Supplementary information: A detailed computational study on binding of kinase inhibitors into the β-Cyclodextrin: Inclusion complex formation

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1. Setup details and Force field validation

First of all, the molecular identifiers in ATB server for components were: BCD (ATB molid: 345755, and ATB Topology Hash: 98ed9), Drug1 (ATB molid: 364378, and ATB Topology Hash: 7c61b), Drug3 (ATB molid: 364376, and ATB Topology Hash: e23f1), Drug5 (ATB molid: 364377, and ATB Topology Hash: 80d84). Then, simulations were carried out along seven different simulations. The first system which comprises only one β-CD and water molecules as a reference system. The next three systems consisted of only one of these drugs and water molecules. The other three systems were included one of each of these drugs, β-CD, and water molecules. The initial positions of drugs and β-CD were adjusted so that the drugs were placed at a distance of 6 Å above the secondary face (wide open) of β-CD and at the center of the box, as shown in Fig.2, where box lengths in the XYZ dimensions for all systems were 5×5×5 nm^3. Finally, to validate the force field, some properties of the reference system were calculated and compared with other results obtained, one can be seen as follow:

Table S1: The structural properties of βCD in water from our MD simulation in comparison with the previous experimental and MD studies.

Properties \ Force field	This work	53A6[a]	53A6$_{GLYC}$[b]	56A6$_{CARBO}$[c]	56A6$_{CARBO_R}$[d]	CHARMM36[e]	q4md-CD[f]	2016H66[e]	Exp
ψ dihedral angle [°]	122	103.1	118.0	145.6	119.0	126.2	125.0	103.9	127.6[g]
ζ dihedral angle [°]	59.8	149.0	54.8	104.0	61.2	56.0	69.4	51.5	63.2[h]
δ angle [°]	127.4	127.6	128.2	126.0	127.4	127.5	127.3	128.0	128.3[g]
φ dihedral angle [°]	116	78.3	114.2	79.0	110.4	110.4	111.9	114.1	109.8[g]
Circularity[p]	0.98	0.85	0.92	0.82	0.85	0.88	0.89	0.89	0.94[i]
d_{O23}	0.3017	0.621	0.285	0.543	0.340	0.312	0.304	0.304	0.2884[g]
d_{O6}	0.4573	0.507	0.561	0.617	0.554	0.533	0.535	0.531	0.5384[h]
d_{O1}	0.4497	0.486	0.445	0.467	0.434	0.437	0.429	0.437	0.4385[g]
Some other properties of βCD in water from our MD simulation in comparison with the previous experimental and MD studies by different force fields.									
1st rim diameter (nm)	1.18	~1.30(Glycam06)[j], ~1.10(Glycam04, q4md-CD)[j], ~1.20(Amber99SB)[j]							1.01[k]
2nd rim diameter (nm)	1.28	~1.35(Glycam06)[j], ~1.30(Glycam04)[j], ~1.25(Amber99SB, q4md-CD)[j]							1.25[k]
RMSD (nm)	0.11	0.19(Glycam06)[j], 0.11(Glycam04)[j], 0.15(Amber99SB)[j], 0.13(q4md-CD)[j], ~0.25(GROMOS 53A6)[l]							-----
radial of gyration (nm)	0.606	0.6 (CHARMM22)[m]							0.60[k]
diffusion coefficient $\left(10^{-9}\ \frac{m^2}{s}\right)$	0.294	0.280(GROMOS 53A6)[n]							~0.318[o]

[a]Reference [1], [b]Reference [2], [c]Reference [3], [d]Reference [4], [e]Reference [5], [f]Reference [6], [g]Reference [7], [h]Reference [8], [i]Reference [9], [j]Reference [8], [k]Reference [10], [l]Reference [11], [m]Reference [12], [n]Reference [13], [o]Reference [14], [p]ratio of the smallest to the largest distance between any pair of glucose O1 atoms that lie across the ring from each other.

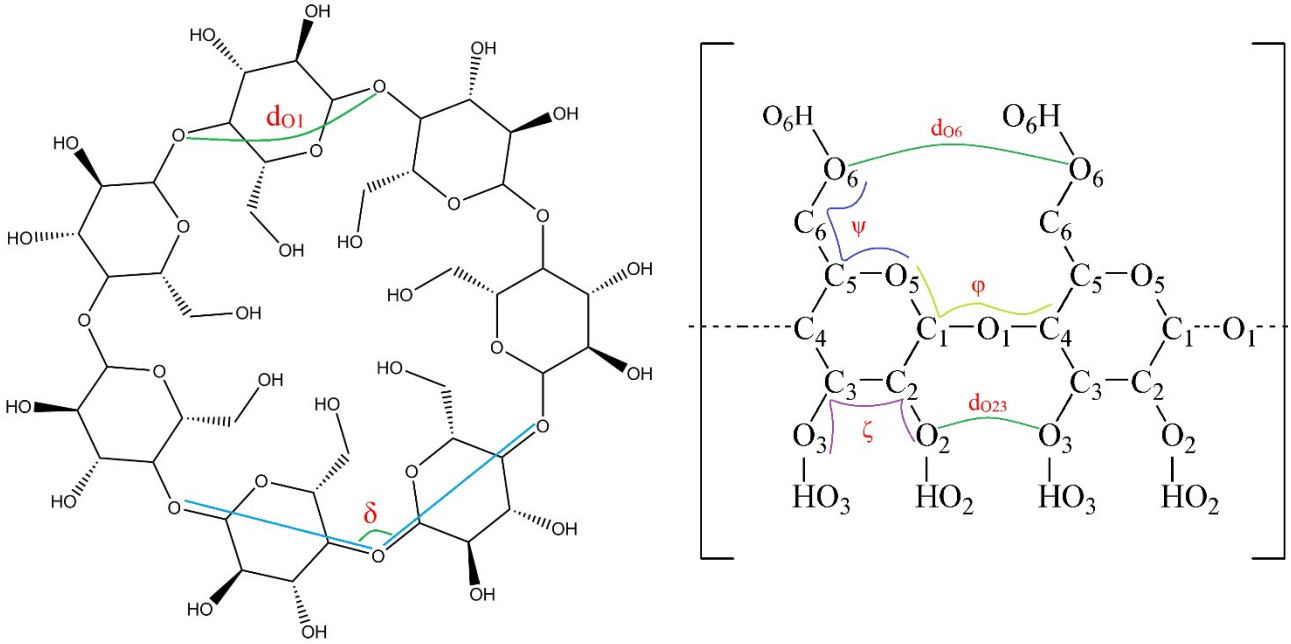
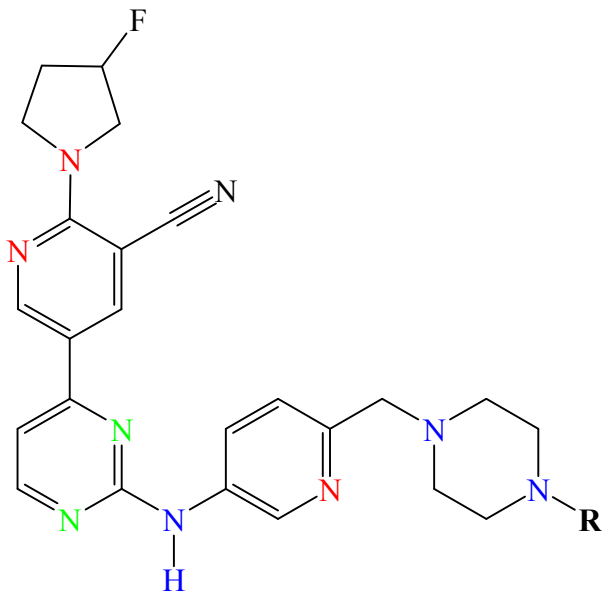


Figure S1: Nomenclature and definitions used in this Article for structural parameters.

2. Main skeleton, and all drugs structures

(a)



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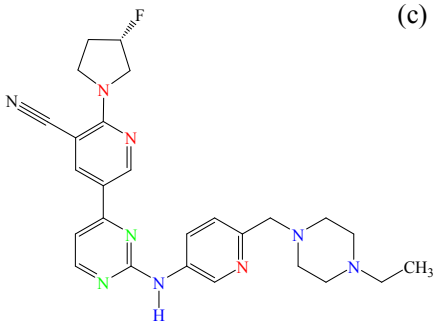
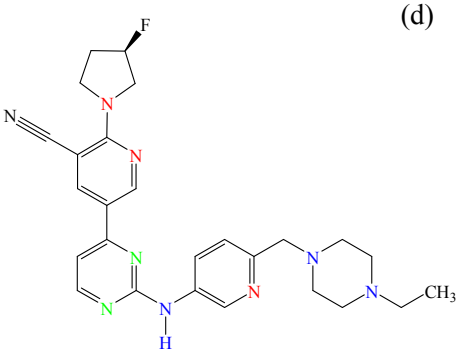
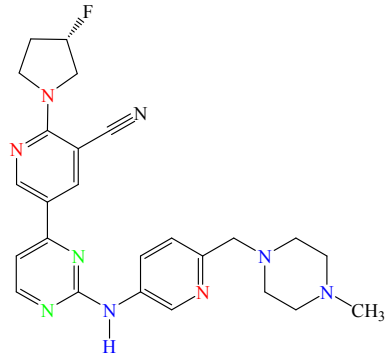


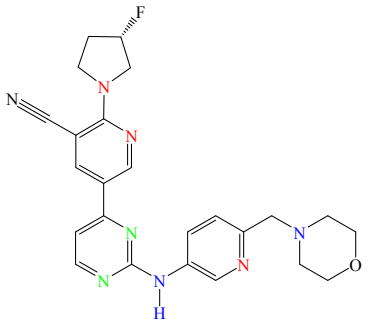
(c)



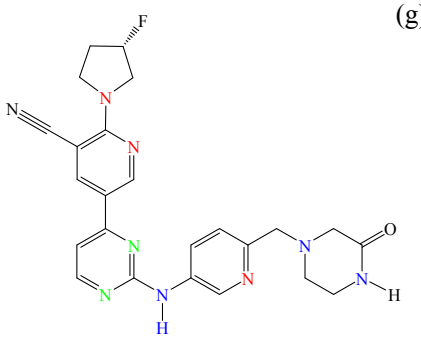
(d)



(e)



(f)



(g)

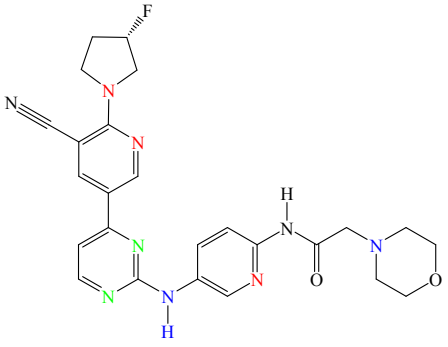


Figure S2: Main skeleton of 5-(Pyrimidin-4-yl)-2-(pyrrolidin-1-yl)nicotinonitrile Compounds (a), Drug1 (b), Drug2 (c), Drug3 (d), Drug4 (e), Drug5 (f), and Drug6 (g).

3. The reasons for selecting drugs

a) From experimental point of view [15], drug1 has the best inhibition among structures, and can make inhibitory potency for all three kinases in experiment, none of other structure can have inhibition in all three kinases. That is why, this structure, as the main structure, was selected for more investigation. Moreover, this structure has rather small HLG (band gap), and high softness and less hardness which shows its good potential for charge transfer and reactivity, as summarized in Table S1 and S2.

b) From electronical point of view, drug3 has the lowest HLG, the highest softness and the lowest hardness among the structures which means it can have the best charge transfer and reactivity in comparison to other structures.

c) From electronical point of view, drug5 has the highest HLG, the lowest softness and highest hardness which means it can have the worst charge transfer and reactivity in comparison to other structures.

Table S2: E_{HOMO}, E_{LUMO}, HLG of Kinase inhibitors with B3LYP/6-31+G(D) method in water.

Inhibitor	E_{HOMO} (eV)	E_{LUMO} (eV)	HLG (eV)
Drug1	-5.747	-1.988	3.759
Drug2	-5.748	-1.979	3.768
Drug3	-5.753	-2.001	3.752
Drug4	-5.776	-2.001	3.774
Drug5	-6.034	-2.005	4.029
Drug6	-5.880	-1.994	3.885

Table S3: Chemical softness (σ) and hardness (η) of all drugs.

Inhibitor	σ (eV)	η (eV)
Drug1	0.532	1.879
Drug2	0.530	1.884
Drug3	0.533	1.876
Drug4	0.529	1.887
Drug5	0.496	2.014
Drug6	0.514	1.943

4. Mean Square Displacement (MSD) of β-CD in the reference system

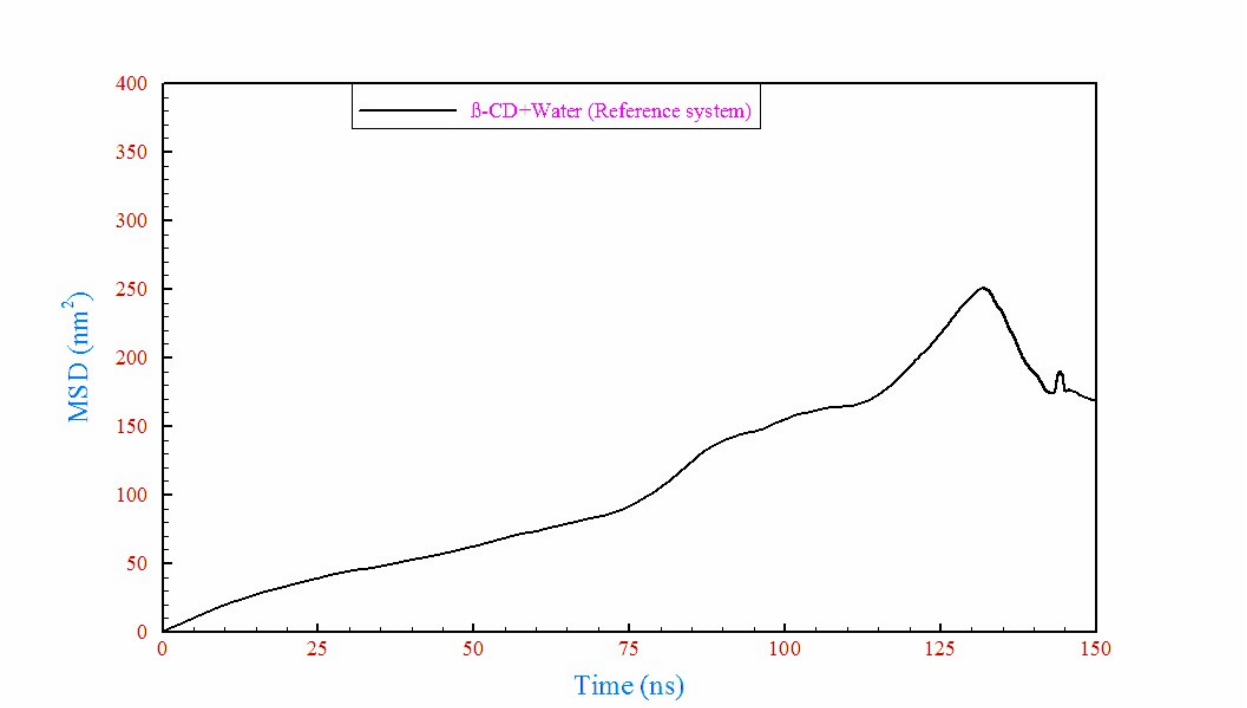


Figure S3: The mean square displacement of β-CD in water

5. Flexibility of β-CD and drugs in different systems: Checking the heavy atoms

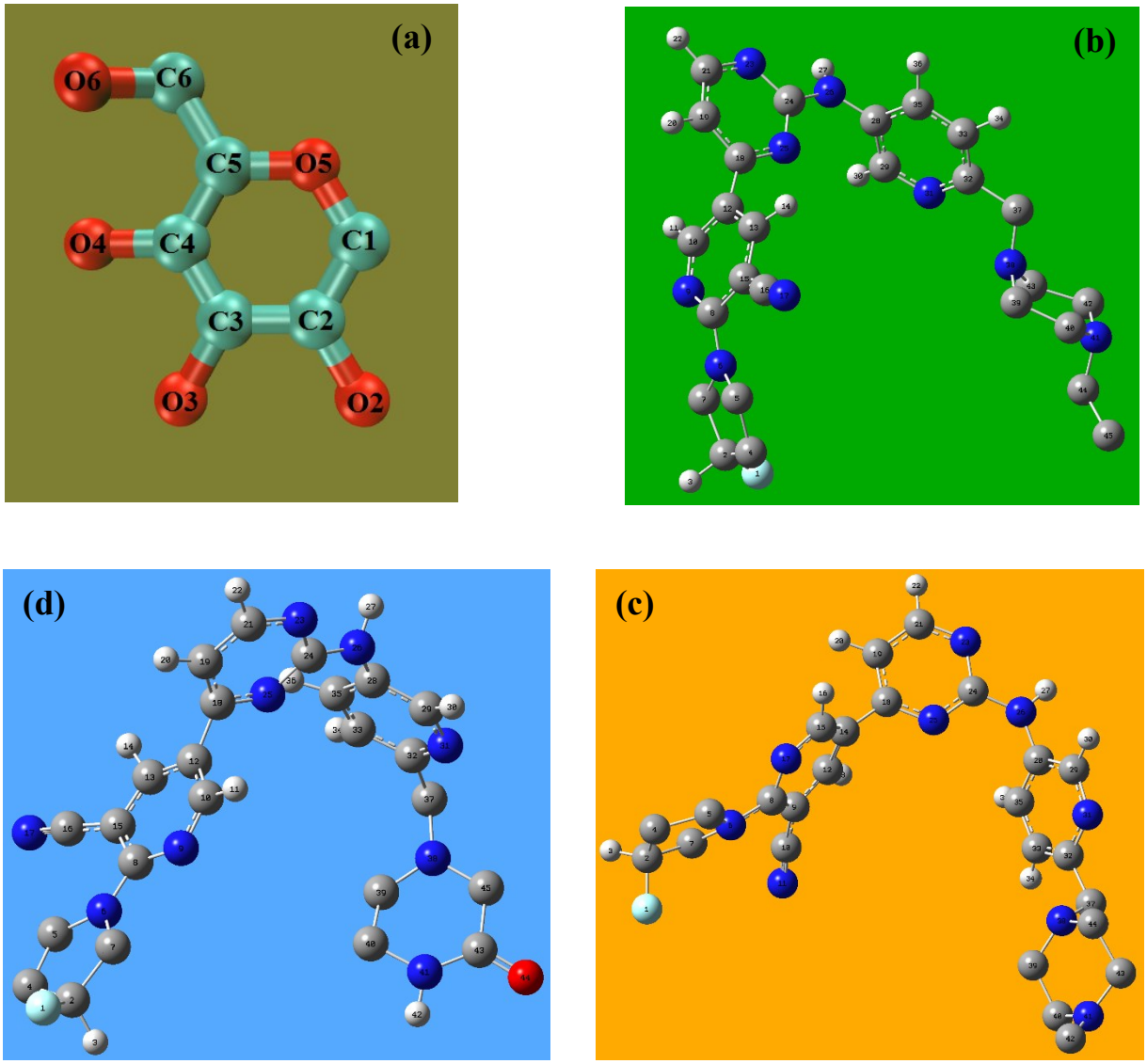


Figure S4: Atom IDs employed for each glucopyranoside unit of the β-CD in the analysis (a), numbering label of atoms in Drug1 (b), Drug3 (c), and Drug5 (d).

6. Free energy discussions based on quantum point of view

MEP images for the mentioned inhibitors mostly demonstrate dark and light blue color with positive charges and neutral charges which represent their hydrophobicity, and they have more tendency to interact with hydrophobe parts of β-cyclodextrin, so the differences in binding energy can be explained as below:

1. According to the optimized structures and MEP, Drug1 has lower steric hindrance by negative charges of C-N branch, so it is more likely to have better binding with β-cyclodextrin.

2. According to the optimized structures and MEP, charge distribution in Drug3 is similar to Drug1, but due to orientation of C-N branch with negative charge, there is one-side steric hindrance of negative charge in this structure, so binding to β-cyclodextrin is weaker than Drug1.

3. According to the optimized structures and MEP, because of present of oxygen in Drug5, this structure is more hydrophile than Drug1 and Drug3, and has to attach from the middle of it. Moreover, this oxygen has made steric hindrance of negative charge for binding with β-cyclodextrin, so it has the weakest binding to β-cyclodextrin.

As a result, because of charge distributions and steric hindrance of negative charges in the optimized structures, binding energies are: Drug1<Drug3<Drug5

7. Reference:

[1] C. Oostenbrink, A. Villa, A.E. Mark, W.F. Van Gunsteren, A biomolecular force field based on the free enthalpy of hydration and solvation: the GROMOS force-field parameter sets 53A5 and 53A6, J. Comput. Chem. 25 (2004) 1656–1676.

[2] L. Pol-Fachin, V.H. Rusu, H. Verli, R.D. Lins, GROMOS 53A6GLYC, an improved GROMOS force field for hexopyranose-based carbohydrates, J. Chem. Theory Comput. 8 (2012) 4681–4690.

[3] H.S. Hansen, P.H. Hünenberger, A reoptimized GROMOS force field for hexopyranose-based carbohydrates accounting for the relative free energies of ring conformers, anomers, epimers, hydroxymethyl rotamers, and glycosidic linkage conformers, J. Comput. Chem. 32 (2011) 998–1032.

[4] W. Plazinski, A. Lonardi, P.H. Hünenberger, Revision of the GROMOS 56A6CARBO force field: Improving the description of ring-conformational equilibria in hexopyranose-based carbohydrates chains, J. Comput. Chem. 37 (2016) 354–365.

[5] J. Gebhardt, C. Kleist, S. Jakobtorweihen, N. Hansen, Validation and comparison of force fields for native cyclodextrins in aqueous solution, J. Phys. Chem. B. 122 (2018) 1608–1626.

[6] H. Zhang, T. Tan, W. Feng, D. Van Der Spoel, Molecular recognition in different environments: β-cyclodextrin dimer formation in organic solvents, J. Phys. Chem. B. 116 (2012) 12684–12693.

[7] W. Saenger, J. Jacob, K. Gessler, T. Steiner, D. Hoffmann, H. Sanbe, K. Koizumi, S.M. Smith, T. Takaha, Structures of the common cyclodextrins and their larger analogues beyond the doughnut, Chem. Rev. 98 (1998) 1787–1802.

[8] C. Cézard, X. Trivelli, F. Aubry, F. Djedaïni-Pilard, F.-Y. Dupradeau, Molecular dynamics studies of native and substituted cyclodextrins in different media: 1. Charge derivation and force field performances, Phys. Chem. Chem. Phys. 13 (2011) 15103–15121.

[9] S. Immel, Computer simulation of chemical and biological properties of saccharides: sucrose, fructose, cyclodextrins, and starch, (1995).

[10] C. Betzel, W. Saenger, B.E. Hingerty, G.M. Brown, Topography of cyclodextrin inclusion complexes, part 20. Circular and flip-flop hydrogen bonding in. beta.-cyclodextrin undecahydrate: a neutron diffraction study, J. Am. Chem. Soc. 106 (1984) 7545–7557.

[11] E. Mixcoha, J. Campos-Terán, A. Piñeiro, Surface adsorption and bulk aggregation of cyclodextrins by computational molecular dynamics simulations as a function of temperature: α-CD vs β-CD, J. Phys. Chem. B. 118 (2014) 6999–7011.

[12] C.W. Yong, C. Washington, W. Smith, Structural behaviour of 2-hydroxypropyl-β-cyclodextrin in water: Molecular dynamics simulation studies, Pharm. Res. 25 (2008) 1092–1099.

[13] W. Khuntawee, P. Wolschann, T. Rungrotmongkol, J. Wong-Ekkabut, S. Hannongbua, Molecular dynamics simulations of the interaction of beta cyclodextrin with a lipid bilayer, J. Chem. Inf. Model. 55 (2015) 1894–1902.

[14] A.C.F. Ribeiro, D.G. Leaist, M.A. Esteso, V.M.M. Lobo, A.J.M. Valente, C.I.A. V Santos, A.M. Cabral, F.J.B. Veiga, Binary mutual diffusion coefficients of aqueous solutions of β-cyclodextrin at temperatures from 298.15 to 312.15 K, J. Chem. Eng. Data. 51 (2006) 1368–1371.

[15] R.B. Kargbo, Kinase Inhibitors for Treatment of Cancer and Inflammation, (2018).