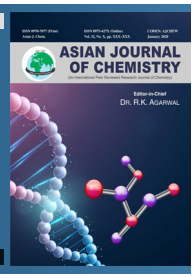
Asian Journal of Chemistry; Vol. 32, No. 2 (2020), 381-384

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22416



Synthesis, Characterization and Antimicrobial Activity of *N*-2-(4-Chlorophenyl)acetyl Derivatives of (*S*)-Amino Acids

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Received: 26 August 2019; *Accepted*: 25 October 2019; *Published online*: 30 December 2019; AJC-19730

This paper reports the synthesis, characterization and antibacterial activity of *N*-2-(4-chlorophenyl)acetyl derivatives of various (*S*)-amino acids such as (*S*)-alanine, (*S*)-phenylalanine, (*S*)-leucine, (*S*)-methionine, (*S*)-proline and (*S*)-tryptophane. These compounds have been successfully synthesized and their structures were confirmed by ^{1}H NMR and ^{13}C NMR and FT-IR spectroscopy. The antimicrobial activity of these six (*S*)-amino acids derivatives have been evaluated by the agar well diffusion method against pathogens both Gram-positive (*S. aureus*) and Gram-negative (*K. aerogenes*, *E. coli* and *P. desmolyticum*as) bacteria and fungi (*A. flavus* and *C. albicans*). All these compounds have shown mild to moderate antimicrobial activity.

Keywords: Amino acid, *N*-2-(4-Chlorophenyl)acetyl chloride, Antibacterial activity, Antifungal activity.

INTRODUCTION

Amino acids are the monomers of proteins which are the main building blocks of all living organisms. Some of the larger and smaller molecules of peptides play vital roles as enzymes, hormones and sometimes involves in the detoxification process. Some of the naturally occurring peptides were shown good biological activity [1]. The activity of these natural peptides is limited due to average biostability, bioavailability and many microbes were gained resistant over many naturally occurring antimicrobial agents.

To overcome these problems, our interest has been directed towards the synthesis of stable and more active derivatives of α-amino acids. These compounds may play an important role in the pharmaceutical field on account of their peptidomimetics, high stability, easy laboratory synthesis and low toxicity. It has been reported that based upon the type of groups attached to the α-amino acids, the biological activities such as antimicrobial and anticancer activities would also vary [2]. Purinylamino acid derivatives have been shown activity 10 to 25 times more against *M. tuberculosis* than emblematic tuberculosis drugs [3-5]. Likewise coumarinyl [6,7], pyrazolyl [8,9], thiophenyl [10,11], sulphonamide [12-14] amino acid derivatives have been proved as potentially biologically active [15]. Therefore, herein we report the synthesis, characterization and antimicrobial activity studies of *N*-2-(4-chlorophenyl)acetyl derivatives of (*S*)-alanine (4-CPA), (*S*)-phenylalanine (4-CPPA), (*S*)-leucine (4-CPL), (*S*)-methionine (4-CPM), (*S*)-proline (4-CPP) and (*S*)-tryptophane (4-CPT).

EXPERIMENTAL

Chemicals, reagents and solvents were purchased from Spectrochem Ind. Pvt. Ltd. and SD fine chemicals Ind. Pvt. Ltd. and all were used without further purification. 4-Chlorophenyl acetyl chloride was prepared by the reported method [16]. Melting points were measured in an open capillary tube closed at one end and all reported uncorrected. FT-IR spectra were recorded with PerkinElmer Frontier-ATR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz on Agilent 400 MR DD2 NMR spectrometer with tetramethylsilane (TMS) as an internal standard expressed on δ ppm scale. Thin layer chromatography (TCL) was performed and visualized under UV light, iodine vapour and/or $KMnO_4$ spray. For TLC, silica gel coated aluminum plates (Merck, 60F254) were used. Bacterial strains *Klebsiella aerogenes* (NCIM-2098), *Escherichia coli* (NCIM-5051), *Staphylococcus aureus*

(NCIM-5022) and *Pseudomonas desmolyticum* (NCIM-2028) and fungal strains *Aspergillus flavus* (NCIM544) and *Candida albicans* (NCIM-3100) were purchased from National Chemical Laboratory (NCL), Pune, India. These strains were maintained on nutrient agar slant at 4 °C. Standard antibiotics ciprooxacin and fluconazole were purchased from Hi Media, Mumbai, India.

Synthesis of *N*-2-(4-chlorophenyl) acetyl derivatives amino acids: The corresponding (*S*)-Amino acid (1.0 mmol) was dissolved in minimum volume of water under stirring in a 1-neck round bottom flask surrounded by cooling bath (ice-NaCl) maintaining the temperature of -4 to 0 °C. To this solution, an aqueous solution of NaOH (10 mL, 4.0 mmol) was added and stirred for 4-5 min. Then, the resulting solution was added (4-chlorophenyl) acetyl chloride drop-wise during 3 min under continuous stirring maintaining the temperature below 0 °C. The stirring was continued further for 30 min and then the reaction mixture was poured into ice cold water. This mixture was acidified with dil. HCl forming a white precipitate of *N*-(4-chlorophenyl) acetyl derivative of present α-amino acid. The solid obtained was filtered and dried.

(*S*)-2-[2-(4-Chlorophenyl)acetamido]propanoic acid (4-CPA): White solid; Yield: 70 %; m.p.: 136 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 1.220-1.238 (d, *J* = 7.2 Hz, CH_3, 3H), 3.420 (s, Ar-CH_2, 2H), 4.123-4.160 (m, CH, 1H), 7.230-7.251 (d, *o/m*-Ar-H, 4H), 7.301-7.323 (d, *o/m*-Ar-H, 4H), 8.375-8.393 (d, *J* = 7.20, NH, 1H), 12.485 (s, COOH, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, δ ppm): 17.65 (CH_3), 41.44 (Ar-CH_2), 48.01 (CH), 128.49 (ArC, *o* to Cl), 131.30 (ArC, *m* to Cl), 131.47 (ArC, *p* to Cl), 135.72 (ArC-Cl), 169.94 (CONH), 174.52 (COOH); FT-IR (ATR, ν_{max}, cm^{-1}): 3332 (N-H, amide), 1705 (C=O, acid), 1622 (C=O, amide), 1554 (N-H, ben), 1490 (C-N, amide).

(*S*)-2-[2-(4-Chlorophenyl)acetamido]-3-phenylpropanoic acid (4-CPPA): White solid; Yield: 82 %; m.p.: 155 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.790-3.061 (dq, Ph-CH_2, 2H), 3.328-3.476 (q, Cl-Ar-CH_2, 2H), 4.361-4.417 (m, CH,1H), 7.087-7.260 (m, Ar-H, 9H), 8.369-8.349 (d, *J* = 8 Hz, NH, 1H), 12.5 (s, COOH, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, δ ppm): 37.24 (Ph-CH_2), 41.6 (Cl-Ar-CH_2), 54.0 (CH), 126.77-138.03 (Ar-C), 170.0 (CO, amide), 173.43 (COOH); FT-IR (ν_{max}, cm^{-1}, ATR): 3321 (N-H, amide), 1706 (C=O, acid), 1615 (C=O, amide), 1555 (N-H, ben, amide), 1215 (NH-CO-C, ben).

(*S*)-2-[2-(4-Chlorophenyl)acetamido]-3-(ethylsulfanyl) propanoic acid (4-CPM): Pale yellow viscous liquid; Yield: 80 %; ^{1}H NMR ($CDCl_3$, δ ppm): 1.914-2.032 (m, S-CH_3 and S-CH_2, 5H), 2.404-2.455 (m, CH_2, 2H), 3.561 (s, Ar-CH_2, 2H), 4.622-4.671 (q, CH, 1H), 6.586-6.605 (d, *J* = 8 Hz, NH, 1H), 7.144-7.300 (m, Ar-H, 4H); ^{13}C{^{1}H} NMR (DMSO-d_6, δ ppm): 15.07 (S-CH_3), 30.1 (S-CH_2), 31.278 (CH_2), 41.61 (Ar-CH_2), 51.53 (CH), 128.48 (*o*-ArC), 131.27 (m-ArC), 131.70 (*p*-ArC), 135.72 (C1), 170.38 (CO, amide), 173.69 (COOH). FT-IR (ν_{max}, cm^{-1}, ATR): 3334 (N-H), 3254-2201 (ArC-H), 1740 (acid C=O) 1704 (C=O, amide), 1614 (COO, asym. str.), 1601 (ArC=C), 1555 (N-H ben), 1492 (C-H, ben), 1415 (C-N), 1355 (COO symm str.), 1245 (C-N), 1093 (C-O), 803 (S-C), 763 (C-H, out of plane ben), 644 (N-H, out of plane ben).

(*S*)-2-[2-(4-Chlorophenyl)acetamido]-3-(7a*H*-indol-2-yl)propanoic acid (4-CPT): White solid; Yield: 90 %; m.p.: 174 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.977- 3.179 (m, Indo-CH_2, 2H), 3.411 (s, Ar-CH_2, 2H), 4.443-4.495 (q, CH, 1H), 6.934-7.508 (m, Ar-H, 9H), 8.345 (d, *J* = 8 Hz, NH, 1H), 10.829 (s Indo-NH, 1H), 12.634 (s, COOH, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, δ ppm): 27.59 (Indo-CH_2), 41.53 (Ar-CH_2), 53.49 (C4), 110.25-136.54 (C-aromatic), 170.07 (NHCO), 173.76 (COOH); FT-IR (ν_{max}, cm^{-1}, ATR): 3401 (COOH), 3310 (NH, ring), 1709 (C=O, acid), 1615 (C=O, amide), 1558 (N-H, ben),1250 (C-N).

(*S*)-2-[2-(4-Chlorophenyl)acetamido]-4-methylpentanoic acid (4-CPL): White solid; Yield: 85 %; m.p.: 148 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 0. 878-0.887 (d, *J* = 3.6 Hz, CH_3, 3H), 0. 893-0.902 (d, *J* = 3.6 Hz, CH_3, 3H), 1.485-1.666 (m, CH and CH_2, 3H), 3.554 (s, Ar-CH_2, 2H), 4.557 (bs, CH, 1H), 5.792-5.808 (d, *J* = 6.4 Hz, NH, 1H), 7.180-7.200 (d, *J* = 7.62 Hz, Ar-H, *o* to Cl, 2H); 7.302-7.322 (d, Ar-H, *m* to Cl, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 26.46 (CH_3), 27.98 (CH_3, 3H), 29.52 (CH), 46.29 (Ar-CH_2), 55.52 (chiral CH), 128.49 (ArC, *o* to Cl), 131.30 (ArC, *m* to Cl), 131.47 (ArC, *p* to Cl), 135.72 (ArC-Cl), 169.94 (CONH), 174.52 (COOH); FT-IR (ν_{max}, cm^{-1}, ATR):3328 (N-H, amide), 2967 (ArC-H), 1706 (C=O, acid), 1614 (C=O, amide), 1557 (N-H, ben), 1245 (NH-CO, bend).

(*S*)-1-[(4-Chlorophenyl)acetyl]pyrrolidine-2-carboxylic acid (4-CPP): Pale yellow low melting solid; Yield: 78 %; m.p.: liquid at room temperature; ^{1}H NMR ($CDCl_3$, δ ppm): 1.967-2. 113 (m, pyr-CH_2), 3.427-3.601 (m, pyr-CH_2) 2H), 3.601 (s, Ar-CH_2, 2H), 4.378-4.408 (t, CH, 1H), 7.124-7.253 (m, Ar-H, 4H), 9.4 (s, COOH, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, δ ppm): 22.77 (pyr-CH_2), 29.38 (pyr-CH_2), 31.51 (Ar-CH_2), 47.26 (CH_2), 59.23 (CH), 128.27-131.86 (ArC), 168.72 (CO, amide), 174.05 (COOH); FT-IR (ATR, ν_{max}, cm^{-1}): 2979 (ArC-H), 1732 (C=O, acid), 1625 (C=O, amide), 1245 (N-C, ben).

Antimicrobial activity: The antibacterial and antifungal activities have been studied for the *N*-2-(4-chlorophenyl)acetyl derivatives of six (*S*)-amino acids. The bacterial strains used were *K. aerogenes*, *E. coli* and *P. desmolyticum* as Gram-negative and *S. aureus* as Gram-positive bacteria and fungal strains *A. flavus* and *C. albicans*.

Nutrient agar media and potato dextrose broth were used to culture the bacteria and fungi, respectively. Nutrient agar plates were prepared and swabbed using sterile L-shaped glass rod with 100 µL of 24 h mature broth culture of individual bacterial strains. The wells were crated of 6 mm into the each of the petri plate using sterile cork borer. The solutions of each compound (4-CPA, 4-CPPA, 4-CPM, 4-CPT, 4-CPL and 4-CPP) were prepared in two concentrations of 10 and 20 µg/µL made in DMSO and evaluated their antibacterial activity. Similarly a standard antibiotic 'ciprofloxacin' solution used as a positive control of concentration 0.1 µg/µL. These solutions were added into the wells by sterile micropipette. The plates were incubated at 37 °C for 48 h. After the incubation period, the zone of inhibition of each well was measured and the values were noted. These measurements were made in triplicate for each compound and the average values are reported in Table-1.

For antifungal activity sporulated culture of fungi strains of potato dextrose agar (PDA) slant was incubated at 25 °C for 48-96 h and then were transferred into 10 mL of sterile, 1 % saline solution. From each fungal spore 100 µL suspension was spread on each PDA petri plate using L-shaped glass rod. After spreading on PDA plates using sterile cork borer, made

TABLE-1
ANTIMICROBIAL ACTIVITIES OF *N*-2-(4-CHLOROPHENYL)ACETYL DERIVATIVES OF (*S*)-AMINO ACIDS

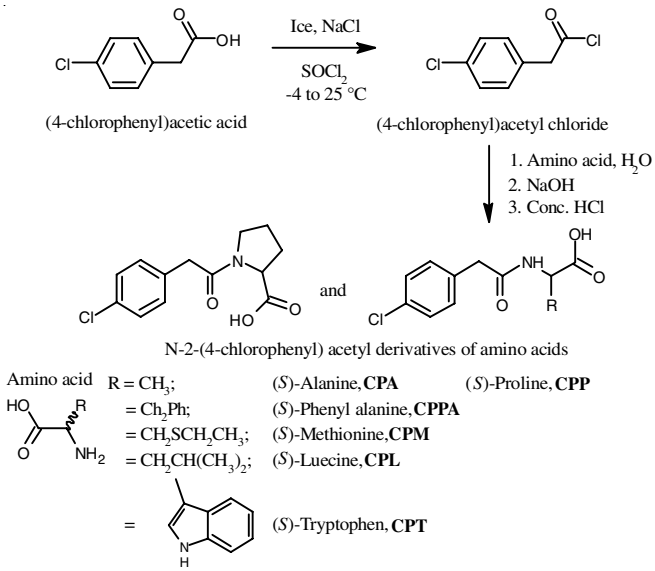
Compound	Conc. (µg/µL)	*K. aerogenes*	*E. coli*	*S. aureus*	*P. desmolyticum*	*A. flavus*	*C. albicans*
Ciprofloxacin	0.1	12.33 ± 0.03	13.67 ± 0.03	14.00 ± 0.00	15.60 ± 0.03	–	–
Fluconazole	4.0	–	–	–	–	10.27 ± 0.03	11.50 ± 0.06
4-CPA	10	4.00 ± 0.00	4.30 ± 0.06	4.10 ± 0.06	3.85 ± 0.00	1.00 ± 0.00	1.50 ± 0.06
	20	6.40 ± 0.17	6.88 ± 0.03	6.56 ± 0.12	6.16 ± 0.00	1.67 ± 0.03	2.33 ± 0.03
4-CPPA	10	2.86 ± 0.00	2.47 ± 0.06	2.32 ± 0.07	2.23 ± 0.00	0.55 ± 0.00	1.60 ± 0.03
	20	4.43 ± 0.07	3.80 ± 0.00	3.63 ± 0.07	3.45 ± 0.03	2.27 ± 0.03	2.33 ± 0.03
4-CPM	10	3.21 ± 0.00	3.08 ± 0.00	2.86 ± 0.00	2.90 ± 0.17	1.00 ± 0.00	1.57 ± 0.03
	20	4.83 ± 0.23	4.67 ± 0.17	4.50 ± 0.07	4.40 ± 0.17	2.50 ± 0.06	3.67 ± 0.03
4-CPT	10	1.12 ± 0.00	1.20 ± 0.06	1.00 ± 0.06	1.36 ± 0.00	1.37 ± 0.03	0.00 ± 0.00
	20	1.66 ± 0.09	1.78 ± 0.06	1.49 ± 0.00	2.02 ± 0.17	2.17 ± 0.03	1.00 ± 0.00
4-CPL	10	3.00 ± 0.00	2.50 ± 0.00	3.30 ± 0.20	2.80 ± 0.00	1.50 ± 0.06	1.00 ± 0.00
	20	4.86 ± 0.00	4.06 ± 0.17	5.41 ± 0.17	4.27 ± 0.07	2.00 ± 0.00	2.33 ± 0.33
4-CPP	10	1.80 ± 0.10	2.30 ± 0.42	2.00 ± 0.00	1.90 ± 0.00	0.75 ± 0.06	1.20 ± 0.00
	20	2.82. ± 0.21	3.40 ± 0.32	3.20 ± 0.26	3.10 ± 0.00	1.32 ± 0.00	1.50 ± 0.03

(Mean ± SE)

wells of 6 mm on each plate. The PDA plates were incubation at 25 °C for 48-96 h. The solutions (10 and 20 µg/µL) of 4-CPA, 4-CPPA, 4-CPM, 4-CPT, 4-CPL and 4-CPP made in DMSO. 50 µL of each of these test solutions transferred into 6 mm wells made above on PDA media plates. Similarly 4 µg/µL solution of standard antifungal drug 'fluconazole' solution made in DMSO and used as a positive control. The zone of inhibition of each well was measured and the values were noted. Triplicates were maintained for each compound and the average values are reported in Table-1.

RESULTS AND DISCUSSION

Synthesis of *N*-2-(4-chlorophenyl) acetyl derivatives of amino acids contains two steps. The first step involves preparation of 4-chlorophenyl acetyl chloride. Thionyl chloride (3 mL, 41 mmol) was taken in a round bottom flask and cooled in a cooling bath (NaCl) and then was added 4-chlorophenyl acetic acid (500 mg, 2.93 mmol) slowly and dropwise maintaining the temperature in the range of 0 to -4 °C under stirring. Then the reaction mixture was brought to room temperature and continued stirring for further 3 h. The excess thionyl chloride was distilled off that resulted 4-chlorophenyl acetyl chloride in 80 % yield. The second step was the acetylation of amino acids to the corresponding *N*-2-(4-chlorophenyl)acetyl derivatives. These *N*-2-(4-chloro phenyl)acetamides of six amino acids were synthesized at 0-4 °C. The reaction mixture was acidified with dil. HCl to the corresponding products in good yields (70-85 %) (**Scheme-I**). Both of these reactions were carried out in fuming hood.



Scheme-I: Synthesis of *N*-2-(4-chlorophenyl)acetyl derivatives of (*S*)-amino acids

Characterization: All the six *N*-2-(4-chlorophenyl)acetyl derivatives of (*S*)-amino acids (4-CPA, 4-CPPA, 4-CPM, 4-CPT, 4-CPL and 4-CPP) were completely characterized by ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopy.

In the IR spectra of all the compounds, the vibrational stretching band for C=O (acid) was appeared at 1709-1706 cm^{-1} except for 4-CPP in which this band was observed at 1732 cm^{-1}. The stretching band for C=O (amide) bond was appeared at lower wavenumber region 1625-1615 cm^{-1}. These observations indicated the formation amide linkage in all the compounds. The N-H bending band was appeared at 1558-1554 cm^{-1}.

In the proton NMR spectrum of 4-CPA the methyl protons were appeared as a doublet at δ 1.220-1.238 ppm. In all the compounds the chiral CH (H4) proton was appeared as a multiplet in the range of 4.123-4.495 ppm [17-19]. The C-$C_6H_4CH_2$ (H1) protons were appeared as a singlet at 3.420 ppm, respectively. In all the compounds, the *ortho* (H7,7') and *meta* (H8,8') protons of 4-chlorophenyl ring were observed as two doublets or multiplets in the range of δ 7.144-7.322 ppm. In 4-CPA, 4-CPM and 4-CPT the COOH proton was appeared at about δ 12.5 ppm as a broad or very broad singlet whereas the CONH (amide) proton was observed at δ 8.37 ppm in 4-CPA and 4-CPP and in 4-CPT the signal was appeared at 10.89 ppm. In 4-CPM and 4-CPL the NH proton was appeared at 6.586 and 5.792 ppm, respectively. In proton NMR spectrum of 4-CPPA the Cl-$C_6H_4CH_2$ (δ 2.466-2.848 and 3.016-3.061 ppm) and $PhCH_2$ (δ 4.361-4.417 ppm) protons were appeared as double of a doublet due to their diastereotopic nature.

The products have been confirmed by their ^{13}C NMR spectra. The signals for CONH carbon (except in 4-CPP and 4-CPL) was appeared in the range of δ 169-171 ppm whereas the

COOH carbon was deshielded and observed in the range of δ 171-175 ppm as shown by other amino acid derivatives [17-19]. In 4-CPL the CONH and COOH carbons were found highly deshielded as they have been appeared at δ ~175 and ~179 ppm, respectively.

The observation from the proton and carbon NMR spectra and FT-IR spectra confirmed the structure of the synthesized amino acid derivatives of 4-chlorophenyl acetyl chloride.

Antibacterial activity: Antimicrobial screening of 4-CPA, 4-CPPA, 4-CPM, 4-CPT, 4-CPL and 4-CPP was done by well diffusion method [20] in agar nutrient medium. The antimicrobial activity was evaluated against both Gram-positive (*S. aureus*) and Gram-negative (*K. aerogenes*, *E. coli* and *P. desmolyticum*as) bacteria. Two concentrated solutions (10 and 20 μM) made in DMSO of compounds were employed for antibacterial activity studies. The average values (in mm) of zone of inhibition of synthesized compounds measured in triplicate are recorded in Table-1. The results of antimicrobial activity studies demonstrated that the synthesized amino acid derivatives have been capable to inhibit the metabolic growth of the investigated bacteria and the toxicity increases with dosage of any of the above tested compounds. Among the compounds tested, 4-CPA has shown highest antibacterial activity against all the pathogens and nearly 50 % when compared with standard, ciprofloxacin.

All the synthesized compounds were screened for antifungal activity. Two fungi used for the activity studies. Two concentrated solutions of each compound were prepared and experiments were carried out in triplicate. The average values zone of inhibition observed for each compound was recorded in Table-1. Fluconazole was used as a standard antifungal drug. All the compounds exhibited antifungal activity.

Conclusion

N-2-(4-Chlorophenyl) acetyl derivatives of (*S*)-amino acids were successfully synthesized and characterized by FT-IR and NMR spectroscopies. The synthesized compounds were found to act as antimicrobial agents and the their activity increases with increasing dosage of the respective compounds. The results also revealed that these compounds could be better antibacterial than antifungal agents.

ACKNOWLEDGEMENTS

Authors are thankful to UGC for providing financial support under the project MRP(S)-1043/11-12/KABA019/UGC-SWRO.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. A. Sánchez and A. Vázquez, *Food Qual. Saf.*, **1**, 29 (2017); https://doi.org/10.1093/fqs/fyx006.
2. D.V. Grishin, D.D. Zhdanov, M.V. Pokrovskaya and N.N. Sokolov, *All Life*, **13**, 11 (2020); https://doi.org/10.1080/21553769.2019.1622596.
3. A.K. Pathak, V. Pathak, L.E. Seitz, W.J. Suling and R.C. Reynolds, *Bioorg. Med. Chem.*, **21**, 1685 (2013); https://doi.org/10.1016/j.bmc.2013.01.054.
4. Y. Voynikov, G. Stavrakov, J. Tencheva and P. Peikov, *Compt. Rend. Acad. Bulg. Sci.*, **66**, 1399 (2013).
5. Y. Voynikov, V. Valcheva, G. Momekov, P. Peikov and G. Stavrakov, *Bioorg. Med. Chem. Lett.*, **24**, 3043 (2014); https://doi.org/10.1016/j.bmcl.2014.05.026.
6. M.M. El-Kerdawy, M. Eisa, A. Barghash and A. Marouf, *Sulfur Lett.*, **10**, 57 (1989).
7. M.E.A. El-Fattah, *Arch. Pharm. Res.*, **21**, 723 (1998); https://doi.org/10.1007/BF02976765.
8. O.A. Fathalla and M.E.A. Zaki, *Indian J. Chem.*, **37B**, 484 (1998).
9. E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke and I. Ugi, *Angew. Chem.*, **7**, 380 (1968); https://doi.org/10.1002/anie.196803801.
10. M.J. McKennon, A.I. Meyers, K. Drauz and M. Schwarm, *J. Org. Chem.*, **58**, 3568 (1993); https://doi.org/10.1021/jo00065a020.
11. J. Humljan, M. Kotnik, A. Boniface, T. Solmajer, U. Urleb, D. Blanot and S. Gobec, *Tetrahedron*, **62**, 10980 (2006); https://doi.org/10.1016/j.tet.2006.08.030.
12. H.M. Hassan, M.M. Abdelall, A.M. El-Naggar, M.E. Tamer and R.A. Bayoumi, *J. Am. Sci.*, **7**, 378 (2011).
13. M. Al-Amin and M.I. Rabiul, *Bangladesh J. Pharmacol.*, **1**, 21 (2006).
14. R.A. El-Sayed, *Phosphorus Sulfur Silicon Rel. Elem.*, **131**, 207 (1997); https://doi.org/10.1080/10426509708031609.
15. C. Cabrele, T.A. Martinek, O. Reiser and L. Berlicki, *J. Med. Chem.*, **57**, 9718 (2014); https://doi.org/10.1021/jm5010896.
16. K. Phukan, M. Ganguly and N. Devi, *Synth. Commun.*, **39**, 2694 (2009); https://doi.org/10.1080/00397910802663428.
17. A. Siebert, M. Wysocka, B. Krawczyk, G. Cholewiñski and J. Rachoñ, *Eur. J. Med. Chem.*, **143**, 646 (2018); https://doi.org/10.1016/j.ejmech.2017.11.094.
18. C.E. Satheesh, P. Raghavendra Kumar, P. Sharma, K. Lingaraju, B.S. Palakshamurthy and H. Raja Naika, *Inorg. Chim. Acta*, **442**, 1 (2016); https://doi.org/10.1016/j.ica.2015.11.017.
19. C.E. Satheesh, P. Raghavendra Kumar, N. Shivakumar, K. Lingaraju, P. Murali Krishna, H. Raja Naika and A. Hosamani, *Inorg. Chim. Acta*, **495**, 118929 (2019); https://doi.org/10.1016/j.ica.2019.05.028.
20. A. Sen and A. Batra, *Int. J. Curr. Pharm. Res.,* **4**, 67 (2012).