Electronic Supplementary Material (ESI) for Dalton Transactions.

Supporting information

Structural insight and in silico prediction of pharmacokinetic parameters of alkaline earth metals compounds: strontium and barium with non-steroidal anti-inflammatory drug nimesulide

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Synthesis

Nimesulide, strontium hydroxide and barium hydroxide were delivered from Sigma-Aldrich and used without preliminary purification. Melting points were determined on a Büchi M-565 (Flawil, Switzerland) capillary apparatus and were uncorrected.

Compound 1
Nimesulide (0.050 g, 0.162 mmol) and strontium hydroxide (0.020 g, 0.162 mmol) were dissolved in 20 mL of an ethanol/water mixture (1:1 v/v) and heated for 20 min to dissolve the sample. The solution was allowed to evaporate at room temperature for a few days to give yellow crystals of compound **2** (m.p. = 244°C).

Compound 2
Nimesulide (0.050 g, 0.162 mmol) and barium hydroxide (0.028 g, 0.162 mmol) were dissolved in 20 mL of an ethanol/water mixture (1:1 v/v) and heated for 20 min to dissolve the sample. The solution was allowed to evaporate at room temperature for a few days to give orange crystals of compound **1** (m.p. = 221°C).

Single-Crystal X-Ray Diffraction (SCXRD) measurements

SCXRD data were collected on an Oxford Diffraction Gemini R ULTRA Ruby CCD diffractometer MoKα (λ_{Mo}=0.71073 Å, T=293(2) K) (Table 1S, Fig. S1)[1]. CrysAlis RED software [1] (ver. 1.171.41.16a) was used to reduce diffraction data. SHELX package [2] (ver. 2017/1) was used to solve and refine received structures. Interactions were calculated using PLATON (ver. 181115) [3]. PLUTO-78 [4], ORTEPII [5] and Mercury [6] (ver. 2020.2.0) programs were used for preparing graphics. The benzene rings and nitro group in one nimesulide anion in compound **1** have disordered orientations with refined site-occupancy factors of the disordered parts of 0.610(7) and 0.390(7) (the disordered benzene rings were refined as rigid ideal hexagons with d(C–C) = 1.39 Å and constrained with isotropic displacement parameters). All H atoms bound to aromatic C atoms were placed geometrically and refined using a riding model with d(C–H) = 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C) (d(C–H) = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl group). H atoms bound to O atoms from water molecules were located on a Fourier difference map and refined with restraints (DFIX command) with U_{iso}(H) = 1.5U_{eq}(O).

Full crystallographic details the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (deposition No. CCDC 2332827 and CCDC 2332828 for compounds **1** and **2** respectively) and they may be obtained from www: http://www.ccdc.cam.ac.uk, e-mail: deposit@ccdc.cam.ac.uk or The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

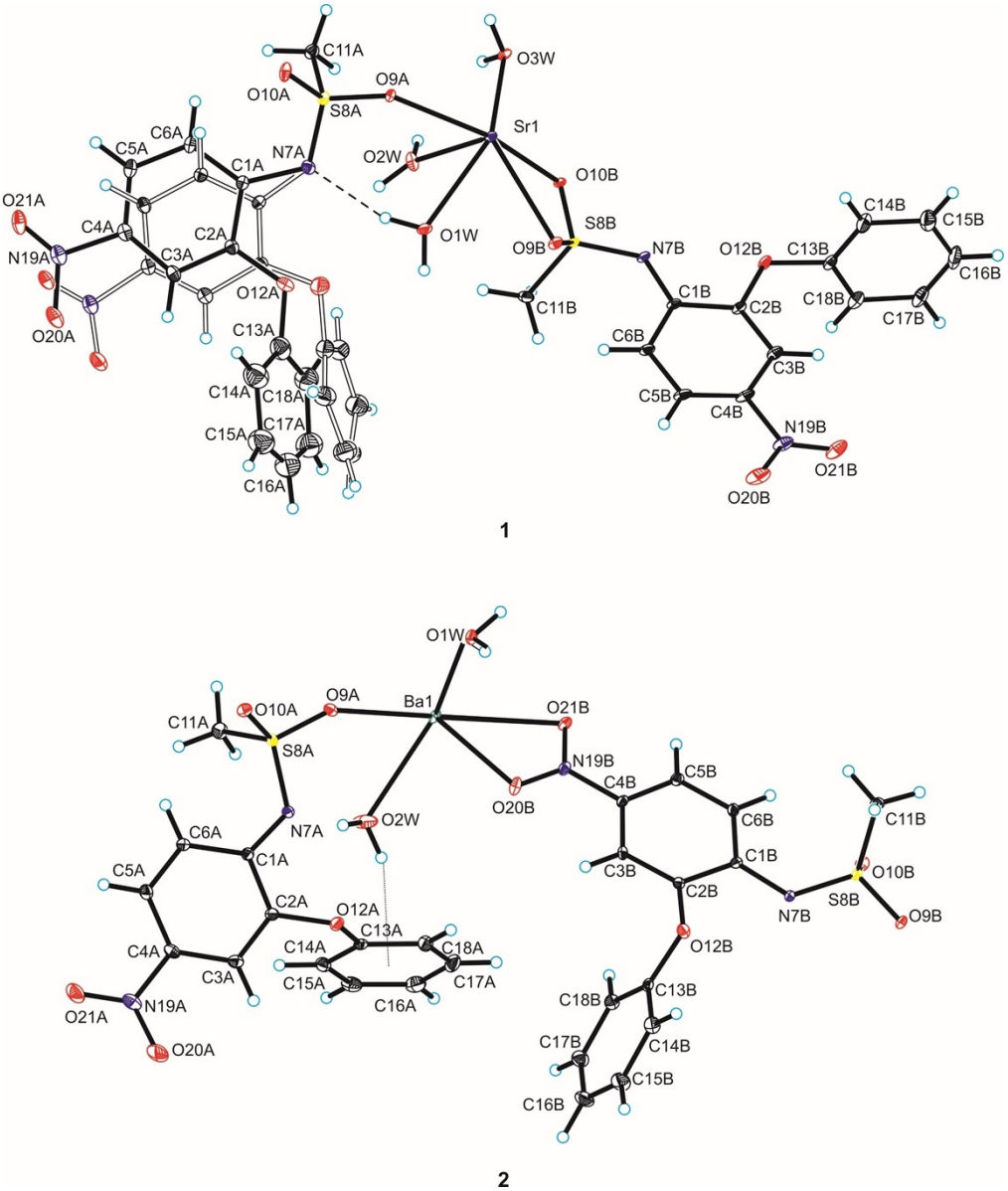

Figure 1S. Asymmetric unit in the crystals of compounds **1** and **2** showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 25% probability level. H atoms are shown as small spheres of arbitrary radius (O–H···N hydrogen bond is represented by dashed lines, whereas O–H···π interactions by dotted line). In the figure of asymmetric unit of compound **1**, the disordered part of the nimesulide anion A is shown with unfilled lines.

References

[1] CrysAlis CCD and CrysAlis RED. Version 1.171.36.24. Oxford Diffraction Ltd. (Yarnton, 2012).

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Table 1S. Crystal data and structure refinement for compounds **1** and **2**.

Compound	**1**	**2**
Chemical formula	$C_{26}H_{28}N_4O_{13}S_2Sr$	$C_{26}H_{26}N_4O_{12}S_2Ba$
Formula weight/g·mol^{-1}	756.26	787.97
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$I2/a$
a/Å	34.835(5)	26.2150(11)
b/Å	7.2995(5)	7.9077(3)
c/Å	14.2995(17)	31.5526(17)
α/°	90	90
β/°	114.459(17)	113.318(6)
γ/°	90	90
V/Å^3	3309.7(8)	6006.6(5)
Z	4	8
T/K	291(2)	291(2)
λ_{Mo}/Å	0.71073	0.71073
ρ_{calc}/g·cm^{-3}	1.518	1.743
F(000)	1544	3152
μ/mm^{-1}	1.823	1.531
θ range/°	3.39 - 25.00	3.33 - 25.00
Completeness θ/%	99.7	99.8
Reflections collected	24319	19993
Reflections unique	5813 [R_{int}=0.1311]	5286 [R_{int}=0.0501]
Data/restraints/parameters	5813/480/580	5286/4/420
Goodness of fit on F^2	0.986	1.020
Final R_1 value (I>2σ(I))	0.0567	0.0358
Final wR_2 value (I>2σ(I))	0.1029	0.0682
Final R_1 value (all data)	0.1351	0.0521
Final wR_2 value (all data)	0.1295	0.0734
CCDC number	2332827	2332828

Table 2S. Hydrogen-bond and X–H···π interactions geometry in the crystals of compounds **1** and **2** (Å,°).

Compound	D–H···A	*d*(D–H) [Å]	*d*(H···A) [Å]	*d*(D···A) [Å]	∠D–H···A (°)
1	O1W–H1WA···N7A	0.90(6)	1.98(6)	2.816(7)	153(6)
	O1W–H1WB···O20B^{i}	0.89(9)	2.21(7)	2.930(8)	138(8)
	O2W–H2WA···O21A^{ii}	0.89(6)	2.18(7)	2.989(9)	151(7)
	O2W–H2WB···O10A^{iii}	0.88(7)	1.98(6)	2.840(6)	167(6)
	O3W–H3WA···O10A^{iii}	0.90(5)	1.86(5)	2.731(7)	161(5)
	O3W–H3WB···N7B^{iv}	0.89(6)	1.90(5)	2.780(6)	170(5)
	C5B–H5B···Cg1B^{i}	0.93	2.78	3.641(9)	154
Symmetry code: (i)1/2-x,1/2+y,3/2-z; (ii)-x,-1-y,-z; (iii)x,-1+y,z; (iv)1/2-x,-1/2+y,1/2-z.					
2	O1W–H1WA···O10A^{i}	0.89(3)	2.27(4)	2.994(4)	139(3)
	O1W–H1WB···O12B^{ii}	0.89(4)	2.58(4)	3.240(4)	132(3)
	O1W–H1WB···N7B^{ii}	0.89(4)	2.01(4)	2.849(4)	158(4)
	O2W–H2WB···N7A	0.88(5)	2.03(5)	2.893(5)	168(7)
	C11B–H11C···O20A^{iii}	0.96	2.58	3.511(6)	163
	C14B–H14B···O10A^{iv}	0.93	2.58	3.492(5)	168
	O2W–H2WA···Cg2A^{v}	0.89(3)	2.51	3.159(5)	130(5)
	C15A–H15A···Cg1A^{iv}	0.93	2.96	3.807(5)	153
Symmetry code: (i)-x,-1/2+y,1/2-z; (ii)1/2-x,3/2-y,1/2-z; (iii)x,3/2-y,-1/2+z; (iv)1/2+x,2-y,z; (v)x,1+y,-z.					

Cg represents the centre of gravity of the rings as follows: Cg1A ring C1A/C2A/C3A/C4A/C5A/C6A, Cg2A ring C13A/C14A/C15A/C16A/C17A/C18A, Cg1B ring C1B/C2B/C3B/C4B/C5B/C6B, Cg2B ring C13B/C14B/C15B/C16B/C17B/C18B.

Table 3S. S–O···π and N–O···π interactions geometry in the crystals of compounds **1** and **2** (Å,°).

Compound	X–Y···A	*d*(X–Y) [Å]	*d*(Y···A) [Å]	*d*(X···A) [Å]	∠X–H···A (°)
1	S8A–O10A···Cg2B^{v}	1.453(4)	3.612(5)	4.391(4)	113.1(2)
	N19A–O21A···Cg1A^{vi}	1.232(9)	3.458(11)	3.710(19)	94.5(13)
	N19B–O21B···Cg2A^{vii}	1.198(8)	3.008(15)	3.871(15)	128.5(6)
Symmetry code: (v)1/2-x,3/2+y,1/2-z; (vi)-x,-y,-z; (vii)1/2-x,-1/2+y,3/2-z.					
2	N19A–O21A···Cg2B^{vi}	1.218(5)	3.215(6)	3.683(6)	102.9(3)
Symmetry code: (vi)1/2-x,1+y,1-z.					

Table 4S. π–π interactions geometry in the crystals of compounds **1** and **2** (Å,°).

Compound	CgI	CgJ	CgI···CgJ[a] [Å]	Dihedral angle[b] [°]	Interplanar distance[c] [Å]	Offset[d] [Å]
1	Cg1A	Cg1A^{ii}	3.903(8)	0.0(6)	3.479(5)	1.770
Symmetry code: (ii)-x,-1-y,-z.						
2	Cg2A	Cg2A^{vi}^{i}	3.684(3)	5.9(2)	3.513(2)	1.770
	Cg1B	Cg1B^{ii}	3.962(2)	0.0(2)	3.283(2)	2.218
Symmetry code: (ii)1/2-x,3/2-y,1/2-z; (vii) 1.2-x,y,1-z.						

[a]Cg···Cg – distance between ring centroids.
[b]Dihedral angle – angle between the mean planes of CgI and CgJ.
[c]Interplanar distance – perpendicular distance from CgI to ring J.
[d]Offset – perpendicular distance from ring I to ring J.

Attenuated Total Reflectance – Fourier Transform Infrared Spectroscopy (ATR–FTIR)

The ATR-FTIR spectra were acquired using a Perkin Elmer Spectrum 2™ instrument (Perkin Elmer, Waltham, USA) equipped with attenuated total reflectance (ATR) accessory. The spectra were recorded at room temperature in the spectral range from 4000 to 500 cm^{-1} at a resolution of 4 cm^{-1} averaging 16 scans for each measurement.

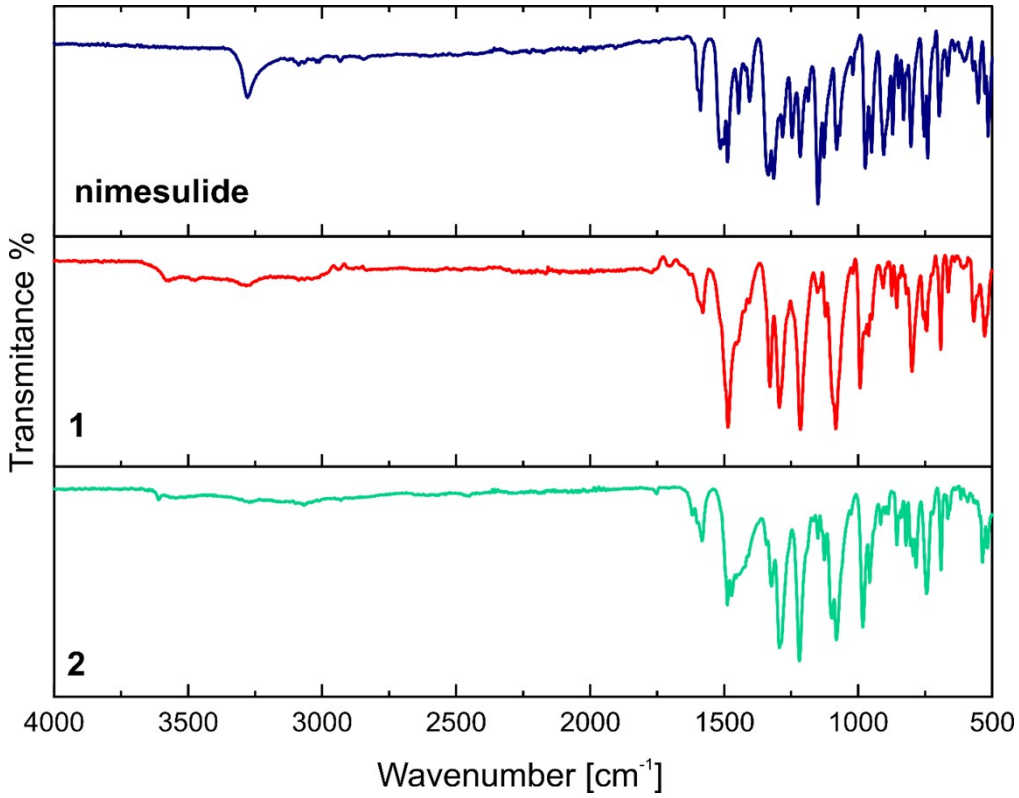


Figure 2S. ATR-FTIR spectra of studied compounds in the range of 4000–500 cm^{-1}.

Nimesulide, ATR-FTIR (cm^{-1}): 3278 (νNH), 1589–1487 (νC=C), 1514 and 1316 (ν_{as} and $\nu_{sym}NO_2$), 1335 and 1150 (ν_{as} and $\nu_{sym}SO_2$), 1282–1069 (νC–N and νC–O).

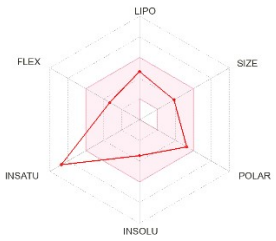
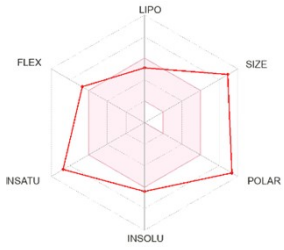
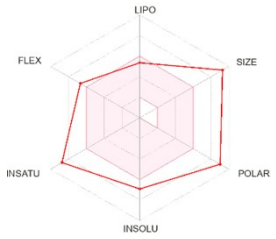
Compound **1**, ATR-FTIR (cm^{-1}): 1582–1486 (νC=C and $\nu_{as}NO_2$), 1329 (ν_{as} SO_2 and/or $\nu_{sym}NO_2$), 1150 (low-intensity band, $\nu_{sym}SO_2$), 1293–1083 (νC–N and νC–O).

Compound **2**, ATR-FTIR (cm^{-1}): 1582–1472 (νC=C and $\nu_{as}NO_2$), 1341 and 1150 (low-intensity bands or shoulders, ν_{as} SO_2 and $\nu_{sym}SO_2$), 1323 ($\nu_{sym}NO_2$), 1293–1081 (νC–N and νC–O).

ADMET analysis

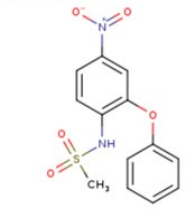
The web-service SWISS-ADME tool by the Swiss Institute of Bioinformatics (http://www.swissadme.ch/) was used to calculate physicochemical descriptors, important for drug discovery [1]. Compounds were analyzed to predict ADME (absorption, distribution, metabolism, and excretion) parameters. The web-service ProTOX II was used for the prediction of the toxicity of the title compounds [2]. For the ADME analysis, the inputs for compounds **1** and **2** were measured crystal structures. For both structures, we have generated the SMILE code and implemented it for analysis.

Table 5S. ADME diagrams for nimesulide and compounds **1** and **2**.

compound	ADME diagram	XLOGP3 [a]	MW [b]	TPSA [c]	LOG S (ESOL) [d]	F. Csp^3 [e]	NRB [f]
nimesulide		2.60	308.31	109.60	-3.48	0.08	5
1		3.42	756.27	222.83	-6.41	0.08	10
2		3.90	787.96	213.60	-6.92	0.08	10

[a] – parameter for lipophilicity calculations [3]; [b] – molecular weight [g/mol]; [c] – topological polar surface area [Å²] [4]; [d] – estimated solubility [5]; [e] – ratio of sp^3 hybridized carbons over the total amount of carbons in molecule; [f] – number of rotatable bonds.

a)



SMILES [O-][N+](=O)c1ccc(c(c1)Oc1ccccc1)NS(=O)(=O)C

Physicochemical Properties	
Formula	C13H12N2O5S
Molecular weight	308.31 g/mol
Num. heavy atoms	21
Num. arom. heavy atoms	12
Fraction Csp3	0.08
Num. rotatable bonds	5
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	80.05
TPSA	109.60 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.78
Log $P_{o/w}$ (XLOGP3)	2.60
Log $P_{o/w}$ (WLOGP)	3.65
Log $P_{o/w}$ (MLOGP)	1.73
Log $P_{o/w}$ (SILICOS-IT)	-0.62
Consensus Log $P_{o/w}$	1.83

Water Solubility	
Log *S* (ESOL)	-3.48
Solubility	1.02e-01 mg/ml ; 3.29e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.55
Solubility	8.67e-03 mg/ml ; 2.81e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.38
Solubility	1.27e-02 mg/ml ; 4.13e-05 mol/l
Class	Moderately soluble

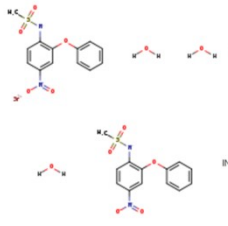
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.33 cm/s

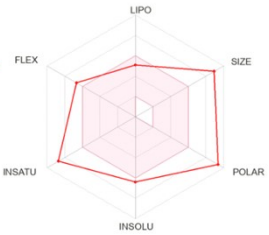
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	Yes
Synthetic accessibility	3.08

b)

Molecule 1





SMILES [O-][N+](=O)c1ccc(c(c1)Oc1ccccc1)[N-]S(=O)(=O)C.[O-][N+](=O)c1ccc(c(c1)Oc1ccccc1)[N-]S(=O)(=O)C.[Sr+2].O.O.O

Physicochemical Properties	
Formula	C26H28N4O13S2Sr
Molecular weight	756.27 g/mol
Num. heavy atoms	46
Num. arom. heavy atoms	24
Fraction Csp3	0.08
Num. rotatable bonds	10
Num. H-bond acceptors	15
Num. H-bond donors	3
Molar Refractivity	168.40
TPSA	222.83 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.00
Log $P_{o/w}$ (XLOGP3)	3.42
Log $P_{o/w}$ (WLOGP)	8.67
Log $P_{o/w}$ (MLOGP)	0.53
Log $P_{o/w}$ (SILICOS-IT)	-0.62
Consensus Log $P_{o/w}$	2.40

Water Solubility	
Log *S* (ESOL)	-6.41
Solubility	2.95e-04 mg/ml ; 3.89e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.78
Solubility	1.26e-05 mg/ml ; 1.66e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.38
Solubility	3.12e-02 mg/ml ; 4.13e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.49 cm/s

Druglikeness	
Lipinski	No; 2 violations: MW>500, NorO>10
Ghose	No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70
Veber	No; 1 violation: TPSA>140
Egan	No; 2 violations: WLOGP>5.88, TPSA>131.6
Muegge	No; 3 violations: MW>600, TPSA>150, H-acc>10
Bioavailability Score	0.17

Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	4.66

c)

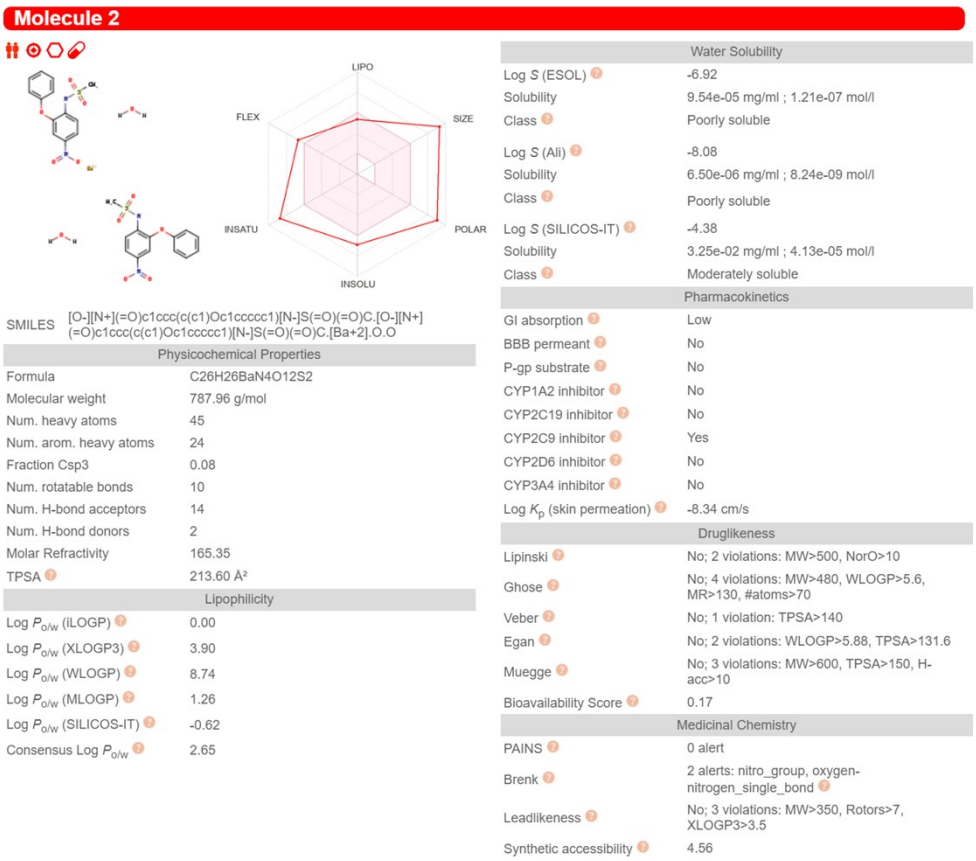


Figure 3S. ADME analysis for nimesulide (a) and for compounds **1** (b) and **2** (c).

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