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Tetrahedron 63 (2007) 86–92
Tetrahedron

# Conformational chirality and chiral crystallization of *N*-sulfonylpyrimidine derivatives

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Received 18 July 2006; revised 29 September 2006; accepted 19 October 2006
Available online 9 November 2006

**Abstract**—New *N*-sulfonylpyrimidine derivatives 1-(*p*-toluenesulfonyl)uracil (**1**), 1-(*p*-toluenesulfonyl)thymine (**2**), 5-bromo-1-(*p*-toluenesulfonyl)uracil (**3**), 1-(methanesulfonyl)uracil (**4**), 1-(1-naphthylsulfonyl)uracil (**5**), and 1-(1-naphthylsulfonyl)thymine (**6**) were prepared by the condensation reaction of silylated pyrimidine derivatives with selected sulfonyl chlorides in acetonitrile. Some members of the series showed unexpected crystal properties as a consequence of their conformational chirality in the solid state. Compounds **1** and **5** exhibited chiral crystallization, which was, in the case of **1**, accompanied by the formation of racemically twinned crystals regardless of the solvent used, while **5** gave a conglomerate of enantiomorphous crystals. For **2**, **3**, and **6**, substituents at the C-5 position of the pyrimidine ring prevented chiral crystallization by influencing the crystal packing. Analysis of the crystal structures of **1**, **4**, and **5**, reveals the influence of the arylsulfonyl group on the occurrence or absence of chiral crystallization.


## 1. Introduction

Spontaneous resolution of racemates by crystallization giving conglomerates of enantiomorphous crystals is an old and well known phenomenon, now belonging to the classics of stereochemistry.[1–3] However, there are a very limited number of apparently achiral organic molecules lacking any element of chirality (center, axes, or plane), which can adopt chiral conformation that could be 'frozen' in the solid state. In such a case, conglomerates of chiral crystals could be obtained and the phenomenon represents an example of spontaneous generation of chirality.[4,5] In addition, the achiral molecules could be chirally organized in the solid state by various non-covalent intermolecular interactions. The latter case exemplifies a supramolecular chirality that could also give conglomerates of enantiomorphous crystals.[6,7] Spontaneous generation of chiral crystals has important implications for the themes such as the occurrence of homochirality in nature,[8] enantioselective synthesis starting from achiral compounds,[9–12] crystal engineering,[13,14] and the preparation of chiral advanced materials possessing a long range order.[15,16] However, the probability of the appearance of chiral crystallization from achiral compounds is very low (only 8%).[5]

Recently, we have prepared a series of novel pyrimidine derivatives **I** (Fig. 1) possessing a sulfonamide and a nucleic base pharmacophore, which exhibit strong antitumor activity and ability to induce apoptosis in treated tumor cells.[17–20]

Crystal structures of the *N*-sulfonylpyrimidine derivatives **1–6** (Fig. 1) revealed that such molecules can adopt chiral conformations possessing M and P helicities (Fig. 2) that

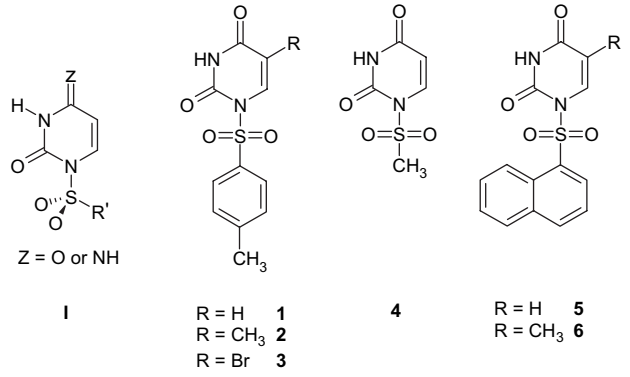


**Figure 1**. *N*-Sulfonylpyrimidines **I** and structures of derivatives **1–6**.

*Keywords*: *N*-1-Sulfonylpyrimidine derivatives; Conformational (molecular) chirality; Spontaneous resolution; Racemic twinning.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.048

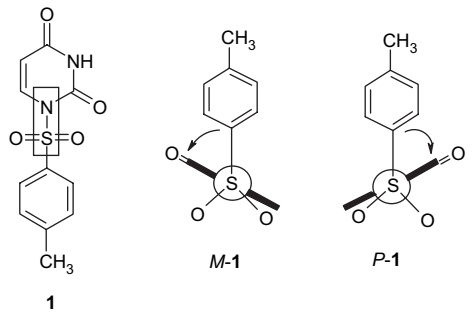
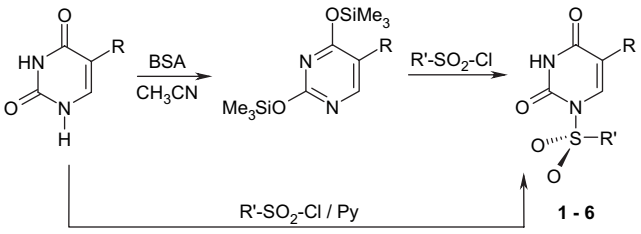



**Figure 2**. Chiral conformations of *N*-sulfonylpyrimidine **1** with M- and P-helicity.




**Scheme 1**. Synthesis of *N*-sulfonylpyrimidine derivatives.

could be frozen in the crystalline state. Here, we present the crystallographic evidence that some members of the series crystallize as conglomerates of enantiomorphous crystals, racemically twinned crystals, or simply as racemic single crystals, depending on the presence or absence of the C-5 pyrimidine substituents and the size of R′ of the $R'SO_2-$ groups. To the best of our knowledge, the phenomenon of chiral crystallization has not been described so far for the compounds of *N*-1-arylsulfonylpyrimidine type and the results presented here may endow new examples for the phenomenon based on a general arylsulfonyl-nucleic base type of structure.

## 2. Results and discussion

### 2.1. Synthesis

As regards biological activity, the *N*-sulfonylpyrimidine derivatives are interesting compounds since they represent a combination of biologically active sulfonylcyclourea and nucleic acid base components.[21–28] Despite extensive biological activities of the components, only very few reports on the synthesis of derivatives combining both active components in the molecule can be found in the literature. Martirosyan et al.[29] isolated 1-(*p*-toluenesulfonyl)uracil as an unwanted product in the transformation of the C-4 keto group of uracil, and Kaldrikyn et al.[30] examined the synthesis of 1-*p*-alkoxybenzenesulfonyl-5-bromouracil derivatives possessing antibacterial activity. According to Tada,[31] benzoyl and arenylsulfonyl-5-fluorouracil derivatives are more active and less toxic than 1-(2-tetrahydrofuryl)uracil in the leukemia L/1210 system. Synthesis and in vitro anticancer activity of 1-sulfonylcytosine derivatives were described in the patent.[19]

Two methods previously described for this series of compounds were used for the preparation of **1**–**6**: (a) condensation of silylated pyrimidine bases with selected sulfonyl chlorides in acetonitrile, and (b) reaction of pyrimidine bases with sulfonyl chlorides in pyridine.[17–19] Silylation of uracil (R=H), thymine ($R=CH_3$), and 5-bromouracil (R=Br) was accomplished with bis(trimethylsilyl)acetamide (BSA) in acetonitrile at 80 °C (Scheme 1).

Silylated derivatives were condensed with *p*-toluenesulfonyl chloride, giving 1-(*p*-toluenesulfonyl)uracil (**1**) (95%), 1-(*p*-toluenesulfonyl)thymine (**2**) (86%), and 5-bromo-1-(*p*-toluenesulfonyl)uracil (**3**) (57%). To improve the overall yield, compound **3** was also prepared by two other routes. The first involved bromination of 1-(*p*-toluenesulfonyl)uracil (**1**) using bromine in $CH_2Cl_2$/DMF at room temperature gave **3** in comparable yield of 54%. The second route used condensation of 5-bromouracil with tosyl chloride in pyridine giving **3** after several recrystallizations from methanol in an even lower yield (45%). Condensation of silylated uracil with methanesulfonyl chloride or 1-naphthalenesulfonyl chloride gave the corresponding 1-(methanesulfonyl)uracil (**4**) in 75% yield and 1-(1-naphthylsulfonyl)uracil (**5**) in 81% yield. Reaction of silylated thymine with 1-naphthalenesulfonyl chloride gave 1-(1-naphthylsulfonyl)thymine (**6**) in 78% yield.

### 2.2. Molecular and crystal structures

Table 1 summarizes the basic crystallographic data for compounds **1**–**6**. 1-(*p*-Toluenesulfonyl)uracil (**1**) was found to exhibit the formation of racemically twinned crystals containing various portions of enantiomerically related blocks (space group $P2_12_12_1$), regardless of the solvent used for crystallization. Evaporation of THF gave crystals of two distinct morphologies, prisms, and rods. Full sphere X-ray data collection was performed on several crystals of both morphologies, and Flack parameters were determined. Typical prisms contain roughly 50% of each homomeric crystal domain, whereas a minor domain contribution ranges roughly from 10 to 40% in rod-shaped crystals. Slow evaporation from DMSO solution gave crystals of a single morphology and the Flack parameter corresponding to the minor domain contribution of less than 25%. The crystals were not of supreme quality and the Flack parameters are somewhat poorly refined, thus, only the data for the structure with roughly 50% of each crystal block are presented in the Table 1.

Unlike **1**, crystallization of 1-(*p*-toluenesulfonyl)thymine (**2**), differing from **1** only in a methyl group at the C-5 position of the pyrimidine ring, gives rise to racemic single crystals with the space group *Pbca*. Comparison of cell parameters of **1** and **2** reveals that the cell of **2** is twice as large as that of **1**, by doubling of one crystallographic axis (Table 1). A closer insight into the crystal packing of both compounds offers the explanation. In **1** (Fig. 3), N3 of molecule **A** is directed toward O4 of molecule **B**, generated by the symmetry operation of the $2_1$ screw axis parallel to *c*. N3 of molecule **B** is oriented toward the O4 of the next molecule **C**, again generated by the same screw axis operation, etc. In such a way, endless N3H···O4 hydrogen bonded homochiral molecular ribbons are formed. A possible substituent at position C-5 of the pyrimidine ring of molecule **B** would obviously disturb such molecular organization, being too close to the O4 of the neighboring molecule and

**Table 1**. Crystallographic data of *N*-sulfonylpyrimidine derivatives **1–6**

| Compound | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| Mol. formula | $C_{11}H_{10}N_2O_4S$ | $C_{12}H_{12}N_2O_4S$ | $C_{11}H_9BrN_2O_4S$ | $C_5H_6N_2O_4S$ | $C_{14}H_{10}N_2O_4S$ | $C_{15}H_{12}N_2O_4S$ |
| $M_r$ | 266.06 | 280.31 | 345.17 | 190.18 | 302.3 | 316.33 |
| Crystal system | Orthorhombic | Orthorhombic | Monoclinic | Monoclinic | Orthorhombic | Monoclinic |
| Space group | $P2_12_12_1$ | *Pbca* | $P2_1/a$ | $P2_1/c$ | $P2_12_12_1$ | $P2_1/c$ |
| *a*/Å | 6.8883(3) | 12.8617(5) | 4.9562(2) | 6.8490(2) | 6.971(2) | 11.8733(5) |
| *b*/Å | 12.3467(5) | 13.8495(5) | 23.540(10) | 8.9117(4) | 10.568(3) | 5.5842(3) |
| *c*/Å | 13.5068(4) | 14.1720(6) | 11.2432(8) | 12.9350(4) | 18.076(4) | 21.4698(13) |
| $\beta$/° | 90.00 | 90.00 | 101.847(5) | 102.381(2) | 90.00 | 100.976(4) |
| *V*/Å$^3$ | 1148.72(8) | 2524.43(17) | 1283.8(6) | 771.14(5) | 1331.7(6) | 1397.14(13) |
| Z | 4 | 8 | 4 | 4 | 4 | 4 |
| $D_x$/g cm$^{-3}$ | 1.540 | 1.475 | 1.786 | 1.638 | 1.508 | 1.503 |
| Solvent used | Methanol | Methanol | Methanol | Methanol | Methanol | Methanol |
| Crystal color | Colorless | Colorless | Colorless | Colorless | Colorless | Colorless |
| Crystal dim. (mm) | 0.12×0.14×0.15 | 0.13×0.14×0.15 | 0.10×0.12×0.18 | 0.18×0.20×0.24 | 0.10×0.12×0.16 | 0.10×0.15×0.18 |
| $\mu$ (Cu K$\alpha$)/mm$^{-1}$ | 2.621 | 2.414 | 6.022 | 3.623 | 2.342 | 2.258 |
| Absorption corr. | None | $\Psi$-Scans | $\Psi$-Scans | $\Psi$-Scans | None | $\Psi$-Scans |
| Total data | 29,252 | 2644 | 2999 | 1692 | 3098 | 2999 |
| Unique data | 2609 | 2644 | 2686 | 1619 | 2651 | 2914 |
| Observed data | 2193 | 2007 | 1620 | 1506 | 2473 | 2092 |
| $R_{int}$ | 0.0789 | 0.0000 | 0.0515 | 0.0927 | 0.0221 | 0.0325 |
| $R_\sigma$ | 0.0615 | 0.0253 | 0.0922 | 0.0189 | 0.0278 | 0.0399 |
| $\theta_{max}$/° | 76.49 | 76.38 | 76.25 | 76.33 | 76.51 | 76.30 |
| *hkl* limits | −8→8; −16→16; −17→17 | −17→0; −16→0; 0→17 | 0→6; 0→29; −14→13 | −8→8; 0→11; 0→16 | −8→8; −13→13; −22→22 | −14→14; 0→7; −27→0 |
| $R_1$ [$F_o$>4$\sigma$($F_o$)] | **0.075**, **0.071**[a] | **0.0426** | **0.0610** | **0.0483** | **0.0295** | **0.0487** |
| $wR_2$ ($F^2$), all data | 0.137, 0.132[a] | 0.1268 | 0.1557 | 0.1326 | 0.0770 | 0.1427 |
| Goodness of fit | 1.191, 1.084[a] | 1.027 | 1.081 | 1.118 | 1.073 | 1.008 |
| Flack parameter | **0.44(3)**, **0.45(3)**[b] | — | — | — | **0.004(18)** | — |
| Variables | 164 | 175 | 173 | 122 | 191 | 203 |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$/eÅ$^{-3}$ | 0.30, −0.25 | 0.26, −0.19 | 0.66, −0.68 | 0.55, −0.59 | 0.21, −0.22 | 0.39, −0.30 |

[a] The values obtained with the TWIN/BASF refinement.
[b] BASF parameter.

hence producing strong repulsive interactions. One of the possible solutions to avoid repulsion and reestablish the sustainable structure would be the rotation of the pyrimidine ring of molecule **B** by 180°. This motion changes the chirality of molecule **B**, and brings its N3H into the position to donate a hydrogen bond to the O4 of molecule **A**, hence forming the hydrogen bonded heterochiral molecular dimer **AB**. This is precisely the molecular arrangement observed in the structure of **2**. Compound **2** crystallizes in a centrosymmetric space group, with the crystal structure being dominated by molecular dimers instead of the zigzag homochiral ribbons like in **1**.

Similar phenomena occurring in some structurally different sulfonyl compounds were recently reported.[32,33] Crystal packing of 5-bromo-1-(*p*-toluenesulfonyl)uracil (**3**) (Fig. 4), expectedly, greatly resembles that of **2**. In this compound, position C-5 of the pyrimidine ring is occupied by a bromine atom, which, like the methyl group in **2**, prevents the formation of homochiral zigzag ribbons and causes the formation of packed heterochiral dimers. Hence, no spontaneous resolution was observed for **3** either.

In order to investigate whether the size and type of the substituent at the sulfonyl group could possibly trigger crystallization of the conglomerate, the synthesis and structural studies of 1-(methanesulfonyl)uracil (**4**) and 1-(1-naphthylsulfonyl)uracil (**5**) were performed. Unlike the case of **1**, which revealed the formation of racemically twinned crystals, its analogue with a small methyl substituent ($CH_3$–$SO_2$–),

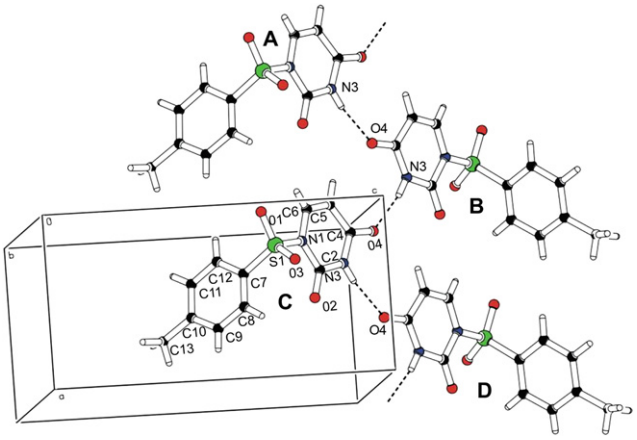



**Figure 3**. Crystal packing of 1-(*p*-toluenesulfonyl)uracil (**1**).

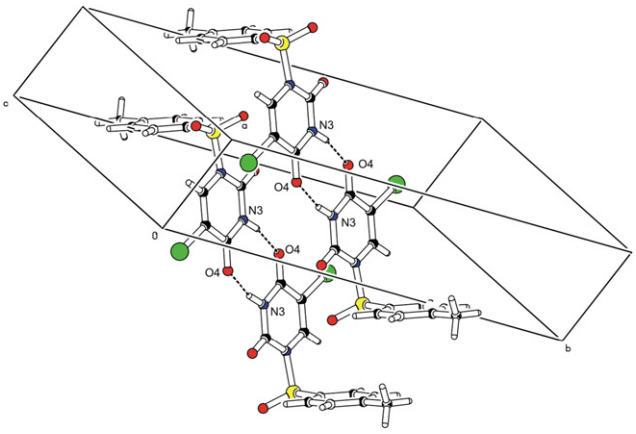



**Figure 4**. Crystal packing of 5-bromo-1-(*p*-toluenesulfonyl)uracil (**3**).

compound **4** crystallizes in a centrosymmetric space group $P2_1/c$. Crystal packing relies on the centrosymmetric dimers. We assumed that the introduction of an Ar–$SO_2$– substituent, sufficiently large to raise the racemization barrier above the value enabling a fast spontaneous enantiomeric interconversion, would result in enantiomerically pure single crystals.[34] Indeed, the randomly selected single crystal (denoted $\mathbf{5_1}$) of the naphthyl analogue **5** exhibited spontaneous chiral crystallization (space group $P2_12_12_1$). As demonstrated by the Flack parameter refinement, no racemic twinning like that in **1** was observed. The crystal and molecular structure of $\mathbf{5_1}$ revealed the exclusive presence of homochiral molecules possessing the M helicity (Fig. 2).

The presence of the conglomerate of **5** is additionally proven by the CD of solid pellets prepared by grinding the single crystal $\mathbf{5_1}$ and randomly selected another single crystal $\mathbf{5_2}$ with KBr.[35] Strong negative ($\mathbf{5_1}$) and strong positive ($\mathbf{5_2}$) CD peaks at $\lambda$=250 nm and two less intensive ones at 278 and 330 nm were observed, which correspond to $\lambda_{max}$ in the absorption spectrum of **5** in acetonitrile (Fig. 5). In contrast, dissolution of each $\mathbf{5_1}$ or $\mathbf{5_2}$ crystal sample in acetonitrile showed no CD peaks, pointing to fast equilibrium between the two enantiomeric conformers in solution.

The crystal packing of **5** is analogous to that of compound **1**, with the molecules connected through hydrogen bonds N3–H···O4*i*, into endless homochiral ribbons. Derivative **6**, differing from **5** only in a methyl group at position C-5 of the pyrimidine ring, crystallized in $P2_1/c$, with the centrosymmetric H-bonded dimers as the main structural motif. Its structure proved again the important role of the C-5 substituent for the absence or occurrence of spontaneous resolution in this class of compounds.

## 3. Conclusions

*N*-1-Sulfonyluracil derivatives **1–6** were prepared by the condensation of silylated pyrimidine bases with different sulfonyl chlorides in acetonitrile. We present the crystallographic evidence that this type of sulfonylpyrimidines exhibit conformational chirality in the solid state by the formation of chiral conformations of opposite helicity (Fig. 2). Analysis of crystal structures of derivatives possessing pyrimidine C-5 substituents (**2**, **3**, and **6**) shows that these derivatives organize in the solid state into heterochiral *meso*-dimers, giving centrosymmetric crystals of the racemic compound. In contrast, the absence of pyrimidine C-5 substituents in **1** and **5** results in the formation of racemically twinned crystals regardless of the solvent used and the formation of the conglomerate of the enantiomerically pure crystals, respectively. Two randomly chosen single crystals of **5** gave mirror like solid-state CD spectra confirming the presence of the conglomerate of enantiomerically pure single crystals. The solid-state supramolecular organization of **1** and **5** is similar, showing in each case the formation of infinite ribbons of intermolecularly hydrogen bonded homochiral molecules. Analysis of such organization reveals that it would be energetically much less favorable for the derivatives with C-5 pyrimidine substituents **2**, **3**, and **6** due to steric repulsion between the carbonyl O4 atom and the substituent in the C-5 position, as seen for the **A/C** and **B/D** molecules in Figure 3. The size and the structure of the sulfonyl substituents (R′, see Fig. 1) also have a profound influence on the occurrence of chiral crystallization. In the series methanesulfonyl **4**, *p*-toluenesulfonyl **1**, and 1-naphthylsulfonyl **5**, the racemic compound, the racemically twinned crystals containing various portions of enantiomerically related blocks and the conglomerate of the enantiomorphous crystals were obtained, respectively. The results presented here along with the observed substituent effects may endow the preparation of various new molecules of the general arylsulfonyl-nucleic base type capable of undergoing chiral crystallization and provide new examples of spontaneous generation of chirality by crystallization of achiral molecules.

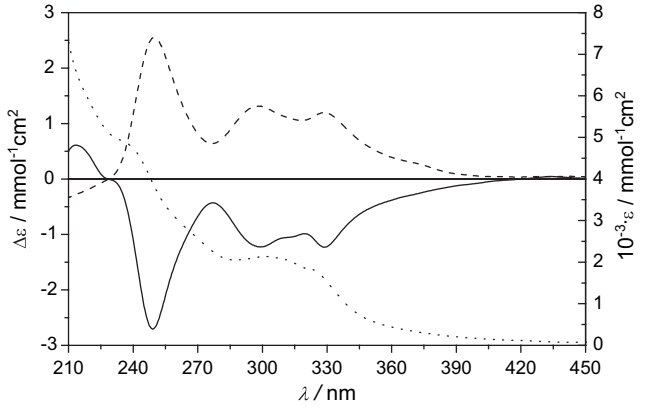



**Figure 5**. Solid-state CD spectra of 1-(1-naphthylsulfonyl)uracil (**5**)/KBr pellet: $\mathbf{5_1}$ (solid line, $c$=4.966×10$^{-3}$ mol dm$^{-3}$, $l$=0.5 mm) and $\mathbf{5_2}$ (dashed line, $c$=3.384×10$^{-3}$ mol dm$^{-3}$, $l$=0.5 mm). Solid-state absorption spectra of $\mathbf{5_1}$ (dotted line, $c$=4.966×10$^{-3}$ mol dm$^{-3}$, $l$=0.5 mm).

## 4. Experimental

### 4.1. General remarks

Solvents were distilled from appropriate drying agents shortly before use. TLC was carried out on DC-plastikfolien Kieselgel 60 $F_{254}$ and preparative thick layer (2 mm) chromatography was done on Merck 60 $F_{254}$. Flash column chromatography was performed on silica gel Merck 0.040–0.063 mm. Melting points were determined on a Kofler hot-stage apparatus and were uncorrected. UV spectra [$\lambda_{max}$/nm, log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$] were taken on a Philips PU8700 UV–Vis spectrophotometer. IR spectra were obtained as KBr pellets on a Perkin–Elmer 297 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker AV 300 and 600 MHz spectrometers using TMS or DMSO-$d_6$ as the internal standard.

### 4.2. Synthesis

**4.2.1. Reactions of silylated pyrimidine bases with different sulfonyl chlorides. General procedure.** A mixture of pyrimidine base (1 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (2 mmol) was heated under reflux in dry acetonitrile (3.3 mL) for 1 h. The solution was cooled to 0 °C and sulfonyl chloride (2 mmol) was added. The reaction mixture was heated for 20 h at 80 °C, cooled, and treated with a small amount of methanol. The resulting solid was filtered off and recrystallized.

**4.2.2. 1-(*p*-Toluenesulfonyl)uracil (1).** Starting materials: uracil (1 g, 8.9 mmol) and *p*-toluenesulfonyl chloride (3.39 g, 17.8 mmol). Recrystallization from hot methanol gave 1-[(4-methylphenyl)sulfonyl]pyrimidine-2,4(1*H*,3*H*)-dione (**1**), 2.25 g (95%) as white crystals: mp=259 °C (lit.[29] mp=238–239 °C); $R_f$=0.65 ($CH_2Cl_2$/MeOH, 9:1); UV (MeOH): $\lambda_{max}$/nm: 235 and 249 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 3.78 and 3.81); lit.[29] $\lambda_{max}$=256 nm (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 3.95).

Additional data for 1-(*p*-toluenesulfonyl)uracil **1**: IR (KBr) $\nu_{max}$/cm$^{-1}$: 3120 (w), 3030 (w), 2830 (w), 1730 (s), 1700 (s), 1615 (w), 1595 (w), 1405 (m), 1355 (m), 1250 (s), 1190 (s), 1170 (s), 1030 (m), 680 (m), 655 (m); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 11.74 (s, 1H, NH), 8.15 (d, 1H, $J_{6,5}$=8.4 Hz, H-6), 7.93 (d, 2H, $J$=8.3 Hz, Ts-b), 7.50 (d, 2H, $J$=8.3 Hz, Ts-c), 5.86 (d, 1H, $J_{5,6}$=8.4 Hz, H-5), 2.42 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 163.07 (s, C-4), 147.54 (s, C-2), 146.64 (s, Ts-d), 138.26 (d, C-6), 133.42 (s, Ts-a), 130.16 (d, Ts-c), 129.19 (d, Ts-b), 104.05 (d, C-5), 21.27 (q, $CH_3$). Anal. Calcd for $C_{11}H_{10}N_2O_4S$ ($M_r$=266.22): C 49.63, H 3.79, N 10.53; found: C 49.62, H 3.65, N 10.51%.

The phenyl proton (Ts) assignments were confirmed by carbon–proton connectivity in the $^1$H/$^{13}$C heteronuclear correlation spectra (HETCOR). Additionally, in the NOESY spectrum of **1**, the assignment of Ts-c protons was proved by their interaction with methyl protons.

**4.2.3. 1-(*p*-Toluenesulfonyl)thymine (2).** Starting materials: thymine (1 g, 7.93 mmol) and *p*-toluenesulfonyl chloride (3.02 g, 15.86 mmol). The reaction mixture was evaporated under reduced pressure and the residue was treated with methylene chloride and filtered. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure, and the crude product was recrystallized from methylene chloride/hexane mixture yielding 5-methyl-1-[(4-methylphenyl)sulfonyl]pyrimidine-2,4(1*H*,3*H*)-dione (**2**) as white crystals: 1.91 g (86%); mp=118–120 °C; $R_f$=0.8 ($CH_2Cl_2$/MeOH, 9:1); UV (MeOH) $\lambda_{max}$/nm: 233 and 252 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 3.85 and 3.92); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3174 (w), 3053 (w), 2824 (w), 1728 (s), 1675 (s), 1590 (m), 1416 (m), 1331 (s), 1251 (s), 1167 (s), 1082 (s), 1034 (s), 987 (s), 886 (m), 812 (m), 743 (m), 674 (m); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 11.74 (s, 1H, NH), 8.04 (d, 1H, $J$=1.3 Hz, H-6), 7.91 (d, 2H, $J$=8.1 Hz, Ts-b), 7.49 (d, 2H, $J$=8.1 Hz, Ts-c), 2.43 (s, 3H, $CH_3$-Ts) 1.86 (d, 3H, $J$=1.3 Hz, C-5–$CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 163.48 (s, C-4), 147.28 (s, C-2), 146.10 (s, Ts-d), 133.44 (s, Ts-a), 132.97 (d, C-6), 129.81 (d, Ts-c), 128.75 (d, Ts-b), 111.54 (s, C-5), 21.15 (q, $CH_3$-Ts), 12.12 (q, C-5–$CH_3$). Anal. Calcd for $C_{12}H_{12}N_2O_4S$ ($M_r$=280.30): C 51.42, H 4.32, N 9.99; found: C 51.39, H 4.36, N 10.02%.

**4.2.4. 5-Bromo-1-(*p*-toluenesulfonyl)uracil (3).**

**4.2.4.1. General procedure.** Starting materials: 5-bromouracil (1 g, 5.24 mmol) and *p*-toluenesulfonyl chloride (2 g, 10.48 mmol). Recrystallization from a hot mixture methanol/water (1:1) gave 5-bromo-1-[(4-methylphenyl)-sulfonyl]pyrimidine-2,4(1*H*,3*H*)-dione (**3**) as white crystals: 1.03 g (57%); mp=248–250 °C; $R_f$=0.63 ($CH_2Cl_2$/MeOH, 20:1); UV (MeOH) $\lambda_{max}$/nm: 233 and 270 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 3.05 and 3.02); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3150 (w), 3050 (w), 2920 (w), 2840 (w), 1750 (s), 1675 (s), 1610 (m), 1590 (m), 1420 (m), 1250 (s), 1175 (s), 1080 (m), 1060 (m), 995 (m); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 12.12 (s, 1H, NH), 8.43 (s, 1H, H-6), 8.00 (d, 2H, $J$=8.1 Hz, Ts-b), 7.51 (d, 2H, $J$=8.1 Hz, Ts-c), 2.44 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 159.06 (s, C-4), 146.77 (s, C-2), 146.65 (s, Ts-d), 136.88 (d, C-6), 132.86 (s, Ts-a), 129.94 (d, Ts-c), 129.35 (d, Ts-b), 98.91 (s, C-5), 21.32 (q, $CH_3$). Anal. Calcd for $C_{11}H_9N_2O_4SBr$ ($M_r$=345.17): C 38.28, H 2.63, N 8.12; found: C 38.34, H 2.47, N 8.10%.

**4.2.4.2. Bromination of 1-(*p*-toluenesulfonyl)uracil (1).** 1-(*p*-Toluenesulfonyl)uracil **1** (200 mg, 0.75 mmol) was dissolved in dry DMF (13 mL), and a solution of bromine in dichloromethane (2.2 mL, 1.65 mmol; 1 mL $Br_2$/25 mL $CH_2Cl_2$) was added dropwise. The red solution was stirred at room temperature for 4 h, and the solvent was evaporated under pressure. Ethanol was added into the remaining oil, and the obtained solid was filtered off and recrystallized from hot water, yielding product **3**, as white crystals, 140 mg (54%), identical to those obtained by the method in Section 4.2.4.1.

**4.2.4.3. Reaction of 5-bromouracil with *p*-toluenesulfonyl chloride in pyridine.** A solution of 5-bromouracil (**2**) (2 g, 10.5 mmol) in dry pyridine (40 mL) was cooled to 0 °C and *p*-toluenesulfonyl chloride (4 g, 21 mmol) was added. After stirring at room temperature overnight, the resulting dark suspension was evaporated under pressure. Methanol was added and the obtained brown solid was filtered off. After a few recrystallizations from the hot methanol/water mixture (1:1), product **3** was obtained in 45% yield.

**4.2.5. 1-(Methanesulfonyl)uracil (4).** Starting materials: uracil (0.5 g, 4.45 mmol) and methanesulfonyl chloride (0.69 mL, 8.9 mmol). Recrystallization from hot methanol gave the analytically pure product 1-(methylsulfonyl)-pyrimidine-2,4(1*H*,3*H*)-dione (**4**) as white crystals: 7.6 g (75%); mp=228–231 °C; $R_f$=0.81 ($CH_2Cl_2$/MeOH, 3:1); UV (MeOH) $\lambda_{max}$/nm: 211 and 245 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 3.86 and 3.93); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3200 (m), 3080 (m), 2950 (w), 2850 (w), 1725 (s), 1695 (s), 1640 (m), 1440 (s), 1360 (s), 1275 (s), 1180 (s), 1170 (s), 970 (s), 820 (m), 780 (m), 760 (m); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 11.87 (s, 1H, NH), 7.87 (d, 1H, $J$=8.3 Hz, H-6), 5.80 (d, 1H, $J$=8.3 Hz, H-5), 3.70 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 163.28 (s, C-4), 148.76 (s, C-2), 138.23 (d, C-6), 103.41 (d, C-5), 41.62 (q, $CH_3$). Anal. Calcd for $C_5H_6N_2O_4S$ ($M_r$=190.18): C 31.58, H 3.18, N 14.73; found: C 31.81, H 3.06, N 14.89%.

**4.2.6. 1-(1-Naphthylsulfonyl)uracil (5).** Starting materials: uracil (0.5 g, 4.46 mmol) and 1-naphthalenesulfonyl chloride (2.08 g, 8.92 mmol). The reaction mixture was evaporated under reduced pressure and the residue was treated with methylene chloride and filtered. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure, and the crude product was recrystallized from methylene chloride/methanol mixture yielding

1-(1-naphthylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-dione (**5**) as white crystals: 1.09 g (81%); mp=185–186 °C; $R_f$=0.71 ($CH_2Cl_2$/MeOH, 9:1); UV (MeOH): $\lambda_{max}$/nm: 209, 233, 300, and 321 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 4.75, 4.62, 4.00, and 3.79); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3430 (w), 3031 (w), 2840 (w), 1733 (s), 1697 (s), 1558 (w), 1542 (w), 1460 (m), 1243 (s), 1176 (m), 1089 (m) 1032 (w), 750 (m), 580 (s); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 11.73 (s, 1H, NH), 8.54 (pt, 2H, Ph, H-6), 8.47 (d, 1H, Ph), 8.21 (br d, 2H, Ph), 7.80 (m, 2H, Ph), 7.72 (t, 1H, Ph), 5.94 (d, 1H, $J_{5,6}$=8.4 Hz, H-5); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 162.54 (s, C-4), 147.06 (s, C-2), 138.01 (d, C-6), 136.92 (d, Ph), 133.97 (d, Ph), 133.59 (s, Ph), 130.61 (s, Ph), 129.81 (d, Ph), 129.55 (d, Ph), 127.36 (d, Ph), 126.87 (s, Ph), 124.60 (d, Ph), 122.25 (d, Ph), 104.10 (d, C-5). Anal. Calcd for $C_{14}H_{10}N_2O_4S$ ($M_r$= 302.31): C 55.62, H 3.33, N 9.27; found: C 55.59, H 3.38, N 9.30%.

**4.2.7. 1-(1-Naphthylsulfonyl)thymine (6).** Starting materials: thymine (0.5 g, 3.96 mmol) and 1-naphthalenesulfonyl chloride (1.85 g, 7.92 mmol). The reaction mixture was evaporated under reduced pressure and the residue was treated with methylene chloride and filtered. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure, and the crude product was recrystallized from hot methanol yielding 5-methyl-1-(1-naphthylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-dione (**6**) as white crystals: 0.98 g (78%); mp=155–157 °C; $R_f$=0.87 ($CH_2Cl_2$/MeOH, 9:1); UV (MeOH): $\lambda_{max}$/nm: 232, 254, 300, and 321 (log $\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$: 4.62, 4.14, 4.08, and 3.84); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3448 (m), 3040 (w), 2850 (w), 1735 (s), 1672 (s), 1427 (m), 1370 (m), 1257 (s), 1174 (s), 1181 (m), 1038 (m), 765 (m), 686 (m), 579 (s); $^1$H NMR (DMSO-$d_6$) $\delta$/ppm: 11.70 (s, 1H, NH), 8.51–8.40 (m, 3H, Ph and H-6), 8.25–8.17 (m, 2H, Ph), 7.77–7.68 (m, 3H, Ph), 1.94 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$/ppm: 163.38 (s, C-4), 147.14 (s, C-2), 136.65 (d, Ph), 133.65 (d, Ph), 133.52 (s, Ph), 132.69 (d, C-6), 130.95 (s, Ph), 129.67 (d, Ph), 129.43 (d, Ph), 127.26 (d, Ph), 126.87 (s, Ph), 124.52 (d, Ph), 122.38 (d, Ph), 112.01 (s, C-5), 12.13 (q, $CH_3$). Anal. Calcd for $C_{15}H_{12}N_2O_4S$ ($M_r$=316.33): C 56.95, H 3.82, N 8.86; found: C 56.91, H 3.80, N 8.81%.

### 4.3. X-ray structural analysis

Data collection was done on an Enraf Nonius CAD4 diffractometer using the graphite monochromated Cu K$\alpha$ radiation. The structures were solved with SIR97[35] and refined with SHELXL97.[36] The models were refined using the full matrix least squares refinement. The atomic scattering factors were those included in SHELXL97. Hydrogen atoms were refined as the riding entities, except for those included in hydrogen bonds, which were located in the Fourier maps and freely refined. In the final steps of refinement, the proposed weighting schemes were applied. Molecular geometry calculations were performed with PLATON,[37] and molecular graphics were prepared using ORTEP-3[38] and CCDC-Mercury.[39]

Crystallographic data (excluding structural factors) for the structures in this paper have been deposited in the Cambridge Crystallographic Data Centre as a supplementary publication (**1**, CCDC 610048; **2**, CCDC 610049; **3**, CCDC 610050; **4**, CCDC 610051; **5**, CCDC 610052; **6**, CCDC 610053). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

**Table 2**. CD and absorption bands in crystal samples of **5**

| **5$_1$** | | **5$_2$** | | **5$_1$** | |
|---|---|---|---|---|---|
| CD | | CD | | A | |
| $\lambda$ (nm) | $\varepsilon$ (mmol$^{-1}$ cm$^2$) | $\lambda$ (nm) | $\varepsilon$ (mmol$^{-1}$ cm$^2$) | $\lambda$ (nm) | $\varepsilon$ (mmol$^{-1}$ cm$^2$) |
| 249 | −2.7 | 250 | 2.55 | | |
| 277 | −0.43 | 276.5 | 0.64 | | |
| 299 | −1.22 | 298 | 1.31 | | |
| 319.5 | −0.99 | 318.5 | 1.06 | 301.5 | 2134.6 |
| 329 | −1.23 | 329 | 1.2 | | |

### 4.4. CD spectroscopy

The solid-state circular dichroism spectra of the single crystal **5$_1$** whose crystal structure was determined and the randomly selected another single crystal **5$_2$** from the same batch were recorded as KBr discs on a JASCO J-810 spectropolarimeter. For each sample, the KBr disc was rotated at ~30° intervals and at least five spectra were averaged to cancel the inevitable slight inhomogeneities in the disc. The value of $\Delta\varepsilon$, given in CD spectra was calculated by using the concentration as molarity of the sample in KBr after correction for density of KBr disc, and using measured thickness of the KBr disc (by micrometer) as a path length (Table 2). Use of absorption for calibration is not recommended, because the absolute value is unreliable due to light scattering.[40]

## Acknowledgements

We thank the Ministry of Science, Education, and Sport of the Republic of Croatia for financial support of this study.

## Supplementary data

Supplementary data, including ortep plots for compounds **1**–**6** and crystal packing for compounds **2**, **4**, **5**, and **6** can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.048.

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