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Thiophosphorylic and Phosophorylic Arylsulfon-Amides as Carbonic Anhidrase Inhibitors

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Sulfonamide carbonic anhydrase inhibitors are extensively studied due to their clinical applications for treatment of glaucoma, gastroduodenal ulcers, neurological disorders, and osteoporosis [1]

$$\begin{array}{ccc}
R & Y & Y & Y & NH-SO_2-Ar \\
R & 1 & R-P & NH-SO_2-Ar \\
1 & 2 & 2
\end{array}$$

R= Ph, C_6H_{11} -c, AlkylO, Dialkylamino; Ar=2-naphthyl, C_6H_4 - X_p ; X=H, Hal, CH₁, CH₂O; Y=O, S

Taking into account that our reports [2, 3] compounds 1 and 2 act as CAI and CAII inhibitors in micromolar range, we decided to investigate the interaction of compounds of type 3 with different CA isozymes

HO
$$\bigcap_{P-NH-SO_2-Ar}$$
 Ar= 2-naphtyl, C₆H₄-X; X=H, 4-Hal, 4-CH₃, 4-CH₃O, 4-NO₂, 2-NO₂

Compounds 3 was synthesized by literature [4] some of them being new, from phosphorous pentachloride, arylsulfonamides and formic acid, were characterized by standard procedures and pKa values (3, $X=2-NO_2$, $pK_1=2,87$, $pK_2=5,55$, $pK_3=9,58$). Inhibitors where assayed by Maren's micromethod [5]. Inhibition data of isozymes CAI, II and IV present K_1 very near values to dichlorophenamide (standard and clinical used inhibitor).

Compounds 3 are much more active than 1 or 2. Like 1 and 2, we proposed a bounding mode for 3 presuming the bound of inhibitor in ionized form within the enzyme active site, with a supplementary bound between the metal center (Zn) and HO-P group. Structure-activity correlations are made.

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