

Antimicrobial Activity of Some Derivatives of 2-Arylidene-1-Benzosuberone

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Abstract: Natural products containing a benzosuberone nucleus are important class of medicinal and pharmaceutical compounds and have recently attracted a considerable amount of attention due to their remarkable broad-spectrum biological activity and antioxidant, anticancer agent. The minimum inhibitory concentration values for a group of 2-arylidene-1-benzosuberone their dibromides and their pyrazolines derivatives were determined for gram-positive and gram negative bacteria and yeast. Some compounds exhibited significant activity against *S. aureus*, *S. epidermidis* and *B. licheniformis*. The structural activity of these compounds is discussed. We hope in future to study the effect of these compounds on growth and morphology.

Key words: Chalcones, benzosuberones, 2-arylidene-1-benzosuberone, biological activity, compounds, pyrazolines

INTRODUCTION

Different organic compounds can act as antibacterial or antifungal agents. Many chalcones and their derivatives showed a good antimicrobial activity (Alvarez-Builla and Barluenga, 2011; Verma and Saraf, 2008; Azab *et al.*, 2013; Al Bahtiti, 2005, 2008, 2007; El-Gohary, 2014; Pati *et al.*, 2007; Bahbahani *et al.*, 2018; Monostory *et al.*, 2003; El-Rayyes and Ramadan, 1987 and El-Salam *et al.*, 2017). The benzosuberone unit constitutes the core structure of several natural products such as colchicines, isocolchicine, allocolchicine, theaflavin, bussealin E, demethylsalvicanol and feveline (Fig. 1) where all these natural products are clinically reported as anti-tumor agents (Stretton and Manson,

1973). several synthetic benzosuberones cited in this article exhibited wide range of therapeutic activities such as bacteriostatic, anti-inflammatory, antidepressants and anti-tumor activities (Farghaly *et al.*, 2016). The most important example of these chalcones is the 3-indolyidene-acetophenone. The new technology enables the synthesis of alpha-benzosuberone with a benzene ring and seven cyclic ketones a new pharmaceutical and agrochemical intermediate as anticonvulsant and a drug for treating density (Stretton and Manson, 1973). Because of this we decided to study the antibacterial activity of a series of 2-arylidene-1-benzosuberones and their derivatives; Compounds prepared previously were evaluated *in vitro* for their antifungal activity (Al Bahtiti, 2007).

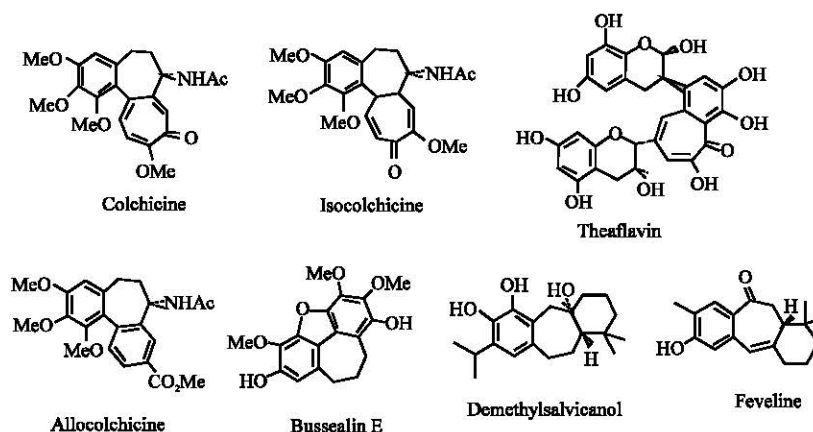


Fig. 1: Some benzosuberone-based natural products

MATERIALS AND METHODS

The organism used in this study for the determination of antimicrobial activity were; *S. epidermidis* (ATCC 12228), *S. aureus* (ATCC 25923), *S. faecalis* (ATCC 19433), *S. faecalis* (ATCC 33186), *S. subtilis* (NCIB 3610), *B. licheniformis* (NCIB 1097), *K. pneumoniae* (ATCC 13883), *P. vulgaris* (ATCC 25922), *A. calcoaceticus* (ATCC 19606), *E. colaceticus* (ATCC 13048), *E. aerogenes* (ATCC 23355) and *C. albicans* (Table 1-4).

Chemicals: The starting materials, namely, atetralone, benzosuberone, aryl aldehydes and hydrazine derivatives were obtained from flukaAG, buchs-swiss. 2-arylidene-benzosuberone was prepared from condensation of benzosuberone with corresponding aryl aldehydes in alkaline medium, the pyrazoline were prepared from the condensation of hydrazine and hydrazine deraratives with corresponding 2-arylidene-1-benzosuberone (Al Bahtiti, 2008; Al Bahtiti, 2008).

Table 1: Minimum Inhibitory Concentration (MIC) of chalcones of the general formula $Ar^1-CH=CH-CO-3-indolyl$

Microorganisms	MIC of compounds $\mu g/mL$ Ar^1				
1-Gram+ve bacteria	C_6H_5O	m-Cl- C_6H_4	p-Cl- C_6H_4	$C_{10}H_7$	C_8H_7
<i>S. epidermidis</i> ATCC 1228	>2000	250	32.5	>2000	250
<i>S. aureus</i> ATCC 25923	>2000	250	65	>2000	250
<i>S. faecalis</i> ATCC 33186	>2000	2000	>2000	>2000	125
<i>S. faecalis</i> ATCC 19433	>2000	2000	32.5	>2000	125
<i>B. subtilis</i> NCIB 3610	>2000	250	2000	>2000	250
2-Gram-ve bacteria					
<i>B. licheniformis</i> NCIB 1097	>2000	2000	250	>2000	250
<i>K. pneumoniae</i> ATCC 13883	>2000	2000	2000	>2000	1000
<i>P. vulgaris</i> ATCC 25922	>2000	1000	2000	>2000	500
<i>S. sonnei</i> ATCC 25931	>2000	500	>2000	>2000	1000
<i>P. aeruginosa</i> ATCC 27853	>2000	2000	>2000	>2000	250
Yeast					
<i>C. albicans</i>	>2000	2000	>2000	>2000	>2000

Table 2: Minimum Inhibitory Concentration (MIC) of chalconesdibromides (XIII)

Microorganisms	MIC of compounds ($\mu g/mL$)				
1-Gram+ve bacteria	IIa	IIk	III	IIIm	XIIIo
<i>S. epidermidis</i> ATCC 1228	>2000	2000	2000	2000	500
<i>S. aureus</i> ATCC 25923	>2000	2000	2000	1000	65
<i>S. faecalis</i> ATCC 19433	2000	2000	2000	2000	500
<i>B. subtilis</i> NCIB 3610	2000	2000	2000	2000	65
2-Gram-ve bacteria					
<i>B. licheniformis</i> NCIB 1097	2000	1000	250	>2000	250
<i>K. pneumoniae</i> ATCC 13883	2000	2000	2000	>2000	1000
<i>P. vulgaris</i> ATCC 25922	2000	1000	2000	>2000	500
<i>S. sonnei</i> ATCC 25931	2000	2000	>2000	>2000	1000
<i>P. aeruginosa</i> ATCC 27853	2000	2000	>2000	>2000	250
Yeast					
<i>C. albicans</i>	2000	2000	>2000	>2000	>2000

Table 3: Minimum Inhibitory Concentration (MIC) of pyrazolines (5,6) and pyrazoles (9 and 10)

Microorganisms	MIC of compounds ($\mu g/mL$)				
1-Gram+ve bacteria	IXf	IXj	Vf	VIb	Xb
<i>S. epidermidis</i> ATCC 1228	125	500	2000	2000	960
<i>S. aureus</i> ATCC 25923	2000	250	2000	1000	65
<i>S. faecalis</i> ATCC 19433	32.5	2000	2000	2000	250
<i>B. subtilis</i> NCIB 3610	125	2000	2000	2000	250
2-Gram-ve bacteria					
<i>B. licheniformis</i> NCIB 1097	32.5	250	2000	>2000	250
<i>A. calcoaceticus</i> ATCC 19606	65	500	500	65	125
<i>E. colaceticus</i> ATCC 13048	2000	250	2000	2000	125
<i>S. marescens</i> ATCC 8100	2000	2000	2000	2000	500
<i>P. aeruginosa</i> ATCC 27853	2000	2000	2000	500	1000
Yeast					
<i>C. albicans</i>	2000	2000	>2000	>2000	>2000

The compounds were tested for their antimicrobial testing *in vitro* by the agar dilution techniques. All compounds were dissolved in DMSO for their antibacterial test solutions were sterilized by membrane filtration. Aliquots of compounds were diluted with melted typtic soya or agar, tryptone, soytone, sodium chloride, agar for bacteria or saturated dextrose agar for yeast to give concentration of 2000, 1500, 1000, 500, 250, 125, 62.5 and 31.3 $\mu\text{g/mL}$. The MIC values were noted after 24 h at 37°C.

Table 4: Key of compounds (Table 2 and 3)

Compounds	Ar
I-XV a	p-OCH ₃ -C ₆ H ₄
I-XV b	p-NO ₂ -C ₆ H ₄
I-XV f	1-naphthyl
I-XV j	C ₅ H ₄ N (3-pyridyl)
I-XV k	C ₅ H ₇ N (1-methylpyrrol)
I-XV l	C ₈ H ₇ (3-indolyl)
I-XV m	2,6-Cl ₂ C ₆ H ₃
I-XV o	C ₇ H ₄ O ₂ (3 and 4-methylene-dioxy phenyl)

RESULTS AND DISCUSSION

Antimicrobial activity screening tests were carried out for chalcones-2-arylidene-1-benzosuberone-dibromides and derivatives. Chalcones derived from 3-indolylidene-acetophenone showed biological activity against Gram-positive bacteria more than Gram-negative bacteria or yeast (Table 1 and Fig. 2). The maximum inhibitory activity was shown by 3-indolylidene-(p-chloroacetophenone), i.e., 32.5 $\mu\text{g/mL}$ of it against *Streptococcus faecalis* (ATCC, 19433) and (12228). This compound showed slight activity against *S. aureus* ATCC (25923). Other substituted compounds derived from 3-indolylidene-acetophenone did not exhibit any microbiological activity. On the other hand, 2-arylidene-1-benzosuberone did not show any biological activity against *S. epidermidis*, *S. faecalis* and *B. licheniformis*. It can be concluded at this respect that

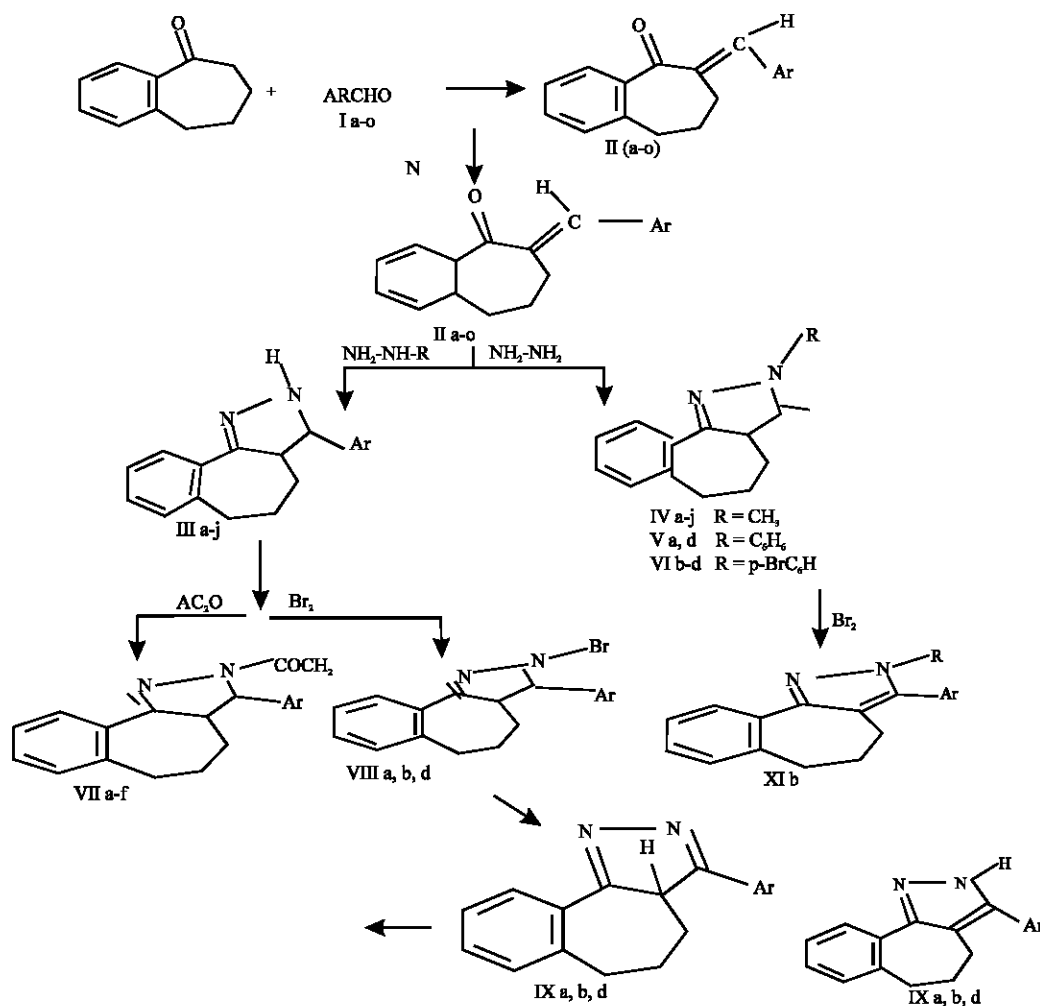


Fig. 2: Synthesis routes to the pyrazolines and pyrazoles compounds

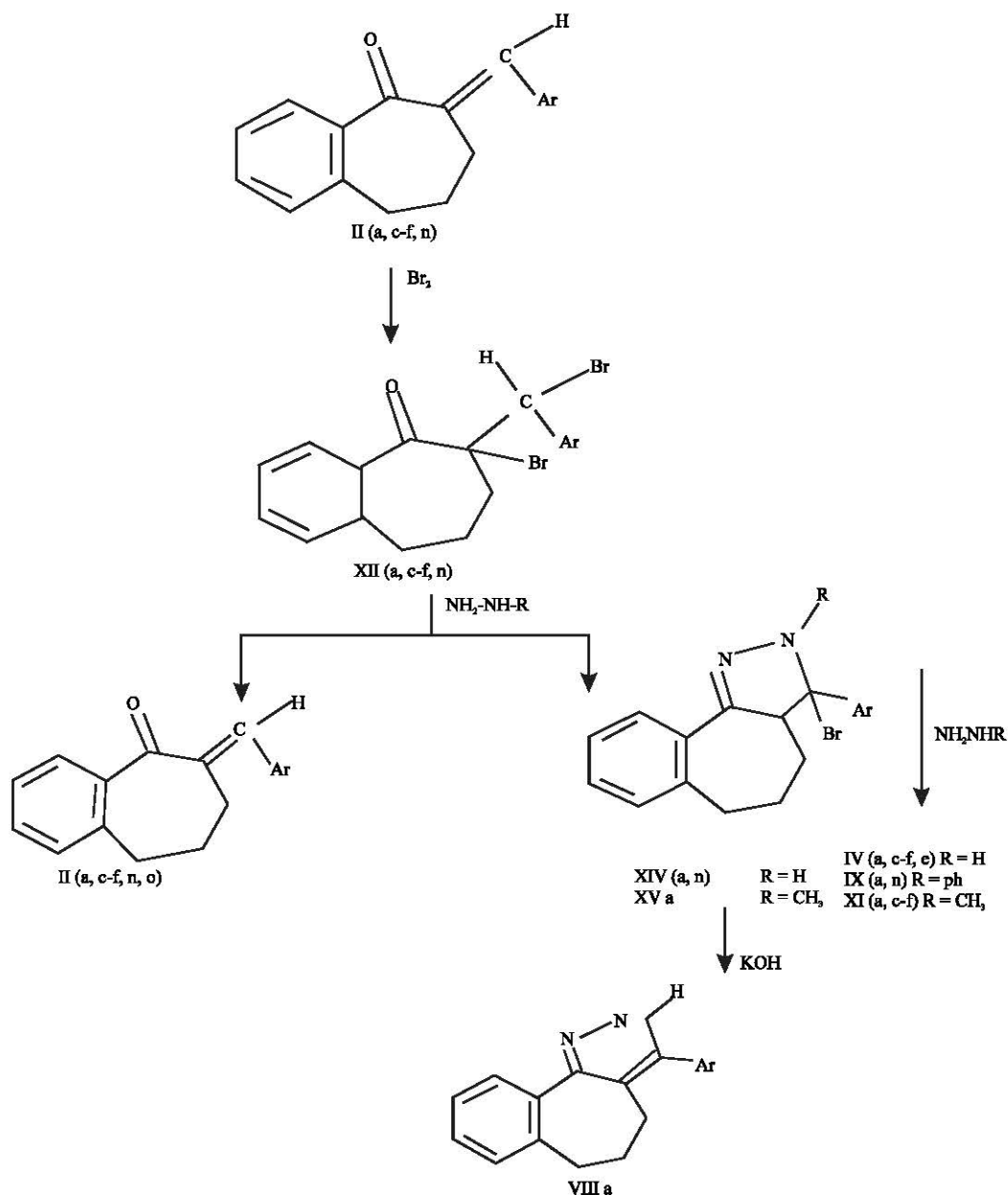


Fig. 3: Synthesis routes to the pyrazolines from dibromo-2-arylidene-1-benzosuberone

the bromine enhances the antibacterial activity shown by the en-one function in the chalcone (Table 2) (Fig. 2 and 3).

The pyrazolines derived from chalcones 4-8 were screened for their microbiological activity and their MIC values showed significant activity against *S. aureus*, *S. epidermidis*, *D. faecalis*, *B. subtilis* and *B. licheniformis* molecular modifications of 2-arylidene-1-indanones leading to increased cytotoxic potencies (Farghaly *et al.*, 2012). It was also shown that the pyrazole (Xb) has an activity against *S. aureus* two

times higher than against *B. licheniformis*, creating another double bond in the system and 4-nitrophenyl substituted group in pyrazole (Xb) may help in inhibitory effect shown (Table 3).

CONCLUSION

In general we can say that compounds (2-10) having active sites as en-one, imine and amine group, show biological activity against microorganisms. Other studies are needed to predict their effect on the inhibition of

growth of microorganisms. We think that such compounds may inhibit the bacterial cell membrane and reduce the uptake of glucose which leads to a less or none cellular acid production. A similar observation has been made by Stretton and Manson (1973) for bronopol (Turek *et al.*, 2017).

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