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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW ARYLTHIOPHENE ANALOGS OF DuP 753

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Abstract : We described synthesis and biological results of analogs of DuP 753 where the central phenyl ring has been replaced by a 2,5-disubstituted thiophene.

Introduction

The renin-angiotensin system (RAS) plays a pivotal role in the regulation of blood pressure and electrolyte fluid balance[1,2]. The octapeptide angiotensin II (A II) is the vasopressive component of the RAS which acts through stimulation of AT_1 receptors[3,4]. Blockade of RAS has been first achieved via the inhibition of angiotensin converting enzyme (ACE) with compounds such as captopril and enalapril[5]. However due to adverse side effects an alternative approach has been developed with inhibitors of the more specific enzyme renin[6]. Recently numerous compounds have been designed in order to antagonize the AT_1 receptor itself. Among them, only non peptidic ones are real candidates for therapeutic use. Losartan (DuP 753)[7] now in phase III clinical trial is the most advanced compound in this field and a lot of analogs have been described where the biphenyltetrazole is usually retained[8]. Using the well-known bioisosteric approach we have investigated the structural and biological effects of replacing the central phenyl ring of DuP 753 by a 2,5-disubstituted thiophene leading to compounds 1-4 (table I).

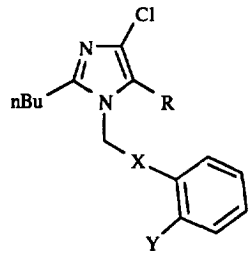
Chemical syntheses were preceded by conformational analysis in order to validate the pertinence of our choice using the sybyl program and high temperature molecular dynamic simulations to explore the conformational space of these compounds. In view on the rather fair resemblance between the molecules examined we decided to embark on the synthesis of compounds 1-4.

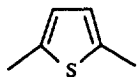
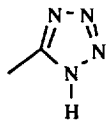
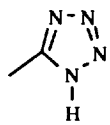
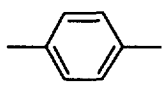
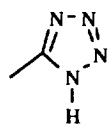
Chemistry

Compounds of Table I were synthesized according to schemes I and II.

Deprotonation of 2-methylthiophene followed by action of triisopropylborate afforded 2-thiopheneboronic anhydride which was condensed either on methyl-2-iodobenzoate or on 2-bromobenzonitrile using the well-known palladium coupling reaction[10,11]. Because of the great tendancy of 2-thiopheneboronic acids to protodeboronation in aqueous solvents[12], we carried out the reaction in 1,2-dimethoxyethane in presence of one equivalent of sodium carbonate. Under these conditions 5 and 6 were obtained respectively with 75 % and 90 % yield.

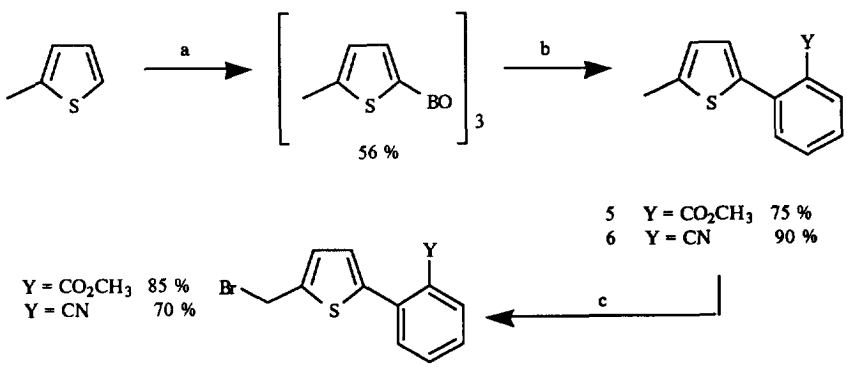
Table I : Structures of the compounds and their IC_{50} on rabbit aorta



Compound[a]	X	Y	R	mp°C	Antagonism of AII IC_{50} rabbit aorta (nM)[b]
1			CH_2OH	104.6	328
2	"	CO_2H	CH_2OH	97.9	4160
3	"		CHO	75.7	330
4	"	CO_2H	CHO	156.8	2000
DuP 753			CH_2OH		6.1
ExP 7711	"	CO_2H	CH_2OH		120

[a] All described compounds were fully characterized including spectroscopic and elemental analysis.
[b] Values were determined according to ref. 9.

Scheme I*

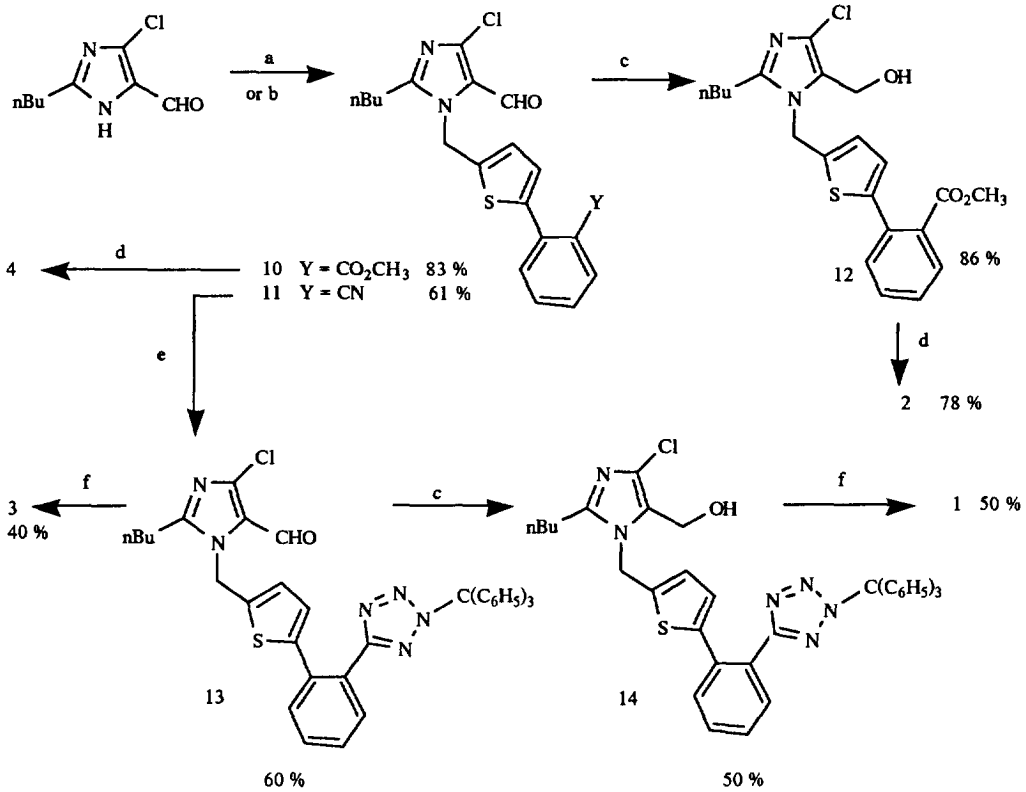


*Reagents : (a) n-BuLi, Et_2O, $B(O\text{-}iPr)_3$, H_3O^+ ; (b) o-$IC_6H_4CO_2CH_3$ or o-BrC_6H_4CN, Pd $(Ph_3P)_4$, Na_2CO_3 (1 equiv), DME ; (c) NBS, AIBN, CCl_4.

Action of N-bromosuccinimide in carbon tetrachloride with AIBN as a radical initiator afforded the alkylbromide derivatives **7** and **8** used without further purification in the next step. Alkylation of the known aldehyde **9** [13-14] with **7** or **8** in DMF with K_2CO_3 as a base gave respectively compounds **10** and **11** with 83 % and 61 % yield.

Hydrolysis of compound **10** led to the final compound **4**, the corresponding tetrazolate **3** was obtained from the nitrile **11** using a previously described procedure [7-15]. Reduction of **10** followed by hydrolysis afforded alcohol **2**. Reduction of **13** and subsequent deprotection of the intermediate gave compound **1**.

Scheme II*



*Reagents : (a) K_2CO_3,DMF, **7** ; (b) K_2CO_3, DMF, **8** ; (c) $NaBH_4$, CH_3OH ; (d) 2N NaOH, H_2O, CH_3OH ; (e) Bu_3SnCl, NaN_3, toluene, ClC $(Ph)_3$, NEt_3 ; (f) 3.4N HCl, CH_3OH.

Biological results and discussion

In vitro antagonist activity was determined by the ability of compounds to antagonize the contractile response to angiotensin II in the isolated rabbit aortic strips[16]. The results are summarized in table I. Compound **1** is 54 times less active than DuP 753. The corresponding carboxylic acid **2** is 35 times less active than EXP 7711. The aldehydes **3** and **4** present the same level of activity as alcohols **1** and **2**.

From these data we can conclude that slight modifications of position and/or orientation of the elements of the pharmacophore are detrimental for the AT1 antagonism. A similar conclusion has been drawn by R.A. Rivero[17] from replacement of the central phenyl ring of L-158, 809 by a 2,5-disubstituted thiophene leading to a 1000 times decrease of binding.

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