Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

FJ6, *N*-methyl-*N*-(4-nitro-2-phenoxyphenyl)-methanesulfonamide

Catherine Michaux,[a]* Caroline Charlier,[a] Fabien Julémont,[b] Bernadette Norberg,[a] Jean-Michel Dogné[b] and François Durant[a]

[a]Lab. Chimie Moléculaire Structurale, Facultés Universitaires N.-D. de la Paix, 61 Rue de Bruxelles, B-5000 Namur, Belgium, and [b]Service de Chimie Pharmaceutique, 1 Avenue de l'Hôpital, B-4000 Liège, Belgium

Correspondence e-mail: catherine.michaux@fundp.ac.be

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.041
wR factor = 0.118
Data-to-parameter ratio = 14.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

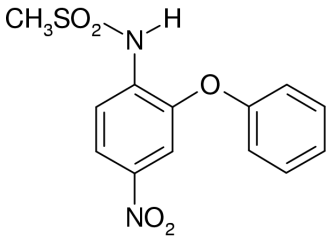
Received 19 September 2001
Accepted 26 September 2001
Online 6 October 2001

FJ6, *N*-methyl-*N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide, $C_{14}H_{14}N_2O_5S$, is an analogue of nimesulide, a selective inhibitor of cyclooxygenase-2. The structure of the title compound has been characterized to understand its inactivity towards cyclooxygenase-2.

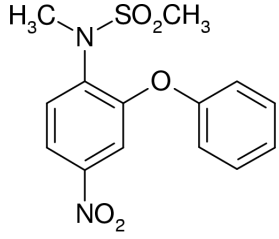
Comment

The crystal structure of *N*-(4-nitro-2-phenoxyphenyl)-methanesulfonamide, nimesulide, (I), has been previously described (Dupont *et al.*, 1995). It is reported as a selective inhibitor of cyclooxygenase-2 (COX-2) (Tavares & Bishai, 1995). In order to study the importance of the NH proton, an analogue of nimesulide, *N*-methyl-*N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide, FJ6, (II), was synthesized and its structure solved (Fig. 1). FJ6 appeared to be inactive as a COX inhibitor (Julémont, 2001).

The sole difference between the two compounds is that the sulfonamide N atom is protonated in nimesulide, while it is methylated in FJ6. The molecular conformation of nimesulide is stabilized by an intramolecular N17—H···O7 hydrogen bond, not available in FJ6. As a result, the orientation of the sulfonamide group differs from that in nimesulide,



(I)



(II)

while the position of the phenoxy group remains unchanged. This can be seen in the superposition of the two compounds (Fig. 2). The inactivity of FJ6 could be partly explained by this change in orientation. Indeed, the displacement of one of the O atoms of the sulfonamide group (O20) could prevent the formation of an hydrogen bond inside the COX-2 active site and consequently yield a less stable enzyme–ligand complex. Furthermore, the two methyl groups in FJ6 could lead to steric clashes in the COX-2 enzyme.

Moreover, S—O bond lengths are observed to be longer in nimesulide [1.431 (2) Å] than in FJ6 [1.418 (2) Å]. This suggests that electronic delocalization is more important for the O atoms of the sulfonamide group in nimesulide than in FJ6. Thus, O atoms of nimesulide will be able to form stronger

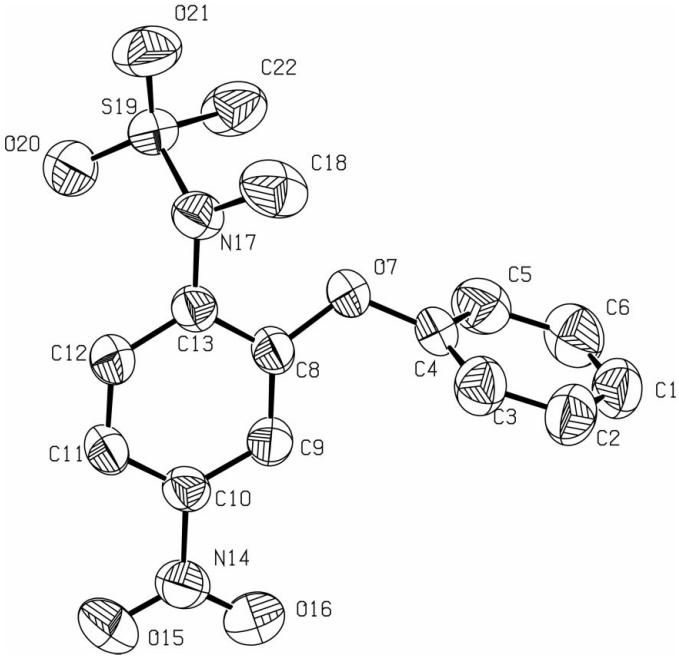


Figure 1
Displacement ellipsoid (50% probability) representation of FJ6.

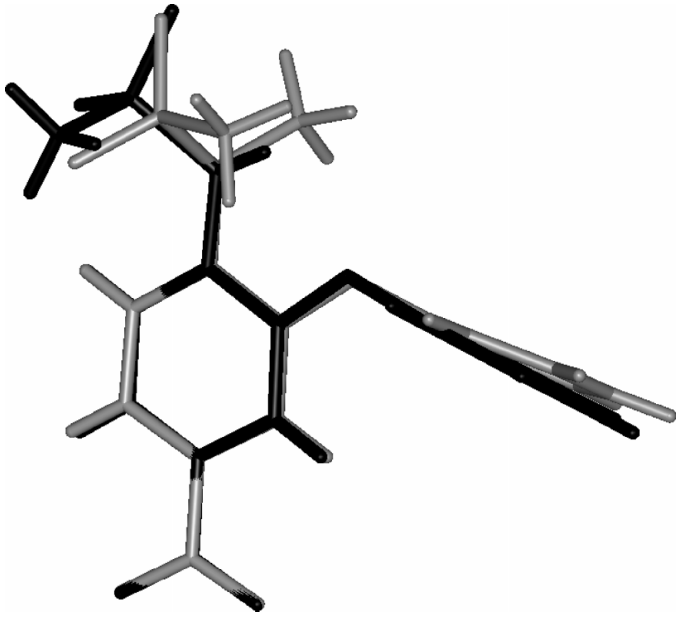


Figure 2
Superposition of nimesulide (in black) and FJ6 (in grey).

hydrogen bonds with COX-2 residues, increasing the interaction between the inhibitor and the enzyme.

In conclusion, the COX inactivity of the title compound could be partially related to its sulfonamide conformation and electronic properties, different from those observed in nimesulide.

Experimental

Crystal source: slow evaporation of a solution of FJ6 with methanol at 277 K gave colourless crystals suitable for X-ray analysis.

Crystal data

$C_{14}H_{14}N_2O_5S$	D_x = 1.423 Mg m^{-3}
M_r = 322.33	Cu $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 24 reflections
a = 14.522 (1) Å	θ = 32–40°
b = 10.439 (1) Å	μ = 2.16 mm^{-1}
c = 10.523 (1) Å	T = 293 (2) K
β = 109.460 (4)°	Polyhedral, colourless
V = 1504.1 (2) Å^3	0.46 × 0.36 × 0.15 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.034
ω/θ scans	θ_{max} = 71.9°
Absorption correction: analytical (de Meulenaer & Tompa, 1965)	$h = -17 \rightarrow 0$
T_{min} = 0.411, T_{max} = 0.743	$k = -11 \rightarrow 12$
5119 measured reflections	$l = -12 \rightarrow 12$
2951 independent reflections	3 standard reflections every 200 reflections
2747 reflections with $I > 2\sigma(I)$	frequency: 60 min
	intensity decay: 5%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.061P)^2 + 0.373P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.041	$(\Delta/\sigma)_{max}$ = 0.005
$wR(F^2)$ = 0.118	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.31 e Å^{-3}
2951 reflections	Extinction correction: *SHELXL*97
203 parameters	Extinction coefficient: 0.0139 (8)
H-atom parameters constrained	

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1992); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *PLATON* (Spek, 2001); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON*; software used to prepare material for publication: *SHELXL*97.

CM thanks the FRIA for financial support. The authors thank the Facultés Universitaires Notre–Dame de la Paix for the use of the Scientific Computing Facility and the French Community of Belgium for financial support.

References

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Dupont, L., Pirotte, B., Masereel, B. & Delarge, J. (1995). *Acta Cryst.* C**51**, 507–509.
Enraf–Nonius (1992). *CAD*-4 *EXPRESS*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Julémont, F. (2001). 10th Forum of Pharmaceutical Sciences, Montréal, May 24–25, 2001.
Meulenaer, J. de & Tompa, H. (1965). *Acta Cryst.* **19**, 1014–1018.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2001). *PLATON*. Utrecht University, The Netherlands.
Tavares, I. A. & Bishai, P. M. (1995). *Arzneimittelforschung*, **10**, 1093–1095.