DOI 10.1007/s11094-025-03341-z
Pharmaceutical Chemistry Journal, Vol. 58, No. 12, March, 2025 (Russian Original Vol. 58, No. 12, December, 2024)

MODERN DIRECTIONS IN THE SEARCH FOR DRUGS IN RELATION TO *Klebsiella pneumoniae* (A REVIEW)

N. N. Stepkina,[1*] A. V. Velikorodov,[1,2] M. A. Samotrueva,[2] and V. Yu. Kotova[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 58, No. 12, pp. 14 – 23, December, 2024.

Original article submitted July 4, 2024.

The emergence and spread of resistant strains of *Klebsiella pneumoniae* leads to a decrease in the effectiveness of antibiotics currently used in therapeutic practice. The search for new drugs against this dangerous pathogen is conducted in several directions, including targeted synthesis of new substances with anti-klebsiellosis activity; the search for new targets for the action of potential drugs, including on the basis of metabolic modeling on the scale of the *K. pneumoniae* genome; screening for antibiotic resistance; identification of potential virulence factors; and a number of other approaches. This review analyzes and summarizes literature data over the past 10 years on the synthesis and study of potential drugs against *K. pneumoniae* using both an empirical approach and molecular docking.

Keywords: anti-klebsiellosis activity; *K. pneumoniae*; resistance; functionally substituted *N*,*O*,*S*-containing heterocyclic compounds; complexes of Schiff bases and other organic ligands with metal ions; functionally substituted aromatic compounds; molecular docking, metabolic modeling on the genome scale.

Klebsiella pneumoniae is one of the five most deadly bacteria for people. Greater than 500,000 deaths from pneumonia were attributed to it in 2019 [1]. It becomes highly virulent and quickly acquires resistance to antibiotics upon entering the blood pool.

K. pneumoniae is a species of Gram-negative facultative anaerobic conditionally pathogenic bacteria. It is rod-shaped with dimensions of 0.5 – 0.8 μm by 1 – 2 μm and is found in the normal microflora of human intestines, skin, and oral cavity. *K. pneumoniae* does not form spores, is immobile, and can develop capsules. It occurs solitary, pairwise, and in clusters.

K. pneumoniae can form biofilms. Biofilms are involved in a minimum of 60% of all cases of chronic and recidivous infections. Bacterial biofilms are shielded from the effects of stressful situations, including the action of antibiotics. Eventually, some of the most alarming consequences for medicine occur, i.e., resistance to antibiotics and antimicrobial agents and ineffective treatment [2].

Many outbreaks of hospital infections are known to be caused by *K. pneumoniae*, being especially aggressive for newborns and resuscitated geriatric patients. Many strains of *K. pneumoniae* produce β-lactamases, enzymes with broad spectra of action that promote resistance to antibiotics used to battle these infections. The presence of other factors leading to multidrug resistance limit the therapeutic possibilities and the use of last-line drugs such as polymyxins, which also is common. The global emergence and spread of resistant strains emphasize the need for novel antimicrobial drugs against *K. pneumoniae* and the bacterial pathogens associated with them [3, 4].

The increase in the drug resistance of many microorganisms pathogenic for humans requires the development of new drugs. The search for new efficacious drugs against *K. pneumoniae* is an urgent task and a timely research area.

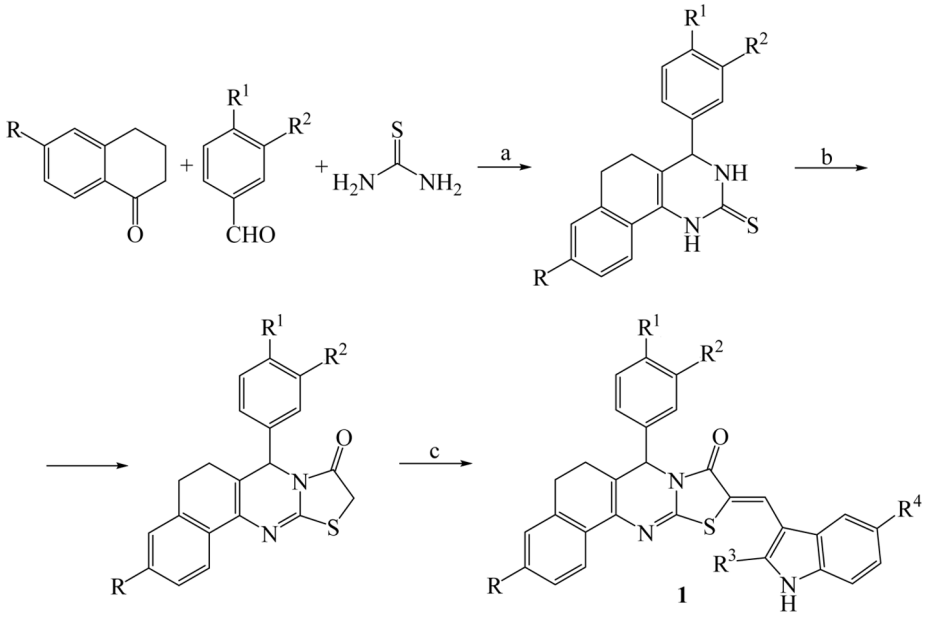
Functionally substituted and hybrid *N*,*O*,*S*-containing heterocyclic compounds

The search for new compounds exhibiting antimicrobial activity against *K. pneumoniae* is currently a vigorous effort. Various heterocyclic compounds exhibit such activity. They include derivatives of enrofloxacin [5], indolylmethylenebenzo-

[1] Tatishchev Astrakhan State University, 20a Tatishcheva St., Astrakhan, 414056 Russia.
[2] Astrakhan State Medical University, Ministry of Healthcare of the Russian Federation, 121 Bakinskaya St., Astrakhan, 414000 Russia.
[*] e-mail: nn_step@mail.ru

[*H*]thiazolo[2, 3]quinazolines (**1**) (Scheme 1) [6], hydrazones prepared by nucleophilic addition of benzotriazole acetic acid hydrazide to substituted benzaldehydes [7], 5-[4-(3-phenyl-4, 5-dihydro-1*H*-pyrazol-5-yl)phenyl]-1*H*-tetrazoles, and hybrids based on 4-substituted quinoline and functionally substituted *bis*-arylimidazole [8].

Scheme 1

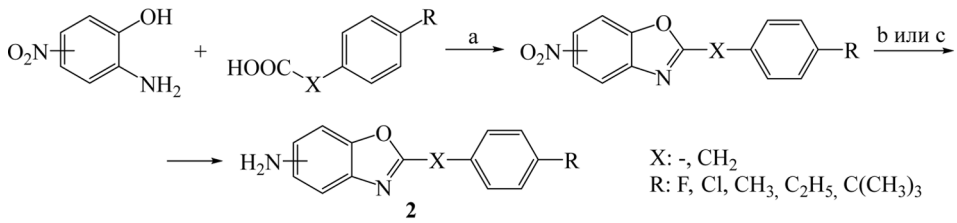


a: poly(4-vinylpyridinium) hydrogen sulfate, 120°C, 10 – 20 min; b: 2-chloro-*N*-phenylacetamide, HOAc, reflux, 4 – 6 h; c: 1*H*-indole-3-carbaldehyde, EtOH, Pip, reflux, 2 – 4 h.

Ionic liquids based on imidazole, pyridine, and pyridazine [9 – 11]; heterocyclic sulfanilamide derivatives [12, 13]; *bis*-heterocycles bonded through various bridging groups [14]; aminoglycoside derivatives [15]; hybrid indanedione heterocycles with dispirooxindolopyrrolidine [16]; 7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid [17]; oligosaccharides structurally related to galactan I and galactan II [18]; and piperine analogs [19] exhibited significant activity against *K. pneumoniae*.

Compounds with oxazole [20]; 1,2,4-triazole [21, 22]; pyrrolopyrimidine-4-thione [23]; 1,2,3-triazole [24, 25]; oxazepane [26]; 1,4-dihydro-1,8-naphthyridine [27]; thiazole [28 – 34]; pyrimidine [35 – 39]; imidazole [40, 41]; thienopyridine [42]; quinoline [20, 43, 44]; quinazoline [45]; pyrazoline [46]; pyrazole [39, 47]; imidazopyridine (purine) [48]; pyran [38]; indole [46, 49, 50]; and chromen-2-one fragments [24, 50, 51] were also active against *K. pneumoniae*. Scheme 2 illustrates the synthesis of benzoxazole derivatives **2**.

Scheme 2

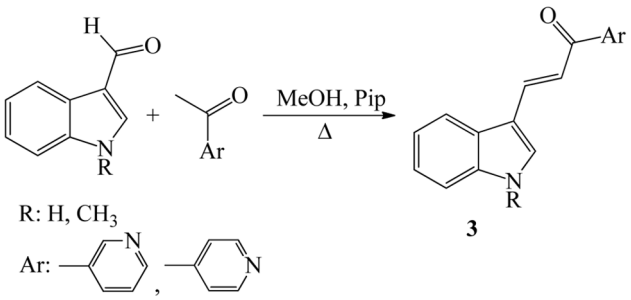


a: polyphosphoric acid; b: 10% Pd(C, H_2, EtOH; c: $NiCl_2 \cdot 6H_2O$, Zn, MeOH.

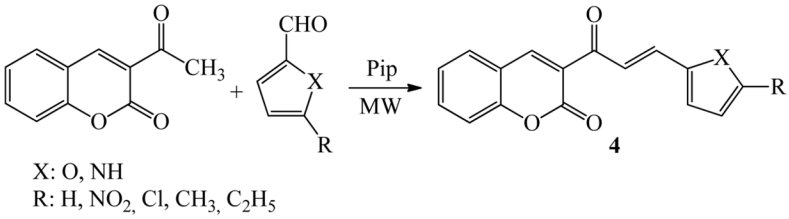
Electron-accepting groups (NO_2, Cl, Br) were found to increase the antimicrobial activity of benzoxazole derivatives against *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, and *A. niger* [52].

Syntheses of chalcones **3** with indole and pyridine fragments (Scheme 3) [49] and chalcones with a chromen-2-one fragment **4** (Scheme 4) [51] have been discussed. Their activity against *K. pneumoniae* was studied.

Scheme 3

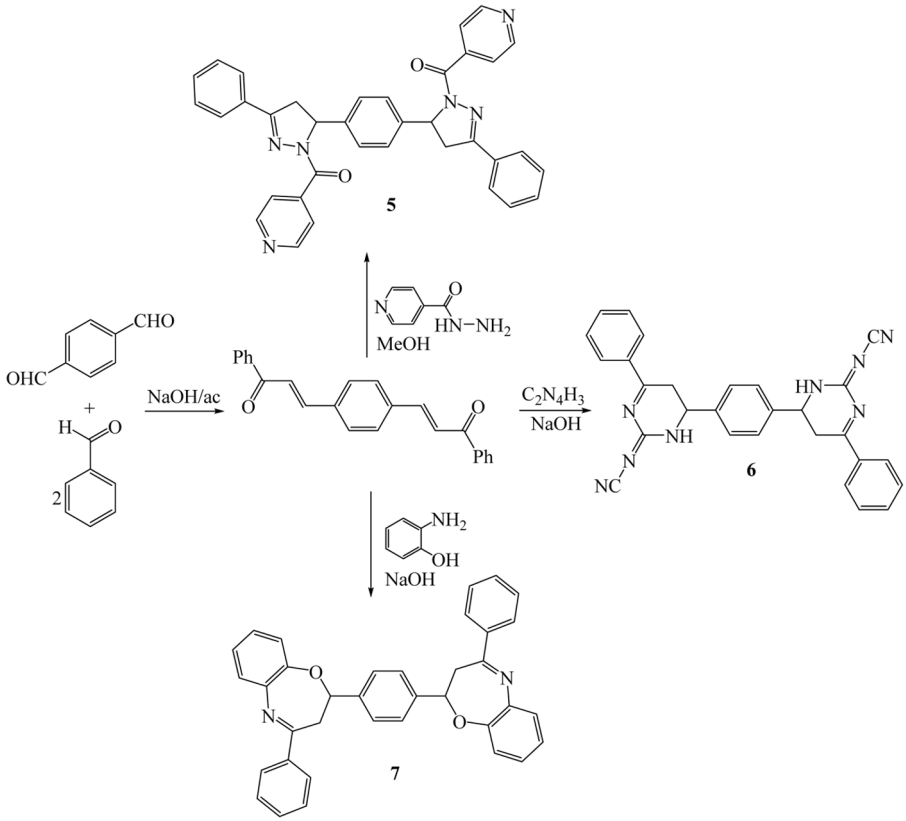


Scheme 4



Farhan, et al. synthesized *bis*-heterocyclic derivatives **5 – 7** from *bis*-chalcones (Scheme 5) [53].

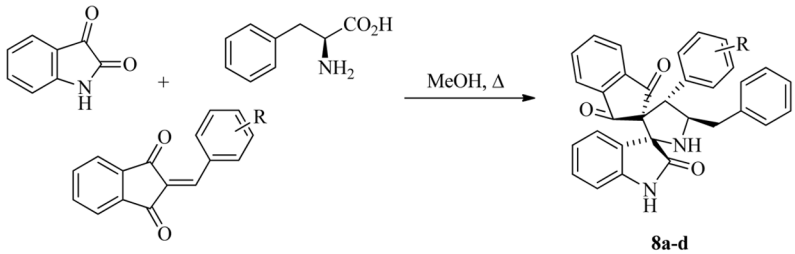
Scheme 5



Compound **7** showed the best biological activity of the three compounds against *E. coli*, *K. pneumoniae*, and *S. aureus*, possibly because of the dihydrooxazepine fragment, which affects the metabolic activity of bacterial cells.

Various hybrid heterocyclic compounds are highly interesting as antimicrobial compounds. Alaqeel, et al. reported the three-component synthesis of a new class of dispirooxindoles **8** via condensation of isatin, arylidene 1,3-indanedione, and L-phenylalanine with refluxing for 24 h in MeOH and studied their antimicrobial activity against *K. pneumoniae* ATCC 13883 (Scheme 6) [54]. The reference drug was ciprofloxacin. Compounds **8a-d** were studied at concentrations from 0.1 to 0.015 mg/mL.

Scheme 6

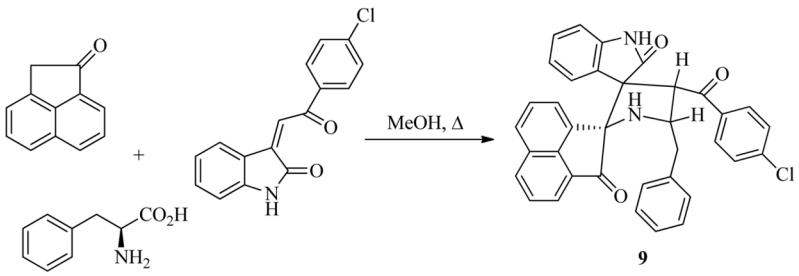


8a-d

Compound **8b** was found to possess the greatest activity against the studied *K. pneumoniae* strain (MIC 0.030 – 0.070 mg/mL). Literature data on the synthesis and assessment of the biological activity, including activity against *K. pneumoniae*, of heterocyclic hybrids in which an imidazole fragment was condensed with a carbo- or heterocyclic subunit have been reviewed [55].

Dispirooxindolopyrrolidine **9** was prepared by three-component condensation of acenaphthenone with L-phenylalanine and (*Z*)-3-[2-(4-chlorophenyl)-2-oxoethylidene]indolin-2-one (Scheme 7). It was shown to possess a broad spectrum of activity against various pathogens, including *K. pneumoniae* [56].

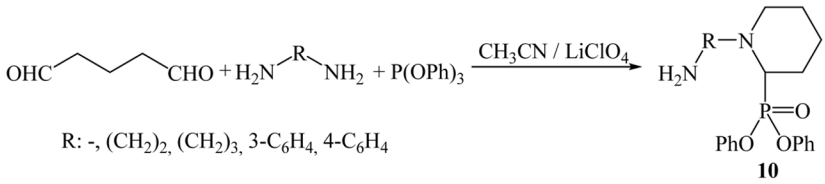
Scheme 7



9

Cyclic α-aminophosphonates (**10**) exhibiting activity against *K. pneumoniae* were prepared by a three-component reaction of glutaraldehyde with various diamines and triphenylphosphite in the presence of $LiClO_4$ in MeCN (Scheme 8) [57].

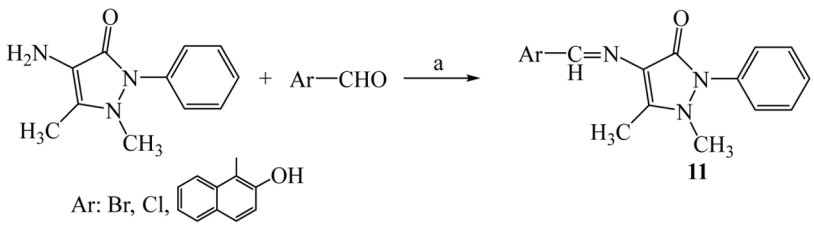
Scheme 8



10

Schiff bases with a 4-aminoantipyrine (pyrazolone) moiety (**11**) and anti-klebsiellosis activity were synthesized (Scheme 9) [58].

Scheme 9

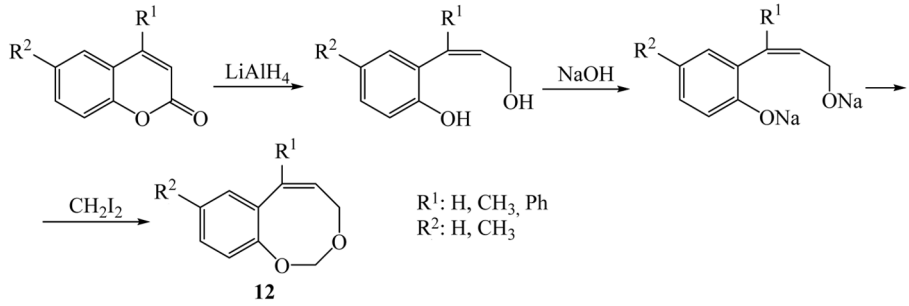


11

a: anhydr. EtOH, H^+, 1 – 2 h.

Coumacine compounds **12** were obtained from coumarin via sequential reduction, reaction with base, and cyclization using diiodomethane (Scheme 10) and exhibited antimicrobial activity against *K. pneumoniae*. This synthetic pathway to coumacine compounds was previously proposed [59]. Coumacine **12** ($R^1 = R^2 = CH_3$) was most active against *K. pneumoniae*.

Scheme 10



The antimicrobial activity against *K. pneumoniae* of pyrano[2,3-*d*]pyrimidine, benzothiazolepyrimidine derivatives, triazole 7-(trifluoromethyl)pyrido[2,3-*d*]pyrimidine derivatives, imidazo[1,2-*a*]pyrimidine compounds, and thiazolo[3,2-*a*]thiochromeno[4,3-*d*]pyrimidine derivatives has been proved [60 – 62]. Antimicrobial activity against experimental septic infection was established for 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine analogs [63].

Thus, a literature analysis showed that the search for compounds with anti-klebsiellosis activity is being conducted most extensively among hybrid heterocyclic compounds with various *N*,*O*,*S*-containing rings.

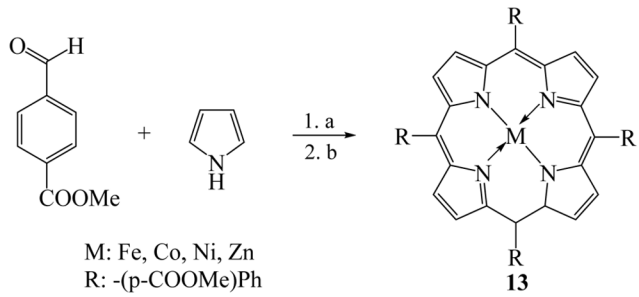
Complexes of Schiff bases and other organic ligands with metal ions

A method for preparing metal complexes of Schiff bases by reacting metal chlorides [Fe(II), Co(II), Ni(II), Cu(II), Zn(II)] with 1,3-diaminopropane and 2-acetylpyrrole in EtOH was developed. All complexes exhibited significant antimicrobial activity against several microorganisms, including *K. pneumoniae*, particularly the Cu complex, which was almost as active as the standard drug ciprofloxacin [64].

Complexes of Pd(II) and Cu(II) with Schiff bases of more complicated structures were also studied [65]. Studies of the antimicrobial activity showed that all synthesized complexes possessed better or similar activity as the reference drugs sulfamethoxazole and sulfisoxazole.

Kumar, et al. synthesized metal complexes [Ni(II), Cu(II), Zn(II), Pd(II)] with Schiff bases based on an imidazole ring and Cu(II) complexes with bidentate Schiff bases and many other Schiff bases acting as ligands of various heterocyclic structures [66]. Dimethylgallium quinolinate complexes were prepared [67]. Metalloporphyrins **13** were prepared by linking pyrrole with a substituted benzaldehyde (methyl 4-formylbenzoate) in CH_2Cl_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and Et_2O followed by metallization using an M(II) salt (Scheme 11). They were highly active against *K. pneumoniae* [68].

Scheme 11



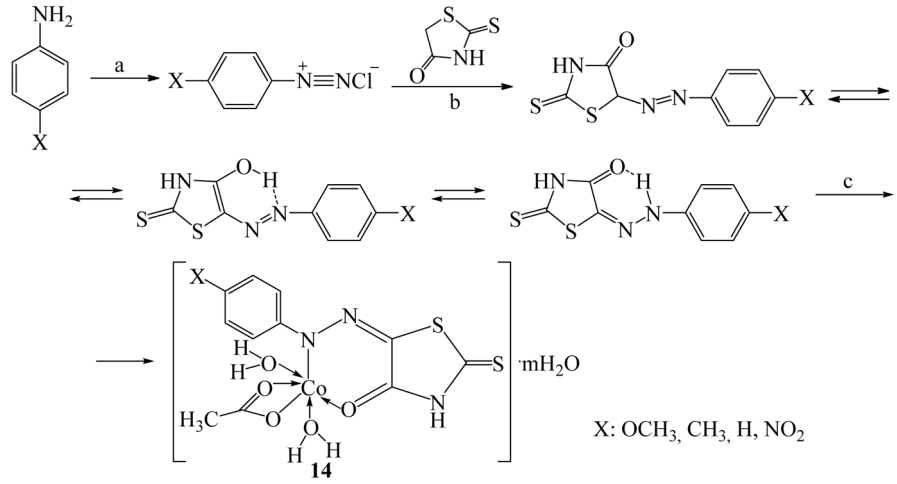
a: CH_2Cl_2, DDQ, Et_2O; b: M(II) salt.

A mixed complex of Ru(III) with 1,10-phenanthroline and guanidine as ligands [69] was synthesized and had activity close to those of ciprofloxacin and chloramphenicol.

Complexes of V(IV), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) with ligands of sulfonamide derivatives [70]; Cu complexes with 2-acetylpyridine-*N*-substituted thiosemicarbazone ligands [71]; a Pd complex with 3,3′-*bis*(1,1′-dinaphthylcamphopyrazole); a Mg complex with tetrapyrazinoporphyrazine [72]; and Ag(I) and Cu(II) complexes with 1,10-phenanthroline-5,6-dione [73] have been obtained. Their activity against *K. pneumoniae* has been studied.

Complexes **14** of Co(II) with 5-(4-arylazo)-2-thioxothiazolidin-4-one that exhibited activity against *K. pneumoniae* were synthesized (Scheme 12) [74].

Scheme 12



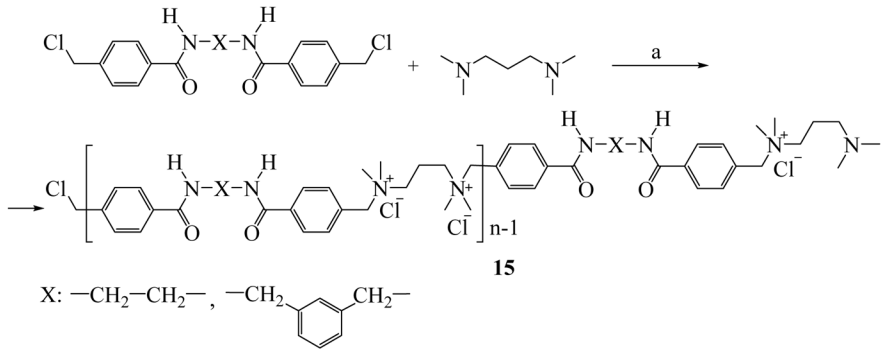
a: $NaNO_2$, HCl, 0 – 5 °C; b: basic solution, 0 – 5 °C; c: $Co(OAc)_2 \cdot 4H_2O$, EtOH, reflux.

Rifampicin-conjugated silver nanoparticles [75] prepared using purified capsular polysaccharide from *K. pneumoniae* ATCC 70063 [76] and gold nanoparticles prepared from Au(III) chloride and intracellular material [77] have been investigated.

Functionally substituted aromatic compounds

Polyionenes **15** are antimicrobial polymers containing robust amide residues of *bis*-halide monomers and tetramethyl-1,3-diaminopropane that were synthesized according to Scheme 13 [78].

Scheme 13



a: DMF, room temperature, 18 h.

Multiple use of imipenem and gentamicin was found to promote the development of drug resistance in *K. pneumoniae*, while repeated use of polyionenes did not cause resistance development because of the antimicrobial mechanism that destroyed the membrane. The polymer demonstrated a lower effective dose than imipenem with lung infection caused by pneumonia with insignificant systemic toxicity. Treatment with the polymer significantly decreased lung injury, markedly reduced the number of *K. pneumoniae* in blood and major organs, and reduced lethality.

Peptide conjugates of nucleic acids were prepared by microwave solid-phase synthesis and were highly active against *K. pneumoniae* [79]. The peptide Mo-CBP_3-PepI [80], phosphinothricin peptide derivatives [81], and other peptides [82 – 84] have been synthesized.

Addition of aryl groups to an aporphine alkaloid structure was shown to increase the sensitivity of *K. pneumoniae* to the antibiotic colistin [85].

Synthesis and molecular docking of compounds with potential anti-klebsiellosis activity

Molecular docking of promising compounds with respect to suppression of *K. pneumoniae* growth garners a significant part of research on the development of new antimicrobial drugs. An approach based on metabolic modeling on the genome scale is also highly promising [86, 87] and is widely used to reveal drug targets on a systemic level for various pathogens, including various *K. pneumoniae* strains [88, 89], and to search for suitable inhibitors among available compounds in chemical libraries.

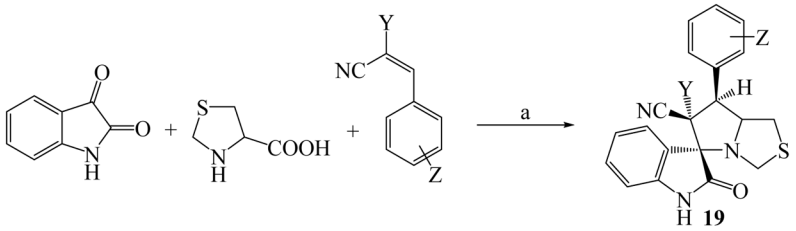
Molecular docking can be used to investigate the mechanism of interaction between compounds and a protein. Higher binding affinity between a protein and drug can help the drug to exhibit higher efficacy. The high affinity of tested compounds for selected biotargets was justified using molecular docking [90 – 97].

Kumar, et al. found that 1-dimethylsulfamoylpyrrolidine-2-carboxylic acid (**16**) showed high binding affinity with the target being analyzed, i.e., protein 1NPB [90]. Visualization of the interacting amino acids within 4 Å showed the formation of an equal number of H-bonds between the fosfomycin(1NPB and **16**(1NPB complexes and an equal number of hydrophobic (3) and polar (2) interactions of the amino acids. The binding energy of **16** ((5.06 kcal/mol) was found to correlate with its antibacterial activity as compared to fosfomycin ((4.63 kcal/mol).

Cordeiro, et al. synthesized *N*-(4-fluoro-3-nitrophenyl)acetamide (**17**) and 2-chloro-*N*-(4-fluoro-3-nitrophenyl)acetamide (**18**) and established that **18** was more active against *K. pneumoniae* [91]. Molecular docking with transferases [glucosamine-6-phosphate synthase (2VF5), FosA (5V3D), penicillin-binding protein 1b (PBP1b, 5HLA), and *K. pneumoniae* fosfomycin-resistant protein FosAKP (6C3U)], hydrolases [β-lactamase (2ZD8) and penicillin-bonding protein 3 (PBP_3, 3PBS)], DNA-gyrase (1AJ6), and topoisomerase IV (1S14) was performed to reveal possible molecular targets at which **17** and **18** interact to manifest an antibacterial effect and to study the effect of a Cl atom on the molecular binding to the enzyme-target active side. Compound **18** showed the best binding energies as compared to **17** for all tested enzymes. This indicated that the Cl atom facilitated more effective binding of the molecule to various protein active sites.

Derivatives of spiroindoline-3,5′-pyrrolo[1, 2-*c*]thiazole (**19**) were synthesized via a multicomponent reaction of substituted isatin, sarcosine, and a 2-arylacrylic acid derivative using 2,2,2-trifluoroethanol (TFE) as the solvent (Scheme 14) [92].

Scheme 14



a: TFE, MW, 5 – 10 min.

Compound	Y	Z	Time (min)	Yield (%)
19a	COOEt	2-thiophenyl	7	91
19b	COOEt	2-Cl, 6-F	6	92
19c	CN	3,4-Cl	9	89
19d	CN	4-NO2	8	88

All obtained compounds were studied for antimicrobial activity as compared to the standard drugs gentamicin and ampicillin. Compound **19c** was found to have high antimicrobial activity against *K. pneumoniae* (0.005 μg/mL). Molecular docking of the synthesized compounds used protein NDM-1 as the target. The docking calculations indicated a strong affinity of **19c** for protein NDM-1.

Compounds **20** and **21** with a piperazine moiety were synthesized (Fig. 1) [93].

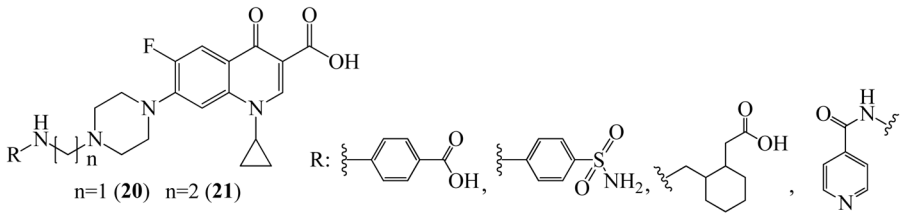
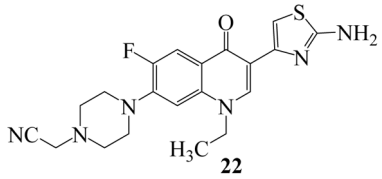


Fig. 1. Derivatives of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**20** and **21**).

Almost all studied compounds showed binding to DNA-gyrase analogous to binding of moxifloxacin. Hydrophobic interactions with DNA bases (adenine and guanine) were observed. H-bonds between the compounds and Ser84/Glu88 were also detected.

Various derivatives with an aminothiazolyl norfloxacin moiety were synthesized. Compound **22** was found to be most active (Fig. 2). Its antimicrobial activity against *K. pneumoniae* and inhibitory activity against DNA-gyrase were investigated. Docking in the complexes with DNA-topoisomerase IV and DNA-gyrase was studied [94].



22

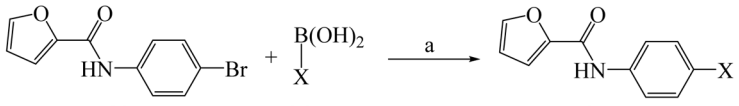
Fig. 2. 2-{4-[3-(2-Aminothiazol-4-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl]piperazin-1-yl}acetonitrile (**22**).

The ability of *K. pneumoniae* to develop drug resistance to highly active compound **22** was tested in this study using the standard drug norfloxacin as a control. The susceptibility of *K. pneumoniae* to **22** remained almost unchanged even after 10 reinoculations, while the MIC of norfloxacin against *K. pneumoniae* sharply increased after several reinoculations, indicating that *K. pneumoniae* more difficultly developed resistance to **22** than to the standard drug norfloxacin. A kinetic experiment using **22** against *K. pneumoniae* showed that the number of viable bacteria decreased by >2.5 log units (CFU/mL) during one hour at a concentration of 4×MIC.

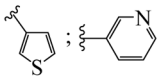
Bacterial DNA-gyrase included in topoisomerase enzymes of type IIA bacteria controls the topological state of DNA during transcription, replication, and recombination and is known as a confirmed target for aminocoumarin and quinolone antibiotics. The analog of aminothiazolyl norfloxacin **22** and the standard drug norfloxacin were selected for studies of their inhibitory activity against *E. coli* DNA-gyrase. Compound **22** was found to exhibit good inhibitory activity against DNA-gyrase (IC_{50} = 16.7 μM) and was more effective than the reference drug norfloxacin (IC_{50} = 18.6 μM). This indicated that replacement of the carboxylic group by a weakly basic 2-aminothiazole moiety could cause antibacterial activity analogous to that of norfloxacin by acting on DNA-gyrase.

Suzuki(Miyaura cross-coupling of *N*-(4-bromophenyl)furan-2-carboxamide (**23**) with various aryl- and heteroarylboronic acids (**24**) in the presence of tetrakis(triphenylphosphine)palladium(0) catalyst and potassium phosphate as a base produced *N*-aryl-substituted amides of furan-2-carboxylic acid (**25**) (Scheme 15) [95].

Scheme 15



23 **24** **25**

X: 2-Cl,4-F-Ph; 4-$COOCH_3$Ph; 2-Ac-Ph; 4-Cl-Ph; 2,4-diCl-Ph; 4-CH_3-Ph; 

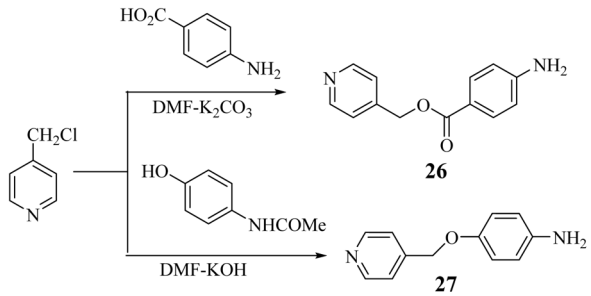
a: 1,4-dioxane, $Pd(PPh_3)_4$, K_3PO_4, 95°C, 8 – 18 h.

Molecular docking was performed for compounds **25** with protein NDM-1 (embelin) as the target.

A mechanism of action of antimicrobial peptides against encapsulated *K. pneumoniae* strains was proposed [96].

Pyridin-4-ylmethyl-4-aminobenzoate (**26**) and 4-(pyridin-4-ylmethoxy)aniline (**27**) were synthesized (Scheme 16) [97]. The reduction in the production of folic acid by bacteria and the destruction of *K. pneumoniae* cellular membranes under their influence were studied.

Scheme 16



Molecular docking of **26** and **27** and *p*-aminobenzoic acid (PABA) as a control was studied against active sites of dihydropteroate synthase (DHPS) (PDB: 3tye) and proteins of the OmgK36 outer membrane from *K. pneumoniae* (PDB: $6rd_3$),

which was chosen based on the resistance of the protein to β-lactam antibiotics, which affected the cell membrane to assess the binding process by which all compounds interacted with essential amino acids of this bacterial protein.

CONCLUSION

Thus, the review showed that the main direction for searching for potential drugs with anti-klebsiellosis activity is the development of methods for synthesizing a broad spectrum of functionalized *N*,*O*,*S*-containing heterocyclic compounds and primarily hybrid structures, aromatic compounds, and metal complexes with various organic ligands. The traditional approach to the search for new drugs was supplemented by widespread use of molecular docking and a search for new targets for potential drugs, including metabolic modeling at the genome scale of *K. pneumoniae*. Screening for resistance to antibiotics and identification of potential virulence factors and some other approaches played a significant role in this research.

Conflict of interest

We declare no conflict of interest.

Financing

The research was supported by a State Task for the Ministry of Healthcare of the Russian Federation No. 123011600118 – 0.

Contribution of authors

All authors contributed equally to the article. AVV and MAS formulated the general concept of the article. AVV and NNS reviewed the literature. NNS, VYuK, and MAS analyzed and interpreted the results. AVV, NNS, and VYuK wrote the article. NNS produced the schemes.

REFERENCES

1. GBD 2019 Antimicrobial Resistance Collaborators, *Lancet*, **400**, 2221 – 2248 (2022); doi: 10.1016/ S0140-6736(22)02185-7.
2. Yu. S. Karpeeva, V. P. Novikova, A. I. Khavkin, et al., *Ross. Vestn. Perinatol. Pediatr.*, **65**(5), 116 – 125 (2020); doi: 10.21508/1027-4065-2020-65-5-116-125.
3. P. I. Pereira Ramos, D. F. Do Porto, E. Lanzarotti, et al., *Sci. Rep.*, **8**(1), e10755 (2018); doi: 10.1038/s41598-018-28916-7.
4. E. V. Anganova, A. V. Vetokhina, L. A. Raspopina, et al., *Zh. Mikrobiol.*, **94**(5), 70 – 77 (2017); doi: 10.51620/0869-2084-2022-67-10-594-599.
5. H. Siddiqui, H. M. Haniffa, A. Ahmed, et al., *Med. Chem.*, **17**(1), 85 – 96 (2021); doi: 10.2174/1573406416666200402151705.
6. R. Gali, J. Banothu, M. Porika, et al., *Bioorg. Med. Chem. Lett.*, **24**, 4239 – 4242 (2014); doi: 10.1016/j.bmcl.2014.07.030.
7. S. S. Saleh, S. Sh. Al-Salihi, and I. A. Mohammed, *Energy Procedia*, **157**, 296 – 306 (2019); doi: 10.1016/j.egypro.2018.11.194.
8. K. U. Sadek, R. A. Mekheimer, M. Abd-Elmonem, et al., *J. Mol. Struct.*, **1286**, e135616 (2023); doi: 10.1016/j.molstruc.2023.135616.
9. A. Aljuhani, W. S. El-Sayed, P. K. Sahu, et al., *J. Mol. Liq.*, **249**, 747 – 753 (2018); doi: 10.1016/j.molliq.2017.11.108.
10. M. M. Santos, C. Alves, J. Silva, et al., *Pharmaceutics*, **12**(8), 694 (2020); doi: 10.3390/pharmaceutics12080694.
11. A. Miskiewicz, P. Ceranowicz, M. Szymczak, et al., *Int. J. Mol. Sci.*, **19**(9), e2779 (2018); doi: 10.3390/ijms19092779.
12. V. Niraimathi and K. B. Durgadevi, *Indo Am. J. Pharm. Sci.*, **3**(3), 305 – 310 (2016).
13. M. A. Qadir, M. Ahmed, and M. Iqbal, *BioMed Res. Int.*, **2015**, Art. ID 938486 (2015); doi: 10.1155/2015/938486.
14. P. Borrego-Munoz, F. Ospina, and D. A. Quiroga, *Molecules*, **26**, 3997 (2021); doi: 10.3390/molecules26133997.
15. A. N. Tevyashova and K. S. Shapovalova, *Khim.-farm. Zh.*, **55**(9), 7 – 23 (2021); *Pharm. Chem. J.*, **55**, 860 – 875 (2021); doi: 10.1007/s11094-021-02510-0.
16. S. I. Alaqeel, A. I. Almansour, N. Arumugamb, et al., *J. Infect. Public Health*, **14**, 1870 – 1874 (2021); doi: 10.1016/j.jiph.2021.10.023.
17. N. Majed, R. Majid, and R. Majed, *J. Pharm. Sci. Res.*, **10**(11), 2964 – 2968 (2018).
18. D. A. Argunov, A. S. Trostianetskaia, V. B. Krylov, et al., *Eur. J. Org. Chem.*, **26**, 4226 – 4232 (2019); doi: 10.1002/ejoc.201900389.
19. K. R. Amperayani, K. N. Kumar, and U. D. Parimi, *Res. Chem. Intermed.*, **44**, 3549 – 3564 (2018); doi: 10.1007/s11164-018-3324-1.
20. D. K. Katariya, A. K. Vyas, P. Bhanderi, et al., *Russ. J. Bioorg. Chem.*, **50**, 1573 – 1582 (2024); doi: 10.1134/S1068162024040289.
21. A. Legru, F. Verdirosa, J.-F. Hernandez, et al., *Eur. J. Med. Chem.*, **226**, 113873 (2021); doi: 10.1016/j.ejmech.2021.113873.
22. A. Shaik, A. T. Rao, D. V. Venkatarao, et al., *Russ. J. Org. Chem.*, **56**, 2179 – 2187 (2020); doi: 10.1134/S1070428020120210.
23. R. J. Nahi and A. S. Razzaq, *Syst. Rev. Pharm.*, **12**(1), 195 – 200 (2021); doi: 10.31838/srp. 2021.1.31.
24. K. Kushwaha, N. Kaushik, Lata, et al., *Bioorg. Med. Chem. Lett.*, **24**, 1795 – 1801 (2014); doi: 10.1016/j.bmcl.2014.02.027.
25. M. Hussain, T. Qadri, Z. Hussain, et al., *Heliyon*, **5**, e02812 (2019); doi: 10.1016/j.heliyon.2019.e02812.
26. A. S. Hassan and A. S. Hame, *Res. J. Biotechnol.*, **14**(1), 109 – 118 (2019).
27. T. Khan, K. Sankhe, V. Suvarna, et al., *Biomed. Pharmacother.*, **103**, 923 – 938 (2018); doi: 10.1016/j.biopha.2018.04.021.
28. S. M. H. Sanad, A. A. M. Ahmed, and A. E. M. Mekky, *Arch. Pharm. Chem. Life Sci.*, **353**(4), e1900309 (2020); doi: 10.1002/ardp. 201900309.
29. K. F. da Cunha, M. de Oliveira Garcia, S. O. Allend, et al., *Braz. J. Microbiol.*, **54**, 2587 – 2595 (2023); doi: 10.1007/s42770-023-01110-2.
30. V. Asati, N. K. Sahu, A. Rathore, et al., *Arabian J. Chem.*, **8**, 495 – 499 (2015); doi: 10.1016/j.arabjc.2011.01.036.

31. S. Maddila, S. Gorle, N. Seshadri, et al., *Arabian J. Chem.*, **9**, 681 – 687 (2016); doi: 10.1016/j.arabjc.2013.04.003.
32. I. Althagafi, N. El-Metwaly, and T. A. Farghaly, *Molecules*, **24**, 1741 (2019); doi: 10.3390/molecules24091741.
33. V. R. Mishra, Ch. W. Ghanavatkar, S. N. Mali, et al., *J. Biomol. Struct. Dyn.*, **38**(6), 1772 – 1785 (2019); doi: 10.1080/07391102.2019.1621213.
34. R. M. Mhaibes, R. K. Khudhur, M. A. Ramadhan, et al., *Caspian J. Environ. Sci.*, **22**(1), 155 – 160 (2023); doi: 10.22124/CJES._2023.7238.
35. J. Zhuang and S. Ma, *ChemMedChem*, **15**(20), 1875 – 1886 (2020); doi: 10.1002/cmdc.202000378.
36. K. Ahmed, M. I. Choudhary, and R. Sh. Z. Saleem, *Eur. J. Med. Chem.*, **259**, e115701 (2023); doi: 10.1016/j.ejmech.2023.115701.
37. R. N. Atiya, N. A. Salih, and R. W. Adam, *Int. J. Drug Deliv. Technol.*, **12**(1), 174 – 179 (2022).
38. M. Aatif, M. A. Raza, Kh. Javed, et al., *Antibiotics*, **11**, 1750 – 1774 (2022); doi: 10.3390/antibiotics11121750.
39. A. A. Zwain, I. Ahmad, R. Kh. J. Ali, et al., *Front. Mater., Sec. Biomater. Bio-Inspired Mater.*, **10**, 1196583 (2023); doi: 10.3389/fmats.2023.1196583.
40. L. A. Mohammed, M. A. Farhan, S. A. Dadoosh, et al., *SynOpen*, **7**, 652 – 673 (2023); doi: 10.1055/a-2155 – 9125.
41. K. R. Al-Jorani, A. J. Kh. Atia, S. J. Lafta, et al., *J. Pharm. Sci. Res.*, **11**(4), 1195 – 1203 (2019).
42. Sh. M. H. Sanad, A. A. M. Ahmed, and A. E. M. Mekky, *J. Heterocycl. Chem.*, **57**(2), 590 – 605 (2020); doi: 10.1002/jhet.3789.
43. S. A. Hameed and H. H. Ibraheem, *Al-Nahrain J. Sci.*, **23**(1), 1 – 6 (2020); doi: 10.22401/ANJS. 23.1.01.
44. F. Ghazal, S. Farooq, A. Wahab, et al., *Future Microbiol.*, **17**(11), 843 – 859 (2022); doi: 10.2217/fmb-2021-0111.
45. A. A. Tsibizova, A. L. Yasenyavskaya, I. N. Tyurenkov, et al., *Sib. Zh. Klin. Eksp. Med.*, **38**(1), 175 – 180 (2023); doi: 10.29001/2073-8552-2023-38-1-175-180.
46. S. Sathiya, B. S. Krishnamoorthy, S. Meenachy, and R. Ravikumar, *Asian J. Pharm. Clin. Res.*, **15**(9), 94 – 97 (2022); doi: 10.22159/ajpcr.2022.v15i9.45089.
47. M. A. Pradeep, N. R. Kumar, D. K. Swaroop, et al., *ChemistrySelect*, **4**, 138 – 144 (2019); doi: 10.1002/slct.201803078.
48. S. N. Mali, A. Anand, M. E. A. Zaki, et al., *Molecules*, **28**, 2801 – 2815 (2023); doi: 10.3390/molecules28062801.
49. A. M. Looga, P. Ambassa, J. Kamga, et al., *Austin J. Anal. Pharm. Chem.*, **6**(2), 1116 – 1120 (2019).
50. Kh. N. U. Basha, Sh. Gnanamani, P. Shanmugam, et al., *J. Heterocycl. Chem.*, **58**, 2000 – 2008 (2021); doi: 10.1002/jhet.4326.
51. M. S. Abdel-Halim, A. M. El-Ganiny, and B. Mansour, *BMC Microbiol.*, **24**, 67 (2024); doi: 10.1186/s12866 – 024 – 03214 – 7.
52. S. Kakkar, S. Tahlan, S. M. Lim, et al., *Chem. Cent. J.*, **12**(1), 92 (2018); doi: 10.1186/s13065-018-0459-5.
53. M. M. Farhan, M. H. A. Al-Jumaili, and E. A. Bakr, *J. Chem. Res.*, **47**(6), 1 – 6 (2023); doi: 10.1177/17475198231218387.
54. S. I. Alaqeel, A. I. Almansour, N. Arumugam, et al., *J. Infect. Public Health*, **14**(12), 1870 – 1874 (2021); doi: 10.1016/j.jiph.2021.10.023.
55. R. Rossi and M. Ciofalo, *Molecules*, **25**(21), 5133 (2010); doi: 10.3390/molecules25215133.
56. A. I. Almansour, N. Arumugam, R. S. Kumar, et al., *J. Infect. Public Health*, **13**(12), 2001 – 2008 (2020); doi: 10.1016/j.jiph.2020.09.016.
57. I. El T. El Sayed, Gh. Fathy, and A. A. S. Ahmed, *Biomed. J. Sci. Tech. Res.*, **23**(4), 17609 – 17614 (2019); doi: 10.26717/BJSTR.2019.23.003936.
58. H. M. Y. Al-Labban, H. M. Sadiq, and A. A. J. Aljanaby, *J. Phys.: Conf. Ser.*, **1294**(4), 052007 (2019); doi: 10.1088/1742-6596/1294/5/052007.
59. Y. F. Mustafa, *Saudi Pharm. J.*, **26**, 870 – 875 (2018); doi: 10.1016/j.jsps.2018.03.010.
60. A. R. Bhat, R. S. Dongre, F. A. Almalki, et al., *Bioorg. Chem.*, **106**, 104480 (2021); doi: 10.1016/j.bioorg.2020.104480.
61. R. N. Kumar, G. J. Dev, N. Ravikumar, et al., *Bioorg. Med. Chem. Lett.*, **26**(12), 2927 – 2930 (2016); doi: 10.1016/j.bmcl.2016.04.038.
62. L. Suresh, P. S. V. Kumar, Y. Poornachandra, et al., *Bioorg. Med. Chem.*, **24**, 3808 – 3817 (2016); doi: 10.1016/j.bmc.2016.06.025.
63. K. V. Savateev, E. N. Ulomsky, V. V. Fedotov, et al., *Russ. J. Bioorg. Chem.*, **43**, 421 – 428 (2017); doi: 10.1134/S1068162017040094.
64. H. Zafar, A. Ahmad, A. U. Khan, et al., *J. Mol. Struct.*, **1097**, 129 – 135 (2015); doi: 10.1016/j.molstruc.2015.04.034.
65. S. Alyar, C. Sen, H. Alyar, et al., *J. Mol. Struct.*, **1171**, 214 – 222 (2018); doi: 10.1016/j.molstruc.2018.06.004.
66. R. Kumar, A. A. Singh, U. Kumar, et al., *J. Mol. Struct.*, **1294**, e136346 (2023); doi: 10.1016/j.molstruc.2023.136346.
67. R. N. Duffin and Ph. C. Andrews, *J. Inorg. Biochem.*, **249**, e112371 (2023); doi: 10.1016/j.jinorgbio.2023.112371.
68. B. B. Beyene, A. M. Mihirteu, M. T. Ayana, et al., *Results Chem.*, **2**, e100073 (2020); doi: 10.1016/j.rechem.2020.100073.
69. A. Abebe and T. Hailemariam, *Bioinorg. Chem. Appl.*, **2016**, Art. ID 3607924 (2016); doi: 10.1155/2016/3607924.
70. A. U. Hassan, S. H. Sumrra, M. A. Raza, et al., *Appl. Organomet. Chem.*, **35**, e6054 (2021); doi: 10.1002/aoc.6054.
71. M. Kaushal, T. S. Lobana, L. Nim, et al., *New J. Chem.*, **43**, 11727 – 11742 (2019); doi: 10.1039/C9NJ01459D.
72. E. S. Alwan, M. S. Bayoumy, and R. M. Mohareb, *Org. Commun.*, **16**(2), 54 – 74 (2023); doi: 10.25135/acg.oc.150.2303.2741.
73. I. Vianez Peregrino, R. Ferreira Ventura, M. Borghi, et al., *Lett. Appl. Microbiol.*, **73**(2), 139 – 148 (2021); doi: 10.1111/lam.13485.
74. Sh. M. Morgan, M. A. Diab, and A. Z. El-Sonbati, *Appl. Organomet. Chem.*, **32**(4), e4305 (2017); doi: 10.1002/aoc.4305.
75. U. Farooq, T. Ahmad, A. Khan, et al., *Int. J. Nanomed.*, **14**, 3983 – 3993 (2019); doi: 10.2147/IJN. S198194.
76. G. N. Maity, Sh. R. Ali, S. Mabhai, et al., *Sci. J. Microbiol.*, Art. ID sjmb-186 (2016); doi: 10.7237/sjmb/186.
77. C. James and G. Kumar, *Arch. Microbiol.*, **204**, 719 (2022); doi: 10.1007/s00203 – 022 – 03325 – 7.
78. W. Lou, Sh. Venkataraman, G. Zhong, et al., *Acta Biomater.*, **78**, 78 – 88 (2018); doi: 10.1016/j.actbio.2018.07.038.
79. A. M. Hansen, G. Bonke, W. F. J. Hogendorf, et al., *Eur. J. Med. Chem.*, **168**, 134 – 145 (2019); doi: 10.1016/j.ejmech.2019.02.024.
80. L. A. C. Branco, P. F. N. Souza, N. A. S. Neto, et al., *Antibiotics*, **11**, 1753 – 1773 (2022); doi: 10.3390/antibiotics11121753.
81. M. V. Demiankova, F. Giovannercole, M. A. Khomutov, et al., *Molecules*, **28**, 1234 – 1244 (2023); doi: 10.3390/molecules28031234.
82. C. M. de Souza, A. P. da Silva, N. G. Oliveira Junior, et al., *Trends Pharmacol. Sci.*, **43**(4), 335 – 348 (2022); doi: 10.1016/j.tips.2021.12.006.
83. P. Morici, W. Florio, C. Rizzato, et al., *Eur. J. Clin. Microbiol. Infect. Dis.*, **36**, 1739 – 1748 (2017); doi: 10.1007/s10096-017-2987-7.
84. K. D. Roberts, Y. Zhu, M. A. K. Azad, et al., *Nat. Commun.*, **13**, e1625 (2022); doi: 10.1038/s41467-022-29234-3.
85. H. Li, A. M. Nemeth, R. J. Melander, et al., *ACS Infect. Dis.*, **10**(4), 1339 – 1350 (2024); doi: 10.1021/acsinfecdis.4c00026.
86. S. Durmus, T. Cakir, A. Ozgur, and R. Guthke, *Front. Microbiol.*, **7**, 21 (2016); doi: 10.3389/fmicb.2016.00021.

87. M. F. Cesur, B. Siraj, R. Uddin, et al., *Front. Cell. Infect. Microbiol.*, **9**, 447 (2020); doi: 10.3389/fcimb.2019.00447.
88. P. I. P. Ramos, D. Fernandez Do Porto, E. Lanzarotti, et al., *Sci. Rep.*, **8**, Art. No. 10755, 1 – 19 (2018); doi: 10.1038/s41598-018-28916-7.
89. C. J. Norsigian, H. Attia, R. Szubin, et al., *Front. Cell. Infect. Microbiol.*, **9**, 161 (2019); doi: 10.3389/fcimb.2019.00161.
90. D. Th. Kumar, P. Lavanya, C. G. P. Doss, et al., *J. Cell. Biochem.*, **118**, 4088 – 4094 (2017); doi: 10.1002/jcb.26064.
91. L. Cordeiro, H. Diniz-Neto, P. Figueiredo, et al., *Molecules*, **25**, No. 17, 3959 – 3977 (2020); doi: 10.3390/molecules25173959.
92. A. Dandia, Sh. Khan, P. Soni, et al., *Bioorg. Med. Chem. Lett.*, **27**(13), 2873 – 2880 (2017); doi: 10.1016/j.bmcl.2017.04.083.
93. S. Tahir, T. Mahmood, F. Dastgir, et al., *Eur. J. Med. Chem.*, **166**, 224 – 231 (2019); doi: 10.1016/j.ejmech.2019.01.062.
94. L.-L. Wang, N. Battini, R. R. Yadav Bheemanaboina, et al., *Eur. J. Med. Chem.*, **167**, 105 – 123 (2019); doi: 10.1016/j.ejmech.2019.01.072.
95. A. Siddiqa, M. Zubair, M. Bilal, et al., *Pharmaceuticals*, **15**, 841 – 854 (2022); doi: 10.3390/ph15070841.
96. C. M. de Souza, A. P. da Silva, N. G. Oliveira Junior, et al., *Trends Pharmacol. Sci.*, **43**(4), 335 – 348 (2022); doi: 10.1016/j.tips.2021.12.006.
97. J. T. P. Matshwele, M. Jongman, T. B. Demissie, et al., *Chem. Afr.*, **6**, 2725 – 2735 (2023); doi: 10.1007/s42250-023-00662-y.