependent manner.**

5 (A-D) HEK293 cells with transient transfection of EGFP-hTau (A-B) and

6 3xFlag-hTau (C-D) were incubated with C004019 of different concentrations (0,
7 0.01, 0.1, 1, 10, 20 μM) for 24 h, and a concentration-dependent tau reduction
8 was detected by Western blotting.

9 (E) C004019 (20 μM) decreased phosphorylated tau in SH-SY5Y cells
10 measured by Western blotting.

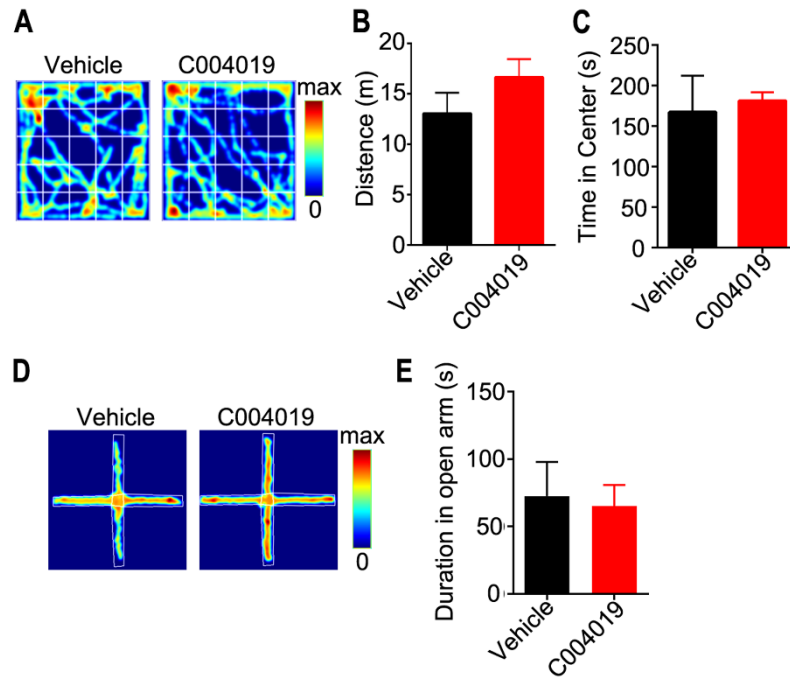
11 (F) Tau binder at high concentrations (20 μM and 200 μM) blocked the effect of
12 C004019 in removing tau proteins in HEK293-hTau cells treated with different
13 concentrations of tau binder (2 μM , 20 μM , and 200 μM) and 20 μM C004019
14 measured by Western blotting.

15 (G) HEK293-hTau cells were incubated with C004019 of different lower
16 concentrations (0, 0.002, 0.004, 0.006, 0.008, 0.01 μM) for 24 h, and a lower
17 concentration-dependent tau reduction was detected by Western blotting, IC_{50}
18 = 0.00785 μM .

19 (H) C004019 induced interaction of tau with E3-ubiquitin ligase (Vhl) in
20 EGFP-hTau cells (left) measured by immunoprecipitation using GFP antibody
21 and Western blotting using anti-Vhl and Tau5, respectively. HEK293 transiently
22 transfected EGFP-vector and treated with C004019 was used as a negative
23 control (right).

24 Data were expressed as mean \pm SEM, (B, D, E, F) *P < 0.05, **P < 0.01, ***P <
25 0.001 vs. 0 μM . Data in (B, D, F, G) were analyzed by one-way ANOVA. Data
26 in (E) were analyzed by Student's t-test.

27



28

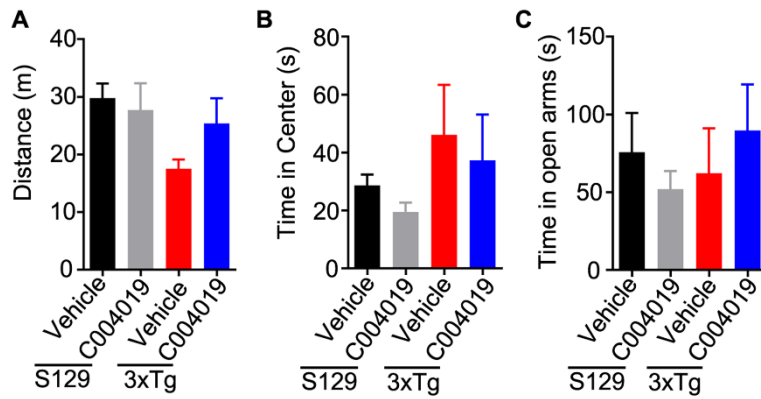
29 **Figure S2 C004019 did not affect motor ability and anxiety level of hTau**
 30 **mice.**

31 **(A-C)** C004019 treatment did not change the movement distance and the time
 32 spent staying in center during open field test (OFT) in hTau transgenic mice.

33 **(D-E)** C004019 did not affect open arm duration in elevated plus maze (EPM)
 34 test.

35 Data were expressed as mean \pm SEM (n = 5 ~ 6 for each group), Data were
 36 analyzed by Student's t-test.

37



38

39 **Figure S3 C004019 did not affect motor ability and anxiety level of**
 40 **3xTg-AD mice.**

41 **(A-B)** C004019 did not affect movement distance and center duration in OFT.

42 **(C)** C004019 did not affect the open arm duration in EPM test.

43 Data were expressed as mean \pm SEM (n = 9 ~ 10 for each group). Data were

44 analyzed by one-way ANOVA.