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Original scientific paper

Synthesis and SAR studies of pyrazole-3-carboxamides and -3-carbonyl thioureides including chiral moiety: Novel candidates as antibacterial agents

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Abstract: A series of tetrasubstituted pyrazole-3-carboxamides (**3a–c**) and pyrazole-3-carbonyl thioureides (**6a–c**) were synthesized and their structures characterized by IR, NMR and elemental analysis. The antibacterial potential against specific Gram-positive and Gram-negative strains and the antifungal activities of all novel compounds were investigated. Structure–activity relationships (SAR) studies and some theoretical parameters (*C*log*P*, *CMR*, *PSA* and *ESP*) of the compounds were performed on these two pyrazole derivatives. Pyrazole-3-carboxylate ester **2** was used for the synthesis of the carboxamide derivatives. The reactions of pyrazole-3-carbonyl isothiocyanate **5** with appropriate chiral amino alcohols were utilized for synthesizing the thioureide derivatives. Both of these types of pyrazole derivatives including a chiral moiety exhibited pronounced antibacterial activities. According to the present *in vitro* study, some of the promising compounds might be new candidates for a new generation of antibacterial drugs.

Keywords: biological activity; chiral amino alcohols; pyrazole; heterocyclic compounds.

INTRODUCTION

Chiral structures are important target molecules in chemistry since they have significant properties, such as catalytic,[1] biological,[2] pharmaceutical,[3] agricultural[4] and industrial implications.[5] Chiral properties have brought a third dimension to the all these fields of science. On the other hand, carboxamide derivatives bearing a chiral stereocentre have also extensive workspace. For example, chiral carboxamides were used as a transporter for drug in pharmaceuticals.[6]

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Furthermore, compounds having thiourea are known to exhibit various biological properties, such as antibacterial,[7] antifungal,[8] antitubercular,[9] antithyroid,[10] anthelmintic,[11] rodenticidal,[12] insecticidal,[13] herbicidal[14] and plant growth regulator[15] activities. However, some thiourea derivatives including chiral moiety not only can serve as catalysts[16] for the synthesis of optically active compounds, but can also be employed as medicines.[17–19] Studies on the biological activities of chiral thioureas are relatively rare and the reported studies showed that they have a broad spectrum of biological activities, such as anti-HIV,[20] anticancer[21] and antiviral.[22]

Some of the biologically active chiral thiourea and amide derivatives are showed in Fig. 1. Since the beginning of this century, pyrazoles, which are an important scaffold of heterocyclic compounds, have increasingly drawn the attention of researchers because of their wider range of properties, particularly for their biological activities. These compounds have been used in the development of agricultural products and in drug research since they have diverse biological activities.[23,24] Some known activities, such as pharmaceutical, agricultural and biological activities of these compounds containing a pyrazole ring system in the structure can be listed as high antihyperglycemic,[25] analgesic,[26] inflammatory,[27] antipyretic,[28,29] anti-bacterial[30] and antidepressant.[31]

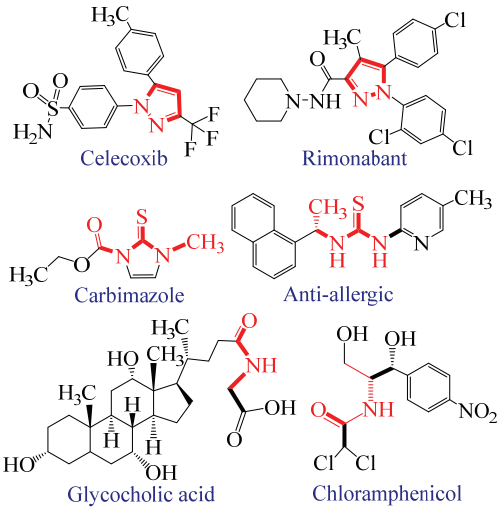

Fig. 1. Some of the important examples of pyrazole, carboxamide and thiourea derivatives.

They provided protection against plant pests,[32] as insecticides[33] and against fungal organisms.[34] They were also found to be hypotensive[35] and anticancer.[36,37] Compounds including synthetic pyrazoles, such as the anti-rheumatic Celecoxib, have been used in the treatment of inflammation[38] and pain.[39] Rimonabant has been used for the treatment of obesity,[40] difenzoquat exerted lethal

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effects against plant pests[41] and tartrazine lemon yellow dye is widely used as a colouring agent for food in the UK and the USA[42] (Fig. 1).

Studies on the implications of the stereochemistry of antibacterial agents have high significance in medicinal chemistry.[43] However, the antimicrobial and antifungal activities of pyrazole-3-carboxamides and 3-carbonyl thioureides containing a chiral stereocentre have not hitherto been reported in the literature. Recently the design, synthesis, and antimicrobial activity of a series of novel carboxamide and thioureide derivatives including the pyrazole scaffold were reported.[44] Encouraged by these successful efforts, we aimed both to expand this study by synthesis new pyrazole derivatives containing chiral moiety and to evaluate the antimicrobial potential against various Gram-positive and Gram-negative strains and antifungal activities of these novel compounds. Moreover, structure––activity relationships (SAR) studies were undertaken and some theoretical parameters of these newly synthesized derivatives were investigated.

EXPERIMENTAL

Materials and equipment

The ^{1}H- and ^{13}C-NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker DRX-400 high performance FT-NMR spectrometer. The NMR spectra were obtained in solutions of DMSO-d_6 and $CDCl_3$. Analytical TLC of all reactions was performed on Merck prepared plates. The infrared spectra were recorded on a Shimadzu IR-470 spectrophotometer. The elemental analyses were obtained with a Carlo Erba Model 1108 apparatus. The optical rotations were taken on a PerkinElmer 341 Model polarimeter. Refraction indices were measured using an Atago Abbe refractometer. The mass spectrum was measured on Thermo Scientific TSQ-Quantum Access LC/MS spectrometers.

Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

Compounds **1** (m.p.: 202–204 °C) and **2** (m.p.: 180 °C) were obtained according to a previous study.[44]

*General procedure for the synthesis of chiral pyrazole-3-carboxamides (**3a**–**c**)*

To compound **2** (0.404 g, 1.0 mmol) dissolved in methanol (5 mL) in the reaction vessel was added dropwise a solution of a chiral amino alcohol (1 mmol, 2-amino-2-phenylethanol, 2-amino-3-methyl-1-butanol and 2-amino-1-butanol, respectively) in methanol (5 mL) at room temperature over 2 h. After the addition, solid product had precipitated that was filtered and washed with diethyl ether. The obtained product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate in 7:1 volume ratio).

*General procedure for the synthesis of chiral pyrazole-3-carbonyl thioureides (**6a**–**c**)*

Compound **1** (0.397 g, 1 mmol) was refluxed with an excess of $SOCl_2$ at 80 °C for about 7 h. The excess $SOCl_2$ was evaporated. The remaining oily product was purified in a dry ether/cyclohexane mixture. As a result, 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl chloride (**4**, m.p.: 145 °C) was obtained, according to the literature.[44] The resulting acylchloride compound (**4**, 1.0 mmol) was dissolved in anhydrous acetone (15 mL) and a solution of 1 mmol ammonium thiocyanate in acetone (5 mL) was added to the reaction vessel. The reaction mixture was refluxed in a round-bottom flask equipped with a condenser

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for 4 h. The solvent was evaporated and the residue was washed with diethyl ether. The solid product was filtered and then the crude product was crystallized from *n*-hexane/diethyl ether. Finally, 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl isothiocyanate (**5**, m.p.: 159–160.5 °C) was obtained.[44]

Compound **5** (0.219 g, 0.50 mmol) dissolved in anhydrous acetone (5 mL) was added dropwise to the appropriate chiral amino alcohol (1 mmol, 2-amino-2-phenylethanol, 2-amino-3-methyl-1-butanol and 2-amino-1-butanol, respectively) in acetone (5 mL). This mixture was kept at room temperature for 4–6 h, after which the reaction mixture was poured onto ice-cold water. The formed precipitate was filtered, dried and the product was purified by crystallization in diethyl ether/*n*-hexane.

Microorganisms and antimicrobial assays

Although the antimicrobial activities of the starting compounds **1** and **2** were previously investigated,[44] their antimicrobial activities were examined again in order to compare together. All samples (**1**, **2**, **3a**–**c**, **5** and **6a**–**c**) were separately tested against *Enterobacter aerogenes* ATCC 13048, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* 6538, *Bacillus megaterium* DSM 32, *Pseudomonas aeruginosa* 9027, *Klebsiella pneumoniae* RSKK 574, *Escherichia coli, Candida albicans, Yarrovia lipolytica and Saccaromyces cerevisiae* ATCC 10231 fungi. All the bacterial and fungal strains examined in the present study were supplied by the Microbiology Laboratory of Muş Alparslan University (Turkey). Penicillin (10 mg), amikacin (30 mg), erythromycin (15 mg), rifampicin (5 mg) and ampicillin (10 mg) antibiotics were used as the reference drugs. The antimicrobial activities of the samples were determined by the well diffusion method.[45,46] For this purpose, the bacterial and fungal strains were cultured overnight at 37 °C in nutrient agar and 25 °C in Sabouraud dextrose agar medium, respectively. 100 µL of suspensions of test microorganisms, containing 1×10^8 colony-forming units (CFU) per mL^{-1} of bacteria cells and 1×10^4 CFU mL^{-1} spores of fungal strains were spread on nutrient agar and Sabouraud dextrose agar medium, respectively. Subsequently, the medium was poured into a Petri dish on a horizontally levelled surface. After the medium had solidified, 9 mm diameter wells per dish were made in the agar medium. Then 0.005, 0.01 and 0.02 g mL^{-1} doses of **1**, **2**, **3a–c**, **5** and **6a–c** suspensions dispersed in DMSO as 50 mg mL^{-1} were loaded into the wells separately. The Petri dishes were incubated at 37 °C for 24 h for bacteria and at 25 °C for 48 h for fungal strains. The average diameters of the inhibition zones were measured by repeating the experiment at least three times.

RESULTS AND DISCUSSION

Chemistry

In the present study, two series of new chiral derivatives, **3a**–**c** and **6a**–**c**, containing a 1,4,5-trisubstituted-pyrazole-3-carbonyl moiety attached to the chirality centre, were synthesized. Initially, 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid (**1**) was synthesized according to a newly published manuscript and the corresponding methyl 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**2**) was obtained by heating the pyrazole-3-carboxylic acid **1** and methanol with a catalytic amount of sulphuric acid.[44] Then, these compounds were derivitized by amino alcohols, (*R*)--2-amino-2-phenylethanol, (*R*)-2-amino-3-methyl-1-butanol and (*R*)-2-amino-1--butanol, respectively. The chiral pyrazole-3-carboxamides compounds were syn-

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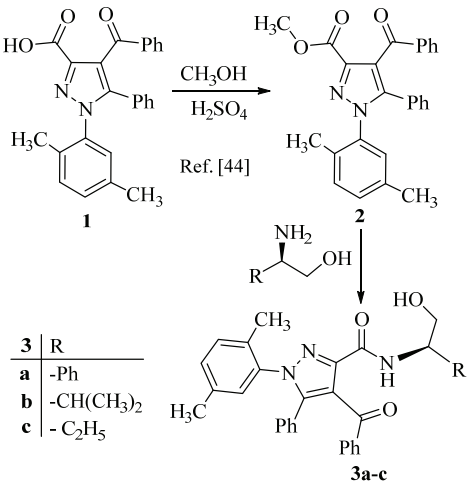
thesized by means of the reaction between methylpyrazole-3-carboxylate **2** and chiral amino alcohols at room temperature (Scheme 1). As a result of this reaction, different new chiral pyrazole-3-carboxamides **3a–c** were obtained in overall yield 72–78 % (Scheme 1).



Scheme 1. Synthesis of pyrazole-3-carboxamides of chiral amines.

All new synthesized compounds were confirmed by analytical and spectral data (see Supplementary material). In the case of compounds **3a**–**c**, the correct structures were established by IR and ^{1}H-NMR spectroscopies in which characteristic –NH absorption bands were observed at 3325–3210 cm^{-1} in the IR spectra. Protons of the hydroxyl signals and NH protons of amide group signals were observed at δ 3.53––2.50 ppm and at δ 8.42–8.34 ppm in the ^{1}H-NMR spectra, respectively.

In order to incorporate potent active pharmacophores, such as pyrazole, thiourea and chiral amino alcohols, in a single molecule, a series of chiral pyrazolo--thiourea derivatives **6a**–**c** were synthesized by the reactions of 4-benzoyl-1-(2,5--dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl isothiocyanate (**5**) with the above-mentioned chiral amino alcohols (Scheme 2). Therefore, first 4-benzoyl-1--(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl chloride (**4**) was obtained by heating pyrazole-3-carboxylic acid (**1**) with excess $SOCl_2$ and then compound **5** was synthesized by heating the pyrazole-3-carbonyl chloride with ammonium thiocyanate in acetone for about 5 h.[44] The chiral thioureide compounds **6a**–**c** were prepared by a basic chemical procedure. Thus **6a**–**c** were synthesized by heating pyrazole-3-carbonyl isothiocyanate (**5**) and the corresponding chiral amino alcohol derivative for 4–6 h as outlined in Scheme 2 (overall yield 60–80 %). These types of heterocyclic compounds including chiral structures are not found in the literature to date. Structure elucidations of the compounds **6a**–**c** were based on ^{13}C-NMR spectroscopy. Benzoyl carbonyl (C=O) signals were

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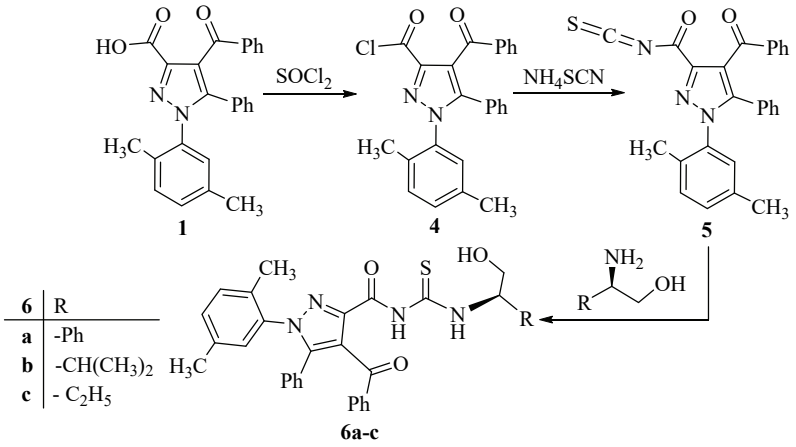
observed at δ 196.8–194.3 ppm, thioamide (C=S) at δ 185.6–180.3 ppm and amide carbonyl (C=O) signals at δ 167.7–165.9 ppm.



Scheme 2. Synthesis of chiral substituted thiourea derivatives **6** *via* pyrazolecarbonyl isothiocyanate **5**.

Biology

Antibacterial activity. The antimicrobial activities of **1**, **2**, **3a**–**c**, **5** and **6a**–**c** against Gram-positive bacteria bacteria (*Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* 6538, *Bacillus megaterium* DSM 32) and Gram-negative bacteria (*Enterobacter aerogenes* ATCC 13048, *Pseudomonas aeruginosa* 9027, *Klebsiella pneumoniae* RSKK 574 and *Escherichia coli* ATCC 25922) as expressed minimal inhibitory concentration (*MIC*). Representative inhibition zone images were showed in Fig. 2. No antifungal activities of the compounds were detected against fungal strains (*Candida albicans*, *Saccharomyces cerevisiae* and *Yarrovia lipolytica* ATCC 10231, data not shown).

TABLE I. The zones of inhibition (mm) of the materials with antibiotics against bacterial strains (*MIC* in μg/mL) *MIC*: minimal inhibitory concentration values with *SEM* = 0.02, –: totally inactive (no inhibition)

Cmpd.	Dose μg/mL	Bacteria						
		Gram-positive bacteria			Gram-negative bacteria			
		B. subtilis	*S. aureus*	*B. megaterium*	*E. aerogenes*	*E. coli*	*P. aeruginosa*	*K. pneumonia*
1	5	12	–	–	–	–	–	15
	10	13	–	–	–	12	14	15
	20	14	–	13	13	16	17	16
2	5	14	12	12	12	14	14	12
	10	10	–	–	12	12	12	12
	20	12	–	10	14	16	16	16

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TABLE I. Continued

Cmpd.	Dose µg/mL	Bacteria						
		Gram–positive bacteria			Gram–negative bacteria			
		B. subtilis	*S. aureus*	*B. megaterium*	*E. aerogenes*	*E. coli*	*P. aeruginosa*	*K. pneumonia*
3a	5	–	–	–	–	10	–	10
	10	14	14	15	12	16	12	15
	20	19	20	16	19	20	21	19
3b	5	11	12	11	10	12	10	10
	10	13	12	15	14	15	12	14
	20	16	22	18	18	16	20	18
3c	5	12	–	–	12	12	–	–
	10	15	11	11	16	15	12	11
	20	16	17	17	18	18	19	15
5	5	–	–	–	–	11	–	13
	10	12	12	12	14	13	–	15
	20	16	17	16	16	17	18	16
6a	5	14	–	13	–	13	13	12
	10	16	15	16	12	15	18	16
	20	18	18	19	19	18	20	18
6b	5	12	12	–	12	–	–	12
	10	15	14	15	15	17	13	14
	20	18	18	18	20	18	17	19
6c	5	13	–	12	–	14	13	–
	10	14	13	13	13	14	13	14
	20	15	15	15	15	15	14	16
Positive controls								
Erythromycin	15	20	21	25	27	19	19	19
Amikacin	30	14	10	–	10	13	–	16
Penicillin	30	21	18	16	16	18	9	19
Ampicillin	10	9	–	10	–	–	–	10
Rifampicin	–	9	–	10	–	–	–	10

The *in vitro* antimicrobial and antifungal activities of the compounds and positive controls were tested in a dose manner (5, 10 and 20 µg mL^{-1}) against ten microorganisms (Table I). The current results indicated that the synthesized compounds showed a broad spectrum of antibacterial activities producing 10–22 mm zones of inhibition. Among the tested compounds, **3b** and **6a** exhibited the highest antimicrobial activities. All tested compounds showed higher antimicrobial activity compared to amikacin and rifampicin, except compound **2**. Compounds **3b** and **6a** had similar or higher antimicrobial activity compared to penicillin.

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Moreover, the obtained data indicated strong antibacterial activity of pyrazole-3-carbonyl derivatives, *i.e.*, **3a**–**c** and **6a**–**c** exhibited pronounced activity against *B. subtilis,* **3a** and **3b** exhibited pronounced activity against *S. aureus*, **3b**, **3c**, **6a** and **6b** exhibited pronounced activity against *B. megaterium*, **3a**–**c**, **6a** and **6b** exhibited pronounced activity against *E. aerogenes*, **3a** exhibited strong activity against *E. coli.* **3a**, **3b** and **6a** exhibited pronounced activity against *P. aeruginosa.*

Compound **3b** exhibited the highest antimicrobial activity against Gram-positive bacteria, followed by **3a** and **3b**. With regards to Gram-negative bacteria, compound **3a** showed the highest antibacterial activity followed by **3b** and **3c**. Compound **6a**–**c** showed similar antibacterial activities against Gram-positive and Gram-negative bacteria. The pattern of the antimicrobial activity potential was **6a** > **6b** > **6c** for both of Gram-positive and Gram-negative bacteria. In general, all compounds had pronounced antimicrobial activities against the bacteria strains. However, *S. aureus* and *B. megaterium* seemed to be more resistant to the compounds and the tested positive controls than the other bacteria strains. There was a positive correlation between antimicrobial activity and the concentrations tested, as shown in Table I.

All tested compounds were pyrazole derivatives with certain modifications. Among the tested compound groups, **3** and **6** had the highest antimicrobial activities. The pronounced antimicrobial activities of compounds **3** and **6** might be explained by the presence of chiral amino alcohol moiety. Relatively higher antimicrobial activities of **3b** and **6a** might be due to the presence of isopropyl and phenyl groups.

The structure–activity relationships (SAR) studies

The synthesized compounds were tested against many different types of bacteria and fungi. Three Gram-positive and four Gram-negative bacteria were applied and some important activities on the bacteria were found. Unfortunately, for all compounds, no inhibition was observed against any of the fungi. The main skeleton of synthesized molecule was 1-(2,5-dimethyl-phenyl)-4-benzoyl-5-phenylpyrazole. Changeable units were selected as ester (**2**), carboxamide (**3a**–**c**), thiocyanate (**5**) and thioureide (**6a**–**c**). All synthesized molecules were prepared at a concentration of 10 mM in DMSO. The molecules with chiral unit showed the best activity against all bacteria. Chiral molecules which have stereogenic centre are important structures because bioactive molecules usually involve the activities of enantiomers. Chiral molecules should play a dominant role in their interactions with bioactive substances. Moreover, they should be applied only to molecules that contain the stereogenic centre in close proximity to the bioactive centre of the molecule, as was the case with the synthesised compounds. Synthetic routes to chiral molecules can be properly turned from achiral structures.

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Molecules having a chiral structure are synthesized by chiral transfer, using a chiral starting material such as chiral amino alcohol.

The ester group should be a derivative with some more potent and suitable groups. For this reason, compound **2** was substituted by (*R*)-amino-alcohol derivatives to obtain compounds **3a**–**c**. The most active derivative of them was found to be **3a**, which bears a phenyl group, against all bacteria except for *S. aureus* and *B. megaterium*. It was found that a bulky group on the (*R*)-amino-alcohol affected the activity against bacteria. To clear this idea, some physicochemical parameters were calculated.[47] Hence, hydrophobic (*C*log*P*: calculated partition coefficient), steric (*CMR*: calculated molecular refractivity) and electronic (*PSA*: polar surface area) parameters for all the synthesized compounds were calculated. The theoretical lipophilicity of **3a**–**c** decreases from **3a** to **3c** and was calculated as 6.67, 6.14 and 5.77, respectively. Calculation of *CMR* and *C*log*P* for **3a**–**c** revealed that *CMR* and *C*log*P* affect the antibacterial activity and increasing them has a positive impact on the biological activity. The worst activity was detected for **3c**, which bears an ethyl group, for which the values for *CMR* and *C*log*P* are 138.43 and 5.77, respectively (Table II). The polar surface areas for **3a**–**c** were calculated and it was seen that there is no change for compounds **3a**–**c**.

TABLE II. Some theoretical parameters for the synthesized molecules

Compound	*PSA* / Å^2	*CMR* / cm^3 mol^{-1}	*C*log*P*
1	69.97	116.47	5.03
2	49.74	120.33	6.31
3a	82	153.7	6.67
3b	82	142.90	6.14
3c	82	138.43	5.77
5	62	129.83	6.90
6a	94	170	6.83
6b	94	159	6.38
6c	94	154	6.02

Thiocyanate group attached to the molecule **5** shown lower activities than **3a**–**c**. On the other hand, activities of **5** on bacteria were moderate. Compounds **6a**–**c** which have thiourea and (R)-amino-alcohol chains were tested against same bacteria and it was calculated that reactivity against bacteria decreased and the most potent molecule of compounds **6a**–**c** was **6a** which bears phenyl ring.

Theoretical parameters of compound **6a**–**c** were also shown that biological activity could be affected by increasing of *CMR* and *C*log*P* (Table II). Moreover, although *CMR* and *C*log*P* of **6c** was very close to **3a**, which has the best potent molecule, biological activity of **6c** is lower in comparison to **3a**. Decreasing of reactivity on bacteria have shown that (R)-amino-alcohol unit should be adjacent to the carbonyl group and there should be no any other chain between carbonyl and (R)-amino-alcohol groups. After SAR study, it was worthy to say that (R)-

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-amino-alcohol unit increase the biological activity against some Gram-(–) and Gram-(+) bacteria.

The electrostatic potential (*ESP*) of **3a** was investigated to understand its H-donor and -acceptor units and its total electronic surface. According to the *ESP* map, the oxygen atoms of the two carbonyl groups and of the alcohol group are H-acceptors and the alcohol group is an H-donor group (Fig. 3).

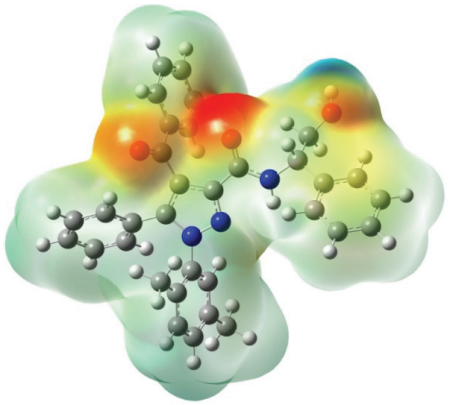

Fig. 3. Electrostatic potential (*ESP*) of **3a**.

The proton of the amide group is less acidic than the others and due to this, this proton might not be a good candidate for proton donation. The rest of molecule showed the expected electronic potential and these surfaces are not worthy of discussion.

CONCLUSIONS

Within this study, a series of tetra-substituted pyrazole-3-carboxamides (**3a**–**c**) and pyrazole-3-carbonyl thioureides (**6a**–**c**) binding a chiral amino alcohol were synthesized and their antibacterial and antifungal properties were investigated. The structure–activity relationships (SAR) studies and some theoretical parameters (*C*log*P*, *CMR*, *PSA* and *ESP*) of these pyrazole-carboxamide and -thioureide derivatives were investigated.

Compound series **3** and **6** exhibited superior antimicrobial activities among the tested compounds. The pronounced antimicrobial activities of compound series of **3** and **6** can be explained by the presence of a chiral amino alcohol moiety. The relatively higher antimicrobial activities of **3b** and **6a** might be due to the presence of isopropyl and phenyl groups.

The present results indicated that the synthesized compounds were active in a broad spectrum against important human pathogenic microorganisms. Therefore, these compounds might be new candidates for efficient antibacterial agents.

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SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И SAR ИСПИТИВАЊЕ ПИРАЗОЛ-3-КАРБОКСАМИДА И 3-КАРБОНИЛ-ТИОУРЕИДА И ХИРАЛНИХ СТРУКТУРА: НОВИ КАНДИДАТИ ЗА АНТИБАКТЕРИЈСКЕ АГЕНСЕ

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Синтетисана је серија пиразол-3-карбоксамида (**3a**–**c**) и пиразол-3-карбохил-тиоуреида (**6a**–**c**), а добијеним дериватима структура је одређена IR, NMR и елементалном анализом. Испитана је антибактеријска активност према специфичним Грам-позитивним и Грам-негативним сојевима бактерија и антифунгална активност свих нових синтетисаних једињења. Урађена је анализа утицаја структуре на активност (structure–activity relationships, SAR) и неких теоријских параметара (Clog*P*, *CMR*, *PSA* и *ESP*). За синтезу карбоксамидних деривата коришћен је пиразол-3-карбоксилатни естар **2**. Реакцијом пиразол-3-карбонил-изотиоцијаната **5** и одговарајућих хиралних алкохола добијени су деривати тиоурее. Обе групе добијених једињења показују запажену антибактеријску активност. Према приказаном *in vitro* испитивању, неки од деривата могу бити кандидати за даља испитивања антибактеријске активности.

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