SYNTHESIS OF POLYFLUOROKETONES CONTAINING AN INDOLE RING AS INHIBITORS OF HUMAN Ca^{2+}- INDEPENDENT PHOSPHOLIPASE A_2

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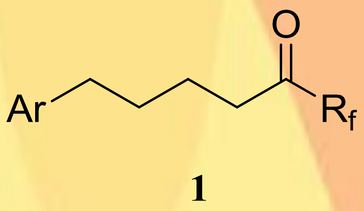
Introduction

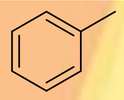
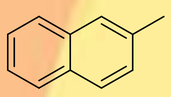
Phospholipase A_2 (PLA_2) enzymes catalyze the hydrolysis of the *sn-2* ester bond of glycerophospholipids producing free fatty acids and lysophospholipids.[1] The main representative of these fatty acids is arachidonic acid, which can be transformed into eicosanoids (prostaglandins, leukotriens, etc) by the action of other enzymes. Lysophospholipids are precursors for other bioactive compounds, such as platelet-activating factor (PAF). PAF and eicosanoids constitute basic mediators of inflammation and other pathophysiological routes. In the superfamily of PLA_2 enzymes, three are the predominant groups found in human tissues; the cytosolic PLA_2 ($cPLA_2$), the calcium-independent PLA_2 ($iPLA_2$) and the secreted PLA_2 ($sPLA_2$).[1] We have recently demonstrated that Ca^{2+}-independent phospholipase A_2 (GVIA $iPLA_2$) plays a key-role in experimental autoimmune encephalomyelitis and that GVIA $iPLA_2$ is a novel target for the development of new therapies for multiple sclerosis.[2]

A series of fluoroketones of the general structure **1** has been presented as $iPLA_2$ inhibitors and the structure-activity relationship has been evaluated.[3,4] Polyfluoroketones **FKGK11** and **FKGK18** proved to be potent and selective inhibitors of GVIA $iPLA_2$ **(Table 1)**. Therefore, to extend this research, we synthesized a variety of polyfluoroketones containing an indole ring and a four carbon atom chain between the ring and the polyfluoroketone group.



1

Table 1[4]

No	Ar	R_f	$X_I(50)$ for $iPLA_2$
FKGK11		C_2F_5	0.0014 ± 0.0001
FKGK18		CF_3	0.0002 ± 0.0000

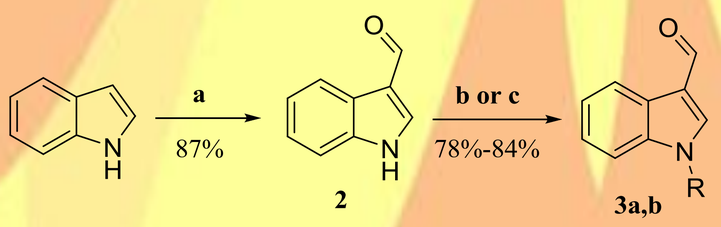
Synthesis

Indole-3-carboxaldehyde **(2)** was obtained from indole using the Vilsmeier - Haack reaction and then it was protected with the tosyl or the methyl group **(Scheme 1)**. These two protected aldehydes along with commercially available indole-5-carboxaldehyde underwent a Horner – Wadsworth – Emmons reaction with triethyl-4-phosphonocrotonate in the presence of a strong base (1,1,3,3-tetramethyl guanidine or NaH) to produce the corresponding unsaturated esters **4a-c** (**Scheme 2)**. After catalytic hydrogenation, we received the saturated esters **5a-d**; in the case of ester **5d** the indole ring was also hydrogenated along with the double bonds. After saponification with NaOH 1N in ethanol, we acquired the corresponding carboxylic acids **6a-d** which were converted to acyl chlorides with the method of oxalyl chloride/DMF. In situ, the acyl chlorides were treated with pyridine and trifluoroacetic anhydride or pentafluoropropionic anhydride to provide the trifluoromethyl ketone 8**d**, and pentafluoroethyl ketones **7a-c**. In the case of pentafluoroethyl ketone 7**c** the reaction conditions of the last step were in consistency with the Vilsmeier – Haack reaction and as a result we obtained the aldehyde derivative **(Scheme 3)**.

Acknowledgments

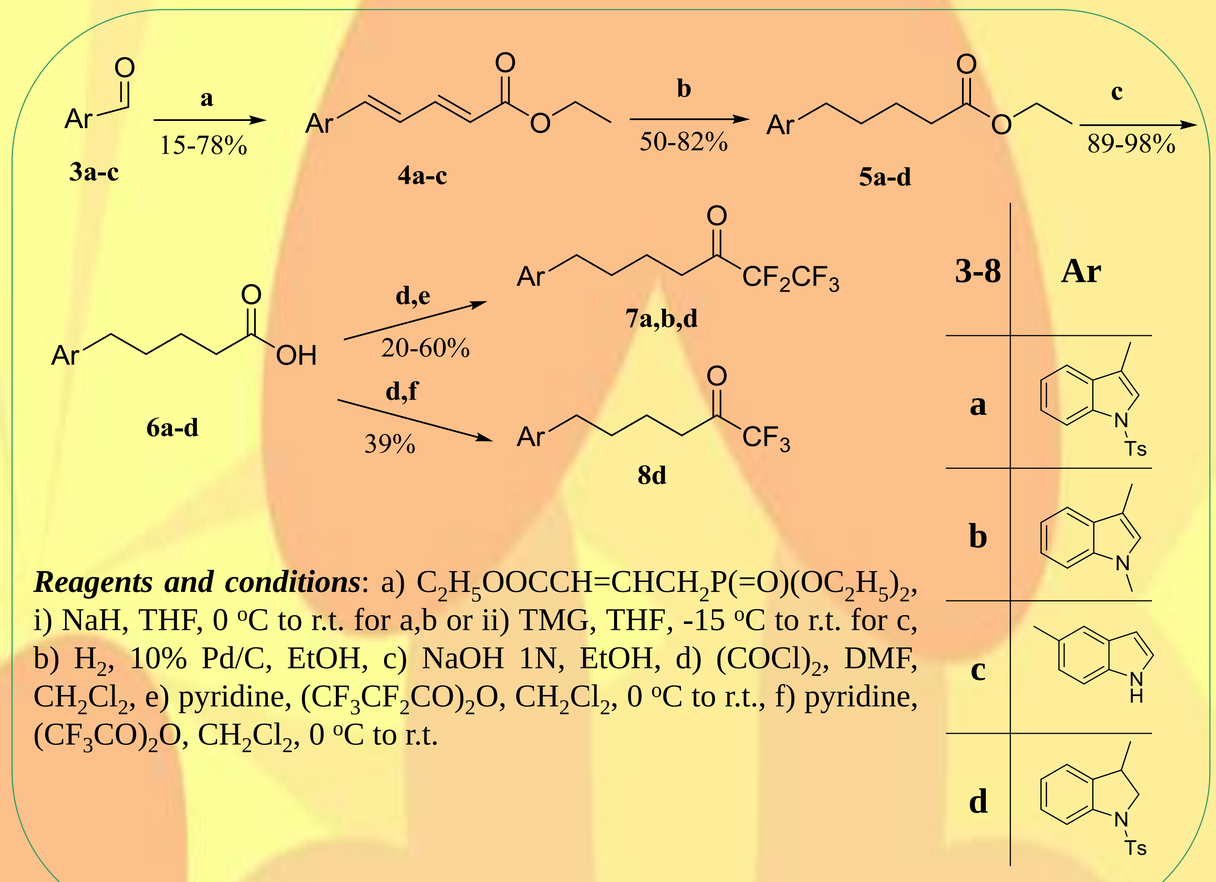
This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: Heracleitus II. Investing in knowledge society through the European Social Fund.

Scheme 1: Synthesis of protected indole-3-carboxaldehyde



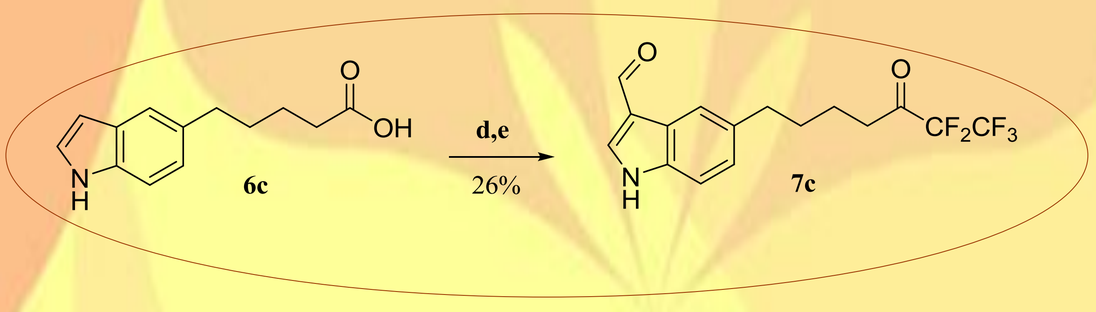
Reagents and conditions: a) DMF, $(COCl)_2$, NaOH 9N, H_2O, b) TsCl, NaOH, CH_2Cl_2, r.t. to 35 °C, c) NaH, CH_3I, THF.

Scheme 2: Synthesis of polyfluoroketones



Reagents and conditions: a) $C_2H_5OOCCH=CHCH_2P(=O)(OC_2H_5)_2$, i) NaH, THF, 0 °C to r.t. for a,b or ii) TMG, THF, -15 °C to r.t. for c, b) H_2, 10% Pd/C, EtOH, c) NaOH 1N, EtOH, d) $(COCl)_2$, DMF, CH_2Cl_2, e) pyridine, $(CF_3CF_2CO)_2O$, CH_2Cl_2, 0 °C to r.t., f) pyridine, $(CF_3CO)_2O$, CH_2Cl_2, 0 °C to r.t.

Scheme 3



Conclusion

Five novel polyfluoroketones were synthesized containing an indole ring and the evaluation of their inhibitory activity is in progress.

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European Union
European Social Fund
OPERATIONAL PROGRAMME EDUCATION AND LIFELONG LEARNING
investing in knowledge society
MINISTRY OF EDUCATION, LIFELONG LEARNING AND RELIGIOUS AFFAIRS
MANAGING AUTHORITY
NSRF 2007-2013
programme for development
EUROPEAN SOCIAL FUND
Co- financed by Greece and the European Union