Supplementary Section

Activation–Deactivation of Inter-Peptide Bond in Fluoro-*N*-(2-hydroxy-5-methyl phenyl)benzamide Isomers, Induced by the Position of the Halogen Atom in the Benzene Ring

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Part S1

Table S1. Crystallographic data of ***o*-FPhB**, ***m*-FPhB**, and ***p*-FPhB** crystalline systems.

	***o*-FPhB**	***m*-FPhB**	***p*-FPhB**
Crystal Data			
Chemical Formula	$C_{14}H_{12}FNO_2$	$C_{14}H_{12}FNO_2$	$C_{14}H_{12}FNO_2$
Molar mass, g	245.25	245.25	245.25
Melting point, K	453 (1)	459 (1)	452 (1)
Solvent for Crystallization	Methanol	Methanol	Methanol
Crystalline system, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$
a	7.3162(2)	7.3676(2)	24.512(3)
b	21.8636(6)	22.2728(7)	5.4218(8)
c	7.8100(2)	7.6478(3)	9.3715(12)
α	90	90	90
β	110.721(2)	110.510(1)	93.896(7)
γ	90	90	90
Volumen,(Å^3)	1168.47(6)	1175.43(7)	1242.6(3)
ϱ, Kg m^{-3}	1.394	1.386	1.311
Z	4	4	4
Radiation type.	Mo Kα	Mo Kα	Mo Kα
μ (mm^{-1})	0.104	0.104	0.098
Crystal size (mm)	0.658, 0.521, 0.474	0.859, 0.634, 0.480	0.722, 0.408, 0.314
Data collection			
Diffractometer	Nonius KappaCCD diffractometer	Nonius KappaCCD diffractometer	Nonius KappaCCD diffractometer

Temperature, (K).	295	295	295
No. of measured, independent, and observed reflections I>2σ(I)	8233, 2389, 2089	8383, 2394, 2100	6008, 2016, 1581
R_{int}	0.0216	0.0175	0.0381
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0449, 0.1196, 1.036	0.0511, 0.1501, 1.055	0.0620, 0.1599, 1.124
No. of reflections	2389	2394	2016
Refined parameters	167	167	167
H-atoms treatment	H atoms treated by constrained refinement	H atoms treated by constrained refinement	H atoms treated by constrained refinement
ΔQ_{max}, ΔQ_{min} (e Å^{-3})	0.191, -0.244	0.503, -0.327	0.170, -0.252

Table S2. Comparison between bond distances, bond angles, and torsion angles for ***o*-FPhB**, ***m*-FPhB**, and ***p*-FPhB**.

	***o*-FPhB**	***m*-FPhB**	***p*-FPhB**
C1-C7	1.499(2)	1.500(2)	1.486(3)
C7-O1	1.2278(18)	1.227(2)	1.234(3)
C7-N1	1.3351(18)	1.339(2)	1.336(3)
N1-C8	1.4106(19)	1.411(2)	1.421(3)
C3-C4	1.372(3)	1.384(2)	1.356(5)
Bond Angles (°)			
N1-C7-C1	117.98(12)	116.81(15)	117.1(2)
C7-N1-C8	128.69(12)	128.92(15)	123.1(2)
N1-C8-C13	125.82(13)	125.59(15)	121.3(3)
Torsion angles (°)			
A-ring with peptide moiety	4.76(9)	1.65(10)	26.24(15)
B-ring with peptide moiety	6.12(8)	5.46(10)	70.26(9)

The ***o*-FPhB** and ***m*-FPhB** structures are almost planar, while for ***p*-FPhB,** an angle between **A** and **B** rings close to 90^0 [83.58(9)]°.

Part S2

Vibrational Frequency Analysis

The title compounds have C_{2h} symmetry and consist of 31 atoms which provide 93 normal modes of vibration, of which 87 are internal modes. The assignments of wavenumbers were

made based on potential energy distribution (PED) using the Vibrational Energy Distribution Analysis (*VEDA 4*) program [33].

Table S3. Experimental and theoretical vibrational frequencies (cm^{-1}).

	***o*-FPhB**		***p*-FPhB**		***m*-FPhB**	
	Exp.	**Calc.**	**Exp.**	**Calc.**	**Exp.**	**Calc.**
υCF	1200	1172	1206	1184	1223	1208
υCC	1613	1602	1585	1606	1619	1600
υCO (carbonyl)	1647	1666	1651	1680	1636	1671
υOH	3107	3730	3092	3744	3196	3730
υNH(amide)	3387	3480	3408	3516	3397	3506

Table S4. Calculated and experimental vibrational frequencies of ***o*-FPhB**, ***m*-FPhB**, and ***p*-FPhB**.

***o*-FPhB**			
Experimental	**DFT**	**Scaled**	Assignment **(%PED)**
3387	3592	3480	⊗NH (amide) (99)
3107	3850	3730	⊗OH (hydroxy)(100)
	3208	3108	⊗CH(Aryl r.) (80)
	3175	3076	⊗CH (Acyl r.) (87)
	3099	3002	⊗CH (Methyl) (79)
1647	1720	1666	⊗CO(Carbonyl) (74)
1612	1654	1602	⊗CC (Acyl r.) (41) + δHNC(Amide-Acyl r.) (12)
1593	1611	1561	⊗CC (Aryl r.) (57)
1553	1586	1537	ϱHNC (amide) (47)
1481	1487	1440	δHCH (Methyl)(76)
1452	1476	1430	δHCC (Aryl r.) (49)
1431	1454	1408	δCC (Acyl r.) (49)
1200	1210	1172	⊗CF (54)
808	831	805	⊗CF (40)
***m*-FPhB**			
EXP	**DFT**	**Scaled**	Assignment **(%PED)**
3408	3615	3516	⊗NH (amide) (100)
3092	3850	3744	⊗OH (hydroxy)(100)
	3209	3122	⊗CH(Aryl r.) (81)
	3176	3089	⊗CH (Acyl r.) (88)
	3100	3015	⊗CH (Methyl) (99)
1651	1727	1680	⊗CO(Carbonyl) (78)
1585	1652	1606	⊗CC (Acyl r.) (50) + δHNC(Amide-Acil r.) (12)
1569	1645	1600	⊗CC (Aryl r.) (56) + ϱCCO (Aryl r.)(11)
1553	1575	1532	δHNC (amide-Acyl r.) (39) + δHCC (Acyl r.) (10)
1481	1486	1445	δHCH (Methyl)(80)

1452	1454	1414	δHCC (Aryl r.) (50)
1431	1461	1421	δCC (Acyl r.) (58)
1206	1217	1184	⊚CF (43)
806	862	838	⊚CF (43)
		***p*-FPhB**	
EXP	**DFT**	**Scaled**	Assignment **(%PED)**
3397	3619	3506	⊚NH (amide) (100)
3196	3850	3730	⊚OH (hydroxy)(100)
	3208	3108	⊚CH(Aryl r.) (97)
	3176	3076	⊚CH (Acyl r.) (88)
	3074	2978	⊚CH (Methyl) (99)
1636	1725	1671	⊚CO(Carbonyl) (76)
1619	1651	1600	⊚CC (Acyl r.) (45) + δHNC(Amide-Acyl r.) (10)

1589	1641	1590	◎CC (Aryl r.) (55) + ϱHCC (Aryl r.)(12)
1537	1575	1526	δHNC (amide-Acyl r.) (42) + δHCC (Acyl r.) (16)
1497	1500	1454	δHCH (Methyl)(80)
1463	1474	1428	δHCC (Aryl r.) (27) + ◎CC (Aryl r.) (55)
1431	1454	1408	δCC (Acyl r.) (49)
1223	1246	1208	◎CF (53)
808	835	819	◎CF (46)

*Acyl ring: Acyl r., Aryl ring: Aryl r., Amide group: Amide, carbonyl group: Carbonyl, Methyl group, Hydroxyl group: Hydroxy

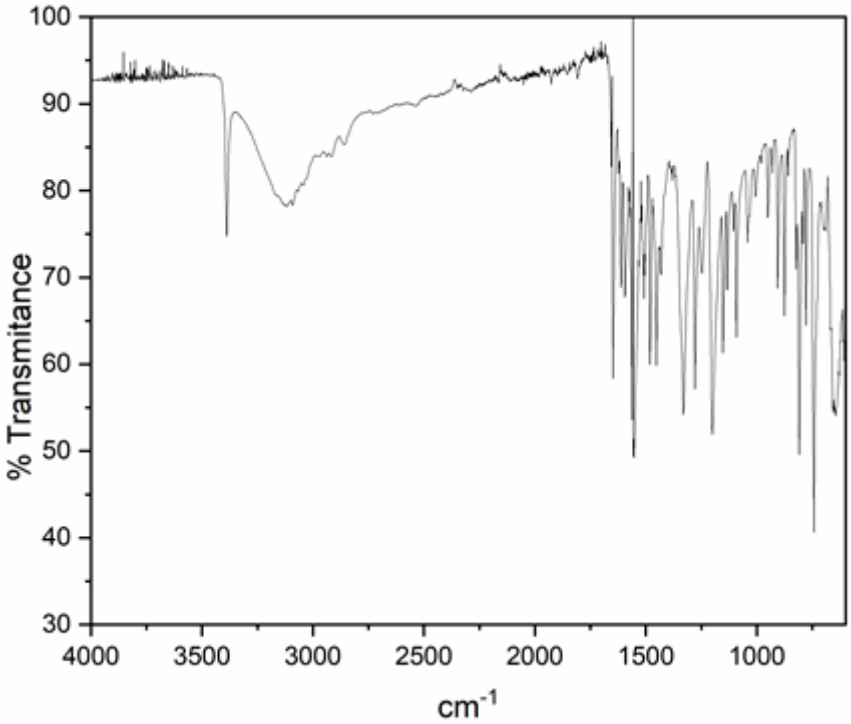


Figure S1. IR Spectrum of *o*-PFhB

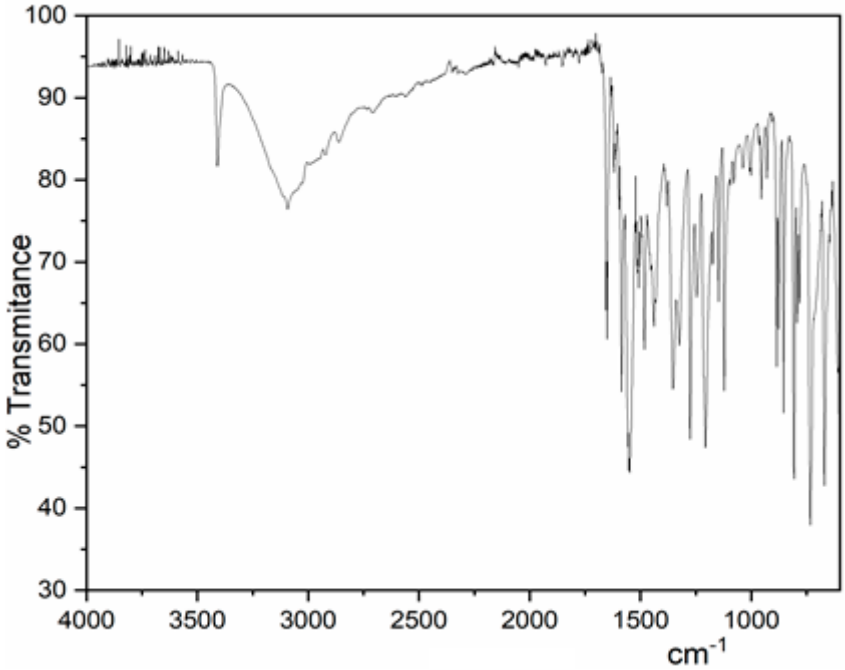


Figure S2. IR Spectrum of *m*-PFhB

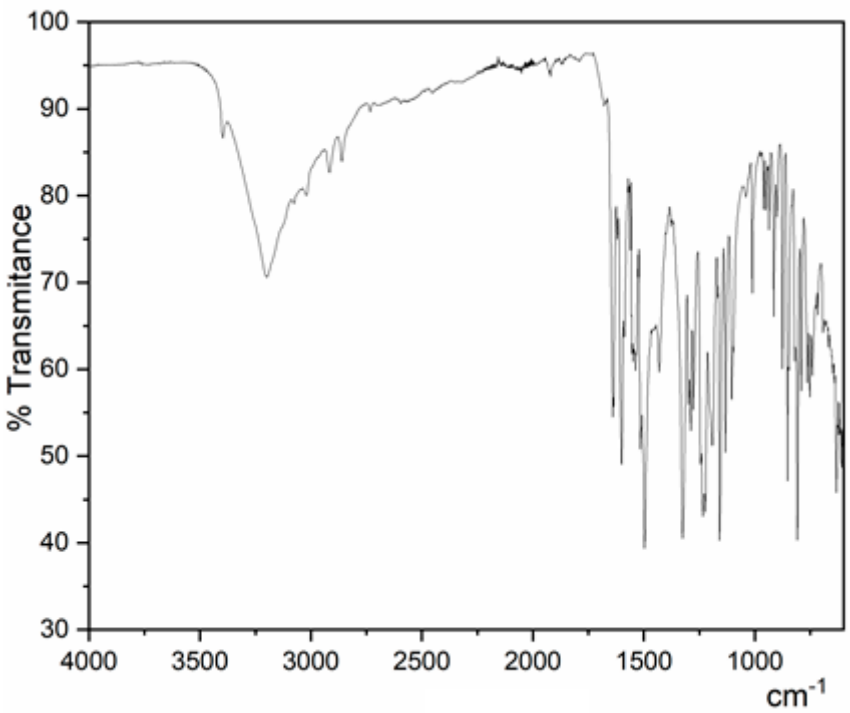


Figure S3. IR Spectrum of *p*-PFhB

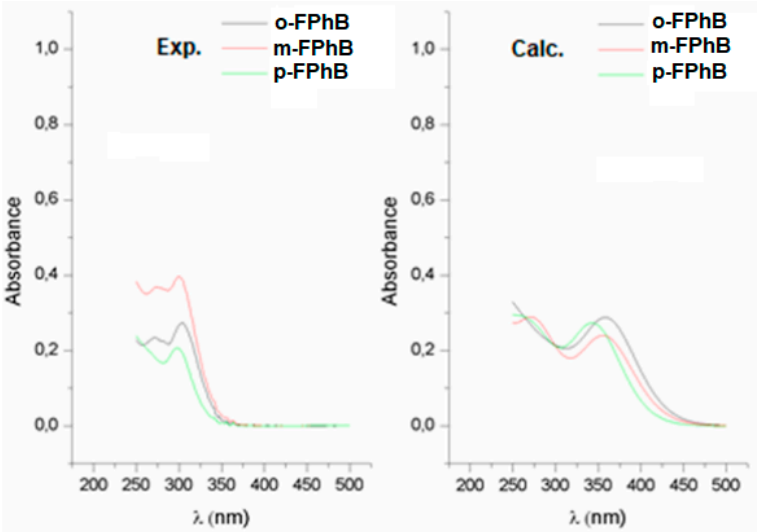
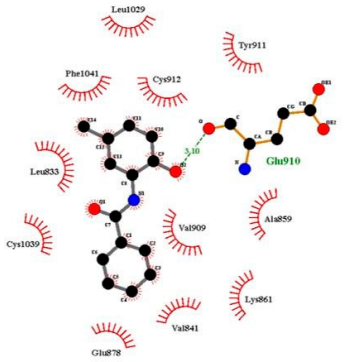
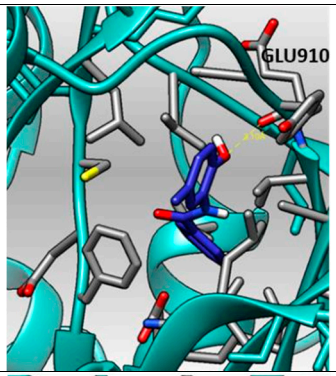
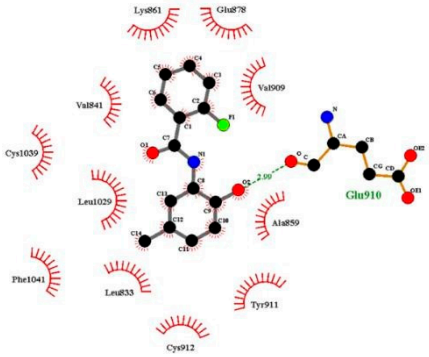
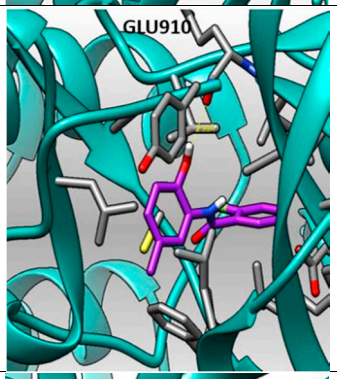
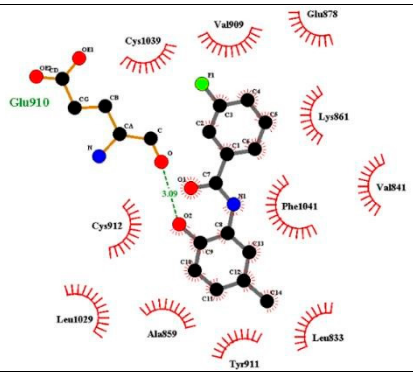
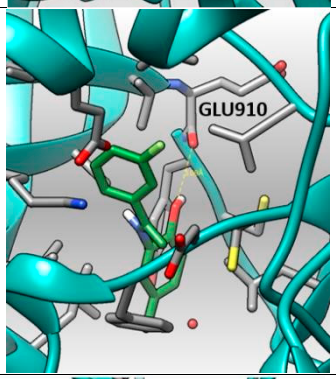
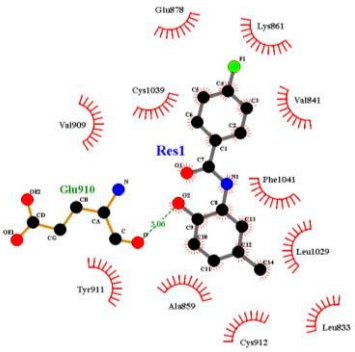
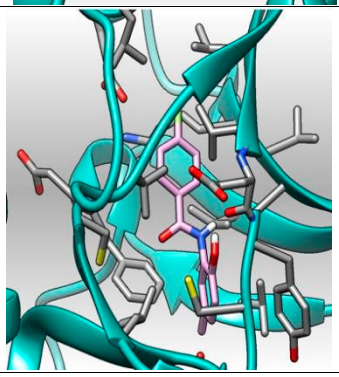


Figure S4. Experimental and theoretical UV-Vis spectra of ***o*-FPhB**, ***o*-FPhB**, and ***o*-FPhB** compounds.

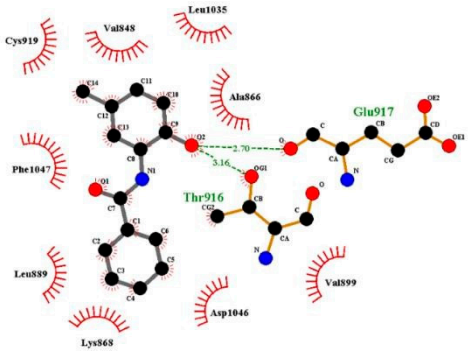
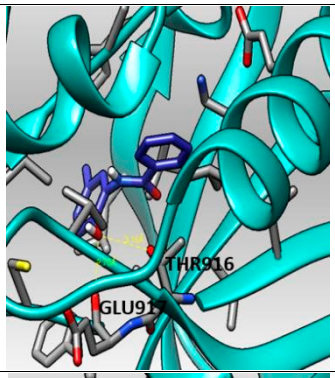
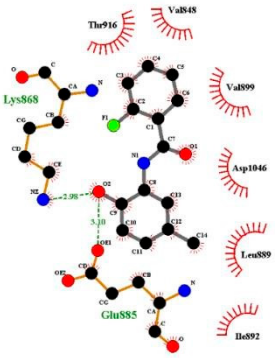
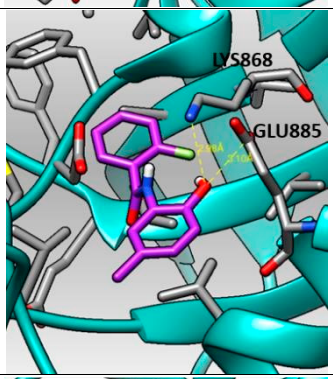
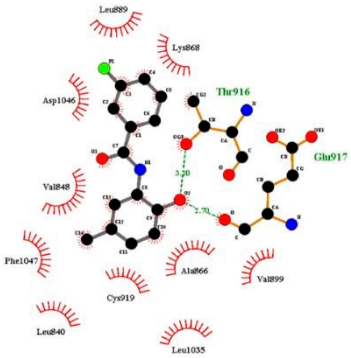
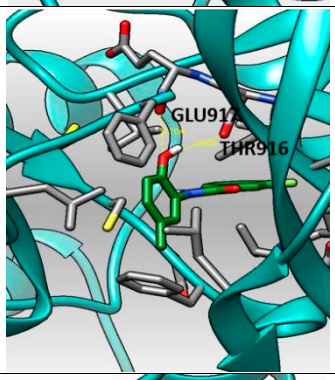
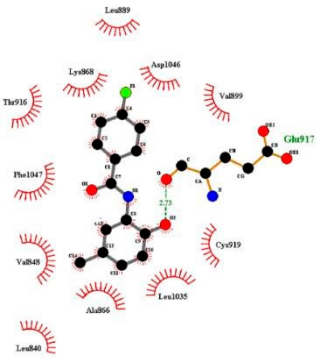
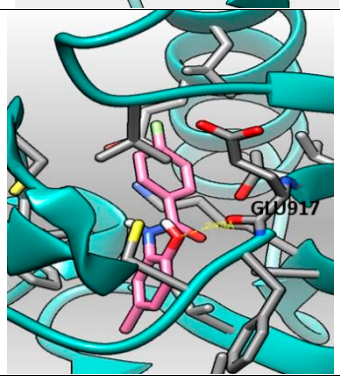
Part S3

Interaction of the 3HNG protein with the different ligands with 2D and 3D representations.

VEGFR-1		
PhB		
***o*-FPhB**		
***m*-FPhB**		
***p*-FPhB**		

The representation in ligplot+ presents the hydrophobic residues with red lines and hydrogen interactions with dotted green lines.

Interaction of the 3U6J protein with different ligands with 2D and 3D representations.

VEGFR-2		
PhB		
***o*-FPhB**		
***m*-FPhB**		
***p*-FPhB**		

The representation in ligplot+ presents the hydrophobic residues with red lines and hydrogen interactions with dotted green lines.

Table S5

Data of the reasoning of an optimized ligand based on the benzamides studied.

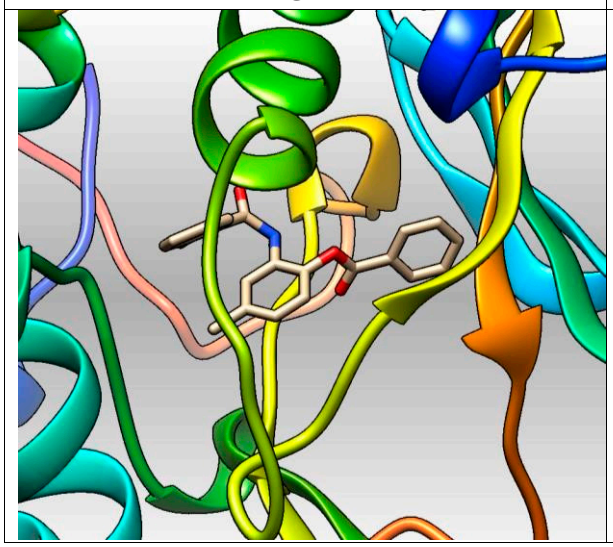
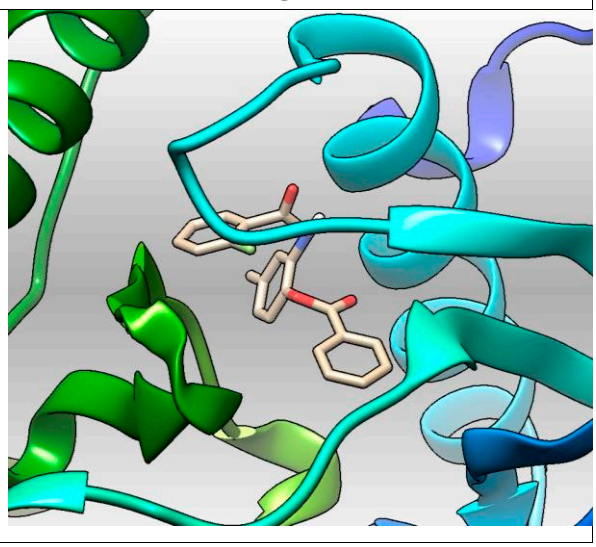
Target protein	Ligand	Energy Kcal/mol	Residues related to hydrogen bonds
VEGFR-1	A-Ester	-9.9	Glu878,Cys912,Glu910
VEGFR-2	A-Ester	-8.5	Glu917

A-Ester, first planning of the optimization of the ligand o-FPhB

Table S6

Most negative binding energy values with VEGFR-1 and VEGFR-2, calculated by molecular docking

Target protein	ligand	Energy kcal/mol	Residues related to hydrogen bonds	hydrophobic residues
VEGFR-1	Axitinib	-12.71	Glu878, Cys912, Glu910, Asp1040	12
	phB	-8.9	Glu910	11
	o-FPhB	-9.4	Glu910	11
	m-FPhB	-9.3	Glu910	11
	p-FPhB	-9.2	-	11
VEGFR-2	Axitinib	-12.39	Glu917 and Asp1046	14
	PhB	-8.5	Glu917 and Thr916	9
	o-FPhB	-9.0	Glu885 and Lys868	6
	m-FPhB	-8.9	Glu917 and Thr916	10
	p-FPhB	-8.7	Glu917	11

A-Ester interaction with VEGFR-1 and VEGFR-2 receptors.

VEGFR-1	VEGFR-2