Some New Carbacylamidophosphates as Inhibitors of Acetylcholinesterase and Butyrylcholinesterase

Khodayar Gholivand[a,*], Ahlam Madani Alizadehgan[a], Fresia Mojahed[a], Gholamreza Dehghan[b], Azadeh Mohammadirad[b], and Mohammad Abdollahi[b]

[a] Department of Chemistry, Faculty of Sciences, Tarbiat Modarres University, P. O. Box 14115-175, Tehran, Iran. E-mail: gholi_kh@modares.ac.ir
[b] Laboratory of Toxicology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, P. O. Box 14155-6451, Tehran, Iran

* Author for correspondence and reprint requests

Z. Naturforsch. **63c**, 241–250 (2008); received August 15/September 17, 2007

The differences in the inhibition activity of organophosphorus agents are a manifestation of different molecular properties of the inhibitors involved in the interaction with the active site of enzyme. We were interested in comparing the inhibition potency of four known synthesized carbacylamidophosphates with the general formula $RC(O)NHP(O)Cl_2$, constituting organophosphorus compounds, where R = CCl_3 (**1**), $CHCl_2$ (**2**), CH_2Cl (**3**) and CF_3 (**4**), and four new ones with the general formula $RC(O)NHP(O)(R')_2$, where R′ = morpholine and R = CCl_3 (**5**), $CHCl_2$ (**6**), CH_2Cl (**7**), CF_3 (**8**), on AChE and BuChE activities. In addition, *in vitro* activities of all eight compounds on BuChE were determined. Besides, *in vivo* inhibition potency of compounds **2** and **6**, which had the highest inhibition potency among the tested compounds, was studied. The data demonstrated that compound **2** from the compound series **1** to **4** and compound **6** from the compound series **5** to **8** are the most sensitive as AChE and BuChE inhibitors, respectively. Comparing the IC_{50} values of these compounds, it was clear that the inhibition potency of these compounds for AChE are 2- to 100-fold greater than for BuChE inhibition. Comparison of the kinetics (IC_{50}, K_i, k_p, K_A and K_D) of AChE and BuChE inactivation by these compounds resulted in no significant difference for the measured variables except for compounds **2** and **6**, which appeared to be more sensitive to AChE and BuChE by significantly higher k_p and K_i values and a lower IC_{50} value in comparison with the other compounds. The LD_{50} value of compounds **2** and **6**, after oral administration, and the changes of erythrocyte AChE and plasma BuChE activities in albino mice were studied. The *in vivo* experiments, similar to the *in vitro* results, showed that compound **2** is a stronger AChE and BuChE inhibitor than the other synthesized carbacylamidophosphates. Furthermore, in this study, the importance of electropositivity of the phosphorus atom, steric hindrance and leaving group specificity were reinforced as important determinants of inhibition activity.

Key words: Carbacylamidophosphate, AChE, BuChE