Structural Tuning of Diclofenac for Enhanced Medicinal Efficacy and Reduced Adverse Effects: An Integrating Computational Validation

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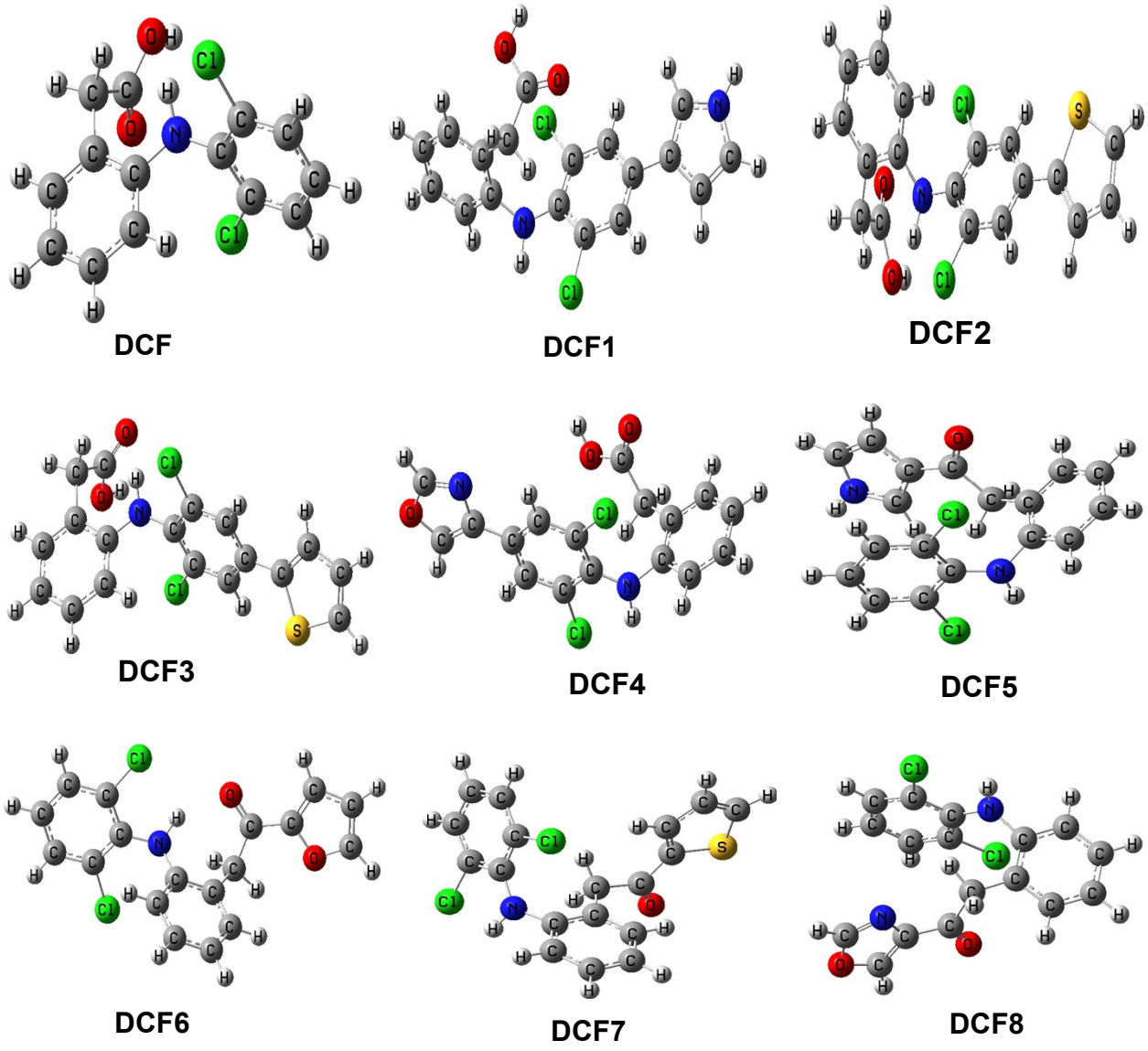
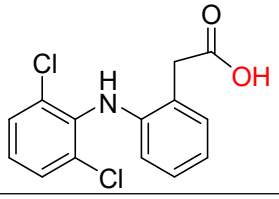
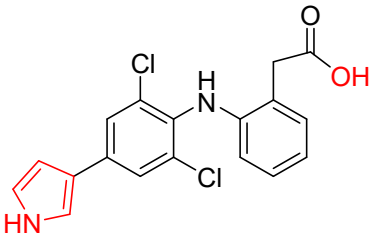
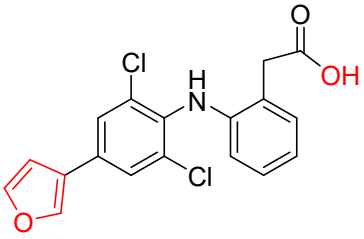
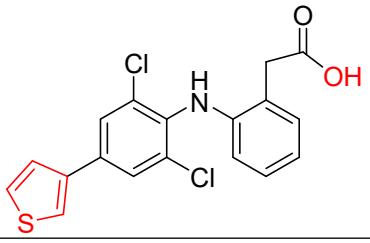
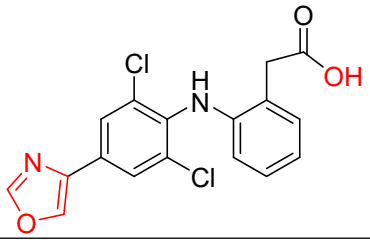
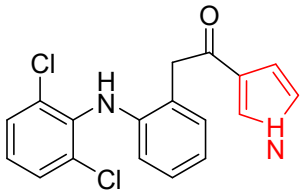
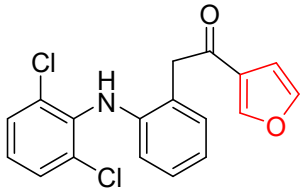


Figure S1 Most stable optimized structures of DCF and its derivatives obtained from DFT calculations.

Table S1 Chemical name, molecular formula (MF), molecular weight (MW), and chemical structure of DCF and its derivatives.

Name	Chemical name/ MF, MW(g/mol)	Chemical structure
DCF	2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid ($C_{14}H_{11}Cl_2NO_2$, 296.15)	
DCF1	2-(2-((2,6-dichloro-4-(1H-pyrrol-3-yl) phenyl) amino) phenyl) acetic acid ($C_{18}H_{14}Cl_2N_2O_2$, 361.22)	
DCF2	2-(2-((2,6-dichloro-4-(furan-3-yl) phenyl) amino) phenyl) acetic acid ($C_{18}H_{13}Cl_2NO_3$, 362.21)	
DCF3	2-(2-((2,6-dichloro-4-(thiophen-3-yl) phenyl) amino) phenyl) acetic acid ($C_{18}H_{13}Cl_2NO_2S$, 378.27)	
DCF4	2-(2-((2,6-dichloro-4-(oxazol-4-yl) phenyl) amino) phenyl) acetic acid ($C_{17}H_{12}Cl_2N_2O_3$, 363.19)	
DCF5	2-(2-((2,6-dichlorophenyl) amino) phenyl)-1-(1H-pyrrol-3-yl) ethan-1-one ($C_{18}H_{14}Cl_2N_2O$, 345.22)	
DCF6	2-(2-((2,6-dichlorophenyl) amino) phenyl)-1-(furan-3-yl) ethan-1-one ($C_{18}H_{13}Cl_2NO_2$, 346.21)	

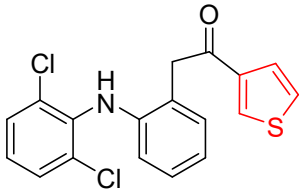
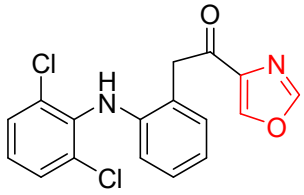
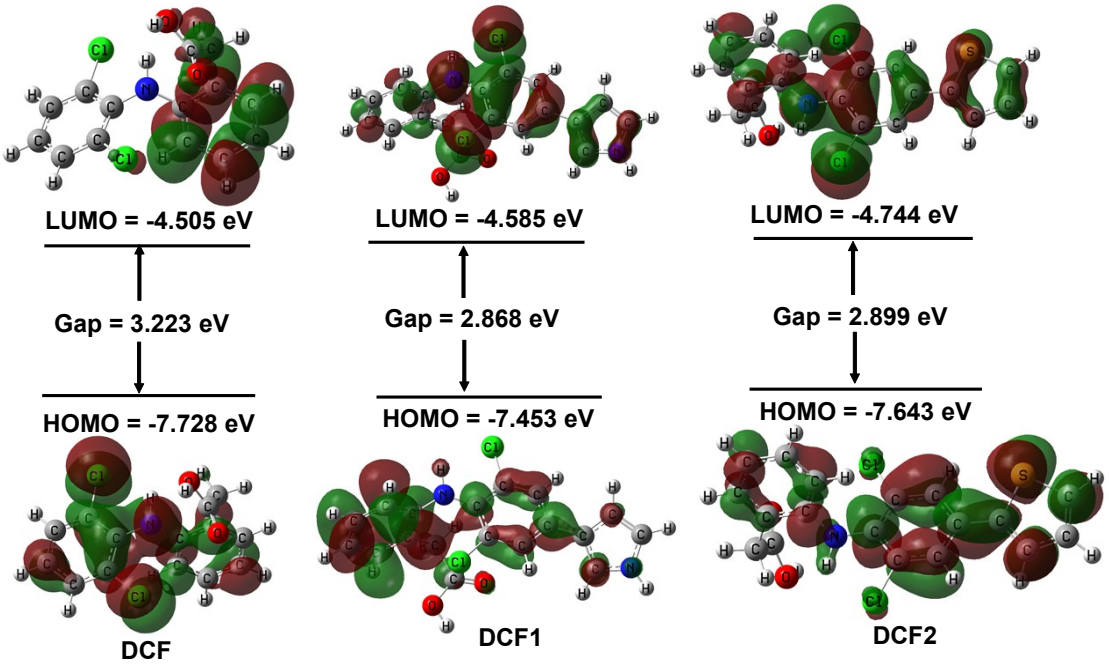
DCF7	2-(2-((2,6-dichlorophenyl) amino) phenyl)-1-(thiophen-3-yl) ethan-1-one ($C_{18}H_{13}Cl_2NOS$, 362.27)	
DCF8	2-(2-((2,6-dichlorophenyl) amino) phenyl)-1-(oxazol-4-yl) ethan-1-one ($C_{17}H_{12}Cl_2N_2O_2$, 347.20)	

Table S2 Electronic energy (Hartree), enthalpy (Hartree), Gibbs free energy (Hartree), and dipole moment (Debye) of all compounds.

Name	Electronic energy	Enthalpy	Gibbs free energy	Dipole moment
DCF	-1665.53	-1665.53	-1665.60	2.36
DCF1	-1874.45	-1874.45	-1874.52	2.15
DCF2	-2217.30	- 2217.29	-2217.37	2.87
DCF3	-2217.30	-2217.30	-2217.37	1.68
DCF4	-1910.37	-1910.37	-1910.45	2.68
DCF5	-1799.20	-1799.20	-1799.28	5.31
DCF6	-1819.08	-1819.08	-1819.15	2.77
DCF7	-2142.05	-2142.05	-2142.12	3.57
DCF8	-1835.12	-1835.12	-1835.20	2.87

Table S3 Energy (eV) of *HOMOs, LUMOs*, gap, hardness (η), softness (S), chemical potential (μ), electronegativity (χ), and electrophilicity (ω) of all compounds.

Name	$\epsilon HOMO$	$\epsilon LUMO$	Gap	η	S	μ	χ	ω
DCF	-5.94	-1.09	4.85	2.42	0.20	-3.51	3.52	2.54
DCF1	-5.43	-0.91	4.51	2.25	0.22	-3.17	3.17	2.23
DCF2	-5.81	-1.72	4.09	2.04	0.24	-3.76	3.76	3.46
DCF3	-5.76	-3.25	2.51	1.25	0.40	-4.50	4.50	8.10
DCF4	-5.87	-1.40	4.47	2.23	0.22	-3.63	3.63	2.95
DCF5	-5.93	-1.15	4.77	2.38	0.21	-3.54	3.54	2.63
DCF6	-5.67	-2.16	3.51	1.76	0.28	-3.91	3.91	4.34
DCF7	-6.08	-2.14	3.94	1.97	0.25	-4.11	4.11	4.28
DCF8	-5.98	-1.83	4.14	2.07	0.24	-3.90	3.90	3.67



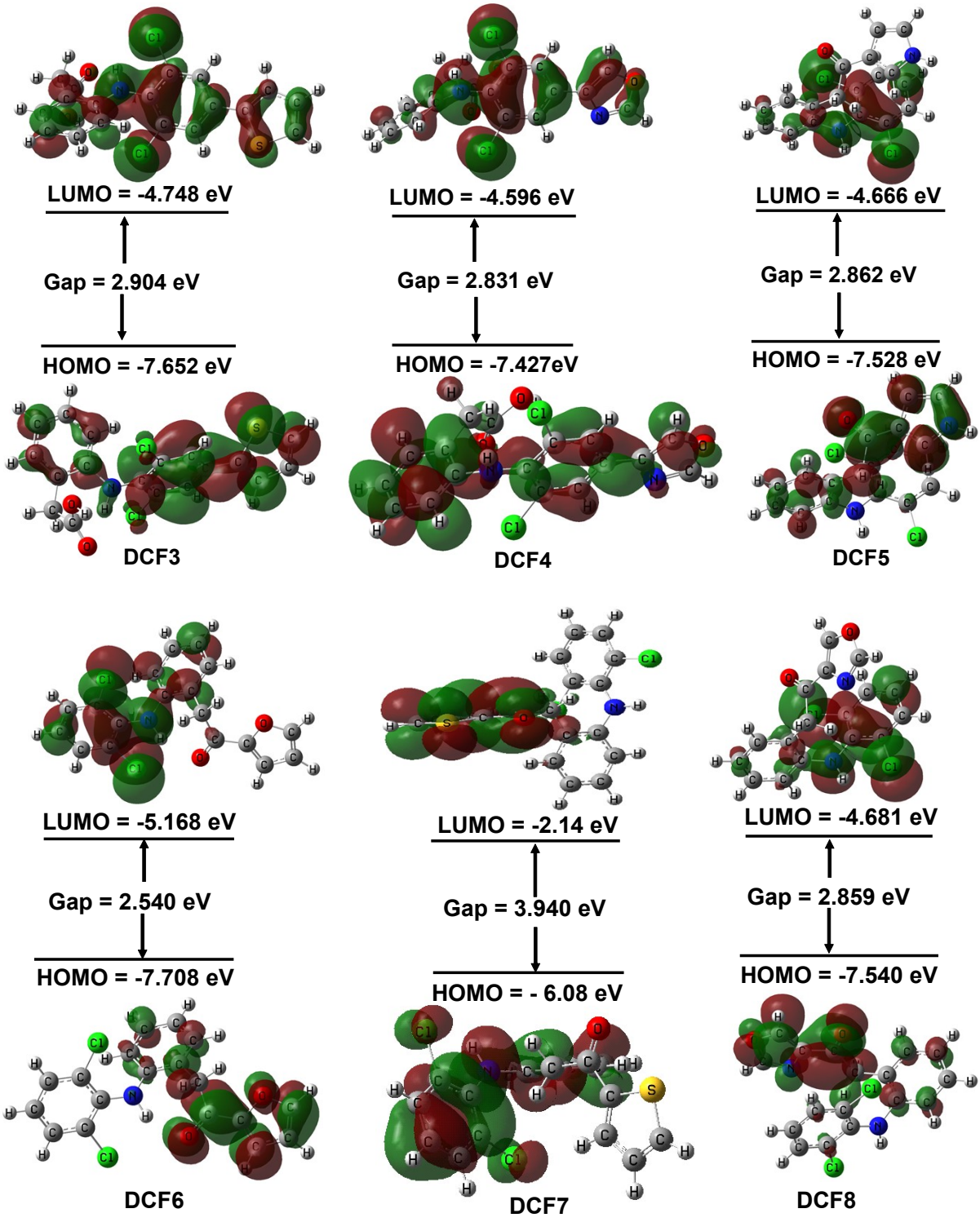


Figure S2 Molecular orbital map of DCF and its derivatives.

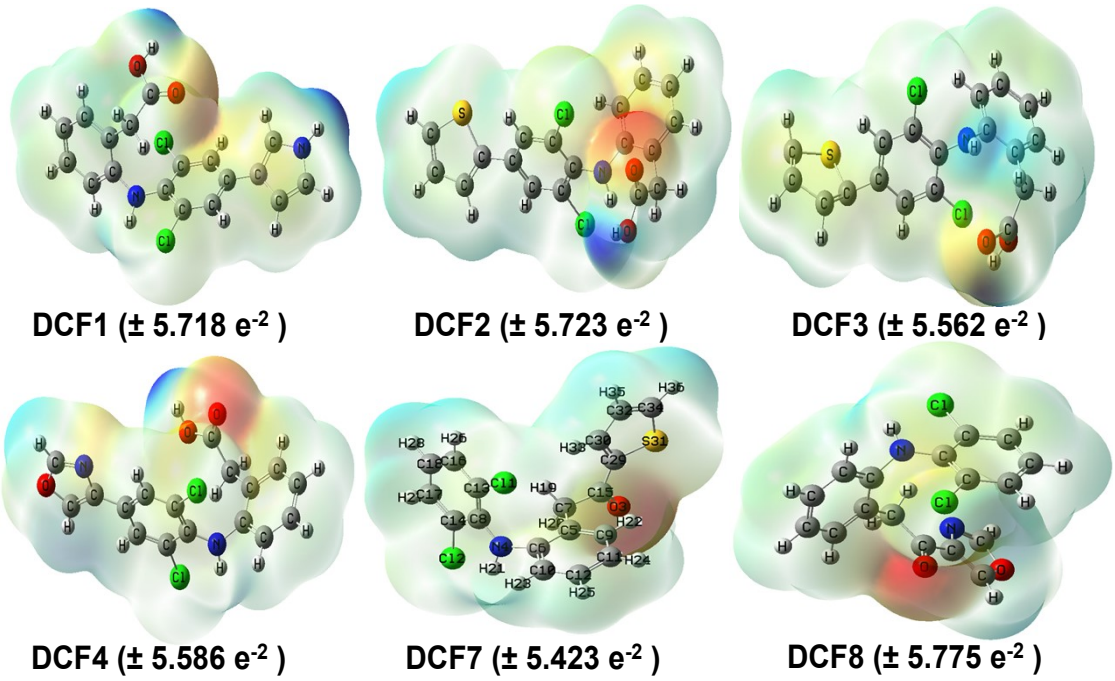


Figure S3 Molecular electrostatic potential map of the rest analogues.

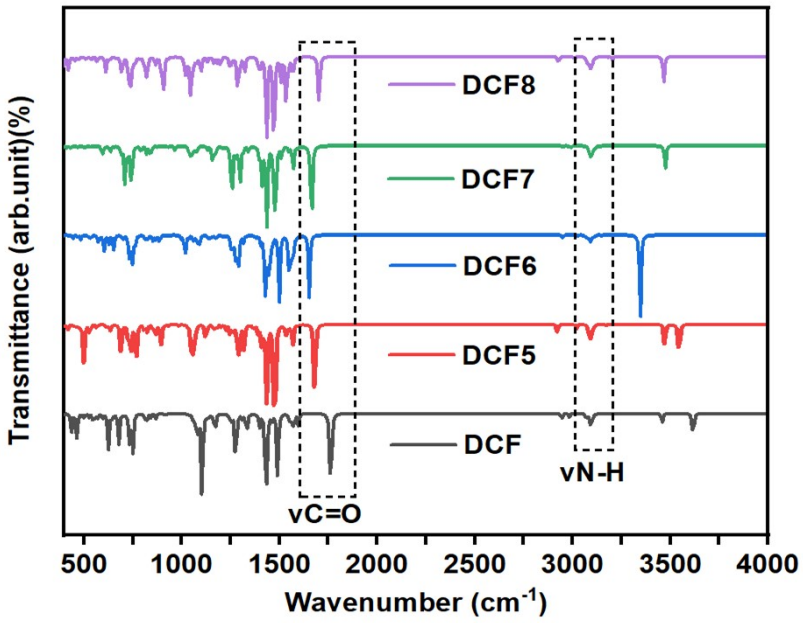


Figure S4 FT-IR spectra of DCF and its rest analogues.

Table S4 Vibrational frequencies of all compounds

Compound	Assignment	Calculated at DFT/B3LYP	
		Scaled frequency (cm^{-1})	Experimentally reported
DCF	νO-H	3617	3600-3650
	νN-H	3457	3300-3500
	νC-H[a]	3090	3000-3100
	νC=O	1763	1690-1720
	νC=C[a]	1550-1597	1450-1600
DCF1	νO-H	3625	3600-3650
	νN-H	3555-3584	3300-3500
	νC-H[a]	3088	3000-3100
	νC=O	1748	1690-1720
	νC=C[a]	1593	1450-1600
DCF2	νO-H	3617	3600-3650
	νN-H	3456	3300-3500
	νC-H[a]	3093	3000-3100
	νC=O	1763	1690-1720
	νC=C[a]	1597	1450-1600
DCF3	νO-H	3625	3600-3650
	νN-H	3461	3300-3500
	νC-H[a]	3066	3000-3100
	νC=O	1744	1690-1720
	νC=C[a]	1573	1450-1600
DCF4	νO-H	3619	3600-3650
	νN-H	3470	3300-3500
	νC-H[a]	3079	3000-3100
	νC=O	1759	1690-1720
	νC=C[a]	1587	1450-1600
DCF5	νN-H	3471-3545	3300-3500
	νC-H[a]	3090	3000-3100
	νC=O	1681	1690-1720
	νC=C[a]	1569	1450-1600
DCF6	νN-H	3346	3300-3500
	νC-H[a]	3174	3000-3100
	νC=O	1653	1690-1720

	νC=C[a]	1573	1450-1600
DCF7	νN-H	3474	3300-3500
	νC-H[a]	3092	3000-3100
	νC=O	1665	1690-1720
	νC=C[a]	1571	1450-1600
DCF8	νN-H	3466	3300-3500
	νC-H[a]	3089	3000-3100
	νC=O	1762	1690-1720
	νC=C[a]	1569	1450-1600

[a=aromatic ring]

Table S5 Electronic absorption of DCF and its newly designed analogs.

Name	Excited state	Wavelength (nm)	Excitation energy (eV)	Configuration composition (%)	Oscillator strength (f)
DCF	$S_0 \rightarrow S_1$	284	4.35	H → L (82.90)	0.0499
DCF1	$S_0 \rightarrow S_1$	795	1.56	H → L (90.14)	0.0173
DCF2	$S_0 \rightarrow S_1$	472	2.62	H → L (97.35)	0.0038
DCF3	$S_0 \rightarrow S_1$	342	3.63	H → L (97.31)	0.4817
DCF4	$S_0 \rightarrow S_1$	329	3.77	H → L (96.87)	0.3558
DCF5	$S_0 \rightarrow S_1$	411	3.06	H → L (88.36)	0.0015
DCF6	$S_0 \rightarrow S_1$	428	2.89	H → L (97.79)	0.0333
DCF7	$S_0 \rightarrow S_1$	665	1.86	H → L (94.42)	0.0816
DCF8	$S_0 \rightarrow S_1$	379	3.27	H → L (99.01)	0.0004

Table S6 Binding affinity and nonbonding interactions of all compounds with the receptor protein.

Name	Binding affinity (kcal/ mol)	Residue in contact	Interaction type	Bond distance (Å)
DCF	-6.6	ARG120	CHB	2.55
		TYR355	CHB	2.47
		TYR115	Pi-Pi T-shaped	5.09
		VAL89	Pi-Alkyl	4.08
		ILE112	Pi-Alkyl	4.63
DCF1	-7.1	ARG120	CHB	2.38
		TYR355	CHB	2.58
		TRP100	Pi-Sigma	2.88
		TRP100	Pi-Pi T-shaped	5.36
		TYR115	Pi-Pi T-shaped	5.12
		ILE112	Pi-Alkyl	4.69
		VAL89	Pi-Alkyl	4.08
DCF2	-7.3	ARG120	CHB	2.59
		ARG120	CHB	2.59
		TYR355	CHB	2.60
		TRP100	Pi-Sigma	2.90
		TYR115	Pi-Pi T-shaped	5.12
		VAL89	Alkyl	4.56
		ILE92	Alkyl	4.13
		LEU93	Alkyl	3.91
		TRP100	Pi-Alkyl	5.31
		ILE112	Pi-Alkyl	4.54
		VAL89	Pi-Alkyl	4.02
		ILE112	Pi-Alkyl	5.32
DCF3	-7.5	THR212	CHB	2.11
		THR212	CHB	2.69
		PHE210	CHB	2.12
		HIS214	C	2.44
		VAL291	Pi-Alkyl	4.51
		VAL291	Pi-Alkyl	4.51
DCF4	-7.0	ARG120	CHB	2.29
		ARG120	C	2.38

		LYS83	Pi-Cation	4.92
		ARG120	Pi-Cation	3.69
		ARG120	Alkyl	4.23
		LEU123	Alkyl	5.06
		LYS83	Pi-Alkyl	5.42
		VAL89	Pi-Alkyl	5.22
		VAL116	Pi-Alkyl	5.00
DCF5	-6.9	GLN461	CHB	2.45
		GLY45	CHB	2.58
		GLU465	CHB	2.02
		GLU465	C	3.03
		GLU465	Pi-Anion	3.16
		PRO153	Pi-Alkyl	4.81
		CYS36	Pi-Alkyl	4.99
		CYS47	Pi-Alkyl	4.20
		PRO153	Pi-Alkyl	4.84
		LEU152	Pi-Alkyl	5.32
		LYS468	Pi-Alkyl	4.87
DCF6	-7.4	SER119	CHB	2.87
		SER119	C	2.60
		TYR115	Pi-Pi T-shaped	5.48
		PRO86	Pi-Alkyl	5.16
		VAL89	Pi-Alkyl	3.97
		VAL89	Pi-Alkyl	4.78
		LEU93	Pi-Alkyl	5.22
		VAL116	Pi-Alkyl	5.30
		ARG120	Pi-Alkyl	5.43
DCF7	-7.3	SER119	CHB	2.42
		ARG120	Pi-Cation	4.91
		ILE112	Alkyl	3.83
		TYR115	Pi-Alkyl	4.57
		LEU93	Pi-Alkyl	4.44
		VAL116	Pi-Alkyl	4.41
		ILE112	Pi-Alkyl	4.53
		PRO86	Pi-Alkyl	5.08

		VAL89	Pi-Alkyl	4.15
DCF8	-7.2	GLY135	CHB	2.74
		GLY135	CHB	1.86
		PRO154	CHB	2.29
		PRO156	CHB	2.59
		VAL155	CHB	2.28
		CYS36	Pi-Alkyl	4.20
		PRO156	Pi-Alkyl	5.43
		CYS36	Pi-Alkyl	5.09
		CYS47	Pi-Alkyl	4.37
		PRO153	Pi-Alkyl	4.55

[CHB = Conventional Hydrogen Bond, C = Carbon Hydrogen Bond]

Table S7 Docking score of DCF and its analogs

Drug	Test 1	Test 2	Test 3	Average	Standard Deviation
DCF	-6.6	-6.9	-6.3	-6.6	±0.30
DCF1	-7.3	-7.4	-6.6	-7.1	±0.43
DCF2	-7.3	-7.7	-6.9	-7.3	±0.40
DCF3	-7.2	-7.5	-7.8	-7.5	±0.30
DCF4	-6.9	-7.3	-6.8	-7.0	±0.26
DCF5	-7.0	-6.8	-6.9	-6.9	±0.10
DCF6	-7.5	-7.1	-7.6	-7.4	±0.26
DCF7	-7.2	-7.6	-7.1	-7.3	±0.26
DCF8	-7.2	-7.0	-7.4	-7.2	±0.20

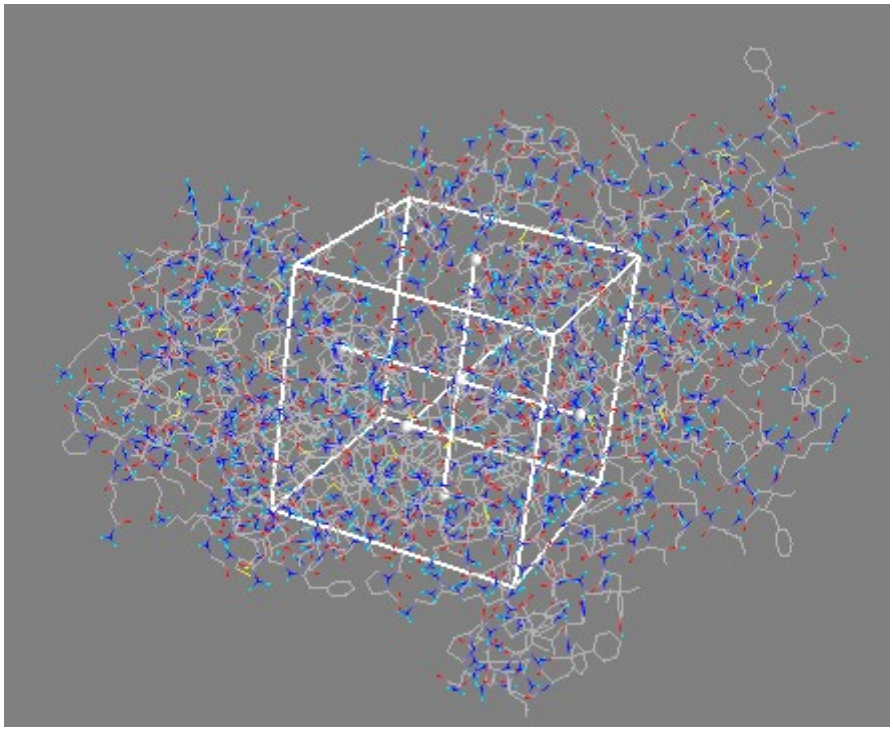


Figure S5: Visual representation of the grid box for site-specific docking in PyRx.

[Dimensions (Angstrom) X: 76.15, Y: 60.46, Z: 64.03]

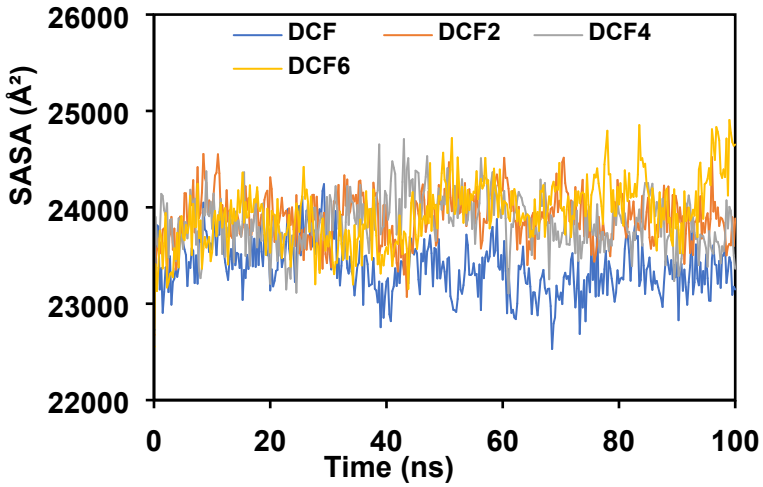


Figure S6 SASA of some DCF-5IKR complexes over 100 ns.

Table S8 Drug likeness parameters of DCF analogues.

Drug	Lipinski (Violation)	Ghose	Veber	Egan	Muegge	BAS	NHD	NHA
DCF	Y (0)	Y	Y	Y	Y	0.85	2	2
DCF1	Y (0)	Y	Y	Y	Y	0.55	3	2
DCF2	Y (0)	Y	Y	Y	Y	0.55	3	2
DCF3	Y (1)	N (1)	Y	N (1)	N (1)	0.56	2	2
DCF4	Y (0)	Y	Y	Y	Y	0.56	2	4
DCF5	Y (1)	N (1)	Y	N (1)	N (1)	0.55	1	1
DCF6	Y (0)	N (1)	Y	Y	N (1)	0.55	1	2
ECF7	Y (1)	Y	Y	Y	N (1)	0.55	1	1
DCF8	Y (0)	Y	Y	Y	Y	0.55	2	3

Y=Yes, N = No, BAS = Bio-availability Score, NHD = Number of H-bond Donors, NHA = Number of H-bond Acceptors.

Figure S7 Radar image of DCF and its analogues.

Table S9 Quantitative structure-activity relationship study of DCF and its newly designed derivatives

Name	Chiv5	Bcutm1	MRVSA9	MRVSA6	PEOEVSA5	GATSv4	J	Diametert	pIC_{50}
DCF	1.344	4.039	40.546	58.073	47.467	0.956	1.936	9.0	3.93
DCF1	1.888	4.077	40.546	70.467	41.401	0.835	1.571	12.0	4.25
DCF2	2.283	4.235	51.883	69.520	47.467	0.791	1.571	12.0	4.30
DCF3	2.283	4.235	51.883	69.520	47.467	0.791	1.571	12.0	4.30
DCF4	1.820	4.075	40.546	64.531	41.401	0.869	1.571	12.0	4.24
DCF5	1.682	4.041	40.360	82.097	47.467	1.105	1.566	11.0	4.24
DCF6	2.085	4.202	51.883	62.898	41.401	0.817	1.571	12.0	4.24
DCF7	1.960	4.207	51.697	80.463	53.534	1.432	1.566	11.0	4.35
DCF8	1.607	4.041	40.360	76.424	47.467	0.878	1.566	11.0	4.26

Note for Table S9:

Chiv5: A molecular descriptor that reflects the Chi molecular shape index, which gauges how complicated a molecule's shape is in connection to its atomic distribution. It offers information about how molecular stiffness or flexibility affects molecular interactions and bioactivity.

bcutm1: A descriptor that measures molecular attributes associated with a molecule's graph structure using the biological coarse-grained unit tensor (BCUT) approach. It exhibits symmetry and compactness, both of which are crucial for comprehending the interactions and behavior of molecules.

MRVSA9: The Molecular Refractivity and Volume Surface Area descriptor quantifies the volume and surface area of a molecule. It is frequently employed to assess the influence of a molecule's size and shape on its bioavailability and interaction with biological targets.

MRVSA6: The surface area of a molecule provides the basis for another MRVSA index. This characteristic aids in determining how a compound's surface area, size, and shape affect its ability to interact with biomolecules or receptors, which is crucial for drug design.

PEOEVSA5: The distribution of electrostatic potential across the surface of a molecule is represented by the Partial Electrostatic Surface Area (PEOEVSA) descriptor. It provides information about solubility and bioactivity by assessing the polarity of the molecule and its capacity to interact with biological receptors.

GATSv4: The spatial distribution of molecular properties (such as charge or dipole moment) throughout the entire molecule is measured by Geary's Autocorrelation of the Lagged Molecular Property (v4) descriptor. It aids in understanding the spatial interactions among multiple molecular components, which is essential for predicting biological activity.

J: The Jaccard Similarity Coefficient: This quantifies the resemblance between two collections, namely molecular descriptors. It is used to compare molecules and assess their structural similarity, and is frequently employed in virtual screening or similarity-based drug design.

Diametert: Denotes the diameter of the molecule, representing the maximum distance between any two atoms within the molecule. This descriptor quantifies the molecule's dimensions and density, which is crucial for comprehending its compatibility with binding sites and interactions with receptors.

pIC_{50}: The negative logarithm of the IC_{50} value (in mol/L), with IC_{50} denoting the concentration of a substance necessary to inhibit 50% of a biological activity. A higher pIC_{50} value signifies increased potency and serves as a measure of the compound's efficacy in blocking a particular biological function.