

The multifunctional dopamine D2/D3 receptor agonists also possess inhibitory activity against the full-length tau441 protein aggregation

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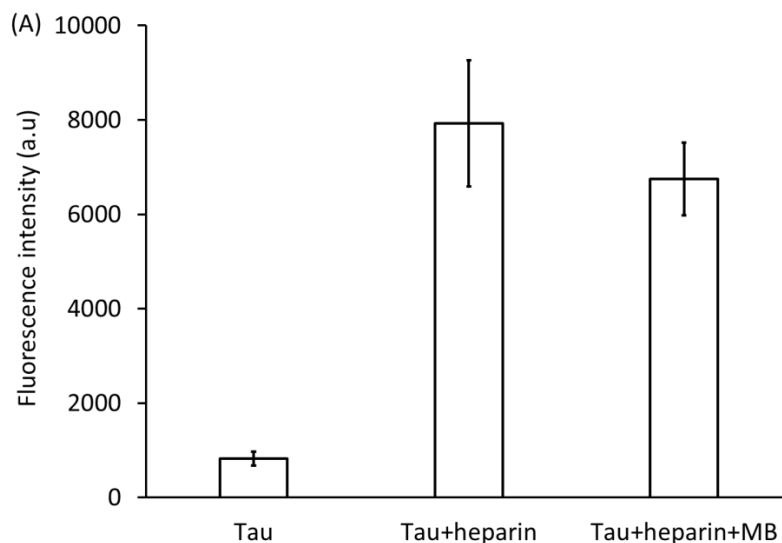


Figure S1. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 5 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

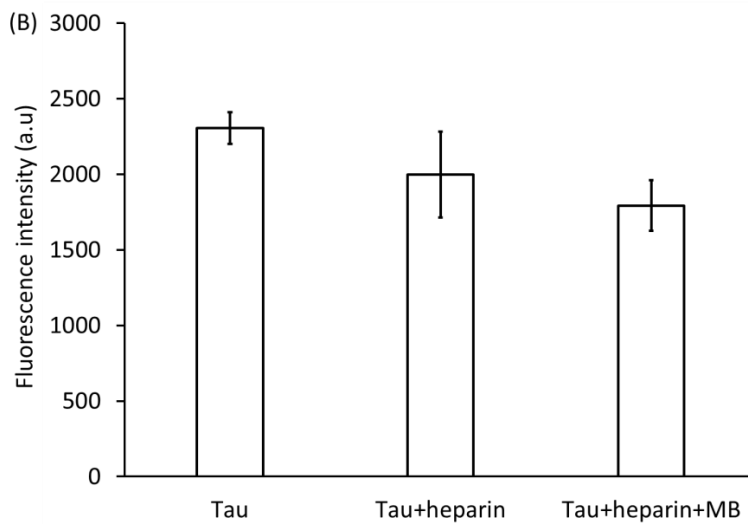


Figure S2. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

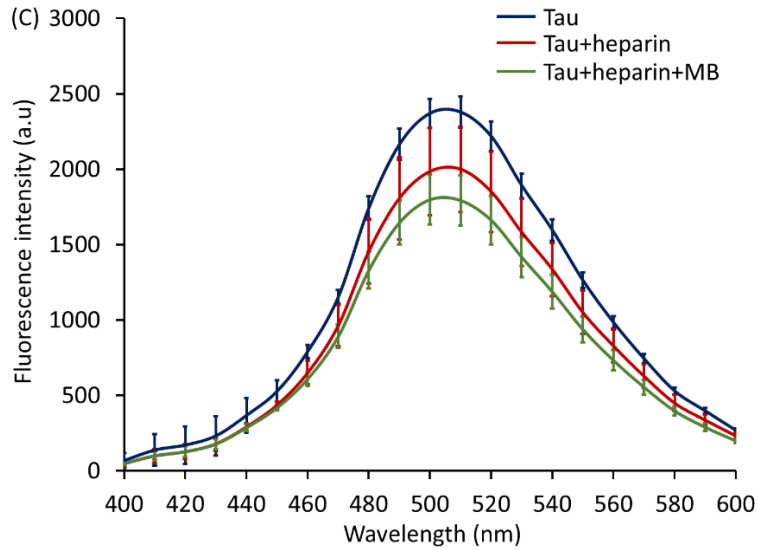


Figure S3. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of MB (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

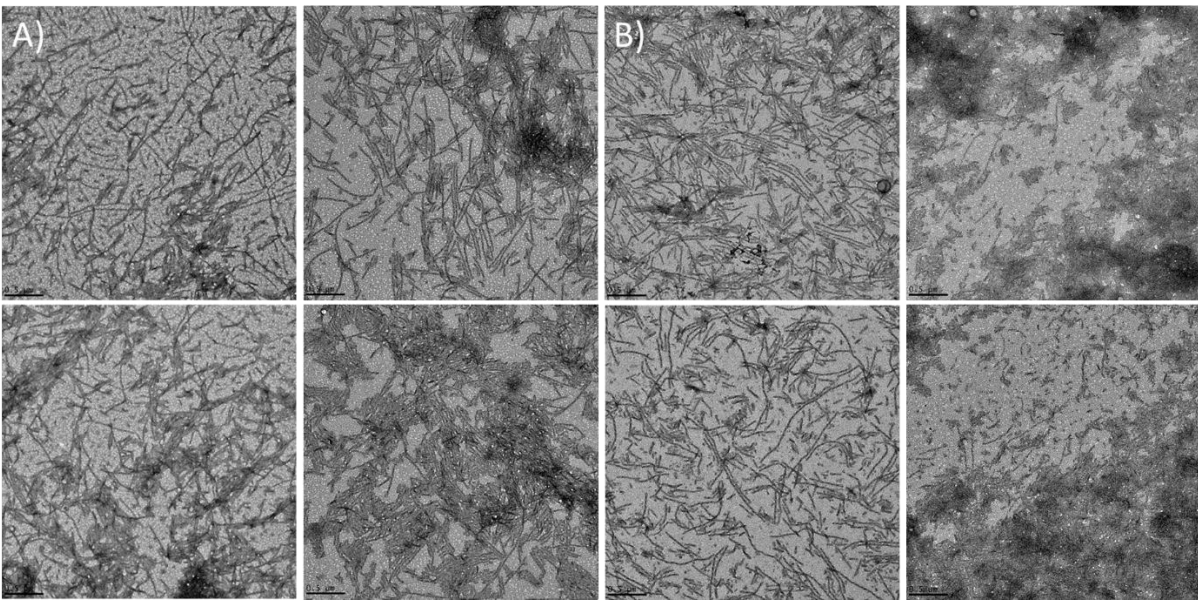


Figure S4. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and MB (final concentration 5 μ M). Magnification 22000x, scale bar 500 nm.

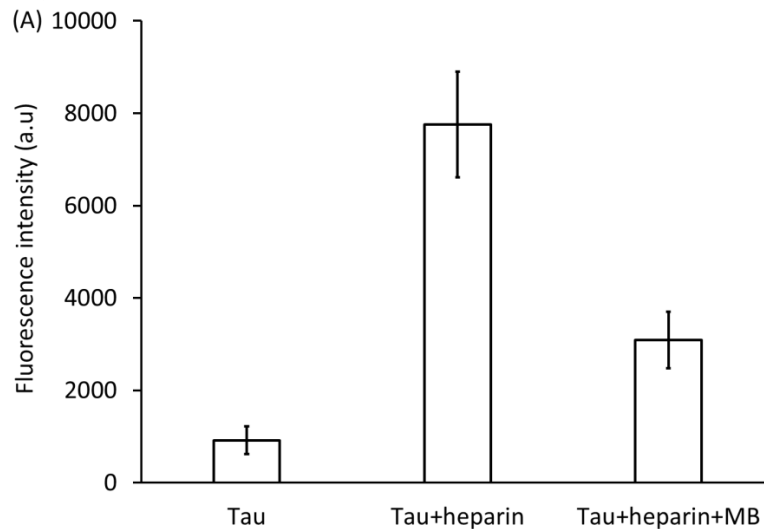


Figure S5. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 40 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

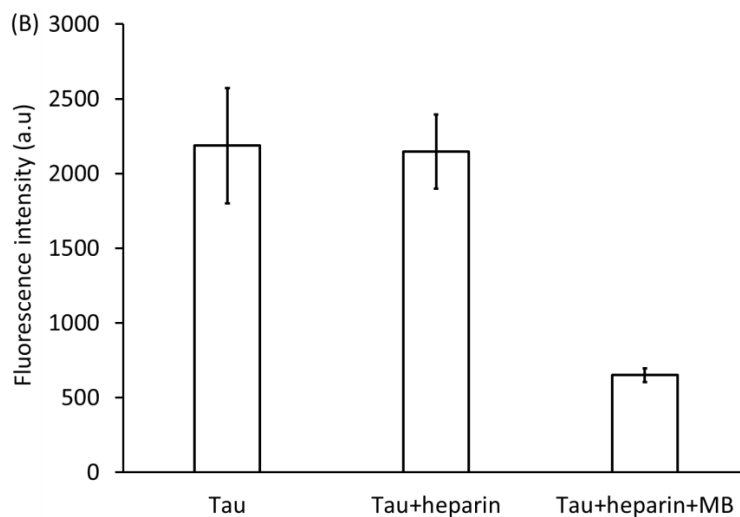


Figure S6. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

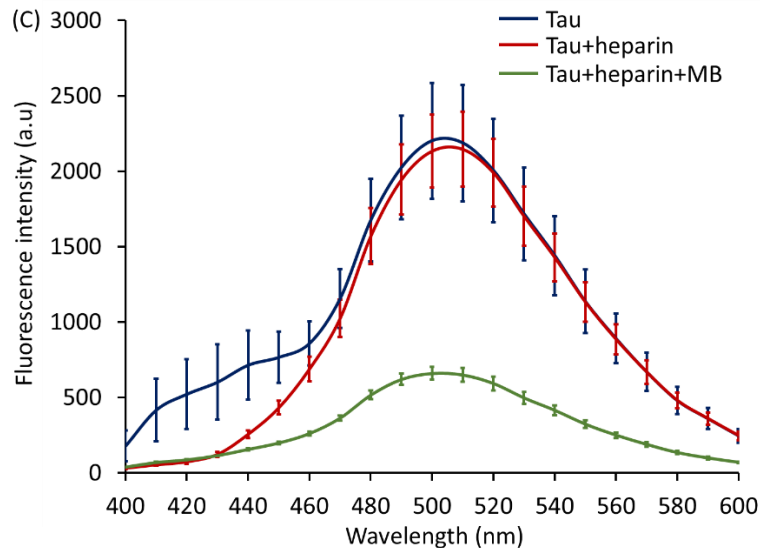


Figure S7. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of MB (final concentration 40 μ M). $\lambda_{\text{EX}} = 350$ nm, $\lambda_{\text{Em}} = 400$ -600 nm.

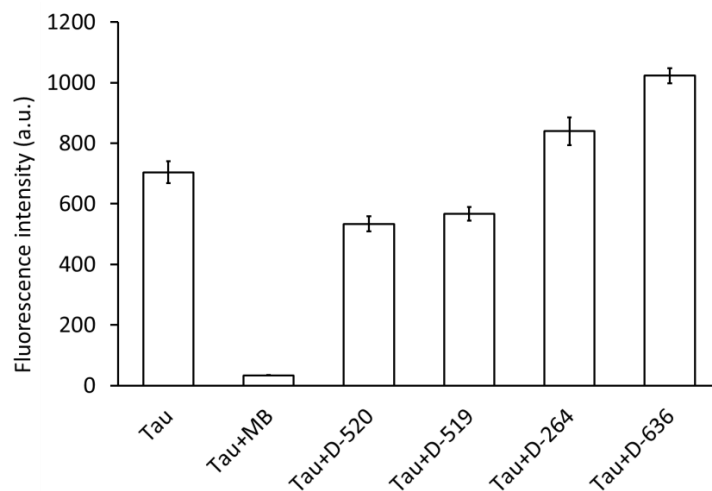


Figure S8. Average fluorescence emission spectra of Bis-ANS-bound samples, in the absence of heparin, after 1 hour of incubation of the samples at 37 °C. a) tau protein in buffer, b) tau protein in buffer and MB, c) tau protein in buffer and D-520, d) tau protein in buffer and D-519, e) tau protein in buffer and D-264, f) tau protein in buffer and D-636. Final concentration of all compounds 120 μ M. $\lambda_{\text{EX}} = 350$ nm, $\lambda_{\text{Em}} = 510$ nm

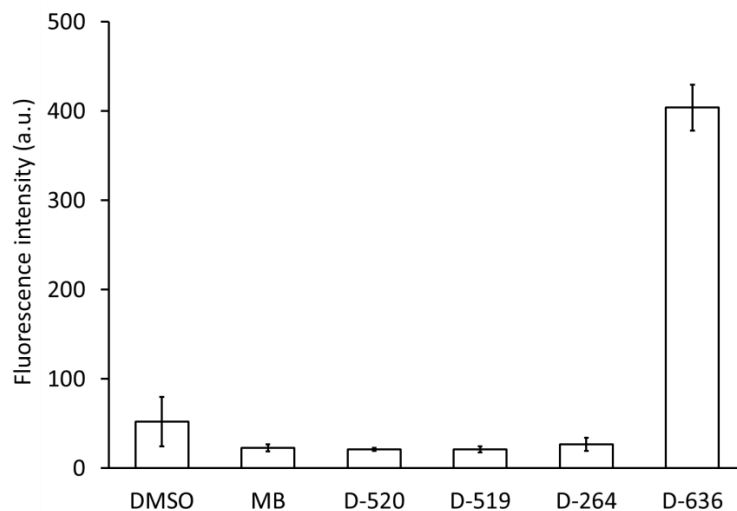


Figure S9. Average fluorescence emission spectra of Bis-ANS-bound samples in the absence of tau or heparin. a) DMSO in tau buffer, b) MB in tau buffer, c) D-520 in tau buffer, d) D-519 in tau buffer, e) D-264 in tau buffer, f) D-636 in tau buffer. Final concentration of all compounds 120 μ M. λ_{Ex} = 350 nm, λ_{Em} = 510 nm

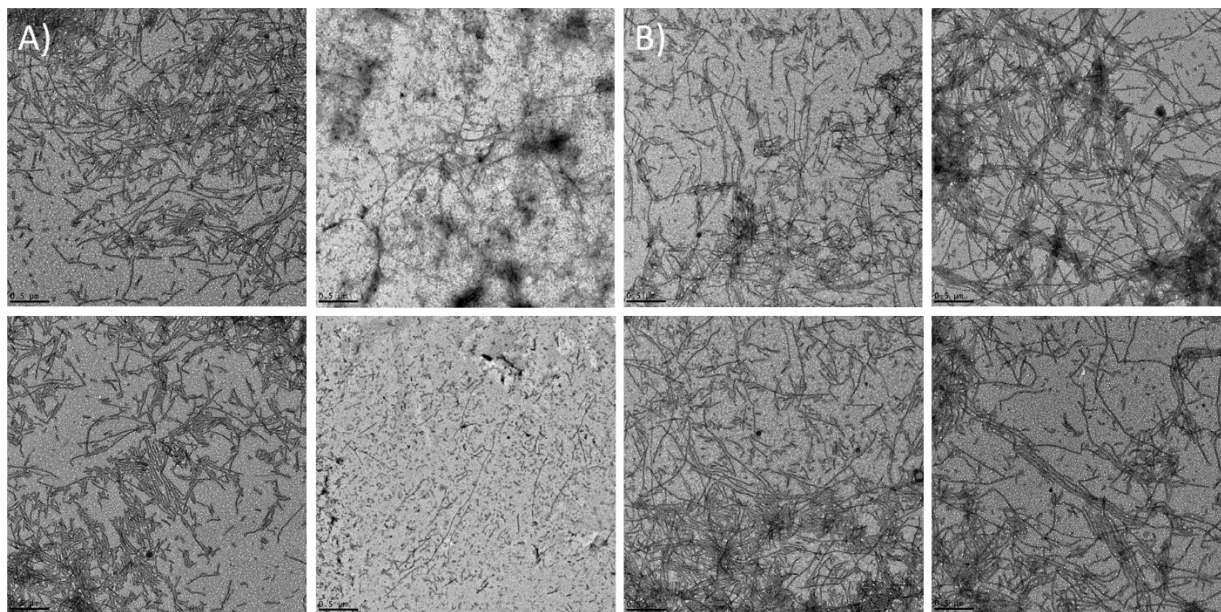


Figure S10. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and MB (final concentration 40 μ M). Magnification 22000x, scale bar 500 nm.

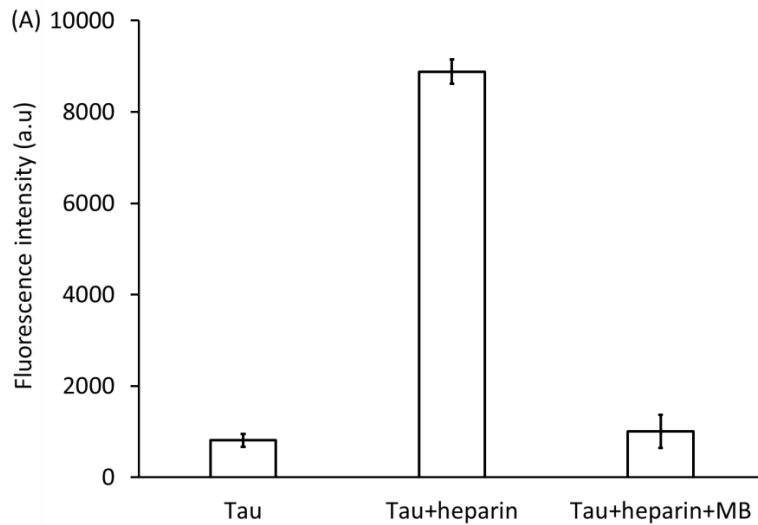


Figure S11. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

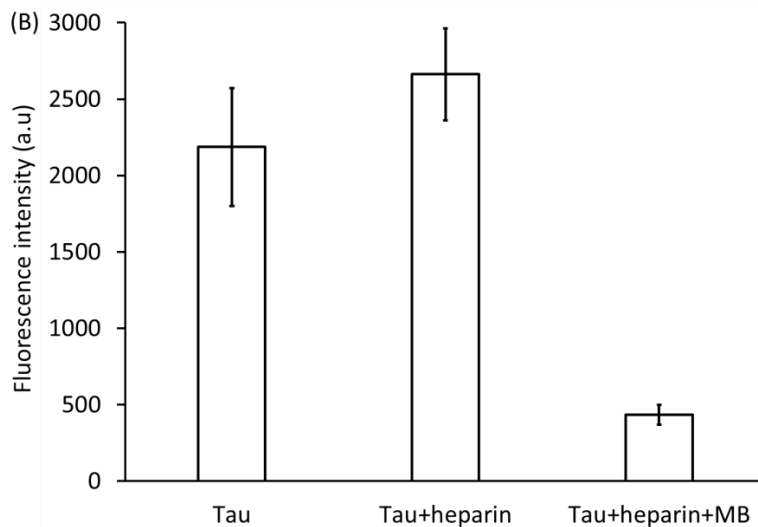


Figure S12. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

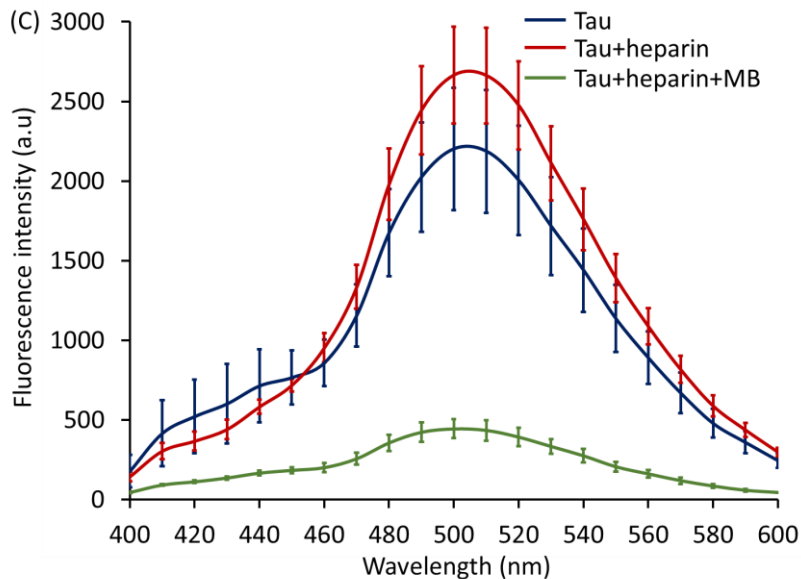


Figure S13. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of MB (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

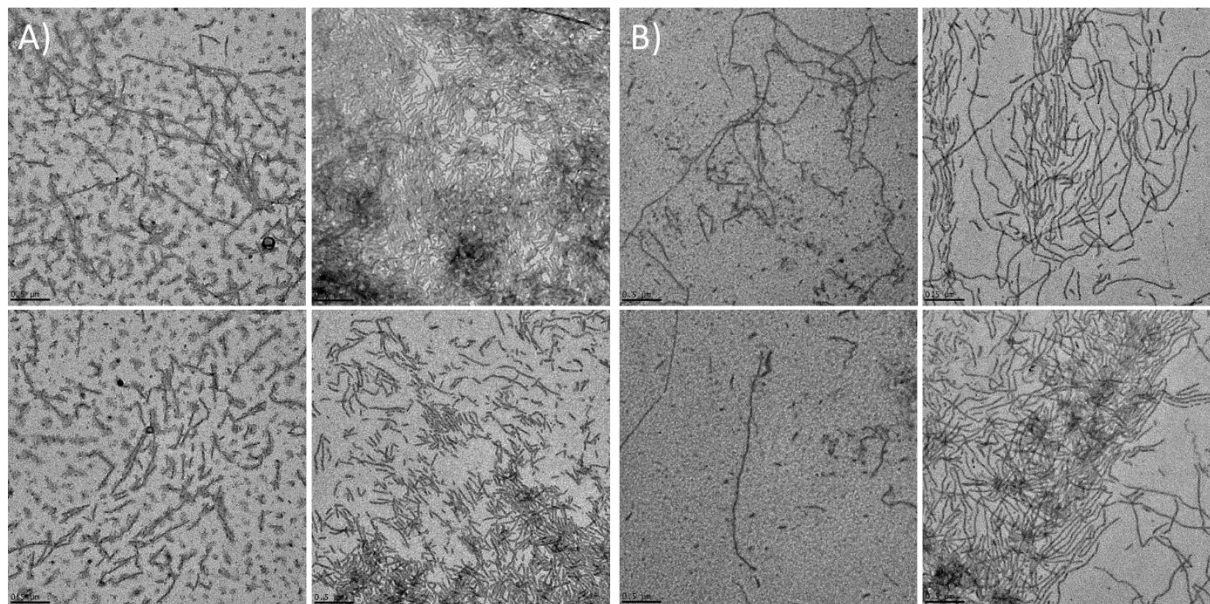


Figure S14. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and MB (final concentration 120 μ M). Magnification 22000x, scale bar 500 nm.

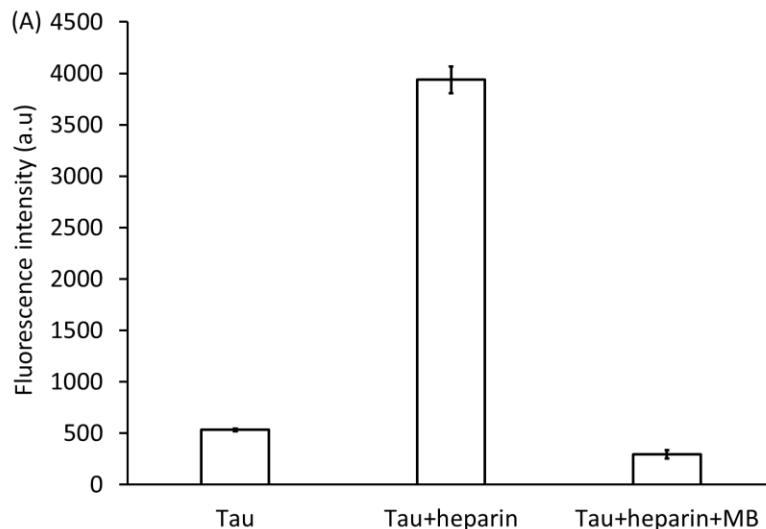


Figure S15. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 250 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

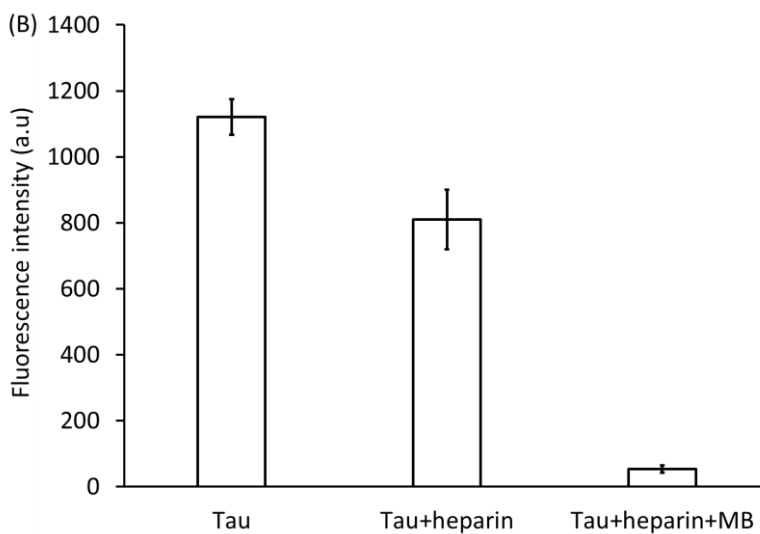


Figure S16. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of MB (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

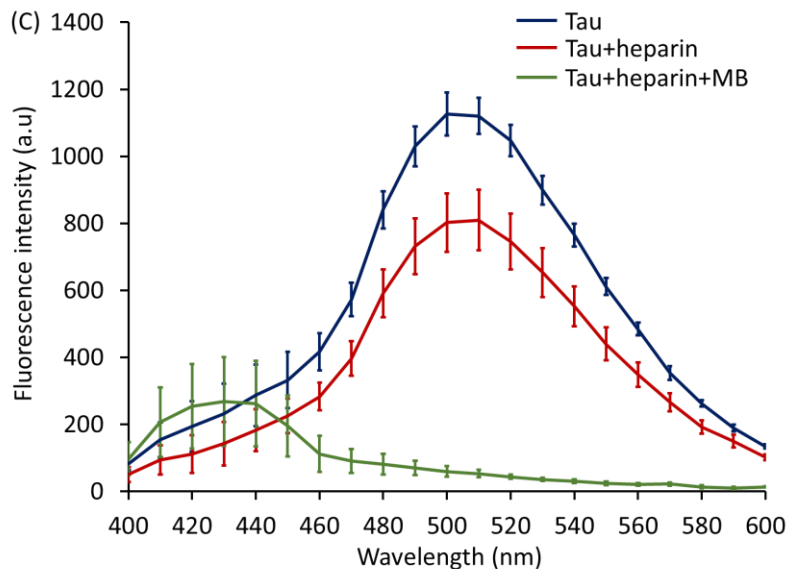


Figure S17. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of MB (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

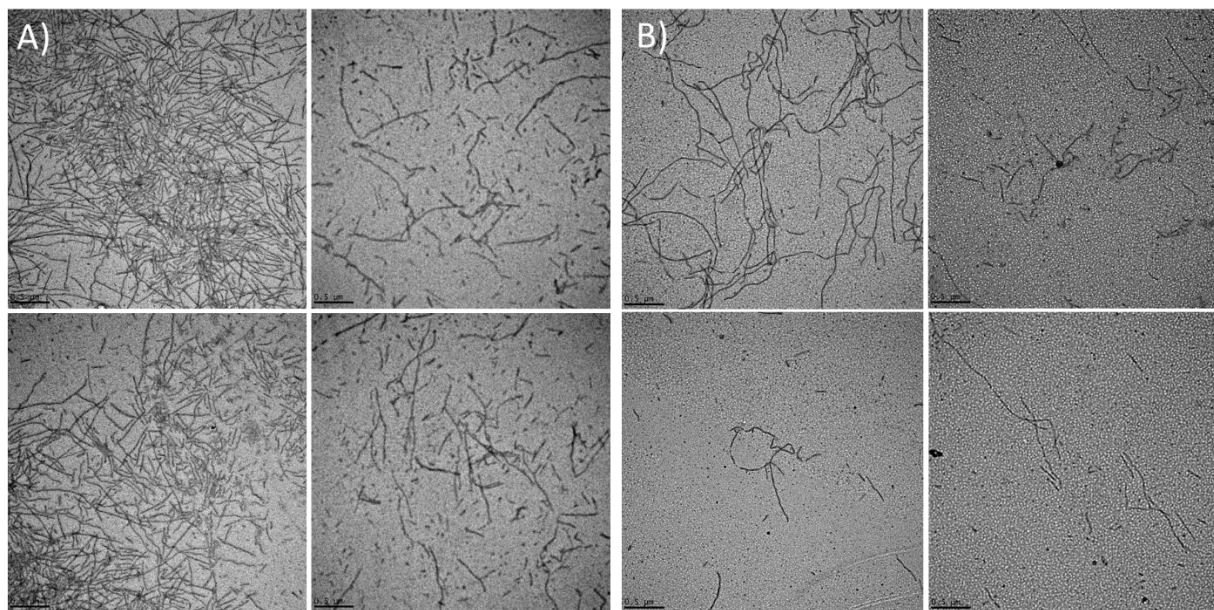


Figure S18. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and MB (final concentration 250 μ M). Magnification 22000x, scale bar 500 nm.

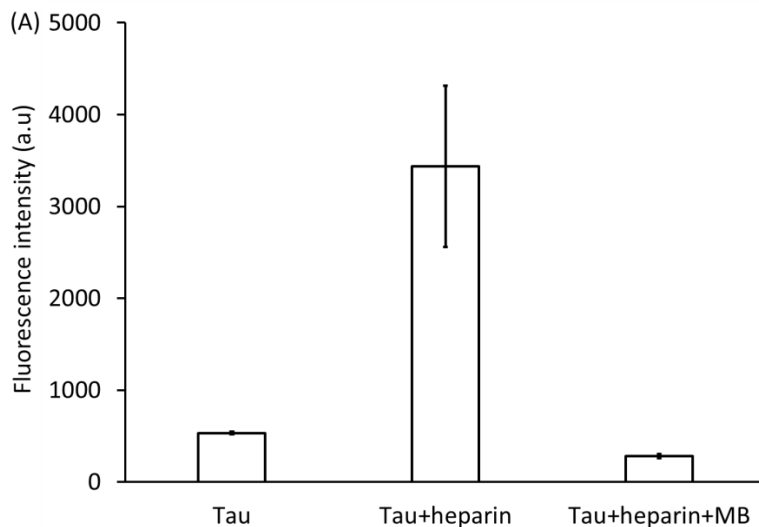


Figure S19. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of MB (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

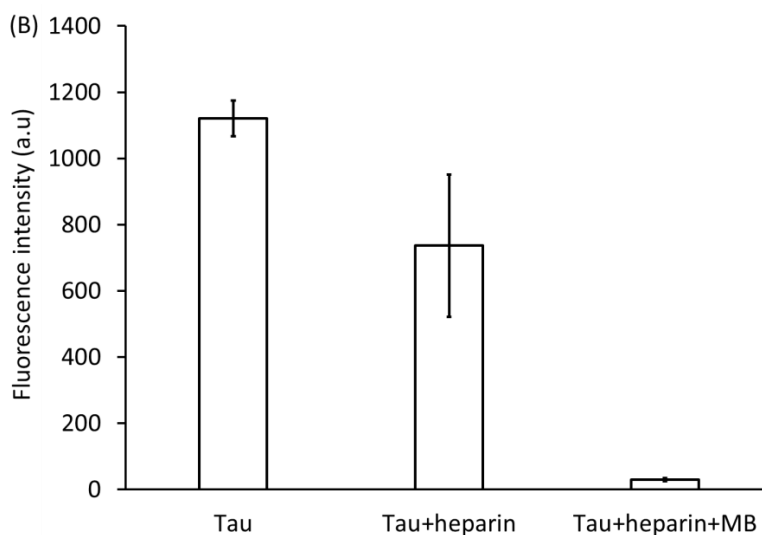


Figure S20. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of MB (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

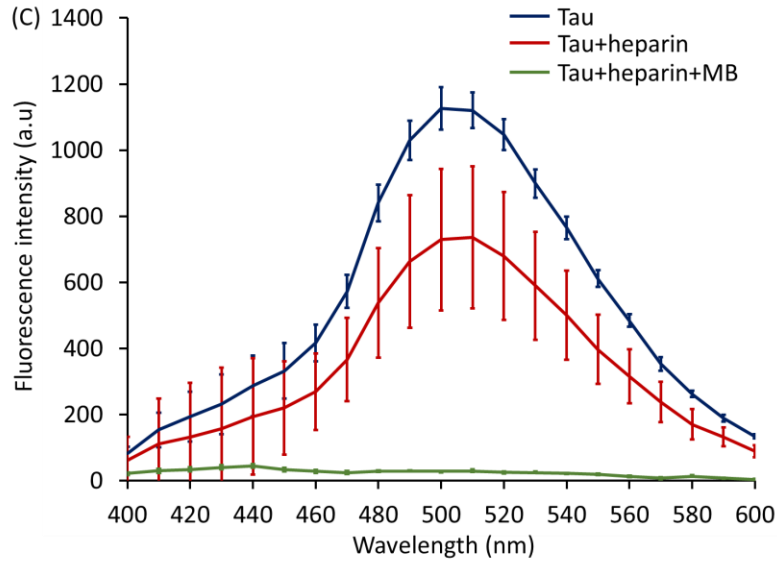


Figure S21. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of MB (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

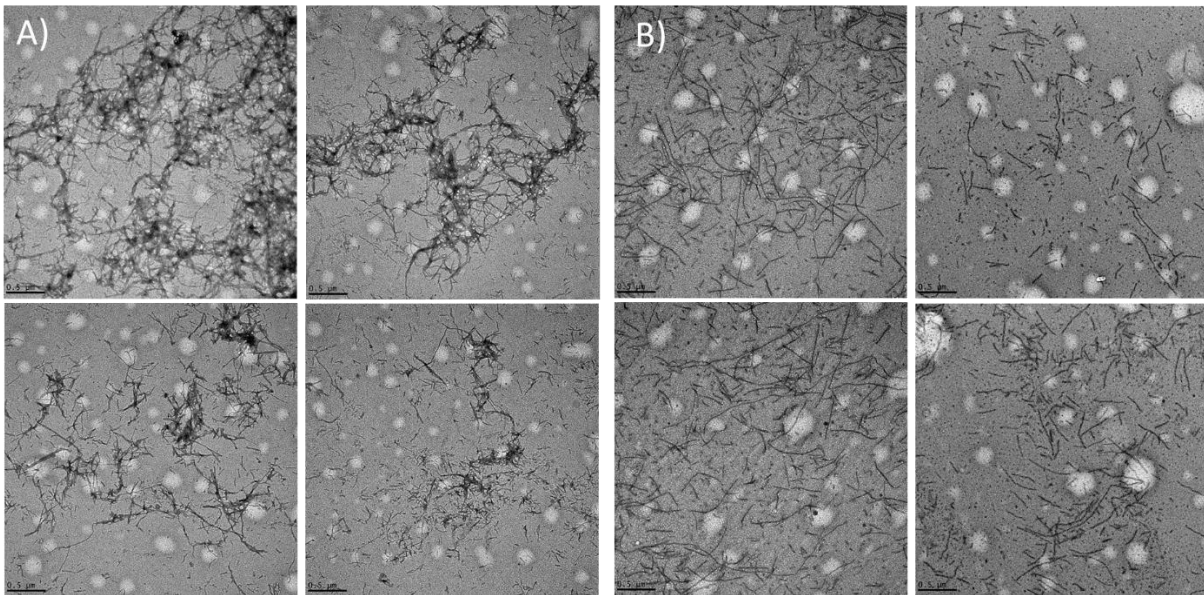


Figure S22. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with MB (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

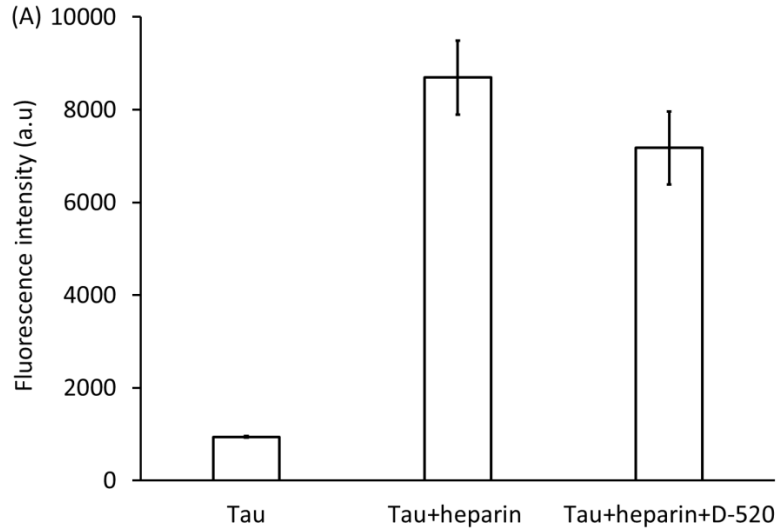


Figure S23. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 5 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

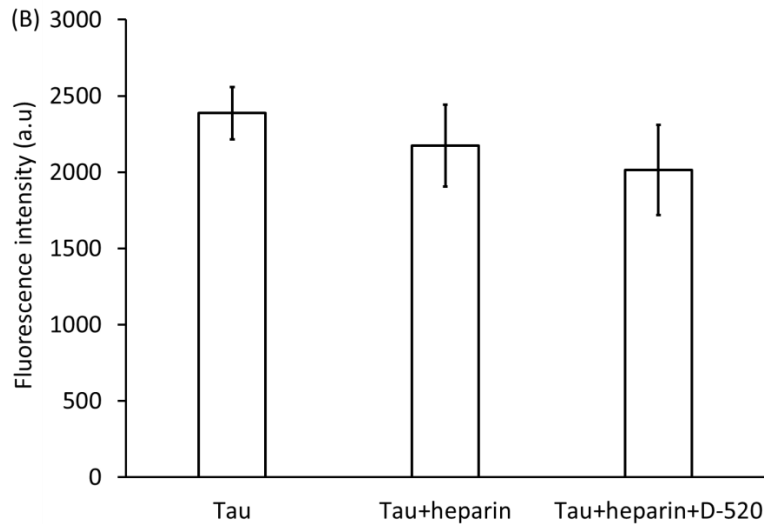


Figure S24. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

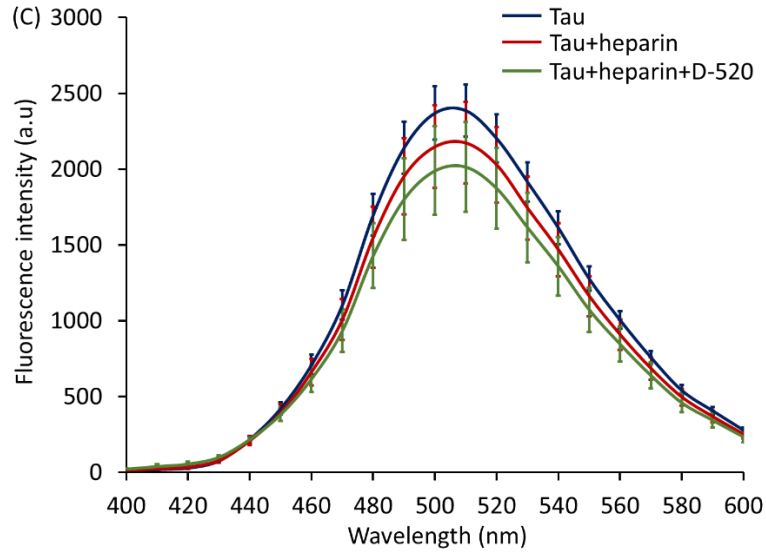


Figure S25. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-520 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

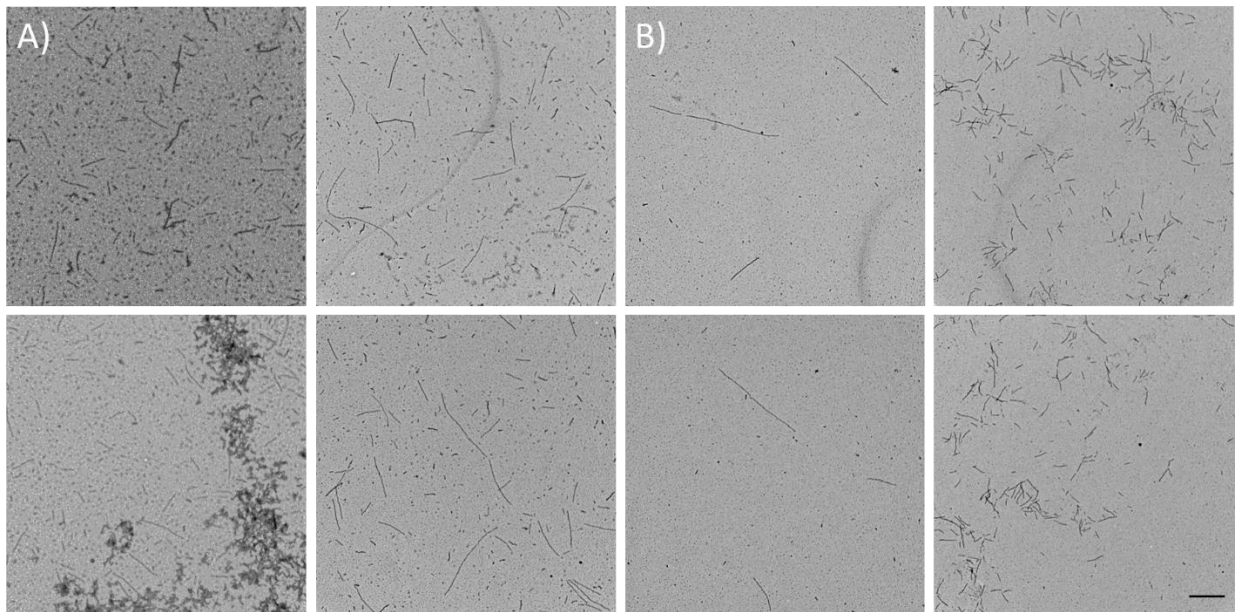


Figure S26. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-520 (final concentration 5 μ M). Magnification 22000x, scale bar 500 nm.

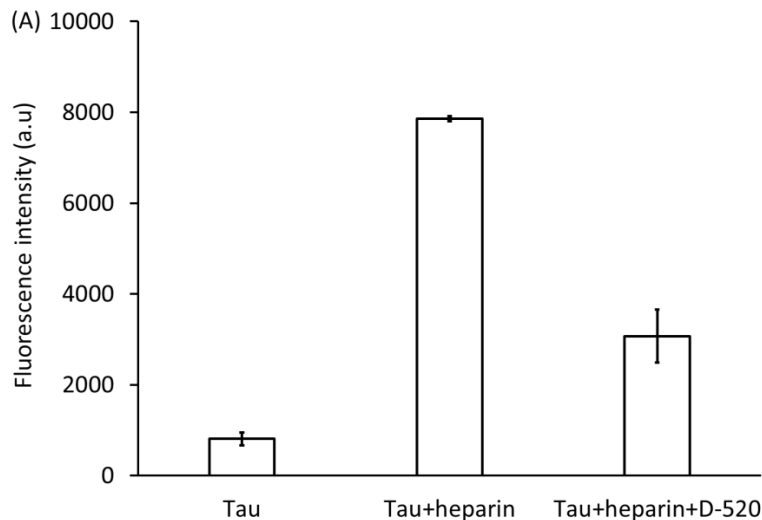


Figure S27. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 40 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

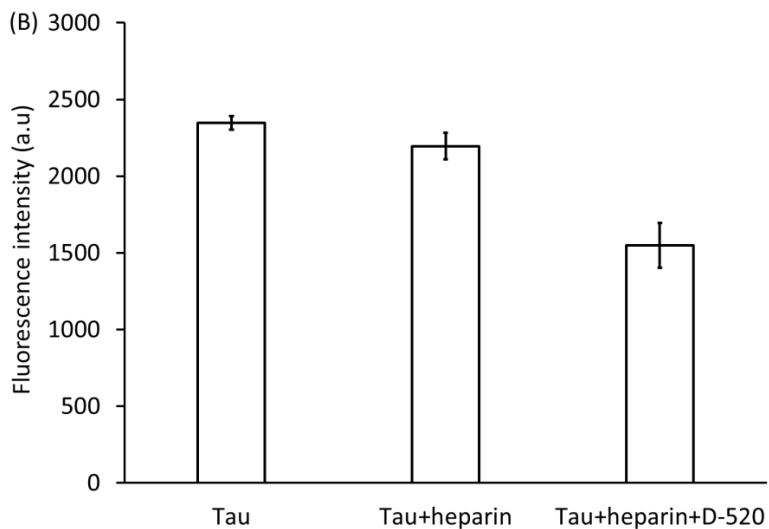


Figure S28. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

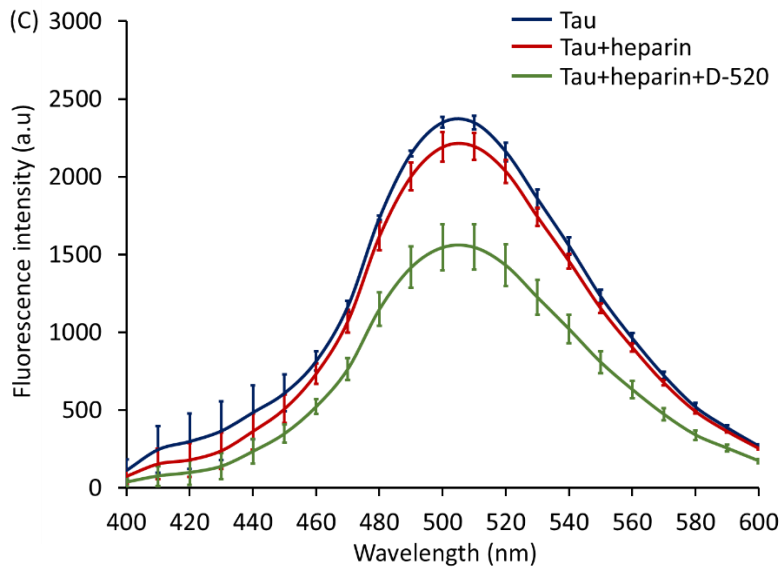


Figure S29. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-520 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

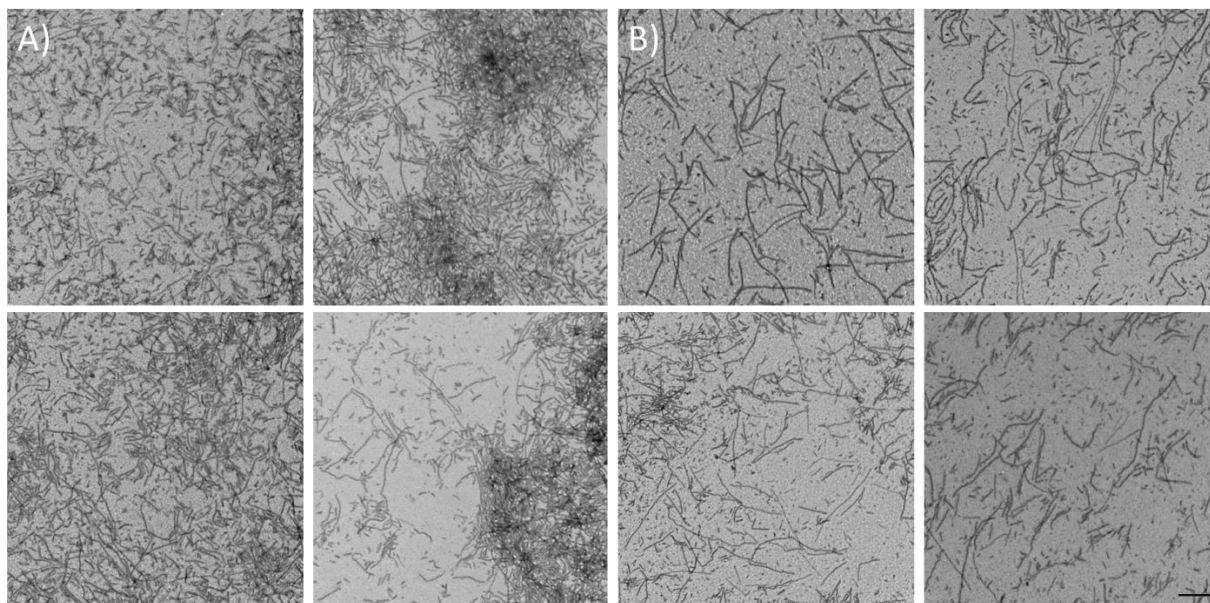


Figure S30. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-520 (final concentration 40 μ M). Magnification 22000x, scale bar 500 nm.

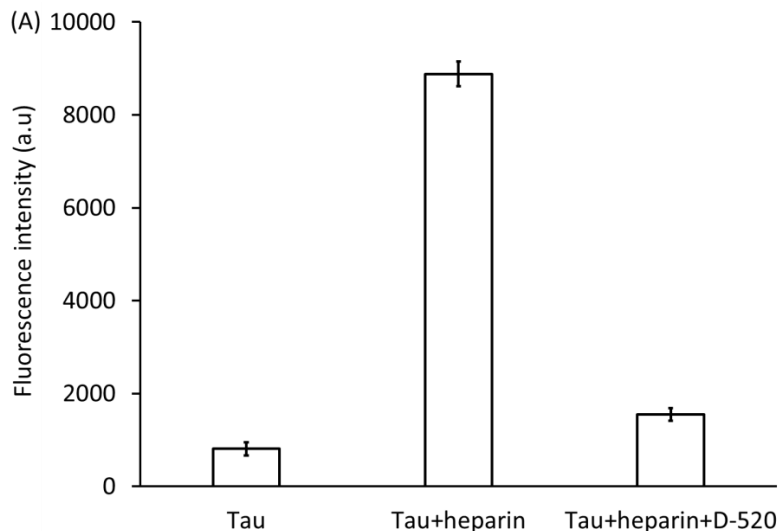


Figure S31. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

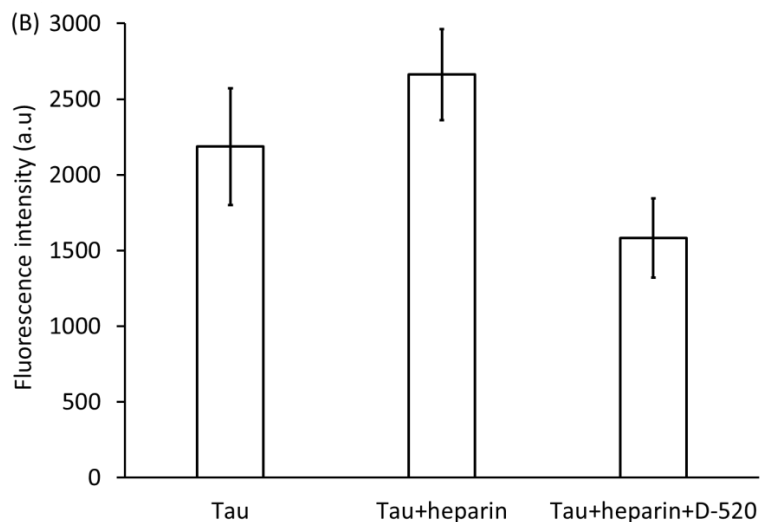


Figure S32. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

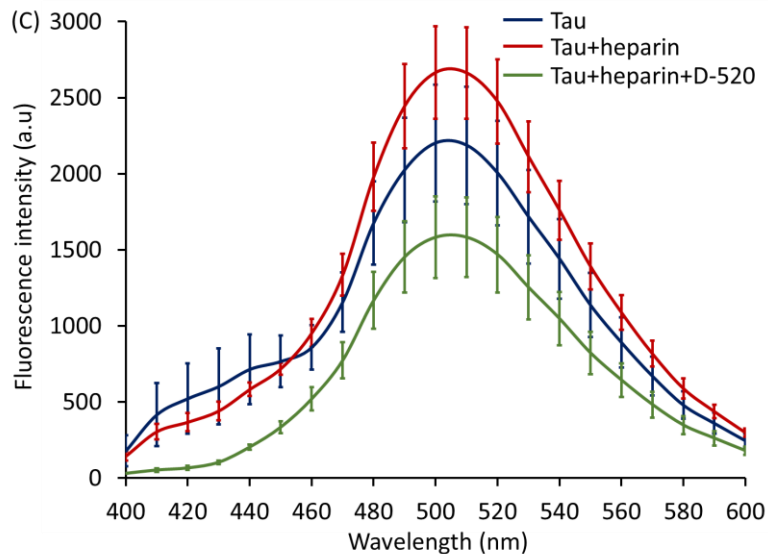


Figure S33. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-520 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

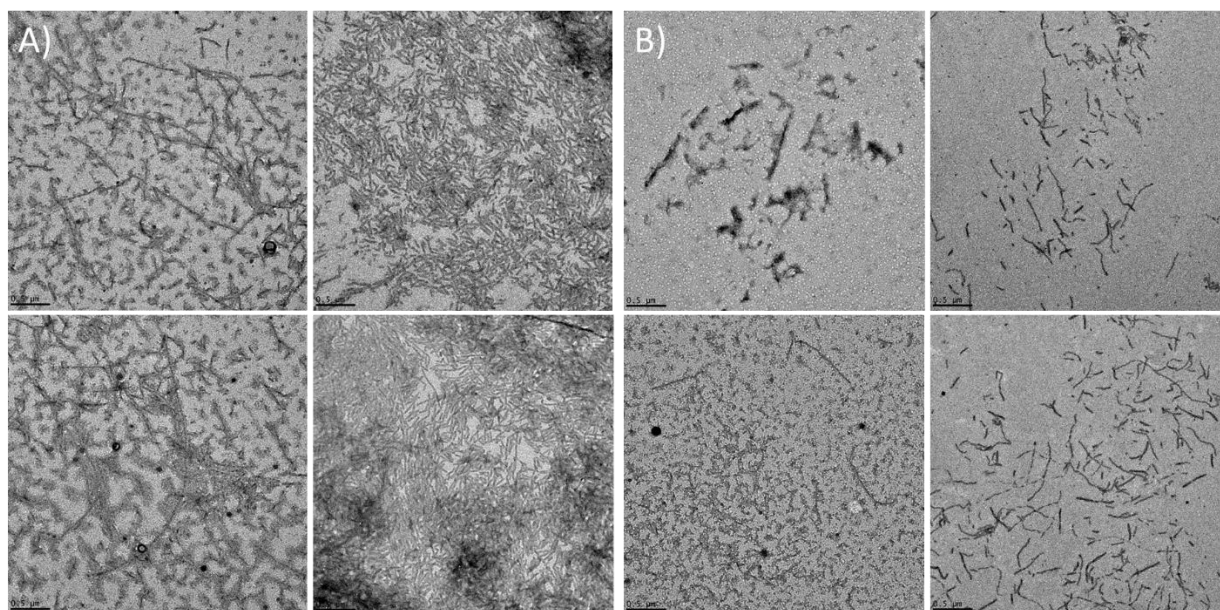


Figure S34. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-520 (final concentration 120 μ M). Magnification 22000x, scale bar 500 nm.

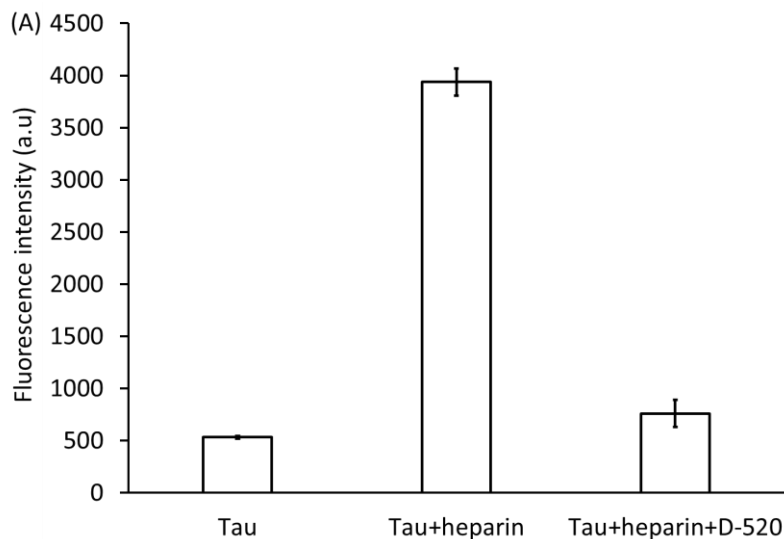


Figure S35. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 250 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

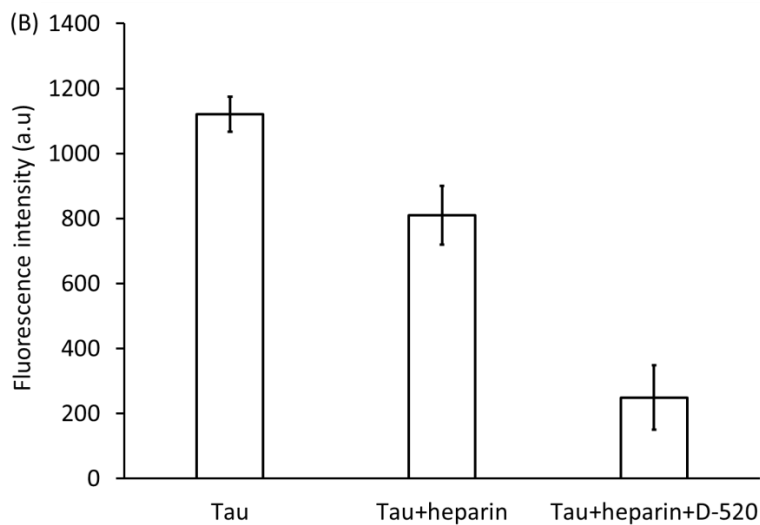


Figure S36. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-520 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

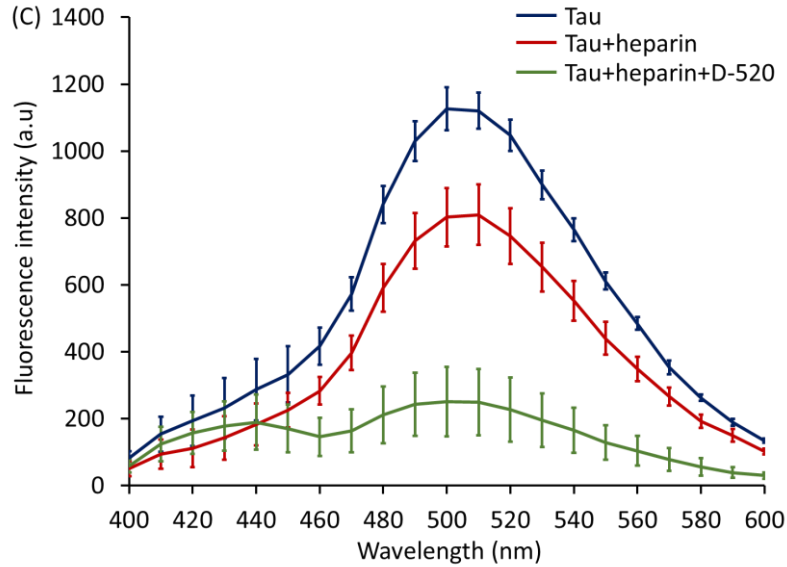


Figure S37. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-520 (final concentration 250 μM). $\lambda_{\text{Ex}}=350\text{ nm}$, $\lambda_{\text{Em}}=400\text{-}600\text{ nm}$.

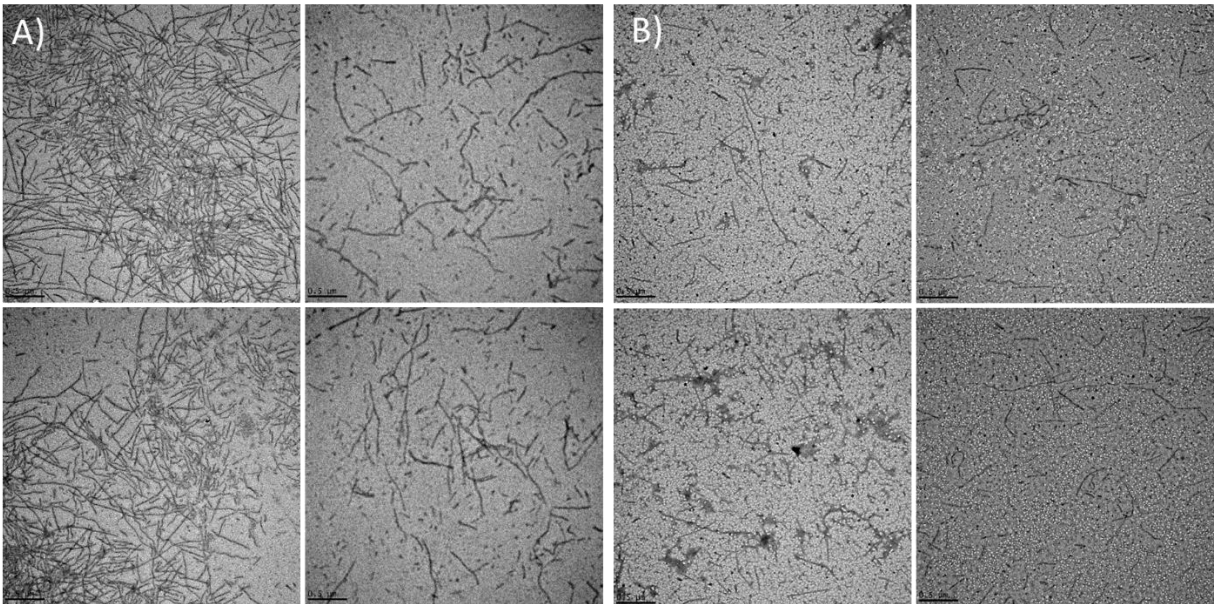


Figure S38. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-520 (final concentration 250 μM). Magnification 22000x, scale bar 500 nm.

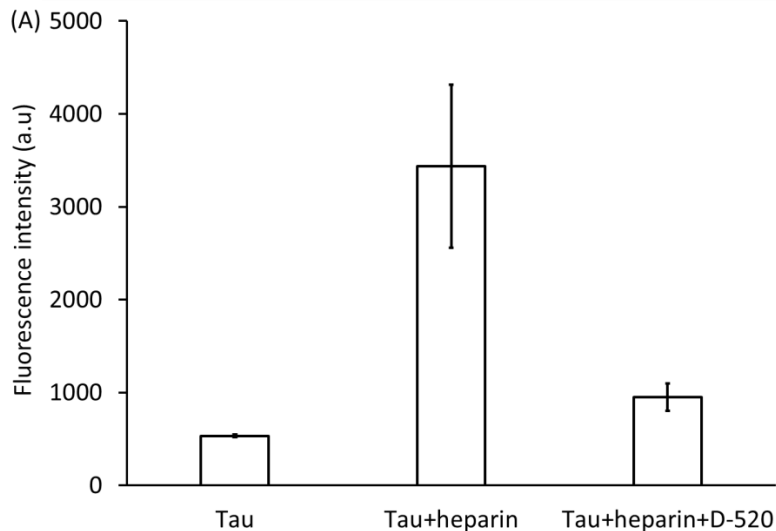


Figure S39. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-520 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

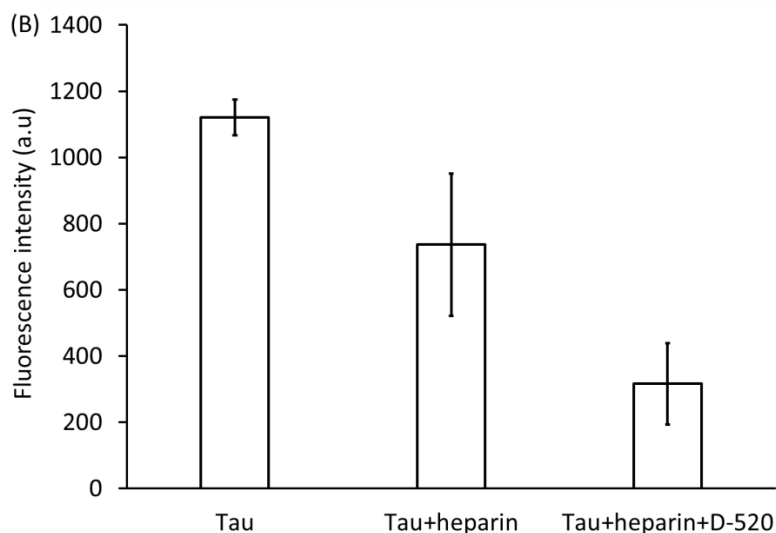


Figure S40. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-520 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

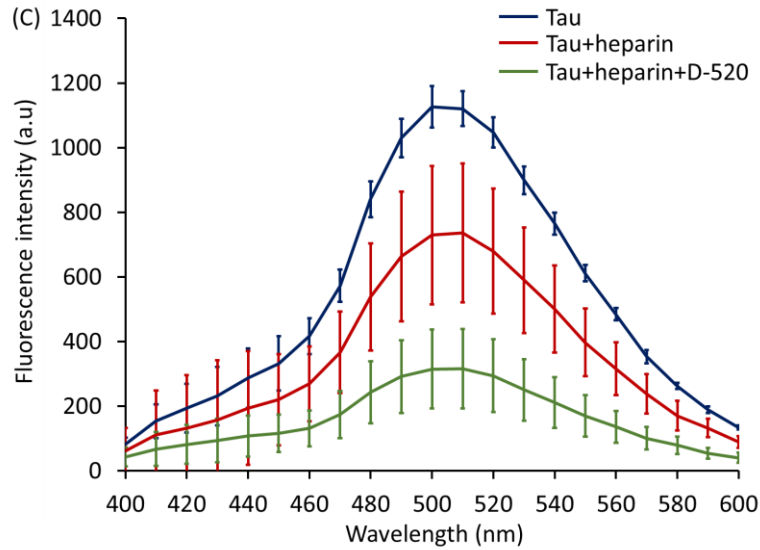


Figure S41. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-520 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

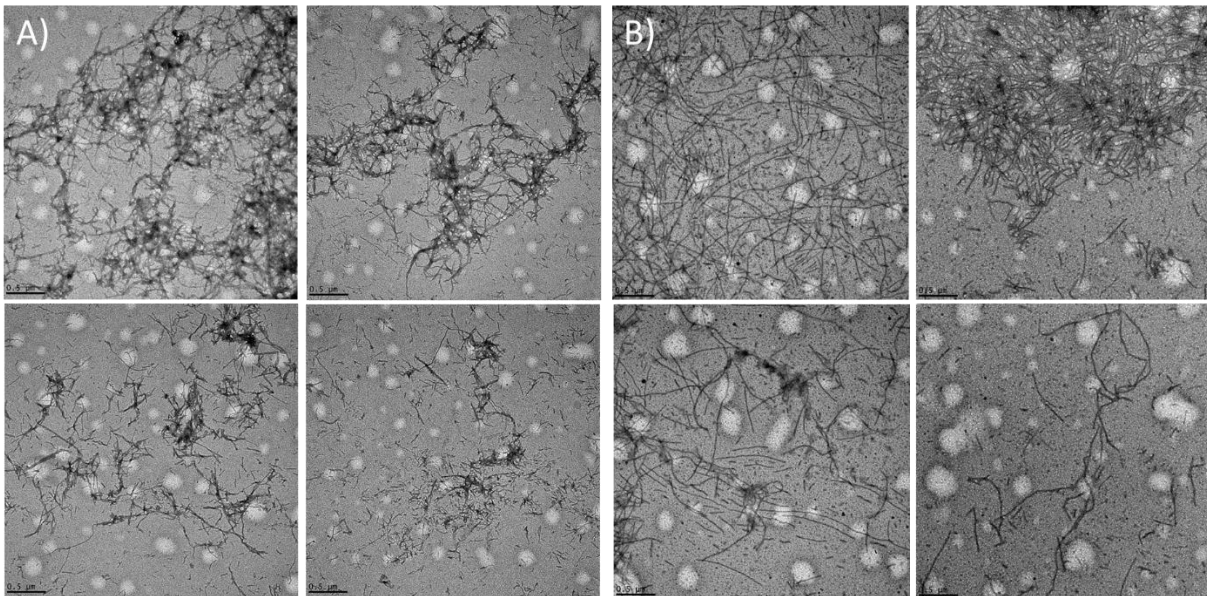


Figure S42. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with D-520 (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

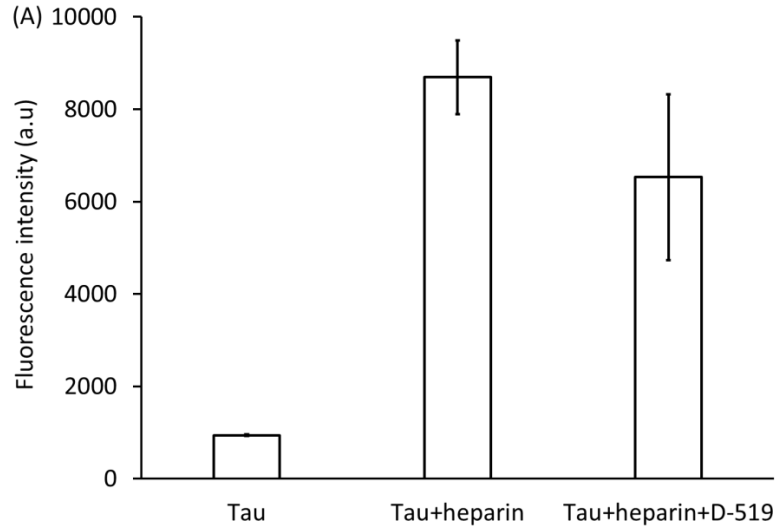


Figure 43. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 5 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

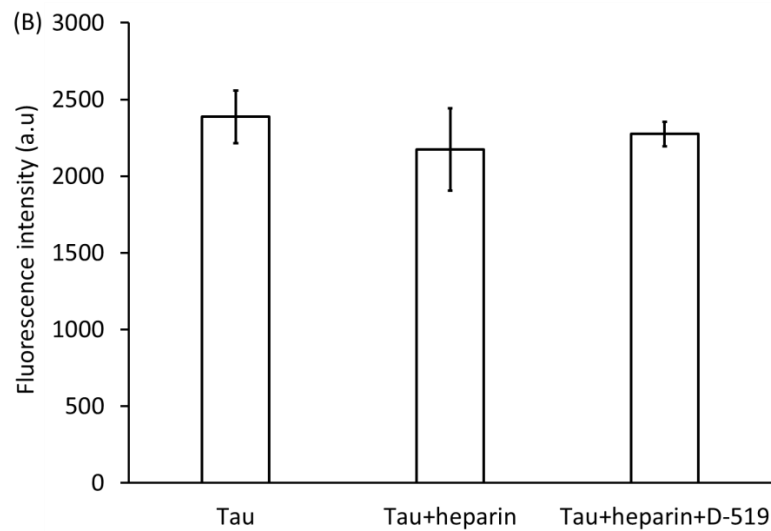


Figure S44. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

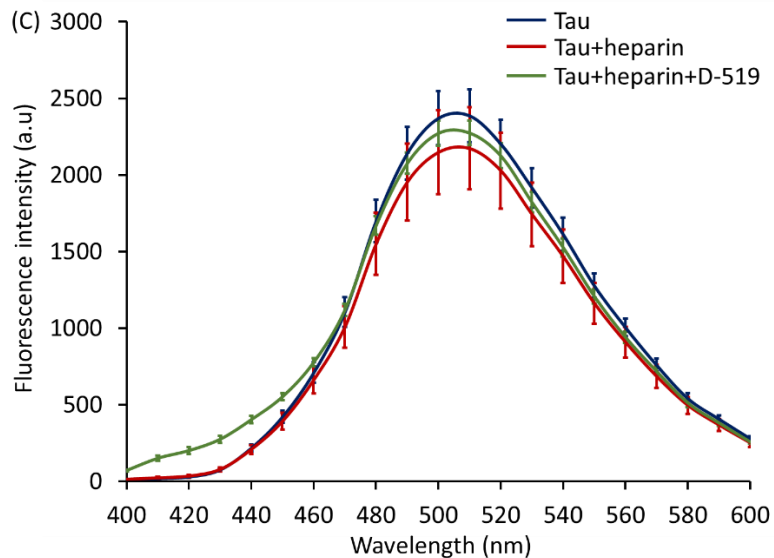


Figure 45. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-519 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

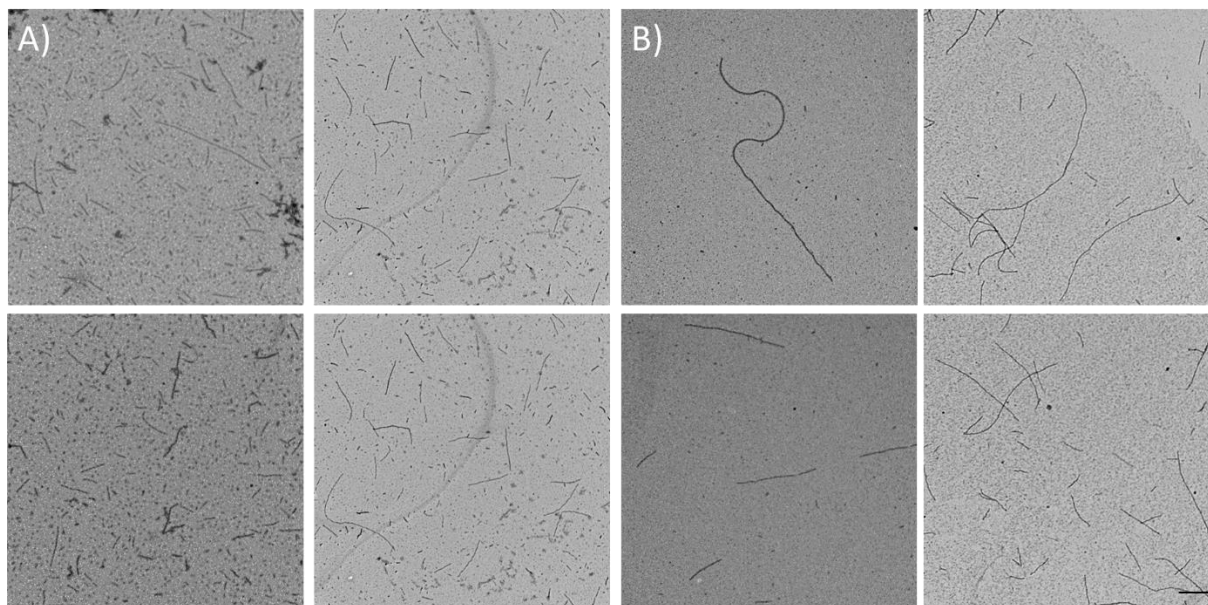


Figure S46. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-519 (final concentration 5 μ M). Magnification 22000x, scale bar 500 nm.

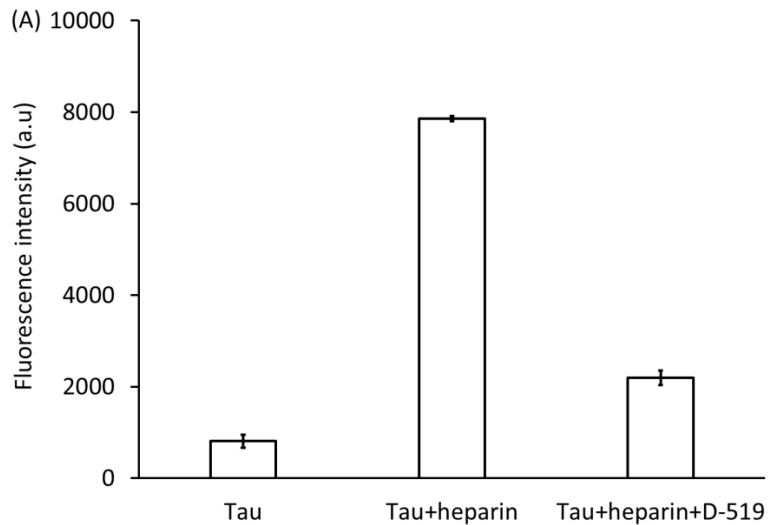


Figure S47. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 40 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

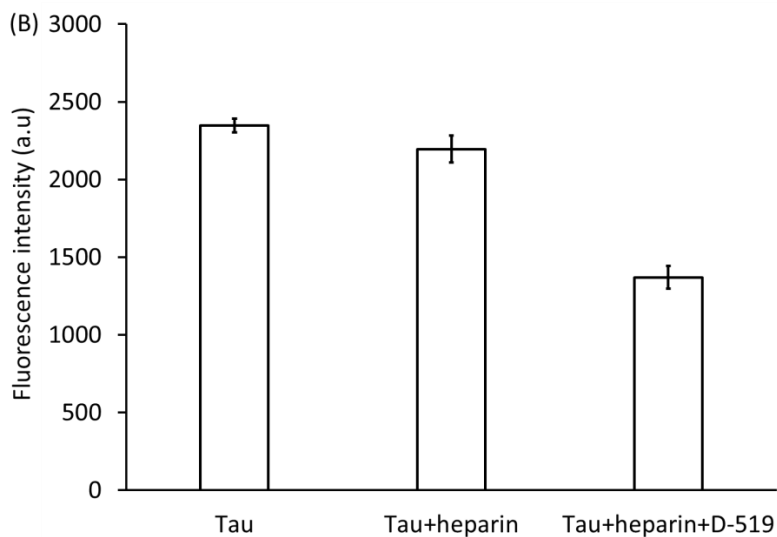


Figure S48. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

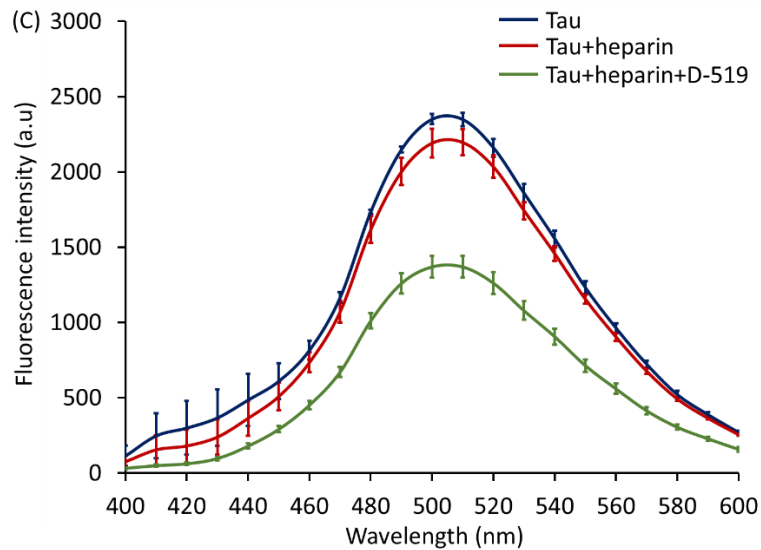


Figure S49. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-519 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

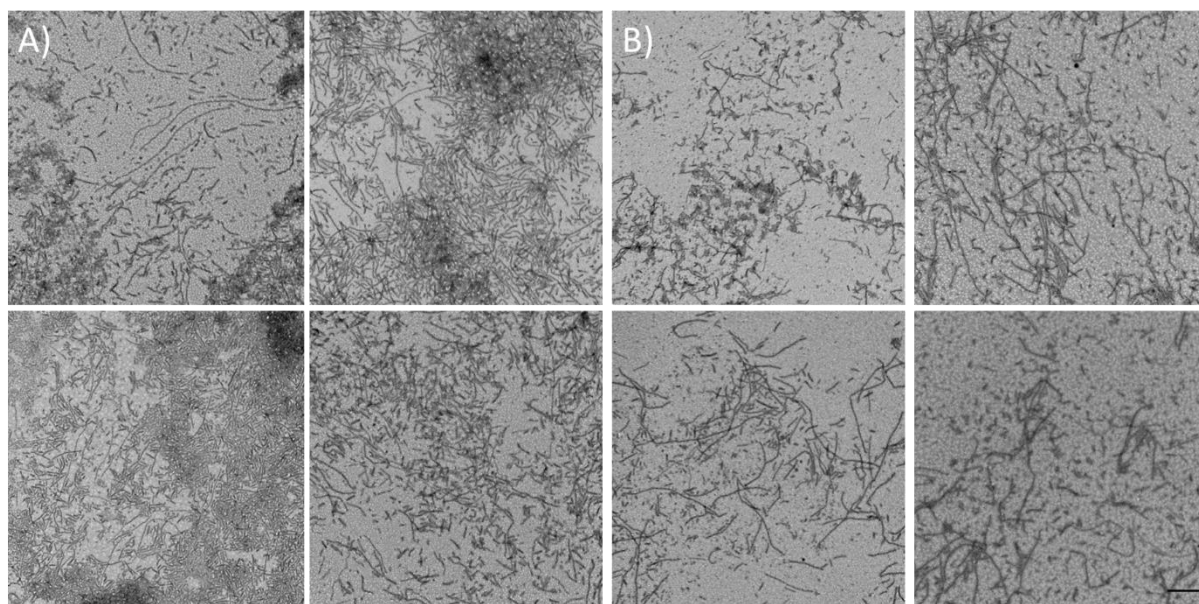


Figure S50. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-519 (final concentration 40 μ M). Magnification 22000x, scale bar 500 nm.

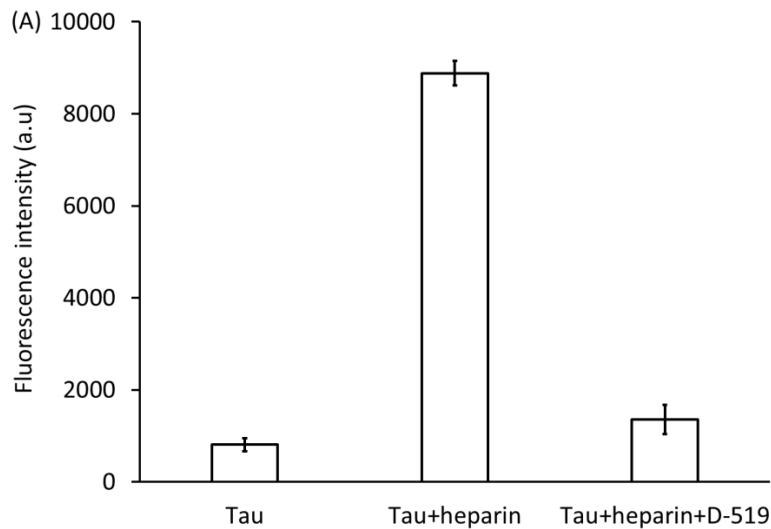


Figure S51. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

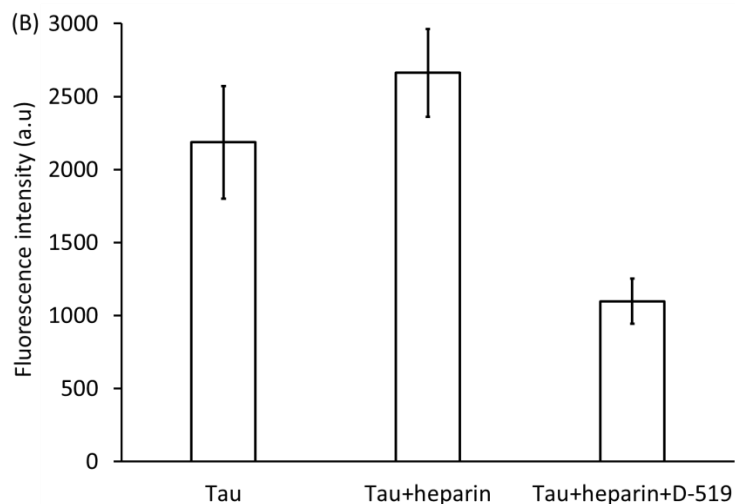


Figure S52. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

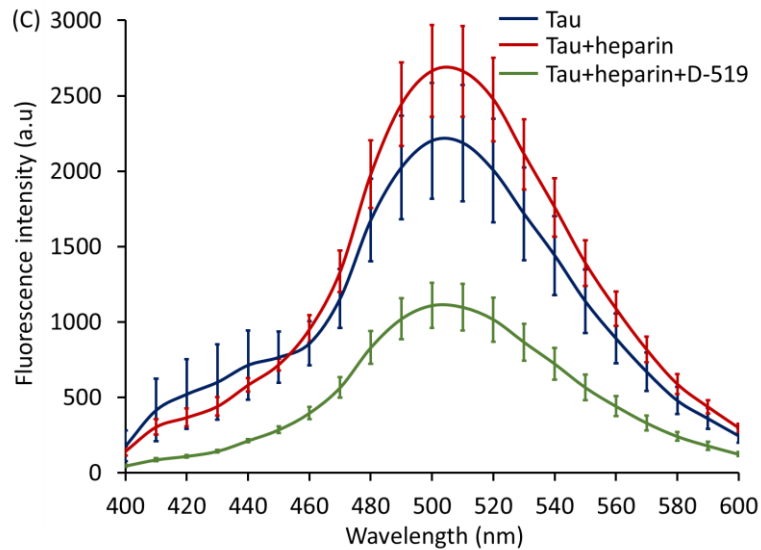


Figure S53. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-519 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

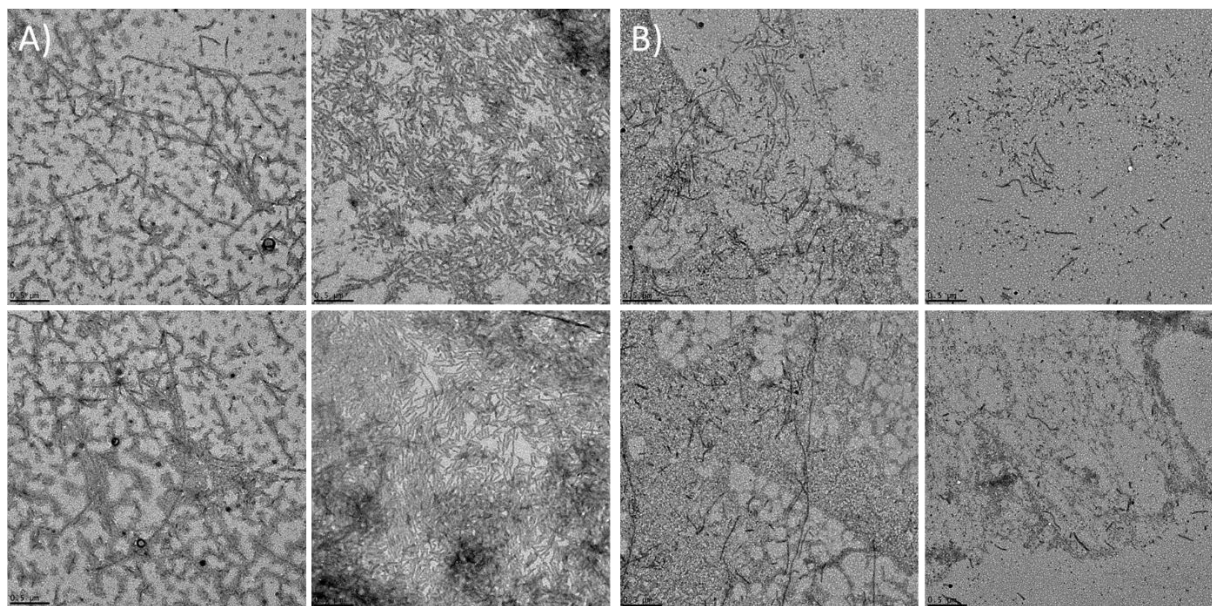


Figure S54. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-519 (final concentration 120 μ M). Magnification 22000x, scale bar 500 nm.

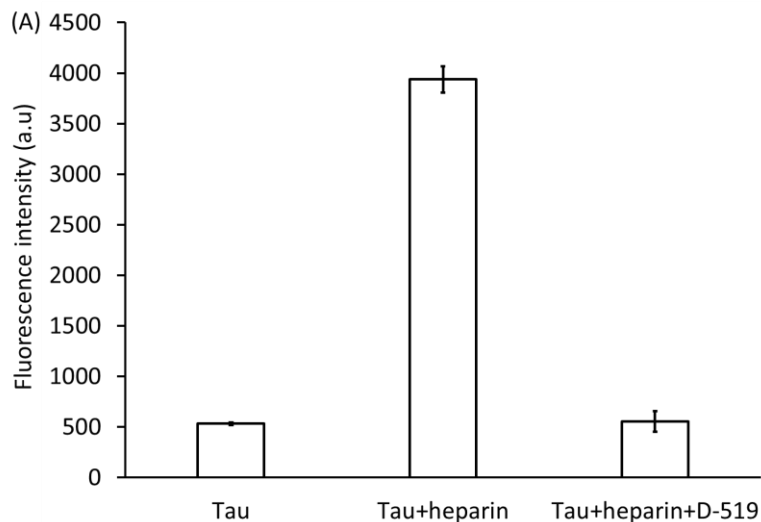


Figure S55. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 250 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

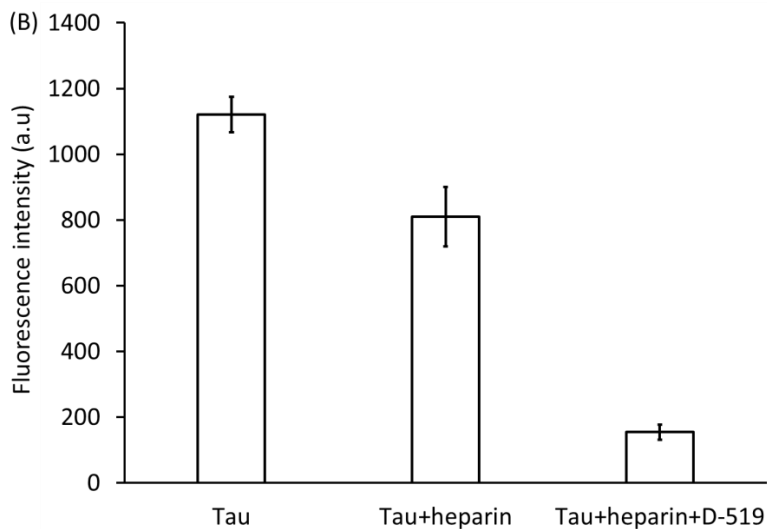


Figure S56. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-519 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

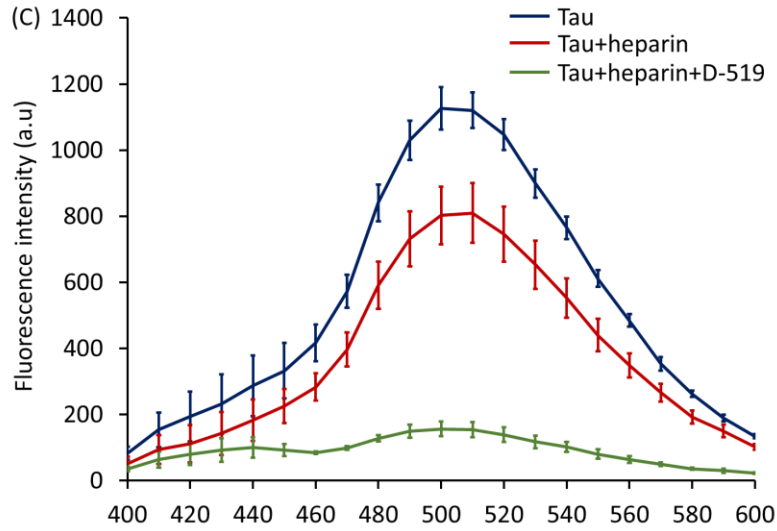


Figure S57. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-519 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

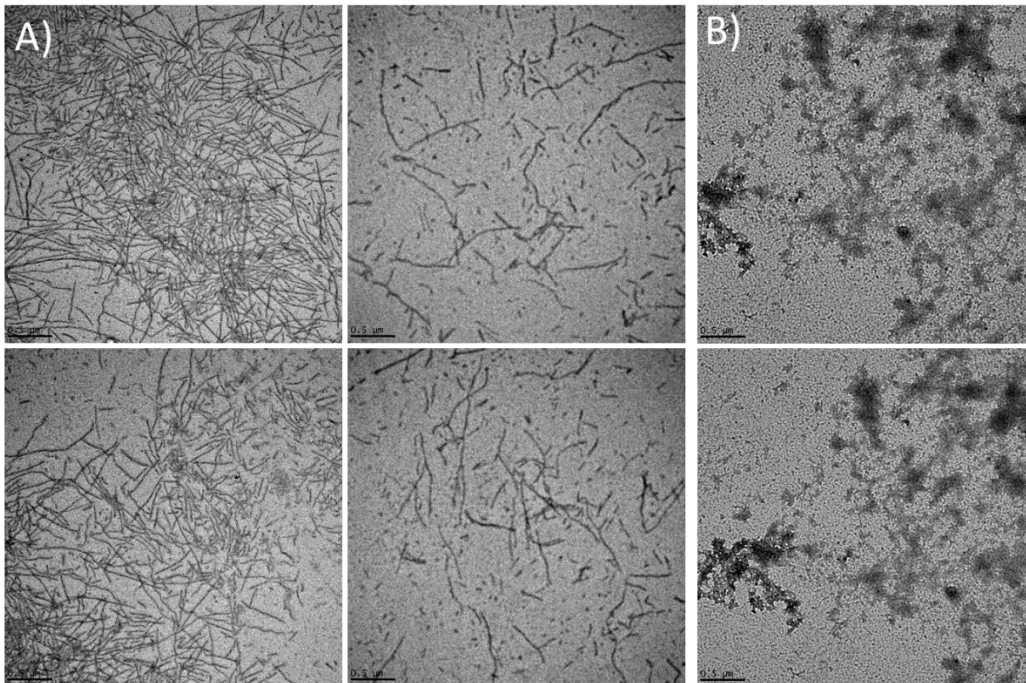


Figure S58. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-519 (final concentration 250 μ M). Magnification 22000x, scale bar 500 nm.

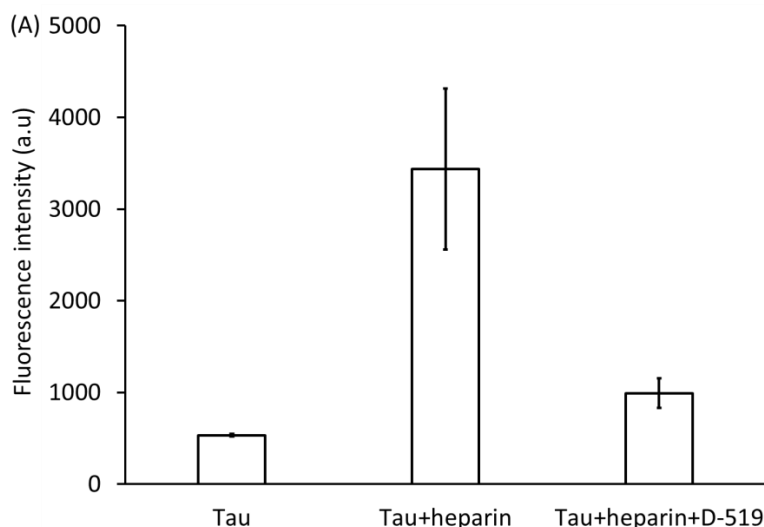


Figure S59. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-519 (final concentration 120 μ M) for 72 more hours. $\lambda_{\text{Ex}}= 550$ nm, $\lambda_{\text{Em}}= 600$ nm.

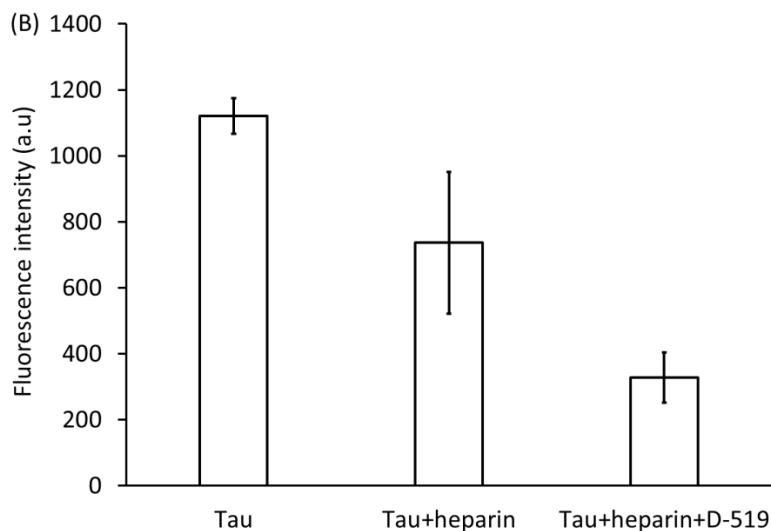


Figure S60. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-519 (final concentration 120 μ M) for 72 more hours. $\lambda_{\text{Ex}}= 350$ nm, $\lambda_{\text{Em}}= 510$ nm.

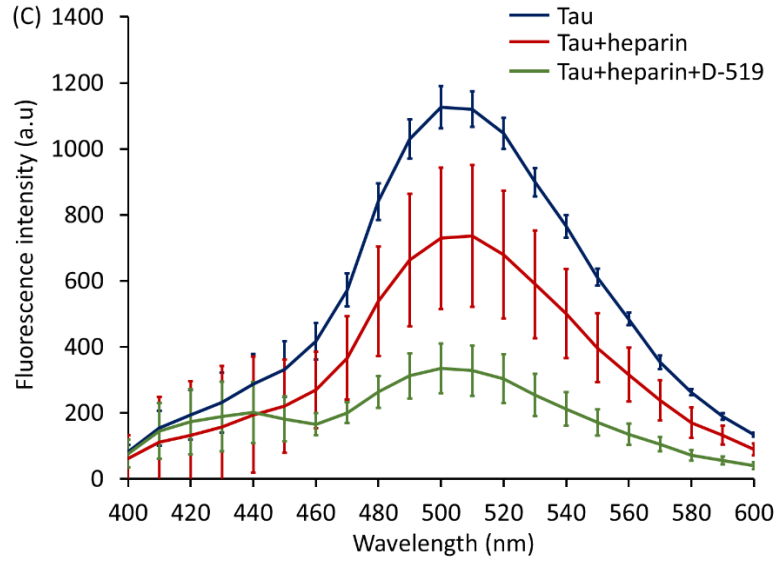


Figure S61. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-519 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

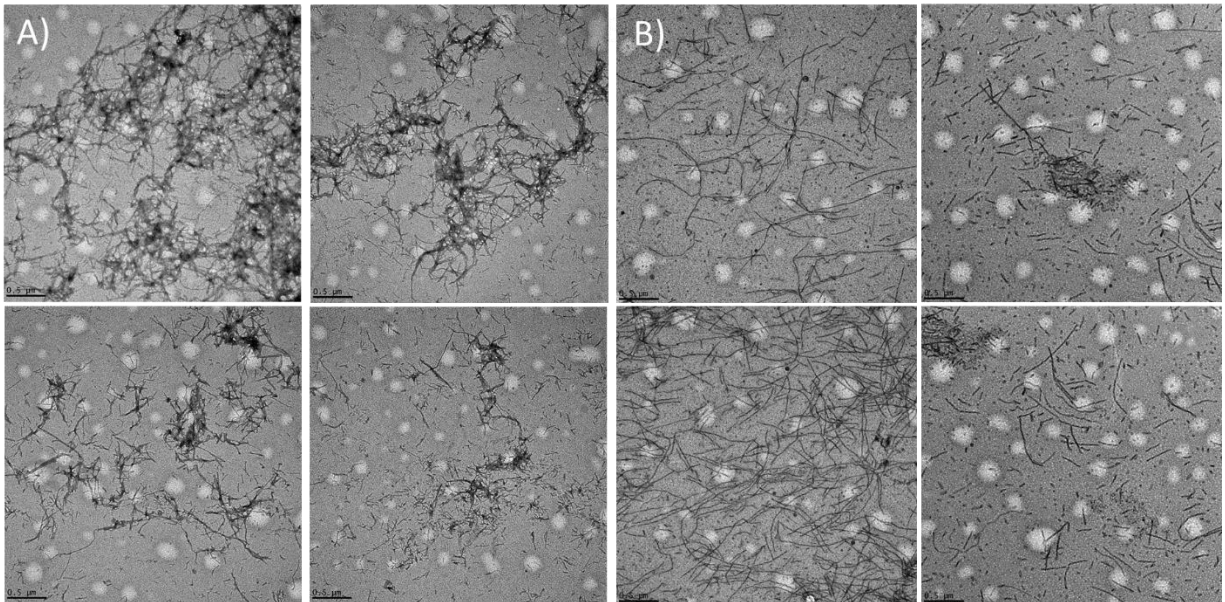


Figure S62. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with D-519 (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

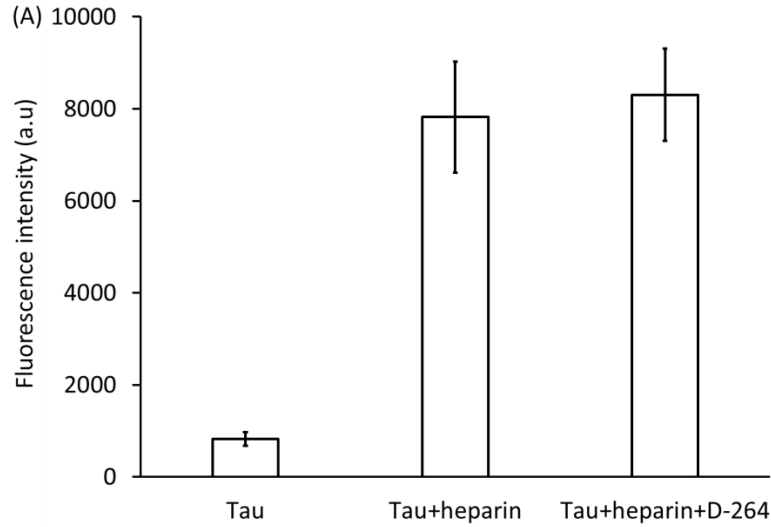


Figure S63. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 5 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

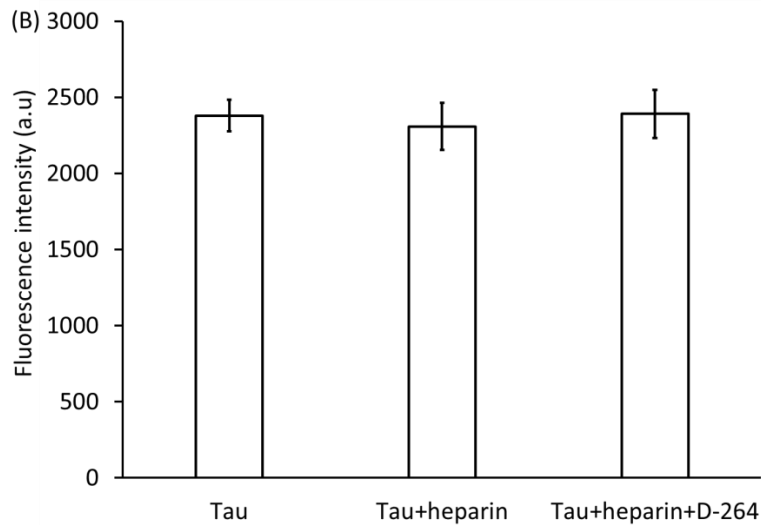


Figure S64. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

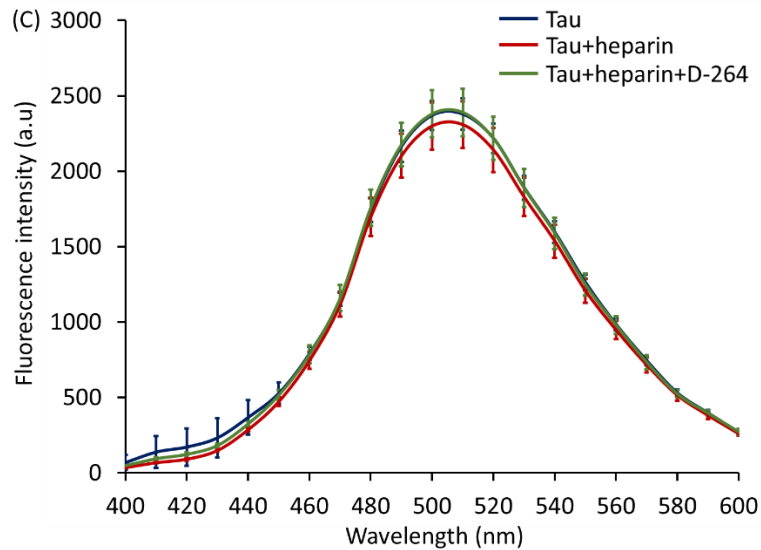


Figure S65. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-264 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

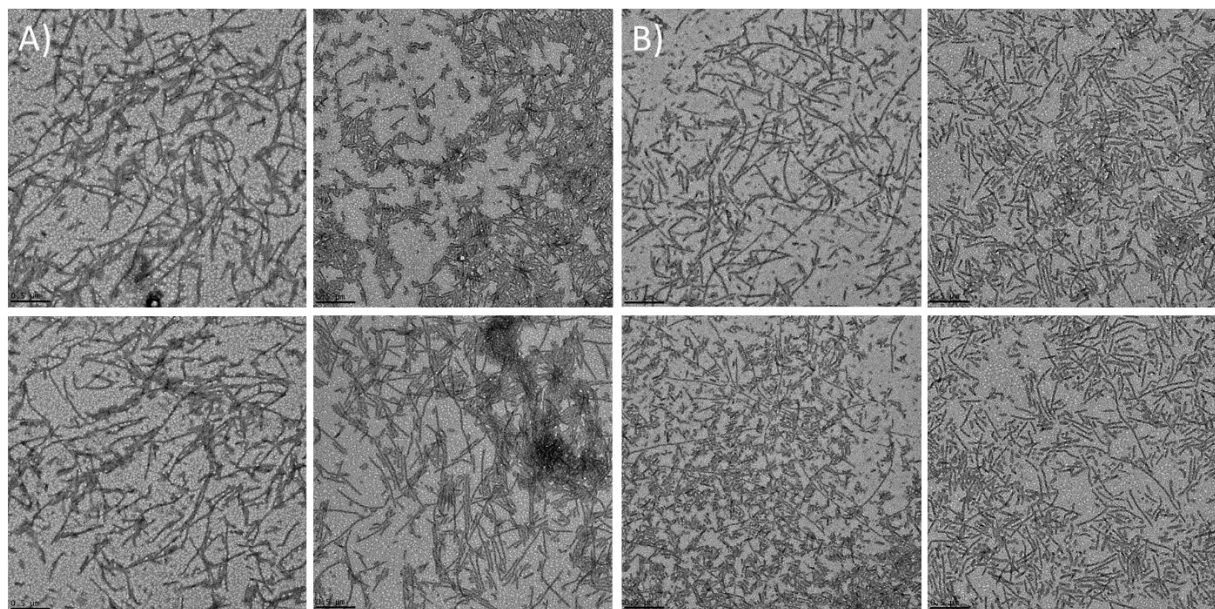


Figure S66. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-264 (final concentration 5 μ M). Magnification 22000x, scale bar 500 nm.

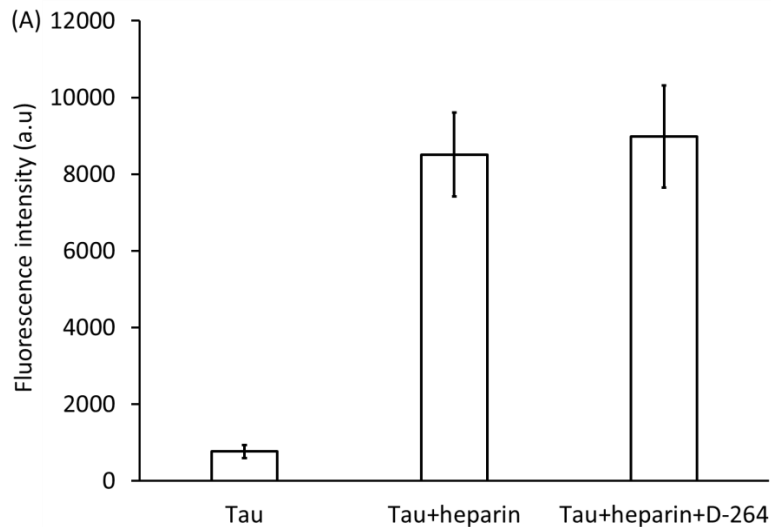


Figure S67. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 40 μ M). $\lambda_{\text{EX}}= 550$ nm, $\lambda_{\text{Em}}= 600$ nm.

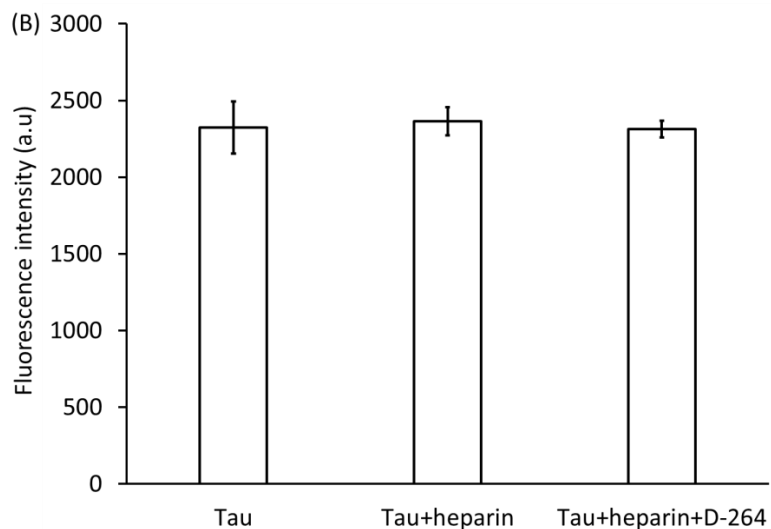


Figure S68. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 40 μ M). $\lambda_{\text{EX}}= 350$ nm, $\lambda_{\text{Em}}= 510$ nm.

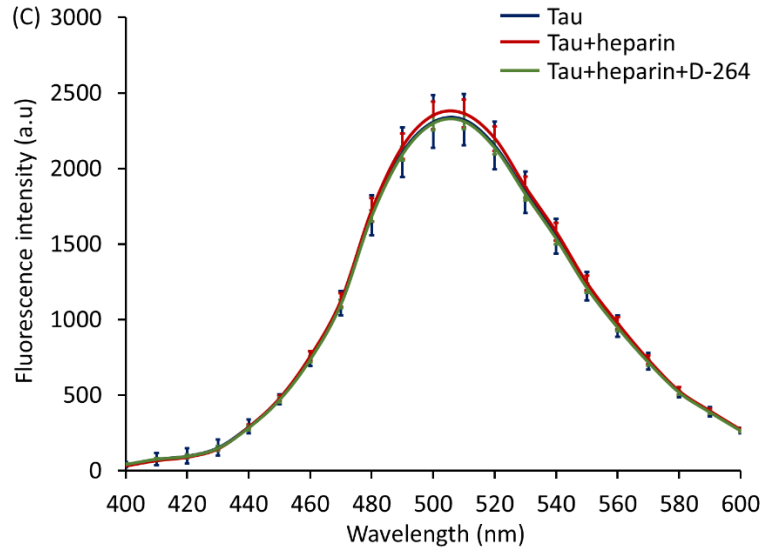


Figure S69. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-264 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

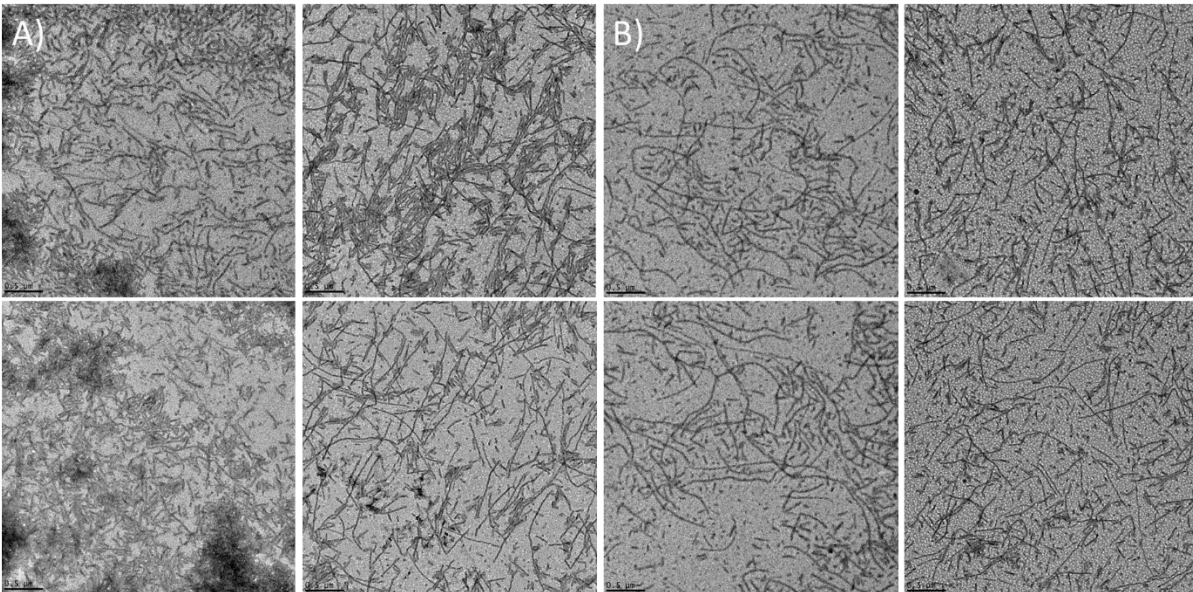


Figure S70. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-264 (final concentration 40 μ M). Magnification 22000x, scale bar 500 nm.

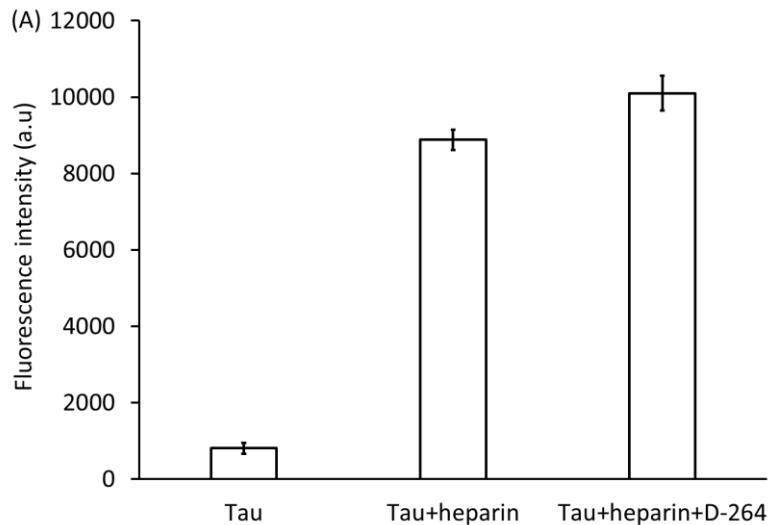


Figure S71. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

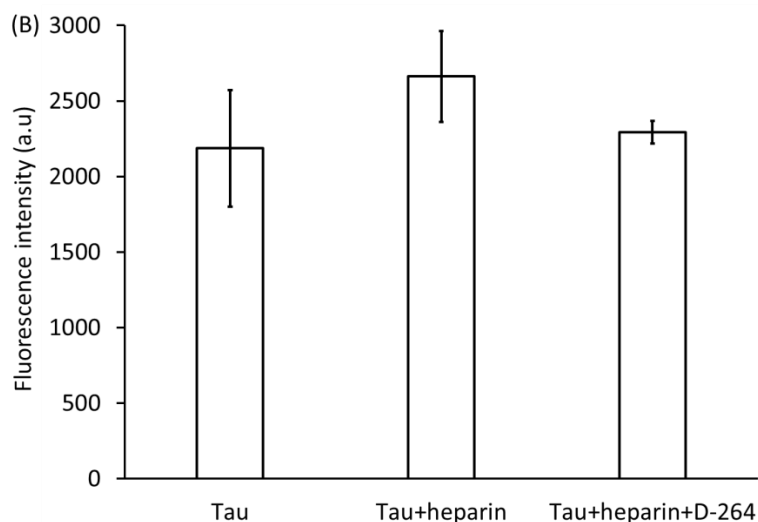


Figure S72. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

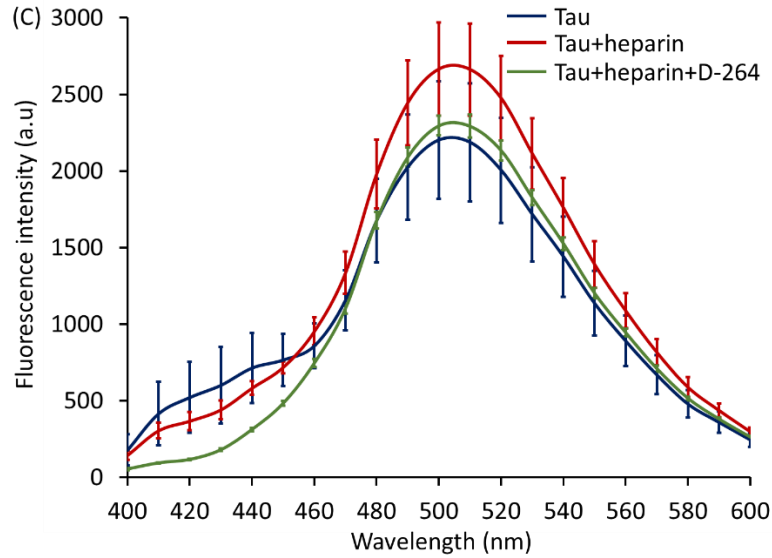


Figure S73. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-264 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

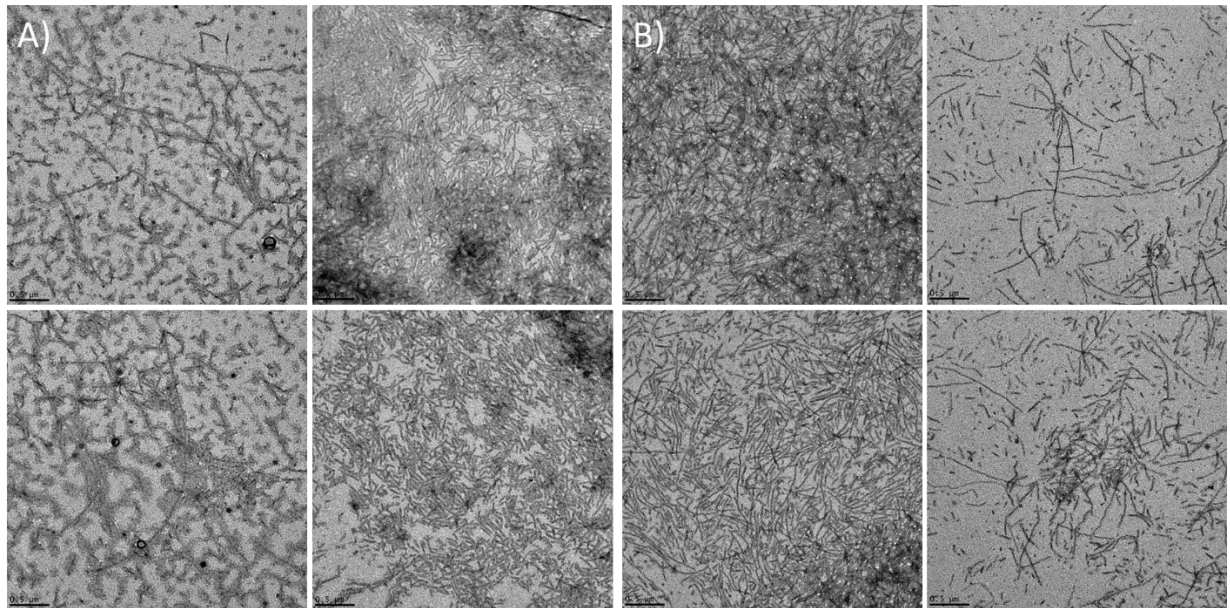


Figure S74. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-264 (final concentration 120 μ M). Magnification 22000x, scale bar 500 nm.

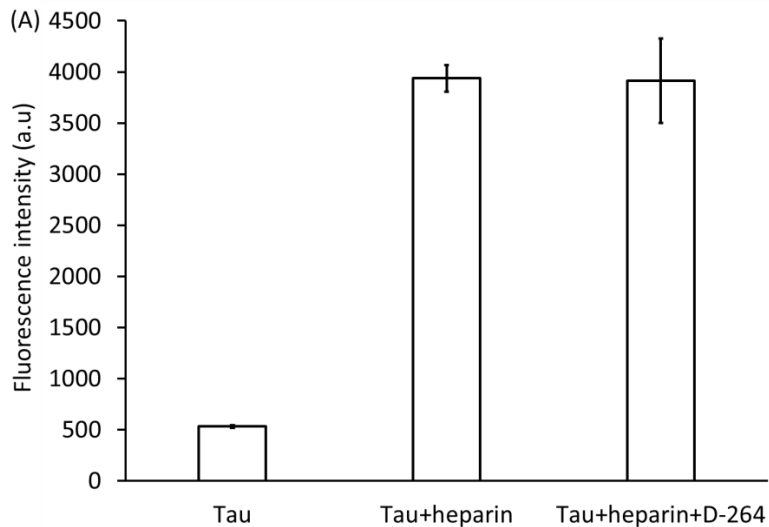


Figure S75. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 250 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

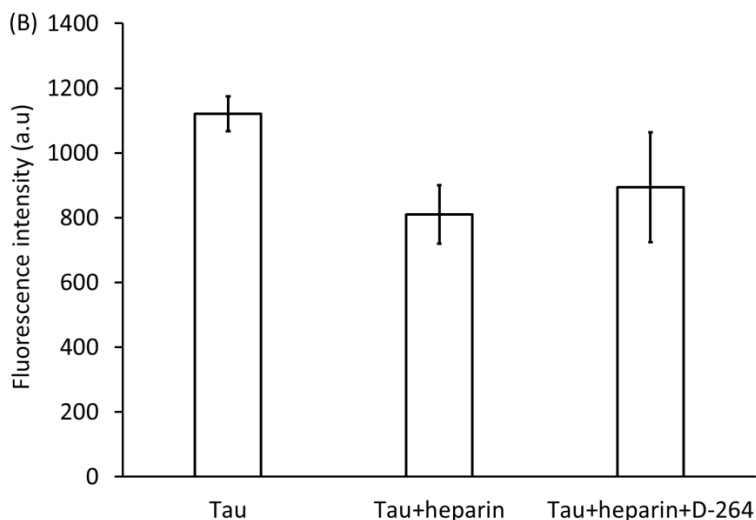


Figure S76. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-264 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

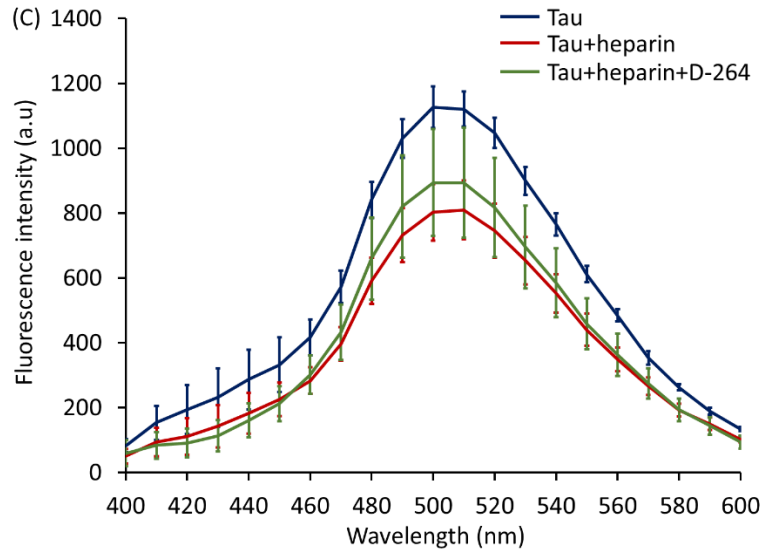


Figure S77. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-264 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

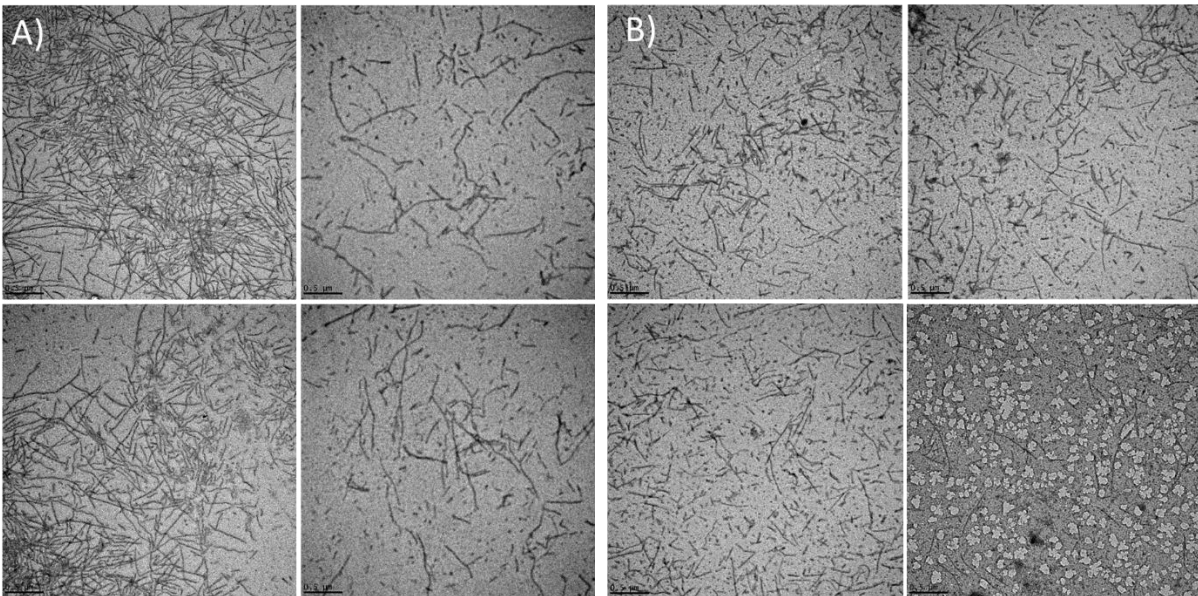


Figure S78. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-264 (final concentration 250 μ M). Magnification 22000x, scale bar 500 nm.

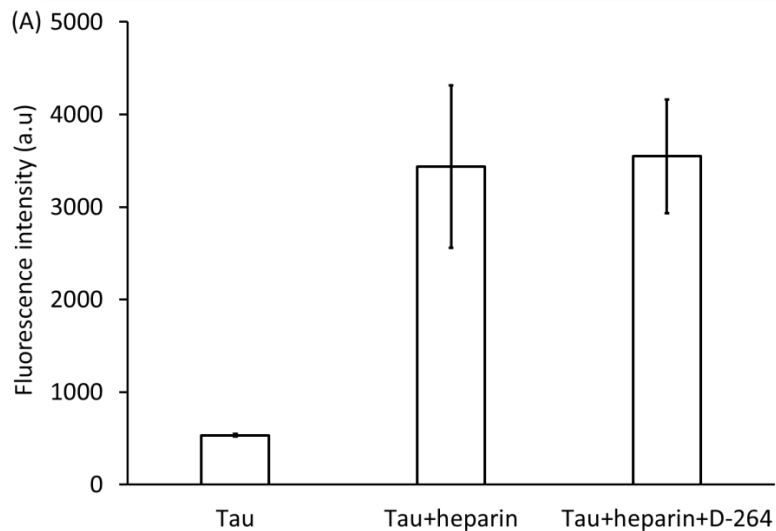


Figure S79. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-264 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

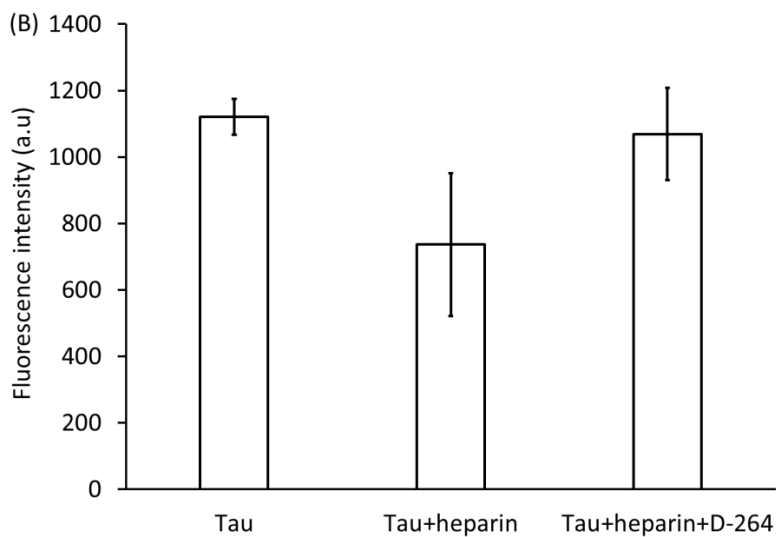


Figure S80. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-264 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

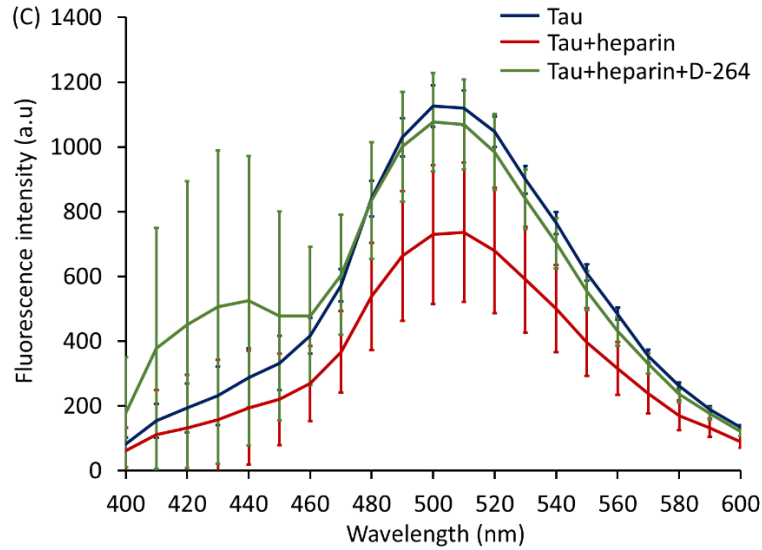


Figure S81. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-264 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

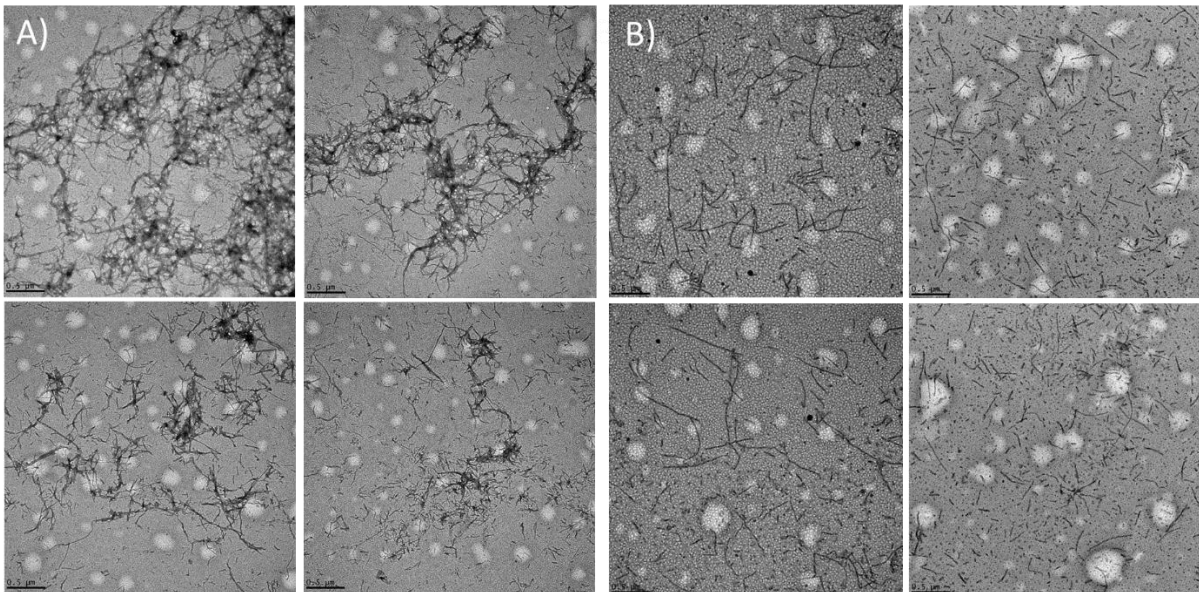


Figure S82. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with D-264 (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

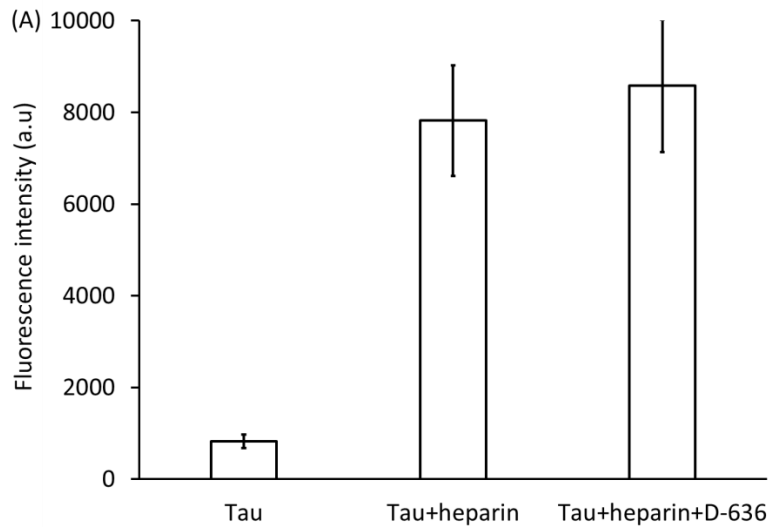


Figure S83. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 5 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

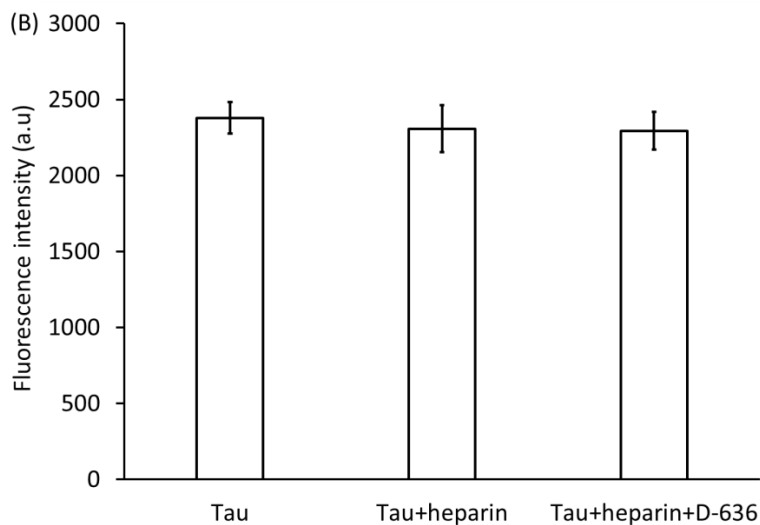


Figure S84. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

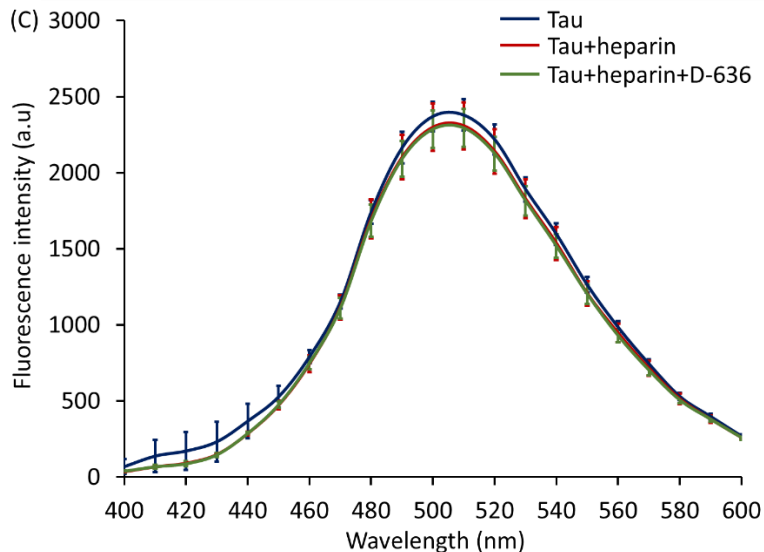


Figure S85. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-636 (final concentration 5 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

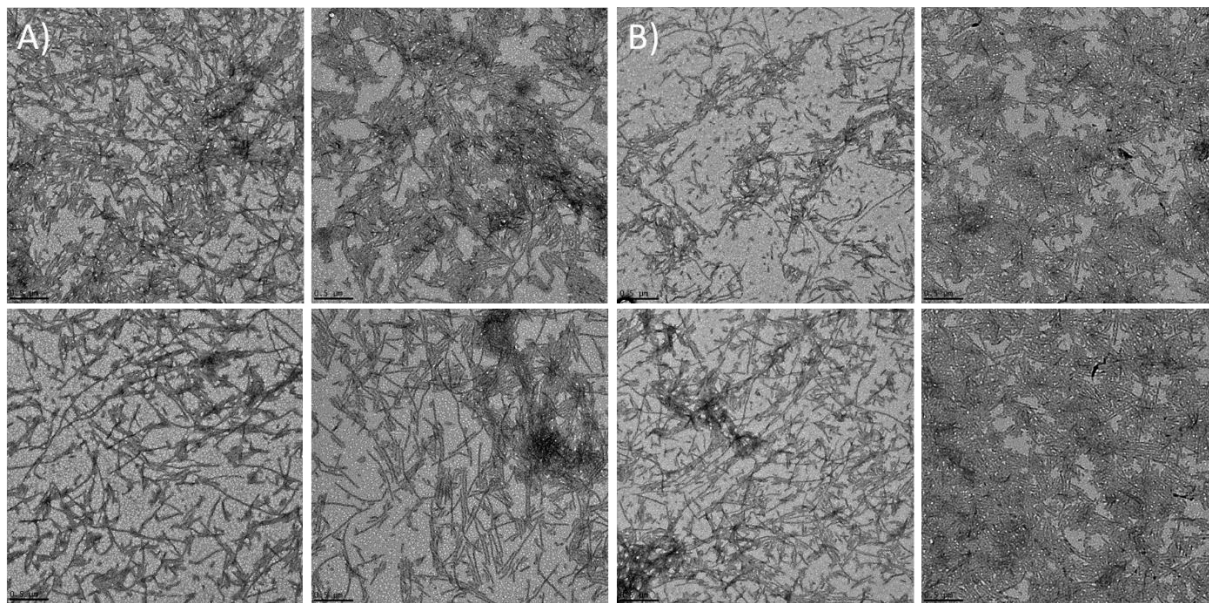


Figure S86. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-636 (final concentration 5 μ M). Magnification 22000x, scale bar 500 nm.

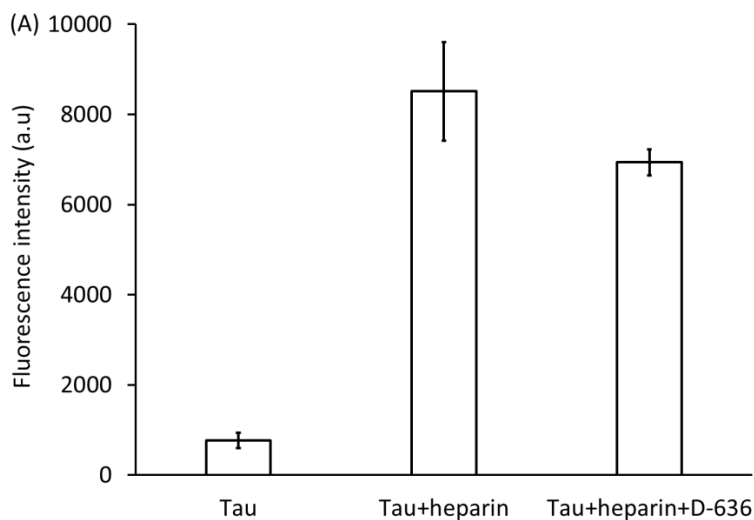


Figure S7. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 40 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

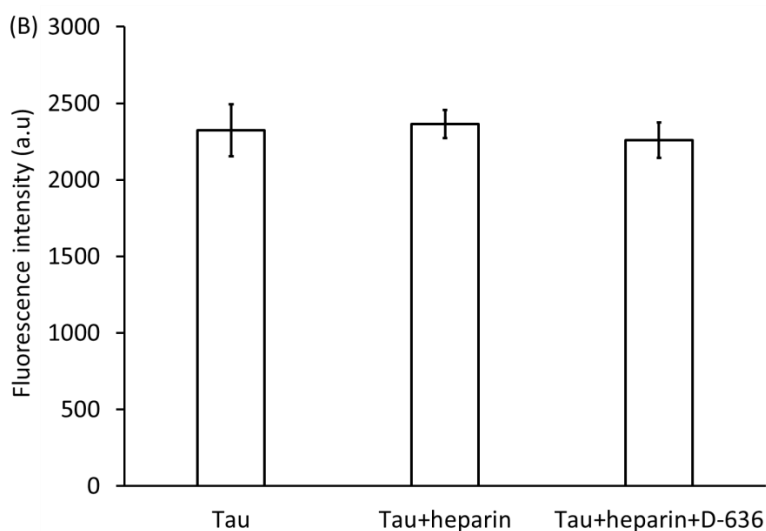


Figure S88. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

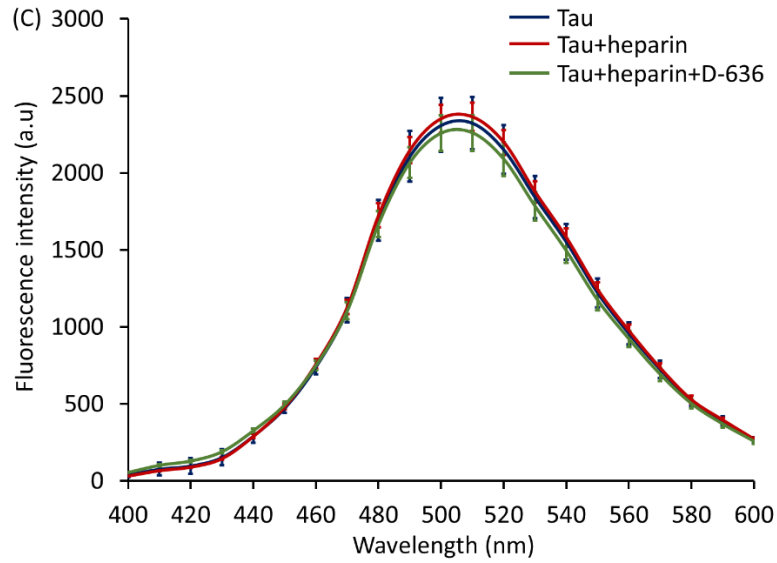


Figure S89. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-636 (final concentration 40 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

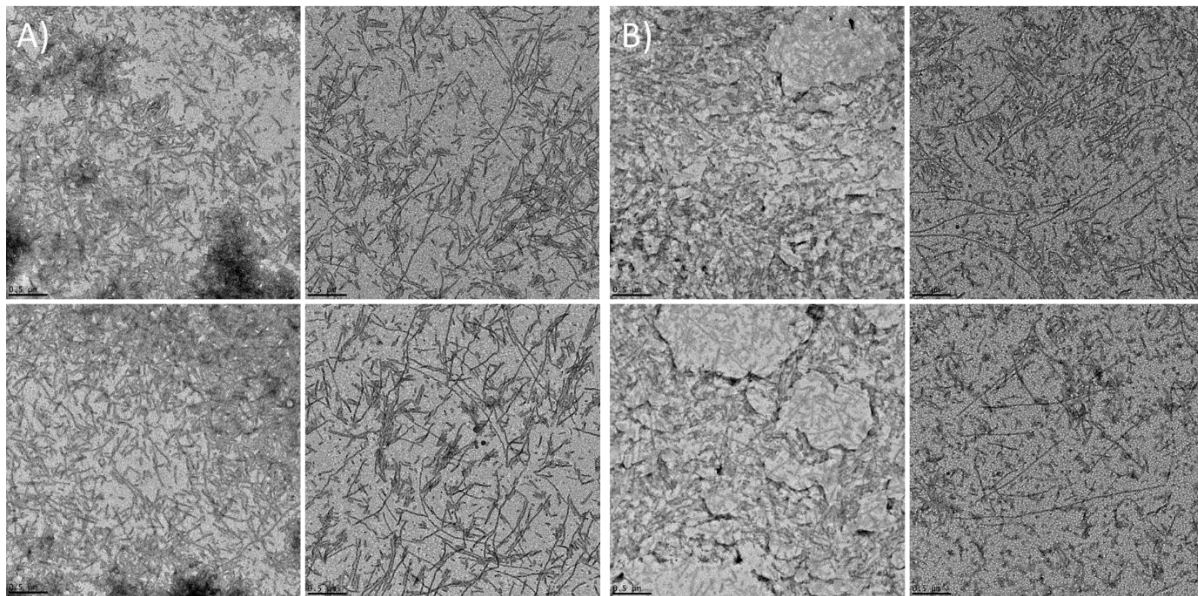


Figure S90. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-636 (final concentration 40 μ M). Magnification 22000x, scale bar 500 nm.

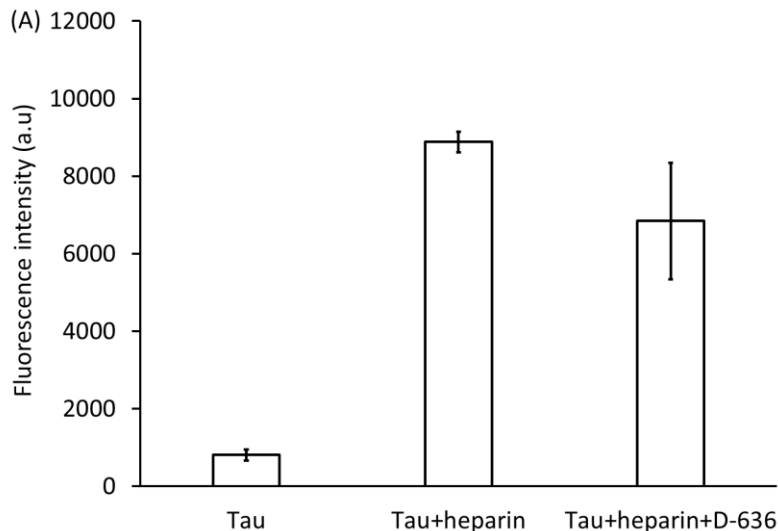


Figure S91. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

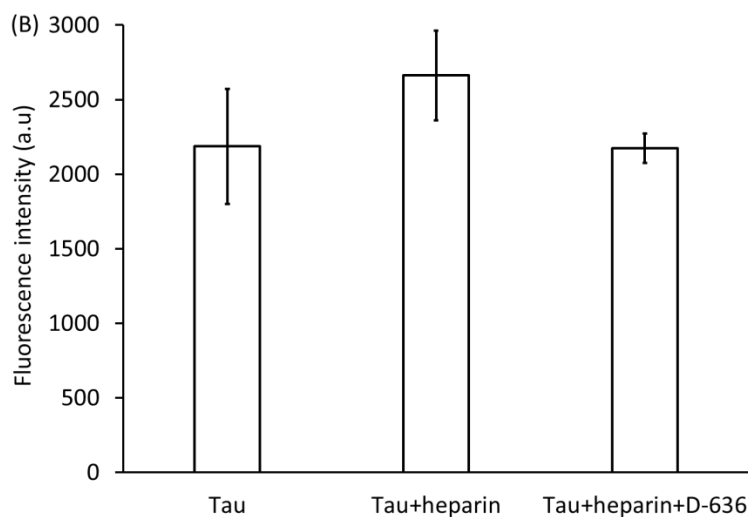


Figure S92. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

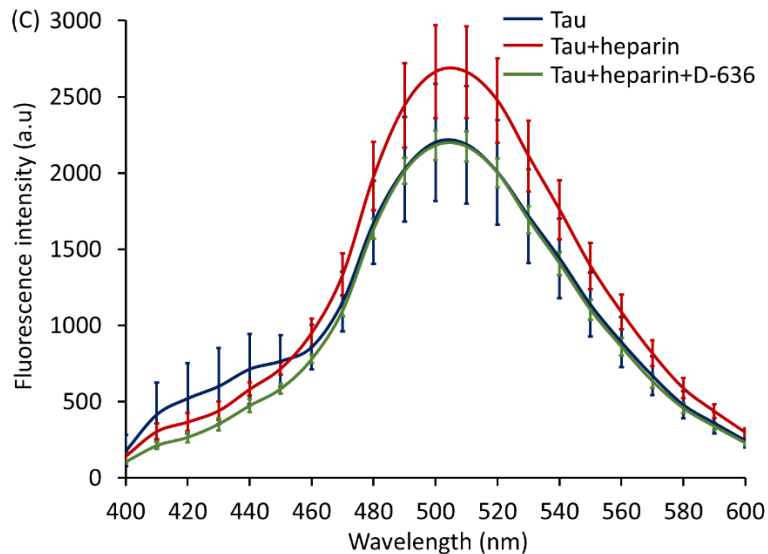


Figure S93. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-636 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

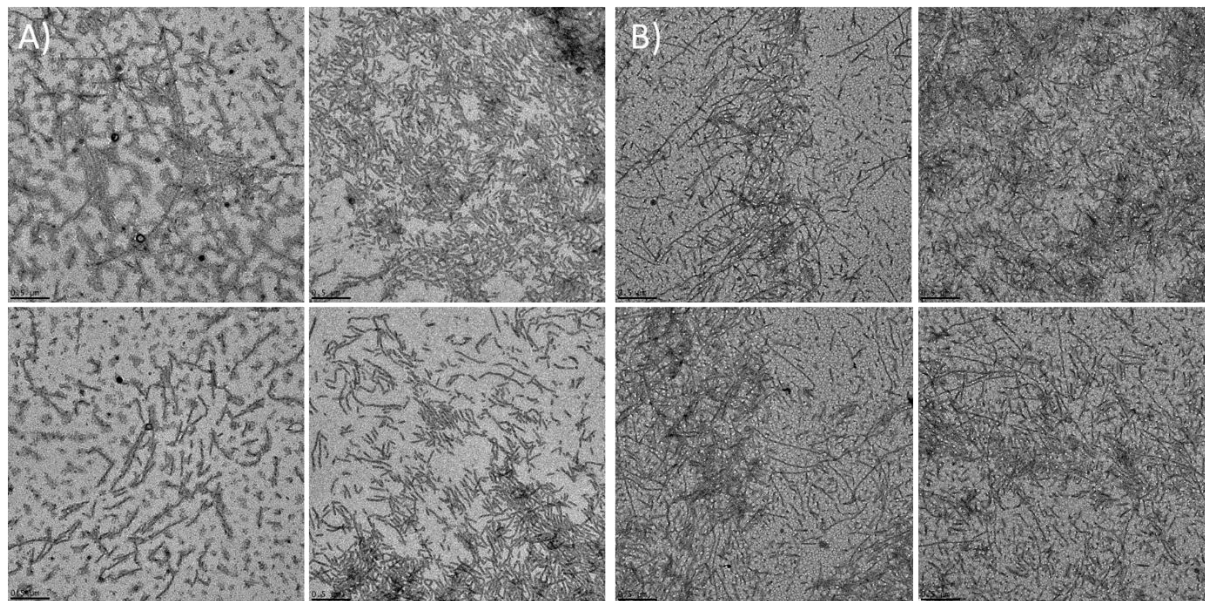


Figure S94. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-636 (final concentration 120 μ M). Magnification 22000x, scale bar 500 nm.

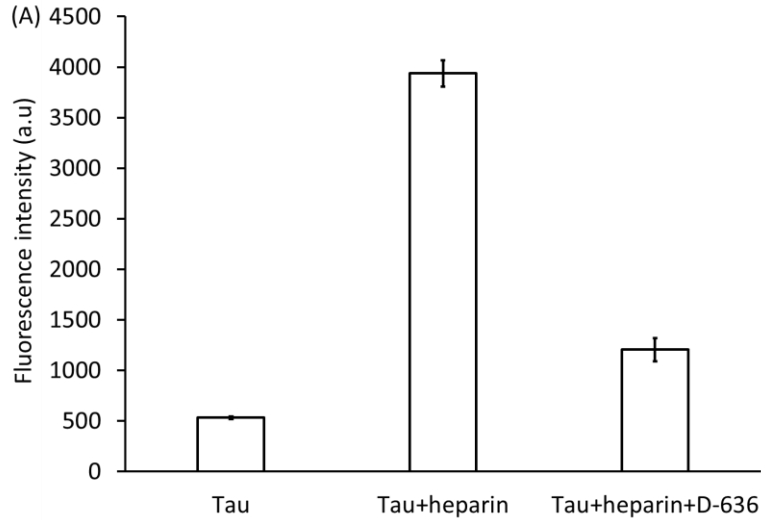


Figure S95. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 250 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

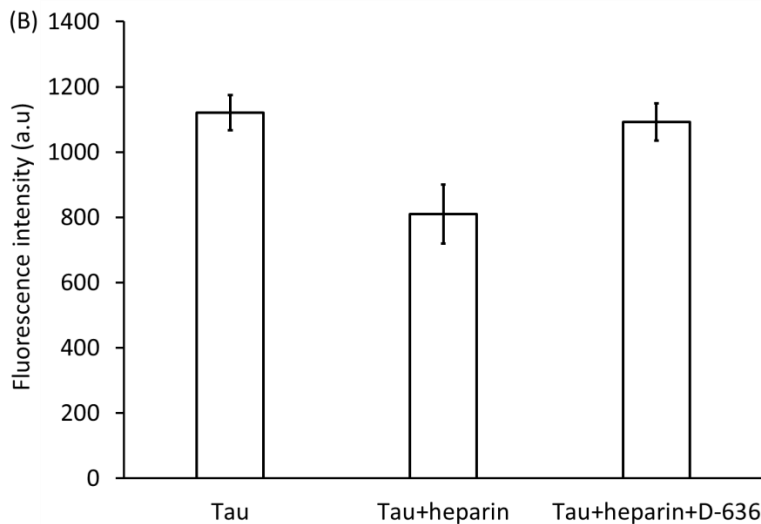


Figure S96. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-636 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

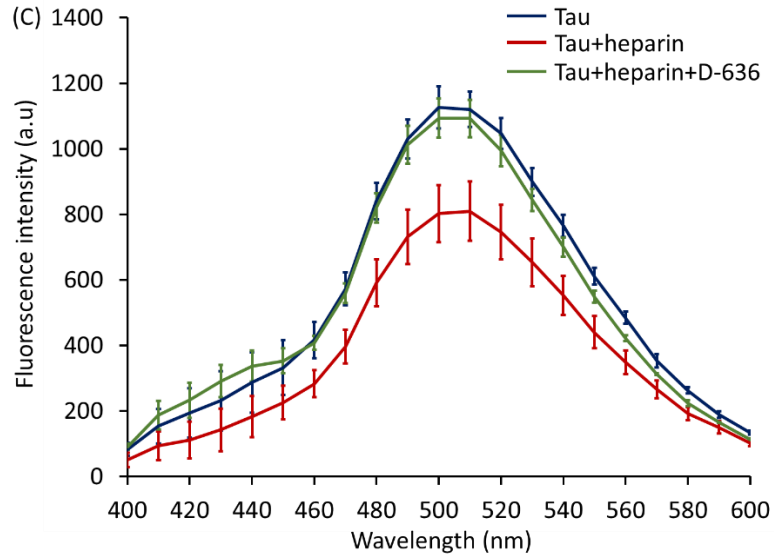


Figure S97. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-636 (final concentration 250 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

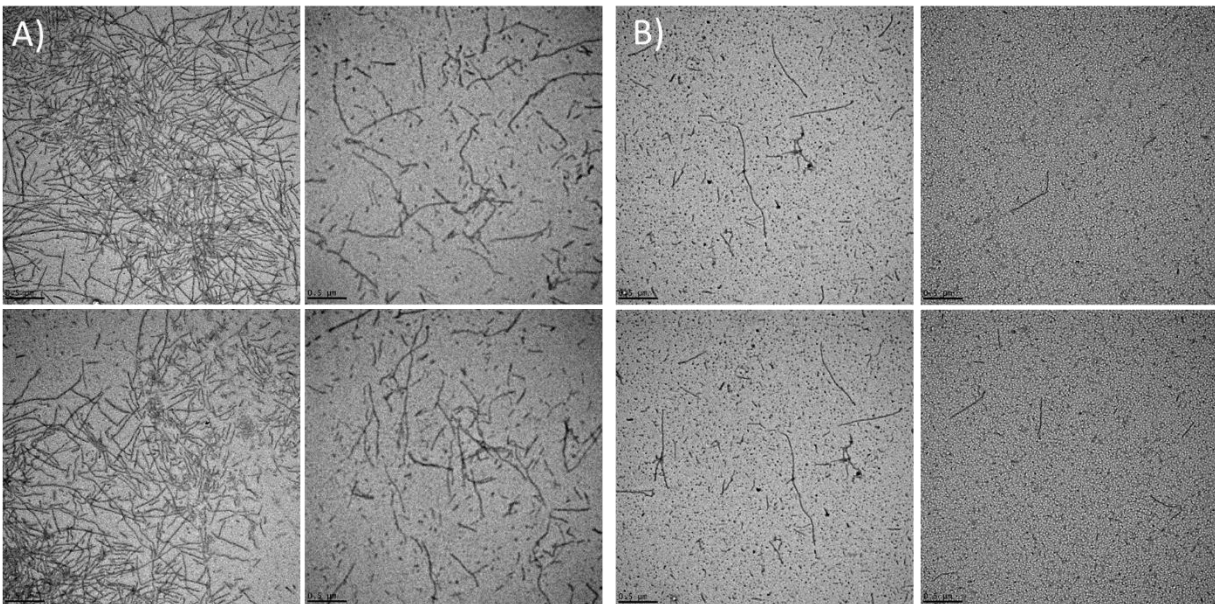


Figure S98. TEM images of tau protein samples incubated for 72 hours at 37 °C. A) aggregated tau with heparin, B) aggregated tau with heparin and D-636 (final concentration 250 μ M). Magnification 22000x, scale bar 500 nm.

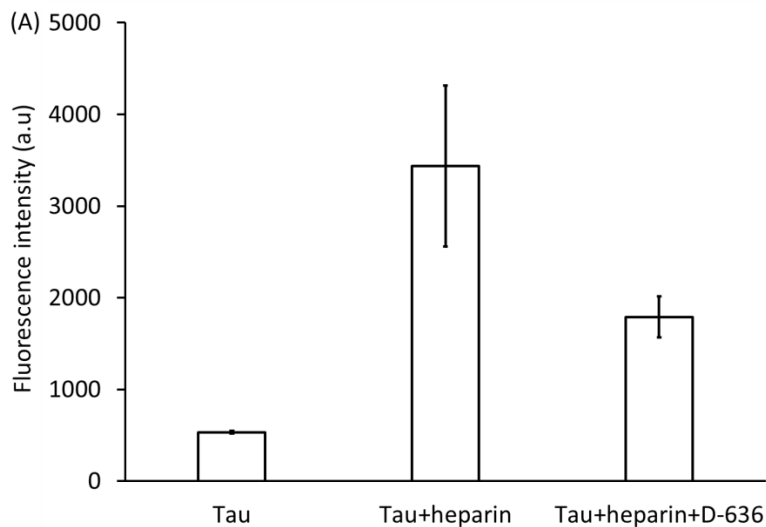


Figure S99. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-636 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

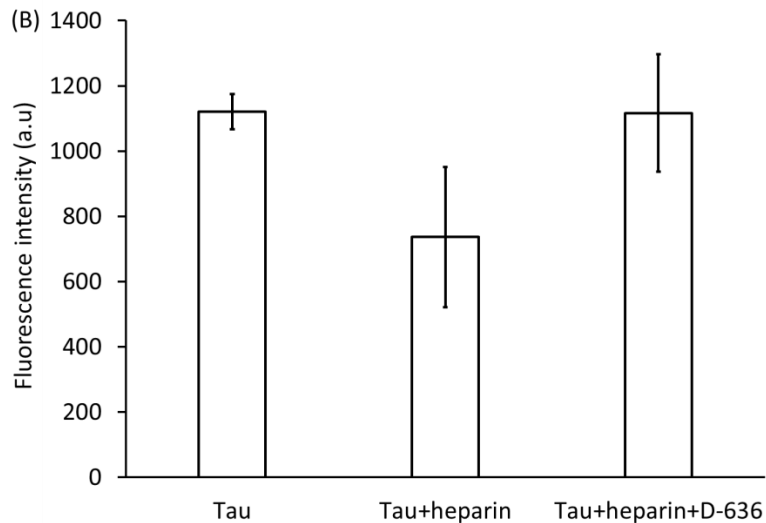


Figure S100. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-636 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

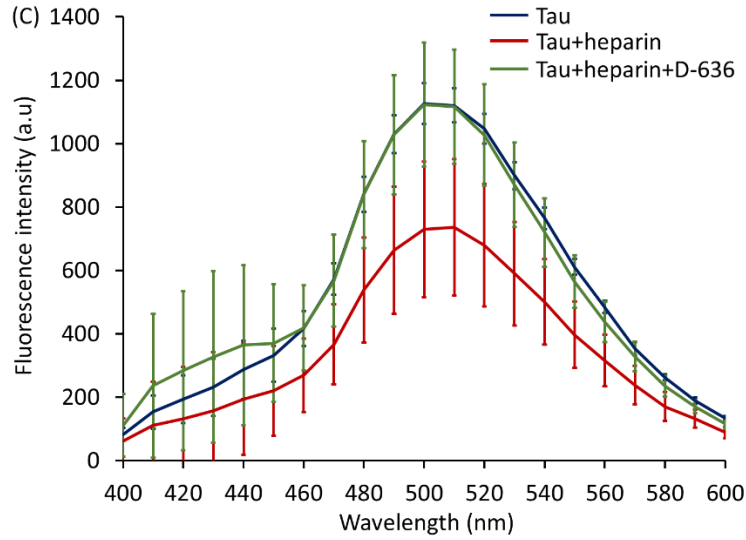


Figure S101. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-636 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

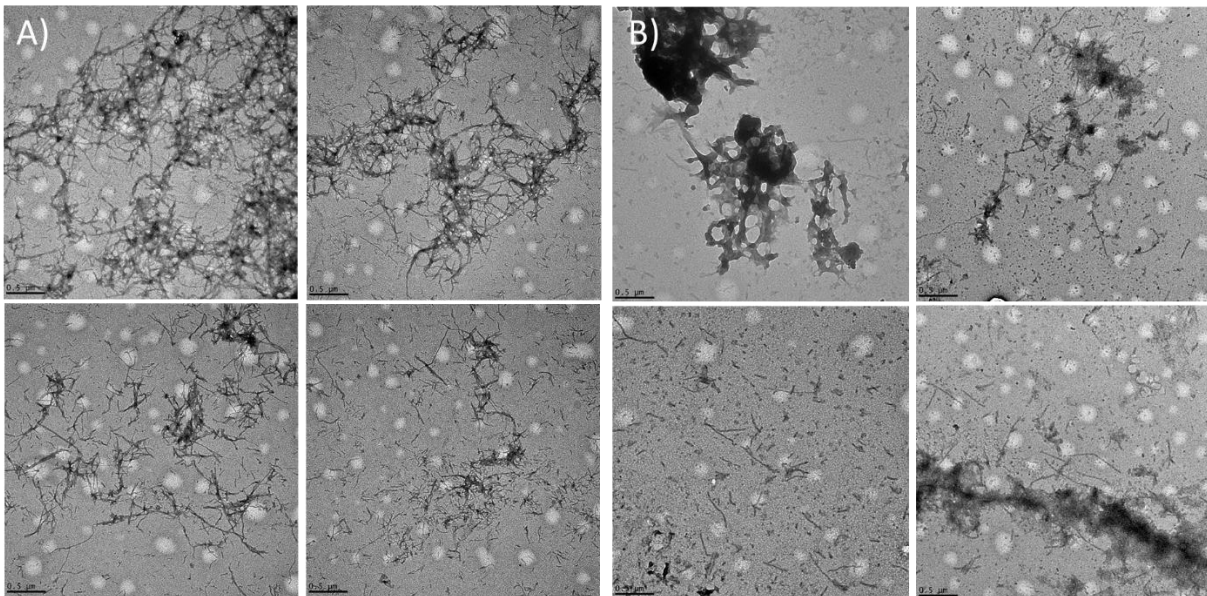


Figure S102. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with D-636 (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

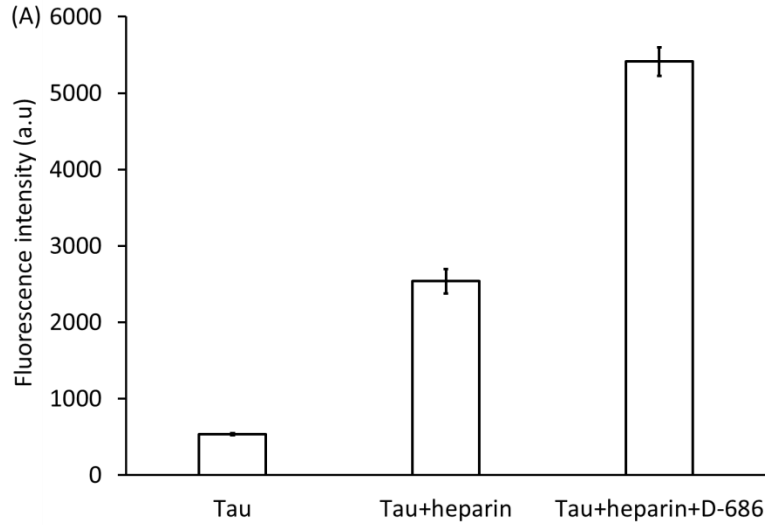


Figure S103. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-686 (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

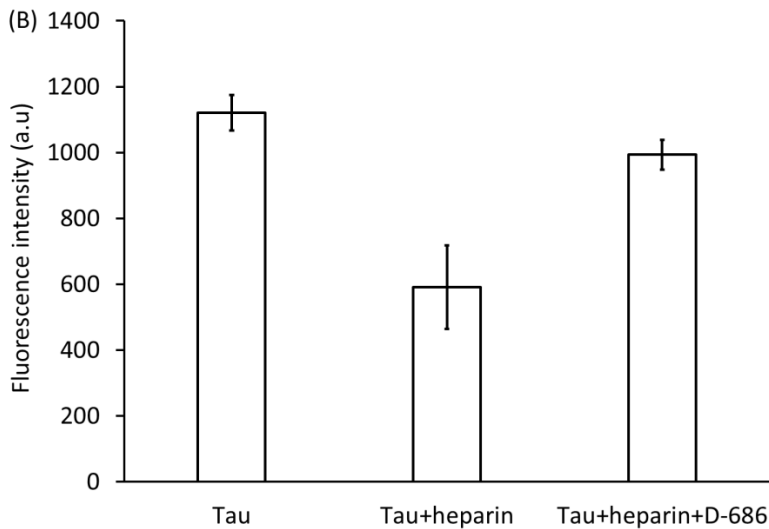


Figure S104. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of D-686 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

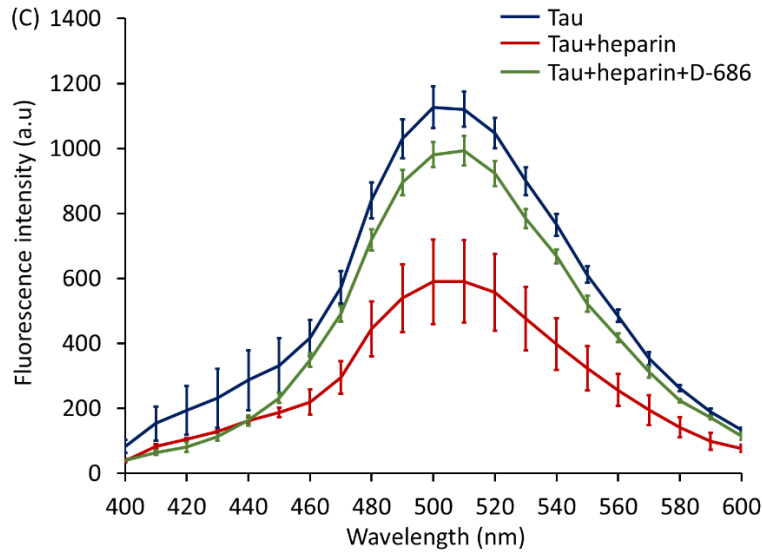


Figure S105. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of D-686 (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

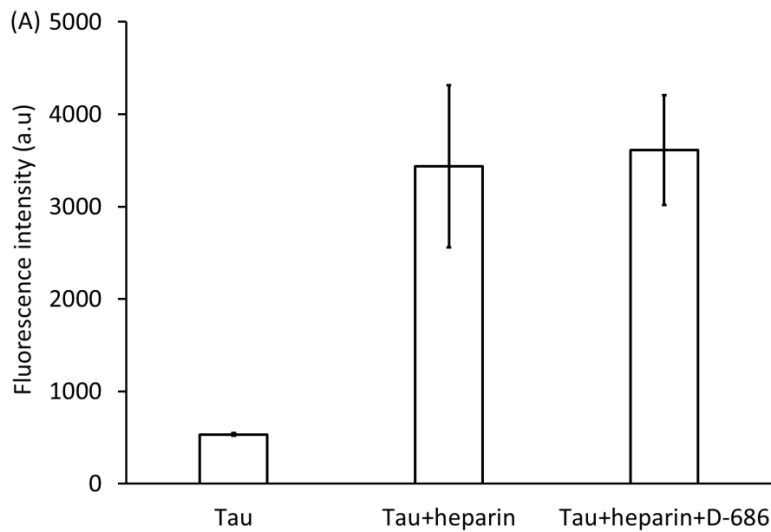


Figure S106. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-686 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

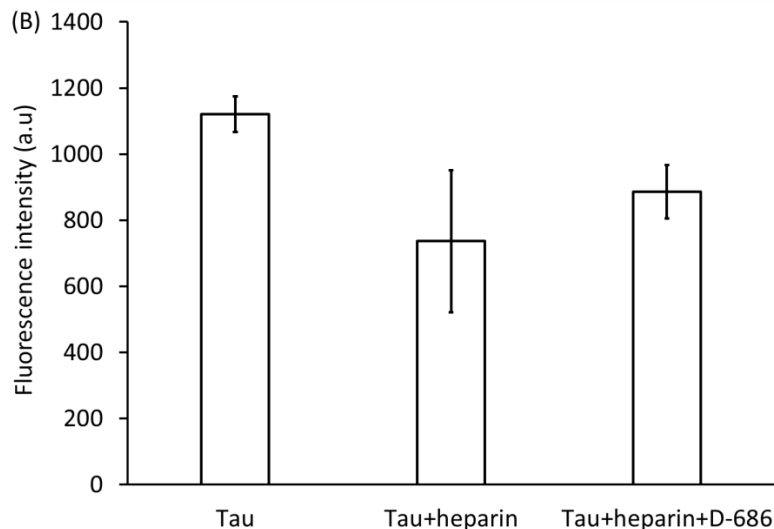


Figure S107. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-686 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

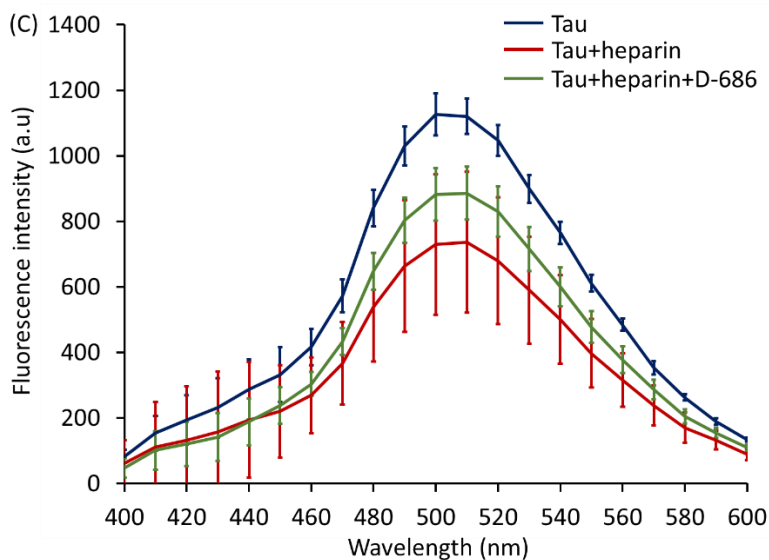


Figure S108. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of D-686 (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

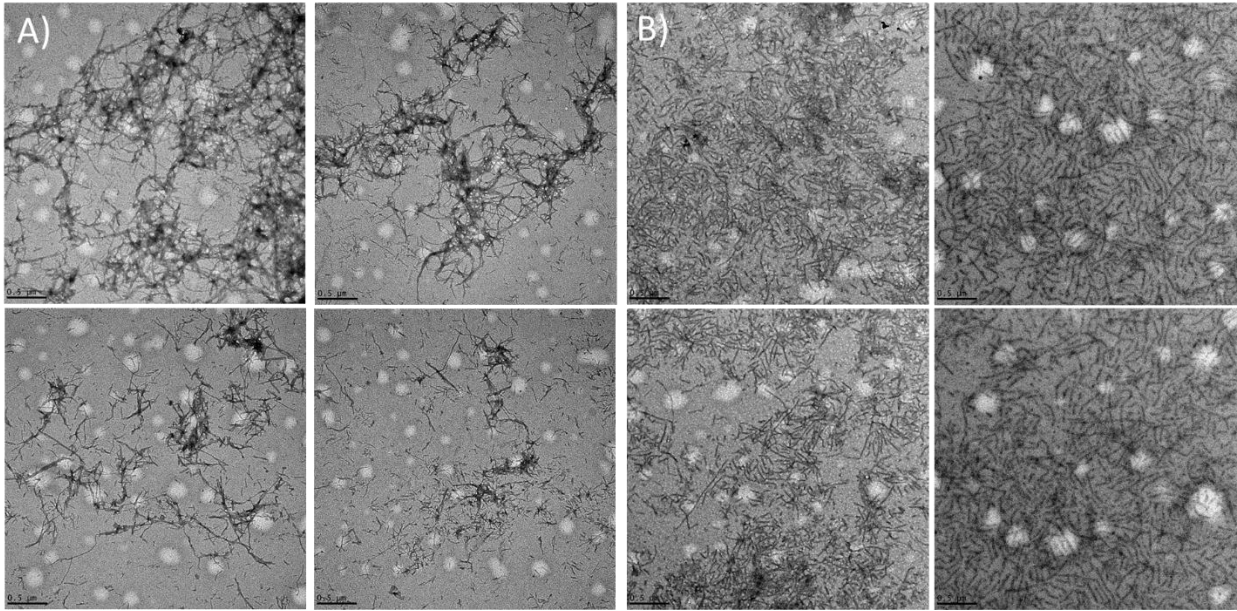


Figure S109. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with D-686 (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

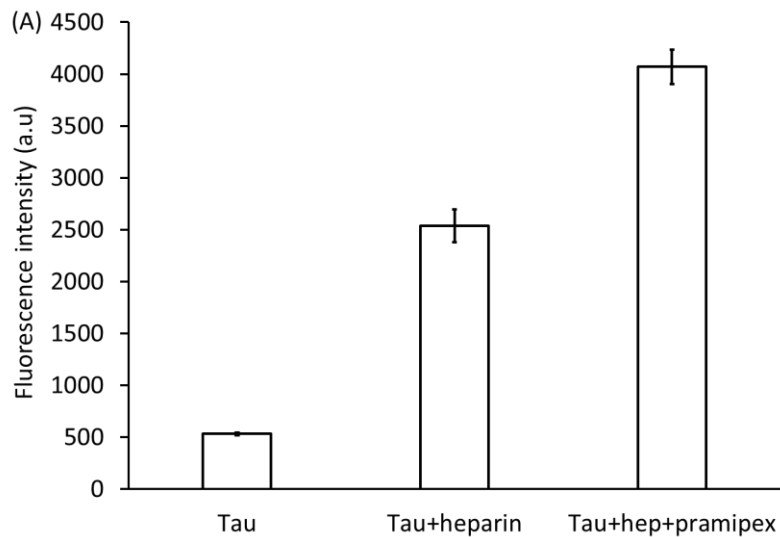


Figure S110. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of Pramipexole (final concentration 120 μ M). λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

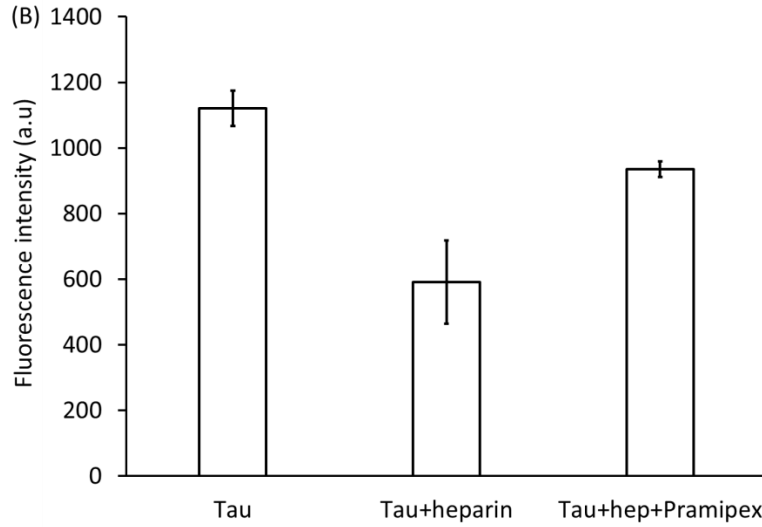


Figure S111. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) aggregated tau with heparin in the presence of Pramipexole (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

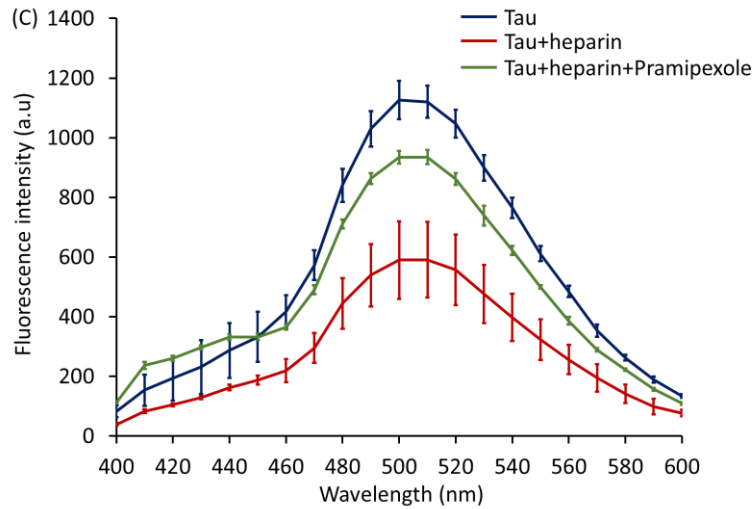


Figure S112. Average fluorescence emission spectra of Bis-ANS-bound samples after 72 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) aggregated tau with heparin in the presence of Pramipexole (final concentration 120 μ M). λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

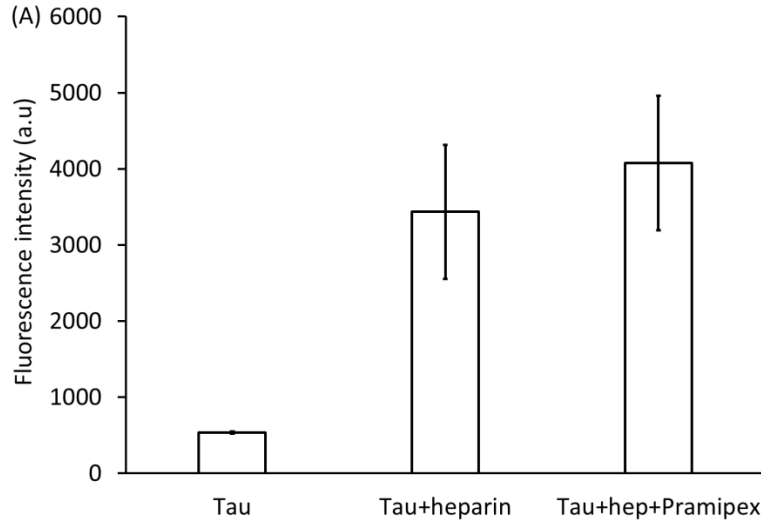


Figure S113. Proteostat aggregation assay. A bar graph showing the average fluorescence intensity after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of Pramipexole (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 550 nm, λ_{Em} = 600 nm.

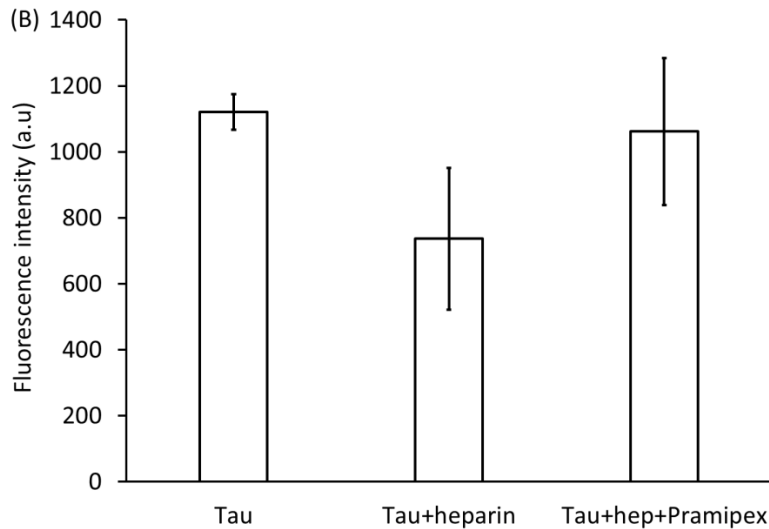


Figure S114. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. a) tau protein in buffer, b) aggregated tau with heparin in buffer, c) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of Pramipexole (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 510 nm.

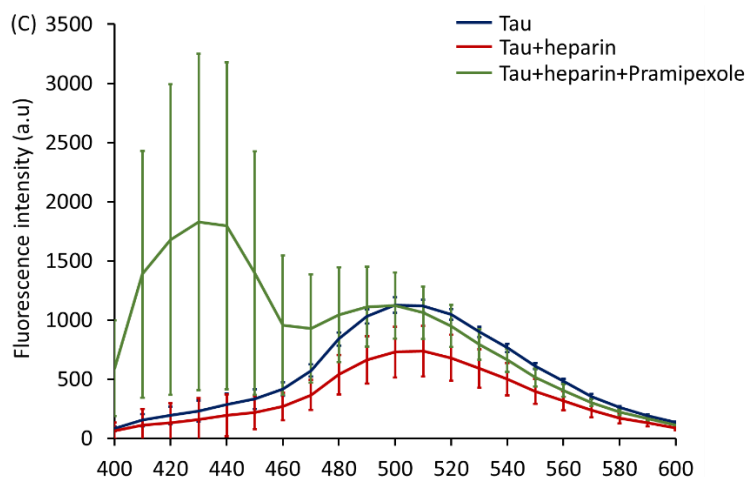


Figure S115. Average fluorescence emission spectra of Bis-ANS-bound samples after 144 hours of incubation of the samples at 37 °C. Blue) tau protein in buffer, red) aggregated tau with heparin in buffer, green) pre-aggregated tau with heparin for 72 hours, then incubated in the presence of Pramipexole (final concentration 120 μ M) for 72 more hours. λ_{Ex} = 350 nm, λ_{Em} = 400-600 nm.

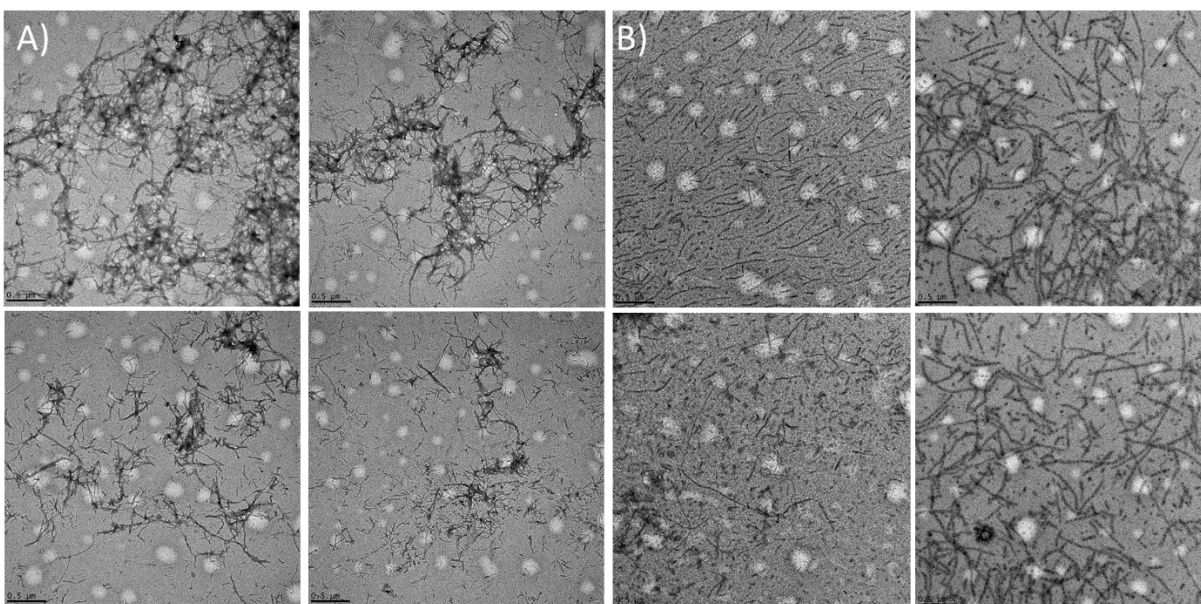


Figure S116. TEM images of tau protein samples incubated for 144 hours at 37 °C. A) aggregated tau with heparin, B) pre-aggregated tau with heparin for 72 hours, then incubated with Pramipexole (final concentration 120 μ M) for 72 more hours. Magnification 22000x, scale bar 500 nm.

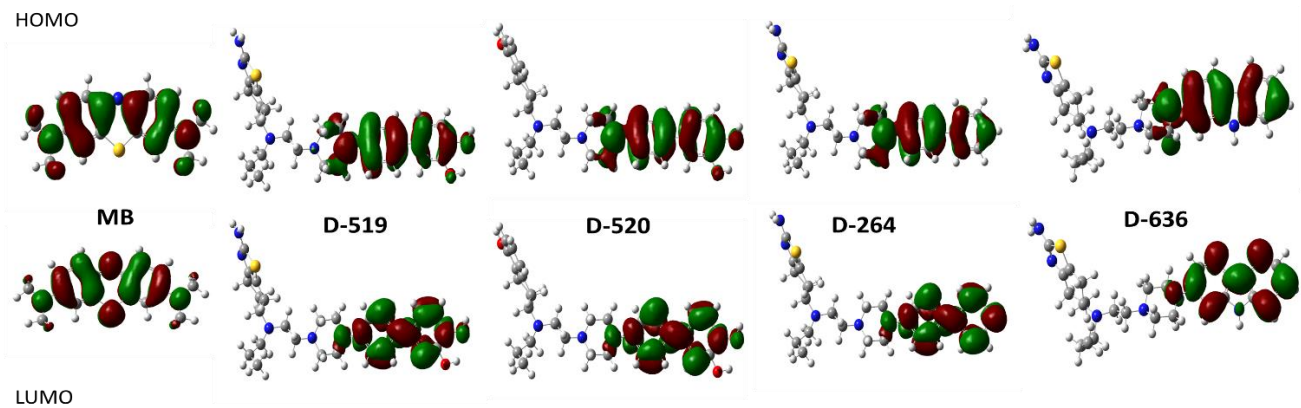


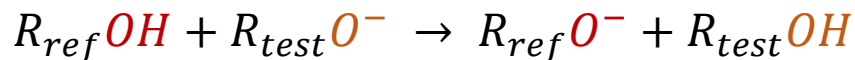
Figure S117. Calculated HOMO and LUMO orbitals for all inhibitors tested (carbon, grey; hydrogen, white; nitrogen, blue; oxygen, red; and sulfur, yellow).

Table S1. Calculated parameters for all inhibitors.

Inhibitor	Dipole moment (D)	HOMO (eV vs. SHE)	LUMO (eV vs. SHE)	HOMO-LUMO gap (eV vs. SHE)
MB	2.15	-8.78	-6.32	2.46
D-519	3.61	-4.87	-0.25	4.62
D-520	3.20	-5.26	-0.65	4.61
D-264	2.76	-5.35	-0.82	4.53
D-636	3.27	-5.24	-0.82	4.42

Table S2. Calculated parameters for inhibitors with exchangeable protons.

Inhibitor	ΔG_{cal} (kcal/mol)	Calculated pK_a
D-636 (N)	0.63	9.54
D-520		
<i>para</i>	13.72	-0.05
<i>meta</i>	-1.68	11.23
D-519		
<i>para</i>	-1.42	11.04
<i>meta</i>	0.63	9.54



$$(R_{ref}O^- + R_{test}OH) - (R_{ref}OH + R_{test}O^-) = \Delta G_{calc}$$

$$pK_a = \frac{-\Delta G_{calc}}{\ln(10) RT}$$