Designing Caspase-1 kinase inhibitors to control acute inflammation of Orthodontic Appliances.

Ashleigh Augello,[1] Earl Benjamin,[1] Ellis Benjamin*[1]
Department of Chemistry, The Richard Stockton College of New Jersey, Galloway NJ 08205-9441.

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Orthodontics is a branch of dentistry that uses tensile force from intraoral or extraoral orthodontic appliances to resolve dental malocclusions. The use of tensile force seeks to remodel periodontal ligament and alveolar bone however this process initiates acute inflammation and necrotic conditions in the periodontium. This acute inflammation arises through multiple mechanisms including that of the inflammasome conversion of pro-interleukin 1β (IL-1β) to the active form.[1,2] Inhibition of one major protein found in the inflammasome, Caspase-1, has been found to block the activation of IL-1β thereby blocking the acute inflammation initiated by appliance tightening.[3-5] This research sought to understand binding interaction of pharmaceuticals to the protein kinase functionality of the Caspase-1. 22 crystal structures of the kinase of the Caspase-1 protein were docked using IGEMDock to FDA, Alkaloids, Lactams, Lactones, Flavinoids, Sulfanilamide, Cyclic Imides, and NSAIDs drugs to determine structural correlation for the most effective binders. Structural similarities were determined with IGEMDock and vROCS and partition coefficient was determined using DRAGON program. This data found a cluster of approximately 10 drugs to preferentially bind to the Caspase-1 kinase for use as targeted anti-inflammatory treatments. This work will be used in the engineering of improved Caspase-1 kinase inhibitors.

Introduction

This project was designed around structural understanding and pharmaceutical engineering of the Caspase-1 inhibitors. Caspase-1 being a part of a group of proteins termed Inflammasome assists in the initiation of inflammation through the conversion of non-active Interleukin-1β to the active form. This process can be found throughout the body however during times of periodontal tightening of appliances this process is strongly activated causing swelling and cellular damage. Through the inhibition of Caspase-1 a limitation on the amount of inflammation can be achieved thereby limiting any damage from appliance tightening.

Overall Goal

The overall goal of this research was to investigate the interaction of multiple drug candidates to find the best structural motifs for targeted inhibition of the Caspase-1 kinase moiety. Once found similarities between these drugs will allow for a better understanding of the inhibition of Caspase-1 to convert IL-1 beta to its active form.

Experimental Methodology

1. The selection of 21 isoforms of Caspase-1.
2. The screening and analysis of multiple drug candidates using IGemDock.
3. Similarity calculations were done to determine if molecular functionalities showed any preference to increased binding.
4. Selected candidates from IGemDock based on binding energy were tested using Dragon to determine structural similarities.

Methods and Materials

1172 structures were chosen which included, 715 FDA approved, 197 Alkaloids, 73 Imides, 40 Lactams, 36 Lactones, 50 NSAIDs, 25 Sulfanilamide and 37 Flavonoids pharmaceuticals were selected as ligands and computationally bound to 21 isoforms of the Caspase-1 kinase protein using IGEMDock. IGEMDock used two independent docking with the average of both binding to factor in binding selectivity. An ANOVA was done to determine if any discrepancies in binding were seen between proteins. Additionally, grouping of the molecular functionalities were determine to find differences. The best 10 drug candidates on binding energies were selected and structural data such as molecular weight and partition coefficient was collected using Dragon.

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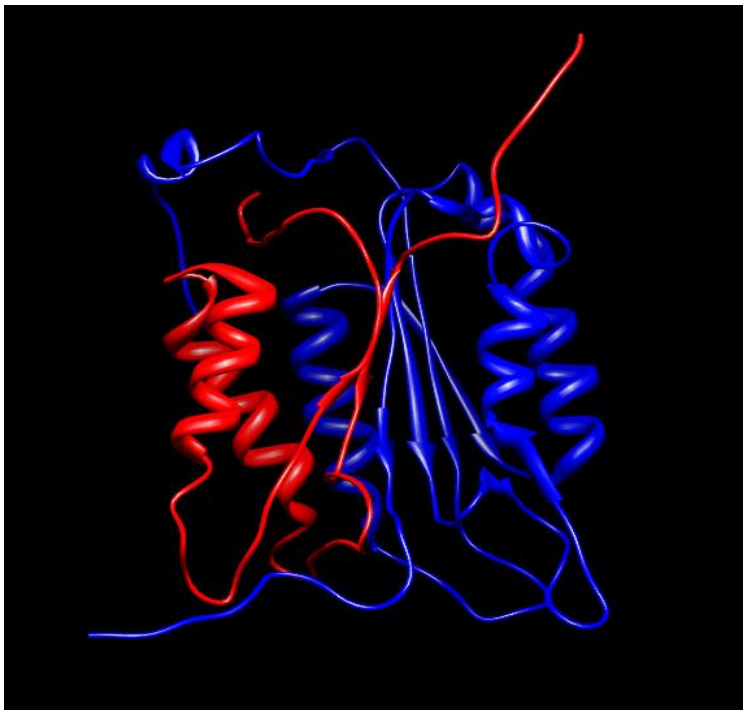

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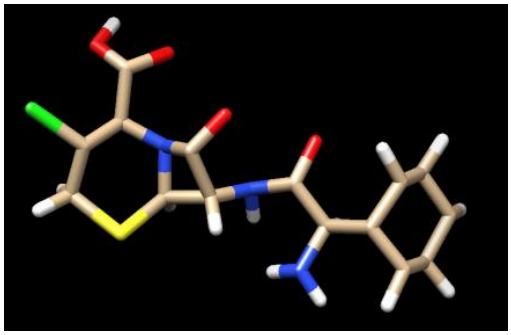

Selected Caspase-1 Proteins

#	PDB	Title
1	1BMQ	Caspase-1 with (3S)-N-METHANESULFONYL-3-({1-[N-(2-NAPHTOYL)-L-VALYL]-L-PROLYL }AMINO)-4-OXOBUTANAMIDE
2	1RWK	Caspase-1 with 3-(2-mercapto-acetylamino)-4-oxo-pentanoic acid
3	1RWM	Caspase-1 w 4-oxo-3-[2-(5-{[4-(quinoxalin-2-ylamino)-benzoylamino]-methyl}-thiophen-2-yl)-acetylamino]-pentanoic acid
4	1RWN	Caspase-1 with 3-{2-ethyl-6-[4-(quinoxalin-2-ylamino)-benzoylamino]-hexanoylamino}-4-oxo-butyric acid
5	1RWO	Caspase-1 with 4-oxo-3-{6-[4-(quinoxalin-2-ylamino)-benzoylamino]-2-thiophen-2-yl-hexanoylamino}-pentanoic acid
6	1RWP	Caspase-1 with 3-{6-[(8-hydroxy-quinoline-2-carbonyl)-amino]-2-thiophen-2-yl-hexanoylamino}-4-oxo-butyric acid
7	1RWV	Caspase-1 with 5-[5-(1-carboxymethyl-2-oxo-propylcarbamoyl)-5-phenyl-pentylsulfamoyl]-2-hydroxy-benzoic acid
8	1RWW	Caspase-1 with 4-oxo-3-[(6-{[4-(quinoxalin-2-ylamino)-benzoylamino]-methyl}-pyridine-3-carbonyl)-amino]-butyric acid
9	1RWX	Caspase-1 with 4-oxo-3-{6-[4-(quinoxalin-2-yloxy)-benzoylamino]-2-thiophen-2-yl-hexanoylamino}-butyric acid
10	1SC3	Caspase-1 C285A mutant with malonate
11	2FQQ	Caspase-1 with 1-methyl-3-trifluoromethyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid (2-mercapto-ethyl)-amide
12	2H4W	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
13	2H4Y	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
14	2H48	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
15	2H51	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
16	2H54	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
17	2HBR	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
18	2HBY	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
19	2HBZ	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
20	3D6F	Caspase-1 x with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid
21	3D6H	Caspase-1 with 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-oxo-pentanoic acid

Summary of 1172 Caspase-1 Drug Candidates vs Proteins (IGEMDock Data)

SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
1BMQ	2344	-170610	-72.786	4710.814
1RWK	2344	-165300	-70.5204	5212.522
1RWM	2344	-168151	-71.7369	5074.381
1RWN	2344	-163282	-69.6594	5881.065
1RWO	2344	-176777	-75.4167	4672.507
1RWP	2344	-164273	-70.0821	5030.453
1RWV	2344	-8286.67	-3.53527	14924.44
1RWW	2344	-81637.8	-34.8284	7517.229
1RWX	2344	-177409	-75.6864	3595.297
1SC3	2344	-161465	-68.8844	5455.578
2FQQ	2344	-137377	-58.6079	5833.411
2H4W	2344	-165211	-70.4826	4604.87
2H4Y	2344	-163409	-69.7136	4713.563
2H48	2344	-151345	-64.5669	4813.009
2H51	2344	-164229	-70.0637	4587.992
2H54	2344	-148951	-63.5457	6207.469
2HBR	2344	-153142	-65.3335	5613.084
2HBY	2344	-155863	-66.4942	4167.689
2HBZ	2344	-162882	-69.4891	4526.049
3D6F	2344	-167902	-71.6303	4295.117
3D6H	2344	-165191	-70.4742	4064.456

ANOVA of 1172 Caspase-1 drug candidates (IGEMDock Data).

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	12473126	20	623656.3	113.3911	0	1.570736
Within Groups	2.71E+08	49203	5500.047			
Total	2.83E+08	49223				

Breakdown of Caspase-1 drug candidates by types (IGEMDock Data).

Classifications	Average	St. Dev.
Alkaloids	-77.0725	11.9241693
Flavinoids	-80.0967	14.52556934
Imide	-78.7396	9.763914453
Lactams	-76.3274	11.08283877
Lactones	-74.2555	48.66880134
NSAIDS	-80.3342	9.816616085
Sulfanilamide	-75.4509	6.765993776

Summary of Caspase-1 Control Drugs (IGEMDock Data).

Caspase 1 Control	
Low Value	-108.466
High Value	-67.7796
Average	-92.8547
Standard Deviation	13.7274

Caspase-1 Drug Candidates Docking Energy (IGEMDock Data).

# of Drugs	Drug Title	Energy
1	FDA - 182-1	-135.5908571
	FDA - 182-0	-134.312
2	FDA - 446-1	-131.7382762
	FDA - 446-0	-127.6165762
3	FDA - 570-0	-126.879
	FDA - 570-1	-126.8675238
4	FDA - 533-0	-120.6307286
	FDA - 533-1	-120.5906476
5	FDA - 284-0	-120.5439048
	FDA - 284-1	-120.3274286
6	FDA - 99-1	-119.2178238
	FDA - 99-0	-117.4931333
7	FDA - 710-1	-115.2388143
	FDA - 710-0	-115.087119
8	FDA - 266-0	-114.8317952
	FDA - 266-1	-114.3862286
9	Alkaloids - 504 -0-1	-121.2985909
	Alkaloids - 504 -0-0	-113.7325909
10	Etoposide-1-0	-115.2324682
	Etoposide-1-1	-94.73515909

Dragon Data of Caspase-1 drug candidates.

NAME	MW	MLOGP	MLOGP2
FDA 2 - 182	516.61	0.391	0.153
FDA 2 - 446	359.04	0.364	0.133
FDA 2 - 570	312.211	-0.009	0
FDA 2 - 533	265.13	3.174	10.076
FDA 2 - 284	281.13	2.402	5.771
FDA 2 - 99	504.72	2.029	4.117
FDA 2 - 266	254.15	0.372	0.139

Dragon Data of Caspase-1 Control Molecules.

NAME	MW	MLOGP	MLOGP2
3NS7_3NS_B_1	388.25	1.509	2.278
2FQQ_F1G_B_1	299.27	2.132	4.544
1SC3_MLI_A_301	100.03	-0.806	0.65
1RWX_YBH_A_501	532.4	2.724	7.422
1RWW_OQB_A_501	476.32	1.606	2.579
1RWV_5PH_A_501	492.33	1.539	2.368
1RWP_HQC_A_501	458.34	1.578	2.491
1RWO_BTH_A_501	542.42	2.917	8.51
1RWN_4QB_A_501	474.32	2.47	6.099
1RWM_Q2Y_A_501	494.38	2.397	5.748
1RWK_158_A_501	194.15	-0.097	0.009
1BMQ_MNO_A_601	512.37	2.089	4.363

Discussion

Multiple compounds were identified as effective based upon their interactions with each protein. Specifically an average energy of -120.317 was found for the drug candidates compared to -92.8547for the control molecules An ANOVA to determine differences between the 21 proteins analyzed indicated major differences. A search of the data indicates that 1RWV and 1RWW shows the greatest differences. Grouping analysis will be used to understand differences in protein active sites. 10 drugs were chosen due to their low binding energies (for both binding interactions). Structural analysis found that many of these molecules are small with similar partition coefficient (-0.009 to 0.3.72) of the top binders similar to that of the control molecules.

Conclusion

By using the computational techniques we were able to identify several molecule that show improved binding efficacy over currently used Caspase-1 inhibitors. These Caspase-1 drug candidates indicated a diverse pool of Caspase-1 binders with improved efficacy. This work can be used to engineer these motifs into novel Caspase-1 inhibitors for improved drug efficacy.

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