Asian Journal of Chemistry; Vol. 34, No. 5 (2022), 1220-1224

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2022.23649

Synthesis and Structural Studies of *N*-Maltosylated Aryl Thiobiurets

ANUJA M. MOPARI[1,*] and GAJANAN V. KORPE[2]

[1]Department of Chemistry, Shri Shivaji College of Arts, Commerce & Science, Akola-444001, India
[2]Department of Chemistry, Shri Shivaji Science College, Amravati-444603, India

*Corresponding author: E-mail: anujamopari@gmail.com

Received: 2 December 2021; *Accepted*: 20 February 2022; *Published online*: 20 April 2022; AJC-20775

The derivatives of urea, thiourea and thiosemicarbazide play an important role in medicinal chemistry by influencing various pharmacological activities. The design and development of novel *N*-maltosides have emerged as an important class of organic compounds. A series of 1-hepta-O-benzoyl-β-D-Maltosyl-5-aryl-2-4-thiobiurets are described in present work. By mixing hepta-O-benzoyl→D-maltosyl isocyanates with various aryl thiocarbamides, 1-hepta-O-benzoyl-β-D-maltosyl-5-aryl-2-4-thiobiurets have been synthesized. The identities of this newly synthesized 1-hepta-O-benzoyl-β-D-Maltosyl-5-aryl-2-4-thiobiurets were characterized by IR, ^{1}H NMR and mass analyses. The compounds tested for antibacterial activity against a wide range of microorganisms, including *Staphylococcus aureus, Escherichia coli*, *Psudomonas aeruginosa* and antifungal activities against *Aspergillus niger* and *Trichoderma*. TLC confirmed the activity of these compounds.

Keywords: Aryl thiocarbamides, *N*-maltosides, Thiobiurets.

INTRODUCTION

Carbohydrates are the most abundant and significant class of naturally occurring organic substances in nature, accounting for nearly all of the world's biomass [1]. Carbohydrates have a lot of functions since each monosaccharide has at least one carbonyl group and multiple hydroxyl groups [2]. Carbohydrates have sparked interest in synthetic and medicinal chemistry because of their biological value. Maltose, often known as malt sugar, is a disaccharide made up of two units of glucose connected by α1→4 links [3]. Two glucose molecules are joined by α1→6 bond in the isomer maltose. Maltose remains formed when diastase hydrolyzes starch. It is present in sprouting seeds like barley when they break down their starch stores to make nourishment [4]. Maltotriose remains produced by adding another glucose unit; successive additions result in dextrin and starch. Hydrolysis can break down maltose into two glucose molecules. Maltose, an enzyme found in living organisms, can quickly accomplish this [5].

Maltose is a sugar, which undergoes mutarotation and lowering. N-maltosides are compounds in which the maltosyl group or derivative exists connected to a nitrogen-containing molecule [6]. Maltosyl isocyanate, the most potent intermediate in sugar chemistry, has been used to make many *N*-maltosides.

Carbohydrate chemistry has emerged as a frontier area of research due to its wide range of applications in the pharmaceutical industries. The literature has remained enriched by discoveries on sugar heterocycles' synthesis and pharmacological action, which have emerged as an introductory organic chemistry class [7]. A reagent containing isocyanate may remain used to crosslink or label hydroxyl-containing compounds such as polysaccharide [8]. Carbohydrate modification can be accomplished without the necessity for prior oxidation of sugar residues to produce reactive aldehyde, as is the case with many protocols [9].

The coupling reaction of amino sugar or sugar and glycosyl isocyanate makes disaccharide urea and carbamates with varied bridging positions as anomers readily available. The reaction of glucosyl bromide with silver cyanate and anhydrous xylene produced glucopyranosyl isocyanate [10]. Carbamide and its derivatives have potent antibacterial properties and are useful reagents in chemical synthesis [11]. Carbohydrates play a crucial function in a wide range of biological activities and there are several benefits [12] due to its low toxicity and immunogenicity.

Unprotected and polar sugars are converted to compounds soluble in many organic solvents by acetylation and benzoylation. The resultant sugar per acetates and benzoates has been used as glycosyl donors in monosaccharide synthesis [13]. The acetyl and benzoyl groups are inexpensive protective groups that can be easily removed [14]. The parent alcoholic components may be recovered using Zemptent's reagent under basic or acidic conditions. Other procedures, such as high pressure, have created pure sugar per acetate [15].

According to the literature, maltosyl bromides are significant intermediates in the chemistry of carbohydrates. In synthesizing oligosaccharides and glycoconjugates, maltosyl bromides are employed as starting materials and essential intermediates [16]. Due to the wide application and simple synthetic route of maltosyl bromide and its derivatives in medicinal, industrial, and biological applications, it appears attractive to synthesize *N*-maltosylated compounds such as thiocarbamides then react these thiocarbamides with hepta-O-benzoyl→D-maltosyl isocyanate. With this view, the interaction of hepta-O-benzoyl-β-D-maltosyl isocyanate with certain aryl thiocarbamides, the corresponding thiobiurets have been synthesized.

EXPERIMENTAL

All the melting points were recorded on Mac digital melting point apparatus and are uncorrected. The structures of the newly synthesized compound were confirmed based on the elemental and spectral analysis. IR spectra were recorded in solid-phase KBr disks on Shimadzu IR Affinity-1 FTIR spectrophotometer [17]. Specific rotations were measured on Equip-Tronics EQ-800 Digital Polarimeter. Thin layer chromatography (TLC) was performed in E. Merck per coated silica gel plates and detected by exposure under harsh UV light [18]. ^{1}H NMR has been obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal reference [19]. The mass spectra were recorded on Jeol SX-102 FAB mass spectrometer.

Synthesis of hepta-O-benzoyl-β-D-maltosyl isocyanates (I): Hepta-O-benzoyl-β-D-maltosyl isocyanates were prepared by the condensation of hepta-O-benzoyl-α-D-maltosyl bromide (0.005 mol, 3.4 g) and lead cyanate (0.005 mol, 1.4g) in boiling xylene (25 mL) medium for 3 h with frequent shaking. After removing lead bromide, the xylene filtrate was triturated with petroleum ether (60-80 ºC) when hepta-O-benzoyl-β-D-maltosyl isocyanates were precipitated out. To afford a pale yellow solid, it was purified by dissolving in a minimum quantity of chloroform and reprecipitating with petroleum ether (60-80 ºC). The homogeneity of the product was checked by TLC (m.p.: 112 ºC).

Synthesis of aryl thiocarbamides (IIa-e): Aryl thiocarbamides were synthesized by reacting the appropriate amount of aryl amine and conc. HCl and ammonium thiocyanate.

Synthesis of 1-hepta-O-benzoyl-β-D-maltosyl-5-aryl-2,4-thiobiurets: Benzene solution of hepta-O-benzoyl-β-D-maltosyl isocyanate (0.005 M, 3.3 g in 1 mL) was added to a benzene solution of 1-phenyl-*S*-benzyl isothiocarbamide (0.005 M, 1.2 g in 10 mL) and the reaction mixture was refluxed over a boiling water bath for 3 h. Afterward, solvent benzene was removed by distillation and resultant syrupy mass was triturated several times with petroleum ether; a granular solid was obtained crystallized from ethanol-water. The homogeneity of the product was checked by TLC (**Scheme-I**). Percent yield, m.p., optical rotation, elemental analysis and R_f values are given in Table-1.

1-Hepta-O-benzoyl-β-D-maltosyl-5-phenyl-2,4-thiobiuret (IIID): IR (KBr, ν_{max}, cm^{-1}): 3489, 3163 (NH), 3064 (Ar C-H), 2958 (aliph. C-H), 1726 (C=O), 1101 (C-O), 1271 (C-N), 1099 (C=S), 1033 (characteristics of maltose); ^{1}H NMR ($CDCl_3$) δ: 8.07-7.29 (35 H, m, aromatic protons), 6.16 (1H, s, NH proton), 6.08 (1H, s, NH proton), 4.16 (1H, s, NH proton), 4.28 (2H methylene), 4.81 (2H methylene, d), 7.27-6.72 (5H, m, arom. protons), 4.16-6.16 (10H, m, maltosyl protons). Mass (*m/z*): 1247.92 (M$^+$); 1043.48 (M+1); 1156.10 (M+2);1095.99 (M+3).

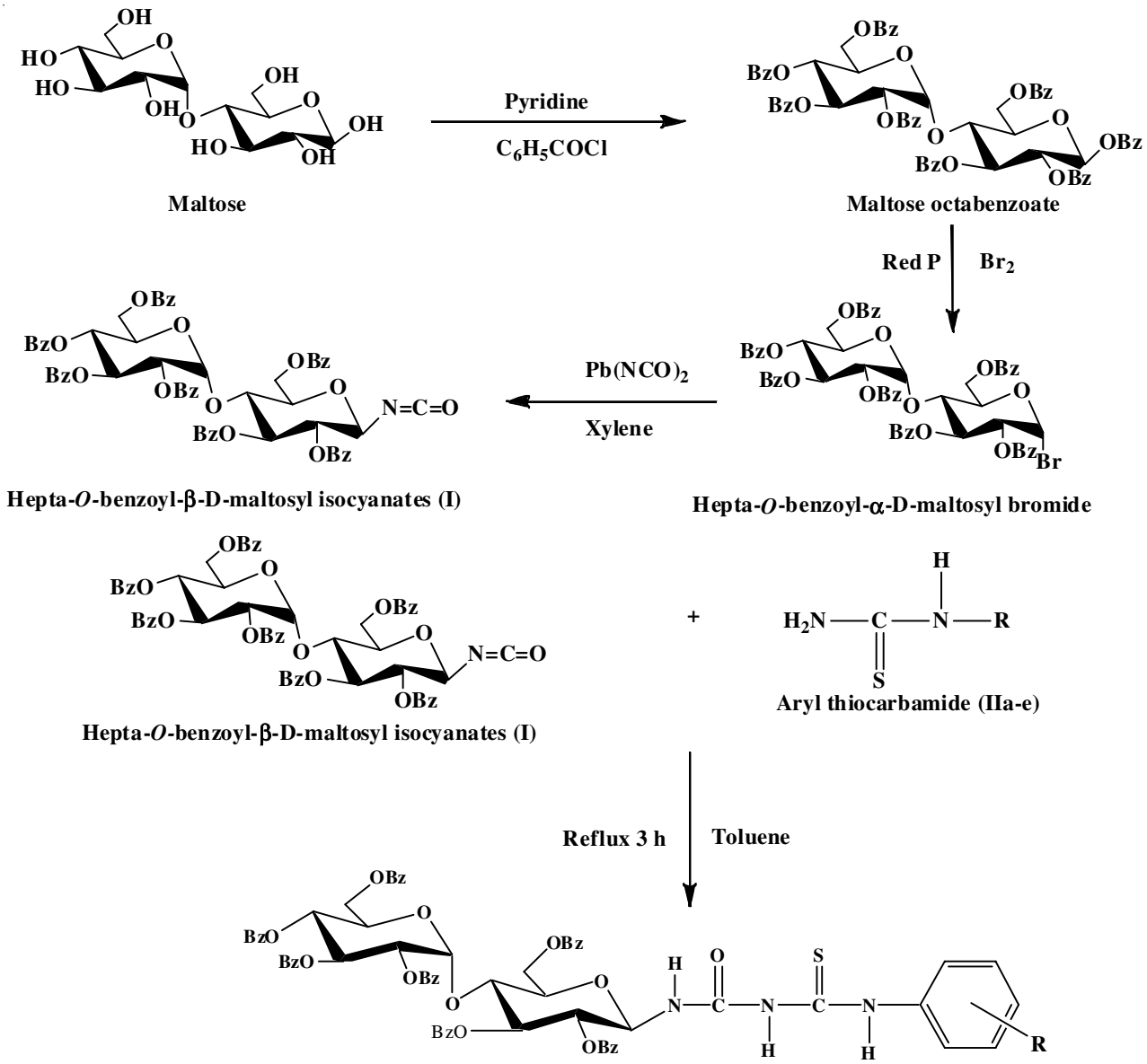
1-Hepta-O-benzoyl-β-D-maltosyl-5-*o*-tolyl-2,4-thiobiuret (IIIE): IR (KBr, ν_{max}, cm^{-1}): 3489,3163 (NH), 3064 (Ar C-H), 2958 (aliph. C-H), 1726 (C=O), 1101 (C-O), 1271 (C-N), 1099 (C=S), 1033 (characteristics of maltose), 711 (monosubstituted benzene); ^{1}H NMR ($CDCl_3$) δ: 8.08-7.25 (35H, m, aromatic protons), 6.14 (1H, s, NH proton), 5.93 (1H, s, NH proton), 3.96 (1H, s, NH proton), 4.48 (2H, methylene), 4.58 (2H, methylene, d), 7.24-7.20 (4H, m, aromatic protons), 2.31 (3H, s, methyl H), 6.20-4.17 (10H, m, maltosyl protons); Mass (*m/z*): 1261.88 (M$^+$); 91.13 (M+1); 1111.87 (M+2); 595.88 (M+3).

1-Hepta-O-benzoyl-β-D-maltosyl-5-*o*-chloro phenyl-2,4-thiobiuret (IIIF): IR (KBr, ν_{max}, cm^{-1}): 3489, 3163 (NH), 3064 (Ar C-H), 2958 (aliph. C-H), 1726 (C=0), 1101 (C-O), 1271 (C-N), 1099 (C=S), 1033 (characteristics of maltose), 813 (mono-substituted benzene); ^{1}H NMR ($CDCl_3$) δ: 8.05-7.26 (35H, m, aromatic protons), 6.17 (1H, s, NH proton), 6.72 (1H, s, NH proton), 4.28 (1H, s, NH proton), 4.28 (2H methylene), 4.58 (2H methylene, d), 7.23-6.72 (4H, m, aromatic protons), 6.21-4.16 (10H, m, maltosyl protons); Mass (*m/z*): 1281.93 (M$^+$); 229.01 (M+1); 1054.16 (M+2); 595.80 (M+3).

1-Hepta-O-benzoyl-β-D-maltosyl-5-*o*-nitrophenyl-2,4-thiobiuret (IIIG): IR (KBr, ν_{max}, cm^{-1}): 3489, 3163 (NH), 3068

TABLE-1
1-HEPTA-O-BENZOYL-β-D-MALTOSYL-5-ARYL-2,4-THIOBIURETS (**IIID–IIIH**)

Compound	m.p. (°C)	Yield (%)	Elemental analysis (%): Found (required)		R_f value	$(\alpha)_D^{32}$ (c, in $CHCl_3$)
			N	S		
IIID	178	68.30	3.23 (3.37)	2.51 (2.57)	0.87	+140 .22
IIIE	177	72.14	3.29 (3.33)	2.50 (2.54)	0.93	+60 50
IIIF	180	65.42	3.21 (3.28)	2.44 (2.50)	0.76	+135.35
IIIG	185	64.09	3.28 (3.35)	2.47 (2.50)	0.83	+110.20
IIIH	183	68.70	4.39 (4.43)	2.43 (2.49)	0.80	+88.16



1-Hepta-*O*-benzoyl-β-D-maltosyl-5-aryl-4-thiobiurets
where, R = (a) phenyl, (b) *o*-tolyl, (c) *o*-chloro, (d) *o*-nitro, (e) *o*-methoxy

Scheme-I: 1-Hepta-*O*-benzoyl-β-D-maltosyl-5-aryl-2-4-thiobiurets (**IIID-IIIH**)

(Ar C-H), 2958 (aliph. C-H), 1726 (C=O), 1101 (C-O), 1271 (C-N), 1099(C=S), 1033 (characteristics of maltose), 815 (monosubstituted benzene); ^{1}H NMR ($CDCl_3$) δ ppm: 8.10-7.29 (35H, m, aromatic protons), 6.18 (1H, s, NH proton), 6.08 (1H, s, NH proton), 3.89 (1H, s, NH proton), 4.68 (2H, d, methylene), 4.38 (2H, d, methylene), 8.08-7.63 (4H, m, aromatic protons), 6.20-5.17 (10H, m, maltosyl protons); Mass (*m/z*): 1292.08 (M+); 196.02 (M+1); 1094.29 (M+2); 122.02 (M+3).

1-Hepta-O-benzoyl-β-D-maltosyl-5-*o*-methoxy phenyl-2,4-thiobiuret (IIIH): IR (KBr, ν_{max}, cm^{-1}): 3489, 3163 (NH), 3064 (Ar C-H), 2958 (aliph. C-H), 1726 (C=O), 1101 (C-O), 1271 (C-N), 1099(C=S), 1033 (characteristics of maltose), 721 (monosubstituted benzene); ^{1}H NMR ($CDCl_3$) δ ppm: 8.11-7.15 (35H, m, aromatic protons), 6.14 (1H, s, NH proton), 5.93 (1H, s, NH proton), 3.96 (1H, s, NH proton), 4.48 (2H, methylene), 4.58 (2H, methylene, d), 7.24-7.20 (4H, m, aromatic protons), 3.38 (3H, s, methoxy proton), 6.31-4.1s (10H, m, maltosyl protons); Mass (*m/z*): 1261.66 (M+); 1094.39 (M+1); 181.04 (M+2); 122.00 (M+3).

Antimicrobial activity: The newly synthesized thiobiurets were screened against different pathogenic microbes for their antibacterial and antifungal activities using a standard method using amikacin (100 µg/mL) and fluconazole (100 µg/mL) as standard compounds for antibacterial and antifungal screening, respectively. The medium was prepared by dissolving weighed compounds and was sterilized at 121ºC and 15 lbs/inch pressure for 15 min after sterilization, it was cooled down to about 50 ºC and poured in sterile Petri-plates and allowed to solidify. The media plates were seeded within 24 h old active nutrient broth culture of the test organism in order to obtain lawn culture. A

TABLE-2
ANTIBACTERIAL ACTIVITY OF 1-HEPTA-O-BENZOYL-β-D-MALTOSYL-5-ARYL-2,4-THIOBIURETS (**IIID–IIIH**)

Compounds	Inhibition zone (diameter in mm)				
	Bacteria			Fungi	
	Staphylococcus aureus	*Escherichia coli*	*Psudomonas aeruginosa*	*Aspergillus niger*	*Trichoderma*
IIID	20	18	22	18	19
IIIE	22	20	20	17	22
IIIF	18	18	19	21	14
IIIG	17	19	21	18	20
IIIH	21	17	12	15	13
Amikacin	22	18	21	–	–
Fluconazole	–	–	–	24	23

stainless steel cork borer of 7 mm diameter was used to bore those cavities. The compounds were taken at a concentration of 1 µg/mL using dimethyl sulphoxide (DMSO) as a solvent. In to the well were added 0.1 mL portion of text compounds in medium. The drug solution was allowed to diffuse for about an hour in the medium. The plate was incubated at 37 ºC for 24 h for antibacterial activity. The zone of inhibition observed around the well after respective incubation was measured in mm by using an antibiotic zone reader.

RESULTS AND DISCUSSION

A series of 1-hepta-O-benzoyl-β-D-maltosyl-5-aryl-4-thiobiuret have been synthesized by the interaction of hepta-O-benzoyl-β-D-maltosyl isocyanates with substituted aryl thiocarbamides. All the products were crystallized from ethanol-water before recording the physical data (Table-1). The purity of the compounds was checked by TLC. Carbon and hydrogen were found satisfactory in all the cases and no impurity was detected.

Interpretation of IR spectra indicated that thiobiurates are the main component of the sample, Compounds **IIIE** (*o*-tolyl) and **IIIF** (*o*-chloro), **IIIG** (*o*-nitro), **IIIH** (*o*-methoxy) shows peaks of monosubstituted ring at 711 and 815 cm^{-1}, respectively. The ^{1}H NMR spectra of compound **IIID** show a total of 57 hydrogens, *i.e*. multiplet of 35 benzoylated aromatic-H (protected maltosyl), two N-H (urea) and one aromatic N-H singlet, multiple of five aromatic-H of phenyl substituted ring, characteristics of maltose shows 4H of two methylene and 10H of tetrahydropyran ring. Similarly, other compounds **IIIE** and **IIIF** shows a total of 59 & 56 ^{1}H NMR peaks with differ in characteristics at *o*-tolyl *i.e*. 3H singlet of terminal proton of methyl substituent (**IIIE**) and ^{1}H NMR with four aromatic H coupling.The *o*-chlorophenyl substituent (**IIIF**) with four aromatic H coupling, respectively. Another compound **IIIG** (*o*-nitro) substituent per total hydrogen 56 and compound **IIIH** with *o*-methoxy substituent per total hydrogen 59 shows coupling of 4 aromatic hydrogen, compound **IIIH** shows characteristic peak *i.e*. 3 H singlet of terminal methoxy proton with increase in chemical shift value. The mass spectra show molecular ion peaks of all the compounds accurately and some fragmented ion peaks with their *m/z* value.

Antimicrobial activity: The synthesized compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Psudomonas aeruginosa*. The antimicrobial study of synthesized compounds indicates that compounds **IIID**, **IIIE** and **IIIH** show the most significant activity while compounds **IIIF** and **IIIG** were found to be active against *Staphylococcus aureus* (Table-2). Compound **IIIE** exhibited the most significant activity while all other compounds exhibited moderate activity against *Escherichia coli*. All compounds exhibited significant activity except compound **IIIH**, which is resistant towards *Pseudomonas aeuroginosa*, while compound **IIIF** is active towards *Aspergillus niger* whereas all other compounds are moderately active. Compounds **IIIE** and **IIIG** show a significant activity while compound **IIID** is moderately active. Similarly, compounds **IIIF** and **IIIG** are resistant towards *Tricoderma*.

Conclusion

A new series of 1-hepta-O-benzoyl-β-D-maltosyl-5-aryl-2,4-thiobiuret is synthesized and characterized. It exhibited excellent antibacterial and antifungal activities against the organism tested. The adopted synthetic method is compatible with various sugar derivatives and found to be an efficient and inexpensive with excellent yield.

ACKNOWLEDGEMENTS

The authors are thankful to SAIF/CIL, Panjab University, Chandigarh for providing the spectral data. The authors also thankful to The Principal, Dr. A.L. Kulat for providing the necessary research facilities.

CONFLICT OF INTEREST

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

REFERENCES

1. P.M. Medeiros and B.R.T. Simoneit, *Environ. Sci. Technol*., **42**, 8310 (2008); https://doi.org/10.1021/es801533b
2. S.S. Kulkarni, C.-C. Wang, N.M. Sabbavarapu, A.R. Podilapu, P.-H. Liao, S.-C. Hung, *Chem. Rev*., **118**, 8025 (2018); https://doi.org/10.1021/acs.chemrev.8b00036
3. J. Gangoiti, S.F. Corwin, L.M. Lamothe, C. Vafiadi, B.R. Hamaker and L. Dijkhuizen, *Crit. Rev. Food Sci. Nutr*., **60**, 123 (2020); https://doi.org/10.1080/10408398.2018.1516621
4. A. Alamgir, Vitamins, Nutraceuticals, Food Additives, Enzymes, Anesthetic Aids and Cosmetics, In: Therapeutic Use of Medicinal Plants and their Extracts, Springer, vol. 2, pp. 407-534 (2018).

5. D.C. Okafor, C.E. Ofoedu, A. Nwakaudu and M.O. Daramola, Enzymes as Additives in Starch Processing: A Short Overview, In: Enzymes in Food Biotechnology, Chap. 10, Elsevier, pp. 149-168 (2019); https://doi.org/10.1016/B978-0-12-813280-7.00010-4
6. D.L. Williamson, A.E. Bergman and G. Nagy, *J. Am. Soc. Mass Spectrom.*, **32**, 2573 (2021); https://doi.org/10.1021/jasms.1c00207
7. A. Kumar, S.K. Singh, C. Kant, H. Verma, D. Kumar, P.P. Singh, A. Modi, S. Droby, M.S. Kesawat, H.J.A. Alavilli, S.K. Bhatia, G.D. Saratale, R.G. Saratale, S.-M. Chung and M. Kumar, *Antioxidants*, **10**, 1472 (2021); https://doi.org/10.3390/antiox10091472
8. S. Shah, N. Rangaraj, K. Laxmikeshav and S. Sampathi, *Int. J. Pharm.*, **581**, 119268 (2020); https://doi.org/10.1016/j.ijpharm.2020.119268
9. M. Dunky, Eds.: K.L. Mittal, Wood Adhesives Based on Natural Resources: A Critical Review: Part II. Carbohydrate-Based Adhesives, In: Progress in Adhesion and Adhesives, vol. 6, Chap. 9 (2021); https://doi.org/10.1002/9781119846703.ch9
10. M. Braun, Heterocycles as Chiral Auxiliaries in Asymmetric Synthesis, Springer (2020).
11. A.K. Ghosh and M. Brindisi, *J. Med. Chem.*, **63**, 2751 (2020); https://doi.org/10.1021/acs.jmedchem.9b01541
12. R. Sathasivam and J.-S. Ki, *Mar. Drugs*, **16**, 26 (2018); https://doi.org/10.3390/md16010026
13. L.-Y. Xu, N.-L. Fan and X.-G. Hu, *Org. Biomol. Chem.*, **18**, 5095 (2020); https://doi.org/10.1039/D0OB00711K
14. M.M. Nielsen and C.M. Pedersen, *Chem. Rev.*, **118**, 8285 (2018); https://doi.org/10.1021/acs.chemrev.8b00144
15. A.J. Sayyed, N.A. Deshmukh and D.V. Pinjari, *Cellulose*, **26**, 2913 (2019); https://doi.org/10.1007/s10570-019-02318-y
16. Y. Yu and M. Delbianco, Synthetic Polysaccharides, In: Recent Trends in Carbohydrate Chemistry, Elsevier, pp. 333-371 (2020).
17. S.U. Jadhao and S.P. Deshmukh, *Asian J. Res. Chem.*, **11**, 121 (2018); https://doi.org/10.5958/0974-4150.2018.00025.1
18. N.P. Gurav and S. Medhe, *Anal. Chem. Ind. J.*, **17**, 126 (2018).
19. S. Slassi, M. Aarjane and A. Amine, *J. Mol. Struct.*, **1255**, 132457 (2022); https://doi.org/10.1016/j.molstruc.2022.132457