Spontaneous resolution of $N$-sulfonlpyrimidine compounds induced by chemical modifications

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The title compounds belong to the series of pyrimidine nucleobase derivatives, some of which exhibit significant anticancer activity in vitro.[1] The crystal structures of 1-methylsulfonluracil (1), 1-tosyluracil (2), 1-tosylthymine (2a), 1-tosyl-5-bromouracil (2b), as well as of $\alpha$-naphthyl derivatives of uracil (3) and thymine (3a) are presented (Scheme 1). The conformational chirality was encountered in all compounds, as the consequence of the S-N single bond free rotation hindrance in solid state (atropisomerism).[2]

According to the mutual spacial arrangement of the fiducial groups with respect to the perpendicularly oriented chirality axis (S-N bond), the enatioconformers are denoted as $P$ (plus, clockwise) or, as in the case presented on scheme 2, $M$ (minus, counterclockwise). Fiducial groups are defined at both ends of the chirality axis, in this case: $p$-Tol at the sulfur atom, and C=O group of the pyrimidine ring at the nitrogen atom.

During the crystallization of 2, spontaneous resolution occurred followed by a racemic twinning of homochiral crystal blocks. Homochiral molecules (sp. group $P2_12_12_1$) inside a single block are arranged around the 2, axis parallel to $b$, being connected via the N3-H···O4 H-bonds (Fig. 2). Obviously, a substituent at the position C-5 of the pyrimidine ring would disrupt such a crystal packing, being close to the O4 from the neighbouring molecule (Fig. 2).

Indeed, instead of homochiral molecular ribbons as in 2, centrosymmetric dimers guide the crystal packing of 2a (Fig. 3) and 2b. No resolution occurred.

The decisive role of the 5-substituent to the spontaneous resolution was confirmed by the X-ray structure analysis of 3 and 3a (Figs. 4, 5), where again the CH$_3$ group at the C-5 position inhibited the spontaneous resolution and formation of chiral crystals in the case of 3a.

CONCLUSION

While the presence of C 5 substituent excludes à la Pasteur spontaneous resolution of conformational enantiomers in a studied class of compounds, physical properties of the S-substituent dictate its occurrence, absence and/or extent.

Chiral, twinned and/or racemic crystals were engineered by targeted chemical modifications.