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SYNTHESIS AND STRUCTURE OF NEW HETEROCYCLIC DERIVATIVES OF CURCUMIN

M. Concepción Lozada,[1] Raúl G. Enríquez,[1]* Carlos E. Lobato, [1] Benjamín Ortíz, [1] Manuel Soriano,[1] Dino Gnecco,[2] and William F. Reynolds[3]

[1] Institute of Chemistry, UNAM, Circuito Exterior, Cd. Universitaria, Coyoacan, 04510, México, D. F.

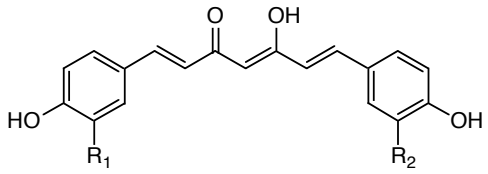
[2] Center of Chemistry, Institute of Science, BUAP, Puebla 72000, México

[3] Department of Chemistry, University of Toronto, Ontario M5S1A1, Canada

Abstract – New heterocyclic derivatives of curcumin (**3**) of different ring size were synthesized by reaction of a key intermediate, 1,7-bis(4-acetoxy-3-methoxyphenyl)hepta-3,5-dione (**5**) with some bi-nucleophilic molecules. These new synthetic derivatives were obtained in good yields and the structure of all compounds was supported by MS, IR, 1D and 2D ^{1}H and ^{13}C NMR spectra and elemental analysis.

INTRODUCTION

Curcumin, 5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one (**3**) is a secondary metabolite and the main yellow compound of *Curcuma longa* rhizomes (Figure 1). It is present together with 5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)hepta-1,4,6-trien-3-one(demethoxycurcumin, **2**), and 5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-1,4,6-trien-3-one (bisdemethoxycurcumin, **1**) in curcuma powder (turmeric), which is the main component of curry powder, a widely used seasoning. The use of *Curcuma* in traditional medicine is widespread in several parts of Asia, but it has also been extended to other continents.[1] This molecule has been the subject of several investigations during last decades, because of important results concerning pharmacological activity. In addition to antioxidant and antitumoral activities,[2-4] curcumin has inhibitory effect in the formation of β-amyloids, which are related to Alzheimer disease,[5] and an effect against integrase enzyme (IN) of HIV-1.[6]



1: $R_1=R_2=H$ bisdemethoxycurcumin
2: $R_1=OCH_3$, $R_2=H$ demethoxycurcumin
3: $R_1=R_2=OCH_3$ curcumin

Figure 1

On the other hand, the hydrogenated derivatives of curcumin are less sensitive to changes in pH or photochemical induced changes in comparison to **3** and as a result there is an increased interest in evaluating the biological activity of such derivatives. Thus, the tetrahydrogenated derivative of curcumin shows a higher antioxidant action than curcumin itself [7] and some derivatives have inhibitory effect in the biotransformation of aflatoxine.[8]

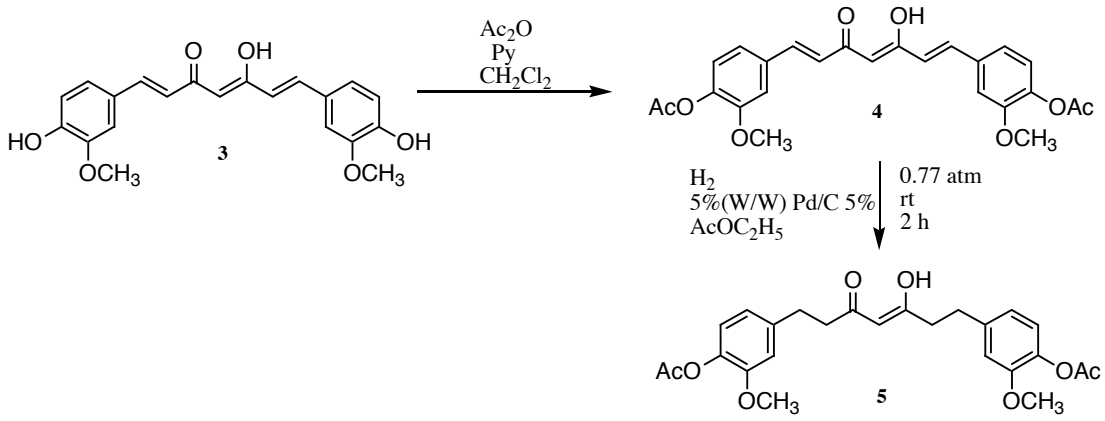
Curcumin belongs to a group of naturally occurring 1,3-diketones in which the carbonyl groups are conjugated with double bonds, thus conferring complex properties to the molecule. The 1,3-diketone system of curcumin was used to obtain the corresponding pyrazol (hydrazinocurcumin). It has stronger antioxidant effect than curcumin.[3] In addition, this heterocyclic derivative is a potent inhibitor of endothelial cell proliferation [9] and a cytotoxic agent.[10]

Following our research on structural modifications of naturally occurring compounds including 1,3-diketones[11] we have demonstrated that different reactivity is observed for □-diketone chemical functionality of curcumin upon suppression of olefinic double bonds by catalytic hydrogenation. We have obtained in this way new heterocyclic derivatives of **3**. Previously, only one heterocyclic derivative *v. gr.* hydrazinocurcumin has been reported after our best possible literature research.[9,10]

This new approach to obtain heterocyclic derivatives of **3** can be useful for the preparation of other heterocycles bearing a more complex chemical functionality in search of increased or more specific bioactivity.

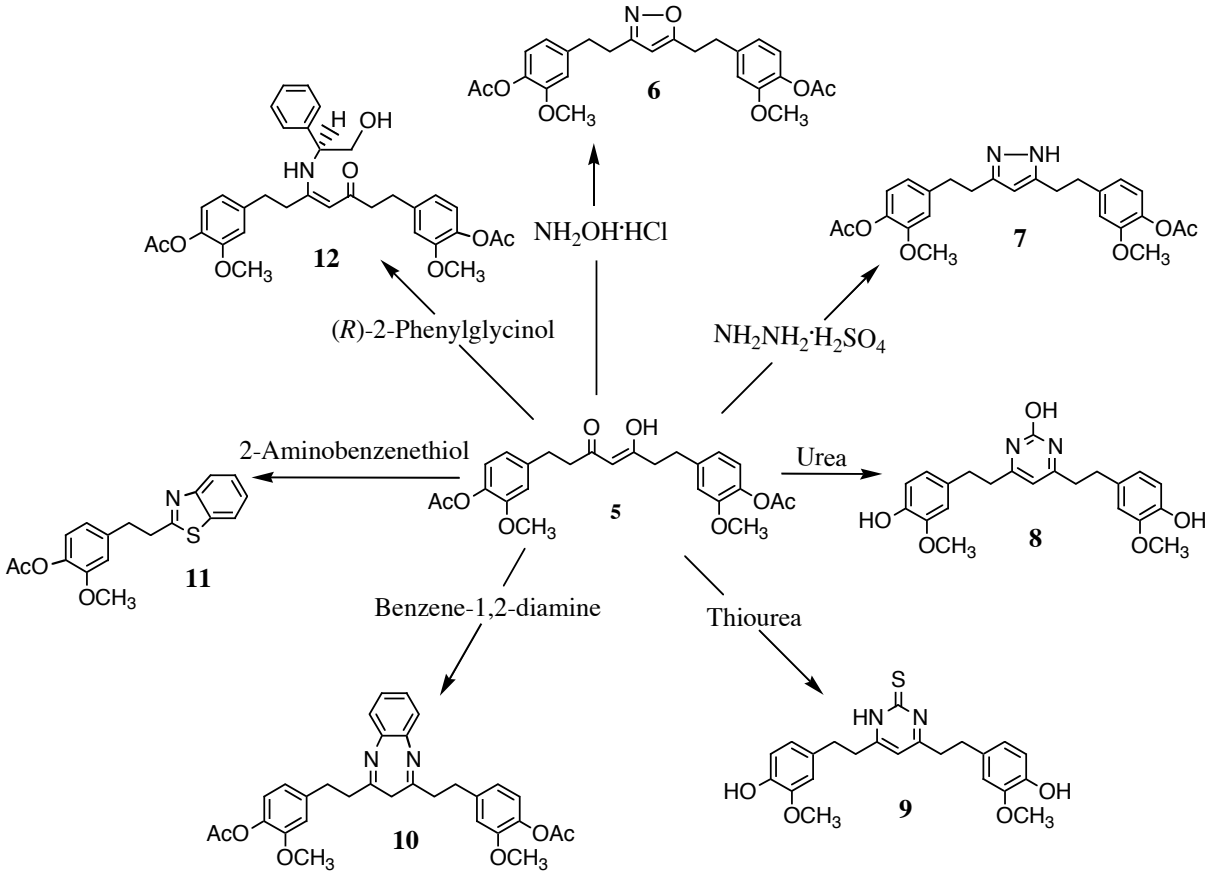
RESULTS AND DISCUSSION

We reduced the extensive conjugation of **3** protecting their phenolic hydroxyl groups. Compound (**4**) was prepared by acetylation of **3** with acetic anhydride and pyridine. Then, **4** was reduced by catalytic hydrogenation with Pd/C (5%) in ethyl acetate at room temperature and 0.77 atm for 2 h. A drastic reduction in the amount of catalyst used going from *ca.* 20% (W/W) down to 5% (Pd/C to 5% from Aldrich) was found as effective as the previously reported data.[12] The synthetic method for preparing compound (**5**) is shown in Scheme 1, and the general reaction pathway leading to heterocycles starting from **5** is given in Scheme 2.



Scheme 1

The azole derivatives (**6**) and (**7**) were obtained by the cyclization of **5** with hydroxylamine hydrochloride and hydrazine sulfate respectively in C_2H_5OH with NaOAc as base (Scheme 2). The symmetrical structure of **5** allowed obtaining only one product in 80 % yield in both cases. The structures of these compounds were determined on the basis of their elemental analysis and spectroscopic data.



Scheme 2

In addition, the crystal structures of azoles (**6**) and (**7**) were confirmed by X-Ray determinations. The ^{1}H NMR spectra of compound (**6**) showed two triplets corresponding to the allylic methylenes and a singlet for the benzylic methylenes. Independent signals were observed for the methoxy groups of the two aromatic rings as expected from symmetry considerations.

The pyrazole (**7**) is an averaged symmetric molecule, due to tautomerism of the acidic hydrogen between the two nitrogens. Therefore, the NMR spectra shows only one signal for the four methylenes, whereas the proton belonging to nitrogen was observed at 7.26 ppm as a small and broad signal which disappears upon addition of D_2O.

The reactions of **5** with urea and thiourea (Scheme 2) to obtain the corresponding pyrimidinol (**8**) and pyrimidinthione (**9**) were carried out in acidic medium (HCl) in CH_3OH, and submitted to reflux for 2 h. For these reactions, the loss of acyl protecting groups was observed. Compound (**8**) was obtained as a yellow solid in 56%. The ^{1}H NMR spectrum showed three signals at 7.18, 7.35 and 7.52 ppm, which were assigned to the three hydroxyl groups. A small and broad signal at 8.79 ppm was attributed to the pyrimidinone-pyrimidinol equilibrium. All these signals disappear upon addition of D_2O. The neighbouring methylene groups were observed as typical AA´BB´systems. Whereas the vinylic proton was observed as singlet at 6.83 ppm, this signal has shown the aromatic character of the ring. The compound (**9**) was obtained as a yellow solid in 53%. The characteristic signals for **9** in ^{1}H NMR spectrum are at 8.68 and 8.66 ppm for the hydroxyl and amine groups, respectively. The vinylic proton was found at 5.73 ppm and a multiplet from 2.48 to 2.75 ppm was observed for the four methylene groups.

The reaction of **5** with benzene-1,2-diamine (Scheme 2) was carried out in reflux of toluene and Amberlite was added as a dehydrating agent. This reaction was incomplete and a substantial amount of starting material was recovered. When the reaction time is increased, no improvement in yield was observed and some secondary undesirable products difficult to separate were obtained. Compound (**10**) was obtained in moderate yield (56%) as dark brown oil and its structure was confirmed by MS, IR and NMR spectrum. The NMR signals showed that **10** is in form of diimine, the most stable form that avoid an annular conjugation of 4n π-electrons around the diazepine (8 π-electrons) or benzodiazepine ring (12 π-electrons). This reaction was carried out in reflux of methanol and the reaction was complete in 4 h and the product was obtained in 80% yield.

Compound (**11**) was obtained from the reaction of **5** with 2-aminobenzenethiol in reflux of toluene and Amberlite, in a similar fashion as compound (**10**). After three days of reaction, no improvement in yield was observed and the reaction was stopped. The product was obtained in 67% yield, as a light brown solid; the preliminary inspection of the ^{1}H NMR spectra of **11** suggested that part of the molecule of curcumin was lost in the reaction. The MS spectrum showed an *m/z* of 327, which agrees with the structure proposal for **11**. The structure of **11** was unambiguously confirmed by crystallographic data of a suitable crystal. The reaction yield of **10** and **11** was moderate, probably due to the molecular size of nucleophile, which is larger than hydroxylamine, hydrazine, urea and thiourea. The reactivity of these

dinucleophile molecules was very different, depending of several factors such as pH, shape and volume of the nucleophile.

When we attempted the reaction of **5** with (*R*)-(-)-2-phenylglycinol to obtain the corresponding enaminone (**12**) in a similar fashion as observed with 2,4-pentanedione[11] no reaction was observed. Instead, the reaction was carried out using a similar procedure as that reported by Meyer,[13] using reflux in toluene for 48 h and *p*-TsOH as catalyst and molecular sieves as dehydrating agent. This reaction is reversible and the product is easily converted to starting material. Therefore, a flash chromatography was carried out for characterization purposes. The identification of **12** was achieved by 2D ^{1}H and ^{13}C NMR and MS spectral measurements.

The ^{1}H NMR spectrum of **12**, showed a typical signal for the N-H of the enaminone *Z* at 11.62 ppm as a doublet with J= 8.55 Hz. Several multiplets from 2.21-2.85 ppm are observed for the methylene groups, a multiplet from 4.79-4.85 ppm belong to the chiral center and a multiplet from 7.25-7.39 ppm was observed for the aryl group belong to (*R*)-(-)-2-phenylglycinol. The MS spectrum shows a molecular ion at *m/z* 575 that agrees with proposed structure. Several attempts to induce cyclization with $BF_3{\cdot}Et_2O$ as Lewis catalyst turned out unsuccessful. These conditions were ineffective for the preparation of the pursued heterocycles.

The synthesis of new heterocyclic derivatives has been possible by employing the β-diketone chemical functionality of curcumin upon suppression of olefinic double bonds. This methodology allowed the preparation of different ring size heterocycles.

EXPERIMENTAL

Curcumin (**3**) and all common reagents and solvents were used as obtained from commercial suppliers. The column chromatography SiO_2 mesh 70-230 from Merck was used for purifications. All solvents used for reactions were HPLC grade. The drying agent for organic solvents was anhydrous Na_2SO_4. IUPAC names of compounds were generated from ChemDraw Ultra from Cambridge Soft Corp and for compounds that are not heterocycles were employed nomenclature for curcuminoids. All melting points were determined with a Fisher-Jones apparatus and are uncorrected; IR spectra were recorded in a Nicolet FT-55X or Perkin Elmer 283-B in KBr. Optical rotation was measured in a Polarimeter JASCO model DIP360 at 589 nm using a 1 dm cell. Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} (*c* g/100 cm^3). MS spectra were obtained in a JEOL JMS-AX505HA mass spectrometer by electronic impact at 70 eV. 1D and 2D ^{1}H and ^{13}C NMR spectra were acquired on a 200 (Varian Gemini), 300 (Bruker Avance) and 300 (Varian Unity) MHz, in $CDCl_3$ or DMSO-d_6 and TMS as the internal reference at room temperature; chemical shifts (d) are given in ppm and coupling constants (J) in Hz. Elemental analyses were performed on a FISONS model EA1108 analyzer.

1,7-Bis(4-acetoxy-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione (4).

To a solution of 5.0 g (13.58 mmol) of **3** dissolved in 100 mL of CH_2Cl_2 in a round bottom flask, 3.3 mL (40.74 mmol) of pyridine was added together with 3.8 mL (40.74 mmol) of acetic anhydride. The mixture was stirred under refluxed conditions for 1 h. Then the solvent was evaporated *in vacuo* and 100 mL of methanol was added affording a yellow precipitate. The precipitate was recrystallized from CH_2Cl_2/CH_3OH solution, 4.9 g (80% yield); mp 156-158 ºC [lit.,[14] 154-155ºC]; IR in KBr, *v* (cm^{-1}): 2939, 1763, 1595, 1508, 1297, 1124; MS *m/z* (rel. int.): 452 M^+(56), 410 $[M-42]^+$(48), 368$[M-84]^+$(45), 350 $[M-102]^+$(100), 190 (65), 177(71), 137(32), 89(6), 43(24); ^{1}H NMR (300 MHz, $CDCl_3$): 2.33 (s, 3H), 3.88 (s, 3H), 5.85 (s, 1H), 6.56 (d, J=16.2, 2H), 7.06 (d, J= 8.1, 2H), 7.12 (d, J=1.5, 2H), 7.16 (dd, J= 8.1, 1.8, 2H), 7.62 (d, J=16.2, 2H,), 15.9 (br s, 1H); ^{13}C NMR (75 MHz): 20.66, 55.90, 101.8, 111.45, 121.04, 123.29, 124.24, 133.96, 139.93, 141.28, 151.40, 168.78, 183.08.

1,7-Bis(4-acetoxy-3-methoxyphenyl)hepta-3, 5-dione (5).

In a round bottom flask appropriate for hydrogenation, a solution of 5 g (11.06 mmol) of **4** in 100 mL of ethyl acetate was stirred with 250 mg of Pd/C (5% w/w) for 2 h at rt under H_2 atmosphere. Then the catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The product precipitated when 100 mL of CH_3OH was added. This precipitate was filtered and recrystallized from CH_2Cl_2/ CH_3OH. 4.03 g (80%); mp 68-70 ºC; IR in KBr, *v* (cm^{-1}): 3506, 1761, 1601, 1510, 1195; MS *m/z* (rel. int.): 456 M^+ (6), 414 $[M-42]^+$(69), 372$[M-84]^+$(100), 137(90), 43(8); ^{1}H NMR (300 MHz, $CDCl_3$): 2.29 (s, 3H), 2.57 (t, J=7.7, 4H), 2.87 (t, J= 7.4, 4H), 3.79 (s, 6H), 5.43 (s, 1H), 6.79 (dd, J= 8.1, 1.9, 2H), 6.83 (d, J=1.9, 2H), 6.97 (d, J=8.0, 2H), 15.4 (br s, 1H); ^{13}C NMR (75 MHz): 20.55, 31.29, 39.83, 55.71, 99.70, 112.49, 112.55, 120.23, 122.53, 137.98, 139.43, 150. 79, 169.06, 192. 77. Anal. Calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C, 66.04; H, 6.23.

3,5-Bis[α-(4-acetoxy-3-methoxyphenyl)ethyl]isoxazole (6).

In a round bottom flask, a solution of 57 mg (0.825 mmol) of $NH_2OH{\cdot}HCl$ and 90 mg (0.825 mmol) of NaOAc in 5 mL of CH_3OH was stirred for 5 min, and then a solution of 250 mg (0.55 mmol) of **5** dissolved in 50 mL of CH_3OH was added and the mixture was heated under reflux for 2 h. The solvent was evaporated and the residue was washed with brine and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4 and filtered. The solvent was evaporated and a light yellow precipitate was formed. The compound was recrystallized from CH_2Cl_2/ CH_3OH. Yield: 199 mg (80%); mp 80-82ºC; IR in KBr, *v* (cm^{-1}): 2938, 1759, 1602, 1511, 1368, 1284, 1199; MS *m/z* (rel. int.): 453 M^+ (7), 411$[M-42]^+$(100), 381$[M-72]^+$(8), 369$[M-84]^+$(97), 137(96), 43(8); ^{1}H NMR (300 MHz, $CDCl_3$): 2.3(s, 6H), 2.94(s, 4H), 2.99(2t, J=4.5, 4H), 3.79 (s, 3H), 3.80 (s, 3H), 5.73 (s, 1H), 6.73-6.79 (m, 2H), 6.81 (d, J=1.8, 2H), 6.94 (d, J=7.8, 2H); ^{13}C NMR (75 MHz): 20.62, 27.83, 34.26, 28.44, 33.47, 55.78, 101.14, 112.46, 112.55,

120.30, 120.39, 122.60, 122.66, 138.07, 138.19, 139.02, 139.64, 150.89, 163.04, 169.10, 169.13, 171.91. Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.40; H, 6.21; N, 3.13.

3,5-Bis[α-(4-acetoxy-3-methoxyphenyl)ethyl]pyrazole (7).

In a round bottom flask, a solution of 87 mg (0.66 mmol) of hydrazine sulfate and 80 mg (0.66 mmol) of NaOAc in 5 mL of CH_3OH and 2 mL of water was stirred for 5 min, then a solution of 250 mg (0.55 mmol) of **5** dissolved in 5 mL of CH_3OH was added and the mixture was heated under reflux for 2 h. The solvent was evaporated and the residue was washed with brine and extracted with CH_2Cl_2, the organic phase was dried with Na_2SO_4 and filtered. The solvent was evaporated and a precipitate was formed. The compound was recrystallized from CH_2Cl_2/CH_3OH. Yield: 199 mg (80%); mp 77-79ºC; IR in KBr, *v* (cm^{-1}): 3360, 2939, 1761, 1602, 1510, 1368, 1281, 1197; MS *m/z* (rel. int.): 452 M^+(10), 410[M-42]$^+$(100), 368[M-84]$^+$(56), 274[M-178]$^+$(21), 232(43), 137(84), 43(6); ^{1}H NMR (300 MHz, $CDCl_3$): 2.30 (s, 6H), 2.92(s, 8H), 3.77(s, 6H), 5.86 (s, 1H), 6.73 (dd, 2H, J=8.1, 2.1), 6.76 (d, J=1.8, 2H), 6.92 (d, J=8.1, 2H); ^{13}C NMR (75 MHz): 20.63, 28.65, 35.48, 55.76, 102.74, 112.58, 120.37, 122.53, 140.03, 137.98, 148.07, 150.79, 169.22. Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.35; H, 6.24; N, 6.19. Found: C, 66.50; H, 6.12; N, 6.15.

4,6-Bis[α-(4-hydroxy-3-methoxyphenyl)ethyl]pyrimidin-2-ol (8).

In a round flask, 200 mg (0.219 mmol) of **5** was dissolved in 50 mL of C_2H_5OH, 35 mg (0.438 mmol) of urea was added with 0.5 mL of HCl, the reaction mixture was heated under reflux for 2 h. The solvent was evaporated *in vacuo* and extracted with CH_2Cl_2. This compound was purified by recrystallization from CH_3OH/ether. Yield: 122 mg (56%); mp 205-206ºC; IR in KBr, *v* (cm^{-1}): 3377, 3240, 2971, 1741, 1618, 1276; MS *m/z* (rel. int.): 396M^+(63), 365[M-31]$^+$(6.0), 259[M-137]$^+$(9.0), 245[M-166]$^+$(9.0), 137(100), 124(15), 94(7); ^{1}H NMR (300 MHz, $CDCl_3$): 2.82-3.02 (m, 8H), 3.82(s, 6H), 6.59 (dd, J= 7.8, 1.8, 2H), 6.71 (d, J=7.8, 2H), 6.83 (s, 1H), 6.85 (d, J=2.1, 2H); ^{13}C NMR (75 MHz): 32.96, 35.3, 33.6, 36.1, 55.57, 104.05, 112.60, 115.37, 120.47, 129.97, 145.18, 147.51, 148.47, 172.41. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.63; H, 6.59; N, 6.90.

4,6-Bis[α-(4-hydroxy-3-methoxyphenyl)ethyl]pyrimidine-2-thione (9).

In a round flask, 250 mg (0.55 mmol) of **5** was dissolved in 50 mL of C_2H_5OH, 50.2 mg (0.66 mmol) of thiourea was added with 0.5 mL of HCl. The reaction mixture was heated under reflux for 2 h. Then, the solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 and washed with HCl (5%) and brine. The extract was dried with Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the product was recrystallized from CH_3OH/ether. Yield: 120 mg (53%); mp 77-79ºC; IR in KBr, *v* (cm^{-1}): 3441, 2929, 1599, 1274; MS *m/z* (rel. int.): 413[M+1]$^+$(1), 372[M-42]$^+$(48), 307[M-105]$^+$(22), 289[M-

123]$^+$(12), 154[M-258]$^+$(92), 137(100), 107(21), 89(17), 77(17); ^{1}H NMR (300 MHz, $CDCl_3$): 2.48-2.75 (m, 8H), 3.68 (s, 3H), 3.72(s, 3H), 5.73 (s, 1H), 6.54 (dd, J=8.1, 1.5, 2H), 6.57 (dd, J=8.1, 1.5, 2H), 6.64 (dd, J=8.1, 1.5, 2H), 6.73 (d, J=1.5, 2H) 6.77 (d, J=1.5, 2H); ^{13}C NMR (75 MHz): 28.37, 39.50, 30.45, 44.77, 55.48, 99.62, 112.43, 115.26, 120.20, 120.26, 129.5, 131.35, 131.57, 144.59, 144.70, 147.37, 193.38, 204.66. Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79; S, 7.77. Found: C, 64.15; H, 5.82; N, 6.72; S, 7.60.

2, 4–Bis[α-(4–acetoxy-3-methoxyphenyl)ethyl]- 3*H*-benzo[*b*][1,4]diazepine (10).

To a solution of 200 mg (0.44 mmol) of **5** in 25 mL of toluene, a catalytic amount of *p*-TsOH was added and stirred in a round flask. Then, 71.3 mg (0.66 mmol) of benzene-1,2-diamine dissolved in 25 mL of toluene was added dropwise and 3 g of Amberlite as dehydrating agent. The mixture was heated under reflux for 72 h. The reaction mixture was filtered to remove the Amberlite and the solvent evaporated *in vacuo*, affording an oily residue. The product was purified by column chromatography (hexane: ethyl acetate, 1:1). Yield: oil, 163 mg (56%); IR in KBr, *v* (cm^{-1}): 3361, 2932, 1759, 1599, 1507, 1195; MS *m/z* (rel. int.): 529[M+1]$^+$(100), 485[M-43]$^+$(6), 359[M-179]$^+$(10), 172(8), 137(87), 43(11); ^{1}H NMR (300 MHz, $CDCl_3$): 2.30(s, 6H), 2.79 (t, J=8.1, 4H), 3.03 (t, J=8.1, 4H), 3.78(s, 3H), 3.82(s, 3H), 6.60 (s, 1H), 6.79 (dd, J= 7.8, 1.8, 2H), 6.82 (d, J=1.8, 2H), 6.94 (d, J=7.8, 2H), 7.22-7.26 and 7.38-7.41(m, 4H); ^{13}C NMR (75 MHz): 20.67, 32.2, 42.34, 55.82, 112.79, 120.44, 122.61, 124.96, 127.67,138.02, 140.15, 140.20, 150.87, 159.67, 169.18. Anal. Calcd for $C_{31}H_{32}N_2O_6$: C, 67.42; H, 6.08; N, 5.82. Found: C, 67.77; H, 6.29; N, 5.66.

2-[2-(4-Acetoxy-3-methoxyphenyl)ethyl]benzothiazole (11).

To a solution of 500 mg (1.1 mmol) of **5** in 60 mL of toluene, a catalytic amount of *p*-TsOH was added and stirred in a round flask. Then, 159 mg (1.27 mmol) of 2-aminobenzenethiol dissolved in 25 mL of toluene was added dropwise with 3 g of Amberlite used as dehydrating agent. The mixture was heated under reflux for 72 h. After, the mixture was filtered to remove the Amberlite, the solvent evaporated *in vacuo* and the product was purified by column chromatography (hexane: ethyl acetate, 1:1). Yield: 241 mg (67%); mp 115-117ºC; IR in KBr, *v* (cm^{-1}): 2938, 1755, 1602, 1514, 1196; MS *m/z* (rel. int.): 327M$^+$(41), 285[M-42]$^+$(81), 149[M-178]$^+$(80), 137(100), 43(7); ^{1}H NMR (300 MHz, $CDCl_3$): 2.30 (s, 3H), 3.19 (d, J=10.2, 1H) and 3.21 (d, J=8.7, 1H), 3.41 (d, J=9.0, 1H) and 3.44 (dd, J=10.2, 0.9, 1H), 3.78 (s, 3H), 6.84 (dd, J= 7.5, 1.8, 1H), 6.85 (s, 1H), 6.96 (d, J=7.5, 1H), 7.36 (td, J=7.2, 1.2, 1H), 7.46 (td, J=7.2, 1.2, 1H), 7.84 (ddd, J=8.1, 1.2, 0.6, 1H), 7.99 (ddd, J=8.1, 1.2, 0.6, 1H); ^{13}C NMR (75 MHz): 20.65, 35.45, 35.93, 55.80, 112.68, 120.50, 121.53, 122.54, 122.73, 124.84, 126.02, 135.04, 138.24, 139.12, 150.95, 153.09, 169.13, 170.66. Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28; S, 9.79. Found: C, 66.14; H, 5.38; N, 4.34; S, 9.65.

1,7-Bis(4-acetoxy-3-methoxyphenyl)-5-(2-hydroxy-1-phenylethylamino)-4-hepten-3-one (12).

To a solution of 0.5 g (1.1 mmol) of **5** in 50 mL of toluene, a catalytic amount of *p*-TsOH was added and stirred in a round flask. Then, 274 mg (2 mmol) of (*R*)-(-)-2-phenylglicinol dissolved in 20 mL of toluene was added dropwise with 3 g of Amberlite. The mixture was heated under reflux for 48 h. Then, the mixture was filtered to remove the Amberlite, the solvent was evaporated *in vacuo* and the product was purified by column chromatography (hexane: ethyl acetate, 1:1). 12% yield; [a] (10^{-1} deg cm^2/g): +135.0° (*c* 1.0, CH_2Cl_2); IR in KBr, *v* (cm^{-1}): 3415, 2939, 1742, 1601, 1515, 1233; MS *m/z* (rel. int.): 575M^+(6), 533[M-42]$^+$(27), 502[M-73]$^+$(7), 460[M-115]$^+$(19), 382[M-193]$^+$(21), 370[M-205]$^+$(16), 336[M-239]$^+$(26), 294(31) 137(100), 91(11), 43(61); ^{1}H NMR (300 MHz, $CDCl_3$): 2.06 (s, 6H), 2.30-2.96 (m, 8H), 3.80 (s, 3H), 3.85 (s, 3H), 4.18 (dd, J=11.40, 7.36, 1H), 4.30 (dd, J=11.40, 4.60, 1H), 4.79 (br td, J=7.45, 4.97, 1H), 5.05 (s, 1H), 5.51 (br s, 1H), 6.49-6.94 (m, 6H), 7.26-7.40 (m, 5H), 11.62 (d, J=8.55, 1H); ^{13}C NMR (75 MHz): 20.79, 31.74, 34.21, 44.25, 55.81, 67.66, 95.44, 110.77, 111.01, 114.14, 114.34, 120.73, 120.78, 126.52, 128.14, 128.97, 131.98, 133.85, 144.15, 146.38, 165.70, 170.75, 197.77. Anal. Calcd for $C_{33}H_{37}NO_8$: C, 68.85; H, 6.48; N, 2.43. Found: C, 68.63; H, 6.71; N, 2.37.

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