SYNTHESIS OF NEW DERIVATIVES OF PYRROLE TUBERCULOSTATICS PROVIDING STRUCTURAL DIVERSITY

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Summary: Nine pyrrole-containing compounds were designed introducing reasonable structural novelties within the framework of the architecture of confirmed tuberculostatics. The new products were synthesized via adopted Paal-Knorr cyclization by condensation of three 1,4-dicarbonyl compounds with a set of substituted anilines, acting as primary amines. Preliminary *in vitro* tests have already registered encouraging anti-*Mycobacterium* tuberculosis activity.

Key words: Paal-Knorr cyclization, pyrrole, synthesis, tuberculostatics

Introduction

Tuberculosis (TB), caused by the bacterial pathogen *Mycobacterium tuberculosis*, continues to be a crucial infectious disease and remains the second leading cause of mortality at our planet [1]. According to the latest World Health Organization (WHO) report, 8.6 million new TB cases have been reported and among them three million people were co-infected with both HIV and *M. tuberculosis* [2-4]. In the last decades the development of new tuberculostatics became a priority in the global research but nevertheless any decisive progress is still missing.

In the search for a reliable starting platform of structures for rational synthesis and evaluations in this area, a significant number of investigations focused on variety of heterocyclic environment and especially on derivatives of pyrrole, such as the known anti-tubercular agent BM212 [5] and some analogs thereof [6] (Figure 1 below**)**.

In the same context, a series of substituted pyrroles synthesized in our laboratory (part of them presented as "Own database" in Figure 1 below) and their up to 100 % inhibitory activity against *M. tuberculosis* or IC50 < 6 μg/ml were recently announced (including in this journal) [7-9]. Reliable structure-activity relationships were derived [10].

As a continuation of previous research in our laboratory, the current study offers 9 new derivatives of pyrrole as candidates for pharmacological evaluations, designed to diversify the available platform of *Mycobacterium tuberculosis* inhibitors.

Experimental part

All commercial chemicals used in this study as starting materials and reagents were purchased from "Merck" (Darmstadt, Germany). The melting points were determined with a capillary digital melting point apparatus IA 9200 Electrothermal AZ9003MK4, Southend-on-Sea, UK. The IR spectra were registered on Specord IR-71, Carl Zeiss, Jena, Germany (KBr). The ^{1}H NMR spectra (250 MHz, 20 ^{o}C) were registered on a Bruker Spectrospin WM250 spectrometer (Faenlanden, Switzerland), using TMS as internal standard.

TLC characteristics of the products were measured on aluminum sheets of silica gel 60 F_{254}, Merck 1.05554 at ambient temperature using a relevant mobile phase (*Rf* value for the new compounds at the relevant mobile phase is given below).

Synthesis of 1-Morpholin-4-yl-butane-1,3-dione as an intermediate:

Ethyl acetoacetate (0.10 moles) was heated to 150 °C and morpholine (0.11 moles) was added carefully and slowly. The mixture was stirred and heated up to 180 °C and the synthesis was carried out under permanent distillation of the resulting ethanol trough vigreux column. The compound crystallized from cold diethyl ether. The precipitate was filtered off and recrystallized from warm ethanol. The physical properties of the product corresponded with those in the literature.

General procedure for the synthesis of 1,4-dicarbonyl compounds (d-f, Figure 2):

Sodium (0.10 moles) was dissolved in anhydrous ethanol (50 mL) and to the resulting solution, cooled to 20-25 °C, 1,3-dicarbonyl compounds (0.10 moles) were added, ensuring that the temperature didn't exceed 30 °C. The mixture was stirred for 15-20 minutes. After cooling, the corresponding α-brominated acetophenone (0.10 moles) was added in portions at a temperature not exceeding 30 °C. The mixture was stirred for 30-40 minutes, benzene (100 mL) was added and the resulting solution was washed successively with 5% HCl and water. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed by rotary vacuum evaporator. The residue consisted in the relevant 1,4-dicarbonyl compound as an oil (compounds **d** and **e**), which was used directly in the next stage of condensation. Compound **f** crystallized from diethyl ether.

General procedure for the synthesis of the targeted pyrrole compounds:

The new products were synthesized via adopted Paal-Knorr cyclization by condensation of three 1,4-dicarbonyl compounds with a set of substituted anilines:

1,4-dicarbonyl compound (0.10 moles) and the relevant substituted aniline (0.12 moles) were dissolved in glacial acetic acid (50 mL). For the preparation of compounds of subseries **2** and **3** the reaction was performed at the boiling point of the mixture and for those of subseries **1** - at 60 °C. The reaction development was monitored by TLC. After reaction completion, the mixture was poured into water. The precipitate was filtered off, washed with water, dried and recrystallized from warm ethanol. If necessary, further wash with ether or hexane could be performed. The reaction time was varied from 2.50 hours to 3.50 hours depending on the reacting compounds (TLC control). Yields: 72-80%.

All compounds were soluble in warm ethanol, chloroform and dimethyl sulfoxide, and insoluble in water and hexane.

1-[1,5-Bis-(4-chloro-phenyl)-2-methyl-1H-pyrrol-3-yl]-ethanone (1a): Yield 80%, mp 141-142 °C, R_f 0.38 ($CHCl_3$). IR (KBr) ν 1720, 1640 (C=O), 1300 (C-N), 820 (*p*-C_6H_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.40 (s, 3H, $COCH_3$), 2.58 (s, 3H, CH_3-2), 6.42 (s, 1H, H-4), 6.98-7.05 (m, 4H, C_6H_4), 7.15-7.35 (m, 4H, C_6H_4).

1-[5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-2-methyl-1H-pyrrol-3-yl]-ethanone (1b): Yield 72%, mp 135-136 °C, R_f 0.36 ($CHCl_3$). IR (KBr) ν 1730, 1610 (C=O), 1300 (C-N), 830 (*p*-C_6H_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.42 (s, 3H, $COCH_3$), 2.48 (s, 3H, CH_3-2), 6.70 (s, 1H, H-4), 6.94-7.00 (m, 3H, C_6H_3), 7.18 (d, *J* 2.1 Hz, 1H, C_6H_4), 7.21 (d, *J* 2.1 Hz, 1H, C_6H_4), 7.27 (d, *J* 2.4 Hz, 1H, C_6H_4), 7.47 (d, *J* 8.5 Hz, 1H, C_6H_4).

1-[5-(4-chloro-phenyl)-1-(3,4-dimethoxy-phenyl)-2-methyl-1H-pyrrol-3-yl]-ethanone (1c): Yield 80%, mp 158-159 °C, R_f 0.57 ($CHCl_3$). IR (KBr) ν 1740, 1610 (C=O), 1310 (C-N), 820 (*p*-C_6H_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.20 (s, 3H, $COCH_3$), 2.45 (s, 3H, CH_3-2), 3.70 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.45 (s, 1H, H-4), 6.78-6.98 (m, 3H, C_6H_3), 7.05-7.12 (m, 4H, C_6H_4).

1,5-Bis-(4-chloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (2a): Yield 79%, mp 130-131 °C, R_f 0.68 ($CHCl_3$). IR (KBr) ν 1720, 1610 (C=O), 1290 (C-N), 1220 (C-O), 820 (*p*-C_6H_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 1.37 (t, *J* 5.6 Hz, 3H, $\underline{CH_3}CH_2$), 2.39 (s, 3H, CH_3-2), 4.31 (q, *J* 5.6 Hz, 2H, $CH_3\underline{CH_2}$), 6.78 (s, 1H, H-4), 6.96 (dd, *J* 2.1 Hz, 2H, C_6H_4), 7.06 (dd, *J* 2.1 Hz, 2H, C_6H_4), 7.15 (dd, *J* 2.1 Hz, 2H, C_6H_4), 7.39 (dd, *J* 2.1 Hz, 2H, C_6H_4).

5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (2b): Yield 80%, mp 139-140 °C, *Rf* 0.67 ($CHCl_3$). IR (KBr) ν 1710, 1600 (C=O), 1280 (C-N), 800 (*p*-C_6H_4) cm-1; 1H NMR (250 MHz, $CDCl_3$) δ, ppm: 1.35 (t, *J* 5.6 Hz, 3H, $\underline{CH_3}CH_2$), 2.41 (s, 3H, CH_3-2), 4.33 (q, *J* 5.6 Hz, 2H, $CH_3\underline{CH_2}$), 6.77 (s, 1H, H-4), 6.93-6.99 (m, 3H, C_6H_3), 7.18 (dd, *J* 2.1 Hz, 2H, C_6H_4), 7.28 (d, *J* 2.6 Hz, 1H, C_6H_4), 7.46 (d, *J* 8.4 Hz, 1H, C_6H_4).

5-(4-chloro-phenyl)-1-(3,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (2c): Yield 78%, mp 116-118 °C, R_f 0.45 ($CHCl_3$). IR (KBr) ν 1730, 1610 (C=O), 1300 (C-N), 820 (*p*-C_6H_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 1.37 (t, *J* 7.1 Hz, 3H, $\underline{CH_3}CH_2$), 2.41 (s, 3H, CH_3-2), 3.75 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.31 (q, *J* 7.1 Hz, 2H, $CH_3\underline{CH_2}$), 6.59 (d, *J* 2.3 Hz, 1H, C_6H_3), 6.73 (d, *J* 2.3 Hz, 1H, C_6H_3), 6.78 (s, 1H, H-4), 6.85 (s, 1H, C_6H_3), 6.98 (d, *J* 2.1 Hz, 1H, C_6H_4), 7.02 (d, *J* 2.1 Hz, 1H, C_6H_4), 7.11 (d, *J* 2.1 Hz, 1H, C_6H_4), 7.15 (d, *J* 2.1 Hz, 1H, C_6H_4).

[1-(4-chloro-phenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl]-morpholin-4-yl-methanone (3a): Yield 75%, mp 182-183 °C, *Rf* 0.53 ($CHCl_3$:C_2H_5OH-10:0.5). IR (KBr) ν 1710, 1620 (C=O), 1250 (C-N), 1120 (C-O), 860 (*p*-C_6H_4), 770,700 (C_6H_5) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.21 (s, 3H, CH_3-2), 3.72-3.78 (m, 8H, morpholinyl-H), 6.36 (s, 1H, H-4), 7.10-7.16 (m, 5H, C_6H_5), 7.26-7.37 (m, 4H, C_6H_4).

[1-(2,4-dichloro-phenyl)-2-methyl-5-phenyl-1H-

pyrrol-3-yl]-morpholin-4-yl-methanone (3b):
Yield 80%, mp 195-196 °C, R_f 0.70 ($CHCl_3$:C_2H_5OH-10:0.5). IR (KBr) ν 1710, 1610 (C=O), 1260 (C-N), 1110 (C-O), 850 (C_6H_3), 780, 730 (C_6H_5) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.23 (s, 3H, CH_3-2), 3.65-3.81 (m, 8H, morpholinyl--H), 6.35 (s, 1H, H-4), 6.95-7.21 (m, 5H, C_6H_5), 7.26 (s, 1H, C_6H_3), 7.31 (d, *J* 2.4 Hz, 1H, C_6H_3), 7.42 (d, *J* 2.4 Hz, 1H, C_6H_3).

[1-(3,4-dimethoxy-phenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl]-morpholin-4-yl-methanone (3c):
Yield 76%, mp 168-169 °C, R_f 0.59 ($CHCl_3$:C_2H_5OH-10:0.5). IR (KBr) ν 1700, 1620 (C=O), 1240 (C-N), 1120 (C-O), 820 (C_6H_3), 770, 710 (C_6H_5) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.22 (s, 3H, CH_3-2), 3.71 (s, 3H, OCH_3), 3.74-3.80 (m, 8H, morpholinyl-H), 3.90 (s, 3H, OCH_3), 6.35 (s, 1H, H-4), 6.61 (d, *J* 2.3 Hz, 1H, C_6H_3), 6.75 (dd, *J* 2.3 Hz, 1H, C_6H_3), 6.82 (s, 1H, C_6H_3), 7.05-7.13 (m, 5H, C_6H_5).

Results and discussions

Design of the targeted structures

The design of the new molecules aimed to diversify the available derivatives of pyrrole, already identified as perspective inhibitors of *M. tuberculosis*. The structural changes being introduced concern three moieties presented in Figure 1: **A**, **B** and **C**.

The most radical change was made in moiety **A**, whereat the N-acyl-chain in the previously developed pyrroles in our laboratory was replaced by R_1-R_3-substituted phenyl, approaching the successful model of BM212 and analogs, and motivated by the presence of the same moiety in series of bioactive products [6,11]. For a comparison of the independent effect of the new moiety **A**, the ester group (R = OC_2H_5) was kept in moiety **B** in three of the products, but R = CH_3 or a morpholino-substituent (as an analog to the piperazine- or thiomorpholine-heterocycle in BM212 an analogs) was also foreseen. In moiety **C**, X = H alternates with X = Cl (unlike Br-substituent in own database) because of its presence in similarly substituted active tuberculostatics [8,12,13].

Synthetic preparations

Synthesis of the targeted pyrrole compounds

Paal-Knorr pyrrole synthesis (according to Figure 2) was chosen as a convenient approach to incorporate the selected substituents in the targeted pyrroles, previously introduced in the participating reaction partners: 1,4-dicarbonyl compounds **(d–f)** and relevant anilines **(a–c):**

Typically Paal-Knorr cyclization is performed in boiling CH_3COOH [14] and the syntheses within subseries **2** and **3** has been conducted under similar conditions. As far as N-acetylation of participating anilines was found to take place as a secondary reaction involving the solvent, the reaction time was reduced to 2.50 hours (TLC control). гг

In order to suppress the parallel condensation of the peculiar carbonyl group in subseries **1** with anilines, a modification was introduced in the routine Paal-Knorr procedure, as the reaction temperature was reduced to 60 °C (in the same solvent) and the reaction time was prolonged up to 3.50 hours (TLC control).

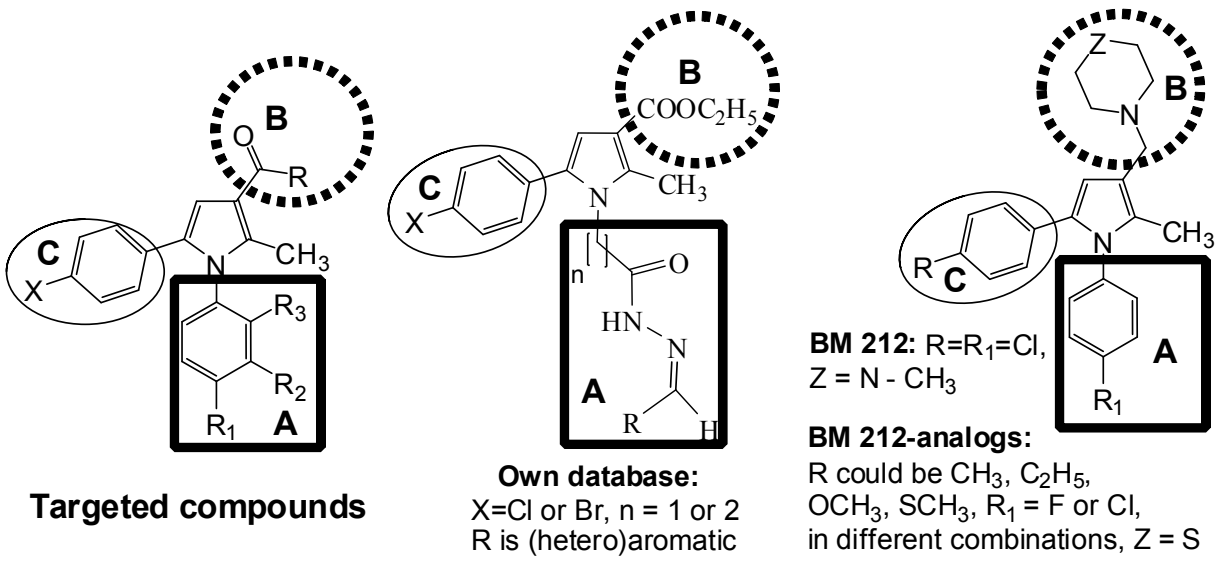
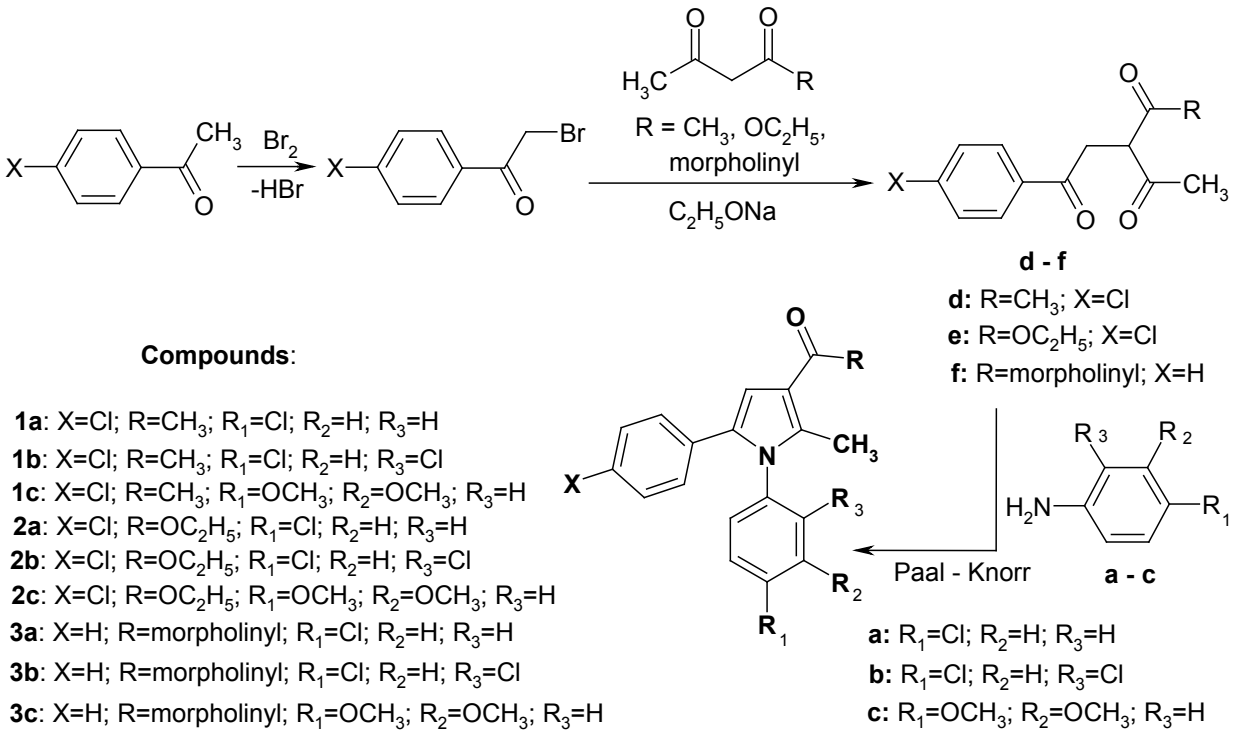


Fig. 1. Specific moieties in the targeted compounds



Compounds:

1a: X=Cl; R=CH_3; R_1=Cl; R_2=H; R_3=H
1b: X=Cl; R=CH_3; R_1=Cl; R_2=H; R_3=Cl
1c: X=Cl; R=CH_3; R_1=OCH_3; R_2=OCH_3; R_3=H
2a: X=Cl; R=OC_2H_5; R_1=Cl; R_2=H; R_3=H
2b: X=Cl; R=OC_2H_5; R_1=Cl; R_2=H; R_3=Cl
2c: X=Cl; R=OC_2H_5; R_1=OCH_3; R_2=OCH_3; R_3=H
3a: X=H; R=morpholinyl; R_1=Cl; R_2=H; R_3=H
3b: X=H; R=morpholinyl; R_1=Cl; R_2=H; R_3=Cl
3c: X=H; R=morpholinyl; R_1=OCH_3; R_2=OCH_3; R_3=H

Fig. 2. A synthetic access to the targeted products via Paal-Knorr cyclization

The total yields were in the range of 72-80% based on the starting ω-bromoacetophenones.

Synthesis of intermediate 1,4-dicarbonyl compounds

The intermediate 1,4-dicarbonyl compounds **d** and **e** were synthesized by condensation of X-substituted ω-bromoacetophenones with relevantly R-substituted commercially available β-dicarbonyl compounds, while compound **f** was synthesized by means of 1-Morpholin-4-yl-butane-1,3-dione prepared as given below. Conditions for C-alkylation were afforded to suppress the concurrent O-targeted reaction intrinsic to this class of ambident compounds [15,16]. The ω-bromoacetophenones, well known as strong lachrymators, were prepared in our laboratory too [17].

Considerations about the synthesis of intermediate 1-Morpholin-4-yl-butane-1,3-dione

The reaction partners could interact in two differ-

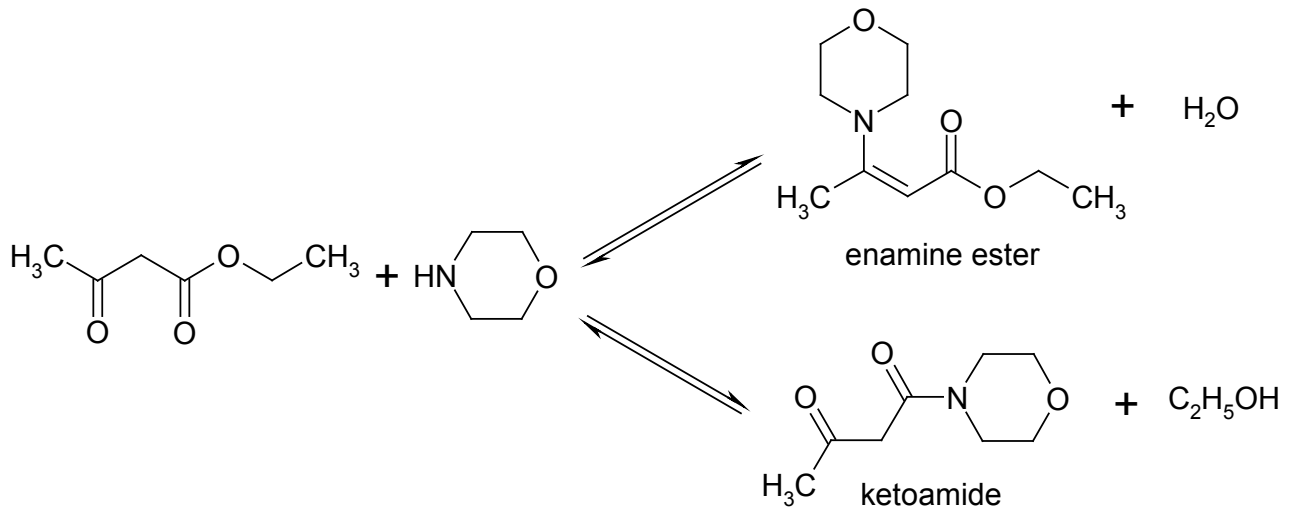


Fig. 3. Synthesis of intermediate 1-Morpholin-4-yl-butane-1,3-dione

ent directions (Figure 3): Higher reaction temperatures (over 150 °C) favor the formation of carboxamides, whereas the performance below 100 °C yields 20-98% of enamines depending on the temperature [18-20]. Therefore, the reaction mixture was heated up to 180 °C and the synthesis was carried out under permanent distillation of the resulting ethanol trough vigreux column. ^{1}H-NMR witnesses for 100% of the title morpholide, m.p. 69-70 °C (68 °C according to the [18, 21]).

The identity of all newly synthesized compounds was proved by ^{1}H NMR and IR spectra, interpreted in Experimental part. Their purity and homogeneity was confirmed by thin layer chromatography (TLC).

A convincing ^{1}H NMR-evidence for the successful cyclisation is the permanent presence of the singlet for H-4 pyrrole proton at 6.35-6.78 ppm. Typical for subseries **1** is the singlet for the protons of R=CH_3 at 2.20-2.42 ppm, replaced in subseries **2** by triplet at 1.35-1.37 ppm and quadruplet at 4.31-4.33 ppm for R=CH_3CH_2 or with multiplet at 3.65-3.81 ppm for the morpholine cycle in subseries **3.**

Conclusion

Paal-Knorr pyrrole synthesis was used as a convenient access to perspective products, comprising the general architecture of confirmed tuberculostatics. The introduced structural variations are a useful base for further optimizations and structure-activity conclusions, aiming better biding capability to the target and higher activity. Of special interest are the effects of the replacements made in moiety **A**, as far as they are not bioisosteric.

In vitro evaluation of the newly synthesized products according to "Antitubercular drug testing program" of National Institute of Allergy and Infectious Diseases (NIAID), an institute of the National Institutes of Health (NIH), USA, registered encouraging anti-*Mycobacterium tuberculosis* activity. More details and some QSAR-trends will be published separately.

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