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Structure Determination and Comparison of BM567, a Sulfonylurea, with Terbogrel, Two Compounds with Dual Action, Thromboxane Receptor Antagonism and Thromboxane Synthase Inhibition

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Abstract—BM567, a sulfonylurea compound—whose crystal structure is here discussed—and terbogrel, are both thromboxane receptor antagonists and thromboxane synthase inhibitors. In this paper, their crystallographic and electronic structures are compared and lead to new synthesis prospects among the sulfonylurea series.

Thromboxane A_2 (TXA_2), an unstable endogenous arachidonic acid metabolite, plays a role in platelet aggregation, and broncho- and vasoconstriction.[1] It is implicated in cardiovascular, renal and pulmonary diseases. Thromboxane synthase inhibitors (TXSIs) and thromboxane receptor antagonists (TXRAs) have been developed to treat these disorders.[2,3] However, TXSIs have not shown clinical efficacy due to the accumulation of PGH_2,[4] a thromboxane receptor agonist. The combination of TXSI and TXRA activity was proved to be better than that of selective compounds[5,6] and different series of compounds with this dual action have been developed.[7–10]

In our laboratory, a series of sulfonylureas, including BM567 (**1**), has been designed and were found to be both TXSIs and TXRAs (Table 1).[11] So they represent a novel chemical family of therapeutic agents.

Here we report the structure determination of BM567 (**1**) and its structural comparison with terbogrel (**2**) with dual action (Table 1).[12]

The molecular electrostatic potential (MEP) has been calculated on both compounds and pK_a of BM567 measured leading to a pharmacophore that provides ideas to improve dual action of BM567.

Crystal Structure of BM567

Crystal structure of BM567 (**1**) was first refined against room temperature data.[13] The pentyl chain was disordered and electron density not well defined, so low temperature data (−80 °C) were collected. The structure refined with this procedure has a lower *R* factor (6.57%) and therefore coordinates corresponding to this model were retained in this work.

Although reduced in the low temperature structure, thermal motion on the pentyl chain was still too high to allow reasonable anisotropic refinement of this chain or clear introduction of disorder. The great flexibility of pentyl is possibly due to its poor stabilisation in the crystal packing.

Based on the torsion angles along the sulfonylurea group (ϕ1, ϕ2, ϕ3 and ϕ4), both molecules (a and b) in the asymmetric unit adopt two distinct conformations (Table 2). Previously, four conformations have been

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obtained on pyrid-3-ylsulfonylurea and sulfonylcyanoguanidine:[14] α, β, γ and δ. Here we find one of these conformations, γ, and a novel conformation, ε (see ORTEP representation in Table 2). They essentially differ by opposite signs of ϕ1 and ϕ2.

The crystal packing of **1** was also analysed. Molecular cohesion is mainly assumed by intra- and intermolecular hydrogen bonds (Table 3).

In particular, one intramolecular hydrogen bond [N7a−H7a...O19a with 2.905(6) Å and N7b−H7b...018b with 2.801(6) Å] involves one oxygen atom of the sulfonyl group and imposes the conformation (in particular ϕ1) to the molecule (Fig. 1). The sulfonylurea moiety is also involved in additional hydrogen bonds (Table 3) and could represent a potential anchoring point for the binding with the TXA_2 receptor or with thromboxane synthase.

Conformation of Terbogrel

The crystal structure of terbogrel (**2**) has been determined previously in our lab from row temperature data. The hairpin-like conformation observed for this molecule (Fig. 2)[15] is in agreement with another report.[12]

Electronic Properties of Terbogrel and BM567

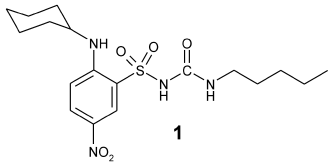
In order to quantify interaction between the receptor sites and **1**, the pK_a of this molecule was first determined by absorption spectrophotometry. Absorbance of BM567 solutions at different pH was measured. As bathochromic shifts of the absorbance peak of solutions of **1** are observed as the pH increases, λ_{max} was expressed as a function of pH. Sigmoid curves are obtained and give access to a pK_a of 4.73 for BM567 (Fig. 3).

Due to this value of pK_a, **1** is ionised at physiological pH. The ionisation site is probably the N20H20 nitrogen of the sulfonylurea (Table 2) adjacent to two withdrawing groups (a sulfone and a carbonyl group).

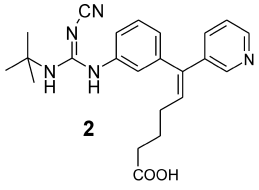
MEP was also calculated (ab initio, 6–31 g*) on the ionised sulfonylurea. This reveals an electronic delocalisation from the ionised N20 nitrogen to the oxygens of the sulfone (−140 kcal/mol) and of the carbonyl (−170 kcal/mol). Thus, not only the N20 alone but all the sulfonamide group (SO_2NHCO) can be involved in a salting bridge with the receptor proteins. This is in agreement with the analysis of the crystal packing already underlining the importance of this group in H bond formation.

For **2**, the pK_a of the molecule should be close to the classical value for a carboxylic acid (around 4.7). So terbogrel is also ionised at physiological pH. The MEP calculated on the ionised (carboxylate) form of terbo-

Table 1. In vitro activity of BM567 and terbogrel



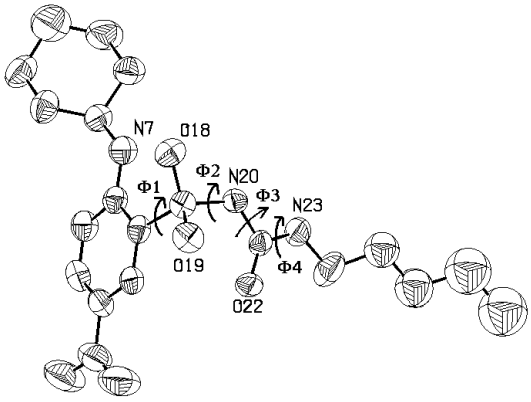
1



2

Compound	TXA_2 receptor antagonism	TXA_2 synthase inhibition
1	IC_{50}: 1.1±0.1 (nM)	97.4% inhibition at 10^{-6} M
2	IC_{50}: 11±6 (nM)	IC_{50}: 4.0±0.5 (nM)

Table 2. Torsion angles along the sulfonylurea group of conformation ε of BM567



Conformer	ϕ1 (°)	ϕ2 (°)	ϕ3 (°)	ϕ4 (°)
γ	68.1(4) (+90)	69.8(4) (+90)	−175.9(3) (180)	−179.2(4) (180)
ε	−79.1(4) (−90)	−65.0(4) (−90)	169.6(3) (180)	−179.1(4) (180)

Table 3. Hydrogen bonds of the two crystal conformations (a and b) of BM567

BM567 Conformer	H bond	D...A (Å)	H...A (Å)	D-H...A (°)
γ	N7a-H7a...O19a	2.905 (6)	2.365	119.8
	N20a-H20a...O22b$_i$	2.900 (5)	2.129	145.9
	N23a-H23a... O22b$_i$	2.898 (5)	2.093	151.6
ε	N7b-H7b...O18b	2.801 (6)	2.114	134.4
	N20b-H20b...O22a	2.712 (5)	1.930	147.3
	N23b-H23b...O18a	3.108 (5)	2.431	134.0
	N23b-H23b...O22a	3.201 (5)	2.481	139.3

i: 1/2−x, 1/2−y, −1/2+z

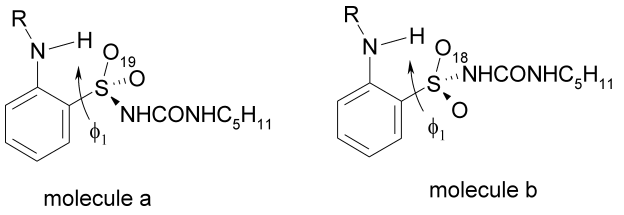


Figure 1. Two possible conformations of the sulfonylurea compounds controlled by intramolecular H bond.

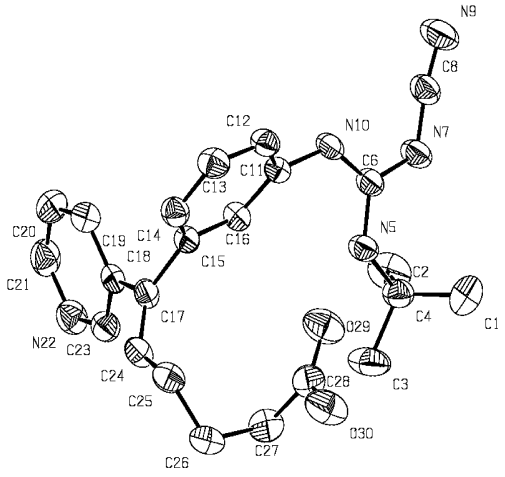


Figure 2. Hairpin-like conformation of terbogrel (**2**) deduced by X-ray crystallography.[15]

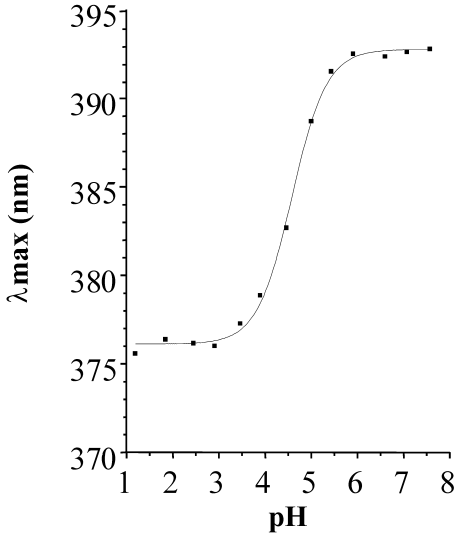


Figure 3. Determination of pK_a of BM567 by absorption spectrophotometry. λ_{max} expressed in term of pH gives access to the pK_a of the molecule (pH at the inflection point of the sigmoid curve).

grel shows a negative zone (−190 kcal/mol) located on the carboxylate group.

According to this analysis, we suggest that the sulfonyl group of BM567 could play a role similar to the one of the carboxylic acid function of terbogrel.

Comparison of BM567 with Terbogrel

Superposition of the crystal structure of terbogrel (**2**) and BM567 (**1**) was performed based on the stereoelectronic characteristics of both molecules. The γ conformation of **1** superimposes better on the hairpin-like conformation of **2** than the ε conformation (Fig. 4).

Negative regions of the MEP calculated on both compounds (corresponding to the sulfonyl group and carboxylate in **1** and **2**, respectively) correspond. The nitro group of BM567 also superimposes on the pyridine nitrogen and corresponds to the basic function required for TXSI activity.[16]

Original ideas about enhancement of dual action of BM567 can emerge from this superposition. In particular, the space occupied by the cyanoguanidine group of terbogrel could be filled by substituting the equatorial 2-position of the cyclohexyl group of BM567 (Fig. 5). This leads to new synthesis prospects among the sulfonylurea nitrobenzenic series.

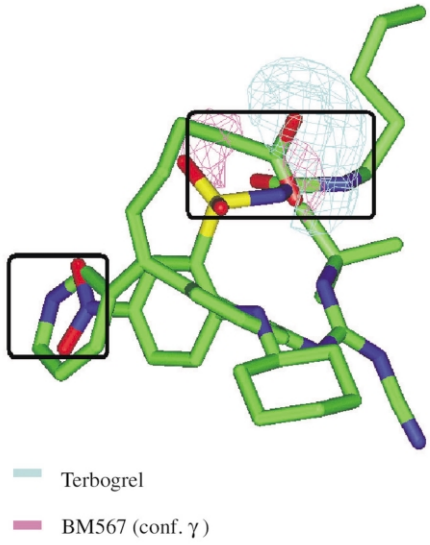


Figure 4. Superposition of terbogrel and BM567 (conformation γ) with their MEP (−150 kcal/mol).

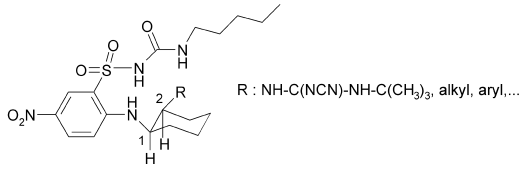


Figure 5. Synthesis prospects among the sulfonylurea BM567.

Conclusions

By comparing crystallographic and electronic properties of BM567 and terbogrel, two compounds with dual action (TXRA and TXSI), two essential anchoring

points for each of these compounds can be potentially identified: sulfonyl and nitro group of BM567 and carboxylate and pyridine nitrogen of terbogrel. Synthesis hypotheses were proposed among the sulfonylurea nitrobenzenic series from the superposition of these two molecules.

Experimental

Crystal source. Crystals of BM567 were obtained by slow evaporation of an ethanol solution.

Crystal, collection and refinement data. $C_{18}H_{28}O_5$, tetragonal, I_4, $a=b=21.388(3)$ Å, $c=18.467(4)$ Å, $V=8448(2)$ Å^3, $Z=16$, $\mu=1.67$ mm^{-1}, $D_x=1.297$ g cm^{-3}, λ (CuK_α) = 1.54178 Å, F(000) = 3520, $T=193$ K, 5574 unique reflections ($R_{int}=0.0452$), $R_1=0.0662$ for 4919 $F_o > 2\sigma(F_{o2})$ and w$R_2=0.1829$, GooF = S = 1.036. Full matrix least-squares on F^2 using the program SHELXL97.[19] Data have been corrected for absorption effects.

Lists of atomic coordinates, displacement parameters, and complete geometry have been deposited with the IUCr.

Programs. Data collection: Enraf-Nonius CAD-4. Cell refinement: Enraf-Nonius CAD-4. Data reduction: HELENA.[17] Solution: SIR97.[18] Refinement: SHELXL97.[19] Molecular graphics: PLATON.[20] Software used to prepare material for publication: SHELXL97.[19]

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