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Substituted quinolines as noncovalent proteasome inhibitors

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ABSTRACT

Screening of a library of diverse heterocyclic scaffolds identified substituted quinolines as inhibitors of the human proteasome. The heterocyclic library was prepared via a novel titanium-catalyzed multicomponent coupling reaction, which rendered a diverse set of isoxazoles, pyrimidines, pyrroles, pyrazoles and quinolines. SAR of the parent lead compound indicated that hydrophobic residues on the benzo-moiety significantly improved potency. Lead compound **25** inhibits the chymotryptic-like proteolytic activity of the proteasome (IC_{50} 5.4 μM), representing a new class of nonpeptidic, noncovalent proteasome inhibitors.

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1. Introduction

Proteins undergo constant proteolytic degradation to regulate intracellular processes and maintain biological homeostasis.[1,2] During this process, redundant and misfolded proteins are tagged with ubiquitin, which marks them for proteolytic degradation by the 26S proteasome. The 26S proteasome is comprised of a barrel shaped 20S core particle (CP) that is capped by two 19S recognition particles (RPs).[3] The 20S CP is a threonine protease that contains three distinct catalytic subunits (β5, β2 and β1) that exhibit chymotrypsin-like (CT-L), trypsin-like (T-L) and caspase-like (Casp-L) activity.[4] The 19S regulatory particle recognizes the ubiquitin tagged proteins and is responsible for the unfolding and translocation of these substrates into the 20S proteolytic core chamber.[5]

Modulation of proteasome function has emerged as an important approach to treat various diseases,[6,7] and several proteasome inhibitors are clinically approved.[8–10] Common themes among proteasome inhibitors are that they are protein mimics comprised of a peptide backbone containing an electrophilic warhead.[11–13] The warhead forms a covalent bond with the ^{1}N terminal Thr in the catalytic site(s) of the 20S core particle and abrogates its enzymatic activity. Thus, all these peptide based suicide inhibitors are competitive inhibitors that bind in the catalytic site(s) of the proteasome.[11] The peptide-based suicide inhibitors bortezomib (Fig. 1, BTZ or Velcade) and carfilzomib (CFZ, Kyprolis) are FDA approved for the treatment of multiple myeloma (MM)[14–17] and mantle cell lymphoma (MCL) and have validated the proteasome as an important clinical target.[18–20]

These suicide inhibitors effectively block global protein proteolysis, which induces apoptosis, but also triggers a transcriptional feedback loop that results in the synthesis of new proteasome subunits.[21] In addition, peptidase cleavage induces the rapid systemic clearance of these inhibitors.[10,22] Although the initial burst of inhibition is highly effective in the induction of apoptosis, the unfavorable pharmacodynamic properties of these peptide-based suicide inhibitors have restricted their use to blood cancers.

Noncovalent and nonpeptidic proteasome inhibition may limit some of these intrinsic pharmacokinetic drawbacks and may translate into a broader clinical profile.[23,24] Relative to covalent binders, reports of noncovalent and nonpeptidic proteasome inhibitors are still scarce, but are gaining recognition as viable alternatives to peptide-based suicide inhibitors.[11]

Examples of nonpeptidic noncovalent proteasome modulators include the phakellins,[25] oxadiazoles,[26] hydroxyureas,[24] imidazolines[27,28] sulfone or piperazine agents,[29] and tamoxifen derivatives.[30]

Substituted quinolines in particular represent a very interesting new class of proteasome inhibitors. Lawrence and co-workers discovered and optimized a novel class of hydrophthoquinone derivates as nonpeptidic, noncovalent proteasome inhibitors.[31,32] These agents, exemplified by PI-083 (Fig. 1), demonstrated selectivity for cancer cells over non-transformed cells, which potentially broadens the range of anticancer activity.[33] Recently, crystallographic screening of compounds revealed a sulfonamide substituted quinoline as a noncovalent inhibitor of only the

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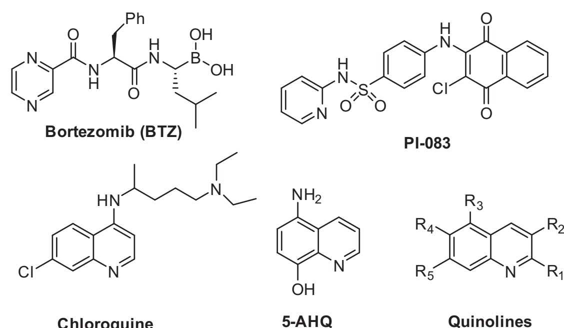

Figure 1. Structures of covalent, peptidic proteasome inhibitors bortezomib, and noncovalent, nonpeptidic proteasome inhibitors PI-083, Chloroquine, 5AHQ and substituted quinolines.

β1/β2 subunits and not the β5 chymotryptic activity, thus identifying a new binding motif.[34]

Several quinolines have also been found to allosterically modulate proteasome activity.[35] NMR studies found that the structurally similar anti-malaria drug chloroquine was found to allosterically modulate proteasome activity by binding to the α/β interface of the Thermoplasma proteasome.[36] Similarly, 5-amino-8-hydroxyquinoline (5-AHQ, Fig. 1) was reported to be a non-competitive inhibitor of the human proteasome.[37] Importantly, 5-AHQ was found effective against bortezomib resistant cell lines, thus exemplifying another advantage of using mechanistically distinct classes of proteasome inhibitors.[27,38,39] It is therefore tempting to speculate that at least some of these noncovalent, nonpeptidic quinolines may occupy a common allosteric binding site.[35]

In our search for noncovalent nonpeptidic proteasome inhibitors, we screened several different classes of heterocyclic scaffolds for their ability to inhibit the chymotryptic activity of the human proteasome. The small diverse library was comprised of various aminocyanopyridines, isoxazoles, pyrazoles and quinolines that were prepared via a titanium-mediated multicomponent coupling reaction (Fig. 2). Of the compounds tested, only the quinolines exhibited low micromolar efficacies for 20S proteasome inhibition. Following the identification of the quinolines as initial hits in the in vitro screen, we characterized its mechanism as a mixed-type inhibition of proteasome modulation, which translated well in cell culture as indicated by the reduction of NF-κB mediated gene expression in a NF-κB-luc reporter assay in HeLa cells. In order to optimize the scaffolds activity, we modified five points of diversity (Fig. 1, R_1–R_5) along the scaffold backbone using the titanium catalyzed multicomponent coupling reaction.

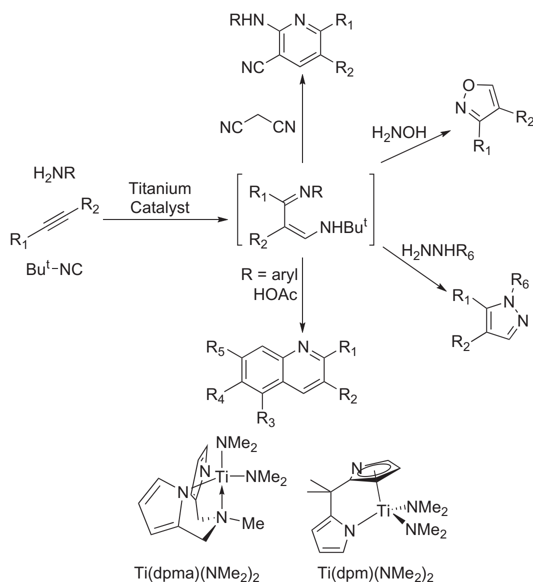

Figure 2. Titanium catalyzed multicomponent coupling reaction to form pyridines, isoxazoles, pyrazoles, and quinolines, as examples.

Herein, we report the synthesis of a novel class of quinoline-based scaffolds and their biological activity towards to 20S proteasome. Importantly, these scaffolds are structurally distinct from the hydro-phthoquinone and 5-AHQ, in that they do not contain, or can readily generate, an electrophilic benzoquinone moiety. In addition, the binding motif is likely different from the sulfonamide-based quinolines,[34] as the compounds described herein are potent inhibitors of chymotryptic-like activity.

2. Results and discussion

2.1. Chemistry

A novel titanium-catalyzed 3-component coupling reaction was applied to generate a small library of diverse heterocyclic scaffolds.[40–42] The titanium chemistry effectively adds an iminyl and amine group across the triple bond of an alkyne, iminoamination, to form unsymmetrical derivatives of 1,3-diimines. The 1,3-diimines, generated in situ, can then be applied to many different heterocyclic syntheses.[40] The quinolines were prepared from the 3-component coupling products using a modified Combes synthesis catalyzed by acetic acid, which rendered highly substituted frameworks in a one-pot procedure (Fig. 2).[43]

The search for proteasome inhibition quickly narrowed to compounds containing the quinoline backbone. Due to the mechanism of the formation of the iminoamination products, the quinolines are all unsubstituted at the 4-position but can be substituted by a range of groups in other sites. The two catalysts employed for the syntheses are shown at the bottom of Figure 2. The ancillary ligands for titanium H_2dpma and H_2dpm are both prepared in a single step from pyrrole.[44–46] The catalysts for this study were isolated as pure compounds before use; however, it is possible to generate the catalysts in situ from the protio-ligand and commercially available $Ti(NMe_2)_4$ as well.[40] The applications of these two catalysts in iminoamination have been discussed elsewhere in detail.[40] In short, more reactive $Ti(dpm)(NMe_2)_2$ is often used for more difficult internal alkyne substrates, while milder $Ti(dpma)(NMe_2)_2$ is often used with sensitive terminal alkynes to avoid potential side reactions. In addition, the two catalysts can direct regioselectivity for the substrates, which broadens the structural diversity.

The synthesis of some of the quinolines follows a similar one-pot synthesis as previously reported.[43] Synthetic details for all new compounds can be found in the Supporting information.

2.2. Biological evaluation

The initial diverse library of compounds was screened in vitro using purified human 20S proteasome and the fluorogenic peptide substrate, Suc-LLVY-AMC, as the substrate for CT-L activity.[47] The rates of hydrolysis were monitored by fluorescence increase at 37 °C over 30 min, and the linear portion of the curves were used to calculate the IC_{50} values. Of the compounds tested, only some of the quinolines exhibited low micromolar efficacies for 20S proteasome inhibition (Fig. S1). Of the quinolines tested, quinoline **7** exhibited modest inhibition of the 20S chymotryptic activity with an IC_{50} of 14.4 μM and was therefore selected for further evaluation and optimization. Interestingly, it appeared that substitutions in the R_1, R_2, R_3 and R_5 positions were required to see any inhibition of proteasome activity (Table 1).

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