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Supplemental Data

The HIV Protease Inhibitor Saquinavir Inhibits HMGB1-Driven Inflammation by Targeting the Interaction of Cathepsin V with TLR4/MyD88

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Supplementary Table S1. ActiTarg-P screen of protease Inhibitors identifies three hit compounds capable of attenuating HMGB1 induced TNF-α in RAW 264.7 macrophages.

Name	Relative TNF-α response %	HIT?	Name	Relative TNF-α response %	HIT?	Name	Relative TNF-α response %	HIT?	Name	Relative TNF-α response %	HIT?	Name	Relative TNF-α response %	HIT?
ST057867	63.8	***hit***	ST057866	99.5		ST057914	108.6		ST057986	122.9		ST057829	96.0	
ST057901	100.4		ST057929	98.6		ST058062	111.7		ST057998	106.7		ST057924	95.8	
ST057883	94.6		ST057983	117.8		ST057984	115.2		ST057781	101.7		ST057691	98.3	
ST057937	101.1		ST057934	110.8		ST057857	92.7		ST057987	106.7		ST057931	96.5	
ST058055	112.8		ST057779	92.2		ST057992	109.4		ST057996	117.4		ST052697	106.0	
ST057887	106.0		ST057796	98.3		ST057947	104.5		ST057952	111.9		ST057890	96.7	
ST057911	106.7		ST057825	79.7		ST057855	96.2		ST057833	91.3		ST057888	108.9	
ST057955	113.5		ST057902	112.6		ST057840	96.2		ST057807	91.2		ST058083	119.3	
ST057832	84.7		ST057851	94.0		ST057875	93.5		ST057949	100.1		ST057862	96.4	
ST057880	124.0		ST057795	102.3		ST057856	105.6		ST057985	130.0		ST057928	118.1	
ST058067	129.0		ST057917	101.1		ST057853	88.8		ST057936	101.4		ST057831	95.3	
ST057994	145.6		ST057057	95.2		ST057861	98.7		ST058079	100.3		ST057945	101.5	
ST058090	107.0		ST057894	100.4		ST057908	96.9		ST058002	120.9		ST057926	115.9	
ST057897	105.0		ST057784	92.2		ST057882	120.7		ST057900	102.8		ST058116	109.4	
ST052689	99.0		ST058076	104.5		ST057852	95.8		ST057780	90.3		ST057878	94.0	
ST058113	119.6		ST058066	122.1		ST057898	104.1		ST057939	109.7		ST057799	89.9	
ST058054	109.9		ST057860	93.3		ST052688	100.7		ST057886	92.7		ST057870	95.9	
ST058075	122.6		ST058112	117.9		ST058008	109.9		ST058064	108.1		ST058043	127.8	
ST057822	88.7		ST057921	108.9		ST057918	102.9		ST058001	132.3		ST058071	107.3	
ST057925	100.5		ST057916	102.7		ST057858	106.5		ST057797	87.2		ST052657	86.8	
ST057909	101.6		ST057905	98.3		ST057944	102.6		ST052667	96.3		ST057844	87.8	
ST057881	95.5		ST057863	98.3		ST058094	112.7		ST057885	97.6		ST057990	117.2	
ST057993	120.2		ST052687	97.0		ST057943	110.2		ST057940	98.6		ST057941	116.9	
ST058091	101.8		ST058003	117.2		ST057912	120.2		ST058078	101.7		ST058084	124.9	
ST057871	100.9		ST058061	98.7		ST057848	102.1		ST057988	106.7		ST058006	120.6	
ST057785	87.6		ST057854	90.1		ST057827	88.5		ST058077	108.1		ST058082	109.8	
ST057864	93.7		ST057874	104.7		ST058060	97.5		ST058000	121.3		ST057989	107.4	
ST058092	105.3		ST057915	102.1		ST058063	97.5		ST057791	98.0		ST058074	125.8	

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Supplementary Table S1. ***Continued.***

ST058056	102.5	ST058065	107.3	ST058114	113.6	ST052696	88.4	ST058005	102.5
ST057872	107.7	ST057850	87.7	ST058080	116.6	ST057845	93.1	ST058107	100.8
ST057838	85.4	ST057873	97.4	ST057859	94.7	ST057938	107.3	ST057892	96.4
ST057865	77.3	ST057903	102.9	ST057798	90.5	ST057950	108.9	ST057956	113.2
ST057951	99.1	ST057919	101.0	ST057999	119.5	ST057995	128.8	ST057846	85.0
ST057884	98.9	ST057922	105.8	ST058059	146.3	ST058068	100.2	ST057836	83.5
ST057889	97.3	ST057847	82.4	ST058007	106.9	ST057907	111.7	ST057835	95.9
ST057904	112.5	ST057906	102.2	ST057991	114.8	ST057981	115.7	ST057879	102.0
ST058057	116.1	ST058058	116.7	ST057913	111.4	ST057982	112.3	ST057953	112.3
ST057910	113.1	ST057920	116.5	ST057979	95.2	ST057843	89.2	ST057834	98.8
ST057876	96.3	ST057849	90.9	ST052655	105.3	ST057923	102.1	ST057927	105.4
ST055416	99.6	ST057808	75.6	ST059023	96.0	ST025517	84.5	ST058974	94.5
ST057893	93.3	ST058009	110.9	ST058014	125.2	ST058045	102.2	ST058096	123.7
ST058072	108.6	ST033470	91.4	ST057812	102.1	ST059022	107.9	ST058042	112.7
ST057841	89.5	ST058261	97.2	ST057974	122.9	ST058041	106.7	ST011763	103.9
ST058176	107.7	ST033332	93.5	ST057800	97.1	ST058264	88.9	ST056692	96.0
ST057891	103.9	ST058023	93.6	ST058012	112.2	ST058040	101.6	ST058031	105.0
ST058085	104.0	ST058015	112.5	ST058020	99.8	ST058101	105.1	ST058189	128.8
ST058173	110.5	ST025586	101.6	ST057977	120.7	ST057960	97.0	ST057970	104.7
ST058093	108.7	ST058046	103.9	ST057969	128.5	ST057961	109.5	ST055689	88.4
ST057957	96.9	ST057811	97.0	ST057975	106.7	ST057816	88.3	ST057803	99.4
ST057782	84.5	ST057967	112.9	ST057793	96.0	ST058311	97.9	ST059722	97.3
ST057896	111.4	ST058024	100.2	ST058016	99.1	ST058032	105.0	ST069152	96.0
ST057842	85.5	ST057809	89.6	ST058017	115.6	ST060149	105.5	ST058106	96.4
ST057930	99.3	ST058257	98.7	ST057962	101.6	ST058102	115.6	ST069167	101.5
ST057830	92.9	ST058051	128.2	ST058044	102.0	ST069147	110.0	ST058095	121.2
ST057868	101.3	ST058037	103.6	ST058025	101.9	ST057978	121.9	ST058932	100.7
ST057877	94.8	ST058310	100.9	ST058100	99.6	ST052895	88.7	ST059357	87.1
ST057933	97.3	ST057776	84.6	ST057773	92.9	ST058519	105.3	ST058521	114.4
ST058070	106.4	ST058177	119.7	ST069148	97.1	ST057806	90.3	ST058186	121.5
ST058086	102.4	ST058097	122.8	ST057971	97.9	ST058021	111.3	ST057965	100.8
ST058260	102.8	ST058018	135.2	ST057973	101.1	ST058206	116.9	ST032255	88.4
ST057828	98.5	ST059396	107.1	ST058036	103.2	ST057787	94.6	ST058193	115.7
ST057932	104.8	ST057814	88.1	ST058175	108.8	ST058198	107.8	ST058214	114.9
ST057954	96.4	ST057968	109.9	ST058262	95.0	ST069156	110.1	ST058301	116.2
ST058171	98.5	ST057778	105.3	ST069144	102.2	ST027884	96.3	ST058144	105.8
ST057948	106.3	ST058053	101.3	ST057813	102.0	ST069154	107.6	ST058142	94.8
ST057895	116.3	ST058033	103.0	ST058258	114.0	ST057959	103.3	ST069155	108.9
ST052658	92.3	ST005021	101.2	ST058052	97.4	ST058223	99.8	ST058143	109.3
ST057942	128.3	ST058029	104.5	ST057972	102.1	ST058099	123.0	ST058141	102.3
ST058259	108.3	ST058098	109.5	ST057777	100.4	ST057694	105.0	ST059353	85.5
ST057935	99.9	ST057775	95.3	ST057772	98.9	ST058022	100.0	ST058980	103.6
ST057824	94.9	ST058027	115.3	ST058103	116.6	ST058190	105.8	ST033516	85.7
ST057056	101.3	ST057786	91.7	ST058104	107.3	ST069158	100.9	ST058039	98.5
ST057789	91.7	ST057792	94.8	ST057818	94.0	ST069145	107.8	ST058241	94.0
ST058174	95.2	ST058028	117.1	ST057801	97.9	ST058520	122.4	ST055843	87.1
ST057997	127.9	ST057794	92.4	ST057805	80.4	ST058191	104.0	ST059355	89.9
ST057869	85.7	ST058111	104.3	ST057958	105.0	ST059391	97.0	ST059356	86.2
ST057790	93.1	ST057976	119.6	ST058185	122.9	ST057774	97.0	ST058019	120.3
ST058073	102.6	ST057815	83.6	ST058034	113.4	ST058931	87.9	ST034238	90.1
ST058172	101.5	ST057964	108.8	ST058050	110.1	ST069151	102.6	ST003381	103.6
ST057837	93.3	ST058263	95.1	ST058105	107.9	ST058195	108.5	ST059352	79.7
ST033471	89.1	ST057804	103.3	ST058038	105.8	ST058168	125.9	ST059350	84.4
ST057823	96.9	ST058035	122.7	ST058979	89.3	ST057963	98.9	ST058238	109.5
ST057899	105.9	ST058013	101.5	ST058048	101.9	ST058047	98.2	ST058203	125.4

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Supplementary Table S1. ***Continued.***

ST058069	115.2	ST057966	109.4	ST057788	100.0		ST069157	98.5	ST058129	104.5
ST058010	110.1	ST057810	92.3	ST003932	104.7		ST058049	104.4	ST059351	86.7
ST057826	89.0	ST058026	108.2	ST057416	90.2		ST058212	125.3	ST058150	98.7
ST058011	123.8	ST058030	103.7	ST058300	101.7		ST057817	97.0	ST058216	117.5
ST059361	90.0	ST059340	86.2	ST055935	93.9		ST040137	106.4	ST059010	103.0
ST058140	104.9	ST059334	88.4	ST054523	93.8		ST059323	87.3	ST059369	103.0
ST058196	106.0	ST059347	86.2	ST058217	112.4		ST059552	100.8	ST019259	83.6
ST069153	99.3	ST059198	89.5	ST047092	92.2		ST059372	109.7	ST059378	99.3
ST055705	92.1	ST058182	107.0	ST015985	108.3		ST058563	91.1	ST059381	95.0
ST058181	102.6	ST011321	96.9	ST058600	91.1		ST058565	97.2	ST059802	107.1
ST069149	101.9	ST059393	90.8	ST015539	101.7		ST058729	99.3	ST059315	83.1
ST058157	111.2	ST069159	99.2	ST059377	93.6		ST059397	116.1	ST058524	95.7
ST058204	116.9	ST011309	95.1	ST058242	101.7		ST059367	101.3	ST058526	101.7
ST057693	98.3	ST011311	98.9	ST015472	105.4		ST058572	95.4	ST015382	105.7
ST011307	103.6	ST033187	93.1	ST019004	99.0		ST039694	86.7	ST058525	90.3
ST059360	84.9	ST059333	111.9	ST059390	92.8		ST059322	85.1	ST015374	103.1
ST058205	116.3	ST059392	91.5	ST059389	113.1		ST037712	97.2	ST056812	118.5
ST058187	98.5	ST055910	97.9	ST058593	92.1		ST059229	103.4	ST025463	94.4
ST058132	109.9	ST058153	97.7	ST058590	105.9		ST059320	91.2	ST031852	97.3
ST058233	95.7	ST059386	93.0	ST059336	87.3		ST058571	88.7	ST059197	89.8
ST034240	93.0	ST058230	94.5	ST018983	92.5		ST058574	89.9	ST065541	101.9
ST058134	120.9	ST058180	98.0	ST034104	89.8		ST021579	88.1	ST024887	98.0
ST058165	122.3	ST033819	93.7	ST059366	98.8		ST059321	86.3	ST027810	105.1
ST058147	92.3	ST059337	86.3	ST015543	108.6		ST059324	97.2	ST039605	91.0
ST025049	92.9	ST058184	112.7	ST048254	108.9		ST058564	100.9	ST055621	98.8
ST058194	124.6	ST069174	100.4	ST058231	100.6		ST058566	101.2	ST032328	88.9
ST051996	94.0	ST058973	93.2	ST058222	103.5		ST058573	93.7	ST056036	93.1
ST059990	93.3	ST059394	90.5	**ST056797**	**58.7**	***hit***	ST058576	96.7	ST040129	98.0
ST058179	100.4	ST058528	93.6	ST058585	99.8		ST058580	100.9	ST059382	97.9
ST058224	90.1	ST015537	106.8	ST059395	94.6		ST058579	102.0	ST059404	104.6
ST059354	101.6	ST058219	116.7	ST059368	94.0		ST058531	97.5	ST040130	107.1
ST058139	103.8	ST059339	85.8	ST058587	98.0		ST058988	88.9	ST010566	103.2
ST058163	110.3	ST065517	113.8	ST058578	106.1		ST059383	97.6	ST019107	97.9
ST059358	88.6	ST068835	107.5	ST059199	94.8		ST058577	96.7	ST019282	96.0
ST058211	117.0	ST058220	121.7	ST058770	92.0		ST059363	101.7	ST050880	78.4
ST058234	91.5	ST059338	85.6	ST056653	92.3		ST059370	113.6	ST058518	99.9
ST058227	102.2	ST059335	86.6	ST058570	111.4		ST015553	105.9	ST059373	105.6
ST058146	130.3	ST059342	89.1	ST058575	83.6		ST058183	104.1	ST059577	79.3
ST058202	120.7	ST059341	100.0	ST015270	107.1		ST030896	93.9	ST019279	87.6
ST059359	89.6	ST011312	94.2	ST058586	93.7		ST018996	92.5	ST059376	94.5
ST058228	101.3	ST028686	99.3	ST058589	98.0		ST069173	96.7	ST058236	112.7
ST058131	114.9	ST059385	87.4	ST056814	83.6		ST034189	87.7	ST058756	87.2
ST058226	102.1	ST011322	100.5	ST020169	93.3		ST027339	88.4	ST058742	109.4
ST047010	87.7	ST027368	108.8	ST058733	98.4		ST058557	89.3	ST059399	95.3
ST058221	100.0	ST055628	110.6	ST058555	110.5		ST058558	90.0	ST058208	113.9
ST058199	110.4	ST059388	104.7	ST058595	90.2		ST058556	91.8	ST059402	92.4
ST058933	115.1	ST058235	106.4	ST058588	94.7		ST031846	94.8	ST059364	100.6
ST011310	91.2	ST015397	102.8	ST058594	96.0		ST059797	96.4	ST059365	106.4
ST057040	86.4	ST059398	95.7	ST058591	106.3		ST058523	95.1	ST058215	115.1
ST058154	98.4	ST069049	97.9	ST058200	110.2		ST058178	146.8	ST037715	85.3
ST058135	131.6	ST059387	102.4	ST041683	106.5		ST059405	116.8	ST058192	110.5
ST043600	89.8	ST058240	102.3	ST058592	93.3		ST058188	98.3	ST019007	94.8
ST058210	112.8	ST030578	93.0	ST070054	91.6		ST027648	91.1	ST059250	91.3
ST026188	104.3	ST059559	89.2	ST059576	85.6		ST065913	99.9	ST059225	96.0
ST059403	98.9	ST024246	103.2	ST066128	101.1		ST057309	93.5	ST058994	98.6

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Supplementary Table S1. ***Continued.***

ST040648	95.2		ST033078	84.8	ST057564	93.0	ST059282	89.3	ST058794	95.6
ST015520	110.6		ST058218	113.7	ST014665	95.5	ST039596	84.8	ST026420	99.0
ST019044	86.1		ST059798	99.9	ST040661	95.8	ST033728	89.2	ST044567	94.0
ST058145	121.2		ST058232	96.4	ST059410	90.6	ST059566	83.4	ST027647	96.4
ST019028	97.8		ST058225	98.6	ST059573	109.7	ST059693	98.8	ST059187	87.3
ST019040	93.2		ST059712	89.1	ST060016	98.2	ST034070	86.8	ST059549	89.1
ST070098	93.3		ST060004	96.5	ST049042	98.0	ST028860	96.5	ST059679	88.2
ST058825	90.8		ST044561	88.7	ST059671	90.3	ST020704	96.9	ST060011	101.3
ST059400	91.2		ST058991	96.1	ST059409	92.5	ST059248	99.2	ST066621	98.5
ST059371	106.3		ST009339	95.5	ST039707	99.1	ST067014	116.6	ST027650	96.7
ST059705	90.5		ST059020	115.8	ST049052	74.7	ST027416	105.1	ST051733	91.8
ST006235	93.5		ST009922	98.3	ST049119	88.5	ST059720	95.1	ST059669	106.8
ST031848	97.2		ST070051	91.5	ST066219	115.2	ST059539	94.5	ST066630	96.9
ST059401	86.8		ST058977	92.7	ST056740	93.3	ST058737	109.7	ST059265	107.0
ST033438	**54.9**	***hit***	ST059799	99.4	ST059005	89.1	ST059553	106.3	ST059565	90.4
ST027661	102.9		ST059191	96.8	ST059574	88.1	ST050875	99.6	ST059280	86.6
ST060018	101.0		ST059805	97.8	ST059672	82.2	ST056127	95.9	ST059545	86.7
ST059697	84.6		ST060033	98.9	ST059498	90.9	ST066220	122.8	ST059493	96.8
ST019001	92.7		ST059804	97.2	ST024819	99.4	ST058688	100.9	ST056810	101.2
ST059374	98.2		ST059806	99.7	ST034218	87.7	ST045060	92.1	ST058759	99.9
ST058997	93.6		ST058812	108.7	ST034217	82.1	ST028857	98.7	ST016933	104.3
ST041113	96.3		ST040810	85.7	ST065980	102.2	ST045115	89.2	ST059270	84.6
ST059803	105.6		ST068867	113.7	ST059698	91.6	ST009804	101.9	ST059212	110.3
ST030919	93.1		ST012362	94.8	ST058752	93.0	ST058704	93.0	ST019664	85.9
ST026169	98.7		ST059575	82.6	ST059538	105.1	ST060012	114.9	ST059558	87.6
ST020707	104.6		ST059800	103.0	ST059991	102.1	ST054336	98.5	ST007270	96.2
ST059808	101.1		ST059408	92.7	ST059670	106.4	ST059992	99.3	ST060014	99.8
ST059406	97.2		ST058982	110.7	ST060006	95.7	ST060009	103.5	ST066627	103.1
ST027566	109.4		ST056728	95.1	ST067017	93.3	ST011968	95.0	ST059262	101.7
ST029608	86.9		ST049127	84.3	ST014593	109.8	ST059689	90.4	ST053182	91.5
ST058197	110.1		ST068868	100.9	ST059003	90.5	ST067080	106.1	ST059259	97.7
ST058229	106.5		ST069978	92.9	ST059718	84.7	ST058866	89.9	ST059691	100.6
ST058237	104.0		ST026424	93.9	ST059673	86.3	ST033057	91.3	ST059694	100.6
ST027011	94.3		ST070052	94.4	ST045738	85.8	ST059251	84.2	ST059695	105.8
ST059380	115.8		ST058930	93.6	ST059195	84.4	ST059564	103.8	ST024131	98.5
ST059379	105.9		ST044566	85.5	ST023393	92.6	ST060008	89.7	ST059272	93.2
ST034062	90.6		ST066635	101.3	ST059665	95.5	ST057310	96.1	ST059218	102.9
ST034063	97.5		ST068871	98.4	ST059278	87.7	ST047172	103.9	ST059678	106.6
ST056811	99.4		ST059271	85.9	ST066637	119.1	ST059711	83.9	ST058703	102.1
ST058207	114.8		ST025481	93.9	ST066625	115.7	ST051357	87.8	ST058702	111.9
ST018989	92.2		ST059572	104.2	ST059719	89.3	ST059484	97.1	ST059686	107.6
ST058213	123.9		ST058955	89.7	ST059724	98.6	ST059486	110.1	ST037711	87.4
ST012135	91.0		ST068875	102.9	ST059264	96.9	ST027649	97.9	ST041925	83.3
ST026203	106.8		ST058995	114.0	ST024806	89.2	ST055076	101.0	ST059258	87.1
ST058239	101.1		ST009316	105.0	ST059536	102.5	ST059567	82.6	ST024809	88.5
ST059710	87.9		ST059506	88.9	ST059193	93.8	ST059988	95.4	ST059677	98.6
ST039594	84.5		ST059532	89.5	ST059708	114.0	ST059509	93.1	ST059999	98.8
ST055882	100.4		ST058699	103.2	ST059548	87.7	ST059279	87.6	ST059989	94.5
ST057567	94.5		ST070001	97.8	ST051739	93.6	ST066521	105.3	ST059535	97.5
ST059571	92.6		ST037776	82.2	ST014592	102.8	ST059185	86.2	ST058922	86.3
ST059497	93.9		ST059192	112.1	ST059563	93.0	ST059184	88.5	ST066228	98.4
ST040638	93.0		ST059489	96.5	ST059267	88.5	ST059675	97.3	ST059274	97.2
ST029446	115.4		ST059485	104.3	ST059228	99.2	ST059194	88.7	ST059681	85.9
ST044643	92.9		ST058754	90.9	ST059823	91.7	ST057290	97.1	ST059178	90.3
ST059562	86.3		ST059285	112.9	ST027769	103.7	ST059230	102.0	ST058683	101.5

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Supplementary Table S1. ***Continued.***

ST059680	83.6	ST059227	98.8	ST059477	101.9	ST066622	95.2	ST040654	94.4
ST060017	92.2	ST067054	97.7	ST059701	88.5	ST034149	86.4	ST040710	100.7
ST059966	97.7	ST059491	95.4	ST066148	100.2	ST059527	116.8	ST027610	99.8
ST037579	94.8	ST059276	90.4	ST059811	116.0	ST027790	93.5	ST059025	89.7
ST059982	93.2	ST058993	93.2	ST059253	94.6	ST066245	94.0	ST059985	98.4
ST059480	90.0	ST014539	111.5	ST059983	100.2	ST059288	88.7	ST031662	96.8
ST059533	99.0	ST026418	102.0	ST026419	101.7	ST059231	94.3	ST059243	93.6
ST059980	96.0	ST059546	89.6	ST059996	91.0	ST066620	91.2	ST057286	104.9
ST059275	103.7	ST051006	90.3	ST058948	99.6	ST067016	101.1	ST059474	95.0
ST067019	96.9	ST059674	84.9	ST066619	93.2	ST040647	96.0	ST034175	81.7
ST059494	93.8	ST040663	100.1	ST059266	94.5	ST066207	111.4	ST019600	98.3
ST059692	99.9	ST058746	104.8	ST059263	85.5	ST058706	92.9	ST034152	93.4
ST059696	90.3	ST058824	96.6	ST059226	99.7	ST060010	93.5	ST040713	89.9
ST039323	99.4	ST058705	95.3	ST059495	101.4	ST057301	93.7	ST057297	103.0
ST050852	100.3	ST059268	85.5	ST027636	91.5	ST060013	95.5	ST059483	94.0
ST059505	94.2	ST059688	90.5	ST059277	84.2	ST057300	109.9	ST051008	100.8
ST066618	97.1	ST066617	112.6	ST026255	100.9	ST059490	91.5	ST059525	88.5
ST045032	106.6	ST059496	110.8	ST059557	89.4	ST059687	114.2	ST066631	96.1
ST059998	92.0	ST059189	89.4	ST057295	96.1	ST066629	99.8	ST040054	100.8
ST066636	110.1	ST014583	99.5	ST059685	97.5	ST039661	86.8	ST058989	88.4
ST059555	83.9	ST059684	91.7	ST066623	104.6	ST059518	95.3	ST039684	92.0
ST059223	89.9	ST059977	108.7	ST057279	108.3	ST059819	100.9	ST053447	89.4
ST059568	93.6	ST055652	90.0	ST040147	104.4	ST057299	101.5	ST009247	101.9
ST059721	104.9	ST059188	94.9	ST040688	99.6	ST034151	94.6	ST051041	100.4
ST059690	89.5	ST059196	90.5	ST069962	95.4	ST059723	108.5	ST059676	93.4
ST059570	91.3	ST044583	90.7	ST060003	118.8	ST059528	90.8	ST057245	104.5
ST059517	95.4	ST016587	98.6	ST060005	95.0	ST059521	90.5	ST029373	93.5
ST066522	111.0	ST059975	97.4	ST059995	117.9	ST059987	109.6	ST031051	101.7
ST066149	114.0	ST059492	87.7	ST059974	89.4	ST059706	98.5	ST059006	88.4
ST059561	82.4	ST059284	95.8	ST059979	94.9	ST059233	90.7	ST040050	94.7
ST025612	90.2	ST051004	87.3	ST059551	88.3	ST019179	97.1	ST040707	94.2
ST059526	96.3	ST019612	99.6	ST059182	111.3	ST059965	90.6	ST054849	98.2
ST034174	90.5	ST030579	93.8	ST068931	90.9	ST058990	82.4	ST059479	93.0
ST059256	85.7	ST058686	106.6	ST067018	96.5	ST037335	89.4	ST059972	87.8
ST039595	82.7	ST053449	77.5	ST059482	90.6	ST047506	104.1	ST059249	93.0
ST040897	89.2	ST039696	89.7	ST059179	96.3	ST066626	116.4	ST055344	90.9
ST040631	85.7	ST059994	111.1	ST059481	90.9	ST060001	100.8	ST065961	103.2
ST059257	93.0	ST065524	97.2	ST059997	97.7	ST058701	102.0	ST027881	94.1
ST059511	98.4	ST014531	101.7	ST007535	99.2	ST027859	96.1	ST040650	106.9
ST059186	85.8	ST059812	95.4	ST058120	107.0	ST040090	88.8	ST026257	96.0
ST058684	94.7	ST057284	99.0	ST040627	107.0	ST040580	89.9	ST019628	99.4
ST059810	104.9	ST056193	115.1	ST059813	101.1	ST040694	104.2	ST040105	97.0
ST059255	110.9	ST059973	90.7	ST059246	109.7	ST040660	104.7	ST040808	82.4
ST040681	96.5	ST065979	107.0	ST057304	94.5	ST014514	95.9	ST040626	104.3
ST060000	101.4	ST059814	97.3	ST020706	98.3	ST024801	95.1	ST030117	105.5
ST057308	96.7	ST008396	95.6	ST057733	107.4	ST040336	99.0	ST016586	100.0
ST059478	114.9	ST040033	101.2	ST040016	106.7	ST023411	97.7	ST058403	91.8
ST040007	103.8	ST040657	101.4	ST060002	99.8	ST053451	111.7	ST040568	96.1
ST014601	98.6	ST026444	98.4	ST030577	94.1	ST029046	106.5	ST040807	106.1
ST058388	96.0	ST039653	81.5	ST029617	98.3	ST008380	93.6	ST040013	87.7
ST029227	91.3	ST034150	90.3	ST018738	94.3	ST027798	98.3	ST034069	91.7
ST057285	93.1	ST040651	97.1	ST001113	99.4	ST039602	89.4	ST031178	95.6
ST039281	91.5	ST040659	100.1	ST039692	83.0	ST039601	91.4	ST040655	98.4
ST059816	103.5	ST059709	91.7	ST059578	88.8	ST040006	98.0	ST040809	92.8
ST059530	95.3	ST059984	104.3	ST038015	83.0	ST040011	99.4	ST001350	96.3

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Supplementary Table S1. ***Continued.***

ST057296	96.7	ST057288	113.2	ST008377	105.4	ST031179	93.1	ST055881	103.8
ST024955	102.5	ST040624	94.7	ST019634	92.2	ST040738	89.8	ST040262	88.2
ST050961	81.3	ST059252	88.3	ST039693	87.4	ST057402	105.6	ST027802	102.8
ST040760	93.6	ST039683	88.3	ST039695	92.9	ST065904	94.5	ST025551	93.3
ST059234	97.4	ST027932	103.5	ST031180	95.3	ST059520	89.5	ST040677	97.6
ST059821	94.8	ST049051	85.0	ST059180	94.5	ST059981	93.3	ST040776	92.1
ST059181	97.3	ST059018	103.9	ST058687	101.4	ST027800	100.7	ST056190	102.1
ST059683	85.1	ST057302	92.0	ST057283	99.2	ST057076	100.0	ST069285	100.2
ST039685	101.5	ST057282	95.7	ST051737	98.2	ST026258	97.8	ST040610	90.0
ST005150	103.2	ST059815	98.8	ST057281	93.7	ST017364	98.2	ST040662	94.1
ST059534	92.7	ST059514	102.1	ST051003	93.4	ST028456	96.0	ST059971	92.2
ST057298	100.4	ST059476	95.4	ST059235	99.4	ST039582	99.8	ST066232	98.4
ST058395	84.8	ST069841	96.7	ST065797	94.4	ST040607	97.8	ST059969	109.0
ST024293	96.5	ST049568	101.2	ST039691	84.6	ST026467	98.0	ST054908	98.0
ST029216	92.0	ST040818	92.8	ST040069	98.4	ST014579	96.7	ST025116	94.3
ST059993	104.7	ST059348	86.1	ST026417	100.6	ST017369	96.5	ST017367	100.9
ST059822	94.4	ST059970	110.1	ST057287	107.1	ST005149	98.7	ST027794	96.4
ST019200	90.4	ST058996	91.1	ST040113	92.2	ST009312	99.8	ST031176	104.1
ST027845	93.6	ST040248	91.5	ST028827	106.7	ST066520	99.6	ST040609	96.4
ST058987	89.1	ST059221	101.1	ST057289	94.4	ST059512	115.6	ST029615	93.3
ST051051	92.3	ST008394	93.9	ST026995	94.4	ST039597	75.3	ST065868	91.6
ST039820	94.6	ST039706	89.3	ST059702	89.6	ST027937	110.4	ST038877	85.5
ST059809	101.0	ST051002	83.0	ST040652	95.3	ST025107	93.0	ST018704	108.8
ST059254	97.5	ST059976	103.4	ST040064	109.9	ST017371	99.2	ST040263	100.2
ST017365	99.0	ST014575	100.9	ST031267	104.2	ST017363	99.0	ST016439	94.3
ST051175	83.9	ST053889	110.7	ST040761	97.0	ST016159	97.1	ST040625	101.2
ST059818	103.3	ST034153	98.6	ST039936	98.6	ST053095	86.3	ST040338	90.2
ST059820	110.9	ST040612	97.6	ST059244	97.6	ST057307	92.2	ST025111	99.6
ST053450	101.6	ST059967	102.5	ST058700	101.5	ST040623	97.5	ST016156	101.8
ST040608	111.7	ST059507	92.3	ST007021	97.1	ST066230	99.4	ST019098	95.1
ST059978	113.8	ST014495	96.3	ST066146	109.2	ST057557	93.3	ST040454	112.9
ST007537	100.7	ST012555	92.6	ST025105	92.1				
ST012552	106.6	ST026468	102.9	ST039980	106.7				
ST040722	97.8	ST025115	91.7	ST020683	94.4				
ST031682	?????	ST035363	94.4	ST025591	102.0				
ST040682	97.0	ST026252	108.1	ST012454	95.9				
ST056192	103.7	ST026261	98.9	ST027895	100.9				
ST016158	102.8	ST027796	91.2	ST010162	108.9				
ST039697	94.7	ST001292	94.8	ST040633	91.1				
ST025110	100.6	ST006389	81.5	ST039987	104.2				
ST017366	96.8	ST019092	92.2	ST055264	87.0				
ST040552	91.2	ST055135	100.5	ST058108	100.8				
ST019093	93.6	ST069314	96.7	ST016624	102.6				
ST008378	91.8	ST009330	94.1	ST025552	99.2				
ST029018	101.3	ST039612	89.2	ST040903	91.5				
ST013863	94.0	ST025112	109.0	ST012500	101.4				
ST012513	101.4	ST040586	99.7	ST055332	93.4				
ST020705	96.9	ST040630	93.0	ST040370	99.1				
ST014528	101.8	ST026551	93.1	ST040023	96.7				
ST056191	98.1	ST039711	95.1	ST008954	95.5				
ST025109	98.3	ST039611	99.5	ST026423	97.2				
ST037805	83.2	ST039616	82.1	ST040340	93.9				
ST023394	98.5	ST033441	93.7	ST055620	95.0				
ST057278	96.7	ST025113	96.7	ST040567	83.4				
ST040343	82.5	ST026464	105.8	ST040333	110.1				

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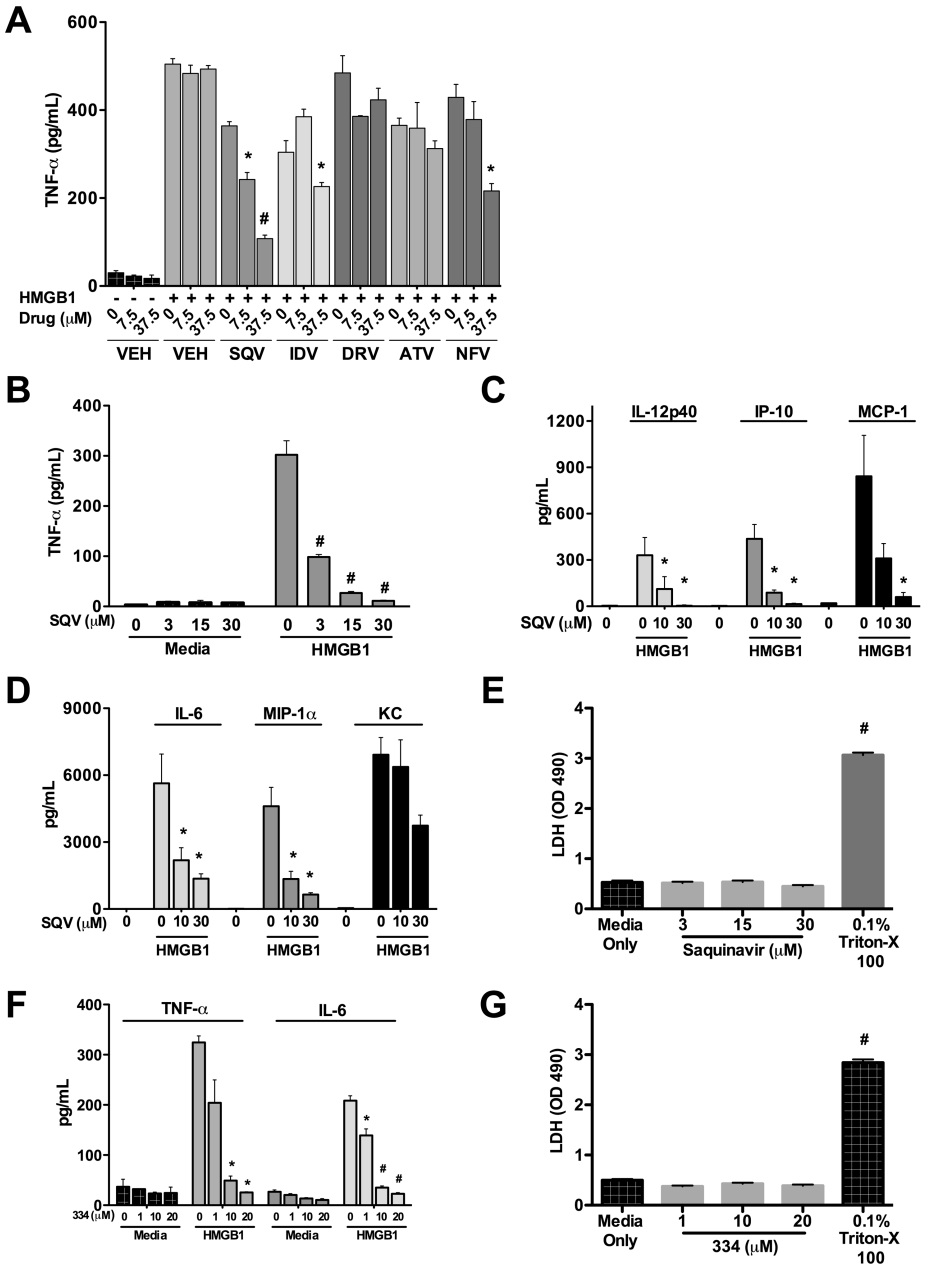
Supplemental Table S1. ***Continued.***

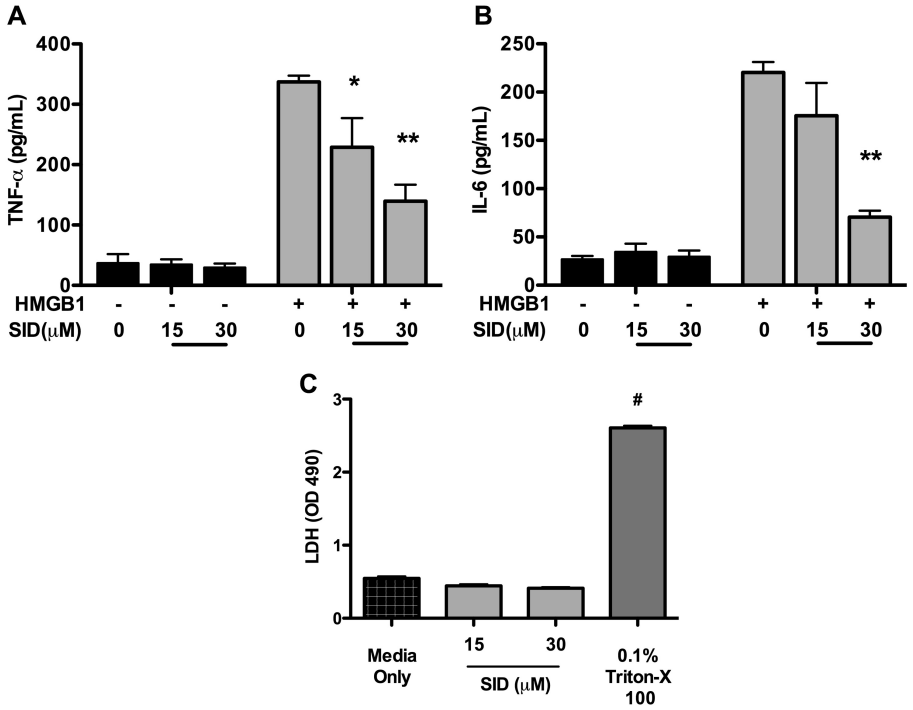
ST040789	99.7	ST030885	95.5	ST055632	90.2
ST027849	90.2	ST056045	98.2	ST009331	91.7
ST040656	93.8	ST040736	104.2	ST040721	102.5
ST019190	98.2	ST040533	109.5	ST024144	97.7
ST016157	108.7	ST054675	97.3	ST040635	88.1
ST014591	101.1	ST040737	103.8	ST025236	93.5
ST007403	99.3	ST028624	94.7	ST040759	90.1
ST040247	100.3	ST039620	86.6	ST014586	94.7
ST040603	104.0	ST019598	96.0	ST058652	98.4
ST035442	87.2	ST035447	80.1		
ST054635	98.5	ST037059	85.0		
ST016585	97.4	ST057735	96.1		
ST040335	106.6	ST024388	91.9		
ST040330	94.1	ST035450	82.8		
ST014519	97.9	ST054799	93.8		
ST014590	99.5	ST027793	92.2		
ST016154	102.8	ST011910	104.2		
ST040379	102.3	ST021061	89.5		
ST026259	96.1	ST026260	99.9		
ST025106	94.3	ST040775	88.8		
ST012315	95.6	ST040249	96.2		
ST027558	106.8	ST040720	93.6		

Supplementary Table S2. Effects of Saquinavir(SQV) and ST033438(334), on the activity of 58 proteases.

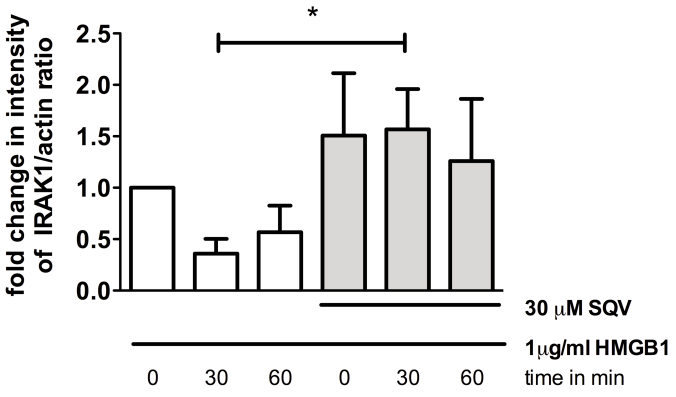
Protease Name	SQV (25 μM)	SQV (5 μM)	334 (20 μM)	334 (1 μM)	**Positive**
20S Proteasome	46.29	0.15	18.16	6.68	97.81
ACE	5.92	9.93	12.42	2.79	90.62
ACE2	-1.44	5.96	3.06	-3.82	94.10
ADAM10	16.71	11.86	**79.66**	8.48	107.98
ADAM17	-20.38	-8.75	0.05	-1.89	85.03
Airway trypsin-like protease/HAT	-7.80	-0.32	-4.17	0.39	N/A
Caspase-1	40.41	27.25	30.66	30.02	99.30
Caspase-2	15.89	20.49	18.55	4.20	78.97
Caspase-3	2.75	2.52	-4.58	-0.84	99.81
Caspase-4	19.83	6.68	24.00	0.87	70.56
Caspase-5	-75.13	-19.84	-27.46	-7.84	104.26
Caspase-6	6.44	29.79	19.77	16.62	75.11
Caspase-7	2.41	0.14	0.91	3.05	100.00
Caspase-8	13.24	13.83	11.18	7.49	99.13
Caspase-9	-1.56	-1.95	-9.75	-5.83	90.57
Caspase-10	-130.63	-34.92	-61.18	-14.02	98.30
Cathepsin B	5.93	4.09	8.29	3.81	99.61
Cathepsin E	**63.32**	35.36	3.41	8.56	107.32
Cathepsin G	-391.16	-78.02	10.54	2.44	83.36
Cathepsin H	-27.44	10.06	9.36	10.88	83.85
Cathepsin K	16.46	4.62	19.95	-5.11	99.01
Cathepsin L	20.02	21.02	29.23	-2.13	96.44
Cathepsin S	0.86	-0.36	-5.96	3.87	86.35
Cathepsin V	**98.89**	**92.57**	**84.12**	**88.81**	95.91
Cathepsin X/Z/P	-5.05	15.64	30.38	17.55	95.97
Complement C1r Subcomponent	-49.43	-30.97	1.37	-0.74	N/A
Complement C1s Subcomponent	-116.58	-29.98	0.62	7.33	N/A
Complement Component C2	36.86	23.99	9.65	-1.39	N/A
Complement MASP3 Catalytic Domain	-81.98	10.45	-4.74	9.31	N/A
DPP3	22.24	9.27	8.68	0.72	98.64
DPP4	-31.46	-28.10	-10.59	-12.78	99.32
DPP7	-0.47	2.72	0.38	-6.65	66.22
DPP8	8.15	3.81	16.68	2.31	98.09
DPP9	10.44	19.91	16.16	8.86	98.20
Factor Xa	-153.44	-31.01	-31.08	6.68	119.08
Factor XIIa	-13.11	-9.62	-1.49	-0.23	102.82
FAP	17.47	-2.35	12.88	1.40	86.78
HIV-1	**91.20**	**85.68**	47.05	-21.62	94.44
KLK-1	5.44	10.66	4.52	3.05	72.36
KLK-2	7.36	12.80	7.88	7.22	96.35
KLK-5	-206.31	-5.19	45.09	11.15	69.62
Legumain	**55.33**	-0.57	6.17	-19.00	97.13
Marapsin/Pancreasin	21.19	7.25	13.31	-7.06	N/A
Matriptase/ST14 Catalytic Domain	10.67	12.00	12.25	9.30	N/A
MMP1	1.20	4.55	3.30	-1.79	99.89
Neprilysin	-14.81	6.61	-29.21	-14.43	97.32
Neprilysin 2	-20.48	11.95	10.51	32.99	93.20
Neutrophil Elastase	0.42	2.78	-0.43	0.40	99.88
Pepsin	-3.90	-8.63	-5.98	-1.56	100.16
Prolyl oligopeptidase/PreP	14.63	9.72	2.34	-4.43	99.09
Proteinase 3	5.80	15.81	35.39	19.91	72.42
Renin	18.14	14.82	4.23	4.01	100.1
Thrombin	10.78	8.71	3.38	-4.97	99.64
Tissue plasminogen activator	3.11	11.26	-0.95	-2.06	100.73
Trypsin	-252.27	-125.06	-104.21	1.27	99.86
Tryptase e /BSSP4	-22.78	-22.65	-54.87	-0.89	N/A
Tryptase,ε II	-3.14	3.84	0.07	5.00	94.29
u-Plasminogen activator/Urokinase	10.05	-3.74	-1.79	-8.13	99.32



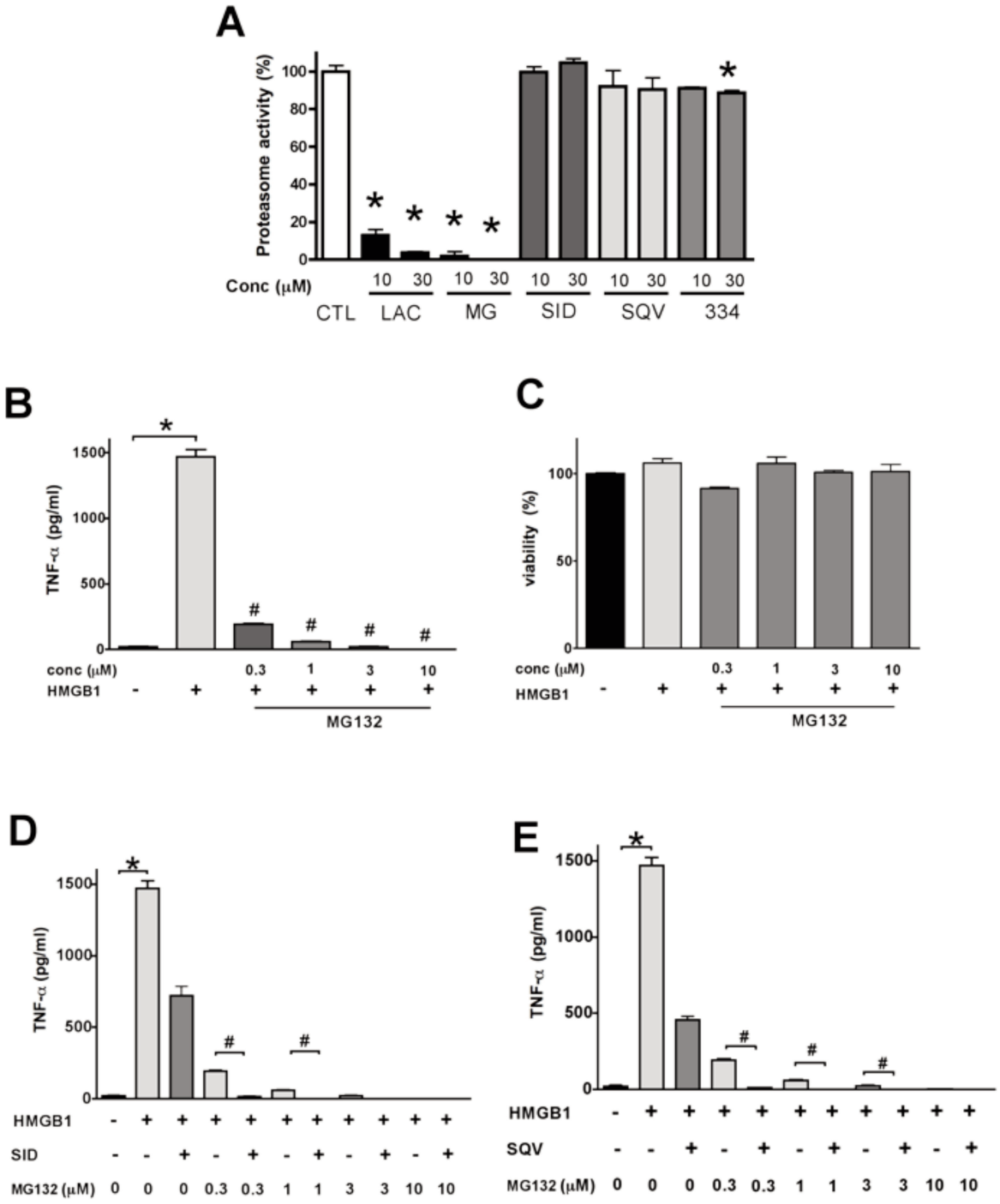
Supplementary Figure S1. Protease inhibitor screen in mouse peritoneal macrophages identifies saquinavir (SQV) and ST033438 (334) as potent inhibitors of HMGB1-induced TNF-α production. (A) The effect of various first generation protease inhibitors on HMGB1-induced TNF-α production in mouse peritoneal macrophages was assessed by ELISA (VEH, vehicle; SQV, saquinavir; IDV, Indinavir; DRV, Darunavir; LPV, Lopinavir; ATV, Atazanavir; NFV, Nelfinavir). Cells were pre-treated for 1 h with drug followed by 18 h of HMGB1 stimulation. (B) Dose-dependent effect of SQV on HMGB1-induced TNF-α production in mouse peritoneal macrophages. (C, D) Dose-dependent effect of SQV on HMGB1-induced IL12p40, IP10, MCP-1, IL6, MIP-1α, and KC production in mouse peritoneal macrophages measured by luminex. (E) Cytotoxicity of SQV was determined by measuring LDH release by mouse peritoneal macrophages after 18 h treatment. (F) Effect of STO33438 (334) on HMGB1-induced TNF-α and IL6 release in mouse peritoneal macrophages. (G) Cytotoxicity of 334 was determined by measuring LDH release by mouse peritoneal macrophages after 18 h treatment.



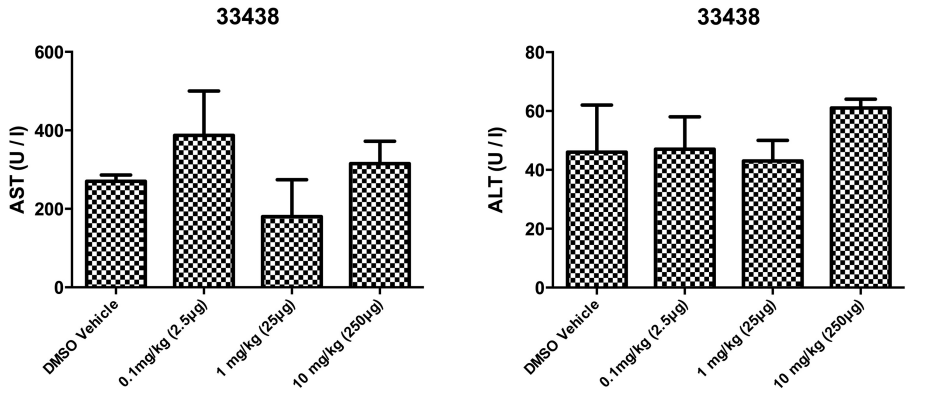
Supplementary Figure S2. The cathepsin inhibitor SID is non-toxic and inhibits HMGB1 induced TNF-α and IL-6 in mouse peritoneal macrophages. (A) Dose dependent effect of SID on HMGB1-induced TNF-α production in mouse peritoneal macrophages and (B) dose dependent effect of SID on HMGB1-induced IL-6 production in mouse peritoneal macrophages assessed by ELISA after 1 h of drug pre-treatment followed by 18 h HMGB1 stimulation (C) Cytotoxicity of SID was determined by measuring LDH release in mouse peritoneal macrophages after 18 h treatment.



Supplementary Figure S3. Quantitated effect of SQV on HMGB1-induced IRAK-1 protein expression. This presents a quantitation of the representative Western blot shown in Fig 3G and includes 4 independent experiments. Band intensities were measured using ImageJ (*imagej.nih.gov/ij/* a Java-based image processing program) (*$P < 0.05$).



Supplementary Figure S4. The mode of action of Saquinavir (SQV) and ST033438 (334) does not rely on proteasome activity. (A) The effect of SQVr, 334 and the cathepsin V inhibitor SID on proteasome activity was tested in a 20S proteasome assay (the catalytic core of the 26S proteasome complex) at 10 and 30 μM. The proteasome inhibitor lactacystin (LAC) and MG132 (MG, N(benzyloxycarbonyl) leucinylleucinylleucinal, Z-Leu-Leu-Leu-al) inhibited proteasome activity by more than 80%, while none of the other compounds resulted in significant changes in proteasome activity at 10 μM, and only 334 caused a significant decrease at 30 μM. (B) The proteasome inhibitor MG132 dose-dependently blocked the TNF-α production induced by HMGB1 (5 μg/ml, 18 hours) in human monocyte-derived macrophages (C) without interfering with cellular viability as assessed by the MTT viability assay. (D) The cathepsin V inhibitor SID and (E) the HIV protease inhibitor SQV potentiate the inhibition by MG132 on HMGB1-induced TNF-α production in human monocyte-derived macrophages (Data presented as mean+SEM, * $p<0.05$, # $p<0.05$ compared to respective groups).



Supplementary Figure S5. Assessment of *in vivo* toxicity of compound 334 Male BALB/c were treated with compound 334(38) at a dose of 0.1, 1.0, and 10 mg/kg or vehicle alone (i.p. in 200µl PBS-DMSO) per day for 3 d followed by measuring plasma ALT and AST levels. Based on these findings, we chose a dose of 5mg/kg for our CLP model presented in Figure 4B.

Supplementary Figure S6. Cathepsin V expression in freshly isolated PBMC Western blot analysis of human PBMC probed against cathepsin V. Expression of cathepsin V in human blood was confirmed using two different antibodies against cathepsin V.