



## Improved synthesis and *in vitro* study of antimicrobial activity of $\alpha,\beta$ -unsaturated and $\alpha$ -bromo carboxylic acids

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**Abstract:** A series of  $\alpha,\beta$ -unsaturated and  $\alpha$ -bromo carboxylic acids were identified as potent antimicrobial agents. The antimicrobial activity was evaluated using the broth microdilution method. All acids **1–12** exhibited a significant activity against nine laboratory control strains of bacteria and two strains of yeast *Candida albicans*. The tested acids were efficiently prepared by optimized phase-transfer-catalyzed (PTC) reactions of ketones with bromoform and aqueous lithium hydroxide in alcoholic solvent with triethylbenzyl ammonium chloride (TEBA) as catalyst.

**Keywords:** antimicrobial activity; one-pot synthesis; ketones; bromoform.

### INTRODUCTION

Fungal and bacterial infections are important problems in phytopathology, agriculture, the food industry and especially in medicine. Bacterial resistance to antimicrobial agents has become a serious problem worldwide, with resistance mechanisms having been identified and described for all known antibiotics currently available for clinical use.<sup>1</sup>

The development of new antimicrobial agents represents an important field in medicinal chemistry, due to the increasing problem of the formation of resistant strains of bacterial pathogens. Natural products often represent important lead structures for the development of new antibiotics.

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The potential antimicrobial activity of  $\alpha,\beta$ -unsaturated carbonyl compounds continues to receive attention, and several substances exhibiting this function, are used in therapy, for example (Fig. 1), ciprofloxacin<sup>2</sup> and minocycline<sup>3</sup> are members of the antibiotics group, and are commonly used to treat a variety of infections. Helenalin,<sup>4</sup> a sesquiterpene lactone with potent anti-inflammatory and antitumor effects, can also reduce the severity of *Staphylococcus aureus* infection in animals. Some  $\alpha,\beta$ -unsaturated carbonyl compounds with different biological activity are shown in Fig. 1. Etacrynic acid<sup>5</sup> is a loop diuretic used to treat high blood pressure. Digoxin<sup>6</sup> is a cardiac glycoside used in the treatment of congestive heart failure and cardiac arrhythmia. Risperidone,<sup>7</sup> a second generation anti-psychotic, is used to treat schizophrenia. Rofecoxib<sup>8</sup> is a non-steroidal anti-inflammatory drug, which has now been withdrawn due to safety concerns. Dimethyl fumarate<sup>9</sup> is used to treat psoriasis.

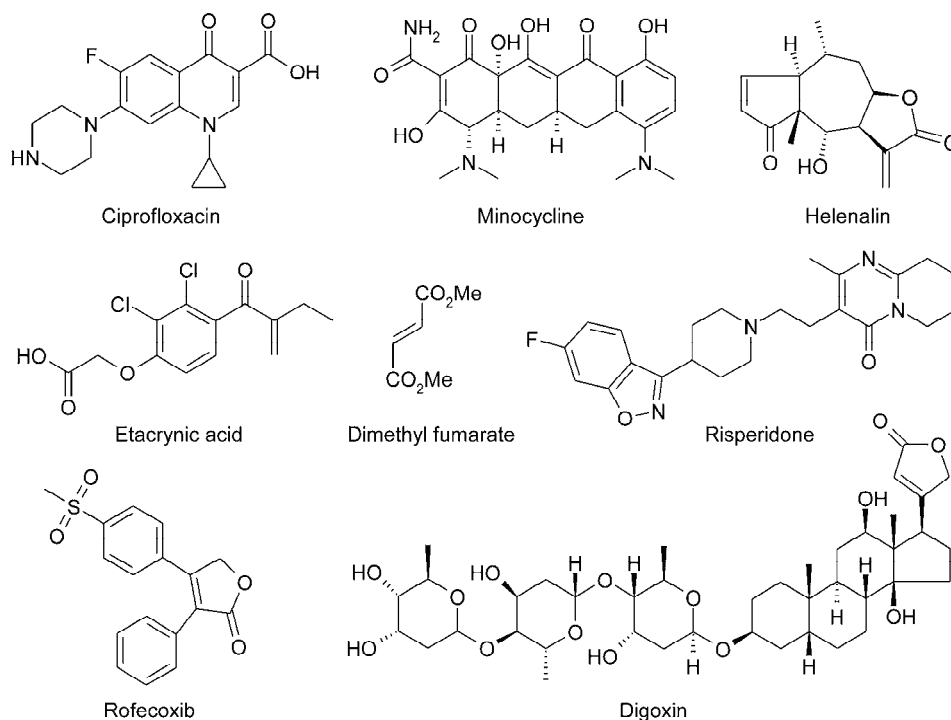


Fig. 1. Structures of several significant  $\alpha,\beta$ -unsaturated carbonyl compounds currently used in medical therapy.

It is generally assumed and confirmed by experimental evidence that the activity of this class of compounds is due to the alkylation of nucleophilic groups, such as amino groups or sulfhydryls, of biomolecules.<sup>10</sup> The reaction involves a

Michael-type addition of the nucleophile to the activated double bond of  $\alpha,\beta$ -unsaturated carbonyl compounds.

The synthesis of  $\alpha,\beta$ -unsaturated carboxylic acids has gained considerable attention<sup>11</sup> because of the biologically important properties of these acids and their use as precursors for the preparation of biologically active compounds.<sup>12</sup> These acids are known for their broad spectrum of activity, for example: antifungal activity of derivatives of tiglic acid and cyclohex-1-enecarboxylic acid.<sup>13</sup> Derivatives of cyclohex-1-enecarboxylic acid are effective in controlling weeds in rice paddies and in vegetable fields.<sup>14</sup> The structural analogue of the anti-epileptic drug sodium valproate (VPA, 2-propylpentanoic acid) possessing an  $\alpha,\beta$ -unsaturated carboxyl group, is 1-cyclohept-1-enecarboxylic acid, which has very low activity.<sup>15</sup> Atropic acid and  $\beta,\beta$ -dimethylatropic acid are plant growth regulators.<sup>16</sup> Pyrethrins are natural organic compounds with potent insecticidal activity. Pyrethrin I and pyrethrin II are structurally related esters with a cyclopropane core, (+)-*trans*-chrysanthemic acid in the case of pyrethrin I. Natural chemical pyrethrins produced by the flowers of pyrethrums (*Chrysanthemum cinerariaefolium* and *C. coccineum*) have the synthetic analog pyrethroid, which now constitutes a major proportion of the synthetic insecticides.<sup>17</sup> A large number of known drugs arise from the reduction of appropriate precursors ( $\alpha,\beta$ -unsaturated carboxylic acids), for example, Ariflo,<sup>18</sup> an orally active second-generation phosphodiesterase type 4 inhibitor (PDE4) inhibitor for the treatment of asthma, as well as non-steroidal anti-inflammatory drugs, such as ibuprofen<sup>19</sup> and naproxen.<sup>20</sup>

## EXPERIMENTAL

### Reagents and chemicals

All used chemicals were of analytical reagent grade, purchased from Aldrich, Fluka or Merck, and were used without further purification.

### Measurements

The NMR spectra for samples were recorded on a Varian Gemini 2000, <sup>1</sup>H-NMR at 200 MHz, <sup>13</sup>C-NMR at 50 MHz, in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as the internal standard. The IR spectra were recorded on Nicolet 6700 FT instrument, and are expressed in cm<sup>-1</sup>. Melting points were determined on a Boetius PMHK apparatus and are not corrected.

### Typical procedure for the synthesis of cyclopent-1-enecarboxylic acid (8)

A flask was charged with LiOH solution (1.18 mol, 49.93 g, in 50 ml H<sub>2</sub>O), *t*-BuOH (250 ml), cyclopentanone (0.059 mol, 5.0 g) and TEBA (0.029 mol, 6.8 g). The mixture was stirred vigorously (large egg-shaped stirring bar) at 45–50 °C (water bath), while bromoform (0.24 mol, 60 g) was added dropwise from a dropping funnel ( $\approx$ 60 min.). The stirring was continued for 24 h at room temperature. Then (0.12 mol, 30 g) of bromoform was added, and the stirring continued for 12 h at room temperature; H<sub>2</sub>O (300 ml) was added and the organic layer (lower one) discarded. The aqueous layer was extracted with toluene (2 $\times$ 70 ml), then acidified with HCl (20 %) to pH around 1. The separated oil was extracted with toluene (3 $\times$ 70

ml), dried (anh.  $\text{MgSO}_4$ ), concentrated and crystallized from toluene. Cyclopent-1-enecarboxylic acid was obtained as white crystals.

#### *In vitro antibacterial activity*

The antimicrobial activity was evaluated using nine laboratory control strains of bacteria, *i.e.*, the Gram-positive *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 12228), *Micrococcus luteus* (ATCC 9341), *Micrococcus flavus* (ATCC 10240), *Enterococcus faecalis* (ATCC 29212), *Bacillus subtilis* (ATCC 6633) and the Gram-negative *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (NCIMB 9111), *Pseudomonas aeruginosa* (ATCC 27853), and two strains of yeast *Candida albicans* (ATCC 10231 and ATCC 10259). A broth microdilution method was used to determine the minimal inhibitory concentrations (MICs) of tested compounds according to the Clinical and Laboratory Standards Institute (CLSI 2005).<sup>21</sup>

All tests were performed in Müller–Hinton broth for the bacterial strains and in Sabouraud dextrose broth for the *Candida albicans*. Overnight broth cultures of each strain were prepared, and the final concentration in each well was adjusted to  $2 \times 10^6$  CFU  $\text{ml}^{-1}$  for the bacteria and  $2 \times 10^7$  CFU  $\text{ml}^{-1}$  for the yeasts. The investigated acids were dissolved to 1 % in dimethyl sulfoxide (DMSO) and then diluted to the highest test concentration. Serial doubling dilutions of the compounds were prepared in 96-well micotiter plates over the concentration range 31.25–1000  $\mu\text{g ml}^{-1}$ . In the tests, triphenyltetrazolium chloride (TTC) (Aldrich, USA) was also added to the culture medium as a growth indicator. The final concentration of TTC after inoculation was 0.05 %. The microbial growth was determined after 24 h incubation at 37 °C for the bacteria and at 25 °C after 48 h for the fungi. The MIC is defined as the lowest concentration of a compound at which the microorganism does not demonstrate visible growth. All determinations were performed in duplicate and two positive growth controls were included.

## RESULTS AND DISCUSSION

Herein, an optimized, convenient synthesis of  $\alpha,\beta$ -unsaturated and  $\alpha$ -bromo carboxylic acids, by phase-transfer-catalyzed reactions of ketones with bromoform and aqueous lithium hydroxide in an alcoholic solvent is reported.

### *Chemistry*

As a part of efforts to synthesize various novel  $\alpha,\beta$ -unsaturated carboxylic acids, a substantially improved and modified synthesis of them has been developed.<sup>22</sup> It also provides access to numerous other conjugated acids.

All the investigated acids (Fig. 2) were synthesized in one-pot phase-transfer reactions of ketones with bromoform (Scheme 1). The acids **1–7**, **11** and **12** were synthesized in satisfactory yields, as is reported in a previous paper.<sup>22</sup> The acids **8–10** were obtained in the improved synthesis in the present work (Scheme 2).

In a previous study, conjugated acids **1–10** were obtained from the corresponding cyclic or aromatic ketones. Bromo acids, 4-bromo-piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester **11** and 4-bromo-piperidine-1,4-dicarboxylic acid monoethyl ester **12** were obtained from 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester and 4-oxo-piperidine-1-carboxylic acid ethyl ester. The published syntheses of the cyclic carboxylic acids **8–10** suffered from low yields (35–75

%).<sup>22</sup> In general, ketones with larger ring size (cycloheptanone and cyclododecanone) were found to be much less reactive than the model ketone (cyclohexanone). Due to steric hindrance, the reaction is slow.<sup>22</sup> Various solvents and reagents were tested, usually resulting in lower yields or giving various side products. Their synthesis presented herein was accomplished in one-step, starting from cyclic ketones, Scheme 2. In this research, the reaction conditions were optimized regarding the reaction temperature, molar ratio of the reactants and the catalyst. Optimal molar proportion of the reagents was found to be 6 eq. of  $\text{CHBr}_3$  and 20 eq. of  $\text{LiOH}$  per 1 eq. of ketone, with solvents ( $t\text{-BuOH}/\text{H}_2\text{O}$ ) and the phase-transfer catalyst TEBA. Lower ratios diminished the yields while higher proportions did not lead to further improvements.

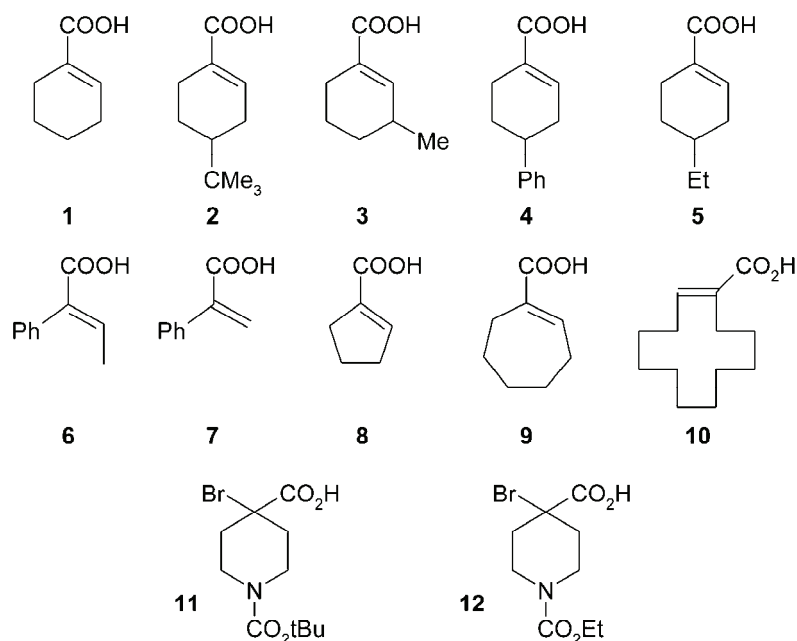
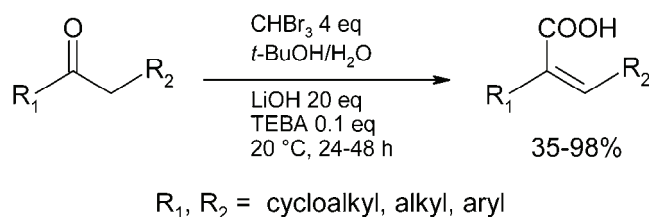
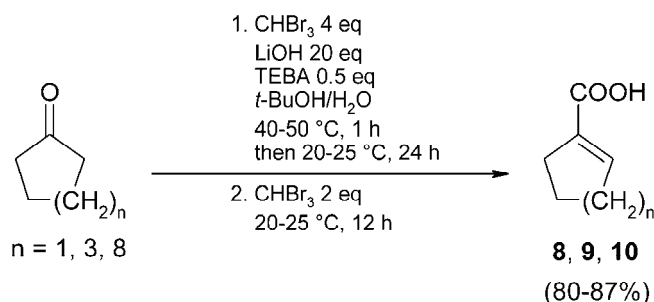


Fig. 2. Investigated acids **1–12**, synthesized in a one-pot phase-transfer reaction of ketones with bromoform.



Scheme 1. One-pot reaction of ketones with bromoform.<sup>22</sup>

Although these kinds of reaction of cyclohexanone and analogs are usually performed at 20 °C,<sup>22</sup> it was found that subsequent heating at 40–50 °C for the first hour of reaction was necessary to achieve nearly quantitative yields, as given in Scheme 2. Finally, acceptable yields and purity of acids **8–10** were obtained using lithium hydroxide (20 eq.), heated *t*-BuOH/H<sub>2</sub>O (40–50 °C) with the gradual addition of bromoform (4 eq., 1 h). After 24 h, the addition of two further equivalents of CHBr<sub>3</sub> dramatically improved the yields and the reaction rate. A number of solvent systems were examined (PhMe/H<sub>2</sub>O, DMSO, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, THF/H<sub>2</sub>O, *i*-PrOH/H<sub>2</sub>O, *t*-BuOH/H<sub>2</sub>O and *t*-PentOH/H<sub>2</sub>O). The optimal yields, purity and reaction rate were achieved in a *t*-BuOH/H<sub>2</sub>O mixture (5:1), in the presence of ≈0.5 eq. of TEBA. The products were isolated and recrystallized from toluene. All the synthesized compounds were fully characterized by instrumental methods, and the purity confirmed by GC, TLC, and MS.



Scheme 2. Optimized one-pot reaction of cyclic ketones with bromoform.

It should be stressed that the reaction protocol presented herein is applicable to a variety of ketones.

#### Characterization data of the compounds

*Cyclopent-1-enecarboxylic acid (8)*. Yield: 5.7 g, 87 %; m.p: 120–121 °C (lit. 121 °C<sup>23</sup>); IR (KBr, cm<sup>-1</sup>): 3100–3150 (O–H stretching of COOH group), 2967 (=C–H stretching of vinyl group), 2863 (–C–H stretching of CH<sub>2</sub> group), 1724 (C=O stretching of COOH group), 1429 (C=C stretching of vinyl group), 1294 (C–O stretching of COOH group), 952 (C=CH bending of vinyl group); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, δ / ppm): 11.08 (1H, s), 6.94 (1H, t, *J* = 2 Hz), 2.49 (4H, m), 2.06 (2H, m); <sup>13</sup>C-NMR (50 MHz CDCl<sub>3</sub>, δ / ppm): 171.02 (CO), 147.07 (CH), 136.07 (C), 33.54 (CH<sub>2</sub>), 30.88 (CH<sub>2</sub>), 23.07 (CH<sub>2</sub>).

*Cyclohept-1-enecarboxylic acid (9)*. Yield: 5.0 g, 85 %; m.p: 53 °C (lit. 51 °C<sup>23</sup>); IR (KBr, cm<sup>-1</sup>): 3150–3200 (O–H stretching of COOH group), 2932 (=C–H stretching of vinyl group), 2860 (–C–H stretching of CH<sub>2</sub> group), 1703 (C=O stretching of COOH group), 1450 (C=C stretching of vinyl group), 1288 (C–O stretching of COOH group), 951 (C=CH bending of vinyl group); <sup>1</sup>H-NMR

(200 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 12 (1H, s), 7.2 (1H, t,  $J = 7$  Hz), 2.6 (2H, m), 2.25 (2H, m), 1.8 (2H, m), 1.6 (4H, m);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 174.04 (CO), 147.46 (CH), 135.89 (C), 31.93 ( $\text{CH}_2$ ), 28.93 ( $\text{CH}_2$ ), 26.82 ( $\text{CH}_2$ ), 26.06 ( $\text{CH}_2$ ), 25.55 ( $\text{CH}_2$ ).

*Cyclododec-1-enecarboxylic acid (10)*. Yield: 4.61 g, 80 %; m.p: 121–122 °C (lit. 120–123 °C<sup>24</sup>); IR (KBr,  $\text{cm}^{-1}$ ): 2958, 2865 (–C–H stretching of  $\text{CH}_2$  group), 1682 (C=O stretching of COOH group), 1424 (C=C stretching of vinyl group), 1280 (C–O stretching of COOH group), 932 (C=CH bending of vinyl group);  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 10.47 (1H, s), 7.14 (1H, t,  $J = 8$  Hz), 2.45 (2H, m), 1.9 (2H, m), 0.95 (16H, m);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 173.13 (CO), 143.22 (CH), 129.56 (C), 43.09 ( $\text{CH}_2$ ), 34.92 ( $\text{CH}_2$ ), 32.42 ( $\text{CH}_2$ ), 32.06 ( $\text{CH}_2$ ), 27.69 ( $\text{CH}_2$ ), 27.40 ( $\text{CH}_2$ ), 27.06 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ), 21.76 ( $\text{CH}_2$ ).

Characterization data of compounds (**1–7**, **11** and **12**) are given in a previous paper.<sup>22</sup>

#### Biological results and discussion

The antimicrobial activity of  $\alpha,\beta$ -unsaturated and  $\alpha$ -bromo-carboxylic acids was tested against ATCC strains of bacteria and two strains of yeast *Candida albicans*. As a standard for the comparison with the synthesized compounds, a well-known drug ampicillin was used. The inhibitory properties of the acids were observed within the concentration range 0.10 to 1.0  $\text{mg ml}^{-1}$ . Minimal inhibitory concentrations (MICs) of tested acids are presented in Table I. The maximum activity was exhibited by the acids **8–10**. The Gram-positive bacteria were more sensitive to the tested acids than the Gram-negative bacteria. The most resistant bacterial strain was the Gram-negative *P. aeruginosa*, which is known to have a high level of intrinsic resistance to virtually all known antimicrobials and antibiotics, due to its very restrictive outer membrane barrier, which is highly resistant even to synthetic drugs.<sup>25</sup>

From the biological data (Table I), it was observed that cyclohex-1-enecarboxylic acid **1** was almost inactive against all the tested strains. As can be seen in Table I, most of the conjugated acids **2–10** generally showed antifungal and antibacterial activity against all the tested fungal and bacterial strains. The activities of compounds **3** and **5** were higher in comparison to those of compounds **2** and **4** because of the steric hindrance (*tert*-butyl and phenyl group) in the series of the substituted cyclohex-1-enecarboxylic acids. The cyclic acids **8–10** showed good inhibitory effects against all the Gram-positive bacteria and the two strains of yeast *C. albicans*. Furthermore, the aromatic acids **6** and **7** showed good antibacterial and antifungal activities. The acids **11** and **12**, the activities of which are unknown in the literature, showed good antifungal activity with an MIC value of



0.1 mg ml<sup>-1</sup>. It is evident that the studied compounds exhibit much lower anti-bacterial activities than ampicillin.

In a previous study,<sup>22</sup> undesirable cytotoxic effects of the investigated compounds were determined on immune competent cells, the normal peripheral blood mononuclear cells. All the compounds examined in this work did not affect proliferation of healthy human blood peripheral mononuclear cells (PBMC and PBMC + PHA),  $IC_{50} > 200 \mu\text{M}$ ; hence, they could be safely used as potential antibiotics.

TABLE I. Antimicrobial activity of the tested  $\alpha,\beta$ -unsaturated and  $\alpha$ -bromo-carboxylic acids (n.t. – not tested)

Microorganism	MIC / mg ml <sup>-1</sup>												Ampicillin
	1	2	3	4	5	6	7	8	9	10	11	12	
<i>S. aureus</i> ATCC 25923	>1.0	0.5	0.5	0.2	1.0	1.0	1.0	0.5	0.5	0.5	1.0	>1.0	0.0005
<i>S. epidermidis</i> ATCC 12228	0.2	0.5	0.2	1.0	0.2	0.5	0.5	0.1	0.2	0.2	1.0	0.5	0.0002
<i>M. luteus</i> ATCC 9341	>1.0	1.0	0.2	0.5	1.0	n.t.	n.t.	0.2	0.2	0.2	n.t.	n.t.	0.002
<i>M. flavus</i> ATCC 10240	1.0	>1.0	0.5	0.1	1.0	n.t.	n.t.	0.2	0.2	0.2	n.t.	n.t.	0.003
<i>E. faecalis</i> ATCC 29212	>1.0	>1.0	1.0	>1.0	1.0	0.2	1.0	0.1	0.2	0.2	>1.0	>1.0	0.0005
<i>B. subtilis</i> ATCC 6633	1.0	1.0	0.2	0.2	0.5	0.2	>1.0	0.2	0.2	0.2	>1.0	1.0	n.t.
<i>E. coli</i> ATCC 25922	>1.0	1.0	1.0	>1.0	>1.0	>1.0	>1.0	0.2	0.5	0.5	>1.0	>1.0	0.002
<i>K. pneumoniae</i> ATCC 13883	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	0.2	0.2	0.5	>1.0	1.0	0.004
<i>P. aeruginosa</i> ATCC 27853	>1.0	1.0	>1.0	>1.0	>1.0	>1.0	>1.0	1.0	0.5	1.0	>1.0	1.0	0.003
<i>C. albicans</i> ATCC 10259	>1.0	1.0	0.5	>1.0	>1.0	0.1	0.2	0.5	0.2	0.5	0.1	0.1	n.t.

### CONCLUSIONS

The tested compounds exhibited significant antimicrobial and antifungal activities and could be considered as the potential antimicrobial agents. Previous cytotoxicity studies revealed low toxicity of these compounds,<sup>22</sup> which renders them as harmless drugs against various microbial and micro-fungal strains. Further studies are planned to elucidate the possible mechanism/mechanisms of action of these compounds.

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## ИЗВОД

ОПТИМИЗАЦИЈА СИНТЕЗЕ И *IN VITRO* ПРОУЧАВАЊЕ АНТИМИКРОБНОГ ДЕЈСТВА  $\alpha,\beta$ -НЕЗАСИЋЕНИХ И  $\alpha$ -БРОМКАРБОКСИЛНИХ КИСЕЛИНА

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У овом раду је приказано *in vitro* испитивање антимикуробног дејства серије  $\alpha,\beta$ -незасићених и  $\alpha$ -бромкарбоксилних киселина и показано је да су оне потенцијално добри антимикуробни агенси. Све киселине **1–12** показале су значајну активност према девет сојева бактерија и два соја гљивица *Candida albicans*. Испитиване киселине синтетисане су у оптимизованој реакцији кетона са бромформом и литијум-хидроксидом у смеси растварача (шериц-бутанол/вода). Као катализатор за пренос између фаза употребљен је триетилбензиламонијум-хлорид (ТЕБА).

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