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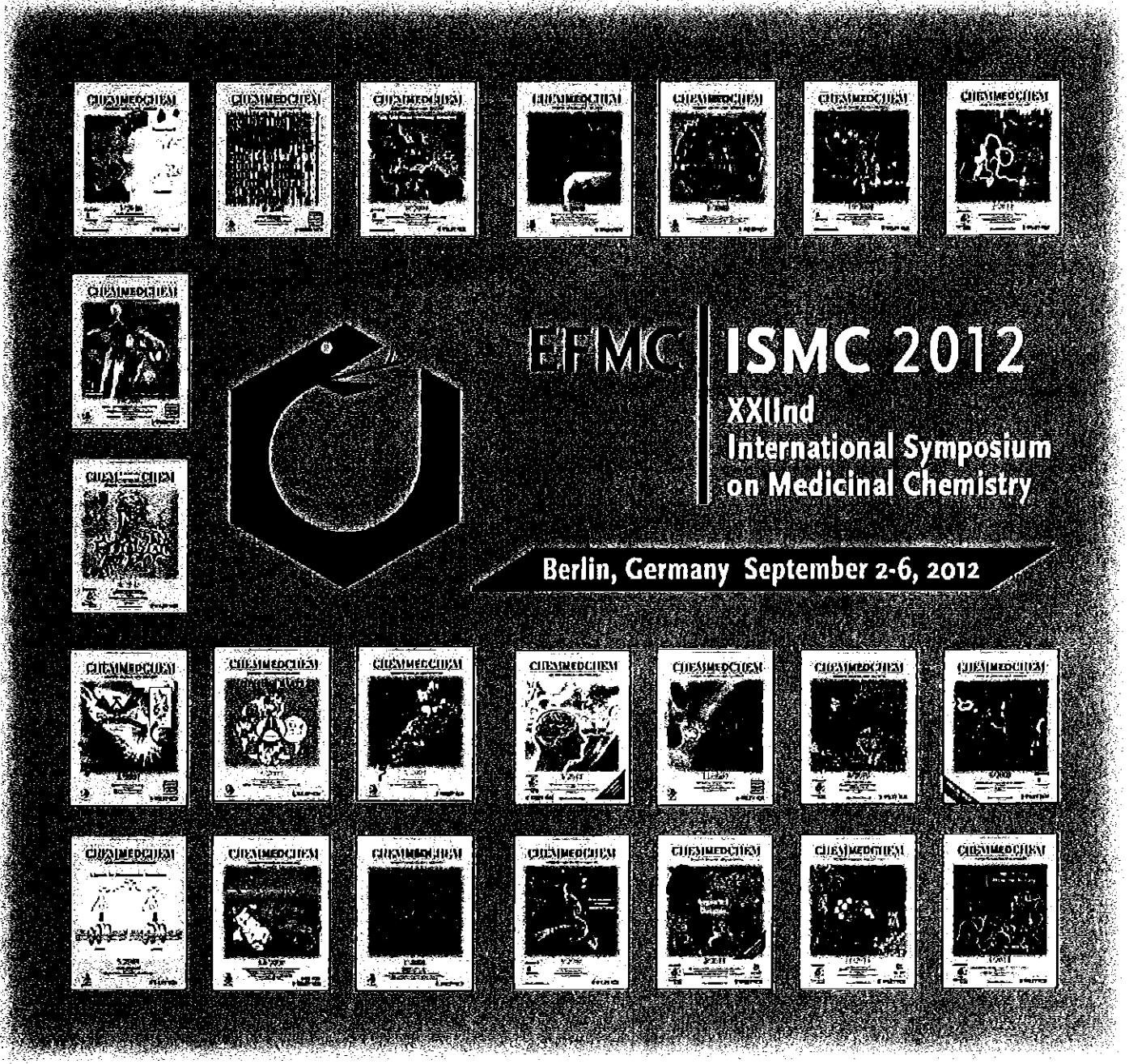

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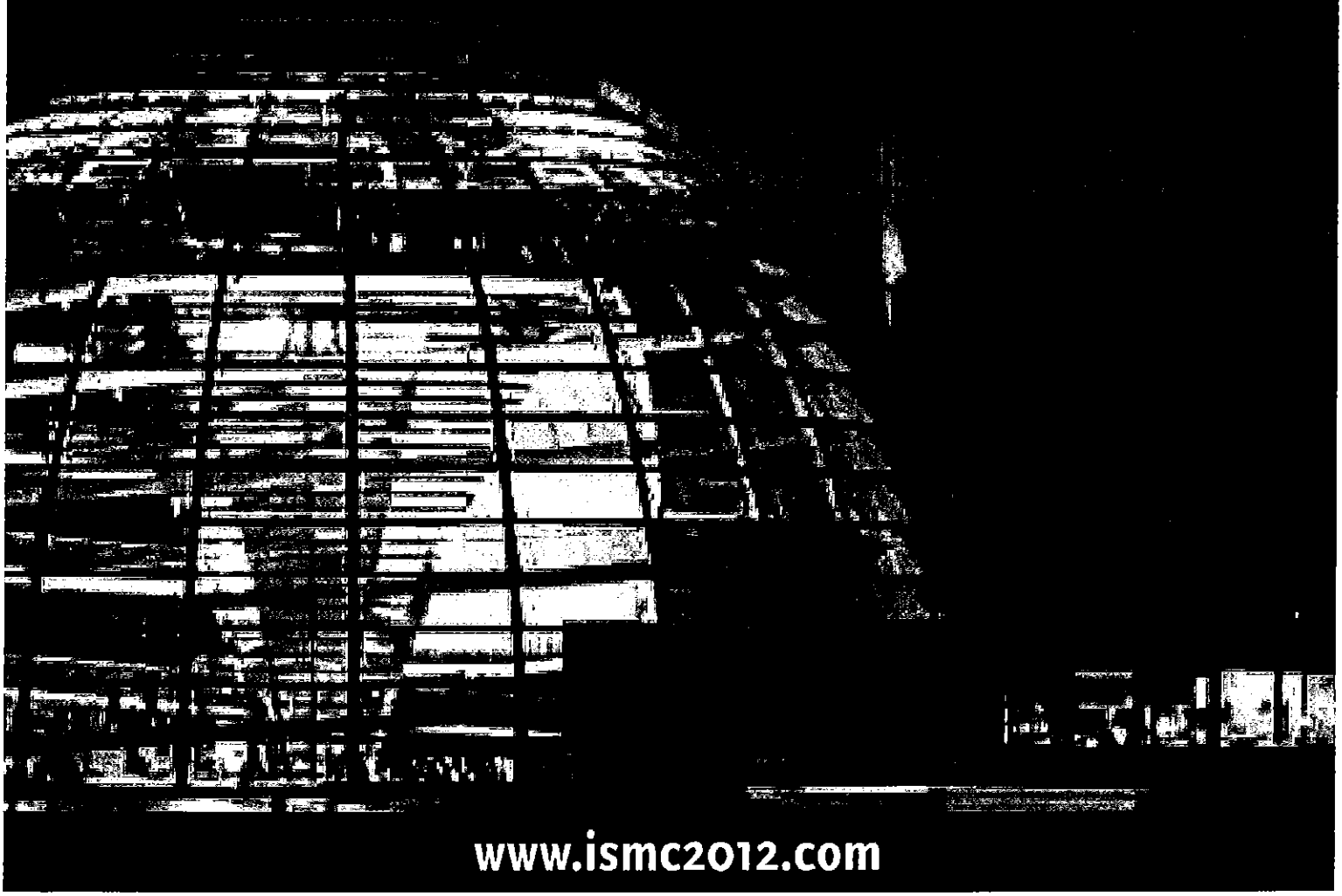

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GDCh Gesellschaft Deutscher Chemiker

EFMC European Federation for Medicinal Chemistry

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Merged Structures as New STAT3 Inhibitors: The Chimera Compounds

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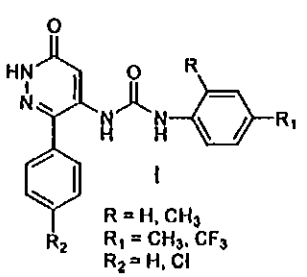
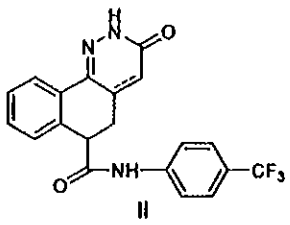
Signal transducer and activator of transcription 3 (STAT3) is a latent cytoplasmic factor belonging to STAT proteins family. These proteins transduce extracellular signals through the cytoplasm and act as transcription factors in the nucleus, regulating cell growth and survival.[1] In particular, STAT3 has been found constitutively activated in a broad spectrum of cancer cell lines and human tumors,[2] and its inhibition specifically suppresses cancer cell survival with only minimal effects in normal cells.[3,4] In the light of these compelling results, STAT3 represents a promising anticancer drug target,[5] and we focused our efforts in the discovery of new compounds inhibiting STAT3. During our ongoing researches,[6,7] we found out several molecules capable of interfering with STAT3 activity. In details, AVS-0288 (a ureidic oxadiazole small molecule, known as an herbicidal agent)[5] and cryptotanshinone (a natural phenanthrene-quinone derivative)[8] were identified by a screening performed on a Korean chemical library, whereas DM6 (a new substituted benzocinnolinone) 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.



I

R = H, CH_3
R_1 = CH_3, CF_3
R_2 = H, Cl



II

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

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The Gram-negative opportunistic pathogen Pseudomonas aeruginosa produces an intercellular alkyl quinolone signaling molecule, the Pseudomonas quinolone signal (PQS). The pqs quorum sensing communication system that is characteristic for *P. aeruginosa* regulates the production of virulence factors and biofilm formation.[1] Therefore, we consider the pqs 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 pqs system.[2] However, as their structures are derived from the natural effector HHQ 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 (±)-trans-U50488 (**1**), which was recently found to stimulate the transcription of pqsABCDE in PAO1,[3] 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 K_D 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.