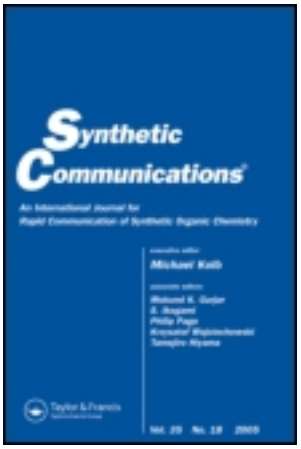


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Simple One-Pot Synthesis of New Derivatives of the Macrocyclic Aminal 1,3,7,9,13,15,19,21-Octaazapentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane (OAPO)

Augusto Rivera [a], Jaime Ríos-Motta [a], Ginna Paola Trujillo [a], Derly Marcela González [a] & Daniel Alcázar [a]

[a] Departamento de Química, Universidad Nacional de Colombia, Ciudad Universitaria, Bogotá, Colombia

Accepted author version posted online: 21 Feb 2012.Version of record first published: 21 Dec 2012.

To cite this article: Augusto Rivera , Jaime Ríos-Motta , Ginna Paola Trujillo , Derly Marcela González & Daniel Alcázar (2013): Simple One-Pot Synthesis of New Derivatives of the Macrocyclic Aminal 1,3,7,9,13,15,19,21-Octaazapentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane (OAPO), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:6, 791-799

To link to this article: http://dx.doi.org/10.1080/00397911.2011.609956

Synthetic Communications®, 43: 791–799, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.609956

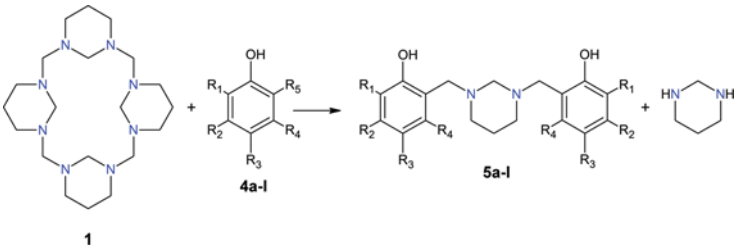
Taylor & Francis
Taylor & Francis Group

SIMPLE ONE-POT SYNTHESIS OF NEW DERIVATIVES OF THE MACROCYCLIC AMINAL 1,3,7,9,13,15,19,21-OCTAAZAPENTACYCLO-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}] OCTACOSANE (OAPO)

Augusto Rivera, Jaime Ríos-Motta, Ginna Paola Trujillo, Derly Marcela González, and Daniel Alcázar

Departamento de Química, Universidad Nacional de Colombia, Ciudad Universitaria, Bogotá, Colombia

GRAPHICAL ABSTRACT



Abstract *A series of 2,2′-(dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(substituted-phenols) was synthesized using a Mannich-type reaction between the macrocyclic aminal 1,3,7,9,13,15,19,21-octaazapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane (OAPO) (**1**) and substituted phenols in basic media. These previously unreported compounds were separated from the reaction mixture by column chromatography in highly pure form with 25–75% yields. The most stable conformer was predicted using AM1-type semiempirical quantum chemical calculations.*

Keywords Anomeric effect; hexahydropyrimidine; Mannich bases; *ortho*-regioselectivity

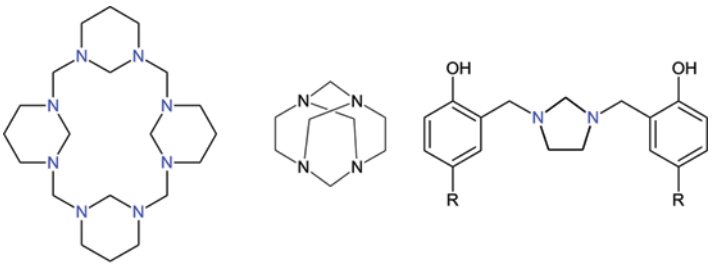
INTRODUCTION

The chemistry of 1,3-diazacyclohexanes has attracted considerable interest in recent years because appropriately functionalized compounds of this ring system either serve as crucial synthetic precursors or are themselves important members of this class of heterocycles.[1] The condensation of 1,3-diamines with aldehydes is the most commonly used method for synthesizing this cyclic aminal.[2,3] In the recent past, Katritzky's group has reported a convenient method for the preparation of

Received June 29, 2011.

Address correspondence to Augusto Rivera, Departamento de Química, Universidad Nacional de Colombia, Ciudad Universitaria, Carrera 30 # 45-03, Bogotá, D.C., Colombia. E-mail: ariverau@unal.edu.co

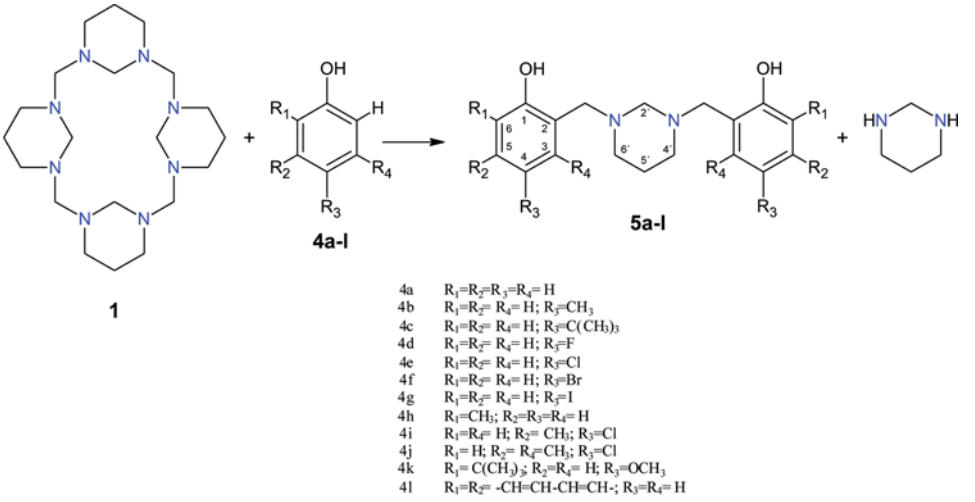
N-monosubstituted hexahydropyrimidines using benzotriazole methodology.[4] More recently, a multicomponent Mannich reaction for the synthesis of N,N′-disubstituted-1,3-diazacyclohexanes has been described.[5] In addition, it is known[6,7] that 1,3-propanediamine reacts easily with formaldehyde in aqueous medium to produce the macrocyclic polyaminal 1,3,7,9,13,15,19,21-octaazapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane (OAPO, **1**), which contains four aminal methylene groups linking four 1,3-diazacyclohexane units. On the other hand, during the course of our work on the reactivity of cyclic aminals, we have already reported the use of these compounds as preformed Mannich electrophiles in basic media. For example, 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD, **2**) reacts with phenolic compounds in basic media, producing the aromatic Mannich-type bases 2,2′-(imidazolidine-1,3-diyldimethanediyl)bis(substituted-phenol) (**3**).[8–11] In a further extension of this methodology, we anticipated that these conditions would be compatible with a one-pot synthesis of N,N′-disubstituted-hexahydropyrimidine derivatives using 1,3,7,9,13,15,19,21-octaazapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane (OAPO, **1**) as the aminomethylating reagent for phenols. Moreover, N,N′-disubstituted-hexahydropyrimidines are interesting compounds because the ring system contains one N-C-N moiety, which is a particularly challenging group known to exhibit peculiar stereoelectronic effects. For example, it has been shown that the conformations of six-membered 1,3-diazacycles are governed by the generalized anomeric effect.[12] The synthesis of the hexahydropyrimidine derivatives **5a–l** provide not only a novel example of aminals usefully employed in Mannich reaction but also an expansion of the scope of the use of cyclic aminals as preformed electrophiles in Mannich condensations in basic media. This Mannich condensation offers simple and efficient access to this family of compounds in a one-pot reaction.



1 **2** **3**

RESULTS AND DISCUSSION

We found that reactions of OAPO (**1**) with substituted phenols (**4a–l**) (OAPO–phenol molar ratio of 1:4) give moderate to good yields of new derivatives of the saturated heterocyclic hexahydropyrimidine system, namely 2,2′-(dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(substituted-phenol) (**5a–l**) (Scheme 1). The experiments were conducted with heating at reflux in 96% ethanol for a time period between 10 and 72 h as specified for each compound in Table 1. Optimization of reaction time was made for each phenol. Reaction times and yields obtained are



Scheme 1. Reaction between OAPO and phenols **4a–l**. (Figure is provided in color online.)

recorded in Table 1. The process was regioselective: The aminomethylation occurred only at the *ortho* position to the phenolic hydroxyl group. The reactions are clean and good yielding, and the products could be easily isolated by simple purification by column chromatography. This one-step reaction was not affected by electronic effects of the substituents on the phenyl ring.

The structures of the compounds **5a–l** were established through rigorous spectroscopic analysis. The infrared (IR) spectra of **5a–l** presented the characteristic bands of the Mannich bases; the presence of intramolecular hydrogen bonds between the phenolic hydroxyl groups and nitrogen atoms is evident. It is important to note that broad bands with maximums at approximately 3150 cm^{-1}, which were attributed to ν(O-H), appeared with strong intensity compared with the signals of **3**, in which an IR continuum was shown. These differences suggest a decrease in

Table 1. 2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(substituted-phenols) (**5a–l**) produced via Scheme 1

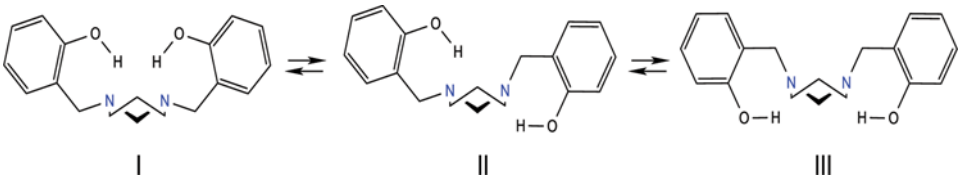
Phenol	Product	Time (h)	Mp (°C)	Yield (%)
4a	5a	48	100–102	38.2
4b	5b	36	114–115	59.5
4c	5c	12	188–190	35.7
4d	5d	36	85–86	26.0
4e	5e	72	121–122	31.3
4f	5f	14	160–161	31.1
4g	5g	36	95–96	26.0
4h	5h	20	116–119	24.4
4i	5i	10	177–179	25.6
4j	5j	15	204–206	37.1
4k	5k	60	130–132	27.0
4l	5l	24	142–144	75.5

hydrogen-bonding strength in **5a–l**, which would be due to the change in the molecular geometry and different nitrogen lone pair orientation in the hexahydropyrimidine ring.

The ^{1}H NMR spectra (400 MHz, $CDCl_3$, 30 °C) of the Mannich bases **5a–l** showed the aromatic protons as an ABX spin system and the hexahydropyrimidine ring protons as a single and two multiplets centered at 3.4, 2.7, and 1.8 ppm, respectively, generated through the interconversion of *axial* and *equatorial* hydrogen atoms. ^{1}H NMR spectra at low temperatures for **5d** showed line broadening for almost all of the signals in the aliphatic regions, which indicated that at low temperatures, conformational isomerism is relatively slow on the NMR time scale, leading to broadened signals. However, variable-temperature studies indicated that the methylene protons at positions 4, 5, and 6 resonated at very similar chemical shifts and were not resolved at 400 MHz. In addition, the benzylic protons appeared at approximately 3.8 ppm. Interestingly, the resonance of these protons appeared at a higher field compared with the corresponding benzylic protons in the closely related Mannich bases ($\delta = 4.0$ ppm). These high-field shifts are attributed to the influence of the C-C anisotropy of the additional methylene (C-5).

For all hexahydropyrimidines **5a–l** obtained, the conformational analysis was performed using the AM1 model, one of the best semiempirical methods suitable for heteroatom-containing systems, and predicted three types of conformers differing in the orientation of the N substituents: axial-equatorial, diequatorial, and diaxial forms (Scheme 2). Because 1,3-diazacyclohexanes, which have no substituents on C2, possess mainly conformers with diequatorial N substitution, AM1-optimized geometries in the gas phase indicated that III is the most stable conformer for **5a**, although the energy difference between the *syn*(III) and *anti*(II) conformations is 1.92 kCal/mol. This energy difference between the *syn* conformer and the *anti* conformer is consistent with the preferential axial *N*-alkylation of hexahydropyrimidine.[13] However, it is well known that in these heterocyclic systems, nitrogen inversion is a much faster process than ring inversion;[7] thus, the interconversion between conformers is very fast. On the other hand, the N–C–N structure is particularly challenging because the problems presented by the aminalic nitrogen atoms are probably enhanced by an anomeric effect analogous to that detected in the case of the O–C–O structure.[14] The AM1 results agree well with the experimental NMR data, especially with the ^{13}C NMR data.

In conclusion, we have developed a novel method for the synthesis of N,N′-disubstituted-hexahydropyrimidine derivatives via one-pot Mannich type reaction. The easy workup procedure, the accessibility of the starting materials, the



Scheme 2. Possible conformers for N,N′-disubstituted hexahydropyrimidines. (Figure is provided in color online.)

operational simplicity of this methodology, and good yields make this method a valid contribution to the existing methodologies for the synthesis of such heterocycles.

EXPERIMENTAL

OAPO was prepared according Ref. 6. Chemicals were used without further purification, and IR spectra were recorded on a Perkin-Elmer Fourier transform FT–IR Paragon spectrometer with a KBr disk. ^{1}H and ^{13}CNMR spectra were measured on a Bruker Advance 400-MHz spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Elemental analyses (C, H, N) were determined in a Carlo-Erba model 1106 analyzer. Melting points (uncorrected) were determined on an Electrothermal 9100 melting-point apparatus. Thin-layer chromatography (TLC) was performed with Merck 60 F254 coated silica-gel plates with visualization by iodine vapor.

General Procedure for the Synthesis of 2,2′(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(substituted-phenols) (5a–l)

Compounds **5a–l** were prepared by the reaction of OAPO with the corresponding phenol as follows:

A solution of OAPO (**1**) (0.5 mmol) in 96% ethanol (5 mL) was added slowly to a stirred solution of the appropriate phenol **(4a–l)** (2.0 mmol) in 96% ethanol (5 mL) heated under reflux. Upon completion of the addition, the reaction mixture was stirred under reflux for the time indicated in Table 1. Then the reflux was stopped, the solvent was removed on a rotary evaporator under vacuum, and the residue obtained was chromatographed on silica gel eluting with benzene/AcOEt (gradient elution with 5% to 20% AcOEt) to afford the respective compound **5a–l**.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)diphenol (5a)

White solid, mp 100–102 °C, yield 38.2%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.68 (s, 4H, Ar-CH_2-N), 3.42 (s, 2H, N-CH_2-N), 2.75 (t, 4H, CH_2-4′ and CH_2-6′), 1.82 (m, 2H, CH_2-5′), 7.16 (t, 2H, ABCD system, $J = 7.49$ Hz, $J = 7.58$ Hz, H-5), 6.98 (d, 2H, ABCD system, $J = 7.22$ Hz, H-3), 6.83 (d, 2H, ABCD system, $J = 8.02$ Hz, H-6), 6.77 (t, 2H, ABCD system, $J = 7.31$ Hz, $J = 7.32$ Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1 (C1), 129.5 (C5), 129.3 (C3), 121.0 (C2), 119.7 (C4), 116.7 (C6), 73.5 (N-CH_2-N), 58.0 (CH_2-Ar), 51.5 (C4′ and C6′), 21.9 (C5′). Elem. anal. calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46%; H, 7.43%; N, 9.39%. Found: C, 72.37%; H, 7.41%; N, 9.35%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-methylphenol) (5b)

White solid, mp 114–115 °C, yield 59.5%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 4H, Ar-CH_2-N), 3.42 (s, 2H, N-CH_2-N), 2.71 (t, 4H, CH_2-4′ and CH_2-6′), 2.22 (s, 6H, CH_3), 1.77 (m, 2H, CH_2-5′), 6.85 (dd, 2H, ABX system, $J = 2.58$ Hz, $J = 8.62$ Hz, H-5), 6.78 (d, 2H, ABX system, $J = 2.64$ Hz, H-3), 6.72 (d, 2H, ABX system, $J = 8.59$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3 (C1), 129.4 (C3 and C5),

128.3(C4), 120.3 (C2), 115.9 (C6), 73.1 (N-CH_2-N), 57.6 (CH_2-Ar), 51.1 (C4′ and C6′), 21.4 (C5′), 20.4 (Ar-CH_3). Elem. anal. calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59%; H, 8.03%; N, 8.58%. Found: C, 73.58%; H, 7.99%; N, 8.57%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-*tert*-butylphenol) (5c)

White solid, mp 188–190 °C yield 35.7%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.79 (s, 4H, Ar-CH_2-N), 3.48 (s, 2H, N-CH_2-N), 2.73 (t, 4H, CH_2-4′ and CH_2-6′), 1.78 (m, 2H, CH_2-5′), 1.26 (s, 18H, *t*-But), 7.18 (dd, 2H, ABX system, J = 2.2 Hz, J = 8.4 Hz, H-5), 6.97 (d, 2H, ABX system, J = 1.9 Hz, H-3), 6.77 (d, 2H, ABX system, J = 8.4 Hz, Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9 (C1), 141.7 (C3), 125.3 (C5), 125.2 (C4), 119.5 (C2), 115.3 (C6), 73.1 (N-CH_2-N), 57.7 (CH_2-Ar), 50.7 (C4′ and C6′), 33.8 [$C(Me)_3$], 31.2 [$C(CH_3)_3$], 21.0 (C5′). Elem. anal. calcd. for $C_{26}H_{38}N_2O_2$: C, 76.06%; H, 9.33%; N, 6.82%. Found: C, 76.01%; H, 9.29%; N, 6.77%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-fluorophenol) (5d)

White solid, mp 85–86 °C yield 26.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.74 (s, 4H, Ar-CH_2-N), 3.39 (s, 2H, N-CH_2-N), 2.74 (t, 4H, CH_2-4′ and CH_2-6′), 1.81 (m, 2H, CH_2-5′), 6.85 (td, 2H, ABX system, J = 8.5 Hz, J = 3.0 Hz, H-5), 6.76 (dd, 2H, ABX system, J = 8.8 Hz, J = 4.8 Hz, H-6), 6.71 (dd, 2H, ABX system, J = 8.6 Hz, J = 2.9 Hz, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1 (C4), (d, J = 236.8 Hz), 153.5 (C1) (d, J = 2.1 Hz), 121.3 (C6), (d, J = 7.0 Hz), 117.0 (C3), (d, J = 7.9 Hz), 115.4 (C5), (d, J = 1.7 Hz), 115.1 (C2), (d, J = 2.6 Hz), 72.7 (N-CH_2-N), 57.3 (CH_2-Ar), 51.2 (C4′ and C6′), 21.6 (C5′). Elem. anal. calcd. for $C_{18}H_{20}F_2N_2O_2$: C, 64.66%; H, 6.03%; N, 8.38%. Found: C, 64.63%; H, 6.01%; N, 8.32%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-chlorophenol) (5e)

White solid, mp 121–122 °C, yield 31.3%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75 (s, 4H, Ar-CH_2-N), 3.37 (s, 2H, N-CH_2-N), 2.73 (t, 4H, CH_2-4′ and CH_2-6′), 1.81 (m, 2H, CH_2-5′), 7.10 (dd, 2H, ABX system, J = 2.58 Hz, J = 8.62 Hz, H-5), 6.95 (d, 2H, ABX system, J = 2.64 Hz, H-3), 6.76 (d, 2H, ABX system, J = 8.59 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1 (C1), 128.9 (C3), 128.5 (C5), 123.9 (C4), 121.9 (C2), 116.7 (C6), 72.6 (N-CH_2-N), 57.2 (CH_2-Ar), 52.2 (C-4′ and C-6′), 21.7 (C5′). Elem. anal. calcd. for $C_{18}H_{20}Cl_2N_2O_2$: C, 58.86%; H, 5.49%; N, 7.63%. Found: C, 58.83%; H, 5.44%; N, 7.62%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-bromophenol) (5f)

Yellow solid, mp 160–161 °C yield 31.1%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.73 (s, 4H, Ar-CH_2-N), 3.37 (s, 2H, N-CH_2-N), 2.73 (t, 4H, CH_2-4′ and CH_2-6′), 1.80 (m, 2H, CH_2-5′), 7.24 (dd, 2H, ABX system, J = 2.40 Hz, J = 8.80 Hz,

Hz, H-5), 7.08 (d, 2H, ABX system, $J = 2.40$ Hz, H-3), 6.72 (d, 2H, ABX system, $J = 8.40$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9 (C1), 131.0 (C3), 130.5 (C5), 121.5 (C4), 117.3 (C2), 110.2 (C6), 71.8 (N-CH_2-N), 56.2 (CH_2-Ar), 50.4 (C4′ and C6′), 20.8 (C5′). Elem. anal. calcd. for $C_{18}H_{20}Br_2N_2O_2$: C, 47.39%; H, 4.42%; N, 6.14%. Found: C, 47.36%; H, 4.39%; N, 6.12%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-iodophenol) (5g)

Yellow solid, mp 95–96 °C yield 26.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.74 (s, 4H, Ar-CH_2-N), 3.59 (s, 2H, N-CH_2-N), 2.74 (t, 4H, CH_2-4′ and CH_2-6′), 1.82 (m, 2H, CH_2-5′), 7.47 (dd, 2H, ABX system, $J = 8.4$ Hz, $J = 2.4$ Hz, H-5), 7.43 (d, 2H, ABX system, $J = 2.4$ Hz, H-3), 6.63 (d, 2H, ABX system, $J = 8.4$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1 (C1), 137.4 (C5), 130.1 (C3), 122.9 (C2), 118.7 (C6), 81.2 (C4), 72.6 (N-CH_2-N), 56.9 (CH_2-Ar), 51.1 (C4′ and C6′), 26.7 (C5′). Elem. anal. calcd. for $C_{18}H_{20}I_2N_2O_2$: C, 39.29%; H, 3.66%; N, 5.09%. Found: C, 39.22%; H, 3.62%; N, 5.08%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(2-methylphenol) (5h)

White solid, mp 116–119 °C yield 24.4%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 4H, Ar-CH_2-N), 3.42 (s, 2H, N-CH_2-N), 2.71 (t, 4H, CH_2-4′ and CH_2-6′), 2.23 (s, 6H, Ar-CH_3), 1.79 (m, 2H, CH_2-5′), 7.03 (d, 2H, ABC system, $J = 8.0$ Hz H-5), 6.84 (d, 2H, ABC system, $J = 8.0$ Hz, H-3), 6.68 (t, 2H, ABC system, $J = 8.0$ Hz, $J = 8.0$ Hz, H-4);^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8 (C1), 130.2 (C5), 126.4 (C3), 125.1 (C2), 119.9 (C6), 118.8 (C4), 73.1 (N-CH_2-N), 57.7 (CH_2-Ar), 51.1 (C4′ and C6′), 21.6 (C5′), 15.7 (CH_3). Elem. anal. calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59%; H, 8.03%; N, 8.58%. Found: C, 73.58%; H, 7.99%; N, 8.57%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-chloro-3-methylphenol) (5i)

White solid, mp 177–179 °C, yield 25.6%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 4H, Ar-CH_2-N), 3.37 (s, 2H, N-CH_2-N), 2.72 (s, 4H, CH_2-4′ and CH_2-6′), 2.27 (s, 6H Ar-CH_3), 1.79 (t, 2H, CH_2-5′), 6.94 (s, 2H, H-3), 6.71 (s, 2H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0 (C1), 136.6 (C3), 128.8 (C5), 124.1 (C4), 119.5 (C2), 118.7 (C6), 72.7 (N-CH_2-N), 56.9 (CH_2-Ar), 51.2 (C4′ and C6′), 21.7 (C5′), 19.8 (CH_3). Elem. anal. calcd. for $C_{20}H_{24}Cl_2N_2O_2$: C, 60.76%; H, 6.12%; N, 7.09%. Found: C, 60.71%; H, 6.09%; N, 7.03%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(4-chloro-3,5-dimethylphenol) (5j)

White solid with irregular form, mp 204–206 °C yield 37.1%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 4H, Ar-CH_2-N), 3.43 (s, 2H, N-CH_2-N), 2.69 (t, 4H, CH_2-4′ and CH_2-6′), 2.31 (s, 6H, CH_3-C3 or CH_3-C5), 2.30 (s, 6H, CH_3-C3 or CH_3-C5), 1.78 (m,

2H, CH_2-5′), 6.62 (s, 2H, H-6); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 156.2 (C1), 136.6 (C3), 134.0 (C5), 125.3 (C4), 116.5 (C2), 73.2 (N-CH_2-N), 54.0 (C4′ and C6′), 50.9 (CH_2-Ar), 21.0 (C5′), 16.6 (CH_3). Elem. anal. calcd. for $C_{22}H_{28}Cl_2N_2O_2$: C, 62.41%; H, 6.67%; N, 6.62%. Found: C, 62.36%; H, 6.65%; N, 6.59%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(2-*tert*-butyl-4-methoxy-phenol) (5k)

White solid, mp 130–132 °C, yield 27.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 10H, Ar-CH_2-N and OCH_3), 3.49 (s, 2H, N-CH_2-N), 2.74 (s, 4H, CH_2-4′ and CH_2-6′), 1.80 (s, 2H, CH_2-5′), 1.43 [s, 18H, $C(CH_3)_3$], 6.83 (d, 2H, AB system, $J = 3.5$ Hz, H-3), 6.47 (d, 2H, AB system, $J = 3.4$ Hz, H-5); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 151.7 (C4), 150.5 (C1), 138.0 (C6), 121.3 (C2), 112.9 (C5), 111.3 (C3), 73.4 (N-CH_2-N), 58.0 (OCH_3), 55.7 (CH_2-Ar), 50.6 (C4′ and C6′), 34.8 [Ar-C-$(CH_3)_3$], 29.4 [$(CH_3)_3$], 21.1 (C5′). Elem. anal. calcd. for $C_{28}H_{42}N_2O_4$: C, 71.46%; H, 8.99%; N, 5.95%. Found: C, 71.41%; H, 8.93%; N, 5.91%.

2,2′-(Dihydropyrimidine-1,3(2*H*,4*H*)-diyldimethanediyl)bis(2-naphthol) (5l)

White solid, mp 142–144 °C, yield 75.5%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.25 (s, 2H, ArCH_2-N), 3.62 (s, 2H, N-CH_2-N), 2.78 (t, 4H, CH_2-4′ and CH_2-6′), 1.84 (m, 2H, CH_2-5′), 7.92 (d, 2H, ABCD system, $J = 8.58$ Hz, H-3), 7.76 (d, 2H, ABCD system, $J = 8.08$ Hz, H-6), 7.69 (d, 2H, AB system, $J = 8.85$ Hz, H-7), 7.43 (t, 2H, ABCD system, $J = 7.77$ Hz, $J = 7.83$ Hz, H-4), 7.26 (t, 2H, ABCD system, $J = 7.04$ Hz, $J = 7.85$ Hz, H-5), 7.04 (d, 2H, AB system $J = 8.86$ Hz, H-8); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 157.2 (C1), 134.0 (C9 and C10), 130.0 (C7), 129.5 (C6), 127.0 (C4), 123.2 (C5), 122.2 (C3), 119.9 (C8), 112.0 (C2), 75.0 (N-CH_2-N), 53.0 (CH_2-Ar), 52.0 (C4′ and C6′), 23.5 (C5′). Elem. anal. calcd. for $C_{28}H_{42}N_2O_4$: C, 78.36%; H, 6.58%; N, 7.03%. Found: C, 78.34%; H, 6.53%; N, 7.01%.

ACKNOWLEDGMENTS

We acknowledge the Dirección de Investigaciones Sede Bogotá (DIB) of Universidad Nacional de Colombia for financial support, and D. M. G. acknowledges the Vicerrectoría Académica de la Universidad Nacional de Colombia for a fellowship.

REFERENCES

1. Axenrod, T.; Sun, J.; Das, K. K.; Dave, P. R.; Forohar, F.; Kaselj, M.; Trivedi, N. J.; Gilardi, R. D.; Flippen-Anderson, J. L. *J. Org. Chem.* **2000**, *65*, 1200–1206.
2. Evans, R. F. *Aust. J. Chem.* **1967**, *20*, 1643–1661.
3. Finch, H.; Peterson, E. A.; Ballard, S. A. *J. Am. Chem. Soc.* **1952**, *74*, 2016–2021.
4. Katritzky, A. R.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 3115–3117.
5. Farrell, J. R.; Niconchuk, J.; Higham, C. S.; Bergeron, B. W. *Tetrahedron Lett.* **2007**, *48*, 8034–8036.

6. Volpp, G. *Chem. Ber.* **1962**, *95*, 1493–1494.
7. Murray-Rust, P.; Ridell, F. G. *Tetrahedron* **1976**, *32*, 427–430, and references therein.
8. Rivera, A.; Maldonado, M. *Tetrahedron Lett.* **2006**, *47*, 7467–7471.
9. Rivera, A.; Ríos-Motta, J.; Navarro, M. A. *Heterocycles* **2006**, *68*, 531–537.
10. Rivera, A.; Ríos-Motta, J.; Quevedo, R.; Joseph-Nathan, P. *Rev. Colomb. Quim.* **2005**, *34*, 105–115.
11. Rivera, A.; Gallo, G. I.; Gayón, M. E.; Joseph-Nathan, P. *Synth. Commun.* **1993**, *23*, 2921–2929.
12. Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.
13. Berges, D. A.; Fan, J.; Devinck, S.; Mower, K. *J. Org. Chem.* **2000**, *65*, 889–894.
14. Carballeira, L.; Mosquera, R. A.; Ríos, M. A. *J. Mol. Struct.* **1988**, *176*, 89–105.