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Synthesis and X-ray structures of new cycloalka[*e*]pyrano[2,3-*b*]pyridine derivatives: novel tacrine analogues

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ABSTRACT

A new series of tacrine (9-amino-1,2,3,4-tetrahydroacridine) analogues consisting of a cycloalka[*e*]pyrano[2,3-*b*]pyridine linked to a quinolyl ring has been synthesized. These compounds were prepared from the appropriately substituted pyran derivative via a Friedländer reaction with selected cycloalkanones in high yields. Single crystal X-ray structures are reported for four compounds.

Alzheimer's disease (AD) is a common neurodegenerative disorder affecting around 7% of the population above 65 years of age.[1] During the past two decades, the acetylcholinesterase (AChE) inhibitors, tacrine (**A**) (Fig. 1), donepezil and rivastigmine have been identified for the treatment of AD.[2] Due to a side effect of hepatotoxicity, tacrine is no longer marketed. It increases serum glutamic-oxaloacetic transaminase (SGOT) activity and serum glutamic-pyruvic transaminase (SGPT) activity in 25–30% of patients. Consequently, a number of other AChE inhibitors have been considered as candidates for the symptomatic treatment of AD with some of them already approved by the United States FDA for general use. They include natural substances such as physostigmine, (−)-huperzine A[3] and galanthamine, also known as Reminyl.[4] Nevertheless, efforts are continuing to synthesize even more effective anticholinesterase drugs than those already in use.

Some new inhibitors have been modelled on tacrine such as bistacrine analogues[5] and others, formally derived from tacrine by molecular duplication, have been synthesized and evaluated.[6]

A number of investigations have been carried out which involved the combination of various heterocycles with the 4*H*-pyrano[2,3-*b*]quinoline moiety which contain the 5,6,7,8-tetrahydroquinolin-4-amine substructure of tacrine **B** (Fig. 1).

These new tacrine analogues, where the aromatic nucleus 'a' has been substituted by a 4*H*-pyran ring and the fused cyclohexyl ring, has been contracted or enlarged to a cyclopentane or a cycloheptane, are potent inhibitors of AChE.[7]

On the other hand, quinolines and their annulated derivatives are important compounds in medicinal chemistry due to their presence in numerous natural products along with their wide-ranging applications as drugs, pharmaceuticals and agrochemicals.[8] For example, quinoline-containing compounds, such as quinine, chloroquine, mefloquine and amodiaquine, are used as efficient drugs for the treatment of malaria. To our knowledge,

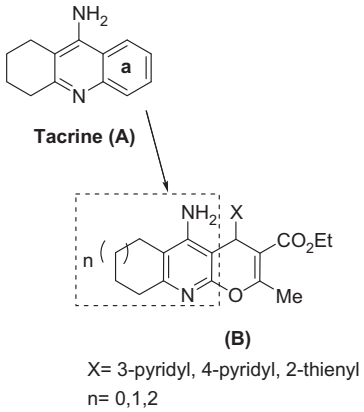

Figure 1. Structure of tacrine (**A**) and some previously synthesized 4*H*-pyrano[2,3-*b*]quinolines (**B**).

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no quinoline–tacrine hybrid has so far been described, although the introduction of the quinoline nucleus has already been used successfully in a number of other cases.[9] The coupling of 4*H*-pyrano[2,3-*b*]quinolines with a quinoline moiety might impart biological activity.

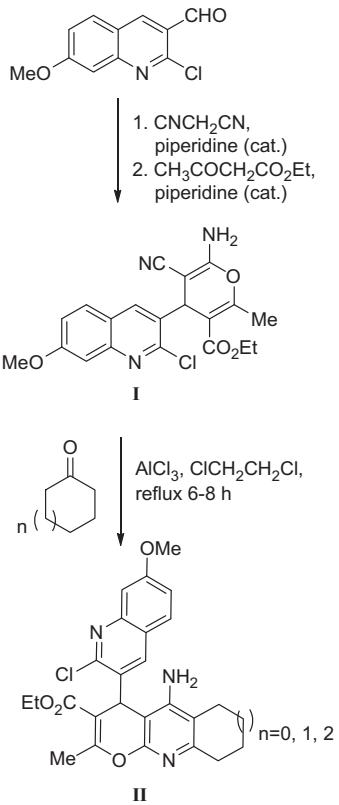
In our previous work, we reported the synthesis of compounds containing heterocycles with diverse functionalities.[10] We report herein our preliminary results concerning the synthesis and the X-ray structures of new tacrine analogues prepared by combining different heterocycles to produce cyclopenta[*b*]pyrano[3,2-*e*]pyridine (**IIa**, $n = 0$), 4*H*-pyrano[2,3-*b*]quinoline (**IIb**, $n = 1$), cyclohepta[*b*]pyrano[3,2-*e*]pyridine (**IIc**, $n = 2$) each of which contains a quinoline ring (Scheme 1).

Polyfunctionalized 2-amino-3-cyano-4*H*-pyrans are well known compounds and their reactivity has been extensively explored.[11] Ethyl 2-amino-4-(2-chloro-7-methoxyquinolin-3-yl)-3-cyano-6-methyl-4*H*-pyran-5-carboxylate (**I**), used in this study was study, was first prepared in one pot by treatment of 2-chloro-7-methoxyquinoline-3-carboxaldehyde with malononitrile/piperidine then ethyl acetoacetate/piperidine.[12]

Single crystals of **I** were grown by evaporation of an EtOAc solution and an X-ray crystallographic analysis confirmed the structural assignment (Fig. 2).

Next we considered the synthesis of compounds containing a 4*H*-pyrano[2,3-*b*]pyridin-5-amine, a quinolyl ring moiety at C-4, and a fused cyclohexane, cyclopentane or cycloheptane ring.

Using 4*H*-pyran **I** and following the standard methodology for the Friedländer reaction (cyclopentanone, aluminium chloride in 1,2-dichloroethane, at reflux),[14] compound **IIa** was obtained in 68% yield after medium-pressure chromatography. The structure of this compound was established by spectroscopic and analytical methods. The ^{1}H NMR spectrum showed characteristic signals, a singlet at 5.36 ppm for H4 (pyran) and a broad singlet at 4.56 ppm for NH_2 (4-aminopyridine nucleus). In the IR spectrum the absorption of a conjugate nitrile was absent, a carbonyl bond (ester) being present at 1695 cm^{-1}. In agreement with this, in the ^{13}C NMR spectrum, typical signals for C3 (106.0 ppm) and C4 (34.5 ppm) of the 4*H*-pyran, and signals of the methyl and methoxy groups [(CH_3C(2): 19.7); (CH_3CH_2O(C3): 14.2 ppm); (CH_3O (C7′ quinolyl): 55.5 ppm)] were also detected.



Scheme 1. Synthetic route for the preparation of 4*H*-pyran (**I**) and Friedländer products **IIa–c** ($n = 0, 1, 2$).

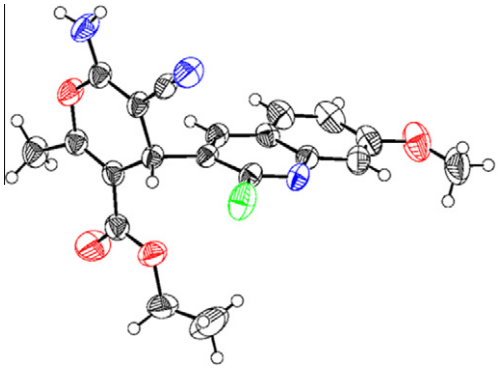


Figure 2. ORTEP plot of the X-ray crystal structure of **I**. Displacement ellipsoids are drawn at the 50% probability level.[13]

We further tested this protocol by using cyclohexanone and cycloheptanone in the Friedländer reaction. Starting from **I**, we obtained compounds **IIb** and **IIc** in 51% and 63% yields, respectively. These products showed analytical and spectroscopic data in good agreement with those observed for product **IIa**.

In recent years, various computational data-mining approaches have been performed to understand the structure–activity relationships of different compounds starting from the crystal structure coordinates. Crystallographic studies can contribute to understanding the reactivity, affinity and the binding properties of molecules.[15]

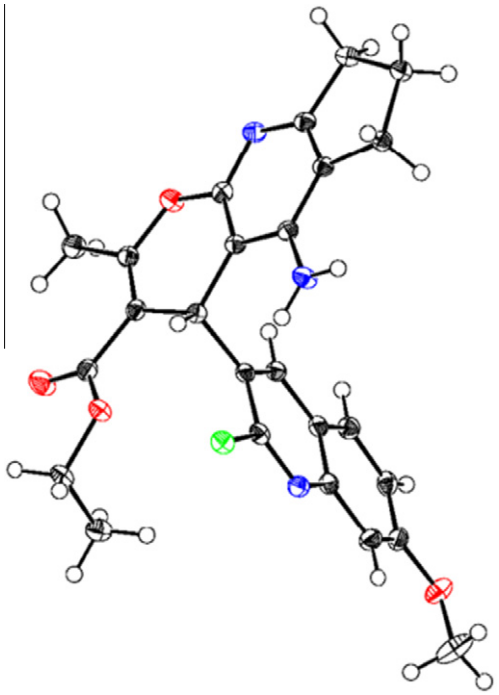


Figure 3. ORTEP plot of the X-ray crystal structure of **IIa**. Displacement ellipsoids are drawn at the 50% probability level.[16]

Thus it was considered of interest to carry out an X-ray diffraction analysis of the new tacrine analogues to help predict their inhibitory effects on specific targets. Our intention was to obtain information on the spatial arrangements of the new compounds. Single crystals of compounds **IIa**, **IIb** and **IIc** were obtained in similar manner as for **I**, and X-ray crystallographic analysis confirmed the structural assignments (Figs. 3–5).

The packing of these crystals structures is stabilized by intra- and intermolecular hydrogen bond interactions involving N and C atoms as donor, and O, Cl and N atoms as acceptors [N–H···N: 3.056(2)–3.1229(14) Å, N–H···Cl: 3.3893(11)–3.5319(11) Å, C–H···Cl: 3.0978(17)–3.1901(18) Å, C–H···O: 2.877(2)–3.3991 (19) Å, C–H···N: 2.922(2)–3.413(2) Å], resulting in the formation of a three-dimensional network and reinforcing the cohesion of the structures.

In conclusion, we have prepared the novel heterocyclic compounds, cyclopenta[*b*]pyrano[3,2-*e*]pyridine, 4*H*-pyrano[2,3-*b*]quinoline and cyclohepta[*b*]pyrano[3,2-*e*]pyridine linked to a quinoline ring. This approach allows a diverse range of compounds to be prepared in good yields the pharmacological actions of these remaining to be investigated.

General method for the synthesis of 6-amino-5-cyano-4-quinolyl-2-methyl-4*H*-pyran (I)

To a solution of 2-chloro-3-formyl-7-methoxyquinoline (1 equiv) in MeOH (0.24 M), under argon, malononitrile (1.1 equiv) and a catalytic amount of piperidine were added. The mixture was stirred at rt for 15–20 min before the addition of ethyl acetoacetate (1.1 equiv) and a few drops of piperidine (cat.) were added. The mixture was stirred at rt for 15–20 min. After concentration of the reaction mixture, the precipitated solid was isolated by filtration and washed with cold MeOH.

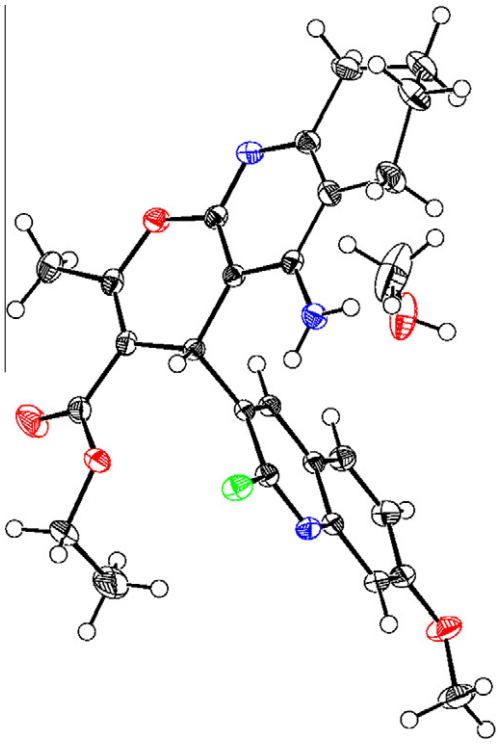


Figure 4. ORTEP plot of the X-ray crystal structure of **IIb** with one molecule of methanol. Displacement ellipsoids are drawn at the 50% probability level. (Disorder 80/20 between several carbon atoms of the cyclohexene ring is not shown for clarity.)[16]

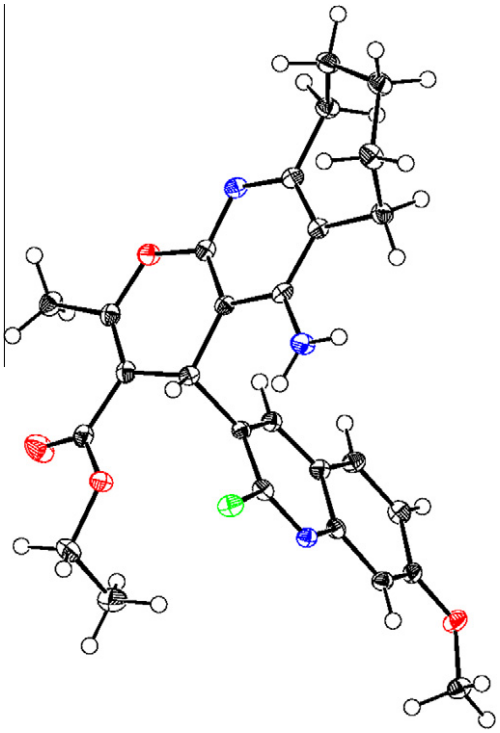


Figure 5. ORTEP plot of the X-ray crystal structure of **IIc**. Displacement ellipsoids are drawn at the 50% probability level.[16]

General method for the Friedländer reaction

$AlCl_3$ (1.5 equiv) was suspended in dry 1,2–dichloroethane (0.15 M) at rt under nitrogen. 4*H*-Pyran **I** (1 equiv) and cycloalkanone (1.5 equiv) were added. The mixture was refluxed for 6–8 h. When the reaction was over (TLC), a mixture of THF/H_2O (1:1) was added at rt, followed by an aqueous solution of sodium hydroxide (10%) until the aqueous solution was basic. After stirring for 30 min, the mixture was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The resultant solid was purified by silica gel chromatography using THF/cyclohexane (1/1.5) as eluent to give the pure compounds.

Acknowledgement

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13. Crystal structure analysis for **I**: $C_{20}H_{18}ClN_3O_4$, *Mr* = 399.82 g mol^{-1}, mp. 240 °C, triclinic, space group $p\bar{1}$, *a* = 9.2321(9)Å, *b* = 9.4823(9)Å, *c* = 11.4986(12)Å, α = 94.202(6), β = 92.334(5), γ = 86.66(3), *V* = 979.28(17)Å^3, *Z* = 2, ρ_c = 1.283 g cm^3, *F*(0 0 0) = 416, crystal size: 0.50 × 0.40 × 0.35 mm.
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16. Crystal structure analysis for **IIa**: $C_{25}H_{24}ClN_3O_4$, *Mr* = 465.92 g mol^{-1}, mp. 197 °C, monoclinic, space group $P2_1/a$, *a* = 9.7506(3)Å, *b* = 13.6830(4)Å, *c* = 16.7647(6)Å, α = 90, β = 105.238(2), γ = 90, *V* = 2158.07(12)Å^3, *Z* = 4, ρ_c = 1.434 g cm^3, *F*(0 0 0) = 976, crystal size: 0.42 × 0.27 × 0.16 mm.
Crystal structure analysis for **IIb**: $C_{26}H_{26}ClN_3O_4$, CH_4O, *Mr* = 511.99 g mol^{-1}, mp 201 °C, monoclinic, space group $P2_1/c$, *a* = 8.8294(3)Å, *b* = 24.2821(8)Å, *c* = 12.1346(4)Å, α = 90, β = 93.911(2), γ = 90, *V* = 2595.56(15)Å^3, *Z* = 4, ρ_c = 1.31 g cm^3, *F*(0 0 0) = 1080, crystal size: 0.46 × 0.41 × 0.21 mm.
Crystal structure analysis for **IIc**: $C_{27}H_{28}ClN_3O_4$, *Mr* = 493.97 g mol^{-1}, mp. 225 °C, triclinic, space group P-1, *a* = 9.1673(7)Å, *b* = 10.8823(9) Å, *c* = 12.6171(11)Å, α = 85.815(3), β = 89.301(3), γ = 77.065(3), *V* = 1223.48(17)Å^3, *Z* = 2, ρ_c = 1.341 g cm^3, *F*(0 0 0) = 520, crystal size: 0.31 × 0.17 × 0.12 mm.
The structures were solved by direct methods and refined by full-matrix least squares analysis on F^2 using SHELXL. Hydrogen atoms were refined on the riding model with isotropic thermal parameters set twenty percent greater than those of their bonding partners. All other atoms were refined anisotropically.
Crystallographic data (excluding structure factors) for compounds **I**, **IIa**, **IIb** and **IIc** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 760170, CCDC 760171, CCDC 824656, CCDC 760173. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.