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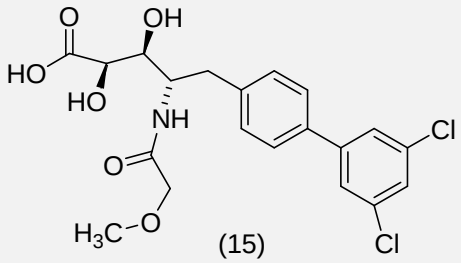
Chicago Discovery Solutions

#CC0651 and related compounds:

Human Cdc34 ubiquitin-conjugating enzyme Allosteric Inhibitor Library.

For more than a decade, researchers have been developing ways to target the ubiquitin-proteasome pathway in cancer. However, only one marketed therapy actually acts on this pathway, which is the proteasome inhibitor Velcade bortezomib that is marketed by Takeda Pharmaceutical Co. Ltd.'s Millennium Pharmaceuticals to treat multiple myeloma and mantle cell lymphoma. Kotz, "Celgene skips SKP2," SciBX 4(28) 2011. Velcade 's broad side-effect profile has prompted a search for better alternatives.

In the ubiquitin-proteasome system (UPS), E2 enzymes mediate the conjugation of ubiquitin to substrates and thereby control protein stability and interactions. The E2 enzyme hCdc34 catalyzes the ubiquitination of hundreds of proteins in conjunction with the cullin-RING (CRL) superfamily of E3 enzymes. In a recent *Cell* article (2011, 145 (7) 1075-87), a new class of molecules, CC0651 and its derivatives, have been shown to modulate the UPS system specifically interacting with the E2 enzyme hCdc34. These compounds had activity in human cells preventing the proliferation of both prostate and colorectal cancer cell lines -- all without decreasing the p27 levels. These are a good class of molecules for the continual study of cancer cells and a great addition for any drug discovery program. CC0651 and various derivatives/intermediates is one of Chicago Discovery Solutions' newest additions to the catalogue.



(15)

CC0651

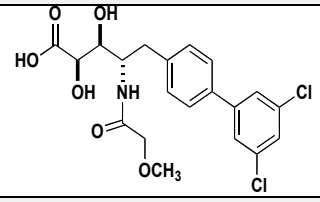
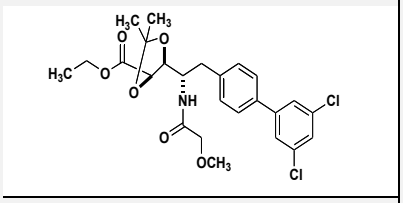
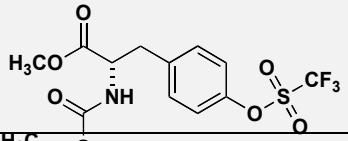
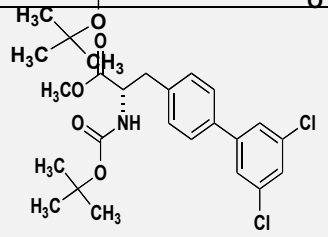
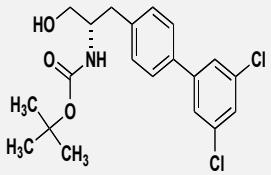
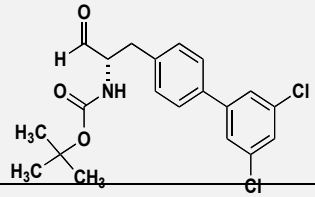
Structure determination revealed that CC0651 inserts into a cryptic binding pocket on hCdc34 distant from the catalytic site, causing subtle but wholesale displacement of E2 secondary structural elements. CC0651 does not affect hCdc34 interactions with E1 or E3 enzymes or the formation of the ubiquitin thioester but instead interferes with the discharge of ubiquitin to acceptor lysine residues. E2 enzymes are thus susceptible to noncatalytic site inhibition and may represent a viable class of drug target in the UPS (Cell. 2011 Jun 24;145(7):1075-87).

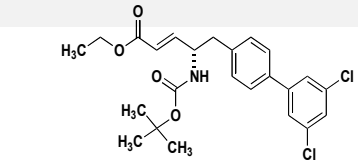
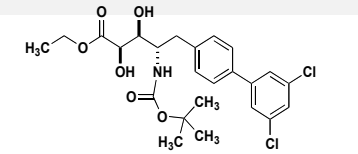
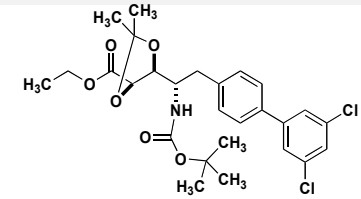
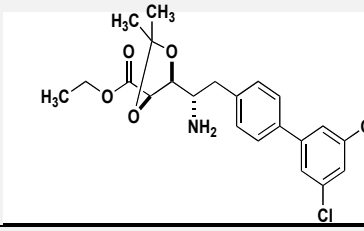
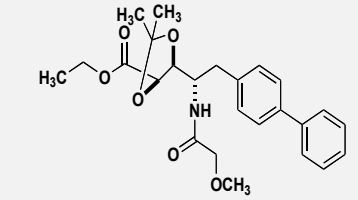
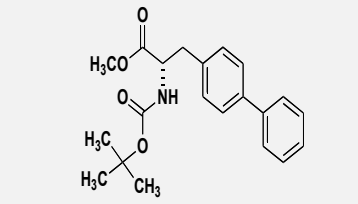
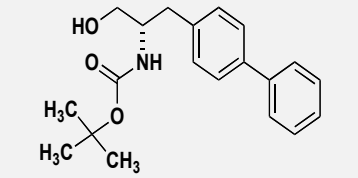
We have designed and synthesized several molecules using computational approaches that will provide novel, biologically active, drug-like chemicals. We are looking for suitable partner to undertake biological activity testing. The Chemistry already developed by us will help us to synthesize previously untapped molecules that may aid in the search for innovative and selective inhibitors. Here

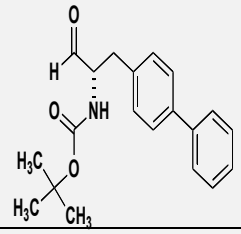
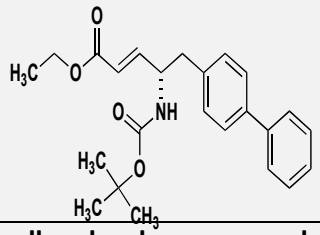
again, we have already established the Chemistry required to make lead molecules. Having established the Chemistry (in-house), we are in position to quickly exploit the chemical space around active molecules so carefully designed by us.

We are very adept at developing novel chemistry or synthetic routes and own a noteworthy portfolio of chemistry and processes: our forte has been efficient project management of technology transfer. We have a team with prior experience of innovating new drug molecules that have reached clinical trials. We have been working to make Chemistry more amenable to analogizing and optimizing that is expected to result in improved activity. We already have analogues of CC 0651 which are unique which are being tested.

Following Analogues and intermediates are available:

	CDS-1080; CC0651	**1319207-44-7**	**CC0651; (2R,3S,4S)-5-[3',5'-dichlorobiphenyl-4-yl)-2,3-dihydroxy-4-(2-methoxyacetamido)petanoic acid**	**C20H21Cl2NO6**	
	CDS-1081	**no CAS#**	**(5R,4S)-4-[1S-methoxyethanoyl amino)-2-[4-[3,5-chloroanylphenyl]phenyl]ethane-5-ethyl ester-2,2-dimethyl-1,3-dioxolane**	**C25H29Cl2NO6**	
	CDS-1082	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(4-phenyltriflate)-propanoic methyl ester**	**C16H20F3NO7S**	
	CDS-1083	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(4-[3,5-dichlorophenyl]phenyl)-propanoic methyl ester**	**C21H23Cl2NO4**	
	CDS-1084	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(4-[3,5-dichlorophenyl]phenyl)-propanol**	**C20H23Cl2NO3**	
	CDS-1085	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(4-[3,5-dichlorophenyl]phenyl)-propanal**	**C20H21Cl2NO3**	

	CDS-1086	**no CAS#**	**(S)-4-(t-Butoxycarbonylamino)-5-[4-[3,5-dichlorophenyl]phenyl)-2-pentenoic acid ethyl ester**	**C24H27Cl2NO4**	
	CDS-1087	**no CAS#**	**(2R,3S,4S)-2,3-bis(oxidanyl)-4-(t-butoxycarbonylamino)-5-[4-[3,5-dichloropheny]phenyl)-2-pentanoic acid ethyl ester**	**C24H29Cl2NO6**	
	CDS-1088	**no CAS#**		**C27H33Cl2NO6**	
	CDS-1089	**no CAS#**		**C22H25Cl2NO4**	
	CDS-1090	**no CAS#**		**C25H31NO6**	
	CDS-1091	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(biphenyl-4-yl)-propanoic methyl ester**	**C21H25NO4**	
	CDS-1092	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(biphenyl-4-yl)-propan-1-ol**	**C20H25NO3**	

	CDS-1093	**no CAS#**	**(S)-2-(t-Butoxycarbonylamino)-3-(biphenyl-4-yl)-propanal**	**C20H23NO3**	
	CDS-1094	**no CAS#**	**(S)-4-(t-Butoxycarbonylamino)-5-(biphenyl-4-yl)-2-pentenoic acid ethyl ester**	**C24H29NO4**	

Chicago Discovery Solutions provides high quality chemical synthesis of small molecular compounds and potential drug candidates. We can supplement your medicinal chemistry program from hit identification through lead optimization. Our medicinal chemists have extensive experience in developing drug candidates from screening hits.

Please contact sales@chicagodiscoverysolutions.com for more information.

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2/21/2014