Supplementary Information

Molecular Interactions of Cinnamil and Quinoxaline Derivatives by Bcl-2 Antiapoptotic Proteins: A Computational Study

Imelda L. Lazcano-Carrasco,[a] Carlos Z. Gómez-Castro,[b] Luis A. Zárate-Hernández,[a] Rosa L. Camacho-Mendoza,[a] Simplicio González Montiel,[a] Marco Franco-Pérez,[c] Julián Cruz-Borbolla[a,*]

[a] Área Académica de Química, Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo, km. 4.5 Carretera Pachuca-Tulancingo, Ciudad del Conocimiento, C.P. 42184, Mineral de la Reforma, Hidalgo, México

[b] SECIHTI Research Fellow. Área Académica de Química, Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo, km. 14.5 Carretera Pachuca-Tulancingo, Ciudad del Conocimiento, C.P. 42184, Mineral de la Reforma, Hidalgo, México

c Departamento de Física y Química Teórica, Universidad Nacional Autónoma de México, Av. Universidad No. 3004, Col. Ciudad Universitaria, Alc. Coyoacán, C.P. 04510 CDMX, México

* Corresponding author e-mail: jcruz@uaeh.edu.mx, qimfranco@quimica.unam.mx

Phone: +52 771 71 72000 x40109

Contents

S1 Chemical reactivity descriptors

Table S1. Equations of the global and local descriptors used in the methodology.

Descriptor	Equation	Reference
Ionizacion potential	$I = E_{N-1} - E_N$	[1]
Electron affinity	$A = E_N - E_{N+1}$	[1]
Electrochemical potential	$\mu = -\frac{I + A}{2}$	[1]
Mulliken electronegativity	$\chi = -\mu$	[2]
Hardness	$\eta = I - A$	[1]
Electrophilicity	$\omega = \frac{\mu^2}{2\eta}$	[1]
Electroaccepting power	$\omega^+ = \frac{(I + 3A)^2}{16(I - A)}$	[3]
Electrodonating power	$\omega^- = \frac{(3I + A)^2}{16(I - A)}$	[3]
Fukui function electrophilic	$f^+(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^+_{v(r)} = \rho_{N+1}(r) - \rho_N(r)$	[4]
Fukui function nucleophilic	$f^-(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^-_{v(r)} = \rho_N(r) - \rho_{N-1}(r)$	[4]
Dual Descriptor	$\Delta f = f^+(r) - f^-(r)$	[5]
Local electrochemical potential	$\mu_e(\boldsymbol{r}) = \begin{cases} \mu^-(\boldsymbol{r}) = -If^-(\boldsymbol{r}) & para\ \omega < 0 \\ \mu^+(\boldsymbol{r}) = -Af^+(\boldsymbol{r}) & para\ \omega > 0 \\ \mu^0(\boldsymbol{r}) = -\frac{1}{2}(If^-(\boldsymbol{r}) + Af^+(\boldsymbol{r})) & para\ \omega = 0 \end{cases}$	[6–8]
Local hardness	$\eta_\tau(\boldsymbol{r}) = \begin{cases} \eta_{PP}(\boldsymbol{r}) - \frac{1}{2}\eta\Delta f(\boldsymbol{r}) & para\ \omega = -1 \\ \eta_{PP}(\boldsymbol{r}) + \frac{1}{2}\eta\Delta f(\boldsymbol{r}) & para\ \omega = +0 \\ \eta(\boldsymbol{r}) & para\ \omega = 0 \end{cases}$	[6–8]

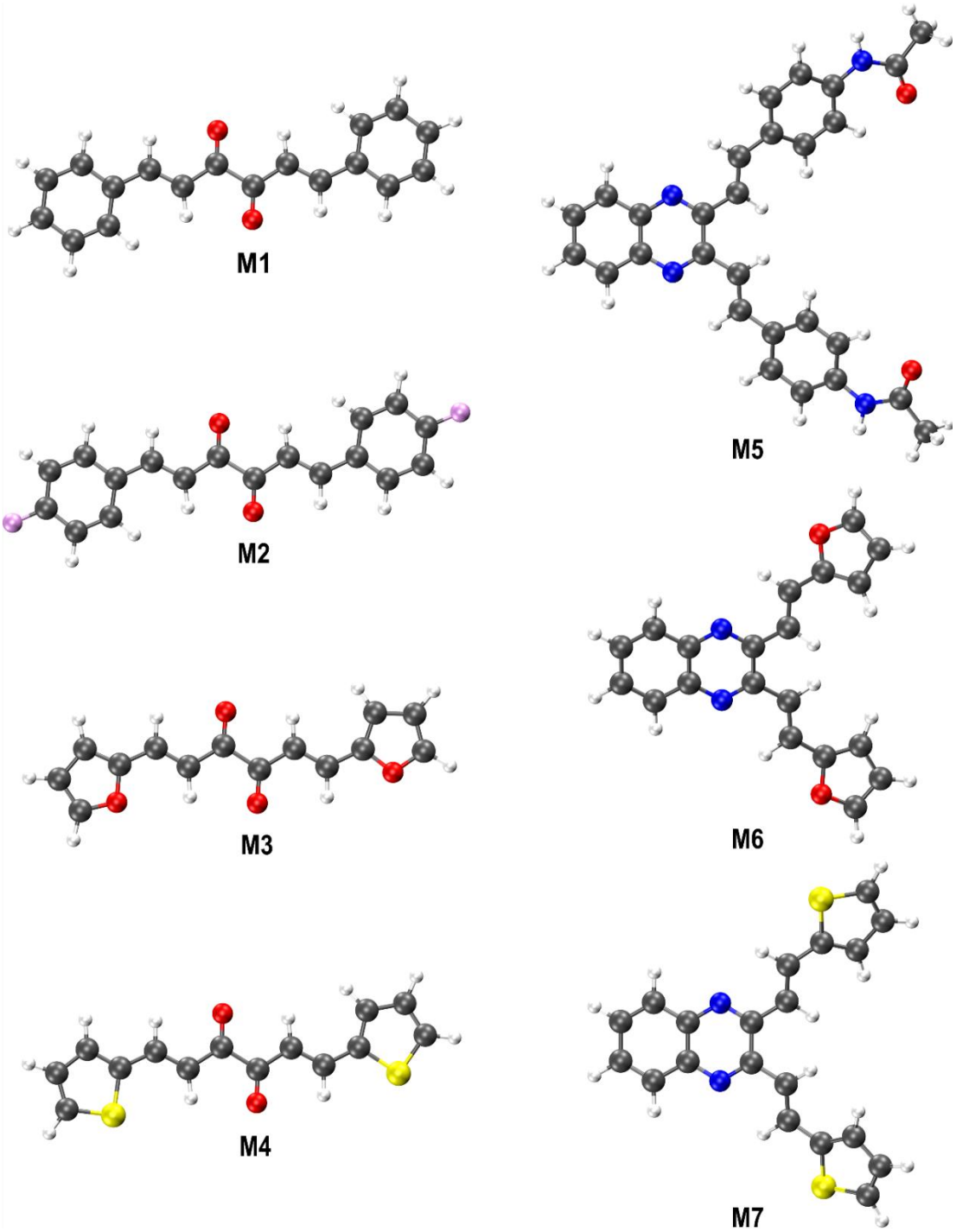

Figure S1. Optimized geometries of the cinnamil and quinoxaline derivatives under analysis.

S2 Molecular docking of the BCl-xl monomeric protein

Table S2. Results from molecular docking analysis, between ligands M1–M7 and in the monomeric protein Bcl-xl

Ligand	Binding sites	Binding energy (kcal/mol)	Inhibition constant (μM)	Binding distance (Å)	Most significant interaction
M1	Leu108	−7.49	3.23	1.973	N-H•••O_{lig}
M2	Ser106	−7.50	3.22	1.861	N-H•••O_{lig}
M3	Ser106	−5.29	133.5	2.989	N-H•••O_{lig}
M4	Leu108	−6.85	9.47	1.970	N-H•••O_{lig}
M5	Ser106	−9.15	0.197	2.160	C-O•••H-N_{lig}
M5	Gly138	−9.49	0.111	2.128	C=O•••H-N_{lig}
M6	Leu108	−9.23	0.170	2.006	N-H•••N-C_{lig}
M7	Leu108	−8.05	1.250	2.685	C=O•••N-C_{lig}

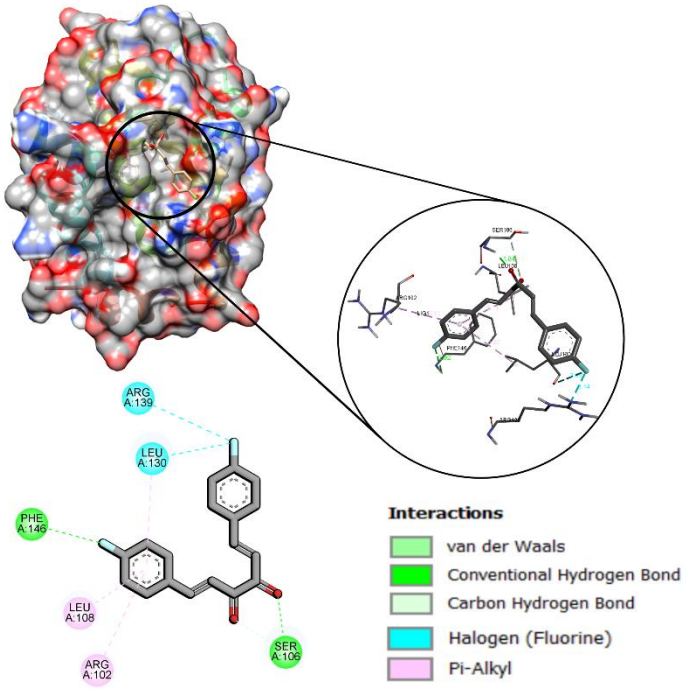

Figure S2. Relevant interactions identified in docking analysis between the ligand **M2** and the Bcl-xl protein.

S3 Chemical reactivity analysis

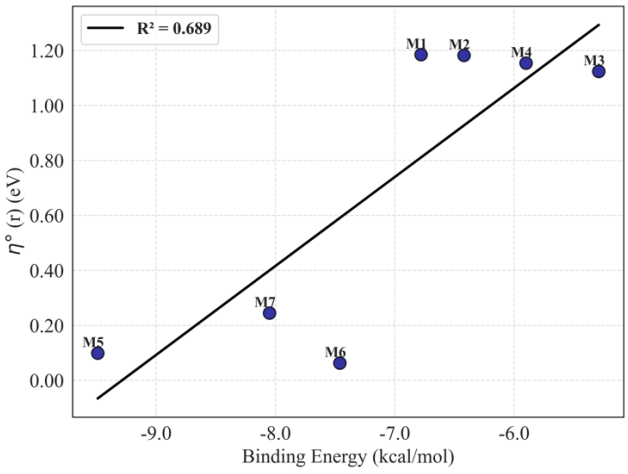

Figure S3. η(r) vs BE profile for inhibitors binding to the Bcl-xl protein.

References

1. López JM, Ensuncho AE, Robles JR. Descriptores globales y locales de la reactividad para el diseño de nuevos fármacos anticancerosos basados en cis-platino(II). Quim Nova. 2013, **36**, 1308–1317.
2. Franco-Pérez M, Gázquez JL. Electronegativities of Pauling and Mulliken in Density Functional Theory. J Phys Chem A. 2019, **123**, 10065–10071.
3. Gázquez JL, Cedillo A, Vela A. Electrodonating and Electroaccepting Powers. J Phys Chem A. 2007, **111**, 1966–1970.
4. Martínez-Araya JI. Why is the dual descriptor a more accurate local reactivity descriptor than Fukui functions? J Math Chem. 2015, **53**, 451–465.
5. Morell C, Grand A, Toro-Labbé A. New Dual Descriptor for Chemical Reactivity. J Phys Chem A. 2005, **109**, 205–212.
6. Franco-Pérez M, Ayers PW, Gázquez JL, Vela A. Local chemical potential, local hardness, and dual descriptors in temperature dependent chemical reactivity theory. Physical Chemistry Chemical Physics. 2017, **19**, 13687–13695.
7. Franco-Pérez M, Polanco-Ramírez CA, Gázquez JL, Ayers PW. Local and nonlocal counterparts of global descriptors: the cases of chemical softness and hardness. J Mol Model. 2018, **24**, 285. DOI: 10.1007/s00894-018-3823-4
8. Franco-Pérez M, Polanco-Ramírez CA, Gázquez JL, Ayers PW, Vela A. Study of organic reactions using chemical reactivity descriptors derived through a temperature-dependent approach. Theor Chem Acc. 2020, **139**, 44. DOI: 10.1007/s00214-020-2557-4