**DEVELOPMENTS ON FURAZAN DERIVATIVES AS POTENTIAL STAT-3 INHIBITORS**

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**Background**

Stat-3 (signal transduction and activator for transcription factor 3) is a latent cytosolic protein that, in its activated form, directly relates extracellular signals (e.g. growth factors, poly-peptide, cytokines) from the plasma membrane to the nucleus(Figure 1). It is involved in cell growth and survival. Stat-3 is the member of Stat family most closely linked to tumour genesis as its signalling might contribute to malignancy by preventing apoptosis, even if the molecular mechanism of oncogenesis by Stat-3 must be clearly defined. Stat-3 is constitutively activated by aberrant upstream tyrosine kinase activities in a broad spectrum of human solid and blood tumours. Since Stat-3 inhibition leads to apoptosis in tumour cells but has no effect in normal cells, it represents a promising target for cancer therapy.

**Research Project**

As a part of our ongoing studies, focused on the discovery of new small molecules as potential Stat-3 inhibitors, we synthesized a series of new furazan derivatives (compounds 2, 3e, 3e) closely related to the reference compound (AVS 0288). We have now prepared compounds 1e-1i, 2d-e and 3d-e in order to better analyze the features required for the inhibition of Stat-3.

**Synthesis**

All products were synthesized starting from the suitable intermediate 4. Compounds 4a, 4b, 4c were prepared according to literature data.

**Scheme 1. Synthesis of urea (1e-i), amide (2d-e) and sulfonamide (3d-e) derivatives**

2d and 3d were solved by direct methods and conventional Fourier synthesis. The refinement of the structures was made by full matrix least-squares on F^2. All non-H-atoms were refined anisotropically and were introduced at calculated positions, in their described geometries and allowed to ride on the attached carbon atom with fixed isotropic thermal parameters.

**Crystallography**

The crystal structure of 2d presents a more extended chain conformation than 3d, as shown by the torsional angles C2-N3-C1-C4 of 178(1)^2 and C2-N3-S1-C4 of 73(1)^2 respectively. The dihedral angle between the mean plane of the oxadiazole and the phenyl ring is 63(1)^2 in 2d and 15(1)^2 in 3d, leading in the latter to a short centroid distance with respect to 2d and AVS-0288.

The crystal packing of both molecules present a three-dimensional network of intermolecular interactions of type, N-H…O, C=H…n, and π-stacking interaction.

**Discussion**

The results from the biological assays clearly show that:

- substitution of the ureidic moiety of the model either with a benzamido (3d-e) or a sulfonamido (3d-e) group caused a significant decrease in activity;
- lack of the chloride group on the phenyl ring linked to the heterocycle brought about complete loss of activity (see 1g vs the model).

According to the principle of vinilogry, the cinnamyl derivatives (2h) are comparable to their analogous 1f, though stereochemistry seems also to play a role.

Finally, the lack of activity of compounds 2d and 3d could be interpreted on the basis of molecular modeling and crystallographic studies, which distinctly show a poor superimposition of these two derivatives with the model.

**References**