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Solvent-free Mannich-type reaction of tetraazatricyclododecane (TATD) with phenols

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ABSTRACT

Solvent-free Mannich-type reactions between the macrocyclic aminal 1,3,6,8-tetraazatricyclo [4.4.1.1^{3,8}]dodecane (TATD) and phenols indicate that the activation of the aromatic ring is critical for controlling the course of reaction. Activated rings form *N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine (tetrahydrosalens), and weakly activated rings form Mannich bases consisting of 1,3-bis[2′-hydroxybenzyl]imidazolidine. When the reaction is conducted using β-naphthol, a Mannich-type reaction occurs followed by a retro-Mannich-type reaction that forms 1,1′-methylene-bis(2-naphthol). The solvent-free reaction between 1,3-bis[2′-hydroxybenzyl]imidazolidine Mannich bases and the macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) allows Mannich bases with high molecular weight to be obtained in a controlled manner.

Aminomethyl phenol derivatives are of great scientific and industrial interest because of their chemical properties. Benzoxazines are a class of aminomethyl phenol derivatives that are benzo-fused heterocycles, which have an increased usefulness for the development of new polymeric materials with excellent mechanical and thermal properties.[1,2] In addition, benzoxazines have recently shown interesting photophysical characteristics, which indicate promise for developing new materials.[3]

Aminomethyl phenol derivatives are another class of benzylamines with differing properties and potential applications as complexing agents, catalyst components, organic synthetic intermediates, and bioactive compounds.[4] Tetrahydrosalens are prominent benzylamine compounds that have four active sites in their structure, two hydroxyls and two amino groups, which can form coordinate bonds with different metal ions.[4] They currently show a potential for use as ligands in the synthesis of olefin polymerization catalysts.[5] These ligands have improved structural flexibility over their dehydrogenated analogues (salen ligands).[6,7]

The Mannich reaction is one of the most popular methods for synthesizing structurally varied benzoxazines and benzylamines.[4,8] A Mannich-type reaction between the macrocyclic aminal TATD **1** and phenols **2** is a useful tool for synthesizing bis-benzoxazines and tetrahydrosalens in two steps.

In the first step, the corresponding imidazolidine, **3**, is obtained with low yields (20–30%).[9] This imidazolidine can react with formaldehyde to form the corresponding benzoxazine **4**,[10] or it can be hydrolyzed to the corresponding benzylamine **5**.[11] These two reactions show good yields (Scheme 1).

The yields of Mannich reactions between the macrocyclic aminal TATD **1**, and phenols depend on the activation of the phenolic ring; some products are reactive and form dimerization **6** and oligomerization compounds, which creates complex mixtures from which it is impossible to isolate the pure products.[12] Additionally, when the reaction is conducted using hindered phenols, the corresponding benzoxazine **4** is formed with good yields instead of the imidazoline (Scheme 2).[12]

The behaviors observed for this reaction indicate that imidazolidine **3** is formed in low yields and that oligomerization products **6** dominate when working with *para*-substituted phenols, whereas when working with highly hindered phenols, the respective benzoxazine **4** is formed, which indicates that the macrocyclic aminal TATD or some other reaction product acts as the formaldehyde donor under these reaction conditions.[12]

Previously published results show that the release of formaldehyde and formation of benzylimidazolidine oligomers play a determinant role in the yield of Mannich-type reactions between phenols and the macrocyclic aminal TATD **1**.[12] To both improve yields and increase the potential of reactions between macrocyclic aminals and phenols, the reaction of TATD **1** with various phenols was studied in this Letter in the absence of a solvent. The results show that the product depends on the reaction conditions, and the compounds obtained when the reaction is performed in the solution are not formed in the absence of a solvent.

For these experiments, we selected *o*-cresol **2a**, *m*-cresol **2b**, and *p*-cresol **2c** to establish the influence of the substituent position on

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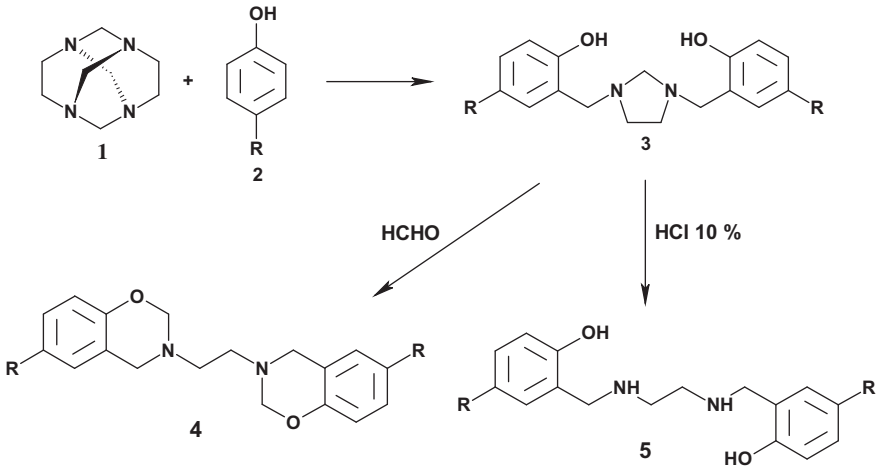
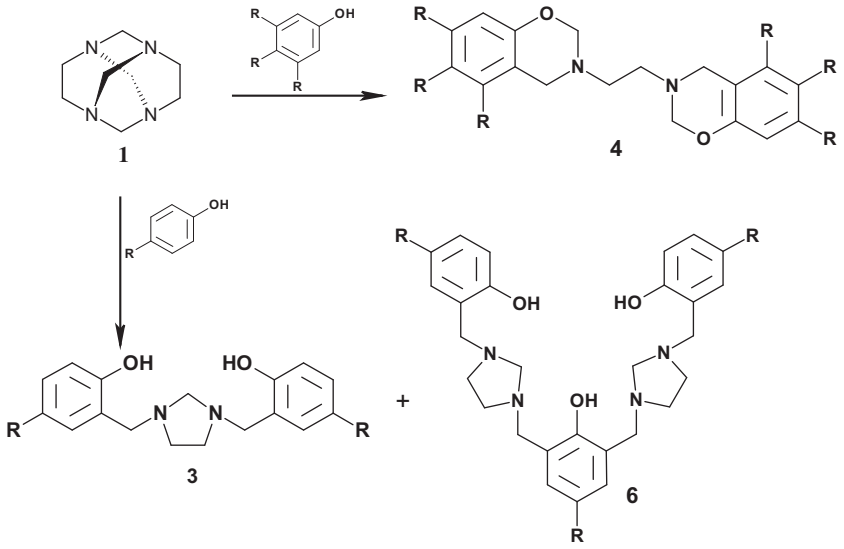


Scheme 1. Bis-benzoxazine and tetrahydrosalen synthesis from imidazolidines.



Scheme 2. Reaction of TATD **1** with phenols.

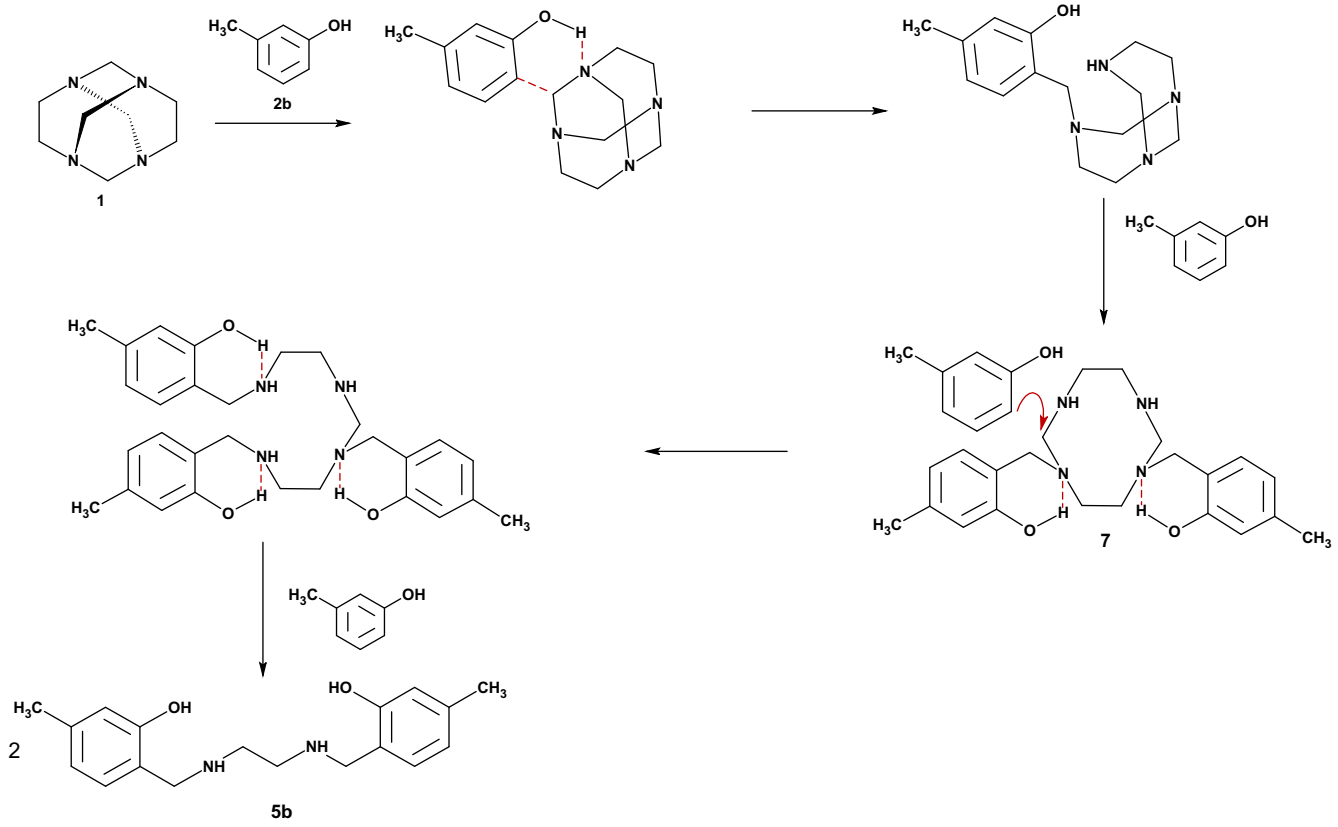
the course of the reaction; *p*-chlorophenol **2d**, 4-chloro-3-methylphenol **2e**, and 4-chloro-3,5-dimethylphenol **2f** were used to establish the effects of the number of substituents on the aromatic ring; 2,6-dimethylphenol **2g** was used to determine if *para* aminomethylation occurs under these conditions; and β-naphthol **2h** was used to establish the behavior of highly activated aromatic compounds.

The reactions with **2a**–**2c** were conducted using a 1:2 TATD **1**:phenol **2** ratio under the experimental conditions reported by Rivera and Quevedo.[13] In all cases, we obtained the corresponding imidazolidine **3a**–**3c** in lower yields than for the solution reaction. One explanation for these low yields is the solidification of the reaction mixture after product formation, which inhibits the reaction.[14]

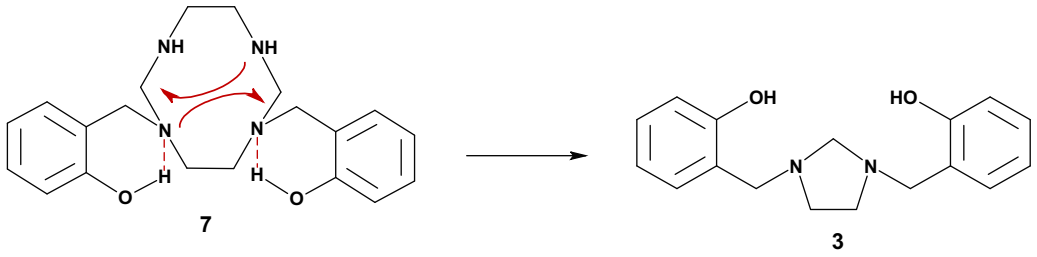
The stoichiometric ratio was changed to 1:4 (TATD **1**:phenol **2**) to prevent solidification. The results allowed for the classification of the phenols employed into two groups according to the Mannich base formed. The first group, which consisted of *m*- and *p*-cresol (**2b**, **2c**), formed the corresponding tetrahydrosalens **5b** and **5c** (Scheme 3). Additional experiments with **2b** at different temperatures (18, 42, 90, and 150 °C) demonstrated that the formation of tetrahydrosalen **5b** was independent of the temperature. They also indicated that a higher yield is obtained at lower temperatures, which is most likely because of a reduction in the polymeric product formation. A possible mechanism is shown in Scheme 3.[14]

The second group of phenols consisted of *o*-cresol **2a**, *p*-chlorophenol **2d**, 4-chloro-3-methylphenol **2e**, 2,6-dimethylphenol **2g**, and 4-chloro-3,5-dimethylphenol **2f** and formed the imidazolidines **3a**, **3d**, **3e**, **3f**, and **3g**, respectively, in better yields than for the solution reactions. The ring is less activated for this second group of phenols and promotes intramolecular cyclization (Scheme 4). Intermediate **7** commonly forms tetrahydrosalens **5** and imidazolidines **3**; the product formed only depends on the nucleophilicity of the aromatic ring.[14]

Once again, the studied phenols can be classified into two groups according to their yields for the Mannich bases **3** or **5** (Table 1). The first group includes *o*-cresol **2a**, *m*-cresol **2b**, *p*-cresol **2c**, *p*-chlorophenol **2d**, and 4-chloro-3-methylphenol **2e** and forms Mannich bases with close to 50% yields. These low yields were most likely due to subsequent oligomerization reactions because the rings had at least two free activated positions. The second group of phenols includes 4-chloro-3,5-dimethylphenol **2f** and 2,6-dimethylphenol **2g** and produces Mannich bases with nearly 100% yields. It is impossible to form oligomers with these phenols



Scheme 3. Formation of tetrahydrosalens **5** via a solvent-free Mannich-type reaction of TATD **1** with phenols **2a**, **2b**.



Scheme 4. Formation of imidazolidine **3** via the solvent-free Mannich-type reaction of TATD **1** with phenols **2a** and **2d**–**2g**.

Table 1
Solvent-free Mannich-type reaction of TATD with phenols

Phenol	Product	Yield (%)
o-Cresol	**3a**	44
m-Cresol	**5b**	45
p-Cresol	**5c**	37
p-Chlorophenol	**3d**	59
4-Chloro-3-methylphenol	**3e**	43
4-Chloro-3,5-dimethylphenol	**3f**	94
2,6-Dimethylphenol	**3g**	91
β-Naphthol	**3h**	94

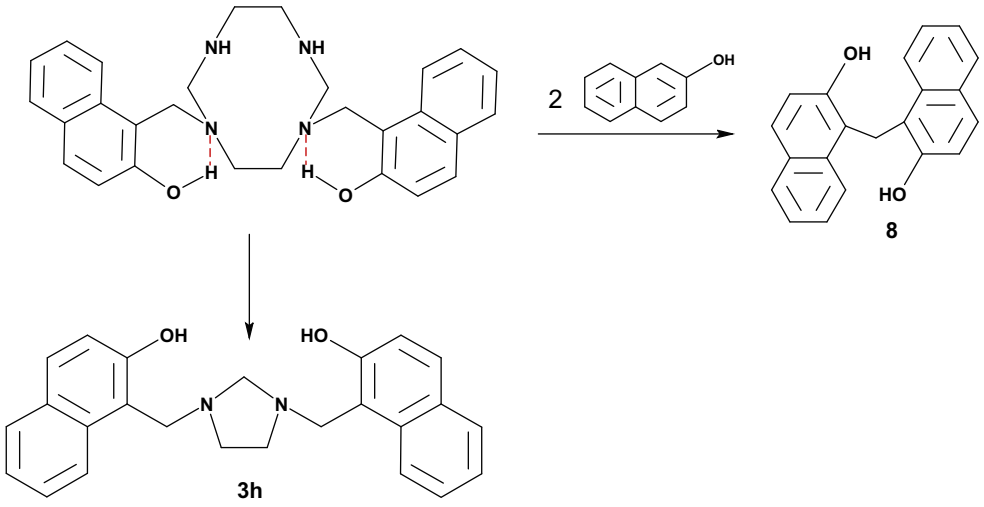
because they are *ortho* to the occupied hydroxyl or blocked by the methyl groups.

The reaction with β-naphthol **2h** behaved differently than the other phenols. In the absence of solvent and 1:4 ratio (TATD **1**:β-naphthol **2h**), Mannich bases of type **3** or **5** did not form, and 1,1′-methylene-bis(2-naphthol) **8** was obtained in good yields (97%).[14] This product may be formed via a retro-Mannich-type reaction between an electrophilic benzylic carbon and a nucleophilic carbon on another β-naphthol unit (Scheme 5).[15] This result shows that the retro-Mannich-type reaction is not restricted to secondary amines and may occur with other phenols under appropriate experimental conditions. The reaction of TATD with β-naphthol in a 1:2 ratio quantitatively formed the corresponding imidazolidine **3h**, (94%) which indicates that an excess of β-naphthol is necessary for the retro-Mannich-type reaction to occur (Scheme 5).

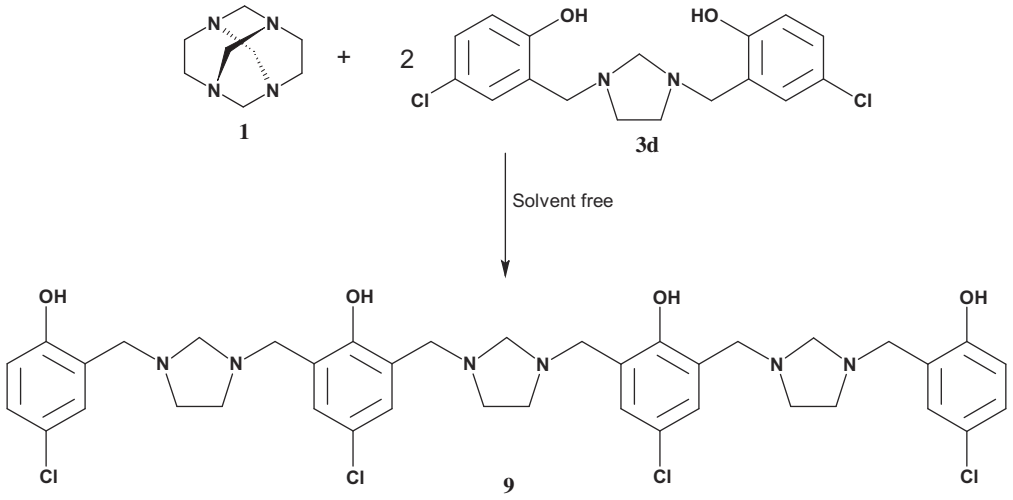
These results indicated that ring activation is critical for determining the course of the Mannich reaction between the macrocyclic aminal TATD and phenols. Oligomer formation appears to be the primary cause of low yields regardless of the Mannich base obtained.

To determine whether benzylimidazolidine oligomer formation occurs under the experimental conditions used, the reaction was conducted between the macrocyclic aminal TATD **1** and the previously synthesized and characterized imidazolidine **3d**. This reaction formed a benzylimidazolidine trimer **9**, which is the product of condensation between one molecule of TATD **1** and 2 of imidazolidine **3d** (Scheme 6), in 76% yields.

The formation of **9** demonstrated that the reactions of macrocyclic aminals with 1,3-bisbenzylimidazolidines depend on the



Scheme 5. Solvent-free Mannich-type reaction of TATD **1** with β-naphthol **2h**.



Scheme 6. Solvent-free Mannich-type reaction of TATD **1** with benzylimidazolidines **3d**.

stoichiometric ratio; when employing a 1:1 (TATD **1**:imidazolidine **3**) ratio, the most abundant product is a heterocalixarene-type molecule,[13] and when employing a 1:2 (TATD **1**:imidazolidine **3**) ratio, the major product is a trimer of benzylimidazolidine **9**. Usually the yield of the Mannich-type reaction between TATD and phenols is low. These low yields are due to the unavoidable formation of oligomers; however, the oligomer synthesis can be directed in a controlled manner toward either cyclic or linear molecules with high molecular weights, which could be useful for developing new materials.

In conclusion, this paper shows that the products resulting from the solvent-free Mannich-type condensation between the macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **1** and phenols depends on the activation of the aromatic ring. Activated rings form *N*,*N*′-bis(2-hydroxybenzyl) ethylenediamine (tetrahydrosalens) **5**. Weakly activated rings form 1,3-bis[2′-hydroxybenzyl]imidazolidines **3**, and when the reaction is conducted using β-naphthol, a Mannich-type reaction occurs before a subsequent retro-Mannich-type reaction that forms the corresponding 1,1′-methylenebis(2-naphthol) **8**. Oligomer formation is a major cause of low yields in this reaction independent of which Mannich base, **3** or **5**, was obtained. The reaction between the Mannich base 1,3 bis[2′-hydroxybenzyl]imidazolidine **3** and macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **1** allows for the controlled synthesis of Mannich bases with a high molecular weight.

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14. Experimental

Reaction of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) ***1*** *with phenols* ***2****:*
A mixture of TATD **1** (0.5 g, 3 mmol) and the corresponding phenol (12 mmol) was heated with stirring at 150 °C for 20 min. The reaction mixture was allowed to cool to room temperature and then suspended in ethanol. The pure product was isolated by filtration and washed with ethanol.

1,3-Bis[2′-hydroxy-3′-methylbenzyl]imidazolidine ***3a****:*
($C_{19}H_{24}N_2O_2$) mp 118–120 °C, yield 44%. ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 6H, CH_3), 2.96 (s, 4H, H-C4, C5), 3.54 (s, 2H, H-C2), 3.88 (s, 4H, Ar-CH_2), 7.05 (d, 2H, H-C4′, J = 7.32 Hz), 6.69 (t, 2H, H-C5′, J = 7.32 Hz), 6.83 (d, 2H, H-C6′, J = 7,32 Hz). ^{13}C NMR δ: 15.6 (CH_3), 51.5 (C4, C5), 58.2 (Ar-CH_2), 74.5 (C2), 120.7 (C1′), 155.7 (C2′). 125.1 (C3′), 130.3 (C4′), 118.8 (C5′), 125.9 (C6′). Elemental analysis: C, 73.0211; H, 7.8884; N, 9.1932.

N,N′-Bis(2-hydroxy-4-methylbenzyl)ethylenediamine ***5b****:*
($C_{18}H_{24}N_2O_2$) mp 150–152 °C, yield 45%. ^{1}H NMR ($CDCl_3$) δ: 2.27 (s, 6H, CH_3), 2.90 (s, 4H, CH_2), 3.60 (s, 4H, Ar-CH_2), 6.70 (d, 2H, H-C3′), 6.60 (d, 2H, H-C6′), 6.80 (dd, 2H, H-C5′).[11]

N,N′-Bis(2-hydroxy-5-methylbenzyl) ethylenediamine ***5c****:*
($C_{18}H_{24}N_2O_2$) mp 140–142 °C, yield 47%. ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 6H, CH_3), 2.96 (s, 4H, CH_2), 3.87 (s, 4H, Ar-CH_2), 6.75 (d, 2H, H-C3′), 6.99 (dd, 2H, H-C4′), 6.77 (d, 2H, H-C6′).[11]

1,3-Bis[2′-hydroxy-5′-chlorobenzyl]imidazolidine ***3d****:*
($C_{17}H_{18}Cl_2N_2O_2$) mp 80–82 °C, yield 59%. ^{1}H NMR ($CDCl_3$) δ: 2.97 (s, 4H, HC-4, C5), 3.52 (s, 2H, H-C2), 3.82 (s, 4H, Ar-CH_2), 7.12 (d, 2H, H-C4′), 6.96 (t, 2H, H-C5′), 6.75 (d, 2H, H-C6′).[10]

1,3-Bis[2′-hydroxy-5′-chloro-4′-methylbenzyl]imidazolidine ***3e****:*
($C_{19}H_{22}Cl_2N_2O_2$) mp 134–135 °C, yield 43%. ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 6H, CH_3), 2.98 (s, 4H, H-C4, C5), 3.53 (s, 2H, H-C2), 3.84 (s, 4H, Ar-CH_2), 6.72 (s, 2H, H-C3′), 6.93 (s, 2H, H-C6′).
^{13}C NMR δ: 19.8 (CH_3), 51.5 (C4, C5), 57.4 (Ar-CH_2), 74.5 (C2), 120.2 (C1′), 155.9 (C2′), 118.6 (C3′), 136.7 (C4′), 124.1 (C5′), 128.2 (C6′). Elemental analysis: C, 59.931; H, 5.779; N, 7.478.

1,3-Bis[2′-hydroxy-5′-chloro-4′,6′-dimethylbenzyl]imidazolidine ***3f****:*
($C_{21}H_{26}Cl_2N_2O_2$) mp 118–120 °C, yield 96%. ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 6H, CH_3), 2.33 (s, 6H, CH_3), 3.01 (s, 4H, H-C4, C5), 3.52 (s, 2H, H-C2), 3.96 (s, 4H, Ar-CH_2), 6.65 (s, 2H, H-C3′). ^{13}C NMR δ: 16.8 (CH_3-C6′), 21.1 (CH_3-C4′), 51.1 (C4, C5), 54.6 (Ar-CH_2), 74.4 (C2), 118.3 (C1′), 156.1 (C2′), 116.5 (C3′), 136.8 (C4′), 125.5 (C5′), 133.7 (C6′).

1,3-Bis[4′-hydroxy-3′,5′-dimethylbenzyl]imidazolidine ***3g****:*
($C_{21}H_{28}N_2O_2$) mp 112–113 °C, yield. 91%. ^{1}H NMR ($CDCl_3$) δ: 2.18 (s, 12H, CH_3), 2.78 (s, 4H, H-C4, C5), 3.32 (s, 2H, H-C2), 3.51 (s, 4H, Ar-CH_2), 6.85 (s, 4H, H-C2′, H-C6′). ^{13}C NMR δ: 16.7 (CH_3), 52.5 (C4, C5), 59.3 (Ar-CH_2), 75.9 (C2), 124.1 (C1′), 129.6 (C2′), 129.9 (C3′), 152.4 (C4′), 129.9 (C5′), 129.6 (C6′).

1,1′-Methylenebis(2-naphthol) ***8****:*
($C_{21}H_{16}O_2$) mp 177–179 °C, yield 97%. ^{1}H NMR (CD_3OD) δ: 4.80 (s, 4H, Ar-CH_2), 7.15 (d, 2H, H-C3′, J = 8.8 Hz), 7.54 (d, 2H, H-C4′, J = 8.8 Hz), 7.59 (d, 2H, H-C5′, J = 8.0 Hz,), 7.09 (td, 2H, H-C6′, J = 8,0 Hz, J = 1,2 Hz), 7.16 (td, 2H, H-C7′, J = 8,0 Hz, J = 8,4 Hz, J = 1,2 Hz), 8.22 (d, 2H, H-C8′, J = 8,4 Hz). ^{13}C NMR δ: 21.8 (Ar-CH_2), 121.0 (C1′), 153.0 (C2′), 118.7 (C3′,), 125.3 (C4′), 128.8 (C5′), 126.5 (C6′), 123,4 (C7′), 129.2 (C8′), 130.6 (C9′), 135.5 (C10′).

Reaction of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD ***1*** *with 1,3-bis[2′-hydroxy-5′-chlorobenzyl]imidazolidine* ***3d****:*
A mixture of TATD (0.1 g, 0.59 mmol) and 1,3-bis[2′-hydroxy-5′-chlorobenzyl]imidazolidine **3d** (0.41 g, 1.18 mmol) was heated with stirring at 150 °C for 20 min and subsequently allowed to cool to room temperature. The crude product was dissolved in methanol and precipitated by changing the polarity with water. The precipitate was purified by column chromatography eluting with ethanol:ethyl acetate mixtures.

1,3-Bis[2′-hydroxy-3′-(3″-(2‴-hydroxy-5‴-chlorobenzyl)-1″-methyleneimidazolidin)-5′-chloro-bencyl]imidazolidine ***9****:*
($C_{39}H_{44}Cl_4N_6O_4$) mp 69 °C, yield 76%. ^{1}H NMR ($CDCl_3$) δ: 2.95 (s, 4H, H-C4 and H-C5), 2,97 (s, 8H, H-C4″ and H-C5″), 3.53 (s, 2H, H-C2), 3.54 (s, 4H, H-C2″), 3.83 (s, 4H, H-C6 and H-C7), 3.89 (s, 4H, H-C6″), 3.79 (s, 4H, H-C7″), 7.05 (d, 2H, H-C6′, J = 2.4 Hz), 7.11 (d, 2H, H-C4′, J = 2.4 Hz), 6.79 (d, 2H, H-C3‴, J = 8.8 Hz), 7.14 (dd, 2H, H-C4‴, J = 8.8 Hz, J = 2.4 Hz), 6.98 (d, 2H, H-C6‴, J = 2.4 Hz). ^{13}C NMR δ: 51.9 (C4 and C5), 51.6 (C4″), 51.8 (C5″), 75.1 (C2), 75.0 (C2″), 55.8 (C6 and C7), 58.0 (C6″), 54.4 (C7″), 125.2 (C1′), 154.4 (C2′), 124.5 (C3′), 128.3 (C4′), 123.6 (C5′), 127.9 (C6′), 123.6 (C1‴), 156.5 (C2‴), 117.6 (C3‴), 128.8 (C4‴), 123.2 (C5‴), 127.9 (C6‴), MALDITOF-MS: m/z 801.2.

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