NEW CHOLINE KINASE INHIBITORS WITH ANTIPROLIFERATIVE ACTIVITY AGAINST *ras*-TRANSFORMED CELLS

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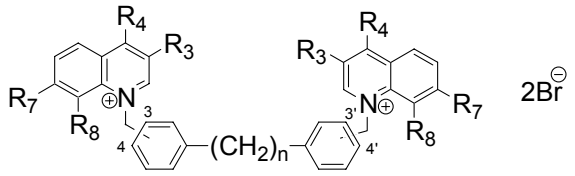
We have recently carried out studies aimed to establish the SARs that define ChoK inhibitory potency and antiproliferative activity of a set of bispyridinium compounds [1]. The aim of this communication specifically focusses on studying the effect to be expected on the biological activities by a variation in the linker that connects the quinolinium cations having electron-releasing groups at their position 4, with other different groups at positions 3, 7 and 8 of the heterocycle (compounds **1)**.



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On one hand, according to their inhibitory activities against human ChoK, it is found that the enzymatic inhibitory potency is closely related to the size of the linker, the 3,3'-biphenyl moiety being the most suitable one, followed by the 4,4'-bibenzyl fragment and finally, the 4,4'-biphenyl one. On the other, the antiproliferative activity against the HT-29 human colon cancer cell line is less influenced by the linker type and by the substituent R_4. The corresponding QSAR equation was obtained for the whole set of compounds for the antiproliferative activity, the electronic parameter σ_R of R_4, the molar refractivity of R_8 (MR_8) and the lipophilic parameters clog *P* and π_{linker}:

$p(IC_{50})_{HT\text{-}29} = -2.66 - 0.03\ (\pm 0.00)\ MR_8^2 + 0.10\ (\pm 0.02)$ clog $P + 1.05\ (\pm 0.31)\ \pi_{linker} - 3.73\ (\pm 0.71)\ \sigma_R$

$n = 40$, $r = 0.920$, $s = 0.223$, $F_{4,35} = 47.856$, $\alpha < 0.001$

Toxicity assays were performed for the most active compounds *in vitro*, the most promising compounds being **1a** ($R_3 = R_7 = R_8 = H$; R_4 = 4-chloro-*N*-methylanilino; n = 2; 4,4'), and **43** ($R_3 = R_8 = H$; R_4 = 4-chloro-*N*-methylanilino; R_7 = Cl; n = 2; 4,4') as a consequence of their interesting antiproliferative activities [$IC_{50\ HT\text{-}29}$ = 0.70 and 0.80 μM] and low toxicity [LD_{50} = 16.7 and 12.5 mg/Kg of mouse]. These biological activities justify further analysis for antitumoural assays under *in vivo* conditions.

[1] Conejo-García, A.; Báñez-Coronel, M.; Sánchez-Martín, R. M., Rodríguez-González, A.; Ramos, A.; Ramírez de Molina, A.; Espinosa, A.; Gallo, M. Á.; Campos, J. M.; Lacal, J. C. Influence of the linker in bispyridinium compounds on the inhibition of human choline kinase. *J. Med. Chem.*, **2004**, *47*, 5433-5440.