Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Crystallography based exploration of non-covalent interactions to design, synthesis of coumarin for stronger protein binding

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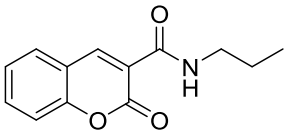
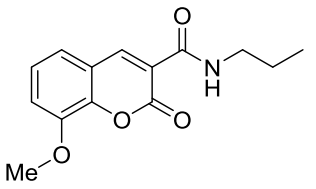
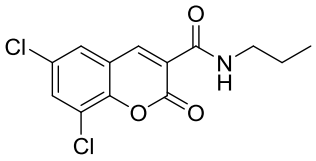
2-Oxo-N-propyl-2H-chromene-3-carboxamide (**HH**). Yield – 80 %, colorless crystalline solid, M.P. 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, H-4), 8.83 (br s, 1H, NH), 7.62–7.70 (m, 2H, H-5, H-7), 7.36–7.43 (m, 2H, H-6, H-8), 3.41–3.47 (m, 2H, –NH–CH2–), 1.59– 1.71 (m, 2H, –CH2–CH2–CH3), 0. 99 (t, J = 7.2 Hz, 3H, CH3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 161.4, 154.4, 148.2, 133.9, 129.8, 125.2, 118.7, 118.6, 116.6, 41.6, 22.7, 11.5.



8-Methoxy-2-oxo-N-propyl-2H-chromene-3-carboxamide (**OME**). Yield – 76 %, colorless crystalline solid, M.P. 160–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (s, 1H, H-4), 8.87 (br s, 1H, –NH–), 7.25–7.32 (m, 2H, H-5, H-6), 7.20 (d, J = 7.5 Hz, 1H, H-7), 4.2 (s, 3H, OCH3), 3.44–3.48 (m, 2H, –NH–CH2–), 1.65–1.73 (m, 2H, –CH2–CH2–CH3), 1.00 (t, J = 7.5 Hz, 3H, CH3); ^{13}C NMR (100 MHz, CDCl3): δ 161.2, 148.5, 147.2, 144.3, 125.2, 121.1, 119.5, 119.0, 115.6, 56.5, 41.7, 22.8, 11.6.



6,8-Dichloro-2-oxo-N-propyl-2H-chromene-3-carboxamide (**2CL**). Yield – 77 %, colorless crystalline solid, M.P. 230–232 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ8.81 (s, 1H, H-4), 8.68 (br s, 1H, –NH–), 7.69 (d, J = 2.0Hz, 1H,H-5), 7.58 (d, J = 2.0Hz, 1H,H-7), 3.41–3.45 (m, 2H, –NH–CH2–), 1.62–1.70 (m, 2H, –CH2–CH2–CH3), 1.00 (t, J = 7.5 Hz, 3H, CH3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 160.0, 148.8, 147.8, 146.8, 133.8, 130.6, 127.4, 122.8, 120.6, 41.9, 22.7, 11.6.



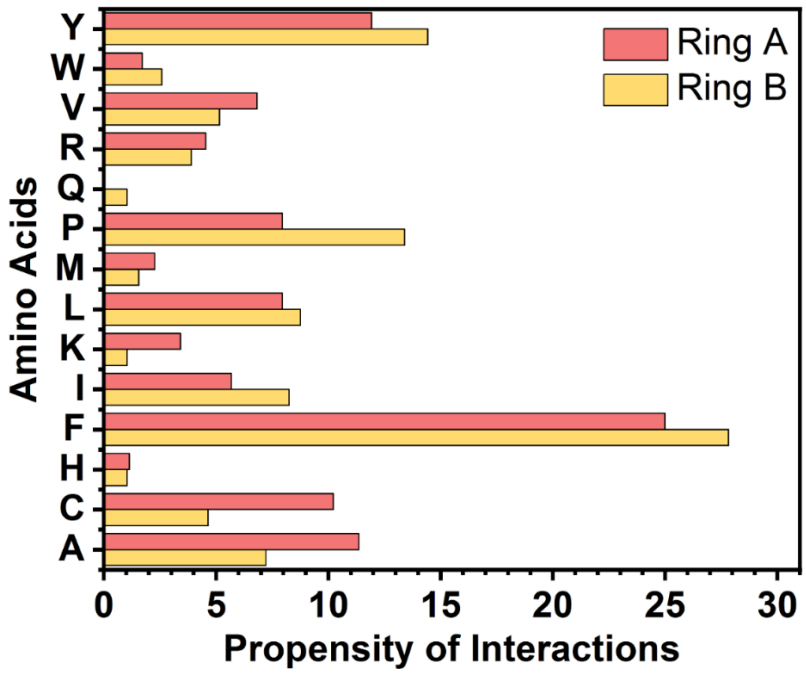
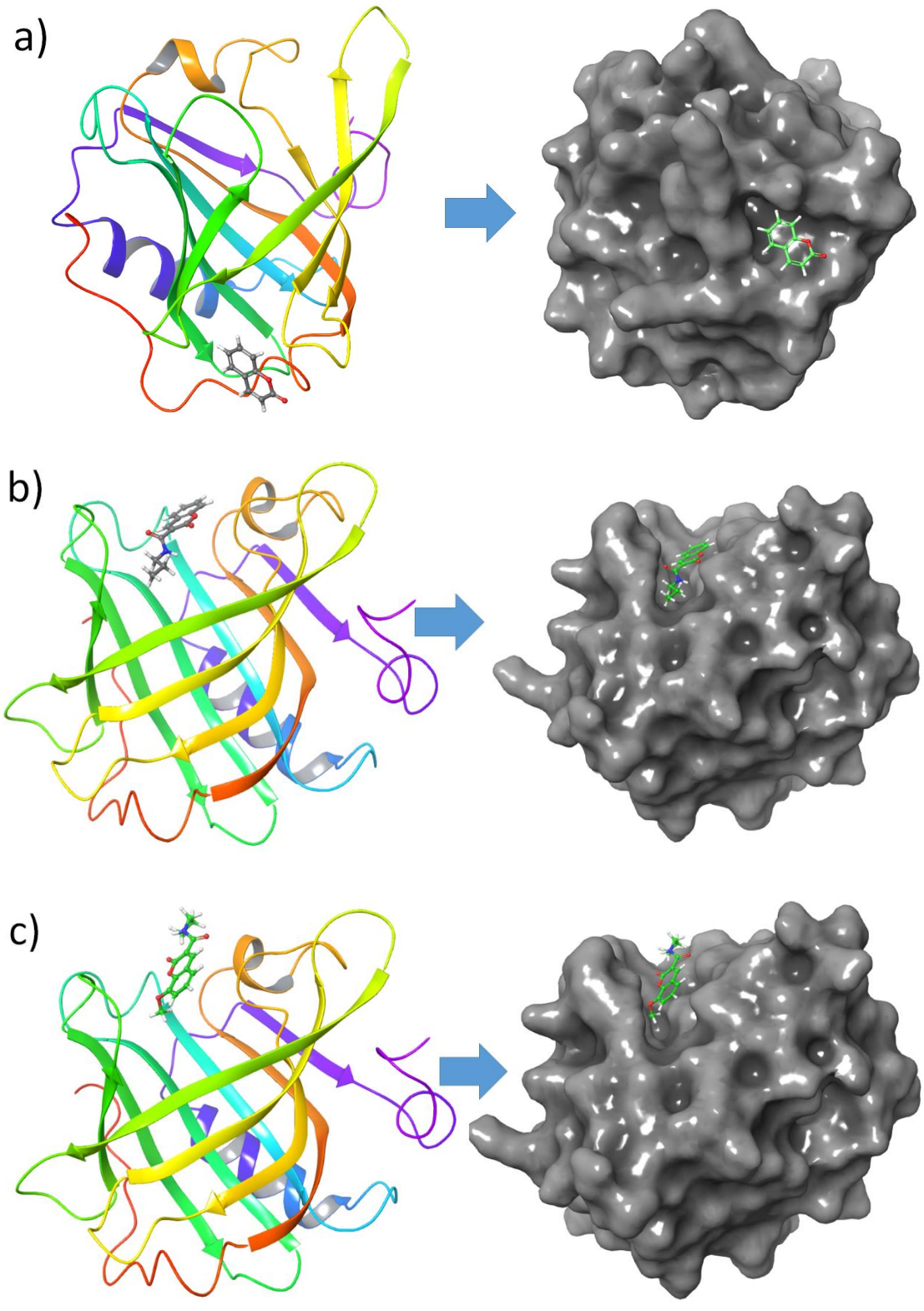


Figure S1. The propensities of interactions between coumarin moiery and the amino acids present in the active site of different protein.


a)
b)
c)

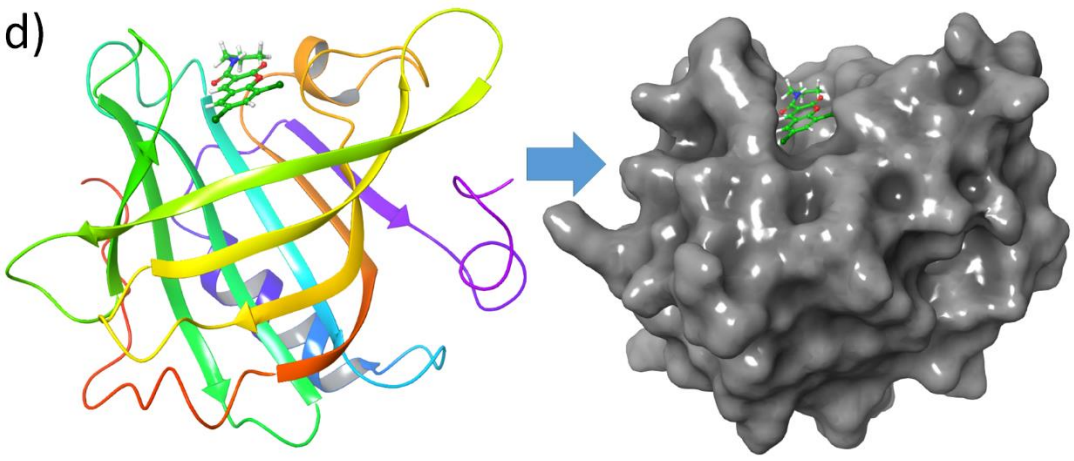


Figure S2. Docking pose of (a) coumarin, (b) **HH**, (c) **OME**, and (d) **2CL** in the BLG protein

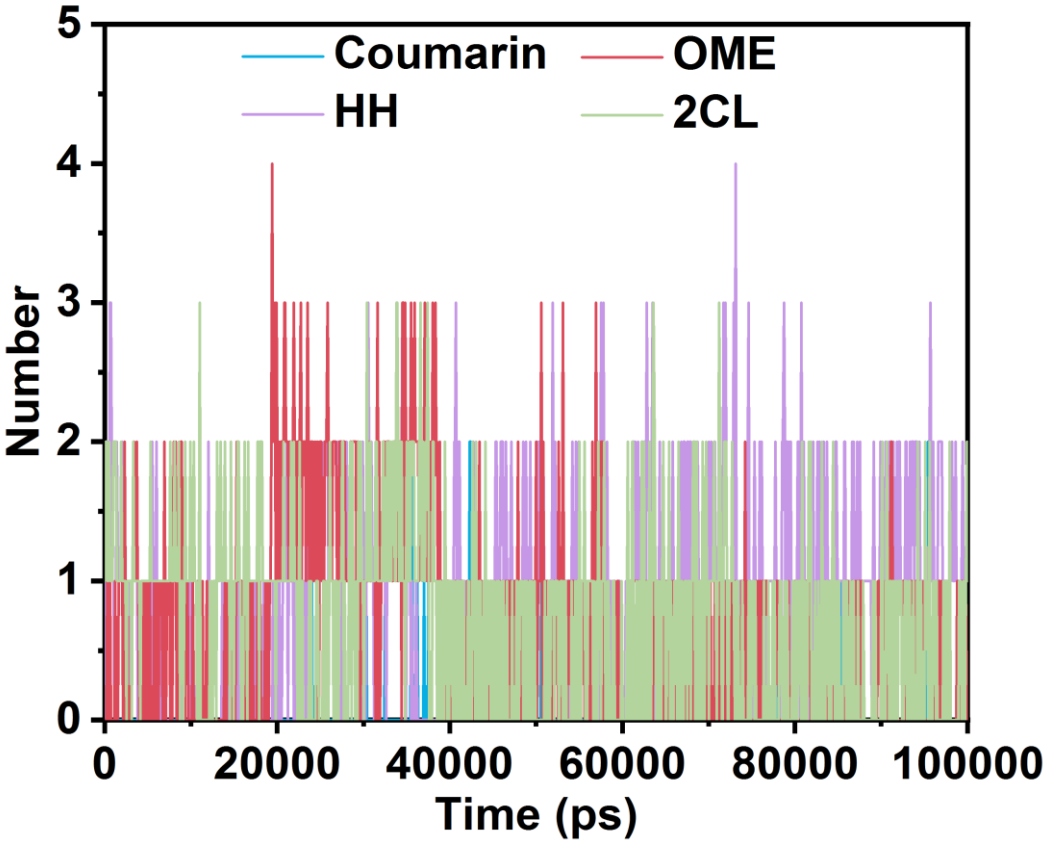


Figure S3. Number of H-bonds vs time plot of different coumarin compounds in their binding site found in the trajectory of MD simulation.

Table S1: PDB Ids of the proteins bound with small molecules having coumarin moieties.

PDB IDs	1aj6, 1cjf, 1kij, 1z11, 2bhj, 2pmj, 2v5w, 2v60, 2ya3, 3crb, 3jsx, 4cet, 4fz3, 4ige, 4igf, 4qa6, 4qa7, 5dc7, 5l13, 5xhs, 6akr, 6jib, 6kg2, 6ljm, 6ljn, 6r6v, 6tt0, 6udl, 6y1u, 6y1v, 7efq, 7lmn, 7lmo, 7lmp, 7lmq, 7lmr, 5l2o, 6dwm, 5ak2, 3ly2, 3u0f, 4ky2, 2qc6, 5exo, 1a54, 5l2n, 5l2m, 3l68, 4utl, 4uti, 3l66, 3l5m, 2v61,2h90, 2h8z, 1z10, 1v5y, 1k3t, 3ml2, 1ttm, 1vdn, 1vai, 6mg5, 1gcz, 7jvv, 5z1b,5efn, 5efk, 5dc8, 5dc6, 5d1c, 5bwl, 4upj, 4qa5, 2pwb.

Table S2: RMSF of selected amino acid residues.

	I12	**Q13**	**L31**	**P38**	**L39**	**I71**	**K75**	**I84**	**A86**	**N90**
BLG	0.15	0.21	0.12	0.18	0.14	0.11	0.12	0.09	0.14	0.11
BLG-Coumarin	0.09	0.18					0.31			
BLG-**HH**			0.14		0.12	0.11		0.13	0.21	0.14
BLG-**OME**			0.13		0.14					0.15
BLG-**2CL**			0.12	0.16	0.14	0.15		0.14	0.25	0.17