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Laboratory note

Synthesis and antibacterial activity of new 4-alkoxy, 4-aminoalkyl and 4-alkylthioquinoline derivatives

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Abstract – 4-Alkoxy-8-methyl-7-nitroquinolines, 4-alkylamino-8-methyl-7-nitroquinolines, 4-alkoxy-2,8-dimethylquinolines, 4-alkylthioquinolines were prepared from 8-methyl-7-nitro-4-quinolone, 8-methyl-7-nitro-4-chloro-quinoline, 2,8-dimethyl-4-quinolone and 4-hydroxyquinoline used as starting material. Compounds were characterized from ^{1}H and ^{13}C NMR spectra. These drugs were tested against selected gram–, gram+ and mycobacteria strains. A promising activity was observed against Mycobacterium smegmatis. © Elsevier, Paris

quinolines / antibacterial agents / structure–activity relationship

1. Introduction

With the aim to clarify structure–antibacterial activity relationships in the field of azaheterocycles, new quinolines were prepared to be compared either with the acridine derivatives previously tested [1] or with a few selected substituted pyridines. The main objective was to discuss the possible role of the heterocyclic moiety. In addition, these tests could be of interest because quinolines have not been extensively investigated until now as antibacterial agents, apart from the hydroxy-substituted derivatives mainly used as urinary tract antiseptics [2]. Actually, the antimicrobial spectra of a few compounds belonging to this series have been reviewed [3].

2. Chemistry

In contrast with the classical way of preparation which requires four steps [4], 8-methyl-4-quinolones **2** and **7** were synthesized in a two-step procedure. Indeed, the 1,2-addition of *o*-toluidine on ethylpropiolate [5] led to the 2-carboethoxyvinylamino-6-toluenes **1** and **6** which were cyclized at 250 °C in phenyl ether [6]. The yield for **2** was 63% while it was only 47% for **7**, probably because the crude mixture was directly cyclized without purification in this case.

Alkylation of **2** and **7** in a basic medium (dimethylformamide/dipotassium carbonate) or under phase transfer catalysis (PTC) conditions gave 4-alkoxy-8-methyl-quinolines **3** and **8**, but yields dramatically decrease when PTC conditions are used.

Phosphorous oxychloride under reflux [4] was used to convert the quinolone **2** in the 4-chloroquinoline **4**. Alkylation of several amines with **4** was achieved by heating the mixture at 130–140 °C for 2 h but no longer, owing to the increasing rate of side products with time.

4-Hydroxyquinoline was treated with tetraphosphorus decasulfide in pyridine at 110 °C, and 4-alkylthioquinolines **10** were then prepared from the 4-quinolinethione **9** obtained by alkylating this compound under PTC conditions but without adding any catalyst.

The 4-thioalkylsubstituted pyridines **11** were prepared under PTC conditions from the 4-thiopyridinone as starting compound. General synthetic pathways are portrayed in *figure 1*. Chemical and spectral data of the compounds prepared are gathered in *tables I–V*. Finally, the acridine derivatives **12** (*figure 2*) were prepared as described in [7].

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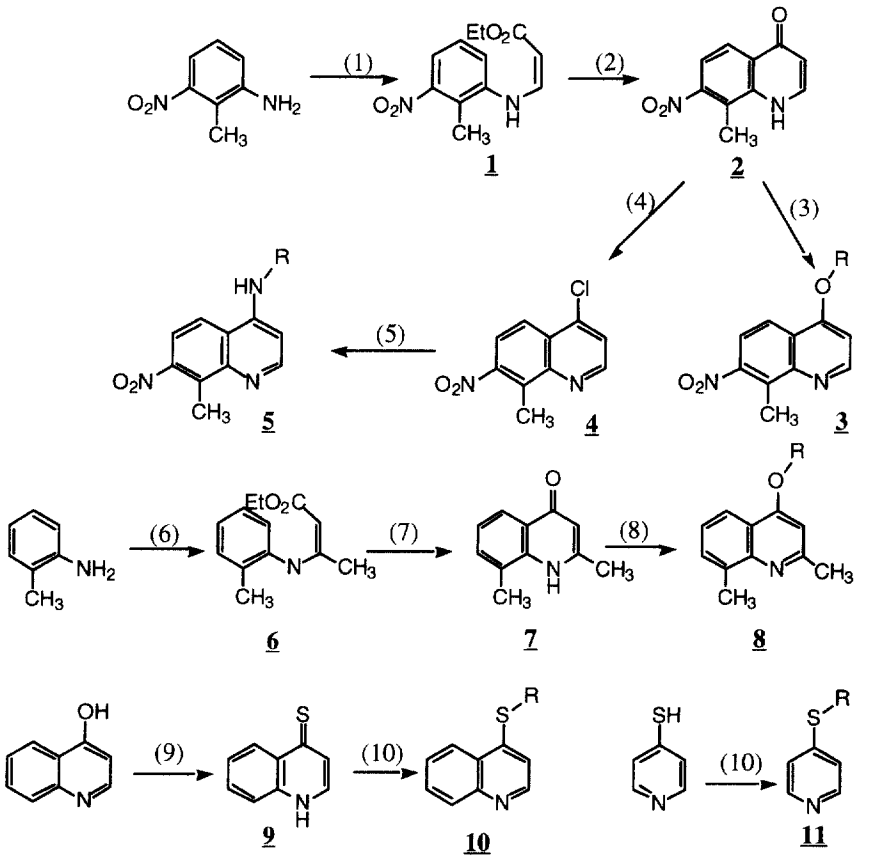
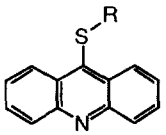


Figure 1.

3. Antibacterial activity

Antibacterial activity was determined using a microplate assay (Biomeck 1000, Beckman Instruments, Palo Alto, CA; A400 Multipoint Inoculator, Denley, Billingshurst, UK). Reference strains (*Escherichia coli* CIP 54127; *Enterobacter aerogenes* CIP 6086; *Staphylococcus aureus* CIP 53154; *Mycobacterium smegmatis* CIP 7326) were grown for 24 h (48 h for *M. smegmatis*) at 37 °C on tryptic soy agar (Difco Laboratories, Detroit, MI) and harvested in the diluent (tryptone 0.1%, NaCl 8%, w/v) or distilled water (*M. smegmatis*). Absorbance at 623 nm was adjusted to obtain 2 x 10^8 (± 1 x 10^8) CFU/mL. Stock solutions of drugs and dilutions were prepared in distilled water. Concentrations tested were 1, 5, 10, 50, 100, 500, 1000, 5000 and 10 000 µM, except when limited by solubility.



12

a : R = CH_2CH_3

b : R = $(CH_2)_2N(CH_2CH_3)_2$

c : R = $(CH_2)_2N(CH_3)_2$

Figure 2.

Growth inhibition was evaluated in nutrient broth supplemented (w/v) with 0.1% dextrose and 0.15% yeast extract (Difco Lab.). After incubation for 48 h (*E. coli*, *E. aerogenes*, *S. aureus*) or 72 h (*M. smegmatis*) at 37 °C, the percentage of growth was calculated from the absorbance measured at 620 nm (Titertek Multiskan, Flow Laboratories, Helsinki, Finland). MIC was defined as the lowest concentration giving less than 20% of growth [8].

MICs were determined for measuring potency while inhibitory indices (I.I.), used for the structure–activity relationship (SAR) studies, were calculated from the growth inhibition curves obtained by plotting the log concentration of drugs versus the percentage of growth. Calculations were performed using the following formula:

$$\text{I.I.} = 100 - \frac{\text{Area under the dose} - \text{response curve}}{\text{M.T.A.}}$$

where M.T.A. means Maximum Theoretical Area corresponding to no activity (100% growth at any concentration). Inhibitory indices range from 0 to 100 as a function of antibacterial activity.

Table I. Chemical and spectral data of compounds **1**, **2**, **3**.

Compound	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$ as solvent)[a], δ (ppm), *J* (Hz)
1	64	83–85	1.32 (t, 3H; *J* = 7.2); 2.41 (s, 3H); 4.21 (q, 2H; *J* = 7.2); 4.99 (d, 1H; *J* = 8.3); 7.23 (d, 1H; *J* = 8.3); 7.40 (m, 2H); 7.39 (t, 1H; *J* = 8.3–11.7); 10.24 (d, 1H; *J* = 11.7)
2	63	> 260	2.53 (s, 3H); 6.20 (d, 1H; *J* = 6.8); 7.69 (d, 1H; *J* = 8.8); 7.98 (d, 1H; *J* = 6.8); 8.13 (d, 1H; *J* = 8.8); 11.51 (m, 1H)
3a	73	118–120	1.57 (t, 3H; *J* = 7.0); 2.93 (s, 3H); 4.26 (q, 2H; *J* = 7.0); 6.80 (d, 1H; *J* = 5.2); 7.76 (d, 1H; *J* = 9.2); 8.12 (d, 1H; *J* = 9.2); 8.81 (d, 1H; *J* = 5.2)
3b	53	54–56	1.12 (t, 6H; *J* = 7.1); 2.68 (q, 4H; *J* = 7.1); 2.95 (s, 3H); 3.05 (t, 2H; *J* = 6.1); 4.28 (t, 2H; *J* = 6.1); 6.86 (d, 1H; *J* = 5.2); 7.80 (d, 1H; *J* = 9.1); 8.13 (d, 1H; *J* = 9.1); 8.85 (d, 1H; *J* = 5.2)
3c	15	84–86	2.32 (s, 6H); 2.83 (t, 2H; *J* = 5.6–5.7); 2.88 (s, 3H); 4.23 (t, 2H; *J* = 5.6–5.7); 6.85 (d, 1H; *J* = 5.1); 7.76 (d, 1H; *J* = 9.1); 8.12 (d, 1H; *J* = 9.1); 8.81 (d, 1H; *J* = 5.1)
3d	28	113–115	1.06 (t, 12H; *J* = 6.5); 2.96 (s, 3H); 2.98 (t, 2H; *J* = 6.9); 3.05 (m, 2H; *J* = 6.5); 4.12 (t, 2H; *J* = 6.9); 6.85 (d, 1H; *J* = 5.2); 7.81 (d, 1H; *J* = 9.1); 8.17 (d, 1H; *J* = 9.1); 8.85 (d, 1H; *J* = 5.2)
3e	12	46–48	2.13 (qt, 2H; *J* = 6.7); 2.29 (s, 6H); 2.55 (t, 2H; *J* = 7.0); 2.97 (s, 3H); 4.28 (t, 2H; *J* = 6.4); 6.87 (d, 1H; *J* = 5.2); 7.83 (d, 1H; *J* = 9.1); 8.17 (d, 1H; *J* = 9.1); 8.85 (d, 1H; *J* = 5.2)
3f	36	127–129	2.63 (t, 4H; *J* = 4.7); 2.96 (s, 3H); 2.97 (t, 2H; *J* = 5.7); 2.97 (s, 3H); 3.73 (t, 4H, *J* = 4.7); 4.35 (t, 2H; *J* = 5.7); 6.85 (d, 1H; *J* = 5.1); 7.83 (d, 1H; *J* = 9.1); 8.13 (d, 1H; *J* = 9.1); 8.86 (d, 1H; *J* = 5.1)
3g	55	78–80	1.48 (qt, 2H; *J* = 5.0–5.5); 1.62 (qt, 4H; *J* = 5.0–5.8); 2.58 (t, 4H; *J* = 5.0–5.5); 2.97 (s, 3H); 2.95 (q, 2H; *J* = 5.8); 4.35 (t, 2H; *J* = 5.8); 7.86 (d, 1H; *J* = 5.2); 7.83 (d, 1H; *J* = 9.1); 8.16 (d, 1H; *J* = 9.1); 8.87 (d, 1H; *J* = 5.2)
3h	51	64–66	1.46 (m, 2H; *J* = 4.7); 1.61 (qt, 4H; *J* = 5.2); 2.14 (qt, 2H; *J* = 6.4–7.6); 2.42 (qt, 4H, *J* = 5.1); 2.56 (t, 2H; *J* = 7.3); 2.93 (s, 3H); 4.26 (t, 2H; *J* = 6.3); 6.85 (d, 1H; *J* = 5.2); 7.78 (d, 1H; *J* = 8.1); 8.12 (d, 1H; *J* = 9.1); 8.83 (d, 1H; *J* = 5.2)
3i	34	101–103	1.83 (qt, 4H; *J* = 3.0–3.5); 2.66 (t, 4H; *J* = 3.5); 2.96 (s, 3H); 3.07 (t, 4H, *J* = 5.8); 6.85 (d, 1H; *J* = 5.2); 7.82 (d, 1H; *J* = 9.2); 8.17 (d, 1H; *J* = 9.2); 8.86 (d, 1H; *J* = 5.2)

[a]Except for **2**: DMSO-d_6.

Table II. Chemical and spectral data of compounds **4**, **5**.

Compound	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$ as solvent)[a], δ (ppm), *J* (Hz)
4	71	121–123	2.99 (s, 3H); 7.63 (d, 2H; *J* = 4.6); 7.96 (d, 2H; *J* = 9.2); 8.20 (d, 2H; *J* = 9.2); 8.91 (d, 2H; *J* = 4.6)
5b	74	68–70	1.20 (t, 6H; *J* = 7.3); 2.51 (s, 3H); 3.15 (q, 4H; *J* = 7.3); 3.46 (t, 2H; *J* = 6.6); 3.85 (t, 2H; *J* = 6.6); 6.81 (d, 1H; *J* = 7.1); 7.76 (d, 1H; *J* = 9.2); 8.08 (d, 1H; *J* = 9.2); 8.33 (d, 1H; *J* = 7.1)
5c	71	60–62	2.37 (s, 3H); 2.80 (s, 6H); 3.42 (t, 2H; *J* = 6.3); 3.87 (t, 2H; *J* = 6.3); 6.83 (d, 1H; *J* = 7.2); 7.68 (d, 1H; *J* = 9.3); 8.00 (d, 1H; *J* = 9.3); 8.28 (d, 1H; *J* = 7.2)
5d	32	189–191	1.30 (d, 12H; *J* = 6.4); 2.52 (s, 3H); 3.49 (m, 3H; *J* = 7.2); 3.76 (m, 2H; *J* = 6.4); 3.99 (t, 2H; J_1 = 6.4; J_2 = 7.2); 6.94 (d, 1H; *J* = 7.2); 7.76 (d, 1H; *J* = 9.2); 8.11 (d, 1H; *J* = 9.2); 8.42 (d, 1H; *J* = 7.2)
5e	21	150–152	2.16 (m, 2H; *J* = 5.0–7.1); 2.42 (s, 3H); 2.85 (s, 6H); 3.25 (qt, 2H; *J* = 5.0); 3.64 (t, 2H; *J* = 7.1); 6.87 (d, 1H; *J* = 7.2); 7.72 (d, 1H; *J* = 9.2); 8.01 (d, 1H; *J* = 9.2); 8. 30 (d, 1H; *J* = 7.2)
5f	15	88–90	2.55 (t, 4H; *J* = 4.6); 2.80 (t, 2H; J_1 = 5.1; J_2 = 6.3); 2.95 (s, 3H); 3.34 (q, 2H; J_1 = 4.8; J_2 = 5.1); 3.76 (t, 4H; *J* = 4.6); 6.01 (m, 1H); 6.50 (d, 1H; *J* = 5.2); 7.68 (d, 1H; *J* = 9.2); 7.80 (d, 1H; *J* = 9.2); 8.67 (d, 1H; *J* = 5.2)
5g	32	137–139	1.49 (qt, 2H; *J* = 4.7); 1.61 (qt, 4H; J_1 = 5.0; J_2 = 5.7); 2.45 (d, 4H; *J* = 4.7); 2.42 (t, 2H; *J* = 5.7); 2.91 (s, 3H); 3.28 (q, 2H; *J* = 5.0); 6.28 (s, 1H); 6.45 (d, 1H; *J* = 5.3); 7.73 (d, 2H; *J* = 9.2); 8.62 (d, 1H; *J* = 5.3)
5h	14	119–121	1.03 (d, 3H; *J* = 6.2); 1.47 (m, 2H; *J* = 5.5–9.8); 1.81 (m, 5H; *J* = 6.0–9.8); 2.07 (m, 2H); 2.37 (m, 2H); 3.06 (s, 3H); 3.32 (m, 4H; *J* = 5.5–8.8); 6.41 (d, 1H; *J* = 5.3); 7.75 (d, 2H; *J* = 9.2); 7.88 (d, 1H; *J* = 9.2); 8.63 (d, 1H; *J* = 5.3)
5i	21	239–241	2.00 (m, 4H); 2.15 (m, 3H); 3.36 (m, 6H); 3.7 (m, 2H); 6.35 (d, 1H; *J* = 5.8); 7.26 (d, 1H; *J* = 9.3); 7.38 (d, 2H; *J* = 9.3); 8.05 (d, 1H; *J* = 5.3)

[a]Except for **5d**,**e**,**h**: D_2O.

4. Results and discussion

The preliminary screening involved three typical strains with different envelopes, e.g. *E. coli*, *S. aureus* and *M. smegmatis*. In addition to this, *E. aerogenes* was selected because of the resistance against this bacterial strain previously noted with nitroxoline.

Inhibitory indices and MICs are collected in *table VI*. The compounds evaluated were slightly less active against gram+ and gram– strains than oxine [3] or nitroxoline [9] which can be considered as reference drugs in the quinoline series. Indeed, MICs for *E. coli* are 1 mM in the case of oxine and 0.05 mM in the case of nitroxoline while MICs for *S. aureus* are 0.05 mM for both strains. Most of the compounds prepared as well as the reference drugs show a very good activity against mycobacteria.

Contrary to MICs which are only end-points, inhibitory indices allow the treatment of data. That is why mean I.I. values of either chemical series or substituent types are gathered in *tables VII* and *VIII* with the purpose of being used in the SAR study.

At first, one can note that compounds **5** (mean I.I. = 42) are the most promising, globally speaking. This is due to their balanced activity spectra. Compounds **3**, in spite of very low indices for all bacteria strains tested, deserve attention because of their high specific indices for *M. smegmatis*. Actually, the growth of *M. smegmatis* is significantly inhibited whatever the series evaluated. However, with reference to this, it must be emphasized that the diisopropylaminoethyl (**e**) substituted derivatives (mean I.I. = 54) are the most active or among the most active. Similarly, but to a lesser extent, this is the case with the diethylaminoethyl (**b**) and piperidinoethyl (**g**) substituted derivatives. The latter substituent is also of interest against *S. aureus*, except in case of **5**.

In addition to this, the morpholinoethyl (**f**) substituent (mean I.I. = 26) is a less favourable substituent while the piperidinoethyl (**g**) one (mean I.I. = 40) is much more favourable on condition that all results are equally taken into consideration.

Activity does not strongly depend on the nature of the side chain with other strains tested. Finally, *Enterobacter aerogenes* is poorly sensitive to the alkoxyderivatives **3** and **8**.

Nevertheless, the activity of the series can be ordered as **5** > **3** > **10** > **8** while the susceptibility of strains will be ordered as *M. smegmatis* > *E. coli* > *S. aureus* > *E. aerogenes*. Hence, on the basis of inhi-

Table III. Chemical and spectral data of compounds **7**, **8**.

Compound	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$ as solvent)[a], δ (ppm), *J* (Hz)
7	47	259–261	2.40 (s, 3H); 2.52 (s, 3H); 5.94 (s, 1H); 7.17 (t, 1H; *J* = 7.6); 7.45 (d, 1H; *J* = 6.6); 7.92 (d, 1H; *J* = 7.9); 10.42 (m, 1H)
8a	72	59–61	1.52 (t, 3H; *J* = 7.0); 2.68 (s, 3H); 2.76 (s, 3H); 4.17 (q, 2H; *J* = 7.0); 6.55 (s, 1H); 7.29 (t, 1H; J_1 = 8.2; J_2 = 7.1); 7.48 (d, 1H; *J* = 6.7); 8.01 (d, 1H; *J* = 8.2)
8b	30	158–160	1.28 (t, 6 H; *J* = 7.3); 2.52 (s, 3H); 2.68 (s, 3H); 3.29 (q, 4H; *J* = 7.3); 3.74 (t, 2H; *J* = 4.4); 4.62 (t, 2H; *J* = 4.4); 6.98 (s, 1H); 7.45 (t, 1H; J_1 = 8.1; J_2 = 7.4); 7.62 (d, 1H; *J* = 7.0); 7.92 (d, 1H; *J* = 8.1)
8c	25	54–56	2.39 (s, 6H); 2.69 (s, 3H); 2.76 (s, 3H); 2.87 (t, 2H; *J* = 5.6); 4.23 (t, 2H; *J* = 5.6); 6.59 (s, 1H); 7.29 (t, 1H; *J* = 7.5); 7.48 (d, 1H; *J* = 6.9); 8.00 (d, 1H; *J* = 8.20)
8d	24	69–71	1.07 (d, 12H; *J* = 6.6); 2.69 (s, 3H); 2.76 (s, 3H); 2.97 (t, 2H; *J* = 7,1); 3.09 (m, 2H; *J* = 6.5); 4.06 (t, 2H; *J* = 7.1); 6.62 (s, 1H); 7.29 (t, 1H; J_1 = 8.2; J_2 = 7.3); 7.49 (d, 1H; *J* = 6.5); 8.01 (d, 1H; *J* = 8.2)
8e	20	177–179	2.32 (m, 2H); 2.35 (s, 3H); 2.58 (s, 3H); 2.89 (s, 6H); 3.34 (t, 2H; *J* = 8.1); 4.30 (t, 2H; *J* = 5.6); 6.81 (s, 1H); 7.34 (t, 1H; J_1 = 7.9; J_2 = 7 5); 7.48 (d, 1H; *J* = 6.9); 7.78 (d, 1H; *J* = 8,0)
8f	48	79–81	2.61 (t, 4H; *J* = 4,6); 2.68 (s, 3H); 2.76 (s, 3H); 2.90 (t, 2H; *J* = 5.5); 3.71 (t, 4H; *J* = 4.6); 4.24 (t, 2H; *J* = 5.6); 6.56 (s, 1H); 7.29 (t, 1H; J_1 = 8.1; J_2 = 7.0); 7.48 (d, 1H; *J* = 6.6); 7.94 (d, 1H; *J* = 7.6)
8g	17	50–52	1.46 (q, 2H; *J* = 4.9); 1.61 (q, 2H; *J* = 5.3); 2.58 (t, 4H; *J* = 4.7–5.4); 2.69 (s, 3H); 2.76 (s, 3H); 2.93 (t, 2H; *J* = 5.9); 4.29 (t, 2H; *J* = 5.9); 6.61 (s, 1H); 7.30 (t, 1H); *J* = 7.9); 7.49 (d, 1H; *J* = 7.0); 7.90 (d, 1H; *J* = 8.1)
8h	20	81–83	1.45 (q, 2H; *J* = 4.8); 1.60 (q, 4H; *J* = 4.9–5.8); 2.10 (q, 2H; *J* = 6.2–7.9); 2.41 (m, 4H; *J* = 4.8); 2.54 (t, 2H; *J* = 7.0–7.9); 2.69 (s, 3H); 2.76 (s, 3H); 4.18 (t, 2H; *J* = 6.2); 6.61 (s, 1H); 7.29 (t, 1H; 7.5–8.2); 7.48 (d, 1H; *J* = 6.9); 7.99 (d, 1H; *J* = 8.2)
8i	34	109–111	1.95 (m, 4H; *J* = 3.3–6.6); 2.50 (s, 3H); 2.79 (s, 3H); 3.23 (m, 2H; *J* = 3.8–7.4); 3.74 (m, 2H; *J* = 4.8–5.5); 3.86 (t, 2H; *J* = 4.4); 4.76 (t, 2H; *J* = 4.4); 7.20 (s, 1H); 7.20 (s, 1H); 7.50 (t, 1H; J_1 = 8.0; J_2 = 7.4); 7.66 (d, 1H; *J* = 7.4); 8.08 (d, 1H; *J* = 8.0)

[a]Except for **7**: DMSO-d_6; **8c**,**i**: D_2O.

bition indices, the most promising compounds are directed towards *M. smegmatis* and correspond to 8-methyl-7-nitro-4-alkoxyquinoline **3** or to 8-methyl-7-nitro-4-alkylaminoquinoline **5**, which are substituted with diisopropylaminoethyl (**e**), diethylaminoethyl (**b**) or piperidinoethyl (**g**) groups. Besides, experimental results are in full agreement with this, since the lowest MICs are observed with compounds **5b**, **3g** and **5g**.

Moreover, on the one hand, comparison between similarly substituted compounds from series **10** and **11** (*table IX*) shows a significant decrease in activity in the case of a monocyclic substrate.

On the other hand, the increase in inhibitory effect from the quinoline derivatives **10** to the similarly substituted acridine thioethers **12** [7, 10] is made evident from the results collected in the same *table IX*.

Thus, the heterocyclic moieties could be ordered as follows: thiopyridine < thioquinoline < thioacridine, with respect to the activity investigated.

5. Experimental protocols

Melting points were determined on a Köfler hot bank and are given uncorrected. NMR spectra were recorded on a Bruker ARX 200 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed on a Technicon CHN autoanalyzer. Analyses agree to within ± 0.4% with theoretical values. The ^{1}H-NMR abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), m (multiplet).

5.1. 2-Carboethoxyvinylamino-6-nitrotoluene 1

6 g of 2-methyl-3-nitroaniline (0.038 mol) was dissolved in methanol and an equimolar amount of ethylpropiolate was added. The solution was heated at 80 °C for 4 h, before heating at 40 °C was maintained for 2 days. Then the mixture was kept cool overnight. The precipitate was collected by filtration, washed with cold methanol and recrystallized from methanol.

5.2. 8-Methyl-7-nitro-4-quinolone 2

In a round bottom flask, 75 mL of phenyl ether was heated at 120 °C. Then 2 g (8 mmol) of **1** was added and the temperature was quickly raised to and kept at 250 °C for 15 min under

Table IV. Chemical and spectral data of compounds **9**, **10**.

Compound	Yield (%)	Mp (°C)	^{1}H NMR (D_2O as solvent)[a], δ (ppm), *J* (Hz)
9	81	156–158	7.31 (d, 1H; *J* = 6.6); 7.48 (d, 1H; *J* = 6.5); 7.68 (d, 1H; *J* = 8.1); 7.76 (t, 1H; *J* = 6.5)
10a	62	168–170	1.60 (t, 3H; *J* = 7.4); 3.34 (q, 2H; *J* = 7.4); 7.52 (d, 1H, *J* = 6.1); 7.81 (t, 1H; J_1 = 7.7; J_2 = 7.8); 8.01 (t, 1H; J_1 = 7.8; J_2 = 7.7); 8.26 (d, 1H; *J* = 8.5); 8.74 (d, 1H; *J* = 6.0); 8.77 (d, 1H; *J* = 8.4)
10b	50	160–162	1.42 (t, 6H; *J* = 7.3); 3.22 (q, 4H; *J* = 7.3); 3.27 (t, 2H; *J* = 7.2); 3.80 (t, 2H; *J* = 8.0); 7.57 (t, 1H; J_1 = 6.8; J_1 = 8.3); 7.74 (d, 1H; *J* = 4.8); 7.75 (t, 1H; J_1 = 6.8; J_2 = 8.3); 8.05 (d, 1H; *J* = 8.4); 8.13 (d, 1H; *J* = 8.3); 8.84 (d, 1H; *J* = 4.8)
10c	45	132–134	2.90 (s, 6H); 3.62 (t, 2H; *J* = 5.1); 3.59 (t, 2H; *J* = 5.1); 7.45 (d, 1H; *J* = 6.0); 7.61 (m, 1H; *J* = 3.2); 7.81 (m, 2H); 8.00 (d, 1H; *J* = 8.5); 8.52 (d, 1H; *J* = 6.0)
10d	66	150–152	1.20 (d, 12H; *J* = 6.6); 3.43 (t, 2H; *J* = 6.2); 3.64 (d, 2H; *J* = 6.2); 3.68 (m, 2H; *J* = 6.6); 7.58 (d, 1H; *J* = 6.3); 7.66 (t, 2H; *J* = 4.2); 7.71 (t, 1H; *J* = 4.2); 7.89 (d, 2H; *J* = 8.6); 8.15 (d, 1H; *J* = 8.6); 8.60 (d, 1H; *J* = 6.3)
10e	55	109–111	2.04 (qt, 2H; J_1 = 7.7; J_2 = 7.3); 2.68 (s, 6H); 3.11 (t, 2H; *J* = 7.7); 3.16 (t, 2H; *J* = 7.3); 7.26 (d, 1H; *J* = 8.0); 7.35 (d, 1H; *J* = 8.3); 7.46 (d, 1H; *J* = 8.0); 7.59 (t, 2H; J_1 = 6.3; J_1 = 8.3); 8.27 (d, 1H; *J* = 6.3)
10f	56	155–157	3.41 (m, 4H; *J* = 4.0); 3.56 (t, 2H; J_1 = 5.6; J_1 = 3.1); 3.72 (t, 2H; J_1 = 3.1; J_2 = 5.6); 3.91 (t, 4H; *J* = 4.0); 7.60 (d, 1H; *J* = 8.3); 7.72 (m, 1H; *J* = 6.2); 7.90 (t, 2H; *J* = 6.2); 8.12 (d, 1H; *J* = 8.3); 8.63 (d, 1H; *J* = 6.2)
10g	19	210–212	1.71 (m, 2H); 1.74 (m, 4H); 3.21 (m, 8H); 6.77 (d, 1H; *J* = 5.0); 7.22 (t, 1H; J_1 = 5.9; J_2 = 7.5); 7.48 (t, 1H; *J* = 5.9–7.4); 7.53 (d, 1H; *J* = 7.5); 8.13 (d, 1H; *J* = 5.0)
10h	23	189–191	1.32 (m, 2H); 1.61 (m, 4H); 1.93 (qt, 2H; *J* = 7.5); 2.77 (qt, 4H; *J* = 7.1); 3.05 (qt, 2H; *J* = 5.0–5.6); 3.31 (m, 2H); 6.70 (d, 1H; *J* = 4.9); 7.17 (t, 1H; J_1 = 3.9; J_2 = 8.5); 7.33 (t, 1H; *J* = 8.5); 7.44 (t, 2H; *J* = 3.9); 8.03 (d, 1H; *J* = 4.9)
10i	37	47–49	1.97 (m, 4H; *J* = 4.0–6.5); 3.7 (t, 2H; 6.0); 3.28 (m, 4H; *J* = 4.0–6.5); 3.32 (t, 2H; *J* = 6,0); 6.77 (d, 1H; *J* = 5.4); 7.18 (t, 1H; *J* = 5.7–6.0); 7.32 (d, 1H; *J* = 6.7); 7.39 (t, 1H; *J* = 6.0–6.7); 7.42 (d, 1H; *J* = 5.7); 8.03 (d, 1H, *J* = 5.4)

[a]Except for **10c**: $CDCl_3$; **10e**: DMSO-d_6.

Table V. Chemical and spectral data of compounds **11**.

Compound	Yield (%)	Mp (°C)	^{1}H NMR (D_2O as solvent)[a], δ (ppm), *J* (Hz)
11a	62	168–170	1.25 (t, 3H; *J* = 7.4); 3.06 (q, 2H; *J* = 7.4); 7.61 (d, 2H; *J* = 7.1); 8.23 (d, 2H; *J* = 7.1)
11b	72	179–181	1.17 (t, 6H; *J* = 7.3); 3.20 (q, 4H; *J* = 7.3); 3.45 (t, 2H; *J* = 6.7); 3.51 (t, 2H; *J* = 6.1); 7.71 (d, 2H; *J* = 7.0); 8.36 (d, 2H; *J* = 7.0)
11c	72	195–197	2.90 (s, 6H); 3.62 (t, 2H; *J* = 5.1); 3.59 (t, 2H; *J* = 5.1); 7.72 (d, 2H; *J* = 7.2); 8.38 (d, 2H; *J* = 7.2)
11e	48	186–188	1.25 (d, 12H; *J* = 5.6); 3.44 (t, 2H; *J* = 8.0); 3.52 (t, 2H; *J* = 9.8); 3.73 (q, 2H; *J* = 5.6); 7.71 (d, 2H; *J* = 6.1); 8.37 (d, 2H; *J* = 6.1)

Table VI. Inhibitory indices and MICs (mM)[a] of quinoline derivatives.

Compound	*E. coli*		*E. aerogenes*		*S. aureus*		*M. smegmatis*	
	I.I.	MICs	I.I.	MICs	I.I.	MICs	I.I.	MICs
10a	43	0 5	36	1	32	1	49	0.5
10b	28	5	34	5	29	5	46	1
10c	36	1	29	5	33	10	31	5
10d	33	5	32	5	35	10	37	1
10e	26	5	20	10	31	10	45	0.5
10f	27	5	12	50	< 10	10	14	5
10g	41	1	30	50	44	5	28	5
10h	37	1	36	10	36	5	24	5
10i	41	1	34	5	33	50	24	5
8a	30	5	25	5	25	50	35	1
8b	27	10	27	10	< 10	50	30	5
8c	32	5	26	10	34	5	44	5
8d	36	10	30	10	< 10	50	45	5
8e	28	5	20	50	< 10	50	60	0.1
8f	25	5	30	10	14	50	35	1
8g	23	5	< 10	10	41	5	36	5
8h	37	10	27	50	12	50	30	50
8i	34	5	< 10	50	31	50	65	0.1
3a	–	–	–	–	–	–	–	–
3b	41	1	17	10	35	10	49	0.5
3c	46	1	29	5	11	10	39	0.5
3d	46	1	25	5	43	10	58	0.5
3e	36	5	< 10	50	52	10	69	0.05
3f	32	5	10	10	44	10	49	0.5
3g	42	1	18	50	66	0.1	55	0.05
3h	44	1	23	10	30	10	44	0.5
3i	–	–	–	–	–	–	–	–
5a	–	–	–	–	–	–	–	–
5b	42	1	41	1	46	5	77	0.01
5c	47	1	44	1	46	10	53	0.5
5d	46	5	24	5	28	5	38	1
5e	49	5	30	5	31	5	40	1
5f	45	5	38	5	17	50	27	5
5g	54	0.5	49	0.5	34	5	73	0.05
5h	54	0.5	43	0.5	29	5	43	0.5
5i	52	0.5	20	5	34	5	38	1
oxine[b]	39	1	43	0.5	56	0.05	58	0.05
nitroxoline[b]	59	0.05	48	0.1	65	0.05	59	0.05

[a]–: unevaluated activity due to compound solubility; [b]selected as reference drugs.

nitrogen flow. After cooling to 60–70 °C, 250 mL of petroleum ether were added. The precipitate obtained was filtered off, washed with petroleum ether, stirred with methanol, filtered off and dried. The compound obtained was used without purification.

*5.3. 8-Methyl-7-nitro-4-alkoxyquinolines **3**: general procedure*

A mixture of 5 mmol of **2**, 7.5 mmol of alkylating agent, 15 mL of *N,N*-dimethylformamide and 5 mmol of anhydrous potassium carbonate was heated at 80 °C for 3–5 h with stirring. Then 100 mL of water was added. The mixture was extracted with chloroform, dried over magnesium sulfate before the solvent was evaporated. The residue obtained was washed with ethyl ether under stirring and filtered off. **3a** was recrystallized from methanol, **3b** was recrystallized from ethyl ether and **3e** was recrystallized from absolute ethanol, and **3c,d,f–i** were recrystallized from chloroform.

*5.4. 4-Chloro-8-methyl-7-nitroquinoline **4***

A mixture of 1.02 g (5 mmol) of **2** and 15 mL of phosphorus oxychloride was heated at 80 °C for 3 h. After cooling to room

Table VII. Mean values of inhibitory indices for quinoline compounds.

Chemical series	Bacterial strains[a]				Mean I.I. for all of bacteria
	E.C.	E.A.	S.A.	M.S.	
3	41	16	40	52	37
5	49	36	33	49	42
8	30	21	17	42	28
10	35	29	30	33	32
Mean I.I. for all of series	39	26	30	44	

[a]E.C.: *Escherichia coli*; E.A.: *Enterobacter aerogenes*; S.A.: *Staphylococcus aureus*; M.S.: *Mycobacterium smegmatis*.

temperature, the mixture was poured into ice. The resulting solution was carefully alkalinized to pH 8–9 with aqueous ammonia before being extracted with chloroform. The organic phases were dried over calcium sulfate and the solvent was removed under reduced pressure. The crude mixture obtained was stirred in warm methanol in the presence of animal charcoal. After filtration, the solvent was removed and the residue was recrystallized from chloroform.

5.5. 4-Alkylamino-8-methyl-7-nitroquinolines ***5****: general procedure*

A stirred mixture of 4.5 mmol of **4** and 45 mmol of alkylamine was heated at 130–140 °C with stirring for 2 h. After cooling, the solution was neutralized with 10% aqueous potassium hydroxide. The precipitate obtained was filtered off, dissolved in chloroform before the solvent was removed by evaporation. Bases were recrystallized from chloroform, apart from **5d,e,i** that were purified as hydrochlorides.

5.6. 2,8-Dimethyl-4-quinolone ***7***

A mixture of 6 g (56 mmol) of *o*-toluidine, 7.28 g (56 mmol) of ethyl acetoacetate, 9.7 g (56 mmol) calcium sulfate, 30 mL of absolute ethanol and a few drops of acetic acid was heated at 80 °C with stirring. After 2 h, calcium sulfate was filtered off. The solvent was evaporated. Cyclization was achieved as described with **2**. The last precipitate was washed with ethyl ether and recrystallized from ethanol.

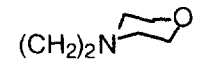
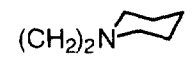
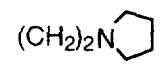
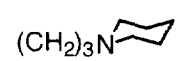
5.7. 2,8-Dimethyl-4-alkoxyquinolines ***8****: general procedure*

These compounds were prepared according to the procedure described with **3** but **8c,e,i** were purified as hydrochlorides by dissolving the bases in a mixture of hydrochloric ether acid and compounds were recrystallized from absolute ethanol.

5.8. 4-Thioquinolone ***9***

A mixture of 2.17 g (15 mmol) of 4-hydroxyquinoline and 3.33 g (7.5 mmol) of tetraphosphorus decasulfide and 40 mL of

Table VIII. Mean values of inhibitory indices for all of strains correlated with quinoline substituents in the quinoline series.

Substituents	Bacterial strains[a]				Mean I.I. for all of bacteria
	E.C.	E.A.	S.A.	M.S.	
a CH_2CH_3	37	31	29	42	35
b $(CH_2)_2N(CH_2CH_3)_2$	35	30	28	51	36
c $(CH_2)_2N(CH_3)_2$	40	32	31	42	36
d $(CH_2)_3N(CH_3)_2$	40	28	27	45	35
e $(CH_2)_2N[CH(CH_3)_2]_2$	35	18	29	54	34
f 	32	20	19	31	26
g 	40	24	46	48	40
h 	43	32	27	35	34
i 	42	18	33	42	34
Mean I.I. for all of the substituents	38	26	30	43	

[a]E.C.: *Escherichia coli*; E.A.: *Enterobacter aerogenes*; S.A.: *Staphylococcus aureus*; M.S.: *Mycobacterium smegmatis*.

Table IX. Comparison between similarly substituted derivatives from series **10**, **11** and **12**.

Compounds	*E. coli*	*S. aureus*	*M. smegmatis*	Mean I.I. for all of bacteria
11a	8	22	18	16
10a	43	32	49	41
12a	37	42	55	45
11b	7	12	26	15
10b	28	29	46	34
12b	34	32	59	42
11c	6	14	25	15
10c	36	33	31	33
12c	56	42	56	51

pyridine was heated at 110 °C with stirring for 3 h. After cooling to room temperature, the mixture was poured into 200 mL of water and extracted with chloroform. The solvent was evaporated and the residue washed with ethyl ether. The crude mixture was finally recrystallized from ethanol.

*5.9. 4-Alkylthioquinolines **10** and 4-alkylthiopyridines **11**: general procedure*

A mixture of 0.5 g of the starting compound (3.10 mmol) of **9** or 0.5 g of 4-thio-pyridinone (4.5 mmol), 10 mmol of alkylating agent, 30 mL of toluene, 15 mL of 50% aqueous potassium hydroxide was refluxed with stirring for 24–72 h. The organic layer was separated, washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was purified as hydrochloride.

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