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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-AMINO-2-(4-CHLOROPHENYL)1,1-DIFLUOROPROPYL PHOSPHONIC ACID

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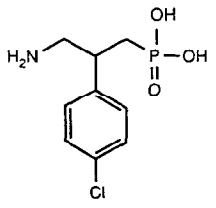
Abstract : *The synthesis of the α-difluoro analogue (1) of the $GABA_B$ antagonist phaclofen (2) is described along with its action on a $GABA_B$ functional assay.*

Biological receptors for the neurotransmitter GABA are subdivided into $GABA_A$ and $GABA_B$.[2] There are no potent $GABA_B$ antagonists described, only a number of weakly binding compounds which include the phosphonic acid, phaclofen (**2**)[3] and the partial agonist 3-APPA (**3**),[4] and the sulphonic acid, saclofen (**4**).[5]



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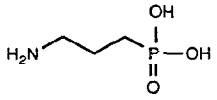

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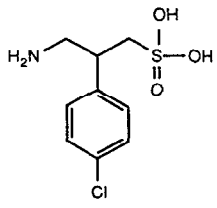

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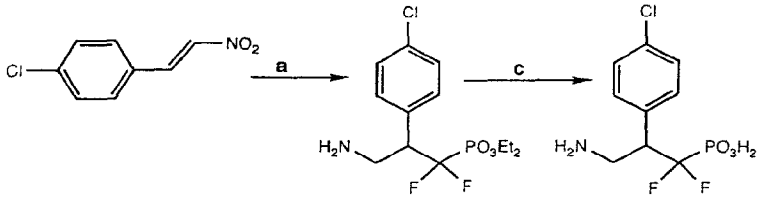
The antagonist activity of the phosphonic acids **2** and **3** as well as their low affinity for the $GABA_B$ receptor, compared to their carboxylic acid analogues, might be due to the unique ability of phosphonic acids to be diionized at physiological pH. However, for simple alkylphosphonic acids, the second ionization pk_a[2] will not be complete at physiological pH.[6] Thus, offering the possibility that additional features of the phosphonate group, other than diionization, may be responsible for the antagonist activity. To explore whether complete diionization is a prerequisite for this change in activity, the α-difluoro analogue of phaclofen (**1**) was synthesized and tested on a relevant biological assay. The presence of the two proximal fluorine atoms, should lower the second pk_a[2] to about 6, ensuring over 95% diionization at physiological pH,[7] without significantly increasing the steric bulk α- to the phosphonic acid.

Our synthetic strategy is outlined below. The lithium anion of diethyldifluoromethanephosphonate[8] reacted in a 1,4 addition to 4-chloro-β-nitro styrene **5** at -78°C to give the nitro compound **6** in 78% yield

after purification. Catalytic reduction of the nitro group occurred readily using Raney nickel in an atmosphere of hydrogen giving the amine **7** in 72% yield. De-esterification with concentrated hydrochloric acid produced the final product as the hydrochloride salt. Treatment with propylene oxide gave the racemic difluorinated phaclofen **1** in 53% yield as the zwitterion : mp 278-279°C; 200 MHz ^{1}H NMR (D_2O) δ 7.44 (m, 4H, ArH), 3.77 (m, 2H, CH_2), 3.44 (m, 1H, ArCH).



5 b 6 : R = NO_2 ; 7 : R = NH_2 1

a) Li $CF_2PO_3Et_2$; b) H_2, Raney Ni, EtOH ; c) i)12M HCl, Δ, ii) Propylene oxide , MeOH/ EtOH

On a $GABA_B$ functional assay, the rat anococcygeus,[9] **1** surprisingly showed very weak agonist activity ($EC_{50} \approx 300$ μM) and no antagonism of the effects of a $GABA_B$ agonist. This is in stark contrast to the weak antagonist activity described for phaclofen.[3] This observation suggests that diionization of the acidic moiety may be detrimental for $GABA_B$ antagonist activity.

References and Notes

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