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Synthesis of 3-(4-substituted benzoylmethyl)-2-benzoxazolinones and screening antimicrobial activities

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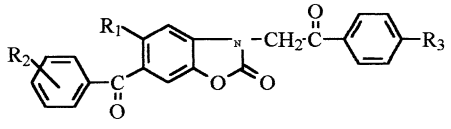
Abstract

A number of 3-(4-substituted benzoylmethyl)-2-benzoxazolinones have been synthesized by reacting with 2-benzoxazolinone and 4-substituted phenacyl bromide in ethanol. Their chemical structures were confirmed by IR, ^{1}H NMR and elemental analysis. For screening antimicrobial activity, minimum inhibitory concentration (MIC) values were determined against two Gram positive, one Gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*) and three yeast-like the fungi (*Candida albicans*, *Candida krusei*, *Candida parapsilosis*). © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: 3-Substituted-2-benzoxazolinones; Synthesis; Antibacterial agents; Antifungal agents

1. Introduction

After Lespagnol et al. [1] disclosed that 2-benzoxazolones have hypnotic effects, many investigations on 2-benzoxazolinones showed that compounds with this structure have analgesic, antiinflammatory, antineoplastic, anticonvulsant and antimicrobial activities [2–9]. In addition, it has been published that chlorinated 2-benzoxazolinone compounds have valuable fungicidal properties and therefore excellently suitable for the protection of organic material from attack by fungi and from damage due to rot [10]. In this respect, we synthesized 16 new (5-chloro)-6-acyl-3-(4-substituted benzoyl methyl)-2-benzoxazolinones and screened their antimicrobial activities.



R_1 = -H; -Cl
R_2 = 2-F; 3-F; 2,6-diflouro; 2, 5-diflouro
R_3 = -H; -Cl; -Br; -CH_3

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2. Experimental

2.1. Chemistry

M.p.s were determined on a Thomas Hoover Capillary m.p. apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrometer 1720 X as KBr disc (γ/cm). ^{1}H NMR spectra in DMSO-d_6 and $CHCl_3$ were obtained on a Bruker AC 80 MHz spectrophotometer using TMS as an internal standard (chemical shift in δ, ppm). Elemental analyses were performed with a Perkin–Elmer Model 240C and Leco CHNS-932 at The Scientific and Technical Research Council of Turkey.

2.1.1. 6-Acyl-2-benzoxazolinones

2-Benzoxazolinone and/or 5-chloro-2-benzoxazolinones were reacted with appropriate carboxylic acid in polyphosphoric acid (PPA) according to the literature [11,12].

2.1.2. 4-Non-substituted/substituted benzoyl–methyl bromides

These compounds were synthesized by treating appropriate acetophenones with bromine in glacial AcOH according to the method reported earlier [13].

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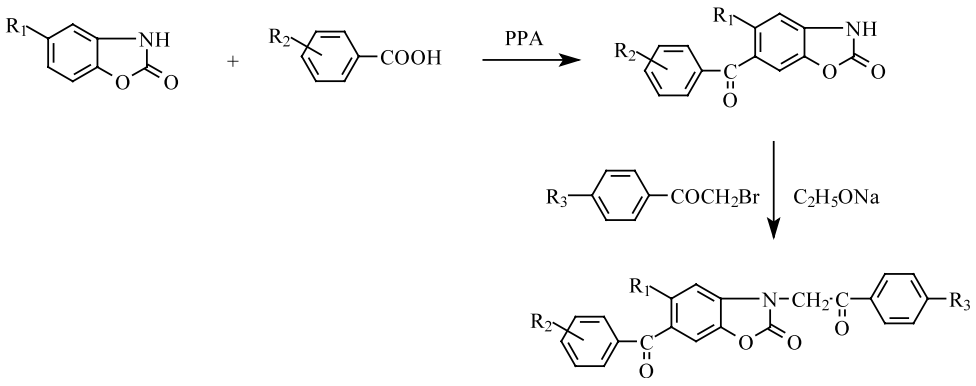
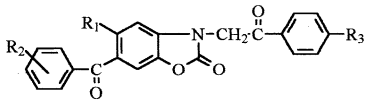


Scheme 1. Synthesis of the compounds.

Table 1
Physical and chemical data of 6-acyl-3-(4-substituted benzoylmethyl)-2-benzoxazolinones



Com. no	R_1	R_2	R_3	Empirical Formula	MW	Yield (%)	m.p. (°C)	Elemental Calculated	Analysis Found
1	-Cl	2-F	-H	$C_{22}H_{13}FClNO_4$	409.80	70.31	205	C: 64.48 H: 3.20 N: 3.42	C: 64.45 H: 3.45 N: 3.42
2	-Cl	3-F	-H	$C_{22}H_{13}FClNO_4$	409.80	48.03	217	C: 64.48 H: 3.20 N: 3.42	C: 64.00 H: 2.75 N: 3.42
3	-Cl	2-F	-Cl	$C_{22}H_{12}FCl_2NO_4$	444.25	85.76	190	C: 59.48 H: 2.72 N: 3.15	C: 59.21 H: 2.69 N: 3.10
4	-Cl	3-F	-Cl	$C_{22}H_{12}FCl_2NO_4$	444.25	78.90	223	C: 59.48 H: 2.72 N: 3.15	C: 59.19 H: 2.27 N: 3.17
5	-Cl	2-F	-Br	$C_{22}H_{12}FClBrNO_4$	488.70	68.61	192	C: 54.07 H: 2.45 N: 2.86	C: 53.77 H: 2.47 N: 2.81
6	-Cl	3-F	-Br	$C_{22}H_{12}FClBrNO_4$	488.70	76.61	230	C: 54.07 H: 2.45 N: 2.86	C: 53.74 H: 2.19 N: 2.86
7	-Cl	2-F	$-CH_3$	$C_{23}H_{15}FClNO_4$	423.83	55.75	198	C: 65.18 H: 3.57 N: 3.30	C: 65.26 H: 3.63 N: 3.34
8	-Cl	3-F	-CH3	$C_{23}H_{15}FClNO_4$	423.83	65.18	207	C: 65.18 H: 3.57 N: 3.30	C: 64.68 H: 3.13 N: 3.29
9	-H	2,5 diF	-H	$C_{22}H_{13}F_2NO_4$	393.34	79.49	180	C: 67.18 H: 3.33 N: 3.56	C: 67.13 H: 3.02 N: 3.49
10	-H	2,6 diF	-H	$C_{22}H_{13}F_2NO_4$	393.34	70.94	154	C: 67.18 H: 3.33 N: 3.56	C: 67.25 H: 2.88 N: 3.52
11	-H	2,5 diF	-Cl	$C_{22}H_{12}F_2ClNO_4$	427.79	73.68	240	C: 61.71 H: 2.80 N: 3.27	C: 60.98 H: 2.22 N: 3.10
12	-H	2,6 diF	-Cl	$C_{22}H_{12}F_2ClNO_4$	427.79	77.19	217	C: 61.71 H: 2.80 N: 3.27	C: 62.30 H: 2.16 N: 3.19
13	-H	2,5 diF	-Br	$C_{22}H_{12}F_2BrNO_4$	472.25	84.74	217	C: 55.90 H: 2.54 N: 2.96	C: 56.02 H: 2.25 N: 2.90
14	-H	2,6 diF	-Br	$C_{22}H_{12}F_2BrNO_4$	472.25	66.95	227	C: 55,90 H: 2.54 N: 2.96	C: 56.48 H: 1.97 N: 2.92
15	-H	2,5 diF	$-CH_3$	$C_{23}H_{15}F_2NO_4$	407.37	58.97	172	C: 67.75 H: 3.68 N: 3.44	C: 68.13 H: 3.64 N: 3.25
16	-H	2,6 diF	-CH3	$C_{23}H_{15}F_2NO_4$	407.37	54.49	171	C: 67.75 H: 3.68 N: 3.44	C: 67.90 H: 3.82 N: 3.45

Table 2
Spectral data for compounds **1**–**16**

Comp. number	IR (cm^{-1})		^1H NMR (ppm)	
	Lactam C=O	Methyl ketone C=O	Aromatic ring	$-CH_2$ (s)
1	1780	1700	7.20–8.10	5.60
2	1772	1700	7.30–8.25	5.67
3	1777	1703	7.25–8.20	5.65
4	1775	1704	7.00–8.00	5.20
5	1780	1705	7.20–8.15	5.65
6	1776	1705	7.40–8.10	5.60
7	1779	1694	7.20–8.10	5.60
8	1780	1697	7.30–8.10	5.65
9	1784	1694	6.90–8.10	5.15
10	1777	1692	6.90–8.10	5.13
11	1776	1693	6.90–8.10	5.23
12	1766	1689	6.80–8.10	5.20
13	1775	1694	6.90–8.05	5.27
14	1768	1689	6.80–8.00	5.15
15	1780	1691	6.85–8.00	5.20
16	1780	1694	6.80–8.00	5.20

2.1.3. 6-Acyl-3-(4-substituted benzoylmethyl)-2-benzoxazolinones

To the solution of sodium 6-acyl-2-benzoxazolinones in alcohol, equimolar α-bromo-4-substituted acetophenone was added. The solution was refluxed on an oil bath for 4 h and then cooled. The crude product was filtered, washed with water, dried and crystallized from a suitable solvent [14] (Scheme 1).

2.2. Microbiology

Minimal inhibitory concentrations (MICs) were determined by broth microdilution following the procedures recommended by the National Committee for Clinical Laboratory Standards. Two Gram positive and one Gram negative bacteria were used as quality control strains. For testing antifungal activities of the compounds, these reference strains were tested: *Candida albicans* ATCC 90028, *Candida krusei* ATCC 6258, *Candida parapsilosis* ATCC 22019 [15,16].

Mueller–Hinton broth (Difco Laboratories, Detroit, MI, USA) was used when testing bacterial strains. For *Candida* species, RPMI-1640 medium with L-glutamin, buffered with MOPS (ICN, FLOW; Aurora, OH, USA) was used. The inoculum densities were 5×10^5 cfu/ml for bacteria and fungi, respectively.

The compounds under the test were dissolved in 100% DMSO and the final twofold concentrations were prepared from 512 to 0.5 μg/ml. Ampiciline and fluconazole were used as antibiotic reference powders for bacteria and fungi, respectively. The doubling concentrations used for both of them were 64–0.0625 μg/ml. Microtiter plates were incubated for 18–24 h at 35 °C for testing bacteria strains. For yeast-like fungi, MICs were determined after incubation for 48 h at 35 °C. MICs were defined as the lowest concentrations of the antimicrobial agents that inhibited visible growth of the microorganism.

Table 3
Biological activity results

Comp.	Bacteria			Fungi		
	E. coli (ATCC 25922)	*P. aeruginosa* (ATCC 27853)	*S. aureus* (ATCC 29213)	*C. albicans* (ATCC 90028)	*C. krusei* (ATCC 6258)	*C. parapsilosis* (ATCC 22019)
1	128	256	512	128	128	128
2	128	256	256	128	64	128
3	128	128	256	128	128	128
4	256	128	128	128	128	128
5	256	128	256	128	64	128
6	256	128	256	128	128	128
7	128	256	256	128	128	128
8	128	128	64	128	128	128
9	128	128	128	128	128	128
10	128	128	128	128	128	128
11	128	128	64	128	128	128
12	64	128	128	64	64	128
13	128	128	128	128	128	128
14	128	128	128	128	64	128
15	256	128	128	128	128	128
16	128	128	128	128	128	128
Ampicilin	2		0.5			
Flucanazole				0.25	32	1

3. Results and discussion

All the compounds were synthesized using the procedure given in the above by reacting 2-benzoxazolinone sodium salt with appropriate phenacyl bromide in ethanol. The synthesis results are presented in Table 1. The IR and ^{1}H NMR spectra of the compounds are given to evidence the structure of the compounds. Spectral data of 6-acyl-3-(4-substituted benzoylmethyl)-2-benzoxazolinone derivatives are shown in Table 2. Antimicrobial activity results of the compounds were evaluated against two Gram-positive, one Gram-negative bacteria, and three different fungi by comparing with standards. These results are given in Table 3.

4. Conclusions

The structure of the compounds was confirmed by IR, ^{1}H NMR and elemental analysis. In IR spectra of the compounds, the bands seen at 1775–1785 (lactam C=O) and 1680–1705 (CH_2–C=O)/cm are in accordance with the assumed structures. Furthermore, N–H stretching bands belonging to 2-benzoxazolinone ring disappeared with the reaction of benzoylmethyl bromides. In the ^{1}H NMR spectra of the compounds, the signals of aromatic ring protons were observed as multiplet at about 7.00–8.00 ppm and methylene protons were seen as singlets at 5.2–5.7 ppm that proved the presence of benzoylmethyl moiety. In elemental analysis the results support the structures with $\pm$0.4% of the theoretical values. Antimicrobial activity results of the compounds were evaluated against two Gram-positive, one Gram-negative bacteria, and three different fungi by comparing with standards.

Acknowledgements

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