SUPPLEMENRATY MATERIALS

Amyloid-Mimicking Toxic Nanofibers Generated via Self-assembly of Dopamine

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Table S1. List showing the concentration-fluctuations of dopamine in different tissues under different conditions

Organism/Tissue	Concentration	Reference
Human serum	10-80 pg/mL	(Lechin et al. 1990)·(Cuche et al. 1990)·(Hamner and Diamond 1993; Lechin et al. 1994)
The striatal region of mouse brain	10-20 nM	(Keefe, Zigmond, and Abercrombie 1993)
Pedunculopontine tegmentum (PPTg), subthalamic nucleus of rat brain	Hundreds of μM to mM levels in case of burst spike firing pattern	(Floresco et al. 2003)·(Grace 1991)
Nucleus accumbens of the rat brain	Efflux of Dopamine in synaptic cleft 25 mM per vesicles	(Garris et al. 1994)
Vesicles from the striatum in rat	33,000 dopamine molecules per vesicle equivalent to 100 mM	(Omiatek et al. 2013)
Dopamine concentration in dopaminergic neuron	0.1 mM to 1 mM	(Michel and Hefti 1990), (Jonsson 1971)

Table S2. Selected list of important aromatic metabolites and the related pathologies. (Shaham-Niv, et al 2015; Sade et al 2018)

Metabolites[a]	Metabolite-linked Diseases
Phenylalanine	Phenylketonuria
Tyrosine	Tyrosinaemia II
Orotic acid	Ornithine transcarbamylase deficiency
Cystine	Cystinuria, cystinosis
Tryptophan	Hypertryptophanemia
Histidine	Histidinaemia
Quinolinic acid	Alzheimer's disease
Dopamine	Parkinson's disease
Succinate	Cancer, Succinate dehydrogenase deficiency
Homogentisic acid	Alkaptonuria
Homocysteine	Alzheimer's disease

[a] Red colored metabolites have been reported to self-assemble and form cytotoxic amyloid-like nanostructures

Table S3. List showing the concentration-fluctuations of dopamine in different tissues under exposure to different toxic conditions

Organism/Tissue	Dopamine Concentration Up/Down	Conditions	Reference
CNS of human	Increased extracellular dopamine	Drugs abuse such as cocaine, heroin or methamphetamine of HIV patient	(Gaskill et al. 2013)
Mouse rat brain	Decrease	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) drug	(Lee et al. 2013)
Rat brain	Increases	Phenelzine use for treatment of depression and anxiety disorders	(Matveychuk et al. 2013)
Striatum of rats	Increase	Methyl mercury toxicity	(Faro et al. 1997)
Rat brain	Increase (in synaptic cleft)	Zn^{2+} Sn^{2+} toxicity	(Komulainen and Tuomisto 1981)
Rat	Increase	Pb^{2+} toxicity	(Jones and Miller 2008; Zuch, O'Mara, and Cory-Slechta 1998),(Szczerbak et al. 2007)
Rat brain	Increased extracellular dopamine	Amphetamine, It is used in the treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity	(Daberkow et al. 2013)
Xenopus oocytes	Increase	3,4- Methylenedioxymethamphetamine (MDMA) a drug abuse	(Monte et al. 1993; Hondebrink et al. 2013)
Rat medial prefrontal cortex and hippocampus	Increase	Asenapine. Use to treat acute schizophrenia, manicepisodes, bipolar I disorder	(Huang et al. 2008)
In the nucleus accumbens of adult rat	Increase	Protein restriction diet	(Naneix et al. 2020)
Dorsal striatum of rat	Increase	Ketamine drug, antidepressant	(Usun et al. 2013)
Human brain	Increase	Drug abuse cocaine	(Wanat, Willuhn, and Phillips 2009)
Human ventral striatum	Increase	Cannabis	(Urban et al. 2012)
Striatal synaptosomes of mice	Increase	Dithiocarbamate (pesticide)	(Barlow et al. 2003)
Human brain	Increase	Nicotine/cigarette smokers	(Takahashi et al. 2008)
Human brain	Decrease	Dementia with Lewy bodies	(Walker et al. 2002)

Table S4. List showing the concentration-fluctuations of dopamine-transporters under exposure to different toxic conditions

Organism/Organ	**Dopamine Transporter (DAT)**	**Vesicular monoamine transporter 2 (VMAT2)**	**Conditions**	**Reference**
Drosophila	Decrease	-	Methylphenidate drug	(Berglund et al. 2013)
Human brain	Decrease	-	Alcohol dependence (AD) and major depression (MD)	(Yen et al. 2016)
Human brain	Decrease	-	With age	(Volkow et al. 1994; Karrer et al. 2017; van Dyck et al. 2002)
Rat brain	Decrease	-	Amphetamine drug, It is used in the treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity	(Daberkow et al. 2013)
Human brain (Striatum)	Decrease		In PD patient	(Voon et al. 2014)·(Lin et al. 2017; Nutt, Carter, and Sexton 2004; Fazio et al. 2018)
Human brain striatal	-	Decrease	Cocaine abuse	(Narendran et al. 2012)
Human brain	-	Decrease	PD patient	(Cho et al. 2019)

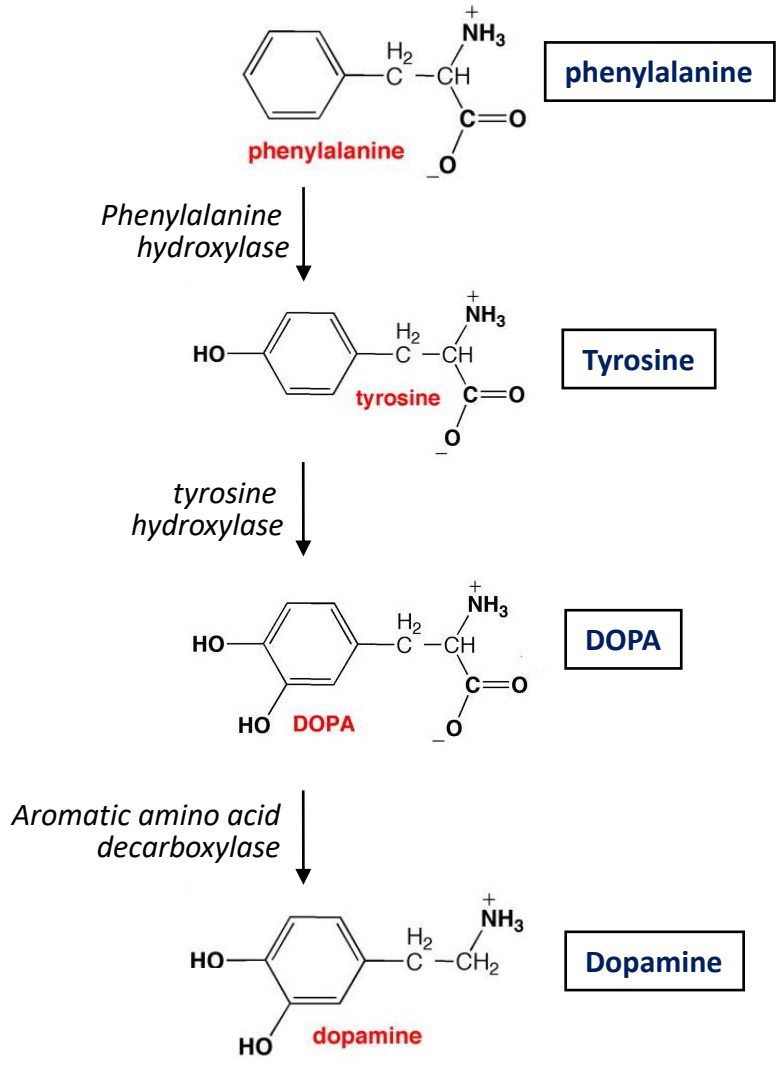


Figure S1. Schematic illustration of the synthesis of dopamne from its aromatic precursors, tyrosine and phenylalanine. (adapted from S. Colette Daubner et. al , Arch Biochem Biophys. 2011)

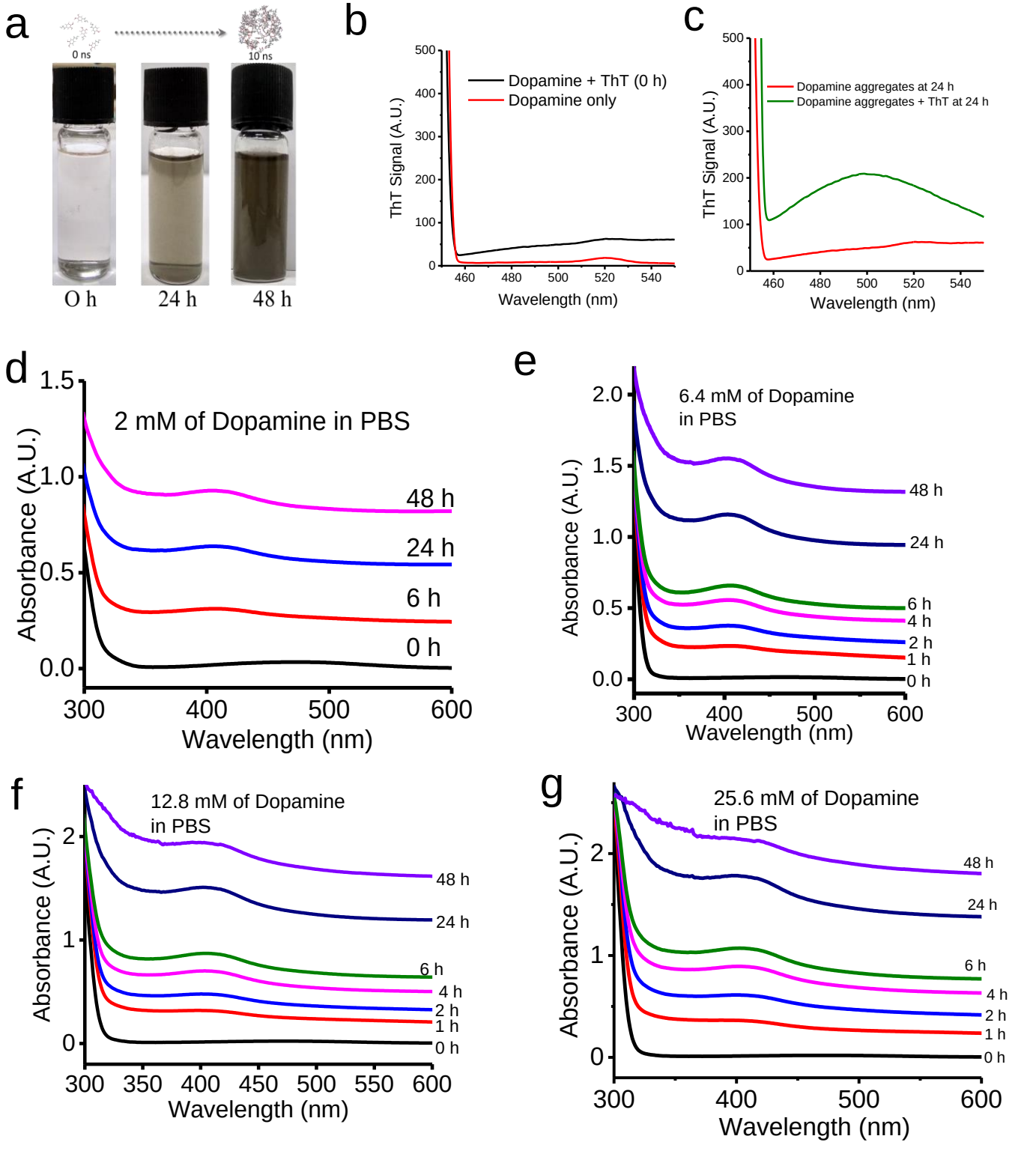


Figure S2 : ***a,*** Visualization of dopamine aggregation confirmed both oxidation and aggregation. ***b,*** (—) Fluorescence emission of [Thioflavin T dye + dopamine solution] at 0 h; (—) fluorescence emission of [only dopamine solution] at 0 h. ***c,*** Fluorescence signal of dopamine in the presence (—) and absence (—) of ThT at 24 h time point. For data shown in ***b*** and ***c*** **,** the excitation λ was 440 nm and emission maxima were observed at 490 nm, indicating that there is no interference of dopamine with the ThT signal. ***d,*** Change in the absorbance spectra of 2 mM dopamine incubated at 37 ºC in PBS, shows gradual rise in the turbidity, confirming the dopamine oxidation and aggregation. ***e-g,*** Change in the absorbance spectra of different concentrations of dopamine solution, as labeled.

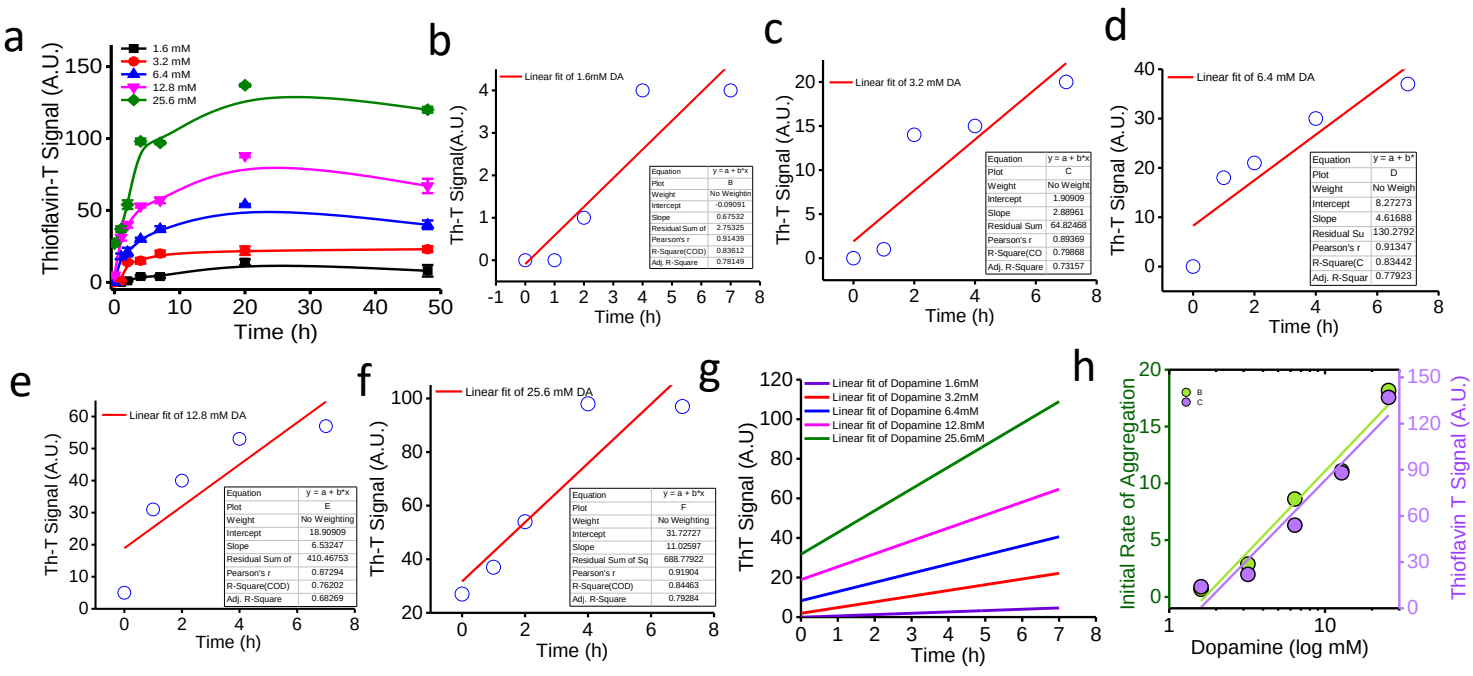


Figure S3: Analysis of rate of the aggregation of dopamine at different concentrations *a,* Thioflavin-T data showing dose-dependent dopamine aggregation in PBS at 37 °C, as labeled. ***b,*** linear fit of initial time points of the aggregation reactions of dopamine at 1.6 mM. ***c,*** linear fit of initial time points of the aggregation reactions of dopamine at 3.2 mM. ***d,*** linear fit of initial time points of the aggregation reactions of dopamine at 6.4 mM. ***e,*** linear fit of initial time points of the aggregation reactions of dopamine at 12.8 mM. ***f,*** linear fit of initial time points of the aggregation reactions of dopamine at 25.6 mM. ***g,*** Comparison of the linear fit curves obtained from dopamine aggregation reactions at different concentrations (1.6 mM to 25.6 mM), as labeled. ***h,*** Double Y plot signifying the correlation between the extent of aggregation and the rate of aggregation, as labeled.

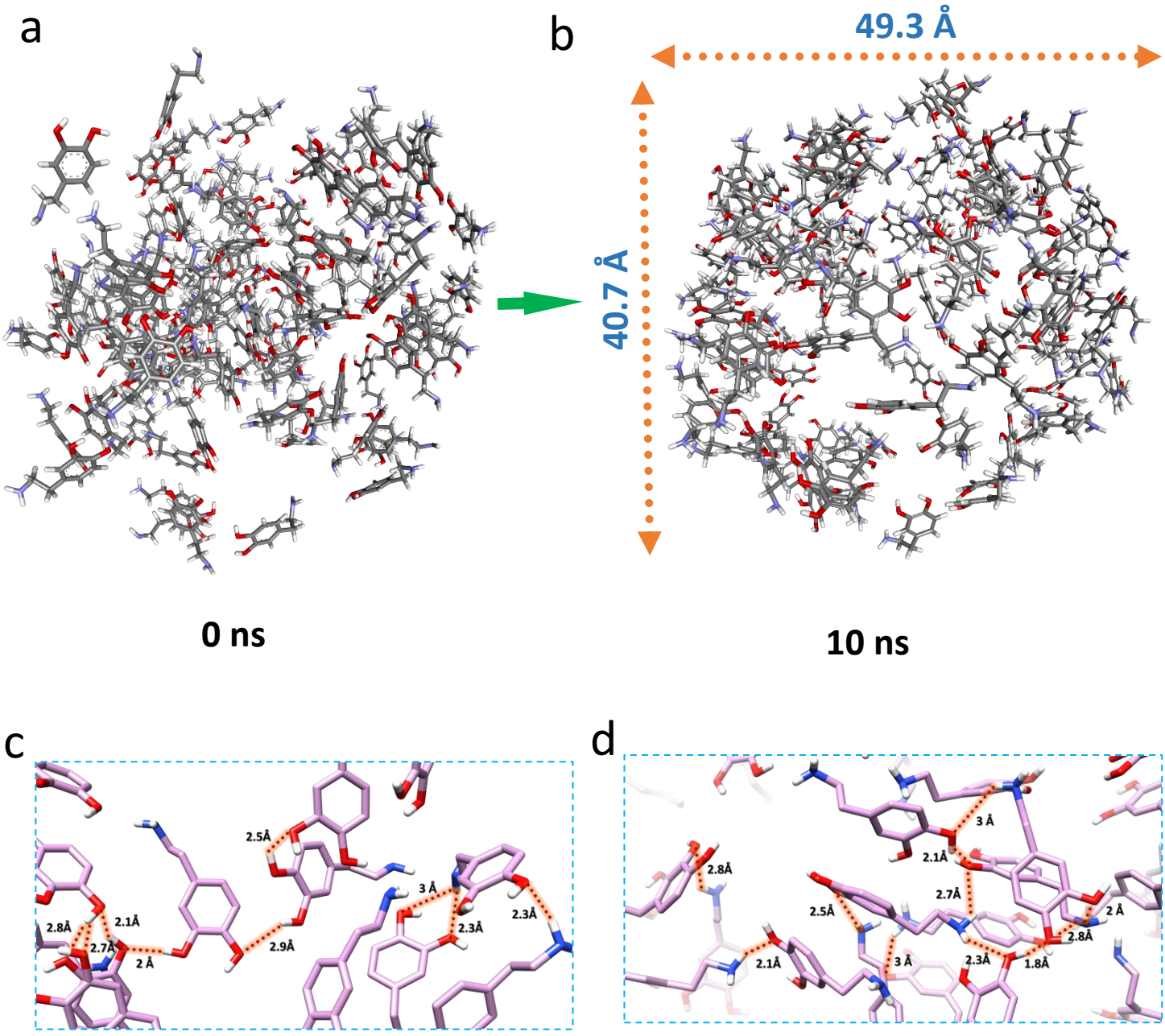
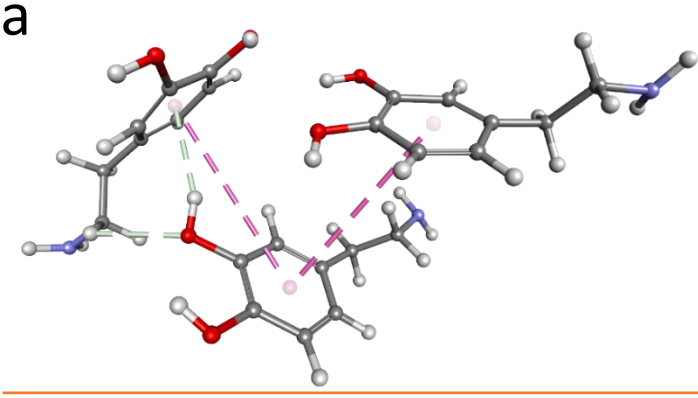


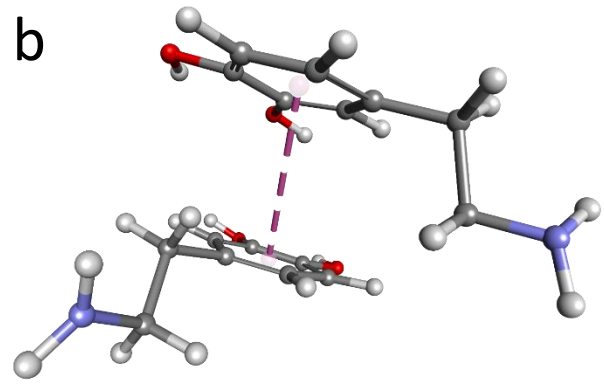
Figure S4. Simulated dopamine nanostructure stabilized by non-covalent interactions. ***a,*** Dopamine molecules at 0 s before simulation. ***b,*** simulated dopamine nanoarchitecture at 10 ns. ***c, d*** Snapshots of simulated nanostructure revealing intermolecular H-bonding interactions between dopamine molecules.

a



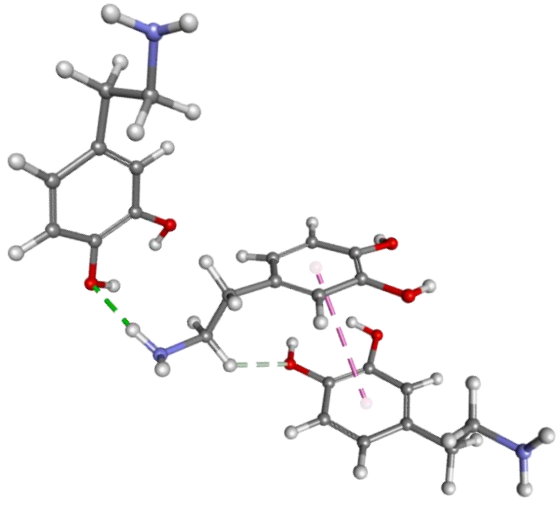
Interacting residues	Bond length (Å)	Type of Interaction
DA9 - DA98	5.5	Pi-Pi Stacked
DA51 - DA98	5.7	Hydrophobic
DA98:H21 - DA51	2.8	Hydrogen Bond
DA51:H14- DA98:O1	2.7	Hydrogen Bond

b



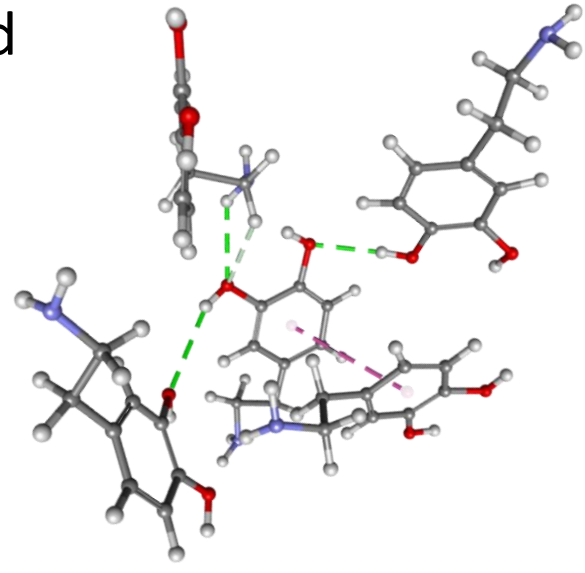
Interacting residues	Bond length (Å)	Type of Interaction
DA97 - DA99	4.4	Pi-Pi Stacked

c



Interacting residues	Bond length (Å)	Type of Interaction
DA36:H20 - DA35:O2	2.3	Hydrogen Bond
DA36:H14 - DA69:O2	2.7	Hydrogen Bond
DA36 -DA69	4.4	Pi-Pi Stacked

d



Interacting residues	Bond length (Å)	Type of Interaction
DA14:H22 - DA62:O2	2.2	Hydrogen Bond
DA43 - DA62	4.3	Pi-Pi Stacked
DA62:H21 -DA96:O1	2.8	Hydrogen Bond
DA2:H14 - DA62:O1	2.8	Hydrogen Bond
DA2:H20 - DA62:O1	2.5	Hydrogen Bond

Figure S5. ***a-d,*** Intermolecular interactions between dopamine (DA) molecules in the simulated nanostructure: Intermolecular interaction between dopamine molecules through π–π interaction patterns and rigid hydrogen-bonding. The hydrogen bonds formed between the carboxylate and amino group which add to the stacking between each molecules. The detailed list of interacting functional groups are given in the respective tables.

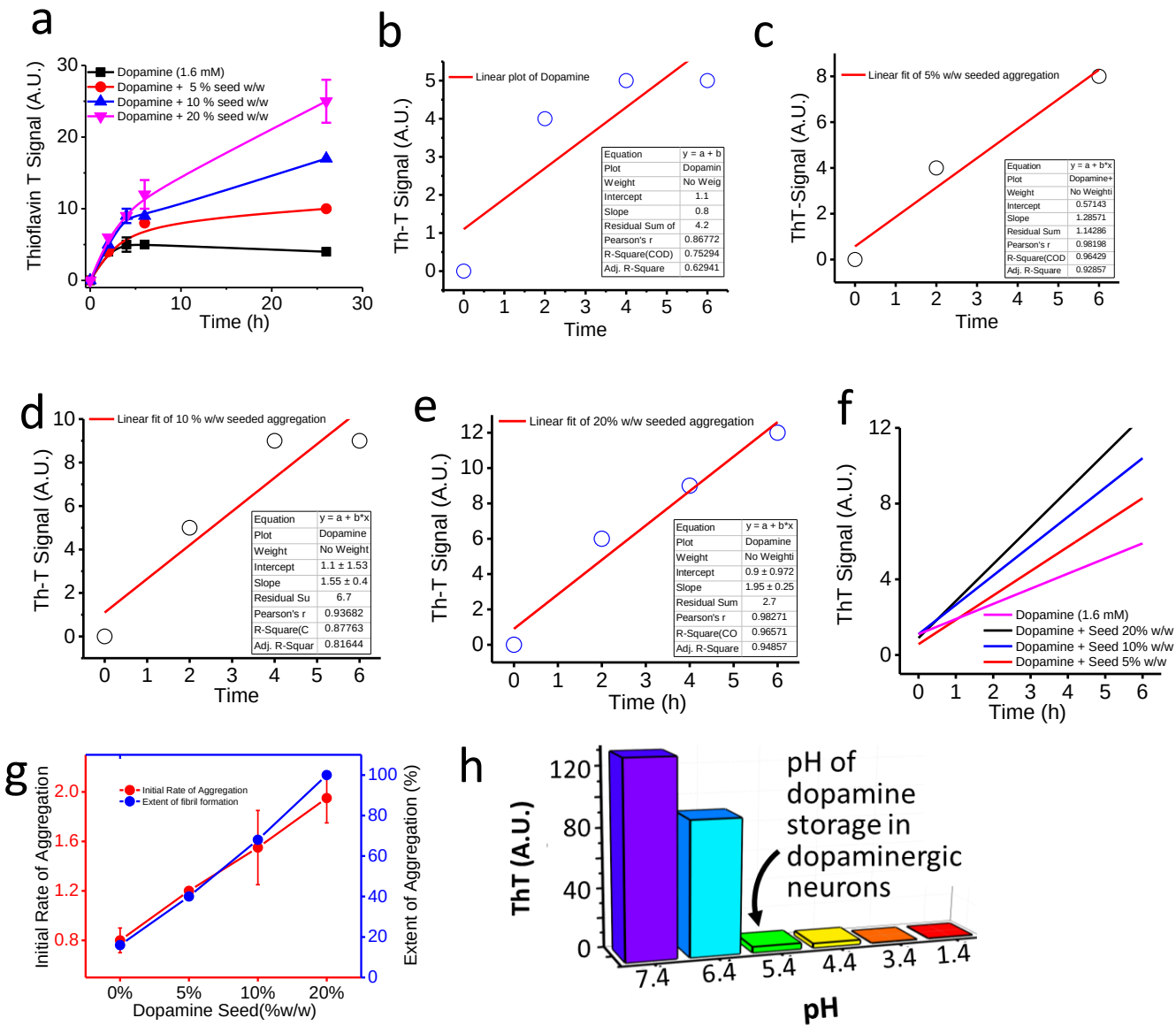


Figure S6. **Analysis of the rate of self-seeded aggregation of dopamine in dose-dependent manner.** ***a,*** Thioflavin-T data showing self-seeded aggregation, as labelled. ***b,*** Linear fit of initial time points of the control aggregation reaction. ***c,*** Linear fit of initial time points of the aggregation reaction at 5 % w/w seed of dopamine. ***d,*** Linear fit of initial time points of the aggregation reaction at 10 % w/w seed of dopamine. ***e,*** Linear fit of initial time points of the aggregation reaction at 20 % w/w seed of dopamine. ***f,*** Comparison of linear fits of the dopamine's self-seeded aggregation reactions, as labelled. ***g,*** Double Y plot showing correlation between the rate of aggregation and the extent of aggregation. ***h,*** Histograms reflecting the extent of aggregation (from the ThT signal at 48 h) of dopamine in different pH conditions, indicating no aggregation at pH 5.4 and below.

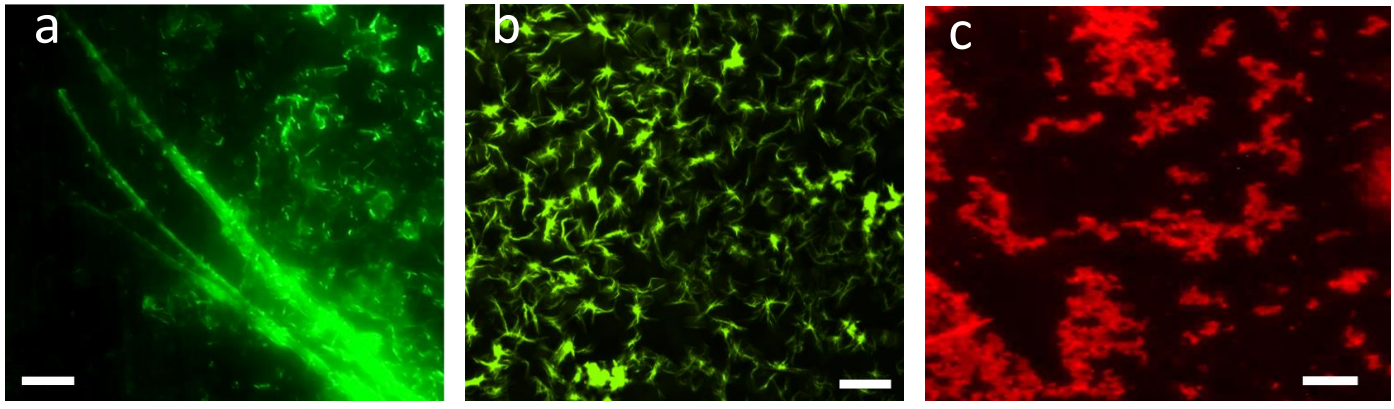


Figure S7. a, b, Thioflavin-T stained images of dopamine aggregates. Scale bar 10 μm. ***c,*** Congo red-stained images of dopamine aggregates. Scale bar 10 μm.

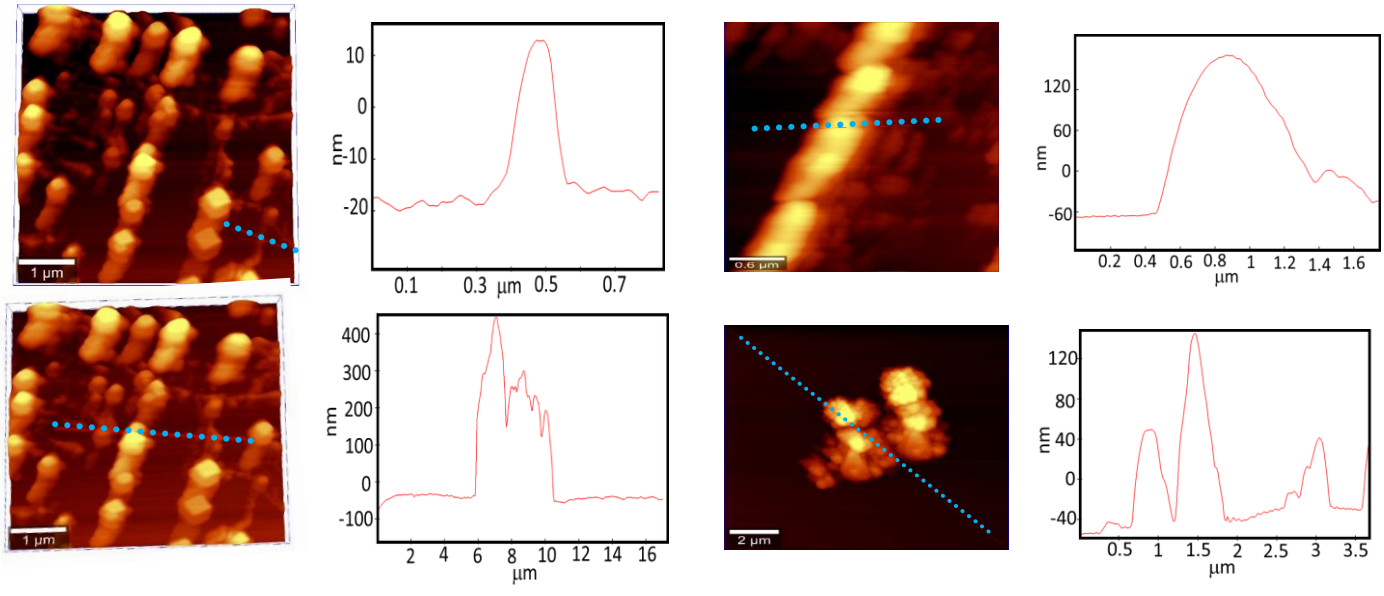


Figure S8. Analysis of the surface topology and dimensions of the dopamine-generated nanostructures as detected by atomic force microscopy (AFM) experiments, as labelled.

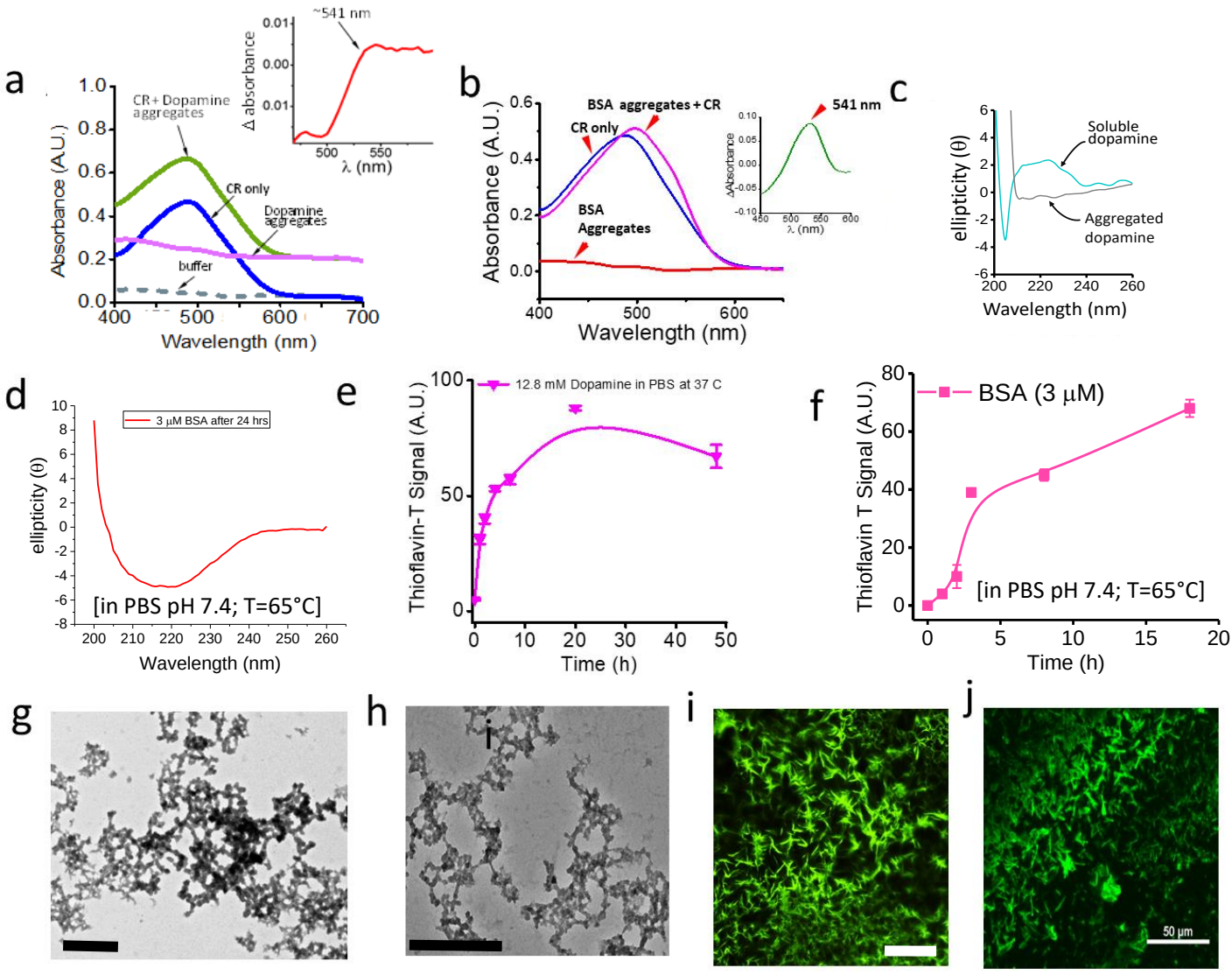


Figure S9 : **Comparison of characteristic properties of both dopamine nanostructures and amyloid fibrils of bovine serum albumin**. ***a*** and ***b,*** data from Congo red assay; ***c*** and ***d,*** data from CD; ***e*** and ***f,*** data from ThT kinetics. ***g*** and ***h,*** data from TEM (200 nm Scale bar); ***i*** and ***j,*** data from ThT stained fluorescence imaging (Scale bar 50 μm). BSA aggregation was induced by incubating 3 μM of BSA at 65° C and the aggregates were collected after 24 h time point for CD, TEM and microscopic and Congo red (CR) analysis.

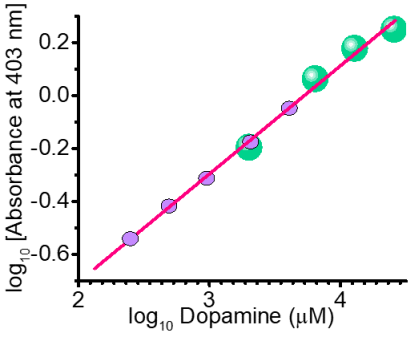
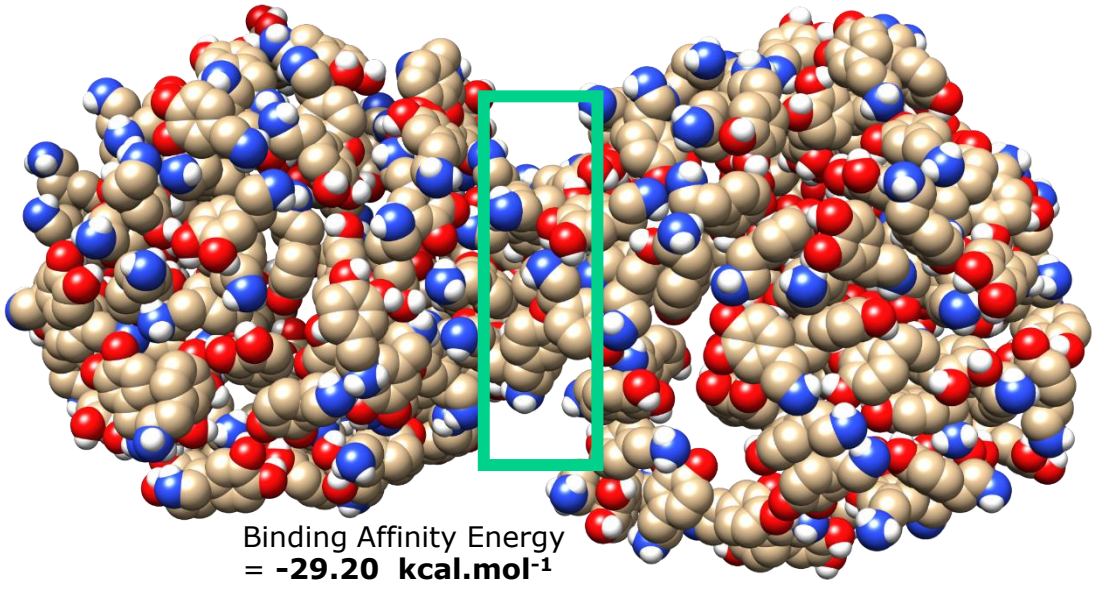
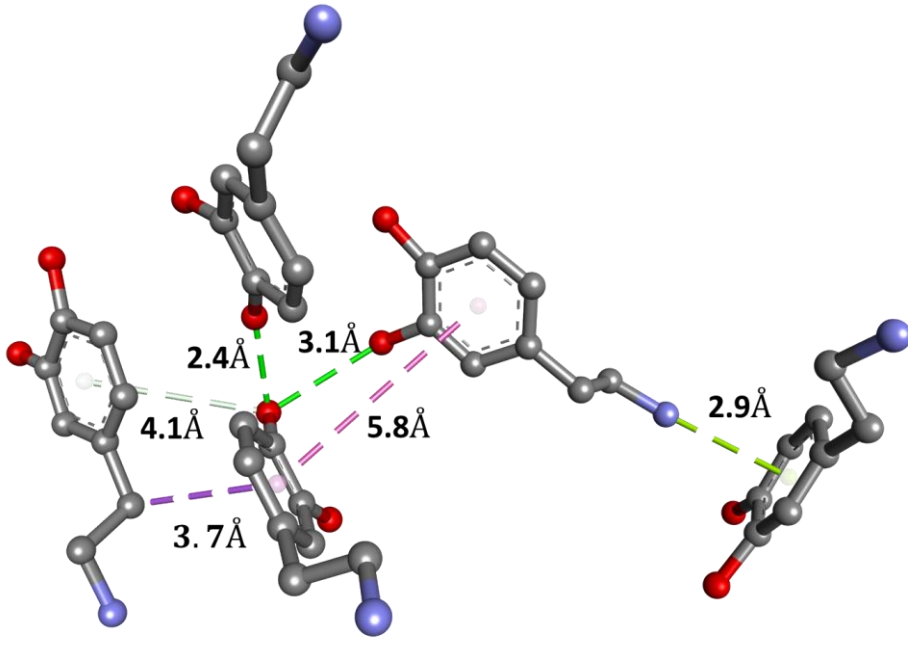


Figure S10 : Linear fit (—) of experimental data points(●) obtained from turbidity assay (absorbance at 403 nm) of dopamine self assemblies. Extrapolation of the linear fit allowed us to predict the turbidity signal (●).





Interacting Molecules	Bond Length (Å)	Type of Interaction
A:Dopamine33:O2 - B:Dopamine17:O2	2.4	Hydrogen Bond
A:Dopamine40:O1 - B:Dopamine17:O2	3.1	Hydrogen Bond
B:Dopamine17:O2 - A:Dopamine92	4.1	Pi-Donor
A:Dopamine92:C4 - B:Dopamine17	3.7	Hydrophobic
A:Dopamine40:N3 - B:Dopamine34	2.9	Pi-Lone Pair
A:Dopamine40 - B:Dopamine17	5.8	Hydrophobic

Figure S11. Rigid docking data displaying the interaction between two simulated dopamine nanostructures during their complex formation. ***a,*** Docked complex between two dopamine nanoassemblies. The binding affinity energy = -29 kcal.mol^{-1}, as indicated. ***b,*** Snapshot of the interacting domains indicates the type of interactions and the interacting functional groups. ***c,*** The detailed list of interacting functional groups and the type of non-covalent interactions are shown in the table.

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