

Synthesis and antibacterial activity of 2-substituted 5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives

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Summary — A series of 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines and 2-amino- and 2-(1-piperazinyl)-5-(1,2-diarylethyl)-4,6-dichloropyrimidines were synthesized *via* organozinc reagents. These new pyrimidine derivatives were tested against human bacterial flora. Biological tests showed that 5-[1-(4-chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine is very active against a wide range of bacterial flora of the axilla and foot, while 2-amino and 2-(1-piperazinyl)-4,6-dichloropyrimidine derivatives display a great selectivity against *Corynebacterium xerosis* and *Arcanobacterium haemolyticum* of the human axilla.

pyrimidine derivative / barbituric acid / antibacterial activity

Introduction

Various pyrimidine derivatives have been described with a wide range of pharmacological activities which are valuable for medical applications. For instance, the preparation and anticancer screening of ring-polychlorinated pyrimidines were reported by Gershon *et al* [1]. Trimethoprim or 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, which is active against Gram-positive and Gram-negative aerobic bacteria, was studied by Brogden *et al* [2]. Other authors such as Seydel *et al* showed that trimethoprim derivatives display different bactericidal effects against *Escherichia coli* and *Mycobacteria* [3, 4]. Giammanco *et al* tested brodimoprim or 2,4-diamino-5-(4-bromo-3,5-dimethoxybenzyl)pyrimidine and metioprim or 2,4-diamino-5-(4-methylthio-3,5-dimethoxybenzyl)pyrimidine against *Shigella* isolates [5]. More recently, brodimoprim for the treatment of bacterial respiratory tract infections was studied by Salmi *et al* [6].

We previously reported our studies on pyrimidine derivatives and described a simple method to synthesize 5-substituted barbituric acids *via* organozinc reagents. We show here that these 5-substituted

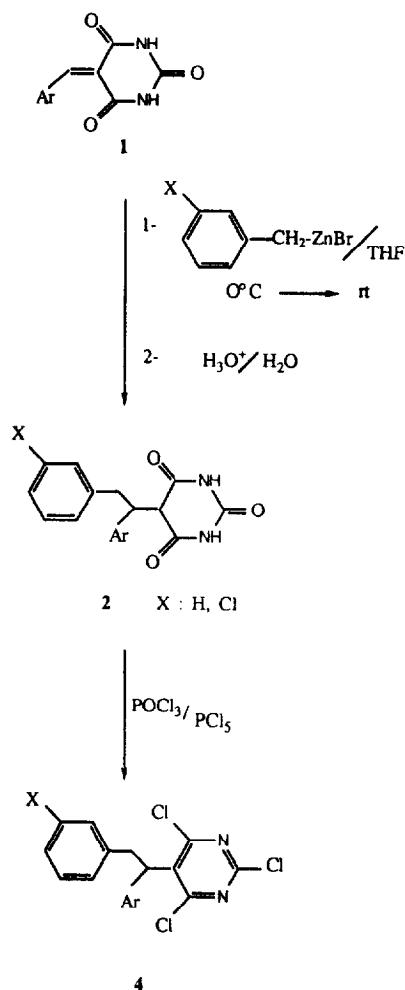
barbituric acids can be used as starting materials to prepare 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidine derivatives. From these trichloropyrimidines, we then obtained 2-amino- and 2-(1-piperazinyl)-5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives. These compounds and the series of trichloropyrimidines were tested against human bacterial flora.

Chemistry

Scheme 1 shows that 5-(1,2-diarylethyl)barbituric acids **2** were obtained following the 1,4-addition of benzylzinc bromide **3** to 5-benzylidenobarbituric acids **1** [7]. These 5-benzylidenobarbituric acids **1** are easily prepared by condensing barbituric acid with various aromatic aldehydes [8]. In our previous paper [7], we proved that the organozinc reagent **3** also undergoes hydrogen-metal exchange with both NH sites of the substrates **1**. The reaction therefore only leads to substantial yields of products **2** (table I) if three molecular equivalents of organozinc reagent **3** are used.

The reaction of the mixture of phosphorus oxychloride and phosphorus pentachloride with 5-(1,2-diarylethyl)barbituric acids **2** (scheme 1) gave the corresponding 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidine derivatives **4** (table II).

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Scheme 1. Synthesis of 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines **4**.

The ease with which the 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines **4** may be obtained renders them particularly useful as precursors for the synthesis of other pyrimidine derivatives. For instance, compound **4c** reacts at the reflux of the solvent with an excess of concentrated ammonium hydroxide resulting in the corresponding 2-amino derivative **5c** (table II) according to scheme 2.

The piperazinyl derivatives **6c** and **6f** were also prepared according to the procedure reported in scheme 2 by heating the corresponding trichloropyrimidines **4c** and **4f** (table II) with an excess of piperazine at reflux of the ethanol.

The product purity was checked on the basis of elution profiles in a capillary gas chromatography procedure, according to the conditions reported in the *Experimental protocols*, before biological tests.

Table I. 5-(1,2-Diarylethyl)barbituric acids **2**.

Compound	Ar	X	Yield ^a (%)	Molecular formula
2a	C ₆ H ₅	H	75	C ₁₈ H ₁₆ N ₂ O ₃ (308.3)
2b	3-ClC ₆ H ₄	H	70	C ₁₈ H ₁₅ ClN ₂ O ₃ (342.8)
2c	4-ClC ₆ H ₄	H	75	C ₁₈ H ₁₅ ClN ₂ O ₃ (342.8)
2d	2-BrC ₆ H ₄	H	70	C ₁₈ H ₁₅ BrN ₂ O ₃ (387.2)
2e	4-BrC ₆ H ₄	H	75	C ₁₈ H ₁₅ BrN ₂ O ₃ (387.2)
2f	4-ClC ₆ H ₄	Cl	86	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₃ (377.2)

^aYield after treatment with sodium hydroxide.

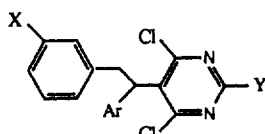
Pharmacology

For antibacterial activity research, the synthesized pyrimidine derivatives were tested on the germs which represent certain cutaneous microflora. Details of bacterial colonies are shown in table III. These results were obtained from human sampling of healthy or sick subjects. The minimal inhibitory concentrations (μg/ml) obtained with the nine 2-substituted 5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives against bacterial flora of the axilla and the foot are reported on table IV.

Results and discussion

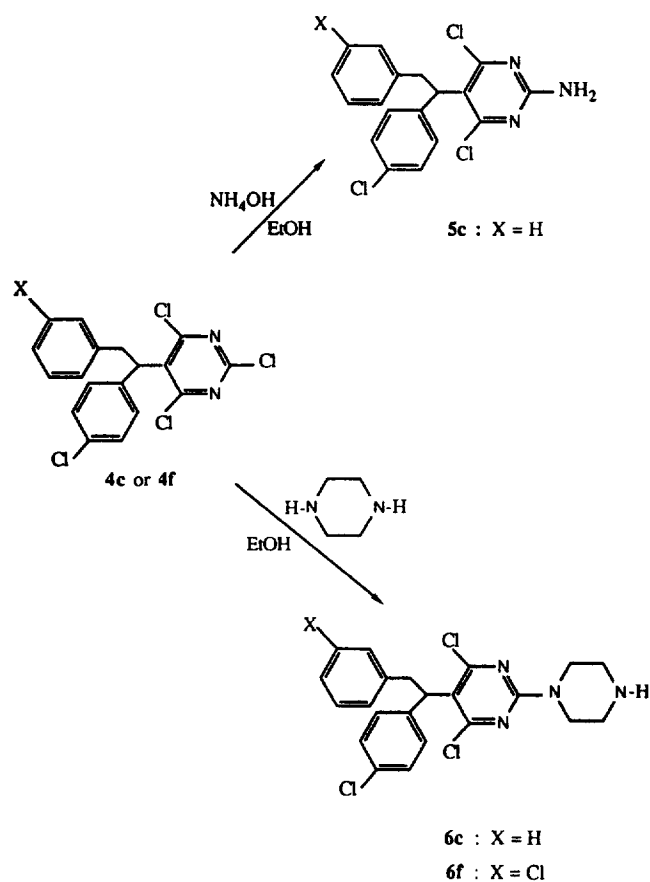
Scheme 1 shows a convenient method for the synthesis of 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidine derivatives **4** from 5-(1,2-diarylethyl)barbituric acids **2**.

The ¹H NMR spectrum at 200 MHz of 5-substituted barbituric acids **2** displays a doublet in the range of chemical shifts δ 3.40–3.50 ppm for COCHCO proton with a coupling constant ³*J* of about 3.2 Hz. The barbituric ring of compounds **2** exhibits broad singlets in the range of chemical shifts δ 8.0–10.0 ppm for the two NH protons. As expected these characteristic signals of the barbituric ring disappear in the NMR spectra of the corresponding trichloropyrimidines **4**. The ¹H NMR structures of the ethyl chain are characteristic of the 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines **4**. In particular, the tertiary proton exhibits a multiplet in the range of chemical shifts δ 3.80–4.50 ppm for compounds **2**, while its signal is a triplet in the range of chemical shifts δ 5.10–5.20 ppm with a coupling constant ³*J* of about 8.5 Hz for compounds

Table II. 2-Substituted-5-(1,2-diarylethyl)-4,6-dichloropyrimidines **4** (Y = Cl), **5** (Y = NH₂) and **6** (Y = 1-piperazinyl).


Compound	Ar	X	Y	Yield ^a (%)	Molecular formula	Analyses ^b
4a	C ₆ H ₅	H	Cl	65	C ₁₈ H ₁₃ Cl ₃ N ₂ (363.7)	C, H, Cl, N
4b	3-ClC ₆ H ₄	H	Cl	58	C ₁₈ H ₁₂ Cl ₄ N ₂ (398.1)	C, H, Cl, N
4c	4-ClC ₆ H ₄	H	Cl	50	C ₁₈ H ₁₂ Cl ₄ N ₂ (398.1)	C, H, Cl, N
4d	2-BrC ₆ H ₄	H	Cl	45	C ₁₈ H ₁₂ Cl ₃ BrN ₂ (442.6)	C, H, Br, Cl, N
4e	4-BrC ₆ H ₄	H	Cl	58	C ₁₈ H ₁₂ Cl ₃ BrN ₂ (442.6)	C, H, Br, Cl, N
4f	4-ClC ₆ H ₄	Cl	Cl	53	C ₁₈ H ₁₁ Cl ₅ N ₂ (432.6)	C, H, Cl, N
5c	4-ClC ₆ H ₄	H	NH ₂	84	C ₁₈ H ₁₄ Cl ₃ N ₃ (378.7)	C, H, Cl, N
6c	4-ClC ₆ H ₄	H	R	74	C ₂₂ H ₂₁ Cl ₃ N ₄ (447.8)	C, H, Cl, N
6f	4-ClC ₆ H ₄	Cl	R	84	C ₂₂ H ₂₀ Cl ₄ N ₄ (482.2)	C, H, Cl, N

R = 1-piperazinyl. ^aYield after recrystallization; ^banalyses indicated by the symbols of the elements were within $\pm 0.4\%$ of theoretical values.

**Scheme 2.** Synthesis of 2-amino-5-[1-(4-chlorophenyl)-2-phenylethyl]-4,6-dichloropyrimidine **5c**, 2-(1-piperazinyl)-5-[1-(4-chlorophenyl)-2-phenylethyl]-4,6-dichloropyrimidine **6c** and 2-(1-piperazinyl)-5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]-4,6-dichloropyrimidine **6f**.**Table III.** References of axillary and foot bacterial flora species used for *in vitro* experiments and the laboratories which furnished them.

Flora	Reference
Axillary bacterial flora^a	
<i>Staphylococcus xylosus</i>	CIP 81.66 ATCC 29.971
<i>Staphylococcus epidermidis</i>	CIP 55.109 NCTC 98.55
<i>Staphylococcus haemolyticus</i>	CIP 81.56 ATCC 29.970
<i>Corynebacterium xerosis</i>	CIP 52.16
<i>Micrococcus luteus</i>	CIP 53.45, ATCC 93.41
<i>Arcanobacterium haemolyticum</i>	CIP 103.370T, ATCC 93.45
Foot bacterial flora^b	
<i>Staphylococcus epidermidis</i>	1S2
<i>Staphylococcus hominis</i>	8S2
<i>Staphylococcus cohnii</i>	6S3
<i>Corynebacterium</i> sp g C	3C3
<i>Corynebacterium</i> sp g B	16C3
<i>Corynebacterium</i> sp g D2	19C1
<i>Micrococcus luteus</i>	1C5
<i>Micrococcus sedentarius</i>	7B5
<i>Acinetobacter</i> sp	H5DC1
<i>Moraxella</i> sp	H7SV1
<i>Alcaligenes</i> sp	H5DC1

^aObtained from the Pasteur Institute (Paris); ^bbacteria from Dr Marshall, Laboratory of Bacteriology, University of Leeds (UK); obtained from healthy feet.

Table IV. Pharmacological evaluation of the 2-substituted 5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives.

	4a	4b	4c	4d	4e	4f	5c	6c	6f
Axillary bacterial flora									
<i>Staphylococcus xylosus</i>	>1000	>1000	20	>1000	300	>500	100	100	100
<i>Staphylococcus epidermidis</i>	>1000	>1000	100	>1000	300	>500	100	100	75
<i>Staphylococcus haemolyticus</i>	>1000	>1000	100	>1000	500	>500	100	100	50
<i>Corynebacterium xerosis</i>	>1000	>1000	20	>1000	300	>500	30	30	30
<i>Micrococcus luteus</i>	>1000	>1000	20	>1000	500	>500	100	100	100
<i>Arcanobacterium haemolyticum</i>	>1000	>1000	10	>1000	100	300	10	10	10
Foot bacterial flora									
<i>Staphylococcus epidermidis</i>	>1000	>1000	>100	>1000	500	>500	100	100	75
<i>Staphylococcus hominis</i>	>1000	>1000	100	>1000	500	>500	100	100	75
<i>Staphylococcus cohnii</i>	>1000	>1000	100	>1000	500	>500	100	100	75
<i>Corynebacterium</i> sp g C	>1000	>1000	100	>1000	500	>500	100	100	75
<i>Corynebacterium</i> sp g B	>1000	>1000	30	>1000	500	>500	100	100	50
<i>Corynebacterium</i> sp g D ₂	>1000	>1000	30	>1000	300	>500	100	50	50
<i>Micrococcus luteus</i>	>1000	>1000	20	>1000	500	>500	100	100	75
<i>Micrococcus sedentarius</i>	>1000	>1000	30	>1000	300	>300	100	100	75
<i>Acinetobacter</i> sp	>1000	>1000	>1000	>1000	>1000	>500	>500	50	30
<i>Moraxella</i> sp	>1000	>1000	300	>1000	>1000	>500	500	100	50
<i>Alcaligenes</i> sp	>1000	>1000	1000	>1000	>1000	>500	>500	>500	>500

Values give the minimum inhibitory concentrations (MIC in µg/ml) obtained with nine 2-substituted 5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives tested *in vitro* against six species of axillary bacterial flora and 11 species of foot bacterial flora.

4, except for the derivative 4d, which shows a doublet of doublets at δ 5.04 ppm with coupling constants $^3J = 7.1$ and 9.2 Hz. ^1H NMR analysis is not sufficient to completely characterize the structure of amino 5c and piperazinyl 6c and 6f derivatives. In this case, it was necessary to confirm their structures by mass spectrometry as shown in the *Experimental protocols*.

Among the six trichloropyrimidines 4 used for biological tests, 5-[1-(4-chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4c is very active against human bacterial flora. 5-[1-(4-Bromophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4e and 5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine 4f are also active against the same flora. Comparison with the other derivatives 4 seems to prove that the *para*-halogenated phenyl ring in position 1 of the ethyl chain favors this biological activity. The chlorinated compound 4c gives better results than the corresponding brominated analogue 4e. 2-Amino-5-[1-(4-chlorophenylethyl)-2-phenylethyl]-4,6-dichloropyrimidine 5c, 2-(1-piperazinyl)-5-[1-(4-chlorophenyl)-2-phenylethyl]-4,6-dichloropyrimidine 6c and 2-(1-piperazinyl)-5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]-4,6-dichloropyrimidine 6f are also very active against bacterial flora with a strong selective activity with *Corynebacterium xerosis* and *Arcanobacterium haemolyticum*.

There are several compounds which are remarkable for their antibacterial properties. Some of our compounds are considered for two microflora areas. In the

case of foot flora, according to Marshall *et al* [10], the exoenzyme bacteria responsible for the nauseous odors are inhibited, particularly in the case of compounds 4c, 5c, 6c and 6f. In the case of the axilla, a very special flora is produced along with other germs *C. xerosis* [11–13]. This aerobic bacterium plays a particular role in the excretion of an enzyme: 5- α -reductase is responsible for development of nauseous sterols [14–17]. Compounds 4c, 5c, 6c and 6f are all active against this germ. These four products are also very active against *A. haemolyticum*.

In conclusion, in this work we have examined the most effective products with a structure–activity relationship study. In certain conditions, the addition of the piperazine ring on position 2 of the pyrimidine nucleus (compounds 6c and 6f) increases the antibacterial efficacy. In this investigation, we showed that pyrimidine derivatives 4c and 5c, active against the undesirable bacteria of both the foot and the axilla, could be proposed for their deodorant properties. Moreover, these preliminary satisfactory results should encourage the synthesis of new pyrimidine derivatives for improving antibacterial properties. Their toxicity remains to be tested.

Experimental protocols

Infrared spectra were recorded on a Perkin-Elmer IR 1310 spectrometer and ultraviolet spectra on a Secomam S 1000 spectrometer. ^1H -NMR spectra were recorded on a Brüker AM 200 (200 MHz) spectrometer using CDCl_3 , acetone- d_6 or

DMSO- d_6 as solvent and tetramethylsilane as internal standard; mass spectra were obtained on a Hewlett Packard HP 5989A spectrometer (electronic impact at 70 eV). Thin-layer chromatographic analysis was conducted using silica-gel 60F₂₅₄ TLC plates from Merck and compounds were revealed by UV detection. Melting points were not corrected. The purity of the synthesized compounds was verified by gas chromatography (GC, HP 5890A, II) coupled with mass spectrometer.

A 25 m x 0.2 mm fused silica capillary column OVI (HP1) Hewlett Packard was directly inserted into the ion source of the HP quadrupole mass spectrometer through a heated (250°C) interface box. Helium was used as a carrier gas, with a flow rate through the column of 0.7 ml/min. The temperature remained at 70°C for 1 min and was then programmed up to 300°C at 10°C/min. The final time was 60 min. The temperature of the ion source was 200°C and the energy of bombarding electrons was 70 eV.

Elemental analyses were within $\pm 0.4\%$ of theoretical values and were determined in the Laboratory of Service Central d'Analyse du CNRS (Vernaison, France).

5-Benzylidene barbituric acids 1. General procedure

The 5-benzylidenearbituric acids were obtained according to a described method [8] by condensing the aromatic aldehyde (50 mmol) with barbituric acid from Janssen (6.4 g, 50 mmol) dissolved in hot water (60 ml). The precipitate was filtered off, washed with small quantities of hot water and dried. Compounds 1 were prepared in 90–95% yields.

5-Benzylidenearbituric acid 1a. The reaction was performed with benzaldehyde from Janssen (5.3 g, 50 mmol) to yield compound 1a (10.2 g, 95% yield); IR (KBr) 3210 (NH), 1740, 1670 (C=O), 1580, 1560 (aromatic ring) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 7.43–7.58 (m, 3H arom); 8.08 (d, 2H arom, $^3J = 7.8$ Hz); 8.29 (s, 1H, Ar-CH=); 11.24 (s, 1H, NH); 11.40 (s, 1H, NH).

5-(3-Chlorobenzylidene)barbituric acid 1b. The reaction was performed with 3-chlorobenzaldehyde from Janssen (7.0 g, 50 mmol) to yield compound 1b (11.4 g, 91% yield); IR (KBr) 3240 (NH), 1640 (C=O), 1595, 1575, 1555 (aromatic ring) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 7.44–7.60 (m, 2H arom); 7.86 (d, 1H arom, $^3J = 7.3$ Hz); 8.16 (s, 1H arom); 8.23 (s, 1H, ArCH=); 11.28 (s, 1H, NH); 11.43 (s, 1H, NH).

5-(4-Chlorobenzylidene)barbituric acid 1c. The reaction was performed with 4-chlorobenzaldehyde from Janssen (7.0 g, 50 mmol) to yield compound 1c (11.5 g, 92% yield); IR (KBr) 3270 (NH), 1755, 1700, 1645 (C=O), 1593, 1570, 1547 (aromatic ring) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 7.29 (m, 2H arom, $^3J = 8.5$ Hz); 7.84 (d, 2H arom, $^3J = 8.5$ Hz); 8.00 (s, 1H, ArCH=); 11.02 (s, 1H, NH); 11.17 (s, 1H, NH).

5-(2-Bromobenzylidene)barbituric acid 1d. The reaction was performed with 2-bromobenzaldehyde from Janssen (9.2 g, 50 mmol) to yield compound 1d (13.2 g, 90% yield); IR (KBr) 3250, 3200 (NH), 1740, 1680 (C=O), 1595, 1580 (aromatic ring) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 7.38 (m, 2H arom); 7.70 (d, 2H arom, $^3J = 8.0$ Hz); 8.23 (s, 1H, Ar-CH=); 11.25 (s, 1H, NH); 11.48 (s, 1H, NH).

5-(4-Bromobenzylidene)barbituric acid 1e. The reaction was performed with 4-bromobenzaldehyde from Janssen (9.2 g, 50 mmol) to yield compound 1e (13.7 g, 93% yield); IR (KBr) 3210 (NH), 1755, 1705, 1675 (C=O), 1595, 1570, 1550 (aromatic ring) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 7.67 (d, 2H arom, $^3J = 8.5$ Hz); 7.98 (d, 2H arom, $^3J = 8.5$ Hz); 8.61 (s, 1H, Ar-CH=); 11.26 (s, 1H, NH); 11.41 (s, 1H, NH).

Organozinc reagents 3. General procedure

According to the procedure described by Gaudemar [9] benzylzinc bromide or 3-chlorobenzylzinc bromide was obtained by reaction between benzyl bromide from Aldrich (7.18 g, 42 mmol) or 3-chlorobenzyl bromide from Aldrich (8.63 g, 42 mmol) and zinc from Labosi (2.75 g, 42 mmol) in dry THF (20 ml), blanketed under nitrogen gas at 25–30°C. The organozinc derivatives 3 were used *in situ* for the synthesis of compounds 2a–f.

5-(1,2-Diarylethyl)barbituric acids 2. General procedure

According to a previously described method [7], a solution of the benzylzinc bromide 3 (42 mmol) in THF was cooled at 0°C and the 5-benzylidenearbituric acid 1 (10 mmol) was added with stirring and cooling. The temperature of the mixture quickly rose to 30°C. When it began to fall the cooling bath was removed. After stirring at room temperature for 1 h, the mixture was hydrolysed with crushed ice (30 g) and concentrated hydrochloric acid (5 ml); ether (30 ml) was then added. The two phases were separated and the aqueous layer was extracted with ether (4 x 20 ml). The combined organic phase was washed with brine (50 ml), dried with anhydrous sodium sulfate and evaporated to give the crude solid product 2. For purification, the crude product was dissolved in aqueous 2 N sodium hydroxide (40 ml). The aqueous layer was washed with ether (40 ml). Strong hydrochloric acid (10 ml) was then added to precipitate product 2. This product was dissolved in ether (100 ml), washed with brine (4 x 20 ml) and dried with anhydrous sodium sulfate. The solvent was removed under vacuum.

5-(1,2-Diphenylethyl)barbituric acid 2a. The reaction of benzylzinc bromide 3 (42 mmol) with 5-benzylidenearbituric acid 1a (2.16 g, 10 mmol) yielded 5-(1,2-diphenylethyl)barbituric acid 2a (2.31 g, 75% yield); mp 98–100°C; IR (KBr) 3215 (NH), 3100, 3020 (CH arom), 2910, 2840 (CH, CH₂), 1705, 1690 (C=O), 1600, 1495 (aromatic rings) cm^{-1} ; UV (EtOH) 214, 269 nm; $^1\text{H-NMR}$ (acetone- d_6) δ ppm: 3.11 (dd, 1H, $^2J = 13.6$ Hz, $^3J = 5.7$ Hz, Ar-CH); 3.39 (d, 1H, $^3J = 3.1$ Hz, CO-CH-CO); 3.59 (dd, 1H, $^2J = 13.6$ Hz, $^3J = 10.6$ Hz, Ar-CH); 3.85 (m, 1H, Ar-CH); 7.18 (m, 5H arom); 7.34 (s, 5H arom); 9.31 (broad s, 2H, 2NH).

5-[1-(3-Chlorophenyl)-2-phenylethyl]barbituric acid 2b. The reaction of benzylzinc bromide 3 (42 mmol) with 5-(3-chlorobenzylidene)barbituric acid 1b (2.50 g, 10 mmol) yielded 5-[1-(3-chlorophenyl)-2-phenylethyl]barbituric acid 2b (2.40 g, 70% yield); mp 136–138°C; IR (KBr) 3210 (NH), 3080, 3010 (CH arom), 2940, 2845 (CH, CH₂), 1760, 1705 (C=O), 1595, 1560 (aromatic rings) cm^{-1} ; UV (EtOH) 216, 267 nm; $^1\text{H-NMR}$ (acetone- d_6) δ ppm: 3.09 (dd, 1H, $^2J = 13.7$ Hz, $^3J = 6.7$ Hz, Ar-CH); 3.45 (d, 1H, $^3J = 3.6$ Hz, CO-CH-CO); 3.50 (dd, 1H, $^2J = 13.7$ Hz, $^3J = 9.9$ Hz, Ar-CH); 3.82 (m, 1H, Ar-CH); 6.90–7.30 (m, 9H arom); 9.90 (broad s, 2H, 2NH).

5-[1-(4-Chlorophenyl)-2-phenylethyl]barbituric acid 2c. The reaction of benzylzinc bromide 3 (42 mmol) with 5-(4-chlorobenzylidene)barbituric acid 1c (2.50 g, 10 mmol) yielded 5-[1-(4-chlorophenyl)-2-phenylethyl]barbituric acid 2c (2.57 g, 75% yield); mp 124–126°C; IR (KBr) 3200 (NH), 3045 (CH arom), 2920, 2840 (CH, CH₂), 1755, 1705, 1695 (C=O), 1595, 1570, 1490 (aromatic rings) cm^{-1} ; UV (EtOH) 209, 212, 216, 267 nm; $^1\text{H-NMR}$ (acetone- d_6) δ ppm: 3.07 (dd, 1H, $^2J = 13.8$ Hz, $^3J = 6.7$ Hz, Ar-CH); 3.42–3.55 (m, 2H, Ar-CH and CO-CH-CO); 3.80 (m, 1H, Ar-CH); 6.89–7.27 (m, 9H arom); 9.85 (broad s, 2H, 2NH).

5-[1-(2-Bromophenyl)-2-phenylethyl]barbituric acid 2d. The reaction of benzylzinc bromide **3** (42 mmol) with 5-(2-bromobenzylidene)barbituric acid **1d** (2.95 g, 10 mmol) yielded 5-[1-(2-bromophenyl)-2-phenylethyl]barbituric acid **2d** (2.71 g, 70% yield); mp 84–88°C; IR (KBr) 3220 (NH), 3080, 3010 (CH arom), 2910, 2840 (CH, CH₂), 1750, 1710, 1690 (C=O), 1595, 1492 (aromatic rings) cm⁻¹; UV (EtOH) 209, 267 nm; ¹H-NMR (CDCl₃) δ ppm: 3.07 (dd, 1H, ²J = 14.0 Hz, ³J = 6.6 Hz, Ar-CH); 3.28 (dd, 1H, ²J = 14.0 Hz, ³J = 9.8 Hz, Ar-CH); 3.52 (d, 1H, ³J = 3.2 Hz, CO-CH-CO); 4.53 (m, 1H, Ar-CH); 7.00–7.70 (m, 9H arom); 8.26 (broad s, 1H, NH); 8.40 (broad s, 1H, NH).

5-[1-(4-Bromophenyl)-2-phenylethyl]barbituric acid 2e. The reaction of benzylzinc bromide **3** with 5-(4-chlorobenzylidene)barbituric acid **1e** (2.95 g, 10 mmol) yielded 5-[1-(4-bromophenyl)-2-phenylethyl]barbituric acid **2e** (2.90 g, 75% yield); mp 110–114°C; UV (EtOH) 216, 264 nm; IR (KBr) 3210 (NH), 3040, 3020 (CH arom), 2920, 2830 (CH, CH₂), 1750, 1700 (C=O), 1590, 1565, 1485 (aromatic rings) cm⁻¹; ¹H-NMR (CDCl₃) δ ppm: 3.10 (dd, 1H, ²J = 13.8 Hz, ³J = 5.9 Hz, Ar-CH); 3.43 (d, 1H, ³J = 3.2 Hz, CO-CH-CO); 3.54 (dd, 1H, ²J = 13.8 Hz, ³J = 11.0 Hz, Ar-CH); 3.89 (m, 1H, Ar-CH); 7.05 (d, 2H arom, ³J = 8.5 Hz); 7.10–7.25 (m, 5H arom); 7.35 (d, 2H arom, ³J = 8.5 Hz); 7.86 (broad s, 1H, NH); 7.90 (broad s, 1H, NH).

5-[1-(4-Chlorophenyl)-2-(3-chlorophenyl)ethyl]barbituric acid 2f. The reaction of 3-chlorobenzylzinc bromide **3** with 5-(4-chlorobenzylidene)barbituric acid **1f** (2.50 g, 10 mmol) yielded 5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]barbituric acid **2f** (3.24 g, 86% yield); mp 118–122°C; UV (EtOH) 212, 216, 265 nm; IR (CHCl₃) 3210 (NH), 3100 (CH arom), 2910, 2860 (CH, CH₂), 1705 (C=O), 1595, 1570, 1490 (aromatic rings) cm⁻¹; ¹H-NMR (CDCl₃) δ ppm: 3.08 (dd, 1H, ²J = 13.8 Hz, ³J = 6.0 Hz, Ar-CH); 3.41 (d, 1H, ³J = 3.2 Hz, CO-CH-CO); 3.54 (dd, 1H, ²J = 13.8 Hz, ³J = 10.7 Hz, Ar-CH); 3.86 (m, 1H, Ar-CH); 7.08 (d, 2H arom, ³J = 8.5 Hz); 7.17 (m, 4H arom); 7.32 (d, 2H arom, ³J = 8.5 Hz); 7.75 (broad s, 2H, 2NH).

5-(1,2-Diarylethyl)-2,4,6-trichloropyrimidines **4**. General procedure

According to a previously described method [1], a mixture of barbituric acid **2** (5 mmol) and phosphorus oxychloride from Prolabo (1.53 g, 10 mmol) was heated under reflux (105°C) overnight. After cooling to room temperature, phosphorus pentachloride from Janssen (3.12 g, 15 mmol) was added. Refluxing was then continued overnight. After cooling, the reaction mixture was poured onto ice and allowed to stand 30 min. Product **4** was extracted with ether (3 × 20 ml), decolorized with charcoal and then filtered. The organic layer was treated with 2 N sodium hydroxide (10 ml) and washed with brine until neutrality. The organic phase was then dried with anhydrous sodium sulfate and the solvent was removed. The residue was purified by recrystallization.

5-(1,2-Diphenylethyl)-2,4,6-trichloropyrimidine 4a. The reaction with barbituric acid **2a** (1.54 g) yielded 5-(1,2-diphenylethyl)-2,4,6-trichloropyrimidine **4a** (1.18 g, 65% yield); GC/MS: *R*_t = 32 min; mp 128–130°C (EtOH); IR (KBr) 3020 (CH arom), 2930 (CH, CH₂), 1600, 1520, 1495 (aromatic rings), 1450 (CH, CH₂) cm⁻¹; UV (EtOH) 209, 270 nm; ¹H-NMR (CDCl₃) δ ppm: 3.59 (d, 2H, ³J = 8.4 Hz, Ar-CH₂); 5.20 (t, 1H, ³J = 8.4 Hz, Ar-CH); 7.00–7.31 (m, 10H arom); MS *m/z* M⁺: 362 (9.3%, C₁₈H₁₃N₂³⁵Cl₃⁺); M⁺ + 2: 364 (8.9%, C₁₈H₁₃N₂³⁵Cl₃³⁷Cl⁺); M⁺ + 4: 366 (3%, C₁₈H₁₃N₂³⁵Cl₃³⁷Cl₂⁺); M⁺ + 6: 368 (5%, C₁₈H₁₃N₂³⁷Cl₃⁺); 91 (100%, C₇H₇⁺); 271 (14.7%, C₁₁H₆N₂³⁵Cl₃⁺); 273 (14.6%, C₁₁H₆N₂³⁵Cl₂³⁷Cl⁺); 65 (12.2%, C₅H₅⁺).

5-[1-(3-Chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4b. The reaction with barbituric acid **2b** (1.71 g) yielded **4b** (1.15 g, 58% yield); mp 120–122°C (EtOH); IR (KBr) 3020 (CH arom), 2920 (CH, CH₂), 1590, 1560, 1520, 1490 (aromatic rings), 1450 (CH, CH₂) cm⁻¹; UV (EtOH) 270 nm; ¹H-NMR (CDCl₃) δ ppm: 3.55 (d, 2H, ³J = 8.5 Hz, Ar-CH₂); 5.15 (t, 1H, ³J = 8.5 Hz, Ar-CH); 7.10–7.36 (m, 9H arom); MS *m/z* M⁺: 396 (3%, C₁₈H₁₂N₂³⁵Cl₄⁺); M⁺ + 2: 398 (4.1%, C₁₈H₁₂N₂³⁵Cl₃³⁷Cl⁺); M⁺ + 4: 400 (2%, C₁₈H₁₂N₂³⁵Cl₂³⁷Cl₂⁺); M⁺ + 6: 402 (0.4%, C₁₈H₁₂N₂³⁵Cl₃³⁷Cl₃⁺); 91 (100%, C₇H₇⁺); 65 (7.6%, C₅H₅⁺).

5-[1-(4-Chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4c. The reaction with barbituric acid **2c** (1.71 g) yielded **4c** (1.0 g, 50% yield); mp 142–143°C (EtOH); silica-gel preparative TLC (*n*-hexane/CHCl₃: 80/20; *R*_f = 0.57); GC/MS: *R*_t = 24.9 min; IR (KBr) 3030 (CH arom), 2930 (CH, CH₂), 1600, 1525, 1495 (aromatic rings), 1450 (CH, CH₂) cm⁻¹; UV (EtOH) 270 nm; ¹H-NMR (CDCl₃) δ ppm: 3.58 (d, 2H, ³J = 8.6 Hz, Ar-CH₂); 5.14 (t, 1H, ³J = 8.6 Hz, Ar-CH); 7.00–7.36 (m, 9H arom); MS *m/z* M⁺: 396 (2.8%, C₁₈H₁₂N₂³⁵Cl₄⁺); M⁺ + 2: 398 (3.9%, C₁₈H₁₂N₂³⁵Cl₃³⁷Cl⁺); M⁺ + 4: 400 (1.8%, C₁₈H₁₂N₂³⁵Cl₂³⁷Cl₂⁺); M⁺ + 6: 402 (0.4%, C₁₈H₁₂N₂³⁵Cl₃³⁷Cl₃⁺); 91 (100%, C₇H₇⁺); 305 (6.9%, C₁₁H₅N₂³⁵Cl₄⁺); 307 (8.5%, C₁₁H₅N₂³⁵Cl₃³⁷Cl⁺); 309 (4%, C₁₁H₅N₂³⁵Cl₂³⁷Cl₂⁺); 174 (4.8%, C₁₀H₅N³⁵Cl⁺); 65 (12.2%, C₅H₅⁺).

5-[1-(2-Bromophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4d. The reaction with barbituric acid **2d** (1.94 g) yielded **4d** (1.0 g, 45% yield); mp 152–154°C (EtOH); GC/MS: *R*_t = 25.3 min; IR (KBr) 3010 (CH arom), 2910 (CH, CH₂), 1600, 1560, 1510, 1490 (aromatic rings), 1455 (CH, CH₂) cm⁻¹; UV (EtOH) 208, 270 nm; ¹H-NMR (CDCl₃) δ ppm: 3.48 (d, 1H, ³J = 9.2 Hz, Ar-CH); 3.49 (d, 1H, ³J = 7.1 Hz, Ar-CH); 5.04 (dd, 1H, ³J = 7.1 Hz and 9.2 Hz, Ar-CH); 7.00–7.18 (m, 6H arom); 7.35 (t, 1H arom, ³J = 7.9 Hz, ⁴J = 1.4 Hz); 7.46 (dd, 1H arom, ³J = 7.9 Hz, ⁴J = 1.4 Hz); 7.59 (dd, 1H arom, ³J = 7.8 Hz, ⁴J = 1 Hz); MS *m/z* M⁺: 440 (3%, C₁₈H₁₂N₂⁷⁹Br³⁵Cl₃⁺); M⁺ + 2: 442 (5.9%, C₁₈H₁₂N₂⁷⁹Br³⁵Cl₂³⁷Cl⁺ and/or C₁₈H₁₂N₂⁸¹Br³⁵Cl₃⁺); M⁺ + 4: 444 (3.8%, C₁₈H₁₂N₂⁸¹Br³⁵Cl₂³⁷Cl⁺ and/or C₁₈H₁₂N₂⁷⁹Br³⁵Cl₃³⁷Cl₂⁺); M⁺ + 6: 446 (1%, C₁₈H₁₂N₂⁸¹Br³⁵Cl₃³⁷Cl₂⁺ and/or C₁₈H₁₂N₂⁷⁹Br³⁷Cl₃⁺); M⁺ + 8: 448 (0.1%, C₁₈H₁₂N₂⁸¹Br³⁷Cl₃⁺); 91 (100%, C₇H₇⁺); 351 (3.8%, C₁₁H₅N₂⁸¹Br³⁵Cl₃⁺ and/or C₁₁H₅N₂⁷⁹Br³⁵Cl₂³⁷Cl₂⁺); 235 (7.6%, C₁₁H₅N₂³⁵Cl₂⁺); 237 (5%, C₁₁H₅N₂³⁵Cl₃³⁷Cl⁺); 174 (6.4%, C₁₀H₅N³⁵Cl⁺); 65 (9.3%, C₅H₅⁺).

5-[1-(4-Bromophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4e. The reaction with barbituric acid **2e** (1.94 g) yielded **4e** (1.28 g, 58% yield); mp 133–134°C (EtOH); GC/MS: *R*_t = 25.3 min; IR (KBr) 3030 (CH arom), 2930 (CH, CH₂), 1605, 1515, 1490 (aromatic rings), 1450 (CH, CH₂) cm⁻¹; UV (EtOH) 208, 267 nm; ¹H-NMR (CDCl₃) δ ppm: 3.55 (d, 2H, ³J = 8.3 Hz, Ar-CH₂); 5.12 (t, 1H, ³J = 8.3 Hz, Ar-CH); 6.94–7.19 (m, 7H arom); 7.39 (d, 2H arom, ³J = 8.5 Hz); MS *m/z* M⁺: 440 (1.6%, C₁₈H₁₂N₂⁷⁹Br³⁵Cl₃⁺); M⁺ + 2: 442 (3.1%, C₁₈H₁₂N₂⁷⁹Br³⁵Cl₂³⁷Cl⁺ and/or C₁₈H₁₂N₂⁸¹Br³⁵Cl₃⁺); M⁺ + 4: 444 (2%, C₁₈H₁₂N₂⁸¹Br³⁵Cl₂³⁷Cl⁺ and/or C₁₈H₁₂N₂⁷⁹Br³⁵Cl₃³⁷Cl₂⁺); M⁺ + 6: 446 (0.6%, C₁₈H₁₂N₂⁸¹Br³⁵Cl₃³⁷Cl₂⁺ and/or C₁₈H₁₂N₂⁷⁹Br³⁷Cl₃⁺); M⁺ + 8: 448 (0.06%, C₁₈H₁₂N₂⁸¹Br³⁷Cl₃⁺); 91 (100%, C₇H₇⁺); 349 (4.1%, C₁₁H₅N₂⁷⁹Br³⁵Cl₃⁺); 351 (8.1%, C₁₁H₅N₂⁸¹Br³⁵Cl₃⁺ and/or C₁₁H₅N₂⁷⁹Br³⁵Cl₂³⁷Cl₂⁺); 353 (5.1%, C₁₁H₅N₂⁸¹Br³⁵Cl₂³⁷Cl⁺ and/or C₁₁H₅N₂⁷⁹Br³⁵Cl₃³⁷Cl₂⁺); 235 (7.4%, C₁₁H₅N₂³⁵Cl₂⁺); 237 (4.8%, C₁₁H₅N₂³⁵Cl₃³⁷Cl⁺); 174 (5.5%, C₁₀H₅N³⁵Cl⁺); 65 (10.8%, C₅H₅⁺).

5-[1-(4-Chlorophenyl)-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine 4f. The reaction with barbituric acid **2f** (1.88 g) yielded **4f** (1.15 g, 53% yield); GC/MS: $R_t = 26.1$ min; IR (KBr) 3025 (CH arom), 2920 (CH₂, CH), 1600, 1550, 1495 (aromatic rings), 1450 (CH, CH₂) cm⁻¹; UV (EtOH) 270 nm; ¹H-NMR (CDCl₃) δ ppm: 3.53 (d, 2H, ³J = 8.4 Hz, Ar-CH₂); 5.13 (t, 1H, ³J = 8.4 Hz, Ar-CH); 6.86–7.29 (m, 8H arom); MS m/z M⁺: 430 (8.5%, C₁₈H₁₁N₃³⁵Cl₅⁺); M⁺ + 2: 432 (13.6%, C₁₈H₁₁N₃³⁵Cl₄³⁷Cl⁺); M⁺ + 4: 434 (8.7%, C₁₈H₁₁N₃³⁵Cl₃³⁷Cl₂⁺); M⁺ + 6: 436 (2.7%, C₁₈H₁₁N₃³⁵Cl₂³⁷Cl₃⁺); M⁺ + 8: 438 (0.6%, C₁₈H₁₁N₃³⁵Cl³⁷Cl₄⁺); 305 (76%, C₁₁H₅N₃³⁵Cl₄⁺); 307 (100%, C₁₁H₅N₃³⁵Cl₃³⁷Cl⁺); 309 (48.4%, C₁₁H₅N₃³⁵Cl₂³⁷Cl₂⁺); 311 (10.4%, C₁₁H₅N₃³⁵Cl³⁷Cl₃⁺); 269 (8.3%, C₁₁H₅N₃³⁵Cl₃⁺); 271 (8.8%, C₁₁H₅N₃³⁵Cl₂³⁷Cl⁺); 125 (16.9%, C₇H₇³⁵Cl⁺); 127 (5.6%, C₇H₇³⁷Cl⁺).

2-Amino-5-[1-(4-chlorophenyl)-2-phenylethyl]-4,6-dichloropyrimidine 5c

5-[1-(4-Chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4c (184 mg, 462 μ mol) was stirred at reflux for 15 h with 28% ammonium hydroxide (10 ml) and ethanol (35 ml). The aqueous layer was then extracted with chloroform (6 x 20 ml). The combined organic layer was washed with brine (5 x 10 ml) and dried with Na₂SO₄. The solvent was evaporated and the residue recrystallized from acetone. Product **5c** (146 mg, 385 μ mol) was obtained in 84% yield; GC/MS: $R_t = 27.2$ min; IR (KBr) 3317, 3190 (NH₂), 3032 (CH arom), 2968, 2937 (CH, CH₂), 1632, 1568, 1552, 1540, 1496 (aromatic rings) cm⁻¹; ¹H-NMR (CDCl₃) δ ppm: 3.49 (d, 2H, ³J = 8.1 Hz, Ar-CH₂); 4.98 (t, 1H, ³J = 8.1 Hz, Ar-CH); 5.24 (s, 2H, NH₂), 6.95–7.65 (m, 9H arom); MS m/z M⁺: 377 (3.8%, C₁₈H₁₄N₃³⁵Cl₃⁺); M⁺ + 2: 379 (3.7%, C₁₈H₁₄N₃³⁵Cl₂³⁷Cl⁺); M⁺ + 4: 381 (1.2%, C₁₈H₁₄N₃³⁵Cl³⁷Cl₂⁺); M⁺ + 6: 383 (0.1%, C₁₈H₁₄N₃³⁷Cl₃⁺); 286 (100%, C₁₁H₇N₃³⁵Cl₃⁺); 288 (94%, C₁₁H₇N₃³⁵Cl₂³⁷Cl⁺); 290 (30.7%, C₁₁H₇N₃³⁵Cl³⁷Cl₂⁺); 292 (3.4%, C₁₁H₇N₃³⁷Cl₃⁺); 216 (12.8%, C₁₁H₇N₃³⁵Cl⁺); 214 (12.6%, C₁₁H₇N₃³⁵Cl⁺); 180 (6.7%, C₁₁H₇N₃⁺); 91 (16.5%, C₇H₇⁺); 65 (9.8%, C₅H₅⁺).

2-(1-Piperazinyl)-5-[1-(2-diarylethyl)-4,6-dichloropyrimidines 6c and 6f. General procedure

5-[1-(4-Chlorophenyl)-2-phenylethyl]-2,4,6-trichloropyrimidine 4c (2.79 g, 7 mmol) or **5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine 4f** (3.03 g, 7 mmol) and piperazine from Aldrich (1.20 g, 14 mmol) in absolute ethanol (30 ml) were heated at reflux for 15 h. The organic layer was then removed under vacuum. The residue was treated with 2 N sodium hydroxide (40 ml) and the solid dissolved in CH₂Cl₂ (6 x 20 ml). The combined organic layer was washed with brine (5 x 10 ml) and dried with Na₂SO₄. The solvent was evaporated to give product **6c** or **6f**.

2-(1-Piperazinyl)-5-[1-(4-chlorophenyl)-2-phenylethyl]-4,6-dichloropyrimidine 6c. The reaction yielded product **6c** (2.10 g, 67% yield); mp 80–82°C; GC/MS: $R_t = 30.7$ min; IR (KBr) 3330 (NH), 3020, 3090 (CH arom), 2830 (CH, CH₂), 1565, 1515, 1480 (aromatic rings) cm⁻¹; UV (EtOH) 261 nm; ¹H-NMR (CDCl₃) δ ppm: 1.66 (s, 1H, NH); 2.80 (t, 4H, ³J = 5.0 Hz, CH₂NCH₂); 3.49 (d, 1H, ³J = 6.7 Hz, Ar-CH); 3.5 (d, 1H, ³J = 9.5 Hz, Ar-CH); 3.63 (t, 4H, ³J = 5.0 Hz, CH₂NCH₂); 4.98 (m, 1H, Ar-CH); 7.08–7.20 (m, 9H arom); MS m/z M⁺: 446 (5.3%, C₂₂H₂₁N₄³⁵Cl₂⁺); M⁺ + 2: 448 (6%, C₂₂H₂₁N₄³⁵Cl³⁷Cl⁺); M⁺ + 4: 450 (0.9%, C₂₂H₂₁N₄³⁵Cl₂³⁷Cl⁺); 355 (100%, C₁₅H₁₄N₄³⁵Cl₂⁺); 357 (96.1%, C₁₅H₁₄N₄³⁵Cl³⁷Cl⁺); 359 (30.3%, C₁₅H₁₄N₄³⁵Cl³⁷Cl⁺); 313 (8.5%, C₁₃H₁₀N₄³⁵Cl₂⁺); 91 (15.1%, C₇H₇⁺); 84 (29.4%, C₄H₈N₂⁺); 69 (47%, C₄H₇N⁺); 56 (49%, C₂H₄N₂⁺).

2-(1-Piperazinyl)-5-[1-(4-chlorophenyl)-2-(3-chlorophenyl)ethyl]-4,6-dichloropyrimidine 6f. The reaction yielded product **6f** (2.85 g, 84% yield); mp 110–114°C; silica-gel preparative TLC (CH₃CN/28% NH₄OH 90:10; $R_f = 0.59$); UV (EtOH) 274 nm; IR (KBr) 3430 (NH), 3020 (CH arom), 2920, 2830 (CH, CH₂), 1565, 1515, 1480 (aromatic rings) cm⁻¹; ¹H-NMR (CDCl₃) δ ppm: 1.55 (s, 1H, NH); 2.78 (t, 4H, ³J = 5.0 Hz, CH₂NCH₂); 3.47 (d, 1H, ³J = 7.8 Hz, Ar-CH₂); 3.61 (t, 4H, ³J = 5.0 Hz, CH₂NCH₂); 4.95 (t, 1H, ³J = 7.8 Hz, Ar-CH); 7.00–7.20 (m, 8H arom); MS m/z M⁺: 480 (6.9%, C₂₂H₂₀³⁵Cl₄N₄⁺); M⁺ + 2: 482 (8.8%, C₂₂H₂₀³⁵Cl₂³⁷ClN₄⁺); M⁺ + 4: 484 (4.2%, C₂₂H₂₀³⁵Cl₃³⁷ClN₄⁺); M⁺ + 6: 486 (0.96%, C₂₂H₂₀³⁵Cl³⁷Cl₃N₄⁺); 355 (100%, C₁₅H₁₄³⁵Cl₃N₄⁺); 357 (97.8%, C₁₅H₁₄³⁵Cl₂³⁷ClN₄⁺); 359 (32.2%, C₁₅H₁₄³⁵Cl³⁷Cl₂N₄⁺); 361 (4%, C₁₅H₁₄³⁷Cl₃N₄⁺); 125 (13.6%, C₇H₇³⁵Cl⁺).

Pharmacology

Bacteria were grown on 1.3% culture medium (AES laboratories, Combourg) with 1.5% Agar Petri dishes. The compound suspensions were added at increasing concentrations first to the sterilized culture broth, kept at 40°C, and then distributed into Petri dishes before solidification. Bacteria were applied to the surface Agar with a Steers multipoint inoculator. This method was described previously by Viollon [18]. Cultures were incubated for 24 h at 37°C.

The lowest concentration of compounds that completely inhibited bacterial growth was considered to be the minimum inhibitory concentration (MIC), expressed in μ g/ml. The experiments were performed and compared with control tests.

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