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Tailoring the Structure of α-hydroxyphosphonates and α-phosphoryloxyphosphonates to Target Sarcoma Cells

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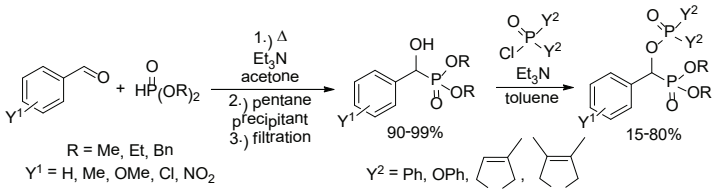
The synthesis of α-hydroxyphosphonates is an evergreen field in organophosphorus chemistry due to the bioactivity of the products. The most common synthetic route towards α-hydroxyphosphonates is the addition of dialkylphosphite to an oxo compound (Pudovik reaction). This reaction is usually carried out under solvent-free conditions in the literature. However, during the work-up procedure, a considerable amount of organic solvents is used. We have elaborated a new, green procedure for the synthesis of α-hydroxyphosphonates by reducing the use of organic solvents to the minimum [1]. The α-hydroxyphosphonates so obtained were subjected to phosphorylations and phosphinoylations to afford α-phosphoryloxyphosphonates and α-phosphinoyloxyphosphonates as new compounds (Scheme 1) [2].



Scheme 1 Synthesis and phosphorylation/phosphinoylation of α-hydroxyphosphonates

α-Hydroxyphosphonates and α-phosphoryloxyphosphonates obtained by us were screened against Mes-Sa human sarcoma cell line as potential cytotoxic agents. Among α-hydroxyphosphonates, dibenzyl esters were found as hits [3], while among α-phosphinoyloxyphosphonates phenyl-containing derivatives showed moderate cytotoxic activity. The next idea was the combination of the scaffolds of the hit molecules. The reaction of dibenzyl 1-hydroxy-1-phenylmethyl-phosphonates with diphenyl phosphinic chloride resulted in more effective compounds with IC_{50} values of 8-9 μM (Figure 1). These results are promising for further investigation of these compounds as potential cytotoxic agents.

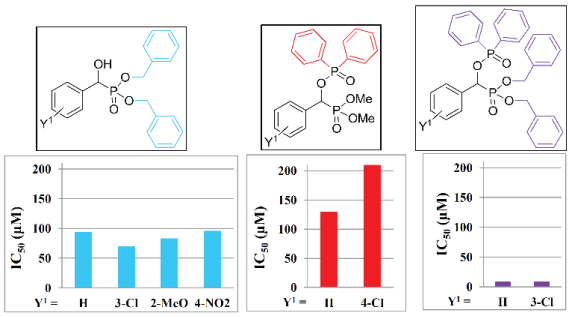


Figure 1 Cytotoxic effect of α-hydroxyphosphonates and α-phosphinoyloxyphosphonates

[1] Keglevich G., Rádai Z., Kiss N. Z.*Green Process. Synth.***2017**,*6*, 197-201.

[2] Rádai, Z.; Hodula, V.; Kiss, N. Z.; Kóti, J.; Keglevich, G. *Mendeleev Commun.***2019**, *29*, in press.

[3] Rádai Z., Szeles P., Kiss N.Z., Hegedűs L., Windt T., Nagy V., Keglevich G. *Heteroatom Chem.***2018**,e21436.

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Biography:

Zita Rádai graduated from the Budapest University of Technology and Economics in 2016 as a pharmaceutical engineer. She has been a PhD student since 2016 at the Department of Organic Chemistry and Technology at the same university, under the supervision of Professor Dr. György Keglevich. Her main fields of interest cover organophosphorus chemistry, microwave-assisted chemistry and green synthesis. She is the author or co-author of about twenty research or review articles and book chapters.