Recent Developments in the Synthesis of Acetylcholinesterase Inhibitors

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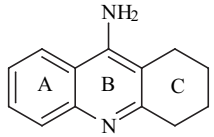
Abstract: The acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitory activities of a series of pyrano[2,3-*b*]quinolines (**2**, **3**), [1,8]naphthyridines (**5**, **6**), 4-amino-2,3-diaryl-5,6,7,8-tetrahydrofuro[2,3-*b*]quinolines (**11**-**13**)/ 4-amino-6,7,8,9-tetrahydro-2,3-diphenyl-5*H*-cyclohepta[*e*]furo[2,3-*b*]pyridine (**14**), 4-amino-5,6,7,8-tetrahydro-2,3-diphenylthieno[2,3-*b*]quinoline (**15**)/ 4-amino-6,7,8,9-tetrahydro-2,3-diphenyl-5*H*-cyclohepta[*e*]thieno[2,3-*b*]pyridine (**16**) are described. These compounds are tacrine analogues that have been prepared from readily available polyfunctionalized ethyl [6-amino-5-cyano-4*H*-pyran]-3-carboxylates (**9**, **10**), ethyl [6-amino-5-cyanopyridine]-3-carboxylates (**7**, **8**), 2-amino-3-cyano-4,5-diarylfurans (**17**-**19**) and 2-amino-3-cyano-4,5-diphenylthiophene (**20**) *via* Friedländer condensation with selected ketones. These compounds are competitive and, in a few cases, non-competitive inhibitors for AChE, the most potent being compound (**14**), though three-fold less active than tacrine. The BuChE inhibitory activity is only significant in compounds **11** and **14**, ten-fold less active than tacrine. Furthermore, the products **12** and **13** are selective and moderate AChE inhibitors.

Key Words: Tacrine analogues; AChE/BuChE inhibitors; pyrano[2,3-b]quinolines; [1,8]naphthyridines; furo (thieno)[2,3-b] quinolines; furo (thieno) [2,3-b] pyridines.

INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible, neurological disorder. The clinical presentation is characterized by core deficits in cognition (memory, praxis and language), and is commonly associated with a variety of psychiatric disturbances and a marked deterioration in behaviour. It is the most common form of dementia associated with both severe disability in carrying out the activities of everyday life and reduced life expectancy after disease onset compared to age matched controls. By virtue of its protracted, unremitting course, AD can produce a significant impact upon the emotional health of caregivers and the economic integrity of the health care system [1]. AD affects particularly the elderly population and is the fourth leading cause of death of people over 65 years in western countries, preceded only by heart disease, cancer and stroke [2].

Despite the research effort directed towards discovering the cause of AD with the hope of developing a safe and effective therapy, present interventions in this disease only serve as palliative although it became clear treatments modulating neurotransmitter function remain a viable therapeutic approach [1]. The "cholinergic hypothesis" [3-5], which has been proposed to explain the pathology and symptoms of geriatric memory dysfunction with cholinergic deficiencies, has been one of the most useful and productive approaches for designing new potential therapeutic agents for the treatment of AD. An impressive amount of research has been directed by this rationale that brought about the development of drugs with an AChE inhibition profile. AChE is the enzyme responsible for the catabolism of extra cellular acetylcholine (ACh), therefore its inhibition leads to an increase in the bioavailability of ACh at the synaptic cleft, thus improving cholinergic neurotransmission [3-5].



Tacrine (**1**)

Fig. (1).

Tacrine (**1**, 9-amino-1,2,3,4-tetrahydroacridine, THA) (Figure 1) was the first acetylcholinesterase inhibitor (AChEI) approved in the USA for the treatment of AD in 1993 [6]. However, hepatotoxicity, cholinergic adverse effects, and interactions with drugs metabolized through the isoenzyme P450IA2 have limited its use [6,7]. THA is also a strong inhibitor of butyrylcholinesterase (BuChE) and it was suggested that THA peripheral adverse effects were mainly due to its remarkable ability to inhibit BuChE [8,9]. This enzyme is found not only in association with neuronal cells in brain, but also with glial cells and, in particular, at the level of the blood-brain barrier [10]. Its presence was detected in cardiac muscle and, in especially high amounts in liver, suggesting a role in lipid metabolism as well as in the degradation of a variety of drugs and in the activation of others [10]. Anyhow, the physiological role of BuChE remains to be fully elucidated in both the brain and systemic circulation but it may serve as a scavenger in the detoxification of certain xenobiotics, thus limiting the amounts reaching the CNS [10]. Despite its peripheral adverse effects, tacrine represents an important reference for the design of more selective and effective analogues [11-14]. Furthermore, studies in rats have shown that tacrine

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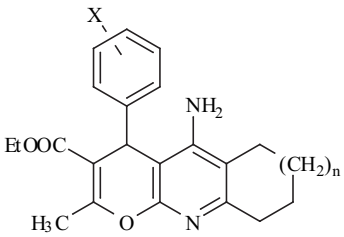
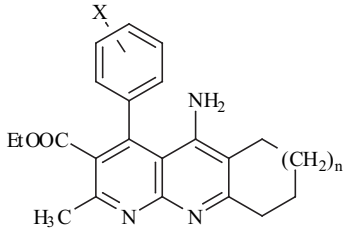


A (n= 0, 1)



C (n= 0, 1, 2)

Chart 1.

increased the synthesis, turnover and release of serotonin, norepinephrine and dopamine and also inhibited the reuptake of those neurotransmitters [7]. These are important findings as in AD besides the cholinergic depletion, deficits for other neurotransmitter systems have also been observed [2,15].

One of the most successful strategies in lead optimization is the bioisosteric replacement of aromatic moieties using heterocyclic scaffolds to: (I) improve intrinsic pharmacological activity, (II) increase selectivity, (III) increase bioavailability or (IV) modulate drug metabolism. Heterocyclic moieties combine volume, electronic and physical properties that are ideal to modulate drug-receptor interactions [16].

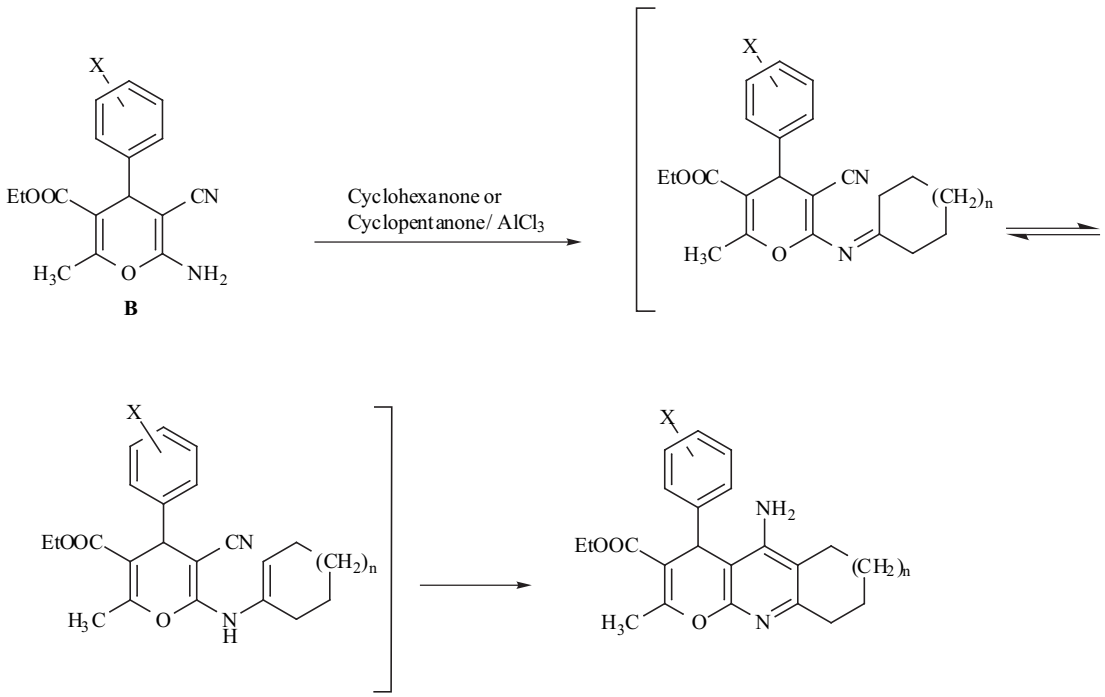
In this context, we have been very recently involved in the synthesis and biological evaluation of new acetylcholinesterase inhibitors related to tacrine (**1**), and in this review we will summarize our recent results on this subject.

SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRANO[2,3-*B*]QUINOLINE AND [1,8]NAPHTHYRIDINE DERIVATIVES AND PRELIMINARY STRUCTURE-ACTIVITY RELATIONSHIPS

Chemistry

The synthesis of differently substituted 4*H*-pyran[2,3-*b*]quinoline-3-carboxylic acid derivatives (A) (Chart 1) [17,18] was achieved by Friedländer [19] condensation of 4*H*-pyran-3-carboxylic acid derivatives (B) with the selected ketones, under Lewis-acid catalysis (Scheme 1). Proceeding this way, compounds 2a-f and 3 have been obtained [17] in mild reaction conditions and convenient chemical yields.

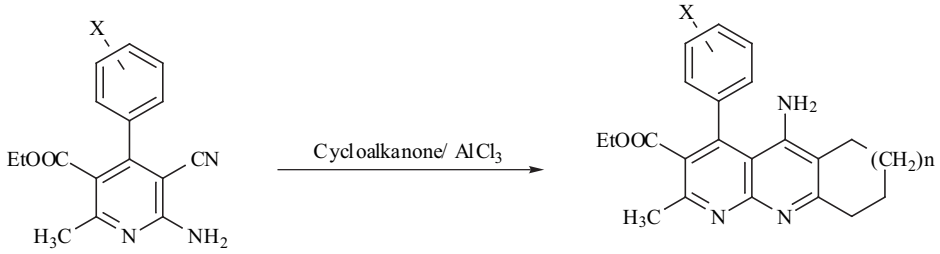
We have also addressed our attention to the analogous cycloannulated [1,8]naphthyridine ring system [18] (**C**) (Chart 1) in order to extend the Friedländer [19] reaction to the corresponding densely functionalized 6-amino-5-cyanopyridines of type (**D**) [20-22] (Scheme 2). This would



B

2 (n= 1) [(**a**): X= H; (**b**): *p*-CH_3; (**c**): *p*-Cl; (**d**): *p*-CN; (**e**): *p*-OCH_3; (**f**): *m*-NO_2]
3 (n= 0) (X= H)

Scheme 1. Mechanism for the Friedl nder reaction, and synthesis of the tacrine-like analogues 2 and 3.



D **C**

Scheme 2. Strategy for the synthesis of new tacrine-like analogues of type C.

enable us to have a new set of compounds for the AChE inhibitory assays and to compare their pharmacology with compounds of type **A** (Chart 1) for structure-activity relationship purposes.

As in our previous approach [17] our selection was based on the synthesis of bioisosteres [23,24] of tacrine with additional substitution.

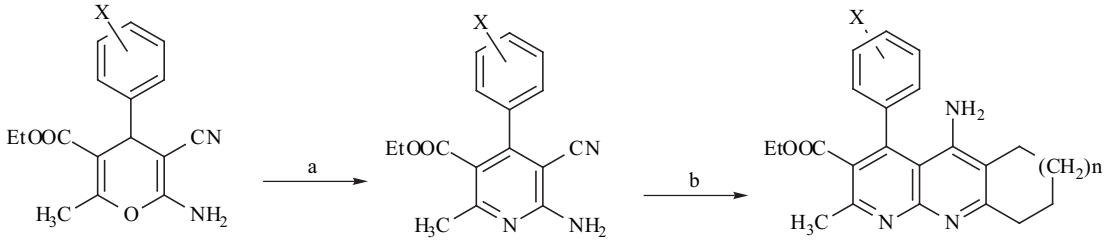
The naphthyridine nucleus is well known, it has been extensively synthesized and incorporated into biologically active molecules [25], and seemed to us as an excellent candidate for the "substitution" of the aromatic A/B rings in tacrine (**1**) (Chart 1).

The synthesis of the target compounds **5** and **6** was achieved starting from pyridines **7** and **8**, respectively, under standard Friedländer reaction conditions [19] with cyclopentanone, cyclohexanone or cycloheptanone (n= 0, 1 and 2, respectively) as the cycloalkanone partner. These pyridines have been described before and were readily prepared from the corresponding 4*H*-pyran-3-carboxylic acid derivatives (**9**, **10**) [26] by reaction with ammonium acetate in glacial acetic acid. Compounds **7** and **8** showed spectroscopic data in good agreement with the reported compounds [20-22]. For the initial experiments and as well as in compounds **2** and **3**, the selection of the substituents at the aromatic ring has been prompted by the easy availability of pyrans of the type (**B**) (Scheme 1) and by the anti-AChE activity observed for compound **2e** (Scheme 1). Besides, the size of the cycloannulated ring was also a major concern. On the whole, this has moved us to select and prepare compounds **5a-c** (X= H, n= 0, 1, 2; lead product) and **6a-c** (X= *p*-OCH_3, n= 0, 1, 2) (Scheme 3).

The heteroannulation reaction proceeded smoothly to provide the expected compounds **5** [**5a**: 15% (n= 0); **5b**: 60% (n= 1); **5c**: 57% (n= 2)] and **6** [**6a**: 15% (n= 0); **6b**: 74% (n= 1); **6c**: 80% (n= 2)] (Scheme 3) from moderate to good yields, with the cyclopentanone giving the worst results (15%). In spite of several trials changing the reaction time or the ratio of reagents, we were unable to improve these yields. All the new compounds showed excellent analytical and spectroscopic data, in agreement with the proposed structure [27].

Biological Evaluation

The standard methodology was utilized to characterize the enzyme inhibitors described herein: AChE inhibitory activity was assayed by the method of Ellman [28] using AChE from bovine erythrocytes; BuChE inhibitory activity determinations were carried out similarly using human serum BuChE. From the AChE inhibitory activity the following data were obtained (see Table 1). Comparing with tacrine (**1**) (IC_{50} 1,3 $\pm$ 0,1 x 10^{-7}), we can see that all the assayed compounds were of lower activity, the most active compounds being **5b** and **2e** (around 6–7 fold less potent). These compounds have cyclohexane rings annulated onto the aromatic nucleus, with X= H or *p*-OCH_3, respectively. Among the pyran-like tacrine analogues (compounds **2** and **3**), the cyclopentaannulated analogue **3** was the least active. In the cyclohexaannulated analogues, the most active



9 X= H
10 X=*p*-OCH_3

7 X= H
8 X=*p*-OCH_3

5 X= H (n= 0, 1, 2)
6 X=*p*-OCH_3 (n= 0, 1, 2)

Reagents: a. For X= H (Ref. 26); For X= *p*-OCH3 (Ref. 26) ; b. Cycloalkanone [Cyclopentanone (n= 0), Cyclohexanone (n= 1), Cycloheptanone (n= 1)], $(CH_2)_2Cl_2$, reflux/ $AlCl_3$

Scheme 3. Synthesis of tacrine-like compounds 5 and 6.

compound corresponded to product **2e** with the strongest electron donor power. However, the substituent electronic abilities do not seem to play a determinant effect, as compound **2b** (X= *p*-CH_3) or **2f** (X= *m*-NO_2) have a similar IC_{50} value.

In the pyridine-like THA analogues of type **5** (X= H), the most active derivative corresponded to the cyclohexaannulated derivative **5b**, while in compounds **6** (X= *p*-OCH_3), the most active was the cycloheptaannulated analogue. In any case, in compounds **5** or **6**, the most active concerned the aryl, unsubstituted, cyclohexaannulated derivative **5b**.

Table 1. Compounds 2, 3, 5 and 6 IC_{50} (M) Values for Activities on AChE and BuChE. Results are Expressed in (x ± SEM)

Compound	AChE (IC_{50}) (M)	BuChE (IC_{50}) (M)
TACRINE	$1.3 \pm 0.1 \times 10^{-7}$	$4.4 \pm 0.2 \times 10^{-8}$
PYRANOPYRIDINES		
Cyclohexa (n= 1)		
2a (X= H)	$1.56 \pm 0.1 \times 10^{-6}$	$> 3.0 \times 10^{-3}$
2b (X= *p*-CH_3)	$1.82 \pm 0.1 \times 10^{-6}$	
2c (X= *p*-Cl)	$1.93 \pm 0.2 \times 10^{-6}$	
2d (X= *p*-CN)	$3.47 \pm 0.8 \times 10^{-6}$	
2e (X= *p*-OCH_3)	$8.68 \pm 0.4 \times 10^{-7}$	$6.18 \pm 0.6 \times 10^{-6}$
2f (X= *m*-NO_2)	$1.89 \pm 0.8 \times 10^{-6}$	
Cyclopenta (n= 0)		
3 (X= H)	$3.90 \pm 0.7 \times 10^{-6}$	$3.35 \pm 2.0 \times 10^{-4}$
NAPHTHYRIDINES		
5a (X= H) **Cyclopenta (n= 0)**	$1.19 \pm 0.1 \times 10^{-5}$	
5b (X= H) **Cyclohexa (n= 1)**	$8.22 \pm 1.6 \times 10^{-7}$	$5.03 \pm 0.6 \times 10^{-6}$
5c (X= H) **Cycloheptа (n= 2)**	$2.10 \pm 0.1 \times 10^{-5}$	
6a (X= *p*-OCH_3) **Cyclopenta (n= 0)**	$1.37 \pm 0.3 \times 10^{-5}$	
6b (X= *p*-OCH_3) **Cyclohexa (n= 1)**	$8.97 \pm 1.6 \times 10^{-6}$	
6c (X= *p*-OCH_3) **Cycloheptа (n= 2)**	$1.35 \pm 0.7 \times 10^{-6}$	$8.06 \pm 2.6 \times 10^{-5}$

The most potent compound of each group was tested on BuChE. Data are depicted in Table 1. All the examined compounds inhibited AChE more strongly than BuChE. The most active anti-BuChE derivative was compound **5b**, which was also the most active as AChE inhibitor. It is important to recall that compound **2a** showed a strong specificity for AChE. As for the other "pyranoquinolines," compounds **2e** and **3** are 10-fold and 100-fold more selective, respectively. In regard to the "benzonaphthyridines", compounds **5b** and **6c** showed selectivities in the range of 10-fold. These data are very promising as tacrine peripheral cholinergic adverse effects [8,9] may be associated with its ability in inhibiting BuChE, and suggest future structural modifications for activity improvement.

Table 2. Effects of the Drugs (50-400 μM) on the V_{max} and K_m Values of Enzyme AChE Compared to Control Values in the Absence of Inhibitors. NS = Not Significant, * p < 0.05, ** p < 0.01

Compound	V_{max} (min^{-1})	K_m (mM)	Antagonism
Control (n= 4)	0.39± 0.04	135 ± 20	
2a (X= H)	0.41± 0.03 NS	225 ± 10	* Competitive
2e (X= *p*-OCH_3)	0.05± 0.01 **	120 ± 10	NS Non-competitive
3 (X= H)	0.40± 0.03 NS	220 ± 10	* Competitive
5b (X= H)	0.11± 0.01 **	185 ± 30	NS Non-competitive
6c (X= *p*-OCH_3)	0.42± 0.01 NS	230 ± 20	* Competitive

Finally, a series of experiments were carried out in order to determine the type of antagonism in compounds **2a**, **2e**, **3**, **5b** and **6c**. The data are displayed in Table 2. It is important to bear in mind that the most active AChE and BuChE inhibitors (**2e** and **5b**) are non-competitive inhibitors.

SYNTHESIS AND BIOLOGICAL ACTIVITY OF FURO (AND THIENO) [2,3-*B*] QUINOLINE AND FURO (AND THIENO) [2,3-*B*] PYRIDINE DERIVATIVES AND PRELIMINARY STRUCTURE-ACTIVITY RELATIONSHIPS

Chemistry

Following the work in this area and looking for more potent and selective AChE/BuChE inhibitors, next we drove our attention to new THA analogues, modifying ring A (Figure 1) by incorporating a five-member aromatic ring system instead of the benzene ring present in THA (**1**). This strategy has also been previously analyzed in part by other authors [29-32]. These results are interesting but suggest that other structural functional changes are feasible in order to improve biological data regarding the AChE/BuChE inhibitory activity. Thus, we have designed the new THA analogues 4-amino-2,3-diaryl-5,6,7,8-tetrahydrofuro[2,3-*b*]quinolines (**11-13**), 4-amino-6,7,8,9-tetrahydro-2,3-diphenyl-5*H*-cyclohepta[*e*]furo[2,3-*b*]pyridine (**14**), 4-amino-5,6,7,8-tetrahydro-2,3-diphenylthieno[2,3-*b*]quinoline (**15**) and 4-amino-6,7,8,9-tetrahydro-2,3-diphenyl-5*H*-cyclohepta[*e*]thieno[2,3-*b*]pyridine (**16**) (Chart 2) [33]. In these molecules we have incorporated the furo and thieno aromatic five ring systems with two phenyl rings (substituted or not) at C-2 and C-3. We have also altered the size of the saturated annulated ring, fusing a cyclohexa or a cyclohepta carbocycle.

The synthesis of compounds **11-14** has been achieved *via* Friedländer condensation [19] using 2-amino-3-cyano-4,5-diarylfurans (**17-19**) with cyclohexanone or cycloheptanone. 2-Amino-3-cyanofuranes **17** [34], **18** [35] and **19** [36] (Chart

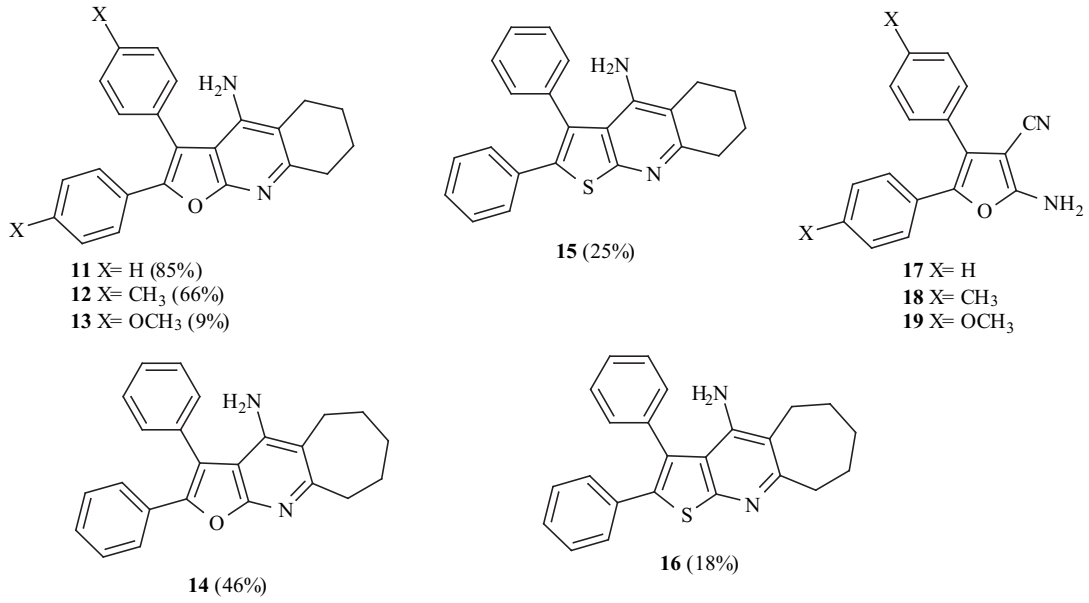


Chart 2.

2) are known compounds and have been prepared from the commercial corresponding α-hydroxybenzyl aryl ketones by condensation with malonodinitrile. As shown in chart 2 the expected furoquinolines were obtained in low to good yield. All the analytical and spectroscopic data are in good agreement with these structures.

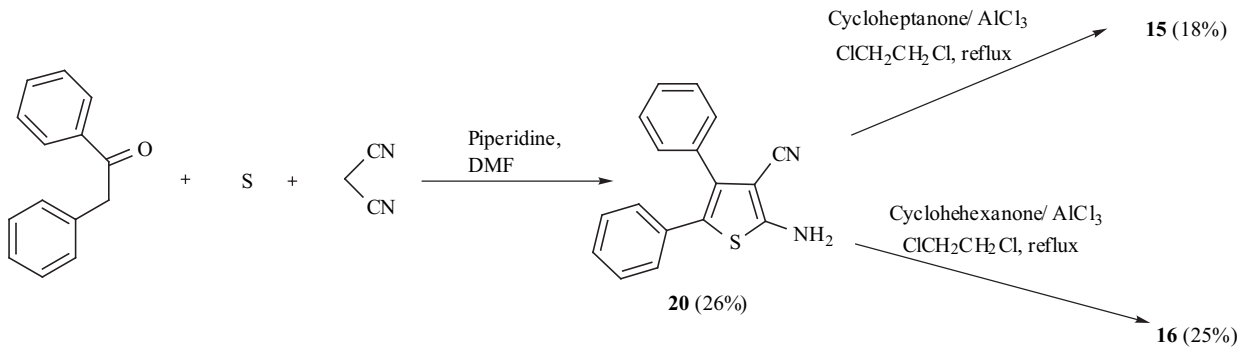
The synthesis of compounds **15** and **16** has also been accomplished *via* Friedländer condensation [19] of 2-amino-3-cyano-4,5-diphenylthiophene (**20**) with cyclohexanone or cycloheptanone, as depicted in Scheme 4. Precursor 2-amino-3-cyano-4,5-diphenylthiophene (**20**) was not known, and for its synthesis we have followed the method reported by Gewald for other related compounds [36,37]. Starting from commercial phenylacetophenone, malonodinitrile and sulfur, under mild basic catalysis (piperidine), product **20** was obtained in 26% yield. The analytical and spectroscopic data of compound **20** were in good agreement with this structure. The thiophene THA analogues **15** and **16** were obtained in yields of 25 and 18%, respectively by carrying out the Friedländer reaction [19].

Biological Evaluation

The AChE inhibitory activity was assayed by the method of Ellman [28] using AChE from bovine erythrocytes and

Table 3. IC_{50} (M) Values for Activities on AChE and BuChE of Compounds 11-16. Results are Expressed in (x ± SEM)

Compound	AChE (IC_{50}) (M)	BuChE (IC_{50}) (M)
TACRINE	$1.3 \pm 0.1 \times 10^{-7}$	$4.4 \pm 0.2 \times 10^{-8}$
FURO[2,3-*b*]QUINOLINES		
11	$4.4 \pm 0.8 \times 10^{-7}$	$3.7 \pm 0.4 \times 10^{-7}$
12	$3.8 \pm 0.2 \times 10^{-7}$	$> 10^{-4}$
13	$4.6 \pm 0.8 \times 10^{-7}$	$> 10^{-4}$
THIENO[2,3-*b*]QUINOLINES		
15	$> 10^{-4}$	$> 10^{-4}$
CYCLOHEPTA[*e*]FURO[2,3-*b*]PYRIDINES		
14	$3.2 \pm 0.5 \times 10^{-7}$	$7.7 \pm 1.2 \times 10^{-7}$
CYCLOHEPTA[*e*]THIENO[2,3-*b*] PYRIDINES		
16	$> 10^{-4}$	$> 10^{-4}$



Scheme 4. Synthesis of tacrine analogues 15 and 16.

BuChE inhibitory activity determinations were carried out similarly using human serum BuChE (see Table 3). The most striking observation concerns compounds with the thiophene moiety (**15**, **16**) that showed no significant inhibitory activity. In contrast with these results, the analogous furan derivatives (**11** and **14**, **12** and **13** as well) were strong AChE inhibitors. Comparing with THA (**1**) (IC_{50} 1.3 ± 0.1 x 10^{-7} M), all the tested compounds evoked slightly lower activity (between 2 to 4-fold), with **14** as the most active compound (around 2.4-fold less active than THA). The data regarding the activity of these compounds on BuChE are also displayed in Table 3. As we have seen for AChE, the thiophene-related compounds are devoid of any activity against BuChE. Conversely, in the furan series (**11**-**14**), the most active was the furo[2,3-*b*]quinoline **11**, roughly ten-fold less active than THA, followed by the cyclohepta[*e*]furo[2,3-*b*]pyridine **14**, seventeen-fold less active than THA. Products **12** and **13** showed no significant BuChE inhibitory activity.

Concerning the selectivity for AChE *versus* BuChE in the active products, compounds **11** and **14** exhibited values of the same magnitude. Compounds **12** and **13**, which were strong AChE inhibitors, interestingly, showed no significant activity on BuChE. As tacrine peripheral cholinergic adverse effects [3,8,9] may be associated to its ability in inhibiting BuChE very strongly, future structural modifications of these compounds may be performed for activity improvement and possible therapeutic interest. Very interestingly, Valenti [8] and co-workers have recently described the synthesis and biological evaluation of a series of annulated carbocyclic and/or heterocyclic aromatic tacrine analogues at ring-A having an aromatic ring-C that showed a potent AChE inhibitor profile with strong specificity for AChE *versus* BuChE.

Table 4. Effects of the Drugs (50-400 μM) on the V_{max} and K_m Values of AChE Enzyme Compared to Control Values in the Absence of Inhibitors

Compound	V_{max} (min^{-1})	K_m (mM)	Antagonism
Control (n ≥ 4)	0,323 ± 0,021	120 ± 4	
14	0,260 ± 0,021 (NS)	160 ± 9 (*)	Competitive
11	0,270 ± 0,016 (NS)	159 ± 17 (*)	Competitive
13	0,369 ± 0,036 (NS)	184 ± 8 (*)	Competitive
12	0,358 ± 0,027 (NS)	177 ± 20 (**)	Competitive

NS: no significant. * $p < 0,05$; ** $p < 0,01$.

Finally, a series of experiments were carried out in order to determine the type of antagonism in compounds **11**-**14**. From the data shown in Table 4, we conclude that all these compounds are competitive inhibitors.

CONCLUSIONS

In summary, we have reported the synthesis and preliminary results for AChE and BuChE inhibitory activity of a series of pyrano[2,3-*b*]pyridine (**2**, **3**) and naphthyridine (**5**, **6**) derivatives. These molecules have been prepared from readily available polyfunctionalized ethyl [4*H*-pyran and 6-amino-5-cyanopyridine]-3-carboxylates *via* Friedländer condensation with selected ketones. The most active compounds in these series correspond to pyrano- or pyridine-like tacrines with saturated cyclohexane rings. The type of the substituent at the aromatic ring in C4 does not seem to have a deep influence on the inhibitory activity. Overall, the substitution of a benzene ring in tacrine (**1**) by a pyran or a pyridine ring gives analogues with strong AChE inhibition, with lower values, but very close to those shown by tacrine (**1**).

We have also prepared series of new furo (and thieno)[2,3-*b*]quinoline and furo (and thieno)[2,3-*b*]pyridine derivatives (**11**-**14**, **15**, **16**). Interestingly, while the furan like derivatives **12** and **13** are strong AChE inhibitors and selective *versus* BuChE, the thieno analogues (**15** and **16**) are devoid of any biological activity.

Work is now in progress to extend this chemistry to another related precursors, test the biological activity and perform molecular modelling in order to have a clearer picture of the enzyme-substrate interactions.

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