ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 12, pp. 1767–1774. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © L.V. Chinh, T.N. Hung, N.T. Nga, T.T.N. Hang, T.T.N. Mai, V.A. Tarasevich, 2014, published in Zhurnal Organicheskoi Khimii, 2014, Vol. 50, No. 12, pp. 1786–1793.

Synthesis and Antimicrobial Activity of Chalcones Containing Benzotriazolylmethyl and Imidazolylmethyl Substituents

L. V. Chinh[a], T. N. Hung[a], N. T. Nga[a], T. T. N. Hang[b], T. T. N. Mai[a], and V. A. Tarasevich[c]

[a] *Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology, Hanoi, Vietnam*

[b] *Vietnam National University, Hanoi, Vietnam*

[c] *Institute of New Materials Chemistry, National Academy of Sciences of Belarus, ul. F. Skoriny 36, Minsk, 220141 Belarus*
e-mail: tar@ichnm.basnet.by

Received August 29, 2014

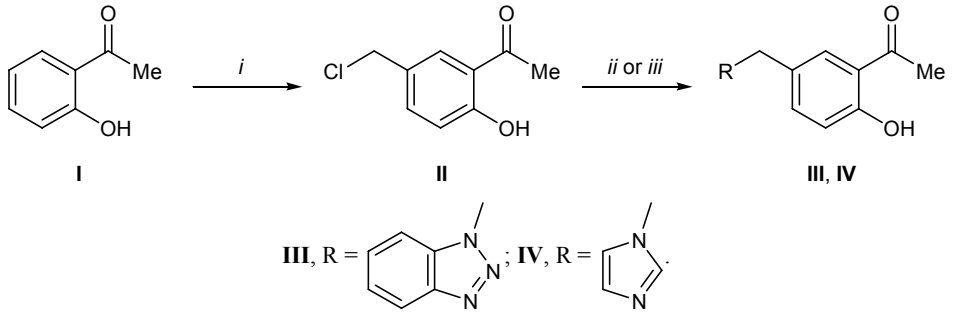
Abstract—Methods have been developed for the synthesis of new 1*H*-benzotriazol-1-ylmethyl- and 1*H*-imidazol-1-ylmethyl-substituted chalcones starting from 2-hydroxyacetophenone. The procedures include chloromethylation, N-alkylation, and Claisen–Schmidt condensation. The presence of an imidazole fragment on the ring A and piperazine fragment on the ring B of the resulting chalcones increases their antimicrobial activity (minimum inhibitory concentration 12.5–50.0 μg/mL), whereas introduction of a benzotriazole fragment reduces the antimicrobial activity.

DOI: 10.1134/S1070428014120094

In recent years chalcone derivatives containing nitrogen heterocycles have attracted increased attention due to broad spectrum of their biological activity [1], in particular antifungal and antibacterial [2]. We believed that introduction of triazole and imidazole fragments into chalcone molecules could affect their biological activity.

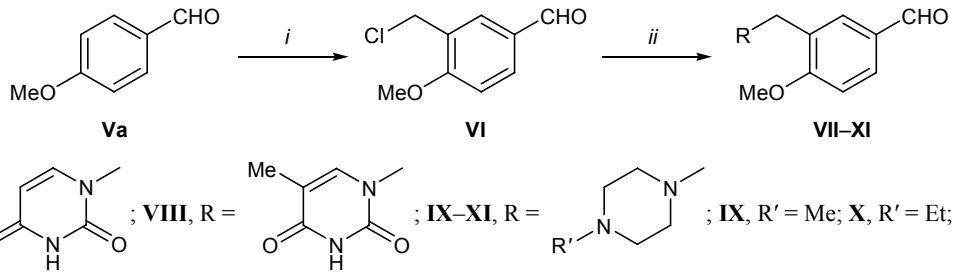
Imidazole and triazole derivatives constitute the two main classes of antimicrobial azoles; imidazole and triazole rings are structural fragments of well known drugs, such as nitroimidazole, ketoconazole, miconazole, albaconazole, fluconazole, isavuconazole, terconazole, and posaconazole [3–10], which are used for the treatment of many systemic fungal infections. New antifungal imidazole derivatives are now being developed, and imidazole derivatives are widely represented among numerous and efficient medicines. Simultaneously, triazole derivatives are considered to be promising drugs for antifungal chemotherapy due to broad spectrum of their activity and reduced toxicity as compared to imidazole analogs [11]. Nevertheless, there are no published data on the synthesis and antifungal or antibacterial activity of chalcones containing benzotriazole and imidazole fragments attached to the

Scheme 1.



Reagents and conditions: *i*: paraformaldehyde, concd. aq. HCl, 35°C, 8 h; *ii*: benzotriazole, K_2CO_3, DMF, MW, 20 min; *iii*: imidazole, K_2CO_3, DMF, MW, 20 min.

Scheme 2.



Reagents and conditions: *i*: (1) 37% aq. formaldehyde, $ZnCl_2$, concd. aq. HCl, 50°C, 30 min; (2) reflux; *ii*: 4-R-piperazine, K_2CO_3, DMF, MW, 10 min.

ring A. To fill this gap, in the present work we synthesized new chalcones with benzotriazolylmethyl and imidazolylmethyl substituents and tested them for antifungal and antibacterial activity.

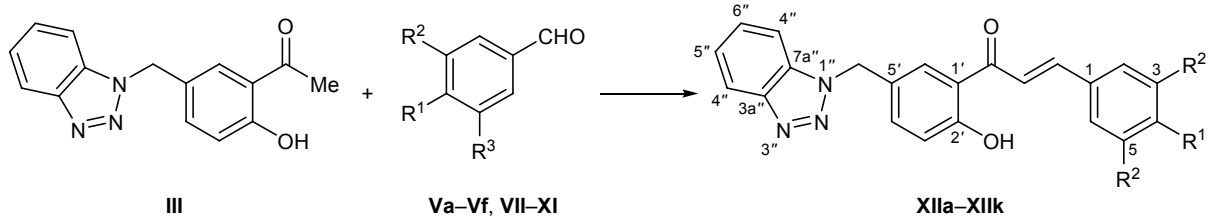
The key intermediate products were prepared starting from 2-hydroxyacetophenone (**I**). In the first step, chloromethylation of 2-hydroxyacetophenone (**I**) according to the known procedure [12] gave 5-chloromethyl-2-hydroxyacetophenone (**II**) which was used to alkylate benzotriazole and imidazole under microwave irradiation at 50°C (250 W, 20 min). We thus obtained 5-(1*H*-benzotriazol-1-ylmethyl)-2-hydroxyacetophenone (**III**) and 2-hydroxy-5-(1*H*-imidazol-1-ylmethyl)acetophenone (**IV**) in 55 and 59% yield, respectively (Scheme 1).

By reaction of 4-methoxybenzaldehyde (**Va**) with formaldehyde and HCl in the presence of $ZnCl_2$ [13] we synthesized 3-chloromethyl-4-methoxybenzaldehyde (**VI**) which was brought into reactions with uracil, thymine, *N*-methylpiperazine, *N*-ethylpiperazine, and *N*-phenylpiperazine to obtain aldehydes **VII**–**XI** (Scheme 2). Aldehydes **VII** and **VIII** were isolated in 55–56% yield.

The final step was the Claisen–Schmidt condensation of ketones **III** and **IV** with 4-methoxybenzaldehyde (**Va**), 3-methoxybenzaldehyde (**Vb**), 4-isopropylbenzaldehyde (**Vc**), 4-methylbenzaldehyde (**Vd**), 3-hydroxy-4-methoxybenzaldehyde (**Ve**, isovanillin), 3,4,5-trimethoxybenzaldehyde (**Vf**), 3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl)-4-methoxybenzaldehyde (**VII**), 4-methoxy-3-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl)benzaldehyde (**VIII**), 4-methoxy-3-(4-methylpiperazin-1-ylmethyl)benzaldehyde (**IX**), 3-(4-ethylpiperazin-1-ylmethyl)-4-methoxybenzaldehyde (**X**), and 4-methoxy-3-(4-phenylpiperazin-1-ylmethyl)benzaldehyde (**XI**), which afforded the corresponding benzotriazolylmethyl-substituted chalcones **XIIa**–**XIIk** in 46–67% yield (Scheme 3) and imidazolylmethyl-substituted analogs **XIIIa**–**XIIIg** in 45–70% yield (Scheme 4). The reactions of ketone **IV** with aldehydes **Vf** and **IX**–**XI** were accompanied by formation of many by-products, and we failed to isolate the desired chalcones.

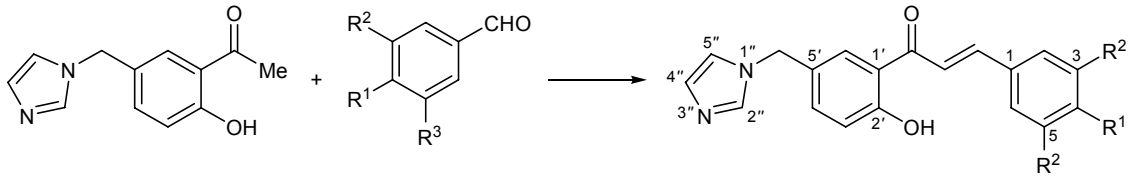
The product structure was confirmed by IR and NMR spectroscopy and high-resolution mass spectrometry. Signals in the ^1H and ^{13}C NMR spectra of compounds **XIIk** and **XIIIa** were assigned using heteronuclear single quantum coherence (HSQC) technique. It was found that signals from the ketone moiety of all chalcones **XII** and **XIII** were generally consistent with those of initial ketones **III** and **IV** and that signals from the aldehyde moiety differed depending of the initial aldehyde.

Scheme 3.



V, **XII**, R^1 = OMe, $R^2 = R^3$ = H (**a**); $R^1 = R^3$ = H, R^2 = OMe (**b**); R^1 = *i*-Pr, $R^2 = R^3$ = H (**c**); R^1 = Me, $R^2 = R^3$ = H (**d**); R^1 = OMe, R^2 = OH, R^3 = H (**e**); $R^1 = R^2 = R^3$ = OMe (**f**); **XII**, R^1 = OMe, R^2 = 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl, R^3 = H (**g**); $R^1 = R^3$ = H, R^2 = 5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl (**h**); R^1 = OMe, R^2 = 4-methylpiperazin-1-ylmethyl, R^3 = H (**i**); R^1 = OMe, R^2 = 4-ethylpiperazin-1-ylmethyl, R^3 = H (**j**); R^1 = OMe, R^2 = 4-phenylpiperazin-1-ylmethyl, R^3 = H (**k**).

Scheme 4.



IV **Va–Ve**, **VII**, **VIII** **XIIIa–XIIIg**

XIII, R^1 = OMe, R^2 = R^3 = H (**a**), R^1 = R^3 = H, R^2 = OMe (**b**), R^1 = *i*-Pr, R^2 = R^3 = H (**c**), R^1 = Me, R^2 = R^3 = H (**d**), R^1 = OMe, R^2 = OH, R^3 = H (**e**), R^1 = OMe, R^2 = 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl, R^3 = H (**f**), R^1 = R^3 = H, R^2 = 5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl (**g**).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Impact-410 spectrometer with Fourier transform. The NMR spectra were measured on a Bruker Avance 500 instrument (500 MHz); the chemical shifts are given relative to tetramethylsilane. The high-resolution mass spectra were obtained on a Varian FT-ICR (Fourier transform ion cyclotron resonance) mass spectrometer. The progress of reactions was monitored by TLC on Merck 60F254 silica gel plates; spots were visualized using an UV lamp (λ 254 nm). Silica gel (40–230 mesh) was used for column chromatography.

1-[5-(Chloromethyl)-2-hydroxyphenyl]ethanone (II). Paraformaldehyde, 2.43 g (81 mmol), was added to a solution of 9.9 g (73 mmol) of 2-hydroxyacetophenone (**I**) in 160 mL of concentrated aqueous HCl. The mixture was stirred for 8 h at 35°C, diluted with water, and extracted with methylene chloride (3× 100 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Yield 10.0 g (75%), mp 77–79°C. Compound **II** was used in further syntheses without additional purification.

Compounds III and IV (*general procedure*). A mixture of 1.19 g (10 mmol) of benzotriazole or 0.68 g (10 mmol) of imidazole, 1.8 g (13.3 mmol) of potassium carbonate, 2.07 g (15 mmol) of compound **II**, and 238 mg of butyl(triethyl)ammonium bromide in 25 mL of anhydrous dimethylformamide was subjected to microwave irradiation for 20 min under stirring at 50°C (250 W). The mixture was concentrated under reduced pressure, and the residue was diluted with chloroform (60 mL) and extracted with distilled water (4×60 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from methanol (**III**) or ethyl acetate (**IV**).

1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]ethanone (III). Yield 55%, white crystals, mp 128–130°C. IR spectrum, ν, cm^{-1}: 3448 (O–H), 3040 (C–H), 1640 (C=O), 1618 (C=C), 769 (δC–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.63 s (3H, CH_3), 5.93 s (2H, CH_2), 6.93 d (1H, 3-H, J = 8.5 Hz), 7.39 t (1H, 5′-H, J = 7.5 Hz), 7.47 d.d (1H, 4-H, J = 2.0, 8.5 Hz), 7.53 t (1H, 6′-H, J = 7.5 Hz), 7.91 d (1H, 7-H, J = 8.5 Hz), 8.02 d (1H, 6-H, J = 2.0 Hz), 8.04 d (1H, 4′-H, J = 8.5 Hz), 11.81 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.1, 50.3, 110.8, 118.2, 119.2, 120.7, 124.1, 126.7, 127.4, 131.0, 132.5, 135.6, 145.4, 160.2, 203.5. Found: *m*/*z* 268.10805 [M + H]$^+$. $C_{15}H_{14}N_3O_2$. Calculated: M + H 268.10857.

1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]ethanone (IV). Yield 59%, light yellow crystals, mp 96–98°C. IR spectrum, ν, cm^{-1}: 3448 (O–H), 3141, 3094 (C–H), 1655 (C=O), 1511–1639 (C=C), 757 (δC–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.62 s (3H, CH_3), 5.13 s (2H, CH_2), 6.90 s (1H, 4′-H), 6.95 d (1H, 3-H, J = 8.5 Hz), 7.21 s (1H, 5′-H), 7.44 d.d (1H, 4-H, J = 2.0, 8.5 Hz), 7.77 s (1H, 2′-H), 7.89 d (1H, 6-H, J = 2.0 Hz), 11.88 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.9, 48.7, 118.0, 119.3, 120.5, 128.4, 128.7, 130.8, 135.7, 137.2, 160.2, 203.9. Found: *m*/*z* 217.09715 [M + H]$^+$. $C_{12}H_{13}N_2O_2$. Calculated: M + H 217.09772.

3-(Chloromethyl)-4-methoxybenzaldehyde (VI). A mixture of 50 g (0.37 mol) of 4-methoxybenzaldehyde (**Va**), 75 g of 40% aqueous formaldehyde, 250 mL of 36% aqueous HCl, and 15 g (0.11 mol) of zinc(II) chloride was vigorously stirred for 30 min at 50°C and was then heated for 30 min under reflux. After cooling, the aqueous phase was removed, and the organic phase was diluted with chloroform (200 mL), washed with 10% aqueous sodium hydroxide and water to neutral reaction, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from hexane. Yield 57.6 g (85%), mp 59–60.5°C.

Compounds VII and VIII (*general procedure*). A mixture of 1.0 g (8.9 mmol) of uracil or 1.12 g

(8.9 mmol) of thymine, 1.8 g (13.3 mmol) of potassium carbonate, 1.8 g (9.8 mmol) of 3-(chloromethyl)-4-methoxybenzaldehyde (**VI**), and 212 mg of butyl(triethyl)ammonium bromide in 25 mL of anhydrous dimethylformamide was vigorously stirred for 20 min under microwave irradiation (70°C, 300 W). The mixture was concentrated under reduced pressure, the residue was diluted with chloroform (50 mL) and extracted with distilled water (3×50 mL), and the organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from methanol.

3-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl)-4-methoxybenzaldehyde (VII). Yield 56%, white crystals, mp 192–194°C. IR spectrum, ν, cm^{-1}: 3041, 2840 (C–H), 1727, 1674 (C=O), 1598 (C=C), 817 (δC–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.94 s (3H, OCH_3), 4.86 s (2H, CH_2), 5.61 d (1H, 5′-H, J = 8.0 Hz), 7.25 d (1H, 5-H, J = 8.0 Hz), 7.60 d (1H, 2-H, J = 2.0 Hz), 7.69 d (1H, 6′-H, J = 8.0 Hz), 7.90 d.d (1H, 6-H, J = 2.0, 8.0 Hz), 9.87 s (1H, CHO), 11.31 s (1H, 3′-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 101.0, 111.3, 125.3, 128.8, 129.2, 132.5, 146.1, 150.9, 161.8, 163.7, 191.3. Found: m/z 261.08698 $[M + H]^+$. $C_{13}H_{13}N_2O_4$. Calculated: M + H 261.08747.

4-Methoxy-3-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl)benzaldehyde (VIII). Yield 55%, white crystals, mp 201–203°C. IR spectrum, ν, cm^{-1}: 3154, 2836 (C–H), 1684 (C=O), 1595 (C=C), 813 (δC–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.79 s (3H, CH_3), 3.94 s (3H, OCH_3), 4.82 s (2H, CH_2), 7.25 d (1H, 5-H, J = 8.5 Hz), 7.55 m (2H, 2-H, 6′-H), 7.90 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 9.86 s (1H, CHO), 11.32 s (1H, 3′-H). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 11.9, 56.2, 108.7, 111.3, 125.4, 128.3, 129.2, 132.3, 141.7, 150.9, 161.7, 164.3, 191.4. Found: m/z 275.10263 $[M + H]^+$. $C_{14}H_{15}N_2O_4$. Calculated: M + H 275.10308.

Piperazine derivatives IX–XI (*general procedure*). A mixture of 10.0 mmol of 1-methylpiperazine, 1-ethylpiperazine, or 1-phenylpiperazine, 2.07 g (15 mmol) of potassium carbonate, 1.84 g (10 mmol) of 3-(chloromethyl)-4-methoxybenzaldehyde (**VI**), and 238 mg (1 mmol) of butyl(triethyl)ammonium bromide in 25 mL of anhydrous dimethylformamide was stirred for 10 min at 70°C under microwave irradiation (300 W). The mixture was concentrated under reduced pressure, and the residue was diluted with chloroform (60 mL), and washed with distilled water (4×60 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure, and the residue was purified by column chromatography using hexane–ethyl acetate as eluent.

Chalcones XIIa–XIIk and XIIIa–XIIIg (*general procedure*). Potassium hydroxide, 224 mg (4 mmol), was added to a mixture of 1 mmol of ketone **III** or **IV** and 1.1 mmol of aldehyde **Va**–**Vf** or **VII**–**XI** in 15 mL of anhydrous ethanol, and the mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure, and the residue was treated with water, neutralized with 10% aqueous HCl, and extracted with ethyl acetate (3×20 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by column chromatography using hexane–ethyl acetate (1:1) as eluent.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (XIIa). Yield 63%, yellow crystals, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3423 (O–H), 3051 (C–H), 1634 (C=O), 1588–1601 (C=C), 838 (δC–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.87 s (3H, OCH_3), 5.84 s (2H, CH_2), 6.95 d (2H, 3-H, 5-H, J = 8.5 Hz), 6.99 d (1H, 3′-H, J = 8.5 Hz), 7.38 m (1H, 5″-H), 7.43 m (4H, α-H, 4′-H, 6″-H, 7″-H), 7.59 d (2H, 2-H, 6-H, J = 8.5 Hz), 7.87 d (1H, β-H, J = 15.5 Hz), 7.89 d (1H, 6′-H, J = 2.0 Hz), 8.08 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 51.7, 55.5, 109.6, 114.6, 117.0, 119.3, 120.1, 120.2, 124.1, 124.9, 127.1, 127.7, 130.8, 132.7, 135.4, 146.1, 146.3, 162.3, 163.6, 193.3. Found: m/z 386.14992 $[M + H]^+$. $C_{23}H_{20}N_3O_3$. Calculated: M + H 386.15038.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(3-methoxyphenyl)prop-2-en-1-one (XIIb). Yield 65%, yellow crystals, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3421 (O–H), 3064 (C–H), 1645 (C=O), 1575 (C=C), 826 (δC–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.88 s (3H, OCH_3), 5.84 s (2H, CH_2), 7.00 d (2H, 4-H, 3′-H, J = 8.5 Hz), 7.13 d (1H, 2-H, J = 2.0 Hz), 7.22 d (1H, 6-H, J = 8.5 Hz), 7.36 m (2H, 5-H, 5″-H), 7.44 m (3H, 4′-H, 6″-H, 7″-H), 7.49 d (1H, α-H, J = 15.5 Hz), 7.85 d (1H, β-H, J = 15.5 Hz), 7.88 d (1H, 6′-H, J = 2.0 Hz), 8.08 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 51.7, 55.5, 109.6, 113.1, 116.9, 119.4, 119.5, 119.9, 120.0, 120.2, 124.2, 125.1, 127.7, 129.0, 130.1, 132.7, 135.6, 135.7, 146.2, 146.3, 160.0, 163.6, 193.3. Found: m/z 386.14992 $[M + H]^+$. $C_{23}H_{20}N_3O_3$. Calculated: M + H 386.15045.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(4-isopropylphenyl)prop-2-en-1-one

(XIIc). Yield 69%, yellow crystals, mp 135–137°C. IR spectrum, ν, cm^{-1}: 3432 (O–H), 3062 (C–H), 1637 (C=O), 1562–1606 (C=C), 838 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 d [6H, CH(CH_3)$_2$, J = 7.0 Hz], 2.96 m [1H, C**H**(CH_3)$_2$], 5.81 s (2H, CH_2), 6.99 d (1H, 3′-H, J = 8.5 Hz), 7.30 d (1H, 5-H, J = 8.5 Hz), 7.37 m (1H, 5″-H), 7.43 m (3H, 4′-H, 6″-H, 7″-H), 7.48 d (1H, α-H, J = 15.5 Hz), 7.56 d (2H, 2-H, 6-H, J = 8.5 Hz), 7.88 d (1H, β-H, J = 15.5 Hz), 7.89 d (1H, 6′-H, J = 2.0 Hz), 8.09 d (1H, 4″-H, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.7, 34.2, 51.7, 109.6, 118.6, 119.4, 120.1, 120.2, 124.1, 125.0, 127.2, 127.7, 129.0, 131.9, 132.6, 135.4, 146.3, 146.4, 152.8, 163.6, 193.4. Found: m/z 398.18630 $[M + H]^+$. $C_{25}H_{24}N_3O_2$. Calculated: M + H 398.18681.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(4-methylphenyl)prop-2-en-1-one (XIId). Yield 61%, white crystals, mp 175–177°C. IR spectrum, ν, cm^{-1}: 3445 (O–H), 3102 (C–H), 1636 (C=O), 1564–1606 (C=C), 838 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, CH_3), 5.84 s (2H, CH_2), 6.99 d (1H, 3′-H, J = 8.0 Hz), 7.24 d (2H, 3-H, 5-H, J = 8.0 Hz), 7.37 m (1H, 5″-H), 7.43 m (3H, 4′-H, 6″-H, 7″-H), 7.48 d (1H, α-H, J = 15.5 Hz), 7.53 d (2H, 2-H, 6-H, J = 8.0 Hz), 7.87 d (1H, β-H, J = 15.5 Hz), 7.89 s (1H, 6′-H), 8.08 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.6, 51.7, 109.5, 118.4, 119.4, 120.1, 120.2, 124.1, 125.0, 127.6, 131.6, 132.7, 135.4, 135.5, 141.9, 146.3, 146.4, 152.8, 163.6, 193.4. Found: m/z 370.15500 $[M + H]^+$. $C_{23}H_{20}N_3O_2$. Calculated: M + H 370.15547.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)prop-2-en-1-one (XIIe). Yield 37%, yellow crystals, mp 126–128°C. IR spectrum, ν, cm^{-1}: 3440 (O–H), 3050 (C–H), 1639 (C=O), 1568 (C=C), 834 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.96 s (3H, OCH_3), 5.84 s (2H, CH_2), 6.89 d (1H, 3-H, J = 8.5 Hz), 6.99 d (1H, 3′-H, J = 8.5 Hz), 7.14 d.d (1H, 2-H, J = 2.0, 8.5 Hz), 7.27 s (1H, 6-H), 7.37 m (2H, α-H, 5″-H), 7.44 m (3H, 4′-H, 6″-H, 7″-H), 7.82 d (1H, β-H, J = 15.5 Hz), 7.87 d (1H, 6′-H, J = 2.0 Hz), 8.09 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 51.7, 56.1, 109.6, 110.7, 113.3, 117.6, 119.4, 120.1, 120.2, 123.4, 124.2, 125.0, 127.7, 128.0, 131.3, 132.6, 135.3, 146.1, 146.2, 149.6, 163.6, 193.3. Found: m/z 402.14483 $[M + H]^+$. $C_{23}H_{20}N_3O_4$. Calculated: M + H 402.14534.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (XIIf). Yield 60%, white crystals, mp 148–150°C. IR spectrum, ν, cm^{-1}: 3444 (O–H), 2962 (C–H), 1657 (C=O), 1570 (C=C), 825 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.92 s (3H, OCH_3), 3.95 s (6H, OCH_3), 5.84 s (2H, CH_2), 6.85 s (2H, 2-H, 6-H), 7.01 d (1H, 3′-H, J = 8.5 Hz), 7.40 m (5H, α-H, 4′-H, 5″-H, 6″-H, 7″-H), 7.81 d (1H, β-H, J = 155 Hz), 7.85 s (1H, 6′-H), 8.06 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 51.6, 56.4, 61.4, 106.2, 109.5, 118.8, 119.4, 120.0, 120.1, 124.1, 125.1, 127.7, 128.9, 132.6, 132.7, 135.4, 146.3, 146.4, 153.5, 163.2, 163.5, 193.1. Found: m/z 446.17105 $[M + H]^+$. $C_{25}H_{24}N_3O_5$. Calculated: M + H 446.17158.

(*E*)-1-(5-{3-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-oxoprop-1-en-1-yl}-2-methoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (XIIg). Yield 57%, yellow crystals, mp 263–265°C. IR spectrum, ν, cm^{-1}: 3447 (O–H, N–H), 3033 (C–H), 1640–1703 (C=O), 1569–1610 (C=C), 838 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.96 s (3H, OCH_3), 4.93 s (2H, CH_2), 5.69 d (1H, 5-H, J = 7.5 Hz), 5.88 s (2H, CH_2), 7.00 d (2H, 3′-H, 5-H, J = 8.5 Hz), 7.40 m (1H, 5″-H), 7.47 m (4H, 4′-H, 6″-H, 6‴-H, 7″-H), 7.54 d (1H, α-H, J = 15.5 Hz), 7.63 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.81 d (1H, 2-H, J = 2.0 Hz), 7.86 d (1H, β-H, J = 15.5 Hz), 8.05 s (1H, 6′-H), 8.07 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 47.2, 51.4, 55.5, 101.3, 109.7, 111.0, 118.0, 118.9, 119.3, 119.9, 123.7, 124.3, 127.2, 127.7, 129.3, 131.4, 131.7, 135.3, 145.2, 145.3, 145.6, 151.3, 159.8, 163.0, 164.4, 193.3. Found: m/z 510.17720 $[M + H]^+$. $C_{28}H_{24}N_5O_5$. Calculated: M + H 510.17768.

(*E*)-1-(5-{3-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-oxoprop-1-en-1-yl}-2-methoxybenzyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (XIIh). Yield 56%, yellow crystals, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3446 (O–H, N–H), 3035 (C–H), 1639–1681 (C=O), 1589–1612 (C=C), 835 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.90 s (3H, CH_3), 3.95 s (3H, OCH_3), 4.92 s (2H, CH_2), 5.86 s (2H, CH_2), 6.98 d (1H, 5-H, J = 8.0 Hz), 7.00 d (1H, 3′-H, J = 8.0 Hz), 7.38 m (1H, 5″-H), 7.46 m (4H, 4′-H, 6″-H, 6‴-H, 7″-H), 7.51 d (1H, α-H, J = 15.5 Hz), 7.59 d.d (1H, 6-H, J = 2.0, 8.0 Hz), 7.76 d (1H, 2-H, J = 2 Hz), 7.85 d (1H, β-H, J = 15.5 Hz), 8.02 d (1H, 6′-H, J = 2.0 Hz), 8.08 d (1H, 4″-H, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.3, 46.6, 51.6, 55.8, 109.7, 110.4, 111.0, 118.2, 119.1, 119.9, 120.1, 124.3, 124.5, 125.1, 127.4, 127.7, 129.4, 131.0, 131.8, 132.6, 135.5, 140.9, 145.3, 146.0, 151.4, 159.7, 162.7,

164.2, 192.6. Found: m/z 524.19285 $[M + H]^+$. $C_{29}H_{26}N_5O_5$. Calculated: M + H 524.19336.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-[4-methoxy-3-(4-methylpiperazin-1-ylmethyl)phenyl]prop-2-en-1-one (XIIi). Yield 52%, yellow crystals, mp 196–198°C. IR spectrum, ν, cm^{-1}: 3444 (O–H), 2938 (C–H), 1637 (C=O), 1557–1600 (C=C), 831 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.17 s (3H, NCH_3), 2.55 s (4H, 3‴-H, 5‴-H), 2.61 s (4H, 2‴-H, 6‴-H), 3.90 s (3H, OCH_3), 3.62 s (2H, CH_2), 5.85 s (2H, CH_2), 6.92 d (1H, 5-H, J = 8.5 Hz), 6.99 d (1H, 3′-H, J = 8.5 Hz), 7.37 m (1H, 5″-H), 7.43 m (3H, 4′-H, 6″-H, 7″-H), 7.47 d (1H, α-H, J = 15.5 Hz), 7.55 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.74 s (1H, 2-H), 7.90 d (1H, β-H, J = 15.5 Hz), 7.98 d (1H, 6′-H, J = 2.0 Hz), 8.08 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 45.9 (NCH_3), 51.8, 52.9, 55.0, 55.5, 55.7, 109.6, 110.8, 117.2, 119.3, 120.2, 124.1, 124.9, 126.8, 126.9, 127.6, 129.1, 129.6, 131.3, 132.6, 135.3, 146.4, 146.5, 160.5, 163.4, 193.3. Found: m/z 498.24997 $[M + H]^+$. $C_{29}H_{32}N_5O_3$. Calculated: M + H 498.25048.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-[3-(4-ethylpiperazin-1-ylmethyl)-4-methoxyphenyl]prop-2-en-1-one (XIIj). Yield 51%, yellow crystals, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3431 (O–H), 2933 (C–H), 1636 (C=O), 1589–1603 (C=C), 834 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 s (3H, $CH_2C\mathbf{H}_3$), 2.46 m (2H, $C\mathbf{H}_2CH_3$), 2.62 s (8H, 2‴-H, 3‴-H, 5‴-H, 6‴-H), 3.63 s (2H, CH_2), 3.89 s (3H, OCH_3), 5.85 s (2H, CH_2), 6.92 d (1H, 5-H, J = 8.5 Hz), 6.98 d (1H, 3′-H, J = 8.5 Hz), 7.36 m (1H, 5″-H), 7.43 m (3H, 4′-H, 6″-H, 7″-H), 7.47 d (1H, α-H, J = 15.5 Hz), 7.55 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.73 s (1H, 2-H), 7.90 d (1H, β-H, J = 15.5 Hz), 7.97 s (1H, 6′-H), 8.08 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.8, 21.7, 52.2, 52.7, 52.9, 55.6, 109.6, 110.7, 117.1, 119.4, 120.1, 124.1, 124.9, 126.9, 126.8, 127.6, 129.1, 129.6, 131.3, 132.6, 135.3, 146.3, 146.5, 160.5, 163.5, 193.3. Found: m/z 512.26562 $[M + H]^+$. $C_{30}H_{34}N_5O_3$. Calculated: M + H 512.26613.

(*E*)-1-[5-(1*H*-Benzotriazol-1-ylmethyl)-2-hydroxyphenyl]-3-[4-methoxy-3-(4-phenylpiperazin-1-ylmethyl)phenyl]prop-2-en-1-one (XIIk). Yield 45%, yellow crystals, mp 202–203°C. IR spectrum, ν, cm^{-1}: 3444 (O–H), 2909 (C–H), 1637 (C=O), 1558–1601 (C=C), 832 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.73 m (4H, 2‴-H, 6‴-H), 3.27 m (4H, 3‴-H, 5‴-H), 3.68 s (2H, CH_2), 3.91 s (3H, OCH_3), 5.81 s (2H, CH_2), 6.83 t (1H, *p*-H, J = 8.5 Hz), 6.94 d (3H, 5-H, *o*-H, J = 8.5 Hz), 6.98 d (1H, 3′-H, J = 8.5 Hz), 7.23 m (2H, *m*-H), 7.34 m (1H, 5″-H), 7.41 m (3H, 4′-H, 6″-H, 7″-H), 7.48 d (1H, α-H, J = 15.5 Hz), 7.56 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.79 s (1H, 2-H), 7.91 d (1H, β-H, J = 15.5 Hz), 7.97 s (1H, 6′-H), 8.05 d (1H, 4″-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 49.1, 51.7, 53.1, 55.6, 55.7, 109.6, 110.8, 116.1, 117.3, 119.3, 119.7, 120.1, 124.0, 125.0, 126.9, 127.6, 129.1, 129.8, 131.3, 132.6, 135.3, 146.3, 151.3, 160.5, 163.6, 193.3. Found: m/z 560.26562 $[M + H]^+$. $C_{34}H_{34}N_5O_3$. Calculated: M + H 560.26619.

(*E*)-1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (XIIIa). Yield 54%, yellow crystals, mp 163–165°C. IR spectrum, ν, cm^{-1}: 3445 (O–H), 3096 (C–H), 1638 (C=O), 1570–1604 (C=C), 836 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.86 s (3H, OCH_3), 5.12 s (2H, CH_2), 6.94 d.d (3H, 3-H, 5-H, 5″-H, J = 2.0, 8.5 Hz), 7.01 d (1H, 3′-H, J = 8.5 Hz), 7.12 s (1H, 4″-H), 7.30 d.d (1H, 4′-H, J = 2.5, 8.5 Hz), 7.41 d (1H, α-H, J = 15.5 Hz), 7.61 d.d (3H, 2-H, 2″-H, 6-H, J = 2.5, 8.5 Hz), 7.69 d (1H, 6′-H, J = 2.0 Hz), 7.90 d (1H, β-H, J = 15.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 50.3, 55.5, 114.6, 117.0, 119.2, 119.5, 119.8, 120.1, 126.2, 127.1, 128.5, 130.7, 130.8, 135.2, 135.7, 137.3, 146.2, 163.8, 164.7, 193.2. Found: m/z 337.15467 $[M + H]^+$. $C_{20}H_{21}N_2O_3$. Calculated: M + H 337.15501.

(*E*)-1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]-3-(3-methoxyphenyl)prop-2-en-1-one (XIIIb). Yield 55%, yellow crystals, mp 96–98°C. IR spectrum, ν, cm^{-1}: 3418 (O–H), 3118 (C–H), 1639 (C=O), 1563–1588 (C=C), 840 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.87 s (3H, OCH_3), 5.12 s (2H, CH_2), 6.93 s (1H, 5″-H), 7.00 d.d (1H, 4-H, J = 4.0, 8.5 Hz), 7.03 d (1H, 3′-H, J = 8.5 Hz), 7.11 s (1H, 4″-H), 7.15 s (1H, 2-H), 7.26 d (1H, 6-H, J = 8.5 Hz), 7.31 d.d (1H, 4′-H, J = 2.0, 8.5 Hz), 7.36 t (1H, 5-H, J = 8.5 Hz), 7.51 d (1H, α-H, J = 15.5 Hz), 7.56 s (1H, 2″-H), 7.68 d (1H, 6′-H, J = 2.0 Hz), 7.88 d (1H, β-H, J = 15.5 Hz), 12.84 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 50.1, 55.4, 113.9, 116.8, 119.0, 119.5, 119.8, 119.9, 121.3, 126.4, 128.5, 130.0, 130.1, 135.3, 135.7, 137.2, 146.1, 160.0, 163.5, 193.3. Found: m/z 337.15467 $[M + H]^+$. $C_{20}H_{21}N_2O_3$. Calculated: M + H 337.15512.

(*E*)-1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]-3-(4-isopropylphenyl)prop-2-en-1-one (XIIIc). Yield 63%, yellow crystals, mp 140–142°C.

IR spectrum, ν, cm^{-1}: 3447 (O–H), 3095 (C–H), 1643 (C=O), 1579 (C=C), 826 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 d [6H, $CH(CH_3)_2$, J = 7.0 Hz], 2.96 m [1H, $CH(CH_3)_2$], 5.12 s (2H, CH_2), 6.93 s (1H, 5″-H), 7.02 d (1H, 3′-H, J = 8.0 Hz), 7.12 s (1H, 4″-H), 7.30 br.s (3H, 3-H, 4′-H, 5-H), 7.51 d (1H, α-H, J = 15.5 Hz), 7.59 s (2H, 2-H, 6-H), 7.62 s (1H, 2″-H), 7.70 s (1H, 6′-H), 7.92 d (1H, β-H, J = 15.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.7, 34.2, 50.3, 119.1, 119.5, 120.0, 126.3, 127.2, 128.6, 129.0, 129.8, 132.0, 135.3, 137.3, 146.4, 152.8, 163.5, 193.4. Found: m/z 349.19105 $[M + H]^+$. $C_{22}H_{25}N_2O$. Calculated: M + H 349.19106.

(*E*)-1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]-3-(4-methylphenyl)prop-2-en-1-one (XIIId). Yield 62%, yellow crystals, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3442 (O–H), 3095 (C–H), 1641 (C=O), 1577–1606 (C=C), 838 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.40 s (3H, CH_3), 5.11 s (2H, CH_2), 6.92 s (1H, 4″-H), 7.01 d (1H, 3′-H, J = 8.0 Hz), 7.11 s (1H, 5″-H), 7.55 d (2H, 3-H, 5-H, J = 8.0 Hz), 7.59 s (1H, 2″-H), 7.70 d (1H, 6′-H, J = 2.0 Hz), 7.90 d (1H, β-H, J = 15.5 Hz), 12.89 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.6, 50.2, 118.4, 119.0, 119.5, 119.9, 126.2, 128.5, 128.8, 129.8, 131.6, 135.2, 137.2, 141.9, 146.4, 163.4, 193.3. Found: m/z 321.15975 $[M + H]^+$. $C_{20}H_{21}N_2O_2$. Calculated: M + H 321.16000.

(*E*)-1-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)-phenyl]-3-(3-hydroxy-4-methoxyphenyl)prop-2-en-1-one (XIIIe). Yield 39%, yellow crystals, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3448 (O–H), 3000 (C–H), 1637 (C=O), 1561–1611 (C=C), 827 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.86 s (1H, OCH_3), 5.17 s (1H, CH_2), 6.48 d (1H, 3′-H, J = 8.5 Hz), 6.91 s (1H, 5″-H), 7.03 d (1H, 5-H, J = 8.5 Hz), 7.24 s (1H, 4′-H), 7.30 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.37 d (1H, 2-H, J = 2.0 Hz), 7.45 d.d (1H, 4′-H, J = 2.0, 8.5 Hz), 7.60 m (3H, α-H, β-H, 2″-H), 8.25 d (1H, 6′-H, J = 2.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 48.8, 55.7, 111.9, 114.8, 118.1, 118.9, 119.3, 120.7, 122.8, 127.3, 128.4, 128.7, 130.2, 135.5, 137.1, 145.6, 146.8, 150.8, 161.2, 193.0. Found: m/z 353.14958 $[M + H]^+$. $C_{20}H_{21}N_2O_4$. Calculated: M + H 353.15001.

(*E*)-1-(5-{3-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)phenyl]-3-oxoprop-1-en-1-yl}-2-metoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (XIIIf). Yield 49%, yellow crystals, mp 201–203°C. IR spectrum, ν, cm^{-1}: 3447 (O–H, N–H), 1634 (C=O), 1639–1716 (C=C), 827 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.90 s (3H, OCH_3), 4.85 s (2H, CH_2), 5.18 s (2H, CH_2), 5.58 d.d (1H, 5‴-H, J = 2.0, 8.0 Hz), 6.94 s (1H, 5″-H), 6.99 d (1H, 3′-H, J = 8.5 Hz), 7.18 d (1H, 5′-H, J = 8.5 Hz), 7.26 s (1H, 4″-H), 7.45 d.d (1H, 4′-H, J = 2.0, 8.5 Hz), 7.62 d (1H, 2″-H, J = 2.0 Hz), 7.65 d (1H, 6‴-H, J = 8.0 Hz), 7.80 d (1H, α-H, J = 15.5 Hz), 7.82 d (1H, β-H, J = 15.5 Hz), 7.84 s (1H, 2-H), 7.92 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 8.15 d (1H, 6′-H, J = 2.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.8, 48.8, 55.9, 100.8, 111.6, 118.1, 119.3, 119.7, 120.9, 124.8, 126.8, 128.3, 128.6, 130.0, 130.3, 130.7, 135.4, 137.1, 144.7, 145.9, 150.9, 159.5, 160.9, 163.8, 192.9. Found: m/z 461.18195 $[M + H]^+$. $C_{25}H_{25}N_4O_5$. Calculated: M + H 461.18211.

(*E*)-1-(5-{3-[2-Hydroxy-5-(1*H*-imidazol-1-ylmethyl)phenyl]-3-oxoprop-1-en-1-yl}-2-methoxybenzyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (XIIIg). Yield 49%, yellow crystals, mp 209–211°C. IR spectrum, ν, cm^{-1}: 3448 (O–H, N–H), 1641–1685 (C=O), 1567–1606 (C=C), 832 (δC–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.89 s (3H, CH_3), 3.95 s (3H, OCH_3), 4.91 s (2H, CH_2), 5.19 s (2H, CH_2), 6.98 s (1H, 4″-H), 7.00 m (2H, 3′-H, 5-H), 7.17 s (1H, 5″-H),7.37 d.d (1H, 6-H, J = 2.0, 8.5 Hz), 7.40 s (1H, 2-H), 7.46 d (1H, α-H, J = 15.5 Hz), 7.60 d.d (1H, 4′-H, J = 2.0, 8.5 Hz), 7.74 s (1H, 6‴-H), 7.78 s (1H, 2″-H), 7.85 d (1H, β-H, J = 15.5 Hz), 7.90 s (1H, 6H), 12.9 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.4, 46.1, 50.2, 55.9, 110.3, 111.1, 118.0, 119.1, 119.3, 120.0, 125.1, 127.3, 128.7, 129.0, 130.0. 130.2, 131.8, 135.3, 137.2, 140.6, 145.4, 151.5, 159.7, 163.3, 164.8, 193.1. Found: m/z 475.19760 $[M + H]^+$. $C_{26}H_{27}N_4O_5$. Calculated: M + H 475.19791.

Antimicrobial and antifungal activity of compounds XII and XIII. The antimicrobial and antifungal activity of chalcones **XII** and **XIII** was assessed by the microbroth dilution method [14, 15]. Compounds were assumed to be inactive if the minimum inhibitory concentration (MIC) exceeded 50 μg/mL. Chalcones **XII** and **XIII** showed no activity against mycelial fungi and yeasts. Benzotriazole derivatives **XIIi**–**XIIk** were active against gram-positive bacteria *Bacillus subtillis* and *Staphylococcus aureus* (MIC 25 and 12.5, 12.5 and 12.5, and 12.5 and 12.5 μg/mL, respectively). Imidazolylmethyl derivatives **XIII** were found to exhibit considerably higher antimicrobial activity which also depended on the nature and position of substituents in the aldehyde component. Chalcone **XIIIb** having a methoxy group in position *3* of the ring B was active against both gram-negative and

gram-positive bacteria *Pseudomonas aeruginosa*, *Bacillus subtillis*, and *Staphylococcus aureus* (MIC 50, 12.5, and 25 μg/mL, respectively), whereas its 4-methoxy analog **XIIIa** inhibited the growth of only gram-negative *Pseudomonas aeruginosa* (MIC 25 μg/mL). The presence of an alkyl group in position *4* increased the activity of compounds **XIIIc** and **XIIId** against gram-positive bacteria *Bacillus subtillis* and *Staphylococcus aureus* (MIC 25, 12.5 and 25, 50 μg/mL, respectively).

This study was performed under financial support by the Vietnam Science and Technology Foundation (NAFOSTED; project no. 104.01.67.09).

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