Stabilization of protein–protein interactions by small molecules

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Protein–protein interactions (PPIs) are implicated in every disease and mastering the ability to influence PPIs with small molecules would considerably enlarge the druggable genome. Whereas inhibition of PPIs has repeatedly been shown to work successfully, targeted stabilization of PPIs is underrepresented in the literature. This is all the more surprising because natural products like FK506, rapamycin, brefeldin, forskolin and fusicoccin confer their physiological activity by stabilizing specific PPIs. However, recently a number of very interesting synthetic molecules have been reported from drug discovery projects that indeed achieve their desired activities by stabilizing either homo- or hetero-oligomeric complexes of their target proteins.

Introduction

Small molecule modulation of protein–protein interactions (PPIs) has been recognized as a promising approach in drug discovery [1–3]. However, in the vast majority of cases, PPI modulation is exclusively recognized as inhibition, understandably motivated by a number of wonderful success stories that have been published in recent years. Of these, two of the most prominent examples are the nutlins developed by Roche [4,5], which inhibit the negative regulation of the tumor suppressor p53 by the ubiquitin ligase mouse double minute 2 homolog (MDM2), and navitoclax from Abbott (ABT263), which disrupts the interaction of the antiapoptotic protein Bcl-2 and apoptosis-executing proteins like Bad, Bid and Bak [6–8]. Further prominent examples are molecules that inhibit the interaction of human leukemia-derived growth factor (LDGF) with HIV integrase [9], disrupt the binding of KRas and phosphodiesterase (PDE)δ [10], transform an active tumor necrosis factor (TNF)α trimer into an inactive dimer [11] or inhibit the binding of PPI modules like the clathrin terminal domain (CTD), or bromodomains with their partners [12,13].

A number of natural products have been shown to mediate their physiological activity by stabilizing PPIs, for a review see [14]. These molecules are ample proof of the concept of small molecule PPI interface binding which results in functional stabilization of regulatory protein complexes leading to significant physiological effects. In addition to these examples from nature itself, there are meanwhile a number of small molecules known that have been found to modulate the function of their protein target by stabilizing their homo or hetero complexes. Interestingly, many of them have been identified during screening of PPI inhibitors, for example RO2443 and phenothiazines that inhibit the function of MDMX and the protein S100A4, respectively. A few molecules have also been found in approaches directly dedicated to identifying PPI stabilizers, for example pyrrolidone1. In this review we summarize the current state of PPI stabilization by small molecules, including natural products and synthetic molecules.

Cyclosporin A

Cyclosporin A (CsA) is a cyclic undecapeptide produced by the ascomycete *Tolypocladium inflatum*, initially isolated in 1970 from a Norwegian soil sample and shown to display immunosuppressive properties [15]. Its chemical structure inclusive of *N*-methylated peptide bonds, the atypical amino acids aminobutyric acid and (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt) and D-alanine is biosynthesized by a nonribosomal process [16] (Table 1). The conformational, physicochemical and pharmacokinetic properties of CsA, most notably its oral absorption profile [17], continue to inspire chemists [18–20], and its effective immunosuppressant action supported FDA registration in 1983 [21]. The molecular target

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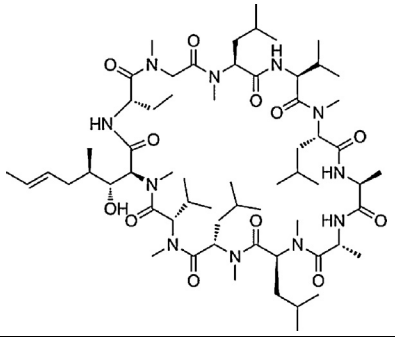
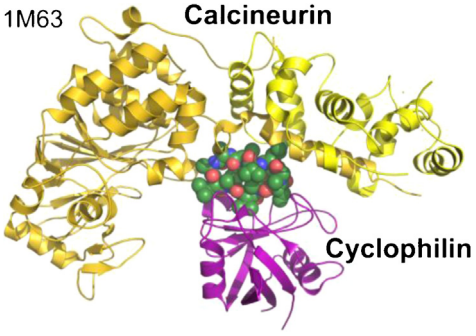
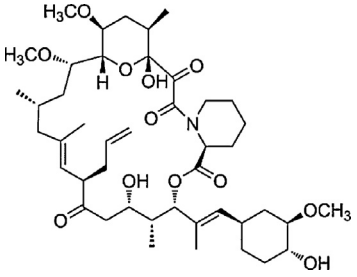
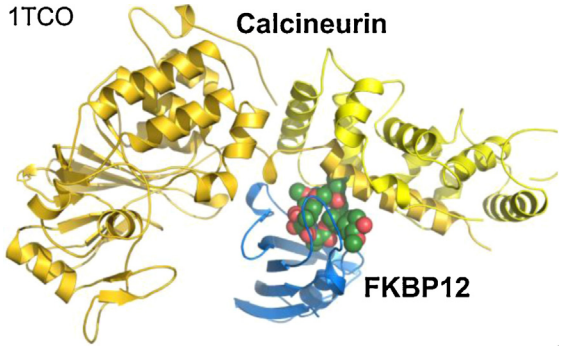
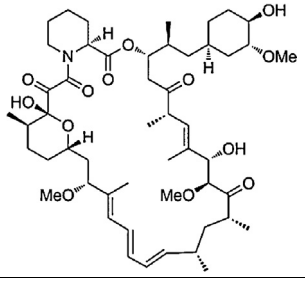
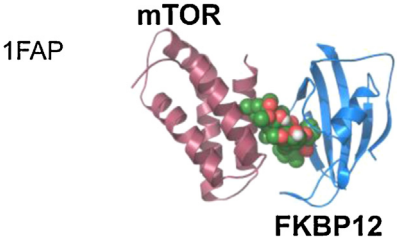
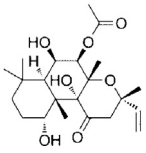
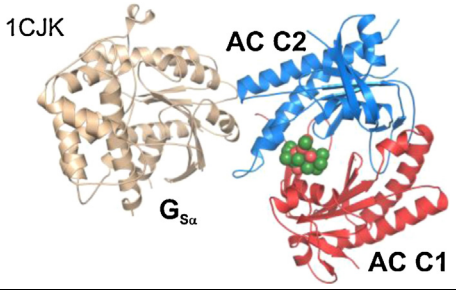
TABLE 1

Natural products that stabilize protein–protein interactions (PPIs)

PPI stabilizer	Structure	Protein–protein complex (PDB)
Cyclosporine A		
FK506		
Rapamycin		
Forskolin		
Fusicoccin A