Studio della riproducibilità di modelli 3D-QSAR ottenuti mediante il portale 3d-qsar.com. Applicazione a ligandi del dominio pseudochinasico della TYK2.



Facoltà di Farmacia e Medicina Corso di Laurea in Biotecnologie Farmaceutiche Tesi Sperimentale in Chimica Farmaceutica a.a. 2020/2021

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Obiettivo dello studio





SMILES	IC50(nM)
NC(=O)C1=CN=C2N1N=C(NC1=CC(=CC(=C1)C#N)C(F)(F)F)C=C2NC1CC1	480
NC(=O)C1=CN=C2N1N=C(NC1=CC=CC=C1)C=C2NC1CC1	32
CC1=CC(NC2=NN3C(=CN=C3C(NC3CC3)=C2)C(N)=O)=CC(C)=C1	22
CC1=CC(F)=CC(NC2=NN3C(=CN=C3C(NC3CC3)=C2)C(N)=O)=C1	24
NC(=O)C1=CN=C2N1N=C(NC1CCCCC1)C=C2NC1CC1	220
CNC1=CC(NC2=CC(C)=CC(C)=C2)=NN2C(=CN=C12)C(N)=O	7
CCNC1=CC(NC2=CC(C)=CC)=C2)=NN2C(=CN=C12)C(N)=O	17
CC1=CC(NC2=NN3C(=CN=C3C(NC3CCC3)=C2)C(N)=O)=CC(C)=C1	110





Calcolo dei MIF e generazione del modello matematico-statistico

Allineamento







Valutazione della riproducibilità dei modelli 3D-QSAR

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II portale 3d-qsar.com









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TYK2 e la sua funzione immunologica









Aspetti strutturali











BMS-986165





	Featured Article
Cite This: J. Med. Chem. 2019, 62, 8973-8995	pubs.acs.org/jmc

Highly Selective Inhibition of Tyrosine Kinase 2 (TYK2) for the Treatment of Autoimmune Diseases: Discovery of the Allosteric Inhibitor BMS-986165









Schema dello studio





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Dataset







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Analisi Conformazionale



Py-ConfSearch Karrer	Conf Search fo	or Dataset	TYK2_Inl	hibitors_M (95)				
Conf Searches	Search							
Make Conf Search	Conf Search ID	Status		Method	Max Confs	CG Maxiters	SD Maxiters	Force Field
	3490	completed	Results	balloon	50	50	50	MMFF94
	3637	completed	Results	rdkit	50	50		MMFF94
Molecules	3682	completed	Results	openbabel	50	50	50	GAFF
 My Molecules 								



Balloon





Openbabel



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RDkit



Allineamento







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Py-CoMFA 👷 Rame 👻	Py-CoMFA , Kome - Compare 3-D QSAR Models for Dataset and its children: TYK2_Inhibitors_M (95)												
Models	Show All	1 /32 Search											
My 3-D QSAR Models	Model ID	Dataset	Status		Maps	nTrMois	External Pred	r ² STE(PC)	q² STE(PC)	r² ELE(PC)	q² ELE(I		
	227179	51155.TYK2_Inhibitors_M_least_active	completed	<u>Results</u>	Missing	61	False	0.921 (5)	0.514 (5)	0.651 (4)	0.121		
Dataset	227180	51156.TYK2_Inhibitors_M_most_active	completed	<u>Results</u>	Missing	61	False	0.387 (1)	0.205 (1)	0.202 (2)	-0.030		
	227181	51160.TYK2_Inhibitors_M_heaviest	completed	<u>Results</u>	Missing	61	False	0.391 (1)	0.220 (1)	0.260 (2)	0.048		
 My Datasets 	227182	51161.TYK2_Inhibitors_M_longest	completed	<u>Results</u>	Missing	61	False	0.320 (1)	-0.149 (1)	0.533 (3)	-0.064		
	227183	51163.TYK2_Inhibitors_M_most_flexible	completed	<u>Results</u>	Missing	61	False	0.391 (1)	0.220 (1)	0.260 (2)	0.048		
User	227184	51164.TYK2_Inhibitors_M_most_rigid	completed	<u>Results</u>	Missing	61	False	0.389 (1)	0.025 (1)	0.086 (1)	-0.194		
Parametri di default:			completed	Res C	Ottimi	zzazio	ne trar	nite VI	PO:				
\mathbf{P} roho = C 2			completed Res . Drobo = 0.2 H2 H D N are 0.2										
• Probe = 0.5			• Prope = C.3. \square 3, \square .P, N.am, O.2										
 Grid Spacing = 2 Å 	Å		completed	Re:	Gri	id Spa	cing =	1, 3.5,	0.1				
			completed	Res			Ŭ						
 Grid Extension = 5 	δA		completed	Res	Gri	id Exte	nsion	= 1, 10	D, 1				
Dielectric costant =	= 8		-	·	Die	electric	costa	nt = 1,	80, 1				
 Min/Max energy of 	fcutoff	value = 30 kcal/mol		•	Mir	n/Max	energy	y of cu	toff val	ue = 5	, 35,		
• Minimum sigma =	0.05			•	Mi	nimum	sigma	a = 0.1	, 1.0, 0	0.1			



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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.925	0.511	5	C.3.H3	1.3	7	13	5	0.5
Tyk2_inhibitor_S	0.942	0.535	6	C.3	2	5	8	30	0.05
Tyk2_inhibitor_C	0.852	0.447	4	0.2	1.3	5	80	27	0.6

$r^2 = 0.906 \pm 0.048, q^2 = 0.498 \pm 0.045$





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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.883	0.563	5	C.3.H3	1.3	7	13	5	0.5
Tyk2_inhibitor_S	0.915	0.640	6	N.am	1.5	2	37	15	1
Tyk2_inhibitor_C	0.815	0.570	4	C.3.H3	2.4	1	69	16	0.4

$r^2 = 0.871 \pm 0.051, q^2 = 0.591 \pm 0.043$





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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.801	0.452	3	N.am	2.8	4	61	16	1
Tyk2_inhibitor_S	0.972	0.439	6	0.2	2	1	62	15	0.2
Tyk2_inhibitor_C	0.650	0.379	2	C.3.H3	2.2	3	42	26	0.1

$r^2 = 0.808 \pm 0.161, q^2 = 0.423 \pm 0.039$



TYK2_inhibitor_M

TYK2_inhibitor_S

TYK2_inhibitor_C



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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.898	0.543	6	N.am	2.8	4	61	16	1
Tyk2_inhibitor_S	0.817	0.470	4	O.2	2	1	62	15	0.2
Tyk2_inhibitor_C	0.876	0.580	5	C.3.H3	2.2	3	42	26	0.1

$r^2 = 0.864 \pm 0.042, q^2 = 0.531 \pm 0.056$





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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.907	0.576	4	C.3.H3	1.5	2	61	5	0.9
Tyk2_inhibitor_S	0.856	0.565	4	0.2	2.2	4	50	24	0.4
Tyk2_inhibitor_C	0.891	0.600	4	N.am	2	9	6	30	1

$r^2 = 0.885 \pm 0.026, q^2 = 0.580 \pm 0.017$





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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.778	0.664	3	H.P	1.8	10	76	24	0.4
Tyk2_inhibitor_S	0.720	0.647	2	N.am	3.4	6	42	20	0.9
Tyk2_inhibitor_C	0.827	0.618	4	C.3	2	5	8	30	0.05

$r^2 = 0.775 \pm 0.054, q^2 = 0.643 \pm 0.023$



TYK2_inhibitor_M

TYK2_inhibitor_S

TYK2_inhibitor_C



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Balloon	r ²	q²	OPC	Р	GS	GE	3	CO	MS
Tyk2_inhibitor_M	0.864	0.487	4	H.P	2.5	4	17	21	0.8
Tyk2_inhibitor_S	0.975	0.535	6	C.3.H3	1.4	9.0	58	9	0.4
Tyk2_inhibitor_C	0.938	0.526	4	H.P	1.3	2	16	5	0.7

$r^2 = 0.926 \pm 0.057, q^2 = 0.516 \pm 0.026$





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- I modelli finali risultano avere una certa distribuzione di valori, con una dispersione che risulta essere bassa
- La deviazione standard misurata mostra una certa costanza.
- L'interpretazione grafica porta agli stessi risultati sia tra i diversi modelli ottenuti partendo dalla stessa analisi conformazionale sia tra modelli ottenuti da analisi conformazionali differenti.

Questi risultati dimostrano che la procedura applicata mediante il portale 3d-qsar.com permette di definire modelli altamente affidabili e riproducibili dimostrando che la field-based 3D-QSAR è uno strumento valido da poter utilizzare in drug design.



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