Tricyclic pyridazinones: development on new STAT3 inhibitors

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Introduction

Signal transducer and activator of transcription 3 (STAT3) is a member of the Jak family which comprises seven subfamily (STAT1-6, Sa, Sb, Sc). They are ubiquitously expressed, and their deregulation is associated with the growth and development of many cancer types. In many solid tumors, STAT3 is found in a constitutively active form, phosphorylated at Y705, constituting an important target for the design of new anticancer drugs. The development of new anticancer drugs with interesting pharmacological properties and reduced side effects is a major goal of cancer research.

Chemistry (I)

The starting reagents for compounds 12 were obtained from the Tianjin Donlen Bio-Technology Co. Ltd. Compounds 12 were synthesized by the general procedure for the synthesis of all compounds. General procedure for the synthesis of all compounds.

Synthesis of the starting reagents for compounds 12 and 13.

Docking studies

The VX11 structure, co-crystallized with a DNA fragment, 52 was downloaded from the Protein Data Bank (PDB-ID 1G8Q) and was optimized by GAMESS (0.30) using the OPLS force field. The B3LYP level with the 6-31G(d) basis set and the energy of the optimized CX-4 model is 8.90 kcal/mol.

Crystallography

Crypotanshinone crystal structure (green) with the position of the aromatic ring as well as the size of the central ring. The overlap shows that the two compounds match very well.

Biology evaluation

A conformational study of the reference compound Cryptotanshinone B and of a parent compound with pyridazinone structure 4a was carried out. Attention was focused on the flexibility of the A and C rings, and, for 12, on the possible inversion of C ring.

Modeling studies

A conformational study of the reference compound Cryptotanshinone B and of a parent compound with pyridazinone structure 4a was carried out. Attention was focused on the flexibility of the A and C rings, and, for 12, on the possible inversion of C ring.

Conclusions

Based on the structural analogy between Cryptotanshinone and a tricyclic pyridazinone moiety, we investigated in a previous study, we have now synthesized a novel series of novel derivatives as potential STAT3 inhibitors. Receptor pharmacological results showed that several compounds were involved with activity similar or even better ($\Delta E$) than that of the model in the literature above. Considering the different conformational distributions, at different concentrations, after 24h treatment with the tested compounds and Cryptotanshinone, which was used as reference.

References