EFMC-ISM C 2012 is organised by the German Chemical Society (GDCh) Division of Medicinal Chemistry and the German Pharmaceutical Society (DPhG) Section of Pharmaceutical/Medicinal Chemistry
P228
Merged Structures as New STAT3 Inhibitors: The Chimera Compounds

Arianna Gelain, Daniela Masciocchi, Stefania Villa, Silvia Dell’Orto, Fiorella Meneghetti, Alessandro Pedretti, Daniela Barolco, Laura Legnani, Lucio Toma, Byoung-Mog Kwon, Shintaro Nakano, Akira Asai

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Via L. Mungialloli 25, 20133 Milano, Italy
Dipartimento di Chimica, Università degli Studi di Pavia, Via Taramelli 12, 27100 Pavia, Italy
Laboratory of Chemical Biology and Genomics, Korea Research Institute of Bioscience & Biotechnology and Department of Biomolecular Science, Korea University of Science and Technology, Eonan-Dong, Yuseong-gu, Daedeon 305-333, South Korea
Center for Drug Discovery, Graduate School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga Ku, Shizuoka, 422-8526, Japan

Signal transducer and activator of transcription 3 (STAT3) is a latent cytoplasmic factor belonging to STAT proteins family. These proteins transduce extracellular signals through the cytoplasm and act as transcription factors in the nucleus, regulating cell growth and survival.1,2 In particular, STAT3 has been found constitutively activated in a broad spectrum of cancer cell lines and human tumors,3,4 and its inhibition specifically suppresses cancer cell survival with only minimal effects in normal cells.5,6 In the light of these compelling results, STAT3 represents a promising anticancer drug target,7,8 and we focused our efforts in the discovery of new compounds inhibiting STAT3. During our ongoing researches,9,10 we found out several molecules capable of interfering with STAT3 activity. In details, AVS-0288 (a ureidoxazolamide small molecule, known as an herbicidal agent)11 and cryptotanshinone (a natural phenanthrene-quinone derivative)12 were identified by a screening performed on a Korean chemical library, whereas DM6 (a new substituted benzocinnallone) was synthesized in our laboratory. Since these compounds showed an interesting STAT3 inhibitory activity in the dual-luciferase assay, we decided to perform conformational studies and merge their scaffolds with the aim to improve their inhibitory profile. Therefore, starting from these superimpositions, we designed and synthesized the chimera compounds (general formulas I and II). Their synthesis, crystallographic studies as well as their biological evaluation will be discussed.

References


P229
Identification of Small-Molecule Antagonists of the Pseudomonas aeruginosa Transcriptional Regulator PQSR: Biophysically Guided Hit Discovery and Optimization

Tobias Klein, Claudia Henn, Johannes C. de Jong, Christina Zimmer, Dominik Pistorius, Rolf Müller, Anke Steinbach, Rolf W. Hartmann

Helmholtz-Institut für Pharmazeutische Forschung Saarland (HIPS), Campus C2.3, 66123 Saarbrücken, Germany
Department of Pharmaceutical and Medicinal Chemistry, Saarland University, Campus C2.3, 66123 Saarbrücken, Germany
Department of Pharmaceutical Biotechnology, Saarland University, Campus C2.3, 66123 Saarbrücken, Germany

The Gram-negative opportunistic pathogen Pseudomonas aeruginosa produces an intercellular alkyl quinolone signaling molecule, the Pseudomonas quinolone signal (PQS). The pqA quorum sensing communication system that is characteristic for P. aeruginosa regulates the production of virulence factors and biofilm formation.11 Therefore, we consider the pqA system as a novel target to limit P. aeruginosa pathogenicity without affecting bacterial viability. Recently, we reported on the first antagonists of the transcriptional regulator PqsR, a key player of the pqA system.12 However, as their structures are derived from the natural effector HQQ, they have insufficient physicochemical properties to be used as a drug.

Here, we present the discovery and optimization of small molecules targeting PqsR. We applied a rational design strategy that involves the simplification of the κ-opioid receptor agonist (1)-trans-5,7-U50488 (1), which was recently found to stimulate the transcription of pqAABCDE in PAO1,13 into smaller fragments and analogues. In combination with surface plasmon resonance (SPR) biosensor analysis this approach led to the identification of PqsR binders with good ligand efficiencies (LEs). Determination of thermodynamic binding signatures using isothermal titration calorimetry (ITC) and functional characterization in an E. coli reporter gene assay confirmed a promising hit that was elaborated to the potent hydroxamic acid-derived PqsR antagonist 11. This compound shows a Kᵢ value of 4.1 μM and remarkably it is also potent in P. aeruginosa. Beyond this, site-directed mutagenesis together with thermodynamic analysis provided insights into the energetic characteristics of protein-ligand interactions suggesting the presence of hydrogen bonds and CH/π interactions.