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Topics in Medicinal Chemistry

Aims and Scope

Drug research requires interdisciplinary team-work at the interface between chemistry, biology and medicine. Therefore, the new topic-related series Topics in Medicinal Chemistry will cover all relevant aspects of drug research, e.g. pathobiochemistry of diseases, identification and validation of (emerging) drug targets, structural biology, drugability of targets, drug design approaches, chemogenomics, synthetic chemistry including combinatorial methods, bioorganic chemistry, natural compounds, high-throughput screening, pharmacological in vitro and in vivo investigations, drug-receptor interactions on the molecular level, structure-activity relationships, drug absorption, distribution, metabolism, elimination, toxicology and pharmacogenomics.

In general, special volumes are edited by well known guest editors.

In references Topics in Medicinal Chemistry is abbreviated Top Med Chem and is cited as a journal.

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Shelli R. McAlpine • Adrienne Lesley Edkins
Editors

Heat Shock Protein Inhibitors

Success Stories

With contributions by

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Preface

Protein folding and degradation are key cellular processes that must be carefully regulated in the crowded and compartmentalised cellular environment. The physiological process of proteostasis must also be maintained in times of stress, where an additional burden is placed on cells due to alterations in protein structure and function. The ability of the cell to maintain appropriate protein homeostasis under both physiological conditions and during cellular upheaval is largely dependent on a phenomenon known as the stress response. The stress response is an evolutionarily conserved and often predictable response that results in the upregulation or activation of a cohort of proteins, known collectively as molecular chaperones that serve to ameliorate the consequences of protein misfolding. Selected members of the heat shock proteins (e.g. Hsp90 and Hsp70) represent the largest and best-characterised family of molecular chaperones.

Many heat shock proteins (Hsps) function as molecular chaperones, regulating a range of processes associated with protein homeostasis, including protein folding, aggregation suppression and protein degradation. The activities of these Hsps are finely tuned and usually driven by the formation of complexes with cofactors. Understanding the mechanistic details by which these Hsps function as molecular chaperones has led to their analysis in human diseases. Hsps have been implicated in either the aetiology or prevention of many human diseases, ranging from cancer to Alzheimer's and infectious diseases. Hsps have been identified as putative drug targets for therapeutic intervention. In this book, the authors provide critical insight into the identification and development of inhibitors against selected Hsps as future therapies for human disease.

Specifically, topics include discussions on Hsp90, Hsp70, Hsp47, Hsp40 and Hsp27. Describing inhibitors that modulate Hsp90 or Hsp70 or a combination of these two inhibitors provides an overview of the most recent drugs targeting these Hsps. Finally, these chapters provide insight into potential new routes for modulating these Hsps. However, despite these success stories, there are currently no Hsp inhibitors that have completed clinical trials and are in routine use for treating patients. As discussed within these chapters, there are opportunities to develop new

molecular inhibitors for these therapeutically relevant Hsps. The wide range of Hsps and their functional control of the cell make these chaperones highly relevant to all therapeutic areas.

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