Synthesis of benzylpiperazine derivatives containing the pyrazine moiety with potential activity against *M. tuberculosis*

Síntese de derivados da benzilpiperazina contendo a fracção pirazina com potencial actividade contra a *M. tuberculosis*

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Ana Carolyne Sombra Nery
Mestre em Ciência, Gestão, Pesquisa e Desenvolvimento na Indústria Farmacêutica pelo Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Instituição: Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Endereço: Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro - RJ, Brazil
E-mail: ana_nery@id.uff.br

Claudia Regina Brandão Gomes
Doutora em Química Orgânica pela Universidade Federal Fluminense
Instituição: Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Endereço: Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro - RJ, Brazil
E-mail: claudia.gomes@far.fiocruz.br

Alessandra Campbell Pinheiro
Doutora em Química pela Universidade Federal do Rio de Janeiro
Instituição: Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Endereço: Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro - RJ, Brazil
E-mail: alessandra.pinheiro@far.fiocruz.br

Victor Facchinetti
Doutor em Química pela Universidade Federal Fluminense
Instituição: Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Endereço: Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro - RJ, Brazil
E-mail: victor.luz@far.fiocruz.br

Marcus Vinícius Nora de Souza
Doutor em Química Orgânica e Biogânica pela Universite de Paris XI (Paris-Sud) - França Federal
Instituição: Instituto de Tecnologia em Fármacos – Fundação Oswaldo Cruz
Endereço: Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro - RJ, Brazil
E-mail: marcus.nora@far.fiocruz.br

RESUMO
A tuberculose (TB) ainda é um problema de saúde pública global, apesar dos esforços e recentes avanços na medicina e farmacologia. A Organização Mundial da Saúde estima que em 2018, 1,5 milhões de pessoas morreram em todo o mundo devido à tuberculose. Nesse contexto, é urgente

a busca por novas moléculas que possam oferecer mais eficácia, menor tempo de tratamento, com menores efeitos adversos conta TB. O presente trabalho descreve a síntese de oito novas benzilpiperazinas contendo o núcleo pirazina, com potencial atividade antituberculose. As moléculas foram planejadas de maneira racional, utilizando-se a técnica de hibridação molecular, a partir do fármaco pirazinamida e do núcleo benzilpiperazina. As substâncias propostas foram obtidas a partir de um processo sintético simples e reprodutivo, em rendimentos baixos.

Palavra chaves: benzilpiperazina, pirazina, tuberculose.

ABSTRACT

Tuberculosis (TB), remains a global health challenge, despite the many efforts and recent advances in medicine and pharmacology. The World Health Organization estimates that 1.5 million people worldwide died due to TB infection in 2018. In this context, the search for novel molecules that can offer higher potency, shorter treatment times, and fewer side effects is urgent. This work describes the synthesis of eight new benzylpiperazines containing the pyrazine moiety, with potential activity against TB. The structures were rationally planned using the molecular hybridization technique, from the drug pyrazinamide and the benzylpiperazine core. All proposed substances were obtained from a simple and reproductible synthetic process, in low yields.

Keywords: benzylpiperazine, pyrazine, tuberculosis.

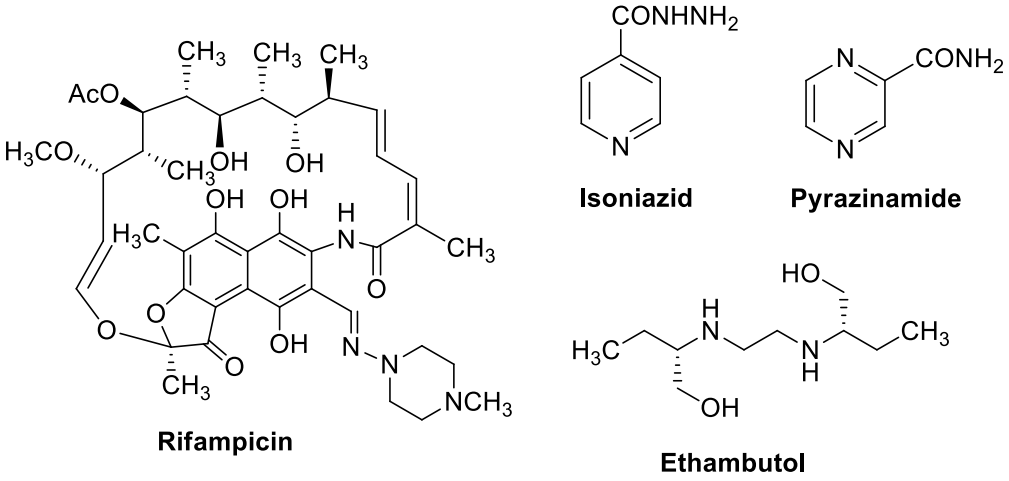
1 INTRODUCTION

Tuberculosis (TB) remains a worldwide health challenge, despite the many advances seen in medicine and pharmacology [1]. According to the World Health Organization (WHO), 1/4 of the population harbors latent *Mycobacterium tuberculosis* (WHO, 2020). There is an ongoing effort to reduce the TB burden, however, this disease is still one of the top 10 causes of death with 10 million incident TB cases and 1.5 million deaths globally estimated for 2018 (WHO, 2020). In Brazil, official data shows that 72.788 new cases of TB have been reported in 2018. In some states, such as Amazonas and Rio de Janeiro, the incidence rate of tuberculosis nearly doubles compared to the national average (BRAZIL, 2018).

Since this disease mainly affects developing countries, there is little funding for the prevention, diagnosis, and treatment of TB (ALVAREZ, 2009). This reality has started to change due to the co-infection of TB with the Human Immunodeficiency Virus and the advent of drug-resistant TB strains. However, data from the Treatment Action Group (TAG) and Stop TB (TAG, 2019) shows that investment in TB research (US$ 0.9 billion/2018) is still small when compared to other diseases, such as HIV (US$ 7.8 billion/2019) (UNAIDS, 2019) or even to the neglected disease Malaria (US$ 3.1 billion/2017) (WHO, 2018a). Even though the first-line drugs, isoniazid, pyrazinamide, ethambutol and rifampicin **(Figure 1)** (RABAHI, 2017) are usually enough to treat

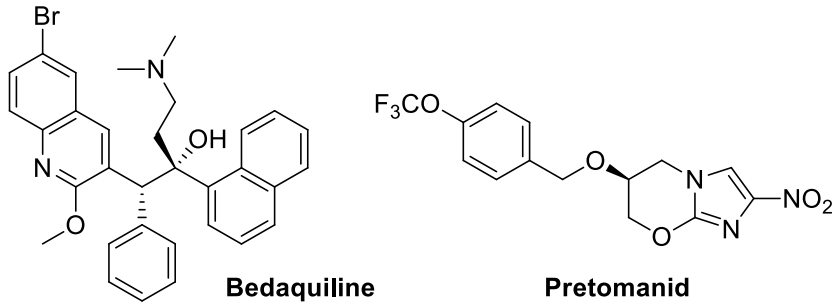
non-resistant TB infections, this lack of funding severely limits the options when facing drug-resistant strains (WHO, 2018b).

Figure 1. First-line treatment for TB.



At the end of 2012, the US Food and Drug Administration (FDA) granted accelerated approval to bedaquiline for the treatment of resistant TB. This was the first FDA-approved drug to treat tuberculosis in 40 years (MAHAJAN, 2013). In 2019, pretomanid, a drug developed by the TB-Alliance, received limited approval by the FDA to be used in combination with bedaquiline and linezolid (TB ALLIANCE, 2019). Still, the search for novel molecules that can effectively treat TB, while showing fewer side effects, is important.

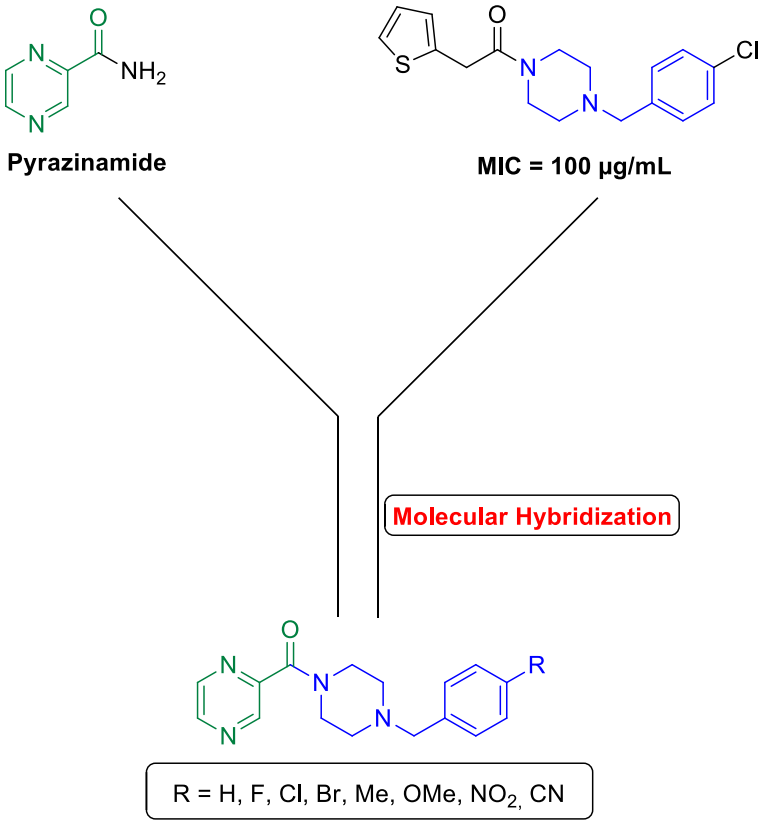
Figure 2. New drugs approved for the treatment of resistant TB.



In this context, heterocycles, such as piperazine and pyrazine, emerge as prominent core structures on the search for novel bioactive molecules, not only due to their synthetic versatility but also for their unique physicochemical properties. For example, benzylpiperazines and their derivatives reportedly have activity against *M. tuberculosis* (HE; ALIAN; DE MONTELLANO, 2007; TANGALLAPALLY *et al*., 2007; da SILVA, 2013). In our ongoing effort to discover new

structures with potential activity against TB, we designed a series of benzylpiperazine derivatives containing the pyrazine nucleus using the molecular hybridization strategy **(Figure 3).**

Figure 3. Design of new prototypes with potential activity against TB.



2 MATERIALS AND METHODS

All reagents were used as obtained from commercial suppliers without further purification. Melting points were determined on a Buchi Melting Point B-545 and are uncorrected. NMR spectra were recorded using a Bruker DRX 400 (400 MHz for ^{1}H and 100 MHz para ^{13}C), Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) in $CDCl_3$ or D_2O with TMS as the internal standard. Mass spectrometry analyses were performed on a Bruker Ion Trap using electrospray ionization. Samples were introduced by the standard direct insertion probe method. Gas Chromatography analyses were performed in an Agilent 6890 with mass detector Agilent model 5973 (70eV) and column Agilent 122-5532 DB-5MS (5% diphenyl: 95% dimethylpolysiloxane).

3 GENERAL PROCEDURE FOR THE SYNTHESIS OF ALCOHOLS 2a-h

The corresponding benzaldehyde (20 mmol) was added to a 100mL round-bottom flask containing 30mL of methanol. Then, $NaBH_4$ was then added slowly to the reaction under an ice bath (0°C) (CHAIKIN; BROWN, 1949). The reaction was kept at room temperature under a

nitrogen atmosphere and magnetic stirring for 6h until completion (TLC). The reaction medium was neutralized with aqueous HCl (1M), the solvent removed and the resulting oil solubilized in ethyl acetate (20 mL) and washed with 3 portions of water (20 mL). The desired alcohols were obtained after the evaporation of the organic phase.

4 GENERAL PROCEDURE FOR THE SYNTHESIS OF CHLORIDES 3a-h

The corresponding alcohol **2a-h** (20 mmol) was added to a 50mL round-bottom flask containing 15mL of dichloromethane, on an ice bath. Then, 5mL (70 mmol) of distilled thionyl chloride was then added to the reaction under stirring and the mixture was kept in an inert atmosphere for 16h (AMGEN INC, 2009). The solvent and excess thionyl chloride were then evaporated and substances **3a-h** used in the next step without further purification.

5 SYNTHESIS OF PIPERAZINE DICHLORIDRATE

Ethanol (100 mL) and piperazine (20 mmol) were added to a 500 mL round-bottom flask, under heavy stirring, followed by the dropwise addition of HCl (37%) until pH = 1. The pure product was obtained in quantitative yields after filtration and washing of the precipitate with cold ethanol (CRAIG; YOUNG, 1962).

6 GENERAL PROCEDURES FOR THE SYNTHESIS OF BENZYLPIPERAZINES 4A-H

Piperazine (20 mmol), piperazine dichloriridrate (20 mmol), and ethanol (50 ml) were added to a round-bottom flask (100 mL) under heavy stirring and reflux until the complete solubilization of the solid was seen. The reaction mixture is then transferred to another 100 mL round-bottom flask, containing 20 mmol of the corresponding benzyl chloride **3a-h**, kept under reflux, and stirring for 2h (MEHANNA; KIM, 2005). Piperazine dichloridrate was removed by filtration and the solvent removed, resulting in the crude product, which was solubilized in water and purified by extraction with ethyl acetate (3 x 20 mL). The desired benzylpiperazines **4a-h** were obtained as hydrochlorides after the evaporation of the aqueous layer.

7 SYNTHESIS OF 2-PYRAZINOYL CHLORIDE 6

Thionyl chloride (5 mL e 70 mmol) was added dropwise (0°C) to a round-bottom flask containing pyrazinoic acid (5 mL) and dichloromethane (10 mL). The reaction was stirred at room temperature for 16h. Excess of thionyl chloride was then removed and the product used in the next step immediately, without further purification (BISPO *et al*., 2012).

8 GENERAL PROCEDURE FOR THE SYNTHESIS OF SUBSTANCES 7a-h

The free base benzylpiperazine (2.5 mmol), was added to a 50 mL flask containing 15 mL of triethylamine and 10 mL of dichloromethane under heavy stirring. The mixture was then added to a round-bottom flask containing 5mmol of 2-pyrazinoyl chloride and the reaction kept at room temperature for 3h (LAHA; PATEL; SHARMA, 2017). The solvent was then removed and the resulting oil solubilized in ethyl acetate (20 mL) and washed with $NaHCO_3$ 5% w/v (5 x 20 mL). The organic layer was removed and the crude product purified by column chromatography (Silica Gel) with gradient hexane/chloroform as eluent.

(4-benzylpiperazin-1-yl)(pyrazin-1-yl)methanone ***(7a)***

$C_{16}H_{17}N_4O$

M.W.: 282.14

Yield: 24%

^{1}H NMR (500 MHz, CDCl3)**:** δ = 8.92 (s, 1H, H3'), 8.62 (d, 1H, *J* = 2.3, H6'), 8.53-8.52 (m, 1H, H5'), 7.32-7.27 (m, 5H, H2/6 e H3/5), 3.84 (sl, 2H, H3' ou H5''), 3.61 (t, 2H, *J* = 4.6, H3'' ou H5''), 3.55 (s, 2H, CH2), 2.58 (t, 2H, *J* = 4.8, H2'' ou H6''), 2.47 (t, 2H, *J* = 4.6, H2'' ou H6'')

^{13}C NMR (125 MHz, CDCl3)**:** δ = 165.0 (C=O), 149.4 (C2'), 145.6 (C3'), 145.2 (C6'), 142.6 (C5'), 137.5 (C1), 129.1 (C2/6), 128.4 (C3/5), 127.4 (C4), 62.8 (CH2), 53.2 (C2'' ou C6''), 52.6 (C2'' ou C6''), 47.2 (C3'' ou C5''), 42.5 (C3'' ou C5'')

ESI: 283 ([M + H]+, 100%)

(4-(4-fluorobenzyl)piperazin-1-yl)(pyrazin-2-yl)methanone ***(7b)***

$C_{16}H_{17}FN_4O$

M.W.: 300.13

Yield: 20%

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ = 8.93 (d, 1H, *J* = 1.4, H3'), 8.63 (d, 1H, *J* = 2.5, H6'), 8.53 (dd, 1H, J = 2.6, 1.5, H5'), 7.30-7.26 (m, 2H, H2/6), 7.04-6.98 (tt, *J* = 2.9, 8.9, 2H, H3/5), 3.84 (t, 2H, *J* = 5.1, H3'' ou H5''), 3.61 (t, 2H, *J* = 5.1, H3'' ou H5'') 3.52 (s, 2H, CH2), 2.57 (t, 2H, *J* = 5.2, H2'' ou H6''), 2.46 (t, 2H, J = 5.0, H2'' ou H6'')

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ = 165.0 (C=O), 162.1 (d, $^1J_{C,F}$ = 243.8, C4), 149.4 (C2'), 145.6 (C3'), 145.3 (C6'), 142.6 (C5'), 133.2 (d, $^1J_{C,F}$ = 2.9, C1), 130.6 (d, $^1J_{C,F}$ = 7.9, C2/6), 115.2 (d, $^1J_{C,F}$ = 21.1, C3/5), 61.9 (CH_2), 53.1 (C2'' ou C6''), 52.5 (C2'' ou C6''), 47.1 (C3'' ou C5''), 42.5 (C3'' ou C5'')

IR: 2949 (CH2), 1627 (C=O), 1507, 1297 e 1145 (pyrazine), 1218 (C-N), 1016 (C-O) **ESI**: 301 ($[M + H]^+$, 100%).

*(4-(4-chlorobenzyl)piperazin-1-yl)(pyrazin-2-yl)methanone (**7c**)*

$C_{16}H_{17}ClN_4O$

M.W.: 316.10

Yield:11%

M.P. (°C): 68-69ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8,94 (d, 1H, J = 1,5, H3'), 8,63 (d, 1H, J = 2,6, H6'), 8,53 (dd, 1H, J = 2,5, 1,5, H5'), 7,31-7,25 (m, 4H, H2/6 e H3/5), 3,83 (t, 2H, J = 5,1, H3'' ou H5''), 3,61 (t, 2H, J = 5,1, H3'' ou H5''), 3,51 (s, 2H, CH2), 2,56 (t, 2H, J = 5,1, H2'' ou H6''), 2,46 (t, 2H, J = 4,9, H2'' ou H6'')

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ = 165.0 (C=O), 149.4 (C2'), 145.6 (C3'), 145.3 (C6'), 142.5 (C5'), 136.1 (C4), 133.0 (C1), 130.3 (C2/6), 128.5 (C3/5), 62.0 (CH_2), 53.2 (C2'' ou C6''), 52.6 (C2'' ou C6''), 47.2 (C3'' ou C5''), 42.5 (C3'' ou C5'').

GC/EI: 316 [M], 209 [M-107], 125 [M-191]

*(4-(4-bromobenzyl)pyperazin-1-yl)(pyrazin-2-yl)methanone (**7d**)*

$C_{16}H_{17}BrN_4O$

M.W.: 360.05

Yield: 30%

^{1}H NMR(500 MHz, $CDCl_3$): δ = 8.93 (s, 1H, H3'), 8.62 (d, 1H, *J* = 2.3, H6'), 8.53 (s, 1H, H5'), 7.45 (d, 2H, *J* = 8.2, H3/5), 7.21 (d, 2H, *J* = 8.1, H2/6), 3.83 (sl, 2H, H3'' ou H5''), 3.61 (sl, 2H, H3'' ou H5''), 3.50 (s, 2H, CH_2), 2.56 (t, 2H, *J* = 4,2, H2'' ou H6''), 2.46 (m, 2H, H2'' ou H6'')

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (C=O), 149.6 (C2'), 145.8 (C3'), 145.5 (C6'), 142.7 (C5'), 136.7 (C4), 131.7 (C1), 130.9 (C3/5), 121.3 (C2/6), 62.3 (CH_2), 53.4 (C2'' ou C6''), 52.8 (C2'' ou C6''), 47.3 (C3'' ou C5''), 42.7 (C3'' ou C5'')

ESI: 361 ([M + H]+, 100%)

*(4-(4-methoxibenzyl)pyperazin-1-yl)(pyrazin-2-il)methanone (**7e**)*

$C_{17}H_{20}N_4O_2$

M.W.: 312.15

Yield: 12%

^{1}H NMR (500 MHz, $CDCl_3$)**:** δ = 8.92 (d, 1H, *J* = 1.0, H3'), 8.62 (d, 1H, *J* = 2.4, H6'), 8.53 (sl, 1H, H5'), 7.23 (d, 2H, *J* = 8.4, H2/6), 7.21 (d, 2H, *J* = 8.5, H3/5), 3.83 (m, 2H, H3'' ou H5''), 3.80 (s, 3H, OCH_3), 3.61 (t, 2H, *J* = 4,5, H3'' ou H5''), 3.50 (s, 2H, CH_2), 2.56 (t, 2H, *J* = 4.6, H2'' ou H6''), 2.46 (t, 2H, *J* = 4.3, H2'' ou H6'')

^{13}C NMR (125 MHz, $CDCl_3$)**:** δ = 165.2 (C=O), 159.2 (C4), 149.6 (C2'), 145.8 (C3'), 145.4 (C6'), 142.8 (C5'), 130.6 (C1), 130.5 (C2/6), 114.19(C3/5), 62.5 (CH_2), 55.8 (CH_3), 53.3 (C2'' ou C6''), 52.7 (C2'' ou C6''), 47.4 (C3'' ou C5''), 42.7 (C3'' ou C5''), 21.1 (CH3)

ESI: 313 ([M + H]+, 100%)

*(4-(4-methylbenzyl)piperazine-1-yl)(pyrazin-2-il)methanone (**7f**)*

$C_{17}H_{20}N_4O$

M.W.: 296.16

Yield: 11%

M.P. (°C): 58-59ºC

^{1}H NMR (500 MHz, $CDCl_3$)**:** δ = 8.92 (s, 1H, H3'), 8.62 (d, 1H, *J* = 2.3, H6'), 8.53-8.52 (m, 1H, H5'), 7.20 (d, *J* = 7.7, 2H, H2/6) 7.13 (d, *J* = 7.7, 2H, H3/5), 3.83 (sl, 2H, H3'' ou H5''), 3.60 (t, 2H, *J* = 4.4, H3'' ou H5''), 3.52 (s, 2H, CH_2), 2.57 (t, 2H, *J* = 4.6, H2'' ou H6''), 2.47 (t, 2H, *J* = 4.3, H2'' ou H6''), 2.34 (s, 3H, CH_3)

^{13}C NMR (125 MHz, $CDCl_3$)**:** δ = 165.0 (C=O), 149.4 (C2'), 145.6 (C3'), 145.2 (C6'), 142.6 (C5'), 137.0 (C4), 134.2 (C1), 129.1 (C3/5), 129.0 (C2/6), 62.5 (CH_2), 53.2 (C2'' ou C6''), 52.5 (C2'' ou C6''), 47.2 (C3'' ou C5''), 42.5 (C3'' ou C5''), 21.1 (CH_3)

GC/EI: 296 [M], 189 [M-107], 105 [M-191]

*(4-(4-nitrobenzyl)piperazine-1-yl)(pyrazin-2-yl)methanone (**7g**)*

$C_{16}H_{17}N_5O_3$

M.W.: 327.13

Yield: 11%

M.P. (°C): 133-134ºC

^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 8.95 (s, 1H, H3'), 8.64 (d, 1H, H6'), 8.53 (s, 1H, H5'), 8.20 (d, 2H, *J* = 6.8, H3/5) 7.54 (sl, 2H, H2/6), 3.86 (s, 2H, H3'' ou H5''), 3.66 (s, 4H, CH_2 e H3'' ou H5''), 2.61 (s, 2H, H2'' ou H6''), 2.51 (s, 2H, H2'' ou H6'')

^{13}C NMR (125 MHz, $CDCl_3$)**:** δ = 165.0 (C=O), 149.2 (C2'), 147.4 (C4) 145.8 (C3'), 145.4 (C6'), 142.4 (C5'), 129.5 (C2/6), 123.7 (C3/5), 61.9(CH2), 53.3 (C2'' ou C6''), 52.7 (C2'' ou C6''), 47.1 (C3'' ou C5''), 42.3 (C3'' ou C5'')

ESI: 328 ([M + H]+, 100%)

*(4-((4-(pyrazine-2-carbonyl)pyperazin-1-yl)methyl)benzonitrile (**7h**)*

$C_{17}H_{17}N_5O$

M.W.: 307.14

Yield: 15%

M.P. (°C): 127-128ºC

^{1}H NMR (500 MHz, $CDCl_3$)**:** δ = 8.94 (s, 1H, H3'), 8.64 (d, 1H, *J* = 1.9, H6'), 8.54 (s, 1H, H5'), 7.63 (d, 2H, *J* = 7.9, H2/6) 7.49 (d, 2H, *J* = 6.6, H3/5), 3.85 (s, 2H, H3'' ou H5''), 3.65 (s, 2H, H3'' ou H5''), 3.62 (s, 2H, CH_2), 2.59 (s, 2H, H2'' ou H6''), 2.49 (s, 2H, H2'' ou H6'')

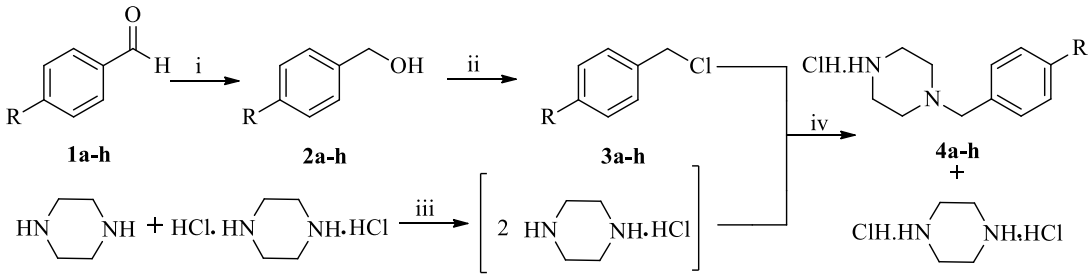
^{13}C NMR (125 MHz, $CDCl_3$)**:** δ = 165.2 (C=O), 149.4 (C2'), 145.9 (C3'), 145.6 (C6'), 143.7 (C5'), 142.7 (C1), 132.5 (C3/5), 129.7 (C2/6), 118.9 (CN), 111.4 (C4), 62.4 (CH2), 53.5 (C2'' ou C6''), 52.9 (C2'' ou C6''), 47.3 (C3'' ou C5''), 42.6 (C3'' ou C5'')

GC/EI: 307 [M], 200 [M-107], 116 [M-191]

9 RESULTS AND DISCUSSION

The key-intermediates benzylpiperazines **4a-h** were synthesized as described in Scheme **1**. Alcohols **2a-h** were either commercially available (Merck) or obtained through the reduction of the corresponding benzaldehydes **1a-h** with $NaBH_4$ (CHAKIN; BROWN, 1949). The benzyl chlorides **3a-h** were readily synthesized from the corresponding alcohols using thionyl chloride at room temperature (BROWN, 2009). Finally, benzylpiperazines **4a-h** were obtained as hydrochlorides through the *in situ* formation of piperazine monochloridrate followed by the one-pot reaction with the corresponding benzyl chlorides (MEHANNA; KIM, 2005; CRAIG; YOUNG, 1962). This approach was preferred when compared to others, such as the reductive amination of the corresponding benzaldehydes, due to the much easier workup. The *in situ* formation of 2 equivalents of piperazine monochloride also allows the easy *N*-monoalkylation while saving reagents when compared to other alkylation methodologies that use 4-5 equivalents of piperazine. Moreover, the piperazine dichloridrate can be filtered, washed with cold ethanol, and reused in other reactions. It is important to mention that the freebase benzylpiperazine was obtained by extraction with $NaOH_{(aq.)}$ 50% (20 mL) and dichloromethane (20 mL) under heavy stirring for 2h, after evaporation of the organic layer.

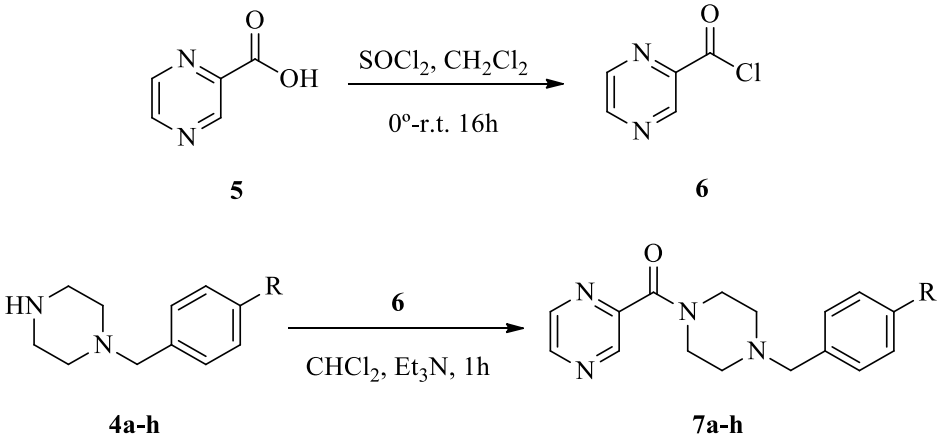
Scheme 1: Synthesis of the key-intermediates benzylpiperazines **4a-h.**



i. a) $NaBH_4$ (0,5 eq), EtOH,0ºC-r.t. b) HCl 1M.
ii. $SOCl_2$, r.t.
iii. EtOH, 78ºC.
iv. EtOH, 78ºC.

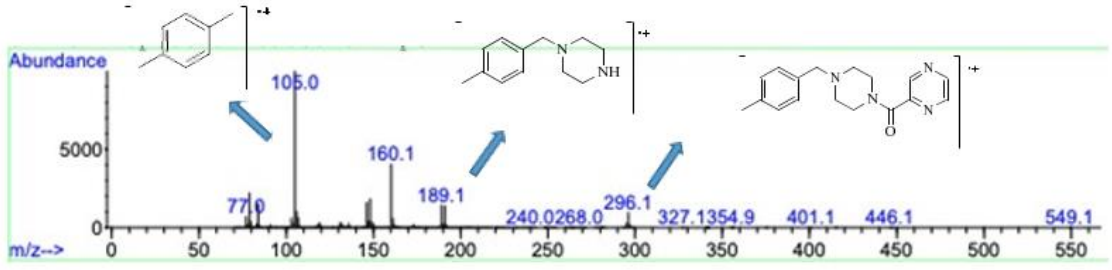
The compound 2-pyrazinoyl chloride **6** was prepared using the classic reaction with thionyl chloride in dichloromethane and then, was allowed to react with the corresponding benzylpiperazines (free base) in dichloromethane in the presence of triethylamine at room temperature **(Scheme 2).** The crude products were purified by column chromatography with gradient hexane/ethyl acetate, affording the pure products 7a-h in low yields (10-30%).

Scheme 2: Synthesis of the desired products **7a-h.**



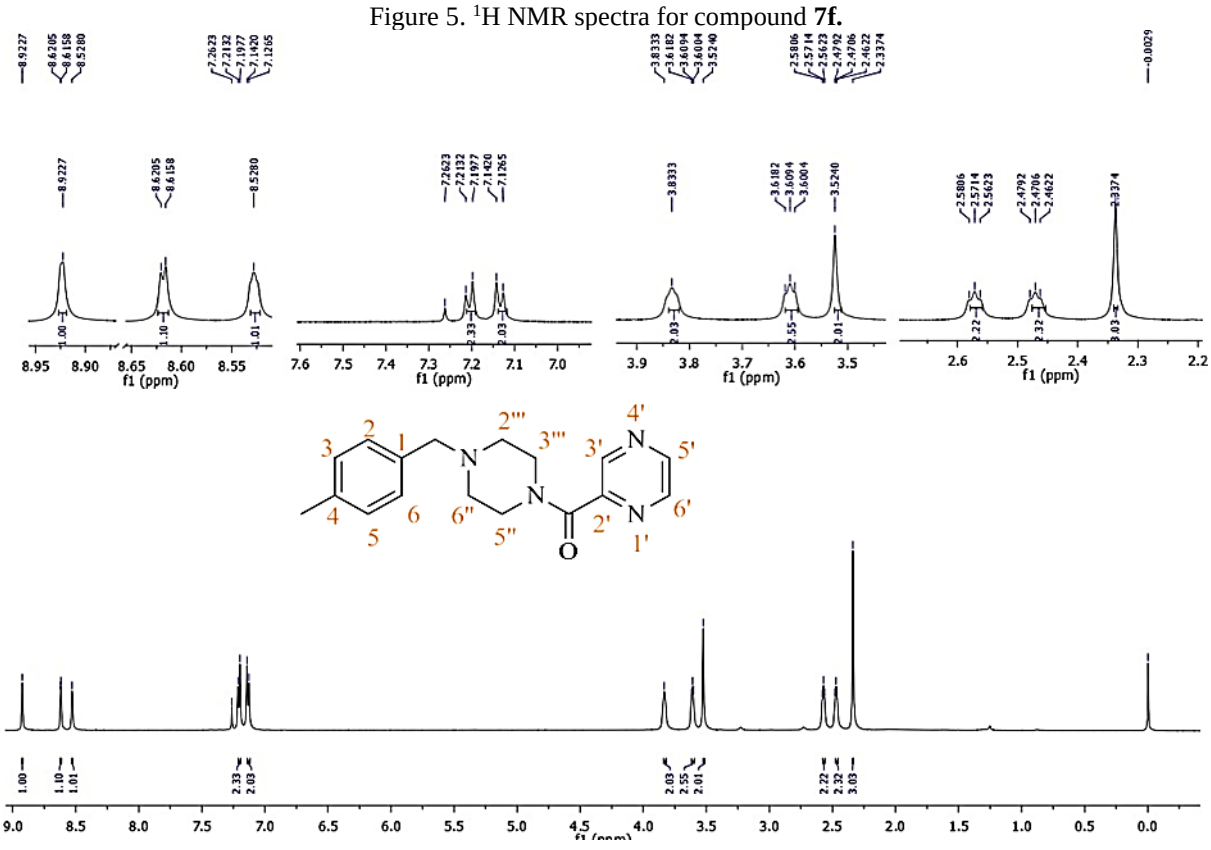
All compounds were characterized by ESI-MS or GC-MS, besides ^{1}H and ^{13}C NMR spectra in 1D and 2D. All spectral data is in full agreement with the proposed structures. As an exemplification, GC-MS analysis of substance 7f shows a single peak with 26.1min of retention time while the EI-MS shows the molecular ion mass (m/z = 296) and some characteristic fragmentations **(Figure 4).**

Figure 4. EI-MS spectra for compound **7f** and some characteristic fragmentations



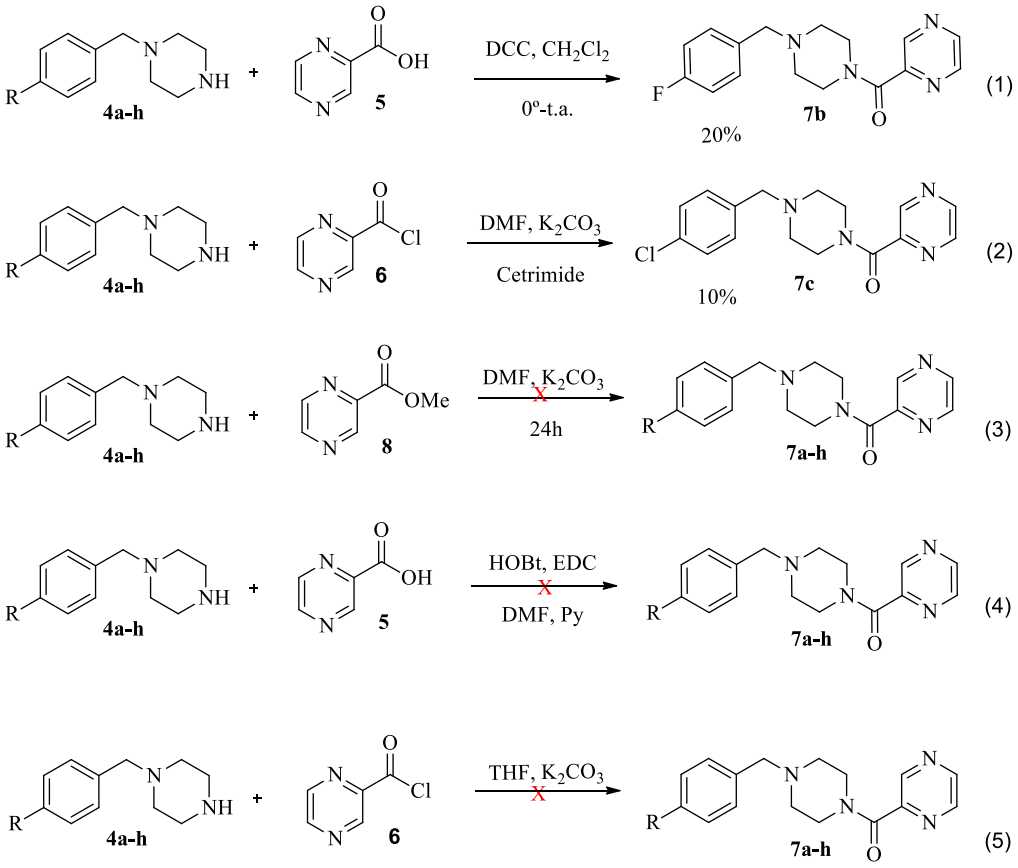
In the ^{1}H NMR spectra of compound **7f (Figure 5)** we can easily identify the hydrogens from the pyrazine nucleus at 8.92, 8.62 and 8.53 ppm, the benzylic hydrogens at 7.26 and 7.13 ppm, the four triplets that characterize the piperazine moiety and, finally, two singlets in 3.53 (CH_2) and 2.34 (CH_3). All ^{13}C carbon signs were unequivocally assigned by analysis of the ^{13}C-DEPT spectra and 2D NMR spectra (COSY, HSQC, and HMBC). All spectra are available in the supplementary data section.

Figure 5. ^{1}H NMR spectra for compound **7f.**



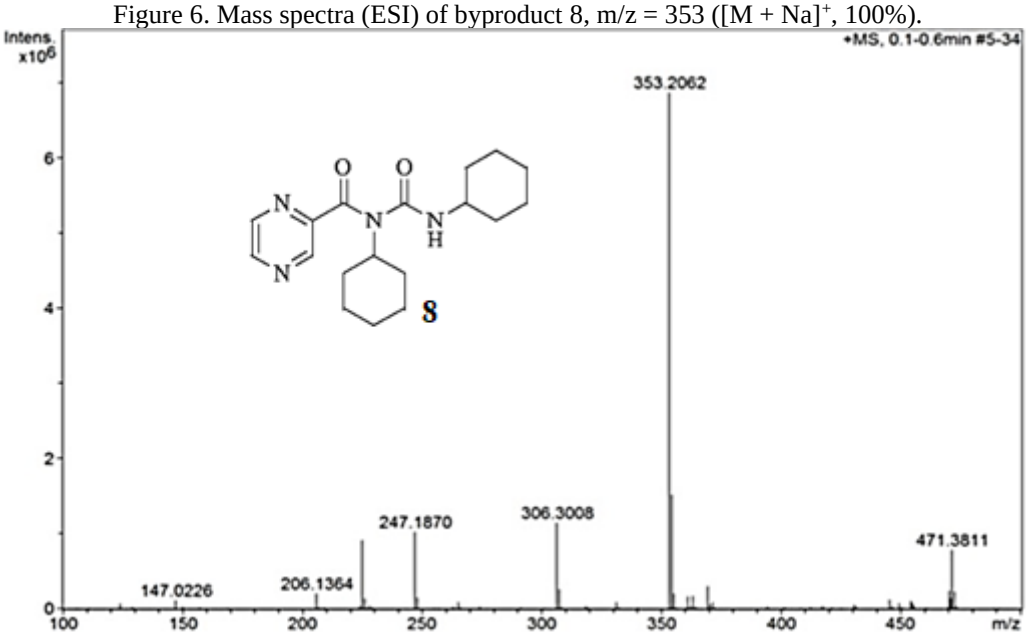
In an attempt to optimize the synthesis and achieve better yields, many different reaction conditions and methodologies were tested. A few examples are shown in Scheme **3**.

Scheme 3. Some coupling conditions attempted for the synthesis of substances **7a-h**.



Even though it was possible to synthesize substances **7b** and **7c** using methodologies (1) and (2), these reaction conditions did not display improved yield, and purification of the desired products was harder. In methodology (1) we isolated structure **8 (Figure 6),** formed by the rearrangement of the initial DCC-carboxylic acid adduct (PINHEIRO *et al*, 2007), as the major product, whereas in methodology (2) (LUCCHESE; MARZORATI, 2000) the formation of an emulsion during the liquid-liquid extraction step, due to the presence of the catalyst (cetrimide), made the work-up tedious and resulted in very low yields. In methodologies (3), (4), and (5), the formation of many by-products was observed.

Figure 6. Mass spectra (ESI) of byproduct 8, m/z = 353 ([M + Na]$^+$, 100%).



10 CONCLUSION

Eight unpublished pyrazine derivatives containing the benzylpiperazine moiety were synthesized and characterized by spectroscopic and spectrometric methods; however, low yields were obtained. Even so, the reported methodology is easy, reproducible, and could be used to prepare other benzylpiperazine derivatives with potential biological activity. The antitubercular activity of these compounds is currently under investigation.

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