Molecular Quantum Similarity, Chemical Reactivity and Database Screening of 3D Pharmacophores of the Protein Kinases A, B and G from Mycobacterium Tuberculosis

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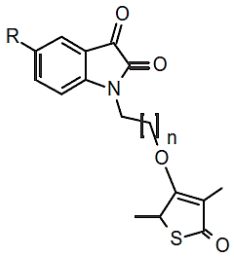
Supporting Information (SI)

Chibale's Database (DB):

Table S1. Chibale's Database. Tacked of the reference: *R. H. Hans; I. J. F. Wiid; P. D. van Helden; B. Wanc; S. G. Franzblau; J. Gut; P. J. Rosenthal;* ***K. Chibale****. Bioorg. Med. Chem. Lett.* ***2011****, 21, 2055–2058.*



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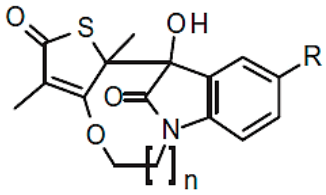

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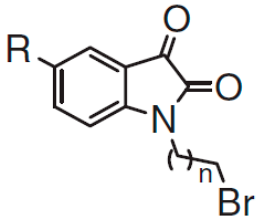


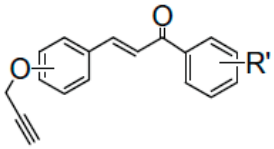
27-37

Compound	R	n	Clog P
1R	Br	1	2.88
1S	Br	1	2.88
2R	Cl	1	2.73
2S	Cl	1	2.73
3R	F	1	2.16
3S	F	1	2.16
4R	I	1	3.14
4S	I	1	3.14
5R	CH_3	1	2.34
5S	CH_3	1	2.34
6R	H	1	1.84
6S	H	1	1.84
7R	H	2	2.11
7S	H	2	2.11
8R	H	3	2.16
8S	H	3	2.16
9R	H	4	2.69
9S	H	4	2.69
10R	H	5	3.22
10S	H	5	3.22

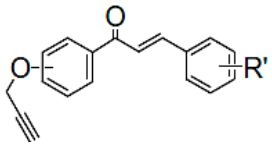
11RR	H	3	2.12
11RS	H	3	2.12
11SR	H	3	2.12
11SS	H	3	2.12
12RR	Br	3	3.12
12RS	Br	3	3.12
12SR	Br	3	3.12
12SS	Br	3	3.12
13RR	I	3	3.38
13RS	I	3	3.38
13SR	I	3	3.38
13SS	I	3	3.38
14RR	F	3	2.40
14RS	F	3	2.40
14SR	F	3	2.40
14SS	F	3	2.40
15RR	Cl	3	2.97
15RS	Cl	3	2.97
15SR	Cl	3	2.97
15SS	Cl	3	2.97
16RR	CH_3	3	2.62
16RS	CH_3	3	2.62
16SR	CH_3	3	2.62
16SS	CH_3	3	2.62
17RR	NO_2	3	2.16
17RS	NO_2	3	2.16
17SR	NO_2	3	2.16
17SS	NO_2	3	2.16
18RR	H	4	2.68
18RS	H	4	2.68
18SR	H	4	2.68
18SS	H	4	2.68
19RR	Cl	4	3.53
19RS	Cl	4	3.53
19SR	Cl	4	3.53
19SS	Cl	4	3.53
20RR	Br	4	3.68
20RS	Br	4	3.68
20SR	Br	4	3.68
20SS	Br	4	3.68
21RR	I	4	3.94
21RS	I	4	3.94
21SR	I	4	3.94
21SS	I	4	3.94
22RR	H	5	3.24
22RS	H	5	3.24

22SR	H	5	3.24
22SS	H	5	3.24
23RR	Cl	5	4.09
23RS	Cl	5	4.09
23SR	Cl	5	4.09
23SS	Cl	5	4.09
24RR	F	5	3.52
24RS	F	5	3.52
24SR	F	5	3.52
24SS	F	5	3.52
25RR	Br	5	4.24
25RS	Br	5	4.24
25SR	Br	5	4.24
25SS	Br	5	4.24
26RR	I	5	4.50
26RS	I	5	4.50
26SR	I	5	4.50
26SS	I	5	4.50
27	H	1	1.30
28	H	2	1.62
29	H	3	2.00
30	I	3	3.31
31	Cl	3	2.90
32	Br	3	3.04
33	F	3	2.32
34	CH_3	3	2.50
35	NO_2	3	2.13
36	H	4	2.53
37	H	5	3.06

Table S2. Chibale's Database. Tacked of the reference: *R. H. Hans; E. M. Guantai; C. Latega; P. J. Smith; B. Wanc; S. G. Franzblau; J. Gut; P. J. Rosenthal;* ***K. Chibale****. Bioorg. Med. Chem. Lett.* ***2010****, 20, 942–944.*



38-46



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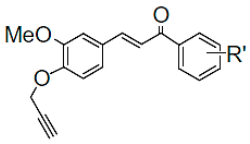

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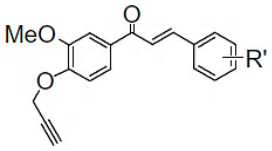
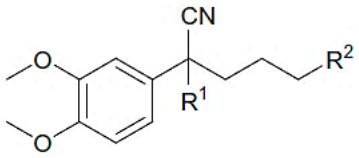


59-60

Compound	Substitution	R´	Clog P
38	Ortho	4-OMe	4.36
39	Ortho	2,4-diOMe	4.45
40	Ortho	2,3,4-triOMe	3.74
41	Meta	4-OMe	4.36
42	Meta	2,4-diOMe	4.45
43	Meta	2,3,4-triOMe	3.74
44	Para	4-OMe	4.36
45	Para	2,4-diOMe	4.45
46	Para	2,3,4-triOMe	3.74
47	Ortho	4-OMe	4.36
48	Ortho	2,4-diOMe	4.45
49	Ortho	2,3,4-triOMe	3.74
50	Meta	4-OMe	4.36
51	Meta	2,4-diOMe	4.45
52	Meta	2,3,4-triOMe	3.74
53	Para	4-OMe	4.36
54	Para	2,4-diOMe	4.45
55	Para	2,3,4-triOMe	3.74
56	-	4-OMe	4.10
57	-	2,4-diOMe	4.13
58	-	2,3,4-triOMe	3.38
59	-	2,4-diOMe	4.13
60	-	2,3,4-triOMe	3.38

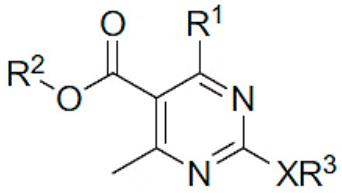
Table S3. Chibale's Database. Tacked of the reference: *K. Singh; M. Kumar; E. Pavadai; K. N. Digby; F. Warner; P. G. Ruminski;* ***K. Chibale****. Bioorg. Med. Chem. Lett.* ***2014****, 24 2985–2990.*



Compound	R^1	R^2	pIC_{99}
61R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-amine	-2.699
61S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-amine	-2.699
62R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.699
62S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.699
63R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-dyethyl-amine	-3.000
63S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-dyethyl-amine	-3.000
64R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-propyl-amine	-2.699
64S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-propyl-amine	-2.699
65R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-phenyl-amine	-3.000
65S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-phenyl-amine	-3.000
66R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-cyclopropyl - amine	-2.097
66S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-cyclopropyl - amine	-2.097
67R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-dymethyl -amine	>-3.000
67S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-dymethyl -amine	>-3.000
68R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl -amine	>-3.000
68S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl -amine	>-3.000
69R	$CH(CH_3)_2$	piperidine	-3.000
69S	$CH(CH_3)_2$	piperidine	-3.000
70R	$CH(CH_3)_2$	Oxy-piperidine	-3.000

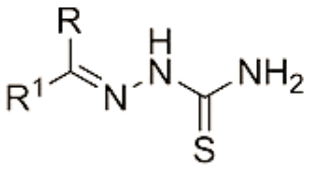
70S	$CH(CH_3)_2$	Oxy-piperidine	−3.000
71R	$CH(CH_3)_2$	Hydroxy-piperidine	-3.000
71S	$CH(CH_3)_2$	Hydroxy-piperidine	-3.000
72R	$CH(CH_3)_2$	dypiperidine	-2.699
72S	$CH(CH_3)_2$	dypiperidine	-2.699
73R	$CH(CH_3)_2$	Hydroxy-phenyl-piperidine	-2.398
73S	$CH(CH_3)_2$	Hydroxy-phenyl-piperidine	-2.398
74R	$CH(CH_3)_2$	phenyl-piperazine	-2.398
74S	$CH(CH_3)_2$	phenyl-piperazine	-2.398
75R	$CH(CH_3)_2$	2-piridine- piperazine	-2.398
75S	$CH(CH_3)_2$	2-piridine- piperazine	-2.398
76R	$CH(CH_3)_2$	2-Fluore-phenyl-piperazine	-1.795
76S	$CH(CH_3)_2$	2-Fluore-phenyl-piperazine	-1.795
77R	H	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
77S	H	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
78R	CH_3	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
78S	CH_3	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
79R	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
79S	$CH(CH_3)_2$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-3.000
80R	$(CH_2)_2CH_3$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.699
80S	$(CH_2)_2CH_3$	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.699
81R	Cyclopentyl	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.097
81S	Cyclopentyl	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-2.097
82R	Ciclohexyl	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-1.796
82S	Ciclohexyl	1,2-dymethoxy-phenyl-ethyl-methyl-amine	-1.796

Table S4. Chibale's Database. Tacked of the reference: *K. Singh; K. Singh; B. Wan; S. Franzblau;* ***K. Chibale****; J. Balzarini. Eur. J. Med. Chem.* ***2011****, 46, 2290-2294.*



Compound	R^1	R^2	X	R^3	pIC_{50}
83	H	C_2H_5	NH	H	-
84	C_6H_5	C_2H_5	NH	H	-
85	H	C_2H_5	NH	C_6H_5 CH_2	-
86	C_6H_5	C_2H_5	NH	C_6H_5 CH_2	-1.805
87	C_6H_5	CH_3	NH	C_6H_5 CH_2	>-2.107
88	C_6H_5	C_2H_5	NH	$(CH_2)_3OH$	>-2.107
89	C_6H_5	C_2H_5	NH	$CH(CH_3)_2$	
90	C_6H_5	C_2H_5	NH	N-C_4H_9	-2.071
91	C_6H_5	C_2H_5	NH	CH_2CH_2 (1H-indol-2-yl)	-
92	C_6H_5	C_2H_5	NH	2-OHC_6H_4	-2.086
93	C_6H_5	C_2H_5	NH	4-OHC_6H_4	-
94	C_6H_5	C_2H_5	NH	3-$NH_2C_6H_4$	-1.494
95	C_6H_5	C_2H_5	NH	-$(CH_2)_2$-CH_2-(CH_2)-	>-2.107
96	C_6H_5	C_2H_5	N	-$(CH_2)_2$-O-$(CH_2)_2$-	-2.098
97	C_6H_5	C_2H_5	O	C_2H_5	-

Table S5. Chibale's Database. Tacked of the reference: *S. D. Khanye; B. Wan; S. G. Franzblau; J. Gut; P. J. Rosenthal; G. S. Smith;* ***K. Chibale****. J. Organomet. Chem.* ***2011****, 696, 3392-3396.*



Compound	R	R^1	pIC_{50}
98	H	3-methoxy-4-hydroxy-Fenyl	>-2.107
99	CH_3	3, 4-dicloro-fenyl	-1.068
100	CH_3	3-bromo-fenyl	>-2.107
101	CH_3CH_2	3-bromo-fenyl	-2.107
102	CH_3CH_2	3, 4-dicloro-fenyl	>-2.107
103	CH_3	4-bromo-fenyl	>-2.107

Molecular Quantum Similarity Indices.

Table S6. Carbó index of Overlap for Pkn A inhibitors (see **Table 8**).

C, OI[a]	1	2	3	4
1	1.000			
2	0.369	1.000		
3	0.367	0.684	1.000	
4	0.250	0.409	0.441	1.000

[a]C: Compound, OI: Overlap Index.

Table S7. Euclidean Distance of Overlap for Pkn A inhibitors.

C, ED[a]	1	2	3	4
1	0.000			
2	5.643	0.000		
3	5.874	4.191	0.000	
4	6.317	5.663	5.699	0.000

[a]**C**: Compound, **ED**: Euclidean Distance.

Table S8. Carbó index of Coulomb for Pkn A inhibitors (see **Table 8**).

C, CI[a]	1	2	3	4
1	1.000			
2	0.798	1.000		
3	0.787	0.893	1.000	
4	0.779	0.855	0.902	1.000

[a]C: Compound, CI: Coulomb Index.

Table S9. Euclidean Distance of Coulomb for Pkn A inhibitors.

C, ED[a]	1	2	3	4
1	0.000			
2	36.434	0.000		
3	41.062	30.021	0.000	
4	40.699	33.932	29.140	0.000

[a]**C**: Compound, **ED**: Euclidean Distance.

Table S10. Carbó index of Overlap for Pkn B inhibitors (see **Table 9**).

C, OI[a]	5	6	7	8	9	10	11	12	13	14	15	16	17
5	1.000												
6	0.268	1.000											
7	0.440	0.365	1.000										
8	0.266	0.792	0.287	1.000									
9	0.468	0.291	0.634	0.298	1.000								
10	0.438	0.654	0.390	0.720	0.308	1.000							
11	0.473	0.723	0.388	0.737	0.400	0.741	1.000						
12	0.481	0.644	0.444	0.581	0.397	0.832	0.728	1.000					

13	**0.289**	**0.576**	**0.443**	**0.634**	**0.289**	**0.592**	**0.553**	**0.419**	**1.000**				
14	**0.237**	**0.694**	**0.394**	**0.627**	**0.244**	**0.572**	**0.558**	**0.549**	**0.520**	**1.000**			
15	**0.364**	**0.418**	**0.406**	**0.410**	**0.336**	**0.429**	**0.432**	**0.424**	**0.368**	**0.463**	**1.000**		
16	**0.460**	**0.327**	**0.390**	**0.336**	**0.290**	**0.234**	**0.327**	**0.423**	**0.463**	**0.315**	**0.330**	**1.000**	
17	**0.458**	**0.462**	**0.509**	**0.454**	**0.323**	**0.540**	**0.534**	**0.615**	**0.498**	**0.412**	**0.448**	**0.318**	**1.000**

Table S11. Euclidean Distance of Overlap for Pkn B inhibitors.

C, ED[a]	5	6	7	8	9	10	11	12	13	14	15	16	17
5	**0.000**												
6	**5.350**	**0.000**											
7	**4.363**	**5.026**	**0.000**										
8	**5.508**	**3.122**	**5.464**	**0.000**									
9	**4.070**	**5.123**	**3.419**	**5.251**	**0.000**								
10	**4.536**	**3.824**	**4.763**	**3.536**	**4.877**	**0.000**							
11	**4.450**	**3.452**	**4.825**	**3.455**	**4.612**	**3.241**	**0.000**						
12	**4.208**	**3.786**	**4.396**	**4.223**	**4.389**	**2.512**	**3.236**	**0.000**					
13	**5.275**	**4.346**	**4.708**	**4.131**	**5.129**	**4.151**	**4.384**	**4.820**	**0.000**				
14	**6.046**	**4.073**	**5.458**	**4.554**	**5.891**	**4.720**	**4.818**	**4.762**	**5.074**	**0.000**			
15	**5.246**	**5.305**	**5.104**	**5.453**	**5.232**	**5.130**	**5.163**	**5.037**	**5.529**	**5.518**	**0.000**		
16	**5.497**	**6.310**	**5.823**	**6.366**	**6.099**	**6.584**	**6.239**	**5.684**	**5.665**	**6.762**	**6.467**	**0.000**	
17	**4.573**	**4.860**	**4.384**	**5.015**	**4.961**	**4.367**	**4.443**	**3.895**	**4.693**	**5.571**	**5.134**	**6.317**	**0.000**

[a]**C**: Compound, **ED**: Euclidean Distance.

Table S12. Carbó index of Coulomb for Pkn B inhibitors (see **Table 9**).

C, CI[a]	5	6	7	8	9	10	11	12	13	14	15	16	17
5	**1.000**												
6	**0.777**	**1.000**											
7	**0.877**	**0.666**	**1.000**										
8	**0.778**	**0.965**	**0.716**	**1.000**									
9	**0.846**	**0.655**	**0.887**	**0.675**	**1.000**								
10	**0.853**	**0.910**	**0.776**	**0.925**	**0.774**	**1.000**							
11	**0.900**	**0.890**	**0.736**	**0.899**	**0.795**	**0.961**	**1.000**						
12	**0.887**	**0.875**	**0.808**	**0.863**	**0.789**	**0.969**	**0.953**	**1.000**					
13	**0.774**	**0.897**	**0.841**	**0.928**	**0.589**	**0.932**	**0.842**	**0.701**	**1.000**				
14	**0.780**	**0.970**	**0.831**	**0.947**	**0.763**	**0.925**	**0.897**	**0.896**	**0.874**	**1.000**			
15	**0.794**	**0.836**	**0.830**	**0.828**	**0.759**	**0.843**	**0.835**	**0.820**	**0.796**	**0.874**	**1.000**		
16	**0.805**	**0.683**	**0.799**	**0.683**	**0.650**	**0.698**	**0.733**	**0.769**	**0.853**	**0.759**	**0.787**	**1.000**	
17	**0.870**	**0.807**	**0.854**	**0.821**	**0.714**	**0.883**	**0.895**	**0.915**	**0.815**	**0.788**	**0.792**	**0.794**	**1.000**

[a]C: Compound, CI: Coulomb Index.

Table S13. Euclidean Distance of Coulomb for Pkn B inhibitors.

C, ED[a]	5	6	7	8	9	10	11	12	13	14	15	16	17
5	**0.000**												
6	**34.606**	**0.000**											
7	**18.446**	**40.538**	**0.000**										
8	**36.673**	**14.941**	**39.947**	**0.000**									
9	**19.719**	**41.11**	**17.222**	**42.397**	**0.000**								
10	**27.279**	**22.507**	**32.025**	**21.809**	**32.610**	**0.000**							

11	22.591	24.722	33.275	24.977	30.302	14.026	0.000						
12	21.295	26.322	26.813	28.981	28.085	13.047	14.921	0.000					
13	34.609	24.620	30.367	21.269	43.709	19.559	29.395	39.319	0.000				
14	39.249	15.284	35.985	19.339	41.100	23.487	27.168	28.240	29.438	0.000			
15	39.427	34.015	37.069	35.127	42.358	33.220	34.002	35.626	37.719	30.667	0.000		
16	48.184	53.255	48.202	53.458	56.833	51.996	49.466	47.505	38.722	47.559	44.986	0.000	
17	26.887	33.097	27.878	32.914	36.500	24.881	23.262	20.993	32.264	37.488	37.796	44.481	0.000

[a]**C**: Compound, **ED**: Euclidean Distance.

Table S14. Carbó index of Overlap for Pkn G inhibitors (see **Table 10**).

C, OI[a]	18	19	20	21	22	23	24	25	26	27
18	1.000									
19	0.685	1.000								
20	0.734	0.775	1.000							
21	0.800	0.872	0.868	1.000						
22	0.688	0.894	0.814	0.800	1.000					
23	0.609	0.850	0.739	0.767	0.904	1.000				
24	0.634	0.853	0.730	0.755	0.892	0.993	1.000			
25	0.631	0.884	0.741	0.801	0.885	0.915	0.911	1.000		
26	0.651	0.745	0.586	0.670	0.708	0.702	0.695	0.675	1.000	
27	0.640	0.661	0.532	0.582	0.620	0.616	0.613	0.623	0.734	1.000

[a]C: Compound, OI: Overlap Index.

Table S15. Euclidean distances of Overlap for Pkn G inhibitors.

C, ED[a]	18	19	20	21	22	23	24	25	26	27
18	0.000									
19	3.216	0.000								
20	3.078	2.891	0.000							
21	2.518	2.077	2.203	0.000						
22	3.239	1.940	2.645	2.622	0.000					
23	3.613	2.297	3.131	2.824	1.854	0.000				
24	3.508	2.279	3.189	2.903	1.961	0.492	0.000			
25	3.558	2.043	3.149	2.649	2.057	1.762	1.810	0.000		
26	3.492	3.057	4.001	3.428	3.297	3.323	3.369	3.504	0.000	
27	3.873	3.819	4.556	4.183	4.058	4.068	4.089	4.063	3.441	0.000

[a]**C**: Compound, **ED**: Euclidean Distance.

Table S16. Carbó index of Coulomb for Pkn G inhibitors (see **Table 10**).

C, CI[a]	18	19	20	21	22	23	24	25	26	27
18	1.000									
19	0.963	1.000								
20	0.941	0.957	1.000							
21	0.981	0.987	0.964	1.000						
22	0.951	0.980	0.971	0.977	1.000					
23	0.935	0.971	0.951	0.972	0.988	1.000				
24	0.941	0.972	0.950	0.971	0.987	0.999	1.000			

25	**0.942**	**0.977**	**0.939**	**0.970**	**0.977**	**0.984**	**0.983**	**1.000**		
26	**0.960**	**0.978**	**0.943**	**0.973**	**0.972**	**0.969**	**0.966**	**0.963**	**1.000**	
27	**0.946**	**0.938**	**0.911**	**0.922**	**0.920**	**0.912**	**0.910**	**0.918**	**0.939**	**1.000**

[a]C: Compound, CI: Coulomb Index.

Table S17. Euclidean distances of Coulomb for Pkn G inhibitors.

C, ED[a]	18	19	20	21	22	23	24	25	26	27
18	**0.000**									
19	**11.270**	**0.000**								
20	**16.237**	**13.729**	**0.000**							
21	**7.867**	**6.810**	**13.404**	**0.000**						
22	**13.274**	**8.338**	**11.399**	**9.363**	**0.000**					
23	**15.600**	**10.460**	**14.404**	**10.659**	**6.758**	**0.000**				
24	**14.907**	**10.374**	**14.623**	**10.946**	**7.177**	**1.246**	**0.000**			
25	**15.660**	**10.067**	**16.114**	**11.885**	**9.995**	**8.260**	**8.432**	**0.000**		
26	**12.266**	**8.926**	**15.551**	**10.164**	**10.173**	**10.879**	**11.158**	**12.248**	**0.000**	
27	**20.063**	**20.148**	**22.069**	**22.594**	**21.746**	**22.381**	**22.609**	**21.446**	**19.593**	**0.000**

[a]**C**: Compound, **ED**: Euclidean Distance.