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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Studies on the synthesis of some new substituted benzylamino and phenyl-acrylamido-methyl flavone derivatives

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Abstract The synthesis and biological activity of a new series of 2-{3-[substituted benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVa-e) and N-substituted benzyl-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Va-e) derivatives are reported. The synthesized compounds were tested *in vitro* for antifungal and antibacterial activities. Compound IVa showed the best antifungal activity compared with miconazole (CAS 22916-47-8). Compound IVc indicated the best antibacterial activity compared with the control drug ampicillin (CAS 69-53-4).

Keywords Flavone derivatives · Antimicrobial activity · Synthesis

Introduction

Flavonoids are polyphenols that are ubiquitously found in a wide variety of edible plants, fruits, nuts, seeds, and plant-derived beverages, such as juice and tea (Seyoum et al., 2006). Additionally, they have been described as health-promoting, disease-preventing dietary supplements, and have many biological activities as antibacterial and antiviral agents (Havsteen, 2002). They are extremely safe and associated with low toxicity, making them excellent candidates for chemopreventive agents (Moon et al., 2006). The cinnamoyl and the benzylamino groups are

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good pharmacogenic moieties to obtain potent antimicrobial activities (López et al., 2004; Wang et al., 2006)

The intriguing biological activity and unique structure of these compounds prompted us to undertake a synthetic study of new flavone derivatives containing benzylamino and cinnamoyl moieties. Previously, we reported that the synthesis and antimicrobial evaluation of some new flavone derivatives with cinnamoyl and benzylamino groups at 4′ position showed a comparable activity to that of ampicillin and miconazole against *Escherichia coli* and *Candida albicans*, respectively (Bozdağ-Dündar et al., 2005). As part of our ongoing research, in this study we explain the synthesis and antimicrobial testing of new flavone derivatives having N-substituted benzylaminomethyl and N-substituted benzyl-N-phenyl-acrylamido-methyl at 3′ position, with the aim of evaluating the difference in activity of these isomeric flavonyl compounds.

Materials and methods

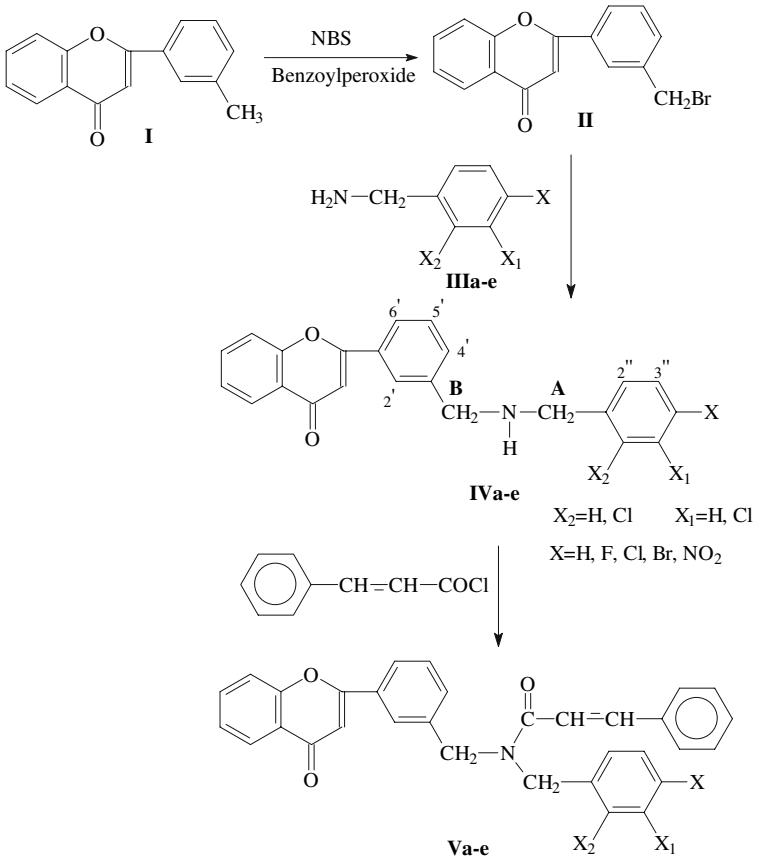
Chemistry

Melting points were determined with a Büchi SMP-20 melting-point apparatus (Büchi, Flawil, Switzerland) and used uncorrected. All the instrumental analyses were performed by the Instrumental Analysis Laboratory of Scientific and Technical Research Council of Turkey (Tubitak, Ankara, Turkey), with a Shimadzu IR-470 spectrometer (Jasco, Tokyo, Japan, with IR spectra recorded using potassium bromide discs), a Bruker DPX 400 nuclear magnetic resonance (NMR) spectrometer [Bruker, Rheinstetten, Germany, with ^{1}H NMR spectra measured in $CDCl_3$ and all chemical shifts reported as δ(ppm) values], and a VG Platform II Mass spectrometer (Micromass, Manchester, England). Elementary analyses were performed on a Leco CHNS 932 analyzer (Leco, St. Joseph, USA) and satisfactory results ±0.4% of calculated values (C, H, and N) were obtained. For the chromatographic analysis Merck Silica Gel 60 (230-400 mesh ASTM) was used. The chemical reagents used in the synthesis were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, MI, USA). 3′-Methyl flavone (I) (Cramer and Elsching, 1956), 3′-bromomethyl flavone (II) (Tunçbilek and Ertan, 1999) were synthesized according to the literature.

Chemical synthesis

Synthesis of 3′-Bromomethyl flavone (II)

A mixture of N-bromosuccinimide (0.01 mol) and 3′-methyl flavone (0.01 mol) (I) was dissolved in 90 ml carbon tetrachloride, and benzoyl peroxide (0.1 g) was added. The reaction mixture was refluxed for 7 h and filtered while still hot. The crude product was crystallized from toluene [II, m.p.: 137°C (Tunçbilek and Ertan, 1999)].



Scheme 1 General synthesis of compounds IVa-e and Va-e

Synthesis of compounds IVa-e

3′-Bromomethyl flavone (II) (0.01 mol) and substituted benzylamine derivatives (IIIa-e) (0.01 mol) were stirred in 5 ml dimethyl formamide (DMF) and NaH (0.01 mol) under a nitrogen atmosphere at room temperature for two days (Scheme 1). The mixture was diluted with water and filtered. The filtrate was purified by column chromatography using silica gel 60 (230–400 mesh ASTM) as the adsorbent and $CHCl_3$ as the eluent.

2-[3-(benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVa)

Yield (%): 45.6, m.p.: 188°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1644 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 3.89 (s, 2H, **A**), 3.95 (s, 2H, **B**), 6.88 (s, 1H, 3-H), 7.29−7.42 (m, 5H, Ar-H), 7.45 (ddd, 1H, 6-H), 7.48–7.58 (m, 2H, 4′, 5′-H), 7.62 (d, 1H, $j_{8,7}$ = 7.94 Hz, 8-H), 7.74 (ddd, 1H, 7-H), 7.85 (dd, 1H, 6′-H),

7.97 (s, 1H, 2′-H), 8.27 (dd, 1H, $j_{5,6}$ = 7.94 Hz, $j_{5,7}$ = 1.59 Hz, 5-H). MS (70 eV) m/z: 341.7 (M^+), 250, 235, 221, 121, 120, 106, 105, 102, 101, 92, 64, 63, 57, 43.3 (100%); anal. calcd. for $C_{23}H_{19}NO_2 \bullet 0.3H_2O$ C:79.68, H:5.66, N:4.04%; found: C:79.74, H:5.41, N:3.92%.

2-{3-[(4-fluoro-benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVb)

Yield (%): 25.9, m.p.:86–88°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1640 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 3.82 (s, 2H, A), 3.89 (s, 2H, B), 6.84 (s, 1H, 3-H), 7.00−7.05 (m, 2H, 2″,6″-H), 7.32–7.35 (m, 2H, 3″,5″-H), 7.42 (ddd, 1H, 6-H), 7.46−7.54 (m, 2H, 4′, 5′-H), 7.58 (d, 1H, $j_{8,7}$ = 8.40 Hz, 8-H), 7.71 (ddd, 1H, 7-H), 7.82 (dd, 1H, 6′-H), 7.92 (s, 1H, 2′-H), 8.23 (dd, 1H, $j_{5,6}$ = 8.00 Hz, $j_{5,7}$ = 1.60 Hz, 5-H). MS (70 eV) m/z: 358.6 (M^+), 250.1, 221.9, 123.0, 120.0, 109.1, 94.8, 92.0, 62.7 (100%); anal. calcd. for $C_{22}H_{18}FNO_2 \bullet 0.3H_2O$ C:75.65, H:5.09, N:3.84%; found: C:75.65, H:4.69, N:3.84%.

2-{3-[(4-chloro-benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVc)

Yield (%): 65.6, m.p.: 88°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1635 (γ pyrone CO) 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 3.87 (d, 2H, A), 3.93 (d, 2H, B), 6.85 (s, 1H, 3-H), 7.21−7.62 (m, 6H, 2″, 6″, 6, 4′, 5′, 8-H), 7.73 (ddd, 1H, 7-H), 7.88 (dd, 1H, 6′-H), 7.92 (d, 2H, 3″,5″-H), 8.02 (s, 1H, 2′-H), 8.25 (dd, 1H, 5-H). MS (70 eV) m/z: 375 (M^+), 376 (M^{+1}), 377 (M^{+2}), 250.1, 221.9, 123.0, 120.0, 109.1, 94.8, 92.0, 62.7 (100%); anal. calcd. for $C_{22}H_{18}ClNO_2 \bullet 0.1H_2O$ C:73.25, H:4.83, N:3.72%; found: C:72.99, H:4.75, N:3.64%.

2-{3-[2,4-dichloro-benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVd)

Yield (%): 53.1, m.p.: 119°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1633 (γ pyrone CO) 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 3.95 (s, 2H, A), 3.97 (s, 2H, B), 6.86 (s, 1H, 3-H), 7.27 (dd, 1H, 3″-H), 7.41–7.58 (m, 5H, 2″, 5″, 6, 4′, 5′-H), 7.61 (d, 1H, $j_{8,7}$ = 8.28 Hz, 8-H), 7.73 (ddd, 1H, 7-H), 7.85 (dd, 1H, 6′-H), 8.00 (s, 1H, 2′-H), 8.25 (dd, 1H, $j_{5,6}$ = 7.95 Hz, $j_{5,7}$ = 1.54 Hz, 5-H); MS (70 eV) m/z: 409.9 (M^+), 410.9 (M^{+1}), 412 (M^{+2}), 236.1 (100%), 220.9, 161.1, 159.1, 121.2, 120.1, 92.2, 63.2; anal. calcd. for $C_{22}H_{17}Cl_2NO_2$ C:67.32, H:4.18, N:3.41%; found: C66.92, H:4.59, N:3.32%.

2-{3-[3,4-dichloro-benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one (IVe)

Yield (%): 48.0, m.p.: 117°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1633 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 3.88 (s, 2H, A), 3.95 (s, 2H, B), 6.89 (s, 1H, 3-H), 7.42−7.57 (m, 6H, 2″, 3″, 6″, 6, 4′, 5′-H), 7.61 (d, 1H, $j_{8,7}$ = 8.43

Hz, 8-H), 7.75 (ddd, 1H, 7-H), 7.85 (dd, 1H, 6′-H), 8.00 (s, 1H, 2′-H), 8.25 (dd, 1H, $j_{5,6}$ = 7.97 Hz, $j_{5,7}$ = 1.51 Hz, 5-H).MS (70 eV) m/z: 409.9 (M^+), 412.1 (M^{+2}), 413.5 (M^{+3}), 250.2 (100%), 235.7 (100%), 220.9, 161.1, 159.1, 121.2, 120.1, 92.2, 63.2 anal. calcd. for $C_{22}H_{17}Cl_2NO_2$•0.4H_2O C:66.16, H:4.27, N3.36%; found: C:65.97, H:4.36, N:3.37%.

Synthesis of compounds Va-e

IVa-e (0.01 mol) and cinnamoyl chloride (0.01 mol) were stirred in 5 ml of dioxane/ $N(C_2H_5)_3$ (0.01 mol) at room temperature for 24 h (Scheme 1). The mixture was diluted with water and filtered. The filtrate was purified by column chromatography using silica gel 60 (230−400 mesh ASTM) as the adsorbent and CH_2Cl_2:*n*-hexane (2:1) as the eluent.

N-benzyl-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Va)

Yield (%): 60.0, m.p.: 95°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1646 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.70 (d, 2H, **A**), 4.79 (d, 2H, **B**), 6.81 (s, 1H, 3-H), 6.95 (d, 1H, =CH-Ar), 7.34–7.50 (m, 13H, 6,4′,5′,6′,10-Ar-H), 7.57 (d, 1H, $j_{8,7}$ = 8.40 Hz, 8-H), 7.70 (ddd, 1H, 7-H), 7.78 (d, 1H, =CH-CO), 7.87 (dd, 1H, 6′-H), 7.92 (s, 1H, 2′-H),8.23 (dd, 1H, $j_{5,6}$ = 8.40 Hz, $j_{5,7}$ = 1.60 Hz, 5-H); MS (70 eV) m/z: 471.4 (M^+), 472.3 (M^{+1}), 235.9, 223.9, 131.0, 121.2, 91 (100%), 76.8, 63.0; anal. calcd. for $C_{32}H_{25}NO_3$•0.3H_2O C:80.50, H:5.36, N:2.93%; found: C:80.17, H:5.70, N:2.63%.

N-(4-fluoro-benzyl)-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Vb)

Yield (%): 37.2, m.p.: 126–128°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1642 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.72 (t, 4H, **A**, **B**), 6.82 (s, 1H, 3-H), 6.91 (dd, 1H, =CH-Ar), 7.03−7.12 (m, 2H, 2″, 6″-H), 7.22 (ddd, 1H, 6-H), 7.27−7.55 (m, 9H, 4′,5′,3″, 5″, 5-Ar-H), 7.58 (d, 1H, $j_{8,7}$ = 8.00 Hz, 8-H), 7.70 (ddd, 1H, 7-H), 7.78 (d, 1H, =CH-CO), 7.86–7.92 (m, 2H, 2′,6′-H), 8.24 (dd, 1H, $j_{5,6}$ = 7.60 Hz, $j_{5,7}$ = 1.60 Hz, 5-H); MS (70 eV) m/z: 490.3 (M^{+1}) (100%), 301.4, 278.4, 235.4, 131.3, 109.1; anal. calcd. for $C_{32}H_{24}FNO_3$•1.4H_2O C:74.68, H:5.21, N:2.72%; found: C:74.76, H:5.43, N:2.49%.

N-(4-chloro-benzyl)-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Vc)

Yield (%): 47.0, m.p.: 129°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1631 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.72 (t, 4H, A, B), 6.81

(s, 1H, 3-H), 6.89 (d, 1H, =CH-Ar), 7.2 (d, 2H, 2″, 6″-H), 7.24–7.57 (m, 11H, 4′,5′,6,8, 3″, 5″, 5-Ar-H), 7.68 (ddd, 1H, 7-H), 7.77 (d, 1H, = CH-CO), 7.88 (dd, 1H, 6′-H), 7.92 (s, 1H, 2′-H), 8.22 (d, 1H, $j_{5,6}$ = 7.60 Hz, 5-H); MS (70 eV) m/z: 505 (M^+), 506.3 (M^{+1}) (100%), 507 (M^{+2}), 301.4, 235.4, 149.4, 147.5, 125.3, 86.0, 69.0; anal. calcd. for $C_{32}H_{24}ClNO_3$ 0.3 Hexane C:76.30, H:5.31, N:2.64%; found: C:76.30, H:5.60, N:2.68%.

N-(2,4-dichloro-benzyl)-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Vd)

Yield (%): 60.7, m.p.: 98°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1636 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.75 (d, 2H, A), 4.83 (d, 2H, B), 6.75 (d, 1H, =CH-Ar), 6.82 (s, 1H, 3-H), 6.92−7.51 (m, 11H, 6,4′,5′,2″,3″,5″,5-Ar-H), 7.58 (d, 1H, $j_{8,7}$ = 8.40 Hz, 8-H), 7.71 (ddd, 1H, 7-H),7.80 (d, 1H, =CH-CO), 7.86–7.92 (m, 2H, 2′,6′-H), 8.24 (d, 1H, $j_{5,6}$ = 7.60 Hz, 5-H); MS (70 eV) m/z: 540.2 (M^{+1}) (100%), 541 (M^{+2}), 542.3 (M^{+3}), 301.4, 235.4, 197.3, 161.4, 131.3, 121.2, 102.1, 69.0; anal. calcd. for $C_{32}H_{23}Cl_2NO_3$•0.6 Hexane C:72.21, H:5.31, N:2.36%; found: C:72.32, H:5.66, N:2.08%.

N-(3,4-dichloro-benzyl)-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide (Ve)

Yield (%): 50.6, m.p.: 148°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 1635 (γ pyrone CO); 1H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.72 (d, 2H, A), 4.82 (d, 2H, B), 6.87 (s, 1H, 3-H), 6.97 (d, 1H, =CH-Ar), 7.13 (d, 1H, $j_{a,b}$=8.80 Hz, 2″-H), 7.22 (d, 1H, $j_{b,a}$=7.6 Hz, 3″-H), 7.32–7.64 (m, 10H, 4′,5′,6,8,6″,5-Ar-H), 7.75 (ddd, 1H, 7-H), 7.83 (d, 1H, =CH-CO), 7.90−7.95 (m, 1H, 6′-H), 7.99 (s, 1H, 2′-H), 8.29 (d, 1H, $j_{5,6}$ = 8.00 Hz, 5-H); MS (70 eV) m/z: 540.3 (M^{+1}), 541 (M^{+2}), 542.3 (M^{+3}), 301.4, 261.3, 197.3, 175.3, 99.1 (100%); anal. calcd. for $C_{32}H_{23}Cl_2NO_3$ C:71.12, H:4.29, N:2.59%; found: C:71.37, H:4.17, N:2.54%.

Antimicrobial activity

The disk diffusion method was used for assessing antibacterial activity against *Staphylococcus aureus* ATCC 250 (American Type Culture Collection, Manassas, VA, USA), *Escherichia coli* RSKK 313 (Refik Saydam Kültür Kolleksiyon, Ankara, Turkey) and antifungal activity against *Candida albicans* RSKK 628 (Refik Saydam Kültür Kolleksiyon, Ankara, Turkey). Cultures of each bacteria and yeast strain, kept in Mueller-Hinton broth (Difco, Detroit, MI, USA), at 37°C for 18−24 h and diluted with the same broth to 10^5 cfu/ml, were pipetted into the Mueller-Hinton agar (Difco) plates prepared according to the procedure. Paper disks (8 mm in diameter) embedded into 3000 $\mu g.ml^{-1}$ compound solution were put onto the surface of the inoculated plates, placed in an incubator at

37°C for 18−24 h, and then examined. Most of the compounds were found to be effective against the tested microorganisms by measuring the diameter of the growth inhibition zone according to Bauer et al. (1966).

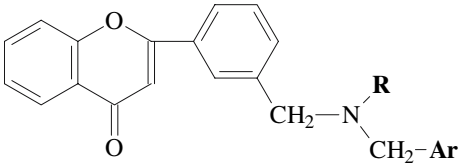
Results and discussion

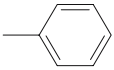
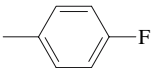
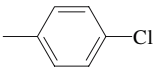
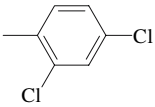
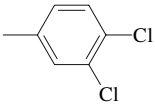
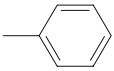
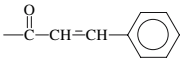
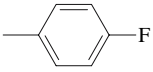
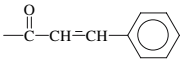
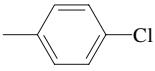
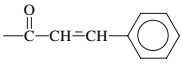
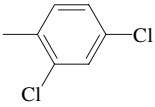
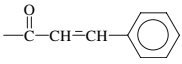
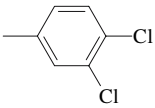
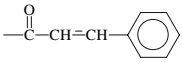
The general Baker-Venkataraman method (Cramer and Elsching, 1956) was used to prepare 3′-methyl flavone (I). The methyl group of the flavone was converted to bromomethyl with N-bromosuccinimide and a catalytic amount of benzoyl peroxide. The derivatives IVa-e were synthesized starting with bromomethylflavone (II) and treating with the appropriate substituted benzylamine derivatives (IIIa-e) in the presence of NaH/DMF under a nitrogen atmosphere. Compounds Va-e were obtained reacting with cinnamoyl chloride and IVa-e in dioxane/$N(C_2H_5)_3$ (Scheme 1). The structure of N-substituted benzylaminomethyl (IVa-e) and N-substituted benzylcinnamamidomethyl flavone derivatives (Va-e) was elucidated by elementary analysis, ^{1}H-NMR, mass spectral data, and infrared (IR) findings. All spectral data were in accordance with assumed structures. IR spectra of the compounds showed γ-pyrone C=O stretching bonds at 1631−1646 cm^{-1}. In the ^{1}H-NMR spectra, characteristic flavone protons were observed between 6.81 and 8.29 ppm. Benzylic CH_2 protons for IVa-e and Va-e, A and B were observed at 3.82–3.95 and 3.89–3.97 ppm as a singlet except IVc (observed as a doublet), 4.70–4.75 and 4.79–4.83 ppm as a doublet except Vb-c (observed as a triplet A+B), respectively. In the mass spectra, N-substituted benzylaminomethyl (IVa-e) flavone derivatives have molecular (M^+) ion peaks. The compounds IVc, IVd, Va-e have M^{+1}, the compounds IVc-e, Vc-e have $M^{+2,}$ and the compounds IVe, Vd-e have M^{+3} ion peaks.

All of the new compounds were tested for their antimicrobial activity by the agar diffusion method (Bauer et al., 1966), using *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli*, comparing their activities with those of miconazole and ampicillin (Table 1). The resulting inhibition zones against *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli* were 10–25 mm, 10–25 mm, and 10–12 mm, respectively. Compounds IVa, IVe, and Vc exhibited activity against *Escherichia coli* (inhibition zones: 10, 12, and 12 mm, respectively). Compound IVc showed high activity against *Staphylococcus aureus* (inhibition zone: 25 mm). Compounds IVa-e and Va were active against *S. aureus* (inhibition zones: 16, 15, 25, 10, 16, and 10 mm, respectively), while Vb-e was inactive. Beside, the benzylaminomethyl flavone derivatives IVa-e were found to be more active than cinnamoyl flavone derivatives Vb-e against *S. aureus*.

Compound IVa showed high activity against *Candida albicans* (inhibition zone: 25 mm). Compounds IVd-Va-b were inactive against *Candida albicans*. However, surveying the values for *C. albicans* it should be pointed out that flavonyl compounds showed more activity than the tested bacteria except compounds IVa-e, Va against *S. aureus*.

Table 1 Antimicrobial activities (quoted as growth inhibition diameter in mm) of compounds IVa-e and Va-e



Compound	Ar	R	*C. albicans*	*S. aureus*	*E. coli*
IVa		-H	25	16	10
IVb		-H	20	15	*
IVc		-H	15	25	*
IVd		-H	*	10	*
IVe		-H	10	16	12
Va			*	10	*
Vb			*	*	*
Vc			13	*	12
Vd			15	*	*
Ve			15	*	*
Miconazole			35	–	–
Ampicillin			–	30	20

*No activity. -: Not tested

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