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Synthesis of diphenoxyadamantane alkylamines with pharmacological interest

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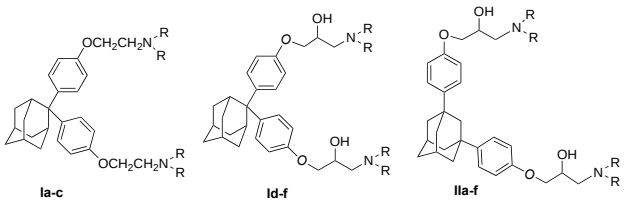

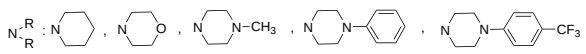

$N(CH_2CH_2OH)_2$, $N(CH_3)_2$, $N(CH_2)_3CH_3$, $N(CH_2)_5CH_3$

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ABSTRACT

In this work, the synthesis and the pharmacological evaluation of diphenoxyadamantane alkylamines **Ia-f** and **IIa-f** is described. The new diphenoxy-substituted adamantanes share structural features present in trypanocidal and antitubercular agents. 1-Methylpiperazine derivative **Ia** is the most potent against *T. brucei* compound, whilst its hexylamine congener **IIf** exhibits a significant antimycobacterial activity.

Neglected Tropical Diseases (NTDs) represent a plethora of infections (17 according to WHO)[1] caused by various pathogenic agents, such as viruses, bacteria, protozoa and helminths, which affect population in developing countries in Africa, Asia and America. Human African Trypanosomiasis (HAT) and American trypanosomiasis or Chagas disease are among the diseases which received the minimum interest and funding from the pharmaceutical industry and therefore called as the most neglected diseases.[2] Trypanosomatids, flaggelated Kinetoplastida protozoan, are the cause of trypanosomiasis and display two main strains that infect humans: *Trypanosoma brucei* and *Trypanosoma cruzi*, which correspond to the two types of trypanosomiasis.

Tuberculosis (TB) is one of the three major microbial lethal threats, alongside HIV/AIDS and malaria, to humans history in developing and industrialized countries worldwide. WHO estimates that there were 1.6 million TB deaths in 2017, and 0.3 million deaths resulting from coinfection of TB and HIV.[3] *Mycobacterium tuberculosis* (Mtb), the etiologic pathogen agent of TB, is being investigated to find new targets for antitubercular therapy. Besides the gravity of the disease, TB receives insufficient funding and research for new drugs is less intense compared to other diseases. Only two new drugs have been approved, bedaquiline and delamanid, to complement the current four-drug regimen over the last 60 years.[4]

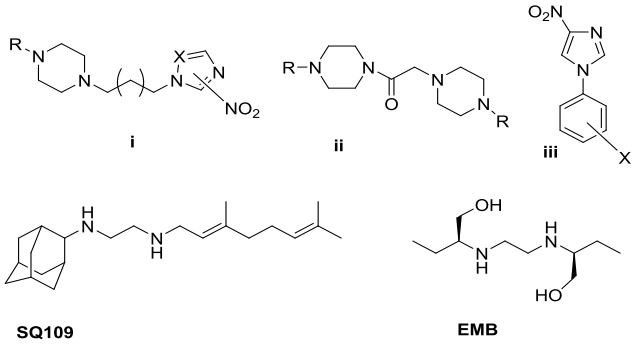


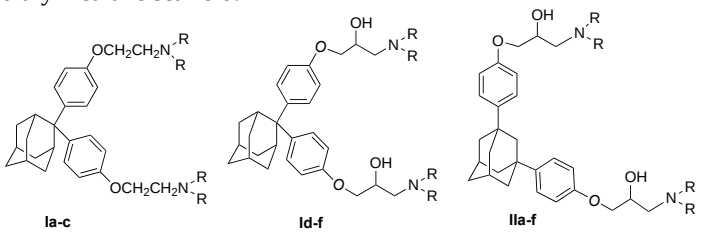
Figure 1. Derivatives with trypanocidal and tuberculocidal activity.

Various reports in literature display functionalized piperazine backbones of derivatives with trypanocidal activity.[5,6] Based on our previous work on adamantane substituted derivatives with pharmacological activity against trypanosomiasis,[7-12] we now describe the preparation of a series of adamantane diphenoxy

alkylamines **Ia-f** and **IIa-f** (**Figure 2**). The new adducts possess the adamantane core connected through a phenoxy moiety to the side chain of alkylamine. The termini of their side chains consist of a piperazine moiety, with a variety of substituents (derivatives **Ia-c**). In addition, morpholine and diethanolamine were used as more polar functional groups at the same site.

In derivatives **Id-f** and **IIa-f** the ethanolamine side chain was modified to 1-amino-2-propanol, which is an important feature in diverse antimicrobial agents.[13-16] Moreover, this *β*-aminoalcohol motif has been linked with antimycobacterial action.

Ethambutol[17] is the main representative of this category of antitubercular agents. The 1,2-diamine congeners, such as the adamantane derivative SQ-109[18,19] and the camphane aminoalcohols[20] exhibit very low toxicity and improved pharmacokinetic properties. Our lab has also reported antimycobacterial adamantane derivatives[21-23] bearing a diarylmethane scaffold.[24]



cmpd	*N*RR	cmpd	*N*RR
Ia	1-methylpiperazine	**IIa**	piperidine
Ib	1-phenylpiperazine	**IIb**	morpholine
Ic	1-(4-fluoromethyl)phenylpiperazine	**IIc**	1-methylpiperazine
Id	1-methylpiperazine	**IId**	dimethylamine
Ie	morpholine	**IIe**	butylamine
If	diethanolamine	**IIf**	hexylamine

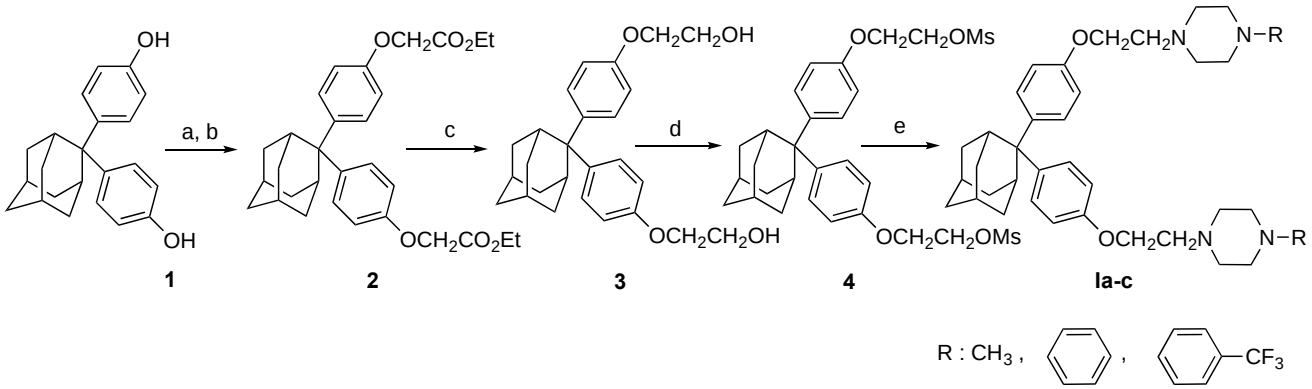
Figure 2. Diphenoxyadamantane alkylamines **Ia-f** and **IIa-f**.

The synthesis of the new adamantane piperazines **Ia-c** is depicted in **Scheme 1**.

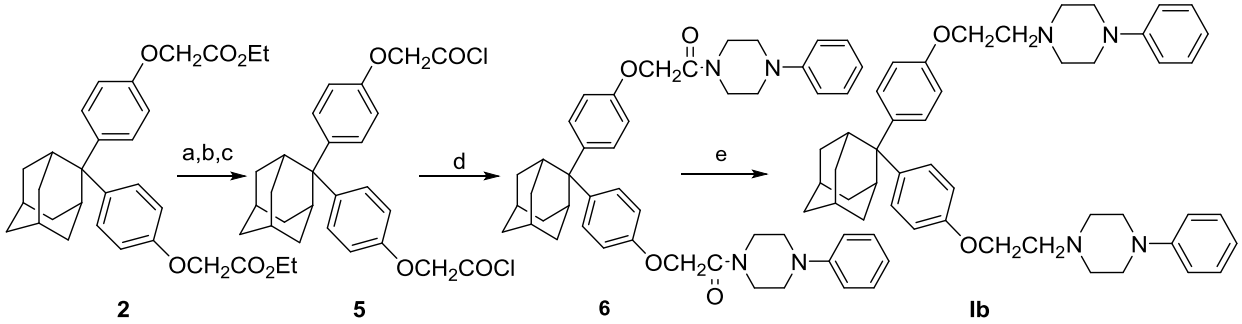
The starting material, 2,2-adamantanediyl-di(4-phenol) **1**[25] is acylated to form the diester **2**. This ethoxycarbonylmethylation is accomplished in the presence of sodium hydride in DMF, under heating at 80 °C for 72 h, generating first the phenoxy anion, which subsequently reacts with ethyl chloroacetate in the presence of cat. sodium iodide. Sodium iodide promotes halogen exchange and accelerates the nucleophilic substitution. Lower temperature or shorter heating time afforded a mixture of monoacylated and diacylated esters in a ratio of 1:2. Moreover, the use of sodium carbonate in acetone leads to the monosubstituted adduct. Reduction of the diester **2** with lithium aluminum hydride in dry THF gave dialcohol **3**, which was functionalized with methane sulfonyl chloride in the presence of pyridine to afford the corresponding methane sulfonate **4**. The latter was treated with the appropriate piperazine to give the desired adamantane piperazines **Ia-c**.

For comparison purposes, adamantane phenylpiperazine **Ib** was also synthesized by the reaction sequence shown in **Scheme 2**.

In the second synthetic pathway, diphenoxyethyl acetate **2** was converted to the diphenylacetimide **6** *via* the intermediate chloride **5**. The diester **2** was saponified to the corresponding acid, treated with thionyl chloride and then converted to diacylchloride **5**. The latter was coupled with 1-phenylpiperazine to afford the diphenylacetamide **6**, which was reduced by lithium aluminum hydride in dry THF to the respective phenylpiperazine **Ib**. The second synthetic route gives **Ib** in an overall yield of 19% (from the ester), whilst the first method in 24%.



Scheme 1. *Reagents and conditions*: (a) NaH / DMF dry; (b) NaI, ethyl chloroacetate, 80 °C, 72 h; (c) i. $LiAlH_4$ / THF, rt, 2 h, ii. H_2O/OH^-, ~ 0 °C; (d) MsCl/Py/THF-EtOH or *n*-BuOH, 40 °C, 1 h; (e) appropriate piperazine, Δ, 24 h.



Scheme 2. *Reagents and conditions*: (a) NaOH / EtOH-H_2O, reflux; (b) $SOCl_2$, reflux; (c) benzene; (d) appropriate piperazine, Δ, 1 h; (e) i. $LiAlH_4$ / THF, Δ, 1 h, ii. H_2O/OH^-, ~ 0 °C

The preparation of 2-hydroxypropylene derivatives **Id-f** and **IIa-f** is shown in **Scheme 3**.

The method for the epoxide formation of the two isomeric alcohols, 4,4'-(adamantane-2,2-diyl)diphenol (**1**) and 4,4'-(adamantane-1,3-diyl)diphenol (**7**)[26], has been patented,[27] and followed only for the generation of the phenoxy anion. Thereafter, as a result of considerable experimentation, we modified the procedure as follows: portions of sodium hydroxide were added over a period of 2 h into a mixture of the corresponding diphenol and epichlorohydrin in MIBK and DMSO, which was heated at 45 °C. Subsequently, the temperature of the reaction mixture was increased to 75 °C and after 4 h, the desired disubstituted epoxide **8** was produced. However, the 1,3-substituded isomeric phenol **7** did not give a sole product, but a mixture of mono and double substituted epoxide in a ratio of 1:5. To rectify this, the 4,4'-(adamantane-1,3-diyl)diphenol (**7**) was heated, instead, for 24 h to give the 1,3-bis(4-glycidyloxyphenyl)adamantane (**9**) in 81.5% yield.

The *O*-alkylation of phenols with epichlorohydrin is well documented in literature[28,29]. Apart from the formation of 3-aryloxy-1,2-epoxypropane **i**, the epoxide ring opening affords the chloroalcohol **ii**[30] (**Figure 3**). The IR spectral data confirmed the formation of the respective open-form chloroalcohol; IR ν (OH) = 3556 cm^{-1} in the case of diphenol **1** and IR ν (OH) = 3436 cm^{-1} in the case of diphenol **7**.

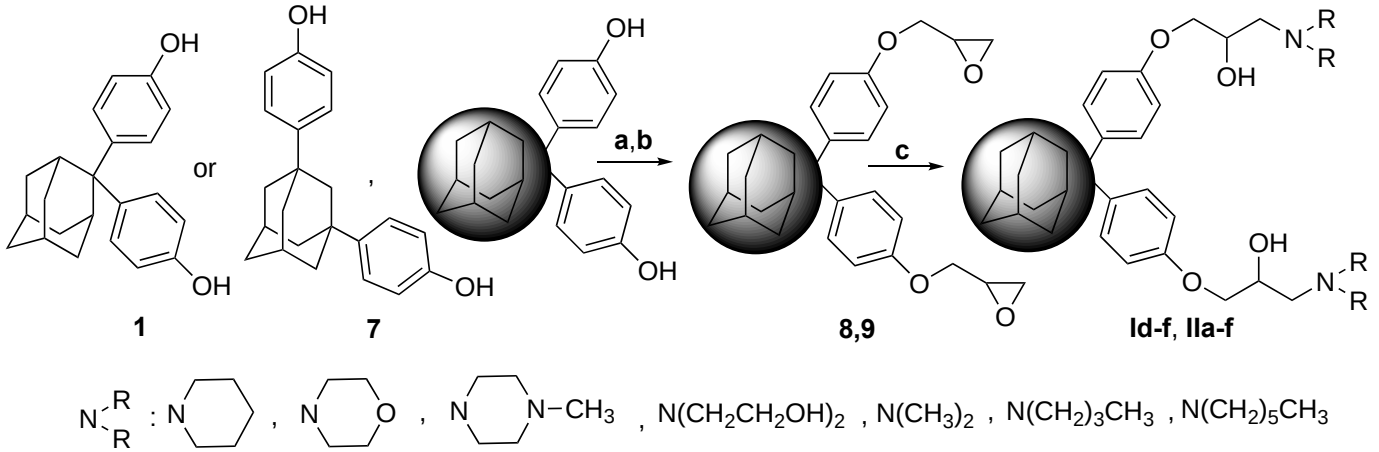
The coupling of the corresponding amine with either of the *O*-alkylated diphenols **1** and **7** leads to the same final aminoalcohols. Aminalcohols **Id-f** and **IIa-f** were prepared by two different methods, either under conventional heating in an autoclave or microwave irradiation using *i*-PrOH as solvent in both of methods.

The *in vitro* results from the anti-*T.brucei* screening are summarized in **Table 1**.

The 1-methylpiperazine derivatives **Ia**, **Id** and **IIc** seem to be more potent in comparison to their congeners. Bulky substituents, such as 1-phenylpiperazine and 1-(4-fluoromethyl)-phenylpiperazine, have a negative impact on potency. Moreover, the ethanolamine spacer seems to enhance the trypanocidal activity, while the 2-hydroxypropylene linker in the side chain decreases the positive role in potency of the end groups. Derivatives **Id** and **IIc** have lower activity than the **Ia** adduct. On the other hand, the amimoalkane groups at the functional end of the side chains (derivatives **IId**, **IIe** and **IIf**) corroborate the argument that small substituents enhance the activity. The 4 carbon atom length of the amino substitution seems to enhance the activity.The butylamine derivative **IIe** was found more active than its congeners. Based on the promising trypanocidal potency of 1-methylpiperazine derivative **Ia (**SI=6.5, the ratio of IC_{50} values obtained with L6 cells and *T. brucei*), we will prompt our efforts toward decreasing the cytotoxicity of future analogues.

The *in vitro* antimycobacterial test results of the new adamantane derivatives against replicating *M. tuberculosis* H37Rv and non-replicating SS18b, assessed by REMA,[31-33] are presented in **Table 2**.

The antimycobacterial activity of the 1-methylpiperazine adducts **Ia** and **Id** is notable, whilst **IIc**'s is marginal. On the other hand, aminoalkanes **IIe** and **IIf** seem to have the best activity against *M. tuberculosis*. The bulky substitution is proven, and in this case, to a have negative impact on the antimycobacterial efficacy. The polar heads at the side chain (congener **If**) do not enhance the antimycobacterial activity, either.



Scheme 3. *Reagents and conditions*: a) epichlorohydrin, NaOH / MIBK-DMSO dry, 45 °C, 2 h; (b) 75 °C, 24 h; (c) appropriate amine, *i*-PrOH, 110 °C, autoclave, 24 h; (d) appropriate amine, *i*-PrOH, 110 °C, microwave, 30 min.

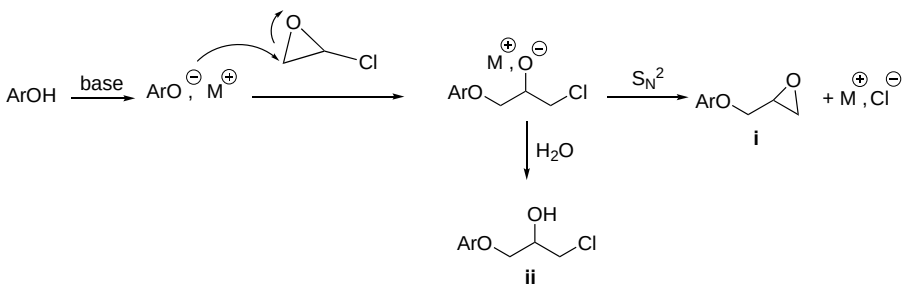


Figure 3. Mechanism of *O*-alkylation of phenol.

Table 1
Trypanocidal activity of the most active diphenoxyadamantane alkylamines **Ia-f** and **IIa-f**

Cmpd	*T. brucei* IC_{50} (μM)[a]	*T.brucei* IC_{90} (μM)[a]	L cells IC_{50} (μM)
Ia	0.051±0.008	0.070±0.017	0.33±0.06
Id	0.114±0.002	0.138±0.002	0.54±0.02
IIa	0.250±0.006	0.292±0.002	0.27±0.02
IIc	0.176±0.003	0.207±0.003	0.26±0.01
IId	0.171±0.017	0.235±0.007	0.29±0.02
IIe	0.093±0.003	0.110± 0.002	0.55±0.02
IIf	0.205±0.004	0.272±0.006	0.45± 0.03

[a]IC_{50} and IC_{90}; concentration that inhibits growth by 50% and 90%, respectively

Table 2
Antimycobacterial activity of most active diphenoxyadamantane alkylamines **Ia-f** and **IIa-f**

Cmpd	H37Rv MIC[a] (μg/mL)	SS18b Imax	SS18b Inhib. at 1 μg/mL
Ia	3.3	100%	0.04
Id	6	NT	NT
If	17.4	N.T	N.T
IIa	7	99%	0.17
IIc	14.5	95%	5%
IIe	2.7	100%	50%
IIf	0.06	0%	0%
RIF	0.0008	54%	13%
EMB	0.03	0%	0%

[a]MIC: minimum inhibition concentration

The new adamantane derivatives presented herein are doubly substituted by a phenoxyl, incorporating various aminoalkyl side chains. The 1-methylpiperazine derivative **Ia** is the most active against *T. brucei*, while hexylamine **IIf** exhibits the higher antimycobacterial potency among its analogs. The ethylene spacer of the side chain leads to enhanced activity compared to the 2-hydroxypropylene linker. These preliminary results will be utilized in future studies on phenyl-substituted adamantane derivatives with a trypanocidal and antitubercular potency devoid of toxicity against mammalian cells.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

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