Spontaneous resolution of *N*-sulfonylpyrimidine compounds induced by chemical modifications

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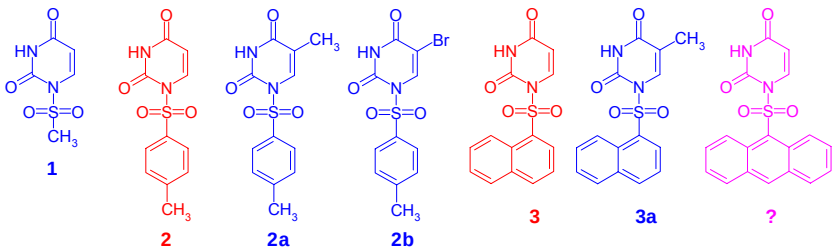
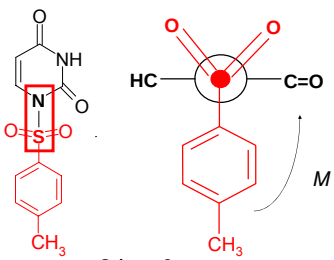
The title compounds belong to the series of pyrimidine nucleobase derivatives, some of which exhibit significant anticancer activity *in vitro*.[1] The crystal structures of 1-methylsulfonyluracil (**1**), 1-tosyluracil (**2**), 1-tosylthymine (**2a**), 1-tosyl-5-bromouracil (**2b**), as well as of α-naphthyl 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]



Scheme 1



Scheme 2

According to the mutual spacial arrangement of the fiducial groups with respect to the perpendicularly oriented chirality axis (S-N bond), the enantioconformers 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.

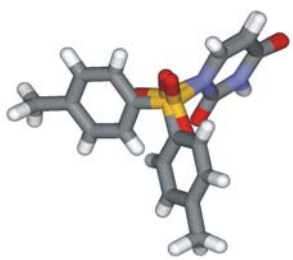


Fig. 1 Overlap of *M* and *P* enantioconformers of **2**

During the crystallization of **2**, spontaneous resolution occured 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_1 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, beeing to close to the O4 from the neighbouring molecule (Fig. 2).

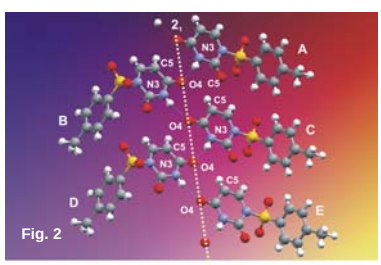


Fig. 2

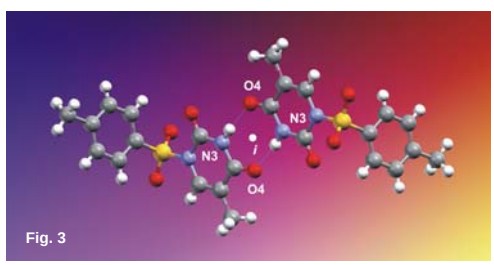


Fig. 3

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

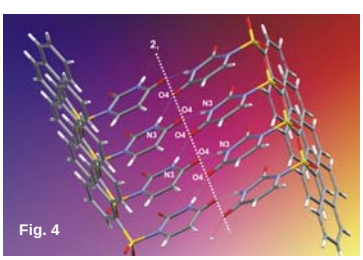


Fig. 4

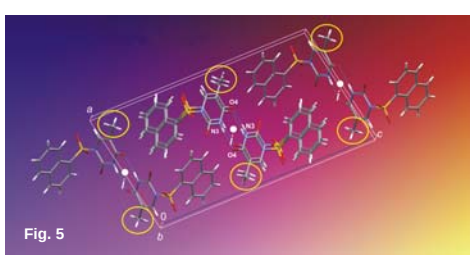


Fig. 5

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**.

[1] Ruđer Bošković Institute (B. Žinić, M. Žinić, I. Krizmanić), EP 0 877 022, 2003.
[2] I.D. Cunningham, S.J. Cooles, M.B. Hursthouse, *Chem. Comm.* (2000) 61-62.

Spontaneous resolution, occuring in **2** and **3,** but not in **1** (Scheme 1, Fig. 6) suggested also **the role of the S-substituent** to the spontaneous resolution of these compounds. This is yet to be confirmed with a bulky S-substituent, such as antracene (Scheme 1), with which the spontanteous resolution also in liquid phase is expected to be achieved.

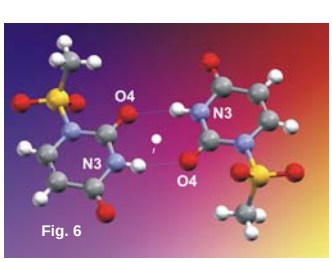


Fig. 6

CONCLUSION

While the presence of Ć 5 substituent excludes *á la Pasteur* spontaneous resolution of conformational enantiomers in a studied class of compounds, physical properties of the S-substituent dictate its occurance, absence and/or extent.
Chiral, twinned and/or racemic crystals were engineered by targeted chemical modifications.