Supplementary information

Synthesis, crystal structure, inhibitory activity and molecular docking of coumarins/sulfonamides containing triazolyl pyridine moiety as potent selective carbonic anhydrase IX and XII inhibitors

Yassine Aimene,[1,2,3] Romain Eychenne,[2,3] Frederic Rodriguez,[2,3] Sonia Mallet-Ladeira,[4] Nathalie Saffon-Merceron,[4] Jean-Yves Winum,[5] Alessio Nocentini,[6] Claudiu T. Supuran,[6] Eric Benoist,[2,3*] Achour Seridi.[1*]

[1] Laboratoire de Chimie Physique, Université 8 Mai 1945, B.P.401, Guelma 24000, Algeria
[2] CNRS, Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, SPCMIB, UMR 5068, 118, Route de Narbonne, CEDEX 09, F-31062 Toulouse, France
[3] Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, SPCMIB , Université de Toulouse, UMR 5068, 118, Route de Narbonne, CEDEX 09, F-31062 Toulouse, France
[4] Institut de Chimie de Toulouse (ICT-UAR 2599), 118 Route de Narbonne, CEDEX 09, 31062 Toulouse, France
[5] IBMM, Univ Montpellier, CNRS, ENSCM, 34296 Montpellier, France
[6] Neurofarba Department, Section of Pharmaceutical and Nutriceutical Sciences, Università degli Studi di Firenze, Via Ugo Schiff 6, 50019 Sesto Fiorentino, Florence, Italy

*Corresponding authors: Achour Seridi: Tel +213666821635: E-mail address :seridi_a@yahoo.fr ,seridi.achour@univ-guelma.dz (A. SERIDI)ID: orcid.org/0000-0002-2288-544X; Eric Benoist, Tel +33561556480, E-mail address: benoist@chimie.ups-tlse.fr (E. BENOIST) 0000-0003-0764-9024.

Table S1: Selected experimental bond lengths [Å] and angles [°] for **2a** and **2b**

Tables S2: Selected experimental bond lengths [Å] and angles [°] for **3a** and **3b**

Table S3: Hydrogen bonds for **2a**, **2b**, **3a** and **3b** [Å and °]

Table S4: Estimated free energy of binding (Kcal mol^{-1}), H-bond interactions number and Zn—N distances (Å) in the interaction region of the HCA IX—inhibitor complexes

Figure S1: Alignment of isoforms IX of hCA (pdb codes: 5fl4 and 5dvx) within the active site of hCA II (pdb code: 3f8e).

Figure S2: Molecular views of **2a** (top) and **2b** (bottom) with 50% ellipsoidal probability; hydrogen atoms have been omitted for clarity, except H on N5 atom (**2a**).

Table S1: Selected experimental bond lengths [Å] and angles [°] for **2a** and **2b**

Bond Lengths	**2a**	**Bond Lengths**	**2b**
N2-N3	1.316(3)	N2-N3	1.312(1)
N3-N4	1.344(3)	N1-N2	1.351(1)
N4-C7	1.334(3)	N1-C13	1.345(1)
N2-C6	1.362(3)	N3-C14	1.367(1)
C6-C7	1.366(3)	C13-C14	1.377(1)
C8-N4	1.468(3)	C12-N1	1.455(1)
C6-C5	1.466(3)	C14-C15	1.463(1)
Bond Angles		**Bond Angles**	
C6-N2-N3	108.7(2)	C14-N3-N2	108.7(1)
N2-N3-N4	107.2(2)	N1-N2-N3	107.4(1)
N3-N4-C7	110.8(2)	N2-N1-C13	110.9(1)
N3-N4-C8	120.1(2)	N2-N1-C12	119.8(1)
N4-C7-C6	105.4(2)	N1-C13-C14	104.6(1)
N2-C6-C7	107.9(2)	N3-C14-C13	108.3(1)
N2-C6-C5	123.1(2)	N3-C14-C15	122.4(1)
C6-C5-N1	115.2(2)	C14-C15-N4	116.0(1)
C4-C5-C6	122.1(2)	C14-C15-C16	121.0(1)

Tables S2: Selected experimental bond lengths [Å] and angles [°] for **3a** and **3b**

Bond lengths [Å]	**3a**	**Bond lengths [Å]**	**3b**
Re1-Cl1	2.489(1)	Re1-Cl1	2.468(1)
Re1-C3	1.917(4)	Re1-C1	1.923(2)
Re1-C2	1.910(4)	Re1-C2	1.961(2)
Re1-C1	1.921(4)	Re1-C3	1.918(2)
Re1-N1	2.201(3)	Re1-N1	2.206(1)
Re1-N2	2.156(3)	Re1-N2	2.148(2)
O2-C3	1.148(5)	O1-C1	1.151(2)
O3-C2	1.134(5)	O3-C2	1.094(2)
O1-C1	1.146(5)	O2-C3	1.152(2)
Bond angles [°]		**Bond angles [°]**	
C3-Re1-C2	87.9(2)	C1-Re1-C2	91.6(1)
C1-Re1-C3	90.2(2)	C1-Re1-C3	90.5(1)
C2-Re1-C1	89.6(2)	C2-Re1-C3	89.3(1)
C3-Re1-N2	171.4(2)	C1-Re1-N2	171.3(1)
C2-Re1-N2	94.9(2)	C2-Re1-N2	90.9(1)
C1-Re1-N2	97.9(2)	C3-Re1-N2	97.8(1)
C3-Re1-N1	97.3(2)	C1-Re1-N1	97.2(1)
C2-Re1-N1	93.3(2)	C2-Re1-N1	94.0(1)
C1-Re1-N1	172.0(2)	C3-Re1-N1	171.5(1)
C3-Re1-Cl1	90.6(1)	C1-Re1-Cl1	91.9(1)
C2-Re1-Cl1	176.6(1)	C2-Re1-Cl1	176.0 (1)
C1-Re1-Cl1	93.4(1)	C3-Re1-Cl1	92.6(1)
N1-Re1-N2	74.5(1)	N1-Re1-N2	74.3(1)
N1-Re1-Cl1	83.9(1)	N1-Re1-Cl1	83.6(1)
N2-Re1-Cl1	86.2(1)	N2-Re1-Cl1	85.4(1)
O2-C3-Re1	178.1(4)	O1-C1-Re1	177.9(2)
O3-C2-Re1	177.3(3)	O3-C2-Re1	177.9(2)
O1-C1-Re1	178.4(4)	O2-C3-Re1	177.9(2)

Table S3: Hydrogen bonds for **2a**, **2b**, **3a** and **3b** [Å and °]

	D A	**D—H** [Å]	**H•••A** [Å]	**D•••A** [Å]	**D—H•••A** [°]
2a	N5-H5a...O4	0.83(3)	2.07(3)	2.885(3)	171(3)
	N5-H5b...N6#1	0.87(3)	2.17(3)	3.037(3)	170(3)
	N10-H10a...O3#2	0.79(3)	2.29(3)	2.871(3)	131(3)
	N10-H10b...O1#3	0.85(3)	2.17(3)	2.977(4)	158(3)
	C9-H9A…O2#4	0.99	2.60	3.125(3)	113
	C9-H9B…O4#5	0.99	2.57	3.423(3)	144
	C11-H11…O4#5	0.95	2.49	3.374(3)	154
	C12-H12…O2	0.95	2.56	2.906(3)	102
	C22-H22…N3#6	0.95	2.55	3.747(1)	163
	C29-H29…O4	0.95	2.52	2.895(3)	103
2b	C8-H8…O1#1	0.95	2.47	3.341(1)	153
	C11-H11A…O1#1	0.99	2.43	3.409(1)	169
	C13-H13…N2#2	0.95	2.44	3.303(1)	152
3a	N5-H5a...Cl1#1	0.99(6)	2.36(6)	3.280(4)	156(4)
	N5-H5b...O5#2	0.89(6)	2.11(6)	2.944(6)	158(5)
	C4-H4…O2#3	0.95	2.42	3.224(5)	143
	C6-H6…O1#4	0.95	2.60	3.453(1)	150
	C10-H10…Cl1#5	0.95	2.71	3.636(4)	166
	C17-H17…O5	0.95	2.50	2.882(6)	104
3b	C10-H10...Cl1#1	0.95	2.73	3.651(2)	165
	C11-H11B…O6#2	0.99	2.47	3.039(2)	117
	C12-H12A…O7'#2	0.99	2.44	3.102(8)	124
	C12-H12A…O7#2	0.99	2.40	3.13(4)	130
	C22-H22A…O7#3	0.98	2.43	3.30(4)	148
	C24'-H24E…O5#1	0.98	2.51	3.479(10)	170

(**2a**) #1 -x+1,-y+1,-z+1, #2 -x+1/2,y+1/2,z, #3 -x+1/2,y-1/2,z, #4 1-x,-1/2+y,1/2-z, #5 1-x,1/2+y,1/2-z, #6 x,3/2-y,1/2+z; (**2b**) #1 x,1/2-y,1/2+z, #2x,3/2-y,-1/2+z ; (**3a**) #1 x+1,-y+1/2,z-1/2 #2 x,-y+1/2,z+1/2, #3 -1-x,1-y,2-z, #4 -1+x,y,-1+z, #5 x,y,-1+z ; (**3b**) #1 -1+x,y,z, #2 1-x,-y,1-z, #3 x,1+y,z.

Table S4: Estimated free energy of binding (Kcal mol^{-1}), H-bond interactions number and Zn—N distances (Å) in the interaction region of the HCA IX—inhibitor complexes

Compounds	ΔG_b	H-bond number	Zn–N (Å)
2a	-8.24	03	2.18
3a	-8.21	02	2.25
1P-2b	-8.07	03	—
2P-2b	-9.35	05	—
1P-3b	-8.90	04	—
2P-3b	-10.11	05	—

Figure S1: Alignment of isoforms IX of hCA (pdb codes: 5fl4 and 5dvx) within the active site of hCA II (pdb code: 3f8e).

The crystal structures of the inhibitors are represented by different colors: yellow for 5-(1-naphthalen-1-yl-1,2,3-triazol-4-yl)thiophene-2-sulfonamide (ligand id: 9fk), green for 2-hydroxy-cinnamic acid derivative (ligand id: te1) and red for 2-amino-2-hydroxymethyl-propene-1,3-diol (ligand id: gol). The violet colored dashed line shows the bond interactions of the zinc ion with three histidines and fourth with water molecule or deprotonated nitrogen of the sulfonamide group.

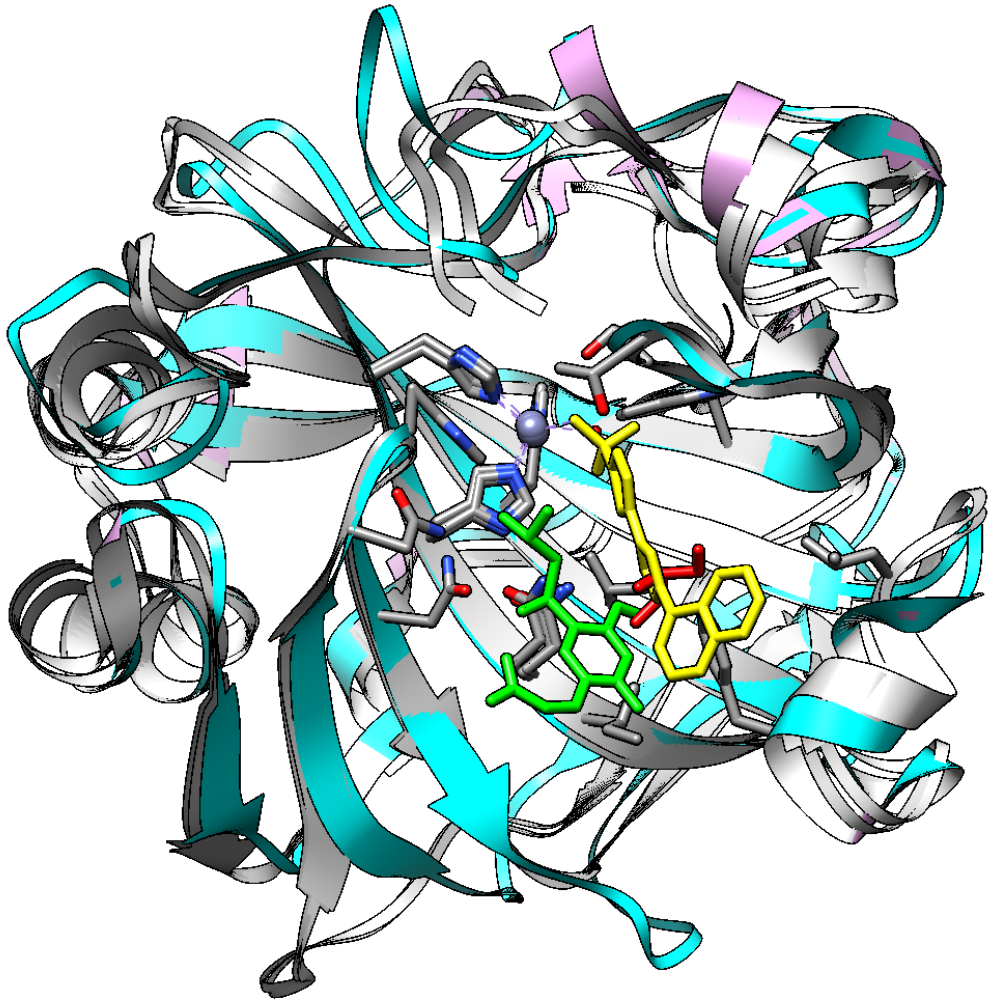

Figure S2: Molecular views drawing of **2a** (top) and **2b** (bottom) with 50% ellipsoidal probability; hydrogen atoms have been omitted for clarity, except H on N5 atom (**2a**).