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SOLVENT-FREE SYNTHESIS OF 2-(1*H*-BENZIMIDAZOL-1-YL-METHYL)-4-SUBSTITUTED 1-HYDROXYARYL BY THE TWO COMPONENT MANNICH REACTION BETWEEN 6*H*,13*H*-5:12,7:14-DIMETHANEDIBENZO[*d,i*][1,3,6,8]TETRAAZECINE (DMDBTA) AND PHENOLS

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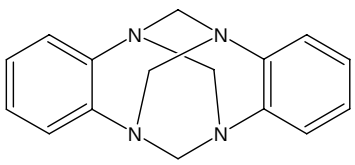
Abstract – A new series of Mannich bases (**7a-e**) were synthesized with good yields, in a single pot by a two component Mannich-type reaction under solvent-free conditions from 6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d,i*][1,3,6,8]-tetraazecine (DMDBTA **1**) and phenols (**6a-e**) at 150 ºC. The mechanism of formation of those Mannich bases and their subsequent thermal decomposition into 1*H*-benzimidazole (**8**) and respective *ortho*-methylated phenols (**9a-f**) by an *o*-quinone-methide intermediate are also discussed.

INTRODUCTION

The Mannich reaction is a three-component condensation reaction involving an active hydrogen-containing compound, formaldehyde and a secondary amine. The amino alkylation of aromatic substrates by the Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds.[1] Mannich bases have been reported as potential biological agents. They have been found to have applications as antitubercular, antimalarial, vasorelaxing, anticancer and analgesic drugs and are also used in the polymer industry as paints and surface active agents.[2]

During the course of our ongoing efforts to synthesize nitrogen-containing heterocycles using Mannich condensations with phenols and aminals in basic medium, we have demonstrated that the reaction between the 6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d,i*][1,3,6,8]tetraazecine (DMDBTA **1**) and some electron-rich phenols at reflux in propan-2-ol yielded both 1-methyl-1*H*-benzimidazole (**2**) and the respective Mannich bases (i.e. 2-(1*H*-benzimidazol-1-ylmethyl)-4-chloro-3,5dimethylphenol (**3**) and

1-(1*H*-benzimidazol-1-ylmethyl)-2-naphthol (**4**). However, when electron-deficient phenols were used, no aminomethylation occurred and instead 1:4,6:9,11:14,16:19-tetramethylentetrabenzo[*b,g,l,q*] [1,4,6,9,11,14,16,19]octaazaeicocina (TTBOE **5**), a cyclodimerization product of DMDBTA, was isolated.[3]



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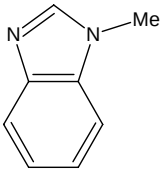

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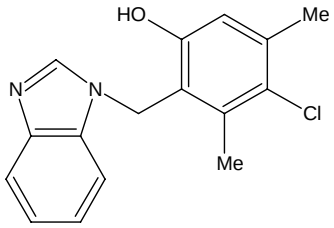

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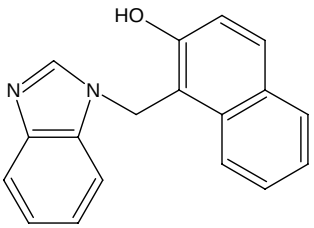

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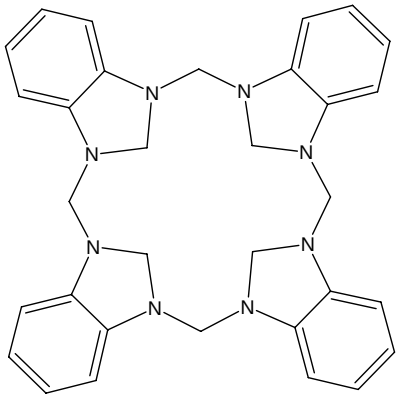


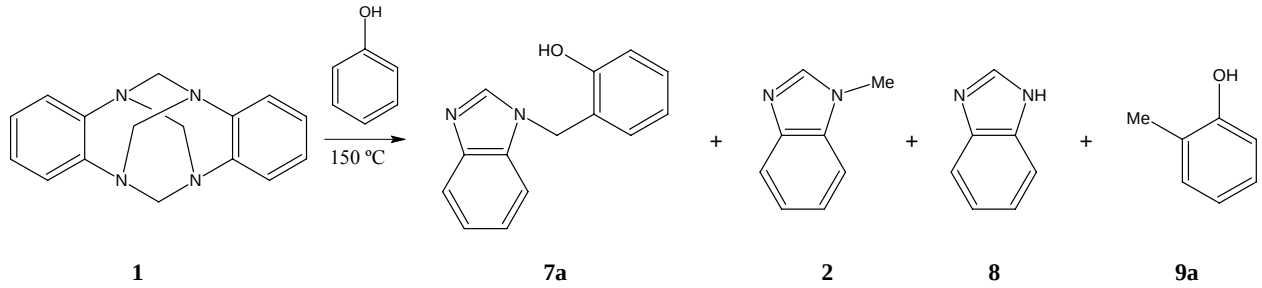
5

Benzimidazole and its derivatives have been used in diverse areas of chemistry and are very important intermediates in organic reactions. Therefore, the preparation of benzimidazoles has gained considerable attention in recent years. Despite their importance from pharmacological, industrial, and synthetic points of view comparatively few methods for the preparation of benzimidazoles have been reported.[4] Nevertheless, 1-substituted-benzimidazoles have been studied to a considerable lesser extent than 2-substituted-benzimidazoles.

We were eager to explore new reaction conditions to optimize the Mannich base production and avoid the cyclodimerization of **1**. As solvent-free conditions may enable reactions that can not be effected by traditional solution synthesis, and recent reports have established that these conditions can be used in Mannich type reactions,[5] we attempted the reaction of **1** with phenols under solvent-free conditions. Herein, we wish to disclose our results of two component Mannich-type reactions using a series of phenols and the cyclic aminal DMDBTA in solvent-free conditions. To explore the full scope and versatility of this method, various conditions were investigated, including time and temperature variations and different substituents on the phenyl rings. We found that Mannich bases **4** and **7a-e** readily decompose into 1*H*-benzimidazole (**8**) and respective *ortho*-methylated phenols (**9a-f**) when they are heated under solvent-free conditions.

RESULTS AND DISCUSSION

Initially, the two component Mannich reaction of DMDBTA (1 mmol) and phenol (2 mmol) was examined under conditions previously developed by our group for another aminal.[6] ^{1}H NMR analysis of the reaction mixture revealed a characteristic singlet around δ 8.28 in the ^{1}H NMR spectrum (δ 144.8 in the ^{13}C NMR spectrum) indicating the formation of benzimidazole-type products. In addition, a singlet at δ 5.37 in the ^{1}H NMR spectrum and a peak at δ 43.7 in the ^{13}C NMR spectrum showed the presence of a *N*-methylene carbon. Additionally, HMBC analysis showed strong three-bond correlations between an upfield shift at δ 43.7 and two protons of aromatic region. Further purification and NMR analysis established the structure of the main product as 2-(1*H*-benzimidazol-1-ylmethyl)phenol (**7a)**. GC-MS analyses confirmed that this reaction, besides yielding **7a**, gave 1-methyl-1*H*-benzimidazole (**2**) in moderate yield, and 1*H*-benzimidazole (**8**) and *o*-cresol (**9a**) in low yields (Scheme 1).



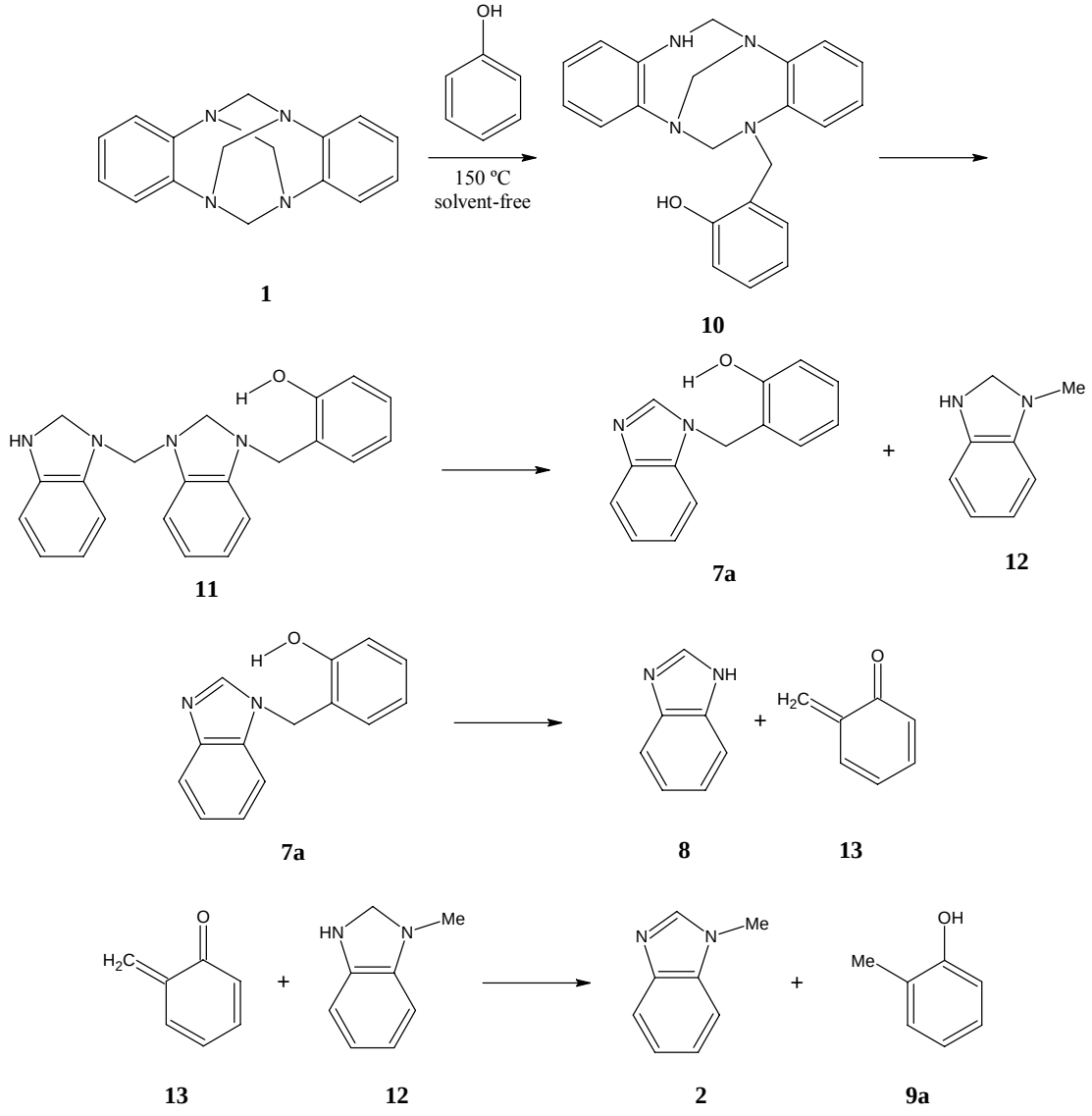
1 **7a** **2** **8** **9a**

Scheme 1. Reaction between **1** and phenol under solvent free conditions.

We propose that the formation of compounds **7a**, **2**, **8** and **9a** demonstrates that the reaction proceeds via competitive steps. These conversions involve initial Mannich-type reaction between the aminal cage and the phenol to give **10** as a highly reactive intermediate (Scheme 2), which easily undergoes an intramolecular rearrangement to produce 2-((3-(2,3-dihydro-*1H*-benzo[*d*]-imidazol-1-yl)methyl)-2,3-dihydro-*1H*-benzo-[*d*]imidazol-1-yl)methylphenol (**11**), which is itself an aminomethylphenol (*ortho*-Mannich base) able to form O–H···N intramolecular hydrogen bonds. The presence of this intramolecular interaction in this intermediate decreases its relative stability. We assume that **11** undergoes decompositions by a 1,3-hydrogen shift and subsequent expulsion of 1-methyl-2,3-dihydro-*1H*-benzo[*d*]imidazole (**12**) to initially afford **7a** (Scheme 2).

Concomitantly, thermal decomposition of Mannich base **7a** into 1*H*-benzimidazole (**8**) and *o*-quinone methide (QM) intermediate **13** by a retro-Michael reaction followed by reduction of the QM induced by 1-methyl-2,3-dihydro-*1H*-benzo[*d*]-imidazole (**12**, Scheme 2), afforded the byproducts 1-methyl-1*H*-benzimidazole (**2**) in moderate yields and *o*-cresol (**9a**) in low yields. This presumption was confirmed by heating **7a** under solvent-free conditions in the absence of phenol. So, only 1*H*-benzimidazole (**8**) and *o*-cresol (**9a**) were detected by ^{1}H-NMR and GC-MS. Currently, further efforts to explain this fact are

under way in our laboratory. In fact, *o*-quinone methide intermediates have previously been suggested as long-lived intermediates in retro-Mannich reactions,[7-11] and their involvement in the electrocyclic ring closure of enols from vinyl quinones have been previously substantiated by multinuclear NMR.[12] Compared with solvent conditions,[3] the formation of the QMs seems to be caused by the increase in the temperature of the reaction.



Scheme 2. Proposed pathway for the formation of **7a** and byproducts.

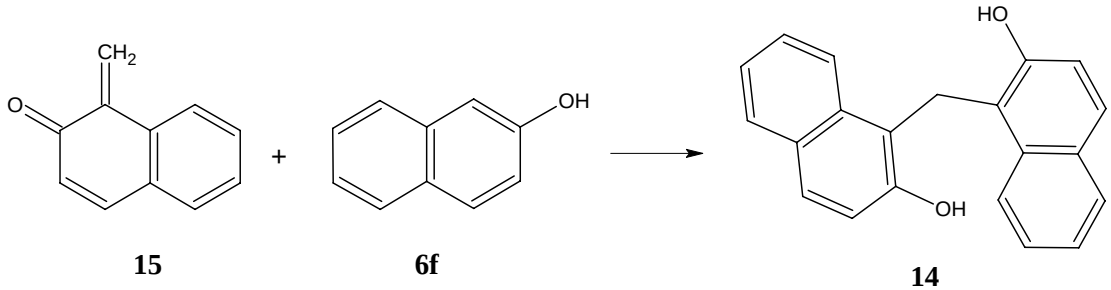
To optimize reaction conditions, reactions with various temperatures and times were screened using the model reaction, and GC-MS was used to monitor the progress of the reaction. Next, in order to examine the effect of substituents and the scope of the reaction, different reactions under solvent-free conditions were conducted by using five (**6a-e**) electron-rich or electron-deficient substituted phenols and *β*-naphtol (**6f**). GC-MS analyses established that the reaction between DMDBTA and phenols **6a-f** (including *β*-naphtol) under solvent-free conditions yielded 2-(1*H*-benzimidazol-1-ylmethyl)-4-susbtituted-1-

hydroxyaryl (**4** and **7a-e**) as main products (except when *p*-nitrophenol was used), 1-methyl-1*H*-benzimidazole (**2**) in moderate yield, and 1*H*-benzimidazole (**8**) and *o*-methylated phenols (**9a-f**) in low yields (Table 1). It was found that the electronic effect of the substituents had some influence on the yields. Perhaps the presence of a strong intramolecular hydrogen bond interaction reduces the stability and, consequently, yield of the Mannich base.

Table 1. The reaction of **1** with phenols and *β*-naphthol under solvent-free conditions.

	Phenol	**Products** (yield %)			
6a	phenol	**7a**	(35.5)	**9a**	(25.3)
6b	*p*-cresol	**7b**	(45.2)	**9b**	(15.8)
6c	*p*-methoxyphenol	**7c**	(35.8)	**9c**	(25.4)
6d	*p*-chlorophenol	**7d**	(44.8)	**9d**	(17.4)
6e	*p*-nitrophenol	**7e**	-	**9e**	(40.6)
6f	*β*-naphthol	**4**	(65.7)	**9f**	(12.7)

In addition, when *β*-naphthol was used 1,1´-methylbis(2-naphthol) (**14**) was also isolated at 26.2%. Based on the results, we concluded that the formation of **14** was understandable due to the major nucleophilicity of *β*-naphthol. In this case the QM intermediate **15** (Scheme 3) underwent either an *in situ* reduction induced by 1-methyl-2,3-dihydro- *1H*-benzo[*d*]imidazole **12** to give **9f** and **2** or a Michael-type addition with *β*-naphthol (**6f**) to afford **14**.QMs are also known to be good Michael acceptors, and the subsequent nucleophilic attack on the exocyclic methylene group proceeds smoothly to afford benzylic products.[13]



15 **6f** **14**

Scheme 3. Proposed pathway for the formation of **14**.

EXPERIMENTAL

6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d,i*][1,3,6,8]tetraazecine (DMDBTA, **1**) was prepared following the procedure described in the literature.[14] Without additional purifications, we used as received the following phenols obtained from Merck: phenol, *p*-cresol, *p*-methoxyphenol, *p*-chlorophenol, *p*-nitrophenol, and *β*-naphthol. Infrared spectra were recorded as KBr disc on a Perkin-Elmer Paragon FT-IR instrument.

NMR spectra were performed in DMSO-d_6 or CD_3OD at room temperature on a Bruker AMX 400 Avance. Melting points were taken with an Electrothermal apparatus and were uncorrected. Column chromatography was performed over silica gel (200–300 and 230–400 mesh Merck). Thin layer chromatography (TLC) was carried out on plates pre-coated with Merck silical gel F254.

Combined GC–MS analysis was performed on a Hewlett-Packard 5973 mass spectrometer at 70 eV coupled to a Hewlett-Packard 6890 gas chromatograph. An HP5-MS column (0.25 μm phase thickness, 30 m x 0.25 mm i.d.) programmed from 90 °C (1 min) to 300 °C (15 °C/min) was used. The carrier gas was helium with a constant flow rate set to 1.1 mL/min. The injector and detector temperatures were 250 °C and 280 °C respectively. An aliquot of 2 μL of the respective crude reaction was injected with a split (1:5). Elemental analysis was done on a Carlo Erba instrument.

General procedures for the synthesis of Mannich bases 7a-f

DMDBTA (52 mg, 0.50 mmol) was intimately mixed with X mg (1.00 mmol) of the respective phenol and the reaction mixture was stirred and gently heated to 150 ^oC. After 5 min, the viscous liquids so obtained stood overnight, allowing the reaction mixtures to solidify. The resulting crude product was extracted three successive times with chloroform at room temperature, dried over Na_2SO_4 and evaporated under reduced pressure. The sample of solid residue was taken and dissolved in $CHCl_3$, and was analyzed by gas chromatography using mass spectrometry detection. In order to obtain more quantity of products, the $CHCl_3$ extract was initially separated by chromatography on a silica gel column eluted with C_6H_6/AcOEt (10:0 to 7:3).

Data for new compounds

2-(1*H*-Benzimidazol-1-ylmethyl)phenol (7a): White solid, yield (35.5%), mp 215-217 ^oC; Anal. Calcd for $C_{14}H_{12}N_2O$ (224.25): C, 74.98; H, 5.39; N, 12.49. Found: C, 75.02; H, 5.34; N, 12.53; IR (KBr): ν 3048, 1501, 1457, 1267 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H, H-2'), 7.63 (dd, J = 1.8, 6.8 Hz, 1H, H-4'), 7.56 (dd, J = 1.8, 6.8 Hz, 1H, H-7'), 7.18 (m, 2H, H-5' y 6'), 7.13 (m, 1H, H-5), 7.10 (d, J = 7.6 Hz, 1H, H-3), 6.85 (d, J = 7.8 Hz, 1H, H-6), 6.7 (t, J = 7.6 Hz, 1H, H-4), 5.37 (s, 2H, Ar-C$\underline{H_2}$), ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.5 (C1), 144.8 (C2'), 143.2 (C3'a), 133.9 (C7'a), 130.1 (C3), 129.7 (C5), 122.8 (C2), 122.1 (C5' and C6'), 119.5 (C4'), 119.5 (C4), 115.7 (C6), 111.1 (C7'), 43.7 (Ar-$\underline{C}H_2$). LR-MS *m/z* (%) 224 (10, M^+), 118 (100), 91 (10), 77 (15).

2-(1*H*-Benzimidazol-1-ylmethyl)-4-methylphenol (7b): White solid, yield (45.2%), mp 210-212 ^oC, Anal. Calcd for $C_{15}H_{14}N_2O$ (238.28): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.65; H, 5.88; N, 11.72; IR

(KBr): ν 3449, 1498, 1463, 1256 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H, H-2'), 7.62 (dd, *J* = 1.1, 7.0, 1H, H-4'), 7.57 (dd, *J* = 1.1, 7.2, 1H, H-7'), 7.18 (m, 2H, H-5' y 6'), 6.93 (s, 1H, H-3), 6.91 (d, *J* = 8.1 Hz, 1H, H-5), 6.73 (d, *J* = 8.1Hz, 1H, H-6), 5.32 (s, 2H, Ar-C$\underline{H}_2$), 2.1 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8 (C-1), 144.4 (C-2'), 143.2 (C-3'a), 133.7 (C-7'a), 129.8 (C-3), 129.5 (C-5), 122.3 (C-4), 122.2 (C-2), 121.4 (C-5' and 6'), 119.3 (C-4'), 115.2 (C-6), 110.6 (C-7'), 43.1 (Ar-$\underline{C}H_2$), 20.0 ($\underline{C}H_3$). LR-MS (%) 238 (20, M^+), 221 (17), 207 (20), 131 (4.5), 118 (81), 91 (20), 77 (12.2).

2-(1*H*-Benzimidazol-1-ylmethyl)-4-methoxyphenol (7c): Brown solid, yield (35.8%), mp 194-196 °C, Anal. Calcd for $C_{15}H_{14}N_2O_2$ (254.28): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.89; H, 5.53; N, 11.06; IR (KBr): ν 3386, 2918, 1596, 1481, 1285, 1220, 1155 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.08 (s, 1H, H-2'), 7.67 (m, 1H, H-4'), 7.48 (m, 1H, H-7'), 7.18 (m, 2H, H-5' y 6'), 6.89 (d, 1H, H-6), 6.87 (m, 1H, H-5), 6.4 (s, 1H, H-3)**;** ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0 (C-4), 151,9 (C-1), 144,4 (C-2'), 143,2 (C-3'a), 134,2 (C-7'a), 122,6 (C-5'), 121,8 (C-6'), 119,7 (C-4'), 116,4 (C-6), 115,7 (C-5) 114,4 (C-3), 111,1 (C-7), 55,8 ($\underline{C}H_3$), 43,7 (Ar-$\underline{C}H_2$). LR-MS (%): 254 (17, M^+), 131 (100), 118 (3.3), 77 (11.6).

2-(1*H*-Benzimidazol-1-ylmethyl)-4-chlorophenol (7d): Brown solid, yield (44.8%), mp 320-322 ^oC, Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.0; H, 4.29; N, 10.83; Cl, 13.70. Found: C, 65.04; H, 4.25; N, 10.85; Cl, 13.68; IR (KBr) ν 3047, 1603, 1505, 1428, 1281, 1257 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 8.27 (s, 1H, H-2'), 7.63 (dd, 1H, *J* = 7.0, 2.4 Hz, H-4'), 7.52 (dd, 1H, *J* = 7.0, 2.4 Hz, H-7'), 7.25 (m, 2H, H-5' y 6'), 7.16 (d, 1H, *J* = 9.0 Hz, H-5), 7.13 (s, 1H, H-3), 6.84 (d, 1H, *J* = 9.0 Hz, H-6), 5.43 (s, 2H, Ar-C$\underline{H}_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 154.2 (C-1), 143.8 (C-2'), 142.5 (C-3'a), 133.8 (C-7'a), 128.9 (C-3 and C-5), 124.1 (C-4), 123.7 (C-2), 122.8 (C-5'), 122.1 (C-6'), 118.6 (C-4'), 116.2 (C-6), 110.3 (C-7'), 43.2 (Ar-$\underline{C}H_2$). LR-MS. *m/z* (%): 258(30, M^+) , 241 (13), 223 (3.7), 131 (7.4), 118 (100), 91 (25), 77 (9.8).

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