Eur J Med Chem (1995) 30, 633–639

Short communication

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

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(Received 8 December 1994; accepted 15 March 1995)

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-benzylidenebarbituric acids **1** [7]. These 5-benzylidenebarbituric 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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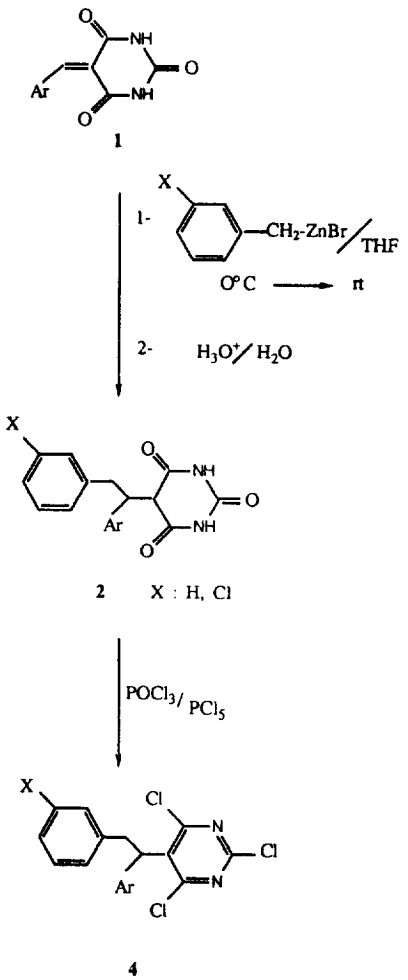


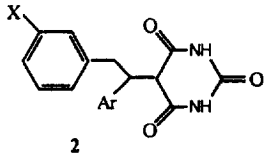
Scheme 1. Synthesis of 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines **4**.

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_6H_5	H	75	$C_{18}H_{16}N_2O_3$ (308.3)
2b	3-ClC_6H_4	H	70	$C_{18}H_{15}ClN_2O_3$ (342.8)
2c	4-ClC_6H_4	H	75	$C_{18}H_{15}ClN_2O_3$ (342.8)
2d	2-BrC_6H_4	H	70	$C_{18}H_{15}BrN_2O_3$ (387.2)
2e	4-BrC_6H_4	H	75	$C_{18}H_{15}BrN_2O_3$ (387.2)
2f	4-ClC_6H_4	Cl	86	$C_{18}H_{14}Cl_2N_2O_3$ (377.2)

[a]Yield after treatment with sodium hydroxide.

Pharmacology

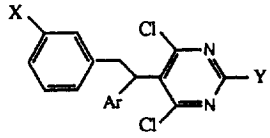
For antibacterial activity research, the synthesized pyrimidine derivatives were tested on the germs which represent certain cutaneous microflora. Details of bacterial colonies are shown in table III. These results were obtained from human sampling of healthy or sick subjects. The minimal inhibitory 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**.

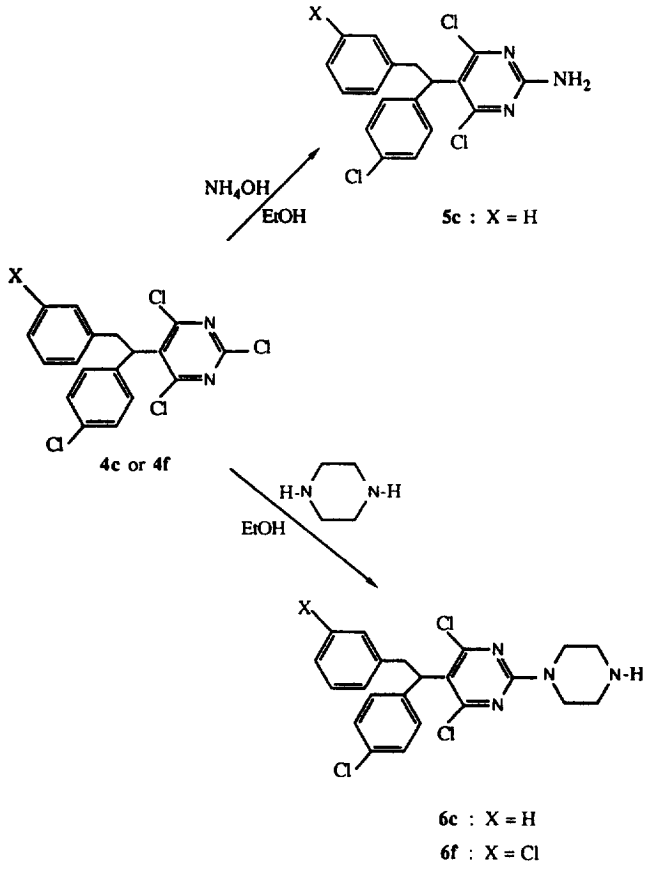
The ^1H NMR spectrum at 200 MHz of 5-substituted barbituric acids **2** displays a doublet in the range of chemical shifts δ 3.40–3.50 ppm for COCHCO proton with a coupling constant ^3J of about 3.2 Hz. The barbituric ring of compounds **2** exhibits broad singlets in the range of chemical shifts δ 8.0–10.0 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 ^3J of about 8.5 Hz for compounds

Table II. 2-Substituted-5-(1,2-diarylethyl)-4,6-dichloropyrimidines **4** (Y = Cl), **5** (Y = NH_2) and **6** (Y = 1-piperazinyl).



Compound	*Ar*	*X*	*Y*	*Yield*[a] *(%)*	*Molecular formula*	*Analyses*[b]
4a	C_6H_5	H	Cl	65	$C_{18}H_{13}Cl_3N_2$ (363.7)	C, H, Cl, N
4b	3-ClC_6H_4	H	Cl	58	$C_{18}H_{12}Cl_4N_2$ (398.1)	C, H, Cl, N
4c	4-ClC_6H_4	H	Cl	50	$C_{18}H_{12}Cl_4N_2$ (398.1)	C, H, Cl, N
4d	2-BrC_6H_4	H	Cl	45	$C_{18}H_{12}Cl_3BrN_2$ (442.6)	C, H, Br, Cl, N
4e	4-BrC_6H_4	H	Cl	58	$C_{18}H_{12}Cl_3BrN_2$ (442.6)	C, H, Br, Cl, N
4f	4-ClC_6H_4	Cl	Cl	53	$C_{18}H_{11}Cl_5N_2$ (432.6)	C, H, Cl, N
5c	4-ClC_6H_4	H	NH_2	84	$C_{18}H_{14}Cl_3N_3$ (378.7)	C, H, Cl, N
6c	4-ClC_6H_4	H	R	74	$C_{22}H_{21}Cl_3N_4$ (447.8)	C, H, Cl, N
6f	4-ClC_6H_4	Cl	R	84	$C_{22}H_{20}Cl_4N_4$ (482.2)	C, H, Cl, N

R = 1-piperazinyl. [a]Yield after recrystallization; [b]analyses indicated by the symbols of the elements were within ±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]	
Staphylococcus xylosus	CIP 81.66
	ATCC 29.971
Staphylococcus epidermidis	CIP 55.109
	NCTC 98.55
Staphylococcus haemolyticus	CIP 81.56
	ATCC 29.970
Corynebacterium xerosis	CIP 52.16
Micrococcus luteus	CIP 53.45, ATCC 93.41
Arcanobacterium haemolyticum	CIP 103.370T, ATCC 93.45
Foot bacterial flora[b]	
Staphylococcus epidermidis	1S2
Staphylococcus hominis	8S2
Staphylococcus cohnii	6S3
Corynebacterium sp *g C*	3C3
Corynebacterium sp *g B*	16C3
Corynebacterium sp *g D2*	19C1
Micrococcus luteus	1C5
Micrococcus sedentarius	7B5
Acinetobacter sp	H5DC1
Moraxella sp	H7SV1
Alcaligenes sp	H5DC1

[a]Obtained from the Pasteur Institute (Paris); [b]bacteria 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									
Staphylococcus xylosus	>1000	>1000	20	>1000	300	>500	100	100	100
Staphylococcus epidermidis	>1000	>1000	100	>1000	300	>500	100	100	75
Staphylococcus haemolyticus	>1000	>1000	100	>1000	500	>500	100	100	50
Corynebacterium xerosis	>1000	>1000	20	>1000	300	>500	30	30	30
Micrococcus luteus	>1000	>1000	20	>1000	500	>500	100	100	100
Arcanobacterium haemolyticum	>1000	>1000	10	>1000	100	300	10	10	10
Foot bacterial flora									
Staphylococcus epidermidis	>1000	>1000	>100	>1000	500	>500	100	100	75
Staphylococcus hominis	>1000	>1000	100	>1000	500	>500	100	100	75
Staphylococcus cohnii	>1000	>1000	100	>1000	500	>500	100	100	75
Corynebacterium sp *g C*	>1000	>1000	100	>1000	500	>500	100	100	75
Corynebacterium sp *g B*	>1000	>1000	30	>1000	500	>500	100	100	50
Corynebacterium sp *g* D_2	>1000	>1000	30	>1000	300	>500	100	50	50
Micrococcus luteus	>1000	>1000	20	>1000	500	>500	100	100	75
Micrococcus sedentarius	>1000	>1000	30	>1000	300	>300	100	100	75
Acinetobacter sp	>1000	>1000	>1000	>1000	>1000	>500	>500	50	30
Moraxella sp	>1000	>1000	300	>1000	>1000	>500	500	100	50
Alcaligenes 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. ^{1}H 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-[l-(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, particulary 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 efficacity. 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. ^{1}H-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 $60F_{254}$ 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 ±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-benzylidenebarbituric 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-Benzylidenebarbituric 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}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}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}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}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}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-benzylidenebarbituric 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-benzylidenebarbituric 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, CH_2), 1705, 1690 (C=O), 1600, 1495 (aromatic rings) cm^{-1}; UV (EtOH) 214, 269 nm; ^{1}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, CH_2), 1760, 1705 (C=O), 1595, 1560 (aromatic rings) cm^{-1}; UV (EtOH) 216, 267 nm; ^{1}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, CH_2), 1755, 1705, 1695 (C=O), 1595, 1570, 1490 (aromatic rings) cm^{-1}; UV (EtOH) 209, 212, 216, 267 nm; ^{1}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, CH_2), 1750, 1710, 1690 (C=O), 1595, 1492 (aromatic rings) cm^{-1}; UV (EtOH) 209, 267 nm; ^{1}H-NMR ($CDCl_3$) 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, CH_2), 1750, 1700 (C=O), 1590, 1565, 1485 (aromatic rings) cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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 ($CHCl_3$): 3210 (NH), 3100 (CH arom), 2910, 2860 (CH, CH_2), 1705 (C=O), 1595, 1570, 1490 (aromatic rings) cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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 x 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, CH_2), 1600, 1520, 1495 (aromatic rings), 1450 (CH, CH_2) cm^{-1}; UV (EtOH) 209, 270 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.59 (d, 2H, ^3J = 8.4 Hz, Ar-CH_2); 5.20 (t, 1H, ^3J = 8.4 Hz, Ar-CH); 7.00–7.31 (m, 10H arom); MS *m/z* $M^{+\cdot}$: 362 (9.3%, $C_{18}H_{13}N_2{}^{35}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 2: 364 (8.9%, $C_{18}H_{13}N_2{}^{35}Cl_2{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 366 (3%, $C_{18}H_{13}N_2{}^{35}Cl^{37}Cl_2{}^{+\cdot}$); $M^{+\cdot}$ + 6: 368 (5%, $C_{18}H_{13}N_2{}^{37}Cl_3{}^{+\cdot}$); 91 (100%, $C_7H_7{}^+$); 271 (14.7%, $C_{11}H_6N_2{}^{35}Cl_3{}^+$); 273 (14.6%, $C_{11}H_6N_2{}^{35}Cl_2{}^{37}Cl^+$); 65 (12.2%, $C_5H_5{}^+$).

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, CH_2), 1590, 1560, 1520, 1490 (aromatic rings), 1450 (CH, CH_2) cm^{-1}; UV (EtOH) 270 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.55 (d, 2H, ^3J = 8.5 Hz, Ar-CH_2); 5.15 (t, 1H, ^3J = 8.5 Hz, Ar-CH); 7.10–7.36 (m, 9H arom); MS *m/z* $M^{+\cdot}$: 396 (3%, $C_{18}H_{12}N_2{}^{35}Cl_4{}^{+\cdot}$); $M^{+\cdot}$ + 2: 398 (4.1%, $C_{18}H_{12}N_2{}^{35}Cl_3{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 400 (2%, $C_{18}H_{12}N_2{}^{35}Cl_2{}^{37}Cl_2{}^{+\cdot}$); $M^{+\cdot}$ + 6: 402 (0.4%, $C_{18}H_{12}N_2{}^{35}Cl^{37}Cl_3{}^{+\cdot}$); 91 (100%, $C_7H_7{}^+$); 65 (7.6%, $C_5H_5{}^+$).

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/$CHCl_3$: 80/20; R_f = 0.57); GC/MS: R_t = 24.9 min; IR (KBr) 3030 (CH arom), 2930 (CH, CH_2), 1600, 1525, 1495 (aromatic rings), 1450 (CH, CH_2) cm^{-1}; UV (EtOH) 270 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.58 (d, 2H, ^3J = 8.6 Hz, Ar-CH_2); 5.14 (t, 1H, ^3J = 8.6 Hz, Ar-CH); 7.00–7.36 (m, 9H arom); MS *m/z* $M^{+\cdot}$: 396 (2.8%, $C_{18}H_{12}N_2{}^{35}Cl_4{}^{+\cdot}$); $M^{+\cdot}$ + 2: 398 (3.9%, $C_{18}H_{12}N_2{}^{35}Cl_3{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 400 (1.8%, $C_{18}H_{12}N_2{}^{35}Cl_2{}^{37}Cl_2{}^{+\cdot}$); $M^{+\cdot}$ + 6: 402 (0.4%, $C_{18}H_{12}N_2{}^{35}Cl^{37}Cl_3{}^{+\cdot}$); 91 (100%, $C_7H_7{}^+$); 305 (6.9%, $C_{11}H_5N_2{}^{35}Cl_4{}^+$); 307 (8.5%, $C_{11}H_5N_2{}^{35}Cl_3{}^{37}Cl^+$); 309 (4%, $C_{11}H_5N_2{}^{35}Cl_2{}^{37}Cl_2{}^+$); 174 (4.8%, $C_{10}H_5N^{35}Cl^+$); 65 (12.2%, $C_5H_5{}^+$).

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, CH_2), 1600, 1560, 1510, 1490 (aromatic rings), 1455 (CH, CH_2) cm^{-1}; UV (EtOH) 208, 270 nm; ^{1}H-NMR ($CDCl_3$) 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* $M^{+\cdot}$: 440 (3%, $C_{18}H_{12}N_2{}^{79}Br^{35}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 2: 442 (5.9%, $C_{18}H_{12}N_2{}^{79}Br^{35}Cl_2{}^{37}Cl^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{81}Br^{35}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 4: 444 (3.8%, $C_{18}H_{12}N_2{}^{81}Br^{35}Cl_2{}^{37}Cl^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{79}Br^{35}Cl^{37}Cl_2{}^{+\cdot}$); $M^{+\cdot}$ + 6: 446 (1%, $C_{18}H_{12}N_2{}^{81}Br^{35}Cl^{37}Cl_2{}^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{79}Br^{37}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 8: 448 (0.1%, $C_{18}H_{12}N_2{}^{81}Br^{37}Cl_3{}^{+\cdot}$); 91 (100%, $C_7H_7{}^+$); 351 (3.8%, $C_{11}H_5N_2{}^{81}Br^{35}Cl_3{}^+$ and/or $C_{11}H_5N_2{}^{79}Br^{35}Cl_2{}^{37}Cl^+$); 235 (7.6%, $C_{11}H_5N_2{}^{35}Cl_2{}^+$); 237 (5%, $C_{11}H_5N_2{}^{35}Cl^{37}Cl^+$); 174 (6.4%, $C_{10}H_5N^{35}Cl^+$); 65 (9.3%, $C_5H_5{}^+$).

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, CH_2), 1605, 1515, 1490 (aromatic rings), 1450 (CH, CH_2) cm^{-1}; UV (EtOH) 208, 267 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.55 (d, 2H, ^3J = 8.3 Hz, Ar-CH_2); 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* $M^{+\cdot}$: 440 (1.6%, $C_{18}H_{12}N_2{}^{79}Br^{35}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 2: 442 (3.1%, $C_{18}H_{12}N_2{}^{79}Br^{35}Cl_2{}^{37}Cl^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{81}Br^{35}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 4: 444 (2%, $C_{18}H_{12}N_2{}^{81}Br^{35}Cl_2{}^{37}Cl^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{79}Br^{35}Cl^{37}Cl_2{}^{+\cdot}$); $M^{+\cdot}$ + 6: 446 (0.6%, $C_{18}H_{12}N_2{}^{81}Br^{35}Cl^{37}Cl_2{}^{+\cdot}$ and/or $C_{18}H_{12}N_2{}^{79}Br^{37}Cl_3{}^{+\cdot}$); $M^{+\cdot}$ + 8: 448 (0.06%, $C_{18}H_{12}N_2{}^{81}Br^{37}Cl_3{}^{+\cdot}$); 91 (100%, $C_7H_7{}^+$); 349 (4.1%, $C_{11}H_5N_2{}^{79}Br^{35}Cl_3{}^+$); 351 (8.1%, $C_{11}H_5N_2{}^{81}Br^{35}Cl_3{}^+$ and/or $C_{11}H_5N_2{}^{79}Br^{35}Cl_2{}^{37}Cl^+$); 353 (5.1%, $C_{11}H_5N_2{}^{81}Br^{35}Cl_2{}^{37}Cl^+$ and/or $C_{11}H_5N_2{}^{79}Br^{35}Cl^{37}Cl_2{}^+$); 235 (7.4%, $C_{11}H_5N_2{}^{35}Cl_2{}^+$); 237 (4.8%, $C_{11}H_5N_2{}^{35}Cl^{37}Cl^+$); 174 (5.5%, $C_{10}H_5N^{35}Cl^+$); 65 (10.8%, $C_5H_5{}^+$).

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 (CH_2, CH), 1600, 1550, 1495 (aromatic rings), 1450 (CH, CH_2) cm^{-1}; UV (EtOH) 270 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.53 (d, 2H, ^3J = 8.4 Hz, Ar-CH_2); 5.13 (t, 1H, ^3J = 8.4 Hz, Ar-CH); 6.86–7.29 (m, 8H arom); MS *m/z* $M^{+\cdot}$: 430 (8.5%, $C_{18}H_{11}N_2{}^{35}Cl_5^{+\cdot}$); $M^{+\cdot}$ + 2: 432 (13.6%, $C_{18}H_{11}N_2{}^{35}Cl_4{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 434 (8.7%, $C_{18}H_{11}N_2{}^{35}Cl_3{}^{37}Cl_2^{+\cdot}$); $M^{+\cdot}$ + 6: 436 (2.7%, $C_{18}H_{11}N_2{}^{35}Cl_2{}^{37}Cl_3^{+\cdot}$); $M^{+\cdot}$ + 8: 438 (0.6%, $C_{18}H_{11}N_2{}^{35}Cl^{37}Cl_4^{+\cdot}$); 305 (76%, $C_{11}H_5N_2{}^{35}Cl_4^+$); 307 (100%, $C_{11}H_5N_2{}^{35}Cl_3{}^{37}Cl^+$); 309 (48.4%, $C_{11}H_5N_2{}^{35}Cl_2{}^{37}Cl_2^+$); 311 (10.4%, $C_{11}H_5N_2{}^{35}Cl^{37}Cl_3^+$); 269 (8.3%, $C_{11}H_4N_2{}^{35}Cl_3^+$); 271 (8.8%, $C_{11}H_4N_2{}^{35}Cl_2{}^{37}Cl^+$); 125 (16.9%, $C_7H_6{}^{35}Cl^+$); 127 (5.6%, $C_7H_6{}^{37}Cl^+$).

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 µmol) 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 Na_2SO_4. The solvent was evaporated and the residue recrystallized from acetone. Product **5c** (146 mg, 385 µmol) was obtained in 84% yield; GC/MS = R_t = 27.2 min; IR (KBr) 3317, 3190 (NH_2), 3032 (CH arom), 2968, 2937 (CH, CH_2), 1632, 1568, 1552, 1540, 1496 (aromatic rings) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.49 (d, 2H, ^3J = 8.1 Hz, Ar-CH_2); 4.98 (t, 1H, ^3J = 8.1 Hz, Ar-CH); 5.24 (s, 2H, NH_2), 6.95–7.65 (m, 9H arom); MS *m/z* $M^{+\cdot}$: 377 (3.8%, $C_{18}H_{14}N_3{}^{35}Cl_3^{+\cdot}$); $M^{+\cdot}$ + 2: 379 (3.7%, $C_{18}H_{14}N_3{}^{35}Cl_2{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 381 (1.2%, $C_{18}H_{14}N_3{}^{35}Cl^{37}Cl_2^{+\cdot}$); $M^{+\cdot}$ + 6: 383 (0.1%, $C_{18}H_{14}N_3{}^{37}Cl_3^{+\cdot}$); 286 (100%, $C_{11}H_7N_3{}^{35}Cl_3^+$); 288 (94%, $C_{11}H_7N_3{}^{35}Cl_2{}^{37}Cl^+$); 290 (30.7%, $C_{11}H_7N_3{}^{35}Cl^{37}Cl_2^+$); 292 (3.4%, $C_{11}H_7N_3{}^{37}Cl_3^+$); 216 (12.8%, $C_{11}H_7N_3{}^{35}Cl^+$); 214 (12.6%, $C_{11}H_5N_3{}^{35}Cl^+$); 180 (6.7%, $C_{11}H_6N_3^+$); 91 (16.5%, $C_7H_7^+$); 65 (9.8%, $C_5H_5^+$).

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 CH_2Cl_2 (6 x 20 ml). The combined organic layer was washed with brine (5 x 10 ml) and dried with Na_2SO_4. 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, CH_2), 1565, 1515, 1480 (aromatic rings) cm^{-1}; UV (EtOH) 261 nm; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.66 (s, 1H, NH); 2.80 (t, 4H, ^3J = 5.0 Hz, CH_2NCH_2); 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, CH_2NCH_2); 4.98 (m, 1H, Ar-CH), 7.08–7.20 (m, 9H arom); MS *m/z* $M^{+\cdot}$: 446 (5.3%, $C_{22}H_{21}N_4{}^{35}Cl_3^{+\cdot}$); $M^{+\cdot}$ + 2: 448 (6%, $C_{22}H_{21}N_4{}^{35}Cl_2{}^{37}Cl^{+\cdot}$); $M^{+\cdot}$ + 4: 450 (0.9%, $C_{22}H_{21}N_4{}^{35}Cl^{37}Cl_2^{+\cdot}$); 355 (100%, $C_{15}H_{14}N_4{}^{35}Cl_3^+$); 357 (96.1%, $C_{15}H_{14}N_4{}^{35}Cl_2{}^{37}Cl^+$); 359 (30.3%,$C_{15}H_{14}N_4{}^{35}Cl{}^{37}Cl_2^+$); 313 (8.5%, $C_{13}H_{10}N_3{}^{35}Cl_3^+$); 91 (15.1%, $C_7H_7^+$); 84 (29.4%, $C_4H_8N_2^{+\cdot}$); 69 (47%, $C_4H_7N^{+\cdot}$); 56 (49%, $C_2H_4N_2^{+\cdot}$).

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 (CH_3CN/28% NH_4OH 90:10; R_f = 0.59); UV (EtOH) 274 nm; IR (KBr) 3430 (NH), 3020 (CH arom), 2920, 2830 (CH, CH_2), 1565, 1515, 1480 (aromatic rings) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.55 (s, 1H, NH); 2.78 (t, 4H, ^3J = 5.0 Hz, CH_2NCH_2); 3.47 (d, 1H, ^3J = 7.8 Hz, Ar-CH_2); 3.61 (t, 4H, ^3J = 5.0 Hz, CH_2NCH_2), 4.95 (t, 1H, ^3J = 7.8 Hz, Ar-CH), 7.00–7.20 (m, 8H arom); MS *m/z* $M^{+\cdot}$: 480 (6.9%, $C_{22}H_{20}{}^{35}Cl_4N_4^{+\cdot}$); $M^{+\cdot}$ + 2: 482 (8.8%, $C_{22}H_{20}{}^{35}Cl_2{}^{37}ClN_4^{+\cdot}$); $M^{+\cdot}$ + 4: 484 (4.2%, $C_{22}H_{20}{}^{35}Cl_2{}^{37}Cl_2N_4^{+\cdot}$); $M^{+\cdot}$ + 6: 486 (0.96%, $C_{22}H_{20}{}^{35}Cl^{37}Cl_3N_4^{+\cdot}$); 355 (100%, $C_{15}H_{14}{}^{35}Cl_3N_4^+$); 357 (97.8%, $C_{15}H_{14}{}^{35}Cl_2{}^{37}ClN_4^+$); 359 (32.2%, $C_{15}H_{14}{}^{35}Cl{}^{37}Cl_2N_4^+$); 361 (4%, $C_{15}H_{14}{}^{37}Cl_3N_4^+$); 125 (13.6%, $C_7H_7{}^{35}Cl^+$).

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 µg/ml. The experiments were performed and compared with control tests.

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