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SYNTHESIS OF NEW POTENTIAL HIV-1 INTEGRASE INHIBITORS

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Abstract – A synthesis of some 1,2-(hetero)arylsubstituted ethanone and 1,3-(hetero)arylsubstituted 3-hydroxypropenone derivatives, designed as potential HIV-1 integrase inhibitors, is reported. The microwave-assisted synthesis was applied in several reactions achieving reductions in reaction times and high yields. All compounds prepared were tested to explore their potential anti-HIV activity.

INTRODUCTION

The currently available anti-HIV drugs target the viral reverse transcriptase or protease enzymes. However, the actual number of therapeutic options is limited because of interactions between drugs, additive toxicity, and the increasing incidence of resistance to current antiretroviral regimens, which underscores the importance to develop new anti-AIDS agents.[1] Only recently the integrase enzyme (IN) has become an attractive therapeutic target for the discovery of novel anti-HIV drugs.[2]

HIV integrase is involved in the integration of HIV DNA into host chromosomal DNA that proceeds in a series of distinct steps.[3] First, IN cleaves the two terminal nucleotides from each 3' end of the viral DNA (3' processing). In the second step, called strand transfer, IN catalyzes staggered nicking of the target chromosomal DNA and joining of each 3' end of the viral DNA to the 5' ends of the host DNA. Divalent metals such as Mg^{2+} or Mn^{2+} are required for both 3' processing and strand transfer.[3]

It is important to emphasize that this enzyme has no known functional analog in human cells and even though a number of compounds has been reported to inhibit HIV-1 IN in biochemical assays, at present clinically useful inhibitors are not available. Promising anti-integrase drugs are being developed with two compounds in early clinical trials: Shionogi/GlaxoSmithKline S-1360 in Phase II[4] and Merck's L-

870,810 in Phase I.[5]

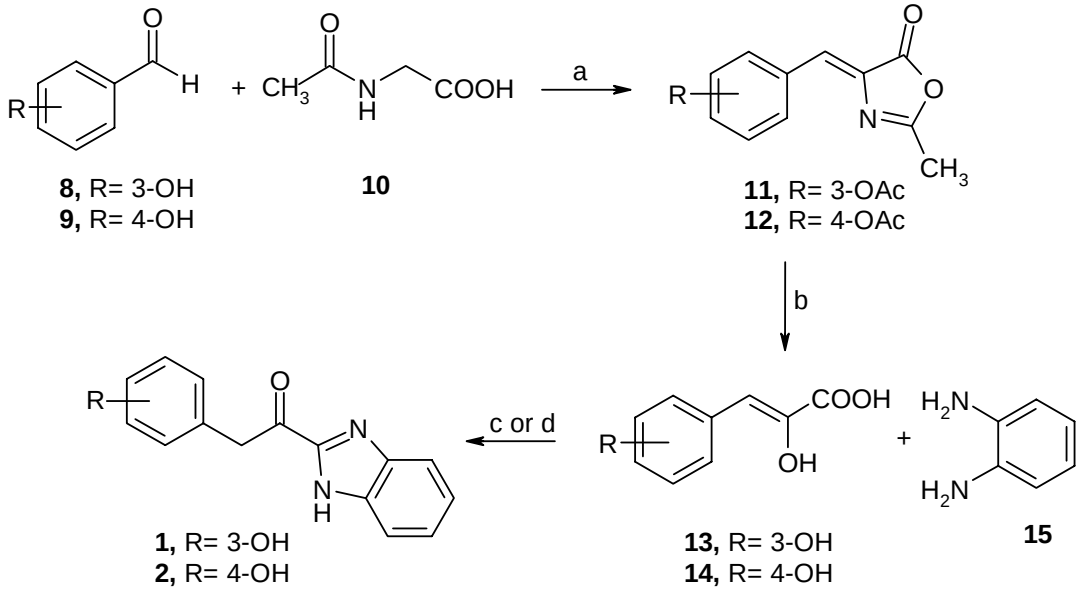
A wide variety of molecules has been reported as IN inhibitors[6] and some of them are hydroxylated aromatic compounds and/or derivatives containing keto functionality.[7] It has been suggested that they may interact with the catalytic domain of IN by interfering with the coordination of the metal ions that are required for the phosphoryl transfer reaction.[3]

On these bases, we planned the synthesis of potential IN inhibitors (**1-7**) characterized in their structure by both hydroxylated functions and carbonyl groups in a spatial arrangement able to coordinate metal ions. Furthermore, we introduced in several derivatives a benzimidazole nucleus whose imine nitrogen has a well-known ability to complex divalent cations.[8] For the synthesis of some intermediates as well as final products the microwave-assisted approach has been employed to achieve reductions in reaction times, higher yields, cleaner and more reproducible reactions than for traditional synthetic processes.

RESULTS AND DISCUSSION

A synthesis of 1-(1*H*-benzimidazol-2-yl)-2-(3- or 4-hydroxyphenyl)ethanones (**1**) and (**2**) was accomplished according to the reaction sequence reported in Scheme 1.

4-Benzylidene-4*H*-oxazol-5-ones (**11-12**) were obtained by condensation of 3- or 4-hydroxybenzaldehyde (**8** or **9**) and *N*-acetylglycine (**10**). In the reported Erlenmeyer approach[9] the reaction was carried out at 120°C for 5 h whereas with the application of microwave-assisted technology, the reaction is completed in only 5 min and compounds (**11-12**) were easily isolated by conventional work-up in high yields. The subsequent acid hydrolysis afforded the corresponding α-hydroxycinnamic acids (**13-14**).

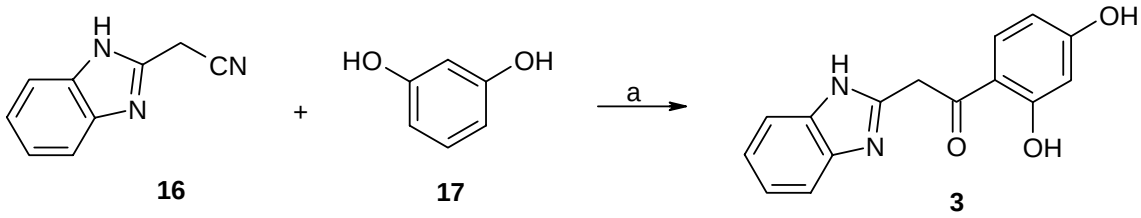


Reagents and conditions: a) dry NaOAc, Ac_2O, 120°C, 5 min, 300 W; b) 2N HCl, 120°C, 1 h; c) H_2O, 120°C, 2 h; d) H_2O, two steps: 110°C, 5 min, 250 W; 110°C, 3 min, 250 W.

Scheme 1

The intermediates (**13-14**) by condensation with 1,2-phenylenediamine hydrochloride (**15**) afforded derivatives (**1-2**). This reaction were performed both by means of traditional heating and microwave irradiation which shortened the reaction times, affording the desired products in good yields.

2-(1*H*-Benzimidazol-2-yl)-1-(2,4-dihydroxyphenyl)ethanone (**3**) was prepared by reaction of (1*H*-benzimidazol-2-yl)acetonitrile (**16**) with resorcinol (**17**) in acidic medium (Scheme 2).

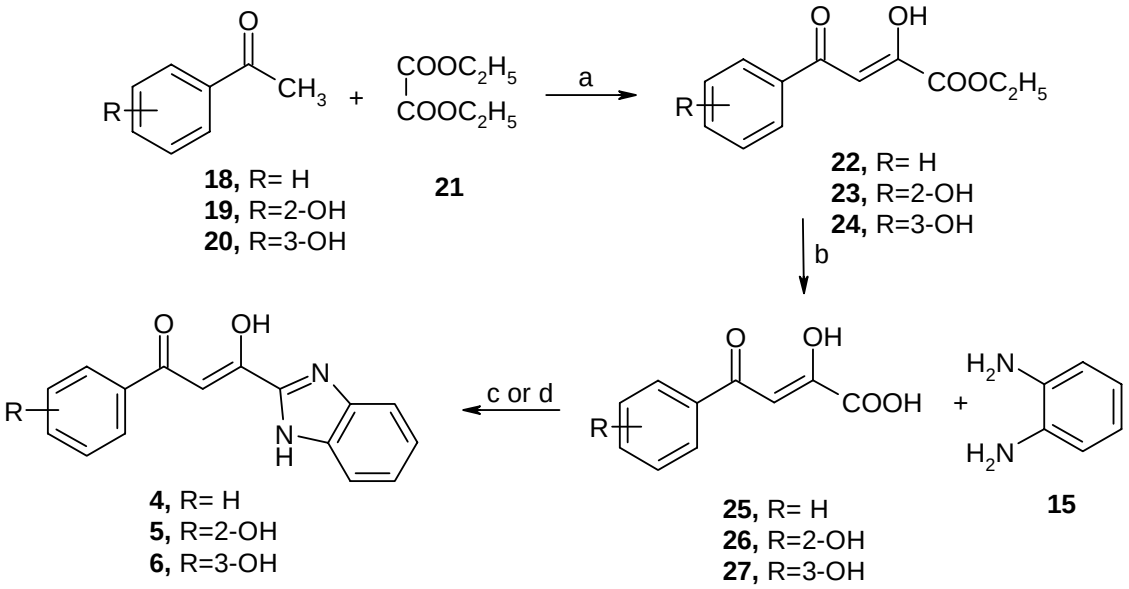


16 **17** **3**

Reagents and conditions: a) gas HCl, $BF_3(C_2H_5)_2O$, C_2H_5OAc, rt, 5 h.

Scheme 2

Scheme 3 shows the synthetic pathway that yielded the 1-aryl-3-(1*H*-benzimidazol-2-yl)-3-hydroxy-propenone (**4-6**). The synthesis of ethyl 2-hydroxy-4-oxo-4-phenylbut-2-enoate (**22-24)** was carried out by reacting the appropriate acetophenone (**18-20**) with diethyl oxalate (**21**) in presence of a catalytic amount of a base. Once more, the microwave-irradiation dramatically shortened the reaction times, affording the desired products in high yields. The intermediates obtained were converted by basic hydrolysis into the corresponding acids (**25-27**) which were subsequently condensed with 1,2-phenylenediamine hydrochloride (**15**) to give final compounds (**4-6**) both in a microwave oven and conventional heating.



18, R= H
19, R=2-OH
20, R=3-OH

21

22, R= H
23, R=2-OH
24, R=3-OH

25, R= H
26, R=2-OH
27, R=3-OH

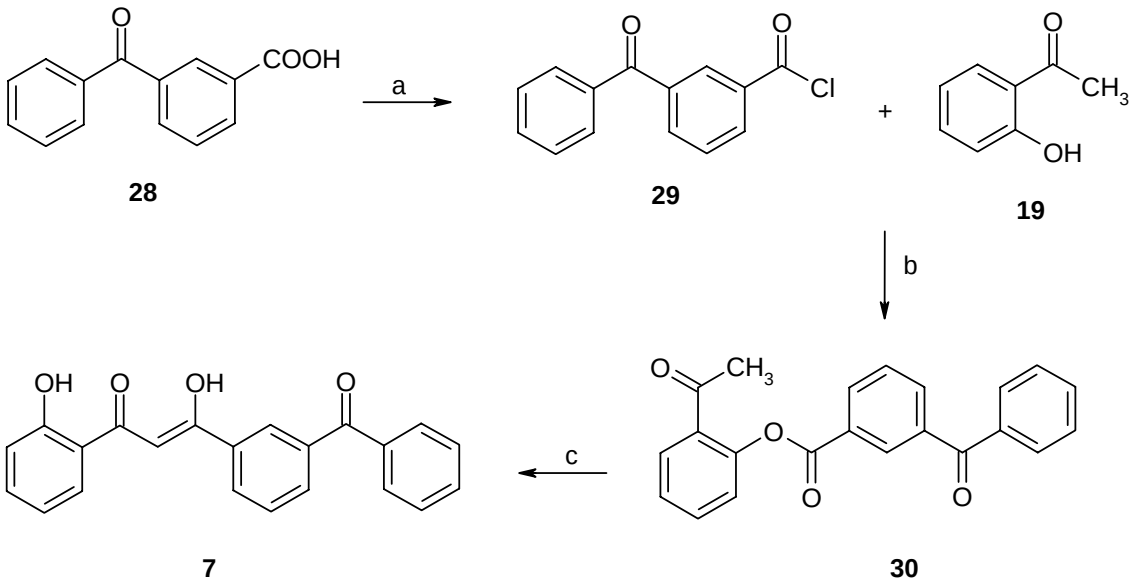
15

4, R= H
5, R=2-OH
6, R=3-OH

Reagents and conditions: a) dry C_2H_5ONa, THF, three separated stages in the same conditions: 25°C, 10 sec, 250 W; b) 1N NaOH, dioxane, r t, 1 h; c) H_2O, 120°C, 2 h; d) H_2O, two stages: 110°C, 5 min, 250 W; 110°C, 3 min, 250 W.

Scheme 3

A synthesis of 3-(3-benzoylphenyl)-3-hydroxy-1-(2-hydroxyphenyl)propenone (**7**) was performed by potassium *tert*-butoxide-catalyzed rearrangement of 2-benzoyloxyacetophenone (**30**) (Scheme 4). This intermediate was prepared by acylation of 2-hydroxyacetophenone (**19**) with 3-benzoylbenzoyl chloride (**29**) in turn obtained from the corresponding acid (**28**) and thionyl chloride.



Reaction conditions: a) $SOCl_2$, Δ, 2 h; b) dry pyridine, rt, 2 h; c) DMF, *t*-C_4H_9OK, rt, 1 h.

Scheme 4

The synthesized compounds (**1-7**) were tested for anti-HIV activity by determining their ability to inhibit the replication of HIV-1 (III_B) in MT-4 cells and the HIV-1 IN in an enzymatic assay. Derivatives (**1**, **3** and **6**) were found to prevent the cytopathic effect of HIV-1 III_B at micromolar concentrations (EC_{50}: 27 μM for **1**, 321 μM for **3** and 7.1 μM for **6**), whereas none of the tested compounds inhibited the HIV-1 integrase enzymatic activity. These results suggest that derivatives (**1**, **3** and **6**) might interfere with HIV replication at a different point in the virus life cycle.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (230-400 mesh). IR spectra were obtained on a Perkin Elmer Spectrum BX FT-IR as nujol mulls. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 spectrometer. Chemical shifts were expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz.

General procedure under microwave irradiation for the synthesis of 4-benzylidene-4*H*-oxazol-5-ones (11-12)

A mixture of aromatic aldehyde (**8** or **9**) (0.001 mol), *N*-acetylglycine (**10**) (140.52 mg, 0.0012 mol) and dry NaOAc (176.90 mg, 0.0013 mol) in Ac_2O (1 mL) were placed in a cylindrical quartz tube (Ø 2 cm). The reaction mixture was then stirred and irradiated in a microwave oven at 300 W for 5 min at 120° C. The mixture was allowed to cool to rt and ice water (5 mL) was added. The resulting precipitate was filtered, washed with ether, dried under vacuum and recrystallized from acetone.

4-(3-Acetoxybenzylidene)-2-methyl-4*H*-oxazol-5-one (**11**): yield 48%, mp 124-126°C; ^{1}H-NMR (δ) 2.34 and 2.42 (2s, 6H, CH_3), 7.10 (s, 1H, CH), 7.16-7.94 (m, 4H, ArH). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.42; H, 4.65; N, 5.96.

4-(4-Acetoxybenzylidene)-2-methyl-4H-oxazol-5-one (**12**): yield 100%, mp 134-136°C; ^{1}H-NMR (δ) 2.32 and 2.41 (2s, 6H, CH_3), 7.16 (s, 1H, CH), 7.17-8.13 (m, 4H, ArH). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67, H, 4.52, N, 5.71. Found: C, 63.78, H, 4.36, N, 5.62.

Conversion of 4-benzylideneoxazol-5-ones (11-12) to α-hydroxycinnamic acids (13-14)

The 4-benzylideneoxazol-5-one (**11** or **12**) (0.001 mol) in 2N HCl (4 mL) was refluxed under stirring for 1 h. The reaction mixture was then filtered while it was still hot after which the obtained filtrate was allowed to cool to rt and extracted with ethyl acetate. The organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was crystallized from ether.

2-Hydroxy-3-(3-hydroxyphenyl)acrylic acid (**13**): yield 92%, mp 172°C (decomp); ^{1}H-NMR (δ) 6.28 (s, 1H, CH), 6.61-7.28 (m, 4H, ArH), 9.15 and 9.32 (2bs, 2H, OH), 13,1 (br s, 1H, COOH). Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.12; H, 4.65.

2-Hydroxy-3-(4-hydroxyphenyl)acrylic acid (**14**): yield 70%, mp 207°C (decomp); ^{1}H-NMR (δ) 6.32 (s, 1H, CH), 6.67-7.60 (m, 4H, ArH), 8.80 and 9.58 (2br s, 2H, OH). Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.87; H, 4.77.

Condensation of 13-14 with 1,2-phenylenediamine hydrochloride

A) Thermal conditions:

A mixture of 1,2-phenylenediamine hydrochloride (**15**) (180.14 mg, 0.001 mol), the appropriate α-hydroxycinnamic acid (**13** or **14**) (0.002 mol) and H_2O (2 mL) was refluxed under stirring for 1-2 h. The reaction mixture was cooled ; in some instances the product precipitated from the acid solution, and in others, the solution was neutralized with 20% ammonium hydroxide to afford a precipitate. The product was collected by filtration and washed first with water and then with ether. The compound was usually recrystallized from aqueous ethanol.

B) Microwave irradiation:

A mixture of 1,2-phenylenediamine hydrochloride (**15**) (90.07 mg 0.0005 mol), the appropriate α-hydroxycinnamic acid (**13** or **14**) (0.001 mol) and H_2O (1 mL) was placed in a cylindrical quartz tube (Ø 2 cm), then stirred and irradiated in a microwave oven for two subsequent periods (irradiation conditions

were [1] P/W 250, t/min 5, T/°C 110, [2] P/W 250, t/min 3, T/°C 110). The conventional work-up was carried out as described in method A.

1-(1*H*-Benzimidazol-2-yl)-2-(3-hydroxyphenyl)ethanone (**1**): yield 32%, mp 264-266°C; IR: 1662 cm^{-1}; ^{1}H-NMR (δ) 4.01 (s, 2H, CH_2), 6.56-7.73 (m, 8H, ArH), 9.28 (s, 1H, OH), 12.32 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.75; H, 4.52; N, 11.43.

1-(1*H*-Benzimidazol-2-yl)-2-(4-hydroxyphenyl)ethanone (**2**): yield 49%, mp 183-185°C; IR: 1672 cm^{-1}; ^{1}H-NMR (δ) 3.98 (s, 2H, CH_2), 6.64-7.72 (m, 8H, ArH), 9.21 (s, 1H, OH), 12.30 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.64; H, 4.53; N, 11.27.

Synthesis of 2-(1*H*-benzimidazol-2-yl)-1-(2,4-dihydroxyphenyl)ethanone (3)

A solution of resorcinol (**17**) (130 mg, 0.0011 mol) and (1*H*-benzimidazol-2-yl)acetonitrile (**16**) (157.18 mg, 0.001 mol) in ethyl acetate (5 mL) was placed in a two-necked, round-bottomed flask equipped with a gas dispersion tube and an air-condenser topped with a drying tube. Boron trifuoride diethyl etherate (85.16 mg, 0.0006 mol) was added to the stirred solution. A stream of dry hydrogen chloride gas was passed into the stirred suspension over a period of 5 h, while the temperature was maintained below 20°C. HCl gas was at first introduced rapidly to saturate the solvent and then in a slow gentle stream. In 1.5 h, a very thick suspension was formed. Stirring was continued for 1 more hour at the end of HCl introduction. The imine hydrochloride was filtered and washed with ethyl acetate, suspended in water and heated at 95-100°C with stirring for 1 h. A pale brown oil separated out and solidified rapidly upon seeding. The solid was collected and washed with water and recrystallized from ethyl acetate to give compound (**3**). Yield 8%, mp 264-267°C; IR: 1648 cm^{-1}; ^{1}H-NMR (δ) 5.04 (s, 2H, CH_2), 6.44-7.86 (m, 7H, ArH), 10.82 (br s, 1H, NH), 11.51 (s, 1H, OH). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.38; H, 4.22; N, 10.78.

General procedure for the synthesis of ethyl 2-hydroxy-4-aryl-4-oxobutenoate (22-24)

A mixture of diethyl oxalate (**21**) (219.21 mg, 0.0015 mol), the appropriate acetophenone (**18-20**) (0.001 mol) and a catalytic amount of $NaOC_2H_5$ in anhydrous THF (2 mL) was placed in a cylindrical quartz tube (Ø 2 cm), then stirred and irradiated in a microwave oven for three subsequent periods in the same conditions (W 250, 10 sec, 25°C). The solvent was evaporated under reduced pressure, the collected solid was washed first with ether and then with 5% HCl and then dried and recrystallized from ether to provide the desired final diketo product (**22-24**).

Ethyl 2-hydroxy-4-oxo-4-phenylbut-2-enoate (**22**): yield 99%, mp 39-41°C; ^{1}H-NMR (δ) 1.42 (t, 3H, J = 7.1, CH_3), 4.40 (q, 2H, J = 7.1, CH_2), 7.09 (s, 1H, CH), 7.49-8.02 (m, 5H, ArH). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.31; H, 5.63.

Ethyl 2-hydroxy-4-(2-hydroxyphenyl)-4-oxobut-2-enoate (23): yield 100%, mp 202-204°C; ^{1}H-NMR (δ) 1.20 (t, 3H, J = 7.3, CH_3), 4.08 (q, 2H, J = 7.3, CH_2), 5.37 (s, 1H, CH), 6.63-7.63 (m, 4H, ArH), 15.70

(s, 1H, OH). Anal.. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.22; H, 5.33.

Ethyl 2-hydroxy-4-(3-hydroxyphenyl)-4-oxobut-2-enoate (24): yield 100%, mp 112-115°C; ^{1}H-NMR (δ) 1.22 (t, 3H, J = 7.1, CH_3), 4.09 (q, 2H, J = 7.1, CH_2), 6.20 (s, 1H, CH), 6.69-7.19 (m, 4H, ArH), 9.40 (s, 1H, OH). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found. C, 61.25; H, 5.43.

General procedure for the synthesis of 2-hydroxy-4-aryl-4-oxobutenoic acid (25-27)

A dioxane solution (2 mL) of derivatives (**22-24**) (0.001 mol) was treated with 1N NaOH (2 mL, 20 mmol) and stirred to rt for 1h. Then the reaction mixture was acidified with conc. HCl to afford a yellow solid that was collected, washed with ether and recrystallized from ethyl acetate.

2-Hydroxy-4-oxo-4-phenylbut-2-enoic acid (**25**): yield 85%, mp 146-148°C; ^{1}H-NMR (δ) 7.18 (s, 1H, CH), 7.50-8.03 (m, 5H, ArH). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.72; H, 4.05.

2-Hydroxy-4-(2-hydroxyphenyl)-4-oxobut-2-enoic acid (**26**): yield 90%, mp 142-145°C; ^{1}H-NMR (δ) 6.91 (s, 1H, CH), 7.51-8.06 (m, 4H, ArH). Anal. Calcd for $C_{10}H_8O_5$: C, 57.70; H, 3.87. Found: C, 57.93; H, 3.74.

2-Hydroxy-4-(3-hydroxyphenyl)-4-oxobut-2-enoic acid (**27**): yield 100%, mp >300°C; ^{1}H-NMR (δ) 6.96 (s, 1H, CH), 7.09-7.48 (m, 4H, ArH), 10.16 (s, 1H, OH). Anal. Calcd for $C_{10}H_8O_5$: C, 57.70; H, 3.87. Found: C, 57.93; H, 3.52.

Synthesis of 3-(1*H*-benzimidazol-2-yl)-3-hydroxy-1-arylpropenone (4-6)

Compounds **(4-6**) were obtained in a microwave oven or by classical heating as described for derivatives (**1-2)** and recrystallized from ether.

3-(1*H*-Benzimidazol-2-yl)-3-hydroxy-1-phenylpropenone (**4**): yield 96%, mp 275-277°C IR: 1689, 1614 cm^{-1}; ^{1}H-NMR (δ) 6.81 (s, 1H, CH), 7.13-7.99 (m, 9H, ArH), 12.05 (br s, 1H, NH), 13.66 (s, 1H, OH). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.88; H, 4.40; N, 10.55.

3-(1*H*-Benzimidazol-2-yl)-3-hydroxy-1-(2-hydroxyphenyl)propenone (**5**): yield 12%, mp 287-289°C; IR: 1652, 1610 cm^{-1};^{1}H-NMR (δ) 6.90-7.90 (m, 8H, ArH, CH), 12.14 (br s, 1H, NH), 12.90 (s, 1H, OH), 13.12 (s, OH). Anal. Calcd for: $C_{16}H_{12}N_2O_3$: C, 68.57, H, 4.32, N, 9.99. Found: C, 68.41, H, 4.18, N, 9.76.

3-(1*H*-Benzimidazol-2-yl)-3-hydroxy-1-(3-hydroxyphenyl)propenone (**6**): yield 25%, mp 265-268°C; IR: 1666, 1608 cm^{-1}; ^{1}H-NMR (δ) 6.74 (s, 1H, CH), 6.94-7.52 (m, 8H, ArH), 9.74 (s, 1H, OH), 12.02 (br s, 1H, NH), 13.58 (s, 1H, OH). Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.74; H, 4.21; N, 10.11.

Synthesis of 3-benzoylbenzoyl chloride (29)

A mixture of 3-benzoylbenzoic acid (**28**) (226.23 mg, 0.001 mol) and thionyl chloride (4 mL, 55 mmol) was refluxed under stirring for 2 h. The solvent was removed under reduced pressure to afford the crude product (**29**).

Synthesis of 2-acetylphenyl 3-benzoylbenzoate (30)

A mixture of **29** (244.45 mg, 0.001 mol) and 2-hydroxyacetophenone (**19**) (109 mg, 0.0008 mol) was stirred in dry pyridine (2 mL) at rt for 2 h. The reaction mixture was then poured into ice-cooled 5% HCl, extracted with $CHCl_3$, washed three times with 5%. $NaHCO_3$ and then washed three times with water. The solvent was removed under reduced pressure to afford a residue purified by silica gel column chromatography eluting with cyclohexane/ethyl acetate 7:3. Yield 99%, mp 118-120°C (ether/cyclohexane); ^{1}H-NMR (δ) 2.56 (s, 3H, CH_3), 7.23-8.62 (m, 13H, ArH). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.45, H, 4.73.

Synthesis of 3-(3-benzoylphenyl)-3-hydroxy-1-(2-hydroxyphenyl)propenone (7)

A solution of *t*-C_4H_9OK (179 mg, 0.0016 mmol) in DMF (1 mL) was added to a solution of **30** (275 mg, 0.0008 mmol) in DMF (1 mL). The mixture was allowed to cool at rt for about 1 h. The reaction mixture was poured into ice-cooled 3% HCl to give a residue which was purified by silica gel column chromatography eluting with cyclohexane/ethyl acetate 7:3. Crystallization from ether gave the corresponding **7** in 64% yields. Mp 113-115°C; IR: 1658, 1618, 1578 cm^{-1}; ^{1}H-NMR (δ) 6.90 (s, 1H, CH), 6.92-8.37 (m, 13H, ArH), 12.03 (s, 1H, OH). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.51, H, 4.87.

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