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Development of New Aromatic Sulfonamides as Potential Antiglaucoma Agents

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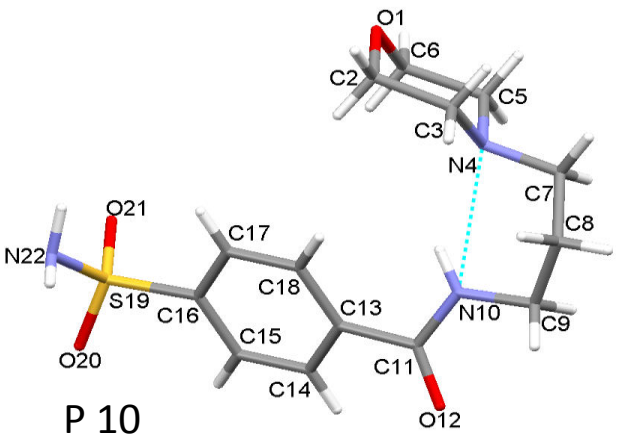
Development of New Aromatic Sulfonamides as Potential Antiglaucoma Agents

Graphical Abstract



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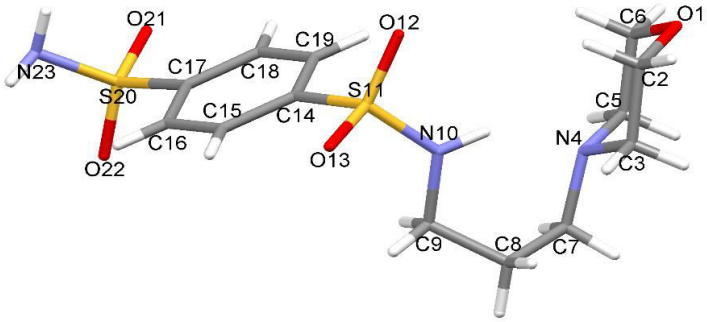

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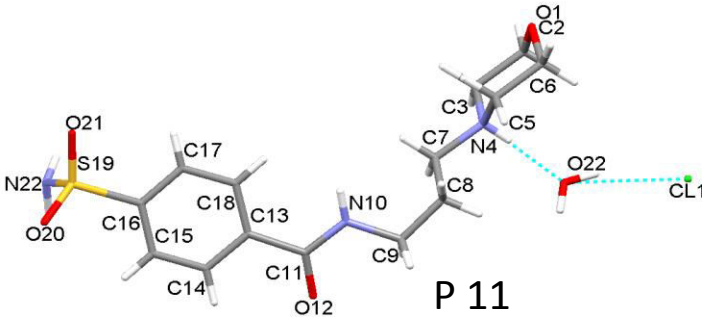

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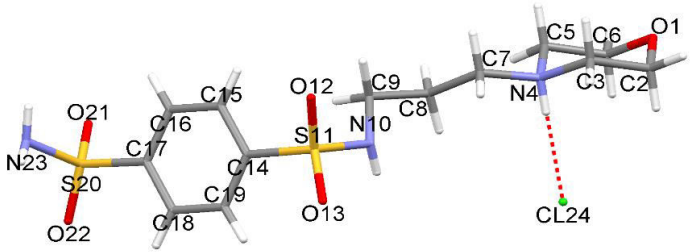

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Molecular drawing of aromatic sulfonamides studied giving the crystallographic atom-numbering scheme

Abstract: Many sulfonamides with the general formula R-SO_2NH_2 constitute an important class of inhibitors of the zinc enzyme carbonic anhydrase (CA) due to their use in antiglaucoma therapy.

Design of new aromatic sulfonamides was carried out using computational methods of theoretical medicinal chemistry as described in our previous works. Of particular interest are the molecular geometries of neutral and anionic species, acidities, and lipophilicities.

Synthesis of the so-designed new aromatic sulfonamides was conducted according to published procedures. Antiglaucoma activity was evaluated in both *in vitro* and *in vivo* conditions. For determination of the intraocular pressure changes the experiment with adult male Chinchilla was used.

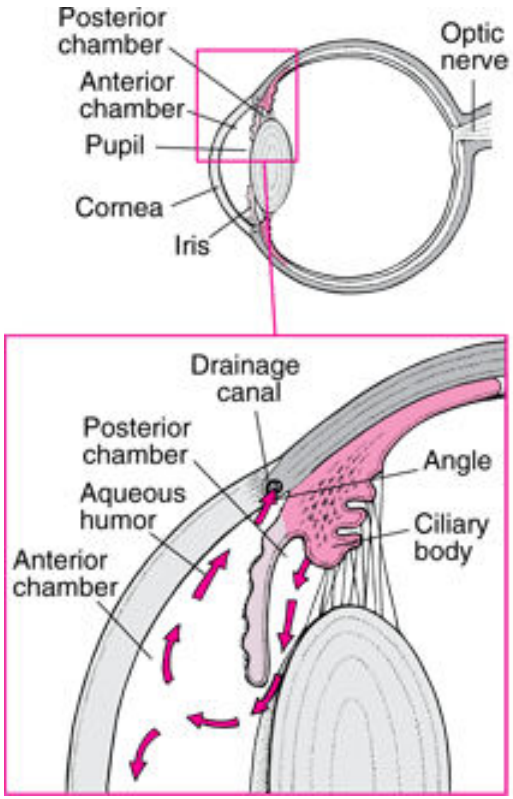
In this lecture we present the design and synthesis of novel drug-like aromatic sulfonamides, namely (4-sulfamoyl-N-(3-morpholinopropyl) benzamide, N-(3-morpholinopropyl)benzene-1,4-disulfonamide, N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) and their hydrochloride salts. They exhibited favorable biological, structural, physicochemical and some pharmacokinetic properties comparable to those obtained for therapeutically useful acetazolamide, dorzolamide and brinzolamide. Data obtained allows us to assume, that new aromatic sulfonamides may represent novel class of compounds for the discovery of new effective antiglaucoma drugs.

Keywords: sulfonamides; carbonic anhydrase inhibitors, antiglaucoma therapy; physicochemical properties

Introduction

It is estimated 2 out of every 100 people over the age of 65 have glaucoma and half of these people don't know it.

(G. H. Cassel, M. D. Billig, H. G. Randall, The Eye Book. The Johns Hopkins University Press. Baltimore, Maryland. 1998.)



Normal Fluid Drainage

Fluid is produced in the ciliary body behind the iris, passes into the front of the eye, and then exits through the drainage canals.

- In glaucoma, the drainage canals become clogged, blocked, or covered.
- Because there is nowhere in the eye for the fluid to go, pressure in the eye increases.
- When the pressure becomes higher than the optic nerve can tolerate, damage to the optic nerve occurs. This damage is called glaucoma.

Carbonic Anhydrase Inhibitors

Carbonic Anhydrases (CAs, EC 4.2.1.1), 14 different isozymes or CA-related proteins (CARP). There are at least five distinct CA families (α, β, γ, δ, and ε).

Higher Vertebrate α-CA Isozymes

Isozyme	Sub-cellular localization
CAI, CAII, CAIII, CAVII, CARPVIII	Cytosol
CAIV, CAIX, CAXII, CAXIV	Membrane bound
CAV	Mitochondria
CAVI	Secreted into saliva
CARPX, CARPXI, CAXIII	Unknown

Physiologically significant reversible reaction catalysed by α-CA Isozymes

$$H_2O + CO_2 \leftrightarrow H^+ + HCO_3^-$$

Sulfonamide Inhibitors of CAs

1940 T. Mann, D. Keilin *Nature*

CA inhibition with sulfanilamide

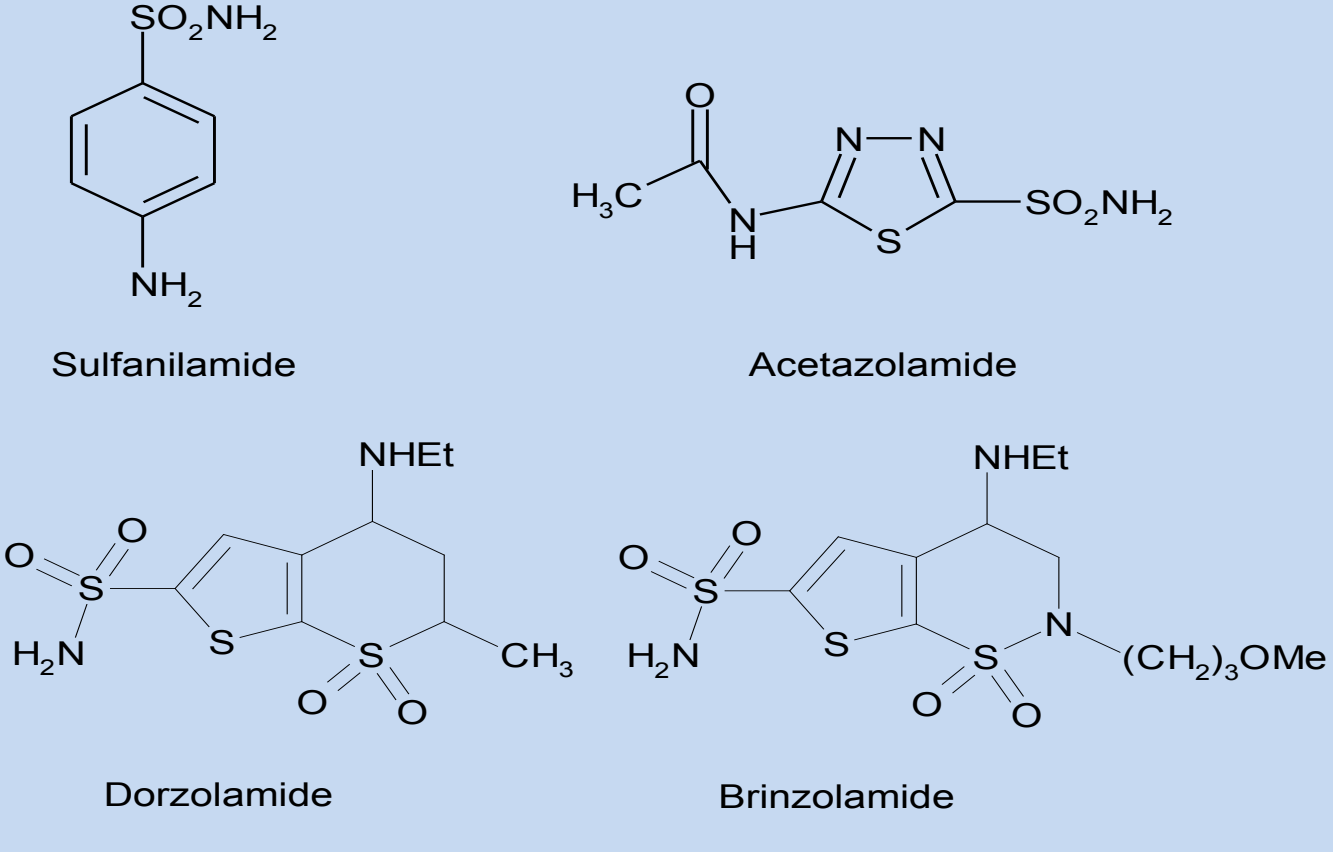
CA inhibitory properties of sulfonamides

- *Antithyroid drugs*
- *Hypoglycemic sulfonamides*
- *Antiglaucoma agents*
- *Novel types of anticancer agents*
- *Novel therapy for Alzheimer's disease….*

C. T. Supuran, Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. *Nature Rev. Drug Discov. 7 (2008) 168 - 181.*

Sulfonamide Inhibitors of CAs as antiglaucoma agents

- Inhibition of carbonic anhydrase isoforms present in the eyes (CA I, II, IV and XII),



Mincione F, Scozzafava A, Supuran CT, The development of topically acting carbonic anhydrase inhibitors as antiglaucoma agents. Curr Pharm Des. 2008;14(7):649-54.

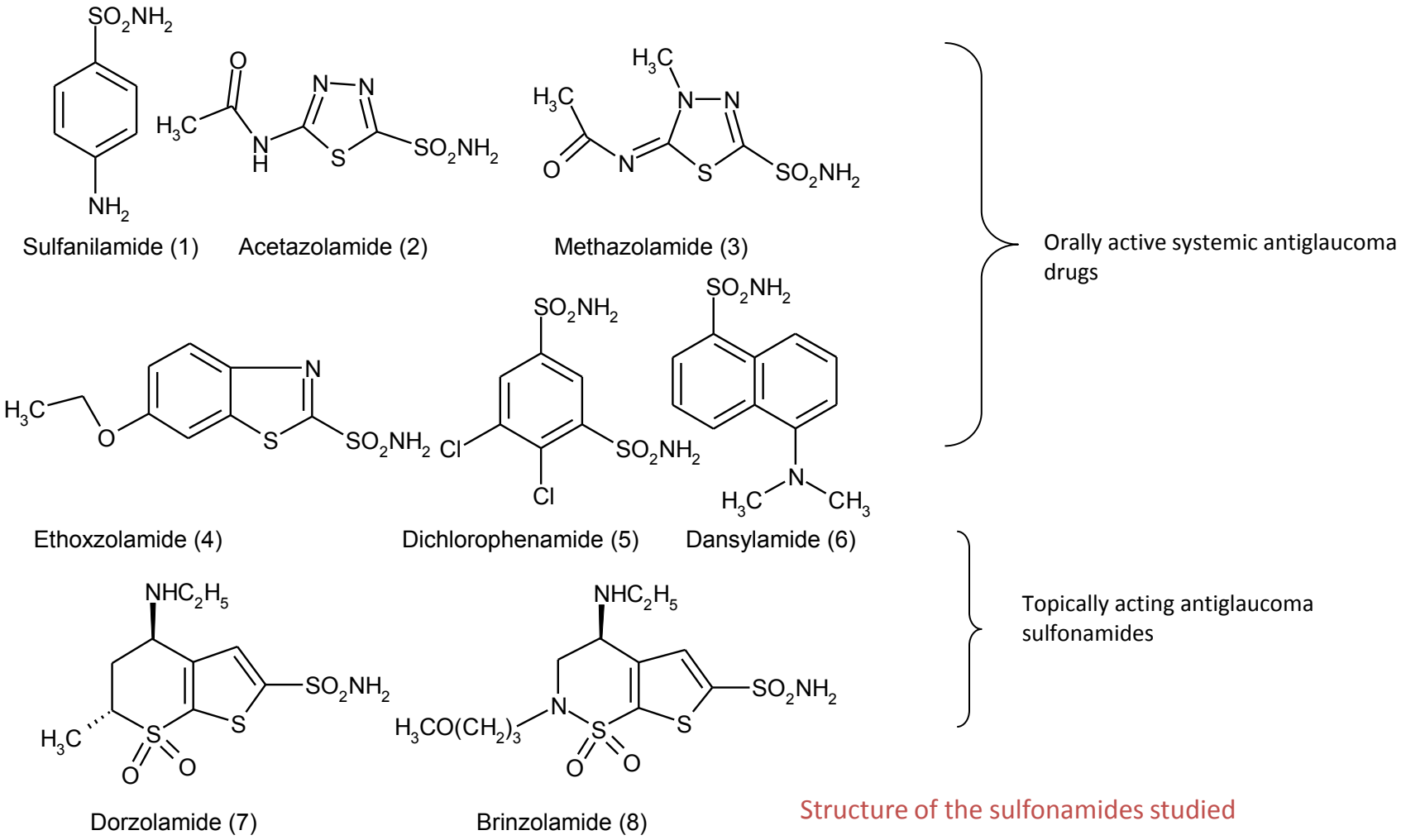
Design and synthesis of new CA inhibitors

Manual Design

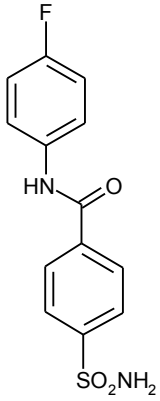
- Operator directs study
- Allows input of designer's ideas
- Useful for identification of a single lead compound
- Slow and limited to designer's originality

Study of Acidity, Lipophilicity and Solubility of Some Biologically Active Sulfonamides

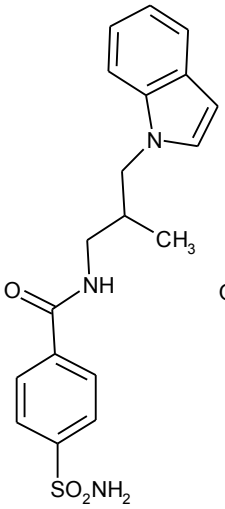
Milan Remko, Claus-Wilhelm von der Lieth, 2004 *Bioorg. & Med. Chem.*



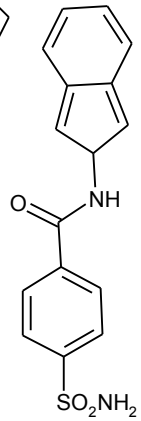
Structure of the sulfonamides studied



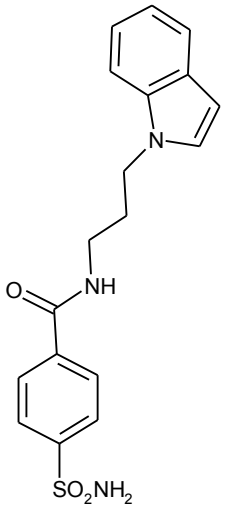
1I9L (9)



A (10)

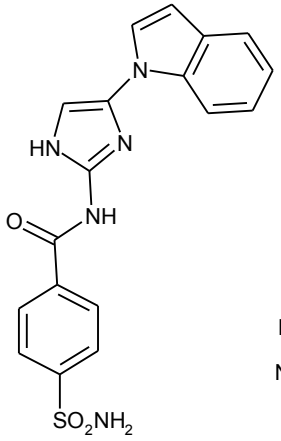


B (11)

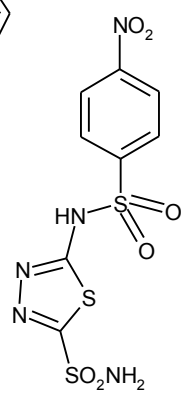


C (12)

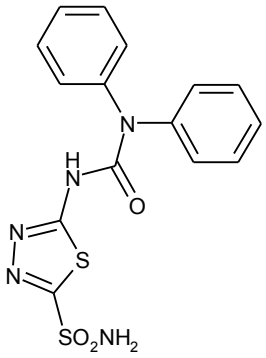
Experimental topically acting antiglaucoma sulfonamides (9 – 13)



D (13)



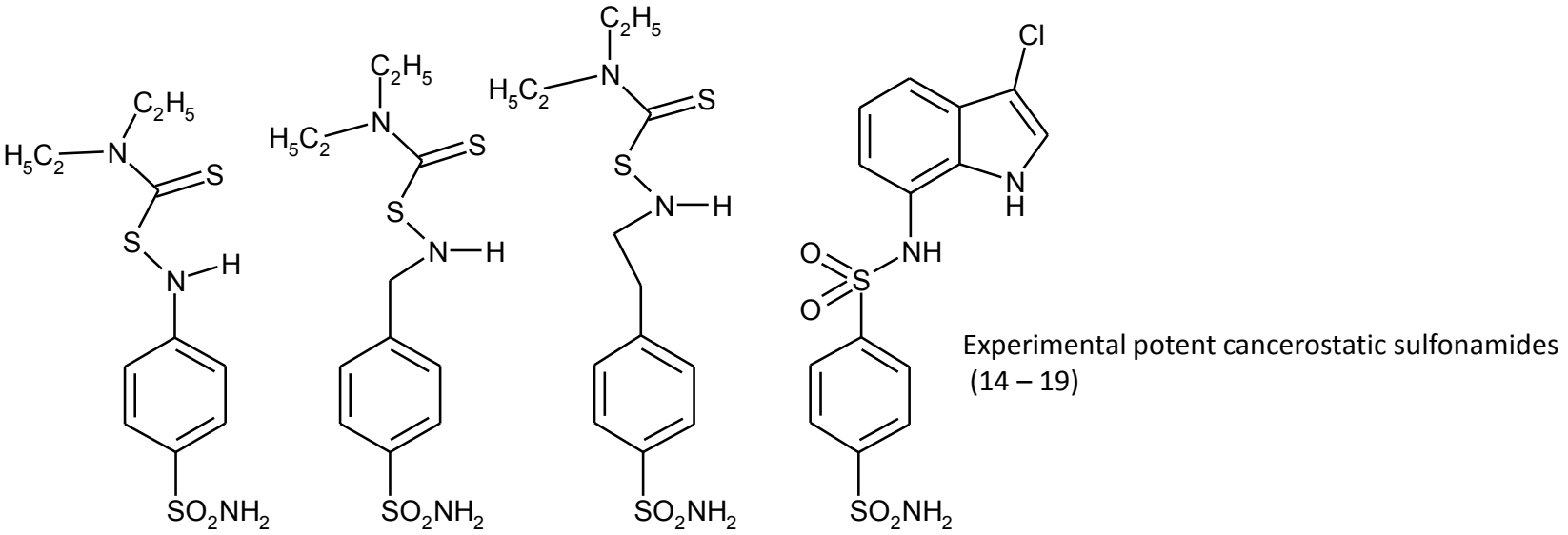
IX (14)



X (15)

Experimental potent cancerostatic sulfonamides (14 – 15)

Structure of the sulfonamides studied



XI (16) XII (17) XIII (18) E7070 (19)

Experimental potent cancerostatic sulfonamides (14 – 19)

Structure of the sulfonamides studied

Drug like properties of the sulfonamide inhibitors

The pK_a values of the sulfonamides studied. pK_i and pK_d are corresponding inhibition and dissociation constants against hCA II, respectively

No.	Compound	pK_a, calc	pK_a, exp	Ref.	pK_i, exp
1	Sulfanilamide	10.1	10.1	35	6.92[b]
2	Acetazolamide	6.5	7.4	28	8
3	Methazolamide	5.9	7.2	28	8.09
4	Ethoxzolamide	6.8	8.0	28	9.16
5	Dichlorphenamide	7.8	8.3	28	7.52
6	Dansylamide	9.6		21	6.03[b]
7	Dorzolamide	7.8	8.4	28	8.05
8	Brinzolamide	7.2		28	8.52
9	1I9L	8.8		30	8.62[b]
10a	A–(R)	9.0		22	10.52[b]
10b	A–(S)	9.1		22	9.63[b]
11	B	8.8			
12	C	8.8			
13	D	8.6			
14	IX	17.1[a]			
15	X	7.2		31	8.09
16	XI	10.9		32	7.32
17	XII	12.6		32	7.89
18	XIII	9.2		32	7.96
19	E7070	8.5		32	7.82

[a]Unrecognized functional group, unreliable results
[b]pK_d values

- The computed pK_a values correlate well with the available experimental pK_a values found in the literature.
- **Aromatic inhibitors 9 – 13 are in the condensed phase by about 1 – 2 pK_a units less acidic than heteroaromatic inhibitors (dorzolamide, brinzolamide and compound X).**
- The calculations showed that methazolamide is also in water solution the most acidic drug of the sulfonamides investigated. Potent systemic antiglaucoma sulfonamides **2** – **5** are by about 2 – 4 units more acidic than the parent sulfanilamide.

Lipophilicity

No.	Compound	LogP (exp.)	ALOGPs	IA LOGP	CLOGP	KoWWiN
1	Sulfanilamide	–0.62	–0.16	–0.47	–0.57	–0.55
2	Acetazolamide	–0.26	–0.39	–0.25	–0.98	–0.72
3	Methazolamide	0.13	–0.20	–0.08	0.09	0.33
4	Ethoxzolamide	2.01	1.87	2.00	2.05	2.08
5	Dichlorphenamide		0.95	–0.04	0.24	1.06
6	Dansylamide	2.01	1.92	2.07	1.80	1.72
7	Dorzolamide		–0.50	0.71	–0.43	0.37
8	Brinzolamide		–0.65	0.22	0.33	0.33
9	1I9L		1.88	1.67	1.67	1.49
10a	A–(R)		2.71	2.61	2.83	2.75
10b	A–(S)		2.71	2.61	2.83	2.75
11	B		1.77	1.45	1.39	1.78
12	C		2.53	2.31	2.43	2.33
13	D		2.72	2.26	2.64	1.53
14	IX		0.48	1.66	–0.07	–0.07
15	X		1.88	1.68	1.37	1.23
16	XI			0.48	1.78	0.88
17	XII			0.22	2.11	0.79
18	XIII			0.10	1.98	1.28
19	E7070		2.22	2.37	2.37	3.53

- **The compounds studied are only slightly or moderate lipophilic.**

- The lipophilicity of the cancerostatic sulfonamides **14 –18** is from relatively narrow interval between –0.07 and 1.98.

- The highly active CAI **10 – 13** are also the most lipophilic compounds among the antiglaucomatics studied. Their lipophilicity is considerably higher than the lipophilicity of the clinically useful topically acting antiglaucoma sulfonamides dorzolamide and brinzolamide

Lipinski parameters of the sulfonamides studied

No.	Compound	No. of Hydrogen Bond Acceptors	No. of Hydrogen Bond Donors	log P, calc.[a]	Formula Weight
1	Sulfanilamide	4	4	–0.16 – (–0.57)	172
2	Acetazolamide	7	3	–0.25 – (–0.98)	222
3	Methazolamide	7	2	–0.08 – 0.09	236
4	Ethoxzolamide	5	2	1.87 – 2.08	258
5	Dichlorphenamide	6	4	–0.04 – 1.06	305
6	Dansylamide	4	2	1.72 – 1.92	250
7	Dorzolamide	6	3	–0.43 – 0.71	324
8	Brinzolamide	8	3	–0.65 – 0.33	383
9	1I9L	5	3	1.49 – 1.88	308
10a	A–(R)	6	3	2.15 – 2.83	371
10b	A–(S)	6	3	2.15 – 2.83	371
11	B	5	3	1.39 – 1.78	314
12	C	6	3	1.86 – 2.53	357
13	D	8	4	1.53 – 2.72	381
14	IX	10	3	–0.07 – 1.66	365
15	X	8	3	1.23 – 1.88	375
16	XI	5	3	0.48 – 1.78	319
17	XII	5	3	0.22 – 2.11	333
18	XIII	5	3	0.10 – 1.98	347
19	E7070	7	4	2.37 – 3.53	385

- The number of hydrogen bond donors (any NH group) is relatively constant (about 2 –4). Less active (K_d ≈ mM) sulfanilamide and dansylamide possess substantially less proton accepting sites (any O and N atoms).
- **It is therefore probable that the number of hydrogen bond acceptor groups is one of the important factors for designing of highly–active (K_d ≈ nM) inhibitors of carbonic anhydrase.** However, the possible differences in the nature of the active site of the various CA isoenzymes can also play important part.

Drug like properties of the sulfonamide inhibitors of CAs

Selection criteria for drug-like properties for sulfonamide agents

- Molecular weight
- lipophilicity
- Acidity and basicity
- solubility
- polar surface area
- Lipinski parameters

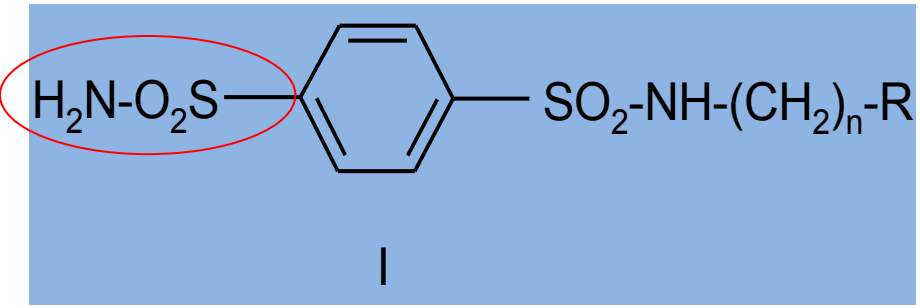
Molecular weight	220 – 400
Octanol/water partition coefficient (clog P)	–0.2 – 2.3
Aqueous solubility (clog S)	(–2) – (–4.5)
pKa	5 – 12.6
No. of hydrogen bond acceptors	4 – 10
No. of hydrogen bond donors	2 – 4
Polar surface area (PSA, Å^2)	80 – 120
Percent of oral absorption (%ABS)	68 – 75

Project

Design, synthesis and testing of new sulfonamide derivatives

About 50 new compounds prepared

- *In vitro* tests
- *In vivo* tests



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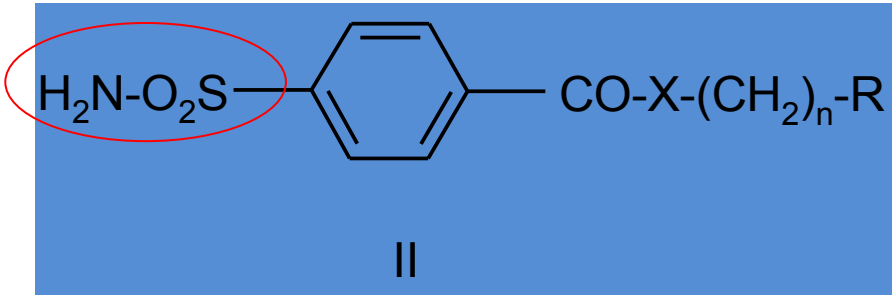


II

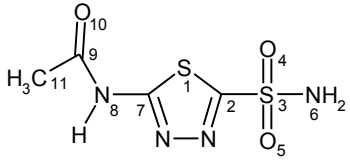
As a prototype of Zn^{2+} ion-coordinated complexes the structure and energetics of 46 species, selected from neutral and charged Lewis bases –irregular substrates of CA– with the zinc cation was examined.

Remko M, Garaj V, Thermodynamics of binding of Zn^{2+} to carbonic anhydrase inhibitors. Mol. Phys. 2003; 101:2357–2368.

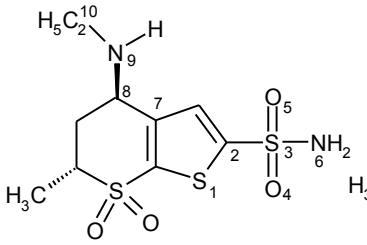
Benchmarks

Molecular structure, pK_a, lipophilicity, solubility and absorption of biologically active aromatic and heterocyclic sulfonamides

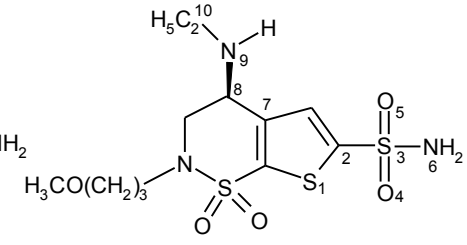
M. Remko, J. Mol. Struct., Theochem, 2010



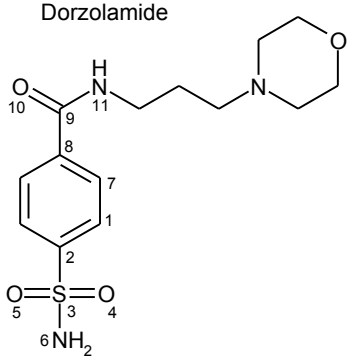
Acetazolamide



Dorzolamide



Brinzolamide



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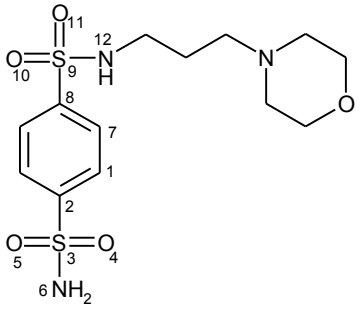

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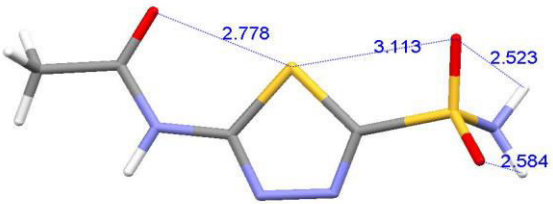
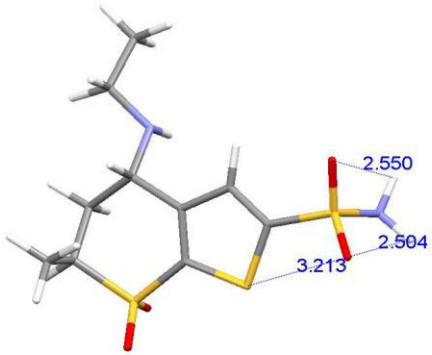
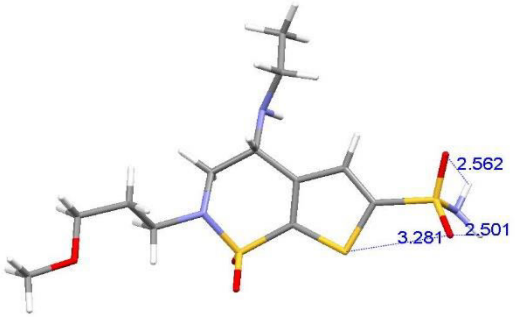


Acetazolamide



Dorzolamide

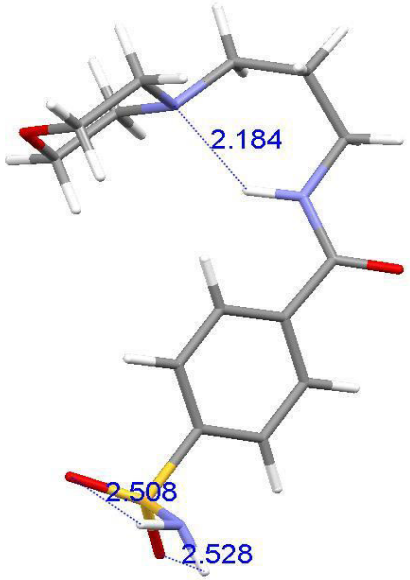


Brinzolamide

$\Delta E^{bac\text{-}opt}$ = 130 kJ/mole (2H4N)

$\Delta E^{bac\text{-}opt}$ = 142 kJ/mole (1CIL)

P10



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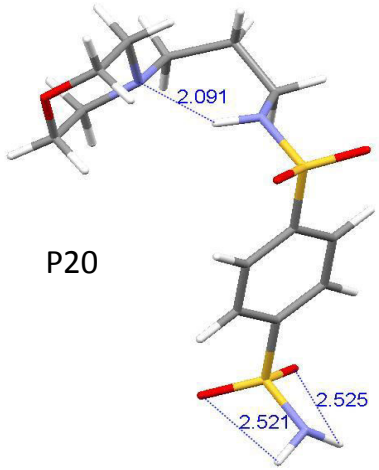


B3LYP/6−311+G(d,p) optimized structures of the sulfonamides investigated

Lipophilicity and Solubility

Calculated partition coefficients and solubilities of the sulfonamides studied

Drug	LogP (exp.)	ALOGPS	KoWWIN	XLOGP2	LogS (exp.)	AB/logS
Acetazolamide	−0.26	−0.39	−0.72	−0.98	−2.36 (0.98 g/L)	−1.73 (4.14 g/L)
Dorzolamide	−1.0	−0.50	0.37	−0.97		−2.81 (0.50 g/L)
Brinzolamide	−1.8	−0.65	0.33	−1.83		−3.18 (0.25 g/L)
P10		0.39	−0.62	−0.30		−1.64 (7.50 g/L)
P20		−0.23	0.03	−0.86		−1.80 (5.76 g/L)

Computed partition coefficients (XLOGP2 method) for drugs studied varied between −0.3 and −1.8.

Compounds are described as slightly lipophilic drugs.

The calculated water solubility of dorzolamide and brinzolamide is comparably low.

Acidity and basicity

The pK_a values of the sulfonamides investigated

Compound	pK_{a}, exp	% Ionized form (exp)	pK_{a}, calc		% Ionized form (calc)	
	Acid function[a]	Acid function[a]	Acid function[a]	Basic function[b]	Acid function[a]	Basic function[b]
Acetazolamide	7.4	50	7.3		56	
Dorzolamide	8.4	9	8.4	8.8	9	96
Brinzolamide			8.5	8.8	7	96
P10			9.7	7.4	0.5	50
P20			9.7	7.4	0.5	50

[a] sulfonamide
[b] amine

The calculated pK_a values of sulfonylamide moiety in the CAI studied are in the range of 7.3 to 9.7 and are characterized as weak organic acids.

Acetazolamide is at physiological pH = 7.4 partially ionized.

Absorption, polar surface area and Rule of Five properties

% ABS = 109 – 0.345 PSA

Y. H. Zhao, M. H. Abraham, J. Lee, A. Hersey, Ch. N. Luscombe, G. Beck, B. Sherborne, I. Cooper, Pharm. Res. 19 (2002) 1446. PSA - the fragment-based method of Ertl and coworkers [P. Ertl, B. Rohde, P. Selzer, J. Med. Chem. 43 (2000) 3714].

Calculated absorption (%ABS), polar surface area (PSA) and Lipinski parameters of the sulfonamides studied

Drug	**%ABS**	**Volume**	**PSA**	**NROTB**	***n* ON acceptors**	***n* OHNH donors**	**Log *P*, calcd[a]**	**Formula weight**
Acetazolamide	69.3	157.11	115.05	2	7	3	–0.69	222.28
Dorzolamide	72.3	250.85	106.33	3	6	3	–0.37	324.49
Brinzolamide	68.0	306.19	118.81	7	8	3	–0.72	383.57
P10	73.9	286.68	101.73	6	7	3	–0.17	327.45
P20	68.0	299.13	118.81	7	8	3	–0.35	363.51

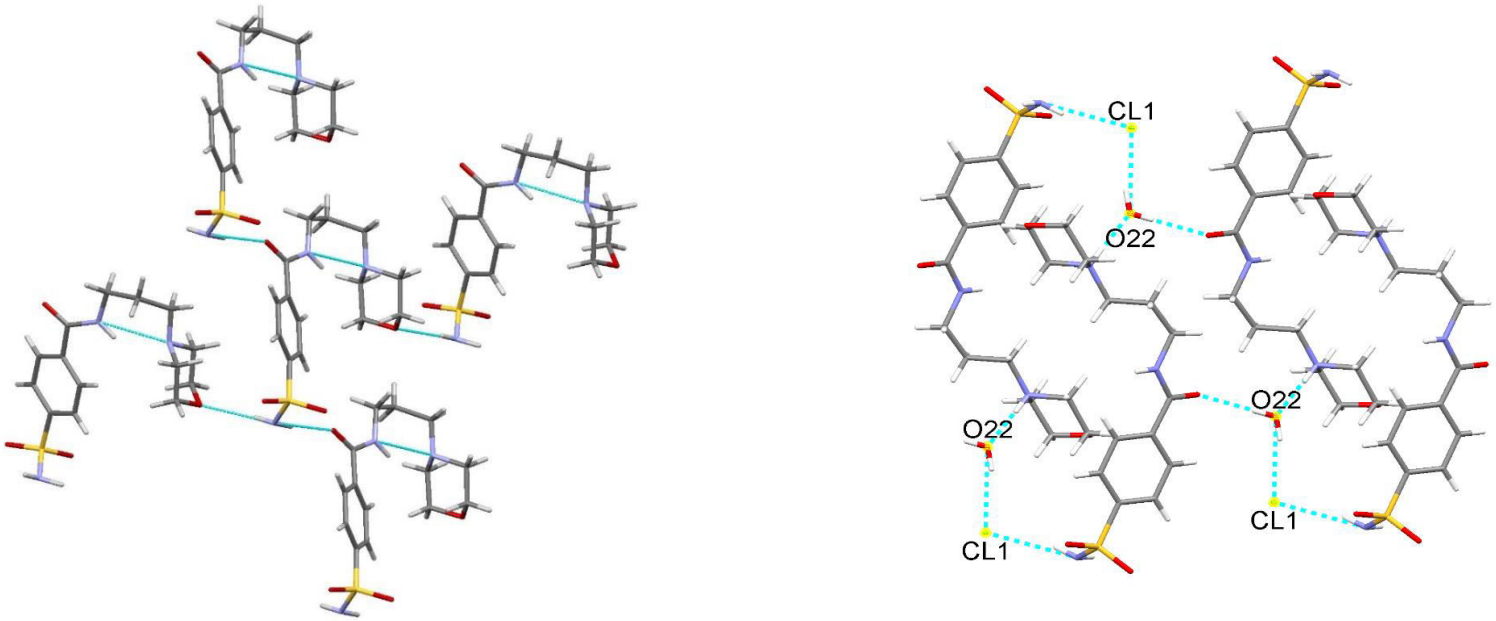
[a]Range of log *P* values obtained by three theoretical methods (ALOGPS, KoWWIN, XLogP2)

Aromatic sulfonamides P10 and P20 exhibit drug-like properties comparable with dorzolamide and/or brinzolamide, and have high probability of being well absorbed.

Synthesis, crystal and molecular structure of two biologically active aromatic sulfonamides and their hydrochloride salts

Milan Remko, Jozef Kožíšek, Jana Semanová, Fridrich Gregáň

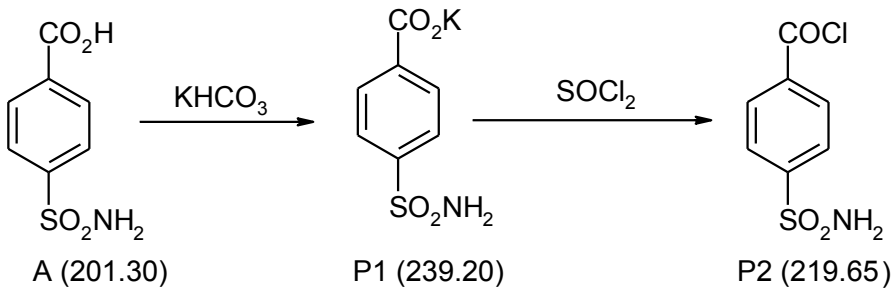
J. Mol. Struct. 2010



Details of the three-dimensional hydrogen-bonding network of P10 and P11 with atoms participating in the drawn hydrogen bonds represented by dashed lines.

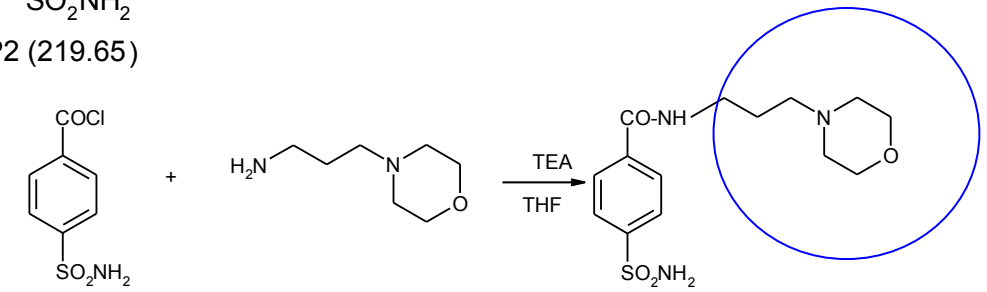
Synthesis of P 10 and P 11 (the tail approach)

Potassium 4-sulfamoylbenzoate P1, 4-Sulfamoylbenzoyl chloride P2



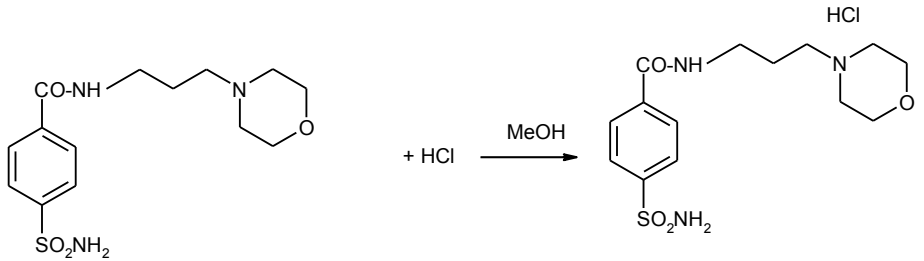
A (201.30) P1 (239.20) P2 (219.65)

4-Sulfamoyl-N- (3-morpholinopropyl) benzamide P10



P2 (219.65) P10 (327.41)

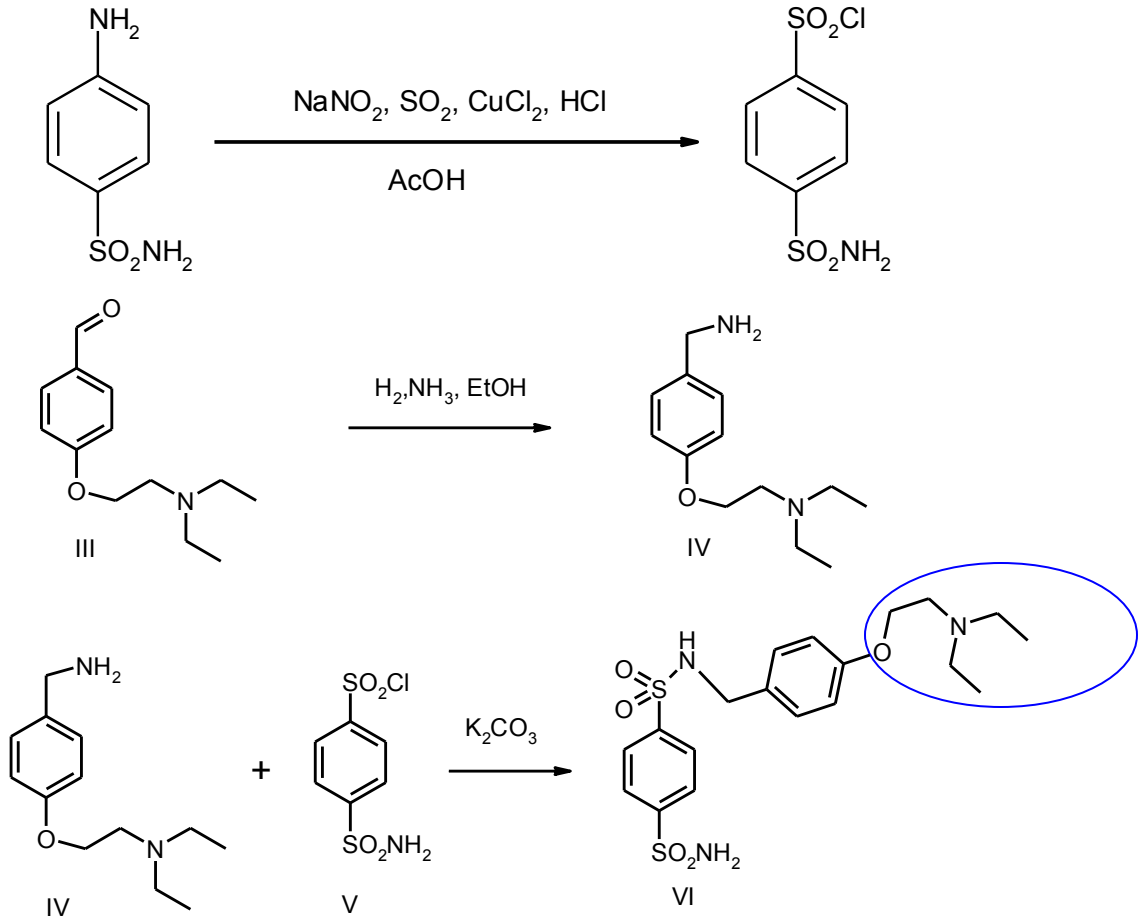
4-Sulfamoyl-N- (3-morfolinopropyl) benzamide – hydrochloride P11



P10 (327.41) P11 (363.86)

"tail" – morpholinopropyl substituent

Synthesis of P 30 (I-3), the tail extension strategy



Extended tail of this derivative contains diethylaminoethoxybenzyl moiety and exploit the strategy of enhanced hydrophobic interactions between hydrophobic moieties of both active site of enzyme and inhibitor.

Pharmacology

- *In vitro* assay – IC_{50}

- The intraocular pressure changes were evaluated in *in vivo* conditions
- The laboratory animals of *Chinchilla species* were used
- The distilled water was used as a control
- Measurement apparatus Tono-Pen®XL
- For each compound and each concentration 10 independent assays were carried out

Three new aromatic sulfonamide inhibitors of carbonic anhydrases I, II, IV and XII

Tab. 1 Biochemical activity IC_{50} (nmol/L) and solubility of the CA inhibitors investigated

Inhibitor	hCA I	hCA II	hCA IV	hCA XII	Solubility
Acetazolamide	250[a]	12[a]	70 (bCA IV)[a]		4.14 g/L
Dorzolamide		3.74[b]	43[c]		0.50 g/L
Brinzolamide			277.15[b]		0.25 g/L
I-1	231.4	215.8	611.1	645.2	7.50 g/L
I-2	57.7	65.8	498.8	517.2	5.76 g/L
I-3	59.8	81.1	507.9	736.7	1.63 g/L

C. T. Supuran, A. Maresca, F. Gregáň, M. Remko, Three new aromatic sulfonamide inhibitors of carbonic anhydrases I, II, IV and XII, J. Enzym. Inhib. Med. Chem. 28 (2013) 289-293.

In vivo studies, P11

Measured intraocular pressure values [mmHg]

	N		0.5 h		1 h		4 h		7 h		25 h		31 h	
n	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE
1	15	14	10	9	9	10	13	11	8	8	12	15	8	9
2	14	15	10	12	12	9	12	10	10	10	13	13	10	16
3	12	12	12	9	18	13	12	13	15	11	13	14	12	13
4	13	14	16	16	13	16	12	11	14	16	13	13	16	15
5	13	16	12	11	8	11	12	9	10	9	13	15	12	12
6	14	16	10	10	9	9	10	10	6	7	12	11	9	9
7	18	17	9	11	11	10	8	8	7	9	10	12	10	9
8	18	18	10	10	10	9	9	9	8	9	13	12	13	10
9	16	15	12	12	9	9	9	9	8	8	13	12	9	9
10	18	16	10	10	11	9	13	11	11	9	13	13	12	10
Average	15.1	15.3	11.1	11	11	10.5	11	10.1	9.7	9.6	12.5	13	11.1	11.2
SD	2.28	1.70	2.02	2.05	2.91	2.32	1.83	1.45	2.95	2.50	0.97	1.33	2.38	2.66
SE ±	0.72	0.54	0.64	0.65	0.92	0.73	0.58	0.46	0.93	0.79	0.31	0.42	0.75	0.84
p(t-test) vs N			0.005	0.000	0.008	0.001	0.003	0.000	0.002	0.000	0.008	0.011	0.003	0.003
p(t-test) L vs R		0.413		0.457		0.338		0.119		0.468		0.175		0.465

Compound I-4, concentration of 2.5%

N—normal value before application

SD—standard deviation

SE—standard error of the average

LE—left eye

RE—right eye

US008193184B2

(12) **United States Patent**
Gregan et al.

(10) **Patent No.: US 8,193,184 B2**
(45) **Date of Patent: Jun. 5, 2012**

(54) **SUBSTITUTED SULPHONAMIDES, PROCESS FOR THEIR PREPARATION, PHARMACEUTICAL COMPOSITION COMPRISING THEREOF AND THEIR USE**

(75) Inventors: **Fridrich Gregan**, Bratislava (SK); **Milan Remko**, Bratislava (SK); **Elena Slučiakova**, Bratislava (SK); **Jarmila Knapíkova**, Bratislava (SK)

(73) Assignee: **Unimed Pharma, SPOL., S.R.O.**, Bratislava (SK)

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Substituted sulphonamides having the general formula (I) and salts, hydrates and solvates thereof were prepared and described, wherein R^1 is CO or SO_2 and R^2 is NH or O and where R represents linear or cyclic aliphatic chain and n represents number of linking aliphatic chain carbons (n can be 0, 1, 2 or 3), which are useful in the manufacture of the medicaments due to the carboanhydrase inhibition. These compounds are prepared by nucleophilic reaction of an amine with 4-sulfamoylbenzenesulphonyl chloride in the presence of triethylamine excess in tetrahydrofurane or in ether at temperature 0 to 20° C. The compounds show an antiglaucomatic activity.

16 Claims, No Drawings

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